Exact computation of growth-rate fluctuations in random environment

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Abstract. We consider a general class of Markovian models describing the growth in a randomly fluctuating environment of a clonal biological population having several phenotypes related by stochastic switching. Phenotypes differ e.g. by the level of gene expression for a population of bacteria. The time-averaged growth rate of the population, $\Lambda$, is self-averaging in the limit of infinite times; it may be understood as the fitness of the population in a context of Darwinian evolution.

The observation time $T$ being however typically finite, the growth rate fluctuates. For $T$ finite but large, we obtain the variance of the time-averaged growth rate as the maximum of a functional based on the stationary probability distribution for the phenotypes. This formula is general. In the case of two states, the stationary probability was computed by Hufton, Lin and Galla [10], allowing for an explicit expression which can be checked numerically.

Keywords: evolutionary dynamics, mutation-selection models, uncertainty relation, fluctuating environment, fluctuation relations, stochastic thermodynamics, growth rate.

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1 Introduction

General context. We consider in the present work a general class of dynamical models describing the growth of several subpopulations in a randomly evolving environment. The interaction between the subpopulations manifests itself only through random transitions. The subpopulations at time $t$ are assumed to be large enough to take a kinetic limit and neglect fluctuation effects, so that the only randomness in the dynamics comes from the environment. The latter is modelized by a time-continuous Markov process $(s(t))_{t \geq 0}$ switching between a finite number of values.

We take our inspiration from biology, where such 'mutation'-selection models are considered [11, 16, 9, 10] as a general framework to discuss Darwinian evolution, see also e.g. [14] for a discussion of immune strategies along the same lines. We consider the population of a given biological species. Subpopulations are characterized by their phenotype $x$; their differential fitnesses are accounted for by a $x$-dependent growth-rate $k_x$. In this context, random transitions ('mutations') between the subpopulations are a simple model for phenotypic switching; see e.g. the recent book [12] for a modern confrontation of Lamarck’s and Darwin’s viewpoints. In general, differential gene expressions mediated by interacting networks of genes and proteins, in particular, epigenetics, account for random phenotypic changes. Known examples concern e.g. the residual resistance of bacteria [1] or cancer cells [15] to drugs, or the level of expression of the lactose permease of E. Coli [3, 4]; see [7] for a discussion of the rôle of noise in genetic circuits and more examples pertaining to stem cell differentiation and developmental evolution. An important restriction is made here by assuming that growth rates $k_x$ are independent of the environment: the organisms do not "sense" the environment and mutate "blindly". Perfect sensing allows maximization of growth rate by switching at time $t$ to the state $x$ maximizing $(k(x|s(t)))_{x \in X}$; however, sensing comes at a cost, so actual biological strategies are probably best described as lying somewhere in-between these two ideal cases.

Under lenient conditions (ergodicity of the phenotypic switching generator $P_{\text{pheno}}$, see below) the time-averaged growth-rate of the total population $N := \sum_x N_x$, namely,

$$\frac{1}{T} \Lambda_{[0,T]} := \frac{1}{T} \ln(N(T)/N(0))$$

(1)
is known to be a self-averaging quantity, namely,

$$\lambda := \lim_{T \to \infty} \frac{1}{T} \Lambda_{[0,T]}$$  \hspace{1cm} (2)

is a constant. However, at a given, finite time-horizon \( T \), the variance \( \text{Var}(\frac{1}{T} \Lambda_{[0,T]}) \) of \( \frac{1}{T} \Lambda_{[0,T]} \) is non-zero, and scales like \( 1/T \) due to the central limit theorem. Therefore, when \( T \to \infty, \frac{1}{T} \text{Var}(\Lambda_{0,T}) \) converges to a finite, positive quantity which we denote (by abuse of notation) \( \text{var}(\lambda) \), and call asymptotic growth-rate variance. This is the main quantity of interest in this article.

Our interest for the variance of the growth-rate arose out of a previous work \([5]\) on a much simpler, scalar problem of maximization of capital growth rate known in the mathematical finance community as Kelly’s model. The variance of the growth rate is then interpreted as a risk in biology, bound to influence evolution on the long term. The word ‘risk’, taken out of its original financial context, may sound at best metaphorical. In finite-time protocols, however, fluctuations (measured by the variance), and also the form of the Pareto front associated to the multi-objective optimization, have been discussed in details there.

The variance of the growth rate may presumably also be interpreted as a risk in biology, bound to influence evolution on the long term. The word ‘risk’, taken out of its original financial context into this biological context, may sound at best metaphorical. In finite-time protocols, however, the variance of the relative time-integrated growth rate is naturally interpreted as a ‘risk’ for a given species in a situation where two (or more) species living in the same environment are competing. Let us discuss this point specifically in a discrete-time dilution protocol. We consider two species \( a = 1, 2 \) growing without any interaction in the same environment history \( (s(t))_{t \geq 0} \), with concentration vectors \( N^a_t = ((N^a_{at})_x(t))_{t \geq 0} \). The total concentration of species \( a \) at time \( t \) is \( N^a(t) := \sum_x N^a_x(t) \). The protocol (P) is the following: at time \( T \), we apply a global dilution factor to both species, so that the total concentration \( N(T) = N^1(T) + N^2(T) \) is back to its initial value \( N(0) \). By convention we assume that \( N(0) = 1 \). In the idea, the dilution could be repeated periodically with time-period \( T \); instead of a deterministic dilution, we could use a ‘Fisher-Wright’ type procedure where a small number of molecules is drawn with replacement from a large pool. Here we content ourselves with protocol (P), which is the simplest possible case. Let \( \Lambda^a_{[0,T]} \) be the time-integrated growth rate of species \( a \); by definition, the concentration at time \( T \) is \( N^a(T) = N^a(0) e^{\Lambda^a_{[0,T]}} \). Let \( n^a(t) = \frac{N^a(t)}{N(0)} \) be the relative concentrations. The instantaneous growth rate is \( \lambda^a(t) = \frac{d\Lambda^a_{[0,t]}}{dt} \). Then

$$\frac{dN^a}{dt} = \lambda^a(t) N^a(t), \quad \frac{dN}{N} = n^1 \lambda^1 + n^2 \lambda^2$$  \hspace{1cm} (3)

