Models of Switching in Biophysical Contexts

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Plan

Plan

- **I** Thoughts on biophysical modelling
- **II** Switching between states
- **III** Microscopic dynamics: model linear feedback switch
- **IV** Macroscopic dynamics: population growth in a catastrophic environment

References:

P. Visco, R. J. Allen, M. R. Evans, Phys. Rev. Lett. 2008, Phys. Rev. E 2009

P. Visco, R. J. Allen, S. N. Majumdar, M. R. Evans, Biophysical Journal 2010

Physics vs Biology

Physics

- Unifying Principles
- Effective Theories; minimal models
- Mathematical “proof”
  e.g. Free energy minimisation

Biology

- System details
- Models with many parameters to fit data
- Argumentation
  e.g. Evolutionary pressures

What can physicists bring to biophysical modelling?

Ideas from (statistical) physics

- many particle behaviour
- non equilibrium phenomena
- fluctuations and stochastic effects
- idea of scales

Model building savoir faire

- minimal models
- exact solutions; good approximations

What can physicists bring to biophysical modelling?

Ideas from (statistical) physics

- many particle behaviour
- non equilibrium phenomena
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Model building savoir faire

- minimal models
- exact solutions; good approximations

What physicists shouldn't bring

- Arrogance and ignorance

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I Thoughts on biophysical modelling

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III Microscopic dynamics: model linear feedback switch

IV Macroscopic dynamics: population growth in a catastrophic environment

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II Switching: Basic Biology for Physicists

Gene

- Stretch of DNA $\sim$ 1000 base pairs long
- Transcription by RNAp $\rightarrow$ mRNA
  Translation $\rightarrow$ amino acids $\rightarrow$
  production of proteins $\rightarrow \ldots \rightarrow$ Phenotype

Regulation

- regulatory sites at ends of gene
  known as 'operators'
- gene switched off/on by binding of repressors/enhancers known as
  'Transcription factors'
- genes can produce transcription factors for themselves or other genes
  $\rightarrow$ genetic network

Heterogeneity

- Populations of bacteria are often heterogeneous even if environmentally and genetically identical
- Happens when bacteria frequently switches between different states:
  - Multistable genetic switches
  - Stochastic “oscillation” between different states
- It represents a strategy against environmental changes and stresses
- Examples:
  - Bacterial persistence
  - Phase variation (e.g.: fimbriae)

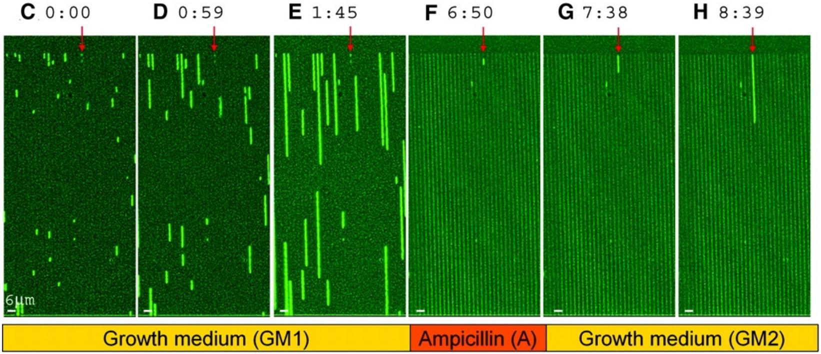
Example: Bacterial persistence

Non persistent state

- Vulnerable to antibiotics
- Fast growth

Persistent state

- Resists against antibiotics
- Very slow growth



Balaban, Merrin, Chait, Kowalik, Leibler, Science, 2004

Examples of population "strategies"

"Bet Hedging" – small fraction of population in unfit "persistor state" which can survive catastrophes e.g. antibiotics

"Once and for all" – Population splits into groups with long lived phenotypes i.e. bistability

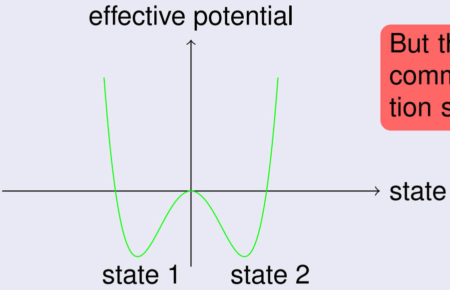
Defence against immune response – small fraction of population in fit state since too successful a population would evoke an immune response

