Towards assessing therapy failure in HIV disease: estimating in vivo fitness characteristics of viral mutants by an integrated statistical-mechanistic approach

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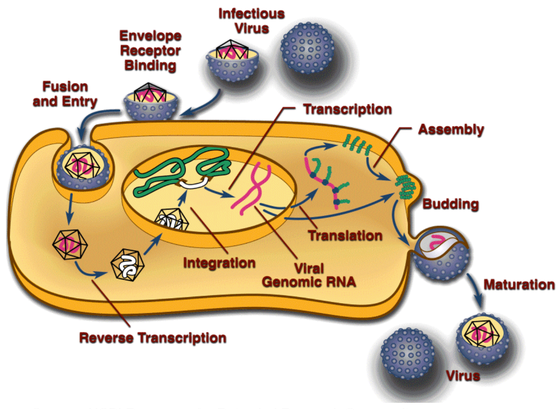
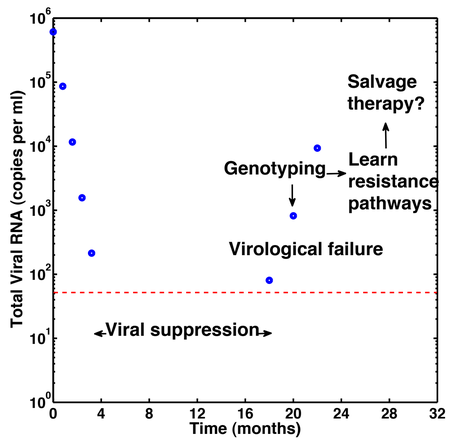
Background

Mechanistic viral infection models have long been used to investigate *in vivo* viral dynamics [1], while statistical models [2] have been applied to learn mutational schemes from genotyping data after virological failure in patient cohorts.

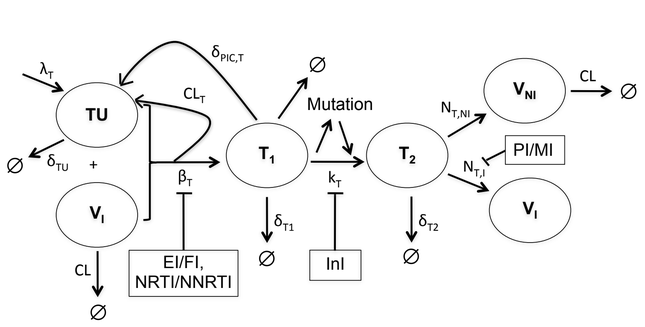


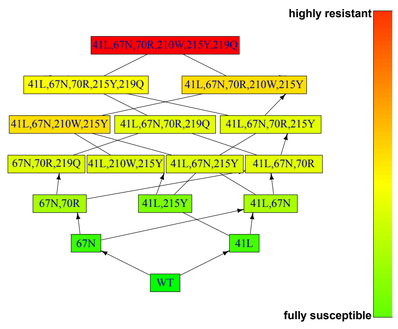
Source : NCBI Resources for Retroviral Research Community



We developed a methodology to integrate these two modelling strategies and then evaluated our combined approach by estimating fitness characteristics of various mutants arising under anti-HIV therapy with zidovudine (ZDV), a reverse transcriptase inhibitor and indinavir (IDV), a protease inhibitor.

Objective

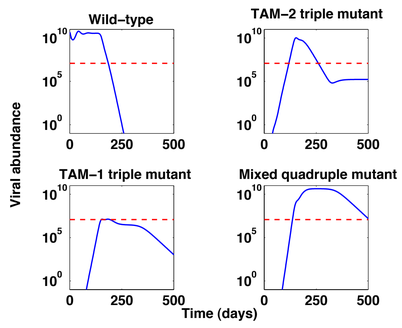




Viral dynamics model

Deterministic/stochastic simulations

Viral load predictions
(mechanistic rebound times of mutants)



Realistic incorporation of mechanism of action

Statistical genotype lattices (clinical data)

