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NUMERICAL OPTIMIZATION OF BINARY MIXTURES

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ABSTRACT

Important quality of binary mixtures of drugs is the synergism - the combined action is greater than the sum of individual effects. The non-linearity of the dose-response relationship gives the opportunity to formulate optimization and computing tasks on the identified model of experimental data. Analytical solutions for optimization of drug combinations with a maximum synergy (minimal combination index), with minimal cost or constant amount of components while maintaining the therapeutic effect are proposed. The optimization of the drug combinations allows decreasing the doses of individual drugs, thereby lowering the cost of treatment and reducing the side effects. Numerical algorithms to calculate important parameters of binary mixtures, such as individual dose reduction index for each compound, total dose reduction index and dose ratio are realized. The approach is implemented in the computer program KORELIA-Ident.

KEYWORDS: **isobolographic analysis, combined drug effects, synergism, dose-time response, modelling.**

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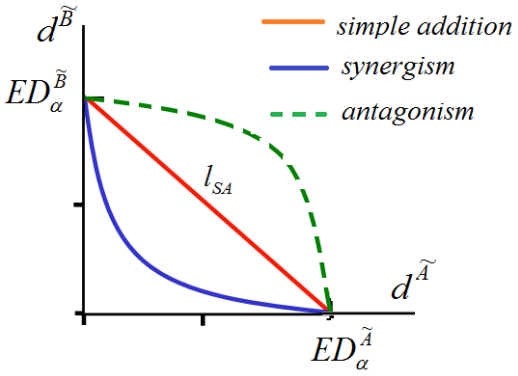
INTRODUCTION

The study of the effects of binary mixtures derived by combining the compound $\widetilde{A}$ and compound $\widetilde{B}$ is implemented with a chosen probability **α**% of influence upon the population.[1] The required data for modeling the dose-response relationship of a two-component mixtures are effective doses (or concentrations) $ED_{\alpha}^{\widetilde{A}}$ and $ED_{\alpha}^{\widetilde{B}}$, respectively of $\widetilde{A}$ and $\widetilde{B}$. The graphical representation of the two-component effective dose $ED_{\alpha}^{\widetilde{A}\widetilde{B}}$ is a continuous curve, known as an isobolic curve or isobologram. An isobologram is a graph with equipotency sum of doses. It may represents one of the three possible cases, known as a simple addition, antagonism and synergism (Figure 1).

Figure 1
Isobolographic curves: equieffective dose mixtures for constant α%



The presence of two or more components in a mixture is a prerequisite for significant changes in their physico-chemical properties.[2,3] Therefore such mixtures are subject to testing and assessment. The synergism in binary mixtures is a valuable property, the effect of which is reduction of the cost of the mixture and decrease of its toxicity. That allows the choice of different proportions of the components while still maintaining the same level of efficacy. This is helpful if one drug has a serious side effect that can be greatly lessened by the addition of a second drug. Carefully selected combinations can give better effect in smaller concentrations. An approach for planning and determination of doses of binary mixtures is discussed by Yankov K et.al.[4]. An isobolic curve by a quadratic function, in particular hyperbole is identified.[5] Akaike's information criteria is used to choose the best model. :

The identified isobolic curve defines a continuous set of binary combinations. This allows introducing an additional requirements which must be met by the two components. The non-linearity of the isobolic curve together with the additional constraints suggests the need of an optimization tasks. This work aims to formulate some optimization problems for the determination of the binary mixtures and to propose an algorithms for their realization.

Key features of binary mixtures

Object of study in this article is the curve representing the synergy. Its identification function enables the use of linear algebra for a simulation study of drug influence. The identification of the isobolic curve is based on the quadratic model ***H(Q,p)*** is [5]

$$\mathrm{H}(Q,p) \;:\; \left\| \; d^{\widetilde{A}} \; d^{\widetilde{B}} \; 1 \; \right\| . \begin{Vmatrix} A & C & D \\ C & B & E \\ D & E & F \end{Vmatrix} . \begin{Vmatrix} d^{\widetilde{A}} \\ d^{\widetilde{B}} \\ 1 \end{Vmatrix} = 0 \qquad (1)$$

where:

$p(d^{\widetilde{A}}, d^{\widetilde{B}}, 1)$ - binary mixture in homogeneous coordinates;

$d^{\widetilde{A}}$ - dose of drug $\widetilde{A}$

$d^{\widetilde{B}}$ - dose of drug $\widetilde{B}$

$Q = \{A, B, C, D, E, F\}$ - the identification vector with the coefficients of the equation;

If $A = B = 0$ the model is hyperbola.

