Probability of fixation of a new mutant and the ancestral recombination-selection graph: Application to the Hill-Robertson effect

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Two-locus selection model

gamete

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mortality	$1 - s$	$1 - cs$	$1 - cs$	1	$0 < c, s < 1$

Two-locus selection model

gamete	A / B	A / b	a / B	a / b	
mortality	1 - s	1 - cs	1 - cs	1	$0 < c, s < 1$
frequency			x	$1 - x$	

Two-locus selection model

gamete	A / B	A / b	a / B	a / b	
mortality	1 - s	1 - cs	1 - cs	1	$0 < c, s < 1$
frequency	ε	0	$x - \varepsilon$	$1 - x$	probability x
	0	ε	x	$1 - x - \varepsilon$	probability $1 - x$

Linkage disequilibrium

$$D = x_{AB} - x_A x_B = (\varepsilon - \varepsilon x)x + (-\varepsilon x)(1 - x) = 0$$

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Epistasis

positive if $1 - s < (1 - cs)^2$

negative if $1 - s > (1 - cs)^2$

Recombination

Recombination

↑

Negative linkage disequilibrium

Recombination

↑

Negative linkage disequilibrium

↗ ↖

Negative epistasis
in an infinite population

Random drift
in a finite population
(Hill and Robertson 1966)

Moran model for population of size N

- At each time step, one offspring produced by two individuals at random
- Recombinant offspring with probability $r = \frac{\rho}{N}$

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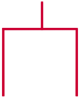
- Type-specific replacement with probability $s = \frac{\sigma}{N}$ and then with conditional probability

$$\begin{cases} 0 & \text{if } AB \\ 1 - c & \text{if } Ab \text{ or } aB \\ 1 & \text{if } ab \end{cases}$$

Ancestral recombination-selection graph (ARSG)

Backwards in time with $\frac{N^2}{2}$ time steps as unit of time as $N \to \infty$



coalescence C of each pair of lineages at rate 1

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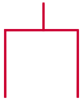

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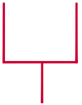

recombination R of each lineage at rate $\frac{\rho}{2}$

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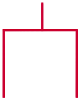

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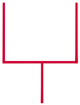
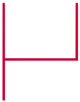


recombination R of each lineage at rate $\frac{\rho}{2}$



selection S of each lineage at rate $\frac{\sigma}{2}$

Probability of fixation of A

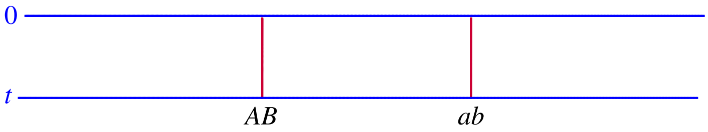
$$x_A(0)+\frac{\sigma}{N^2}\sum_{\tau\geq 0}E\left[x_{AB}(\tau)x_{ab}(\tau)+cx_{Ab}(\tau)x_{ab}(\tau)+(1-c)x_{AB}(\tau)x_{aB}(\tau)\right]$$

Calculation

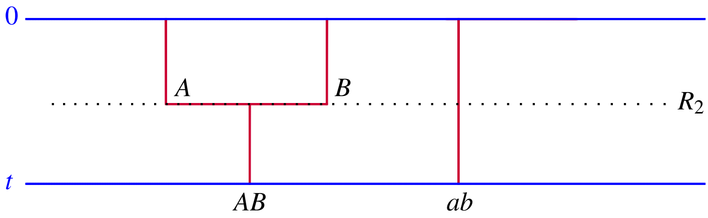
$$\frac{2}{N^2}\sum_{\tau\geq 0} E\left[x_{AB}(\tau)x_{ab}(\tau)\right] \quad \rightarrow \quad \int_0^{\infty} E\left[x_{AB}(t)x_{ab}(t)\right]dt$$

