Quantifying the role of population subdivision in evolution on rugged fitness landscapes

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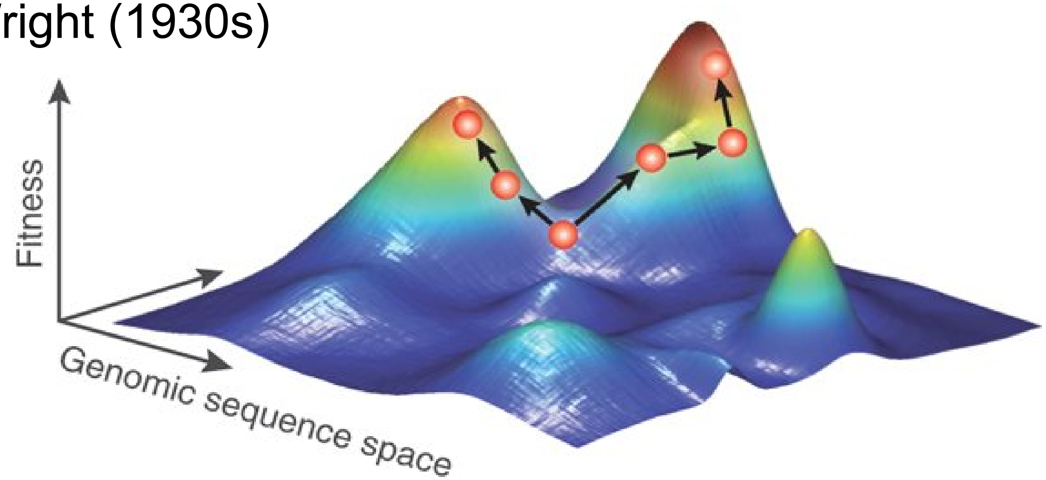
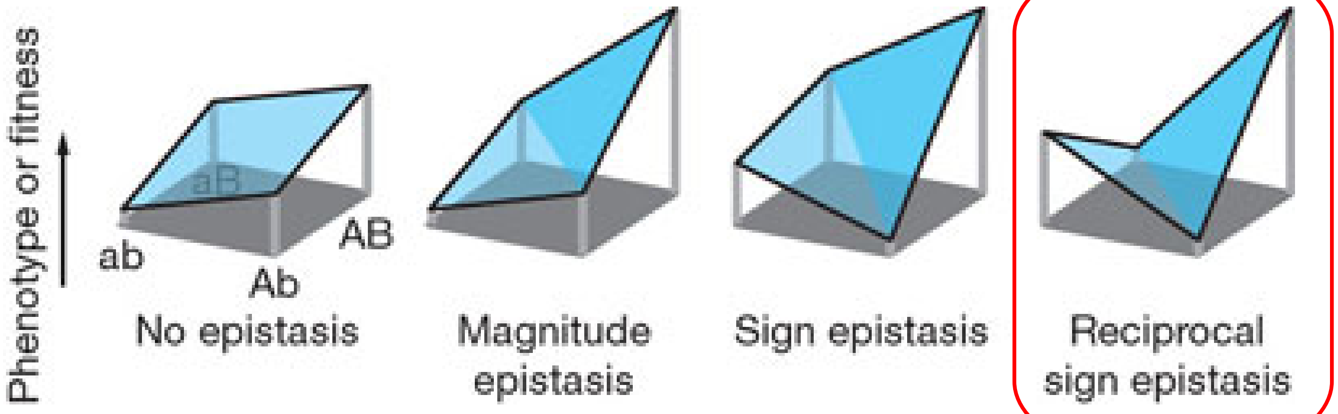
Introduction

- **Fitness landscape**

Wright (1930s)



- **Origin of fitness valleys: epistasis**



Can give rise to multiple peaks

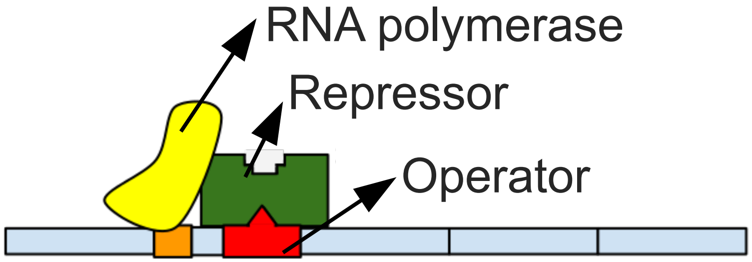
Poelwijk, Kiviet, Weinreich and Tans (2007)

Introduction

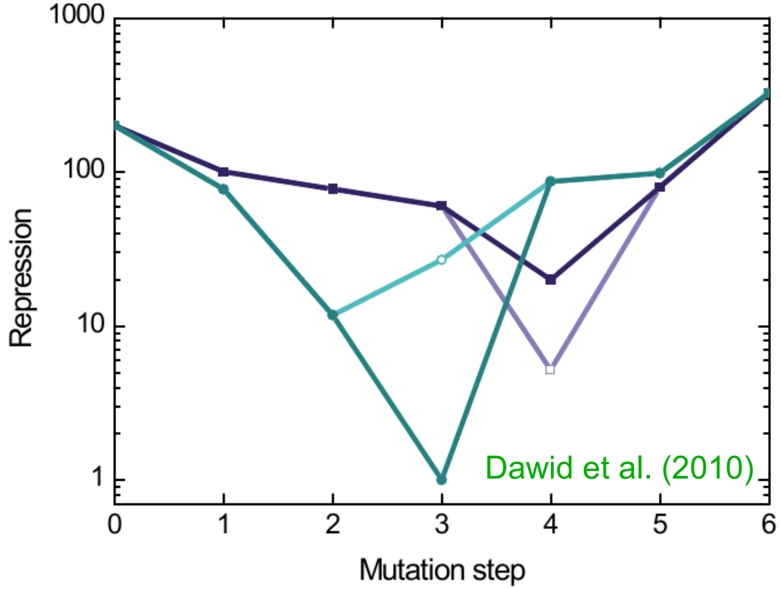
- **Molecular example**

Co-evolving systems → fitness valleys

The *lac* operon:

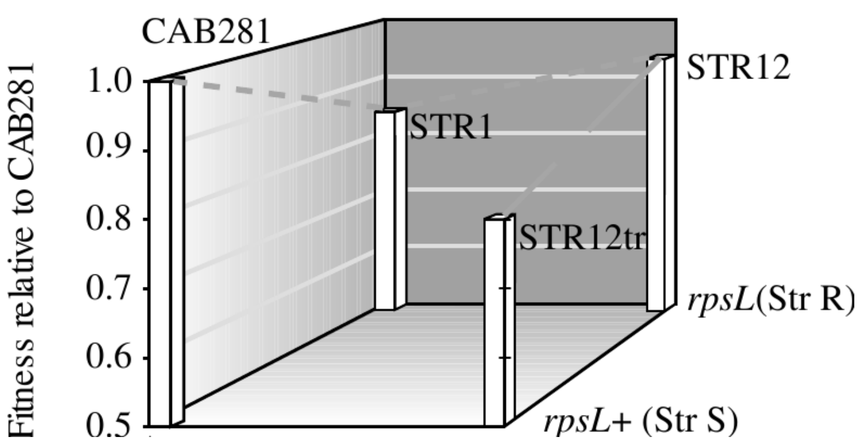


Wikimedia



Dawid et al. (2010)

- **Fitness costs in the evolution of antibiotic resistance**



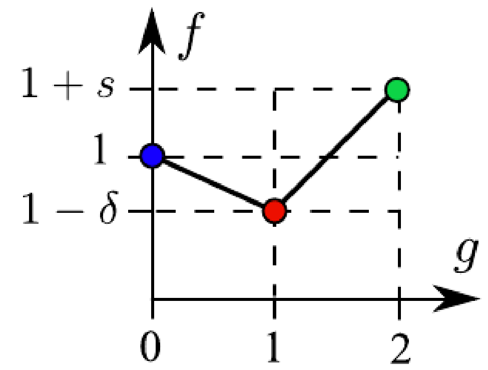
Evolution of streptomycin resistance in *E. coli*

Schrag, Perrot and Levin (1997)