Average waiting time to different mutations (*in vivo*)

Resistance factors (learned statistically)

Combination desirable

Realistic mutation schemes

Objective: ***Assess causes of treatment failure and aid choice of salvage regimen***

Methods

Viral dynamics model: We used a two stage viral dynamics model [3] parametrized in terms of infection rates, fitness costs (s) and mechanistic resistance factors (res). We modelled drug effect by inhibiting targeted reactions:

$$k_i \to k_{\mathrm{wt}} \cdot (1 - s_i) \cdot (1 - \varepsilon_i)$$

$$\varepsilon_i = \frac{C_{\mathrm{drug}}/\mathrm{IC50}^i_{\mathrm{mech}}}{1 + C_{\mathrm{drug}}/\mathrm{IC50}^i_{\mathrm{mech}}} \qquad \mathrm{res}_i = \frac{\mathrm{IC50}^i_{\mathrm{mech}}}{\mathrm{IC50}^{\mathrm{wt}}_{\mathrm{mech}}}$$

Statistical resistance model: We used conjunctive Bayesian networks (CBNs) that were learned from clinical data (the HIV Stanford database) by EM-algorithm and predicted average waiting times to different mutations. Phenotypic resistance factors (RF) were learned from *in vitro* data by isotonic regression:

$$\mathrm{RF}_i = \frac{\mathrm{IC50}^i_{\mathrm{pheno}}}{\mathrm{IC50}^{\mathrm{wt}}_{\mathrm{pheno}}}$$

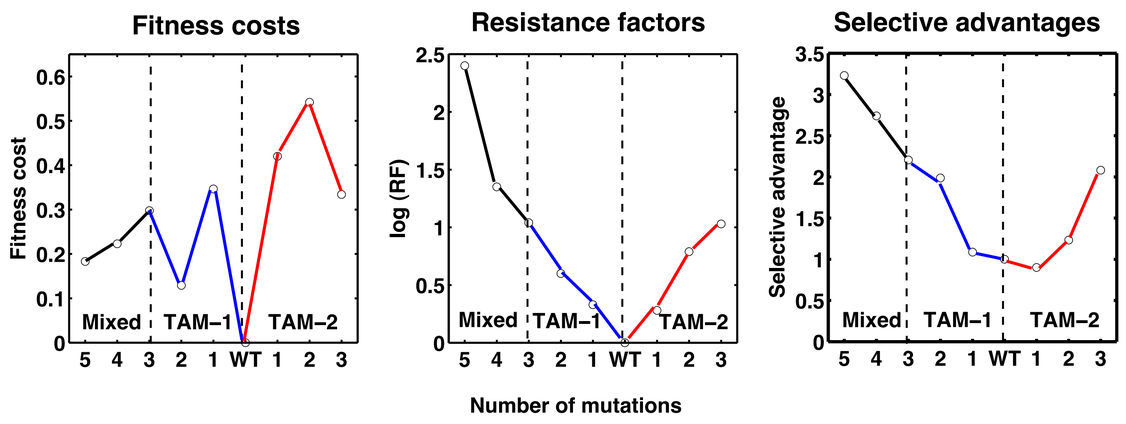
Results

Linking mechanistic and phenotypic resistance factors: We showed that for our drug effect model, res = RF under the conditions of the phenotypic replication assay.

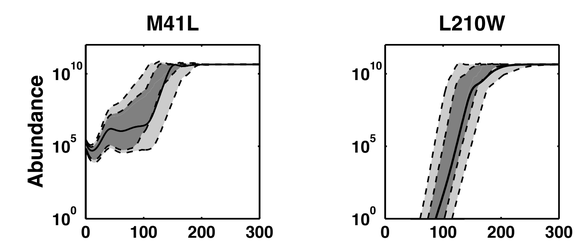
Linking mechanistic and statistical waiting times to mutations: Average statistical waiting times to different mutations were computed from the CBN representation. Analogous mechanistic waiting times were written as

$$T_{j,\mathrm{mech}} = \inf\{t \geq 0 : \sum_{\substack{m_i \in \mathcal{G} \\ m_i \ni j}} V_{m_i}(t) > 0.2 \cdot V_{\mathrm{tot}}(t) \ \text{ and } V_{\mathrm{tot}}(t) > \mathcal{D}\}.$$

