The red queen in the kingdom of recombination

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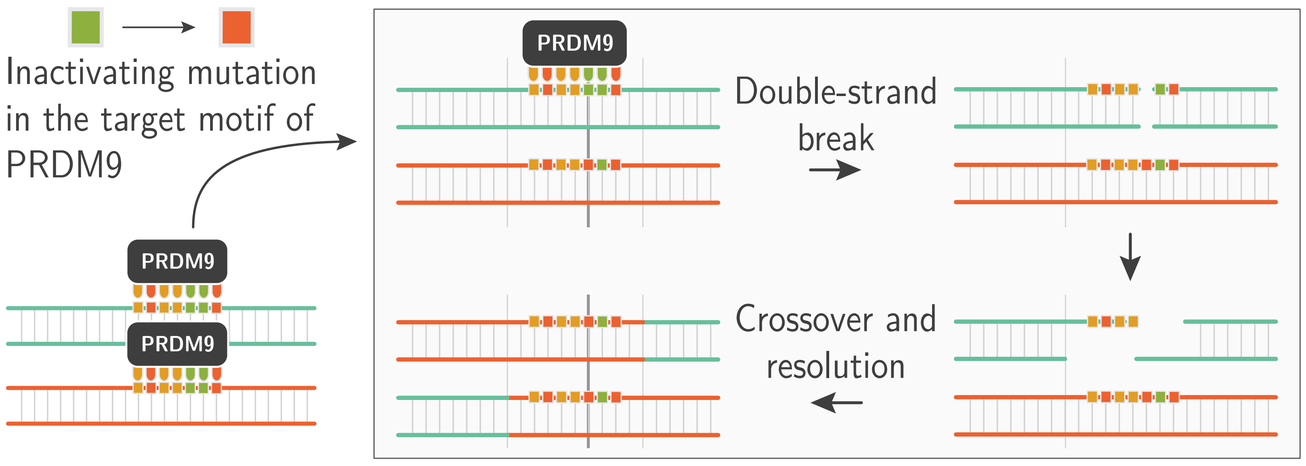
In humans and many other species, recombination events cluster in narrow hotspots distributed across the genome, whose location is determined by the Zing-finger protein PRDM9. Surprisingly, hotspots are not shared between human and chimpanzee, suggesting that hotspots are short-lived. To explain this fast evolutionary dynamics of recombination landscapes, an intra-genomic Red-Queen model, based on the interplay between two antagonistic forces, has been proposed. On the one hand, biased gene conversion, mediated by double-strand breaks, results in a rapid extinction of hotspots in the population. On the other hand, the resulting genome-wide depletion of recombination induces strong positive selection favoring new Prdm9 alleles recognizing new sequence motifs across the genome, thereby restoring normal levels of recombination. Thus far, however, this Red-Queen scenario has not been formalized as a quantitative model.

Here, we propose a detailed population-genetic model of the Red-Queen dynamic of recombination. This model was implemented as a Wright-Fisher simulator, allowing exploration of the behavior of the model (in terms of the implied mean equilibrium recombination rate, diversity at the PRDM9 locus, or turnover rate) as a function of the parameters (effective population size, mutation rate). In a second step, analytical results, based on self-consistent mean-field approximations, were derived. These analytical results reproduce the scaling relations observed in the simulations, offering key insights about the detailed population-genetic mechanisms of the Red-Queen model. These insights and scaling relations can now be tested against empirical data currently available in mammals.

