Evolving strategies for life in an uncertain world

Oana Carja
University of Pennsylvania

OSG All hands Meeting, March, 2017

“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, mutagents, toxins, radiation...”

Dubnau and Losick, 2006

Environmental variation is commonplace yet unpredictable across biological systems from the adaptive immune system, the microenvironment in cancerous neoplasms, to populations of pathogens under drug pressure.

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Can organisms prepare for this environmental stochasticity?

Environmental variation is commonplace yet unpredictable across biological systems from the adaptive immune system, the microenvironment in cancerous neoplasms, to populations of pathogens under drug pressure.

How do populations survive environmental stochasticity? How do they manage to persist and keep one's footing on an ever-changing landscape?

Can organisms prepare for this environmental stochasticity?

Can evolution prepare populations for this environmental stochasticity?

"another rule which may prove useful can be derived from our theory. This is the rule that it is advisable to divide goods which are exposed to some danger into several portions rather than risk them all together"

Daniel Bernoulli, 1738

same genes, different phenotypes

wrinkled and smooth *P.fluorescens* lines

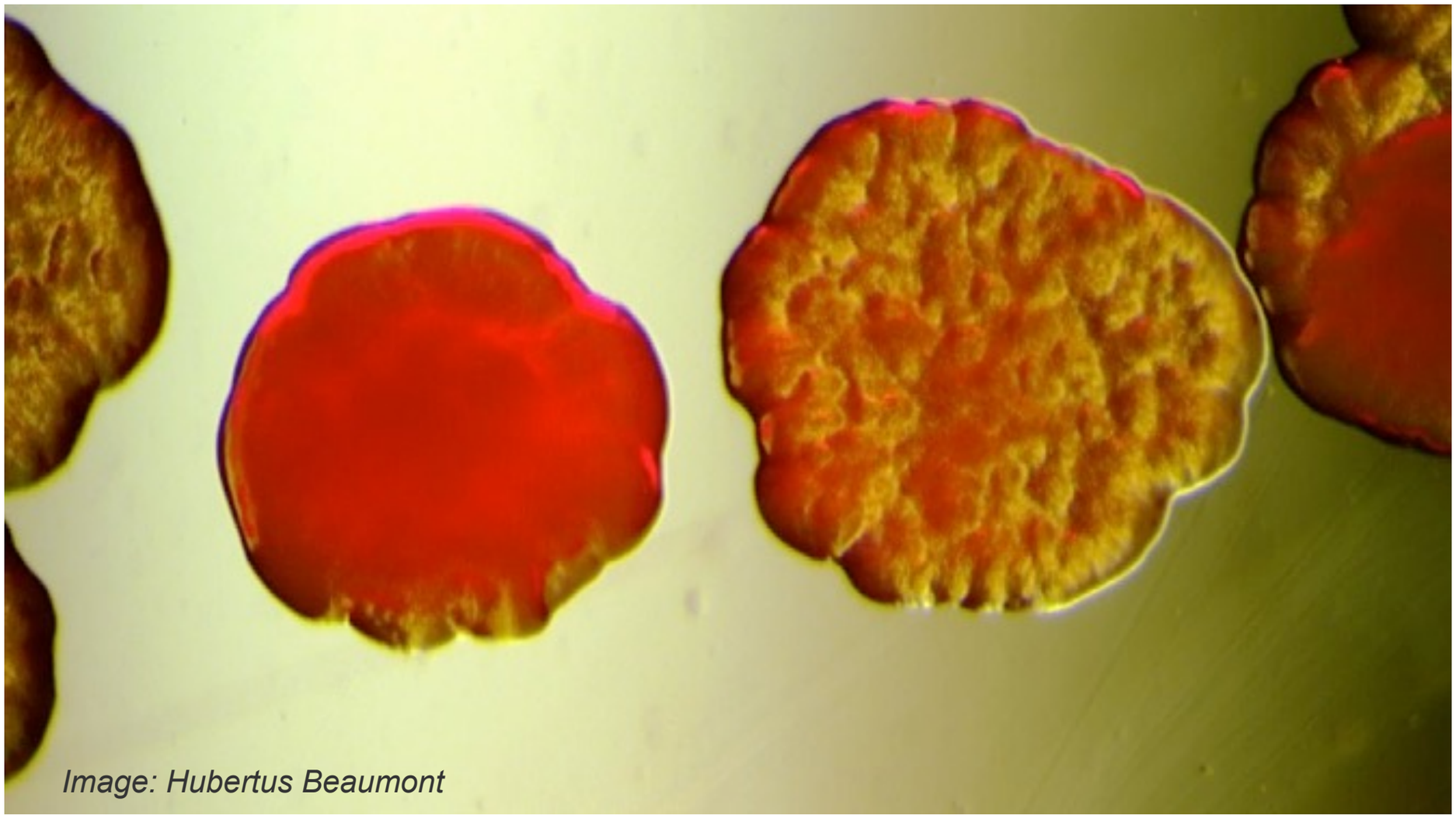


Image: Hubertus Beaumont

Research

Transcriptional variation in the malaria parasite *Plasmodium falciparum*

Núria Rovira-Graells,[1,2] Archna P. Gupta,[3] Evarist Planet,[1] Valerie M. Crowley,[1] Sachel Mok,[3] Lluís Ribas de Pouplana,[1,4] Peter R. Preiser,[3] Zbynek Bozdech,[3,5] and Alfred Cortés[1,2,4,5]

[1]*Institute for Research in Biomedicine (IRB), 08028 Barcelona, Catalonia, Spain;* [2]*Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-Universitat de Barcelona), 08036 Barcelona, Catalonia, Spain;* [3]*School of Biological Sciences, Nanyang Technological University, 637551 Singapore;* [4]*Institució Catalana de Recerca i Estudis Avançats (ICREA), 08010 Barcelona, Catalonia, Spain*

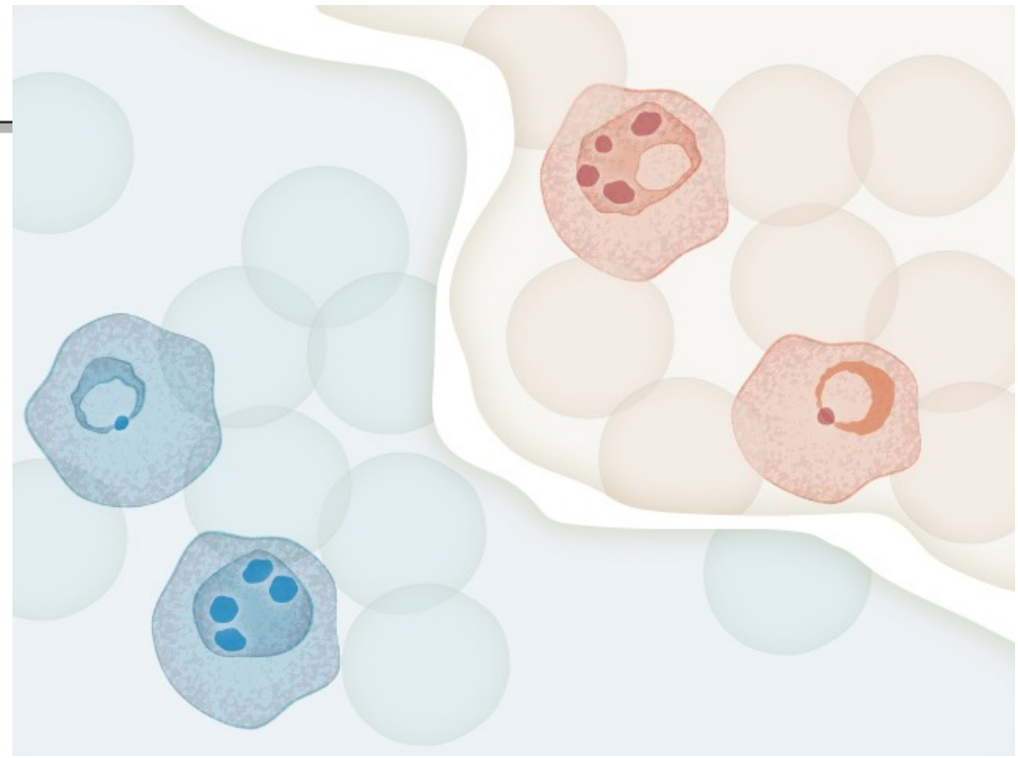
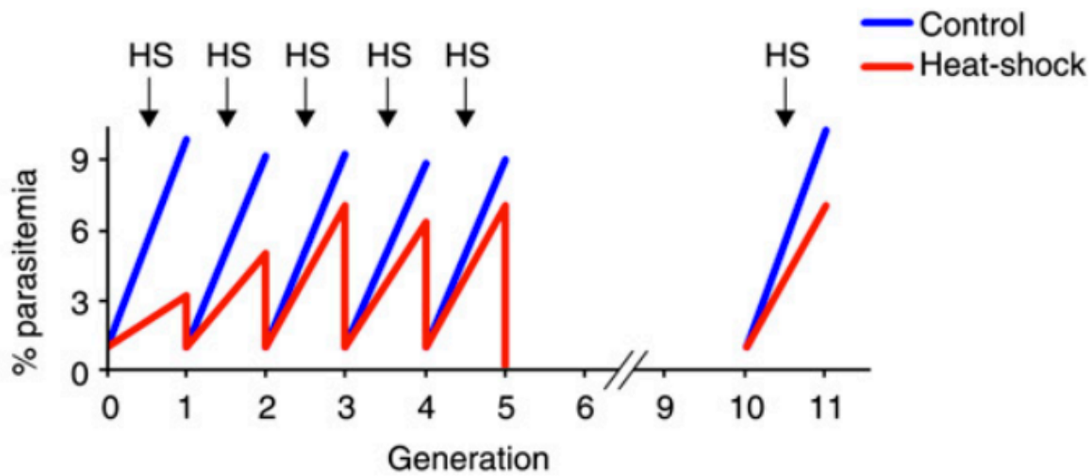


