

# Modeling recombination's role in the evolution of HIV drug resistance

R. K. Belew

M. W. Chang

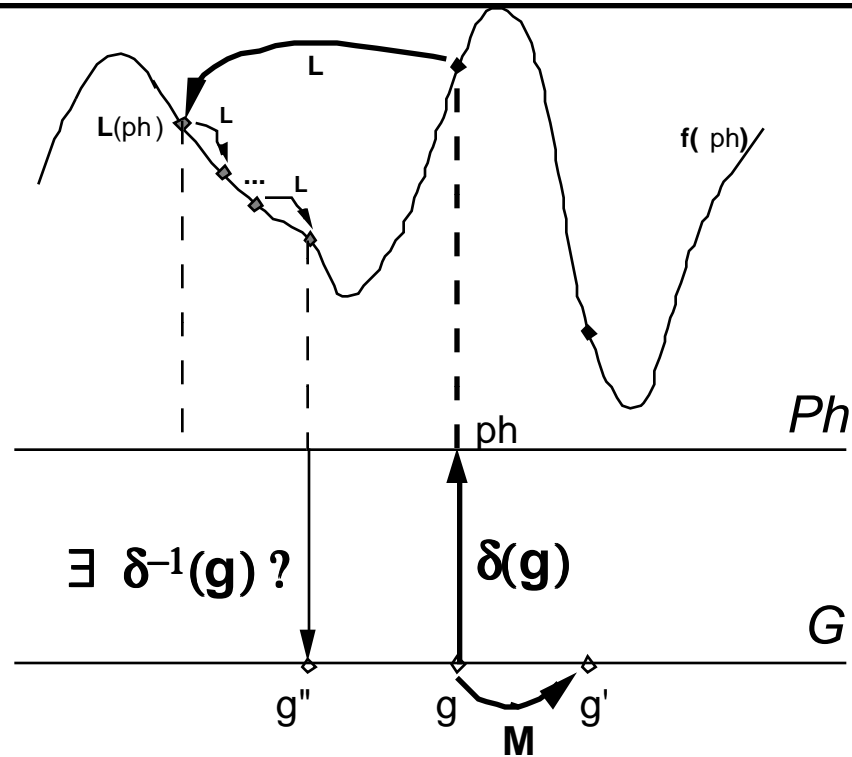
ALifeX - 5 Jun 06

(expanded, **color** version of manuscript at [www.cogsci.ucsd.edu/~rik](http://www.cogsci.ucsd.edu/~rik) )

## Preview

- Background / context
- Recombination in HIV
- hivPop: discrete-event simulation tool
- Results
- Work to do!

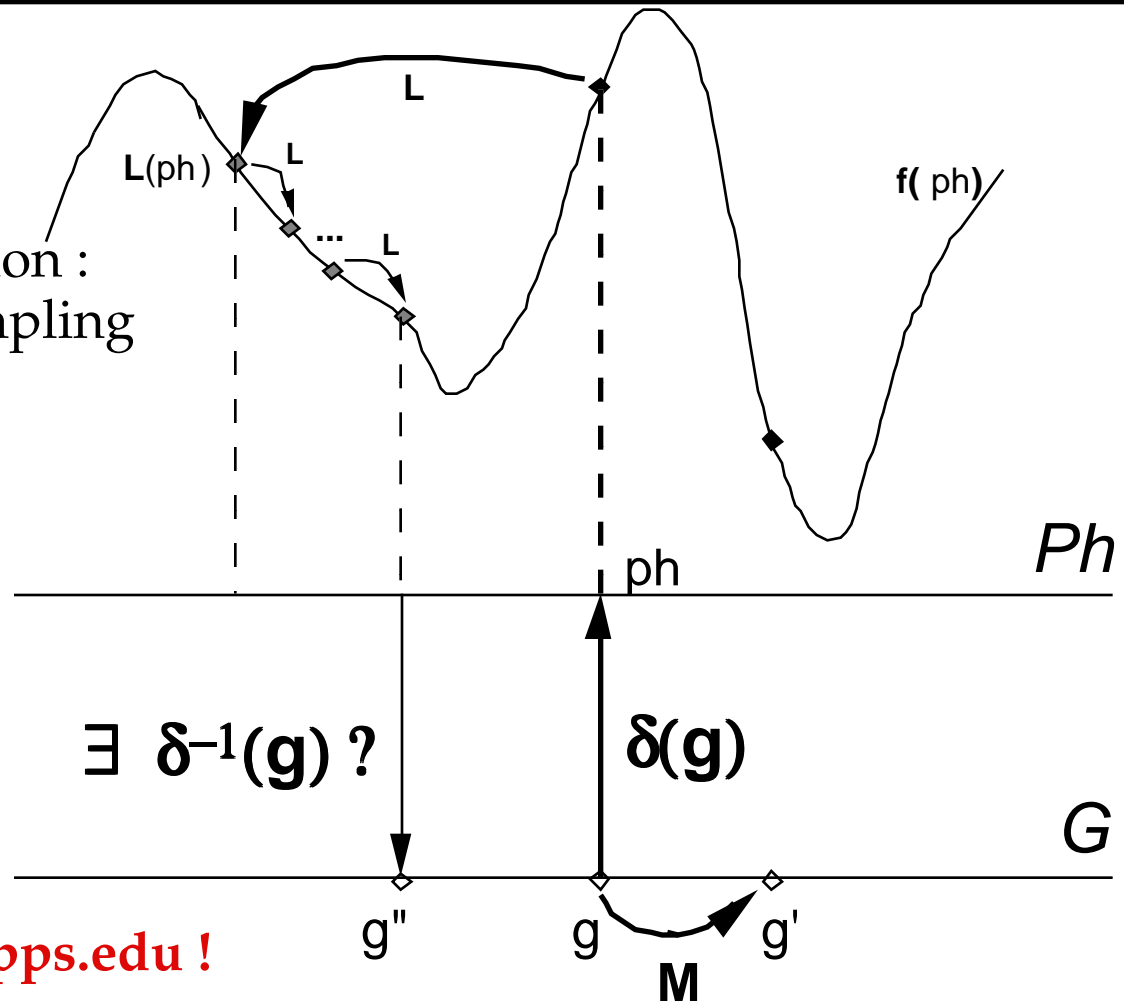
# Learning + evolution



- Engineering view: Hybridized global optimization
- Biological view: genotype / phenotype
- Competitive Co-evolution

