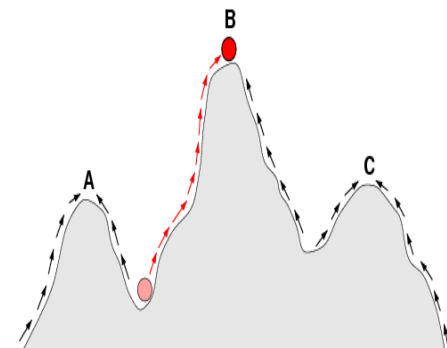


Fitness Landscape by Environment Interactions Inform Treatment Models in *P. falciparum*

C.Brandon Ogbunu
KITP “Superbugs”
September 2014



Acknowledgments

- **Daniel Weinreich (EEB, Brown)**
- **C. Scott Wylie (EEB, Brown)**
- Daniel Hartl (OEB, Harvard)
- Bruce Birren (The Broad Institute)
- Ibrahim Diakite (Harvard School of Public Health)
- Sanjay Basu (Department of Medicine, Stanford)

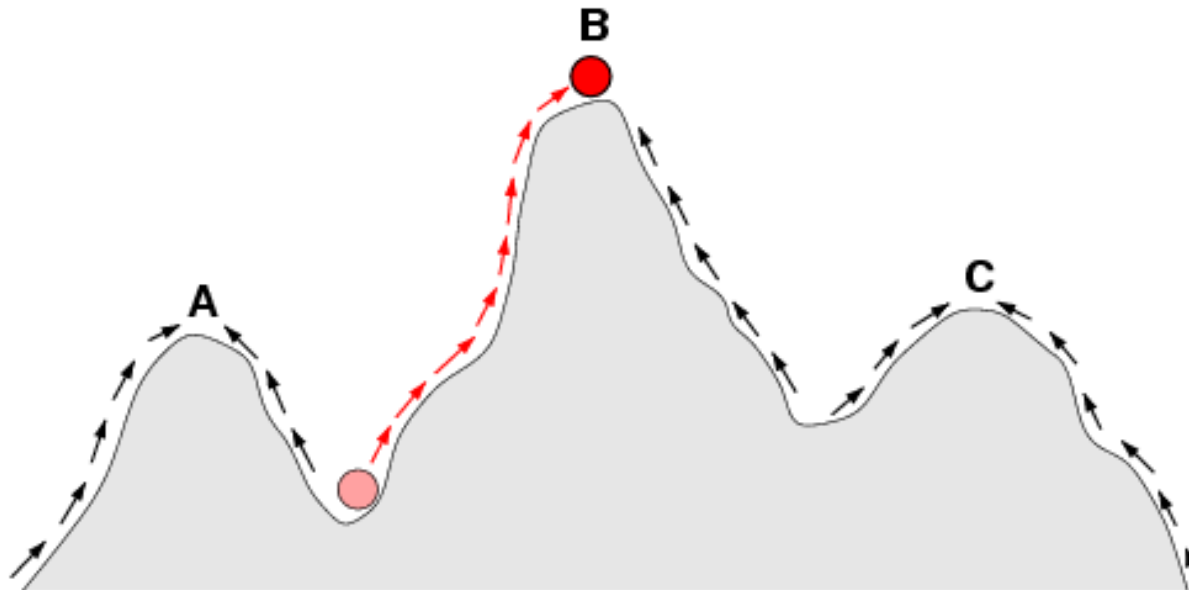
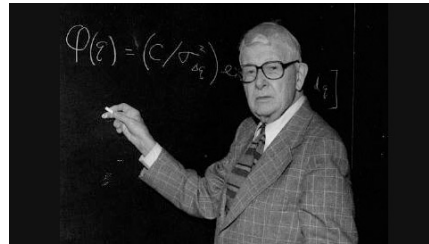
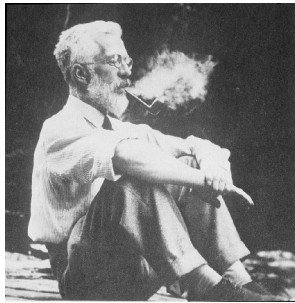


Can we improve on the fitness
landscape metaphor and how
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Can we improve on the fitness
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would it help us?

Is the fitness landscape metaphor still useful in evolutionary biology?

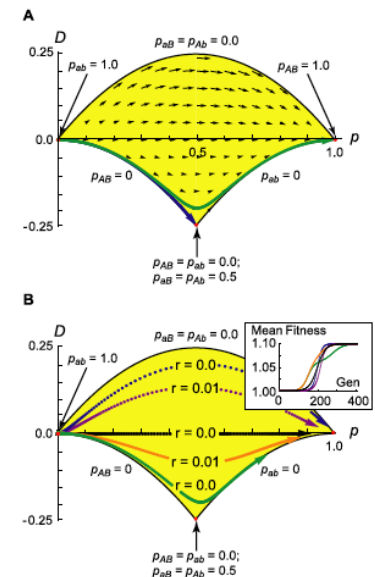


Is the fitness landscape metaphor still useful in evolutionary biology?

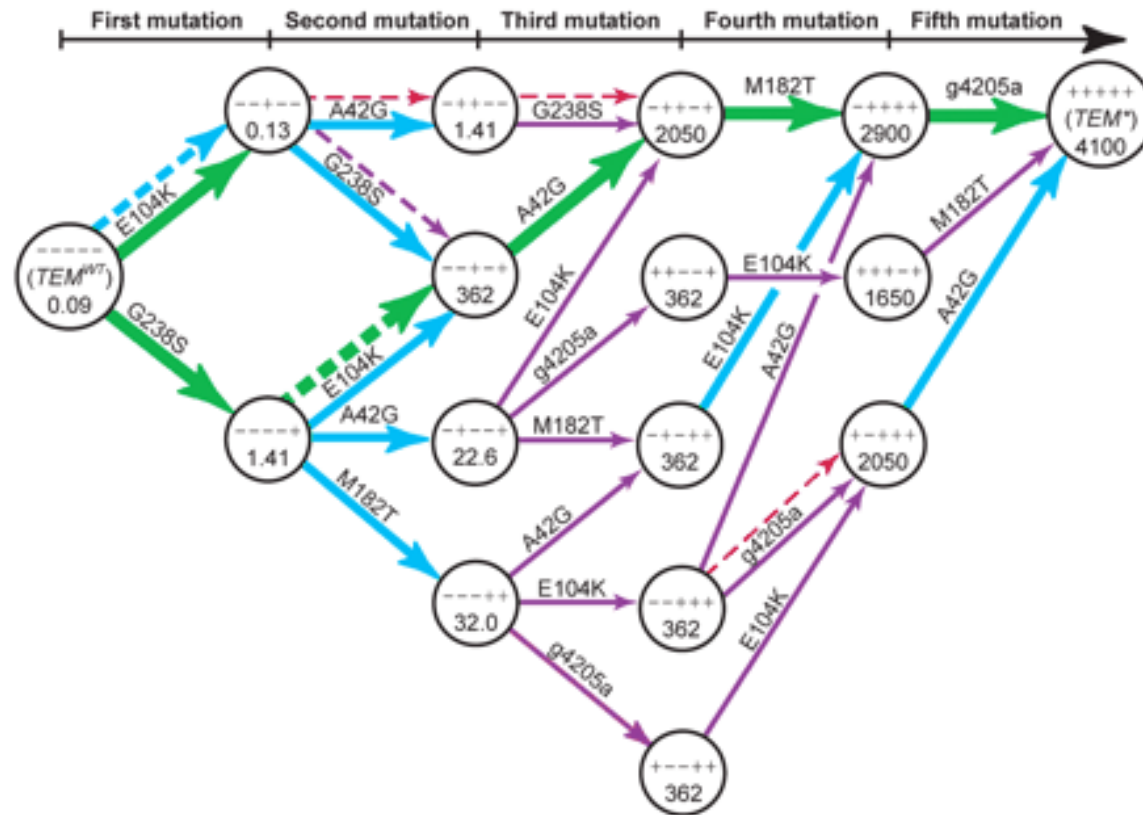
Quantitative analyses of empirical fitness landscapes

$$\begin{aligned}
 f(\vec{\sigma}) &= b_1^{(0)} \Lambda_{\vec{\sigma}}^{10} + \sum_{j=1}^{\binom{L}{1}} b_j^{(1)} \Lambda_{\vec{\sigma}}^{j1} + \sum_{j=1}^{\binom{L}{2}} b_j^{(2)} \Lambda_{\vec{\sigma}}^{j2} + \dots + b_1^{(L)} \Lambda_{\vec{\sigma}}^{1L} \\
 &= \tilde{a}^{(0)} + \sum_{j=1}^L \tilde{a}_j^{(1)} \tilde{\sigma}_j + \sum_{\substack{j,k=1 \\ j>k}}^L \tilde{a}_{jk}^{(2)} \tilde{\sigma}_j \tilde{\sigma}_k + \dots + \tilde{a}^{(L)} \tilde{\sigma}_1 \tilde{\sigma}_2 \dots \tilde{\sigma}_L,
 \end{aligned}$$

Finding the boundary between evolutionary basins of attraction, and implications for Wright's fitness landscape analogy

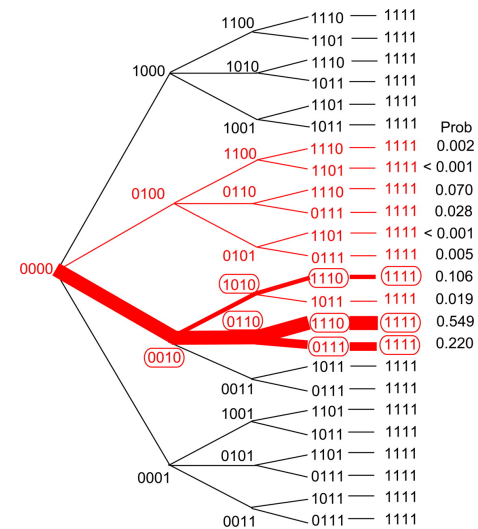
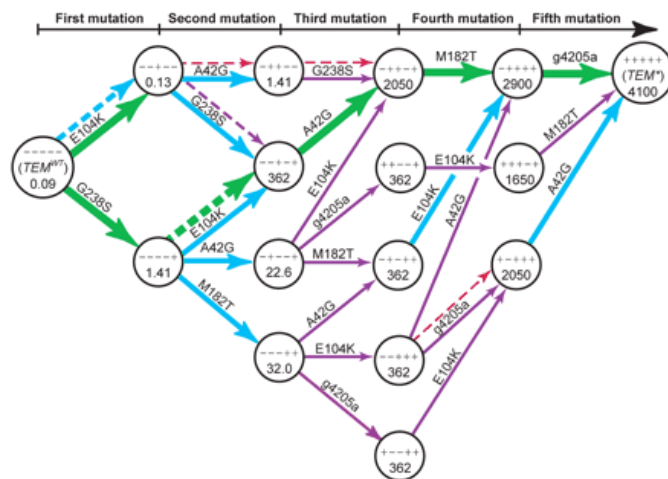


Weinreich Method (2006)



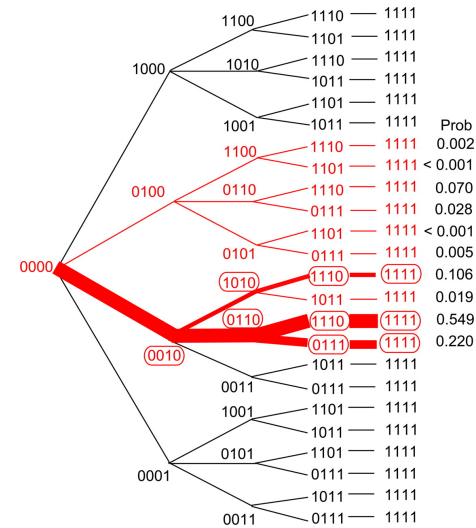
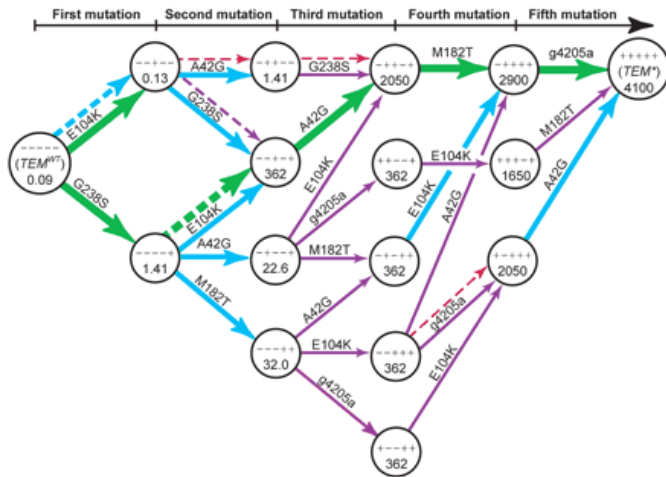
Weinreich Method (2006)

- Experimentally derived fitness nodes
- Recapitulate entire mutational networks
- Determine the accessibility of pathways
- Potentially relates to findings in nature



Weinreich Method (2006)

- IC_{50} does not equal fitness
- Limitations: No environmental dimension
- Address in non-SSWM context
- Connect, more directly, to the problem of treatment

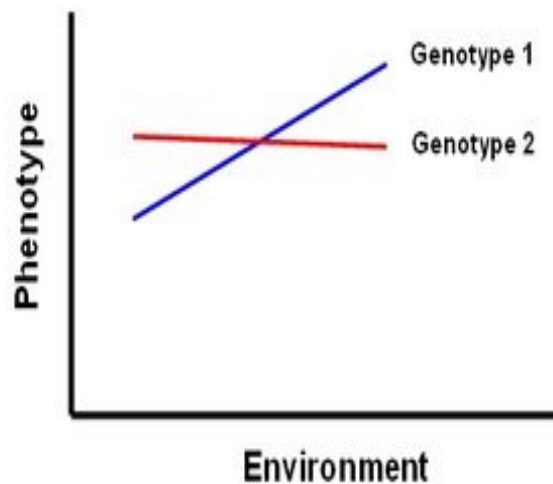


Aims

1. Develop a modified fitness landscape that contains information on fitness across environments
 - a. Analyze fitness landscape structure by environment
 - b. Effects of mutation by environment
 - c. Network properties of alleles by environment

