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cancer evolution

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A CONTINUOUS PHENOTYPE SPACE MODEL OF CANCER EVOLUTION

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ABSTRACT. It was suggested that the ability of cancer to avoid immune response pressure (that should be expected to be capable to annihilate cancer at its early stage) can be attributed to the ability of the cancer cells to evolve. The goal of this notice is to illustrate this possibility by the means of mathematical modelling. In this notice, we construct a simple mechanistic model of cancer evolution, which is based upon a classical model of cancer-immune response interaction. Numerical simulations confirm the hypothesis that if cancer mutates fast enough and if immune response is not sufficiently strong, then cancer is able to avoid immune response pressure by evolution.

1. INTRODUCTION

The very general term "cancer" usually refer a set of diseases caused by an atypical growth of a certain kind of cells. This cells are typically replicate considerably faster than normal cells do, and are able to mutate quickly. Such high mutability enables cancer cells under some circumstances to mislead the immune system and avoid immune response pressure (that normally should be expected to be able to clean the cancer up).

The objective of this notice is to explore the possibility of cancer evolutionary escape off the immune response pressure. With this objective in mind, we construct a simple model of cancer evolution, which is based on well-known models of cancer-immune response interaction [3, 5, 10]. To develop a model of cancer evolution we are using an approach that was developed in [1, 2, 8]. In these papers that were dealing with within-host viral evolution, simultaneous existence of a multitude of pathogen genotypes was postulates, and these multiple genotype was arranged into a continuous variant space. In this space distance between variants can be defined in some way, and, hence, random mutations can be modelled. In [1, 2, 8] random mutations were modelled by diffusion in the continuous variant space. However, taking into consideration the particularities of the model, in this notice we find that it would be more appropriate to use an integral operator to model the mutations. Applying this general approach to model in [3, 5, 10], we derive a PDE model of cancer evolution. We perform a non-dimensionalization of this model, and, finally, we numerically integrate the differential equations of the model for given initial conditions. Numerical simulations confirm the hypothesis

that the ability of cancer to evolve can be responsible for its persistence under immune response pressure.

2. Model

To derive a model of cancer evolution, we use a simple classical model that describes the interaction between cancer cells and immune response (see [3, 5, 10]):

$$
(1) \qquad \frac{dx}{dt} = ax\left(1 - \frac{x}{k}\right) - \beta xy,
$$

$$
(2) \qquad \frac{dy}{dt} = c\frac{x}{\gamma + x}(1 + ey) - my - b\beta xy.
$$

In this model, $x(t)$ and $y(t)$ are concentrations of cancer cells and immune response cells, respectively, at time t. The other parameters of the model are positive constants. This model postulates a logistic growth of cancer cells, with per capita reproduction rate a and carrying capacity k. The term βxy accounts for killing of the cancer cells by immune effector cells, and hence parameter β is the efficiency of the immune response against this type of cancer cells. The term $c\frac{x(t)}{\gamma + x(t)}(1 + ey(t))$ represents proliferation of the immune response cells. Specifically, factor $\frac{x(t)}{\gamma + x(t)}$ accounts for the activation of immune response by cancer cells. For low levels of $x(t)$, the activation of the immune response system is proportional to $x(t)$. As $x(t)$ grows, the rate of activation grows asymptotically to a certain constant level. Apart from the activation of immune response, term $c\frac{x(t)}{\gamma + x(t)}(1 + ey(t))$ also takes account of the proliferation of immune response cells by cloning. Term my represents the natural death of the immune effector cells; thus, $1/m$ is an average life time of the immune cells. Term $b\beta xy$ takes into account the death of immune cells by exhaustion. This implies that an immune cell can kill only a limited number of cancer cells, and then, after a certain number of killings, the cell gets exhausted and dies by apoptosis.

In order to construct a model of evolution on the basis of this model, we assume the existence of multiple variants of cancer cells and postulate that these are distributed in a continuous variant space. In this notice we assume that the variant space is one-dimensional and is parameterized by a parameter s. Similarly, immune response cells, which emerge in response to a specific variant of cancer cells, are also represented by their density in the same continuous space of variants. We denote by $x(t, s)$ the density distribution of cancer cells by variants s at time t, and, likewise, by $y(t, s)$ the density distribution of the immune response cells by variants s at time t.

