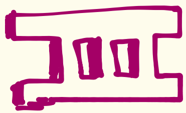
Increasing paths on the hypercube

joint with Eric Brunet & Zhan Shi

Paris-Bath meeting on branching structures



Le retour de la vengeance

Motivation

Population with asexual reproduction

A genome with L loci (= location of genes)

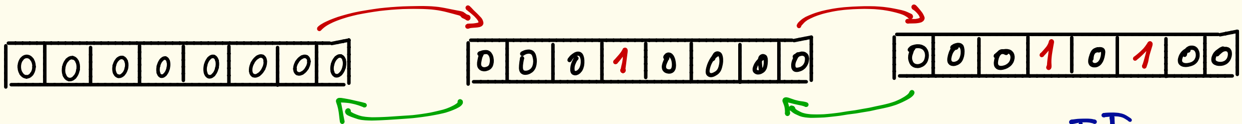
or with L sites (= DNA letter)

$\Rightarrow$ 2 viable types (alleles) for each gene:

- the wilde type (0)
- the mutant type (1)

$0 \longrightarrow 1$ forward mutation

$0 \longleftarrow 1$ backward mutation



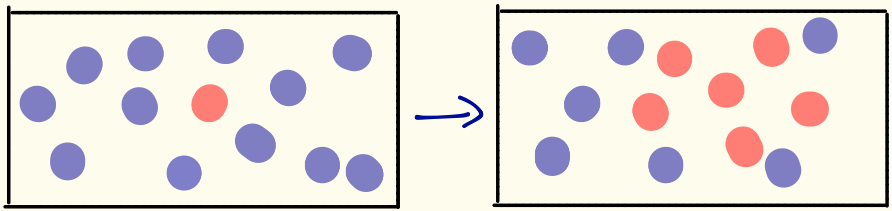
1 mutation

2 mutation.

when a mutation occurs, only 1 gene affected.

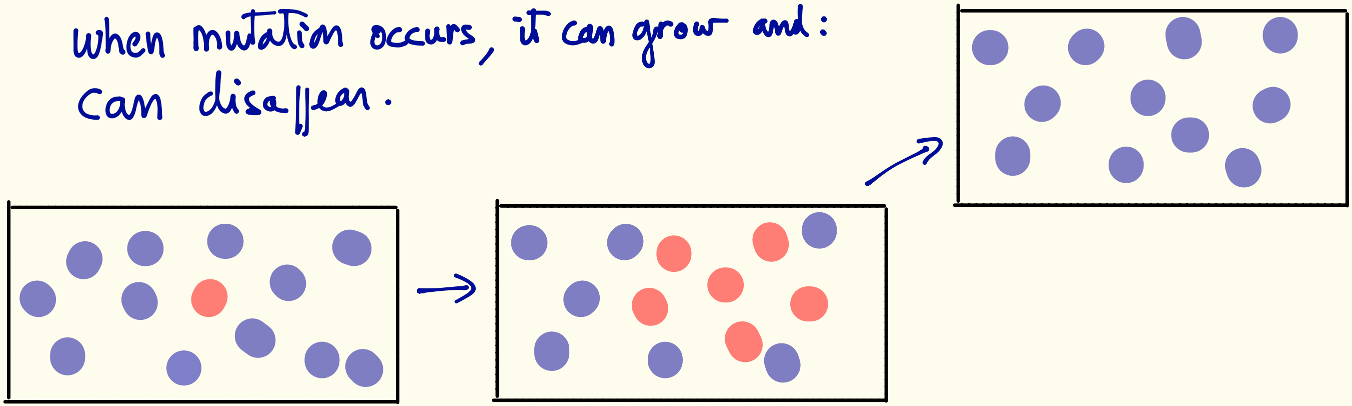
Low mutation rate, small population

when mutation occurs, it can grow and:



Low mutation rate, small population

when mutation occurs, it can grow and:
can disappear.



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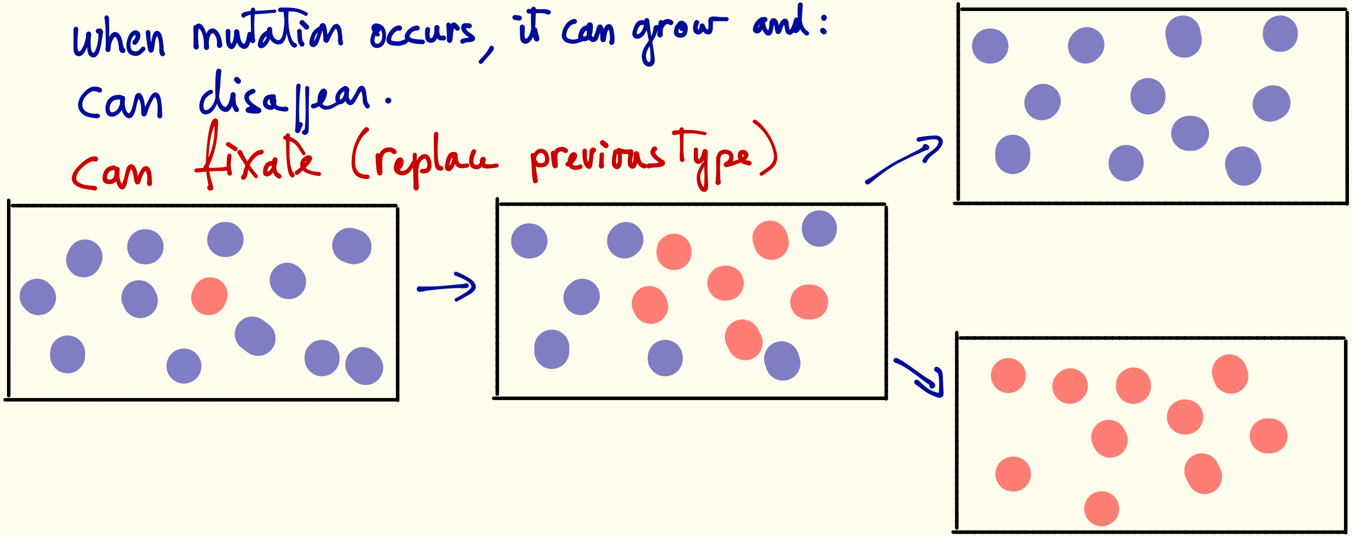
can fixate (replace previous type)