1. Qualitative model

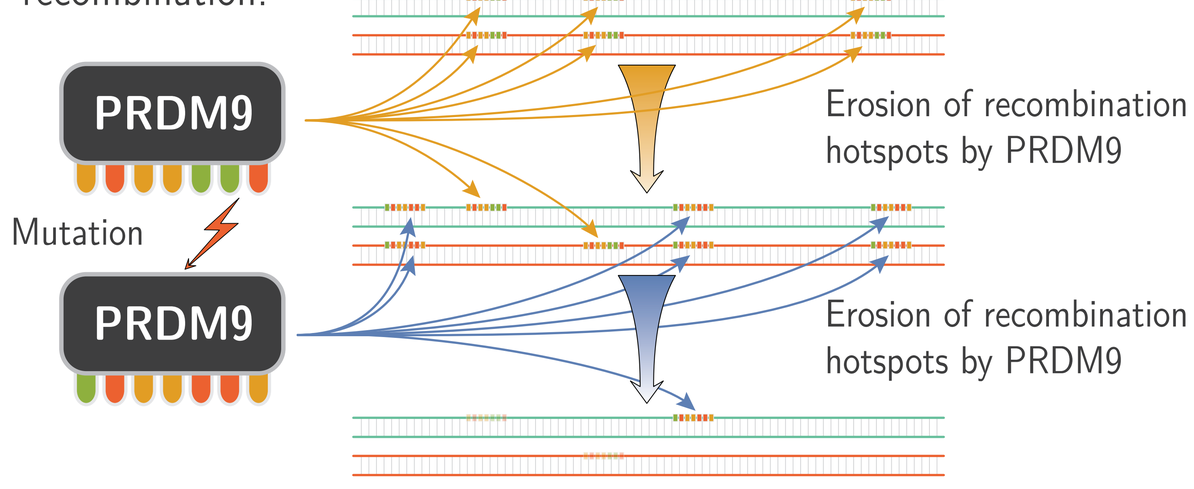
Hotspots location is determined by sequence motifs targeted by PRDM9.
PRDM9 binding triggers a double strand break event, intiating recombination.

Molecular mechanism of recombination results in biased gene conversion in favour of inactive mutant motifs. Leading to extinction of hotspots genome wide at the population level.



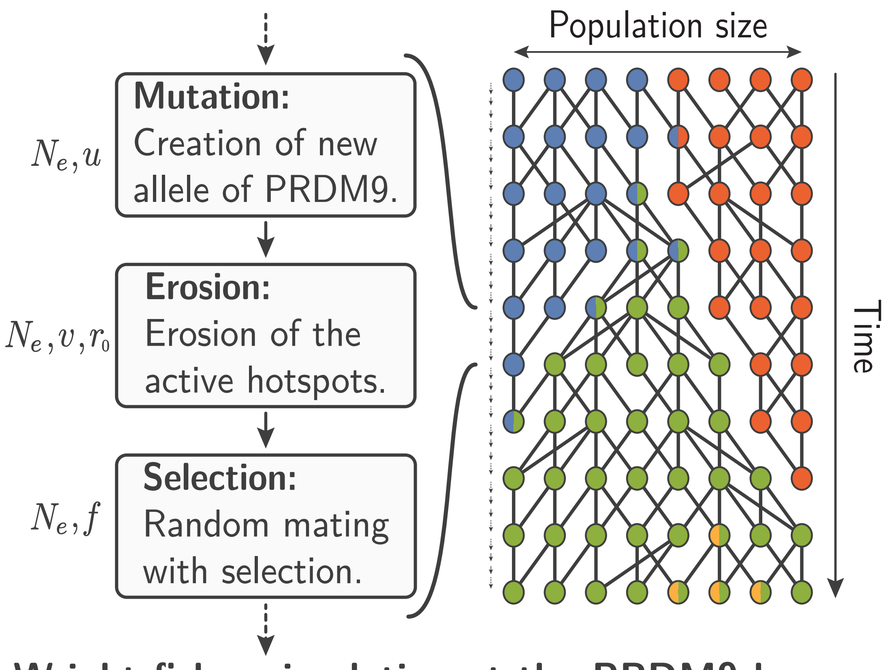
Extintion of hotspots by biased gene conversion

Depleted recombination induces positive selection on new PRDM9 alleles recognizing new sequence motifs. Thus restoring genome wide recombination.



