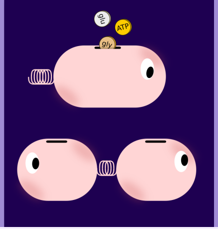
Economic Principles in Cell Biology

Paris, July 10-14, 2023



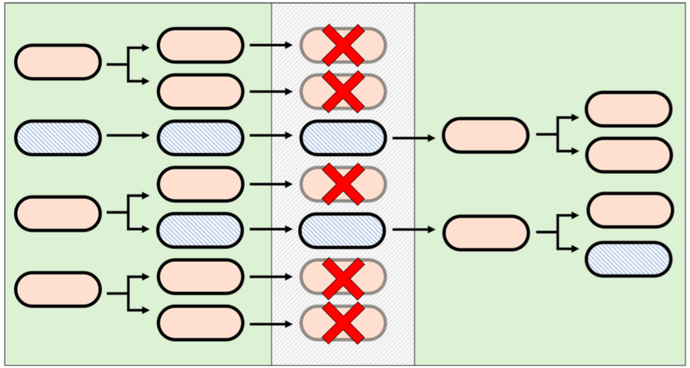
Growth in uncertain environments

Olivier Rivoire

Introduction

Bacterial persistence: experiments

Bacterial persistence: elementary model



- 2 states R: growing (R=1) / dormant (R=0)
- 2 environments E: antibiotics (E=+) / no antibiotics (E=-)

- multiplication factor in one generation f(R,E)

	E = -	*E = +*
R = 0	1	1
R = 1	0	2

- probability for antibiotics (E=+) : p
- probability to be dormant (R=0): u

(drawn at each generation)

Question: given f(R,E) and p, optimal transition rate u ?

Meta question: optimal in what sense?

Bacterial persistence: elementary model

Two limits: (1) Large population
(2) Long time

(1) Given Nt cells at generation t, fraction u of cells with R=0 (dormant), 1-u with R=1 (growing)

If no antibiotics (E=+): $N_{t+1} = A_+ N_t$ $\quad A_+ = u + 2(1-u) = 2 - u$

If antibiotics (E=-): $N_{t+1} = A_- N_t$ $\quad A_- = u$

(2) Over T generations, fraction p of generations with E=- (antibiotics), fraction 1-p with E=+ (no antibiotics)

$$N_T = (A_-)^{pT}(A_+)^{(1-p)T} N_0$$

$$N_T = e^{\Lambda T} N_0$$

$$\Lambda = p \ln A_- + (1-p) \ln A_+ = p \ln u + (1-p)\ln(2-u)$$

$$u = \begin{cases} 2p \ , & \text{if } 0 < p \le 1/2. \\ 1, & \text{if } 1/2 < p \le 1. \end{cases}$$

Conclusion: optimal transition rate u adapted to the uncertainty p of the environment

General model with sensing

- n states R
- M environments E, probability p(E)
- multiplication factor f(R,E)
- switching probability u(R|S) where S is a cue (previously just u(R), recovered if S is independent of E)
- probability q(S|E) for S given E

Muliplicative factor given E,S: $N_{t+1} = A(E,S)N_t$ $A(E,S) = \sum_R f(R,E)u(R|S)$

Growth rate: $\Lambda = \sum_{S,E} q(S|E)p(E) \ln A(S,E)$

Geometric mean $\Lambda = \langle \ln A(S,E) \rangle_{S,E}$ not arithmetic mean $\Lambda = \ln \langle A(S,E) \rangle_{S,E}$

Arithmetic vs geometric means

Growth is not an additive but a multiplicative process!

Didactic example:

A=2 with p=1/2 or A=1/3 with p=1/2

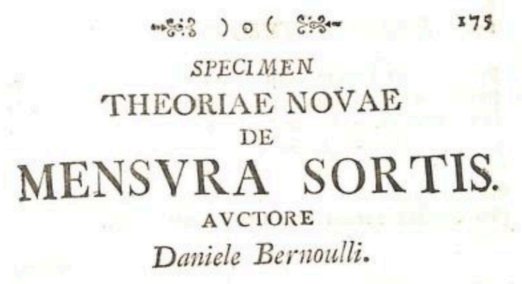
arithmetic mean = (1/2)(2+1/3) > 1

geometric mean = (2*1/3)^(1/2) < 1

Back to the simple model of bacterial persistence:

optimal geometric mean: u =

optimal arithmetic mean: u = 0 — very risky strategy that leads to extinction if E=- even occur!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SPECIMEN
THEORIAE NOVAE
DE
MENSVRA SORTIS.
AVCTORE
Daniele Bernoulli.

