Jürgen Pilz · Teresa A. Oliveira ·
Karl Moder · Christos P. Kitsos *Editors*

Mindful Topics on Risk Analysis and Design of Experiments

Selected contributions from ICRA8, Vienna 2019

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Preface

In principle, risk is defined as an exposure to the chance of injury or loss. Practically, it is a hazard or dangerous chance and is wondering about the probability that something unpleasant will take place. Therefore, the probability of damage, caused by external or internal factors, has to be evaluated. The essential factors influence the increment of the risk which is asked to be determined. That is why eventually we are referring to relative risk (RR) as one factor might influence the risk in a way that is different from that of another factor. Certainly, interest must be focused on providing qualitative methods to measure the relative risk.

In decision theory, risk is well defined through the appropriate definition of "rules" and a solid Bayesian background. But a number of applications from epidemiology, toxicology, economics, and engineering do not really obey this framework. The logit and probit models provided the first opportunities to work separated from the decision theory. Other techniques have been developed meanwhile approaching the RR in a number of applications.

In epidemiological studies, it is needed to identify and quantitatively assess the susceptibility of a portion of the population to specific risk factors. It is assumed that they have been equally exposed to the same possible hazardous factors. The difference, at the early stage of the research study, is only to a particular factor which acts as a susceptibility factor. In such a case, statistics provide the evaluation of the RR.

Under this line of thought, we started the ICCRA (= International Conference on Cancer Risk Assessment) conferences on August 22, 2003, in Athens, and we proceeded in Santorini, 2007 and 2009. We moved to Limassol, Cyprus 2011, with the essential adjustment to ICRA (= International Conference to Risk Analysis). ICRA5 moved to Tomar, Portugal, 2013, where actually was established the extension of RA to bioinformatics, management, and industry. The SRPRINGER volume in 2013 provides the appropriate evidence. One step forward, further from game theory, towards more fields pertaining to risk, was offered by the second SPRINGER volume, in 2018. Meanwhile, ICRA6 moved to Barcelona, Spain, ICRA7 to Chicago, USA, and ICRA8 in 2019 to Vienna, Austria.

The Vienna ICRA8 conference was a crossroad: Risk analysis performed with design of experiments in a joint conference. How close or how far are the two statistical lines of though it is really a big issue. It seems difficult to see common ground between decision theory and Fisher's foundation in 1922. You might be closer if you think in terms of clinical trials. We really enjoyed the joint meeting. That is why the present volume is divided in two parts:

Part I: Risk Analysis Development
Part II: Experimental Design Theory

Since the time that Quincy Wright (1890–1970) in his excellent book "A study of War" offered a development of simple indexes evaluating risk, for such an important issue as the war, has passed some time. New indexes, new strategies, and new statistical insight have been developed and SPRINGER volumes try to reflect this improvement and excellent evolution; we try to follow and guide with ICRA conferences.

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Contents

Risk Analysis

Asset and Liability Risk Management in Financial Markets

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Abstract. Most financial organisations depend on their ability to match the assets and liabilities they hold. This managerial challenge has been traditionally modelled as a series of optimisation problems, which have been mostly solved by using exact methods such as mathematical and stochastic programming. The chapter reviews the main works in this area, with a special focus on three different problems: duration immunisation, multi-stage stochastic programming, and dynamic stochastic control. Hence, the main results obtained so far are analysed, and the open challenges and limitations of the current methods are identified. To deal with these open challenges, we propose the incorporation of new heuristic-based algorithms and simulation-optimisation methods.

1 Introduction

All financial companies need to manage the risk associated with their liabilities. This is achieved by properly selecting a convenient set of assets from the market, which are then assigned to cover liabilities, thus reducing the risk of bankruptcy. However, both assets and liabilities are exposed to an innumerable amount of external factors, which need to be factored in order to maintain and update the allocation map between assets and liabilities. The asset and liability management (ALM) challenge refers to the set of methods and techniques used to identify those assets that offer an optimal match with a set of given liabilities. ALM can be seen as an optimisation problem: the financial institution has to establish a particular strategy, which gives rise to an objective function subject to a set of constraints. The optimisation problem typically maximises the company's value function, it minimises the price of the selected assets, it maximises the expiration value or terminal wealth, or combines several aforementioned objectives.

The management of assets and liabilities is of paramount importance for financial institutions, such as banks, insurance companies, and pension funds. Although all of them are part of the financial system, they differ in terms of

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the nature of their liabilities. Accordingly, the strategy of selecting the adequate assets to match their liabilities also varies across different financial institutions. Among the different types of institutions, banks take deposits as their main liability. These deposits vary over time. Insurance companies also have time-varying liabilities, which are derived from insurance policies they underwrite. A portfolio of an insurance company tends to be large in order to benefit from the law of large numbers. Pension funds project their liabilities into the future, when the individual is expected to retire. Due to the time consideration, the role of an interest rate becomes relevant in the ALM process. It is also essential to model the stochastic behaviour of the random variables in the optimisation problem, i.e.: liabilities, assets, interest rates, and/or inflation. Due to the stochastic and dynamic nature of assets and liabilities, it is reasonable to assume that the initial asset selection might need to be updated throughout time, as new information becomes available, so the match between assets and liabilities is re-optimised taking into account the new data. Thus, the financial institution's assets are re-balanced in each period by selling and buying asset shares in order to benefit from portfolio returns. These considerations lead us to three main techniques in ALM. Firstly, the duration theory, which aims to define an immunisation strategy so that the value associated with the portfolio of assets matches, at any time, the value of the liabilities. Hence, a change in the interest rate will not affect the balance. Secondly, one can consider a single-period version of the problem or a multi-period one, in which the optimal asset selection is determined at each stage. Also, the problem can be deterministic – by simplifying some characteristics – or stochastic in nature. In the latter case, we have to provide a stochastic process for each asset, which might include random variables in the objective function and even probabilistic constraints. Thirdly, if time is regarded as continuous, the problem becomes a stochastic control optimisation one, which gives rise to a system of differential equations. As shown in Fig. 1, the interest of the scientific community in asset and liability management (ALM) has been increasing during the last decades.

The contribution of this chapter is threefold. Firstly, it reviews the main works in this area, with a special focus on three different problems: duration immunisation, multi-stage stochastic programming, and dynamic stochastic control. Secondly, the main results obtained so far are analysed, and the open challenges and limitations of the current methods are identified. Thirdly, the incorporation of new heuristic-based algorithms and simulation-optimisation methods is proposed in order to deal with these open challenges. The rest of the chapter is structured as follows: Sect. 2 provides a review of existing work on duration immunisation. Section 3 analyses applications of stochastic programming to ALM. Section 4 completes a review on stochastic control applied to ALM. Section 5 discusses the need for considering new simulation-optimisation approaches in dealing with these problems. Finally, Sect. 6 highlights the main conclusions of this work and propose some open research lines.

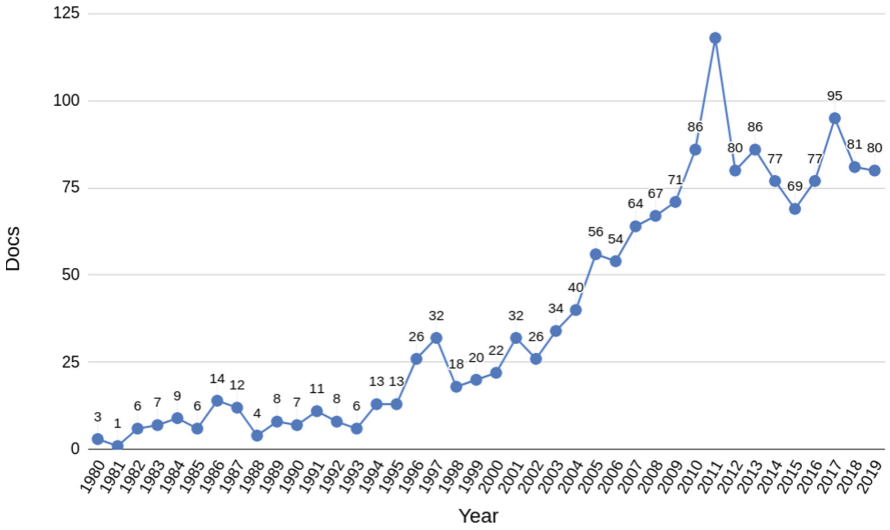

Fig. 1. Evolution of Scopus-indexed documents related to ALM.

2 Duration Immunisation

Under the assumption of deterministic cash flows on both sides, assets and liabilities, and constant interest rates, Macaulay [51] sought to devise a strategy for matching values of assets and liabilities. The present value (PV) of a fixed cash flow (CF), recorded at times $t \in \{0, 1, \ldots, T\}$, and with a constant interest rate i, is commonly defined as:

$$PV = \sum_{t=0}^{T} \frac{CF_t}{(1+i)^t}. \tag{1}$$

If the goal is to provide immunisation against variations in the interest rate, we need to compute the derivative of the present value with respect to the interest rate i:

$$\frac{1}{PV}\frac{dPV}{di} = -\frac{D}{1+i}, \tag{2}$$

where D is called the Macaulay Duration and is described as:

$$D = \frac{\sum_{t=0}^{T} t \cdot CF_t (1+i)^{-t}}{PV}. \tag{3}$$

The immunisation in this approach consists in selecting a set of assets that satisfy two conditions: *(i)* the present value of the assets matches the one of the liabilities; and *(ii)* the time duration of assets also matches the one of liabilities. Under these conditions, it is possible to conceive that 'slight' changes in the interest rate will not have a noticeable effect on the values of assets and liabilities.

If more pronounced changes in the interest rate are expected, then it might be necessary to add a third condition, the so-called convexity requirement, which corresponds to the second derivative of the price with regard to a change in the interest rate change in a Taylor's series. This approach is clearly focused on potential changes in the interest rate, and constitutes the first ALM strategy analysed in the scientific literature.

The first works about immunisation where formalised by Fisher and Weil [28], who defined the conditions under which the value of an investment in a bond portfolio is protected against changes in the level of interest rates. The hypotheses of this work are: i)the portfolio is valued at a fixed horizon date, and ii) the interest rate changes only by a parallel shift in the forward rates. Fong and Vasicek [30] consider a fixed income portfolio whose duration is equal to the length of a given investment horizon. They prove that, given a change in the term structure of interest rates, there is a lower limit to the value of the portfolio. This lower limit depends on two factors: the interest rate change and the structure of the portfolio. Consequently, they postulate that it is possible to optimise the exposure of the portfolio under interest rate changes. Bierwag et al. [5] study the properties of cash flow dispersion in duration hedged portfolios. They show that minimising this dispersion is not independent of stochastic processes, and that the optimisation of the immunisation by minimising cash-flow dispersion is only valid under specific convexity conditions. Zenios [69] highlights a frequent presence of a mismatch between assets and liabilities in the financial industry, and shows a complex case of portfolios containing mortgage-backed securities under the term structure volatility. Among others, techniques based on duration are explored by this author. Seshadri et al. [61] embed a quadratic optimiser in a simulation model, which is used to generate patterns of dividends and market values, thus computing the duration of capital. This method is used to refine the ALM strategy, and is applied to the Federal Home Loan Bank of New York. Gajek [31] introduces the requirement of 'solvency' for a defined benefit pension plan, i.e., under a scenario with a relatively low interest rate, the assets are chosen to be the smallest concave majorant of the accumulated liability cash flow. Ahlgrim et al. [1] study the risk for property-liability insurers of movements in interest rates. Their paper considers that liability cash flows, affected by future claim payouts, change with interest rate shifts due to the correlation between inflation and the interest rate. This study concludes that the effective duration is lower than the one measured by traditional methods. Benkato et al. [3] analyse the case of eight banks in Kuwait, showing that this sample of banks adjusted their portfolio of assets and liabilities by matching their respective Macaulay's duration.

3 Multi-stage Stochastic Programming

The allocation of assets in an ALM context is carried out at specific times. When the manager performs a transaction, she has to cope with transaction costs, asset values that are dependent on the moment, and liquidity constraints, among other

variables. The main goal is to meet the liabilities, but other objectives can be selected simultaneously, e.g.: maximising the terminal wealth of the company, minimising the risk in terms of volatility, etc. As financial markets run in scenarios under uncertainty, the problem can be regarded as a multi-stage stochastic program [47]. Numerous approaches have been studied in the literature, but all of them share a common structure. On the side of the constraints, two basic sets of equations are defined: the cash-flow accounting and the inventory balance equations at each time point. At this point, the volume of each asset class and its values are recorded, together with information on the number of assets that are purchased and sold. On the objective function side, the common goal is to maximise expected utility subject to terminal wealth. In order to solve the optimisation problem, a scenario tree has to be defined. This represents a lattice of possibilities for each asset, liability, and other elements in the program, including interest rate, inflation, among others. Each node is associated with a probability, and the whole lattice needs to be considered to calculate the expected values. In this regard, Boender et al. [6] study the role played by these scenarios in ALM. Following Mulvey et al. [54], we can synthesise the multi-stage stochastic program as follows:

$$Max \sum_{s=1}^{S} \pi_s U(w_\tau^s) \tag{4}$$

subject to:

$$\sum_i x_{i,0}^s = w_0, \tag{5}$$

$$\sum_i x_{i,\tau}^s = w_\tau, \tag{6}$$

$$x_{j,t}^s = (1 + \rho_{j,t-1}^s) x_{j,t-1}^s + p_{j,t}^s - d_{j,t}^s, \tag{7}$$

$$x_{0,t}^s = (1 + \rho_{0,t-1}^s) x_{0,t-1}^s + \Sigma_j d_{j,t}^s - \Sigma_j p_{j,t}^s - b_{t-1}^s (1 + \beta_{t-1}^s) + b_t^s, \tag{8}$$

where s represents one possible scenario, π_s is the probability of scenario s, w^s is the terminal wealth in scenario s, A is the number of assets, $i \in \{0, 1, \ldots, A\}$, $j \in \{1, 2, \ldots, A\}$, x_j is the amount of money invested in asset i, x_0 is the vault cash, $p_{j,t}^s$ is the purchase of asset j in time t in scenario s, $d_{j,t}^s$ is the amount of asset j sold in time t in scenario s, $\rho_{j,t}^s$ is the yield of asset j in time t in scenario s, $\rho_{0,t}^s$ is the riskless interest rate, b_t^s is the amount of money borrowed in time t in scenario s, and β_t^s is the borrowing rate in time t in scenario s. Finally:

$$x_{0,t}^s \geq l_t, \tag{9}$$

where l_t is the liability cash flow at time t.

Numerous works have been searching for a better and more realistic description of the financial system. Hence, Kusy and Ziemba [48] study a model with legal, financial, and bank-related policy considerations. They apply the model to a 5-year period for a Canadian bank. Giokas and Vassiloglou [32] discuss a multi-objective programming model for the Commercial Bank of Greece, taking

into account institutional characteristics, financial, legal, and bank-related policy considerations. Oğuzsoy and Güven [56] present a multi-period stochastic linear model for ALM in banking, assuming a set of deterministic rates of return on investment and cost of borrowing. They also consider a set of random deposit levels, liquidity, and total reserve requirements. Mulvey et al. [53,54] show how the Towers Perrin company plans assets and liabilities to deal with pension-related payments. The model performs an economic projection, spanning a long-term horizon (10 to 40 years), and finding strategies via a dynamic assets and liabilities allocation over a range of different scenarios. Nielsen and Zenios [55] study how to apply a multi-period stochastic program to the problem of funding single-premium deferred annuities, for which they consider government bonds, mortgage-backed securities, and derivative products. Klaassen [44] shows that, in general, scenarios do not consider the variation over time of some asset prices. Therefore, the solution found by stochastic programming cannot be considered as optimal in a real-world application. The paper remarks the crucial importance of respecting the free of arbitrage hypothesis while defining scenarios. Consiglio et al. [18] develop a pension fund problem, in which uncertainty affects both assets and liabilities in the form of scenario-dependent payments or borrowing costs. Cariño et al. [9–11] describe the Russell-Yasuda Kasai model. This model, created by the Russell company and the Yasuda Fire and Marine Insurance Co., determines an optimal strategy in a multi-period scenario, and it adds the characteristics of the complex Japanese regulation, such as legal or taxes limitations. In their first publication, [9] compare the multistage programming model with the classical mean-variance model, resulting in an extra income of 42 basis points. Kouwenberg [46] develops a scenario-generation method and applies it to a multi-stage stochastic program for a Dutch pension fund, where the objective function consists of minimising the average of contribution rates, taking into account the degree of risk aversion. The scenario-tree model is compared to a fixed mix model as shown in Fig. 2.

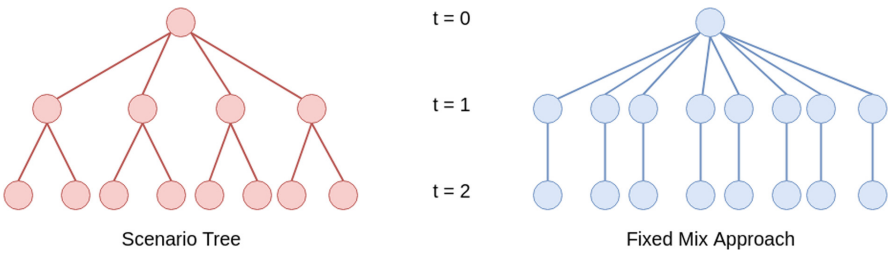

Fig. 2. Differences between scenario trees and fixed mix approaches. Source: [29]

As sophisticated scenarios are generated in combination with many trading dates, the number of variables in the mathematical programming model tends to explode. Gondzio and Kouwenberg [35] deal with the computational complexity of this problem, identifying a bottleneck in memory management. They

solve a stochastic problem with near 5 million scenarios, more than 12 million constraints, and 25 million variables. Gondzio and Grothey [34] also solve non-linear programming models using an interior point solver and a massive parallelisation environment. Bogentoft et al. [7] study the effects of the conditional value at risk (CVaR) as a risk measure, the weighted average of the value at risk (VaR), and the losses exceeding the VaR. They also select similar paths in the scenario creation, simplifying the problem to representative samples. With this technique, they are able to solve problems with a very large number of elements and scenarios. Høyland and Wallace [40] show that regulation in Norway is not beneficial for the insurance industry, according to the results of a simple stochastic problem that integrate legal issues. Fleten et al. [29] compare a fixed mix model with a multi-stage stochastic program (dynamic model). The fixed mix model keeps constant the proportion among the assets, while the dynamic model changes the proportion in each stage. The conclusion is that the dynamic model dominates the fixed mix approach. Dash and Kajiji [22] implement a non-linear model based on the Markowitz's mean-variance approach [52] for the optimisation of property-liability insurers. Hibiki [38] compares the results of two different approaches, which model the evolution of assets both using a scenario tree and a hybrid tree (simulation paths). Zhang and Zhang [70] improve Hibiki's model by introducing the CVaR as a risk measure, and market imperfections. A genetic algorithm is used to solve the new model. Consiglio et al. [19,20] study the optimisation problem derived from a liability that includes complex conditions, such as guarantees, surrender options, and bonus provisions. This leads to a non-linear optimisation problem. Papi and Sbaraglia [60] solve a problem with two assets, where one of the assets is risky, and the other risk-free. They use a recourse algorithm. Ferstl and Weissensteine [27] analyse a multi-stage stochastic program, where the asset return follows an auto-regressive process. The goal is to minimise the CVaR. In general, the models do not place limits on the number of assets, which might be a quite unrealistic assumption in practice. Nevertheless, Escudero et al. [26] propose an approach based on discrete variables, limiting the number of transactions or the number of assets in each time. The model is solved with a recourse algorithm. Berkelaar and Kouwenberg [4] introduce a singular objective function, which consists of a liability-relative draw-down optimisation approach. Both assets and liabilities are modelled as auto-regressive processes. Gülpinar et al. [36,37] treat the problem under the robust optimisation perspective, deriving in a feasible computational tractability. These approaches deal with uncertainty in both assets and interest rates, and are focused on investment products with guarantees, such as guaranteed investment contracts and equity-linked notes. Zhou et al. [71] construct a program based on the classical mean-variance efficient frontier. Their approach considers quadratic transaction costs. They propose tractability models with and without the risk-less asset, and derive the pre-commitment and time-consistent investment strategies through the application of an embedding scheme and a backward induction approach.

4 Dynamic Stochastic Control

The random behaviour of assets and other market elements, such as interest rate or inflation, are frequently modelled as a geometric Brownian process in a continuous time context. ALM is not an exception. Thus, it is possible to consider a stochastic objective function that also incorporates dynamic equations regulating changes in market elements. Following Chiu and Li [13], we consider $n+1$ assets, where asset 0 is considered to be risk-less while the other n assets follow a random walk. The dynamic equation for the price P_0 of a risk-less asset can be written as:

$$dP_0 = P_0\alpha_0(t)dt, \tag{10}$$

where $P_0(0) > 0$ and $\alpha_0(t)$ is the free risk interest rate.

Since the asset is deemed risk-less, no random component is needed in the dynamic equation. By contrast, for the price P_i of a risky asset i, the following equations are used:

$$dP_i = P_i(\alpha_i(t)dt + \sum_{j=1}^{n} \sigma_{ij}(t)dW_j(t)), \tag{11}$$

where $i \in \{1, 2, \ldots, n\}$, $P_0(0) > 0$, and $W_1(t), \ldots, W_n(t)$ are independent Wiener processes. Also, $\alpha_i(t)$ represents the interest rate for asset i, while σ_{ij} is the covariance matrix of assets. A typical mean-variance optimisation problem, maximising the terminal wealth, is shown below:

$$Max_{u(t)}E[S(T)] \tag{12}$$

subject to

$$Var[S(T)] < \sigma, \tag{13}$$

where $u(t) = (u_0, u_1, \ldots, u_n)(t)$ is the amount of money invested in each asset, $S(T) = \sum_{i=0}^{n} P_i(T) - L(T)$ is the terminal wealth, $L(T)$ is the terminal value of the liabilities, and σ is the user-defined threshold for the tolerated risk. Of course, it is also possible to consider other objectives based on a specific utility function.

Several authors have proposed different approaches relative to this basic model. Thus, for example, Chiu and Li [13] assume uncertain liabilities, which follow a Wiener process that is correlated with the assets. Devolder et al. [24] solve a defined contribution pension problem where the benefits are paid as annuities. To find an analytical solution, they consider one risky asset and one risk-less asset. The paper shows how the strategy changes immediately before and immediately after the beginning of an annuity, and depending on the utility functions as objective functions. Briys and De Varenne [8] study a profit-sharing policy in an insurance company. With this policy, the policyholder has the right to receive a guaranteed interest rate and a percentage of the company's revenues. The results are used to evaluate different aspects of regulatory measures that are frequently encountered in life-insurance business, such as rate ceilings, capital ratios, and asset restrictions. Barbarin and Devolder [2] develop a model, in

which assets are a mix of stocks, bonds, and cash, while liabilities are the result of a guaranteed technical rate to the premium, plus a participation rate in the case of a surplus. The paper integrates a risk-neutral approach with a ruin probability. VaR and CVaR conditions are tested by including an investment guarantee. Koivu et al. [45] explore the effects of Finnish regulation within a stochastic model for a pension insurance company. Seven economic factors, pertaining to Finland and the EU, are described as a vector equilibrium correction model. This vector is then used to determine the behaviour of assets and liabilities. Xie et al. [67] formulate a mean-variance portfolio selection model where assets follow a geometric Brownian motion, while liabilities follow a Brownian motion with a drift. The model also features correlations among assets and liabilities. They derive explicitly the optimal dynamic strategy and the mean-variance efficient frontier by using a general stochastic linear-quadratic control technique. Related to this, Xie [66] assumes that risk stock prices are governed by a Markov regime-switching geometric Brownian motion. Detemple and Rindisbache [23] explore a dynamic asset allocation problem with liabilities, where preferences are assumed to be von Neumann Morgenstern [64], where a running utility function is defined over dividends (withdrawals in excess of net benefit payments), and a terminal utility function defined over liquid wealth in excess of a floor. Chiu and Li [14] study how to minimise an upper bound of the ruin probability, which measures the likelihood of the final surplus being less than a given target level. They identify this criterion as the safety-first ALM problem. Not only does the paper study this problem in continuous time, but it also solves the problem in a discrete time context and compares results from the two approaches. The model drives to a mathematical definition regarding the type of investors ('greedy' or not), which is based on the level of disaster. An approach for pension funds can be found in Josa-Fombellida and Ricón-Zapatero [41], who consider a stochastic interest rate, where the investor faces the choice among a risky stock, a bond and cash. Zeng and Li [68] analyse a simple but realistic model, which features one risky asset, one risk-free asset, and one liability. The risky asset follows an exponential Levy Process, which allows simulating potential discontinuities in its random walk. The model comprises two objective functions (i.e., it considers two different optimisation problems). The first function is based on a 'benchmark' model: a predefined target value b is considered, and the mean of the quadratic distance between b and the terminal wealth is minimised. The second function is based on the classical mean-variance portfolio selection model. The optimisation problem in Chiu and Wong [15] consists of minimising the variance of terminal wealth in a context of co-integrated assets. Specifically, in this paper, the insurer deals with the payment of uncertain insurance claims, which are assumed to follow a compound Poisson process. In general, there is a lack in the literature regarding the study of time-consistency optimisation of asset allocations in an ALM context – i.e., most studies consider time-dependent investment strategies. This gap is bridged by Wei et al. [65] considering a Markov regime-switching model. These authors conclude that the time-consistency equilibrium control in this context is state dependent, where that dependency is generated

by the uncontrollable liability process. Chiu and Wong [16] study the problem under a market with correlations among risky assets, where these correlations change randomly over time. In this problem, the objective is to minimise the variance of terminal wealth, given an expected terminal wealth. The liabilities are assumed to follow a compound Poisson process, and the problem becomes a linear-quadratic stochastic optimal control problem with volatility, correlations, and discontinuities – all of them with random behaviour. In a context of low interest rates, the stochastic behaviour becomes relevant. Chiu and Wong [17] also solve a model with liabilities that follow a compound Poisson process, with a stochastic interest rate distributed according to a Cox-Ingersoll-Ross model [21]. The model consists of maximising the expected constant relative risk averse (CRRA) utility function. Along similar lines, Chang [12] formulates a model where the interest rate is driven by the Vasicek model [63], and liabilities follow a Brownian motion with drift. Likewise, Liang and Ma [50] approach a pension fund with mortality risk and salary risk, with a CRRA utility function. Pan and Xiao [57] solve a problem with liquidity constraints and stochastic interest rates, which follow a Hull-White process [39]. This paper compares the two utility functions that feature CRRA, and constant absolute risk averse, CARA. In another work [58], these authors also include inflation risk under a mean-variance framework. They also consider a non-common variety of assets, such as a default-free zero coupon bond, an inflation indexed bond, as well as the typical risky assets and risk-free asset. Also, they assume that liability follows a geometric Brownian motion process. Finally, to complete this survey, Li et al. [49] solve a classical mean-variance model with stochastic volatility, which introduces a novel asset; a derivative whose price depends on the underlying price of the risky stock.

5 Need for Metaheuristics and Simheuristics

The growing complexity of the problems being addressed highlights the need for faster approaches such as metaheurisics [33]. These algorithms will be needed as the models introduce further constraints to account for real-life circumstances. In this regard, Soler-Dominguez et al. [62] and Doering et al. [25] provide quite complete and up-to-date reviews on financial applications of metaheuristics, including risk management and portfolio optimisation problems. In this sense, Kizys et al. [43] have proposed a heuristic approach to solve a *NP-hard* variant of the portfolio optimisation problem. Furthermore, the fact that two or more objectives have to be considered simultaneously to account for the complexity will require multi-objective optimisation methods.

Different simulation-optimisation methods are gaining popularity in the application to stochastic combinatorial optimisation problems in different application areas [42]. Despite the success of simheuristics in solving stochastic optimisation problems in different areas, just a few works have focused on the area of finance. Thus, for example, Panadero et al. [59] propose a simheuristic for solving a multi-period project selection problem. Even though financial data is characterised by macro- as well as firm-level uncertainty, to the best of our

knowledge, none of the finance-related problems analysed in this work has been addressed with the use of simheuristics so far, which makes this an interesting avenue for future research.

6 Conclusions and Future Work

The optimal asset allocation subject to liabilities is a financial problem widely studied in the literature. Broadly speaking, the wealth of strategies can be divided into two categories. The first category is based on immunising the value of the selected assets under changes in the interest rate, which is an accountable approach. The second category is based on cash-flow matching, which is an operational approach. The immunisation approach is based on the concept of duration. The potential of application is very limited because: *(i)* it is a short time approach, and *(ii)* it only works when the interest rate is constant and its shift is small. In addition, the cash-flow matching can bifurcate into continuous time models and discrete time models. The continuous time models show a limitation in the sense that they need to be restrictive analytical models in order to use stochastic differential equations. Hence, it is a method more oriented to knowing the 'good' strategy in qualitative terms, than in obtaining optimal assignment configurations. Finally, the most realistic approach is the multi-stage stochastic program, since it permits to easily model characteristics of the real market. Nevertheless, these models can grow very fast in the number of equations and variables, which eventually make them extremely difficult to solve in short computing times.

Due to the limitations found by exact methods in solving large-scale and stochastic versions of the analysed problems, some research opportunities arise, including: *(i)* the use of heuristic-based algorithms that can provide reasonably good results to complex and large-scale financial problems in short computing times; *(ii)* the introduction of novel simulation-optimisation approaches – other than stochastic programming – that can cope, in a more natural way, with the uncertainty existing in the problems considered in this work; *(iii)* the introduction of the aforementioned methodologies will also allow us to consider richer and more realistic versions of the multi-stage stochastic programming problem; and *(iv)* lastly, we also see a clear opportunity to generalise the use of these optimisation methodologies to support decision making at the level of the individual consumer.

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References

1. Ahlgrim, K.C., D'Arcy, S.P., Gorvett, R.W.: The effective duration and convexity of liabilities for property-liability insurers under stochastic interest rates. Geneva Pap. Risk Insur. Theor. **29**(1), 75–108 (2004)

2. Barbarin, J., Devolder, P.: Risk measure and fair valuation of an investment guarantee in life insurance. Insur. Math. Econ. **37**(2), 297–323 (2005)
3. Benkato, O., Haddad, M., Al-Loughani, N., Baur, M.: Coping with the risk of interest rate fluctuations: the case of Kuwait banks. J. Bus. Econ. Res. (JBER) **1** (2011)
4. Berkelaar, A., Kouwenberg, R.: A liability-relative drawdown approach to pension asset liability management. J. Asset Manag. **11**(2–3), 194–217 (2010)
5. Bierwag, G.O., Fooladi, I., Roberts, G.S.: Designing an immunized portfolio: is m-squared the key? J. Bank. Finan. **17**(6), 1147–1170 (1993)
6. Boender, G., Dert, C., Heemskerk, F., Hoek, H.: A scenario approach of ALM. In: Handbook of Asset and Liability Management, pp. 829–860. Elsevier (2008)
7. Bogentoft, E., Romeijn, H.E., Uryasev, S.: Asset/liability management for pension funds using CVaR constraints. J. Risk Finan. **3**(1), 57–71 (2001)
8. Briys, E., De Varenne, F.: Life insurance in a contingent claim framework: pricing and regulatory implications. GENEVA Pap. Risk Insur. Theory **19**(1), 53–72 (1994)
9. Cariño, D.R., et al.: The Russell-Yasuda Kasai model: an asset/liability model for a Japanese insurance company using multistage stochastic programming. Interfaces **24**(1), 29–49 (1994)
10. Cariño, D.R., Myers, D.H., Ziemba, W.T.: Concepts, technical issues, and uses of the Russell-Yasuda Kasai financial planning model. Oper. Res. **46**(4), 450–462 (1998)
11. Cariño, D.R., Ziemba, W.T.: Formulation of the Russell-Yasuda Kasai financial planning model. Oper. Res. **46**(4), 433–449 (1998)
12. Chang, H.: Dynamic mean-variance portfolio selection with liability and stochastic interest rate. Econ. Model. **51**, 172–182 (2015)
13. Chiu, M.C., Li, D.: Asset and liability management under a continuous-time mean-variance optimization framework. Insur. Math. Econ. **39**(3), 330–355 (2006)
14. Chiu, M.C., Li, D.: Asset-liability management under the safety-first principle. J. Optim. Theory Appl. **143**(3), 455–478 (2009)
15. Chiu, M.C., Wong, H.Y.: Mean-variance asset-liability management: cointegrated assets and insurance liability. Eur. J. Oper. Res. **223**(3), 785–793 (2012)
16. Chiu, M.C., Wong, H.Y.: Mean-variance asset-liability management with asset correlation risk and insurance liabilities. Insur. Math. Econ. **59**, 300–310 (2014)
17. Chiu, M.C., Wong, H.Y.: Optimal investment for insurers with the extended CIR interest rate model. Abstract Appl. Anal. **2014** (2014)
18. Consigli, G., Dempster, M.A.H.: Dynamic stochastic programming for asset-liability management. Ann. Oper. Res. **81**, 131–161 (1998)
19. Consiglio, A., Cocco, F., Zenios, S.A.: Asset and liability modelling for participating policies with guarantees. Eur. J. Oper. Res. **186**(1), 380–404 (2008)
20. Consiglio, A., Saunders, D., Zenios, S.A.: Asset and liability management for insurance products with minimum guarantees: the UK case. J. Bank. Finance **30**(2), 645–667 (2006)
21. Cox, J.C., Ingersoll Jr., J.E., Ross, S.A.: A theory of the term structure of interest rates. Econometrica J. Econ. Soc., 385–407 (1985)
22. Dash, G., Kajiji, N.: A nonlinear goal programming model for efficient asset-liability management of property-liability insurers. INFOR Inf. Syst. Oper. Res. **43**(2), 135–156 (2005)
23. Detemple, J., Rindisbacher, M.: Dynamic asset liability management with tolerance for limited shortfalls. Insur. Math. Econ. **43**(3), 281–294 (2008)

24. Devolder, P., Bosch Princep, M., Dominguez Fabian, I.: Stochastic optimal control of annuity contracts. Insur. Math. Econ. **33**(2), 227–238 (2003)
25. Doering, J., Kizys, R., Juan, A.A., Fitó, À., Polat, O.: Metaheuristics for rich portfolio optimisation and risk management: current state and future trends. Oper. Res. Perspect., 100121 (2019)
26. Escudero, L.F., Garín, A., Merino, M., Pérez, G.: On multistage stochastic integer programming for incorporating logical constraints in asset and liability management under uncertainty. CMS **6**(3), 307–327 (2009)
27. Ferstl, R., Weissensteiner, A.: Asset-liability management under time-varying investment opportunities. J. Bank. Finance **35**(1), 182–192 (2011)
28. Fisher, L., Weil, R.L.: Coping with the risk of interest-rate fluctuations: returns to bondholders from Naïve and optimal strategies. J. Bus. **44**(4), 408–431 (1971)
29. Fleten, S., Høyland, K., Wallace, S.W.: The performance of stochastic dynamic and fixed mix portfolio models. Eur. J. Oper. Res. **140**(1), 37–49 (2002)
30. Fong, H.G., Vasicek, O.A.: A risk minimizing strategy for portfolio immunization. J. Financ. **39**(5), 1541–1546 (1984)
31. Gajek, L.: Axiom of solvency and portfolio immunization under random interest rates. Insur. Math. Econ. **36**(3), 317–328 (2005)
32. Giokas, D., Vassiloglou, M.: A goal programming model for bank assets and liabilities management. Eur. J. Oper. Res. **50**(1), 48–60 (1991)
33. Glover, F.W., Kochenberger, G.A.: Handbook of Metaheuristics, vol. 57. Springer, New York (2006). https://doi.org/10.1007/978-1-4419-1665-5
34. Gondzio, J., Grothey, A.: Solving nonlinear financial planning problems with 10^9 decision variables on massively parallel architectures. WIT Trans. Model. Simul. **43** (2006)
35. Gondzio, J., Kouwenberg, R.: High-performance computing for asset-liability management. Oper. Res. **49**(6), 879–891 (2001)
36. Gülpinar, N., Pachamanova, D.: A robust optimization approach to asset-liability management under time-varying investment opportunities. J. Bank. Finance **37**(6), 2031–2041 (2013)
37. Gülpınar, N., Pachamanova, D., Çanakoğlu, E.: A robust asset-liability management framework for investment products with guarantees. OR Spectrum **38**(4), 1007–1041 (2016)
38. Hibiki, N.: Multi-period stochastic optimization models for dynamic asset allocation. J. Bank. Finance **30**(2), 365–390 (2006)
39. Hull, J., White, A.: Pricing interest-rate-derivative securities. Rev. Finan. Stud. **3**(4), 573–592 (1990)
40. Høyland, K., Wallace, S.W.: Analyzing legal regulations in the Norwegian life insurance business using a multistage asset-liability management model. Eur. J. Oper. Res. **134**(2), 293–308 (2001)
41. Josa-Fombellida, R., Rincón-Zapatero, J.P.: Optimal asset allocation for aggregated defined benefit pension funds with stochastic interest rates. Eur. J. Oper. Res. **201**(1), 211–221 (2010)
42. Juan, A.A., Kelton, W.D., Currie, C.S., Faulin, J.: Simheuristics applications: dealing with uncertainty in logistics, transportation, and other supply chain areas. In: Proceedings of the 2018 Winter Simulation Conference, pp. 3048–3059. IEEE Press (2018)
43. Kizys, R., Juan, A.A., Sawik, B., Calvet, L.: A biased-randomized iterated local search algorithm for rich portfolio optimization. Appl. Sci. **9**(17), 3509 (2019)
44. Klaassen, P.: Discretized reality and spurious profits in stochastic programming models for asset/liability management. Eur. J. Oper. Res. **101**(2), 374–392 (1997)

45. Koivu, M., Pennanen, T., Ranne, A.: Modeling assets and liabilities of a Finnish pension insurance company: a VEqC approach. Scand. Actuar. J. **2005**(1), 46–76 (2005)
46. Kouwenberg, R.: Scenario generation and stochastic programming models for asset liability management. Eur. J. Oper. Res. **134**(2), 279–292 (2001)
47. Kouwenberg, R., Zenios, S.A.: Stochastic programming models for asset liability management. In: Handbook of Asset and Liability Management, pp. 253–303. Elsevier (2008)
48. Kusy, M.I., Ziemba, W.T.: Bank asset and liability management model. Oper. Res. **34**(3), 356–376 (1986)
49. Li, D., Shen, Y., Zeng, Y.: Dynamic derivative-based investment strategy for mean-variance asset-liability management with stochastic volatility. Insur. Math. Econ. **78**, 72–86 (2018)
50. Liang, Z., Ma, M.: Optimal dynamic asset allocation of pension fund in mortality and salary risks framework. Insur. Math. Econ. **64**, 151–161 (2015)
51. Macaulay, F.R.: Some Theoretical Problems Suggested by the Movements of Interest Rates, Bond Yeilds and Stock Prices in the United States Since 1856. National Bureau of Economic Research, New York (1938)
52. Markowitz, H.: Portfolio selection. J. Finan. **7**(1), 77–91 (1952)
53. Mulvey, J.M., Gould, G., Morgan, C.: An asset and liability management system for towers Perrin-Tillinghast. Interfaces **30**(1), 96–114 (2000)
54. Mulvey, J.M., Rosenbaum, D.P., Shetty, B.: Strategic financial risk management and operations research. Eur. J. Oper. Res. **97**(1), 1–16 (1997)
55. Nielsen, S.S., Zenios, S.A.: A stochastic programming model for funding single premium deferred annuities. Math. Program. Ser. B **75**(2), 177–200 (1996)
56. Oğzsoy, C.B., Güven, S.: Bank asset and liability management under uncertainty. Eur. J. Oper. Res. **102**(3), 575–600 (1997)
57. Pan, J., Xiao, Q.: Optimal asset-liability management with liquidity constraints and stochastic interest rates in the expected utility framework. J. Comput. Appl. Math. **317**, 371–387 (2017)
58. Pan, J., Xiao, Q.: Optimal mean-variance asset-liability management with stochastic interest rates and inflation risks. Math. Methods Oper. Res. **85**(3), 491–519 (2017)
59. Panadero, J., Doering, J., Kizys, R., Juan, A.A., Fito, A.: A variable neighborhood search simheuristic for project portfolio selection under uncertainty. J. Heuristics, 1–23 (2018)
60. Papi, M., Sbaraglia, S.: Optimal asset-liability management with constraints: a dynamic programming approach. Appl. Math. Comput. **173**(1), 306–349 (2006)
61. Seshadri, S., Khanna, A., Harche, F., Wyle, R.: Method for strategic asset-liability management with an application to the federal home loan bank of New York. Oper. Res. **47**(3), 345–360 (1999)
62. Soler-Dominguez, A., Juan, A.A., Kizys, R.: A survey on financial applications of metaheuristics. ACM Comput. Surv. (CSUR) **50**(1), 15 (2017)
63. Vasicek, O.: An equilibrium characterization of the term structure. J. Financ. Econ. **5**(2), 177–188 (1977)
64. Von Neumann, J., Morgenstern, O., Kuhn, H.W.: Theory of Games and Economic Behavior (Commemorative Edition). Princeton University Press (2007)
65. Wei, J., Wong, K.C., Yam, S.C.P., Yung, S.P.: Markowitz's mean-variance asset-liability management with regime switching: a time-consistent approach. Insur. Math. Econ. **53**(1), 281–291 (2013)

66. Xie, S.: Continuous-time mean-variance portfolio selection with liability and regime switching. Insur. Mathe. Econ. **45**(1), 148–155 (2009)
67. Xie, S., Li, Z., Wang, S.: Continuous-time portfolio selection with liability: mean-variance model and stochastic LQ approach. Insur. Math. Econ. **42**(3), 943–953 (2008)
68. Zeng, Y., Li, Z.: Asset-liability management under benchmark and mean-variance criteria in a jump diffusion market. J. Syst. Sci. Complex. **24**(2), 317–327 (2011)
69. Zenios, S.A.: Asset/liability management under uncertainty for fixed-income securities. Ann. Oper. Res. **59**(1), 77–97 (1995)
70. Zhang, X., Zhang, K.: Using genetic algorithm to solve a new multi-period stochastic optimization model. J. Comput. Appl. Math. **231**(1), 114–123 (2009)
71. Zhou, Z., Zeng, X., Xiao, H., Ren, T., Liu, W.: Multiperiod portfolio optimization for asset-liability management with quadratic transaction costs. J. Ind. Manag. Optim. **15**(3), 1493–1515 (2019)

A Critical Discussion on Systemic Risk Measures

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Abstract. Risk Analysis is becoming a recurrent subject in research, attracting the attention of researchers in a consistent way. More recently and motivated by the last collapse of the financial system, systemic risk is getting special attention as well as becoming a tool widely applied for detect financial institutions systemic risk contributions. We start with Adrian and Brunnermeier [3] work, where they introduced first time the concept of $CoVaR$, and $\Delta CoVaR$ of a financial institution, as well as a methodology to estimate $\Delta CoVaR$ using financial market public data. This paper will then discuss the assumptions taken along that methodology, analyse the characteristics of each risk measured used, and discussed alternatives to measure the individual contribution of a single entity to the systemic risk of a financial system [5]. At the moment, there are not yet a consensus in accepting existing measures and methodologies as good enough to correctly identify the biggest contributors to systemic risk [8]. As conclusion, a modified methodology to estimate individual contributions for systemic risk using market data is presented.

Taking as starting point the methodology described by Adrian and Brunnermeier [20], where they introduced first time the concept of $CoVaR$, that stands to conditional Var, to estimate $\Delta CoVaR$ of a financial institution and based in financial market public data, this paper will discuss the assumptions taken along the referred methodology.

By analysing the characteristics of each risk measured used, such as Var, $CoVaR$ and $\Delta CoVaR$, this paper will discuss alternative approaches to measure the individual contribution of a single entity to the systemic risk of a financial system.

1 Introduction

While analysing financial systems, it was noticed that negative shocks suffered by an individual financial institution can easily spread and affect other entities in that system [1]. This way, measuring and analyzing systemic risk phenomena and consequences has been a topic of interest among policy makers. Since the last financial crisis, this analysis becomes even of more importance.

Systemic risk may not be assessed using only institution's individual risk measurements [2].

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As financial entities are typically highly connected to each other, this may cause also a high exposure to negative systemic events, even if at the individual level those institutions have low risk. The risk assumed by a systemic institution may cause negative spillovers not covered by risk requirements.

A very relevant question is, what are the sources of system vulnerabilities. In other words, which are the institutions systemically more important or contribute the most to the increase in system vulnerability.

The objective of this paper is to analyze assumptions made and compare possible options to identify institutions with the highest contribution to systemic risk. We follow the definition of $CoVaR$ introduced by Adrian and Brunnermeier [20], which is measured as the Value at Risk *(VaR)* of a financial institution conditional on the VaR of another institution. By defining the difference between these measures as $\Delta CoVaR$, we can estimate the contribution of each institution to systemic risk.

The remainder of this paper is structured as follows: Sect. 2 gives a theoretical background and introduces the most relevant concepts used. Section 3 describes the specification of the model to be implemented with details and steps to be performed. Section 4 describes the data set used and shows the main results. Finally, Sect. 5 includes the concluding remarks.

2 Theoretical Background and Main Concepts

2.1 *Var* - Value at Risk

Value at Risk or VaR is a central tool in risk, asset, and portfolio risk. And it also plays a key role in systemic risk. VaR is defined as the maximum loss an asset/portfolio/institution can incur at a defined significance level α (Fig. 1).

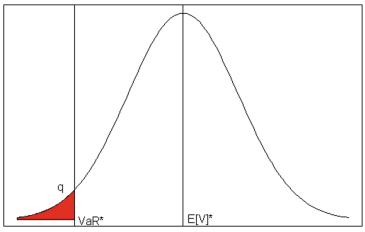

Fig. 1. Graphic representation of VaR

VaR is the maximum expected loss over a given period at a given level of confidence. Represents the value at potential risk of loss, regarding an asset/portfolio/institution, in a specific time period and specific significance level α. This probability represents a quantile for risk. With a random variable X and a distribution function F that model losses, verified for an asset in a time period. VaR_α is defined as:

$$VaR_\alpha = F^{-1}(1-\alpha) \tag{1}$$

A *VaR* of d days at $\alpha\%$ significance level means that on % of d days, we won't see a loss higher than the *VaR*, but for the $(1-\alpha)\%$ of times the loss will be higher.

For example, a 1 day *VaR* at the 99% confidence level of 5% means that on only 1 of every 100 days we will see a loss higher that 5% of the initial capital [15].

The concept of *VaR* becomes central to the study of systemic risk, constituting a fundamental concept for the definition of several of the most significant systemic risk measures mentioned in the literature. Yet this method faces challenges dealing with the risk associated with events involving volatility component with dependencies between extremes values in distinct data sets and modeling extreme values with volatility.

VaR can be calculated in numerous ways and we will focus on the following ones:

- Historic *VaR*
- Parametric *VaR*
- Extreme Value Theory (EVT) *VaR*

2.2 *CoVaR*

CoVaR measures and estimate the impact on the *VaR* of the system concerned when a particular institution is in a financial stress situation, which is also measured by the individual *VaR* of that institution [6].

With *CoVaR* one intends to answer the following questions:

- What is the system-wide *VaR* when a particular institution is under financial stress?
- What is the impact on the system's *VaR* when an institution enters financial stress? Here we refer to another concept, $\Delta CoVaR$.

As mentioned earlier, *CoVaR* calculation is based on *VaR*, which in turn is determined for a specific q quantile. This way *CoVaR* will also be associated with this arbitrarily chosen q. *CoVaR* can also be interpreted as a conditioned value, so $CoVaR^{j|i}$ represents the *VaR* of institution j, conditioned by the occurrence of a certain event, $O(X_i)$ that affected institution i.

Considering a system with compound by N institutions and with i and j assuming values between 1 and N, *CoVaR* can also be interpreted as a conditional value, so $CoVaR^{j|i}$ represents the *VaR* of institution j, conditioned by the occurrence of a particular event, designated $O(X_i)$ that affected institution i at any given time t [19].

The $CoVaR_q^{j|i}$, is thus the value such that:

$$Pr(X_j \leq CoVaR^{j|O(X_i)}|O(X_i)) = q \tag{2}$$

where:

- X_j represents the institution j return
- q is the desired quantile
- $O(X_i)$ represent the occurrence of an event the impacts institution i return

In order to build a methodology for determining the systemic importance of each institution in the systemic risk of the system, we need to further specify the type of events we will focus on and have as relevant for conditioning *VaR*. As a conditioning event $O(X^i)$ is usually chosen because the institution i is in financial stress (not necessarily insolvent), so $X^i = VaR_q^i$ is defined.

From the setting above, $CoVaR$ comes:

$$Pr(X^j \leq CoVaR^{j|i}|X^i = VaR_q^i) = q \tag{3}$$

This way $CoVaR_q^{j|i}$ tell us, Var_q for institution j when institution j is in a loss situation in the quantile q, or VaR_q.

The correlation between both institutions will determine the magnitude of the impact.

On the other hand, if we consider institution j as the financial system as a whole (or a significant part of it), then $CoVaR_q^{j|i}$ represents the VaR_q of the financial system when institution i is under financial stress, defined as being in its VaR_q.

The value obtained for measuring $CoVaR$ becomes of greater interest if it is possible to compare this measurement with a reference value and to gauge the difference between the two. Thus, one technique used to measure systemic risk is to measure the difference when an institution moves from a normal situation to a stress situation. It is normal to assume that the institution's assets are at median levels, and in stress when those assets are at VaR_q.

The difference between both situations is defined as $\Delta CoVaR$.

2.3 $\Delta CoVaR$

$\Delta CoVaR$ is also a systemic risk measure [20]. This measure is based on the Value-at-Risk, *VaR* concept. The *VaR* concept refers to the expected maximum loss for a predefined *VaR* significance level (α). $CoVaR$ is the *VaR* risk *conditional* upon verification of a particular critical event (a crisis) defined by $C(r_{it})$. $CoVaR$ is defined by:

$$Pr(r_{jt} \leq CoVaR_r^{j|C(r_{it})}|C(r_{it})) = \alpha \tag{4}$$

where r_{it} and r_{jt} represents the return of institution i and institution j at time t respectively.

The $\Delta CoVaR$ concept is defined as the difference between the system-wide *Var* conditioned by the agent i being subject to a critical event and the system *VaR* calculated for the event that the critical event does not occurs.

There are several alternatives for defining the $C(r_{it})$ critical event. One possibility is to consider the loss to be equivalent to *VaR*:

$$\Delta CoVaR_{it}(\alpha) = CoVaR_t^{m|r_{it}=VaR_{it}(\alpha)} - CoVaR_t^{j|r_{it}=Median(r_{it})} \tag{5}$$

An alternative definition considers as critical event when losses exceed a previously defined amount *VaR* [12].

$$\Delta CoVaR_{it}(\alpha) \leq CoVaR_t^{j|r_{it}=VaR_{it}(\alpha)} - CoVaR_t^{j|r_{it}=Median(r_{it})} \tag{6}$$

Formally $\Delta CoVaR$ is defined as:

$$\Delta CoVaR_q^{j|i} = CoVaR_q^{j|X^i=VaR_q^i} - CoVaR_q^{j|X^i=Median^i} \tag{7}$$

Which represents the deviation from the threshold defined for the significant loss region for an institution j when institution i changes from a "normal" loss situation to a significant loss.

Assuming that j represents an entire financial system $\Delta CoVaR_q^{j|i}$ provides an estimate of the contribution of institution i to systemic risk, in this case in response to the question: how much system risk increases due to a stressful situation in the institution i.