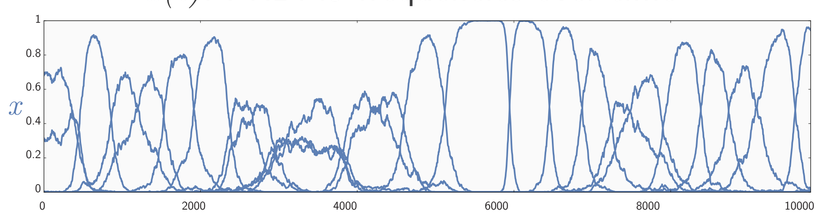
Positive selection on PRDM9

2. Simulation model

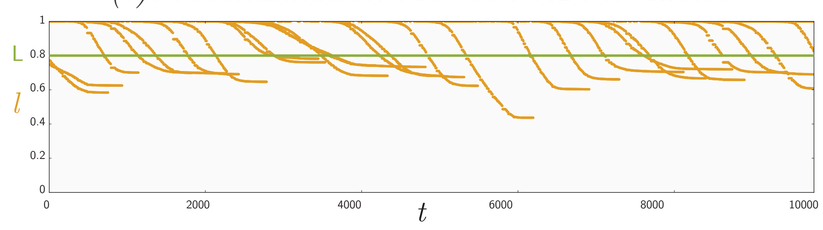


Wright-fisher simulation at the PRDM9 locus

$x(t)$: PRDM9 frequencies over time



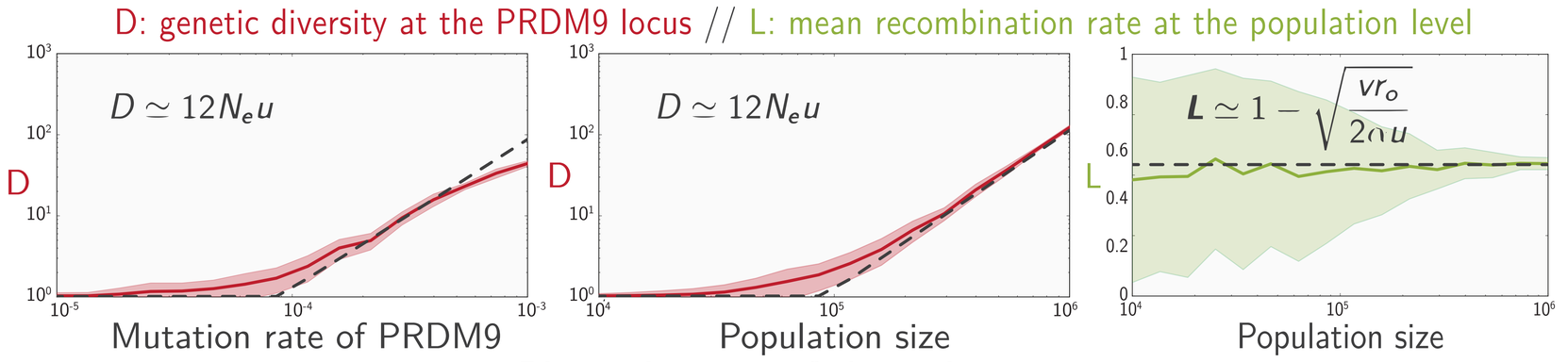
$l(t)$: recombination rate of PRDM9 alleles



Trajectory of simulations

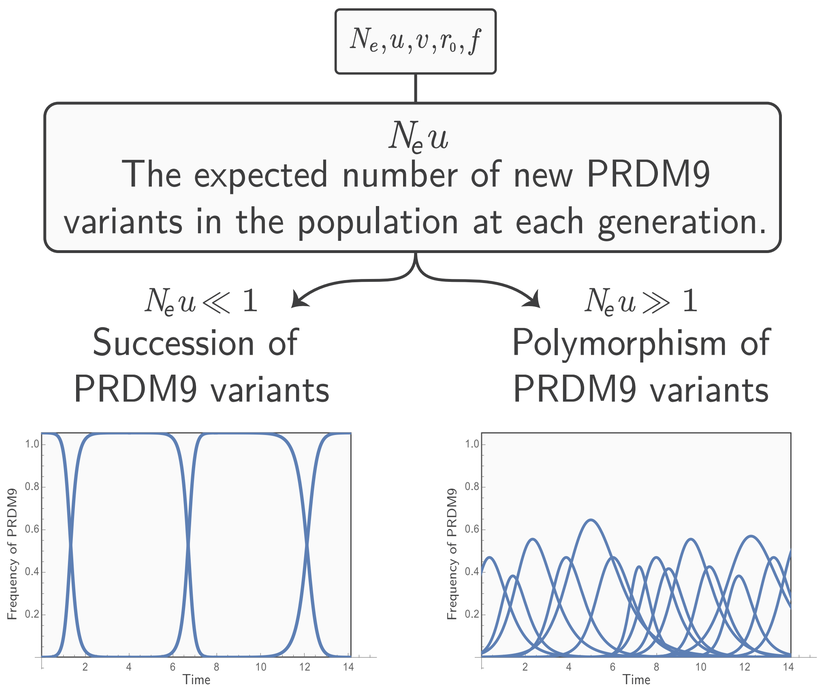
Equilibrium values of D and L are plotted against parameters of the model.

