

The Red-Queen model of recombination hotspots evolution

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S-51 Causes and consequences of recombination rate evolution

What is the equilibrium recombination rate determined by the Red-Queen model of recombination hotspots?

Recombination is concentrated in hotspots

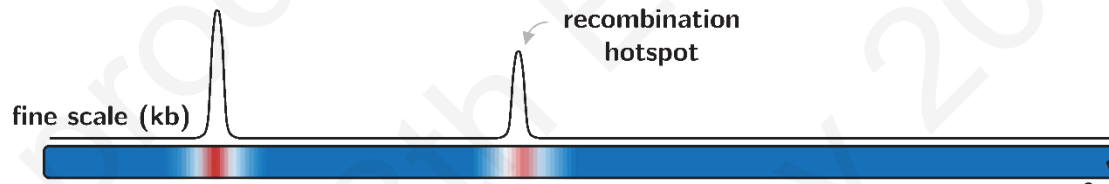
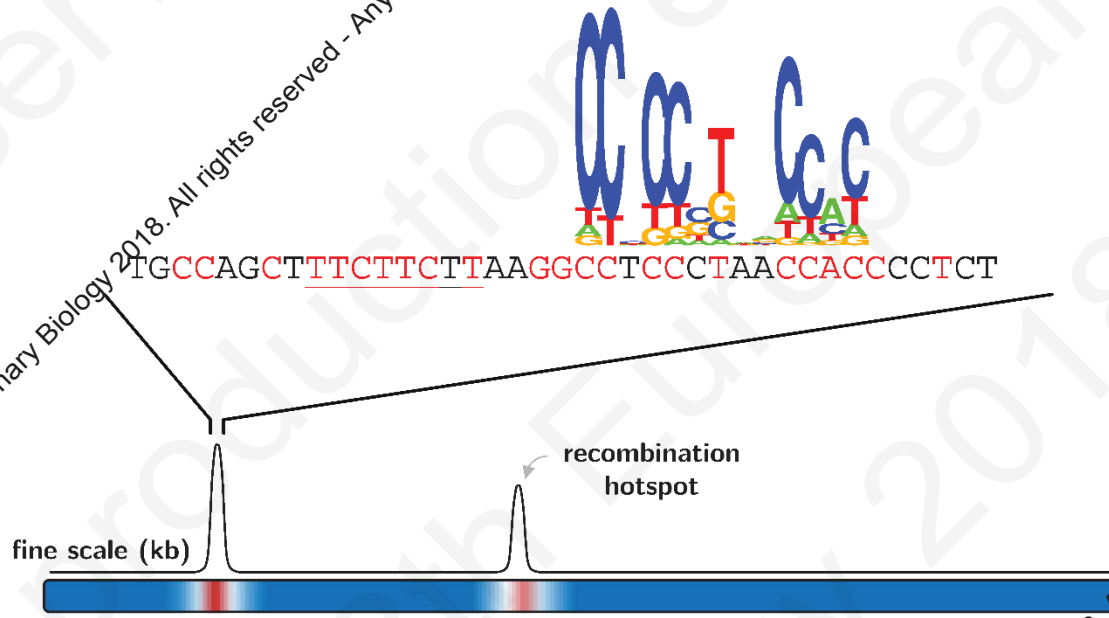


Figure adapted from Dapper (2017)

- Hotspots are short lived, not shared between human and chimpanzee.

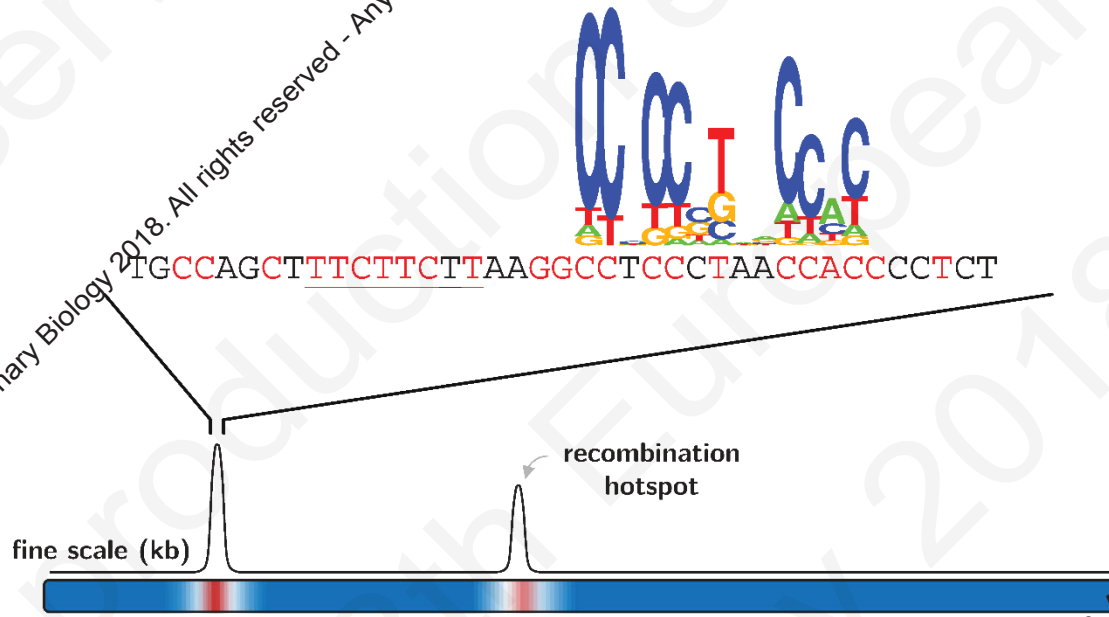
Recombination is concentrated in hotspots containing a specific motif



