

## Pareto frontier visualization in multi-criteria search for efficient therapy strategies: HIV infection example

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**Abstract** — Visualization of the Pareto frontier is a new approach in multi-criteria decision making, i.e. searching for efficient decisions taking multiple decision criteria into account. In this paper, visualization of the Pareto frontier is used in the process of multi-criteria search for efficient strategies of HIV therapy. By using a non-linear mathematical model of virus dynamics, which takes into account the phenomenon of virus variability under the influence of a drug, we show that in the framework of the model it is possible to construct a therapy strategy that balances the conflicting requirements imposed on the therapy process.

The main goal of the paper is to show that the multi-criteria method based on Pareto frontier visualization can effectively support a search for efficient strategies of therapy of virus diseases. For this reason, the method is applied to an abstract model of cell infection by viruses, while virus mutations are taken into account.

Generally speaking, the aim of any decision process is to determine the best decision among a number of available decision options (called feasible decisions) according to the preferences of the decision makers, analysts, researchers, or other people. The concept of the best decision can be easily formalized for a single-criterion optimization problem: the best decision must maximize (or minimize) the single optimization criterion over the set of feasible decisions, i.e. the feasible set.

In the process of searching for a preferable efficient solution of a complicated decision problem one often has to take several conflicting performance indicators into account. For many years, researchers have tried to avoid the multi-criteria formalization of such problems by specifying the most important performance indicator as the single optimization criterion and using other indicators as a source of *a priori* constraints. However, such approach usually fails to solve the problem, since it constructs a decision whose criterion value is not balanced with the values of the constraints. The reason consists in the fact that the constraints are set without knowing the dependence of the criterion value on the constraints.

To avoid such a deadlock, multi-criteria decision support techniques are used

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that take all important performance indicators into account by considering them as criteria. They provide an effective tool for constructing decisions that consider different requirements and provide a balance of conflicting goals (e.g., [1, 12]). In this paper we apply a method that can be used in the important class of multi-criteria decision problems, i.e., multi-criteria optimization (MCO) problems. In the framework of MCO problems, the direction of the improvement of any particular criterion is given in advance: one has to maximize or minimize it (while the values of the other criteria are constant). For example, it is preferable to have a lower cost of the therapy if the results of the therapy are the same.

From the very beginning, it is important to stress the following difference between single-criterion optimization and MCO. Normally there is a single optimal decision that solves a single-criterion optimization problem. In contrast, in a MCO problem, because of the presence of several criteria, a set of mathematically equivalent optimal decisions does exist. Such a decision set is called the Pareto optimal set. The Pareto optimal set consists of the decisions which cannot be improved, i.e. improving the value of one criterion requires deteriorating the value of at least one other criterion (formal definitions are given later). The Pareto optimal set may contain a large number of decisions, often it is infinite.

Any decision from the Pareto optimal set corresponds to a Pareto optimal criterion vector that can be considered as a point of the criterion space. The Pareto optimal criterion points form the Pareto optimal criterion set. It has a property which is extremely important from the point of view of real-life applications. Let us consider the feasible criterion set, i.e., the set of all criterion points that can be obtained if the feasible decisions are used. Then the Pareto optimal criterion set is a part of the frontier of the feasible criterion set. For this reason, the Pareto optimal criterion set is usually called the Pareto frontier. A decision, which is the best one according to the preferences of the decision maker, must belong to the Pareto optimal decision set and its criterion vector must belong to the Pareto frontier. Due to it, the Pareto frontier plays an important role in analysis of MCO problems.

Multiple methods have been proposed for supporting decision makers, analysts, researchers, and other interested persons (for the sake of simplicity, they will be denoted as users) in the process of searching for the most preferable decision from the set of mathematically equivalent Pareto optimal decisions. A wide variety of such methods is described, for example, in the book [19]. The MCO methods are usually classified as *a priori* (or decision rule-based) methods, interactive (or progressive) methods, and *a posteriori* (or Pareto frontier) methods. The classification is done in accordance to the stage at which the users are involved in the decision process.

In this paper, we apply a method that belongs to *a posteriori* (or Pareto frontier) methods. These methods start with constructing or approximating the Pareto frontier. Then the user is informed about the Pareto frontier. He/she is not asked questions concerning his/her preferences before or during the informing procedure (except for relatively simple questions about the improvement directions for particular criteria). Only after the informing process is completed, the user is asked to specify a preferable point that belongs to the Pareto frontier. It is important that he/she

does not need to do it immediately, since in the Pareto frontier methods expressing preferences in the form of a single-shot specification of the preferred Pareto optimal criterion point may be separated in time from the exploration of the frontier. Human beings need time to find a balance between the criteria, thus, this opportunity is a very important feature of the Pareto frontier methods (see [18]).

If there are only two criteria, the Pareto frontier is displayed in the criterion plane. In this case it is usually named the tradeoff curve. The tradeoff curve gives information on the frontiers of feasible criterion values and on criterion tradeoffs, i.e. on the cost of improving one criterion by deteriorating another one. This knowledge helps the user to specify the preferred criterion point deliberately. Then the preferred decision is computed automatically.

