Three Lectures about :
“Evolutionary Processes and Patterns of Biodiversity”

Lecture 1/3 : Genealogy of one or many genes

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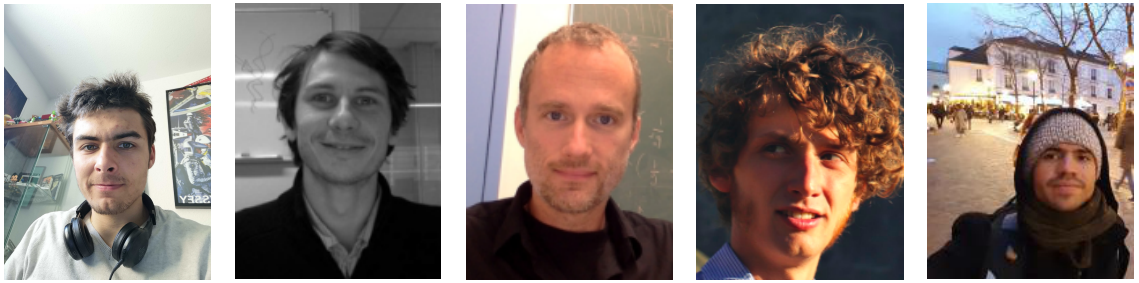
IICD & Probability and Society Initiative Joint Seminar Series
Columbia University
October 9, 2020

SMILE : An interdisciplinary group in Paris

Below : SMILE members in May 2020

Jasmine 12/01 | François 15/01 | Guillaume T. 25/02 | Pete 29/03 | Emmanuel 18/04

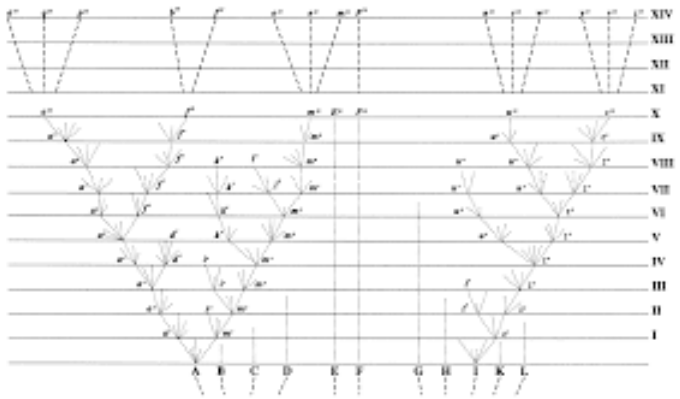
Laura 21/05 | Jean-Jil 24/05 | Felix 05/09 | Rob 16/09 | Julie 21/09 | Elise 10/10



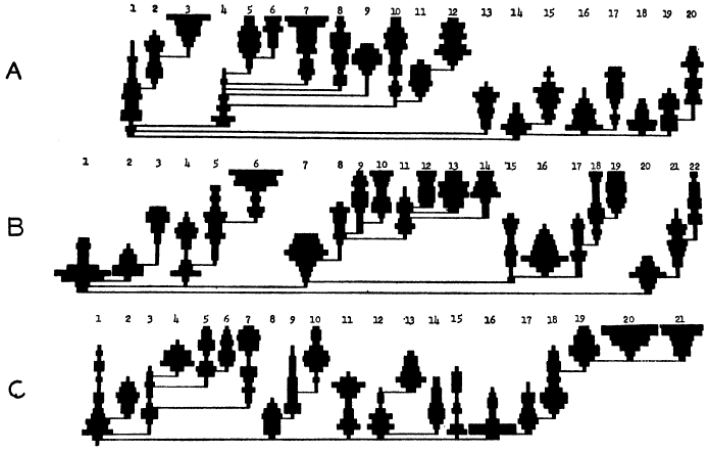
Léo 07/11 | Guillaume A. 09/12 | Amaury 16/12 | Philibert 30/12 | Alejandro

SMILE = **S**tochastic **M**odels for the **I**nference of **L**ife **E**volution

Evolution as a generic process



Darwin (1859)



Raup et al (1973)

- Darwin, Wallace, Lamarck : Evolution is a generic process
- 1920-30's First models of micro-evolution ('population genetics')
  - 1924–34 Haldane "A mathematical theory of natural and artif selection"
  - 1931 Wright "Evolution in Mendelian populations"
  - 1937 Fisher "The wave of advance of advantageous genes"
- 1960-70's First models of macro-evolution
  - 1925 Yule "A mathematical theory of evolution, based on..."
  - 1967 Cavalli-Sforza & Edwards "Phylogenetic analysis : models and estimation procedures"
  - 1973 Farris "A probability model for inferring evolutionary trees"
  - 1973 Raup, Gould, Schopf & Simberloff "Stochastic models of phylogeny and the evolution of diversity"
  - 1985 Felsenstein "Phylogenies and the comparative method"

Outline

Introduction : genetic diversity, relatedness, genealogy

- Sample n individuals from a population and sequence their DNA.

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- **Q. What diversity do you expect to observe in this sample of DNA sequences ?**

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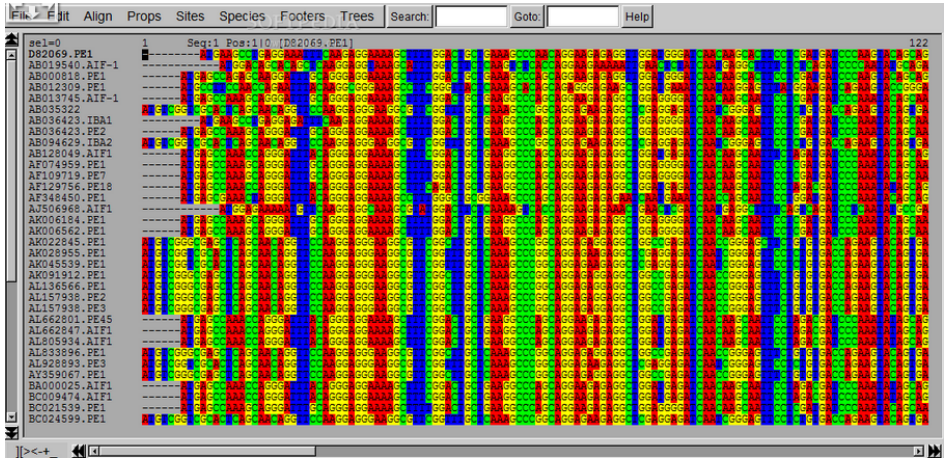

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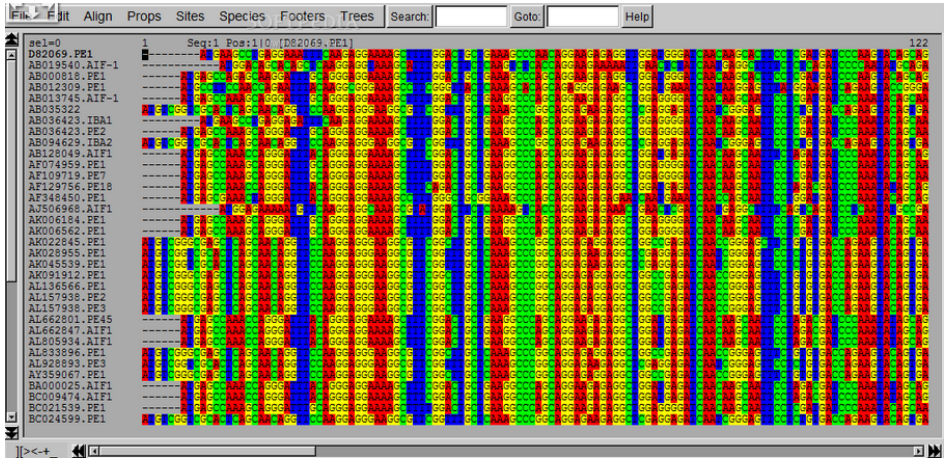

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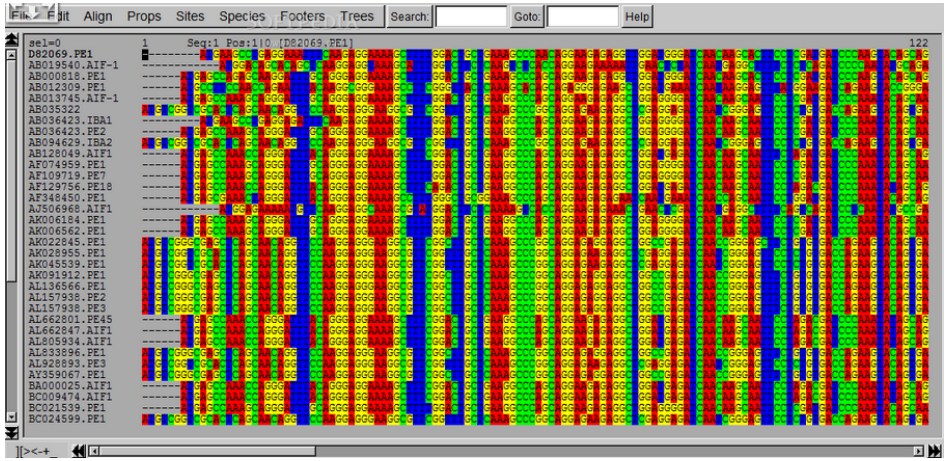

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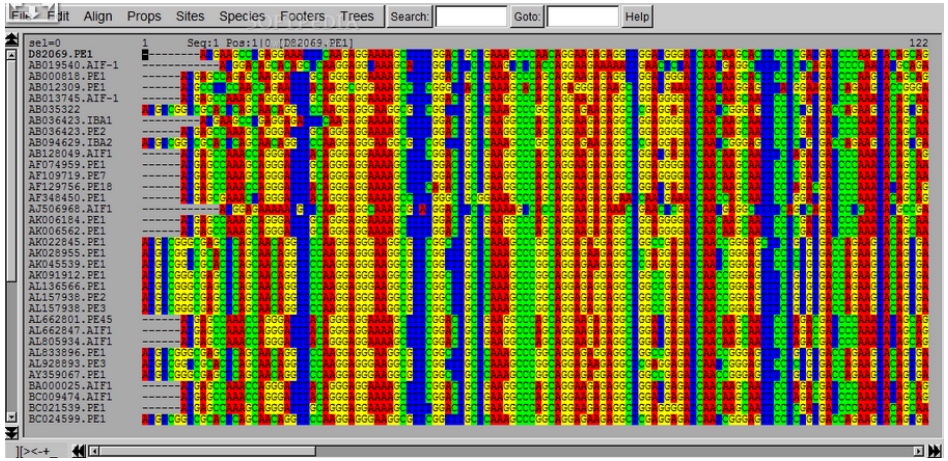

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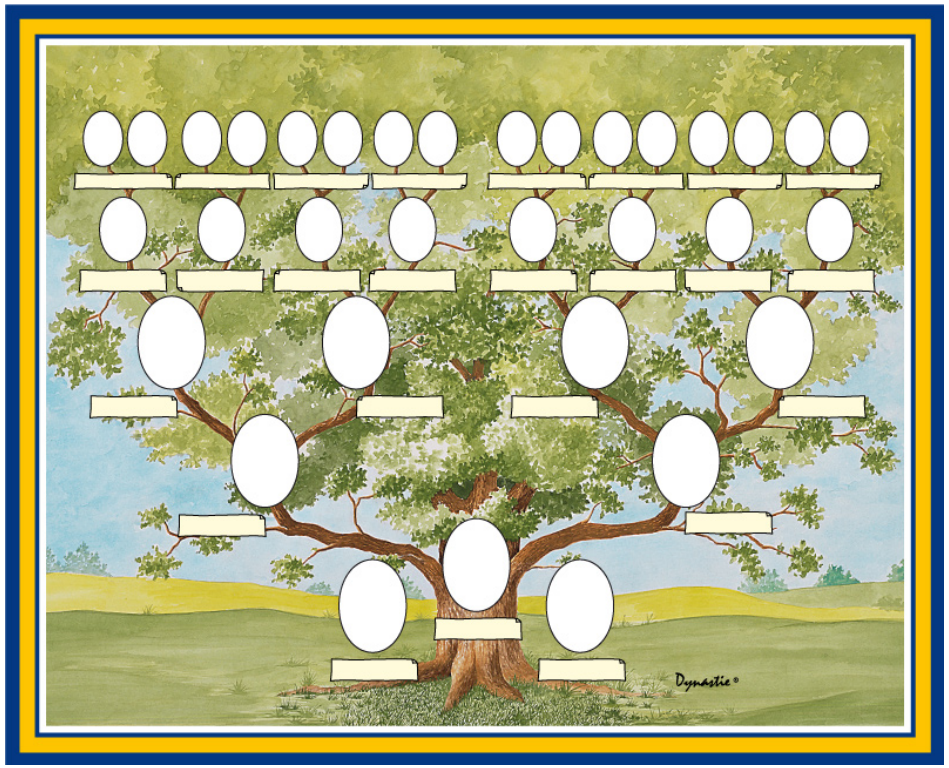

A pedigree = 2 parents ($\neq$ genealogy = 1 parent)

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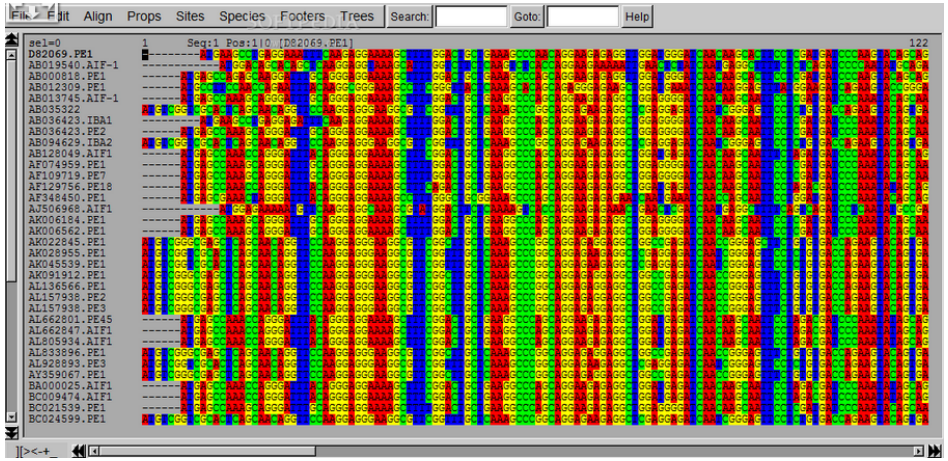