The equation (1) is a constraint for all optimization problems related to binary mixtures.

In the literature a number of parameters that provide quantitative assessment of multi-mixtures are discussed. Some of these parameters can be subject of optimization according to some optimization criteria. The goal in this work is to determine for which of them can be formulated extreme tasks that need be solved.

Combination index equation

The combination index (CI) equation is an important parameter formulated by Chou and Talalay.[6] It is calculated by the equation:

$$CI = \frac{d^{\tilde{A}}}{ED_{\alpha}^{\tilde{A}}} + \frac{d^{\tilde{B}}}{ED_{\alpha}^{\tilde{B}}} \qquad (2)$$

where :

$d^{\tilde{A}}, d^{\tilde{B}}$ are doses in combination that produce an effect with probability ***α***%

$ED_{\alpha}^{\tilde{A}}$ - ***α***% effective dose for compound $\tilde{A}$ when given alone.

$ED_{\alpha}^{\tilde{B}}$, - ***α***% effective dose for compound $\tilde{B}$ when given alone.

CI gives a quantitative definition of the interaction between two drugs. If CI=1, then there is an additive effect. For synergism CI has the values between 0 and 1. CI takes values greater than 1 for antagonism. Quantitative criteria for describing the degrees of synergism or antagonism are proposed in Table 1.[7]

Table 1
Degrees of synergism or antagonism

Synergism		**Antagonism**	
Range of CI	**Description**	**Range of CI**	**Description**
< 0.1	Very strong synergism	1.10–1.20	Slight antagonism
0.1–0.3	Strong synergism	1.20–1.45	Moderate antagonism
0.3–0.7	Synergism	1.45–3.3	Antagonism
0.7–0.85	Moderate synergism	3.3–10	Strong antagonism
0.85–0.90	Slight synergism	> 10	Very strong antagonism
0.90–1.10		Nearly additive	

Dose-reduction index equation

The dose-reduction index (DRI) is a measure of how many times the dose of each drug in a mixture combination may be reduced at a given effect level, with respect the doses of each drug alone.[8,9] The dose reduction is an indication of how toxicity is reduced while the desired therapeutic effect is maintained. The individual dose-reduction ratios for drug $\tilde{A}$ *and drug* $\tilde{B}$ *are defined by the equations*

$$r_{\tilde{A}} = \frac{ED_{\alpha}^{\tilde{A}}}{d^{\tilde{A}}}; \qquad r_{\tilde{B}} = \frac{ED_{\alpha}^{\tilde{B}}}{d^{\tilde{B}}} \qquad (3)$$

DRI value for the binary drug mixture is a sum of the individual dose-reduction ratios:

$$DRI = r_{\tilde{A}} + r_{\tilde{B}} \qquad (4)$$

The value of DRI defines the next three cases [8]:

DRI: =1 - there is no dose reduction; >1- favorable dose-reduction; <1 - unfavorable dose-reduction.

DRI is unbounded above function, so this parameter may be used as a criterion for the evaluation and comparison, but not for optimization. The increasing of DRI is a clear sign for reducing the toxicity of the drug, but it does not necessarily an evidence of synergism - slight antagonism may also lead to DRI greater than 1. Also a mixture with a minimum CI may have a higher toxicity compared to other combinations of compounds.