In multi-criteria problems with more than two criteria (so-called many-criteria or high-order MCO problems), the user needs to study the optimal criterion points located at the multidimensional Pareto frontier and the related criterion tradeoffs. There are two main approaches to informing the users about the Pareto frontier in the high-order MCO problems. First, a large number of points of the Pareto frontier can be provided in the form of a list (for details see, for example, [19,23]). However, the tradeoff information is lost in this case. Moreover, it is known that selecting from the large lists of multi-criteria alternatives is too complicated for the user [14]. Alternative idea consists in visualizing the Pareto frontier.

Generally speaking, visualization, that is, transformation of symbolic data into geometric information, can support human beings in forming a mental picture of the data. Visualization on the basis of computer graphics has proved to be a convenient technique that can help people to assess information in diverse problems. It can be successfully applied in the Pareto frontier methods too, see [18].

The idea to approximate and visualize the Pareto frontier was introduced by S. Gass and T. Saaty in 1955 [7] for linear decision problems with two criteria. In our paper, the high-order Pareto frontier is visualized by using the Interactive Decision Maps (IDM) technique, which has proved to be a convenient tool for solving this task. It has been successfully used for constructing efficient strategies in economic, environmental and other problems (see [16]). In the framework of the IDM technique, the Edgeworth-Pareto Hull (EPH) of the feasible criterion set is considered, i.e. the largest set that has the same Pareto frontier as the feasible set. The EPH is approximated instead of the Pareto frontier in the IDM technique. To visualize the Pareto frontier, the IDM technique displays the sets of two-criterion slices of the EPH in a dialogue with the user. The frontiers of such slices include tradeoff curves for the pairs of criteria (for fixed values of other criteria). By this the user is informed of the criterion values and the criterion tradeoffs.

To find the preferred decision, the IDM technique is combined with methods that use preference information in the form of the preferred criterion point (goal). The goal approach introduced by Charnes and Cooper [4] applies a single-shot identification of a goal and subsequent computing of a feasible decision, whose output is the closest one (in some sense) to the identified goal. Multiple real-life applications of the goal methods prove that the goal approach is convenient for users. However,

the classic goal methods have a disadvantage: if the feasibility information is unknown, a goal may happen to be distant from the feasibility frontier — it may be too ambitious or too pessimistic. This may result in a decision which is not the best one for the user. The IDM technique refines the goal approach by informing the user of the feasibility of the goals. With a help of the IDM technique, the user identifies the Pareto-optimal goal directly at one of the tradeoff curves. As the result, the risk of too ambitious or too pessimistic goals vanishes: a Pareto-optimal decision is found, which results in the goal identified by the user. Such a procedure has got the name of the Feasible Goals Method (FGM), see [16]. In this paper, the IDM/FGM technique is applied in the process of the multi-criteria search for efficient strategies of therapy of a virus infection. For definiteness, we consider the HIV viruses.

In spite of a considerable success in the therapy of the HIV infection, the therapy does not result in a complete recovery of the patient. The contemporary therapy methods slow down the process of lymphocytes infection by HIV viruses and support a sufficient number of normal (healthy) lymphocytes, i.e. the condition that permits the infected persons to live a full life during a relatively long period. However, the medicaments that support such condition are very expensive. The last circumstance is an essential barrier for spreading the contemporary therapy methods in under-developed countries.

Another obstacle is the ability of HIV viruses to mutate. It results in the situation when, along with the basic type of viruses, numerous mutant species (clones) exist. Normally, the death rate of the mutant species is sufficiently high and their quantity is small as compared with the quantity of the Wild Type (WT) viruses. The situation changes if WT viruses are the subject of a medical treatment. A final result of using a drug is the appearance of resistant mutants, which cause the same harm to the health as WT viruses. On the other hand, stopping the therapy process leads to an unavoidable growth of the fraction of the WT viruses. It is important to stress that the presence of drugs in the body can have a direct negative effect on the health as well. Therefore, in the process of developing a HIV-infection therapy, one needs to consider several requirements:

- the number of lymphocytes infected by the WT and mutant viruses should be on an acceptable level during the therapy and should be sufficiently small at the end of the therapy;
- the quantity of the drug in the body should be not too high and should be safe for the patient's health;
- the number of healthy lymphocytes should be on an acceptable level during the therapy and should be sufficiently high at the end of the therapy;
- the cost of the therapy course should not be too high.

To solve this problem by using a multi-criteria optimization method, we apply the mathematical modelling of the HIV infection treatment. Mathematical models

of virus dynamics have been studied in multiple publications, see, for example, the monographs [20, 21], as well as the papers [10, 11, 22]. To construct a treatment strategy on the basis of a HIV model, optimization methods were applied, for example, in [2, 6, 8, 13, 24]. In these studies, the only optimization criterion was used: it was either the integral functional of a weighted sum of the number of normal and infected lymphocytes, as well as the square of the control function, or the functional that represents such a sum at the end of the process. It is clear that by using one criterion, one cannot guarantee the values of other performance indicators to be satisfactory. Say, the number of infected lymphocytes or the drug concentration may happen to be dangerously high and the number of normal lymphocytes may happen to be dangerously low for the life of the patient.

Using the multi-criteria approach permits studying various real-life medical problems, in which the development of the therapy strategy depends on many factors. In particular, using such approach one can find a suitable therapy strategy depending on the health and the financial capacity of the patient.