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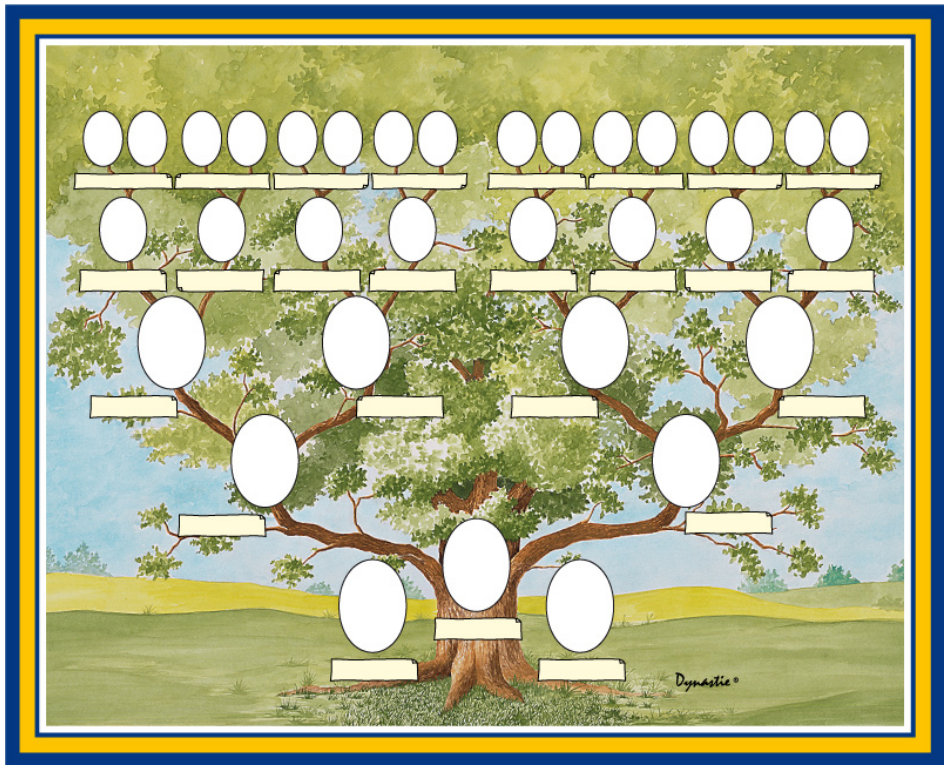

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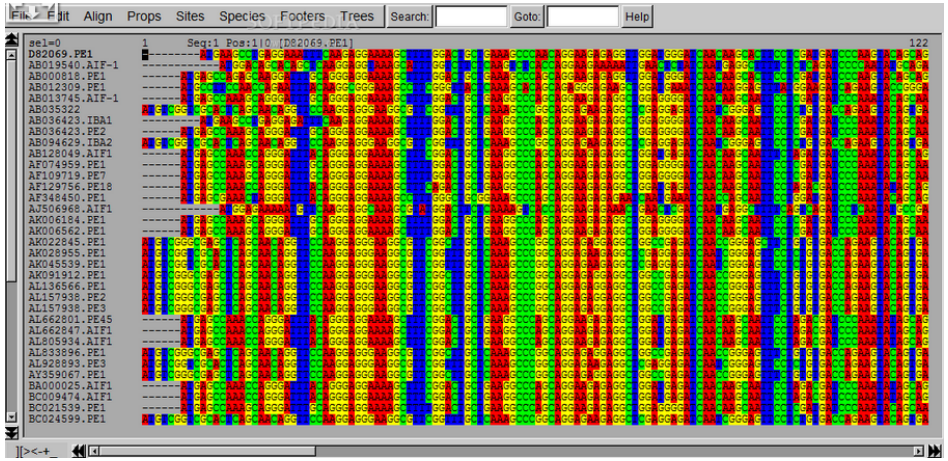
  ⇒ Different loci have different genealogies



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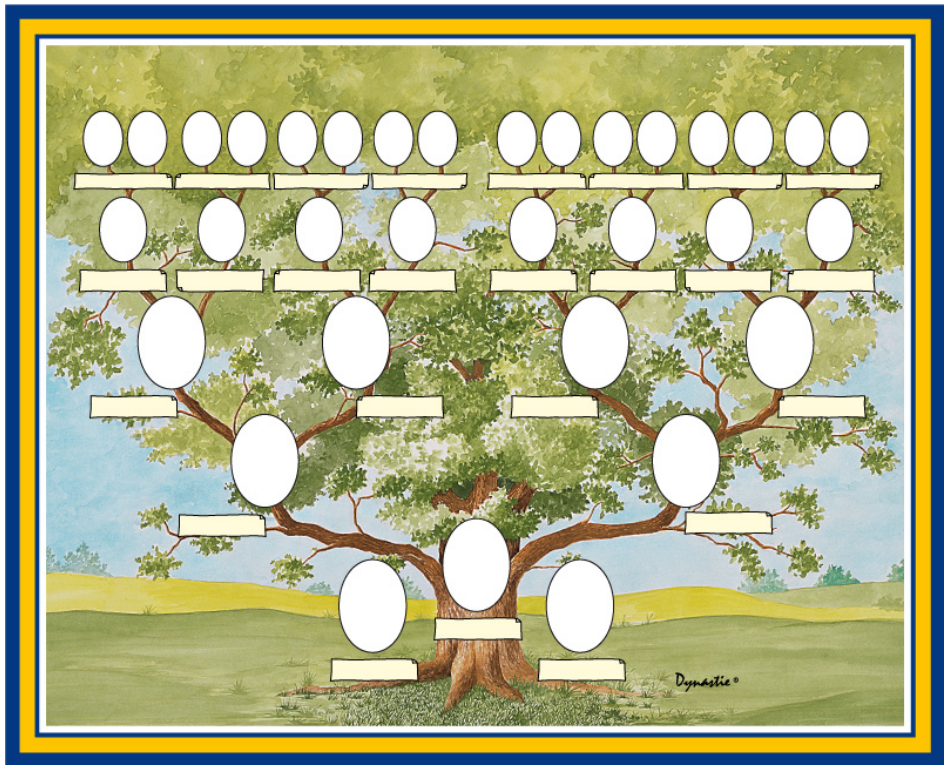

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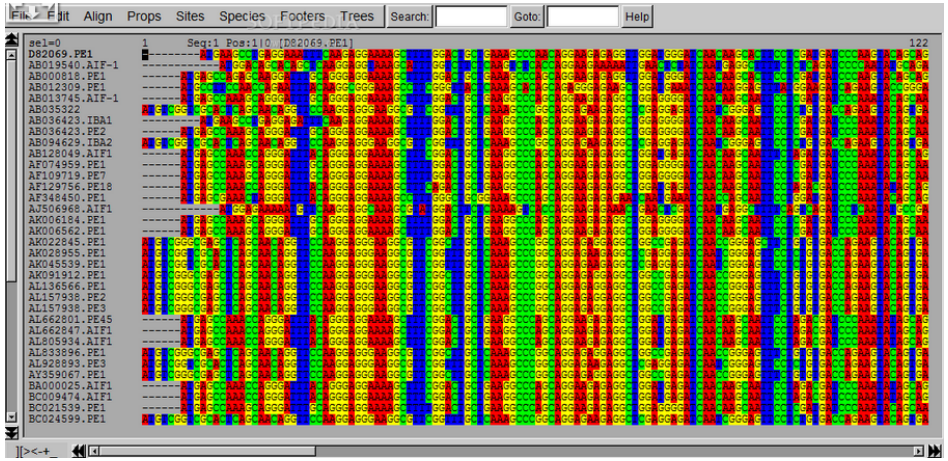

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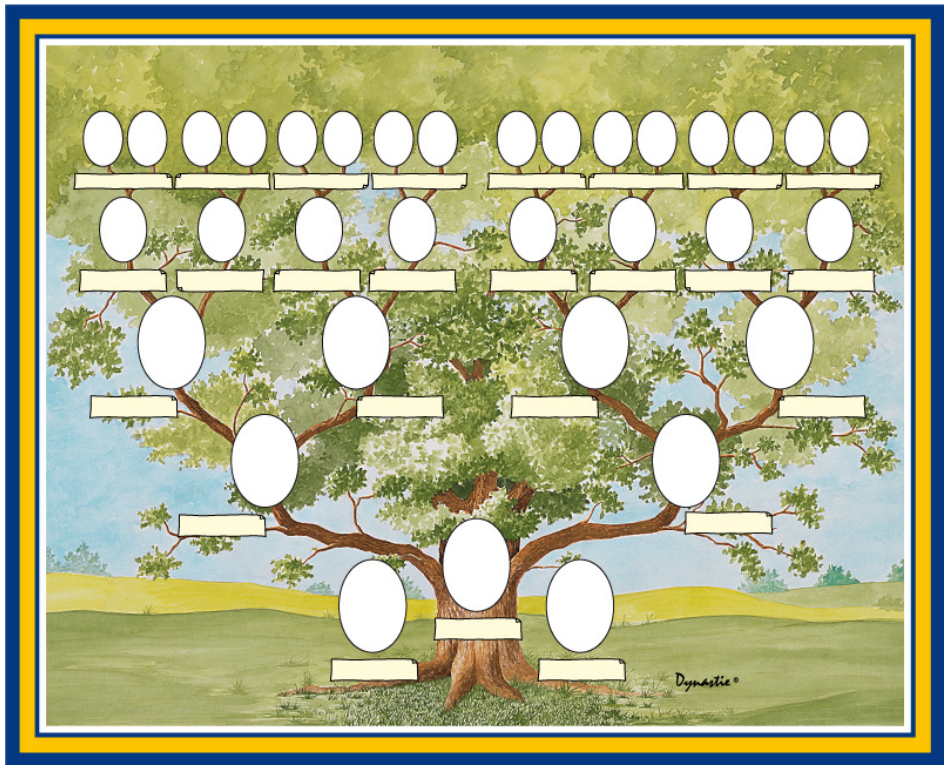

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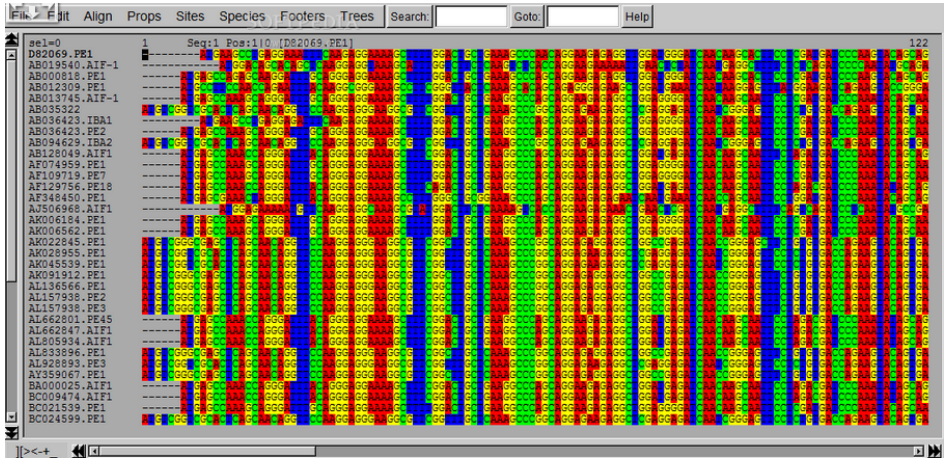

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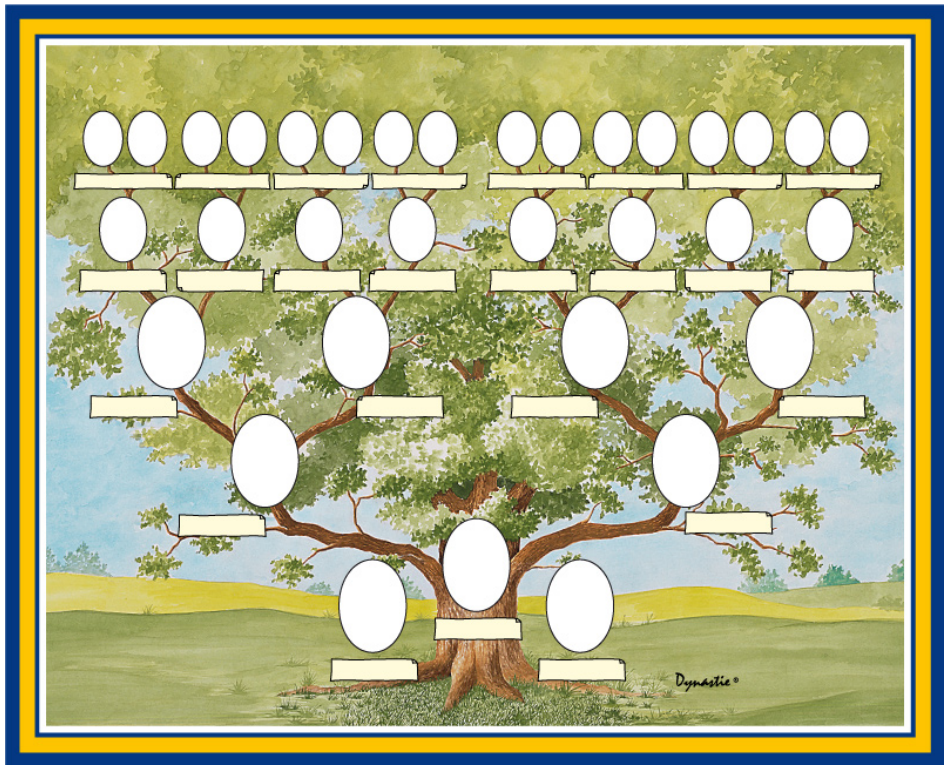

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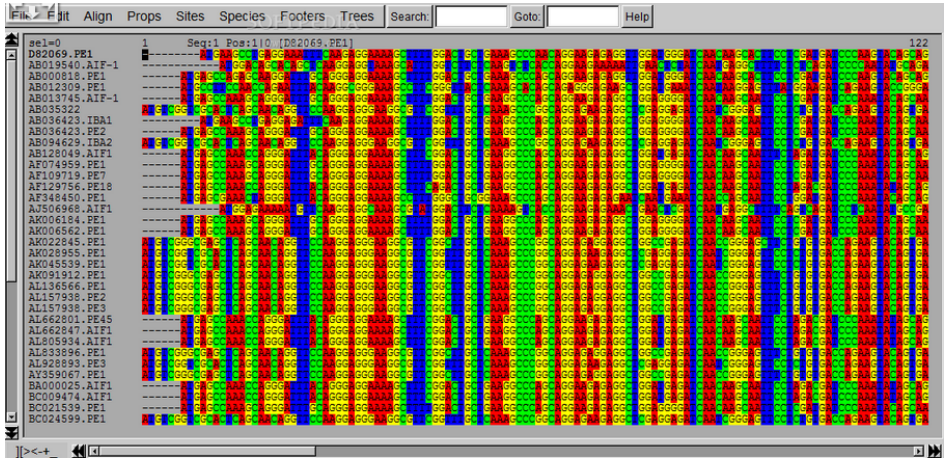
  - In diploid species, each chromosome is in two copies in each cell
  - Each parent contributes one copy of each chromosome : the 2 copies have ≠ ancestries
  - Even loci located on same chr don't have the same genealogy ⟵ recombination