At time \( T \), after dilution concentrations \( (N^1(T), N^2(T)) \) become \( (n^1(T), n^2(T)) \). Considering species \( a = 1 \),

$$\frac{dn^1}{dt} = \frac{dN^1}{N} - n^1 \frac{dN}{N} = \lambda^1 n^1 - n^1 (n^1 \lambda^1 + n^2 \lambda^2) = (\lambda^1 - \lambda^2)n^1(1 - n^1)$$  \hspace{1cm} (4)
Integrating the differential equation between \( t = 0 \) and \( t = T \),

\[
\int \frac{dn^1}{n^1(1 - n^1)} = \ln \left( \frac{n^1(T)/n^2(T)}{n^1(0)/n^2(0)} \right) = \Lambda^1_{[0,T]} - \Lambda^2_{[0,T]} \tag{5}
\]

We now define

\[
p(t) := \ln \left( \frac{n^1(t)/n^2(t)}{n^1(0)/n^2(0)} \right) \tag{6}
\]

to be the selective advantage of species 1 relative to species 2. Then

\[
\text{Var}(p(T)) = \text{Var}(\Lambda^1_{[0,T]} - \Lambda^2_{[0,T]}) \tag{7}
\]

In the particular case when species 2 does not grow, we find simply that the variance of the selective advantage of species 1 is \( \text{Var}(\Lambda^1_{[0,T]}) \), which gives a justification for the study of this quantity, which is closely related to the quantity called 'risk' in the case of Kelly's model. The general case could be studied in the same framework of this article by considering phenotype \( x \) of species \( a \) as a 'superphenotype' indexed by \( (a, x) \), with no mutation possible between superphenotypes \( (a, x), (a', x') \) with \( a \neq a' \), yielding a block-diagonal evolution matrix; the \( \Lambda^a_{[0,T]} \)'s are then interpreted as 'partial' integrated growth rates for each of the two blocks.

We postpone a discussion of our results after a more detailed mathematical presentation of our model.

**Model.** We fix two finite sets, the **phenotypic space** \( \mathcal{X} \), and the **environmental space** \( S \). Our growth model is defined by a linear differential equation,

\[
\frac{d}{dt} \vec{N}(t) = P(t)\vec{N}(t), \tag{8}
\]

in coordinates, \( \frac{d}{dt} N_x(t) = \sum_{y \in \mathcal{X}} P_{x,y}(t)N_y(t) \), where \( \vec{N}(t) = (N_x(t))_{x \in \mathcal{X}} \) is a vector representing the concentrations at time \( t \) of the different phenotypes \( x \) of a given clonal population. Diagonal coefficients represent the instantaneous growth rate of each phenotype, whereas off-diagonal coefficients represent the effect of transition rates between phenotypes. The time-dependence of the generator of time evolution \( P \) comes through a varying environment, described by a trajectory \( (s(t))_{t \geq 0} \) in the external environmental space \( S \). The operators \( P(t) \) can be split into the sum of two operators,

\[
P(t) = \mathbf{P}^{\text{growth}}(s(t)) + \mathbf{P}^{\text{pheno}} \tag{9}
\]

where:

- \( \mathbf{P}^{\text{growth}}(s(t)) \) is a diagonal growth matrix, with coefficients \( (\mathbf{P}^{\text{growth}}(s(t)))_{x,x} = k(x|s(t)) \).

Each coefficient is the difference of a replication rate and of a death rate, so it can be positive or negative. Resulting growth rates \( k(x|s(t)) \) depend on the current environmental state \( s(t) \).
\[ P_{\text{pheno}} = (P_{\text{pheno}})_{x,y \in \mathcal{X}}, \quad P_{xy}^{\text{pheno}} = \begin{cases} \pi_{x|y} & (x \neq y) \\ -\pi_x & (x = y) \end{cases} \]
is a Markov generator representing random transitions from phenotype \( y \) to phenotype \( x \), with \( \pi_x := \sum_{y \neq x} \pi_{y|x} \) inverse holding time. We assume that \( P_{\text{pheno}} \) (contrary to \( P_{\text{growth}} \)) is independent of the environment. Also (as mentioned above), we assume the Markov process to be irreducible, or equivalently, ergodic. Note that the fact that the sum \( \sum_{x \in \mathcal{X}} P_{xy}^{\text{pheno}} \) of coefficients on a column vanishes is equivalent to the conservation of the total concentration \( \sum_{x \in \mathcal{X}} N_x \) when \( k = 0 \).

In the case e.g. of two states \(|X| = |S| = 2\), \( P(s(t)) = P_1 \) or \( P_2 \) depending on whether \( s(t) = 1 \) or \( 2 \), and
\[
P_1 = \begin{pmatrix} (k(1|1) - \pi_1) & \pi_{1|2} \\ \pi_{2|1} & (k(2|1) - \pi_2) \end{pmatrix}, \quad P_2 = \begin{pmatrix} (k(1|2) - \pi_1) & \pi_{1|2} \\ \pi_{2|1} & (k(2|2) - \pi_2) \end{pmatrix}.
\]
The time-evolution \((s(t))_{t \geq 0}\) of the environment is given by an irreducible continuous-time Markov process,
\[
s' \overset{k_{s'|s}}{\rightarrow} s, \quad s' \neq s \in S
\]
with rates \( (k_{s'|s})_{s \neq s'} \). The transition rate out of state \( s' \) (inverse holding time) is \( k_{s'} := \sum_{s \neq s'} k_{s'|s'} \).

Let \( N(t) := \sum_x N_x(t) \) be the total population. For simplicity, we assume that the population at time 0 is normalized, i.e. \( N(0) = 1 \). The Lyapunov exponent characterizing the system in the long-time limit is the average growth rate of the population, namely, \( \lambda := \lim_{T \to \infty} \frac{1}{T} \Lambda_{[0,T]} \), where \( \Lambda_{[0,T]} := \log(N(t)) \), see eqs. (1), (2).