- Hotspots are short lived, not shared between human and chimpanzee.
- Human hotspots are enriched in a sequence motif.
- Human motif is not enriched in chimpanzee hotspots.
- Human motif has been depleted in the human lineage.

Wall *et al* (2003), Ptak *et al* (2004), Winckler *et al* (2005), Myers (2008)

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- Human hotspots are enriched in a sequence motif.
- Human motif is not enriched in chimpanzee hotspots.
- Human motif has been depleted in the human lineage.
- Why are chimpanzee & human hotspots not using the same motif?
- Why are human motifs depleted in the human lineage?

Wall *et al* (2003), Ptak *et al* (2004), Winckler *et al* (2005), Myers (2008)

PRDM9

- PRDM9 determines the location of hotspots, by binding to the motif and then recruiting the recombination machinery.

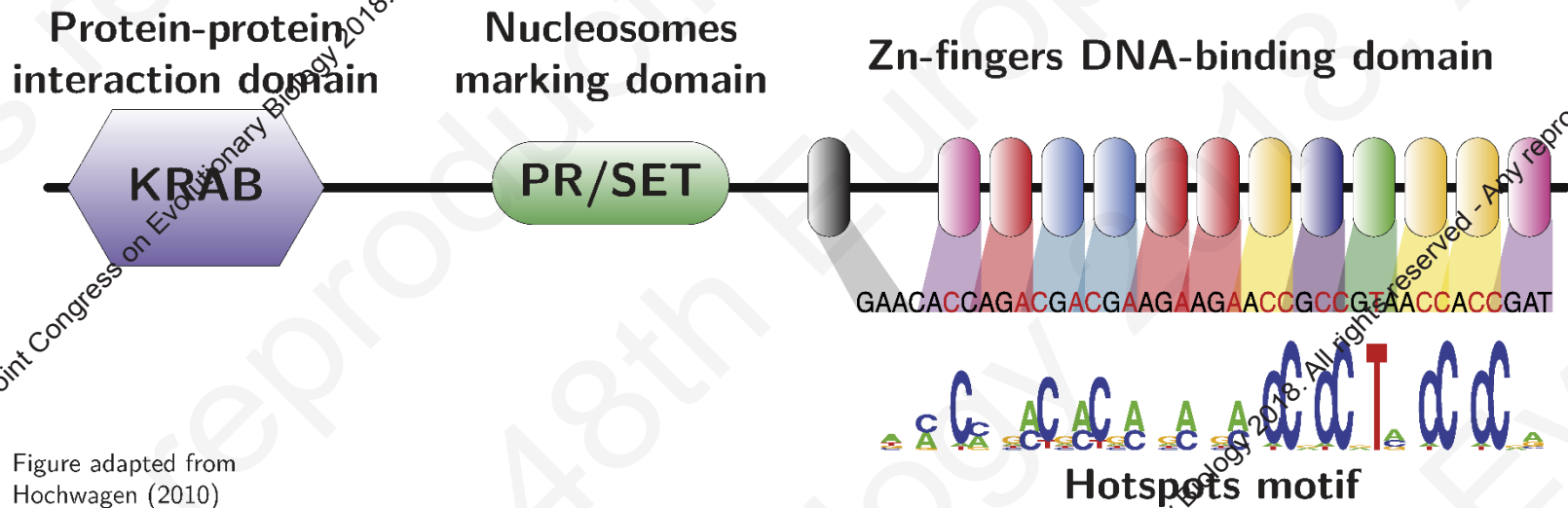


Figure adapted from Hochwagen (2010)

- PRDM9 is fast evolving protein, different in Chimpanzee, with both a high dN/dS and a high mutation rate.

