

## A METHOD OF LOWER AND UPPER SOLUTIONS FOR CONTROL PROBLEMS AND APPLICATION TO A MODEL OF BONE MARROW TRANSPLANTATION

LORAND GABRIEL PARAJDI <sup>a,b</sup>, RADU PRECUP <sup>c,d,\*</sup>, IOAN ȘTEFAN HAPLEA <sup>e</sup>

<sup>a</sup>Department of Mathematics  
 West Virginia University  
 P.O. Box 6201, Morgantown, WV 26506, USA  
 e-mail: lorand.parajdi@mail.wvu.edu

<sup>b</sup>Department of Mathematics  
 Babeș–Bolyai University  
 M. Kogălniceanu Street, No. 1, 400084 Cluj-Napoca, Romania

<sup>c</sup> Institute of Advanced Studies in Science and Technology  
 Babeș–Bolyai University  
 M. Kogălniceanu Street, No. 1, 400084 Cluj-Napoca, Romania  
 e-mail: r.precup@math.ubbcluj.ro

<sup>d</sup>Tiberiu Popoviciu Institute of Numerical Analysis  
 Romanian Academy  
 P.O. Box 68-1, 400110 Cluj-Napoca, Romania

<sup>e</sup>Department of Internal Medicine  
 Iuliu Hațieganu University of Medicine and Pharmacy  
 Victor Babeș Street, No. 8, 400012 Cluj-Napoca, Romania  
 e-mail: happlea.ioan.stefan@gmail.com

A lower and upper solution method is introduced for control problems related to abstract operator equations. The method is illustrated on a control problem for the Lotka–Volterra model with seasonal harvesting and applied to a control problem of cell evolution after bone marrow transplantation.

**Keywords:** control problem, lower and upper solutions, fixed point, approximation algorithm, numerical solution, medical application.

### 1. Introduction

In the work of Haplea *et al.* (2021) we have introduced a controllability principle for a *general control problem* related to operator equations. It consists in finding  $(w, \lambda)$ , a solution to the system

$$\begin{cases} w = N(w, \lambda), \\ w \in W, \quad \lambda \in \Lambda, \quad (w, \lambda) \in D \end{cases} \quad (1)$$

involving the fixed point equation  $w = N(w, \lambda)$ . Here  $w$  is the *state variable*,  $\lambda$  is the *control variable*,  $W$  is the *domain of the states*,  $\Lambda$  is the *domain of controls* and  $D \subset W \times \Lambda$  is the *controllability domain* given expression to a certain condition/property imposed on  $w$ , or on both  $w$  and  $\lambda$ . There are no structures imposed on the sets  $W$ ,  $\Lambda$  and  $D$  and no enforced properties for the mapping  $N$  from  $W \times \Lambda$  to  $W$ .

We say that the equation  $w = N(w, \lambda)$  is *controllable* in  $W \times \Lambda$  with respect to  $D$ , if problem (1) has a

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\*Corresponding author

solution  $(w, \lambda)$ . In case the solution is unique, we say that the equation is *uniquely controllable*.

In order to describe the idea of solving the general control problem, define the sets

$$\Sigma := \{(w, \lambda) \in W \times \Lambda : w = N(w, \lambda)\},$$

$$\Sigma_1 := \{w \in W : \text{there is a } \lambda \in \Lambda \text{ with } (w, \lambda) \in \Sigma\}.$$

Obviously, the solutions of to the control problem (1) are the elements of  $\Sigma \cap D$ .

Consider now the set-valued map  $F : \Sigma_1 \rightarrow \Lambda$  given by

$$F(w) := \{\lambda \in \Lambda : (w, \lambda) \in \Sigma \cap D\}.$$

Thus,  $F$  yields the expression for the control variable corresponding to the state variable.

The next result is a general principle for solving the control problem (1).

**Proposition 1.** *If for some extension  $\tilde{F} : W \rightarrow \Lambda$  of  $F$  from  $\Sigma_1$  to  $W$ , there exists a fixed point  $w \in W$  of the set-valued map*

$$\tilde{N}(w) := N(w, \tilde{F}(w)),$$

i.e.,

$$w = N(w, \lambda), \tag{2}$$

for some  $\lambda \in \tilde{F}(w)$ , then the couple  $(w, \lambda)$  is a solution to the control problem (1).

*Proof.* From (2), one has  $(w, \lambda) \in \Sigma$ . Hence  $w \in \Sigma_1$  and hence  $\tilde{F}(w) = F(w)$ . Then  $\lambda \in F(w)$  and, from the definition of  $F$ , it follows that  $(w, \lambda) \in D$ . Thus  $(w, \lambda)$  is a solution to (1). ■

In many applications,  $F$  and  $\tilde{F}$  are single-valued maps and  $F$  can be extended to  $W$  by the simple use of its expression on  $\Sigma_1$ .

Two applications for a system modeling cell dynamics related to leukemia have been included the work of Haplea et al. (2021) (see also Parajdi et al., 2023) and three others in that of Precup (2022), of which two are self-control problems. Many other illustrations of the above principle can be derived from the rich literature in control theory (see, e.g., Coron, 2007).

The aim of this paper is to give an algorithm for the approximation of the solutions of general control problems. It basically consists of a bisection method for the control variable inside an interval associated to a pair of lower and upper solutions. The notions of lower and upper solutions for a general control problem are defined accordingly.

## 2. Lower and upper method for control problems

First, in the present set-framework we introduce the notions of lower and upper solutions to a control problem. To this aim, we assume a certain partition of the solution domain,

$$W \times \Lambda = \underline{D} \cup \overline{D}, \quad \underline{D} \cap \overline{D} = D$$

which allows us to say that the condition of controllability is targeted from the left or from the right. Thus, we can give the following definition.

**Definition 1.** By a lower (resp. upper) solution to problem (1) we mean a pair  $(w, \lambda) \in \Sigma \cap \underline{D}$  ( $\Sigma \cap \overline{D}$ ).

In contrast to the statement of the controllability principle presented above, given in unstructured sets, from now on we shall assume a certain topological structure of the sets and accordingly the continuity of the map  $N$ . The topological framework is a natural one for approximation methods, when a certain meaning is required for the terms of the approximant and for the method convergence.