The article consists of four sections. In Section 2 the mathematical model of the therapy process of the HIV infection is described; it takes into account the ability of the WT viruses to mutate. The multi-criteria optimization problem is formulated in the same section. The multi-criteria optimization technique based on visualization of the high-order Pareto frontier is described in Section 3. Finally, application of the Pareto frontier visualization technique in the process of searching for HIV therapy that satisfies the conflicting requirements is described in Section 4. The developed therapy strategy is analyzed in the same section. The paper ends up with the Summary.

## 1. Mathematical model

In our model we consider an organism as a whole, without distinguishing blood, lymphonoduses etc. The influence of the medical drug on the HIV viruses dynamics is described by the mathematical model that includes four differential equations. There are four state variables in the model:

- the number of uninfected (normal) lymphocytes,  $n$ ;
- the number of lymphocytes infected by the WT virus,  $I_1$ ;
- the number of lymphocytes infected by the mutant virus,  $I_2$ ;
- the quantity of the medical drug in the body of the patient,  $h$ .

Note that only one mutant virus is considered in the model. The differential equations look as follows:

$$\begin{aligned}
\dot{n} &= \lambda - \beta_1(h)I_1n - \beta_2(h)I_2n - dn \\
\dot{I}_1 &= \beta_1(h)(1 - \mu(h))I_1n - \alpha_1I_1 \\
\dot{I}_2 &= \beta_1(h)\mu(h)I_1n + \beta_2(h)I_2n - \alpha_2I_2 \\
\dot{h} &= -\gamma h - (\gamma_1I_1 + \gamma_2I_2)h + u(t)
\end{aligned}$$

Here  $\lambda, d, \alpha_1, \alpha_2, \gamma, \gamma_1, \gamma_2$  are the given parameters, and  $\beta_1(h), \beta_2(h), \mu(h)$  are three functions given later.

Note that in the framework of the model, uninfected lymphocytes are reproduced at a constant rate  $\lambda$ . In general, the rate of uninfected lymphocytes reproduction in an organism with a healthy immune system is not constant. We use the maximal possible value of the rate, since the case is considered when the organism uses its maximum ability for struggling against the virus infection.

The therapy functions  $\beta_1(h)$  and  $\beta_2(h)$  describe the influence of the drug on the infection process. Namely, the influence of the drug consists in the blockage of the infection process. The following functions are used in the model:

$$\beta_i(h) = \delta_i + \frac{r_i}{1 + k_i h} \quad (1.1)$$

where  $i = 1, 2$  and  $\delta_i, r_i, k_i$  are given positive parameters. As one can see, the value of  $\beta_i(h)$ ,  $i = 1, 2$ , equals to  $\delta_i$ ,  $i = 1, 2$ , if the drug is absent. Increasing the drug quantity  $h$  results in the decrement of the values  $\beta_1(h)$  and  $\beta_2(h)$ . Such properties of the functions correspond to the increasing ability to block the infection process.

The function  $\mu(h)$  describes the influence of the drug on the process of the growth of the fraction of the lymphocytes infected by the mutant virus. As we have already mentioned, the increment of the drug influence results in the growth of the fraction of the mutant viruses; thus, the fraction of the lymphocytes infected by the mutant virus is increasing, too. To represent this property, the following monotonic function is used

$$\mu(h) = \mu_0 + \frac{mh}{A + h} \quad (1.2)$$

where  $\mu_0, m, A$  are some given positive parameters.

Parameters  $\gamma_1$  and  $\gamma_2$  characterize the consumption of the drug in the therapy process. They do not depend on the drug concentration.

The function  $u(t)$  is the control function to be found. It determines the quantity of drug injected in a unit of time. The following constraints represent the limits of drug injection that must be satisfied at any time-moment  $t$  from the time period under study denoted by  $[0, T]$ :

$$0 \leq u(t) \leq R, \quad t \in [0, T]. \quad (1.3)$$

The value  $R$  must be given in advance.

For the time period under consideration, i.e.  $[0, T]$ , one year (360 days) was taken. It was divided in twelve time intervals, 30 days each. We assume that the day

dose of the drug injection that satisfies the constraint (1.3) is not changed during each of the twelve time intervals. It means that the control function  $u(t)$ , i.e. the dose of the drug, is described by twelve parameters. These twelve parameters constitute the decision variables, which have to be found during the decision making process.

The initial values of the state variables are assumed to be known

$$n(0) = n_0, \quad I_1(0) = I_1^0, \quad I_2(0) = I_2^0, \quad h(0) = 0. \quad (1.4)$$

The following six criterions were used in the multicriteria optimization:

$$\begin{aligned} y_1 &= \int u(t) dt \\ y_2 &= \max h(t) \\ y_3 &= I_1(T) + I_2(T) \\ y_4 &= \max(I_1(t) + I_2(t)) \\ y_5 &= n(T) \\ y_6 &= \min n(t). \end{aligned}$$

The first criterion describes the total quantity of the drug applied during the period of the therapy  $[0, T]$ . This criterion characterizes the cost of the drug. The second criterion describes the maximal quantity of the drug in the body during the time of the therapy. It is clear that it is desirable to decrease the values of the first and of the second criteria.

The third and the fourth criteria are related to the sum of the lymphocytes infected by the WT and the mutant viruses. The third criterion describes this value at the end of the therapy. The fourth criterion describes the maximal number of the infected lymphocytes during the therapy process. These criteria should be decreased, as well.

The two last criteria describe the number of healthy lymphocytes at the end of the therapy process and the minimal number of healthy lymphocytes during the therapy process. It is necessary to maximize the values of these criteria.

