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Original article

# Modeling analgesic drug interactions using support vector regression: A new approach to isobolographic analysis

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ABSTRACT

**Background:** Modeling drug interactions is important for illustrating combined drug actions and for predicting the pharmacological and/or toxicological effects that can be obtained using combined drug therapy. **Aim:** In this study, we propose a new and universal support vector regression (SVR)-based method for the analysis of drug interactions that significantly accelerates the isobolographic analysis. **Methods:** Using SVR, a theoretical model of the dose–effect relationship was built to simulate various dose ratios of two drugs. Using the model could then rapidly determine the combinations of doses that elicited equivalent effects compared with each drug used alone. **Results:** The model that was built can be used for any level of drug effect and can generate classical isobolograms to determine the nature of drug interactions (additivity, subadditivity or synergy), which is of particular importance in the case of novel compounds endowed with a high biological activity for which the mechanism of action is unknown. In addition, this method is an interesting alternative allowing for a meaningful reduction in the number of animals used for in vivo studies. **Conclusions:** In a mouse model of toxic peripheral neuropathy induced by a single intraperitoneal dose of oxaliplatin, the usefulness of this SVR method for modeling dose–effect relationships was confirmed. This method may also be applicable during preliminary investigations regarding the mechanism of action of novel compounds.



## 1. Introduction

Drug combinations are often used for therapeutic purposes to achieve an enhanced effect without the need to use an excess amount of either agent. The use of low-dose drug combinations, i.e., combined drug therapy (CDT), instead of high doses of single drugs is one method that successfully improves the efficacy of pharmacotherapy for numerous diseases (Gunduz, Karadag, & Ulugol, 2011). This approach, compared to monotherapy, not only achieves a more enhanced therapeutic effect due to a beneficial pharmacological interaction but also provides the opportunity for safer treatment (Gilron et al., 2005; Gunduz et al., 2011). In experimental pharmacology, to illustrate the mode of action of drug combinations, graphs known as isobolograms are often used. These graphs are plotted in Cartesian coordinates and illustrate the dose combinations that produce the same effect level, which is often taken to be half of the maximum effect. In its standard form, the plot is constructed as a straight line of additivity, connecting intercepts that represent the individually effective doses, e.g., $ED_{50}$ or $D_{50}$ for binary effects or continuous effects, respectively (Tallarida, 2000; Tallarida, 2001). This line serves to distinguish additive from non-additive interactions, as the tested combination may be situated at or beyond this line. If the drugs work via a similar mechanism of action, the effect of their combination is additive, although agonists sometimes display either super-additive (synergistic) or sub-additive interactions. The situation becomes more complex when considering that different proportions of the same drug combination can induce synergy, addition or subadditivity (Grabovsky & Tallarida, 2004).

The characterization and the description of the interaction give not only quantitative information that is of particular therapeutic importance, but they may also explain the mechanism of action, thus facilitating a better understanding of a compound's pharmacological properties. Based on the literature, one drawback of studies carried out using isobolographic analyses is that the majority of studies describe the nature of the interaction between two drugs by only testing one or two dose ratios (Tallarida, 2000). This is due to complex computations necessary for the analysis and the need to conduct a large number of in vivo experiments, which is not only time-consuming but also significantly increases the number of experimental animals used in these studies. Importantly, based on such results, it is not possible to describe a generalized interaction between two co-administered drugs. Interactions can only be described for the particular ratios tested (usually 1:1 and 1:3), and therefore, this method does not describe the nature of

*Abbreviations:* CDT, combined drug therapy; OXPT, oxaliplatin.

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the interaction between the two drugs in a generalized manner (Miranda & Pinardi, 2004). Furthermore, the same drug combination used in the same proportion and dose rate but administered by a different route may alter the nature of the interaction.

We therefore propose a new approach to the analysis of drug interactions based on support vector regression (SVR). To the best of our knowledge, SVR has never been used in the context of isobolographic analyses.

