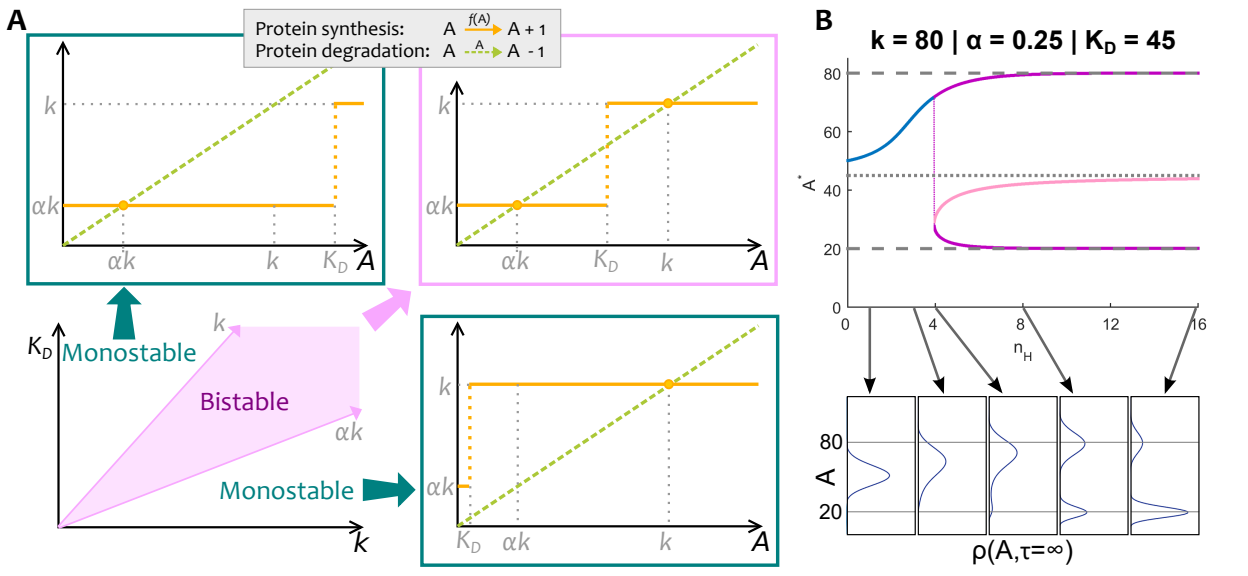
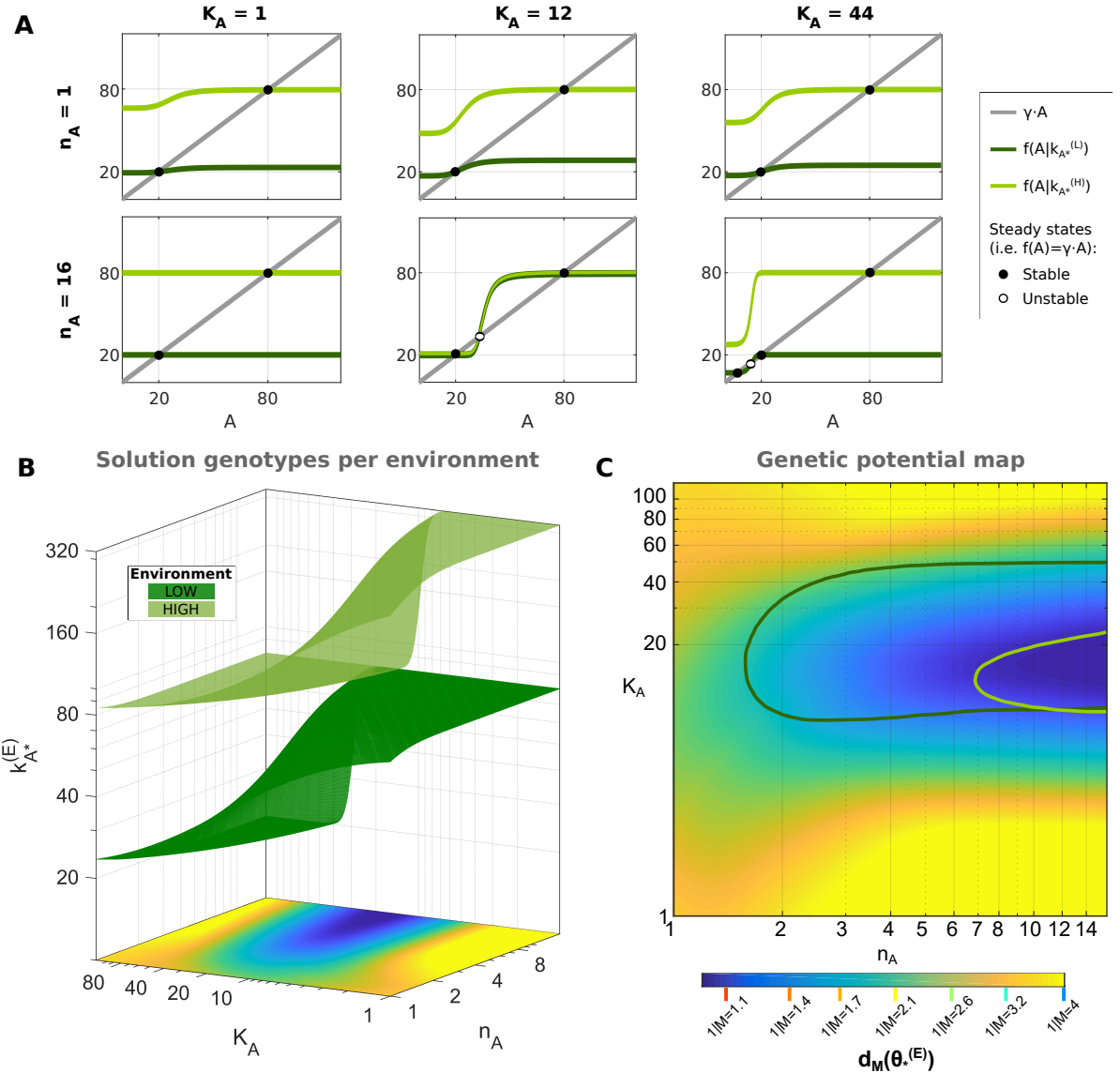
