Stability of recombination hotspots and mutation load

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Le Cross-over

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Team meeting 11/02/2022

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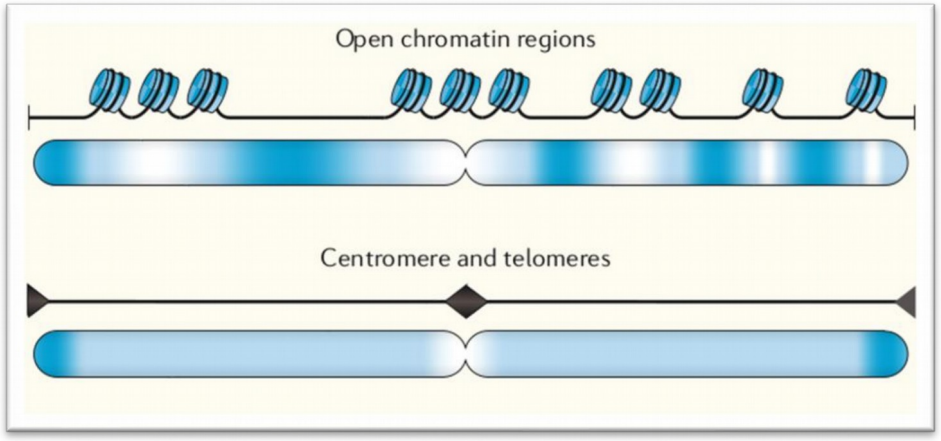
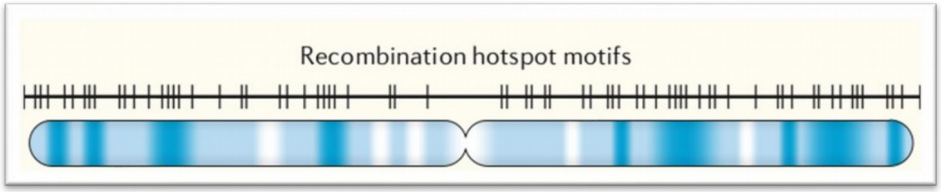
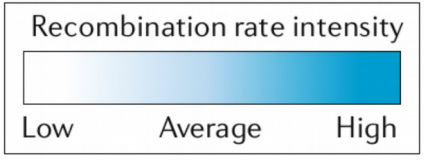
Recombination rate varies along the genome at different scales

At the Mb scale



At the kb scale





Some species have recombination hotspots, others not.

What are the advantages and disadvantages of having recombination hotspots ?

Why are hotspots a good thing ?

Increase fertility

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Facilitate homolgy search by limiting the number of sites in a large genome.

Decrease the time of gametogenesis and enhance fertility.

1st order selection on modifyer of recombination heterogeneity

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Recombination in hotspots is far more elevated than what would be needed to break genetic linkage

Why are hotspots a bad thing ?

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The dark side of recombination…

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gbgc

Advantage and disadvantage of gBGC

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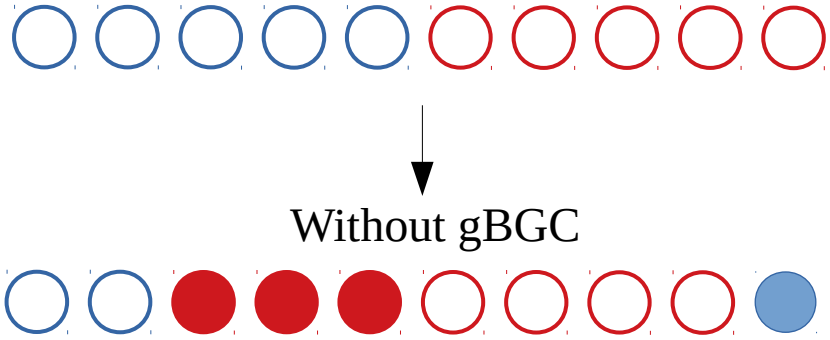
If there is a mutation bias towards AT



