Phenotypic switching as a mechanism to circumvent fitness valleys

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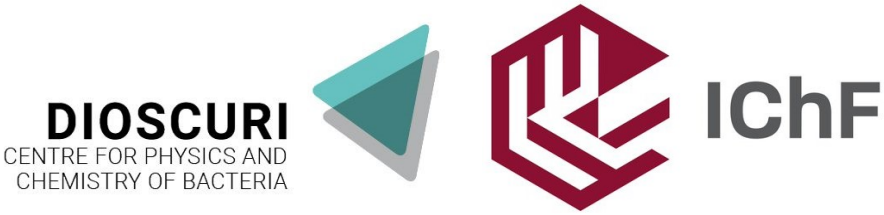

Yerevan, 30 June 2022

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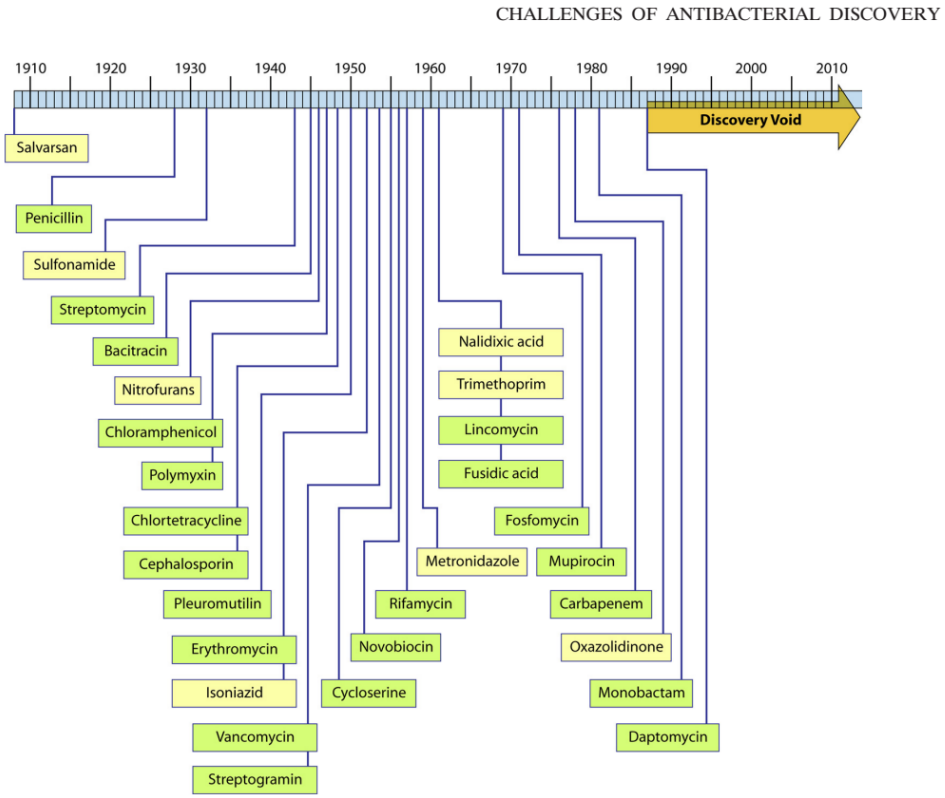
THE ROYAL SOCIETY OF EDINBURGH

Motivation: bacterial infections

Responsible for 1.3M deaths/year worldwide. May increase to 10M/y by 2050.

Resistance to antibiotics is a concern



Better prevention, diagnostics, and treatment required

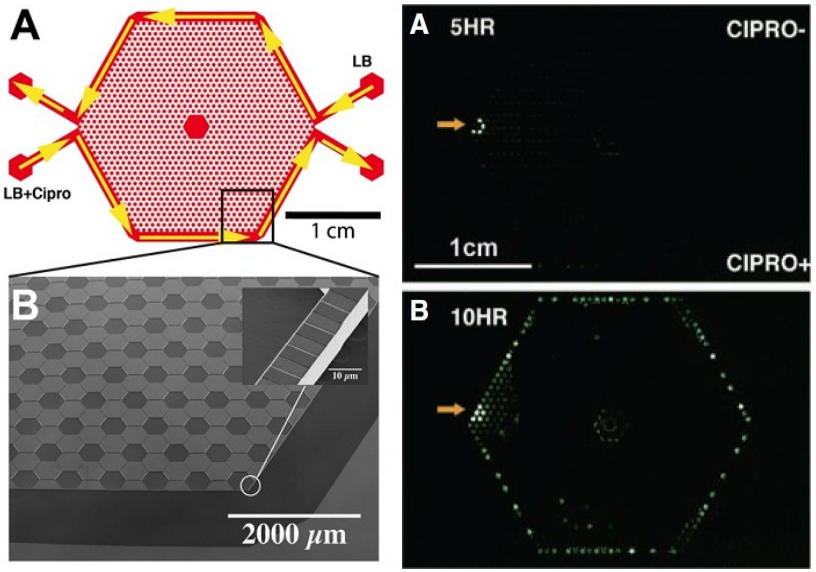
What we do:

quantitative understanding of bacterial infections and antibiotic resistance

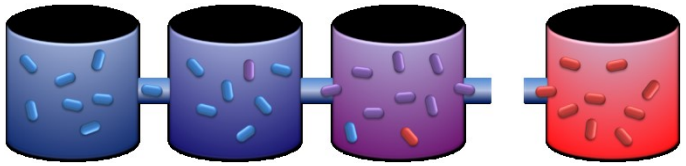
- modelling
- experiments

Rapid evolution of resistance in drug gradients – insight from modelling

Q. Zhang, et al., Science **333**, 1764-1767 (2011)

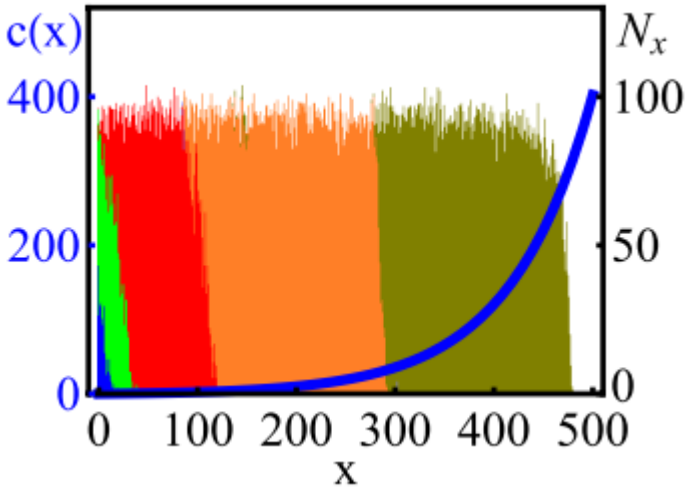


P.Greulich, B. Waclaw, R. Allen, Phys. Rev. Lett. **109**, 088101 (2012)

