

Mathematics and Computation in Phenotypic Switching

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Biological Motivation

Bistability in *Bacillus subtilis* K-state (competence) system requires a positive feedback loop

Hédia Maamar and David Dubnau*
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Newark NJ 07103, USA.

Hadden and Nester, 1968; Haseltine-Cahn and Fox, 1968). Transcriptional profiling has revealed that well over 100 genes in this distinct subpopulation, many of which have no obvious role in transformation, are induced con-

Genetic competence (uptaking DNA from environment) in bacterium *B. subtilis* is a phenotypic switch

MicroReview

Bistability in bacteria

David Dubnau* and Richard Losick^{2,3*}

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Noise in Gene Expression Determines Cell Fate in *Bacillus subtilis*

Hédia Maamar,† Arjun Raj,*† David Dubnau‡

“The world inhabited by bacteria and other microorganisms is perilous. These tiny creatures must cope with the vicissitudes of an environment that undergoes perpetual alterations in temperature, salinity, pH, availability of nutrients, challenged by antibiotics, mutagens, toxins, radiation...”

Dubnau and Losick, Bistability in Bacteria, 2006

*ENZYME INDUCTION AS AN ALL-OR-NONE PHENOMENON**

BY AARON NOVICK AND MILTON WEINER

DEPARTMENT OF MICROBIOLOGY AND COMMITTEE ON BIOPHYSICS, UNIVERSITY OF CHICAGO

Communicated by W. H. Taliaferro, April 21, 1957

Lactose utilization network in *E. coli*
is a phenotypic switch

**Predicting stochastic gene expression
dynamics in single cells**

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Edited by Nancy J. Kopell, Boston University, Boston, MA, and approved March 19, 2006 (received for review November 14, 2005)

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**Multistability in the lactose
utilization network of
*Escherichia coli***

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Bacterial Persistence: A Model of Survival in Changing Environments

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Bacterial persistence (switching between phenotypic states with different growth rates) in *E. coli* as a phenotypic switch

Bacterial Persistence as a Phenotypic Switch

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Lukasz Kowalik,¹ Stanislas Leibler¹

Stochastic switching: evolutionary bet-hedging mechanism

Stochastic switching as a survival strategy in fluctuating environments

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Nature, Nurture, or Chance: Stochastic Gene Expression and Its Consequences

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Evolution of Stochastic Switching Rates in Asymmetric Fitness Landscape

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Exact Results for the Evolution of Stochastic Switching in Variable Asymmetric Environments

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Phenotypic Diversity, Population Growth, and Information in Fluctuating Environments

Edo Kussell* and Stanislas Leibler



QUESTIONS: When is switching adaptive? What are optimal rates of switching?

Stochastic switching regarded as a bet-hedging strategy by which genetically identical individuals are able to express different phenotypes in different environments.

Population Genetic Background

A haploid modifier model with constant environment

Genotypes	AB	Ab	aB	ab	
Frequencies	x_1	x_2	x_3	x_4	$(x_1 + x_2 + x_3 + x_4 = 1)$
Fitnesses	w_1	w_2	w_3	w_4	

Mutation at A/a $AB \leftrightarrow aB$ at rate μ_B

Controlled by B/b $Ab \leftrightarrow ab$ at rate μ_b

B/b is selectively “neutral” $w_1 = w_2, \quad w_3 = w_4$

Recombination: $AB/ab \rightarrow$

AB	Ab	aB	ab
$r/2$	$(1-r)/2$	$(1-r)/2$	$r/2$

Problem: What mutation rate will the population evolve?

Write x'_1, x'_2, x'_3, x'_4 for AB, Ab, aB, ab frequencies in the next generation. The dynamical system is

$$wx'_1 = (1 - \mu_B)w_1(x_1 - rD) + \mu_B w_3(x_3 + rD)$$

$$wx'_2 = (1 - \mu_b)w_2(x_2 + rD) + \mu_b w_4(x_4 - rD)$$

$$wx'_3 = (1 - \mu_B)w_3(x_3 + rD) + \mu_B w_1(x_1 - rD)$$

$$wx'_4 = (1 - \mu_b)w_4(x_4 - rD) + \mu_b w_2(x_2 + rD)$$

$$w = \sum w_i x_i - rD(w_1 - w_2 - w_3 + w_4), \quad D = x_1 x_4 - x_2 x_3.$$

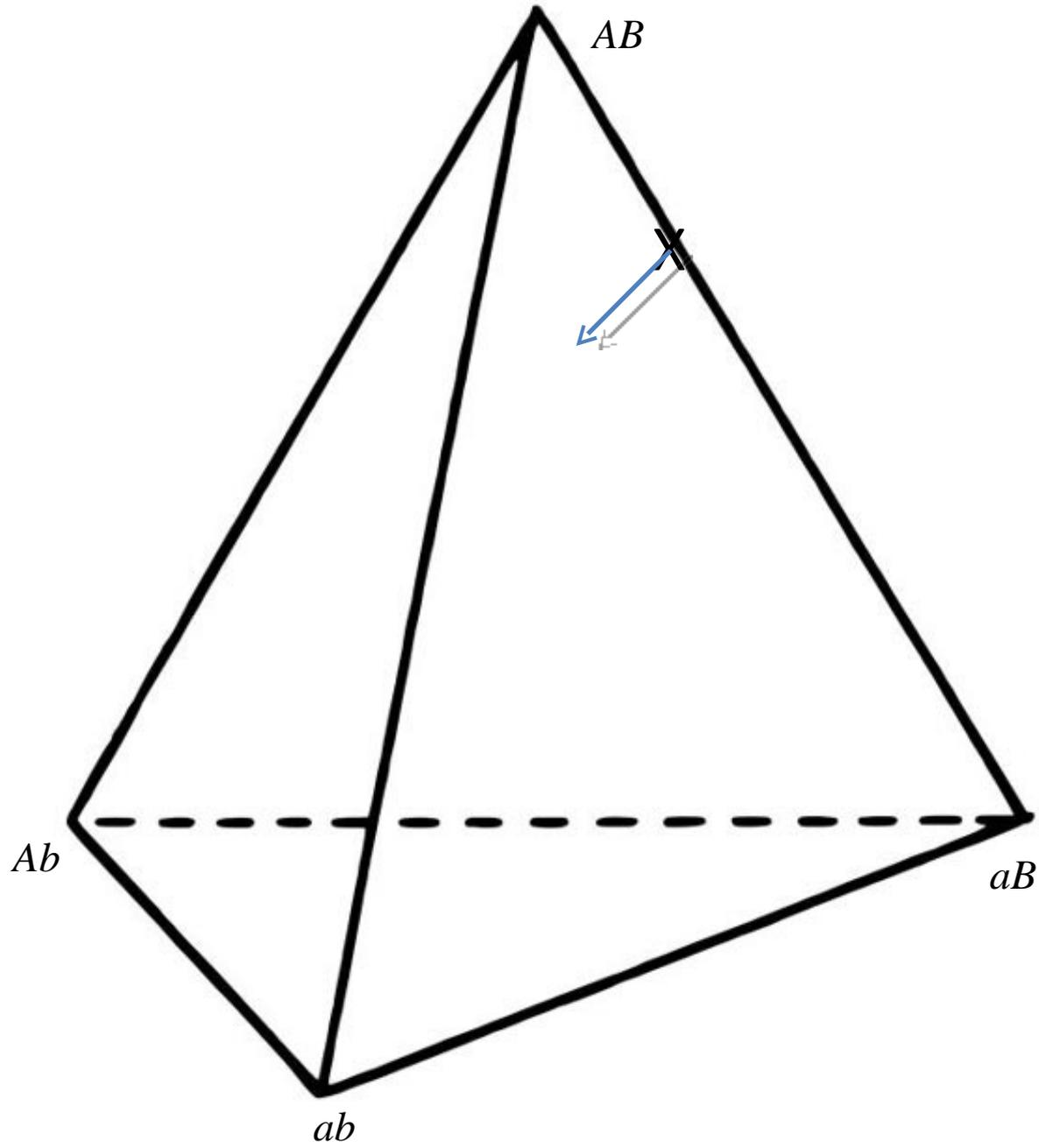
Since B/b is neutral, $w_1 = w_2, w_3 = w_4, w = \sum w_i x_i$.

