The numerical load

Understanding the interaction between demography and genetics

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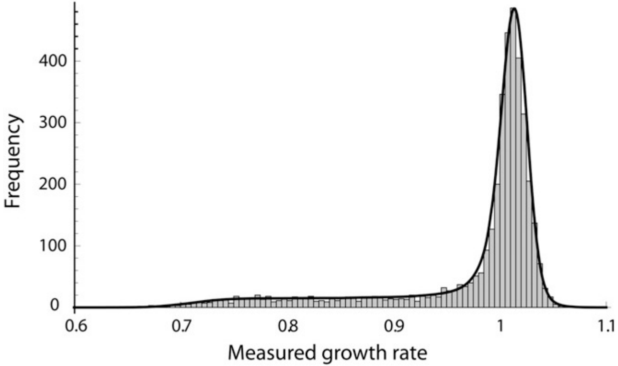
Mutations keep on coming...



Agrawal and Whitlock 2011

Estimating the genetic load L

Wright-Fisher Model

- Fixed population size (depends on N_e)
- Selection : **Reproduction** or on **Zygote survival**?

$\rightarrow$ Demographic parameters are neglected in models studying L

(Bataillon and Kirkpatrick 2000, Glémin 2003, Roze and Rousset 2004)

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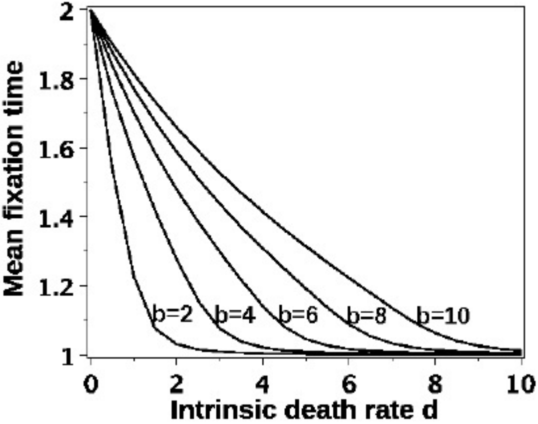
Fixation

Mutational meltdown (Coron et al. 2013)



Can we predict the effect of mutations on population size?

Clarke (1973): **The Numerical load**

$$NL = \frac{N_0 - N_{mut}}{N_0}$$

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  - Fundamental model (Deterministic Wright-Fisher Model)

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$\rightarrow$ Limited model

General model

A single, bi-allelic locus (A, the Wild-type and a the mutant).
Sexual reproduction (with selfing).

Ordinary Differential Equations:

$$\frac{dN_t}{d_t} = \underbrace{R_t^N}_{R_t^X + R_t^Y + R_t^Z} - \underbrace{M_t^N}_{M_t^X + M_t^Y + M_t^Z} \qquad \begin{array}{l} X = aa \\ Y = Aa \\ Z = AA \end{array}$$

where R_t^N is the total birth rate and M_t^N is the total death rate.

General model

$$R_t^X = b\left(\alpha\left(X_t + \frac{1}{4}Y_t\right) + (1-\alpha)\left(\frac{X_t}{N_t}X_t + \frac{1}{2}\frac{Y_t}{N_t}X_t + \frac{1}{2}\frac{X_t}{N_t}Y_t + \frac{1}{4}\frac{Y_t}{N_t}Y_t\right)\right)$$

$$R_t^Y = b\left(\alpha\left(\frac{1}{2}Y_t\right) + (1-\alpha)\left(\frac{1}{2}\frac{Y_t}{N_t}Y_t + \frac{1}{2}\frac{X_t}{N_t}Y_t + \frac{1}{2}\frac{Z_t}{N_t}Y_t + \frac{1}{2}\frac{Y_t}{N_t}X_t + \frac{Z_t}{N_t}X_t + \frac{1}{2}\frac{Y_t}{N_t}Z_t + \frac{X_t}{N_t}Z_t\right)\right)$$

$$R_t^Z = b\left(\alpha\left(Z_t + \frac{1}{4}Y_t\right) + (1-\alpha)\left(\frac{Z_t}{N_t}Z_t + \frac{1}{2}\frac{Y_t}{N_t}Z_t + \frac{1}{2}\frac{Z_t}{N_t}Y_t + \frac{1}{4}\frac{Y_t}{N_t}Y_t\right)\right)$$

where α is the self-ferlisation rate, b the inherent birth rate.

$$M_t^X = qX_t\frac{N_t}{K^X}$$

$$M_t^Y = qY_t\frac{N_t}{K^Y}$$

$$M_t^Z = qZ_t\frac{N_t}{K^Z}$$

where K is the carrying capacity and q the inherent death rate.