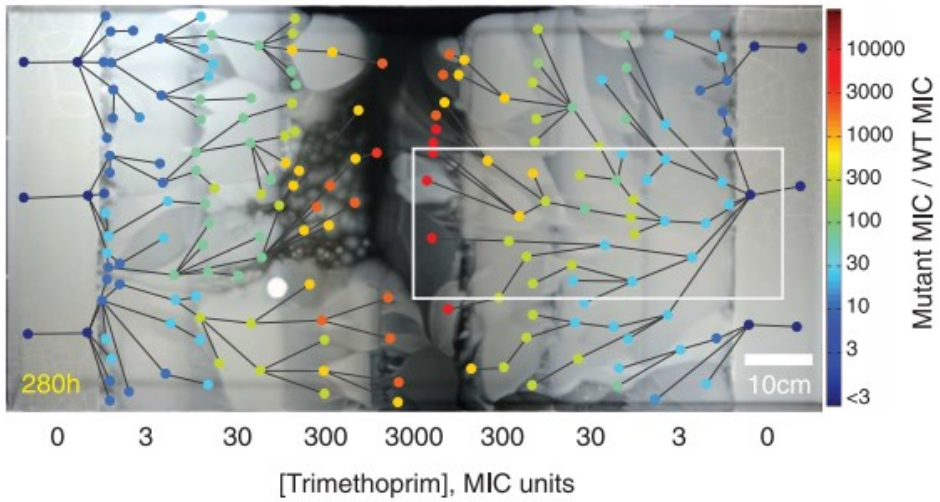


low drug concentration

high drug concentration



M. Baym, et al, Science **353**, 1147 (2016)

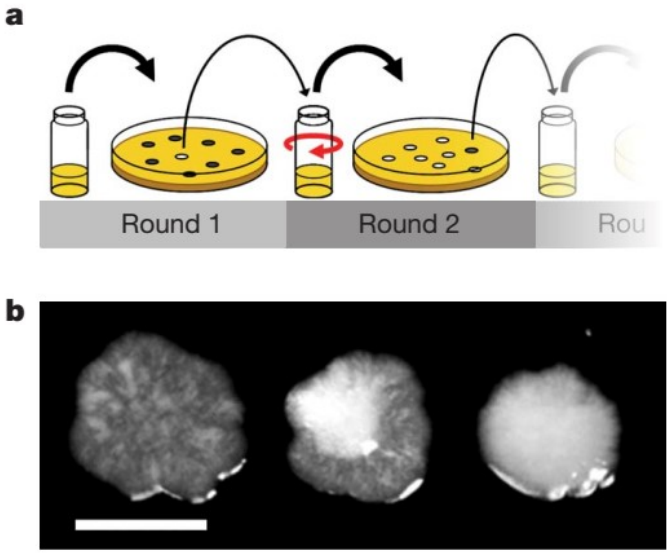


Phenotype switching

Phenotypic plasticity: capacity to change phenotype in response to environmental changes – without change to its genotype. All organisms do it.

Stochastic phenotype switching (SPS) occurs without any sensing mechanism - this is what we're interested in.

A `bet-hedging' strategy: beneficial for when environmental changes are frequent and unpredictable.



SPS is commonly observed in bacteria

experimental

- **H. J. E. Beaumont, et al., Nature 462, 90 (2009).**
- Y. Ito, et al., Mol Syst Biol **5**, 264 (2009).
- A. Solopova, et al., PNAS **111**, 7427 (2014).
- M. Arnoldini, et al., PLoS Biol **12**, e1001928 (2014).
- H. Hasman, et al., Journal of Bacteriology **182**, 1089 (2000).

theory

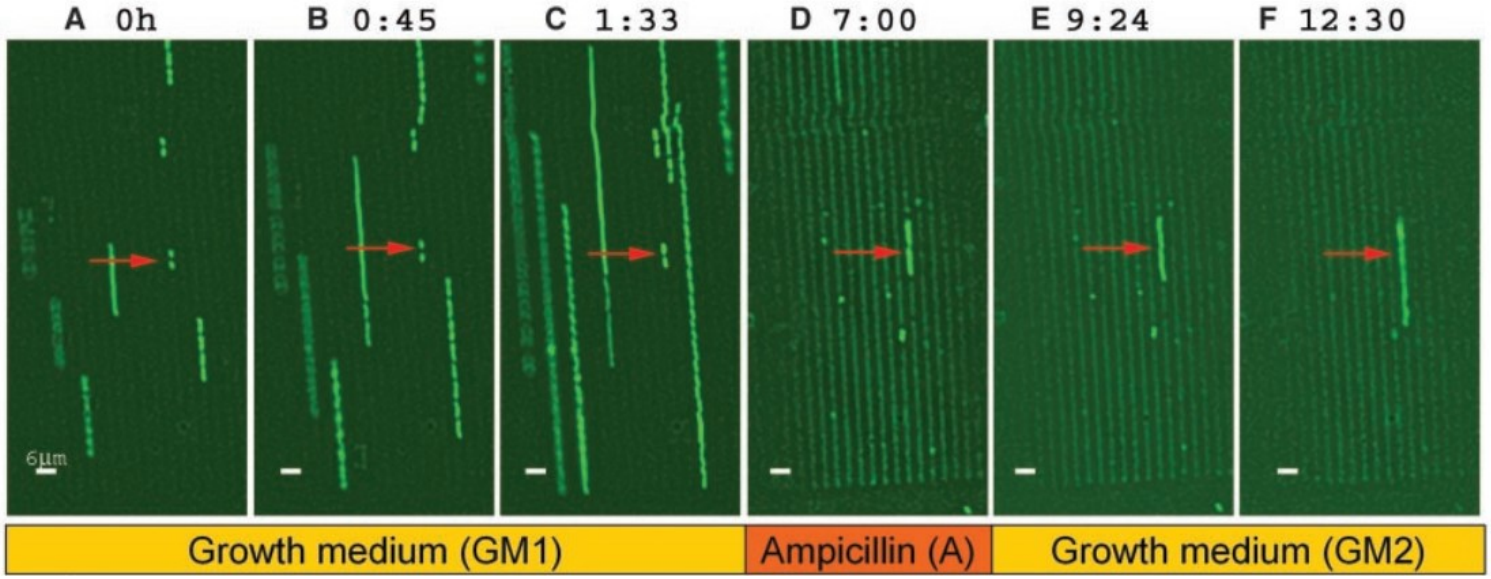
- E. Kussell and S. Leibler, Science **309**, 2075 (2005).
- P. Ashcroft, et al., J. R. Soc. Interface **11**, 20140663 (2014).
- A. Taitelbaum, et al., Phys. Rev. Lett. **125**, 048105 (2020).

theory+experiment

- N. Q. Balaban, et al., Science **305**, 1622 (2004).
- M. Acar, et al., Nature Genetics **40**, 471 (2008).

