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How does HIV-1 drug resistance evolve at a population level?

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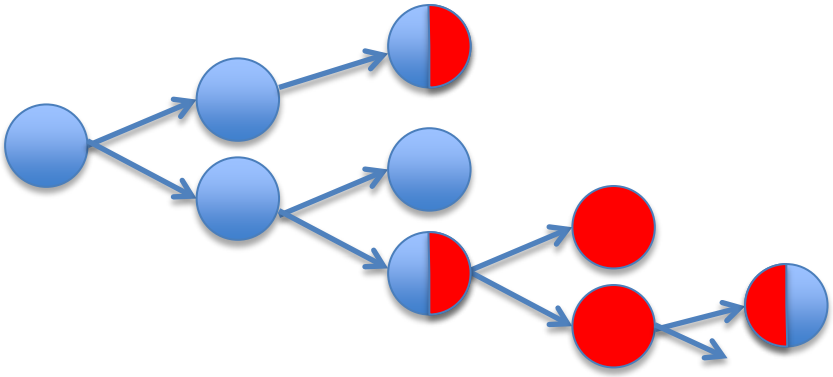
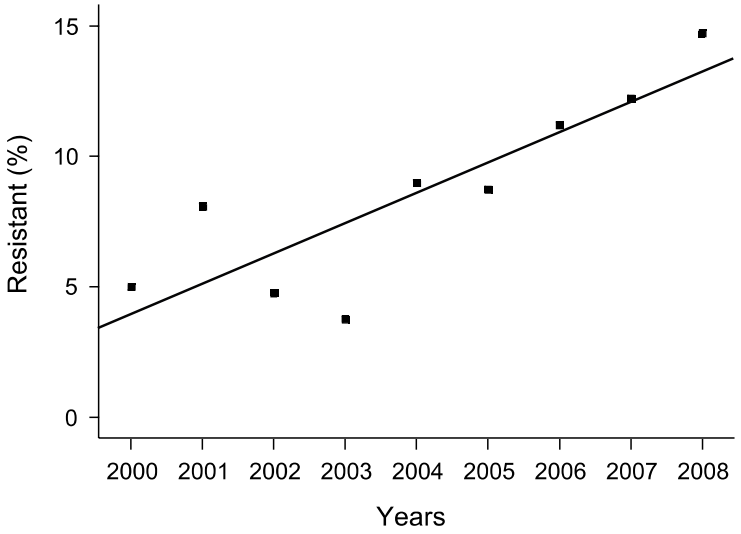
HIV drug resistance

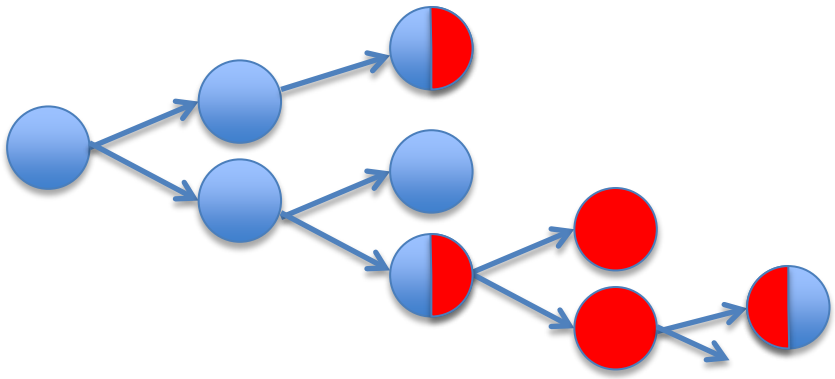
- Many drugs and drug regimens available (Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents 2012).
- Treatment failure by resistance mutations is common (Gupta et al. Lancet Infectious Diseases, 2009).
- Transmitted drug resistance is increasing (Yerly et al. AIDS, 2009).
- Some evidence for reversion to drug-sensitive wild type, but transmitted drug resistance can persist (Little et al. Journal of Virology, 2008).





Questions

- What are the rates of drug resistance evolution and reversion?
- How transmissible are resistant strains?
- Can there be a self-sustaining epidemic of resistant virus?