Assume that  $W$  is a metric space,  $\Lambda = \text{conv}\{\underline{\lambda}_0, \overline{\lambda}_0\}$  is a segment of a normed space with norm  $\|\cdot\|$ , i.e.,  $\text{conv}\{\underline{\lambda}_0, \overline{\lambda}_0\} = \{(1-\sigma)\underline{\lambda}_0 + \sigma\overline{\lambda}_0 : \sigma \in [0, 1]\}$ , and that the sets  $\underline{D}$  and  $\overline{D}$  are closed.

In addition, assume that the following conditions are satisfied:

- (H1) The problem admits a lower solution of the form  $(\underline{w}_0, \underline{\lambda}_0)$  and an upper solution  $(\overline{w}_0, \overline{\lambda}_0)$ .
- (H2) For each  $\sigma \in [0, 1]$ , there exists a unique  $w =: S(\sigma) \in W$  with  $(w, \lambda) \in \Sigma$  for  $\lambda = \lambda(\sigma) := (1-\sigma)\underline{\lambda}_0 + \sigma\overline{\lambda}_0$ .
- (H3) The map  $S : [0, 1] \rightarrow W$  is continuous.

We use now the bisection method represented as Algorithm 1. The algorithm leads either to a solution when it stops, or to two sequences  $(\underline{\sigma}_k)$  and  $(\overline{\sigma}_k)$  such that

- (i)  $0 \leq \underline{\sigma}_1 \leq \dots \leq \underline{\sigma}_k \leq \underline{\sigma}_{k+1} \leq \dots \leq 1$  and  $(S(\underline{\sigma}_k), \lambda(\underline{\sigma}_k)) \in \underline{D}$ ,
- (ii)  $0 \leq \dots \leq \overline{\sigma}_{k+1} \leq \overline{\sigma}_k \leq \dots \leq \overline{\sigma}_1 \leq 1$  and  $(S(\overline{\sigma}_k), \lambda(\overline{\sigma}_k)) \in \overline{D}$ ,
- (iii)  $0 \leq \overline{\sigma}_k - \underline{\sigma}_k = 1/2^k$ .

Then the sequences  $(\underline{\sigma}_k)$  and  $(\overline{\sigma}_k)$  are convergent and by virtue of (iii) their limits are equal, say  $\sigma^*$ . Clearly,  $\sigma^* \in [0, 1]$ . Furthermore, using the continuity of  $S$  and the fact that  $\underline{D}, \overline{D}$  are closed, from  $(S(\underline{\sigma}_k), \lambda(\underline{\sigma}_k)) \in \underline{D}$  we obtain  $(S(\sigma^*), \lambda(\sigma^*)) \in \underline{D}$ . Similarly  $(S(\sigma^*), \lambda(\sigma^*)) \in \overline{D}$ . Hence  $(S(\sigma^*), \lambda(\sigma^*)) \in D$ ,

**Algorithm 1.** Bisection method.

Let  $\underline{\sigma}_0 = 0$  and  $\overline{\sigma}_0 = 1$ . For  $k \geq 1$  execute

**Step 1.** Calculate

$$\sigma := \frac{\underline{\sigma}_{k-1} + \overline{\sigma}_{k-1}}{2}$$

and find  $S(\sigma)$ .

**Step 2.** If  $(S(\sigma), \lambda(\sigma)) \in D$ , then  $(S(\sigma), \lambda(\sigma))$  is a solution of the control problem; otherwise, update

- (a)  $\underline{\sigma}_k := \sigma, \overline{\sigma}_k := \overline{\sigma}_{k-1}$  if  $(S(\sigma), \lambda(\sigma)) \in \underline{D} \setminus D$ ,
- (b)  $\underline{\sigma}_k := \underline{\sigma}_{k-1}, \overline{\sigma}_k := \sigma$  if  $(S(\sigma), \lambda(\sigma)) \in \overline{D} \setminus D$ ,

then set  $k := k + 1$  and go to Step 1.

that is,  $(S(\sigma^*), \lambda(\sigma^*))$  solves the control problem, which proves the algorithm convergence. Thus, we have proved the following result.

**Theorem 1.** Under the assumptions (H1)–(H3), Algorithm 1 is convergent to a solution  $(w^*, \lambda^*)$  to the control problem (1).

**Remark 1.** Theorem 1 guarantees that the algorithm finishes after a finite number of iterations under the stopping criterion of the form

$$\|\overline{\sigma}_k - \underline{\sigma}_k\| \leq \varepsilon,$$

for any given  $\varepsilon$  with  $0 < \varepsilon < 1$ . Then any of the pairs  $(S(\underline{\sigma}_k), \lambda(\underline{\sigma}_k))$  and  $(S(\overline{\sigma}_k), \lambda(\overline{\sigma}_k))$ , where  $k$  corresponds to the last iteration, can be considered an approximation of a solution to the control problem. The error for the control parameter  $\lambda$  is less than or equal to  $(\|\underline{\Delta}_0\| + \|\overline{\lambda}_0\|)\varepsilon$ .

**Remark 2.** The above result does not require any ordering between  $\underline{\Delta}_0$  and  $\overline{\lambda}_0$ .

**Remark 3.** For specific applications, the computer implementation of the above algorithm needs additionally an approximation procedure for the solution operator  $S$ . Then the algorithm is in fact applied to an approximation  $S_{\text{approx}}$  of  $S$ . Such approximations can be done using the method of successive approximations (guaranteed by the Banach and Perov fixed point theorems) (Precup, 2002), Newton’s method, techniques of upper and lower solutions, continuation and discretization methods, etc. (Kelley, 1995; Langtangen and Mardal, 2019).

**2.1. Example.** Consider the Lotka–Volterra model with seasonal harvesting (Rahmani Doust, 2015),

$$\begin{cases} x' = ax(1 - by) - g(t), \\ y' = -cy(1 - dx) - h(t), \end{cases} \quad (3)$$

where  $g, h \in L^1(0, T)$ .

