An individual-based model for the Lenski experiment, and the deceleration of the relative fitness

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Joint work with Noemi Kurt and Anton Wakolbinger

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PROBABILISTIC STRUCTURES IN EVOLUTION
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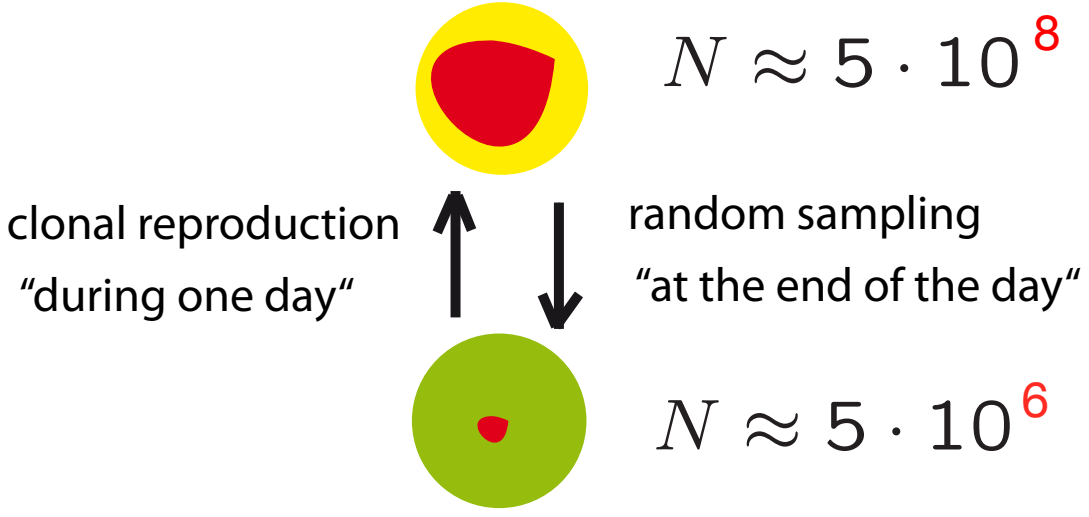
The Lenski experiment (one day cycle)



Relative fitness

Measuring adaptation

- A population of size A_0 of the unevolved strain and a population of size B_0 of the evolved strain perform a direct competition.
- The respective population sizes at the end of the day are denoted by A_1 and B_1.
- The (empirical) *relative fitness* $F(B|A)$ of strain B with respect to strain A is

$$F(B|A) = \frac{\log(B_1/B_0)}{\log(A_1/A_0)}.$$

Lenski, Travisano, PNAS, 1994

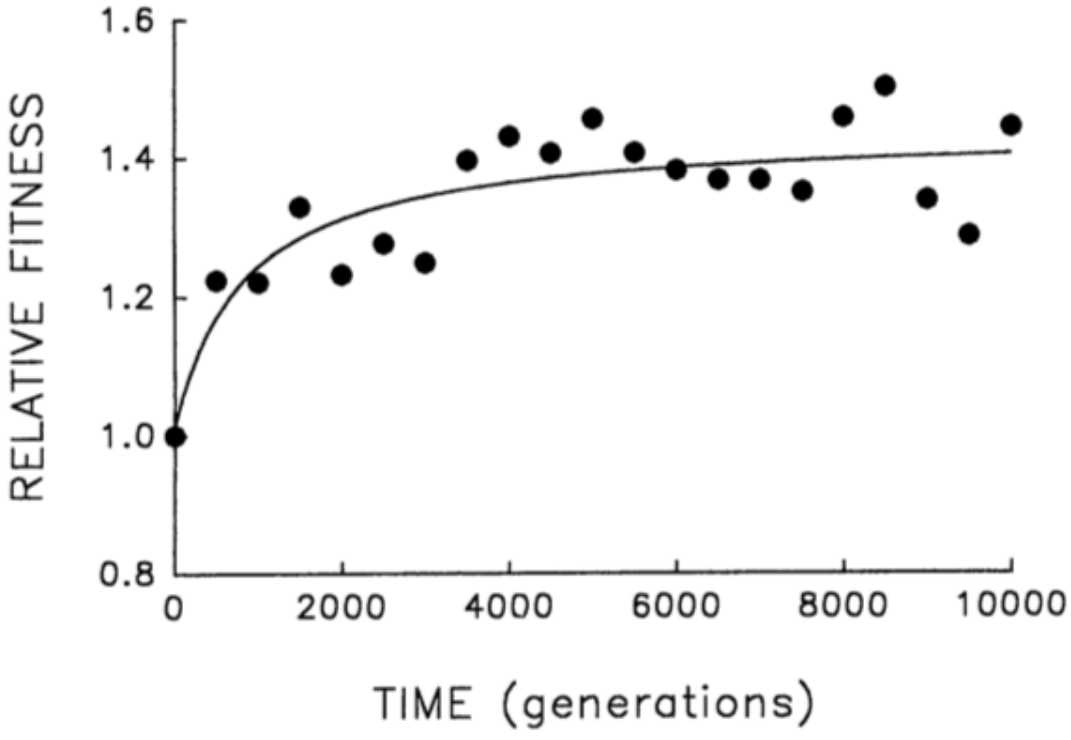
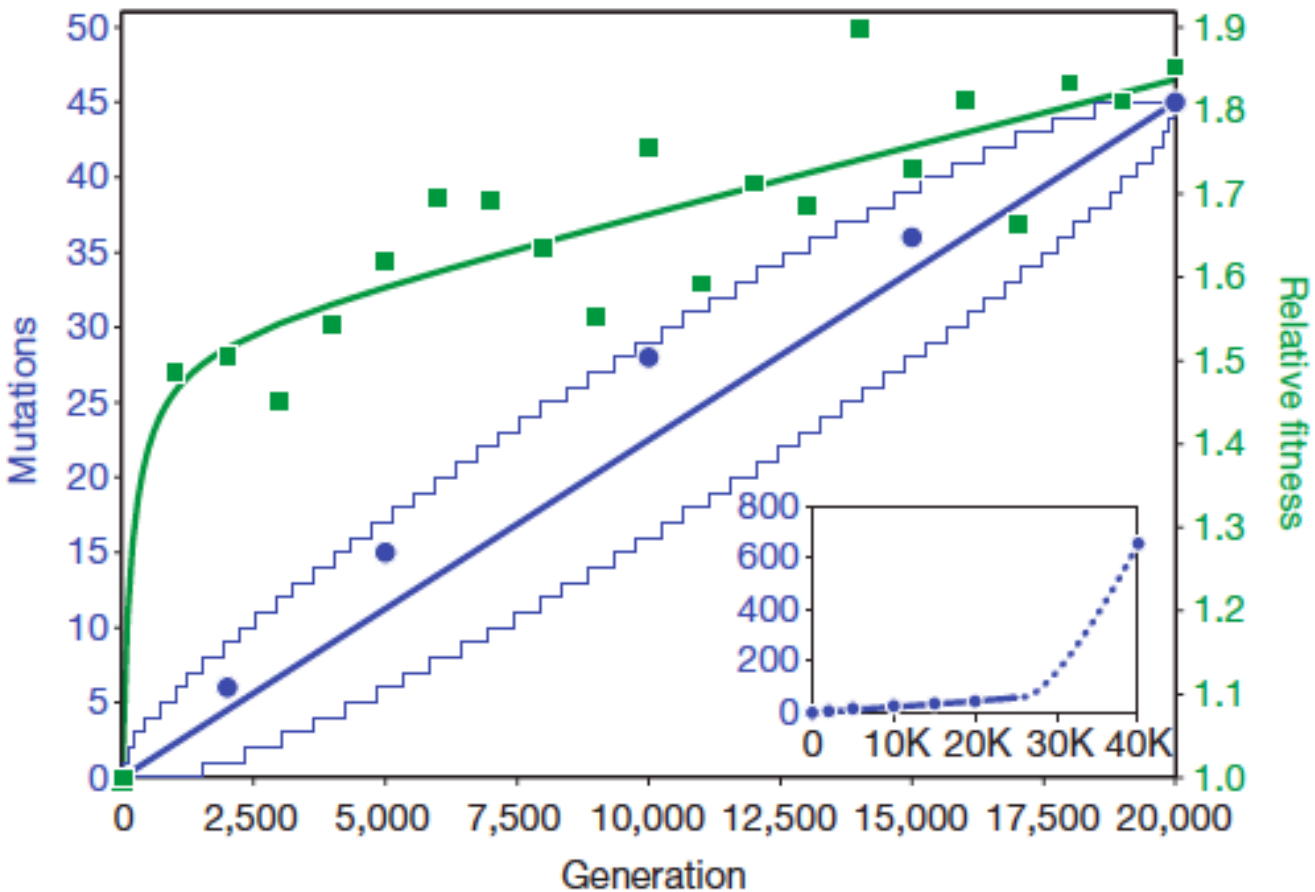


FIG. 4. Trajectory for mean fitness relative to the ancestor in one population of *E. coli* during 10,000 generations of experimental evolution. Each point is the mean of three assays. Curve is the best fit of a hyperbolic model.

Barrick, Yu, Yoon, Jeong, Oh, Schneider, Lenski, Kim, Nature 2009

$$\omega(t) = 1 + at/(t + b)$$



Wiser, Ribeck, Lenski, Science express 13-11-12

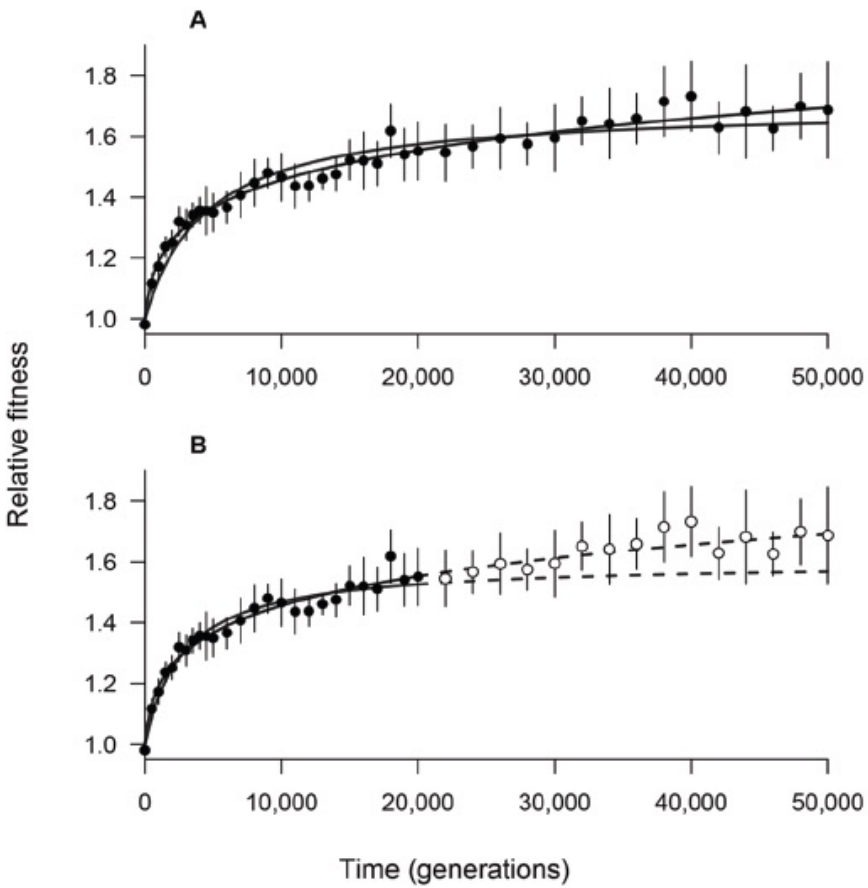


Fig. 2. Comparison of hyperbolic and power-law models. (**A**) Hyperbolic (red) and power-law (blue) models fit to the set of mean fitness values (black symbols) from all 12 populations. (**B**) Fit of hyperbolic (solid red) and power-law (solid blue) models to data from first 20,000 generations only (filled symbols), with model predictions (dashed lines) and later data (open symbols). Error bars are 95% confidence limits based on the replicate populations.

$$w(t) = (1 + ct)^{1/2g}$$

Questions

- Which curve describes better the trajectory of the relative fitness?
- Why is the relative fitness decelerating?

Possible explanations

- Clonal interference
- Epistasis
- The design of the experiment

Epistatic vs non-epistatic models

Epistasis by diminishing returns

The gain in the reproduction rate provided by the n-th successful mutation is a decreasing function of n. (Wiser et al model)

Epistatic vs non-epistatic models

Epistasis by diminishing returns

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No epistasis a priori

The gain in the reproduction rate provided by the n-th successful mutation is a constant $\varrho > 0$.