While $CoVaR$ estimates can be used to infer the extent of systemic losses caused by stress in an institution, $\Delta CoVaR$ estimates can be used as a measure of the contribution to systemic risk.

2.4 Probability of Rare Events - Extreme Values Theory

One of the *Var* method limitations relies on the difficulty in the deal with estimates of the extreme values (in the tails) of the loss distribution. Traditional methods used to calculate the *VaR* are based on the entire distribution of the data, which shows difficulties estimating the distribution at the tails. Extreme Values Theory is a methodology that is useful to deal with events in the tail of a distribution.

One method is identify the extreme values (maximum or minimum) verified in each period (block), called *block maxima* method. Another method consists in to define a level that splits the sample into extreme values and "standard" values. The distribution associated to *block maxima*, designated as M_n, where n represents the block dimension is given by Fisher and Tippett [9,11].

Theorem 1 (Fisher–Tippett–Gnedenko). *Be X_n a sequence of random variables i.i.d. If exists constants $c_n > 0, d_n \in R$ and some non-degenerated distribution function F, such as:*

$$\lim_{n\to\infty} P\Big(\frac{M_n - d_n}{c_n} \leq x\Big) = F(x) \tag{8}$$

then limit function F belongs to one of the three extreme value distributions:

$$\textit{Fréchet:} \qquad \Phi_\alpha(x) = \begin{cases} 0, & x \leq 0 \\ e^{-x^{-\alpha}}, & x > 0 \end{cases} \tag{9}$$

$$\textit{Weibull:} \qquad \Psi_\alpha(x) = \begin{cases} e^{-(-x^{\alpha})}, & x \leq 0 \\ 1, & x > 0 \end{cases} \tag{10}$$

$$\textit{Gumbel:} \qquad \Lambda(x) = e^{-e^{-x}}, x \in R \tag{11}$$

These three functions can be written with a unique expression using μ and σ to represent location and scale parameters:

$$H(x|\mu,\sigma,\xi) = \begin{cases} e^{-(1+\frac{\xi(x-\mu)}{\sigma})^{-1/\xi}} if \xi \neq 0 \\ e^{-e^{-x}} if \xi = 0 \end{cases} \tag{12}$$

where μ is the location parameter, σ is scale parameter and XI is the shape parameter. This distribution is called the Generalized Extreme Value (*GEV*) distribution [18].

An alternative to model extreme values is the POT (*peak over threshold*) distribution, an excess distribution function, where the distribution of observed values above a certain value, is considered.

Considering a F distribution function of a random variable X, the function F_u represents the distribution function of x values above the u limit. F_u, is the conditional excess distribution function, formalized by:

$$F_u(y) = P(X - u \leq y | X > u), 0 \leq y \leq x_F - u \tag{13}$$

where u is a previously defined limit value, y represents the excess, and $x_F \leq \infty$ is the limit of F on right tail. Extreme value theory allows to apply Pickants theorem to estimate F_u [17]:

Theorem 2 (Pickands).
For a large class of underlying distribution functions F the conditional excess distribution function $F_u(y)$, for u large, is well approximated by $G_{\varepsilon,\sigma}(y)$ (also called *Generalized Pareto Distribution* - GPD)*:*

$$F_u(y) \approx G_{\xi,\sigma}(y), u \to \infty \tag{14}$$

where

$$G_{\xi,\sigma}(y) = \begin{cases} 1 - \left(1 + \frac{\xi}{\sigma} y\right)^{-\frac{1}{\xi}}, & \xi \neq 0 \\ 1 - e^{y/\sigma}, & \xi = 0 \end{cases} \tag{15}$$

for $y \in [0, (x_F - u)]$ if $\xi \geq 0$ and $y \in [0, -\frac{\sigma}{\xi}]$, if $\xi \leq 0$.

2.5 Quantile Regression

$CoVaR$ and $\Delta CoVaR$ estimation can be achieved by applying quantile regression.

Quantile regression is a suitable estimation method for studying the behavior of "non-average" individuals. Quantile regression estimates several lines for different associated quantiles, instead of just checking the impact of X on the average Y, as is done in linear regression by Ordinary Least Squares (OLS).

While a model specified with OLS has the form $Y = X\beta + e$, hence the condition $\mathbf{E}[e] = 0$ implies that $\mathbf{E}[Y|X] = X\beta$, a quantile regression model will verify the effect that the X predictors will have on the Y quantiles, such that the i^{th} quantile of the Y variable is defined as:

$$Q_q(Y) = inf\{y|F_Y(y) \geq q \tag{16}$$

where $F_Y(y) = P(Y \leq y)$ is the cumulative distribution function of Y. Intuitively, the q^{th} quantile of Y is the $Q_q(Y)$ limit value where there is exactly q percent chance that Y values are less than $Q_q(Y)$. It is easy to see that $0 \leq q \leq 1$ (by the probability axiom) and that $Q_q(Y)$ is a non-decreasing function of q.

Thus, in quantile regression, the regression model will be given by:

$$Q_q(Y|X = x) = x^T\beta(q) = \beta_0(q) + x_1\beta_1(q) + x_2\beta_2(q) + ... + x_k\beta_k(q) \tag{17}$$

(assuming without loss of generality that there are k —1 regressors). $\beta(q)$ is the marginal effect of the explanatory variables X on the i^{th} quantile of Y, which effect may vary depending on the chosen quantile. This approach is quite relevant for dependent variables whose distribution presents asymmetry, heavy tails or heteroscedasticity.

The optimization of the i^{th} quantile is similar to the OLS. Estimation of the quantile regression will also be achieved by least squares,

$$\mathbf{E}[Y] = \min_{\alpha} \mathbf{E}[(Y - \alpha)^2] \tag{18}$$

which is equivalent to finding the solution to:

$$\min_{\alpha} \sum_{i=1}^{n} (y_i - x_i^T\beta)^2 \tag{19}$$

In the case of quantile regression, the optimization is done for every i^{th} quantile of Y.

3 Methodology

This methodology is proposed as a tool to evaluate the systemic market risk contribution of each entity, and subsequently, identify the entities that are bringing more risk to the entire system as well. The proposal here is to estimate those contributions by using public available market information.

We will take as our system a financial system composed of a set of most important European banks.

The proposed methodology is implemented over 5 steps:

1. Estimate asset values
2. Estimate institution value change impact on system value change
3. Obtain $CoVaR$ for each Institution
4. Including time variation
5. Identify the most risky institutions

3.1 Methodology Description

Step 1: Estimate Asset Values
Harvesting data to support any research is usually a challenging process. Institution financial details frequently are not available on the public domain and are informed only on a periodic basis. So this methodology is an option to obtain Var and $CoVaR$ based on market public data that brings additional clarity to the process as well as allows us to access and calculate those risk measures at any point in time. As an assumption, to use publicly available data, the market value, the market capitalization of each institution reflects the book value of the assets. Also, the market value of the system is assumed as the aggregation of the market value of all the institutions belonging to that system. So, as step 1, for this method, we have to collect data and calculate the respective market capitalization for each day and for each institution and estimate the capitalization for all the system as well. The process could be summarised as follows:

- Obtain the data:
  - collect stock prices
  - Balance sheet equity (BVE) and total assets (BVA)
  - in this work we will use stock prices, in weekly base (Fridays price)
- market value of equity (MVE)
  - stock price × shares outstanding
- Assume market value of assets (MVA)
  - book value of assets (BVA) * (MVE/BVE)
  - means market-to-book ratios for equity and assets are equal
- Define system asset value as the sum of institutions $MVA_t^{sys} = \sum MVA_t^i$, for a pointy in time t
- getting returns as: $X_t^i = \frac{(MVA_t^i - MVA_{t-}^i)}{MVA_{t-}^i}$; for institutions and system

Step 2: Estimate System Impact of an Institution Value Change
To establish a relation between system returns and the returns of each institution, we will apply a quantile regression where system return is the dependent variable and institution return is the explanatory variables. By using quantile regression we are not including any specific assumption over the returns and return's distribution. This way we will get the β parameter from the quantile regression that establishes such relation:

Quantile Regression, proposed by Koenker and Basset (1978) [16], is frequently used to model specific conditional quantiles of the response but the full potential is in the capacity to modeling the entire conditional distribution [4]. Even if it is computationally more expensive if we compare it with standard least squares regression models, but also exhibits some important properties such as:

- does not make any assumption on the distribution of the errors
- deals very well with the tail of a distribution
- so, it is a proper way to estimate the $CoVaR$ which is found on the lower quantiles of a dependent variable

Run a $q\%$ quantile regression with the returns of the system as the dependent variable and the return of each institution as independent variables. The regression model is specified as follows:

$$X_t^{sys} = \alpha + \beta X_t^i + \epsilon_t \tag{20}$$

regress the system return on each institution return.

Step 3: Obtain *CoVaR* for Each Institution
In this step, we compute the $CoVaR$ for the system using the β parameters obtained from quantile regression. System $CoVaR$ estimate is based on the VaR of each institution, by using α and β parameters we got from the previous step. Apply both to each institution's VaR and we have an estimate to $CoVaR$

To obtain $\Delta CoVaR$ we need to use also the institution VaR at quantile 50%, which corresponds to the VaR at the median. This represents the VaR in a situation where there are no stress in the market. Applying the β parameter, which is specific of each institution, to the difference between VaR estimated at quantile q and VaR estimated at quantile 0.5, we have an $\Delta CoVaR$ estimate.

1. Obtain VaR for each institution:
2. Obtain the median for each institution
3. Obtain institution $CoVaR$ by applying:

$$CoVaR_q^{sys|i} = \hat{\alpha}_q^i + \hat{\beta}_q^i VaR_q^i \tag{21}$$

4. Obtain institution ΔCoVaR by applying:

$$\Delta CoVaR_q^{sys|i} = \hat{\beta}_q^i (VaR_q^i - VaR_{0.5}^i) \tag{22}$$

Step 4: Adding Time Variation
In the original paper Adrian and Brunnermeier [20] included an additional layer of assumptions making the institution returns, X dependent on a set of state variables and assuming an underlying factor model for asset returns, where the return on each asset depends linearly on these factors:

- A set of lagged state variables $M - t - 1$ (to be defined shortly)
- The system-wide growth in assets X^{sys}

This way, the asset growth of each financial institution will depend on selected lagged state variables, while the growth rate of system assets depends on individual bank asset growth and lagged state variables.

As we aim is to remove additional assumptions from the model, an alternative to avoid this extra layer of assumptions is to applying a rolling windows technique as a way to include time variance to have an analysis through time [7]. The caveat here is we will lose a part of the initial data set. Defining a window length, for example, 3 years of data, we will be moving this window day by day, or week by week and apply all the previous steps to each one of those time windows. In the end we will get a time series for VaR, $CoVaR$ and $\Delta CoVaR$. Another caveat we can refer to regarding using this method is also the high computational cost of it. Despite some of its shortcomings, the rolling-window procedure is handy to implemented and easy to interpret also without including additional assumptions (Fig. 2).

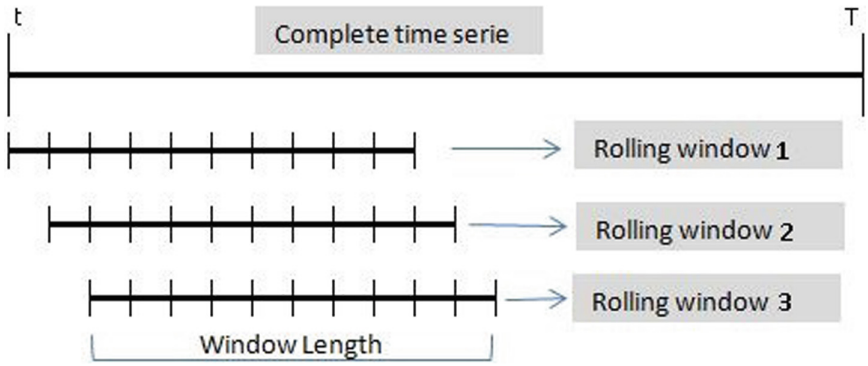

Fig. 2. Rolling windows

Step 5: Identify the Most Risky Institutions
The most systemic risky institutions will be identified by the ΔCoVaR. Institution with bigger ΔCoVaR are associated with bigger systemic risk.

3.2 Calculating *VaR*

There are plenty of different ways to obtain VaR and distinct methods to calculate them. All these methods have a common base but then will diverge in how they, in fact, calculate VaR. Usually, those methods also have a common problem in assuming that the future will follow the past.

What are the options to obtain VaR? We will discuss here three different approaches:

- Historical VaR.
- Analytic VaR (Variance CoVaRiance, Parametric)
- Extreme Value VaR

While the first ones are standard in literature and across the industry, the last one mentioned is not yet so broadly used [10].

Historical *VaR*. With this method we will be looking at the data, that is the returns during a period of time and check off for the value at specific quantile q previously defined. The advantage in this method is we don't need to have also any special assumption or knowledge about returns distribution. So it is straight forward to apply and implement and namely:

- Normality Assumption is not required.
- Works on historical returns.

Historical *VaR* Calculation:

- Step 1: Collect data on historical returns for an institution. These returns over a time interval = desired *VaR* time period.
- Step 2: from this info, make a histogram of historical return data.
- Step 3: *VaR* is the return associated with the cumulative probability from the left tail of the histogram that equals q quantile.

Therefore, one can associate the following advantages with this methodology [14]:

- Because it is non-parametric, the historical method does not require normality assumption
- Easy to understand and implement.
- Based only on historical information.
- Is consistent with the risk factor changes being from any distribution

Parametric *VaR*. Parametric *VaR* is also a popular way to calculate *VaR*. Actually, this method will be using returns information in order to estimate the parameters, as average and variance for a theoretical distribution that will then be fitted to returns data series.

The most common distribution associated with the returns under this method is perhaps the normal distribution, and in this case, the method is called also the variance-covariance method where the returns are assumed to be normally distributed.

- The most common measure of risk is standard deviation of the distribution of returns.
- Higher volatility = higher risk = potential for higher losses.
- Using standard deviation and some assumptions about returns, we can derive a probability distribution for returns.

With this methodology we are taken the following assumptions:

- Variance-Covariance *VaR* assumes that asset returns are normally distributed with known mean and standard deviation over a specified time-period
- CoVaRiances (correlations) among assets are known for the same time interval.

Inputs into the *VaR* calculation:

- Market values of all securities in the portfolio
- Their volatilities

The assumption is that the movement of the components of the portfolio are random, and drawn from a normal distribution.

Extreme Value Theory and *VaR*. Extreme value theory can be used to investigate the properties of the Left tail of the empirical distribution of a variable X^i.

By applying extreme value theory we don't have to make assumptions on returns distribution as well. In fact we don't need to know the distribution either. As, in terms of *VaR* we are looking for the behaviour on the extremes, and what we really need here is to modulate the behaviour on the tail of the distribution, in this case in the left tail [13].

By using EVT to model extremes behavior it also means:

- follows mathematical theory of the behaviour of extremes
- the body and the tail of data do not necessarily belong to the same underlying distribution
- does not require particular assumptions on the nature of the original underlying distribution of all the observations

Additionally, with GPD we can consider the following properties:

- GPD is an appropriate distribution for independent observations of excesses over defined thresholds
- GPD can be used to predict extreme portfolio losses

The two methods to model extremes, GPD and GEV could be proved equivalent, and both methods requires to set an arbitrary value, the time interval in the GEV and the threshold in the GPD. Analyzing differences between the two methods, we have that while the GPD method requires only two parameters GEV method requires three. The most relevant difference between the methods relies upon in the way it identifies the extremes. In the case of GEV, it relies on *T-maxima* (picks in time intervals of duration T), which can include observations of lower magnitude than the threshold defined for GDP, and this way obtains more data. On another hand, if in the same interval we have several observations over the threshold, all will be considered with GDP, but some could be discarded with GEV.

One drawback of GDP application, in this case, is related to the definition of a threshold, which means also to establish an arbitrary definition of a *"crisis"*. With GEV we don't need to make this assumption.

So, by applying Fisher-Trippett theorem we can get an expression for the extreme value distribution. Then we can select only a few data samples, estimate parameters, tail, scale, and location parameters, and fit this extreme value distribution. The idea here is to pick only a small number of the most extreme values we have on the data set, the worst 5 returns, for instance in each time window was been used.

4 Application

We took as our system the European banking system, compounded by the biggest banks in Europe, circa 50 European banks, that are also part of the *STOXX* European banking index.

4.1 Data

The proposed approach only relies on publicly available market data, such as stock returns as they are believed to reflect all information about publicly traded firms.

Based on the list of banks that are part of the *STOXX Europe 600* Banks index, corresponding to the biggest and most important banks in Europe, information on daily quotations for each title, public available for consultation at https://finance.yahoo.com/.

The original data set used was compounded by the daily quotations of the 52 biggest banks in Europe over the last 20 years. Subsequently, information on the number of shares issued was also collected for each of the institutions. This data, together with other information such as daily exchange rates were also collected in order to build a capitalization daily series of each institution (in euro).

This data set was later reduced to include only weekly closing prices for each financial institution. From this series, a series corresponding to the weekly returns (in percentage) was obtained from each of the institutions and for the entire system as well.

The overlapping rolling window was applied over periods of three years each. For each one of these periods was estimated VaR, $CoVaR$ and $\Delta CoVaR$, forming new time series related to each institution, representing the risk position for each institution in each point in time (week).

In order to keep guarantee the anonymization of the institutions used to elaborate this research, the real designation of each financial institutions was pseudonymized and replaced by a tag as Bank01 ... to Bank52.

4.2 Comparing VaR, $CoVaR$ and $\Delta CoVaR$

In order to compare the performance of each one of the models we will used a simple measure to count the *breaks* on VaR verified by using each method. Lets consider a break on VaR whenever $loss_{t+1} > VaR_t^q$.

$$break_{t-1}(i) = \begin{cases} 1 \text{ if } loss_t > VaR_{t-1}^q \\ 0 \text{ otherwise} \end{cases} \tag{23}$$

where i represents institution i, and t a point in time.

The measure used will be simple the count of break observed over the period in analyse, or:

$$\sum break_{t-1}(i) \tag{24}$$

As of when we are analyzing risk and in special systemic risk, we are interested in extreme cases localized on extreme of left tail of the distribution. The first results we are looking into were obtained using a quantile not so *"extreme"*, but yet a popular one: 5%.

Using BANK26 bank results as an example, and comparing the three methods discussed regarding *VaR*, EVT shows better performance:

- EVT *VaR*: 28 breaks
- Parametric *VaR*: 45 breaks
- Historical *VaR*: 55 breaks

In this case EVT *VaR* presents a better fit returning fewer breaks than parametric and historic methods (Fig. 3).

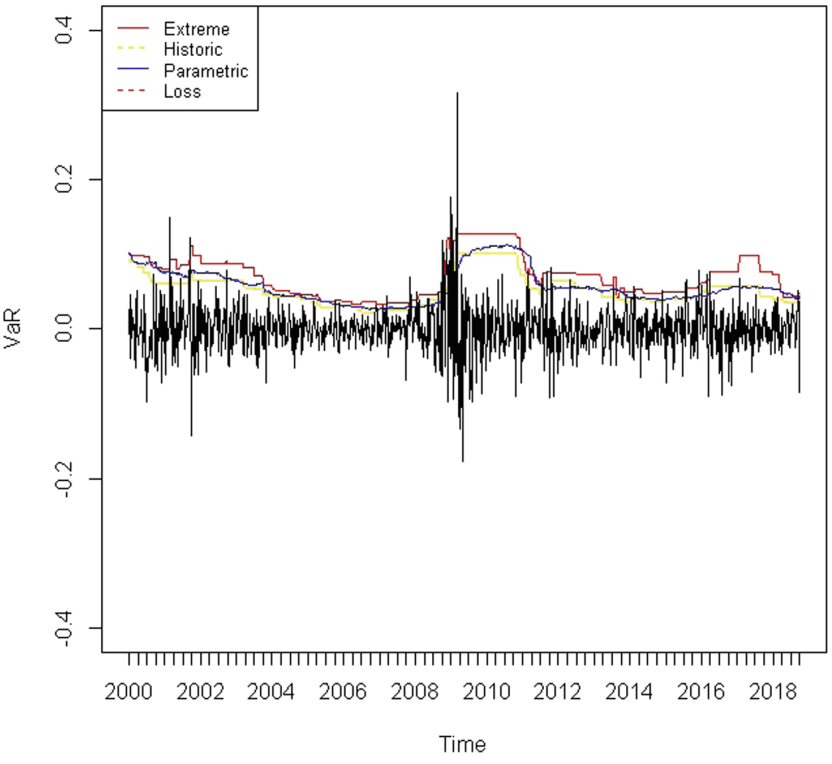

Fig. 3. BANK26 *VaR* results with $q = 0.05$

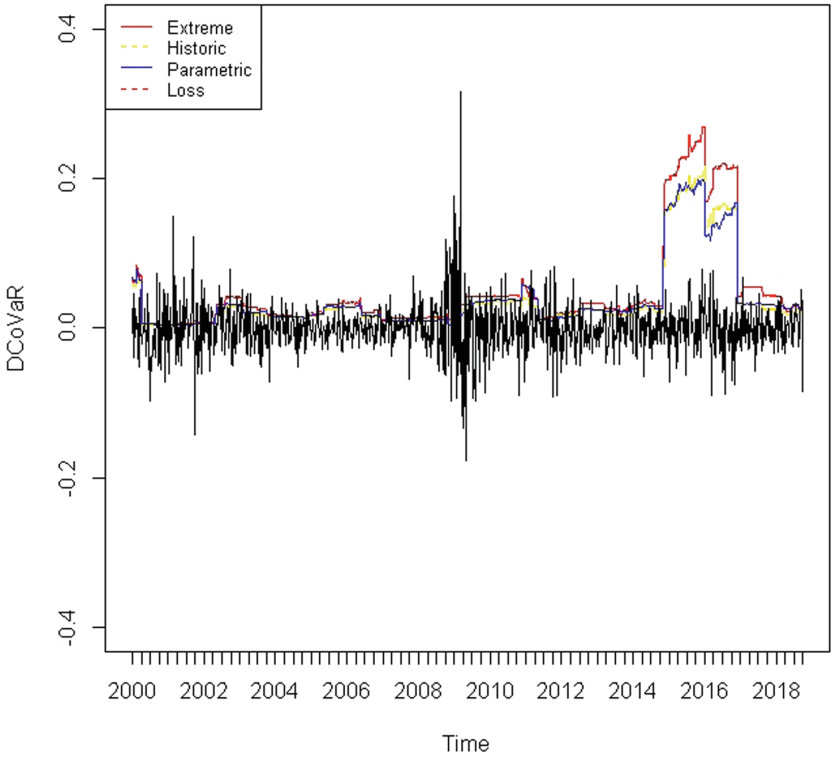

Fig. 4. BANK26 $\Delta CoVaR$ results with $q = 0.05$

The graph above represents *VaR* evolution along the period in analyze. Returns in the period are included as well in order to compare those figures with *VaR*.

In the next two graphs, we reduced the quantile q value in order to analyze the behavior of *VaR* and $\Delta CoVaR$ when we move further on the tail of the risk distribution (Fig. 4).

Comparing the three methods for a very extreme q, EVT *VaR* returns in general lower risk estimates when compared with parametric and historic methodologies. Is not clear if in this case, the EVT performs better since it the number of Var breaks increase when a smaller quantile is used.

In any case, if we are instead looking a more extreme quantile, it seems that Extreme Value Theory is not following the new demand for less risk, and in fact, we are getting some more breaks with Extreme Value Theory than with Historic and Parametric *VaR* (Figs. 5).

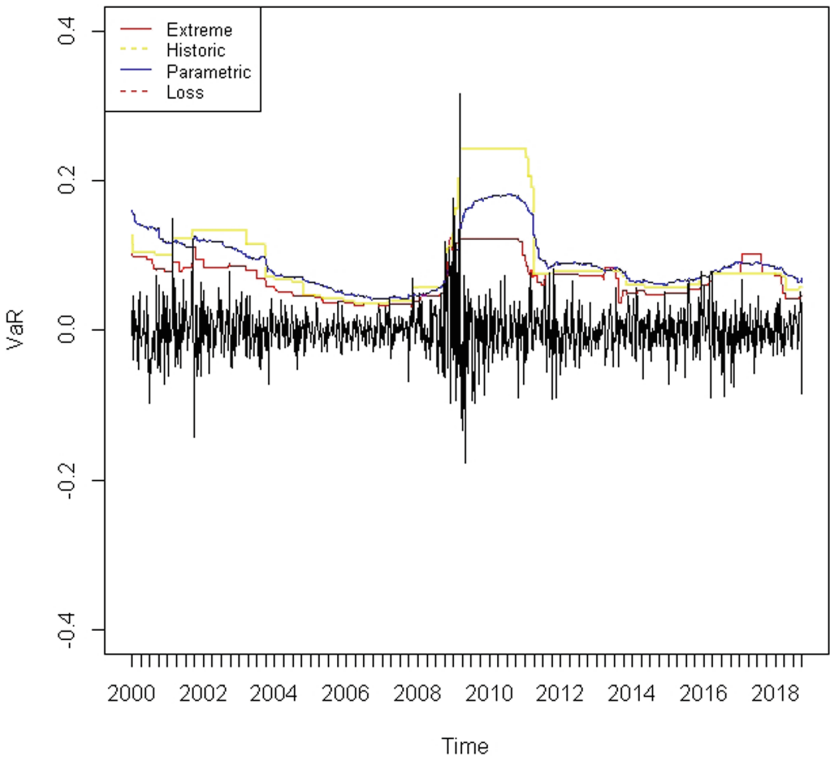

Fig. 5. BANK26 VaR results with $q = 0.005$

4.3 Identifying Systemic Risky Financial Institutions

This systemic importance rank a measure is not necessarily linked to a possible situation of the distress of a particular financial institution. Instead, it reflects the expected additional impact costs given such an event in financial system.

The above table lists financial institutions ordered by its systemic risk estimated impact. In brackets is the % of $\Delta CoVaR$ in system VaR, representing the impact of a significant event in that financial institution reflected in system VaR (Fig. 6 and Table 1).

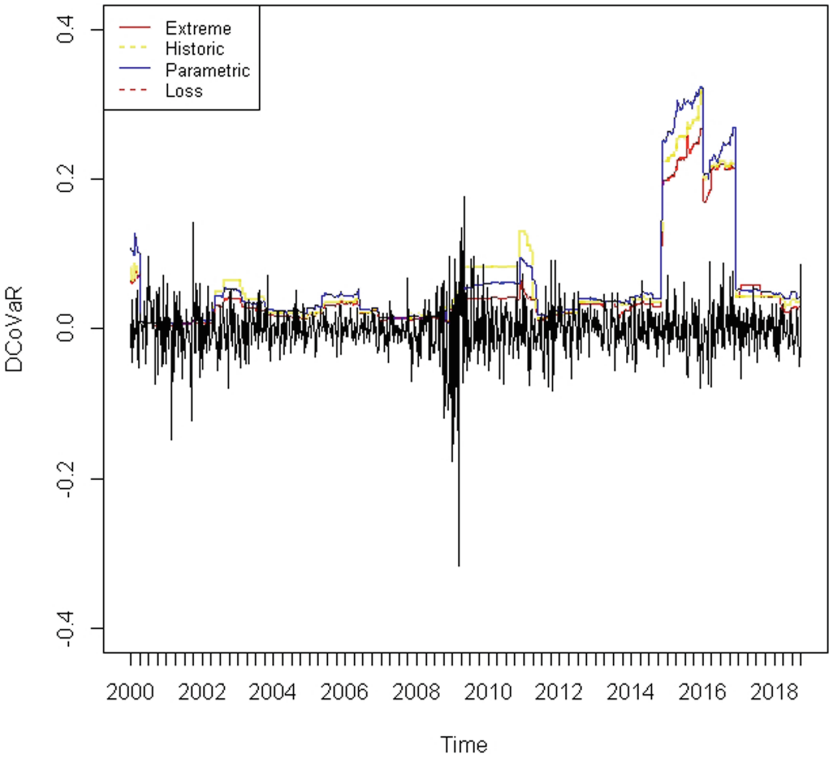

Fig. 6. BANK26 $\Delta CoVaR$ results with $q = 0.005$

Table 1. Top 10 financial institutions by $\Delta CoVaR$ - June 2018

Rank	Historic	Parametric	EVT	
1	BANK26 (7,4%)	BANK26 (9,9 %)	BANK26 (8,9%)	
2	BANK40 (5,6%)	BANK40 (6,6 %)	BANK40 (7,7%)	
3	BANK27 (5,2%)	BANK27 (5,9 %)	BANK45 (6,3%)	
4	BANK45 (5,1%)	BANK45 (5,2 %)	BANK27 (5,8%)	
5	BANK28 (4%)	BANK20 (5 %)	BANK28 (5,1%)	[a]
6	BANK20 (3,6%)	BANK28 (4,4 %)	BANK20 (4,5%)	
7	BANK41 (3,3%)	BANK41 (3,6 %)	BANK41 (3,8%)	
8	BANK38 (2,5%)	BANK38 (3,5 %)	BANK38 (3,3%)	
9	BANK25 (2,5%)	BANK25 (3,1 %)	BANK25 (3,2%)	
10	BANK02 (2,2%)	BANK02 (2,7 %)	BANK44 (2,8%)	

[a] in () $\Delta CoVaR$ % on system VaR.

5 Conclusions

We had used Adrian and Brunnermeier's [20] $CoVaR$ methodology which is defined as the VaR of the whole financial system given that one of the financial institutions is in distress. Quantile regression is employed to estimate the daily VaR and then $CoVaR$. In these processes, we use the equity market return and market volatility.

Using data collected for the period 1998 to 2018, our results indicate that BANK26 is the largest contributor to the banking sector's systemic risk in Europe. Our findings also indicate that the contribution of institutions to systemic risk is linked to the size of the institution, with the larger institutions contributing more than the smaller ones.

By comparing the three different methods to obtain VaR, Historic and Parametric methods are given similar results. When comparing with those mythologies, EVT VaR offers a better fit (less violations of VaR value by loss).

Analysing how all three methods had identified systemic risky financial institutions we observed that:

- All methods identify a very similar top ten of risky institutions
- Historic and parametric approaches more close
- Some changes on positions but with a similar set of institutions

However, EVT requires very few data as input (only used 5 records in each window) on our example. Depending on the scenario of use, this feature could be advantageous. This characteristic makes it suitable to be used in scenario analyses, for instance since it will be easier to get reliable results using a limited data set as input.

In terms of identifying the riskiest financial institutions, we can say the results are coincident only noticed some slight changes in the rank position for some banks depending on the method used.

As final remarks, it tends to have fewer breaks with extreme value theory. Regarding $\Delta CoVaR$ it is giving consistent results and estimates over the three different methods Extreme Value Theory, because it needs only a few data samples, and doesn't need any specific assumptions or knowledge about returns distribution, could be a good option to use in scenarios evaluation and scenario analysis. It also open the door to answers for questions like:

"If institution i incur on those losses, what could be the impact on the overall system."

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References

1. Acharya, V., et al.: Measuring systemic risk. Rev. Financ. Stud. **30**(1), 2–47 (2017)
2. Acharya, V., Engle, R., Pierret, D.: Testing macroprudential stress tests: the risk of regulatory risk weights. J. Monet. Econ. **65**, 36–53 (2014)

3. Adrian, T., Brunnermeier, M.K.: CoVaR. National Bureau of Economic Research (2011)
4. Allen, D.E., Gerrans, P., Powell, R., Singh, A.K.: Quantile regression: its application in investment analysis. JASSA **1**(4), 7 (2009)
5. Benoit, S., Colliard, J.-E., Hurlin, C., Pérignon, C.: Where the risks lie: a survey on systemic risk. Rev. Finan. **21**(1), 109–152 (2017)
6. Chernozhukov, V., Umantsev, L.: Conditional value-at-risk: aspects of modeling and estimation. Empirical Econ. **26**(1), 271–292 (2001)
7. Chong, J., Hurn, A.: Testing for speculative bubbles: revisiting the rolling window. Queensland University of Technology, School of Economics and Finance (2016)
8. Delbaen, F.: Coherent risk measures on general probability spaces. In: Advances in Finance and Stochastics, pp. 1–37. Springer, Heidelberg (2002). https://doi.org/10.1007/978-3-662-04790-3_1
9. Embrechts, P., Resnick, S., Samorodnitsky, G.: Limiting forms of the frequency distribution of the largest or smallest member of a sample. Mathe. Proc. Cambridge Philos. Soc. **24**(2), 180–190 (1928)
10. Fallon, W., et al.: Calculating value-at-risk. Wharton School, University of Pennsylvania (1996)
11. Fisher, R.A., Tippett, L.H.C.: Living on the edge. Risk **11**(1), 96–100 (1998)
12. Girardi, G., Ergün, A.T.: Systemic risk measurement: multivariate GARCH estimation of CoVaR. J. Bank. Finan. **37**(8), 3169–3180 (2013)
13. Levine, D.: Modeling tail behavior with extreme value theory. Risk Manag. **17**, 14–18 (2009)
14. Jadhav, D., Ramanathan, T.V.: Parametric and non-parametric estimation of value-at-risk. J. Risk Model Validation **3**(1), 51 (2009)
15. Kaplanski, G., Kroll, Y.: VaR risk measures versus traditional risk measures: an analysis and survey. J. Risk **4**(3), 1–27 (2002)
16. Koenker, R., Bassett Jr., G.: Regression quantiles. Econometrica J. Econ. Soc., 33–50 (1978)
17. Pickands III, J.: Statistical inference using extreme order statistics. Ann. Stat. JSTOR **24**(2), 119–131 (1975)
18. Pisarenko, V.F., Sornette, A., Sornette, D., Rodkin, M.V.: Characterization of the tail of the distribution of earthquake magnitudes by combining the GEV and GPD descriptions of extreme value theory. Pure Appl. Geophys. **171**(8), 1599–1624 (2014)
19. Rockafellar, R.T., Uryasev, S.: Conditional value-at-risk for general loss distributions. J. Bank. Finan. **26**(7), 1443–1471 (2002)
20. Adrian, T., Brunnermeier, M.K.: CoVaR. Am. Econ. Rev. **106**(7), 1705–1741 (2016)

Model Oriented Statistical Analysis for Cancer Problems

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Abstract. The target of this paper is to refer on model oriented data analysis for cancer problem. There is a solid background on statistical modelling and we provide a compact review of these models, applied mainly for (experimental) carcinogenesis. For particular cases, different methods can be applied. A typical example is the skin cancer of melanoma and the adopted analysis due to the EFSA Delphi method.

1 Statistical Models in Carcinogenesis

In principle, in (experimental) Carcinogenesis and in most of Ca problems, we are considering, two classes of stochastic models depending on whether dose levels or time are treated as random variables. The fundamental assumption is that the probability of developing cancer is likely to increase with increasing doses of carcinogen [63,64]. Let D to represent the random variables of the dose level of carcinogen, that induces a tumour in an individual agent and T the time at which an individual develops a tumour. Then, we assume that, an individual can develop tumour, at dose level d at a particular time t, with probability $P(d,t)$. The probability $P(d,t)$ can be represented either restricted on time or restricted on dose as

$$P(d,t) = P(X \leq d|t) = F(d), \quad P(d,t) = P(T \leq t|d) = G(t) \tag{1}$$

In principle, the underlying mechanism of the process is not usually known, and therefore a Nonparametric feature exists, as we do not know neither $F(d)$ nor $G(t)$. We try to overpass this problem approaching mainly the F function acting as a c.d.f. There are special guidelines for carcinogenic risk, see [63,64]. We are looking for that a model, which provides a satisfactory approximation to the true process, using the Kolmogorov test to provide evidence the model we choose is the right one [66], restrict our interest on evaluating $F(d)$, for the $G(t)$ see case [17,39,48–50]. Practically, under some assumptions, the models "fits" to the data, see [11,13,14]. We shall face and discuss such case in Sect. 4. Therefore the assumed correct model can be for prediction, and we do not try different

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models, to find the one we would like to assume although this occurs in practice. This needs Biological experience and knowledge for the underlying mechanism and is a hazardous procedure. We are working on Sect. 4 considering a data set for melanoma, adopting an adjusted EFSA Delphi method to analyse the data set with a number of different $F(d)$ distributions.

Considering (1) the survival distribution is defined as

$$S(t,d) = 1 - P(t,d)$$

If the dose dependency is not considered the model can be considered simplified to $P(t) = 1 - \exp(-\theta t^{\lambda})$, a Weibull distribution. More, advanced definition of $S(t)$ can be considered, see [66] that now, when we consider the case to is fixed and a sufficient small it can be considered [66]

$$P(d) = 1 - S(t_0, d) \quad \text{or} \quad S(t_0, d) = 1 - P(d)$$

while for the practical cases when the estimated parameter has be obtain an estimate $\hat{S}(t, d_t)$ is given by the non parametric Kaplan-Meier estimator [22]. A generalized approach based on the Generalized Normal Distribution (GND) was discussed in [62] were the hazard function was evaluated for the GND.

Historically, Iverson and Arley [30], in their pioneering quantitative model of carcinogenesis, proposed that transformed cells are subject to a pure linear birth process and a clone of transformed cells is detected if it exceeds a certain threshold. The Arley-Iversen model can be modified in two different ways to account for this finding:

(i) It could assume that only one step is needed for the transformation of a normal to a malignant cell.
(ii) To assume that a tumour arises from a single transformed cell.

An improvement was from Nordling [51] who assumed that κ specific mutational events have to occur for a normal cell to transform into a malignant cell and called this the *multi-hit theory*. Armitage and Doll [5], modified the multi-hit theory: they assumed that a certain sequence of irreversible cell alterations has to be followed. Moreover the quantitative implication of this approach, known as *multi-stage theory* was masterly investigated, see also [3,4].

Example 1: Let us consider the case of a constant, continuously applied dose d. Moreover the transformation rate from each stage, to the next, is assumed to increase linearly with the dose. In mathematical terms this is equivalent to: the transformation rate from the stage $i-1$ to the next stage i is assumed to be equal to $a_i + b_i d_i$, where $a_i > 0$ and $b_i \geq 0$. The parameter a_i presents the spontaneous transformation rate, in the absence of dosing (i.e. $d = 0$). Suppose that a tumour will develop before time t if all κ transformations have occurred in sequence: the commutative probability function that the κ - th change has occurred is then given by [37,43]

$$F(d;t) = 1 - \exp[-(a_1 + b_1 d)(a_2 + b_2 d) \cdots (a_\kappa + b_\kappa d) t^{\kappa}/\kappa!] \tag{2}$$

As the main assumption was that the transformation rate from each stage to the next on is linear, model (2) can be written as

$$F(d) = 1 - \exp[-(\theta_0 + \theta_1 d + \cdots + \theta_\kappa d^\kappa)] \tag{3}$$

where $\theta_i,\ i = 0, 1, \ldots, \kappa$ are defined through the coefficients of the linear transformation assumed between stages, i.e. $\theta_i = \theta_i(t) = \alpha_i + \beta_i t$. The most usual forms of (3) model are the multistage linear model and the multistage model. Notice that the dangerous point is to consider model (3) only for the Mathematical point of view and consider solely values of κ, while the biological inside on the coefficients of model (3) is crucial: are linear function of dose level, with complicates Biological interpretation. Therefore the value of κ is essential: describes that the susceptible cell can be transformed through κ distinct stages in order to be a malignant one the multistage model describes the phenomenon, and not just an extension to a non-linear mathematical model. Same line of thought exists for the coefficients $\theta_i = \theta_i(t)$.

Example 2: It was noticed that for some cancers (e.g. lung cancer) the cancer incidence rate increases with age, as log incidence is linear related to log age, there a log-log linear model describes the mechanism. In case that the time independence is assumed and the mutation rates are supposed to be small the hazard function [13] can be written as

$$\lambda(t) = c(t - t_0)^{\kappa - 1}, \quad c > 0, \quad \kappa \geq 1, \tag{4}$$

where t_0 is fixed for the growth of tumour and κ the number of stages. The above hazard function is the basis of the Armitage - Doll model, which may be considered biologically inappropriate for very old persons. As based on the fact that the very old cells lose their propensity to divide, and, therefore, are more refractive to new transformations. Thus, the "plateau" at older ages may simply reflect a compensating mechanism, while for a development with covariates see [59]. In [62] the Normal Distribution has been extended to Generalized Normal Distribution and the (GND) hazard rate for the GND has been evaluated.

It is easy to see that for the Armitage-Doll hazard function, corresponds the density function

$$f(t) = c(t - t_0) \exp\left[-\frac{c}{\kappa}(t - t_0)^\kappa\right]. \tag{5}$$

The target of low dose exposure is to estimate effects of low exposure level of agents, known already and to identify if there are hazardous to human health. Therefore the experimentation is based on animals and the results are transferred to humans. There is certainly a Relative Risk to this transformation [67], which is usually based on a scaling model of the form aB^β, see [43] for details with a, β being the involved parameters and B the body weight. So, the target to calculate the probability of the occurrence of a tumour during the individual's lifetime is exposed to an agent of dose d during lifetime is replacing humans with animals. Moreover, the idea of "tolerance dose distribution" was introduced to provide a statistical link and generate the class of dose risk functions.

Consider a nutshell - a tumour occurs at dose level d if the individuals' resistance/tolerance is broken, then the excess tumour risk is given by

$$F(d) = P(D \leq d) = P(\text{"}Tolerance\text{"} \leq d)$$

It is assumed that there is a statistical model which approximates $F(d)$, which from a statistical point of view is a cumulative distribution function. Then the dose level d is linked with binary response Y as

$$Y_i = \begin{cases} 1 \; success \; with \; probability \; F(d) \\ 0 \; failure \; with \; probability \; 1 - F(d) \end{cases}$$

For the assumed (usually nonlinear) model $F(d)$, the vector of parameters θ involved also needs to be estimated i.e. $F(d) = F(d;\theta)$. See also [27], as far as the safe dose concerns.

When the proportion of "successes", as a response in a binary problem, is the proportion of experimental animals killed by various dose levels of a toxic substance [23], called this experimental design *bioassay*. The data are called *quanta* or *dose response*, the corresponding probability function is known as *tolerance distribution*. Firstly, the probability of success p is described linearly as a function of the dose d. Typical examples are the Probit and Logit Models [13,14], and the problem of existence of parameter estimation is crucial [60].

If the cancer occurs when a portion of the tissue sustains a fixed number of "hits"; cancer is observed. When the first such portion has sustained the required number of "hits", then the One-Hit model is considered.

Example 3: The best known tolerance distribution was proposed by Finney [23], in his early work, the *probit model* of the form

$$P(d) = \Phi(\mu + \sigma d)$$

with Φ being, as usual, the cumulative distribution function of the normal distribution and μ and σ are location and scale parameters estimated from the data. For a compact review of applications of such methods see [19] while for a theoretical development see [34,41,44]. Practically, the logarithm of dose is used that implies a log normal tolerance distribution. The Normal, Lognormal and Beta distributions, among others, were adopted, under the statistical package SHELF to face melanoma Ca problem, see Sect. 3.

Example 4: The most commonly used parametric model for carcinogenesis is the Weibull model

$$P(T \leq t) = 1 - e^{-(\theta t)^{\kappa}} \tag{6}$$

With t being time to tumour, and with hazard function $\lambda(t) = \kappa\theta^{\kappa}t^{\kappa-1}$.

For the parameters θ, $\kappa > 0$, it is assumed when the Weibull model can exhibit a dose-response relationship that is either sub-linear (shape parameter $\kappa > 1$) or subralinear ($\kappa < 1$), and has a point of inflection at $x = ((\kappa-1)/\kappa)^{1/\kappa}$.

The Weibull distribution is used in reliability theory as a lifetime distribution.

Due to its flexibility, the Weibull model is suited to describe incidence data as they arise in animal experiments and in epidemiological studies.

The Weibull model has been extensively discussed for tumorigenic potency by Dewanji et al. (1989) [17], through the survival functions and the maximum likelihood estimators.

We proceed on the evaluation of the maximum likelihood estimation (MLE)

Propotition 2. For the Weibull model (6) parameters (κ, θ), both assumed unknown, the corresponding hazard function is $h(t) = \kappa\theta^{\kappa}t^{\kappa-1}$. Thus, the maximum likelihood function, from a censored, sample is

$$Lik(\kappa, \theta) = \prod h(t_i) \prod s(t_i) = \prod \kappa\theta^{\kappa} t_i^{\kappa-1} \prod e^{-(\theta t_i)^{\kappa}}$$

See Appendix I for calculations.

2 Different Classes of Cancer Models

The quantitative methods in cancer related to Relative Risk (RR) for the human health, has been tackled, for various aspects, under the Mathematical-Statistical line of thought in [20]. The models we discussed above has been extensively applied at the early stages, while new methods have been developed, and we present one in Sect. 4 discussing a Melanoma Analysis. There are different approaches with more complicated models and other classes of cancer models which we briefly discuss in this Section [33,35,56,61].

The *mechanistic models* have been named so because they are based on the presumed mechanism of the carcinogenesis. The main and typical models of this class are the dose response models, used in risk assessment, based on the following characteristics:

- ▷ There is no threshold dose below which the carcinogenic effect will not occur.
- ▷ Carcinogenic effects of chemicals are induced proportionally to dose (target tissue concentration) at low dose levels.
- ▷ A tumour originates from a single cell that has been damaged by one of the two reasons
  - (i) either the parent compound or
  - (ii) one of its metabolites.

In principle there are two different approaches in cancer modelling:

(i) Those models that consider the whole organism as the modelling unit and describe the time to overt tumour in this unit.
(ii) Models that describe the formation of carcinomas at the level of the cell, since knowledge is accumulating about the cellular biological events leading to cancer.

Hence, the mechanistic class of models can be subdivided into those models that describe the process on the level of the organism or on the level of individual cells.

The sub-class of *Global models*, includes those models that on the level of the whole organism, are closely related to statistical models, in that they also

describe the time to detectable carcinoma. Typical example is, the *cumulative damage model* is motivated by reliability theory. This model considers that the environmental factors cause damage to a system, which although does not fail "immediately", eventually fails whenever the accumulating damage exceeds a threshold.

The *Cell Kinetic models* is another sub-class and attempts to incorporate a number of biological theories, based on the line of thought that the process of carcinogenesis is on the cellular level. There has been a common understanding among biologists that the process of carcinogenesis involves several biological phenomena including mutations and replication of altered cells.

Cell kinetic models are subdivided to sub-classes by the method, which is used for their analysis, in Multistage Models and Cell Interaction Models, as follows.

(i) Multistage Models

The main class of *cell kinetic* models comprises *multistage models*, which describe the fate of single cells, but does not take into account interactions between cells. In these models mutations and cell divisions are described. These models stay analytically tractable because cells are assumed to act independently to each other. The pioneering work of Moolgavkar and Venzon [50] formulates a two - stage model with stochastic clonal expansion of both normal and intermediate cells. They eventually introduced a very helpful mathematical technique to analyse a two - stage model with deterministic growth of normal cells and stochastic growth of intermediate cells. Moreover Moolgavkar and Knudson [48] showed how to apply this latter model to data from epidemiological studies.

The death-birth process was used by Kopp - Schneider [39], who contributes essentially to incidence data from animal experiments and epidemiological studies, and provides the appropriate definitions and understanding for the underlying probabilistic mechanism, see also paragraph (ii) bellow the GMS and MVK class of models.

(ii) Cell Interaction Models

The *Cell interaction* sub-class of models incorporating both the geometrical structures of the tissue and communication between cells are too complicated for analytical results. These models aim to describe the behaviour (described by a number of simulations) of complex tissues in order to test biological hypotheses about the mechanism of carcinoma formation.

The Generalised Multistage Models (GMS) or Cell Interaction Models and the Moolgavkar - Venzon - Knudson Models (MVK) are based on the following assumptions:

- ▷ Carcinogenesis is a stochastic multistage process on cell level.
- ▷ Transition between stages is caused by an external carcinogen, but it may also occur spontaneously.

Cell death and division is important in MVK models. The normal, intermediate and malignant cells are depending on time. Intermediate cells arise from a

normal cell due to a Poisson process with known rate. A single intermediate cell may die with rate β, divide into two intermediate cells with rate α, or divide into one intermediate and one malignant cell with rate μ. Therefore, the process gives rise to the three steps:

- *initiation*
- *promotion*
- *progression*

which are very different from the biological point of view. If an agent increases the net cell proliferation $\alpha - \beta$, the cancer risk will also increase [43,49].

These cell kinetic models were used to describe the time to tumour as a function of exposure to a carcinogenic agent. Two objectives guide this research. On one hand, the models can be used to investigate the mechanism of tumour formation by testing biological hypotheses that are incorporated into the models. On the other hand, they are used to describe the dose-response relationship for carcinogens. Hence, they present one step on the way to risk assessment which goes from first indications of carcinogenity over qualitative findings to quantitative relationships obtained from the application of models to data from animal experiments. Finally, an inter-species adjustment can be used to transfer the results from animal experiments to the human situation. This is sometimes a problem, even the number of animals in the experiment creates problem. That is why we think, despite the small number of observations, real data analysis might be helpful, as the one we present for melanoma bellow.

Certainly one of the problems in the cancer risk assessment is the extrapolation from the experimental results to human [67]. There are also different scale parameters and are discussed in comparisons of $LD10 \equiv L_{.1}$. These parameters are based on different species and a given set of chemicals. That is still interest is focused on low dose, which is equivalent to calculate the percentile L_p, $p \in (0, 1)$ for "small" p, $0 < p \leq 0.1$ [38].

Although different terminology is adopted for the percentile point, like MTD, maximum tolerance dose, TD, tumorigenic dose, ED, estimated dose, LD, lethal dose the point remains the same: adopt that model which will provide the best downwards extrapolation to L_p, as it has no meaning to perform experiments below an unknown level of dose.

From the statistical point of view $F(d)$ is the cumulative distribution function, for the underlying probability model, describing the phenomenon. The notation d is referred to the dose level. Moreover, $F(d)$ is rather an assumed approximation, than a known deterministic mechanism for the phenomenon which describes. Therefore it needs an estimation and we would strongly recommend a Kolmogorov-Smirnov test [66] to verify its approximation.

Theorem 1 *(Kitsos [36]). Within the class of Multistage Models*

$$F(d) = 1 - \left(\sum_{i=0}^{s} \theta_i d^i \right) \tag{7}$$

the iterative scheme presented below

$$L_{p,n+1} = L_{p,n} - \left(n \sum_{i=0}^{s} r_i \right)^{-1} (y_n - p), \quad n = 1, 2, \cdots \tag{8}$$

with r_i *defined as*

$$r_i = \theta_i i L_p^{i-1} (1 - p) \tag{9}$$

converges to the L_p*, in mean square, i.e.* $L_{p,n} \xrightarrow{m.s.} L_p$ *and* $F(L_p) = p$.

Corollary 1: The iterative scheme (7) minimizes the variance of L_p in the limit, i.e. provides a limiting D - optimal design.

Corollary 2: The optimum iterative scheme (8) minimizes entropy of the limiting design.

Corollary 3: Within the Multistage Models class of models there exists at least one iterative scheme which converge in mean square to the p-th percentile of the distribution.

This theoretical result also works for "small" n as it has been tested with a simulation study [26]. The percentiles are applied in the next section in a Melanoma Analysis, from the dataset collected in Greece.