Start with only B present.

A fixed point exists $x_1^*, x_3^* > 0$ ($x_2^* = x_4^* = 0$).

Under what conditions will allele b increase in frequency starting near (x_1^*, x_3^*) ?

Local stability of $(x_1^*, 0, x_3^*, 0)$ in simplex (x_1, x_2, x_3, x_4) .



Initial increase of allele b

$$\begin{aligned} w^* x_2' &= (1 - \mu_b)w_2(x_2 + rD^*) + \mu_b w_4(x_4 - rD^*) \\ w^* x_4' &= (1 - \mu_b)w_4(x_4 - rD^*) + \mu_b w_2(x_2 + rD^*), \end{aligned} \tag{1.16}$$

where

$$w^* = w_1 x_1^* + w_3 x_3^*, \quad D^* = x_1^* x_4 - x_3^* x_2. \tag{1.17}$$

From (1.16), the matrix \mathcal{L} associated with this linear transformation is

$$\frac{1}{w^*} \begin{bmatrix} (1 - \mu_b)w_2 - r[(1 - \mu_b)w_2 - \mu_b w_4]x_3^* & \mu_b w_4 + r[(1 - \mu_b)w_2 - \mu_b w_4]x_1^* \\ \mu_b w_2 + r[(1 - \mu_b)w_4 - \mu_b w_2]x_3^* & (1 - \mu_b)w_4 - r[(1 - \mu_b)w_4 - \mu_b w_2]x_1^* \end{bmatrix}. \tag{1.18}$$

The eigenvalues of \mathcal{L} satisfy the equation $M(z) = \det(\mathcal{L} - z\mathbf{I}) = 0$, where \mathbf{I} is the 2×2 identity matrix.

The positive eigenvalue of \mathcal{L} is less than 1 if $M(1) > 0$ and $M'(1) > 0$ and is larger than 1 if $M(1) < 0$.

Result. The unique internally stable equilibrium $\underline{x}^* = (x_1^*, 0, x_3^*, 0)$ is externally stable when $\mu_b > \mu_B$, and is externally unstable when $\mu_b < \mu_B$ provided $0 \leq r < 1$. Thus when $0 \leq r < 1$, evolution reduces mutation rates.

Result. The mean fitness $w^* = w_1 x_1^* + w_3 x_3^*$ at equilibrium is a decreasing function of μ_B .

Phenotypic Evolution in Fluctuating Environments

At generation i , for $i = 1, 2, \dots, k$, the fitness parameters are

$$\begin{array}{l} \text{gamete: } AB \quad Ab \quad aB \quad ab \\ \text{fitness: } w_1^i \quad w_2^i \quad w_3^i \quad w_4^i \end{array} \quad (2.1)$$

where

$$w_2^i = w_1^i, \quad w_4^i = w_3^i. \quad (2.2)$$

If at the beginning of generation i , for $i = 1, 2, \dots, k$, the population state has the frequency vector $\underline{x} = (x_1, x_2, x_3, x_4)$, then after that generation the new frequency vector $\underline{x}' = (x'_1, x'_2, x'_3, x'_4)$ is given by $\underline{x}' = T_i(\underline{x})$, where T_i is given by

$$\begin{aligned} w^i x'_1 &= (1 - \mu_B) w_1^i (x_1 - rD) + \mu_B w_3^i (x_3 + rD) \\ w^i x'_2 &= (1 - \mu_b) w_2^i (x_2 + rD) + \mu_b w_4^i (x_4 - rD) \\ w^i x'_3 &= (1 - \mu_B) w_3^i (x_3 + rD) + \mu_B w_1^i (x_1 - rD) \\ w^i x'_4 &= (1 - \mu_b) w_4^i (x_4 - rD) + \mu_b w_2^i (x_2 + rD), \end{aligned} \quad (2.3)$$

where the mean fitness w^i in generation i is

$$w^i = \sum_{\ell=1}^4 w_\ell^i x_\ell. \quad (2.4)$$

If the population state at the beginning of the k generation process is $\underline{y} = (y_1, y_2, y_3, y_4)$, then after generation k it is $\underline{y}' = (y'_1, y'_2, y'_3, y'_4)$ where $\underline{y}' = T\underline{y}$ and the transformation T is given by the composition of the k transformations

$$T = T_k \circ T_{k-1} \circ \cdots \circ T_1 . \quad (2.5)$$

If we denote by \underline{y}^i the population state at the start of generation i , for $i = 1, 2, \dots, k$, where $\underline{y}^1 = \underline{y}$, then the mean fitness associated with the transformation T is

$$w = w(\underline{y}) = \prod_{i=1}^k w^i(\underline{y}^i) . \quad (2.6)$$

Suppose only AB, aB present ($x_2 = x_4 = 0$).

$$w^i x_1^{i+1} = (1 - \mu_B)w_1^i x_1^i + \mu_B w_3^i x_3^i,$$

$$w^i x_3^{i+1} = (1 - \mu_B)w_3^i x_3^i + \mu_B w_1^i x_1^i.$$

$w^i = w_1^i x_1^i + w_3^i x_3^i$. Transform to $u^i = x_1^i / x_3^i$.

$$u^{i+1} = f_i(u^i) = \frac{(1-\mu_B)w_1^i u^i + \mu_B w_3^i}{\mu_B w_1^i u^i + (1-\mu_B)w_3^i}.$$

Linear fractional; retains form under continued iteration and converges to a unique fixed point $(x_1^*, 0, x_3^*, 0)$.

This is the new starting point for evolution of allele b .

Ab, ab appear near the “equilibrium” $(x_1^*, 0, x_3^*, 0)$ in (x_1, x_2, x_3, x_4) space while the evolution under $T_k \circ T_{k-1} \circ \dots \circ T_1 = T$ proceeds. Write $\underline{x} = (x_1, x_2, x_3, x_4)$

$$\underline{x}' = T\underline{x} = \underline{x}^* + \underline{\varepsilon}',$$

where

$$\underline{\varepsilon}' = \mathcal{L}^* \underline{\varepsilon}^T.$$

Eigenvalues of $\mathcal{L}_{\text{ex}}^*$ determine local stability. These are extremely difficult to characterize in general. Go to special cases.

Symmetric fluctuation

	AB	Ab	aB	ab
Environment I	w_1	w_1	w_3	w_3
Environment II	w_3	w_3	w_1	w_1

Period 2: I, II, I, II,

Result. The fixed point $(x_1^*, 0, x_3^*, 0)$ is locally stable to invasion by allele b is $\mu_B > \mu_b$ and locally unstable when $\mu_b > \mu_B$ for all $0 \leq r < 1$.

Result. The mean fitness is an increasing function of μ_B .

Period 4: I, I; II, II; I, I ... , symmetric fitnesses

	<i>AB</i>	<i>Ab</i>	<i>aB</i>	<i>ab</i>
time 1	w_1	w_1	w_3	w_3
time 2	w_1	w_1	w_3	w_3
time 3	w_3	w_3	w_1	w_1
time 4	w_3	w_3	w_1	w_1

- i. The mean fitness achieves a maximum at $\mu_B = 1/2$.
- ii. The mutation rate $\mu_B = 1/2$ cannot be invaded by any allele *b* that gives $\mu_b < 1/2$ or $\mu_b > 1/2$.
- iii. For symmetric fitnesses, for cycles with period $m = 2n$, with $r = 0$ and $0 < \mu_B < 1$, if allele *b* gives $\mu_b = 0$ it cannot invade, and if $\mu_b = 1$ it cannot invade.
- iv. Mutation rates μ_M that are critical points of the mean fitness w^* in the case $r = 0$ also entail that at $\mu_m = \mu_M$, $\partial\lambda/\partial\mu_m = 0$.

Approximations and numerical analyses of the symmetric case have proposed that for cycles of period $2n$, the stable mutation rate is $1/n$. Not proved yet and seems to fail for $n = 3$.