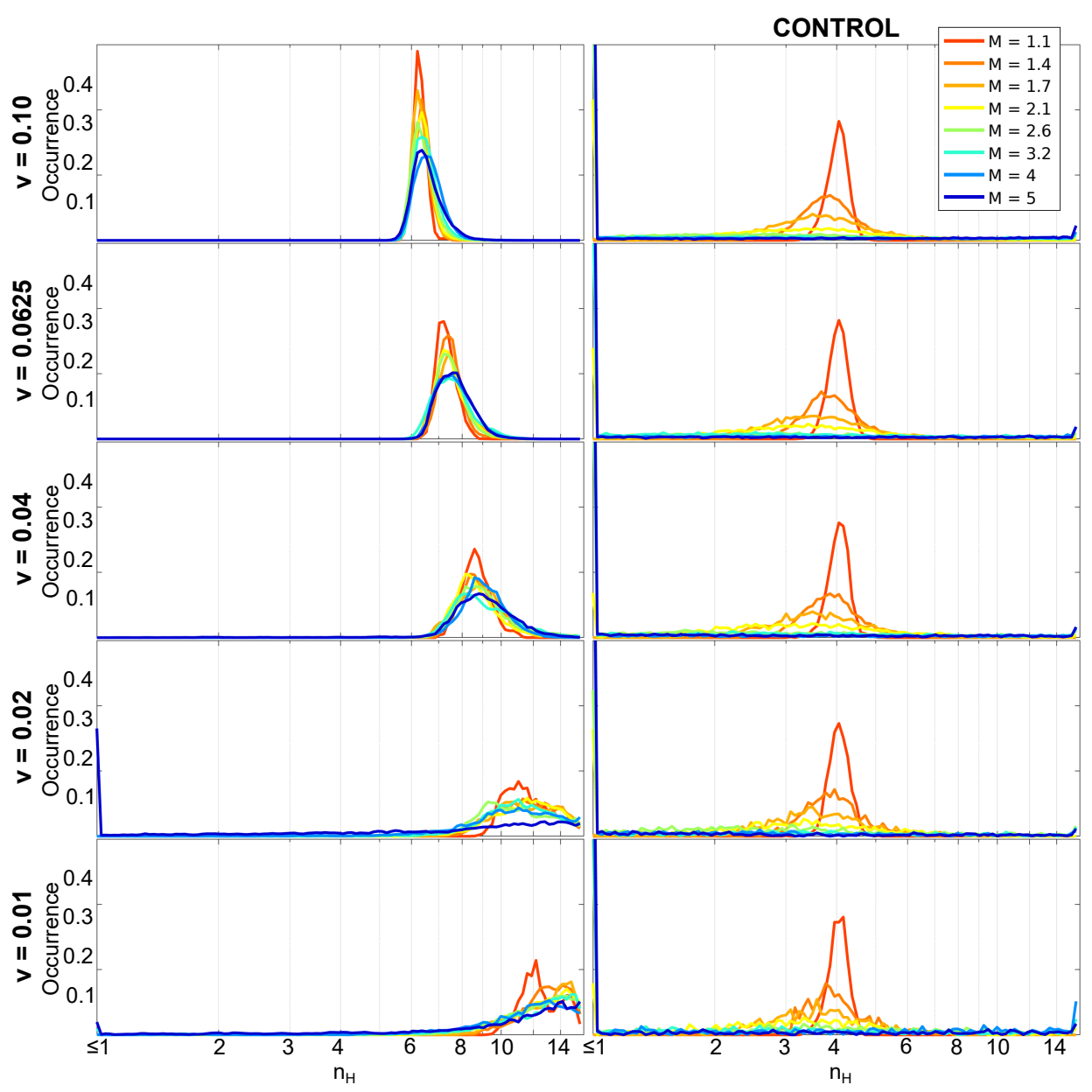
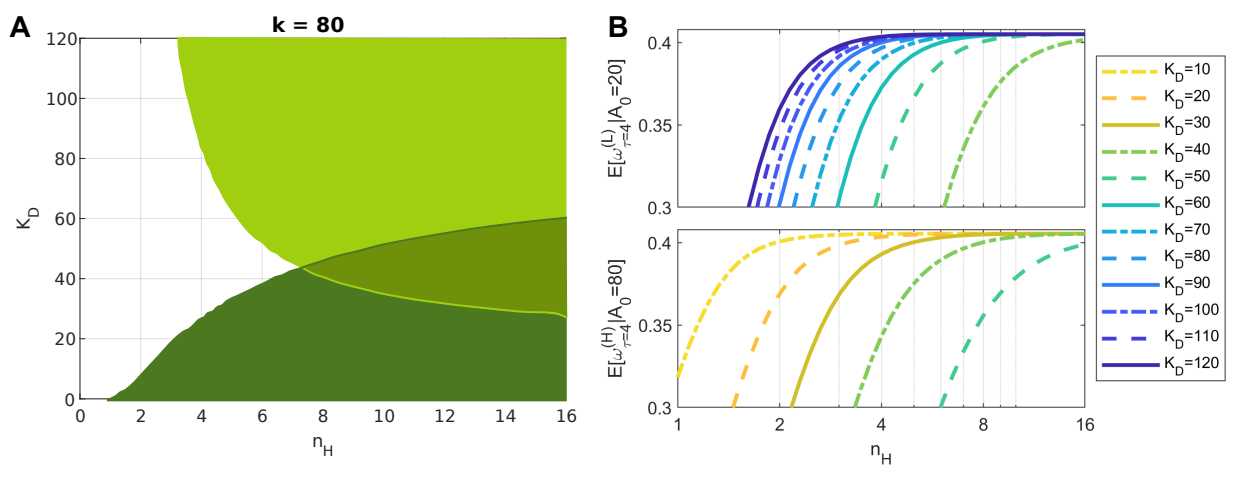