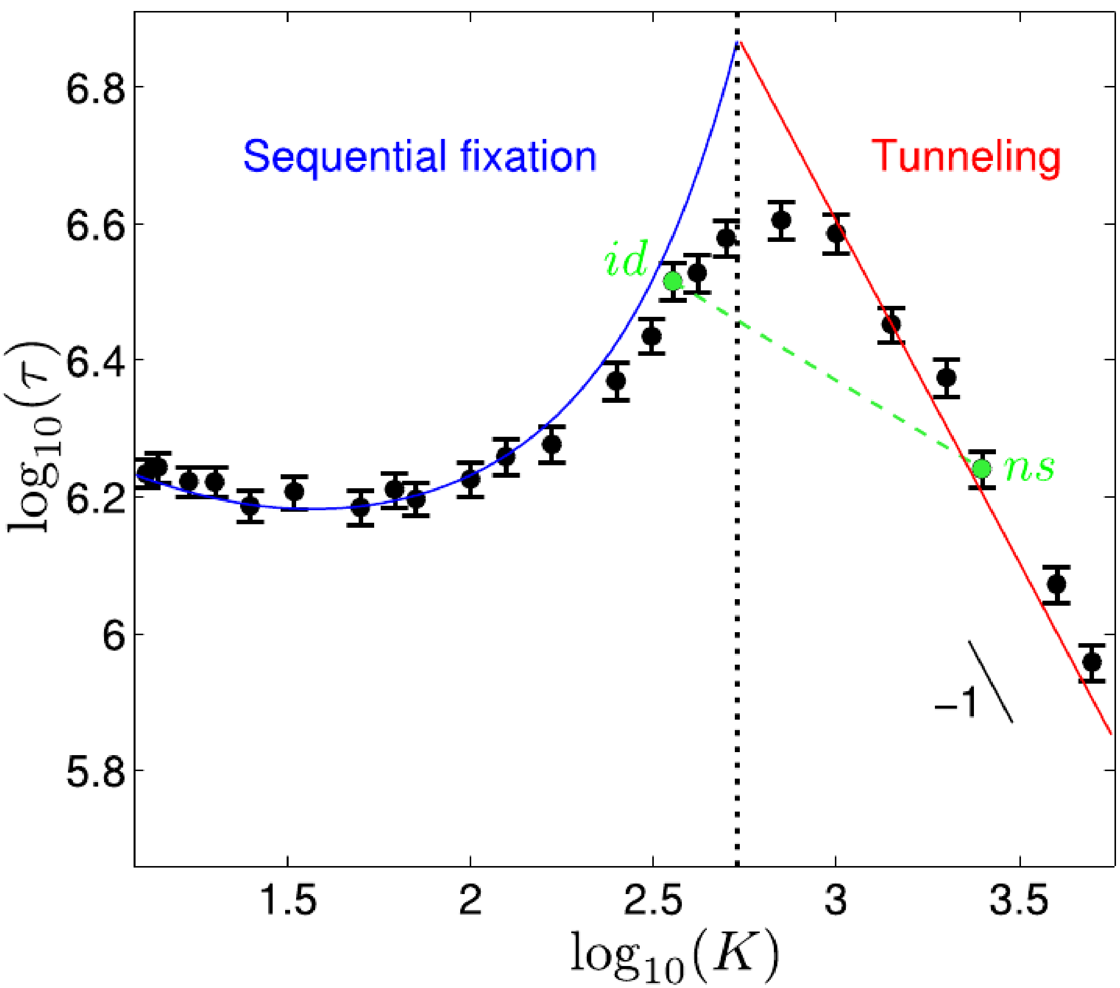
Introduction

- **Effect of population size on fitness valley crossing**

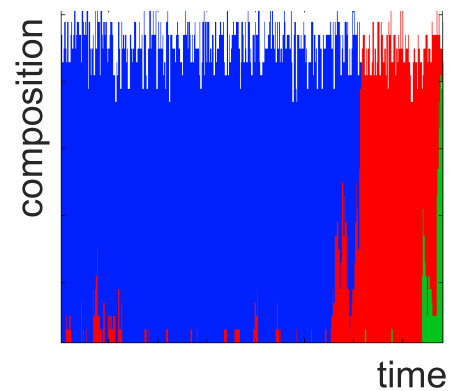
Smaller population → stochasticity is more important
Deleterious / neutral mutations can drift to fixation



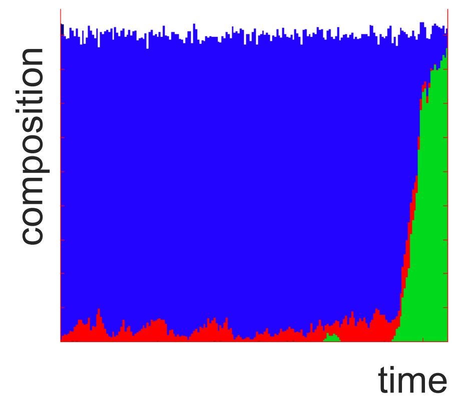
- **Valley crossing time vs. population size: two regimes**



Weinreich and Chao (2005)
Weissman, Desai, Fisher and Feldman (2009)



Sequential fixation



Tunneling

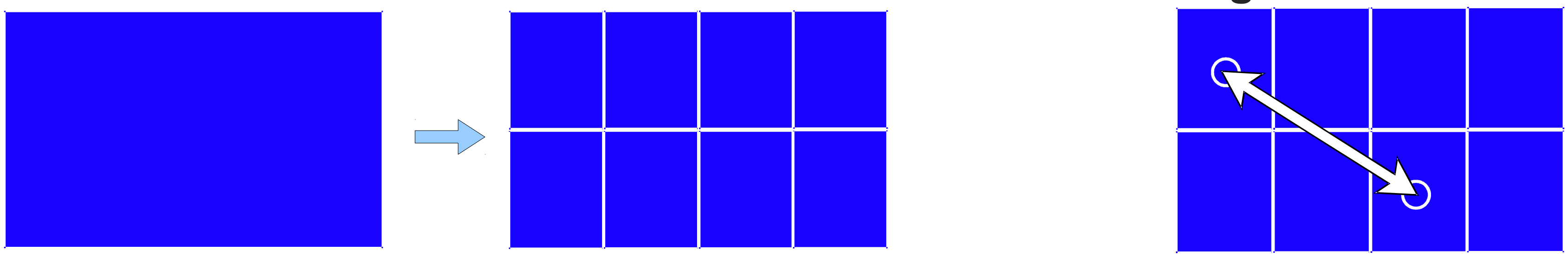
Question & Model

Population subdivision: a minimal model

Asexual population
Fixed size

Demes with
identical size

Migration

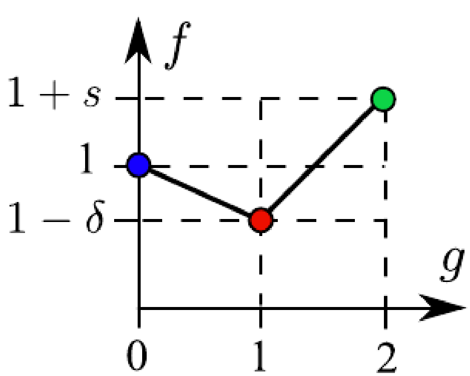


→ **Can subdivision with migration *(alone)* accelerate fitness valley crossing?**
If yes, under what conditions, and how much?