Asymmetrical Fluctuating Selection

	AB	Ab	aB	ab
Environment 1:	$w_1 = 1 - s_1$	$w_2 = 1 - s_1$	$w_3 = 1$	$w_3 = 1$
Environment 2:	$\hat{w}_1 = 1$	$w_1 = 1$	$w_3 = 1 - s_3$	$w_3 = 1 - s_3$

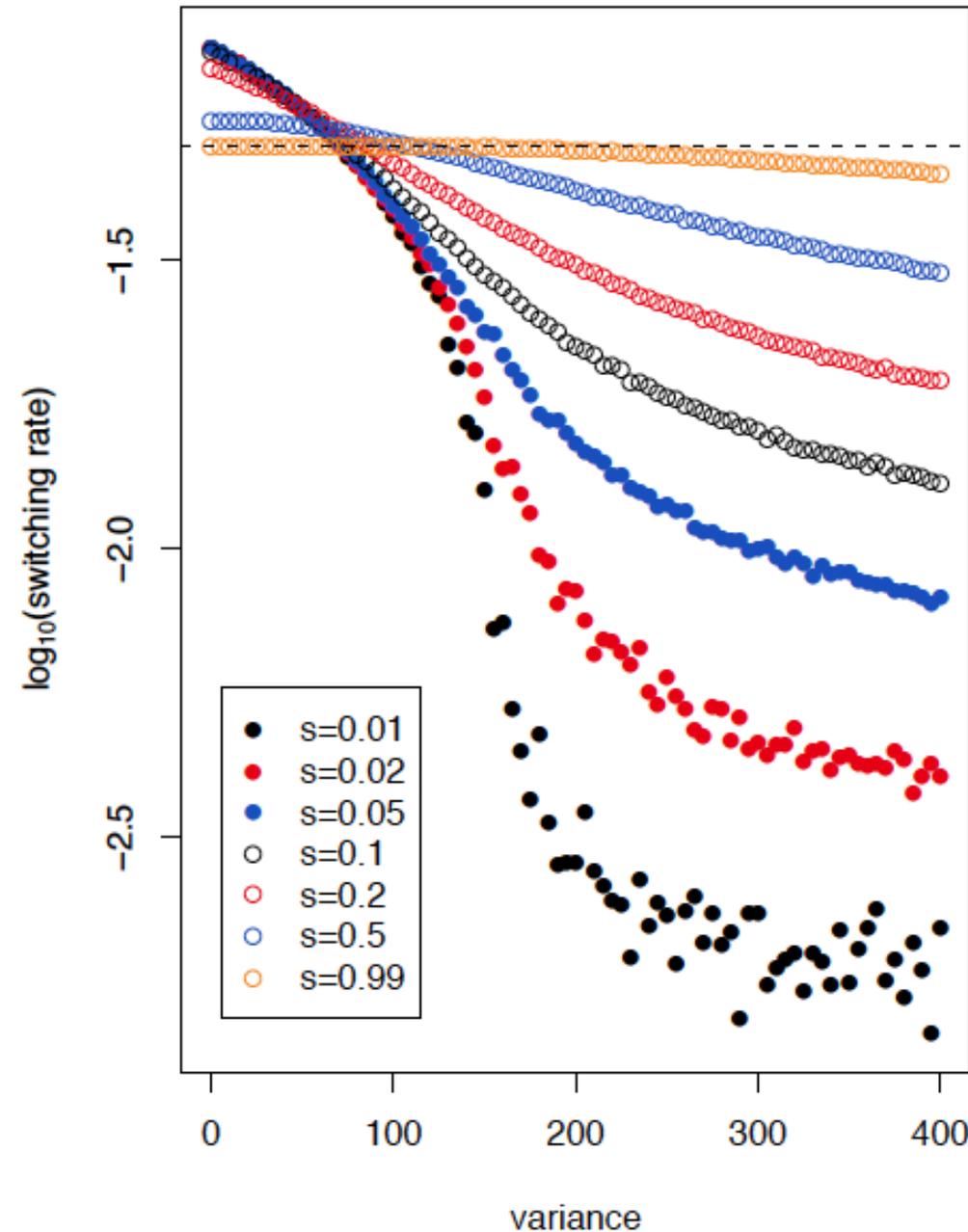
Selection due to A/a ; mutation controlled by B/b

Each environment lasts N generations.

Three “natural” cases:

1. $N \sim \text{gamma}(\alpha, \beta)$: $E(N) = n = \alpha\beta$, $\text{Var}(N) = \alpha\beta^2$;
2. N fixed (periodic selection);
3. N exponential ($\alpha = 1$): change at rate $1/n$ each generation.

What is the stable mutation (switching) rate?



Evolution of stochastic switching rates in symmetric fitness landscapes, i.e., $s = s_0 = s_1$. The \log_{10} evolutionary stable switching rate on the x-axis depends both on the fitness cost of being maladapted in both environments (s) and the variance of the distribution of waiting times. The mean waiting time is fixed at $n = 20$ and the variance ranges from zero, which corresponds to a periodic environment where the environment changes exactly every 20 generations, to 400, which corresponds to an exponential distribution ($\alpha = 1, \beta = 20$) where the environment changes with probability 0.05 at each generation. Different values of s are plotted using the colored empty and filled circles given in the legend. Dashed line is $1/n$.