Dose ratio R

If in a binary mixture the doses of both components are $d^{\tilde{A}}$ and $d^{\tilde{B}}$, the ratio:

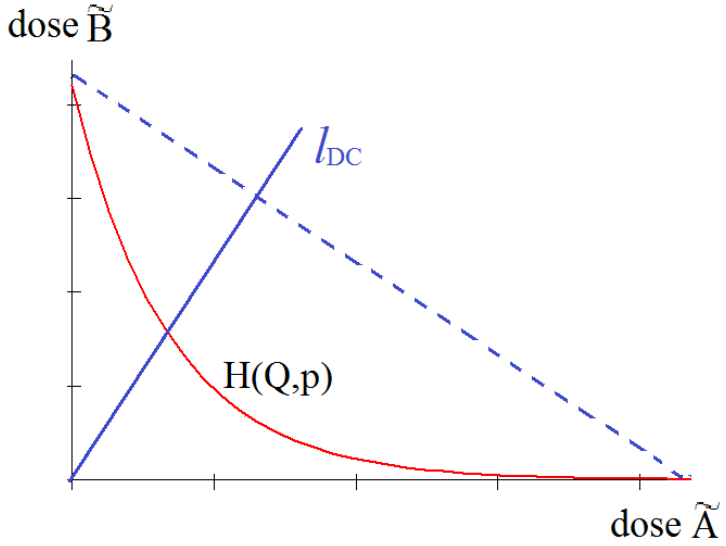
$$R = \frac{d^{\tilde{B}}}{d^{\tilde{A}}} \qquad (5)$$

is called the dose ratio. The possible quantitative combinations of two agents while maintaining their ratio is represented by a straight line through the origin. Such mixtures with constant dose ratio are defined as dosage combinations.[10] The equation of the dosage combinations l_{DC} (ray of constant dose ratio R) (Figure 2) is:

$$l_{DC}: \left\| R \quad -1 \quad 0 \right\| . \left\| \begin{matrix} d^{\tilde{A}} \\ d^{\tilde{B}} \\ 1 \end{matrix} \right\| = 0 \qquad (6)$$

Figure 2

Line l_{DC} of dosage combinations of drugs $\tilde{A}$ and $\tilde{B}$ at a constant proportion R



When R is given, the permissible dose is the intersection of l_{DC} with H(Q,p).

2.4. Mixtures with constant total amount of components

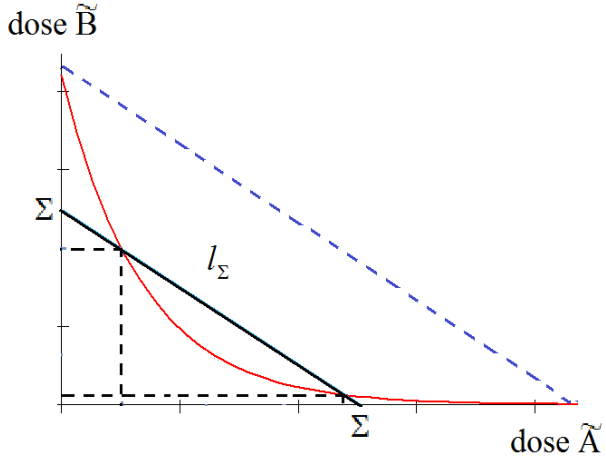
In mixtures of this kind the total quantity ***Σ*** of the two components is constant, ensuring the same effect of $ED_{\alpha}^{\tilde{A}\tilde{B}}$, i.e:

$$d^{\tilde{A}} + d^{\tilde{B}} = \Sigma \qquad (7)$$

That is the line l_{Σ} (Figure 3) with equation:

$$l_{\Sigma}: \left\| 1 \quad 1 \quad -\Sigma \right\| . \left\| \begin{matrix} d^{\tilde{A}} \\ d^{\tilde{B}} \\ 1 \end{matrix} \right\| = 0 \qquad (8)$$

Figure 3
Constant weight mixture



Price of a two-component mixture

Let $P_{\tilde{A}}$ and $P_{\tilde{B}}$ are the price per unit of quantity of drug $\tilde{A}$ and drug $\tilde{B}$ respectively. Then the price $P_{\tilde{A}\tilde{B}}$ of the mixture is:

$$P_{\tilde{A}\tilde{B}}\left(d^{\tilde{A}},d^{\tilde{B}}\right)= \left\| P_{\tilde{A}} \quad P_{\tilde{B}} \quad 0 \right\| . \left\| \begin{matrix} d^{\tilde{A}} \\ d^{\tilde{B}} \\ 1 \end{matrix} \right\| \qquad (9)$$