We assume that a cancer cell produces new cells in the process of cell division. In this process, the majority of the daughter cells are of the same variant. However, with some probability, due to mutations a cell is also able to produce

daughter cells of other variants. Although this process is probabilistic, we are using a deterministic model, as ultimately we are only interested in evolution of cancer cells.

Let us denote by $a(s)$ the per capita reproduction rate of variant s and by $\xi(r, s)$ the probability that a variant s produces a cell of variant r. As above, k is the carrying capacity. Then, the simplest generalization of the logistic growth is the following growth rate of the variant s at time t:

$$(3) \qquad \left(1 - \frac{\int_0^\infty x(t, r)dr}{k}\right) \int_0^\infty a(r)\xi(s, r)x(t, r)dr.$$

Here the value of $\int_0^\infty a(r)\xi(s, r)x(t, r)dr$ is the sum of all mutations over all possible variants into variant s. The kernel $\xi(s, r)$ satisfies the equalities

$$\int_0^\infty \xi(s, r)ds = \int_0^\infty \xi(s, r)dr = 1.$$

In this notice, we use a gaussian distribution with center r and small variance to model $\xi(s, r)$. However, other kernels are also possible. Furthermore, while the reproduction rate is defined in (3) as a function $a(s)$, further in this paper we will set $a(s) = a = const$, as there is no real-life evidence that the reproduction rate significantly changes with variant.

Factor $\left(1 - \frac{\int_0^\infty x(t, r)dr}{k}\right)$ models the limitation of the growth due to the limited carrying capacity of the tumor. This term implies that all variants consume the same amount of resources. Here $\int_0^\infty x(t, r)dr$ is the total amount of cancer cells at time t.

We assume that a cancer variant actives variant-specific immune response cells, and hence the immune cells activated in this process are labeled with the same s as the cancer cells that activate these particular cells. However, at the same time we assume that immune response cells can with some probability kill cancer cells of variants different from the one that activated them. That is, we take into consideration the so-called cross-immunity. Let us denote by $\beta(s)$ the efficacy of the immune response cells of variant s against the cancer variant s. We define $\eta(s, r)$ as the relative efficacy of the immune response cells of variant s when killing cancer cells of variant r. Then, the simplest generalization of the bilinear term βxy in (1) is

$$(4) \qquad x(t, s) \cdot \int_0^\infty \beta(r)\eta(r, s)y(t, r)dr.$$

Please note that in this case $\eta(r, s)$ is not a probability distribution function (that is, it is not a kernel), but a function that satisfies $\eta(s, s) = 1$ whereas $\eta(r, s) < 1$ holds for all $r \neq s$. To model this function, we use an unnormalized gaussian function $\eta(r, s) = e^{(r-s)^2/(2\sigma^2)}$. The value σ can be viewed as a typical width of the function, which is assumed small and decreasing as $|r - s|$ grows.

Using equations (3) and (4) we can derive a differential equation for cancer cells growth as following:

$$(5) \qquad \frac{\partial x(t,s)}{\partial t} = \left(1 - \frac{\int_0^\infty x(t,r)dr}{k}\right) \int_0^\infty a(r)\xi(s,r)x(t,r)dr -$$
$$- \int_0^\infty \beta(r)\eta(r,s)y(t,r)x(t,s)dr.$$

