

# **Mathematics and Computation in Phenotypic Switching**

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# Biological Motivation

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

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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<sup>1\*</sup> and Richard Losick<sup>2,3\*</sup>  
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<sup>3</sup>The Miller Institute, The University of California,  
Berkeley, CA 94720, USA.

## 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, 1967*

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

## Predicting stochastic gene expression dynamics in single cells

Jerome T. Mettetal<sup>\*†</sup>, Dale Muzzey<sup>\*‡</sup>, Juan M. Pedraza<sup>\*</sup>, Ertugrul M. Ozbudak<sup>\*</sup>, and Alexander van Oudenaarden<sup>\*§</sup>

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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

Nathalie Q. Balaban,<sup>1,2\*</sup> Jack Merrin,<sup>1</sup> Remy Chait,<sup>1</sup>  
Lukasz Kowalik,<sup>1</sup> Stanislas Leibler<sup>1</sup>

# Stochastic switching: evolutionary bet-hedging mechanism

Stochastic switching as a survival strategy in fluctuating environments

Murat Acar<sup>1,2</sup>, Jerome T Mettetal<sup>1,2</sup> & Alexander van Oudenaarden<sup>1</sup>

## 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

Bernadett Gaál,<sup>\*,†</sup> Jonathan W. Pitchford<sup>‡,§,¶</sup> and A. Jamie Wood<sup>†,§,¶,||</sup>

## 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  $\mu_B$

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

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

Recombination:  $AB/ab \rightarrow AB \quad Ab \quad aB \quad ab$   
 $r/2 \quad (1-r)/2 \quad (1-r)/2 \quad r/2$

**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

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

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

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

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

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

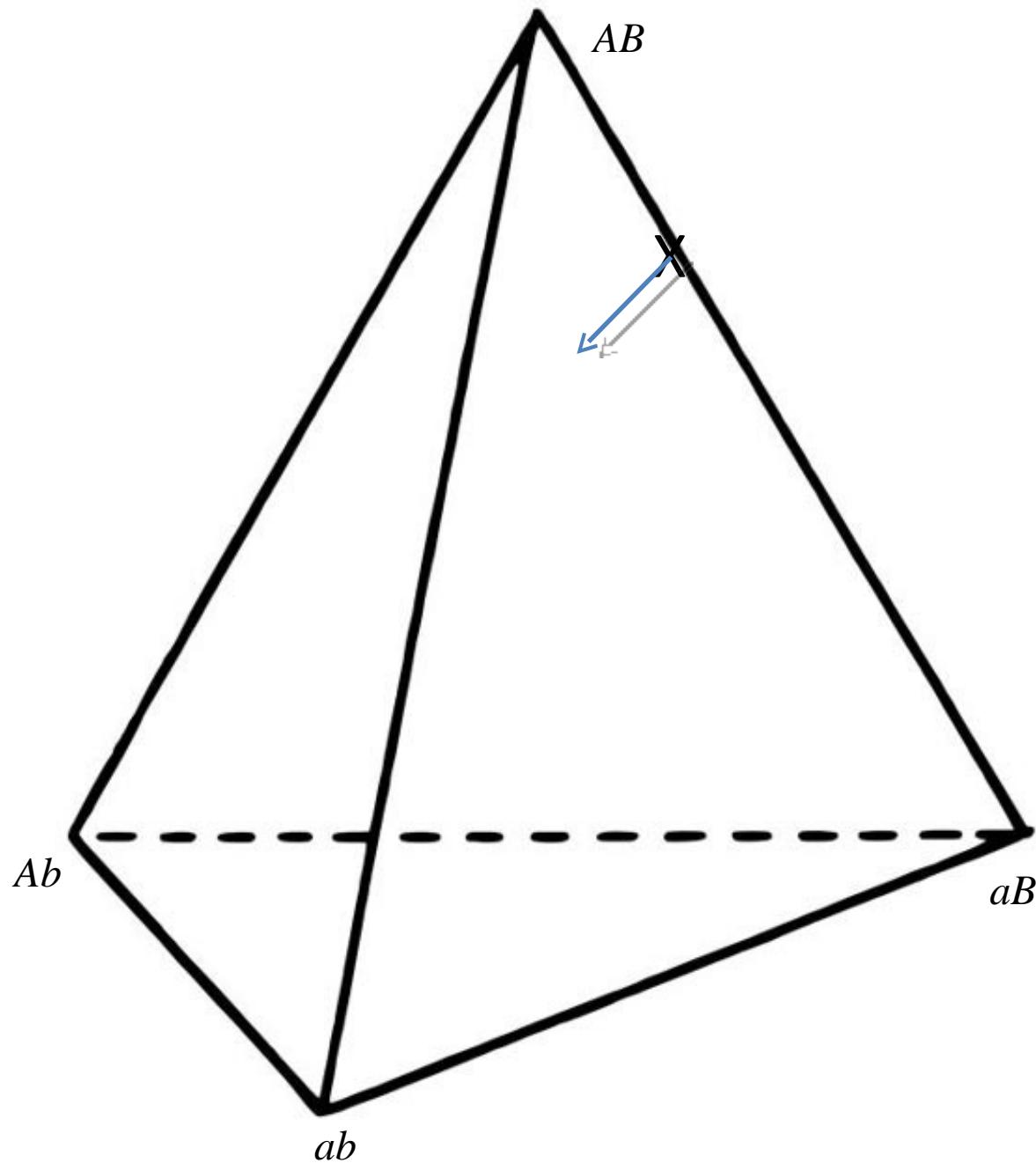
Since  $B/b$  is neutral,  $w_1 = w_2$ ,  $w_3 = w_4$ ,  $w = \sum w_i x_i$ .

