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Modeling artificial immunity against mammary carcinoma

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Abstract

A typical, and unfortunately very spread, endogenous cancer is represented by the mammary carcinoma. Lollini et al.[1] prevented mammary carcinogenesis in HER-2/neu transgenic mice using the Triplex cellular vaccine under a Chronic schedule (vaccine cycles started at 6 weeks of age and continued up to the end of the experiment). When the vaccine is administered, immune system (IS) cells are stimulated to duplicate in order to eliminate tumor cells, going back to normal levels after cancer eradication. However, in endogeneous tumors, newborn cancer cells will be formed and then vaccine administrations are necessary to stabilize the cancer – immune system competition. Thus the system is unstable and will be stabilized by the external action of the vaccine.

The question whether the Chronic protocol is the minimal vaccination protocol yielding complete protection from tumor onset, or whether a lower number of vaccination cycles would provide a similar degree of protection, is still an open question. In order to answer to this question we presented in [2] an agent-based model of IS responses to vaccination. However computational models do not allow a qualitative and asymptotic analysis, neither an easy investigation of parameters' space. For this reason we are actually working on a ODE model that is realized upon the same conceptual scheme used for the computational model. The model equations are shown as follows:

$$\frac{dVC}{dt} = k_{in}(t) - (\mu_4 + \alpha_1 TC + \alpha_2 Ab + \alpha_3 NK) \cdot VC \tag{1}$$

$$\begin{aligned}\frac{dTAAv}{dt} &= \alpha_{10}(\mu_4 + \alpha_1 TC + \alpha_2 Ab + \alpha_3 NK) \cdot VC + \\ &\quad -(\mu_{10} + \mu_{11} B + \alpha_{14} Ab + \mu_{15} MP + \mu_{16} DC) \cdot TAAv\end{aligned} \tag{2}$$

$$\frac{dMP}{dt} = \alpha_{15} TAAv + \alpha_{16} TAAc - \mu_{17} MP \tag{3}$$

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$$\frac{d\,DC}{dt} = \alpha_{17}TAAv + \alpha_{18}TAAc - \mu_{18}DC \tag{4}$$

$$\frac{d\,B}{dt} = \alpha_{20}TH + (\alpha_{21}IL2 - \mu_{20}) \cdot B \tag{5}$$

$$\frac{dTH}{dt} = \alpha_{22}TAAv + \alpha_{23}TAAc + \alpha_{24}VC + (-\mu_{21} + \alpha_{25}IL2 + \alpha_{26}IL12) \cdot TH \tag{6}$$

$$\frac{d\,IL12}{dt} = \alpha_{75} \cdot k_{in}(t) - (\mu_5 + \alpha_{27}TH + \alpha_{28}TC + \alpha_{29}NK) \cdot IL12 \tag{7}$$

$$\frac{d\,IL2}{dt} = \alpha_{30}TH - (\mu_{30} + \alpha_{31}B + \alpha_{32}TC) \cdot IL2 \tag{8}$$

$$\frac{d\,CC}{dt} = \left[\left(1 - \frac{CC}{c_{max}}\right)\right] \cdot [k_1\,CC] + p_1 - (k_2NK + k_3TC + k_4Ab) \cdot CC \tag{9}$$

$$\frac{d\,TC}{dt} = \alpha_{40} \cdot VC + (\alpha_{41} - \mu_{40}) \cdot TC \tag{10}$$

$$\frac{dTAAc}{dt} = \alpha_{50}(k_2NK + k_3TC + k_4Ab) \cdot CC - (\mu 50 + \\ +\mu_{61}B + \alpha_{62}Ab + \mu_{63}MP + \mu_{64}DC) \cdot TAAc \tag{11}$$

$$\frac{d\,AB}{dt} = \alpha_{70}B - (\mu_{70} + \alpha_{71}CC + \alpha_{72}VC + \alpha_{73}TAAc + \alpha_{74}TAAv) \cdot AB \tag{12}$$