Image courtesy of Lauren Solomon, Broad Communications

the more transcriptionally diverse parasite adapted more rapidly to periodic changes in temperature meant to mimic periodic febrile episodes

more diverse



less diverse

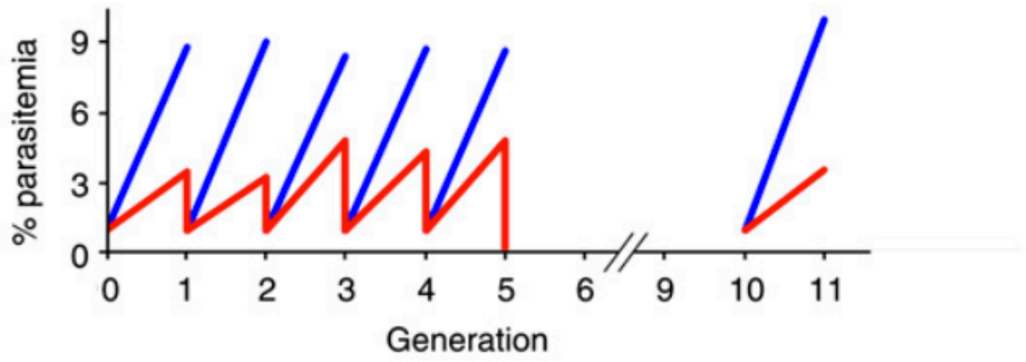


Figure: Rovira-Graells et al, *Genome Research*, 2014

phenotypic variance as an evolutionary strategy in uncertain environments

Herpes viruses hedge their bets

Michael P. H. Stumpf*†‡, Zoë Laidlaw§, and Vincent A. A. Jansen¶

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Communicated by Robert May, University of Oxford, Oxford, United Kingdom, September 9, 2002 (received for review April 24, 2002)

Theory

Switch to Standard View

An Evolutionary Role for HIV Latency in Enhancing Viral Transmission

Igor M. Rouzine, Ariel D. Weinberger, Leor S. Weinberger

DOI: http://dx.doi.org/10.1016/j.cell.2015.02.017 | CrossMark

Bacterial Persistence as a Phenotypic Switch

Nathalie Q. Balaban,[1,2]* Jack Merrin,[1] Remy Chait,[1] Lukasz Kowalik,[1] Stanislas Leibler[1]

Article Info

A chromatin-mediated reversible drug tolerant state in cancer cell subpopulations

Sreenath V. Sharma[1], Diana Y. Lee[1], Bihua Li[1], Margaret P. Quinlan[1], Fumiyuki Takahashi[1], Shyamala Maheswaran[1], Ultan McDermott[1], Nancy Azizian[1], Lee Zou[1], Michael A. Fischbach[1], Kwok-Kin Wong[2], Kathleyn Brandstetter[2], Ben Wittner[1], Sridhar Ramaswamy[1], Marie Classon[1,*,#], and Jeff Settleman[1,*,#]

[1] Massachusetts General Hospital Cancer Center, 149 13th Street, Charlestown, MA 02129

[2] Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115

Bistability, Epigenetics, and Bet-Hedging in Bacteria

Jan-Willem Veening,[1,3] Wiep Klaas Smits,[2,3] and Oscar P. Kuipers[3]

[1]Institute for Cell and Molecular Biosciences, Newcastle University, Newcastle upon Tyne NE2 4HH, United Kingdom; email: j.w.veening@ncl.ac.uk

[2]Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139; email: smitswk@mit.edu

[3]Molecular Genetics Group, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, 9751 NN Haren, The Netherlands; email: o.p.kuipers@rug.nl

bacterial persistence

High levels of antibiotic tolerance and persistence are induced by the commercial anti-microbial triclosan

Corey S. Westfall and Petra Anne Levin*

Department of Biology, Washington University in St. Louis, St. Louis, MO 63130, USA

Banned from consumer soaps effective September 2017 by the US Food and Drug Administration, the antimicrobial triclosan remains approved for use in products ranging from toothpaste to cleansers employed in healthcare settings[10]. In contrast to bactericidal antibiotics, which kill pathogens outright, triclosan is a bacteriostatic drug that inhibits growth by targeting enoyl-acyl carrier protein reductase to interfere with early steps in fatty acid synthesis[11].

1000-fold higher than the expected frequency of persisters in an untreated population[4]. At the 20 hour time point, 90,000 cells per mL were viable in 100 ng/mL ciprofloxacin and 30 cells per mL in 1000ng/mL ciprofloxacin. In contrast, we observed only 20 cells/ml after 20 hours of growth in 100 ng/mL ciprofloxacin alone. Cells cultured in 1,000 ng/mL ciprofloxacin alone had no observable colonies (<10 cells per mL).

Westfall and Levin, Biorxiv, 2016

1. genetically identical populations, with two or more available phenotypes, with each phenotype beneficial in a different environmental state

2. phenotypic states are partly heritable by offspring cells; rates of change greater than genetic mutation

3. the rate of 'phenotypic mutation' is itself under genetic control

(Levin and Rosen, 2006)

1. genetically identical populations, with two or more available phenotypes, with each phenotype beneficial in a different environmental state

2. phenotypic states are transient, partly heritable by offspring cells; rates of change greater than genetic mutation

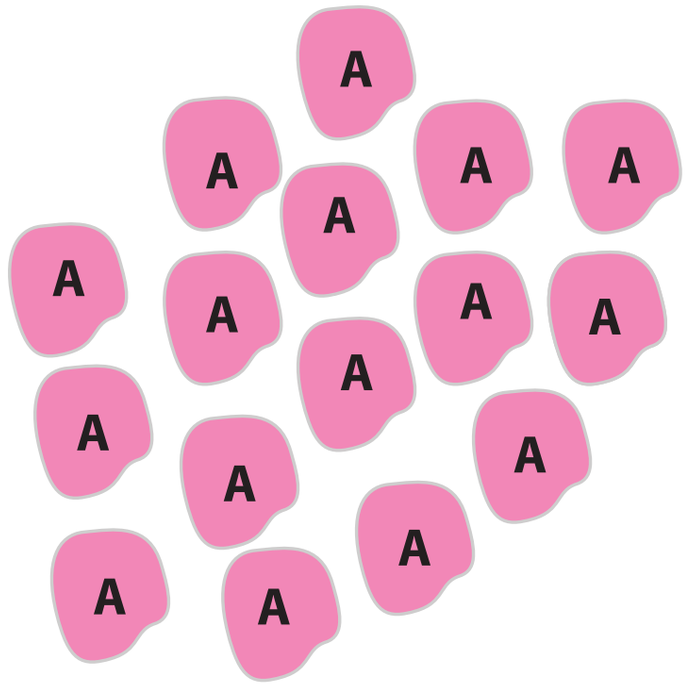
3. the rate of 'phenotypic mutation' is itself under genetic control

(Levin and Rosen, 2006)

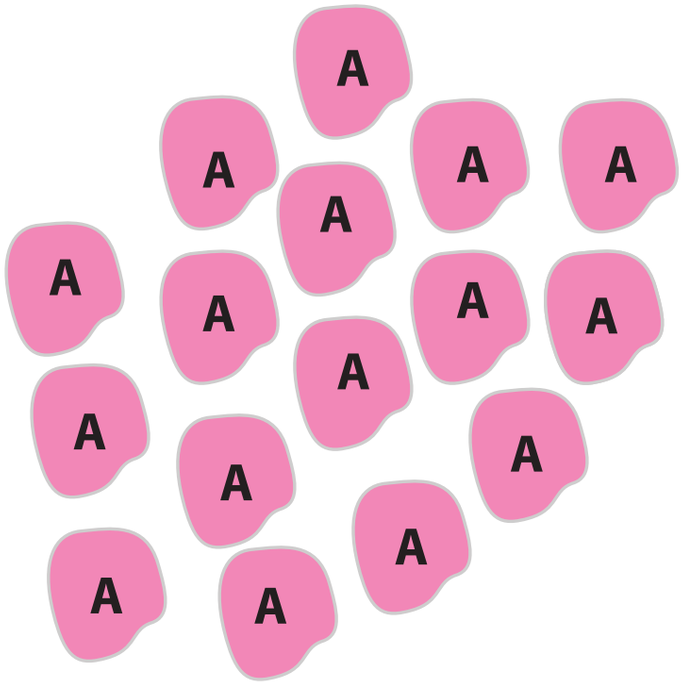
By tuning the rates at which variability is produced, populations may increase their long-term adaptability.

What is the evolutionary advantage of a phenotypically-plastic allele?

