Vester's Sensitivity Model for Genetic Networks with Time-Discrete Dynamics

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Abstract. We propose a new method to explore the characteristics of genetic networks whose dynamics are described by a linear discrete dynamical model $x_{t+1} = Ax_t$. The gene expression data x_t is given for various time points and the matrix A of interactions among the genes is unknown. First we formulate and solve a parameter estimation problem by linear programming in order to obtain the entries of the matrix A. We then use ideas from Vester's *Sensitivity Model*, more precisely, the *Impact Matrix*, and the determination of the *Systemic Roles*, to understand the interactions among the genes and their role in the system. The method identifies prominent outliers, that is, the most active, reactive, buffering and critical genes in the network. Numerical examples for different datasets containing mRNA transcript levels during the cell cycle of budding yeast are presented.

Keywords: Linear Programming, Parameter Estimation, Discrete Dynamical System, Sensitivity Analysis, Genetic Networks, Operational Research, Systems Biology.

1 Introduction

The recent availability of big amounts of gene expression data has enhanced the study of genetic networks, which is a challenging and promising topic. The main goal of these studies is to understand and estimate the dynamical interrelations among the genes in the network. Several approaches were developed in the recent years to model the regulatory interactions. They differ by the mathematical techniques that came to application: modeling by graphs, Bayesian networks, Boolean networks, discrete and continuous dynamical systems (or systems of ordinary differential equations). For more information we refer to Jong [14], Bansal et al. [17], or Ay et al. [1], for instance, and the references therein. Furthermore, suitable

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mathematical tools for the understanding of the networks are constantly broadening the spectrum of possibilities to study such systems, see Weber [11], Defterli et al. [19] and [20], Defterli [18], Weber [12], Yee et al. [16], Jong et al. [15].

In this present work, we use a discrete linear model to describe the dynamics of the network. We assume that the expression level of any gene at a certain point in time is the result of the weighted sum of the expression level of all the other genes at the previous point in time only [7], with respect to a given time discretization. Denote by $G := \{1, \ldots, n\}$ the set of genes and by T the finite set of time steps. The set T' contains all but the last time step of T. Then

$$x_{t+1,i} = \sum_{j \in G} a_{i,j} x_{t,j}, \qquad \forall\, i \in G, t \in T', \tag{1}$$

where $x_t = (x_{t,1}, x_{t,2}, \ldots, x_{t,n})^\top \in \mathbb{R}^n$ is a vector with the expression level of the genes in G at time step t. Here, $A = (a_{i,j}) \in \mathbb{R}^{n \times n}$ is a matrix, where the influence coefficient $a_{i,j}$ represents the ability of gene j to regulate gene i. To solve such models, linear regression has frequently been used, see for example Zhang et al. [22], Someren et al. [6], Someren et al. [7], or Bansal et al. [17]. These methods are facing the problem that there is usually much more genes than time steps, which leads to non-unique (or multiple) possible solutions. However, these methods do not allow for a control on the obtained solution. In our method, we compute the matrix A by means of linear programming. We minimize the L_1-norm of the matrix A, in order to get the simplest matrix that can explain the system's dynamical behavior (cf. Occam's razor).

Our core question is, is there more information that can be retrieved from analyzing the matrix A? We try to gain insights into the behavior of the individual genes and their role in the system as a total. In the economical literature, we found a method called *Sensitivity Model* (or *Paper Computer*), proposed by Vester and von Hesler in 1980 [9] (usually referred to as Vester's model). Vester's model has its background in the area of network thinking, combining elements from system dynamics, fuzzy logic and bio-cybernetics. It is important to clarify that in spite of the name, the model has nothing to do with the concept of sensitivity analysis associated with optimization problems. The main purpose of this model is to provide a system dynamic modeling tool capable of handling and analyzing complex systems by setting out the inner structures, hence enabling further interventions (control/regulation) on the system. Cole [3], Wolf et al. [5], and Neumann et al. [10] present some of the most common areas of use of Vester's model. Nevertheless, the model has a context-independent structure, so that it can be applied to new areas, as we demonstrate in this work.