SPS example – bacterial persistence

Escherichia coli can switch between normal and persister states. Persister cells grow at a slower rate than the normal cells but are resistant to antibiotics

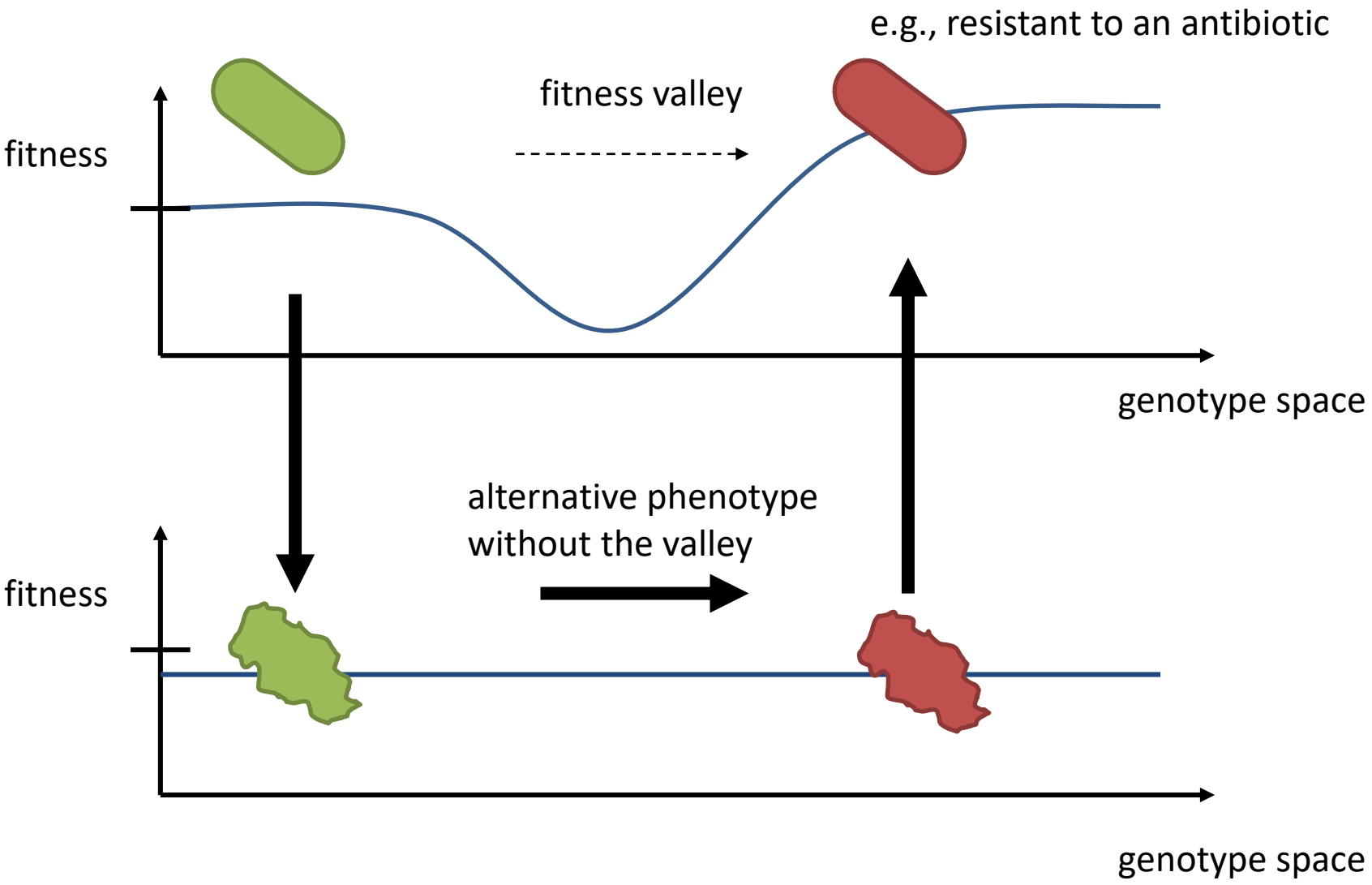


Balaban et al. Science 2004

Could persistence speed up evolution by providing a “safe haven” for bacteria to try out different mutations?

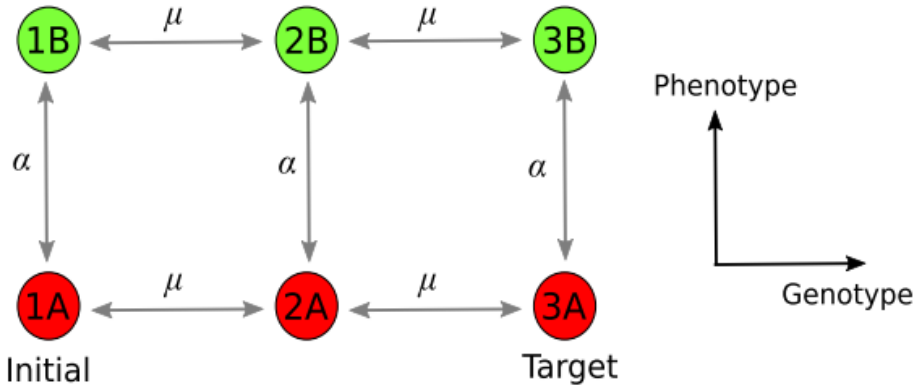
More generally: Could phenotype switching help to avoid fitness valleys?

A 1-slide summary of this talk:

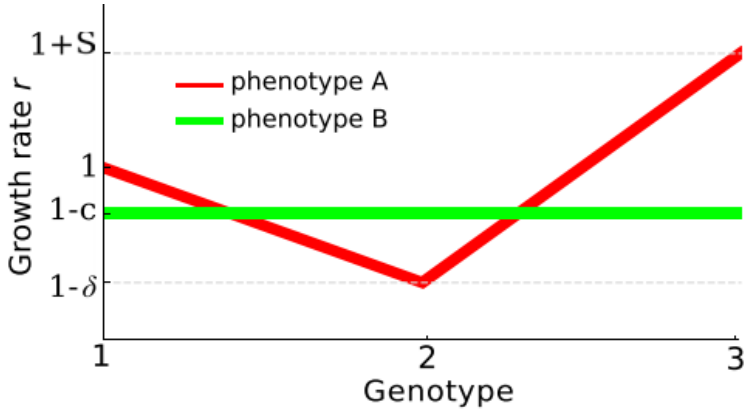


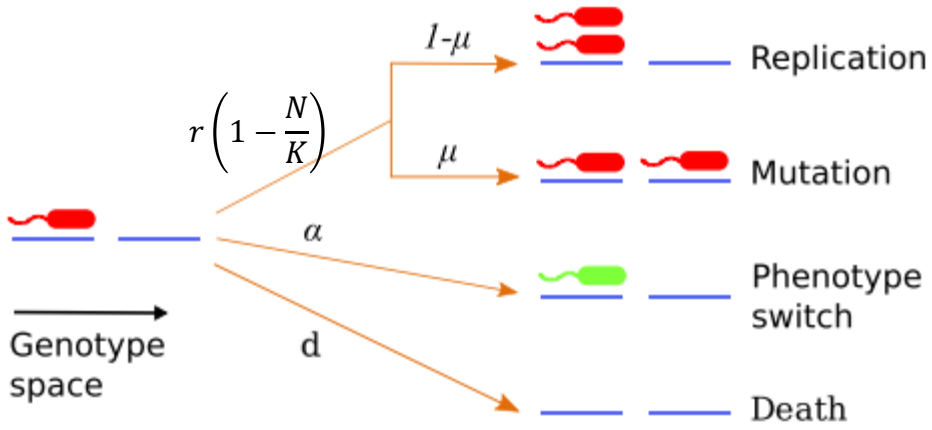
A simple model

3 genotypes x 2 phenotypic states



Fitness landscape





Important parameters:

α – switching rate

δ – valley depth

μ – mutation probability

K – carrying capacity

More formally…

State: $C = (n_{1A}, n_{2A}, n_{3A}, n_{1B}, n_{2B}, n_{3B}),$ $\quad n_i = 0, \dots, K$

Master equation

$$\frac{\partial P(C,t)}{\partial t} = \sum_{C' \neq C} (P(C',t)w(C' \to C) - P(C,t)w(C \to C'))$$

$w(C \to C')$ are transition rates, for example

$$w(\{n_{1A}, \dots, n_{1B}, \dots\} \to \{n_{1A} - 1, \dots, n_{1B} + 1, \dots\}) = \alpha \quad \text{phenotype switching}$$

$$w(\{n_{1A}, \dots\} \to \{n_{1A} + 1, \dots) = (1 - \mu) r_{1A} \left(1 - \frac{N}{K}\right) \quad \text{growth}$$

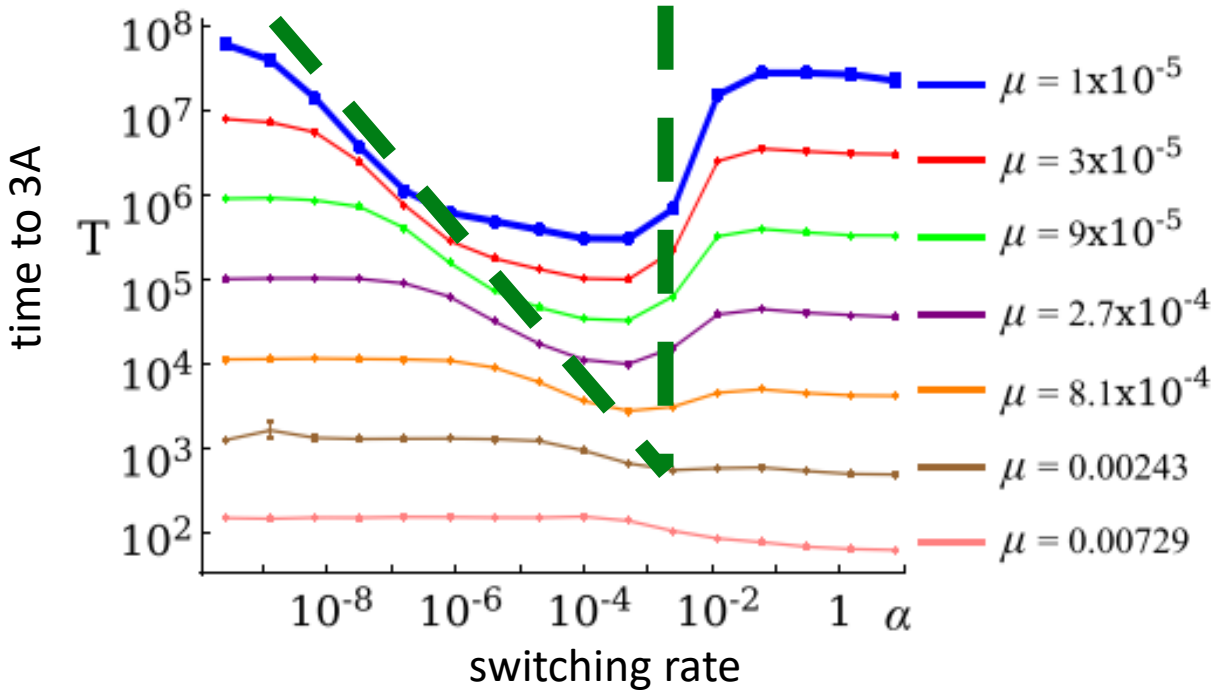
etc.

We simulate the model on a computer using different techniques depending on which observable we are interested in (exact kinetic MC, tau-leaping)
Approximate analytic solutions available in some regimes (won't talk much about it)

Results for no fitness cost for the 2nd phenotype ($c = 0$)

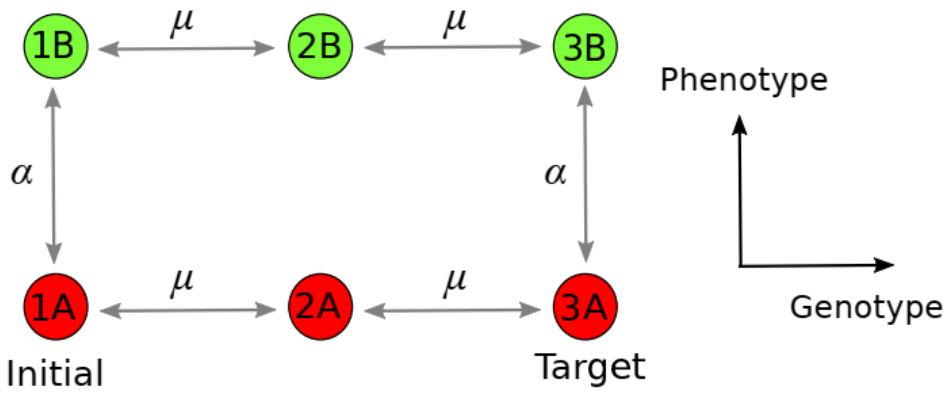
We measure the time to obtain a single organism of the best-adapted phenotype 3A

Small system (K=100), low mutation ($\mu = 10^{-5} \ldots 10^{-2}, K\mu < 1$), $\delta = 0.4, d = 0.1$