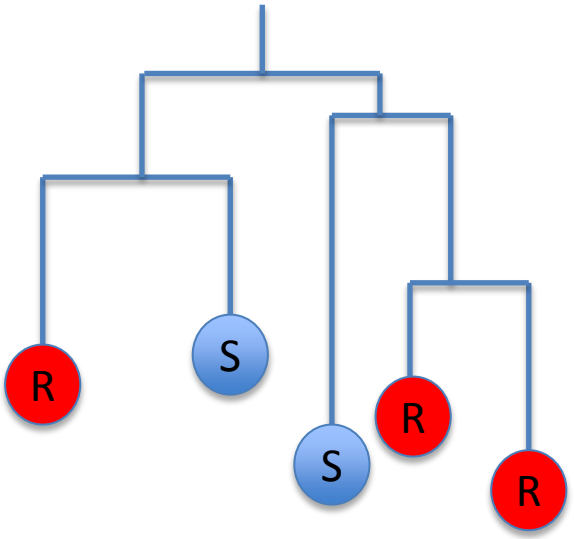
- Cohort studies/medical records:
  - Measure incidence of transmitted drug resistance.
  - Measure rates of treatment failure/presence of drug resistance mutations.
  - Measure reversion of *de novo* and transmitted resistance.

- Do these individual rates apply to the whole population?

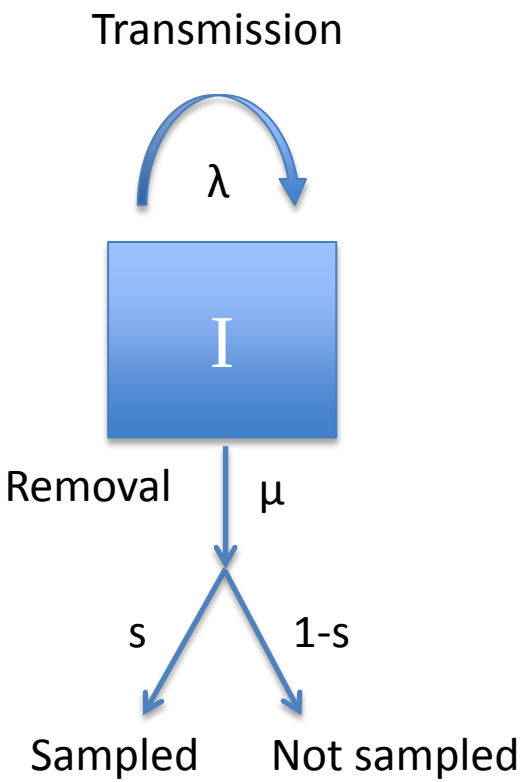
Measure at the population level

- Potential for study based on HIV genetic data.
- *pol* gene routinely collected to test for transmitted resistance.
- From such data we could:
  - Reconstruct phylogeny.
  - Identify drug resistance.

- What does the phylogeny tell us about drug resistance evolution?

