Ph.D. in Information Technology
Thesis Defense

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Matteo ITALIA – XXXVI Cycle

IN SILICO MODELLING, ANALYSIS, AND CONTROL OF COMPLEX DISEASES: ADDRESSING CLINICAL QUESTIONS, PERSONALIZED TREATMENTS, AND HEALTHCARE MANAGEMENT

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Abstract:

Human diseases are often associated with complex and dynamical characteristics. Complexity is caused by a combination of multiple genetic, metabolic, environmental, lifestyle, and still many unknown or uncertain intertwined factors. Dynamism refers to illnesses associated with striking changes in the dynamics of some bodily functions. Indeed, most complex diseases show the typical structural traits of complex systems, such as positive and negative feedbacks in cellular communication, high degrees of inter- and intra-cellular connections, and interactions across different spatio-temporal scales, from molecules and fast metabolic dynamics to the entire body and slower evolutionary responses. Additionally, the related dynamical processes show the typical phenomena of complex nonlinear dynamics, such as self-sustained metabolic and neural oscillations, emergent behaviours in cell populations, such as neuronal synchronization and cancer evolutionary adaptation, wave propagation of infectious contacts, and bifurcations, for example, the transition from a constant treatment to a dynamic optimal drug administration. Complexity and dynamism are hence two complementary sides of the same coin in a severe disease framework.
Understanding and controlling the evolution of a complex disease and how to treat each patient optimally are important challenges that benefit the contributions of mathematics, physics, engineering, and systems and control theory in particular. There are still many open questions, especially in the applications of personalized medicine. The improvement in digital and information technology, biological data collection, effective data analysis methods, and the ever-increasing computational power available facilitate the developmentand perfecting of these approaches.
My research fits into this multidisciplinary context, known as in silico medicine. The general aim is to provide modelling-informed support to healthcare. To this endeavour, we develop and analyze mathematical models designed to investigate the complexity of the disease under study. The models, once calibrated and validated on available data, are used to answer clinical questions and optimize healthcare management policies and treatments in a future perspective of personalized medicine. In this Thesis, healthcare problems of genetic, neurological, and epidemiological complex diseases are investigated, specifically, several types of cancers showing fast pharmacoresistant response, the Restless Legs Syndrome (RLS) neurological disorder, and the Covid-19 pandemic.
The impact of improving cancer treatments is just immense scientifically, as well as socially and economically. Going more into detail, my investigations related to cancers aim to overcome drug resistance. Thus, a cell-based (CB) and a population-based (PB) evolutionary model of cancer growth and evolution under chemotherapy are designed to investigate optimal treatment strategies. Here, optimal drug scheduling is faced in a CB framework for the first time, and the PB model is the first optimized model describing neuroblastoma under cyclophosphamide and vincristine. The principal finding is that it is

possible to understand, predict, and even steer the evolution of cancer drug resistance, transforming it into a weakness to be exploited by optimal treatments. This result suggests that current constant/static protocols, which typically fail due to the development of cancer drug resistance, should be replaced by effective dynamical and personalized protocols. Within the framework of neuroblastoma treatment, the MYCN enigma is addressed, investigating the complex relation between the MYCN gene and treatment outcomes. Using a calibrated gene regulatory network, the impact of MYCN regulation on apoptosis is studied through the ARF-MDM2-p53 signalling pathway, aligning findings with clinical observations and proposing promising personalized treatments. Moreover, another study investigates how it is possible to effectively treat melanoma and overcome its acquired resistance to vemurafenib by adopting the SynGeNet method, which exploits a combination of gene expression data and network-based analysis. The results suggest promising drug combinations that are confirmed in vitro. The finding should be confirmed in clinical trials before real applications.
In the context of the RLS disease, a specific clinical question is addressed about periodic leg movements (PLM), the principal disorder of RLS-affected people. Specialists conjecture that a single neuronal generator could trigger PLM, in lieu of two (or more) asynchronous generators controlling the left and right legs (single-generator hypothesis). To support the conjecture, we design and calibrate on real data the first in silico model simulating PLM based on a single-generator and the famous integrate-and-fire neuron model. Since our model-simulated data did not statistically differ significantly from the real data, we support the single-generator hypothesis triggering PLM. This finding helps in the understanding of the PLM nature and RLS disease.
Finally, we propose a compartment model for the global spread of Covid-19 including vaccination. We divide the world into two macro interconnected nodes representing high- and middle-to-low-income countries for the sake of simplicity, but the model can be generalized to more nodes. The parameters are calibrated on publicly available real data. Vaccine administration strategies are explored, varying both the vaccine availability and their distribution for the first time. The main message is that stopping this pandemic requires actions to increase vaccine access, and the needed increase is less severe by adopting global equitable access. The good news is that the benefits of applying these actions are still relevant, were we ready to implement them now. These findings are crucial to stopping Covid-19 and future similar threats, thus potentially bringing terrific benefits worldwide.
In conclusion, the Thesis proposes an engineered *modus operandi* to tackle complex dynamical problems in medicine. New mathematical models are designed, calibrated and validated on real data, for each of the considered diseases. New insights are provided in each case. Optimal personalized treatments are proposed for several types of cancers, a specific clinical question is addressed for the RLS sleep disorder, while vaccination control policies are suggested to stop the Covid-19 pandemic.

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