Ancestral processes with selection

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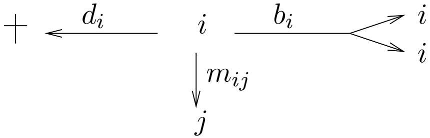
Agenda

1. mutation-selection differential equation
   & multitype branching process
   - forward and backward
   - ancestral distribution, variational principle
     (with H.-O. Georgii, 2007)

2. Moran model with selection and mutation
   - forward and backward
   - ancestral distribution, lookdown ancestral selection graph
     (with A. Wakolbinger, S. Kluth, U. Lenz, 2015, 2016, 2018)

MuSe Model

individual = (geno)type $i \in S$ (finite)



(Malthusian) fitness: $r_i := b_i - d_i$

LLN

$y_i(t)$ abundance of type i at time t $\quad (i \in S)$

$$\dot{y}_i(t) = r_i y_i(t) + \sum_{j:j \neq i} \big(y_j(t) m_{ji} - y_i(t) m_{ij}\big)$$

or

$$\dot{y}(t) = y(t)\big(\overbrace{\underset{\substack{\uparrow \\ m_{ij}}}{\mathcal{M}} + \underset{\substack{\uparrow \\ r_i}}{\mathcal{R}}}^{\mathcal{A}}\big)$$

with solution

$$y(t) = y(0)\,\mathrm{e}^{t\mathcal{A}}$$

MuSe differential equation

relative frequencies:

$$\dot{p}_i(t) = (r_i - \bar{r}(t))p_i(t) + \sum_{j:j \neq i} (p_j(t)m_{ji} - p_i(t)m_{ij})$$

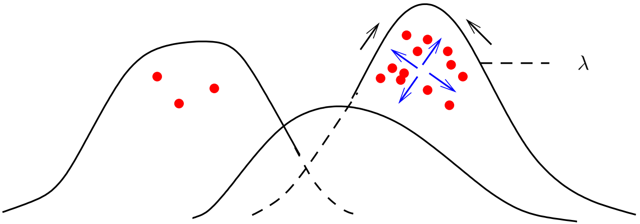
$$p_i(t) := \frac{y_i(t)}{\sum_j y_j(t)}, \qquad \bar{r}(t) := \sum_j r_j p_j(t)$$

MuSe Equilibrium

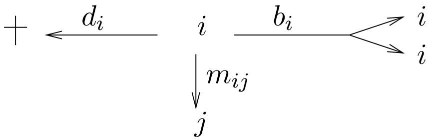
$\mathcal{M}$ irreducible $\rightsquigarrow$ Perron-Frobenius: $p\mathcal{A} = \lambda p \quad (\langle p, 1 \rangle = 1)$

$$p(t) \xrightarrow{t \to \infty} p \quad \text{(stationary type distribution)}$$

$$\lambda = \sum_i r_i p_i = \langle p, r \rangle = \bar{r} \qquad \text{(equilibrium mean fitness)}$$



Multitype Branching

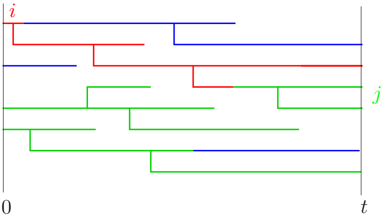


i-individual:

waiting time $\sim \mathcal{E}(a_i), \quad a_i = b_i + d_i + \sum_{j:\, j \neq i} m_{ij}$

then: birth, death, mutation to j with probability $\dfrac{b_i}{a_i}, \dfrac{d_i}{a_i}, \dfrac{m_{ij}}{a_i}$

Multitype branching



$(Z(t))$, $Z(t)$ counting measure on S
$Z_j(t)$ # ind. of type j at time t
first-moment generator: $\mathcal{A} = \mathcal{M} + \mathcal{R}$

$\mathbb{E}^i(Z_j(t)) = (\mathrm{e}^{t\mathcal{A}})_{ij}$
assumption: $\lambda > 0 \rightsquigarrow$ branching supercritical
(with asymptotic growth rate λ)

Connections "branching" $\leftrightarrow$ "MuSe":

1. $$\frac{Z(t)}{|Z(t)|} \overset{t\to\infty}{\longrightarrow} p \overset{\infty\leftarrow t}{\longleftarrow} p(t)$$
   $\uparrow$
   a.s., on {non-extinction} (Kesten–Stigum '66)

   p left PF-EV of $\mathcal{A}$ (stationary distribution of types)

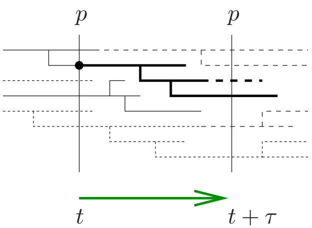
2. $$\mathbb{E}^i(|Z(t)|\,\mathrm{e}^{-\lambda t}) \overset{t\to\infty}{\longrightarrow} h_i \overset{\infty\leftarrow t}{\longleftarrow} \frac{\sum_j(\,\mathrm{e}^{t\mathcal{A}})_{ij}}{|p(0)\,\mathrm{e}^{t\mathcal{A}}|}$$