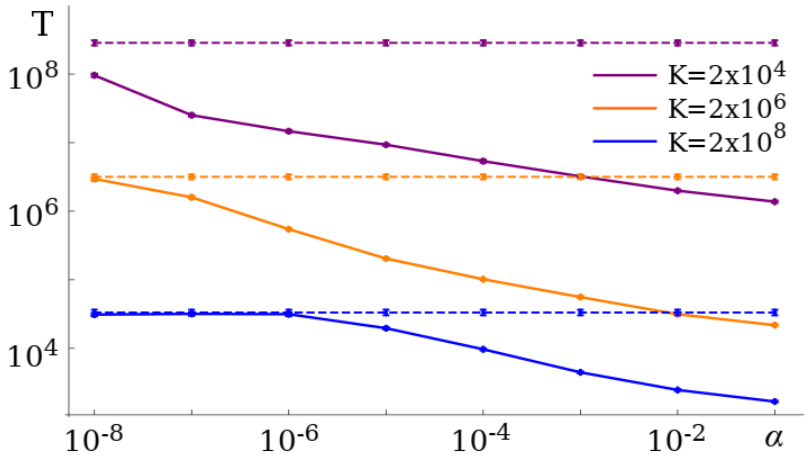


Optimal switching rate exists for a broad range of mutation rates

Time to adaptation decreases monotonically in the absence of 2A←→2B transition

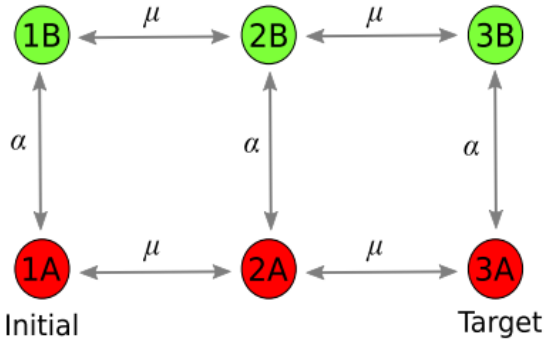


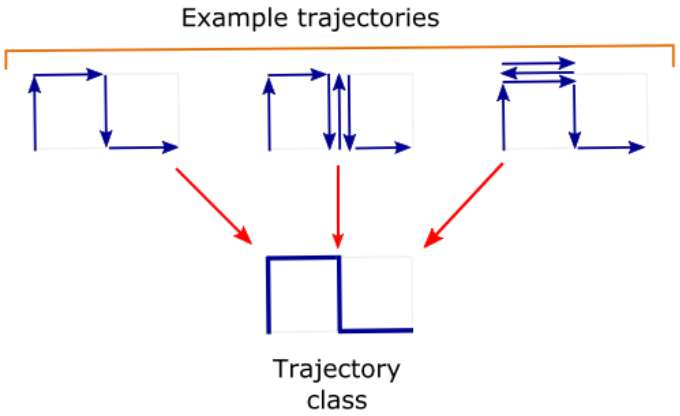
$\mu = 10^{-6}$



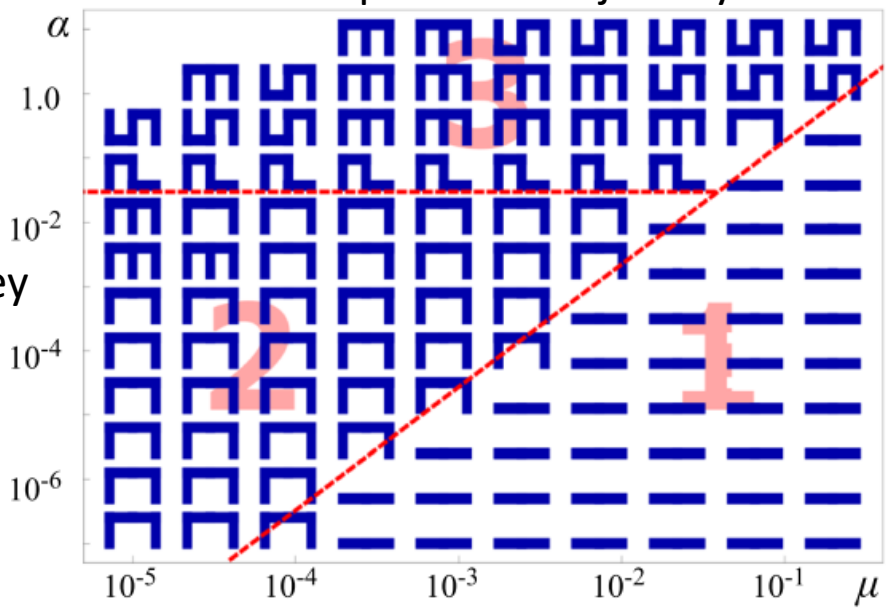
Reason:
rapid transitions 2A←→2B (absent here) create an effective fitness valley at genotype 2

Fastest trajectories avoid the fitness valley





Most probable trajectory:



3 = mixed trajectories (responsible for increase in T for large α)

2 = going around the valley (switch from A to B)

1 = going through the valley

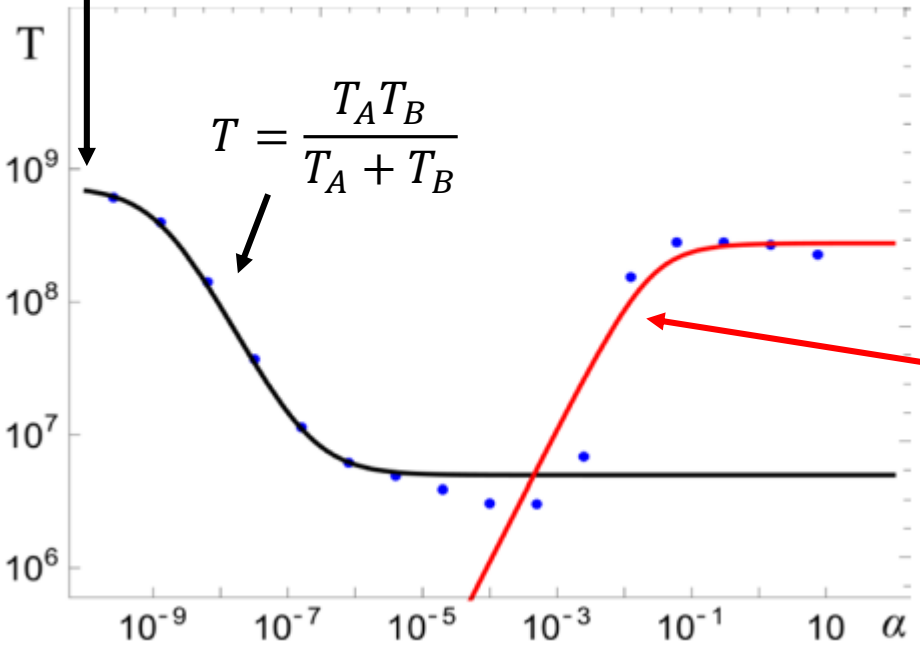
Time to adaptation for different trajectories

$$T_A \approx \frac{1}{(1-d)K\mu^2 d(1/\delta - 1)}$$

tunnelling through the barrier for **small α**

$$T_B \approx \frac{1}{\alpha} + \frac{5}{\mu d}.$$

switching to the alternate phenotype B for **intermediate α**



large α: tunnelling through the "effective" fitness valley made of combined 2A and 2B:

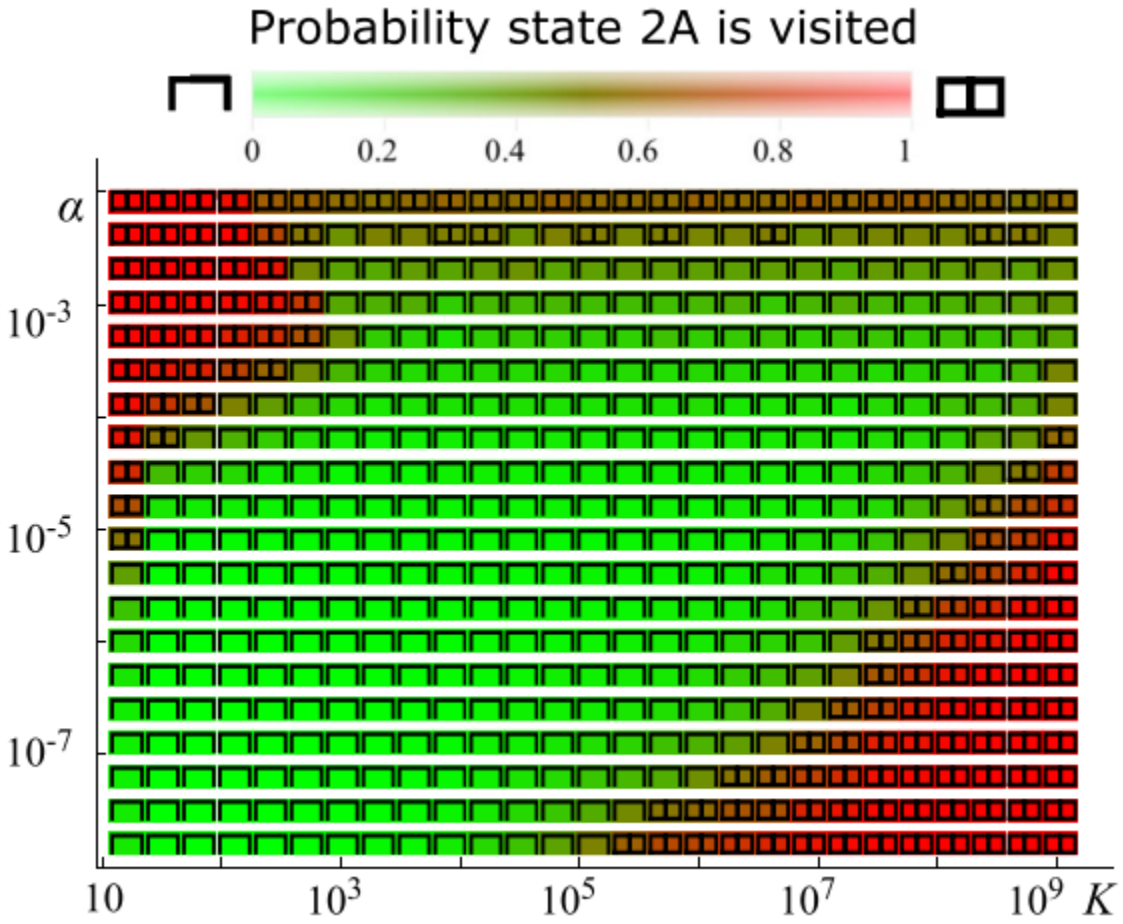
$$T_{\text{comb,ST}} \approx \frac{1}{(1-d)K\mu^2 d(1/(1-r_{2,\text{comb}}) - 1)}$$

$$\begin{aligned} r_{2,\text{comb}} &= n_{2A} r_{2A} + n_{2B} r_{2B} \\ &= \frac{(d+\alpha)(2-\delta) + \sqrt{\delta^2(\alpha+d)^2 - 4\alpha^2(\delta-1)}}{2(2\alpha+d)} \end{aligned}$$

Phenotype switching is favoured in a large region of parameter space

u (upper) trajectory:
avoids state 2A

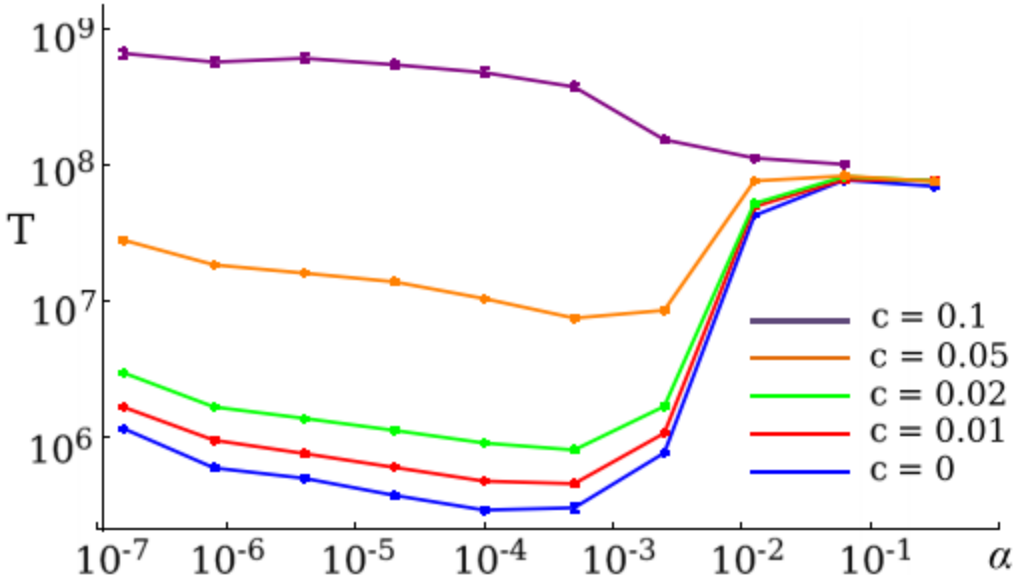
v (valley) trajectory:
visits state 2A



Here $\mu = 10^{-6}, \alpha \sim 10^{-3}, K \sim 10^{9}$ - biologically realistic values

Switching phenotypes remains advantageous also for fitness cost $c > 0$

$K = 100, \delta = 0.9, d = 0.1, \mu = 10^{-5}$

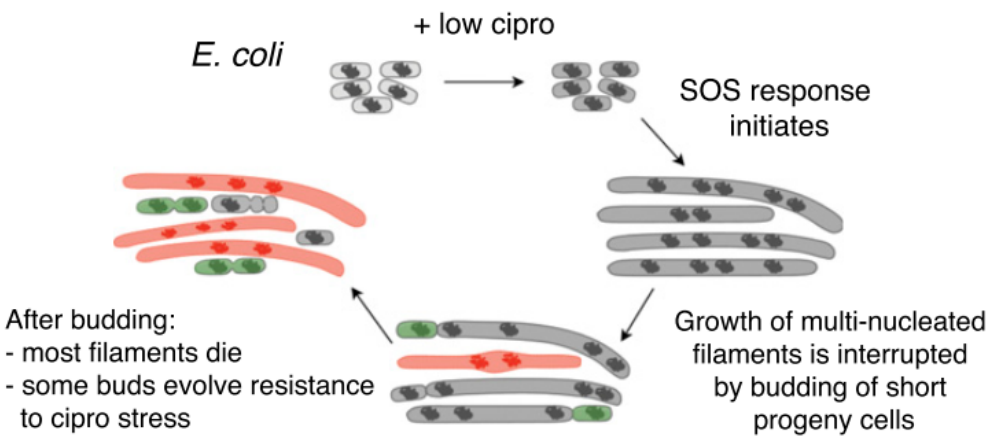


- phenotype switching still reduces time to adaptation
- no optimal switching rate for larger c

Experimental evidence?

