

# Understanding the effects of pharmaceutical promotion: a neural network approach guided by genetic algorithm-partial least squares

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**Abstract** With escalating healthcare costs and increasing concerns about optimizing use of medicine, there is an unresolved debate over years around the potential impact of pharmaceutical promotion on physicians' prescribing behaviors. What should be the appropriate balance of promotion dollars to physicians? We use three major brands in the US antibiotic universe to explore this issue, presenting a theoretical framework for better understanding the cause-and-effect relationship between common promotional spending and prescription responsiveness. Using simulations we demonstrate that neural networks guided by genetic algorithm-partial least squares is able to provide managers with better understanding of physicians' prescribing activities without an appreciably lower predictive accuracy when compared to that obtained by a standalone neural network modeling.

**Keywords** Antibiotic · Genetic algorithm · Partial least squares · Neural networks · Optimization · Physicians' prescribing behavior · Pharmaceutical promotion · Promotional effectiveness · Promotion effects · Promotional spending

## 1 Introduction

A successful pharmaceutical sales and marketing strategy requires the ability to effectively and appropriately optimize the curious blend of a promotional cocktail. However,

making high-stakes decision like this has always been difficult. As the complexities of market have deepened in recent years—spurred by consumers, media and policy-makers that pharmaceutical promotion practices have accelerated the rise in healthcare cost, it has become more critical than ever that companies understand well every dollar they are spending on physician-oriented marketing. Specifically, a good understanding of the outcomes associated with a wide range of spending levels would clearly be valuable in helping to reduce unnecessary expenditure, as well as in identifying promotional expenditure that needs augmentation. While there had previously been extensive study conducted to determine the effectiveness of common promotion modes like media spending, sampling as well as detailing ([1–9] and related references therein), the list of research on promotional response in the prescription marketplace is still relatively short [10–13]. This is partly due, perhaps, to difficulties related to accurate and comprehensive data collection, confidentiality issues, and so forth.

Today, most strategic decisions in promotion budget allocation are of qualitative or of policy nature but some of them are quantitative. The qualitative approach includes managers' hunches, experts' opinions or panel consensus [14]. The risk is that these experience-based judgments are too static to accommodate in time the changing dynamics of the marketplace that often require decisions to be quickly revised. The classical quantitative approach, based on multiple linear regression analysis, while substantively appealing, is sometimes hampered in practice due to the difficulty of accurately assessing the interrelations between variables that are convoluted. A more managerially useful approach is therefore to embrace a less stressful tool that could predict observed variation in response variable(s) without knowledge about the nature of the relationship

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between the response and predictor variables; i.e., data go in and a prediction comes out. Of particular interest is the neural network approach put forth by Lim and Kirikoshi for measuring the impact of physician-directed promotion on prescription yield [12, 13]. However, neural networks are often affected by an effect called *overfitting* when the network size becomes too bulky with many predictor variables. In other words the large number of variables maximizes the amount of information and could be advantageous in building neural network models with improved fit to the training set, but on the contrary the increased number of variables often causes a substantial reduction in the predictive ability of the model. The combination of a genetic algorithm with neural networks is an efficient way of reducing network size and thus reducing the risk of overfitting. Prior research has shown that among the numerous methods of variable selection genetic algorithms have often achieved promising results [15].

In this study, we exploit the desirable characteristics of genetic algorithms, partial least squares and neural networks to build predictive models for understanding the relevance and limitations of promotional spending on prescription responsiveness. This new methodology integrates a genetic algorithm-partial least squares (GAPLS) analysis with neural networks to create a *hybrid* modeling approach. A two-step approach is created that attempts to utilize the most relevant subset of promotional spending variables (that best characterize the variation in prescription yield) selected by GAPLS to train a neural network. Subsequently, the trained neural network is tested via a *leave-one-out* cross validation procedure, and the result is a highly accurate predictive model that possesses a desirable balance between predictive accuracy and model complexity. The inclusion of PLS is meant for capturing the linear relationships between promotional spending variables and prescription yield. Neural networks are then used to account for the nonlinearities in the data or to implicitly help extend GAPLS linear models to cope with the nonlinearities. In a broad sense, this hybrid modeling approach utilizes the basic concept of *refining* or *filtering* in an attempt to minimize noise in the data. Likewise, neural networks guided by genetic algorithm (GANN) can also serve as an alternative for variable selection but performing GANN on a large number of variables is computationally slow compared with standard statistical analyses [16]. Therefore, it is computationally efficient if one can first extract as much information as possible from a given data set using GAPLS before presenting the most relevant variables to neural networks for model-free non-linear mapping. Further, we could argue that a weakness of a GANN is that variable selection has a certain level of *randomness*; i.e., different executions of a GANN do not necessarily provide identical

subsets of variables [17]. This fact can be justified by the existence of multiple optimum solutions within a search space of a problem. Indeed, we can still yield satisfactory solutions if a GANN is used since different combinations of variables may also be able to discern the cause-and-effect relationship between promotional spending and prescription responsiveness. Yet, PLS is introduced in particular to supplement the GA for facilitating the search process to elude the infeasible solutions, and lead to the global optimal solution. Thus, the combination of a GAPLS with neural networks is a fast and efficient way of selecting an optimal set of promotional spending variables that are responsible for the variation in prescription responsiveness besides improving the quality of analysis.

The outcome of this study accomplishes two objectives. First, the amount and implementation of promotional activities can be optimized for maximum return given a good understanding of the relevance and limitations of each promotion mode. Second, if the impact of individual promotional spending element can be measured, then this is perhaps a testament to the way the efficacy of interventions to reduce the harmful consequences of pharmaceutical marketing could be validated given a growing number of public beliefs that physician-directed promotion has grown too heavy-handed and is undermining medical professionalism.

## 2 Materials and methods

### 2.1 Data

This study utilized database collected by a pharmaceutical consulting firm on 3 major brands (for simplicity termed brand A, B and C henceforth) in the US antibiotic universe. Brand names are masked in order to protect the commercial competitive advantage of these products in the marketplace. For each brand there are altogether 71 time-series monthly data of 11 promotional spending variables as predictor variables and total prescription volumes as response variable (Table 1). Descriptive statistics for the data sets analyzed are presented in Table 2. In summary, the main characteristics with each data set include non-stationarity of the variance, seasonality and either an upward or downward trend in the mean.

‘Calls’ (CAL) measures the total number of visits made by pharmaceutical reps to physicians whereas ‘Contacts’ (CON) is a product-level report of promotional actions that is provided by physicians. A CON can be a full product discussion with a physician, a drug fair set up at the hospital for physicians or a delivery of a product sample. Several products may be discussed during a single call, resulting in the possibility of multiple CONs in a CAL.

