How physics helps understand evolving biological systems

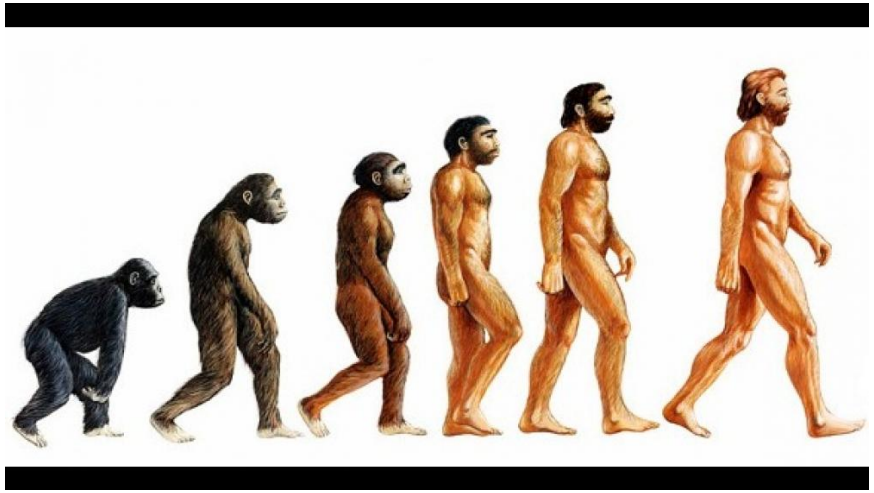
Diana Fusco (df390@cam.ac.uk)

Biological Physics Course

Outline

- Evolution as a physical process
- Intro about evolutionary processes
  - Mutations
  - Selection
  - Noise
- Evolution in well-mixed populations: Luria-Delbrück experiment
- Beyond the well-mixed paradigm: introducing space
- Reaction-diffusion to describe spatial population dynamics
  - Example 1: Emergence of resistance in an antibiotic gradient
  - Example 2: Maintenance of diversity in 3-species system

How evolution affects our life and society

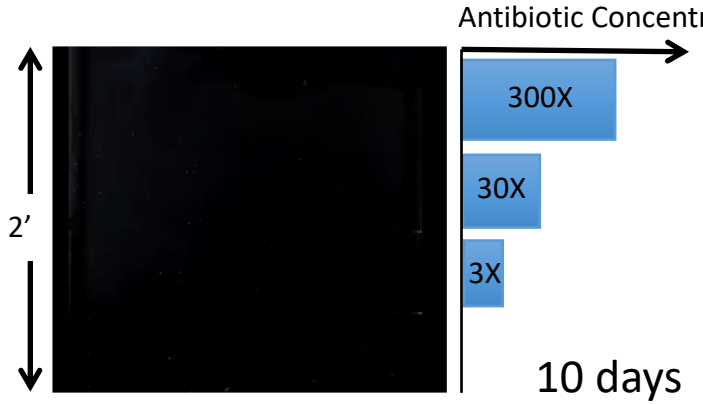


Millions of years

Using evolving systems as problem-solving computers

They harnessed the power of evolution

The power of evolution is revealed through the diversity of life. The 2018 Nobel Laureates in Chemistry have taken control of evolution and used it for purposes that bring the greatest benefit to humankind. Enzymes produced through directed evolution are used to manufacture everything from biofuels to pharmaceuticals. Antibodies evolved using a method called phage display can combat autoimmune diseases and in some cases cure metastatic cancer.



Baym et al., *Science* 2016

Antibiotic resistance
and cancer progression

Understand

↓

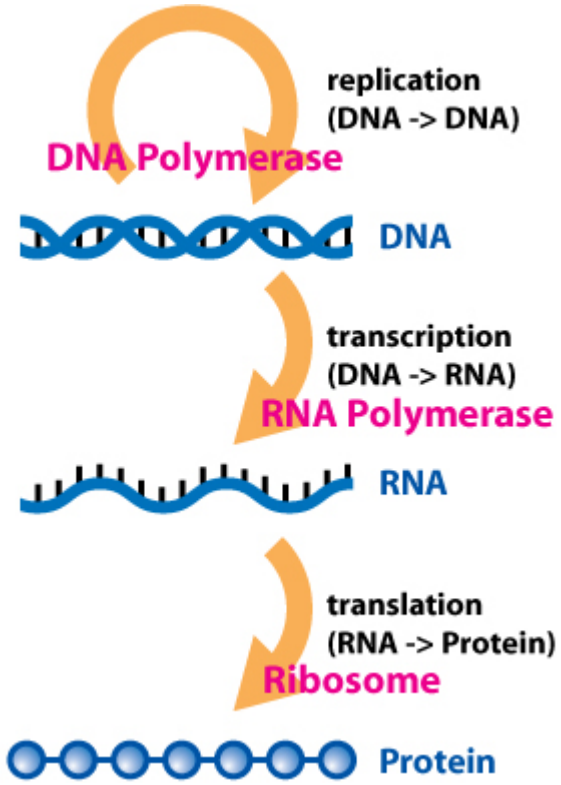
Predict

↓

Control

Evolution's key ingredients: Mutations, Selection and Noise

Central Dogma of Molecular Biology



- Errors occur in any of these steps
- Replication errors cause genetic mutations that are transferred from mother to daughter
- Note: genetic changes are not the only type of inheritable changes. See for instance

Trerotola *et al. Human Genomics* (2015) 9:17
DOI 10.1186/s40246-015-0041-3

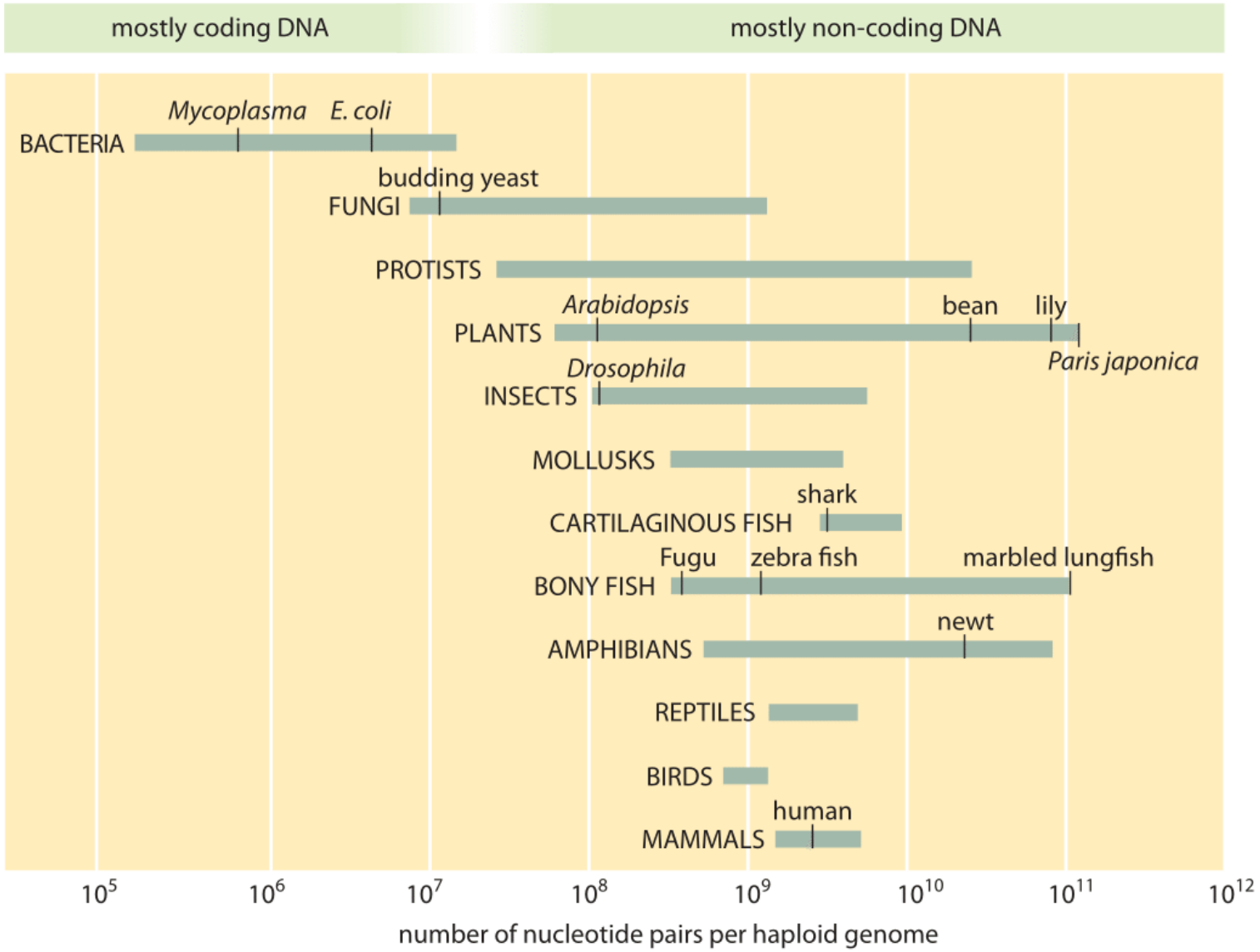
Human Genomics

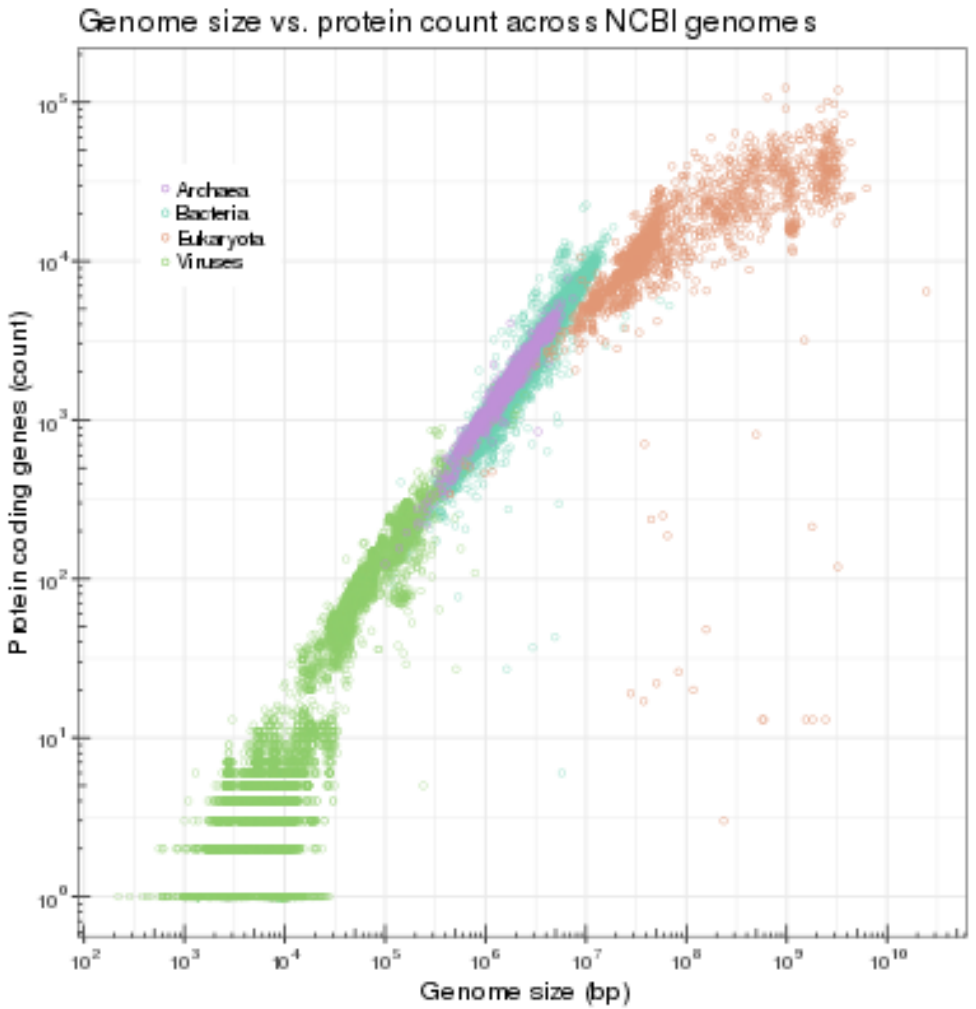
REVIEW Open Access

Epigenetic inheritance and the missing heritability

Marco Trerotola[1], Valeria Relli[1], Pasquale Simeone[1] and Saverio Alberti[1,2*]

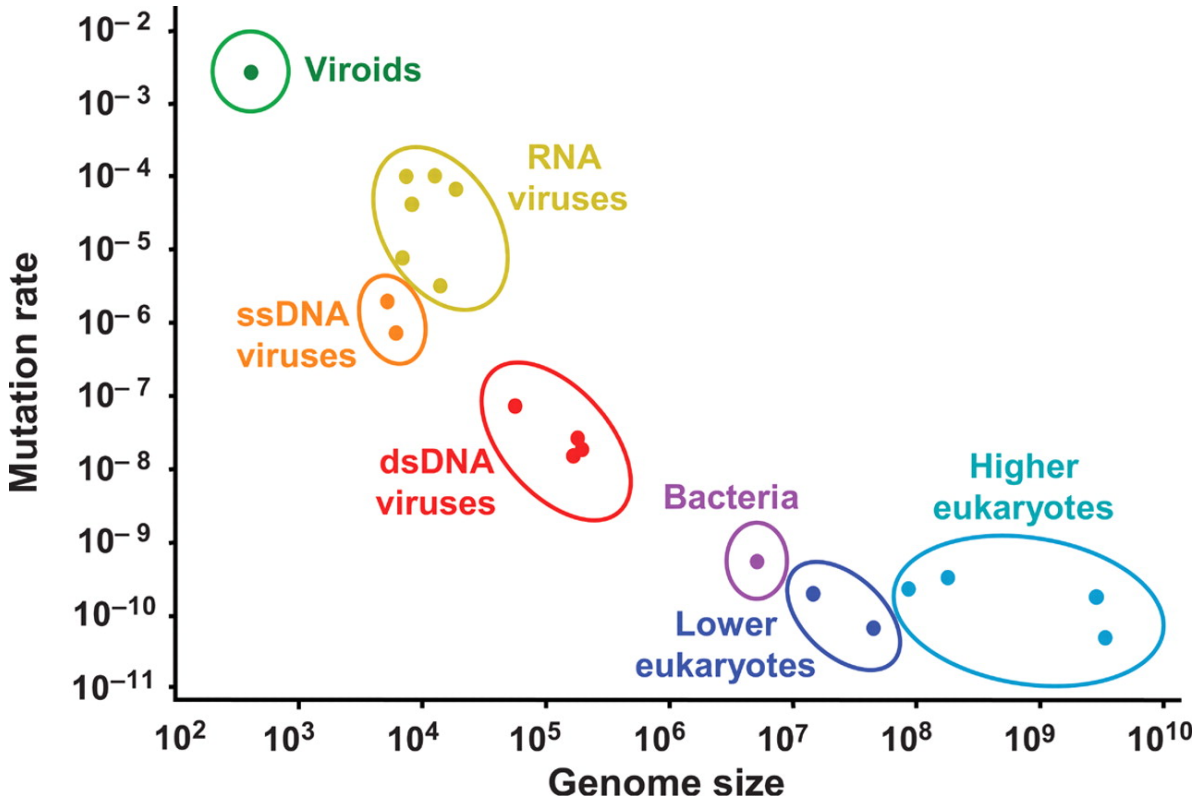
The genome and its numbers:





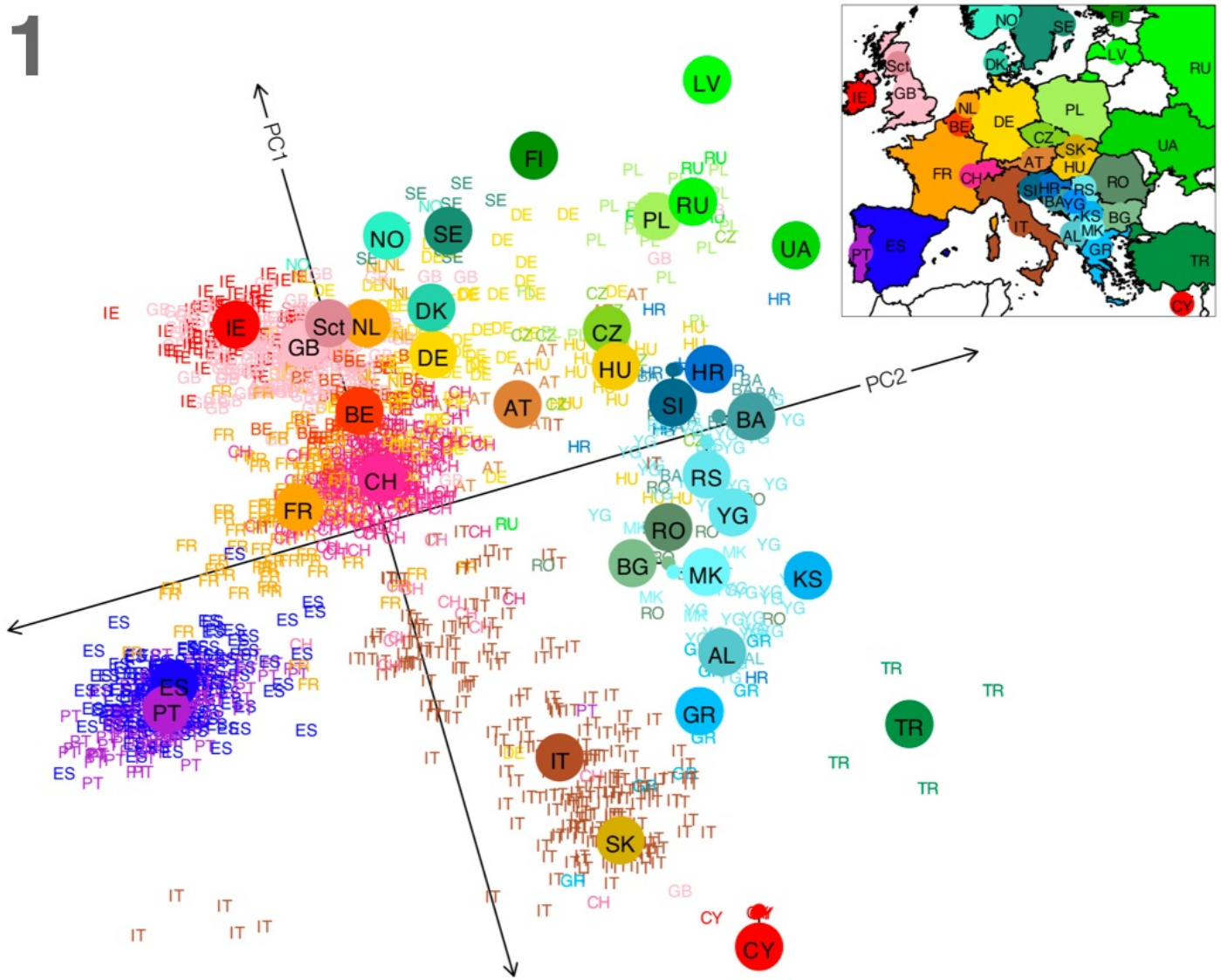
The genome and its numbers:

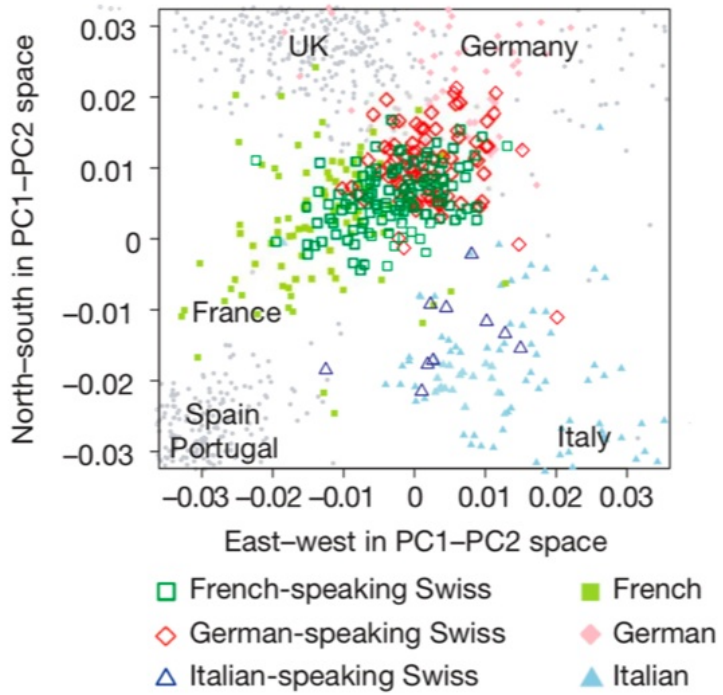
organism	mutations/ base pair/ replication	mutations/ base pair/ generation	mutations/ genome/ replication	BNID
multicellular				
human *H. sapiens*	10^{-10}	$1–4 \times 10^{-8}$ (mitochondria: 3×10^{-5})	0.2–1	105813, 10(109959, 10 111228
mouse *M. musculus*	2×10^{-10}	10^{-8}	0.5	100315, 106
D. melanogaster	3×10^{-10}	10^{-8}	0.06	100365, 106
C. elegans	$10^{-10}–10^{-9}$	10^{-8}	0.02–0.2	100290, 100 103520, 107
unicellular				
bread mold *N. crassa*		10^{-10}	0.003	100355, 100
budding yeast		$10^{-10}–10^{-9}$	0.003	100458, 1004
E. coli		$10^{-10}–10^{-9}$	0.0005–0.005	106748, 1002
DNA viruses				
bacteriophage T2 & T4		2×10^{-8}	0.004	103918, 1039
bacteriophage lambda		10^{-7}	0.004	100222, 1057
bacteriophage M13		10^{-6}	0.005	106788
RNA viruses				
bacteriophage Qβ		10^{-3}	7	106762
poliovirus		10^{-4}	1	106760
vesicular stomatitis virus		3×10^{-4}	4	106760
influenza A		10^{-5}	1	106760
RNA retroviruses				
spleen necrosis virus		2×10^{-5}	0.2	106762
moloney murine leukemia virus		4×10^{-6}	0.03	106760
rous sarcoma virus		5×10^{-5}	0.4	106762



Despite larger variations in genome size and mutation rate, the rate per genome does not vary too much across organisms.

