Modeling cancer evolution: evolutionary escape under immune system control

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Abstract. It can be expected that adequate immune response should be able to annihilate cancer at a very early stage of its appearance. However, in some cases cancer is able to persist avoiding immune response. One can conject that cancer is able to avoid immune response control due to a succession of mutations leading to the development of immune-resistant cells. In order to illustrate this possibility, in this paper we present a $2^n$--dimensional mathematical model that describes interaction of \textit{n} subtypes of tumor cells with corresponding genotype-specific immune response. The model postulates that there is a probability for tumor cells of each of \textit{n} subtype to produce offsprings of other types. Each of the subtypes activates the genotype-specific immune response with a possibility of suppressing cancer cells of other genotypes (the cross-immunity). Numerical simulations show that if cancer cells are able to mutate comparatively fast and if immune response is not strong enough, then, despite immune system pressure, cancer is able to persist.

1. Introduction
Cancer is a general term used to define a group of diseases, which can affect almost any part of the body and is characterized by the uncontrolled growth of abnormal cells that have lost the ability to regulate their lifespan. This phenomenon allows these cells to expand beyond their usual boundaries and invade surrounding tissues and organs, creating new cancer sources, known as malignant tumors. The process in which tumor
cells spread throughout the body is called metastasis and is the main reason of cancer patients death [9].

A remarkable feature of cancer is its ability to persist in the presence of immune response, which could be expected to be able to annihilate the abnormal cells at a very early stage of their appearance. It can be conjectured that the ability of cancer to persist under pressure of immune response is related to the ability of cancer cells to mutate. Cancer cells mutate in the cells division process. Eventually, after a succession of mutations, an immune-resistant subtype of cancer cells arises with a specific genotype that allows it and its descendants to evade immune system attacks [2,10].

In order to illustrate this possibility, in this paper we construct a mathematical model of cancer growth under immune response pressure. In order to develop this mathematical model, we start with the following simple model of cancer-immune response interaction:

\[
\frac{dx}{dt} = ax(1- bx) - cxy, \\
\frac{dy}{dt} = gx(x + s) - \mu y - pxy.
\]

In this model, equation (1) describes the growth of tumor cells population of size \(x(t)\) while equation (2) models the dynamics of immune effector cells population of size \(y(t)\).

The model postulates that in the absence of immune response tumor grows according to the logistic law with a per capita reproduction rate \(a\) and the maximum carrying capacity \(1/b\). The immune effector cells, of population size \(y(t)\), kill cancer cells with a bilinear rate \(cxy\), where \(c\) is the immune response strength. The activation of immune response is induced by cancer cells with rate \(gx/(x + s)\). The effector cells are removed (are dying) with rate \(\mu y\). They also can be inactivated due to the interaction with tumor cells (due to exhaustion) with bilinear rate \(pxy\).

Models of this type are fairly common in the literature on cancer dynamics; for example, see [1,3,7,8] and bibliography therein.

The dynamics of system (1), (2) is located in the nonnegative quadrant of a 2-dimensional real space,

\[\mathbb{R}_2^+ = \{x \geq 0, y \geq 0\} .\]

It is evident that system (1), (2) has a tumor-free equilibrium state at \((x^*, y^*) = (0, 0)\), and it is easy to verify by the Lyapunov’s Indirect Method (see [13]) that this equilibrium is always unstable (a saddle point). This implies that for this particular model the total eradication of the tumor cells population for finite time is impossible. (It can be only considered for infinite time \(t \rightarrow \infty\).) This is due to the fact that the phase space of the system is continuous with respect to variables \(x(t)\) and \(y(t)\). However, in the real life there always is a positive finite critical value below which tumor survival is impossible. One can consider this value to be one cancer cell. Then, if there is a solution such that \(x(t)\) goes below this threshold (e.g., \(x = 1\)), one should conclude the complete elimination of the cancer cells population.

2. Mathematical model of cancer evolution

To develop a model of cancer evolution, we make the following assumptions:
(i) The simultaneous existence of multiple cancer cell genotypes in a given population. In this paper we assume the existence of $n$ genotypes.

(ii) A probability for a cancer cell to mutate in the process of cell division. A mutation of a type into another occurs with a certain pre-defined probability. The probability of a mutation of type $i$ to type $j$ (where $i = 1, ..., n$) is lower the larger the difference $|i - j|$ is.

