Entrenchment and Evolution of drug resistance in HIV

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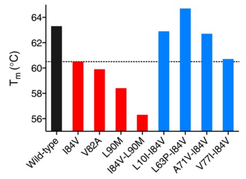
Co-evolutionary model of HIV

Motivation



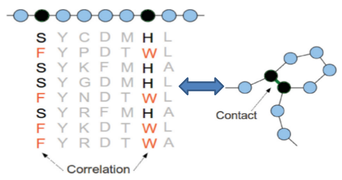
Accessory mutations maintain stability in drug-resistant HIV-1 protease [2]

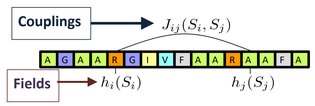
Drug-resistance mutations like I84V-L90M are very detrimental yet occur in roughly **~10%** of drug-treated patient sequences in the Stanford HIV Database. If so detrimental, what mechanisms lead to their presence in ~10% of sequences in the Stanford HIVDB?

The fitness effects of a mutation at one point in the genome is dependent on the full pattern of mutations at all other points: '**Epistasis**'.

We built a Potts statistical model (based on a protein multiple sequence alignment) to understand the role epistasis plays in large patterns of resistance mutations in HIV-1.

Potts statistical models to understand the role of epistasis





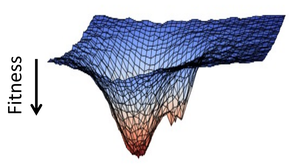
Couplings reflect epistatic interaction strengths.

Potts statistical energy:

$$E(S) = \sum_i h^i_{S_i} + \sum_{ij} J^{ij}_{S_i S_j}$$

Probability of sequence appearing in the MSA

$$P_S \propto e^{-E(S)}$$

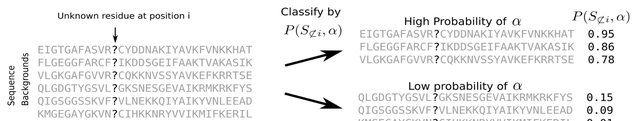


Potts Statistical Energy Landscape (probability)

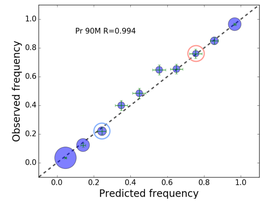
The Potts statistical energy of a protein sequence S, E(S), defines a "**prevalence**" landscape reflecting the protein sequence's likelihood or "**fitness**".

E(S) allows us to:
- **Score the effect of mutations**
- **Explore the effects of epistasis**

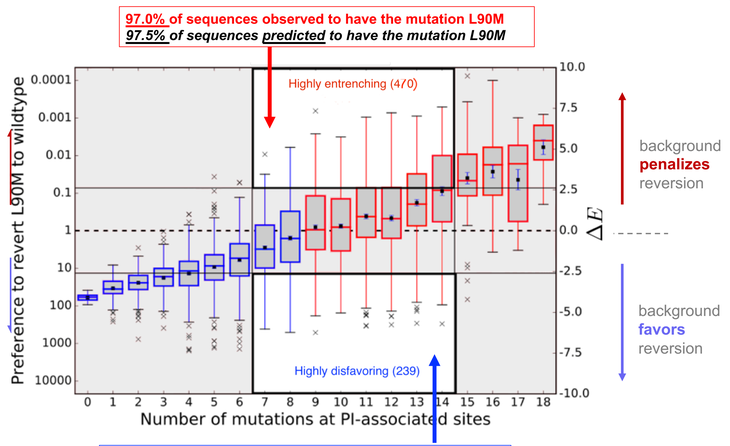
Verifying "Epistasis" in HIV



Given a background, the Potts model accurately predicts the likelihood of a residue occurring at the missing position based on the knowledge of the epistatic interactions with the background.



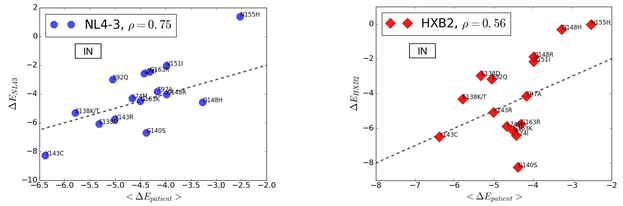
"Entrenchment" of drug resistance in HIV



As accessory mutations accumulate, primary resistance mutations which are generally deleterious in the wild-type background can become favorable or "**entrenched**" in backgrounds with compensatory mutations such that there is a fitness penalty for reversion of the primary mutation.

Entrenchment of drug resistance →transmitted resistance → non-reversal on halting drug therapy.

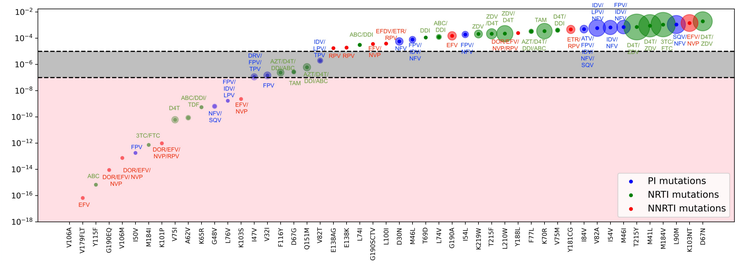
Epistatic effects in specific backgrounds



Epistatic effects of mutations (shown in HIV IN) can vary widely from patient viral sequences to laboratory clones (like NL4-3, HXB2),

Drug-resistance testing in HIV is carried out in backgrounds of specific laboratory clones like NL4-3, HxB2, etc, and can result in wrong regimen selection, indicating that the way forward may be "personalized medicine".

Are entrenching sequences pre-existent in drug-naïve individuals?



We used reweighting techniques (UWHAM) to estimate the likelihoods of highly entrenching sequences for drug-resistance mutations otherwise only observed in the drug-experienced population to be present in the drug-naïve population.

The consequence? Drug resistance can arise much faster if highly entrenching sequences are pre-existent.

References

1. Biswas, Avik, et al. "Epistasis and entrenchment of drug resistance in HIV-1 subtype B." *Elife* 8 (2019): e50524.

2. Chang, Max W., and Bruce E. Torbett. "Accessory mutations maintain stability in drug-resistant HIV-1 protease." *Journal of molecular biology* 410.4 (2011): 756-760.