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 $b$

$$\begin{aligned} w^*x'_2 &= (1 - \mu_b)w_2(x_2 + rD^*) + \mu_bw_4(x_4 - rD^*) \\ w^*x'_4 &= (1 - \mu_b)w_4(x_4 - rD^*) + \mu_bw_2(x_2 + rD^*), \end{aligned} \tag{1.16}$$

where

$$w^* = w_1x_1^* + w_3x_3^*, \quad D^* = x_1^*x_4 - x_3^*x_2. \tag{1.17}$$

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

$$\frac{1}{w^*} \begin{bmatrix} (1 - \mu_b)w_2 - r[(1 - \mu_b)w_2 - \mu_bw_4]x_3^* & \mu_bw_4 + r[(1 - \mu_b)w_2 - \mu_bw_4]x_1^* \\ \mu_bw_2 + r[(1 - \mu_b)w_4 - \mu_bw_2]x_3^* & (1 - \mu_b)w_4 - r[(1 - \mu_b)w_4 - \mu_bw_2]x_1^* \end{bmatrix}. \tag{1.18}$$

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

# Phenotypic Evolution in Fluctuating Environments

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

gamete:	$AB$	$Ab$	$aB$	$ab$	(2.1)
fitness:	$w_1^i$	$w_2^i$	$w_3^i$	$w_4^i$	

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

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

$\mathcal{L}^* = \mathcal{L}_k \cdot \mathcal{L}_{k-1} \cdot \dots \cdot \mathcal{L}_1$  has the form

$$\mathcal{L}^* = \begin{bmatrix} & 1 & 3 & 2 & 4 \\ \mathcal{L}_{\text{in}} & * & * & & \\ & * & * & & \\ 0 & 0 & & & \\ 0 & 0 & \mathcal{L}_{\text{ex}} & & \end{bmatrix} \begin{matrix} 1 \\ 3 \\ 2 \\ 4 \end{matrix}. \quad (2.20)$$

The eigenvalues of  $\mathcal{L}$  are therefore those of  $\mathcal{L}_{\text{in}}$  and  $\mathcal{L}_{\text{ex}}$ , where  $\mathcal{L}_{\text{in}}$  determines the internal stability of  $\underline{x}^*$ , confined to the boundary with only  $B$  present. As  $\underline{x}^*$  is stable there, these eigenvalues are less than one in magnitude.  $\mathcal{L}_{\text{ex}}$  in the linear approximation of  $T$  near  $\underline{x}^*$  (the equilibrium with  $B$  fixed) involving only the gametes  $AB, aB$ . Moreover

$$\mathcal{L}_{\text{ex}} = \mathcal{L}_k^{\text{ex}} \cdot \mathcal{L}_{k-1}^{\text{ex}} \cdot \dots \cdot \mathcal{L}_1^{\text{ex}}, \quad (2.21)$$

where  $\mathcal{L}_i^{\text{ex}}$ , for  $i = 1, 2, \dots, k$  is the submatrix of  $\mathcal{L}_i$  with only the  $b$  allele present.

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  $b$  if  $\mu_B > \mu_b$  and locally unstable when  $\mu_b > \mu_B$  for all  $0 \leq r < 1$ .

**Result.** The mean fitness is an increasing function of  $\mu_B$ .

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

	$AB$	$Ab$	$aB$	$ab$
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  $\mu_B = \frac{1}{2}$ .
- ii. The mutation rate  $\mu_B = \frac{1}{2}$  cannot be invaded by any allele  $b$  that gives  $\mu_b < \frac{1}{2}$  or  $\mu_b > \frac{1}{2}$ .
- 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  $\mu_M$  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

	$AB$	$Ab$	$aB$	$ab$
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Environment 1:  $w_1 = 1 - s_1$     $w_2 = 1 - s_1$     $w_3 = 1$     $w_3 = 1$

Environment 2:  $\widehat{w}_1 = 1$     $w_1 = 1$     $w_3 = 1 - s_3$     $w_3 = 1 - s_3$

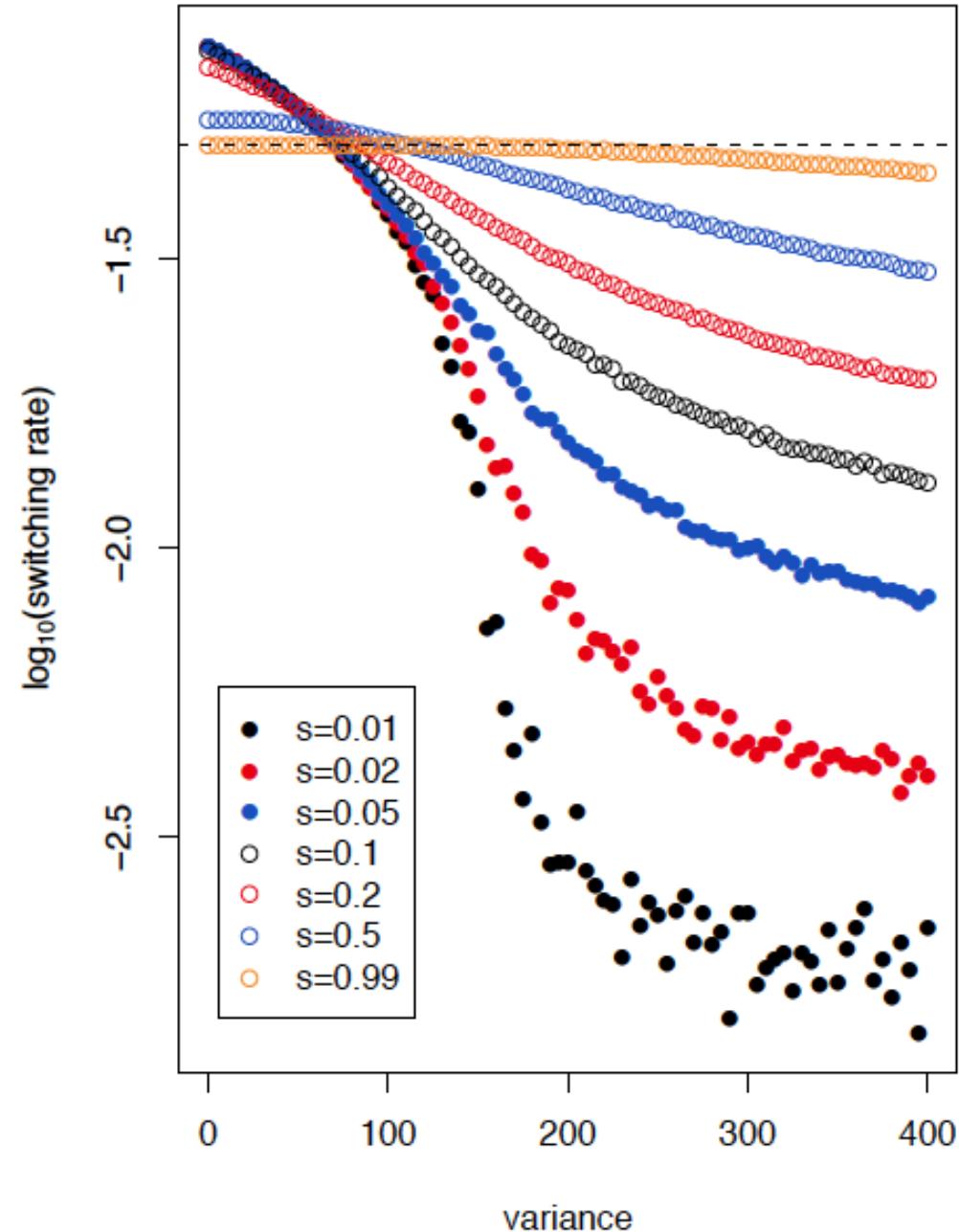
Selection due to  $A/a$ ; mutation controlled by  $B/b$

Each environment lasts  $N$  generations.