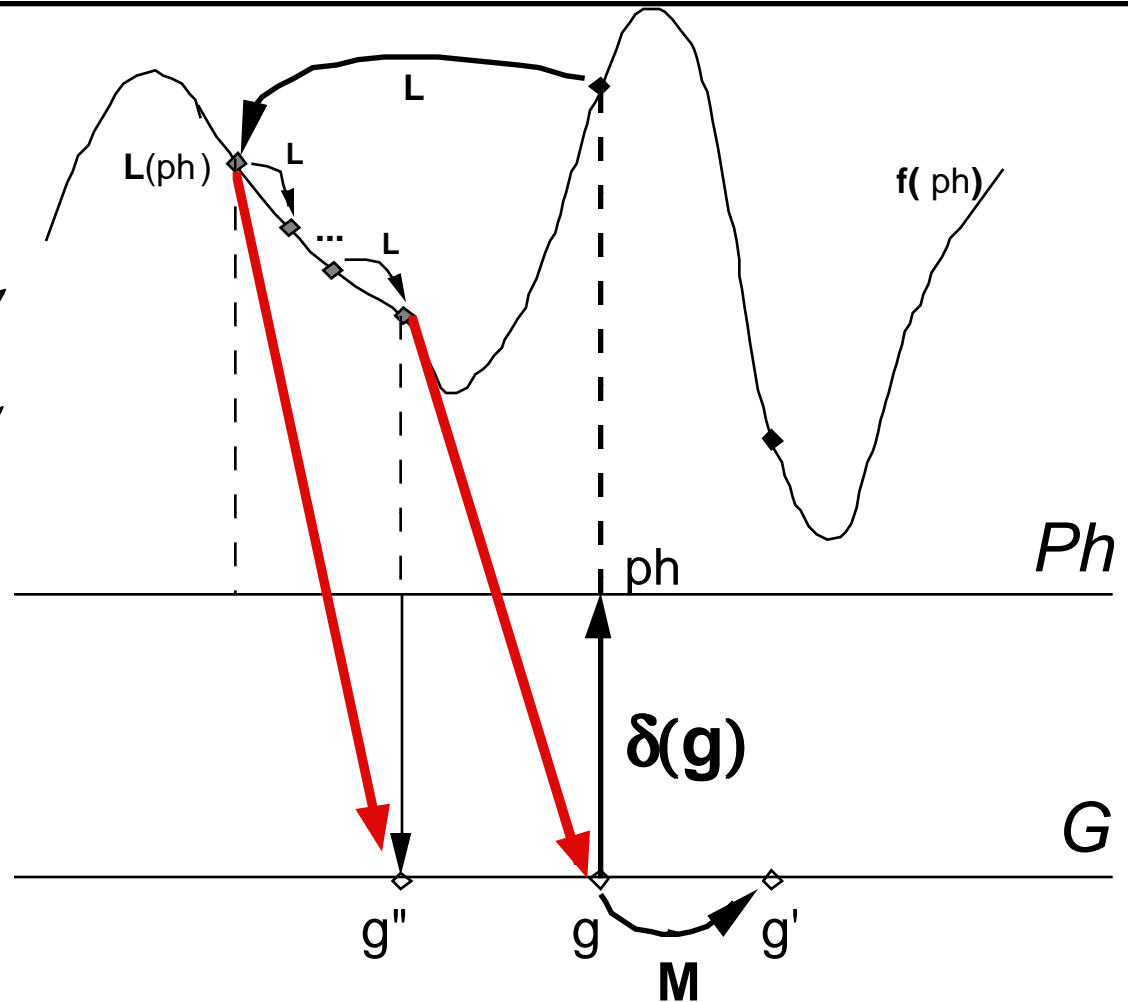
# Engineering view: Hybridized global optimization

- Evolutionary computation : global optimization sampling
- Learning: local gradient search
- [W. Hart, PhD 1994]
- “Lamarckian GA” at core of AutoDock [Morris et al, 1998]
- *AutoDock movie*
- **FightAidsAtHome.scripps.edu !**



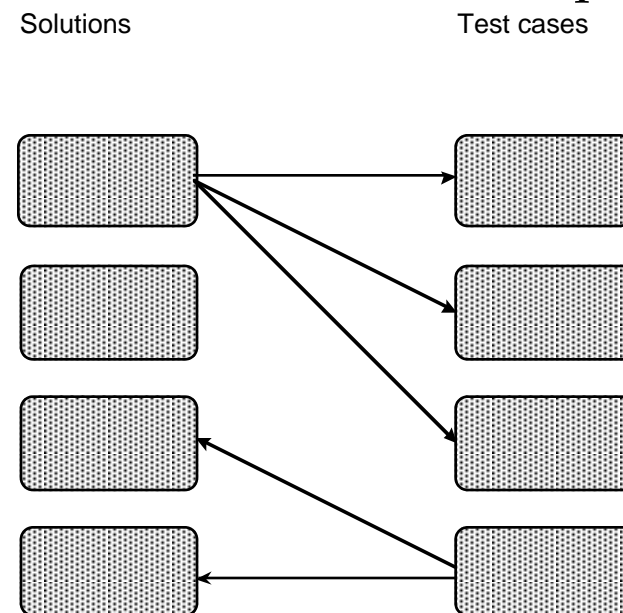
# Biological view: genotype / phenotype

- Information flow between 'representations'
- 'Developmental' process
- "Phenotypic hiding"



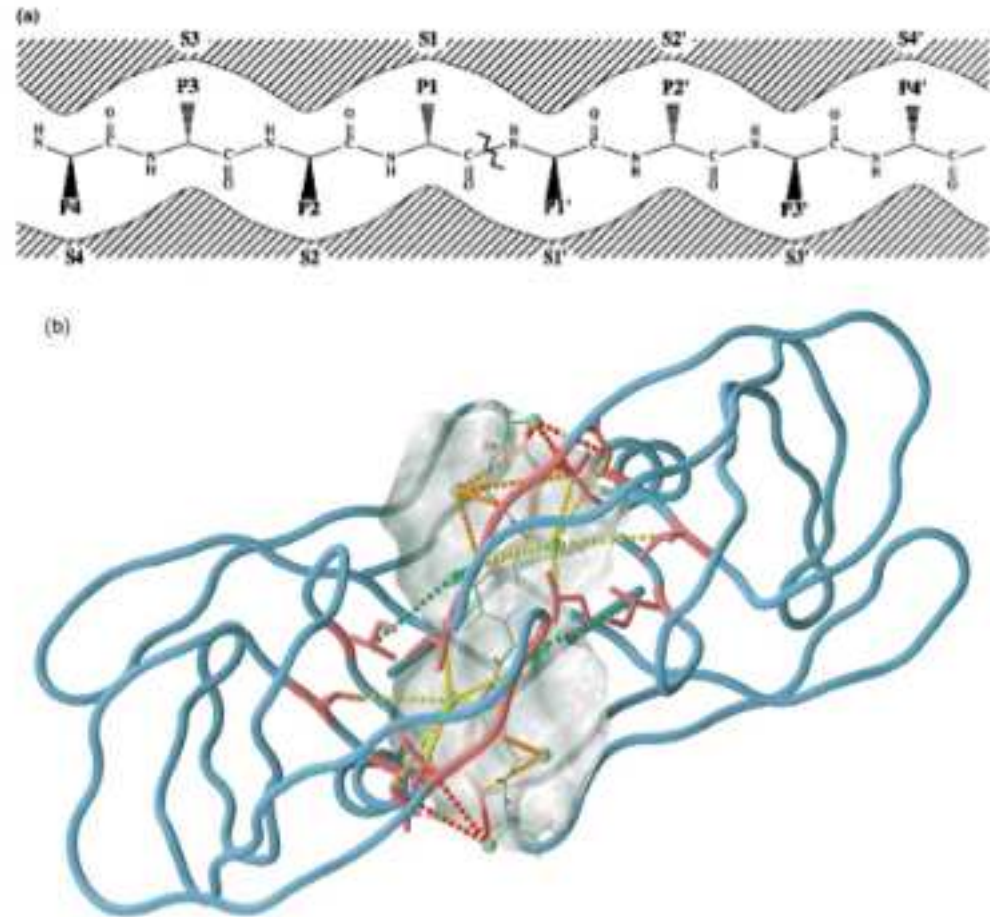
# Competitive Co-evolution

- [C. Rosin, PhD 1997]
- Use genetic algorithm to evolve solutions to a problem
- Simultaneously evolve a separate population of test cases
- Fitness of an individual in one population measured via competition with individuals from the other
- Let's play a game: HIV vs. drugs!

