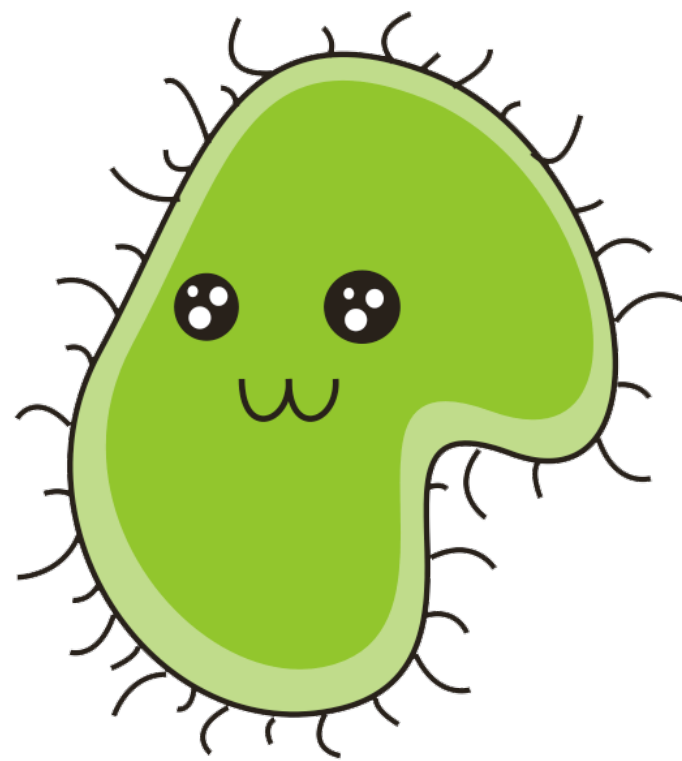


Evolution of antibiotic resistance

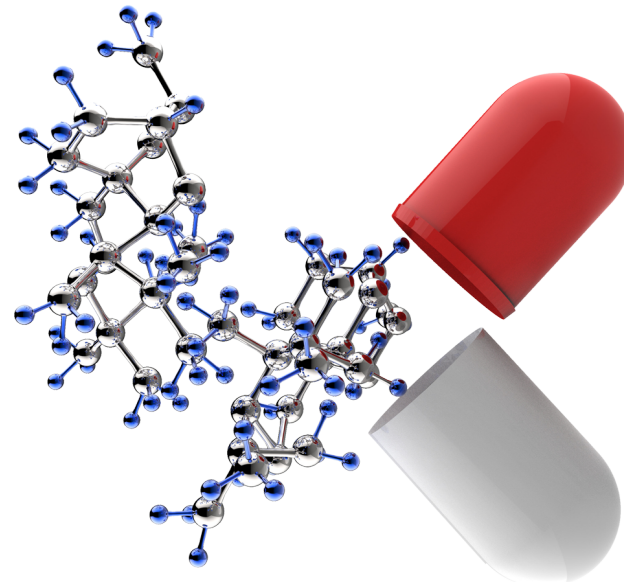
1d. using fitness landscape from Weinreich et al.

Introducing the system

bacteria + antibiotic



bacteria responds via
protein(s) coded by
B-lactamase gene



$2^5 = 32$
possible
sequences



wild type
5 single point mutations

$5! = 120$
fastest pathways
to get there



path of
evolution?

