A Discrete Variant Space Model of Cancer Evolution

Andrei Korobeinikov and Stefano Pedarra

Abstract In this paper, we suggest a discrete variant space model of cancer evolution. The model is reasonably simple, deterministic, and is formulated as a system of ordinary differential equations. The model is based on the concept of "multi-strain modeling" (or quasi-species), which is successfully applied in modeling of the infectious disease dynamics and viral dynamics. The model constructed in this paper is mechanistic; that is, it is based upon a set of explicitly stated assumptions and hypothesis ("the first principles"). This implies that model's parameters, as well as results obtained, can be immediately interpreted, and that a further model development, e.g., incorporation into the model factors such as anticancer therapies, immune response, etc., is a reasonably straightforward procedure. To illustrate this model applicability, results of numerical simulations, as well as their biological interpretations, are provided.

1 Introduction

The term "cancer" refers to a group of diseases, which can affect almost any tissue and organ and are characterized by the uncontrolled growth of abnormal cells, which cell cycle is much faster than that of the normal cells. Cancer appears as a result of a series of mutations of normal cells, which occur during the DNA replication process or as a result of a somatic mutation. Cancer cells are usually characterized by their genome instability, and as a consequence of this, by extremely high levels

A. Korobeinikov is supported by Ministerio de Economía y Competitividad of Spain via grant MTM2015-71509-C2-1-R.

A. Korobeinikov (✉)
Centre de Recerca Matemàtica, Campus de Bellaterra, Edifici C, 08193 Barcelona, Spain
e-mail: akorobeinikov@crm.cat

Departament de Matemàtiques, Universitat Autònoma de Barcelona, Barcelona, Spain

S. Pedarra
Dipartimento di Matematica "Tullio Levi-Civita", Università degli Studi di Padova, Padova, Italy
e-mail: stefano.pedarra@studenti.unipd.it

A. Korobeinikov et al. (eds.), *Extended Abstracts Spring 2018*,
Trends in Mathematics 11, https://doi.org/10.1007/978-3-030-25261-8_4

of mutability and evolvability. The genome instability, as well as the mutability and evolvability of cancer, is one of the cancer hallmarks [3–5]. As a result of this very high mutability, a typical tumor is composed of a very large number of cancer genotypes. Moreover, the mutability, evolvability, and the resulting genetic diversity of cancer make its treatment very difficult.

The mentioned genome instability, high mutability, and evolvability of cancer makes its study from the point of view of evolutionary biology essential. Accordingly, there is a growing interest and a certain progress in mathematical modeling of cancer evolution. Usually, a mathematical model of cancer evolution utilizes the idea of quasi-species (or multi-strain modeling) and is formulated in the form of a system of ordinary differential equations, partial differential equations, or integrodifferential equations (see, e.g., [9–11, 14, 15], and bibliography therein; the same conceptual ideas were also developed and applied for mathematical modeling of viral evolution [1, 2, 6–8, 13]). In this paper, we use these ideas to construct a reasonably simple mechanistic model of cancer evolution on the basis of the model of cancer and normal cells competition.

2 Model

In order to model cancer evolution, let us assume that there is a system composed of the normal cells and cancer cells of n different genotypes, where $n \to \infty$ or is a very large number. Let us denote the size of cell population of the ith genotype at time t by $C_i(t)$ and the size of the normal cells population by $C_0(t)$. We assume that (i) all the cells reproduce and die; (ii) there are limited resources, which limit populations growth through inhibiting the reproduction and accelerating the death; (iii) cells of the different genotypes have to compete for these limited resources; (iv) in the process of mitosis, with some probability p_{ij}, a cell of the ith genotype can produce a mutant daughter cell of the jth genotype, which, subsequently, goes to the jth population; and (v) as a result of somatic mutation, with probability $q_{i,j}$ a cell of the ith genotype can move to the jth genotype.