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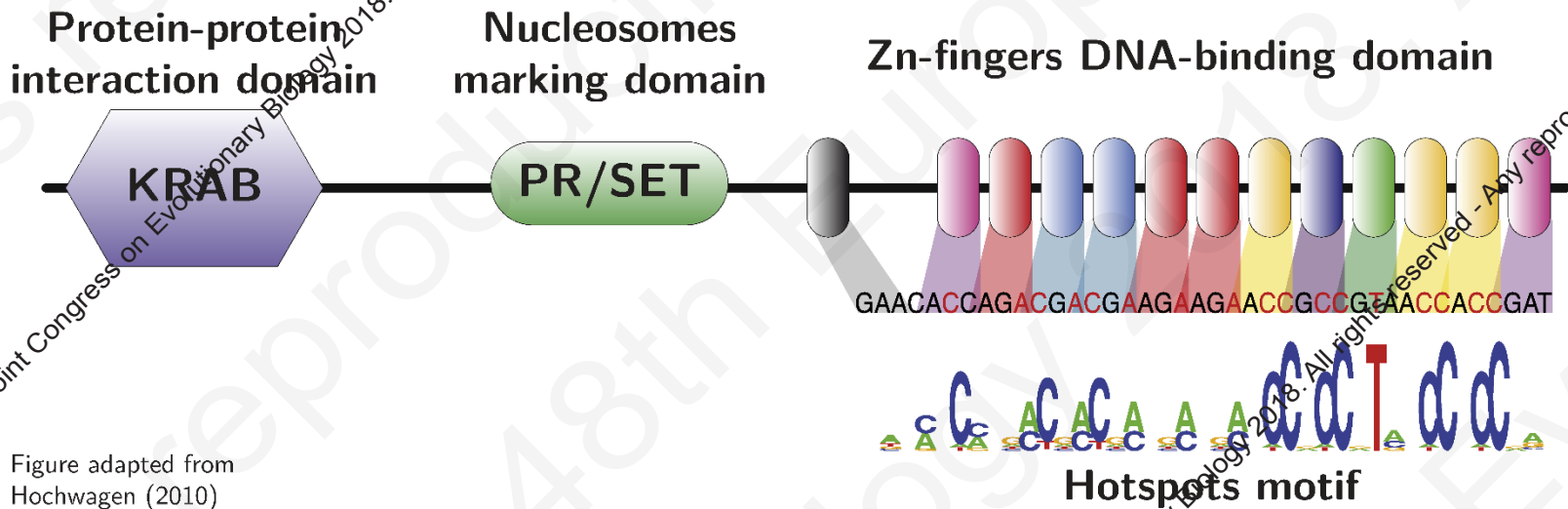
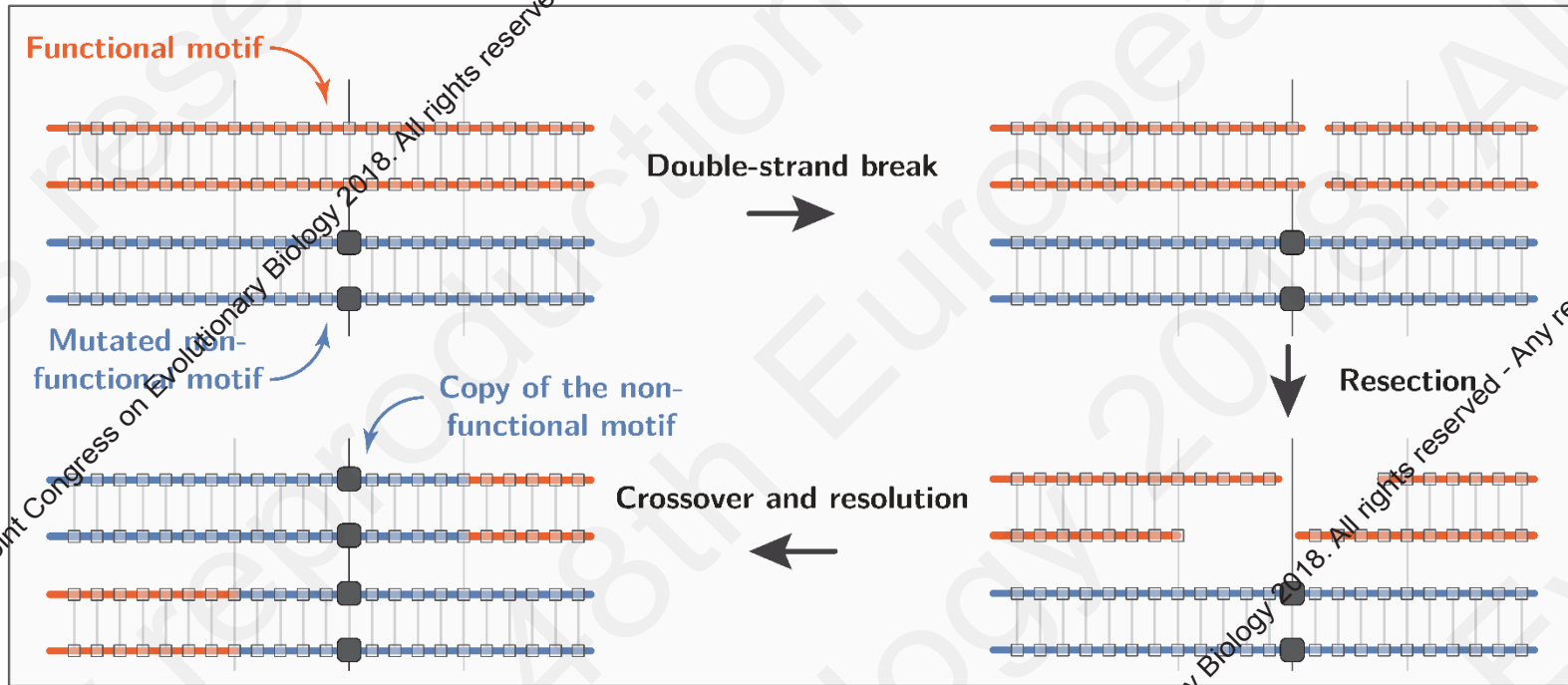