In order to make the system consistent we have now to define an equation for $y(t,s)$. To derive this equation, we are going to consider activation, reproduction, natural death and the exhaustion of immune cells. As in model (2), we model the growth of immune cells of variant s at time t by term

$$(6) \qquad c\frac{x(t,s)}{\gamma + x(t,s)}(1 + ey(t,s)).$$

For the death of the immune cells, we consider both natural death, with rate $my(t,s)$, and death due to exhaustion, which in this case is represented by term

$$(7) \qquad b\int_0^\infty \beta\eta(s,r)x(t,r)y(t,s)dr.$$

That is, this term implies that killing rate of an immune effector cell of type s is, on average, $\int_0^\infty \beta\eta(s,r)x(t,r)dr$ cancer cells. Please note that for a given variant s, this term summarizes all the cancer cells that get killed by this particular immune cell variant, whereas in equation (5), in contrast, we summarize, for a given cancer variant s, all the immune cells that kill cancer cells of this variant. Finally, we assume here that immune effector cells of all variants kill an average of $1/b$ cancer cells before get exhausted, which is the reason why the factor b appears in the equation. With these assumptions, using equations (6) and (7), we finally come to equation

$$(8) \quad \frac{\partial y(t,s)}{\partial t} = c\frac{x(t,s)}{\gamma + x(t,s)}(1 + ey(t,s)) - my(t,s) - b\int_0^\infty \beta\eta(s,r)x(t,r)y(t,s)dr$$

It may be noteworthy that a discrete variant space model equivalent to this model is reported in [9].

3. Non-dimensionalization of the equations

Let us define a set of non-dimensional variables $\bar{x}$, $\bar{y}$, $\bar{t}$ and $\bar{s}$, and a set of constants (scales) X, Y, T and S, such that

$$(9) \qquad t = \bar{t}T \implies \bar{t} = \frac{t}{T},$$

$$(10) \qquad s = \bar{s}S \implies \bar{s} = \frac{s}{S},$$

$$(11) \qquad x(t,s) = \bar{x}(\bar{t},\bar{s})X \implies \bar{x}(\bar{t},\bar{s}) = \frac{x(t,s)}{X},$$

(12) $$y(t,s) = \bar{y}(\bar{t},\bar{s})Y \implies \bar{y}(\bar{t},\bar{s}) = \frac{y(t,s)}{Y}.$$

As constant S does not appear explicitly in any of the equations (and hence, in fact, variable s is non-dimensional), we set $S = 1$. Then, after substitution of (9–12) in (5, 8), the equations of our model are

$$\frac{X}{T}\frac{\partial \bar{x}}{\partial \bar{t}} = \left(1 - \frac{X\int_0^\infty \bar{x}d\bar{r}}{k}\right)\int_0^\infty aX\xi(\bar{s},\bar{r})\bar{x}(\bar{t},\bar{r})d\bar{r} - \bar{x}XY\int_0^\infty \beta(\bar{r})\eta(\bar{r},\bar{s})\bar{y}(\bar{t},\bar{r})d\bar{r},$$

$$\frac{Y}{T}\frac{\partial \bar{y}}{\partial \bar{t}} = c\frac{X\bar{x}}{\gamma + X\bar{x}}(1 + eY\bar{y}) - mY\bar{y} - bXY\bar{y}\int_0^\infty \beta(\bar{r})\eta(\bar{s},\bar{r})\bar{x}(\bar{t},\bar{r})d\bar{r}.$$

After algebraic simplification, the equations become

(13)
$$\frac{\partial \bar{x}}{\partial \bar{t}} = \left(1 - \frac{X\int_0^\infty \bar{x}d\bar{r}}{k}\right)aT\int_0^\infty \xi(\bar{s},\bar{r})\bar{x}(\bar{t},\bar{r})d\bar{r} - \bar{x}TY\int_0^\infty \beta(\bar{r})\eta(\bar{r},\bar{s})\bar{y}(\bar{t},\bar{r})d\bar{r},$$

(14)
$$\frac{\partial \bar{y}}{\partial \bar{t}} = c\frac{T}{Y}\frac{X\bar{x}}{\gamma + X\bar{x}}(1 + eY\bar{y}) - mT\bar{y} - bXT\bar{y}\int_0^\infty \beta(\bar{r})\eta(\bar{s},\bar{r})\bar{x}(\bar{t},\bar{r})d\bar{r}.$$