We start at the Lotka–Volterra model of competing populations which is a usual basis for cancer modeling [12]:

$$\dot{C}_i(t) = r_i C_i \left(1 - \frac{1}{K} \sum_{j=0}^{n} b_{ij} C_j\right), \tag{1}$$

where $i = 0, 1, 2, \ldots, n$. In these equations, $r = (r_i)_{i=0}^{n}$ represents the vector of the growth rates, the elements of matrix $B = (b_{ij})_{i,j=0}^{n}$ represent the relative competitive capabilities of the genotypes and K is the carrying capacity of the system. To introduce into this model, a possibility of mutations that occur during DNA replication, it is necessary to separate the birth and the death rates, as these mutations occur in the process cell reproduction. For these two processes, we have

$$\text{birth rate of the } i\text{-th population} = a_i C_i \left(1 - \frac{h_i}{K} \sum_{k=0}^{n} b_{ik} C_k\right), \tag{2}$$

$$\text{death rate of the } i\text{-th population} = -d_i C_i \left(1 + \frac{g_i}{K} \sum_{j=0}^{n} b_{ik} C_k\right). \tag{3}$$

Here, a_i and d_i are the per capita birth and death rates of the ith genotype cells, and h_i and g_i are weights that fine-tune the relative impacts of the lack of resources and competition on the proliferation and death rates, respectively. These parameters are related to r_i by the equalities $r_i = a_i - d_i$ and $r_i = a_i h_i + d_i g_i$.

Then, using an approach suggested in [9], we can introduce a possibility of mutation into the model modifying the birth term (2). Then the growth of the ith genotype population is represented by the following equation:

$$\dot{C}_i = \sum_{j=0}^{n} \left(p_{ji} a_j C_j \left(1 - \frac{h_j}{K} \sum_{k=0}^{n} b_{jk} C_k\right)\right) - d_i C_i \left(1 + \frac{g_i}{K} \sum_{k=0}^{n} b_{ik} C_k\right) + \sum_{j=0}^{n} q_{ji} C_j - \sum_{j=0}^{n} q_{ij} C_i \,. \tag{4}$$

Here, the diffusion-like term $\sum_{j=0}^{n} q_{ji} C_j - \sum_{j=0}^{n} q_{ij} C_i$ represents the somatic mutations. All the parameters of this model are positive real numbers, except for the weights h_i and g_i and the elements of probability matrices $P = (p_{ij})$ and $Q = (q_{ij})$, which can be zero.

This discrete variant space model is formulated as a system of ODEs. An equivalent continuous variant space model is formulated in [11].

To non-dimensionalize the system (4), we introduce nondimensional variables $x_i(\tau)$ and τ as the following:

$$x_i = b_{ii} C_i / K \,, \qquad \tau = T t \,, \qquad T = p_{00} a_0 h_0 + d_0 g_0. \tag{5}$$

Please note that d_0 and p_{00} are always positive, whereas h_0 and g_0 cannot be equal to 0 simultaneously and, hence, T is always positive. Substituting these variables into the system (4) and separating the linear and the nonlinear parts of the equations, we rewrite the system in the following form:

$$\frac{dx_i}{d\tau} = \sum_{j=0}^{n} u_{ij} x_j - \sum_{j=0}^{n} \sum_{k=0}^{n} v_{ij} f_{jk} x_j x_k \,, \quad i = 0, \ldots, n \,. \tag{6}$$

Here,

$$u_{ij} = \begin{cases} \frac{(p_{jj} a_j + q_{jj} - d_j - \sum_{k=0}^{n} q_{jk}) e_{ij}}{T} & \text{if } j = i \,, \\ \frac{(p_{ji} a_j + q_{ji}) e_{ij}}{T} & \text{if } j \neq i \,, \end{cases} \qquad v_{ij} = \begin{cases} \frac{(p_{jj} a_j h_j + d_j g_j) e_{ij}}{T} & \text{if } j = i \,, \\ \frac{p_{ji} a_j h_j e_{ij}}{T} & \text{if } j \neq i \,, \end{cases}$$

and $f_{ij} = b_{ij} / b_{jj}$ and $e_{ij} = b_{ii} / b_{jj}$.

