OPTIMIZATION TASKS FOR BINARY MIXTURES

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Abstract. *An important characteristic of two-component drugs is that the effect is not an arithmetic sum of the effects of the individual ingredients. When the action of the generic component increases, and with smaller doses, the desired drug effect is achieved, the phenomenon is called "synergism". When the effect decreases, that is a case of antagonism. Scientific interest for investigation is the synergism. With appropriate choice of the ratio of the two components, a number of beneficial results can be achieved, such as cost and toxicity reduction in parallel with an increase in the drug effect. These conditions are inconsistent, and the optimization task is nonlinear. In the present work, some optimization tasks are formulated for binary mixtures and solutions are offered with the unidentified Lagrange multipliers.*

Keywords: *optimization, Lagrange multipliers, synergism, modelling, binary mixtures.*

1. INTRODUCTION

An important problem in pharmacology and toxicology is the determination of the dose of a drug to treat the patient. For this purpose, the term "Effective dose ED_a " is used. This is the amount of the agent that for a certain time T_a affects the population with probability $p=a$. The determination of ED_a is done by constructing the distribution function $p(d)$ depending on the progressive increasing dose d . The inflection point of $p(d)$ is used in practice - it corresponds to a 50% effect on the sample ($p(d)=0.5$) and is labeled with ED_{50} . This is a parameter that is referred as a characteristic of each drug. A model for dose-response curve identification with modified logistic function is proposed in [8]. The task of determining an effective dose is complicated when a mixture of two active ingredients is present. The effective dose ED_a^{AB} of a two-component mixture of two agents A and B at doses d^A and d^B is a spatial surface $S_{DR}=[d^A \times d^B \times a]$ and its production is associated with a large volume of experimental work [9]. When selecting a specific value of a , a plane curve is obtained, which is called an isobologram (Figure 1). It makes the analysis of the quantitative interaction between the two substances lighter. On the axes are placed the doses of the two drugs and the isobologram shows the quantity of each of them, which gives an equivalent therapeutic effect. The construction of this curve is necessary because the combination of two preparations often results in an effect that is different from their application on their own. The following three cases are possible [5].

1. The two agents are interchangeable and the superposition principle applies to them. The effect is additive, and the isobologram is straight I_{SA} .
2. The equivalent effect of both drugs is reduced at the same time. Such agents are known as antagonists.
3. The efficacy of the mixture is increased, i.e. with smaller doses of both drugs, the desired therapeutic effect is achieved. Such interaction is called synergism. This means that a properly selected dose of both agents will produce a drug with the required therapeutic effect, but in smaller quantities, with lower toxicity and, of course, with a lower cost.

In the latter two cases, the isobologram can be modeled with various functions, and the most appropriate one can be selected by additional criteria [10]. Analytical determination of the isobologram allows the use of modern mathematical and computational methods for the modeling and testing of binary mixtures [4]. The fact that the synergism curve is non-linear determines the possibility of formulating optimization tasks on binary mixtures.

The present work aims to identify and solve two optimization tasks concerning binary mixtures using the Lagrange multipliers.

Figure 1. Isobolog curves for two-component mixture

2. PRINCIPLE OF LAGRANGE MULTIPLIER

A subset X of the Euclidean space R^n is given, and a function f defined in X . A point x^* in X is searched, such for each $x \in X$, $f(x^*) \leq f(x)$ is fulfilled. In this case, the set X is given by a system of inequalities and equalities:

$$X = \{ x \in R^n : g_i(x) \leq 0, i = \overline{1, m}, h_j(x) = 0, j = \overline{1, s} \} \quad (1)$$

where: $g_i(x)$, $h_j(x)$ - continuous and differentiable in R^n .

Lagrange Theorem. Let x^* is a local minimum of a function f with constraints "equality" $h_j(x)$. Suppose, that f is differentiable in x^* and $h_j(x)$ have continuous private derivatives in the vicinity of x^* . Then there exist numbers $\lambda_0, \lambda_1, \dots, \lambda_s$, not all equal to zero, such that:

$$L(x, \lambda) = \lambda_0 f'(x^*) + \sum_{j=1}^s \lambda_j h'_j(x^*) = 0 \quad (2)$$

$L(x, \lambda)$ is named Lagrange function, and λ_j are called Lagrange multipliers [1,6]. Lagrange's multipliers allow the extreme condition to be combined with an additional requirement that it meet certain constraints.

3. PARAMETERS OF BINARY MIXTURES.

There are different numerical parameters for evaluating and comparing binary mixtures. Objects of interest will be those which are described with non-linear equations and are subject to optimization.

In [10] a hyperbolic function was proposed for drug interaction modeling of binary mixtures:

$$H(d^A, d^B) = C.d^A.d^B + D.d^A + E.d^B + F / 2 = 0 \quad (3)$$

This equation will be the constraint condition for solving optimization tasks.

3.1. Combination index

Combination index **CI** is an important parameter formulated by Chou [2,3] and Tallalida [7]. It is calculated with the expression:

$$CI = \frac{d^A}{ED_{\alpha}^A} + \frac{d^B}{ED_{\alpha}^B} \quad (4)$$

CI gives a quantitative estimate of the interaction of two-component drugs, determining the type of drug interaction:

- ✓ **CI** < 1 : synergism
- ✓ **CI** = 1 : additive effect - line I_{SA}
- ✓ **CI** > 1 : antagonism

For a two-component mixture, the purpose is to maximize synergism, which means **CI** has a minimum value. The minimum of **CI** is the point of the all-curve that is as far as possible from the additive line I_{SA} (Figure 2).