antibiotic resistant

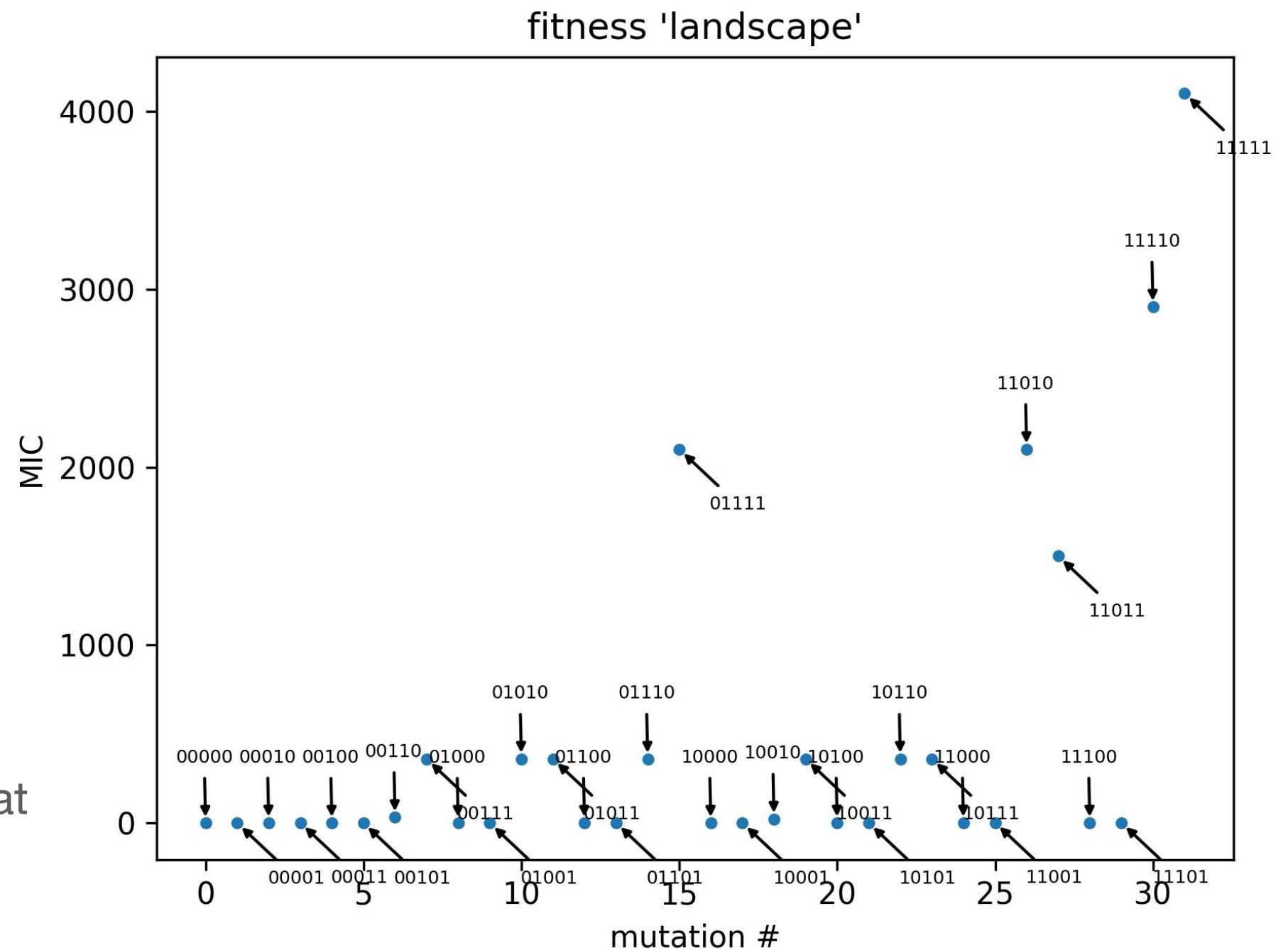


Experimental fitness landscape

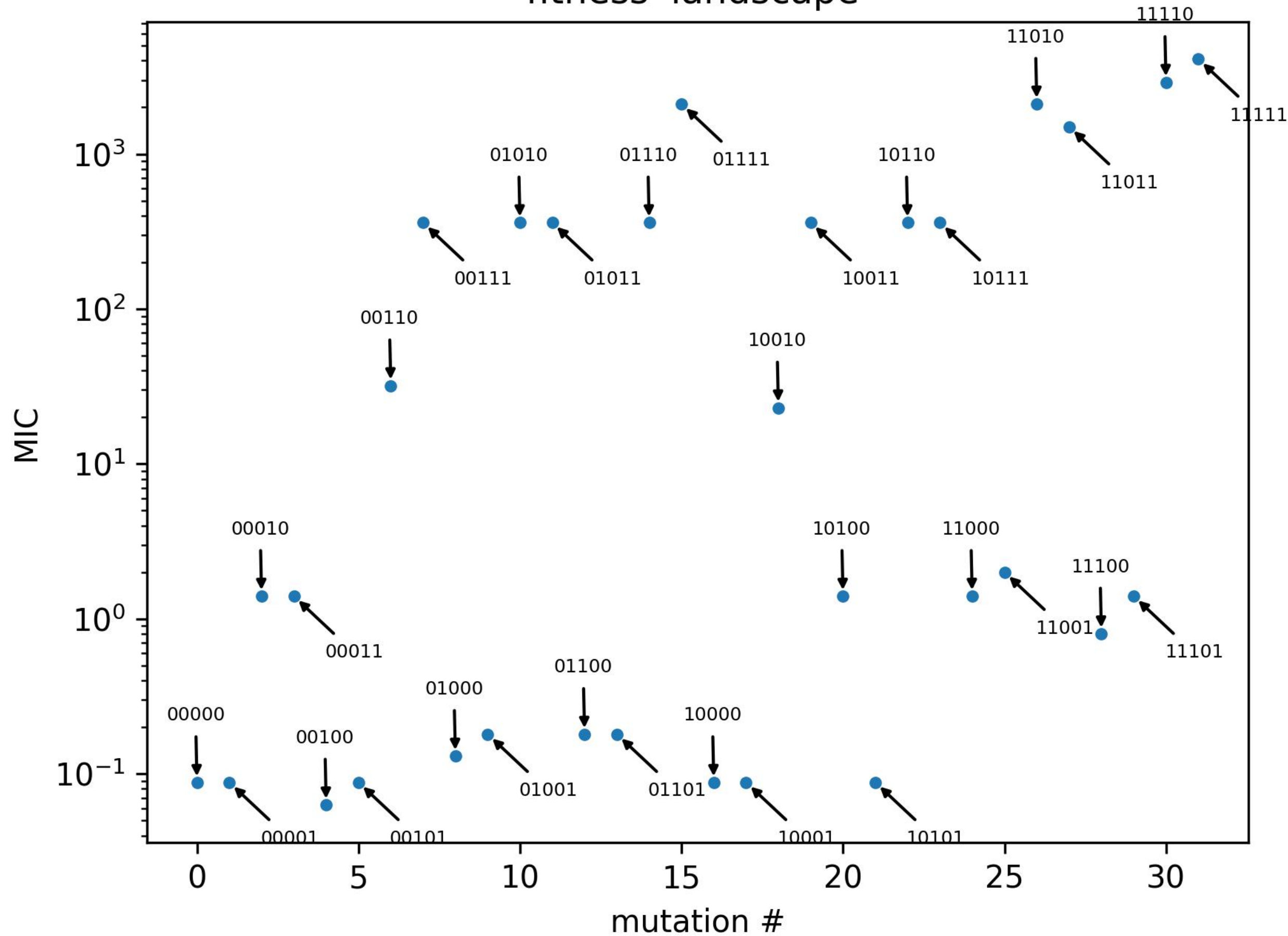
taken from Weinrich et al. 2006

create all 32 sequences
measure the minimum
inhibitory concentration
(MIC)