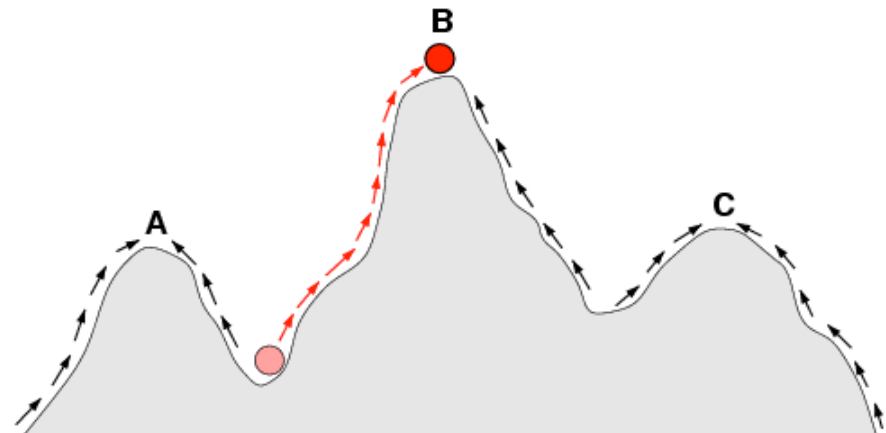
2. Drug therapy-inspired simulations of population dynamics (non-SSWM)
 - a. Model probable trajectories
 - b. Model under standing genetic variation
 - c. Model with drug cycling

We can combine information from the norm of reaction with the fitness landscape



Norm of Reaction

+



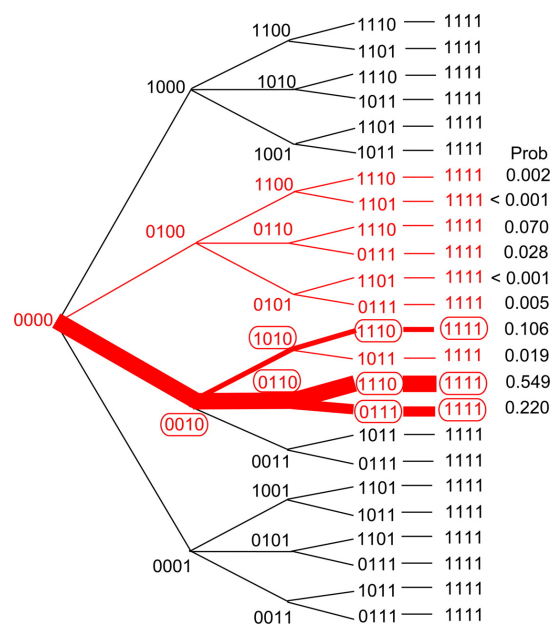
Fitness Landscape

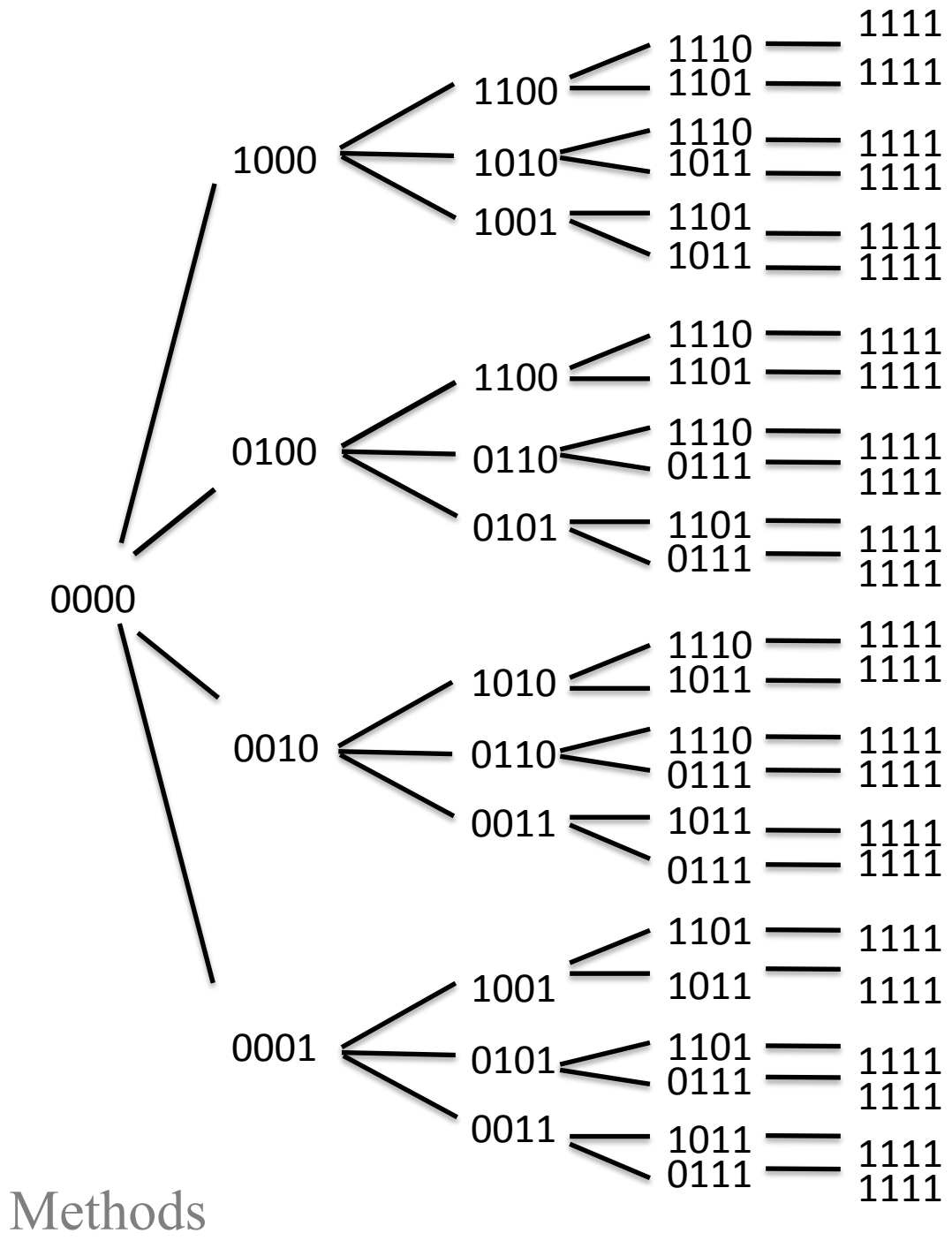
Stepwise acquisition of pyrimethamine resistance in the malaria parasite

Elena R. Lozovsky^{a,1}, Thanat Chookajorn^{b,1}, Kyle M. Brown^c, Mallika Imwong^c, Philip J. Shaw^d,
Sumalee Kamchonwongpaisan^d, Daniel E. Neafsey^e, Daniel M. Weinreich^f, and Daniel L. Hartl^{a,2}

^aDepartment of Organismic and Evolutionary Biology, Harvard University, Cambridge, MA 02138; ^bDepartment of Biochemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand; ^cDepartment of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand; ^dNational Center for Genetic Engineering and Biotechnology (BIOTEC), Pathumthani 12120, Thailand; ^eBroad Institute, Cambridge, MA 02142; and ^fDepartment of Biology, Brown University, Providence, RI 02912

Contributed by Daniel L. Hartl, May 28, 2009 (sent for review April 7, 2009)

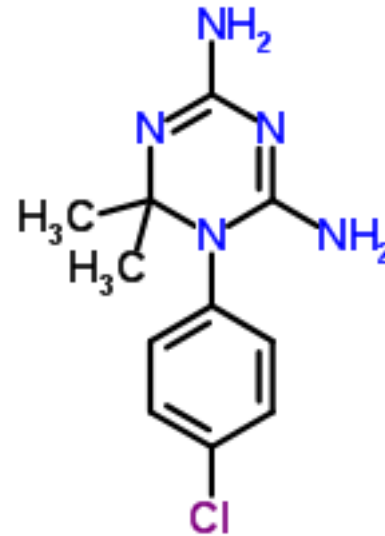
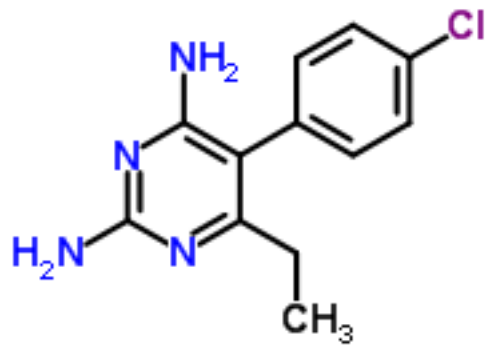