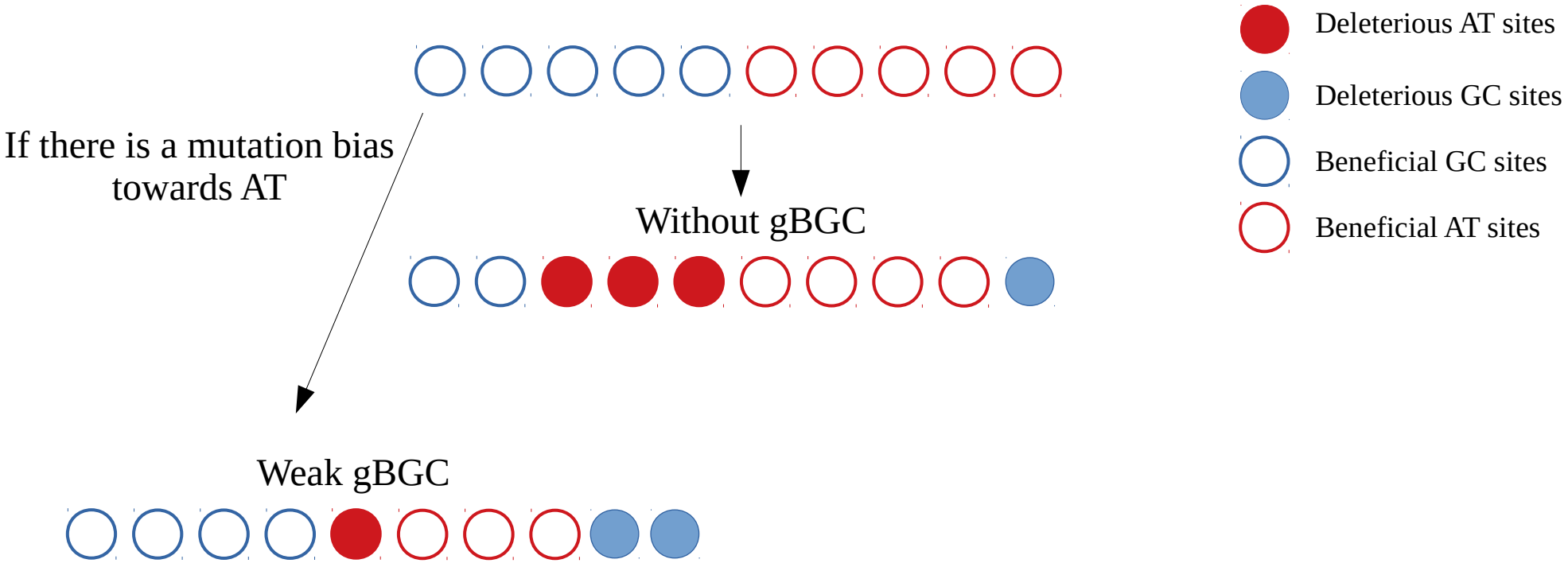
Deleterious AT sites

Deleterious GC sites

Beneficial GC sites

Beneficial AT sites

Advantage and disadvantage of gBGC



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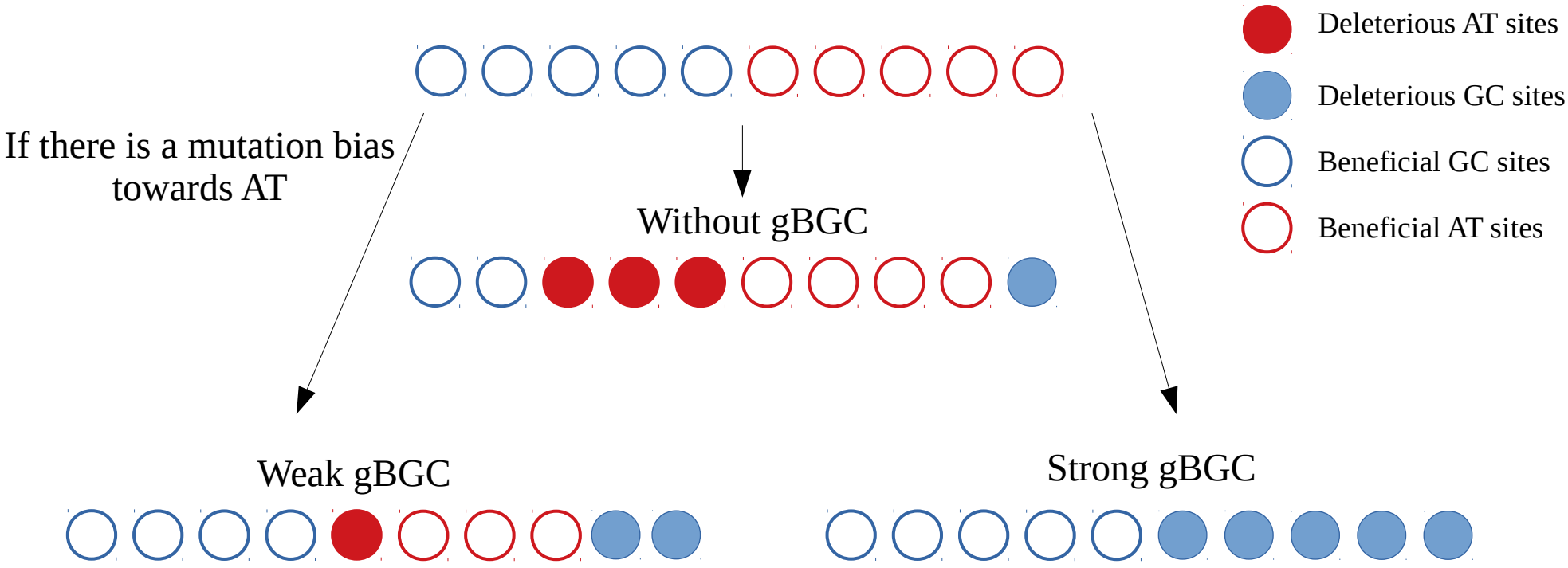

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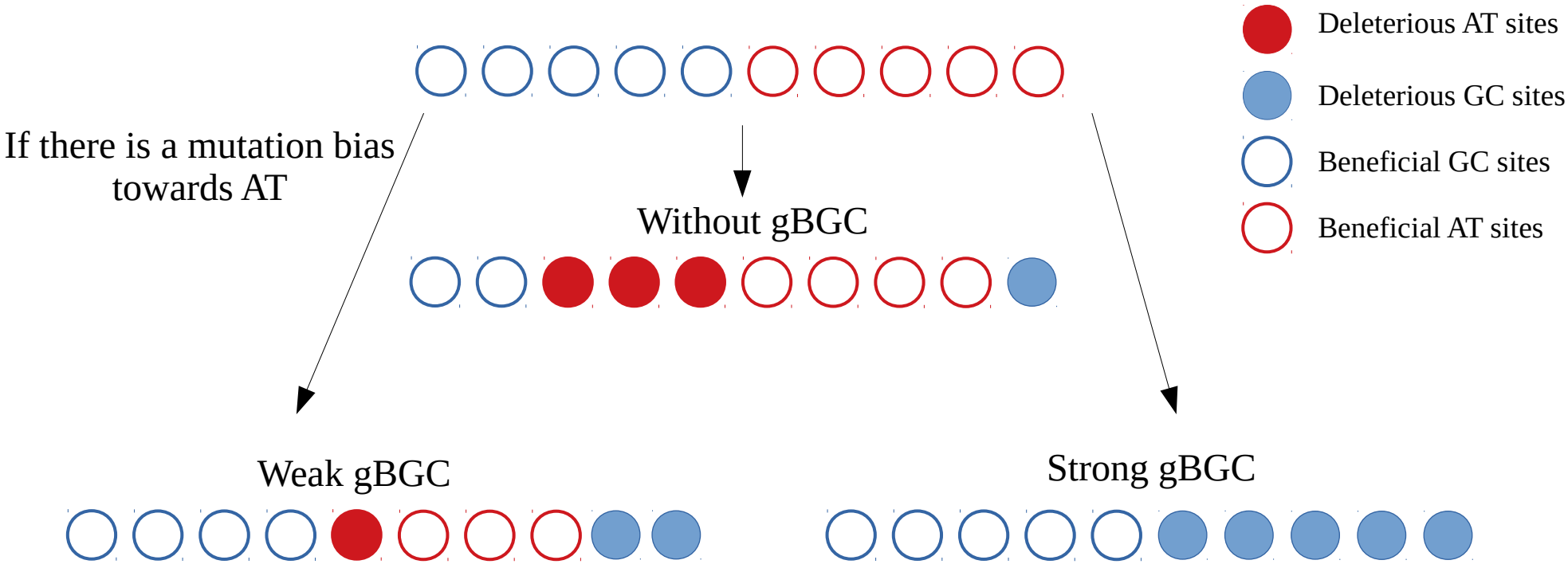