Genetic variation encodes history





courtesy: John Novembre, UCLA

Evolution's key ingredients: Mutations, Selection and Noise

Mutations create diversity in the population

Selection enriches for fit individuals and purges less fit ones

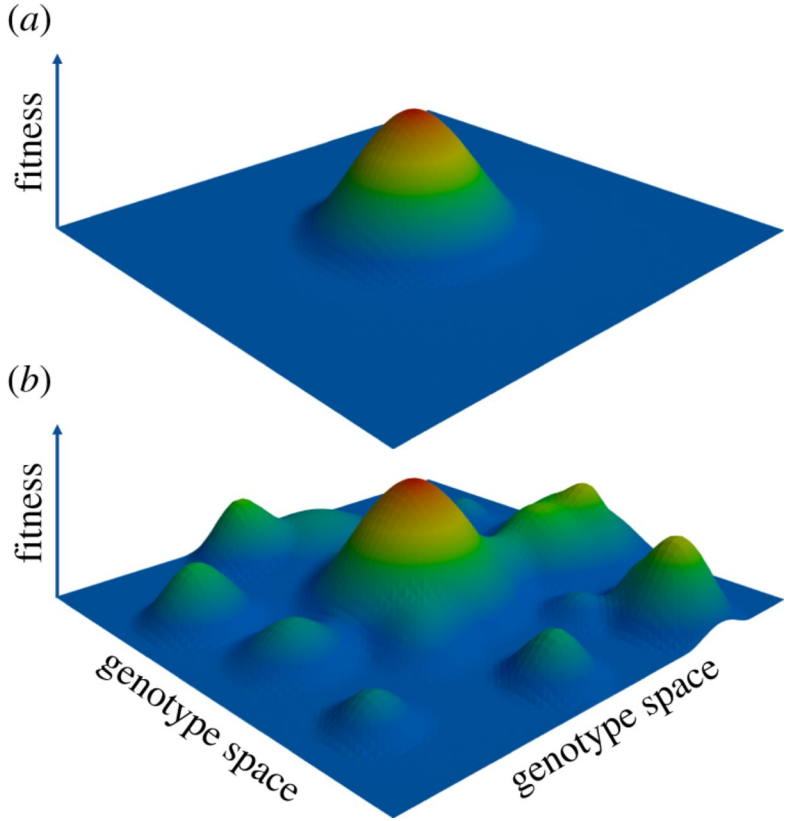


Conceptually similar to a Metropolis algorithm:

- Propose a random move (mutation)
- Accept or reject depending on relative energy (selection)

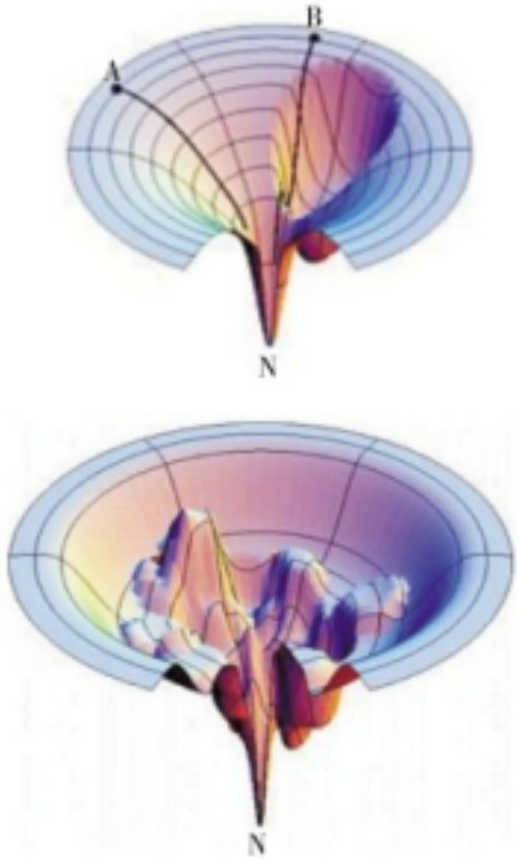
Evolution's key ingredients: Mutations, Selection and Noise

Over many cycles (generations), population adapts to its fittest point

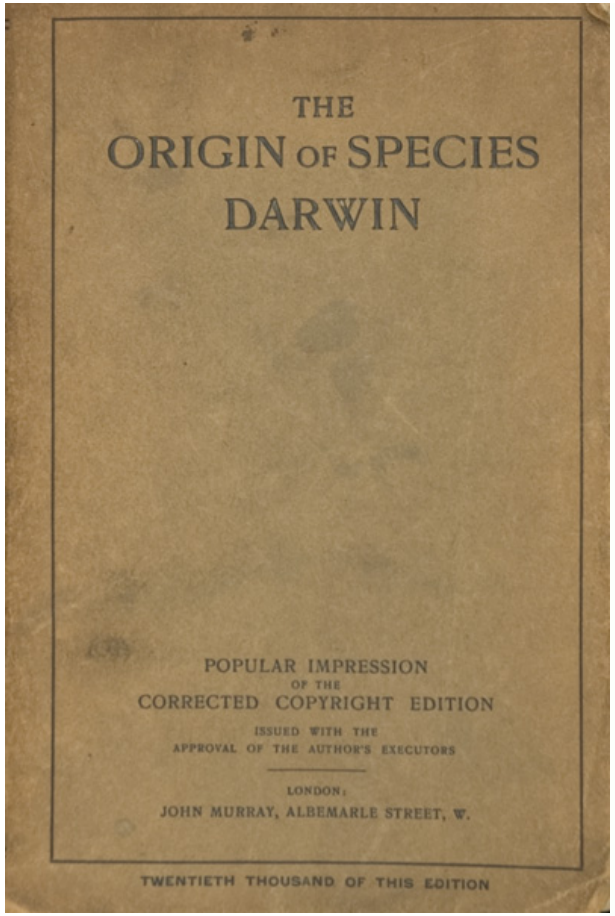


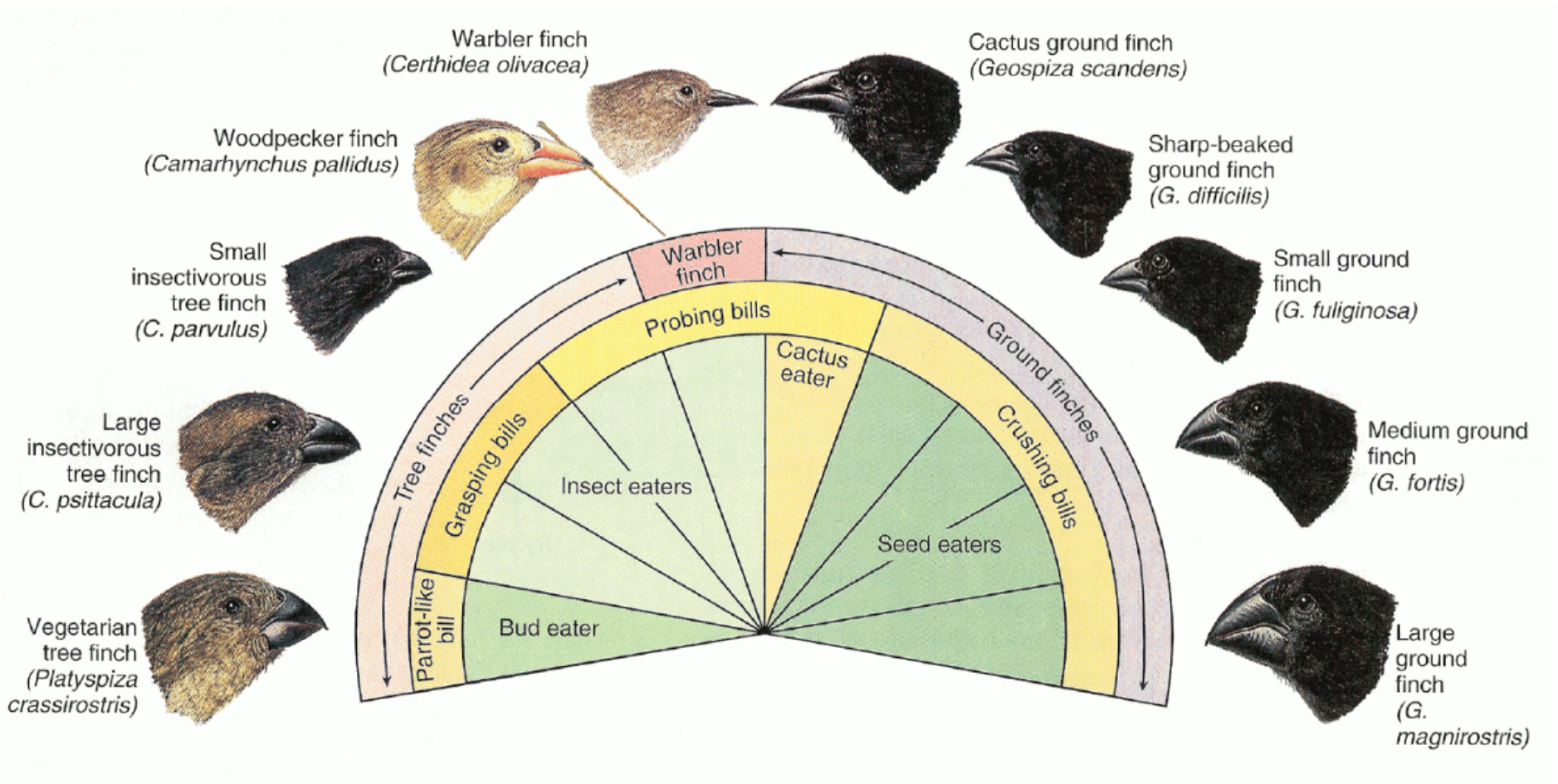
Fitness landscapes (as energy landscapes) can be very rough

Similarly to how a Monte Carlo finds the minimum energy configuration

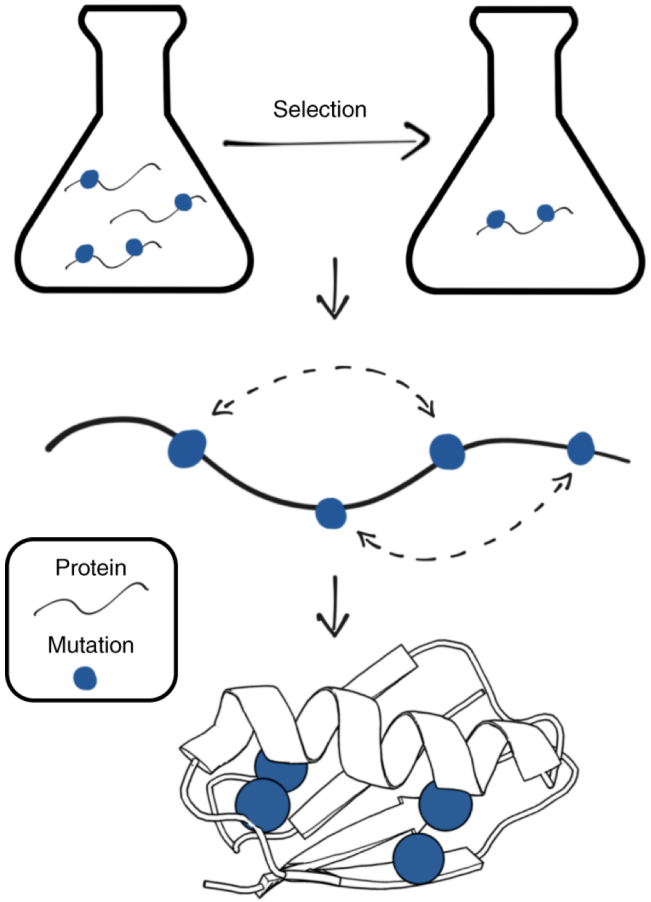


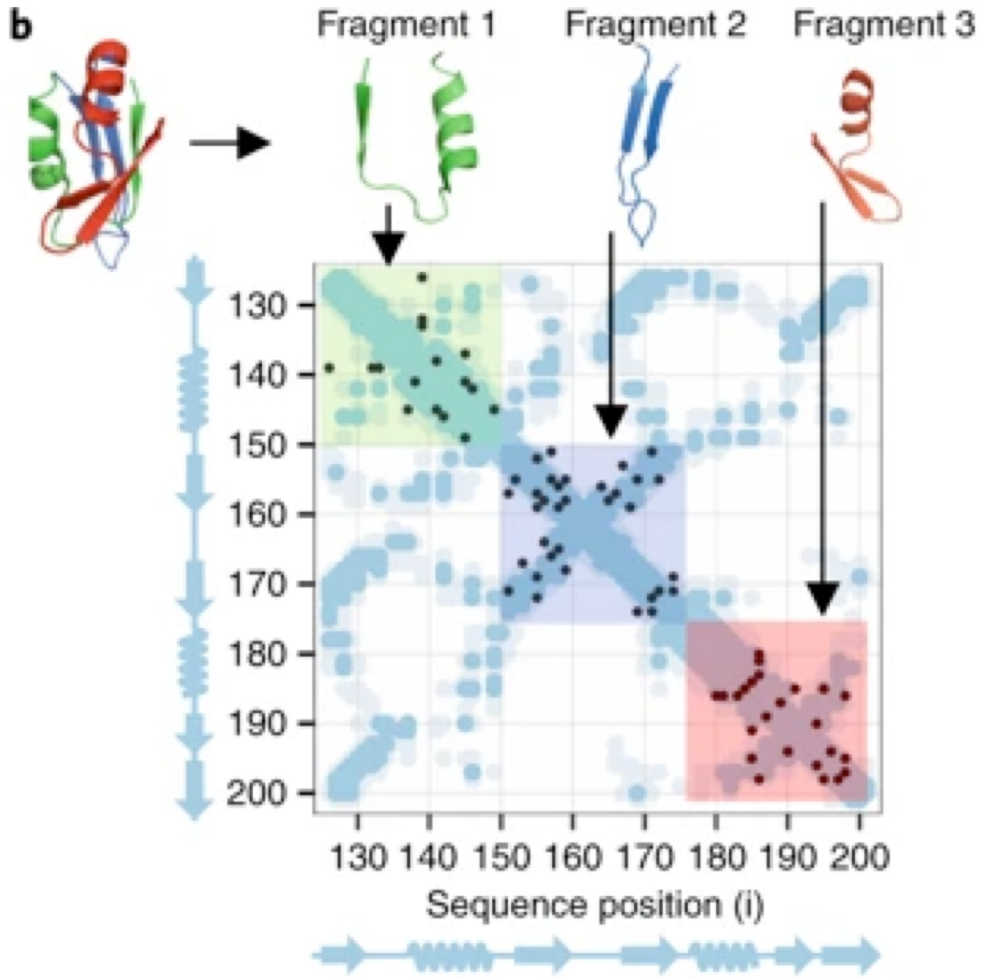
Mutation+selection=adaptation





Selection can pose constraints that can be useful to infer important information





Rollins et al., Nat. Genet. (2019)

Evolution's key ingredients: Mutations, Selection and Noise

Mutations create diversity in the population

Selection enriches for fit individuals and purges less fit ones



Conceptually similar to a Metropolis algorithm:

- Propose a random move (mutation)
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Evolution's key ingredients: Mutations, Selection and Noise

Mutations create diversity in the population

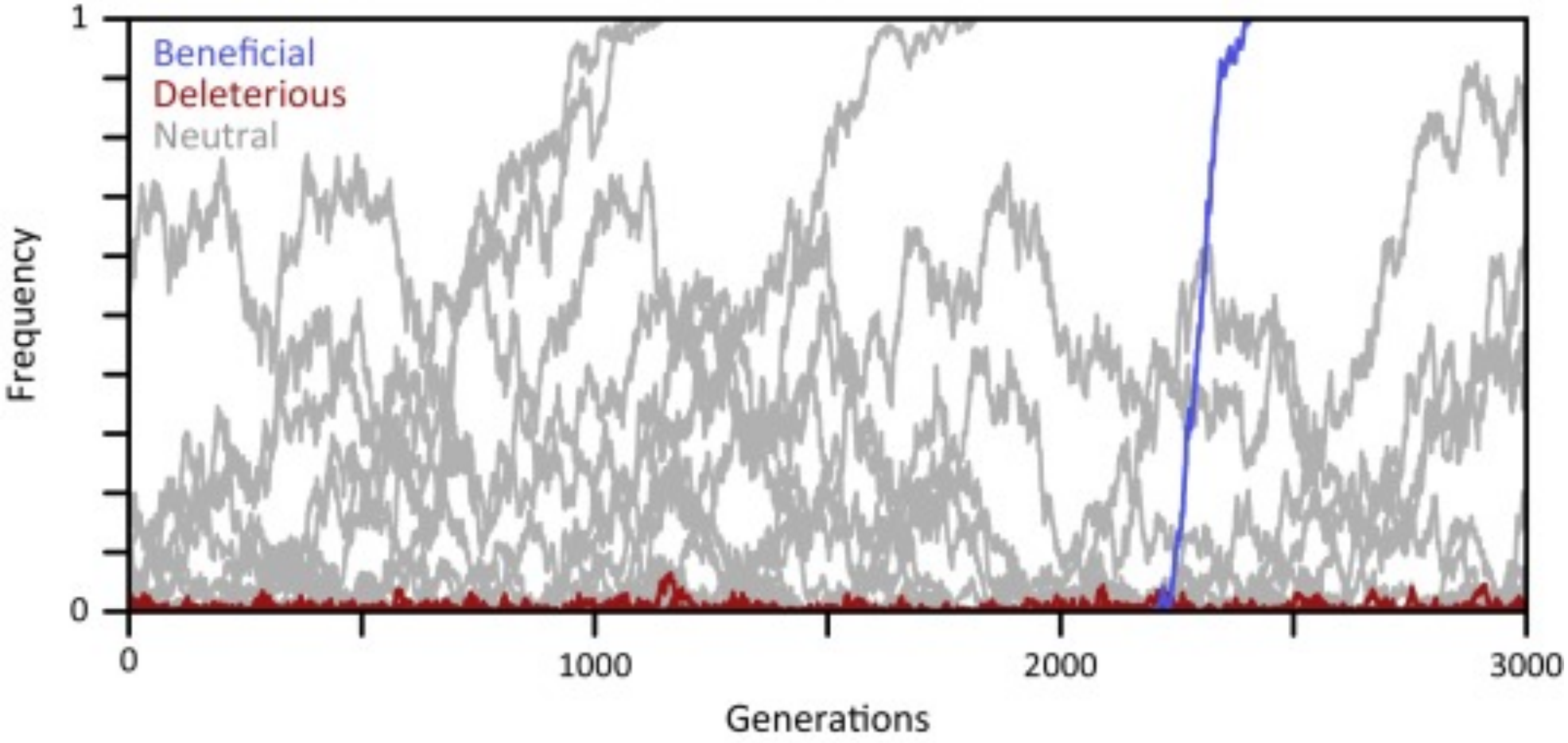
Selection enriches for fit individuals and purges less fit ones



Conceptually similar to a Metropolis algorithm:

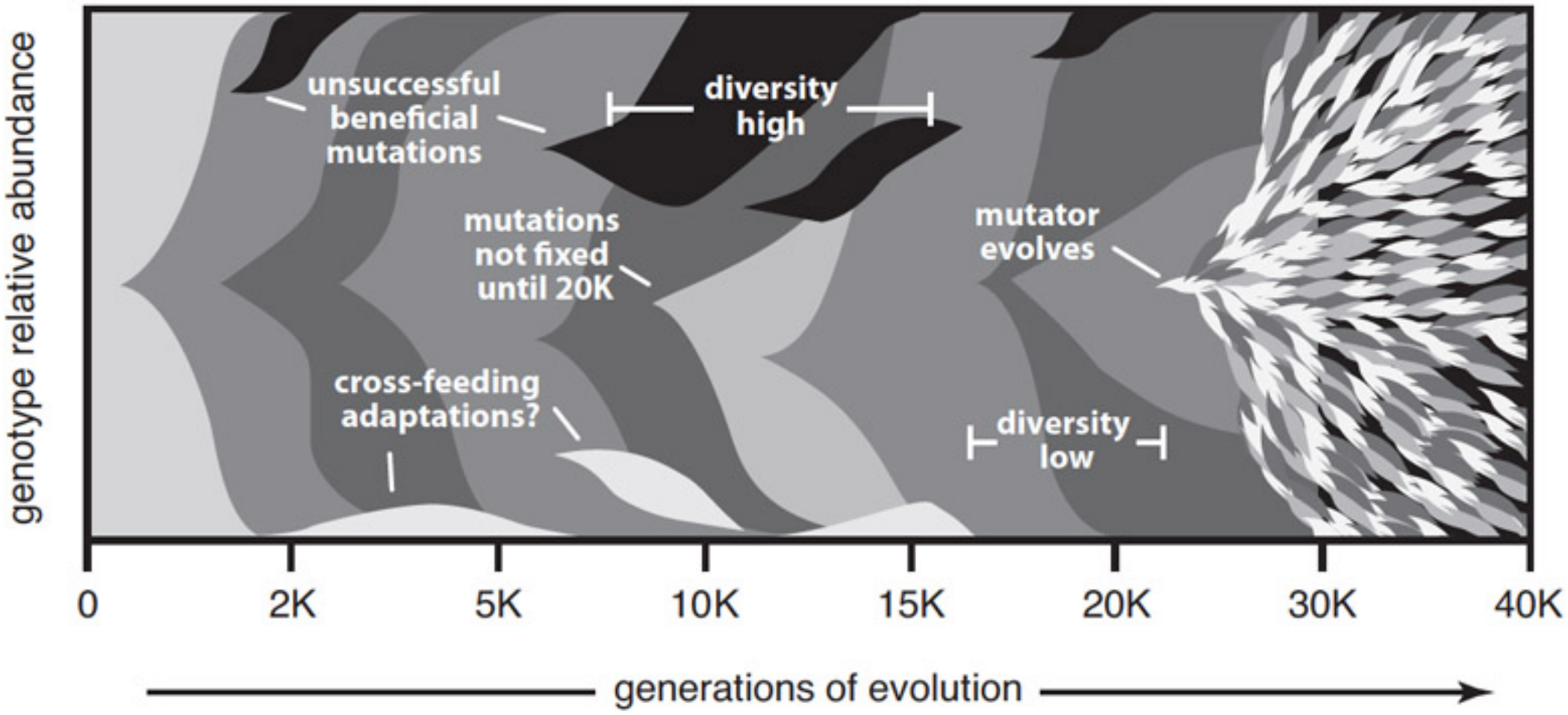
- Propose a random move (mutation)
- Accept or reject depending on relative energy (selection)
- However, biological populations can be very far from the thermodynamic limit of large N -> very noisy

Putting everything together: mutations trajectories over time



Trends in Genetics

Putting everything together: mutations trajectories over time

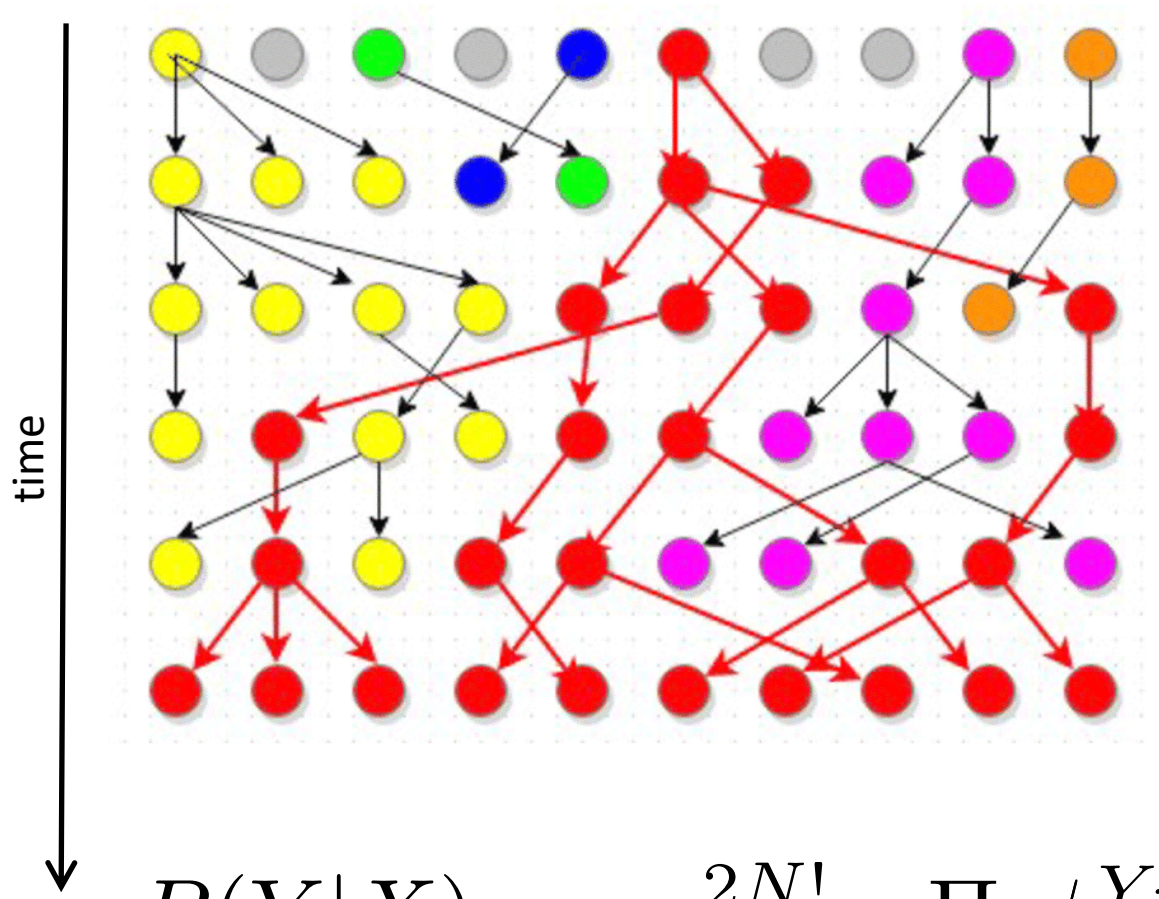


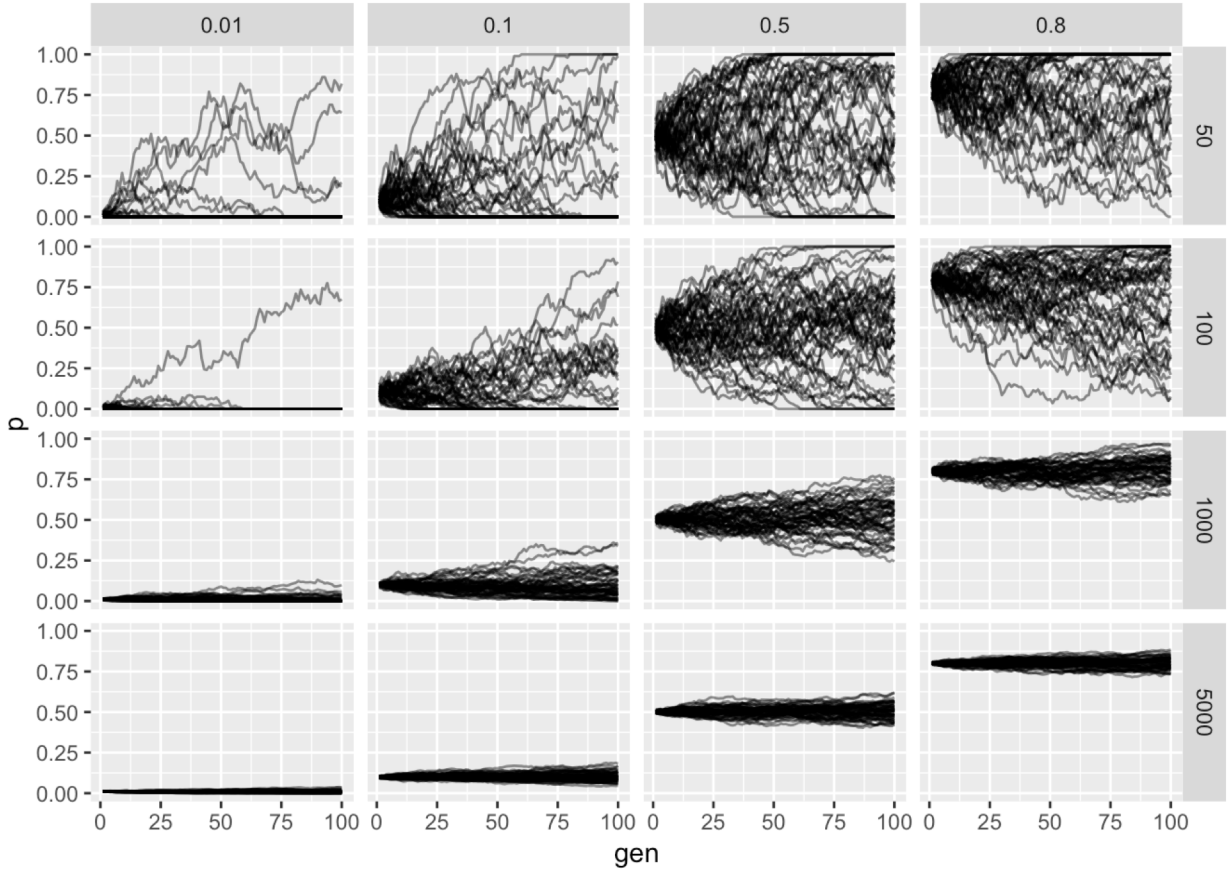
Lenski's Long Term Evolutionary Experiment (since 1988)