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- PRDM9 is fast evolving protein, different in Chimpanzee, with both a high dN/dS and a high mutation rate.
- Why are human motifs depleted in the human lineage?

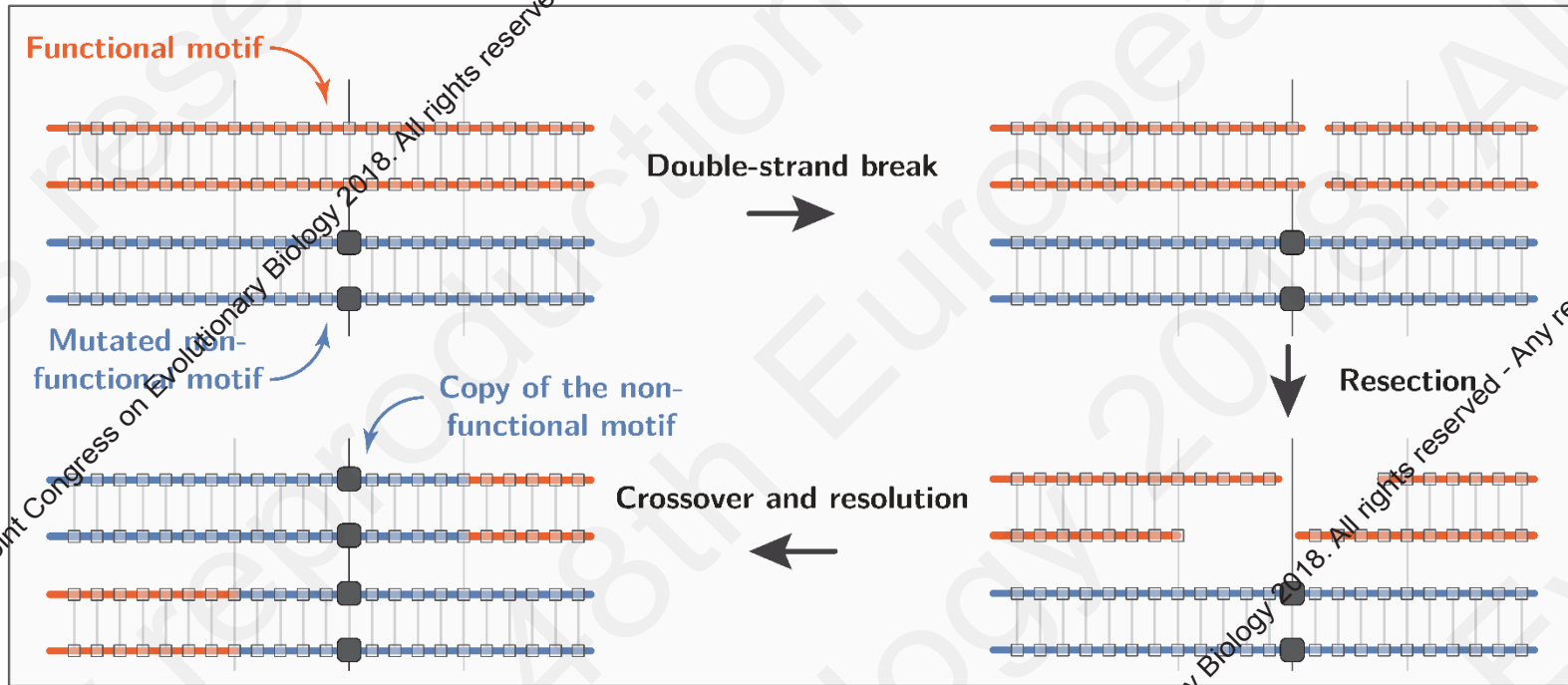
Motifs at the hotspots are architects of their own destruction



- Biased Gene Conversion favors a mutated motif over a functional motif.
- Mutations disrupting the motif are "selected for".
- Motifs (and thus hotspots) are not conserved.