Calculation

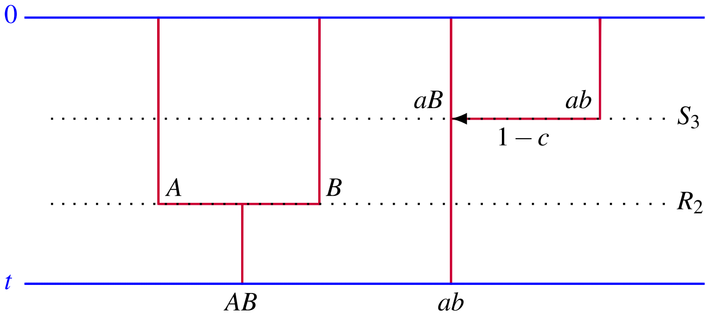
$$\frac{2}{N^2}\sum_{\tau\geq 0} E\left[x_{AB}(\tau)x_{ab}(\tau)\right] \rightarrow \int_0^\infty E\left[x_{AB}(t)x_{ab}(t)\right]dt$$
$$\approx E(T_2)x_{AB}(0)x_{ab}(0)+$$



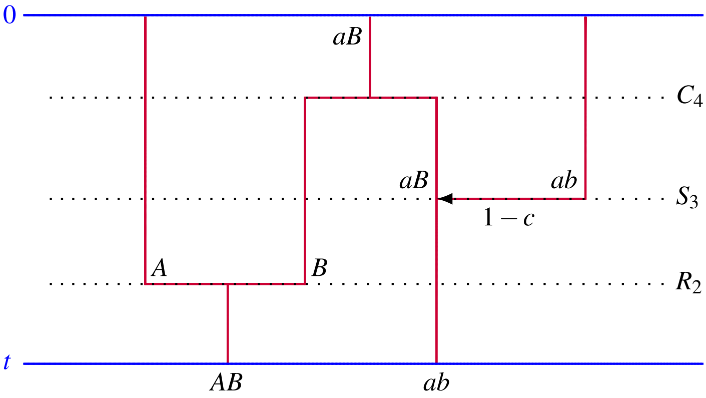
$$P(R_2)E(T_3)x_A(0)x_B(0)x_{ab}(0)+$$



$$(1-c)P(R_2)P(S_3)E(T_4)x_A(0)x_B(0)x_{aB}(0)x_{ab}(0)+$$



$$(1-c)P(R_2)P(S_3)P(C_4)E(T_3)x_A(0)x_{aB}(0)x_{ab}(0)+$$



Result with positive epistasis ($c < \frac{1}{2}$)

$$P(A \text{ fixation}) \approx \varepsilon + \frac{\varepsilon\sigma}{2}(c + x(1-2c)) + \frac{\varepsilon\sigma^2}{12}(c^2 + x(1-2c)(1+2c(1-x)))$$

Result with positive epistasis ($c < \frac{1}{2}$)

$$
\begin{aligned}
P(A \text{ fixation}) \approx \varepsilon \quad & + \quad \frac{\varepsilon\sigma}{2}(c + x(1-2c)) \\
& + \quad \frac{\varepsilon\sigma^2}{12}(c^2 + x(1-2c)(1+2c(1-x))) \\
& + \quad \frac{\varepsilon\rho\sigma^2}{432} x(1-x)(1-2c)(3-c)
\end{aligned}
$$

Result with no epistasis ($c = \frac{1}{2}$)

$$P(A \text{ fixation}) \approx \varepsilon + \frac{\varepsilon\sigma}{4} + \frac{\varepsilon\sigma^2}{48} - \frac{\varepsilon\sigma^3}{192} x(1-x)$$

Result with no epistasis ($c = \frac{1}{2}$)

$$
\begin{aligned}
P(A \text{ fixation}) \approx \varepsilon \quad & + \quad \frac{\varepsilon\sigma}{4} + \frac{\varepsilon\sigma^2}{48} \\
& - \quad \frac{\varepsilon\sigma^3}{192} x(1-x) \\
& + \quad \frac{19\varepsilon\rho\sigma^3}{3456} x(1-x)
\end{aligned}
$$

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- The approach allows us to get approximations of any order with respect to σ and ρ, and this with relative ease
- The results are valid for a wide class of models and can be extended to other classes

Thanks!