16 alleles, 24
different pathways

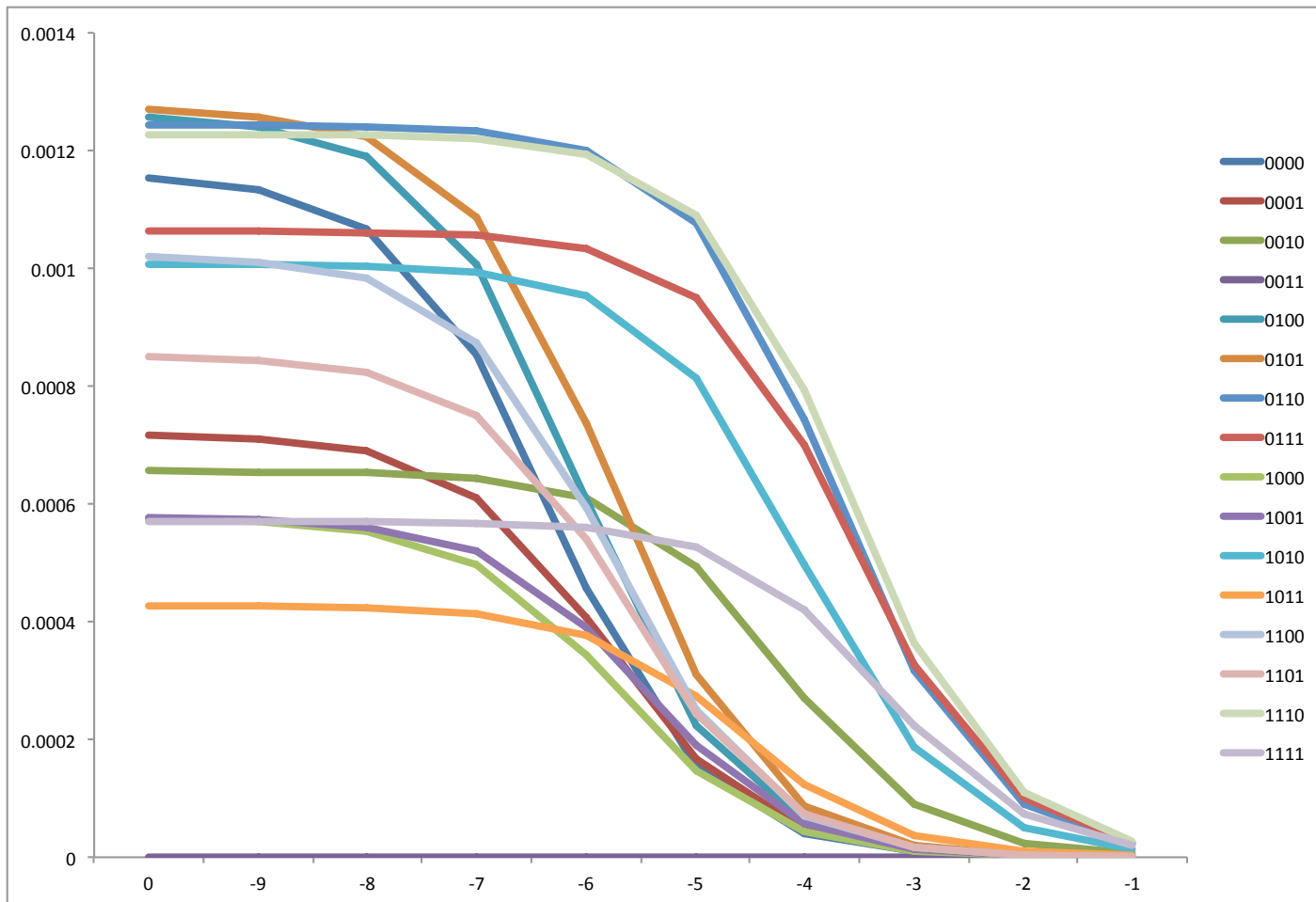
Methods

The Environment

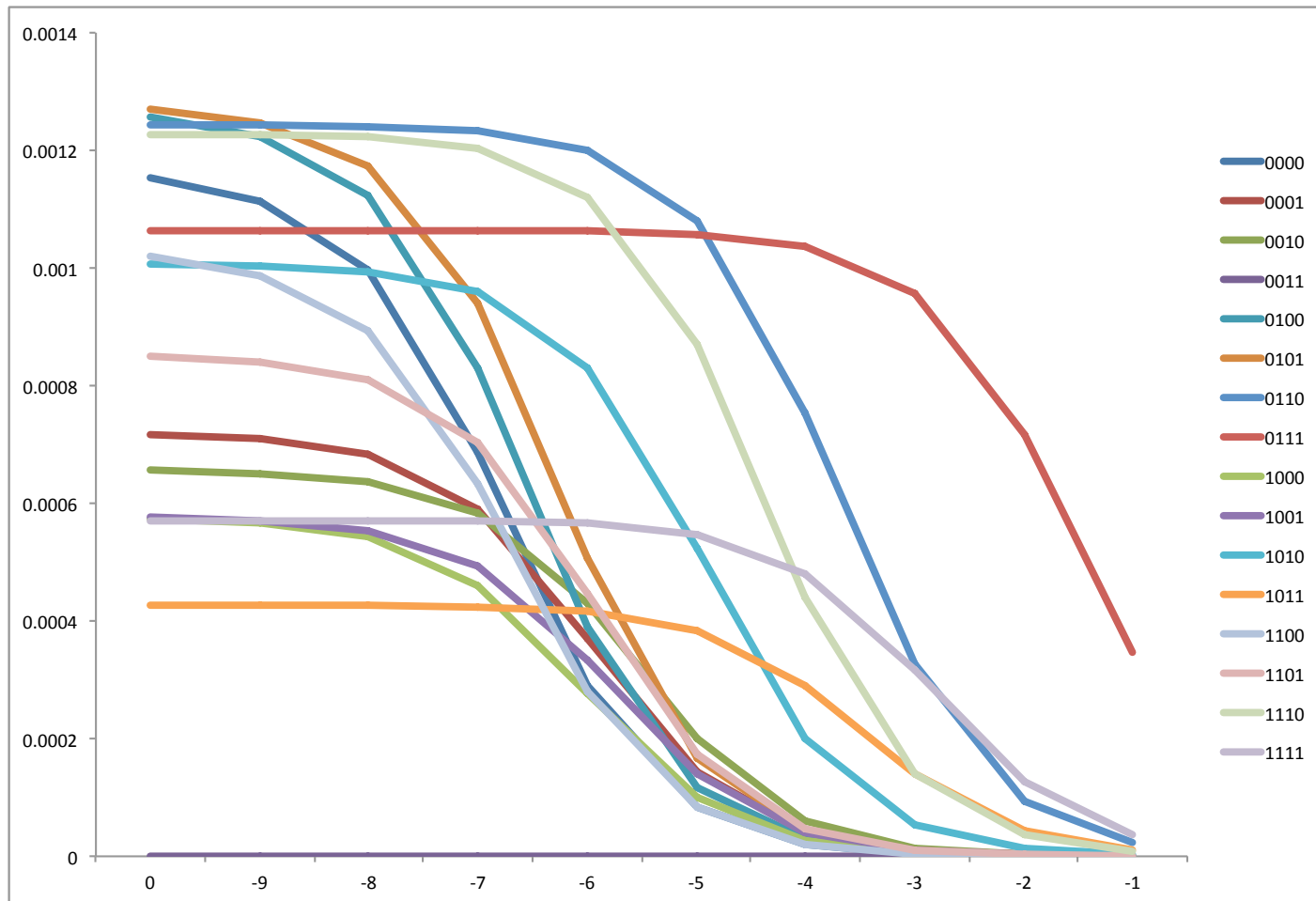


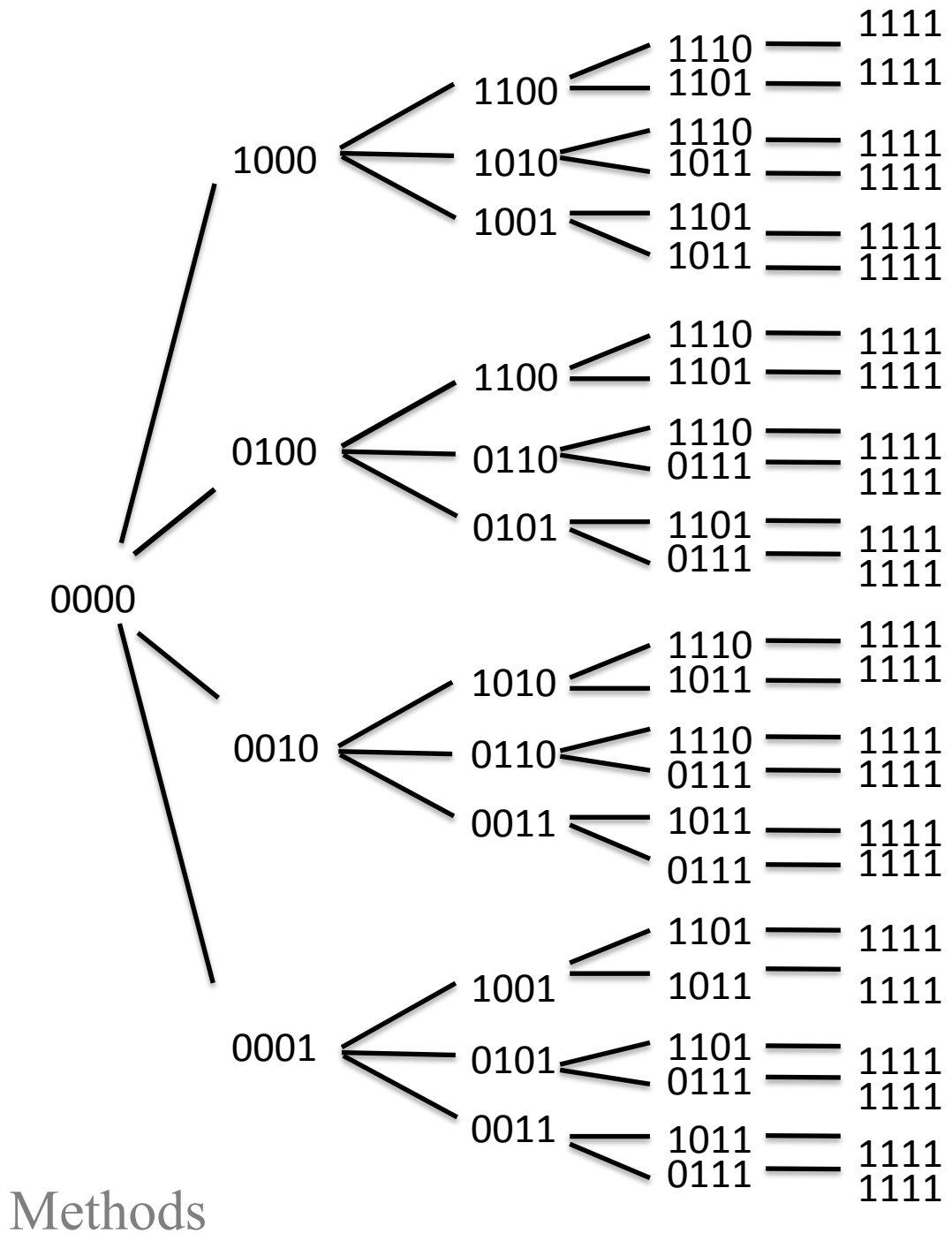
Concentrations ranging from
0 to 100 μM

Growth rate by environment (Pyrimethamine)



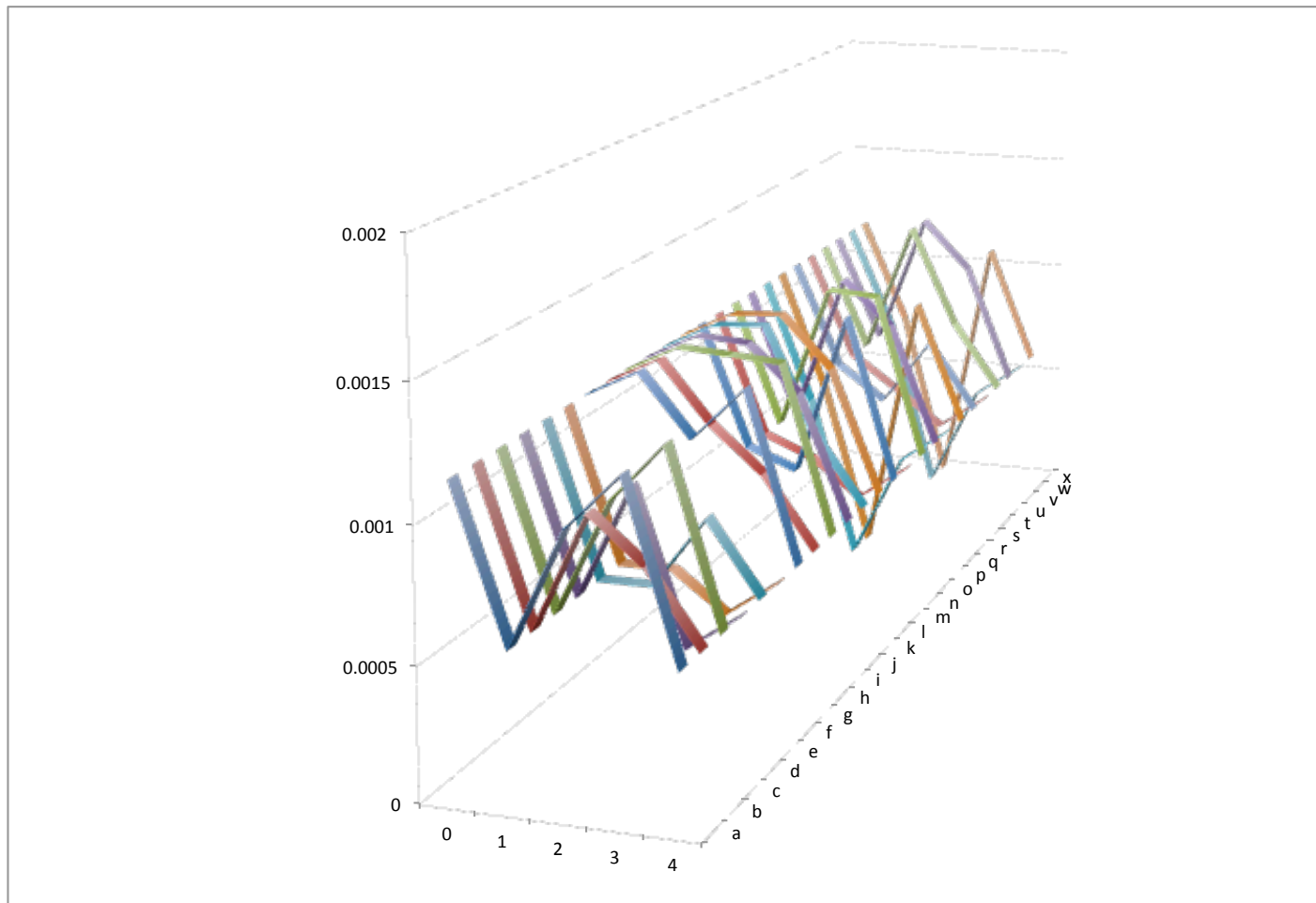
Growth rate by environment (Cycloguanil)





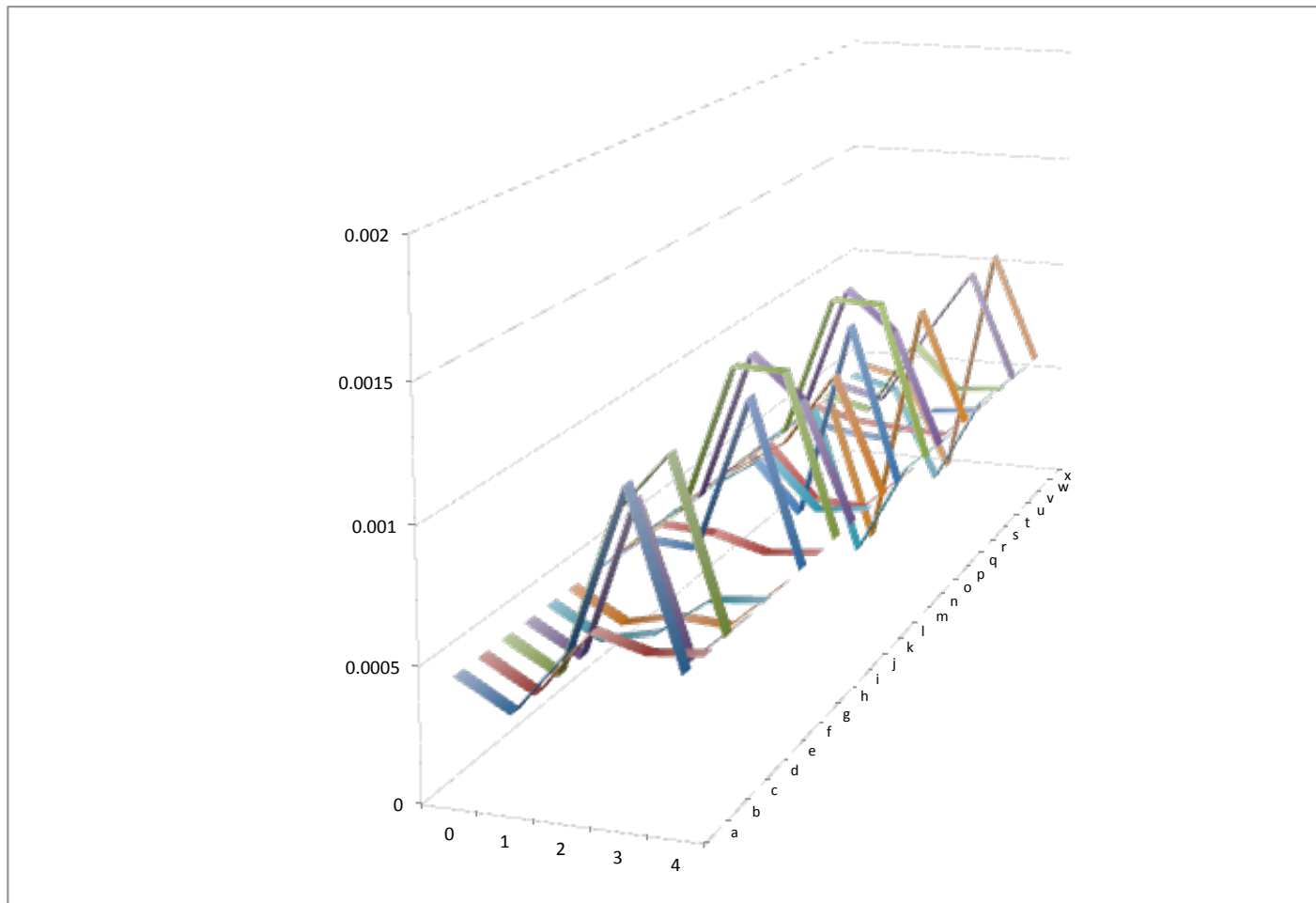
24 possible pathways
towards maximal
drug resistance
(0000 → 1111)

Trajectories by Environment (No drug)