Vaccine cells (VC) are administered through intraperitoneal injections following a predefined dosage. Inoculation is modeled by a function $k_{in}(t)$ which returns the number of vaccine cells inoculated into the host at time t if a that time an injection is scheduled. As the vaccine cells come from the external, this is the only source element in equation (1). Vaccine cells die for natural death (μ_4), killed by Cytotoxic T cells (TC), Natural killer cells (NK) or by specific antibodies (AB). Antigens released by vaccine cells ($TAAv$) are proportional to the number of vaccine cells that die. This is the source element of the first part of equation (2). $TAAv$ are subjected to degradation and phagocytosis by antigen presenting cells, i.e. by B cells, macrophages (MP), dendritic cells (DC). Moreover AB can bind to free antigens producing immune complexes. MP and DC activation (eqns. 3 and 4) depends mainly by tumor associated antigens released by VC and cancer cells (CC). MP and DC can die and can undergo to resting status ($-\mu_{17}MP$ and $-\mu_{18}DC$ terms). Antigen activated B (eqn. 5) can be stimulated to duplicate by helper T cells (TH) positive feedback. Interleukin 2 ($IL2$) plays an adjuvant role in this stimulation process. Death is modeled by $\mu_{20}B$ term.

Equation (6) models the priming of TH which can be primed through interactions with specialized antigen presenting cells, by major histocompatibility class II / peptide complex presentation. Presentation is not directly modeled, so the number of activated TH is estimated from the number of $TAAv$, $TAAc$ and VC present in the system. $IL2$ and $IL12$ also contribute to this priming. The death factor is modeled by $-\mu_{21}TH$ term. $IL12$ (eqn. 7) is introduced through vaccine administration, so it depends on the dosage. It is subjected to normal degradation ($-\mu_5 IL12$) and it is partially absorbed for mitotic and stimulation signals by TC and TH priming and NK activation. $IL2$

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stimulates TH priming and primed TH produce further IL2. It is subjected to normal degradation ($-\mu_{30} IL2$) and it is partially absorbed for mitotic and stimulation signals in TC priming and B duplication. Equation (9) describes CC dynamics. The term $\left[\left(1-\frac{CC}{c_{max}}\right)\right] \cdot [k_1\, CC]$ models CC growth. p_1 models the continuous production of newborn cancer cells due to transgenic nature of the host. The other terms describe CC death mainly due by NK, AB, TC actions. TC priming (eqn. 10) depends mainly by VC allogeneic major histocompatibility class I complex. Duplication factor is modeled by $\alpha_{41} TC$ term whereas the normal death factor is modeled by $-\mu_{40} TC$ term. $TAAc$ (eqn. 11) are proportional to the number of CC that die. This is the source element of the first part of the equation. $TAAc$ are subjected to degradation and phagocytosis by B, MP and DC. AB can also bind to free antigens producing immune complexes. Equation (12) describes AB dynamics. AB are released by B cells that differentiate into plasma B cells and are subjected to normal degradation (modeled by $-\mu_{70} AB$ term). Moreover they disappear in absolving their functions: binding to specific targets, i.e. CC, VC, $TAAv$ and $TAAc$. NK are constant an do not vary during the experiment (e.g. $d/dt\ NK = 0$). Initial Cauchy conditions are set to 0 for all the equations except for NK whose initial value is set according the leukocyte formula observed "in vivo".

Using known data from literature and data coming directly from the "in vivo" experiment we were able to find a tentative tuning for the model, capable to show a reasonable IS response that reflects the one observed in "in vivo" experiments and in the computational model. With this tuning we can try to describe the state of the "immune system – cancer competition" using three fundamental variables: the number of CC (representing the foreign pathogen), the number of TC representing the cellular response and the number of AB, principal outcome of the humoral response. Thus it is possible to represent the evolution of the system in a 3-D states space using the variables' curves, with the time representing the curves parameter, as shown in [3]. We firstly analyze the untreated scenario. In this scenario the number of cancer cells grows with no control up to the saturation threshold (Figure 1(a)). Figure 1(b) shows that the immune system is unable to engage in fight against cancer cells. The second scenario is represented by the administration of the Early vaccination schedule, composed by three vaccine cycles starting at the beginning of the experiment. A vaccine cycle consists of two vaccine administrations over two weeks followed by two weeks of rest [1]. The effect of the schedule is to contrast the initial growth of tumor cells (Figure 1(b)). This effect is presented in Figure 1(d) as a large loop in which the cancer cells growth is reduced by TC and AB action. After this initial phase, cancer cells start to grow again with no constraints and the straight line is similar to the plot of the untreated case. Finally we consider the Chronic schedule. This schedule consists on repeated Early cycle administrations for the entire life of the host. Looking at Figure 1(e) one can see that after an initial burst, cancer cells are eradicated and their level is kept near to 0. Figure 1(f) shows that the system (immune system - cancer) is stabilized and an equilibrium region is reached.