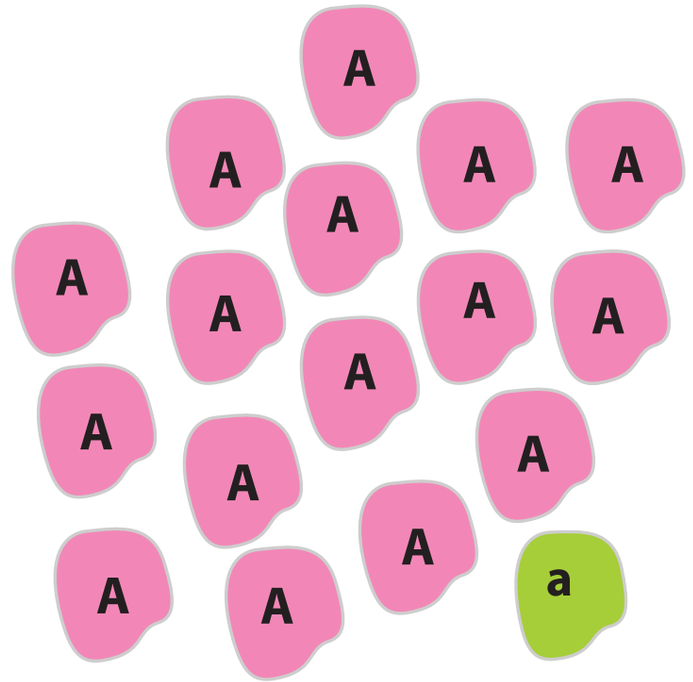
population of **A** individuals



population of **A** individuals



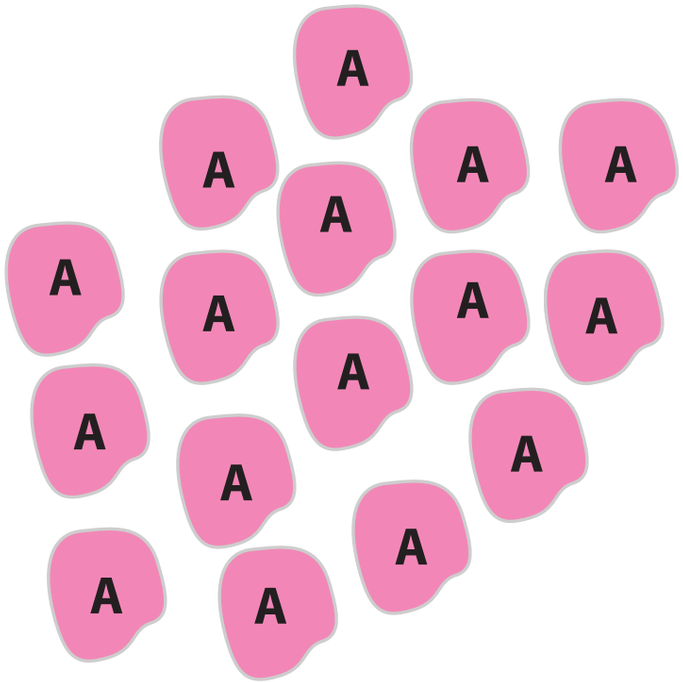
introduce one **a** individual



Genotype	A	a
Phenotype	ϕ_A	ϕ_a

phenotypic range of **a** allele

population of **A** individuals



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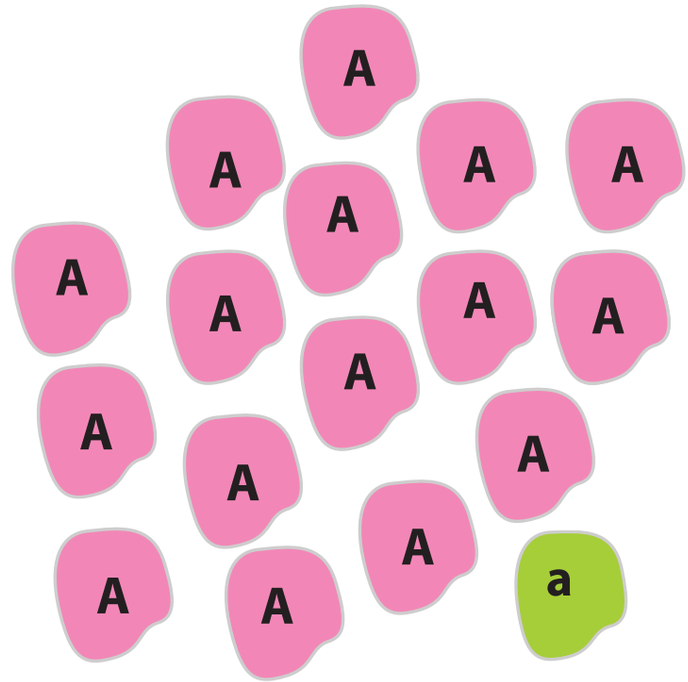
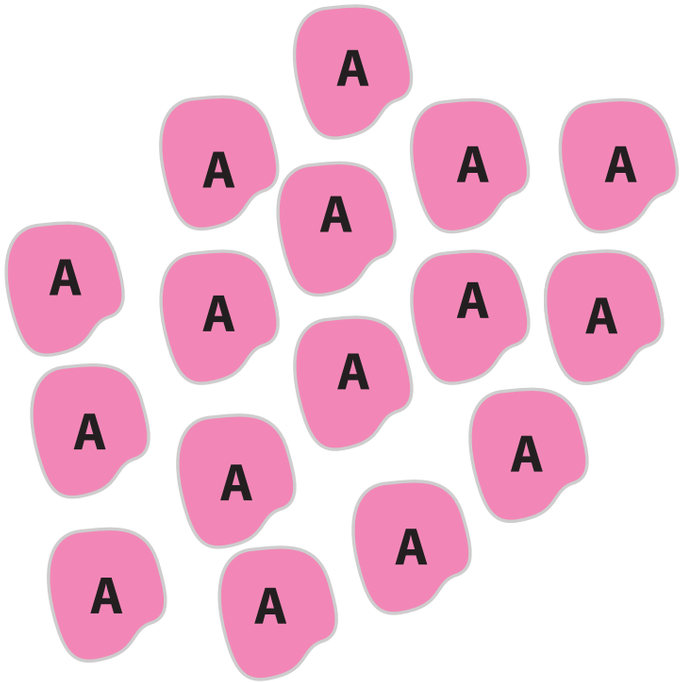


Genotype	A	a
Phenotype	ϕ_A	ϕ_a

phenotypic range of **a** allele

What is the fixation probability of an allele that increases phenotypic variability?

population of **A** individuals



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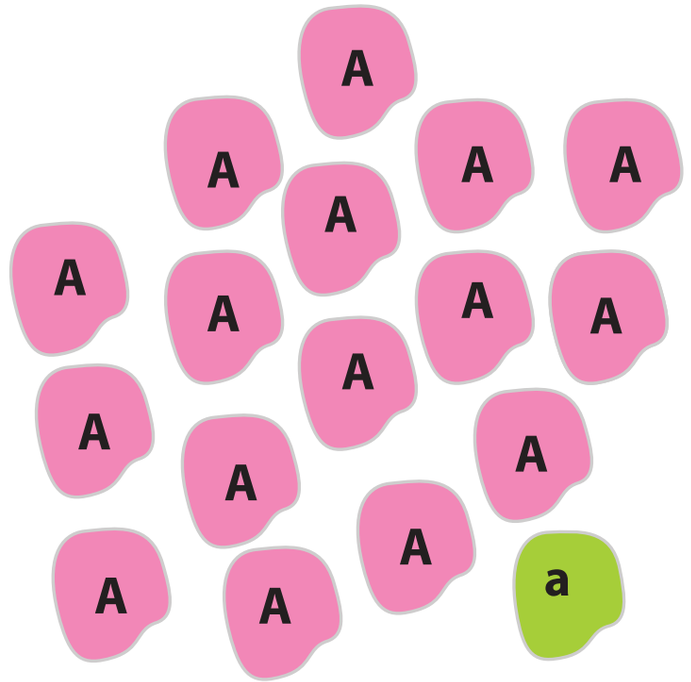


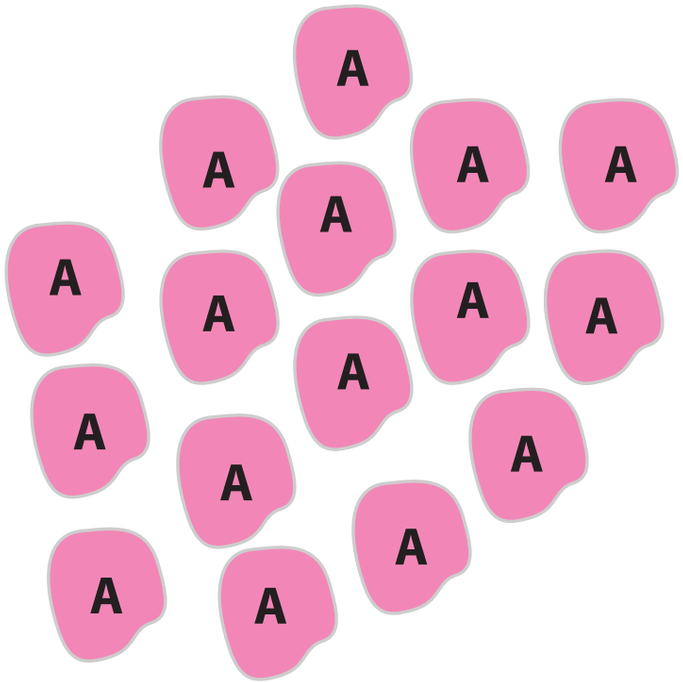
Genotype	A	a
Phenotype	ϕ_A	ϕ_a

phenotypic range of **a** allele

What is the fixation probability of an allele that increases phenotypic variability **(or, alternatively, allele controlling variation in regulatory function at other protein-coding loci)?**