In the limit when the time-scale of environmental transitions is much larger than the time-scale of phenotypic transitions (see Kussell-Leibler [11]), the system aligns most of the time in the direction corresponding to the highest eigenvalue of \( P(t) \), and it can be argued that \( \lambda \) is largest when phenotypic switching rates follow closely environmental transition rates, implying in particular a bet-hedging strategy for the population, i.e. the coexistence of different phenotypes at all times, including those not maximizing the instantaneous growth rate. In this limit, both \( \lambda \) and \( \text{var}(\lambda) \) may be computed. However, they cannot in general. See [9,10] for a detailed discussion of the two-state model \(|X| = |S| = 2\), and [9,10,14] for phase diagrams also involving other strategies.

Formally, the solution of (8) may be written as a time-ordered integral,
\[
[A](t) = \exp\left( \int_0^t dt' \; P(t') \right)[A](0). \quad \text{Except in very simple cases, however, the integral cannot be computed. Discretizing time, one obtains instead products of random matrices. The long-time limit is deterministic due to self-averaging, but not obtained as the result of an explicit computation. One may also try to solve for the joint probability distribution \( P_t(\phi, s) \) by means of a master equation, where \( s \in S \) and \( \phi := \left( \frac{N_s(t)}{N(t)} \right)_{x \in \mathcal{X}} \) is a vector giving the proportion of each phenotype in the population. Since the trajectory \((\phi(t))\) between two successive environment jump times is deterministic, this gives rise to a piecewise deterministic Markov process (PDMP for short). It is proved in Hufton-Lin-Galla-McKane [9,10] that \( P_t(\phi, s) \) converges when \( t \to \infty \).}
to a stationary distribution \( P_{\text{stat}}(\phi, s) \), from which one deduces the asymptotic environment-dependent density \( \rho_s(x) := \int \phi_x P_{\text{stat}}(\phi, s) \, d\phi \). One then concludes to the existence when \( T \to \infty \) of a time-averaged density \( \bar{\rho} := \frac{1}{T} \int_0^T dt \, \delta_{x(t), x} \) w.r. to all environmental trajectories \( - \), which identifies by the ergodic theorem with the average of \( \rho_s \) over environmental states,

\[
\bar{\rho}(x) := \lim_{T \to \infty} \frac{1}{T} \int_0^T dt \rho_t(x) = \sum_s Q_s \rho_s(x). \tag{11}
\]

See next paragraph for notations. Unfortunately, \( P_{\text{stat}} \) can be computed in closed form only in the case of two states.

**Further hypotheses and notations.** We assume that the environmental Markov chain satisfies local balance, namely, the stationary measure \( \mathcal{P} \) for the environmental Markov chain \( \mathcal{Q} \) satisfies

\[
\mathcal{P}(s') \mathcal{Q}(s') = \kappa(s'|s) \mathcal{P}(s). \tag{10}
\]

We further denote \( Q_{[0,T]} \) the law of environmental trajectories \( s : [0, T] \to \mathbb{R} \) under the stationary environmental Markov chain, and by \( Q_{[0,T]}[\cdots] \) or (for short) \( \langle \cdots \rangle \) the expectation with respect to \( Q_{[0,T]} \).

**Results of the article.** Our results concern the asymptotic growth-rate variance, by definition,

\[
\text{var}(\lambda) = \lim_{T \to \infty} \frac{1}{T} \left( \langle (\Lambda_{[0,T]})^2 \rangle - \langle \Lambda_{[0,T]} \rangle^2 \right). \tag{12}
\]

Our first result, holding for an arbitrary number of phenotypes and environmental states (see Theorem 2.2), yields \( \text{var}(\lambda) \) as the solution of a variational formula obtained in terms of the stationary PDMP probability measure \( \mathcal{P} \).

This result is somewhat abstract since \( \mathcal{P} \) is not known in general. However, in the case when there are only two phenotypic and two environmental states (\( |\mathcal{X}| = |S| = 2 \)), \( \mathcal{P} \) is known from the work of Hufton, Lin, Galla and McKane \( \langle 9, 10 \rangle \), which allows an explicit computation of the variance in terms of a double integral, see Theorem 3.1. Our result has been checked numerically by L. Dinis and D. Lacoste, and is used in our work in preparation \( \langle 6 \rangle \) to explore the Pareto front featuring the mean and the variance of the time-averaged growth rate, in close analogy with \( \langle 5 \rangle \).

**Plan of the article.** Our general results are presented in Section 2. The explicit computation in the particular case (\( |\mathcal{X}| = |S| = 2 \)) is given in Section 3.

## 2 Stationary distribution and variational formula for the growth-rate variance

**Hufton-Lin’s PDMP reformulation.** The state of the system at time \( t \) is characterized by (i)
the total concentration \( N(t) := \sum_{x \in X} N_x(t) \) and by the relative fractions \( \phi_x(t) := \frac{N_x(t)}{N(t)} \); (ii) the environmental state \( s(t) \). Rewriting (8) in terms of these new variables, one gets (see [16] or [9])

\[
\frac{d(\log N)}{dt} = \frac{dN/\ dt}{N} = \sum x \ k(x|s)\phi_x
\]

(13)

\[
\frac{d\phi_x}{dt} = \frac{1}{N} \frac{dN_x}{dt} - \phi_x \frac{d(\log N)}{dt} = v_x(\phi|s)
\]

(14)

with

\[
v_x(\phi|s) := \left\{ k(x|s)(1 - \phi_x) - \sum_{y \neq x} k(y|s)\phi_y \right\} \phi_x - \pi_x\phi_x + \sum_{y \neq x} \pi(x|y)\phi_y.
\]

(15)

Since \( \log(N(t)) = \int_0^t dt' \sum x k(x|s(t'))\phi_x(t') \), time-trajectories \((\phi(t); s(t))_{t \geq 0}\) suffice to determine the time concentrations. Note that \( \sum_s \phi_s = 1 \) is a conserved quantity.