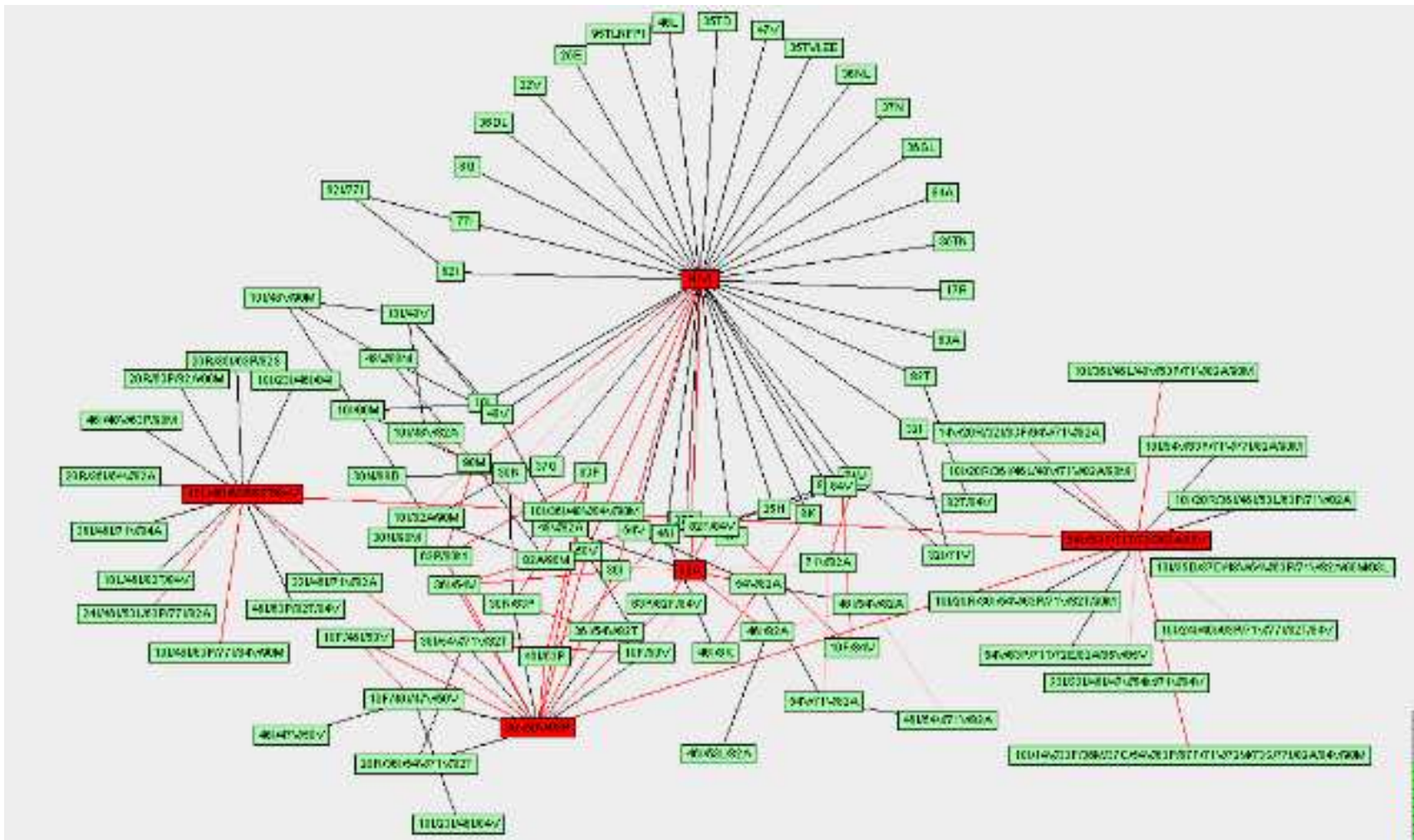


# Let's play a game: HIV vs. drugs!

- AutoDock estimates of energies for fitness
- Against evolving HIV
- Found robust inhibitor: good against wildtype but also wrt/ wide range of mutants
- [Rosin et al, PNAS99, JMB99]

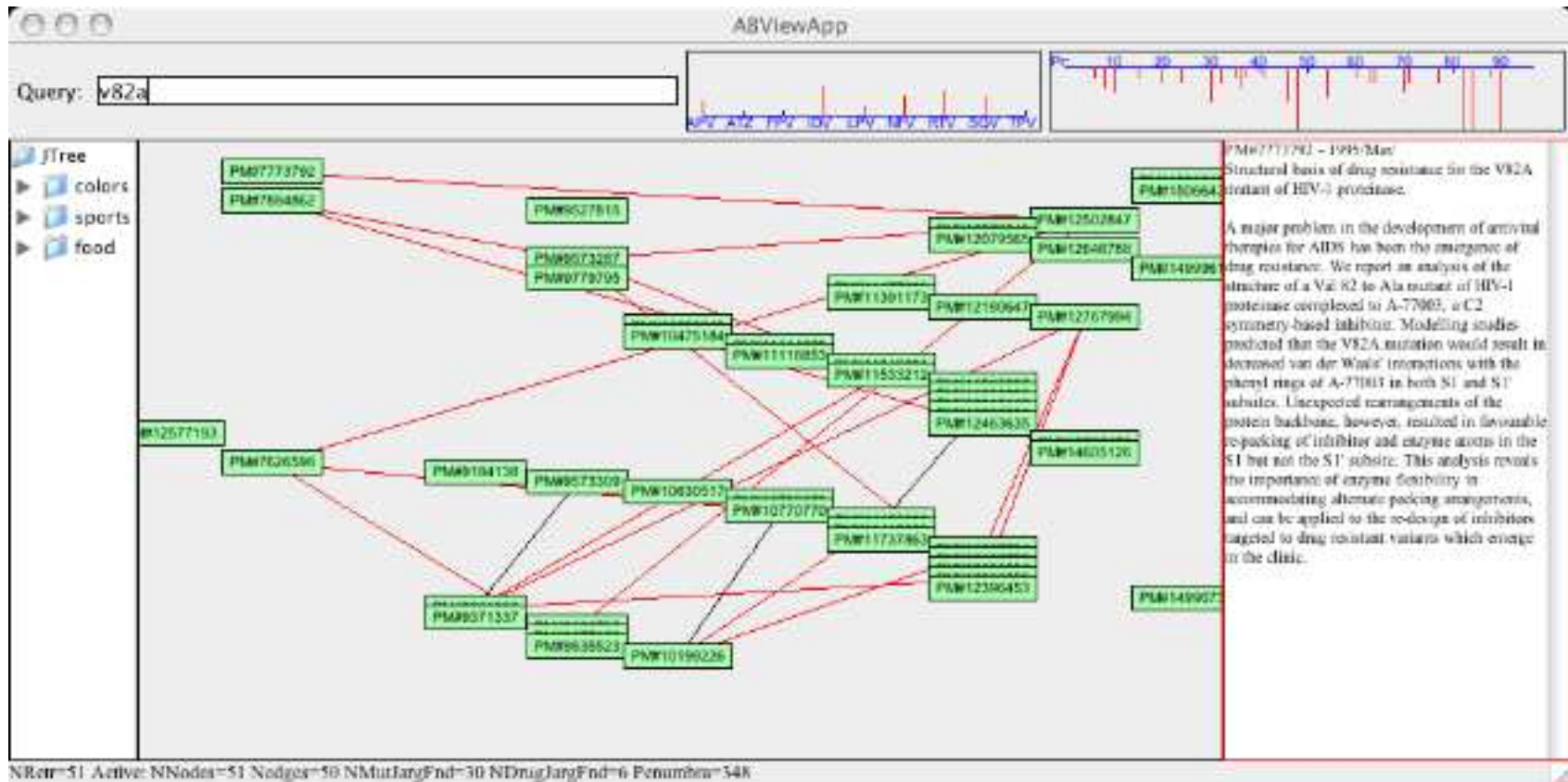


# Knowledge of real HIV mutation patterns





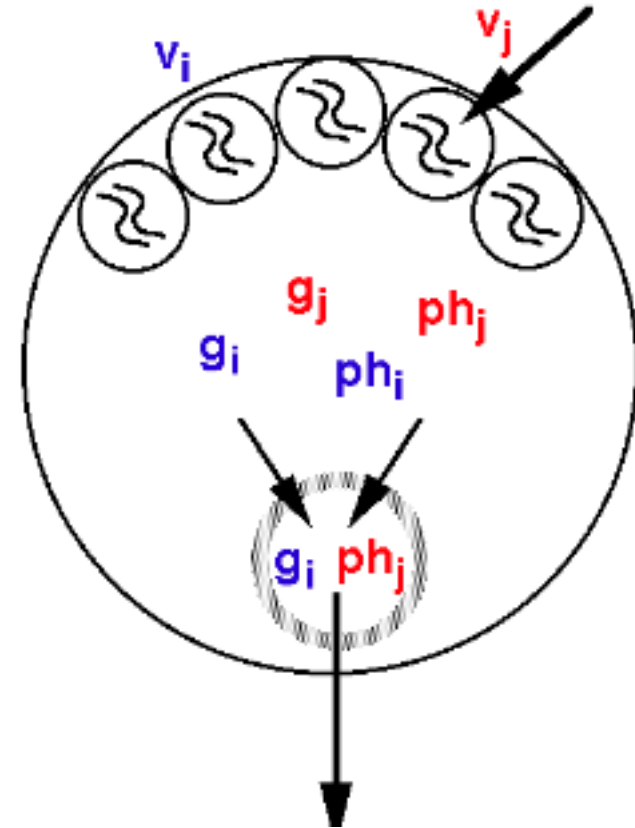
# Keeping up with the literature!