Some other basic terminology:

- Fixation: all the individuals in a population carry such mutation
- Establishment: the mutation frequency is beyond fluctuations and growing deterministically
- Extinction: the mutation has been purged from the population
- Lineage: tracing of an individual ancestor over time
- Coalescence: when two lineages become one (backwards in time). Equivalent to branching forward in time
- Time to most recent common ancestor: how many generations ago you can find the common ancestor to your current sample

Neutral models: Wright-Fisher model



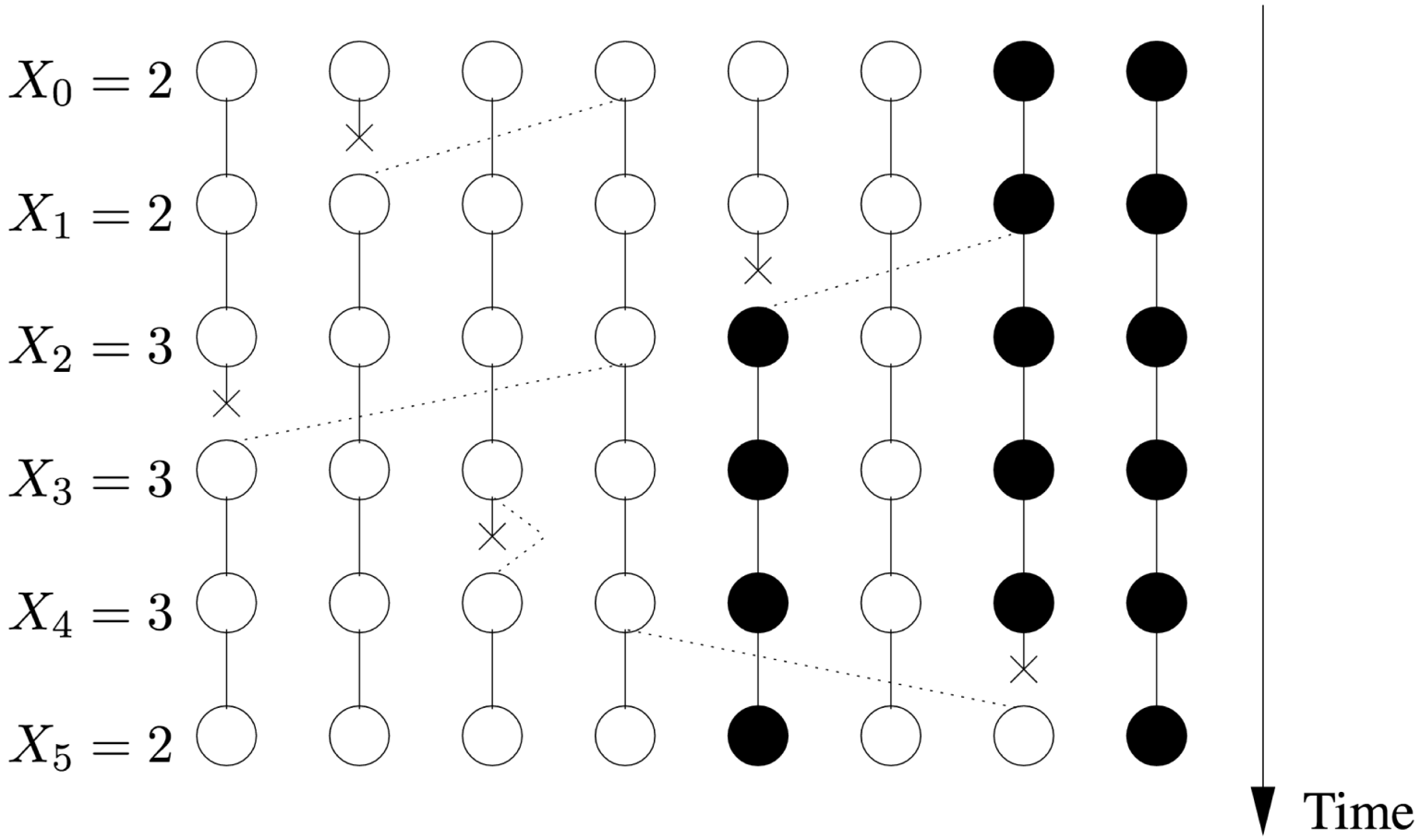


$$P(Y|X) = \frac{2N!}{Y_1!...Y_K!}\Pi_i \psi_i^{Y_i}$$

$$\psi_i = X_i/2N$$

Neutral models: Moran model

- Population has constant size N
- Generations can overlap
- At each time, two random individuals are chosen (they can be the same): one replicates, the other dies

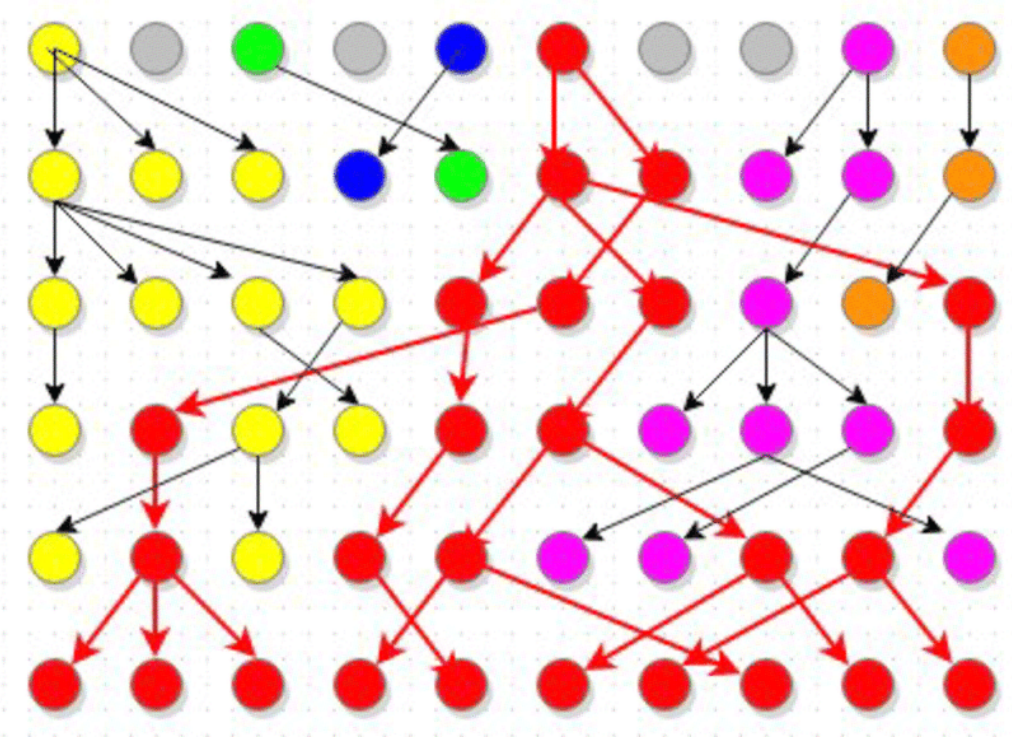


Loss of heterozygosity (Wright-Fisher model)

$$H_{t+1} = \frac{1}{2N} \times 0 + (1 - \frac{1}{2N}) H_t.$$

$$H_t = (1 - \frac{1}{2N})^t H_0$$

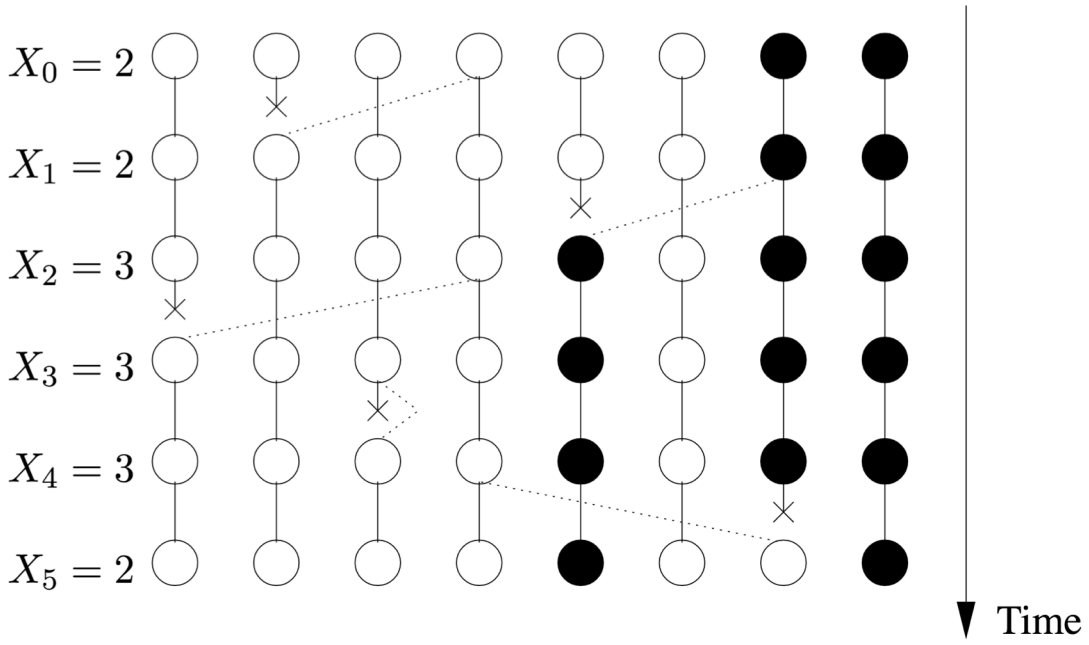
$$H_t = H_0 \exp(-\frac{t}{2N})$$



Heterozygosity in biallelic population (Moran model)

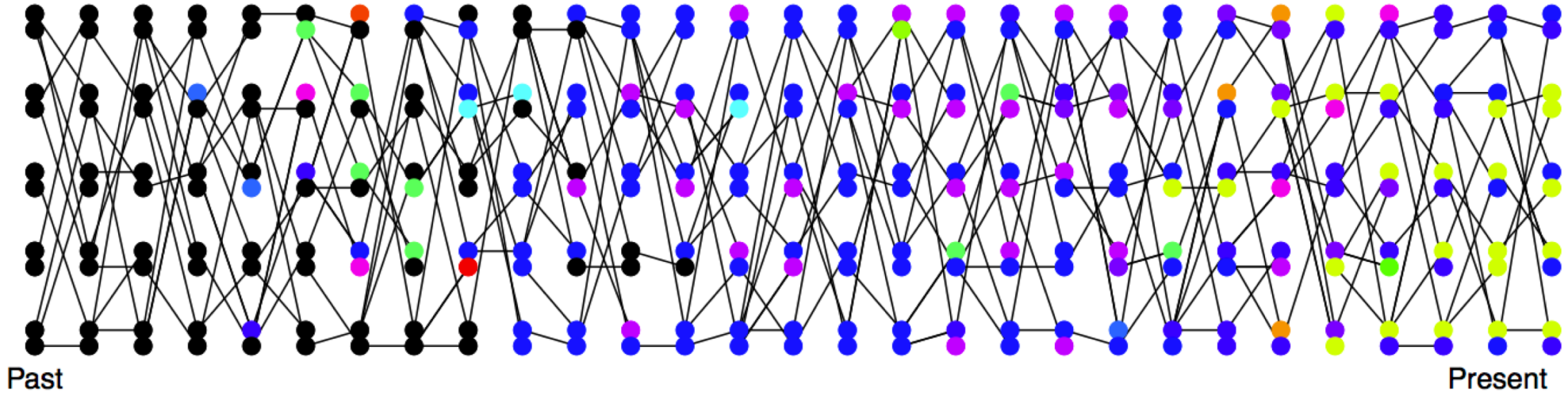
$$H_t = 2\frac{X_t}{M}\left(1 - \frac{X_t}{M}\right)$$

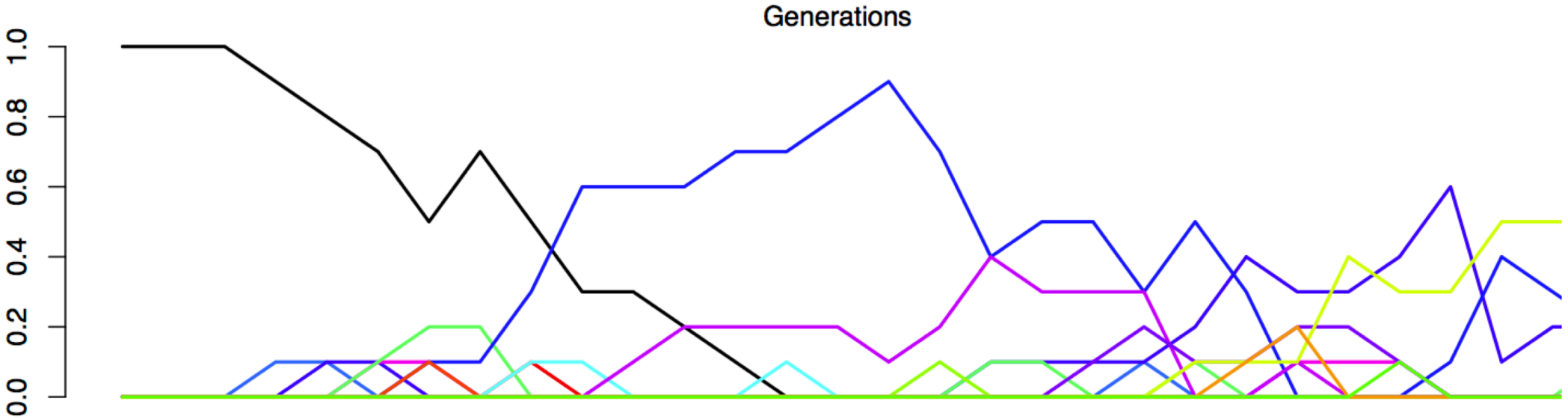
$$\begin{aligned}
\mathbb{E}(H_{t+1}) &= \frac{2}{M}\mathbb{E}\left(X_{t+1}\left(1 - \frac{X_{t+1}}{M}\right)\right) \\
&= \frac{2}{M}\left\{\mathbb{E}(X_{t+1}) - \frac{\mathbb{E}(X_{t+1}^2)}{M}\right\} \\
&= \frac{2}{M}\left\{\mathbb{E}(X_{t+1}) - \frac{\mathrm{var}(X_{t+1}) + \mathbb{E}(X_{t+1})^2}{M}\right\} \\
&= \frac{2}{M}\left\{X_t - 2\frac{X_t}{M^2} + 2\frac{X_t^2}{M^3} - \frac{X_t^2}{M}\right\} \\
&= H_t\left(1 - \frac{2}{M^2}\right)
\end{aligned}$$



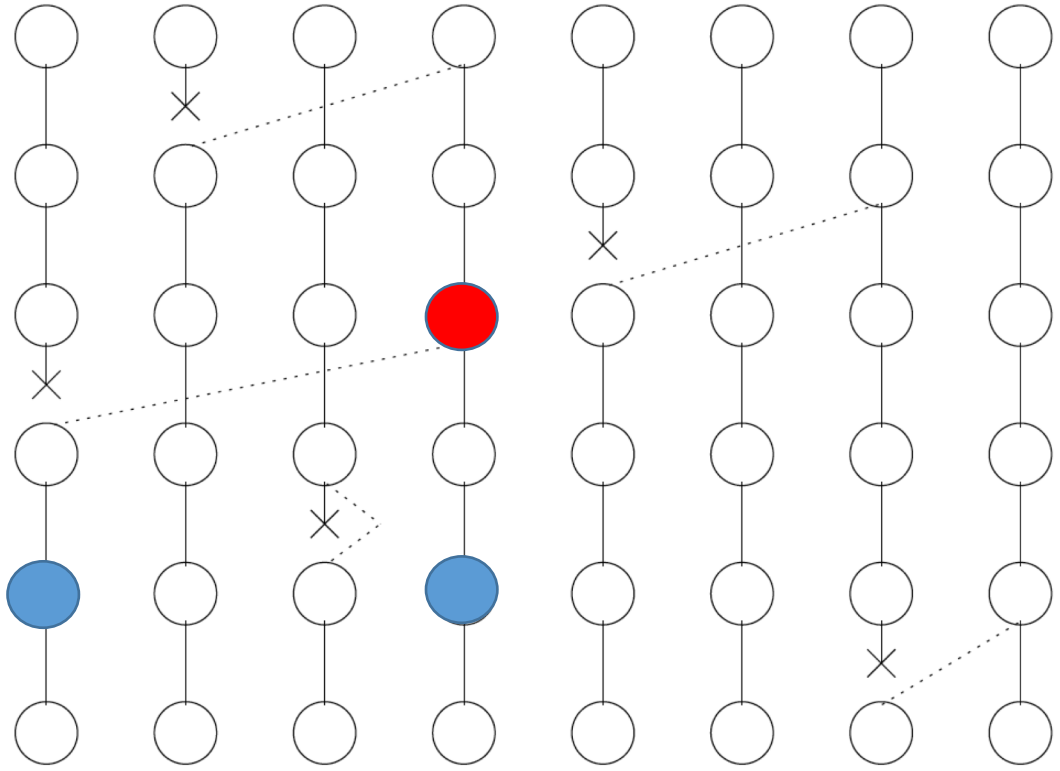
$$\mathbb{E}(H_t) = H_0\left(1 - \frac{2}{M^2}\right)^t \approx H_0 \exp(-2t/M^2)$$

Diversity maintained by mutations





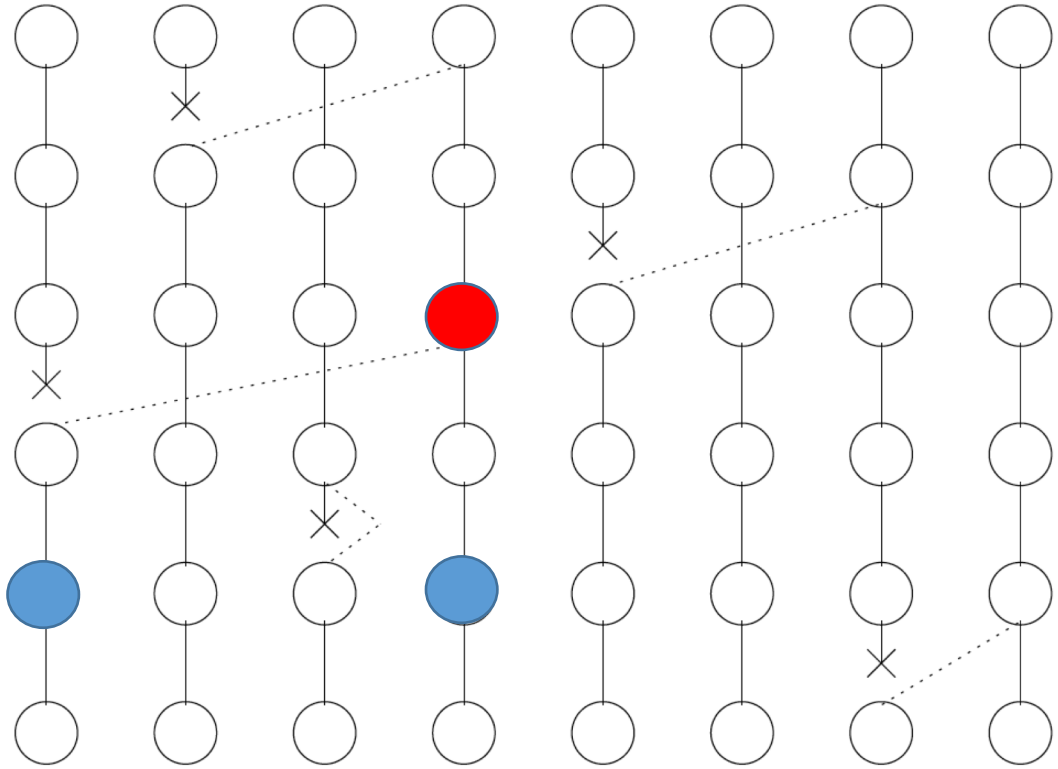
Diversity maintained by mutations



$$P_{\text{coal}} = (1 - \frac{1}{2N})\frac{1}{2N}(1-\mu)^4$$

Time

Diversity maintained by mutations



$$P_{\text{coal}} = (1 - \frac{1}{2N})\frac{1}{2N}(1-\mu)^4$$

$$P_{\text{coal}}(t+1) = \frac{1}{2N}(1-\frac{1}{2N})^t(1-\mu)^{2(t+1)}.$$

$$P_{\text{coal}}(t+1) = \frac{1}{2N}(1-\frac{1}{2N})^t(1-\mu)^{2t}.$$

$$P_{\text{coal}}(t+1) \approx \frac{1}{2N}\exp[-t(2\mu + 1/(2N))],$$

Time

Diversity maintained by mutations

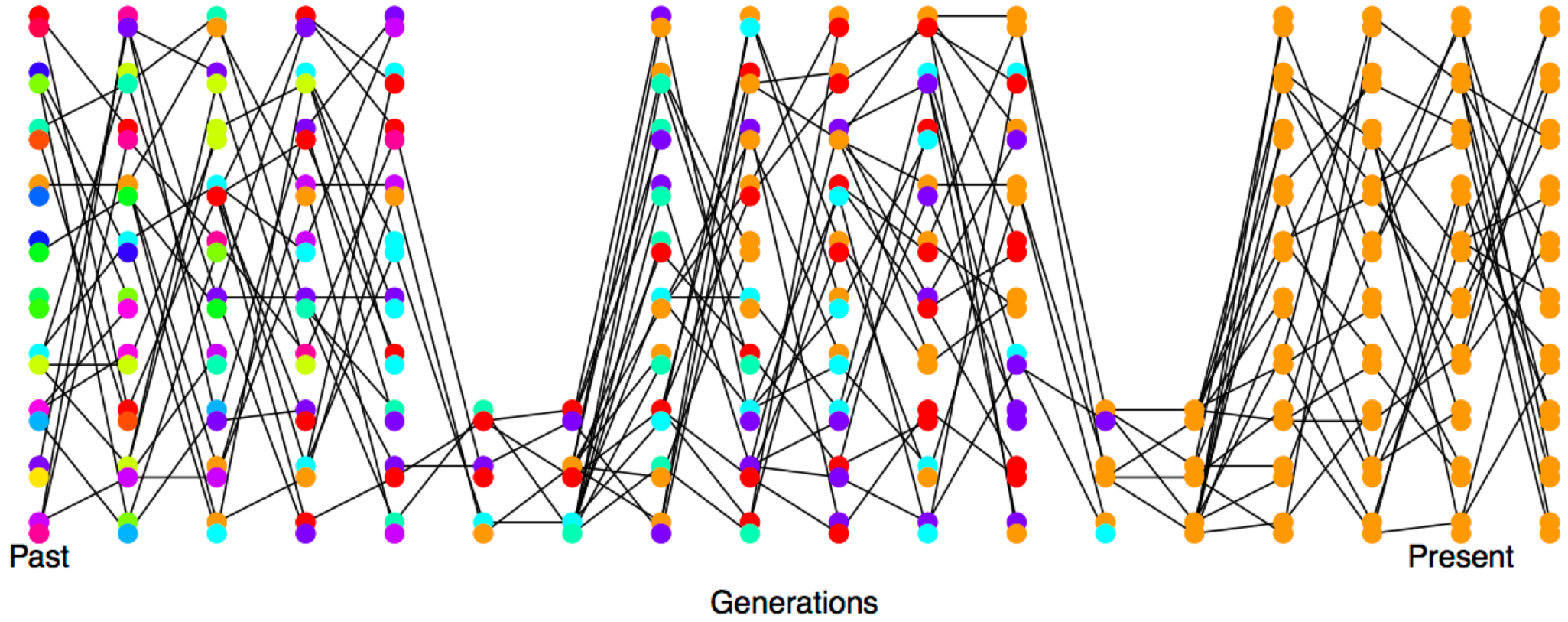
$$P_{\text{coal}}(t+1) \approx \frac{1}{2N} \exp[-t(2\mu + 1/(2N))],$$

$$P_{\text{coal}} = \sum_{t=1}^{\infty} P_{\text{coal}}(t)$$

$$P_{\text{coal}} \approx \frac{1}{2N} \int_0^{\infty} \exp[-t(2\mu + 1/(2N))]dt = \frac{1}{1+4N\mu}$$

