Agent based modeling of viral infections: an investigation across several spatio-temporal scales

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6. Summary and Conclusions

Infectious diseases are a threat for our modern society due to the increased population density on Earth, so being able to understand and predict the dynamics of infectious diseases is extremely important. Viral infections are by their nature complex adaptive multiscale phenomena. Their microscopic dynamics within cells leads to the emergence of macroscopic effects within individuals and populations. For this reason viral infections should be studied at different spatio-temporal scales and, eventually, as a single multiscale hierarchical model.

One of the grand challenges of computational science is to develop such a multiscale model able to replicate the biological mechanisms from the molecular to epidemiological levels. However, our understanding of the biological and computational complexity is still far from complete.

In this thesis we have investigated the complexity of the interplay between viruses, immune system and drugs at several spatio-temporal scales (from molecular and cellular scales up to the scale of virtual patients). Our contribution has both computational and biological aspects. In the computational domain we have developed new models at intracellular and cellular levels and introduced the use of mutual information to the analysis of an established agent-based model. We have shown that ABM can be used to model viral infections at each spatio-temporal scale and that it is a suitable modeling framework to create a multiscale model to simulate viral infection and the immune response to them. In the biological domain we improved the understanding of the dynamics of HIV infection under cART, providing an insight into the causes of the failure of structured treatment interruptions and quantified the duration of a period of sustained immune response to temporary cART during primary infection.

For the computational domain our first contribution is the development of a stochastic model of HIV-1 intracellular replication. We simulate the HIV life cycle within a single cell, from the capsid release into the cytoplasm until the production of new viral genome, keeping track of the main viral proteins and genetic materials inside the cell. We use two different simulation approaches to implement the model and compare them on the basis of the amount of integrated cDNA and the amount of transcribed viral mRNA after one round of viral replication. We identify the need for the diffusion-based approach of additional experimental data on the movement of HIV proteins within the cytoplasm.

Our second contribution, this time at intercellular scale, is a framework able to support in vitro experiments by simulating both cellular growth and viral replication in a monolayer of cells. This framework is conceived to allow the future implementation of the lower spatio-temporal scale dynamics instrumental to an accurate simulation of the new viral particles released from infected cells. We also evaluate the critical role played by some parameters and using our model we concretely helped the experimental biologists to identify an issue in their cell line that explained the discrepancy between our simulations and the experimental results of the infection.

The last significant contribution in the computational domain is to have considered for the first time the flow of mutual information in the complex network formed by the immune cells and the virus at the scale of individual patients.

The significant contributions in the biological domain focus on the new insight on the dynamics of HIV infection at the scale of individual patients. Our new approach that measures the mutual information between cells types during untreated HIV infection allows us to interpret the results observed in the Primo-SHM clinical trial. The PRIMO-SHM clinical study observed that starting a temporary cART within 6 months post infection lowers for a long period of time the viral set point, delaying the need to restart the cART treatment. Our

study explains and quantifies the temporary beneficial effect of cART observed in the PRIMO-SHM study. We observe a known, short phase of long-lasting sustained response during the acute phase followed by a yet unknown plateau of roughly ten months that was never observed before during which the sustained response of the immune system is still more intense than the one relative to the chronic phase.
We show that the role of provirus in the dynamics of HIV infection was so far underestimated. We predict that the amount of HIV reservoirs both in macrophages and latently infected resting/memory $CD4^+$ T lymphocytes are sufficient to cause a failure of the STI schedules tested so far in clinical trials regardless of drug resistance. This observation may have relevant implications for the design of future treatment strategies. We also predict that the temporary reduction of the size of HIV reservoirs is the cause of the temporary beneficial effects observed in the Primo-SHM clinical trial, confirming the key role of provirus in the HIV dynamics. It is worth noticing that a recent study published in Cell highlights the previously neglected role of provirus as the possible reason for our inability to cure HIV.
Lastly we also show that, without the emergence of drug resistance, it is possible to find an optimized STI whose efficacy is close to that of a continuous treatment with a reduction of 40% in drug administration. In addition by showing the failure of the "8 Weeks On / 4 Weeks Off " STI we show that adherence to the optimal treatment schedule is more important than the amount of drug taken over the treatment period.