In the context of genetic networks we want to understand the regulatory interactions from a systemic point of view. Hereto, we adapt Vester's ideas to characterize the genes by analyzing them based on their relations and their effect on the system as whole. We aim to obtain information about the structure and the functioning of the genetic network.

2 The Method

Our method consists of two steps. In the first step, we compute the matrix A of the discrete dynamical system, using linear programming. In the second step, we analyze A to derive dynamical properties of the genes involved in the network, using Vester's Sensitivity Model.

2.1 Linear Programming

We consider a linear model that describes the interactions among the genes according to equation (1). Our objective then is to estimate the entries of A. For this, we use a dataset containing measured gene expression data x_t, within a finite time horizon of discrete time steps $t \in T$. The parameter $x_{t,i}$ contains gene expression data for gene $i \in G$ at time step $t \in T$. The entries of the matrix A are decision variables $a_{i,j} \in \mathbb{R}$. The auxiliary variables $a^+_{i,j}$ and $a^-_{i,j}$ are used to linearize the nonlinear matrix norm $\|\cdot\|_1$.

We intend to find a matrix A that describes the dynamics of the network, therefore explaining the interaction among the genes. Applying the principle of parsimony, of all the possible matrices that can be used for this, we want to find one with the "simplest structure", that is, a matrix whose entires are the smallest possible in absolute value. This could result in the estimation of a sparse matrix, which according to [22] should be the case for regulatory systems. With this in mind, we want to minimize the following objective function:

$$\|A\|_1 = \sum_{i,j \in G} \left|a_{i,j}\right| = \sum_{i,j \in G} \left(a^+_{i,j} + a^-_{i,j}\right). \tag{2}$$

We linearize the expression $|a_{i,j}|$ by

$$a_{i,j} = a^+_{i,j} - a^-_{i,j}, \qquad \forall\, i,j \in G. \tag{3}$$

Equation (1) gives already the first constraint of the linear model, providing the relation between gene expression data subsequent in time,

$$x_{t+1,i} = \sum_{j \in G} a_{i,j} \cdot x_{t,j}, \qquad \forall\, i \in G,\ t \in T'. \tag{4}$$

Moreover, we impose a certain condition on the structure of the matrix A, i.e., the diagonal must be zero. This is necessary to apply Vester's method, where this setting is required for the *Impact Matrix* (see below for a more detailed explanation). For our application, it translates to the fact that a gene cannot influence itself. Hence

$$a_{i,i} = 0, \qquad \forall\, i \in G. \tag{5}$$

Summing it up, the linear programming model then is as follows:

$$\min (2),\ \text{subject to } (3), (4), (5). \tag{6}$$

2.2 Vester's Sensitivity Model

Vester's Sensitivity Model for an analysis of dynamical systems is described by a recursive structure of 9 steps altogether, see Vester [8]. In the following, we briefly describe the principal steps proposed by Vester in his model that are also relevant to our method.

Initially one has to describe the system, that means, express it in terms of the key elements (or variables) that are the most relevant. (In our application that means to select a set of genes G that should be studied as a system.) In general, this results in a reduction of the complexity providing a much more compact (practical) representation of the system. Next, the relations between the selected representative variables are studied in order to determine the magnitude of the influences among them. These influences are of great importance since they determine the behavior of the system. (In our application, this step is practically carried out by solving the linear program (6).)