D Bernoulli, Exposition of a new theory on the measurement of risk (1738)

Value and cost of information

$$\Lambda = \sum_{S,E} q(S|E)p(E)\ln A(S,E) \qquad\qquad A(E,S) = \sum_{R} f(R,E)u(R|S)$$

Without sensing and with f(R,E)=f(E)delta (R,E) (Kelly case, see 2nd part)

$$\Lambda = \sum_{E} p(E)\ln(f(E)u(E)) = \sum_{E} p(E)\ln f(E) + \sum_{E} p(E)\ln p(E) - \sum_{E} p(E)\ln(p(E)/u(E))$$

Value of sensing, again with f(R,E)=f(E)delta (R,E)

With no sensing, i.e. S independent of E, optimal growth rate

With sensing, i.e. given q(S|E), optimal growth rate

Value of sensing: $\Lambda^*(q) - \Lambda^*(\emptyset) = \sum_{S,E} q(S|E)p(E)\ln q(S|E)$

Biologically, also a cost c(q) that increases with precision => a trade-off and optimal sensor

Analogies with financial investment

Biology	**Finance**
Individual	Currency unit
Environment $p(E)$	Market state
–	Investor
Phenotype decisions $u(R)$	Investment strategy
Multiplicative rate $f(R, E)$	Immediate return
Environmental cue $P(S\|E)$	Side information

Major difference: information is centralized in finance, distributed in biology

Implication: one sensor per cell, heterogeneity that is beneficial

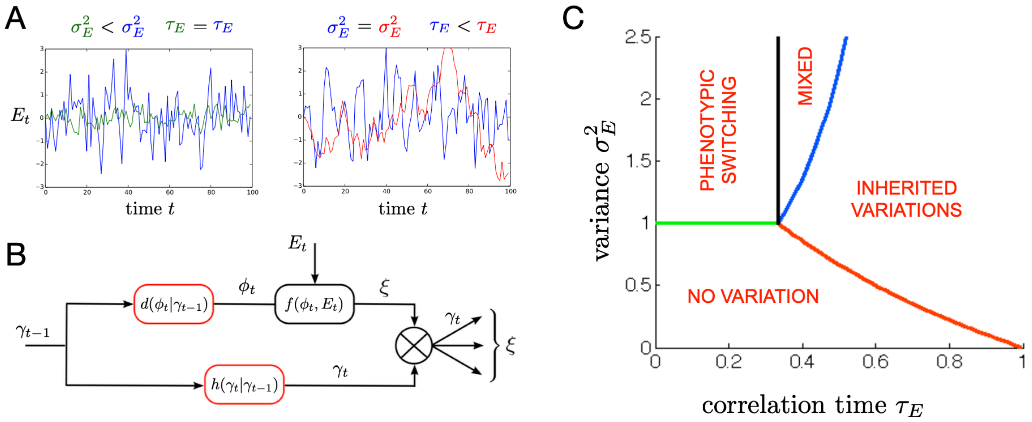
$$\Lambda = \sum_{S,E} q(S|E)p(E)\ln A(S,E) \quad < \quad \Lambda = \sum_{S,E} p(E)\ln A(S,E)q(S|E)$$

Warning: what is optimal for a population may not be evolutionary stable!

Conflict between levels of selection!