What is the fixation probability of an allele that increases phenotypic variability?

population of **A** individuals



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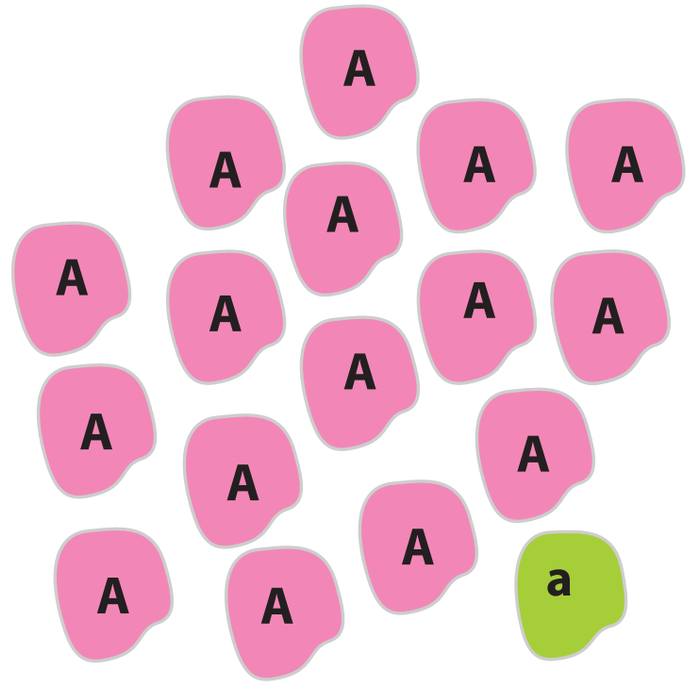
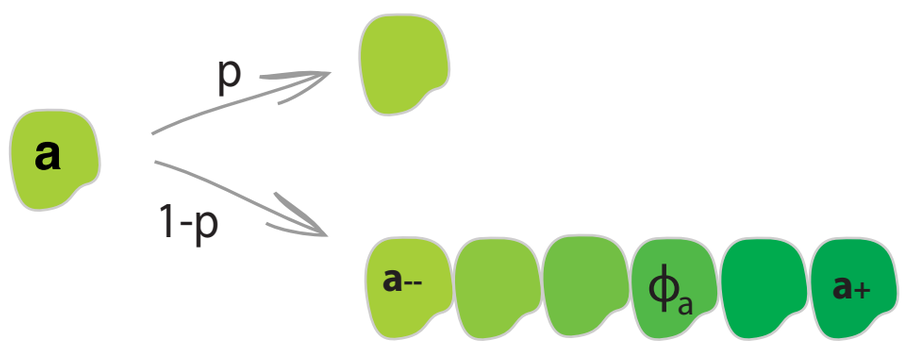


phenotypic range of **a** allele



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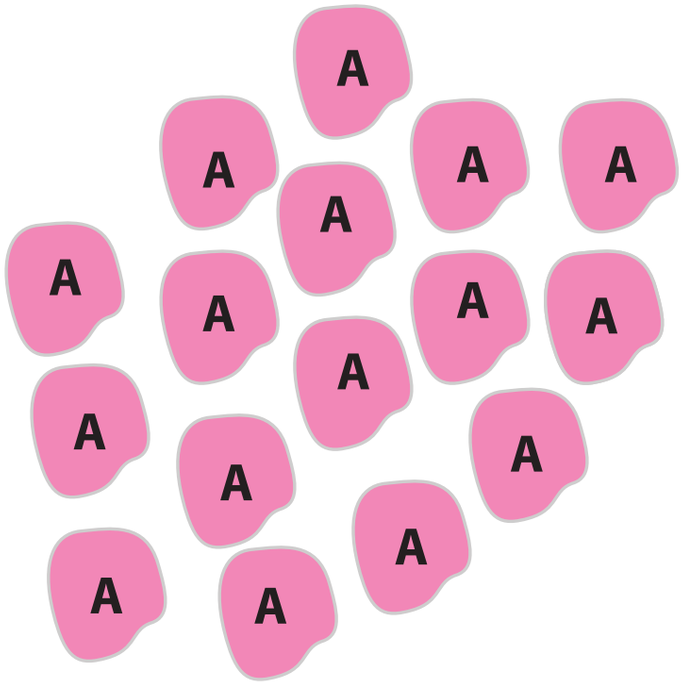

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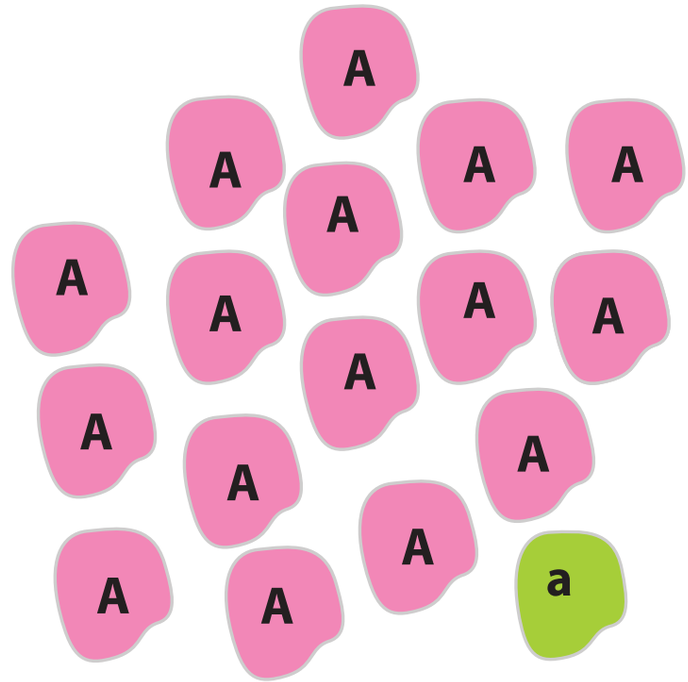