3 Melanoma Analysis: Biological Insight and Management of Disease

Melanoma is a malignant tumor arising from melanocytes, typically in the skin. Melanoma is the most dangerous type of skin cancer [1,2,7,24]. The primary cause of melanoma is ultraviolet light (UV) exposure in those with low levels of skin pigment. An individual's skin pigmentation is the result of genetics, biological parents' genetic makeup, and exposure to sun. The UV light may be from either the sun or from other sources, such as tanning lamps. Those with many moles, a history of affected family members, and who have poor immune function (in general, deliberately induced immunosuppression is performed to prevent the body from rejecting an organ transplant) are at greater risk [29,32, 46]. A human who is undergoing immunosuppression, or whose immune system is declared as a weak one, for some other reasons (mainly chemotherapy), is said to be immunocompromised is a state in which the immune system's ability to fight successfully infectious disease and cancer is compromised or entirely absent. A number of rare genetic defects such as xeroderma pigmentosum also increase risk [6]. Diagnosis is by biopsy and analysis of any skin lesion that has signs of being potentially cancerous. For an excellent survival analysis example, adopting Kaplan and Meier approach [31], see [22]. Certainly a Relative survival of the disease is calculated by dividing the overall survival after diagnosis by the survival, as observed in a similar population not diagnosed with that disease [45,46].

Using sunscreen and avoiding UV light may prevent melanoma [42], while treatment is typically removal by surgery [15]. In those with slightly larger cancers, nearby lymph nodes may be tested for spread. Most people are cured if spread has not occurred.

In principle Kaplan-Meier (KM) [31] curves and log-rank tests are most useful when the predictor variable is categorical (e.g., drug vs. placebo), or takes a small number of values (e.g., drug doses 0, 20, 50, and 100 mg/day) that can be treated as categorical. The log-rank test and KM curves don't work easily with quantitative predictors such as gene expression, white blood count, or age. For quantitative predictor variables, an alternative method is Cox proportional hazards regression, analysis [13]. When measuring overall survival by using the Kaplan-Meier or actuarial survival methods, is that unfortunately, the evaluated estimates include two causes of death. The deaths from melanoma and the deaths from other causes such as age, other cancers, or any other possible cause of death. We emphasize that in general, survival analysis is interested in the deaths by a disease, therefore a "cause-specific survival analysis" is adopted to measure melanoma survival. Thus, there are two ways in performing a cause-specific survival analysis "competing risks survival analysis" and "relative survival."

The likelihood that it will come back or spread depends how thick the melanoma is, how fast the cells are dividing, and whether or not the overlying skin has broken down. A large study validated the importance of tumor depth as one of the three most important prognostic factors in melanoma. That is in real life, the complicated and elegant statistical models, as in Sect. 3 might proved not such helpful. In practise the principle "keep it simple and soft" might be proved important. Breslow's depth also accurately predicted the risk for lymph node metastasis, with deeper tumors being more likely to involve the nodes.

The above studies showed that depth was a continuous variable correlating with prognosis. However, for staging purposes, the most recent AJCC (=American Joint Committee on Cancer) guidelines use cutoffs of 1 mm, 2 mm, and 4 mm to divide patients into stages (Table 1).

Table 1. Gershenwald and Scolyer, (2018), American Cancer Society, 2019 (years 2008–13)

Stage	Breslow thickness	Approximate 5 years survival
T1	<1 mm	99%
T2	1–2 mm	80–96%
T3	2.1–4 mm	32–93%
T4	>4 mm	23%

Melanoma was the ninth most common cancer in 2012 in Europe, with 50% approximately of melanomas harbors activating BRAF mutations [8]. The prevalence of melanoma in Greece has increased the recent years and is approximately 3–4 events per 100,000 inhabitants [25]. The development of BRAF and MEK

inhibitors (BRAFis and MEKis) as well as of immune checkpoint inhibitors have changed the management of advanced stage melanoma and improved the outcomes of patients with this malignancy [57].

Activating BRAF mutations drive constitutive MAPK pathway activation, with subsequent proliferation and enhanced cellular survival, making BRAF kinase a promising therapeutic target. Immunotherapies, on the other hand, can have lasting benefits regardless of BRAF status [18]. In Greece, no available data exist for the management of Adults receiving treatment for advanced injectable melanoma that is regionally or distantly (stage IIIB or IV M1c) metastatic. Eliciting probability distributions from melanoma experts for the transition to different stages of disease (pre-progression, post progression terminal care is a laborious but also very interesting procedure. The objective of this study is to apply and evaluate a modified Delphi [10] method to elicit probability distributions related to advanced BRAF-mutated melanoma.

The information was collected by experts on the disease from major Medical Departments around Greece, where 1000 approximately patients with advanced melanoma are treated per year. A modified EFSA Delphi method was used. This corresponds to the first phase of a SHELF elicitation [54], using the tertile method assessment of individual judgements. A tertile is a division of a set of observations into three defined intervals such that each range contains 33% of the total observation. Each expert should specify their upper and lower tertiles by considering the range from L to U and dividing it into three equally likely intervals [10,54].

Healthcare resource use (HCRU) related to advanced BRAF-mutated melanoma is based on the information collected by experts on the disease from major Medical Departments around Greece, where 1000 approximately patients with advanced melanoma are treated per year. A modified EFSA (=European Food Safety Authority) Delphi method [21] was used. This corresponds to the first phase of a SHELF (=Sheffield Elicitation Framework) elicitation [53], using the tertile method assessment of individual judgements. A tertile is a division of a set of observations into three defined intervals such that each range contains 33% of the total observation. Each expert should specify their upper and lower tertiles by considering the range from L to U and dividing it into three equally likely intervals [10,54]. In place of the second phase - the group judgements - Delphi iteration process took place. The experts' judgements and rationales are relayed anonymously back to the experts and they are asked to provide revised judgments. After the two rounds, the experts' individual probability distributions are averaged to provide the final aggregate distribution [10].

Here is a short description of our approach and analysis.

Material and Methods

The questions analyzed in this paper out of the selected ones, are the following:

1. What proportion (%) of patients has had brain metastases since the start of the follow-up?
2. What proportion (%) of patients has had in transit metastases since the start of follow-up?

We are referring to:
Expert, $i = 1, 2, 3$, Question $k = 1, 2$,
p^{th} percentile. $L_{0.05}$ is the 5^{th} percentile ($p_1 = 5\%$), $L_{0.5}$ is the 50^{th} percentile, i.e. the median ($p_2 = 50\%$) and $L_{0.95}$ the 95^{th} percentile ($p_3 = 95\%$), see Sect. 3.
$q_{p_y ik}$ the value of the elicited p_y^{th} percentile for expert i question k.

We defined a surprise as the event that the observed value that lies outside the 5–95 range [9]:

$$c_{ik} = \begin{cases} 0 \text{ if } \ q_{p_1 ik} < T_k < q_{p_3 ik} \\ 1 \text{ otherwise} \end{cases}$$

where,
T_k : Observed value estimating the true value for question k. If the rate of surprises is above 10%, the judgements have a tendency towards overconfidence [47].
The R language (package "SHELF") was used for this particular analysis, [54].

The rate of surprises (D-RS) was successively calculated.

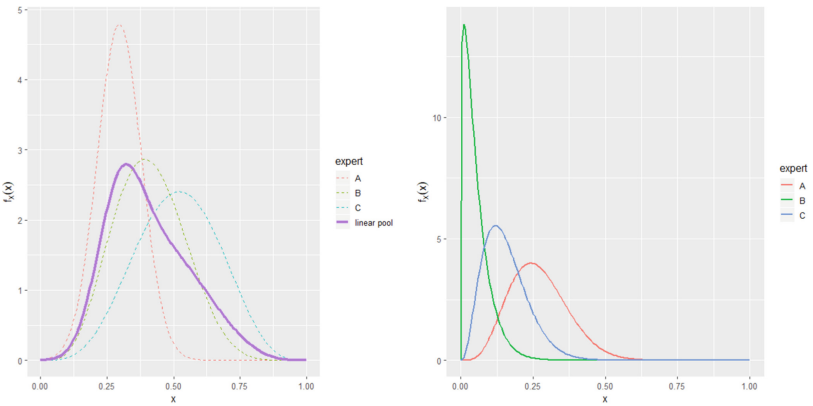

Fig. 1. Various distributions assumed of each expert for two datasets

Results

The process of averaging the density functions is known as the linear opinion pool (with equal weights). We use it in SHELF simply as a benchmark. Figures 1.(i), 1.(ii) present the individual assumed distribution (as it is expressed in Table 2) of each expert as well as the linear pooling. By inspecting the sum of squared differences, between elicited and fitted probabilities, we see that the normal distribution fits better for Expert A, and the Beta distribution fits better for Expert B and Expert C in the question 1 (Fig. 1.(i)). In the question 2, the normal distribution fits better for Expert B whereas Beta distribution fits better for Experts A and C, see Fig. 1.(ii).

Table 2. Comparing different probability distribution for two data sets D_1, D_2 relating to Fig. 1

	Normal		Log Normal		Beta		Gamma		t		Log t	
Expert	D_1	D_2	D_1	D_2	D_1	D_2	D_1	D_2	D_1	D_2	D_1	D_2
A	0.0177	0.0088	0.0243	0.0128	0.0198	0.0086	0.0219	0.0103	0.0231	0.0165	0.0286	0.0189
B	0.0396	0.0324	0.0398	0.0491	0.0375	0.0364	0.0390	0.0376	0.0471	0.0410	0.0475	0.0536
C	0.0343	0.0302	0.0362	0.0347	0.0329	0.0295	0.0354	0.0309	0.0390	0.0393	0.0388	0.0417

EFSA Delphi Method

Applying the second round the group agrees on consensus judgements [21]. Now, we elicit a single 'consensus' distribution from the experts. Experts are invited to revise their original judgements having seen what the other experts think. The group judgements are used as a basis for fitting a probability distribution, that is the outcome of the elicitation process, and so must be selected carefully and with full approval of the experts [52].

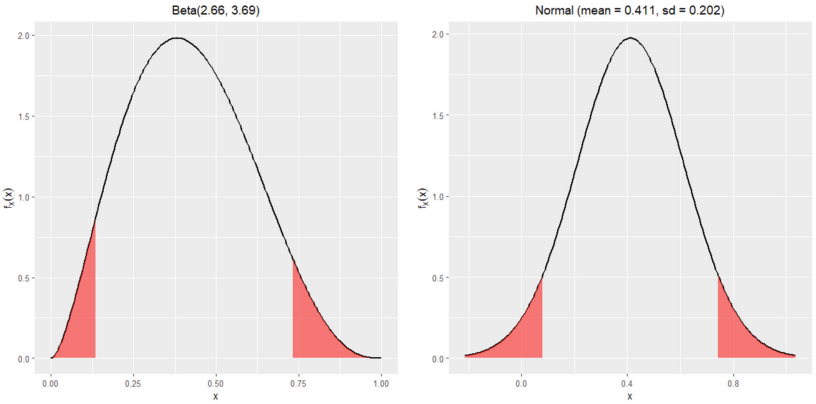

Fig. 2. Various distributions assumed of each expert for two datasets

The final fitted distributions by questions 1 and 2 are shown in Figs. 2.(i), 2(ii) implied by this distribution.

Conclusions

The modified Delphi Method using as percentiles (p) the tertiles (τ) with feedback to achieve consensus seems to be an effective method to reduce heuristics and biases. Providing people with more feedback seemed to help reducing overconfidence, since feedback serves as a tool allowing people to correct their errors [26] (Table 3).

Table 3. Comparing different probability distribution for two data sets D_1, D_2 relating to Fig. 2

	Normal		Log Normal		Beta		Gamma		t		Log t	
elicited	D_1	D_2	D_1	D_2	D_1	D_2	D_1	D_2	D_1	D_2	D_1	D_2
0.330	0.344	0.332	0.337	0.322	0.335	0.325	0.339	0.324	0.344	0.332	0.337	0.322
0.500	0.478	0.497	0.489	0.518	0.490	0.509	0.485	0.512	0.478	0.497	0.489	0.518
0.660	0.670	0.662	0.666	0.648	0.669	0.654	0.667	0.653	0.670	0.662	0.666	0.648

4 Discussion

As data synthesis studies are the most common type of "evaluation studies", future work might concentrate on further improvements to these types of elicitation design in order to a stronger support to researchers and decision makers and a better allocation of limited resources. In particular, research might investigate strategies to limit the anchoring and adjustment heuristic which can substantially degrade the quality of an economic evaluation in healthcare. The appropriate adjustment will referred in a compact line of thought.

The target of this paper was to discuss the existence of different classes of statistical models which try to approach the Biological insight, under which a normal cell is transformed to a malignant one. For most of these models there is an appropriate software, in all the cancer research centers, not that friendly to non experts users. Moreover different cancers as well as the burden of disease need different approach [39,40], as the biological description is different and different characteristics are related to them [59], and the treatment and care are different [65].

Such a different case, we adopted the skin cancer of Melanoma, which appears different characteristics and a complex disease management. An EFSA Delphi method was applied under a friendly software (SHELF) for statistical package. Some of the results were presented and discussed in Sect. 3 while other will present elsewhere under different approach.

In any case the descriptive statistical analysis is not enough to conclude about the Ca mechanism, and almost in all cases there is a need for further statistical analysis to analyze the problem under investigation. A model oriented data analysis is what we would like to suggest for Cancer models, in the spirit of [20,55].

Appendix I

Proof of Proposition 2

The corresponding log likelihood function (logLik(.)) and Fisher's information are evaluated as

$$l = \log(L(\kappa, \theta)) = d \log \kappa + \kappa d \log \theta + (\kappa - 1) \sum \log t_i - \theta^{\kappa} \sum t_i^{\kappa}. \qquad (10)$$

To evaluate Fisher's information matrix the second derivatives of the log-likelihood l are

$$I_{\theta\theta} = \frac{\partial^2 l}{\partial \theta^2} = \frac{\partial}{\partial \theta}\left(\frac{\kappa d}{\theta} - \kappa\theta^{\kappa-1}\sum t_i^{\kappa}\right) = -\frac{\kappa d}{\theta^2} - \kappa(\kappa-1)\theta^{\kappa-2}\sum t_i^{\kappa},$$

$$I_{\theta\kappa} = \frac{\partial^2 l}{\partial \theta \partial \kappa} = \frac{d}{\theta} - \theta^{\kappa-1}(1+\kappa\log\theta)\sum t_i^{\kappa} - \kappa\theta^{\kappa-1}\sum t_i^{\kappa}\log t_i,$$

$$I_{\kappa\kappa} = \frac{\partial^2 l}{\partial \kappa^2} = -\frac{d}{\kappa^2} - \theta^{\kappa}\sum t_i^{\kappa}[\log(\theta t_i)]^2$$

Fisher's information matrix is $I = (I_{ij})$, $i, j = \theta, \kappa$ and the covariance matrix is the inverse of Fisher's information matrix. As far as for the MLE it is obtained through the first derivatives as bellow.

The first derivatives with respect κ and θ, of the log-likelihood function are

$$U_{\theta} = \frac{\partial l}{\partial \theta} = \frac{\kappa d}{\theta} - \kappa\theta^{\kappa-1}\sum t_i^{\kappa}$$

$$U_{\kappa} = \frac{\partial l}{\partial \kappa} = \frac{d}{\kappa} + d\log\theta + \sum \log t_i - \theta^{\kappa}\sum t_i^{\kappa}\log(\theta t_i).$$

If κ is given, the maximum likelihood estimator (MLE) θ^* of θ can be evaluated explicitly from $U_{\theta} = 0$ as

$$U_{\theta} = 0 \Leftrightarrow \frac{\kappa d}{\theta} - \kappa\theta^{\kappa-1}\sum t_i^{\kappa} = 0 \Leftrightarrow \frac{d}{\theta} = \theta^{\kappa-1}\sum t_i^{\kappa} \Leftrightarrow d$$
$$= \theta^{\kappa}\sum t_i^{\kappa} \Leftrightarrow \theta^{\kappa} = \frac{d}{\sum t_i^{\kappa}}$$

Eventually the MLE of θ

$$\theta^* = \left(\frac{d}{\sum t_i^{\kappa}}\right)^{1/\kappa}. \tag{11}$$

Substitution into the equation $U_{\kappa} = 0$ yields the maximum likelihood estimator κ^*. Equation (11), although is non linear, does not contain θ and therefore can be solved by a one-dimensional iterative scheme in κ.

References

1. American Cancer Society: Survival rates for melanoma (2019). https://www.cancer.org/cancer/melanoma-skin-cancer/detection-diagnosis-staging/survival-rates-for-melanoma-skin-cancer-by-stage.html
2. Arden, K.C., Anderson, M.J., Finckenstein, F.G., Czekay, S., Cavenee, W.K.: Detection of the t(2; 13) chromosomal translocation in alveolar rhabdomyosarcoma using the reverse transcriptase-polymerase chain reaction. Genes Chromosom. Cancer **16**(4), 254–260 (1996)

3. Armitage, P.: Multistage models of carcinogenesis. Environ. Health Perspect. **63**, 195–201 (1985)
4. Armitage, P.: The assessment of low-dose carcinogenicity. Biometrics **28**(Sup.), 119–129 (1982)
5. Armitage, P., Doll, R.: The age distribution of cancer and a multi-stage theory of carcinogenesis. Br. J. Cancer **8**(1), 1 (1954)
6. Azoury, S.C., Lange, J.R.: Epidemiology, risk factors, prevention, and early detection of melanoma. Surg. Clin. North Ame. **94**(5), 945–962, vii (2014)
7. Bowman, D., Chen, J.J., George, E.O.: Estimating variance functions in developmental toxicity studies. Biometrics **51**(4), 1523 (1995). https://doi.org/10.2307/2533282
8. Boursault, L., et al.: Tumor homogeneity between primary and metastatic sites for BRAF status in metastatic melanoma determined by immunohistochemical and molecular testing. Public Libr. Sci. One **8**(8), e70826 (2013)
9. Budescu, D., Du, N.: Coherence and consistency of investors' probability judgments. Manage. Sci. **53**(11), 1731–1744 (2007)
10. CfWI: Elicitation methods: applying elicitation methods to robust workforce planning. Centre for Workforce Intelligence. Technical Paper Series No. 0011 (2015)
11. Cogliano, V.J., Kitsos, C.: Modeling I. Folia Histochemica et Cytobiologica. Supplement **39**(1) (2001)
12. Carayanni, V., Kitsos, C., Nisiotis, C.S.: Application of experts elicitation methods in probabilistic form to collect resource use data in health care. The case of skin cancer. Sustain. Dev. Cult. Tradit. J., 82–91 (2019). Special Volume in Honor of Professor George I. Theodoropoulos
13. Cox, D.R.: Regression models and life-tables. J. Roy. Stat. Soc. Ser. B (Methodol.) **34**(2), 187–202 (1972)
14. Cox, D.R., Snell, E.J.: Analysis of Binary Data. 32. CRC Press (1989)
15. Cancer Research UK: Preventing melanoma (2009). https://web.archive.org/web/20080522113412/. http://www.cancerhelp.org.uk/help/default.asp?page=3007
16. Crump, K.S., Guess, H.A., Deal, K.L.: Confidence intervals and test of hypotheses concerning dose response relations inferred from animal carcinogenicity data. Biometrics **34**(2), 437–451 (1977)
17. Dewanji, A., Venzon, D.J., Moolgavkar, S.H.: A stochastic two-stage model for cancer risk assessment. II. The number and size of premalignant clones. Risk Anal. **9(2)**, 179–187 (1989)
18. Dummer, R., et al.: Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. **19(5)**, 603–615 (2018)
19. Edler, L.: Statistical methods for toxicity detection and testing. In: Chyczewski, L., Nicklinski, J., Pluggers, E. (eds.) Endocrine Disrupters and Carcinogenic Risk Assessment, vol. 340, p. 290. IOS Press (2002)
20. Edler, L., Kitsos, C.P.: Recent advances in Quantitative Methods in Cancer and Human Health Risk Assessment. Wiley (2005)
21. EFSA: Guidance on expert knowledge elicitation in food and feed safety risk assessment. Eur. Food Saf. Authority J. **12**(6), 3734 (2014)
22. Everitt, S.B.: Statistical Methods for Medical Investigations, 2nd edn. Edward Arnold, New York (1994)
23. Finney, D.J.: Probit Analysis. Cambridge University Press, Cambridge (1971)
24. Gershenwald, J.E., Scolyer, R.A.: Melanoma staging: American Joint committee on cancer (AJCC) and beyond. Ann. Surg. Oncol. **25**(8), 2105–2110 (2018)

25. Greek Melanoma Study Association (2019). https://www.elemmel.gr/
26. Gonzalez-Vallejo, C., Bonham, A.: Aligning confidence with accuracy: revisiting the role of feedback. Acta Physiol. (Oxf) **125**(2), 221–239 (2007)
27. Hartley, H.O., Sielken, R.L.: A biometrics invited paper. Estimation of "Safe Doses" in carcinogenic experiments. Biometrics **33**(1), 1–30 (1977)
28. Hayat, M.J., Howlader, N., Reichman, M.E., Edwards, B.K.: Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) program. Oncologist **12**(1), 20–37 (2007)
29. IARC: Monographs on the evaluation of the carcinogenic Risk to Humans. Suppl. **7**, 79–80 (1987)
30. Iversen, S., Arley, N.: On the mechanism of experimental carcinogenesis. Acta Pathologica Microbiologica Scandinavica **27**(6), 773–803 (1950)
31. Kaplan, E.L., Meier, P.: Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. **53**(282), 457–481 (1958)
32. Kawai, A., Woodruff, J., Healey, J.H., Brennan, M.F., Antonescu, C.R., Ladanyi, M.: SYT-SSX gene fusion as a determinant of morphology and prognosis in synovial sarcoma. N. Engl. J. Med. **338**(3), 153–160 (1998)
33. Kitsos C.P.: Cancer Bioassays: A Statistical Approach, 326. LAMBERT Academic Publisher, Saarbrucken (2012)
34. Kitsos, C.P.: On the logit methods for Ca Problems (design and fit). Commun. Dependability Qual. Manag. **10**(2), 88–95 (2007)
35. Kitsos, C.P.: The cancer risk assessment as an optimal experimental design. In: Chyczewski, L., Nicklinski, J., Pluggers, E. (eds.) Endocrine Disrupters and Carcinogenic Risk Assessment, vol. 340, pp. 329–337. IOS Press (2002)
36. Kitsos, C.P.: Optimal designs for estimating the percentiles of the risk in multistage models of carcinogenesis. J. Math. Methods Biosci. **41**(1), 33–43 (1999)
37. Kitsos, C.P.: The role of covariates in experimental carcinogenesis. Listy Biometryczne-Biometrical Lett. **35**, 95–106 (1998)
38. Kitsos, C.P.: Optimal designs for percentiles at multistage models in carcinogenesis. Biom. J. **41**(1), 33–43 (1997)
39. Kopp-Schneider, A.: Carcinogenesis models for risk assessment. Stat. Methods Med. Res. **6**(4), 317–340 (1997)
40. Kopp-Schneider, A., Geiser, I., Edler, L.: Complex mechanistic carcinogenicity modeling. NATO Science Series Sub Series I Life and Behavioural Sciences. In: Endocrine Disrupters and Carcinogenic Risk Assessment, vol. 340, pp. 317–328. IOS Press (2002)
41. Lagakos, S.W., Schoenfeld, D.A.: Properties of proportional-hazards score tests under misspecified regression models. Biometrics 1037–1048 (1984)
42. Levy, S.B.: Sunscreens and Photoprotection. Medscape (2018)
43. Luebeck, G.E., Watanabe, K., Travis, C.: Biologically based models of carcinogenesis. In: Perspectives on Biologically Based Cancer Risk Assessment, pp. 205–241. Springer, Boston (1999)
44. McCullagh, P., Nelder, J.A.: Generalized Linear Models. Chapman and Hill (1989)
45. Mihajlovic, M., Vlajkovic, S., Jovanovic, P., Stefanovic, V.: Primary mucosal melanomas: a comprehensive review. Int. J. Clin. Exp. Pathol. **5**(8), 739 (2012)
46. Mendes, J.J.A.: Pathology of endocrine disrupters. In: Chyczewski, L., Nicklinski, J., Pluggers, E. (eds.) Endocrine Disrupters and Carcinogenic Risk Assessment, vol. 340, p. 88. IOS Press (2002)
47. Morgan, G.: Use (and abuse) of expert elicitation in support of decision making for public policy. Proc. Natl. Acad. Sci. **111**(20), 7176–7184 (2014)

48. Moolgavkar, S.H., Knudson, A.G.: Mutation and cancer: a model for human carcinogenesis. JNCI J. Nat. Cancer Inst. **66(6)**, 1037–1052 (1981)
49. Moolgavkar, S.H., Luebeck, E.G.: Multistage carcinogenesis: population-based model for colon cancer. JNCI J. Nat. Cancer Inst. **84(8)**, 610–618 (1992)
50. Moolgavkar, S.H., Venzon, D.J.: Two-event models for carcinogenesis: incidence curves for childhood and adult tumors. Math. Biosci. **47**(1–2), 55–77 (1979)
51. Nordling, C.O.: A new theory on the cancer-inducing mechanism. Br. J. Cancer **7**(1), 68 (1953)
52. O'Hagan, A.: Expert knowledge elicitation: subjective but scientific. Am. Stat. **73**(supl), 69–81 (2018)
53. O'Hagan, A.: Eliciting and using expert knowledge in metrology. Metrologia **15**, 237–244 (2014)
54. O'Hagan, A., Oakley, J.: SHELF 2.0 (2014). http://www.tonyohagan.co.uk/shelf/SHELFv2_0.zip
55. Oliveira, T., Kitsos, C.P., Oliveira, A., Grilo, L.: Recent Studies on Risk Analysis and Statistical Modeling. Springer, Cham (2018). https://doi.org/10.1007/978-3-319-76605-8
56. Patz Jr., E.F., Goodman, P.C., Bepler, G.: Screening for lung cancer. N. Engl. J. Med. **343**(22), 1627–1633 (2000)
57. Pelster, M.S., Amaria, R.N.: Combined targeted therapy and immunotherapy in melanoma: a review of the impact on the tumor microenvironment and outcomes of early clinical trials. Ther. Adv. Med. Oncol. **11** (2019)
58. Petersen, T.: Fitting parametric survival models with time-dependent covariates. J. Roy. Stat. Soc. Ser. C (Appl. Stat.) **35**(3), 281–288 (1986)
59. Prentice, R.L., Kalbfleisch, J.D.: Hazard rate models with covariates. Biometrics, 25–39 (1979)
60. Silvapulle, M.J.: On the existence of maximum likelihood estimators for the binomial response models. J. Roy. Stat. Soc. Ser. B (Methodol.), 310–313 (1981)
61. Solakidi, S., Vougias, E.C., Sekeris, E.C.: Biological carcinogenesis: theories and models. In: Elder, L., Kitsos, P.C. (eds.) Recent Advances in Quantitative Methods in Cancer and Human Risk Assessment, pp. 63–77. Wiley, Chichester (2005)
62. Toulias, L.T., Kitsos, C.P.: Hazard rate and failure lifetime for the generalized normal distribution. In: Oliveira, A.J., Kitsos, C.P., Oliveira, A., Grilo, L. (eds.) Recent Studies on Risk Analysis and Astatistical Modeling, pp. 165–180. Springer, Cham (2018)
63. Epa, U.S.: Guidelines for Carcinogenic Risk Assessment. EPA, Washington, DC (1999)
64. U.S. EPA: Guidelines for Exposure Assessment, pp. 33992–34003. Federal Register 51, Washington, DC (1992)
65. Varricchio, C.G.: A Cancer Source Book for Nurses. Jones and Bartlett Publishers, Boston (2004)
66. Wosniok, W., Kitsos, C., Watanabe, K.: Statistical issues in the application of multistage and biologically based models. In: Perspectives on Biologically Based Cancer Risk Assessment, pp. 243–273. Springer, New York (1998)
67. Zapponi, G.A., Loizzo, A., Valente, P.: Carcinogenic risk assessment: some comparisons between risk estimates derived from human and animal data. Exp. Pathol. **37**(1–4), 210–218 (1989)

Two-Stage Clonal Expansion Model Using Conditional Likelihood to Discern the Initiation and Promotion Effects: Numerical Study

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Abstract. The two-stage clonal expansion (TSCE) model has been developed to investigate the mechanistic processes in cancer development on carcinogenesis based on the knowledge of molecular biology. The model assumes three states of cells (normal, intermediate, and malignant) and four transition rate parameters to describe the rate at which a cell changes its state. Despite the need for statistically sound and biologically meaningful estimation methods, no reliable inference method has yet been established. A major trouble with TSCE model is that iteration algorithms searching for the maximum likelihood estimates of the model's parameters are generally non-convergent.

Regarding the problem, Nakamura and Hoel [10] proposed a new likelihood termed "conditional likelihood". This study conducted simulations with small sample sizes to assess the performance of the conditional likelihood to distinguish between the initiation and promotion effects. Data generation was performed using parameter values based on dioxin [6] and radiation [3] experimental data. Several estimation models were applied to each dataset to determine whether it was generated from the initiation or the promotion model. The correct identification rate was 98%.

1 Introduction

The Two-Stage Clonal Expansion Model was proposed by Moolgavkar *et al.* [8]. TSCE model involves four parameters: μ_1, β, δ, and μ_2. A normal cell is transformed into an intermediate cell at a constant rate μ_1 per unit time per cell. Each intermediate cell is subject to three events: *birth, death or mutation* (Fig. 1).

Specifically, each intermediate cell undergoes clonal expansion by dividing into two intermediate cells at a rate of β, death at a rate of δ, or division into one intermediate cell and one malignant cell at the rate of μ_2. Once a malignant cell has developed, it will replicate into a detectable tumor in a relatively short

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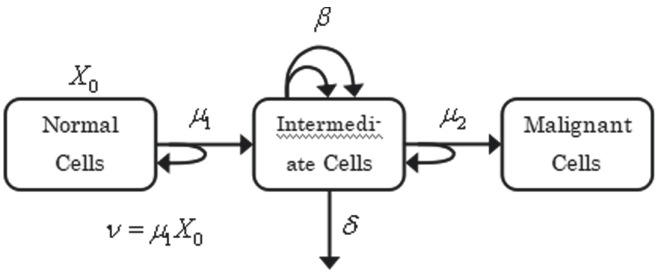

Fig. 1. Two-stage clonal expansion model

period of time; therefore, the formation of one malignant cell is usually associated with the development of detectable cancer.

Let $X_0, Y(t), Z(t)$ denote the number of normal, intermediate and malignant cells, at time t respectively. X_0 is assumed to be constant. Hereafter, ν denotes $\mu_1 X_0$. The endpoint is the appearance of the first malignant cell.

Define

$$S(t) = Pr\{Z(t) = 0 | X_0, Y(0) = 0, Z(0) = 0\}$$

where $S(t)$ is the probability of no malignant cell at time t. Kopp-Schneider *et al.* [7] obtained the exact form of $S(t) = \exp\{-\Lambda(t)\}$ as follows.

$$\Lambda(t) = \frac{\nu}{\beta}\left\{\frac{t(R+\beta-\delta-\mu_2)}{2} + \log\frac{R-(\beta-\delta-\mu_2)+(R+\beta-\delta-\mu_2)\,e^{-Rt}}{2R}\right\}$$

$$R^2 = (\beta+\delta+\mu_2)^2 - 4\beta\delta = (\beta-\delta-\mu_2)^2 + 4\beta\mu_2$$

where $\Lambda(t)$ is a cumulative hazard function. Hereafter, the likelihood using $\Lambda(t)$ is termed the original likelihood. Since ν, β, δ, and μ_2 are jointly unidentifiable with censored survival data, some identifiable set of parameters are proposed [4].

Changing parameters such that

$$\Psi = \beta - \mu_2 \quad \text{and} \quad \eta = \nu/\beta$$

$$\Lambda(t) = \eta\left\{\frac{t(R+\Psi)}{2} + \log\frac{R-\Psi+(R+\Psi)\,e^{-Rt}}{2R}\right\}$$

The parameters Ψ, η and R are identifiable, as is

$$\rho = \nu\mu_2 = \eta(R^2 - \Psi^2)/4$$

The parameters Ψ and ρ are of interest in most applications and have been biologically interpreted as the net proliferation rate and the overall mutation rate, respectively [8,9]. Portier *et al.* [13] and Sherman *et al.* [14], however, cautioned on the estimability with those identifiable parameters:

"The likelihood function for those parameters were extremely flat that resulted in frequent non-convergences or large variance estimates. Therefore, some assumptions on parameters are normally added in determining MLE of parameters. Estimated parameters are, however, quite different with the different assumptions. New statistical methods for the estimation of parameters (e.g. new likelihoods) are needed".

Since the iteration algorithms searching for the MLE of those identifiable parameters using the original likelihood hardly converges, no simulation studies been reported that revealed the performance of the original likelihood with individual survival data. This fact hinders the proper use and dissemination of TSCE model. Thus, Hornsby [5] cautioned:

"Different studies that have used slightly different methods or datasets have yielded different conclusions. The carcinogenesis models need to be carefully applied, and the conclusions they yield should be treated with caution".

Hence, Nakamura and Hoel [10] proposed a new likelihood, termed *"conditional likelihood"*, obtained by putting $\delta = 0$ in the above cumulative hazard $\Lambda(t)$:

$$\Lambda^*(t) = \frac{\nu^*}{\beta^*}\left(\beta^* t + \log\frac{\mu_2^* + \beta^*\exp\{-(\beta^* + \mu_2^*)t\}}{\beta^* + \mu_2^*}\right)$$

This makes the likelihood function simple. But, *what is the biological meaning of those parameters?* To answer the question, Nakamura and Hoel [10] claim that it holds exactly that

$$\Psi = \beta^* - \mu_2^*, \quad \rho = \nu^*\mu_2^* \quad \text{and} \quad \eta = \nu^*/\beta^* \tag{1}$$

The unbiasedness of MLE for ρ and Ψ obtained using (1) has been confirmed by a series of simulation studies [11,12,16,17] with $n = 500$ and $d = 400$. The conditional likelihood has been applied to radiation and dioxin experimental data [2,10,11,15].

The objective of this study is to examine the most interesting, yet never has been addressed issue; that is, the discerning ability of the TSCE model to discern between the Initiation and Promotion effects of carcinogenesis agents using the conditional likelihood.

2 Methods

For each parameter θ and an exposure dose D, we assume a log-linear dose-response model

$$\log\theta = \log\theta\_a + \log\theta\_bD$$

where $\log\theta\_a$ is a constant and $\log\theta\_b$ is a dose-rate effect of D.

2.1 Parameter Setting and Data Generation

Table 1 presents the three combinations of parameters used for the generation of survival data. For each combination, 100 independent survival data were generated for producing 100 independent MLEs. The sample size was fixed to be 500, of which 100 were censored.

Table 1. Models used for Generating Data

Model	$\log \Psi\_a$	$\log \Psi\_b$ $\times 100$	$\log \rho\_a$	$\log \rho\_b$ $\times 100$	$\log \eta\_a$	$\log \eta\_b$ $\times 100$
Initiation	-4.9	–	-17.0	0.42	-0.08	0.72
Promotion	-3.3	0.35	-35.0	–	1.7	-0.35
Full	-4.9	-0.1	-17.0	0.42	-0.08	0.72

For the Initiation model, the values of the parameters were determined based on the results from an analysis of the JANUS experimental data on radiation effects in mice [10], where MLE were described as $\log \rho\_a = -17.37$, $\log \rho\_b = 0.00424$, $\log \Psi\_a = -4.852$ and $\log \Psi\_b = -0.000345$. According to the radiation biology, $\log \Psi\_b = -0.000345$ was unexpected since the radiation was not considered to affect the promotion rate. However, calculating the expected number of cells [14], Portier [10] presented the following novel view; "the number of intermediate cells in those rats would be too large if the promotion rate remains the same with the increased initiation rate". Thus, we set $\log \Psi\_a = -4.9$, a little less than -4.853 and $\log \Psi\_b = 0$ in the Initiation model.

On the other hand, those for the promotion model were obtained from an analysis of the Dioxin experimental data by Kociba *et al.* [6]. They dealt with female Sprague-Dawley rats maintained for two years on diets supplying 0, 1, 10 and 100 pg/kg/day and observed for each animal the date of death and the presence or absence of hepatocellular carcinoma or adenoma. The results of the analysis were described in Nakamura and Hoel [11].

To assess the ability of estimating both $\log \Psi\_b$ and $\log \rho\_b$ simultaneously, the Full model was also dealt with. The values of the parameters for the model were the same as those for the Initiation model except for $\log \Psi\_b$, where we set $\log \Psi\_b < 0$ following the Portier's novel view. The dose level for the Initiation and Full models are 0, 50, 100, 250 and 500 with 100 cases each. Whereas, those for the Promotion model are 0, 1, 10 and 100 with 125 cases each.

2.2 Models for the Estimation of Parameters

Table 2 shows the models used for the estimation of parameters using the survival data generated as described in Sect. 2.1, namely Full initiation (FI), Initiation (I), Promotion (P), Semi complete (SC) and Complete (C) models. All estimation models include the three base parameters $\log \nu^*\_a$, $\log \beta^*\_a$, and $\log \mu_2^*\_a$.

The initiation effect $\log \nu^*\_b$ is included other than the P-model, the promotion effect $\log \beta^*\_b$ is included other than the two initiation models, and $\log \mu_2^*\_b$ is included in the FI and C models. Hereafter, FI-model, I-model, P-model, SC-model and C-model will be used to distinguish from the modes for the data generation.

Table 2. Models used for estimating parameter values

Model	$\log \nu^*\_b$	$\log \beta^*\_b$	$\log \mu_2^*\_b$
Full initiation (FI)	○	×	○
Initiation (I)	○	×	×
Promotion (P)	×	○	×
Semi complete (SC)	○	○	×
Complete (C)	○	○	○

2.3 Algorithm Searching for MLEs

We applied the Newton-Raphson iteration algorithm for searching for MLEs. The convergence criterion was to satisfy the following three conditions simultaneously:

(1) The norm of the score vector was less than 0.01.
(2) The main diagonal elements of I^{-1} are all positive, where I is the observed information matrix.
(3) The norm of the difference between the new and the old parameter vectors < 0.00001.

The MLEs of ρ and Ψ are obtained by transforming the MLEs of ν^*, β^*, and μ_2^* using (1). That is,

$$\begin{aligned} \log \Psi\_a &\approx \log \beta^*\_a \\ \log \Psi\_b &\approx \log \beta^*\_b \\ \log \rho\_a &= \log \nu^*\_a + \log \mu_2^*\_a \\ \log \rho\_b &= \log \nu^*\_b + \log \mu_2^*\_b \end{aligned} \tag{2}$$

where $\approx$ denotes an approximate equality. As described in Sect. 3, since $\mu_2^*\_b$ is about 1000 times smaller than ν^*_b or β^*_b, it is ignored in (2).

2.4 Model Selection Strategy

First, either I-model or P-model was selected according to AIC [1]. Then, either the selected model or SC-model was selected based on the likelihood ratio test.

3 Results and Discussion

Table 3 presents the average of MLE and the proportions of the selected models for each parameter. The average number of iterations until convergence is also shown. It turned out that $\mu_2^*\_b$ badly affected the convergence of the iterations. It was also found that $\mu_2^*\_b$ is about 1000 times smaller than ν^*_b or β^*_b, resulting in that $\log \mu_2^*\_b$ little affects the value of MLE of $\log \Psi$ and $\log \rho$. The fact accords with the findings in cell biology and has been generally observed [9].

Thereby, the results concerning FI-model and C-model were omitted in Table 3. Since ρ and Ψ are biologically interesting but η was not, the results on η was also omitted.

Non-convergence is frequent when either I-model or SF-model, both including the initiation effect $\log \rho\_b$, is applied to the Promotion model.

First, the results demonstrate that MLEs were approximately unbiased when the estimation model was the same as the true model.

The error rate of incorrectly selecting the P-model for the two Initiation models is only 2% (4 out of 200). In contrast, the error rate of incorrectly selecting the I-models for the Promotion model is 7%. As for the Full model, 30 out of 100 estimated $\log \Psi\_b = 0$. Nevertheless, regarding the ability to distinguish between the initiation and promotion effects, the error rate is 2% (2/100), since the 30 cases detect the initiation effects. In conclusion, the conditional-likelihood approach has high ability to distinguish between the two effects.

Table 3. Estimates of parameters

Initiation Model	$\log \Psi\_a$	$\log \Psi\_b$ ×100	$\log \rho\_a$	$\log \rho\_b$ ×100	Convergence Rate(%)	% Selection
True value	**−4.9**	–	**−17**	**0.42**		
I-model*	−4.86	–	−17.5	0.454	100	91
SC-model	−4.81	−0.022	−17.7	0.537	100	7
P-model	−5.13	0.129	−16.5	–	100	2

Full Model	$\log \Psi\_a$	$\log \Psi\_b$ ×100	$\log \rho\_a$	$\log \rho\_b$ ×100	Convergence Rate(%)	% Selection
True value	**−4.9**	**−0.1**	**−17**	**0.42**		
I-model	−5.07	–	−16.7	0.132	100	30
SC-model*	−4.85	−0.109	−17.5	0.478	100	68
P-model	−5.13	0.0385	−16.4	–	100	2

Promotion Model	$\log \Psi\_a$	$\log \Psi\_b$ ×100	$\log \rho\_a$	$\log \rho\_b$ ×100	Convergence Rate(%)	% Selection
True value	**−3.3**	**0.35**	**−35**	**–**		
I-model	−3.07	–	−36.9	8.16	78	7
SC-model	−3.27	−0.0812	−36.0	6.29	39	0
P-model*	−3.30	0.350	−35.2	–	100	93

* denotes the true models.

4 Concluding Remarks

We conclude that the conditional likelihood approach has a practically sufficient ability to distinguish between the initiation and promotion effects. This approach does not require any additional prerequisites, allowing a broader application of the TSCE model.

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References

1. Akaike, H.: Information theory and an extension of the maximum likelihood principle. Research Memo. No. 46, The Institute of Statistical Mathematics (1971)
2. Baker, G.S., Nakamura, T., Hoel, D.G.: Comparison of two models of cancer risk estimation: a statistical analysis. Eur. J. Oncol. **11**, 165–176 (2006)
3. Grahn, D., Lombard, L.S., Carnes, B.A.: The comparative tumorigenic effects of fission neutrons and cobalt-60 g rays in the B6CF1 mouse. Radiat. Res. **129**, 19–36 (1992)
4. Heidenreich, W.F., Brugmans, M.J.P., Little, M.P., Leenhouts, H.P., et al.: Analysis of lung tumour risk in radon-exposed rats: An intercomparison of multi-step modeling. Radiat. Environ. Biophys. **39**, 253–264 (2000)
5. Hornsby, C., Page, K.M., Tomlinson, I.P.: What can we learn from the population incidence of cancer? Armitage and Doll revisited. Lancet Oncol. **8**, 1030–1038 (2007)
6. Kociba, R.J., Keyes, D.G., Beyer, J.E., Carreon, R.M., et al.: Results of a two-year chronic toxicity and oncogenicity study of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in rats. Toxicol. Appl. Pharmacol. **46**(2), 279–303 (1978)
7. Kopp-Schneider, A., Portier, C.J., Sherman, C.D.: The exact formula for tumor incidence in the two-stage model. Risk Anal. **14**, 1079–1080 (1994)
8. Moolgavkar, S.H., Venzon, D.: Two-event models for carcinogenesis: curves for childhood and adult tumors. Math. Biosci. **47**, 55–77 (1979)
9. Moolgavkar, S.H.: Carcinogenesis modeling: from molecular biology to epidemiology. Ann. Rev. Public Health **7**, 151–169 (1986)
10. Nakamura, T., Hoel, D.G.: Comparing cancer risks between radiation and dioxin exposure based on two-stage model. Environmetrics **14**, 203–211 (2003)
11. Nakamura, T., Hoel, D.G.: Mathematical base for valid inference with two-stage clonal expansion model–conditional likelihood. International invited session. In: 26th International Biometrics Conference, Kobe (2012)
12. Nogami, S., Yoshida, Y., Nakamura, T.: On the reliability of maximum likelihood estimates in the two-Stage clonal expansion carcinogenesis model. In: By, E. (ed.) International Conference on Statistical Methods for Risk Analysis, pp. 43–44. Lutz, Lisbon (2007)
13. Portier, C., Masri, E.I.: Statistical research needs in mechanistic modeling for carcinogenic risk assessment. Stat. Methods Med. Res. **6**, 305–315 (1997)
14. Sherman, C.D., Portier, C.: Eyes closed: simple, intuitive, statistically sound, and efficient methods for estimating parameters of clonal growth cancer models. Risk Anal. **18**, 529–534 (1988)

15. Tessier, G.S., Lam, C.F., Nakamura, T., Hoel, D.G.: Two-stage models applied to gamma and neutron exposed mice. Eur. J. Oncol. **6**, 297–301 (2001)
16. Yoshida, Y., Sato, S., Nakamura, T.: Small sample performance of the two-stage carcinogenesis model, invited session. In: 56th World Statistical Congress, Risbon (2007)
17. Yoshida, Y., Sato, S., Takatsuji, T., Nakamura, T.: Statistical inference on two-stage clonal expansion model. In: ISI-ICRA3, Greece (2009)

Business Failure Prediction Models: A Bibliometric Analysis

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Abstract. The business failure prediction (BFP) research area is attracting renewed attention due to increasing complexity and uncertainty of modern markets, as witnessed by financial crisis in last decade. Since many predictive models have been developed using various analytical tools, it should be important to capture the development of the BFP models, underlying their limitations and strengths. Using the Web of Science database, the purpose of this paper is to investigate the evolution of the scientific studies in the field of BFP within a bibliometric analysis. The research production from 1990 to 2019 is analyzed, and the most relevant research products in the field are identified and classified by papers, authors, institutions and countries. Moreover, the most influential key-words are clustered according to similarity and visualized in a network. Finally, the social structure between countries and affiliations are investigated in order to capture the relationship between authors.

1 Introduction

The recent financial crisis showed the increasing vulnerability in complex business relations and brought evidence of the fragile financial stability of numerous firms. Hence, academics, practitioners and regulators focused on the development of business failure prediction (BFP) models that attempt to predict the financial distress.

Since the first BFP models appeared in the 1960s, many different techniques have been suggested and applied, such as univariate model [8], multiple discriminant analysis [3,14,16], logit and probit analysis [24,35], survival analysis [18,21,31], classification trees and artificial neural networks [30,34], and machine learning [17,19].

The literature on methodological issues associated with corporate failure prediction models is well-documented in a number of reviews [1,2,4,6,7,9,15,20,22,28,32,33]. In some of them, the authors have reviewed and classified a list of articles on the prediction of business failures according to some characteristics, such as country, industrial sector, time period, financial ratios and models/methods employed. Moreover, they have discussed the evolution of BFP studies, highlighting the main differences between different approaches implemented, also through a comparison in terms of accuracy performance [7,9,15,20,28,32]. In some others [1,2,4,22,33], the authors have underlined the trend and evolution of the

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methodological issues on the BFP by means of a systematic literature review performed using some bibliographic sources, such as Google Scholar[1], Web of Science (WoS)[2] or Business Source Complete (EBSCO)[3].

Starting with this background, our study contributes to the existing body of BFP literature through a study based on bibliometric analysis that provides a comprehensive overview of the research area under investigation. Indeed, a bibliometric analysis is the most suitable method for studying the conceptual and intellectual structures of a research area [12] and it allows to obtain an overview of the main thematic trends in the field. The time period under analysis ranges from 1990 to 2019. The information is collected from the Web of Science (WoS) database, actually the largest database in academic research. To cover our study we deal with two specific research hypotheses:

RH1 (*impulsive structure hypothesis*): The research area of BFP followed a peculiar trend characterized by endogenous (new methods and techniques) and exogenous facts, such as economic crises and emerging markets.

RH2 (*conceptual structure hypothesis*): The trend influenced the collaboration patterns among scholars in the field and it gave raise to emerging key-topics.

To pursue our goals, we elaborate a research design that is described in the Sect. 2. In Sect. 3, we provide the main results of the bibliometric analysis performed on the dataset extracted from WoS. In Sect. 4, discussion and future research directions are given.

2 Research Methodology

In this study, we perform a bibliometric analysis of the literature on statistical models for business failure prediction (BFP). Bibliometrics is a research field within library and information sciences that studies and classifies the bibliographic material by using quantitative methods [11,26]. Over the years, it has become very popular for assessing the state of the art of a scientific discipline, classifying bibliography and developing representative summaries of the leading results. A detailed analysis of the development of research could help to selectively appraise the different facets of the business failure prediction field and thus to create a better basic understanding of the topic and depict the current research scene.

The methodological framework to perform the bibliometric review can be divided into three essential phases: data collection, data analysis and data visualization.

In the data collection phase, after delimiting the research area and goals, we select the database that could provide the data for the analysis, define the criteria for searching and selecting articles, and create a data-frame to collect the selected

[1] https://www.scopus.com/home.uri.
[2] https://clarivate.com/webofsciencegroup/solutions/web-of-science/.
[3] https://www.ebsco.com/.

articles. Among all on-line academic databases, we opt for the "Web of Science". In particular, the search is performed on the *Web of Science Core Collection*, that has access to more than 21.000 journal and 1.5 billion cited references going back to 1900. The WoS Core Collection works within citation indexes that contain the references cited by the authors of the publications covered by different sources, such as journals, conference proceedings and books.

The topic under analysis consists of four terms: `Business`, `Failure`, `Prediction` and `Models`. To ensure that the research includes all the related terms, we consider four search strings using Boolean expressions. Moreover, we search all papers whose topics (i.e. title, publication, abstract, keywords, and research area) include at least a search term belonging to the four sets of search terms we select.

A search string that capture all these words is thus designed with the following query:
(`failure` OR `bankruptcy` OR `default` OR `insolvency` OR `distress`) AND (`predict*` OR `forecast*` OR `classif*`) AND (`statist*`) AND (`method` OR `model` OR `analysis` OR `technique`) AND (`busines*` OR `compan*` OR `firm*` OR `enterprise` OR `corporate` OR `bank*`).

The wildcard "*" is used to cover different occurrences of the terms, such "prediction" and "predicting" for the "predict*", and "classification" and "classifying" for the term "classif*". The condition "or" is used to take into account that some terms are considered as synonyms. For example, bankruptcy, insolvency, default, financial distress or failure are often synonyms for failure of firms and financial institutions. The condition "and" is used in order to join the different combinations of words.

We delimit our results using a combination of filtering criteria, as shown in Fig. 1. By querying the Web of Science database in the period between 1990 and 2019, we initially find out 991 papers.

The refinement by language (only English), document type (only journal articles), WoS index and categories and source title is done to improve the search quality. For the Web of Science categories, since the topic of business failure prediction is multidisciplinary, we collect articles from different research areas, such as Operations research, Management science, Computer Science, Economics, Management, Business finance, Statistics, Probability, Mathematics interdisciplinary applications, Social sciences mathematical methods. At the end, a set of 497 papers is obtained for our bibliometric analysis.

