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Mathematical Modeling of Prostate Cancer Dynamics and Therapy

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Abstract: This study considers a mathematical model for selecting an optimal chemotherapy-based treatment strategy for prostate cancer, with the goal of minimizing the integral of the squared deviation of the PSA tumor marker from its normal value over the entire course of treatment. The optimal strategy is obtained by solving a nonlinear programming problem using the method of local variations. It should be noted that mathematical modeling of biological processes is a complex and not always fully formalizable problem. Verifying the adequacy of such models requires the joint efforts of teams of biologists and physicians and constitutes a separate task. Undoubtedly, the main and decisive role in the fight against cancer belongs to advances in biology and medicine. On the other hand, the success of mathematical methods in many related scientific fields makes it reasonable to hope that the results of mathematical modeling of cancer dynamics, together with appropriate experimental validation, may suggest new ways to choose treatment protocols.

Keywords: Mathematical model, prostate cancer, system of nonlinear differential equations, method of local variations

1. INTRODUCTION

Prostate cancer is one of the most common diseases among men. This type of malignant neoplasm ranks second worldwide among oncological diseases, and sixth in mortality within the same group of diseases [1, 4, 8]. It should be noted that mathematical modeling of biological processes is a complex and not always fully formalizable problem. Verifying the adequacy of such models requires the joint efforts of teams of biologists and physicians and constitutes a separate task. Undoubtedly, the main and decisive role in the fight against cancer belongs to advances in biology and medicine. On the other hand, the success of mathematical methods in many related scientific fields makes it reasonable to hope that the results of mathematical modeling of cancer dynamics, together with appropriate experimental validation, may suggest new ways to choose treatment protocols.

Cancer is a complex, dynamically evolving system characterized by dysregulation of the cell cycle, leading to uncontrolled cell proliferation (division) and the ability to invade surrounding tissues. Existing treatment protocols, such as chemotherapy, face the problem of obtaining adequate information about the stage of disease progression and the toxicity of therapeutic agents. In the case of prostate cancer, there is an effective indicator that makes it possible to determine the stage of disease progression with fairly high probability. This is a blood test for the quantitative assessment of the oncological marker PSA (prostate-specific antigen).

The aim of this work is to develop a mathematical model of prostate cancer therapy based on stabilizing the PSA oncological marker within limits that ensure the patient's safe

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vital activity. To achieve this goal, a mathematical model is used that describes the complex biochemical process of PSA dynamics proposed in [3]. This process depends significantly both on the quantitative characteristics of the number of diseased and healthy tumor cells and on the degree of chemotherapeutic drug action on tumor cells.

In [5], a mathematical model of prostate cancer therapy was considered with the goal of achieving a balance between cancerous and healthy cells that ensures the patient's safe vital activity, based on Pontryagin's maximum principle. The optimal treatment protocol obtained in that work belongs to the class of maximum-dose (MD) treatment strategies, which is based on the idea that, to achieve the maximum effect, the drug should be administered in maximum doses during periods of greatest sensitivity of the dominant cancer cells, which coincides with the initial phase of rapid growth, making these cells more vulnerable to the drug. A significant drawback of such a strategy is the fact that, during the active suppression of dominant cell growth, a response occurs in the form of mutations, resulting in numerous therapy-resistant genotypes. In addition, such a strategy leads to a significant increase in the toxic burden on the patient's body.

Uniform (metronomic) therapy (UT) consists of administering the drug in relatively small doses over a long period of time and is used when the goal of therapy is long-term disease control. This strategy is less toxic and reduces the likelihood of resistant clones and angiogenesis, and is also better tolerated by patients. Moreover, this type of treatment strategy is closest to real treatment protocols, in which the drug is administered regularly at fixed intervals.

Adaptive therapy (AT) is the most modern approach, based on the principles of evolutionary dynamics. The adaptive strategy seeks long-term disease control by maintaining a balance between dominant (sensitive) and resistant cell populations.

This type of therapy is based on regular monitoring of the number of tumor cells, which is not always feasible in practice. In the case of prostate cancer, such monitoring is available in the form of PSA oncological marker measurement. All this makes it possible to consider the problem of finding uniform and adaptive treatment strategies for prostate cancer based on PSA marker monitoring.