Boulton et al (1997), Pineda-Krch and Redfield (2005), Coop & Myers (2007)

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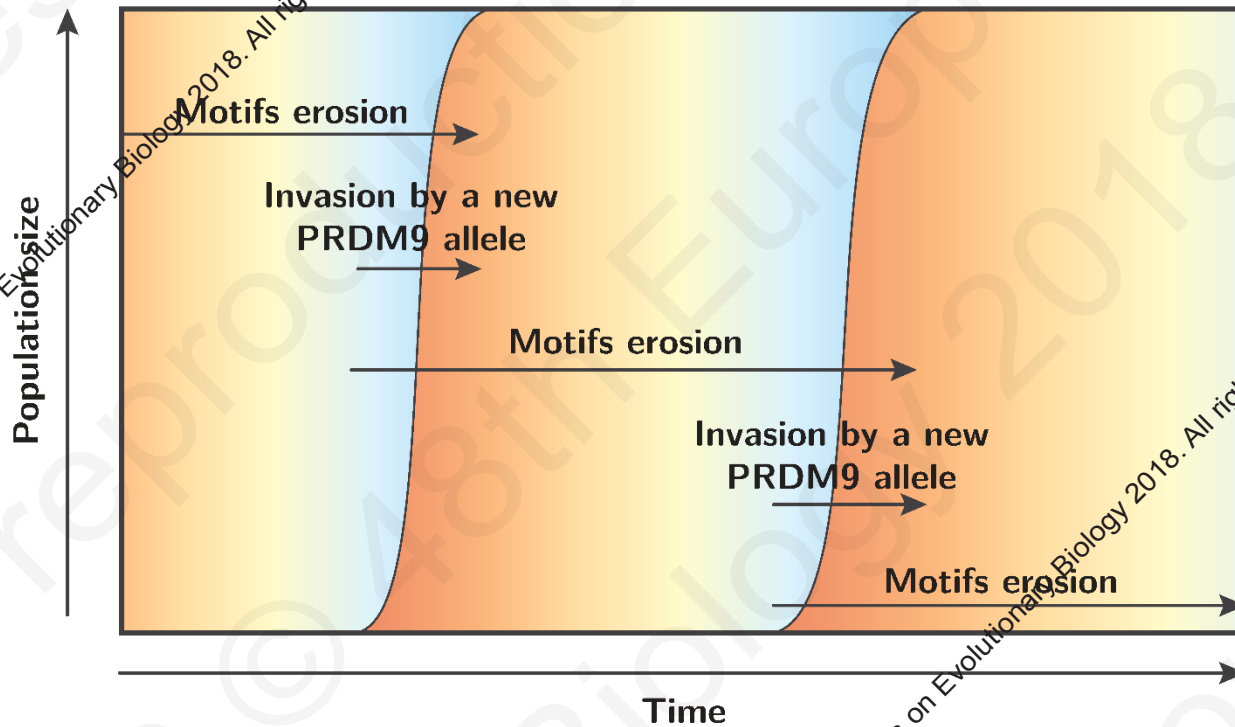


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- Whom is running after whom?

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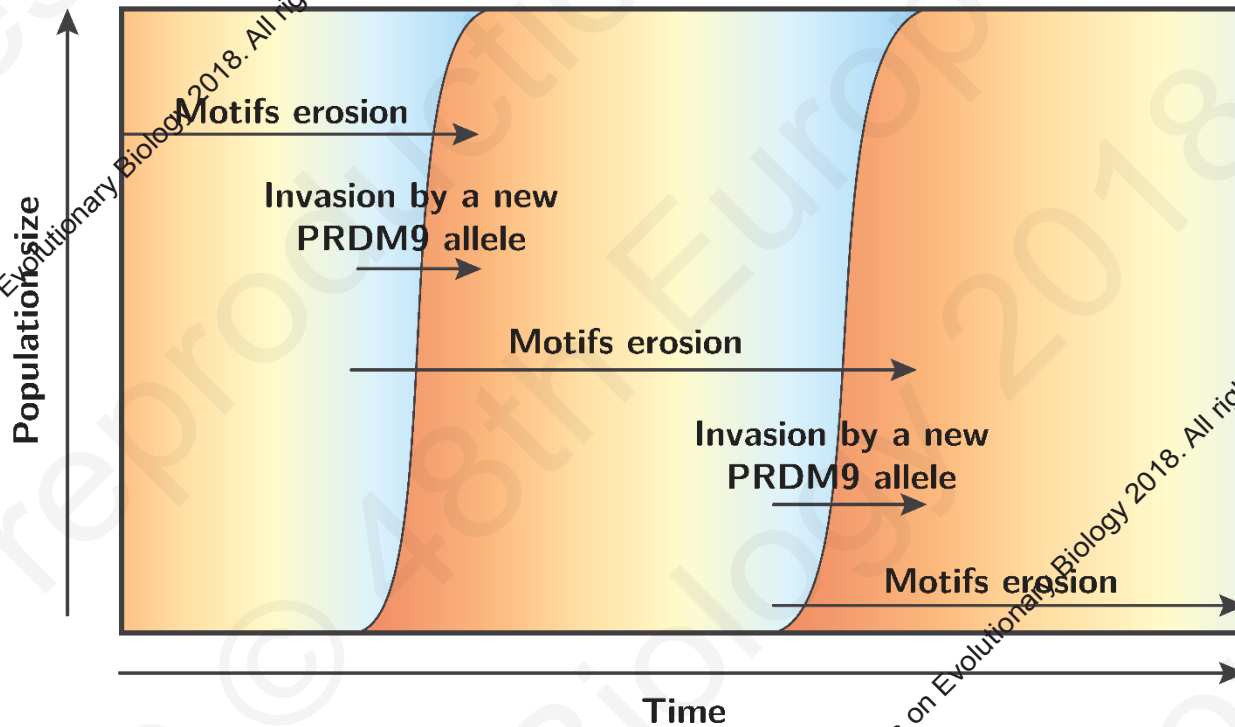
Erosion-invasion cycle

