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Combination therapies and intra-tumoral competition: Insights from mathematical modeling

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ABSTRACT

Drug resistance is one of the major obstacles to a successful treatment of cancer and, in turn, has been recognized to be linked to intratumoral heterogeneity, which increases the probability of the emergence of cancer clones refractory to treatment. Combination therapies have been introduced to overcome resistance, but the design of successful combined protocols is still an open problem. In order to provide some indications on the effectiveness of medical treatments, a mathematical model is proposed, comprising two cancer populations competing for resources and with different susceptibilities to the action of immune system cells and therapies: the focus is on the effects of chemotherapy and immunotherapy, used singularly or in combination. First, numerical predictions of the model have been tested with experimental data from the literature and next therapeutic protocols with different doses and temporal order have been simulated. Finally the role of competitive interactions has been also investigated, to provide some insights on the role of competitive interactions among cancer clones in determining treatment outcomes.

1. Introduction

The idea that cancer is an evolutionary disease and that its development occurs by the same processes through which animals and humans have emerged (Nowell, 1976) has gained, nowadays, a wide acceptance and has deeply influenced not just our understanding of cancer but also the development of antitumoral therapies (Basanta et al., 2012; Greaves and Maley, 2012; Merlo et al., 2006; Misale et al., 2015).

The twin forces of evolution, mutation and selection, are at work also in case of cancer: mutations at molecular level start the process of tumorigenesis and ensure cancer heterogeneity, whereas evolutionary pressures select the fittest species. The result is a process occurring at multiple scales (Bellomo et al., 2008); for instance cancer heterogeneity arises at the microscopic level via mutations and it is expressed at macroscopic level as a variety of clonal types forming a community regulated by different types of interactions such as competition, cooperations, mutualism (Tabassum and Polyak, 2015).

The growth of cancer types is further shaped by the interactions with different environmental factors: in the history of life powerful protective mechanisms have evolved to ensure the survival of organisms with large bodies and long lives. In particular the immune system ensures that many tumors are routinely eradicated.

In conclusion, cancer can be considered an ecosystem (Hillen and Lewis, 2014; Pacheco et al., 2014) formed by coexisting populations, embedded in an environment comprising normal and immune cells (Marusyk et al., 2012). Growth of tumor species depends on how effectively they are able to access resources and, on the other hand, on how successfully they develop mechanisms to prevent detection and elimination by the immune system (Hanahan and Weinberg, 2011).

The multiplicity of species in cancer populations has a clear relevance for the design of therapies as heterogeneity is a major factor in cancer drug resistance, see e.g. Saunders et al. (2012); even though a therapy can decimate a cancer type, one or more variants of the tumor population exist which are resistant, driving to the resurgence of treatment-refractory disease (Gerlinger and Swanton, 2010). This observation has led to the idea of combination therapy, in which agents with different actions are combined, thus increasing the likelihood of synergistic antitumoral effects, (DeVita and Schein, 1973; Saunders et al., 2012). The design

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of combined protocols is a challenging problem and specifically the optimal dosing and timing in the combination of chemotherapy and immunotherapy is still an open issue, (Slovin, 2012).

Not surprisingly, given the relevance of the problem, there exist a large literature on mathematical models of cancer dynamics. For a review see for instance Eftimie et al. (2011), Bellomo et al. (2008), Wilkie (2013) and references therein. In particular several contributions can be found in the framework of population dynamics: among others on tumor immune interaction, several populations are considered in De Pillis et al. (2006) and Wilson and Levy (2012) and spatial-temporal dynamics in Al-Tameemi et al. (2012). The effects of therapies are studied in the context of evolutionary dynamics (Gatenby et al., 2009a, 2009b), while the immunotherapy are considered in Eladdadi et al. (2014), Frascoli et al. (2014), Bunimovich-Mendrazitsky et al. (2008) and the optimization of therapeutic protocols in Ledzewicz and Schättler (2017) and Carrere (2017).

Population theory takes into account influences of the environment such as limited amount of resources, interactions among species and predation, see e.g. Murray (2002); therefore it is able to provide a suitable frame of reference to investigate the ecology of cancer. In this paper, the effects of evolutionary pressures on tumor development and on the outcomes of the therapies are investigated with a model situated in this theoretical framework: two populations of cancer cells compete for resources and are subjected to the action of the immune system and of the therapies.

The rest of the paper is organized as follows. In Section 2 the mathematical model is formalized and its asymptotic behavior is studied and next in Section 3, parameter estimation and corresponding sensitivity analysis are performed by comparisons with experimental data. Finally Section 4 is devoted to the analysis of the role of temporal order in the administration of therapies, with an emphasis to intra-tumoral competition. Specifically, the focus is on the effects of chemotherapy and immunotherapy, used singularly or in combination. Therapeutic protocols of different time duration, intensity and order of administration are explored.

2. Mathematical model

As mentioned earlier, the model has been developed in the framework of population dynamics (Murray, 2002) to describe the evolution of cancer and immune system. Heterogeneity of cancer is taken into account by considering two cancer clones or populations, with $x_1 = x_1(t)$ and $x_2 = x_2(t)$ denoting ambiguously both the cancer type and the corresponding number of tumor cells for each clone. The number of immune cells is represented by $z = z(t)$.