- AnnotatedBlast [Belew, Chang, SIGIR-Bio04]

# Phenotypic mixing

- Sydney Brenner, 1957
- random packaging of RNA and proteins derived from multiple proviruses within the same cell
- Multiplicity of infection: number of virions infecting same cell



## Recombination - Background

- Sexual species do
  - Why?
- Evolutionary computation
  - To XOver or not?

## HIV exploits recombination too!



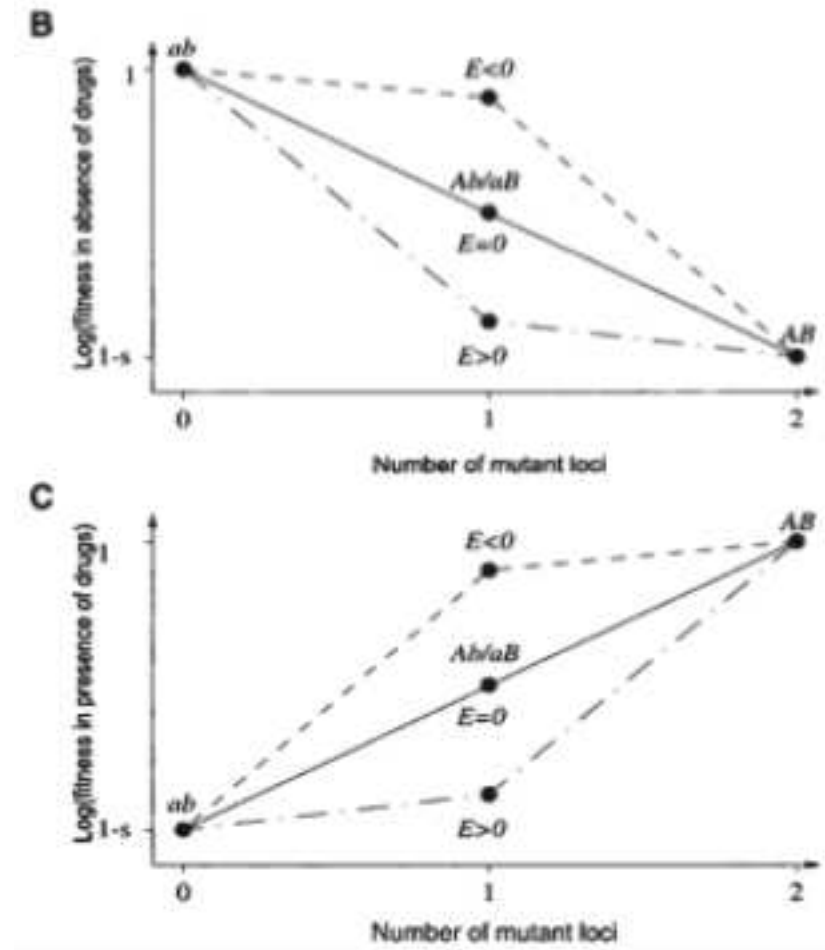
- HIV-1 has  $> 2.8$  crossovers per genome per cycle [zhuang02]

## Does it promote evolution of cross-resistance?

- Inhibitors selected from three (currently approved) primary classes of inhibitors
- HAART “game”: selection of various sequences/combinations of drugs in response to emerging resistance
- Emergence of “super-mutant” resistant to all known drugs?!

## Bretscher04

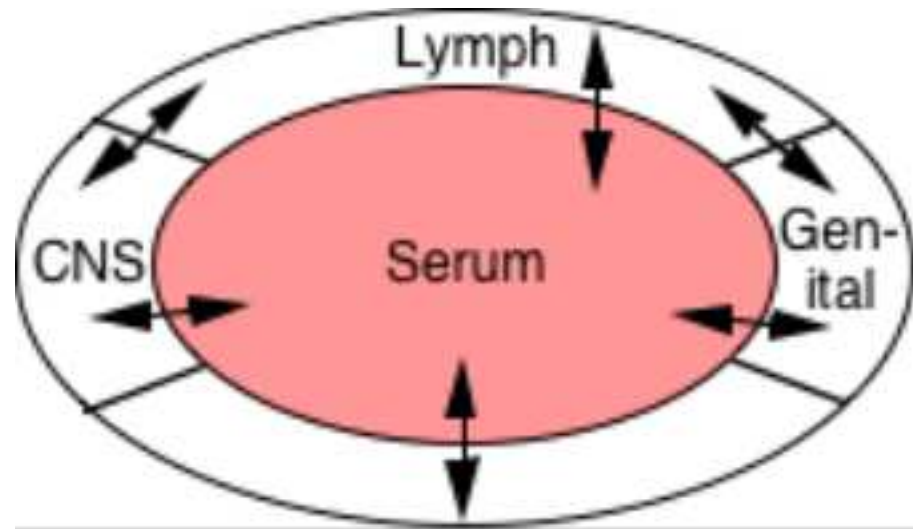
- “... under the most plausible biological assumptions, recombination is expected to slow down the rate of evolution of multi-drug-resistant virus during therapy.”
- But using a simple 2 locus, 2 allele genetics
- Multiplicity of infection = 1,2
- Simple fitness Model



## A role for simulation

- Population genetics: Deterministic vs. stochastic models of allele frequency change
- Census vs. effective population sizes
- HIV effective population sizes  $\sim 10^4$  near the cusp of mixed “selection/drift” regime
- Discrete event models
  - aka “agent-based”, “individual-based”
- Complimentary to differential equation models
  - NowakMay
  - Perelson

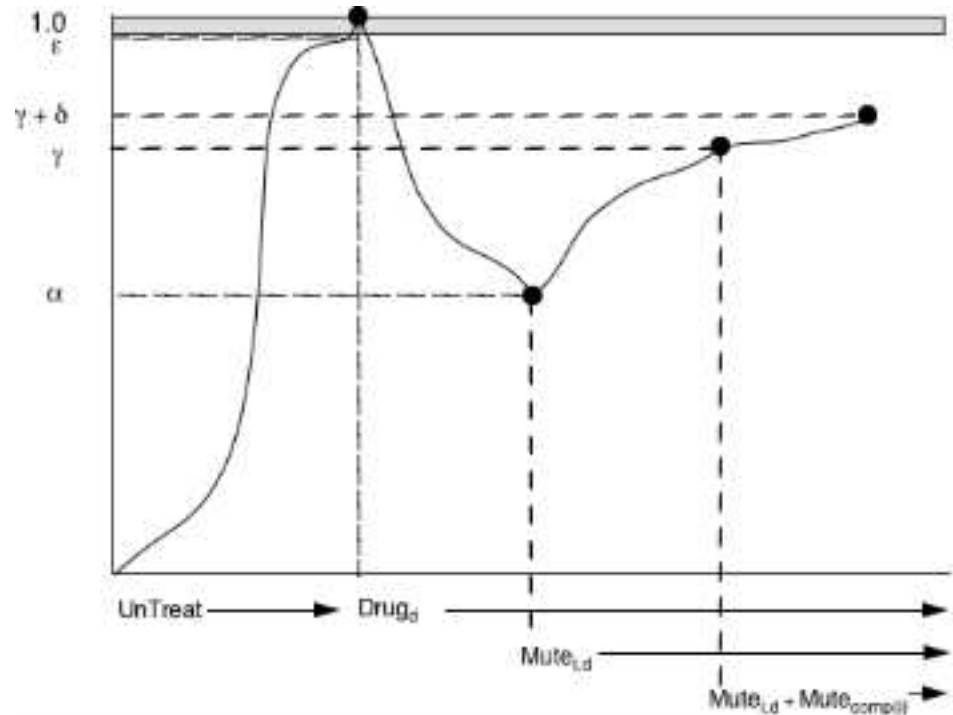
# Viral dissemination



- Serum vs. tissue
  - eg, CNS
- Modeled as constant prob of infection via serum, followed by (random walk) tissue-specific migration
- Tissue-specific genetic refugia
- Tissue-specific bio-availability