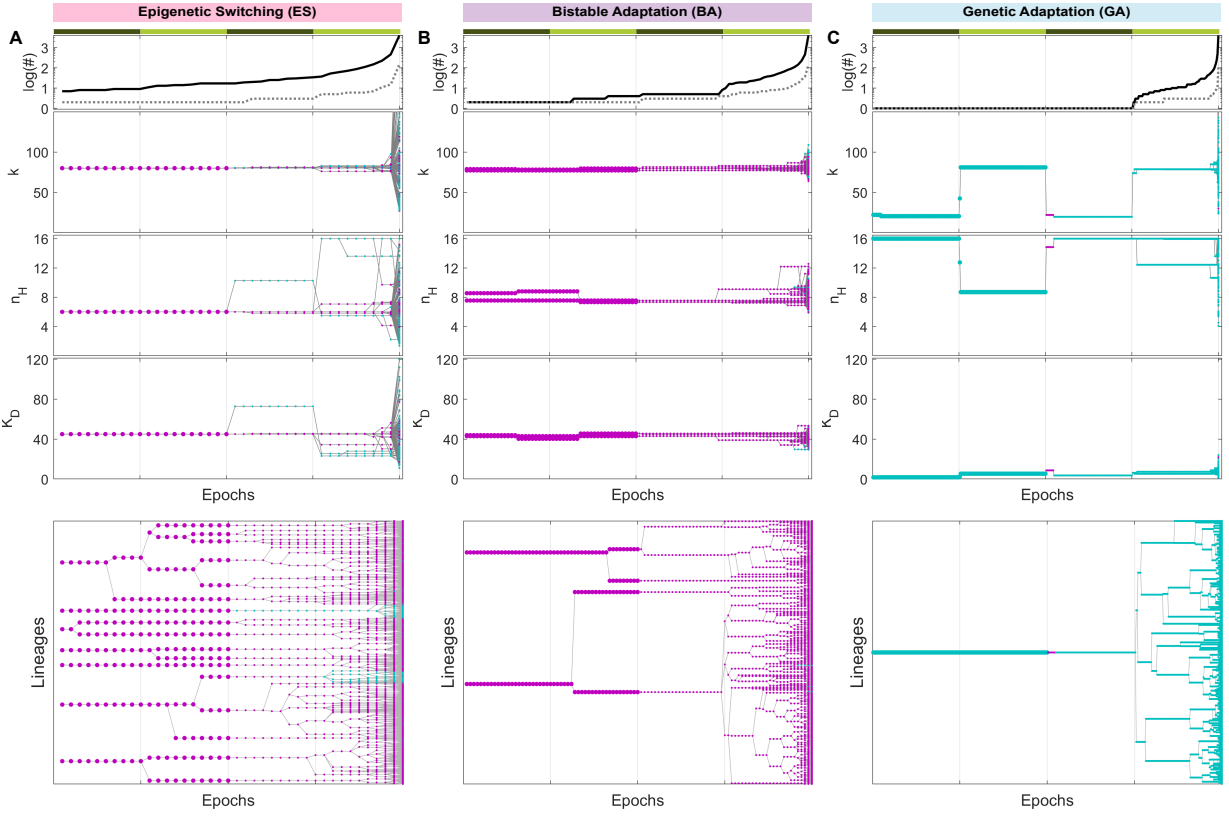
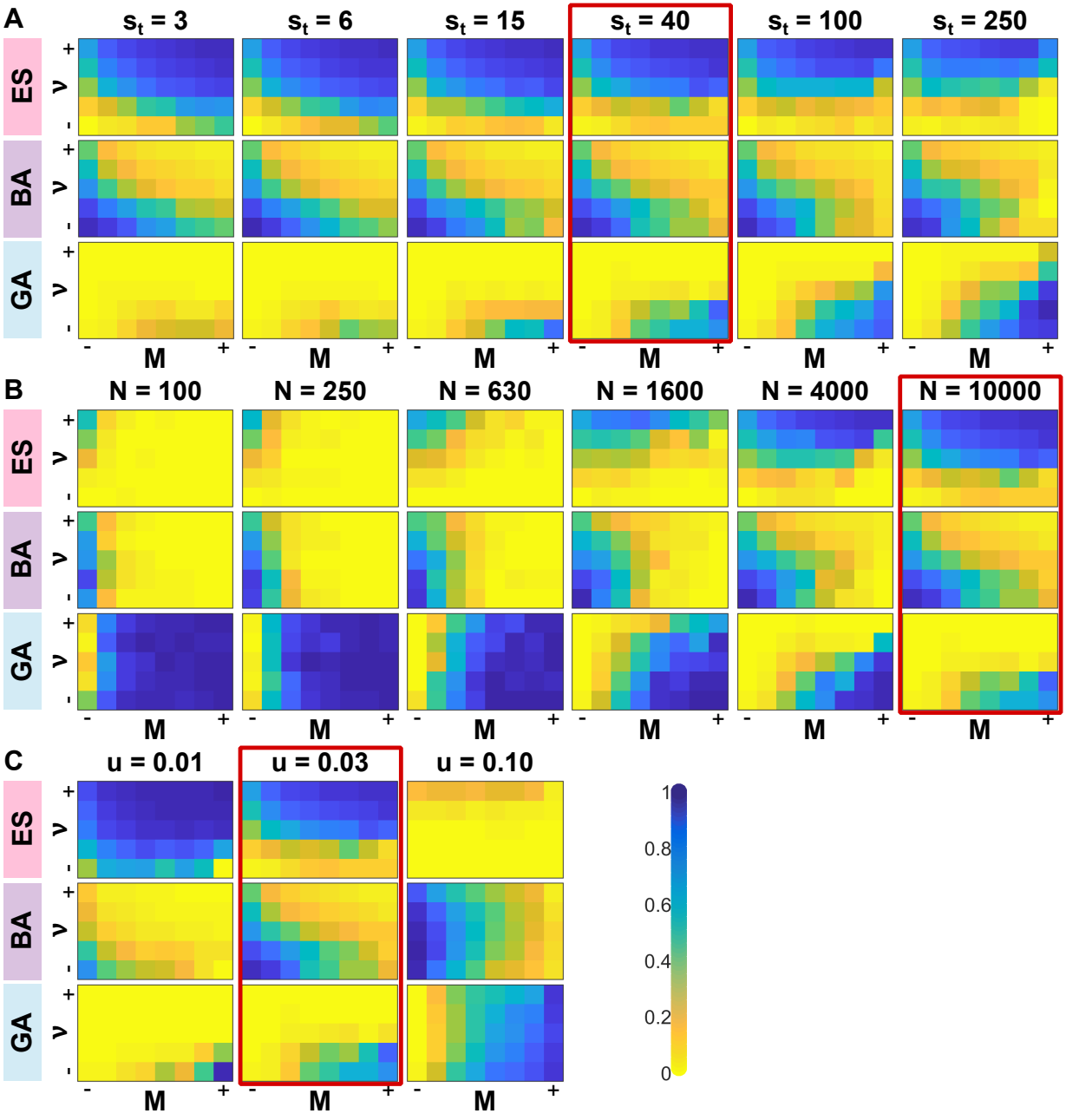