(iii) Specificity of immune response to a cancer cell type. This means that cancer cells of type $i$ activate immune effector cells of type $i$ as well. The activation of immune effector cells is triggered by the presence of cancer cells of a specific genotype and is represented in equation (2) by a term of the Michaelis-Menten kinetics type.

(iv) Cross-immunity. This implies, that immune response activated by cancer cells of type $i$ can also kill cancer cells of other types, but with a lower efficacy. The efficacy of immune effector cells of type $i$ towards cancer cells of type $j$ is inversely proportional to the absolute value $|i - j|$.

Incorporating this set of assumptions into model (1), (2) we obtain the following mathematical model of cancer evolution:

$$
\frac{dx_i}{dt} = \left[ a_i \left( 1 - \sum_{j=1}^{n} A_{ij} \right) x_i + \sum_{j=1}^{n} a_j A_{ji} x_j \right] \left( 1 - \sum_{j=1}^{n} b_j x_j \right) - \left( \sum_{j=1}^{n} c_{ji} x_j \right) x_i, \quad (3)
$$

$$
\frac{dy_i}{dt} = g_i \frac{x_i}{x_i + s_i} - \mu_i y_i - \left( \sum_{j=1}^{n} p_{ji} x_j \right) y_i, \quad (4)
$$

where $i = 1, ..., n$.

In this model, the probabilities of mutations of cancer cells are defined by the $n \times n$ diagonally dominant matrix $A$, where $A_{ij}$ is the probability that a cell of type $i$ produces a cell of type $j$. The string diagonal dominance of the matrix ensures that the probability of mutation of type $i$ cancer cell into a cell of type $j$ decreases as the distance $|i - j|$ increases. The cross-immunity, that is the ability of immune cells activated by type $i$ cancer cells to kill cancer cells of other types, is defined by the $n \times n$ matrix $c_{ji}$, which is also diagonal dominant. For simplicity, we assume that the matrix of inactivation rate of the immune effector cells due to their interaction with tumor cells (exhaustion) $p_{ji}$ is proportional to matrix $c_{ji}$.

For the sake of simplicity, in this paper we assume that cancer cells and immune effector cells of all $n$ types are identical in the sense that values of parameters $a, A, b, c, g, p, s$ and $\mu$ are the same for all types. (That is, values of matrix $A_{ij}, c_{ij}$ and $p_{ij}$ depend on the distance $|i - j|$ only and are independent of $i$.)

The dynamics of model (3)–(4) is located in the nonnegative orthant

$$
\mathbb{R}_{\geq 0}^{2n} = \{ x_i \geq 0, y_i \geq 0 \}.
$$

The authors would like to note that for this model the values of the diagonal elements $A_{ii}$ are irrelevant as they are mutually annihilated in equation (3), and are defined for consistency only. One can choose any nonnegative values for these elements, as long as condition $\sum_{j=1}^{n} A_{ij} \leq 1$ is fulfilled.
3. Localization of compact invariant sets

The Localization of Compact Invariant Sets (LCIS) is a method used to analyze global dynamics of mathematical models defined by ordinary differential equations. This approach was recently successfully applied to tumor growth models [6, 11, 12]. Please see [4, 5] and Appendix A for a short introduction of this method.

Let us suppose that \( \sum_{j=1}^{n} A_{ij} \leq 1 \) holds. Then, by the structure of equation (3), one can see that the minimum and the maximum values of each of \( n \) tumor subpopulations in the absence of immune response are given by the set

\[
K(h_{i+n}) = \left\{ 0 \leq x_i \leq x_{i \text{ max}} = \frac{1}{b_i} \right\},
\]

where \( i = 1, \ldots, n \). We can use this result to estimate ultimate bounds for solutions to equations (4) by applying the LCIS method. Let us now take \( n \) localizing functions

\[
h_i = y_i, \quad i = 1, \ldots, n.
\]