- Biased Gene Conversion (BGC) erodes the motifs targeted by PRDM9.
- Once motifs are depleted, invasion of a new mutant of PRDM9 restores hotspots by targeting 'virgin' motifs.



Erosion-invasion cycle

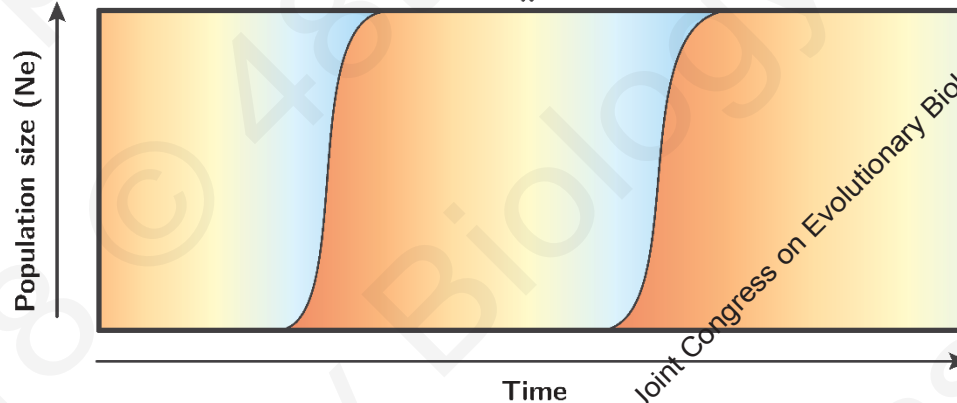
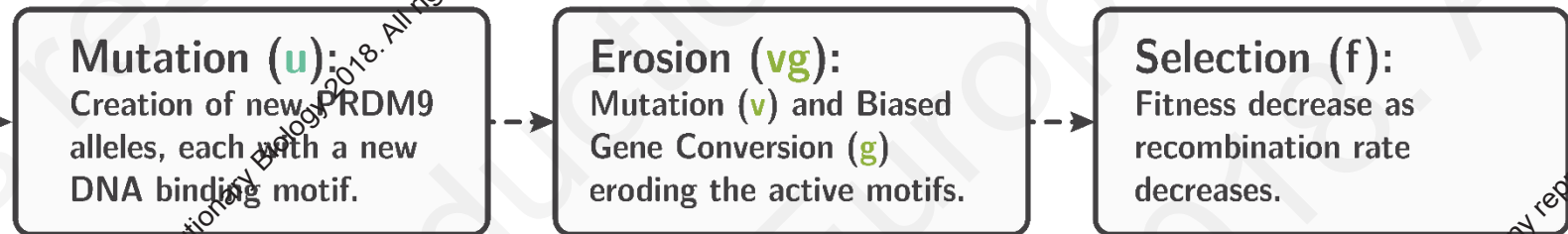
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- On which condition is the PRDM9 locus polymorphic?
- What is the equilibrium recombination rate?

Population genetic modeling

Wright-Fisher simulation with non-overlapping generations



Is the PRDM9 locus polymorphic?

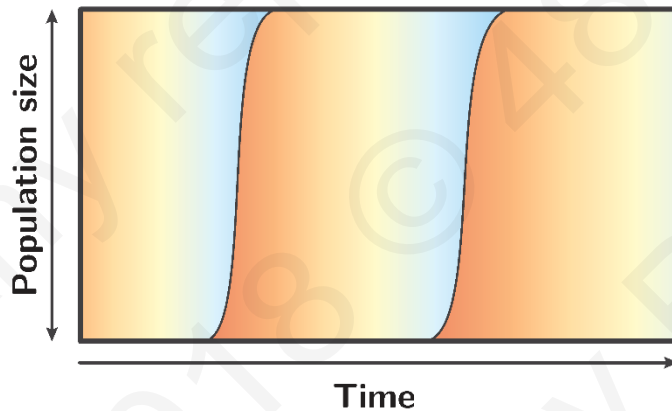
$$N_e, u, v, g, f$$

$$N_e u$$

The expected number of new PRDM9 alleles in the population at each generation.