The time-evolution of the coupled system \( \Phi := (\phi; s) \) is a so-called PDMP (piecewise deterministic Markov process), a particular type of Feller Markov process (see [13], Chap. VII for an introduction) with generator \( \mathbb{L} \) acting on a space \( C_0(\mathbb{R}^X \times S) \) identified with the space of continuous vector-valued \( \mathbb{L} \) functions \( \{ f \equiv (f_s)_{s \in S}, f_s \in C_0(\mathbb{R}^X) \) with components indexed by \( S \),

\[
(\mathbb{L} f)_s(\phi) = \sum_{s'} \mathbb{L}_{s,s'}(\phi)f_{s'}, \quad \mathbb{L}_{s,s'}(\phi) = \begin{cases} v(\phi|s) \cdot \nabla - \kappa_s & s = s' \\ \kappa_{s'|s} & s \neq s' \end{cases}
\]

(16)

with \( v(\phi|s) \cdot \nabla = \sum_{x \in X} v_x(\phi|s)\partial_{\phi_x} \) "convection term" in the space \( \mathbb{R}^X \). Because \( \mathbb{L} = \mathcal{L}_S + \text{diag}(v(\cdot|s) \cdot \nabla) \), where \( \mathcal{L}_S \) is the generator of the environmental Markov chain, it is immediately checked that \( \mathbb{L}(1) = 0 \), where \( 1 = (1, \ldots, 1)' \) is the constant function.

Because the environmental Markov chain is irreducible, it can be proved that the above PDMP has a unique stationary probability measure, \( \mathbb{P} = \mathbb{P}(\phi; s) \). Letting for short \( \mathbb{P}_s(\phi) = \mathbb{P}(\phi; s) \), the normalization condition is \( \sum_s \int d\phi \mathbb{P}_s(\phi) = 1 \). By definition, \( \mathbb{P} \) generates the kernel of the adjoint operator \( \mathbb{L}^* \) in \( L^2(\mathbb{R}^X \times S) \): letting

\[
(\mathbb{L}^* f)_s(\phi) = \sum_{s'} \mathbb{L}_{s,s'}^*(f_{s'}), \quad \mathbb{L}_{s,s'}^*(f) = \begin{cases} -\nabla \cdot (v(\cdot|s) \cdot \kappa_s) & s = s' \\ \kappa_{s'|s} & s \neq s' \end{cases}
\]

(17)

featuring the adjoint operator \(-\nabla \cdot v(\phi|s) := \left(v(\phi|s) \cdot \nabla\right)^* = -\sum_x \partial_{\phi_x}(v_x(\phi|s) \cdot),\) one has \( \mathbb{L}^*(\mathbb{P}) = 0 \). Warning: the dot inside the parenthesis after the drift velocity \( v \) emphasizes that \( \nabla \cdot (v(\cdot|s) \cdot) \) or \( \partial_{\phi_x}(v_x(\phi|s) \cdot) \) is understood as an operator, i.e. it acts on a function component \( f_s \) as \( \nabla \cdot (v(\cdot|s) f_s(\phi)) \) or \( \partial_{\phi_x}(v_x(\phi|s) f_s(\phi)) \).

The natural \( L^2 \) space in this problem is not \( L^2(\mathbb{R}^{|X|} \times S) \) with its standard scalar product

\[
(f, g) := \sum_s \int d\phi \, f_s(\phi)g_s(\phi)
\]

(18)
but the \( \mathbb{P} \)-weighted space \( L^2(\mathbb{P}) \) with scalar product

\[
(f \cdot g)_{\mathbb{P}} := \sum_s \int d\phi \, \mathbb{P}_s(\phi) f_s(\phi) g_s(\phi).
\]

(19)

The adjoint of \( \mathbb{L} \) w. r. to the latter scalar product will be denoted \( \mathbb{L}^\dagger \); since \( (\mathbb{L} f, g)_{\mathbb{P}} = (\mathbb{P} g, \mathbb{L} f) = (\mathbb{P}^{-1} \mathbb{L}^* \mathbb{P} g, f)_{\mathbb{P}} \), one has

\[
\mathbb{L}^\dagger = \mathbb{P}^{-1} \mathbb{L}^* \mathbb{P}.
\]

(20)

Note that \( \text{Ker} \mathbb{L}^\dagger \) is generated by \( \mathbb{1} \).

For the sequel we also need to introduce the \textit{symmetrized generator},

\[
\mathbb{L}_{\text{sym}} := \frac{1}{2}(\mathbb{L} + \mathbb{L}^\dagger).
\]

(21)

By definition, \( \mathbb{L}_{\text{sym}} = \frac{1}{2} \mathbb{P}^{-1}(\mathbb{P} \mathbb{L} + \mathbb{L}^* \mathbb{P}) \). Explicit computation yields for diagonal coefficients

\[
-\frac{1}{2}(\mathbb{P} \mathbb{L} + \mathbb{L}^* \mathbb{P})_{s,s} = \frac{1}{2} \left\{ \mathbb{P}_s(-v(\cdot | s) \cdot \nabla + \kappa_s) + (\nabla \cdot v(\cdot | s) + \kappa_s) \mathbb{P}_s \right\} = \frac{1}{2} \sum_s \partial_{\phi_s} (v_s(\phi | s) \mathbb{P}_s) + \kappa_s \mathbb{P}_s = \frac{1}{2}(\kappa_s \mathbb{P}_s + \sum_{s' \neq s} \kappa_{s | s'} \mathbb{P}_{s'}) \quad \text{(in the last equality we have used the stationarity of \( \mathbb{P} \)}, \quad \text{and for off-diagonal coefficients,}

\[
-\frac{1}{2}(\mathbb{P} \mathbb{L} + \mathbb{L}^* \mathbb{P})_{s,s'} = -\frac{1}{2}(\kappa_s | s' \mathbb{P}_{s'} + \kappa_{s' | s} \mathbb{P}_s) \quad (s \neq s').
\]

Taking scalar products w.r. to the \( \mathbb{P} \)-weighted scalar product compensates the extra \( \mathbb{P}^{-1} \) weight in front of \( \mathbb{L}_{\text{sym}} \), and we then get an explicit expression of the non-negative (degenerate) quadratic form associated to \( -\mathbb{L}_{\text{sym}} \),

\[
\text{Lemma 2.1 (quadratic form associated to} \ -\mathbb{L}_{\text{sym}} \text{)}
\]

\[
(-\mathbb{L}_{\text{sym}} f, f)_{\mathbb{P}} = \frac{1}{2} \int d\phi \, \sum_{s \neq s'} \kappa_{s | s'} \mathbb{P}_{s'}(\phi) (f_s(\phi) - f_{s'}(\phi))^2.
\]