N.B.: Wright's shifting balance theory (1930s)

Here: No geographic structure
No extinction / founding
No environment heterogeneity
Constant migration rate

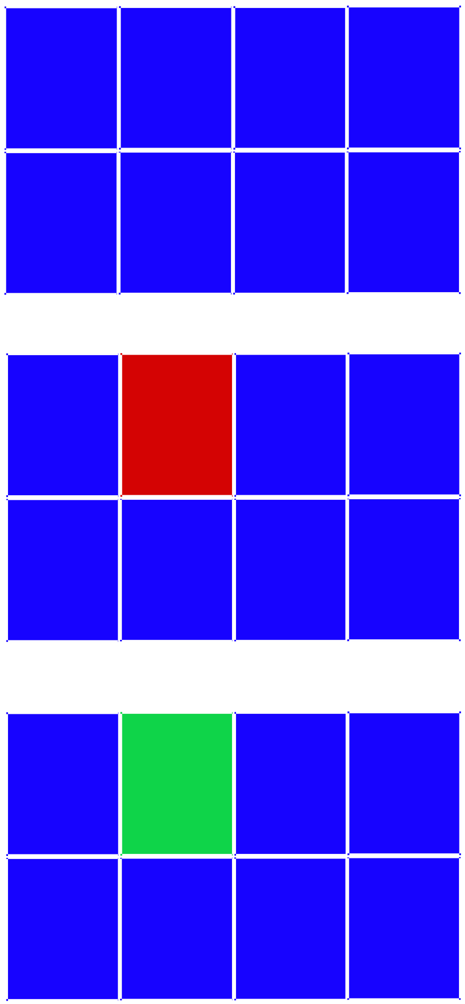
Fitness landscape



- A single valley
- No backward mutations
- A single mutation rate μ + assume $N\mu < 1$

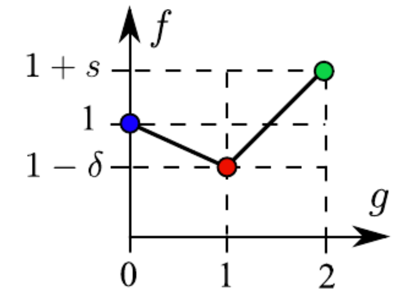
Best scenario

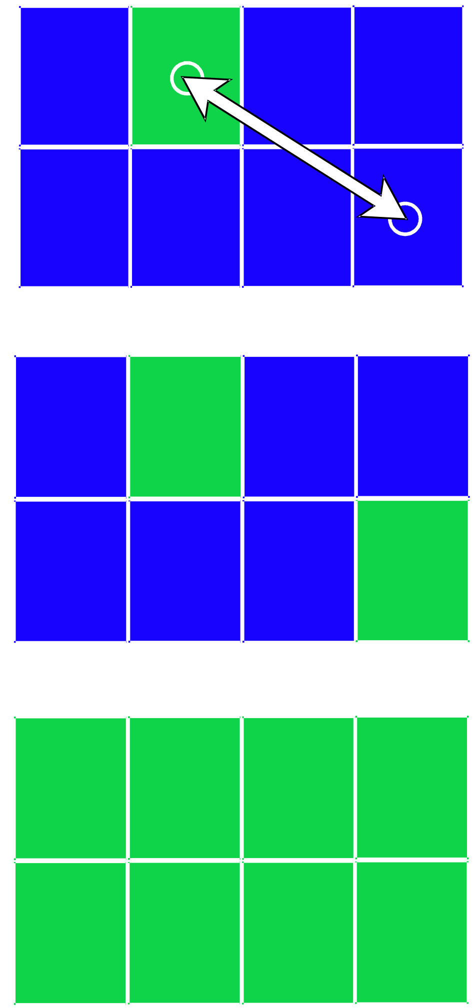
1. Valley crossing by the champion deme



← if demes are in the sequential fixation regime

2. Spreading by migration





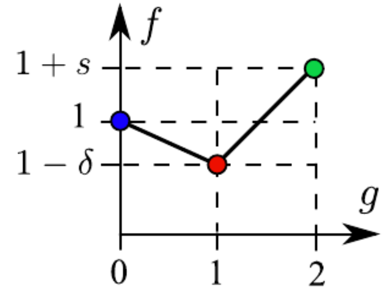
At best: valley crossing time dominated by that of the *champion* (fastest) deme

→ Speedup in this best scenario?

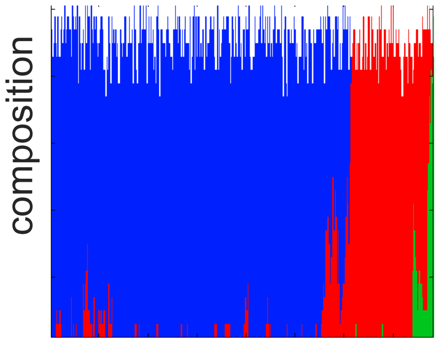
→ Conditions?

Best scenario

- **Crossing by the champion among *D* independent demes**



1. Demes in the sequential fixation regime



Average crossing time for one deme:

$$\tau = \tau_{01} + \tau_{12} = \frac{1}{N\mu d\, p_{01}} + \frac{1}{N\mu d\, p_{12}}$$ Weissman et al. (2009)

Fixation probability of one "j" individual: $p_{ij} = \dfrac{1 - e^{f_i - f_j}}{1 - e^{N(f_i - f_j)}}$

$$\delta \ll 1,\ s \ll 1,\ N\delta \gg 1,\ Ns \gg 1 \rightarrow p_{01} = \frac{e^{\delta} - 1}{e^{N\delta} - 1} \approx \delta e^{-N\delta}$$ and $$p_{12} = \frac{e^{-(\delta+s)} - 1}{e^{-N(\delta+s)} - 1} \approx \delta + s$$

$$\tau_{01} \gg \tau_{12} \quad \rightarrow \quad \tau \approx \tau_{01} = \frac{1}{N\mu d\, p_{01}} \approx \frac{e^{N\delta}}{N\mu d\, \delta}$$

Crossing time ~ exponentially distributed

$\rightarrow$ Average for the champion among *D* demes: $\dfrac{\tau_c}{\tau_{id}} \approx \dfrac{1}{D}$ (*c*: champion; *id*: isolated deme)

$Dp_{01} \ll p_{12}$ (can be generalized)

2. Demes in the tunneling regime

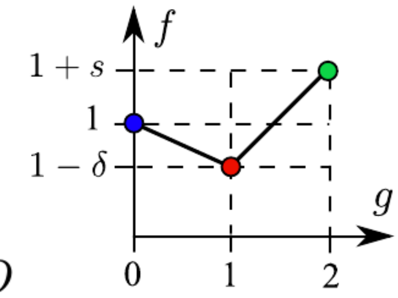
In this case too, $\dfrac{\tau_c}{\tau_{id}} \approx \dfrac{1}{D}$

Best scenario

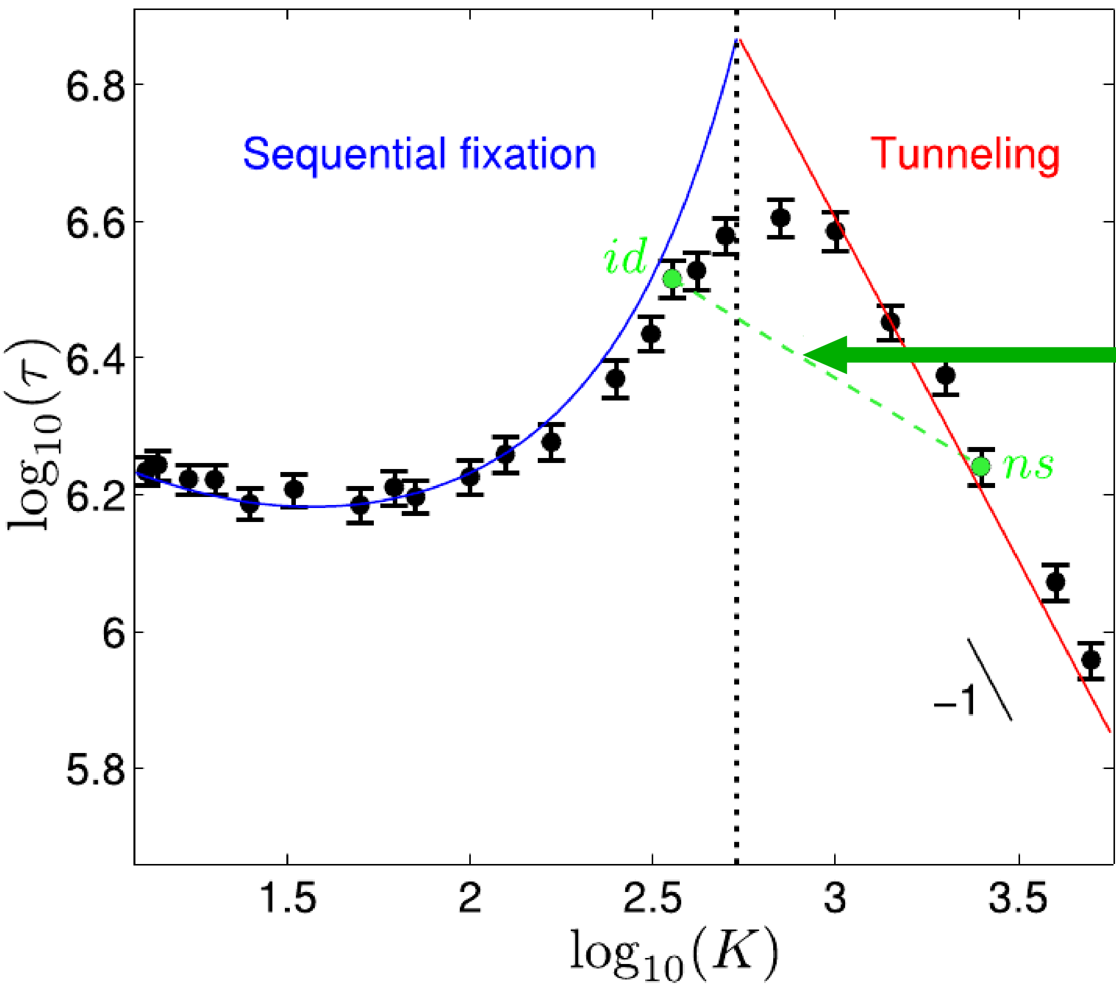
- **Necessary conditions to obtain speedups**