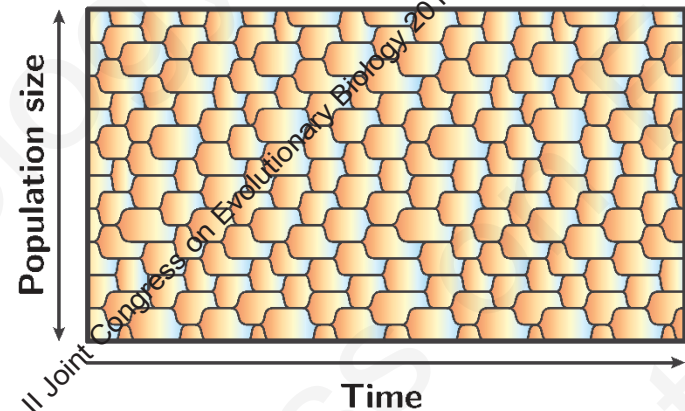
$$N_e u \ll 1$$

Succession of PRDM9 alleles

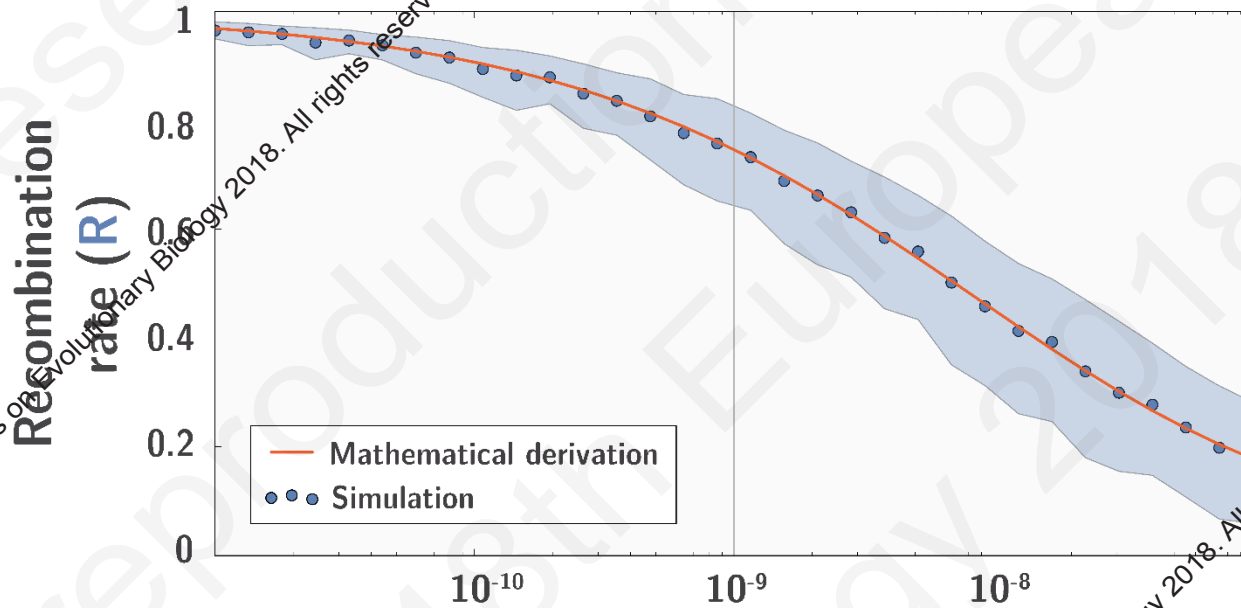


$$N_e u \gg 1$$

Polymorphism of PRDM9 alleles



What is the equilibrium recombination rate?



Erosion rate of motifs (vg)