This preliminary analysis shows that the vaccine, when administered with a Chronic

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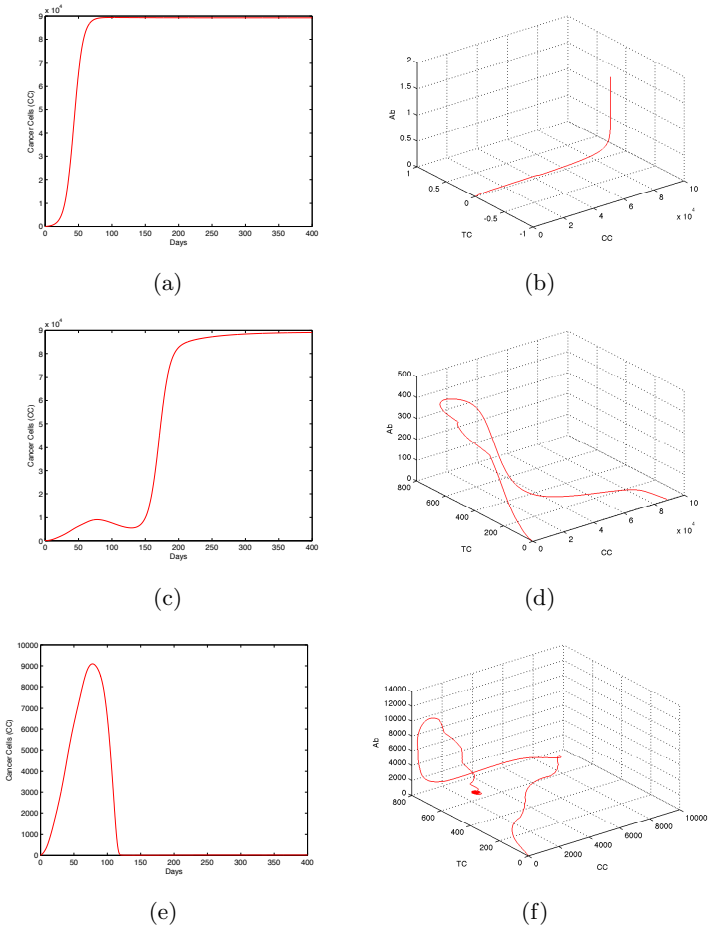
schedule, is able to stabilize the immune system – cancer competition around values that are safe for the host. Asymptotic and sensitivity analyses, as well as analytical study of a simplified model is in progress and results will be presented in due course.

Figures



(a) (b) (c) (d) (e) (f)

Figure 1: 3-D States' space for the untreated, Early and Chronic scenario

References

[1] De Giovanni C., *et. al.*: Immunoprevention of HER-2/neu transgenic mammary carcinoma through an interleukin 12-engineered allogeneic cell vaccine. Cancer Res. 64(11) (2004) 4001-4009.

[2] Pappalardo F., Castiglione,F., Lollini,P.-L., Motta,S.: Modelling and Simulation of Cancer Immunoprevention vaccine. Bioinformatics 21(12) (2005) 2891-2897.

[3] Pappalardo F., Motta S., Lollini P.-L., Mastriani E., Pennisi M. The Stabilization Effect of the Triplex Vaccine, Proc. of the 7th Int. FLINS Conference, Applied Artificial Intelligence, World Scientific, (2006) 587-592.

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