A
Protein synthesis: A f(A) A + 1
Protein degradation: A A - 1
k
αk
αk
k
K_D
A
k
αk
αk
K_D
k
A
K_D
Monostable
Bistable
Monostable
k
αk
k
K_D
k
αk
K_D
αk
k
A
B
k = 80 | α = 0.25 | K_D = 45
A*
80
60
40
20
0
0
4
8
12
16
n_H
A
80
20
ρ(A,τ=∞)


A
K_A = 1
K_A = 12
K_A = 44
n_A = 1
n_A = 16
80
20
20
80
A
γ·A
f(A|k_A*^(L))
f(A|k_A*^(H))
Steady states
(i.e. f(A)=γ·A):
Stable
Unstable
B
Solution genotypes per environment
Environment
LOW
HIGH
320
160
80
40
20
k_A*^(E)
80
40
20
10
1
K_A
1
2
4
8
n_A
C
Genetic potential map
100
80
60
40
20
1
K_A
1
2
3
4
5
6
7
8
10
12
14
n_A
1/M=1.1
1/M=1.4
1/M=1.7
1/M=2.1
1/M=2.6
1/M=3.2
1/M=4
d_M(θ*^(E))

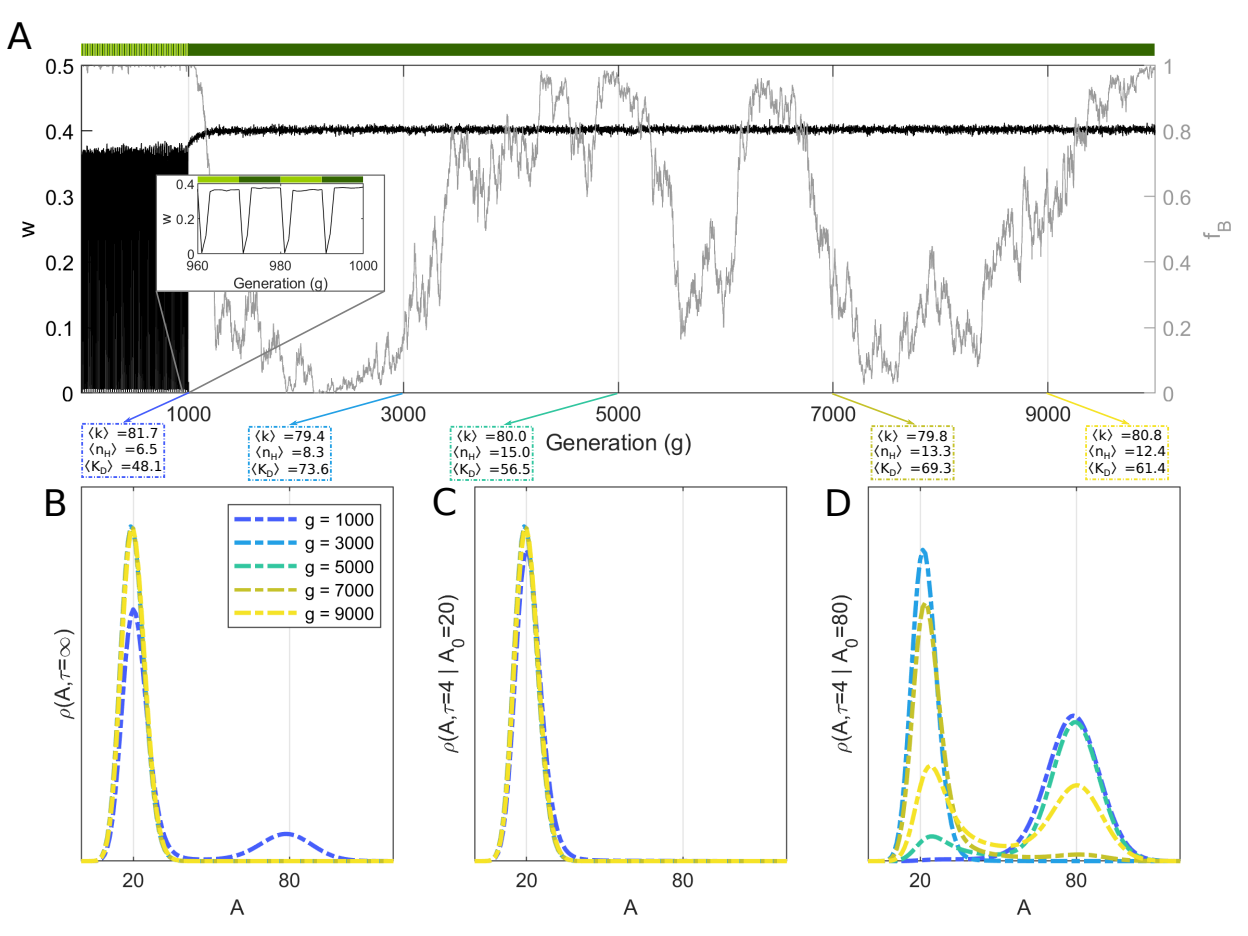

CONTROL
M = 1.1
M = 1.4
M = 1.7
M = 2.1
M = 2.6
M = 3.2
M = 4
M = 5
v = 0.10
v = 0.0625
v = 0.04
v = 0.02
v = 0.01
Occurrence
0.4
0.3
0.2
0.1
≤1
2
3
4
6
8
10
14
n_H

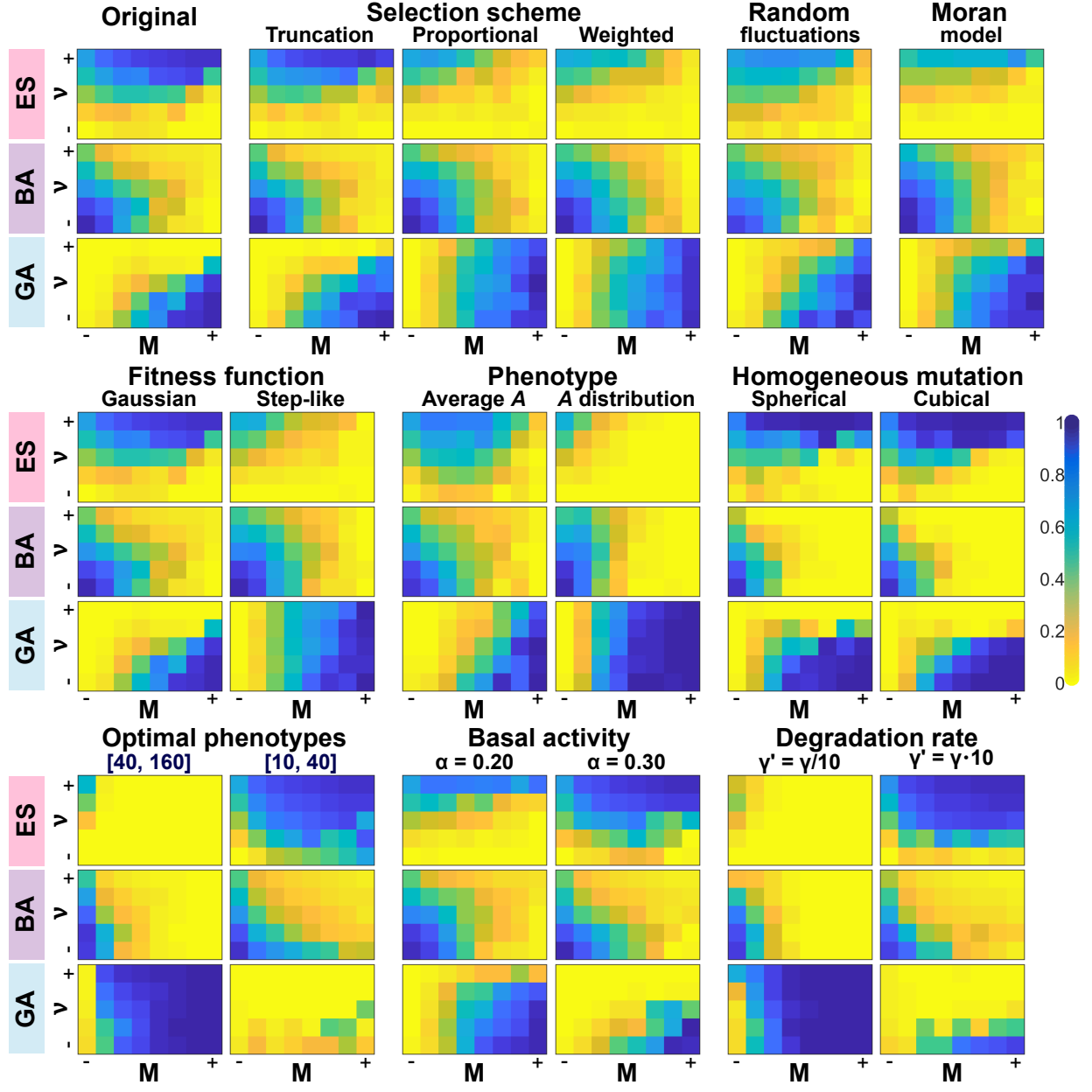

A
k = 80
K_D
n_H
B
E[ω^(L)_{τ=4}|A_0=20]
E[ω^(H)_{τ=4}|A_0=80]
n_H
K_D=10
K_D=20
K_D=30
K_D=40
K_D=50
K_D=60
K_D=70
K_D=80
K_D=90
K_D=100
K_D=110
K_D=120