Figure 2. Minimal value of **CI**.

Target function is:

$$CI(d^A, d^B): \frac{d^A}{ED_{\alpha}^A} + \frac{d^B}{ED_{\alpha}^B} \rightarrow \min \quad (5)$$

under constraint condition (3) the decision to belong to the isobolic curve. The Lagrange function is:

$$\begin{cases} \nabla CI(d^A, d^B) = \lambda \cdot \nabla H(d^A, d^B) \\ H(d^A, d^B) = 0 \end{cases} \quad (6)$$

These conditions lead to the system:

$$\left| \begin{array}{l} \frac{\partial}{\partial d^A} CI(d^A, d^B) = \frac{1}{ED_\alpha^A} \\ \frac{\partial}{\partial d^B} CI(d^A, d^B) = \frac{1}{ED_\alpha^B} \end{array} \right| \left| \begin{array}{l} \frac{\partial}{\partial d^A} H(d^A, d^B) = C.d^B + D \\ \frac{\partial}{\partial d^B} H(d^A, d^B) = C.d^A + E \end{array} \right|$$

After equalization the equivalent members according to the system (6), the solutions for the two doses in function of λ is:

$$\left| \begin{array}{l} d^A = \frac{1 - \lambda.E.ED_\alpha^B}{\lambda.C.ED_\alpha^B} \\ d^B = \frac{1 - \lambda.D.ED_\alpha^A}{\lambda.C.ED_\alpha^A} \end{array} \right| \quad (7)$$

By replacing doses in the limited condition, the solutions for Lagrange's multipliers are obtained:

$$\left| \lambda_{1,2} = \pm \frac{\sqrt{2}}{\sqrt{ED_\alpha^A.ED_\alpha^B.(2.D.E.-C.F)}} \right| \quad (8)$$

Excluding λ from (7) there are two pairs of solutions for the dosages that form the best synergy:

$$CI_{\min}(d^A, d^B): \left| \begin{array}{l} d_{1,2}^A = -\frac{E}{C} \pm \frac{\sqrt{ED_\alpha^A(2DE-CF)}}{C\sqrt{2ED_\alpha^B}} \\ d_{1,2}^B = -\frac{D}{C} \pm \frac{\sqrt{ED_\alpha^B(2DE-CF)}}{C\sqrt{2ED_\alpha^A}} \end{array} \right| \quad (9)$$

For each particular case, with real drugs, it should be checked which of the two decisions is the minimum.

3.2. Price of the two-component mixture

Let P_A and P_B be the unit price per unit of agent **A** and agent **B**. Then, the price P_{AB} of the mixture is:

$$P_{AB}(d^A, d^B): P_A.d^A + P_B.d^B \rightarrow \min \quad (10)$$

The value obtained with (10) must be minimized under a condition (3). Thus the optimization task is formed applying the Lagrange function:

$$\left| \begin{array}{l} \nabla P_{AB}(d^A, d^B) = \lambda \nabla H(Q, p) \\ H(Q, p) = 0 \end{array} \right| \quad (11)$$

For the desired dose values d^A, d^B the equations are:

$$\left\{ \begin{array}{l} \frac{\partial P_{AB}(d^A, d^B)}{\partial d^A} = \lambda H_{d^A}(Q, p) \\ \frac{\partial P_{AB}(d^A, d^B)}{\partial d^B} = \lambda H_{d^B}(Q, p) \\ H(Q, p) = 0 \end{array} \right. \quad (12)$$

After differentiation and solution of the system in relation to the doses, there is obtained:

$$\left\{ \begin{array}{l} d^A = \frac{P_B - \lambda.E}{\lambda.C} \\ d^B = \frac{P_A - \lambda.D}{\lambda.C} \end{array} \right. \quad (13)$$

Substituting doses in the limiting condition is obtained multiplier λ :

$$\lambda_{1,2} = \pm \sqrt{\frac{2.P_A.P_B}{2.D.E - C.F}} \quad (14)$$

A minimum price will be obtained at doses:

$$P_{\min}(d^A, d^B): \left\{ \begin{array}{l} d_{1,2}^A = -\frac{E}{C} \pm \frac{\sqrt{P^B(2DE - CF)}}{C\sqrt{2P^A}} \\ d_{1,2}^B = -\frac{D}{C} \pm \frac{\sqrt{P^B(2DE - CF)}}{C\sqrt{2P^A}} \end{array} \right. \quad (15)$$

It should have in mind that optimization solutions can be contradictory - minimal synergy does not mean a minimum price. The pharmacist should choose what is the right solution, taking into account many other parameters of the medicine [11].

4. CONCLUSION

An important feature of two-component drugs is the synergism - with smaller doses of each agent, the therapeutic effect is maintained. Synergism makes it possible to achieve a reduction in cost and toxicity in an appropriate choice of the ratio of the two components in parallel with an increase in the drug effect.

Two parameters of binary mixtures are considered: combination index and price. These parameters are non-linear, and for them are formulated optimization tasks that are solved applying the Lagrange multipliers. The isobolic curve representing synergism is modeled with a hyperbolic function. It is a limiting condition in solving the problem.

The optimization of binary mixtures allows reducing doses of individual drugs, thus decreasing treatment costs and side effects, enhancing healing effects, and reducing the risk of drug resistance.

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