A virtual laboratory for decision support in viral disease treatment

The Complex Automata Model of HIV-1 Co-receptor Tropism: Mutation Rate Verified

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Introduction

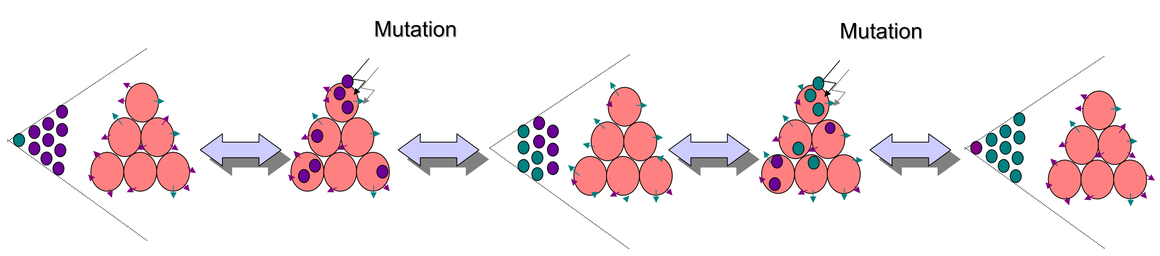
Early infection with human immunodeficiency virus (HIV) is characterized by the predominance of CCR5-tropic (R5) virus. However, over the course of infection CXCR4-tropic (X4) virus appears in the later stage of the infection in approximately 50% of the infected individuals and usually precedes an accelerated CD4+ T cell depletion with rapid disease progression [4], [5].

Objective

To investigate the interaction between HIV-1 quasispecies population and the changes in the target cell co-receptor designation in the disease course. Seek if “the longitudinal niche change” can be an answer to the co-receptor switch?

Model

Schema of co-receptor tropism dynamics



To answer whether “the longitudinal niche change” can be an answer to the co-receptor switch dilemma, we have hypothesized a sterile model in-silico which consists of identically configured, stationary T helper cells and mobile, freely mutating virus population forming new quasispecies in terms of co-receptor tropism for R5, R5X4 or X4, where R5X4 population was defined as the intermediate phenotype.

Materials & Methods

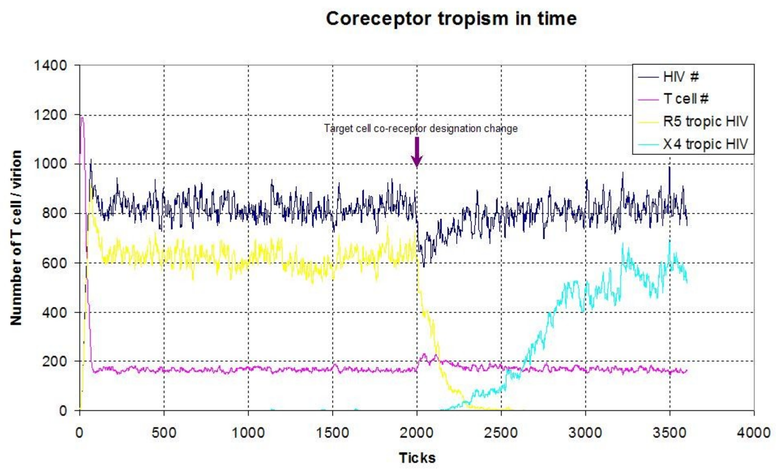
The model has been programmed in the Java based environment of NetLogo 4.0 [8] on 41x41 automata with Cartesian coordinates and discrete time step of six hours. Two kinds of agents are defined:

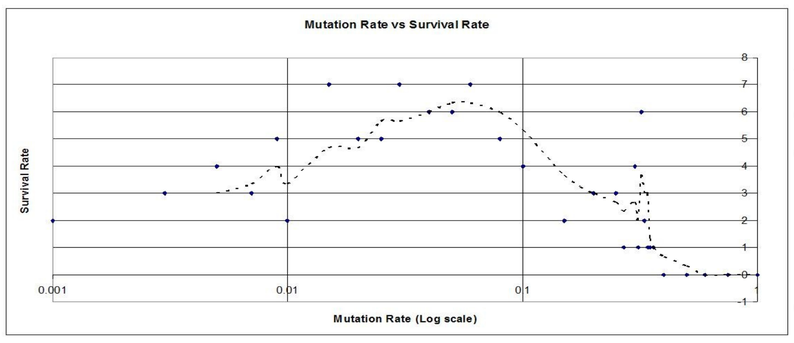
CD4+ T cell agents are stationary with CCR5 and CXCR4 coreceptor designation which is modified throughout the simulation. They have two states healthy or infected.

Virus agents are mobile (random walk), able to bind to an uninfected CD4+ T cell agent and have preference for R5, R5X4 or X4 co-receptor for entry.

The total simulation time has been chosen as thirty months (3600 steps) in which the co-receptor designation of the CD4+ T cell agents have been modified at two different points for investigating the viral response and testing whether the switch can be observed. First is at time step fifty in favor of R5 tropic strain and the next one is at step two thousand in favor of X4 tropic strain.

Results





In the simulations we observed the viral quasispecies population evolving over time, accumulating mutations and converging to R5 or X4 tropic strain as dominant co-variants when it is favourable by the environment.

Another experiment was conducted for investigating the effects of mutation rate on the viral population. It has been observed that slow mutation rate weakens the virus population's ability to cope up with the co-receptor designation change and results in a smaller viral population whereas high mutation rate has a devastating effect on the viral quasispecies.

Conclusion

Bottlenecks in the available target cell population, are important for reinforcing inter-viral competition. As a result, the chance of successive viral clones to be selected against the less favourable ones is increased.

Our results show that the error threshold for HIV-1 mutation rate is about 30 fold the actual mutation rate which is in accordance with in vitro studies by Mansky et al. 2002.

In addition the results of the simulation indicates that the diversity in the virus population, accumulated during the disease course was sufficient to overcome the challenges in co-receptor designation of target cells. Therefore the changes in the environment and target cell range/conformation seem to be the main candidates for being the driving factor of the co-receptor switch in HIV disease course.

References

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