Optimal strategies in correlated environments

Heredity: passing information between generations



Summary and perspectives

Short/intermediate times and finite population: see David

Growth in uncertain environments

D. Lacoste

Outline of the talk

1. Tradeoff in optimal gambling strategies

with L. Dinis, Universitad Complutense, Madrid,
J. Unterberger, Université de Lorraine

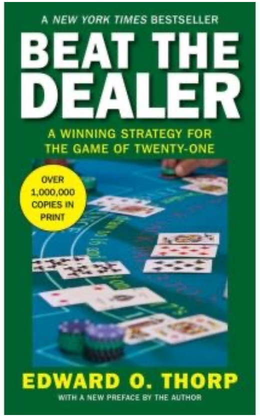
2. Adaptive strategies in gambling

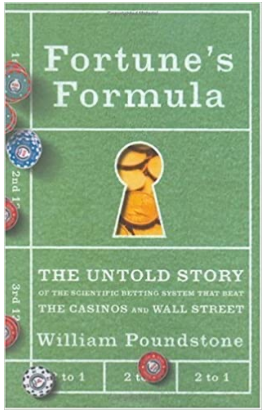
with A. Despons, Laboratoire Gulliver
L. Peliti, Université de Naples

3. Tradeoff for phenotypic switching of populations in varying environments

with L. Dinis, Universitad Complutense, Madrid,
J. Unterberger, Université de Lorraine

Kelly’s formula in popular culture





From card counting method in blackjack. ..

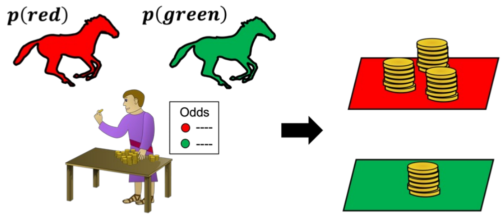
.. to investments on the stock market

A new interpretation of information rate, Kelly J. L. J. (1956)

Kelly’s model as a resource allocation problem

Gambler **Bookmaker**

Bets



Odds

Constraints : $\sum_{x=1}^{M} b_x = 1$ and $r_x := \frac{1}{o_x}$ with $\sum_{x=1}^{M} r_x = 1$ for fair odds

Dynamics : winning horse x is chosen with probability p_x

Then capital is updated : $C_{t+1} = \frac{\mathrm{b}_x}{\mathrm{r}_x} C_t$

Long term growth rate

Log-Capital $\text{log-cap}(t) = \sum_{\tau=1}^{t} \log\left(\frac{\mathrm{b}_{x_\tau}}{\mathrm{r}_{x_\tau}}\right)$

by the law of large numbers : $\frac{\text{log-cap}(t)}{t} \xrightarrow[t\to\infty]{} \mathbb{E}\left[\log\left(\frac{\mathrm{b}_x}{\mathrm{r}_x}\right)\right]$

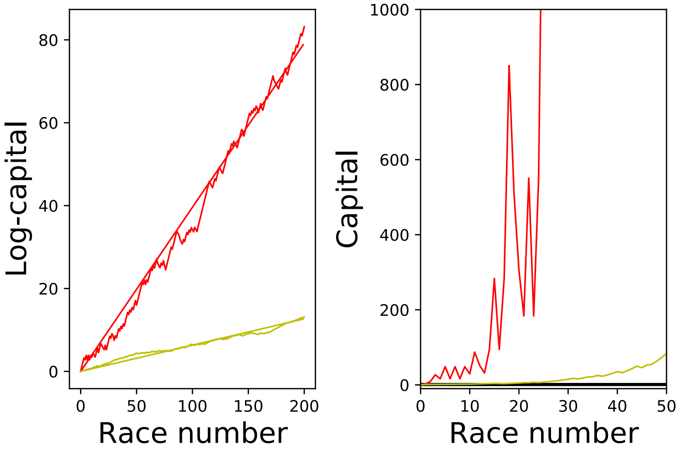
Optimization of the long term growth rate (Kelly's optimal strategy)

$$\langle W \rangle = \mathbb{E}\left[\log\left(\frac{\mathrm{b}_x}{\mathrm{r}_x}\right)\right] = D_{KL}\left(\mathbf{p}||\mathbf{r}\right) - D_{KL}\left(\mathbf{p}||\mathbf{b}\right)$$

This is maximum when $b_x = p_x$ and at this point $\langle W^* \rangle = D_{KL}\left(\mathbf{p}||\mathbf{r}\right) \geq 0$

The gambler makes money when he/she has better knowledge of the winning probabilities than the bookie

Evolution of the capital of the gambler



- Kelly’s strategy dominates on long times all non-optimal strategies

- A general trade-off between the maximization of the growth rate and the minimization of risky fluctuations ?