(22)

Note that \( \mathbb{1} \in \text{Ker} \mathbb{L}_{\text{sym}} \), as was the case for \( \mathbb{L} \) and \( \mathbb{L}^\dagger \), but

\[
\text{Ker} \mathbb{L}_{\text{sym}} = \{ k(\phi) \mathbb{1}, \quad k : \mathbb{R}^\mathcal{X} \to \mathbb{R} \}
\]

(23)

is infinite-dimensional. This is due to the fact that symmetrizing has killed the differential part connecting the different values of \( \phi \). Fixing \( \phi \), one has: \( \text{Ker} \mathbb{L}_{\text{sym}}(\phi) = \mathbb{R} 1 \) with \( 1 = (1 \cdots 1)^t \in \mathbb{R}^\mathcal{X} \), and \( \text{Im} \mathbb{L}_{\text{sym}}(\phi) = 1^\perp(\phi) := \{ k \in \mathbb{R}^\mathcal{X} \mid \sum_x \mathbb{P}_s(\phi)k_x = 0 \} \).

\textbf{Average growth rate}. Let \( \tilde{\mathbb{E}} \) be the average w. r. to the measure \( \tilde{\mathbb{P}} \) of the trajectories of the stationary PDMP. Start from (13), and time-integrate between 0 and \( T \). Since the process is asymptotically stationary, one gets when \( T \to \infty \)

\[
\lambda = (\mathbb{P}, f_{\text{growth}}) = \sum_s \int d\phi \, \mathbb{P}_s(\phi) f_{\text{growth}}(\phi; s)
\]

(24)
where

\[ f_{\text{growth}}(\phi; s) = \sum_x k(x|s)\phi_x \]  

(25)

is the growth functional.

**Variance of the growth rate.** By definition, the variance of the integrated growth rate is equal (up to normalization) to the variance of the integrated growth-rate function \( \int_0^T dt f_{\text{growth}}(\Phi(t)) \), so that

\[ \text{var}(\lambda) = \lim_{T \to \infty} \frac{1}{T} \mathbb{V} \left( \int_0^T dt f_{\text{growth}}(\Phi(t)) \right) \]  

(26)

with \( \mathbb{V}(\cdot) \) variance w.r. to the measure \( \mathbb{P} \) of the trajectories of the stationary PDMP.

**Theorem 2.1 (preliminary formula for the variance)** Let \( \delta f_{\text{growth}} := f_{\text{growth}} - \lambda \), then

\[ \text{var}(\lambda) = 2((-\mathbb{L})^{-1}\delta f_{\text{growth}}, \delta f_{\text{growth}})_\mathbb{P}. \]  

(27)

**Proof.** The result is standard and completely general: it states that \( \frac{1}{T} \mathbb{V} \left( \int_0^T dt f(\Phi_t) \right) \to_{T \to \infty} 2((-\mathbb{L})^{-1}\delta f, \delta f)_\mathbb{P} \) if \( \mathbb{L} \) is a Feller generator, \( f \) is a \( C_0 \) function, and \( \delta f := f - \mathbb{E}[f] \) is the expectation w.r. to the stationary probability measure. Namely (see e.g. \[2\]) \( (-\mathbb{L})^{-1} = \int_0^{+\infty} d\theta \ e^{\theta \mathbb{L}} \) is defined on the subspace of \( C_0 \) functions with zero average, which contains in particular \( \delta f \). Now, letting \( \mathbb{E}[\cdot] := (\mathbb{P}, \cdot) \) be the \( \mathbb{P} \)-average,

\[
\frac{1}{T} \mathbb{V} \left( \int_0^T dt f(\Phi_t) \right) = \frac{2}{T} \int_0^T dt \int_0^t \mathbb{E}[\delta f(\Phi_t)\delta f(\Phi_{t'})]
\]

\[
\sim_{T \to \infty} \frac{2}{T} \int_0^T dt \int_0^t d\theta \mathbb{E}[\delta f \ (e^{\theta \mathbb{L}} \delta f)] \quad \text{by asymptotic stationarity}
\]

\[
= \frac{2}{T} \int_0^T dt \mathbb{E}[\delta f \ (-\mathbb{L})^{-1}(1 - e^{\mathbb{L}})\delta f]
\]

\[
\to_{T \to \infty} 2((-\mathbb{L})^{-1}\delta f, \delta f)_\mathbb{P}.
\]  

(28)

We may now prove our main formula, in the form of a Legendre transform,

**Theorem 2.2 (Variational formula for the variance)** Let \( f \) be a \( C_0 \)-function with 0 average, i.e. \((\mathbb{P}, f) = 0\). Then

\[
\frac{1}{2}((-\mathbb{L})^{-1}f, f)_\mathbb{P} = \sup_a \left\{ (f, a)_\mathbb{P} - \frac{1}{2}((-\mathbb{L}^{-1}\mathbb{L}^\dagger + \mathbb{L}^\dagger\mathbb{L})a, a)_\mathbb{P} \right\}.
\]  

(29)
The supremum in the formula is over the set of all \( C_0 \)-functions \( a \), with the convention that 
\[ \begin{align*}
(-\mathbb{L}_{sym})^{-1} \mathbb{L}^\dagger a, \mathbb{L}^\dagger a_p \equiv +\infty \text{ if } \mathbb{L}^\dagger a \not\in \text{Im } (\mathbb{L}_{sym}) ,
\end{align*} \]
meaning that we can restrict to the subspace of functions \( a \) such that
\[ \mathbb{L}^\dagger a \in \text{Im } (\mathbb{L}_{sym}). \tag{30} \]

Since \( (f,1)_p = 0 \) and \( \mathbb{L}^\dagger 1 = 0 \), one can further restrict to the hyperplane \( 1^\perp := \{ f \mid (f,1)_p = 0 \} \) of zero average functions.

The Theorem is used in the sequel with \( f = \delta f_{\text{growth}} \).