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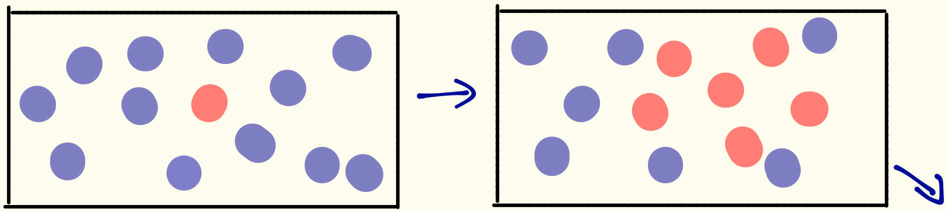
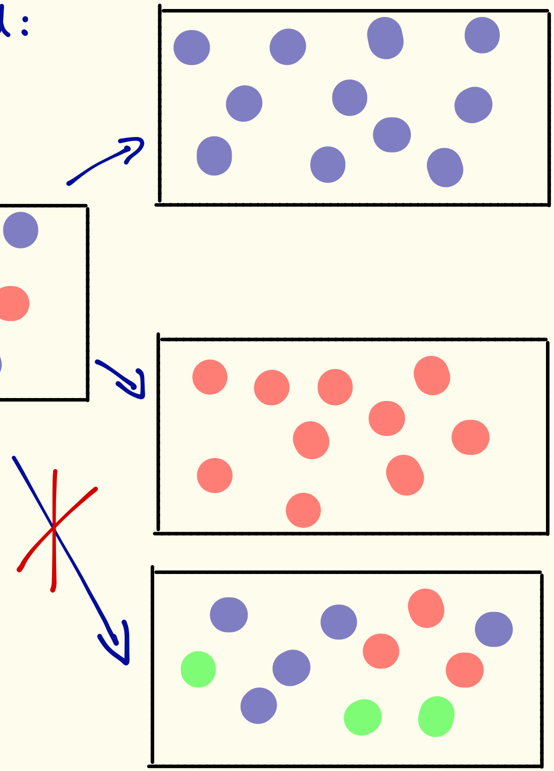
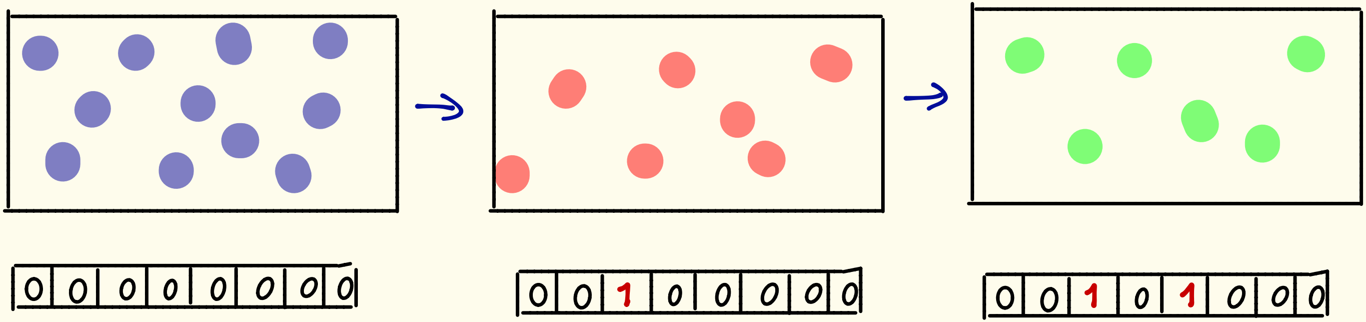




No new mutation can appear before the pop is homogeneous.

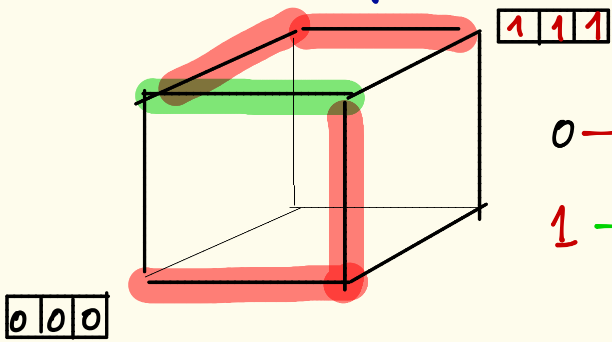
Evolutionary path and hypercube.