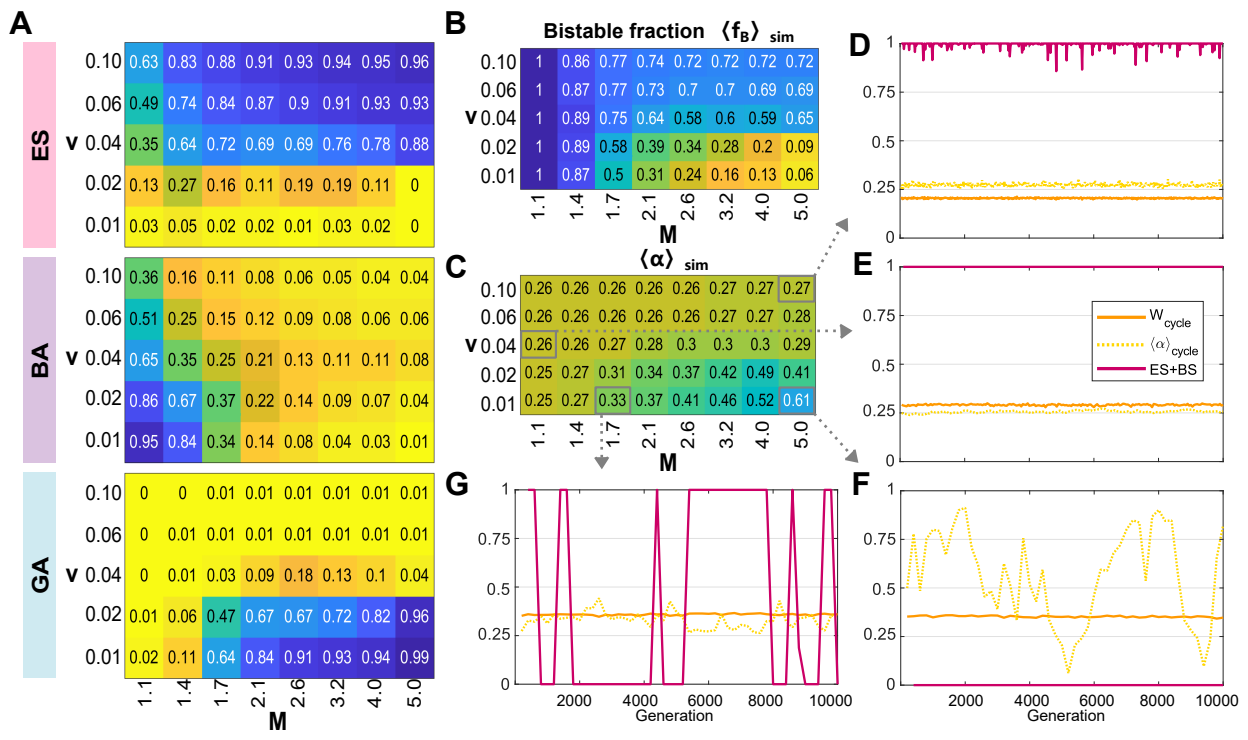

Epigenetic Switching (ES)
Bistable Adaptation (BA)
Genetic Adaptation (GA)
A
B
C
log(#)
k
n_H
K_D
Epochs
Lineages


A
s_t = 3
s_t = 6
s_t = 15
s_t = 40
s_t = 100
s_t = 250
ES
BA
GA
ν
M
+
-
B
N = 100
N = 250
N = 630
N = 1600
N = 4000
N = 10000
C
u = 0.01
u = 0.03
u = 0.10
1
0.8
0.6
0.4
0.2
0


M = 1.1
M = 1.4
M = 1.7
M = 2.1
M = 2.6
M = 3.2
M = 4.0
M = 5.0
v = 0.10
v = 0.06
v = 0.04
v = 0.02
v = 0.01
ES
BA
GA
0 20.5 42.8
0 12.9 23.9
0 0 0
0.2 9.8 71.8
0.1 2.6 14.9
0.1 0.1 0.5
0.2 5.8 81.4
0.1 1.2 10.4
0.1 0.2 0.8
0.1 4.4 85.8
0 0.8 8
0.1 0 0.8
0.1 3.8 88.3
0 0.4 6.7
0 0.1 0.6
0.1 2.9 91.2
0 0.2 4.9
0 0 0.7
0.1 2.8 91.4
0 0.3 4.9
0 0 0.5
0 2.2 93.5
0 0.2 3.7
0 0 0.5
0 22.4 27
0 25 25.6
0 0 0
0.2 13.9 57.8
0.2 7.6 19.7
0.1 0.2 0.4
0.3 9.6 69
0.1 4.1 15.5
0.3 0.4 0.8
0.2 8 75.2
0.1 2.3 13.1
0 0.3 0.9
0.1 5.4 82.1
0.1 1.1 10.2
0.1 0.1 0.7
0 5.5 83.2
0.1 1 9.2
0 0.1 0.8
0 3.8 88.1
0 0.5 6.6
0.1 0.1 0.7
0 3.2 89.6
0 0.3 6.2
0 0.1 0.6
0 20.6 12.7
0 44.9 21.8
0 0 0
0.2 18.3 36.6
0.2 20.9 23.3
0.1 0.3 0.2
0.9 13.5 47.5
0.9 12.8 21.9
0.2 1.4 1
0.9 9.9 61.6
0.8 6.2 17.7
0.5 1.5 0.9
1.2 9.1 60.7
1.8 6.3 15.4
1.5 2.3 1.7
1.2 6.8 67.3
1.4 3.2 12.5
3.1 2.3 2.1
0.2 5.7 79.6
0.1 1 11.3
0.5 0.5 1.1
0.4 5 73.9
0.4 1.5 9.8
6.8 1 1.3
0 10.4 1.3
0 78.3 10
0 0 0
0.3 13 6.7
0.7 64.4 13.5
0.4 0.7 0.3
1.4 11.8 11.7
5.2 48 13.7
1.3 5.5 1.5
2.3 9.8 13.6
10.7 29.3 12.5
7.4 11.9 2.6
2.8 8.5 21
9.5 16.5 11.8
16.2 10.6 3.2
2.6 8.9 23.3
9.3 12.7 11.9
18.3 10.3 2.8
3.7 5.3 21
7.7 7 8.9
33.5 9.9 3.1
1.9 2.4 4.7
5.8 2.9 2.6
71.3 6.6 1.8
0 1.4 0
0 97.2 1.4
0 0 0
0 5.1 0.7
2.3 83.8 5.8
0.7 1.6 0
0.4 6.9 1.2
10.6 60.1 7
3.5 10.1 0.3
1.7 6.1 3.2
16.2 32.9 7.3
15.2 15.9 1.5
3.4 4.9 6
14.4 24.4 6.7
22.2 15.4 2.7
3.1 3.7 5.4
12.8 11.8 6
41.1 14.9 1.2
4.1 3.6 4.9
11.4 8.9 5
46.5 13 2.6
2.2 3 6.9
6.1 7 3.4
63 6.7 1.8
GA BA ES
Current adaptation strategy
Previous adaptation strategy


A
w
f_B
Generation (g)
1000
3000
5000
7000
9000
⟨k⟩ =81.7
⟨n_H⟩ =6.5
⟨K_D⟩ =48.1
⟨k⟩ =79.4
⟨n_H⟩ =8.3
⟨K_D⟩ =73.6
⟨k⟩ =80.0
⟨n_H⟩ =15.0
⟨K_D⟩ =56.5
⟨k⟩ =79.8
⟨n_H⟩ =13.3
⟨K_D⟩ =69.3
⟨k⟩ =80.8
⟨n_H⟩ =12.4
⟨K_D⟩ =61.4
B
C
D
g = 1000
g = 3000
g = 5000
g = 7000
g = 9000
$\rho(A,\tau=\infty)$
$\rho(A,\tau=4 \mid A_0=20)$
$\rho(A,\tau=4 \mid A_0=80)$
A
20
80


Original
Selection scheme
Truncation
Proportional
Weighted
Random
fluctuations
Moran
model
ES
BA
GA
ν
M
Fitness function
Gaussian
Step-like
Phenotype
Average A
A distribution
Homogeneous mutation
Spherical
Cubical
1
0.8
0.6
0.4
0.2
0
Optimal phenotypes
[40, 160]
[10, 40]
Basal activity
α = 0.20
α = 0.30
Degradation rate
γ' = γ/10
γ' = γ·10