**Proof.** Since \( f \in 1^\perp, (-\mathbb{L})^{-1} f \) is well-defined. Let \( g := (-\mathbb{L})^{-1} f \), then
\[ \frac{1}{2}(((-\mathbb{L}))^{-1} f, f)_p = \frac{1}{2}(g, (-\mathbb{L})g)_p = \frac{1}{2}(g, (-\mathbb{L}_{sym})g)_p. \tag{31} \]

We now argue that (though the matrix \( -\mathbb{L}_{sym}(\phi) \) is not one-to-one) the scalar product \((\mathbb{L}_{sym}^{-1} h, h)_p\) may be defined unambiguously when \( h \in \text{Im } (\mathbb{L}_{sym}) \). Namely, \( \text{Ker } \mathbb{L}_{sym}(\phi) = \mathbb{R} 1 \), so \( (\mathbb{L}_{sym})^{-1} h \) is determined only up to the addition of \( c(\phi) 1 \), where \( c(\phi) \) is some scalar function. However, since \( \text{Im } \mathbb{L}_{sym}(\phi) = 1^\perp(\phi) \), the scalar product \((\mathbb{L}_{sym}^{-1} h, h)_p\) is independent of the choice of the function \( c \).

The expression in (31) is equal to \( \sup_h \left\{ (g, h)_p - \frac{1}{2}((-\mathbb{L}_{sym})^{-1} h, h)_p \right\} \), with the same convention, namely, \((((-\mathbb{L}_{sym})^{-1} h, h)_p \equiv +\infty \text{ if } h \not\in \text{Im } (\mathbb{L}_{sym}) \). Namely, the functional \( F : h \mapsto (g, h)_p - \frac{1}{2}((-\mathbb{L}_{sym})^{-1} h, h)_p \) is concave, and attains its maximum at \( h \) satisfying the extremum equation \( \frac{\delta F}{\delta h} = 0 \), namely, \(((-\mathbb{L}_{sym})^{-1} h = g, \text{ or } h = -\mathbb{L}_{sym} g) \).

Since \( \text{Im } \mathbb{L}^\dagger = (\text{Ker } \mathbb{L})^\perp \subset \text{Im } \mathbb{L}_{sym} \), one may replace \( h \) by \( -\mathbb{L}^\dagger a \), with \( a = (-\mathbb{L})^{-1} h \). Then \((g, h)_p = ((-\mathbb{L})^{-1} f, (-\mathbb{L})^{-1} a)_p = (f, a)_p \), yielding (29).

\[ \square \]

**Characterization of the subspace for optimization.** Let
\[ U := \{ a \mid \mathbb{L}^\dagger a \in \text{Im } (\mathbb{L}_{sym}) \}. \tag{32} \]

As already mentioned, \( \mathbb{L}^\dagger a \) belongs to \( \text{Im } (\mathbb{L}_{sym}) \) if and only if \( \forall \phi, \sum_s \mathbb{P}_s(\phi)(\mathbb{L}^\dagger a)(\phi; s) = 0 \). Recalling that \( \mathbb{L}^\dagger = \mathbb{P}^{-1} \mathbb{L}^* \mathbb{P} \), this is equivalent to the condition
\[ \forall \phi, \sum_s \mathbb{L}^*(\mathbb{P}(\phi)a(\phi))(s) = 0. \tag{33} \]

Now, by (17),
\[ \sum_s \left( -\mathbb{L}^*(\mathbb{P}(\phi)a(\phi)) \right) = \sum_s \left( \nabla \cdot (v(\phi|s)\mathbb{P}_s(\phi)a_s(\phi)) + \kappa_s \mathbb{P}_s(\phi)a_s(\phi) \right) - \sum_{s,s'} \kappa_{s|s'} \mathbb{P}_s(\phi)a_{s'}(\phi) \]
Since \( \sum_{s} \kappa_{s|s'} = \kappa_s \), there remains only a "divergence" term (sum over environmental states of weighted divergence of the product \( v(\cdot|s)a_s(\cdot) \)):
\[ \left( a \in U \right) \Rightarrow \left( \forall \phi, \sum_s \nabla \cdot (v(\phi|s)\mathbb{P}_s(\phi)a_s(\phi)) = 0 \right) \tag{34} \]
3 Explicit formula in the two-state model

We assume here that $\mathcal{X} = \{1, 2\}$ and $S = \{1, 2\}$. Since $\phi_1 + \phi_2 = 1$, there is only one free variable, which we choose to be $\phi = \phi_1$, and write for short $\partial = \partial_\phi$. Notations in [10] are similar to ours, with $\mu^A_t \equiv k(A|s)$, $(p, q) \equiv (\pi_1, \pi_2)$, $\lambda \equiv \kappa$, $\Pi(\phi, s) \equiv \mathbb{P}_s(\phi)$, and states and environments indexed by 0, 1 instead of 1, 2. Let $\Delta_s := k(1|s) - k(2|s), s = 1, 2$. We assume in the sequel that $\Delta_1 > 0 > \Delta_2$: phenotype $s$ grows fastest in environment $s$. Then (particularizing the formulas found in the previous section)

$$\begin{aligned}
\begin{cases}
u_1(\phi) = \Delta_1 \phi(1 - \phi) - \pi_1 \phi + \pi_2(1 - \phi) \\
u_2(\phi) = \Delta_2 \phi(1 - \phi) - \pi_1 \phi + \pi_2(1 - \phi)
\end{cases}
\end{aligned}$$

(35)

$$\begin{aligned}
\mathbb{L} = \begin{bmatrix}
u_1 \partial - \kappa_1 & \kappa_1 \\
\kappa_2 & \nu_2 \partial - \kappa_2
\end{bmatrix}, \quad
\mathbb{L}^* = \begin{bmatrix}
-\partial \nu_1 - \kappa_1 & \kappa_2 \\
\kappa_1 & -\partial \nu_2 - \kappa_2
\end{bmatrix}
\end{aligned}$$

