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MATHEMATICAL MODELLING OF INTERACTIONS BETWEEN CANCER AND EFFECTOR CELLS

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ABSTRACT

In this paper we consider a model proposed by Allison *et al.*. We show its drawbacks and modify it in order to adjust it better to empirical data. The modified model takes into account the negative impact of cancer on effector cells. The adjustment of the solutions of both models to experimental data is analysed. We show sample parameters for which the modified model fits the empirically measured data better.

BIOLOGICAL BACKGROUND

In this paper a mathematical model of the adaptive immune response against cancer cells is discussed.

In the bone marrow, due to the interaction with the antigen, the natural killer (NK) cells are activated. NK cells are cytotoxic lymphocytes. They release cytokines and enzymes capable of destroying the antigen causing its lysis or apoptosis.

NK cells can be incubated in the laboratory with Interleukin-2, a type of cytokine. After such stimulation NK cells become lymphokine-activated killer (LAK) cells. LAK cells develop a highly cytotoxic and specific to cancer effector function. Thus they will be subsequently called effector cells. Lymphokine-activated killer cells are able to lyse primary as well as metastatic tumour cells, even those which were previously resistant to the NK cells.

The organism itself cannot effectively fight against cancer cells. However, the abilities of LAK cells indicate that immunotherapy consisting in modifying activity of the immune system could be a promising method of cancer treatment. In the future it may become an alternative or a complement for chemotherapy, radiotherapy or surgery.

ALLISON'S MODEL

Allison *et al.* [1] developed a mathematical model of the immune system response to cancer and compared the solution of the model with empirical data. They proposed the following system of equations

$$\begin{cases} \dfrac{\mathrm{d}C}{\mathrm{d}t} = k_C C - \gamma C E, \\ \dfrac{\mathrm{d}E}{\mathrm{d}t} = k_E E\left(1 - \dfrac{E}{K}\right), \end{cases} \tag{1}$$

where C denotes the number of cancer cells at the moment t, E — the number of effector cells at the moment t, k_C, k_E are the growth rate of the cancer cells and the effector cells, respectively. The

parameter γ stands for the probability that interaction between a cancer and effector cell results in destruction of the cancer cell, while K is carrying capacity for the effector cells.

Model (1) was constructed under the following assumptions: effector cells, when introduced into human body, start interacting with cancer immediately; in the absence of effector cells, growth rate of cancer cells is proportional to their number; natural death rate for the effector cells is negligible during considered time interval; cancer cells don't have impact on effector cells' activity.

System (1) can be solved explicitly. Its solutions reads

$$\begin{cases} C(t) = \dfrac{C_0\,\mathrm{e}^{k_C t}}{(1-\frac{E_0}{K}(1-\mathrm{e}^{k_E t}))^{\frac{\gamma K}{k_E}}}, \\ E(t) = \dfrac{E_0 K}{(K-E_0)\,\mathrm{e}^{-k_E t}+E_0}, \end{cases} \tag{2}$$

where $C_0 = C(0)$ and $E_0 = E(0)$.

MODIFIED MODEL

The main drawback of Allison's model is the assumption that cancer doesn't affect the dynamics of the effector cells. According to biological knowledge, tumour cells produce substances which may inhibit effector cells' activity [5]. Therefore, in the present study, we propose the following, modified system of equation, which takes into account a negative impact of cancer on the effector cells' population:

$$\begin{cases} \dfrac{\mathrm{d}C}{\mathrm{d}t} = k_C C - \gamma CE, \\ \dfrac{\mathrm{d}E}{\mathrm{d}t} = k_E E\Big(1-\dfrac{E}{K}\Big) - \beta CE, \end{cases} \tag{3}$$

where β stands for the probability that interaction between cancer and effector cell will result in deactivation of the latter. Other variables and parameters are defined as in the previous section.

Certain models concerning the impact of tumour cells on the activity of the effector cells have already been developed (e.g. Kuznetsoz, 1992; Roesch, 2014), nevertheless, to the author's knowledge, none of them took into account effector cells carrying capacity.

Unlike system (1), explicit solution to system (3) cannot be found in a general case. Nevertheless, certain properties of these solutions can be determined.