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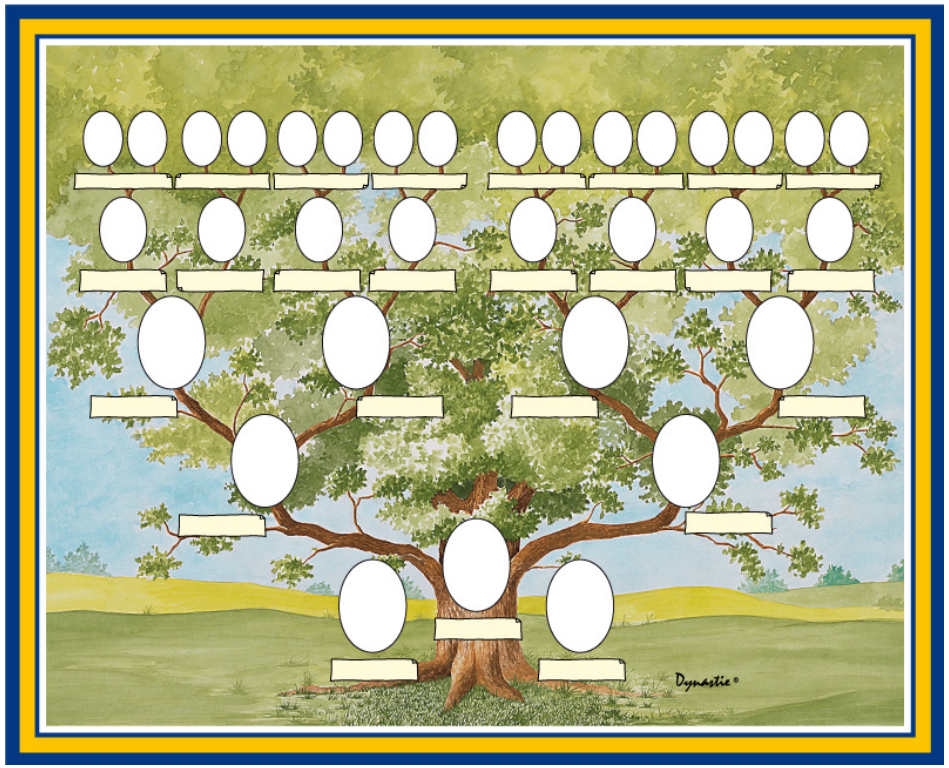

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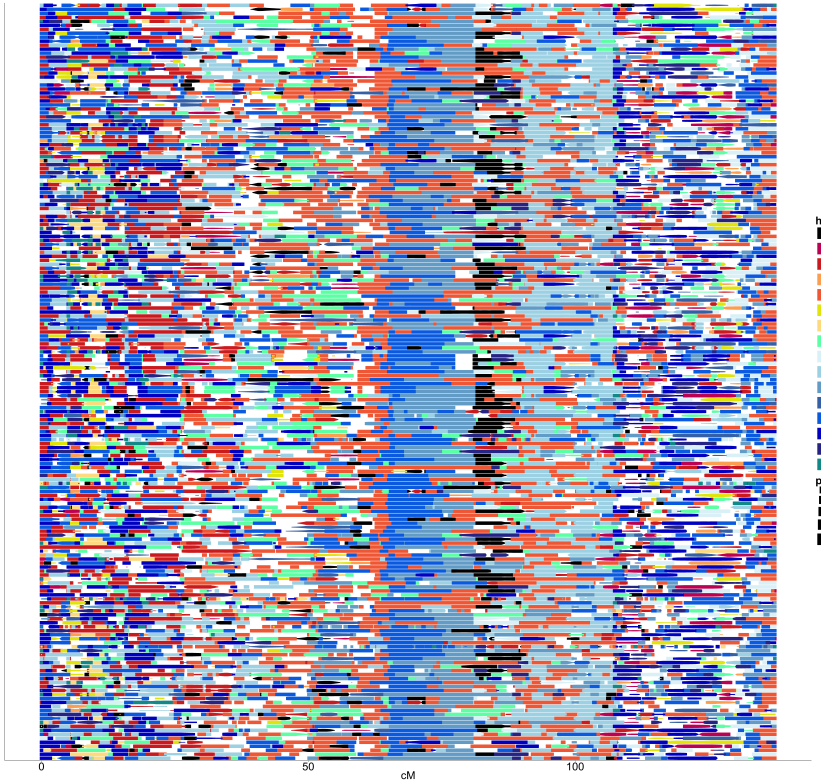
Outline

- Models for the genealogy of one gene, coalescent theory
- Patterns of genetic diversity at one locus, relation to population size
- Models coupling genealogies of several genes
- Applications
  - **Q1.** How does genome-wide diversity inform us on the past demography ?
  - **Q2.** If the genome of each ancestor was painted in a different color, how would the mosaic of colors in the pop look like in the long run ?



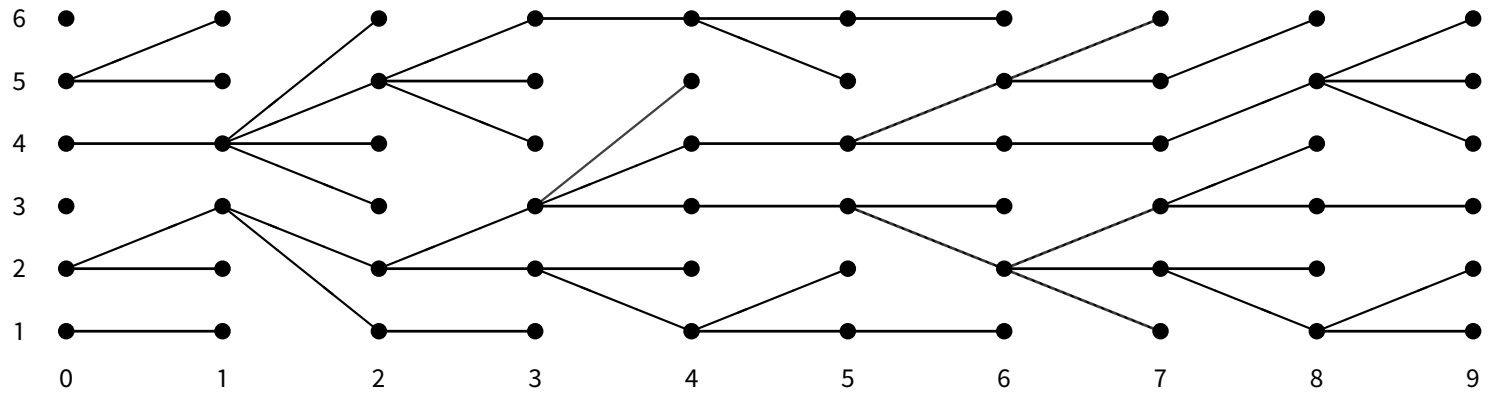
Experimental evolution with C. elegans
16 colors, $n = 300$, $N = 10^4$
Teotónio, Estes, Phillips & Baer (2017)

Outline

Neutral models of population genetics

Wright, Fisher, Cannings...

- The size of the population is constant, fixed equal to $N \gg 1$.
- Individual i of generation t has $\nu_i^{(t)}$ children $\in$ generation $t+1$



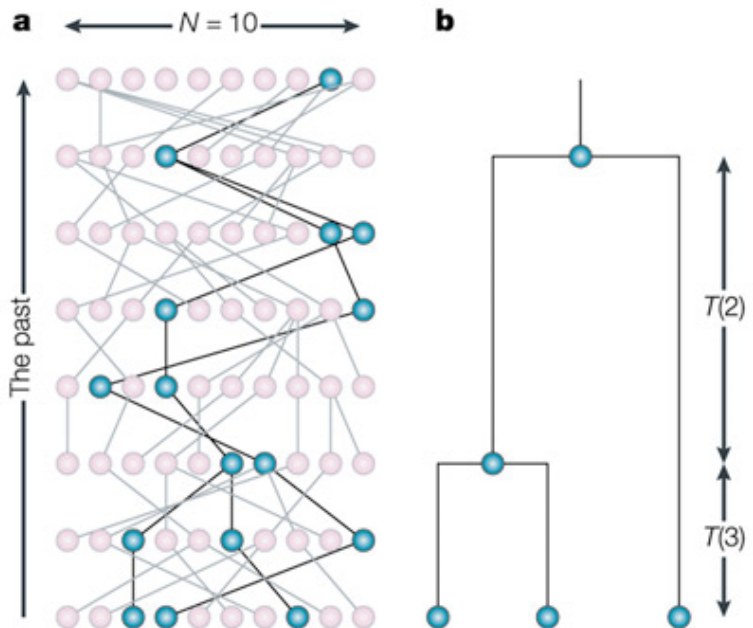
- **Cannings model(s)** : The vectors $(\nu_1^{(t)}, \nu_2^{(t)}, \ldots, \nu_N^{(t)})_{t\in\mathbb{Z}}$ are independent copies of a vector $(\nu_1, \nu_2, \ldots, \nu_N)$ such that
  - $\sum_{i=1}^N \nu_i = N$
  - The law of $(\nu_1, \nu_2, \ldots, \nu_N)$ is invariant by permutation (exchangeable)
- **Wright–Fisher model** : $(\nu_1, \ldots, \nu_N)$ is multinomial with parameters $(N; 1/N, \ldots, 1/N)$ $\Leftrightarrow$ Each ind in generation $t+1$ **picks her parent uniformly and indep'ly** in generation t

The coalescent for two individuals

- Sample 2 individuals uniformly at random and follow their ancestors backwards in time
- Let $T_N(2)$ be the number of generations counted backwards until the two lineages find their **most recent common ancestor (MRCA)**
- Then $T_N(2)$ is geometric with success probability $c_N := \mathbb{P}(\text{ 2 random ind are sisters })$.
- In the Wright–Fisher model, $c_N = 1/N$, otherwise

$$c_N = \mathbb{E}\left(\sum_{i=1}^{N} \frac{\nu_i(\nu_i - 1)}{N(N-1)}\right) = \frac{\mathbb{E}\left(\nu_1(\nu_1 - 1)\right)}{N-1}$$

- If $c_N \to 0$ as $N \to \infty$, then $T_N(2) = O(1/c_N)$ and $c_N T_N(2) \to T(2) \sim \mathcal{E}(1)$.
- Wright-Fisher : $T_N(2) = O(N)$ and $T_N(2)/N \to \mathcal{E}(1)$.



The coalescent for n individuals

Kingman, Griffiths, Möhle...

- Sample n individuals uniformly at random and follow their ancestors backwards in time
- Recall $c_N = \mathbb{P}(\text{ 2 random ind are sisters })$ and set $d_N := \mathbb{P}(\text{ 3 random ind are sisters })$, so that $d_N = 1/N^2$ in the WF model.

Theorem (Möhle's lemma)

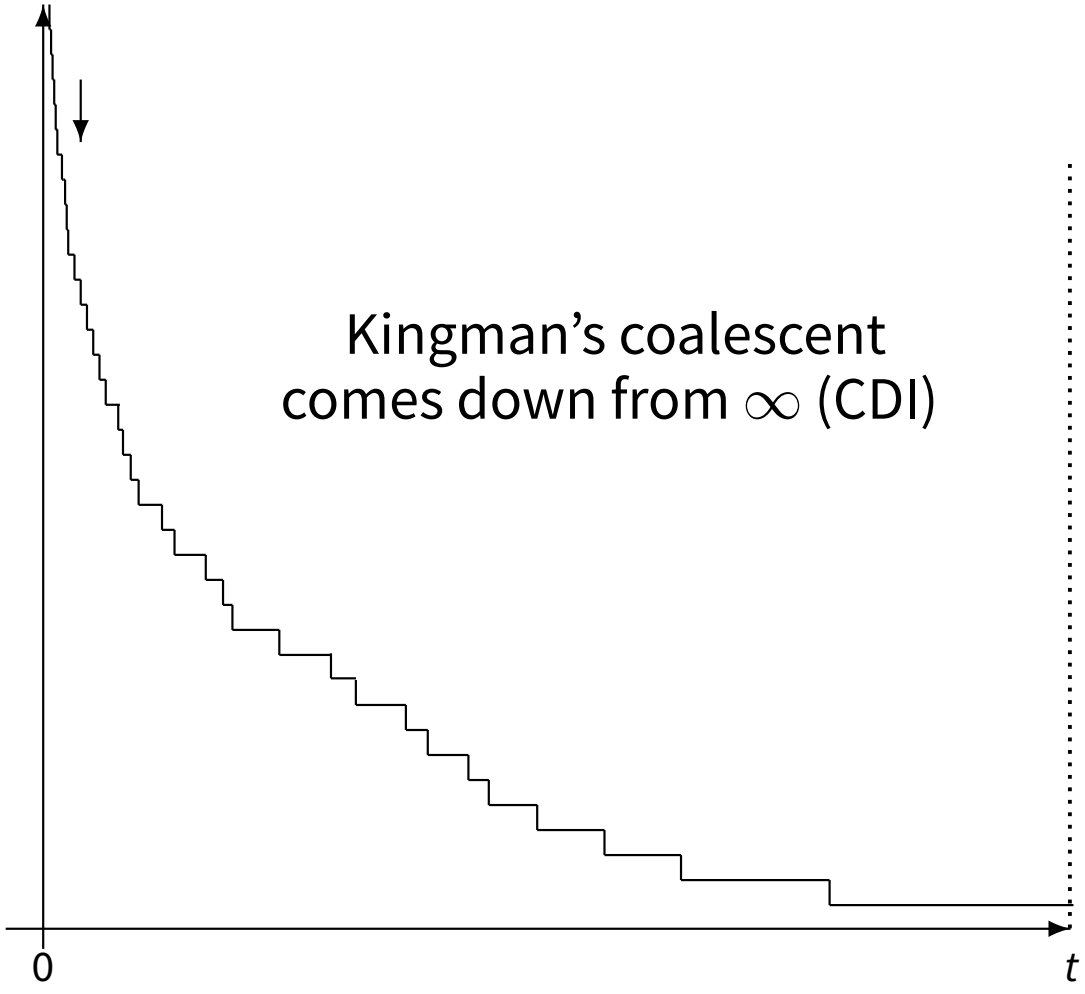
As $N \to \infty$, under the assumption that $d_N/c_N \to 0$, the genealogy of the sample t/c_N units of time ago, converges to **Kingman's coalescent** *:*

1. *The waiting time $T(k)$ from k to $k-1$ lineages is exponential with parameter $\binom{k}{2}$*
2. *The next coalescing pair is chosen uniformly at random.*

- $\Leftrightarrow$ "Each pair of lineages coalesces independently at rate 1"...
- ...Or at rate $1/x(t)$, if pop size $= Nx(Nt)$
- No multiple mergers. Shorter edge lengths close to present. Sampling-consistent.
- The genealogy of n also has length $= O(N)$.