Using SVR, a theoretical model of the dose–effect relationship can be built to simulate various dose ratios for two concomitantly used drugs. SVR is advantageous in that rapid determinations of drug dose combinations that have an equivalent effect as the dose of each drug used alone can be made. This method significantly accelerates isobolographic analyses and effectively reduces the number of animals used in experiments. Notably, the method is universal and can be used for any level of drug effects. Moreover, a properly built SVR model can be used to determine the nature of drug interactions (additivity, subadditivity or synergy). This method may also be applicable during preliminary investigations regarding the mechanism of action of novel compounds.

The validity of the SVR model constructed in this study was then used to determine the interaction between 3-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-dihydrofuran-2-one (LPP1; drug A) and pregabalin (drug B) in the oxaliplatin (OXPT) model of painful peripheral neuropathy in mice. Both LPP1 and pregabalin have shown statistically significant antinociceptive and antiallodynic activity in numerous mouse models of acute and neuropathic pain (Christoph, De Vry, Schiene, Tallarida, & Tzschentke, 2011; Peng et al., 2012; Sałat, Filipek, Wieckowski, & Malawska, 2009; Sałat & Sałat, 2013; Salat et al., 2012; Sałat et al., 2013; Sałat et al., 2014).

### 1.1. Support vector machines in regression mode

Support vector machines (SVMs) (Drucker, Burges, Kaufman, Smola, & Vapnik, 1997) are classification (Suykens & Vandewalle, 1999) and regression (Smola & Scholkopf, 1998) methods that are based upon the methods derived by Vapnik and Chervonenkis (1974). SVMs that address modeling and prediction are referred to as SVRs. Because the formulation of SVR is based on structural risk minimization, the SVR typically shows better performance than the conventional algorithms based on empirical risk minimization such as artificial neural network. SVR has been successfully used to solve problems in many fields, including biomedicine (Salat & Salat, 2012), electrical circuits (Salat & Osowski, 2011), power systems (Salat & Osowski, 2004), and system identification (Chevalier, Hoogenboom, McClendon, & Paz, 2011).

Let us assume that we have a data set of $p$ training samples, $\{(x_1, d_1), (x_2, d_2), \ldots, (x_p, d_p)\}$, where $\mathbf{x_i} \in R^n$, $d_i \in R$. We can introduce a nonlinear mapping $\varphi(\cdot) : R^n \rightarrow H$, where $H$ is a hypothetical feature space and define $\varepsilon$ – insensitive loss function – as follows:

$$L_\varepsilon = |d - y(\mathbf{x})|_\varepsilon = max\{0, |d - y(\mathbf{x})| - \varepsilon\} \tag{1}$$

where $y(\mathbf{x})$ is the estimation of the function. The SVR formula can be expressed as follows:

$$y(\mathbf{x}) = \mathbf{w}^T \varphi(\mathbf{x}) + b \quad \mathbf{w}, \mathbf{x} \in R^n, \quad b \in R \tag{2}$$

where $\mathbf{w}$ is the weight vector, and $b$ is the offset.

Then, $y(\mathbf{x})$ can be determined from the minimization problem as follows:

$$min\, L_\varepsilon = min\ \frac{1}{p} \sum_{i=1}^{p} (|d_i - \mathbf{w} \cdot \varphi(\mathbf{x}_i) - b| - \varepsilon) \tag{3}$$

By introducing slack variables $\xi_i$, $\xi_i^*$ into formula (3), an optimization problem can be formulated as follows:

$$min_{w,b,\xi,\xi_i^*} \ \frac{1}{2}\|\mathbf{w}\|^T + C\sum_{i=1}^{p} \xi_i + C\sum_{i=1}^{p} \xi_i^* \tag{4}$$

which is subject to:

$$\begin{array}{l} d_i - \mathbf{w}^T \varphi(\mathbf{x}_i) - b \le \varepsilon + \xi_i \\ \mathbf{w}^T \varphi(\mathbf{x}_i) + b - d_i \le \varepsilon + \xi_i^* \\ \xi_i,\ \xi_i^* \ge 0 \end{array} \tag{5}$$

The constant $C > 0$ determines the tradeoff between the model flatness and the training error. The flatness in Eq. (2) indicates a small $\mathbf{w}$ value.