(36)

$$\begin{aligned}
-\mathbb{L}^+ &= \begin{pmatrix}
\mathbb{P}_1^{-1} & \mathbb{P}_2^{-1}
\end{pmatrix}
\begin{pmatrix}
\partial \nu_1 + \kappa_1 & \kappa_2 \mathbb{P}_2 \\
-k_1 \mathbb{P}_1 & \partial \nu_2 + \kappa_2 \mathbb{P}_2
\end{pmatrix}
= \begin{pmatrix}
\mathbb{P}_1^{-1} & \mathbb{P}_2^{-1}
\end{pmatrix}
\begin{pmatrix}
\nu_1 \mathbb{P}_1 \partial + \kappa_2 \mathbb{P}_2 \\
-k_1 \mathbb{P}_1 & \nu_2 \mathbb{P}_2 \partial + \kappa_1 \mathbb{P}_1
\end{pmatrix}
\end{aligned}$$

(37)

The stationarity equation $\mathbb{L}^*(\mathbb{P}) = 0$ is equivalent to

$$-(\nu_2 \mathbb{P}_2)' = (\nu_1 \mathbb{P}_1)' = -k_1 \mathbb{P}_1 + k_2 \mathbb{P}_2
$$

(38)

As proved in [10], the stationary probability $\mathbb{P}$ actually satisfies $\nu_1 \mathbb{P}_1 + \nu_2 \mathbb{P}_2 = 0$; substituting for $\mathbb{P}_2$ in the stationarity equation yields a one-dimensional transport equation which can be be solved explicitly. First, 

$$\text{supp}(\mathbb{P}_1) = \text{supp}(\mathbb{P}_2) = (\phi_2^+, \phi_1^+),$$

(39)

where $\phi_1^+$, resp. $\phi_2^+$, is the largest, resp. smallest solution of the quadratic equation $\nu_1(\phi) = 0$, resp. $\nu_2(\phi) = 0$; they correspond to the stable fixed point of the characteristic equation in environment $s$. We let $\phi_s^-$ be the second solutions of $\nu_s(\phi) = 0, s = 1, 2$. Explicitly,

$$\begin{aligned}
\phi_1^+ &= \frac{\Delta_1 - (\pi_1 + \pi_2) \pm \sqrt{\Delta_1 - (\pi_1 + \pi_2)^2 + 4 \pi_1 \pi_2}}{2 \Delta_1}, \\
\phi_2^+ &= \frac{|\Delta_1 + (\pi_1 + \pi_2) \pm \sqrt{\Delta_1 + (\pi_1 + \pi_2)^2 - 4 \pi_1 \pi_2}}{2 |\Delta_2|}.
\end{aligned}$$

(40)

Diagonalizing the generator $P_s = \mathbb{P}^{\text{growth}}(s) + \mathbb{P}^{\text{pheno}}$, $s = 1, 2$, one also sees that eigenvalues are $k_1 \phi_1^\pm$ for $s = 1$, and $k_2(1 - \phi_2^\pm)$ for $s = 2$. Note that

$$\phi_1^- < 0 < \phi_2^+ < \phi_1^+ < 1 < \phi_2^-.$$

(41)
Now,
\[
\mathbb{P}_1(\phi) = \frac{\mathcal{N}_1}{\Delta_1}(\phi_1^+ - \phi)^{g-1}(\phi - \phi_2^+) f_1(\phi) \tag{42}
\]
\[
\mathbb{P}_2(\phi) = \frac{\mathcal{N}_2}{|\Delta_2|}(\phi - \phi_2^+)^{h-1}(\phi_1^+ - \phi)^{g} f_2(\phi) \tag{43}
\]
with
\[
g = \frac{\kappa_1}{\Delta_1(\phi_1^+ - \phi^-)}, \quad h = \frac{\kappa_2}{|\Delta_2|}(\phi_2^- - \phi^+), \tag{44}
\]
positive constants, and
\[
f_1(\phi) = (\phi - \phi_1^-)^{-g-1}(\phi_2^- - \phi)^{-h}, \tag{45}
\]
\[
f_2(\phi) = (\phi - \phi_1^-)^{-g}(\phi_2^- - \phi)^{-h-1} \tag{46}
\]
Normalization constants $\mathcal{N}_1, \mathcal{N}_2$ ensure that $\int_0^1 d\phi \mathbb{P}_s(\phi) = Q_s = \begin{cases} \frac{\kappa_2}{\kappa_1+\kappa_2} & s = 1 \\ \frac{\kappa_1}{\kappa_1+\kappa_2} & s = 2 \end{cases}$. Formulas (10a),(10b) in [10] feature only one normalization constant $\mathcal{N} = \mathcal{N}_1, \mathcal{N}_2$. It actually follows from the vanishing of the probability current that $\mathcal{N}_1 = \mathcal{N}_2$ (indeed, evaluating (26) in [9] at $\phi = \phi_2^+$ yields $\int_{\phi_2^+}^{\phi_1^+} d\phi (\kappa_1 \mathbb{P}_1 - \kappa_2 \mathbb{P}_2)(\phi) = 0$).

Note that $\mathbb{P}_1(\phi)$ vanishes at the left end of the support ($\phi_1^+$); on the other hand, $\mathbb{P}_1$ diverges like $(\phi_1^+ - \phi)^{g-1}$ at the right end of the support ($\phi_1^+$) if $g < 1$. But $v_1$ vanishes to first order at $\phi_1^+$, so $(v_1 \mathbb{P}_1)(\phi) \sim_{\phi \to \phi_1^+} c(\phi_1^+ - \phi)^g \to 0$.

**Plot of $\mathbb{P}_1(\phi)$ ($g < 1$). Parameters:** $|\phi_1^-| = \phi_2^+ = 1 - \phi_1^- = |1 - \phi_2^-| = 0.15$, $h = 0.2$, $g = 0.1$. 