Theorem 1. *For any non-negative initial condition* (C_0, E_0) *there exists a unique, nonnegative solution to system* (3)*, that is well defined for all* $t \geq 0$*.*

Proof. The right hand side of system (3) is locally Lipchitz continuous, thus local existence and uniqueness follows directly from the Picard-Lindelöf Theorem.

The solution to (3) can be written in an implicit form

$$C(t) = C_0 \exp\Big(k_C t - \gamma \int_0^t E(s)\,\mathrm{d}s\Big), \quad \text{and} \quad E(t) = E_0 \exp\Big(k_E t - \int_0^t \Big(\frac{k_E}{K}E(s) + \beta C(s)\Big)\mathrm{d}s\Big).$$

Thus, $C(t) \geq 0$ and $E(t) \geq 0$ for non-negative initial conditions.

Now we prove that each solution to system (3) is defined for every $t > 0$. To this end, it is enough to prove that $C(t)$ and $E(t)$ are bounded on each compact interval $[0, T]$. This fact follows from bounding $C(t)$ by $C_0\,\mathrm{e}^{k_C T}$ and $E(t)$ by $E_0\,\mathrm{e}^{k_E T}$.

To conclude, for any non-negative initial condition (C_0, E_0), there exists a unique, nonnegative and well defined for each $t \geq 0$ solution to system (3). □

Stationary states and their stability

Here, we determine the stationary states of system (3) and their stability.

Theorem 2. *System* (3) *has three stationary states:*

$$A_1 = (0,0), \quad A_2 = (0,K), \quad A_3 = \left(\frac{k_E}{\beta}\left(1 - \frac{k_C}{\gamma K}\right), \frac{k_C}{\gamma}\right).$$

Proof. After equating $\frac{\mathrm{d}E}{\mathrm{d}t}$ and $\frac{\mathrm{d}C}{\mathrm{d}t}$ to 0 the result is obtained immediately. □

Note that the stationary state A_3 is in the first quadrant of the coordinate system if and only if $\frac{k_C}{\gamma K} < 1$. If $\frac{k_C}{\gamma K} = 1$ then $A_3 = A_2$. If $\frac{k_C}{\gamma K} > 1$, the first coordinate of A_3 is negative and this stationary state has no biological interpretation. Thus, we study its stability only for $\frac{k_C}{\gamma K} \leq 1$.

Theorem 3. *The following statements are true:*

(i) *Stationary state A_1 is an unstable node;*

(ii) *If $\frac{k_C}{\gamma K} < 1$ stationary state A_2 is a stable node and if $\frac{k_C}{\gamma K} > 1$ it is a saddle point.*

(iii) *If $\frac{k_C}{\gamma K} < 1$ stationary state A_2 is a saddle point.*

Proof. To check the stability of the preceding stationary states, we use the Lyapunov Linearization Theorem. The Jacobian matrix for system (3) reads

$$J(C,E) = \begin{bmatrix} k_C - \gamma E & -\gamma C \\ -\beta E & k_E - 2\frac{k_E}{K}E - \beta C \end{bmatrix}.$$

For each stationary state we compute the eigenvalues of the matrix J and use the Lyapunov Linearization Theorem to check its stability.

For the stationary state A_1 we have

$$J(A_1) = J(0,0) = \begin{bmatrix} k_C & 0 \\ 0 & k_E \end{bmatrix}.$$

The eigenvalues of $J(0,0)$ are $\lambda_1 = k_C$ and $\lambda_2 = k_E$, thus, the point $(0,0)$ is an unstable node.

For the stationary state A_2, the Jacobi matrix reads

$$J(A_2) = J(0,K) = \begin{bmatrix} k_C - \gamma K & 0 \\ -\beta K & -k_E \end{bmatrix}.$$

The eigenvalues of $J(0,K)$ are $\lambda_1 = k_C - \gamma K$ and $\lambda_2 = -k_E$, and the assertion (ii) follows.