L. Dinis, J. Unterberger, D. L., Eur. Phys. Lett. (2020)

How to define risk ?

By the central limit theorem :

$$\frac{1}{\sigma_W \sqrt{t}} \left(\log \frac{C_t}{C_0} - t\langle W \rangle \right) \xrightarrow[t\to\infty]{} \mathcal{N}(0,1) \text{ normal law}$$

where $\sigma_W^2 = \mathrm{Var}\left[\log\left(\frac{\mathrm{b}_x}{\mathrm{r}_x}\right)\right]$ is the volatility

The volatility is not the best measure of risk but it leads to tractable calculations

In practice, risk is relevant at intermediate time scales $t \ll (\sigma_W / \langle W \rangle)^2$

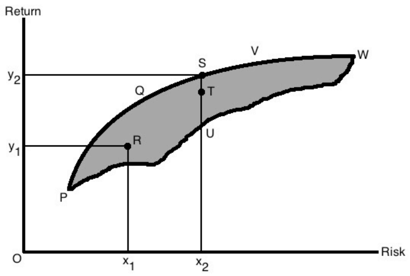
Risk free strategy

Note that the strategy $b_x = r_x$ has $\sigma_W = 0$ and $\langle W \rangle = 0$

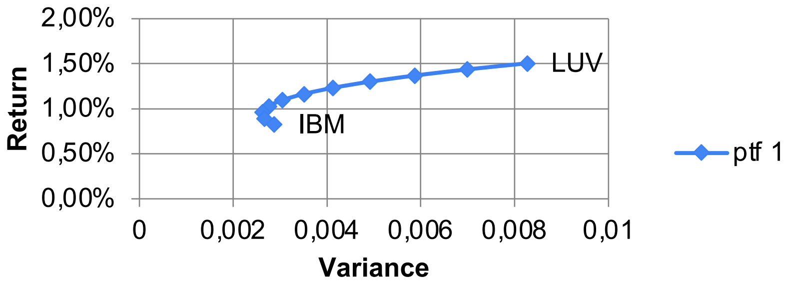
Objective function :

$$J = \alpha\langle W\rangle - (1-\alpha)\sigma_W + \lambda \sum_x b_x$$

- Interpolates between maximization of growth rate for α=1 and the minimization of the fluctuations when α=0
- The optimal solution is parametrized by α, which is a risk aversion parameter.
- Similarities with Markowitz portfolio theory



Markowitz H. (1952)



From Wharton school of finance

Two horses solution

- If p is the probability that the first horse wins, o=1/r the odd then :

$$\langle W \rangle = p \ln(\frac{b}{r}) + (1-p)\ln(\frac{1-b}{1-r})$$

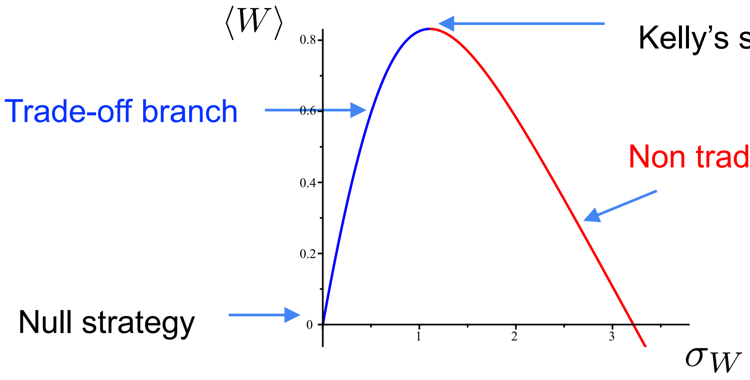
$$\sigma_W^2 = p(1-p)\ln^2 \frac{b(1-r)}{(1-b)r} = \left(\sigma \ln \frac{b(1-r)}{(1-b)r}\right)^2 \quad \text{with} \quad \sigma = \sqrt{p(1-p)}$$