2. PROBLEM STATEMENT

Let u(t) denote the number of healthy cells, v(t) the number of cancer cells, and h(t) the amount of the chemotherapeutic agent at time t. Next, we assume that the rate of drug delivery to the tumor is described by the following differential equation:

$$\frac{\mathrm{d}h(t)}{\mathrm{d}t} = -\gamma h + L(t) \tag{2.1}$$

Here, γ is the dissipation coefficient, and L(t) is the control, that is, the function determining the strategy for choosing drug doses that slow tumor growth. Next, we assume that the function L(t) is given in the following form:

$$L(t) = \sum_{k=1}^{n} c_k \delta(t - t_k) \tag{2.2}$$

Here c_k - the amount of the drug entering the tumor at a given moment t_k , k=1,2,..., n, $\delta(t - t_k)$ - Dirac delta-function. Thus, the choice of the time points t_k and the values c_k determines the treatment strategy and protocol. In the case of uniform (metronomic) therapy, the time points t_k are distributed uniformly over the entire treatment interval [0, T]. In the case of adaptive therapy, these time points are chosen so as to stabilize the PSA level throughout the treatment process. Due to the toxicity of the effect on healthy cells, the total amount of the drug is limited, so the following constraint is imposed on the total sum of all values c_k:

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$$\sum_{k=1}^{n} c_k \leq C_{max} \tag{2.3}$$

where C_{max} is the maximum possible dose of the drug over the entire therapy period.

The next two equations of the model define the dynamics of growth of healthy and cancer cells in the presence of the drug, as well as their competitive interactions.

$$\begin{array}{l} \frac{\mathrm{d}u(t)}{\mathrm{d}t} = r_u(h)u(t)(1-u(t)) - \varepsilon u(t)v(t) \\ \frac{\mathrm{d}v(t)}{\mathrm{d}t} = r_v(h)v(t)(1-v(t)) \end{array} \tag{2.4}$$

Here, the function $r_u(h)$ determines the growth rate of healthy cells, which depends on the amount of the drug present in the system. This dependence is given by the following equation:

$$r_u(h) = r_u^0(1 - \alpha_1 \frac{h(t)}{1+h(t)}) \tag{2.5}$$

A similar dependence for the growth rate of cancer cells is determined by the equation

$$r_v(h) = r_v^0(1 - \alpha_2 \frac{h(t)}{1+h(t)}) \tag{2.6}$$

Here $r_u^0 u$ and r_v^0 are the growth rates of healthy cells and cancer cells, respectively. α_1 and α_2 are positive constants characterizing the sensitivity of healthy cells and cancer cells to the drug, respectively, and ϵ is the coefficient of the intensity of competitive interaction between diseased and healthy cells.

We consider the Cauchy problem for equation (2.1) with the function $L(t)$ given by equation (2.2).

$$\frac{\mathrm{d}h(t)}{\mathrm{d}t} = -\gamma h + L(t), h(0) = h_0 \tag{2.7}$$

The solution to this problem has the form

$$h(t) = \sum_{k=1}^{n} c_k \chi(t - t_k) e^{-\gamma(t-t_k)} \tag{2.8}$$

In this case, Equations (2.4) admit analytical solutions:

$$u(t) = \frac{u_0 e^{\int_0^t g(\tau_1)d\tau_1}}{u_0 \int_0^t e^{\int_0^\tau g(\tau_1)d\tau_1} r_u(\tau)d\tau + 1} \tag{2.9}$$

$$v(t) = \frac{v_0 e^{\int_0^t r_v(\tau)d\tau}}{v_0(e^{\int_0^t r_v(\tau)d\tau} - 1) + 1} \tag{2.10}$$

Here $g(t) = r_u - \varepsilon v$.

The obtained analytical expressions allow efficient computation of the quantities $v(t)$ and $u(t)$ depending on the parameters of the control function $L(t)$, which determines the therapy strategy.

All subsequent experiments will be conducted over a period of 545 days using the following uncontrolled parameters: $\gamma = 0.01$, $\varepsilon = 0.006$, $\alpha_1 = 0.5$, $\alpha_2 = 0.9$, $r_u^0 = 0.1$, $r_v^0 = 0.2$, $u_0 = 0.7$, T = 60.