   $h = (h_i)_{i\in S}$ right PF-EV of $\mathcal{A}$ (asymptotic offspring expectation)

$$\langle p, 1\rangle = 1 = \langle p, h\rangle$$

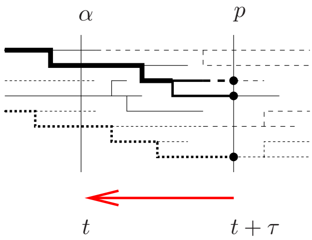
Forward and backward

forward



backward

(NO coalescent)



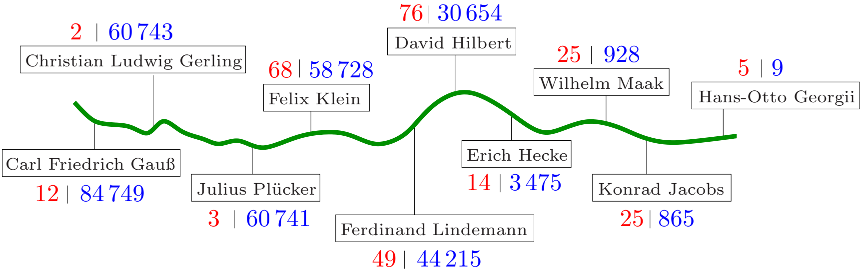
$\tau \to \infty \rightsquigarrow$

$\alpha_i := p_i h_i$

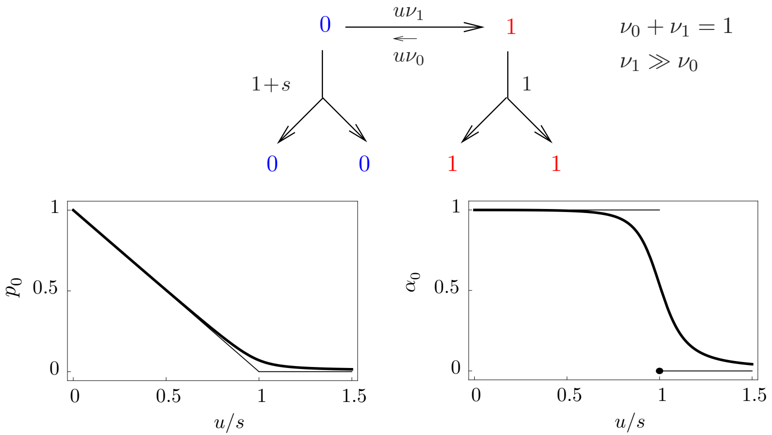
ancestral type distribution

Jagers, Nerman 1992 . . .

Mathematics genealogy project

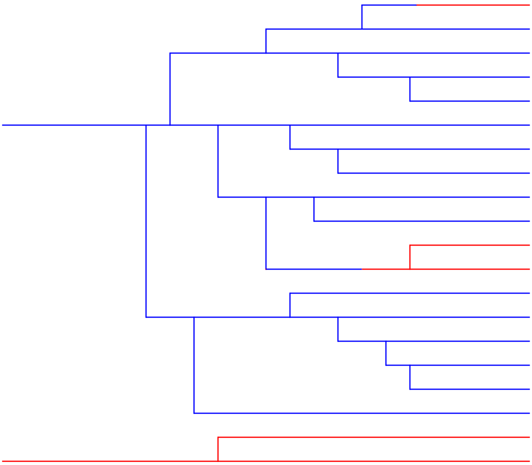


Forward and backward

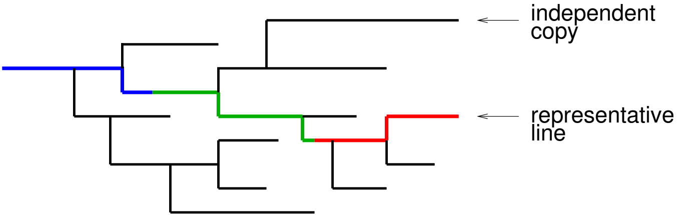


$s = 0.001$, $\nu_0 = 0.005$ and $\nu_0 \to 0$

Forward and backward

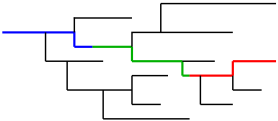


Large deviations



mutation process (M_t) on representative line (M_t type at time t)
(generator $\mathcal{M}$, stationary distribution π)

Large deviations



empirical measure L_t on S: $L_t(j) = \frac{1}{t}\int_0^t \mathbf{1}_{\{M_\tau = j\}}\,\mathrm{d}\tau$ (random!)