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General model

Ordinary Differential Equations:

$$\frac{dN_t}{d_t} = (R_t^X + R_t^Y + R_t^Z) - (M_t^X + M_t^Y + M_t^Z) = 0$$

→ Hardy-Weinberg equilibrium

X	Y	Z
$p^2 + pF$	$2pq(1-F)$	$q^2 + qF$

$F = \frac{\alpha}{2-\alpha}$

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Introducing selection and mutation

We consider that $\alpha = 0$

$$\frac{dX_t}{dt} = \frac{b}{N_t}\left(X_t^2 + X_tY_t + \frac{1}{4}Y_t^2\right) - qX_t\frac{N_t}{K}$$
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Relative Fitnesses (W^G):	W^X	W^Y	W^Z
	$(1-s)$	$(1-hs)$	1

Here we consider selection on:

- Model 1 : Reproduction $\rightarrow G_tW^G$
- Model 2 : Zygote survival $\rightarrow bW^G$

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Introducing selection and mutation

Mutation from $A \to a$ occurs at rate μ

Here we consider mutation on gametes:

$$R_t^X = \frac{b}{N_t}\left(X_t^2 + (1+\mu)X_tY_t + \frac{1}{4}(1+\mu)Y_t^2 + 2\mu X_tZ_t + \mu(1+\mu)Y_tZ_t + (\mu Z_t)^2\right)$$

$$R_t^Y = \frac{b}{N_t}\left(\frac{1}{2}(1-\mu^2)Y_t^2 + (1-\mu)X_tY_t + (1+\mu-\mu^2)Y_tZ_t + 2(1-\mu)X_tZ_t + 2\mu(1-\mu)Z^2\right)$$

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Model 1 $(h = 0)$

Selection on Reproduction :

$$R_t^X = \frac{b}{N_t}\left((1-s)X_t + \frac{(1+\mu)Y_t}{2} + \mu Z_t\right)^2$$

$$R_t^Z = \frac{b}{N_t}\left((1-\mu)Z_t + \frac{(1+\mu)Y_t}{2}\right)^2$$

Model 1 $(h = 0)$

Selection on Reproduction :

$$
\begin{aligned}
R_t^X &= \frac{b}{N_t}\left((1-s)X_t + \frac{(1+\mu)Y_t}{2} + \mu Z_t\right)^2 \\
R_t^Z &= \frac{b}{N_t}\left((1-\mu)Z_t + \frac{(1-\mu)Y_t}{2}\right)^2 \\
R_t^Y &= \frac{2b}{N_t}\left((1-s)X_t + \frac{(1+\mu)Y_t}{2} + \mu Z_t\right)\left((1-\mu)Z_t + \frac{(1-\mu)Y_t}{2}\right) \\
&= 2\sqrt{R_t^X}\sqrt{R_t^Z}
\end{aligned}
$$

Model 1 $(h = 0)$

Propositions:

At equilibrium

- $NL^1 = 2\mu - \mu^2$
- $L^1 = \mu$

Model 1

Proof: $NL^1 = 2\mu - \mu^2$

Equation 1

$$\frac{dN_t}{dt} = b(1 - \frac{X_t s}{N_t})^2 - q\frac{N_t}{K}$$

At equilibrium

$$N^1_{mut} = \frac{bK}{q}\left(1 - \frac{X_{eq} s}{N^1_{mut}}\right)^2 \qquad (1)$$

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Equation 2

$$\frac{dN^A_t}{dt} = 2R^Z_t + R^Y_t - \frac{qN_t}{K}(2Z_t + Y_t)$$

At equilibrium

$$N^1_{mut} = \frac{bK}{q}\left(1 - \frac{X_{eq}s}{N^1_{mut}}\right)(1 - \mu) \qquad (2)$$

Model 1

Proof: $NL^1 = 2\mu - \mu^2$

From Equations (1) and (2)

$$b(1-\mu)\left(1-\frac{X_{eq}s}{N^1_{mut}}\right) = b\left(1-\frac{X_{eq}s}{N^1_{mut}}\right)^2$$