**Table 1** The predictor and response variables under consideration

Variables	Number	Description	Designation
Predictor	1	Calls	CAL
	2	Contacts	CON
	3	Cost of contacts	COC
	4	Cost per contact	CPC
	5	Minutes	MIN
	6	Journal advertising spending	JAS
	7	Ads	ADS
	8	Ad pages circulated	ADP
	9	Samples	SAM
	10	Extended units samples	EUS
	11	Retail value of sample	RVS
Response	12	Total prescription volume	TRx

‘Cost of contacts’ (COC) includes the costs associated with detailing of reps that are directed to physicians. ‘Cost per contact’ (CPC) is an estimate of cost per contact whereas ‘Minutes’ (MIN) is the projected sum of time spent with physicians. ‘Journal advertising spending’ (JAS) captures the expenditure of advertising in medical journals. ‘Ads’ (ADS) measures the number of different layouts of product advertisements in medical journals. If the same ad appears in two journals, it is counted twice. ‘Ad pages circulated’ (ADP) represents the number of total ad pages circulated in journals for a particular product. ‘Sample’ (SAM) shows the projected volume of a product provided as samples to physicians whereas ‘extended units samples’ (EUS) measures the amount of a product sampled as the number of

**Table 2** Descriptive statistics for data sets under investigation

Brand	Variable	Mean	Standard Deviation	Maximum	Minimum
A	CAL	42,791	20,867	77,657	5,361
	CON	56,012	26,521	99,198	7,657
	COC	4,377,300	2,009,407	8,041,793	737,297
	CPC	82	12	114	62
	MIN	207,695	93,616	334,945	32,682
	JAS	75,026	110,348	486,943	0
	ADS	7	8	30	0
	ADP	17	20	82	0
	SAM	1,110,157	702,336	2,614,948	615
	EUS	3,318,395	2,261,919	8,204,439	1,230
	RVS	7,966,567	4,982,242	18,502,700	6,660
	TRx	1,198,586	684,583	2,466,777	84,895
B	CAL	23,521	18,671	66,762	6,393
	CON	28,762	19,831	77,810	8,314
	COC	2,476,365	1,813,626	7,086,679	760,152
	CPC	85	7	105	66
	MIN	126,935	99,199	361,786	26,233
	JAS	76,724	131,534	445,264	0
	ADS	8	11	35	0
	ADP	12	19	71	0
	SAM	363,092	329,976	1,201,558	39,725
	EUS	1,228,302	943,552	3,976,200	88,166
	RVS	2,519,196	2,291,065	9,057,345	272,771
	TRx	614,358	375,063	1,646,070	189,952
C	CAL	47,036	9,427	69,173	29,253
	CON	85,151	15,712	119,339	58,027
	COC	6,347,594	1,432,865	9,534,615	3,481,676
	CPC	74	6	85	56
	MIN	357,428	75,075	601,628	219,272
	JAS	324,422	195,197	727,289	33,455
	ADS	31	15	66	9
	ADP	53	30	112	6
	SAM	540,153	155,005	916,951	244,793
	EUS	2,277,668	656,551	3,932,950	1,109,240
	RVS	10,506,042	3,526,215	19,877,310	4,470,978
	TRx	2,816,959	990,533	6,141,767	1,154,323

packages multiplied by the size of the package in tablets, capsules, milliliters, etc. EUS is appropriate for use when the products being compared are similar in terms of dosage form. ‘Retail value of sample’ (RVS) represents the retail value of SAM and is calculated based on valuing the free samples left with physicians at their average retail price, not at the company’s marginal production costs. ‘Total prescription volume’ (TRx) represents the count of total prescriptions dispensed by pharmacists. During the time spanned by the data sets, none of the brands investigated here spent any expenditure in direct-to-consumer advertisements. Therefore, we exclude them from our analysis without any loss of substantial information.

2.2 Computational details

We used a neural network (NN) guided by a genetic-algorithm partial least squares (GAPLS) to establish the cause-and-effect relationship between promotional spending and variation in the number of prescriptions for each brand. Schematic of key steps for constructing a neural network model guided by genetic algorithm-partial least squares (GAPLS-NN) is summarized in Fig. 1. The appeal of neural networks is that they do not require any particular underlying model formulation or any particular data structure as do regression analysis, logit modeling or factor analysis, for instance. Empirical evidence extolling the value of neural networks versus standard statistical techniques in modeling marketing phenomena can be found elsewhere [18, 19]. The GAPLS approach is developed by combining the genetic algorithms (GAs) and the partial least squares (PLS) approaches. An introduction and overview of the applications of GAs are reported by Jones

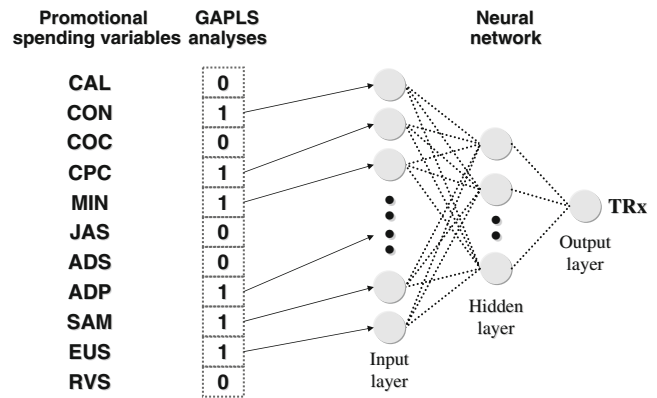
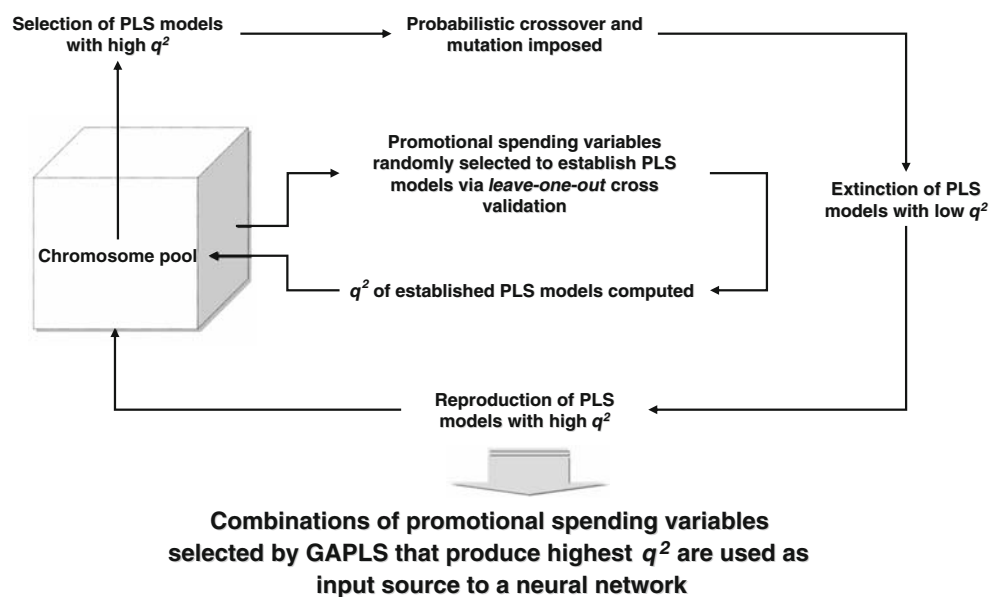