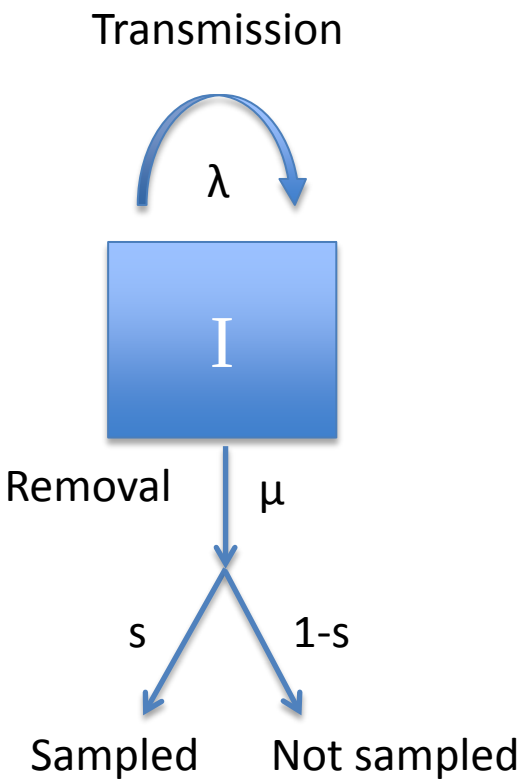


Birth/death model

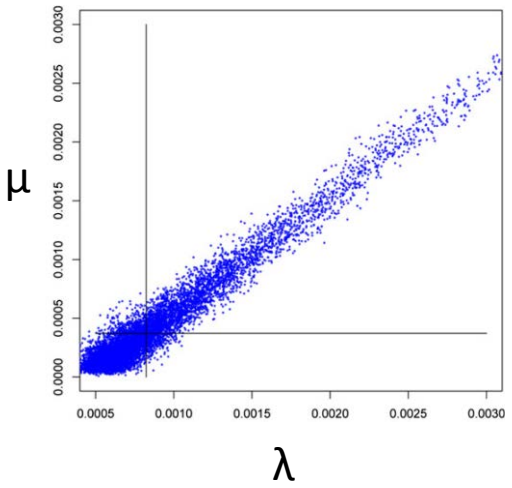


- Model for production of a phylogeny.
- Originally used for modelling macro-evolution (Nee et al. Annual Reviews of Ecology Evolution and Systematics, 2006)
  - "Speciation/extinction" models.
- We use a "transmission/removal model".
- For a set of birth/death parameter values, the likelihood of a previously inferred phylogeny can be calculated.

Estimate parameters



- Analytically tractable to find λ, μ and s.
- Large correlation between λ and μ, hard to estimate independently.

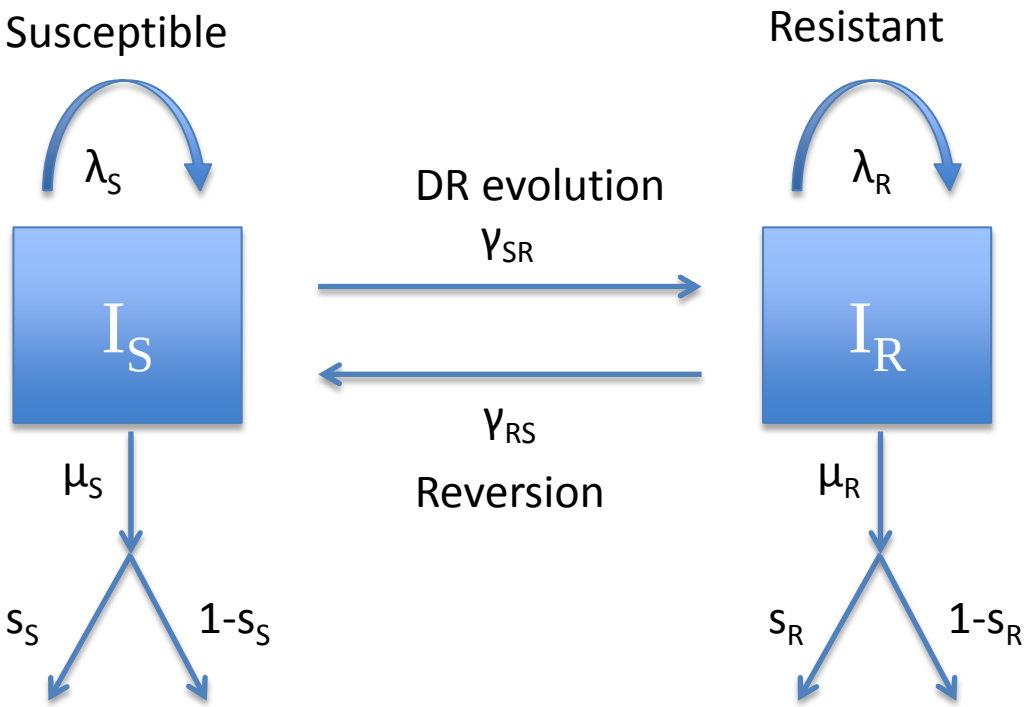


- Used to infer $R_0 = \frac{\lambda}{\mu} = 2.29$
- Basic reproduction number:
  - How many new infections does each infection produce in a susceptible population?
  - Measure of the per generation growth rate of the epidemic.