Our motivation to use *Vester's Sensitivity Model* in the context of genetic networks arose from the formulation of the linear programming model. Not knowing the matrix A at the beginning means that we have no information about the interaction among the genes, consequently the inner structure of the network is unknown for us. Furthermore, even if we estimate such a matrix, we need to achieve certain level of knowledge regarding the structure. Only then we would be able to understand how the system works, this means, understand its behavior and understand what causes the system to behave as it does. Vester's Sensitivity Model states that these questions can be answered by analyzing the *Systemic Role* that the variables, in our case the genes, have. In turn, the *Systemic Role* is determined by the *Indices of Influence*, they summarize the information about the magnitude and the character of the interactions among the genes, and are calculated from the *Impact Matrix*. In this way, we can interpret the results form the linear programming model and achieve our initial objective, that is, to gain insights into the biological processes in genetic network.

The *Impact Matrix* is the matrix that contains the information of all the interactions among the variables in the system. The entries of this matrix reflect the influence of the variable i on the variable j. They are calculated by measuring the (pairwise) effect on the variables when the others change, therefore the name *Impact Matrix*. It is important to remark that variables do not influence themselves, therefore entires along the diagonal are not meaningful. A scale form 0 to 3 was initially proposed by [8] for measuring the effect of one variable in one another answering to the question: If the variable x changes, how does the variables y change?

This scaling does not distinguish between positive and negative influences, that is, only the magnitude of the influence irrespective of the sign is measured. With these values the *Impact Matrix* is built and the following indicators (**AS** and **PS**) and the *Indices of Influence* (**Q** and **P**) are calculated for each variable:

- Active Sum (**AS**): the sum along rows, indicates how large is the effect of the variable on the others.

- Passive Sum (**PS**): the sum along columns, indicates how sensitive is the variable, how does it react to changes in the system.
- Quotient (**Q**): the ratio **AS**/**PS**.
- Product (**P**): the product **AS***PS.

The quotient **Q**, determines how dominant or influenceable a variable is. The larger/smaller the quotient is, the more active/reactive character the variable has, respectively. On the other hand, the product **P** determines how participative a variable is. The larger/smaller the product, the more critical/buffering it is. Hence, the character of each variable is determined by the pair (**Q**, **P**). Highly active variables will be located in the upper left corner of the *System Role plot*, a plot whose axes are **PS** and **AS**. Highly reactive variables will be located in the lower right corner of the same plot. Analogously, highly critical and buffering variables will be found in the upper right and lower left corner, respectively. The rest of the variables (genes) will be located in the area in between these four locations. In other words, the variables are characterized by their dominance/influenceability, and by how participative they actually are, revealing the potential of each of them.

To conclude, let us point out what we use from Vester's Sensitivity Model in our proposed method, and how it is used. In first place, we regard the genetic network as the complex system to study, where the variables are the genes in the datasets and the interactions among them are the influence coefficients $a_{i,j}$ to estimate. That means, we use the estimated matrix A as *Impact Matrix*. This leads to a different scaling with respect to the one proposed in [8], some other scalings can also be found in [13,3]. Moreover, since the influence coefficients come from the solution of a linear programming problem without any constraint on the sign of the decision variables, it is possible that some entries in the matrix are negative. Vester's *Impact Matrix* has only positive entries and therefore we work with the absolute value of the estimated matrix A, without affecting the forthcoming analysis, given that the *Impact Matrix* has information only about the magnitude of the interactions, and not about their sign. We then calculate the indicators **AS**, **PS** and the *Indices of Influence* **Q**, **P**. Afterwards, we identify the most active, reactive, critical and buffering genes in the network, and thus determine their *Systemic Role*. Finally, the corresponding interpretation of their role is briefly discussed.

3 Data

Datasets containing mRNA transcript levels during the cell cycle of budding yeast are considered here, Cho et al. [21], Zhang [22]. The data was collected at 17 time points taken by 10 minute (min.) intervals covering nearly two full cell cycles and containing 5 phases (Early G1, Late G1, S, G2 and M). The complete yeast cell cycle dataset has 6220 genes [21] and shows fluctuation of their expression levels during the 17 time points. Cho et al. [21] identified from this dataset 416 genes based on their peak times and grouped them into the five cell cycle phases. Finally a subset of 384 genes was classified into only one phase

(some genes peak at more than one phase during the cell cycle, see Yeung et al. [16]). Yet a smaller subset with 23 genes was chosen in [18] and studied to analyze and anticipate the time discrete dynamics of the corresponding subnetwork. The genes of this subnetwork cover all the cell cycle phases.

