

Sex, Draft & Survival

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- Speed of adaptation
- Effect of recombination on fixation of deleterious or beneficial mutations
- How does neutral diversity depend on recombination?
- Polymorphism spectra?
- Tunneling probabilities (adaptation through deleterious intermediates)

Facultatively mating haploid population

- Complete reassortment of alleles upon mating
- Polymorphic at many loci (deleterious or beneficial)

Model inspired by HIV evolution

- Additive contributions to fitness
- Tracer mutations to study genealogies and fixation probabilities







Model inspired by HIV evolution

- Facultatively mating haploid population
- Complete reassortment of alleles upon mating
- Polymorphic at many loci (deleterious or beneficial)
- Additive contributions to fitness
- Tracer mutations to study genealogies and fixation probabilities
- Gaussian fitness distribution
- Traveling wave in case of adaptation
- Mutation/selection balance in case of deleterious mutations





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Speed of adaptation





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- Selection moves the distribution upwards (Fisher's theorem)
- Variation has to be replenished by mutations -> self-consistency condition

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$$\frac{\partial}{\partial t}\bar{x}(t) = \sigma^2 = NU_b sp_{fix}(s, r, \sigma)$$

Traveling wave models: Tsimring et al, Rouzine et al, Desai & Fisher,...











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birth rate : $B = 1 + s + x - \bar{x}(t)$

death rate : D = 1

$$w(x,t-dt) = w(x,t)(1 - dt(B + D + r)) + dtB(1 - (1 - w)^2) + dt r \int K_{xy}w(y,t)$$

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comoving frame :
$$x \to x - \bar{x}(t)$$

$$\sigma^2 \partial_x w(x) = r \int_y K_{x,y} w(y) + (x + s - r) w(x) - w(x)^2$$

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Infinitesimal model:

$$K(x|x_1, x_2) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{\left(x - \frac{x_1 + x_2}{2}\right)^2}{\sigma^2}}$$

Integrate over one parent:

$$K(y|x) = \frac{\sqrt{2}}{\sqrt{3\pi\sigma^2}} e^{-\frac{2(y-\frac{x}{2})^2}{3\sigma^2}}$$

Simplified communal model:

$$K(y|x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{y^2}{2\sigma^2}}$$





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$$p_{fix}(s,r,\sigma) \sim e^{-rac{\sigma^2 \log^2 r/s}{2r^2}}$$

Self-consistency condition:

$$\frac{\partial}{\partial t}\bar{x}(t) = \sigma^2 = NU_b sp_{fix}(s, r, \sigma)$$

RAN, Shraiman, Fisher, Genetics, 2010, see also Rouzine & Coffin, Genetics 2005 and TPB 2010



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$$\frac{\partial}{\partial t}\bar{x}(t) = \begin{cases} 2s^2 \left(\frac{r}{s}\right)^2 \frac{\log NU_b}{\ln^2 r/s} & 1 \ll \frac{r^2}{s^2} \ll NU_b/\ln NU_b\\ NU_b s^2 \left(1 - \frac{4NU_b s^2}{r^2} + \dots\right) & \frac{r^2}{s^2} \gg 4NU_b \end{cases}$$

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- In large populations, recombination is limiting adaptation
- In small population, the supply of mutations is limiting

RAN, Shraiman, Fisher, Genetics, 2010, see also Rouzine & Coffin, Genetics 2005 and TPB 2010





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Fixation probabilities?





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Fixation probabilities?





Quasi-neutrality

No effective neutral theory

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Population genetics dominated by draft



Instead of fixation probability, we have to calculate P(n,t)

Population genetics dominated by draft



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Population genetics dominated by draft

Instead of fixation probability, we have to calculate P(n,t)



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Time

t=2

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Population genetics dominated by draft

Instead of fixation probability, we have to calculate P(n,t)

Fitness Size of first clone: $n_1 \sim \frac{1}{x} e^{-\frac{(x+s-r)^2}{2}}$ Fitness distribution # of daughter clones: $\xi = rn_1$ Clone size distribution:







Population genetics dominated by draft

Instead of fixation probability, we have to calculate P(n,t)



Size of first clone: n_1

$$e_1 \sim \frac{1}{x} e^{-\frac{(x+s-r)^2}{2}}$$

of daughter clones: $\xi = rn_1$

Clone size distribution:

$$P(\xi) \sim \frac{e^{-r\sigma^{-1}\sqrt{2\log r\sigma^{-1}\xi}}}{\xi^2}$$

Diverging variance!

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Number of clones

Recursion:

$$C_t(m) = \sum_{m'} p(m, m') C_{t-1}(m')$$

Generating function:

$$\partial_t \Phi(z) = s \Phi(z) - r e^{-r\sqrt{-2\log\Phi(z)}} \Phi(z)$$

$$\rightarrow P(n,t)$$



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 $\Psi(z) = \langle e^{-z \int_0^t n(t)} \rangle_{n(t)}$

$$m'$$

$$\partial_t \Phi(z) = s \Phi(z) - r e^{-r \sqrt{-2 \log \Phi(z)}} \Phi(z)$$

Recursion:

$$C_t(m) = \sum_{m'} p(m, m') C_{t-1}(m')$$



Draft vs Drift



$$P_{sur}(T) \sim e^{\frac{-\sigma^2}{2r^2} \log^2 r^3 \sigma^{-2} T}$$

$$T_{fix} \sim \sigma^2 r^{-3} e^{r\sigma^{-1}\sqrt{2\log N}} \qquad \sim N$$

Quasi- neutral window:

$$s_c \sim r e^{-r\sigma^{-1}\sqrt{2\log N}} \qquad \qquad s_c = N^{-1}$$

Neutral allele frequency spectrum:

$$f(\nu) \sim \frac{e^{r\sqrt{2\log N\nu}}}{\nu^2}$$

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 $\sim \nu^{-1}$

Drift:

 $\sim T^{-1}$

Allele frequency spectra





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Allele frequency spectra





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HIV allele frequency spectrum





Data from Hedskog et al, 2010

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- Lineages stay put
- Variance is maintained by beneficial mutations







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- Lineages deteriorate by mutations
- Asexual, no ratchet: steady, poisson distribution
- Mutation-selection balance
- Variance maintained by deleterious mutations

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Identical results





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Deleterious mutations





Summary & Outlook



- Recombination can limit adaptation
- Lack of recombination in presence of selection changes everything...
- Epistasis?
- Linear Chromosomes?
- Population substructure?
- How do we test theoretical predictions?

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