Models of genetic switches

Existing models for bistable gene regulatory networks

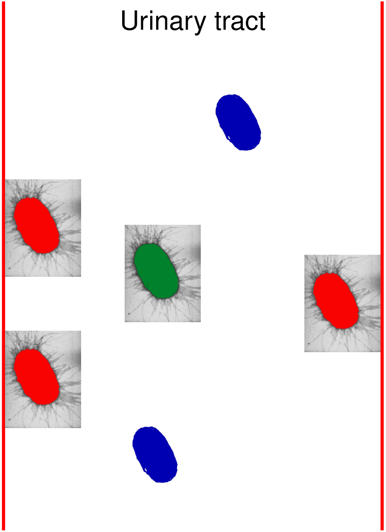
- Mutually repressing genes
- Positive feedback loop

Typically: bistable systems



But this is not how the most common bacterial phase variation systems work!

Example: Uropathogenic *E.Coli*



 Attached, fimbriated

 Detached, fimbriated

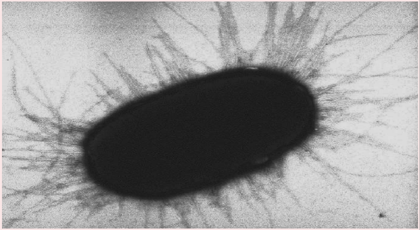
 Detached, non fimbriated

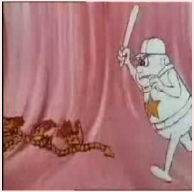
Attached vulnerable to immune system

Detached vulnerable to flushing

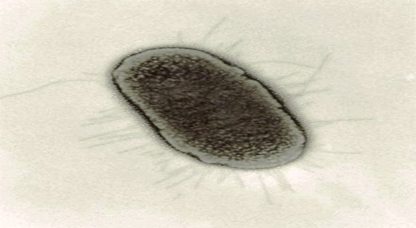
Example: Uropathogenic *E. Coli*

Fimbriated state





Non fimbriated state



The *fim* switch

DNA inversion switch

- *fim* system controls production of fimbriae
- short piece of DNA can be inserted in two orientations
- in one orientation fimbrial genes transcribed and fimbriae produced (“on state”)
- inversion of DNA element mediated by recombinase enzymes
- FimE recombinase which flips the switch on to off is produced more strongly in the on state “orientational control”

III Model of stochastic linear feedback switch

Reaction network

$$\left.\begin{aligned} R_1 &\xrightarrow{k_1} \emptyset \\ S_{\texttt{on}} &\xrightarrow{k_2} S_{\texttt{on}} + R_1 \end{aligned}\right\} \quad \boxed{R_1 \text{ variations}}$$

$$\left.\begin{aligned} S_{\texttt{on}} + R_1 &\xrightarrow{k_3^{\text{on}}} S_{\texttt{off}} + R_1 \\ S_{\texttt{on}} &\underset{k_4}{\overset{k_4}{\rightleftharpoons}} S_{\texttt{off}} \end{aligned}\right\} \quad \boxed{\text{switching reactions}}$$

Reaction rates

k_1 R_1 decay

k_2 R_1 production

k_3^{on} R_1 mediated switching (only `on` to `off`)

k_4 spontaneous switching (both directions)

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In the on state:

$$\frac{dn}{dt} = k_2 - k_1 n$$

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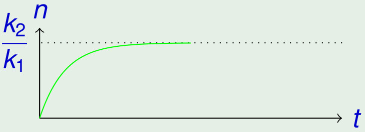
In the on state:

$$n(t) = \frac{k_2}{k_1}[1 - \exp(-k_1 t)]$$



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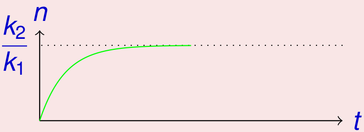
In the `off` state:

$$\frac{dn}{dt} = -k_1 n$$



III Model of stochastic linear feedback switch

Reaction network

$$R_1 \xrightarrow{k_1} \emptyset$$

$$S_{\mathtt{on}} \xrightarrow{k_2} S_{\mathtt{on}} + R_1$$

R_1 variations

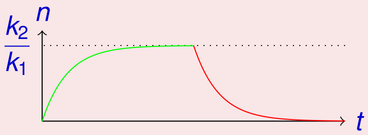
$$S_{\mathtt{on}} + R_1 \xrightarrow{k_3^{\mathrm{on}}} S_{\mathtt{off}} + R_1$$

$$S_{\mathtt{on}} \underset{k_4}{\overset{k_4}{\rightleftharpoons}} S_{\mathtt{off}}$$

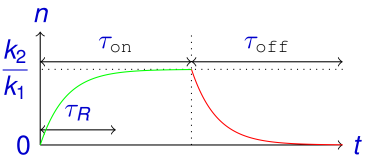
switching reactions

In the `off` state:

$$n(t) = n_0 exp(-k_1 t)$$



Scales



Three timescales

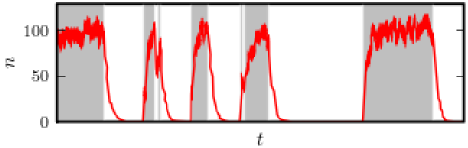
τ_R	relaxation time of n:	$\sim 1/k_1$
$\tau_{\texttt{on}}$	`on` to `off` switching time:	$\sim 1/(\langle n \rangle_{\texttt{on}} k_3^{\texttt{on}} + k_4^{\texttt{on}})$
$\tau_{\texttt{off}}$	`off` to `on` switching time:	$\sim 1/k_4^{\texttt{off}}$

Two n scales

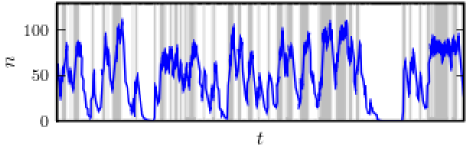
$n_{\texttt{on}}$	asymptotic value of n in the `on` state:	$\sim k_2/k_1$
$n_{\texttt{off}}$	asymptotic value of n in the `off` state:	~ 0

Some examples

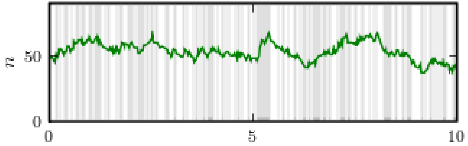
$\tau_R \ll \tau_S$



$\tau_R \sim \tau_S$



$\tau_R \gg \tau_S$



Statistical description

Define

$p_s(n,t)$ probability that there are n enzymes *and* the switch is in position $s \equiv \{\mathtt{on}, \mathtt{off}\}$ at time t.

Master equation

$$
\begin{aligned}
\frac{dp_s(n)}{dt} &= k_1[(n+1)p_s(n+1) - np_s(n)] \\
&+ k_2^s[p_s(n-1) - p_s(n)] \\
&+ n[k_3^{1-s}p_{1-s}(n) - k_3^s p_s(n)] \\
&+ k_4[p_{1-s}(n) - p_s(n)]
\end{aligned}
$$

Removal of R_1

Production of R_1
(if the switch is $\mathtt{on}$)

R_1–mediated switching

spontaneous switching

Steady state: two coupled equations

$$(n+1)k_1 p_{\rm on}(n+1) + k_2 p_{\rm on}(n-1) + k_4 p_{\rm off}(n) = (nk_1 + k_2 + nk_3^{\rm on} + k_4)p_{\rm on}(n)$$

$$(n+1)k_1 p_{\rm off}(n+1) + nk_3^{\rm on} p_{\rm on}(n) + k_4 p_{\rm on}(n) = (nk_1 + k_4)p_{\rm off}(n)$$