We use the initial network with 384 genes form [21] and also the subnetwork with 23 genes as in [18]. The data is normalized across each cell cycle.

3.1 Data Analysis

Correlation analysis has been widely used in the study of gene environment networks with the aim of exploring gene expression data and thus providing insights into regulatory mechanism. Moreover, clustering techniques make use of correlation coefficients to define similarity measures and therefore discover patters in groups of genes with similar expression level data [16], Bendor et al. [2], Someren et al. [7]. It is not in the scope of this work to carry out a correlation analysis of the genes in the mentioned datasets, nevertheless we use a correlation analysis to explore their features to have a clear picture of what can be expected. Figure 1 depicts the correlation coefficients between the genes in the two different datasets. The genes were sorted by phase. As expected, for the majority of the genes in the same cycle phase, high correlation coefficients are observed. The black dashed lines show the grouping by phase. Genes in the same group not only peak in the same cycle phase, but their dynamics along the whole time horizon is also similar (see Figure 2), which was observed for both datasets. Given that the dynamics in each phase is similar, we took the mean expression level as a representative for all the genes in the same phase and plotted it for the different representatives along the time horizon, see Figure 3.

On the other hand, if we calculate the correlation coefficients of the 17 time points where the data was collected, see Figure 4, a periodic behavior is observed. This behavior is not surprising since the time horizon covers almost 2 cell cycles [21], meaning that the expression level of each gene has two observable peaks, each one happening in the phase it was classified into, see Figure 3. It is clear that

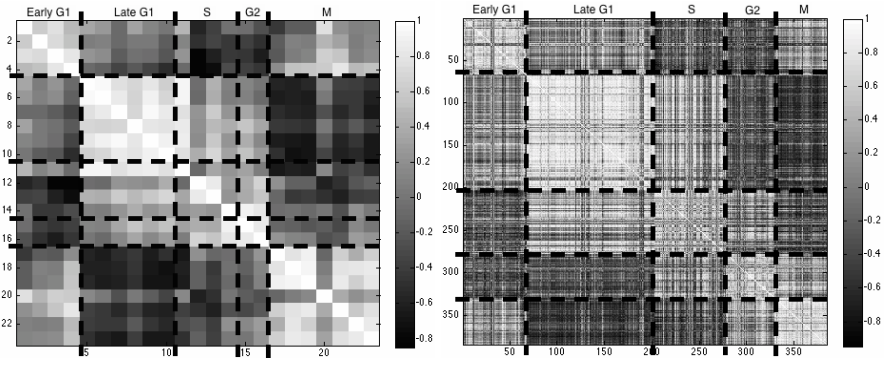

Fig. 1. Gene correlation matrix 23 (left) and 384 (right)

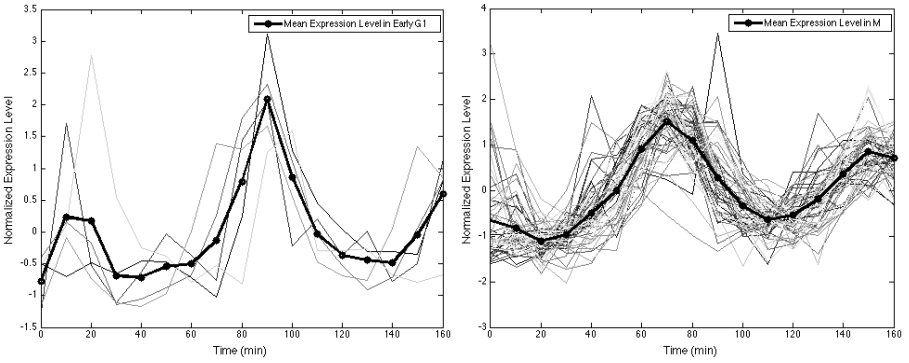

Fig. 2. Genes peaking in *Early G1* for the dataset with 23 genes and in *M* for the dataset with 384 genes