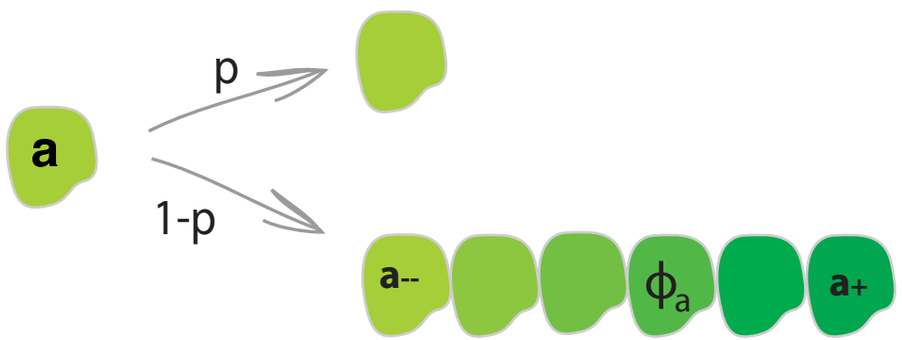
parent - offspring correlation

plasticity

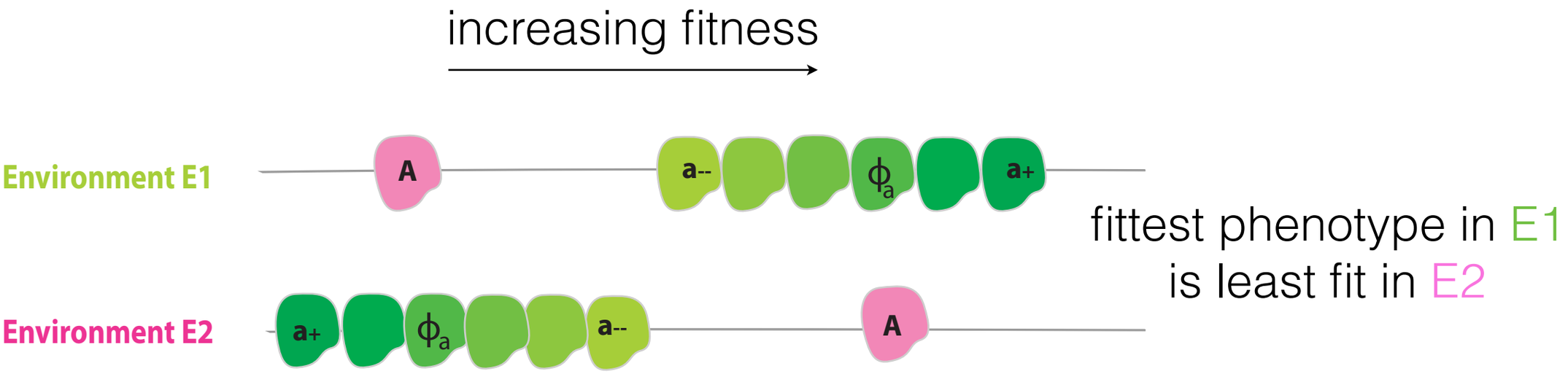
<u>partially heritable phenotype</u>

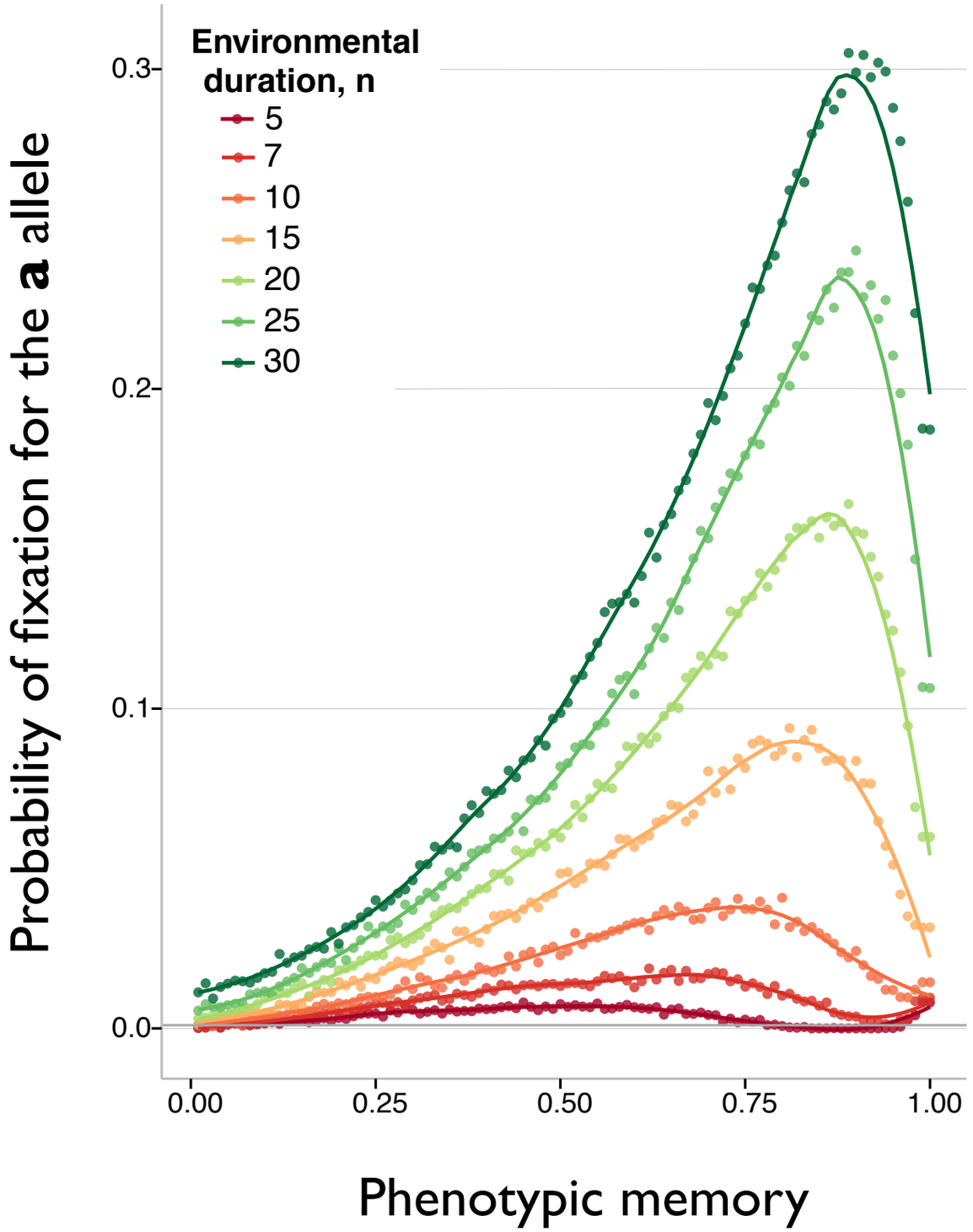
genetic encoding

phenotypic range of **a** allele



changing environments




Environmental duration, n
5
7
10
15
20
25
30
0.3
0.2
0.1
0.0
0.00
0.25
0.50
0.75
1.00
Probability of fixation for the a allele
Phenotypic memory

"adaptation in threatened populations is not
like ordinary adaptation, it is a race against extinction"

(Maynard Smith, 1989)

"adaptation in threatened populations is not like ordinary adaptation, it is a race against extinction"

(Maynard Smith, 1989)

conservation biology

Day, 2005
Waxman and Gavrilets 2005
Willi et al.2006
Chapin et al. 2000
Schindler et al. 2010
Bijlsma and Loeschke 2012
Osmond and de Mazancourt 2013

medical eradication

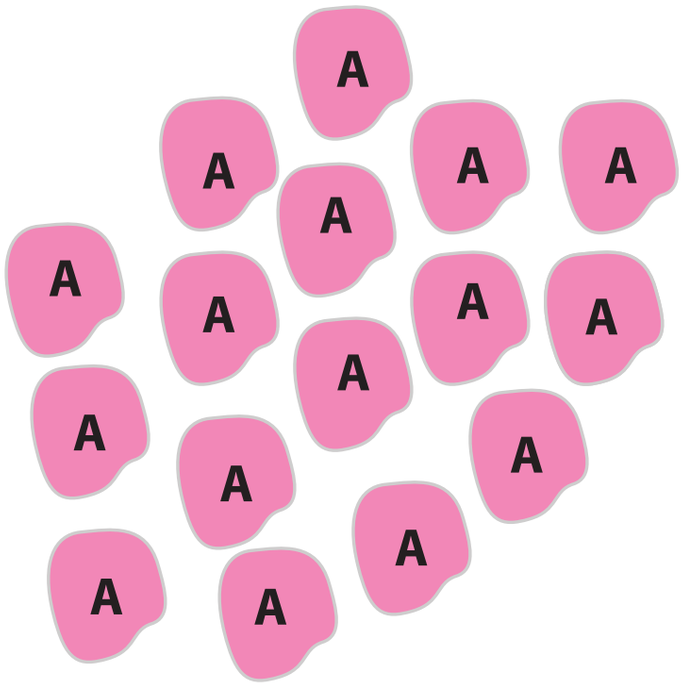
Bell and Collins 2008
Sanjuan et al. 2010
Goldberg et al. 2012
Bock and Lengauer 2012
Gonzalez et al. 2013
Lindsey et al. 2013
Martin et al. 2013
Ramsayer et al. 2013
Carlson et al. 2014
Orr and Unckless 2014
World Health Organization 2014

evolutionary rescue: one abrupt change in environment

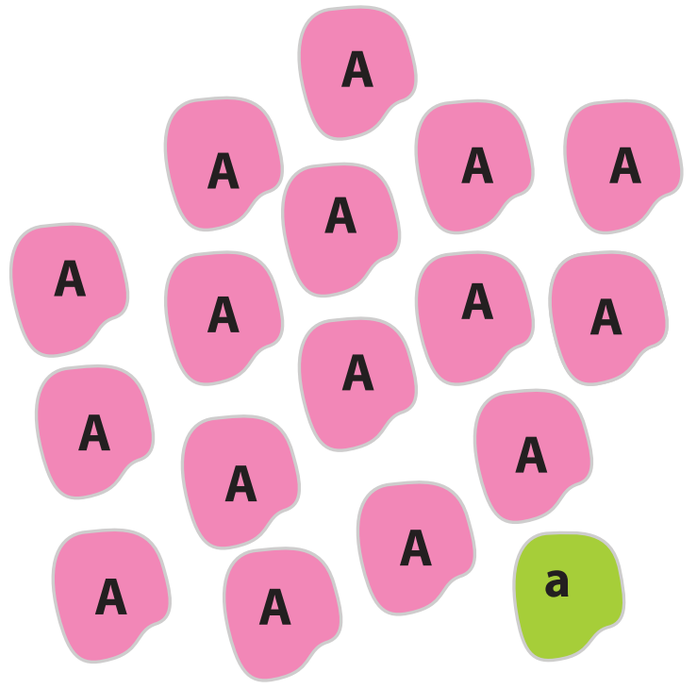
population of **A** individuals

evolutionary rescue: one abrupt change in environment

population of **A** individuals



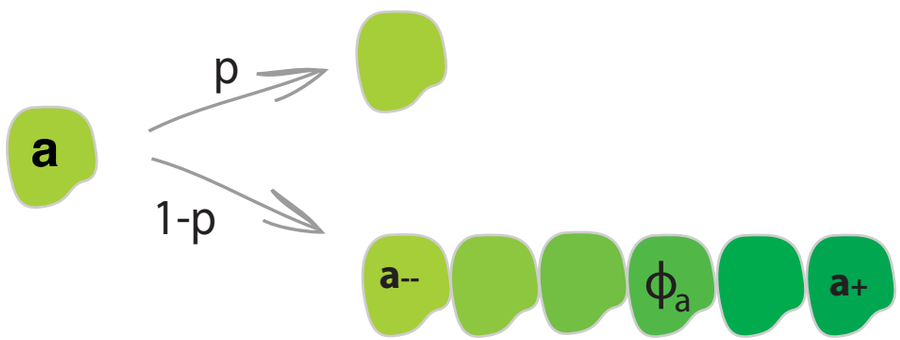
introduce one **a** individual



Genotype	A	a
Phenotype	ϕ_A	ϕ_a
Birth rate	ϕ_A **(1-N/K)**	ϕ_a **(1-N/K)**
Death rate	**1**	**1**

phenotypic range of **a** allele

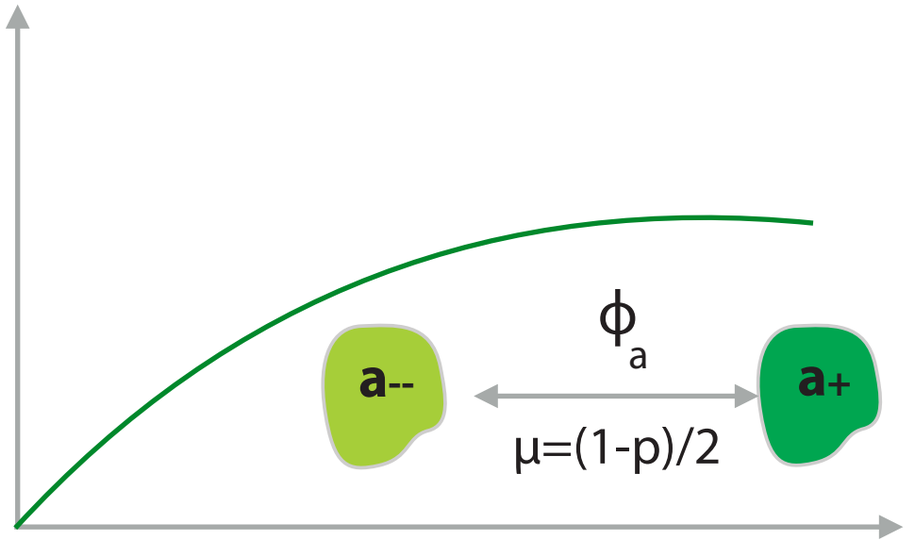
phenotypic memory:



analytical intuition

evolutionary dynamics of **initial** mutant with a **beneficial** phenotype

mutation selection balance:

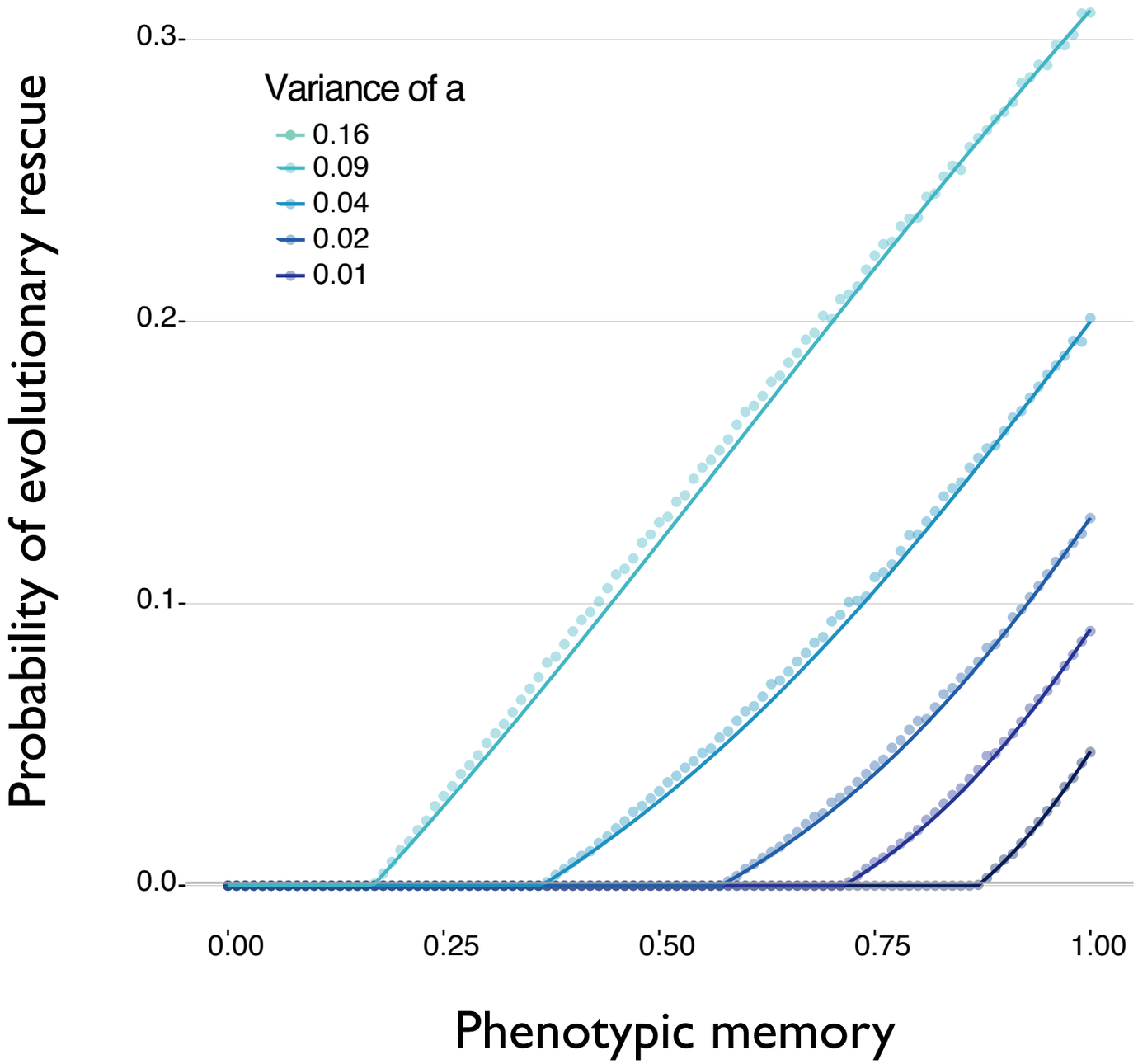


effective selective coefficient of **a** allele

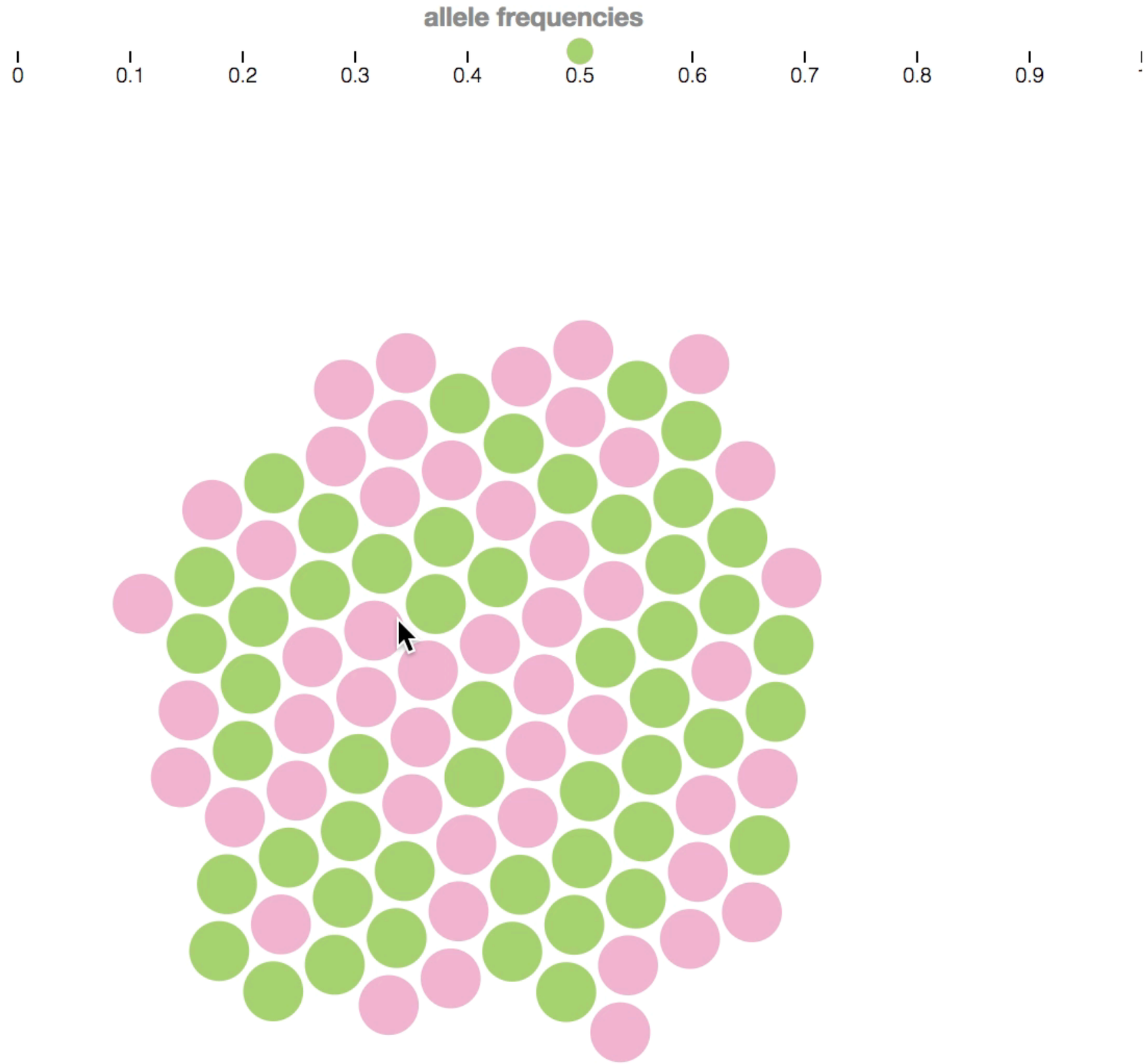
$$f_{a,+} = \frac{\Phi_{a,+} - \Phi_{a,-} - \mu\Phi_{a,-} - \mu\Phi_{a,+}}{2(\Phi_{a,+} - \Phi_{a,-})} + \frac{\sqrt{4\Phi_{a,-}\mu(\Phi_{a,+} - \Phi_{a,-}) + (\Phi_{a,-} - \Phi_{a,+} + \mu\Phi_{a,+} + \mu\Phi_{a,-})^2}}{2(\Phi_{a,+} - \Phi_{a,-})}$$