Note : The coalescent at time t is represented by the partition of $\{1, \ldots, n\}$ induced by the relation $i \sim_t j$ if i and j have found their common ancestor t time units ago

Large sample limit $1 \ll n \ll N$



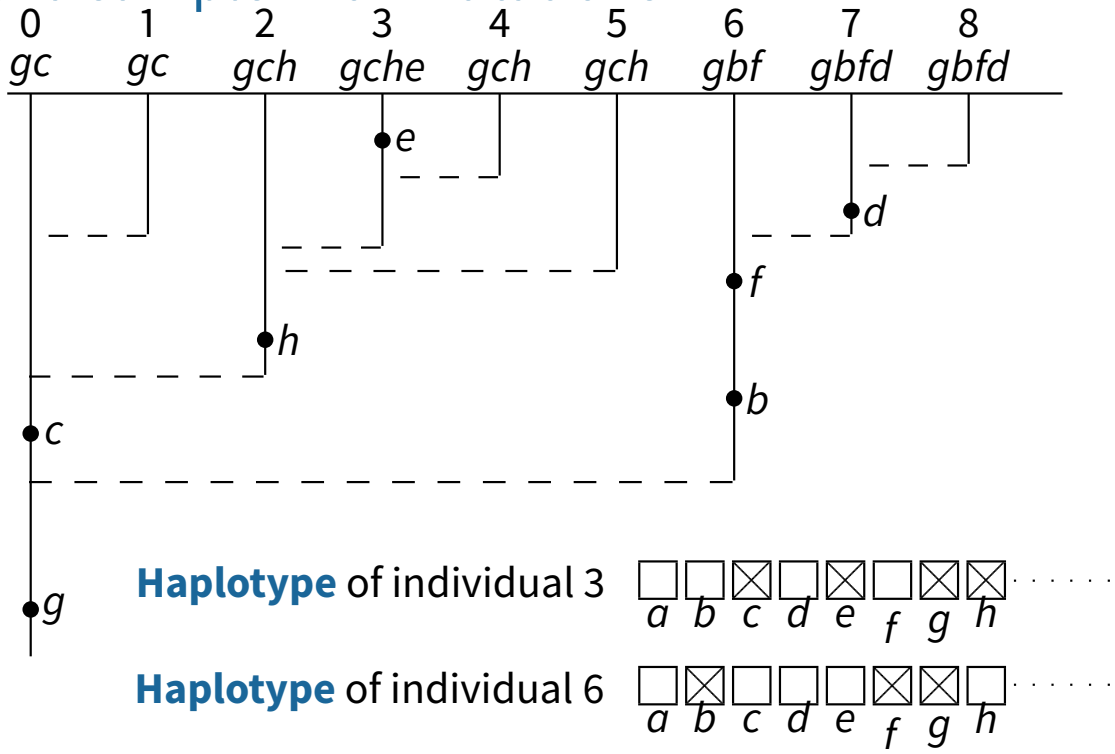
- The process counting the number of lineages in Kingman's coalescent is a pure-death process going from k to $k-1$ at rate $\binom{k}{2}$
- The sojourn time T_k in state k has expectation $\mathbb{E}(T_k) = \binom{k}{2}^{-1}$ so

$$\mathbb{E}\left(\sum_{k\geq 2} T_k\right) = \sum_{k\geq 2} \mathbb{E}(T_k) < \infty,$$

  so $\sum_{k\geq 2} T_k < \infty$ with probability 1.
- There is a unique entrance law $\mathbb{P}_\infty =:$ standard coalescent.

Outline

Genealogy of a sample with mutations



- Mutations are visible if present in $k \in \{1, \ldots, n-1\} =:$ **polymorphic/segregating site**
  $\Rightarrow$ Visible mutations occur within the genealogical tree, with length $= O(N)$
- Goldilocks zone for **proba u_N of gene-wide mutation** at birth :
  - If $Nu_N \ll 1$, no segregating site in sample
  - If $Nu_N \gg 1$, infinitely many segregating sites in sample
  - If $Nu_N = O(1)$, finite number of mutations (Poisson cond on tree length)
- If $Nu_N = O(1)$ and sequence long enough : mutations all occur at different sites
  $=$ infinitely-many-site model

  $\Rightarrow$ Each mutation gives rise to a new haplotype $=$ infinitely-many-allele model

Assumptions and notation

- Population size N, **mutation proba** $u_N \sim \theta/2N$ (recall Goldilocks zone : $Nu_N = O(1)$)

- As $N \to \infty$, convergence to **Kingman's coalescent** with **Poissonian marks rate** $\theta/2$

- $S_n := \#$ polymorphic **sites** $= \sum_k S_n(k)$, where
- $S_n(k) := \#$ polymorphic **sites carried by** k ind (in sample of n)
  $=:$ Site Frequency Spectrum (SFS), $1 \leq k \leq n-1$.

  Note : Conditional on total tree length L_n, S_n is Poisson with parameter $\theta L_n/2$.

- $A_n := \#$ distinct **haplotypes** $= \sum_k A_n(k)$, where
- $A_n(k) := \#$ **haplotypes carried by** k ind (in sample of n)
  $=:$ Allele Frequency Spectrum (AFS), $1 \leq k \leq n$.

  Note : Haplotypes induce the so-called allelic partition of the sample, so

$$\sum_k kA_n(k) = n$$

Law of the allelic partition : Ewens' Sampling Formula

Time reversal argument :

Coalescent (pairwise rate 1) w deaths (rate $\theta/2$)

$\Leftrightarrow$ Birth process (rate 1) with immigration (rate θ)

$\Leftrightarrow$ Chinese restaurant process
$=$ when $(k+1)$-st customer enters the dining room,

- She sits next to customer i with proba $1/(k+\theta)$,
- Or she sits at an empty table with proba $\theta/(k+\theta)$.

Theorem (Ewens 1972)

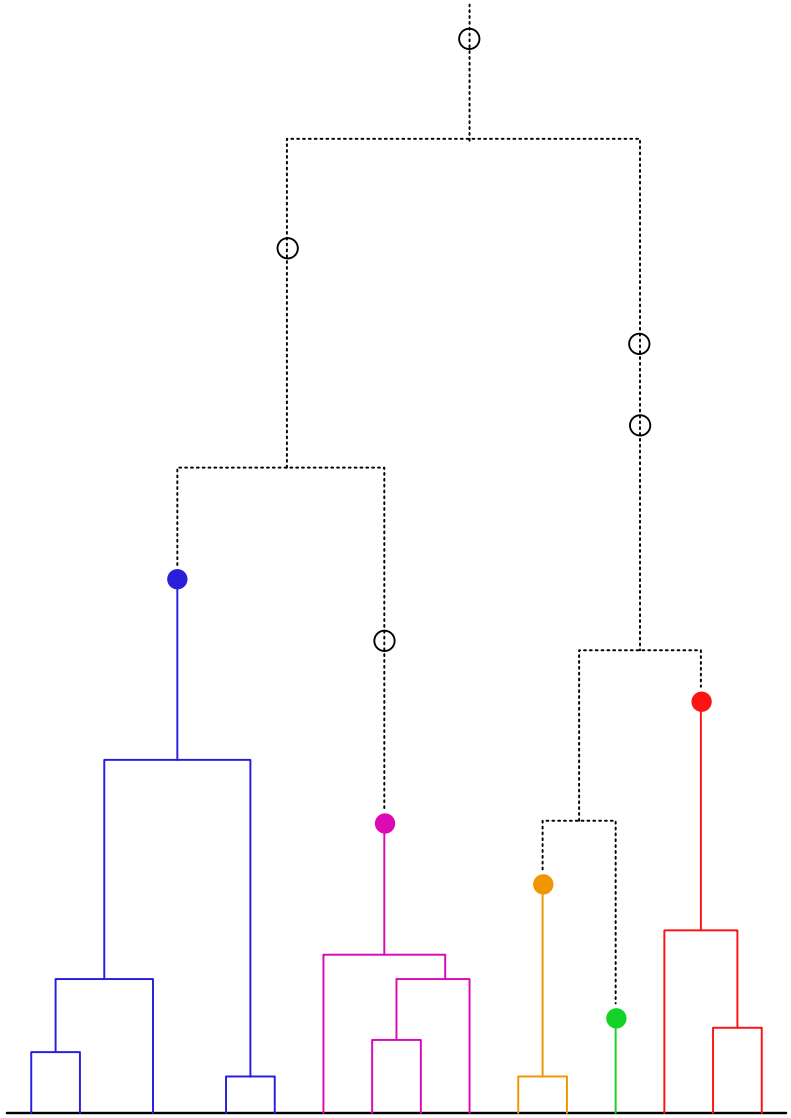
For any vector $(a_1, \ldots, a_n)$ *st* $\sum_{k=1}^n k a_k = n$,

$$\mathbb{P}(A_n(1) = a_1, \ldots, A_n(n) = a_n) = c_{\theta,n} \prod_{k=1}^n \frac{\left(\frac{\theta}{k}\right)^{a_k}}{a_k!}$$

where $c_{\theta,n} := n! \,/\, [\theta(\theta+1)\cdots(\theta+n-1)]$.

$\Leftrightarrow (A_n(1), \ldots, A_n(n)) \overset{(d)}{=} (Y_1, \ldots, Y_n \mid \sum_{k=1}^n k Y_k = n)$:

- Y_k*'s are independent*
- Y_k *is a* **Poisson r.v. with parameter** θ/k.



$n-$coalescent with Poissonian mutations,
each sampled haplotype has its own color

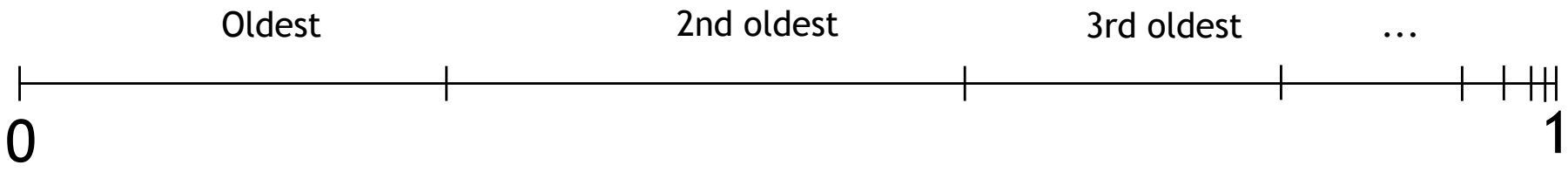
Large sample limit $1 \ll n \ll N$

Ewens, Donnelly & Tavaré...

- As $n \to \infty$,
$$S_n \sim \theta \ln(n) \quad \text{and} \quad A_n \sim \theta \ln(n),$$
with convergence rate $\sqrt{\ln(n)}$.

- Small families (fixed k).
$$\lim_{n\to\infty} A_n(k) \overset{(d)}{=} Y_k,$$
where Y_k denotes a Poisson r.v. with parameter θ/k.

- Large families.
Set $X_n(i) :=$ size of i-th oldest family.
As $n \to \infty$, $\left(n^{-1}X_n(k)\right)_{k\geq 1}$ converges (fdd) to the GEM vector $(P_k)_{k\geq 1}$ defined as
$$P_k := Z_k \prod_{i=1}^{k-1}(1 - Z_i),$$
where the (Z_i) are i.i.d. with density $\theta(1-z)^{\theta-1}$ (Beta $(1,\theta)$).



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- If pop size not constant, $N(t) = Nx(Nt)$, then

$$\mathbb{P}(T_N(2)/N > t) \longrightarrow \exp\left\{-\int_0^t \frac{ds}{x(s)}\right\}$$

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- Assume N constant. If the **value of** $T_N(2)$ can be estimated from diversity, then $1/T_N(2) =$ **estimator of** N

- If pop size not constant, $N(t) = Nx(Nt)$, then

$$\mathbb{P}(T_N(2)/N > t) \longrightarrow \exp\left\{ - \int_0^t \frac{ds}{x(s)} \right\}$$

- Recall that different genes have different genealogies — in theory, if the **distribution of** $T_N(2)$ could be estimated from diversity at many 'independent' loci, the **variations of** N **through time** could be inferred!!

Estimating population size

- Pop size $\uparrow$, relatedness $\downarrow$, diversity $\uparrow$

- If mutation proba u_N known, then any estimator of $\theta = 2Nu_N$ yields an estimate of N. For example θ can be estimated by $S_n / \ln(n)$ (Watterson 1975)

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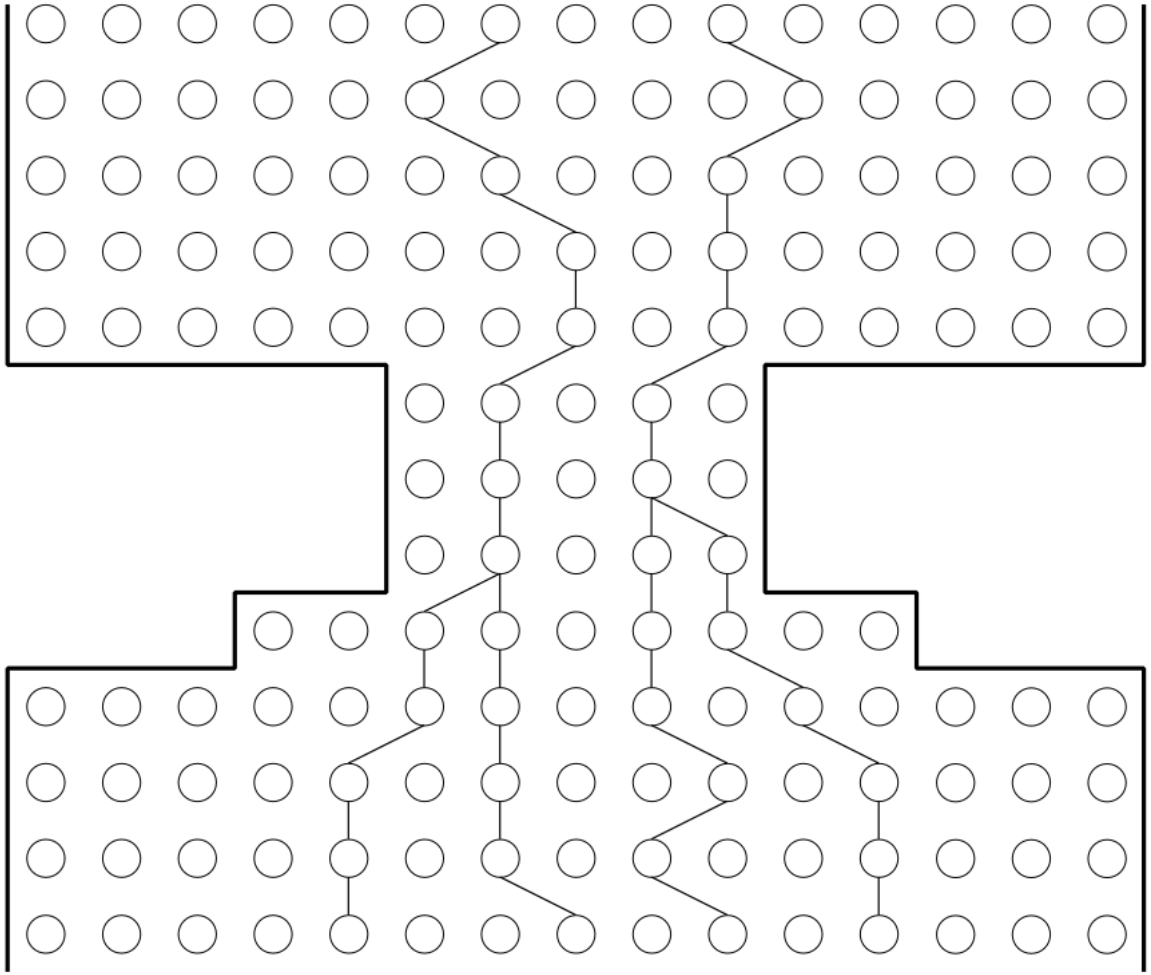
- Requires understanding how genealogies of different genes are coupled...

