A GLOBAL SENSITIVITY ANALYSIS OF A HYBRID PDE–ODE MODEL FOR CANCER-ON-CHIP EXPERIMENTS

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In recent years, the employment of digital twins to support the study of biological phenomena has widely diffused. In this context, digital twins able to reproduce complex phenomena such as organogenesis or tumorigenesis, possibly involve a large number of parameters, which may be also not directly measurable *in vivo/vitro*, and thus require a careful calibration. In this perspective, the global sensitivity analysis offers useful instruments to either identify regions in the space of parameters that result in reasonable scenarios, and to understand how the parameters affect the variability of the outputs of the model.

In the present work, we focus on the hybrid model proposed in [1] to reproduce Cancer-on-chip experiments where tumor cells, treated with chemotherapy drug, secrete chemical signals stimulating the response of immune cells. Specifically, the model consists of a coupled PDE-ODE system where cells are described as point particles while the chemical is characterized by the spatial distribution of their concentration. To investigate this digital twin, a global sensitivity analysis is performed by considering a series of target outputs, properly defined to characterize both the spatial distribution and the dynamics of immune cells. Among all the model parameters, we analyze the role of 13 parameters by performing a first screening using the method of Morris [2, 3], since each numerical simulations is a bit computationally expensive. This analysis confirms that (i) the selected target outputs are actually able to capture both typical and anomalous behaviors of the system; (ii) the considered ranges of parameters result in feasible scenarios (as the one shown in Fig. 1, left panel); (iii) the variability of both cell spatial distribution and their dynamics are mainly affected by 6 parameters (as shown in Fig. 1, right panel). These parameters include all the parameters characterizing the evolution of the chemical signal secreted by the tumor cells, i.e., the diffusion coefficient, the growth rate and the consumption rate; and some of the parameters regulating cell dynamics, i.e., the coefficient of the chemotactic effect, the damping coefficient and the drift velocity.

This is a first step in the investigation of this digital twin that suggests to continue our analysis by focusing on these 6 parameters only and applying more expensive methods able to quantify how much they affect the variance of the target outputs of our interest. In this perspective, we opt for the variance-decomposition based method of Sobol [4, 5] as it is able to quantify the effect of variations in the value of a parameter either one-by-one (main effect) or in combination with other parameters (total effect).

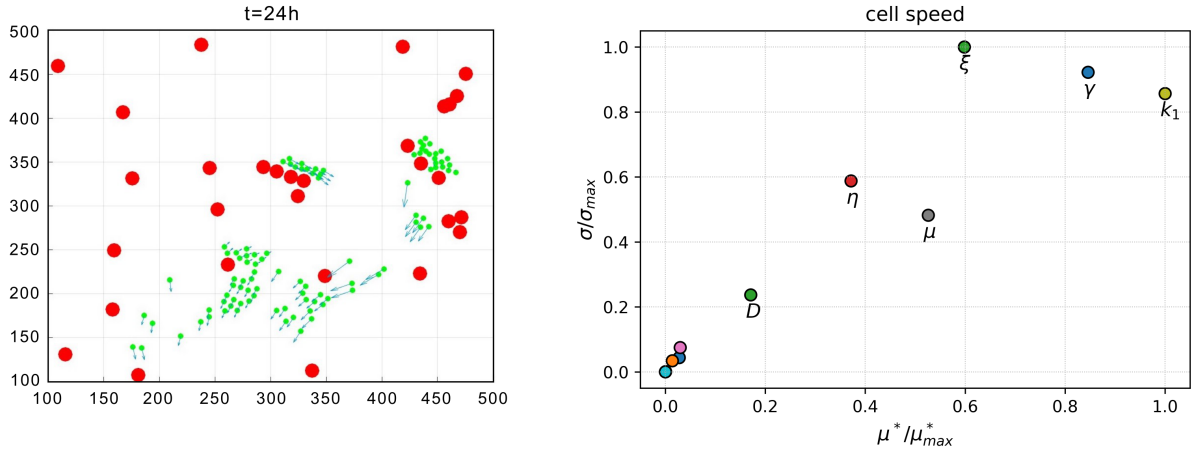

Figure 1: Left panel: Simulated dynamics of immune cells (green circles) in the chip environment with tumor cells (red circles). Right panel: Representative results showing how the parameters affect the velocity of immune cells.

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