For the data analysis phase, we use an open-source R package, called Bibliometrix able to perform comprehensive bibliometric analysis [5]. Data analysis entails descriptive analysis and co-occurrence or coupling data extraction. Different kinds of co-occurrence data can be extracted using different units of analysis (such as authors, documents, keywords, words, and so on). In our study, we analyze the keywords, the countries and the authors' affiliations. For the keywords we study the conceptual structure of the research field under investigation, identifying the most influential keywords. For the countries and affiliations we study the intellectual structure in terms of collaboration networks. Finally, a multiple

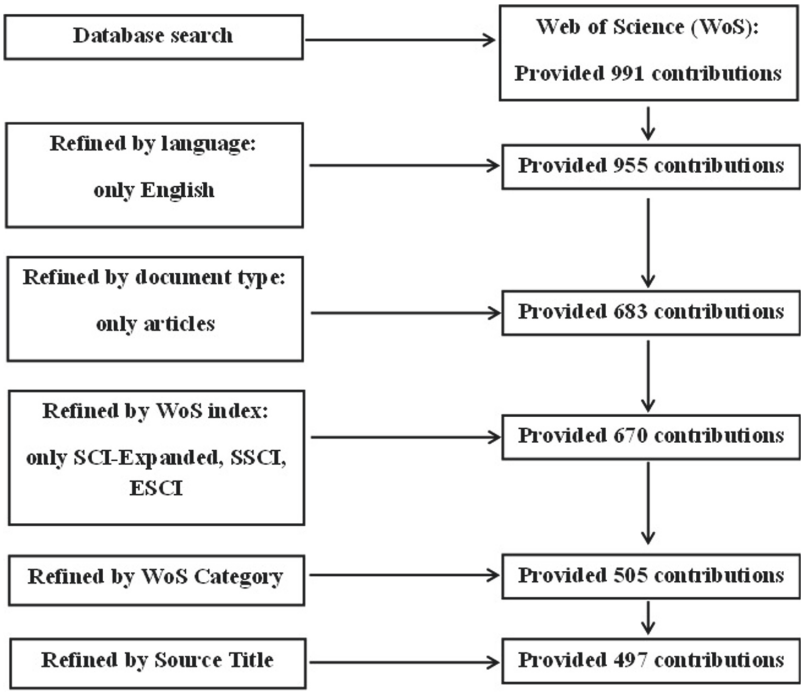


Fig. 1. Filtering process applied for delimiting literature

correspondence analysis and a cluster analysis are performed in order to identify homogeneous profiles and sub-structures.

The visualization phase aims at representing the useful knowledge extracted from the data through bi-dimensional maps, dendrograms, and social networks.

3 Main Results

In Sect. 3.1 we firstly report the main results for the *impulsive structure* research hypothesis **RH1** by focusing on the topics trends in BFP research area. In order to analyze the evolution of these topics by means of bibliometric analysis, we extract some information related to the most influential journals, the most productive countries in terms of number of papers published, corresponding authors and total citations. Then, in Sect. 3.2 we deal with the *conceptual structure* research hypothesis **RH2**, reading the co-occurrences matrices as relational data structures in terms of networks showing the links among authors, topics and countries.

3.1 Trends in the Business Failure Prediction Field

The main information on the dataset extracted from WoS and used for the bibliometric analysis are summarized in Table 1. In particular, the collection

size in terms of number of documents, number of authors, number of sources, number of keywords, timespan, and average number of citations are reported. Furthermore, many different co-authorship indices are shown. In particular, the *Authors per Document index* is calculated as the ratio between the total number of documents and the total number of authors. The *Co-Authors per Documents index* is calculated as the average number of co-authors per document. The index takes into account the author appearances, while for the *Authors per Document* an author is counted only once, even if he/she has published more than one article. The *Collaboration Index* (CI) is calculated as Total Authors of Multi-Authored Documents over Total Multi-Authored Documents. In other word, the Collaboration Index is a Co-authors per Document index calculated only using the multi-authored document set. In our case, 1378 authors write a total number of 497 articles. Collaboration is the key amongst authors whereby only 72 documents are single authored.

The growth trend of scientific content in the field of BFP models is shown in Fig. 2. It can be noted that after the financial crisis in 2008 the number of papers that analyzed the phenomenon of business failure is increased. Moreover, 14% of the papers is published on this topic before 2004, while 12% and 25% are between 2005 and 2008 and between 2009 and 2012 respectively, while the remaining 49% is appeared after 2012. Moreover, the growth rate of the annual scientific production is equal to 15.14%. Furthermore, looking at the average article citations per year, we report that some articles published in 2001 and 2008 are collecting the highest number of average total citations per year, respectively equal to 6.8 and 7.1.

Table 1. Main facts and figures of the BFM database

Description	Results
Documents	497
Sources (Journals, Books, etc.)	240
Keywords Plus (ID)	855
Author's Keywords (DE)	1455
Period	1990–2019
Average citations per documents	25.81
Authors	1142
Author Appearances	1378
Authors of single-authored documents	72
Authors of multi-authored documents	1070
Single-authored documents	81
Documents per Author	0.435
Authors per Document	2.3
Co-Authors per Documents	2.77
Collaboration Index	2.57

Looking at the impact of the 10 top sources (i.e. journals) (Table 2), we can observe that the *Expert Systems with Applications* has a significant contribution to the publication of papers on the BFP and, compared to other journals, it is highly specialized in the subject of business failure. It is followed by the *European Journal of Operational Research*, the *Journal of Banking & Finance*, and the *Journal of the Operational Research Society* in terms of number of documents, H-index and g-index. Instead, looking at the m-index, the top journals are the *Expert Systems with Applications*, the *Applied Soft Computing*, the *European*

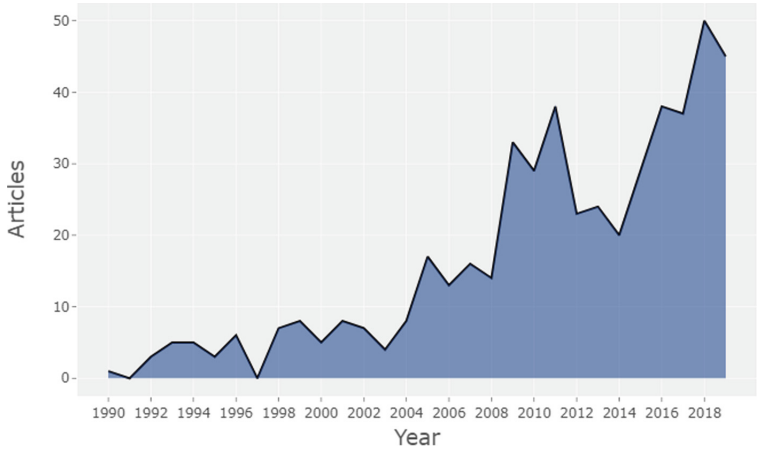


Fig. 2. The WoS publications on business failure prediction models between 1990 and 2019

Table 2. Most influential accounting research journals according to the WoS

Source	TP	H-index	g-index	m-index	TC	PY
Expert Systems with Applications	64	30	54	1.2000	3022	1995
European Journal of Operational Research	26	16	26	0.5333	1068	1990
Journal of Banking & Finance	13	8	13	0.3077	636	1994
Journal of the Operational Research Society	11	7	11	0.3333	185	1999
Knowledge-Based Systems	9	9	9	0.4737	440	2001
Decision Sciences	7	7	7	0.2500	274	1992
African Journal of Business Management	6	2	4	0.2000	16	2010
Applied Soft Computing	6	6	6	0.5454	241	2009
Expert Systems	6	4	6	0.3333	85	2008
Journal of Forecasting	6	5	6	0.4545	132	2009
Decision Support Systems	5	5	5	0.1923	507	1994
Quantitative Finance	5	3	4	0.3333	23	2011
Computational Economics	4	2	4	0.2857	20	2013
Computers & Operations Research	4	4	4	0.2105	151	2001
Economic Modelling	4	3	4	0.3333	66	2011

TP = total papers; TC = Total Citations; PY = year when the journal was included in WoS; $H-$index is the Hirsch index that is an author's (or journal's) number of published articles each of which has been cited in other papers at least h time; $m-$index is defined as H over n, where H is the $H-$index and n is the number of years since the first published paper of the scientist (journal); $g-$index measures the global citation performance of a set of articles.

Journal of Operational Research, the *Knowledge-Based Systems* and the *Journal of Forecasting*. Finally, the highest values of the total citations are observed again for the *Expert Systems with Applications*, the *European Journal of Operational Research*, *the Journal of Banking & Finance* and the *Decision Support Systems*.

Analyzing the trend of content related to the BFP and the dynamics of the top 5 journals (Fig. 3), we can reveal that the *Expert Systems with Applications* has a significant contribution to the spread of papers on the BFP and compared to other journals, it becomes specialized in the subject under analysis after 2005, followed by the *European Journal of the Operational Research Society*.

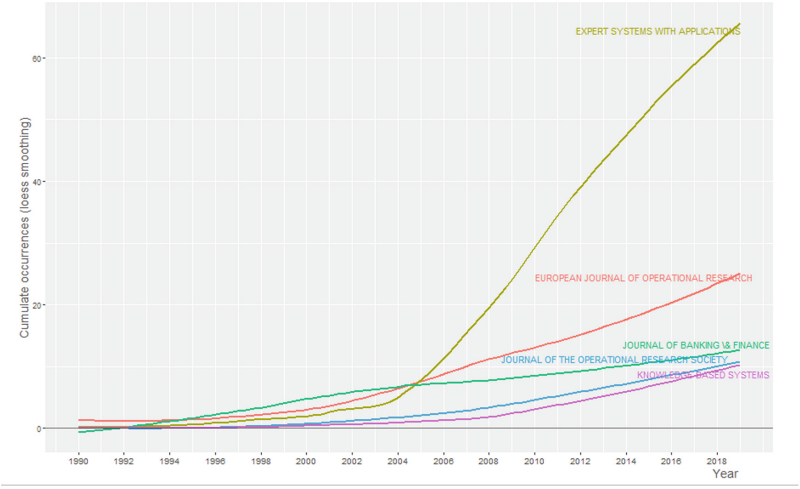


Fig. 3. Trend of content related to the subject at the first 5 scientific journals

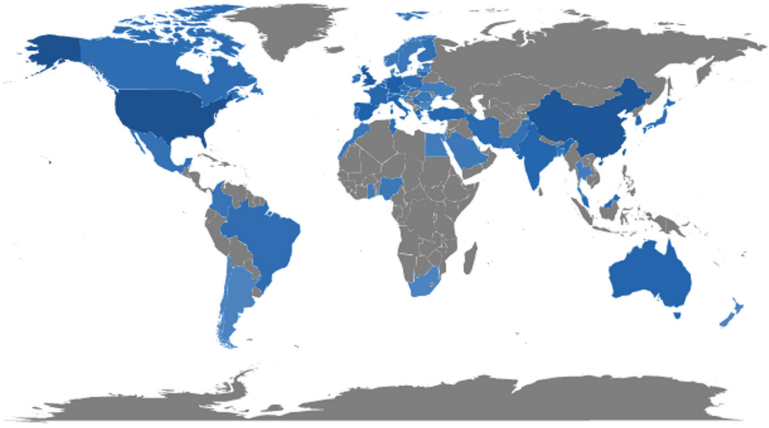


Fig. 4. Country scientific production on map

Instead, the *Journal of Banking & Finance* has been a relevant journal until 2004, becoming less specialized in the topic after 2005.

The top countries' scientific production is shown in Fig. 4, where the color intensity is proportional to the number of publications. Thus, it is possible to learn more about the contribution of different countries in BFP research area.

Table 3 shows the corresponding author's country, underlining how the authors have been collaborating in one country, or different countries. In particular, it illustrates the authors collaboration from different countries on this topic. MCP ratio means *Multiple Country Publications* and measures the international collaboration intensity for a country. The highest international collaboration is for China and Greece, followed by USA. The lowest international collaboration, for countries with a relevant number of publications, is for Taiwan, followed by Australia and India.

Table 3. The top 10 corresponding author's countries

Country	Articles	Freq	SCP	MCP	MCP Ratio
USA	85	0.1728	60	25	0.294
China	59	0.1199	38	21	0.356
United Kingdom	45	0.0915	32	13	0.289
Taiwan	42	0.0854	42	0	0.000
Spain	25	0.0508	19	6	0.240
Australia	16	0.0325	13	3	0.188
India	16	0.0325	13	3	0.188
Greece	14	0.0285	9	5	0.357
Italy	14	0.0285	11	3	0.214
Germany	13	0.0264	10	3	0.231

SCP = Single country publications; MCP = Multiple country publications, that indicates for each country the number of documents in which there is at least one co-author from a different country.

In Table 4 the 10 main countries ordered by total citations are displayed. The average number of citations per article is 15.87 for all countries. The study of the countries influencing the research are on BFP shows that USA is the leader in this field, followed by Taiwan, China, Korea and United Kingdom. In fact, USA, Taiwan and China, with more articles published and total citations, have an average article citation equal to 39.49, 39.9 and 19.17, respectively. Moreover, the results show that leading countries cover more than 60% of the total number of references. In terms of average citation, papers published by researchers in Hong Kong and Korea have maintained the highest citations. In spite of the fact that Korea is the fourth country in terms of published articles, it has the highest average citations per article among the leading countries in total citations.

Table 4. The top 10 total citations per country

Country	Total Citations	Average article citations
USA	3357	39.49
Taiwan	1676	39.90
China	1131	19.17
Korea	845	76.82
United Kingdom	804	17.87
Greece	548	39.14
Italy	537	38.36
Spain	408	16.32
Turkey	399	33.25
India	281	17.56

Collaboration among various countries is shown in Fig. 5. As we can observe from the results, there were strong collaborations from the researchers in USA from one side and other countries such as United Kingdom, Taiwan, Singapore, Canada, Australia. Another strong collaboration is from the researchers in China and other countries such as USA, United Kingdom, India, Bangladesh, Australia. Another relevant collaboration is between UK/Belgium, and Brazil/Italy.

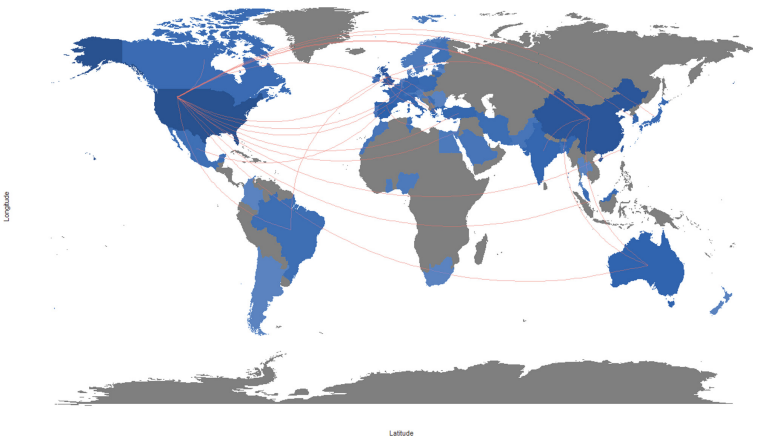
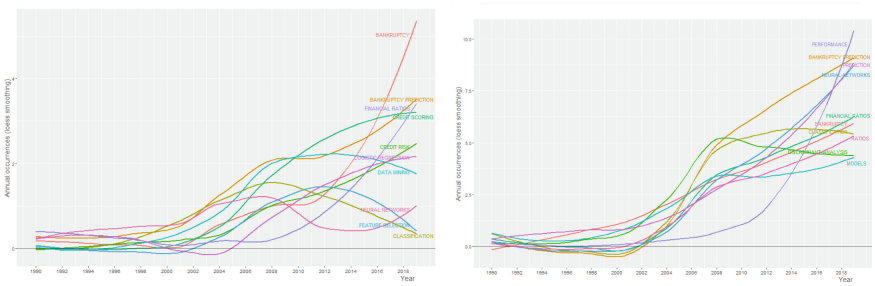


Fig. 5. World Map Collaboration (social structure)

Finally, Fig. 6 shows the ten most used keywords in the BFP articles. Web of Sciences provides two types of keywords: Author Keywords, which are those provided by the original authors (Fig. 6a); and Keywords-Plus, which are those extracted from the titles of the cited references by Thomson Reuters (Fig. 6b). Keywords Plus are automatically generated by a computer algorithm.

The most used author keywords are *bankruptcy prediction* (42), *credit scoring* (37), *bankruptcy* (32), followed by *credit risk*(23), *logistic regression* (23), *financial ratios* (22) and *classification* (21). Looking at the keywords plus, we can see that *bankruptcy prediction* and *prediction* are the most popular (93 and 82, respectively). Moreover, it is very interesting to observe that *bankruptcy prediction* is becoming a common keywords after 2008, while *discriminant analysis* and *classification* are less popular after the crisis. Then, in 2011 *performance* has increased its appearance and in 2018 the increase has overcome by other common keywords.



(a) Authors' keywords (b) Keywords-plus

Fig. 6. The evolution of the top 10 keywords

Drawing some preliminary conclusions, we can distinguish two main periods, divided by the financial crisis in 2008. It is particularly evident that the production and publication of BFP papers are increased at the turn of 2008. Also the most used keywords changed. In fact in the first period the papers were focused on the classification models (i.e. discriminant analysis) and data mining, while in the second period the main interest is on bankruptcy prediction, with a particular attention on financial ratios, on the evaluation of performance and on neural networks. In-depth analysis of the themes emerging from the keywords co-occurrences is provided in the next sub-section where we deal with the conceptual structure of the BFM field.

3.2 Conceptual Structures and Networks

The following analysis aims at capturing the conceptual structure of the research field considering the relations among emerging topics. We consider the co-occurrences between authors' keywords. These keywords represent a subset of the most cited keywords in the papers. Higher weights can be related either to high co-occurrence between different words or high occurrence of each keyword. The Bibliometrics data matrices can be analyzed through classical factorial techniques based on the eigen-decomposition of suitable squared symmetric matrices derived from the original rectangular ones (whose dimensions can be

related to several modes extracted from the database, such as keywords, documents, authors, first author's country, etc.). For instance, starting from the two-mode rectangular matrix *documents per keywords*, each column is binary coded (presence–absence of a keyword in a document) and a Multiple Correspondence Analysis (MCA) for all those keywords whose column sum is greater than a specific threshold (say 5) is produced.

In particular, we carry out the MCA on the BFP bibliometric database to identify groups of keywords with similar profiles of co-occurrences (Fig. 7a). Looking at the first axis, the interpretation of the factorial axes underlines a comparison between the keywords that characterize the use and application of so-called "traditional" statistical models and techniques in scientific documents where the main topic is the forecasting of bankruptcy (close to the origin of the plane) and the keywords that characterize the use and application of so-called "innovative" techniques, that are represented by neural networks, artificial intelligence, classification trees, genetic algorithms, till to the support vector machines (on the right). Interpreting the second factorial axis, moving towards the top side we find a different paradigm that calls for distress prediction models and the case-based reasoning approach applied to business failure.

Based on the results of MCA, a cluster analysis is consistently performed in order to recognize homogeneous groups of words. In our case, we identify five groups (Fig. 7b). The group with the higher number of "similar" words is characterized by the "traditional" statistical models and techniques (discriminant analysis, logistic regression) applied for predicting the default. A second group is identified by the "innovative" methods (artificial intelligence, neural networks, classification tree). A third group is represented by the algorithms used for selecting the set of features (genetic algorithm). The last three groups are less dense and more specific, and they are characterized by case-based reasoning models, support vector machine and generic business failure models, respectively.

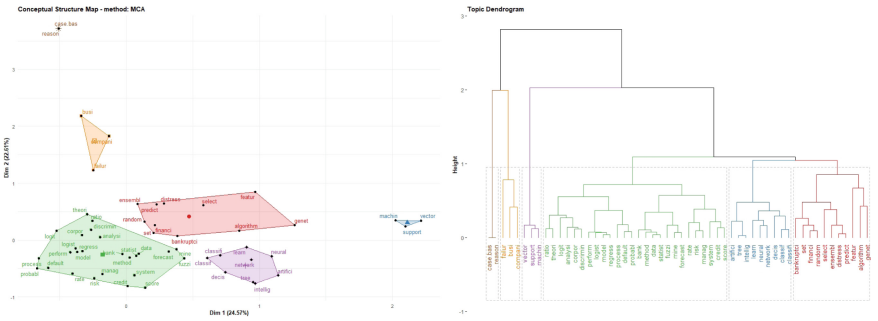


Fig. 7. Conceptual map of MCA and Dendrogram based on keywords-plus

The same data structure used for the factorial technique is then used for a network analysis strategy. Here, the rectangular matrix is seen as an affiliation

matrix that describes a two-mode network, that is a network with two sets of nodes (here *documents and keywords*). Two-mode networks are useful to derive one-mode networks by inner or outer projection (matrix product). For instance, let **X** be the documents × keywords matrix and denote with **X'** its transpose. We can obtain the adjacency matrix (documents × documents) as **XX'** that establish a correspondence between documents that share the same keywords. At our interest we focus on the keywords × keywords adjacency matrix obtained as **X'X**. The diagonal entries hold the occurrence of each keyword, the off-diagonal cells hold the desired co-occurrences between any pairs of keywords. Also in this case a threshold value should be fixed to avoid trivial relationships. In our study we select a quite high threshold (equal to 7), in order to visualize the core themes emerging from the analysis.

The resulting adjacency matrix can be represented as a network graph where each vertex is a word, the vertex size is proportional to the item occurrences (diagonal elements), and the edge size is proportional to the items co-occurrence (non-diagonal elements). The network representing the co-occurrence matrix focuses on understanding the knowledge structure of the scientific field by examining the links between keywords. If the keywords are grouped in small dense part of the graph, they are more likely to reflect a specific topic. According to the definition of community in a strong sense, each node should have more connections within the community than with the rest of the graph [27]. Different algorithms for community detection in networks can be used. Some famous ones are Louvain [10], Walktrap [25], Fastgreedy [13], Leading Eigenvector [23] and Infomap [29]. In our study we use the Louvain algorithm applied to the subset of the 30 most connected keywords. The results are showed in Fig. 8. Looking at the colors it is possible to identify the cluster to which each word belongs.

We may distinguish words related to the traditional and innovative models used for the credit risk. A second group consists of algorithm applicable for feature selection for the failure prediction. In the red group, there are the opposition between traditional methods (logistic and principal component analysis) and innovative techniques (support vector machine). In the blue group there are some keywords related to the macro-area of the business failure and financial crisis.

Finally, we study the social structure that show how authors or institutions relate to others in the field of scientific research, by using the co-authorship network. With these networks, groups of regular authors, influent authors, hidden communities of authors, relevant institutions, etc. can be discovered. Figure 9 shows the social structure between countries and affiliations. Firstly, some countries are isolate and have no connection with the others. Moreover, Latvia, Lithuania, and Sweden are connected with themselves, but they do not have any connections with others. The countries with the higher number of connections are USA, UK, and China.

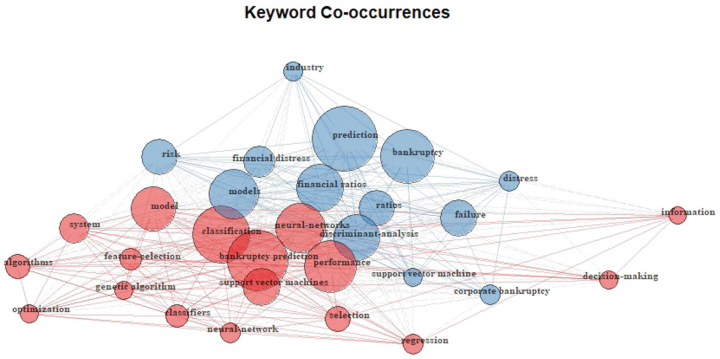
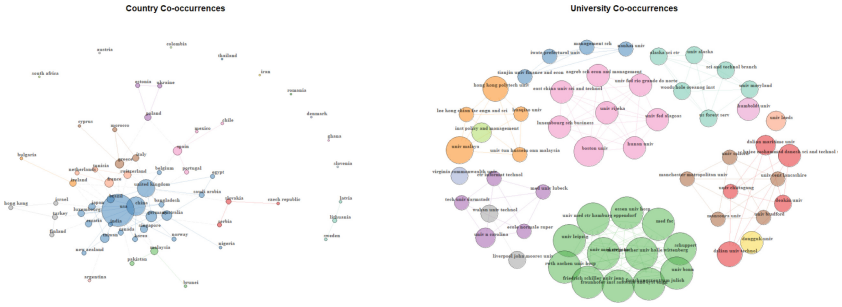


Fig. 8. Network of co-occurrence based on the authors' keywords



(a) Country network (b) University network

Fig. 9. Collaboration network

4 Conclusions and Discussion

This paper aimed to use the bibliometric and social network analysis to create a useful, structured portrayal of the business failure prediction (BFP) research area and to achieve deeper insight into relationships between authors and countries. Moreover, by taking key documents into account, a better understanding was achieved of the structure of citations and co-citations in the context under analysis. Multiple correspondence analysis and cluster analysis enabled to take into consideration the most influential and important keywords, as well as to illustrate the evolution and trend of the most used words in research disciplines related to the BFP by identifying some homogeneous groups. The information for the bibliometric analysis have been downloaded by Web of Science database and covered the period between 1990 and 2019. Two main research questions have been investigated. The first one, *impulsive structure hypothesis*, was focused on identifying a peculiar trend characterized by endogenous (new methods and techniques) and exogenous facts, such as economic crises and emerging markets.

The second research hypothesis, *conceptual structure hypothesis*, aimed at analyzing the collaboration patterns among scholars in the field and the emerging key-topics.

The main results of *impulsive structure* analysis have shown how the number of papers that analyzed the phenomenon of business failure is increased after the financial crisis in 2008. Moreover, it is possible to distinguish an increasing trend. In fact, 14% of the papers on the topic under investigation was published before 2004, while 12% and 25% were produced between 2005 and 2008 and between 2009 and 2012 respectively. Finally, the remaining 49% was appeared after 2012. Moreover, the growth rate of the annual scientific production was equal to 15.14%. Furthermore, looking at the average article citations per year, some articles published in 2001 and 2008 were collecting the highest number of average total citations per year, respectively equal to 6.8 and 7.1. Looking at the international collaboration, the results have shown that the highest international collaboration was in China and Greece, followed by USA, while the lowest international collaboration, for countries with a relevant number of publications, was observed for Taiwan, followed by Australia and India. Then, analyzing the most used keywords, it was very interesting to observe that *bankruptcy prediction* was becoming a common keywords after 2008, while *discriminant analysis* and *classification* were less popular after the crisis. Then, in 2011 *performance* has increased its appearance and in 2018 the increase had overcome by the other common keywords.

The main results of Multiple Correspondence Analysis based on the keywords to identify a *conceptual structure* have revealed that it was observable a clear comparison between the "traditional" statistical models (i.e. discriminant analysis) and "innovative" techniques (i.e. neural networks, artificial intelligence, classification trees, genetic algorithms, support vector machines). Moreover, it was possible to create some homogeneous groups, confirming the results of Multiple Correspondence Analysis. In particular, the group with the higher number of "similar" words was characterized by the "traditional" statistical models and techniques (discriminant analysis, logistic regression) applied for predicting the default. A second group was identified by the "innovative" methods (artificial intelligence, neural networks, classification tree). A third group was represented by the algorithms used for selecting the set of features (genetic algorithm). The last three groups were less dense and more specific, and they were characterized by case-based reasoning models, support vector machine and generic business failure models, respectively.

As future research proposal, a deeper investigation of the information downloaded from the Web of Science is desirable, such as the words in the papers, the most influential references and authors. Moreover, an intra-period analysis should be performed in order to capture the differences that characterize the pre-crisis and post-crisis periods. Finally, it should be interesting to catch potential connections to other research disciplines, by changing the research criteria to enlarge the set of the papers.

References

1. Alaka, H.A., Oyedel, L.O., Owolabi, H.A., Ajayi, S.O., Bilal, M., Akinade, O.O.: Methodological approach of construction business failure prediction studies: a review. Constr. Manag. Econ. **34**(11), 808–842 (2016)
2. Alaka, H.A., et al.: Systematic review of bankruptcy prediction models: towards a framework for tool selection. Expert Syst. Appl. **94**, 164–184 (2018)
3. Altman, E.I.: Financial ratios. Discriminant analysis and the prediction of corportare bankruptcy. J. Finan. **23**(4), 589–609 (1968)
4. Appiah, K.O., Chizema, A., Arthur, J.: Predicting corporate failure: a systematic literature review of methodological issues. Int. J. Law Manag. **57**(5), 461–485 (2015)
5. Aria, M., Cuccurullo, C.: Bibliometrix: an R-tool for comprehensive science mapping analysis. J. Informetr **11**, 959–975 (2017)
6. Aziz, M.A., Dar, H.A.: Predicting corporate bankruptcy: where we stand? Corp. Gov. **6**(1), 18–33 (2006)
7. Balcaen, S., Ooghe, H.: 35 years of studies on business failure: an overview of the classic statistical methodologies and their related problems. Br. Account. Rev. **38**, 63–93 (2006)
8. Beaver, W.H.: Financial ratios as predictors of failure. J. Acc. Res. **4**, 71–111 (1966)
9. Bellovary, J., Giacomino, D., Akers, M.: A review of bankruptcy prediction studies: 1930 to present. J. Financ. Educ. **33**, 1–42 (2007)
10. Blondel, V.D., Guillaume, J.-L., Lambiotte, R., Lefebvre, E.: Fast unfolding of communities in large networks. J. Stat. Mech. Theor. Exp. **10** (2008)
11. Broadus, R.N.: Toward a definition of bibliometrics. Scientometrics **12**, 373–379 (1987)
12. Castriotta, M., Loi, M., Marku, E., Naitana, L.: What's in a name? Exploring the conceptual structure of emerging organizations. Scientometrics **118**, 407–437 (2019)
13. Clauset, A., Newman, M.E.J., Moore, C.: Finding community structure in very large networks. Phys. Rev. E **6** (2004). arXiv:cond-mat/0408187v2 [cond-mat.stat-mech]
14. Deakin, E.B.: A discriminant analysis of predictors of business failure. J. Account. Res. **10**(1), 167–179 (1972)
15. Dimitras, A.I., Zanakis, S.H., Zopounidis, C.: A survey of business failures with an emphasis on prediction methods and industrial applications. Eur. J. Oper. Res. **90**(3), 487–513 (1996)
16. Edmister, R.O.: An empirical test of financial ratio analysis for small business failure prediction. J. Financ. Quantit. Anal. **7**(2), 1477–493 (1972)
17. Härdle, W., Lee, Y., Schafer, D., Yeh, Y.: Variable selection and oversampling in the use of smooth support vector machines for predicting the default risk of companies. J. Forecast. **28**(6), 512–534 (2009)
18. Lane, W., Looney, S., Wansley, J.: An application of the Cox proportional hazards model to bank failure. J. Bank. Finan. **10**, 511–531 (1986)
19. Lensberg, T., Eilifsen, A., McKee, T.E.: Bankruptcy theory development and classification via genetic programming. Eur. J. Oper. Res. **169**(2), 677–697 (2006)
20. Levratto, N.: From failure to corporate bankruptcy: a review. J. Innov. Entrepreneurship, 2–20 (2013)
21. Luoma, M., Laitinen, E.: Survival analysis as a tool for company failure prediction. Omega **19**(6), 673–678 (1991)

22. Merigó, J.M., Yang, J.-B.: Accounting research: a bibliometric analysis. Aust. Account. Rev. **27**, 71–100 (2017)
23. Newman, M.E.J.: Finding community structure in networks using the eigenvectors of matrices. Phys. Rev. E **74**, 3 (2006)
24. Ohlson, J.: Financial ratios and the probabilistic prediction of bankruptcy. J. Account. Res. **18**(1), 109–131 (1980)
25. Pons, P., Latapy, M.: Computing communities in large networks using random walks. arXiv:physics/0512106 [physics.soc-ph] (2005)
26. Pritchard, A.: Statistical bibliography or bibliometrics? J. Doc. **25**, 348–349 (1969)
27. Radicchi, F., Castellano, C., Cecconi, F., Loreto, V., Parisi, D.: Defining and identifying communities in networks. Proc. Natl. Acad. Sci. **101**, 2658–2663 (2004)
28. Ravi, P., Ravi, K.V.: Bankruptcy prediction in banks and firms via statistical and intelligent - a review. Eur. J. Oper. Res. **180**(1), 1–28 (2007)
29. Rosvall, M., Bergstrom, C.T.: Maps of random walks on complex networks reveal community structure. PNAS **105**(4), 1118–1123 (2008)
30. Serrano, C.: Feedforward neural networks in the classification of financial information. Eur. J. Financ. **3**(3), 183–202 (1997)
31. Shumway, T.: Forecasting bankruptcy more accurately: a simple hazard model. J. Bus. **74**, 101–124 (2001)
32. Sun, J., Li, H., Huang, Q.-H., He, K.Y.: Predicting financial distress and corporate failure: a review from the state-of-the-art definitions, modeling, sampling, and featuring approaches. Knowl. Based Syst. **57**, 41–56 (2014)
33. Tunger, D., Eulerich, M.: Bibliometric analysis of corporate governance research in German-speaking countries: applying bibliometrics to business research using a custom-made database. Scientometrics **117**(3), 2041–2059 (2018)
34. Wilson, R.L., Sharda, R.: Bankruptcy prediction using neural networks. Decis. Support Syst. **11**(5), 545–557 (1994)
35. Zmijewski, M.E.: Methodological issues related to the estimation of financial distress prediction models. J. Account. Res. **22**, 59–82 (1984)

Use of Previously Published Data in Statistical Estimation

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Abstract. Traditionally, researchers collect and analyze their own data, or use published results to perform meta-analysis. However, they rarely combine the experimental data with already published findings, which is a more efficient and cost effective approach for experimental planning and data analysis. In this work, we present two methods on the use of previously published data. One method targets variance minimization and another minimizes mean squared error (MSE). Bayesian approaches to prior information are not considered in this work. Variance minimization is designed to work in a class of unbiased estimators, where both (1) the estimators based on experimental data and (2) the estimators available as additional information (previously published results) are unbiased. MSE minimization relaxes the unbiasedness assumption on additional information and assumes that bias may be present. The use of these methods is illustrated for the analysis of association between gestational age at birth and third grade academic performance.

Keywords: additional information · variance minimization · association between gestational age and academic performance · mean squared error · asymptotic bias

1 Introduction

While working on their research questions about a quantity of interest θ, scientists usually collect and analyze their own data. In this scenario, researchers deal with a single data set, and the quality of data analysis is often limited by its sample size. Often, this limitation is expressed by the Cramer-Rao lower boundary on variance of estimators of θ.

There is only one way to overcome this limitation for a single data set: the use of additional information. Additional information can come from experts, or from external data sources other than the originally collected data. Additional information can be combined with a given data set using Bayesian methodology [3,6], but Bayesian approaches are not considered in this manuscript.

In this work, two approaches are presented which combine previously published results with a researcher's new data. We show how these approaches for

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the use of additional information apply to the analysis of association between gestational age and third grade academic performance on a standardized reading test. A previous publication that analyzes a similar research question serves as the additional information.

Section 2 introduces the motivating example of association between gestational age and academic performance. Section 3 describes statistical methods on the use of additional information and investigates their large sample properties. In Sect. 4, the narrative returns to the motivating example to estimate the association between gestational age and academic progress incorporating previously published results on association. An R implementation for the use of additional information with an R package located at https://github.com/starima74/AddInf is described in the Appendix. A short summary in Sect. 5 concludes the manuscript.

2 Association Between Gestational Age at Birth and Third Grade Academic Performance

The association between gestational age and academic performance has long been established [1,2]. On average, children born prematurely under-perform in academic performance as compared to full-term birth children. In this article, the full-term birth group are children born with gestational age of 37 to 41 weeks. Moreover, even within the full-term group, the students who were born at 37 weeks have lower standardized academic scores than those who were born at 38, and even more so for those who were born 39:41 weeks [7].

2.1 Previously Published Findings on New York City

Specifically, [7] analyzed a large cohort of 128,050 full-term births to mothers residing in New York City from 1988 to 1992 that linked their gestational age to third grade mathematics and reading standardized scores. Both reading and mathematics scores had means equal to 50 and standard deviations equal to 10. Here, we focus on the reading scores only.

Table 1. Means and SEs of Standard Scores by gestational age (weeks).

Test	37	38	39	40	41	39 : 41
Reading	50.34(.093)	50.69(.060)	50.98(.050)	51.12(.050)	51.18(.065)	51.08(.031)

Table 1 reports means and standard errors of the scores extracted from Figures 1 and 2 of [7], separately for each gestational week of birth. In addition, Table 1 also reports weighted averaged scores and weighted standard error (SE) for weeks 39 : 41 using inverse variance weighting [5]. This weighted estimator secures the smallest variance in the class of linear combinations of mean calculated separately for children born with gestational age (GA) of 39, 40 and 41

weeks. As shown in [5], the difference in standardized scores between weeks 39, 40 and 41 is very small, at most 0.2. These very small differences are practically irrelevant and statistically non-significant (the smallest P-value for pairwise comparisons was 0.025, see Table 2 in [5]). This justifies the use of the aggregated average for 39 : 41 weeks instead if separate analysis of 39, 40, and 41 week scores.

Using data in Table 1, we can calculate differences in academic performance scores between early full-term births (weeks 37 and 38) and weeks 39 : 41. These mean differences and their standard errors are reported in Table 2.

Table 2. Mean differences (SEs) of Standard Scores by gestational age.

Test	Week (I)	Week (J)	Mean Difference (I-J)	SE	P
Reading	37	39 : 41	−0.74	0.098	< 0.0001
Reading	38	39 : 41	−0.39	0.068	< 0.0001

The authors [7] concluded that "Children born at 37 and 38 weeks gestation score significantly lower on reading and math achievement tests than children born at every other week." Further, in their adjusted analyses, they showed that the effect of gestational age continues to be significant. In the three separate regression models controlling for obstetric-level, individual-level, and community-level characteristics, respectively, gestational age was significant.

2.2 Data on Milwaukee Public Schools

To investigate the association between gestational age and standardized mathematics and reading scores among third grade students, Milwaukee Public Schools reading and mathematics test results, 2010 to 2015, were linked with students' birth certificate data from Milwaukee county. This population and time range is different from the New York City study, which creates a new research question: whether the association between gestational age and academic performance continues to exist in Milwaukee?

A technical report [9] analyzed 47,925 third grade test scores from 122 Milwaukee Public Schools. To make the test scores comparable to the New York City study, third grade reading RIT scores [12] were converted to a standardized version with a mean of 50 and a standard deviation (SD) of 10. For students of 37 weeks GA the mean reading score was lower than 39 : 41 week GA students by 0.95 ($SE = 0.277, p < 0.0001$), whereas the score reduction for students 38 week GA was 0.374 ($SE = 0.191, p = 0.0502$)).

After controlling for the effects of gender, weight at birth, testing period (Fall, Winter, or Spring), student race, mother's prenatal cigarette use, enrollment in special education services, indicator of English learner as a second language, school attendance, clustering by school, the reading score for those who were

born at 37 weeks GA was higher by 0.173 ($SE = 0.215, p = 0.4218$) when compared to those who were born at 39 : 41 weeks. Similarly, for those who were born at 38 weeks the adjusted increase in the reading score was equal to 0.116 ($SE = 0.167, p = 0.4905$).

2.3 The Use of Both Data Sources

What the two separate data sources tell us is that the results of unadjusted analyses are consistent between Milwaukee and New York City studies, whereas the adjusted analyses do not coincide. This can be explained by different statistical models and different sets of control variables used by the two studies.

Since unadjusted results are consistent between the two studies, it can be assumed that the unadjusted difference of standardized reading scores is approximately the same, or, if different, the difference is relatively small. This creates an opportunity to combine both studies together to get a more precise estimate of the effect of 37 or 38 week gestational age on third grade reading. Taking into account that both Milwaukee and New York City studies used mutually independent data sources, inverse variance weighting [5] can be used again. The combined difference from both data sources in standardized reading scores between students of 37 and 39 : 41 week(s) GA is -0.763 ($SE = 0.092, p < 0.0001$), and the difference between students of 38 and 39 : 41 week(s) GA is -0.388 ($SE = 0.064, p < 0.0001$). This example clearly shows that the use of additional information improved the estimates (SEs are smaller) and even reversed one of the findings: the P-value for the 38 and 39 : 41 weeks difference was not significant when only Milwaukee data were used and became highly significant when both data sources were combined for the estimation.

The use of New York City data for the analysis of adjusted association requires more complex methods than inverse variance weighting. These methods are presented in Sect. 3.

3 Methodology

Let $\mathbf{X} = (X_1, \ldots, X_n)$ be a random sample of independent and identically distributed random variables with a probability density or measure function $f_X(x)$. The parameter of interest is θ, which is not the only population parameter estimable on $\mathbf{X}$. Potentially relevant additional information can come from an external data source, such as a previously published manuscript which used a similar data source. We consider additional information reported by an estimate of η, $\tilde{\eta}$, and its covariance matrix, $cov(\hat{\eta})$. The estimate $\tilde{\eta}$ is an estimate of a different population parameter η estimable on $\mathbf{X}$. It is expected that this additional information is relevant to the estimation of θ. In this manuscript, the relevancy is quantified by the correlation between $\hat{\theta}$ and $\hat{\eta}$, where "hat" refers to the estimators calculated on $\mathbf{X}$ and "tilde" is used to denote random quantities obtained as additional information. Both θ and η can be finite dimensional vectors.

To incorporate additional information, a class of linear combinations

$$\theta^{\Lambda} = \hat{\theta} + \Lambda\left(\hat{\eta} - \tilde{\eta}\right) \tag{1}$$

is considered and it is assumed that regularity conditions of multidimensional central limit theorem hold. Then, for large samples, the joint distribution of $\hat{\theta}$ and $\hat{\eta}$ can be approximated by a multivariate normal distribution.

We also assume that $E(\hat{\theta}) = \theta$ and $E(\hat{\eta}) = \eta$, and $E(\tilde{\eta}) = \eta + \delta$ where δ is an unknown bias.

As shown in [10], the estimator with the smallest mean squared error (MSE) in the class θ^{Λ} is

$$\theta^{0} = \hat{\theta} - cov\left(\hat{\theta}, \hat{\delta}\right) E^{-1}\left(\hat{\delta}\hat{\delta}^{T}\right)\hat{\delta} \tag{2}$$

with

$$MSE\left(\theta^{0}\right) = cov\left(\hat{\theta}\right) - cov\left(\hat{\theta}, \hat{\delta}\right) E^{-1}\left(\hat{\delta}\hat{\delta}^{T}\right) cov\left(\hat{\delta}, \hat{\theta}\right), \tag{3}$$

where $\hat{\delta} = \hat{\eta} - \tilde{\eta}$, $E(\hat{\theta}) = \delta$, and $E\left(\hat{\delta}\hat{\delta}^{T}\right) = cov\left(\hat{\eta}\right) + cov\left(\tilde{\eta}\right) + \delta\delta^{T}$. For the special case when $\delta = 0$, the class θ^{Λ} becomes the class of unbiased estimators and θ^{0} minimizes variance of θ^{Λ}, see [8].

The difficulty of applying θ^{0} to real data is the unknown covariances, and, most importantly, the unknown δ in its structure. Dmitriev and his colleagues [4] considered the same class of linear estimators but assumed that $\tilde{\eta} = \eta + \delta$ is known to belong to a pre-determined set of possible values and while studying MSE minimization in these settings. They faced similar problems of estimating unknown quantities.

Use of consistent estimators of covariances and the MLE $\hat{\delta}$ leads to

$$\hat{\theta}^{0} = \hat{\theta} - \widehat{cov}\left(\hat{\theta}, \hat{\delta}\right)\left(\widehat{cov}\left(\hat{\eta}\right) + \widetilde{cov}\left(\tilde{\eta}\right) + \hat{\delta}\hat{\delta}^{T}\right)^{-1}\hat{\delta} \tag{4}$$

which partially resolves the issue of unknown second moments with the exception of the still unknown δ^2.

3.1 Sub-optimality of $\hat{\theta}^{0}$ Under $\delta = 0$

The problem with $\hat{\theta}^{0}$ is that under $\delta = 0$, $\sqrt{n}\left(\hat{\theta}^{0} - \theta^{0}\right)$ does not converge to zero (in probability) which makes it asymptotically sub-optimal as compared to θ^{0}. Under $\delta = 0$, the class θ^{Λ} becomes a class of unbiased estimators. If Λ is estimated by

$$\hat{\Lambda} = \widehat{cov}\left(\hat{\theta}, \hat{\delta}\right)\left(\widehat{cov}\left(\hat{\eta}\right) + \widetilde{cov}\left(\tilde{\eta}\right) + \hat{\delta}\hat{\delta}^{T}\right)^{-1}$$

the new estimator $\hat{\theta}^{0}$ does not have the smallest MSE for finite sample sizes. To explore asymptotic properties, we will assume that when n increases, $\sqrt{n}\left(\widehat{cov}\left(\hat{\eta}\right) - cov\left(\hat{\eta}\right)\right) \xrightarrow{p} 0$ and $\sqrt{n}\left(\widehat{cov}\left(\hat{\theta}\right) - cov\left(\hat{\theta}\right)\right) \xrightarrow{p} 0$, which

holds for MLEs of covariances under certain regularity conditions. Similarly, $\sqrt{m}\left(\widetilde{cov}\left(\tilde{\eta}\right) - cov\left(\tilde{\eta}\right)\right) \xrightarrow{p} 0$, where m is the sample size of an external data set used for obtaining additional information $\widetilde{cov}\left(\tilde{\eta}\right)$ and $\tilde{\eta}$. When large sample sizes are considered, both n and m are assumed to be large enough for convergence to be approximately correct. It is important to connect rates of convergence to infinity for n and m. For example, let the ratio n/m converge to a finite positive limit τ.

Further, assume existence of real positive definite asymptotic covariance matrices: $n \cdot cov\left(\hat{\eta}\right) \to \Sigma_{\eta\eta}$, $n \cdot cov\left(\hat{\eta}, \hat{\delta}\right) \to \Sigma_{\eta\delta}$, $n \cdot cov\left(\hat{\delta}\right) \to \Sigma_{\delta\delta}$, and $m \cdot cov\left(\tilde{\eta}\right) \to \mathbf{K}_{\eta\eta}$. Then,

$$\begin{aligned} \hat{\Lambda} &= n \cdot \widehat{cov}\left(\hat{\theta}, \hat{\delta}\right)\left(n \cdot \widehat{cov}\left(\hat{\eta}\right) + n \cdot \widetilde{cov}\left(\tilde{\eta}\right) + n \cdot \hat{\delta}\hat{\delta}^T\right)^{-1} \\ &\to \Sigma_{\eta\delta}\left(\Sigma_{\eta\eta} + \tau\mathbf{K}_{\eta\eta} + \Sigma_{\delta\delta}\Delta\right)^{-1}, \end{aligned} \tag{5}$$

where $\Delta^2 = \lim_{n\to\infty}\left(n \cdot cov\left(\hat{\delta}\right)\right)^{-1}\left(\sqrt{n}\hat{\delta}\right)^2$. To investigate asymptotic behaviour of Δ, δ should be a considered as a function of n. If δ is a scalar, then

- if $\sqrt{n}\delta \to \infty$, then Δ^2 is a degenerate random variable, which forces $\hat{\Lambda}$ shrink to zero in probability.
- if $\sqrt{n}\delta \to h \in [0, +\infty)$, then Δ^2 is a non-central $\chi_1^2\left(h^2\right)$ random variable with 1 degrees of freedom and a non-centrality matrix h^2.

In a special case of unbiased estimation $E\hat{\delta} = 0$, $h = 0$ and Δ^2 becomes the central χ_1^2. In this case, $\hat{\Lambda}$ converges to a random variable and thus is not a consistent estimator of Λ. Moreover, $\hat{\Lambda} \neq \Lambda$.

3.2 Sensitivity Analysis Conditional on $\delta = c$

To address the concern of sub-optimality, [11] introduced a sample size dependent sensitivity parameter c in the estimator

$$\hat{\theta}^0(c) = \hat{\theta} - \widehat{cov}\left(\hat{\theta}, \hat{\delta}\right)\left(\widehat{cov}\left(\hat{\eta}\right) + \widetilde{cov}\left(\tilde{\eta}\right) + c\hat{\delta}\hat{\delta}^T c^T\right)^{-1}\hat{\delta}. \tag{6}$$

A pre-determined fixed vector c reduces the impact of δ estimation, but the estimation is still present and its effect continues to exist making the estimation procedure based on (6) sub-optimal under H_0.

In this manuscript, we address this problem from another angle by considering

$$\hat{\theta}_c^0 = \hat{\theta} - \widehat{cov}\left(\hat{\theta}, \hat{\delta}\right)\left(\widehat{cov}\left(\hat{\eta}\right) + \widetilde{cov}\left(\tilde{\eta}\right) + cc^T\right)^{-1}\hat{\delta}. \tag{7}$$

which, when $c = \delta$, is asymptotically the minimum MSE estimator with

$$cov\left(\hat{\theta}_c^0\right) = cov\left(\hat{\theta}\right) - cov\left(\hat{\theta}, \hat{\delta}\right)\left(cov\left(\hat{\eta}\right) + cov\left(\tilde{\eta}\right) + cc^T\right)^{-1} cov\left(\hat{\delta}, \hat{\theta}\right). \tag{8}$$

The estimator (7) is useful for sensitivity analysis. Instead of struggling with sub-optimality (6) we propose to evaluate ranges of bias leading to a different conclusion. Specifically, we propose to find c_l and c_u which do not change the inference made under the unbiased case $c = \delta = 0$.

4 Association Between Gestational Age and Academic Performance (continuation)

The effect of early (37 weeks) versus normal (39 : 41 weeks) GA on third grade standardized reading test scores was evaluated with Milwaukee Public Schools data (Wisconsin, USA). Students with 37 week GA had 0.952 ($\sqrt{MSE} = 0.277$) lower test scores as compared to children born at normal GA. This decrease changed to an increase of 0.171 ($\sqrt{MSE} = 0.216$) after controlling for factors significantly associated with the difference: gender, birth weight, test administration period (fall, winter, or spring), race, prenatal cigarette use, enrollment in special education, English language learner status, school attendance, and the clustering effect of schools. The estimator $\hat{\theta}^0(c)$ was applied to improve these estimates with the use of a similar previously published study on New York City schools, which reported an unadjusted reduction in third grade standardized reading by 0.726 ($\sqrt{MSE} = 0.084$).

Application of $\theta^0(0)$: Minimum Variance Estimation
The use of this additional information improved the unadjusted and estimates leading to a new estimate of the unadjusted difference $= -0.749(\sqrt{MSE} = 0.080)$ and to a new adjusted difference $= 0.301(\sqrt{MSE} = 0.130)$ at $c^2 = 0$. What this tells is that under the assumption of $\delta = 0$, the confidence interval for the unadjusted difference in standardized reading scores between 37 and 39 : 41 GA is $= -0.749$ with an asymptotic 95% confidence intervals $(-0.592, -0.906)$ and the adjusted difference is $= 0.301(-0.046, -0.556)$. These two confidence intervals are built under the assumption that $\delta = 0$.

Application of $\theta^0(1)$: Minimum MSE Estimation with an Estimated by MLE Bias
If $\delta = c \neq 0$ the confidence cannot be assumed to be at 95%, but what we are interested in is whether 0 belongs to the confidence interval or not.

If we set $c^2 = 1$, then the unadjusted and adjusted differences are $= -0.860(\sqrt{MSE} = 0.158)$ and $= -0.230(\sqrt{MSE} = 0.157)$, respectively. The unknown covariances were estimated using cross validation.

Application of θ^0_δ: MMSE Estimation with Assumed Bias δ
To perform sensitivity analysis we assume a range of specific values of δ and plot asymptotic 95% confidence intervals. Figure 1 highlights two interesting conclusions. First, the impact of additional information vanishes as bias becomes larger. Second, the confidence interval is the smallest when the bias is equal to zero. Moreover, only in a very small neighbourhood of zero the confidence interval does not contain the zero difference in reading scores between 37 weeks and full term gestational age.