Evolutionary path = walk on hypercube

Gillepsie 1983

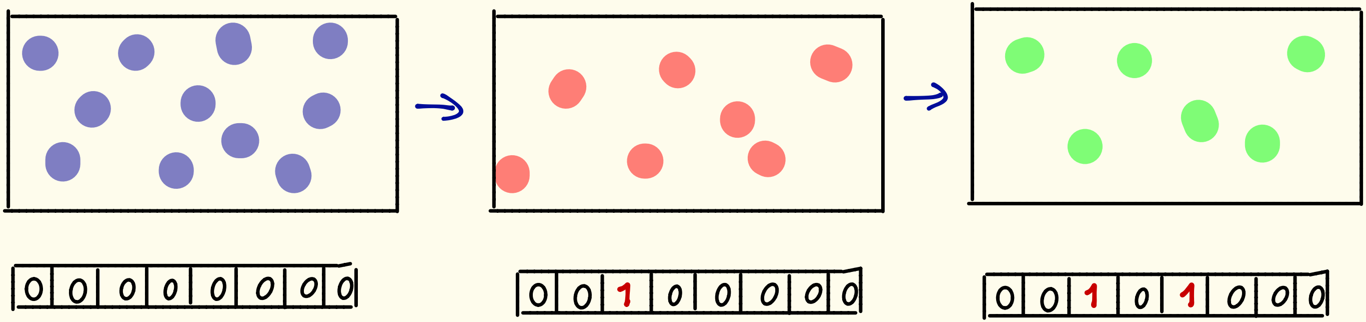
Kauffman Levin 1987



$0 \longrightarrow 1$ forward

$1 \longrightarrow 0$ backword.

Evolutionary path and hypercube.



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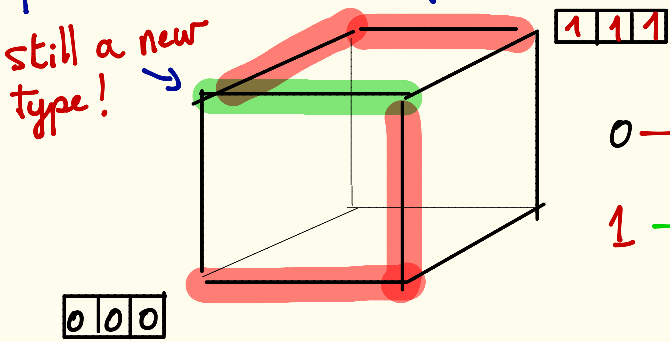

0 → 1 forward

1 → 0 backword.

Fitness and Selection

- $\forall \sigma \in \{0,1\}^L$ (all possible genomes)
  associate a fitness value x_σ

- Strong Selection: mutation can fixate iff increase fitness

$$\boxed{\begin{array}{c}\text{Open or accessible evolutionary path} \\ = \\ \text{Walk on hypercube, fitness values increase along path}\end{array}}$$

$\rightarrow$ Several models for the choice of the x_σ

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→ Several models for the choice of the x_σ

→ We assume the House-of-Cards (HoC) model

(x_σ) are iid r.v. with non-atomic distr.

The model

- $\{0,1\}^L = L$ hypercube
- $(X_\sigma, \sigma \in \{0,1\}^L)$ iid fitness values
- path open if $X_{\sigma_1} < X_{\sigma_2} < \cdots$
- Start from $\sigma_0 = (0,0,\cdots)$

Is there an open path to the fittest site?
How many such paths?

$\longrightarrow$ answer does not depend on the distribution

$\longrightarrow$ fittest is chosen unif. among the 2^L sites

The model

- $\{0,1\}^L = L$ hypercube
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- ~~$(X_\sigma, \sigma \in \{0,1\}^L)$ iid fitness values~~
- Other sites get $X_\sigma \sim U_{[0,1]}$ i.i.d.
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$\boxed{\text{Special value for } \sigma_0 = (0,0,0\ldots,0) \text{ as well}}$

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RESULTS

Fittest site is $(1,1,\dots,1)$ and only forward mutation

- Only $0 \to 1$, never $1 \to 0$.

Nowak Krug '13 ; Hegarty Martinson 2012

$$\mathbb{E}[\#\text{ of open paths}] = \sum_{\text{paths } \alpha} \mathbb{P}(\alpha \text{ is open})$$

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- total # paths $= L!$
- $\mathbb{P}(\alpha \text{ open}) = 1/L!$

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But, cond. on $X_{\sigma_0} = x$, $\mathbb{P}(\alpha \text{ open}) = (1-x)^{L-1}/(L-1)!$

So

$$\boxed{\mathbb{E}^x[\#\text{ open paths}] = L(1-x)^{L-1}}$$

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$$\mathbb{E}^x[\#\text{open paths}] = L(1-x)^{L-1} \begin{cases} \approx L & \text{if } x \lesssim \frac{1}{L} \\ \approx 1 & \text{if } x \approx \ln L/L \\ \ll 1 & \text{if } x \gg \ln L/L \end{cases}$$

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$$\mathbb{P}(\#\text{open paths} > 0) \leq \frac{\ln L + c}{L}$$

Fittest site is $(1,1,\dots,1)$ and only forward mutation

Theorem (Hegarty - Martinsson 2012)

As $L \to \infty$ $\quad \mathbb{P}(\#\text{open paths} > 0) \sim \frac{\ln L}{L}$

If $a(L) \to \infty$

$$\mathbb{P}^{\frac{\ln L - a(L)}{L}}(\#\text{open paths} > 0) \to 1$$

$$\mathbb{P}^{\frac{\ln L + a(L)}{L}}(\#\text{open paths} > 0) \to 0$$

$\to$ Sharp transition around starting fitness $\ln L / L$

Fittest site is $(1,1,\cdots,1)$ and only forward mutation

Idea of proof: 2^{nd} moment. θ = # of open paths

$$\mathbb{E}^x[\theta^2] = \sum_{\text{paths } \alpha} \sum_{\text{paths } \beta} \mathbb{P}^x(\alpha \text{ and } \beta \text{ open}).$$