The daily cycle model[1]

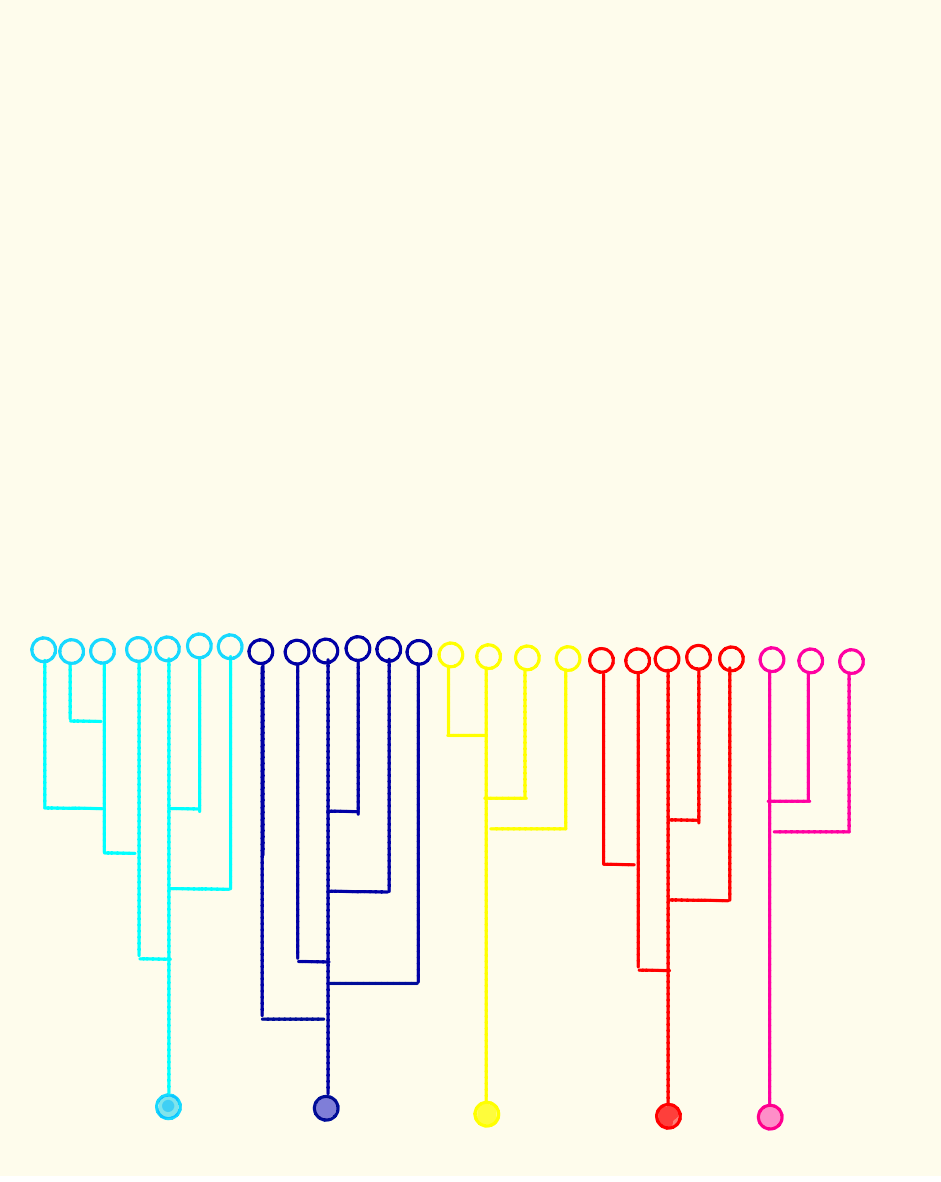
Information about the experiment

- At the beginning of each day there are N individuals.
- Within each day individuals split at constant rate.
- The reproduction process will stop when the glucose has been consumed. (This happens when there are around $100N$ individuals).
- N individuals out of the $\sim 100N$ are uniformly sampled without replacement, to be starting individuals at the next day.

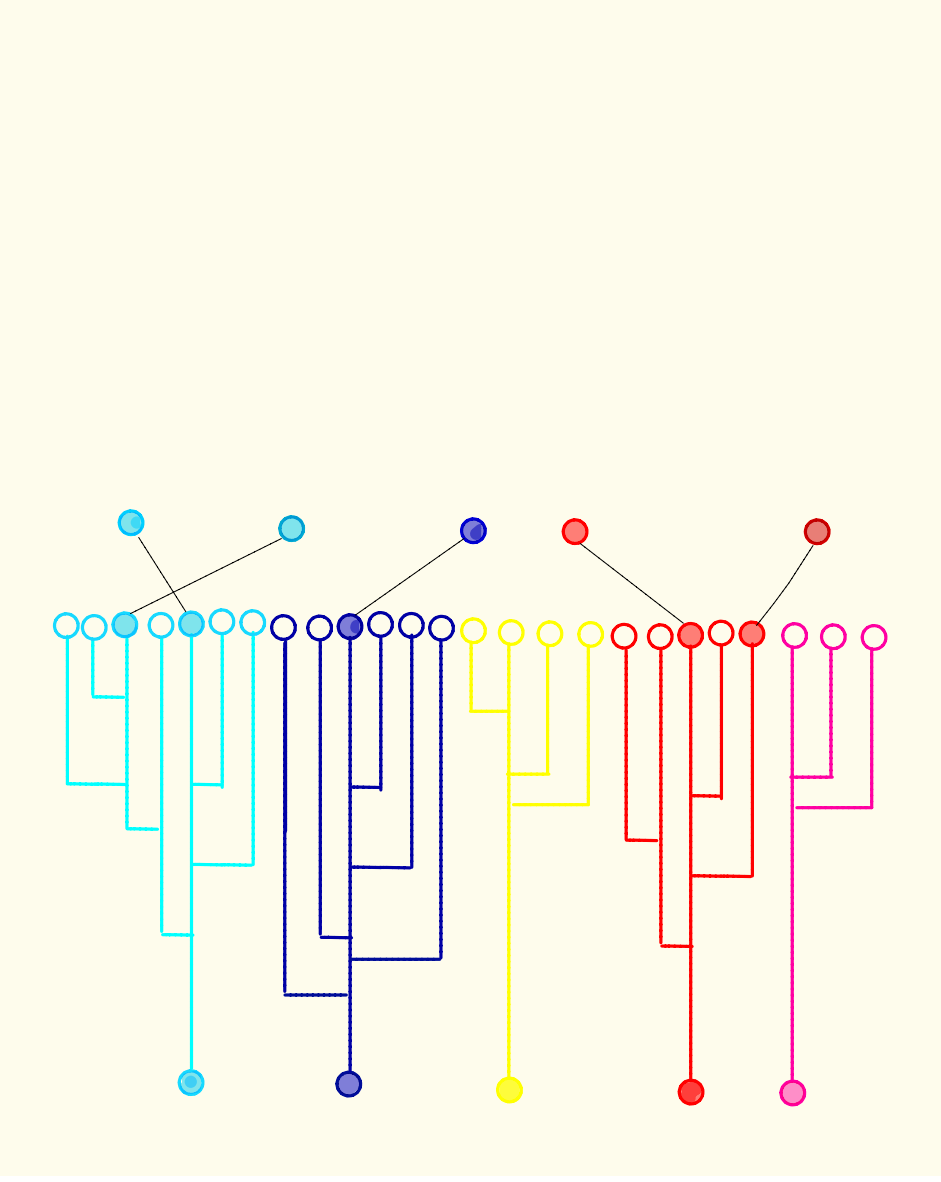
[1] An individual-based model for the Lenski experiment, and the deceleration of the relative fitness. Adrian Gonzalez Casanova, Noemi Kurt, Anton Wakolbinger and Linglong Yuan. (2015) arXiv 1505.0175

Pruned Yule trees

Pruned Yule trees



Pruned Yule trees



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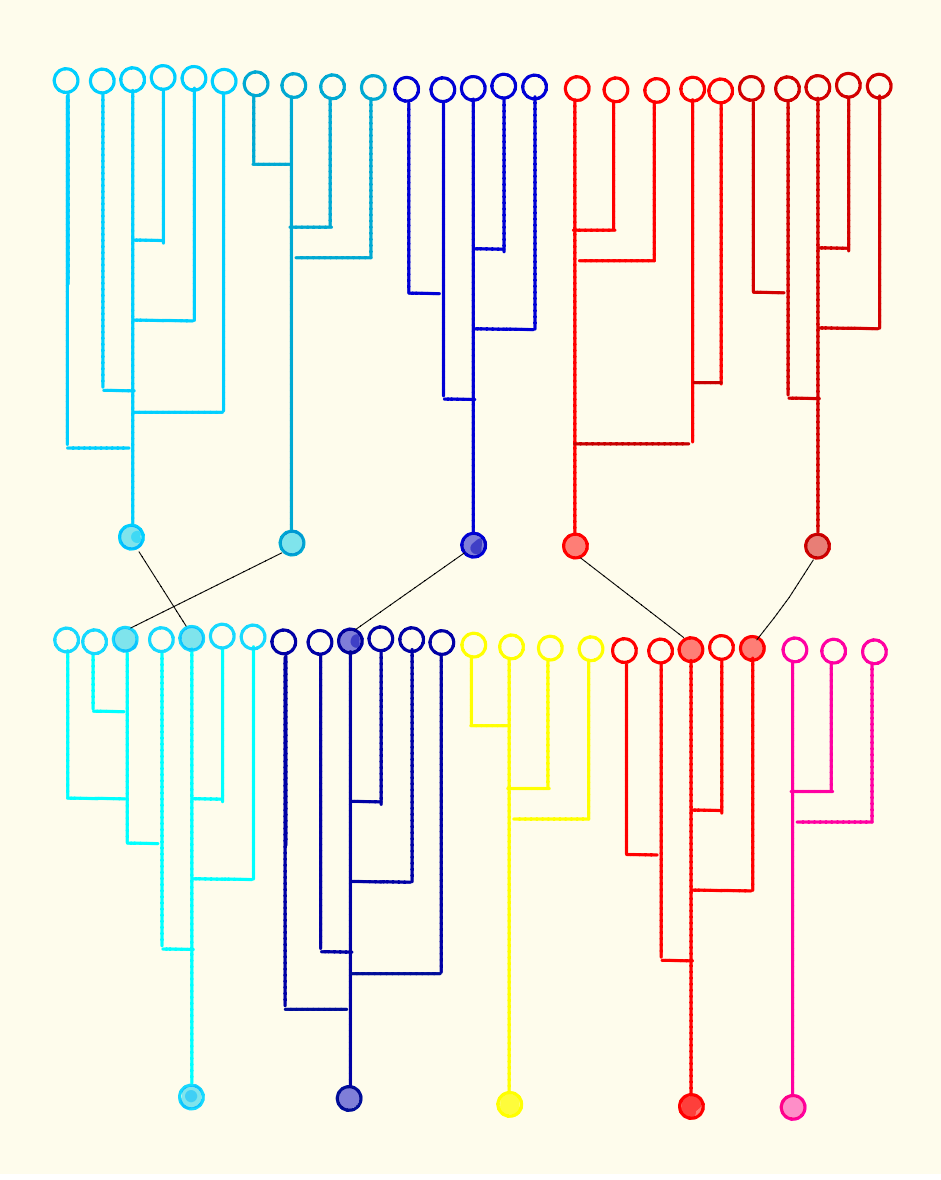