$$s_a = \Phi_{a,-}(1 - f_{a,+}) + \Phi_{a,+}f_{a,+}$$

evolutionary dynamics
of **initial** mutant with
a **beneficial** phenotype



analytical approximations simulations


allele frequencies
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9

analytical intuition

evolutionary dynamics of **initial** mutant with a **beneficial** phenotype

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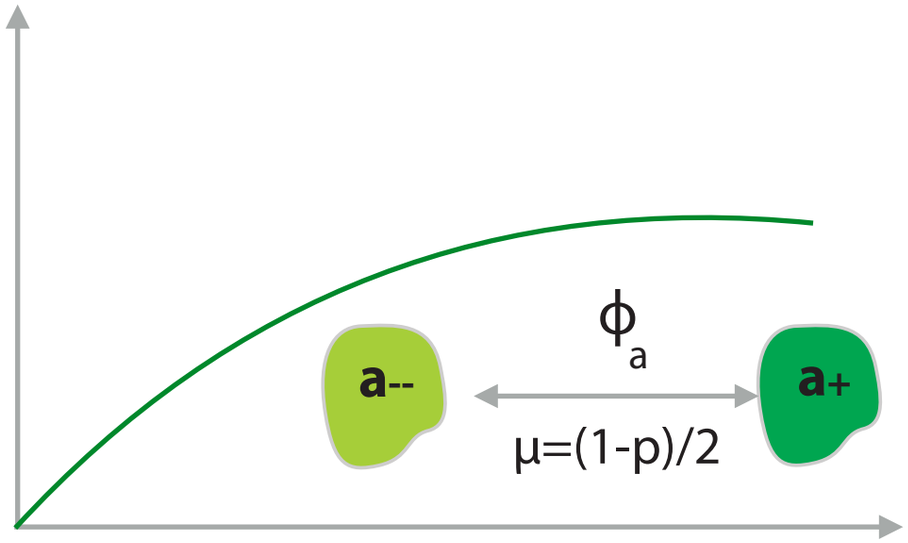

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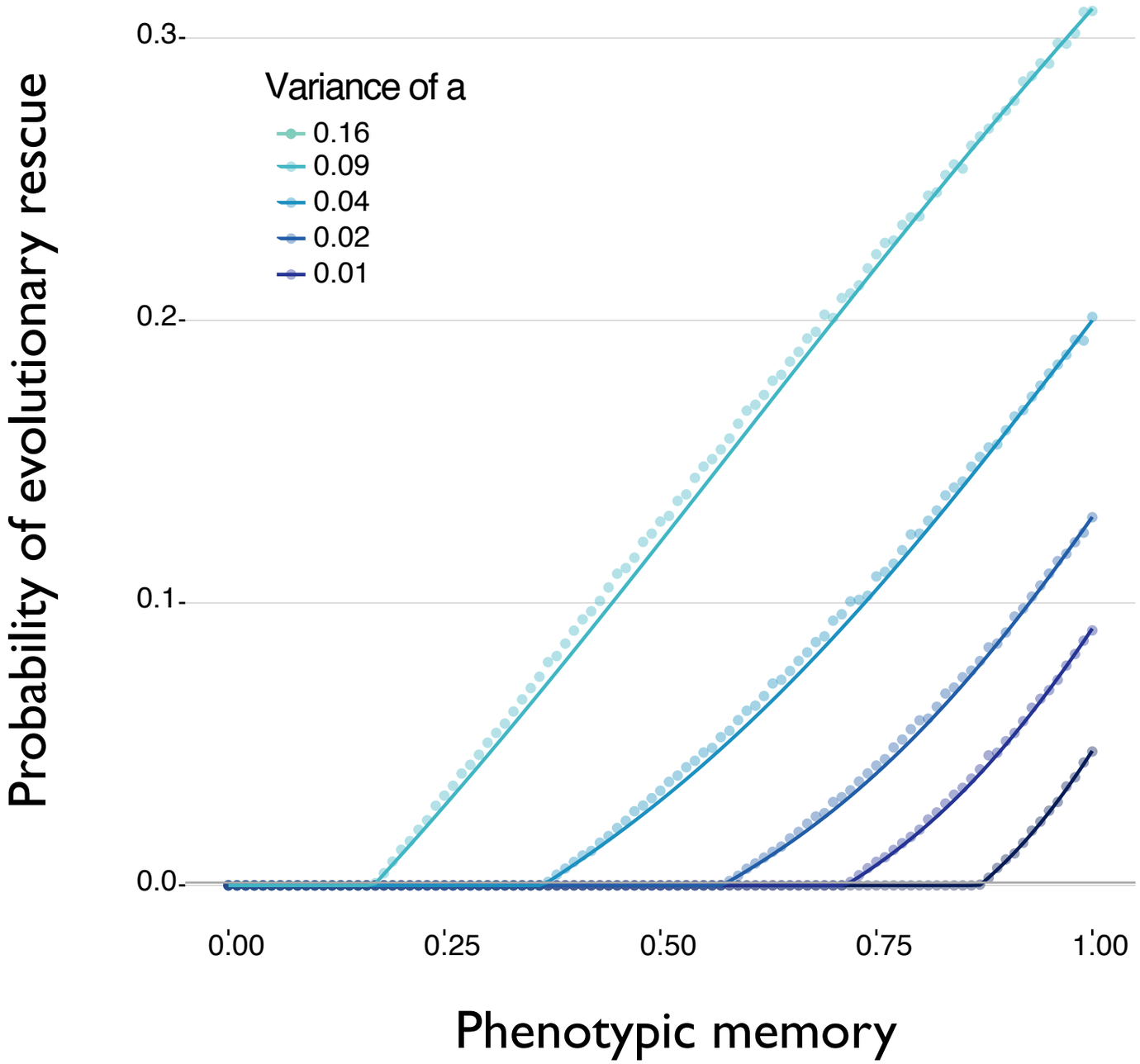
$$s_a = \Phi_{a,-}(1 - f_{a,+}) + \Phi_{a,+}f_{a,+}$$

evolutionary dynamics of **initial** mutant with a **deleterious** phenotype

probability of switching to high fitness phenotype before loss:
mutation as time-inhomogeneous Poisson process

$$\mathbb{P}(\eta) = 1 - \mathrm{e}^{(-\int_0^\infty \mu \mathrm{e}^{-st} dt)} = 1 - \mathrm{e}^{-\frac{\mu}{s}}$$