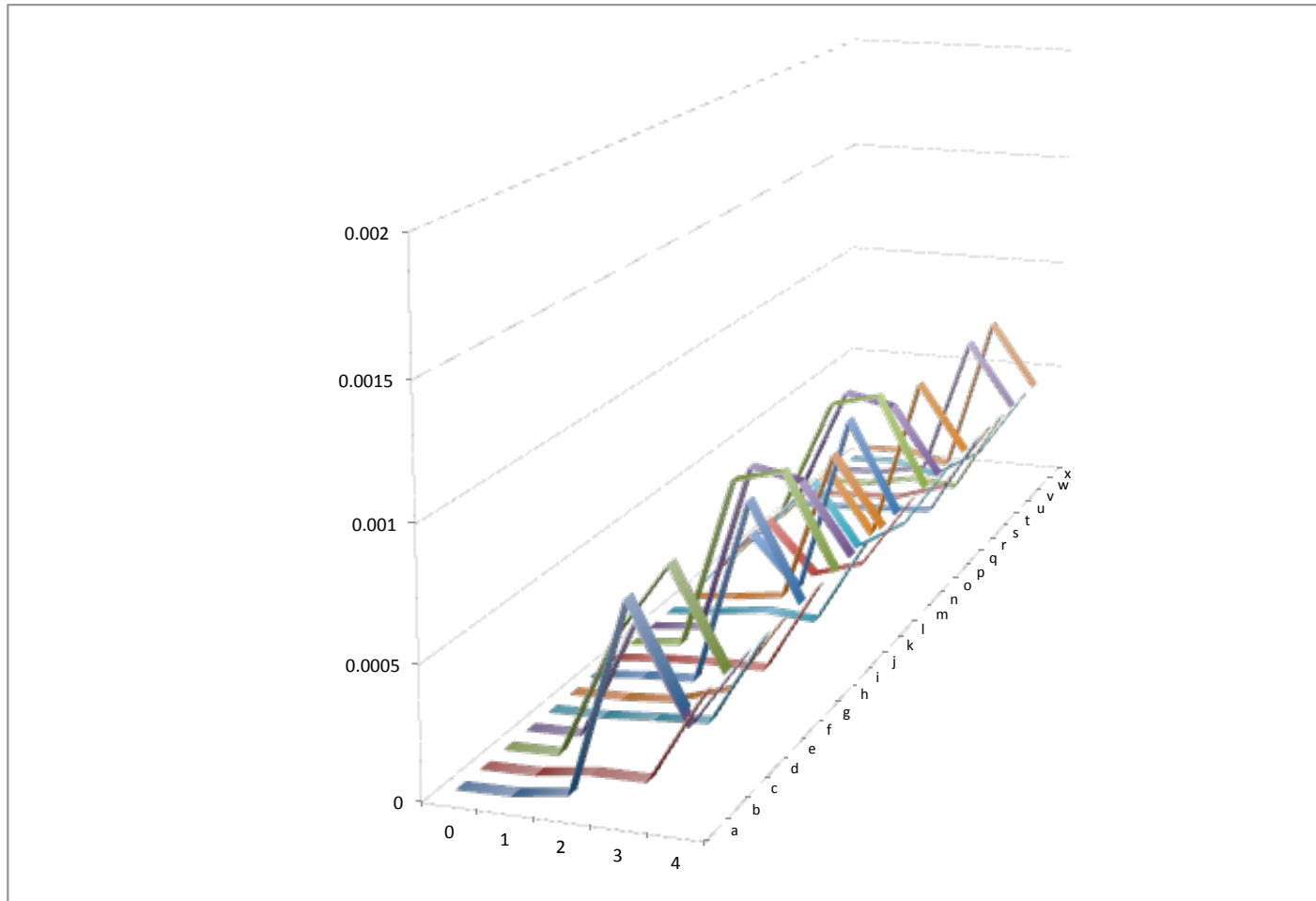
Results

Trajectories by Environment (0.01 ug/L Pyrimethamine)



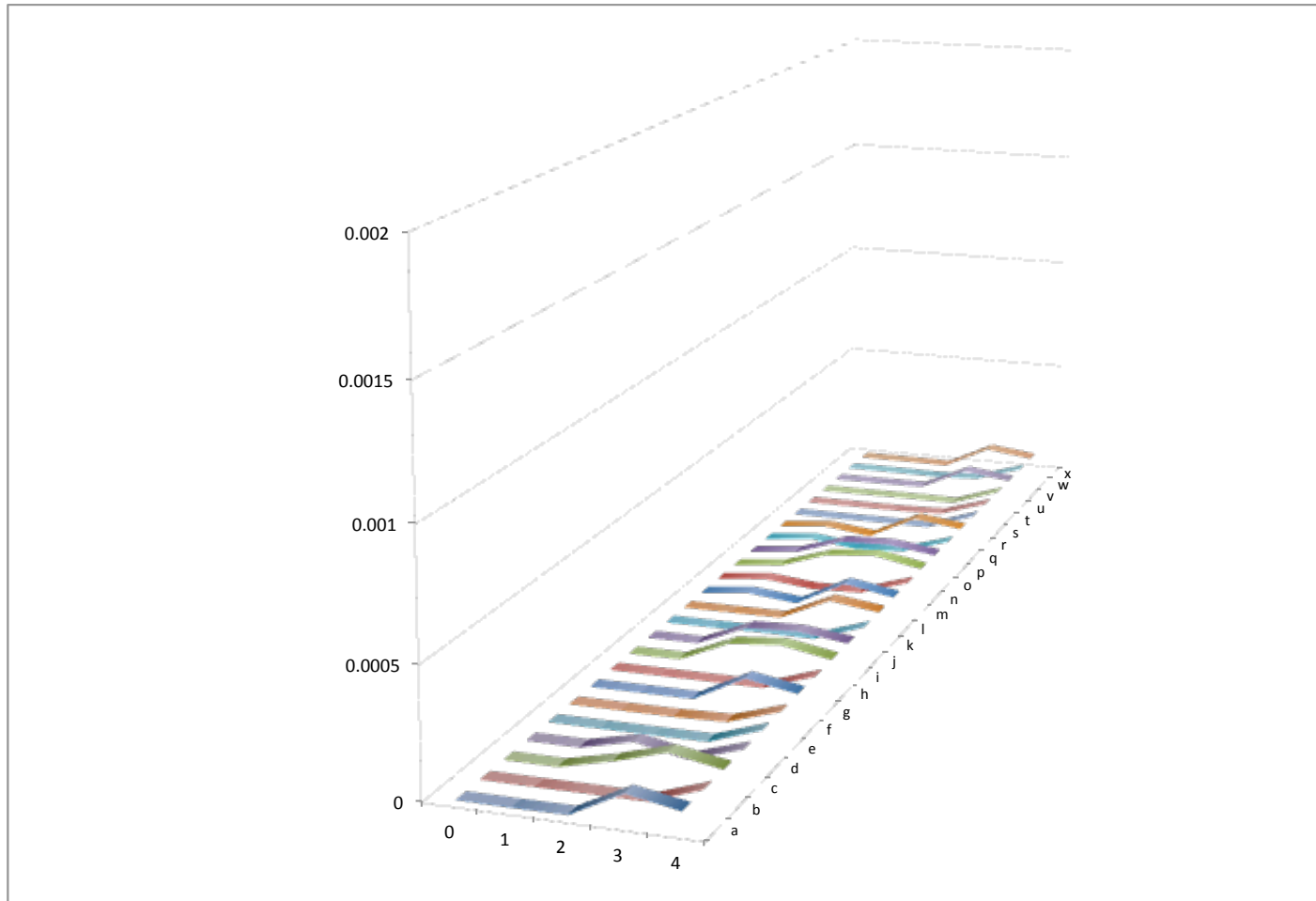
Results

Trajectories by Environment (1.0 ug/ML Pyrimethamine)



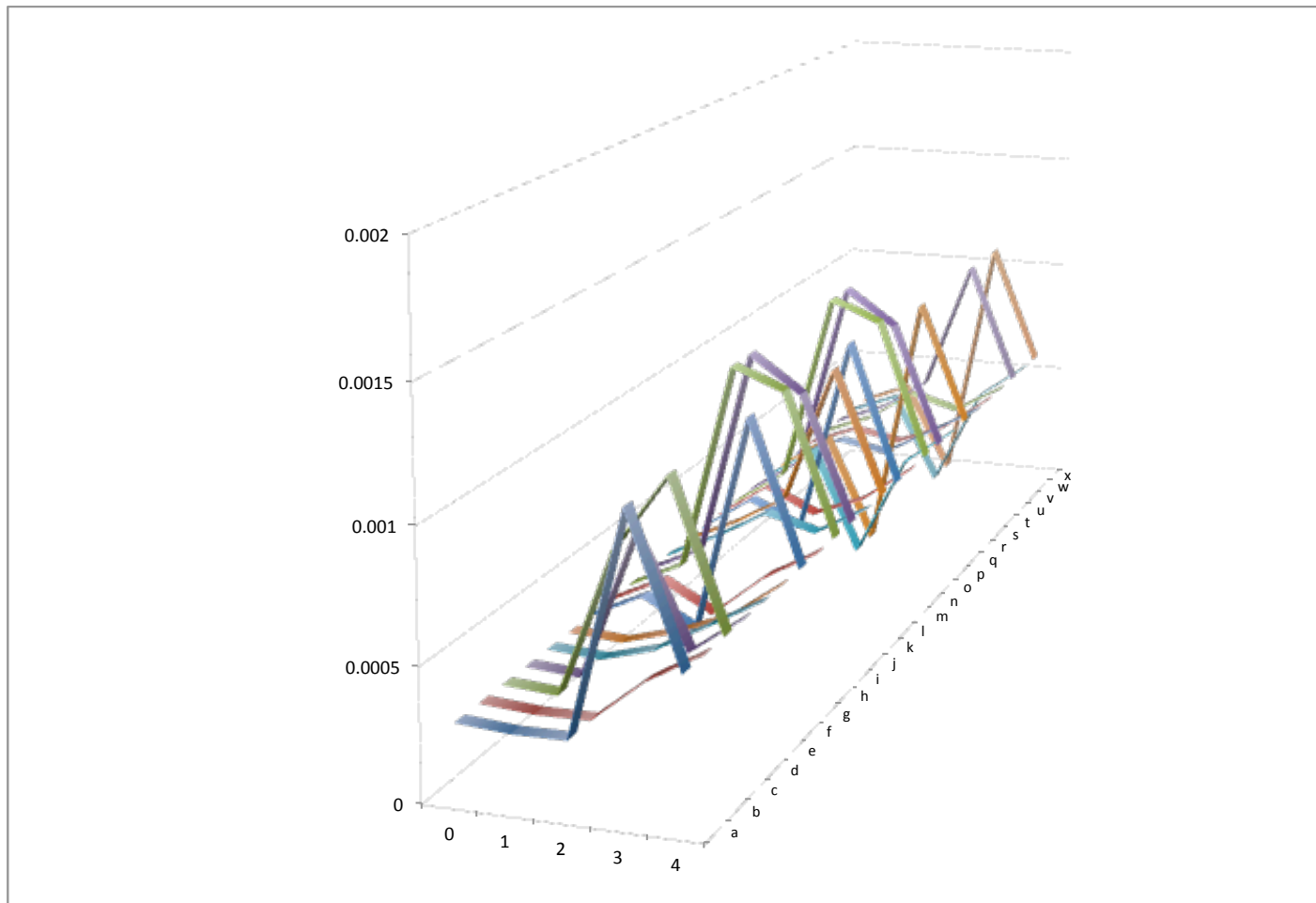
Results

Trajectories by Environment (100 ug/ML Pyrimethamine)



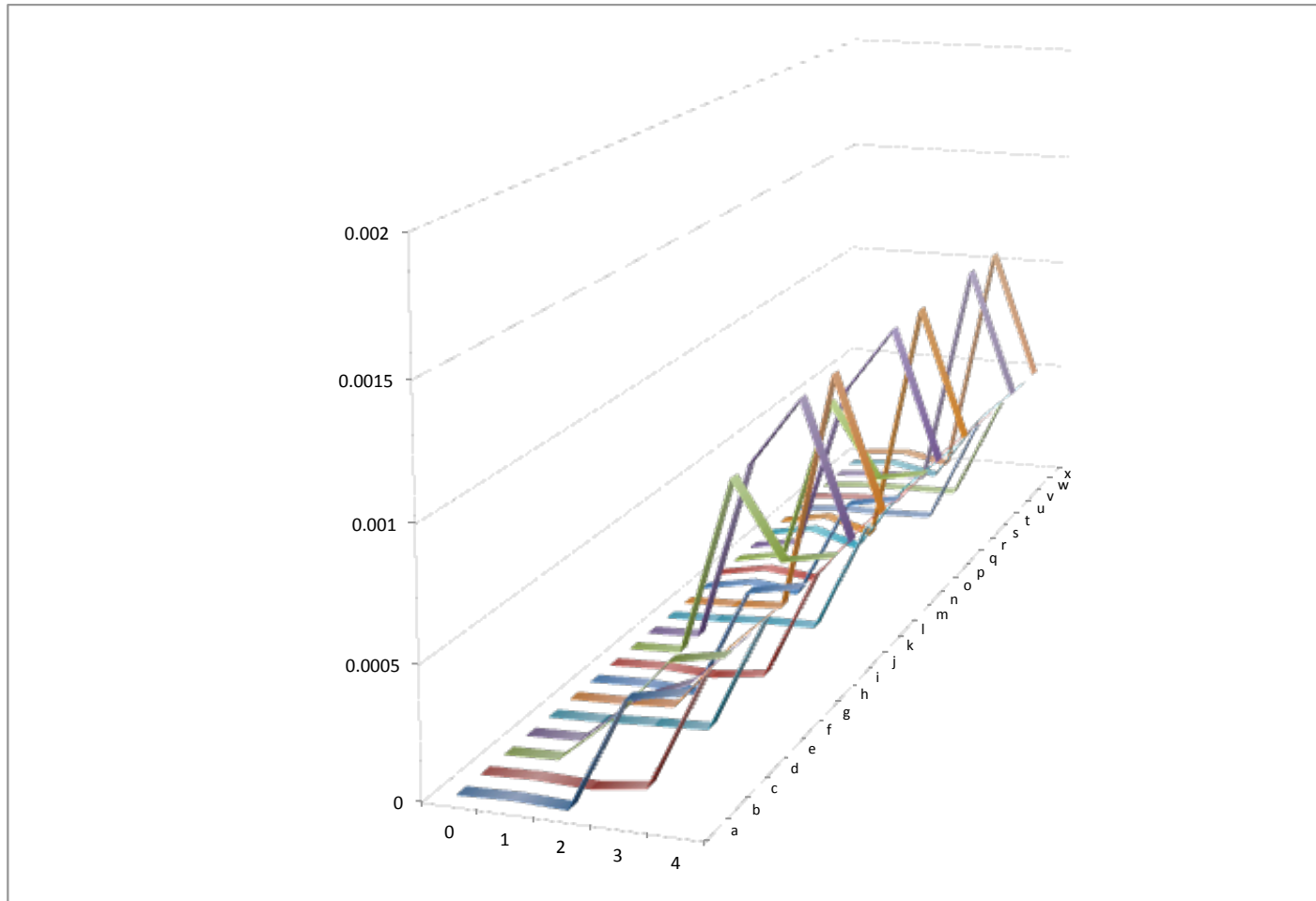
Results

Trajectories by Environment (0.01 ug/L Cycloguanil)