3 Simulations

To illustrate model behavior, we run numerical simulations. In these simulations, we assume that $h_i = 0$ for all $i = 0, \ldots, n$. (That is, a shortage of the resources does not affect the reproduction; it is equivalent to an assumption that a decrease of new births is attributed to an increment of deaths.) Furthermore, we assume that $Q = (q_{ij}) = 0$ for all $i, j = 0, \ldots, n$. (That is, we disregards somatic mutations.) We assume that a cell of the ith genotype can produce a daughter cell only of ith, $(i-1)$th, or $(i+1)$th genotypes with probabilities given by matrix P:

$$P = \begin{bmatrix} 0.9 & 0.1 & 0 & \cdots & \cdots & 0 \\ 0.1 & 0.8 & 0.1 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & 0 & 0.1 & 0.8 & 0.1 \\ 0 & \cdots & \cdots & 0 & 0.1 & 0.9 \end{bmatrix}.$$

In the simulations, the environment carrying capacity $K = 10^5$ cells, and time t is measured in days. Values of the other parameters, as well as, the initial conditions used in the three simulations are summarized the following table:

Parameter	Simulation # 1	Simulation # 2	Simulation # 3
n	50	50	200
a_i	2	10	$4 - 2e^{-i}$
d_i	0.2	0.2	$0.2 - 0.1e^{-i}$
g_i	9	51	19
b_{ij}	$2 - i/n$	$1 + i/n$	$2 - i/n$
$C_i(0)$	$(K-1, 1, 0, \ldots, 0)$	$(K-1, 1, 0, \ldots, 0)$	$(K-1, 1, 0, \ldots, 0)$

Results of the simulations are depicted in Figs. 1, 2, and 3, respectively. In simulation #1, we used $b_{ij} = 2 - i/n$ for all j. This implies that the Darwinian fitness of the genotypes grows as i increases. The initial conditions in the simulation #1 implies that initially, there was present only one mutant cell of the first mutant genotype. The formation of a traveling wave moving in the direction of increasing i is clearly seen in Fig. 1. This implies that in this simulation an average fitness of the tumor population steadily increases.

Please note that in Fig. 1, the populations of genotypes $i = 47$ to 50 remain approximately constant after $t \approx 120$ days: for this simulation, we consider a system of 50 genotypes and, hence, in this simulation, the Darwinian fitness of the 50th genotype is maximal. This enables this genotype, as well as close genotypes 47th to 49th, to eventually prevail in the system. Of course, in a real-life system, the number of possible mutant genotypes n is significantly higher, and, hence, no such steady prevalence of a particular mutant genotypes can be observed.