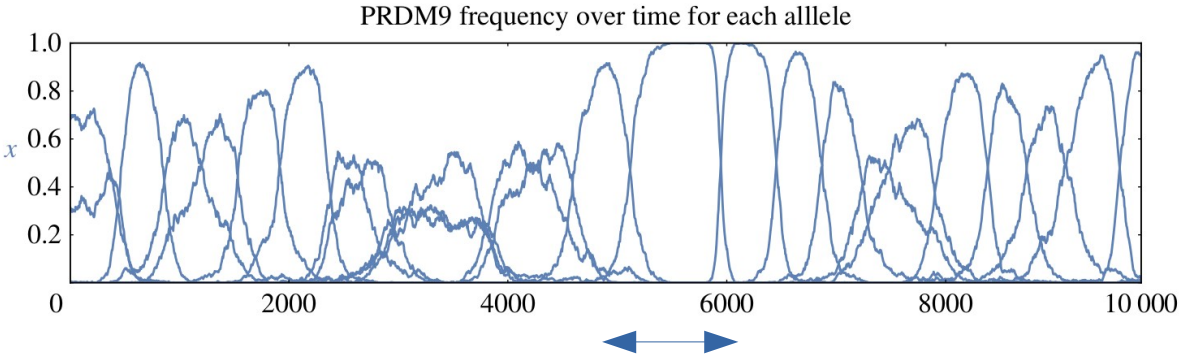
The impact of gBGC on the mutation load has been broadly studied theoretically in Nagylaki 1983, Glemin et al. 2003, Glemin 2010.

Problematic

All previous models assume a constant intensity of gBGC across time.

« I also assume that the gBGC intensity is constant. However, strong gBGC events are thought to be associated with short-lived recombination hotspots, at least in humans (McVean *et al.* 2004; Myers *et al.* 2005). I thus implicitly assume that gBGC/selection dynamics are shorter than the recombination hotspot lifespan. »

S. Glémin 2010



Latrille et al. 2017

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Can short-lived hotspot reduce the mutation load ?

Deterministic model under gBGC and selection

Let x_t be the frequency of a strong (GC) allele at time t.

- We consider deleterious mutations from weak (AT) to strong (GC), with selection coefficient s and dominance h.
- We consider that weak alleles are converted to strong allele in heterozygous due to gBGC with conversion rate b.

Genotype	**Homozygous SS**	**Heterozygous WS**	**Homozygous WW**
Frequency	x_t^2	$2x_t(1-x_t)$	$(1-x_t)^2$
Fitness	$1-s$	$1-hs$	1

Nagylaki (1983), Glémin (2010)

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The frequency of a strong allele at the next generation (x_{t+1}) is thus:

$$x_{t+1} = \frac{(1-s)x_t^2 + (1+b)(1-hs)x_t(1-x_t)}{\bar{\omega}}.$$

And the mean fitness ($\bar{\omega}$) is:

$$\begin{aligned}\bar{\omega} &= (1-s)x_t^2 + (1-hs)2x_t(1-x_t) + (1-x_t)^2, \\ &= 1 - sx_t^2 - 2hsx_t(1-x_t).\end{aligned}$$

- **What is the steady state of strong alleles? Fixed or purged away?**

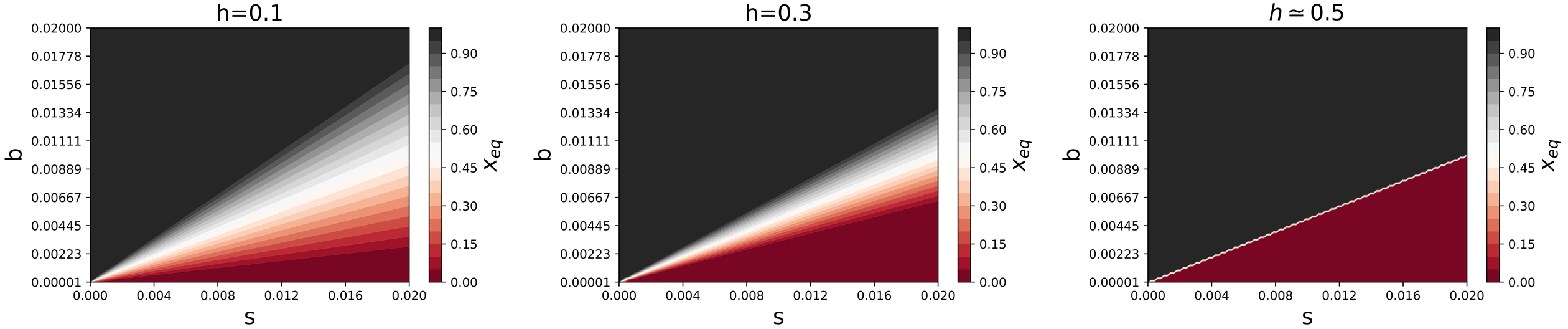
Nagylaki (1983), Glémin (2010)

Equilibrium for the deterministic model under gBGC and selection

At equilibrium, the frequency of a strong allele is:

$$x_{\text{eq}} = \frac{(1-s)x_{\text{eq}}^2 + (1+b)(1-hs)x_{\text{eq}}(1-x_{\text{eq}})}{1 - sx_{\text{eq}}^2 - 2hsx_{\text{eq}}(1-x_{\text{eq}})},$$

$$\Rightarrow x_{\text{eq}} = \frac{b-hs}{s-2hs} \text{ if } h < 1/2.$$



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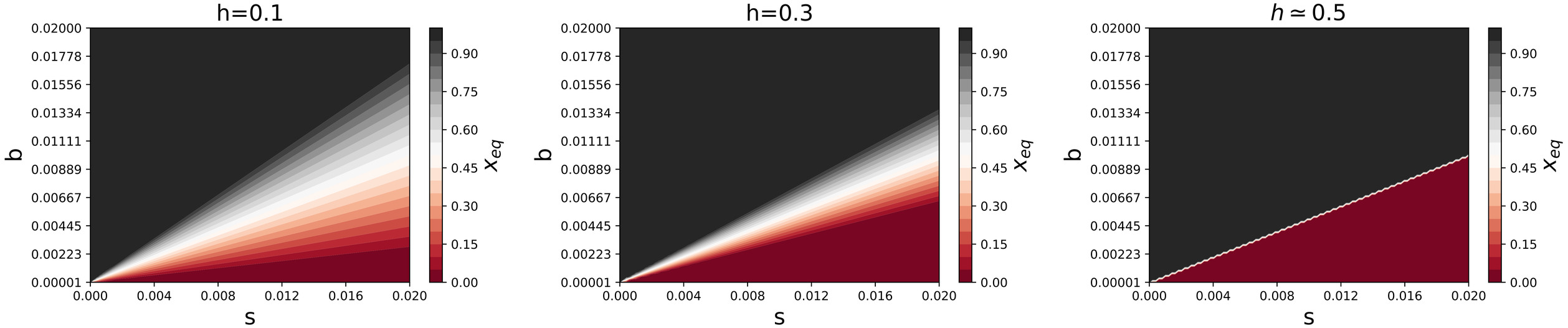