Consider the dynamics of healthy cells and PSA behavior in homeostasis, that is, in the absence of cancer ($v_0 = 0$) and accordingly without drug treatment:

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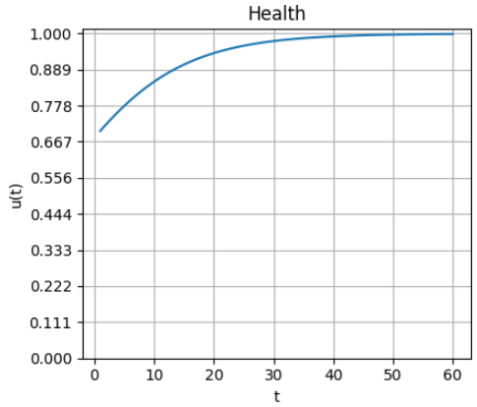

Fig. 2.1. Dynamics of healthy cells in homeostasis, $u(t)$

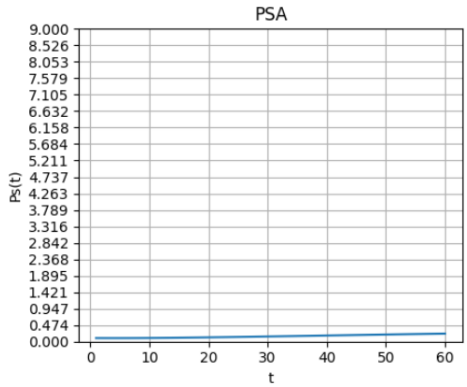

Fig. 2.2. Dynamics of PSA in homeostasis, $Ps(t)$

In this case, healthy cells grow and reach their maximum, while PSA also increases but remains within reference limits corresponding to the patient's healthy state.

Now let us examine the dynamics of healthy cells and PSA in the presence of developing cancer cells at an early stage ($v_0 = 0.5$, $P_{s0} = 5$) without drug therapy.

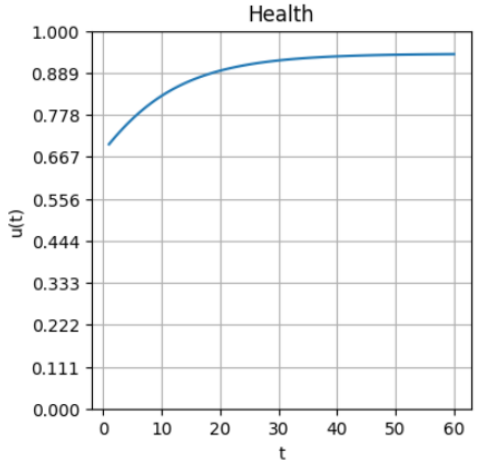

Fig. 2.3. Dynamics of healthy cells without drug in developing oncology, $u(t)$

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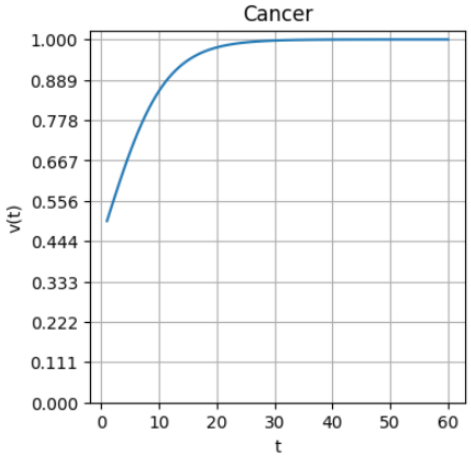

Fig. 2.4. Dynamics of cancer cells without drug, $v(t)$

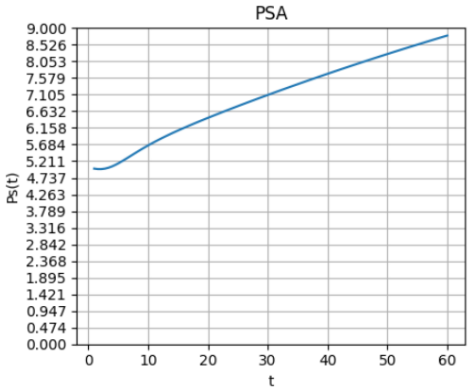

Fig. 2.5. Dynamics of PSA without drug in developing oncology, $Ps(t)$

From Figures 2.3 and 2.5, it follows that healthy cells began to decline rapidly, while cancer cells and PSA show active growth. Note that the PSA value increases and reaches 9, which is a significant exceedance of the norm and indicates serious progression of prostate disease.