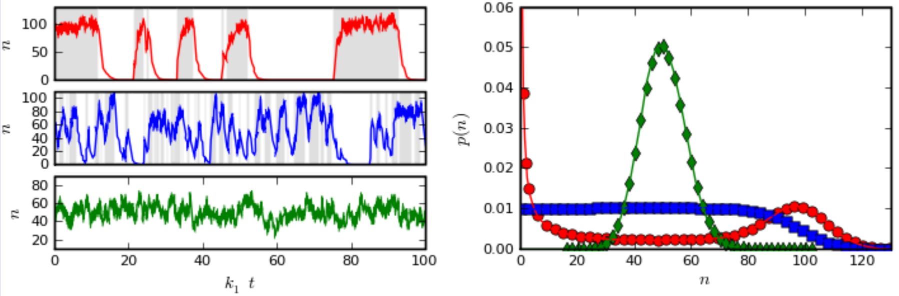
Exact solution

$$\begin{aligned} p_{\rm on}(n) &= a_0 \frac{(u_1-u_0)^n}{n!} \frac{(\eta)_n}{(\zeta)_n} \, {}_1F_1(\eta+n, \zeta+n, u_0) \\ p_{\rm off}(n) &= \kappa\delta_{n,0} + \frac{k_2}{k_1} \frac{p_{\rm on}(n-1)}{n} - p_{\rm on}(n) \end{aligned}$$

where u_1, u_0, η, ζ are combinations of the reaction rates and κ, a_0 are normalising constants

Test against simulations

Plot of $p(n) = p_{\text{on}}(n) + p_{\text{off}}(n)$



$\longrightarrow$ Perfect agreement

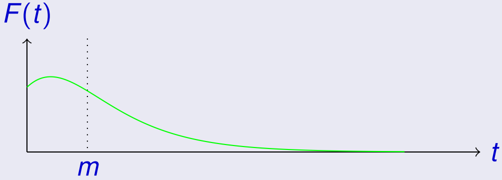
Flipping time distribution

Flipping time distribution

$F_{\mathrm{on}}(t)dt$ probability that the switch flips at time $t \to t + dt$

Compare with mean first passage times and persistence distributions of stochastic processes

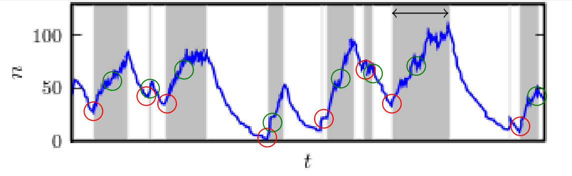
We would like to see peak around typical time to be in on-state



Can the model achieve this? require $\boxed{\left.\frac{dF(t)}{dt}\right|_{t=0} > 0}$

Measurement *ensemble*

$F(T)$ depends on the initial condition of n_i



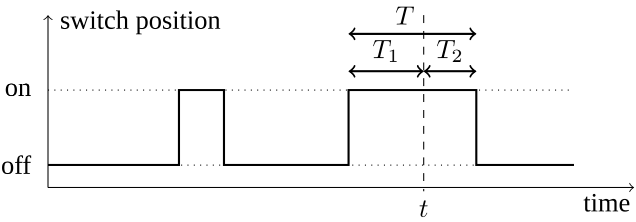
Two choices:

○ *Switch change ensemble* SCE

○ *Steady state ensemble* SSE

Initial distribution $W(n_i)$ defines the *ensemble*

Relation between *ensembles*



Probability that t is an interval T: $\quad \mathrm{Prob}(T)dT = \dfrac{T\,F^{\mathrm{SCE}}(T)dT}{\int_0^\infty T' F^{\mathrm{SCE}}(T')dT'}$

$$\mathrm{Prob}(T_2|T)dT = \frac{\theta(T - T_2)dT}{T} \quad \text{(uniform)}$$

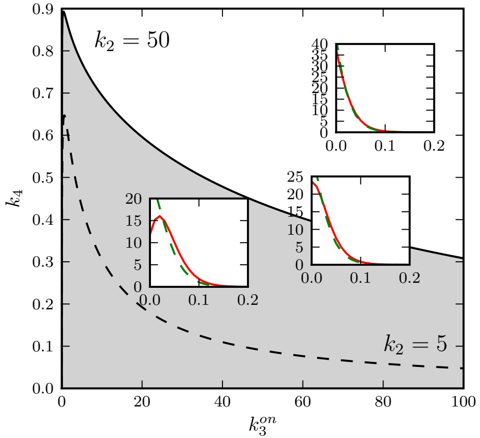
$$F^{\mathrm{SSE}}(T_2) = \int_{T_2}^{\infty} \mathrm{Prob}(T_2|T)\mathrm{Prob}(T)dT = \frac{\int_{T_2}^{\infty} F^{\mathrm{SCE}}(T)dT}{\int_0^\infty T F^{\mathrm{SCE}}(T)dT}$$