Now, we check the stability of the stationary state A_3, assuming that $\frac{k_C}{\gamma K} < 1$. The Jacobi matrix reads

$$J(A_3) = J\left(\frac{k_E}{\beta}(1 - \frac{k_C}{\gamma K}), \frac{k_C}{\gamma}\right) = \begin{bmatrix} 0 & -\frac{\gamma k_E}{\beta} + \frac{k_E k_C}{\beta K} \\ -\frac{\beta k_C}{\gamma} & -\frac{k_E k_C}{\gamma K} \end{bmatrix},$$

and the characteristic polynomial is

$$W_{J(A_3)}(\lambda) = \lambda^2 + \lambda\frac{k_E k_C}{\gamma K} - k_C k_E + \frac{k_E k_C^2}{\gamma K}. \tag{4}$$

Polynomial (4) is a parabola with a positive coefficient of λ^2. The assumption $\frac{k_C}{\gamma K} < 1$ yields $W_{J(A_3)}(0) < 0$, which in turn implies the existence of real positive and real negative roots of the polynomial. This completes the proof. □

If $K = \frac{k_C}{\gamma}$, then $\mathrm{Re}(\lambda_1) = 0$, which means that the Lyapunov Linearization Theorem does not work for the stationary state A_2. Nevertheless, the analysis of phase portrait, presented in the next section, shows that the stationary state A_2 is unstable.

Analysis of the phase portraits

In order to show the global dynamics of the solutions, we analyse the phase portraits. It also allows us to show the instability of the point $A_2 = A_3$ (the case when the Lyapunov Linearization Theorem could not be used).

A few simple computations allow us to find four lines which are null-clines of model (3). The null-clines for the variable C are the lines $C = 0$ and $E = \frac{k_C}{\gamma}$, while for the variable E, the null-clines are the lines $E = 0$ and $E = -\frac{\beta K}{k_E}C + K$. These lines divide $\mathbb{R}^2_+$ into the following regions:

- $B_1 = \{E > \frac{k_C}{\gamma}$ and $E > -\frac{\beta K}{k_E}C + K\}$. In B_1 both C and E are decreasing functions;
- $B_2 = \{E > \frac{k_C}{\gamma}$ and $E < -\frac{\beta K}{k_E}C + K\}$. In B_2, C is decreasing and E is increasing;
- $B_3 = \{E < \frac{k_C}{\gamma}$ and $E > -\frac{\beta K}{k_E}C + K\}$. In B_3, C is increasing and E is decreasing;
- $B_4 = \{E < \frac{k_C}{\gamma}$ and $E < -\frac{\beta K}{k_E}C + K\}$. In B_4 both C and E are increasing functions.

Drawing phase portraits requires considering three cases: $\frac{k_C}{\gamma} < K$, $\frac{k_C}{\gamma} = K$, and $\frac{k_C}{\gamma} > K$.

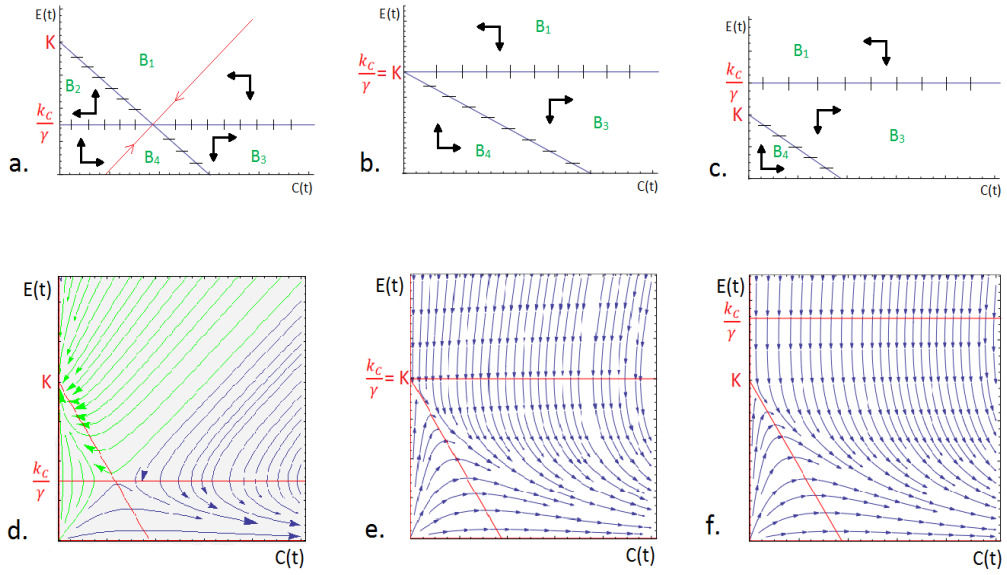

Figure 1. The sketches of the phase portraits are presented in the top row, while in the bottom one we present samples of the phase portraits. In the panels the cases $K > \frac{k_C}{\gamma}$ (the left panel), $K = \frac{k_C}{\gamma}$ (the middle panel) and $K < \frac{k_C}{\gamma}$ (the right panel) are illustrated.