3. Optimization tasks

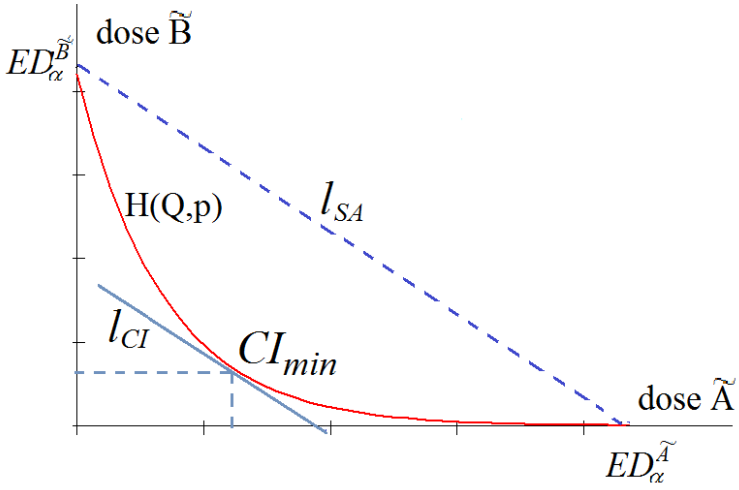
For the features listed in previous part will be formulated optimization problems.

Minimization of the combination index

The aim in creating of binary mixtures is to achieve the maximum synergism, i.e. CI must have a minimum value:

$$CI: \left\| ED_{\alpha}^{\tilde{B}} \quad ED_{\alpha}^{\tilde{A}} \quad -ED_{\alpha}^{\tilde{A}}.ED_{\alpha}^{\tilde{B}} \right\| . \left\| \begin{matrix} d^{\tilde{A}} \\ d^{\tilde{B}} \\ 1 \end{matrix} \right\| \to \min \qquad (10)$$

Figure 4
Minimal value of combination index CI



It is necessary to find a point belonging to the isobolic curve and farthest from the simple addition line I_{SA}. This condition is satisfied from the tangent I_{CI} to $H(Q,p)$, parallel to straight line joining the points $ED_{\alpha}^{\tilde{A}}$ and $ED_{\alpha}^{\tilde{B}}$ (Figure 4). The existence of a minimum is

guaranteed of Lagrange's mean value theorem.[11] Let $f:[a,b]\to R$ be a continuous function in [a, b], differentiable in (a, b). Then there is at least one point $\xi\in(a,b)$ such that:

$$\frac{df(\xi)}{dx}=\frac{f(b)-f(a)}{b-a} \qquad (11)$$

In order to apply the theorem, we define:

$$\begin{aligned} &f(x)=H(Q,p)-\text{identified isobolic function}\\ &a=0\\ &b=ED_{\alpha}^{\tilde{A}}\\ &f(a)=ED_{\alpha}^{\tilde{B}}\\ &f(b)=0\\ &\xi=\left(d^{\tilde{A}},d^{\tilde{B}}\right):\ CI\to\min\ -\text{the solution} \end{aligned} \qquad (12)$$

For a two-component mixture Lagrange's mean value theorem has the form:

$$\frac{dH(Q,p)}{d\left(d^{\tilde{A}}\right)}=\frac{C.F-2.D.E}{2.\left(E+C.d^{\tilde{A}}\right)^2}=-\frac{ED_{\alpha}^{\tilde{B}}}{ED_{\alpha}^{\tilde{A}}}$$

Or:

$$\frac{C.F-2.D.E}{2.\left(E+C.d^{\tilde{A}}\right)^2}=-\frac{ED_{\alpha}^{\tilde{B}}}{ED_{\alpha}^{\tilde{A}}} \qquad (13)$$

The Eq.(13) is solved for $d^{\tilde{A}}$, and then substituting $d^{\tilde{A}}$ in Eq.(1), the dose $d^{\tilde{B}}$ is calculated. The solution for $CI_{\min}\left(d^{\tilde{A}},d^{\tilde{B}}\right)$ (it must be in the first quadrant) is:

$$CI_{\min}\left(d^{\tilde{A}},d^{\tilde{B}}\right):\ \left|\begin{array}{l} d^{\tilde{A}}=-\dfrac{E}{C}\pm\dfrac{\sqrt{ED_{\alpha}^{\tilde{A}}\left(2.D.E-C.F\right)}}{C.\sqrt{2.ED_{\alpha}^{\tilde{B}}}}\\ d^{\tilde{B}}=-\dfrac{D}{C}\pm\dfrac{\sqrt{ED_{\alpha}^{\tilde{B}}.\left(2.D.E-C.F\right)}}{C.\sqrt{2.ED_{\alpha}^{\tilde{A}}}} \end{array}\right. \qquad (14)$$

