Intra-patient evolution of HIV

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Outline

Longitudinal data, envelope gene

• Recombination rate of HIV
• Selection strength in env

Drug resistance evolution

• Ultra-deep sequencing data
• Method to estimate selection strength
HIV evolution

Population size: \( N = 10^{10} \pm ? \)
Genome size: \( L = 10^4 \text{bp} \)
Generation time: \( T = 2d \)
Mutation rate: \( \mu = 3 \times 10^{-5} /\text{bp/\textit{gen}} \)
Recombination rate?? Selection strength??

Outline:
1. Estimation of recombination rate in the envelope gene
2. Estimation of the strength of selection in \textit{env}
3. Dynamics of drug resistance evolution, selection in the \textit{pol} gene
Intra-patient evolution

Since HIV populations evolve at a rate that is several orders of magnitude faster than that of their human hosts, HIV sequences sampled longitudinally will usually accumulate a significant amount of evolutionary change. Longitudinally sampled or "heterochronous" sequences can be obtained in one of two ways: either from a single patient over the course of infection, or from different patients over the duration of an epidemic (Fig. 1).

Interestingly, phylogenies reconstructed from such sequences have distinctive features that reveal the differences in the dynamics of HIV evolution at the inter-host and intra-host levels.

Within each host, the viral population is targeted by both cellular and humoral immune responses, resulting in relatively strong diversifying selection that is most noticeable in the variable regions of the envelope (env) gene. It has been demonstrated that the rate of amino acid substitution in env correlates with the rate of phenotypic escape from neutralizing antibodies. This implies that neutralizing antibody responses cause the relative fitness of different strains within an infection to vary, thus constituting a major force that drives rapid lineage turnover. As a result, intra-host phylogenies of heterochronous env sequences exhibit an asymmetric or "ladder-like" shape, with limited diversity at any one time (Fig. 1).

In contrast, HIV evolution at the inter-host level shows little evidence that HIV transmission is driven by a similar selective process. Inter-host phylogenies of HIV sampled through time are not ladder-like and show the persistence of multiple lineages through time (Fig. 1).

In summary, HIV lineages within a host vary in their ability to survive and infect new cells, whereas different HIV lineages among hosts show little genetic variation in their ability to infect new individuals. Some lineages...
Recombination in HIV

Template switching rate: 3-10 events per replication and genome (Levy et al, 2004)
Recombination in HIV

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Template switching – Levy et al.

Dynamics of HIV-1 recombination in its natural target cells, Levy et al, PNAS, 2004
Template switching – Levy et al.

Dynamics of HIV-1 recombination in its natural target cells, Levy et al, PNAS, 2004

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Recombination in HIV

Relevant effective recombination rate:

Template switching \times\text{ coinfection frequency}

Estimation using population genetic models, Shriner et al. 2004:

\[ \rho = 8 \times 10^{-6} - 1.4 \times 10^{-4} \text{ per site and generation} \]

- implies a very high coinfection frequency
- rests on the assumptions of the neutral coalescent
Data – Shankarappa et al 1999

- 11 Patients (part of the MACS cohort)
- 10-20 samples over up to 10 years
- 10-20 partial env sequences (700bp, C2V5)
- some received therapy at later time points
Recombination in HIV

Crossover

\[ d \]

\[ \Delta t \]
Recombination in HIV

Crossover

\[ d \]

\[ \Delta t \]

\[ P(\text{haplotype present}) \]

Distance [bp]

0.0 0.1 0.2 0.3 0.4 0.5

0 100 200 300 400 500

- recombinant haplotype
- other haplotypes
- weighted mean

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Recombination in HIV

\[ p_{AB}(t) = p_A p_B + (p_{AB}(t_0) - p_A p_B) e^{-\rho d(t-t_0)} \]

\[ \rho \approx \frac{\alpha}{\langle M p_A p_B \rangle} \]
Effective recombination rate

Mean: $1.51 \times 10^{-5}$/gen/site
Median: $1.38 \times 10^{-5}$/gen/site
Std dev: $0.55 \times 10^{-5}$/gen/site

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RN and Thomas Leitner, PLoS Comp Bio, 2010
KITP, 2011
Effective recombination rate

About a factor 50 lower than the template switching rate.

Coinfection < 5%

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RN and Thomas Leitner, PLoS Comp Bio, 2010

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Selection in HIV evolution

\[ \frac{dp}{dt} = p(1 - p)s \]

- \( s = 0.04 \)
- \( \Delta t \)
- \( \Delta p \)
Selection in HIV evolution

Selection for red will affect green

Selection strength: $s = 1\%-2\%$

Turnover in 50-100 generations

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Drug Resistance Evolution

Anti-retroviral drugs:
• Protease inhibitors (PI)
• Nucleoside-Analog Reverse transcriptase inhibitors (NRTI)
• Non-Nucleoside-Analog RT inhibitors (NNRTI)
• Integrase inhibitors

Drug resistance can emerge fast (weeks) or take decades to set in.

Collab: Jan Albert at the Karolinska Institute, Stockholm
• 10000 sequences from each sample
• 180-200 aa of the reverse transcriptase
Drug Resistance Evolution

Figure 1. Frequency of resistance drug resistance mutations M184V, T215Y, L210W and T215C/D before, during and after treatment. Treatment history is indicated by bars below each patient's graph; AZT; zidovudine, 3TC; lamivudine, d4T; stavudine, ddI; didanosine, ABC; abacavir, ddC; zalcitabine, TDF; tenofovir, NNRTI; non-nucleoside reverse transcriptase inhibitors, PI; protease inhibitors. Arrows indicate time for sampling. The dashed horizontal lines indicate the detection limit in each patient. ND: not detectible.

Dissection of HIV-1 Resistance

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Drug resistance evolution

- Tremendous diversity, lots of rare variants (~50 in 120bp)
- Rapid shifts in the population, latency
- Which variant is replacing others, how fast, and why?
The signature of selection

- Observation: Each amino-acid sequence comes in multiple variants
- The abundances of these variants often show a regular pattern

\[ n_0 > n_1 > n_2 \ldots \]
The signature of selection

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\[
\frac{n_i}{n_0} \sim \frac{1}{i}
\]

\[
\frac{n_i}{n_0} = \frac{\mu}{i s}
\]
Signature of a sweep

\[ n_0(t) = e^{(s-\mu)t} \]

\[ \int_0^t dt \mu e^{(s-\mu)t'} \approx \frac{\mu e^{(s-\mu)t}}{s - \mu} = 1 \]

\[ t_i = \frac{1}{s - \mu} \log \frac{i(s - \mu)}{\mu} \]

\[ \frac{n_i(T)}{n_0(T)} = \frac{e^{(s-\mu)(T-t_i)}}{e^{(s-\mu)T}} = \frac{\mu}{i(s - \mu)} \]

Strength of selection: 5-10%
Star-phylogeny
Soft sweeps

\[
\text{relative abundance } n_i / n_0
\]

\[
\text{rank } i
\]
Fast sweep

Rare variants consistent with $\nu = \mu t$

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Genetic hitch-hiking

Selection for red will affect green

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