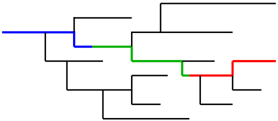
LDP: $\mathbb{P}(L_t \sim \nu) \approx \mathrm{e}^{-t\,I_{\mathcal{M}}(\nu)}$ (large t)

$$\left(\lim_{t\to\infty} \frac{1}{t}\log \mathbb{P}(L_t \in A) = -\inf_{\nu \in A} I_{\mathcal{M}}(\nu)\right)$$

rate function: $I_{\mathcal{M}}(\nu) = \sup_{v>0}\left(-\langle \nu, \frac{\mathcal{M}v}{v}\rangle\right)$

(M_t) reversible $\rightsquigarrow$ $I_{\mathcal{M}}(\nu) = -\left\langle \sqrt{\frac{\nu}{\pi}}, \mathcal{M}\sqrt{\frac{\nu}{\pi}}\right\rangle_\pi$

Variational principle



line with $L_t = \nu$

experiences

- mutation: changes ν

  $\mathbb{P}(L_t \sim \nu)$ decays with $I_{\mathcal{M}}(\nu)$ $\quad$ (> 0 for $\nu \neq \pi$ (stat. distr.), $= 0$ for $\nu = \pi$)

  $L_t \underset{t\to\infty}{\longrightarrow} \pi$ a.s.

- reproduction: duplicates ν at rate r_{M_t} at time t, mean rate $\langle \nu, r\rangle$

Theorem (EB & Georgii 2007)

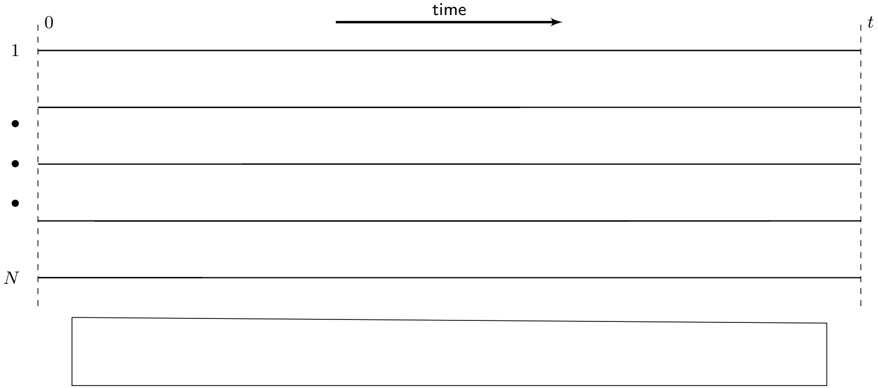
$$\langle p, r\rangle = \lambda = \sup_{\nu \in \mathcal{P}(S)} [\langle \nu, r\rangle - I_{\mathcal{M}}(\nu)] = \langle \alpha, r\rangle - I_{\mathcal{M}}(\alpha)$$

$\langle p, r\rangle$ ↑ "present"; $\langle \nu, r\rangle$ ↑ energy; $I_{\mathcal{M}}(\nu)$ ↑ entropy; $\langle \alpha, r\rangle - I_{\mathcal{M}}(\alpha)$ ↑ "past"

2-type Moran model with mutation and selection

- population of fixed size N
- types: 0 ('fit') and 1 ('unfit')
- individuals of type 1 reproduce at rate 1
- individuals of type 0 reproduce at rate $1 + s^N, \quad s^N \geqslant 0$
- single offspring inherits parent's type and replaces uniformly chosen individual
- mutation at rate $u^N > 0$
- resulting type: 0 with probability ν_0; 1 with probability ν_1 $(\nu_0 + \nu_1 = 1)$

Interacting particle system: untyped



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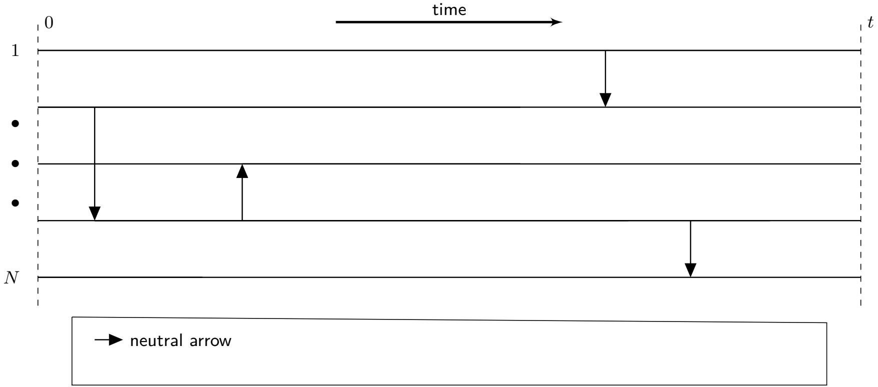
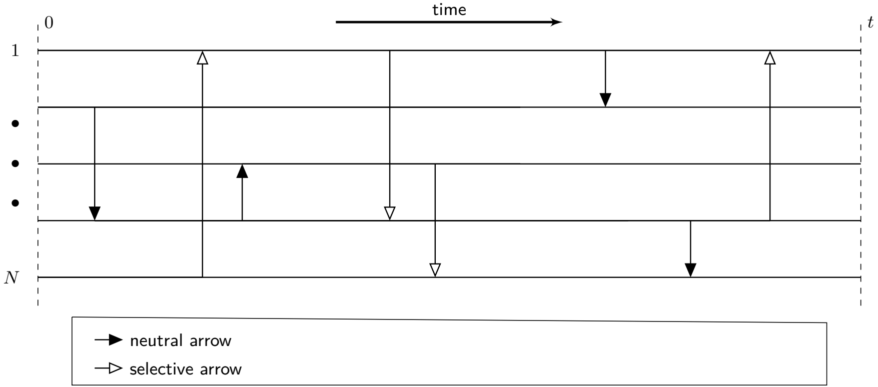