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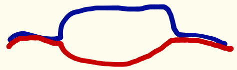
Idea of proof: 2nd moment. θ = # of open paths

$$\mathbb{E}^x[\theta^2] = \sum_{\text{paths }\alpha}\ \sum_{\text{paths }\beta} \mathbb{P}^x(\alpha \text{ and } \beta \text{ open}).$$

If $x = x(L)$ so that $\mathbb{E}^{x(L)}(\theta) \nearrow \infty$ then

$$\mathbb{E}^{x(L)}(\theta^2) \sim 4\left[\mathbb{E}^{x(L)}(\theta)\right]^2$$

($\sum_\alpha \sum_\beta$ dominated by )

Shows $\lim_{L\to\infty} \mathbb{P}^{x(L)}(\theta > 0) = 1$

Fittest site is $(1, 1, \dots, 1)$ and only forward mutation

Summary:

- $\mathbb{E}[\theta] = 1$
- $\mathbb{E}^x[\theta] = L(1-x)^{L-1}$
- $\mathbb{P}(\theta > 0) \sim \log L / L$

Fittest site is $(1,1,\dots,1)$ and only forward mutation

Summary :
- $\mathbb{E}[\theta] = 1$ X : typical $\theta \neq 1$
- $\mathbb{E}^x[\theta] = L(1-x)^{L-1}$ ✓ $\theta \approx \mathbb{E}^x(\theta)$
- $\mathbb{P}(\theta > 0) \sim \log L / L$ value of x for which $\mathbb{E}^x(\cdot) \gtrsim 1$.

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Summary : • $\mathbb{E}[\theta] = 1$ ✗ : typical $\theta \neq 1$

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Theorem (B., Brunet, Shi '13)

If $x(L) = \frac{y}{L}$, as $L \to \infty$,

$$\frac{1}{L}\theta \xrightarrow{\text{law}} e^{-y} \times \mathcal{E} \times \mathcal{E}'$$

where $\mathcal{E}, \mathcal{E}'$ are two indep. exponential variables with mean 1.

Paths with forward and backward mutations, fittest $= (1, 1, \cdots, 1)$

Both $0 \to 1$ and $1 \to 0$ are possible.

Only self-avoiding paths can be open.

- going from $(0, \cdots, 0)$ to $(1, \cdots, 1)$, # of self avoiding paths?

Prop for L large enough $\quad e^{c 2^L} \leq a_L \leq e^{c' (\ln L) 2^L}$

Paths with forward and backward mutations, fittest $= (1,1,\cdots,1)$

- Start from $X_{\sigma_0} = x$
- $\mathbb{P}(\text{path } \alpha \text{ with } p \text{ backsteps open}) = \dfrac{(1-x)^{L+2p-1}}{(L+2p-1)!}$

$$\boxed{\mathbb{E}^x[\theta] = \sum_p a_{L,p} \frac{(1-x)^{L+2p-1}}{(L+2p-1)!}}$$

$(\max p : L+2p \leq 2^L - 1)$

$a_{L,p}$ = # of self avoiding paths with p backsteps.

Paths with forward and backward mutations, fittest = (1,1,..,1)

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Theorem (B. Brunet Shi '13)

$$\left[\mathbb{E}^x[\Theta]\right]^{1/L} \xrightarrow[L\to\infty]{} \sinh(1-x)$$

Corollary: if $x > 1 - \sinh^{-1}(1) \simeq 0.11863\ldots$ $\mathbb{P}^x(\Theta > 0) \to 0$.

Paths with forward and backward mutations

- If fittest site is at distance αL, then

$$[\mathbb{E}^x(\theta)]^{1/L} \to \sinh(1-x)^{\alpha} \cosh(1-x)^{1-\alpha}$$

- If fittest site picked unif.

$$[\mathbb{E}^x(\theta)]^{1/L} \to \sinh(1-x)^{1/2} \cosh(1-x)^{1/2} = \sqrt{\frac{\sinh(2-2x)}{2}}$$

No open path if $x > 1 - \frac{1}{2}\sinh^{-1}(2) = 0.27818\ldots$

<u>conjecture</u> : $\mathbb{P}^x(\theta>0) \to 1$ if $x < x^*$ given above.