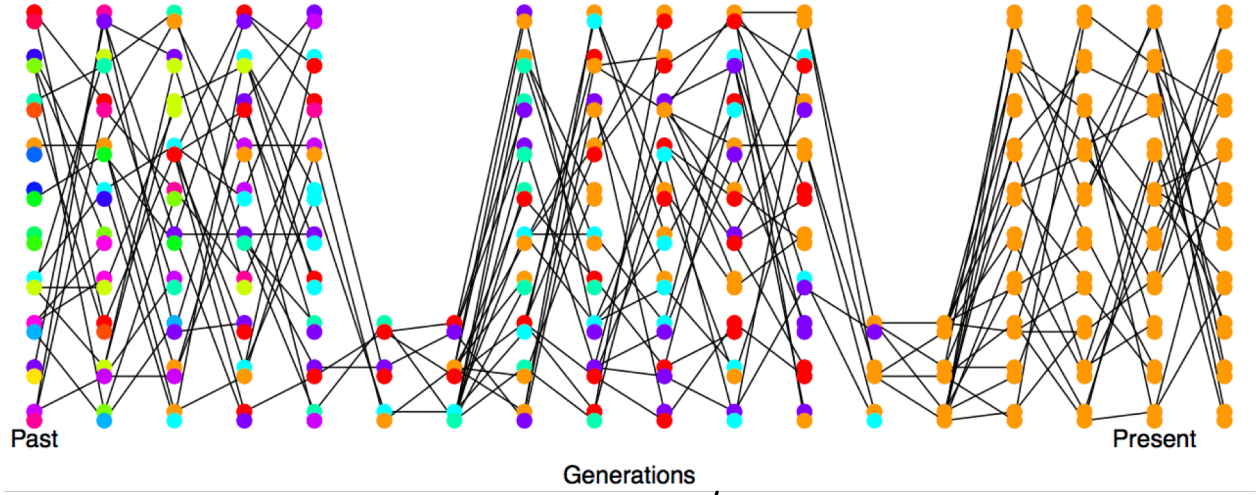
$$H = \frac{4N\mu}{1+4N\mu}.$$

Effective population size



In real populations often the noise is much higher than that predicted by the population size

Effective population size

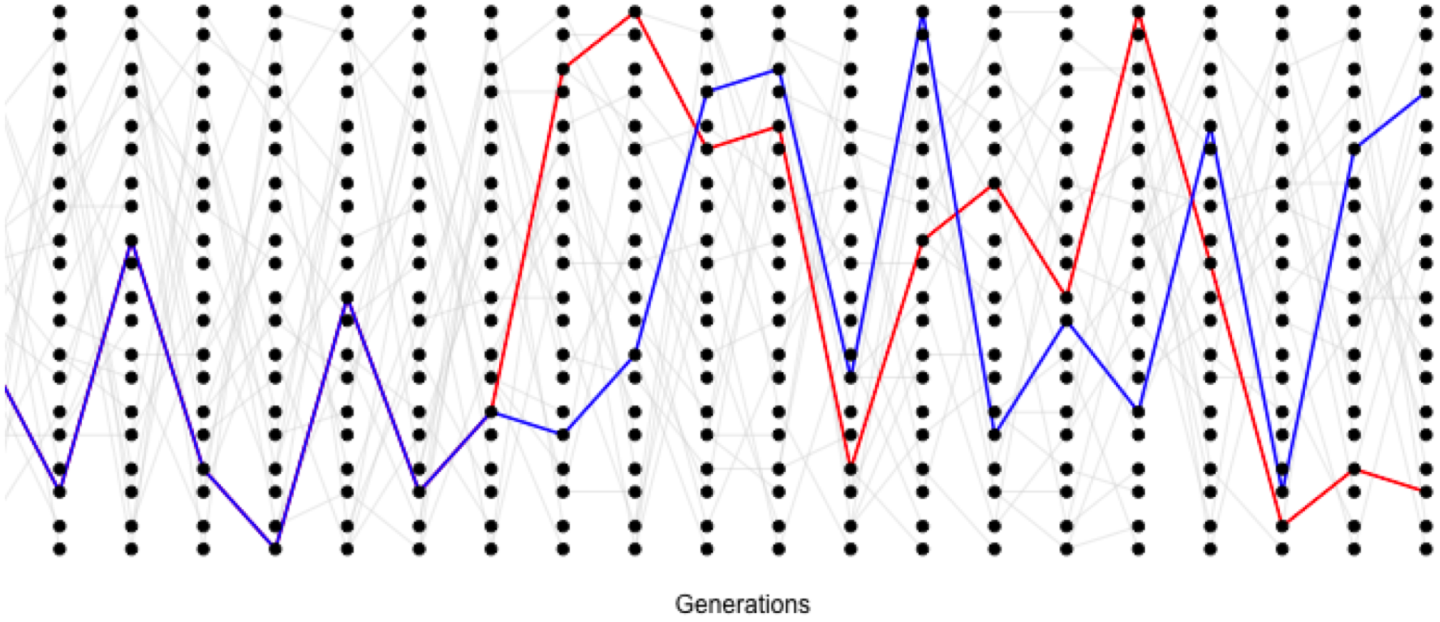


$$\prod_{i=1}^{t}(1-\frac{1}{2N_i}) \approx \Pi_{i=1}^{t} \exp(-1/2N_i) = \exp(-\sum_{i=1}^{t} 1/2N_i).$$

If we compare this exponent to the previous result: $H_t = H_0 \exp(-\frac{t}{2N})$

$$t/2N = \sum_{i=1}^{t} 1/2N_i \qquad N_e = \frac{1}{1/t\sum_{i=1}^{t} 1/N_i}$$

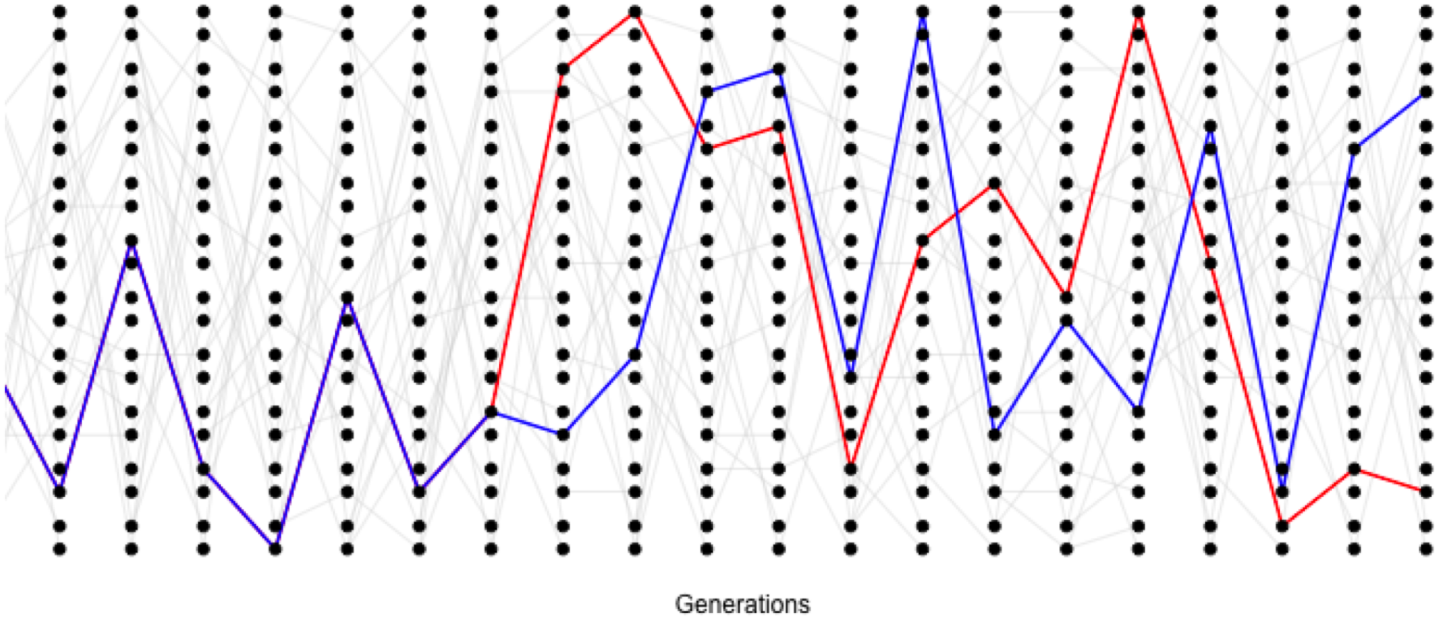
The coalescence and neutral diversity



$$\frac{1}{2N}(1-\frac{1}{2N})^t \approx \frac{1}{2N}e^{-t/2N}$$

Mutations can accumulate along the lineages since the coalescence event

The coalescence and neutral diversity



$$\frac{1}{2N}(1-\frac{1}{2N})^t \approx \frac{1}{2N}e^{-t/2N}$$

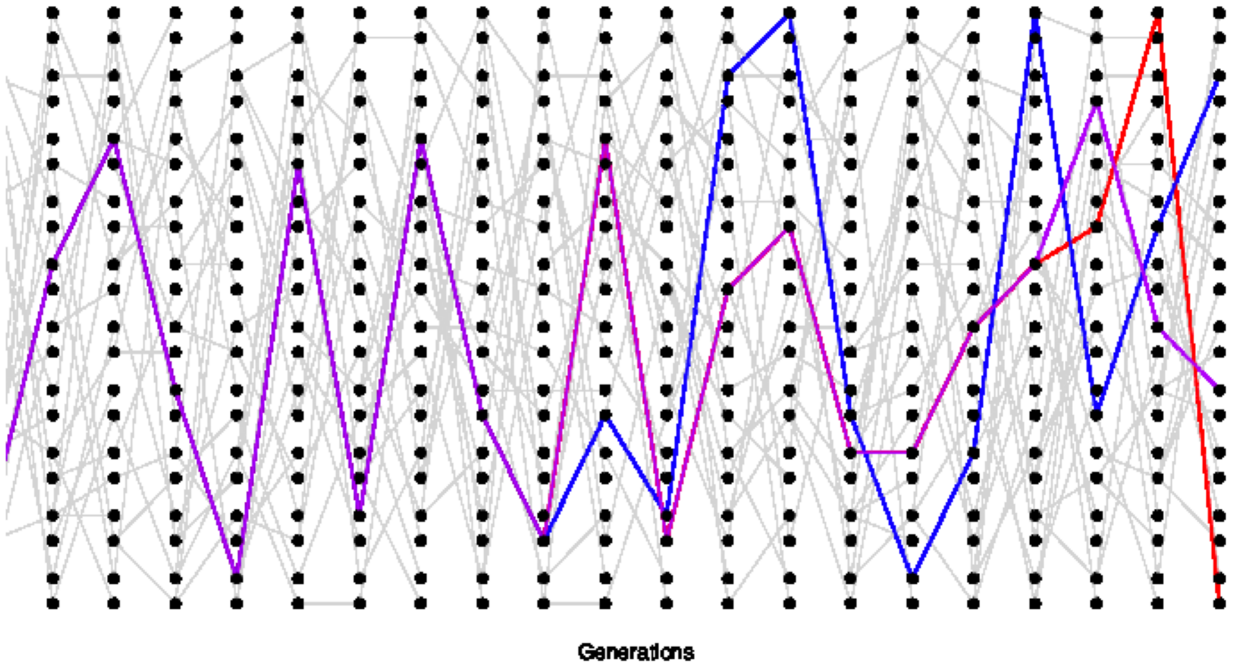
$$P(j|T_2=t) = \binom{2t}{j}\mu^j(1-\mu)^{2t-j} \approx \frac{(2\mu t)^j e^{-2\mu t}}{j!}$$

Mutations can accumulate along the lineages since the coalescence event

$$E(j) = 2\mu E(t) = 4N\mu = \theta$$

What is the variance?

The coalescence and neutral diversity



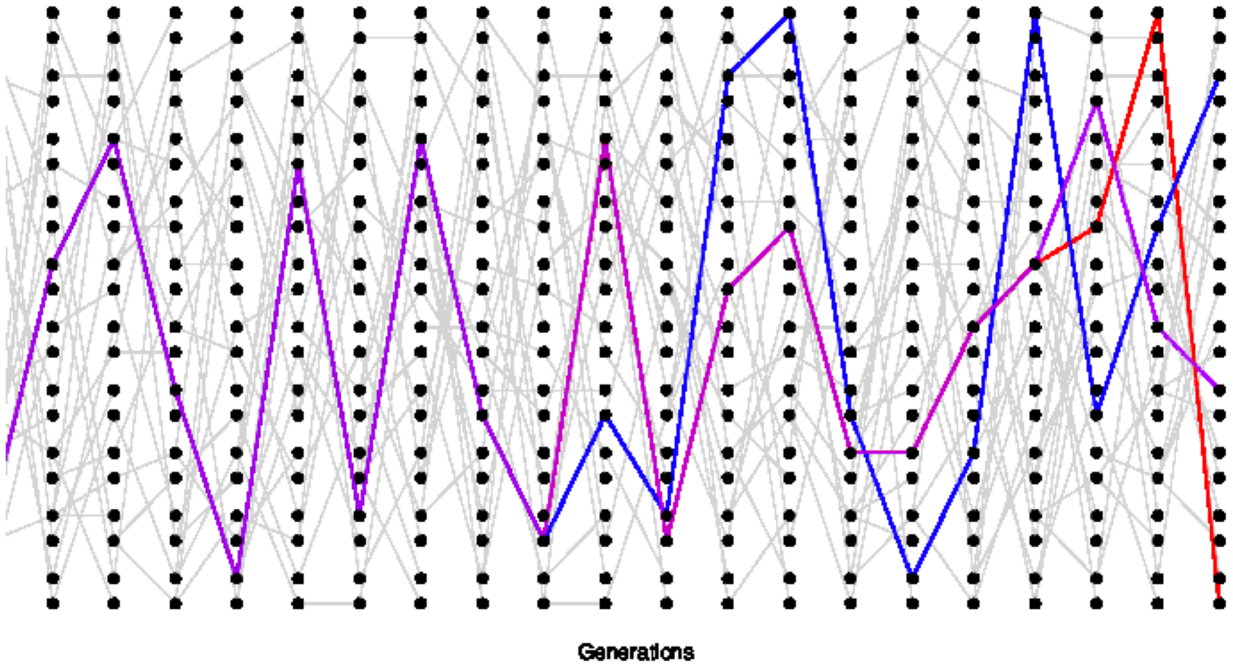
For a sample size i, you have $\binom{i}{2}$ pairs

Assuming N is large enough that you can have at most one coalescence event per generation

Probability of none of them coalescing $(1-\frac{1}{2N})^{\binom{i}{2}} \approx (1-\frac{\binom{i}{2}}{2N})$

$$P_{coal}(t+1) = \frac{\binom{i}{2}}{2N}(1-\frac{\binom{i}{2}}{2N})^t \approx \frac{\binom{i}{2}}{2N}\exp(-\frac{\binom{i}{2}}{2N}t)$$

The coalescence and neutral diversity



For a sample size i, you have $\binom{i}{2}$ pairs

Assuming N is large enough that you can have at most one coalescence event per generation

Probability of none of them coalescing $(1-\frac{1}{2N})^{\binom{i}{2}} \approx (1-\frac{\binom{i}{2}}{2N})$

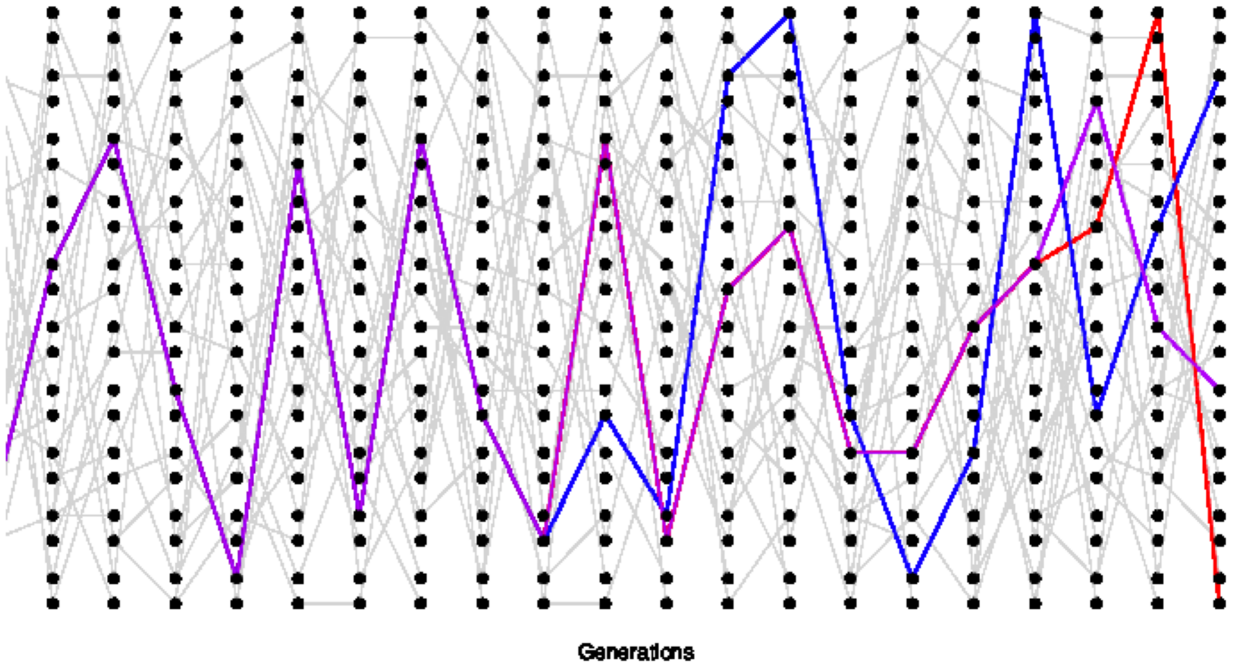
$$P_{coal}(t+1) = \frac{\binom{i}{2}}{2N}(1-\frac{\binom{i}{2}}{2N})^t \approx \frac{\binom{i}{2}}{2N}\exp(-\frac{\binom{i}{2}}{2N}t)$$

$$T_{MRCA} = \sum_{i=2}^{n} T_i.$$

$$E(T_{MRCA}) = \sum_{i=2}^{n} E(T_i) = \sum_{i=2}^{n} \frac{2N}{\binom{i}{2}} = 4N(1-\frac{1}{n})$$

Try to prove it as an exercise

The coalescence and neutral diversity



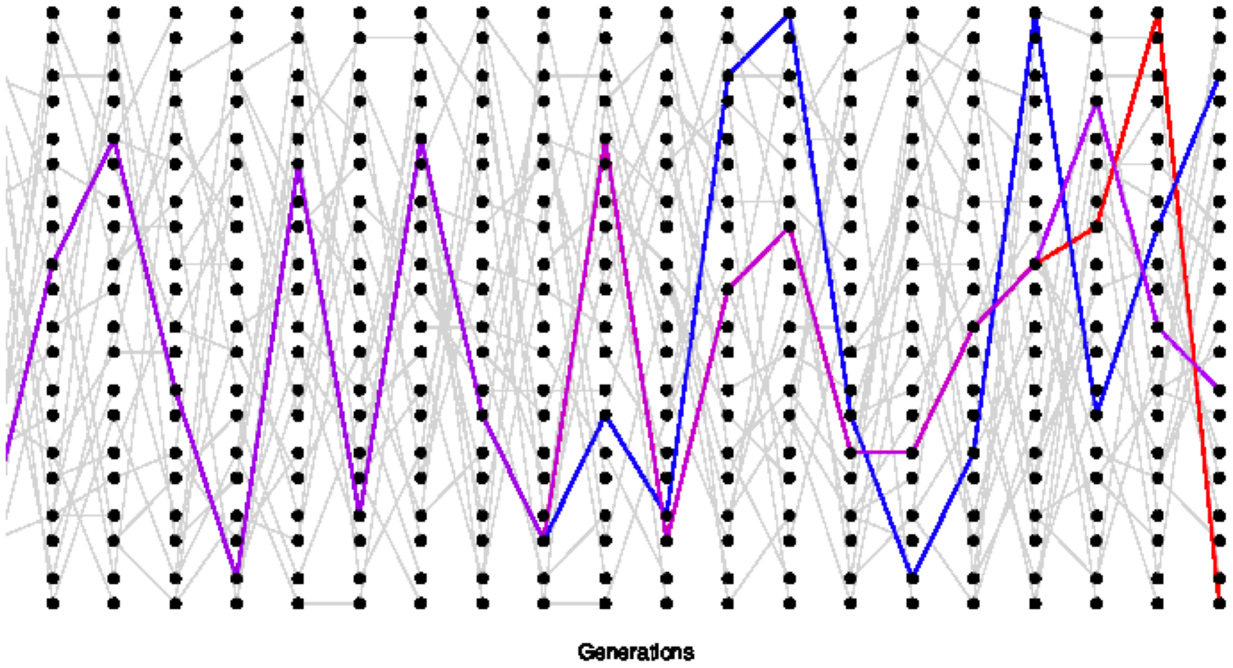
Mutations accumulate along the lineages

$$T_{tot} = \sum_{i=2}^{n} iT_i$$

$$E(T_{tot}) = \sum_{i=2}^{n} i\frac{2N}{\binom{i}{2}} = \sum_{i=2}^{n} \frac{4N}{i-1} = \sum_{i=1}^{n-1} \frac{4N}{i},$$

$$\approx 4N \int_1^{n-1} \frac{di}{i} = 4N \log(n-1)$$

The coalescence and neutral diversity



Mutations accumulate along the lineages

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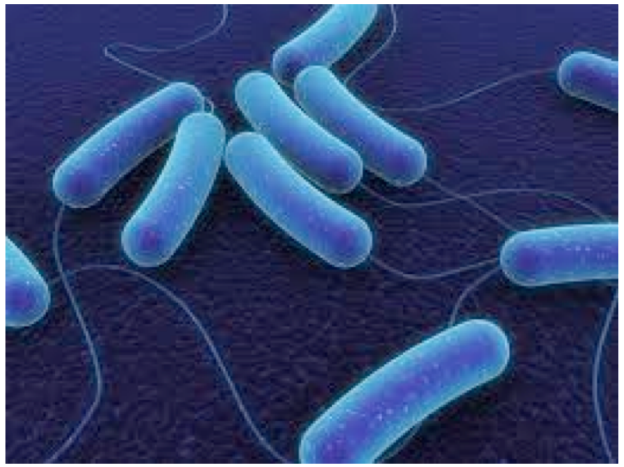
For large sample size n

$$E(S) = \mu E(T_{tot}) = \sum_{i=1}^{n-1} \frac{4N\mu}{i} = \theta \sum_{i=1}^{n-1} \frac{1}{i}.$$

What do we understand so far?
The gold standard of well-mixed populations

- In well-mixed population each individual feels the same environment (mean-field approximation is appropriate)
- Chance of survival of an individual only depends on average parameters
- Noise affects everyone at the same level

Genetic diversity in a well-mixed population: 1943 – Luria and Delbrück experiment

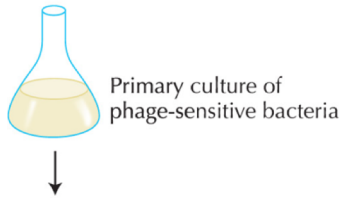




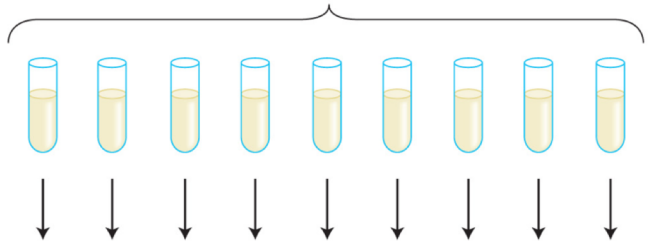
- Induced:
  Occurring **as a result** of stress
- Spontaneous:
  Occurring **at random** and selected for afterwards

Luria, Salvador E., and Max Delbrück. *Genetics* 28.6 (1943): 491.

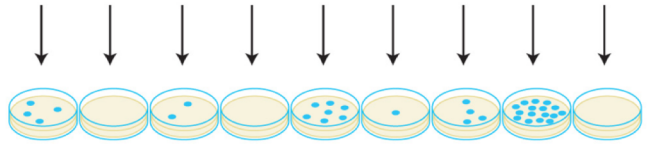
Luria-Delbrück Experiment



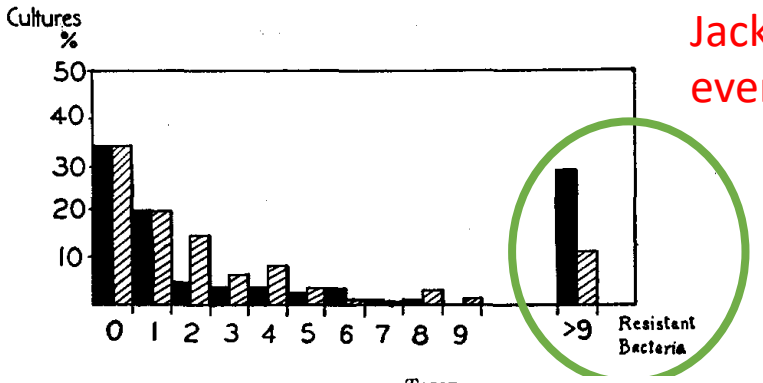
Inoculate O(100) secondary cultures



Inoculate samples into agar medium containing phage



Phage-resistant colonies from samples
of individual secondary cultures



Jackpot events!