Each cancer species is endowed with different phenotypic traits, which determine specific characteristics with respect, for instance, to the ability to access resources and the susceptibility to the action of the immune system or medical treatments. Cancer types are assumed to compete with each other, as arguably, competition is the more important type of intra-tumoral interaction in shaping cancer development (Vivarelli et al., 2012; Wagstaff et al., 2013).

Basic elements determining the evolution of the cell populations are proliferation, predation and competition for resources: the growth of the cancer species is limited by the finiteness of resources and further constrained by inter-specific competition and by the action of the immune system. In turn, the immune system grows because of two factors: it is produced by the organism and its numerous is further enhanced by clonal expansion in presence of cancer.

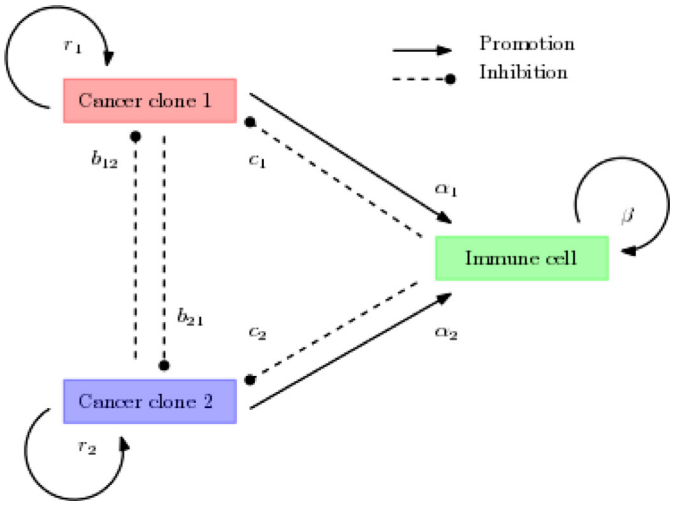

Fig. 1. Schematic representation of the model. The effects of therapies is to change r_i and c_i. See text for explanation.

The model, sketched in Fig. 1, is formalized as a system of ordinary differential equations:

$$\begin{aligned}
\frac{dx_1}{dt} &= \underbrace{r_1 x_1 - \frac{r_1}{K_1}x_1^2}_{proliferation} - \underbrace{\frac{b_{12}}{K_1}x_1x_2}_{competition} - \underbrace{\frac{c_1}{K_1}x_1 z}_{predation} - \underbrace{g_1(t)x_1 - \frac{h(t)}{K_1}x_1 z}_{therapies},\\
\frac{dx_2}{dt} &= r_2 x_2 - \frac{r_2}{K_2}x_2^2 - \frac{b_{21}}{K_2}x_1x_2 - \frac{c_2}{K_2}x_2 z - g_2(t)x_2 - \frac{h(t)}{K_2}x_2 z,\\
\frac{dz}{dt} &= \underbrace{\beta z\left(1 - \frac{z}{H}\right)}_{proliferation} + \underbrace{\frac{\alpha_1}{H}x_1 z + \frac{\alpha_2}{H}x_2 z}_{recognition}.
\end{aligned} \tag{1}$$

Consider tumor species x_1: the first two terms in the RHS of the equation represent the growth of x_1 in isolation, i.e. in absence of other cancer species, of the immune system, and medical treatment. In this case x_1 undergoes a logistic growth and the parameter r_1 is the reproduction rate whereas K_1 corresponds to the carrying capacity, i.e. the maximum value that x_1 can take. Development of x_1 is constrained by the competition with clone x_2 (measured by the competition rate b_{12}) and by the interaction with the immune system (rate c_1). Furthermore the medical treatment (for instance chemotherapy) can act on x_1 and its effects are represented in the model by the term $g_1(t)x_1$ where g_1 takes into account the drugs kinetics in the organism, see De Pillis and Radunskaya (2001). This is equivalent to rewrite the growth term of $f_1(t)x_1 = (r_1 - g(t))x_1$: when $g(t) > r_1$ then $dx_1/dt < 0$, meaning that the cancer can be eradicated by a given treatment.

The cells of immune systems prey on the tumor cells and their action can be enhanced by immunotherapy. In particular, here the focus is on a specific vaccination (DCs transduced with adenovirus containing full-length mouse wild-type p53 (Ad-p53)) that results in the generation of immune system cells (CTLs specific for p53-derived peptide) inducing a specific antitumor immune response (Nikitina et al., 2001). The effect of immunotherapy is then an increased ability by the immune system to recognize and kill cancer cells as proposed in Wilson and Levy (2012) and it is modeled by the term $\frac{h(t)}{K_1}x_1x_2$, $h(t) > 0$, or, equivalently, by defining a new parameter $\kappa_1(t) = c_1 + h(t)$.

The same considerations apply *mutatis mutandis* to tumor species x_2: in particular $f_2(t)$ and $\kappa_2(t)$ are the new growth and predation parameters, defined in a way analogous to what has been done for x_1. In the following, for simplicity's sake, $f_i(t)$, $\kappa_i(t)$ will be denoted by f_i, κ_i.