Inside a day

Let $Y_{i,j}(t)$ be a pure birth process with rate $r \in \mathbb{R}^+$, for every $i \in \mathbb{N}$ and $j \in \{1, 2, ..., N\}$. (Yule Processes with parameter r).
The total population size at time t of day i is

$$\sum_{j=1}^{N} Y_{i,j}(t)$$

Stopping rule

Each day, the reproduction stops at time σ , where

$$\sigma = \inf\{t : E[\sum_{j=1}^{N} Y_{i,j}(t)] = \gamma N\}.$$

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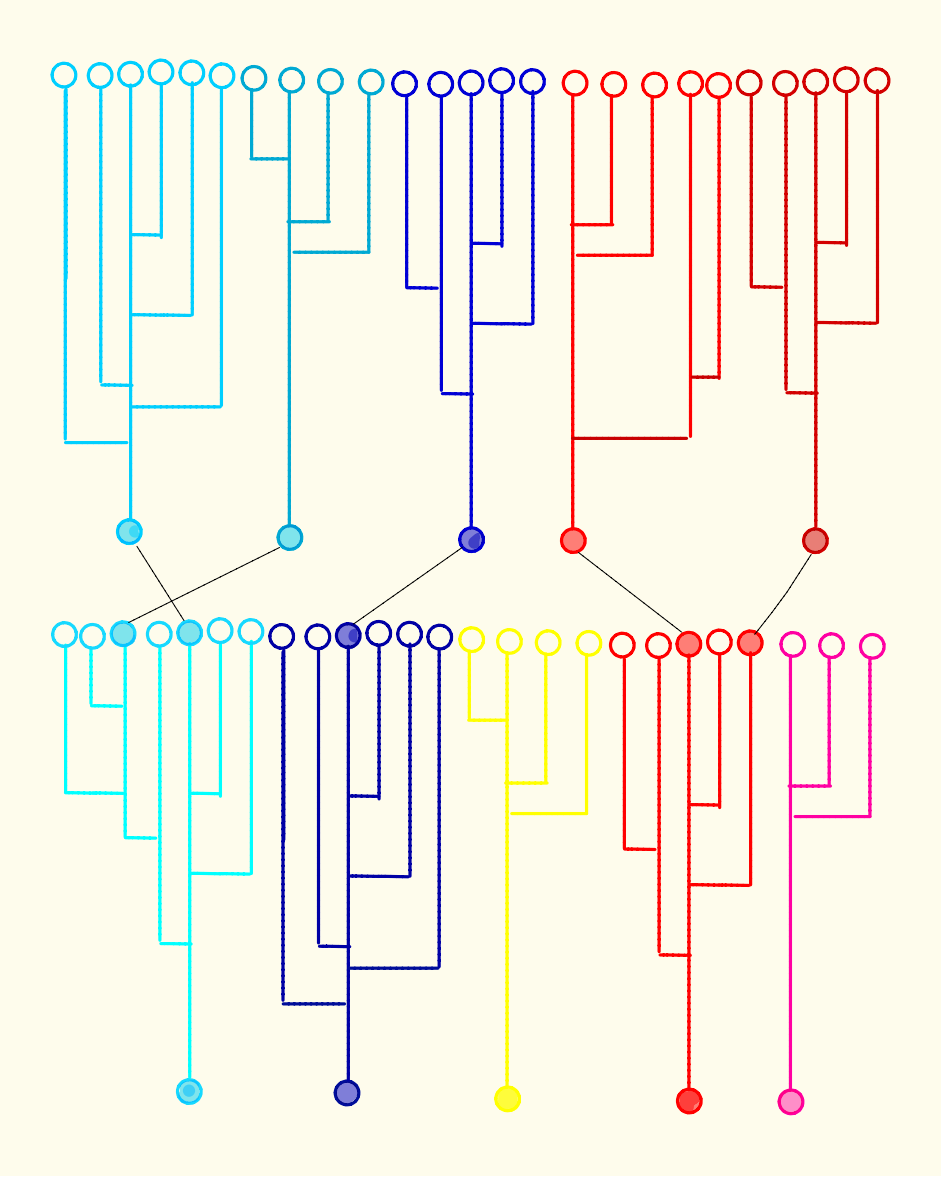
The total population size at the end of the day is

$$\sum_{j=1}^{N} Y_{i,j}(\sigma) \sim \gamma N.$$

Sampling rule

To go from one day to the next, we sample uniformly at random N individuals (out of $\sim \gamma N$), and we say that each sampled individual is a root of a Yule tree in the next day.

We are dealing with a Cannings process.



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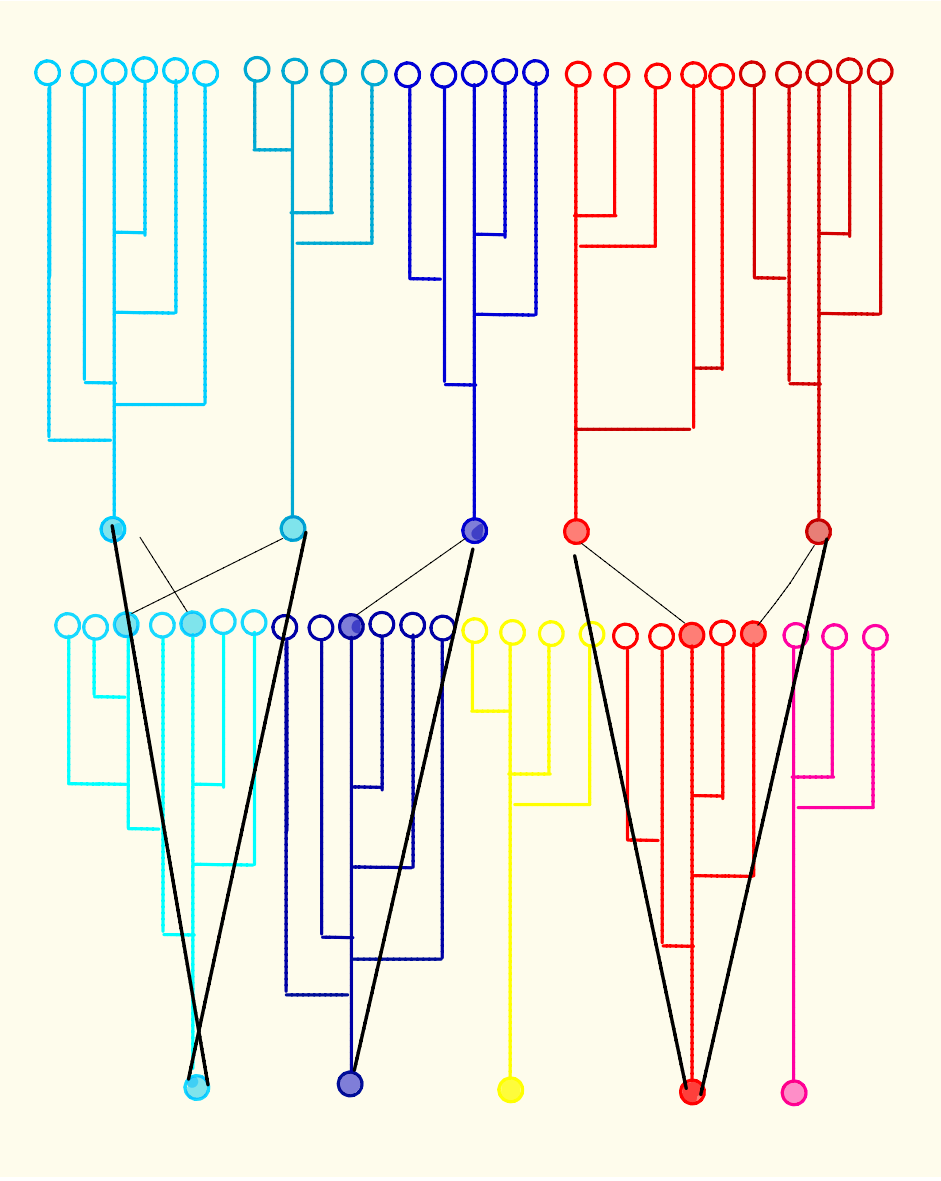

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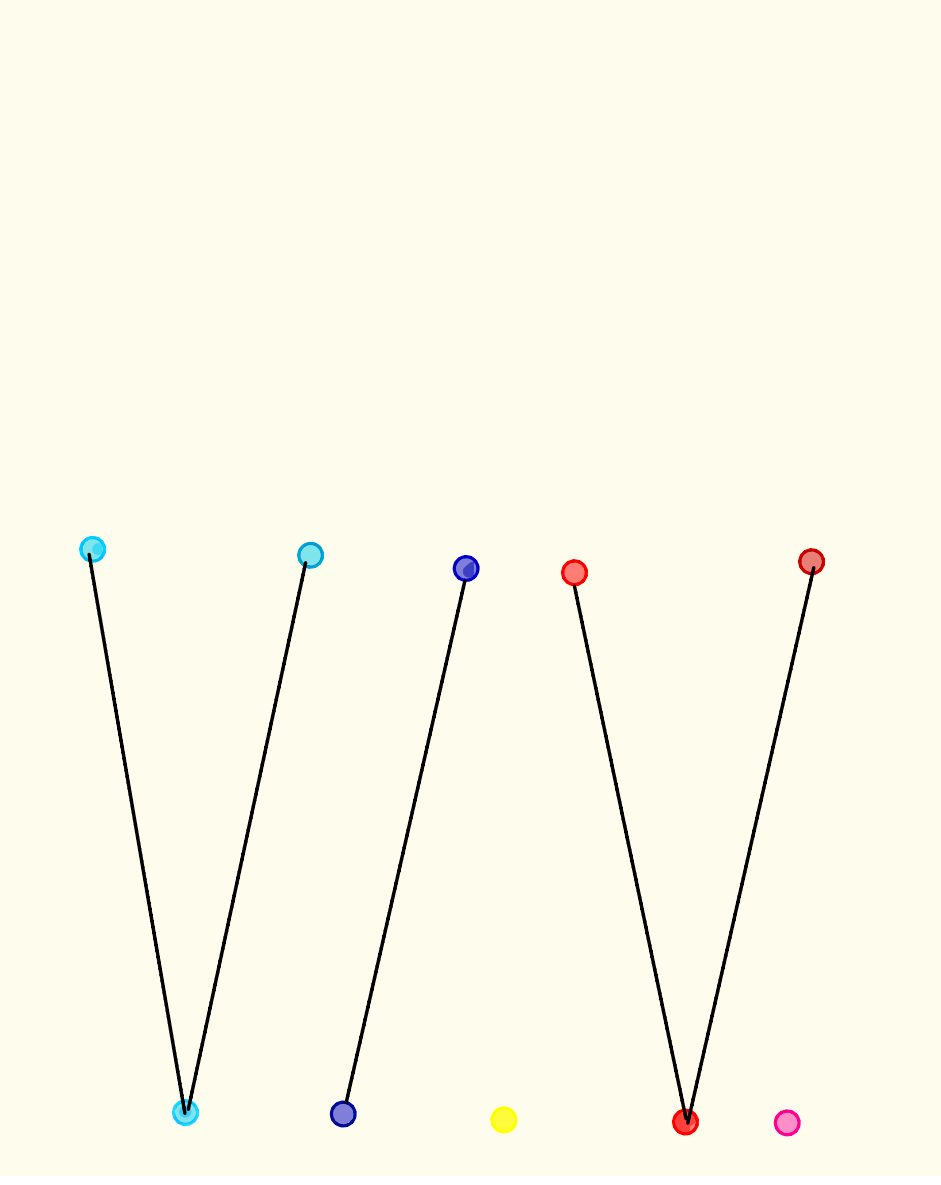

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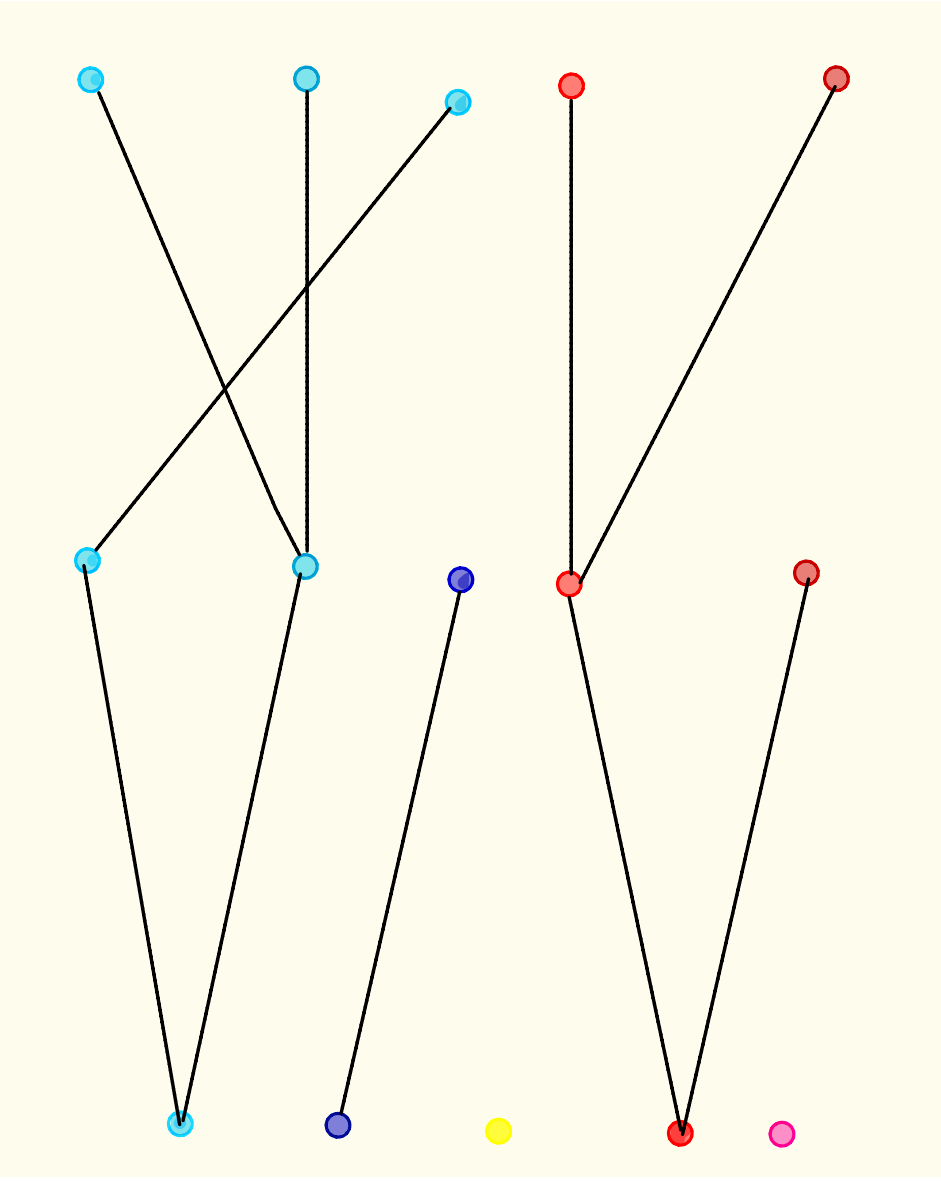


Convergence to Kingman's coalescent

Let $\left(B_i^{(N,n)}\right)_{i\in\mathbb{N}}$ be the ancestral process of a sample of n individuals, when the population at the beginning of each day is N.