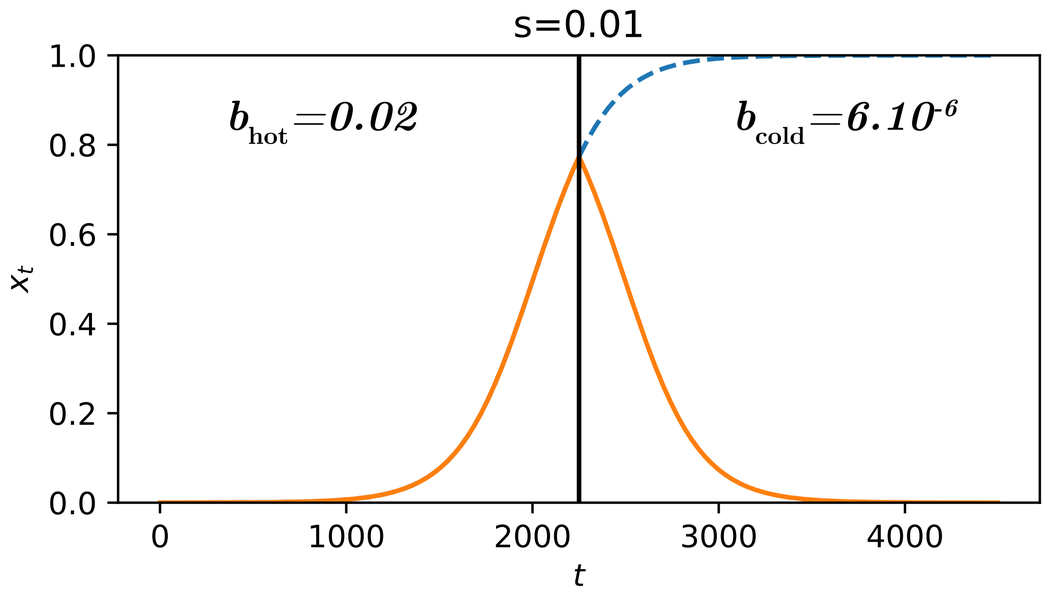
- **If b (gBGC) is strong compared to s (selection), deleterious mutations reach fixation.**
- **If b (gBGC) is weak compared to s (selection), deleterious mutations are purged away.**
- **If b and s are comparable, the mutation is maintained in the population.**
- **But what if b is not constant across time (from b_{hot} to b_{cold})?**

Glémin (2010)

Unstable hotspots in the deterministic model

The hotspots are unstable, with lifespan τ:

$$\begin{cases} t < \tau & \Rightarrow b = b_{\text{hot}} = 0.02, \\ t > \tau & \Rightarrow b = b_{\text{cold}} = 6 \times 10^{-6}. \end{cases}$$



- **Under constant gBGC, the GC allele should have reached fixation (blue line).**

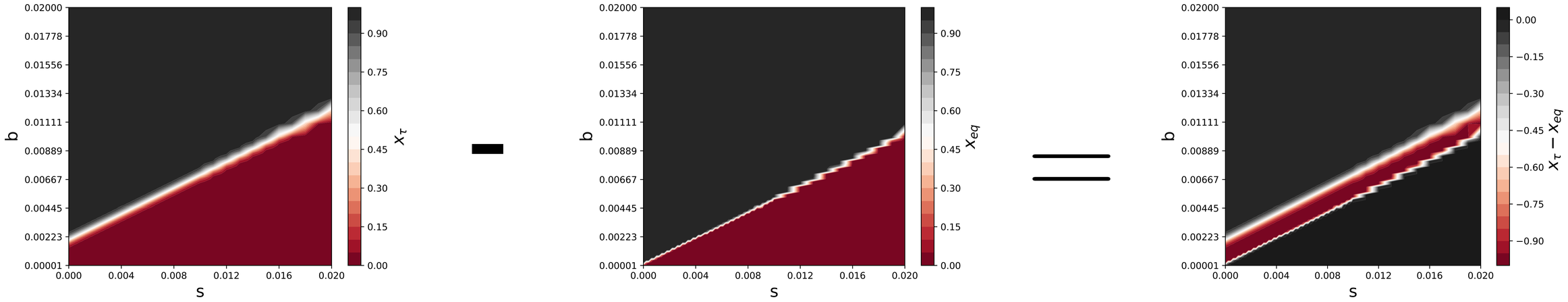
- **But at the end of the hotspot's life, selection overwhelms gBGC and the mutation is purged away (orange line).**

- **For which value of b_{hot}, s and τ does this kind of situation occur ?**

Unstable hotspots in the deterministic model

- x_τ is the frequency of the GC deleterious allele at the end of the hotspot lifespan.
- x_{eq} is the frequency that the allele should have reached if the hotspot were stable.
- The difference between x_{eq} and x_τ represents the benefit of having a short-lived hotspot.

$\tau = 0.5 N_e = 5000$
$h = 0.5$



- Having unstable hotspot is only beneficial for a narrow range of values for b_{hot} and s.