We assume that

(15) $$X = k, \qquad T = \frac{1}{a}, \qquad Y = cT = \frac{c}{a}$$

and define non-dimensional parameters

(16) $$\bar{\beta} = \frac{\beta c}{a^2}, \qquad \bar{m} = \frac{m}{a}, \qquad \bar{\gamma} = \frac{\gamma}{k}, \qquad \bar{e} = e\frac{c}{a}, \qquad \bar{b} = b\frac{k}{ac}.$$

Substituting (15) and (16) into system (13,14), and omitting the bars for convenience of notation, we obtain non-dimensional system

(17)
$$\frac{\partial x(t,s)}{\partial t} = \left(1 - \int_0^\infty x(t,r)dr\right)\int_0^\infty \xi(s,r)x(t,r)dr - \beta x(t,s)\int_0^\infty \eta(r,s)y(t,r)dr,$$

(18)
$$\frac{\partial y(t,s)}{\partial t} = \frac{x(t,s)}{\gamma + x(t,s)}(1 + ey(t,s)) - my(t,s) - b\beta y(t,s)\int_0^\infty \eta(s,r)x(t,r)dr.$$

4. Numerical simulations

To carry out a numerical simulations, we have to define function $\beta(s)$. We assume, in order to compare our results with the results in [9], that function $\beta(s)$ is constant, $\beta(s) = \beta$. Furthermore, to integrate the differential equations one also needs to define initial and boundary conditions. The initial condition that we use is fairly simple: we assume that initially there are 100 cancer cells of a single variant and no cells of other variants. Specifically, we assume that there are 100

cells at point $s = 0.5$, and that at all other points the cancer cell concentration is equal to zero.

We carried out numerical simulations of the model using parameters from [5] and [10]. The values of parameters are summorized in Table 1. The parameters σ_{mut} and σ_{immu} are the variance of the gaussian distributions that model mutation rate $\xi(s, r)$ and the width of cross-immunity $\eta(s, r)$.

TABLE 1. Values of the parameters used in simulations (from [5], [10]).

Meaning	Notation	Value	Units
Cancer cells proliferation rate	a	$4.3 \cdot 10^{-3}$	day^{-1}
Carrying capacity of the tumor	k	10^{14}	cells
Immune cells natural death rate	m	0.0412	day^{-1}
Immune cells killing rate	β	$3.4 \cdot 10^{-10}$	day^{-1}·cells^{-1}
Steepness coefficient of the immune cell recruitment curve	γ	$2 \cdot 10^{7}$	cells
Maximum immune cell activation rate by tumor cells	c	$1.2 \cdot 10^{4}$	cells·day^{-1}
Immune cells proliferation rate	e	$5 \cdot 10^{-4}$	cells^{-1}
$\frac{1}{b}$ is an average number of killing before an immune cell is exhausted	b	0.1	–
Standard deviation of the mutation probability distribution	σ_{mut}	0.02	–
Width of relative efficacy function	σ_{immu}	0.04	–

In the non-dimensional model (17,18), the values of parameters change as described in Section 3. In particular, in these equation $x(t, s)$ represents a fraction of the maximal size of the tumor, k, which is, in our simulation, of 10^{14} cells. Similarly, the value of $y(t, s)$ represents a fraction of the maximal immune response, $\frac{c}{a} \approx 2.8 \cdot 10^{6}$ immune cells. Time values are a fraction of approximately 232 days. The values of the parameters in the non-dimensional model are given in Table 2.

TABLE 2. Values of the parameters in non-dimensional model (17,18).

Parameter	$\bar{m}$	$\bar{\gamma}$	$\bar{\beta}$	$\bar{e}$	$\bar{b}$	σ_{mut}	σ_{immu}
Value	9,58	$2 \cdot 10^{-7}$	0.22	$1.4 \cdot 10^{3}$	$3.58 \cdot 10^{3}$	0.02	0.04

