Evolution of the Ancestral Recombination Graph along the genome in case of selective sweep

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Plan

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1. Introduction
   - Selective sweep with strong selective advantage
   - To extreme cases
2. Evolution of the coalescent tree along the genome
   - Description of the coalescent tree
   - Evolution of the tree
3. Evolution of the ARG along the genome
   - Evolution under neutrality
   - Evolution in case of selective sweep
   - Back to the process of coalescent trees

Haploid population of infinite size.
Genome considered as a single chromosome, identified to $\mathbb{R}$.

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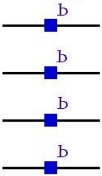

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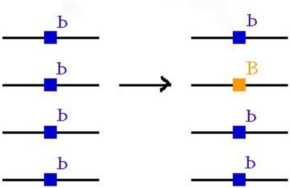

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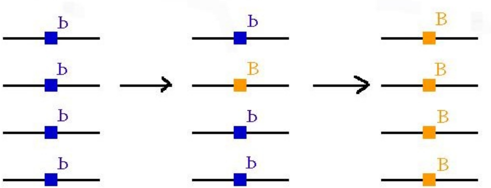
- An advantageous mutation from b to B happens in a SINGLE individual J. Selective advantage of B over b: α.
- B quickly spreads in the population until fixation.



Assume $\alpha \to +\infty$.
The duration of the selective sweep tends to 0 as the selective advantage α goes to $+\infty$, so the selective sweep is instantaneous.

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Sample of n individuals at the end of the selective sweep.

Objective: Study of the evolution of the coalescent tree as the distance from the selected site increases (restriction to $[0, +\infty)$).

Question 1: What is the shape of the coalescent tree near and far from the locus under selection?

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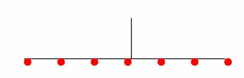
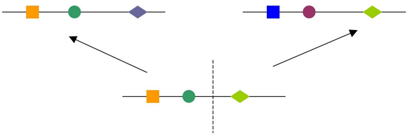
First case: Genealogy at the site under selection (or very close to this site).



Second case: Genealogy far from the site under selection.

Definition

A recombination happens when a portion of the genome is inherited from an individual and the other portion by another individual.



Consider a neutral site at position $x > 0$.

- Without recombination on $[0, x]$ in the sample, same genealogy as the site under selection : comb. (hitchhiking)
- With recombinations on $[0, x]$, no comb anymore.

Far from the site under selection (x large):

Many recombinations on $[0, x]$
$\Rightarrow$ No hitchhiking anymore
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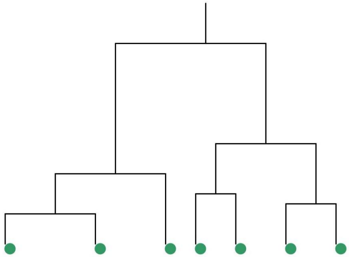
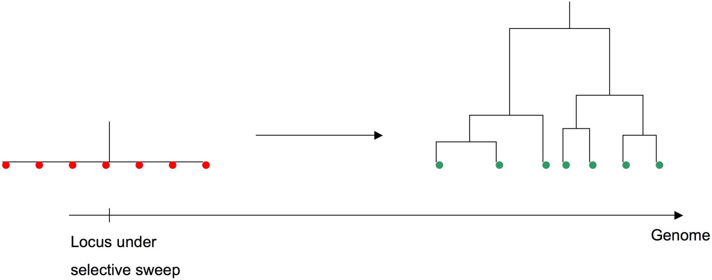
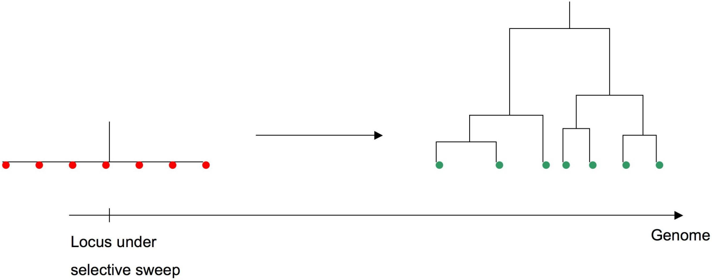
Genealogy of the n-sample: Kingman n-coalescent.
Coalescence rate when k lineages: $\binom{k}{2}$.




Locus under
selective sweep
Genome



Question 2: What is the shape of the coalescent tree at various distances from the selected locus?

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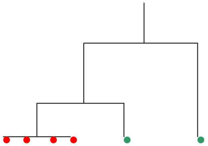
Proposition (Shape of the coalescent tree)

The coalescent tree at locus x is a Kingman $(n - R(x) + 1)$-coalescent, where one leaf is a comb with $R(x)$ teeth. The comb gathers the alleles inherited from J.