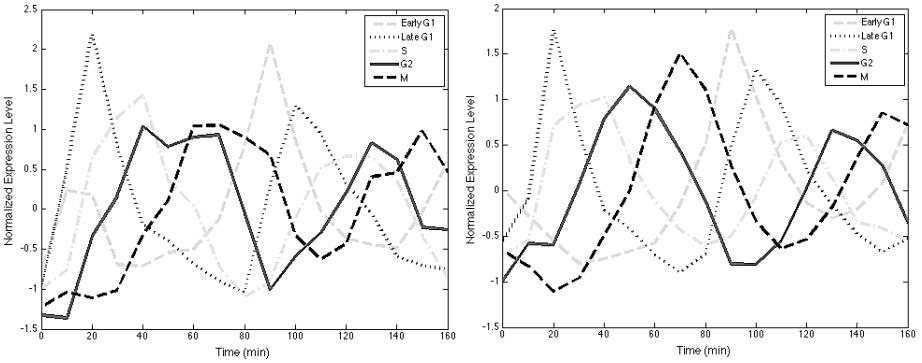

Fig. 3. Mean value for the expression level of genes in each phase; 23 genes (left) and 384 genes (right)

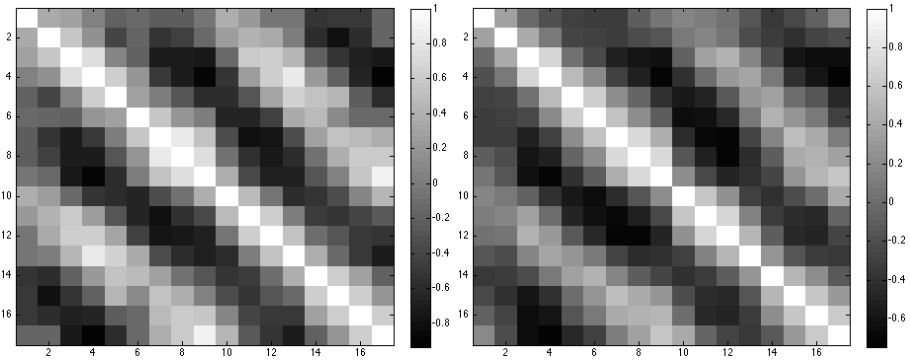

Fig. 4. Time-point correlation matrix; 23 genes (left) and 384 genes (right)

there is high linear dependency among the vector expression level at the time points (correlation coefficients close to zero are very seldom), which indicates that a linear model might give a good enough approximation of the dynamics of the system.

4 Computational Results

We solved the linear programming problem (6) for the selected datasets using AMPL as modeling language and CPLEX 12.5 Optimizer as solver. The resulting matrix A is shown in Figure 5. For the first dataset, the number of nonzeros is 368, for the second dataset it is 6144. For the latter, solution times below a few minutes are currently needed, hence our method could be applicable for bigger datasets with many more genes and time steps.

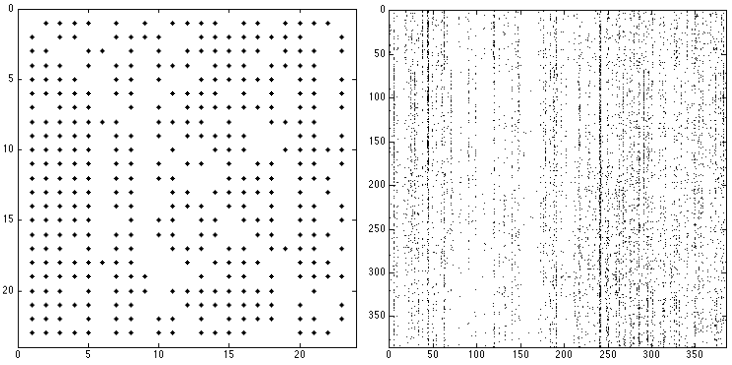

Fig. 5. Nonzero entries in the *Impact Matrix*; 23 genes (left) and 384 genes (right)