A
ES
BA
GA
v
M
0.10 0.63 0.83 0.88 0.91 0.93 0.94 0.95 0.96
0.06 0.49 0.74 0.84 0.87 0.9 0.91 0.93 0.93
0.04 0.35 0.64 0.72 0.69 0.69 0.76 0.78 0.88
0.02 0.13 0.27 0.16 0.11 0.19 0.19 0.11 0
0.01 0.03 0.05 0.02 0.02 0.01 0.03 0.02 0
0.10 0.36 0.16 0.11 0.08 0.06 0.05 0.04 0.04
0.06 0.51 0.25 0.15 0.12 0.09 0.08 0.06 0.06
0.04 0.65 0.35 0.25 0.21 0.13 0.11 0.11 0.08
0.02 0.86 0.67 0.37 0.22 0.14 0.09 0.07 0.04
0.01 0.95 0.84 0.34 0.14 0.08 0.04 0.03 0.01
0.10 0 0 0.01 0.01 0.01 0.01 0.01 0.01
0.06 0 0.01 0.01 0.01 0.01 0.01 0.01 0.01
0.04 0 0.01 0.03 0.09 0.18 0.13 0.1 0.04
0.02 0.01 0.06 0.47 0.67 0.67 0.72 0.82 0.96
0.01 0.02 0.11 0.64 0.84 0.91 0.93 0.94 0.99
1.1 1.4 1.7 2.1 2.6 3.2 4.0 5.0
B
Bistable fraction ⟨f_B⟩ sim
0.10 1 0.86 0.77 0.74 0.72 0.72 0.72 0.72
0.06 1 0.87 0.77 0.73 0.7 0.7 0.69 0.69
0.04 1 0.89 0.75 0.64 0.58 0.6 0.59 0.65
0.02 1 0.89 0.58 0.39 0.34 0.28 0.2 0.09
0.01 1 0.87 0.5 0.31 0.24 0.16 0.13 0.06
1.1 1.4 1.7 2.1 2.6 3.2 4.0 5.0
C
⟨α⟩ sim
0.10 0.26 0.26 0.26 0.26 0.26 0.27 0.27 0.27
0.06 0.26 0.26 0.26 0.26 0.26 0.27 0.27 0.28
0.04 0.26 0.26 0.27 0.28 0.3 0.3 0.3 0.29
0.02 0.25 0.27 0.31 0.34 0.37 0.42 0.49 0.41
0.01 0.25 0.27 0.33 0.37 0.41 0.46 0.52 0.61
1.1 1.4 1.7 2.1 2.6 3.2 4.0 5.0
D
E
W cycle
⟨α⟩ cycle
ES+BS
F
G
Generation
2000 4000 6000 8000 10000
0 0.25 0.5 0.75 1

Evolutionary dynamics of an epigenetic switch in a fluctuating environment

S1 Appendix. Supplementary Table: Previous Work

Authors	Year	Evolutionary strategies	Comparison method	Analytical/ Numerical	Phenotypes	Environment	Fitness	Selection	Explicit cost	Population size	Generations	Comments
Jablonka *et al*.	**1995**	Inducible switching; stochastic switching	Average growth rate	Both	2-discrete	Periodic & random; asymmetric (2 states)	Symmetric	Differential growth rate	Induction delay	Growing (discrete)	Non-overlapping	They compared three different strategies: non-inducible (with a small stochastic transition rate), completely inducible, or an intermediate response (memory), considering some induction delay and the phenotypic memory as a tunable property. They observed that the intermediate response is advantageous under random environmental fluctuations; if the environment is strictly periodic, the inducible system is favored unless fluctuations occur faster than the induction delay.
Lachmann & Jablonka	**1996**	Inducible switching; stochastic switching	Average growth rate	Analytical	2-discrete	Periodic (2 states)	Symmetric	Differential growth rate	None	Growing (discrete)	Non-overlapping	They explored the optimal values for the transition rates under fluctuating environments; they concluded that for non-inducible systems, the optimal rate for random transitions is around the frequency of the environmental fluctuations.
Thattai & van Oudenaarden	**2004**	Inducible switching; stochastic switching	Average growth rate	Analytical	2-discrete	Periodic & random (2 states)	Symmetric	Differential growth rate	None	Growing (continuous)	Continuous time (ODEs)	They considered that the transitions between phenotypic states depend on the environment and explored under which circumstances a transition rate to the "unfit" state different to zero will be selected; they concluded that if the transition to the "fit" state is fast enough –short induction delay–, an homogeneous population will be always favored.
Kussell & Leibler	**2005**	Inducible switching; stochastic switching	Average growth rate	Analytical	*n*-discrete	Random (*n* states)	No explicit assumption	Differential growth rate	Sensing, diversity & induction delay costs	Growing (continuous)	Continuous time (ODEs)	They compared inducible to stochastic transitions but taking in account the cost of sensing, the induction delay and the diversity cost imposed by the stochastic switching. They concluded that a sensor is only worth if the environment is highly uncertain, and the stochastic switching will be favored when the environment changes infrequently.
Kussell *et al*.	**2005**	Stochastic switching	Average growth rate	Both	2-discrete	Periodic; asymmetric (2 states)	Asymmetric	Differential growth rate	None	Growing (continuous)	Continuous time (ODEs)	They considered only stochastic transitions, and they observed that the type of environmental changes determines the strategy to be used.
Wolf *et al*.	**2005**	Fixed; inducible switching; stochastic switching	Average growth rate	Both	*n*-discrete (focus on *n*=2)	Random; asymmetric (*n* states)	Asymmetric	Differential growth rate	None	Growing (discrete)	Non-overlapping	They considered more flexible adaptation strategies, going from ignoring the environment, a deterministic inducible response, stochastic inducible response, to pure stochastic switching. If no sensor exists, stochastic switching is always selected under the time-varying environmental conditions selected here, as well as if the detection of the sensor is bad or long induction delays exist.
Ribeiro	**2008**	Inducible; stochastic switching (bistable genetic circuit)	Invasion	Simulations	Continuous (mechanistic)	Random (2 states)	Symmetric	Truncation selection	None	Fixed (discrete; 1000 individuals)	Non-overlapping	He modeled individual cells as toggle switches and explored the population behavior under a fluctuating environment, considering both inducible systems and pure stochastic switching. He concluded that the optimal noise level depends on the environmental fluctuations, and as noise increases, the fitness increases too in fast fluctuating environments.
Salathé *et al*.	**2009**	Fixed; stochastic switching	Invasion	Simulations	2-discrete (x 2-modifier states)	Periodic & random (2 states)	Asymmetric	Proportional selection scheme	None	Infinite (sub-population frequencies)	Non-overlapping	Assuming an infinite population and following subpopulation frequencies through generations, they explored the impact of asymmetric fitness landscapes. They concluded that with the fitness asymmetry over a certain threshold, unless the selection pressure is very strong in both environments, ignoring the environment becomes optimal over stochastic switching (with an optimal rate approximately equal to the environmental fluctuation frequency).
Gaál *et al*.	**2010**	Fixed; stochastic switching	Average growth rate	Analytical	2-discrete	Periodic; asymmetric (2 states)	Asymmetric	Differential growth rate	None	Infinite (sub-population frequencies)	Continuous time (ODEs)	They observed that as the asymmetry in the environments increases, the selected strategy goes from the optimal stochastic switching population (where the transition rate is assumed equal in both directions) to an equally optimal non-switching and switching populations, to finally being optimal to ignore the environment, even if a local maximum still exists for a switching rate distinct to zero.

