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Mathematical modelling of immune reaction against gliomas: Sensitivity analysis and influence of delays

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ABSTRACT

In the paper we considered a model of immune reaction against malignant glioma. The model proposed by Kronik et al. (Cancer Immunol. Immunother., 2008) describes simplified interactions between tumour cells and five components of the immune system. We studied the effects of uncertainties of the parameters values to the system behaviour. We showed that the tumour growth rate is one of the most important parameters only in case of fast growing tumours, that is for GBM in our case.

On the basis of the performed sensitivity analysis we proposed a reduced model in which the role of time delays in loops appearing in the described interactions is considered. The proposed model includes only two main components of the reaction, that is tumour cells and cytotoxic T-lymphocytes. It occurs that although the reduced system is described by several non-linear terms with three time delays, its dynamics is simple and time delays have hardly any influence on it.

Both considered models confirmed that the non-linearities present in interactions between tumour cells and CTLs play a major role in the system dynamics, while other components or delays can be taken into account as supplementary elements only.

1. Introduction

According to the American Cancer Society report, [1], it was estimated that about 22,340 new cases of brain and other nervous system cancers have been expected to be detected in the US alone during 2011. Moreover, an estimated 13,110 deaths caused by brain and other nervous system cancers should occur, [1]. One could say that it is not such a big number concerning all estimated new cases, i.e. over 1.5 million, [1]. However, the brain is the organ one needs to be very careful with while planing the treatment. Standard radiotherapy, chemotherapy and surgery treatment have major limitations due to the cancer's genomic instability, heterogeneity, and their locations beyond the blood–brain barrier. Within brain cancers, malignant glioma (MG) is one of the most dangerous. It is a highly aggressive cancer since its five-year relative survival rates are very low comparing with other cancers. According to [2] the median survival for the high grade MG varies from 1 year for grade IV to 3–5 years for grade III.

In this paper we follow the ideas of modelling of immune reaction against the MG presented in [3]. The original mathematical model, proposed by Kronik et al. in [3] and later generalised in [4,5], consists of six ordinary differential equations which describe the dynamics of the main components of the analysed processes, that is tumour cells ($T(t)$), cytotoxic T-lymphocytes CTLs ($C(t)$), two cytokines: transforming growth factor beta 1 TGF-β (F_β) and interferon-gamma INF-γ (F_γ), and also the molecules of major histocompatibility complex MHC of class I (M_I) and II (M_{II}).

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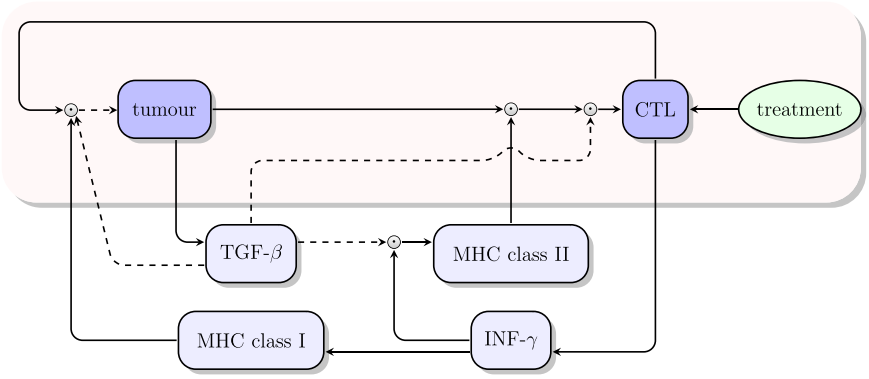

Fig. 1. Scheme of interactions between the components of the human immune system in the brain as described in [3]. The dashed and solid lines indicate the negative and positive influence, respectively. By "treatment" we mean the injection of additional CTLs.

The key two players, they are tumour cells and CTLs, interact with each other through complicated pathways encompassing other considered components, compare Fig. 1. Activated cytotoxic T-lymphocyte can annihilate a tumour cell only if it recognised the latter by identifying modified surface molecule MHC class I. Before that event, activated CTL needs to reach the tumour site starting from the thymus, where it is generated and trained to recognise specific changes in MHC class I molecules. On its way the blood–brain barrier stands which separates circulating blood and the brain extracellular fluid. Unfortunately, transforming growth factor TGF-β, which is actively secreted by tumour cells, decreases its permeability, and hence it decreases the amount of CTLs that can reach the tumour site. TGF-β also has the negative influence on the expression of MHC II molecules and the efficacy of tumour cell lysis by a CTL. MHC class II molecules are necessary to trigger the immune response, as they are recognised by T helper cells which are responsible for the activation and growth of CTLs. To add to this complexity, activated CTLs secrete IFN-γ, which induces MHC class I and II expression on the surface of tumour cells and antigen-presenting cells.

In the generalised model proposed in [4,5] those interactions have been described by the following system of ordinary differential equations

$$\begin{aligned}
\dot{T} &= r(T)T - f_T(F_\beta)g_T(M_I)h(T)CT,\\
\dot{C} &= f_C(T \cdot M_{II})g_C(F_\beta) - \mu_C C + S(t),\\
\dot{F}_\beta &= f_\beta(T) - \mu_\beta F_\beta,\\
\dot{F}_\gamma &= f_\gamma(C) - \mu_\gamma F_\gamma,\\
\dot{M}_I &= f_{M_I}(F_\gamma) - \mu_{M_I} M_I,\\
\dot{M}_{II} &= f_{M_{II}}(F_\beta)g_{M_{II}}(F_\gamma) - \mu_{M_{II}} M_{II},
\end{aligned} \tag{1.1}$$

with non-linearities included mainly to the equations describing tumour cells and CTLs' dynamics. More precisely, the intrinsic per capita growth rate of tumour cells is reflected by the function $r(T)$ of the logistic type, i.e. $r(T) = r\left(1 - \frac{T}{K}\right)$, where K is the tumour maximal size. CTLs destroy tumour cells with the efficiency increasing with the number of MHC class I receptors and decreasing with TGF-β amount. The function $h(T)$ reflects the effect of tumour mass on the tumour cell accessibility to CTLs. The secretion of TGF-β is proportional to the number of tumour cells and this corresponds to the first loop presented in Fig. 1. On the other hand, the number of MHC class I molecules depends on INF-γ amount and the amount of INF-γ increases proportionally to the number of CTLs and that corresponds to the second loop in the model.

The number of CTLs depends on the efficacy of their recruitment which is suppressed by the TGF-β presence. Their recruitment is caused by the presentation of MHC class II molecules on the surface of the tumour cells. The dependence on TGF-β in this process is the third loop we include in the model.

Because of the complex nature of system (1.1), an integral element of its study should be a formal assessment of the effects of uncertainties on its parameters values. This assessment, called sensitivity analysis, helps to understand the behaviour of a model, the coherence between a model and the world, and how different parts of the model interplay, [6]. Moreover, it indicates how uncertainty due to input parameters propagates through the modelled system and therefore, in a biological model, defines variation in which parameter plays a major role in the different clinical expression of the modelled disease. We perform this analysis in Section 2.

Another part of our study is connected with the reduction of the model and time delays introduction. Often time delays are introduced to the model to reflect better reality of considered processes. The interested reader is referred to [7–15] for the mathematical description of the immune system reactions, [16–21], for mathematical models of avascular tumour growth, [22–25] for the models of tumour angiogenesis, [24,26] for modelling the tumour–immune system interactions or [27–29] in the context of HIV-related tumour growth. The different mthods of the delays' introduction usually, but not