General relation from renewal theory: $\boxed{\dfrac{\mathrm{d}F^{\mathrm{SSE}}}{\mathrm{d}T} = -\dfrac{F^{\mathrm{SCE}}(T)}{\langle T \rangle_{\mathrm{SCE}}}}$

Peak in the distribution

- never a peak in SSE
- in SCE require

$$\boxed{k_2 k_3^{\mathrm{on}} - (k_4)^2 - k_3^{\mathrm{on}}(k_1 + 2k_4)\,\langle n \rangle_W - (k_3^{\mathrm{on}})^2 \langle n^2 \rangle_W > 0}$$



Visco, Allen, Evans, PRL **101** 118104 (2008);

IV Population dynamics in changing environments

Consider whether switching rate to a less fit state is advantageous for the population

Previous studies

- Thattai and Van Oudenaarden, Genetics 2004 2 environments, 2 phenotypes, Poissonian environmental changes
- Kussell and Leibler, Science 2005 many environments and phenotypes, different phentotypes have preferred environment
- Random switching between phenotypes good strategy when environmental changes unpredictable

General scenario

- Single environment
- Population of bacteria, say, with two possibles states for individuals:

  Fit state has fast growth
  Unfit (persistor) state has slow growth but withstands catastrophes
- **Catastrophes** occur stochastically, coupled to growth of population
- **Question:** what is best ‘strategy’ of population to maximise growth?

Model

Deterministic growth

Two subpopulations n_A and n_B.

Exponential growth rates $\gamma_A > \gamma_B$

Individuals switch states with rates k_A, k_B

$$\frac{\mathrm{d}n_A}{\mathrm{d}t} = \gamma_A n_A + k_B n_B - k_A n_A \ ,$$

$$\frac{\mathrm{d}n_B}{\mathrm{d}t} = \gamma_B n_B + k_A n_A - k_B n_B \ .$$

Stochastic catastrophes

Catastrophe rate $\beta(n_A, n_B)$

β is the *environmental response function*

When a catastrophe occurs $n_A \to n'_A < n_A$, with probability density $\nu(n'_A|n_A)$.

ν is the *catastrophe strength distribution*

Fitness

Biological definition: instantaneous growth rate of population

Here f is fraction of population in fit state

$$f = \frac{n_A}{n_A + n_B}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \gamma_A n_A + \gamma_B n_B = (\gamma_B + \Delta\gamma f)n$$

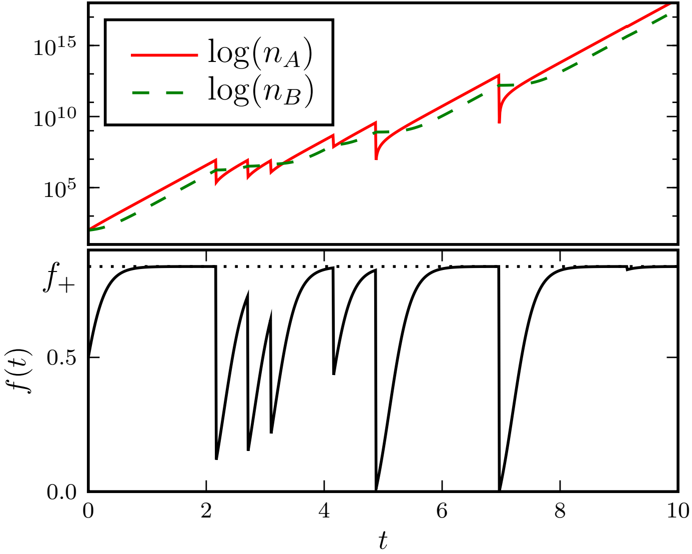
Deterministic growth:

$$\frac{\mathrm{d}f}{\mathrm{d}t} = v(f) = \Delta\gamma(f_+ - f)(f - f_-)\ ,$$

where $\Delta\gamma = \gamma_A - \gamma_B$ and $f_\pm$ are the roots of

$$f^2 - \left(1 - \frac{k_A + k_B}{\Delta\gamma}\right) f - \frac{k_B}{\Delta\gamma} = 0\ .$$