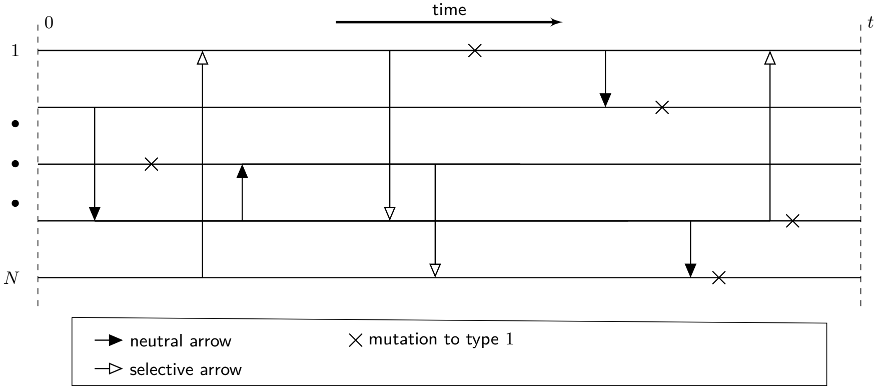
neutral arrows: rate 1,

Interacting particle system: untyped



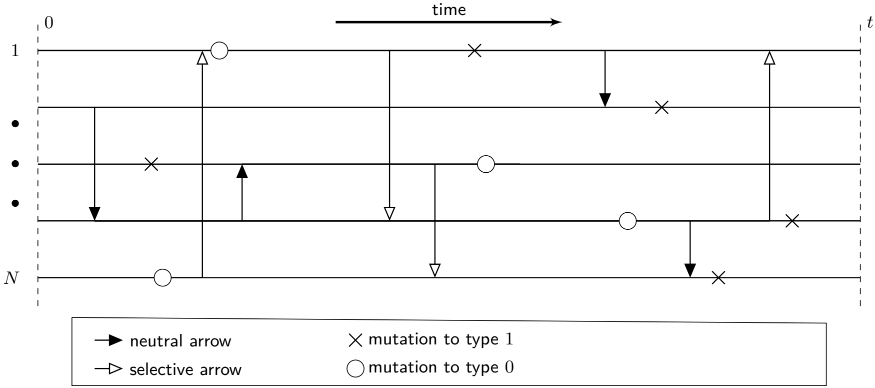
neutral arrows: rate 1, selective arrows: rate s^N,

Interacting particle system: untyped



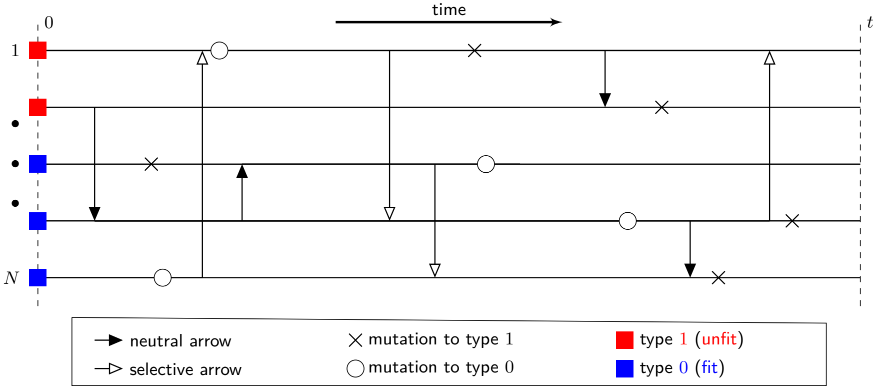
neutral arrows: rate 1, selective arrows: rate s^N,
mutation to type 1: rate $u^N \nu_1$,

Interacting particle system: untyped



neutral arrows:	rate 1,	selective arrows:	rate s^N,
mutation to type 1:	rate $u^N \nu_1$,	mutation to type 0:	rate $u^N \nu_0$