TABLE 3

Distribution of the numbers of resistant bacteria in series of similar cultures.

EXPERIMENT NO.	22		23	
Number of cultures	100		87	
Volume of cultures, cc	.2*		.2*	
Volume of samples, cc	.05		.2	
	Resistant bacteria	*Number of cultures*	*Resistant bacteria*	*Number of cultures*
	0	57	0	29
	1	20	1	17
	2	5	2	4
	3	2	3	3
	4	3	4	3
	5	1	5	2
	6– 10	7	6– 10	5
	11– 20	2	11– 20	6
	21– 50	2	21– 50	7
	51– 100	0	51– 100	5
	101– 200	0	101– 200	2
	201– 500	0	201– 500	4
	501–1000	1	501–1000	0
Average per sample	10.12		28.6	
Variance (corrected for sampling)	6270		6431	
Average per culture	40.48		28.6	
Bacteria per culture	2.8×10^{8}		2.4×10^{8}	
Mutation rate	2.3×10^{-8}		2.37×10^{-8}	
Standard deviation / Average (exp.)	7.8		2.8	
Standard deviation / Average (calc.)	1.5		1.5	

* Cultures in synthetic medium.

Induced mutations -> Narrow-tail distribution

$\mu = 0$ Mutation rate before stress application

$\mu > 0$ Mutation rate after stress application

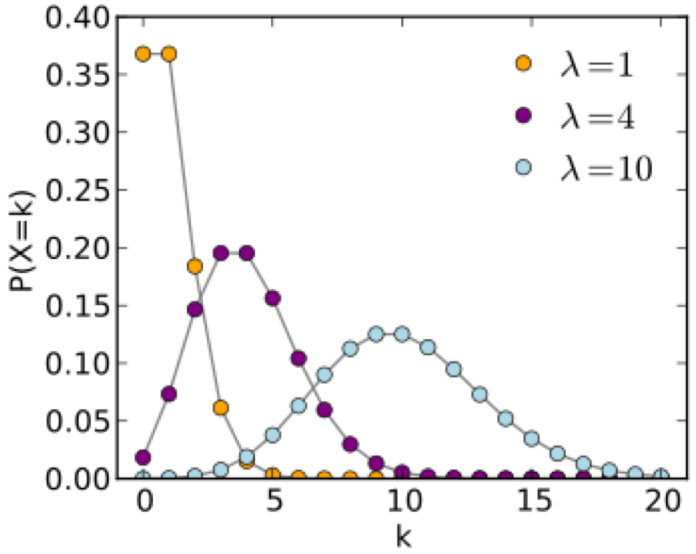
The probability of observing X colonies is Poisson distributed with mean $\lambda = \mu N t_c$

Population size

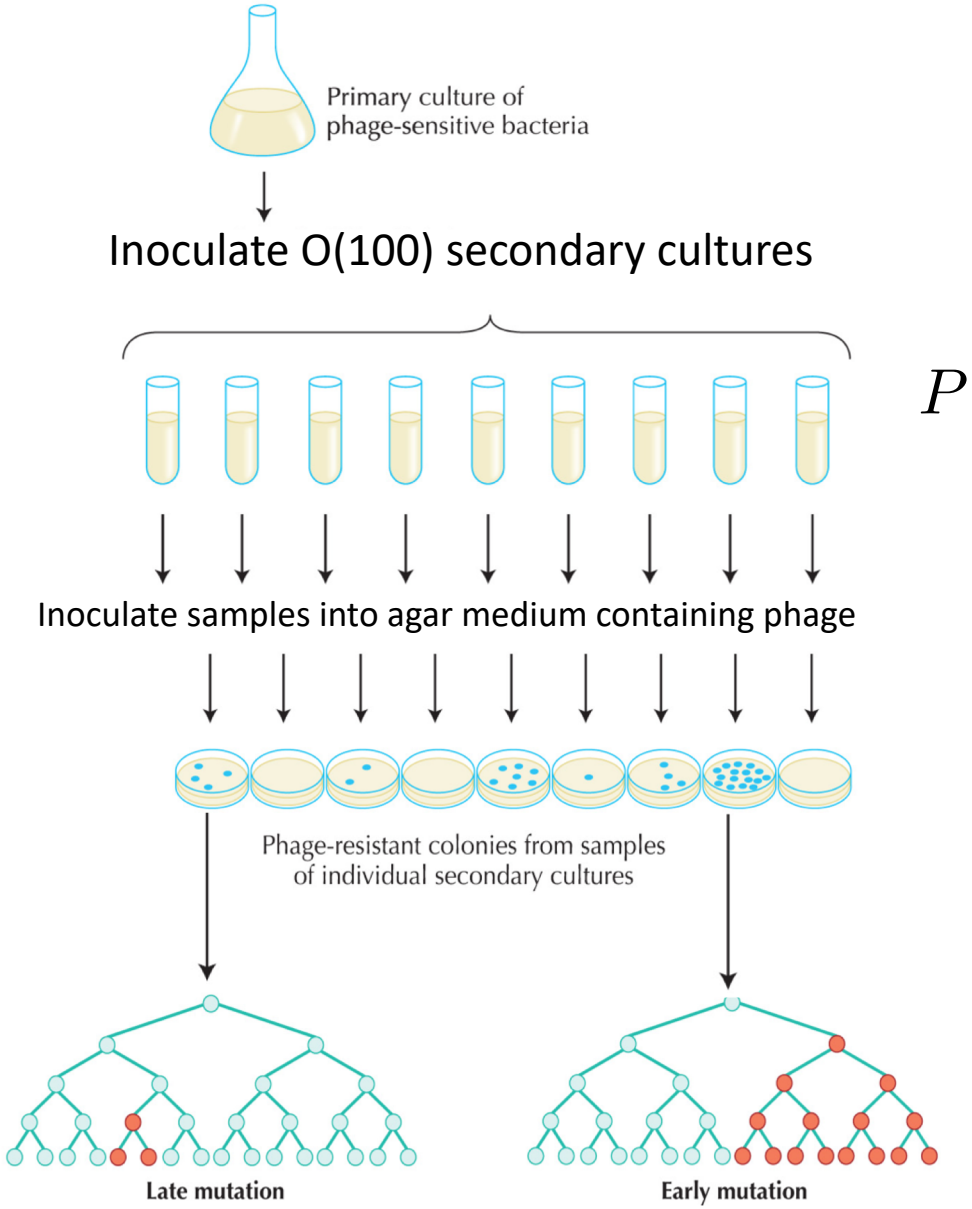
Reaction time

$$P(X = k) = \frac{e^{-\lambda}\lambda^k}{k!}$$

No jackpot events!



Spontaneous mutations -> Long-tail distribution



$$X = N_m/N$$ Stochastic variable: proportion of mutants in the population

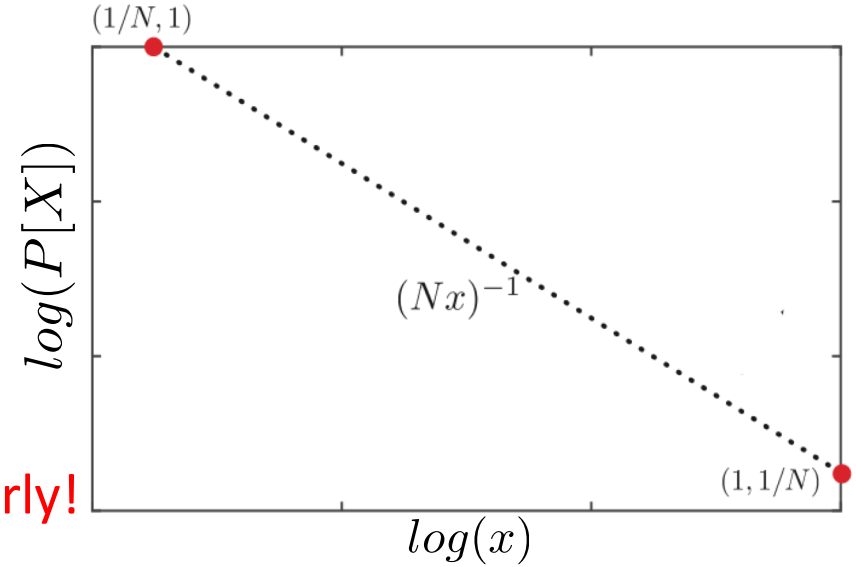
$$= 2^{T-t}/N = 2^{-t} = 1/n(t)$$

$P(X \geq 1/n) =$ P[Mutation arises before population reaches size n]

P[Mutation arises in one of the first n cell divisions]

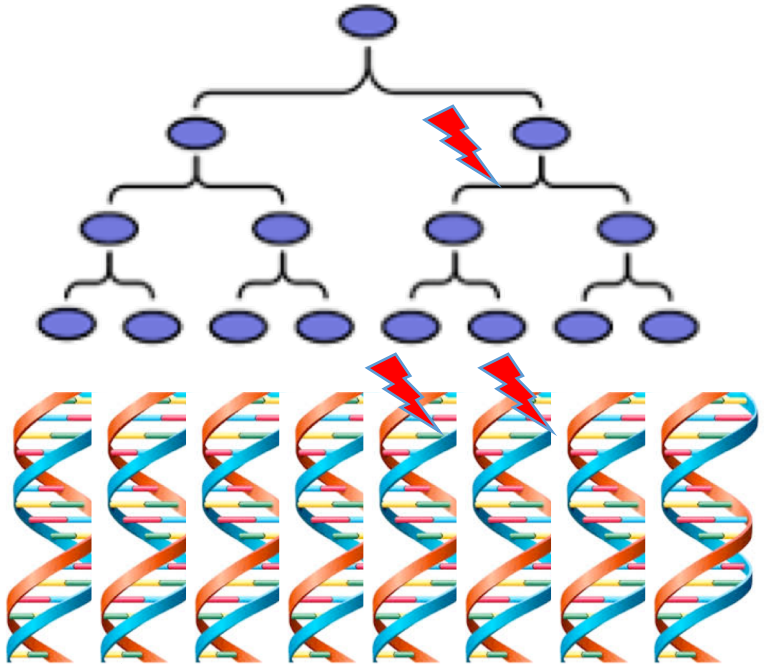
$$= \frac{\mu n}{N}$$

Probability that a mutation has frequency > x



Jackpot events are mutations that occur early!

Getting mutation distribution via sequencing



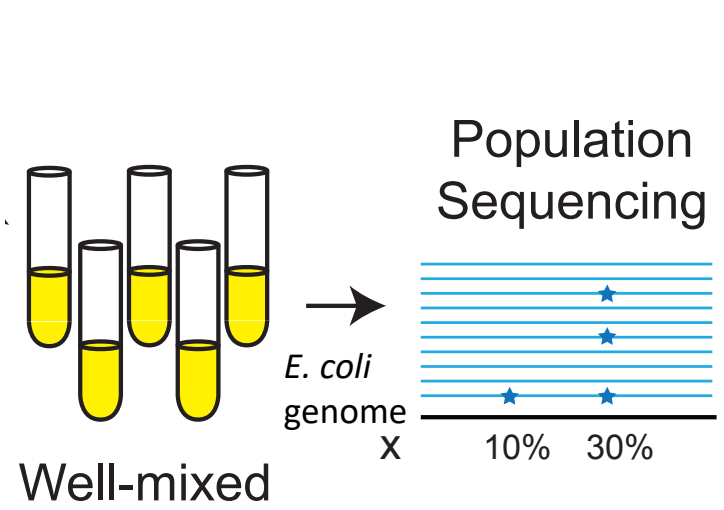
AGGTAGCGTTAGTCAG

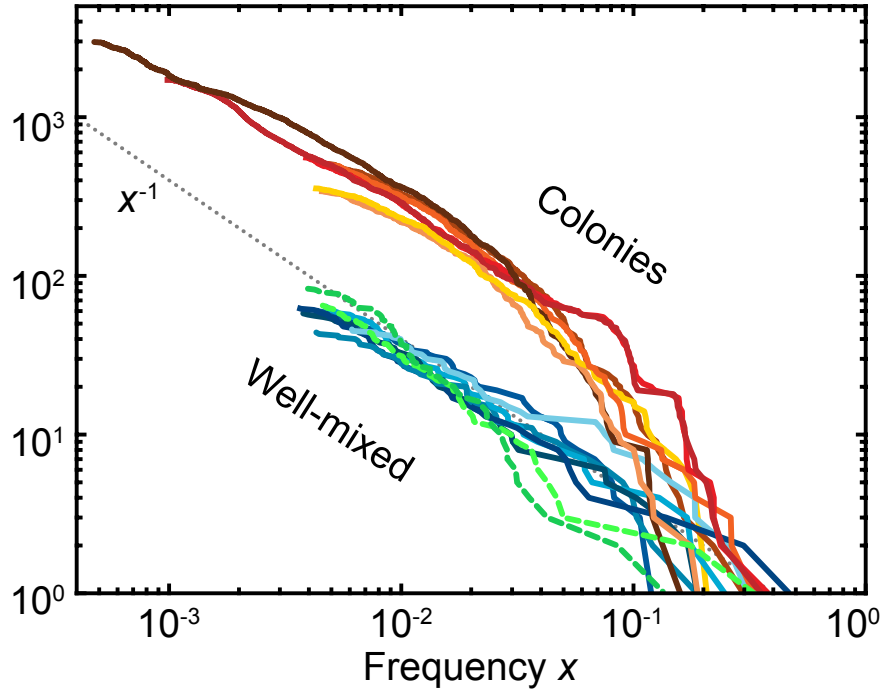
AGGTAGCGTTAGTCAG
AGGTAGCGTTAGTCAG
AGGTAGCGTTAGTCAG
AGGTAGCGTTAGTCAG
AGGTAGCGTTAGTGAG
AGGTAGCGTTAGTGAG
AGGTAGCGTTAGTCAG
AGGTAGCGTTAGTCAG

X=25%

- Check many mutations at once
- Limits in the resolution (min. frequency)
  - Coverage=10^{10}/Genome Length
  - Sequencing errors

Getting mutation distribution via sequencing





Fusco et al., *Nat. Comm.* (2016)

Introducing selection

S is the growth advantage of the mutant compared to non-mutants

$$X = N_m/N = 2^{(1+s)(T-t)}/N \propto [2^{-t}]^{1+s} = 1/n(t)^{1+s}$$

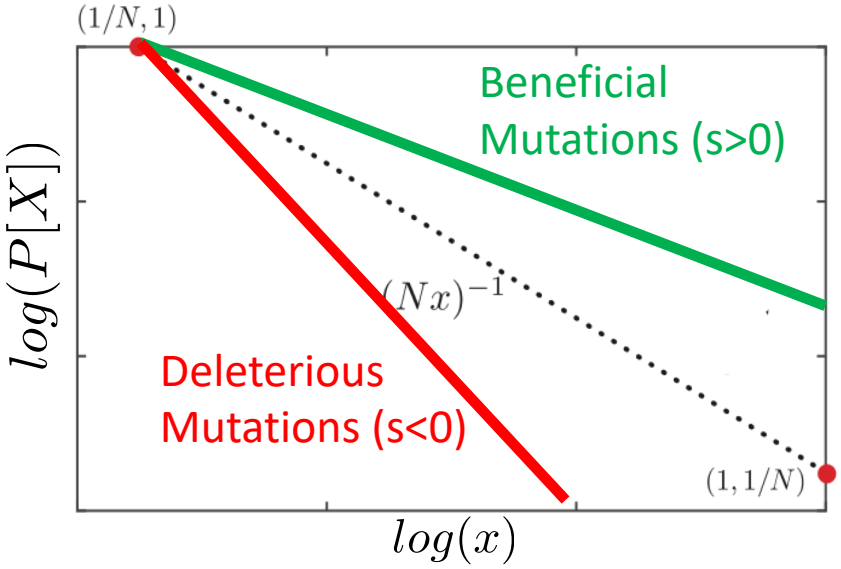
$$P[X \geq 1/n^{1+s}] \propto \frac{n}{N}$$

$$P[X \geq x] \propto x^{-\frac{1}{1+s}} \approx x^{-1+s}$$

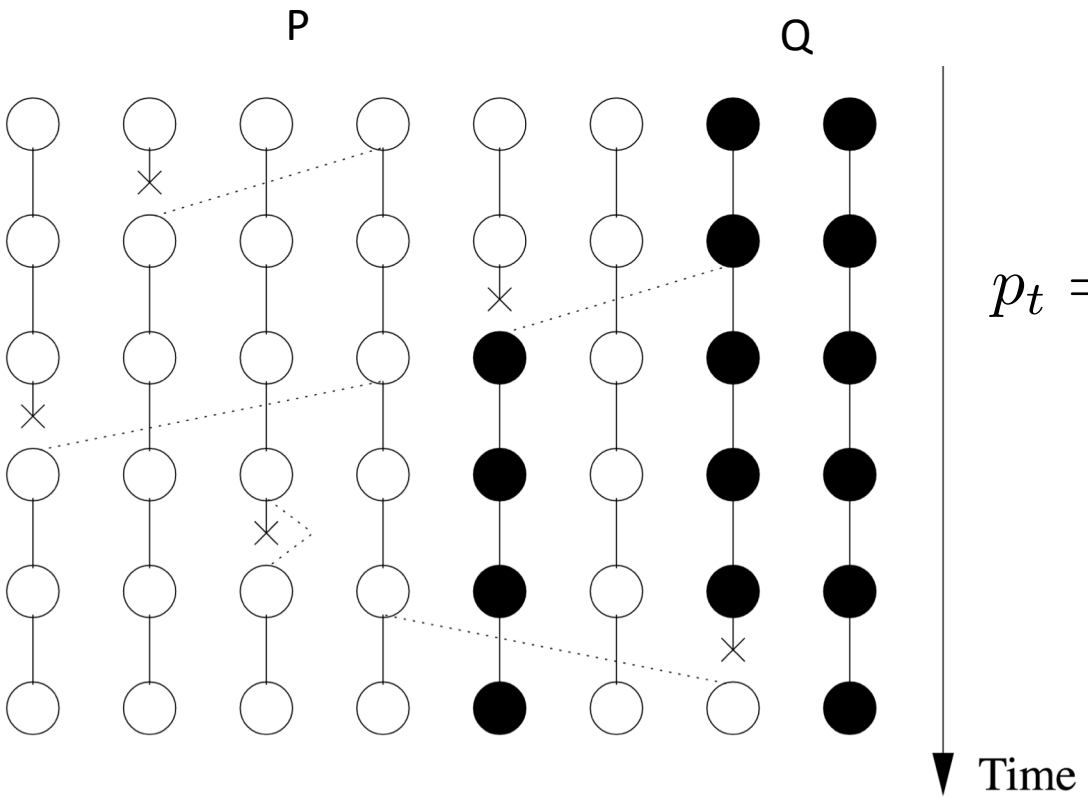
In well-mixed populations, we have a theory that allows to estimate:

- Mutation rate
- Selection effects

Probability that a mutation has frequency > x



Selection: changes in replication rate



P generates on average W1 offspring per generation
Q generates on average W2 offspring per generation

$$P_{t+1} = W_1 P_t \text{ and } Q_{t+1} = W_2 Q_t$$

$$p_t = P_t/(P_t + Q_t) \text{ and } q_t = Q_t/(P_t + Q_t) = 1 - p_t$$

Mean fitness as function of time

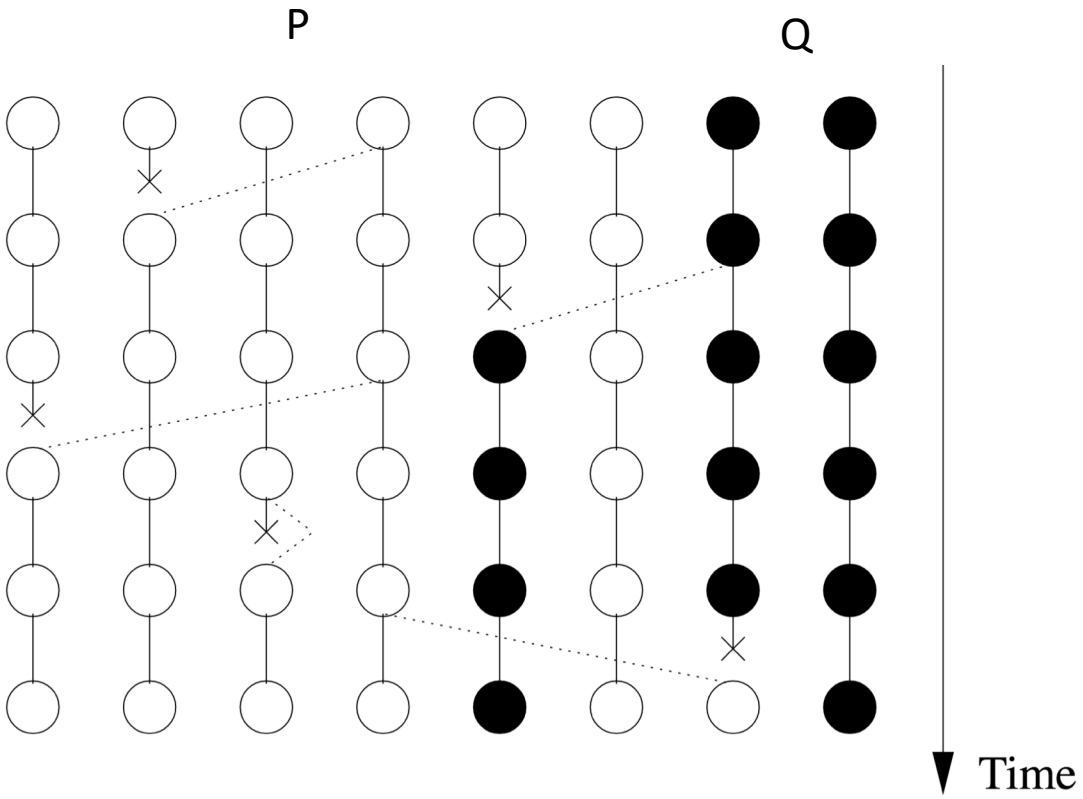
$$\overline{W_t} = W_1 p_t + W_2 q_t,$$

$$p_{t+1} = \frac{P_{t+1}}{P_{t+1} + Q_{t+1}} = \frac{W_1}{\overline{W_t}} p_t = \frac{w_1}{\overline{w}} p_t$$

Fitness can be defined up to a multiplicative constant

$$w_i = W_i/W_1$$

Selection: changes in replication rate



$$p_{t+1} = \frac{P_{t+1}}{P_{t+1} + Q_{t+1}} = \frac{W_1}{\overline{W}_t} p_t = \frac{w_1}{\overline{w}} p_t$$

$$\Delta p_t = p_{t+1} - p_t = \frac{w_1 p_t}{\overline{w}} - p_t = \frac{w_1 - w_2}{\overline{w}} p_t q_t.$$