Three “natural” cases:

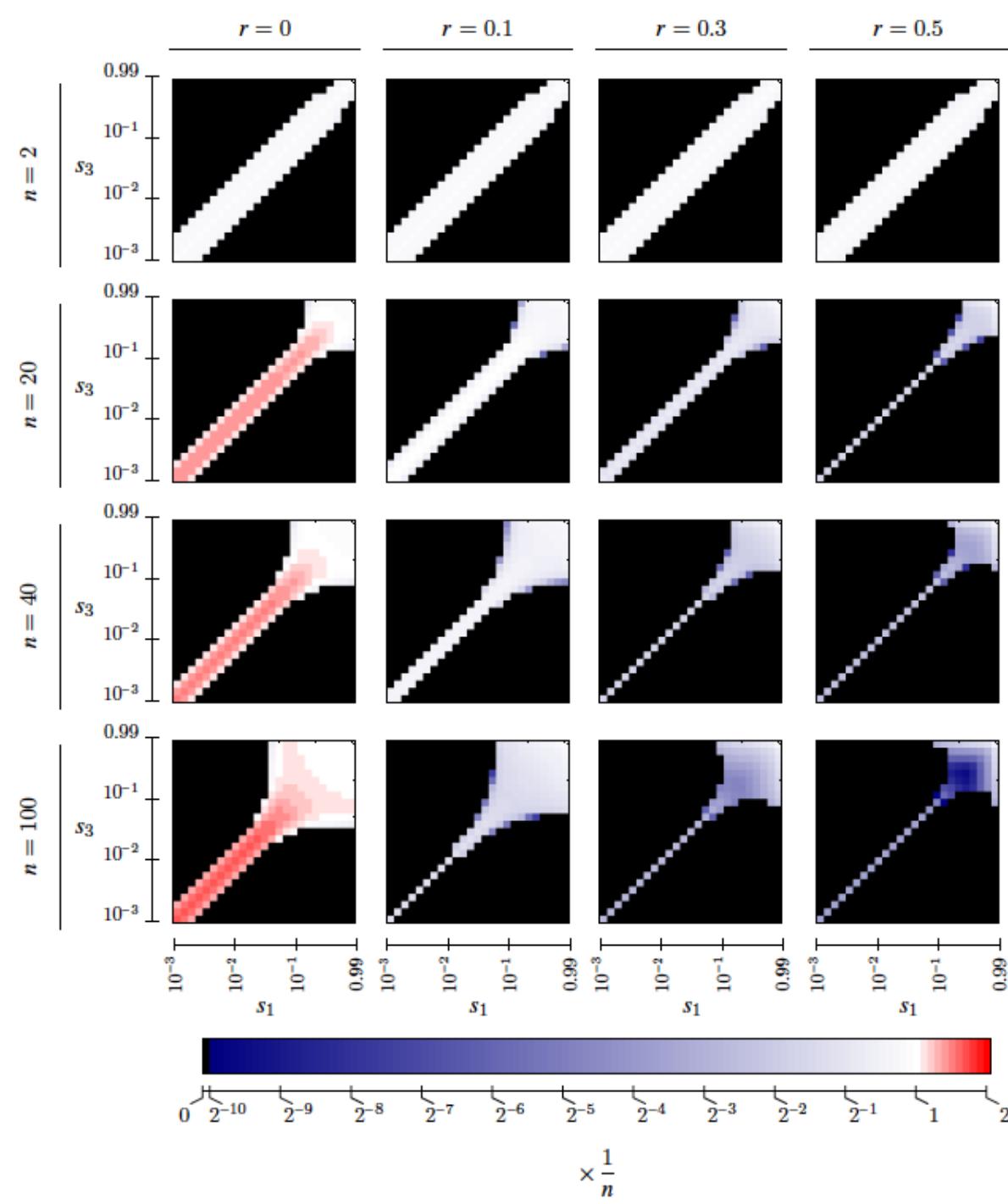
1.  $N \sim \text{gamma}(\alpha, \beta)$ :  $E(N) = n = \alpha\beta$ ,  $\text{Var}(N) = \alpha\beta^2$ ;
2.  $N$  fixed (periodic selection);
3.  $N$  exponential ( $\alpha = 1$ ): change at rate  $1/n$  each generation.

What is the stable mutation (switching) rate?