The example of a bottleneck



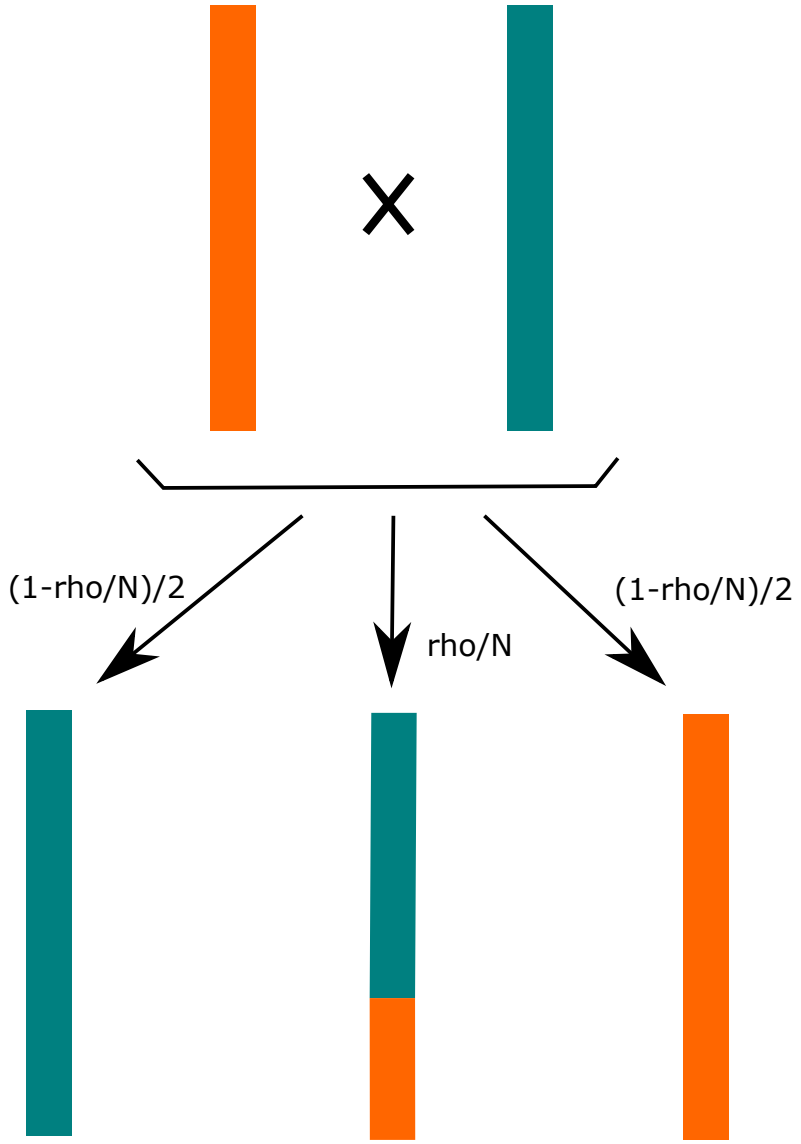
A provisional reduction in population size, or bottleneck

Densities of coalescence times peak at a bottleneck time

Outline

Wright–Fisher model with recombination

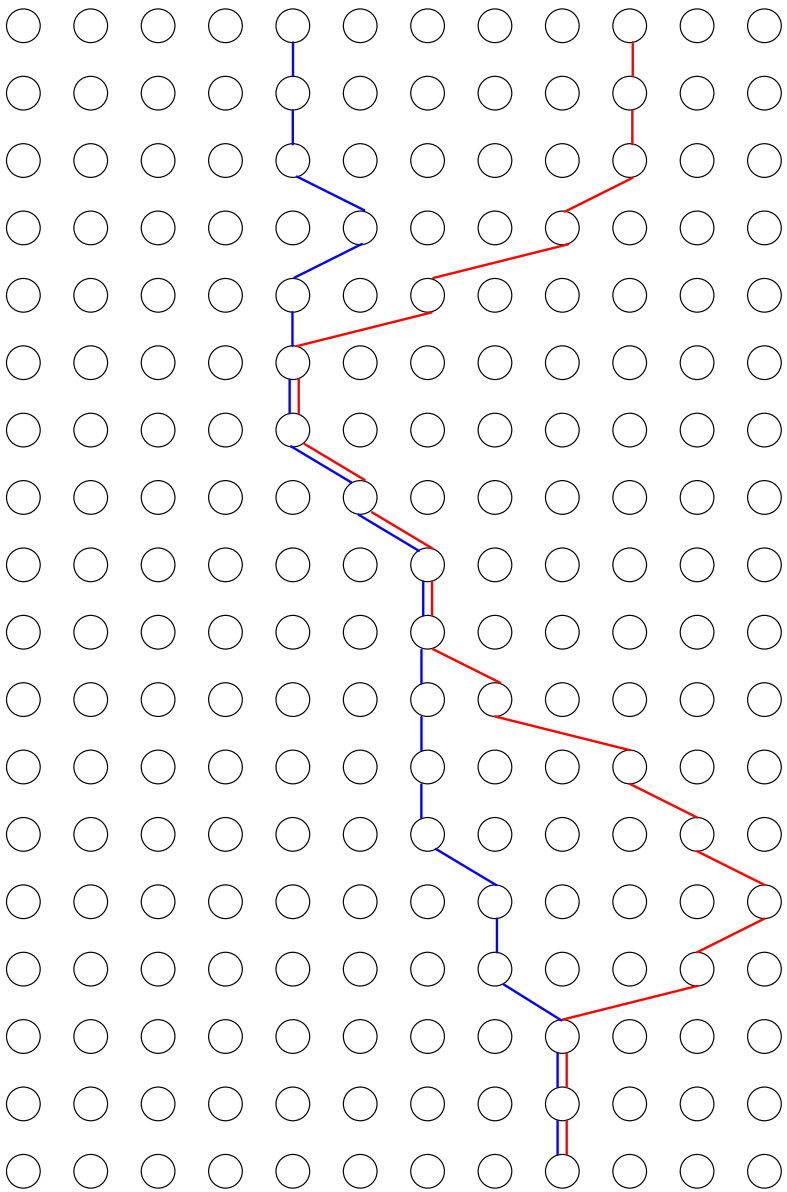
- Constant pop size N, but now : **TWO parents per ind**
- Each ind carries one chromosome $=$ interval $[0, 1]$
- At each generation, each individual chooses her two parents uniformly at random
- The two **parental chromosomes recombine with probability** ρ/N
- ...as a single, uniformly distributed cross-over
- Otherwise, only one of the two chromosomes is passed on.



Ancestral Recombination Graph : 2 sites, $n = 1$

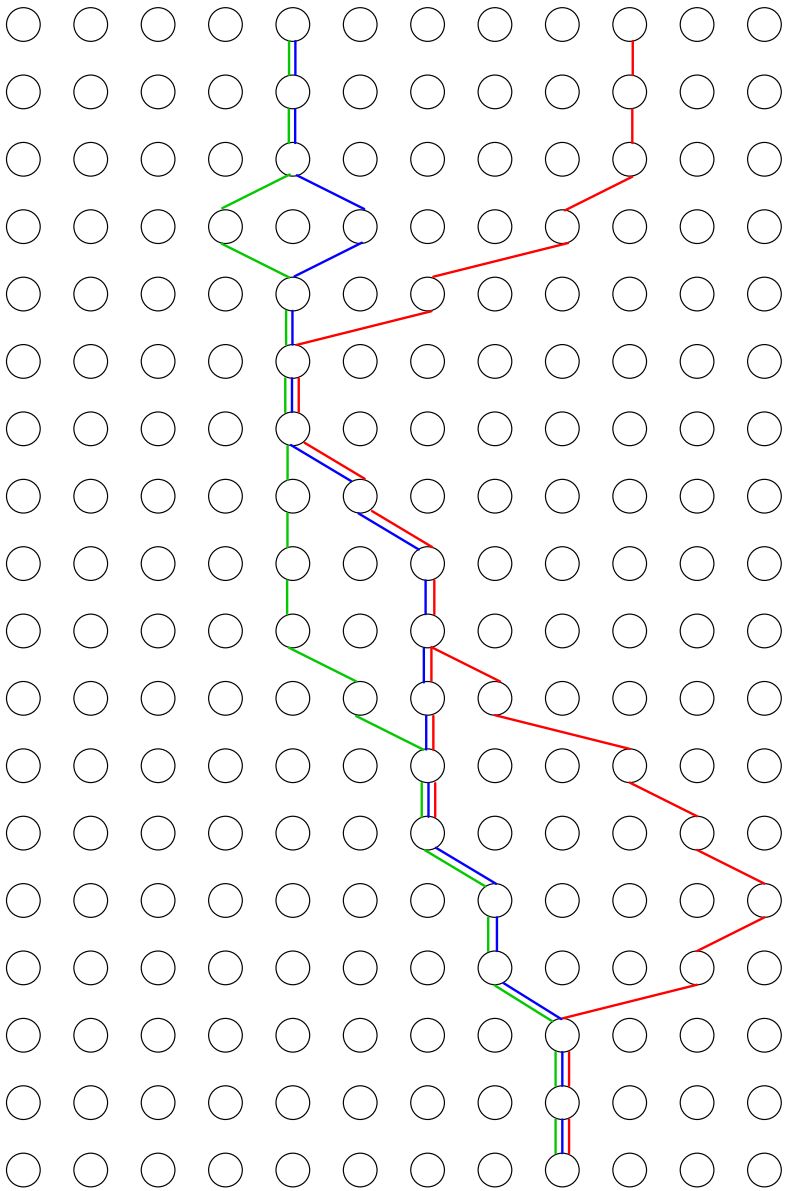
Grifiths & Marjoram, Wiuf & Hein, Jenkins & Song...

- **Sample $n = 1$ individual**
- Consider two sites x and y at distance ℓ and follow their ancestry as time goes backward
- At each generation, the common line of descent $\{x, y\}$ **splits with probability** $\rho\ell/N$
- At each generation, the singleton lines $\{x\}$ and $\{y\}$ coalesce with probability $1/N$
- As $N \to \infty$, the time-rescaled ARG **splits at rate** $\rho\ell$ **and merges at rate** 1.



The Ancestral Recombination Graph : 3 sites, $n = 1$

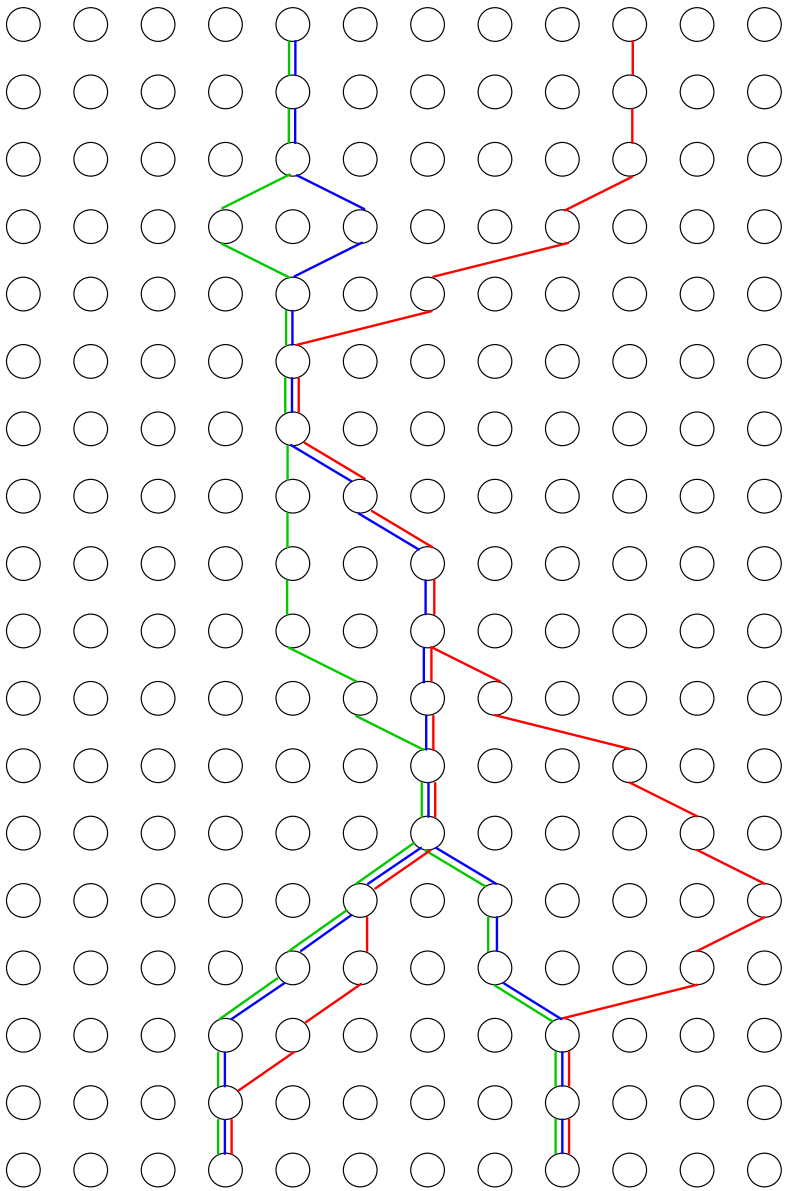
- Sample $n = 1$ individual
- Consider three sites $\{x, y, z\}$ at distances ℓ_1 and ℓ_2
- In the limit $N \to \infty$, the block $\{x, y, z\}$
  - splits into $\{x, y\}$ and $\{z\}$ at rate $\rho\ell_2$
  - splits into $\{x\}$ and $\{y, z\}$ at rate $\rho\ell_1$
- Block $\{x, y\}$..., block $\{y, z\}$..., block $\{x, z\}$...
- Each pair of lines coalesces at rate 1.