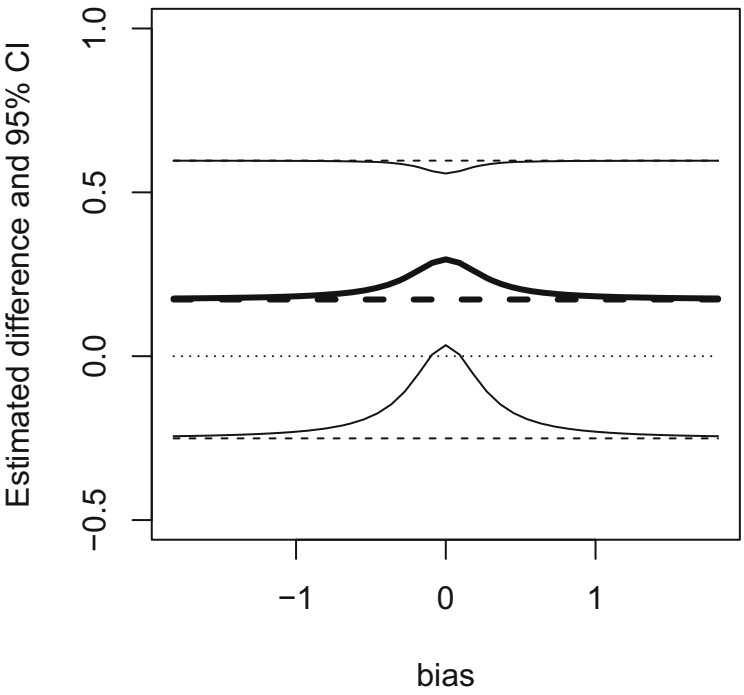

Fig. 1. Sensitivity analysis

5 Conclusion

Accuracy of statistical estimation based solely on experimental or observational data is often limited and cannot be have a higher precision than a particular threshold. This threshold can be determined, for example, by a Cramer-Rao lower bound for variance. Use of previously published data allows overcoming this limitation and produce estimators with better accuracy. We have introduced a sensitivity analysis which helps investigating the impact of bias on minimum MSE statistical procedure combining empirical data with external information. Using Milwaukee county test score data we show that after adjusting for confounding variables the impact of early full-term birth is very small (near 0.2 on the standardized score scale). Moreover, this impact is shown to be only marginally significant when the unadjusted impact 37 week gestational age is nearly identical between New York and Milwaukee cities.

Thus, we conclude that additional information may be helpful for increasing efficiency of statistical procedures, but a sensitivity analysis is an important tool to investigate validity and robustness of such findings.

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Appendix

```
install.packages("devtools")
library(devtools)
install_github("starima74/AddInf", force=TRUE)
library(AddInf)

### A variance covariance matrix of adjuated
### and unadjusted estimates of differences
### in reading scores between children born
### at the gestational age of 37 and 39:41 weeks

K <- matrix(c(0.0467408718, 0.0499675797,
              0.0499675797, 0.0768166235),2,2)

### an estimate of the parameter of interest
### (the adjusted estimate of differences in
### standardized reading scores between children
### born at the gestational age of 37 and 39:41 weeks
thetahat <- 0.173

### an estimate of the auxiliary parameter
### (the unadjusted estimate of differences in
### reading scores between children born at
### the gestational age of 37 and 39:41 weeks
betahat <- -0.952

### (Empty) Additional Information
### (on the auxiliary parameter)
Add.Info.Means <- list()
Add.Info.Vars <- list()
Add.Info.Biases <- list()

### the additional data source says the unadjusted
### difference is -0.74 with a standard error = 0.098
### (variance = 0.009604) this information may
### be biased as it came from a different population
Add.Info.Means[[1]] <- -0.74
Add.Info.Vars[[1]] <- 0.009604
# biased additional information
Add.Info.Biases[[1]] <- 1

### create the data frame where the additional
### information will be saved
Add.Info <- data.frame(Means = rep(NA,1),
                       Vars = rep(NA,1),
```

```
                    Biases = rep(NA,1))

### Adding the additional information to the data frame
Add.Info$Means = Add.Info.Means
Add.Info$Vars = Add.Info.Vars
Add.Info$Biases = Add.Info.Biases

### estimation based on both data sources
res <- MMSE2(K, -0.05, Add.Info, thetahat,
             betahat, eig.cutoff = 1)

### the new estimate and its confidence interval
lo  <- res$Theta.Est - 1.96*sqrt(res$Theta.Est.MSE)
est <- res$Theta.Est
hi  <- res$Theta.Est + 1.96*sqrt(res$Theta.Est.MSE)
c(lo, est, hi)

### the empirical (no additional information)
### estimate and its confidence interval
theta_lo  <- res$Theta.Hat - 1.96*sqrt(res$Theta.Hat.Var)
theta_est <- res$Theta.Hat
theta_hi  <- res$Theta.Hat + 1.96*sqrt(res$Theta.Hat.Var)
c(theta_lo, theta_est, theta_hi)
```

References

1. Abel, K., et al.: Gestational age at birth and academic performance: population-based cohort study. Int. J. Epidemiol. **46**(1), 324–335 (2017)
2. Ahlsson, F., Kaijser, M., Adami, J., Lundgren, M., Palme, M.: School performance after preterm birth. Epidemiology **26**(1), 106–111 (2015)
3. Dempster, A.P., Selwyn, M.R., Weeks, B.J.: Combining historical and randomized controls for assessing trends in proportions. J. Am. Stat. Assoc. **78**(382), 221–227 (1983)
4. Dmitriev, Y.G., Tarassenko, P.F., Ustinov, Y.K.: On estimation of linear functional by utilizing a prior guess. In: Dudin, A., Nazarov, A., Yakupov, R., Gortsev, A. (eds.) Information Technologies and Mathematical Modelling. pp, pp. 82–90. Springer International Publishing, Cham (2014). https://doi.org/10.1007/978-3-319-13671-4_11
5. Hartung, J., Knapp, G., Sinha, B.K.: Statistical Meta-Analysis with Applications, vol. 738. Wiley (2011)
6. Ibrahim, J.G., Ryan, L.M., Chen, M.-H.: Using historical controls to adjust for covariates in trend tests for binary data. J. Am. Stat. Assoc. **93**(444), 1282–1293 (1998)
7. Noble, K.G., Fifer, W.P., Rauh, V.A., Nomura, Y., Andrews, H.F.: Academic achievement varies with gestational age among children born at term. Pediatrics **130**(2), e257–e264 (2012)

8. Tarima, S., Pavlov, D.: Using auxiliary information in statistical function estimation. ESAIM Probab. Stat. **10**, 11–23 (2006)
9. Tarima, S., Patel, K.: The association between gestational age and 3rd grade standardized reading score. Technical report, Medical College of Wisconsin, Division of Biostatistics (2019)
10. Tarima, S.S., Dmitriev, Y.G.: Statistical estimation with possibly incorrect model assumptions. Bull. Tomsk State Univ. Control Comput. Inf. **8**, 78–99 (2009)
11. Tarima, S.S., Vexler, A., Singh, S.: Robust mean estimation under a possibly incorrect log-normality assumption. Commun. Stat. Simul. Comput. **42**(2), 316–326 (2013)
12. Thum, Y.M., Hauser, C.H.: NWEA 2015 MAP norms for student and school achievement status and growth. Technical report, NWEA Research Report. Portland, OR: NWEA (2015)

Experimental Design

An Efficient Operational Matrices to Solve Biochemical Reaction Model with Error Analysis

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1 Introduction

Biochemical reaction model describe the enzyme processes and the basic enzymatic reaction, this complex biological system is given by the scheme

$$E + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Y \xrightarrow{k_2} E + X \tag{1}$$

where E is the enzyme, A the substrate, Y the enzyme-substrate intermediate complex and X the product. The parameters k_1, k_{-1} and k_2 are positive rate constants for each reaction [4]. The time evolution of the scheme can be determined from the solution of the system of coupled nonlinear [7], given as

$$\begin{cases} u'(t) = -\varepsilon u + \varepsilon(u + \alpha - \lambda)v \\ v'(t) = u - (u + \alpha)v \\ w'(t) = \lambda v \end{cases} \tag{2}$$

with the boundary conditions

$$u(0) = 1, \quad v(0) = 0, \quad w(0) = 0$$

where ε, α and λ are dimensionless parameters.

Many methods have been presented to find the solution of a basic enzyme kinetics. Introducing variational iteration method is used to solve a biochemical reaction model [4]. The multistage homotopy analysis method is applied to solve a biochemical reaction model of fractional order [7].

Our motivation for this work is to provide an efficient method to find the solution for the biochemical Reaction Model. Bernstein polynomials method is one of the important methods for solving differential equations [2,3,5]. Bernstein polynomials will be used to find the solutions of the model then correct the previous solutions by using the residual correction procedure.

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2 Description of Method with Application

The Bernstein polynomials of degree m are defined by

$$B_{i,m}(t) = \binom{m}{i} t^i (1-t)^{m-i}, \quad i = 0, 1, \ldots, m$$

where the binomial coefficient is

$$\binom{m}{i} = \frac{m!}{i!\,(m-i)!}.$$

In general, we approximate the functions $u(t)$,$v(t)$, and $w(t)$ with the first $(m+1)$ Bernstein polynomials as

$$\begin{aligned} u(t) &= \sum_{i=0}^{m} c_i B_{i,m}(t) = \mathrm{C}_1^{\mathrm{T}} \phi(t) \\ v(t) &= \sum_{i=0}^{m} c_i B_{i,m}(t) = \mathrm{C}_2^{\mathrm{T}} \phi(t) \\ w(t) &= \sum_{i=0}^{m} c_i B_{i,m}(t) = \mathrm{C}_3^{\mathrm{T}} \phi(t) \end{aligned} \tag{3}$$

where $\mathrm{C}^{\mathrm{T}} = [\mathrm{c}_0, \mathrm{c}_1, \ldots, \mathrm{c}_m]$ and $\phi(t) = [B_{0,m}(t), B_{1,m}(t), \ldots, B_{m,m}(t)]^{\mathrm{T}}$.

The derivatives of the vector $\phi(t)$ can be expressed as $\frac{\mathrm{d}\phi(t)}{\mathrm{d}x} = \mathrm{D}^1 \phi(t)$, see [1,6]. By applying the previous relations on the system (2), we have

$$\begin{aligned} &\mathrm{C}_1^{\mathrm{T}} \mathrm{D}^1 \phi(t) + \varepsilon \mathrm{C}_1^{\mathrm{T}} \phi(t) - \varepsilon (\mathrm{C}_1^{\mathrm{T}} \phi(t) + \alpha - \lambda) \mathrm{C}_2^{\mathrm{T}} \phi(t) = 0 \\ &\mathrm{C}_2^{\mathrm{T}} \mathrm{D}^1 \phi(t) - \mathrm{C}_1^{\mathrm{T}} \phi(t) + (\mathrm{C}_1^{\mathrm{T}} \phi(t) + \alpha) \mathrm{C}_2^{\mathrm{T}} \phi(t) = 0 \\ &\mathrm{C}_3^{\mathrm{T}} \mathrm{D}^1 \phi(t) - \lambda \mathrm{C}_3^{\mathrm{T}} \phi(t) = 0, \end{aligned} \tag{4}$$

Collocation points will be substituting in (4) to find the unknowns c_i, then $u(t)$,$v(t)$, and $w(t)$ will be found, we can find the collocation points by applying Chebyshev roots

$$t_i = \frac{1}{2} + \frac{1}{2\cos((2i+1)\frac{\pi}{2n})}, \quad i = 0, 1, \ldots, m-1. \tag{5}$$

2.1 Residual Correction Procedure

If u_m is Bernstein series solution to (4) and E_n also an approximate solution, $n > m$, then $u_m(t) + E_n$ is the corrected approximate solution for (1). Moreover, we call for $|u(t) - (u_m(t) + E_n)|$ is corrected of absolute error. In the case exact solution not found then we have to find error function, see [2].

Results and Discussion

The model (2) is solved for the case $m = 5$ and $\alpha = 1, \lambda = 0.5, \varepsilon = 0.6$. Some of the error in solutions are found, so we need to improve the solution to get a more accurate solution, residual correction procedure for the case $n = 14$ is applied to correct the solutions. Figure 1 and 2 show the absolute error and the absolute corrected error, for the case $m = 5, n = 14$, we can see the solutions are corrected by applying residual correction procedure which described in (2). Figure 3 shows the results of our technique and compare it with RK4. The results which obtained by using the Bernstein polynomials method with residual correction procedure are more accurate.

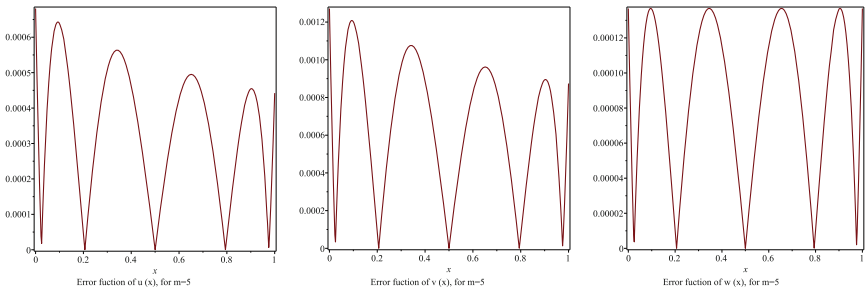

Fig. 1. Absolute of error function for the case $m = 5$.

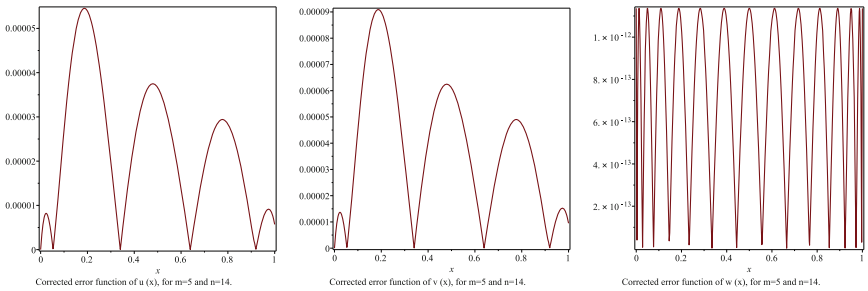

Fig. 2. Absolute corrected of error function, for the case $m = 5$ and $n = 14$.

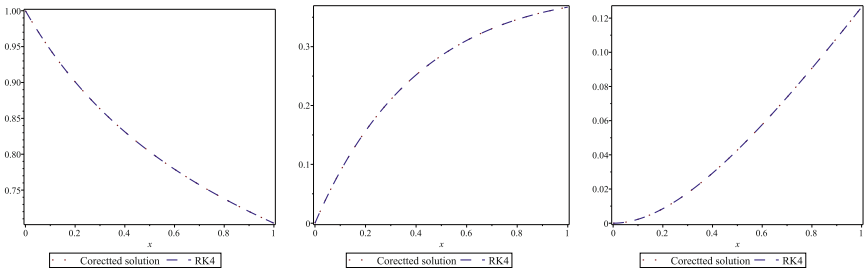

Fig. 3. Corrected solutions for $u(t)$,$v(t)$,$w(t)$ and RK4 for $t \in (0, 1)$.

3 Conclusions

These results show that the Bernstein polynomials method with residual correction procedure has much impact on the accuracy of the solution on this basic enzyme kinetics scheme. The method is easily implemented. First, the results of scheme are obtained and then it is improved by residual correction procedure. The method for different values of m and n is applied.

References

1. Alshbool, M.H.T., Hashim, I.: Multistage Bernstein polynomials for the solutions of the fractional order stiff systems. J. King Saud Univ. Sci. **28**, 280–285 (2016)
2. Alshbool, M.H.T., Bataineh, A.S., Hashim, I., Isik, O.: Solution of fractional-order differential equations based on the operational matrices of new fractional Bernstein functions. J. King Saud Univ. Sci. **29**, 1–18 (2017)
3. Baseri, A., Babolian, E., Abbasbandy, S.: Appl. Math. Comput. 346 (2017)
4. Goha, S., Noorani, M., Hashim, I.: Nonlinear Anal. Real World Appl. **11**, 2264–2272 (2010)
5. Khataybeh, S., Hashim, I., Alshbool, M.: J. King Saud Univ. Sci. (2015)
6. Pandey, K., Kumar, N.: New Astron. **17**, 303–308 (2012)
7. Zurigat, M., Momani, S., Alawneh, A.: Int. J. Comput. Math. **91**, 1030–1040 (2014)

Some Notes on Types of Symmetry for Crossover Designs

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Abstract. Crossover designs are used to assign multiple treatments to the same unit over a period of time. In the search of optimal crossover designs, approximate design theory emerged to be a powerful tool over the last two decades. In its development, the idea of symmetrization plays a crucial role (Kushner 1997). While the construction of exact symmetric designs from the approximate design theory is relatively straightforward; however, to achieve the symmetry, a large number of units is typically required. There exist evidence that concept of symmetry could be generalized. This paper extracts and organizes some key ideas scattered in the literature and formulates them into a systematic way of constructing an important type of symmetric designs. We also give a survey of recent advances on crossover designs and related studies, where new designs could be derived by the methods laid out in this paper.

1 Introduction

Crossover designs are widely used in various fields due to their cost effectiveness and statistical efficiency. Their applications lie in experiments where different treatments, applied to a number of subjects during a sequence of periods, are to be compared. The mathematical development for the problem of finding optimal crossover designs could find its root in the simpler forms of block designs and row-column designs. For these classical problems, combinatorial tools dominated the literature. Many proposed designs, such as the balanced incomplete block design, Latin square, Youden design, and Orthogonal Array, became textbook standards.

In crossover designs, the treatments possess carryover effects in subsequent periods. This additional nuisance factor complicates the problem substantially, in the sense that the order of treatments within a block becomes relevant. However, to handle carryover effects, more sophisticated crossover structures, using combinatorial tools, have been proposed and their statistical properties have been studied. Examples include the (strongly) balanced uniform crossover design, the Type I orthogonal array, and the totally balanced crossover design. Since Hedayat and Afarinejad (1978), the study of optimal crossover designs has been an active area in design of experiments. Excellent surveys of the topic were

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given by Matthew (1988), Ratkowsky et al. (1992), Stufken (1996), Jones and Kenward (2003), Senn (2003), and Bose and Dey (2009).

Designs constructed using combinatorial tools have a natural limitation: they only exist under special configurations of the numbers of treatments, periods, and subjects. For some proposed designs, the optimality only holds within a subclass, while their performance among all possible designs remains unknown. The seminal paper of Kushner (1997) adopted the approach of approximate design theory and derived conditions for universal optimality. These conditions are easy to check and also provide guidelines for constructing optimal or efficient designs for any given configuration. The theory has since been further developed and extended to more complicated models. The purpose of this paper is to extract and organize some key ideas scattered in the literature and propose a systematic way of constructing designs. Such ideas helps enhance the results for related studies, and a short survey of the latter will also be given.

Throughout the paper, we illustrate the ideas for crossover designs, even though many other problems could be tackled in a similar fashion. In a crossover design with p periods, t treatments, and n subjects, the response is typically modeled as

$$Y_{dku} = \mu + \alpha_k + \beta_u + \tau_{d(k,u)} + \gamma_{d(k-1,u)} + \varepsilon_{ku}, \tag{1}$$

Here, Y_{dku} denotes the response from subject u in period k to which treatment $d(k,u) \in \{1,2,...,t\}$ is assigned by design d. ε_{ku} is the corresponding error term. Furthermore, μ is the general mean, α_k is the kth period effect, β_u is the uth subject effect, $\tau_{d(k,u)}$ is the (direct) treatment effect of treatment $d(k,u)$, and $\gamma_{d(k-1,u)}$ is the carryover effect of treatment $d(k-1,u)$ that subject u received in the previous period (by convention $\gamma_{d(0,u)} = 0$).

Let $Y_d = (Y_{d11}, Y_{d21}, ...Y_{dp1}, Y_{d12}, ..., Y_{dpn})'$ be the $np \times 1$ response vector, then Model (1) has the matrix form of

$$Y_d = 1_{np}\mu + Z\alpha + U\beta + T_d^1\tau + T_d^2\gamma + \varepsilon, \tag{2}$$

where $\alpha = (\alpha_1, ..., \alpha_p)'$, $\beta = (\beta_1, ..., \beta_n)'$, $\tau = (\tau_1, ...\tau_t)'$, $\gamma = (\rho_1, ..., \rho_t)'$, $Z = 1_n \otimes I_p$, $U = I_n \otimes 1_p$ with $\otimes$ being the Kronecker product of two matrices, and T_d^1 and T_d^2 denote the treatment/subject and carryover/subject incidence matrices, respectively. Here we assume $\mathbb{E}(\varepsilon) = 0$ and $Var(\varepsilon) = I_n \otimes V$, where V is the nonsingular within subject covariance matrix. The information matrix for the direct treatment effect τ under Model (2) is

$$C_d = C_{d11} - C_{d12}C_{d22}^{-}C_{d21},$$

where $C_{dij} = (T_d^i)'(B_n \otimes \tilde{V})T_d^j, 1 \le i,j \le 2$, with $B_k = I_k - k^{-1}J_k$. Here $^-$ represents a generalized inverse of a matrix and $\tilde{V} = V^{-1} - V^{-1}J_pV^{-1}/1_p'V^{-1}1_p$ with $J_k = 1_k1_k'$ and 1_k the vector of ones of length k. Let T_u^i be the submatrix

of T_d^i associated with the uth subject, we have

$$C_{dij} = \sum_{u=1}^{n} (T_u^i)' \tilde{V} T_u^j - n(\overline{T}_d^i)' \tilde{V} \overline{T}_d^j \tag{3}$$

$$\overline{T}_d^i = n^{-1} \sum_{u=1}^{n} T_u^i$$

Note that C_{dij} depends on V only through $\tilde{V}$. We have $\tilde{V} = B_p$ when $V = I_p$ or $V = I_p + \gamma 1_p' + 1_p \gamma'$. The latter form of the covariance matrix is called a type H matrix. Following Kiefer (1975), we would like to find a design which maximizes $\Phi(C_d)$ with the certain criterion function Φ satisfying

$(C.1)$ Φ is concave.
$(C.2)$ $\Phi(S'CS) = \Phi(C)$ for any permutation matrix S.
$(C.3)$ $\Phi(bC)$ is nondecreasing in the scalar $b > 0$.

A design is said to be *universally optimal* if it maximizes $\Phi(C_d)$ for any Φ satisfying these three conditions. It is well known that a universally optimal design is also optimal under criteria of A, D, E, T, etc.

2 Some Critical Steps in Literature

We begin with the notations that are needed throughout this paper. Let $\Omega_{p,t,n}$ be the collection of all crossover designs with p periods, t treatments and n subjects. Consider a design $d \in \Omega_{p,t,n}$ to be the result of selecting n elements with replacement from $\mathcal{S}$, the collection of all possible t^p treatment sequences. Now define the treatment sequence proportion $p_s = n_s/n$, where n_s is the number of replications of sequence s in the design. For given n, a design is identified by the measure $\xi := (p_s, s \in \mathcal{S})$. In approximate design theory, we ignore the integer constraint of n and search for an optimal measure in the set $\mathcal{P} = \{\xi : \sum_{s\in\mathcal{S}} p_s = 1, p_s \geq 0\}$. An exact design can be constructed from ξ if and only if $\xi \in \mathcal{P}_n := \{\xi \in \mathcal{P} : n\xi \text{ is a vector of integers}\}$. In particular, when p_s is irrational for at least one sequence, then the corresponding measure does not belong to $\mathcal{P}_n$ for any n.

For sequence $s \in \mathcal{S}$, let T_s^1 and T_s^2 be the corresponding direct and carryover incidence matrices. Suppose a design d induces the measure ξ, by (3), we shall have

$$C_{dij} = nC_{\xi ij}$$

$$C_{\xi ij} = \sum_{s\in\mathcal{S}} p_s C_{sij} - (\overline{T}_\xi^i)' \tilde{V} \overline{T}_\xi^j$$

$$C_{sij} = (T_s^i)' \tilde{V} T_s^j$$

$$\overline{T}_\xi^i = \sum_{s\in\mathcal{S}} p_s T_s^i$$

As a result, we have

$$C_d = nC_\xi, \qquad (4)$$
$$C_\xi = C_{\xi 11} - C_{\xi 12}C_{\xi 22}^{-}C_{\xi 21}.$$

Based on (4), in approximate design theory, we try to find the optimal measure $\xi^* \in \mathcal{P}$ to maximize $\Phi(C_\xi)$. Such a measure, ξ^*, is called optimal.

Let $\mathcal{G}$ be the set of all $t!$ permutations on symbols $\{1, 2, ..., t\}$. For permutation $\sigma \in \mathcal{G}$ and sequence $s = (t_1 \cdots t_p)$ with $1 \le t_i \le t$, $1 \le i \le p$, we define $\sigma s = (\sigma(t_1) \cdots \sigma(t_p))$. For measure $\xi = (p_s, s \in \mathcal{S})$, we define $\sigma\xi = (p_{\sigma^{-1}s}, s \in \mathcal{S})$. A measure is said to be *symmetric* if $\sigma\xi = \xi$ for all $\sigma \in \mathcal{G}$. For sequence s, denote by $\langle s \rangle = \{\sigma s : \sigma \in \mathcal{G}\}$ the *symmetric block* generated by s. Symmetric blocks generated by two different sequences are either identical or mutually disjoint. Therefore $\mathcal{S}$ is partitioned into m symmetric blocks, i.e. $\mathcal{S} = \cup_{i=1}^{m} \langle s_i \rangle$, where m is the Bell number indexed by p. For a symmetric measure and a fixed $1 \le i \le m$ we have

$$p_s = p_{\langle s_i \rangle}/|\langle s_i \rangle| \ for \ s \in \langle s_i \rangle, \qquad (5)$$

where $p_{\langle s_i \rangle} = \sum_{s \in \langle s_i \rangle} p_s$ and $|\langle s_i \rangle|$ is the cardinality of $\langle s_i \rangle$. Equation (5) means that p_s is the same for sequences from the same symmetric block. Now are we ready to introduce Lemmas 1–2 and Theorems 1–2 in approximate design sense due to Kushner (1997).

Lemma 1. *There exists a symmetric measure which is universally optimal in* $\mathcal{P}$.

Now define $\hat{C}_{sij} = B_t C_{sij} B_t, 1 \le i, j \le 2$ and $\hat{C}_{\xi ij} = \sum_{s \in \mathcal{S}} p_s \hat{C}_{sij}$. Then we have

$$\hat{C}_{\xi ij} = C_{\xi ij} + B_t(\overline{T}_\xi^i)' \tilde{V} \overline{T}_\xi^j B_t, 1 \le i, j \le 2$$

It is obvious that $C_{\xi 12}$ and $\hat{C}_{\xi 12}$ are the transpose of $C_{\xi 21}$ and $\hat{C}_{\xi 21}$, respectively.

Lemma 2. *For a symmetric measure* $\xi \in \mathcal{P}$ *we have* $C_\xi = q_\xi^* B_t/(t-1)$, *where*

$$q_\xi^* = c_{\xi 11} - c_{\xi 12}^2/c_{\xi 22},$$
$$c_{\xi ij} = tr(\hat{C}_{\xi ij}), 1 \le i, j \le 2.$$

Lemmas 1 and 2 indicate that a symmetric measure is universally optimal if and only if it maximises q_ξ^*. The latter is resolved by Theorem 1 below. To understand the meaning of the theorem, we need to define the following concepts: Let $q_s(x) = c_{s11} + 2c_{s12}x + c_{s22}x^2$, where $c_{sij} = tr(\hat{C}_{sij})$. Obviously, $c_{s12} = c_{s21}$. Let $r(x) = \max_s q_s(x)$, $y^* = \min_{-\infty < x < \infty} r(x)$, x^* to be the unique solution of $q(x) = y^*$ and the support $\mathcal{T} = \{s \in \mathcal{S} | q_s(x^*) = y^*\}$.

Theorem 1. *A symmetric measure is universally optimal if and only if*

$$\sum_{s\in\mathcal{T}} p_s q_s'(x^*) = 0 \tag{6}$$
$$\sum_{s\in\mathcal{T}} p_s = 1$$

where $q_s'(x)$ *is the derivative of* $q_s(x)$ *with respective to* x.

Kushner (1997) has given an algorithm for computing x^*,y^* and $\mathcal{T}$. Note that $q_s(x)$ is invariant with respect to treatment permutations, i.e.

$$q_s(x) = q_{\sigma s}(x), \sigma \in \mathcal{G}. \tag{7}$$

Hence $s \in \mathcal{T}$ implies $\langle s\rangle \subset \mathcal{T}$. Therefore we have the partition $\mathcal{T} = \cup_{i\in I_\mathcal{T}}\langle s_i\rangle$ where $I_\mathcal{T} \subset \{1, 2, ..., m\}$. Hence, like $\mathcal{S}$, the support $\mathcal{T}$ is also a partition of symmetric blocks. In view of (5) and (7), now (6) is reduces to

$$\sum_{i\in I_\mathcal{T}} p_{\langle s_i\rangle} q_{s_i}'(x^*) = 0 \tag{8}$$

One straightforward way to derive a universally optimal measure is to use a symmetric measure satisfying (8). However, this approach necessitates a very large number of subjects for the corresponding exact design. In fact, a symmetric block, say $\langle s\rangle$, has $t!/(t-\eta_s)!$ different sequences, where η_s is the number of distinct symbols (treatments) in s. In particular, we have $\eta_s = min(p, t)$ or $min(p, t) - 1$ for sequences in $\mathcal{T}$ when $\Sigma = I_p$ or more generally when Σ is a type H matrix (Kushner 1998). As another extreme, Kushner (1997) also provided a general optimality condition, which covers all possible universally optimal designs.

Theorem 2. *A measure is universally optimal if and only if*

$$\sum_{s\in\mathcal{T}} p_s(\hat{C}_{s11} + x^*\hat{C}_{s12}) = \frac{y^*}{t-1}B_t, \tag{9}$$
$$\sum_{s\in\mathcal{T}} p_s(\hat{C}_{s21} + x^*\hat{C}_{s22}) = 0, \tag{10}$$
$$\sum_{s\in\mathcal{T}} p_s\tilde{V}(T_s^1 + x^*T_s^2)B_t = 0, \tag{11}$$
$$\sum_{s\in\mathcal{T}} p_s = 1. \tag{12}$$

Note that (9)–(12) is a linear system of equations for proportions. We may multiply n to the equations so that they become linear equations in n_s. As a result, one can find smallest universally optimal design by minimizing $\sum_{s\in\mathcal{T}} n_s$ subject to those linear constraints along with non-negativity requirements. Yet,

it is not straightforward to use the conditions for an arbitrarily given n. The number of equations in (9)–(12) is $2t^2+pt+1$, which is typically a lot larger $|\mathcal{T}|$, and hence there are infinity many solutions in $\mathcal{P}$. However, there could be no solutions at all in $\mathcal{P}_n$ due to the integer constraint. One remedy is to find a point in $\mathcal{P}_n$ *nearest* to the hyperplane as defined by the linear equations. For example, Zheng (2013a) used the Euclidean distance to find the nearest point, which reduce the problem to the integer quadratic programming. Examples obtained there showed that designs derived in this way are highly efficient. However, since the integer quadratic programming is essentially an N-P hard problem and the computation will be prohibitive even when p and t becomes larger.

As a compromise between Theorems 1 and 2, Kushner (1999) proposed using a transitive subgroup of $\mathcal{G}$ and to partition each symmetric block into many smaller sets, for which proportions of the sequences in these sets are equal. Let $\mathcal{H} \subset \mathcal{G}$ be a transitive subgroup and define the *2-orbit* $[(i,j)] = \{(\sigma(i),\sigma(j)) : \sigma \in \mathcal{H}\}$, where (i,j) is a 2-tuple with $1 \le i,j \le t$. Due to the group structure of $\mathcal{H}$, any two 2-orbits, say $[(i,j)]$ and $[(i',j')]$, are either disjoint or identical. Correspondingly, we have the partition of the set of all 2-tuples $\{(i,j) : 1 \le i,j \le t\} = \cup_{v=0}^{g}[(i_v,j_v)] := \cup_{v=0}^{g} H_v$, where $g+1$ is the total number of disjoint orbits with (i_v,j_v) being generator 2-tuples. Without loss of generality we take $(i_0,j_0)=(1,1)$ and we have $H_0 = \{(i,i) : 1 \le i \le t\}$ since $\mathcal{H}$ is transitive. Also define $\Delta_v = (i_{(i,j)\in H_v})_{1\le i,j\le t}, 0 \le v \le g$, where i is the indicator function. Then we have

$$\Delta_0 = I_t, \tag{13}$$

$$\sum_{v=0}^{g} \Delta_v = J_t, \tag{14}$$

$$tr(\Delta'_{v_1}\Delta_{v_2}) = \delta_{v_2}^{v_1}|H_{v_1}|, \tag{15}$$

with δ being the Kronecker delta. For example, if $\mathcal{H}$ is the cyclic group generated by $(12\cdots t)$, we have $\Delta_1 = (i_{j=i+1 \ (mod\ t)})_{1\le i,j\le t}$ and $\Delta_v = (\Delta_1)^v = (i_{j=i+v \ (mod\ t)})_{1\le i,j\le t}$ for $0 \le v \le g = t-1$.

Similarly, we define *H-symmetric* blocks $[s] = \{\sigma s : \sigma \in \mathcal{H}\}$. Due to the subgroup structure of $\mathcal{H}$, we have the partition $\langle s_i\rangle = \cup_{w=1}^{n_i}[s_{i,w}]$, where n_i is the total number of disjoint H-symmetric blocks in $\langle s_i\rangle$ and $s_{i,w}$ are the representative sequences. Define a measure to be *H-symmetric* if $\sigma\xi = \xi$ for all $\sigma \in \mathcal{H}$, i.e.

$$p_s = p_{[s_{i,w}]}/|[s_{i,w}]|, s \in [s_{i,w}], \tag{16}$$

where $p_{[s_{i,w}]} = \sum_{s\in[s_{i,w}]} p_s$. Equation (16) means that p_s is the same for sequences from the same H-symmetric block. For an H-symmetric measure, Kushner (1999) has mentioned that $\hat{C}_{\xi ij} * \Delta_v$ is proportional to Δ_v, where $*$ represents the Hadamard product. By (15), the orthogonality of Δ_v's, we can

derive the following decomposition.

$$\hat{C}_{\xi ij} = c_{\xi ij,0} I_t/t - \sum_{v=1}^{g} c_{\xi ij,v} |H_v|^{-1} \Delta_v, \tag{17}$$
$$c_{\xi ij,v} = -tr(\hat{C}_{\xi ij} \Delta_v'), 0 \le v \le g$$

Let $c_{sij,v} = -tr(\hat{C}_{sij}\Delta_v')$, then we have $c_{\xi ij,v} = \sum_{s\in\mathcal{S}} p_s c_{sij,v}$, $0 \le v \le g$. Applying (13)–(17) to Theorem 2 yields the following theorem (Kushner 1999).

Theorem 3. *An H-symmetric measure is universally optimal if and only if*

$$\sum_{i\in I_\mathcal{T}} \sum_{w=1}^{n_i} p_{[s_{i,w}]}(c_{s_{i,w}11,v} + x^* c_{s_{i,w}12,v}) = \frac{y^*|H_v|}{t(t-1)},$$
$$\sum_{i\in I_\mathcal{T}} \sum_{w=1}^{n_i} p_{[s_{i,w}]}(c_{s_{i,w}21,v} + x^* c_{s_{i,w}22,v}) = 0,$$
$$\sum_{i\in I_\mathcal{T}} \sum_{w=1}^{n_i} p_{[s_{i,w}]} = 1.$$

hold for all $1 \le v \le g$.

Remark 1. By (14) we have $\sum_{v=0}^{g} c_{sij,v} = 0$, hence $v = 0$ is not included in Theorem 3.

Remark 2. When $\mathcal{H} = \mathcal{G}$, we have $g = 1$, $\Delta_1 = J_t - I_t$, $c_{\xi ij,1} = c_{\xi ij}$, $|H_1| = t(t-1)$ and henceforth

$$\hat{C}_{\xi ij} = \frac{c_{\xi ij}}{t} I_t - \frac{c_{\xi ij}}{t(t-1)}(J_t - I_t)$$
$$= c_{\xi ij} B_t/(t-1).$$

Hence Theorem 3 reduces to Theorem 1.

3 Pseudo Symmetric Designs

The advantage of using H-symmetric designs over symmetric designs is that the former requires fewer blocks. One difficulty in using the H-symmetric designs is that the resulting design depends on the choice of the subgroup of permutations and not all choices lead to small designs. As an alternative, here we propose to search for an optimal design in the subclass of pseudo symmetric designs, a subclass that contains the symmetric designs. The calculation of the proportions for the pseudo symmetric designs is as simple (just two equations) as for symmetric designs while the construction of pseudo symmetric designs requires much fewer blocks than symmetric designs.

According to (5) (*resp.* (16)), for a symmetric (*resp.* H-symmetric) measure, we have $C_{\xi ij} = \hat{C}_{\xi ij} = \sum_{s\in\mathcal{S}} p_s \hat{C}_{sij}$, where p_s are the same for sequences within

the same symmetric (*resp.* H-symmetric) blocks. See Kushner (1997, 1999) for details. The blocks are constructed so that $C_{\xi ij}$, $1 \le i, j \le 2$, have certain desirable, but different, structures. In particular, a symmetric measure ensures that $C_{\xi ij}$ is completely symmetric and an H-symmetric measure ensures that $C_{\xi ij}$ is a linear combination of Δ_v, $0 \le v \le g$, and the latter adds up to J_t, i.e. (14). In either case, (9)–(12) reduce to simpler forms so that we can construct universally optimal designs in a more straightforward way.

Both symmetric and H-symmetric designs are constructed via groups of permutations. However, we can construct a desirable block by a collection of mappings, which are not permutations. A permutation is essentially a surjective mapping with $\{1, 2, ..., t\}$ as the domain. Let η_s be the number of distinct treatments in sequence s. When $\eta_s \le t-2$ there are at least two columns and rows of $\hat{C}_{sij}$ whose entries are all zero. Hence, permutations of all t treatments are not necessary. Instead, we only need to consider injective mappings of $\{1, 2, ..., \eta_s\}$ into $\{1, 2, ..., t\}$.

In the study of mapping schemes, we focus on constructing *pseudo symmetric* measures, which is defined to be measures such that $C_{\xi ij} = \hat{C}_{\xi ij}, 1 \le i, j \le 2$, and all these matrices are completely symmetric. By (4.5) of Kushner (1997), a symmetric measure is also pseudo symmetric and hence Lemma 1 is automatically true when the symmetric measure therein is replaced by pseudo symmetric measure. By definition of pseudo symmetric measure, the same is also true for Lemma 2. By examining the proof of Theorem 1, we have Corollary 1. Corollary 2 is a direct result of Theorem 1, Corollary 1 and (7).

Corollary 1. *Lemmas 1 and 2 and Theorem 1 still hold if the symmetric measure therein is replaced by a pseudo symmetric measure.*

Corollary 2. *A pseudo symmetric measure is universally optimal if and only if (8) and (12) hold.*

Lemma 1 indicates that an optimal measure in the subclass of symmetric measures is automatically optimal among $\mathcal{P}$. Now Corollary 1 shows that we can actually search for optimal measures in a larger subclass of pseudo symmetric measures. The difference is that (5) does not have to hold for a general pseudo symmetric measure.

Given sequence $s = (t_1, ..., t_p)$, let $l_i = l_{s,i} = \min\{j : t_j = i\}$ with the convention that the minimum over an empty set is infinity. Without loss of generality, we assume that the sequence under mapping satisfies $l_1 \le l_2 \le \cdots \le l_t$, that is, the first occurrence of a treatment with larger label should be after the first occurrence of a treatment with smaller label. This of course implies $t_1 = 1$, $t_p = \eta_s$ and $\eta_s = \max_{1 \le i \le p} t_i$. Now it is sufficient to restrict ourselves to injective mappings with the domain $\{1, ..., \eta_s\}$ and range $\{1, 2, ...t\}$. A mapping, typically denoted by φ here, is represented by a sequence of η_s distinct numbers, with the location and the number being the domain and image respectively. For example, $\varphi = (243)$ means that $\varphi(1) = 2$, $\varphi(2) = 4$ and $\varphi(3) = 3$. We also define $\varphi(s) = (\varphi(t_1), ..., \varphi(t_p))$. If $s = (11232)$, we have $\varphi(s) = (22434)$.

For sequence s, we associate $\mathcal{M}$ a mapping array with η_s rows. The entries of $\mathcal{M}$ are from $\{1, 2, ..., t\}$ and the columns of $\mathcal{M}$ are mappings, say $\varphi_1, ..., \varphi_h$. Denote by $\mathcal{M}s$ the $p \times h$ array such that the columns are given by $\varphi_1(s), ..., \varphi_h(s)$. For example, for the same sequence $s = (11232)$ and the mapping array

$$\mathcal{M} = \begin{bmatrix} 1\,1\,1\,2\,2\,2\,3\,3\,3\,4\,4\,4 \\ 2\,3\,4\,1\,3\,4\,1\,2\,4\,1\,2\,3 \\ 4\,2\,3\,3\,4\,1\,4\,1\,2\,2\,3\,1 \end{bmatrix}, \tag{18}$$

we have

$$\mathcal{M}s = \begin{bmatrix} 1\,1\,1\,2\,2\,2\,3\,3\,3\,4\,4\,4 \\ 1\,1\,1\,2\,2\,2\,3\,3\,3\,4\,4\,4 \\ 2\,3\,4\,1\,3\,4\,1\,2\,4\,1\,2\,3 \\ 4\,2\,3\,3\,4\,1\,4\,1\,2\,2\,3\,1 \\ 2\,3\,4\,1\,3\,4\,1\,2\,4\,1\,2\,3 \end{bmatrix}.$$

If $\mathcal{M}$ consists of all $t!$ permutations $\{1, 2, ...t\}$, $\mathcal{M}s$ becomes a symmetric design, a stronger structure than pseudo symmetry. Note that one sufficient condition for a measure to be pseudo symmetric is given by

$$(\hat{C}_{\xi ij} =) \sum_{s \in \mathcal{S}} p_s \hat{C}_{sij} = c_{\xi ij} B_t/(t-1), 1 \le i, j \le 2 \tag{19}$$

$$\sum_{s \in \mathcal{S}} p_s T_s^1 B_t = 0 \tag{20}$$

3.1 A General Solution: OA_I of Strength 2

Proposition 1. *(i) Given a sequence s, let $\mathcal{M}$ be an orthogonal array of type I (OA_I) with η_s rows, t symbols and strength 2. Then $\mathcal{M}s$ is a pseudo symmetric design. (ii) The juxtaposition of designs derived in (i) results in a pseudo symmetric design, while the OA_I's used for generating each small design are allowed to be different.*

Proof. Note that (19) and (20) are shown by strength 2 and 1 of OA_I respectively.

Martin and Eccleston (1998) have given a different proof of part (i). Meanwhile, they also commented that "Optimality is much harder to show, and depends on both the assumed dependence structure and the parameter values for a given structure". Finally, they discussed optimal designs through several concrete examples without, however, providing general guidelines for deriving optimal designs. Now, by combining Corollary 2 and Proposition 1, we have

Theorem 4. *For a design constructed by Proposition 1 (ii), if its block proportion also satisfy (8), then the design is universally optimal.*

In Theorem 4, the existence of pseudo symmetric design only relied on the existence of OA_I, which in turn only rely on the values of p and t and not rely on V. The matrix V shall decide the form of (8) and hence the block proportions in order to achieve universal optimality. Of course, the value of n is still restricted by the structure of OA_I as well as the optimal block proportions derived from (8). To be more specific, we can produce pseudo symmetric designs by applying OA_I mappings to sequences $\{s_i : i \in I_{\mathcal{T}}\}$ and make proper numbers of copies of each of them so that (8) is satisfied. This approach will work when the values of the derivatives in (8) are rational, such as when V is a type H matrix. But these values could be irrational for other forms of V, or other models, as the one in Zheng (2015), and we shall look for efficient designs by rounding the proportions to rational numbers. As will be shown in Sect. 3.3, an approximate solution of (8) still yields a highly efficient design, and meanwhile the required n is allowed to be much smaller.

The advantage of pseudo symmetric designs over symmetric designs is that it can achieve higher flexibility in the number of subjects. To see this, assume that $\mathcal{T}$ consists of a single symmetric block, say $\langle s \rangle$. A pseudo symmetric design constructed by OA_I frequently requires only $k = t(t-1)$ subjects, while a symmetric design generated by s requires $t!/(t-\eta_s)! = k(t-2)!/(t-\eta_s)!$ subjects. Both of these two designs are universally optimal; however, the former provides a more flexible solution since it requires fewer subjects than the latter. Clearly, if all the mapping arrays are of strength η_s, the pseudo symmetric design reduces to a symmetric design.

The type of H-symmetric designs as specified by Theorem 7.2 of Kushner (1999) is also related to OA_I with strength 2. However, a necessary condition for such a design to exist is the existence of an OA_I with t rows. See Examples 7.5 and 7.6 in Kushner (1999), where $\mathcal{H}$ is a cyclic permutation group and an alternating permutation group respectively. By the present mapping approach, we only require the existence of an OA_I with η_s rows.

Kunert and Martin (2000b) proved that OA_I is universally optimal among all binary designs. This is a direct result of Corollary 1. To see this, we only have to notice that c_{sij}, $1 \le i, j \le 2$, is constant for all $s \in \langle s^* \rangle$, s^* is the sequence with $t_i = i$, $1 \le i \le p$. For other models than (1), Majumdar and Martin (2004) studied the optimality of $\mathcal{M}s^*$ under various models when $\mathcal{M}$ is either OA_I or orthogonal array of type II. Hedayat and Yan (2008) studied the optimality of $\mathcal{M}s^*$ for the self and mixed carryover effect model when $p = 3$ and the covariance matrix V follows a stationary first-order autoregressive process. The results of these papers could be essentially proved as long as we can show that $\mathcal{T} = \langle s^* \rangle$.

3.2 The Case of $V = I_p$ and $t \ge p - 1$

Recall that s^* is the sequence with $t_i = i$, $1 \le i \le p$ and denote by $s^{\#}$ the sequence with $t_i = i$, $1 \le i \le p-1$ and $t_p = p-1$. Let $\mathcal{M}$ be an OA_I of strength 2 with p rows and t symbols. Stufken (1991) considered the subclass of designs with different proportions of $\mathcal{M}s^* = \mathcal{M}$, $\mathcal{M}s^{\#}$ and another array with the format $\mathcal{M}s$. He showed that the optimal proportions for these arrays are

$1/t(p-1)$ for $\mathcal{M}s^{\#}$ and the remaining proportions for $\mathcal{M}s^{*}$. With the help of Kushner (1998), we can further show that such designs are universally optimal among all designs. He gave the theoretical results regarding $\mathcal{T}$ in two separate cases, namely $t \geq p$ or $t < p$. As a matter of fact, we can refine the result for the special case of $t = p - 1$.

Proposition 2 (Kushner 1998). *Assume V to be of type H. (i) If $t \geq p$, we have $\mathcal{T} = \langle s^{*} \rangle \cup \langle s^{\#} \rangle$. Moreover, a (pseudo) symmetric measure is universally optimal if and only if $p_{\langle s^{\#} \rangle} = 1/t(p-1)$ and $p_{\langle s^{*} \rangle} + p_{\langle s^{\#} \rangle} = 1$. (ii) If $t < p$, $\mathcal{T}$ consists of all sequences whose replications of different treatments do not differ by a number larger than one.*

Proposition 3. *When $V = I_p$ and $t = p - 1$, a pseudo symmetric measure is universally optimal if and only if $p_{\langle s^{\#} \rangle} = 1$.*

Proof. By Theorem 1.a of Kushner (1998), we have $x^{*} = 0$ and hence $q_s'(x^{*}) = 2c_{s12}$. By Corollary 2, the proposition will be proved as long as we can show that $c_{s12} = 0$ for $s \in \langle s^{\#} \rangle$ and $c_{s12} < 0$ for $s \in \mathcal{S} \backslash \langle s^{\#} \rangle$. The former is already shown in the proof of Theorem 1.a of Kushner (1998) and the latter can be shown by similar algebra.

Here, we try to use Patterson's designs to achieve the higher flexiblity in the number of subjects than the OA_I strategy when $V = I_p$ and $t \geq p - 1$. A two way array is called a *Patterson* array if it satisfies the following five conditions.

I. No symbol occurs in a given column more than once.
II. Each symbol occurs in a given row an equal number of times.
III. Each ordered succession of two distinct symbols occur equally often in columns.
IV. In columns with a given symbol in the last row, the other symbols occur equally often.
V. Every two symbols occur together in the same number of columns.

Theorem 5. *Assume $V = I_p$, (i) If $t \geq p$ and $\mathcal{M}_1$ is a Patterson's array with p rows and t symbols, then $\mathcal{M}_1 s^{*}$ is a pseudo symmetric design. (ii) If $t \geq p-1$ and $\mathcal{M}_2$ is a Patterson's array with $p-1$ rows and t symbols, then $\mathcal{M}_2 s^{\#}$ is a pseudo symmetric design. (iii) The juxtaposition of designs produced in (i) and (ii) respectively results in a pseudo symmetric design.*

Proof. By Condition II, we have (20) for all designs as proposed in the theorem, which indicates $C_{\xi ij} = \hat{C}_{\xi ij}$, $1 \leq i, j \leq 2$. For brevity, here we only show the complete symmetry of $\hat{C}_{\xi 12} = B_t[\sum_{s \in \mathcal{S}} p_s (T_s^1)' B_p T_s^2] B_t$, for which it is sufficient to show the complete symmetry of $\sum_{s \in \mathcal{S}} p_s (T_s^1)' B_p T_s^2$. Note that the values of the (i,j)th element of $(T_s^1)' B_p T_s^2$ only depend on the locations of symbols i and j in the sequence s. For the designs produced here, the columns represent the sequences.

For (i), the design produced is $\mathcal{M}_1$ itself and hence the produced sequences correspond to the columns of $\mathcal{M}_1$, i.e. satisfying Property I. For a given sequence

or column, (a) If i is immediately preceded by j, then the (i,j)th element takes the value of $1-1/p$. (b) If the jth element is in the last row, the (i,j)th element takes the value of 0. (c) If the sequence does not have the two symbols simultaneously, the (i,j)th element takes the value of 0. (d) If none of above happens, the (i,j)th element takes the value of $-1/p$. Now Property III guarantees that each off-diagonal element of the $t\times t$ matrix fall into category (a) for the same number of sequences. Properties II and IV guarantees that each off-diagonal element fall into category (b) for the same number of times. Property V guarantees that each off-diagonal element fall into category (c) for the same number of sequences. As a result, each off-diagonal element will fall into category (d) for the same number of sequences. The equality of the diagonal elements of $\sum_{s\in\mathcal{S}} p_s(T_s^1)'B_pT_s^2$ is guaranteed by Property II.

The proof for (ii) is similar and the extension to (iii) is straight forward.

Shah, Bose, and Raghavarao (2005) showed that the Patterson's array is universally optimal among binary designs. The latter is now a direct result of Theorem 5, in view of Corollary 1 (i) and $\mathcal{M}s^*=\mathcal{M}$. Patterson (1952) proposed seven conditions and studied the construction of this desirable structure. In fact, five of the seven conditions are as listed above, and the remaining two conditions are direct results of these five. The proof of Theorem 5 is valid if Condition II is replaced by the weaker condition II': each symbol occurs in the last row an equal number of times. It is not clear if this weaker structure permits alternative methods of construction besides the ones in Patterson (1952). The Patterson array based on Method 1 in Patterson (1952) can be derived from Kushner (1999)'s approach by taking $\mathcal{H}$ to be a cyclic permutation group. In studying optimal designs for the model with self and mixed carryover effects, Kunert and Stufken (2002) proposed a structure called a totally balanced design. A totally balanced design reduces to a Patterson array when the number of symbols is not less than the number of rows.

