

The Strange Case of Dr. Immune System and Mr. Cancer: modeling tumor-immune system interaction.

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1 Two initial questions.

We start with an initial question¹: **Might mathematics be able to give a contribution in clinical oncology ?**

2 The nonlinear world of Tumors!

The generic word "tumor" in reality denotes an entire family of high-mortality diseases [2, 3] each differing from the other, but all characterized by a remarkable lack of symptoms[2, 3] and by time courses that may be classified, in a broad sense, as nonlinear since dynamics of the development of a neoplasm reflects macroscopically a considerable number of intra-cellular and inter-cellular phenomena which are strongly nonlinear and time-varying. As a consequence the behavior of "tumor" is anti-intuitive. This inherent nonlinearity might be the main reason why, despite the enormous strides in prevention[5] and cure [2, 3], "tumors" are one of the leading causes of death worldwide[6], and, unfortunately, are likely to remain so for many years to come[7].

3 Tumors and Immune System (T-IS): a complex evolutionary interaction

Among the many phenomena of interaction involving tumor cells (TCs), here we shall focus on the interactions with the cells of the immune system [3, 8] (IS), which are, broadly speaking, of the Volterrian type[9, 26]. Furthermore, the responses of tumor cells (TCs) to these interactions are characterized by a considerable evolutionary ability via changes by means of mutations to enhance their survival in a hostile environment[10, 11].

The T-IS interaction takes place because TCs are characterized by a vast number of genetic and epigenetic events leading to the appearance of specific antigens, called neoantigens, triggering antitumoral actions by the IS[12]. These observations provided a theoretical basis [13] to the old empirical hypothesis of immune surveillance, i.e. that the IS may act to eliminate tumors [14]. The story of cancer immunobiology is, in fact, very old, but only in recent years, thanks to new molecular techniques (and to large epidemiological studies) a sufficient amount of evidence has been accumulated in favor of this hypothesis[8].

The competitive interaction between TCs and the IS, involves a considerable number of events and molecules, and as such it is extremely complex and, as a consequence, the IS is not able to eliminate a neoplasm in all cases, which may escape from IS control. Of course, a dynamic equilibrium may

¹For anxious people looking forward to know an answer, we give here a general purpose one: 42[1]

also be established, such that the tumor may survive in a microscopic steady state (MISS), which is undetectable by diagnostic equipment [15]. However, consider a tumor which is constrained by the IS in a MISS. Over a long period of time (a significant fraction of the mean life span in men, according to [8]), the neoplasm may develop multiple strategies to circumvent the action of the IS [16, 12, 8, 17], which, in the long term, may allow it to evade immune surveillance and to re-commence growing to its carrying capacity [15]. The tumor has adapted itself to survive in a hostile environment, in which antitumor immune response is activated [15]. In other words the immunogenic phenotype of the tumor is "sculpted" [8] by the interaction with the host's IS. For this reason, the theory of IS-T interaction has been called immunoediting theory by Dunn et al. [8].

Finally, the study of the interaction tumor-immune system led to the proposal and implementation of an interesting therapeutic approach: the immunotherapy [2, 3], consisting in stimulating the IS in order to better fight, and hopefully eradicate, a cancer. In particular, in this paper I will be referring to generic immunostimulations, for example via cytokines.

4 Modelling T-IS interaction and immunotherapy: why ? and how ?

The above illustrated complex nature of T-IS interaction is *per se* a more than important reason to model it mathematically, of course. However, this field of research would be a part of basic science of cancer. However, mathematical modelling may be also precious from a clinical point of view, when modelling immunotherapy. Indeed, the basic idea of immunotherapy is simple and promising, but the results obtained in medical investigations are globally controversial [23, 24, 25], even if in recent years there has been evident progress. One of our main aims will be to illustrate how mathematics may help us to better understand better this kind of therapy, and its clinical trials.

Coming to the mathematical way to model the above interactions, the basic idea of the ecological modelling of TCs-IS interaction of ref. [26, 15] is simple: TCs and effector cells (ECs) of IS are seen as two competing populations. TCs are mainly the prey of the ECs, whose proliferation is stimulated, in turn, by the presence of TCs. However, TCs also induce a loss of ECs; and there is an influx of ECs, whose intensity may depend on the size of the tumor [26]. Based on this simple scheme and on its generalizations, many works have appeared using a finite dimensional approach based on specific models with constant or tunable parameters [27, 28, 29, 30, 31, 32, 33, 34] (and references therein).

However an approach based on a specific model is in contrast with the polymorphic nature of cancer, and it does not allow easily to catch the general features of the TC-IS interaction.

To overcome this problem, in [26, 15, 35] we introduced a new approach based on meta-models (where meta-model means "a family of models") which is a natural and effective way to capture the common features of a such a wide family of diseases as tumors represent.

5 Mathematics meets oncology, oncology meets mathematics.

To conclude, the main aim of this lecture is to show how the above mentioned biomedical nontrivial problems finds a natural way to be mirrored in well known topics of the qualitative theory of differential equations:

- Immune surveillance : locally stable equilibria;
- Biological realism of experimental empirical growth curves of tumors (Gompertz curve [36]): unstable equilibria;
- Experimentally observed oscillations of some neoplastic diseases [37, 38]: existence and uniqueness of limit cycles for ordinary and delay-differential equations;
- Tumor escape from immune surveillance: systems with adiabatically varying parameters, catastrophe theory;

- Puzzling clinical trials of active immunotherapies: stability, unstability;
- Continuous infusion passive therapies: bifurcation theory;
- Boli based passive therapies: numerical simulations of periodically forced nonlinear systems; impulsive differential equations;
- Puzzling clinical trials of passive immunotherapies: separatrix curves, random initial conditions;
- Eradicating a neoplasm: global stability;

6 An answer to the initial question

In the lighth of the correspondances illustrated of the above list, we may say thta there are strong evidences to give the following answer to our initial question: *yes*.

As previously stressed in [39, 40], methods of modern mathematical physics, and in particular the theory of finite and infinite dimensional dynamical systems, may play an important role in oncology of the XXIth century, both from a theoretical point of view and also in the clinical practice, by means of appropriate model-based decision support systems.

We hope that these software systems might become a day by day tool for oncologists as well as the ECG devices are for cardiologists. We would like to stress that we are not speaking of a far misty future. In fact, we believe that, even today, some softwares based on physical-mathematical models might also be cautiously used in clinical practice in a limited but relevant field: discriminating between treatments which would have high probability of failures.

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