Dose-reduction index equation

The values of individual dose-reduction indexes $r_{\tilde{A}},r_{\tilde{B}}$ and DRI are calculated according to Eqs.(3) and (4). As mentioned above, these parameters can be used to compare the reduction of the dose, therefore the toxicity of binary mixtures.

Dose ratio R

For mixtures with a constant ratio of the components, optimization problem can not be formulated. The equation for the dosage combinations $\boldsymbol{I_{DC}}$ (Figure 2) together with the Eq.(1) of the isobolic curve defines the system:

$$\left|\begin{array}{l} l_{DC}:\ \left\| R\quad -1\quad 0\right\|\cdot\left\|\begin{array}{c} d^{\tilde{A}}\\ d^{\tilde{B}}\\ 1\end{array}\right\|=0\\ H(Q,p)=0 \end{array}\right. \qquad (15)$$

The solution is:

$$\left| \begin{array}{l} d_{1,2}^{\tilde{A}} = -\dfrac{D + E.R \pm \sqrt{(D + E.R)^2 - 2.C.F.R}}{2.C.R} \\ d_{1,2}^{\tilde{B}} = R.d_{1,2}^{\tilde{A}} \end{array} \right. \qquad (16)$$

From both solutions the one to be considered is the pair belonging to the first quadrant.

Mixtures with constant total amount of components

The desired total amount ***Σ*** of drugs is given. The system of equations must be solved:

$$\left| \begin{array}{l} l_{\Sigma}: \left\| \begin{array}{ccc} 1 & 1 & -\Sigma \end{array} \right\|. \left\| \begin{array}{c} d^{\tilde{A}} \\ d^{\tilde{B}} \\ 1 \end{array} \right\| = 0 \\ H(Q,\ p) = 0 \end{array} \right. \qquad (17)$$

The following cases are possible depending on the values of ***Σ*** compared to $ED_{\alpha}^{\tilde{A}}$ and $ED_{\alpha}^{\tilde{B}}$.

C1. One solution

$$\left[\left(\Sigma \le ED_{\alpha}^{\tilde{A}}\right) and\ \left(\Sigma \ge ED_{\alpha}^{\tilde{B}}\right)\right] \text{ or } \left[\left(\Sigma \ge ED_{\alpha}^{\tilde{A}}\right) and\ \left(\Sigma \le ED_{\alpha}^{\tilde{B}}\right)\right] \qquad (18)$$

C2. Two solutions

$$\left(\Sigma \le ED_{\alpha}^{\tilde{A}}\right) and\ \left(\Sigma \le ED_{\alpha}^{\tilde{B}}\right) \text{ and } \left(l_{\Sigma} \times H(Q,p) \ne \circ\right) \qquad (19)$$

C3. No solution

$$\left(l_{\Sigma} \times H(Q,p) = \circ\right) \qquad (20)$$

The solution of the system (17) is:

$$\left| \begin{array}{l} d_{1,2}^{\tilde{A}} = \dfrac{(D - E) + C.\Sigma \pm \sqrt{(C.\Sigma)^2 + 2.C.\Sigma.(D + E) + (D - E)^2 + 2.C.F}}{2.C} \\ d_{1,2}^{\tilde{B}} = \Sigma - d_{1,2}^{\tilde{A}} \end{array} \right. \qquad (21)$$

Minimum price of the mixture

The value of the mixture expressed with Eq.(9) must be minimized with constraint Eq.(1). Thus the optimization problem is formed:

$$\left| \begin{array}{l} P_{\tilde{A}\tilde{B}}\left(d^{\tilde{A}}, d^{\tilde{B}}\right): \left\| \begin{array}{ccc} P_{\tilde{A}} & P_{\tilde{B}} & 0 \end{array} \right\|. \left\| \begin{array}{c} d^{\tilde{A}} \\ d^{\tilde{B}} \\ 1 \end{array} \right\| \to \min \\ H(Q,\ p) = 0 \end{array} \right. \qquad (22)$$

