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

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(expanded, color version of manuscript at www.cogsci.ucsd.edu:/~rik)
<table>
<thead>
<tr>
<th>Preview</th>
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<tbody>
<tr>
<td>• Background / context</td>
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<tr>
<td>• Recombination in HIV</td>
</tr>
<tr>
<td>• hivPop: discrete-event simulation tool</td>
</tr>
<tr>
<td>• Results</td>
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<tr>
<td>• Work to do!</td>
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</tbody>
</table>
• 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!

![Diagram of solutions and test cases](image_url)
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
Knowledge of HIV

- immune response
- Transcription, synthesis
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
<table>
<thead>
<tr>
<th>Recombination - Background</th>
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<tbody>
<tr>
<td>• Sexual species do</td>
</tr>
<tr>
<td>• Why?</td>
</tr>
<tr>
<td>• Evolutionary computation</td>
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<td>• To XOver or not?</td>
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</table>
HIV exploits recombination too!

- HIV-1 has > 2.8 crossovers per genome per cycle [zhuang02]
<table>
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<tr>
<th>Does it promote evolution of cross-resistance?</th>
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<tbody>
<tr>
<td>• Inhibitors selected from three (currently approved) primary classes of inhibitors</td>
</tr>
<tr>
<td>• HAART “game”: selection of various sequences/combinations of drugs in response to emerging resistance</td>
</tr>
<tr>
<td>• Emergence of “super-mutant” resistant to all known drugs?!</td>
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</tbody>
</table>
• “... 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

<table>
<thead>
<tr>
<th>Bits</th>
<th>Interpretation</th>
<th>Naive Fit.</th>
<th>Drug Fit.</th>
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<tbody>
<tr>
<td>00</td>
<td>wild-type</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>01</td>
<td>wild-type</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>Drug resistant</td>
<td>0.95</td>
<td>0.6</td>
</tr>
<tr>
<td>11</td>
<td>Drug resist, compen</td>
<td>0.95</td>
<td>0.9</td>
</tr>
</tbody>
</table>
# 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
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

\[
\text{fitness}(M,D) = \frac{RC(M)}{1 + \sum_{d\in D} \frac{[d]}{RF(M,d)}}
\]
<table>
<thead>
<tr>
<th>Extending the model</th>
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<tbody>
<tr>
<td>• Fine-grained reconciliation of discrete event model with differential equation models</td>
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<tr>
<td>• Intra-patient evolution within epidemiological populations</td>
</tr>
<tr>
<td>• Transmission events</td>
</tr>
<tr>
<td>Game-theoretic treatment</td>
</tr>
<tr>
<td>---------------------------</td>
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<tr>
<td>• Recall [Rosin99]: Best single drug against wildtype</td>
</tr>
<tr>
<td>• Patients presenting with specific resistance mutants</td>
</tr>
<tr>
<td>• NB: Individual immune response highly variable</td>
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<tr>
<td>• Idiosyncratic treatment best for them</td>
</tr>
<tr>
<td>• Drug regimes: sequences of drugs designed to shape evolutionary trajectory</td>
</tr>
<tr>
<td>• Public health responses</td>
</tr>
<tr>
<td>• “Prophylactic” use of inhibitors by uninfected individuals</td>
</tr>
<tr>
<td>• eg, VVV cocktail: Viagra+Valium+Viracept!</td>
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<td>• Affecting individuals’ behaviors</td>
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40 million on an infected planet

Skewed “quasi-species” diversity distribution

• http://hiv-web.lanl.gov
## Acknowledgements

- Bill Hart (Sandia)
- Chris Rosin (Parity Computing)
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- 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!