Interacting particle system: typed



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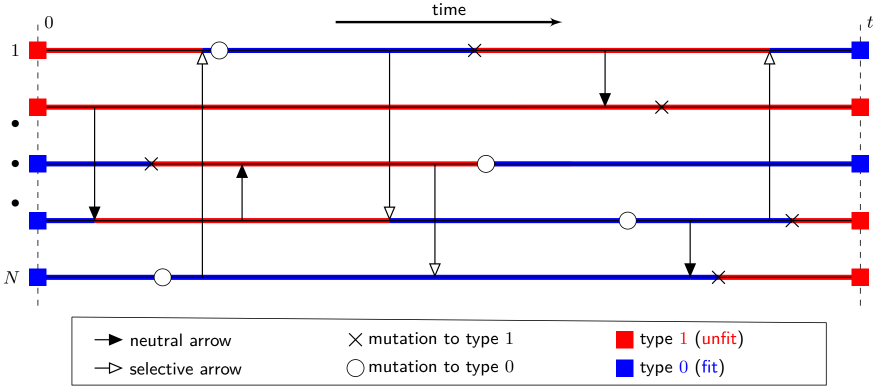

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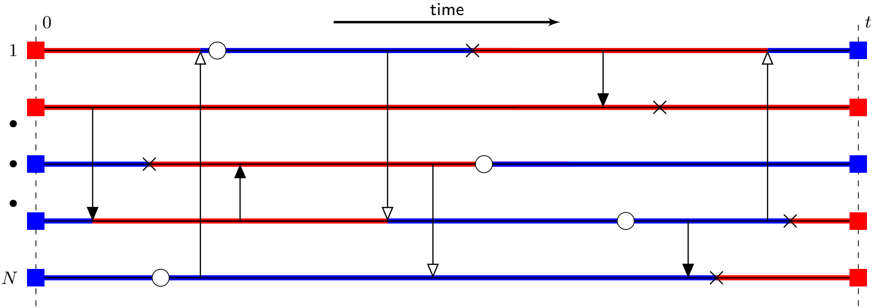
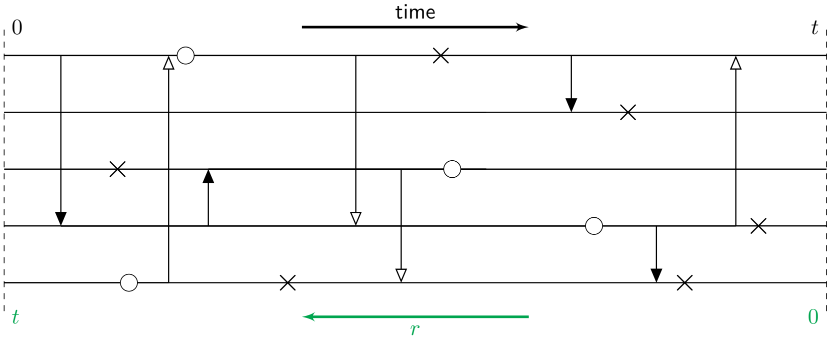


$Y_t^N :=$ proportion of individuals of type 1 at time t in MoMo of size N

Ancestral selection graph (ASG)

Krone and Neuhauser 1997



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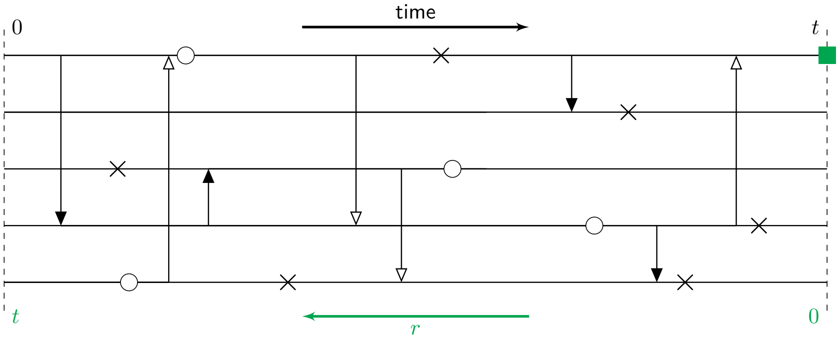

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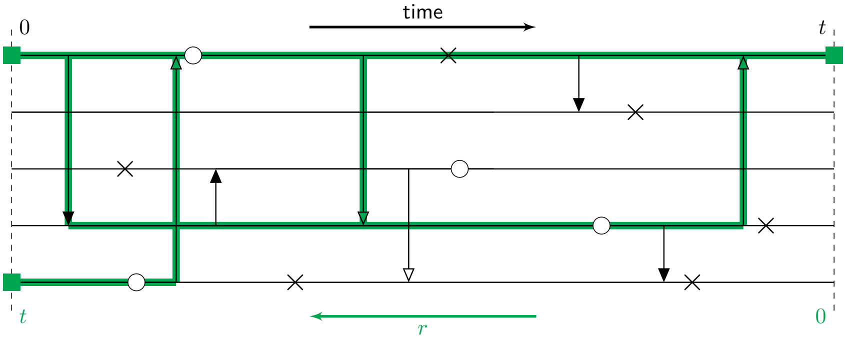