Theorem 3 shows that there is no such stable stationary state, in which the number of both cancer and effector cells is positive (as we can also see in Fig. 1). We show that only two possibilities may happen over time:

(1) The number of effector cells decreases to 0, the number of tumour cells increases to ∞;
(2) The number of cancer cells decreases to 0 and the number of effector cells converges to K. At that time, human body overpowers the cancer.

Let us note that the second situation may take place only if $K > \frac{k_C}{\gamma}$. Moreover it happens only for certain initial conditions (C_0, E_0). On the sample phase portrait for $K > \frac{k_C}{\gamma}$ (Fig. 1d), the solutions which converge to the equilibrium point $(0, K)$ are marked with green. On the sketch of the phase portrait (Fig. 1a) the red line is a sketch of the stable manifold for A_3 and this manifold splits solutions converging to $(0, K)$ from those converging to infinity. For initial conditions located to the left of this curve, the solutions will always converge to the stationary state A_2. In fact, if the

trajectory is over the null-cline $E = k_c/\gamma$, the function C is decreasing and the trajectory is in the region $B_1 \cup B_2$. If the trajectory starts in B_4 left to the stable manifold of A_3, it eventually enters B_2 as E is strictly increasing and the it cannot cross the manifold. Otherwise (for initial conditions to the right of the stable manifold), the number of the effector cells will always decrease to 0. Those are the only two possibilities, since if the solution once appears in B_3 it will never quit this region (because C is increasing and E is decreasing, which follows directly from analysing the signs of the derivatives). Similarly, if the solution appears in B_2 it finally converges to $(0, K)$ (E is increasing and C is decreasing). Thus there are no oscillations around A_3.

For $K = \frac{k_C}{\gamma}$, regardless of the initial condition, the trajectory always eventually enters B_3 and the number of cancer cells converges to infinity.

To conclude, only sufficiently high initial effector cells to cancer cells ratio may help the human body win with the tumour. Otherwise, the immune system will lose with cancer.

NUMERICAL COMPARISON OF THE PRESENTED MODELS

In [1] the following values of parameters were used for the lymphokine-activated killer cells, referred to as LAK cells

$$k_C = 1.54584, \quad k_E = 1.46153, \quad K = 1340000. \tag{5}$$

For the ratio 1 : 30, Allison *et al.* [1] assumed that $\gamma = 0.000267$. Moreover, the authors published the empirically measured change in number of cancer cells for initial condition $(1000, 30000)$ (the experimental data are denoted by dots in Fig. 2).

Their results do not seem plausible. Probably Allison *et al.* made a mistake. Their graph of $C(t)$ perfectly fits the empirical data (see the left panel of Fig. 2). However, after inserting computed parameters k_C, k_E, K, γ into the solution to system (1) it turns out that the graph of $C(t)$ looks differently — it does not fit so good to the empirical data (see the right panel of Fig. 2).

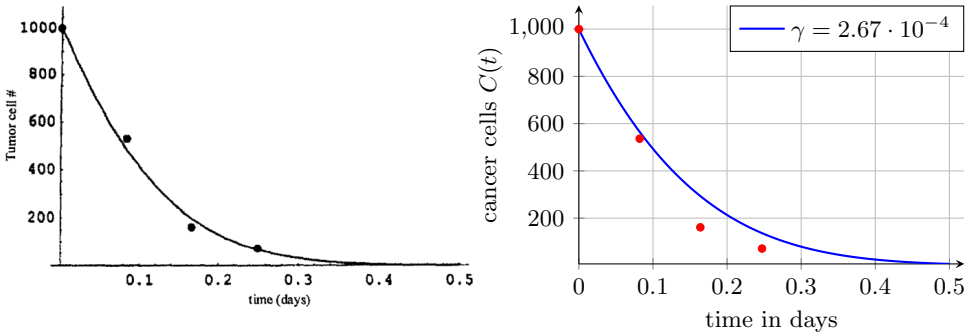

Figure 2. Graph of $C(t)$ reproduced from the article [1] (the left panel); Graph of $C(t)$ for the initial condition $(1000, 30000)$, drew by the author of the present study on the basis of the model proposed by Allison *et al.*, using given parameters (the right panel).