Assume that for two routine harvesting policies  $(g_1, h_1)$  and  $(g_2, h_2)$ , the ratio between the two species  $x(T)/y(T)$  at the end  $T$  of a season is respectively below and above a desired level  $r$ . The control problem is to find the appropriate harvesting policy  $(g, h)$  to achieve the ratio  $r$  considered optimal. Clearly, under some given initial values  $x_0$  and  $y_0$ , the system (3) is equivalently expressed as a fixed point equation

$$\begin{cases} x(t) = x_0 + \int_0^t (ax(s)(1 - by(s)) - g(s)) ds, \\ y(t) = y_0 + \int_0^t (-cy(s)(1 - dx(s)) - h(s)) ds. \end{cases} \quad (4)$$

Compared with the abstract control problem stated in Section 1, here  $w = (x, y)$ ,  $\lambda = (g, h)$ ,  $W = C([0, T]; (0, +\infty)^2)$ ,  $\underline{\Delta}_0 = (g_1, h_1)$ ,  $\overline{\lambda}_0 = (g_2, h_2)$ ,  $\Lambda = \{(g_\sigma, h_\sigma) : \sigma \in [0, 1]\}$ , where  $g_\sigma = (1 - \sigma)g_1 + \sigma g_2$ ,  $h_\sigma = (1 - \sigma)h_1 + \sigma h_2$ ,

$$\begin{aligned} D &= \{(x, y, g, h) : x(T)/y(T) = r\}, \\ \underline{D} &= \{(x, y, g, h) : x(T)/y(T) \leq r\}, \\ \overline{D} &= \{(x, y, g, h) : x(T)/y(T) \geq r\}. \end{aligned}$$

Also, according to Definition 1,  $(x_1, y_1, g_1, h_1)$  and  $(x_2, y_2, g_2, h_2)$  (where  $(x_i, y_i)$  is the solution of system (4) for  $g = g_i$  and  $h = h_i$ ,  $i = 1, 2$ ) are lower and upper solutions to the control problem, respectively.

Notice that it seems natural that the appropriate policy should be an intermediary between the two routine policies. Our algorithm looks for it as a convex combination of the two routine strategies and thus the control problem reduces to finding  $\sigma \in [0, 1]$  for which the solution  $(x, y)$  of the system

$$\begin{cases} x' = ax(1 - by) - g_\sigma(t), \\ y' = -cy(1 - dx) - h_\sigma(t), \end{cases}$$

with  $g_\sigma = (1 - \sigma)g_1 + \sigma g_2$ ,  $h_\sigma = (1 - \sigma)h_1 + \sigma h_2$  and some given initial values  $x_0, y_0$ , satisfies

$$\frac{x(T)}{y(T)} = r.$$

### 3. Control of cell evolution after bone marrow transplantation

There is quite a rich literature in the field of mathematical modeling of hematological processes (for a survey, see the work of Foley and Mackey (2009)). Regarding bone marrow transplantation, few mathematical contributions have been made despite the rich medical and clinical literature (see, e.g., DeConde *et al.*, 2005; Kim *et al.*, 2007).

In the paper by Precup *et al.* (2010) (see also Precup *et al.*, 2018) the following system has been introduced as a model of cell dynamics after bone marrow transplantation:

$$\begin{cases} x' = \frac{a}{1 + b(x + y + z)} \frac{x + y}{x + y + gz} x - cx, \\ y' = \frac{A}{1 + B(x + y + z)} \frac{x + y}{x + y + Gz} y - Cy, \\ z' = \frac{a}{1 + b(x + y + z)} \frac{z}{z + h(x + y)} z - cz. \end{cases} \quad (5)$$

Here  $x(t), y(t), z(t)$  stand respectively for the normal, leukemic and donor cell populations at time  $t$ , after transplant time  $t = 0$  when their concentrations are supposed to have been  $x_0, y_0, z_0 (> 0)$ . Parameters  $a, A$  stand for the growth rates of normal and leukemic cells;  $c, C$  are their cell death rates; and  $b, B$  are their microenvironment sensitivity rates. Also, the parameters  $h, g, G$  stand for the intensity of anti-graft, anti-host and anti-leukemia effects, respectively. They totalize a large number of cell biophysical properties, as well as exterior stimulants and inhibition during the immunotherapy. Values of the parameters  $h, g, G$  close to zero correspond to weak interactions; larger values quantify strong effects and their pre-transplant estimate would be crucial for the transplant strategy (conditioning treatment, dose of infused cells and post-transplant immunosuppressive therapy). We note that the model was improved by Parajdi (2020) by considering, instead of the same sensitivity rate  $b$  for normal and leukemic cells, different sensitivity rates  $b_1$  and  $b_2$ , respectively.

In the paper by Precup *et al.* (2013), the equilibria of system (5) are found and their stability is established in terms of the system parameters. According to the main result of Precup *et al.* (2013) the system has, as the numerical simulations by Precup *et al.* (2012) suggested, only two asymptotically stable equilibria, namely the ‘bad’ equilibrium  $P_2(0, D, 0)$  and the ‘good’ one  $P_3(0, 0, d)$ . The ‘good’ equilibrium is reached when the transplant succeeds. Here, the malignant clone is completely eradicated (together with the patient’s own normal bone marrow cells) and the engraftment is successful. All the bone marrow cells originate in the graft, and thus the corresponding equilibrium point is  $P_3(0, 0, d)$ . The ‘bad’ equilibrium point is reached when the transplant fails in competition with the recipient’s leukemic cells.