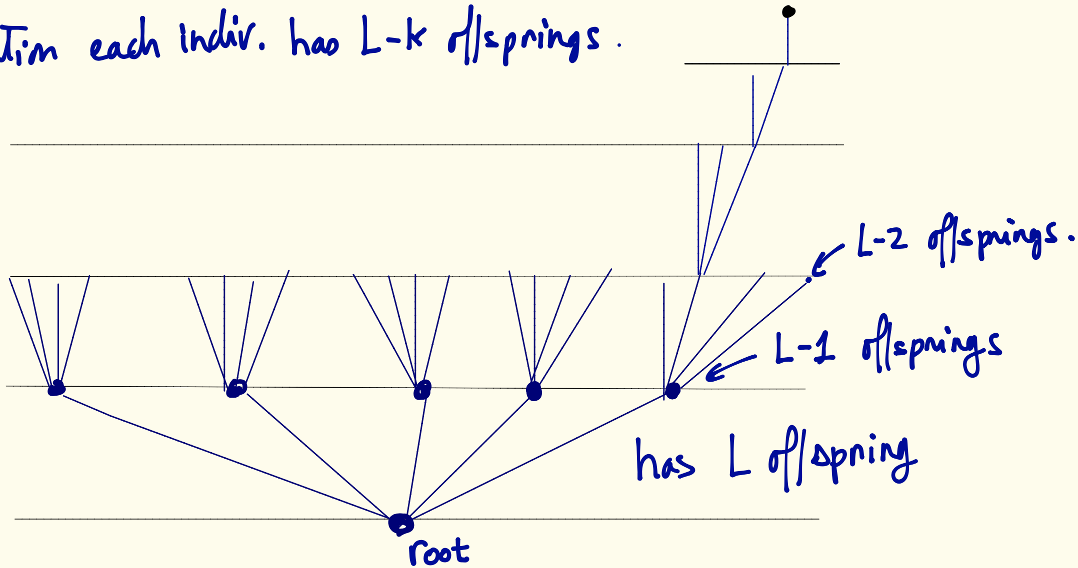
and $\mathbb{P}(\theta>0) \to x^*$

Outlines of proofs

Only forward mutation

Toy model : instead of hypercube consider

In k^{th} generation each indiv. has $L-k$ offsprings.



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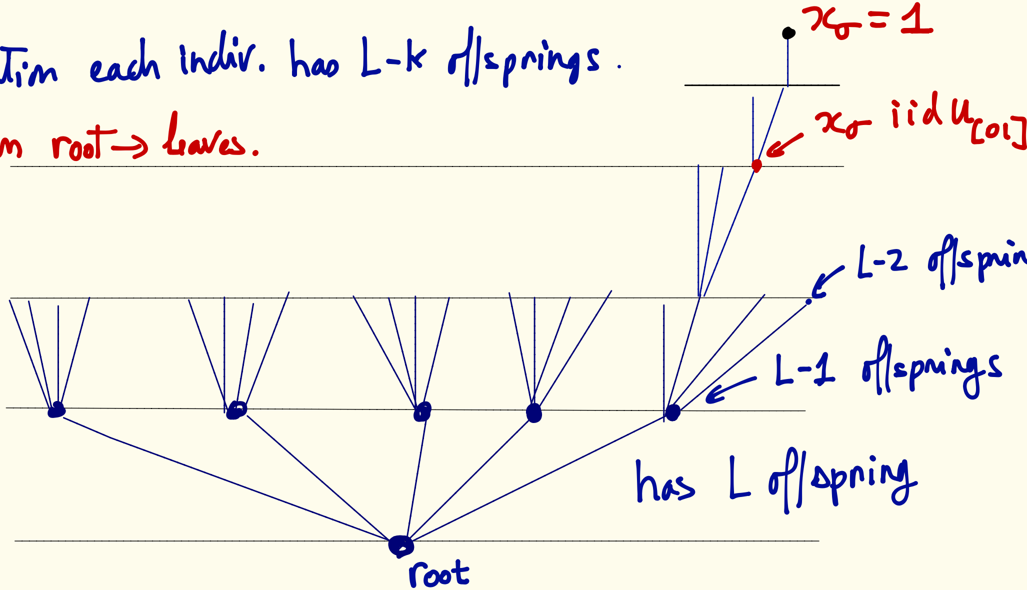
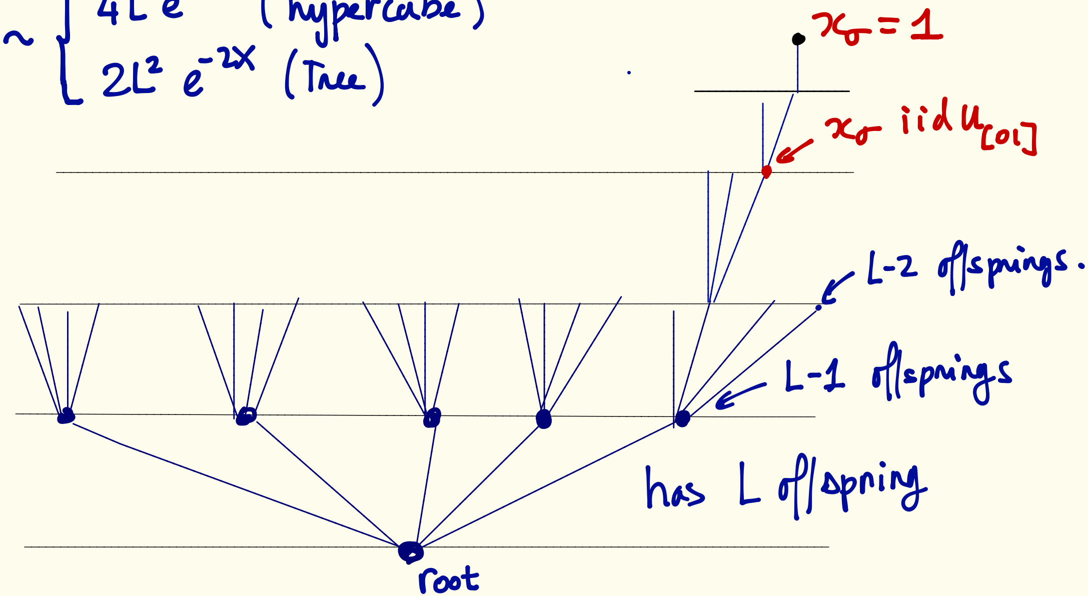
$\Theta = \#$ path open root $\to$ leaves.