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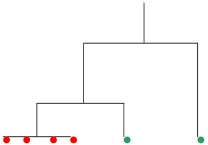

Question 3: Evolution of the process $x \in \mathbb{R}_+ \to R(x) \in \{0, ..., n\}$?

Theorem

The process $x \in \mathbb{R}_+ \to R(x) \in \{0, ..., n\}$ *has the following properties:*

1. $R(0) = n$,
2. *R is a non-homogeneous Markov process whose jump rates are given as follows:*

$$Q_{k,\ell}(x) = \begin{cases} (1 - \frac{1}{2}\exp(-\gamma x))k \times 2\gamma & \textit{if } \ell = k-1, \\ \frac{1}{2}\exp(-\gamma x)(n-k) \times 2\gamma & \textit{if } \ell = k+1, \\ 0 & \textit{if } \ell \notin \{k-1, k, k+1\}. \end{cases}$$

3. $\exists x(\omega) > 0; R(x) = 0 \ \forall x \geq x(\omega)$ *a.s.*

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Question 4: Evolution of the whole coalescent tree along the genome?

Wiuf and Hein, 1999: The process of the coalescent trees along the genome is not Markovian.

To obtain a Markovian process, we must add all the “past”: Ancestral Recombination Graph (ARG).

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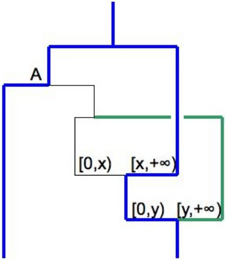
Definition

$ARG(u)$ = graph that sums up the genealogy of the sample, implied by coalescence and recombination events on the portion $[0, u]$.



$0 < x < y$

Question 4': Evolution of the ARG along the genome?

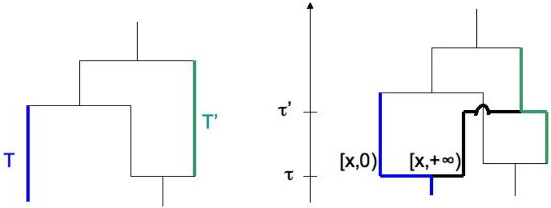
Plan

The ARG is modified:

- when a recombination impacts the ARG during the neutral period that predates the selective sweep (rate $\lambda\times$ total length of the ARG)
- when a recombination occurs during the sweep (rate 2γ)

1) Evolution under neutrality / Recombination during the neutral period:

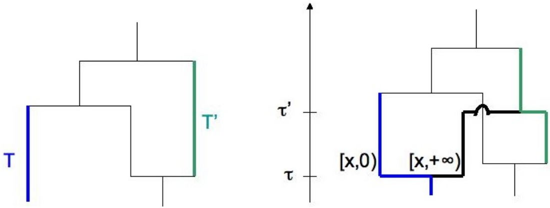
τ: recombination time;
T: branch of the ARG where the recombination happens;
τ': coalescence time of the recombinant lineage;
T': branch of the ARG that coalesces with the recombinant lineage;



$A_t(x)$: number of lineages in ARG(x) at time $t \geq 0$.
$L(x)$: total length of ARG(x) (convention: $L(0) = 1$)
$H(x)$: height of ARG(x) (convention: $H(0) = 1$)

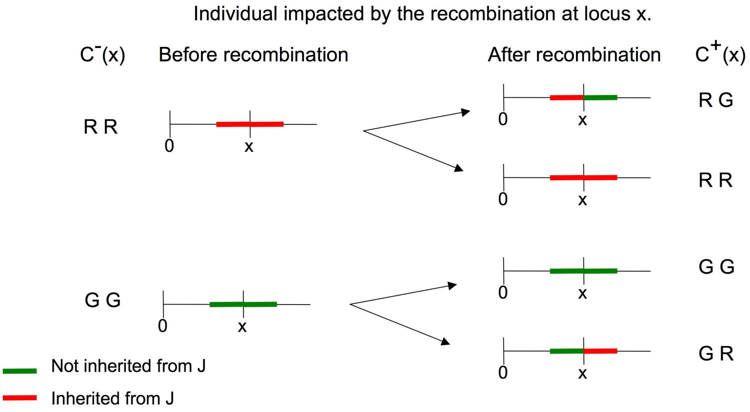
Theorem

1. *The positions of the recombinations are the jump positions of a Poisson process with intensity $\lambda \times L(x)$.*
2. $\mathbb{P}_{(\tau,\tau',T,T')}(dt, dt', \mathcal{T}, \mathcal{T}') = \dfrac{\exp\left(-\int_t^{t'} A_s(x^-)ds\right)}{\int_0^{H(x^-)} A_w(x^-)dw} 1_{t<t'} dt' dt.$



2) Effect of a recombination during the selective sweep

Suppose that a recombination happens at position $x > 0$ during the selective sweep and that $ARG(x^-)$ is given. Then the impact of this recombination is of one of the four types:


Individual impacted by the recombination at locus x.