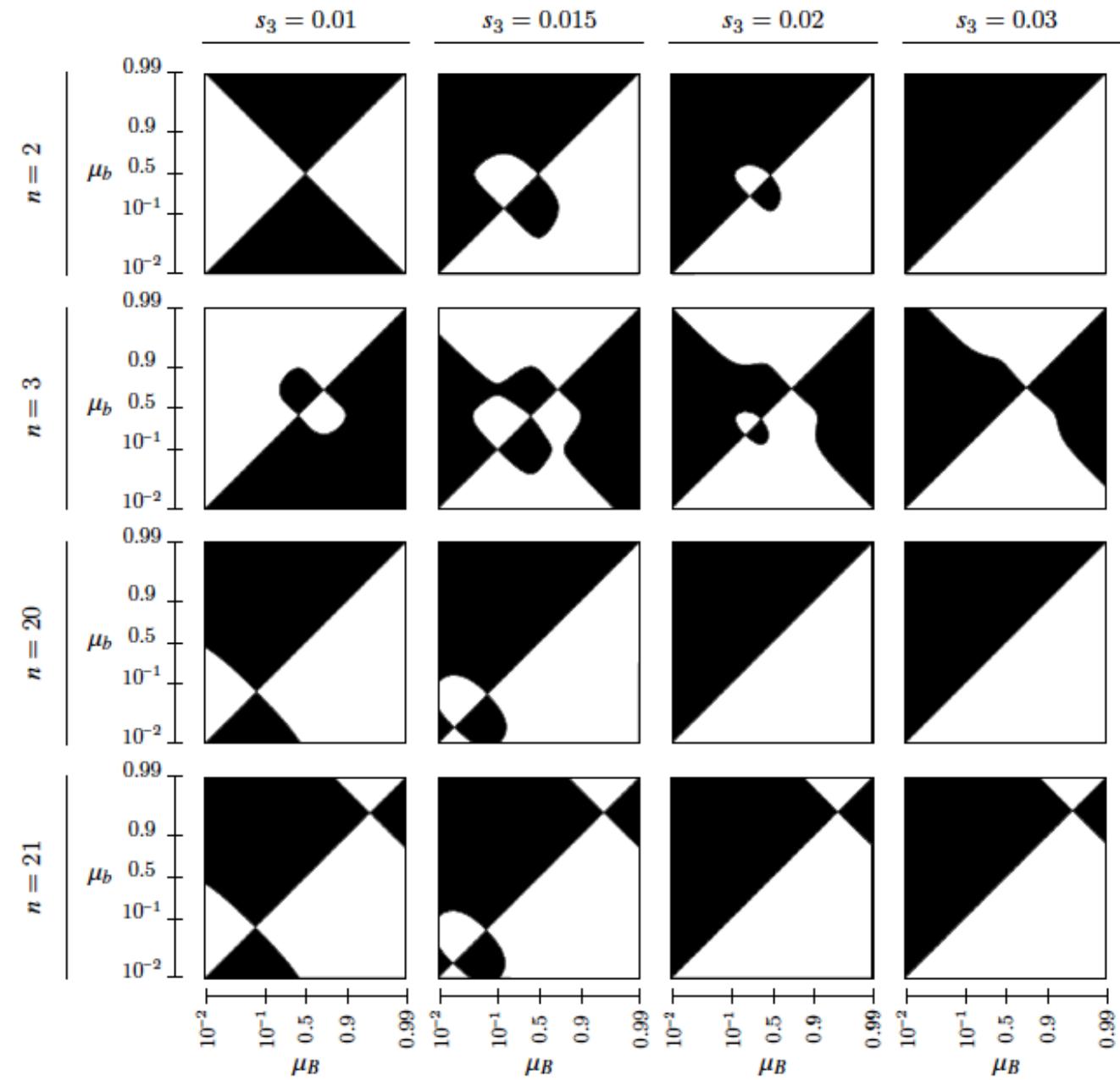


Evolution of stochastic switching rates in symmetric fitness landscapes, i.e.,  $s = s_0 = s_1$ . The  $\log_{10}$  evolutionary stable switching rate on the x-axis depends both on the fitness cost of being maladapted in both environments ( $s$ ) and the variance of the distribution of waiting times. 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  $\mu_B$  and invading mutation rate  $\mu_b$  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  $1 - 0:5$ .

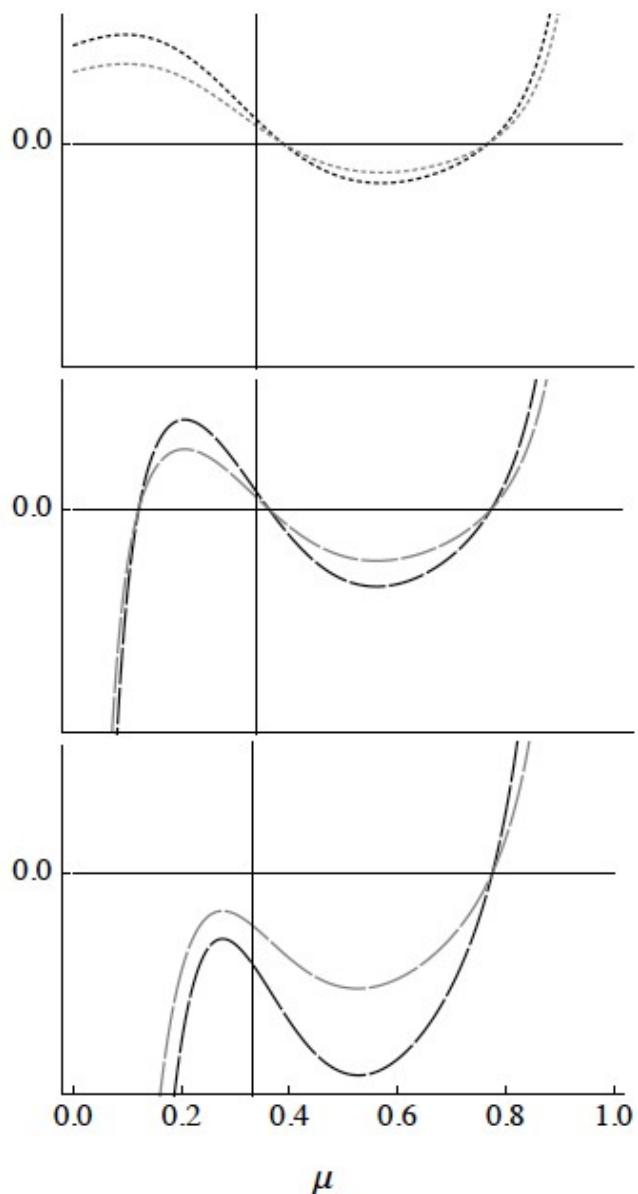


Figure 1: Comparison of  $\frac{\partial \lambda_1}{\partial \mu_m}$  evaluated at  $\mu_m = \mu_M$  (black curves) and  $\frac{\partial w^*}{\partial \mu_M}$  (gray curves) for  $n = 3$ . In all plots,  $s_1 = 10^{-1}$  whereas  $s_3 = 10^{-1}, 10^{-0.8},$  and  $10^{-0.6},$  in the top, middle, and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