Theorem

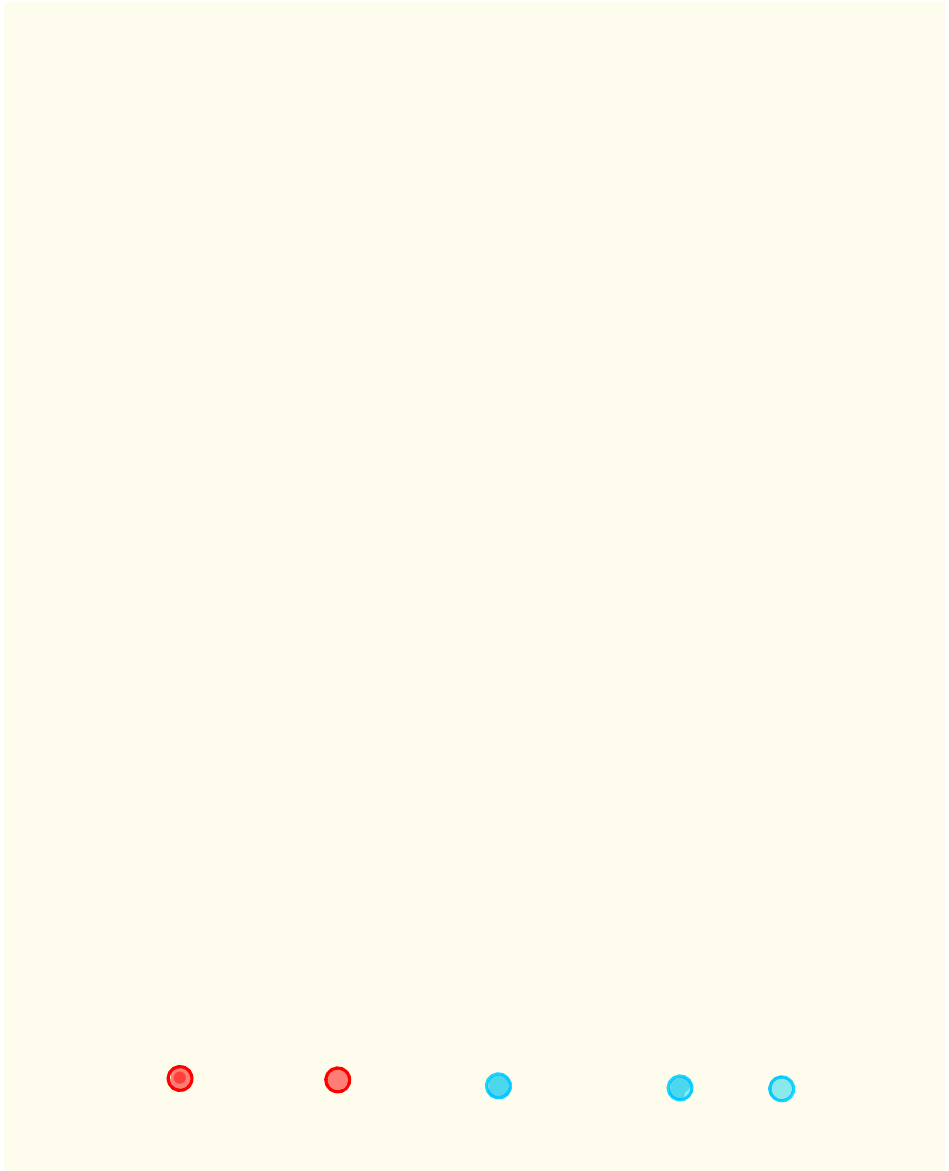
For all $n \in \mathbb{N}$, the sequence of ancestral processes $\left(B^{(N,n)}_{\lfloor Nt/2(1-\frac{1}{\gamma})\rfloor}\right)_{t\geq 0}$ converges weakly on the space of càdlàg paths as $N \to \infty$ to Kingman's n-coalescent.

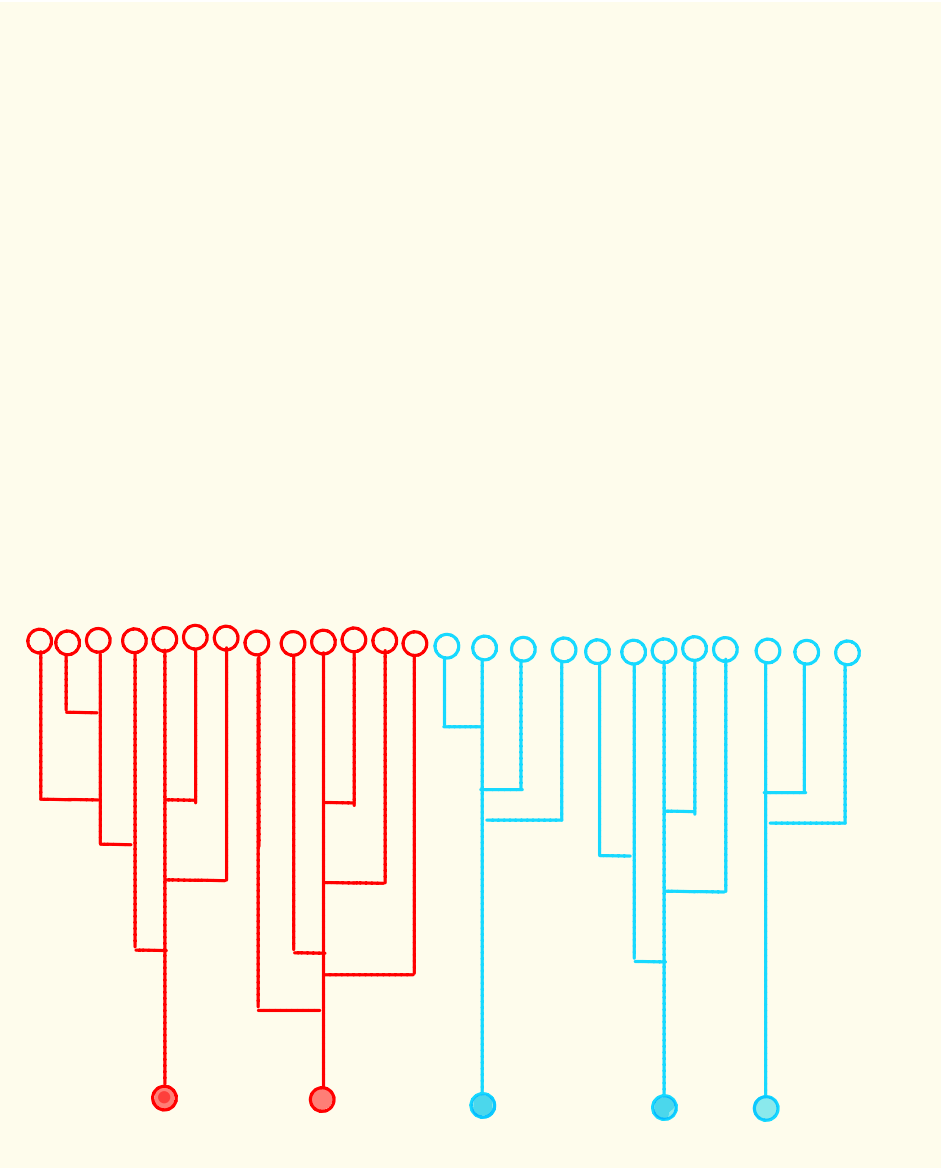
Introducing selective advantage

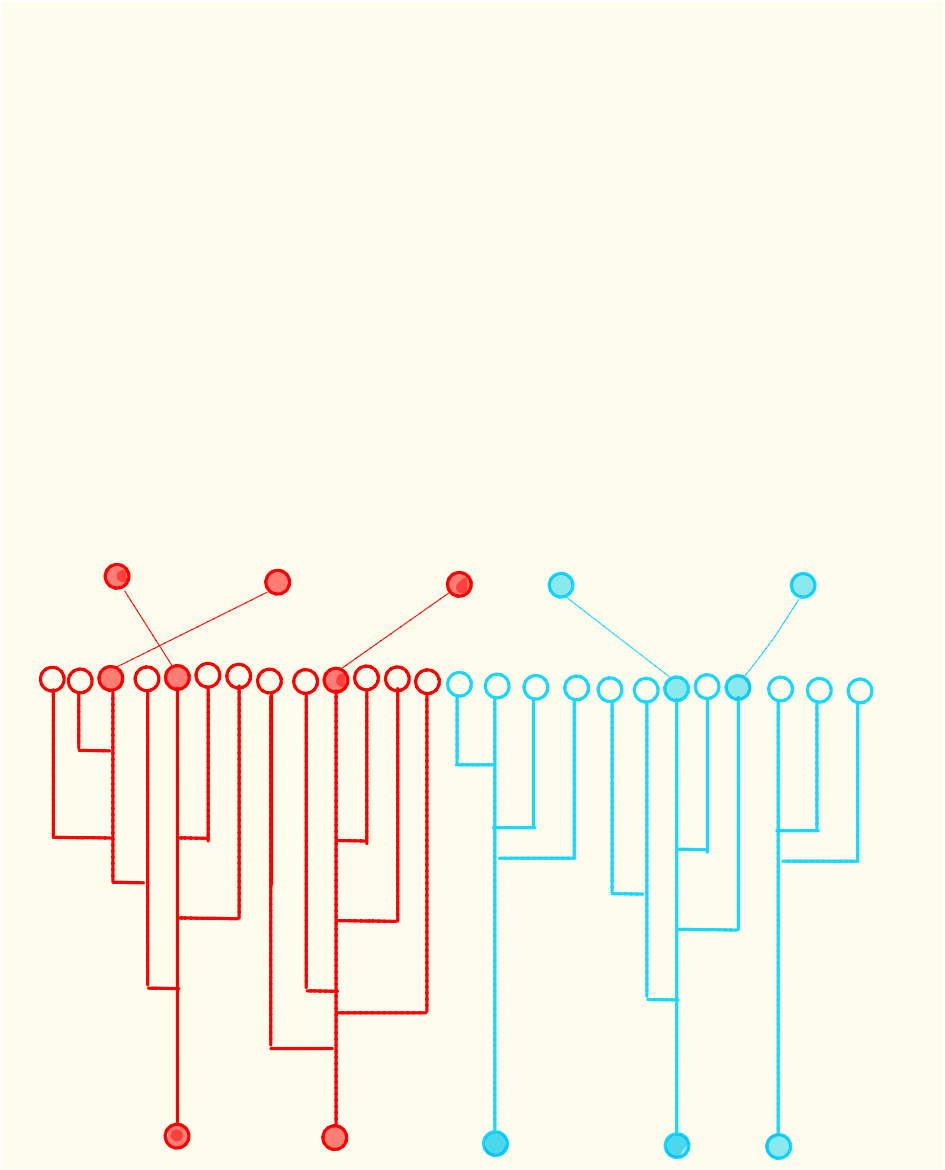
- Assume that some individuals reproduce at rate $r + \varrho_N$ (mutants), while other reproduce at rate r (basis population).
- Stopping rule: the reproduction stops when the expectation of the total population is γN.
- Let $M_i(t)$ be the number of mutants at time t of day i.
- We are interested in the process