At an equilibrium, all bone marrow cells are malignant in nature, and thus the equilibrium point is  $P_2(0, D, 0)$ . Here the values

$$d = \frac{1}{b} \left( \frac{a}{c} - 1 \right)$$

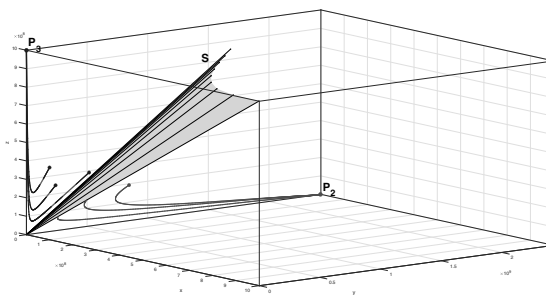


Fig. 1. Separation surface  $S$  of the ‘bad’ and ‘good’ basins of attraction when no treatment is given,  $\lambda = 1$ . Initial conditions in the ‘good’ basin:  $x(0) = 1.2 \times 10^8, y(0) = 0.968 \times 10^7, z(0) = 3 \times 10^8$ ;  $x(0) = 0.905 \times 10^8, y(0) = 1.649 \times 10^7, z(0) = 3.876 \times 10^8$ ;  $x(0) = 2.605 \times 10^8, y(0) = 1.649 \times 10^7, z(0) = 4.076 \times 10^8$ ; and in the ‘bad’ basin:  $x(0) = 2.032 \times 10^8, y(0) = 0.056 \times 10^9, z(0) = 2.438 \times 10^8$ ;  $x(0) = 2.032 \times 10^8, y(0) = 0.456 \times 10^9, z(0) = 2.838 \times 10^8$ ;  $x(0) = 2.032 \times 10^8, y(0) = 0.256 \times 10^9, z(0) = 3.038 \times 10^8$ .

and

$$D = \frac{1}{B} \left( \frac{A}{C} - 1 \right)$$

can be seen as homeostatic normal and cancer levels. Also, the octant of the positive states  $(x, y, z)$  splits into two basins of attraction of the two equilibria, the ‘bad’ basin corresponding to  $(0, D, 0)$ , and the ‘good’ one for  $(0, 0, d)$  (see Fig. 1 and Appendix for its construction). This means that if at a given time  $t_0$  the state  $(x(t_0), y(t_0), z(t_0))$  belongs to the basin of attraction of any of the two equilibria, then the entire trajectory  $(x(t), y(t), z(t))$  for  $t \geq t_0$  remains in the same basin and, as a result, in time, approaches the corresponding equilibrium. Thus, a transplant appears as successful if the initial state  $(x_0, y_0, z_0)$  is located in the good basin, which happens if  $z_0$  is sufficiently large compared with  $x_0$  and  $y_0$ . Also, an unsuccessful transplant could be turned into a successful one if by any methods/therapies one can move the state  $(x, y, z)$  from the bad basin into the good one, or if we can enlarge the good basin to catch the state inside. In fact, for any transplant, one could preventively apply the same strategy in order to move the state  $(x, y, z)$  (even if located in the good basin) away from the separating surface between the two basins, to be sure that further perturbations cannot change the good evolution towards equilibrium  $(0, 0, d)$ .

The source of parameters is the paper by Precup *et al.* (2012). The values are reasonable estimates, as the actual cell kinetics within the stem cell niche are largely inaccessible. We restrict our numerical simulations to the following parameter values:  $a = 0.23, b = 2.2 \times 10^{-8}, c = 0.01, A = 0.43, B = 5.5 \times 10^{-9}, C = 0.03, g = 25,$

$G = 4$  and  $h = 20$ , where  $d = 9.99999999 \times 10^8 < 2.424242423 \times 10^9 = D$ .

From the main result of Precup *et al.* (2013) we have that the separation surface  $S$  of the two basins of attraction intersects the plane  $y = 0$  after the line

$$z = \sqrt{\frac{h}{g}}x,$$

and the plane  $x = 0$  after a curve close to the line

$$z = \frac{\frac{A}{C} - 1}{G}y.$$

Thus, the good basin of attraction increases if at least one of the two lines goes down, which happens if one can make  $h/g$  or/and  $A/C$  decrease, or/and  $G$  increase.

Therefore, the basin of attraction of the good equilibrium  $P_3$  is enlarged if the separation surface  $S$  goes down (see Figs. 2 and 3) and this can be achieved by

- (i) increasing anti-host parameter  $g$ ,
- (ii) increasing anti-cancer parameter  $G$ ,
- (iii) decreasing anti-graft parameter  $h$ ,
- (iv) decreasing the growth rate of cancer cells  $A$ ,
- (v) increasing the death rate of cancer cells  $C$ .

Such changes in these parameters find their counterpart in post-transplant medical practice, namely the following therapies: donor T-lymphocyte infusion (related to  $g$  and  $G$ ), immunosuppressive therapy (related to  $h$ ) and post-transplant consolidation chemotherapy (related to  $A$  and  $C$ ). In the work of Precup *et al.* (2012) a series of imaginary scenarios combining these therapies have been designed and it has been shown that the success depends on their intensity, the time interval in which they are applied and the time after transplantation at which they are initiated.

Denote by  $\lambda_i(t)$ ,  $i = 1, \dots, 5$  the factors with which the parameters  $g, G, h, A$  and  $C$  are modified on a time interval  $[0, T]$ . In medical practice, these factors should be related to the treatment doses necessary to correct the patient's post-transplantation condition. Assume that as functions they belong to  $L^\infty(0, T)$ . For example, we can consider these functions piecewise constant, when the value one on a certain subinterval would correspond to an interruption of the therapy. Also, denote by  $\lambda(t)$  the vector in  $\mathbb{R}^5$  having these components.

Assuming that after transplant one has  $y \simeq 0$  on the time interval  $[0, T]$  and that the patient's condition  $w_0 = (x_0, y_0, z_0)$  is in the bad basin, that is,

$$\frac{z_0}{x_0} < \sqrt{\frac{h}{g}},$$

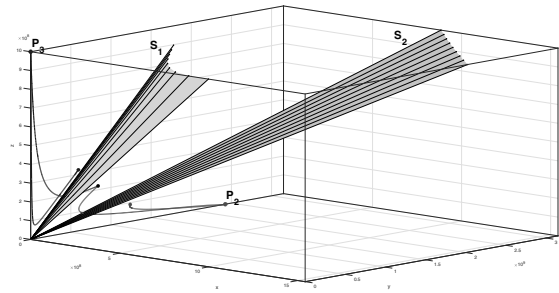


Fig. 2. Separation surface ( $S_1$  goes down) when we consider the treatment, the surface  $S_1$  (no treatment,  $\lambda = 1$ ) and the surface  $S_2$  (with treatment,  $\lambda = 0.04$ ). Initial conditions in the 'good' basin with reference to  $S_1$ :  $x(0) = 2.605 \times 10^8$ ,  $y(0) = 1.649 \times 10^7$ ,  $z(0) = 4.076 \times 10^8$  and in the 'bad' basin of  $S_1$ :  $x(0) = 2.632 \times 10^8$ ,  $y(0) = 0.256 \times 10^9$ ,  $z(0) = 3.038 \times 10^8$ ; in the 'good' basin with reference to  $S_2$ :  $x(0) = 2.632 \times 10^8$ ,  $y(0) = 0.256 \times 10^9$ ,  $z(0) = 3.038 \times 10^8$  and in the 'bad' basin of  $S_2$ :  $x(0) = 2.632 \times 10^8$ ,  $y(0) = 0.656 \times 10^9$ ,  $z(0) = 1.738 \times 10^8$ .