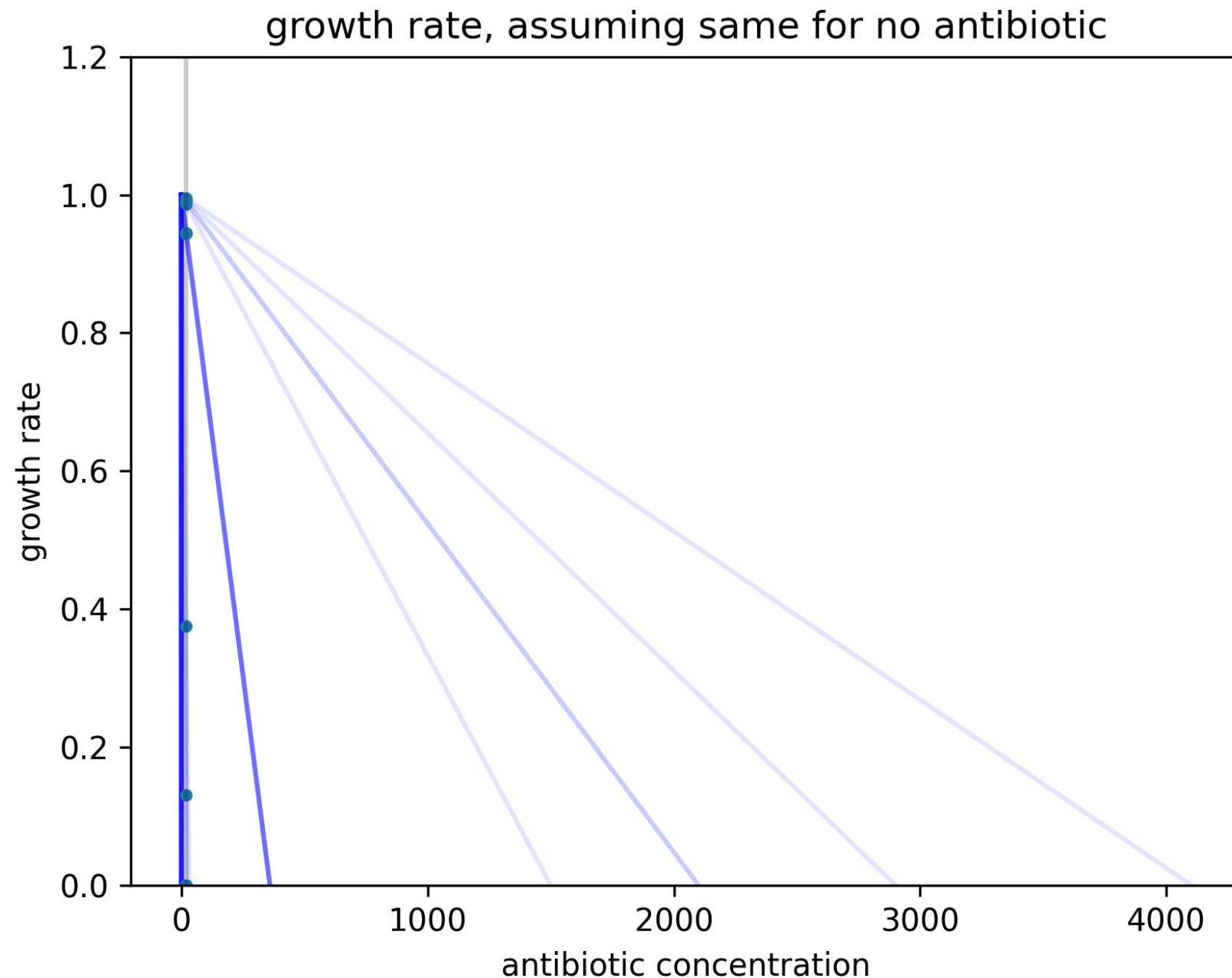
antibiotic concentration at
which there is no more
bacterial growth



fitness 'landscape'