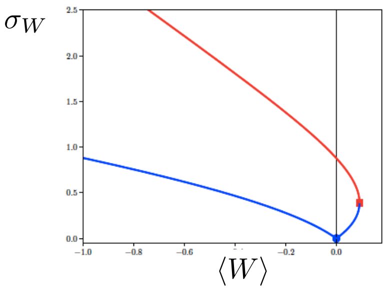
- Risk free strategy is $b = r$ where $\langle W \rangle = \sigma_W = 0$

- Optimal strategy has two branches : $b^{\pm} = p \pm \gamma\sigma,$

  with $\gamma = (1-\alpha)/\alpha$

The efficient border for two horses problem





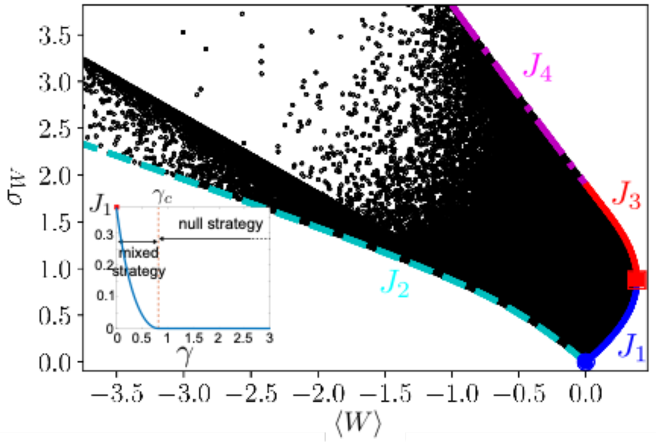
For p<r :

In the $\langle W \rangle \geq 0$ region, $\dfrac{d\sigma_W}{d\langle W \rangle} = \dfrac{\sigma}{p-b}$ becomes infinite near Kelly's strategy

but non-zero near the null strategy where :

$$\frac{d\sigma_W}{d\langle W \rangle} = \frac{1}{\gamma_c} = \frac{\sigma}{|p-r|} \quad \text{and} \quad \frac{d^2\sigma_W}{d\langle W \rangle^2} = \frac{r(1-r)}{\sigma^2\gamma_c^3} > 0$$

Beyond 2 horses : numerical optimization



Modified utility functions :

- Lower front, $\langle W \rangle \geq 0$ region, the front is convex objective function is $J_1 = \alpha\langle W \rangle - (1-\alpha)\sigma_W$
- Lower front, $\langle W \rangle < 0$ region, the front is concave objective function is $J_2 = -(\langle W \rangle - W_0)^2 - k\sigma_W$

In practice, the numerical optimization of the objective function can be carried out using algorithms based on simulated annealing or on Karush-Kuhn-Tücker (KKT) conditions.

Mean-variance trade-offs

- For fair odds, assuming $\langle W \rangle \geq 0$ with q the pdf such that $q_x := r_x / p_x$

$$\sigma_W \geq \frac{\langle W \rangle}{\sigma_q}$$

L. Dinis et al., EPL (2020)

- For non-fair odds with $\langle q \rangle = \sum_x r_x \neq 1$ and $V = -\log \sum_x r_x$

$$\sigma_W \geq \frac{|V - \langle W \rangle|}{\sigma_q} \langle q \rangle$$

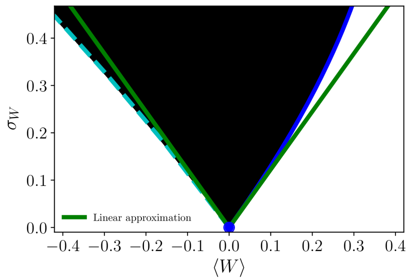
General trade-off between growth rate and risk

