Complex networks and agent-based models of HIV epidemic
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Citation for published version (APA):

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Understanding the dynamics of infectious disease is important in epidemiology in order to understand and prevent the progression and spreading of infectious diseases. For many viral infections social interactions as well as genetic diversity of the transmitted viral agent among individuals dictate the dynamics of infectious disease spreading in a population. Therefore, the infection transmission can be investigated at different spatio-temporal scales, from molecular to epidemiological levels. One particular example is the human immunodeficiency virus (HIV) infection that causes the acute immunodeficiency syndrome (AIDS). HIV infection and AIDS have so far caused the death of millions of people worldwide and have turned out to one of the most severe infectious diseases of our time. Regarding HIV epidemic a wide range of data has been gathered, from genome sequencing and blood samples to social interactions and sexual contacts of infected individuals. Based on these data, many models have been developed to investigate the complexity of HIV dynamics, immune response and drug therapy.

In this thesis, we have looked into HIV-1 data present at different scales (from molecular and cellular to epidemiological scales). We built data-driven models and perform network analysis in order to understand the dynamics of HIV at different scales.

At cellular scale, we proposed a computational model of HIV intra-
Summary and Conclusions

cellular replication where infected cells undergo a single cycle of virus replication. A cell has been modeled as an individual entity with certain states and properties. The model is stochastic and keeps track of the main viral proteins and genetic materials inside the cell. Two simulation approaches were used for implementing the model: rate-based and diffusion-based approaches. The results of the simulation were discussed based on the number of integrated viral cDNA and the number of viral mRNA transcribed after a single round of replication. The model was validated by comparing simulation results with available experimental data. Simulation results gave insights about the details of HIV replication dynamics inside the cell at the protein level. Therefore the model could be used for future studies of HIV intracellular replication in vivo and drug treatment.

We also proposed a novel method to reconstruct HIV transmission networks based on patients genetic, demographic and clinical data. The method is based on real patients data and considers epidemiological factors as well as viral genome data for network construction. We first built a network of HIV infected patients based on their social and treatment information. The network is then combined with a genetic network, to infer a hypothetical infection transmission network. We applied this method to a cohort study of HIV-1 infected patients in central Italy and found that patients who have been highly connected in the network have had longer untreated infection periods. We also found that the network structures for homosexual males and heterosexual populations are heterogeneous, consisting of a majority of “peripheral nodes” that have only a few sexual interactions and a minority of “hub nodes” that have many sexual interactions. Inferring HIV-1 transmission networks using this novel combined approach revealed remarkable correlations between high out-degree individuals and longer untreated infection periods. These findings have signified the importance of early treatment and supported the potential benefit of wide population screening, management of early diagnoses and anticipated antiretroviral treatment to prevent viral transmission and spread. The approach presented here for reconstructing HIV-1 transmission networks can have important repercussions in the design of intervention strategies for disease control.
Reconstruction of the infection transmission networks and understanding HIV dynamics requires insight into viral genome data as well as social interactions. We argue that combining data from different scales is required for a more realistic description of complex systems behavior such as transmission of infectious disease and HIV epidemic.

We presented a formal definition of the CANs concept and reviewed the use of CANs in modeling complex systems. We argue that complex networks provide global-patterns of the system behaviors, while agents capture the individual-level dynamics. The applications of CANs in epidemiology, ecology and economics presented in Chapter 5, show an apparent transition of modeling methodology from simpler ones such as cellular automaton models, to agent models, and then to agent-and-network hybrid models. This complies with our observation that moving towards more comprehensive modeling approaches such as CANs is required for understanding real-world complex systems.