Employing ODEs to Personalize Immunotherapy in Metastatic Melanoma - History and Current State

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In this talk, I will describe the evolution of computational biomedicine over the last half century, from purely theoretical and relatively abstract mathematical models to models that can aid clinicians in making decisions about individual patients' treatment plans. I will describe this evolution through the prism of our work, mainly at IMBM.

In the nineteen eighties, I studied theoretically the dynamics of populations subjected to periodic loss processes that are effective only during part of the life cycle. Model analyses discovered the 'Resonance Phenomenon' in population persistence, namely that population growth is enhanced when the average period of the imposed loss process resembles the population's inherent period, i.e., average generation time. The model's simplicity and the solution's universality implied that this 'resonance phenomenon' can be applied to cancer chemotherapy, and, indeed, it was successfully validated in experiments with cancer-bearing mice. These results showed that simple mathematical models can shed light on cancer therapy. However, clinical realism requires consideration of more complex aspects of oncological treatment, such as drug toxicity, drug resistance, etc. Therefore, we have developed the Virtual Patient concept, which, essentially, is a set of mathematical models for drug pharmacokinetics and pharmacodynamics, disease or toxicity processes, etc. A patient with metastatic chondrosarcoma validated the Virtual Patient we developed. By adjusting model parameters to the patient's cellular and molecular data, we suggested an improved 'resonance-like' regimen for him, which was administered to the real-life patient, significantly improving his survival.

The developed concepts were employed in melanoma immunotherapy by the immune checkpoint inhibitor, pembrolizumab. First, we created a mechanistic, deterministic, non-spatial, non-linear, coupled model of several Ordinary Differential Equations (ODEs) with many parameters. This model satisfactorily retrieved the non-monotonic dynamics that characterize this system. However, the large number of model parameters prevents any possibility of parameter estimation and, therefore, model personalization. Model simplification enabled acceptable personal predictions of the time to disease progression based on only three clinically measured parameters. We improve the model by increasing the size and diversity of the patients' dataset, using it for model training, and expanding it to include all the clinically available immunotherapy drugs.

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