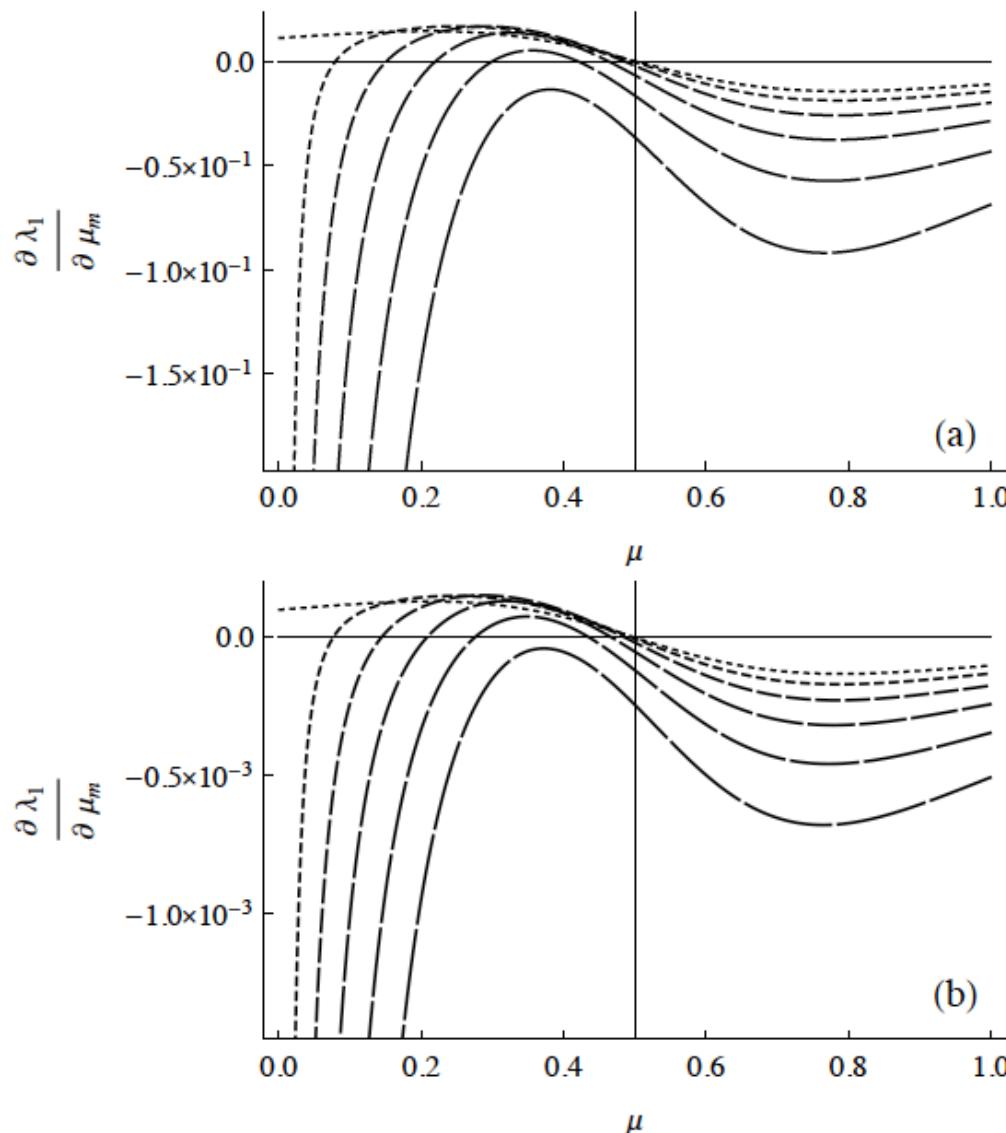


Figure 2: Plot of the derivative of the leading eigenvalue,  $\lambda_1$ , with respect to  $\mu_m$  evaluated at  $\mu_M = \mu_m = \mu$  when  $n = 2$  and  $r = 0$ . In (a),  $s_1 = 1 - w_1 = 10^{-1}$  and the lines from shortest dashes to longest dashes are  $s_3 = 1 - w_3 = 10^{-1}, 10^{-0.9}, 10^{-0.8}, 10^{-0.7}, 10^{-0.6},$  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  $\mu = 1/n = 1/2$ .