Salathé, Van Cleve, Feldman 2009

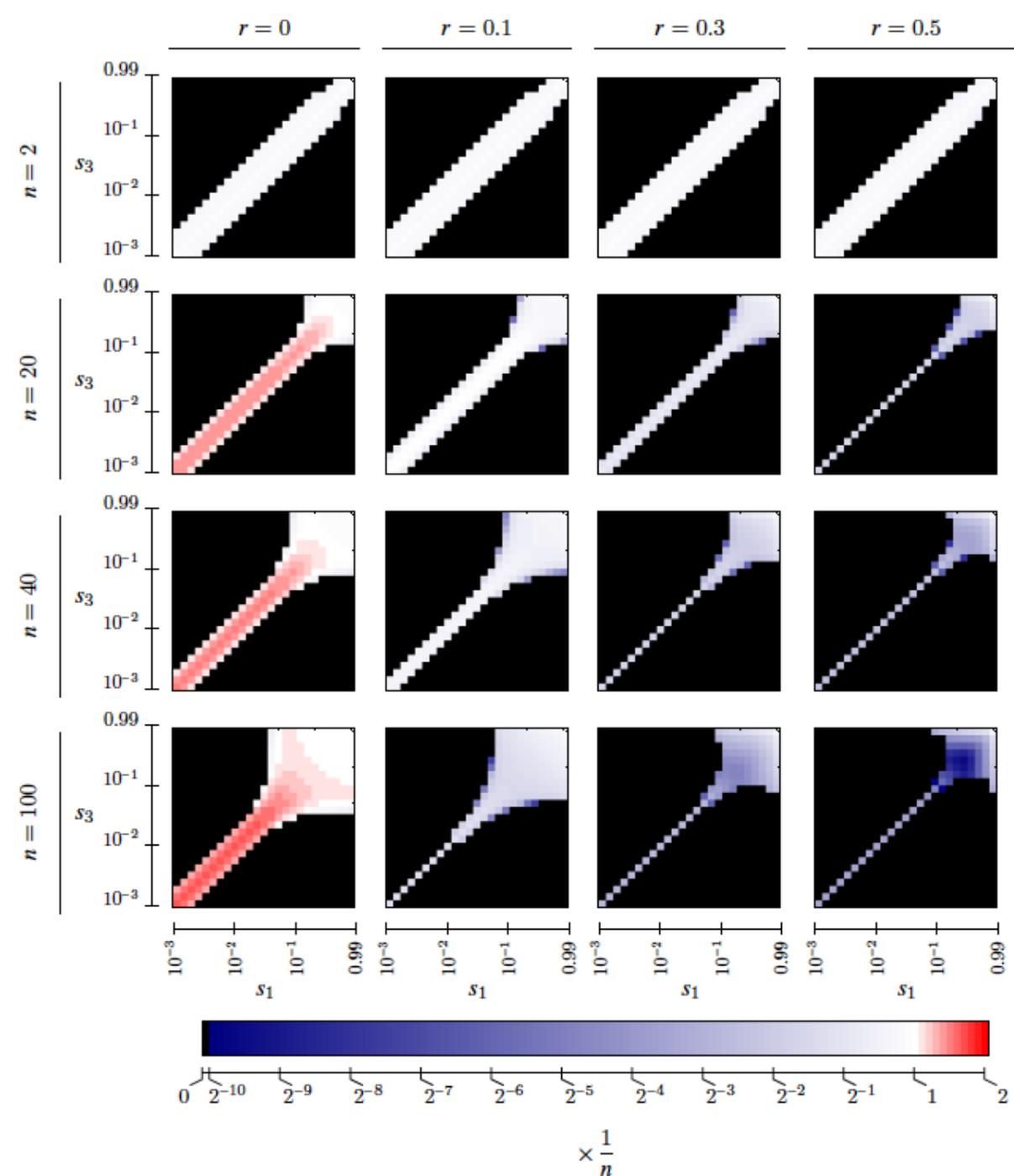


Figure 1: Evolutionarily stable mutation rates as a function of the selection coefficients for the disfavored allele in each environment, s_1 and s_3 , which are plotted logarithmically. The number of generations in each environment, n , is given along the left side of the figure. The recombination rate between the major locus under selection and the modifier locus is given along the top of the figure. The colors denote the stable mutation rate and are given in units of the canonical predicted rate of $1/n$ in the color bar at the bottom of the figure; white is a rate of $1/n$, shades of red are rates higher than $1/n$, and blues are rates lower than $1/n$. Black denotes evolution to zero mutation rate.

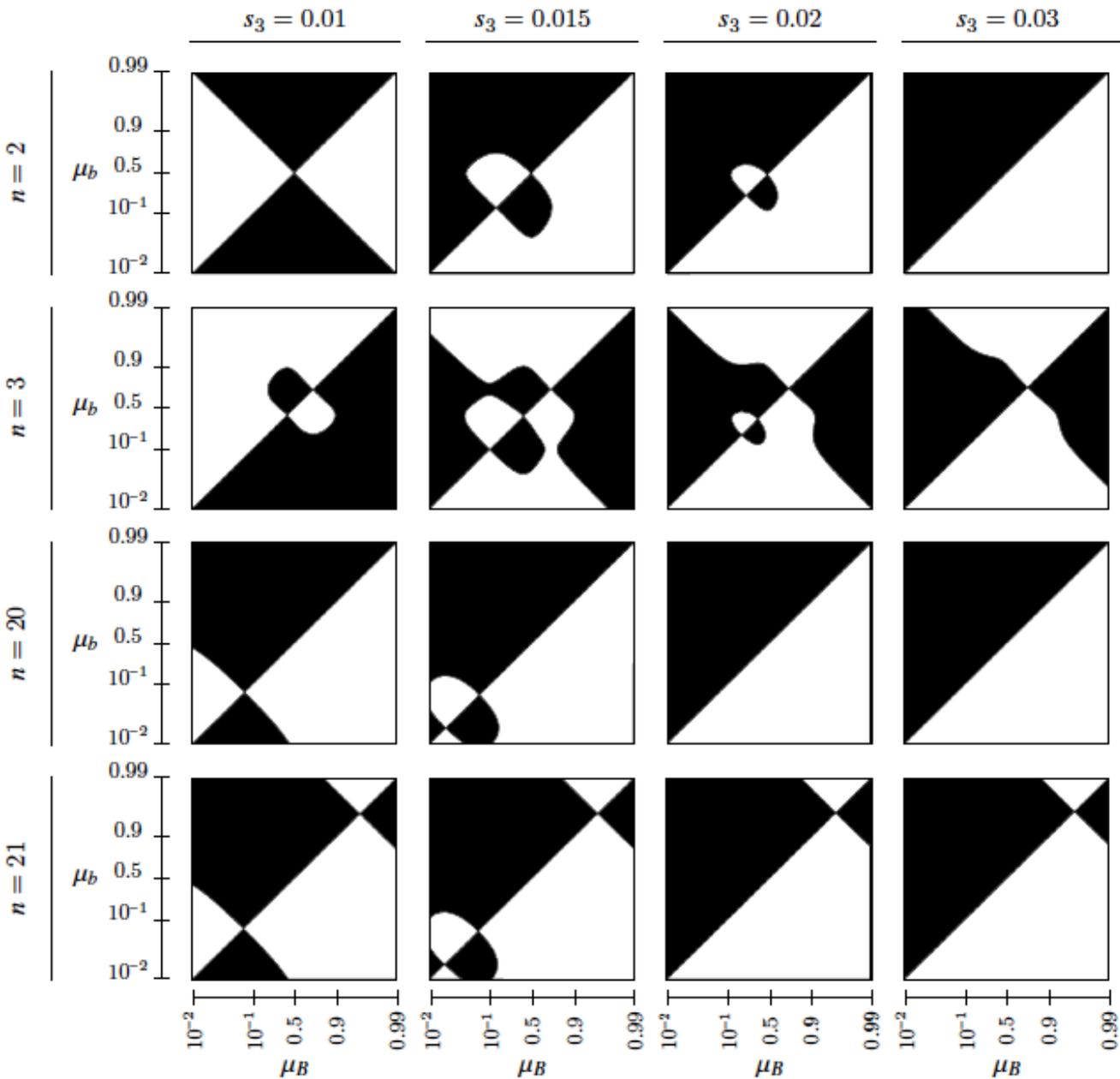


Figure 2: Pairwise invasibility plots for mutation rate modifier. Combinations of resident mutation rate μ_B and invading mutation rate μ_b in the white regions yield a leading eigenvalue greater than one in absolute magnitude; the leading eigenvalue is less than one in the black regions. We assume that $w_1 = 1 - s_1$ and $w_3 = 1 - s_3$ and set $s_1 = 0.01$. Each row denotes a different value for n , the number of generations in each environment. The recombination rate is set to $r = 0$. Note that the x- and y-axis are logarithmically scaled from 10^{-2} to 0.5 and from $1 - 10^{-2}$ to $1 - 0.5$.

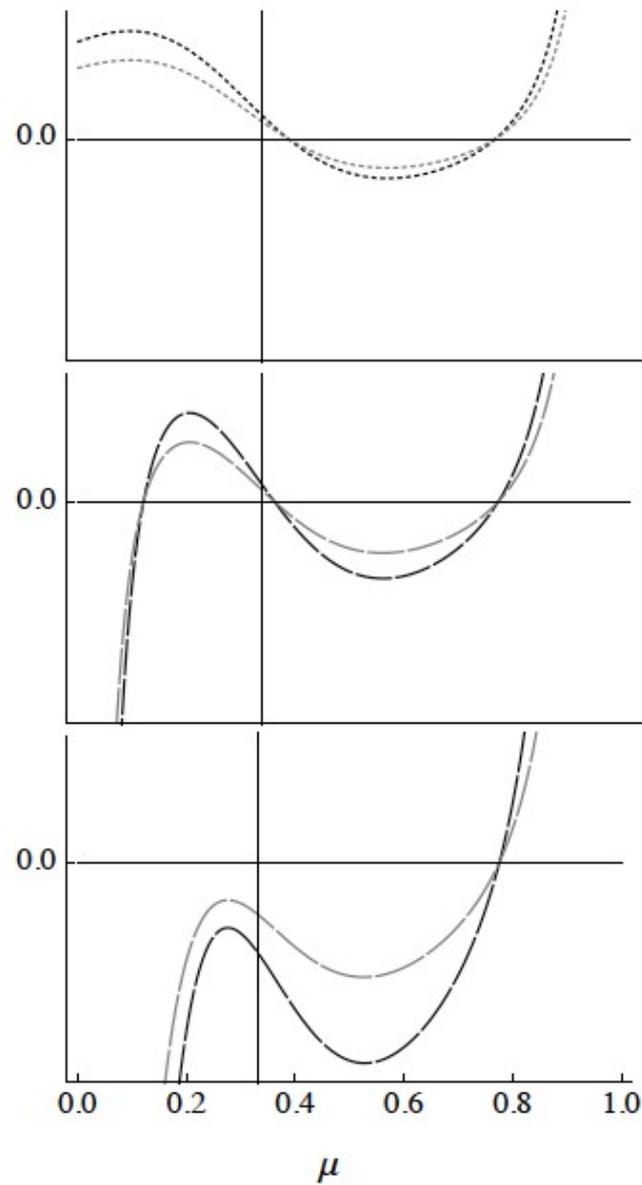


Figure 1: Comparison of $\frac{\partial \lambda_1}{\partial \mu_m}$ evaluated at $\mu_m = \mu_M$ (black curves) and $\frac{\partial w^*}{\partial \mu_M}$ (gray curves) for $n = 3$. In all plots, $s_1 = 10^{-1}$ whereas $s_3 = 10^{-1}$, $10^{-0.8}$, and $10^{-0.6}$, in the top, middle, and bottom plots respectively. The vertical line is located at $\mu = 1/n = 1/3$