Unstable hotspots in the deterministic model

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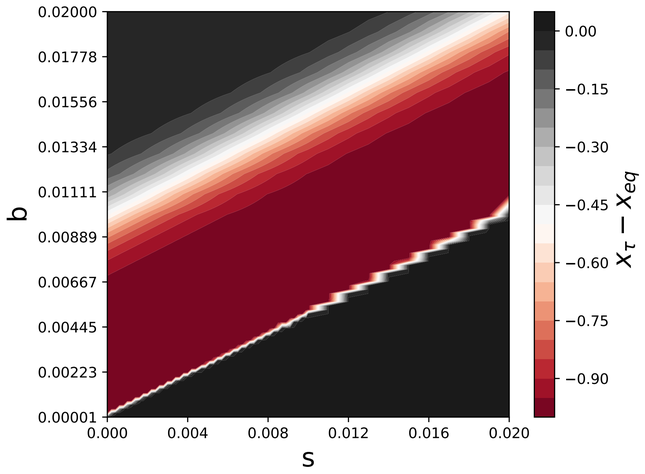
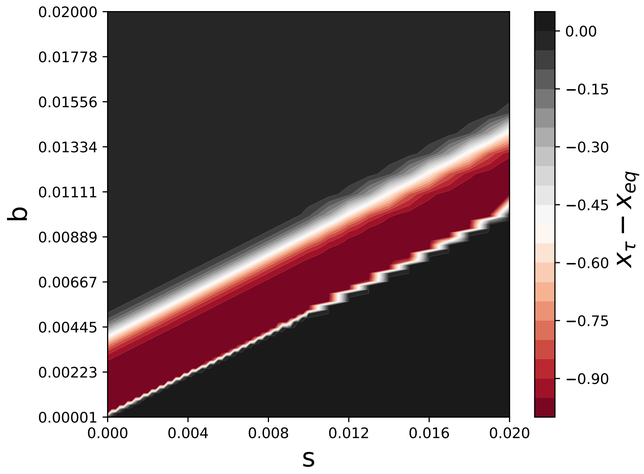
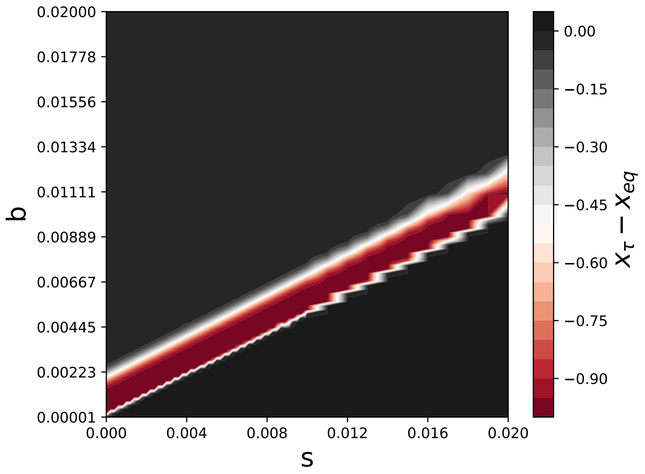


$\tau=0.1N_e=1000$



$\tau=0.25N_e=2500$



$\tau=0.5N_e=5000$

- **Shorter lifespan of hotspots leads to deleterious mutations more efficiently purified away.**
  - **Thus far, we assumed only gBGC and selection but no drift.**
    - **Under drift, is this result still holding?**

Stochastic model under gBGC and selection.

Under a stochastic model, the number of strong alleles is drawn from a binomial distribution:

$$x_{t+1} \sim \frac{1}{2N_{\mathrm{e}}}\mathcal{B}\left(2N_{\mathrm{e}}, p\right),$$

$$p = \frac{(1-s)x_t^2 + (1+b)(1-hs)x_t(1-x_t)}{\bar{\omega}}.$$

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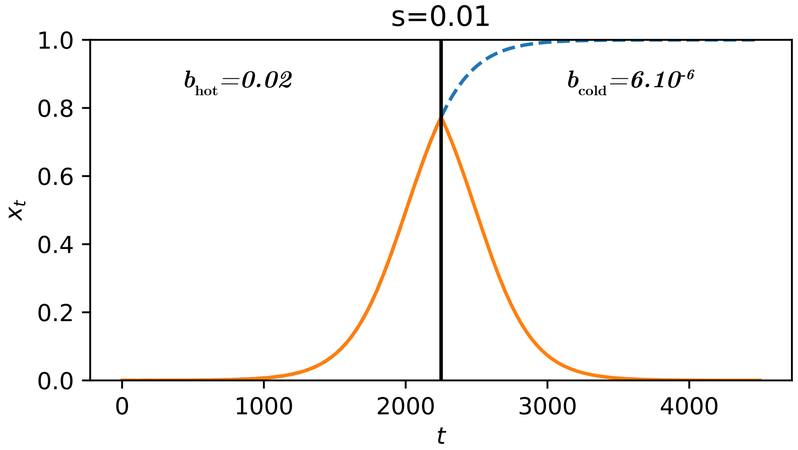
Deterministic



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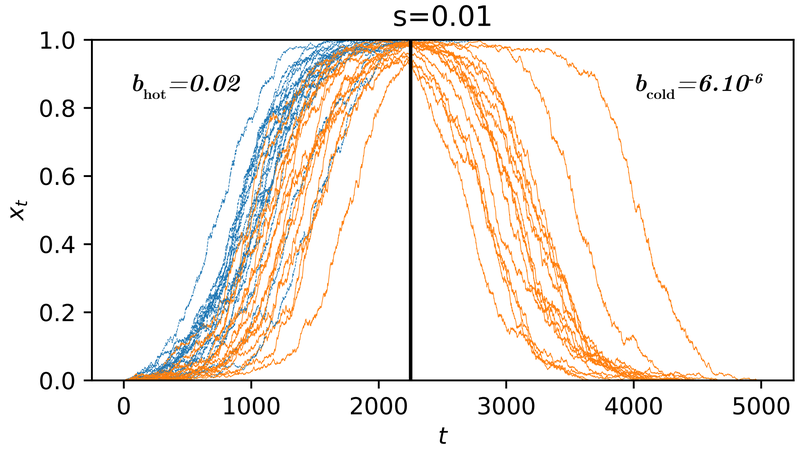

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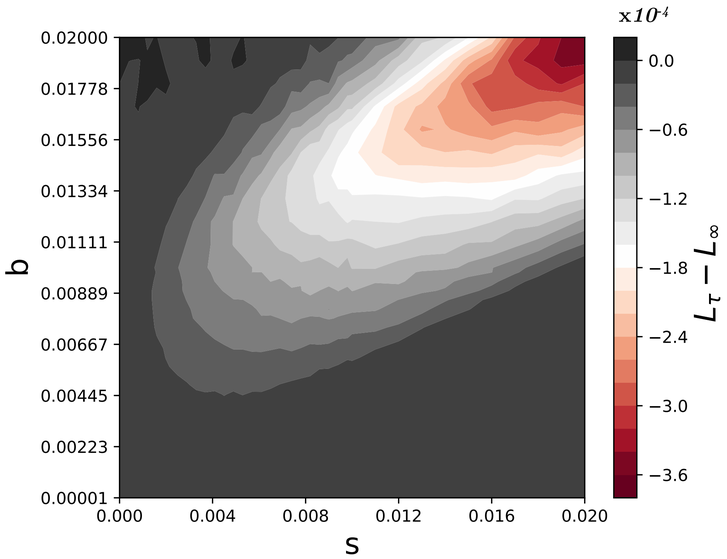
$$\begin{cases} L_\tau \text{ is the load for an unstable hotspot (lifespan } t = \tau), \\ L_\infty \text{ is the load for a constant hotspot.} \end{cases}$$