Understanding the MIC data

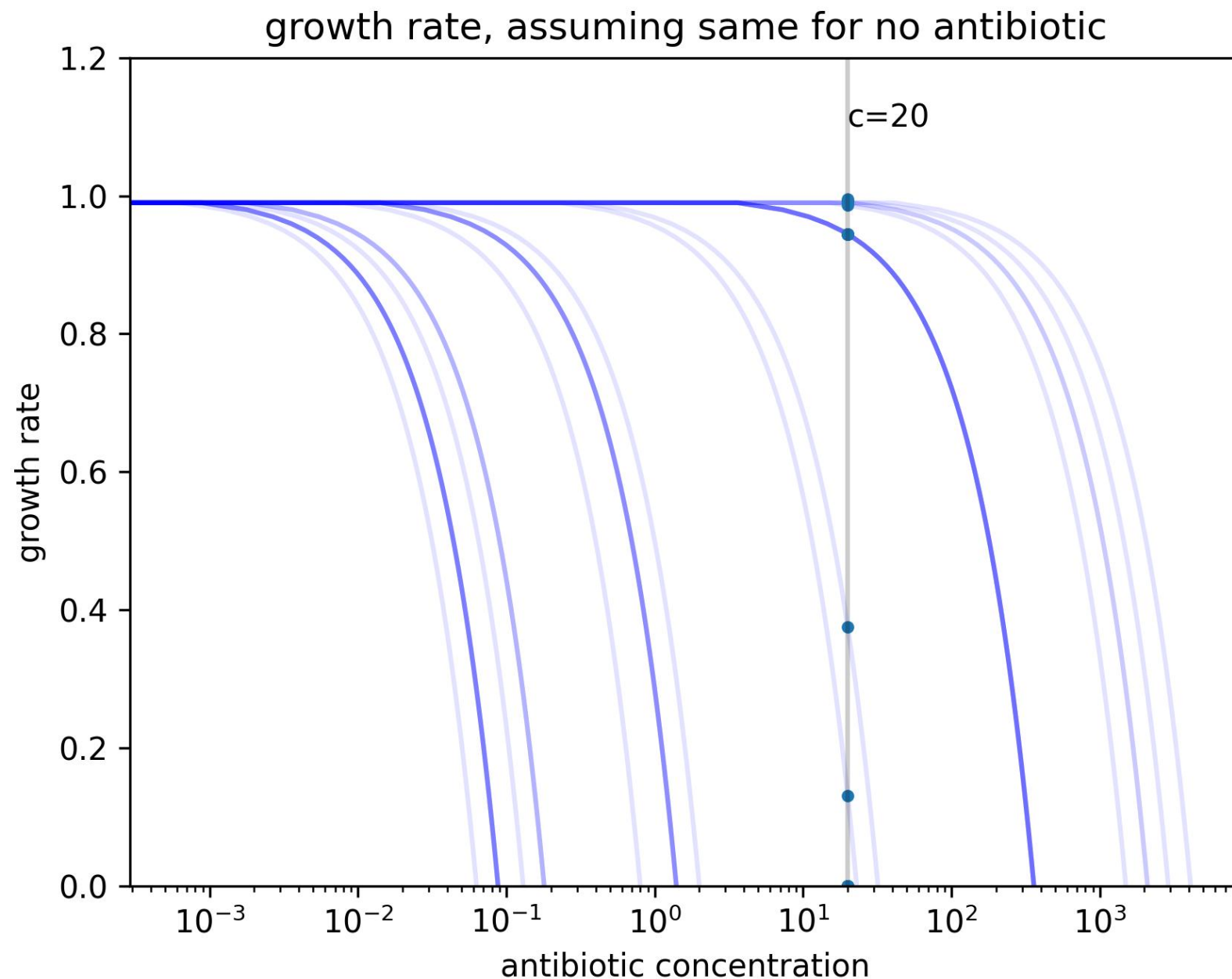


from MIC find growth
rate (here linear)

$$\mu(c) = \frac{-1}{MIC}c + \mu_0$$

$$\dot{n} = \mu(c)n$$

Understanding the MIC data

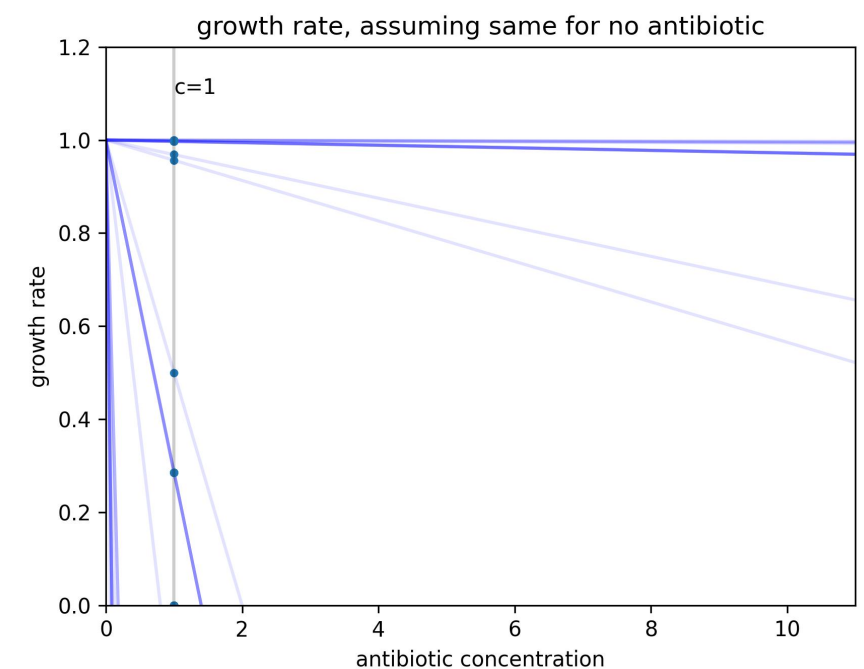


rising antibiotic resistance means:
gradually you get species that don't
die at such concentration