Best scenario → $\tau_m \approx \tau_c$ with $\dfrac{\tau_c}{\tau_{id}} \approx \dfrac{1}{D}$

(m: metapopulation)



Hence, to have a speedup by subdivision ($\tau_m < \tau_{ns}$), we need $\dfrac{\tau_{id}}{\tau_{ns}} < D$



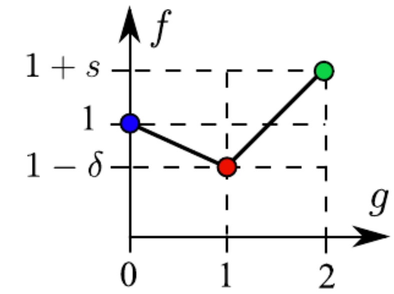
Slope needs to be larger (less negative) than -1

Consequence: Sequential fixation in individual demes is necessary in order to get speedups

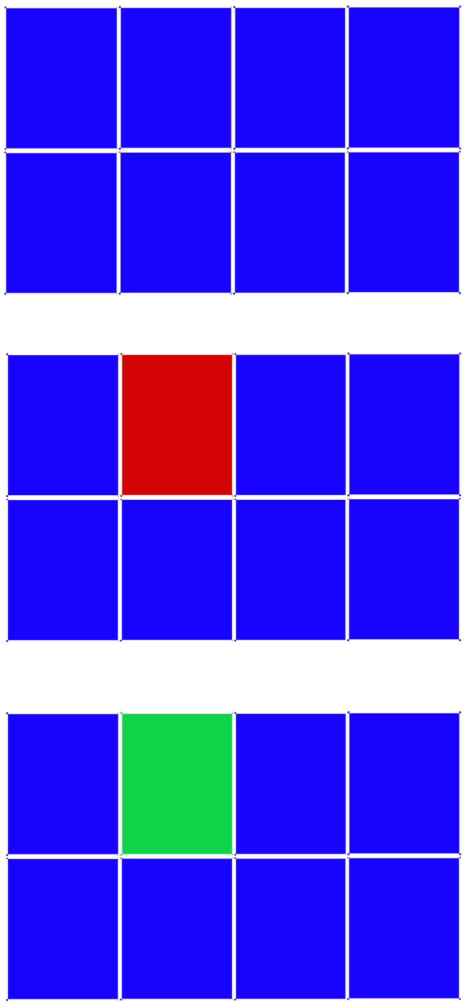
Reciprocally: Demes in the sequential fixation regime → speedups *in the best scenario*

→ **Conditions under which the best scenario is attained?**

Best scenario (reminder)

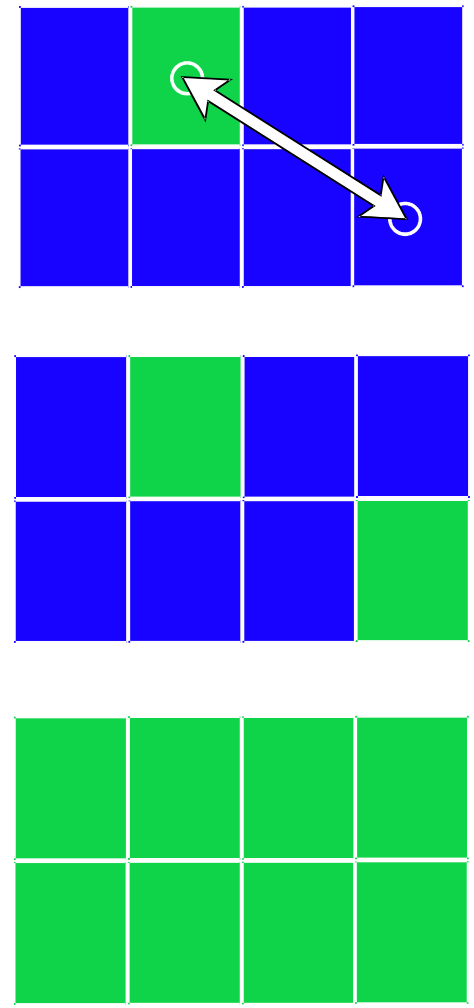


1. Valley crossing by the champion deme



← if demes are in the sequential fixation regime

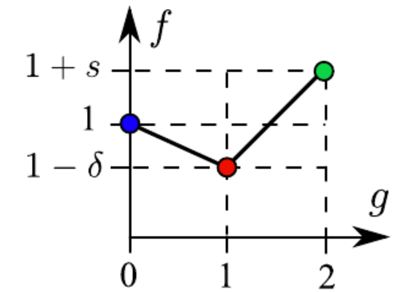
2. Spreading by migration

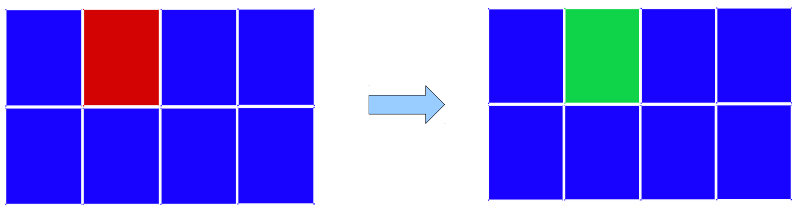


At best: valley crossing time dominated by that of the *champion* (fastest) deme
→ Conditions?

Condition 1: quasi-independence

- **The champion deme must be shielded from migration while in the deleterious state**

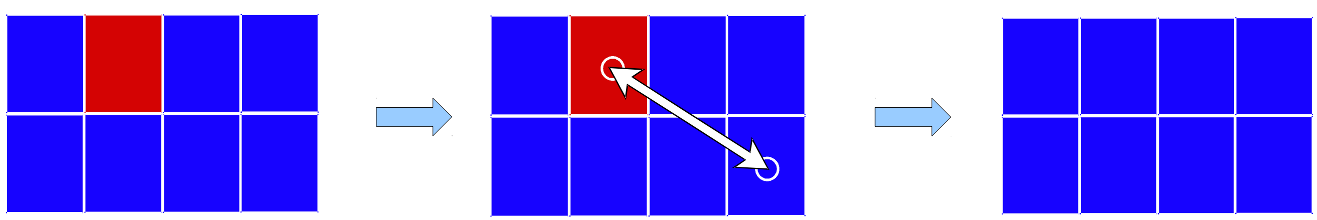




Timescale: $\tau_{12} = \dfrac{1}{N\mu d\, p_{12}}$ with $p_{12} = \dfrac{e^{-(\delta+s)}-1}{e^{-N(\delta+s)}-1} \approx \delta + s$

$\delta \ll 1,\ s \ll 1,\ N\delta \gg 1,\ Ns \gg 1$

must occur faster than



Timescale: $t_e = \dfrac{n_e}{DNm}$ where n_e = average number of migrations for “1” to get extinct

Probability that a migration is relevant: $p_r = \dfrac{2}{D}$

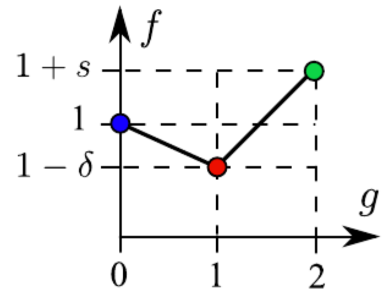
Migrant fixation: $p_{01} = \dfrac{e^{\delta}-1}{e^{N\delta}-1} \approx \delta e^{-N\delta}$ and $p_{10} = \dfrac{e^{-\delta}-1}{e^{-N\delta}-1} \approx \delta$