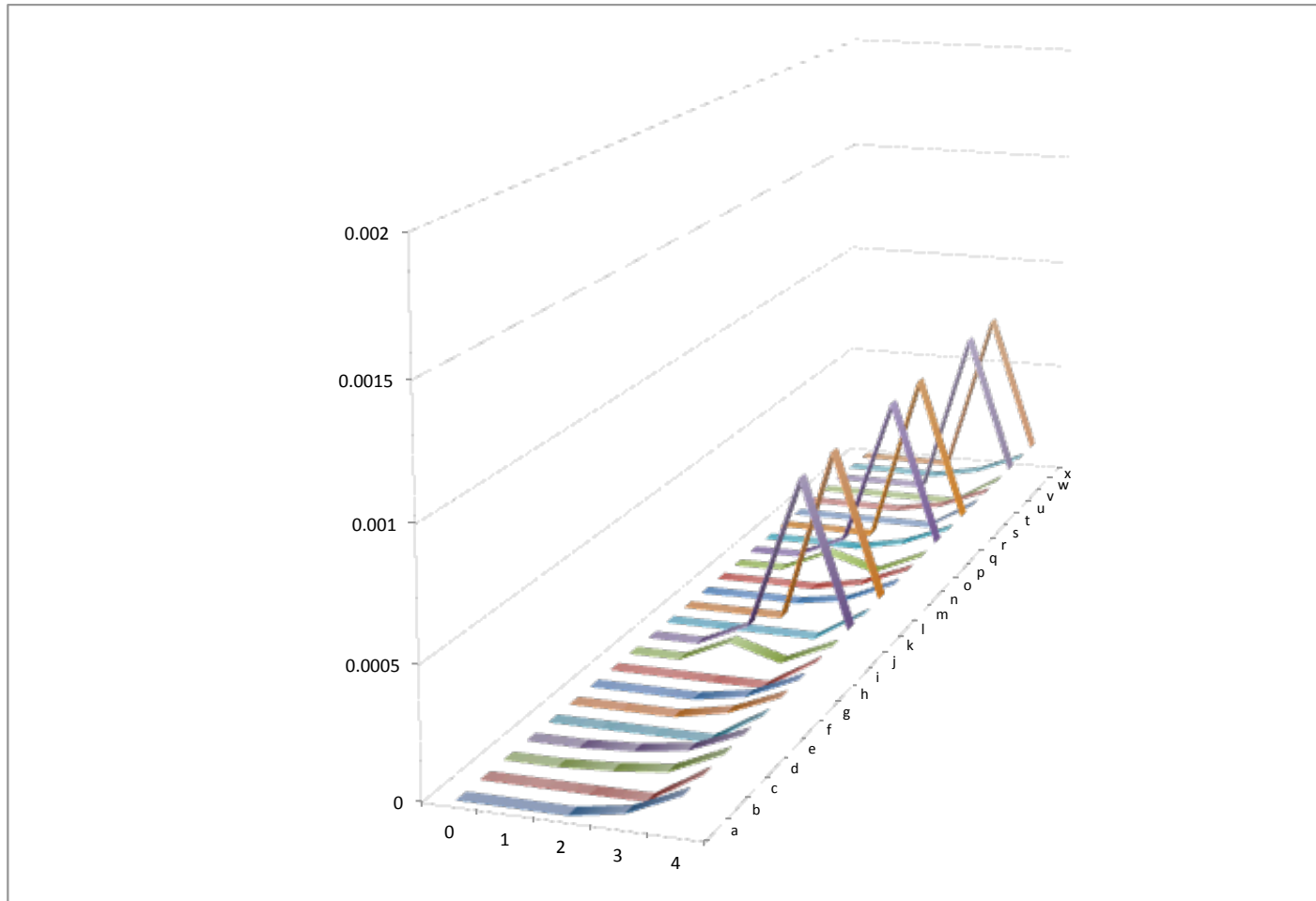
Results

Trajectories by Environment (1.0 ug/ML Cycloguanil)



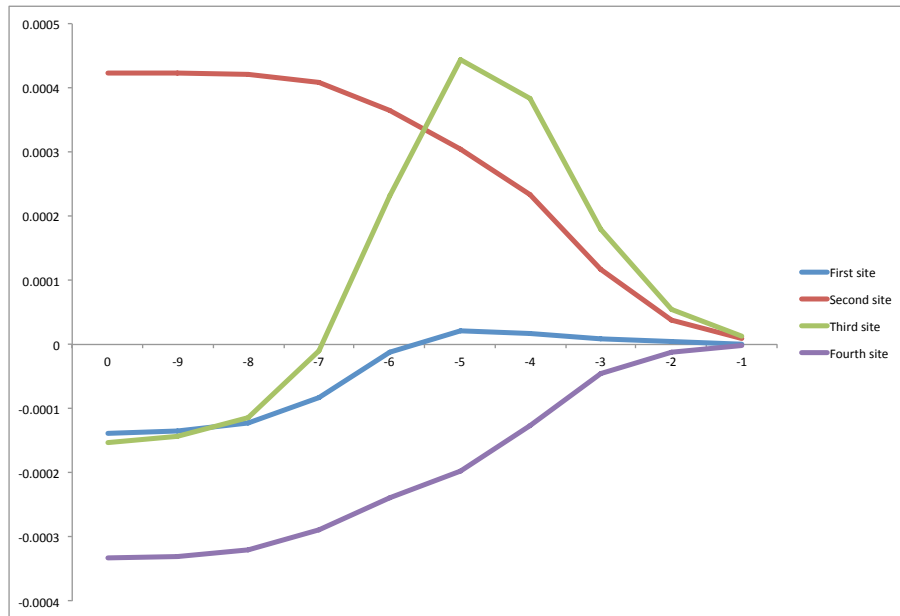
Results

Trajectories by Environment (100 ug/ML Cycloguanil)

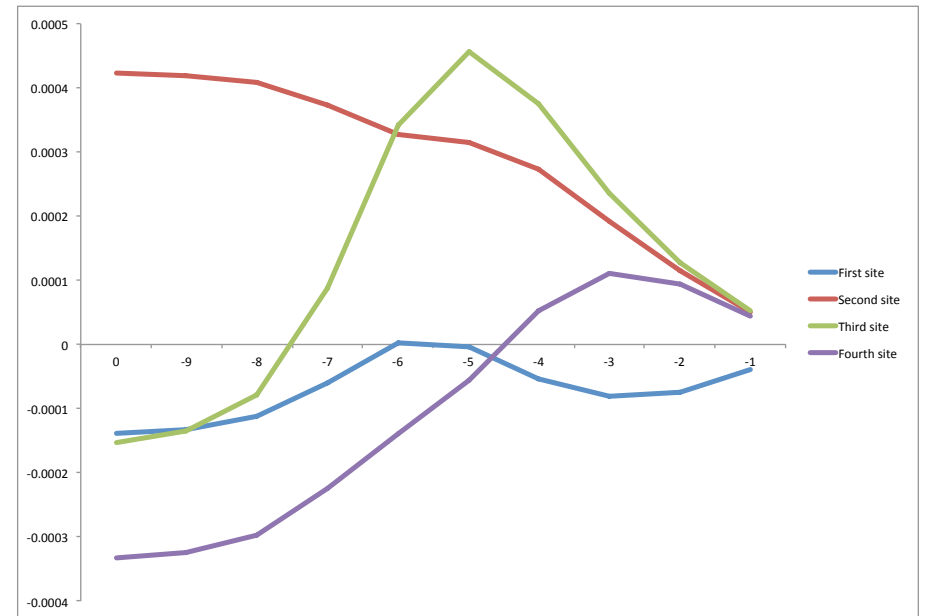


Results

Effect of mutation by environment



Pyrimethamine



Cycloguanil

Can we improve on the fitness
landscape metaphor and how
would it help us?

Can we improve on the fitness
landscape metaphor and **how**
would it help us?

Debate: What is the best way to treat a malaria infection?

The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy

Andrew F. Read^{a,b,1}, Troy Day^c, and Silvie Huijben^a

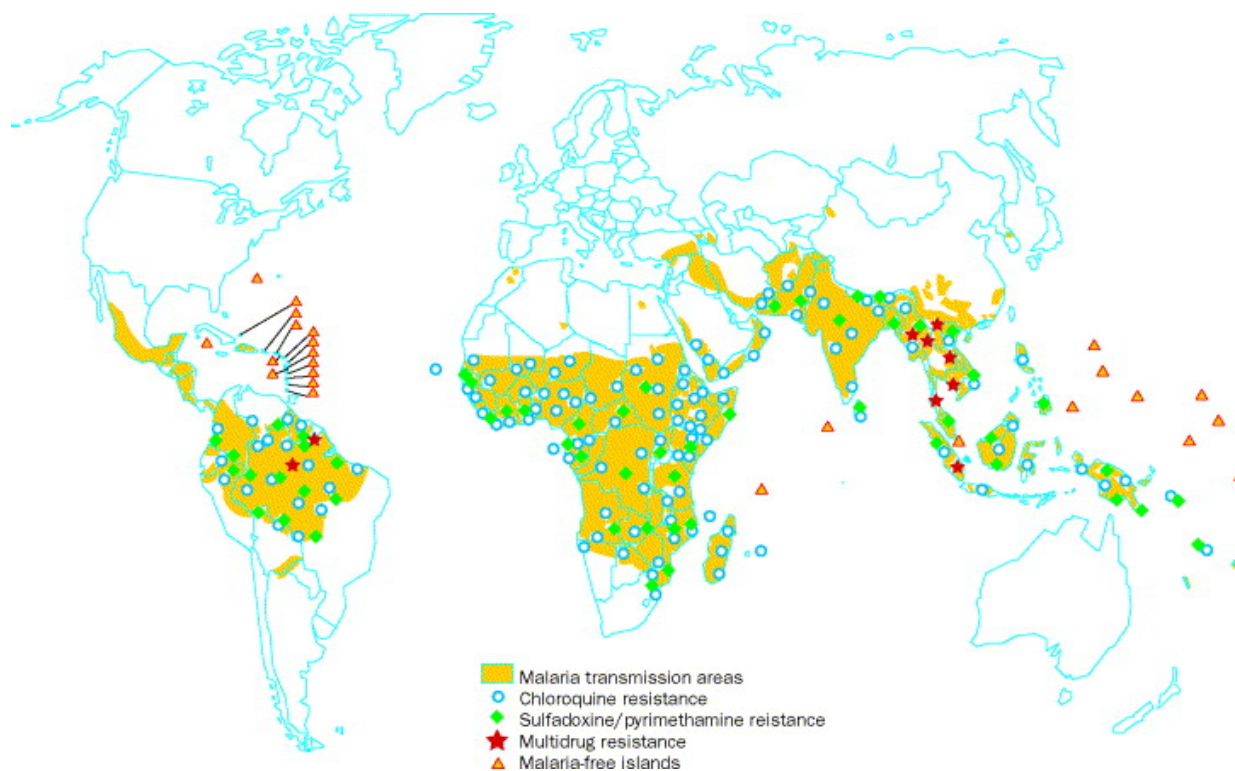
^aCenter for Infectious Disease Dynamics, Departments of Biology and Entomology, Pennsylvania State University, University Park, PA 16802; ^bFogarty International Center, National Institutes of Health, Bethesda, MD 20892; and ^cDepartments of Mathematics, Statistics, and Biology, Queen's University, Kingston, ON, Canada K7L 3N6

Aggressive Chemotherapy and the Selection of Drug Resistant Pathogens

Silvie Huijben^{1a*}, Andrew S. Bell¹, Derek G. Sim¹, Danielle Tomasello^{1ab}, Nicole Mideo¹, Troy Day², Andrew F. Read^{1,3*}

¹ Center for Infectious Disease Dynamics, Departments of Biology and Entomology, Pennsylvania State University, University Park, Pennsylvania, United States of America, ² Departments of Mathematics, Statistics and Biology, Jeffery Hall, Queen's University, Kingston, Ontario, Canada, ³ Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America

Debate: Why are certain resistance alleles in the population?



In particular, how do suboptimal alleles arise in nature?

