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Modeling of breast cancer through evolutionary game theory

Ke'Yona Barton, Corbin Smith, Jan Rychtář and Tsvetanka Sendova

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We present a simple mathematical model of the development and progression of breast cancer based on evolutionary game theory. Four types of cellular populations are considered: stromal (native) cells, macrophages, benign tumor cells, and motile (malignant) tumor cells. Despite the relative simplicity of the model, it provides a way to explore the interactions between the various cell types and suggests potential approaches to managing and treating cancer.

1. Introduction

The third most common cancer in the world is breast cancer, succeeding lung and stomach cancer [Ford et al. 1998]. In women worldwide it is the leading cancer and there are more than 10^6 new cases each year. There are many genes associated with an increased probability of a person developing breast cancer, more commonly known amongst which are the BRCA1 and BRCA2 genes [Ford et al. 1998; Slamon et al. 1987].

There has been a substantial amount of research which makes use of mathematical models based on evolutionary game theory (EGT) and attempts to gain insight into the principal mechanisms that govern the development of cancer; see for example [Basanta et al. 2012; Orlando et al. 2012; Bach et al. 2001; Tomlinson and Bodmer 1997]. EGT, introduced in the 1970s by John Maynard Smith, was first used to analyze contests between rival species, competing for an important resource (e.g., food, territory, etc.). If one takes the view of tumor and stromal (native) cells as species, the same type of mathematical techniques, previously used in an ecological context, can be applied to study the progression of cancer. In recent years this approach has been applied to study various aspects of cancer. For example, [Basanta et al. 2012] uses a three cell species model to investigate prostate cancer tumor-stroma interaction; [Bach et al. 2001] and [Liu and Liu 2012] develop respectively two and three species models to study the synergistic effects of

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interactions between stromal cells and tumor cells, which often result in malignancy. Gatenby and Vincent [2003] conducted a study on tumor cells and used game theory to improve an existing linear model. In other studies, Mansury et al. [2006] and Basanta et al. [2008] employed game theory to model tumor growth in the brain.

Our proposed game-theoretical model of breast cancer builds on the model of [Liu and Liu 2012]. As in that paper, our model incorporates the growth-factor secreting stromal cells (native cells), motile tumor cells and proliferative cells (benign tumor cells). However, our model also incorporates macrophages, which play an important role in the development of breast cancer [Qian and Pollard 2012; Lamagna et al. 2006; Qian et al. 2009; Chen et al. 2011]. Macrophages have been shown to have a complex interaction with tumor cells and act in a dual role — in the beginning stages of cancer, they act as a defense mechanism against cancer by attacking tumor cells; however, they also produce growth factor, which in later stages can actually promote tumor growth [Lamagna et al. 2006; Chen et al. 2011].

Macrophages are large blood cells, produced as a result of the differentiation of monocytes. Monocytes travel through the blood stream and are produced in bone marrow. Once monocytes leave the blood stream, they turn into macrophages. These cells travel the body ingesting and destroying bacteria, cleaning up cellular debris, other harmful particles, dead cells and microbes [Børresen-Dale 2003]. Macrophages play an important role in the development of tumor cells. They ingest and destroy the cells. After they ingest the tumor cells, they use some of the materials in the cell for survival. They produce a growth factor that the macrophages and the tumor cells both benefit from [Mansury et al. 2006].

2. Model

We will assume there are four different types of cells in the body:

(a) the native cells (NC), which are the healthy stromal cells;

(b) the macrophages (MΦ), which are part of the immune system;

(c) the benign tumor cells (BTC), lump-forming cancer cells that lack the ability to metastasize;

(d) the motile tumor cells (MTC), metastatic cancer cells that can invade neighboring tissues.