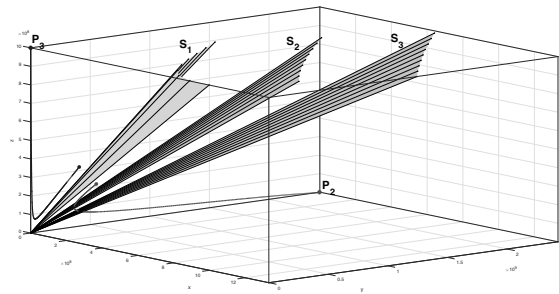


Fig. 3. Separation surfaces ( $S_1$  and  $S_2$  go down) when we consider two distinct values of the treatment, the surface  $S_1$  (no treatment,  $\lambda = 1$ ), the surface  $S_2$  (with treatment,  $\lambda = 0.2$ ) and the surface  $S_3$  (with treatment,  $\lambda = 0.08$ ).

we want to decrease the  $h/g$  ratio to reach the goal

$$\frac{z(T)}{x(T)} > \sqrt{\frac{h}{g}}$$

meaning that the patient's condition is brought to time  $T$  in the good basin, evolving after that to the good attractor  $P_3$ . Obviously, the patient's exposure to corrective therapies should be reduced as much as possible. In order to find such a minimal therapy according to  $\lambda(t)$ , we can apply our lower and upper solution method.

Clearly, for a lower solution  $(\underline{x}_0, \underline{y}_0, \underline{z}_0, \underline{\Delta}_0)$  we can take the vector  $\underline{\Delta}_0 = (1, 1, 1, 1, 1)$  which corresponds to

the absence of any post-transplant therapy. Then

$$\frac{\underline{z}_0(T)}{\underline{x}_0(T)} < \sqrt{\frac{h}{g}}$$

An upper solution  $(\bar{x}_0, \bar{y}_0, \bar{z}_0, \bar{\lambda}_0)$  can be chosen by checking several vector functions  $\lambda(t)$  with step function components satisfying  $0 \leq \lambda_i(t) \leq 1$  for  $i = 3, 4$  and  $\lambda_i(t) \geq 1$  for  $i = 1, 2, 5$ . For it one has

$$\frac{\bar{z}_0(T)}{\bar{x}_0(T)} > \sqrt{\frac{h}{g}}$$

Once this upper solution is found, the algorithm starts and continues until the first step  $k$  at which, for  $\lambda = \lambda(\bar{\sigma}_k)$ , one has

$$\frac{z(T)}{x(T)} \leq \sqrt{\frac{h}{g}} + \delta$$

for an acceptable margin  $0 < \delta < \bar{z}_0(T)/\bar{x}_0(T) - \sqrt{h/g}$ . Then the vector  $\lambda(\bar{\sigma}_k) = (1 - \bar{\sigma}_k)\underline{\lambda}_0 + \bar{\sigma}_k\bar{\lambda}_0$  can be a good approximation to the control  $\lambda$ .

In this case, referring to the general framework, we have  $W = C([0, T]; (0, +\infty)^3)$ ,  $w = (x, y, z)$ ,  $\Lambda = \{\lambda(\sigma) : \sigma \in [0, 1]\}$ , where  $\lambda(\sigma) = (1 - \sigma)\underline{\lambda}_0 + \sigma\bar{\lambda}_0$ ,

$$D = \left\{ (w, \lambda) : \frac{z(T)}{x(T)} = \sqrt{\frac{h}{g}} \right\},$$

$$\underline{D} = \left\{ (w, \lambda) : \frac{z(T)}{x(T)} \leq \sqrt{\frac{h}{g}} \right\},$$

$$\overline{D} = \left\{ (w, \lambda) : \frac{z(T)}{x(T)} \geq \sqrt{\frac{h}{g}} \right\}.$$

Also  $N = (N_1, N_2, N_3)$  is the integral operator associated with the equivalent integral system.

First, we prove that the solution operator  $S$  is well-defined, that is, the condition (H2) holds.

**Lemma 1.** For each  $\lambda = \lambda(\sigma) \in \Lambda$ , the initial value problem  $w = N(w, \lambda)$ ,  $w(0) = w_0$  has a unique solution  $w = S(\sigma) \in W$ .

*Proof.* First, note the Lipschitz continuity of the system nonlinearities with respect to the variables  $x, y$  and  $z$ . Thus the qualitative theory on the Cauchy problem applies to our situation including the result about the behavior of the saturated solutions in a neighborhood of the boundary of the domain where the system is defined, here  $[0, T] \times (0, +\infty)^3$  (see Barbu, 2016, Theorem 2.10). Thus, it remains to prove that the saturated solution to the initial value problem does not fail at the boundary.

Assume the contrary. Then there is a  $t_0 \in (0, T]$  such that  $x(t), y(t), z(t) > 0$  in  $[0, t_0)$  and the limit at  $t_0$  of at

least one of the three functions equals zero. Let  $x(t) \rightarrow 0$  as  $t \rightarrow t_0$ . From the first equation of the system, we have

$$x'(t) \geq -cx(t), \quad t \in [0, t_0),$$

whence  $x(t) \geq x_0 e^{-ct}$ , which leads to a contradiction with our assumption. We get a similar conclusion if  $z(t) \rightarrow 0$  as  $t \rightarrow t_0$ . The same is obtained if  $y(t) \rightarrow 0$  as  $t \rightarrow t_0$ , when the contradiction comes from the estimate  $y(t) \geq y_0 e^{-C \int_0^t \lambda_5(\sigma)(s) ds}$ . ■

Finally, we prove the continuous dependence on  $\sigma$  of the solution  $S(\sigma) = (x, y, z)$ , that is, condition (H3). To this end, we use the technique of equivalent norms, more exactly, the Bielecki norm on  $C[0, T]$  that we present now for the reader's convenience.