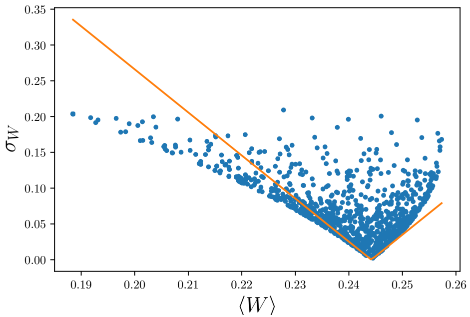
Similar to a tradeoff between precision and dissipation

A. Barato et al., (2015)

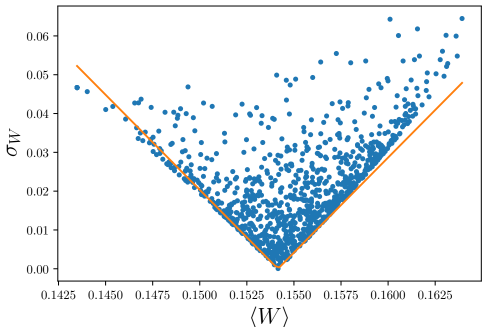
Numerical illustration

Fair odds





Diagonal super-fair odds



Non-diagonal super-fair odds

Game theoretic formulation

- Worst possible case for the gambler corresponds to minimization of

$$\Psi(\mathbf{p}) = \langle W(\mathbf{p}, \mathbf{b}^{\mathrm{KELLY}})\rangle - \lambda \sum_x \mathrm{p}_x$$

$$\mathrm{p}_x = \mathrm{p}_x^* = \frac{\mathrm{r}_x}{\sum_x \mathrm{r}_x}$$

- The general growth rate is

$$\langle W(\mathbf{p}, \mathbf{b})\rangle = D_{KL}(\mathbf{p}||\mathbf{p}^*) - D_{KL}(\mathbf{p}||\mathbf{b}) + V$$

R. Pugatch et al., (2014)

$D_{KL}(\mathbf{p}\|\|\mathbf{p}^*)$	*pessimistic surprise* : things are not as bad as one would think
$-D_{KL}(\mathbf{p}\|\|\mathbf{b})$	*gambler's regret* : gambler plays sub-optimally
V	*value of the game : V<0 for unfair odds, V>0 for super-fair odds*

Non-diagonal odds

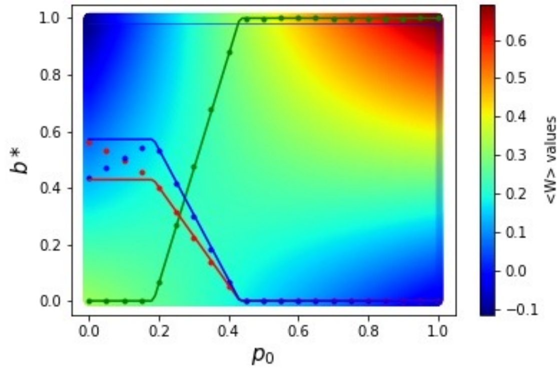
- Now, the growth rate is : $$\langle W(\mathbf{p},\mathbf{b})\rangle = \sum_x \mathrm{p}_x \ln\left(\sum_y \mathrm{o}_{xy}\mathrm{b}_y\right)$$

- When the odds matrix is invertible $\mathrm{r} = \mathrm{o}^{-1}$ and simplex preserving (fully mixing game)

Optimal bets : $$\mathrm{b}_x^* = \sum_y \Omega_{xy}\mathrm{p}_y \quad \text{with} \quad \Omega_{xy} = \frac{\mathrm{r}_{xy}}{\sum_l \mathrm{r}_{ly}}$$

Optimal environment : $$\mathrm{p}_x^* = \frac{\sum_l \mathrm{r}_{lx}}{\sum_{xy} \mathrm{r}_{xy}}$$

$$(\mathrm{b}_x^*, \mathrm{p}_x^*)$$ defines a Nash equilibrium



S. Cavallero, (2023)

2. Adaptive strategies in gambling

- So far, we assumed the gambler knows the probabilities of winning horses,

In practice the gambler does not know this, *he/she must learn it* !