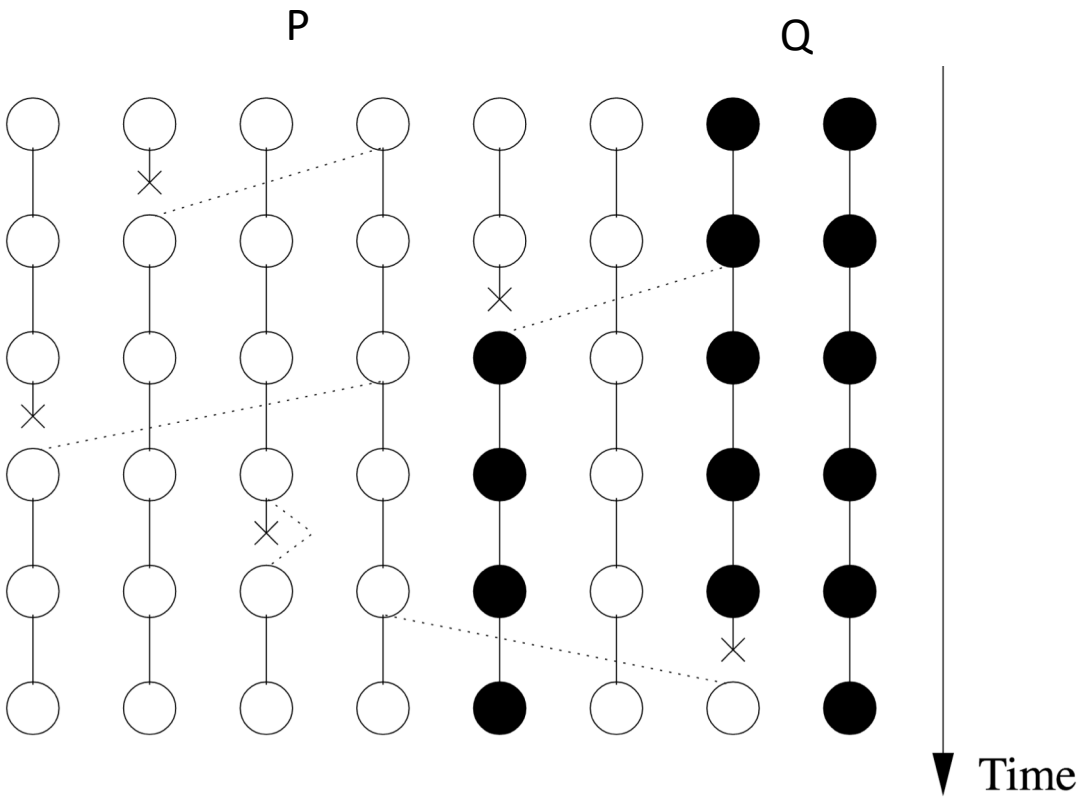
$$p_{t+\tau} = \frac{p_t}{p_t + (w_2/w_1)^\tau q_t}.$$

$$p_\tau = \frac{p_0}{p_0 + (w_2/w_1)^\tau q_0}$$

Often the parameterization w_2/w_1=1-s is used

$$p_\tau = \frac{p_0}{p_0 + (1-s)^\tau q_0}$$

Selection: changes in replication rate



$$p_\tau = \frac{p_0}{p_0 + (1-s)^\tau q_0}$$

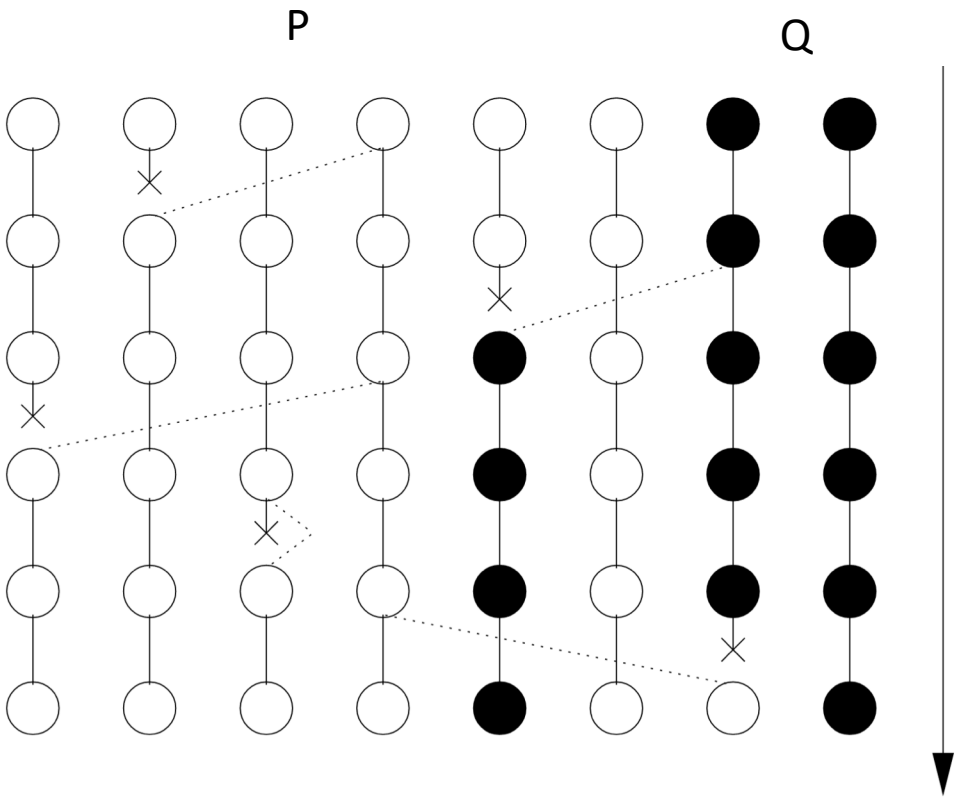
$$\tau = -\log(\frac{p_\tau q_0}{q_\tau p_0}) / \log(1-s) \approx \frac{1}{s}\log(\frac{p_\tau q_0}{q_\tau p_0})$$

For small s

How long it takes for a new mutation to fix?

$$\tau \approx \frac{2}{s}\log(N).$$

Interplay between selection and drift (strong selection)



Number of offspring is Poisson distributed

$$P_i = \frac{(1+s)^i e^{-(1+s)}}{i!}.$$

Probability of loss of the beneficial mutation

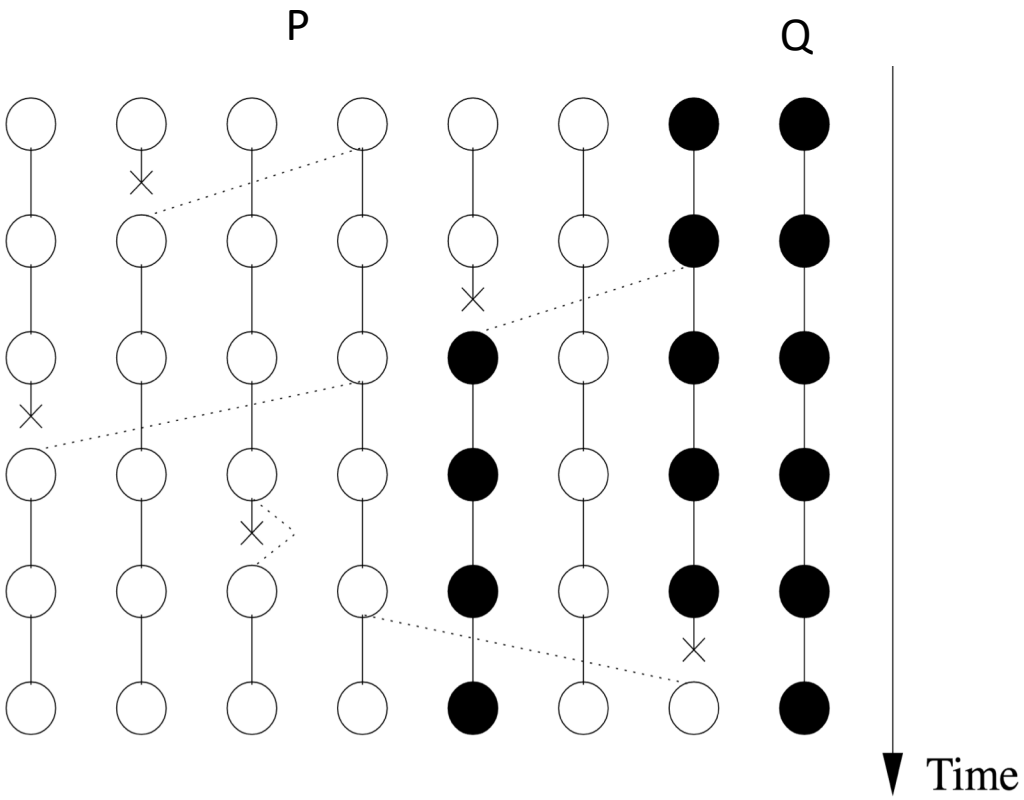
$$P_L = \sum_{k=0}^{\infty} P_k P_L^k = e^{-(1+s)} \left(\sum_{k=0}^{\infty} \frac{(P_L(1+s))^k}{k!} \right) = e^{(1+s)(P_L-1)}$$

Probability of not losing the beneficial mutation

$$1 - P_F = e^{-P_F(1+s)} \approx 1 - P_F(1+s) + P_F^2(1+s)^2/2$$

$$P_F = 2s$$ For small s

Interplay between selection and drift (weak selection)



Assume deterministic change from one generation to the next and then binomial sampling (small s, diploid population)

$$E(\Delta p) = sp(1-p) \qquad \Delta p = p' - p$$

$$Var(\Delta p) = Var(p' - p) = Var(p') = \frac{p'(1-p')}{2N} \approx \frac{p(1-p)}{2N}$$

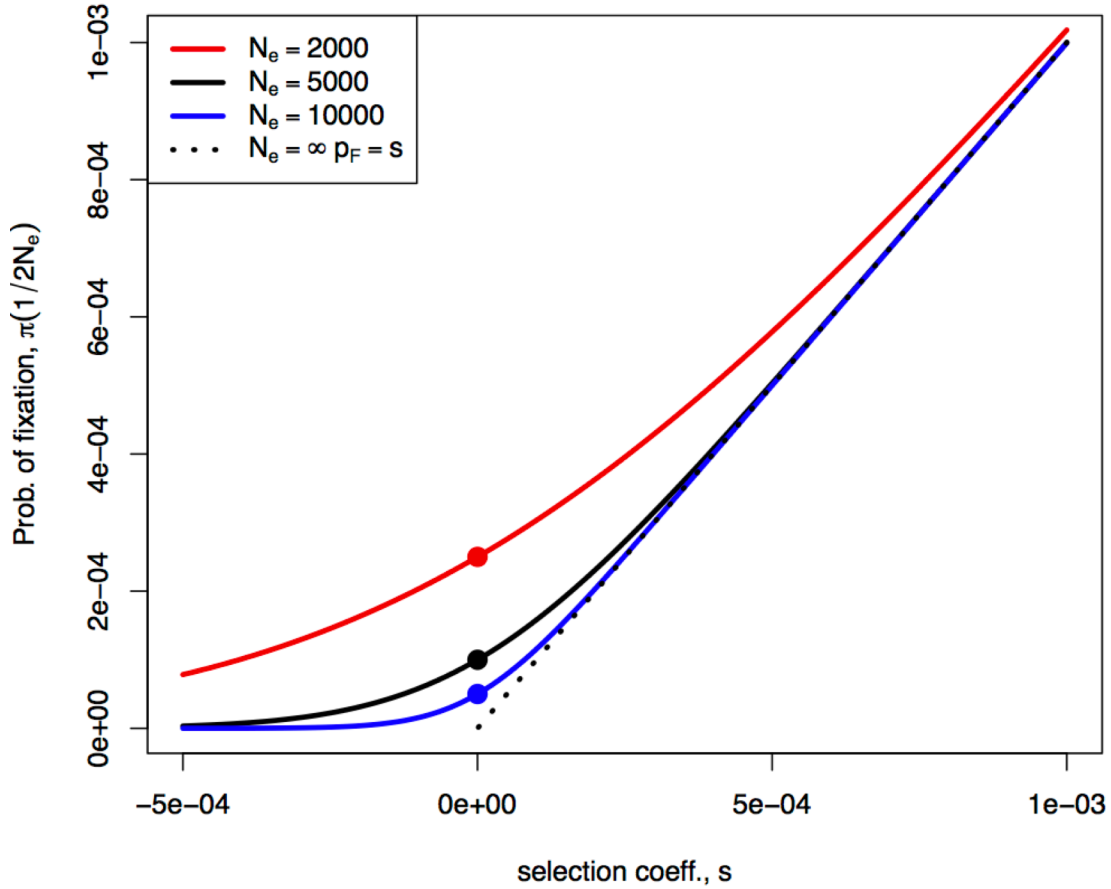
If Ns<<1, drift dominates, otherwise selection does

Probability that allele will eventually fix

$$\pi(p) = \frac{1 - e^{-2Nsp}}{1 - e^{-2Ns}}.$$

Try to prove as exercise

Interplay between selection and drift (weak selection)

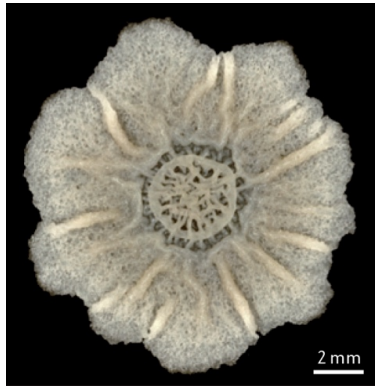


Fixation of beneficial and deleterious mutations (starting at frequency 1/2N)

$$\pi(1/2N) = \frac{1 - e^{-s}}{1 - e^{-2Ns}}.$$

$$\pi(1/2N) \approx \frac{s}{e^{2Ns} - 1}$$

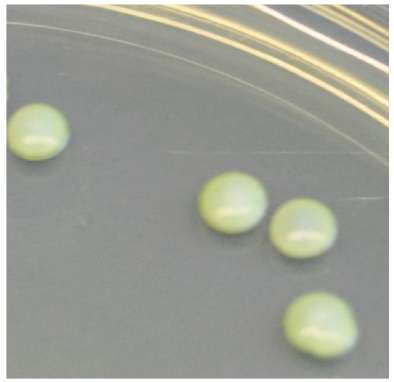
Beyond well-mixed: the role of space



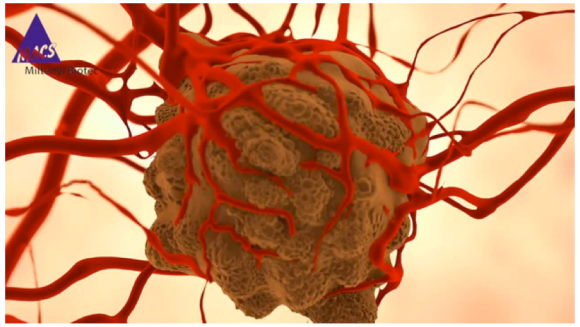
Biofilms

(Bacillus subtilis)

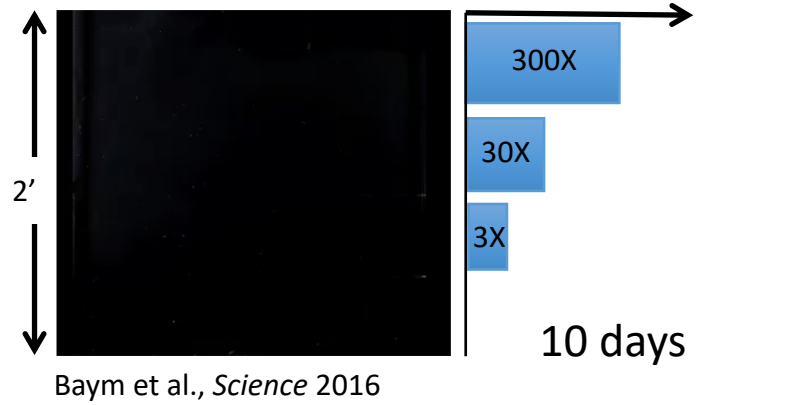
Vlamakis et al., Nat. Rev. Microb. (2013)



Colonies

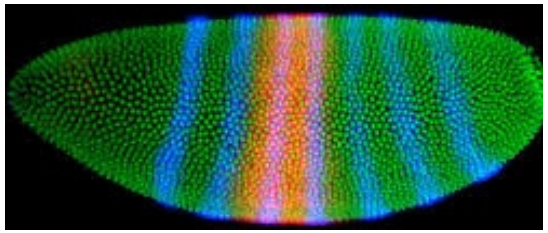


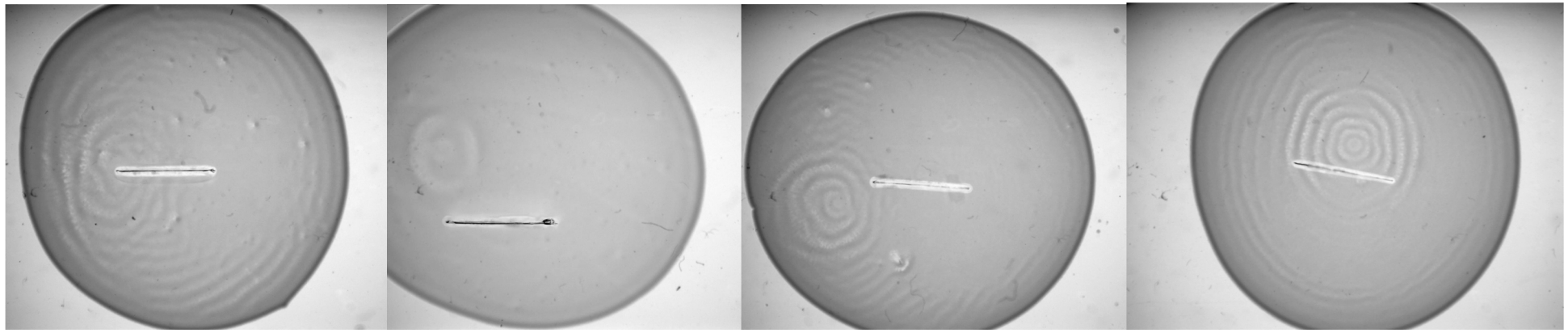
Solid tumors



Baym et al., *Science* 2016

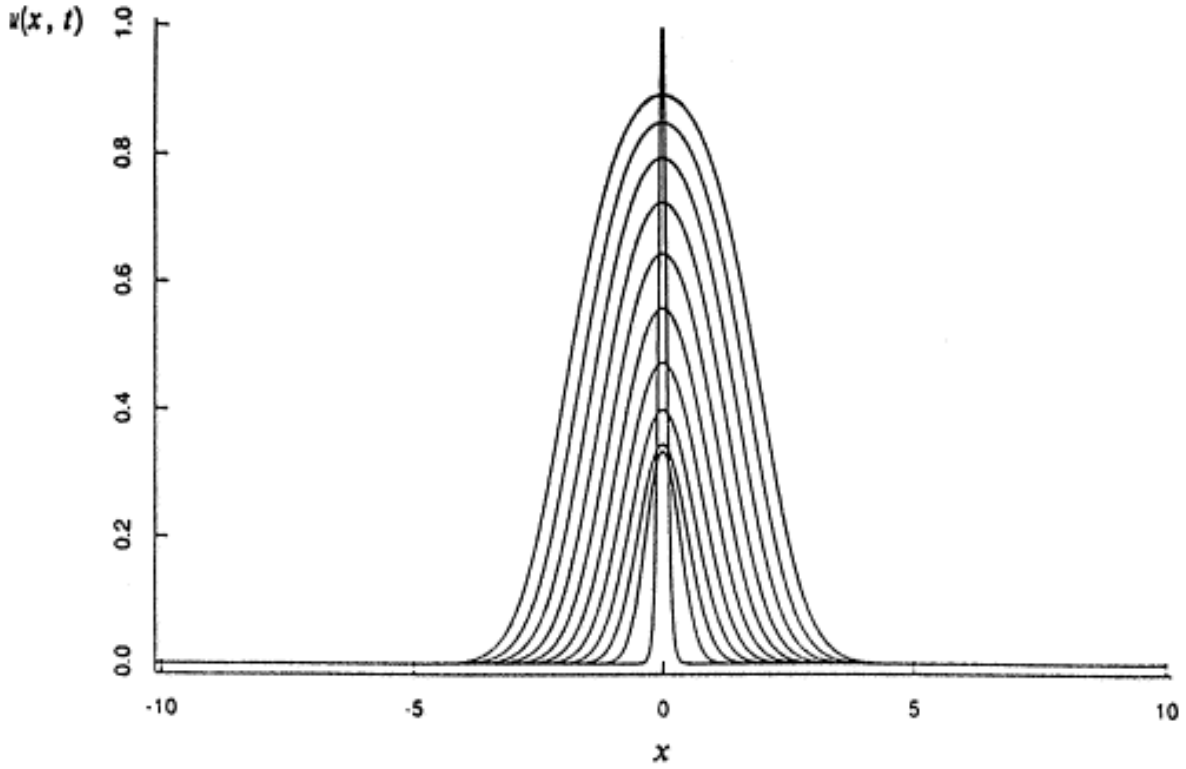
Developing multicellular org.s





Day 1 Day 3 Day 5 Day 7

Reaction-diffusion equation describes spread of a beneficial allele in a spatial population



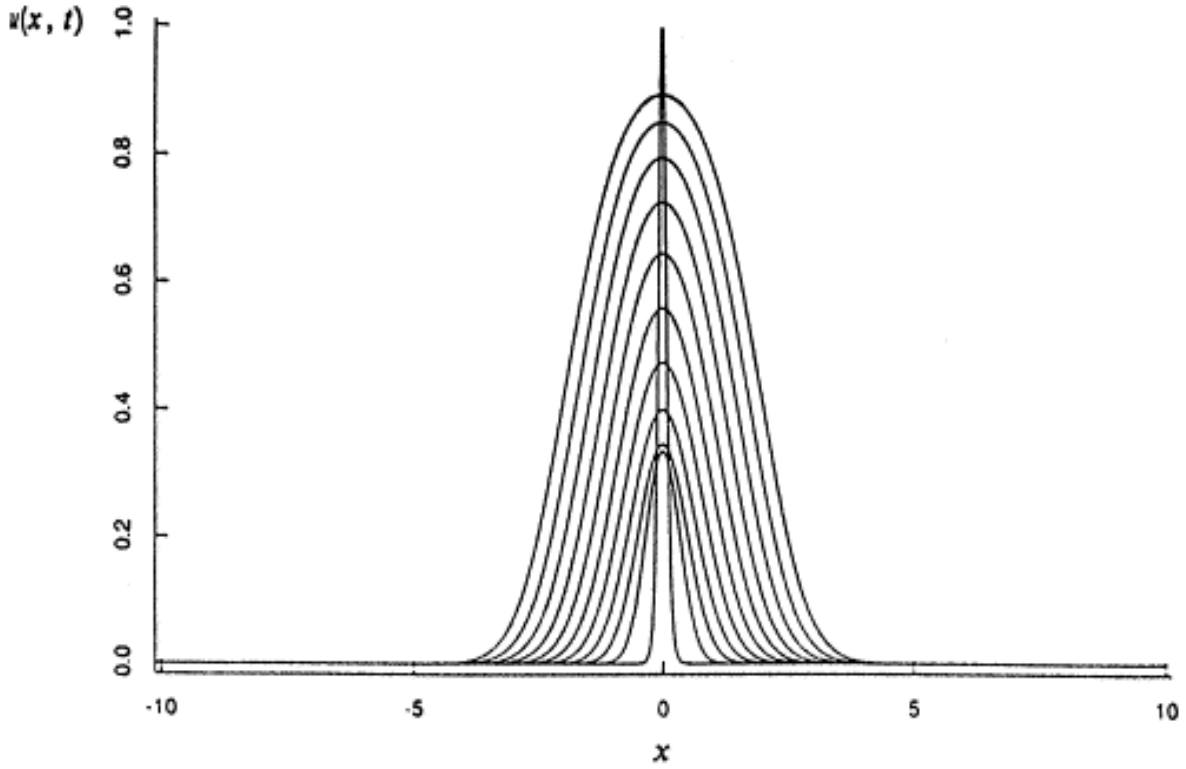
Allele q grows at a rate 1+s and jumps over a distance Δx from a distribution g()=N(0,σ)

$$q(x,t+1) = \int_{-\infty}^{\infty} g(\Delta x) q(x+\Delta x, t) d\Delta x.$$

Let's Taylor expand

$$q(x,t+1) = q(x,t) + \partial_x q|_{x,t} \int_{-\infty}^{\infty} \Delta x g(\Delta x) d\Delta x + 1/2 \partial_x^2 q|_{x,t} \int_{-\infty}^{\infty} \Delta x^2 g(\Delta x) d\Delta x$$

Reaction-diffusion equation describes spread of a beneficial allele in a spatial population



$$q(x, t+1) = q(x,t) + \frac{\sigma^2}{2}\partial_x^2 q.$$

Taking time changes to zero

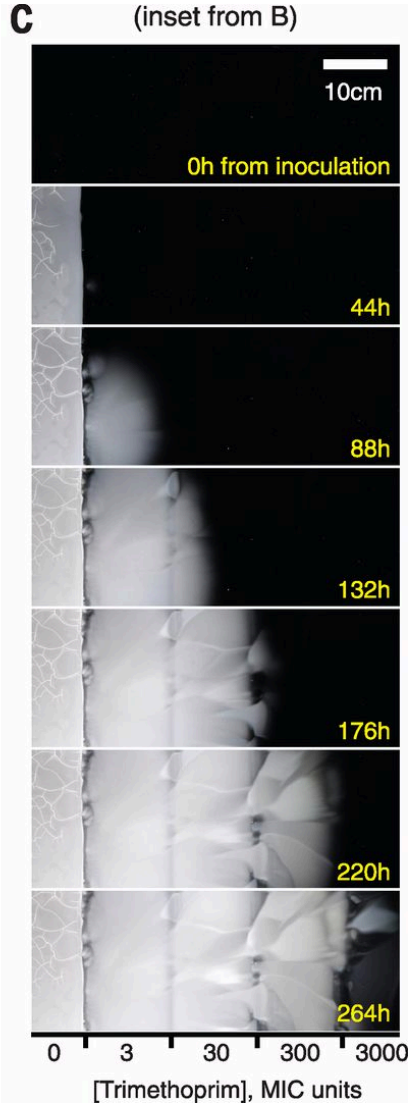
$$\partial_t q = \frac{\sigma^2}{2}\partial_x^2 q$$

Remembering logistic growth and defining $D = \sigma^2/2$

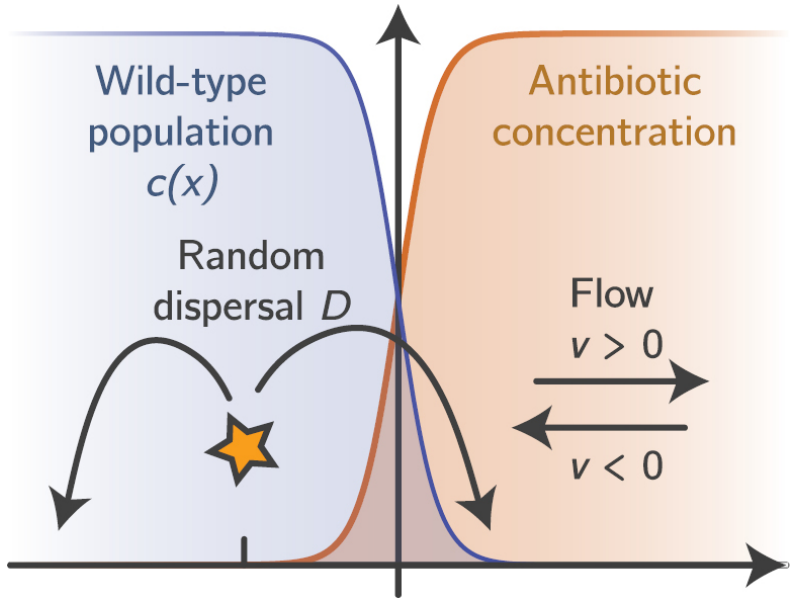
$$\partial_t q(x,t) = sq(x,t)(1-q(x,t)) + D\partial_x^2 q(x,t).$$

This is the Fisher-Kolmogorov equation

Application 1: emergence of resistance



Baym et al., *Science* 2016



Gralka, Fusco, Martis, Hallatschek, *Physical Biology* 2017

$$\partial_t c(x,t) = D\partial_x^2 c + [a_{WT}(x) - b_{WT}(x)]c - a_{WT}(x)c^2$$

Birth Rate Death Rate

Application 1: emergence of resistance

- Birth-death process to describe survival probability $u_x(t)$ that mutation born at position x survives until time t.