Increase erosion rate

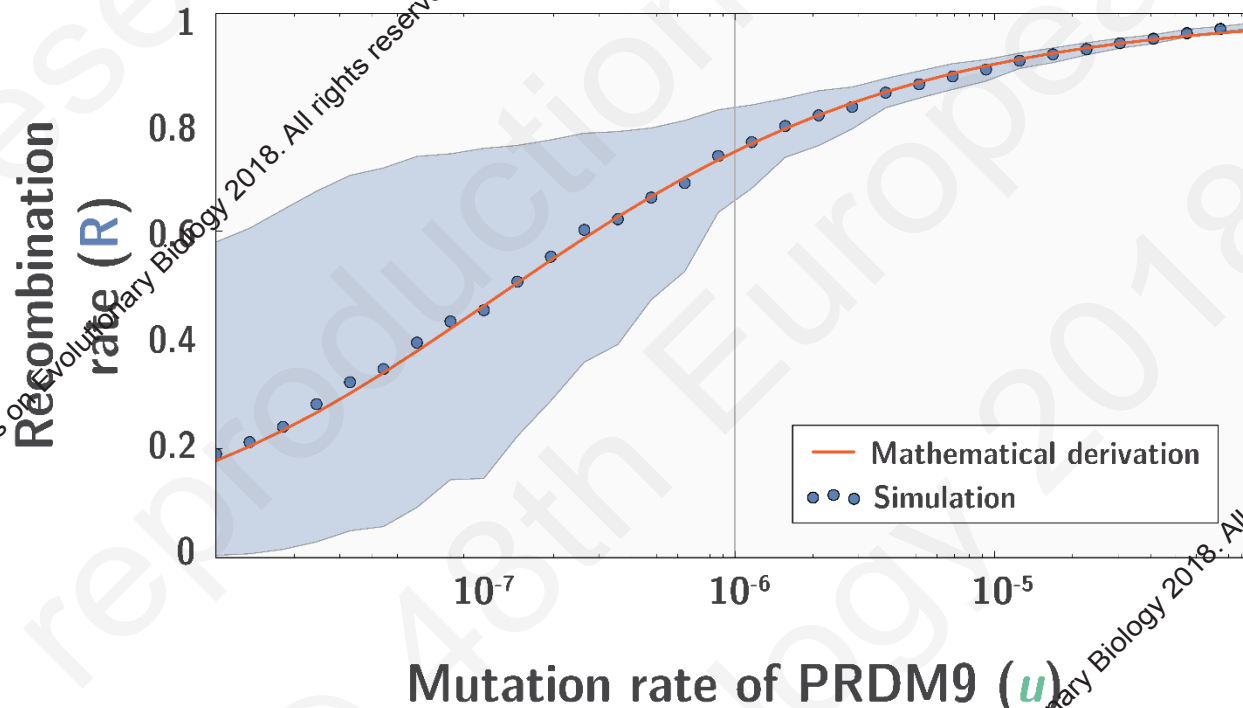


Increase erosion of motifs



Decrease recombination rate

What is the equilibrium recombination rate?



Mutation rate of PRDM9 (u)

Increase mutation rate of PRDM9



Increase invasion rate of PRDM9 alleles and recruitment of 'virgin' motifs



Increase recombination rate

Equilibrium recombination rate in equations

In succession regime assuming the invasion time of a PRDM9 allele is short compared to the lifespan of this allele:

$$R = g \left(\frac{vg}{u} \right) \approx 1 - \sqrt{\frac{vg}{u}}$$

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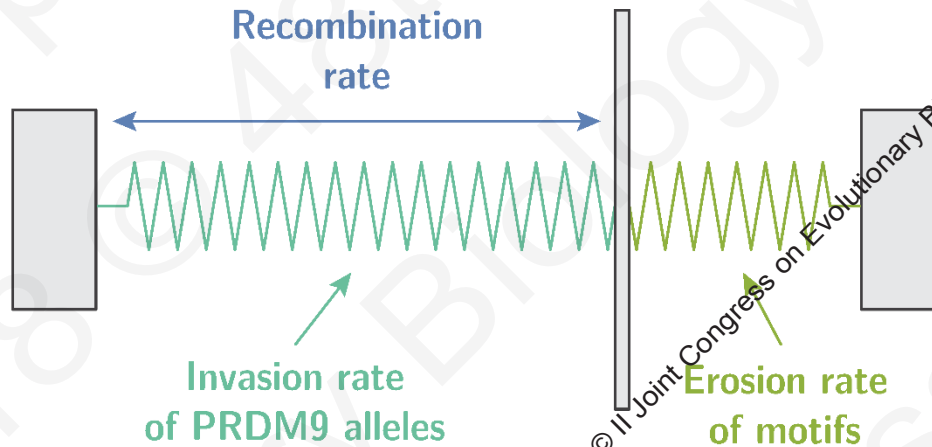
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Conclusions

- Mutation, not selection explains the PRDM9 diversity
- Balance between invasion rate of PRDM9 alleles and erosion rate of motifs determines the equilibrium recombination rate.
- Prediction of the model can be tested in multiple species.
- Calibration in mouse suggests a high mutation rate of PRDM9 ($\sim 3e^{-6}$) and a strong selection coefficient of BGC ($\sim 3e^{-3}$).

Conclusions & Perspectives

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- Balance between **invasion rate of PRDM9 alleles** and **erosion rate of motifs** determines the equilibrium recombination rate.
- Prediction of the model can be tested in multiple species.
- Calibration in mouse suggests a high mutation rate of PRDM9 ($\sim 3e^{-6}$) and a strong selection coefficient of BGC ($\sim 3e^{-3}$).
- Why is PRDM9 mutation rate so high in the first place?
- Is our model compatible with hybrid sterility due to hotspots asymmetry in a meta-population context?

Acknowledgments

- Organizers of the symposium, of the conference.
- The LBBE lab (in Lyon).
- Funding agencies (ANR)
- You for your attention