from MIC find growth
rate (here linear)

$$\mu(c) = \frac{-1}{MIC}c + \mu_0$$

$$\dot{n} = \mu(c)n$$



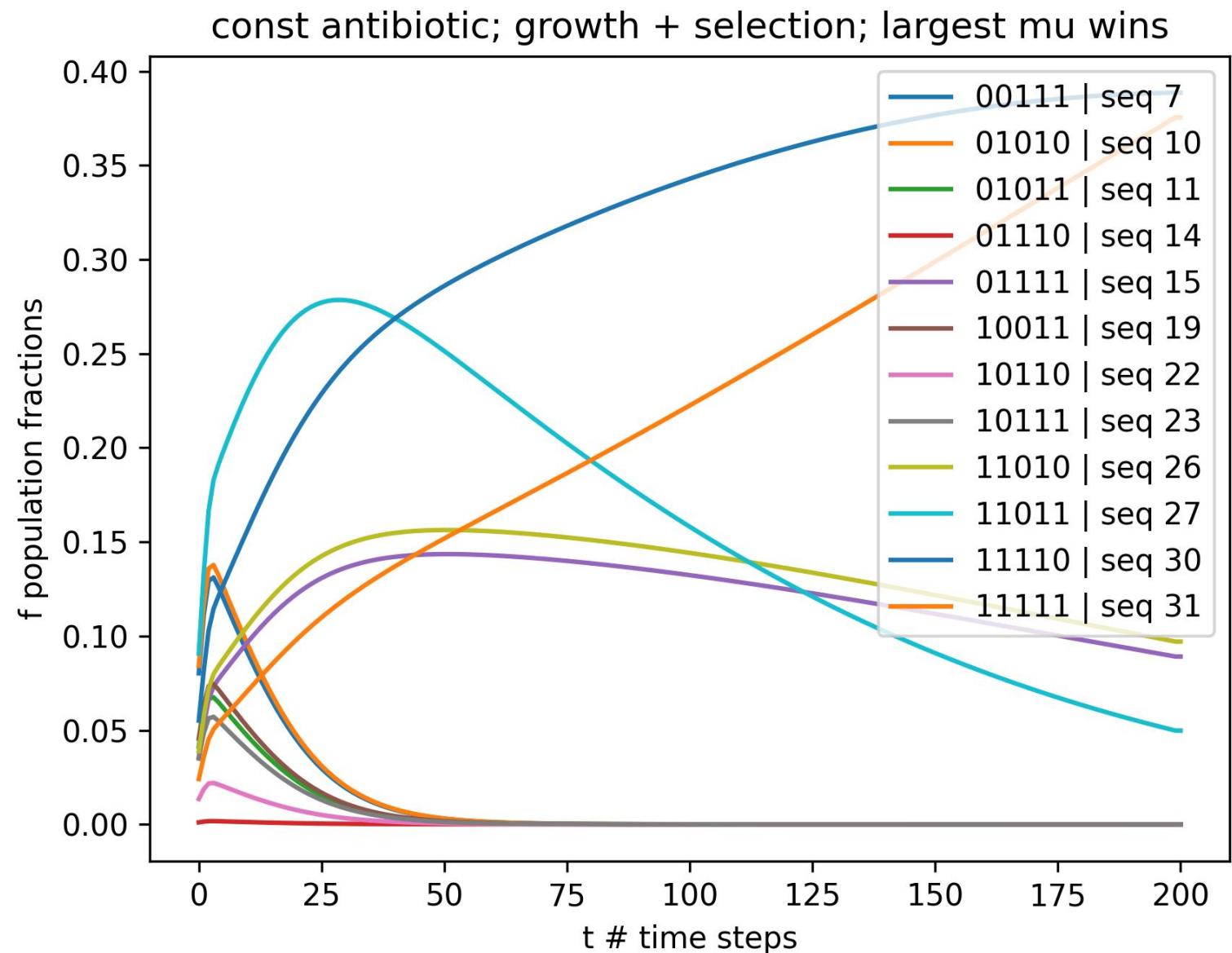
Population growth and selection

$$\dot{f}_a = f_a(\mu_a - \bar{\mu})$$

$$f_a = \frac{n_a}{\sum_i (n_i)}$$

$$\bar{\mu} = \sum_i \mu_i f_i$$

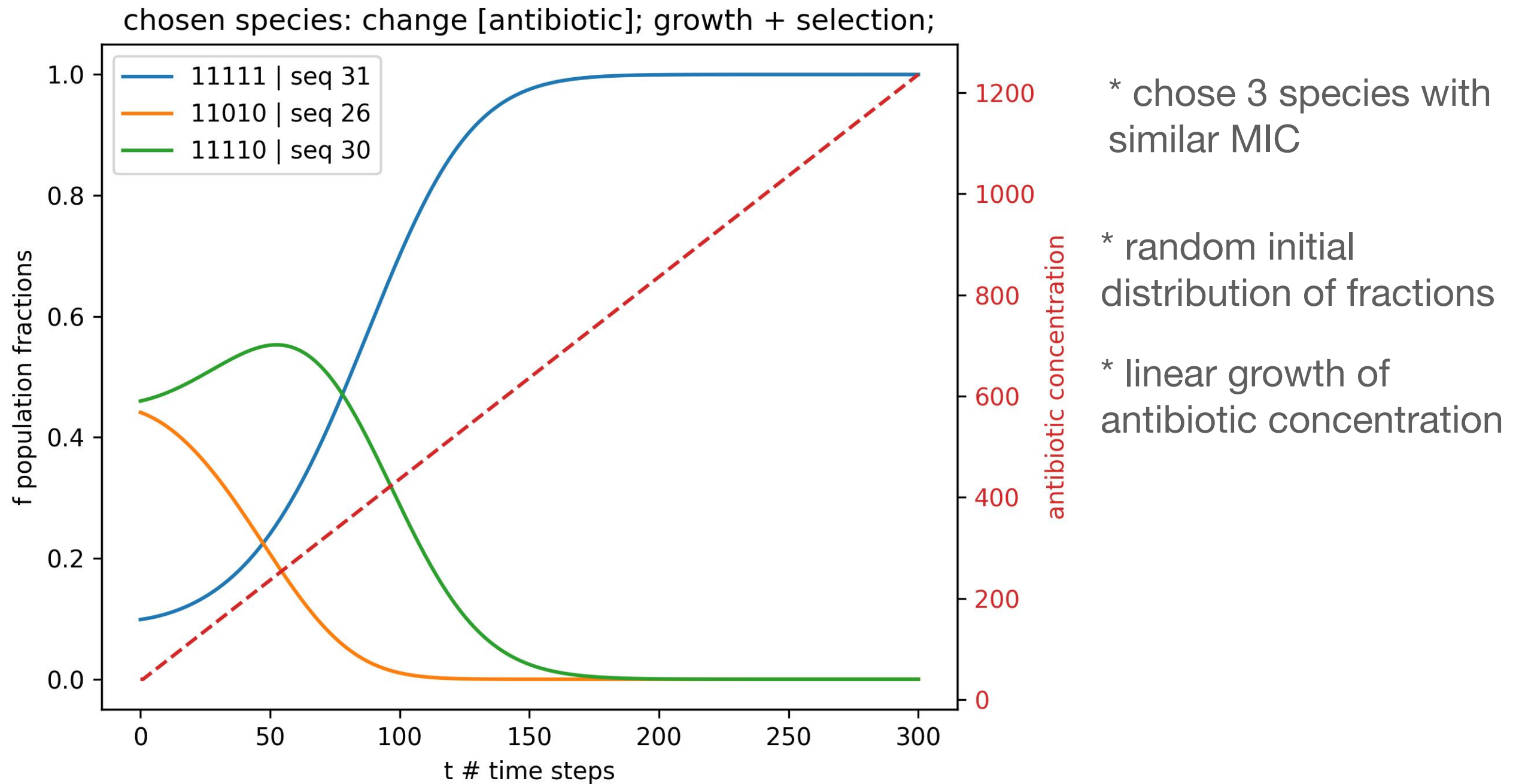
population fraction
equations represent
selection