For any number  $\theta > 0$ , the Bielecki norm  $\|\cdot\|_\theta$  on the space  $C[0, T]$  is given by

$$\|f\|_\theta = \max_{t \in [0, T]} (|f(t)|e^{-\theta t}).$$

**Lemma 2.** The solution operator is continuous from  $[0, 1]$  to  $C([0, T]; \mathbb{R}^3)$ .

*Proof.* From the integral system, using the Lipschitz continuity of the nonlinearities and the Volterra property of the equations, we deduce (see the details below) for  $i = 1, 2, 3$ , the estimates of the form

$$\begin{aligned} \|S_i(\sigma) - S_i(\bar{\sigma})\|_\theta & \\ & \leq \alpha_{i1} \|S_1(\sigma) - S_1(\bar{\sigma})\|_\theta \\ & \quad + \alpha_{i2} \|S_2(\sigma) - S_2(\bar{\sigma})\|_\theta \\ & \quad + \alpha_{i3} \|S_3(\sigma) - S_3(\bar{\sigma})\|_\theta + \beta_i |\sigma - \bar{\sigma}|, \end{aligned} \tag{6}$$

with respect to a Bielecki norm  $\|\cdot\|_\theta$  on  $C[0, T]$  and any number  $\theta > 0$ . They can be expressed in the vector form

$$(I - M) \begin{bmatrix} \|S_1(\sigma) - S_1(\bar{\sigma})\|_\theta \\ \|S_2(\sigma) - S_2(\bar{\sigma})\|_\theta \\ \|S_3(\sigma) - S_3(\bar{\sigma})\|_\theta \end{bmatrix} \leq |\sigma - \bar{\sigma}| \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix},$$

where  $M$  is the matrix  $[\alpha_{ij}]_{1 \leq i, j \leq 3}$  and  $I$  is the identity matrix. Choosing  $\theta$  sufficiently large, we can make the coefficients  $\alpha_{ij}$  small enough so that the spectral radius of the matrix  $M$  is subunitary. Then the matrix  $I - M$  is invertible and its inverse has nonnegative entries. Thus we can multiply by  $(I - M)^{-1}$  keeping the inequality sign the same, and obtain

$$\begin{bmatrix} \|S_1(\sigma) - S_1(\bar{\sigma})\|_\theta \\ \|S_2(\sigma) - S_2(\bar{\sigma})\|_\theta \\ \|S_3(\sigma) - S_3(\bar{\sigma})\|_\theta \end{bmatrix} \leq |\sigma - \bar{\sigma}| (I - M)^{-1} \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix}.$$

This clearly shows the continuity of  $S_1, S_2$  and  $S_3$  with respect to  $\sigma$ .

Finally we will give details regarding the deduction of estimates (6). We will derive the estimate for  $i = 1$ , the cases where  $i = 2$  and  $i = 3$  being similar. For notational simplicity, write  $w = (x, y, z)$ , and  $\bar{w} = (\bar{x}, \bar{y}, \bar{z})$ , the solutions corresponding to  $\lambda := (\lambda_1(\sigma), \dots, \lambda_5(\sigma))$  and  $\bar{\lambda} := (\lambda_1(\bar{\sigma}), \dots, \lambda_5(\bar{\sigma}))$ , respectively. Then, clearly,  $x = S_1(\sigma)$  and  $\bar{x} = S_1(\bar{\sigma})$ . The first equation of the integral system is

$$x(t) = x_0 + \int_0^t f(w(s), \lambda_1(\sigma)) ds,$$

where

$$f(w, \lambda_1(\sigma)) = \frac{a}{1 + b(x + y + z)} \frac{x + y}{x + y + \lambda_1(\sigma)gz} x - cx.$$

A similar expression holds for  $\bar{x}$ . The simple calculation of the partial derivatives of  $f$  shows that these are bounded and, therefore,  $f$  is Lipschitz continuous in all variables. Thus, there are nonnegative constants  $a_1, \dots, a_4$  such that

$$\begin{aligned} &|f(w, \lambda_1(\sigma)) - f(\bar{w}, \lambda_1(\bar{\sigma}))| \\ &\leq a_1|x - \bar{x}| + a_2|y - \bar{y}| \\ &\quad + a_3|z - \bar{z}| + a_4|\lambda_1(\sigma) - \lambda_1(\bar{\sigma})|. \end{aligned}$$

Here we note that  $|\lambda_1(\sigma) - \lambda_1(\bar{\sigma})| = c|\sigma - \bar{\sigma}|$ , where  $c$  is the absolute value of the difference between the first components of the vectors  $\underline{\lambda}_0$  and  $\bar{\lambda}_0$ . Let  $\beta_1 = ca_4T$ . Now, starting to evaluate  $x - \bar{x}$ , we have

$$\begin{aligned} &|x(t) - \bar{x}(t)| \\ &\leq \int_0^t |f(w(s), \lambda_1(\sigma)) - f(\bar{w}(s), \lambda_1(\bar{\sigma}))| ds \\ &\leq \int_0^t a_1|x(s) - \bar{x}(s)| ds + \int_0^t a_2|y(s) - \bar{y}(s)| ds \\ &\quad + \int_0^t a_3|z(s) - \bar{z}(s)| ds + \beta_1|\sigma - \bar{\sigma}|. \end{aligned}$$

Here we make use of the Bielecki norm. Thus, for a positive number  $\theta$ , we can estimate

$$\begin{aligned} &\int_0^t a_1|x(s) - \bar{x}(s)| ds \\ &= a_1 \int_0^t |x(s) - \bar{x}(s)| e^{-\theta s} e^{\theta s} ds \\ &\leq a_1 \|x - \bar{x}\|_\theta \int_0^t e^{\theta s} ds \\ &\leq \frac{a_1}{\theta} \|x - \bar{x}\|_\theta e^{\theta t}. \end{aligned}$$