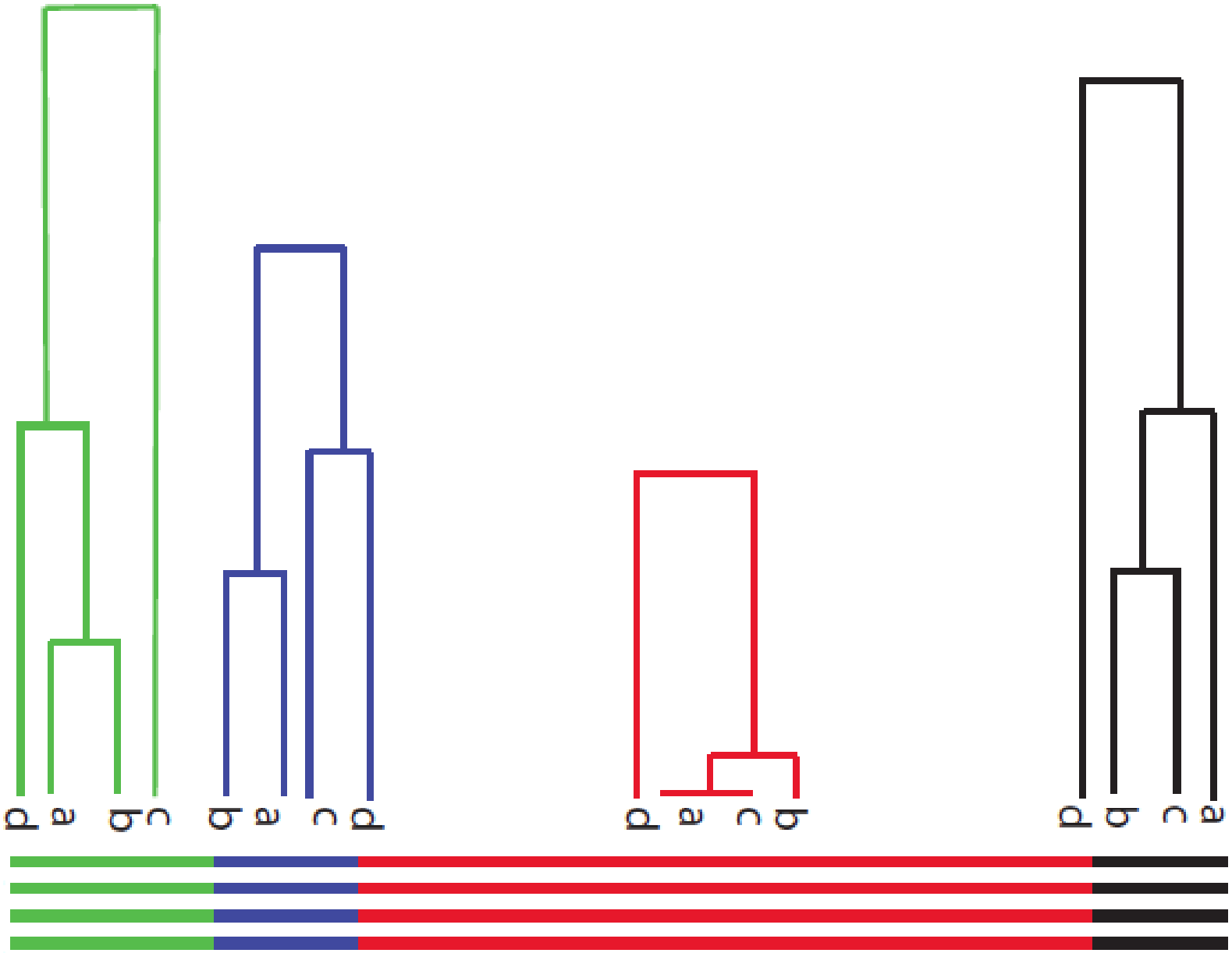
Note : When $n = 1$, the ARG on k loci can be generated by a Markov process valued in the partitions of $\{1, \ldots, k\}$.

The Ancestral Recombination Graph : 3 loci, $n = 2$

- Now sample $n = 2$ individuals
- Now same color-lines can additionally coalesce
- Observe that green and blue loci have the same time to MRCA, $\neq$ red locus.
- Moving along the chromosome, we see a **sequence of trees** ($n = 2$: a sequence of cherries)...
- **IBD segment** ("identical by descent") := maximal connected segment of sites sharing the same genealogy.



Tree sequence



picture by Guillaume Achaz

Shallow trees are carried by a longer IBD segment

Outline

Sequentially Markovian Coalescent (SMC)

McVean & Cardin, Li & Durbin, Schiffels & Durbin...

- ARG : complex dependencies betw gene trees

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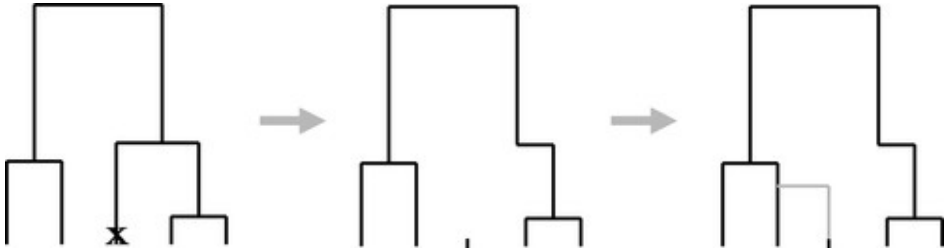

McVean & Cardin (2005)

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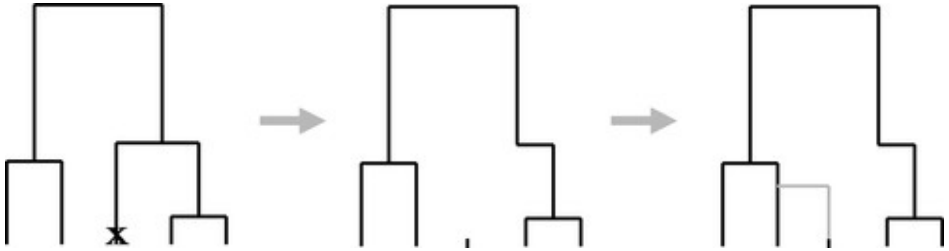

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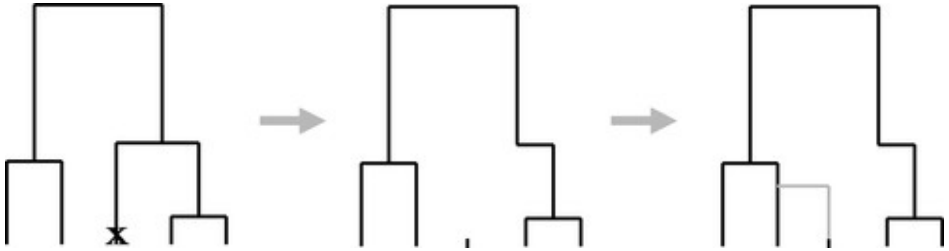

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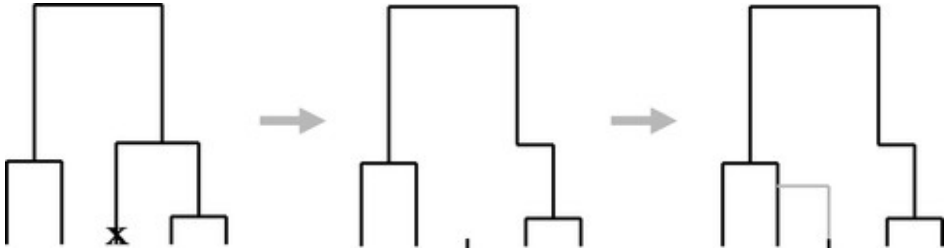

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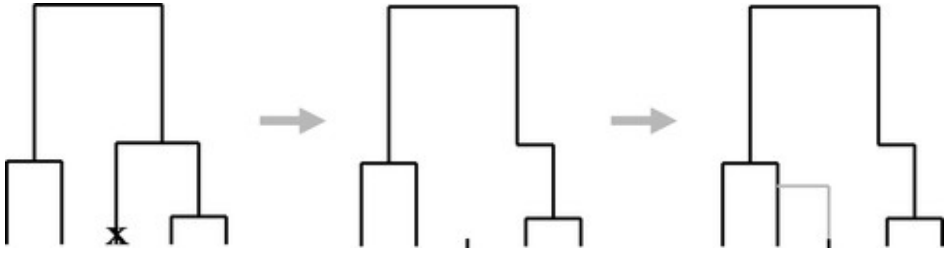

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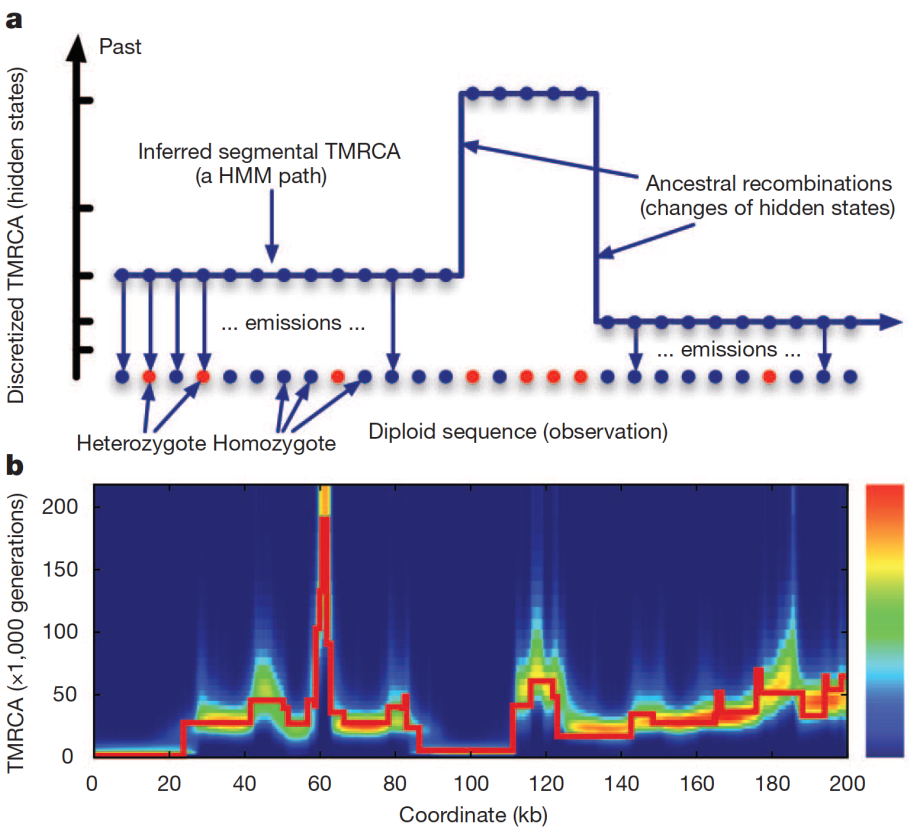

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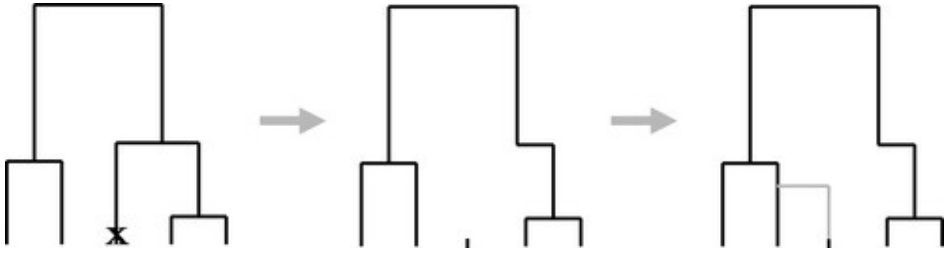

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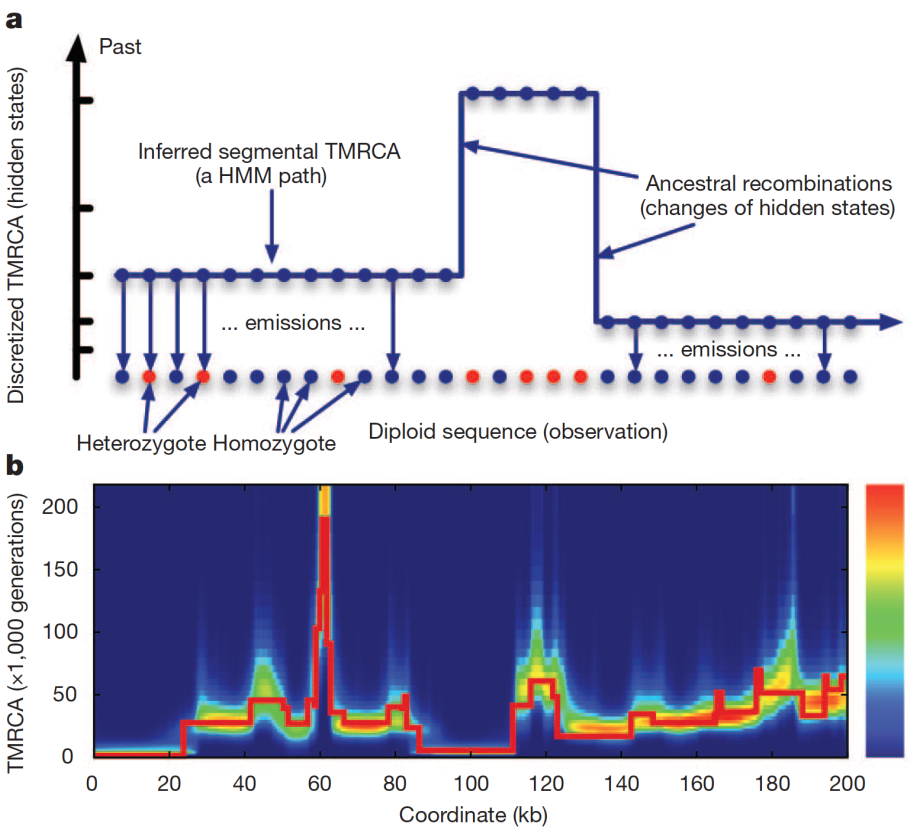