Fig. 2 Schematic illustrating how promotional spending variables selected by GAPLS are used for training a neural network. Promotional spending variables are coded for by binary information genes located on a chromosome in GAPLS. If a gene is active, the corresponding variable is considered important to characterize the variation in TRx and data from the variable will then be used as an input source to a neural network

[20] whereas detailed descriptions about PLS can be found in various literatures and textbooks [21–24]. At the beginning, GAPLS analyses were conducted to acquire the *best* subset of promotional spending variables that would serve as the initial inputs for neural networks (Fig. 2). Subsequently, a neural network is given a set of the selected variables by GAPLS and a set of known TRx. Then the algorithm is asked to discern the best relationship between the inputs (promotional spending variables) and the outputs (TRx).

In order to apply GAPLS approach to the variable selection prior to modeling with neural networks, we define each chromosome consisting of genes to represent subsets of promotional spending variables. Prior to the analysis,

Fig. 1 Schematic of key processes in constructing a GAPLS-NN model. Note that GAPLS searches for the best subset of promotional spending variables and passes them to a neural network



data were preprocessed by means of mean centering and scaling to unit variance in order to remove differences in units between variables. A population, which consists of 100 chromosomes, was initially created by randomly assigning ‘1’ or ‘0’ to all genes located on a chromosome. The value of ‘1’ indicates the presence and a ‘0’ the absence of a variable level. The best chromosomes have the highest probability to survive evaluated by a so-called fitness function. The correlation coefficient,  $r^2$  was used as the fitness function of each chromosome for the training data set. It is defined as follows:

$$r^2 = 1 - \frac{\sum_{t=1}^{71} (y_{t,actual} - y_{t,calculated})^2}{\sum_{t=1}^{71} (y_{t,actual} - \hat{y}_{actual})^2}$$

in which  $y_{t,actual}$  and  $y_{t,calculated}$  are the actual TRx and the calculated TRx in time period  $t$  respectively, and  $\hat{y}_{actual}$  is the average TRx of all the periods in the training set data. The next generation is reproduced by selecting the best chromosomes, mating the chromosomes to reproduce an offspring population, and by occasional crossover and mutation at predefined probability,  $p$  ( $p_{crossover}=0.7, p_{mutation}=0.1$ ). Only top 30% chromosomes with high  $q^2$  values were reproduced; i.e., survival rate equals 30%. The reproduction and evaluation steps were repeated until after confirming no further improvement in the best and average scores of the fitness function. In this study, we ran a series of GAPLS simulations from the very beginning via a *leave-one-out* cross validation procedure. Leave-one-out cross validation procedure systematically removes one case point at a time from the training set. A GAPLS model is then constructed on the basis of this reduced data set and is subsequently used to predict the removed case. This procedure is repeated for all cases so that a complete set of predicted values is obtained. In the leave-one-out cross validation, the cross-validated correlation coefficient,  $q^2$  became the fitness criteria to determine the final ranking of the GAPLS models.

$$q^2 = 1 - \frac{\sum_{t=1}^{71} (y_{t,actual} - y_{t-predicted})^2}{\sum_{t=1}^{71} (y_{t,actual} - \hat{y}_{t-predicted})^2}$$

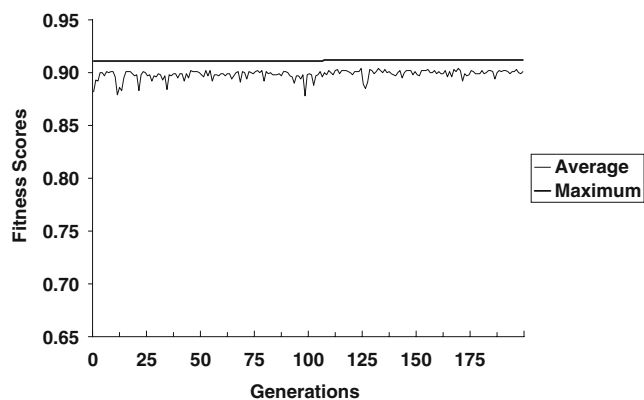
where  $y_{t,predicted}$  is the predicted TRx in time period  $t$ . Similar with  $r^2$ ,  $q^2$  takes a value of 1 for the maximum possible correlation of the data, where a  $q^2$  of 1 indicates perfect prediction. The best model from GAPLS at 200th generation was chosen as the initial input to neural networks of each brand as it is characterized by the highest score of the fitness function as well as by specific promotional spending variable selection that affords such model.

In this study, an error back-propagation algorithm with weight updates occurring after each epoch was used for neural network training. During the training, calibration samples with known TRx were passed through the network. The error between the predicted TRx and the actual TRx is then calculated and used to adjust the weights of the network in a back-propagation step to minimize the error. Before training was initiated, the input values were scaled to minimize the chance of saturation due to large input values. One of the primary goals in training neural networks is to ensure that the networks will perform well on data that they have not been trained on, called *generalization*. Generalization can be achieved by a so-called early stopping procedure and by a reduction of the network size [15]. Early stopping was implemented in this study by ceasing the training when the prediction error starts going up as the networks may start losing their generalization ability above this point. On the other hand, reduction of a network size that maximizes generalization is also an important topic. There are several theories for determining the optimal network size, such as the Network Information Criterion, which is a generalization of the Akaike Information Criterion [25] widely used in statistical inference, the generalized final prediction error [26] and the VC dimension [27], which is a measure of the expressive power of a network. Nonetheless, we experimented with several different numbers of hidden layer nodes and found that the results were not very sensitive to the number of hidden layer nodes following these theories. Alternatively we attempted to use part of the data to check the model in some way, such as cross-validation [28]. Cross-validation is often used to select an optimal architecture from amongst a set of available network configurations. In a recent study cross-validation was found to be suitable at choosing the optimal network architecture, at least on the data sets tested [29]. In a preliminary study we have calculated the mean absolute percentage error (MAPE) defined as follows for neural network models with a configuration of  $x-y-z$  ( $x=1, 2, \dots, 11; y=1, 2, \dots, 10; z=1$ ) in order to find the optimal one, with  $x$  being the number of variables (promotional variables selected by GAPLS) in the input layer,  $y$  being the number of nodes in the hidden layer and  $z$  being one (single response variable; TRx).