Visco *et al*.	**2010**	Fixed; stochastic switching	Average growth rate	Analytical	2-discrete	Responsive (*i.e.* catastrophe rate depends on the population); random (one normal state & instantaneous catastrophe)	Asymmetric	Differential growth rate	None	Growing (continuous)	Continuous time (ODEs)	They explored the selection of stochastic switching under a single environment with occasional and instantaneous catastrophic events whose rate depends on the population structure. They observed that stochastic switching strategy is favored by strong catastrophes, while non-switching by weak catastrophes.
Liberman *et al*.	**2011**	Stochastic switching	Average growth rate & invasion	Both	2-discrete (x 2-modifier states with recombination)	Periodic (2 states)	Symmetric	Differential growth rate	None	Infinite (sub-population frequencies)	Non-overlapping	They took Salathé *et al*. (2009) and Gaál *et al*. (2010) one step forward including recombination in the model; they observed that, under their model, recombination makes unlikely that a stable non-zero transition rate exists.
Libby & Rainey	**2011**	Fixed; stochastic switching	Average probability of being selected	Both	4-discrete	Periodic (one normal state & instantaneous catastrophe)	Symmetric	Strong frequency dependent selection: exclusion rule + bottleneck	Switching cost	Growing (continuous)	Continuous time (ODEs)	They considered a strong frequency-dependent selection, with an exclusion rule for the most fitted subpopulation and bottleneck when the environment changes. Even considering a switching cost –reducing the growth rate on switching genotypes–, exclusion rules are observed to favor switching phenotypes; on the other hand, larger (weaker) bottlenecks permit faster-growing, non-switching types to pass through to the next "round" outgrowing the switching type.
Carja & Feldman	**2012**	Stochastic switching	Probability of survival	Simulations	*n*-discrete	Periodic (2 states)	Symmetric	Proportional selection scheme	None	Fixed (discrete; 10000 individuals)	Non-overlapping	They found that phenotypic variability increases in populations under fast fluctuating environments, but this effect disappears as the fluctuations become less frequent.
Kuwahara & Soyer	**2012**	Genetic adaptation; stochastic switching (bistable genetic circuit)	Natural selection	Simulations	Continuous (mechanistic)	Periodic & random (2 states)	Symmetric (binary function)	Proportional selection scheme	None	Fixed (discrete; 1000 individuals)	Non-overlapping	They not only included a mechanistic model, but considered the genetic adaptation to explore the adaptive origin of stochastic epigenetic switches under fluctuating environments. They observed that bistability emerges and is maintained only in a limited range of evolutionary conditions, and suggested that its selection occurs only as a byproduct of the selection for evolvability. Noteworthy, they assumed a "binary" fitness function which would not favor the underlying bimodal distribution in a bistable system.
Carja *et al.*	**2013**	Stochastic switching	Invasion	Both	4-discrete (x 2-modifier states with recombination)	Periodic & random (*n* states)	No explicit assumption	Differential growth rate	None	Infinite (sub-population frequencies)	Non-overlapping	An extension of Liberman *et al*. (2011) model; they reached similar conclusions.
Furrow & Feldman	**2014**	Inducible switching; stochastic switching	Invasion	Simulations	2-discrete (x 2-modifier states with 2 epigenetic states)	Periodic & random (2 states)	Asymmetric	Differential growth rate	Epigenetic regulation	Infinite (sub-population frequencies)	Non-overlapping	They expanded the classical modifier model (e.g. Salathé *et al*., 2009) to consider inducible switching and the associated cost. They observed that the environmental fluctuation frequency influences the conditions for evolution of epigenetic regulation (either induced or stochastic switching).
Carja *et al.* (*Genetics*)	**2014**	Stochastic switching	Invasion	Both	2-discrete (x 2-modifier states with recombination)	Periodic (2 states)	Symmetric	Differential growth rate	None	Infinite (sub-population frequencies)	Non-overlapping	They took Salathé *et al*. (2009) one step forward including migration in the model, and study the evolution of switching rates in the presence of both spatial and temporal heterogeneity in selection pressures. They observed that the evolutionary dynamics of the system are mainly governed by the environmental fluctuation rate.
Carja *et al.* (*PNAS*)	**2014**	Stochastic switching	Invasion	Both	4-discrete (x 2-modifier states with recombination)	Periodic & random (2 states)	Asymmetric	Differential growth rate	None	Infinite (sub-population frequencies)	Non-overlapping	They took Salathé *et al*. (2009) and Liberman *et al*. (2011) one step forward including migration in the model, and compare it to the effect of mutation and recombination as sources of phenotypic variation; they observed that, under their model, these three essentially different evolutionary forces respond very similar to fluctuating selection.

Botero *et al.*	**2015**	Inducible switching; genetic adaptation	Natural selection	Simulations	Continuous	Periodic (continuous)	Symmetric	Proportional selection scheme	Phenotypic plasticity	Fixed (discrete; 5000 individuals)	Non-overlapping	They used an abstract model which, while simple, can still display plasticity, bet-hedging, and genetic adaptation. Testing multiple environmental variation patterns, they observed that different adaptive responses consistently evolve under different timescales and predictabilities of the environmental variation.
Lin *et al.*	**2015**	Fixed; stochastic switching	Frequency	Simulations	2-discrete	Periodic (2 states) + bottlenecks	Symmetric	Differential growth rate	None	Growing (discrete)	Continuous time	They explored the origin of the stochastic transitions in fluctuating environments distinguishing between standing variation and *de novo* mutations using both an experimental and a mathematical model. They concluded that the contribution of each of these mechanisms on the adaptation process depends on the fluctuation timescales.
Belete & Balázsi	**2015**	Stochastic switching	Average growth rate	Both	2-discrete	Periodic; asymmetric (2 states)	Asymmetric	Differential growth rate	None	Fixed (discrete; 10000 individuals)	Non-overlapping	They explored the stochastic switching rate dependency to the environmental fluctuation frequency in asymmetric environments and fitness as the environmental duration shorten. In this limit, they observed that the previously described optimal switching rate matching environmental fluctuation frequency does not always hold.
Gómez-Schiavon & Buchler	**-**	Genetic adaptation; stochastic switching (bistable genetic circuit)	Natural selection	Simulations	Continuous (mechanistic)	Periodic & random (2 states)	Symmetric (Lorentzian function)	Tournament selection scheme	None	Fixed (discrete; 10000 individuals)	Non-overlapping	-

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Belete MK & Balázsi G (2015). Optimality and adaptation of phenotypically switching cells in fluctuating environments. *Physical Review E, 92(6), 62716*.

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Carja O & Feldman M (2012). An equilibrium for phenotypic variance in fluctuating environments owing to epigenetics. *J R Soc Interface, 9(August 2011), 613–623*.

Carja O, Liberman U & Feldman MW **(2013)**. Evolution with stochastic fitnesses: A role for recombination. *Theoretical Population Biology, 86, 29–42*.

Carja O, Liberman U & Feldman MW **(2014)**. Evolution in changing environments: Modifiers of mutation, recombination, and migration. *Proceedings of the National Academy of Sciences, 111(50), 17935–17940*.

Carja O, Liberman U & Feldman MW **(2014)**. The evolution of phenotypic switching in subdivided populations. *Genetics, 196(4), 1185–1197*.

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Epigenetic switching as a strategy for quick adaptation while attenuating biochemical noise

Mariana Gómez-Schiavon[1,2,3,4] and Nicolas E. Buchler[2,3,5,6]

[1] *Program in Computational Biology & Bioinformatics, Duke University, Durham, NC 27708*

[2] *Center for Genomic & Computational Biology, Duke University, Durham, NC 27710*

[3] *Department of Biology, Duke University, Durham, NC 27708*

[4] *Current Address: Department of Biochemistry and Biophysics, UCSF, San Francisco, CA, USA*

[5] *Department of Physics, Duke University, Durham, NC 27708*

[6] *Current Address: Department of Molecular Biomedical Sciences, North Carolina State University, NC, USA*

S2 APPENDIX. ALTERNATIVE ASSUMPTIONS DETAILS.