Typical trajectory



Piecewise Deterministic Markov Processes

- used extensively in context of queueing theory

- Catastrophes triggered when a threshold is reached
- Our choice:

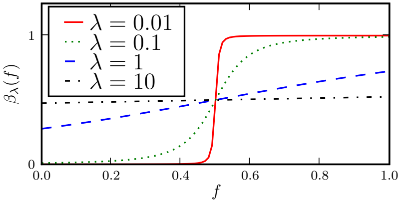
$$\beta_\lambda(f) = \frac{\xi}{2}\left(1 + \frac{f - f^*}{\sqrt{\lambda^2 + (f - f^*)^2}}\right)$$

parameters

ξ plateau value

f^* threshold value

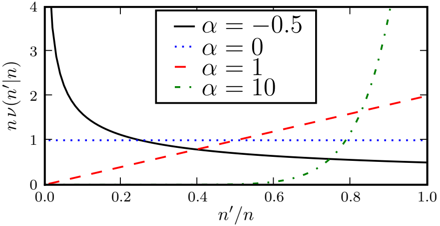
λ sharpness of the transition



Catastrophe strength

$n_A \to n'_A = u \times n_A$, where $0 < u < 1$ is a random number sampled from:

$$P(u) = (\alpha + 1)u^{\alpha} \qquad \alpha > -1$$



$-1 < \alpha < 0$ strong catastrophes

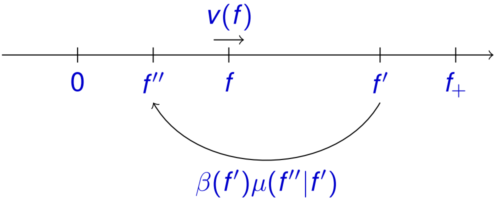
$\alpha > 0$ weak catastrophes

- To each jump $n_A \to n'_A$ corresponds a jump $f \to f'$
- Catastrophe strengh distribution $\mu(f'|f)$, where

$$\mu(f'|f) = \Theta(f - f')\frac{d}{df'}\frac{m(f')}{m(f)} \quad \text{with} \quad m(f) = \left(\frac{f}{1-f}\right)^{1+\alpha}$$

Exact Solution for Stationary State

Constant flux condition



Recall

- $\dfrac{df}{dt} = v(f)$
- $\mu(f''|f') = \dfrac{d}{df''}\dfrac{m(f'')}{m(f')}$
- $m(f) = \left(\dfrac{f}{1-f}\right)^{1+\alpha}$

$$p(f)v(f) = \int_f^{f_+} df' \int_0^f df''\, p(f')\beta(f')\mu(f''|f')$$

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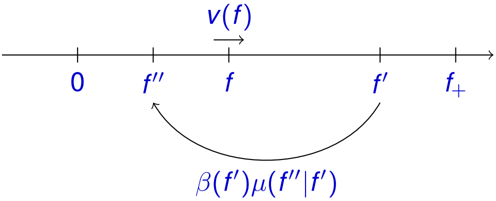

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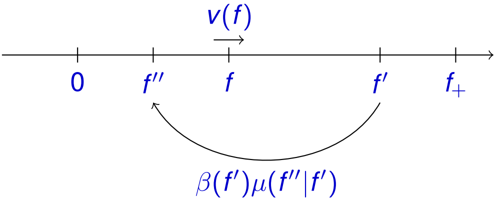

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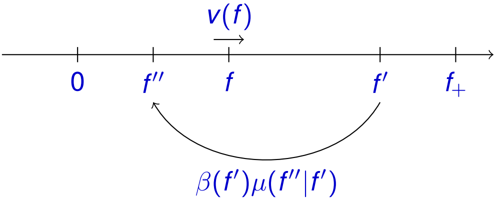