For each one of the genes we compute the values **AS**, **PS**, **Q** and **P**. We plot all the genes in the *Systemic Role plot*, where each gene is represented by a two dimensional point with coordinates $(\mathbf{AS}, \mathbf{PS})$. Furthermore, we color the genes according to the phase they belong to, in order to check whether there is a relation between the role of a gene and the phase it peaked in. Figure 6 shows that there is no evidence supporting that such relation exists, that means, irrespective of the phase they belong to, they have different roles. In other words, our method provides additional information that cannot be gained by a correlation analysis. Figure 7 reassures this position, here we selected one gene, marked with an asterisk (*), and colored the rest of the genes according to the correlation coefficient to this gene. Also here no clusters were observed indicating that such relation in fact exists.

Now we want to draw the attention to the *Systemic Roles* of the genes, highlighting the prominent outliers in the network in order to understand what their character reveals. Let us start stating that for the 23 dataset a clear configuration for the roles can be observed. The relatively most active gene belongs to

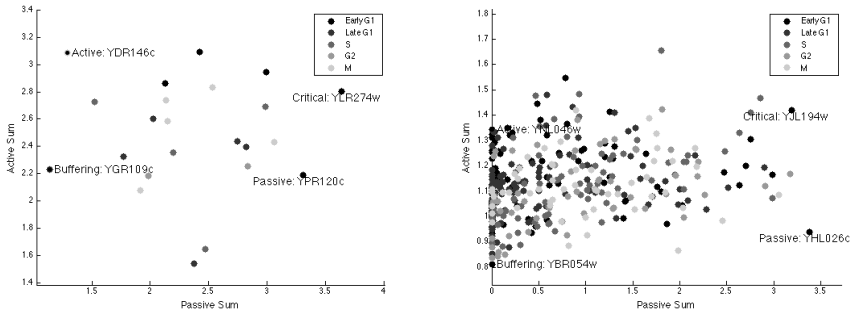

Fig. 6. *Systemic Role plot* colored by phase; 23 genes (left) and 384 genes (right)

the *M* phase and is YDR146c. It regulates many other genes and is regulated just by few. Being a transcription factor [21], it influences the other genes by contributing to specific biochemical processes. As for the interpretation of its role, we can say it is a dominant gene. It could be used as lever; if changes were to happen to its gene expression level, significant changes could be produced on the other genes and therefore the cell cycle could present alterations. This is the prototype of gene that can be used to trigger some desired effect.

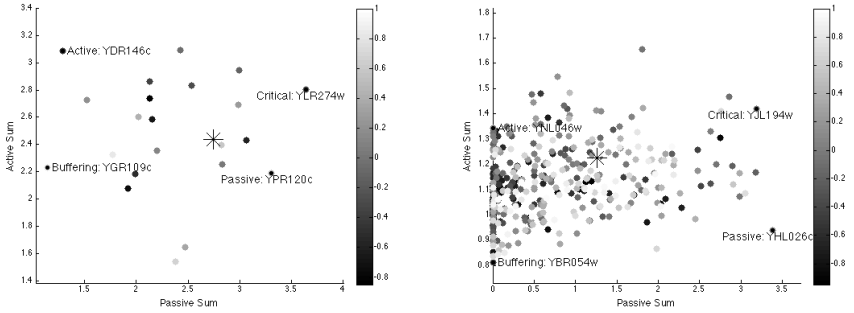

Fig. 7. *Systemic Role plot* colored by correlation coefficient to the gene marked with asterisk (*); 23 genes (left) and 384 genes (right)