Only forward mutation

- Same expecation
- $\mathbb{E}^{y/L}(\theta) \sim \begin{cases} 4L^2 e^{-2X} \text{ (hypercube)} \\ 2L^2 e^{-2X} \text{ (Tree)} \end{cases}$



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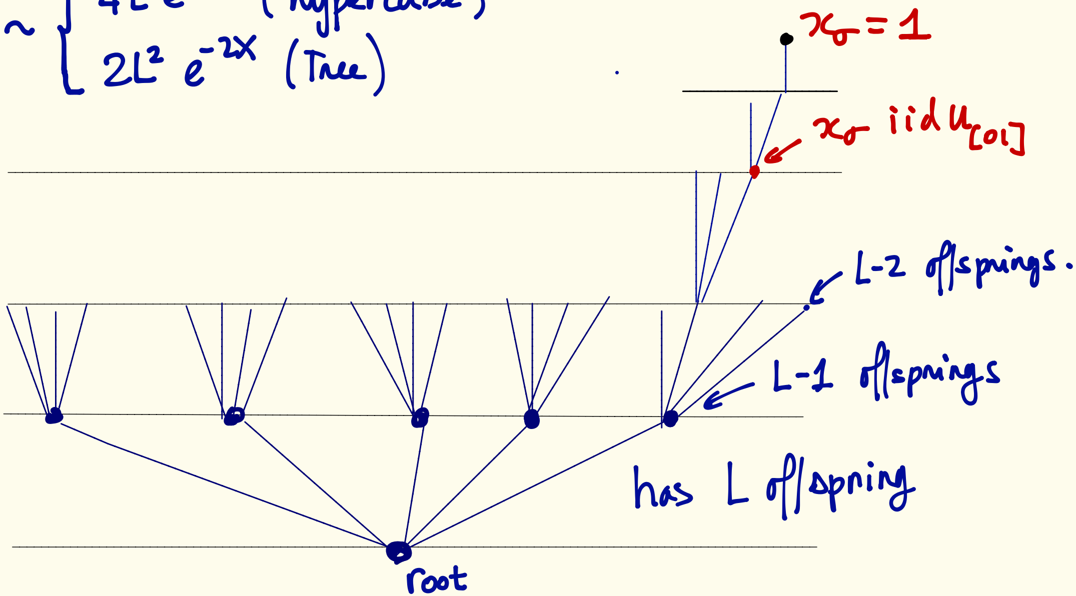

Thm (BBS): If $x = y/L$ $\quad \frac{\theta}{L} \xrightarrow{\text{law}} e^{-y}\mathcal{E}$

Only forward mutation

$$\Theta = \sum_{|\sigma|=1} (\text{open paths going through } \sigma) = \sum_{|\sigma|=1} \Theta_\sigma$$

Only forward mutation

$$\Theta = \sum_{|\sigma|=1} (\text{open paths going through } \sigma) = \sum_{|\sigma|=1} \Theta_\sigma$$ independent!

$$G(\lambda, x, L) := \mathbb{E}^{x}\left[e^{-\lambda \Theta}\right]$$

$$= \left[\qquad \qquad \right]^{L}$$

Only forward mutation

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$$G(\lambda, x, L) := \mathbb{E}^x\left[e^{-\lambda\Theta}\right]$$

$$= \left[x + \qquad\qquad\qquad \right]^L$$

Only forward mutation

independant !

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$$G(\lambda, x, L) := \mathbb{E}^x\left[e^{-\lambda\Theta}\right]$$

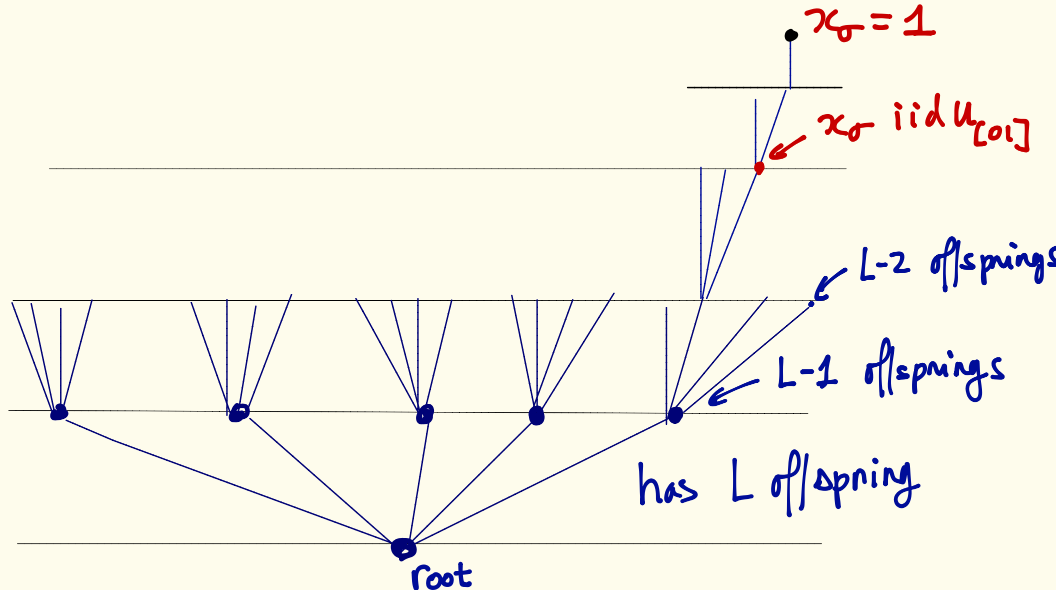
$$= \left[x + \int_x^1 dy\, G(\lambda, y, L-1)\right]^L, \quad G(\lambda, x, 1) = e^{-\lambda}$$

$$\lim_L G\left(\frac{\mu}{L}, \frac{X}{L}, L\right) = ?$$

Only forward mutation

$\theta = $ (# open paths) $\quad \theta_k = \mathbb{E}[\theta \mid \mathcal{F}_k] \quad \mathcal{F}_k = $ (info up to level k)

$$\theta_k = \sum_{|\sigma|=k} \mathbb{1}_{\{\sigma \text{ open}\}} (L-k)(1-x_\sigma)^{L-k-1}$$