$$MAPE = \frac{\sum_{t=1}^{71} |\%e_t|}{71}$$

where  $|\%e_t|$  denotes the absolute value of the percentage error in time period  $t$ . A negative MAPE value, which indicates under-predictions relative to the actual TRx, is possible. MAPE is used because of its popularity in the forecasting literatures and because it is not prone to changes in the magnitude of the time series to be forecasted [30]. In





**Fig. 3** The best and the average fitness scores of GAPLS optimization as a function of generation for brand A

comparison to mean error, which is determined simply as the average error value and affected by outliers (large positive and negative errors can cancel each other out resulting in a zero error), or mean absolute error, which deemphasizes outliers by their average, the MAPE is a more meaningful measurement as it produces results calculated as the average absolute error in percentage terms, which are easily interpretable. Further, MAPE is a more useful result than a mean error particularly when forecasting TRx that fluctuates greatly from month to month. The evolution of prediction error was also monitored during training. For each brand the model with the highest  $q^2$  together with its MAPE decreased and converged to a minimum was adopted as the optimal network configuration.

The standalone neural networks that utilized all the 11 promotional spending variables for modeling were also trained in the same way described above.

All simulations were run on a standard laptop of Pentium III 650-MHz using the commercially available chemometrics software Chemish version 4.40.

### 3 Results

Figure 3 shows the graph of the best and the average fitness scores at different generation. Due to space constraints, we only gave brand A as an example in this section but the results of other brands are available on request. Overall, the

average value of the fitness score for the whole population converges to a high number in the course of calculation.

As GAPLS selects only a few relevant promotional spending variables to correlate with the variation in TRx, there is a possibility that not all brands may share the same combination of variables. Indeed, the GAPLS results in different subsets of promotional spending variables that characterize the change in TRx for each brand (Table 3). Interestingly, each brand shared in some way, on average, three common spending elements among one another; i.e., variables associated with visits by reps to physicians (CAL, CON, COC, CPC and MIN), advertising (JAS, ADS, ADP) and sampling (SAM, EUS and RVS).

Good statistical results were obtained for GAPLS–NN. This reveals the usefulness of our approach to determine the potential impacts of promotional spending on TRx. All brands had the  $r^2$  values ranging from 0.650 to 0.924 and  $q^2$  values ranging from 0.569 to 0.903 whereas the MAPE values were confined within 6% range on averaging all brands. It is worth noting that the  $r^2$ ,  $q^2$  and MAPE results obtained from GAPLS–NN closely resemble the results from the standalone NN modeling, indicating that a neural network architecture less complex (GAPLS–NN) than a standard design (standalone NN) can produce comparatively accurate characterization of the effects of promotion, reflected by the  $r^2$  value. Further, we also need to acknowledge that these simpler networks also outperform the standard architecture in terms of out-of-sample prediction for brand A and C, reflected by the  $q^2$  value.

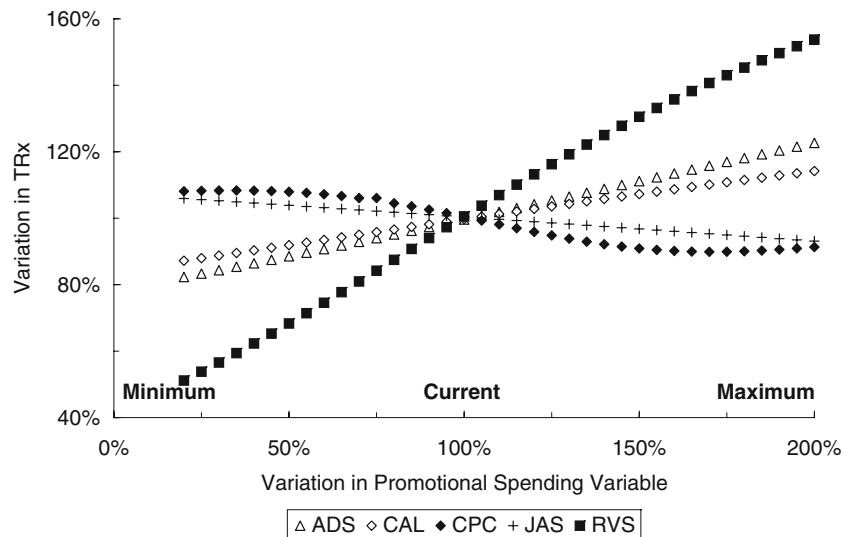
In order to understand the influence of each individual promotional spending variable on TRx, we performed a graphical sensitivity analysis for each brand. First, the optimal neural network model under investigation was trained in a normal way. After training the variation of TRx was monitored on changing the value of one promotional spending variable while holding other variables constant. This procedure was repeated for all other variables. Changes in the outcome of TRx gave an idea of the influence of individual variables on the probabilities of prescription creation, respectively. The exact optimal spending levels can then be read off the graphs. TRx as a function of individual promotional spending variables

**Table 3** Comparison of simulation results deriving from NN and GAPLS–NN

Brand	Variables Selected by GAPLS	$t$	NN			GAPLS–NN		
			$r^2$	$q^2$	MAPE <sub>calculated</sub>	$r^2$	$q^2$	MAPE <sub>calculated</sub>
A	CAL, CPC, JAS, ADS, RVS	71	0.931	0.900	6.5%	0.924	0.903	7.9%
B	CON, CPC, MIN, ADP, SAM, EUS	71	0.878	0.843	7.5%	0.880	0.842	6.9%
C	CPC, ADS, ADP, SAM, EUS	71	0.675	0.557	3.5%	0.650	0.569	3.9%

$t$  Number of time periods,  $r^2$  correlation coefficient,  $q^2$  cross-validated  $r^2$ , MAPE<sub>calculated</sub> mean absolute percentage error for TRx of the training data set