We tested the robustness of our results to alternative choices and assumptions in the presented model by: changing the used evolutionary model (Section A), allowing the environment to fluctuate randomly between the two possible states with mean frequency ν (Section B), using the average protein number or the distribution of protein numbers over the individual life span as phenotype (Section C), changing the fitness function to a Gaussian or a step-like function with similar span around the optimal phenotypes (Section D), implementing different selection schemes (Section E), as well as different mutation schemes (Section F). Additionally, more quantitative aspects of the model were perturbed by exploring other optimal phenotypes for the environments (Section G), basal activity α values (Section H), and different degradation rate γ values (Section I). In addition, we allowed the basal activity α parameter to evolve simultaneously with $\{k, n_H, K_D\}$ (see S10 Fig).

A. Moran model

Wright-Fisher and Moran models are the most common options to simulate evolution. In our main simulations, we implemented a version of the Wright-Fisher model with non-overlapping generations. Alternatively, we tested a Moran model, where the reproduction and death events are treated as stochastic events allowing overlapping generations. At each time step, an individual is chosen for reproduction using the defined tournament selection scheme, and an individual is randomly chosen from the population for death to keep the population size N fixed. N time steps occur in the previously defined lifespan time, such that the reproduction rate (and then mutation) is equivalent to the original model.

B. Environmental random fluctuations

The environmental fluctuations in our main simulations were regular and periodic with frequency ν. We tested whether stochastic fluctuations with frequency ν produced different results; even though previous work demonstrated little difference between the two types of fluctuations [1–4]. In these alternative simulations, the environment fluctuates randomly between the two possible states with mean frequency ν.

C. Phenotype definition

Our simulations evaluated the protein number (phenotype) at the end of Gillespie simulation (individual life span) to calculate a fitness score given by a Lorentzian function centered the optimal phenotype. We also tested alternative phenotype definitions: (1) the life-time average protein number to assign its fitness score to each individual in the population, or (2) the life-time protein number distribution to calculate the average fitness score for each individual in the population.

D. Fitness functions

We also changed the shape of the fitness function from a Lorentzian to a Gaussian fitness function:

$$\omega_g^{(E)}(A) = e^{-\frac{(A-A^{(E)})^2}{2\sigma^2_{(E)}}} \tag{S1}$$

where $\sigma^2_{(E)}$ is equal to the width in the Lorentzian fitness function (v^2); or a step-like function:

$$\omega_s^{(E)}(A) = \begin{cases} 1 & \text{if } (A - A^{(E)})^2 \leq 2\sigma^2_{(E)} \\ 0, & \text{otherwise} \end{cases} \tag{S2}$$

where $\sigma^2_{(E)}$ is equal to the width in the Lorentzian fitness function (v^2).

E. Selection schemes

We used Tournament selection to select the next generation of cells based on the fitness of the individuals in the current generation. Other common selection schemes are Truncation, Proportional, and Weighted selection [5].

In the truncation selection scheme, only a certain fraction of the best individuals can be selected, each with the same probability. Blickle & Thiele (1995) calculated the truncation fraction that resulted in the same selection strength as a given tournament size (Table I). They estimated that $s_t = 40$ corresponds to a 0.04 truncation fraction. We used this fraction in our Truncation selection simulation.

Using the proportional selection scheme, the probability of an individual to be selected is proportional to its fitness value. Similarly, in the weighted selection scheme, a random

TABLE I. **Evolutionary parameters**

	Parameter	**Range**	**Units**
N	Population size	$\{100, 250, 630, 1600, 4000, 10000\}$	individuals
ν	Environmental fluctuation frequency	$\{0.01, 0.02, 0.04, 0.0625, 0.10\}$	1/generation
s_t	Selection pressure (i.e. tournament size)	$\{3\,(47\%), 6\,(\textit{24\%}), 15\,(\textit{10\%}),$ $40\,(4\%), 100\,(\textit{1.7\%}), 250\,(\textit{0.7\%})\}$[a]	individuals
u	Mutation rate	$\{0.01, 0.03, 0.10\}$	(1/individual) (1/generation)
M	Mutation step-size (i.e. maximum fold change)	$\{1.1, 1.4, 1.7, 2.1, 2.6, 3.2, 4.0, 5.0\}$	

[a] The equivalence between tournament size and truncation selection is shown in parenthesis. The numbers in italics were inter- and extrapolated from the values presented in [5].

individual is picked from the population and is cloned into the new population if a uniformly distributed random number (from the interval [0,1]) is below its fitness. Importantly, the selection strength cannot be directly tuned in either of these two schemes.

F. Mutation scheme

Our simulations used a spherically symmetric 3D mutation scheme to permit co-variation in biophysical parameters in a single mutational step. Co-variation is expected in a natural system as a single mutation can simultaneously affect multiple biophysical parameters; and the spherical space is a natural interpretation of M as the maximum mutation step-size, making it the maximum fold-change "distance" from the parental genotype. The actual mutation step size was determined by the radius of the spherical mutation, which was a uniformly distributed random value between 0 and 1 ($r \sim U(0,1)$). Such a radial density produces a non-uniform density of mutations with highest densities close to the parental phenotype because volume scales as r^3. We tested homogeneous spherical mutation by substituting r in Eqs. (5-7) with $\sqrt[3]{r}$ and a homogeneous cubic mutation where three uniformly distributed random value between -1 and 1 ($r_i \sim U(-1,1)$) for each biophysical parameter. We also verified that mutating only one parameter at a time (1D mutation) and increasing

the range of biophysical parameters to allow higher nonlinearity ($10^{-2} \leq n_H \leq 24$) and weaker DNA dissociation constants ($10^{-2} \leq K_D \leq 10^3$) did not fundamentally change our results.

G. Optimal phenotypes

The main simulations were performed with the LOW environment selecting for an optimal phenotype $A^{(L)} = 20$ proteins and HIGH environment for an optimal phenotype $A^{(H)} = 80$ proteins. The effects of doubling ($A^{(L)} = 40$ proteins, $A^{(H)} = 160$ proteins) and dividing by two ($A^{(L)} = 10$ proteins, $A^{(H)} = 40$ proteins) these values were explored.

H. Basal activity

At high levels of nonlinearity, the lowest protein level is $k \cdot \alpha$ and the highest protein level is k. A bistable, epigenetic switch has two solutions, each well-adapted to one of the environments only when the ratio $R = A^{(L)}_{opt}/A^{(H)}_{opt} = \alpha$ (S1 Fig). Any mismatch between α and R will disfavor epigenetic switching because an epimutation from an adapted mode will jump to a maladapted mode, after which the descendants must accumulate genetic mutations to further adapt. We explored the effect of other values of basal activity parameter ($\alpha = 0.2$, and $\alpha = 0.3$), but adjusting the LOW optimal phenotype accordingly ($A^{(L)} = 16$ proteins, and $A^{(L)} = 24$ proteins, respectively).

The rate of epimutation is sensitive to the frequency and magnitude of stochastic events. The magnitude of stochastic events is inversely proportional to the total number of molecules. A higher rate of epimutation for smaller numbers of molecules is expected. The rate of epimutation should also increase as the two modes become closer. Thus, we expect a higher rate of epimutation for larger α.

I. Degradation rate

The protein degradation rate (γ) sets the timescale between stochastic events (i.e. faster protein degradation leads to more stochastic events per unit time during a Gillespie simula-

tion). Thus, we expect a higher rate of epimutation for larger γ.

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