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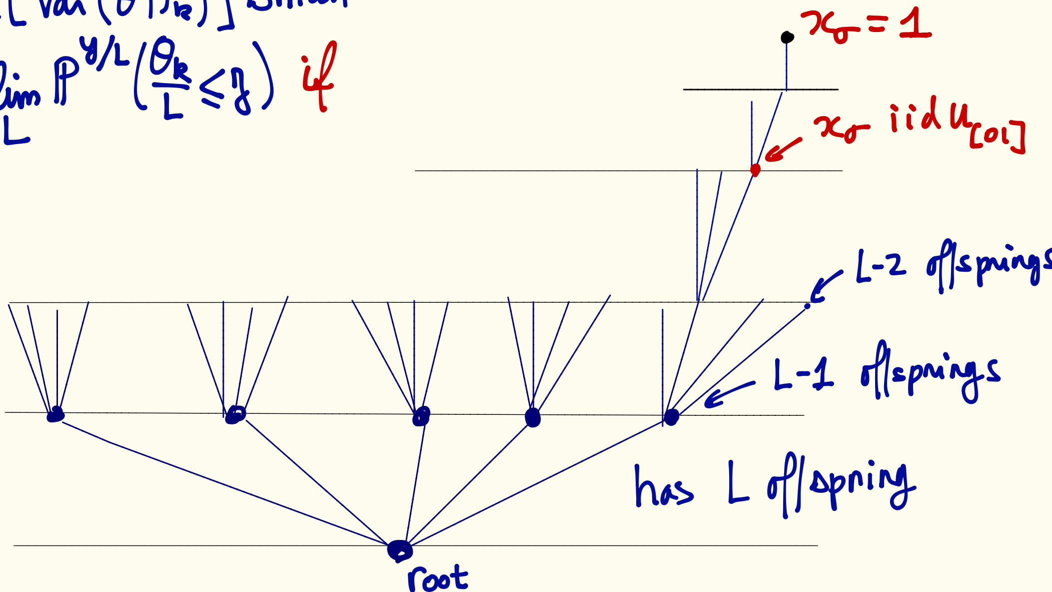
Idea: $\theta \approx \theta_k$ if $\mathbb{E}[\mathrm{Var}(\theta \mid \mathcal{F}_k)]$ small

$$\lim_{L\to\infty} \mathbb{P}^{y/L}\left(\frac{\theta}{L} \leq z\right) = \lim_{k} \lim_{L} \mathbb{P}^{y/L}\left(\frac{\theta_k}{L} \leq z\right) \text{ if}$$



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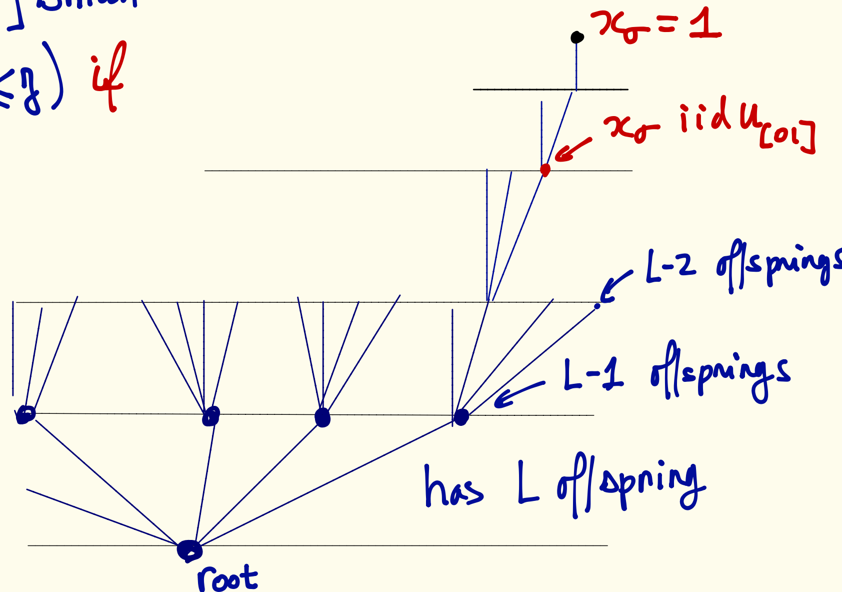
$$\lim_{k} \lim_{L} \mathbb{E}^{y/L}\left[\mathrm{Var}\left(\frac{\theta}{L} \,\Big|\, \mathcal{F}_k\right)\right] = 0$$

but $\lim_{L} \mathbb{E}^{y/L}\left[\mathrm{Var}\left(\frac{\theta}{L} \,\Big|\, \mathcal{F}_k\right)\right] = \frac{e^{-2y}}{2^k}$

$\Rightarrow$ $\boxed{\text{In the } L\to\infty, k\to\infty \text{ limit } \frac{\theta}{L} \text{ and } \frac{\theta_k}{L} \text{ have same dist}}$



$$\Theta_k = \sum_{|\sigma|=1} \mathbb{1}_{x_\sigma > x} \left(\Theta_{k-1}^{(\sigma)} \ (L-1)\text{ tree rooted in } \sigma \right)$$

$$G_k(\lambda, x, L) := \mathbb{E}^x\left[e^{-\lambda \Theta_k}\right] = \left[1 - \int_x^1 dy \left(1 - \int_x^1 dy \left(1 - G_{k-1}(\lambda, y, L-1)\right)\right)\right]^L$$

$$G_0(\lambda, x, L) = e^{-\lambda L (1-x)^{L-1}}$$

$$G_k\left(\frac{\mu}{L}, \frac{y}{L}, L\right) = \mathbb{E}^{y/L}\left(e^{-\mu \Theta_k / L}\right) = \left[1 - \frac{1}{L}\int_y^L dY \left(1 - G_{k-1}\left(\frac{\mu}{L}, \frac{y}{L}, L-1\right)\right)\right]^L$$