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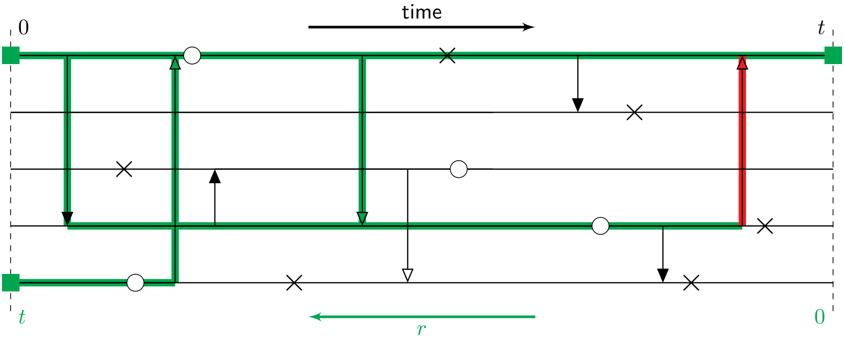

- *branching:* rate $s^N(N-n)/N$ per line (n current number of lines)

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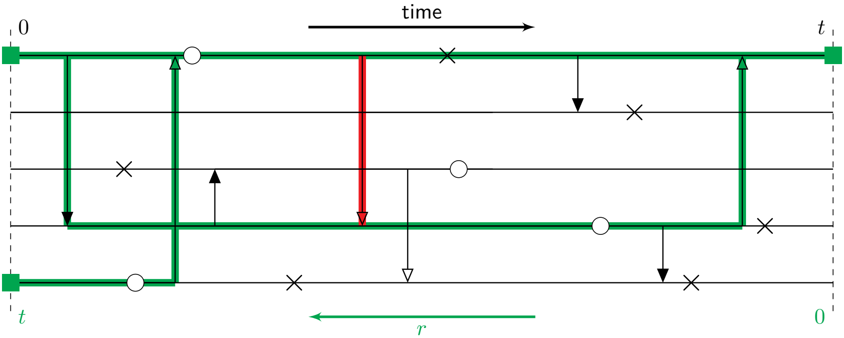

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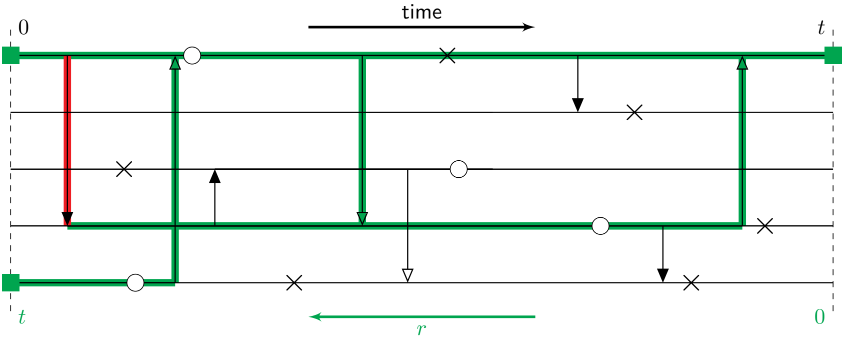

- *branching:* rate $s^N(N-n)/N$ per line (n current number of lines)
- *coalescence:* rate $1/N$ per pair

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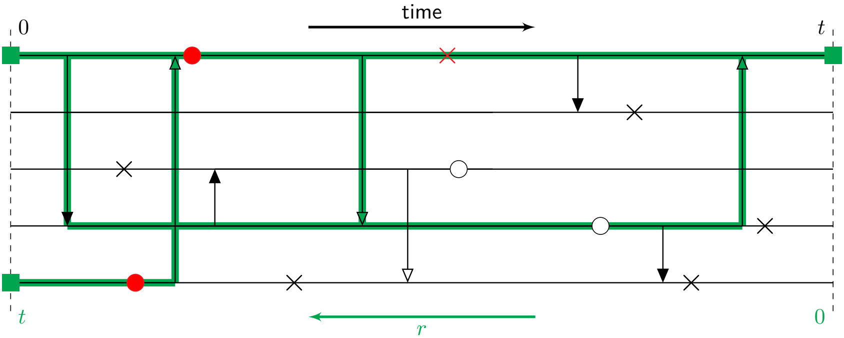
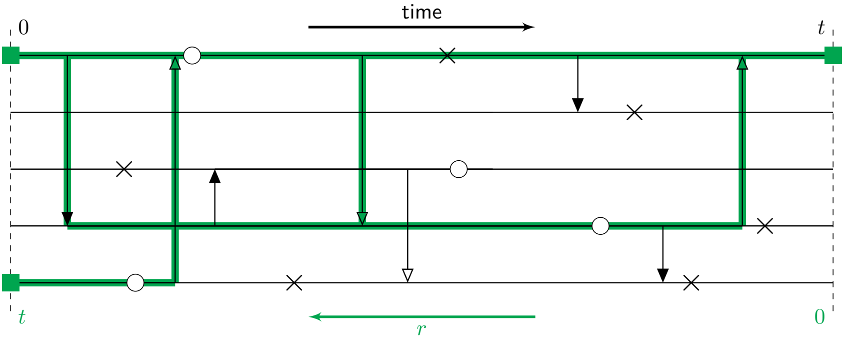