**Fig. 4** Estimated change in TRx following a variation in the individual promotional spending variable for brand A

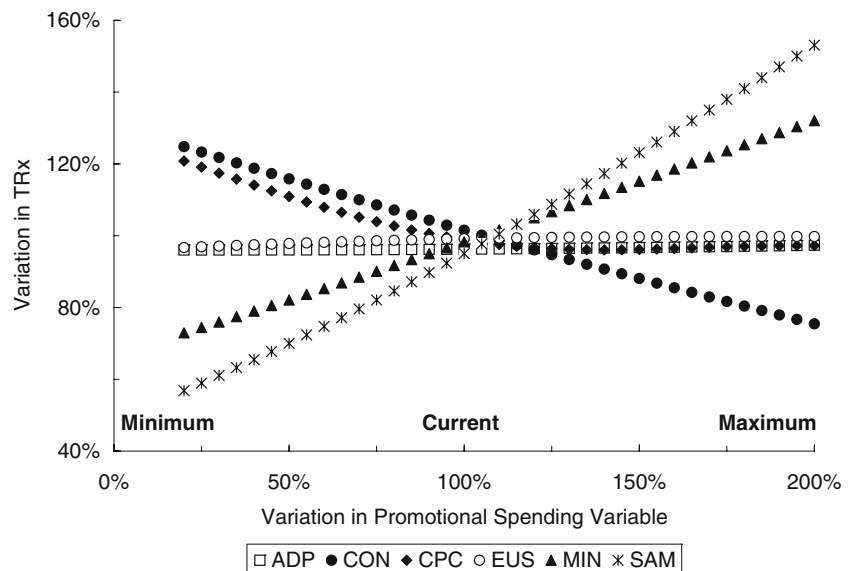


selected by GAPLS for each brand is plotted in Figs. 4, 5 and 6, respectively. These graphs are easy to interpret. For example for brand A to generate extra prescription, CAL, ADS and RVS are of credible impacts on physicians’ prescribing whereas for brand B, the importance of SAM and MIN could not be neglected. Further, though increasing CAL frequency is an effective way to generate more TRx for brand A, it is now interesting to see that modifying RVS seems more appropriate (Fig. 4). Clearly, activating SAM intensity in brand C causes the curve to trend upward resulting in an increase in TRx but not in an explosive manner as one might expect (Fig. 6). This suggests that there is a diminishing marginal return for SAM in this brand. On the other hand, the effect of ADP on TRx in brand B is so small to be negligible, indicating that ADP is not really of importance for brand B (Fig. 5). Overall, the influence of CPC, ADS, SAM and RVS on TRx is nonlinear but of a minimal magnitude.

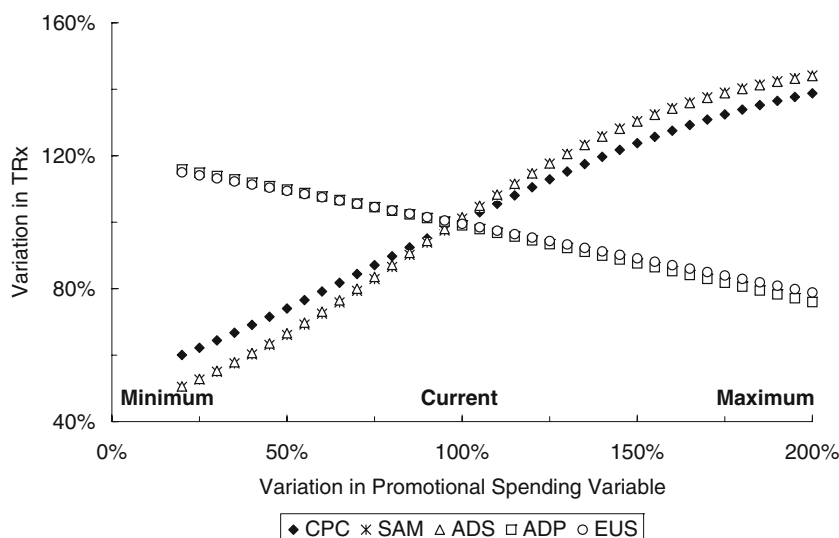
**4 Discussions**

Promotion budget allocation—one of the industry’s most important marketing tools is also one of its least understood. Today misallocation of promotional resources is endemic to many large pharmaceutical companies. Many managers still think that determining where and how promotion budgets should be allocated seemed virtually impossible. One of the primary reasons leading to this belief lies on the fact that marketing in the prescription drug market sharply contrasts with those typically adopted in other industries. Patient is not the ultimate consumer that pharmaceutical companies are marketing to per se. In addition, the main purpose of prescription drugs cannot be consumption for consumption’s sake. More (use and prescriptions) is not necessarily or always better unless better is defined as improved public health. Under such circumstances, promotion budget allocation indirectly

**Fig. 5** Estimated change in TRx following a variation in the individual promotional spending variable for brand B



**Fig. 6** Estimated change in TRx following a variation in the individual promotional spending variable for brand C



becomes part of a complex system of healthcare that must be ruled by science and careful human judgment, not merely the profit motive. Together, these added complexity to conceptually design an optimal promotional cocktail. However, optimizing a curious blend of a promotional cocktail requires more than assessing the effects of individual promotional spending but also counts on improving its efficiency through integration, because even if a spending element has a positive effect to augment prescription creation, adding another element may create a synergy on the overall performance in some cases. Therefore, a manager should have a very good understanding of the relevance and limitations of his/her promotional spending to fully leverage the marketing engine. Although doubling sampling frequency is an effective way to get physicians to write prescriptions, in some instances modifying other promotional spending may be more relevant.

Pharmaceutical companies in general and the prescription drug companies in particular employ a combination of marketing effort, namely, personal detailing, advertising and sampling for bringing product information to the attention of prescribing physicians. According to a pharmaceutical consulting firm, IMS Health Inc., promotional spending of pharmaceutical companies has been climbing at a 14% annual rate since 1999, and is expected to maintain momentum in coming years. In 2003 the industry spent nearly \$20 billion in promotional activities with an increase of nearly 21% [31]. Among all spending categories, detailing and sampling continue to dominate, accounting for close to 60% of all expenditures since 1999 [31]. Are these spending getting values in return, or are they merely wasteful? The aim of this study is to identify the relative influences of these spending on generating prescriptions and to help managers optimize their promotional cocktail to yield a healthier return on investment using a

neural network approach guided by genetic algorithm-partial least squares (GAPLS-NN).

#### 4.1 The effect of promotion

Each brand investigated here shared different combinations of predictor variables in describing the variation in TRx. In brand A, CAL, CPC, JAS, ADS and RVS appear to be important whereas the remaining two brands are characterized by other different sets of promotional spending variables, respectively (Table 3). This observed heterogeneity among brands leads us to infer that promotional spending of each brand can easily be optimized if the relevant spending variables selected by GAPLS are taken into consideration instead of looking into a wide array of variables.

Further, nonlinearity of promotional spending is clearly evident, suggesting a very complex relationship between promotional spending and prescription responsiveness (Figs. 4, 5, and 6). A common belief in the investment of promotional spending on physician-directed marketing is that doubling the magnitude of a spending would also double the probability of prescription creation. This might be true in the past when there were still fewer reps calling on the physicians. Today, we have nearly 90,000-plus sales force in the US prescription drug market because of blockbusters striving for reach and frequency [31]. With the increase in the number of salespeople, most physicians nowadays have decided to make less time for their reps. When there is already a good coverage, the physicians who are called on are less susceptible to the promotional efforts of reps. Under such circumstance there now appear to be good reasons for believing that efforts of finding out exactly where and how companies should spend their promotion fund can be connected with competitive advantage in years to come.