The concentrations of the various types of cells are denoted by ϱ_{NC}, $\varrho_{\mathrm{M}\Phi}$, ϱ_{BTC} and ϱ_{MTC} respectively. The concentrations are between 0 and 1 and satisfy $\varrho_{\mathrm{NC}} + \varrho_{\mathrm{M}\Phi} + \varrho_{\mathrm{BTC}} + \varrho_{\mathrm{MTC}} = 1$.

We will now set up costs and benefits for each type of cell. Both the native cells and macrophages produce growth factor, which benefits all types of cells. As in [Archetti 2013], the cost of producing the growth factor, c_{G}, and the benefits of the

symbol	meaning
ϱ_{NC}	concentration of native cells
$\varrho_{\mathrm{M}\Phi}$	concentration of macrophages
ϱ_{BTC}	concentration of benign tumor cells
ϱ_{MTC}	concentration of motile tumor cells
c_{G}	cost of producing the growth factor
b_{G}	benefits of receiving the growth factor
c_{S}	cost of sharing the spaces
$c_{\mathrm{M},\mathrm{M}\Phi}$	cost of the ability to move for MΦ
$c_{\mathrm{M,MTC}}$	cost of the ability to move for MTC
b_{R}	benefits of reproducing quickly
c_{D}	cost of being destroyed by macrophages
W_X	net benefit for a given type of cells $X \in \{\mathrm{NC}, \mathrm{M}\Phi, \mathrm{BTC}, \mathrm{MTC}\}$

Table 1. Model parameters and notation.

growth factor, b_{G}, will be assumed to be the same for all types of the cells. The macrophages and motile tumor cells can move and we will assume that the ability comes at the costs $c_{\mathrm{M},\mathrm{M}\Phi}$, and $c_{\mathrm{M,MTC}}$ respectively. The native cells and benign tumor cells stay in place and thus have to share the resources with other native and benign tumor cells, which comes at the cost c_{S}. The cancer cells can reproduce faster than native cells or macrophages, which we model by additional benefit b_{R} to the cancer cells, but the cancer cells can be destroyed by macrophages, which we model by additional cost c_{D} to the cancer cells. Overall, when the concentrations of the cells are ϱ_{NC}, $\varrho_{\mathrm{M}\Phi}$, ϱ_{BTC} and ϱ_{MTC}, the net benefits (benefits minus the costs) to each type of the cells are

$$W_{\mathrm{NC}} = b_{\mathrm{G}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{M}\Phi}) - c_{\mathrm{G}} - c_{\mathrm{S}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{BTC}}), \tag{1}$$

$$W_{\mathrm{M}\Phi} = b_{\mathrm{G}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{M}\Phi}) - c_{\mathrm{G}} - c_{\mathrm{M},\mathrm{M}\Phi}, \tag{2}$$

$$W_{\mathrm{BTC}} = b_{\mathrm{R}} + b_{\mathrm{G}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{M}\Phi}) - c_{\mathrm{S}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{BTC}}) - c_{\mathrm{D}}\varrho_{\mathrm{M}\Phi}, \tag{3}$$

$$W_{\mathrm{MTC}} = b_{\mathrm{R}} + b_{\mathrm{G}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{M}\Phi}) - c_{\mathrm{M,MTC}} - c_{\mathrm{D}}\varrho_{\mathrm{M}\Phi}. \tag{4}$$

For example, (1) reads that a native cell (a) benefits from the growth factor produced by (other) native cells and the macrophages, shown by the term $b_{\mathrm{G}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{M}\Phi})$, (b) pays the cost of producing the growth factor itself, shown by the term c_{G}, and (c) pays the cost of sharing the space with other native cells and benign tumor cells, shown by the term $c_{\mathrm{S}}(\varrho_{\mathrm{NC}} + \varrho_{\mathrm{BTC}})$.

The notation and model parameters are summarized in Table 1.