A natural idea is to use *past race results*

This idea is implemented in card games strategies and in finance

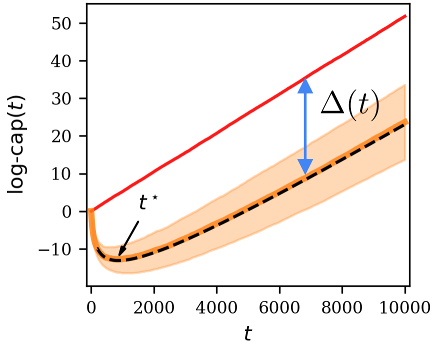
- Here, we use *Laplace's rule of succession*

$$b_x^{t+1} = \frac{n_x^t + 1}{t + M}$$

E. T. Jaynes, 2003

for t uncorrelated races and M horses. This follows from Bayesian inference with uniform prior

The learning time and the gambler's regret



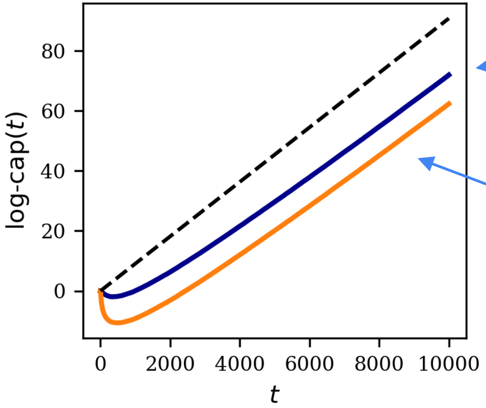
$$\Delta(t) = \text{log-cap}^{\text{Kelly}}(t) - \text{log-cap}(t)$$

$$\Delta(t) = \sum_{i=1}^{t} \left[\log p_{x_i} - \log b_{x_i}(i) \right]$$

Asymptotic regret : $\langle \Delta \rangle (t) = \langle \Delta \rangle (t_0) + \frac{M-1}{2} \log \frac{t}{t_0 + 1}$

Burn-in time (or learning time) : $t^\star = \frac{M-1}{2} \frac{1}{D_{KL}(\mathbf{p} \| \mathbf{r})}$

Modified Laplace's rule



Non-uniform prior exploiting the information contained in the bookmaker's odds distribution

Uniform prior

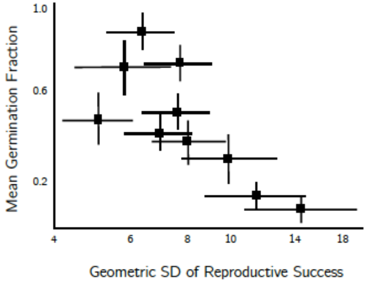
- Initial capital loss is reduced but the asymptotic regret and the learning time are unchanged
- Non-uniform prior only useful if the odds distribution is closer to the horse distribution than the uniform distribution

A. Despons, L. Peliti, D. L., J. Stat. Mech., 093405 (2022)

3. Trade-off for phenotypic switching of populations in varying environments

Trade-off in bet-hedging strategies of desert plants

Eriophyllum lanosum, a species of wildflower in the southwestern US



Venable (2007)

Germination fraction vs. standard deviation in reproductive success

Ecological evidences

ECOLOGY LETTERS

Ecology Letters, (2020) **23**: 274–282 doi: 10.1111/ele.13430

LETTER

Mean growth rate when rare is not a reliable metric for persistence of species

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..The problem becomes particularly severe when an increase in the amplitude of stochastic temporal variations leads to an increase in $\mathbb{E}[r]$ since at the same time it enhances random abundance fluctuations and the two effects are inherently intertwined…

Gambling/finance		**Biology/ecology**
Currency unit	→	Individual
Race result/market state	→	Environment
Bets/investment	→	Phenotype switching
Races	→	Environmental events
Odds	→	Reproduction rate
Capital growth rate	→	Population growth rate
Probability of bankruptcy	→	Extinction probability

- Sub-populations of two phenotypes growing in two environments $\frac{d}{dt}\mathbf{N}(t) = M_{S_i}\mathbf{N}(t)$ for $i \in \{1,2\}$

$$M_{S_1} = \begin{pmatrix} k_{A1} - \pi_1 & \pi_2 \\ \pi_1 & k_{B1} - \pi_2 \end{pmatrix} \text{ and } M_{S_2} = \begin{pmatrix} -\pi_1 + k_{A2} & \pi_2 \\ \pi_1 & k_{B2} - \pi_2 \end{pmatrix}.$$