Computing its Lie derivative, we find the set

\[
S(h_i) = \left\{ \mu_i y_i = \frac{g_i x_i}{x_i + s_i} - \left( \sum_{j=1}^{n} p_{ji} x_j \right) y_i \right\},
\]

such that \( S(h_i) = \{ L_i h_i = 0 \} \) holds. The Iterative Theorem yields

\[
S(h_i) \cap K(h_{i+n}) \cap \mathbb{R}_{\geq 0}^{2n} \subset \left\{ y_i \leq \frac{g_i x_{i \text{ max}}}{\mu_i (x_{i \text{ max}} + s_i)} \right\},
\]

and, therefore, we come to localization set

\[
K(h_i) = \left\{ 0 \leq y_i \leq \frac{g_i}{\mu_i (1 + b_i s_i)} \right\}, \quad i = 1, \ldots, n.
\]

We just proved the following proposition:

**Proposition.** All compact invariant sets of system (3), (4) are located inside polytope

\[
K_{BPID} = K(h_i) \cap K(h_{i+n}),
\]

where

\[
K(h_{i+n}) = \left\{ 0 \leq x_i \leq x_{i \text{ max}} = \frac{1}{b_i} \right\},
\]

\[
K(h_i) = \left\{ 0 \leq y_i \leq y_{i \text{ max}} = \frac{g_i}{\mu_i (1 + b_i s_i)} \right\},
\]

and \( i = 1, \ldots, n \).

Proposition implies that for all \( t > 0 \) all solution to system (3), (4) initiated in the nonnegative orthant remain in this orthant and are bounded. That is, the model is well-defined.
4. Numerical simulations
In order to illustrate the idea that mutations and evolution of cancer cells can be accountable for the persistence of cancer despite immune response pressure, we run simulations for system (3), (4) for \( n = 20 \). Descriptions and values of the model parameters used in these numerical simulations are summarized in Table 1. Please note that the values in Table 1 ensure annihilation of cancer by immune response when there is no possibility of mutation (that is, when all \( A_{ij} \equiv 0 \)).

| Parameter | Description | Value and units |
|-----------|-------------|----------------|
| \( a \)   | Cancer cells proliferation rate | \( 4.31 \times 10^{-1} \, \text{day}^{-1} \) |
| \( A \)   | Probability of production a cancer cell of type \( j \) by a cell of type \( i \) | \( - - \) |
| \( b \)   | \( b^{-1} \) is tumor carrying capacity | \( 1.02 \times 10^{-14} \, \text{cells}^{-1} \) |
| \( c \)   | Killing rate of cancer cells by immune effector cells | \( 3.41 \times 10^{-10} \, (\text{cell} \times \text{day})^{-1} \) |
| \( g \)   | Minimal rate of immune cells activation by cancer cells | \( 1.2 \times 10^4 \, \text{cell} \times \text{day}^{-1} \) |
| \( s \)   | \( g/s \) is maximal rate of immune cells activation by cancer cells | 1 \, \text{cell} |
| \( \mu \) | Death rate of immune cells | \( 5 \times 10^{-4} \, \text{day}^{-1} \) |
| \( p \)   | Effector cells inactivation rate due to exhaustion | \( 2 \times 10^{-11} \, (\text{cell} \times \text{day})^{-1} \) |

Table 1. Descriptions, values and units of model parameters.

Figure 1 shows the dynamics of 20 cancer cell subtypes and Figure 2 shows the corresponding cancer-specific immune responses. It can be seen in these Figures that, after a short low-level outbreak of a newly-emerging cancer cell type, specific immune response is activated and eliminates this particular type. However, the activation of genotype-specific immune response requires some time, and during this period, however short it is, new subtypes of cancer cell appear due to mutations. Thus, while immune response is able to control each of the cancer cell subtypes, due to ability to mutate cancer still persists in a host. Figure 3 shows the dynamics of total tumor burden \( \sum_{i=1}^{n} x_i(t) \): it can be seen that after a short transition period the tumor size remains constant.

5. Conclusions
Model (3), (4) demonstrates, that, due to its ability to mutate and evolve, cancer is able to persist within a host even when each cancer subtype is eventually annihilated by the immune response. Our simulations show that while each time the immune system controls a tumor subtype, another subtype emerges, and that the total tumor cell levels remain above the threshold of clinical detectability, see [7]. One can expect that, through a process of these continuous mutations, a certain genotype will eventually appear that
Figure 1. Dynamics of 20 subtypes of cancer cells under a sufficiently strong immune response.

Figure 2. Cancer-specific immune response. Please note that in this figure the time required by a response to settle down to zero level is comparatively large. This reflects the fact that memory cells are present long after disappearance of a pathogen or a cancer cell subtype that activated them.