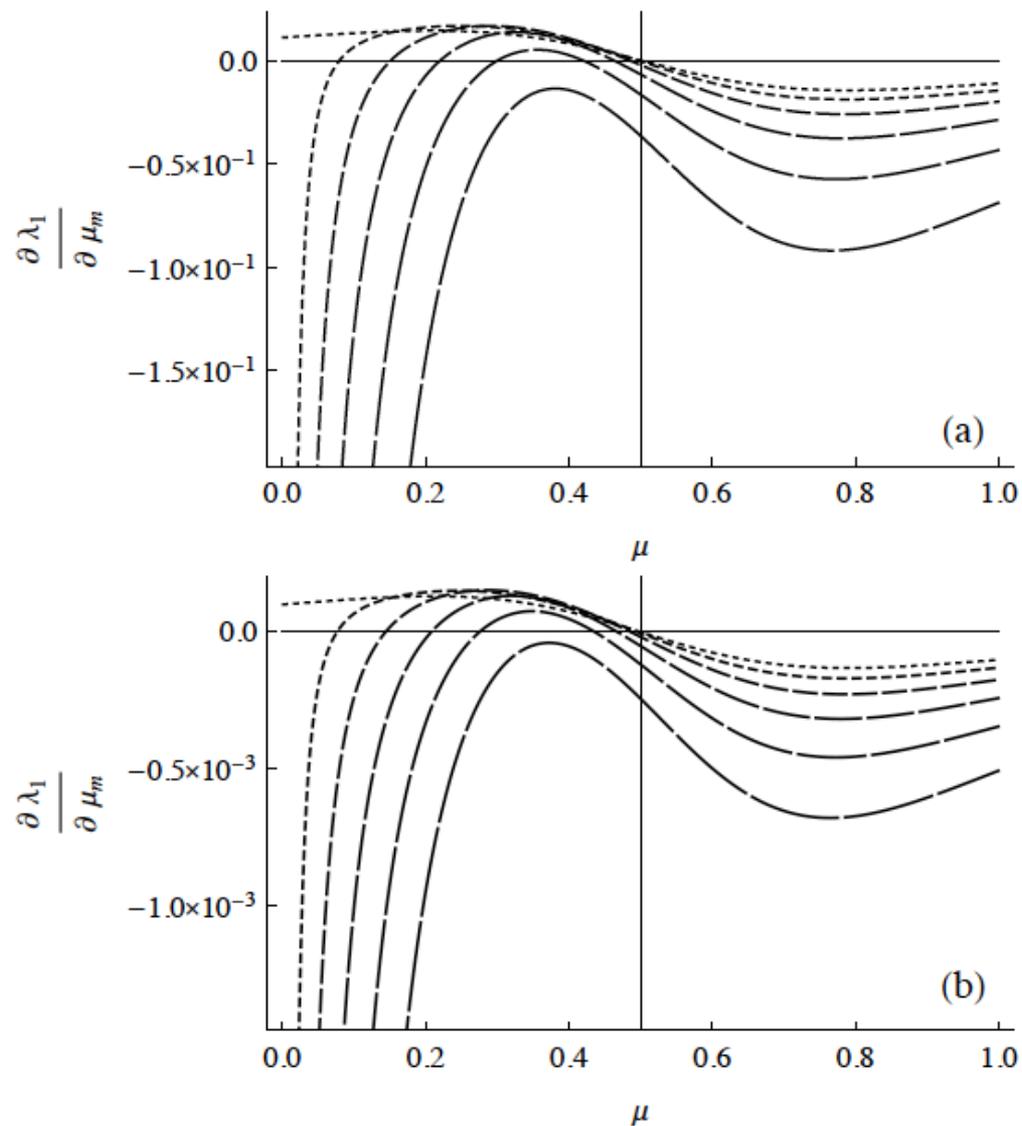


Figure 2: Plot of the derivative of the leading eigenvalue, λ_1 , with respect to μ_m evaluated at $\mu_M = \mu_m = \mu$ when $n = 2$ and $r = 0$. In (a), $s_1 = 1 - w_1 = 10^{-1}$ and the lines from shortest dashes to longest dashes are $s_3 = 1 - w_3 = 10^{-1}, 10^{-0.9}, 10^{-0.8}, 10^{-0.7}, 10^{-0.6}$, and $10^{-0.5}$. In (b), $s_1 = 0.01$ and the lines from shortest dashes to longest dashes are $s_3 = 10^{-2}, 10^{-1.9}, 10^{-1.8}, 10^{-1.7}, 10^{-1.6}$, and $10^{-1.5}$. The vertical line is located at $\mu = 1/n = 1/2$.