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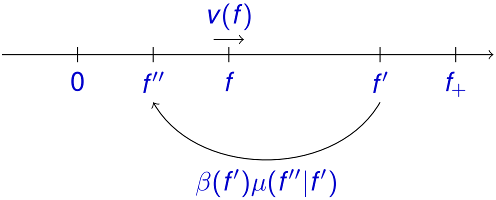

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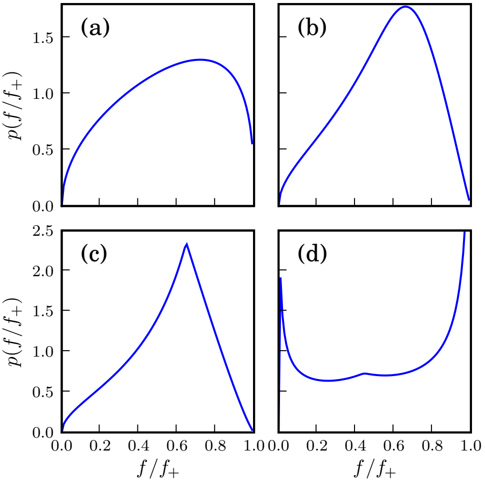
- $\mu(f''|f') = \dfrac{d}{df''}\dfrac{m(f'')}{m(f')}$
- $m(f) = \left(\dfrac{f}{1-f}\right)^{1+\alpha}$

$$\frac{d}{df}\frac{p(f)v(f)}{m(f)} = -\frac{p(f)\beta(f)}{m(f)}$$

$$\boxed{p(f) = C\frac{m(f)}{v(f)}\exp\left(-\int\frac{\beta(f)}{v(f)}\right)}$$

Examples

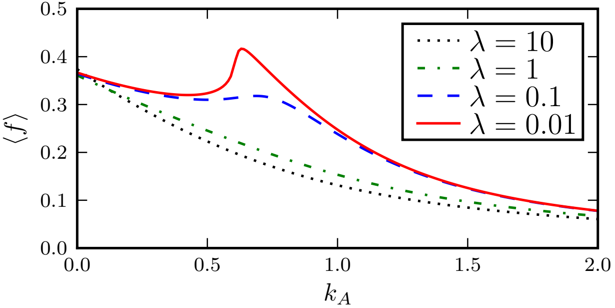


Optimal strategies

We characterise the population strategy by the value of k_A, which is the control parameter for the population balance.

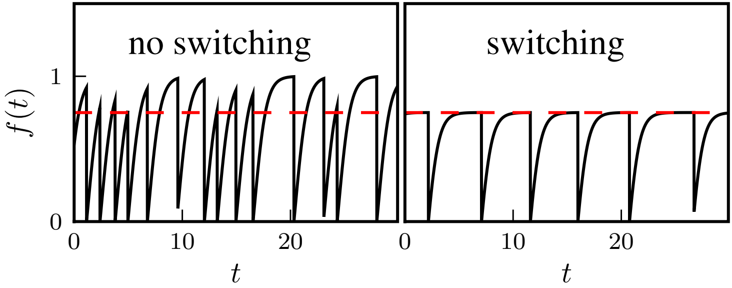
We define **Optimal Strategies** as the values of k_A which maximise the average fitness $\langle f \rangle$ in the stationary state.

Two optimal strategies emerge:



Two possible optimal strategies

1. $k_A = 0$ (no switching to unfit state)
2. $k_A \simeq k_A^*$ where k_A^* yields $f_+ = f^*$
   (saturation fitness = response threshold)



Conclusions for population dynamics in changing environments

- New kind of environments
  - Catastrophic
  - Responsive
- Switching can be a good strategy
- Threshold mechanism (different from bet hedging)
- Two main strategies:

  no switching: grow faster oblivious to catastrophes

  switching: grow slower but try not to get caught
- Outlook: Generalise to saturating populations

Summary

Plan

I Thoughts on biophysical modelling
II Switching between states
III Microscopic dynamics: model linear feedback switch
IV Macroscopic dynamics: population growth in a catastrophic environment

References:

P. Visco, R. J. Allen, M.R. Evans, Phys. Rev. Lett 2008, Phys. Rev. E 2009
P. Visco, R. J. Allen, S. N. Majumdar, M.R. Evans, Biophysical Journal 2010