time step dt=1 is arbitrary

*c = 40; start with
randomly distributed
values for f

Selection at changing antibiotic



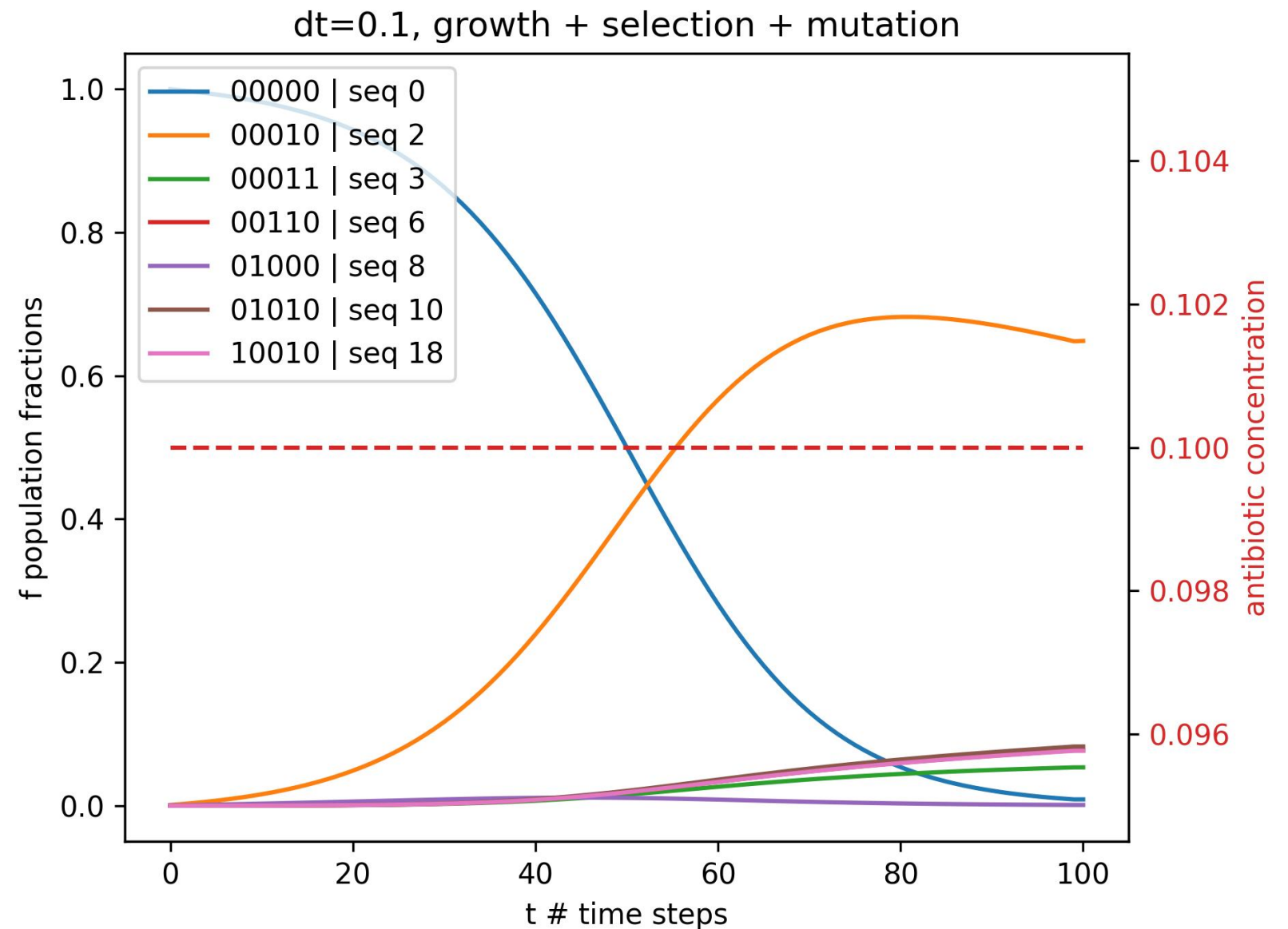
Simulating mutation

$$\dot{f}_i = \mu_i \sum_j f_j q_{ij} - \bar{\mu} f_i$$

$$Q(h_{ij}) = \begin{cases} 0.01 & \text{if } h_{ij} = 1 \\ 0.95 & \text{if } h_{ij} = 0 \\ 0 & \text{otherwise} \end{cases}$$