Idealized model, not meant to reproduce any specific experiment

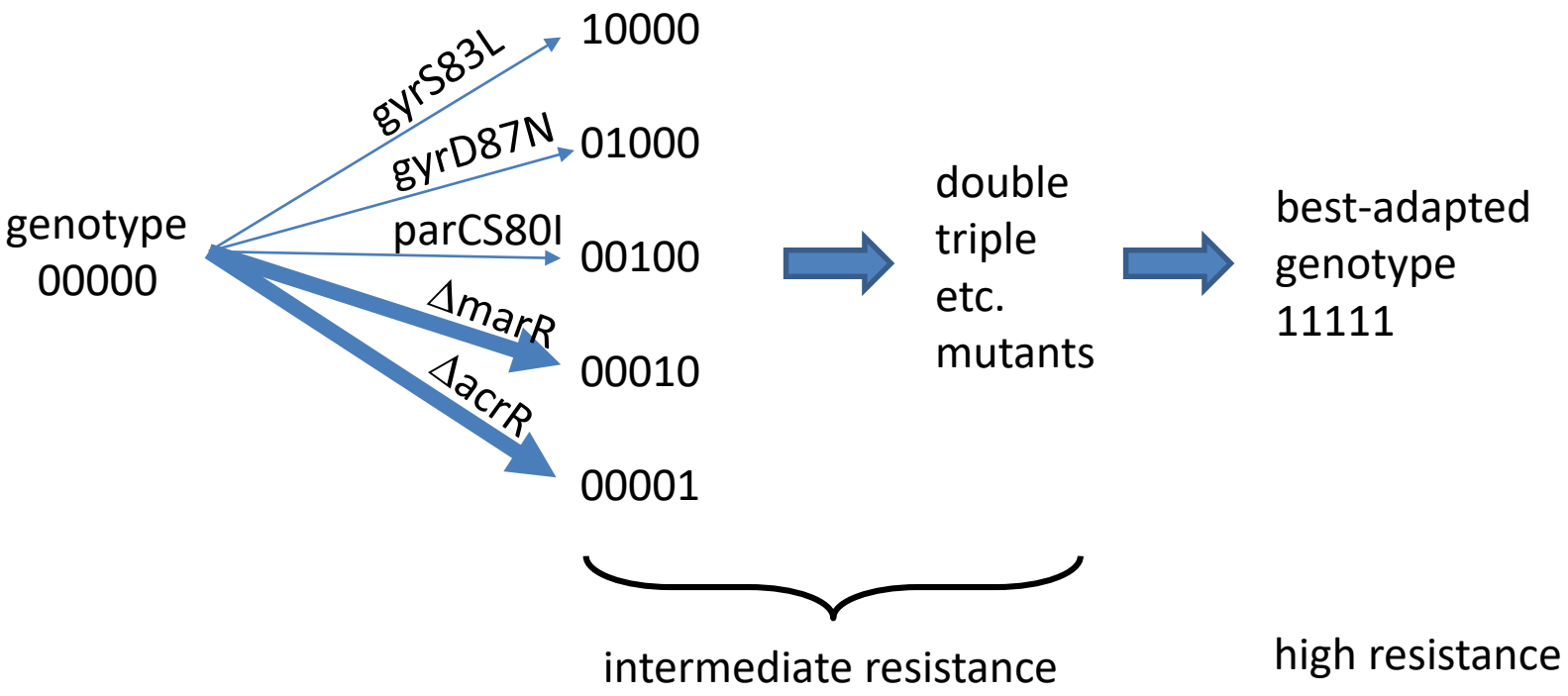
However: some evidence that a similar mechanism may be relevant for the antibiotic ciprofloxacin



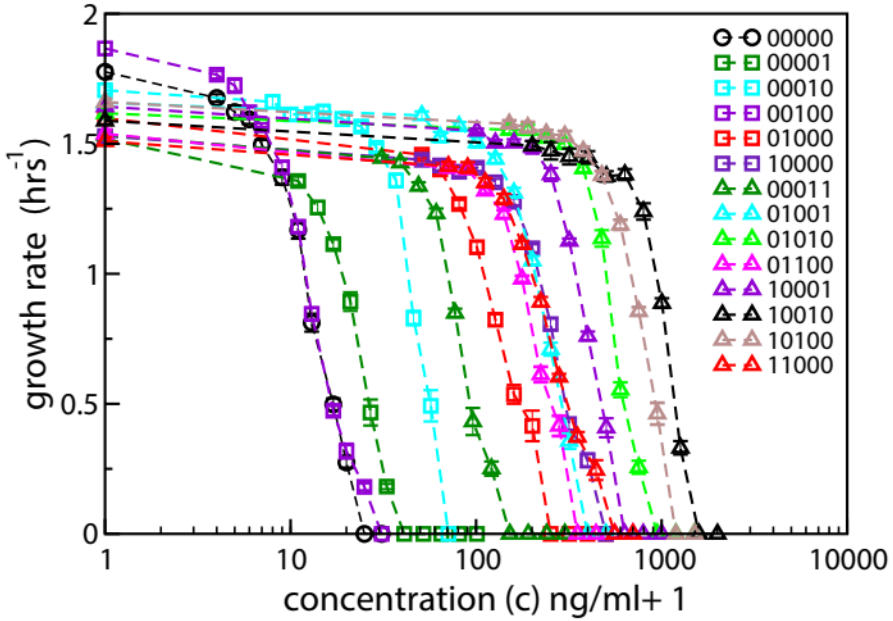
J. Bos, Q. Zhang, S. Vyawahare, E. Rogers, S. M. Rosenberg, and R. H. Austin, *Emergence of Antibiotic Resistance from Multinucleated Bacterial Filaments*, PNAS 2015.

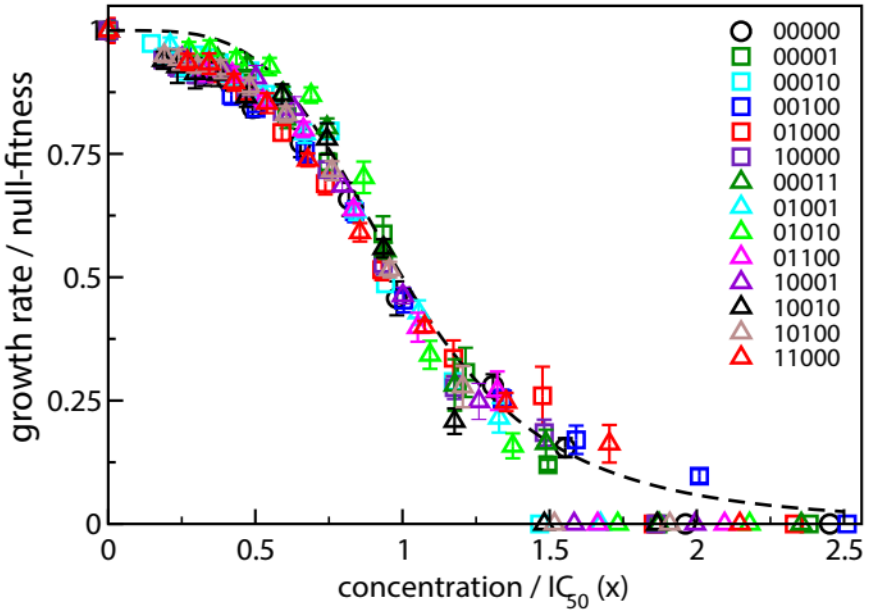
Evolution of resistance to the antibiotic ciprofloxacin

5 specific mutations increase resistance of *E. coli* by 3 orders of magnitude
We represent mutants by binary sequences:



The fitness of mutants depends on antibiotic concentration





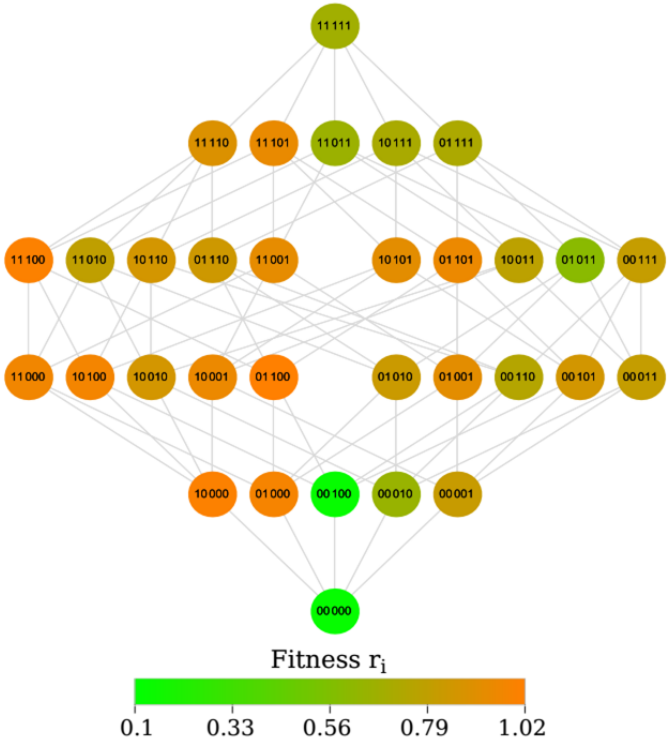
the curve

growth rate(antibiotic conc.)

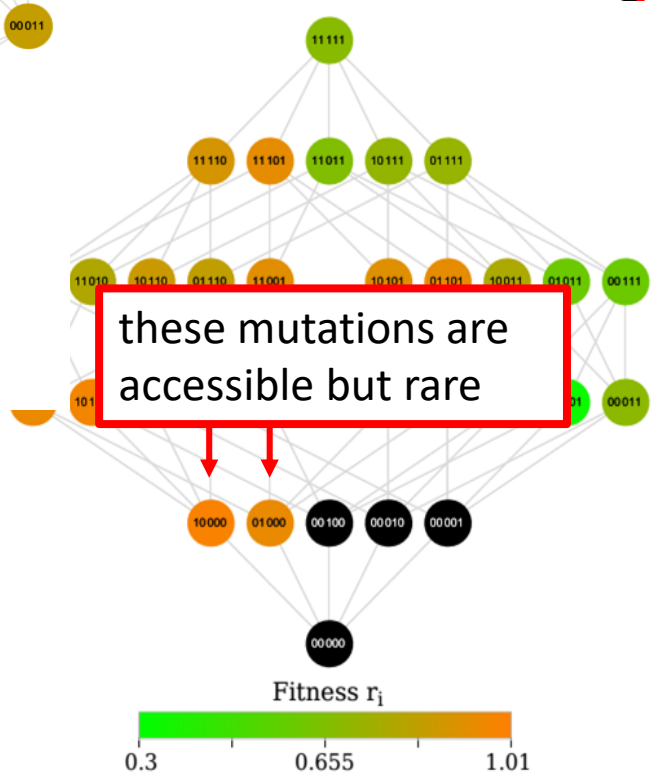
has the same shape for all mutants

S. G. Das, et al., ELife **9**, e55155 (2020).

Fitness landscapes

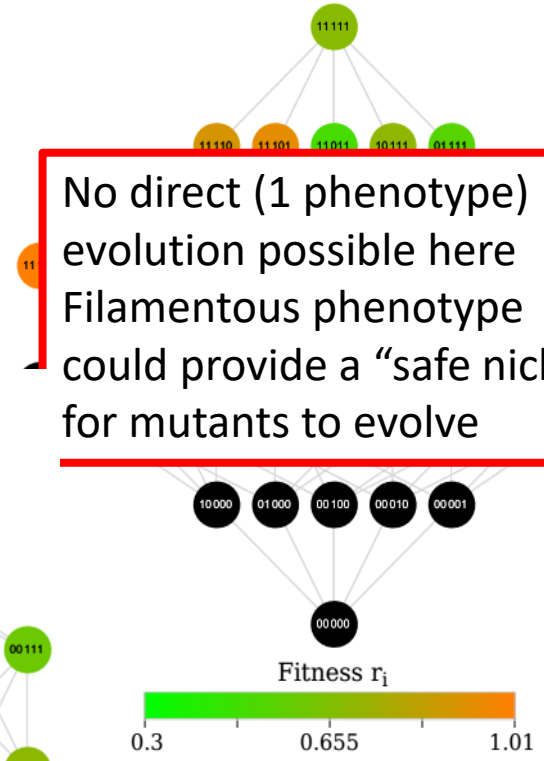


sub-inhibitory Cipro (0.9x MIC WT)



these mutations are accessible but rare

intermediate Cipro (3x MIC WT)



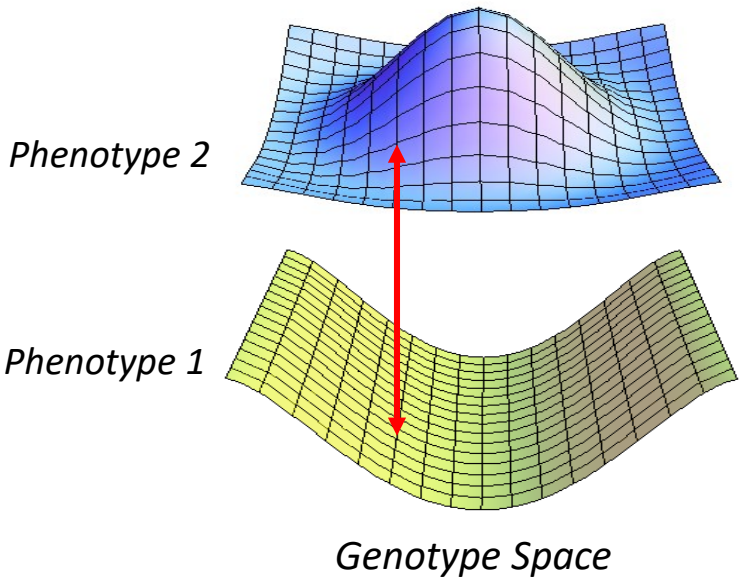
No direct (1 phenotype) evolution possible here Filamentous phenotype could provide a “safe niche” for mutants to evolve

high Cipro (60x MIC WT)

= lethal genotype

Conclusions

- stochastic phenotype switching ubiquitous in microbes
- possible roles: division of labour, bet hedging
- here: **provides a way to circumvent fitness valleys by switching to an alternate fitness landscape**
- speed gain: potentially orders of magnitude
- some evidence that it may be relevant for antimicrobial resistance evolution



Paper:
A. C. Tadrowski, M. R. Evans, and B. Waclaw, Scientific Reports **8**, 8941 (2018).

Also
Bacterial growth: A statistical physicist's guide
RJ Allen, B Waclaw, *Reports on Progress in Physics* 82 (1), 016601 (2018)