The results of numerical simulation are shown in Figures 1 and 2. Please note that, although our computations have been run from $t = 0$, the concentration of cancer cells for $t < 0.03$ is so low, compared to the levels reached later, that it cannot be seen in the figures. Therefore we have plotted the solution for $t > 0.03$. These Figures clearly demonstrate the formation of two symmetric pulse-type travelling waves of evolution going into opposite directions. Two traveling waves, rather than a single wave, form in these simulations because the fitness (which for this model is $\beta(s)$) of all cancer variants was assumed to be the same, and, hence, both directions of the variant space are equivalent. These simulations demonstrate that the model can be used for cancer evolution simulations and confirm that evolution enables cancer to avoid the immune response pressure.
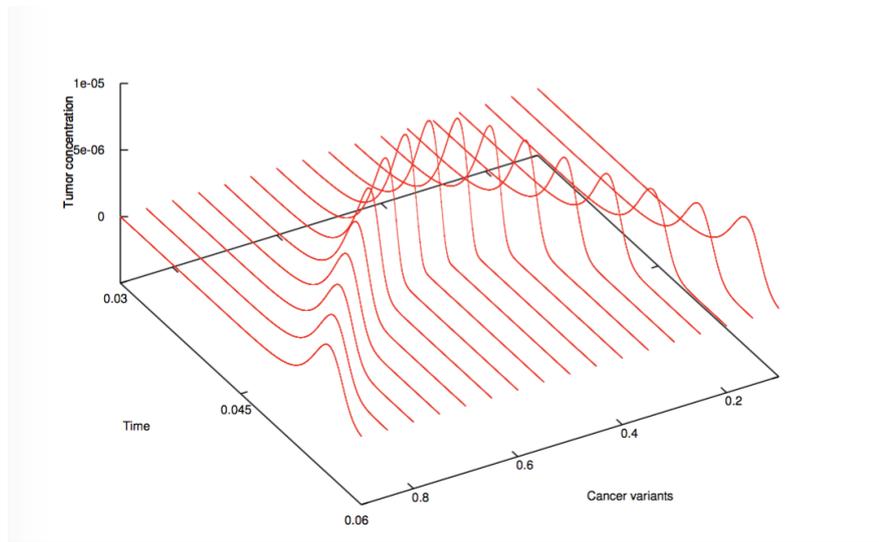

FIGURE 1. Formation of two symmetric pulse-type traveling waves of evolution going in opposite directions from the initial variant at $s = 0.5$.

Acknowledgments

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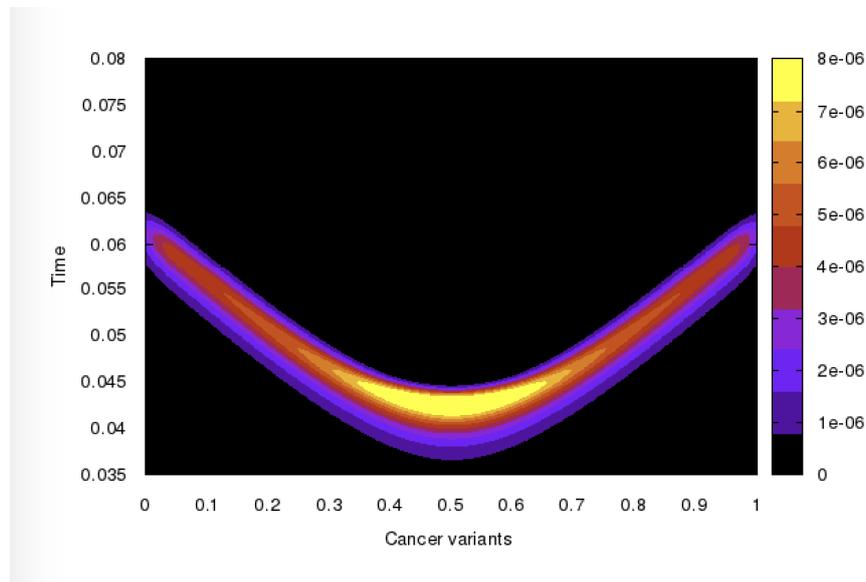
FIGURE 2. The formation and propagation of two traveling wave of evolution, going in opposite directions in the variant space from the initial variant at $s = 0.5$. In this picture, the concentration of cancer cells is represented by color; see legend on the right-hand side of the plot.

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