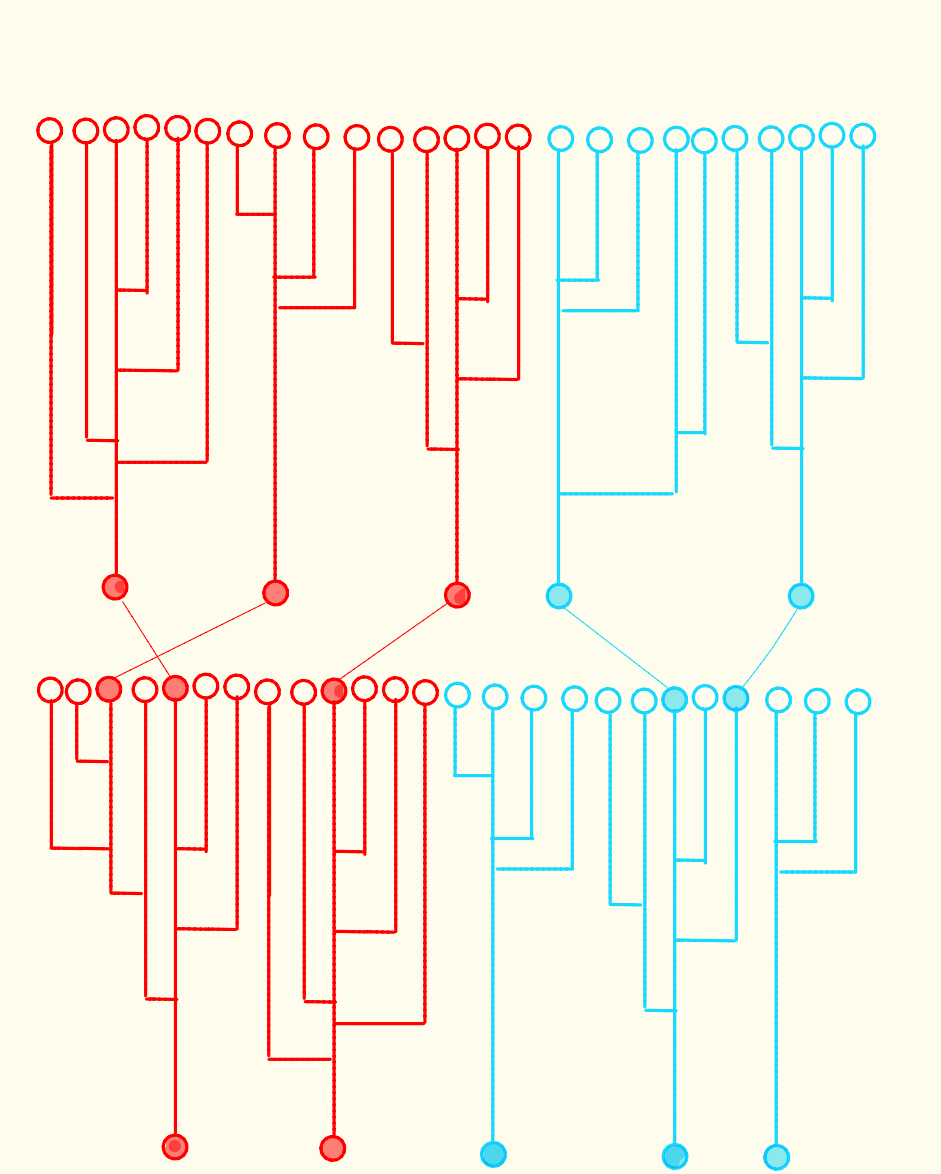
$$\{K_i\}_{i\in\mathbb{N}} := \{M_i(0)\}_{i\in\mathbb{N}},$$

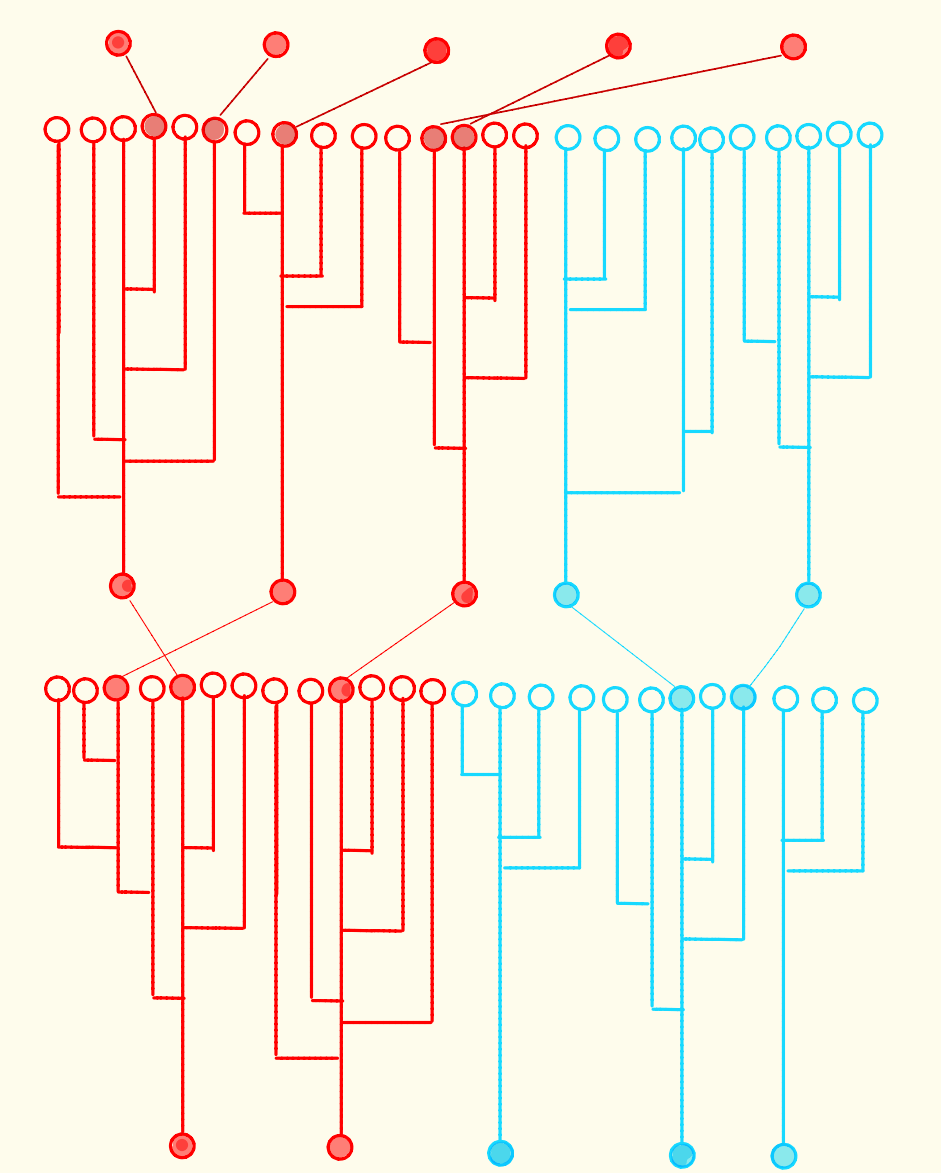
which is constructed recursively using uniform sampling.









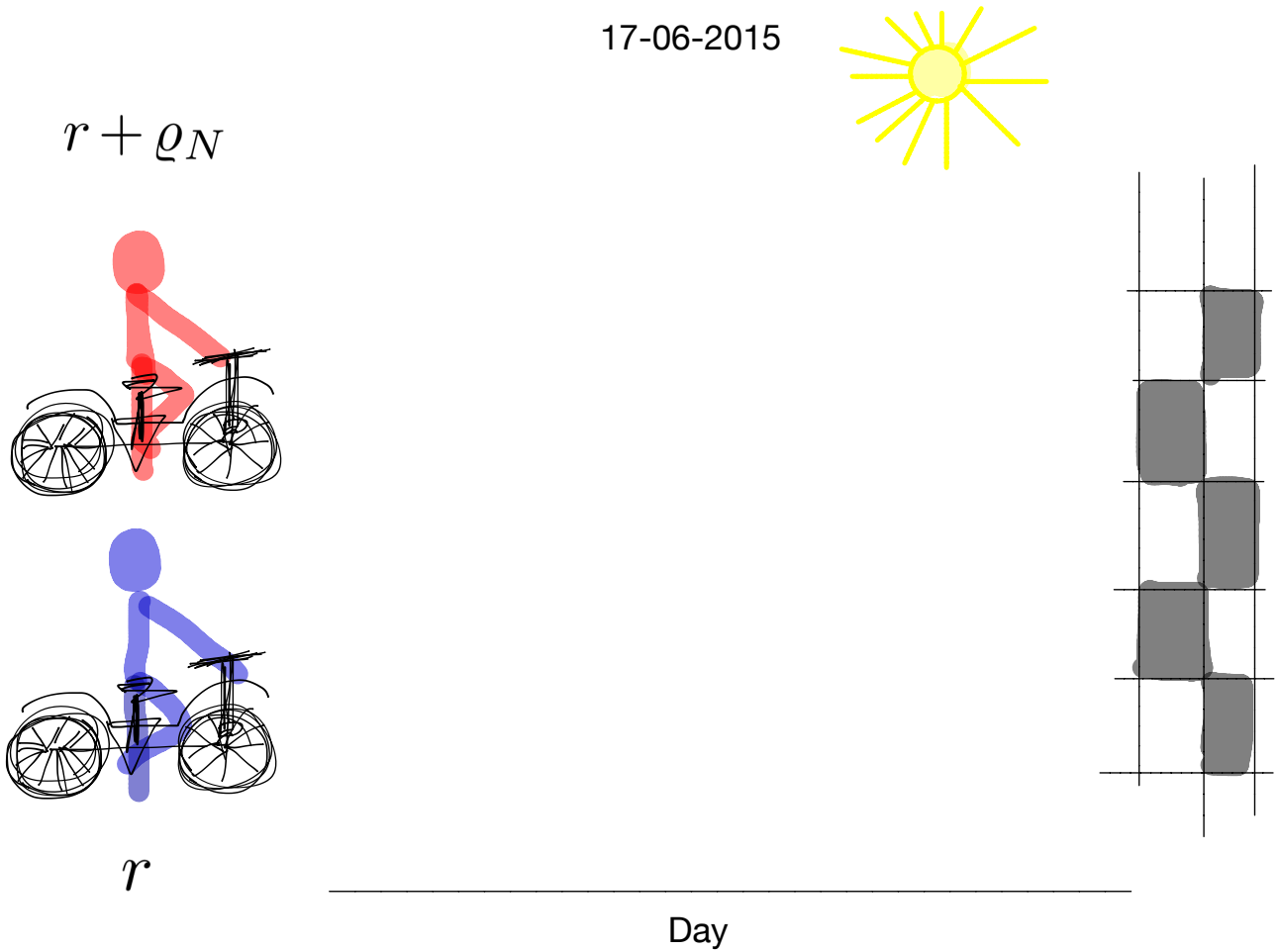


Selective advantage

Basic population reproduces at rate r.
Mutants reproduce at rate $r + \varrho_N$.

$$\mathbb{E}[K_1 | K_0 = 1] = 1 + \varrho_N \frac{\log \gamma}{r} + o(\varrho_N).$$

Race until the sun is gone



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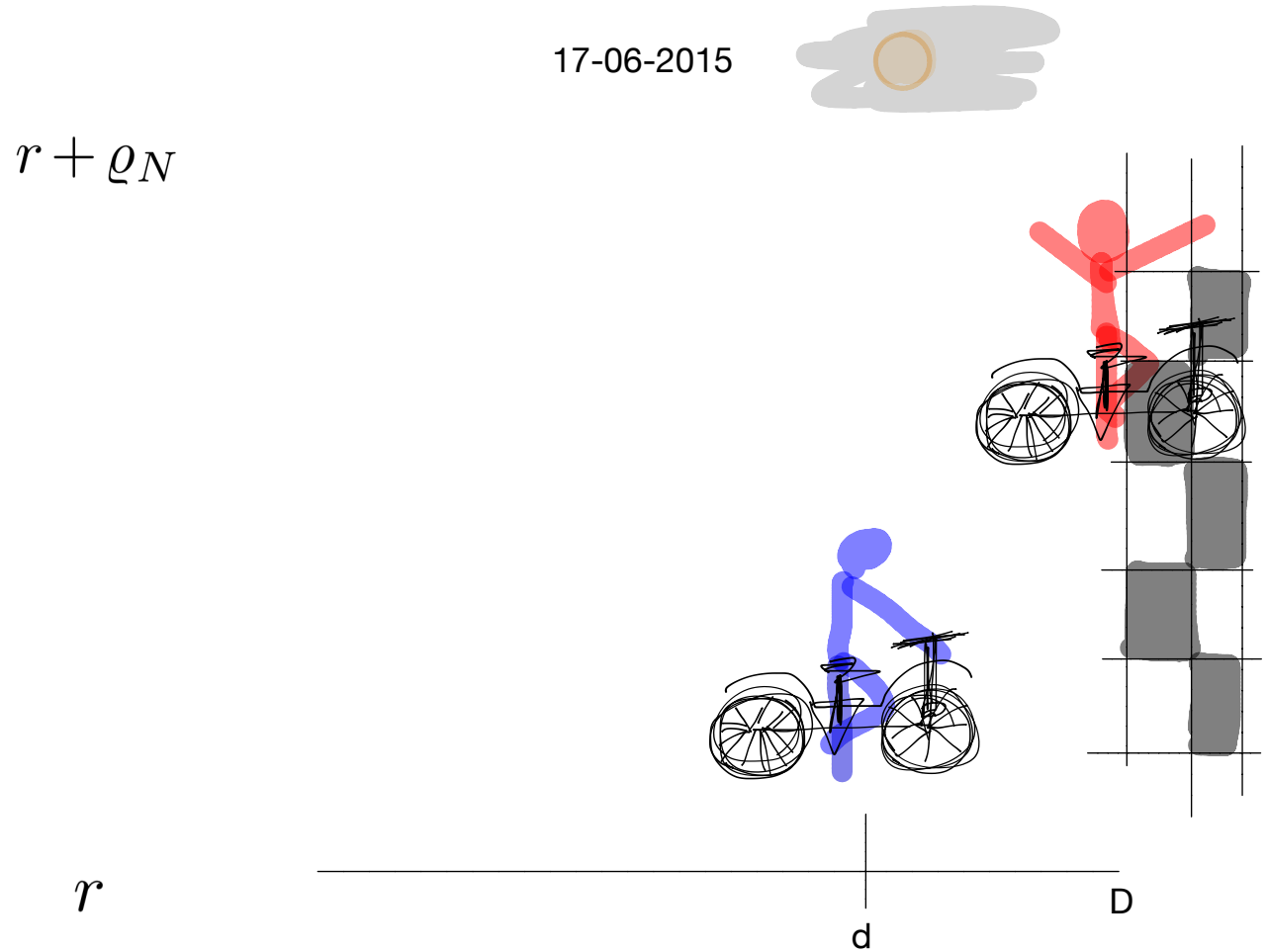

