Modeling Evolutionary Dynamics of HIV Infection

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Abstract. We have modelled the within-patient evolutionary process during HIV infection. We have studied viral evolution at population level (competition on the same receptor) and at species level (competitions on different receptors). During the HIV infection, several mutants of the virus arise, which are able to use different chemokine receptors, in particular the CCR5 and CXCR4 coreceptors (termed R5 and X4 phenotypes, respectively). Phylogenetic inference of chemokine receptors suggests that virus mutational pathways may generate R5 variants able to interact with a wide range of chemokine receptors different from CXCR4. Using the chemokine tree topology as conceptual framework for HIV viral speciation, we present a model of viral phenotypic mutations from R5 to X4 strains which reflect HIV late infection dynamics. Our model investigates the action of Tumor Necrosis Factor in AIDS progression and makes suggestions on better design of HAART therapy.

1 Introduction

Evolutionary biology was founded by Charles Darwin on the concept that organisms share a common origin and have subsequently diverged through time. Molecular phylogenetics has provided a statistical framework for estimating historical relationships among organisms, and it has supplied the raw data to test models of evolutionary and population genetic processes. Those have found practical uses in tracing the origins of pandemias and the routes of infectious disease transmission. Our ability to obtain molecular data has increased dramatically over the last two decades and large data sets describing a wide range of evolutionary distances are used in population genetic, phylogeny and epidemiological studies. Nevertheless, phylogenetic methods based on sequence information represent often an oversimplification when we aim at capturing the short time dynamics, i.e. the early stages of the speciation process. Population genetics focuses on this topic by investigating the behavior of mutations in populations. This discipline is related to the other important idea that Darwin expressed in The Origin of Species [1], that the exquisite match between a species and its environment is explained with natural selection, a process in which individuals with

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beneficial mutations leave more offspring. Here we combine predictive quantitative theories of HIV evolution in the context of the selection pressure generated by the virus competition and the immune response. In particular phylogenies of the natural target of the HIV viruses, i.e. their cell receptors is combined with population genetics mathematical models. We show that combining the two leads to a better understanding of the complex molecular interaction underlying the macroscopically observable phenomena of HIV infection.

The smallest scale of molecular evolution generates genetic variability at population level. A special case is that of quasispecies which are clouds of very similar genotypes that appear in a population at mutation-selection balance [2]. Since the number of targets (the substrate) is limited, fitter clones tend to eliminate less fit mutants, which are subsequently regenerated by the mutation mechanism [3]. They are the combined result of mutations and recombination. Other sources of variability result from co-infection (simultaneous viral infection), superinfection (delayed secondary infection). On the contrary, selection and random drift decrease variability. The fact that deleterious or less fitted variants are not instantaneously counter selected allows for the coexistence and co-evolution of different strains of a virus within the same host. Although the conditions for the formation and survival of new strains have not always been understood, small scale evolution such as variability at population level may experience different mutation/selection balance than the genetic variability estimated from sequence analysis which represent fixed genotypes. Indeed, recent studies show that the rate of molecular evolution appears to accelerate when measured over evolutionary short timescales [4], which strongly contrast with substitution rates inferred in phylogenetic studies. Molecular virology studies appear the natural benchmark, given that viruses have usually very high mutation rates and large populations. We aim at modelling viral multi strain short and long term evolutionary dynamics during the immune response. The multi strains can be thought as viral populations. Since there is a tremendous lack of studies attempting at integrating population and phylogenetic studies, our work represents the efforts to link speciation at small and large evolutionary scale. This may result in a better understanding how to use the topology and branch lengths of existing species to predict future evolution.

In the next section we describe the relevant feature of the immune response which represents the selection pressure playing a key role in the speciation process. Then we use data from chemokine receptor sequences to estimate the rate of phenotype change in the virus and use this data to derive a selection-mutation model based on a set of differential equations. In the results we show that the models introduced are suited to model both short and long term evolutions. In particular we first show an example of speciation dynamics of viral population mediated by the immune system response. Then we model the phenotypic switch in co-receptor usage in HIV-1 infection and we also make some observations on the better design for HAART therapy. Finally we draw our conclusions.