The solution to the optimization problem in Eq. (4) is given by the saddle point of the Lagrangian, as follows:

$$\begin{array}{l} J(w, \xi, \xi^*, \alpha, \alpha^*, \gamma, \gamma^*) = \frac{1}{2}\|\mathbf{w}\|^2 + C\sum_{i=1}^{p} \xi_i + C\sum_{i=1}^{p} \xi_i^* - \\ -\sum_{i=1}^{p} \alpha_i^* \left(d_i - \mathbf{w}^T \varphi(\mathbf{x}_i) - b + \varepsilon + \xi_i^*\right) + \\ -\sum_{i=1}^{p} \alpha_i \left(\mathbf{w}^T \varphi(\mathbf{x}_i) + b - d_i + \varepsilon + \xi_i\right) - \sum_{i=1}^{p} (\gamma_i \xi_i + \gamma_i^* \xi_i^*) \end{array} \tag{6}$$

It follows from the saddle point condition that the partial derivatives of $J$ with respect to the primal variables ($\mathbf{w}$, $\xi_i$, $\xi_i^*$) must be excluded for optimality. The variables $\alpha_i$, $\alpha_i^*$, $\gamma_i$, and $\gamma_i^*$ must satisfy the positivity constraints. The formulation of the dual problem involving the Lagrange multiplier $\alpha$ is equivalent to finding an expression, as follows:

$$min_{\alpha,\alpha^*} \ \frac{1}{2}(\alpha - \alpha^*)^T Q(\alpha - \alpha^*) + \varepsilon \sum_{i=1}^{p} (\alpha_i + \alpha_i^*) + \sum_{i=1}^{p} d_i(\alpha_i - \alpha_i^*) \tag{7}$$

which is subject to:

$$\begin{array}{l} \sum_{i=1}^{p} (\alpha_i - \alpha_i^*) = 0 \\ 0 \le \alpha_i, \alpha_i^* \le C \end{array} \tag{8}$$

where $Q_{ij} = k(\mathbf{x_i}, \mathbf{x_j}) = \varphi^T(\mathbf{x_i})\varphi(\mathbf{x_j})$ is the kernel function in accordance with Mercer's condition (Vapnik, 1998). The kernel function has been defined as a linear dot product of the nonlinear mapping.

After solving the problem in Eq. (4), the regression function can be written as follows:

$$y(\mathbf{x}) = \sum_{j=1}^{K} (\alpha_i^* - \alpha_i)\, k(\mathbf{x}, \mathbf{x_i}) + b \tag{9}$$

where $K$ is the number of so-called support vectors (SV). The vector $\mathbf{x_i}$, associated with the coefficient $\alpha_i$, is called a support vector, and only those vectors have an effect on $y(\mathbf{x})$.

The selection of the coefficients $\varepsilon$ and $C$ is of utmost importance. The constant $\varepsilon$ determines the margin within which the error is neglected. The smaller its value, the more support vectors will be determined by the algorithm. The constant $C$ is the weight, which determines the tradeoff between the complexity of the network and the error of approximation and is measured by the slack variables ($i = 1, 2 \ldots, p$).

## 2. Materials and methods

### 2.1. Study design

The experimental study consisted of the following steps:

1. The induction of peripheral neuropathy using OXPT and the selection of neuropathic animals for further pain tests.
2. In vivo testing of various doses of LPP1 and pregabalin administered alone or in combination, and data collection for SVR.
3. The construction of a dose–effect model using SVR.