(Stadler et al. 2012 Mol Biol Evol)

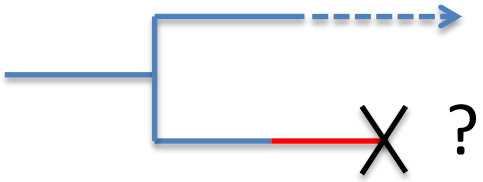
Two strain model

- Birth-death model for each strain.
- Includes rates of mutation back and forth.



Simulating a tree

- Produce birth/death tree with give rates of DR evolution and reversion.
  - From root to tip.
  - At each point a branch can:
    - Transmit (bifurcate).
    - Switch DR status.
    - Die/become uninfectious.
    - Upon death, sampling may occur.
    - So on until n tips are sampled.
    - Tree is reconstructed from *sampled* tips.



Testing the model

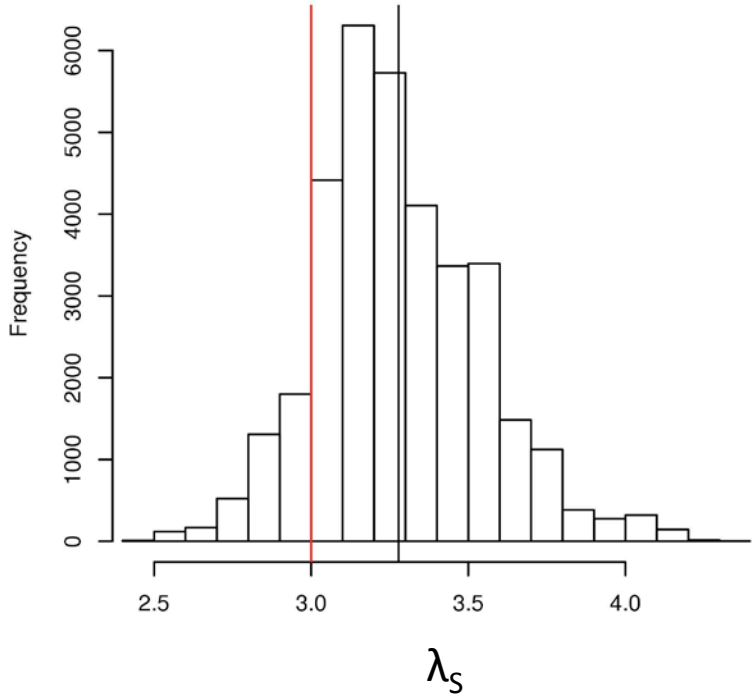
- "True" parameter values picked at random.
- Tree with n tips constructed.
- MCMC to estimate the parameters.

- Too many: fix sampling probabilities.
  - Arguably the easiest parameter to estimate from epidemiological data.

- Posterior estimates of parameters.

λ_S , λ_R	Transmission rates
μ_S , μ_R	Death rates
s_S , s_{Rv}	Sampling probabilities
γ_{SR} , γ_{RS}	Drug resistance mutation rates

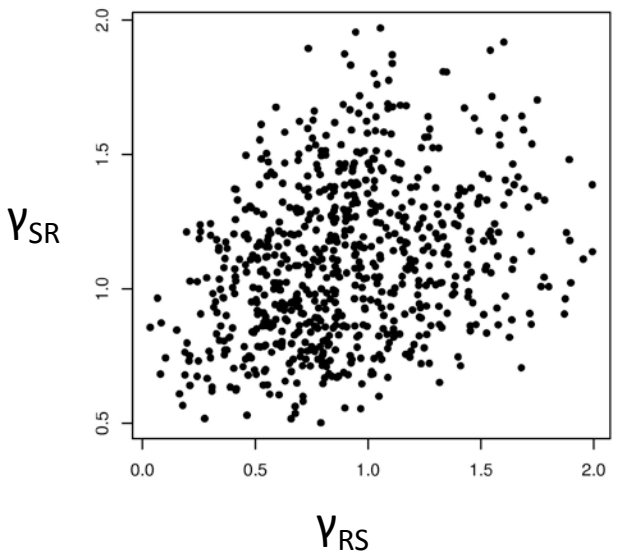
True value
Mean estimate



Correlations

- Correlations between parameters:
  - Problems searching parameter space.