Migration to/from neighboring sites

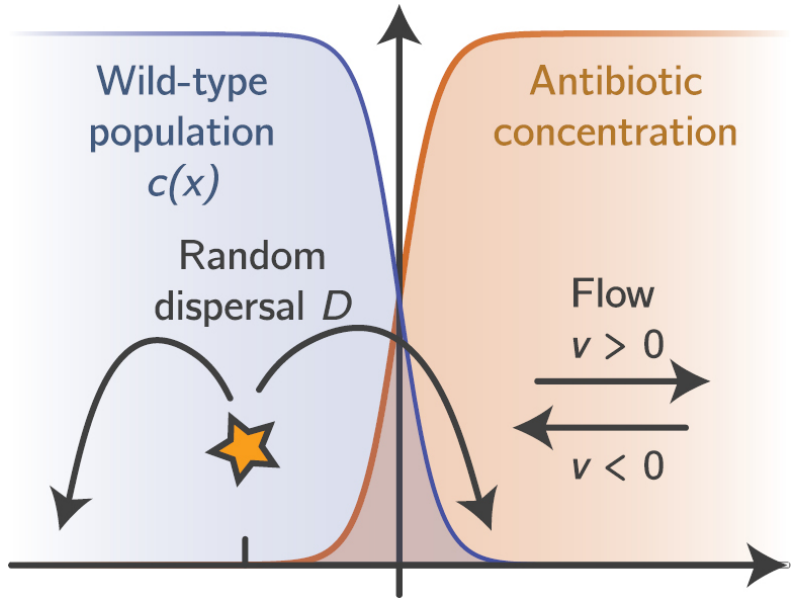
$$u_x(t+\epsilon) = \epsilon a(x)\left\{1-[1-u_x(t)]^2\right\}+\{1-\epsilon[a(x)+b(x)]\}u_x(t)+\epsilon D[u_{x+\delta x}(t)+u_{x-\delta x}(t)-2u_x(t)]$$

Survival of at least 1 lineage upon replication

Nothing happens

$$\partial_t u = D\partial_x^2 u + [a(x)-b(x)]u - a(x)u^2$$

$$\partial_t c(x,t) = D\partial_x^2 c + [a_{WT}(x)-b_{WT}(x)]c - a_{WT}(x)c^2$$



Gralka, Fusco, Martis, Hallatschek, *Physical Biology* 2017

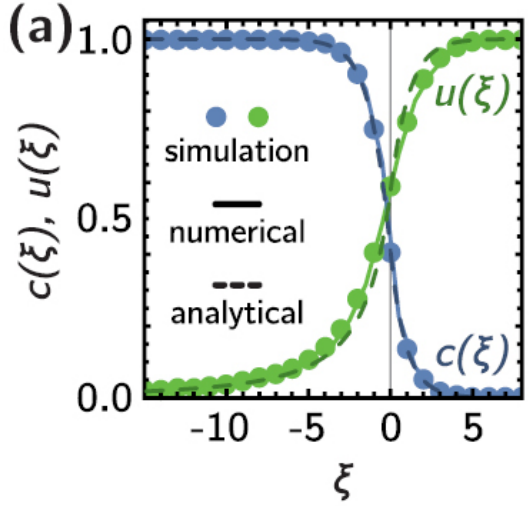
Application 1: emergence of resistance

- Step-like antibiotic profile $a(x) = 1 \quad b(x) = 2\Theta(x)$

$$0 = \partial_x^2 c + [1 - 2\Theta(x)]c - c^2$$ Steady-state for c(x)

Solve by mechanical analogy with a particle in a potential

$$\partial_x^2 c = a = F = -\frac{dU}{dc}$$



Gralka, Fusco, Martis, Hallatschek, *Physical Biology* 2017

$$x < 0 \Rightarrow U(c) = c^2/2 - c^3/3$$

Boundary conditions

$$c(-\infty) = 1$$
$$c(0) = c_0$$
$$E = K + U = 1/6$$

$$x > 0 \Rightarrow U(c) = -c^2/2 - c^3/3$$

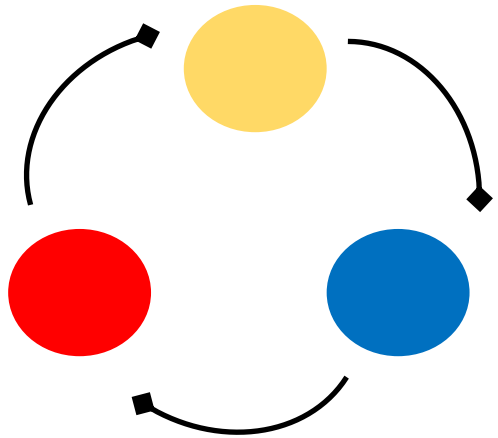
Boundary conditions

$$c(+\infty) = 0$$
$$c(0) = c_0$$
$$E = K + U = 0$$

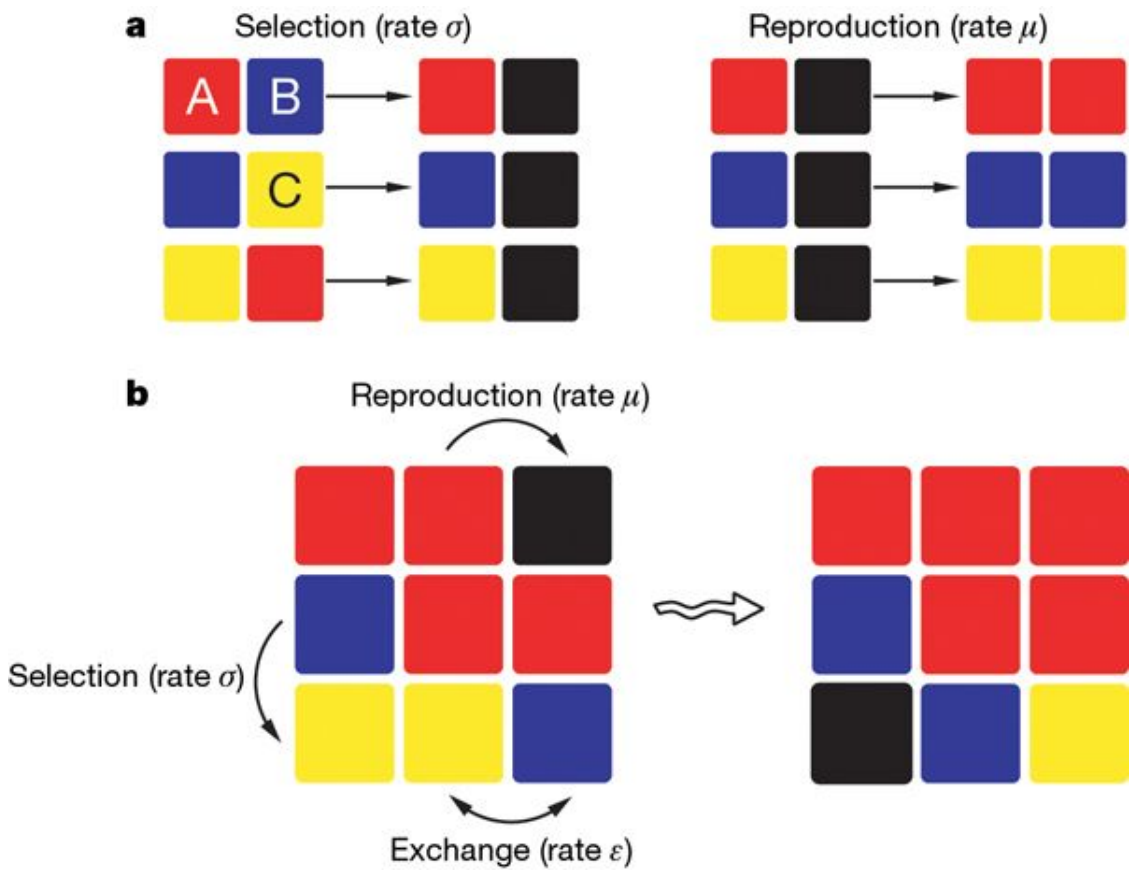
$$v = \frac{dc}{dx} = \sqrt{2K} = \sqrt{2E - 2U(c)} \qquad x = \int_{c_0}^{c(x)} \frac{dc'}{\sqrt{2E - 2U(c')}}$$

Application 2: Maintenance of diversity

While mutations create diversity, selection and noise remove it.
How can diversity be maintained? Space helps!

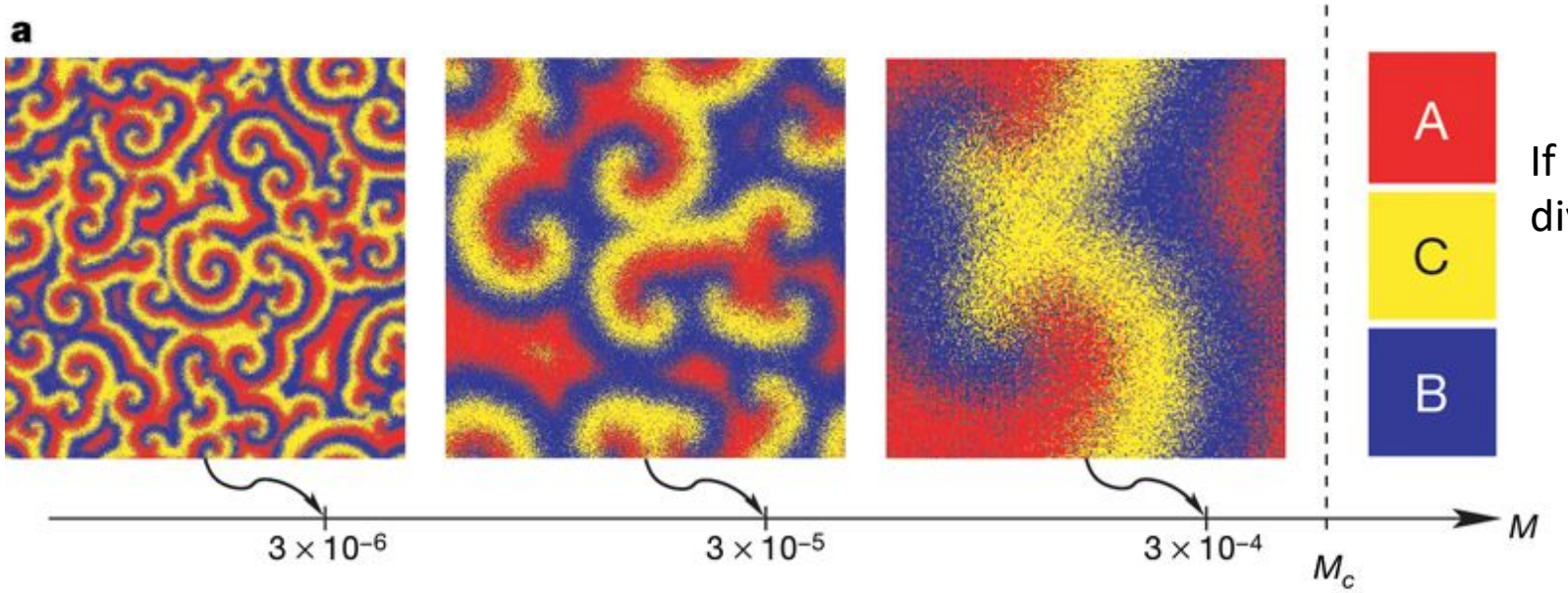


Rock-paper-scissor dynamics that mimics three species competing with each other (toxin-antitoxin systems in bacteria, phage-bacteria ecologies)

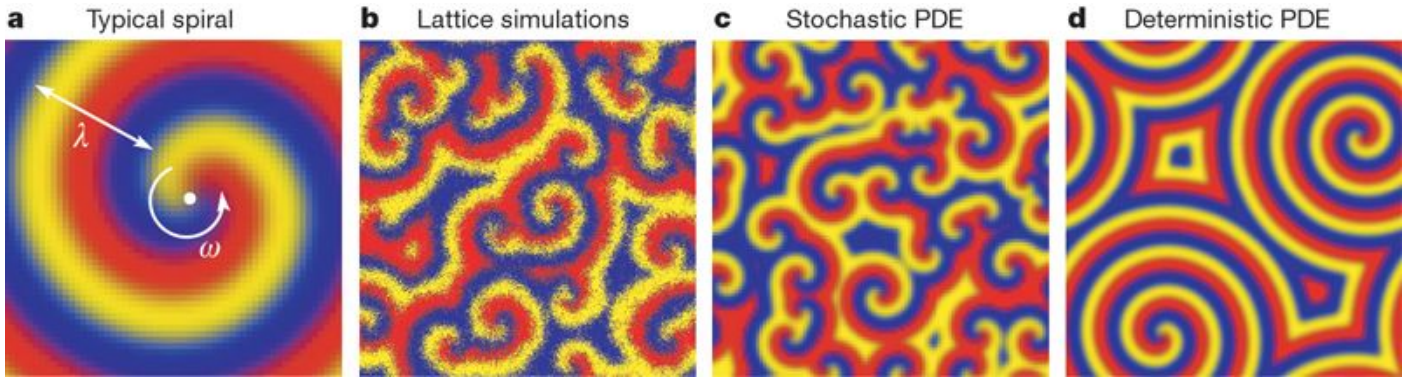


Reichenbach et al, *Nature* 2007
Kerr et al, *Nature* 2002

Application 2: Maintenance of diversity



If dispersal is too high (well-mixed limit), diversity is lost

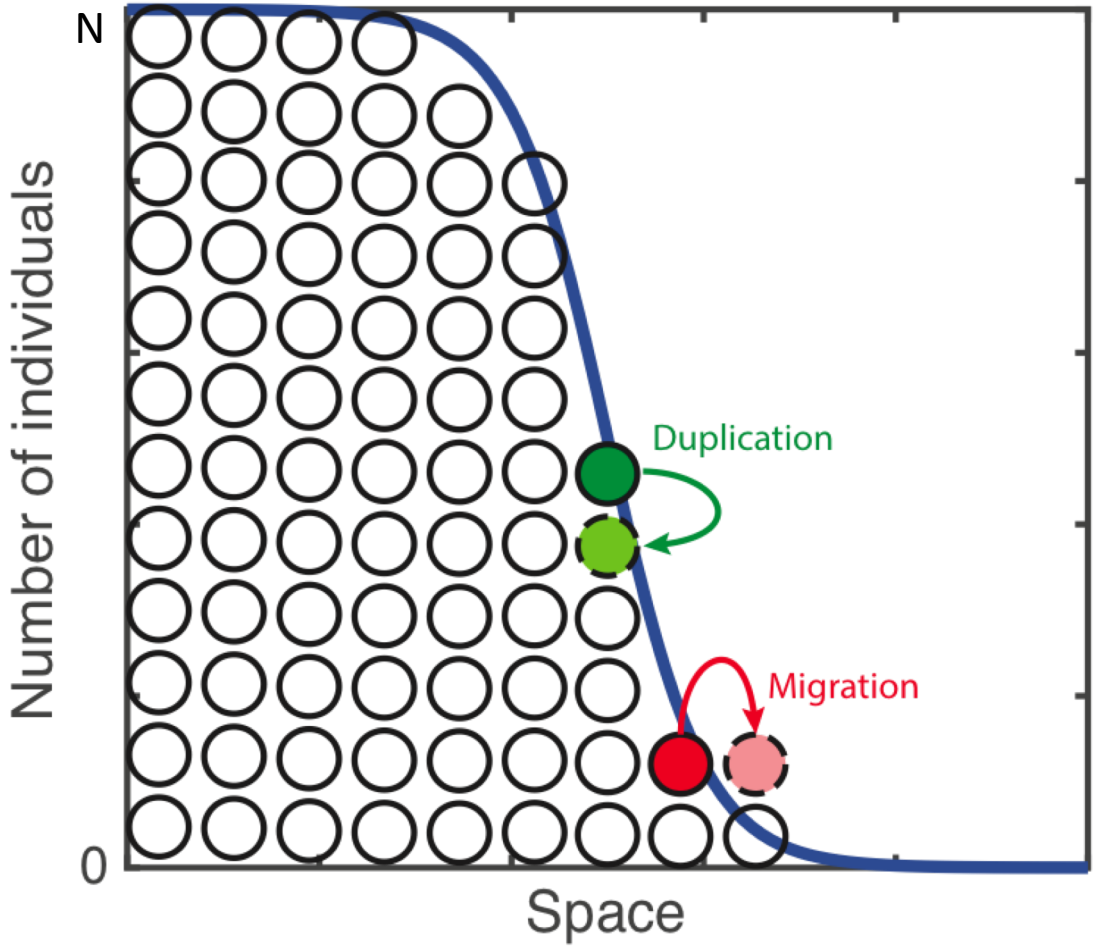


You can write system of stochastic PDEs (coupled reaction-diffusion like) and solve numerically.
Noise is necessary to move away from initial conditions

http://demonstrations.wolfram.com/BiodiversityInSpatialRockPaperScissorsGames/

Reichenbach et al, *Nature* 2007

Stochastic FKPP equation: spatial range expansion



$$q(t+dt) = \begin{cases} q+1 & \text{with prob. } \frac{dt}{N} q(N-q) \\ q & \text{with prob. } 1 - \frac{dt}{N} q(N-q) \end{cases}$$

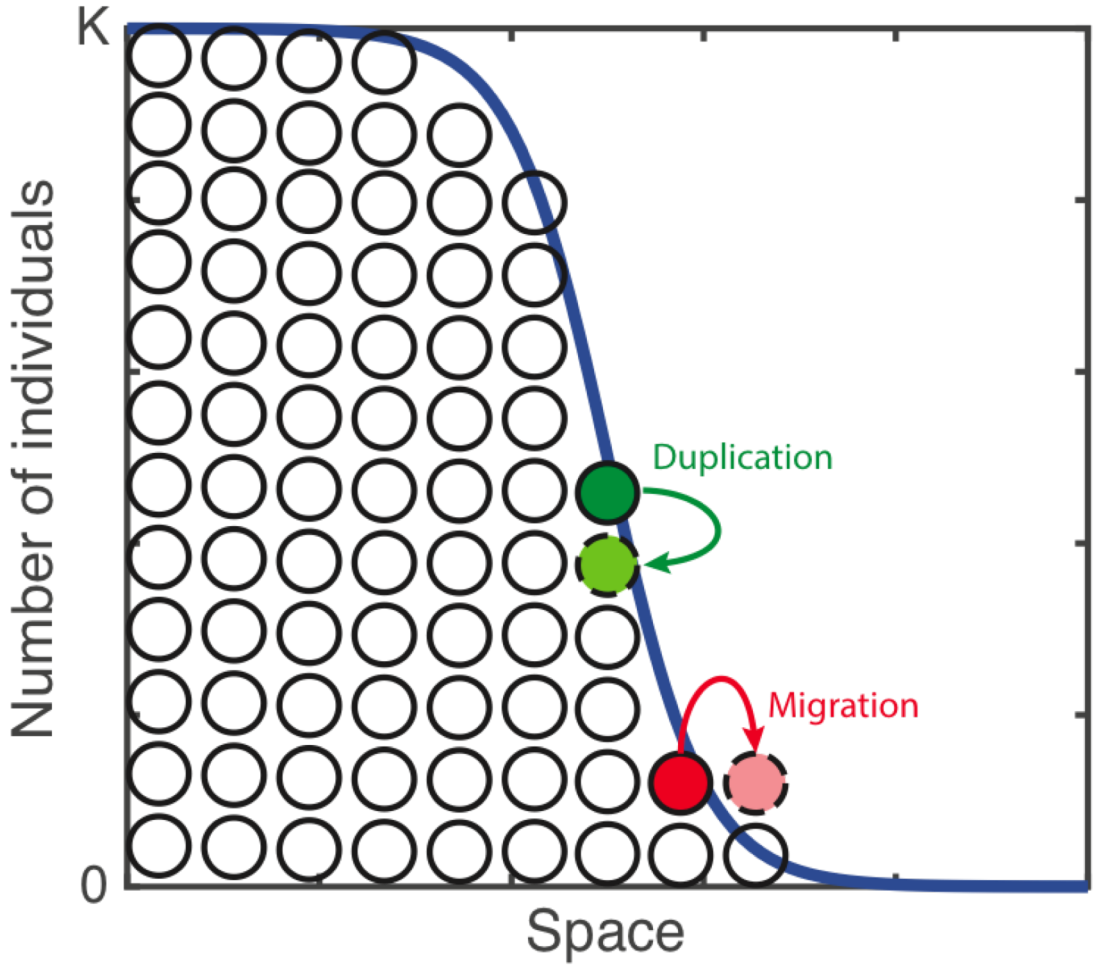
$$\langle q(x,t+dt) \rangle = q(x,t) + \frac{dt}{N} q(x,t)(N - q(x,t))$$

$$Var(q(x,t+dt) = \frac{dt}{N} q(x,t)(N - q(x,t))$$

Defining the white noise R_t with mean 0 and variance 1

$$q(x,t+dt) = q(x,t) + \frac{dt}{N} q(x,t)(N - q(x,t)) + R_t \sqrt{\frac{dt}{N} q(x,t)(N - q(x,t))}$$