Making similar estimates for  $y$  and  $z$  and setting  $\alpha_{ij} = a_j/\theta$  ( $j = 1, 2, 3$ ), we obtain

$$\begin{aligned} &|x(t) - \bar{x}(t)| \\ &\leq (\alpha_{11} \|x - \bar{x}\|_\theta + \alpha_{12} \|y - \bar{y}\|_\theta + \alpha_{13} \|z - \bar{z}\|_\theta) e^{\theta t} \\ &\quad + \beta_1 |\sigma - \bar{\sigma}|. \end{aligned}$$

Dividing by  $e^{\theta t}$  and taking the maximum for  $t \in [0, T]$  leads to

$$\begin{aligned} \|x - \bar{x}\|_\theta &\leq \alpha_{11} \|x - \bar{x}\|_\theta + \alpha_{12} \|y - \bar{y}\|_\theta \\ &\quad + \alpha_{13} \|z - \bar{z}\|_\theta + \beta_1 |\sigma - \bar{\sigma}|, \end{aligned}$$

which is our estimate (6) for  $i = 1$ . It should be noted that the coefficients  $\alpha_{ij}$  obtained in this way can be made as small as desired by choosing  $\theta$  sufficiently large. ■

**Remark 4.** Assuming that after transplantation one has  $x \simeq 0$  on the time interval  $[0, T]$ , we may apply similarly the algorithm in order to reach alternatively the goal

$$\frac{z(T)}{y(T)} > \frac{A}{G} - 1.$$

#### 4. Conclusions

The first main objective of this work was to formulate a method of lower and upper solutions for solving control problems and an algorithm of numerical implementation. The convergence of the algorithm was proved and for its good understanding, a simple example of a control problem related to the Lotka–Volterra model was presented.

The second main objective was the control of cell evolution after bone marrow transplantation. The discussion took place around a previously introduced transplant model. The model has two attractors. The ‘good’ one corresponds to the successful transplant and the ‘bad’ one corresponds to the failed transplant. The patient’s state after transplantation is described by the  $(x, y, z)$ -coordinates representing the healthy and malignant cell populations of the patient and, respectively, of the cell population from the donor. The result of the transplant depends on the location of the point  $(x, y, z)$  in one or the other of the basins of attraction of the two attractors. The goal is that by enlarging the basin of the ‘good’ attractor, the patient’s condition immediately after the transplant, which is in the ‘bad’ basin, will be caught in the widened ‘good’ basin. This widening of the ‘good’ basin can be obtained by changing five parameters of the model that can be put in correspondence with a series of specific consolidation therapies. It is described how the method of lower and upper solutions can be used to control the transplant model.

An auxiliary objective, but extremely important for the implementation of the method, is achieved in

Appendix, through a numerical method for constructing the separation surface between the two basins of attraction.

We believe that these mathematical results together with clinical, pharmaceutical, and laboratory studies, could be of real interest in order to optimize therapeutic consolidation scenarios after transplantation, aimed at contributing to the eradication of leukemia.

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**Lorand Gabriel Parajdi** received his BSc degree in pure mathematics, his MS degree in applied mathematics, and his PhD degree in mathematics, all at Babeș–Bolyai University, Romania. In 2020 he became an assistant professor in the Department of Mathematics, Faculty of Mathematics and Computer Science, Babeș–Bolyai University. Currently, he is a postdoctoral research associate in mathematical biology at the Eberly College of Arts and Sciences, West Virginia University, USA. His fields of interest are ordinary differential equations, partial differential equations, mathematical modelling in medicine and biology, and nonlinear dynamics.

**Radu Precup** is a professor at Babeș–Bolyai University and a researcher at the Institute of Advanced Studies in Science and Technology—STAR-UBB Institute and at the Tiberiu Popoviciu Institute of Numerical Analysis of the Romanian Academy. Since 2021 he has been a corresponding member of the academy. He has authored four books and more than 190 articles. His fields of interest are nonlinear functional analysis, ordinary and partial differential equations and mathematical modeling.

**Ioan Ștefan Haplea** graduated in 2002 from the Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania, as a general practitioner. He received his MSc in medical informatics from the University of Medicine and Pharmacy, F-Cluj-Napoca, in 2003. He is currently a resident medical doctor of internal medicine. His research interests include medical informatics as well as mathematical modeling in medicine and biology.



### Appendix

#### Numerical method for constructing a separation surface between two basins of attraction

We aim to build numerically a surface  $S$  that separates the basin of attraction of the ‘good’ attractor (when the bone marrow transplant succeeds) from the basin of the ‘bad’ attractor (when the transplant fails). Let  $C$  be the curve at the intersection between the surface  $S$  and the horizontal plane at  $z = \tilde{z}$ . For numerical tractability, we approximate the surface  $S$  by a ruled surface which connects the origin of the axes with the curve  $C$ .

The surface  $S$  intersects the plane  $x = 0$  approximately along the line

$$z = \frac{\frac{A}{C} - 1}{G} y,$$

and the plane  $y = 0$  along the line

$$z = \sqrt{\frac{h}{g}} x.$$

The above two lines intersect the plane  $z = \tilde{z}$  at the points

$$M_0 = \left( 0, \frac{G}{\frac{A}{C} - 1} \tilde{z}, \tilde{z} \right), \quad M_1 = \left( \sqrt{\frac{g}{h}} \tilde{z}, 0, \tilde{z} \right),$$

respectively. We wish to compute the coordinates of  $N - 1$  points on the curve  $C$ . To this end, we perform two steps.