r=0.29



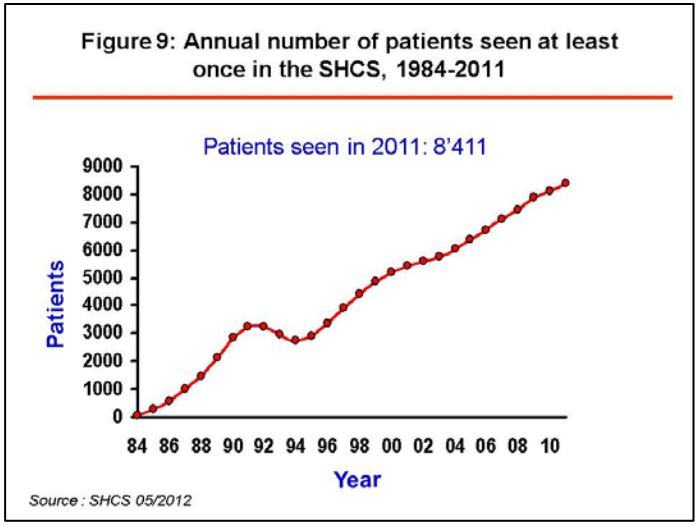
- Use informative priors.
- Use clinically relevant summary measures.
- Basic reproduction numbers important if resistance transmits easily.

$$R_{0R} = \frac{\lambda_R}{\mu_R}$$

- If resistance spreads poorly, within-host rates of evolution become more important.
  - Evolutionary rate ratio: $\frac{\gamma_{SR}}{\gamma_{RS}}$
  - Net evolutionary rate: $\gamma_{SR} - \gamma_{RS}$

Future application to data

- Application to Swiss HIV Seroconverters Cohort.
- Well-sampled drug resistance data.



- Important in predicting risk of resistance following roll-out in high prevalence areas.
- In absence of data, attempt to extrapolate to Sub-Saharan African settings.

Genotypic resistance

- What is considered genotypic resistance?
  - Identify particular mutations?
    - (Stanford Drug Resistance Database)
  - Use geno2pheno?
    - (Beerenwinkel et al. Nucleic Acids Research, 2003)
  - Problems with independence of drug resistance and phylogenetic data.

- Within-host diversity.
  - Individuals may carry sensitive and resistant strains.
  - Use earliest available data for each individual.
  - Can this strain mix be modelled without many more parameters?

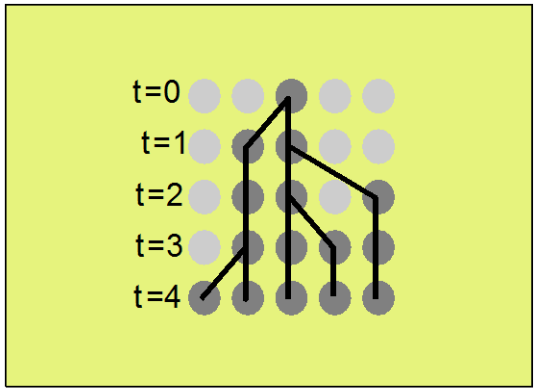
Conclusions

- Drug resistance and its transmission are increasingly important.
- HIV genetic data and birth/death framework can be used to estimate parameters.
  - Transmission and removal rates.
  - Rates of drug resistance evolution and reversion.
- Test methods on simulated data.
- Correlations between parameters requires consideration.
- Future applications to data.
  - Address what constitutes resistance.

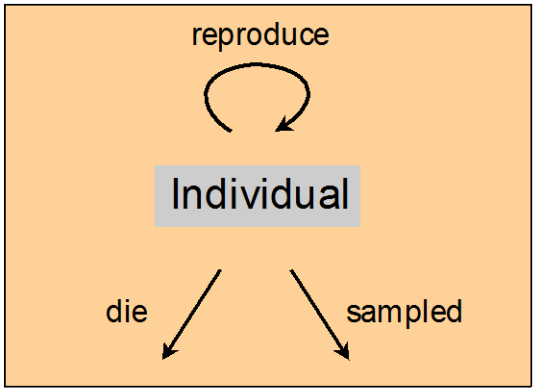
Acknowledgements

- ETH
  - Resistance Club
  - Roland Regoes
- Swiss HIV Seroconverters Cohort
  - Roger Kouyos
  - Huldrych Günthard
- CNRS Montpellier
  - Matthew Hartfield
  - Samuel Alizon