3.3 An Example

Now, for the case $p=4$, $t=7$ and $V=I_p$, we compare the flexibility, i.e. the number of subjects, associated with the symmetric, H-symmetric and pseudo-symmetric measures discussed and introduced in this paper. Since the juxtaposition of two optimal designs under the discussion of this paper is still optimal, we look for the smallest possible numbers of subjects in order for these types of designs to be optimal.

To construct a symmetric design, we must have: (i) $p_{\langle s^{\#}\rangle}=1/t(p-1)=1/21$ and $p_{\langle s^*\rangle}=20/21$, where $s^*=(1234)$ and $s^{\#}=(1233)$; (ii) Sequences in each of the two symmetric blocks should be evenly weighted. Since $|\langle s^*\rangle|=7\times6\times5\times4=840$ and $|\langle s^{\#}\rangle|=7\times6\times5=210$. Since $|\langle s^*\rangle|=4|\langle s^{\#}\rangle|$ and $p_{\langle s^*\rangle}=20p_{\langle s^{\#}\rangle}$, the minimum number of subjects can be achieved by making one copy of $\langle s^{\#}\rangle$ and 5 copies of $\langle s^*\rangle$. As a result, we have $n=210\times21=4410$. If we use a pseudo symmetric design constructed by OA_I, whose number of columns could be as small as $t(t-1)=42$, the minimum size of the design then reduces to

$n = 42 \times 21 = 882$. The H-symmetric design with $\mathcal{H}$ the cyclic subgroup yields the same size, i.e. $n = 882$. However, the last approach only works when t is prime.

A symmetric design with $p_{\langle s^* \rangle} = 1$ has the efficiency lower bound of 0.9861. To construct such a design, the minimum number of columns of such a design will be $n = 840$. A pseudo symmetric design constructed by OA_I with $p_{\langle s^* \rangle} = 1$, having the same efficiency, only needs $n = 42$. By using the following Patterson array (Patterson 1952), we can further reduce the size to $n = 14$.

$$\begin{array}{c|c} 1\,2\,3\,4\,5\,6\,7 & 1\,2\,3\,4\,5\,6\,7 \\ 2\,3\,4\,5\,6\,7\,1 & 7\,1\,2\,3\,4\,5\,6 \\ 4\,5\,6\,7\,1\,2\,3 & 5\,6\,7\,1\,2\,3\,4 \\ 7\,1\,2\,3\,4\,5\,6 & 2\,3\,4\,5\,6\,7\,1 \end{array}$$

4 Recent Advances on Related Problems

Here we would like to go through several examples to showcase that the approximate design theory has become a powerful tool in deriving optimal crossover or other similar designs. Some of the following result can be further enhanced by exploring the H-symmetric and/or pseudo symmetric designs as illustrated Sects. 2 and 3.

One possible concern with Model (1) is from the patient noncompliance in clinical trials, namely some will drop out of the study before the end of the p periods. As a result, the optimal design under full compliance may no longer be optimal or even efficient any more, and sometimes these designs could be even disconnected, see Godolphin (2004). By assuming the dropout mechanism to be completely random, we can utilize the observed data by standard least square estimates, and the information matrix, C_d, can be still derived in a smilier way as in this paper, except that this matrix is a random functional of the dropout realization. Low, Lewis, and Prescott (1999) focused on the criteria of $E\Phi_A(C_d)$, where Φ_A is the A-criterion function and the expectation is taken with respect to the distribution of dropout realization. They carried out direct search for efficient designs in the pool of Latin squares. Combinatorial tools are adopted by Bose and Bagchi (2008) and Majumdar, Dean, and Lewis (2008). They constructed designs optimal for the cases of full compliance or the case when all patients drop out at a certain period. The latter is justified by protecting for the worst case when all patients drop out at the earliest possible period. In fact, the complexity in calculating the expectation in $E\Phi_A(C_d)$ has prohibited the usage of combinatorial tools. Zheng (2013a) proposed to use a surrogate criterion function, which allows for studying the problem in the framework of approximate designs theory. Necessary and sufficient conditions of the universal optimality are derived for both pseudo symmetric designs and asymmetric designs. Further, a formula is given to evaluate the efficiency of any given design under the true criteria of $E\Phi(C_d)$.

Another variant of Model (1) is motivated by fact that sometimes treatments with strong direct effect may also tend to have stronger carryover effects. One

way to deal with this issue is by a proportional model, where the carryover effects are assumed to be proportional to their direct effects, i.e. $\gamma = \lambda\tau$ for a constant λ. This small modification lead us to a nonlinear model where the information matrix C_d depends on unknown parameters τ and λ. Kempton et al. (2001) adopted the Bayesian design approach and defined the criterion of $E\Phi_A(C_d)$. Here the expectation is taken with respect to the prior distributions of τ and λ, which are assumed to be multivariate normal and uniform distribution respectively. They proposed the strongly neighbour-balanced design and proved its A-optimality. The later research are all carried out in approximate design. Bailey and Kunert (2006) adopted the local optimal design for λ by replying on a good guess of it in design stage and adopt the Bayesian design for τ while relaxing the prior distribution to be any exchangeable distribution. They proved the A-optimality of totally balanced design (Kunert and Stufken 2002) when λ is smaller than a bound which is further controlled by $1/(p-1)$. This indicates that the optimality will not hold when the carryover effects has a moderate positive proportionality with the direct effect. Bose and Stufken (2007) assumed λ to be known even in data analysis stage, and as a consequence the optimality problem reduces to a linear model case. For the same problem as in Bailey and Kunert (2006), Zheng (2013b) derived the optimality conditions for criteria A, D, E and T. The idea therein can be implemented to deal with other criteria functions. Furthermore, Zheng (2013b) allowed for the general within subject covariance matrix.

The additivity assumption in Model (1) has been frequently challenged. One remedy is to assume the full interaction between the direct and carryover effects. Early works by Sen and Mukerjee (1987) and Park et al. (2011) used the combinatorial tools while the recent work by Bailey and Druilhet (2014) adopted Kushner's approximate design theory. To achieve a balance for the trade-off between bias and variance, the self and mixed carryover effect model was first proposed and studied by Afsarinejad and Hedayat (2002) for the special case of $p = 2$. To deal with longer sequences, we have to resort to approximate design theory, which is the case for all follow up works. Kunert and Stufken (2002) proved that a totally balanced design, if it exists, is universally optimal when $t > 3$ and $3 < p < 2t$. They also showed that a generalized Latin square with some extra properties will be optimal whenever $p = t$ or $p = 2t$. Kunert and Stufken (2008) extended the work by focusing on the special case of $t = 2$. Hedayat and Yan (2008) showed that Type I orthogonal array is optimal when the correlation between observations is a stationary first-order autoregressive process and p is 3 or 4. Druilhet and Tinsson (2009, 2014) considered optimal circular designs, where there exists a pre-period as a copy of the last period so that the treatment in the pre-period has carryover effect on the first period. Wilk and Kunert (2015) extended Hedayat and Yan (2008)'s result to the case of $t \geq p \geq 4$.

Motivated by agricultural and other applications, researchers have proposed the interference model where each treatment applied at a certain unit will have side effects on all neighboring units. When the unites within a block is arranged in

a one-dimensional space, Kunert and Martin (2000a) investigated the case when p is 3 or 4, which is extended by Kunert and Mersmann (2011) to $t \geq p \geq 5$. The results are in the format of Theorem 1. Following their work, Zheng (2015) achieved the following generalization: (i) The linear equation as in Theorem 2 is derived. (ii) It allows for any numbers of $p \geq 3$ and $t \geq 2$. (iii) It allows for any within-block covariance matrix. Moreover, the Kiefer's equivalence theorem are derived and it can be used to find sequences set $\mathcal{T}$ without locating the x^* value. The arguments developed therein shed light on other models with at least two sets of treatment-related nuisance parameters. Recently, Li, Zheng, and Ai (2015) derived optimal designs for estimating both the direct and total effects when the side effects are proportional to the direct effects while the within block covariance matrix is allowed to be of any form.

One variant of the interference model is the circular design, in which each block has a guard plot at each end so that each plot within the block has two neighbors. In early research, combinatorial tools dominated. See for instance Gill (1993) and Druilhet (1999). Also see Filipiak and Markiewicz (2003), who assumed random side effects, and Bailey and Druilhet (2004) for estimating the total effects. Subsequently, research used approximate design theory. For example, Filipiak and Markiewicz (2005) considered special correlated observations, for which only left side neighbor effects exist; Filipiak and Markiewicz (2007) considered again the random side effects model; Filipiak (2012) studied the special case of equal left and right side effects; Druilhet and Tinsson (2012) tackled the original problem by deriving pseudo symmetric designs. All of these papers assume that the within block covariance matrix is proportional to the identity matrix. Recently, Zheng et al. (2017) made a big leap forward in two directions. (i) The within block covariance matrix is arbitrarily. (ii) The general linear equations system is established as the necessary and sufficient condition for universal optimality.

5 Discussions

The main idea of approximate design theory (Kushner 1997) is symmetrization, which allows us to restrict consideration to the subclass of symmetric designs. The optimization within this subclass reduces to finding the maxmin of design-based quadratic functions, and the latter are typically computable by an algorithm. The issue with such an approach is that the existence of exact symmetric designs is rare due to the equal replications of sequences within a symmetric block. To remedy this, Kushner (1999) proposed H-symmetric designs by using subgroup of permutations. Here we propose the idea of pseudo symmetric designs for the same purpose. We illustrated that the latter is easier to implement and sometimes provides a better flexibility on the requirement of n, namely the number of subjects. To achieve further flexibility, we may round up the sequence proportions as in the example in Sect. 3.3. The construction of pseudo symmetric designs are worthy of study for other models.

Kushner (1997) has also provided a useful tool to check the universal optimality of any arbitrary design, namely the linear equations in Theorem 2. Note that

the solution to the linear equations exist in $\mathcal{P}_n$ for only selected number of n, i.e., for many cases there does not exist a universally optimal exact design. Hence it remains an open question of how to utilize it to construct optimal or efficient designs. One approach is the find a point in $\mathcal{P}_n$ *nearest* to the hyperplane defined by the linear equations. For example, Zheng (2013a) used Euclidean distance to find the nearest point, which reduce the problem to the integer quadratic programming. Examples obtained there showed that designs derived in this way are highly efficient. However, since integer quadratic programming is essentially an N-P hard problem, and the computation will be prohibitive when p and t become larger.

By using approximate design theory, we shall be able to find optimal designs for new models and enhance results for old models. It is technically more challenging to derive the general optimality condition as in Theorem 2 than the optimality condition for (pseudo) symmetric designs. Such results have their value, paving the way to the construction of asymmetric crossover designs. A further fundamental problem is to develop procedures of deriving exact designs based on the theorems in approximate design theory.

References

Afsarinejada, K., Hedayat, A.S.: Repeated measurements designs for a model with self and simple mixed carryover effects. J. Stat. Plann. Infer. **106**, 449–459 (2002)

Bailey, R.A., Druilhet, P.: Optimality of neighbor-balanced designs for total effects. Ann. Stat. **32**, 1650–1661 (2004)

Bailey, R.A., Druilhet, P.: Optimal cross-over designs for full interaction models. Ann. Stat. **42**, 2282–2300 (2014)

Bailey, R.A., Kunert, J.: On optimal crossover designs when carryover effects are proportional to direct effects. Biometrika **93**, 613–625 (2006)

Bose, M., Bagchi, S.: Optimal crossover designs under premature stopping. Utilitas Math. **75**, 273–285 (2008)

Bose, M., Dey, A.: Optimal Crossover Designs. World Scientific Publishing Company, Singapore (2009)

Bose, M., Stufken, J.: Optimal crossover designs when carryover effects are proportional to direct effects. J. Stat. Plann. Infer. **137**, 3291–3302 (2007)

Druilhet, P.: Optimality of circular neighbour balanced designs. J. Stat. Plan. Infer. **81**, 141–152 (1999)

Druilhet, P., Tinsson, W.: Optimal repeated measurement designs for a model with partial interactions. Biometrika **96**, 677–690 (2009)

Druilhet, P., Tinsson, W.: Efficient circular neighbour designs for spatial interference model. J. Stat. Plann. Infer. **142**, 1161–1169 (2012)

Druilhet, P., Tinsson, W.: Optimal cross-over designs for total effects under a model with self and mixed carryover effects. J. Stat. Plann. Infer. **154**, 54–61 (2014)

Filipiak, K.: Universally optimal designs under an interference model with equal left- and right-neighbor effects. Stat. Probab. Lett. **82**, 592–598 (2012)

Filipiak, K., Markiewicz, A.: Optimality of circular neighbor balanced designs under mixed effects model. Stat. Probab. Lett. **61**, 225–234 (2003)

Filipiak, K., Markiewicz, A.: Optimality and efficiency of neighbor balanced designs for correlated observations. Metrika **61**, 17–27 (2005)

Filipiak, K., Markiewicz, A.: Optimal designs for a mixed interference model. Metrika **65**, 369–386 (2007)
Gill, P.S.: Design and analysis of field experiments incorporating local and remote effects of treatments. Biometrical J. **35**, 343–354 (1993)
Godolphin, J.D.: Simple pilot procedures for the avoidance of disconnected experimental designs. J. R. Stat. Soc. Ser. C **53**, 133–147 (2004)
Hedayat, A.S., Afarinejad, K.: Repeated measurements designs, II. Ann. Stat. **6**, 619–628 (1978)
Hedayat, A.S., Yan, Z.: Crossover designs based on type I orthogonal arrays for a self and simple mixed carryover effects models with correlated errors. J. Stat. Plann. Infer. **138**, 2201–2213 (2008)
Jones, B., Kenward, M.G.: Design and Analysis of Cross-over Trials, 2nd edn. Chapman and Hall, London (2003)
Kempton, R.A., Ferris, S.J., David, O.: Optimal change-over designs when carry-over effects are proportional to direct effects of treatments. Biometrika **88**, 391–399 (2001)
Kiefer, J.: Construction and optimality of eneralized Youden designs. In: Srivistava, J.N. (ed.) A Survey of Statistical Design and Linear Models, North-Holland, Amsterdam (1975)
Kunert, J., Martin, R.J.: On the determination of optimal designs for an interference model. Ann. Stat. **28**, 1728–1742 (2000)
Kunert, J., Martin, R.J.: Optimality of type I orthogonal arrays for cross-over models with correlated errors. J. Stat. Plann. Infer. **87**, 119–124 (2000)
Kunert, J., Mersmann, S.: Optimal designs for an interference model. J. Stat. Plann. Infer. **141**, 1623–1632 (2011)
Kunert, J., Stufken, J.: Optimal crossover designs in a model with self and mixed carryover effects. J. Am. Stat. Assoc. **97**, 898–906 (2002)
Kunert, J., Stufken, J.: Optimal crossover designs for two treatments in the presence of mixed and self-carryover effects. J. Am. Stat. Assoc. **103**, 1641–1647 (2008)
Kushner, H.B.: Optimal repeated measurements designs: the linear optimality equations. Ann. Stat. **25**, 2328–2344 (1997)
Kushner, H.B.: Optimal and efficient repeated-measurements designs for uncorrelated observations. J. Am. Stat. Assoc. **93**, 1176–1187 (1998)
Kushner, H.B.: H-symmetric optimal repeated measurements designs. J. Stat. Plann. Infer. **76**, 235–261 (1999)
Li, K., Zheng, W., Ai, M.: Optimal designs for the proportional interference model. Ann. Stat. **43**, 1596–1616 (2015)
Low, J.L., Lewis, S.M., Prescott, P.: Assessing robustness of crossover designs to subjects dropping out. Stat. Comput. **9**, 219–227 (1999)
Majumdar, D., Dean, A.M., Lewis, S.M.: Uniformly balanced repeated measurements designs in the presence of subject dropout. Statistica Sinica **18**, 235–253 (2008)
Majumdar, D., Martin, R.J.: Efficient designs based on orthogonal arrays of type I and II for experiments using units ordered over time or space. Stat. Methodol. **1**, 19–35 (2004)
Martin, R.J., Eccleston, J.A.: Variance-balanced change-over designs for dependent observations. Biometrika **85**, 883–892 (1998)
Matthews, J.N.S.: Recent development in crossover designs. Internat. Statist. Rev. **56**, 117–127 (1988)
Park, D.K., Bose, M., Notz, W.I., Dean, A.M.: Efficient crossover designs in the presence of interactions between direct and carry-over treatment effects. J. Stat. Plann. Infer. **141**, 846–860 (2011)

Patterson, H.D.: The construction of balanced designs for experiments involving sequences of treatments. Biometrika **39**, 32–48 (1952)
Ratkowsky, D.A., Evans, M.A., Alldredge, J.R.: Cross-over Experiments: Design, Analysis, and Application. Marcel Dekker, New York (1992)
Sen, M., Mukerjee, R.: Optimal repeated measurements designs under interaction. J. Statist. Plann. Infer. **17**, 81–91 (1987)
Senn, S.: Cross-over Trials in Clinical Research, 2nd edn. Wiley, Chichester (2003)
Shah, K.R., Bose, M., Raghavarao, D.: Universal optimality of Patterson's crossover designs. Ann. Stat. **33**, 2854–2872 (2005)
Stufken, J.: Some families of optimal and efficient repeated measurements designs. J. Stat. Plann. Infer. **27**, 75–83 (1991)
Stufken, J.: Optimal crossover designs, Handbook of Statistics 13. In: Ghosh, S., Rao, C.R. (eds.) Design and Analysis of Experiments, North-Holland, Amsterdam, pp. 63–90 (1996)
Wilk, A., Kunert, J.: Optimal crossover designs in a model with self and mixed carryover effects with correlated errors. Metrika **78**, 161–174 (2015)
Zheng, W.: Universally optimal crossover designs under subject dropout. Ann. Stat. **41**, 63–90 (2013)
Zheng, W.: Optimal crossover designs for the proportional model. Ann. Stat. **41**, 2218–2235 (2013)
Zheng, W.: Universally optimal designs for two interference models. Ann. Stat. **43**, 501–518 (2015)
Zheng, W., Li, K., Ai, M.: Identification of universally optimal circular designs for the interference model. Ann. Stat. **45**, 1462–1487 (2017) ¡error l="304" c="Invalid command: paragraph not started." /¿ proportional to direct effects. Journal of Statistical Planning and Inference 137, ¡error l="304" c="Invalid command: paragraph not started." /¿ 3291-3302

Optimal Stress Levels in Accelerated Degradation Testing for Various Degradation Models

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Abstract. Accelerated degradation tests are used to provide accurate estimation of lifetime characteristics of highly reliable products within a relatively short testing time. Data from particular tests at high levels of stress (e.g., temperature, voltage, or vibration) are extrapolated, through a physically meaningful statistical model, to attain estimates of lifetime quantiles at normal use conditions. The gamma process is a natural model for estimating the degradation increments over certain degradation paths, which exhibit a monotone and strictly increasing degradation pattern. In this work, we contribute with analytical results in regards to optimal design for accelerated degradation testing with single failure mode that corresponds to single response component. The univariate degradation process is expressed using a gamma model where the concept of generalized linear model is introduced to facilitate the derivation of an optimal design. Subsequently, we extend the univariate model to characterize optimal designs for accelerated degradation tests under different bivariate degradation models. The first bivariate model includes two gamma processes as marginal degradation models. The second bivariate models is expressed by a gamma process along with a mixed effects linear model for the marginal components. Design optimization is conducted with respect to the minimum asymptotic variance criterion for estimating some quantile of the failure time distribution. Sensitivity analysis is considered to study the behavior of the resulting optimal designs under misspecifications of parameter values.

Keywords: Accelerated degradation test · Gamma model · Linear mixed-effects model · The multiplicative algorithm · Elfving's theorem · Locally c-optimal design

1 Introduction

Along with the enormous advances of industrial technologies, the companies are forced to manufacture highly reliable products in order to compete in the industrial market. During the design stage, it is extremely significant to assess the reliability related properties of the product. One of the proposed methods

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to handle this issue is accelerated life testing (ALT). However, it is difficult to obtain enough failure time data to satisfy the requirement of ALT because of the high-reliable property of products. Hence, accelerated degradation test (ADT) is suggested in order to give estimations in relatively short periods of time about the life time and reliability of the system under study. ADT might be divided into three classes, constant stress ADT (CSADT), step stress ADT (SSADT) and progressive ADT. In our model, we consider the optimal planning of CSADT where the testing units are divided into groups where each group is tested under distinct stress combination. Numerous researches have considered the implementation of ADT to provide reliability estimations. Tsai et al. (2016) derived an algorithm-based optimal ADT procedure by minimizing the asymptotic variance of the MLE of the mean time to failure of a product, where the sample size and termination time of each run of the ADT at a constant measurement frequency were determined. Zhang et al. (2015) suggested an analytical optimal ADT design method for more efficient reliability demonstration by minimizing the asymptotic variance of decision variable in reliability demonstration under the constraints of sample size, test duration, test cost, and predetermined decision risks. Considering linear mixed effects model (LMEM), (Weaver and Meeker 2013) utilized also the minimum asymptotic variance criterion to develop optimal design as well as compromise design plans for accelerated degradation tests. Further, (Ankenman et al. 2003) provided D-optimal experimental designs for the estimation of fixed effects and two variance components, in the presence of nested random effects. The authors show that the designs when the samples are distributed as uniformly as possible among batches result in D-optimal designs for maximum likelihood estimation. For the non-linear case, (Bogacka et al. 2017) presented D-optimal experimental designs for non-linear mixed effects models, where a categorical factor with covariate information is a design variable combined with another design factor. Moreover, (Sinha and Xu 2011) studied the performance of the locally D-optimal sequential designs for analyzing generalized linear mixed models. The authors demonstrate that one could attain considerable gain in efficiency from the maximum likelihood estimators when data are augmented with the sequential design scheme rather than the much simpler uniform design scheme. Considering Gamma process models, (Tsai et al. 2012) discussed the problem of cost-constrained optimal design for degradation tests based on a gamma degradation process with random effects. The authors provide further an analytical assessment of the effects of model mis-specification that occur when the random effects are not taken into consideration in the gamma degradation model. In addition, (Pan and Sun 2014) introduced reliability model of the degradation products with two performance characteristics based on a gamma process, and then present the corresponding SSADT model. Next, under the constraint of total experimental cost, the optimal settings such as sample size, measurement times, and measurement frequency are obtained by minimizing the asymptotic variance of the estimated 100αth percentile of the product's lifetime distribution. In order to predict the lifetime of the population from ADT, (Wang et al. 2015) considered gamma process with a time transformation and

random effects. They present a deducing method for determining the relationships between the shape and scale parameters of gamma process and accelerated stresses. Duan and Wang (2019) discussed optimal design problems for CSADT based on gamma processes with fixed effect and random effect. They prove that, for D-optimality,V-optimality and A-optimality criteria, optimal CSADT plans with multiple stress levels degenerate to two stress-level test plans only using the minimum and maximum stress levels under model assumptions. Lim (2015) developed statistical methods for optimal designing ADT plans under the total experimental cost constraint and assuming that the degradation characteristic follows a gamma process model. In addition, the author derives compromise plans to provide means to check the adequacy of the assumed acceleration model. ADT with the presence of competing failure modes is an important reliability area to be addressed. Therefore, the study of the statistical inference of ADT with competing failures is of great significance. (Haghighi and Bae 2015) introduced a modeling approach to simultaneously analyze linear degradation data and traumatic failures with competing risks in an SSADT experiment. Moreover, a methodology for ALT planning when there are two or more independent failure modes was discussed by (Pascual 2007). The author assumed that the failure modes have respective latent failure times, and the minimum of these times corresponds to the product lifetime. The latent failure times are assumed to be independently Weibull distributed with known, common shape parameter. Considering accelerated destructive degradation tests (ADDT), (Shi and Meeker 2014) proposed methods to find unconstrained and constrained optimum test plans for competing risk applications under a V-optimality criterion that aim to minimize the large-sample approximate variance of a failure-time distribution quantile at use conditions. The authors consider linearly degraded response models with an application for an adhesive bond. In regards to nonparametric methods of evaluation, Balakrishnan and Qin (2019) introduced some approximation techniques of the first passage time distribution of the degradation processes incorporating random effects if the process type is unknown. The authors approximate the density function of some stochastic degradation processes, i. e. Gamma process and inverse Gaussian process, by inverting the empirical Laplace transform using the empirical saddle-point method. Palayangoda et al. (2020) extended the work of (Balakrishnan and Qin 2019) by proposing some improved techniques based on saddle-point approximation where numerical examples and Monte Carlo simulation studies are used to illustrate the advantages of the proposed techniques. Further, Balakrishnan et al. (2017) considered the theoretical aspects as well as the application of Gamma processes in degradation analysis. The authors give some statistical properties of degradation models based on Gamma processes under different tests.

The rest of this article is organized as follows. Section 2 is devoted to analytically develop optimal experimental designs for a univariate gamma model. In Sect. 3 we introduce an optimal design considering a bivariate gamma process where the corresponding failure modes do not interact. In Sect. 4, we characterize

a c-optimal design for an ADT with a bivariate degradation model given that one of the marginal response components follows a gamma process model where the other follows a LMEM. The paper closes with a short discussion in Sect. 5. All numerical computations were made by using the R programming language (R Core Team 2020).

2 Accelerated Degradation Testing Based on a Gamma Process

The gamma process is a natural stochastic model for degradation processes in which degradation is assumed to occur gradually over time in a sequence of independent increments. In this section, we assume that the testing unit has a single dependent failure mode where the degradation path is characterized by a gamma process model in terms of a standardized time variable t. In addition, it is assumed that there is a single stress variable and its (standardized) stress level x can be chosen by the experimenter from the experimental region $\mathcal{X} = [0, 1]$. The subsequent subsections clarify the approximation of the gamma model with a generalized linear model approach. Further, we explain the derivation of the corresponding information matrix in order to obtain an optimal experimental design with respect to the asymptotic variance of a quantile of the failure time distribution.

2.1 Model Formulation

A gamma process Z_t is a stochastic process with independent gamma distributed increments. The process can be parameterized by the rate γ and a scale parameter ν. If the process is observed at k subsequent time points t_j, $0 < t_1 < ... < t_k$, then the jth degradation increment $Y_j = Z_{t_j} - Z_{t_{j-1}}$ is gamma distributed with shape $\gamma\delta_j$ and scale ν, where $\delta_j = t_j - t_{j-1}$ is the length of the jth time interval and $Z_{t_0} = 0$ at $t_0 = 0$.

We assume that the stress variable x only affects the rate $\gamma = \gamma(x)$ of the gamma process and, hence, the shape parameters $\gamma(x)\delta_j$ of the increments while the scale parameter ν is fixed and known. We further assume that the rate $\gamma(x)$ is given by a linear trend in the stress variable with a logarithmic link,

$$\gamma(x) = e^{\beta_0 + \beta_1 x}, \tag{1}$$

where the intercept β_0 and the slope β_1 are to be estimated. When a unit is tested under stress level x during a time interval of length δ, the degradation increment Y has density

$$f_Y(y) = \frac{y^{\gamma(x)\delta - 1} e^{-y/\nu}}{\Gamma(\gamma(x)\delta)\nu^{\gamma(x)\delta}}, \tag{2}$$

where $\Gamma(\alpha) = \int_0^\infty z^{\alpha-1} e^{-z} \mathrm{d}z$ is the gamma function. The mean of the increment is given by

$$\mu(x) = \mathrm{E}(Y) = \gamma(x)\delta\nu = e^{\beta_0 + \beta_1 x}\delta\nu. \tag{3}$$

Thus the mean $\mu(x)$ is linked to the linear predictor $\beta_0 + \beta_1 x$ by a scaled log link. Hence, the model assumptions fit into the concept of generalized linear models.

To be more specific, in accelerated degradation testing n distinct testing units are tested at potentially different stress settings x_i which are held fixed over time for each unit $i = 1, ..., n$. Measurements are made at predetermined time points $t_1, ..., t_k$ which are identical for all units. The degradation increments Y_{ij} when testing unit i during the jth time interval of length $\delta_j = t_j - t_{j-1}$ are independent gamma distributed with shape $\gamma(x_i)\delta_j$ and scale ν.

2.2 Estimation and Information

Denote by $\boldsymbol{\beta} = (\beta_0, \beta_1)^T$ the vector of unknown parameters. By (2) the log-likelihood of a single degradation increment Y is given by

$$\ell(\boldsymbol{\beta}; y) = (e^{\beta_0+\beta_1 x}\delta - 1)\ln(y) - y/\nu - \ln\left(\Gamma(e^{\beta_0+\beta_1 x}\delta)\right) - e^{\beta_0+\beta_1 x}\delta\ln(\nu) \quad (4)$$

when the stress level x is applied and the increment is measured over a time interval of length δ. The elemental Fisher information matrix $\mathbf{M}_{\boldsymbol{\beta}}(x, \delta)$ related to a single increment can be calculated as minus the matrix of expected second order derivatives of the log-likelihood,

$$\mathbf{M}_{\boldsymbol{\beta}}(x, \delta) = q(\beta_0 + \beta_1 x + \ln(\delta)) \begin{pmatrix} 1 & x \\ x & x^2 \end{pmatrix}, \quad (5)$$

where q is defined by $q(z) = e^{2z}\psi_1(e^z)$ and $\psi_1(\alpha) = \mathrm{d}^2 \ln(\Gamma(\alpha))/\mathrm{d}\alpha^2$ is the trigamma function.

Because the increments $Y_{i1}, ..., Y_{ik}$ measured at times $t_1, ..., t_k$ are statistically independent within a unit i, the log-likelihood $\ell(\boldsymbol{\beta}; y_{i1}, ..., y_{ik}) = \sum_{j=1}^{k} \ell(\boldsymbol{\beta}; y_{ij})$ of a unit i is the sum of the log-likelihoods for the single observations Y_{ij}. Thus also the information matrix $\mathbf{M}_{\boldsymbol{\beta}}(x_i)$ of a unit is the sum of the information of the single increments,

$$\mathbf{M}_{\boldsymbol{\beta}}(x_i) = \sum_{j=1}^{k} \mathbf{M}_{\boldsymbol{\beta}}(x_i, \delta_j) = \lambda(\beta_0 + \beta_1 x_i) \begin{pmatrix} 1 & x_i \\ x_i & x_i^2 \end{pmatrix}, \quad (6)$$

where the "intensity" $\lambda(z) = \sum_{j=1}^{k} q\big(z + \ln(\delta_j)\big)$ accounts for the contribution of the non-linearity at $z = \beta_0 + \beta_1 x_i$ to the information.

Furthermore, because measurements are statistically independent between units, both the log-likelihood $\ell(\boldsymbol{\beta}; y_{11}, ..., y_{nk}) = \sum_{i=1}^{n} \ell(\boldsymbol{\beta}; y_{i1}, ..., y_{ik})$ and the information

$$\mathbf{M}_{\boldsymbol{\beta}}(x_1, ..., x_n) = \sum_{i=1}^{n} \mathbf{M}_{\boldsymbol{\beta}}(x_i) \quad (7)$$

for the whole experiment summarize the log-likelihood and the information of the units, respectively. This information matrix $\mathbf{M}_{\boldsymbol{\beta}}(x_1, ..., x_n)$ provides a measure for the performance of the experiment as its inverse is proportional to the

asymptotic variance covariance matrix for the maximum likelihood estimator of $\boldsymbol{\beta}$.

In an accelerated degradation experiment the stress variable x is under control of the experimenter. For each unit i, the setting x_i of the stress variable adjusted to i may be chosen from an experimental region $\mathcal{X}$. The collection $x_1, ..., x_n$ of these settings is called the design of the experiment. An optimal design then aims at minimizing an optimality criterion which is a function of the information matrix.

Finding optimal designs $x_1, ..., x_n$ is, in general, a difficult task of discrete optimization. To circumvent this problem we follow the approach of approximate designs propagated by Kiefer (1959). For this first note that by (7) the information matrix $\mathbf{M}_{\boldsymbol{\beta}}(x_1, ..., x_n) = \sum_{i=1}^{m} n_i \mathbf{M}_{\boldsymbol{\beta}}(x_i)$ does only depend on the set of mutually distinct settings $x_1, ..., x_m$, say, in the design and their corresponding frequencies $n_1, ..., n_m$, $\sum_{i=1}^{m} n_i = n$. For approximate designs the requirement of integer numbers n_i of testing units at stress level x_i is relaxed. Then methods of continuous convex optimization can be employed to find optimal designs, see (Silvey 1980), and efficient designs with integer numbers n_i can be derived by proper rounding the optimal solutions to nearest integers. For this approach the sample size n does not play a role on the optimization step when proportions $w_i = n_i/n$ are considered. This approach is, in particular, of use when the number n of units is sufficiently large which is appropriate in the present non-linear setup, where asymptotic performance is measured. Moreover, in this approach, the frequencies n_i will be replaced by proportions $w_i = n_i/n$, because the total number n of units does not play a role in the optimization. Thus an approximate design ξ is defined by a finite number of settings x_i from the experimental region $\mathcal{X}$ with associated weights $w_i > 0$, $i = 1, ..., m$, $\sum_{i=1}^{m} w_i = 1$. Accordingly, the corresponding standardized, per unit information matrix is defined as

$$\mathbf{M}_{\boldsymbol{\beta}}(\xi) = \sum_{i=1}^{m} w_i \mathbf{M}_{\boldsymbol{\beta}}(x_i) \tag{8}$$

so that "exact" designs $x_1, ..., x_n$ are properly embedded by $\mathbf{M}_{\boldsymbol{\beta}}(\xi) = (1/n)\mathbf{M}_{\boldsymbol{\beta}}(x_1, ..., x_n)$.

As the information matrix depends on the parameter vector $\boldsymbol{\beta}$ only through the linear predictor $\beta_0 + \beta_1 x$, a canonical transformation can be employed which simultaneously maps experimental settings x to $z = \beta_0 + \beta_1 x$ and the parameters β_0 and β_1 to the standardized value $\beta_0 = 0$ and $\beta_1 = 1$ for analytical solutions, see Ford et al. (1992).

When all time intervals have the same length $\delta_j = \delta$, $j = 1, ..., k$, the influence of the repeated measurements reduces to $\lambda(z) = k\, q\big(z + \ln(\delta)\big)$ for the intensity and, hence, to a multiplicative factor k in the information matrix. Thus, for common design criteria, the number k of measurements is immaterial for design optimization.

2.3 Optimality Criterion Based on the Failure Time Distribution

In degradation testing we are interested in characteristics of the failure time distribution of soft failure due to degradation under normal use condition x_u. It is supposed that the gamma process $Z_{u,t}$ describing the degradation under normal use condition has the rate $\gamma(x_u) = e^{\beta_0+\beta_1 x_u}$ as in Eq. (1) and scale ν. Typically the normal use condition x_u is not contained in the experimental region $\mathcal{X}$, $x_u < 0$. Further it is natural to assume that the degradation paths are strictly increasing over time. Then a soft failure due to degradation is defined as exceedance of the degradation path over a failure threshold z_0. The failure time T under normal use condition is defined as the first time t the degradation path $Z_{u,t}$ reaches or exceeds the threshold z_0, i. e., $T = \inf\{t \geqslant 0;\, Z_{u,t} \geqslant z_0\}$. In order to derive certain characteristics of the distribution of the failure time, we determine its distribution function $F_T(t) = \mathrm{P}(T \leqslant t)$. For this note that $T \leqslant t$ if and only if $Z_{u,t} \geqslant z_0$. The degradation $Z_{u,t}$ at time t is gamma distributed with shape $\gamma(x_u)t$ and scale ν. Hence, the distribution function of the failure time T can be expressed as

$$\begin{aligned} F_T(t) &= \mathrm{P}(Z_{u,t} \geqslant z_0) \\ &= \frac{1}{\Gamma(\gamma(x_u)t)} \int_{z_0}^{\infty} (z/\nu)^{\gamma(x_u)t-1} e^{-z/\nu} \nu^{-1} \mathrm{d}z \\ &= Q(\gamma(x_u)t, z_0/\nu) \end{aligned} \tag{9}$$

where $Q(s,z) = \Gamma(s,z)/\Gamma(s)$ is the regularized gamma function and $\Gamma(s,z) = \int_z^{\infty} x^{s-1}e^{-x}\mathrm{d}x$ the incomplete gamma function.

We will be interested in some quantile t_α of the failure time distribution. In the case of a continuous distribution function $F_T(t)$, the α-quantile t_α satisfies $F_T(t_\alpha) = \alpha$, i. e., it represents the time up to which under normal use conditions $\alpha \cdot 100$ percent of the units fail and $(1-\alpha)\cdot 100$ percent of the units persist. The distribution function and, hence, the quantile $t_\alpha = t_\alpha(\boldsymbol{\beta})$ depends on the parameter vector $\boldsymbol{\beta}$ in which the quantile t_α is a decreasing functions of the linear predictor $\beta_0 + \beta_1 x_u$.

With this functional relationship the maximum likelihood estimator for the quantile t_α is given by $\widehat{t}_\alpha = t_\alpha(\widehat{\boldsymbol{\beta}})$, where $\widehat{\boldsymbol{\beta}}$ is the maximum likelihood estimator of $\boldsymbol{\beta}$. The performance of these estimators is measured by their asymptotic variance $\mathrm{aVar}(\widehat{t}_\alpha)$, and design optimization will be conducted with respect to the minimum asymptotic variance criterion, i. e. an optimal design minimizes $\mathrm{aVar}(\widehat{t}_\alpha)$. This criterion is commonly used in planning degradation tests when experimenters are interested in accurately estimating reliability properties of a system over its life cycle.

If the distribution function $F_T(t)$ is strictly increasing with continuous density $f_T(t) = F_T'(t)$, the asymptotic variance can be derived by the delta method from the information matrix in Sect. 2.2 as

$$\mathrm{aVar}(\widehat{t}_\alpha) = \mathbf{c}^T \mathbf{M}_{\boldsymbol{\beta}}(\xi)^{-1}\mathbf{c}, \tag{10}$$

where $\mathbf{c} = \partial t_\alpha(\boldsymbol{\beta})/\partial\boldsymbol{\beta}$ is the vector of partial derivatives of $t_\alpha = F_T^{-1}(\alpha)$ with respect to the components of the parameter vector $\boldsymbol{\beta}$ evaluated at the true values

of $\boldsymbol{\beta}$. Let $g(s) = Q(s, z_0/\nu)$ be the regularized gamma function with the second argument fixed to z_0/ν, then $t_\alpha = g^{-1}(\alpha)/\gamma(x_u)$ by (9) and the vector $\mathbf{c}$ of partial derivatives can be written as $\mathbf{c} = -t_\alpha(1, x_u)^T$, where the minus sign and the scaling factor t_α do not affect the optimization problem. Hence, the minimum asymptotic variance criterion is equivalent to a c-criterion with $\mathbf{c} = (1, x_u)^T$, i. e., extrapolation of the linear predictor $\beta_0 + \beta_1 x_u$ at the normal use condition x_u, and standard optimization methods for c-criteria can be employed. In particular, the design optimization does not depend on which quantile t_α is to be estimated, and the obtained design is simultaneously optimal for all α.

Because the information matrix $\mathbf{M}_{\boldsymbol{\beta}}(\xi)$ depends on the parameter vector $\boldsymbol{\beta}$, this affects the design optimization. Hence, nominal values have to be assumed for these parameters, and locally optimal designs can be obtained for those nominal values. Numerical calculations indicate that the locally optimal designs ξ^* are supported on the endpoints of the design region $\mathcal{X}$, i. e., they are of the form $\xi^* = \xi_{w^*}$, where ξ_w denotes a design with weight $w_1 = w$ on $x_1 = 0$ and weight $w_2 = 1 - w$ on $x_2 = 1$. Under this premise the optimal weight w^* can be determined analytically by Elfving's theorem Elfving (1952),

$$w^* = \frac{(1 + |x_u|)\sqrt{\lambda(\beta_0 + \beta_1)}}{(1 + |x_u|)\sqrt{\lambda(\beta_0 + \beta_1)} + |x_u|\sqrt{\lambda(\beta_0)}} \tag{11}$$

for (standardized) normal use condition $x_u < 0$. This optimal weight w^* is a decreasing function in the distance $|x_u|$ between the normal use condition and the lowest stress level $x_1 = 0$, and it decrease from $w^* = 1$ when formally letting $x_u = 0$ to $\sqrt{\lambda(\beta_0 + \beta_1)}/(\sqrt{\lambda(\beta_0 + \beta_1)} + \sqrt{\lambda(\beta_0)})$ for $x_u \to -\infty$, where this lower bound is larger than 0.5 since $\beta_1 > 0$ and the intensity $\lambda(z)$ is an increasing function in z.

Concerning the parameters β_0 and β_1 the optimal weight w^* is increasing in the slope parameter β_1 while it does not seem to be sensitive with respect to the intercept parameter β_0 as will be illustrated in Fig. 3 and Fig. 4 below for some nominal values. Therefore it is of interest to check how a misspecification of the nominal values for $\boldsymbol{\beta}$ may affect the performance of a locally optimal design $\xi^* = \xi_{w^*}$. To measure the performance we make use of the concept of efficiency

$$\mathrm{eff}_{\mathrm{aVar}}(\xi; \boldsymbol{\beta}) = \frac{\mathrm{aVar}_{\boldsymbol{\beta}}(\widehat{t}_\alpha; \xi^*_{\boldsymbol{\beta}})}{\mathrm{aVar}_{\boldsymbol{\beta}}(\widehat{t}_\alpha; \xi)} \tag{12}$$

of a design ξ with respect to the asymptotic variance for estimating t_α when $\boldsymbol{\beta}$ is the true value of the parameter, where $\mathrm{aVar}_{\boldsymbol{\beta}}(\widehat{t}_\alpha; \xi)$ denotes the asymptotic variance of $\widehat{t}_\alpha$ at $\boldsymbol{\beta}$, when the design ξ is used, and $\xi^*_{\boldsymbol{\beta}}$ is the locally optimal design at $\boldsymbol{\beta}$. This efficiency attains a value between 0 and 1. It can be interpreted as the proportion of units needed, when the locally optimal design $\xi^*_{\boldsymbol{\beta}}$ is used, to obtain the same precision in the asymptotic variance as for the design ξ under consideration. Thus high values of the efficiency are advantageous for a design to be used.

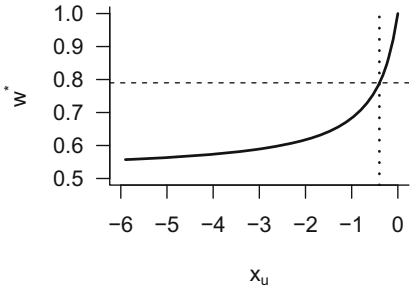

Fig. 1. Optimal weights w^* in dependence on the normal use condition x_u for the univariate gamma process in the example of Subsect. 2.4

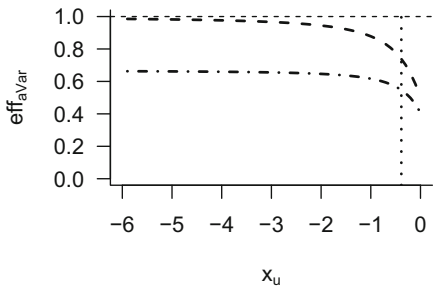

Fig. 2. Efficiency of $\bar{\xi}_2$ (solid line) and $\bar{\xi}_3$ (dashed line) in dependence on the normal use condition x_u in the example of Subsect. 2.4

2.4 Numerical Example

In this example we consider an accelerated degradation experiment as described in Subsect. 2.1 with standardized normal use condition $x_u = -0.4$, underlying gamma process with scale parameter $\nu = 1$ and degradation threshold $z_0 = 5.16$. We will be interested in estimating the median $t_{0.5}$ of the failure time T due to degradation. The standardized observation times are $t_j = 0.25$, 0.5, 0.75 and 1, i. e., there are $k = 4$ degradation increments measured on time intervals of constant length $\delta = 0.25$. With respect to the location parameters we assume the nominal values $\beta_0 = 0.23$ for the intercept and $\beta_1 = 0.53$ for the slope. For these parameter values, the distribution function $F_T(t)$ of the failure time T is exhibited in Fig. 7 below as F_{T_1}. The corresponding median failure time $t_{0.5} = 5.39$ for which $F_T(t_{0.5}) = 1/2$ is indicated in Fig. 7 by a dashed vertical line.

To find the optimal design ξ^* for estimating the median failure time t_α, we apply the multiplicative algorithm following (Torsney and Martín-Martín 2009) for the standardized stress parameter x on a grid with increments of size 0.01 on the design region $\mathcal{X} = [0, 1]$. The optimal design ξ^* is found to be of the form ξ_w with optimal weight $w^* = 0.79$ at the lowest stress level ($x = 0$) and weight $1 - w^* = 0.21$ at the highest stress level ($x = 1$) in the experiment.

For illustrative purposes, the optimal weight w^* is plotted in Fig. 1 as a function of the normal use condition x_u when the nominal values of the other parameters are held fixed.

For the normal use condition x_u close to the lowest value $x = 0$ of the design region, the optimal weight w^* approaches 1, and w^* decreases to 0.516 when x_u is far away from the design region ($x_u \to -\infty$). The nominal value $x_u = -0.4$ and the corresponding optimal weight $w^* = 0.79$ are indicated in Fig. 1 by a vertical and a horizontal dashed line, respectively. To imagine the gain in applying the optimal design ξ^*, we exhibit the efficiency (12) of commonly used standard designs $\bar{\xi}_2$ and $\bar{\xi}_3$ in Fig. 2, when the nominal values for the other parameters

are held fixed. In this comparison the designs $\bar{\xi}_m$ are uniform on m equidistant stress values $x_1, ..., x_m$ covering the whole range of the design region $0 \leqslant x \leqslant 1$. In particular, $\bar{\xi}_2$ is of the form ξ_w with $w = 1/2$, and $\bar{\xi}_3$ assigns weight $1/3$ to each of the endpoints ($x = 0$) and ($x = 1$) and to the midpoint ($x = 0.5$) of the design region.

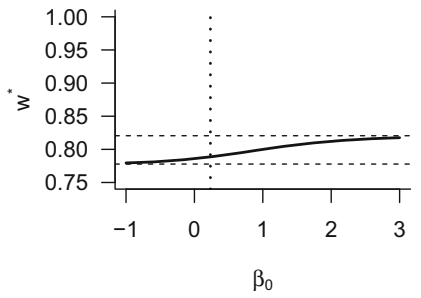

Fig. 3. Dependence of the optimal weight w^* on β_0 in the example of Subsect. 2.4

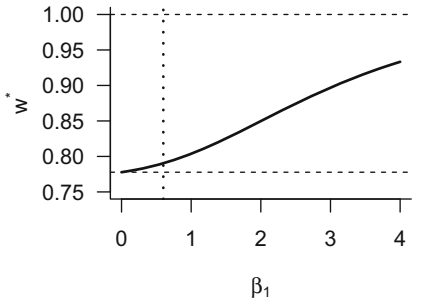

Fig. 4. Dependence of the optimal weight w^* on β_1 in the example of Subsect. 2.4

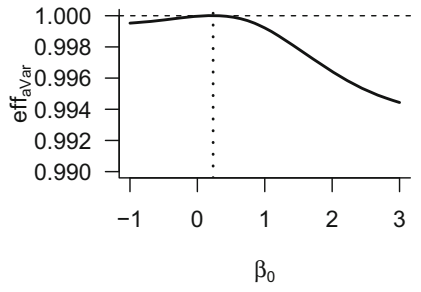

Fig. 5. Efficiency of ξ^* in dependence on β_0 in the example of Subsect. 2.4

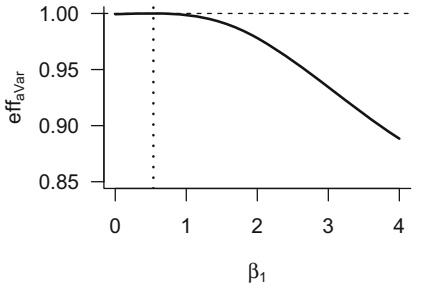

Fig. 6. Efficiency of ξ^* in dependence on β_1 in the example of Subsect. 2.4

The nominal value $x_u = -0.4$ of the normal use condition is indicated in Fig. 2 by a vertical dotted line. The uniform two-point design $\bar{\xi}_2$ shows a high efficiency at values x_u which are sufficiently far from the standardized design region. This is in accordance with the similarity of the weights in $\bar{\xi}_2$ and in the optimal design ξ^* for such values. For x_u close to the lowest experimental stress level $x = 0$ the efficiency of $\bar{\xi}_2$ drops to 50 %. The uniform three-point design $\bar{\xi}_3$ shows a much lower efficiency throughout. At the nominal value $x_u = -0.4$ the efficiency of the uniform two- and three-point designs $\bar{\xi}_2$ and $\bar{\xi}_3$ is $\mathrm{eff}_{\mathrm{aVar}}(\bar{\xi}_2; \boldsymbol{\beta}) = 75\,\%$ and

$\text{eff}_{\text{aVar}}(\bar{\xi}_3; \boldsymbol{\beta}) = 55\,\%$, respectively. That means that for the optimal design ξ^* only 75% of units are required compared to the design $\bar{\xi}_2$ and 55 percent of units compared to the design $\bar{\xi}_3$ to achieve the same accuracy for estimating the median failure time.

To assess the sensitivity of the locally optimal design $\xi^* = \xi_{w^*}$ we plot the optimal weights w^* in dependence on the intercept and slope parameters β_0 and β_1 in Fig. 3 and Fig. 4, respectively, while the other nominal values are held fixed.

In order to judge the performance of the locally optimal design $\xi^* = \xi^*_{\boldsymbol{\beta}}$ at the proposed nominal values $\beta_0 = 0.23$ and $\beta_1 = 0.53$ of the location parameters under misspecifications, we show the efficiency in dependence on the intercept and slope parameters β_0 and β_1 in Fig. 5 and Fig. 6, respectively, while the other parameters are held fixed to their nominal values. Figure 5 displays that the optimal design ξ^* maintain its efficiency under misspecifications of β_0. In contrast, Fig. 6 depicts that misspecifications of the slope β_1 substantially affects the efficiency of the design ξ^* and more attention should be paid to a correct specification of the nominal value for the slope parameter opposite to the intercept.

3 Bivariate Accelerated Degradation Testing with Two Gamma Processes

We consider now the optimal design problem for a bivariate degradation process incorporating serially two independent failure modes which means that a failure of the system occurs when one of the two components fail.

3.1 Model Formulation

We assume that in the two degradation components takes place according to independent gamma processes Z_{1t} and Z_{2t}, respectively, as described in Sect. 2, where for both processes Z_{lt} the rate $\gamma_l(x) = e^{\beta_{l0}+\beta_{l1}x}$ depends on the same standardized accelerating stress variable $x \in \mathcal{X} = [0, 1]$ via a linear trend $\beta_{l0} + \beta_{l1}x$ under the log link as in (1). By assumption the degradation increments $Y_{ilj} = Z_{lt_j} - Z_{lt_{j-1}}$ of both components during the jth time interval of length δ_j are all gamma distributed with shape $\gamma_l(x_i)\delta_j$ and scale ν_l, $l = 1, 2$, and independent.