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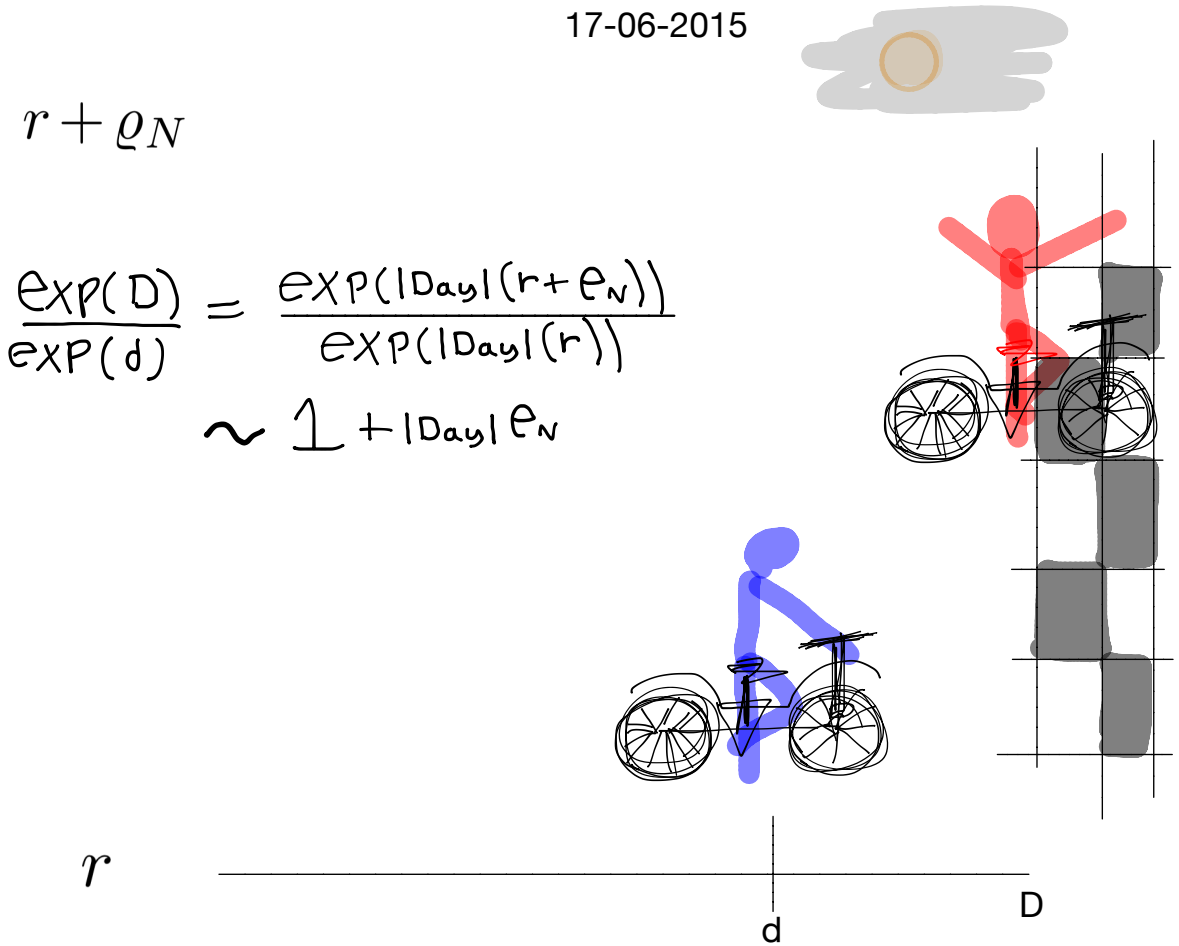

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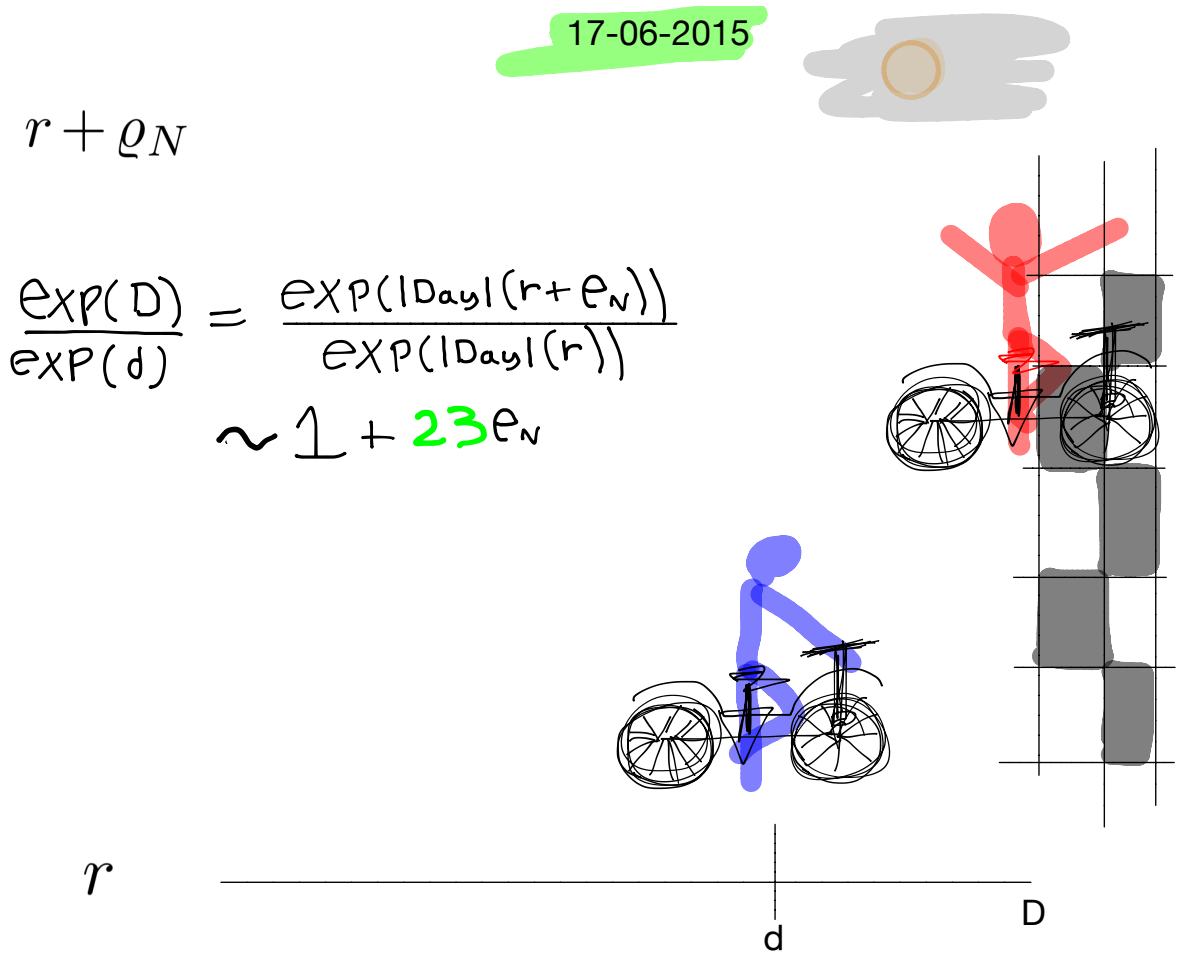

Race until the sun is gone

$r + \varrho_N$

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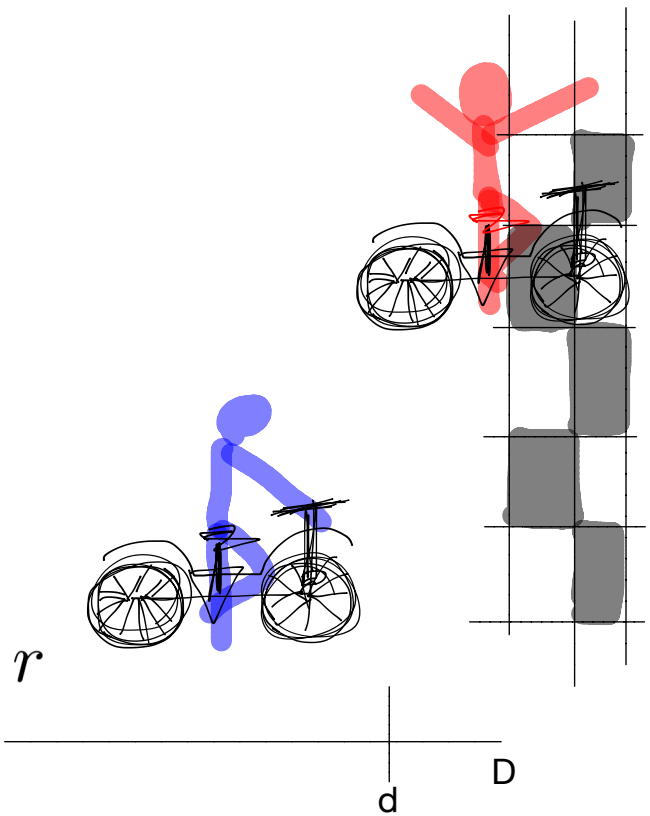
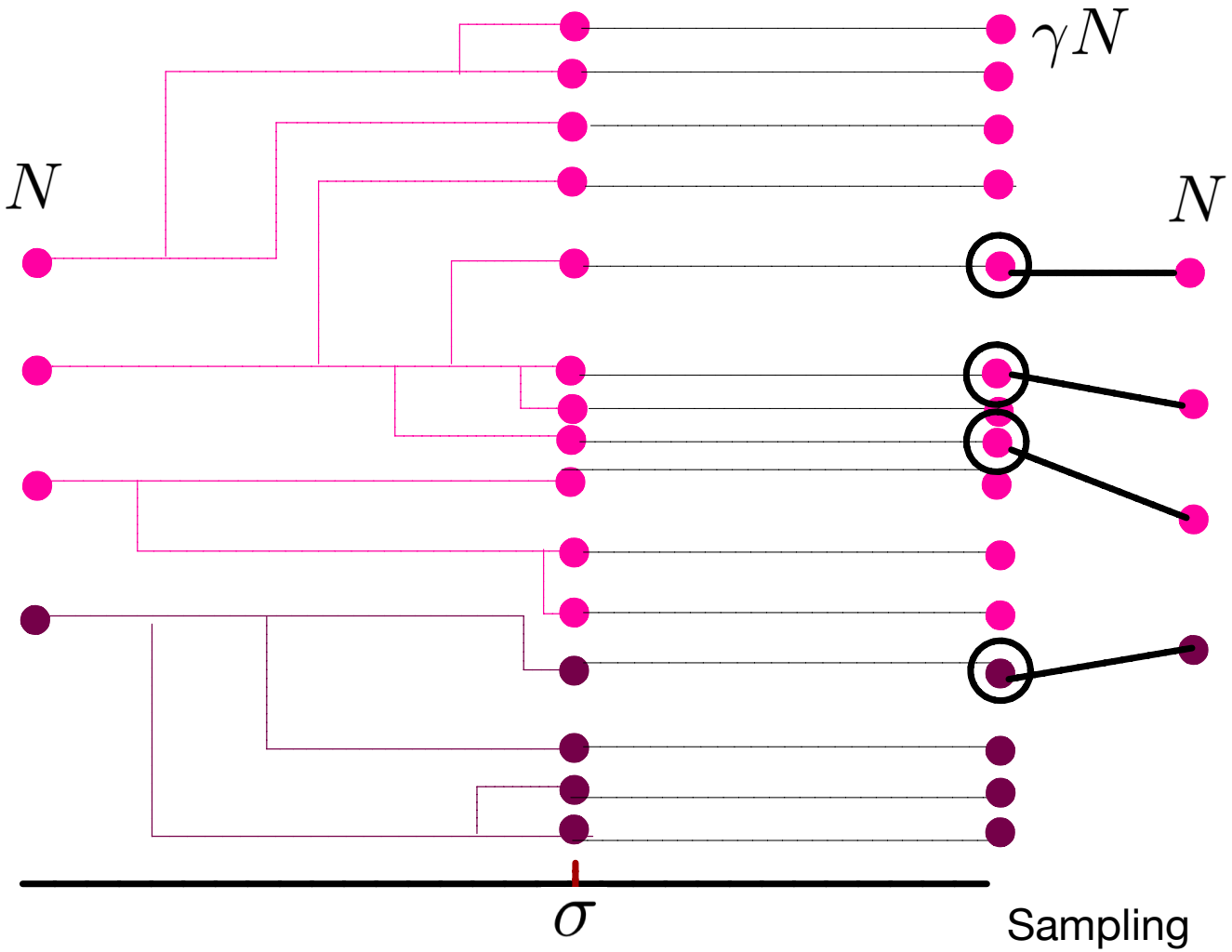