*Step 1.* Consider an even partition of the segment  $M_0M_1$ , i.e., a series of points

$$M_{k/N} = (x_k, y_k, \tilde{z}), \quad k = 1, \dots, N - 1,$$

where

$$y_k = \frac{\frac{G}{C} - 1}{\sqrt{\frac{g}{h}}} \left( \sqrt{\frac{g}{h}} \tilde{z} - x_k \right)$$

such that  $M_{k/N} \in M_0M_1$  and

$$|M_0M_{k/N}| = \frac{k}{N} |M_0M_1|,$$

so that the points  $M_{k/N}$  divide the segment  $M_0M_1$  into  $N$  equal parts. Equivalently, in vector notation

$$\overrightarrow{OM}_{k/N} = \overrightarrow{OM}_0 + \frac{k}{N} \overrightarrow{M_1M_0}.$$

Componentwise, we have

$$x_k = x_{M_0} + \frac{k}{N} (x_{M_1} - x_{M_0}) = \frac{k}{N} \sqrt{\frac{g}{h}} \tilde{z},$$

$$y_k = y_{M_0} + \frac{k}{N} (y_{M_1} - y_{M_0}) = \left( 1 - \frac{k}{N} \right) \frac{G}{\frac{A}{C} - 1} \tilde{z}.$$

*Step 2.* For each  $k = 1, 2, \dots, N - 1$  we compute the following: in the plane  $z = \tilde{z}$  the normal to  $M_0M_1$  at  $M_{k/N}$  and, on this normal, two series of equidistant points  $\underline{S}_i, \overline{S}_i$ , spaced at  $\varepsilon$  from each other

$$x_{\underline{S}_i} < x_{M_{k/N}}, \quad x_{\underline{S}_i} > x_{M_{k/N}},$$

$$|\underline{S}_i M_{k/N}| = i\varepsilon, \quad |\overline{S}_i M_{k/N}| = i\varepsilon, \quad i = 1, 2, \dots;$$

in other words, the points are situated on the normal to  $M_0M_1$ , on opposite sides of  $M_{k/N}$ . Vectorially

$$\overrightarrow{OS}_i = \overrightarrow{OM}_{k/N} - i\varepsilon \vec{v},$$

$$\overrightarrow{OS}_i = \overrightarrow{OM}_{k/N} + i\varepsilon \vec{v},$$

where  $\vec{v}$  is the unit vector orthogonal to  $\overrightarrow{M_1M_0}$ , that is,

$$\vec{v} = \frac{1}{\sqrt{\left(\frac{G}{\frac{A}{C} - 1} \tilde{z}\right)^2 + \left(\sqrt{\frac{g}{h}} \tilde{z}\right)^2}} \left( \frac{G}{\frac{A}{C} - 1} \tilde{z}, \sqrt{\frac{g}{h}} \tilde{z} \right).$$

Componentwise, for all points  $\underline{S}_i, \overline{S}_i$  we have

$$x_{\underline{S}_i} = x_k - i\varepsilon x_{\vec{v}}$$

$$= \frac{k}{N} \sqrt{\frac{g}{h}} \tilde{z} - i\varepsilon \frac{\frac{G}{\frac{A}{C} - 1} \tilde{z}}{\sqrt{\left(\frac{G}{\frac{A}{C} - 1} \tilde{z}\right)^2 + \left(\sqrt{\frac{g}{h}} \tilde{z}\right)^2}},$$

$$y_{\underline{S}_i} = y_k - i\varepsilon y_{\vec{v}}$$

$$= \left( 1 - \frac{k}{N} \right) \frac{G}{\frac{A}{C} - 1} \tilde{z}$$

$$- i\varepsilon \frac{\sqrt{\frac{g}{h}} \tilde{z}}{\sqrt{\left(\frac{G}{\frac{A}{C} - 1} \tilde{z}\right)^2 + \left(\sqrt{\frac{g}{h}} \tilde{z}\right)^2}}$$

and, respectively,

$$x_{\overline{S}_i} = x_k + i\varepsilon x_{\vec{v}}$$

$$= \frac{k}{N} \sqrt{\frac{g}{h}} \tilde{z} + i\varepsilon \frac{\frac{G}{\frac{A}{C} - 1} \tilde{z}}{\sqrt{\left(\frac{G}{\frac{A}{C} - 1} \tilde{z}\right)^2 + \left(\sqrt{\frac{g}{h}} \tilde{z}\right)^2}},$$

$$y_{\overline{S}_i} = y_k + i\varepsilon y_{\vec{v}}$$

$$= \left( 1 - \frac{k}{N} \right) \frac{G}{\frac{A}{C} - 1} \tilde{z}$$

$$+ i\varepsilon \frac{\sqrt{\frac{g}{h}} \tilde{z}}{\sqrt{\left(\frac{G}{\frac{A}{C} - 1} \tilde{z}\right)^2 + \left(\sqrt{\frac{g}{h}} \tilde{z}\right)^2}}.$$

To find an approximation to the surface  $S$  we have employed the following pseudocode algorithm (implemented in Matlab R2021a):

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FOR each  $k = 1, 2, \dots, N - 1$  we test whether the point  $M_{k/N}$  lies inside the *good* or the *bad* basin of attraction, by following the trajectory of the solution that starts from that point (integrating using the coordinates of the point  $M_{k/N}$  as initial conditions).

IF the trajectory leads to the *bad* attractor, we test in sequence the orbits of the points  $\underline{S}_i, i = 1, 2, \dots$ , until we reach the first point whose orbit lands on the *good* attractor. The midpoint of the segment determined by the last two tested points will belong, within an  $\varepsilon/2$  approximation, to the curve  $C$  / surface  $S$ .

IF the trajectory leads to the *good* attractor, we test in sequence the orbits of the points  $\overline{S}_i, i = 1, 2, \dots$ , until we reach the first point whose orbit lands on the *bad* attractor. The midpoint of the segment determined by the last two tested points will belong, within an  $\varepsilon/2$  approximation, to the curve  $C$  / surface  $S$ .

END\_FOR

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Every point on the curve  $C$ , as found above, is then connected with the origin. The resulting ruled surface is a rough but useful approximation of the surface  $S$ , computable in linear time with respect to  $N$  and  $1/\varepsilon$ .

Concerning the parameters for these simulations (see Figs. 1–3), the following values are taken:  $a = 0.23, b = 2.2 \times 10^{-8}, c = 0.01, A = 0.43, B = 5.5 \times 10^{-9}, C = 0.03, g = 25, G = 4, h = 20$ , where  $d = 9.99999999 \times 10^8 < 2.424242423 \times 10^9 = D$ . In all the simulations we used  $N = 10, \varepsilon = 10^8, \tilde{z} = 10^9$ .

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