Similarly to the models presented in [Basanta et al. 2008; Liu and Liu 2012; Bach et al. 2001], the situation described by (1)–(4) could be modeled as a matrix

game when the interactions between individual cells are assumed to be pairwise and the payoff matrix is given by

payoff to ↓	encounter with → MTC	MΦ	NC	BTC
MTC	$b_R - c_{M,MTC}$	$b_R - c_{M,MTC} - c_D + b_G$	$b_R - c_{M,MTC} + b_G$	$b_R - c_{M,MTC}$
MΦ	$-c_G - c_{M,M\Phi}$	$b_G - c_G - c_{M,M\Phi}$	$b_G - c_G - c_{M,M\Phi}$	$-c_G - c_{M,M\Phi}$
NC	$-c_G$	$b_G - c_G$	$b_G - c_G - c_S$	$b_G - c_G - c_S$
BTC	b_R	$b_R + b_G - c_D$	$b_R + b_G - c_S$	$b_R - c_S$

(5)

To make sure that the entries of matrix (5) are nonnegative, it is customary to add a fixed number (for example 1) to all of them.

3. Results

We are interested in deriving conditions which ensure that the cancer cells (or at least the metastatic tumor cells) eventually die out.

3.1. ***Coexistence of native cells and macrophages.*** We first derive conditions on the parameters which ensure a healthy organism; i.e., the coexistence of native cells and macrophages (with no tumor cells) is an evolutionarily stable state (ESS). The assumption that there are only native cells and macrophages requires that $\varrho_{BTC} = 0$ and $\varrho_{MTC} = 0$ and consequently $\varrho_{NC} + \varrho_{M\Phi} = 1$. Subtracting (2) from (1) yields

$$W_{NC} - W_{M\Phi} = c_{M,M\Phi} - c_S \varrho_{NC}. \tag{6}$$

Recall that the net benefit from interaction (fitness) for the native cells is denoted by W_{NC} and for the macrophages, by $W_{M\Phi}$. It follows from (6) that

$$W_{NC} \gtreqless W_{M\Phi} \quad \text{if and only if} \quad \varrho_{NC} \lesseqgtr \frac{c_{M,M\Phi}}{c_S}$$

(in other words, native cells do better than macrophages if there are too many macrophages, and vice versa). Consequently, the only candidates for the stable healthy proportion of the cells are $\varrho_{NC} = c_{M,M\Phi}/c_S$ and $\varrho_{M\Phi} = (c_S - c_{M,M\Phi})/c_S$.

Since, in this scenario, we would like for the ESS to include no tumor cells, we need to derive the conditions which ensure that tumor cells (in tiny amounts) still do worse than the native cells. Subtracting (1) from (3) yields

$$W_{BTC} - W_{NC} = b_R + c_G - c_D \varrho_{M\Phi}, \tag{7}$$

while subtracting (2) from (4) yields

$$W_{MTC} - W_{M\Phi} = b_R + c_G + (c_{M,M\Phi} - c_{M,MTC}) - c_D \varrho_{M\Phi}. \tag{8}$$

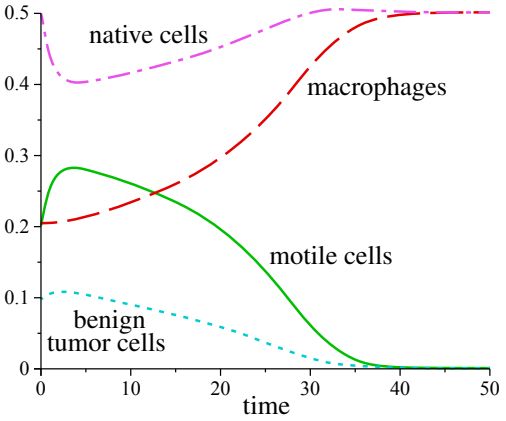

Figure 1. If (9) is satisfied, then the tumor cells eventually extinct. In this figure the values of the parameters are as follows: $b_{\mathrm{R}} = 1$, $c_{\mathrm{G}} = 2$, $b_{\mathrm{G}} = 4$, $c_{\mathrm{D}} = 7$, $c_{\mathrm{M,MTC}} = c_{\mathrm{M,M\Phi}} = 1$, $c_{\mathrm{S}} = 2$.