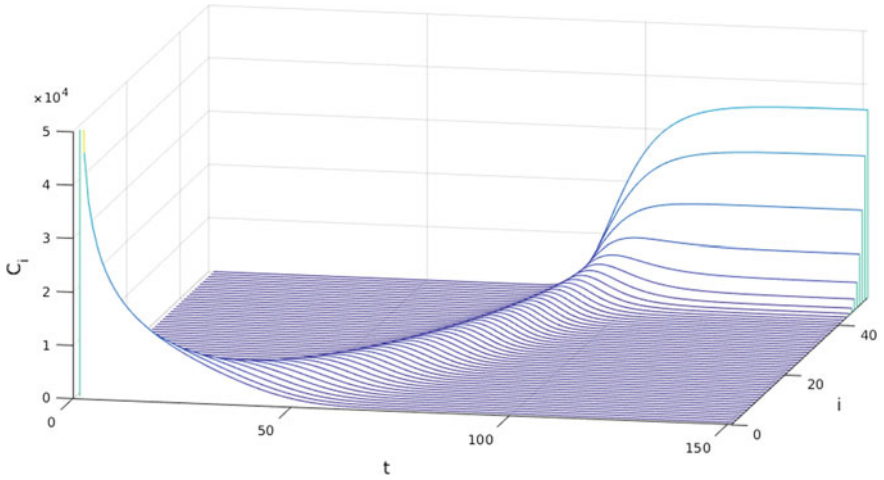

Fig. 1 Simulation #1: variation of the genotype abundance in time

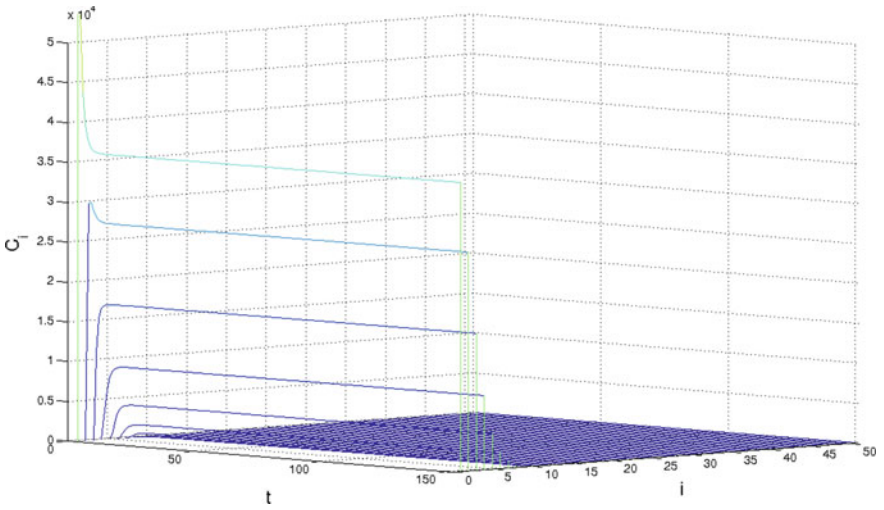

Fig. 2 Simulation #2: variation of the genotype abundance in time

Figure 2 shows the results of simulation #2. For this simulation, in contrast to simulation #1, we take $b_{ij} = 1 + i/n$. This implies that the Darwinian fitness decreases as i grows. The simulation confirms an intuitive expectation that in such a case, for whatever large levels of mutation probabilities, the mutations are unable to fix in the system and the mutant cells will be eventually removed from the tissue.

In the simulation #3, we consider the impact of the proliferation rates on the evolution. It is a well-known fact that cancer cells proliferate faster than the healthy cells and that the proliferation rates depend, above all, on the degree of differentiation.