And so:

$$N^1_{mut} = \frac{bK}{q}(1-\mu)^2$$

$$NL^1 = 2\mu - \mu^2$$

Model 1

Proof: $L^1 = \mu$

From Equations (1) and (2)

$$X_{eq}^1 = \frac{bK(1-\mu)^2\mu}{qs}$$

$$L = \frac{W^{max} - W}{W^{max}}$$

$$L^1 = \mu$$

Genetic load L as predicted by Deterministic Wright-Fisher Model

Model 2 $(h = 0)$

Selection on Zygote survival $(b^G = W^G b)$:

$$\frac{dX_t}{dt} = \frac{b(1-s)}{N_t}\left(X_t^2 + (1+\mu)X_tY_t + \frac{1}{4}(1+\mu)Y_t^2 + 2\mu X_tZ_t + \mu(1+\mu)Y_tZ_t + (\mu Z_t)^2\right) - qX_t\frac{N_t}{K}$$

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At equilibrium

- $NL^2 = \mu$ $\qquad N_{mut}^2 = \frac{bK}{q}(1-\mu)$
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Genetic load L does not follow Wright-Fisher Model expectations

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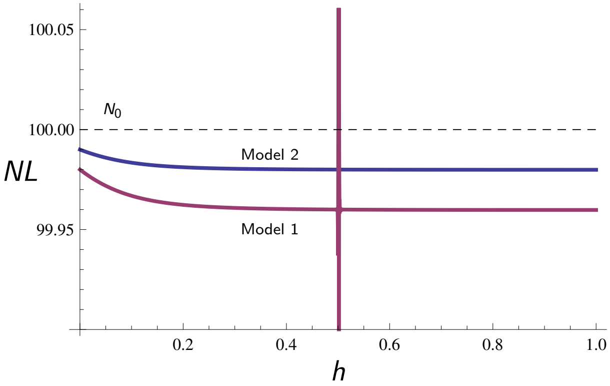
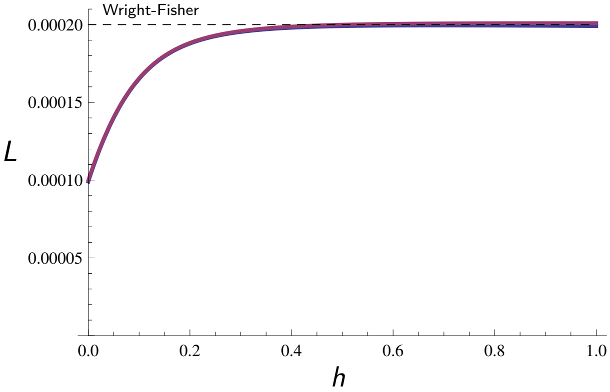
Numerical Load *NL*



Genetic Load L



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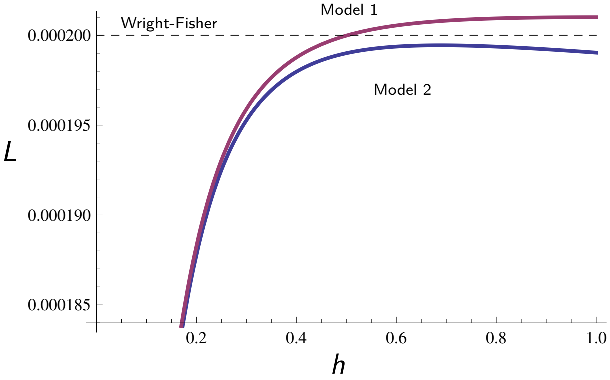

Linking the demographic and the genetic load

$NW = \frac{NL}{N_0}$ $\qquad W = 1 - L$

	W	NW
Model 1	$1-\mu$	$(1-\mu)^2$
Model 2	$1-\frac{\mu(1-s)}{1-\mu}$	$1-\mu$

Selection on reproduction : Double selection? $\rightarrow W_{male}\ W_{female}$

Selection on zygotes : Individual selection that depends on s

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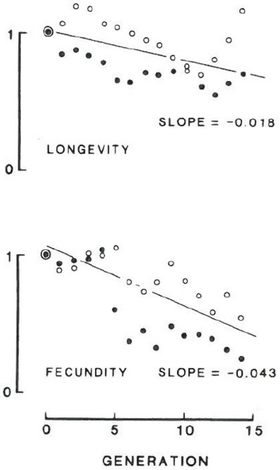
Timing of selection

	Model 1	Model 2
L	μ	$\frac{\mu(1-s)}{1-\mu}$



With or without demography?

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- How accurate is the Wright-Fisher model?

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Perspectives

- Selection, Mutation and Reproduction models
- Multi-locus model

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Thank you for your attention