It follows that, in a healthy body where $\varrho_{\mathrm{M\Phi}} = (c_{\mathrm{S}} - c_{\mathrm{M,M\Phi}})/c_{\mathrm{S}}$, both the benign tumor cells and the motile tumor cells do worse than healthy cells if and only if

$$b_{\mathrm{R}} + c_{\mathrm{G}} + \max\{0, c_{\mathrm{M,M\Phi}} - c_{\mathrm{M,MTC}}\} < c_{\mathrm{D}} \frac{c_{\mathrm{S}} - c_{\mathrm{M,M\Phi}}}{c_{\mathrm{S}}}. \tag{9}$$

In particular, increasing the value of c_{D} (or the ability of macrophages to destroy tumor cells) or decreasing the value of b_{R} (the reproductive advantage of the tumor cells) ensures that the fitness of both types of tumor cells is smaller than the fitness of the native cells and the macrophages and that the body will stay healthy.

Moreover, when condition (9) is satisfied, and the initial state of the system involves relatively small amounts of tumor cells, the tumor cells eventually go extinct; see for example Figure 1, which shows the evolution of the four cell types under the replicator dynamics [Hofbauer and Sigmund 1998]

$$\frac{d}{dt}\varrho_{\text{cell type}} = \varrho_{\text{cell type}}(W_{\text{cell type}} - \overline{W}), \tag{10}$$

where $\overline{W}$ is the average fitness, given by

$$\overline{W} = \sum_i \varrho_i W_i.$$

The summation index i varies over all four cell types.

3.2. ***Coexistence of native cells, macrophages, and benign tumor cells.*** We note that if $c_{\mathrm{M,M\Phi}} \le c_{\mathrm{M,MTC}}$, then by (7) and (8), motile tumor cells do worse than benign tumor cells in a healthy body. It is thus possible that the body will be able to

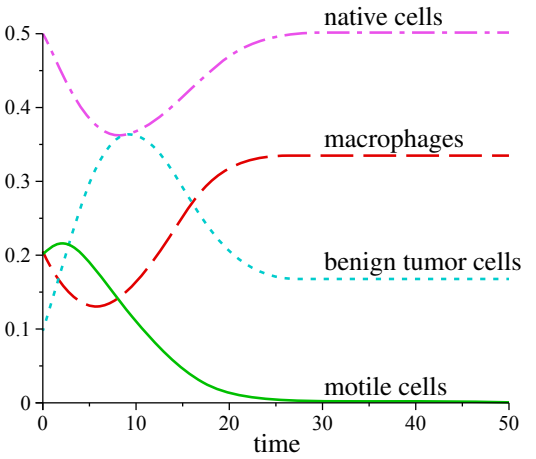

Figure 2. If (13) holds, then the motile tumor cells eventually extinct even when the benign tumor cells can stay in the body. The parameters are as follows: $b_R = 1$, $c_G = 2$, $b_G = 4$, $c_D = 7$, $c_{M,MTC} = 1$, $c_{M,M\Phi} = 0.8$, $c_S = 1.2$

get rid of the dangerous motile tumor cells even if it is not able to get rid of the less dangerous benign tumor cells. This is the situation that we will investigate now.