The failure times T_1 and T_2 of the components for soft failure due to degradation are defined as in Subsect. 2.3. The failure of the system occurs when either of the two components fail, and the failure time T of the system is defined by $T = \min\{T_1, T_2\}$. Because of the independence of the underlying processes, the failure times T_1 and T_2 of the components are independent.

3.2 Information

Denote by $\boldsymbol{\beta}_l = (\beta_{l1}, \beta_{l2})^T$ the marginal parameter vector associated with the lth failure mode. Because of the independence of the components the

joint log-likelihood of $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_l$ is the sum $\ell(\boldsymbol{\beta}_1, \ell(\boldsymbol{\beta}_2; y_{111}, ..., y_{n2k}) = \ell(\boldsymbol{\beta}_1; y_{111}, ..., y_{n1k}) + \ell(\boldsymbol{\beta}_2; y_{121}, ..., y_{n2k})$ of the log-likelihoods $\ell(\boldsymbol{\beta}_l; y_{1l1}, ..., y_{nlk})$ of the components given by 4. Hence, the maximum likelihood estimators $\widehat{\boldsymbol{\beta}}_l$ of $\boldsymbol{\beta}_l$ in the whole system coincides with those in the marginal models and the joint information matrix $\mathbf{M}_{\boldsymbol{\beta}_1,\boldsymbol{\beta}_2}(x_1, ..., x_n)$ for all parameters is block diagonal, $\mathbf{M}_{\boldsymbol{\beta}_1,\boldsymbol{\beta}_2}(x_1, ..., x_n) = \begin{pmatrix} \mathbf{M}_{\boldsymbol{\beta}_1}(x_1, ..., x_n) & \mathbf{0} \\ \mathbf{0} & \mathbf{M}_{\boldsymbol{\beta}_2}(x_1, ..., x_n) \end{pmatrix}$, where the diagonal blocks $\mathbf{M}_{\boldsymbol{\beta}_l}$ are the marginal information matrices for the single failure modes as specified in Subsect. 2.2. Accordingly, for approximate designs ξ the standardized information matrix

$$\mathbf{M}_{\boldsymbol{\beta}_1,\boldsymbol{\beta}_2}(\xi) = \begin{pmatrix} \mathbf{M}_{\boldsymbol{\beta}_1}(\xi) & \mathbf{0} \\ \mathbf{0} & \mathbf{M}_{\boldsymbol{\beta}_2}(\xi) \end{pmatrix}. \tag{13}$$

is also block diagonal with the marginal information matrices $\mathbf{M}_{\boldsymbol{\beta}_l}(\xi)$ on the diagonal.

3.3 Optimality Criterion Based on the Failure Time Distribution

As in Sect. 2.3 we are interested in characteristics of the failure time distribution of soft failures due to degradation under normal use condition x_u. The marginal failure times T_l under normal use condition are defined as the first time t the degradation path $Z_{u,lt}$ reaches or exceeds the corresponding threshold z_{l0}, i. e., $T_l = \inf\{t \geqslant 0;\, Z_{u,lt} \geqslant z_{l0}\}$. A failure of the system occurs if one of the components fail. Hence, the failure time T of the system is defined by $T = \min\{T_1, T_2\}$. Because of the independence of the components the survival function $1 - F_T(t) = \mathrm{P}(T_1 > t, T_2 > t)$ factorizes into the marginal survival functions $1 - F_{T_l}(t)$. Hence, the failure time distribution of the system can be expressed as

$$F_T(t) = 1 - (1 - F_{T_1}(t))(1 - F_{T_2}(t)), \tag{14}$$

where $F_{T_l}(t) = Q(\gamma_l(x_u)t, z_{l0}/\nu_l)$ by (9).

As in Subsect. 2.3, we will consider quantiles t_α of the failure time distribution. Also here the distribution function F_T and, hence, the quantile $t_\alpha = t_\alpha(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2)$ is a function of the parameters and the maximum likelihood estimate $\widehat{t}_\alpha = t_\alpha(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2)$ of the quantile t_α is based on the maximum likelihood estimates $\widehat{\boldsymbol{\beta}}_l$ of $\boldsymbol{\beta}$ for the components.

The task of designing the experiment is to provide an as precise estimate of the α-quantile as possible, i. e., to minimize the asymptotic variance $\mathrm{aVar}(\widehat{t}_\alpha)$ of $\widehat{t}_\alpha$ at the normal use condition. As in Subsect. 2.3 the asymptotic variance can be obtained as $\mathrm{aVar}(\widehat{t}_\alpha) = \mathbf{c}^T \mathbf{M}_{\boldsymbol{\beta}_1,\boldsymbol{\beta}_2}(\xi)^{-1} \mathbf{c}$, where $\mathbf{c} = (\mathbf{c}_1^T, \mathbf{c}_2^T)^T$ and $\mathbf{c}_l = \partial t_\alpha(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2)/\partial \boldsymbol{\beta}_l$ is the vector of partial derivatives of t_α with respect to the parameter vector $\boldsymbol{\beta}_l$ evaluated at the true values of $\boldsymbol{\beta}_l$. Differently from the univariate case in Subsect. 2.3 there is no explicit formula for t_α. Therefore, the general form of the gradient vectors $\mathbf{c}_l$ will be derived by the implicit function theorem as

$$\frac{\partial t_\alpha}{\partial \boldsymbol{\beta}_l} = -\frac{1}{f_T(t_\alpha)} \frac{\partial F_T(t_\alpha)}{\partial \boldsymbol{\beta}_l} \tag{15}$$

in terms of the failure time distribution $F_T(t)$, where $f_T(t) = \partial F_T(t)/\partial t$ is the density of T. The common scaling factor $c_0 = -1/f_T(t_\alpha)$ is irrelevant for the optimization problem. Hence, the components of the c-criterion vector $\mathbf{c} = (\mathbf{c}_1^T, \mathbf{c}_2^T)^T$ can be reduced to $\mathbf{c}_l = \partial F_T(t_\alpha)/\partial \boldsymbol{\beta}_l$. Based on Eq. 14, the gradient vectors $\mathbf{c}_l$ can be expressed as $\mathbf{c}_l = c_l(1, x_u)^T$ similar to the univariate case, where

$$c_l = \kappa_l \left(1 - F_{T_{l'}}(t_\alpha)\right) \left(\frac{\Gamma(\kappa_l)}{\Gamma(\kappa_l + 1)^2} (z_{l0}/\nu_l)^{\kappa_l} \, {}_2F_2(\kappa_l, \kappa_l; \kappa_l + 1, \kappa_l + 1; -z_{l0}/\nu_l) + \left(Q(\kappa_l, z_{l0}/\nu_l) - 1\right) \left(\ln(z_{l0}/\nu_l) - \psi(\kappa_l)\right)\right) \tag{16}$$

is a positive constant depending on $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$, $\kappa_l = \gamma_l(x_u)t_\alpha$ is the shape parameter for an increment of the lth marginal process during time t_α, ${}_2F_2$ denotes the generalized hypergeometric function

$${}_2F_2(\kappa, \kappa; \kappa + 1, \kappa + 1; -z) = 1 + \sum_{k=1}^{\infty} \left(\frac{\kappa}{\kappa + k}\right)^2 \frac{(-z)^k}{k!},$$

and l' is the index of the respective other component, i. e., $l' = 2$ if $l = 1$ and vice versa. For further details see (Tsai et al. 2012).

Since the information matrix in (13) is block-diagonal, the optimality criterion

$$\mathrm{aVar}(\widehat{t_\alpha}) = c_0^2(c_1^2(1, x_u)\mathbf{M}_{\boldsymbol{\beta}_1}(\xi)^{-1}(1, x_u)^T + c_2^2(1, x_u)\mathbf{M}_{\boldsymbol{\beta}_2}(\xi)^{-1}(1, x_u)^T) \tag{17}$$

is a weighted sum of the optimality criteria for the single components stated in Subsect. 2.3 and constitutes, hence, a compound criterion.

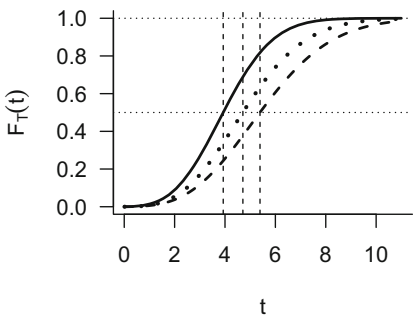

Fig. 7. Failure time distributions $F_T(t)$ (solid line), $F_{T_1}(t)$ (dashed line), and $F_{T_2}(t)$ (dotted line) for the bivariate gamma process in the example of Subsect. 3.4

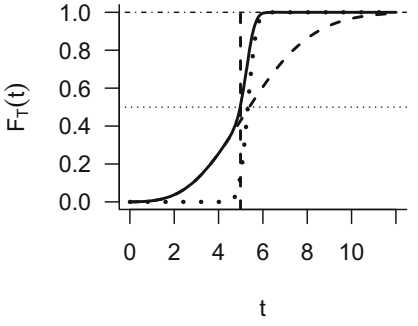

Fig. 8. Failure time distributions $F_T(t)$ (solid line), $F_{T_1}(t)$ (dashed line), and $F_{T_2}(t)$ (dotted line) for the bivariate model with a gamma process (T_1) and a linear mixed effect (T_2) component for the example of Subsect. 4.6

In the special case that the nominal values are identical for both components, i. e., $\boldsymbol{\beta}_1 = \boldsymbol{\beta}_2$, the optimal design ξ^* for a single component will also be optimal for the bivariate failure process, independent of α. In general, however, the optimal design for the bivariate failure process has to be a compromise of the marginal optimal designs for the components.

3.4 Numerical Example

In this example we consider an accelerated degradation experiment with two failure components following two independent gamma processes. The first process is specified as in Subsect. 2.4 with scale parameter $\nu_1 = 1$, degradation threshold $z_{10} = 5.16$ and nominal values $\beta_{10} = 0.23$ for the intercept and $\beta_{11} = 0.53$ for the slope. For the second process we assume a scale parameter $\nu_2 = 0.88$, a degradation threshold $z_{20} = 4.60$ and nominal values $\beta_{20} = 0.31$ for the intercept and $\beta_{21} = 0.35$ for the slope. As in Subsect. 2.4 the standardized normal use condition is $x_u = -0.40$ and the processes are measured at $k = 4$ standardized time points $t_j = 0.25$, 0.5, 0.75 and 1 with time intervals of constant length $\delta = 0.25$. Also here we will be interested in estimating the median failure time $t_{0.5}$.

The distribution function $F_T(t)$ of the combined failure time T given by (14) is plotted in Fig. 7 together with the distribution functions $F_{T_1}(t)$ and $F_{T_2}(t)$ of the failure times T_1 and T_2 in the components. The median failure time $t_{0.5} = 3.93$ satisfying $F_T(t_{0.5}) = 1/2$ is indicated there together with the median failure times for the single components by dashed vertical lines.

For estimating the median failure time, also here the optimal design is sought numerically by means of the multiplicative algorithm on an equidistant grid of step size 0.01 on the design region. The locally optimal design obtained is of the form $\xi^* = \xi_{w^*}$ assigning optimal weights $w^* = 0.78$ to the lowest stress level $x = 0$ and $1 - w^* = 0.22$ to the highest stress level $x = 1$ in the design region. This optimal weight is close to the solution for the first component (see Subsect. 2.4) and shows a similar behavior, when the value of the normal use condition is altered. Similar considerations hold for the sensitivity with respect to misspecifications of the nominal values of the parameters.

4 Bivariate Accelerated Degradation Testing with a Gamma Process and a Linear Mixed Model

In Sect. 3 we considered a degradation process with two response components where each is modeled by a gamma model. In this section we consider a bivariate process with two different degradation models. The first degradation mode is modeled by a gamma process as in Sect. 2. As in Sect. 3 the degradation increments of this component are denoted by Y_{i1j} for unit i during a time intervals of length $\delta_j = t_j - t_{j-1}$, $j = 1, ..., k$. The second degradation mode is given by a linear model with random intercept which will be described in the subsequent subsection and is a special case of the model treated in (Shat and Schwabe 2021).

Both failure modes are influenced by the same standardized accelerating stress variable $x \in \mathcal{X} = [0, 1]$. Apart from that the degradation modes are assumed to be independent and, hence, do not have an interactive effect. As before, also here a failure of the system occurs when at least one of the marginal degradation paths exceeds its corresponding failure threshold.

4.1 Model Formulation of the Second Degradation Component: Linear Mixed Model

Here we consider a linear regression model, similar to the model presented by (Weaver and Meeker 2013), for a single stress variable x. Measurements Y_{i2j} of the second component at unit i are taken at the same time points $t_1, ..., t_k$ as for the first component and additionally at the beginning of the degradation experiment, $t_0 = 0$, $j = 0, ..., k$. These measurements are described by a hierarchical model. For each unit i the observation Y_{i2j} at time point t_j is given by

$$Y_{i2j} = \mu_i(x_i, t_j) + \varepsilon_{ij}, \tag{18}$$

where $\mu_i(x, t)$ is the mean degradation path of the second marginal response of unit i at time t, when stress x is applied to unit i, and ε_{ij} is the associated measurement error at time point t_j. The mean degradation $\mu_i(x, t)$ is given by a linear model equation in the stress variable x and in time t with stress-time interaction,

$$\mu_i(x, t) = \beta_{i20} + \beta_{21}x + \beta_{22}t + \beta_{23}xt \tag{19}$$

where only the intercept is unit specific and the time and stress effects are the same for all units. Hence, the response is given by

$$Y_{i2j} = \beta_{i20} + \beta_{21}x_i + \beta_{22}t_j + \beta_{23}x_i t_j + \varepsilon_{ij}. \tag{20}$$

The measurement error ε_{ij} is assumed to be normally distributed with zero mean and a time independent error variance $\sigma_\varepsilon^2 > 0$. Moreover, the error terms are assumed to be independent within a unit over time.

On the aggregate level it is assumed that the units are representatives of a larger entity. The unit specific intercept β_{i20} is modeled as a random effect, i. e., β_{i20} is normally distributed with mean β_{20} and variance $\sigma_0^2 > 0$. All measurement errors ε_{ij} and random effects β_{i20} are assumed to be independent. For transferring the results, it is assumed that the model defined in Eq. (20) also holds for units under normal use condition x_u.

4.2 Information for the Second Degradation Component: Linear Mixed Model

To derive the information matrix in the mixed effects model we first write the model in vector notation. Denote by $\boldsymbol{\beta}_2 = (\beta_{20}, \beta_{21}, \beta_{22}, \beta_{23})^T$ the vector of fixed effect (aggregate) location parameters and by $\boldsymbol{\varsigma} = (\sigma_0^2, \sigma_\varepsilon^2)^T$ the vector of variance parameters. The $(k+1)$-dimensional vector of observations $\mathbf{Y}_{i2} = (Y_{i20}, ..., Y_{i2k})^T$

at unit i is multivariate normal with expectation $\mathrm{E}(\mathbf{Y}_{i2}) = (\mathbf{D} \otimes (1, x_i))\,\boldsymbol{\beta}_2$, where $\mathbf{D} = \left((1, t_0)^T, ..., (1, t_k)^T\right)^T$ is the "design" matrix for the time variable and "$\otimes$" denotes the Kronecker product, and compound symmetric covariance matrix $\mathrm{Cov}(\mathbf{Y}_{i2}) = \mathbf{V}$ with diagonal entries $\sigma_0^2 + \sigma_\varepsilon^2$ and off-diagonals σ_0^2. The elemental information matrix (per unit) $\mathbf{M}_{\boldsymbol{\beta}_2,\boldsymbol{\varsigma}}(x_i) = \begin{pmatrix} \mathbf{M}_{\boldsymbol{\beta}_2}(x_i) & \mathbf{0} \\ \mathbf{0} & \mathbf{M}_{\boldsymbol{\varsigma}} \end{pmatrix}$ of the linear mixed model component is block diagonal with the elemental information matrices $\mathbf{M}_{\boldsymbol{\beta}_2}(x) = (\mathbf{D}^T\mathbf{V}^{-1}\mathbf{D}) \otimes \begin{pmatrix} 1 & x \\ x & x^2 \end{pmatrix}$ for the location parameters and $\mathbf{M}_{\boldsymbol{\varsigma}}$ for the variance parameters on the diagonal, where $\mathbf{M}_{\boldsymbol{\varsigma}}$ does not depend on the setting x of the stress variable.

Accordingly, also for an approximate design ξ, the standardized information matrix

$$\mathbf{M}_{\boldsymbol{\beta}_2,\boldsymbol{\varsigma}}(\xi) = \begin{pmatrix} (\mathbf{D}^T\mathbf{V}^{-1}\mathbf{D}) \otimes \mathbf{M}(\xi) & \mathbf{0} \\ \mathbf{0} & \mathbf{M}_{\boldsymbol{\varsigma}} \end{pmatrix} \tag{21}$$

of the second component is block diagonal, where $\mathbf{M}(\xi) = \sum_{i=1}^{m} w_i \begin{pmatrix} 1 & x_i \\ x_i & x_i^2 \end{pmatrix}$ is the standardized information matrix of linear fixed effect regression model which does not depend on the parameters. For further details of the linear mixed model see (Shat and Schwabe 2021).

4.3 Failure Time Distribution for the Second Degradation Component: Linear Mixed Model

As mentioned in Sect. 2.3 we are interested in characteristics of the failure time distribution of soft failure due to degradation. Therefore it is assumed that the model equation $\mu_u(t) = \beta_{u20} + \beta_{21}x_u + \beta_{22}t + \beta_{23}x_u t$ is also valid under the normal use condition, where μ_u denotes the mean degradation path for a unit "u" under the normal use condition x_u and β_{u20} is the random intercept of u. We further denote by $\mu(t) = \mathrm{E}(\mu_u(t)) = \beta_{20} + \beta_{21}x_u + \beta_{22}t + \beta_{23}x_u t$ the aggregate degradation path under normal use condition.

A soft failure due to degradation for the second response component is defined as the exceedance of the degradation over a failure threshold y_{20}. This definition is based on the mean degradation path $\mu_u(t)$ and not on a "real" path subject to measurement errors. The failure time T_2 under normal use condition is then defined as the first time t the mean degradation path $\mu_u(t)$ reaches or exceeds the threshold y_{20}, i. e. $T_2 = \min\{t \geqslant 0;\, \mu_u(t) \geqslant y_{20}\}$. Because the random intercept β_{u20} is involved in the mean degradation path, the failure time T_2 is random.

As in the previous sections, we will describe the characteristics of the failure time T_2 by its distribution function $F_{T_2}(t)$. We note that $T_2 \leqslant t$ if and only if $\mu_u(t) \geqslant y_{20}$ and, hence, we can derive

$$F_{T_2}(t) = \mathrm{P}(\mu_u(t) \geqslant y_{20}) = \Phi((\mu(t) - y_{20})/\sigma_0), \tag{22}$$

where Φ denotes the distribution function of the standard normal distribution. For later use we also state the gradient

$$\partial F_{T_2}(t)/\partial \boldsymbol{\beta}_2 = \sigma_0^{-1}\varphi\left((\mu(t_\alpha) - y_{20})/\sigma_0\right)(1, t)^T \otimes (1, x_u)^T \tag{23}$$

of $F_{T_2}(t)$ with respect to the vector $\boldsymbol{\beta}_2$ of location parameters (cf. (Shat and Schwabe 2021)), where φ denotes the density of the standard normal distribution.

4.4 Estimation and Information in the Combined Model

The combined model parameters $\boldsymbol{\beta}_1$, $\boldsymbol{\beta}_2$ and $\boldsymbol{\varsigma}$ can be estimated by means of the maximum likelihood method. As stated in Subsect. 3.3, in the combined model the maximum likelihood estimates coincide with those for the single components because of the independence between the failure modes. Accordingly, the combined information matrix for all parameters is block diagonal with the information matrices for the components on the diagonal. In view of (21) the information matrix of an approximate design ξ is given by

$$\mathbf{M}_{\boldsymbol{\beta}_1,\boldsymbol{\beta}_2,\boldsymbol{\varsigma}}(\xi) = \begin{pmatrix} \mathbf{M}_{\boldsymbol{\beta}_1}(\xi) & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{M}_{\boldsymbol{\beta}_2}(\xi) & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{M}_{\boldsymbol{\varsigma}}(\xi) \end{pmatrix}, \tag{24}$$

where $\mathbf{M}_{\boldsymbol{\beta}_2}(\xi) = \mathbf{D}^T\mathbf{V}^{-1}\mathbf{D} \otimes \mathbf{M}(\xi)$ and $\mathbf{M}_{\boldsymbol{\beta}_1}(\xi)$ as in Subsect. 2.2.

4.5 Optimality Criterion Based on the Joint Failure Time

The combined failure time T is defined as the minimum of the marginal failure times T_1 and T_2 for the single components derived in Subsects. 2.3 and 4.3. As in Subsect. 4.5, the survival function of the joint failure time T factorizes and, hence, the distribution function $F_T(t)$ can be expressed as $F_T(t) = 1 - (1 - F_{T_1}(t))(1 - F_{T_2}(t))$. The quantiles $t_\alpha = t_\alpha(\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \boldsymbol{\varsigma})$ are functions of both the location parameters $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ as well as on the variance parameters $\boldsymbol{\varsigma}$, in general. Consequently, the maximum likelihood estimate of a quantile t_α is given by $\widehat{t}_\alpha = t_\alpha(\widehat{\boldsymbol{\beta}}_1, \widehat{\boldsymbol{\beta}}_2, \widehat{\boldsymbol{\varsigma}})$ in terms of the maximum likelihood estimates $\widehat{\boldsymbol{\beta}}_1$, $\widehat{\boldsymbol{\beta}}_2$ and $\widehat{\boldsymbol{\varsigma}}$ of the parameters $\boldsymbol{\beta}_1$, $\boldsymbol{\beta}_2$ and $\boldsymbol{\varsigma}$ in the components. The asymptotic variance of $\widehat{t}_\alpha$ can again be obtained by the delta method and the implicit function theorem. By the block diagonal structure of the information matrix and the decomposition of the distribution function of the failure time we get

$$\mathrm{aVar}(\widehat{t}_\alpha) = f_T(t_\alpha)^{-2}\left(c_1^2\,(1, x_u)\mathbf{M}_{\boldsymbol{\beta}_1}(\xi)^{-1}(1, x_u)^T + c_2^2\,(1, x_u)\mathbf{M}(\xi)^{-1}(1, x_u)^T + c_{\boldsymbol{\varsigma}}^2\right), \tag{25}$$

where $f_T(t)$ is the density of T, c_1 is defined as in (16) with the distribution function $F_{T_2}(t_\alpha) = \Phi((\mu(t_\alpha) - y_{20})/\sigma_0)$ of the linear mixed effect model inserted,

$$c_2 = (1 - Q\,(\gamma(x_u)t_\alpha, z_{10}/\nu_1))\,\sigma_0^{-1}\varphi\,((\mu(t_\alpha) - y_{20})/\sigma_0)\left((1, t_\alpha)\left(\mathbf{D}^T\mathbf{V}^{-1}\mathbf{D}\right)^{-1}(1, t_\alpha)^T\right)^{1/2} \tag{26}$$

by (21) and (23), and $c_{\boldsymbol{\varsigma}}^2 = \mathbf{c}_{\boldsymbol{\varsigma}}^T\mathbf{M}_{\boldsymbol{\varsigma}}^{-1}\mathbf{c}_{\boldsymbol{\varsigma}}$ is a constant independent of ξ in which $\mathbf{c}_{\boldsymbol{\varsigma}} = \partial F_{T_2}(t_\alpha)/\partial\boldsymbol{\varsigma}$ is the gradient of $F_{T_2}(t_\alpha)$ with respect to the vector $\boldsymbol{\varsigma}$ of variance parameters.

The criterion (25) is a weighted sum of the optimality criteria for the single components and constitutes, hence, a compound criterion, where the weights

depend on both vectors $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ of location parameters as well as on the variance parameters $\boldsymbol{\varsigma}$ of the linear mixed model component, in general. Due to convexity the optimal weight w^* for the system lies in the range of the optimal weights w_1^* and w_2^* for the components, $\min\{w_1^*, w_2^*\} \leqslant w^* \leqslant \max\{w_1^*, w_2^*\}$.

4.6 Numerical Example

In this example we consider an accelerated degradation experiment with two failure components in which the first component follows a gamma process and the second is described by a linear mixed model with random intercept as described in Subsect. 4.1. The gamma process is specified as in Subsects. 2.4 and 3.4 with scale parameter $\nu_1 = 1$, degradation threshold $z_{10} = 5.16$ and nominal values $\beta_{10} = 0.23$ for the intercept and $\beta_{11} = 0.53$ for the slope. For the linear model we assume a degradation threshold $y_{20} = 3.73$ and nominal values $\beta_{20} = 2.35$ for the aggregate intercept, $\beta_{21} = 0.06$ for the slope in the stress variable x, $\beta_{22} = 0.28$ for the slope in time t, $\beta_{23} = 0.04$ for the stress-time interaction xt, $\sigma_0 = 0.08$ for the standard deviation of the random intercept, and $\sigma_\varepsilon = 0.09$ for the standard deviation of measurement errors. As before the standardized normal use condition is $x_u = -0.40$ and both degradation processes are measured at the $k = 4$ standardized time points $t_j = 0.25, 0.5, 0.75$ and 1 with time intervals of constant length $\delta = 0.25$. Additionally, the degradation of the second component is measured initially at $t_0 = 0$, i. e., at the beginning of the experiment. Also in the present setting we will be interested in estimating the median failure time $t_{0.5}$.

The distribution function $F_T(t)$ of the combined failure time T is plotted in Fig. 8 together with the distribution functions $F_{T_1}(t)$ and $F_{T_2}(t)$ of the failure times T_1 and T_2 in the components. The median failure time $t_{0.5} = 4.99$ satisfying $F_T(t_{0.5}) = 1/2$ is indicated there by a dashed vertical line.

For estimating the median failure time, also here the optimal design is sought numerically by means of the multiplicative algorithm on an equidistant grid of step size 0.01 on the design region. As in the univariate case the algorithm indicates that the optimal design ξ^* is of the form ξ_w. Under this premise the optimal value of w^* can be determined by a simple line search on a sufficiently dense grid. The resulting optimal designs which assigns optimal weights $w^* = 0.78$ to the lowest stress level $x = 0$ and $1 - w^* = 0.22$ to the highest stress level $x = 1$ in the design region.

To assess the robustness of the locally optimal design we examine how the optimal weight w^* varies when the underlying parameter values are modified. Computations indicate that the optimal weight does not change much in the nominal values of the parameters $\boldsymbol{\beta}_2$ and $\boldsymbol{\varsigma}$ for the linear mixed effects degradation model in the second component. This property is in accordance with the fact that the design criterion depends on the values of $\boldsymbol{\beta}_2$ and $\boldsymbol{\varsigma}$ only through the weighting factors c_1^2 and c_2^2 while the marginal information matrix $\mathbf{M}(\xi)$ does not. However, similar to the univariate case, there may be moderate changes with respect to the parameters $\boldsymbol{\beta}_1$ of the gamma degradation model in the first component. Additionally, the optimal weight w^* may switch between the marginal

optimal weights w_1^* and w_2^* for the marginal failure models depending on which of the marginal failure modes is dominant in the bivaraite system.

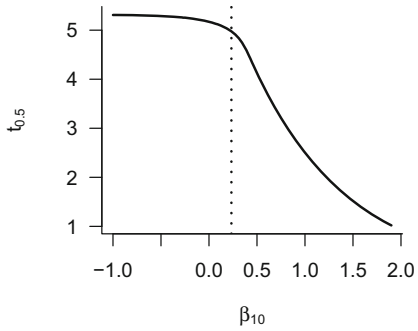

Fig. 9. Dependence of $t_{0.5}$ on β_{10} for the example in Subsect. 4.6

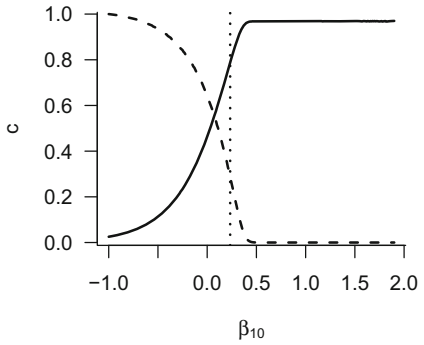

Fig. 10. Dependence of the coefficients c_1 (solid line) and c_2 (dashed line, standardized) on β_{10} for the example in Subsect. 4.6

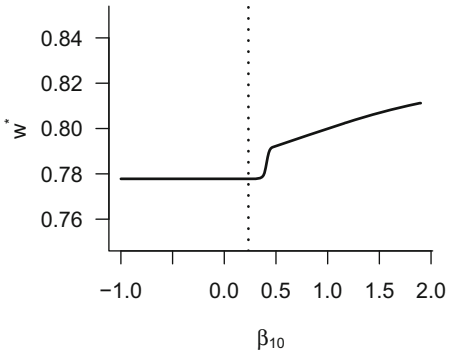

Fig. 11. Dependence of w^* on β_{10} for the example in Subsect. 4.6

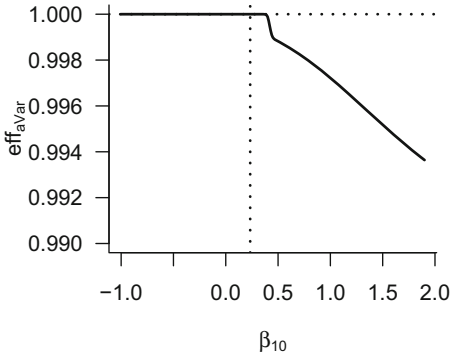

Fig. 12. Efficiency of ξ^* in dependence on β_{10} for the example in Subsect. 4.6

We will demonstrate this behavior in the case when the intercept β_{10} of the gamma model component varies while all other parameters are fixed to their nominal values. In Fig. 9 we plot the median failure time $t_{0.5}$ and the weighting coefficients c_1 and c_2, respectively, in dependence on β_{10}. For negative values of β_{10}, the failure time T_2 of the first component decreases and the failure of the bivariate system is dominated by the second component. Then the median

failure time $t_{0.5}$ approaches its marginal counterpart 5.32 in the second component. For increasing values of β_{10}, the failure of the first component becomes dominant and the median failure time $t_{0.5}$ behaves as in the marginal model for the first component. In particular, $t_{0.5}$ is decreasing in β_{10} and becomes smaller than 1 for $\beta_1 > 1.92$. Hence, only values $\beta_{10} \leqslant 1.92$ are reasonable to be considered because otherwise no acceleration would be required to obtain failure due to degradation under normal use conditions. The dominance of the failure components is also reflected in Fig. 10 where the weighting coefficients c_1 and c_2 are shown in dependence on β_{10}. There the second coefficient c_2 is standardized by its maximum for purposes of comparison. For negative values of β_{10}, the coefficient c_2 of the second component dominates the asymptotic variance (25) while the dominance is reversed for $\beta_{10} > 0.5$.

This change in dominance has also an impact on the optimal weights w^* as exhibited in Fig. 11. For negative values of β_{10}, the optimal weight w^* coincides with its marginal counterpart in the second component while, for $\beta_{10} > 0.5$, the optimal weight w^* is as in the univariate model for the first component (see Subsect. 2.4). Caused by the change in dominance, there is a small, but pronounced change in the optimal weight when β_{10} varies from 0.35 to 0.50. This shift is also visible in the efficiency of the locally optimal design ξ^* at the given nominal values when the intercept parameter β_{10} is misspecified, as shown in Fig. 12. For values of β_{10} less than the nominal value $\beta_{10} = 0.23$, the locally optimal design ξ^* has an efficiency of nearly 1, up to $\beta_{10} = 0.35$. Then there is a small, instantaneous decrease in efficiency to 0.999 for β_{10} between 0.35 and 0.50. For larger values of β_{10} the efficiency smoothly decreases as in the univariate model for the first component (see Subsect. 2.4). For the maximal value $\beta_{10} = 1.92$ the efficiency of ξ^* is still remarkably high with a value of about 0.9936. In all of Figs. 9, 10, 11 and 12 the nominal value $\beta_{10} = 0.23$ is indicated by a dotted vertical line.

With respect to the slope parameter $\beta_{20} \leqslant 0$ of the gamma component, the failure is dominated by the second component. Hence, neither the optimal weight is affected by β_{20}, nor the efficiency of the locally optimal design ξ^* differs reasonably from 1. In total, the locally optimal design ξ^* at the given nominal values appears to be robust against misspecifications of the parameters within a meaningful range.

5 Concluding Remarks

The design stage of highly reliable systems requires a sophisticated assessment of the reliability related properties of the product. One approach to handle this issue is to conduct accelerated degradation testing. Accelerated degradation tests have the advantage to provide an estimation of lifetime and reliability of the system under study in a relatively short testing time. The majority of existing literature deals with this issue by considering a single failure mode, which may not be sufficiently representative in many cases.

In this work, we propose optimal experimental designs for ADTs with single response components and extend it to the case of multiple response components

with repeated measures. Two bivariate degradation models are considered. The marginal degradation functions are described by two gamma process models in the first bivariate model, and a gamma process with a linear model with a random intercept in the second one. In this context it is desirable to estimate certain quantiles of the joint failure time distribution as a characteristic of the reliability of the product. The purpose of optimal experimental design is to find the best settings for the stress variable to obtain most accurate estimates for these quantities.

In the present model for accelerated degradation testing, it is assumed that stress remains constant within each testing unit during the whole period of experimental measurements but may vary between units. Hence, in the corresponding experiment a cross-sectional design between units has to be chosen for the stress variable(s) while for repeated measurements the time variable varies according to a longitudinal time plan within units. In particular, the same time plan for measurements is used for all units in the test. It is further assumed that the marginal response components are uncorrelated.

The multiplicative algorithm is utilized to obtain optimal experimental designs for the single response case as well as the two bivariate degradation models. The sensitivity analysis shows that the optimal designs of the univariate model as well as the bivariate model with two marginal gamma processes are robust against misspecifications of the corresponding parameter vectors and depend mainly on the normal use condition of the stress variable. For the bivariate model with two different marginal models the sensitivity analysis establishes that the resulting optimal design is slightly dependent on the nominal parameter values.

Although only gamma processes and LMEM are considered as marginal degradation models here, the underlying methods can be extended to other marginal failure modes, like Wiener processes, inverse Gaussian processes and non-linear mixed effects degradation models. Another object of interest would be to consider optimality criteria accounting for simultaneous estimation of various characteristics of the failure time distribution.

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References

Ankenman, B.E., Aviles, A.I., Pinheiro, J.C.: Optimal designs for mixed-effects models with tow random nested factors. Statistica Sinica **13**(2), 385–401 (2003)

Balakrishnan, N., Qin, C.: Nonparametric evaluation of the first passage time of degradation processes. Appl. Stochast. Models Bus. Ind. **35**(3), 571–590 (2019)

Balakrishnan, N., Tsai, C.-C., and Lin, C.-T. (2017). Gamma degradation models: inference and optimal design. In: Chen, DG., Lio, Y., Ng, H., Tsai, TR. (eds.) Statistical Modeling for Degradation Data, ICSA Book Series in Statistics, pp. 171–191. Springer, Singapore https://doi.org/10.1007/978-981-10-5194-4_9

Bogacka, B., Latif, M.A.H.M., Gilmour, S.G., Youdim, K.: Optimum designs for nonlinear mixed effects models in the presence of covariates. Biometrics **73**(3), 927–937 (2017)

Duan, F., Wang, G.: Optimal design for constant-stress accelerated degradation test based on gamma process. Commun. Stat. Theor. Methods **48**(9), 2229–2253 (2019)

Elfving, G.: Optimum allocation in linear regression theory. Ann. Math. Stat. **23**(2), 255–262 (1952)

Ford, I., Torsney, B., Wu, C.J.: The use of a canonical form in the construction of locally optimal designs for non-linear problems. J. R. Stat. Soc. Ser. B **54**(2), 569–583 (1992)

Haghighi, F., Bae, S.J.: Reliability estimation from linear degradation and failure time data with competing risks under a step-stress accelerated degradation test. IEEE Trans. Reliab. **64**(3), 960–971 (2015)

Kiefer, J.: Optimum experimental designs. J. R. Stat. Soc. Ser. B **21**(2), 272–304 (1959)

Lim, H.: Optimum accelerated degradation tests for the gamma degradation process case under the constraint of total cost. Entropy **17**(5), 2556–2572 (2015)

Palayangoda, L.K., Ng, H.K.T., Butler, R.W.: Improved techniques for parametric and nonparametric evaluations of the first-passage time for degradation processes. Appl. Stoch. Models Bus. Ind. **36**(4), 730–753 (2020)

Pan, Z., Sun, Q.: Optimal design for step-stress accelerated degradation test with multiple performance characteristics based on gamma processes. Commun. Stat. Simul. Comput. **43**(2), 298–314 (2014)

Pascual, F.: Accelerated life test planning with independent weibull competing risks with known shape parameter. IEEE Trans. Reliab. **56**(1), 85–93 (2007)

R Core Team: R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria (2020)

Shat, H., Schwabe, R.: Experimental designs for accelerated degradation tests based on linear mixed effects models (2021). arXiv:2102.09446

Shi, Y., Meeker, W.Q.: Planning Accelerated Destructive Degradation Tests with Competing Risks, chapter 22, pp. 335–356 (2014)

Silvey, S.D.: Optimal Design. Chapman and Hall, London (1980)

Sinha, S.K., Xu, X.: Sequential D-optimal designs for generalized linear mixed models. J. Stat. Plann. Infer. **141**(4), 1394–1402 (2011)

Torsney, B., Martín-Martín, R.: Multiplicative algorithms for computing optimum designs. J. Stat. Plann. Infer. **139**(12), 3947–3961 (2009)

Tsai, C.-C., Tseng, S.-T., Balakrishnan, N.: Optimal design for degradation tests based on gamma processes with random effects. IEEE Trans. Reliab. **61**(2), 604–613 (2012)

Tsai, T., Sung, W., Lio, Y.L., Chang, S.I., Lu, J.: Optimal two-variable accelerated degradation test plan for gamma degradation processes. IEEE Trans. Reliab. **65**(1), 459–468 (2016)

Wang, H., Xu, T., Mi, Q.: Lifetime prediction based on gamma processes from accelerated degradation data. Chin. J. Aeronaut. **28**(1), 172–179 (2015)

Weaver, B.P., Meeker, W.Q.: Methods for planning repeated measures accelerated degradation tests. Appl. Stochast. Models Bus. Ind. **30**(6), 658–671 (2013)

Zhang, C., Lu, X., Tan, Y., Wang, Y.: Reliability demonstration methodology for products with gamma process by optimal accelerated degradation testing. Reliab. Eng. Syst. Saf. **142**, 369–377 (2015)

Testing Interaction and Estimating Variance Components in Block Designs - Based on a Linear Model

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Abstract. Randomized complete block designs (RCBD) introduced by [3] are probably the most widely used experimental designs. Despite many advantages, they suffer from one serious drawback. It is not possible to test interaction effects in analysis of variance (ANOVA) as there is only one observation for each combination of a block and factor level. Although there are some attempts to overcome this problem none of these methods are used in practice, especially as most of the underlying models are non-linear. A review on such tests is given by [6] and [1].

Here a new method is introduced which permits a test of interactions in block designs. The model for RCBDs is linear and identical to that of a two factorial design. The method as such is not restricted to simple block designs, but can also be applied to other designs like Split-Plot-design, Strip-Plot-design, ... and probably to incomplete block designs.

ANOVA based on this method is very simple. Any common statistical program packages like SAS, SPSS, R, ... can be used. Although a test on interaction in two- or multi- factorial designs makes sense only for fixed and a certain class of mixed models, the proposed method can also be used for estimating variance components in any kind of block models (fixed, random, mixed) if the sample size is not too small.

1 Introduction

A Randomized complete block design is a kind of two-factorial design which is based on the model:

$$y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + e_{ijk} \tag{1}$$

y_{ijk} ... observation k at level α_i of factor A and level β_j of factor B $(k = 1, \ldots, n)$

μ ... overall mean

α_i ... effect of level i of factor A $\quad i = 1, \ldots, a$

β_j ... effect of level j of factor B $\quad j = 1, \ldots, b$

$(\alpha\beta)_{ij}$ ... interaction effect at level α_i of factor A and at level β_j of factor B

e_{ijk} ... error term at level α_i of factor A, at level β_j of factor B and at replication k $\quad k = 1, \ldots, n$.

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https://doi.org/10.1007/978-3-031-06685-6_10

Depending on the chosen model, mean square errors include different kinds of variance components (Table 1).

Table 1. Variance components of mean square values in a two factorial design for different kind of models

Source of variation	Fixed effects model	Random effects model	Mixed effects model
Main A	$\sigma^2 + \frac{bn}{a-1}\sum_i \alpha_i^2$	$\sigma^2 + n\sigma_{ab}^2 + bn\sigma_a^2$	$\sigma^2 + n\sigma_{ab}^2 + \frac{bn}{a-1}\sum_i \alpha_i^2$
Main B	$\sigma^2 + \frac{an}{b-1}\sum_j \beta_i^2$	$\sigma^2 + n\sigma_{ab}^2 + an\sigma_b^2$	$\sigma^2 + \kappa n\sigma_{ab}^2 + an\sigma_b^2$
Interaction $A \times B$	$\sigma^2 + \frac{n}{(a-1)(b-1)}\sum_{i,j}(\alpha\beta)_{ij}^2$	$\sigma^2 + n\sigma_{ab}^2$	$\sigma^2 + n\sigma_{ab}^2$
Error	σ^2	σ^2	σ^2

κ depends on the side condition about interaction.

$$\kappa = \begin{cases} \text{cov}(ab_{ij}, ab_{ij'}) = 0 & 1 \quad (j \neq j') \\ \sum_{i=1}^{a} ab_{ij} = 0 & 0 \quad \forall\ j \end{cases}$$

As one may see from Table 1 a test on main effects in a fixed model is based on the error term, in a random model on interaction mean squares and in the mixed model approach either on the error term or the interaction term (depending on the definition of κ).

In the follow this article focuses primarily on fixed models or mixed models where $\kappa = 0$.

Several authors tried to find a solution for testing interaction in block designs. A short selection of these models can be found below.

1.1 Tukey's Test

The first one who proposed a block model which includes interaction was [12].

$$y_{ij} = \mu + \alpha_i + \beta_j + \lambda \times \alpha_i \times \beta_j + e_{ij}$$

λ ... interaction parameter

Here the interaction term is bound to the height of the factor levels which is a very strong restriction. [11] showed that Tukey's test can be derived as a test of $H_0 : \lambda = 0$.

1.2 Johnson and Graybill's Test

Another solution to the problem of interactions in block designs is given by the following model [5]:

$$y_{ij} = \mu + \alpha_i + \beta_j + \Phi \times \xi_i \times \eta_j + e_{ij}$$

Limitations to interaction are not that strict as with Tukey's model, but some additional assumptions have to be made ($\sum_{i=1}^{a} \xi_i = 0$, $\sum_{j=1}^{b} \eta_j = 0$, $\sum_{i=1}^{a} \xi_i^2 = 1$, $\sum_{j=1}^{b} \eta_j^2 = 1$).

1.3 Mandel's Test

[7] assumes a systematic type of row column interaction. The underlying "Mandel-row" model is given by

$$y_{ij} = \mu + \alpha_i + \beta_j + \gamma_i \times \beta_j + e_{ij}$$

γ_j ... interaction parameter depending on row i

Other models including non-linear interaction effects can be found by [2,4, 8,9] and [10].

2 Deriving Sum of Squares for Error Term and Interaction in Block Designs

Deriving sum of squares and mean squares in a block model is based on a common two-factorial design.

2.1 Sum of Squares in Two Factorial Designs

The sum of squares value for interaction in case of a balanced design can be calculated as

$$SS_{AB} = n \sum_{i=1}^{a} \sum_{j=1}^{b} (\bar{x}_{ij.} - \bar{x}_{i..} - \bar{x}_{.j.} + \bar{x}_{...})^2.$$

with $(a-1)(b-1)$ number of degrees of freedom.

The sum of squares value for the error term is given by

$$SS_E = \sum_{i=1}^{a} \sum_{j=1}^{b} \sum_{k=1}^{n} (x_{ijk} - \bar{x}_{ij.})^2.$$

with $ab(n-1)$ number of degrees of freedom.

In block designs the number of observations (n) for each combination of a factor level and a block is equal to 1. It follows, that:

- $\bar{x}_{ij.}$ for each combination of factor and block levels is identical to x_{ij1}.
- degree of freedom for the error sum of squares becomes zero.
- $MS_E = \frac{SS_E}{df_E}$ can not be estimated.

In the follow we the mean square value for interaction ($MS_{AB} = \frac{SS_{AB}}{df_{AB}}$) serves as an error term – assuming, that no interaction effects exist. That's a very daring assumption, since almost all tow-factorial experiments show interactions (no matter whether significant or not).

2.2 Separating Error from Interaction in Block Designs

In a two factorial design the following restrictions are usually assumed in regard to interaction:

- The sum of all interaction effects within a block is equal to zero ($\sum_{i=1}^{a}(\alpha\beta)_{ij} = 0 \qquad \forall j \quad j = 1, \ldots, b$).
- The sum of all interaction effects within a certain factor level is equal to zero ($\sum_{j=1}^{b}(\alpha\beta)_{ij} = 0 \qquad \forall i \quad i = 1, \ldots, a$).

To separate the error term from interaction we may look at a Latin square like block design (Fig. 1)

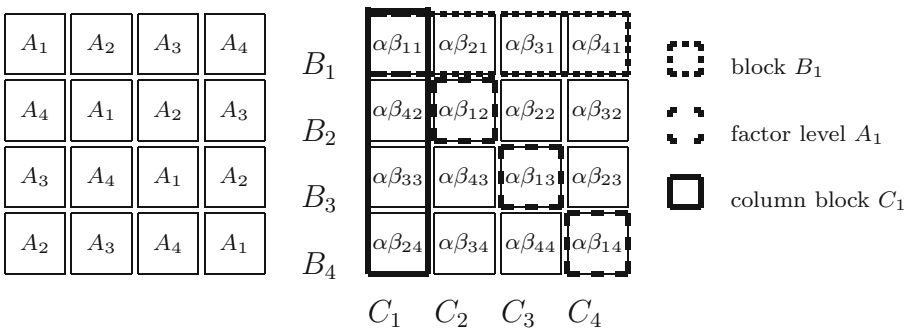

Fig. 1. Block plan and corresponding interaction terms in a Latin square like block design

Looking at Fig. 1, there is obviously no reason why one should not restrict the sum of interaction effects within a column block to zero, too

$$\sum_{i=1,j=1}^{a,b} (\alpha\beta)_{ij^k} = 0 \qquad \forall k \quad k = 1, \ldots, c. \tag{2}$$

Using this restriction has some important implications:

- Within a column block all levels of a factor are included exactly one time. As a common restriction $\sum_{i=1}^{a} \alpha_i = 0$. So the mean value of a column block does not include any factor effects.
- In Latin Square like block designs a column block comprises all levels of blocks. Usually it is assumed, that these effects sum up to zero ($\sum_{j=1}^{b} \beta_j = 0$). So the mean value of a column block does not include any block effects.

As a consequence of these two last restrictions and of restriction 2 the mean value of a column block encloses only some error effects besides μ. This enables

us to separate error variance and interaction variance by calculating the sum of squares for column blocks.

$$SS_{column\ block} = SS_E = a \sum_{k=1}^{c} (\bar{x}_{c_k} - \bar{x}_{..})^2 \tag{3}$$

The error sum of squares for the error term (SS_{E^*}) in a common block design actually is the sum of squares value for interaction. So the difference zu SS_E obviously gives the sum of squares for interaction.

$$SS_{AB} = SS_{E^*} - SS_E \tag{4}$$

or alternatively $SS_{AB} = SS_T - SS_A - SS_B - SS_E$.

Degrees of freedom are defined as:

$$\begin{aligned} df_E &= c - 1 \ = b - 1 \\ df_{AB} &= df_T - df_A - df_B - df_E \ = \ (a-2)(b-1) \end{aligned}$$

Mean squares are calculated the usual way:

$$MS_E = SS_E/df_E, \qquad MS_{AB} = SS_{AB}/df_{AB}$$

Until now we restricted or model to a Latin Square design. The method as such can be applied to any kind of block design. Figure 2 depicts interaction terms in a 5×2 block design.

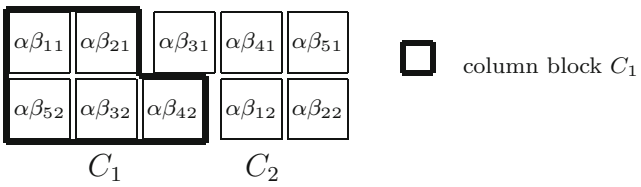

Fig. 2. Interaction terms in an arbitrary block design

Within a column block all levels of the interesting factor are included. By definition, the sum of all interaction effects within a column block is zero. The number of block effects however is different. For example, the first column block of Fig. 2 contains 2 times the effect of the first and 3 times the effect of the second block. Since we can estimate these block effects using the block means, we are able to correct for this biased column block.

3 Illustrative Example

The example in Fig. 3 shows a block design [A] with 3 blocks and 4 factor levels.

Based on the experimental design 3 column blocks were defined [B]. Each column block comprises every level of factor A. So their effects sum up to zero. Interaction effects within each column block sum up to zero too, but block effects do not, as in every column block a different number of block effects is included. So we have to correct for these effects. To do this, we need to calculate block means, factor level means, uncorrected column block means and the overall mean.

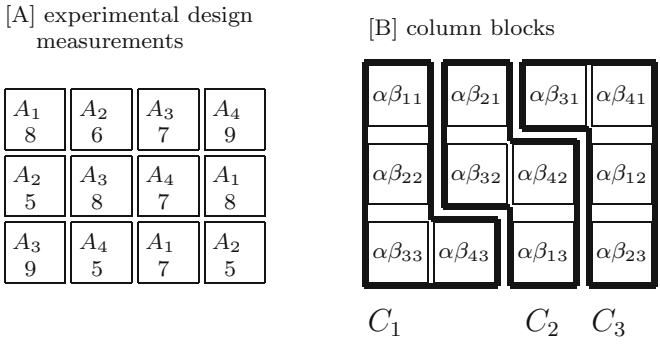

Fig. 3. Illustrative example including experimental design and corresponding measurements [A] and defined column blocks with interaction effects [B].

overall	factor $\bar{x}_{A_i}$				block $\bar{x}_{B_j}$			uncorrected col. block $\bar{x}_{C_k}$		
$\bar{\bar{x}}$	1	2	3	4	1	2	3	1	2	3
7.0	$7.\overline{6}$	$5.\overline{3}$	8.0	7.0	7.5	7.0	6.50	6.75	7.00	7.25

3.1 Calculation of Column Block Means

Each uncorrected column block mean includes a specific block effect several times (e.g. The first column block C_1 includes 2 times block effect 3, C_2 includes 2× block effect 2, C_3 includes 2× block effect 1). So we have to correct this additional block effects. The effect of a block can be calculated as the difference between the block mean and the overall mean.