Gene YPR120c belongs to the *Late G1* phase. It emerges as the most reactive gene, which means that its expression level is highly sensitive to alterations in the expression level of other genes, but the cell cycle would not change much with changes in its expression level. Such kind of genes are consider to have a damping function, since the effects will not propagate in the system, in spite of being highly sensitive. Its function is as cell cycle regulator [21], this might be the

reason behind its highly reactive character. This gene needs a lot of information from the system, i.e., from other genes and therefore is influenced by relatively many.

As the most critical we observe gene YLR274w belonging to the *Early G1* phase. It has highly regulator capabilities but at the same time is highly regulated, which makes it a "risky" gene and difficult to control. This goes in accordance with its function in the cell cycle as DNA replicator [21].

Finally the most buffering gene turned out to be YGR109c, it also belongs to the *Late G1* phase. This gene is the one with the lowest "activity" in the system (inert element), it does not regulate nor is regulated by others. Such genes, could be regarded as "stable", since their state is the one changing the least through the time horizon. If we compare it with gene YPR120c acting both as cycle regulators [21], we can say that the regulatory function of the first one is relatively smaller. In turn it does not use much information from the other genes and thus it is more difficult to change its expression level.

In general we can say that the network as a whole has a buffering character, most of the genes tend to be located in the lower left corner which correspond to the buffering part of the *Systemic Role plot*. Moreover, if we describe the system with just one point in this plot, taking for example the mean value, this point would be closest to the buffering corner than to any other corner in the plane.

A similar analysis can be made for the dataset with 384 genes as for the most active, reactive, buffering and critical genes. Both, the pattern in the *Impact Matrix* and the fact that the matrix is more sparse than the one in the 23 case, explain the accumulation of genes near to the Active Sum axis. The pattern (vertical lines) suggest that the genes are more reactive, in the sense that there are relatively more genes with low passive sum than in the first dataset.

5 Conclusions and Future Work

We introduced a new method for exploring structural features of genetic networks with linear time-discrete dynamics of the form $x_{t+1} = Ax_t$, where A is a matrix of influence coefficients. We solved a parameter estimation problem by linear programming in order to obtain a matrix A that describes the dynamics of the network and has the minimum L_1 norm possible for two different datasets (with gene expression data given at various time points). Features of the datasets were investigated using correlation analysis. Afterwards we used some of the central ideas of the *Sensitivity Model* proposed by Vester [8] to understand the interactions among the genes in the network and characterize each one of them according to their role in the system. More precisely, we let the estimated matrix A be the *Impact Matrix* that explains the influences among the variables (genes) in the system (genetic network). We then proceeded to calculate the *Indices of Influence* $\mathbf{Q}$ and $\mathbf{P}$, which reflect the active/reactive and critical/buffering character of the genes. No evidence of a relation between the *Systemic Role* of the genes and their phase group nor the correlation coefficient corresponding to a specific gene was observed. Finally, and with the aim understanding what the

Systemic role concept brings into play, we identified the most active, reactive, critical and buffering genes in the network and analyzed the interpretation given by the Vester's Sensitivity Model to such elements, i.e., as levers (active), risk factors (critical), measuring sensors (reactive) and inert elements (buffering).

In our future studies, we will extend this method in different ways. On one hand we would like to make use of genetic network features to make a more realistic estimation of the matrix A. Furthermore, will use different models to describe the dynamics of the network such as piecewise linear differential equations, also known as hybrid systems, and later on, stochastic hybrid systems with jumps (cf. Temoçin et al. [4]). It would also be interesting to consider different types of norms during estimation process. With respect to the ideas used form Vester, one could think of developing a more accurate definition of roles considering more extensively the possible combinations of the indexes **Q** and **P**, in such a way that more specific features of genetic networks are taken into account.

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