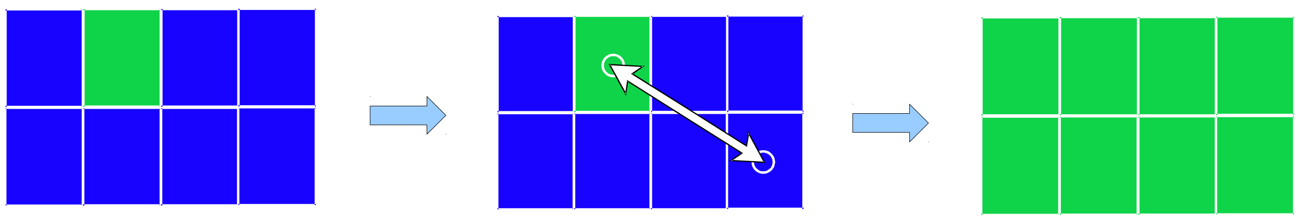
$n_e \approx \dfrac{1}{p_r p_{10}(1-p_{01})} \approx \dfrac{D}{2\delta}$

→ **First condition:** $\tau_{12} < t_e \rightarrow \boxed{\dfrac{m}{\mu d} < \dfrac{1}{2}\left(1+\dfrac{s}{\delta}\right)}$: upper bound on the migration rate

Condition 2: fast spreading

- **Spreading of the beneficial mutation must be faster than valley crossing by the champion deme**





Timescale: $t_s = \frac{n_s}{DNm}$ where n_s = average number of migrations for “2” to spread

$$n_s = \sum_{i=1}^{D-1} n_{i\to i+1} = \sum_{i=1}^{D-1} \frac{1}{p_{i\to i+1}}$$ i: number of “2” populations

$$p_{i\to i+1} = r_i p_{02}(1-p_{20}) \approx r_i s$$

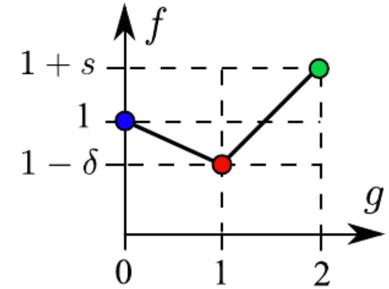
Probability that a migration is relevant: $r_i = \frac{2i(D-i)}{D(D-1)}$

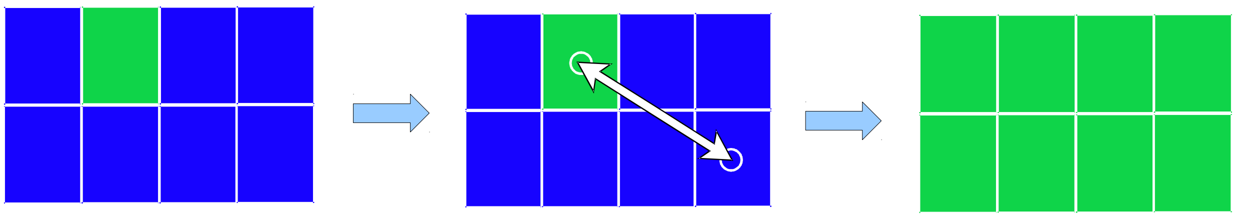
$$\rightarrow n_s \approx \frac{D-1}{s}\sum_{i=1}^{D-1}\frac{1}{i} \approx \frac{D\log D}{s}$$

Hence, $t_s \approx \frac{\log D}{Nsm}$

Condition 2: fast spreading

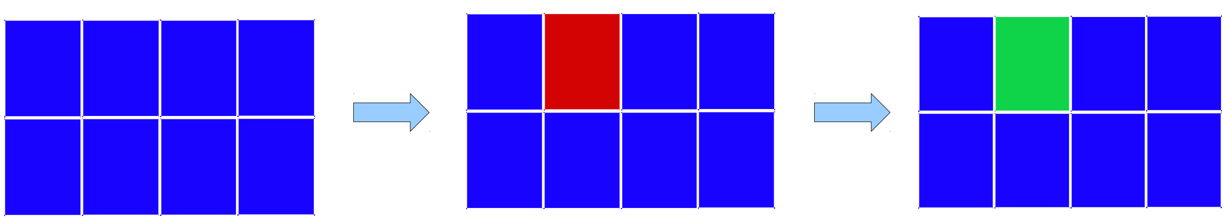
- **Spreading of the beneficial mutation must be faster than valley crossing by the champion deme**





must occur faster than

Timescale: $t_s \approx \dfrac{\log D}{Nsm}$



Valley crossing by the champion deme

Timescale: $\tau_c \approx \dfrac{\tau_{id}}{D} \approx \dfrac{e^{N\delta}}{DN\mu d\,\delta}$

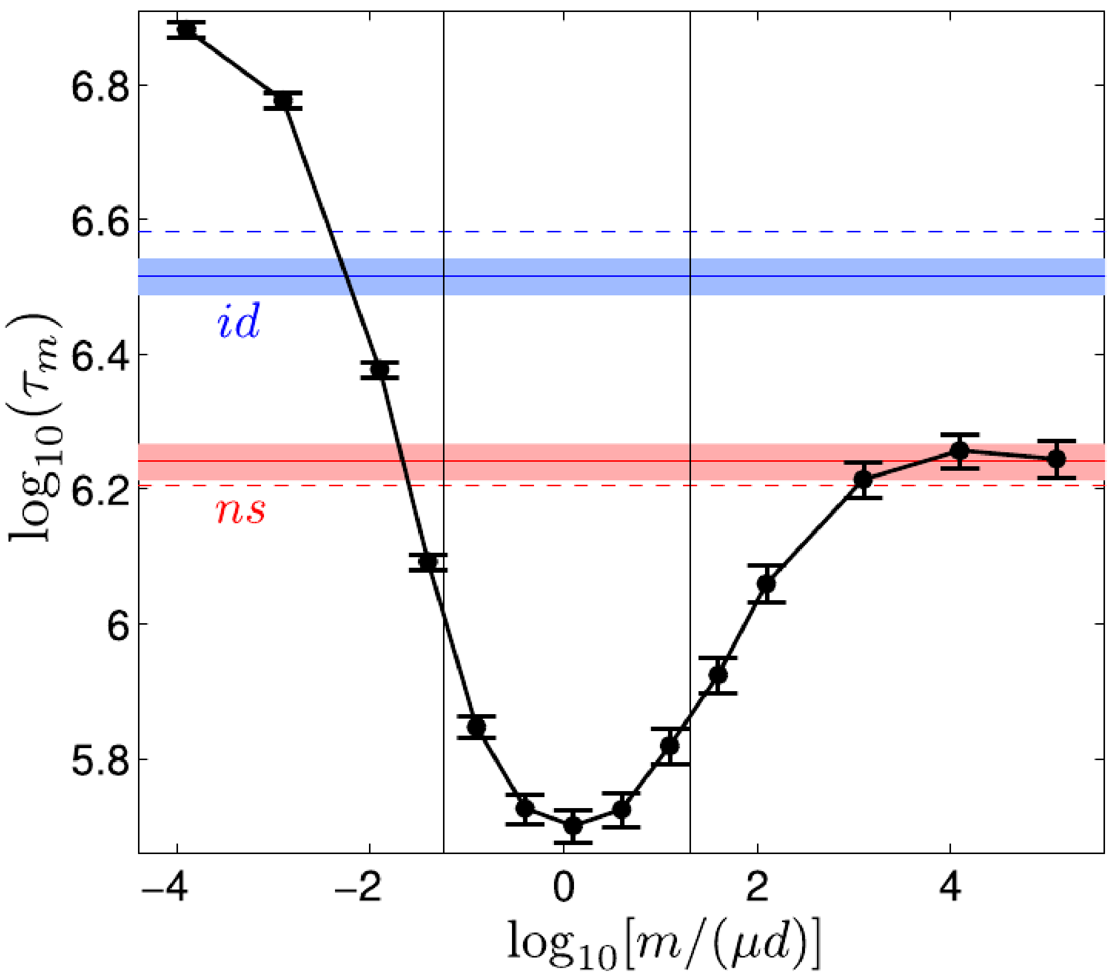
$\rightarrow$ **Second condition:** $t_s < \tau_c \;\; \rightarrow \;\; \boxed{\dfrac{\delta e^{-N\delta}}{s} D \log D < \dfrac{m}{\mu d}}$: lower bound on the migration rate