A least squares optimization by repeated rounds of simulated annealing and simplex search algorithms was used to estimate fitness costs of ZDV mutants:



Excellent agreement with literature on various features is observed. The clustering of mutations along the well-known TAM-1 and TAM-2 pathways is noted. The TAM-1 mutants are observed to incur a lower fitness cost compared to their TAM-2 counterparts.



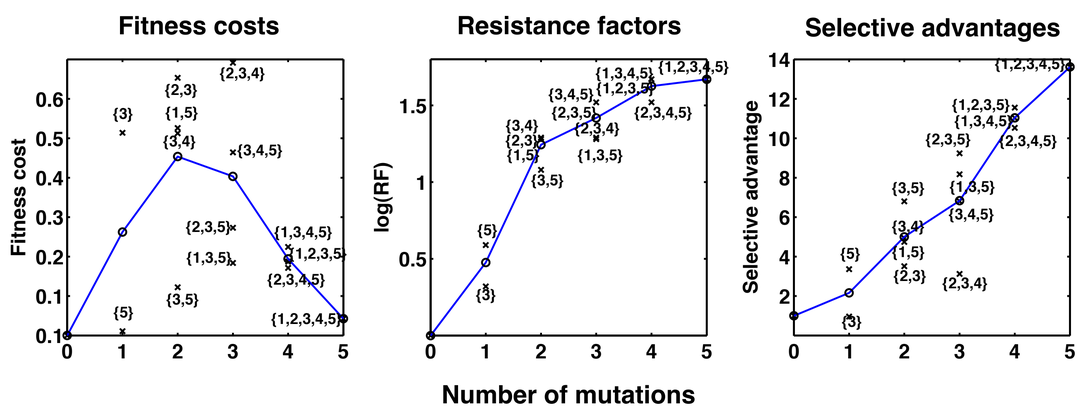
We also estimated fitness characteristics in the presence of ZDV by using the selective advantage for a mutant i given by

$$\mathrm{SA}_i = \frac{(1 - s_i) \cdot (1 - \varepsilon_i)}{(1 - \varepsilon_{\mathrm{wt}})}.$$

This quantity captures the combined effects of fitness costs and resistance factors.

Since we used a mechanistic model, we also had access to time course accumulation of different mutations. Further, our setting also allowed us to examine epistatic effects (not shown).

To demonstrate the generality of our approach, we also estimated fitness costs for mutants arising under IDV therapy. Here again, we note excellent agreement with established fitness characteristics:



We recovered the staircase feature in the protease inhibitor fitness landscape. We also note the compensatory role played by the mutation A71V (site 3). Initial mutations confer significant resistance while also incurring large fitness costs. The incentive for later mutations appears to be a recovery in fitness.

Conclusions

Such an integrated statistical-mechanistic modelling approach has several advantages. It utilizes realistic mutation schemes while retaining mechanistic features of the viral dynamics. Further work includes extending the approach to multiple drug regimens and examining treatment switching outcomes. Fitness landscapes also play an important role in treatment interruptions and novel therapeutic approaches such as targetting the error catastrophe [5].

References

[1] Ho DD et al. (1995) Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373: 123-126, [2] Beerenwinkel N et al. (2005) Estimating HIV evolutionary pathways and the genetic barrier to drug resistance. J Infect Dis 191: 1953–1960, [3] von Kleist M et al (2009) Drug-class specific impact of antivirals on the reproductive capacity of HIV. PLoS Comput Biol 6(3): e1000720, [4] Beerenwinkel N et al (2009) Markov models for accumulating mutations. Biometrika 96: 645-661, [5] Crotty et al (1999) RNA virus error catastrophe : Direct molecular test by using ribavirin, PNAS 98:6895-900

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