# Fitness

- Drug's affect on naive wildtype
- First resistance mutation
- Second compensatory mutation



Bits	Interpretation	Naive Fit.	Drug Fit.
00	wild-type	1.0	0.3
01	wild-type	1.0	0.3
10	Drug resistant	0.95	0.6
11	Drug resist, compen	0.95	0.9

## Model parameters

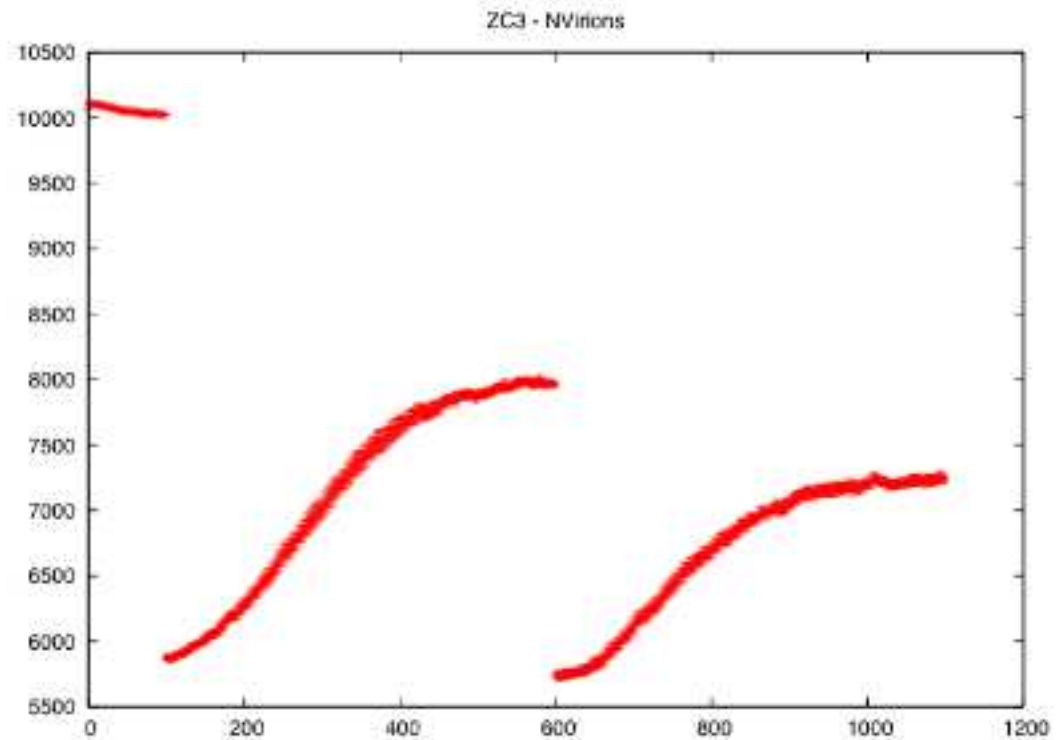
- $10^3$  cells
- 10 virions/cell
- 1100 generations
  - 100 naive
  - 500 subsequent to treatment by Drug1
  - 500 subsequent to treatment by Drug2
- Mutation =  $10^{-4}$ /gene

# Results

- NVirions
- Genetic variability
- Phenotypic mixing
- Affect of recombination

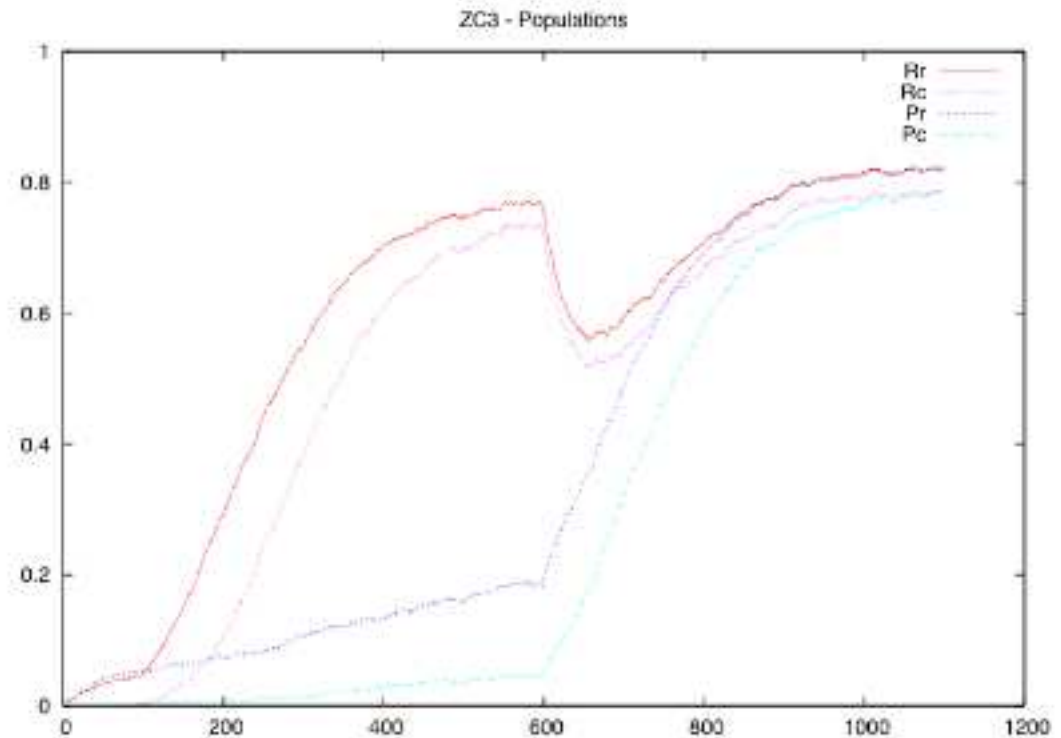
# NVirions

Each drug initially reduces population sizes, with resistance then causing it to rise again



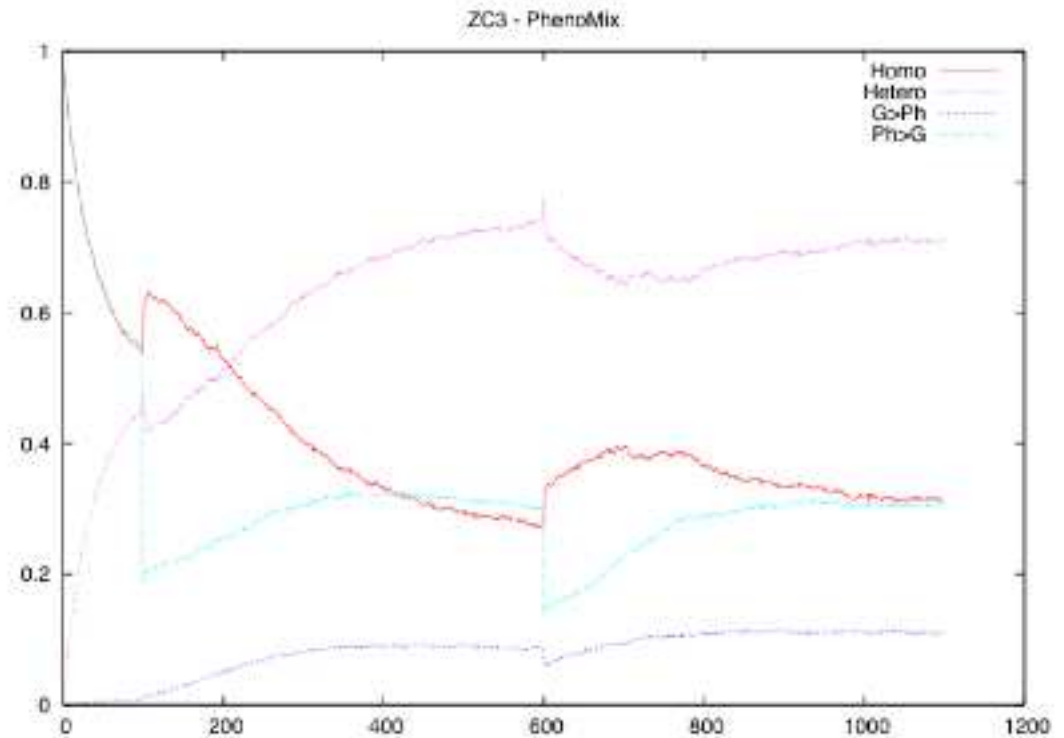
# Genetic variability

- 1x mutants both present in quasi-species
- Drugs cause resistance mutations to arise