- **Prediction:**

$\dfrac{\delta e^{-N\delta}}{s} D \log D \ll \dfrac{m}{\mu d} \ll \dfrac{1}{2}\left(1 + \dfrac{s}{\delta}\right)$ $\rightarrow$ optimal scenario, and $\dfrac{\tau_m}{\tau_{id}} \approx \dfrac{1}{D}$

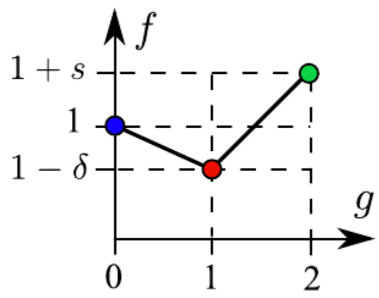
Test: stochastic simulation

- **Simulation (Gillespie algorithm) → crossing time vs. migration rate**



Parameter values:

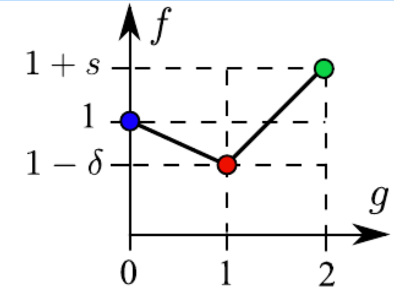
s = 0.3
δ = 0.006
K = 357
D = 7
μ = 8 x 10^{-6}
d = 0.1



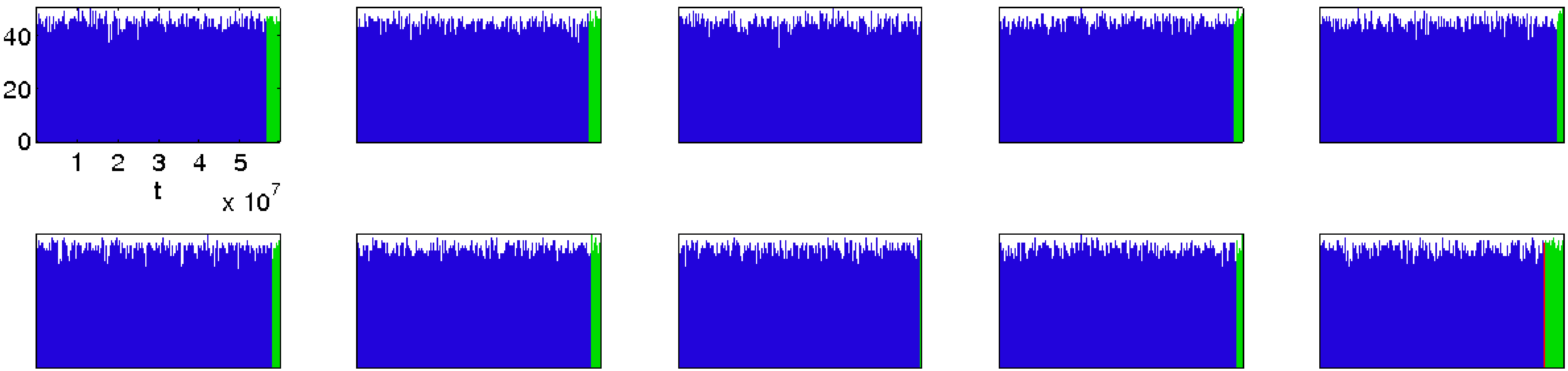
Minimum → $\left.\begin{aligned} \tau_m &= (5.02 \pm 0.14) \times 10^5 \\ \tau_{id} &= (3.28 \pm 0.10) \times 10^6 \end{aligned}\right\}$ → factor of 6.54, close to D = 7

Test: stochastic simulation

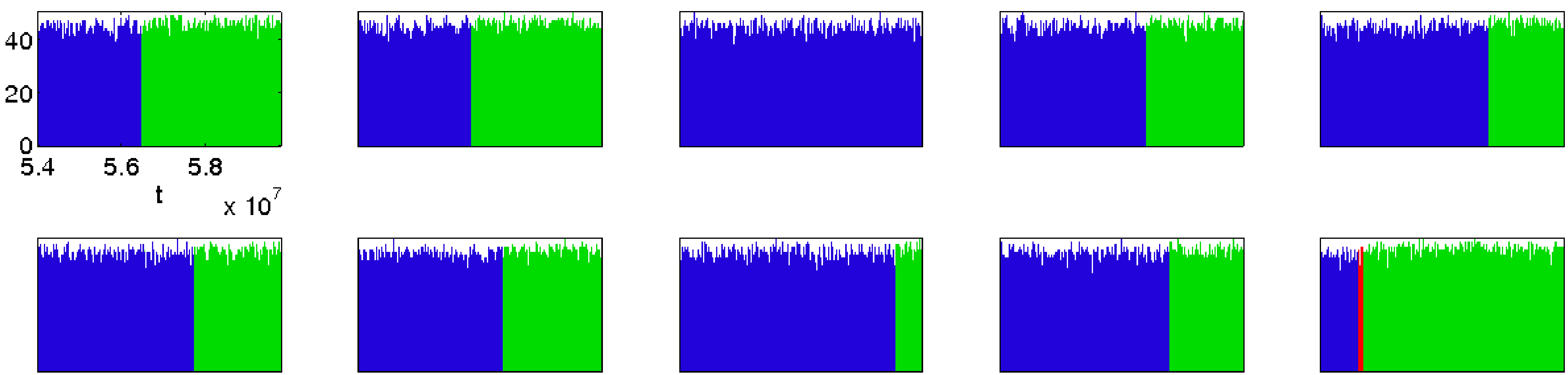
- **Valley crossing at the optimum**



One realization:



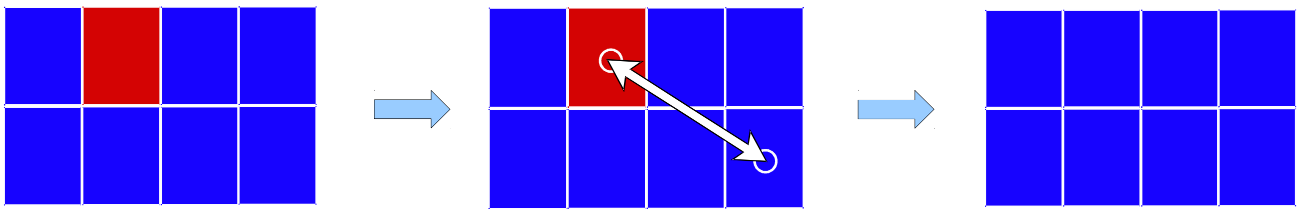
End of the process:



Generalizing

- **Beyond $N\delta$ >> 1: shallow valleys, plateaus, etc.**

$N\delta \gg 1,\ Ns \gg 1$ $\rightarrow$ simple derivation of numbers of migrations until extinction or fixation



$$p_{01} = \frac{e^{\delta} - 1}{e^{N\delta} - 1} \approx \delta e^{-N\delta}$$

$$p_{10} = \frac{e^{-\delta} - 1}{e^{-N\delta} - 1} \approx \delta$$

- **A finite Markov chain**

$i \in [0, D]$: number of demes that have fixed the mutation (e.g., “1”)

At each migration step, i can change
Outcome of the next migration only depends on current value of i
Two absorbing states: $i = 0$ and $i = D$

} finite Markov chain

- **Transition probabilities**

$$P_{i \to i+1} = r_i\, p_{01}(1 - p_{10})$$

$$P_{i \to i-1} = r_i\, p_{10}(1 - p_{01})$$

$$P_{i \to i} = 1 - (P_{i \to i+1} + P_{i \to i-1})$$

Probability that a migration is relevant:

$$r_i = \frac{2i(D - i)}{D(D - 1)}$$

The matrix of transition probabilities is tri-diagonal $\rightarrow$ simple case!

