Ancestral recombination-selection graph and fixation probability

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IMS 2010 Gothenburg
9-13 August

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Application to the Hill-Robertson effect

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Two-locus selection model

type

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	0	ε	x	$1 - x - \varepsilon$	probability $1 - x$

Linkage disequilibrium

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Epistasis

positive AB fitter than expected $(1-s) < (1-cs)^2$

negative AB less fit than expected $(1-s) > (1-cs)^2$

absent AB as fit as expected $(1-s) = (1-cs)^2$

Recombination

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↑

Negative linkage disequilibrium $D < 0$

Recombination

↑

Negative linkage disequilibrium $D < 0$

↗

Negative epistasis
in an infinite population

Recombination

Negative linkage disequilibrium $D < 0$

Hill-Robertson

Negative epistasis
in an infinite population

Random drift
in a finite population

Recombination makes more likely

the fixation of beneficial mutants

in finite populations

Moran model for population of size 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)

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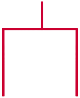
Backwards in time with $\frac{N^2}{2}$ time steps as unit of time as $N \to \infty$



coalescence C of each pair of lineages at rate 1
(Kingman 1982)

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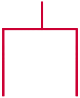

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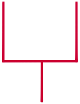

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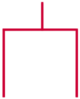

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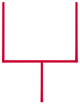

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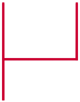

selection S of each lineage at rate $\frac{\sigma}{2}$
(Krone and Neuhauser 1997)

Probability of fixation of A

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

Calculation

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

$E\left[x_{AB}(t)x_{ab}(t)\right] = P(AB$ and ab in this order at time $t)$

where t is for time in units of $\frac{N^2}{2}$ time steps as $N \to \infty$

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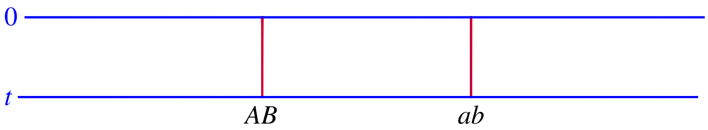
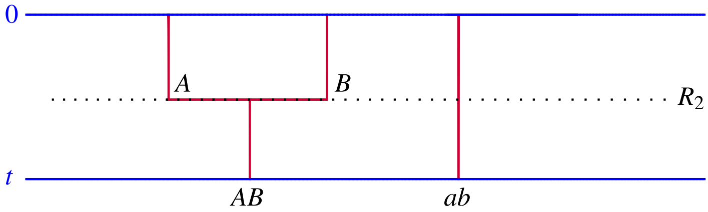
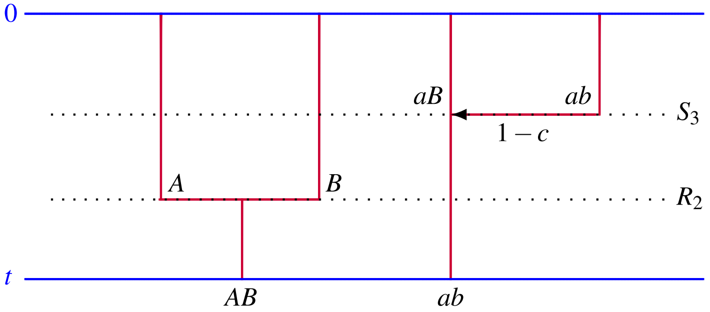
$$E(T_2)x_{AB}(0)x_{ab}(0) +$$



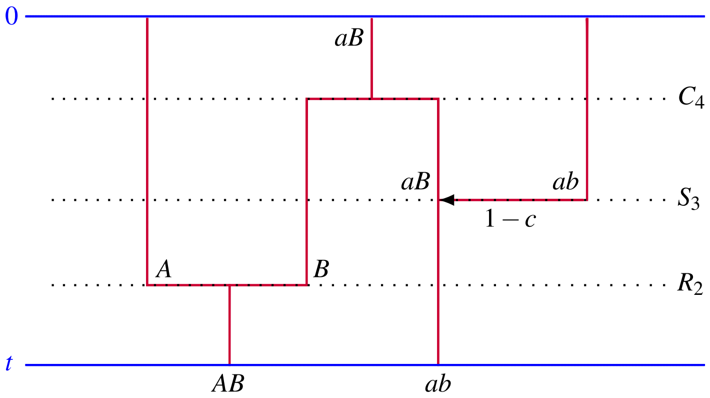
$$P(R_2)E(T_3)x_A(0)x_B(0)x_{ab}(0) +$$



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



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



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

$$
\begin{aligned}
P(A \text{ fixation}) \approx \varepsilon \quad & + \quad \frac{\varepsilon\sigma}{2}(c + x(1-2c)) \\
& + \quad \frac{\varepsilon\sigma^2}{12}(c^2 + x(1-2c)(1+2c(1-x))) \\
& - \quad \frac{\varepsilon\sigma^3}{24}x(1-x)(c + x(1-2c))
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& + \quad \boxed{\frac{\varepsilon\rho\sigma^2}{432} x(1-x)(1-2c)(3-c)}
\end{aligned}
$$

positive term in ρ

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

$$\begin{aligned} P(A \text{ fixation}) \approx \varepsilon \quad & + \quad \frac{\varepsilon\sigma}{4} + \frac{\varepsilon\sigma^2}{48} - \frac{\varepsilon\sigma^3}{192} x(1-x) \\ & - \quad \frac{\varepsilon\sigma^4}{11520}(1 + 15x - 29x^2 + 14x^3) \end{aligned}$$

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

$$P(A \text{ fixation}) \approx \varepsilon + \frac{\varepsilon\sigma}{4} + \frac{\varepsilon\sigma^2}{48} - \frac{\varepsilon\sigma^3}{192} x(1-x) - \frac{\varepsilon\sigma^4}{11520}(1 + 15x - 29x^2 + 14x^3) + \frac{19\varepsilon\rho\sigma^3}{3456} x(1-x)$$

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Final comments

- The analysis confirms the Hill-Robertson effect in favor of recombination in finite populations with positive or no epistasis

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- The same approach can be used to study factors of evolution in multilocus models

Thanks!