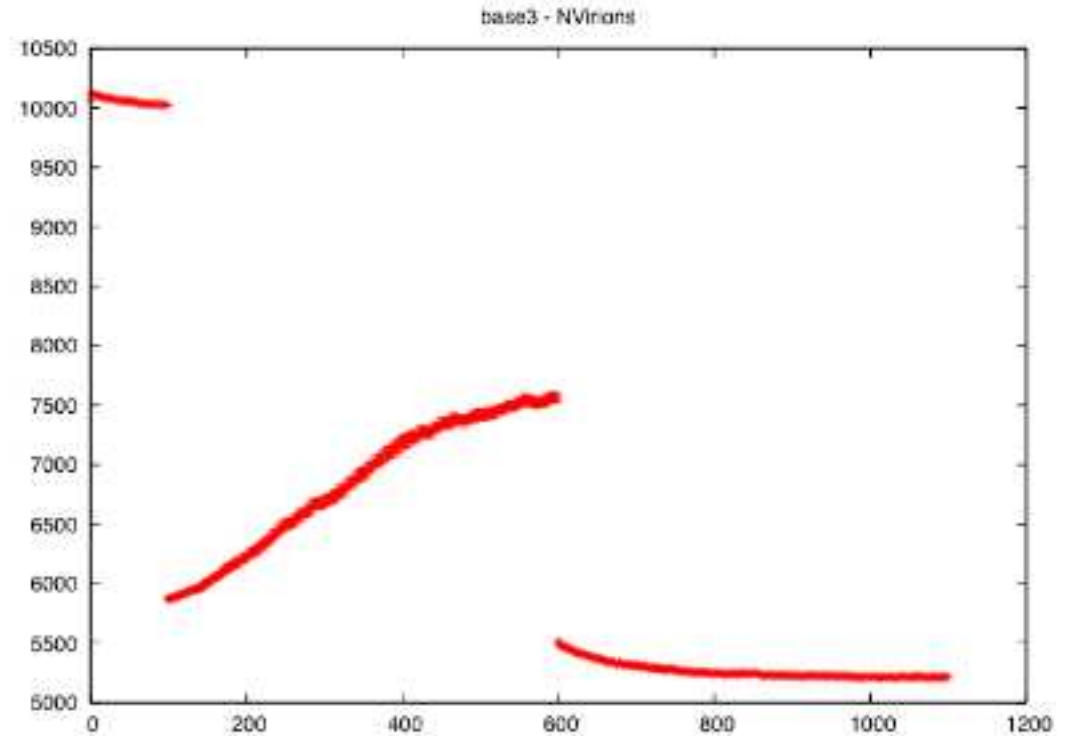
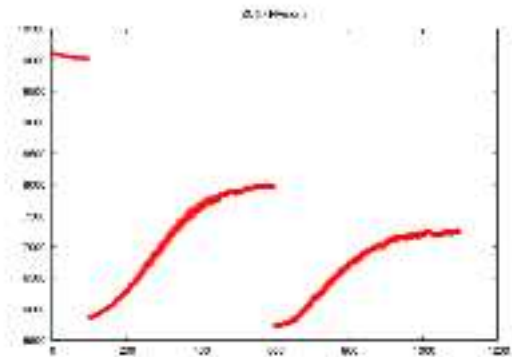
# Phenotypic mixing

- Homogeneous  
-> Hetero
- NB:  
simulation's  
ability to track  
all varieties of  
selective  
contingencies



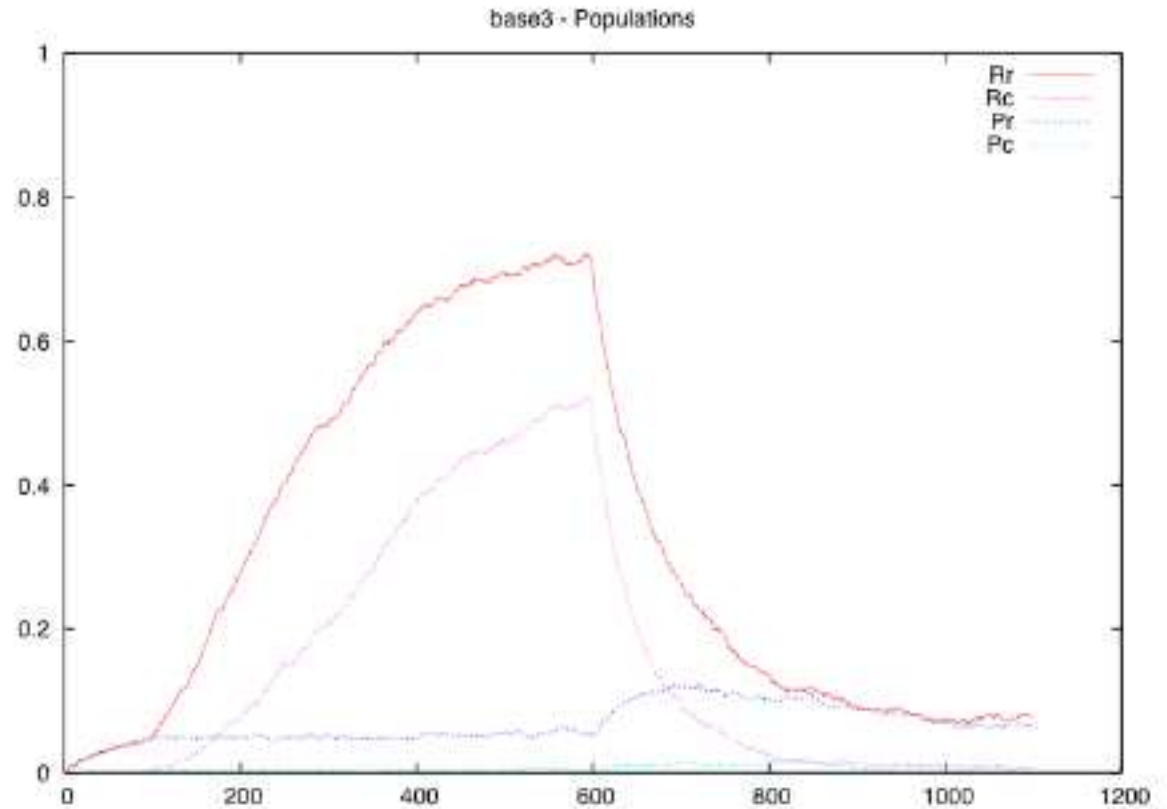
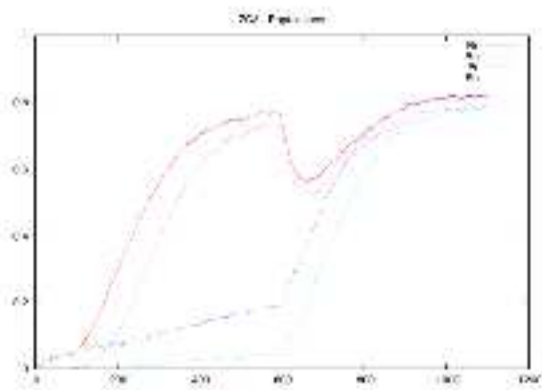
# NVirions w/ XOver