$$\frac{exp(D)}{exp(d)} = \frac{exp(lDayl(r+e_N))}{exp(lDayl(r))}$$

$$\sim 1 + 1\, e_N$$

The *effective competition time*, and its dependence on *r*



Let $\pi_N := \mathbb{P}(\exists i \in \mathbb{N} : K_i = N \,|\, K_0 = 1)$, and $\tau^N := \tau^N_{\text{fix}} \wedge \tau^N_{\text{ext}}$.

Theorem (Probability and speed of fixation)

Under the assumptions of our model, as $N \to \infty$,

$$\pi_N \sim \frac{\gamma}{\gamma - 1} \frac{\varrho_N \log \gamma}{r}.$$

Moreover, for any $\delta > 0$ there exists $N_\delta \in \mathbb{N}$ such that for all $N \geq N_\delta$

$$\mathbb{P}(\tau^N > \varrho_N^{-1-3\delta}) \leq (7/8)^{\varrho_N^{-\delta}}.$$

The weak mutation - moderate selection model (Assumption A)

i) Beneficial mutations add ϱ_N to the reproduction rate of the individual that suffers the mutation.

ii) In each generation, with probability μ_N there occurs a beneficial mutation. The mutation affects only one (uniformly chosen) individual, and every offspring of this individual also carries the mutation.

iii) There exists $0 < b < 1/2$, and $a > 3b$, such that $\mu_N \sim N^{-a}$ and $\varrho_N \sim N^{-b}$ as $N \to \infty$.

$$\mu_N << \varrho_N$$

We define the fitness of the population at the beginning of day i with respect to that at the beginning of day 0 as

$$F_i := \frac{\log \frac{1}{N} \sum_{j=1}^{N} e^{R_{i,j} t}}{\log e^{r_0 t}}$$

where $R_{i,j}, j = 1, \ldots, N$ are the reproduction rates of the individuals present at the beginning of day i, and t is a given time for which the two populations are allowed to grow together.

If the whole population reproduces at the same rate (R_i), then

$$F_i = \frac{R_i}{r_0}$$

where $r_0 := R_0$.

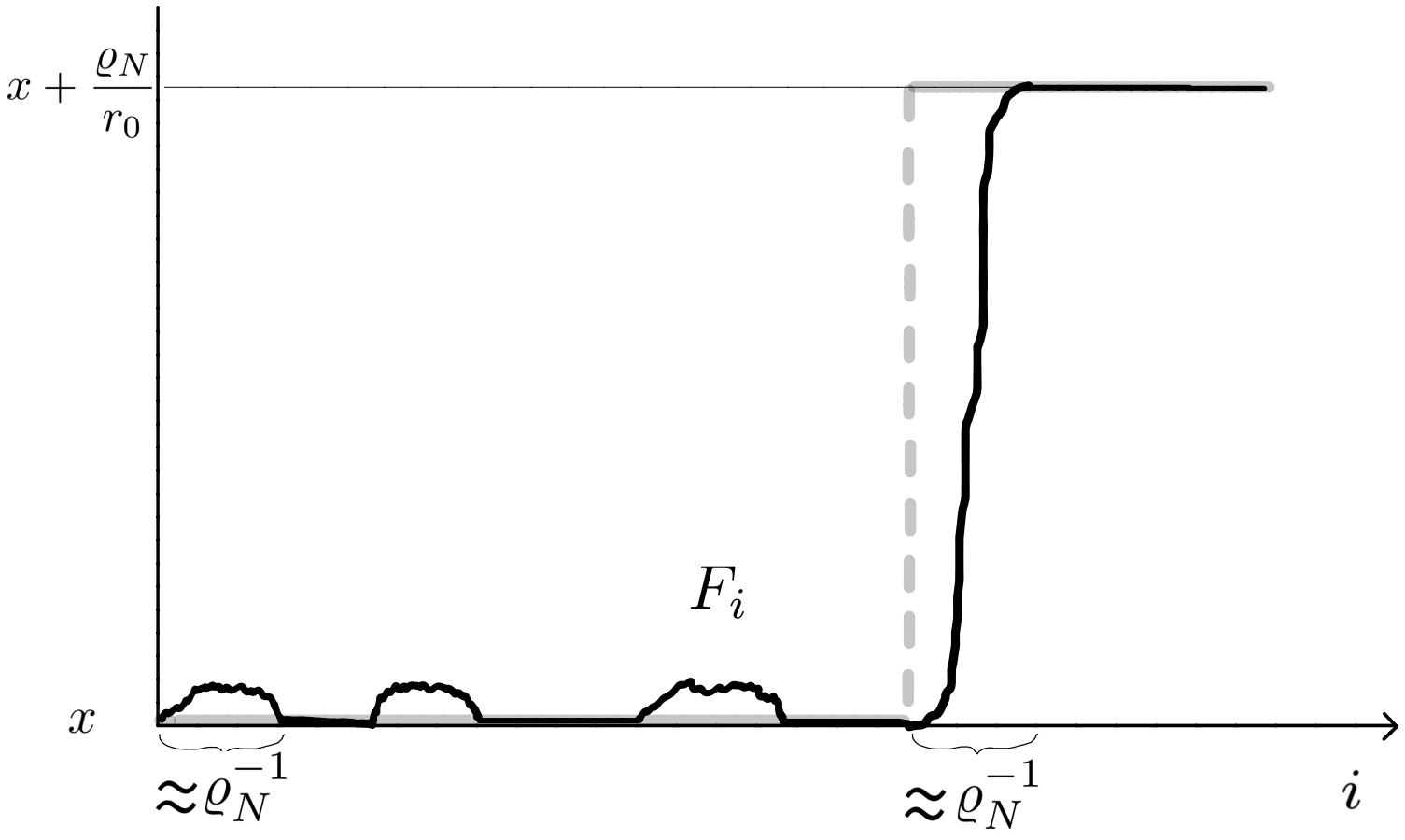


Figure: The number of attempts to go to fixation, when the reproduction rate of the basic poulation is x, is distributed Geometric with parameter $\pi_N \sim \varrho_N \frac{C(\gamma)}{x}$.

Theorem (Convergence of the relative fitness process)

Assume $R_{0,j} = r_0$ for $j = 1, ..., N$, and let $(F_i)_{i \in \mathbb{N}_0}$ be the process of relative fitness. Then under Assumption A, the sequence of processes $(F_{\lfloor (\varrho_N^2 \mu_N)^{-1} t \rfloor})_{t \geq 0}$ converges in distribution as $N \to \infty$ locally uniformly to the deterministic function

$$f(t) = \sqrt{1 + \frac{\gamma \log \gamma}{\gamma - 1} \frac{2t}{r_0^2}}, \ t \geq 0 \, .$$

Table: Our model compared with Wiser et al.

	Our model	Wiser et al
Clonal interference	No	Yes
Epistasis	No	Yes
Design of the experiment	Yes	No
	$f(t) = (1 + \frac{2C(\gamma)t}{r_0^2})^{1/2}$	$w(t) = (1 + ct)^{1/2g}$

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If we include Epistasis in our model, by assuming that the selective advantage provided by a single mutation to an individual that reproduce at rate x is $\varrho_N^{(x)} = x^q \varrho_N$, for some $q > -1$, then

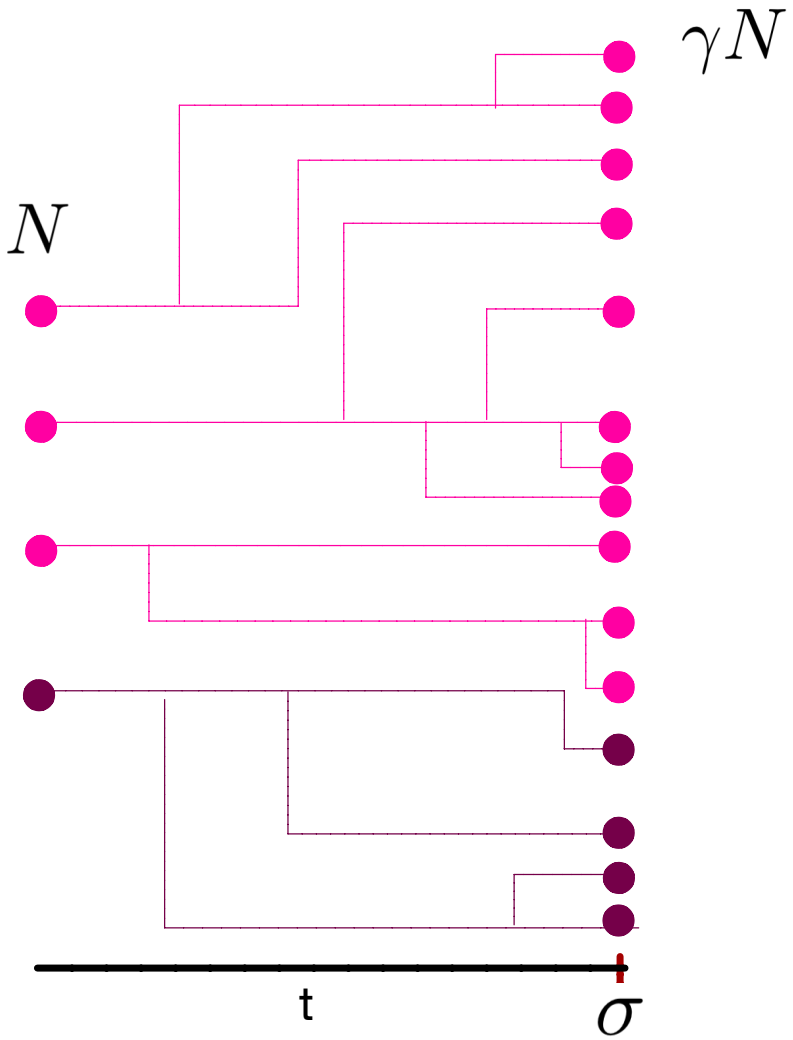
$$h(t) = \left(1 + \frac{2(1+q)C(\gamma)}{r_0^2} t\right)^{\frac{1}{2(1+q)}}$$

Main part of the proof:

Fixation probability and fixation/extinction time of one single mutant

(complemented by the proof of the absence of clonal interference under the stated assumptions)

The "within days" process of the number of mutants



The "within days" process of the number of mutants

A population starting with k mutants with reproduction rate $r + \varrho_N$ and $N - k$ non-mutants with reproduction rate r is modelled by :

$$Y_t^{(N,k)} = M_t^{(k)} + Z_t^{(N-k)}$$

where $(M_t^{(k)})$ is a Yule process with rate $r + \varrho_N$
and $(Z_t^{(N-k)})$ is a Yule process with rate r.

(M_t^k) and (Z_t^{N-k}) are independent.

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The population stops at time σ_k defined by

$$\mathbb{E}[Y_{\sigma_k}^{(N,k)}] = \gamma N.$$

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Then

$$M_{\sigma_k}^k \overset{(d)}{=} NB(k, e^{-(r+\varrho_N)\sigma_k}),\ Z_{\sigma_k}^{N-k} \overset{(d)}{=} NB(N-k, e^{-r\sigma_k}).$$

$NB(\cdot,\cdot)$: negative binomial distribution.