#### 4.1.1 Detailing

The results in Fig. 5 show that MIN has a positive impact on TRx for brand B. That is, we interpret that prescription creation will be enhanced if reps of brand B spend more time with their physicians than if they spend less. Füsün et al. find that physicians are expected to benefit from spending time with reps, because the information they receive ultimately leads to higher patient recovery rates that speak well of the physicians' competence and expertise [8]. This finding albeit fairly encouraging, nevertheless may not be viable in practice unless a close pharma-physician relationship is warranted. A recent survey from a consulting firm, Cap Gemini Ernst & Young brought to the fore a staggering 38% of the surveyed physicians have decided to make less time for their reps [32]. Although spending more time with reps may be useful for physicians, it inevitably takes away their valuable work time.

One could expect the direct effect on TRx induced by the increase in MIN corresponds with that induced by the intensity in CON. Interestingly, the MIN curve for Brand B is upward sloping while its CON curve is downward sloping (Fig. 5). One possible interpretation for this intriguing result is that the adverse effects of excessive CON can be attributed to frustration caused by waste of time, fatigue with the promotion, or perception that the company is too desperate or too aggressive from the physicians' view. Therefore, for both the MIN and CON results to hold, attempt to make a call as lengthy as possible, with a sales force highly trained to deliver fewer calls as efficient as possible is a prerequisite for brand B to generate additional TRx. In other words, the company would need to argue the *informative* view of detailing than with a *persuasive* view. At the very least, the primary purpose for a rep of brand B visit to his/her physician is to bring value added information or service rather than just to *signal* his/her presence with a charming greeting. The majority of physicians do not view the health industry as a business—they are *scientists*—and would prefer to have intelligent and well-balanced conversations with the reps that come knocking at their doors. In other words, a rep's visit to his/her physician should be based on a clear exchange of objective and neutral scientific information and finally, unbiased by commercial arguments. When looking at how to make a rep-physician interaction more valuable, it is necessary for companies to take a more tailored and targeted view to physicians and their individual needs and wants, adopting a differentiated detailed strategy. There is some evidence from companies innovating in this area that there are three aspects to doing this successfully. They are attitudinal segmentation, customer relationship management (CRM) and a trained sales force [32].

In other instances, activating CPC intensity does not seem to generate more TRx for brand A and B except in the

case of brand C for which the reverse holds true (Figs. 4, 5 and 6). In a broad sense we interpret CPC as the *quality* of CON. This is a rough approximation that accounts for the difficulty and complexity of assessing the physician's overall impression of the rep's visits. If we were to expound on the reasons TRx of brand A and B respond negatively with CPC, an intuitive explanation would be a higher quality of call can also be perceived by the physicians as an indication of higher drug cost for the patients because of the detailing costs and efforts associated with it. Therefore, we expect that physicians trying to accommodate their patients' price sensitivity will act in a price-sensitivity way to forgo the prescriptions of brand A and B when the CPC is elevated. Physicians nowadays are increasingly competing for patients and therefore, prices may be expected to influence the choice of drugs prescribed by the physicians [8]. However, this is just a speculation as we lack relevant information.

#### 4.1.2 Journal advertising

A common belief in the marketing literature of experience and credence goods is that advertising can be perceived as a credible signal of high quality [33]. Nevertheless, TRx of brand A responded negatively to the intensity of JAS (Fig. 4). These results suggest that JAS does not accomplish the effective role of creating product awareness and brand recognition, a context for the use and to boost TRx of brand A. Given the broad substitutability among many brands in the US antibiotic universe and the similar claims competitive companies make, the prescription choice decision, oftentimes critical, is increasingly harder to make. Therefore, in these situations the impacts of JAS as a signal of quality would become less of a concern. Or, since the primary aims of JAS are to create product awareness and brand recognition by focusing on the differentiating characteristics of the product, this may involve provide information about the existence and availability of competitors that broadens the consideration set on the competitive brands and thus decreases TRx sensitivity. There is a host of diverging arguments that lead to various implications about the role played by advertising of pharmaceuticals. Instead of strongly arguing one way or another about the impact of this spending at this point, we believe that it is best to leave this for future research when more data are available.

As with all advertising JAS is likely to be influenced by effects such as memory decay and fading impact of past advertising with time. In other words, not all JAS results in TRx generation. In order to alter prescribing paradigm the physician must be appealed to several times before he/she will notice and remember the message. The human mind tends to forget most of what it is exposed to. Research in the B2B market has shown that when a message is

introduced less than half of it is remembered after the first day [34]! However, that is part of the nature of investing in JAS. It would not make sense to count only the dollars that resulted in exposures because the money spent on JAS that did not result in exposure is still part of the investment.

To the best of our knowledge, this analysis is the first attempt at an exploratory study on the effects of ADS and ADP on prescriptions' choice behavior. To date, little is known about ADS and ADP. Most of the previous research on medical journal advertising has focused on the quality and accuracy of pharmaceutical advertisements, gender and racial content in advertisements, and ethical issues revolving around editorial responsibility for advertisement placement [35]. For the brands investigated here, the analysis found that TRx of brand A and C maintained a consistently high yield with increasing ADS, although somewhat faster in brand C than in brand A (Figs. 4 and 6). With regard to changes in ADP, TRx responds only weakly for brand B but reveals a precipitous decline for brand C (Figs. 5 and 6). Taken together ADS and ADP, the results suggest that ADS was an important driver of TRx creation for brand C, but that its effect waned soon when ADP is taken into consideration. For brand C to increase its prescriptions, we therefore recommend the company to strike a good balance between ADS and ADP rather than to focus on either one of them as both are of the same nature and coexist.

#### 4.1.3 Sampling

We find that there is a distinct positive correlation between SAM and TRx for brand B and C (Figs. 5 and 6). The same kind of positive correlation is also found between RVS and TRx for brand A indicating that sampling has a substantial direct impact on the prescription probability of these brands (Fig. 4). Within the pharmaceutical industry, sampling is a critical driver in the promotion and adoption of new accounts (i.e., inclusion of the drug in the physician's armamentarium or evoked set) for reps. However, there are data and compelling arguments that hint at the negative impact of sampling in another way [9]. Similar with advertising, criticism continues to be leveled at the industry's aggressive sampling to physicians. A full discussion of the pros and cons of sampling is beyond the scope of this article. Setting aside this issue, the results suggest that brand B and C are operating on the increasing part of the curve if sampling is intensified above 100% (Figs. 5 and 6). Particularly for brand C, an increase in TRx may be forthcoming but it is not going to be economically viable to exceed 150% as sampling above this level is expected to trigger cannibalization and therefore overrides the TRx pitch persuasiveness. In contrast, elevating sampling to 150% level is still considered acceptable for brand B (Fig. 5). Furthermore, we find that there is a

significant, negative relationship between EUS and TRx for brand C, indicating that intensifying EUS is counterproductive. Bearing in mind that SAM and EUS are of the same nature, we find this result surprising given that SAM is explained to have a positive effect on TRx in our previous argument. Unfortunately, we cannot provide a logical explanation for this finding because our data do not contain the necessary information. However, this issue warrants further examination with the right kind of data, of which we hope to investigate in the future.

