Combining and Optimising the Innovative Cancer Therapies Based to the Mechanistic Modeling

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Quantitative systems pharmacology (QSP) proved to be a powerful tool to elucidate the underlying pathophysiological complexity that is intensified by the biological variability. Therapies combining immunotherapy with more traditional therapeutic approaches, including chemotherapy and radiation, are increasingly being used. In this work we consider a combination therapy of cancer. One therapy is a radiation which eliminates a tumor volume and activates dendritic cells so that they induce the T cells to infiltrate the tumor. The other drug is a check-point inhibitor, which enables the T cells to remain active against the cancer cells. These combinations are purposed to amplify the immune response against the tumor cells and modulate the suppressive tumor microenvironment (TME). In order to get the best performance from these combinatorial approaches and derive rational regimen strategies, a better understanding of the interaction of the tumor with the host immune system is needed. The objective of the current work is to provide new insights into the dynamics of immune-mediated TME and immune-oncology treatment. As a case study, we will use a recent QSP model by Kosinsky et al. [2] that aimed to reproduce the dynamics of interaction between tumor and immune system upon administration of radiation therapy and immunotherapy. Adopting a dynamical systems approach, we here investigate the qualitative behavior of the representative components of this QSP model around its key parameters. The ability of T cells to infiltrate tumor tissue, originally identified as responsible for individual therapeutic inter-variability [2], is shown here to be a saddle node bifurcation point for which the dynamical system oscillates between two states: tumor-free or maximum tumor volume. By performing a bifurcation analysis of the physiological system, we identified equilibrium points and assessed their nature. We then used the traditional concept of basin of attraction to assess the performance of therapy. We showed that considering the therapy as input to the dynamical system translates into the changes of the trajectory shapes of the solutions when approaching equilibrium points and thus providing information on the issue of therapy.

References

[1] A. Balti, D. Zugaj, F. Fenneteau, P.-O. Tremblay, and F. Nekka. Dynamical systems analysis as an additional tool to inform treatment outcomes: The case study of a quantitative systems pharmacology model of immuno-oncology. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 31(2), 2021.

[2] Y. Kosinsky, S. J. Dovedi, K. Peskov, V. Voronova, L. Chu, H. Tomkinson, N. Al-Huniti, D. R. Stanski, and G. Helmlinger. Radiation and PD-(l)1 treatment com-

binations: Immune response and dose optimization via a predictive systems model. *Journal for ImmunoTherapy of Cancer*, 6(1), 2018.