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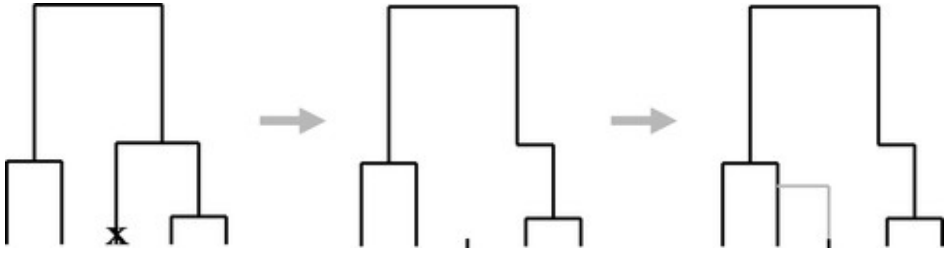
  - Shallow tree = Long segment, low density of heterozygous sites
  - Deep tree = Short segment, high density of heterozygous sites



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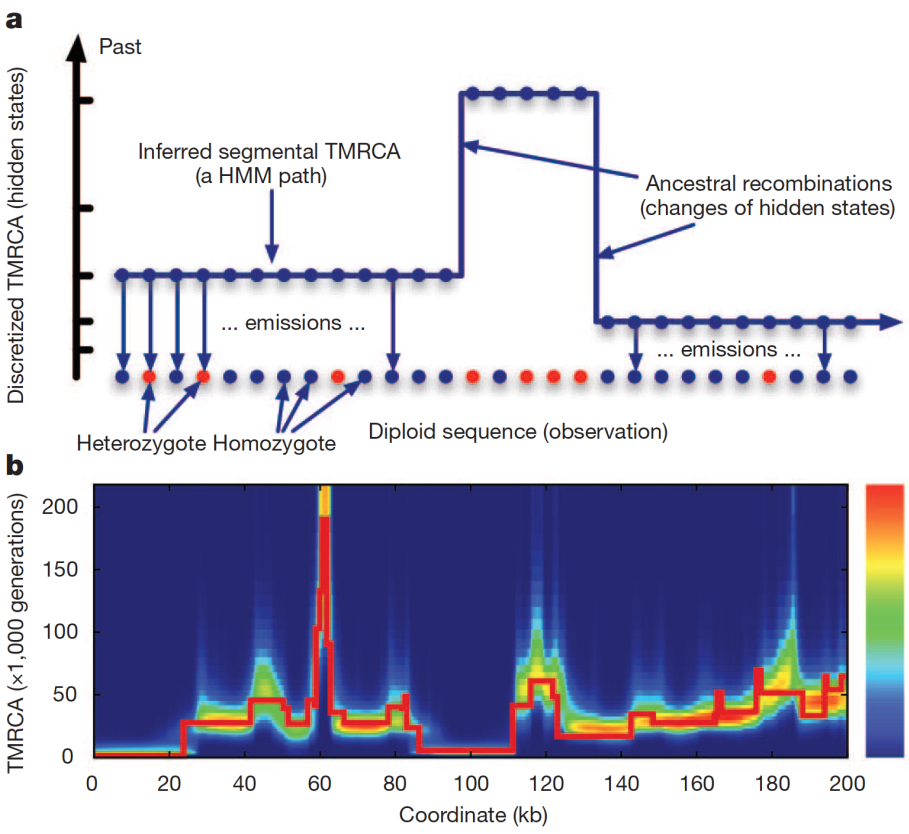
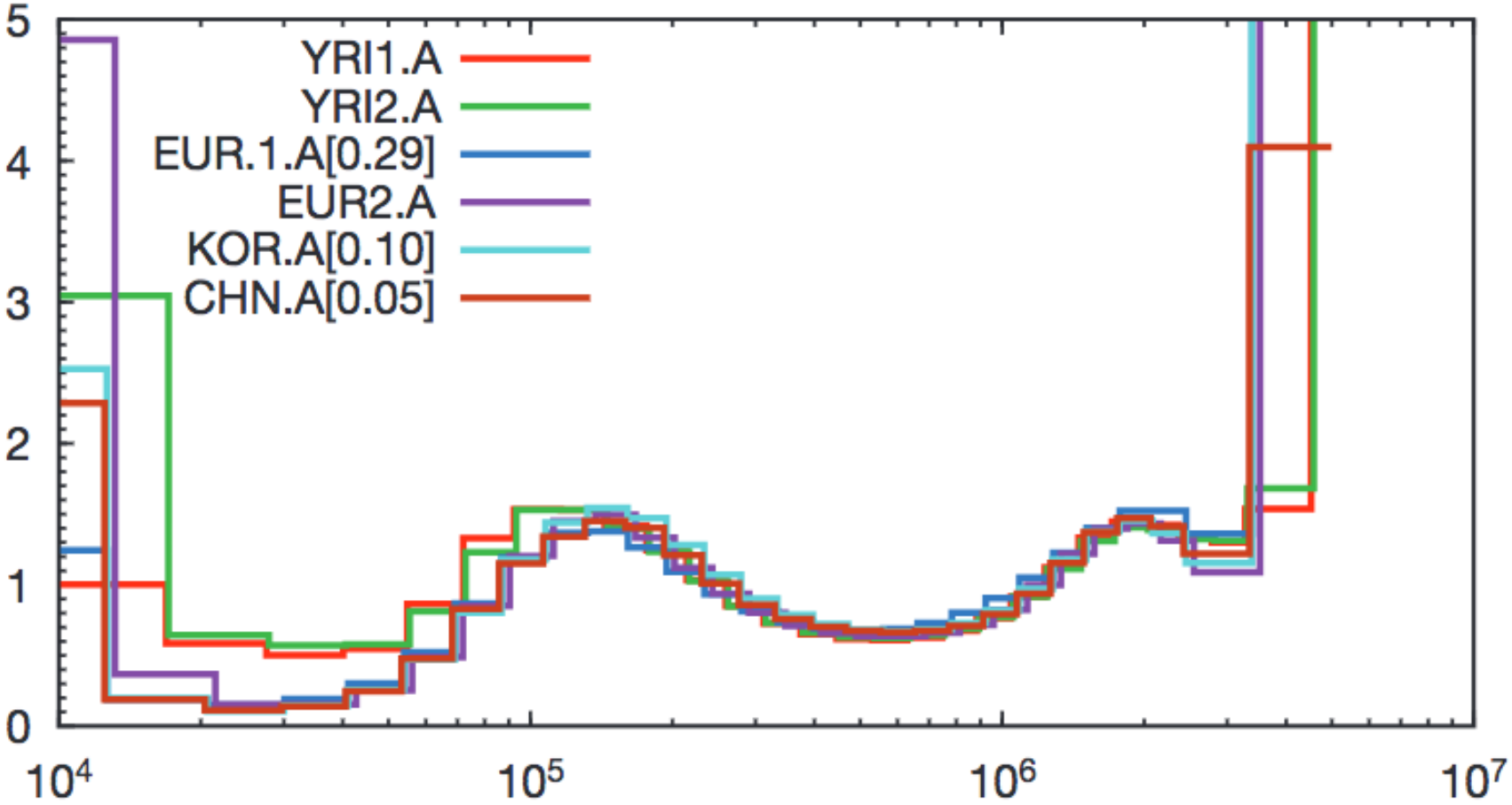


Li & Durbin (2011)

Inference of demographic history of human ancestry by PSMC

Generation time = 25 years, mutation proba $u = 2.5 \times 10^{-8}$ per generation per bp



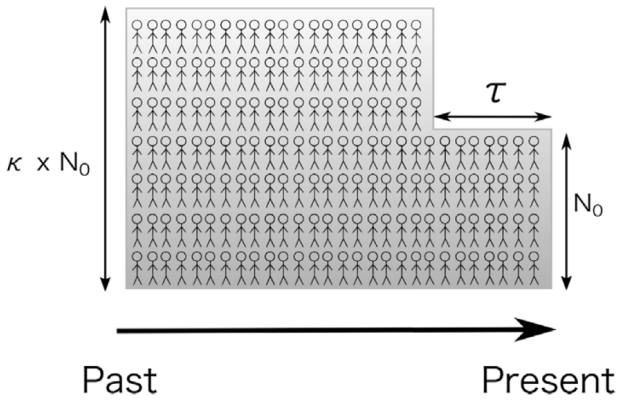
Li & Durbin (2011)

- Severe bottleneck 10–60 kyr ago
- Differentiation of genetically modern humans starting as early as 100–120 kyr ago
- Elevated pop size betw 60 and 250 kyr ago, possible artefact due to pop substructure (involving small, separately evolving isolated pops).

A quantitative assessment of extinction risk

Kerdoncuff, Lambert & Achaz, "Testing for population decline using maximal linkage disequilibrium blocks" *TPB* 2020

- Goal : detect decline $\kappa N_0 \rightarrow N_0, \tau N_0$ generations ago

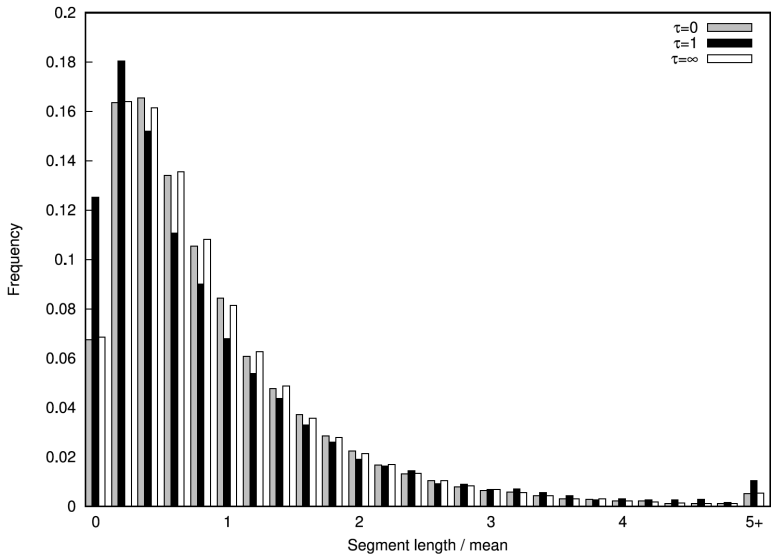


- Maximum LD block = maximal segment with mutations compatible with a single tree

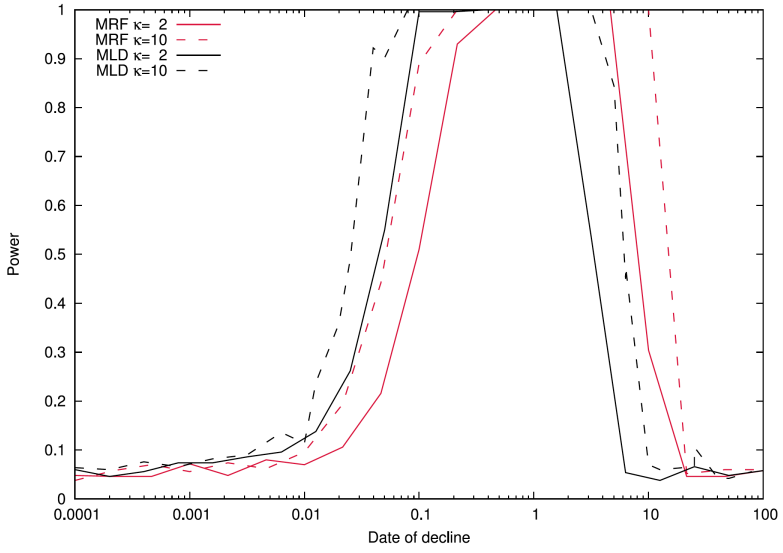
- Normalized distribution of MLD block lengths insensitive to pop size, sensitive to pop size variations

- Example. Power $> 50\%$ for $n = 10$ and a smooth, recent decline ($\kappa = 2, \tau = 0.05$).

- Requires good quality sequences. Sensitive to population structure.