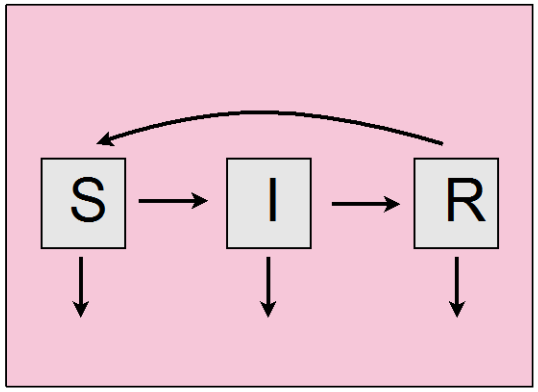
Linking phylogenetics and epidemiology



- **standard model:**
  - population genetics
- **analytical understanding:**
  - very good
- **Biological realism:**
  - poor
  - constant pop size
  - discrete time
  - sparse sampling
  - birth equals death

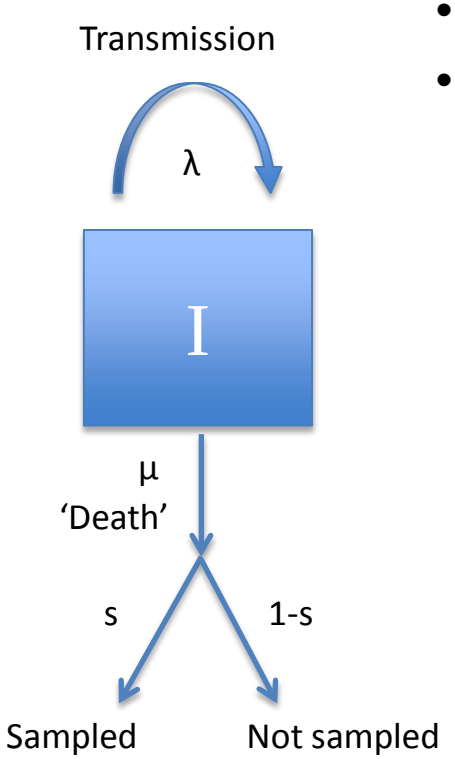


- **standard model:**
  - species trees
- **analytical understanding:**
  - good
- **Biological realism:**
  - better
  - inc/decreasing pop size
  - continuous time
  - sparse or dense sampling
  - birth/death independent

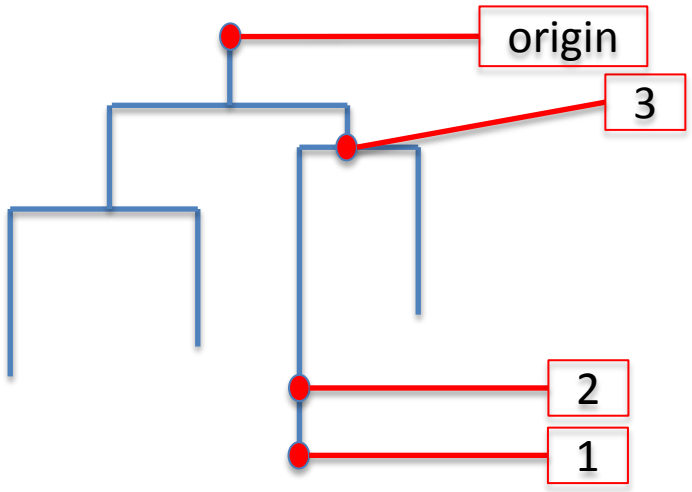


- **standard model:**
  - epidemiology
- **analytical understanding:**
  - poor
- **Biological realism:**
  - good
  - changing pop size
  - continuous time
  - accounts for temporal changes of susceptibles/infecteds

Birth-death models



- Estimate parameters from an inferred phylogeny.
- Calculate likelihood from tips upwards.
  - How likely is this subtree given the model?
  - p(1)=p(Death and sampling)
  - p(2)=p(No death and no sampled transmissions) * p(1).
  - p(3)=p(Transmission)*p(3a)*p(3b).
  - Likelihood = p(origin)



(Stadler 2010 J Theo Biol)