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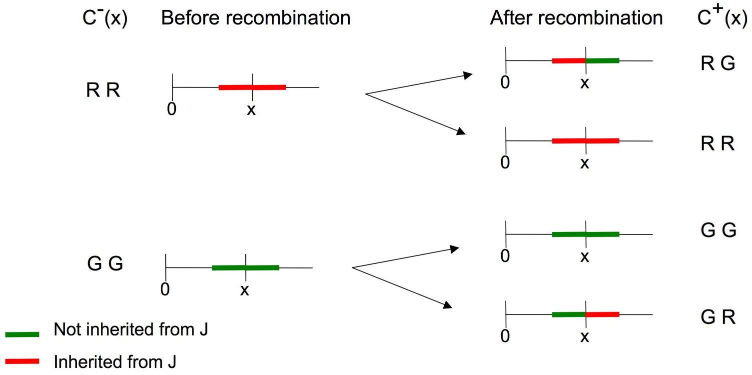
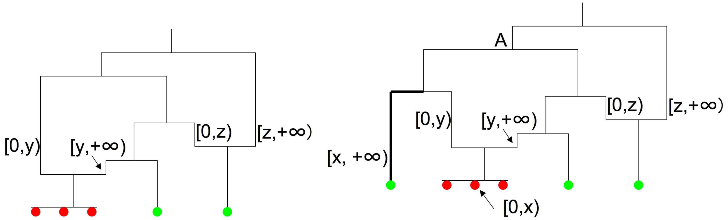


🟩 Not inherited from J

🟥 Inherited from J

$$\begin{aligned} & \mathbb{P}(C^+(x)=RG|R(x^-)=k;\text{recomb at }x) \\ = \; & \mathbb{P}(C^+(x)=RG|C^-(x)=RR;\text{recomb at }x)\mathbb{P}(C^-(x)=RR|R(x^-)=k) \\ = \; & \left(1-\frac{1}{2}e^{-\gamma x}\right)\frac{k}{n} \end{aligned}$$

Modification of the ARG:



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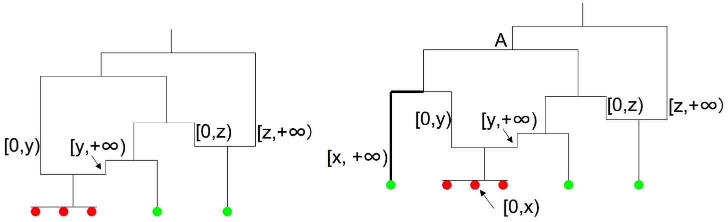
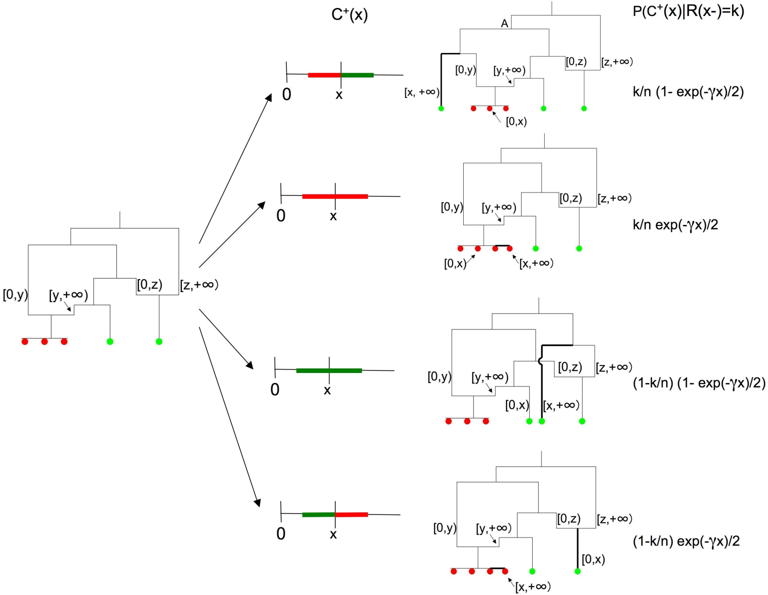


Let I be the impacted tooth of $\mathcal{P}(x^-)$.

$$\mathbb{P}_{(I,\tau',T')}(\mathcal{I}, dt', \mathcal{T}') = \frac{1}{|\mathcal{P}(x^-)|} \exp\left(-\int_0^{t'} A_s(x^-)ds\right) 1_{t'\in\mathcal{T}'} dt'.$$

$A_t(x)$: number of lineages in ARG(x) at time $t \geq 0$.
Coalescence of the new branch at rate $A_t(x)$.