Non-SSWM Assumption via PK/PD Style Models

- From IC_{50} and Drugless growth rate to $[R]$ to the Malthusian parameter, $[r]$
- From $[r]$ to exponential growth model

$$R = \frac{R_a}{1 + \left(\frac{D}{IC_{50}}\right)^m}$$

$$R = 1 + r$$

$$r = \frac{R_a}{1 + \left(\frac{D}{IC_{50}}\right)^m} - 1$$

$$N(t) = [N(t-1) + N_{mut}(t-1)]e^r$$

Model Assumptions and Limitations

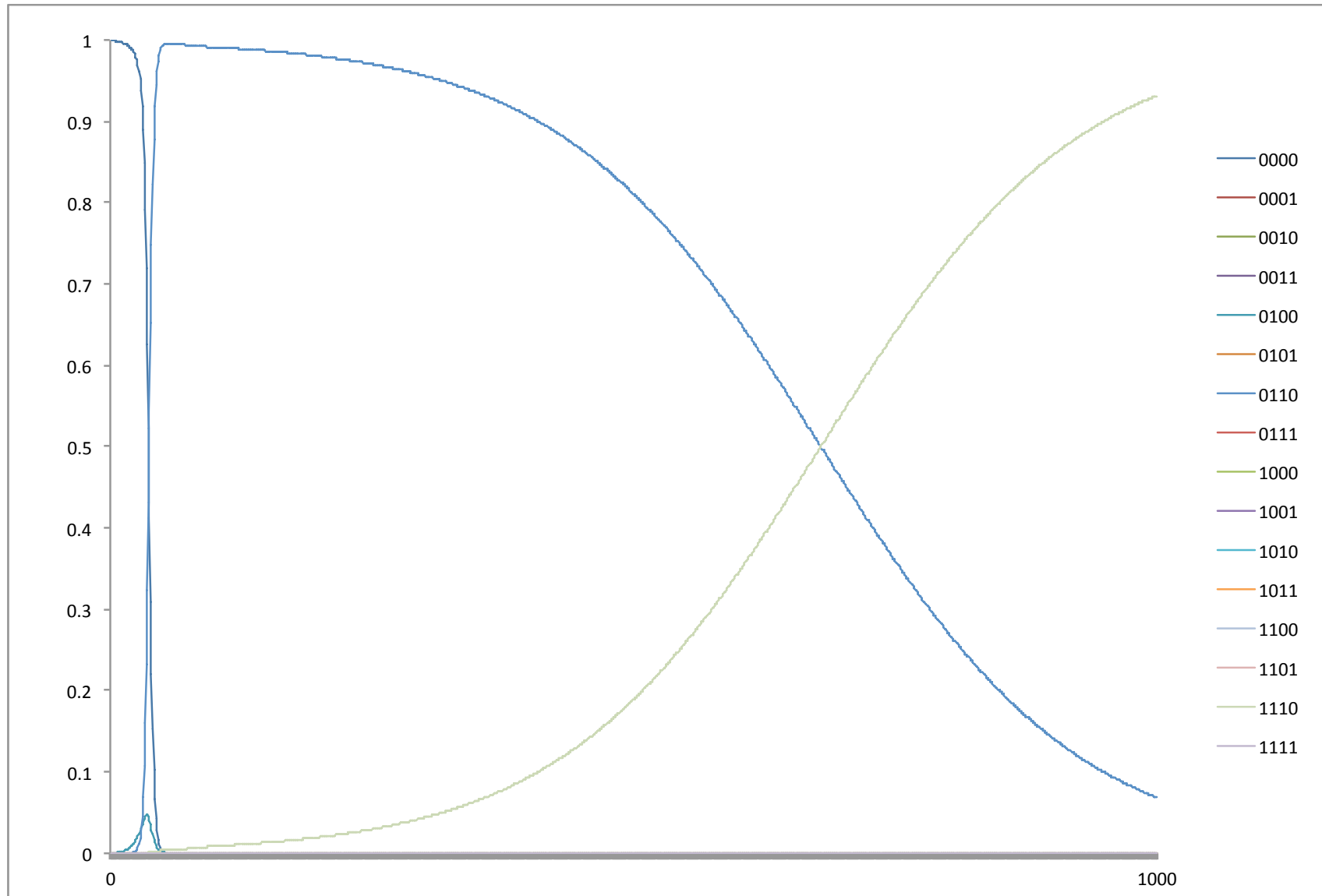
- Growth rates and IC_{50} values are from model systems + *in vitro*
- DHFR is the sole resistance determinant
- High transmission background
- No interlocus antagonistic pleiotropy
- Limited decay
- No competition

Model is necessarily simple, and can be tweaked to fit a range of questions

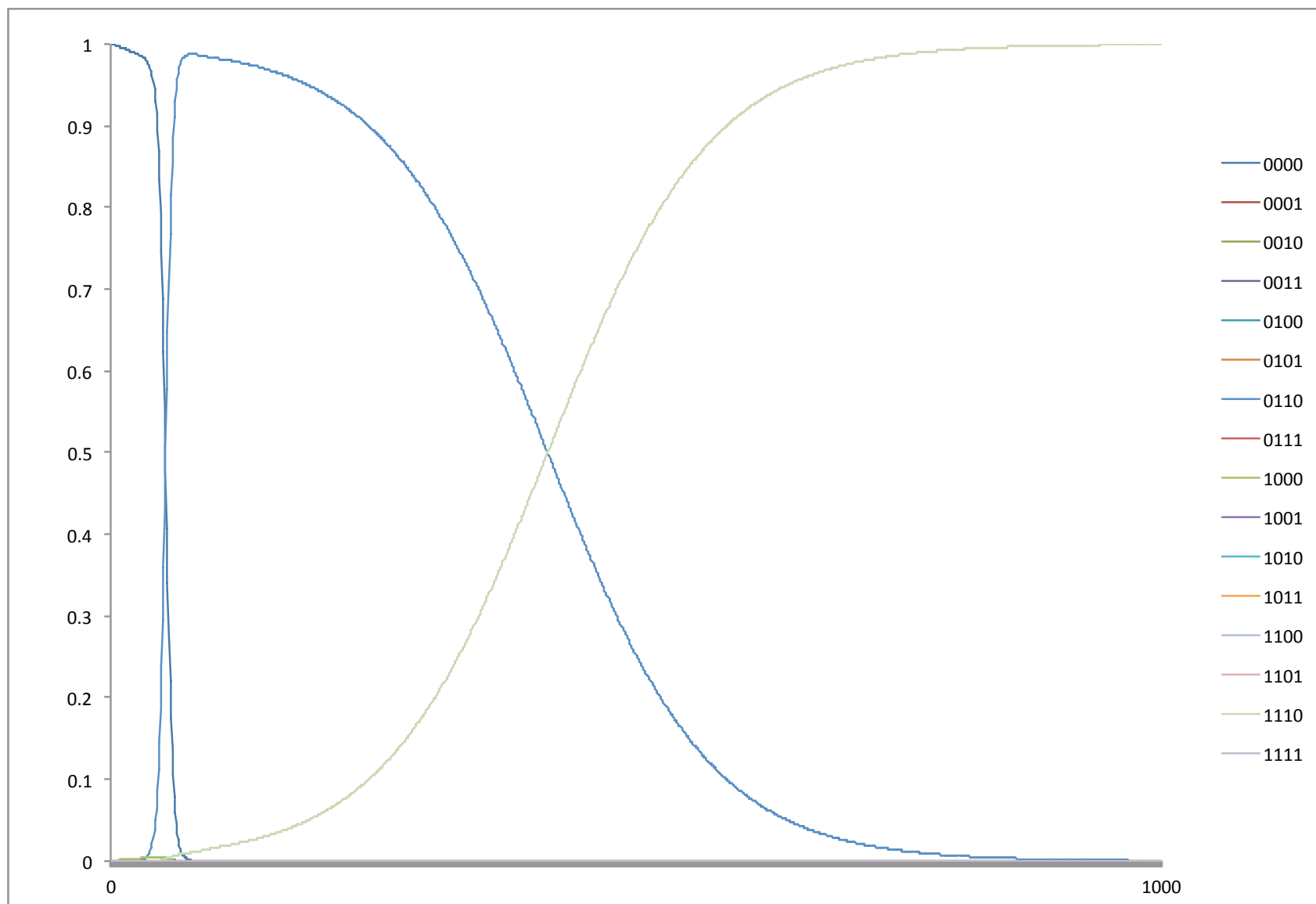
Scenario I: Trajectories

- Examine the preferred trajectories at a range of drug concentration, at two drugs
- Maximal resistance: 0000→
- Reversion: ←1111
- Mutations limited to one-step neighbors
- Mutation rate: 10^{-9} mutations per site per generation

Pyrimethamine, 0.01 ug/L



Pyrimethamine, 1.0 ug/L



Cylcoguanil, 0.01 ug/ML

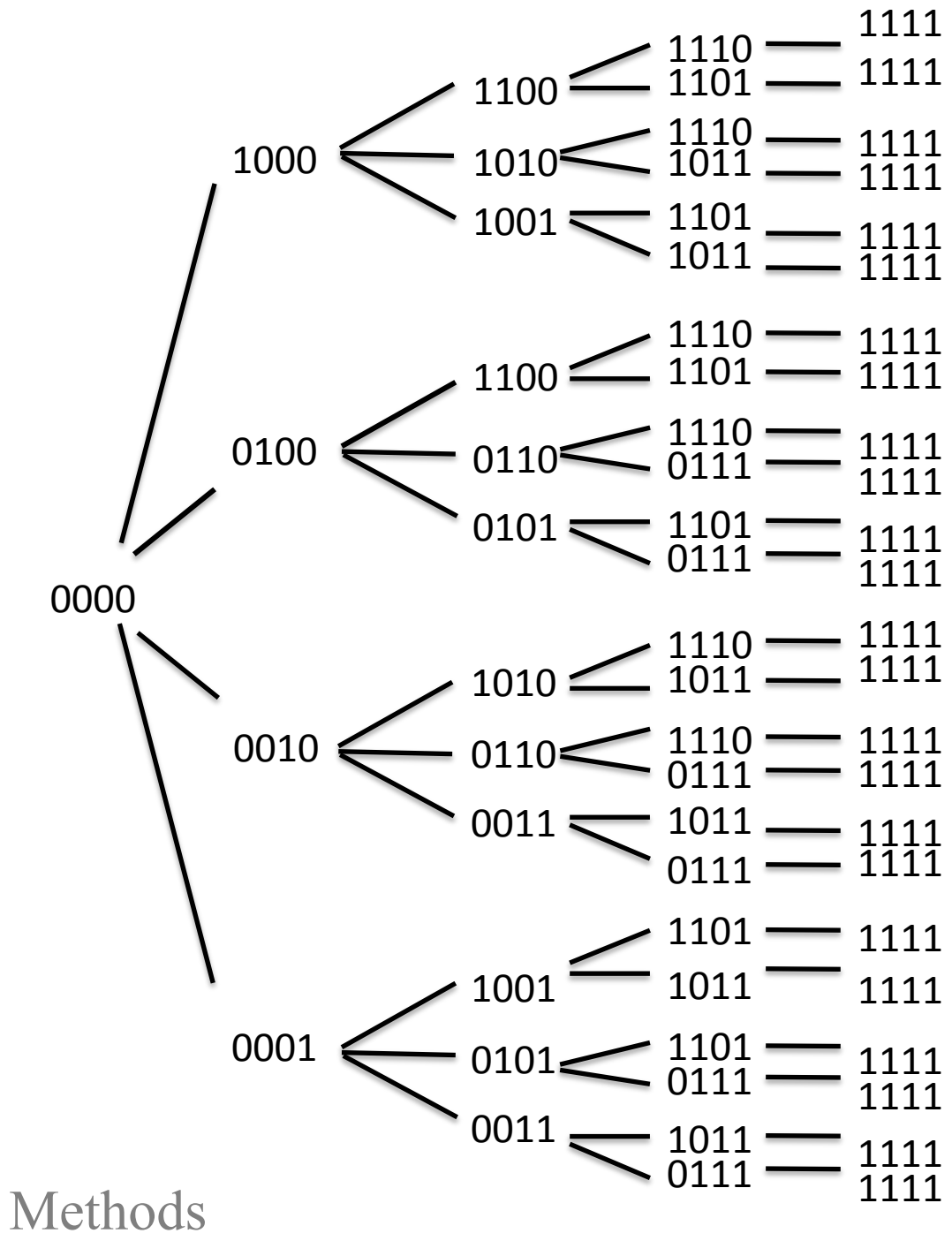


Cylcoguanil, 1.0 ug/ML



Trajectory summary

- Recapitulate pathways as in the Weinreich method, in a non-SSWM setting
- Steps occur in sensible order
- Unexpected allele (0101) in the reversion evolution with no drug
- Time to fixation speaks to being trapped on a peak



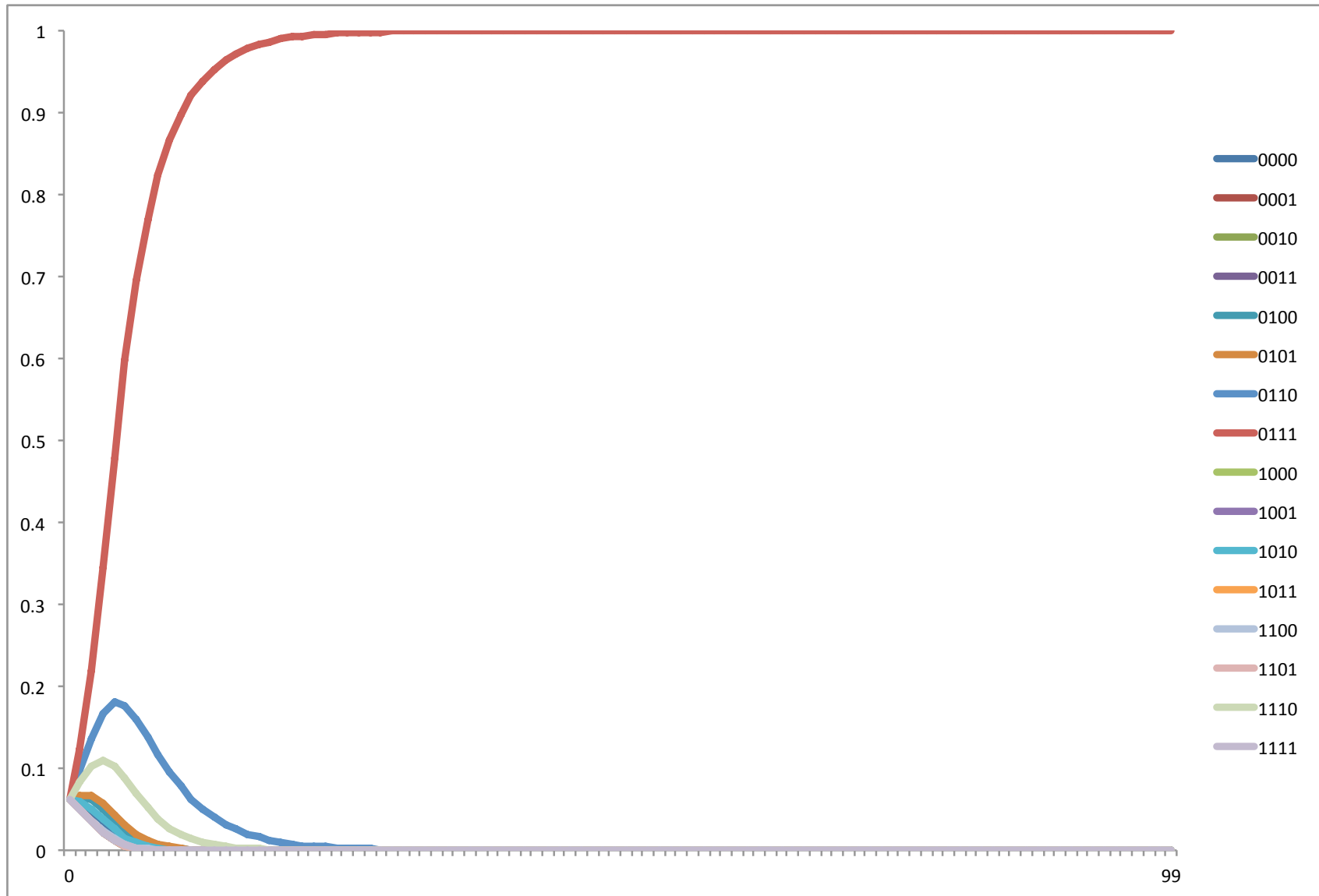
24 possible pathways
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Methods