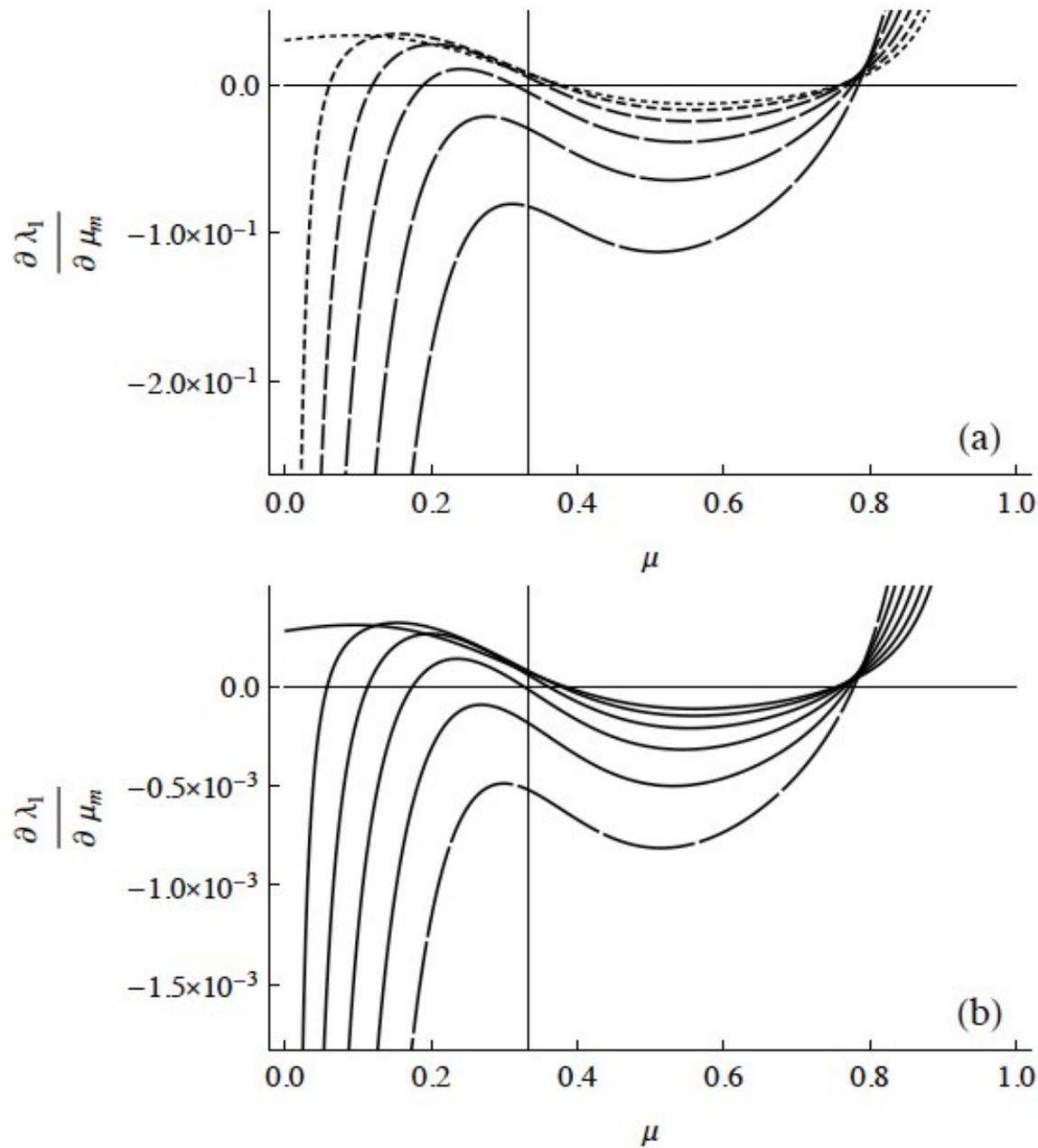


Figure 3: Same as Figure 2 except $n = 3$. The vertical line is located at $\mu = 1/n = 1/3$

Temporal and Spatial Fluctuations in Selection

General framework:

deme		E_x					E_y			
genotype		AB	Ab	aB	ab		AB	Ab	aB	ab
fitness		w_{x_1}	w_{x_2}	w_{x_3}	w_{x_4}		w_{y_1}	w_{y_2}	w_{y_3}	w_{y_4}
frequency		x_1	x_2	x_3	x_4		y_1	y_2	y_3	y_4

$$w_{x_1} = w_{x_2}, w_{y_1} = w_{y_2}, w_{x_3} = w_{x_4}, w_{y_3} = w_{y_4}$$

Next generation \underline{x}' , \underline{y}' : m is migration rate (both ways)

$$\begin{aligned} x'_1 &= (1 - m)\tilde{x}_1 + m\tilde{y}_1 & y'_1 &= (1 - m)\tilde{y}_1 + m\tilde{x}_1 \\ x'_2 &= (1 - m)\tilde{x}_2 + m\tilde{y}_2 & y'_2 &= (1 - m)\tilde{y}_2 + m\tilde{x}_2 \\ x'_3 &= (1 - m)\tilde{x}_3 + m\tilde{y}_3 & y'_3 &= (1 - m)\tilde{y}_3 + m\tilde{x}_3 \\ x'_4 &= (1 - m)\tilde{x}_4 + m\tilde{y}_4 & y'_4 &= (1 - m)\tilde{y}_4 + m\tilde{x}_4, \end{aligned}$$

$$\begin{aligned} w_x \tilde{x}_1 &= (1 - \mu_B) w_{x_1} (x_1 - rD_x) + \mu_B w_{x_3} (x_3 + rD_x) \\ w_x \tilde{x}_2 &= (1 - \mu_b) w_{x_2} (x_2 + rD_x) + \mu_b w_{x_4} (x_4 - rD_x) \\ w_x \tilde{x}_3 &= (1 - \mu_B) w_{x_3} (x_3 + rD_x) + \mu_B w_{x_1} (x_1 - rD_x) \\ w_x \tilde{x}_4 &= (1 - \mu_b) w_{x_4} (x_4 - rD_x) + \mu_b w_{x_2} (x_2 + rD_x) \end{aligned}$$

$$\begin{aligned} w_y \tilde{y}_1 &= (1 - \mu_B) w_{y_1} (y_1 - rD_y) + \mu_B w_{y_3} (y_3 + rD_y) \\ w_y \tilde{y}_2 &= (1 - \mu_b) w_{y_2} (y_2 + rD_y) + \mu_b w_{y_4} (y_4 - rD_y) \\ w_y \tilde{y}_3 &= (1 - \mu_B) w_{y_3} (y_3 + rD_y) + \mu_B w_{y_1} (y_1 - rD_y) \\ w_y \tilde{y}_4 &= (1 - \mu_b) w_{y_4} (y_4 - rD_y) + \mu_b w_{y_2} (y_2 + rD_y), \end{aligned}$$

$$D_x = x_1 x_4 - x_2 x_3, \quad D_y = y_1 y_4 - y_2 y_3, \quad w_x = \sum_{i=1}^4 w_{x_i} x_i, \quad w_y = \sum_{i=1}^4 w_{y_i} y_i.$$

Symmetric Selection

		E_x					E_y			
		<i>AB</i>								
<i>fitness</i>		$1 + s$	$1 + s$	1	1	1	1	$1 + s$	$1 + s$	

When $x_2 = x_4 = y_2 = y_4 = 0$, B is fixed and there is a “symmetric” equilibrium.

Result

1. On the boundary, where only allele B is present, there is a unique “symmetric equilibrium” $(\mathbf{x}^*, \mathbf{y}^*)$ with

$$\mathbf{x}^* = (x^*, 0, 1 - x^*, 0), \quad \mathbf{y}^* = (1 - x^*, 0, x^*, 0),$$

where \mathbf{x}^* is the unique positive root of the quadratic equation

$$Q(x) = sx^2 + [(s + 2)(m + \mu_B - 2m\mu_B) - s]x - (m + \mu_B - 2m\mu_B) = 0.$$

2. $(\mathbf{x}^*, \mathbf{y}^*)$ is internally stable on the boundary with only B present.
3. If $0 < m, \mu_B < \frac{1}{2}$, then $\mathbf{x}^* > \frac{1}{2}$.

An “asymmetric” equilibrium may exist:

$$(\hat{x}, 0, 1 - \hat{x}, 0)(\hat{y}, 0, 1 - \hat{y}, 0),$$

which is near $(1, 0, 0, 0) (1, 0, 0, 0)$ when μ_B is small.

$$\mathbf{L}_{\text{ex}} = \begin{pmatrix} (1-m)A & (1-m)B & mC & mD \\ (1-m)D & (1-m)C & mB & mA \\ mA & mB & (1-m)C & (1-m)D \\ mD & mC & (1-m)B & (1-m)A \end{pmatrix}$$

$A, B, C, D > 0$; all functions of s, r, μ_b, μ_B .

Similarity Transformation

Write

$$\mathbf{P} = \begin{bmatrix} 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

Then

$$\mathbf{P}\mathbf{L}_{\text{ex}}\mathbf{P}^{-1} = \begin{pmatrix} \mathbf{M} & \mathbf{0} \\ * & \mathbf{N} \end{pmatrix}.$$

Hence stability is determined by two quadratics.

No Temporal Fluctuation

Result. When $0 < m, \mu_B, \mu_b < 1/2$, the symmetric equilibrium $(\mathbf{x}^*, \mathbf{y}^*)$ is externally stable to the introduction of the new modifier allele b if $\mu_b > \mu_B$ and is unstable if $\mu_b < \mu_B$. Therefore, the reduction principle holds and zero is the only uninvadable switching rate.

Periodic Fluctuating Selection

	E_x		E_y	
	A	a	A	a
Type 1 selection:	$1 + s$	1	1	$1 + s$
Type 2 selection:	1	$1 + s$	$1 + s$	1

In general, k rounds of type 1 selection followed by ℓ rounds of type 2 selection. Simplest case $k = \ell = 1$.

Result. When $0 < m, \mu_B < 1$ and $s > 0$, a unique symmetric equilibrium (\bar{x}, \bar{y}) exists such that

$$\bar{x} = (\bar{x}, 0, 1 - \bar{x}, 0), \quad \bar{y} = (1 - \bar{x}, 0, \bar{x}, 0).$$

\bar{x} is the unique positive root of $R(x) = 0$, where

$$R(x) = sx^2 + [2 - m_B(s + 2)]x - (1 - m_B),$$

with $m_B = m + \mu_B - 2m\mu_B$. If, in addition, $0 < m, \mu_B < \frac{1}{2}$, then $0 < \bar{x} < \frac{1}{2}$.