h=0.5



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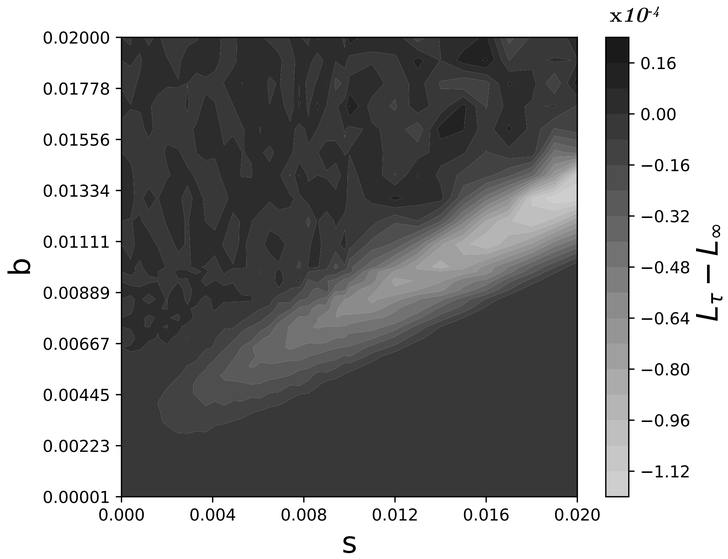

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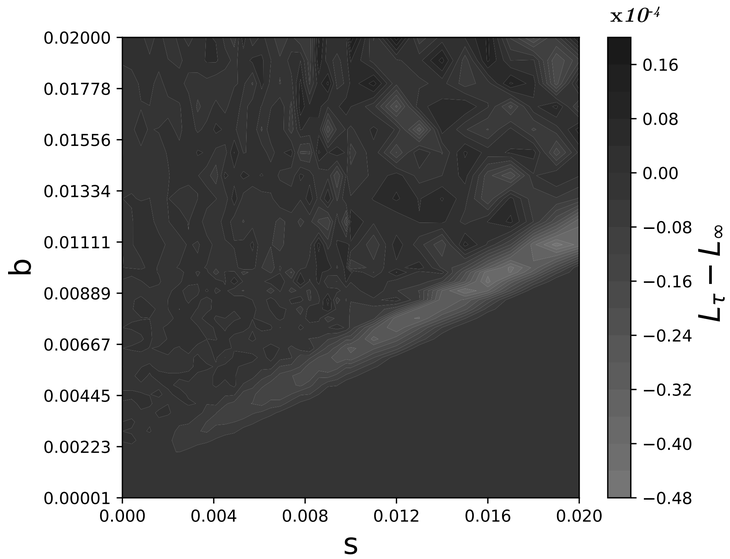

τ=0.5N_e=5000

- **If hotspots are lasting more than $0.5N_e$, we barely see any advantage of unstable hotspots.**

Biological relevance : PRDM9-dependent hotspots

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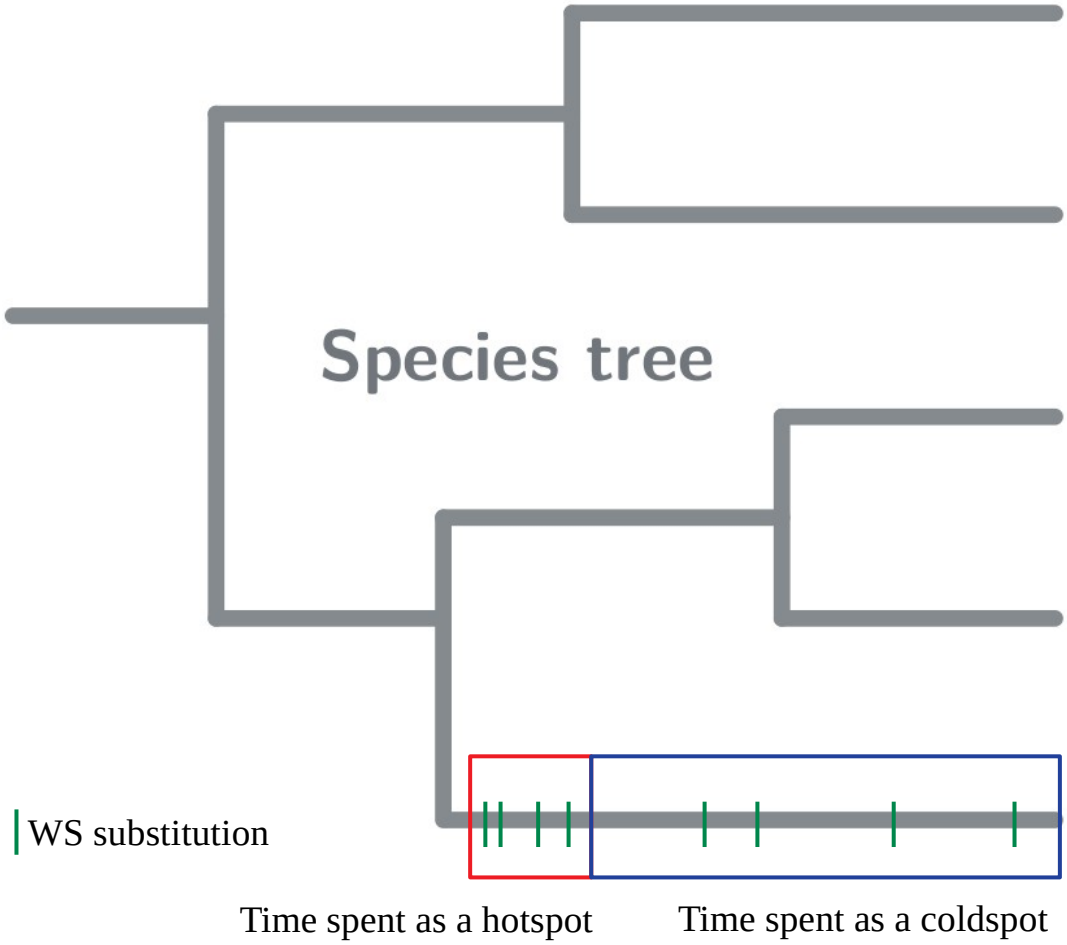
If those values are the same in humans, the gBGC/selection dynamic should not be affected that much by the hotspots lifespan.