#### 4.2 Assessment of model validity

On an absolute scale, the  $q^2$  and  $r^2$  values obtained with brand C were less promising when compared to that of other brands (Table 3). We speculate that prescription patterns of brand C might be strongly influenced by factors other than the predictor variables included in this study. Several other predictor variables that may be combined include physicians' psychographics (e.g., inertia, loyalty to brand C), patients' demographics (e.g., the severity of disease states, concomitant medication, constraints by managed care organizations formularies, reimbursement status), or even behavioral specifics unique to the interaction between the physician and the patient (e.g., some patients may be more health conscious and like to get more involved in his/her drug selection by the physician whereas others may want to leave the treatment decision solely to the physician).

In any case during the neural network training phase, the appropriateness and the generalization ability of the model were justified by partitioning the available data into two subsets: a training set (used to estimate model parameters) and a validation set (used to check the generalization ability of the model on holdout samples). The validation set is meant to stop the training before the neural network learns idiosyncrasies present in the training set. The same data were used for developing the model and validating it, but in such a way that external validation is simulated. Because established models have a predictive purpose in that they are used in understanding the effects of common promotion modes, preference is thus given to models that exhibit robust performance across the training as well as validation data. Generalization ability of the established models could be further appreciated by the small difference between  $r^2$  and  $q^2$  values suggesting that the significance of  $q^2$  values obtained is unlikely to be a chance correlation.

## 5 Conclusions

In this paper, we presented a framework for understanding the effects of pharmaceutical promotion using a hybrid

neural network model guided by genetic algorithm-partial least squares (GAPLS-NN). We used GAPLS to evaluate many possible combinations of promotional spending variables and finally to select the best subset from the evaluated combinations. A neural network was employed to establish the cause-and-effect relationship between promotional spending and variation in the volume of prescriptions using the best subset of variables. Our results support the idea that the GAPLS-NN approach can provide managers with better understanding of physicians' prescribing activities without an appreciably smaller  $q^2$  value when compared to that obtained by a standalone neural network modeling. In fact, a reliable prediction of the effects of promotion would allow managers to efficiently allocate promotion resources. Our work also provides additional evidence that there exist strong nonlinear dependencies between promotional spending and prescription responsiveness, of which linear models often fail to cope with. Because not all promotional spending has the same potential for managers, this approach provides a new tool in which tradeoffs can be better understood in the context of designing a promotional cocktail. Lastly, policymakers and consumer advocates can apply this approach to assess the relevance of various promotional spending of pharmaceutical companies.

## 6 Practical challenges

We have shown that our GAPLS-NN model is a promising approach in helping managers to understand the possibility of his/her promotional cocktail. In this section, we address a few issues that should be considered before implementing this approach.

The major drawback with this approach is the difficulty to understand and interpret why certain variables are preferred but some are not during the data dimensionality reduction by GAPLS. Because GAPLS selects only the model that is characterized by the highest score of the fitness function as well as by specific predictor variables that afford such model, there is a possibility that not all brands may share the same combination of variables. Nevertheless, we do not see this as a major shortcoming from the practical point of view, and in fact there are probably more factors that would lead us to compromise than there are to combat.

Firstly, each brand is assumed to have its own *trend*; the best choice of predictor variables for one brand is sub optimal for the other. This means different brands may or may not respond in the same manner as the others given exactly the same level of promotional endeavor, and the same theory holds for early adopters as well as laggards in the lifecycle of a brand likewise. Instead, one should

continually morph and tweak his/her promotional mix to be most relevant to a particular brand at all times. Therefore, the fact that the subset of the selected predictor variables is distinct for the three brands has not been viewed as surprising in the first place. Putting it another way, this finding is indeed encouraging because it is this very substantial heterogeneity observed in the selected predictor variables that helps bring back the argument on whether pharmaceutical promotion across brands depends upon the level of evidence and consensus on drug use. For instance, results in Table 3 show that CAL in brand A was perceived as much more credible than those in brand B and C. By no means is the implication of the simulation outcome that CAL expenditure should be toned down for brand B and C. What the results suggest is that, CAL may not serve as an attractive investment in prescription creation, and generating incremental prescription from CAL for brand B and C is not as simple as just increasing the intensity of this element. The basic recommendation, therefore, boiled down to the following: Yes, companies of brand B and C should strongly consider this point before choosing CAL for the field test. Another good way to appreciate the power of this heterogeneity is through addressing the following insights that are likely to be of interest to managers: (1) What is the promotion tactics of my competitive product? (2) How well balanced are the various promotion modes across brands in the competitive class? (3) To what extent did past promotional campaigns of my competitor succeed in creating instability in new prescriptions and market share? Within companies operating in the same class (here, antibiotic), several key facts emerged from the simulation provided by this framework may suggest that the current COC was grossly underfunded and considerably *out of balance* for competitive brand X, that SAM could stabilize the uptake of market share for brand Y, that the manager was spending too much on some modalities and not enough on others for house brand, and so forth. One popular way of budgeting in pharmaceutical industry nowadays is to seek *competitive parity*. Under that method, if the competitor spends \$20 million in SAM, a company reasons that it must also match the expenditure of its opponent. Once guesswork could be removed from the process of determining the probable outcome of expenditure for a competitor, the whole notion of promotion is elevated beyond the realm of an expense to that of an investment. When that happens, no amount is too much to spend if it is assured to deliver the quantifiable return.

Secondly, it is particularly noteworthy that all the established models could indeed be split into two hierarchies where on the lower level, they were characterized by the highest score of the predictive ability as well as by *different* predictor variables that afford such models whereas on the upper level, each of them shared in some

way, on average, three *common* elements with the others; i.e., variables associated with visits by representatives to physicians (CAL, CON, COC, CPC and MIN), advertising (JAS, ADS, ADP) and sampling (SAM, EUS and RVS). In a broad sense, the upper hierarchy does provide a rough approximation that accounts for the consistency in the choice of predictor variables across brands. This also partly explains the reason why we did not see the difference in the combination of variables for different brands as a limitation of this methodological approach.