- Little rebound after D2



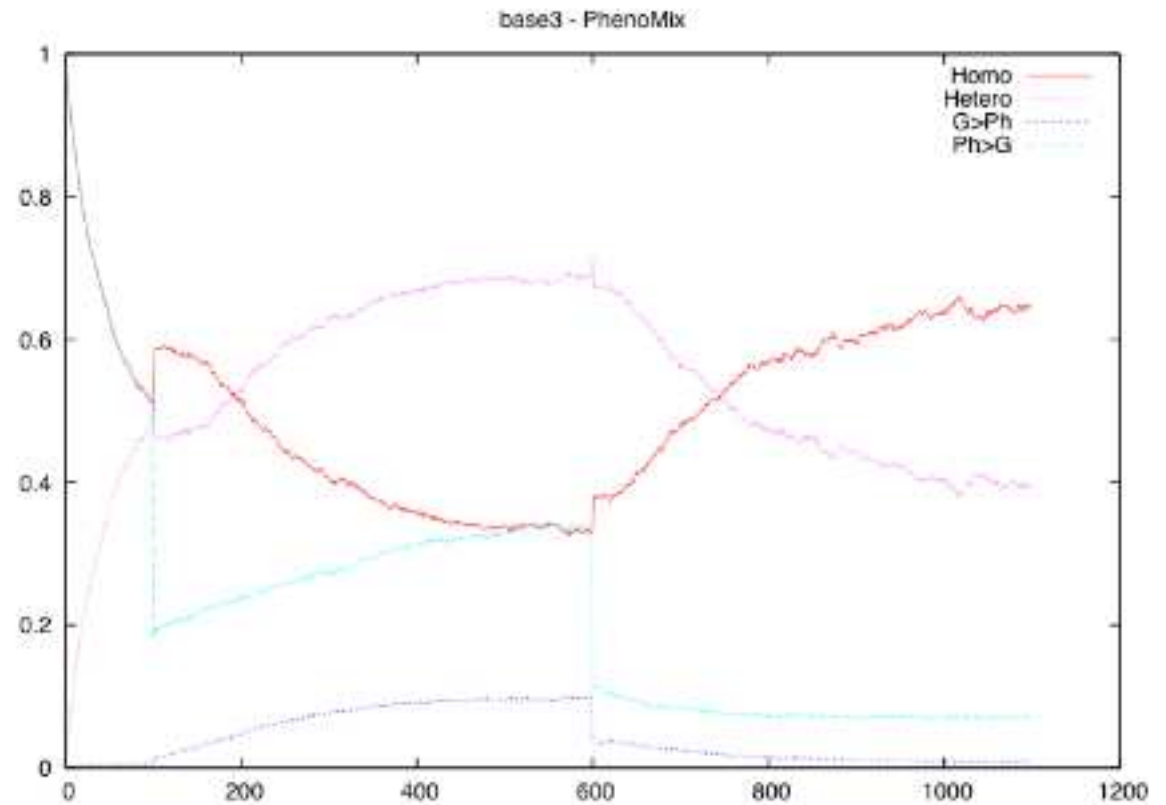
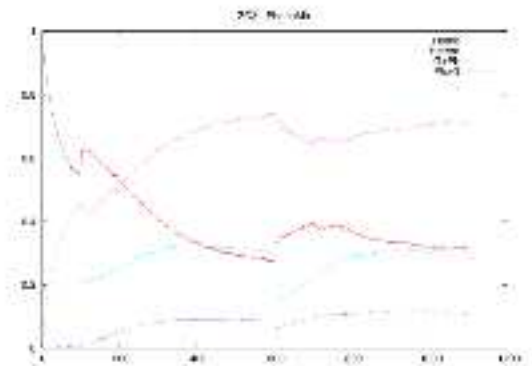
# Genetic variability w/ XOver

- Slight increase in D2-resist, -comp mutants
- D1-resist, -comp reduced

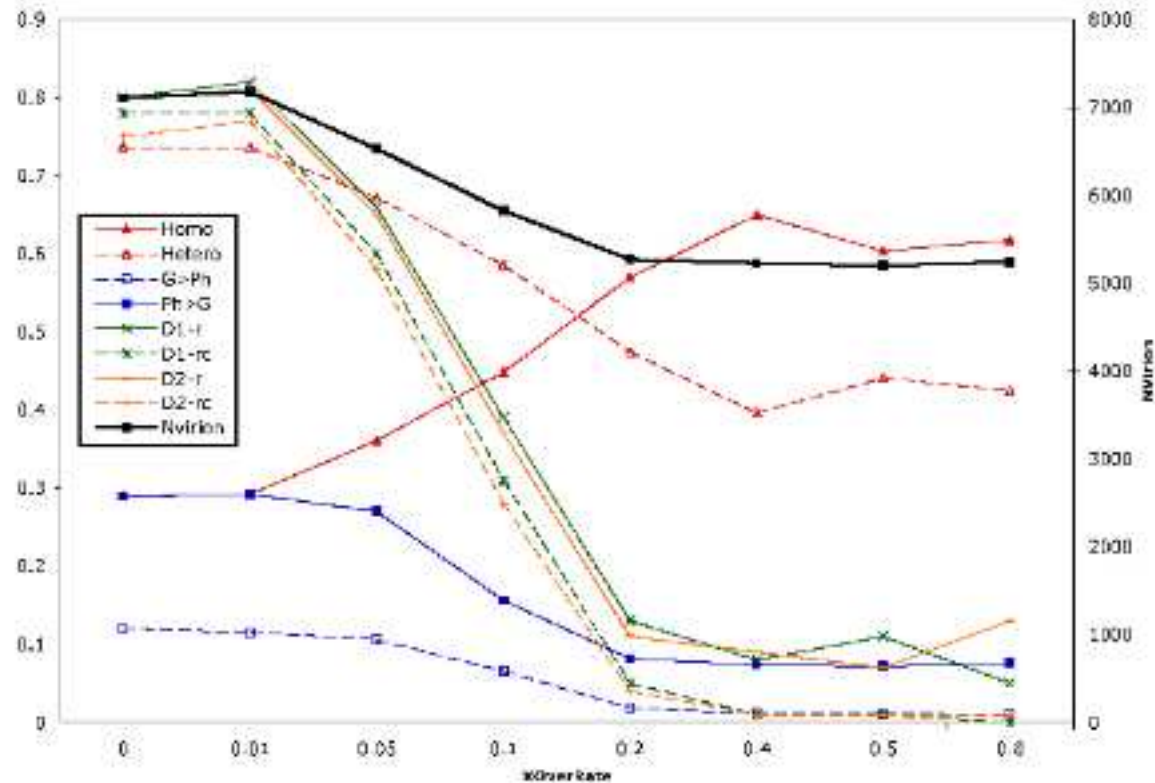


# Phenotypic mixing w/ XOver

- Homo > hetero
- PhenoMix reduced



# Recombination rate sensitivity



- XOver > 0.1 suffices
- In comparison to 2.8 observed [Zhuang02]

## Next steps

- Better fitness modeling
- Extending the model
- Game-theoretic treatment

## Better fitness modeling

- Growing databases of drug/mutant interactions
- RC: Replication capacity of mutants wrt/ wildtype
- RF: Resistance factor of sequence mutations wrt/ drug
- Estimators trained against existing datasets
- [d] Tissue-specific drug concentrations

$$fitness(M, D) = RC(M) / \left( 1 + \sum_{d \in D} \frac{[d]}{RF(M, d)} \right)$$