Let $L(t)$ be some chosen therapy strategy. The quality functional of the chosen therapy strategy is defined as the integral value of the squared difference between the current PSA value and the normal value over the entire treatment process $0 < t < T$. The equations describing the dependence of the PSA oncological marker on the quantities $u(t)$ and $v(t)$ are given by the following system:

$$\begin{cases} \frac{\mathrm{d}R(t)}{\mathrm{d}t} = \alpha_R - \lambda_R R(t) - k_f^D R(t)D(t) + k_r^D A - k_f^T RT + k_r^T A \\ \frac{\mathrm{d}D(t)}{\mathrm{d}t} = \beta_T \frac{T(t)}{k_T + T(t)} - \lambda_D D(t) - k_f^D R(t)D(t) + k_r^T A(t) \\ \frac{\mathrm{d}T(t)}{\mathrm{d}t} = f(T_s) - \lambda_T T(t) - \beta_T \frac{T(t)}{k_T + T(t)} - k_f^T R(t)T(t) + k_r^T A_t(t) \\ \frac{\mathrm{d}A(t)}{\mathrm{d}t} = -\lambda_A A(t) + k_f^D R(t)D(t) - k_r^D A(t) \\ \frac{\mathrm{d}A_t(t)}{\mathrm{d}t} = -\lambda_{A_t} A_t(t) + k_f^T R(t)T(t) - k_r^T A_t(t) \\ \frac{\mathrm{d}P(t)}{\mathrm{d}t} = \beta_P(A(t) + A_t(t) + \phi) - \alpha_P P(t)U_{frac} - \gamma_P P(t)\frac{(v(t)\eta_v)^2}{k_P + (v(t)\eta_v)^2} - \lambda_P P(t) \\ \frac{\mathrm{d}Ps(t)}{\mathrm{d}t} = \alpha_P P(t)U_{frac} + \gamma_P P(t)\frac{(v(t)\eta_v)^2}{k_P + v(t)\eta_v} - \lambda_{Ps} Ps(t) \end{cases} \tag{2.11}$$

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$$T_s = a_{T_s} t^2 + b_{T_s} t + c_{T_s} \tag{2.12}$$

$$f(T_s) = \frac{a_T T_s}{b_T + T_s} + C_T \tag{2.13}$$

$$P_{vol} = \frac{a_V t^{d_V}}{b_V^{d_V} + t^{d_V}} \tag{2.14}$$

$$U_{frac} = V_C \frac{u(t)\eta_u}{P_{vol}} \tag{2.15}$$

- R - concentration of free androgen receptors (nM);
- D - concentration of dihydrotestosterone (nM);
- T - concentration of testosterone (nM);
- A - concentration of androgen receptors activated by dihydrotestosterone (nM);
- A_t - concentration of androgen receptors activated by testosterone (nM);
- P - concentration of PSA in tissues (nM);
- P_s - concentration of PSA in blood serum (nM);
- T_s - concentration of serum testosterone (nM);
- $f(T_s)$ - rate of testosterone delivery to prostate tissues;
- P_{vol} - volume of the prostate gland (mm^3);
- U_{frac} - fraction of prostate tissue occupied by cells;
- η_u - maximum number of healthy cells in the prostate;
- η_v - maximum number of cancer cells in the body.

This system and its parameters are described in more detail in [3]

3. APPLICATION OF DISCRETE OPTIMIZATION METHODS FOR CONSTRUCTING UNIFORM AND ADAPTIVE TREATMENT STRATEGIES

For the application of discrete optimization methods, the Python programming language [6] and its environment (the SciPy package [7] and others) will be used.