As the result, we have got the nonlinear multicriteria optimization problem with 6 criteria and 12-dimensional decision vector. To solve the problem we use the technique for visualization of the Pareto frontier.

## 2. Visualization technique

Let us start with several definitions used in multi-criteria optimization (MCO). It is assumed here that the decisions are the points of the linear decision space  $R^n$ . Below we denote the set of feasible decisions by  $X$ . The space of the criteria is assumed to be the  $m$ -dimensional linear space  $R^m$ . Any point  $x \in X$  results in the criterion point  $y \in R^m$ , which can be computed by using the given vector-function

$$f(x) = (f_1(x), \dots, f_m(x)).$$

Thus, the set of criterion points that can be obtained by using the feasible decisions, the feasible criterion set  $Y$ , is given by  $Y = f(X)$ . Note that in contrast to the set  $X$ , the set  $Y$  is not given in advance.

As usually in MCO, we have to define the improvement directions of the criteria. For the sake of simplicity, in this section we consider the case where all criteria must be maximized. We assume that a criterion point  $y$  dominates the criterion point  $y'$ , i.e.  $y$  is better than  $y'$ , if  $y \geq y'$  and  $y \neq y'$ . In other words, we use the Pareto domination. Then, the Pareto (non-dominated) frontier of the set  $Y$  is of interest, which is defined as

$$P(Y) = \{y \in Y : \{y' \in Y : y' \geq y, y' \neq y\} = \emptyset\}.$$

Let  $\mathbf{R}_-^m$  be the non-positive orthant in  $\mathbf{R}^m$ . The set

$$Y_P = Y + \mathbf{R}_-^m$$

is called the Edgeworth–Pareto Hull (EPH) of the set  $Y$ . Along with the points of the set  $Y$ , the EPH includes all criterion points dominated by the points of the set  $Y$ . It is important for the EPH to be the maximal set that satisfies  $P(Y_P) = P(Y)$ .

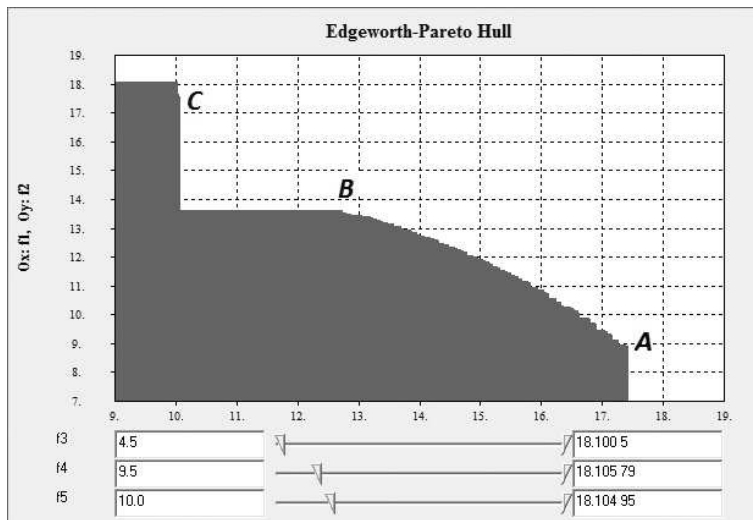
The main feature of the Interactive Decision Maps (IDM) technique that we use in this paper consists in approximating the EPH and in subsequent interactive study of the Pareto frontier by displaying two-criteria slices of the EPH approximation. To define a two-criteria slice of the EPH, one has to relate two criteria to the axes and to set fixed values for the rest of criteria. Mathematically, a two-criteria slice is defined as follows. Let us by  $(y_1, y_2)$  denote two ‘axis’ criteria, and by  $z$  denote the remaining criteria, whose values are given as  $z = z^*$ . A two-criteria slice of the set  $Y_P$ , parallel to the plane  $(y_1, y_2)$  and related to  $z = z^*$  is defined as

$$G(Y_P, z^*) = \{(y_1, y_2) : (y_1, y_2, z) \in Y_P, \quad z = z^*\}.$$

Note that in the case of the maximization problem, a slice of  $Y_P$  contains such combinations of values  $(y_1, y_2)$ , for which there exists a vector  $z, z \geq z^*$ , so that the values  $(y_1, y_2)$  are feasible. An example of a two-criteria slice of an EPH approximation for a non-linear five-criterion model is provided in Fig. 1.

In Fig. 1, the values of criteria  $f_1$  and  $f_2$  are related to the horizontal and vertical axis, respectively, and the ranges of three other criteria are defined by the sliders of the scroll-bars. Note that the equalities  $f_3 = 4.5, f_4 = 9.5, f_5 = 10.0$ , which are set fixed by the left sliders of the scroll-bars, define the slice. The Pareto frontier of the slice  $(f_1, f_2)$  is approximately given by the part of the frontier between the points  $A$  and  $B$  and by a small part of its frontier near the point  $C$ . Roughly speaking, it is the tradeoff curve among criteria  $f_1$  and  $f_2$  if the values of the rest of criteria are not lower than the values given by the left sliders. One can move the left sliders to study the influence of criteria  $f_3, f_4, f_5$  on the tradeoff curve. The right sliders of the scroll-bars are not used while studying the EPH in the maximization case: they are needed in the case of minimization.