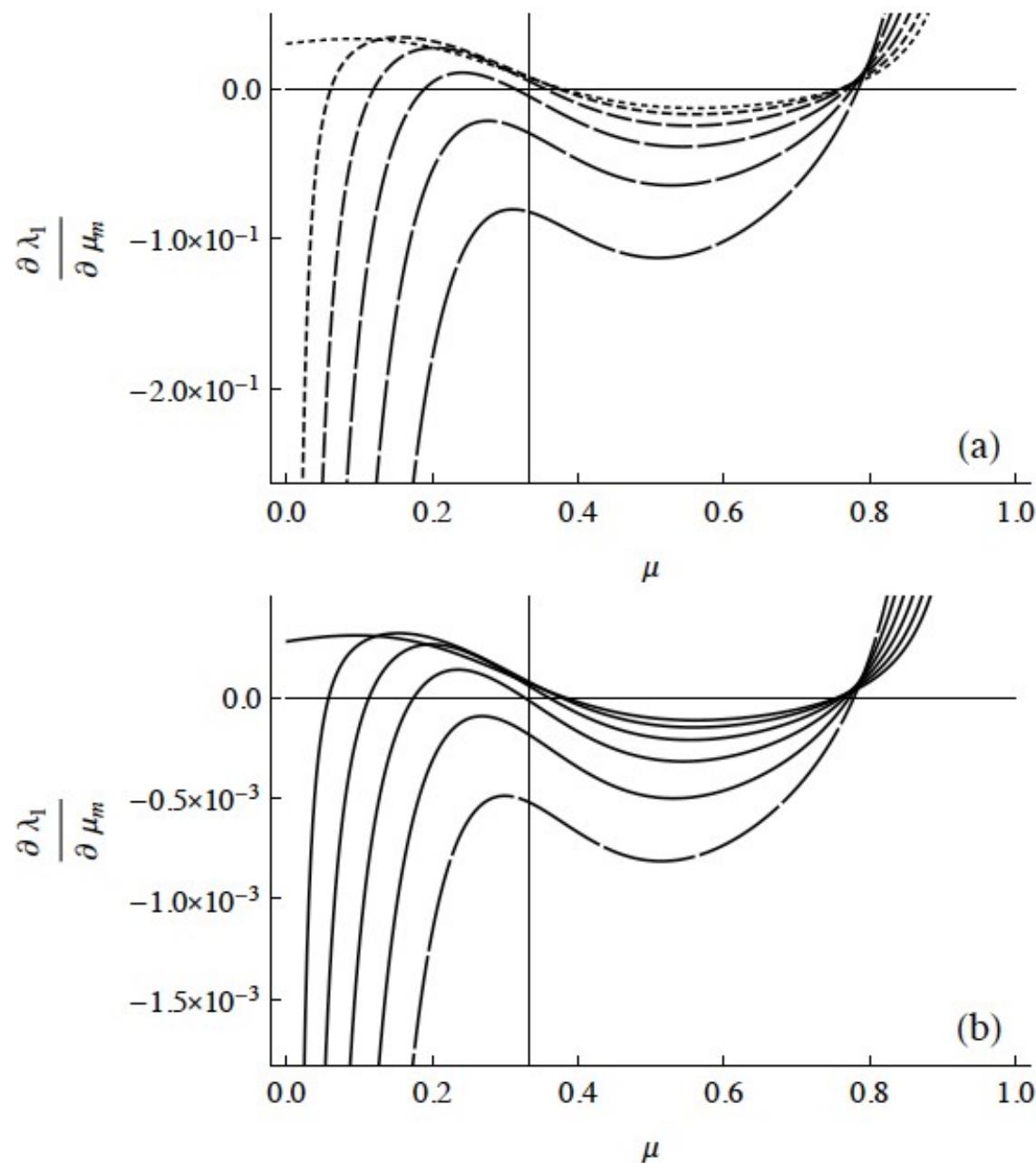


Figure 3: Same as Figure 2 except  $n = 3$ . The vertical line is located at  $\mu = 1/n = 1/3$

# Temporal and Spatial Fluctuations in Selection

General framework:

deme	$E_x$				$E_y$			
genotype	$AB$							
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)

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

$$w_x \tilde{x}_1 = (1 - \mu_B) w_{x_1} (x_1 - rD_x) + \mu_B w_{x_3} (x_3 + rD_x)$$

$$w_x \tilde{x}_2 = (1 - \mu_b) w_{x_2} (x_2 + rD_x) + \mu_b w_{x_4} (x_4 - rD_x)$$

$$w_x \tilde{x}_3 = (1 - \mu_B) w_{x_3} (x_3 + rD_x) + \mu_B w_{x_1} (x_1 - rD_x)$$

$$w_x \tilde{x}_4 = (1 - \mu_b) w_{x_4} (x_4 - rD_x) + \mu_b w_{x_2} (x_2 + rD_x)$$

$$w_y \tilde{y}_1 = (1 - \mu_B) w_{y_1} (y_1 - rD_y) + \mu_B w_{y_3} (y_3 + rD_y)$$

$$w_y \tilde{y}_2 = (1 - \mu_b) w_{y_2} (y_2 + rD_y) + \mu_b w_{y_4} (y_4 - rD_y)$$

$$w_y \tilde{y}_3 = (1 - \mu_B) w_{y_3} (y_3 + rD_y) + \mu_B w_{y_1} (y_1 - rD_y)$$

$$w_y \tilde{y}_4 = (1 - \mu_b) w_{y_4} (y_4 - rD_y) + \mu_b w_{y_2} (y_2 + rD_y),$$

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

# Symmetric Selection

	$E_x$				$E_y$			
	$AB$	$Ab$	$aB$	$ab$	$AB$	$Ab$	$aB$	$ab$
<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  $\mu_B$  is small.

Evolution of mutation by invasion of  $\mathbf{x}^*$   $\mathbf{y}^*$  by allele  $b$ .

$$\begin{pmatrix} \mathbf{x}' \\ \mathbf{y}' \end{pmatrix} = \begin{pmatrix} \mathbf{x}^* \\ \mathbf{y}^* \end{pmatrix} + \begin{pmatrix} \boldsymbol{\varepsilon}' \\ \boldsymbol{\delta}' \end{pmatrix} = \begin{pmatrix} \mathbf{x}^* \\ \mathbf{y}^* \end{pmatrix} + \mathbf{L}^* \begin{pmatrix} \boldsymbol{\varepsilon} \\ \boldsymbol{\delta} \end{pmatrix}$$

$$\mathbf{L}^* = \begin{pmatrix} \varepsilon_1 & \varepsilon_3 & \delta_1 & \delta_3 & \varepsilon_2 & \varepsilon_4 & \delta_2 & \delta_4 \\ & \mathbf{L}_{\text{in}}^* & & & * & & & \\ & 0 & & & & \mathbf{L}_{\text{ex}}^* & & \end{pmatrix} \begin{pmatrix} \varepsilon_1 \\ \varepsilon_3 \\ \delta_1 \\ \delta_3 \\ \varepsilon_2 \\ \varepsilon_4 \\ \delta_2 \\ \delta_4 \end{pmatrix}$$

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

$A, B, C, D > 0$ ; all functions of  $s, r, \mu_b, \mu_B$ .

## 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

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

Hence stability is determined by two quadratics.

## No Temporal Fluctuation

*Result.* When  $0 < m, \mu_B, \mu_b < \frac{1}{2}$ , 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  $\ell$  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  $\mu_B$  in a constant environment,
- ii. an increasing function of  $\mu_B$  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.