As we see, the graphs presented in Fig. 2 do not overlap. Probably the mistake has been made during computing the parameters of the model, most likely the parameter γ, as it is the only one that was changed in [1]. We manipulate the parameters β and γ in order to find sample values for which the modified model fits the reality better than the one proposed by Allison *et al.*

The modified model fits the empirical data better for parameters, for which the Allison's model forecasts faster decrease of the number of tumour cells than it really happens. It is due to the fact that in the modified model, the number of effector cells grows slower than in Allison's work.

To see for which β and γ the modified model fits the empirical data best, we used the Particle Swarm Optimization (PSO) method. We obtained the following results, minimizing MSE (mean square error) and the average relative MSE, respectively:

(1) $\beta = 3.59 \cdot 10^{-9}$ and $\gamma = 3.26 \cdot 10^{-4}$. MSE = 5328, average relative MSE = 3.107%;
(2) $\beta = 5.89 \cdot 10^{-4}$ and $\gamma = 3.61 \cdot 10^{-4}$. MSE = 8147, average relative MSE = 1.306%.
In the left panel of Fig. 3 the adjustment of (3) to the empirical data for the parameters given above is presented.

For the Allison's model, parameter γ that fits the empirical data best, obtained with the PSO method, while minimizing MSE and the average relative MSE respectively, is:
(1) $\gamma = 3.26 \cdot 10^{-4}$. MSE = 5328, average relative MSE = 3.115%;
(2) $\gamma = 3.49 \cdot 10^{-4}$. MSE = 7135, average relative MSE = 1.313%.
The adjustment of (1) to the empirical data for the parameters given above is presented in the right panel of Fig. 3.

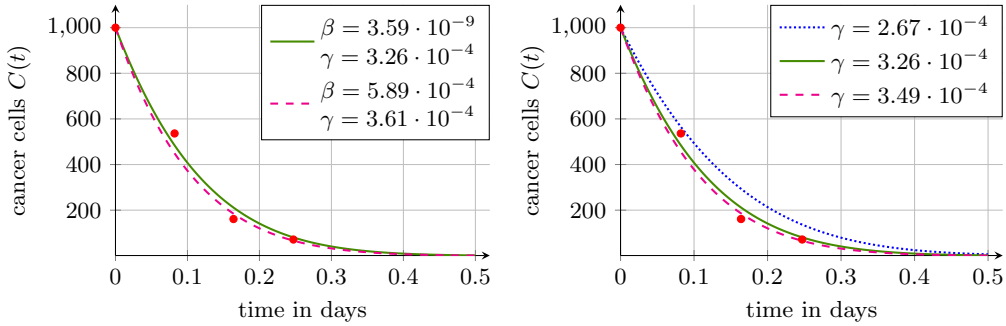

Figure 3. Solution to (3) (left panel) and to (1) (right panel) fitted to experimental data. The solid green line is a solution that minimises MSE. The dashed pink line is a solution that minimises relative MSE. The blue dotted line is a solution for $\gamma = 2.67 \cdot 10^{-4}$ (the parameter given in [1]). The rest of parameters defined by (5).

As we can see, for some parameters γ and β given above, the modified model fits the empirical data better then the model proposed by Allison *et al.* Further research is needed to ascertain the real values of β and γ for different initial conditions.

CONCLUSIONS

Depending on the values of the parameters k_C, k_E, K, γ, one of the two discussed models is better adjusted to empirically obtained data. It is essential to repeat the measurements in order to judge which model is more plausible and predicts better the change of the number of the cancer cells in time, depending on the initial condition. Further research is necessary to improve the model of the interactions between tumour and effector cells. Cancer treatments exploiting immunotherapy may significantly benefit from enhancing the discussed models.

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