Stability (invasion of b) is determined by $L_{\text{ex}} = L_{\text{ex}}^2 L_{\text{ex}}^1$.

Result. The internally stable unique symmetric equilibrium (\bar{x}, \bar{y}) , in the case of selection fluctuating with period 2, is externally stable when $\mu_B > \mu_b$ and is unstable when $\mu_B < \mu_b$, for all $0 \leq r \leq 1$ and $0 < m < \frac{1}{2}$. Thus, in this case, higher switching rates are favored, and the evolutionarily stable mutation rate is 1.

Result. The mean fitness at the symmetric equilibrium is

- i. a decreasing function of μ_B in a constant environment,
- ii. an increasing function of μ_B in a period 2 cycling environment.

Result. In the period 4 symmetric case, if $r = 0$, the mean fitness $\bar{w} = \bar{w}(m_B)$ achieves a maximum at $m_B = \frac{1}{2}$.

Result. In the period 4 symmetric case with $0 \leq r \leq 1$ and for all migration rates, the mutation rate $\mu_B = \frac{1}{2}$ cannot be invaded by mutation rates either smaller or larger than $\frac{1}{2}$. Thus, $\mu_B = \frac{1}{2}$ is the stable mutation rate.

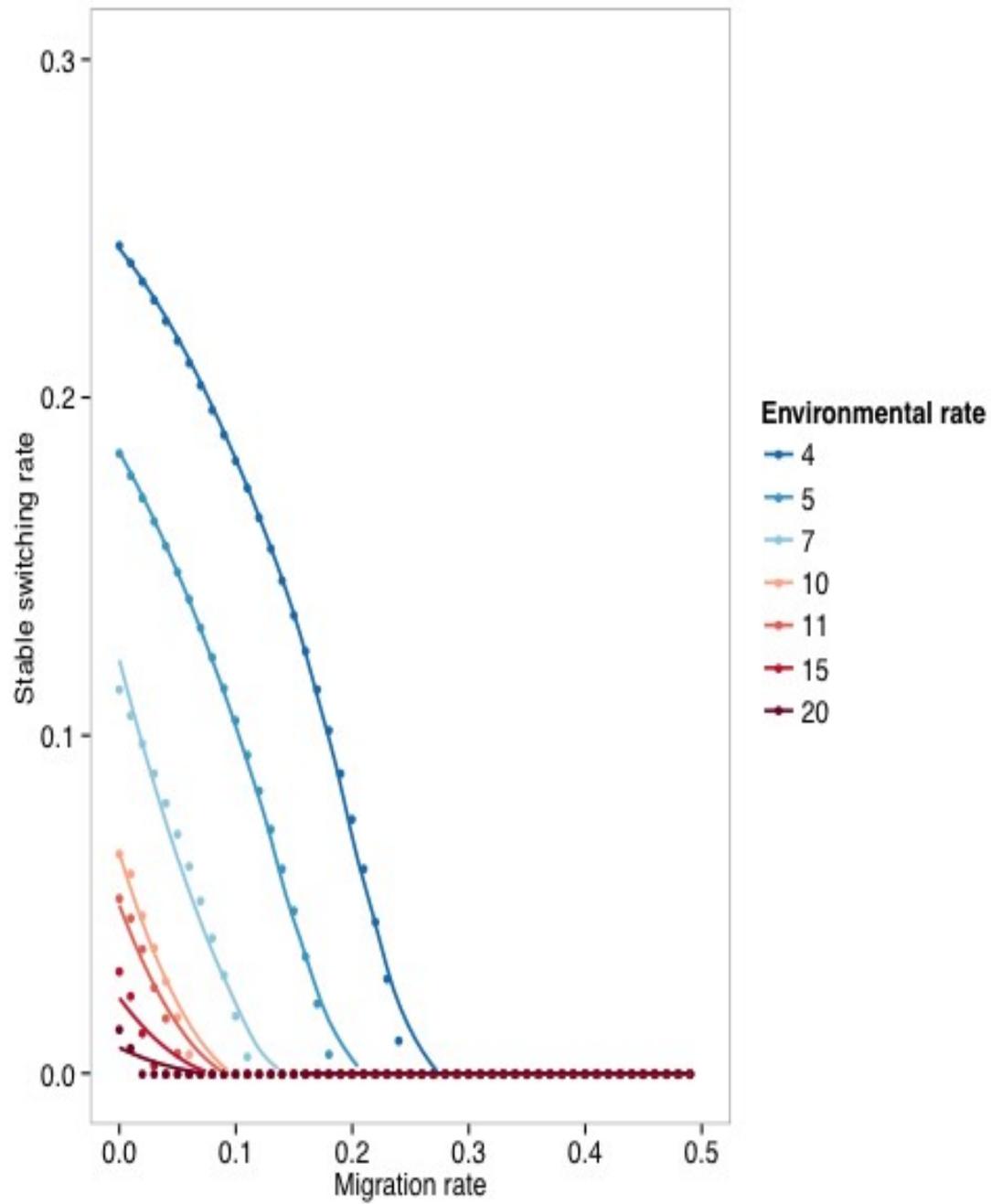
Note:

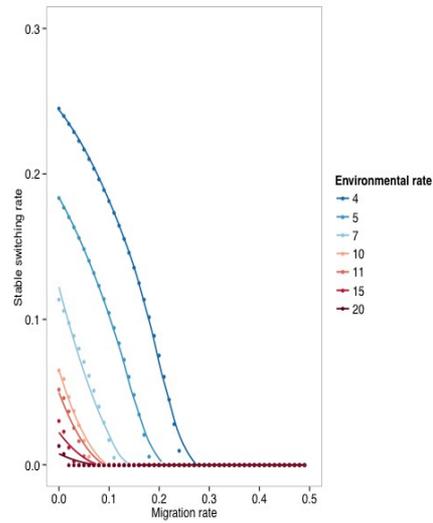
$$L_{\text{ex}} = \underbrace{L_{\text{ex}}^2 L_{\text{ex}}^2 \cdots L_{\text{ex}}^2}_k \underbrace{L_{\text{ex}}^1 L_{\text{ex}}^1 \cdots L_{\text{ex}}^1}_\ell$$

is strictly positive and of the form

$$\begin{pmatrix} a & e & h & d \\ b & f & g & c \\ c & g & f & b \\ d & h & e & a \end{pmatrix}.$$

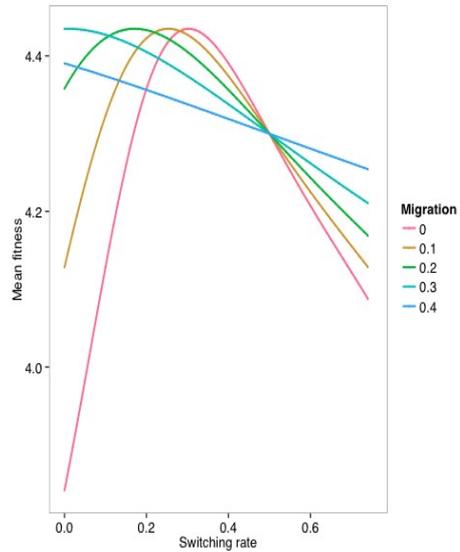
Hence two quadratics for stability,
but they can be very, very messy.