The number of migration steps before absorption can be expressed analytically

Ewens (1979)

Generalizing

- **Optimal parameter range**

$$n_s p_{01} \ll \frac{m}{\mu d} \ll \frac{n_e p_{12}}{D}$$

Exact expressions for n_s and n_e (number of migration steps before absorption)

Case of the plateau (δ = 0): optimal speedup is obtained for $\frac{1}{Ns} D \log D \ll \frac{m}{\mu d} \ll \frac{Ns}{2} \log D$

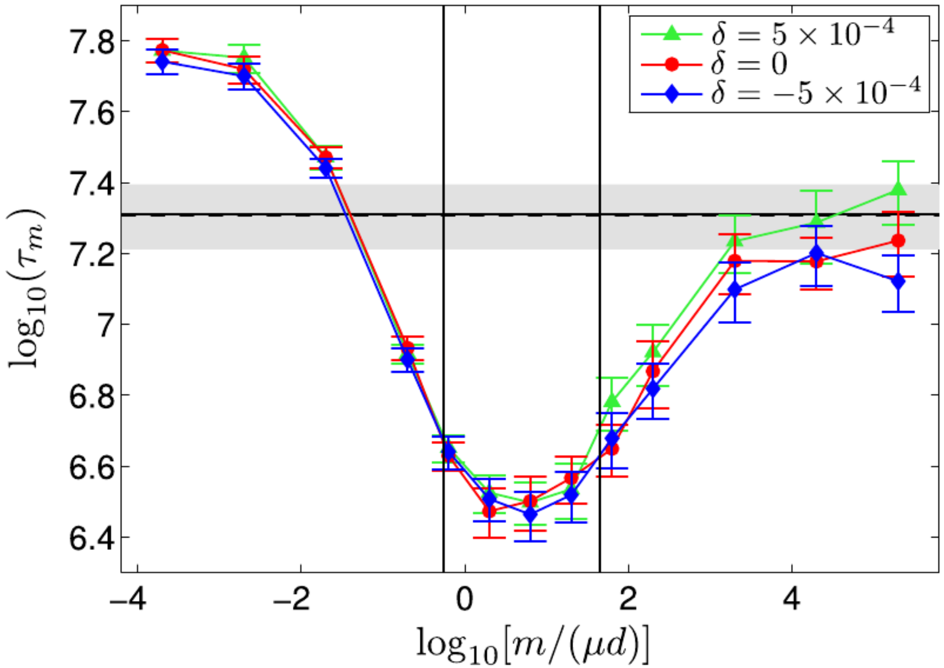
- **Effectively neutral intermediates**

Effectively neutral intermediate: $|\delta| < \max(\sqrt{\mu s}, 1/N)$: includes weakly beneficial ones

$\rightarrow$ plateau results hold

Weissman et al. (2009)

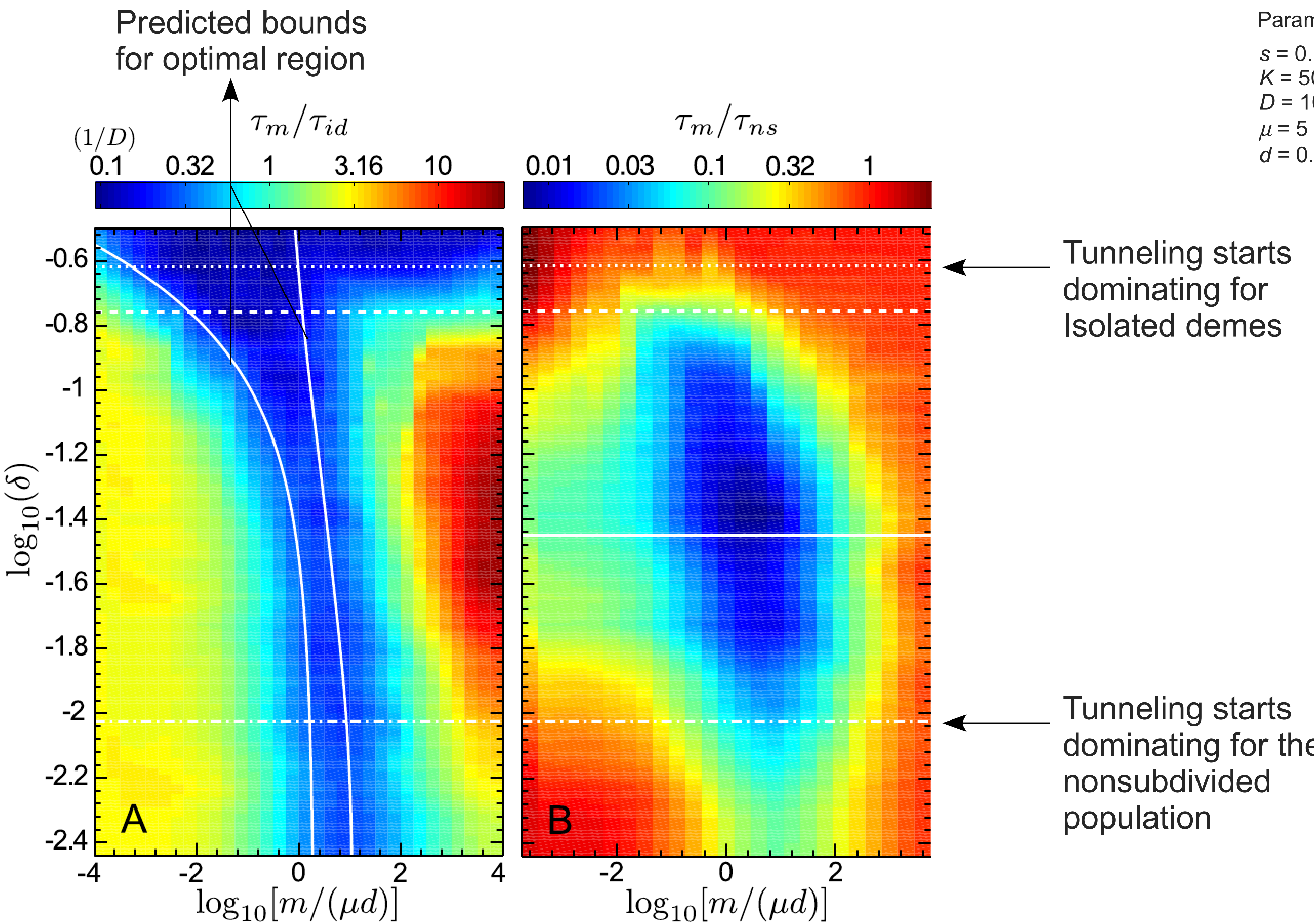
Example:



Parameter values:

s = 0.5
N = 130
D = 10
μ = 5 x 10^{-7}
d = 0.1

Heatmaps



Parameters:

s = 0.3
K = 50
D = 10
μ = 5 10^{-6}
d = 0.1

Highest speedup & trade-off

Highest possible speedup by subdivision

Optimal case → speedup gained by subdividing a population: $\dfrac{\tau_m}{\tau_{ns}} = \dfrac{\tau_c}{\tau_{ns}}$

Assume:

- isolated deme in the sequential fixation regime
- nonsubdivided population in the tunneling regime

$$2\sqrt{\mu s} \ll \delta \ll 1 \quad \rightarrow \quad \frac{\tau_m}{\tau_{ns}} = \mu s \frac{e^{N\delta} - 1}{\delta^2}$$

At fixed *N*, this ratio is minimal for $\delta \approx \dfrac{1.594}{N}$ (→ importance of general calculations)