Consequences on estimations of B=4Neb



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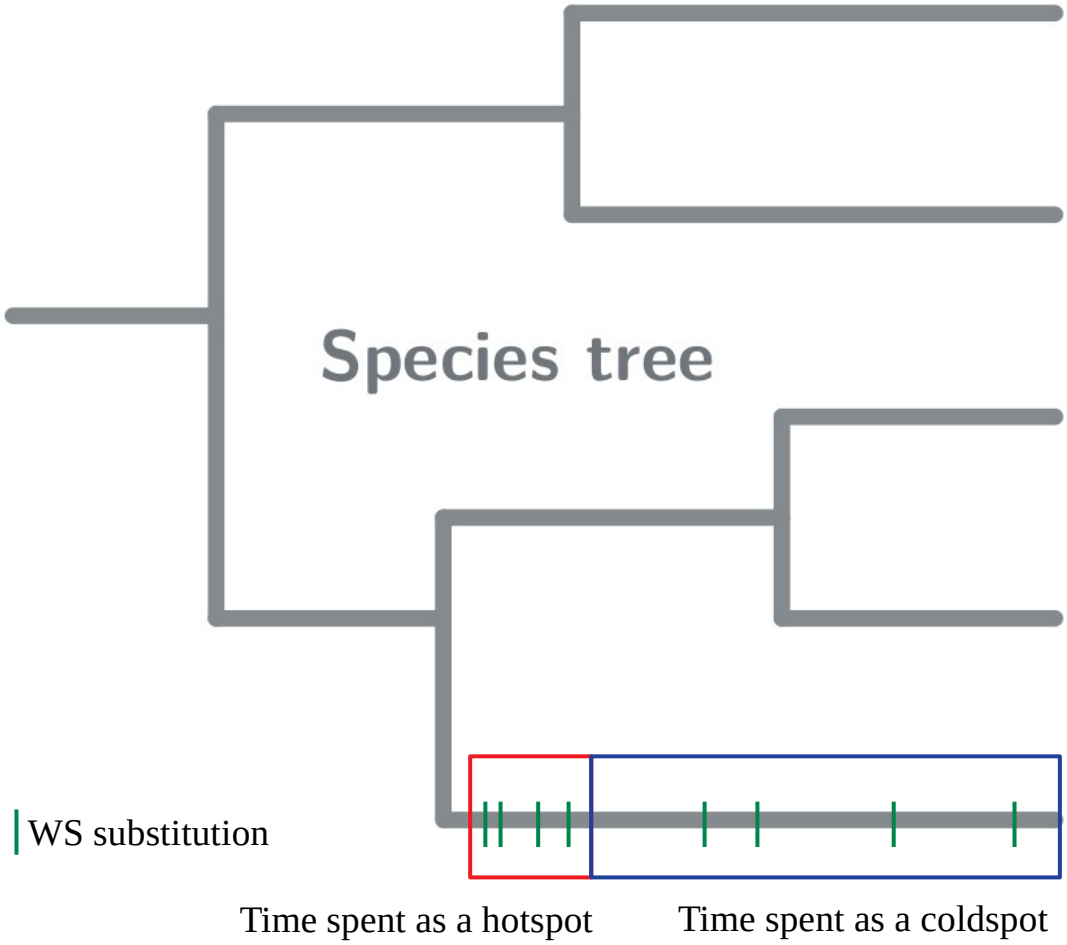

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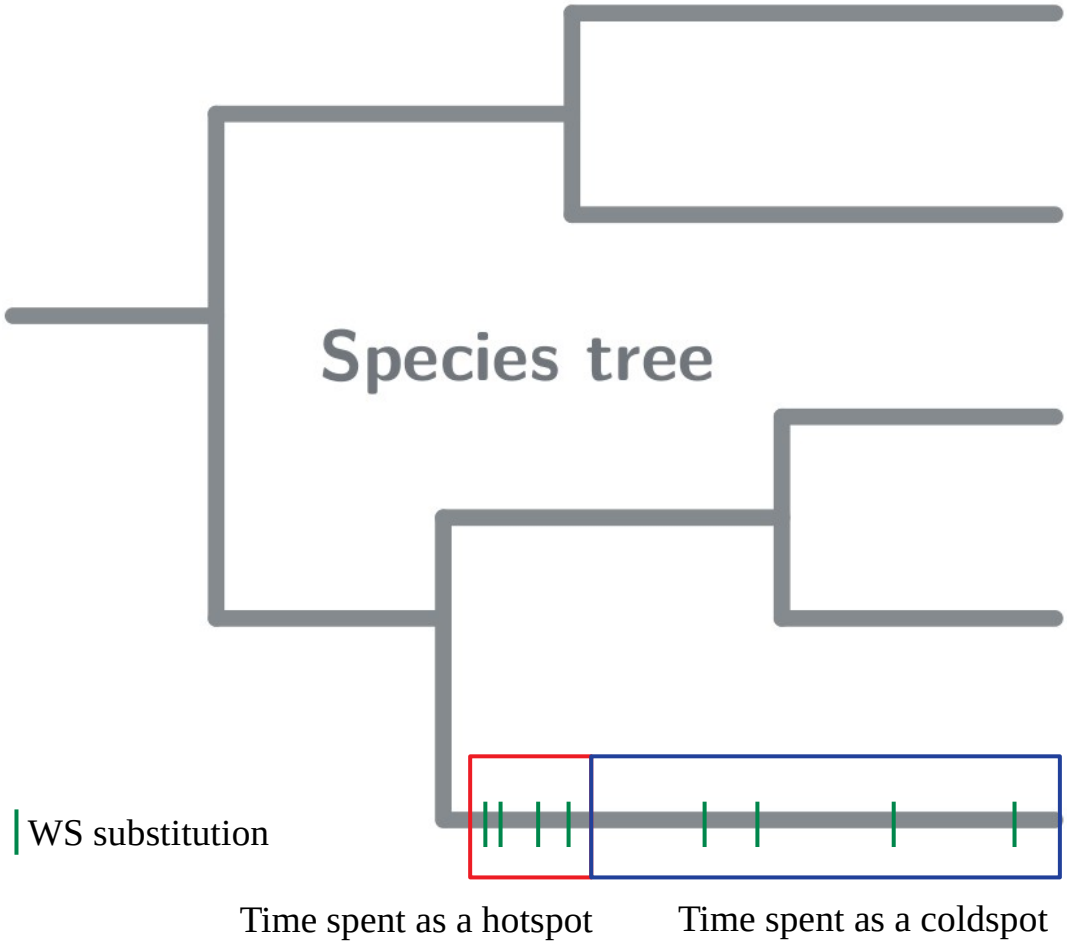

