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A multi-scale approach for deciphering HIV infection

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Chapter 6

Summary and Conclusions

"Understanding the dynamics of infectious-diseases demands a holistic approach"

Neil Ferguson, 12 April 2007

In nature, complex macroscopic behavior emerges from underlying microscopic processes. Our hope to understand, quantify and predict this behavior depends on our ability to couple the microscopic processes to larger spatial and time scales.

However, the inherent complexity and the range of spatial and temporal scales in nature, challenge any existing mathematical model and computational capacity. Especially troubling is "the problem of the scales" ranging from nanometers and nanoseconds in molecular interactions, to hundreds of kilometers and tens of years in infectious disease pandemics. Even the recent developments in our computational techniques and the ongoing exponential growth in computational power will not suffice to computationally track all natural processes at their finest spatio-temporal scales. Our only alternative is a holistic approach where data and models on all levels are converged.

The research presented in this manuscript is motivated by the same fundamental concept; the percolation of the virus (information) through its life cycle and the importance of small changes in this process translating back to the clinical observations. Throughout this thesis we have followed the road lid by this idea.

Our approach should not be mistaken with directly coupled models where on some stage a result of one model/simulation is used automatically as input to another stage. Instead, we start from a rather detailed level. First, we analyze that level and build the next level by introducing spatial and/or temporal scales on the results of the previous one.

In chapter 1 we have addressed research questions we set out to answer: How does HIV hijacks the cellular machinery; are there any crucial pathways or proteins for the virus; can we predict the type of cells HIV is interacting with by analyzing HIV-human protein interactions; what can we learn about the evolutionary dynamics of HIV by modeling the interactions between HIV and types of different immune system cells and finally, do those interactions of HIV with various cell types have an effect on the disease course.

In this thesis we systematically approached those questions from a computational science perspective. We have started from the protein interaction level and focused on untangling the interplay between HIV and various cell types of the human immune system.

After the brief introduction to the human immune system, HIV and other necessary background in chapter 1, chapter 2 focuses on explaining some of the problems related to HIV infection and the current state of the field today.

The impact of computational science in HIV research is explained on various components of the experimental platform ViroLab. We showed how molecular dynamics simulations are used for predicting possible drug resistance mutations, immune system modeling at the cellular level can be used to estimate the condition of the immune system and how population level complex-network simulations can be utilized for determining the epidemiological outcomes of the infection.

In chapter 3, we focused on the protein interactions between HIV and human proteins and the underlying HIV-1 human protein interaction network. We analyzed this network for network centrality, connectivity as well as overrepresented significant network motifs.

Our results on the network analysis indicated that infection with HIV results in a reprioritization of cellular processes reflected by an increase in the relative importance of the transcriptional machinery and proteasome formation. We argue that during the evolution of HIV some interaction patterns were favorable for the virus and thus are conserved. This resulted in a system where virus proteins interact with central host proteins for direct control, and with proteasomal proteins for indirect control over the cellular processes.

In addition to being vital for the survival of the host cell by degrading HIV proteins early in the infection, proteasomes became significantly important also for the virus, due to their role in regulation of the concentration of the innate antiviral host factors such as APOBEC3G/F and CD317 (Interaction targets of HIV proteins Vpu and Vif).

Using network motifs we have identified recurring patterns that have consequences in the virus-host dynamics. Specifically, inferred network motifs indicated significant over-representation of positive and negative feedback patterns between the virus and the host, which were not reported earlier in any virus-host system.

In chapter 4, we started with the HIV-1 human protein interaction network and spatially restricted our focus to surface membrane proteins (SMP) interacting with HIV.

Later, we have introduced and validated a domain independent algorithm for discovering potential interaction partners based on similarity and graph theory. We have applied this algorithm for predicting “potential missing links in our protein interaction network” based on their functional similarities with the proteins readily available. This resulted in identification of 21 SMPs potentially permit, mediate or enhance HIV infection in different cell/tissue types in HIV-infected individuals.

Among those 21 SMPs, ten were involved in a cascade of events in HIV infection from serving as co-receptors for cell entry (CCR1 and CCBP2), mediating transinfection (DARC), activating immune cells (CD97) to inducing viral production from latently infected cells (CSF3R, TNFRSF3 and CD2). We also presented eleven original predictions that are potential HIV interacting factors. In particular, the platelet glycoprotein Ib (GPIb) is a surface membrane protein of platelets. Additionally, the relaxin receptors RXFP1 and RXFP2 are expressed on the acrosome of elongated spermatids. Their association with HIV might explain the different rates of evolution observed in seminal versus blood plasma of infected patients. Moreover, either one or both receptors might be involved in viral hijacking of the spermatozoa in viral transmission. In conclusion, our findings from chapter 4 constitute the necessary background for future research investigating the role of SMPs in HIV infection.

In chapter 5 we focused on two of the co-receptors of HIV-1 (CCR5 and CXCR4) described in chapter 4 and introduced an evolutionary model of HIV-1 co-receptor tropism in detail. The computational model introduced a clear temporal scale for studying the longitudinal dynamics of HIV tropism and the co-receptor switch.

A computational model has been implemented as an agent based model with special emphasis on the spatial characteristics of virus/cell interactions in the lymph nodes. Robustness of the computational model is verified through perturbation analysis of the key model parameters. The model was designed to evaluate the fitness of the viral quasispecies by tuning the co-receptor tropism. Hence, the emergence rate of the X4 tropic variants, the factors leading to it and the necessary conditions for the co-receptor switch, are investigated to elucidate whether accumulation of mutations induce the co-receptor switch.

For this we have developed and verified an intuitive simulation platform of HIV-1 tropism for testing potential hypotheses. We demonstrated that the natural evolution of the viral population over time resulted in the co-receptor switch without inherent assumption of the X4-tropic variant superiority. In addition, our studies indicate that there is an optimum mutation rate for the co-receptor switch and interestingly, it coincides with the experimentally reported mutation rate of HIV-1.

Furthermore the time of the co-receptor switch was found to be dependent on the fluctuations in the HIV population size. Population bottlenecks clearly increased the chance of a co-receptor switch.

Another observation was that the R5-tropic variants benefited from the emergence of the X4-tropic variants and they together outcompete dual-tropic variants. This leads to sympatric speciation of HIV-1 in-vivo. This implies a strong link to in-vivo compartmentalization of the virus while adapting to its host. Based on our results we hypothesize that the target cell range has major influence on determining the dominant viral phenotype in terms of co-receptor tropism. Hence the size, constitution and homeostatic properties of different immune system cell types are potentially fundamental for understanding the longitudinal dynamics of co-receptor tropism of HIV-1.

The work presented here spans from a rather general motivation of the research interest in the multi-scale aspects of virus-host interactions to a detailed study of the spatio-temporal scales in virus tropism. Therefore it bridges the gap between the protein interaction data (without spatio-temporal scale) of HIV and human proteins, all the way up to the clinical observation of the co-receptor switch of HIV infection (where both time and space are of foremost importance) with the focus on extra-cellular proteins.