Its minimal value is $\dfrac{\tau_m}{\tau_{ns}} \approx 1.544\, N^2 \mu s$

Heatmaps → optimal valley depth: $\delta \approx 0.035 \approx 10^{-1.45}$

A trade-off in the choice of *D*

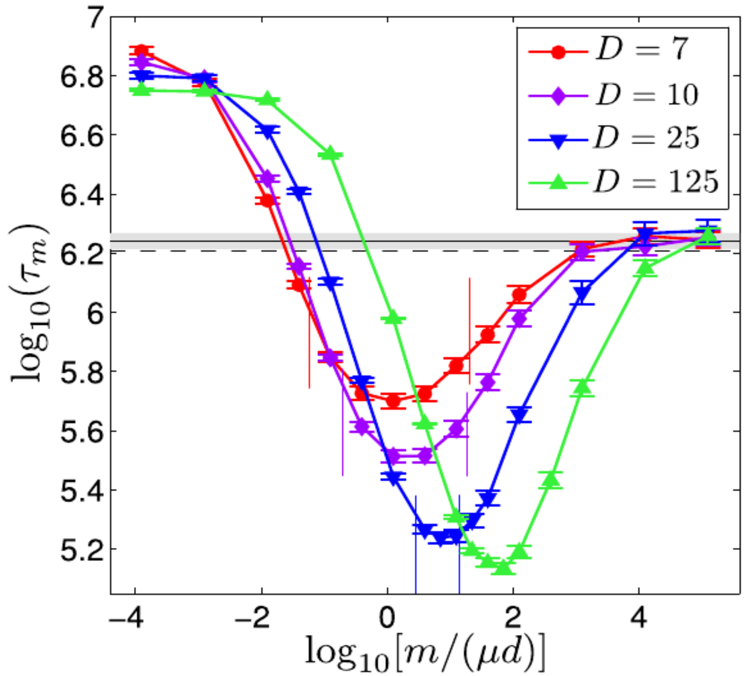
Fixed $\mathcal{N} = ND$ → highest speedup: $\dfrac{\tau_m}{\tau_{ns}} \approx 1.544 \dfrac{\mathcal{N}^2 \mu s}{D^2}$

Increase *D* → gain more speedup

But $\dfrac{\delta e^{-N\delta}}{s} D \log D \ll \dfrac{m}{\mu d} \ll \dfrac{1}{2}\left(1 + \dfrac{s}{\delta}\right)$

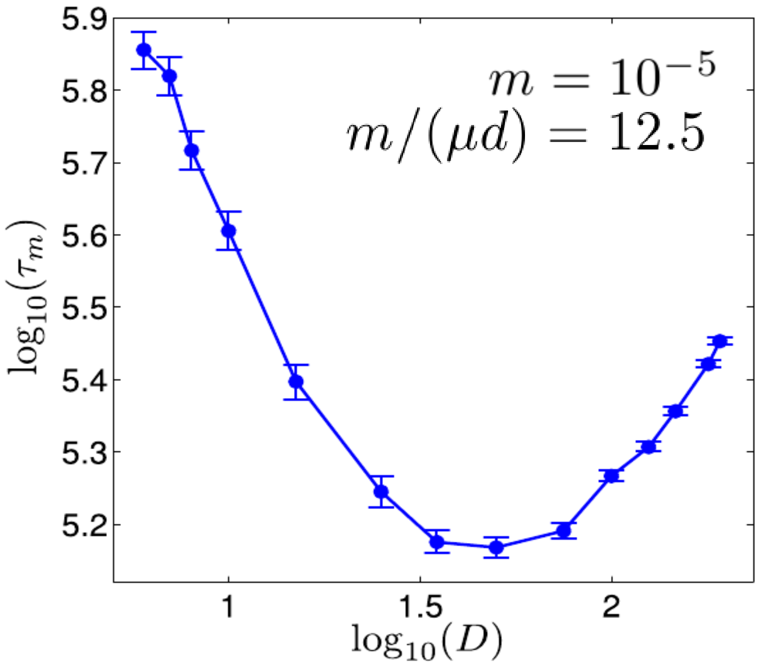
Increase *D* → narrower optimal parameter range

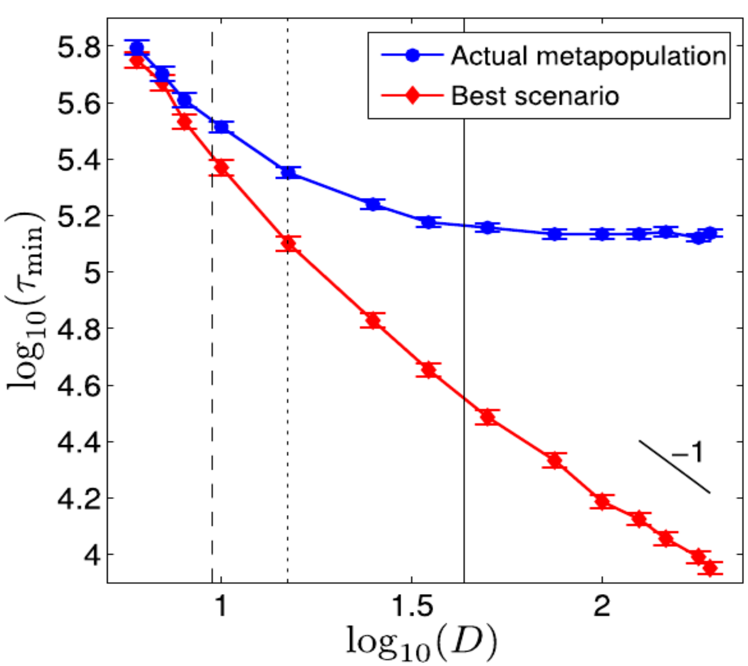
Varying the degree of subdivision



Parameter values:

s = 0.3
δ = 0.006
$D\ K$ = 2500
$\mu = 8 \times 10^{-6}$
d = 0.1





Application

▪ An example

E. coli $\rightarrow \mu \approx 8.9\times 10^{-11}$ Wielgoss et al. (2011)

Take $N = 5 \times 10^4$ (small but realistic) Rozen et al. (2008)

$D = 100$ (96-well plates)

Plateau $\rightarrow$ sequential fixation below $N_\times = 1/\sqrt{\mu s}$

$s = 10^{-2}$ $\rightarrow$ isolated demes in the sequential fixation regime
for $0 \leq \delta \lesssim 2.2 \times 10^{-4}$

The optimal range of migration rates spans 2 to 4 orders of magnitude depending on δ

Speedup factor from 18 to 2.7×10^2

▪ More generally

For given *N* and *D*, we can predict:
- for which valleys subdivision speeds up crossing
- the highest speedups obtained
- the range of migration rates for which they are reached

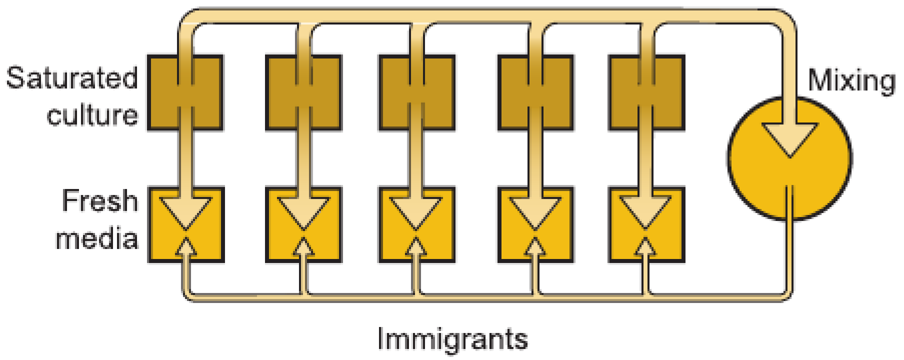
Conclusion

- **Summary**

- Subdivision with migration (alone) can significantly accelerate fitness valley & plateau crossing
- Sufficiently small demes (performing sequential fixation) are necessary
- Effect of varying the degree of subdivision

- **Some related experimental studies**

- Kryazhimskiy, Rice and Desai (2012) → evolution of subdivided populations of yeast



→ no evidence of any advantage of subdivided populations

- Nahum, Godfrey-Smith, Harding, Marcus, Carlson-Stevermer and Kerr (BioRXiv 2014)
  → evolution of subdivided populations of bacteria
  → some advantage of subdivision

→ Importance of understanding quantitatively the conditions under which subdivision is beneficial

Conclusion

Perspectives

- More complex population structure (different sizes)
  → already treated: large population + islands
- Case of sexual populations (recombination)
- Spatial structure (expanding front)
- Effect of population subdivision on the evolution of antibiotic resistance

Acknowledgements

David J. Schwab

Ned S. Wingreen

The Princeton Biophysics Journal Club

For more information

A.-F. Bitbol and D.J. Schwab, *Quantifying the role of population subdivision in evolution on rugged fitness landscapes*, PLoS Computational Biology, 10(8): e1003778 (2014)
DOI: 10.1371/journal.pcbi.1003778

Preprint: ArXiv 1308.0278

Thanks!