The optimization problem statement is formulated as follows:

$$\begin{cases} F(t) = \int_0^T (P_{s_0} - P_s(t))^2 dt \to min \\ t \in [0, T] \\ u(t) \geq U_{min} \\ v(t) \leq V_{max} \\ \sum_{k=1}^n c_k \leq C_{max} \\ u(t), v(t), U_{min}, V_{max} \in [0, 1] \\ P_{s_0}, P_s(t), C_{max} \in \mathbb{R}_+ \end{cases} \tag{3.16}$$

Consider the case of metronomic therapy strategy. In this case, with a fixed total amount of the drug satisfying constraint (2.3), it is necessary to choose the distribution of values c_k, $k = 1, 2, \ldots, m$, which determine the intensities of drug effects, such that the functional

$$F(t) = \int_0^T (P_{s_0} - P_s(t))^2 dt \tag{3.17}$$

reaches its minimum value under the condition of uniform distribution of drug administration times at intervals $\Delta t = T/m$. Here and below, P_{s_0} is the normal level of the PSA oncological marker, and $P_s(t)$ is the current PSA level.

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In this case c_i = 110, m = 30, Δt = 2. For the maximum drug dose C_{max}, we will take the number 3300 (the sum of all c_i).

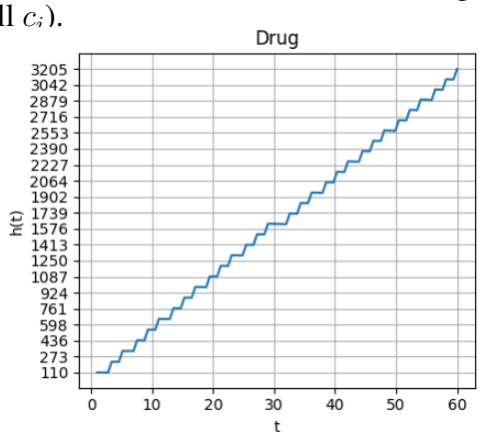

Fig. 3.6. Drug dynamics under metronomic therapy, $h(t)$

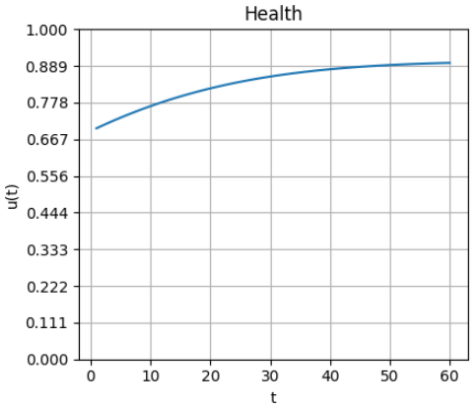

Fig. 3.7. Healthy cells dynamics under metronomic therapy, $u(t)$

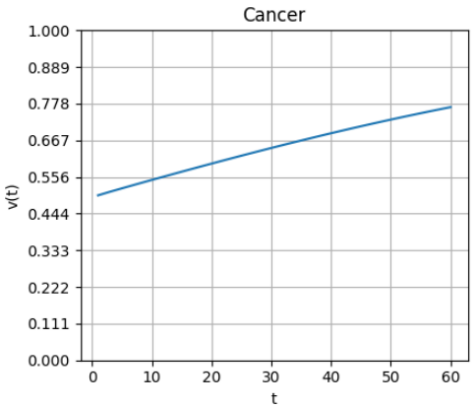

Fig. 3.8. Cancer cells dynamics under metronomic therapy, $v(t)$

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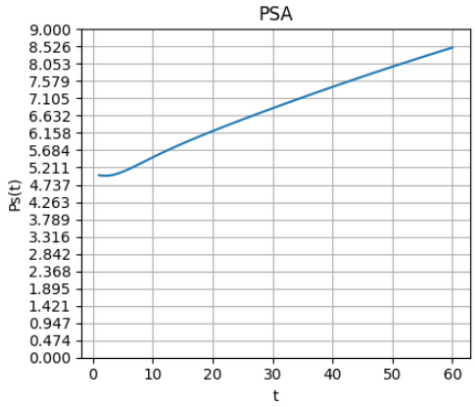

Fig. 3.9. PSA dynamics under metronomic therapy, $Ps(t)$

Based on Figures 3.6–3.9, we see that metronomic therapy slowed the growth of cancer cells and also reduced the PSA level. These results show good reduction of PSA value from 9 to 8.5.

Consider the case of adaptive therapy strategy. This case differs from the previous one in that instead of uniform distribution of drug administration times at equal intervals, the time intervals are chosen together with the values c_k, $k = 1, 2, \ldots, m$, using the method of local variations [2], which determine the drug effect intensity that delivers the minimum to functional (3.17).