This optimization problem is appropriate to solve using Lagrange multipliers.[12] To find critical points of a function $P_{\tilde{A}\tilde{B}}\left(d^{\tilde{A}}, d^{\tilde{B}}\right)$ on a $H(Q,p) = 0$, the following system of simultaneous equations must be solved:

$$\left| \begin{array}{l} \nabla P_{\tilde{A}\tilde{B}}\left(d^{\tilde{A}}, d^{\tilde{B}}\right) = \lambda.\nabla H(Q,p) \\ H(Q,p) = 0 \end{array} \right. \qquad (23)$$

where λ is the Lagrange multiplier.

For unknowns $d^{\tilde{A}}, d^{\tilde{B}}$ and λ a three equations are obtained:

$$\left|\begin{array}{l} \dfrac{\partial P_{\tilde{A}\tilde{B}}\left(d^{\tilde{A}}, d^{\tilde{B}}\right)}{\partial d^{\tilde{A}}} = \lambda . H_{d^{\tilde{A}}}(Q,p) \\ \dfrac{\partial P_{\tilde{A}\tilde{B}}\left(d^{\tilde{A}}, d^{\tilde{B}}\right)}{\partial d^{\tilde{B}}} = \lambda . H_{d^{\tilde{B}}}(Q,p) \\ H(Q,p) = 0 \end{array}\right. \qquad (24)$$

After differentiation:

$$\left|\begin{array}{l} P_{\tilde{A}} = \lambda \dfrac{2.D.E + C.F}{2.\left(C.d^{\tilde{A}} + E\right)^2} \\ P_{\tilde{B}} = \lambda \\ H(Q,p) = 0 \end{array}\right. \qquad (25)$$

First solve for λ in terms of $d^{\tilde{A}}$ and $d^{\tilde{B}}$ to remove **λ** from the equations. Then the value of $d^{\tilde{A}}$ is obtained and the decision for $d^{\tilde{B}}$ is obtained from the constraint:

$$\left|\begin{array}{l} d_{1,2}^{\tilde{A}} = -\dfrac{E}{C} \pm \dfrac{\sqrt{P_{\tilde{B}}.\left(2.D.E - C.F\right)}}{C.\sqrt{2.P_{\tilde{A}}}} \\ d_{1,2}^{\tilde{B}} = -\dfrac{2D.d_{1,2}^{\tilde{A}} + F}{2\left(C.d^{\tilde{A}} + E\right)} \end{array}\right. \qquad (26)$$

If suppose that $P_{\tilde{A}} = P_{\tilde{B}} = 1$ the minimum amount $\left(d^{\tilde{A}} + d^{\tilde{B}}\right)$ of the mixture can be calculated.

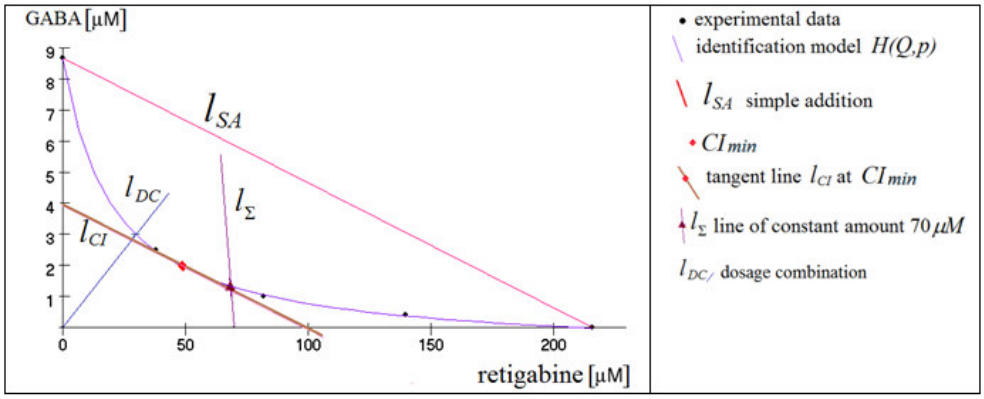
If the prices and effective doses of the components are sufficiently different, then searching the minimal price or the minimal quantity is meaningless.