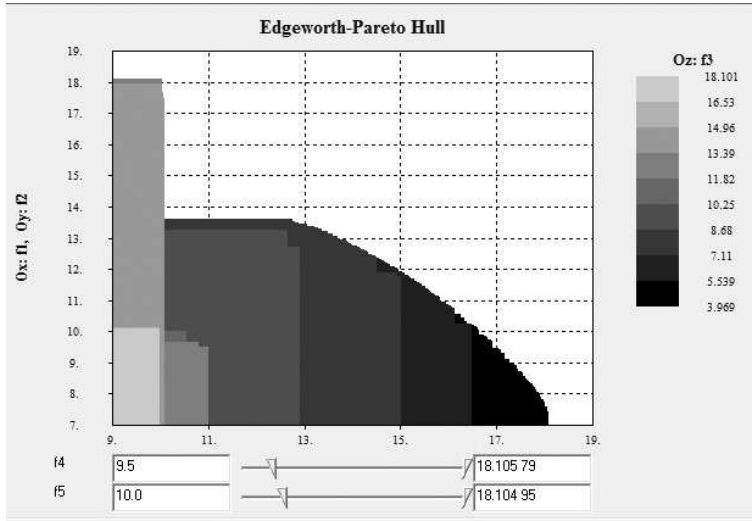
**Figure 1.** A two-criteria slice of an EPH approximation.

In the IDM technique, two-criteria slices are usually displayed in the form of *decision maps*. To define a particular decision map, in addition to relating two criteria to the axes, one has to specify a color-associated criterion among the rest of criteria. A decision map is a set of superimposed differently colored slices, for which the value of the color-associated criterion changes, while the values of the remaining criteria are set fixed. It is important that the frontiers of the slices of the EPH displayed at a decision map do not intersect — the upper slice belongs to the lower one. An example of a gray copy of a color decision map is provided in Fig. 2.

Here, in contrast to Fig. 1, the values of criterion  $f_3$  are associated with different colors (shades of gray in the figure). The relation among the color (shading) and the value range of the criterion  $f_3$  is given in the palette located to the right of the decision map. One can see, for example, that the maximal values of  $f_3$  (more than 16.5) can be achieved only for small values of  $f_1$  and  $f_2$  (not greater than 10.0). However, the values of  $f_3$  greater than 15.0 can be achieved for relatively high values of  $f_2$ . Once again, the user can apply the sliders for studying the effect of the criteria associated with the scroll-bars.

As we have already said, to select a preferable decision, the IDM technique is combined with a method that uses preference information in the form of the preferable criterion point (goal) identified by the user directly at one of the tradeoff curves. One of the goal methods developed on the basis of the IDM technique is the Feasible Goals Method (FGM), in which a decision is found that results in the identified goal. Implementation of the FGM method depends on the method for approximating the EPH, which, in turn, depends on the properties of the decision problem.

If the EPH is convex (for example, the set  $X$  is convex and the vector function  $f(x)$  is linear), its approximation can be constructed in the form of the solution set of



**Figure 2.** A decision map (gray copy).

a linear inequalities system using the methods for polyhedral approximation of convex multi-dimensional sets [16]. Such an approximation supports instant displaying the decision maps. After the exploration of the Pareto frontier and identification of a goal, the associated decision is found by using a special single-criterion optimization problem (see [16] for details).

If the EPH is not convex, it can be approximated by a finite system of cones with vertices that are close to the Pareto frontier. Denoting the set of such vertices by  $T$ , we can describe an approximation of the EPH as

$$T^* = T + \mathbf{R}_-^m. \quad (2.1)$$

The finite set  $T$  is called the approximation base. Approximating the non-convex EPH in form (2.1) provides an opportunity of fast computing the two-criteria slices of the EPH in the non-linear case.

There are a lot of studies (see, for example, [19]) that develop various methods for approximating the Pareto frontier by a finite number of criterion points. In principle, these points can be used as the approximation base. Fairly often, it is proposed to solve a large number of single objective optimization problems for determining such points. However, one has to take into account that solving just one non-linear non-convex global optimization problem may be not a simple task in a general case [9]. Thus, the approach based on a straightforward application of classic optimization methods can be effectively used only in simple cases. Another approach to constructing a finite number of objective points that approximate the Pareto frontier can be based on application of multi-criteria evolutionary methods that can be applied in a general case [5]. However, the problem is still far from being

solved, since the evolutionary methods concentrate mainly on problems with two or three criteria.

In the IDM technique, hybrid methods are used for constructing the approximation base. They combine global random search, gradient-based methods of local optimization, and evolutionary methods (see for details [3, 17]). There are examples of successful approximation of such approach in complicated non-linear problems with several hundreds of decision variables and more than three criteria [15]. Constructing the EPH approximation in this complicated problem, a weak notebook was used. It took several dozen hours to complete this job.

Integrating random search with local optimization is a standard approach in global nonlinear single-criterion optimization [9]. Such optimization methods are called two-phase optimization methods. In the framework of nonlinear IDM technique, two-phase optimization methods are applied in multi-criteria problems for approximating the EPH as a part of hybrid methods. Random search is generally used: points of the feasible decision set  $X$  are generated randomly and the related criterion points are computed. To apply the local optimization technique in multi-criteria optimization, one has to use scalar functions of the criteria. In the IDM technique, the scalar functions depend on the parameters associated with random criterion points, from which the scalar local optimization starts. To apply the approximation technique for the optimization of complicated mathematical models, simulation-based optimization is applied: using a code that computes the criterion vector  $y = f(x)$  for any feasible decision vector  $x \in X$ , the gradient of the scalar function is approximated and used in a gradient-based search for a local maximum (or minimum) of the scalar function. It is important that one does not need to know any special feature of the model: the ability of the code to compute the value of  $f(x)$  is sufficient. Due to the random search, the nonlinear IDM technique can find the Pareto optimal points even in the case of a fairly large number of local minima of the criteria. The process of EPH approximation ends with the application of a multi-criteria evolutionary method [3].