$C^+(x)$

$P(C^+(x)|R(x-)=k)$

$k/n\ (1-\exp(-\gamma x)/2)$

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$(1-k/n)\ (1-\exp(-\gamma x)/2)$

$(1-k/n)\ \exp(-\gamma x)/2$

Theorem (Answer 4': Evolution of the ARG along the genome)

1. *$ARG(0)$ is a comb with n teeth.*
2. *The recombinations positions follow a Poisson process with parameter $2n\gamma + \lambda L(x)$, where $L(x)$ is the total length of ARG(x).*
3. *At the position x of a jump:*
    - *With probability $\frac{\lambda L(x^-)}{2n\gamma+\lambda L(x^-)}$, the recombination occurs during the neutral period. The comb is unchanged and the graph is modified as under neutrality.*
    - *With probability $\frac{2n\gamma}{2n\gamma+\lambda L(x^-)}$, the recombination occurs during the selective sweep and the evolution of the comb and the graph is one of the 4 cases presented above.*

Back to question 4 : Evolution of the whole coalescent tree along the genome?

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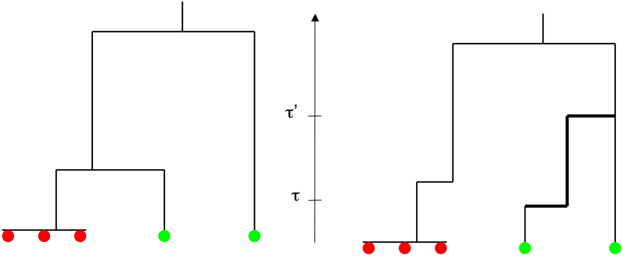
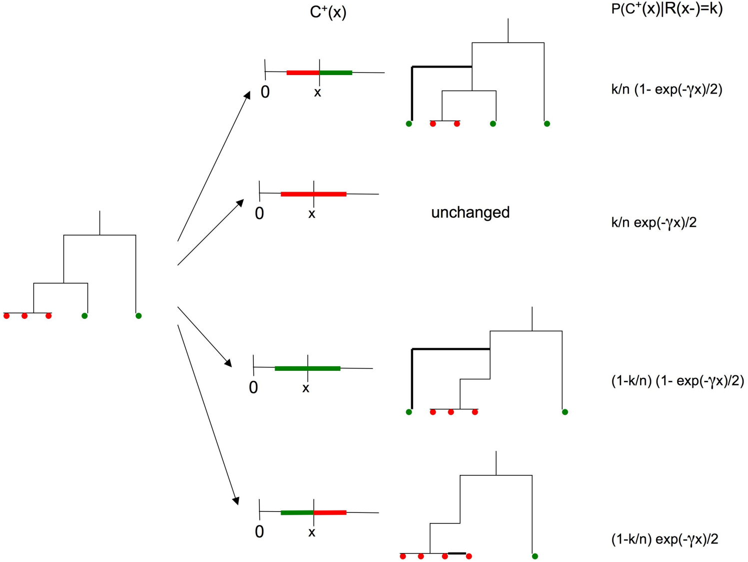
1) If the recombination occurs during the neutral period, a part of a branch is suppressed and a new one is created and coalesces with another branch of the tree.



2) If the recombination occurs during the selective sweep:



$C^+(x)$

$P(C^+(x)|R(x-)=k)$

$k/n\ (1-\exp(-\gamma x)/2)$

unchanged

$k/n\ \exp(-\gamma x)/2$

$(1-k/n)\ (1-\exp(-\gamma x)/2)$

$(1-k/n)\ \exp(-\gamma x)/2$

$$\nu(x) := 1 - \frac{R(x^-)}{n} \frac{\exp(-\gamma x)}{2}$$

Theorem (Answer 4: Evolution of the whole coalescent tree along the genome)

1. *Tree(0) is a comb with n teeth.*
2. *The recombination positions follow a Poisson process with parameter* $2n\gamma\nu(x) + \lambda\tilde{L}(x)$*, where* $\tilde{L}(x)$ *is the total length of tree(x).*
3. *At the position x of a jump:*
    - *With probability* $\frac{\lambda\tilde{L}(x^-)}{2n\gamma\nu(x)+\lambda\tilde{L}(x^-)}$*, the recombination occurs during the neutral period. The comb is unchanged and the tree is modified as under neutrality.*
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THANK YOU FOR YOUR ATTENTION !