In discussing model interpretability, it is useful to bear in mind a key tradeoff in developing the model. From the viewpoint of understanding the relevance and limitations of each promotional spending, managers should always use the model with the highest predictive accuracy, even if it is based upon this framework. The reduction of the variable aids managers by focusing attention on a smaller number of key drivers of prescription responsiveness, and aids the marketing researchers by allowing a relatively simple post hoc analysis. Even a complicated model such as neural networks can be more easily understood if constructed from only a few variables. On the other hand, in testifying the true effect of promotion from the policymakers' and consumer advocates' viewpoints, it may be necessary to undertake additional work (say, using regression or decision trees) to facilitate understanding.

Another issue of concern is whether or not the GAPLS–NN model on the same data sets of other time periods results in the same promotional spending variable subsets. In PLS, the principal components are determined by the maximum variance of the predictor variables (11 promotional spending variables) and by a maximum correlation with the response variable(s) (TRx). There are as many principal components as variables to predict, but for the best model only the primary, most important principal components are used. Therefore, it is likely that we may observe different variable subsets if data sets of different time periods are substituted for modeling. This is due to the fact that strong correlations typically exist among the predictor variables that are available to the researcher. For example, the variables CON, CAL and COC are perfectly cross-correlated (e.g., correlation coefficient  $r^2$  between CON and COC for brand A is 0.982, etc.); indicating that one of these variables could easily substitute for the other in a given model. However, even if different variable subsets were selected by GAPLS, we would expect that performance in terms of  $q^2$  value would be stable, provided the crucial information on representatives' visits, advertising and sampling is adequately encapsulated. This claim is further supported by Lim and Kirikoshi who successfully formulated a good predictive model for characterizing the variation in prescription yield of an antibiotic drug [12].

Since the study was examined in a very homogeneous context, the wider applicability of the results could probably be questioned. In particular, the modeling frame is comprised of only major brands within the antibiotic class. They may produce spuriously optimistic outcomes when tested but fail in practice if products other than this therapeutic class are substituted for testing. Simply the brands were selected for this study, in part, because of their familiarity and availability of data to conduct the analyses. Therefore, it would be particularly relevant for brand-specific analyses to considerably strengthen the wider applicability of this approach. Such a set-up would help explain the underlying phenomenon more effectively. This is a challenging subject for future research given data availability. Although it is not believed that current framework would apply directly to the universe of products, two reasons suggest why this approach is valuable as a useful tool for predicting the effects of promotion on prescription yield. Firstly, with spending on promotion growing substantially over the past few years, it is obvious that no effective strategy is being adopted, because measuring the impact of promotion in advance and with a specific level of certainty seemed virtually impossible—let alone making the necessary changes. Secondly, given the easy access to a wide variety of data afforded by information technology nowadays, a systematic way of selecting promotional modalities that are responsible for the variation in prescription responsiveness is of paramount importance in modeling such data sets. Considering that the framework will operate without any knowledge about the nature of the relationship between the outcome and the predictor variables due to its reasonable simplicity and a high degree of automation, prospective examination to adapt to changing circumstances by most managers appears to be warranted.

Our particular focus in this study is directed toward establishing the cause-and-effect relationship between common promotional modalities and variation in the volume of prescription yield, of which could eventually be used to develop a methodology through which the effects of promotion on prescribing activities of physicians can be evaluated and optimized based on selected spending elements. The underlying approach is to combine a GAPLS with neural networks to select the optimal subset of promotional spending variables that are responsible for the variation in prescription responsiveness. One should keep in mind that the results of this study are not meant to supplant managers' decision-making for specific product circumstances. Individual managers know better about their products, their physicians and the particular context they face, so that information should greatly influence the final budget allocations. What this study does is to provide general guidance of what to do incrementally. Most



companies would readily allocate whatever their managers requested if they were assured of a worthwhile return. By conducting the framework proposed here as part of their promotional planning, they can uncover all the possibilities open to them and know which one works best before the field test. It is a matter of selecting the best option, because theoretically, all forms of promotional spending can work if they are managed correctly, under the proper circumstances, and budgeted properly. In aggregate maybe that incremental dollar should go toward CON. But it is not as literal as saying, “GAPLS–NN is a magic wand”. It does not replace veteran managers, but rather provides them with a more disciplined way for allocating a given budget across promotional modalities. The real challenge is determining how to apply the knowledge extracted through this framework to business advantage.

### 7 Managerial relevance of research for business market managers and policymakers

Our analysis provides managers valuable insight into where and how they should and should not spend on promotion. For instance intelligence like this helps reduce cannibalized prescriptions from over-sampling and fine-tune sampling in ways that result in additional prescriptions for the same level of sampling. Appropriate balance is everything as physicians are expected to respond more favorably when they are presented with the exact amount of sampling that they feel are catered to them. Rather than giving physicians more than they want, this approach helps give physicians what they exactly want. Providing it too much will not necessarily enhance more prescription creation, but giving out too less might lead to fewer prescriptions. The irony is that promotion is a necessary preemptive strategy as under-spending one’s brands may indirectly lead to the physician’s prescribing of the competitor’s brands.

Managers absolutely have tremendous intuition about their budget allocation. They know it better than anyone in the organization, but it is still too hard for a manager to tell if the prescriptions generated is necessarily aligned with the levels of spending or to tease out the individual impact of one spending element versus the other. For example there is something called the *momentum effect* in certain market, which means that if a rep leaves a sample with his/her physician today, the physician will be thinking about prescribing that rep’s drug next week or the week after and so forth based on what was delivered to him/her today [36]. Our approach is designed to help managers understand the impact of individual promotional spending relative to the others. Through the analysis, managers are able to answer question like “What is the optimal way to allocate the calls associated with a fixed budget?”

Concern about physician-directed promotion relates to its use in the absence of society’s consensus or strong evidence for proper use. However, solid evidence to justify the appropriateness of promotional spending is not easy to obtain. Nevertheless, we believe our analysis sheds light on issues of interest to policymakers and consumer advocates. It helps to disperse concerns related to potential waste of resources in pharmaceutical marketing by showing the optimal level of promotional expenditures necessary to generate maximum return on investment. If an optimal level of spending ruled by marketing science could be established, promotional activities should be regarded as useful because they primarily provide beneficial information to physicians. Therefore, the criticism that these activities may unethically influence physicians’ prescriptions can be overruled. If, however, an inordinate level of spending is thrown in just to influence the physicians’ prescribing paradigm, then the role of promotional spending should be reviewed as exceeding optimal level of spending has dissipative economic impact on the company and potentially on society. The framework outlined here is hoped to help enlighten further dialogues to know whether—on balance—promotional spending of pharmaceutical companies is reasonable or not.

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