Figure 3. The dynamics of the total tumor burden $\sum_{i=1}^{n} x_i(t)$. 
will be able to successfully resist immune control, prevail over other types and grow to the maximum carrying capacity. Then this genotype will be able to induce the angiogenesis process which could lead to the metastasis of tumor cells with all characteristics needed to evade host’s immune response.

In these simulations we assumed $n = 20$. Of course, in real life the number of cancer genotypes is higher by several orders of magnitude. However, $n = 20$ is sufficient to illustrate the idea of cancer persistence due to evolutionary scape. Furthermore, for illustrative purpose and to stress the idea that cancer can persists under immune response pressure even without increasing its Darwinian fitness, we assume that all cancer genotypes have the same properties. Of course, in real life situation mutations lead to an increasing diversity of phenotypical traits. Due to natural selection driven by immune response, this diversity leads to increasing Darwinian fitness of cancer cells. In this particular case, the increasing Darwinian fitness means increasing resistance to immune response, till eventually immune-resistant genotype appears.

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Appendix A. Localization of compact invariant sets method
The Localization of Compact Invariant Sets method is used to determine a domain in the state space where all compact invariant sets are located. As examples of compact invariant sets, one may recall equilibrium points, periodic orbits, homoclinic and heteroclinic orbits, invariant tori and chaotic attractors. The relevance of this analysis is due to the fact that it is useful to study the long-time dynamics of a system.

Let us consider an autonomous nonlinear system of the form:

$$\dot{x} = f(x),$$

(A.1)

where $f$ is a $C^\infty$-differentiable vector function and $x \in \mathbb{R}^n$ is the state vector. Let $h(x) : \mathbb{R}^n \to \mathbb{R}$ be a $C^\infty$-differentiable function, by $h|_B$ we denote the restriction of $h$ on a set $B \subset \mathbb{R}^n$. The function $h$ used in this statement is called localizing function, and we assume that $h$ is not a first integral of (A.1). By $S(h)$ we denote the set $$\{x \in \mathbb{R}^n \mid L_f h(x) = 0\},$$ where $L_f h(x) = (\partial h/\partial x) f(x)$ represents the Lie derivative of (A.1). Let us define $h_{\text{inf}} := \inf\{h(x) \mid x \in S(h)\}$ and $h_{\text{sup}} := \sup\{h(x) \mid x \in S(h)\}$. Then the general theorem concerning the localization of all compact invariant sets of a dynamical system establishes the following

**Theorem A.1.** See [4, 5]. Each compact invariant set $\Gamma$ of (A.1) is contained in the localization set $K(h) = \{h_{\text{inf}} \leq h(x) \leq h_{\text{sup}}\}$.

If we consider the location of all compact invariant sets inside domain $U \subset \mathbb{R}^n$, we have set $K(h) \cap U$, with $K(h)$ defined by Theorem A.1. It is evident that if all compact
invariant sets are located in the sets $Q_1$ and $Q_2$, with $Q_1, Q_2 \subset \mathbb{R}^n$, then they are located in the set $Q_1 \cap Q_2$ as well.

Suppose that we are interested in the localization of all compact invariant sets located in some subset $Q$ of the state space $\mathbb{R}^n$. We formulate the following Proposition:

**Proposition A.2.** (See [4, 5].) If $Q \cap S(h) = \emptyset$, then the system (A.1) has no compact invariant sets located in $Q$.

A refinement of the localization set $K(h)$ is realized with help of the Iterative Theorem stated as follows:

**Theorem A.3.** (See [4, 5].) Let $h_m(x), m = 0, 1, 2, \ldots$ be a sequence of $C^\infty$-differentiable functions. Sets

$$K_0 = K(h_0), \quad K_m = K_{m-1} \cap K_{m-1,m}, \quad m > 0,$$

with

$$K_{m-1,m} = \{x : h_{m,inf} \leq h_m(x) \leq h_{m,sup}\},$$

$$h_{m,sup} = \sup_{S(h_m) \cap K_{m-1}} h_m(x),$$

$$h_{m,inf} = \inf_{S(h_m) \cap K_{m-1}} h_m(x),$$

contain any compact invariant set of the system (A.1) and

$$K_0 \supseteq K_1 \supseteq \ldots \supseteq K_m \supseteq \ldots .$$

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