More precisely, we will want to see under what conditions it is possible to have $\varrho_{MTC} = 0$ as a stable condition. As in Section 3.1, subtracting (2) from (1) yields

$$W_{NC} - W_{M\Phi} = c_{M,M\Phi} - c_S(\varrho_{NC} + \varrho_{BTC}). \tag{11}$$

An ESS requires that the fitnesses of each of the coexisting types of cells be equal to each other. In particular, $W_{NC} = W_{M\Phi}$ and since $\varrho_{MTC} = 0$, we also get $\varrho_{NC} + \varrho_{BTC} = 1 - \varrho_{M\Phi}$. Thus, it follows from (11) that, as in Section 3.1,

$$\varrho_{M\Phi} = \frac{c_S - c_{M,M\Phi}}{c_S}. \tag{12}$$

Since subtracting (2) from (4) still yields (8), we get that no motile tumor cells are possible only if

$$b_R + c_G + c_{M,M\Phi} - c_{M,MTC} < c_D \frac{c_S - c_{M,M\Phi}}{c_S}. \tag{13}$$

Thus, if it is difficult to ensure that condition (9) is satisfied for a patient, one can still attempt to satisfy (13), for example by increasing the value of $c_{M,MTC}$ (the cost of movement for the tumor cells) or decreasing the value of $c_{M,M\Phi}$ (the cost of movement for the macrophages), and thus prevent the development of metastatic cancer.

Figure 2 shows the evolution of the concentrations of the four cell types as a function of time under the replicator dynamics (10) when (9) is not satisfied but

(13) still holds. We can see that the benign tumor cells stay in the body but the motile tumor cells die out.

Note that in the case when $c_{\mathrm{M,MTC}} < c_{\mathrm{M,M}\Phi}$, the motile tumor cells can thrive in the body whenever benign tumor cells can.

4. Conclusions and discussion

In this paper we presented and analyzed a game-theoretical model of breast cancer. We have extended the model of [Liu and Liu 2012] by explicitly incorporating the macrophages. As observed in [Qian and Pollard 2012; Lamagna et al. 2006; Qian et al. 2009; Chen et al. 2011] and confirmed by the analysis of our model, the macrophages indeed play a crucial role in the development and prevention of cancer.

Our model suggests at least three possible ways of cancer treatment. One is to increase the damage to the tumor cells caused by macrophages (or in a similar fashion, increase the ability of macrophages to destroy tumor cells). Another way is to decrease the reproductive advantage of the tumor cells, i.e., their ability to reproduce much more quickly than healthy cells. And a third way is to increase the cost of mobility for the tumor cells. The last scenario may not completely prevent the cancer from developing in the body, but it may prevent dangerous metastatic tumors.

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2018 vol. 11 no. 4

Modeling of breast cancer through evolutionary game theory 541
Ke'Yona Barton, Corbin Smith, Jan Rychtář and Tsvetanka Sendova

The isoperimetric problem in the plane with the sum of two Gaussian densities 549
John Berry, Matthew Dannenberg, Jason Liang and Yingyi Zeng

Finiteness of homological filling functions 569
Joshua W. Fleming and Eduardo Martínez-Pedroza

Explicit representations of 3-dimensional Sklyanin algebras associated to a point of order 2 585
Daniel J. Reich and Chelsea Walton

A classification of Klein links as torus links 609
Steven Beres, Vesta Coufal, Kaia Hlavacek, M. Kate Kearney, Ryan Lattanzi, Hayley Olson, Joel Pereira and Bryan Strub

Interpolation on Gauss hypergeometric functions with an application 625
Hina Manoj Arora and Swadesh Kumar Sahoo

Properties of sets of nontransitive dice with few sides 643
Levi Angel and Matt Davis

Numerical studies of serendipity and tensor product elements for eigenvalue problems 661
Andrew Gillette, Craig Gross and Ken Plackowski

Connectedness of two-sided group digraphs and graphs 679
Patreck Chikwanda, Cathy Kriloff, Yun Teck Lee, Taylor Sandow, Garrett Smith and Dmytro Yeroshkin

Nonunique factorization over quotients of PIDs 701
Nicholas R. Baeth, Brandon J. Burns, Joshua M. Covey and James R. Mixco

Locating trinomial zeros 711
Russell Howell and David Kyle

1944-4176(2018)11:4;1-5