If the EPH is approximated in form (2.1), the Pareto-optimal criterion points of the approximating base  $T$  are found along with the Pareto-optimal decisions in the process the gradient-based search. By identifying the goal, the user simultaneously identifies the cone  $y^+ + \mathbf{R}^m$  that contains the goal. Thus, the criterion point  $y^+$  that belongs to the approximation base  $T$  and the decision  $x^+$  are found, for which it holds  $y^+ = f(x^+)$ . The decision  $x^+$  is considered to be the best one for the user among the points of the approximating base.

We end this section with the main steps of the IDM/FGM technique:

*Step 1.* Approximating the EPH.

*Step 2.* Application of the IDM technique for exploration of the Pareto frontier.

*Step 3.* Identification of the preferred Pareto-optimal criterion point (feasible goal).

*Step 4.* Construction and display of the decision that results in the identified goal.

### 3. Model study

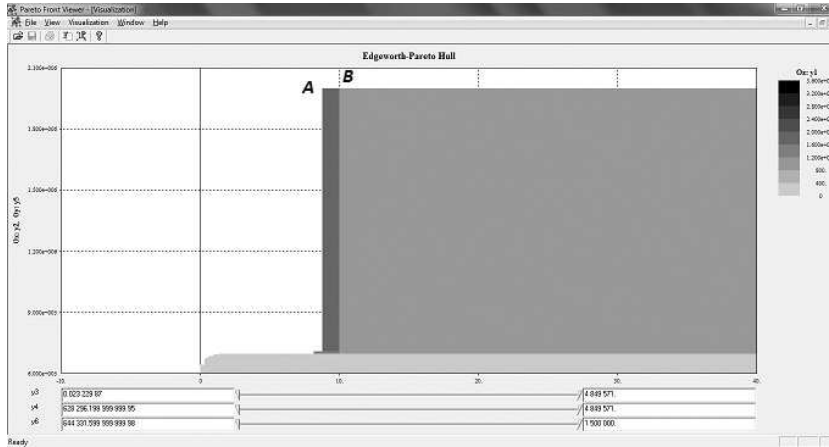
The model has been studied for plausible values of the parameters. Therefore, we do not provide the parameters that were used in the study. The initial data were selected by us to consider a patient with a low rate of healthy lymphocytes, a high rate of lymphocytes infected by the WT virus, and a low rate of lymphocytes infected by the mutant virus, namely  $n_0 = 1.5 \times 10^6$ ,  $I_1 = 5 \times 10^5$ ,  $I_2 = 15 \times 10^3$ . Such numbers of lymphocytes seem plausible for an infected patient before the therapy starts.

For testing the model we studied the case of the absence of treatment ( $u(t) = 0$  at all time moments  $t \in [0, T]$ ). After a relatively short time period (about two months), the number of healthy lymphocytes decreases from 1.5 million to about 0.5 million and the number of lymphocytes infected by the WT virus grows several times. The number of lymphocytes infected by the mutant virus is growing very slowly in the absence of drugs, and their influence is not important. Because of a small number of healthy lymphocytes and a large number of infected lymphocytes, a complete loss of immunity takes place.

Let us apply the IDM/FGM technique for constructing a therapy strategy that provides a balance of six criteria listed above. Approximating the EPH required several hours of computing using a standard notebook. The IDM technique allowed exploring the Pareto frontier for all six criteria. Dozens of different decision maps were displayed and animated. The study helped to understand possible criterion values, as well as the tradeoffs between the criteria. A black and white copy of one of the color decision maps is given in Fig. 3. At the horizontal axis, the values of the criterion  $y_2$  (the maximal amount of the drug in the body over the treatment period) are given. At the vertical axis, the values of criterion  $y_5$  are provided, i.e. the number of the healthy lymphocytes by the end of treatment. The value of the criterion  $y_2$  has to be minimized, and the value of the criterion  $y_5$  has to be maximized. Thus, the left upper frontiers of the slices are of interest in the study. The shade of gray (color at the computer display) is related to the value of the criterion  $y_1$ , i.e. the quantity of the drug used during the treatment procedure.

In Fig. 3, the values of the criteria  $y_3$  and  $y_4$  (the number of infected lymphocytes at the end of the treatment and their maximum number during the treatment), as well as the criterion  $y_6$  (minimum of the healthy lymphocytes for the entire period of treatment) are given at the scroll-bars. Note that we are interested in decreasing the values of  $y_3$  and  $y_4$  and increasing the value of  $y_6$ . This is why the right sliders are used to study the influence of the criteria  $y_3$  and  $y_4$  and the left slider in the case of  $y_6$ . It is important to note that any attempt to lower the value of  $y_3$  and  $y_4$  or to increase the value of  $y_6$  results in a qualitative change of the decision map: a number of slices of the decision map disappear. This is why the full ranges of the criteria  $y_3$ ,  $y_4$  and  $y_6$  are considered.