Stochastic FKPP equation: spatial range expansion



$$\partial_t q = \frac{q(N-q)}{N} + \eta_t \sqrt{\frac{q(N-q)}{N}}$$

Defining the population density $c = q/N$

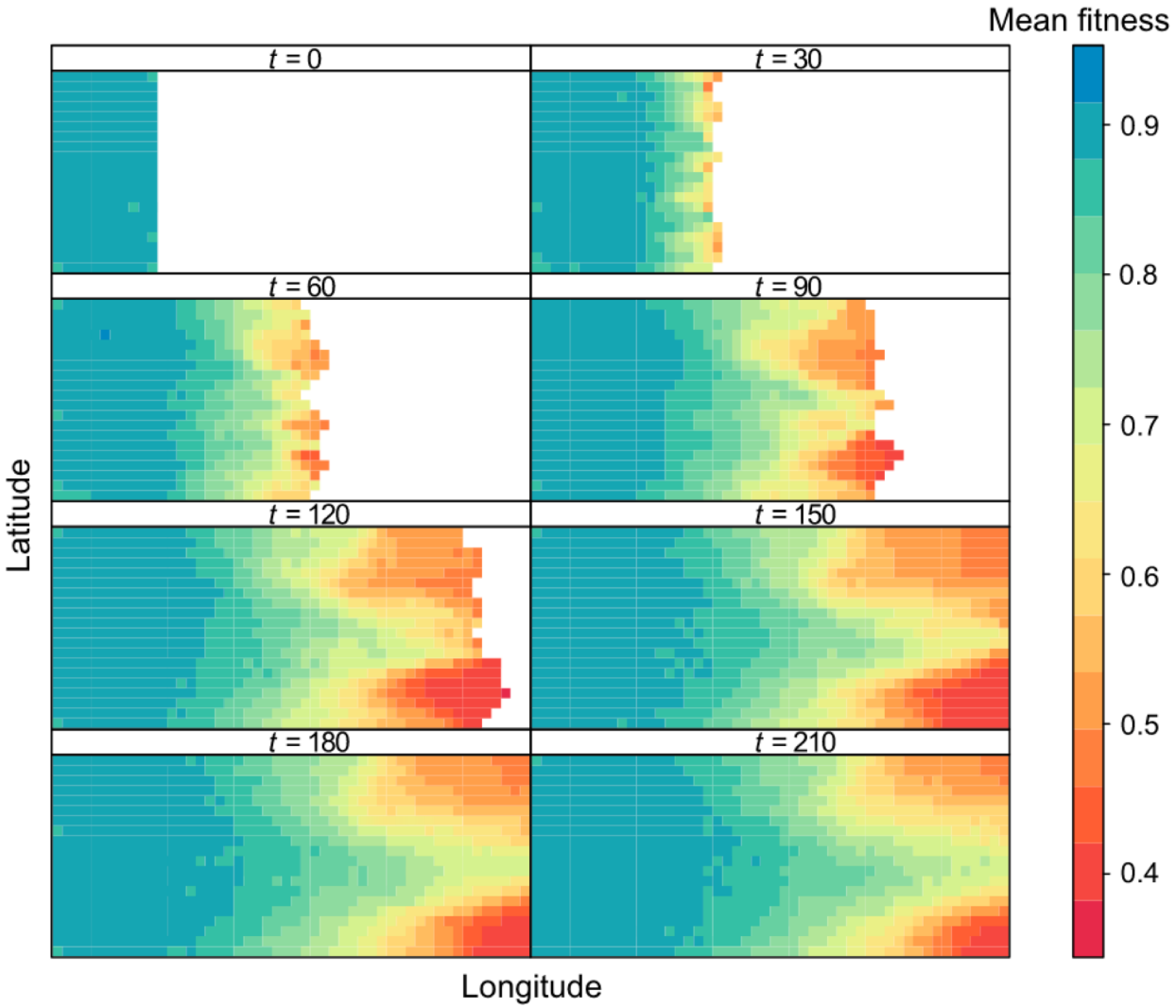
and adding the diffusion term, we find:

$$\partial_t c = \partial_x^2 c + c(1-c) + \eta_t \sqrt{\frac{c(1-c)}{N}}$$

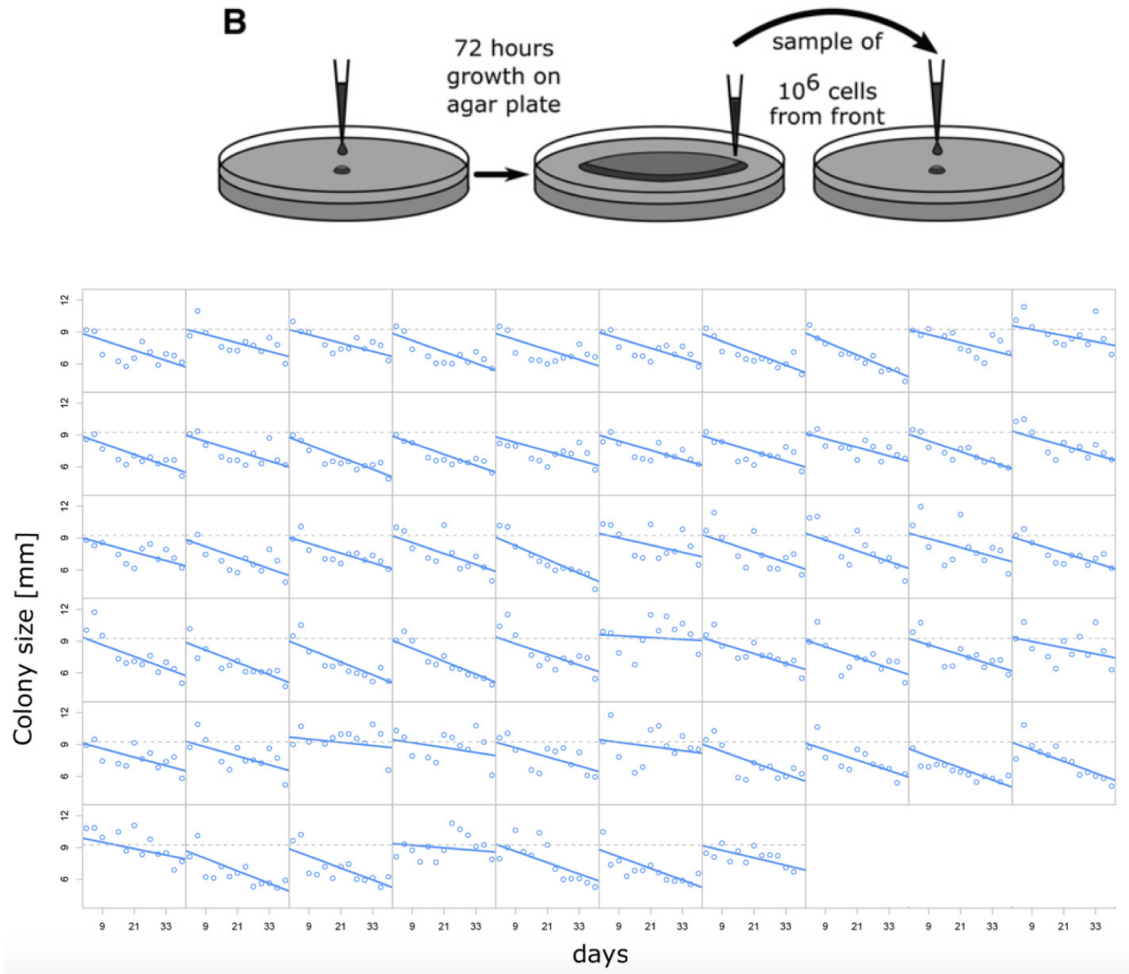
At the front, there's only few individuals, then c~1/N
Growth term and noise are comparable in strength

Weak mutations behave like neutral

Stochastic FKPP equation: expansion load

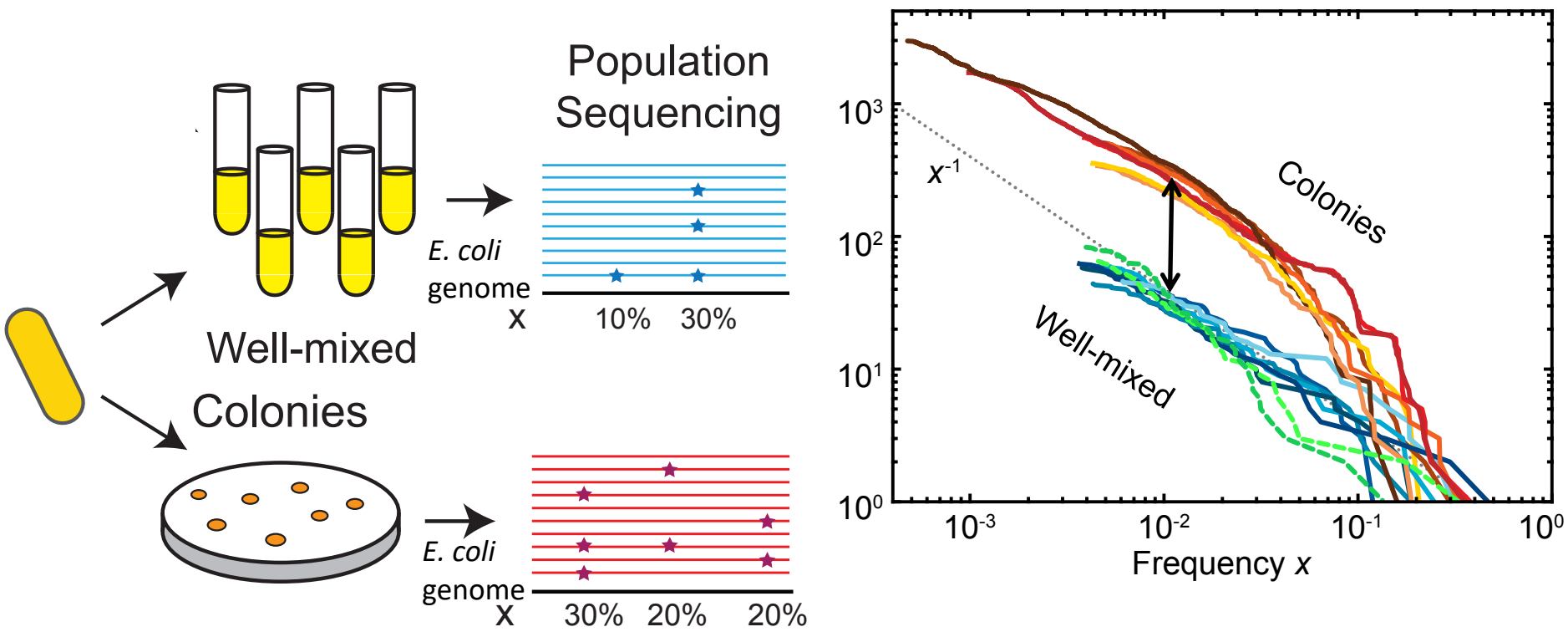


Peischl & Excoffier, Mol. Ecol. 2015



Bosshard et al., Genetics 2017

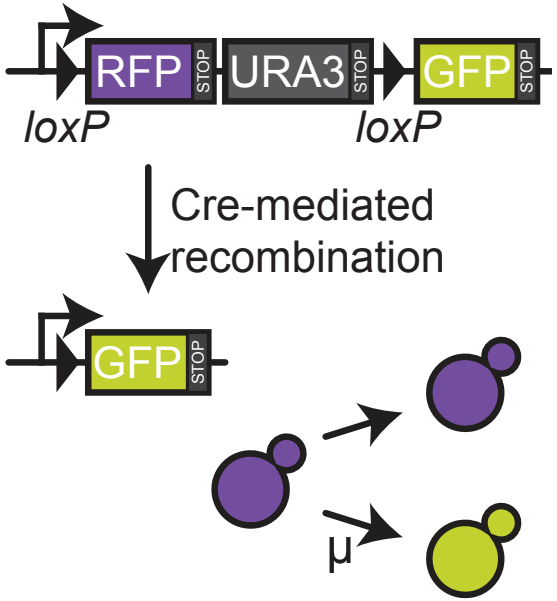
Genetic diversity in range expansions



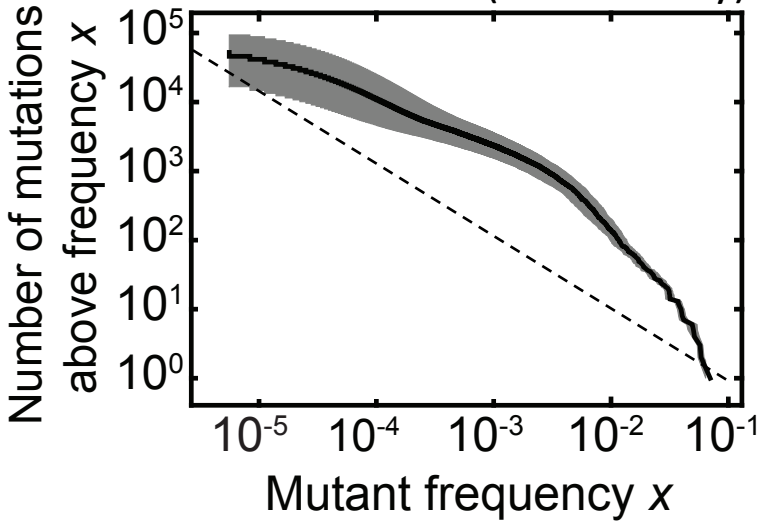
Fusco et al., *Nat. Comm.* (2016)

When/where do the jackpots appear?





Rine Lab (UC Berkeley)

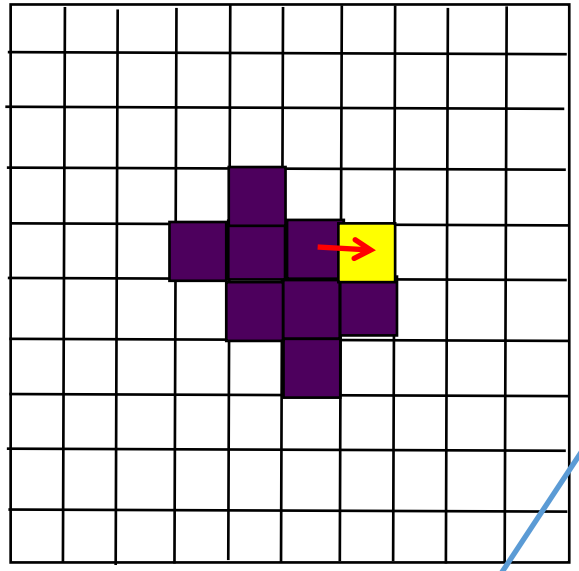


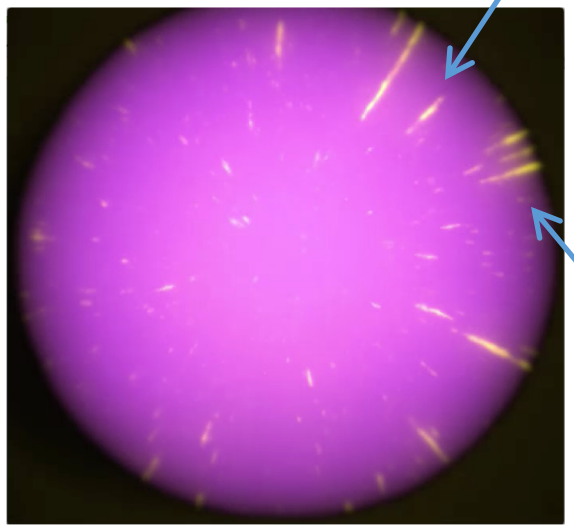
S. cerevisiae switcher strain

Purple→Yellow, $\mu \approx 10^{-3}$

Simulating colonies using minimal surface growth

Eden model

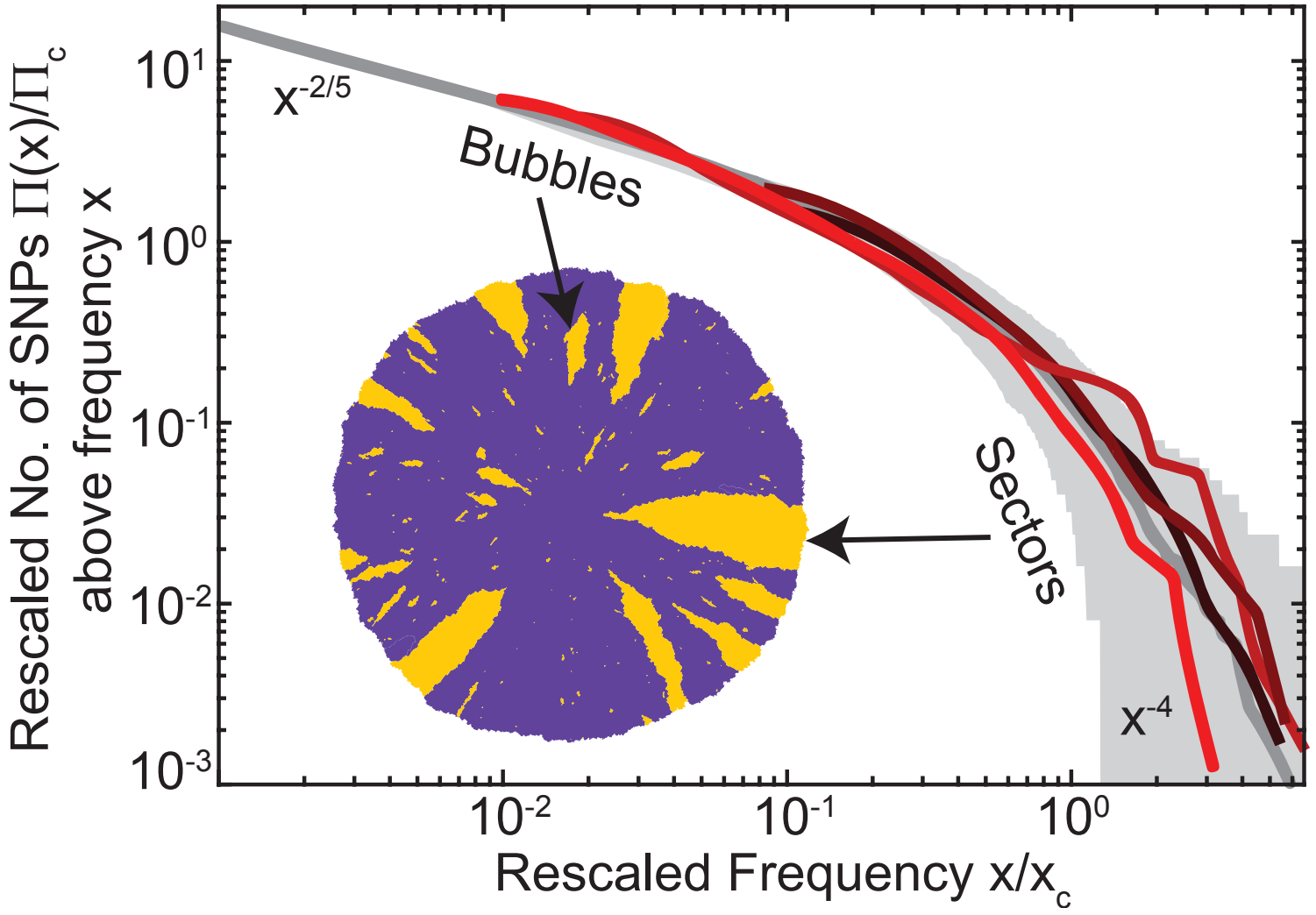




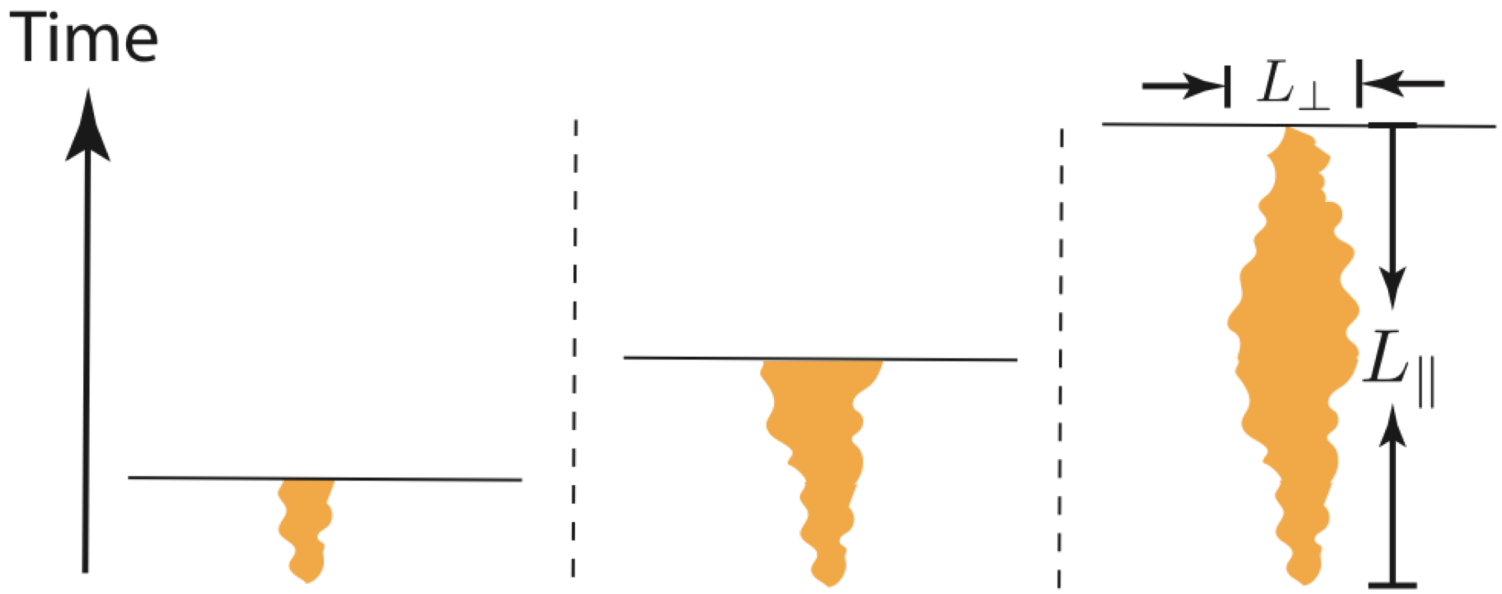
Bubbles

Sectors

Simulations agree with sequencing results



Boundaries are like random-walks



$$L_\perp^z =< R^z > \sim T = L_\parallel$$

$$A \sim L_\perp L_\parallel \Rightarrow A \sim L_\perp^{z+1}$$

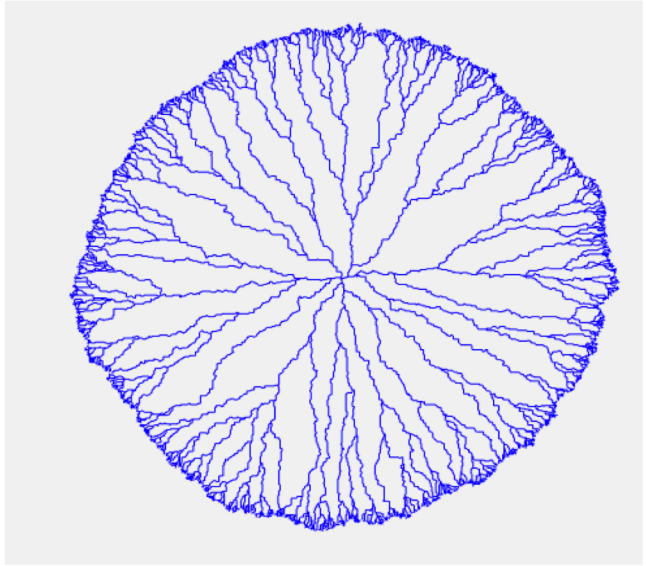
$z = 2$ Diffusive RW

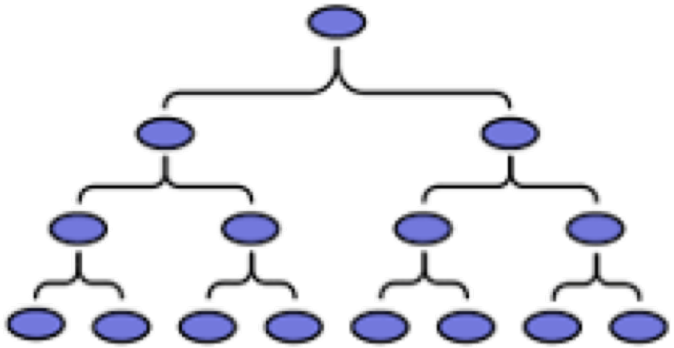
$z = 3/2$ Superdiffusive RW (Kardar-Parisi-Zhang)

$$P[A > a] = P[L_\perp > l_\perp(a)] = l_\perp^{-1}(a) = a^{-\frac{1}{z+1}}$$

Surface growth and allele surfing

Individuals at the front are more likely to stay at the front and keep their offspring at the front





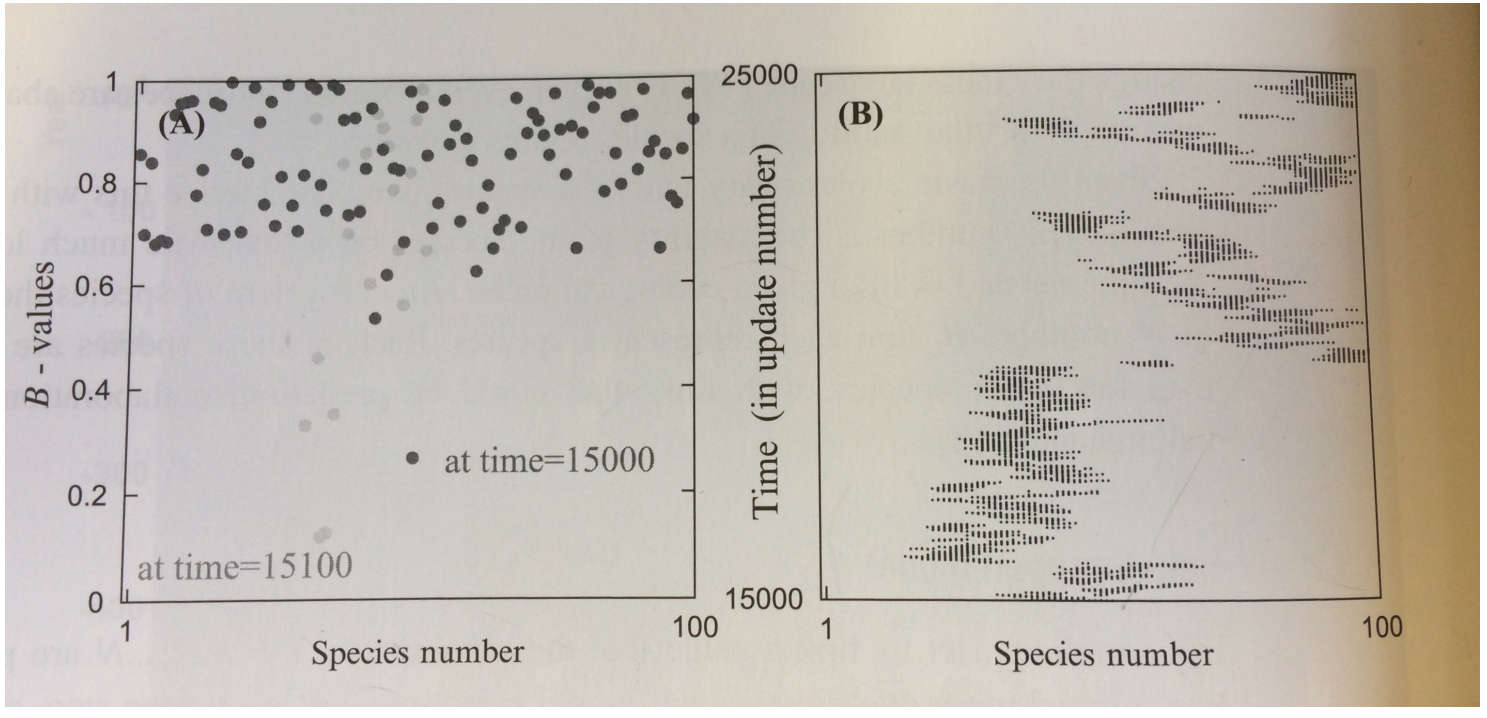
Well-mixed tree

Evolution of species: Bak-Sneppen model

Define a vector (B1,….BN) which defines the stability of a species

At each time step, find the minimum B_i and replace it and its nearest neighbors with random number [0,1]





Models of life, Sneppen

Evolution of species: Bak-Sneppen model

Dynamic tends to localize

Emergence of a critical Bc, which is the minimum that gives stability

Variants of the model change Bc (dimension, neighbor update, etc…)