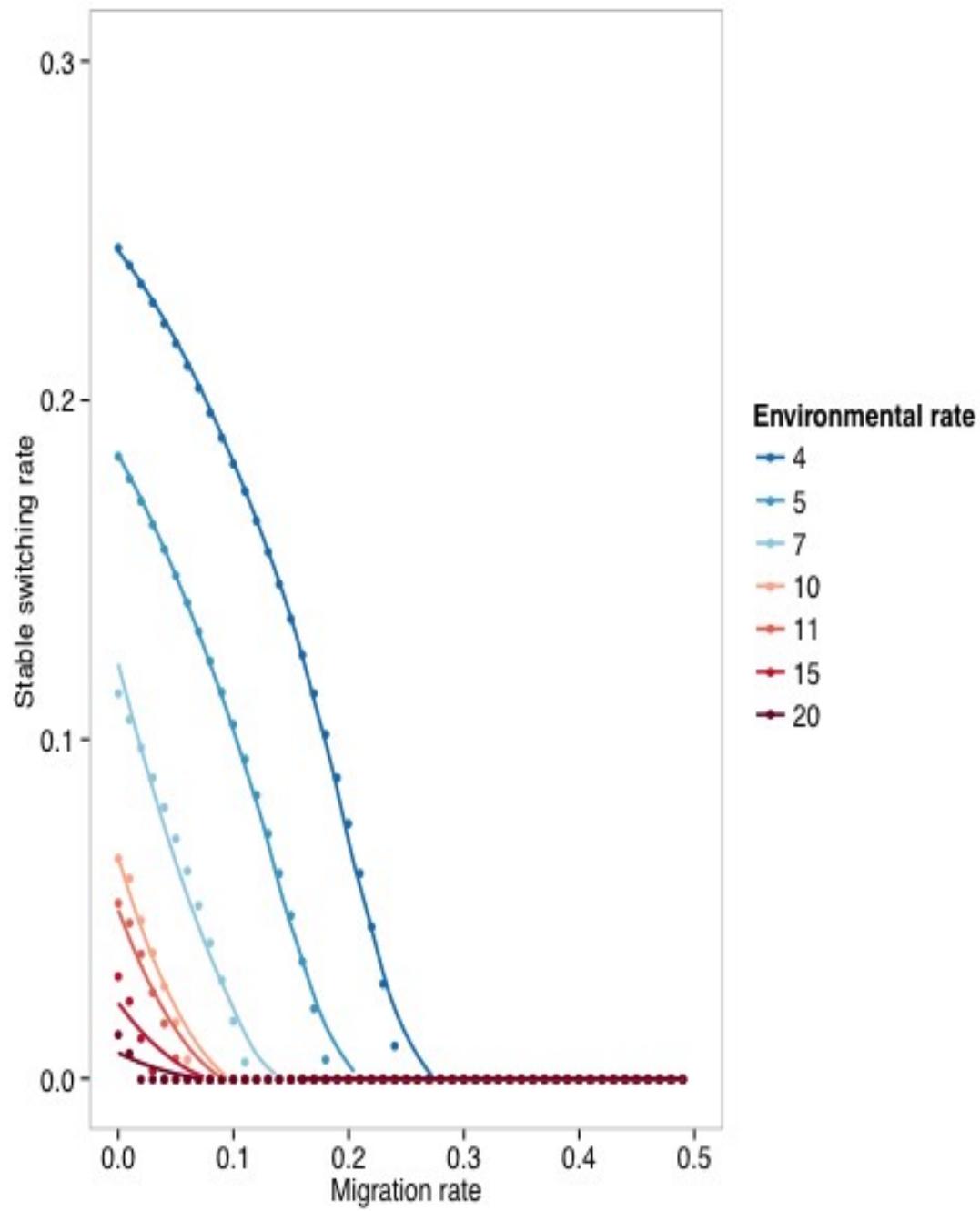
Note:

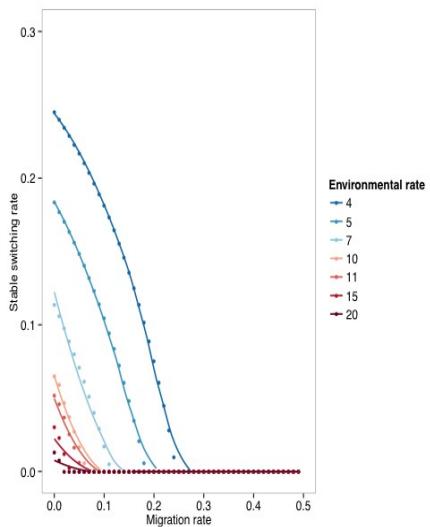
$$L_{\text{ex}} = \underbrace{L_{\text{ex}}^2 L_{\text{ex}}^2 \cdots L_{\text{ex}}^2}_k \quad \underbrace{L_{\text{ex}}^1 L_{\text{ex}}^1 \cdots L_{\text{ex}}^1}_{\ell}$$

is strictly positive and of the form

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

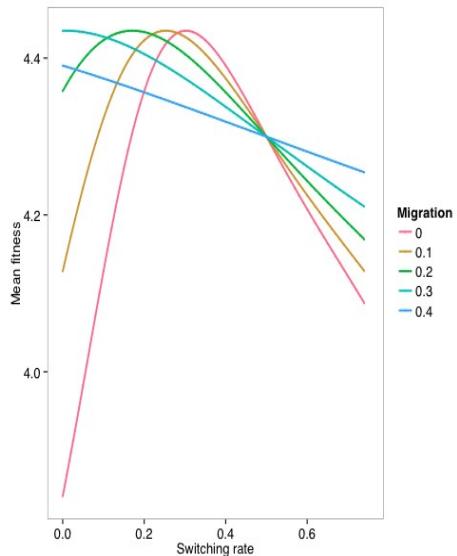
Hence two quadratics for stability,  
but they can be very, very messy.