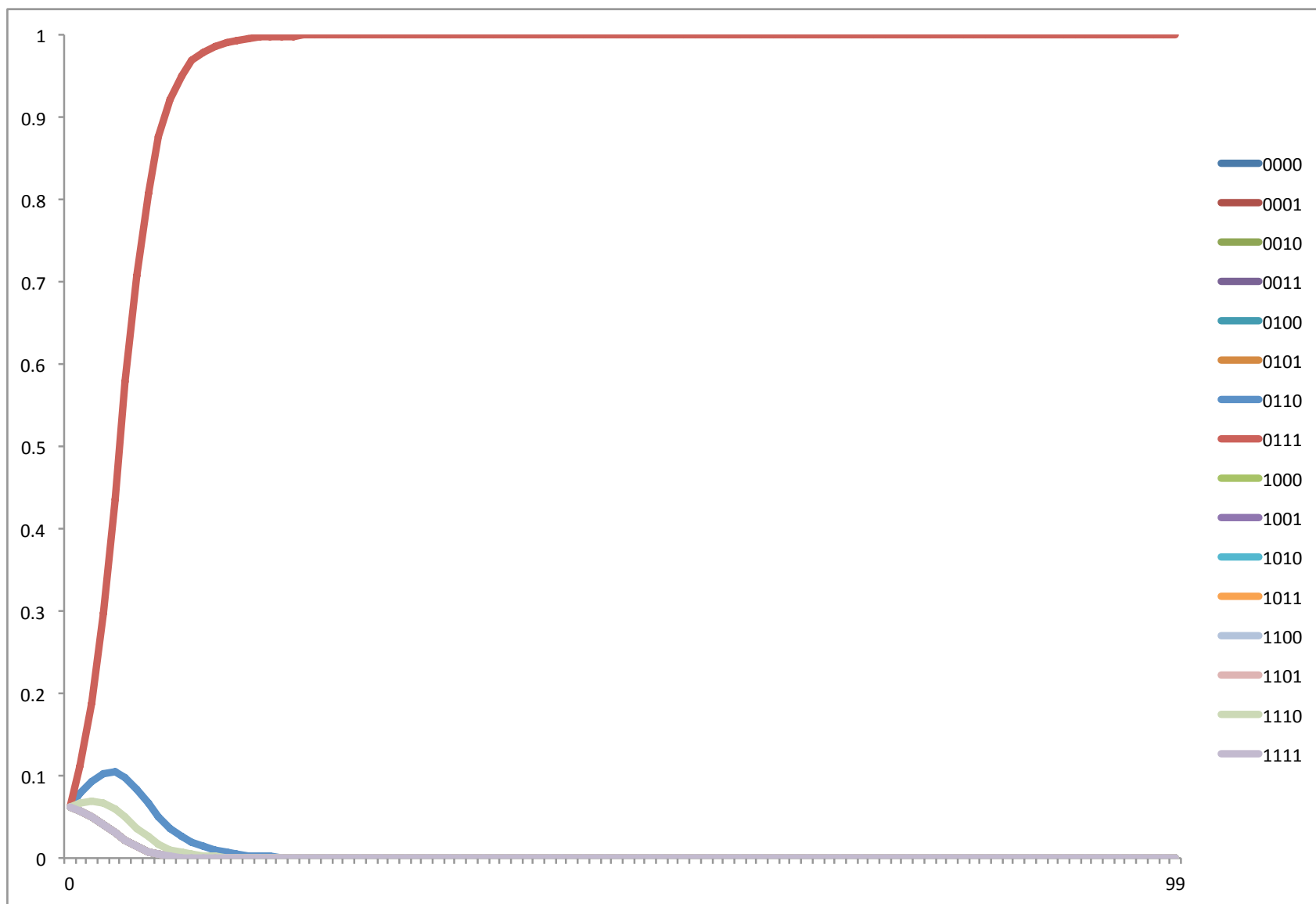
Scenario 2: Standing genetic variation

- Used to basic questions about the dynamics of evolution in a mixed population
- Equal proportion of each of the resistant 16 alleles (starting with 10)
- Mutations limited to one-step neighbors
- Mutation rate: 10^{-9} mutations per site per generation

0.01 ug/ML Cycloguanil



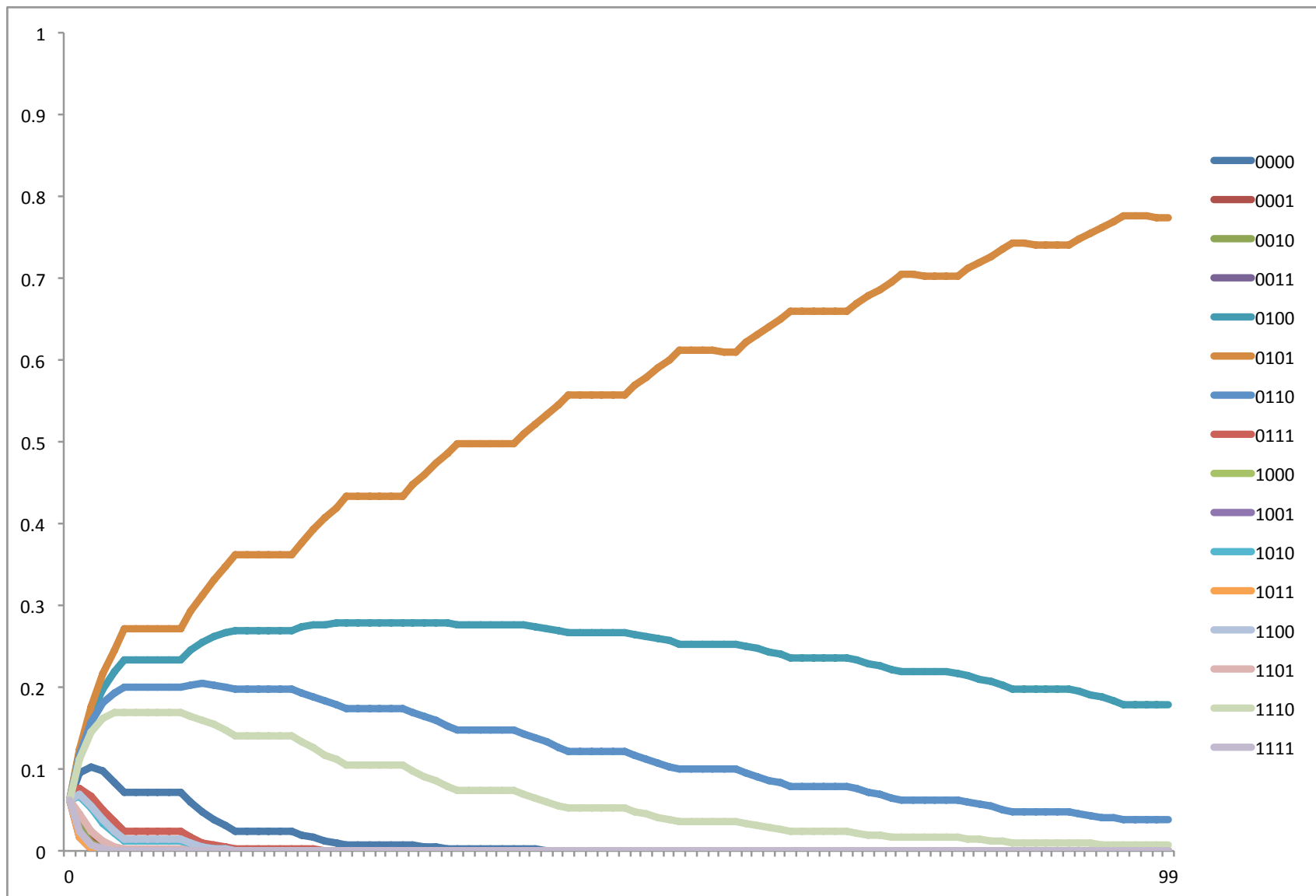
1.0 ug/ML Cycloguanil



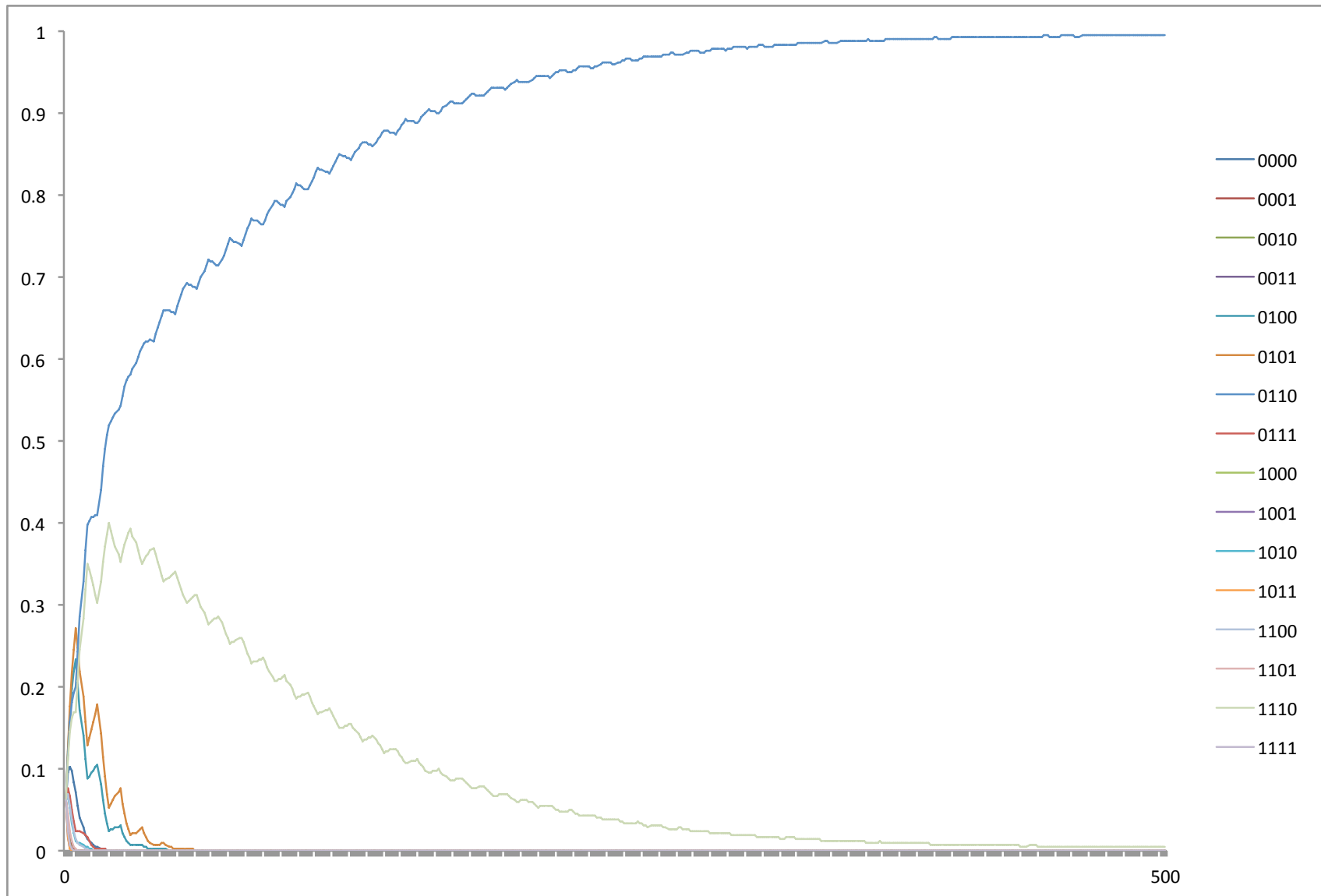
Scenario 3: Drug switching

- Two treatment kinds: on/off for five generations at a time or pyrimethamine/cycloguanil switching for five generations at a time
- In clinical terms, analogous to cycling, or to varying levels of patient adherence