EXAMPLE

A retigabine interaction with the GABA (γ-Aminobutyric acid) will be discussed.[13] The experimental data are plotted on Figure 5. The effective concentration at α=35% for retigabine is $ED_{35}^{r} = 216\mu M$ and for GABA is $ED_{35}^{G} = 8.67\mu M$.

Figure 5

Experimental data and identified model of combinations of retigabine with GABA



The identified model is hyperbola with equation [5]:

$$\mathrm{H}(Q,p) = \left\| d^r \; d^G \; 1 \right\| \cdot \begin{Vmatrix} 0 & -0.353 & -0.418 \\ -0.353 & 0 & -8.470 \\ -0.418 & -8.470 & 146.760 \end{Vmatrix} \cdot \begin{Vmatrix} d^r \\ d^G \\ 1 \end{Vmatrix} = 0 \qquad (27)$$

This equation is the constraint for the optimization tasks. At this example will be applied described in the part 'Optimization tasks' algorithms.

Minimization of the combination index

According to the Eq.(14) a minimization of the CI is performed. The calculated doses are respectively:

$$\begin{cases} d^r = 52.731 \mu M \\ d^G = 1.896 \mu M \end{cases}$$

The minimal combination index is CI_{min} = 0.4628. The degree of synergy according to Table 1 is evaluated on "Synergism".

Dose-reduction index

After calculating the CI, the values of individual dose-reduction index r_r, r_G Eq.(3) and DRI Eq.(4) are calculated. In this case the values are:

$$\begin{cases} r_r = 4.096; \\ r_G = 4.574 \\ DRI = 8.670 \end{cases}$$

Dose ratio R

In Table 2 the doses of the two drugs and their corresponding parameters for several values of the Dose ratio ***R*** are shown.

Table 2

Comparison of binary mixtures with different values of R.

R	0,02	0.05	0.1	0.2	0.5
d^r [μM]	67.22	43.52	29.935	19.814	11.1
d^G [μM]	1.35	2.176	2.994	3.963	5.55
r_r	3.213	4.963	7.216	10.901	19.460
r_G	6.165	3.744	2.712	2.059	1.562
DRI	9.378	8.707	9.928	12.960	21.022
CI	0.4734	0.4686	0.5074	0.5773	0.6914

The non-linear dependence of the parameters of the mixture depending on the quantities of the components shows how important it is to find a balance between them - a task that is difficult to achieve without the use of specialized computer software.

Mixtures with constant total amount of components

Table 3 shows the calculated values of the components according to Eq.21 for different values of the total amounts. The selected amounts in the example correspond to Case 1, Eq.(18), so the solution Eq.(21) is unique. The case at Σ = 70 μM, line l_Σ is shown in Figure 5.

Table 3

Mixtures with constant total amount of components

dose	Σ [μM]					
	10	20	30	50	70	80
d^r	2.144	15.147	26.505	47.897	68.633	78.887
d^G	7.856	4.853	3.495	2.103	1.367	1.113

Table 3 can be expanded similarly to Table 2, but in this case it is not necessary.

Minimum price of the mixture

A glance on the online retail pricing shows that retigabine is about 3000 times more expensive than GABA. Because the prices and effective doses of these components were sufficiently different, searching the minimal price or minimal quantity is meaningless.

CONCLUSION

In this article an optimization solution for synergistic effect of binary mixtures is proposed. Key features of isobolic curve used in practice are discussed.

Computing and optimization tasks are formulated on the identified model of experimental data. Analytic solutions for optimizing drug combinations are proposed and quantifying of the parameters of the mixtures is presented. The optimization of the drug combinations allows decreasing the doses of individual drugs, thereby lowering the cost of treatment, reducing side effects, enhancing the healing effects and reducing the risk of drug-resistance. The approach is implemented in the computer program KORELIA-Ident. Korelia-Ident offers friendly user interface for data input and graphical output of results. The program is easy and rapid to use, requiring minimum computer knowledge and produces rapidly the desired results.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

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