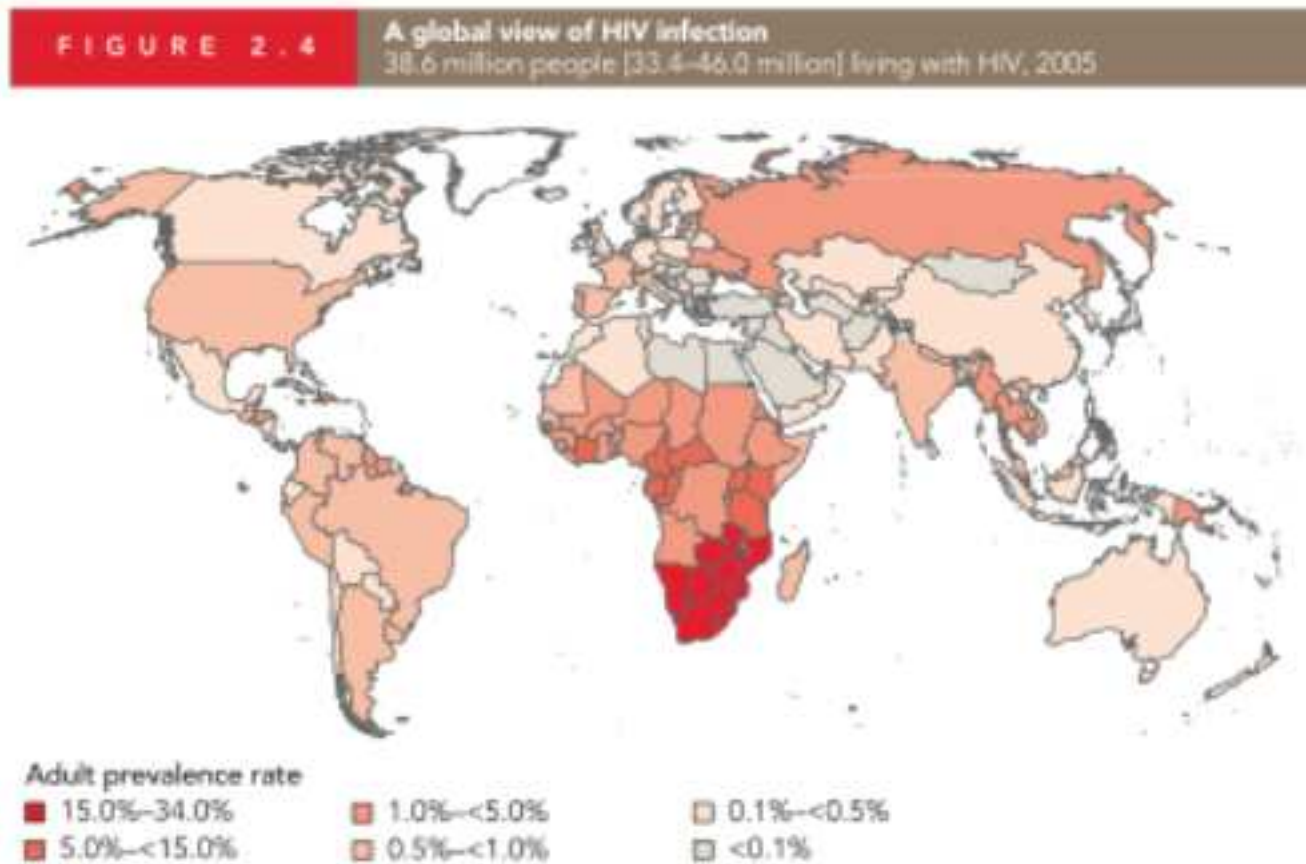
## Extending the model

- Fine-grained reconciliation of discrete event model with differential equation models
- Intra-patient evolution within epidemiological populations
- Transmission events

## Game-theoretic treatment

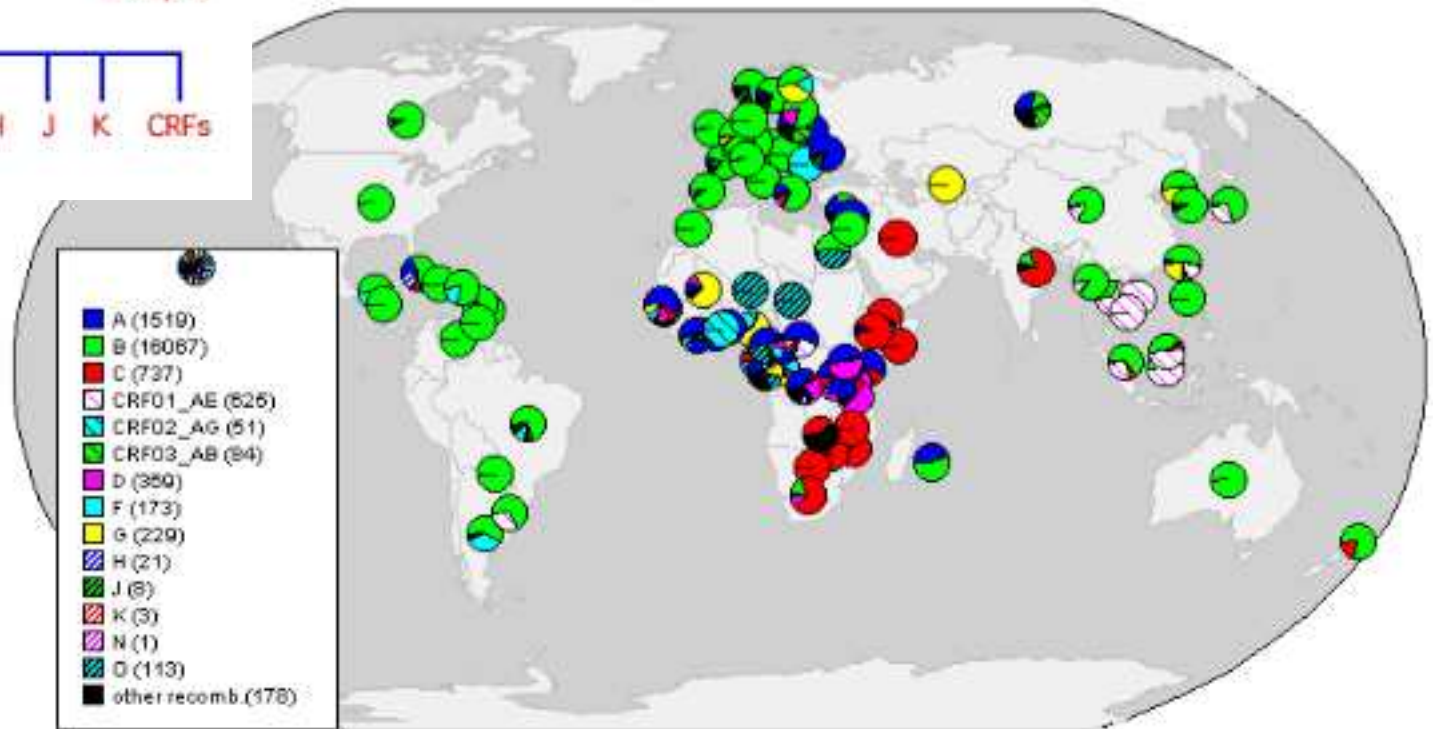
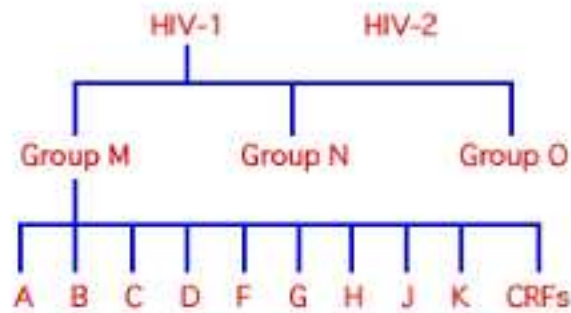
- Recall [Rosin99]: Best single drug against wildtype
- Patients presenting with specific resistance mutants
  - NB: Individual immune response highly variable
  - Idiosyncratic treatment best for them
- Drug regimes: sequences of drugs designed to shape evolutionary trajectory
- Public health responses
  - “Prophylactic” use of inhibitors by uninfected individuals
  - eg, VVV cocktail: Viagra+Valium+Viracept !
  - Affecting individuals’ behaviors

# 40 million on an infected planet



- [http://www.unaids.org/en/HIV\\_data/2006GlobalReport/](http://www.unaids.org/en/HIV_data/2006GlobalReport/)

# Skewed “quasi-species” diversity distribution



- <http://hiv-web.lanl.gov>

## Acknowledgements

- Bill Hart (Sandia)
- Chris Rosin (Parity Computing)
- Max Chang
- Art Olson, The Scripps Research Inst
  - David Goodsell
  - Garrett Morris
  - William Lindstrom

## Summary

- HIV closes the reality gap!
- Like any other living system, it embodies extraordinary complexity
  - Recombination
  - Phenotypic mixing
- Large volumes of high-throughput data becoming available
- Optimization, modeling, games, ... are all relevant

## Summary (cont.)

- ALifers marshall many of these useful skills
- ALife provides a particularly unifying perspective on how the various factoids come together
- Please help!