If we want to calculate the mean of C_1 we have reduce the sum for this column block by the effect of block 3, to get an unbiased estimator. The effect of block 3 is calculated es the difference between $\bar{x}_{B_3} - \bar{\bar{x}}$. So an unbiased estimation of column block 1 for the example given above can be calculated based on the sum of this column block and the effect size of block 3 (ef_{B_3}) as this is included in the sum for this column block.

uncorrected sum: $\sum_{j=1}^{n} x_{1j} = 8+5+9+5 = 27$
effect size block 3: $ef_{B_3} = \bar{x}_{B_3} - \bar{\bar{x}} = 6.5 - 7.0 = -0.5$
corrected sum: $\sum_{j=1}^{n} x_{1j} - ef_{B_3} = 27 - (-0.5) = 27.5$
corrected mean: $\bar{x}_{C_1} = \frac{\sum_{j=1}^{n_f} x_{1j} - ef_{B_3}}{n_f} = \frac{27.5}{4} = 6.875$

Similarly, we can derive all other correction factors and column block means.

$\bar{x}_B - \bar{\bar{x}}$		
1	2	3
0.5	0.000	-0.5

corrected column block means $\bar{x}_C$		
1	2	3
6.875	7.000	7.125

3.2 Calculation of Sum of Squares and Degrees of Freedom

Sum of squares for blocks, factors, total and the (uncorrected) error is calculated the usual way and can be done with any statistical package for a common block design.

Sum of squares for the error term is calculated by the corrected column block means:

$$SS_E = n_f \sum_{k=1}^{n_c b} (\bar{x}_{cb_k} - \bar{\bar{x}})^2 = 4((6.875-7.0)^2 + (7.000-7.0)^2 + (7.125-7.0)^2) = 0.125$$

From evaluating a common block design we get $SS_E^* = 9.\overline{3}$. As mentioned above this actually includes possible interaction effects. By subtracting SS_E from SS_{E^*} we find the sum of squares value for interaction.

$$SS_{IA} = SS_E^* - SS_E = 9.\overline{3} - 0.125 = 9.208\overline{3}$$

Degrees of freedom for factor, block and total are those of a common block design. Degrees of freedom for main effects and interaction effects are calculated as follows:

$$\begin{aligned} df_E &= c - 1 = b - 1 & 3 - 1 &= 2 \\ df_{AB} &= df_E^* - df_E & 6 - 2 &= 4 \\ &= (a-2)(b-1) & (4-2)(3-1) &= 4 \end{aligned}$$

3.3 ANOVA Table

Based on calculations for a common block design and those of 3.2 we find results as shown in an ANOVA Table 2.

As can be seen from Table 2, separating interaction from the error of the common block model dramatically changes the result. If interaction is possible or can be expected, it should be included in the model regardless of whether it is significant or not.

Table 2. Example of analysis of variance for the interaction model in compare to that of a common block model

block design with Interaction						common block design				
Effect	*df*	*SS*	*MS*	*F*	Prob	*df*	*SS*	*MS*	*F*	Prob
Factor	3	$12.66\overline{6}$	$4.222\overline{2}$	$67.5\overline{5}$	0.0146	3	$12.\overline{6}$	$4.\overline{2}$	2.71	0.1377
Block	2	2.000	1.0000	16.00	0.0588	2	2.0	1.0	0.64	0.5585
Int.act.	4	9.208	2.3021	$36.8\overline{3}$	0.0266					
Error	2	0.125	0.0625			6	$9.\overline{3}$	$1.\overline{5}$		
Total	11	24.000				11	24.0			

4 Simulations

To get an idea about the power of the interaction model several simulations were performed. A Fortran program (as well as a SAS macro and a R script) was developed to calculate ANOVA results for both the interaction model as well as for the common block model. Simulation were based on 100000 runs each.

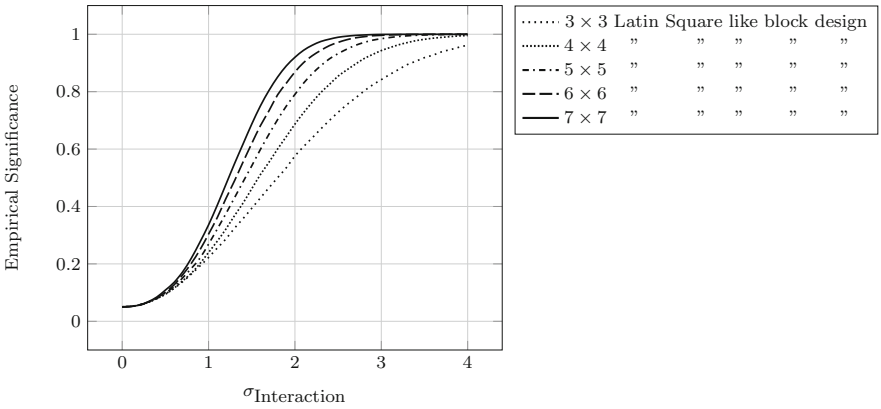

Fig. 4. Empirical power of the test on interaction as a function of the standard deviation of interaction for different sized Latin Square like block designs ($\sigma_E = 1$).

Figure 4 illustrates the empirical power of a test on interaction in 3×3 to 7×7 Latin Square like block designs. The standard deviation for this effect varied from 0 to 4 in steps of 0.5. The standard deviation for the error term (σ_E) was held constant and set to 1. As one would expect the power increases if sample size increases too. Thus, for example the power for the test on interaction in 7×7 design is about 92% if the standard deviation of the interaction is twice as high as that of the error (99.9% if it is three times as high). Whereas power in a 3×3 design is about 58% respectively 84%.

In block analysis one is primarily interested in the test regarding the main effect. Figure 5 displays the power for a 3×3 and 7×7 Latin Square like block

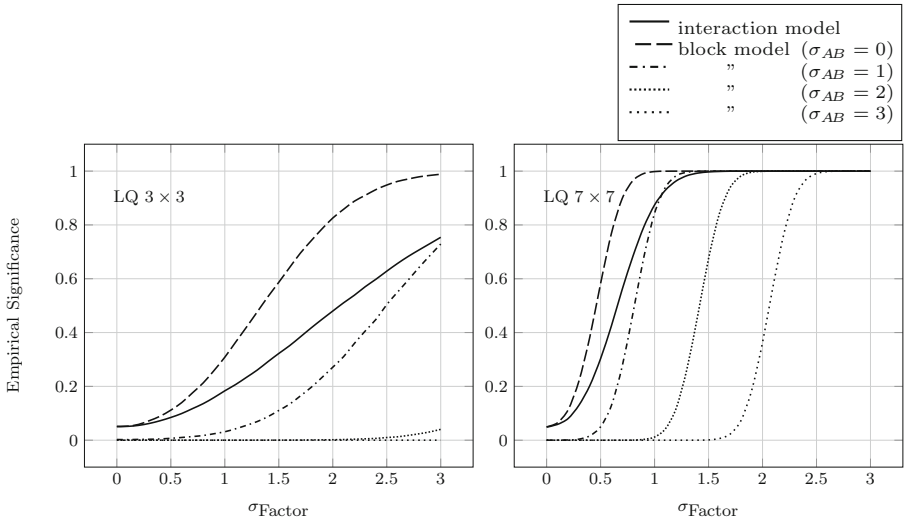

Fig. 5. Empirical power of the test on the main effect as a function of the standard deviation of this effect for 3×3 and 7×7 different Latin Square like block designs ($\sigma_E = 1$).

design. Four different standard deviations for interaction were taken into account ($\sigma_{AB} = 1, 2, 3, 4$). If there is no interaction the power for the common block analysis is highest (dashed curve). In this situation the interaction model is over parameterized and thus its power decreases. Whereas in those situations where the standard deviation of the interaction corresponds at least to that of the error, the interaction model (solid line) is best in most cases.

In addition, Fig. 5 shows another unwanted effect for the common block model. Depending on the level of interaction, there is a certain range in which it is impossible for the common block model to find any significant result for the main effect (although one awaits at least $\alpha\%$ of significant cases even in the absence of any influences).

Results for 5×3 and 7×4 block designs in regard to the main effect are presented in Fig. 6. Again common block analysis is best in those situations were no interaction exists. Depending on the size of interaction the power of the interaction model gets more and more superior. Contrary to statistical theory, type I error rate is zero (although it should be α) in many situations where interaction exists and the main effect is low.

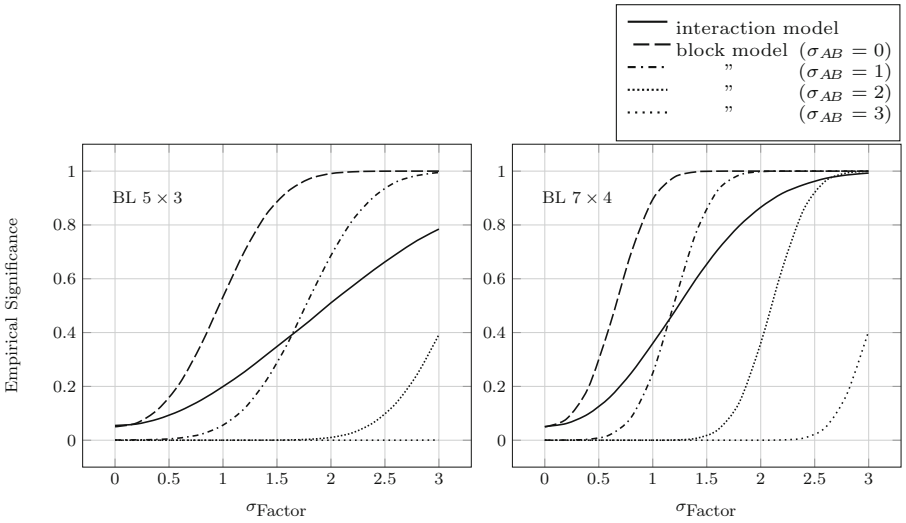

Fig. 6. Empirical power of the test on the main effect as a function of the standard deviation of this effect for different block designs ($\sigma_E = 1$).

5 Estimating Variance Components

The method described here is based on fixed effect model reps. a model with a special definition of interaction (Table 1, $\kappa = 0$). In this case we can estimate the Least Squares (LSQ) variance component for interaction as

$$MS_{AB} = \sigma^2 + n\sigma^2_{ab} \qquad \sigma^2 \equiv MS_E$$

$$\sigma^2_{ab} = \frac{MS_{AB} - MS_E}{n}$$

In block-designs:

$$n = 1 \quad \Longrightarrow \quad \sigma^2_{ab} = MS_{AB} - MS_E$$

A usual assumption in estimating variance components of interaction based on restricted maximum likelihood (REML) estimation is $\text{cov}(ab_{ij}, ab_{ij'}) = 0, (j \neq j')$ In Fig. 7 both methods are compared for different heights of variance components of interaction (σ^2_{ab}) in compare to the error variance (σ^2).

As long as the variance component for interaction is similar to the of the error variance, there is almost no difference between different estimation methods. In 7 the height of the variance component for interaction is 9 time as high as that of the error variance. Even in this rather extreme situation the differences between LSQ and REML estimation is negligible with at least 6 blocks and 6 levels of the factor. This means the proposed method can be used to estimate variance components in any mixed and random effects model approach with an appropriate sample size.

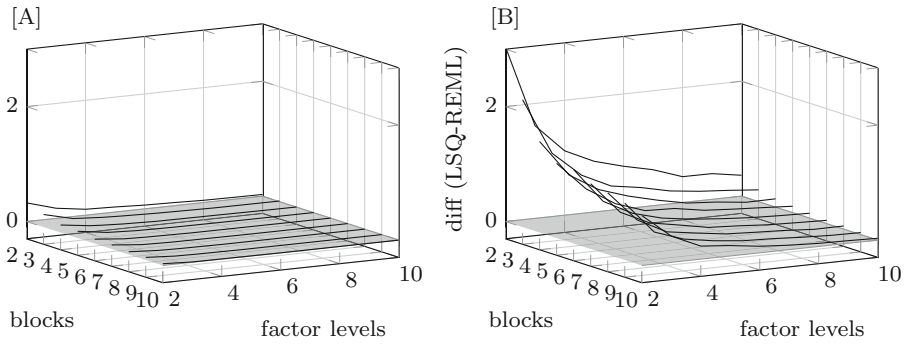

Fig. 7. Comparison of REML and LSQ estimation of variance components for interaction assuming $\sigma^2_{ab} = \sigma^2$ ([A]) and $\sigma^2_{ab} = 9\sigma^2$ ([B])

6 Conclusions

The method presented here allows for testing interaction in different kind of block designs. It can also be used for estimating variance components of interaction and main effects for mixed and random effect models in block designs. There are some additional advantages in compare to other methods:

- It is based on a linear model and as such comprises all previously developed non linear models.
- It is very easy to use and any statistical package like SAS, R, SPSS can be used with just a few simple additional calculations.
- There are no uncommon restrictions.
- It can be used not only for common block designs or Latin Squares, but for any statistical model that has a suitable block structure as for instance Split-Plot Designs or maybe even incomplete block designs (although one has to use least-square means here).
- The power of the method is good in respect to interaction and even more for the main effect, if interaction exists.

Block analysis is based on at least a two factorial design (Table 1). Depending on the model (fixed, random, mixed) main effects are tested against either the error sum of squares or that of the interaction. For a fixed and a special kind of mixed effects models (Table 1, $\kappa = 0$) an assessment of the main and block effect must be made by means of the error. In all other situations you have to test against means squares of the interaction. Interaction itself always has to be tested against the error.

So far, means squares for the error term were not or only available under the very restrictive assumptions of non linear models. With the method presented here this test now is possible even in a random or mixed effect surrounding (Table 1, $\kappa = 1$). Although the basic assumption ($\kappa = 1$) is different to that of the fixed model, it doesn't really matter for estimating variance components.

References

1. Alin, A., Kurt, S.: Testing non-additivity (interaction) in two-way ANOVA tables with no replication. Stat. Methods Med. Res. **15**, 63–85 (2006)
2. Barhdadi, A., Froda, S.: An exact test for additivity in two-way tables under biadditive modelling. Commun. Stat. Theor. Methods **39**, 1960–1978 (2010)
3. Cochran, W.G., Cox, D.R.: Eperimental Designs, 2nd edn. Wiley, New York (1957)
4. Gollob, H.F.: A statistical model which combines features of factor analysis and analysis of variance. Psychometrica **33**, 73–115 (1968). https://doi.org/10.1007/BF02289676
5. Johnson, D.E., Graybill, F.A.: An analysis of a two-way model with interaction and no replication. J. Am. Stat. Assoc. **67**, 862–869 (1972)
6. Karabatos, G.: Additivity test. In: Everitt, B.S., Howell, D.C. (eds.) Encyclopedia of Statistics in Behavioral Science, Wiley, Heidelberg, pp. 25–29 (2005)
7. Mandel, J.: Non-additivity in two-way analysis of variance. J. Am. Stat. Assoc. **56**, 878–888 (1961)
8. Mandel, J.: The partitioning of interaction in analysis of variance. J. Res. Nat. Bur. Stand. B Math. Sci. **3**, 309-328 (1969)
9. Mandel, J.: A new analysis of variance model for non-additive data. Technometrics **13**, 1–18 (1971)
10. Rasch, D., Rusch, T., Simeckova, M., Kubinger, K.D., Moder, K., Simecek, P.: Tests of additivity in mixed and fixed effect two-way ANOVA models with single sub-class numbers. Stat. Papers **50**(4), 905–916 (2009)
11. Scheffé, H.: The Analysis of Variance, 2nd edn., pp. 45–56. Springer, New York (1959)
12. Tukey, J.W.: One degree of freedom for non-additivity. Biometrics **5**, 232–242 (1949)

Optimal Designs for Prediction in Two Treatment Groups Random Coefficient Regression Models

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Abstract. The subject of this work is two treatment groups random coefficient regression models, in which observational units receive some group-specific treatments. We provide A- and D-optimal designs (optimal group sizes) for the estimation of fixed effects and the prediction of random effects. We illustrate the obtained results by a numerical example.

1 Introduction

The subject of this paper is optimal designs in two treatment groups random coefficient regression (RCR) models, in which observational units receive some group-specific kinds of treatment. These models are typically used for cluster randomized trials. For some real data examples see e. g. Piepho and Möhring (2010).

Optimal designs for fixed effects models with multiple groups are well discussed in the literature (see e.g. Bailey (2008), ch. 3). In models with random coefficients, the estimation of population parameters (fixed effects) is usually of prior interest (see e.g. Fedorov and Jones (2005), Kunert et al. (2010), Van Breukelen and Candel (2018)). Optimal designs for the prediction of random effects in models with known population parameters have been considered in detail in Gladitz and Pilz (1982). Prus and Schwabe (2016) provide analytical results for the models with unknown population mean under the assumption of the same design for all individuals. Multiple group models with fixed group sizes were briefly discussed in Prus (2015), ch. 6.

Here, we consider two groups models with unknown population parameters and group specific designs. We provide A- and D-optimality criteria for the estimation and the prediction of fixed and random effects, respectively. Our main focus is optimal designs for the prediction.

The paper is structured in the following way: In Sect. 2 the two groups RCR model will be introduced. Section 3 presents the best linear unbiased estimator for the population parameter and the best linear unbiased predictor for individual random effects. Section 4 provides analytical results for the designs, which are optimal for the estimation or for the prediction. The paper will be concluded by a short discussion in Sect. 5

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2 Two Treatment Groups RCR Model

In this work we consider RCR models with two treatment groups G_1 and G_2, where observational units (people, plots, studies, etc.) receive group-specific kinds of treatment, T_1 and T_2, respectively. Further we will use the term "individuals" instead of "observational units" for simplicity. The first group includes n_1 individuals and the second group n_2 individuals. The groups sizes n_1 and n_2 are to be optimized and the total number of individuals $N = n_1 + n_2$ in the experiment is fixed. The k-th observation at the i-th individual is described for the first group by

$$Y_{1ik} = \mu_{1i} + \varepsilon_{1ik}, \quad i = 1, \ldots, n_1, \quad k = 1, \ldots, K \tag{1}$$

and for the second group by

$$Y_{2ik} = \mu_{2i} + \varepsilon_{2ik}, \quad i = n_1 + 1, \ldots, N, \quad k = 1, \ldots, K, \tag{2}$$

where K is the number of observations per individual, which is assumed to be the same for both groups, ε_{1ik} and ε_{2ik} are the observational errors in the first and the second groups with zero expected value and the variances $\mathrm{var}(\varepsilon_{1ik}) = \sigma_1^2$ and $\mathrm{var}(\varepsilon_{2ik}) = \sigma_2^2$, respectively. μ_{1i} and μ_{2i} are the individual response parameters.

As it has been already mentioned above, we optimize the group sizes n_1 and n_2. Therefore, we define the individual parameters for all individuals for both groups: $\boldsymbol{\theta}_i := (\mu_{1i}, \mu_{2i})^\top$, $i = 1, \ldots, N$. The parameters can be interpreted as follows: Let individual i be in the second group. Then the parameter μ_{1i} describes the response, which would be observed at individual i if the individual had received treatment T_1, and μ_{2i} is the usual response parameter of the individual. The latter parametrization allows to identify the best kind of treatment for each individual (for future treatments), which can be useful in practical situations where only one treatment per individual is possible.

The individual parameters are assumed to have an unknown mean $\mathrm{E}(\boldsymbol{\theta}_i) = (\mu_1, \mu_2)^\top =: \boldsymbol{\theta}_0$ and a covariance matrix $\mathrm{Cov}(\boldsymbol{\theta}_i) = \mathrm{diag}(\sigma_1^2\, u, \sigma_2^2\, v)$ for given dispersions $u > 0$ and $v > 0$. All individual parameters $\boldsymbol{\theta}_i$ and all observational errors $\varepsilon_{1i'k}$ and $\varepsilon_{2i''k'}$, $i, i', i'' = 1, \ldots, N$, $k, k' = 1, \ldots, K$, are assumed to be uncorrelated.

Note that this model is not a particular case of the RCR models considered by Prus and Schwabe (2016). In contrast to that paper, here the expected values for the response parameters μ_{1i} and μ_{2i} in the first and the second groups are not the same (which is equivalent to different regression functions in the parametrization using $\boldsymbol{\theta}_i$) and group sizes are non-fixed. Therefore, the approach proposed by Prus and Schwabe (2016) cannot be used.

Further we focus on the following contrasts: the population parameter $\alpha_0 = \mu_1 - \mu_2$ and the individual random parameters $\alpha_i = \mu_{1i} - \mu_{2i}$, $i = 1, \ldots, N$. α_0 describes the difference between the mean parameters μ_1 and μ_2 in the first and in the second group, respectively, and α_i may be interpreted as the difference for individual i between the present response and the response, which could have been observed if the individual had received another treatment. We search for

the designs (group sizes), which are optimal for the estimation of α_0 or for the prediction of α_i.

3 Estimation and Prediction

In this section we concentrate on the estimation of the population parameter α_0 and the prediction of the individual parameters α_i. We use the standard notation $\bar{Y}_1 = \frac{1}{n_1}\sum_{i=1}^{n_1}\frac{1}{K}\sum_{k=1}^{K} Y_{1ik}$ and $\bar{Y}_2 = \frac{1}{n_2}\sum_{i=n_1+1}^{N}\frac{1}{K}\sum_{k=1}^{K} Y_{2ik}$ for the mean response in the first and the second treatment group, respectively, and obtain the following best linear unbiased estimator (BLUE) for α_0.

Theorem 1. *a) The BLUE for the population parameter α_0 is given by*

$$\hat{\alpha}_0 = \bar{Y}_1 - \bar{Y}_2. \tag{3}$$

b) The variance of the BLUE $\hat{\alpha}_0$ is given by

$$\operatorname{var}(\hat{\alpha}_0) = \frac{\sigma_1^2(Ku+1)}{Kn_1} + \frac{\sigma_2^2(Kv+1)}{Kn_2}. \tag{4}$$

Further we use the notation $\bar{Y}_{1i} = \frac{1}{K}\sum_{k=1}^{K} Y_{1ik}$ and $\bar{Y}_{2i} = \frac{1}{K}\sum_{k=1}^{K} Y_{2ik}$ for the mean individual response for individuals in the first and in the second treatment group, respectively. We obtain the next result for the best linear unbiased predictor (BLUP) for the individual response parameter α_i.

Theorem 2. *The BLUP for the individual response parameter α_i is given by*

$$\hat{\alpha}_i = \begin{cases} \frac{Ku}{Ku+1}\bar{Y}_{1i} + \frac{1}{Ku+1}\bar{Y}_1 - \bar{Y}_2, \text{ ind. "i" in G1} \\ \bar{Y}_1 - \frac{Kv}{Kv+1}\bar{Y}_{2i} - \frac{1}{Kv+1}\bar{Y}_2, \text{ ind. "i" in G2}. \end{cases} \tag{5}$$

The next theorem presents the mean squared error (MSE) matrix for the total vector $\hat{\boldsymbol{\alpha}} := (\hat{\alpha}_1, ..., \hat{\alpha}_N)^\top$ of all BLUPs $\hat{\alpha}_i$ for all individuals.

Theorem 3. *The MSE matrix of the vector $\hat{\boldsymbol{\alpha}}$ of individual predictors is given by*

$$\operatorname{Cov}(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha}) = \begin{pmatrix} \mathbf{A}_{11} & \mathbf{A}_{12} \\ \mathbf{A}_{12}^\top & \mathbf{A}_{22} \end{pmatrix} \tag{6}$$

for

$$\mathbf{A}_{11} = \left(\frac{\sigma_1^2}{K(Ku+1)n_1} + \frac{\sigma_2^2(Kv+1)}{Kn_2}\right)\mathbf{1}_{n_1}\mathbf{1}_{n_1}^\top + \sigma_1^2\left(\frac{u}{Ku+1} + v\right)\mathbf{I}_{n_1},$$

where $\mathbf{1}_m$ denotes the vector of length m with all entries equal to 1, $\mathbf{I}_m$ is the $m \times m$ identity matrix and $\otimes$ denotes the Kronecker product,

$$\mathbf{A}_{12} = \left(\frac{\sigma_1^2}{Kn_1} + \frac{\sigma_2^2}{Kn_2}\right)\mathbf{1}_{n_1}\mathbf{1}_{n_2}^\top$$

and

$$\mathbf{A}_{22} = \left(\frac{\sigma_1^2(Ku+1)}{Kn_1} + \frac{\sigma_2^2}{K(Kv+1)n_2}\right)\mathbf{1}_{n_2}\mathbf{1}_{n_2}^\top + \sigma_2^2\left(u + \frac{v}{Kv+1}\right)\mathbf{I}_{n_2}.$$

Proofs of Theorems 1, 2 and 3 are deferred to Appendix.

4 Experimental Design

We define the experimental (exact) design for the RCR model with two treatment groups G_1 and G_2 as follows:

$$\xi := \begin{pmatrix} G_1 & G_2 \\ n_1 & n_2 \end{pmatrix}.$$

For analytical purposes, we generalize this to the definition of an approximate design:

$$\xi := \begin{pmatrix} G_1 & G_2 \\ w & 1-w \end{pmatrix},$$

where $w = \frac{n_1}{N}$ and $1-w = \frac{n_2}{N}$ are the allocation rates for the first and the second groups, respectively, and only the condition $0 \leq w \leq 1$ has to be satisfied. Then only the optimal allocation rate w^* to the first group has to be determined for finding an optimal design.

Further we search for the allocation rates, which minimize variance (4) of the BLUE $\hat{\alpha}_0$ and MSE matrix (6) of the BLUP $\hat{\boldsymbol{\alpha}}$ and concentrate on the A- (average) and D- (determinant) optimality criteria.

4.1 Optimal Designs for Estimation of Population Parameter

For the estimation of the population parameter α_0 both A- and D-criteria may be considered to be equal to variance (4) of the BLUE $\hat{\alpha}_0$. We rewrite the variance of the estimator in terms of the approximate design and receive the following optimality criterion (neglecting the constant factor $(KN)^{-1}$):

$$\Phi_{\alpha_0}(w) = \frac{\sigma_1^2(Ku+1)}{w} + \frac{\sigma_2^2(Kv+1)}{1-w}. \tag{7}$$

Criterion function (7) can be minimized directly. The optimal allocation rate for the estimation of the population parameter α_0 is is given by

$$w^*_{\alpha_0} = \frac{1}{1+\sqrt{\frac{\sigma_2^2(Kv+1)}{\sigma_1^2(Ku+1)}}}. \tag{8}$$

Note that the optimal allocation rate $w^*_{\alpha_0}$ to the first group increases with increasing observational error variance σ_1^2 and the dispersion u of random effects for the first group and decreases with variance parameters σ_2^2 and v for the second group. Note also that if the observational error variance is the same for both groups ($\sigma_1^2 = \sigma_2^2$), $w^*_{\alpha_0}$ is larger than 0.5 for $u > v$ and smaller than 0.5 for $u < v$.

4.2 Optimal Designs for Prediction of Individual Response Parameters

We define the A-criterion for the prediction of the individual response parameters $\boldsymbol{\alpha} = (\alpha_1, ..., \alpha_N)^\top$ as the trace of MSE matrix (6):

$$\Phi_{A,\alpha} := \operatorname{tr}\left(\operatorname{Cov}\left(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha}\right)\right). \tag{9}$$

We extend this definition for approximate designs and receive the following result (neglecting the constant factor K^{-1}).

Theorem 4. *The A-criterion for the prediction of the individual response parameters* $\boldsymbol{\alpha} = (\alpha_1, ..., \alpha_N)^\top$ *is given by*

$$\begin{aligned}\Phi_{A,\alpha}(w) = c_1 &+ \sigma_1^2 \left(\frac{Ku+1}{w} + Nw \left(\frac{Ku}{Ku+1} + Kv \right) \right) \\ &+ \sigma_2^2 \left(\frac{Kv+1}{1-w} + N(1-w) \left(\frac{Kv}{Kv+1} + Ku \right) \right),\end{aligned} \tag{10}$$

where

$$c_1 = \sigma_1^2 \left(\frac{1}{Ku+1} - Ku - 1 \right) + \sigma_2^2 \left(\frac{1}{Kv+1} - Kv - 1 \right).$$

For this criterion no explicit formulas for optimal allocation rates can be provided. For given dispersion matrix of random effects (given values of u an v), the problem of optimal designs can be solved numerically. In this work we are however interested in the behavior of optimal designs with respect to the variance parameters. Therefore, we consider some special cases, which illustrate this behavior.

Special Case 1: $\sigma_1^2 = \sigma_2^2$ and $u = v$
If the variances σ_1^2 and σ_2^2 of the observational errors as well as the dispersions u and v (and consequently the variances $\sigma_1^2\, u$ and $\sigma_2^2\, v$) of the random effects are the same for both groups, A-criterion (10) simplifies to

$$\Phi_{A,\alpha}(w) = c_2 + \frac{1}{w} + \frac{1}{1-w}, \tag{11}$$

where

$$c_2 = \frac{NKu'(Ku'+2)+2}{(Ku'+1)^2} - 2$$

for $u' = u = v$ (neglecting the factor $Ku' + 1$ and the observational errors variance). We obtain for this criterion the optimal allocation rate $w^*_{A,\alpha} = 0.5$, which is also optimal for estimation in the fixed-effects model ($u = v = 0$).

Special Case 2: $\sigma_1^2 = \sigma_2^2$
If only the variances σ_1^2 and σ_2^2 of the observational errors are the same for both groups, the A-criterion for the prediction simplifies to

$$\begin{aligned}\Phi_{A,\alpha}(w) = c_3 &+ \frac{Ku+1}{w} + Nw \left(\frac{Ku}{Ku+1} + Kv \right) \\ &+ \frac{Kv+1}{1-w} + N(1-w) \left(\frac{Kv}{Kv+1} + Ku \right),\end{aligned} \tag{12}$$

where

$$c_3 = \frac{1}{Ku+1} + \frac{1}{Kv+1} - K(u+v) - 2,$$

(neglecting the observational errors variance). The behavior of the optimal allocation rate will be considered for this case in a numerical example later.

The D-criterion for the prediction of $\boldsymbol{\alpha} = (\alpha_1, ..., \alpha_N)^\top$ can be defined as the logarithm of the determinant of MSE matrix (6):

$$\Phi_{D,\alpha} := \log\det\left(\mathrm{Cov}\left(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha}\right)\right). \tag{13}$$

For approximate designs we obtain the next result.

Theorem 5. *The D-criterion for the prediction of the individual response parameters* $\boldsymbol{\alpha} = (\alpha_1, ..., \alpha_N)^\top$ *is given by*

$$\Phi_{D,\alpha}(w) = b_1 + w\,N\log\left(\frac{\sigma_1^2(Kv+1)}{\sigma_2^2(Ku+1)}\right) + \log\left(\frac{\sigma_1^2(1-w)+\sigma_2^2\,w}{w(1-w)}\right), \tag{14}$$

where

$$b_1 = \log\left(\frac{(\sigma_2^2)^{N-1}(v+u(Kv+1))^{N-2}(Ku+1)(K(u+v)+1)}{\sigma_1^2K^2N(Kv+1)^{N-1}}\right).$$

Proof. We compute the determinant of MSE matrix (6) using the formula for block-matrices

$$\det\left(\mathrm{Cov}\left(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha}\right)\right) = \det\left(\mathbf{A}_{11}\right)\det\left(\mathbf{A}_{22} - \mathbf{A}_{12}^\top\mathbf{A}_{11}^{-1}\mathbf{A}_{12}\right).$$

Then we rewrite the result in terms of the approximate design and receive criterion (14).

Also for this criterion no finite analytical solutions for optimal designs can be provided. We consider the same special cases as for the A-criterion.

Special Case 1: $\sigma_1^2 = \sigma_2^2$ and $u = v$
If the variances of the observational errors and the variances of the random effects are the same for the first and the second treatment groups, the D-criterion for the prediction is given by

$$\Phi_{D,\alpha}(w) = b_2 - \log\left(w(1-w)\right), \tag{15}$$

where $b_2 = b_1 + \log(\sigma^2)$ for $\sigma^2 = \sigma_1^2 = \sigma_2^2$. Then we obtain the optimal allocation rate $w^*_{D,\alpha} = 0.5 = w^*_{A,\alpha}$, which is also optimal for the fixed-effects model.

Special Case 2: $\sigma_1^2 = \sigma_2^2$
If the variances of the observational errors are the same for both groups and the dispersions u and v of random effects may be different, we receive the following D-criterion for the prediction:

$$\Phi_{D,\alpha}(w) = b_2 + w\,N\log\left(\frac{Kv+1}{Ku+1}\right) - \log\left(w(1-w)\right). \tag{16}$$

If we additionally assume different dispersions of random effects ($u \neq v$), we obtain the next result for the optimal designs.

Theorem 6. *If the variances of the observational errors are the same and the dispersions of the random effects are different for the first and the second treatment groups, the D-optimal allocation rate for the prediction of the individual response parameters* $\boldsymbol{\alpha} = (\alpha_1, ..., \alpha_N)^\top$ *is given by*

$$w^*_{D,\alpha} = \frac{1}{2a}\left(a + 2 - \sqrt{a^2+4}\right), \tag{17}$$

where

$$a = N \log\left(\frac{Kv+1}{Ku+1}\right).$$

Note that the optimal allocation rate $w^*_{D,\alpha}$ to the first group increases with u and decreases with v. It can be easily proved that $w^*_{D,\alpha}$ is larger than 0.5 if $u > v$ and smaller than 0.5 if $u < v$.

For further considerations we rewrite the optimal allocation rate (17) as a function of the ratio $q = \frac{u}{v}$ of the variances of random effects in the first and the second groups and the variance parameter u:

$$a = N \log\left(\frac{Ku/q+1}{Ku+1}\right).$$

Than it is easy to verify that $w^*_{D,\alpha}$ increases with u for $q > 1$ $(u > v)$ and decreases for $q < 1$.

4.3 Numerical Example

In this section we illustrate the obtained results for the prediction of the individual response parameters by a numerical example. We consider the two groups RCR model with $N = 60$ individuals, $K = 5$ observations per individual and the same variance of observational errors for both treatment groups: $\sigma_1^2 = \sigma_2^2$ (special case 2). We fix the ratio $q = \frac{u}{v}$ of the variances of random effects in the first and the second groups by $q = 3$, $q = 1$ and $q = 0.3$. Figures 1 and 2 illustrate the behavior of the optimal allocation rates for the A- and D-criteria in dependence of the rescaled random effects variance in the first group $\rho = u/(1+u)$, which is monotonic in u and has been used instead the of random effects variance itself to cover all values of the variance by the finite interval $[0, 1]$.

As we can observe on the graphics, the optimal allocation rate to the first group increases with the rescaled variance ρ from 0.5 for $\rho \to 0$ to 0.910 for the A-criterion and to 0.985 for the D-criterion for $\rho \to \infty$ if $q = 3$. If $q = 0.3$, the optimal allocation rate decreases from 0.5 to 0.083 and 0.014 for the A- and D-criterion, respectively. For $q = 1$ the model coincides with that considered in special case 1 and the optimal design remains the same $(w^*_{A,\alpha} = w^*_{D,\alpha} = 0.5)$ for all values of u.

Figures 3 and 4 exhibit the efficiencies of the balanced design $w = 0.5$ for the prediction in the two groups model for the A- and D-criteria. For computing the A- and D-efficiencies, we use the formulas

$$\text{eff}_A = \frac{\Phi_{A,\alpha}(w^*_{A,\alpha})}{\Phi_{A,\alpha}(0.5)} \tag{18}$$

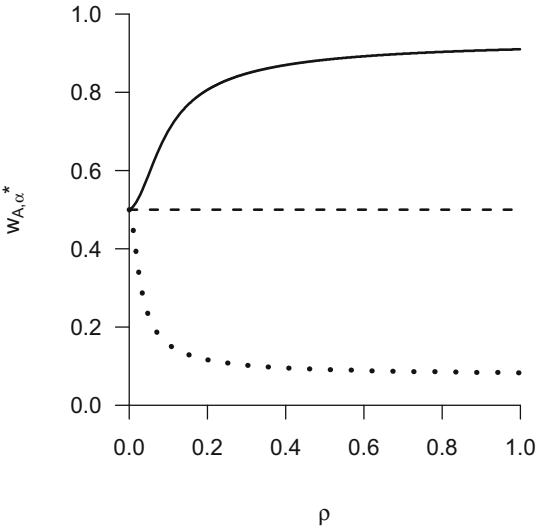

Fig. 1. A-optimal allocation rate w^* for variance ratios $q = 3$ (solid line), $q = 1$ (dashed line) and $q = 0.3$ (dotted line)

and

$$\text{eff}_D = \left(\frac{\exp(\Phi_{D,\alpha}(w^*_{D,\alpha}))}{\exp(\Phi_{D,\alpha}(0.5))} \right)^{\frac{1}{N}}, \tag{19}$$

respectively.

As we can observe, the efficiency of the balanced design decreases with increasing values of ρ from 1 for $\rho \to 0$ to 0.655 and 0.615 if $q = 3$ and to 0.618 and 0.585 if $q = 0.3$ for the A- and D-criteria, respectively. For $q = 1$ the balanced design is optimal for the prediction, which explains the efficiency equal to 1 for all values of the variance.

5 Discussion

In this work we have considered RCR models with two treatment groups. We have obtained the A- and D-optimality criteria for the estimation of the population parameter and the prediction of the individual response. For a particular case of the same observational error variance for both groups, we illustrate the behavior of the optimal designs by a numerical example. The optimal allocation rate to the first treatment group turns out to be larger than 0.5 if the variance of individual random effects in the first group is larger than in the second group. Otherwise, the optimal allocation rate is smaller than 0.5. The efficiency of the balanced design, which assigns equal group sizes, is relatively high only for small values of the variances of random effects. The efficiency decreases fast with increasing variance.

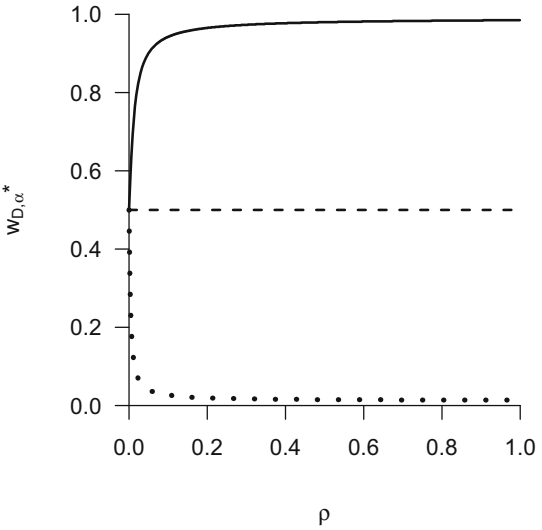

Fig. 2. D-optimal allocation rate w^* for variance ratios $q = 3$ (solid line), $q = 1$ (dashed line) and $q = 0.3$ (dotted line)

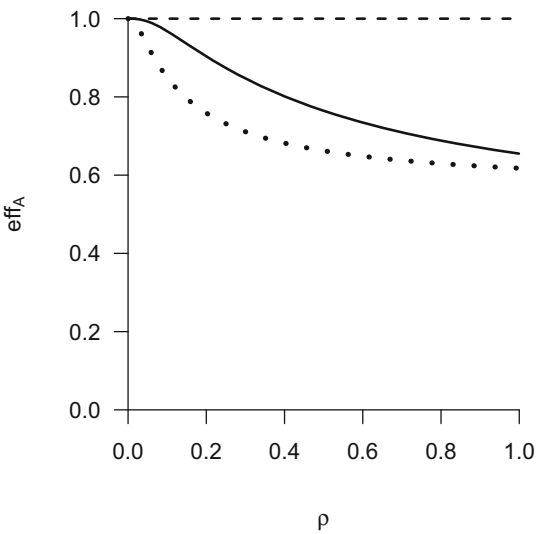

Fig. 3. A-efficiency of the balanced design $w = 0.5$ for variance ratios $q = 3$ (solid line), $q = 1$ (dashed line) and $q = 0.3$ (dotted line)

For simplicity, we have assumed a diagonal covariance matrix of random effects. For more general covariance structure further considerations are needed. We have also assumed the same number of observations for all individuals. Optimal designs for models with different numbers of observations for different individuals may be one of the next steps in the research. Moreover, optimal designs for RCR models with more than two groups can be investigated in the future. Furthermore, some research on more robust design criteria (for example, minimax or maximin efficiency), which are not sensible with respect to variance parameters, may be an interesting extension of this work.

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Appendix

Proofs of Theorems 1, 2, 3 and 4

The two treatment groups RCR model described by formulas (1) and (2) may be recognized as a special case of the general linear mixed model

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{\gamma} + \boldsymbol{\varepsilon} \tag{20}$$

with specific design matrices $\mathbf{X}$ and $\mathbf{Z}$ for fixed and random effects, respectively. $\boldsymbol{\varepsilon}$ are the observational errors, $\boldsymbol{\beta}$ denotes the fixed effects vector and $\boldsymbol{\gamma}$ are the random effects. The random effects and the observational errors are assumed to have zero mean and to be all uncorrelated with corresponding full rank covariance matrices $\operatorname{Cov}(\boldsymbol{\gamma}) = \mathbf{G}$ and $\operatorname{Cov}(\boldsymbol{\varepsilon}) = \mathbf{R}$.

In model (20) the BLUE for $\boldsymbol{\beta}$ and the BLUP for $\boldsymbol{\gamma}$ are solutions of the mixed model equations

$$\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\gamma}} \end{pmatrix} = \begin{pmatrix} \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{Z} \\ \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{Z} + \mathbf{G}^{-1} \end{pmatrix}^{-1} \begin{pmatrix} \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{Y} \\ \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{Y} \end{pmatrix} \tag{21}$$

if the fixed effects design matrix $\mathbf{X}$ has full column rank (see e.g. Henderson et al. (1959) and Christensen (2002)). According to Henderson (1975), the joint MSE matrix for both $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\gamma}}$ is given by

$$\operatorname{Cov}\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma} \end{pmatrix} = \begin{pmatrix} \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{Z} \\ \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{Z} + \mathbf{G}^{-1} \end{pmatrix}^{-1}. \tag{22}$$

To make use of the theoretical results available for the general linear mixed model, we rewrite the two groups RCR model in form (20):

$$\mathbf{Y} = \begin{pmatrix} \mathbf{1}_{Kn_1} e_1^\top \\ \mathbf{1}_{Kn_2} e_2^\top \end{pmatrix} \boldsymbol{\beta} + \begin{pmatrix} \mathbf{I}_{n_1} \otimes \left(\mathbf{1}_K e_1^\top\right) & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{n_2} \otimes \left(\mathbf{1}_K e_2^\top\right) \end{pmatrix} \boldsymbol{\gamma} + \boldsymbol{\varepsilon}, \tag{23}$$

where $\boldsymbol{\beta} = \boldsymbol{\theta}_0$, $\boldsymbol{\gamma} = \boldsymbol{\theta} - (\mathbf{1}_N \otimes \mathbf{I}_2)\,\boldsymbol{\beta}$, $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_N)$ and e_m denotes the m-th unit vector. The covariance matrices of the random effects and the observational errors in model (23) are given by $\mathbf{G} = \mathbf{I}_N \otimes \operatorname{diag}(\sigma_1^2\, u, \sigma_2^2\, v)$ and $\mathbf{R} = \text{block-diag}(\sigma_1^2\, \mathbf{I}_{Kn_1}, \sigma_2^2\, \mathbf{I}_{Kn_2})$, respectively.

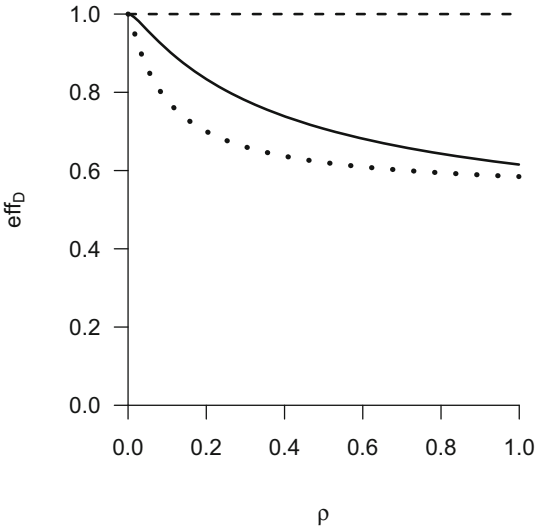

Fig. 4. D-efficiency of the balanced design $w = 0.5$ for variance ratios $q = 3$ (solid line), $q = 1$ (dashed line) and $q = 0.3$ (dotted line)

Using formula (21) we obtain the BLUEs $\hat{\mu}_1 = \bar{Y}_1$ and $\hat{\mu}_2 = \bar{Y}_2$ for the fixed effects and the BLUPs

$$\hat{\mu}_{1i} = \begin{cases} \frac{Ku}{Ku+1}\,\bar{Y}_{1i} + \frac{1}{Ku+1}\,\bar{Y}_1, & \text{ind. } "i" \text{ in } G_1 \\ \bar{Y}_1, & \text{ind. } "i" \text{ in } G_2 \end{cases} \tag{24}$$

and

$$\hat{\mu}_{2i} = \begin{cases} \frac{Kv}{Kv+1}\,\bar{Y}_{2i} + \frac{1}{Kv+1}\,\bar{Y}_2, & \text{ind. } "i" \text{ in } G_2 \\ \bar{Y}_2, & \text{ind. } "i" \text{ in } G_1 \end{cases} \tag{25}$$

for the random effects. Then the BLUE and the BLUP for the contrasts α_0 and α_i can be computed as $\hat{\alpha}_0 = \hat{\mu}_1 - \hat{\mu}_2$ and $\hat{\alpha}_i = \hat{\mu}_{1i} - \hat{\mu}_{2i}$ and result to formulas (3) and (5), respectively. Variance (4) of the estimator $\hat{\alpha}_0$ can be determined directly.

Using formula (22) we obtain the following joint MSE matrix for both $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\gamma}}$:

$$\operatorname{Cov}\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma} \end{pmatrix} = \begin{pmatrix} \mathbf{C}_{11}\ \mathbf{C}_{12} \\ \mathbf{C}_{12}^{\top}\ \mathbf{C}_{22} \end{pmatrix}, \tag{26}$$

where

$$\mathbf{C}_{11} = \begin{pmatrix} \frac{\sigma_1^2(Ku+1)}{Kn_1} & 0 \\ 0 & \frac{\sigma_2^2(Kv+1)}{Kn_2} \end{pmatrix},$$

$$\mathbf{C}_{12} = -\begin{pmatrix} \frac{1}{n_1}\,\sigma_1^2\,u\,\mathbf{1}_{n_1}^{\top} \otimes e_1^{\top} & \mathbf{0} \\ \mathbf{0} & \frac{1}{n_2}\,\sigma_2^2\,v\,\mathbf{1}_{n_2}^{\top} \otimes e_2^{\top} \end{pmatrix}$$

and

$$\mathbf{C}_{22} = \begin{pmatrix} \mathbf{B}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{B}_2 \end{pmatrix}$$

for

$$\mathbf{B}_1 = \sigma_1^2 \left(\frac{Ku^2}{n_1(Ku+1)} \mathbf{1}_{n_1} \mathbf{1}_{n_1}^\top \otimes (e_1 e_1^\top) + \mathbf{I}_{n_1} \otimes \operatorname{diag}\left(\frac{u}{Ku+1}, v \right) \right)$$

and

$$\mathbf{B}_2 = \sigma_2^2 \left(\frac{Kv^2}{n_2(Kv+1)} \mathbf{1}_{n_2} \mathbf{1}_{n_2}^\top \otimes (e_2 e_2^\top) + \mathbf{I}_{n_2} \otimes \operatorname{diag}\left(u, \frac{v}{Kv+1} \right) \right).$$

The MSE matrix of the prediction $\hat{\boldsymbol{\theta}}$ can be written in terms of joint MSE matrix (26):

$$\operatorname{Cov}\left(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta} \right) = (\mathbf{1}_N \otimes \mathbf{I}_2)\, \mathbf{C}_{11} \left(\mathbf{1}_N^\top \otimes \mathbf{I}_2 \right) + (\mathbf{1}_N \otimes \mathbf{I}_2)\, \mathbf{C}_{12} + \mathbf{C}_{12}^\top \left(\mathbf{1}_N^\top \otimes \mathbf{I}_2 \right) + \mathbf{C}_{22}. \tag{27}$$

Using this formula we obtain

$$\operatorname{Cov}\left(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta} \right) = \begin{pmatrix} \mathbf{H}_{11} & \mathbf{H}_{12} \\ \mathbf{H}_{12}^\top & \mathbf{H}_{22} \end{pmatrix},$$

where

$$\mathbf{H}_{11} = \mathbf{1}_{n_1} \mathbf{1}_{n_1}^\top \otimes \begin{pmatrix} \frac{\sigma_1^2}{K(Ku+1)n_1} & 0 \\ 0 & \frac{\sigma_2^2(Kv+1)}{Kn_2} \end{pmatrix} + \sigma_1^2 \mathbf{I}_{n_1} \otimes \begin{pmatrix} \frac{u}{Ku+1} & 0 \\ 0 & v \end{pmatrix},$$

$$\mathbf{H}_{12} = \mathbf{1}_{n_1} \mathbf{1}_{n_2}^\top \otimes \begin{pmatrix} \frac{\sigma_1^2}{Kn_1} & 0 \\ 0 & \frac{\sigma_2^2}{Kn_2} \end{pmatrix}$$

and

$$\mathbf{H}_{22} = \mathbf{1}_{n_2} \mathbf{1}_{n_2}^\top \otimes \begin{pmatrix} \frac{\sigma_1^2(Ku+1)}{Kn_1} & 0 \\ 0 & \frac{\sigma_2^2}{K(Kv+1)n_2} \end{pmatrix} + \sigma_2^2 \mathbf{I}_{n_2} \otimes \begin{pmatrix} u & 0 \\ 0 & \frac{v}{Kv+1} \end{pmatrix}.$$

Then we present the MSE matrix of the predictor $\hat{\boldsymbol{\alpha}}$ in form

$$\operatorname{Cov}\left(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha} \right) = \left(\mathbf{I}_N \otimes \mathbf{1}_2^\top \right) \operatorname{Cov}\left(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta} \right) \left(\mathbf{I}_N \otimes \mathbf{1}_2 \right)$$

and receive result (6) of Theorem 3.

References

Bailey, R.A.: Design of Comparative Experiments. Cambridge University Press (2008)

Christensen, R.: Plane Answers to Complex Questions: The Theory of Linear Models. Springer, New York (2002)

Fedorov, V., Jones, B.: The design of multicentre trials. Statistical Methods in Medical Research **14**, 205–248 (2005)

Gladitz, J., Pilz, J.: Construction of optimal designs in random coefficient regression models. Mathematische Operationsforschung und Statistik, Series Statistics **13**, 371–385 (1982)

Henderson, C.R.: Best linear unbiased estimation and prediction under a selection model. Biometrics **31**, 423–477 (1975)

Henderson, C.R., Kempthorne, O., Searle, S.R., von Krosigk, C.M.: The estimation of environmental and genetic trends from records subject to culling. Biometrics **15**, 192–218 (1959)

Kunert, J., Martin, R.J., Eccleston, J.: Optimal block designs comparing treatments with a control when the errors are correlated. Journal of Statistical Planning and Inference **140**, 2719–2738 (2010)

Piepho, H.P., Möhring, J.: Generation means analysis using mixed models. Crop Science **50**, 1674–1680 (2010)

Prus, M. (2015). *Optimal Designs for the Prediction in Hierarchical Random Coefficient Regression Models*. Ph.D. thesis, Otto-von-Guericke University, Magdeburg

Prus, M., Schwabe, R.: Optimal designs for the prediction of individual parameters in hierarchical models. Journal of the Royal Statistical Society: Series B **78**, 175–191 (2016)

Van Breukelen, G.J.P., Candel, J.J.M.: Efficient design of cluster randomized trials with treatment-dependent costs and treatment-dependent unknown variances. Statistics in Medicine **37**, 3027–3046 (2018)

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