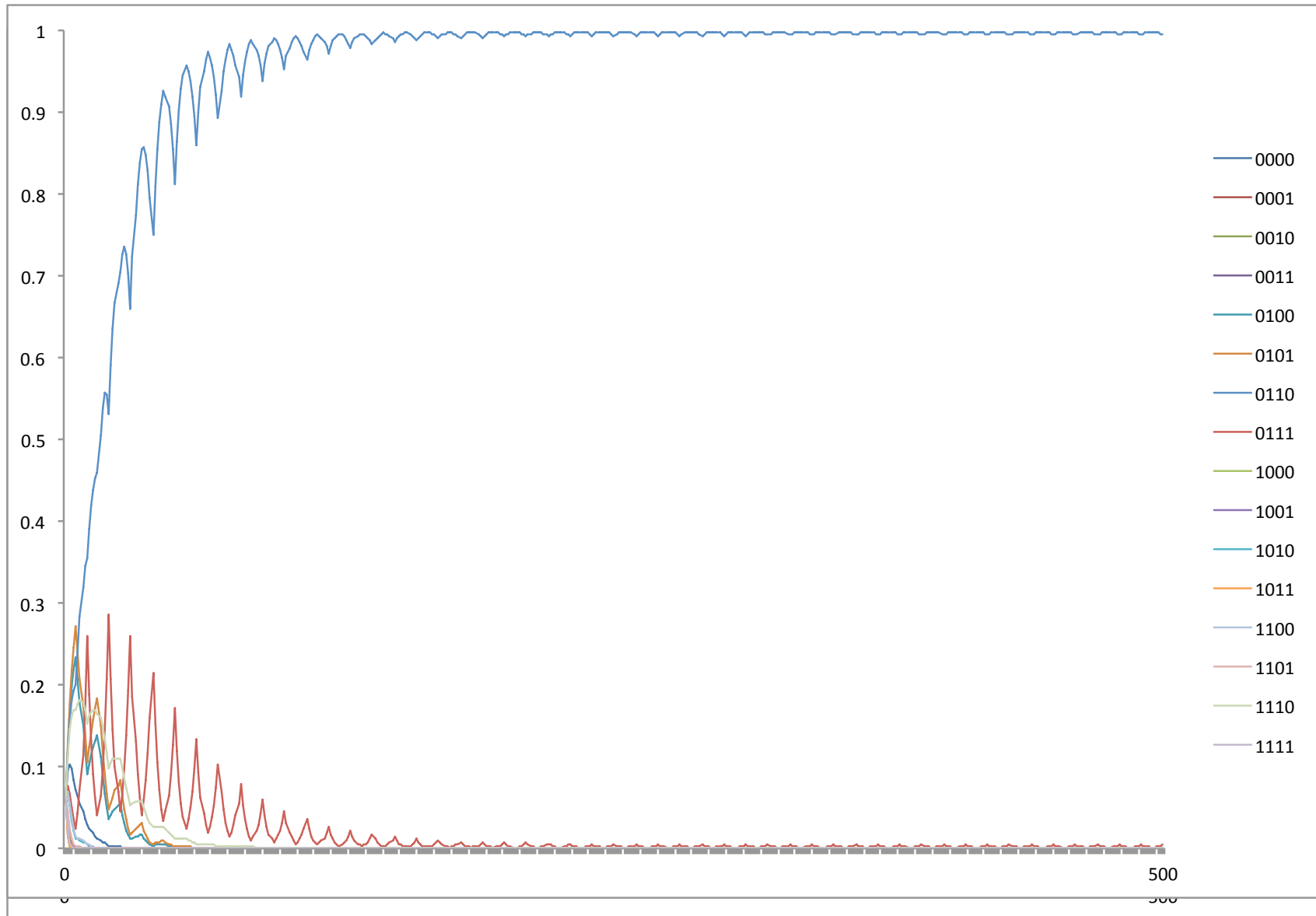
No drug + 100 ug/ML Pyrimethamine



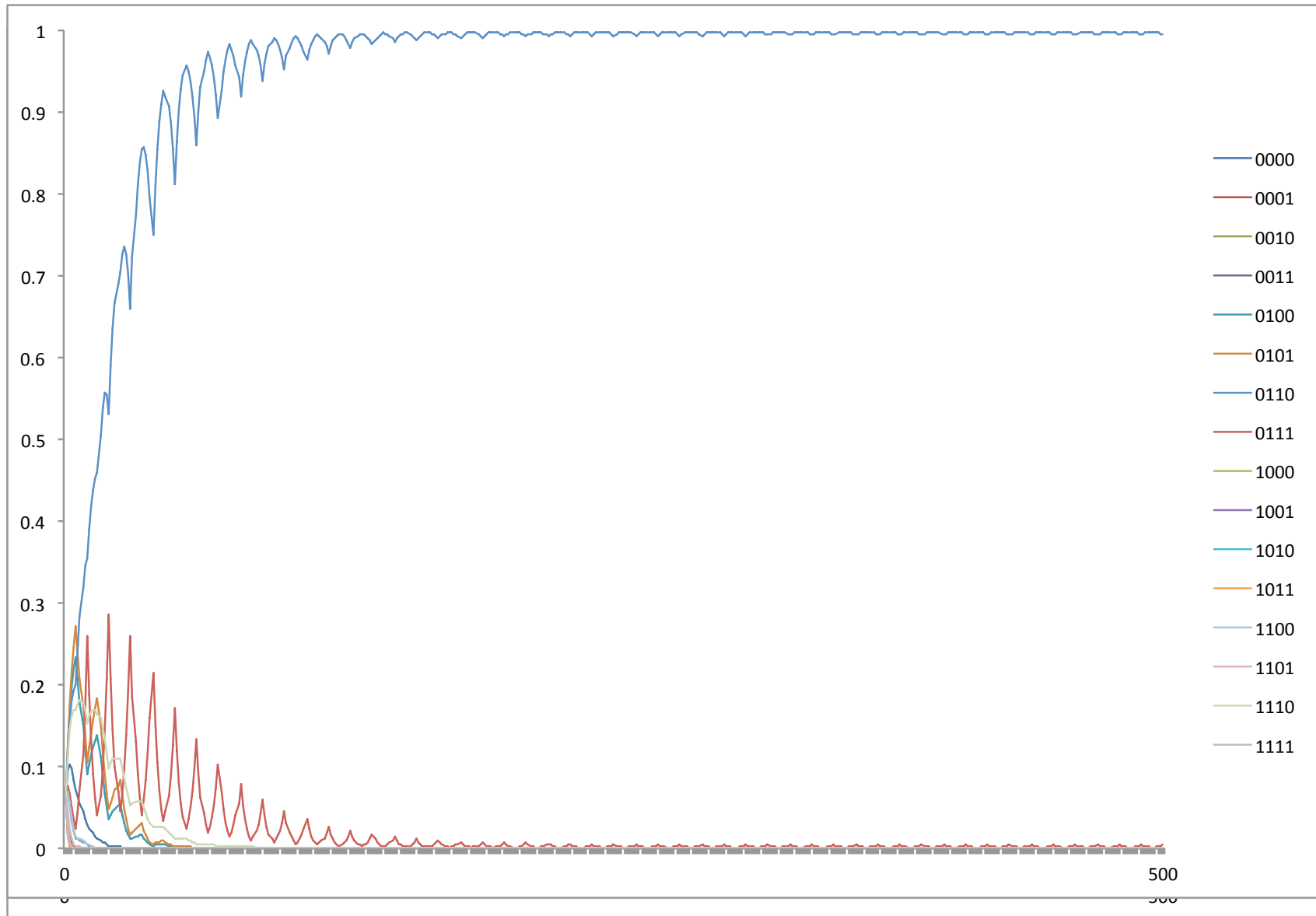
No drug + 0.01 ug/ML Pyrimethamine



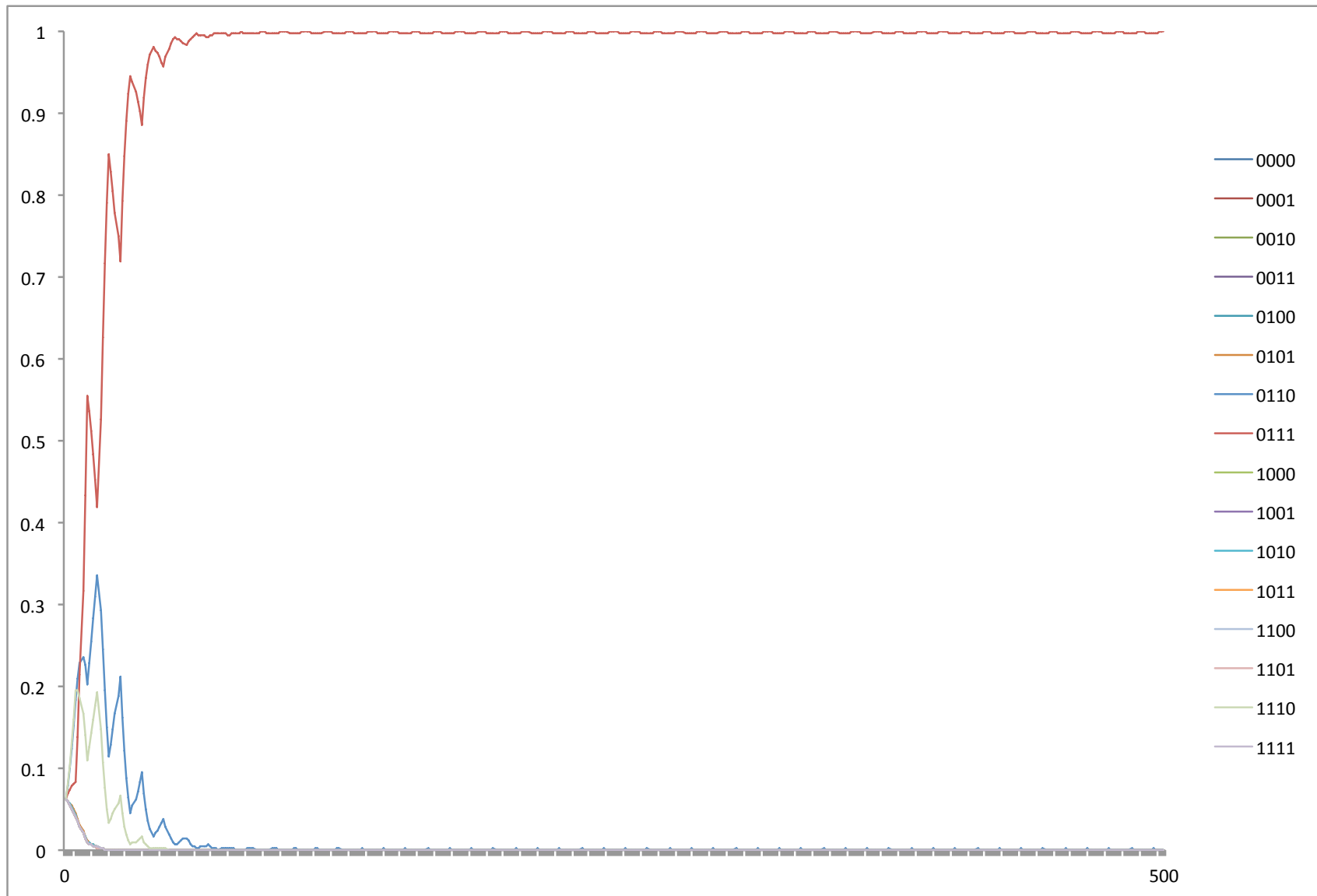
No drug + 0.01 ug/ML Cycloguanil



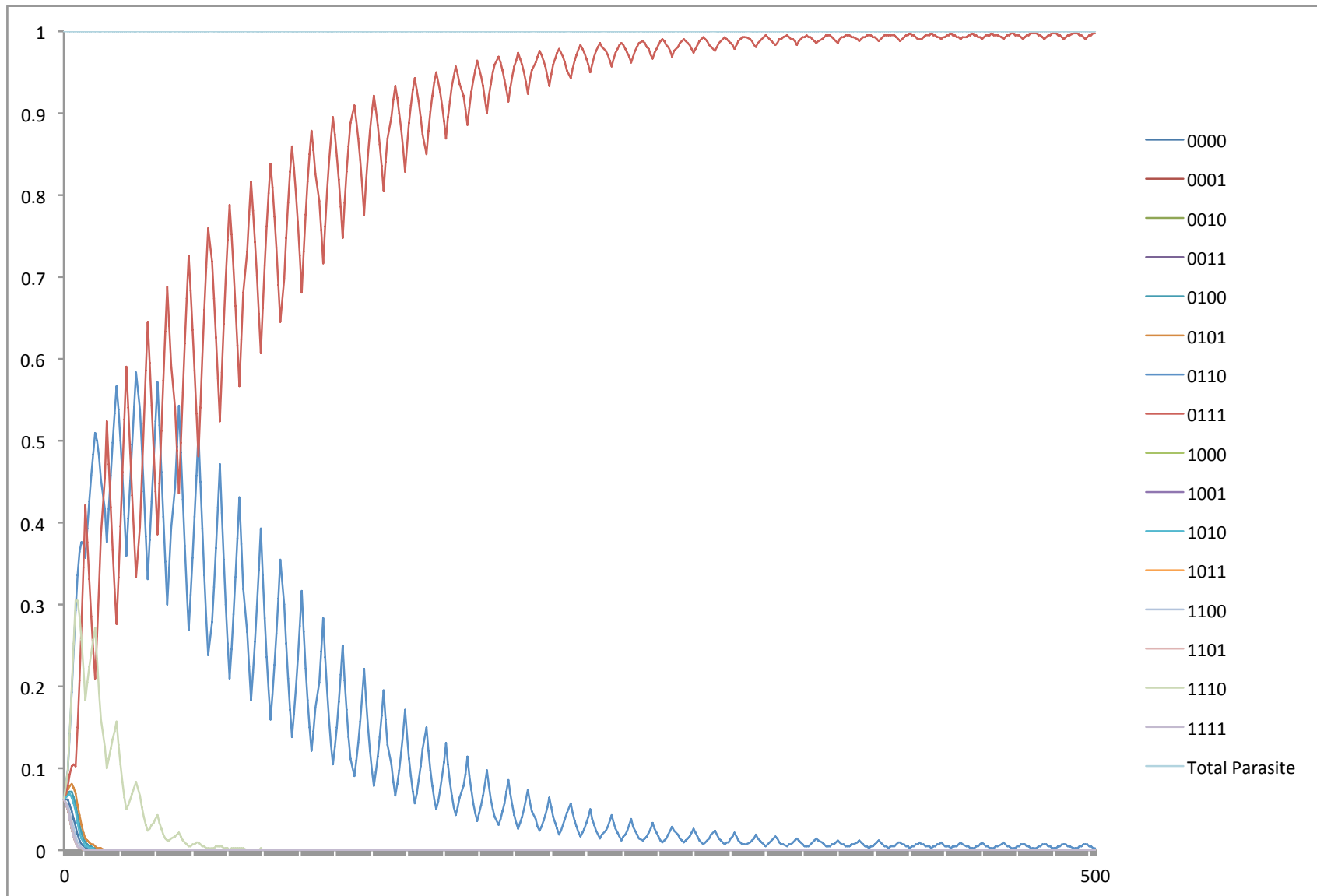
No drug + 0.01 ug/ML Cycloguanil



1.0 ug/ML + 1.0 ug/ML



0.01 ug/ML + 0.01 ug/ML



Brief summary

- Drug resistance is not necessarily drug fitness
- Less potent drug can be stronger selective agent
- The most fit in changing environment is sometimes neither the most resistant or best replicator

Present and future

Epidemiological and Immunological details

- What they do and do not say

Pharmacological details

- What they do, and do not contribute

Population genetics details

- Soft sweeps
- Recombination