evolutionary dynamics
of **initial** mutant with
a **beneficial** phenotype



evolutionary dynamics
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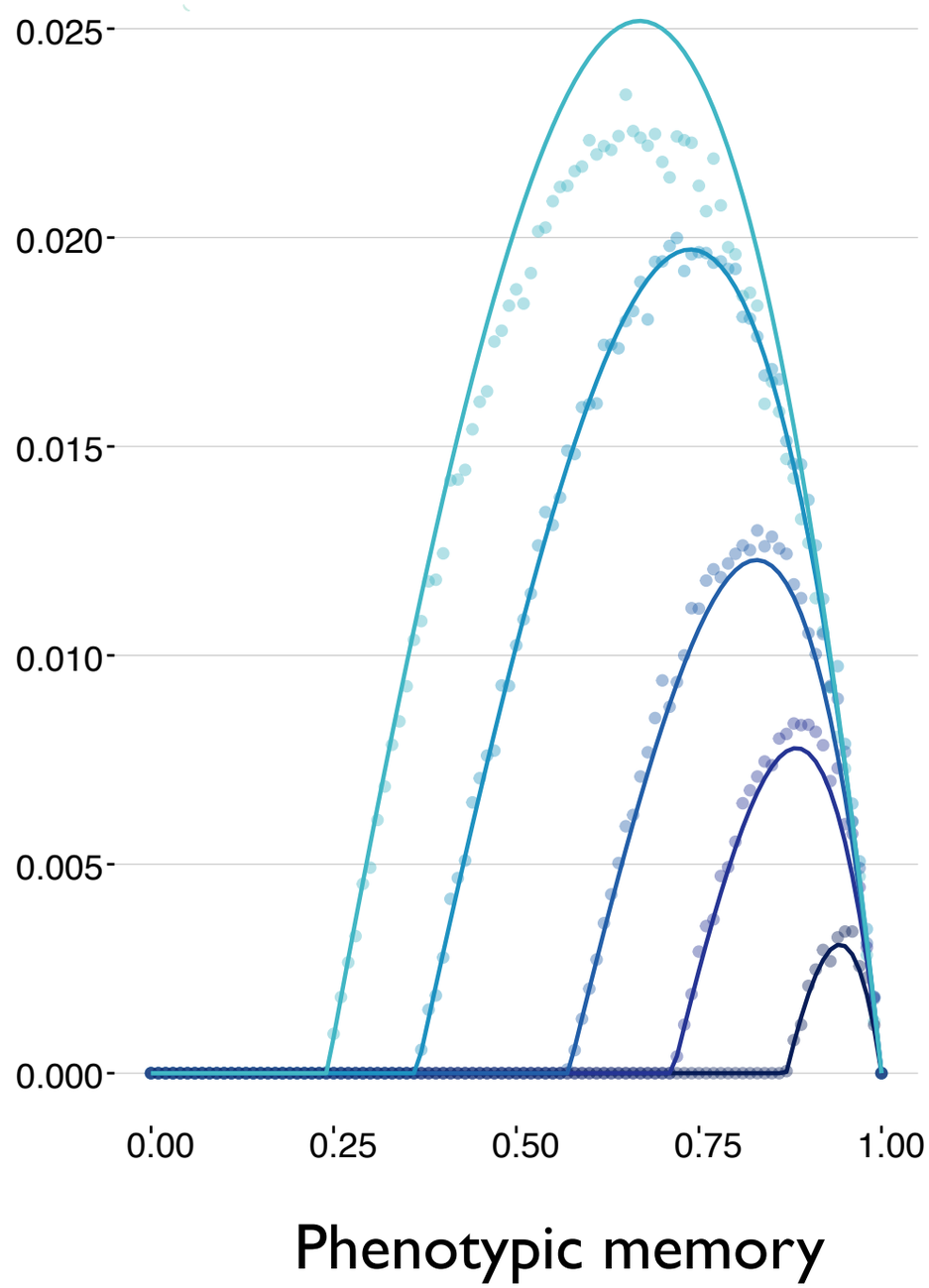
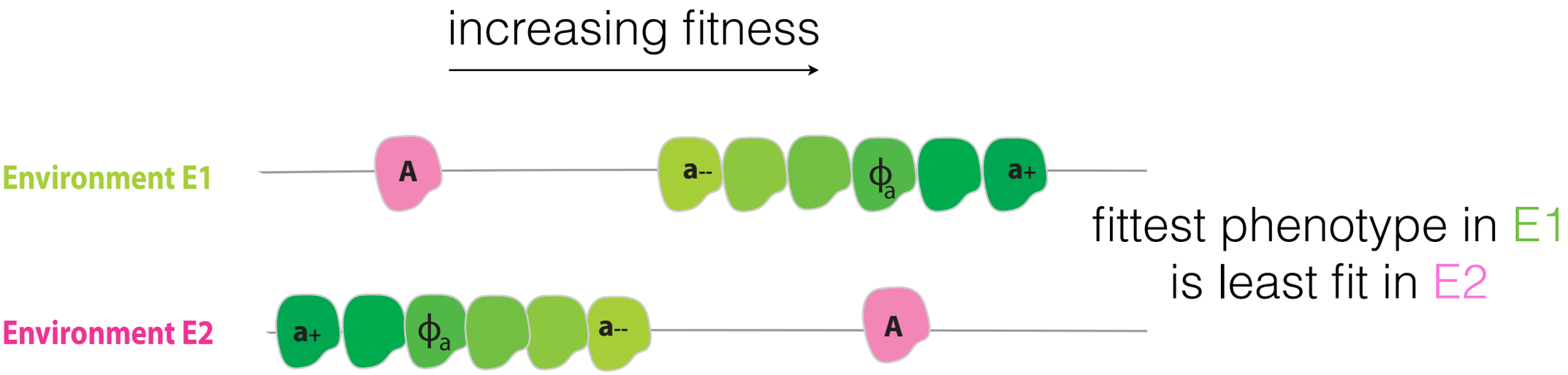
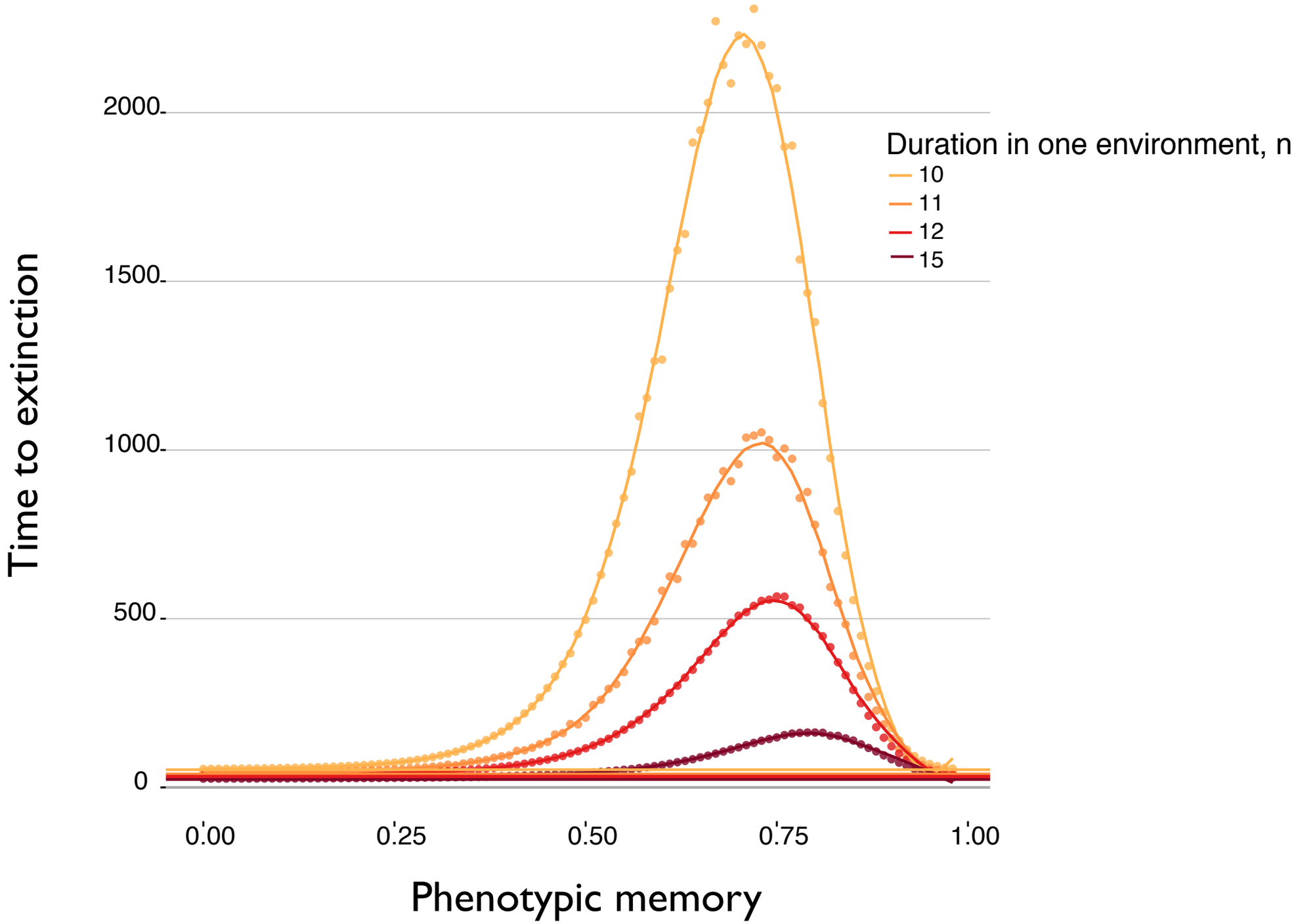


analytical approximations simulations

changing environments

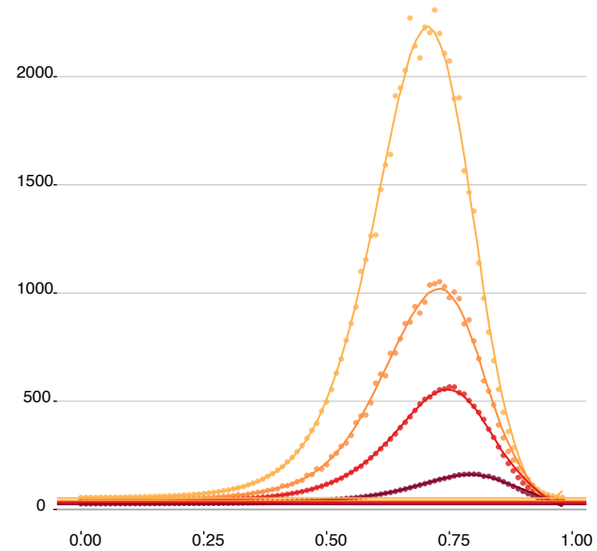


changing environments



Carja, Plotkin, bioRxiv, https://doi.org/10.1101/092718

There is an **optimum phenotypic memory** that maximizes fixation probability, evolutionary rescue, times to extinction of an invader allele with phenotypic variance.



What does this mean for **treatment strategies**?

Choose strategies that minimize probability of invasion and eventual fixation: effective interventions are treatments that **disrupt the molecular memory to either extreme**.

Thank you!

Work presented in collaboration with:

Marc Feldman, Stanford

Uri Liberman, Tel Aviv University

Joshua Plotkin, University of Pennsylvania

Life's infinite variety is the result of a single mechanism: natural selection. Even more remarkable, this mechanism is of a type very familiar to computer scientists: iterative search, where we solve a problem by trying many candidate solutions, selecting and modifying the best ones, and repeating these steps as many times as necessary. Evolution *is* an algorithm. Paraphrasing Charles Babbage, the Victorian-era computer pioneer, God created not species but the algorithm for creating species. The "endless forms most beautiful" Darwin spoke of in the conclusion of *The Origin of Species* belie a most beautiful unity: all of those forms are encoded in strings of DNA, and all of them come about by modifying and combining those strings. Who would have guessed, given only a description of this algorithm, that it could produce you and me? If evolution can learn us, it can conceivably also learn everything that can be learned, provided we implement it on a powerful enough computer. Indeed, evolving programs by simulating natural selection is a popular endeavor in machine learning. Evolution, then, is another promising path to the Master Algorithm.

Evolution is the ultimate example of how much a simple learning algorithm can achieve given enough data. Its input is the experience and fate of all living creatures that ever existed. (Now *that's* big data.)

The Master Algorithm, Pedro Domingos