In the decision map, the lightest shade of gray represents the minimal application of drug ( $0 \leq y_1 \leq 400$ ). As one can see, the number of healthy lymphocytes by the end of the treatment period (the criterion  $y_5$ ) does not exceed 0.4 million at this



**Figure 3.** Shades of the gray copy of the color decision map.

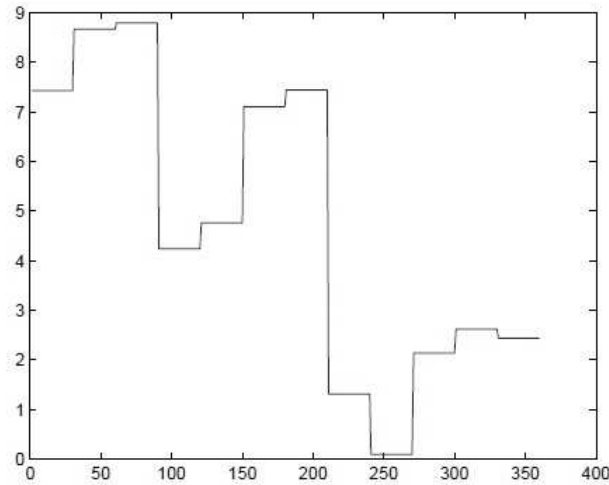
slice, which means a complete loss of immunity. Thus, it is necessarily to consider alternative values of  $y_1$  that are related to different slices of the EPH.

As can be seen, it is possible to increase the number of healthy lymphocytes by the end of the treatment ( $y_5$ ) up to 2 million, if application of the drug ( $y_1$ ) is between 800 and 1200 units (gray area in Fig. 3). Note that the dependence of  $y_5$  on  $y_1$  has a jump: application of the drug ( $y_1$ ) ranging from 400 to 800 units does not increase the value of  $y_5$ . The dependence of  $y_5$  on the amount of the drug in the body ( $y_2$ ) is not continuous, either: if  $y_2$  is about 10 units, the value of  $y_5$  increases abruptly from 0.4 million to about 2 million.

Let us consider the dark gray strip that appears when the drug application ( $y_1$ ) increases to the range from 1600 to 2000 units. Though such an increase in the drug application does not produce in a significant change of the number of healthy lymphocytes at the end of the treatment period ( $y_5$ ), it allows to achieve the same value of  $y_5$  for a smaller value of  $y_2$ , i.e., the maximal amount of drug in the body (about 9 units).

Consider the criterion point A located in the left upper corner of the dark gray band that arises as the result of the drug application in the range from 1600 to 2000 units. The point A is related to the criterion values  $y_1 = 1711$ ,  $y_2 = 8.80$ ,  $y_3 = 1451$ ,  $y_4 = 743000$ ,  $y_5 = 2 \times 10^6$ ,  $y_6 = 1.5 \times 10^6$ . Note that the number of infected lymphocytes at the end of treatment is about 1.5 thousand (in contrast to about half million in the beginning of the course). The maximal number of infected lymphocytes during the course is not greater than the initial number. The number of healthy lymphocytes in the end of course, as has already been stated, is approximately equal to 2 million, which is quite satisfactory. The number of healthy lymphocytes for the entire period of treatment does not fall below its initial value of 1.5 million.

Let us now consider the criterion point B located in the upper left corner of the area that corresponds to the drug application in the range from 800 to 1200 units. The point B has the following criterion values:  $y_1 = 959$ ,  $y_2 = 10.0$ ,  $y_3 = 12913$ ,  $y_4 =$



**Figure 4.** Graph of the daily dose of the drug that results in the criterion point A.

628000,  $y_5 = 2 \times 10^6$ ,  $y_6 = 1.5 \times 10^6$ . As one can see, the drug application decreases nearly by half to 960 units as compared with point A. Thus, a significant reduction of the treatment cost is achieved. Moreover, the number of healthy lymphocytes at the end of the treatment and the minimal number of healthy lymphocytes during the treatment remain the same. Thus, for reducing the drug application, one needs to offset it by an increase of the maximal amount of drug in the body during the course up to 10 units and by an insignificant growth of the number of infected lymphocytes at the end of the treatment.

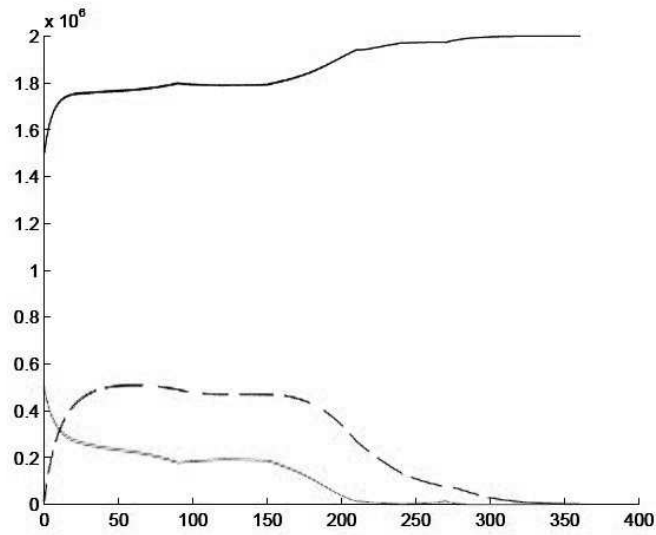
Let us compare the treatment strategies that result in points A and B in details. In Fig. 4 the graph is provided that displays the dependence of the daily dose of the drug on time for the criterion point A.