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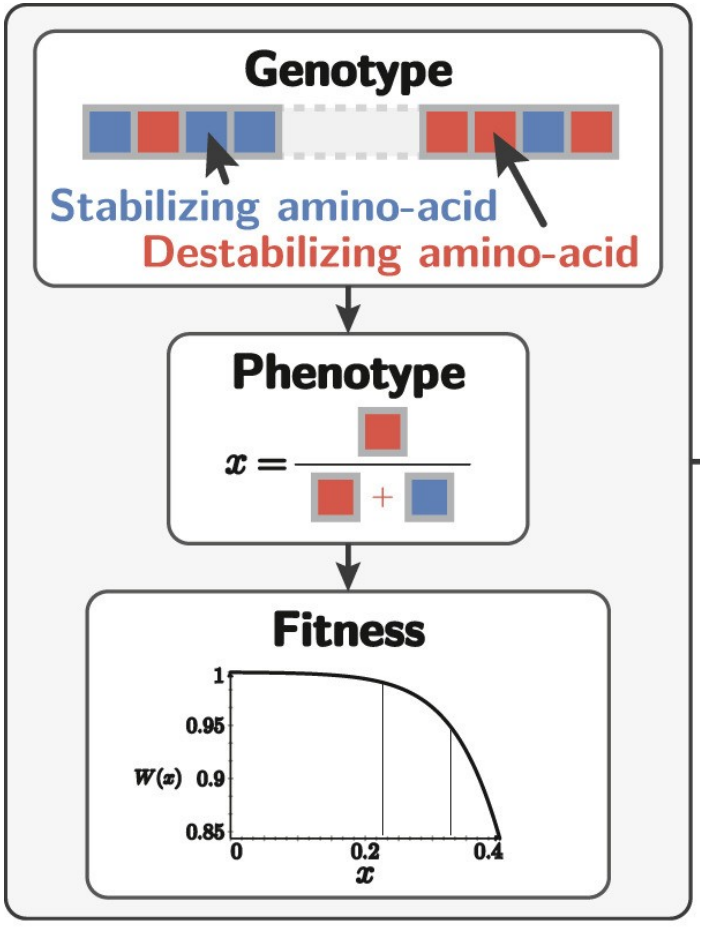
Our results suggest that the mean B integrated over time estimated from neutral substitutions is valid even for PRDM9-induced hotspots.

Accounting for fitness landscape and epistasis



Individual genotype to fitness

Latrille and Lartillot 2021

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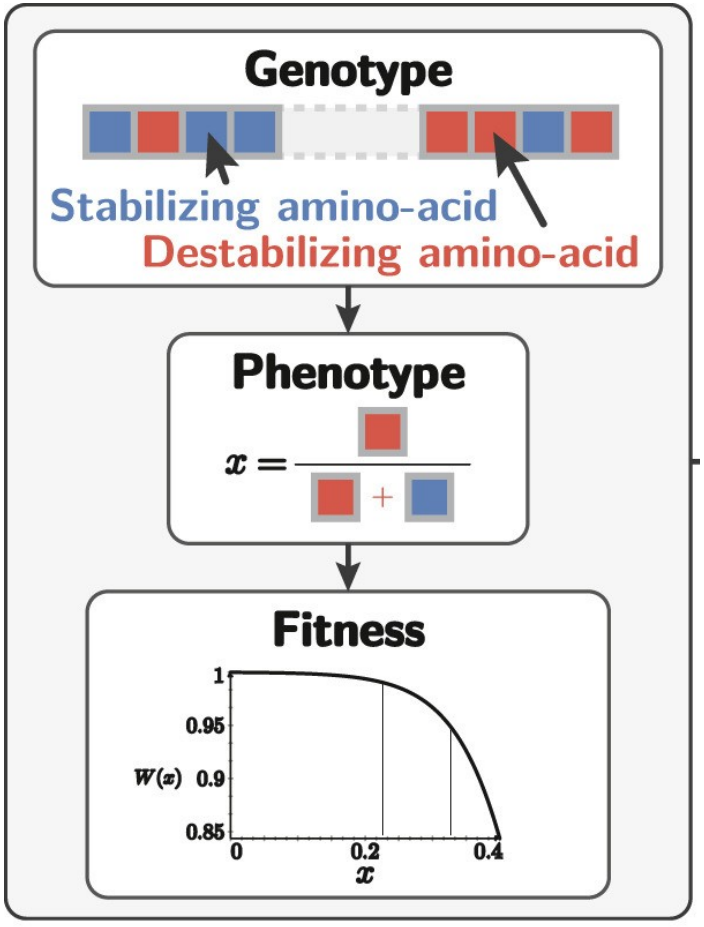

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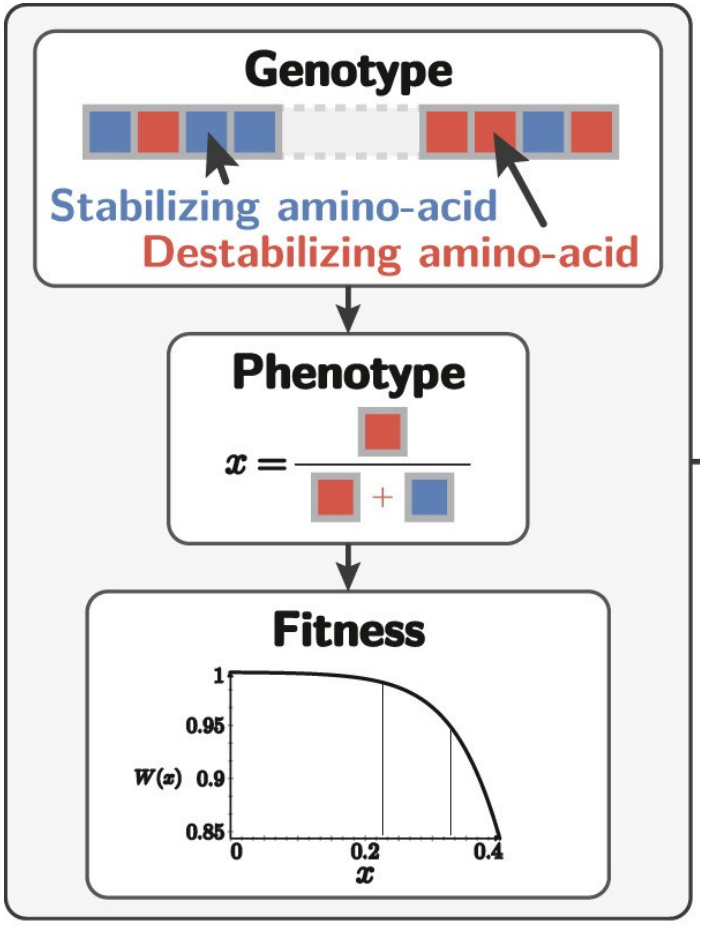

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Under this condition, having unstable hotspots can limit the deleterious effects of gBGC on fitness.

Thank you for your attention !

Questions ? Suggestions ?