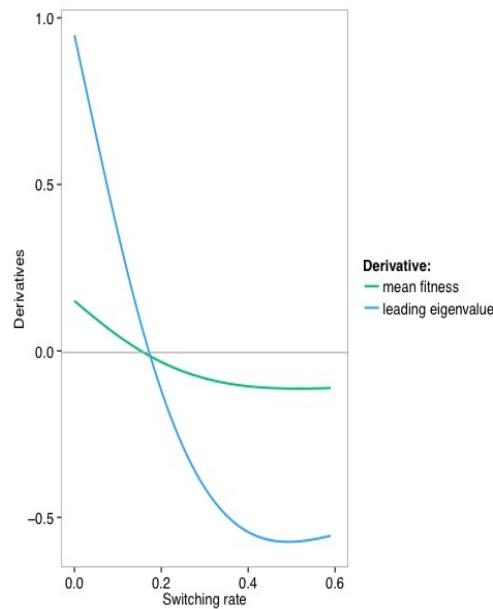
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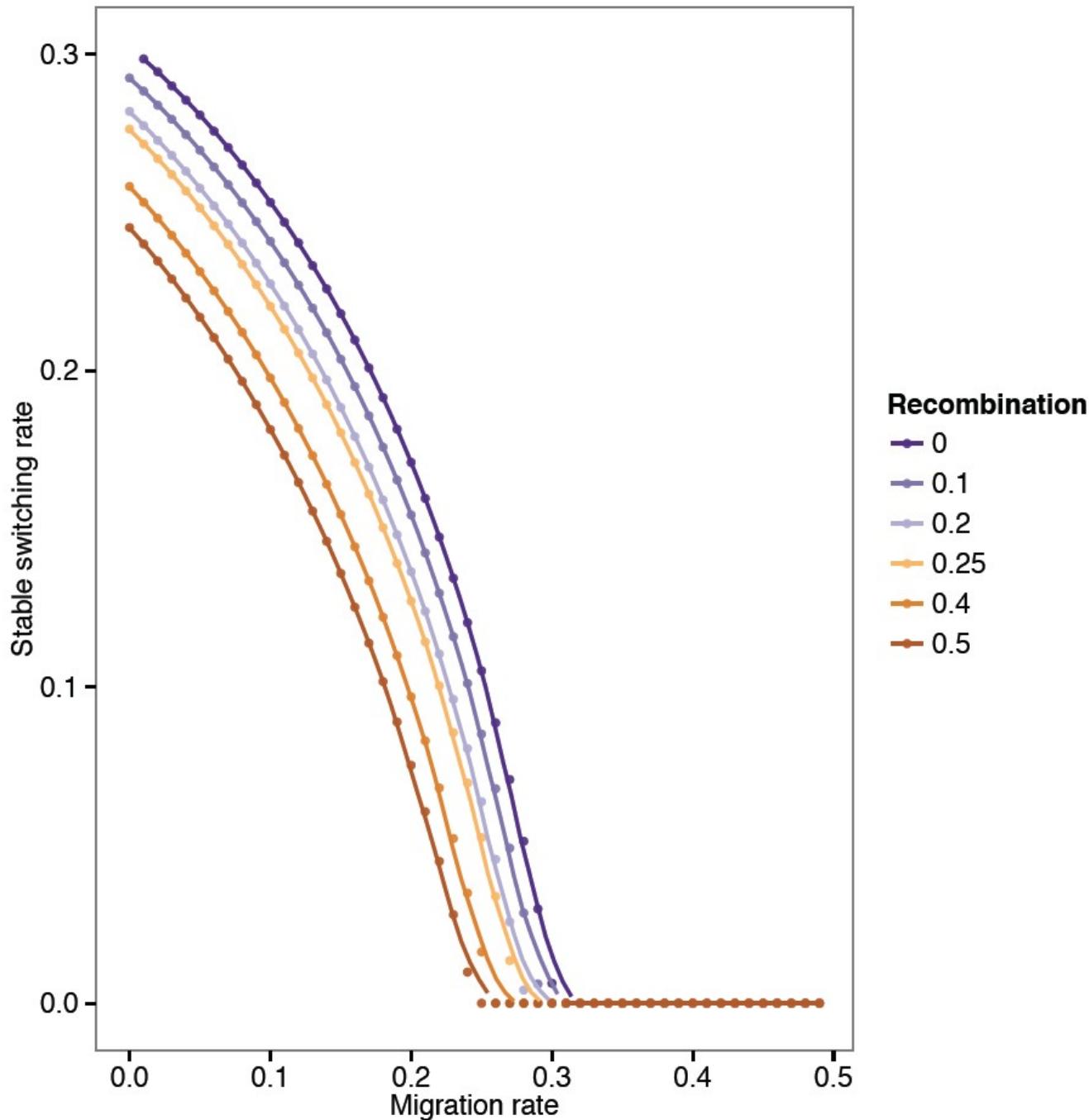
maximum mean fitness

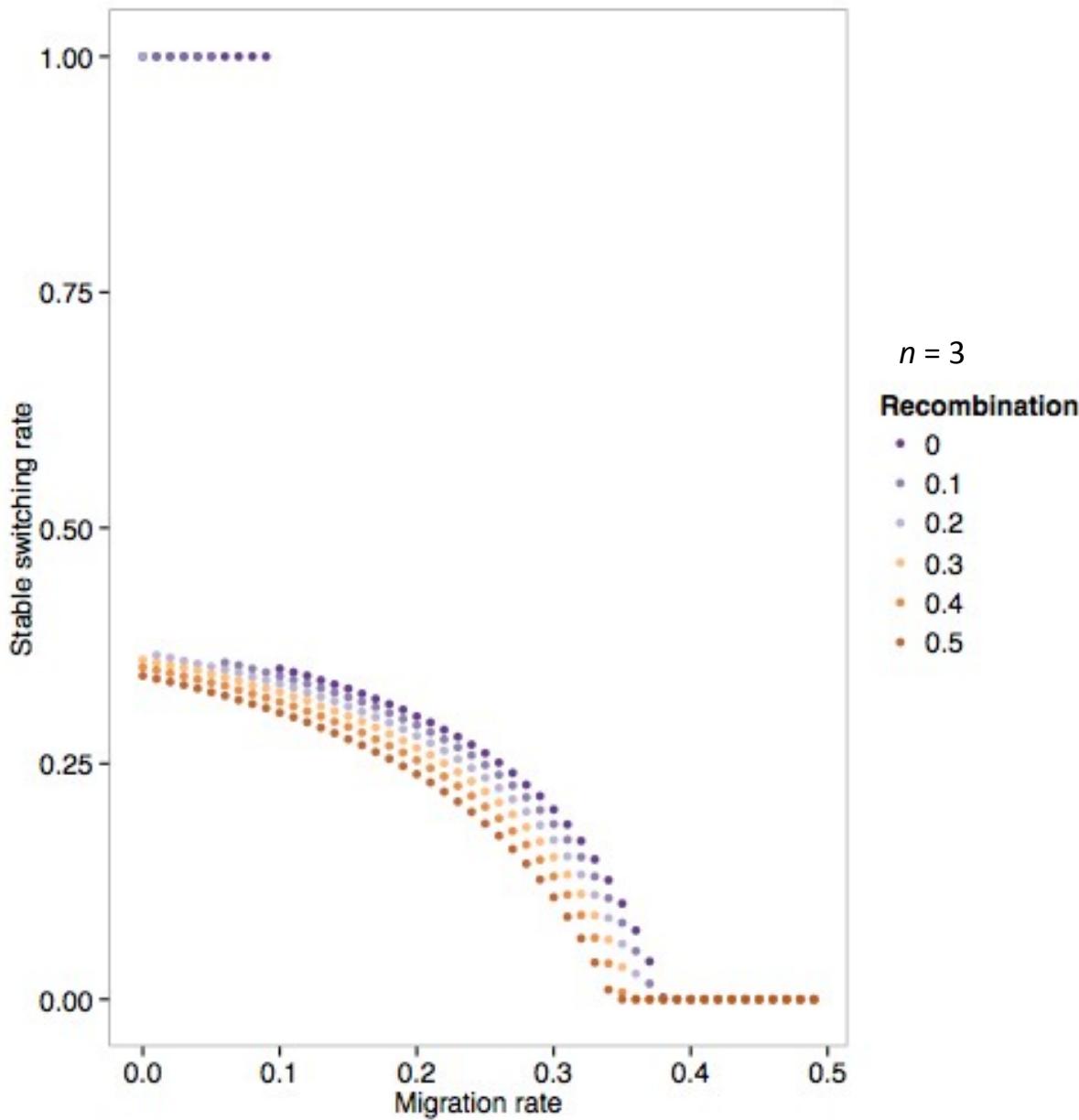


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stability







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