Figure 5 contains the graphs for the criterion point A that describe the dynamics of healthy lymphocytes (the solid curve emanating from the point 1.5), of lymphocytes infected with the virus of the WT type (the solid curve emanating from the point 0.5), and lymphocytes infected with the mutant virus (the dashed curve emanating from the point 0).

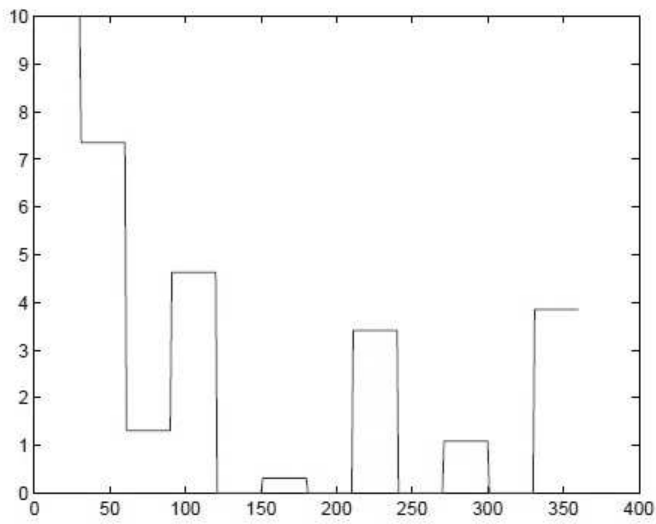
These graphs show that the drug is extensively used during the first seven months. By this time the number of WT-infected lymphocytes is substantially reduced. Simultaneously, the number of lymphocytes infected with the mutant virus increases from zero to 0.5 million. Then, the intensity of treatment weakens, however, the low intensity of treatment is sufficient for reducing the number of lymphocytes infected with the mutant virus to virtually zero.

Now let us consider the graph that displays the dependence of the daily dose of the drug on time for the criterion point B (see Fig. 6).

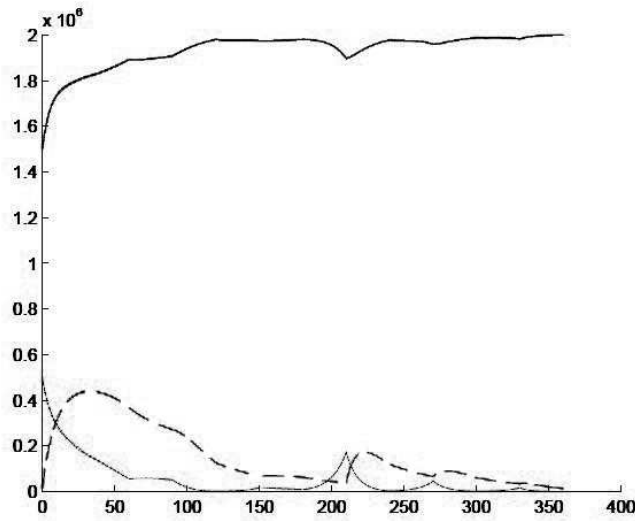
As one can see, the schedule of the daily doses of the drug, which results in the criterion point B, is substantially different from the schedule related to the criterion point A. In the case of the criterion point B, a month-long low intensity treatment



**Figure 5.** Dynamics of healthy lymphocytes, lymphocytes infected with the virus of the WT type and lymphocytes infected with the mutant virus (criterion point A).



**Figure 6.** Graph of the daily dose of the drug that corresponds to the criterion point B.



**Figure 7.** Dynamics of healthy lymphocytes, lymphocytes infected with the virus of the WT type and lymphocytes infected with the mutant virus (criterion point B).

follows an intensive treatment during the first two months. Then, a month-long medium-intensity treatment follows. The subsequent treatment is almost periodic with a period of four months. A four-month period consists of two months with low to medium intensity, each of which is preceded by a month with no treatment. The resulting dynamics of healthy lymphocytes, lymphocytes infected with the WT virus, and lymphocytes infected with the mutant virus is shown in Fig. 7.

As one can see, the dynamics of infected lymphocytes is different from the lymphocyte dynamics that corresponds to the criterion point A (see Fig. 5). The number of lymphocytes infected by the WT virus is rapidly decreasing. Moreover, the number of lymphocytes infected by the mutant virus is kept in the range of 0.4 million and later reduced to practically zero.

Thus, the analysis of the Pareto frontier has helped to develop a treatment strategy that differs from the more traditional strategy that corresponds to the criterion point A. The constructed strategy is characterized by the reduced treatment cost, fewer infected lymphocytes, and a more sparing schedule.

#### 4. Summary

The model that is used in this study is an abstract model of a virus disease. Thus, the results of the study cannot be used in therapy immediately: a more precise description of the illness and a calibration of the model are required. However, the results provided here prove that Pareto frontier visualization is an effective technique for constructing balanced therapy strategies. It is possible to apply the method for analysis of different criteria or modifications of the model. For example, more compli-



cated models of the HIV infection that take into account several types of the mutant virus or complicated immunity models can be studied. Therapy strategies for other kinds of diseases can be developed as well.

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