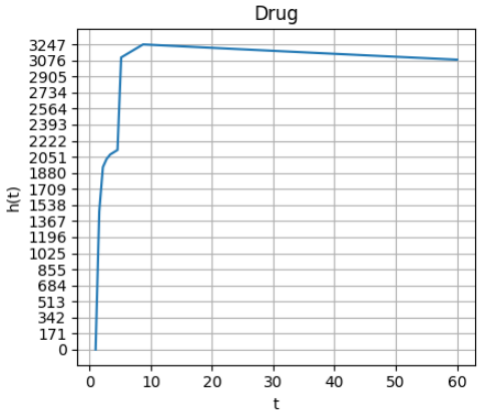

Fig. 3.10. Drug dynamics under adaptive therapy by local variations method, $h(t)$

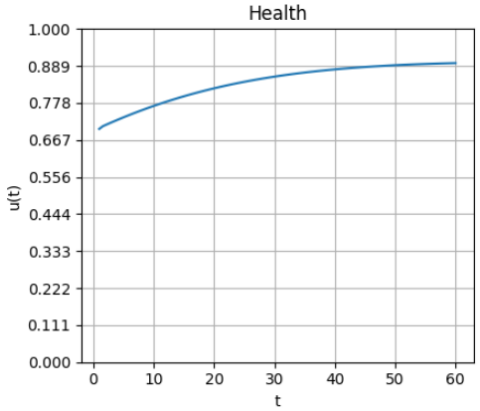

Fig. 3.11. Healthy cells dynamics under adaptive therapy by local variations method, $u(t)$

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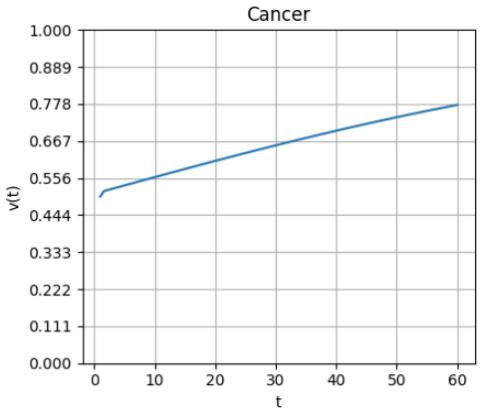

Fig. 3.12. Cancer cells dynamics under adaptive therapy by local variations method, $v(t)$

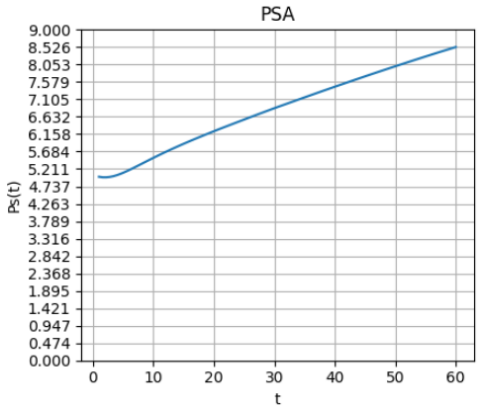

Fig. 3.13. PSA dynamics under adaptive therapy by local variations method, $Ps(t)$

Treatment protocol obtained: t_k = [1.59, 2.19, 2.78, 3.38, 3.97, 4.57, 5.17, 5.76, 6.36, 6.95, 7.55, 8.15, 8.74], c_k = [1468.46, 473.44, 87.5, 50, 25, 25, 986.1, 25, 25, 25, 25, 25, 2].

Adaptive therapy represents a prostate cancer treatment protocol that differs from the previous one and proposes administering maximum drug doses on the first two days and on the fifth day, while giving small doses (c_k ¡ 100) uniformly during the remaining first eight days.

This strategy reduced the PSA level to 8.5, thereby achieving the same result as metronomic therapy. However, the achieved PSA level is still quite high.

4. CONCLUSION

Thus, analytical solutions were obtained for the drug, healthy cells, and cancer cells equations. Numerical solutions for the blood serum PSA marker were constructed. Graphs of the dynamics of healthy cells, cancer cells, drug, and PSA marker in homeostasis and prostate cancer development without treatment were presented. Optimal metronomic and adaptive therapy strategies were obtained, and corresponding graphical solutions were constructed.

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