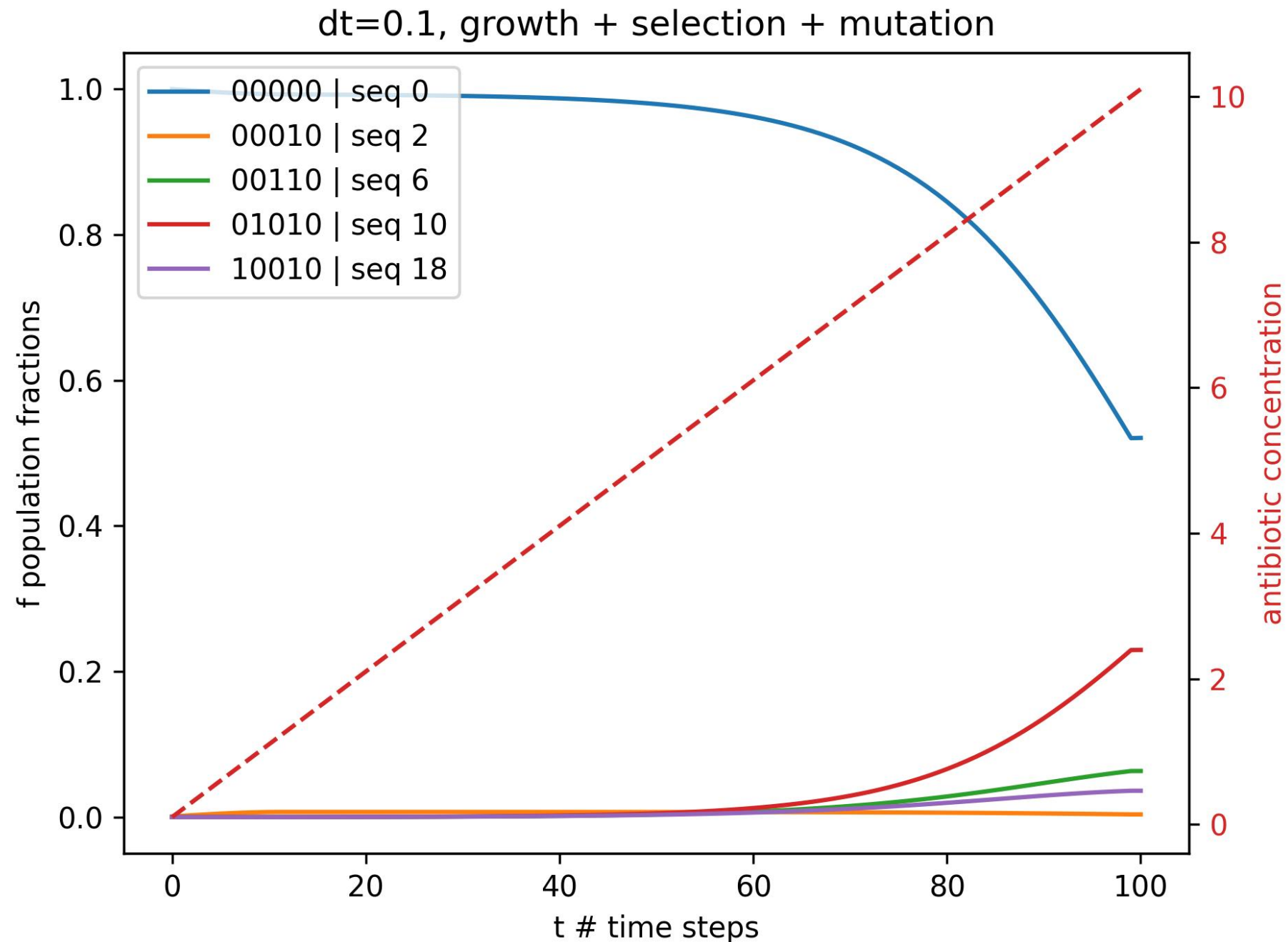
h is hamming distance

Q is probability of mutation



Simulating mutation

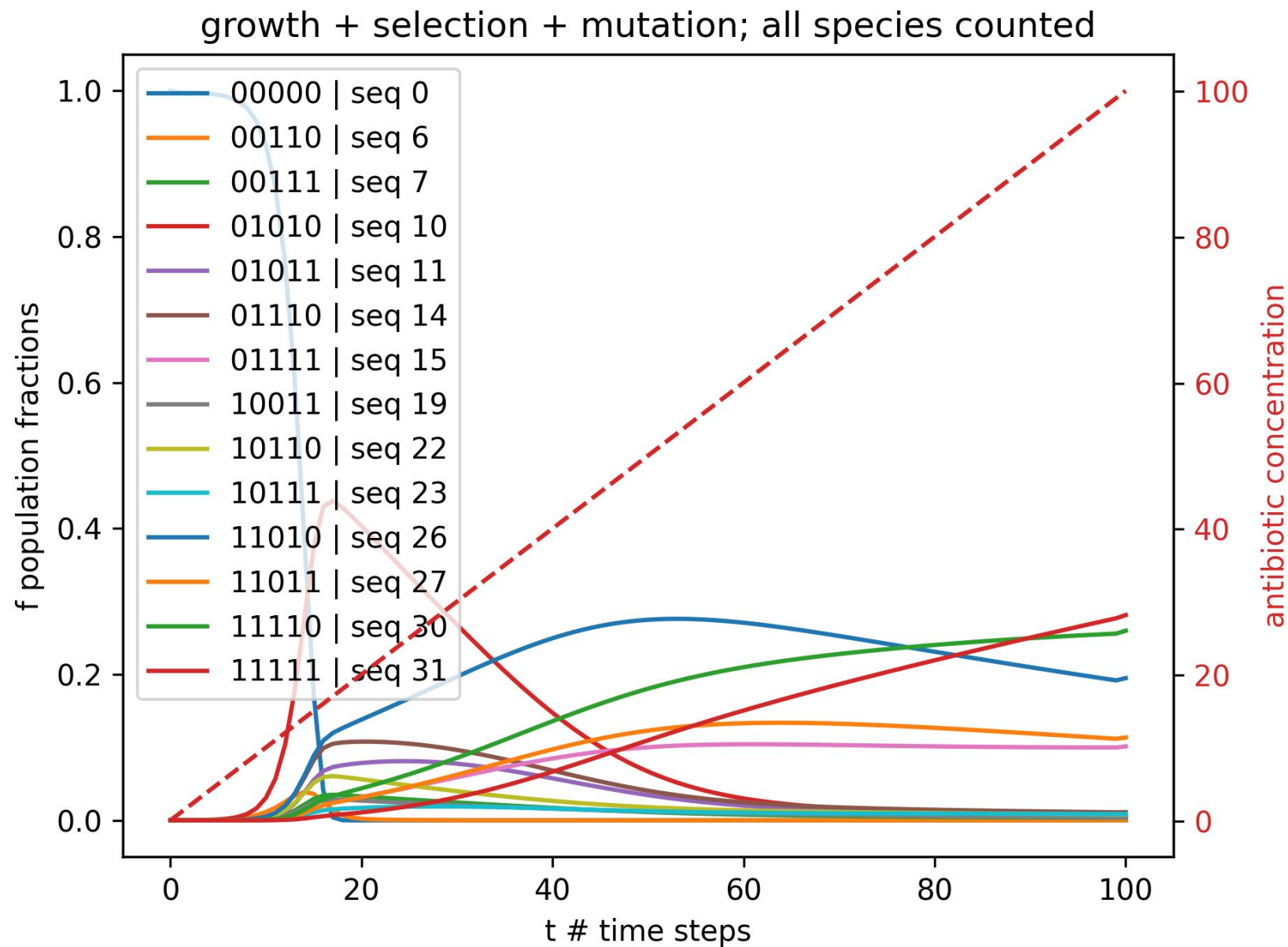
$$\dot{f}_i = \mu_i \sum_j f_j q_{ij} - \bar{\mu} f_i$$



time step and probability of
mutation occurring are
arbitrary chosen

Simulating mutation

$$\dot{f}_i = \mu_i \sum_j f_j q_{ij} - \bar{\mu} f_i$$



so what next?

viruses: implement real time \rightarrow model how long until a new variant emerges; the parameters are the difficult part

simulate evolution pathways: record where species come from

weaknesses:

- * no real time
- * deterministic eqns

code: <https://github.com/mimifilova/StatBiophys23>