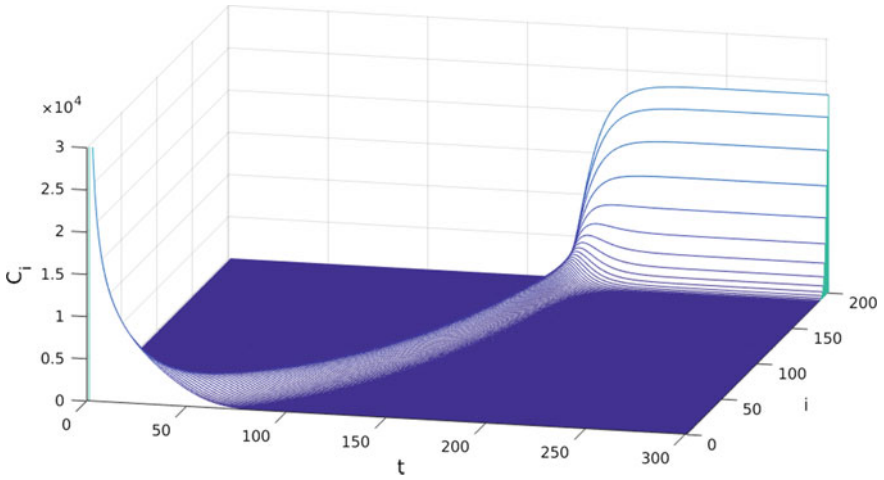

Fig. 3 Simulation #3: variation of the genotype abundance in time

Accordingly, in the simulation #3, we used $a_i = 4 - 2e^{-i}$ and $d_i = 0.2 - 0.1e^{-i}$, in combination with the same b_{ij} as in simulation #1. Figure 3 shows the results of simulation #3. As one can expect, in this case, a traveling wave of evolution is forming as well. However, it moves faster than in the simulation #1, where the proliferation and death rates were constant. Moreover, it is easy to see that in this case the speed of the traveling wave notably decreases as i grows (and as a_i and d_i grow).

It is hardly surprising that the system behavior in the simulations #1 and #3 is very similar: the only difference is the higher speed of the traveling wave in simulation #3. In both these simulations, the mean genotype number grows converging to the last genotype that has the highest level of the Darwinian fitness. The variance of the genotype distribution in the population initially grows until it reaches, at a certain time t^*, its maximum value, and then it slowly decreases. Such a behavior is intriguing and counterintuitive.

The analysis of the simulation results suggests that the comparative values of the competition factors b_{ij} mostly determine the system behavior and that changes of these values can change the system qualitative behavior.

References

1. A.A. Archibasov, A. Korobeinikov, V.A. Sobolev, Asymptotic expansions of solutions for a singularly perturbed model of viral evolution. Comput. Math. Math. Phys. **55**(2), 240–250 (2015)
2. A.A. Archibasov, A. Korobeinikov, V.A. Sobolev, Passage to the limits in a singularly perturbed partial integro-differential system. Differ. Equ. **52**(9), 1115–1122 (2016)

3. Y.A. Fouad, C. Aanei, Revisiting the hallmarks of cancer. Am. J. Cancer Res. **7**(5), 1016–1036 (2017)
4. D. Hanahan, R.A. Weinberg, The hallmarks of cancer. Cell **100**(1), 57–70 (2000)
5. D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation. Cell **144**(5), 646–674 (2011)
6. A. Korobeinikov, Immune response and within-host viral evolution: immune response can accelerate evolution. J. Theor. Biol. **456**, 74–83 (2018)
7. A. Korobeinikov, A. Archibasov, V. Sobolev, Order reduction for an RNA virus evolution model. Math. Biosci. Eng. **12**(5), 1007–1016 (2015)
8. A. Korobeinikov, A. Archibasov, V. Sobolev, Multi-scale problem in the model of RNA virus evolution. J. Phys. Conf. Ser. **727**, 012007 (2016)
9. A. Korobeinikov, K.E. Starkov, P.A. Valle, Modeling cancer evolution. J. Phys. Conf. Ser. **811**, 012004 (2017)
10. D. Masip, A. Korobeinikov, A continuous phenotype space model of cancer evolution. J. Phys. Conf. Ser. **811**, 012005 (2017)
11. D. Moreno-Martos, A. Korobeinikov, A mathematical model of cancer evolution. Trends Math. Res. Perspect. CRM Barcelona **11**, Summer 2018, Birkhäuser, Basel (2018)
12. J.D. Murray, *Mathematical Biology I, An Introduction*, 3rd edn. (Springer, New York, 2002)
13. S. Pagliarini, A. Korobeinikov, A mathematical model of marine bacteriophage evolution. R. Soc. Open Sci. **5**, 171661 (2018)
14. J. Sardanyés, R. Martínez, C. Simó, R.V. Solé, Abrupt transitions to tumor extinction: a phenotypic quasispecies model. J. Math. Biol. **74**, 1589–1609 (2017)
15. R.V. Solé, S. Valverde, C. Rodríguez-Caso, J. Sardanyés, Can a minimal replicating construct be identified as the embodiment of cancer? Bioessays **36**, 503–512 (2014)