Only forward mutation, Tree model

$\mathcal{F}_k$ = info on k 1st levels

$$\Theta_k = \mathbb{E}[\Theta \mid \mathcal{F}_k] = \sum_{|\sigma|=k} \mathbb{1}_{\sigma \text{ open}} \underbrace{(L-k)}_{=(L-k)!/(L-k-1)!} (1-x_\sigma)^{L-k-1} = \# \text{leaves} > \sigma \times \mathbb{P}(\sigma \to \text{leaf open})$$

we proceed in two steps :

1) Show that $\lim_{L} \mathbb{P}_{y/L}\left(\frac{\Theta}{L} \leq \xi\right) = \lim_{k} \lim_{L} \mathbb{P}_{y/L}\left(\frac{\Theta_k}{L} \leq \xi\right)$

2) Show that $\frac{\Theta_k}{L} \xrightarrow{\mathcal{L}} \mathcal{E}$ when $L \to \infty$ and then $k \to \infty$.

Step 1:

upper bound
$$\mathbb{P}\left(\frac{\theta}{L} \leq \xi \,\middle|\, \mathcal{F}_k\right) \leqslant \mathbb{1}\left\{\frac{\theta_k}{L} \leq \xi + \delta \,\middle|\, \mathcal{F}_k\right] + \mathbb{P}\left[\frac{|\theta - \theta_k|}{L} \geqslant \delta \,\middle|\, \mathcal{F}_k\right]$$

Chebyshev $\quad \mathbb{P}\left(\frac{|\theta - \theta_k|}{L} \geqslant \delta \,\middle|\, \mathcal{F}_k\right) \leqslant \frac{\mathrm{Var}(\theta \,|\, \mathcal{F}_k)}{L^2 \delta^2}$

$$\Rightarrow \mathbb{P}_{y/L}\left(\frac{\theta}{L} \leq \xi\right) \leqslant \mathbb{P}_{y/L}\left(\frac{\theta_k}{L} \leq \xi + \delta\right) + \frac{\mathbb{E}_{y/L}\left[\mathrm{Var}(\theta / \mathcal{F}_k)\right]}{L^2 \delta^2}$$

need: $\lim_k \limsup_L \frac{1}{L^2} \mathbb{E}_{y/L}\left[\mathrm{Var}(\theta \,|\, \mathcal{F}_k)\right] = 0$

lower bound $\quad$ same argument

Step 2

$$G_k(\lambda, x, L) = \mathbb{E}^x\left[e^{-\lambda \theta_K}\right]$$

$\theta_0 = \mathbb{E}^x[\theta]$ $\quad G_0(\lambda, x, L) = \exp\left(-\lambda L (1-x)^{L-1}\right]$

$$G_k(\lambda, x, L) = \left[x + \int_x^1 dy\, G_{k-1}(\lambda, y, L-1)\right]^L \qquad = \left[\mathbb{E}^x\left(e^{-\theta_k(\sigma)}\right)\right]^L$$

$$= \left[1 - \int_x^1 dy\, (1 - G_{k-1}(\lambda, y, L-1)\right]^L$$

Fix k, let $L \to \infty$

$\forall a, \forall b$ $\quad G_k\left(\frac{\mu}{L+a}, \frac{y}{L+b}, L\right) \xrightarrow[L\to\infty]{} \tilde{G}_k(\mu, y)$

$$= \exp\left(-\int_X^\infty \left[1 - \tilde{G}_{k-1}(\mu, Y)\right] dY\right.$$

with $\tilde{G}_0(\mu, y) = \exp\left[-\mu e^{-y}\right]$

$\Rightarrow$ from $\frac{y}{L}$, $\quad \theta_K / L$ has a limit

Paths with forward and backward mutations, fittest = (1,1,⋯,1)

Both $0 \to 1$ and $1 \to 0$ are possible.

Only self-avoiding paths can be open.

- going from $(0,\cdots,0)$ to $(1,\cdots,1)$, # of self avoiding paths ?

0 backstep : $a_{L,0} = L!$ (length L)

1 backstep : $a_{L,1} = L! \, \frac{L(L-1)(L-2)}{6}$ (length $L+2$)

2 backsteps $a_{L,2} = L! \times \cdots$

p backsteps (length $L+2p$) $a_{L,p} \sim L! \times \frac{L^{3p}}{6^p \, p!}$ (p fixed, L large)

a_L = # self avoiding path : $a_1 = 1$ $a_2 = 2$ $a_3 = 18$

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How many open?

Only forward mutation, Tree model

The natural way to do this would be to look at

$$G(x,\lambda,L) = \mathbb{E}^{x}\left[e^{-\lambda\theta}\right]$$

$$G(x,\lambda,1) = e^{-\lambda}, \quad G(x,\lambda,L) = \prod_{i=1}^{L} \mathbb{E}\left[e^{-\lambda\theta_i}\, \mathbb{1}_{x_i>x} + \mathbb{1}_{x_i<x}\right]$$

$$= \left[x + \int_x^1 dz\, G(z,\lambda,L-1)\right]^L$$

Problem: when L vary both # of levels and size of levels vary