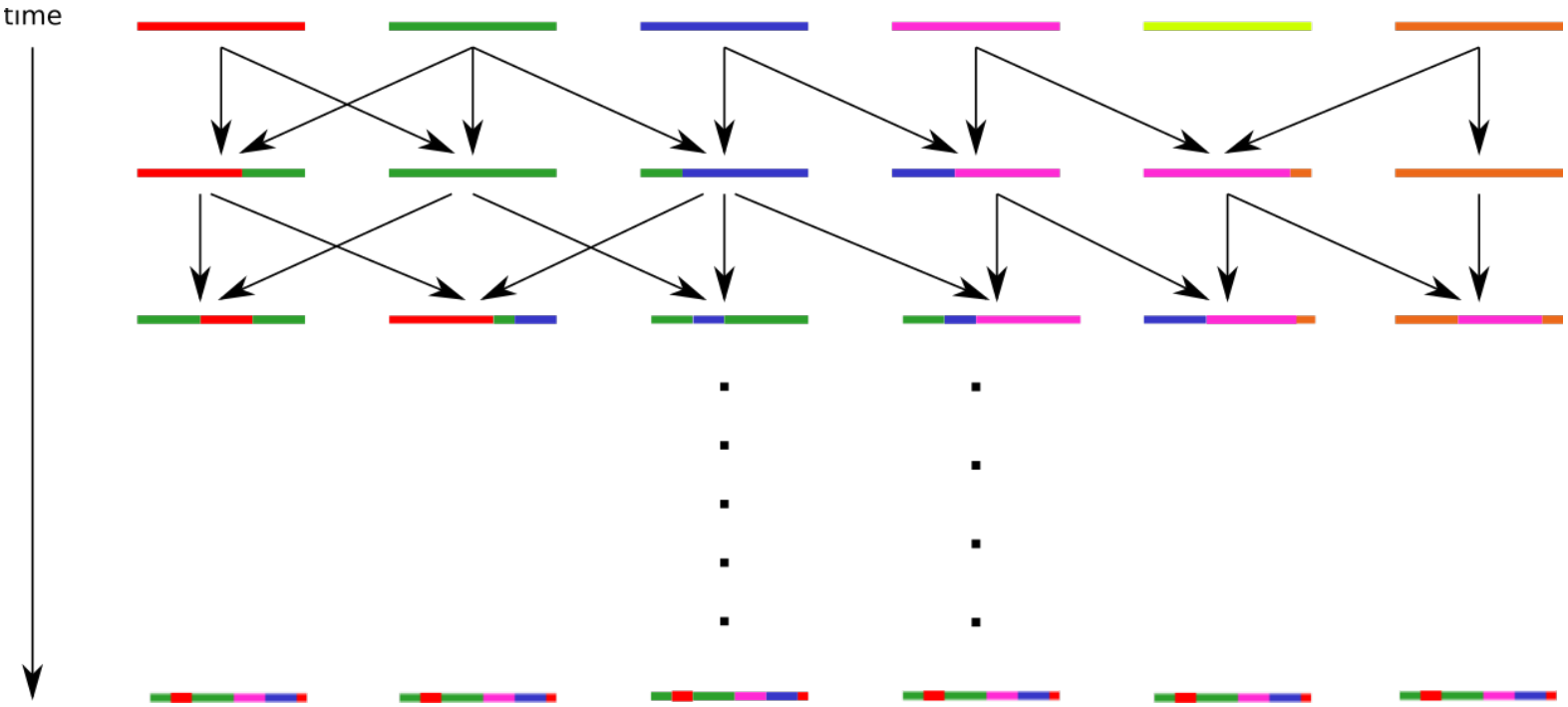
$n = 10, \kappa = 3$



$n = 10, \kappa = 2$ or 10

Chromosome painting

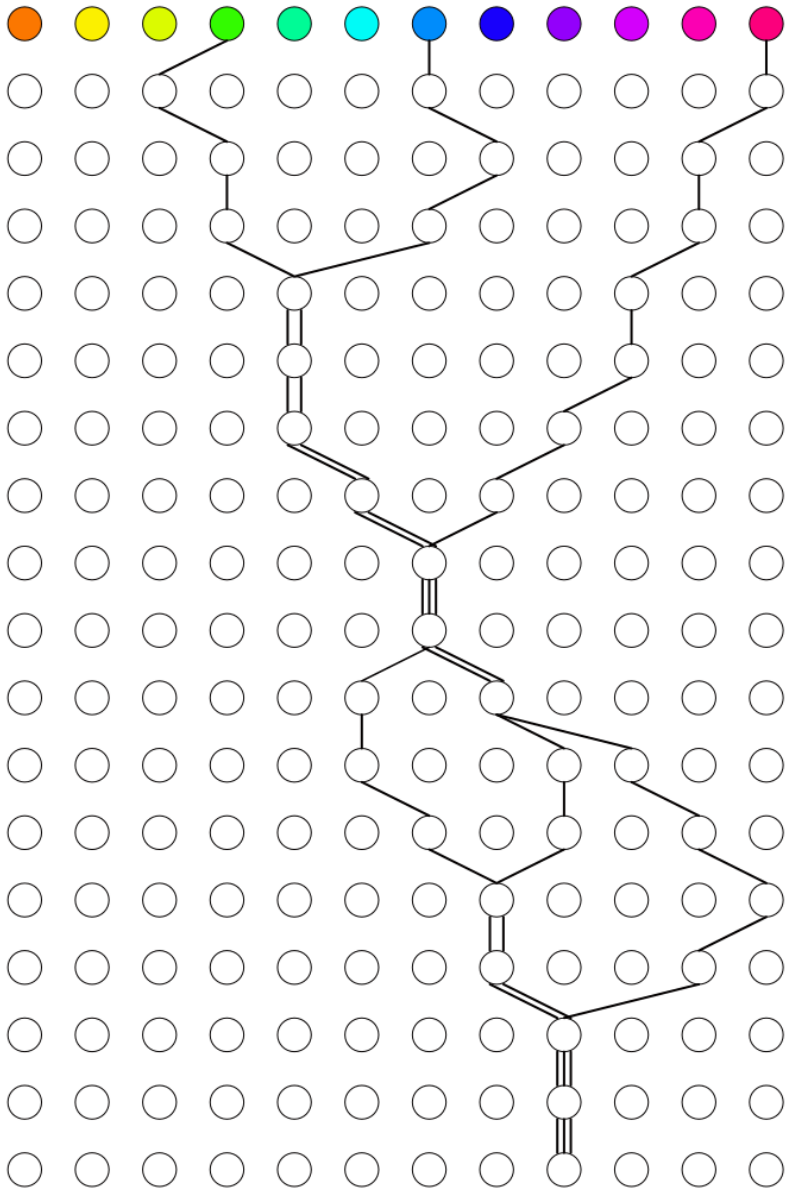
- Recall Wright–Fisher model with pop size N, recombination prob ρ/N (here $\rho = R$)
- Chromosome $=$ interval $[0, R]$
- Start with N ind and paint each of these N initial sequences with a different color.
- After some fixed amount of time, pick one individual at random : how does the mosaic of colors on this chromosome look like ?
- When time is sufficiently large, all individuals carry the same fixed chromosome : How does the fixed mosaic look like ?



picture by Verónica Miró Pina

The Ancestral Recombination Graph – cont'd

- Recall that when $n = 1$, the ARG can be described by a partition of $[0, R]$, induced by the relation of common ancestry
- Initial state : coarse partition
- The fixed mosaic is given by the stationary distribution of this partitioning process

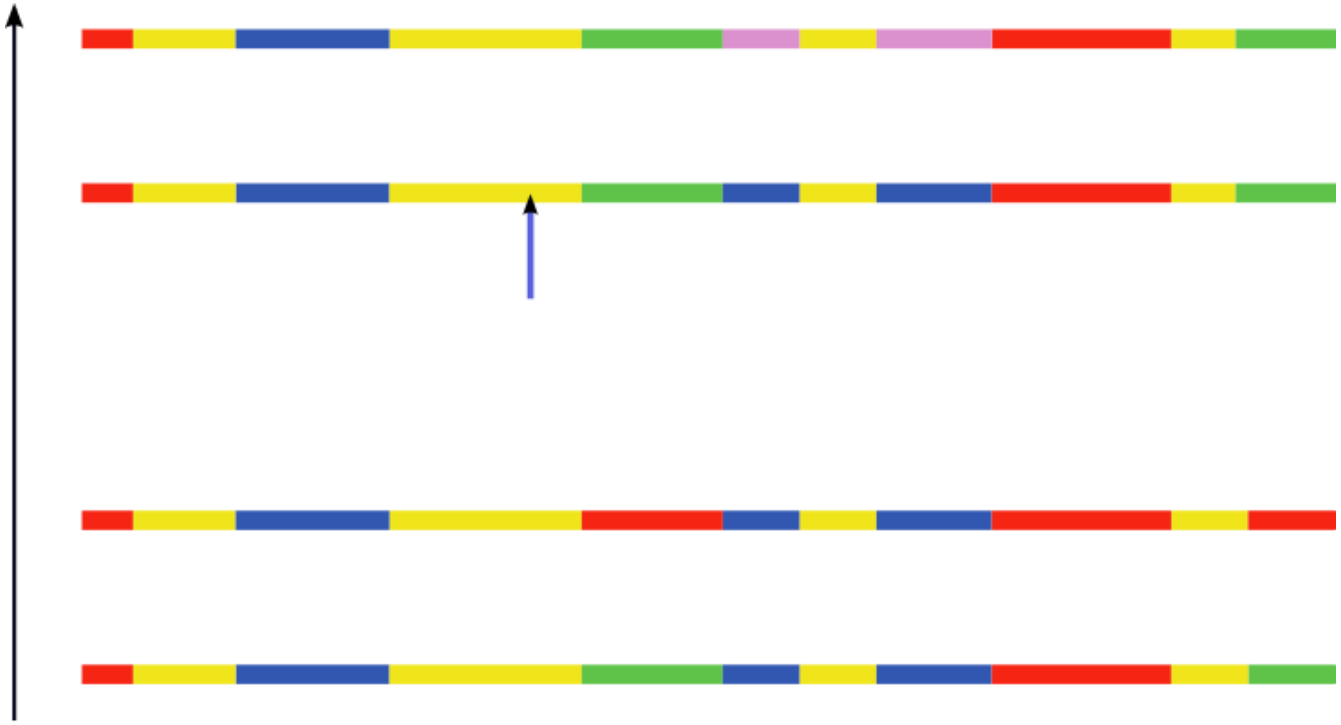


The partitioning process

Esser, Probst & Baake, Lambert, Miró Pina & Schertzer

Recall recombinations fall at rate 1 per unit time, per unit length.

- Each cluster (here, blue) independently splits into two at rate equal to its diameter at a point uniformly distributed in its convex hull
- Each pair of clusters (here, red and green) independently coalesces at rate 1



Zooming out logarithmically on the fixed mosaic

Lambert, Miró Pina & Schertzer "Chromosome painting : how recombination mixes ancestral colors" *Ann Appl Prob* (2020)

- Recall $0 \sim x$, if x carries same color as left extremity of chromosome (say, red)
- Define length of cluster containing 0

$$L_R := \int_0^R \mathbb{1}_{0\sim x}\, dx$$

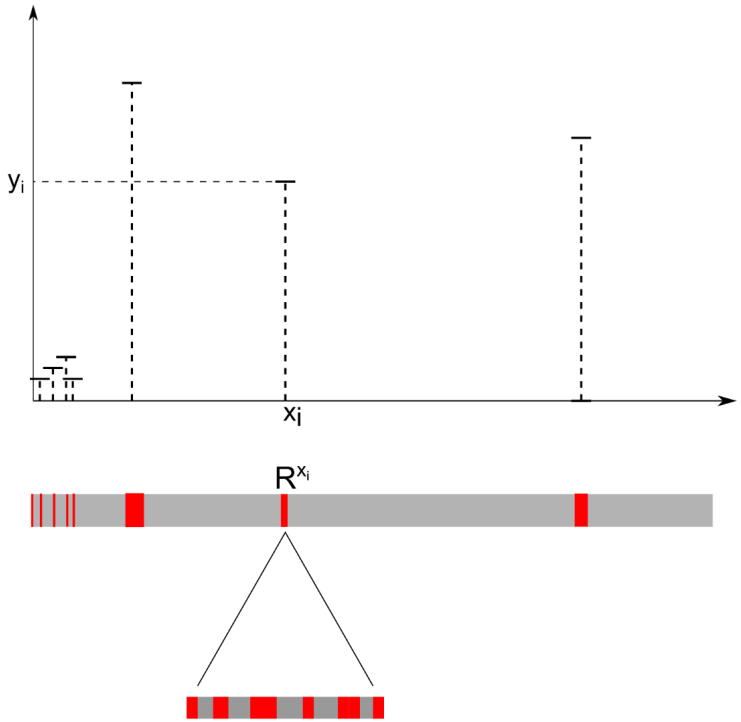
and for $0 \leq a \leq b \leq 1$,

$$\vartheta_R([a,b]) := \frac{1}{\log(R)} \int_{R^a}^{R^b} \mathbb{1}_{0\sim x}\, dx$$

Theorem (L., Miró Pina & Schertzer 2020)

As $R \to \infty$,

- $L_R / \log(R) \to \mathcal{E}(1)$
- $\vartheta_R \to \sum_i y_i \delta_{x_i}$ *where (x_i, y_i) are the atoms of a PPP with intensity $x^{-2} e^{-y/x} dx\, dy$.*



In the logarithmic scale, the segments IBD with 0 are distributed according to the scale-invariant PPP (intensity $x^{-1}dx$) and the length of segment at R^x is exponential with mean $x \log(R)$.

Insert shows complex geometry of these segments at finer scale not described in the Theorem.

Number of ancestors contributing to today's genomes

Theorem (L., Miró Pina & Schertzer 2020)

Let $\epsilon > 0$ *and let* $M_\epsilon(R) =$ *number of clusters in* $[0, R]$ *with length larger than* $\epsilon \ln(R)$. *Then*

$$\lim_{\epsilon \to 0} \lim_{R \to \infty} \frac{\ln(R)}{R} M_\epsilon(R) = 1 \qquad \text{in probability.}$$

Conjecture (Wiuf and Hein 1997)

There exists a constant $c \approx 1.38$ such that

$$\lim_{R \to \infty} \frac{\ln(R)}{R} M(R) = c \qquad \text{(in law, a.s.?)}$$

Collaborators

Guillaume ACHAZ (SMILE) . . . . . 

Élise KERDONCUFF (SMILE) . . . . . 

Verónica MIRÓ PINA (SMILE) . . . . . 

Emmanuel SCHERTZER (SMILE) . . . . . 

Outline

Books

Durrett, R. (2008) *Probability models for DNA sequence evolution.*

Wakeley, J. (2009) *Coalescent theory.*

Etheridge, A. (2011) *Some mathematical models from population genetics — École d'été de probabilités de Saint-Flour XXXIX-2009.*

Ewens, W.J. (2012) *Mathematical population genetics.*

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Lambert, “Population dynamics and random genealogies”, *Stoch Models* (2008)

Berestycki, “Recent progress in coalescent theory”, *Ensaios matem* (2009)

Lambert, “Probabilistic models for the (sub)tree(s) of life”, *Braz J Probab Stat* (2017)

Lambert, “Random ultrametric trees and applications”, *ESAIM P& S* (2018)

Papers

Kingman, “The coalescent”, *Stoch Proc Appl* (1982)

Donnelly & Tavaré “The ages of alleles and a coalescent”, *Adv Appl Prob* (1986)

Griffiths & Marjoram, “An ancestral recombination graph”, *IMA volume : Progress in Population Genetics and Human Evolution* (1997)

Wiuf & Hein, “On the number of ancestor to a DNA sequence”, *Genetics* (1997)

Möhle, “Robustness results for the coalescent” *J Appl Prob* (1998)

McVean & Cardin, “Approximating the coalescent with recombination” *Philos Transac RS* (2005)

Jenkins & Song, “An asymptotic sampling formula for the coalescent with recombination”, *Ann Appl Probab* (2010)

Li & Durbin, “Inference of human population history from individual whole-genome sequences”, *Nature* (2011)

Liu & Fu, “Exploring population size changes using SNP frequency spectra”, *Nature Genetics* (2015)

Régnier*, Achaz*, Lambert, Cowie, Bouchet & Fontaine, “Mass extinction in poorly known taxa”, *PNAS* (2015)

Esser, Probst & Baake, “Partitioning, duality, and linkage disequilibria in the Moran model with recombination”, *J Math Biol* (2016)

Lapierre, Lambert & Achaz, “Accuracy of demographic inferences from Site Frequency Spectrum : The case of the Yoruba population” *Genetics* (2017)

Kerdoncuff, Lambert & Achaz, “Testing for population decline using maximal linkage disequilibrium blocks” *Theoret Popul Biol* (2020)

Lambert, Miró Pina & Schertzer, “Chromosome painting : how recombination mixes ancestral colors” *Ann Appl Prob* (2020)

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