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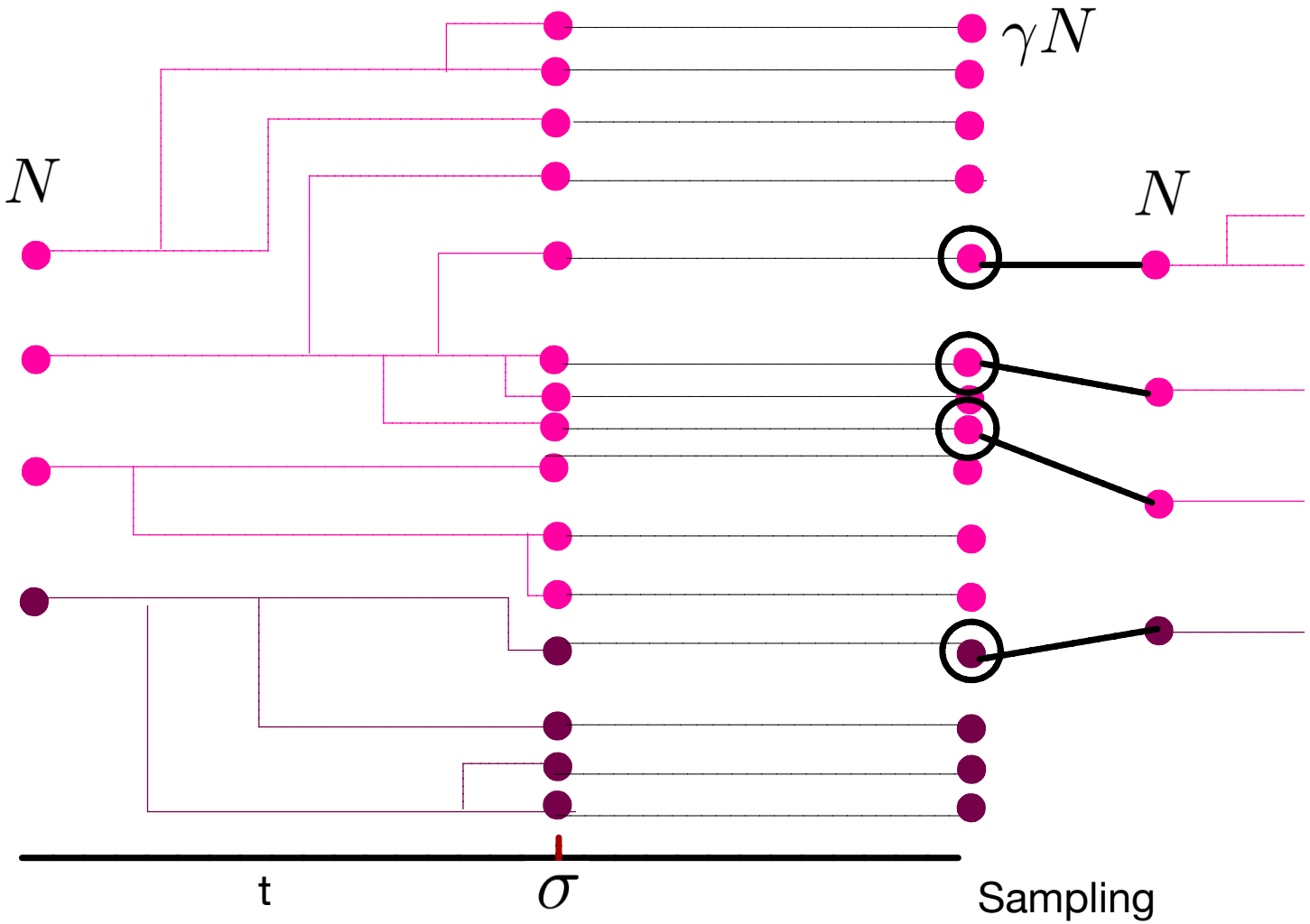
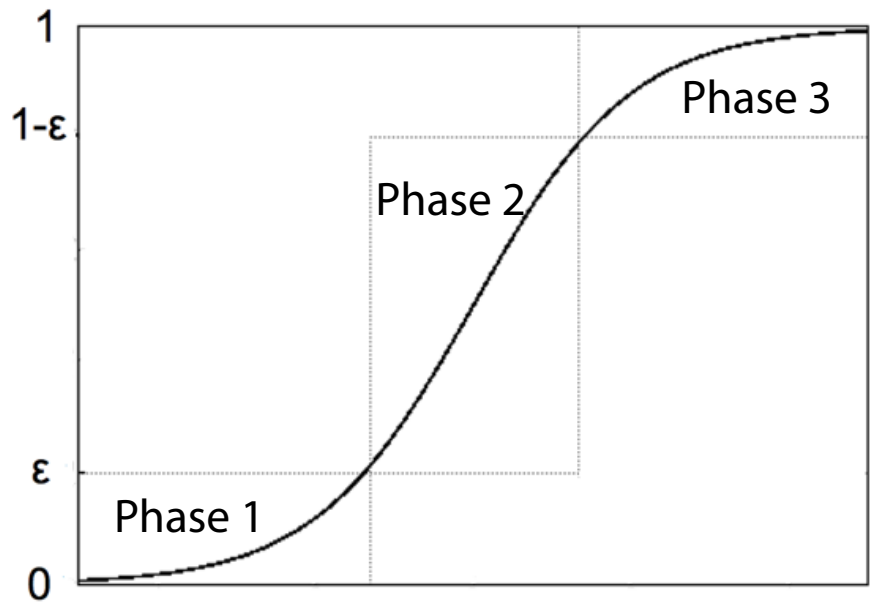


The "between days" process of the number of mutants

The transition of the number of mutants from day $i-1$ to day i:

Given $\{K_{i-1} = k,\ M_{\sigma_k}^{(k)} = M,\ Z_{\sigma_k}^{(k)} = Z\}$,
K_i is a hypergeometric random variable with parameters $M + Z, M, N$.

Three phases of a sweep



ODE approximation for the middle phase of the sweep

Proposition

The process $(\frac{1}{N}K_{\lfloor \varrho_N^{-1} t \rfloor})_{t \geq 0}$ *with* $K_0 = \lfloor xN \rfloor, x \in [0,1]$ *converges in distribution to a function* g *defined by*

$$g'(t) = g(t)(1 - g(t))\frac{\log \gamma}{r}, \quad g(0) = x.$$

Conclusion: For any $0 < \varepsilon < 1/2$ the number of mutants increases from $\lfloor \varepsilon N \rfloor$ to $\lfloor (1-\varepsilon)N \rfloor$ with high probability in an order of ϱ_N^{-1} days.

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Question: How about the onset and the final phase of the sweep?

A coupling with near-critical Galton-Watson processes

Assume at the end of one day there are M mutants, Z non-mutants.
Let $\Gamma := \frac{M+Z}{N} \quad (\sim \gamma)$.
Then, given Γ, each individual will be sampled with probability $1/\Gamma$.

The difficulty

Exchangeable but not independent sampling!

Independent sampling+independent reproduction=Galton-Watson process.

A coupling with near-critical Galton-Watson processes

Recall

k is the mutant number at the beginning of a day.
M (resp. Z) is the number of mutants (resp. non-mutants) at the end of that day.

We index the mutants at the end of the day by $j = 1, 2, \ldots, M$. Let

$$X_j := \mathbf{1}_{j-\text{th mutant is sampled}}.$$

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Another way to represent the hypergeometric sampling:
Let $(U_j)_{j\in\mathbb{N}}$ be i.i.d uniform variables on $[0, 1]$.
Let $\tilde{X}_1 := \mathbf{1}_{U_1<1/\Gamma}$ and for any $j > 1$

$$\tilde{X}_j := \mathbf{1}_{U_j<\frac{N-\sum_{l=1}^{j-1}\tilde{X}_l}{\Gamma N-(j-1)}}.$$

A coupling with near-critical Galton-Watson processes

Fact

$$(\tilde{X}_j) \overset{(d)}{=} (X_j), j = 1, 2, \ldots, M.$$

Advantage of using $\tilde{X}_j = \mathbf{1}_{U_j < \frac{N - \sum_{l=1}^{j-1} \tilde{X}_l}{\Gamma N - (j-1)}}$:

one can give uniform deterministic lower and upper bounds which capture $\frac{N - \sum_{l=1}^{j-1} \tilde{X}_l}{\Gamma N - (j-1)}$ with high probability.

A coupling with near-critical Galton-Watson processes

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Independence arises!

A coupling with near-critical Galton-Watson processes

For given $0 < \alpha < 1/2$, let

$J := \inf\{j : \frac{N - \sum_{l=1}^{j-1} \tilde{X}_l}{\Gamma N - (j-1)} \notin [\frac{1}{\gamma} - N^{-\alpha}, \frac{1}{\gamma} + N^{-\alpha}]\}$.

Consequence: for any j,

$$\underline{X}_j \leq \tilde{X}_j \leq \overline{X}_j \text{ on the event } \{J > j\}$$

where $\underline{X}_j := \mathbf{1}_{U_j \leq \frac{1}{\gamma} - N^{-\alpha}}$ and $\overline{X}_j := \mathbf{1}_{U_j \leq \frac{1}{\gamma} + N^{-\alpha}}$.

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Lemma

Starting with $k \leq \varepsilon N$ mutants $(0 < \varepsilon < 1)$, there exists a constant $c > 0$ independent of N, s.t.

$$\mathbb{P}(J > M) \geq 1 - e^{-cN^{1-2\alpha}} \text{ as } N \to \infty.$$

A coupling with near-critical Galton-Watson processes

Using the "independent sampling" variables $(\underline{X}_j)$ and $(\overline{X}_j)$, one can define two Galton-Watson processes $(\underline{K}_i)$ and $(\overline{K}_i)$ which obey the following

Theorem

Let $T_1^N := \inf\{i \geq 1 : K_i \geq \varepsilon N\}$.
For $0 < \varepsilon < 1/\gamma$, $\overline{K}_0 \geq K_0 \geq \underline{K}_0$, $K_0 \leq \varepsilon N$, *and* $h \in \mathbf{N}_0$,

$$\mathbb{P}(\overline{K}_{\min\{i,T_1^N\}} \geq K_{\min\{i,T_1^N\}} \geq \underline{K}_{\min\{i,T_1^N\}}, \forall i \leq h) \geq (1 - 2e^{-cN^{1-2\alpha}})^h.$$

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Consequence: Starting with 1 mutant, one can approximate the extinction probability, as well as the hitting probability and hitting time to $\geq \varepsilon N$ through the two (near-critical) Galton-Watson processes $(\underline{K}_i)$ and $(\overline{K}_i)$.

$$\mathbb{E}[\underline{K}_1|\underline{K}_0 = 1] = 1 + \frac{\log\gamma}{r}\varrho_N + o(\varrho_N), \mathbb{E}[\overline{K}_1|\overline{K}_0 = 1] = 1 + \frac{\log\gamma}{r}\varrho_N + o(\varrho_N).$$

A coupling with near-critical Galton-Watson processes

Theorem (Phase 1)

For any $0 < \varepsilon < 1/\gamma$, *as* $N \to \infty$

$$\frac{\varrho_N \log \gamma}{r} \frac{\gamma}{\gamma - 1}(1 - \varepsilon) + o(1) \leq \mathbb{P}_1(\exists i : K_i \geq \varepsilon N) \leq \frac{\varrho_N \log \gamma}{r} \frac{\gamma}{\gamma - 1} + o(1)$$

For any $\delta > 0$,

$$\liminf_{N \to \infty} \mathbb{P}_1(0 < K_i < \varepsilon N, \forall i \leq \varrho_N^{-1-\delta}) \leq \frac{\varepsilon}{1 - \varepsilon}$$

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Theorem (Phase 3)

Let $m \geq 1$ *and* $0 < \varepsilon < 1/m\gamma$. *For any* $k \geq (1 - \varepsilon)N$ *and* $\delta > 0$,

$$\liminf_{N \to \infty} \mathbb{P}_k(K \text{ reaches } N \text{ in at most } \varrho_N^{-1-\delta} \text{ days }) \geq 1 - 2/m.$$

Résumé

Phase 1: Starting with 1,
the process (K_i) reaches εN with probability $\sim \frac{\varrho_N \log \gamma}{r} \frac{\gamma}{\gamma - 1}$,
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Résumé

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Phase 3: Reaching N from $(1-\varepsilon)N$ has high probability,
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of relative fitness which is decelerating as time increases.

This is because (i) each beneficial mutation
was assumed to add ρ_N to the individual reproduction rate r,
and (ii) the fixation probability turned out to decrease as r increases.

Thank you for your attention!