- Gambling problem was *scalar*, this one is *vectorial.* Explicit results only in some limits

  Ex: for the average growth rate in the adiabatic limit E. Kussel, S. Leibler (2005)

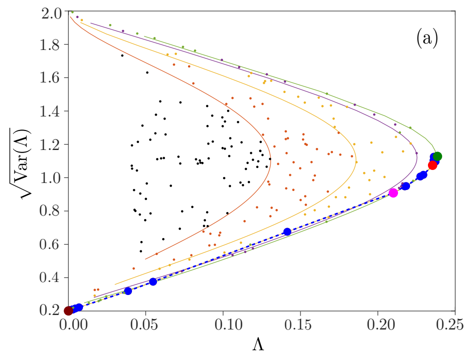
  Optimal condition is $\boxed{\pi_i = \kappa_i}$ the analog of Kelly's strategy

- So far, we focused on long term growth rate (*infinite horizon*) but populations are finite and may go extinct in a finite time (*finite horizon*)

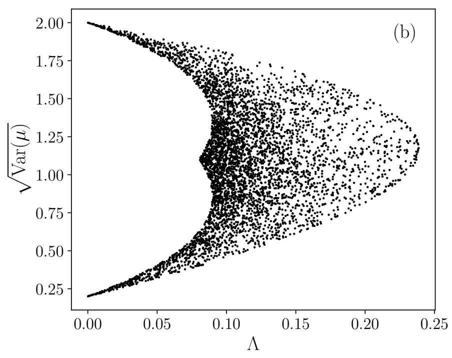
Instantaneous growth rate $\mu(s) = \frac{d}{ds}(\ln N(s)),$ finite time growth rate $\Lambda_t = \frac{1}{t}\int_0^t \mu(s)ds$

and $\mathrm{Var}(\Lambda) = \lim_{t\to\infty} t\mathrm{Var}(\Lambda_t)$ is the equivalent of the volatility

Pareto-optimal tradeoff



Exact growth rate



Instantaneous growth rate

- Pareto diagram is controlled by two time scales

$$T_{env} = \frac{1}{2}(1/\kappa_1 + 1/\kappa_2) \quad \text{and} \quad T = \frac{1}{2}(1/\pi_1 + 1/\pi_2)$$

- There is a trade-off branch terminating at a point (similar to Kelly's strategy)

  with a vertical slope, both for exact and for approximate growth rates

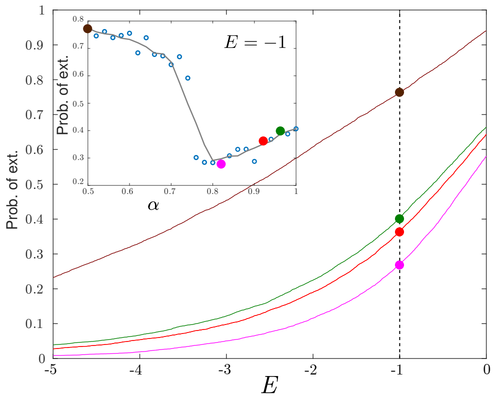
A link between fluctuations and population extinction

- Comparison between

  - optimal trajectories at Kelly's point (green)

  - suboptimal ones along the Pareto front

- If ln(N)< E at some time in the trajectory, the population is considered extinct



Extinction threshold

In the region of fast growth, it is advantageous for a population to trade growth for less risky fluctuations

The probability of extinction along the Pareto front is non-monotonic

L. Dinis, J. Unterberger, D. L., J. Stat. Mech., 053503 (2022)

Conclusion

- Kelly's gambling model helps understanding adaptation strategies of biological systems in a varying environment (bet-hedging)

- There is a general trade-off between growth rate and risk

- On going : extend the notion of risk beyond fluctuations to describe extinction

  Search of experimental confirmation

Chapter 'cells in the face of uncertainty' with D. Tourigny and O. Rivoire