Studying long-lasting diseases using an agent-based model of the immune response

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Personalized medicine strategies are gaining momentum nowadays, enabling the introduction of targeted treatments based on individual differences that can lead to greater therapeutic efficacy by reducing adverse effects. Despite its crucial role, studying the contribution of the immune system (IS) in this context is difficult because of the intricate interplay between host, pathogen, therapy, and other external stimuli. To address this problem, a multidisciplinary approach involving in silico models can be of great help. In this perspective, we will discuss the use of a well-established agent-based model of the immune response, C-ImmSim [1, 3], to study the relationship between long-lasting diseases and the combined effects of IS, drug therapies and exogenous factors such as physical activity and dietary habits.

C-ImmSim simulates the dynamics of various computational entities involved in the immune response. Cellular entities, such as adipocytes, lymphocytes, antigen-presenting cells, antigens, antibodies, immune complexes and intercellular signaling molecules are included in the model. In addition, simple pharmacokinetic (PK) and pharmacodynamic (PD) models based on experimental data are implemented to simulate the effect drugs against specific targets. A key element of the model is its stochastic nature: fixed values of parameters produce realizations of the dynamics that can differ from each other in the immunological initial state (immune repertoire, basal concentrations of metabolites, systemic inflammatory cytokines, and blood leukocyte counts), and in the occurrence of probabilistic events. This allows us to associate each simulation run with a virtual patient, thus mimicking the evolution of disease within a virtual cohort of individuals by simulating multiple virtual patients. Over the years, C-ImmSim was used to simulate several diseases. Here we discuss three main applications.

Metabolic homeostasis, inflammation and diabetes

We developed an integrated, multilevel patient-specific model for the simulation and prediction of metabolic and inflammatory processes in the onset and progress of the type 2 diabetes (T2D), as part of the two projects "*Multiscale Immune System SImulator for the Onset of Type 2 Diabetes integrating genetic, metabolic and nutritional data*" (MISSION-T2D) and "*Physics informed machine learning-based prediction and reversion of impaired fasting glucose management*" (PRAESIIDIUM).

To reproduce the metabolic and inflammatory processes that determine the transition

to T2D pathophenotypes, C-ImmSim has been equipped with a model based on differential equations to take into account the contribution of physical activity and food intake to the inflammatory state of an individual [6, 7], and that considers both the glucose regulation due to the balance between glucagon and insulin. The kinetics of oxygen consumption, the dynamics of epinephrine and the production of the cytokine IL-6 as a function of physical exercise are also included [5, 7] and the model is personalized on the individual functional capacity and based on age, sex, anthropometric characteristics, and current fitness status. Absorption of glucose, alanine and triglycerides are computed starting from the ingestion of carbohydrates, proteins, and fats. Periods of excessive caloric intake determine the volume growth of adipocytes that, over a certain volume threshold, secrete cytokines in a process that can eventually result in a continuous inflammatory state [8].

Mycobacterium tubercolosis infection

We used an in silico approach for the management of tubercolosis due to Mycobacterium tuberculosis (Mtb) infection, as part of the project "European Accelerator of Tuberculosis Regime" (ERA4TB).

In order to simulate the Mtb infection occurring in the lung, we model the bacterium as an agent able to move and interact with macrophages and lymphocytes. These interactions are described by a set of specific rules that allow to reproduce the phenotypes and associated behaviours of Mtb, such as the small replication rate of non-phagocytosed bacteria, the switch between fast- and slow-replicating Mtb engulfed by macrophages, the transition to a latent state invisible to the IS to mimic the presence of granulomas, and the spread of bacteria following both the burst of infected macrophages and the reactivation of granulomas [4]. As a result, a variety of long term behaviours is explored by the simulated dynamics, that can be classified into clinical states. We are able, in particular, to both reproduce the key characteristics of the disease (e.g., bacterial load dynamics) as well as the epidemiological curves in presence of treatment.

Cancer therapy and hepatoblastoma

Finally, we used C-ImmSim to model and predict standard and experimental therapies for each child with hepatoblastoma (HB), the most common pediatric liver cancer, as part of the project "Individualized Paediatric Cure" (iPC).

HB is a liver cancer with high heterogeneity that can be classified into two main subtypes: C1, characterized by a high percentage of fetal cells and high survival rates, and C2, with a high percentage of proliferative embryonal cells and corresponding to a significant reduction in the survival probability [2]. We introduce a population of cancer cells constituted by 2 subtypes, non-aggressive (NC) and aggressive (AC) cancer cells, that differ in their duplication time. We use these cell types to discriminate between C1 and C2 cancer subtypes [9]. Both cell types can interact with the IS. The interaction is very weak in the absence of treatment and is enhanced by cell death induced by drug therapy. The model was validated both by reproducing survival curves and clinical percentages and by using statistical methods such as factor analysis and linear discriminant analysis.

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