- *branching:* rate $s^N(N-n)/N$ per line (n current number of lines)
- *coalescence:* rate $1/N$ per pair
- *mutation:* rates $u^N\nu_0$, $u^N\nu_1$ per line

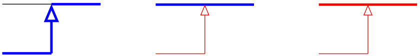
Ancestral selection graph (ASG)

Krone and Neuhauser 1997



draw types at time 0 from $(1 - Y_0^N, Y_0^N)$ and propagate them forward

respect pecking order



$\rightsquigarrow$ type at present together with true ancestral line

Diffusion limit

$N \to \infty \qquad$ s.t. $\quad Ns^N \to \sigma, \qquad Nu^N \to \theta, \quad Y_0^N \to y_0$

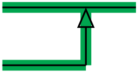
$\rightsquigarrow (Y_{tN}^N) \xrightarrow{d}$ Wright–Fisher diffusion (Y_t)

$$
\begin{aligned}
\mathrm{d}Y_t &= \sqrt{Y_t(1-Y_t)}\,\mathrm{d}W_t - \sigma Y_t(1-Y_t)\,\mathrm{d}t + (1-Y_t)\theta\nu_1\,\mathrm{d}t - Y_t\theta\nu_0\,\mathrm{d}t,\\
Y_0 &= y_0, \quad (W_t) \text{ standard Brownian motion}
\end{aligned}
$$

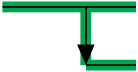
$\theta > 0,\ 0 < \nu_0 < 1, t \to \infty \rightsquigarrow\ Y_t \xrightarrow{d} \widetilde{Y}$

ASG in diffusion limit

- branching at rate σ per line

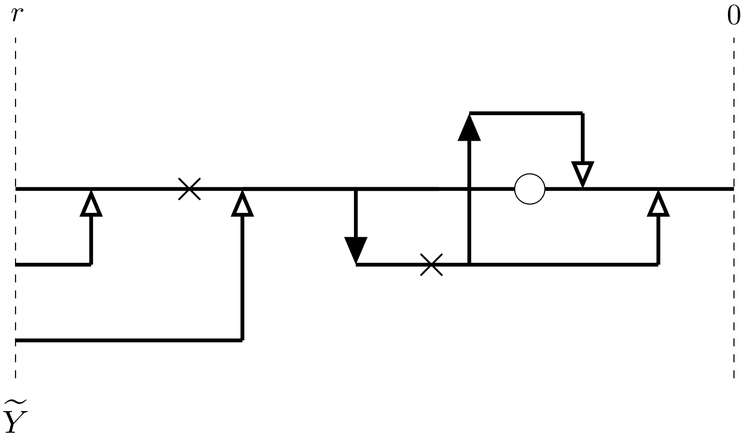


- coalescence events at rate 1 per pair

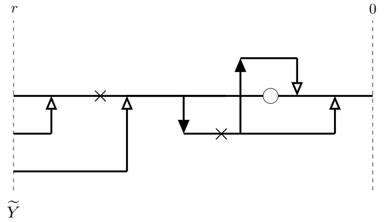


- mutation superimposed on lines at rate $\theta\nu_0$ and $\theta\nu_1$

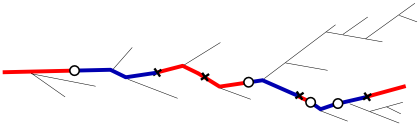
ASG in diffusion limit



Ancestral type



$I_r \in \{0, 1\}$
$:=$ ancestral type at time r



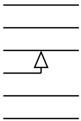
long-term success
bias towards type 0

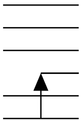
$$r \to \infty \rightsquigarrow I_r \xrightarrow{d} \tilde{I}$$

$$\mathbb{P}(\tilde{I} = 0),\ \mathbb{P}(\tilde{I} = 1)?$$

Ordering the ASG (w/o mutation)

arrange lines according to pecking order (exchangeability!)





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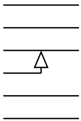

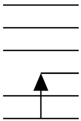

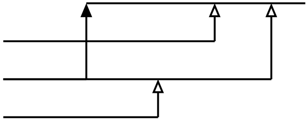

ancestral line is

- lowest type-0 line if there is one
- immune line otherwise

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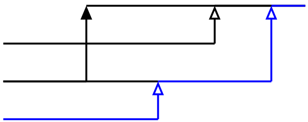

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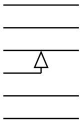

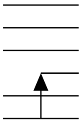

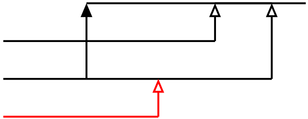

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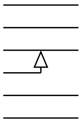

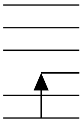

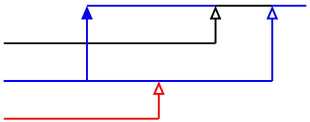

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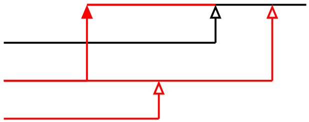

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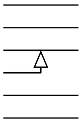
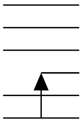
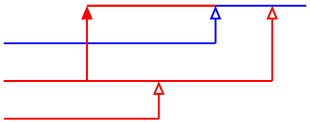
- immune line otherwise

Ordering the ASG (w/o mutation)

arrange lines according to pecking order (exchangeability!)