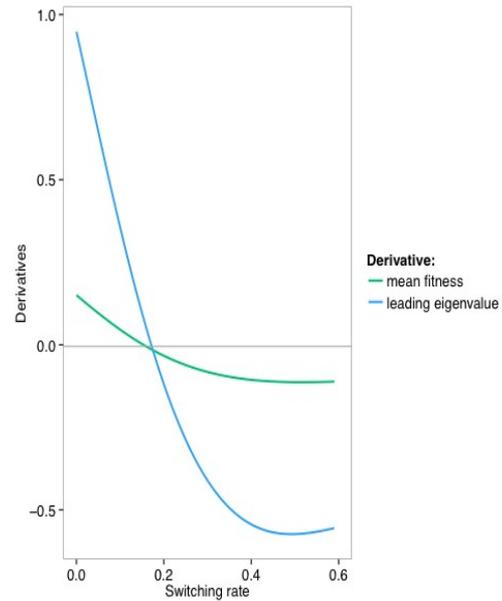
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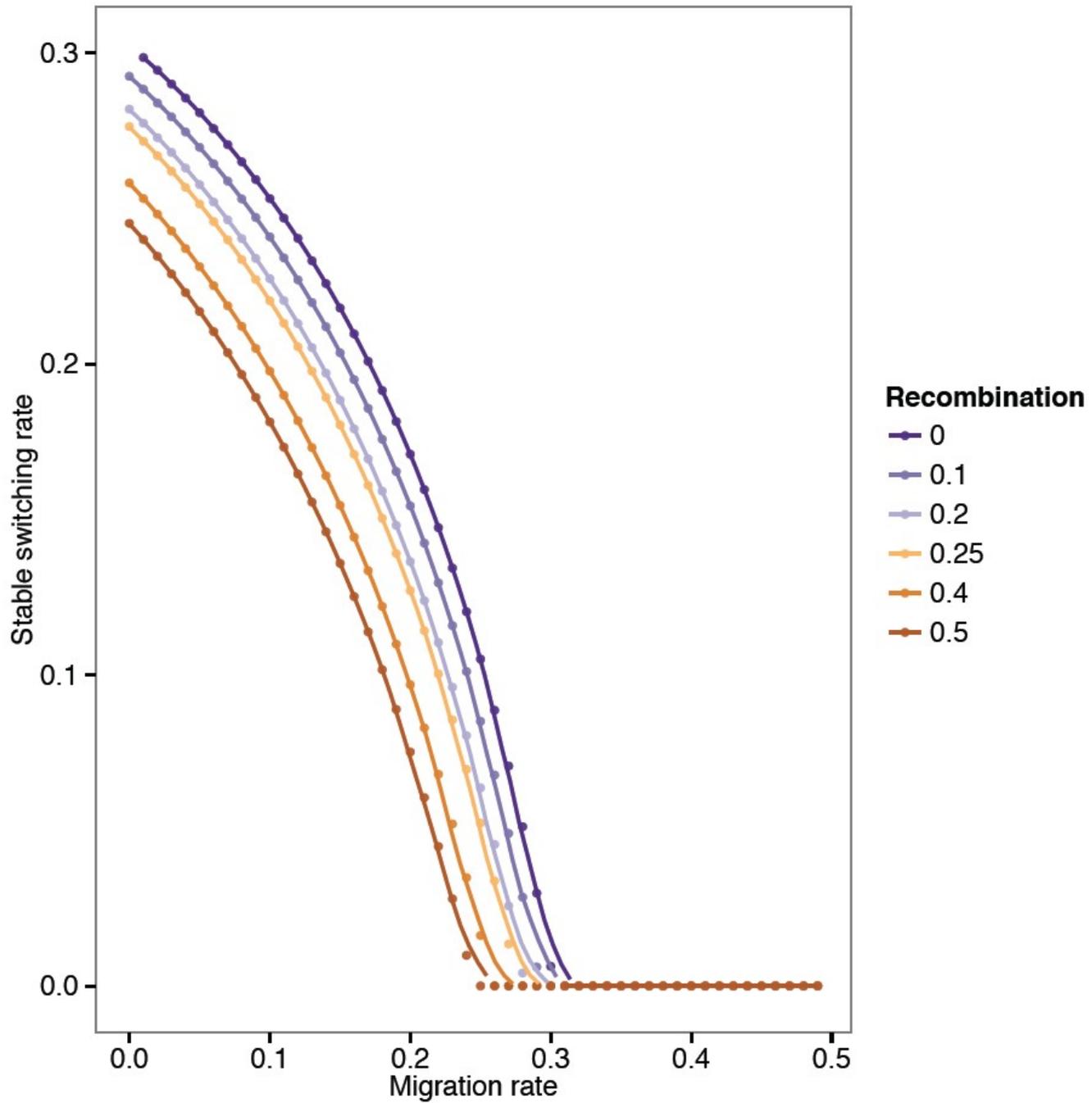
maximum mean fitness

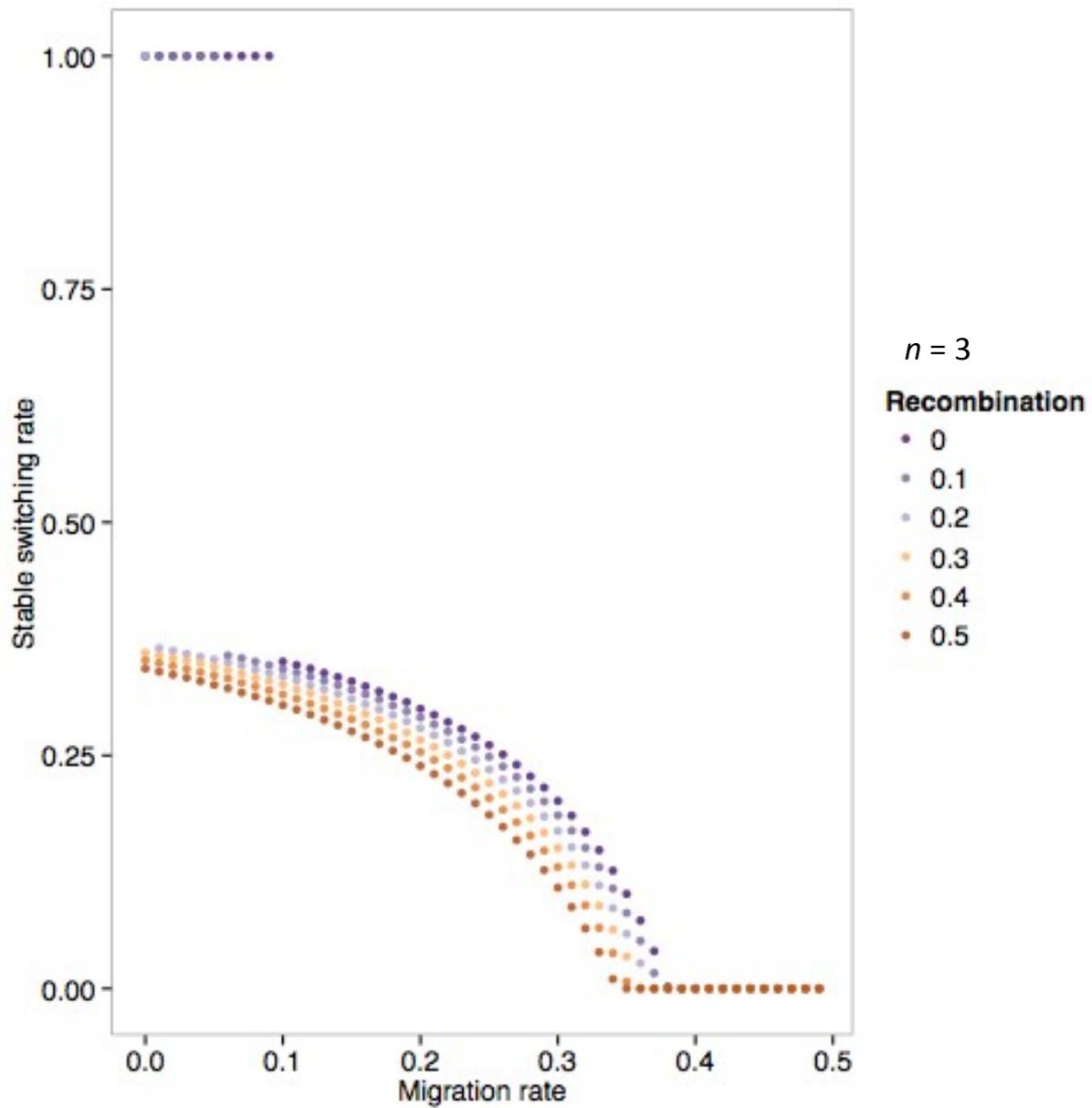


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stability







- Uri Liberman
- Marcel Salathé
- Jeremy Van Cleve
- Oana Carja