D: genetic diversity at the PRDM9 locus // L: mean recombination rate at the population level



Phase diagram of the red queen

3. Analytical approximation

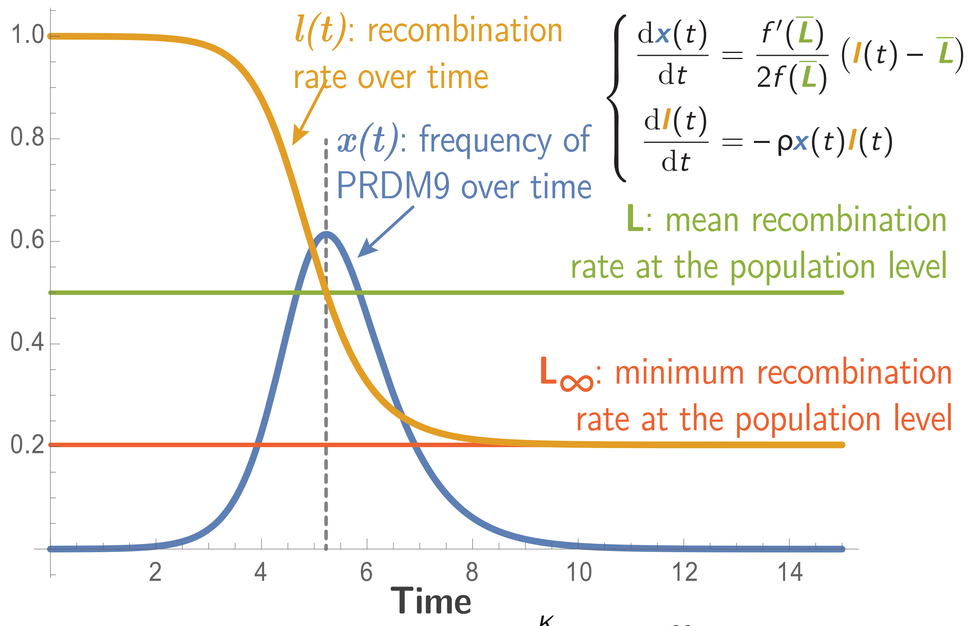


Transition between two regimes

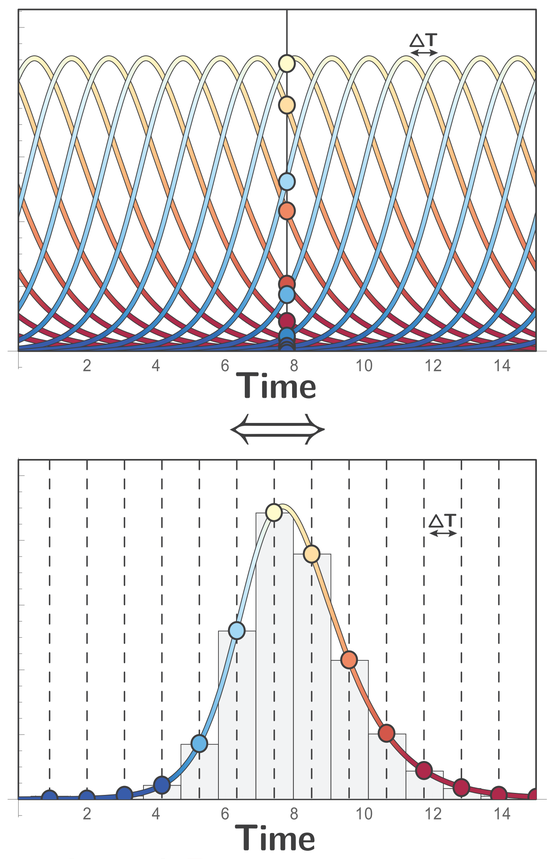
Succesion or polymorphism at the PRDM9 locus

Mean-field approximation in polymorphic regime

- No drift / Many PRDM9 alleles / Small recombination load



$$(2N_e u\, 2s(L))^{-1} = \Delta T = \Delta T \sum_i^K x_i \simeq \int_0^\infty x(t) dt = \frac{1 - L_\infty}{L}$$



Self-consistent estimation of summary statistics L and D.

Conclusion

- Main scaling relations observed in simulations are recovered analytically:
  - PRDM9 diversity (D) increases with population size and mutation rate at the PRDM9 locus, in polymorphic regime.
  - Mean recombination rate (L) is independent of population size, in both regimes.
  - Turn-over rate decreases with population size in succesion regime, but is independent of population size in polymorphic regime.
- These predictions will now be tested against empirical data (in mammals).
- More complex models (e.g. including population structure) will be explored.

Parvanov *et al* (2010), Baudat *et al* (2010), Coop & Myers (2007), Myers *et al* (2010)