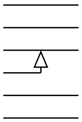


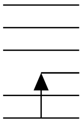
ancestral line is

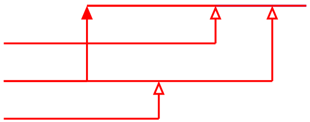
- lowest type-0 line if there is one
- immune line otherwise

Ordering the ASG (w/o mutation)

arrange lines according to pecking order (exchangeability!)







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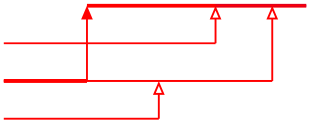

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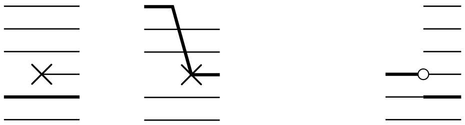
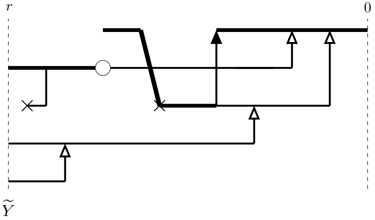
Pruning upon mutation





ancestral line is

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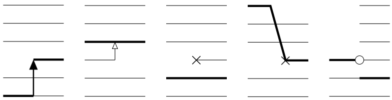
The line-counting process of the pruned ASG

L_r = number of lines at time r

(L_r) Markov chain in continuous time with rates from



stationary distribution $(r \to \infty)$:

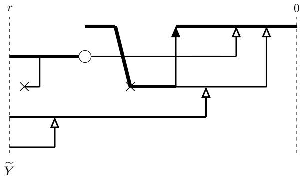
$$a_n := \mathbb{P}(\widetilde{L} > n), \quad n \geqslant 0$$

first-step analysis $\rightsquigarrow$ (Fearnhead's) recursion:

$$(n+1+\theta+\sigma)a_n = (n+1+\theta\nu_1)a_{n+1} + \sigma a_{n-1}, \quad n > 0,$$

$$a_0 = 1, \quad \lim_{n\to\infty} a_n = 0.$$

Type of ancestral line



Theorem (Lenz, Kluth, EB, Wakolbinger 2015)

The type distribution of the ancestral line in the distant past is given by

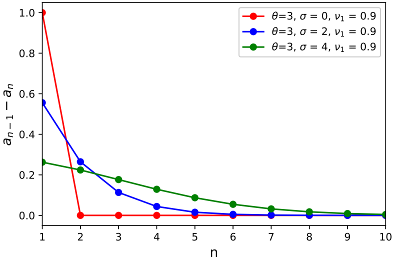
$$\mathbb{P}(\tilde{I} = 1 \mid \widetilde{Y}) = \sum_{n>0} (a_{n-1} - a_n) \widetilde{Y}^n$$

$$\mathbb{P}(\tilde{I} = 1) = \sum_{n>0} (a_{n-1} - a_n) b_n, \quad \mathbb{P}(\tilde{I} = 0) = \sum_{n \geqslant 0} a_n (b_n - b_{n+1}),$$

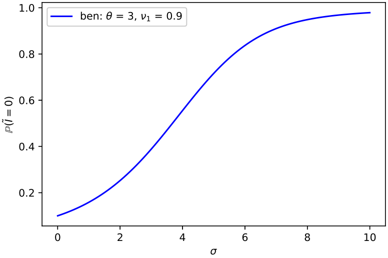
where $\quad b_n := \mathbb{E}(\widetilde{Y}^n).$

The bias towards type 0

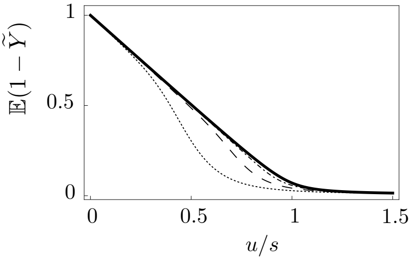
distribution of $\widetilde{L}$

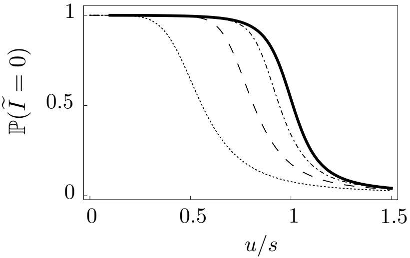


probability of fit ancestor



Forward and backward





$$s = 0.001,\ \nu_0 = 0.005$$

$\sigma = Ns$, $\vartheta = Nu$ with $N = 10^4$, $N = 3 \cdot 10^4$, $N = 10^5$

ToDo

Large devations and variational principle for (multitype) MoMo?