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Then,

\[
\mathbb{P}(-\mathbb{L}_{sym}) = -\frac{1}{2} \mathbb{P}(\mathbb{L} + \mathbb{L}^\dagger)
\]

\[
= \frac{1}{2} \begin{bmatrix}
\mathbb{P}_1(-u_1 \partial + \kappa_1) & -\mathbb{P}_1 \\
-\mathbb{P}_2 u_2 \partial + \kappa_2)
\end{bmatrix}
+ \frac{1}{2} \begin{bmatrix}
u_1 \mathbb{P}_1 \partial + \kappa_2 \mathbb{P}_2 & -\mathbb{P}_2 \\
-\mathbb{P}_1 \partial + \kappa_1 \mathbb{P}_1
\end{bmatrix}
\]

\[
= \frac{1}{2}(\kappa_1 \mathbb{P}_1 + \kappa_2 \mathbb{P}_2) \times \begin{bmatrix}
1 & -1 \\
-1 & 1
\end{bmatrix}
\]

whence

\[
(-\mathbb{L}_{sym} f, f)_\mathbb{P} = \frac{1}{2} \int d\phi (\kappa_1 \mathbb{P}_1(\phi) + \kappa_2 \mathbb{P}_2(\phi))(f_1(\phi) - f_2(\phi))^2
\]

as a particular case of Lemma 2.1.

Note also that the kernel of \(-\mathbb{L}_{sym}(\phi)\) is (as expected) \(\mathbb{R}(1, 1)^t\) for any fixed \(\phi\). Its lines \((L_1), (L_2)\) are proportional with \((L_1) = \frac{\mathbb{P}_1}{\mathbb{P}_2}(L_2) = \frac{\mathbb{P}_2}{\mathbb{P}_1}(L_2)\), so

\[
\text{Im}(-\mathbb{L}_{sym}) = \mathbb{R}\left(\mathbb{P}_2(\phi), -\mathbb{P}_1(\phi)\right)
\]

for any fixed \(\phi\). If \(f \in \text{Im}(-\mathbb{L}_{sym})\), then \((-\mathbb{L}_{sym})^{-1} f = (\kappa_1 \mathbb{P}_1 + \kappa_2 \mathbb{P}_2)^{-1} \left(\begin{bmatrix}
\mathbb{P}_1 f_1 \\
\mathbb{P}_2 f_2
\end{bmatrix}\right)\) modulo \(\phi\)-dependent vectors in the direction \(\left(\begin{bmatrix}
1 \\
1
\end{bmatrix}\right)\). (Namely, letting \(f \in \text{Im}(-\mathbb{L}_{sym})\) so that \(\mathbb{P}_1 f_1 = -\mathbb{P}_2 f_2\), \(\mathbb{P}(-\mathbb{L}_{sym})(\kappa_1 \mathbb{P}_1 + \kappa_2 \mathbb{P}_2)^{-1} \left(\begin{bmatrix}
\mathbb{P}_1 f_1 \\
\mathbb{P}_2 f_2
\end{bmatrix}\right) = \frac{1}{2} \left(\begin{bmatrix}
1 & -1 \\
-1 & 1
\end{bmatrix}\right) \left(\begin{bmatrix}
\mathbb{P}_1 f_1 \\
\mathbb{P}_2 f_2
\end{bmatrix}\right) = \mathbb{P}\left(\begin{bmatrix}
f_1 \\
f_2
\end{bmatrix}\right).\)

Characterization of the subspace for optimization. Recall from (32) that \(U = \{a \mid \mathbb{L}^\dagger a \in \text{Im}(\mathbb{L}_{sym})\}\). The divergence operator \(\nabla\cdot\) is one-dimensional here, yielding the equation \(\partial(u_1 \mathbb{P}_1 a_1 + u_2 \mathbb{P}_2 a_2) = 0\). We thus have \(u_1 \mathbb{P}_1 a_1 = -u_2 \mathbb{P}_2 a_2 + c\) for some constant \(c\), i.e., assuming that \(c = 0\) (see below)

\[
a_1 = a_2.
\]

Then, if \(a_1 = a_2\),

\[
-\mathbb{L}^\dagger a = \mathbb{P}^{-1} \left(\begin{bmatrix}
u_1 \mathbb{P}_1 a_1' \\
\nu_2 \mathbb{P}_2 a_2'
\end{bmatrix}\right) = \left(\begin{bmatrix}
u_1 a_1' \\
\nu_2 a_2'
\end{bmatrix}\right)
\]

so

\[
\frac{1}{2}(-\mathbb{L}_{sym})^{-1} \mathbb{L}^\dagger a, \mathbb{L}^\dagger a)_\mathbb{P} = \frac{1}{2} \left(\begin{bmatrix}
u_1 a_1' \\
\nu_2 a_2'
\end{bmatrix}\right)
\]

\[
= \int_{\phi_2^*}^{\phi_1^*} \frac{d\phi}{\kappa_1 \mathbb{P}_1(\phi) + \kappa_2 \mathbb{P}_2(\phi)}
\]

(52)
From the latter expression it follows that \( \frac{1}{2}((-L_{\text{sym}})^{-1}L^\dagger a, L^\dagger a)_p = +\infty \) if \( c \neq 0 \). Namely, suppose adding \( \frac{c}{v_i p_i} \) to \( a_1 \); we get successively \( \frac{c}{v_i p_i} \sim_{\phi \to \phi_1^+} c_1(\phi_1^+ - \phi)^{-\varepsilon}; \frac{c}{v_i p_i} \sim_{\phi \to \phi_1^+} c_2(\phi_1^+ - \phi)^{-\varepsilon-1}; (v_1(\phi)P_1(\phi)a_1'(\phi))^2 \sim_{\phi \to \phi_1^+} c_3(\phi_1^+ - \phi)^{-2}; (\kappa_1 P_1(\phi) + \kappa_2 P_2(\phi))^{-1} \sim_{\phi \to \phi_1^+} c_4(\phi_1^+ - \phi)^{-\varepsilon}. \) Thus the integrand in (52) is not integrable in a neighborhood of \( \phi_1^+ \) if \( c \neq 0 \).

**Growth functional.** By definition,

\[
f_{\text{growth}}(\phi) = \left( \begin{array}{c} f_{\text{growth},1}(\phi) \\ f_{\text{growth},2}(\phi) \end{array} \right) = \left( \begin{array}{c} k(1|1)\phi + k(2|1)(1 - \phi) \\ k(1|2)\phi + k(2|2)(1 - \phi) \end{array} \right)
\]

and, if \( a_1 = a_2 \),

\[
(f_{\text{growth}} - \lambda, a)_p = \int_{\phi_1^+}^{\phi_2^+} d\phi a_1(\phi) \left\{ \begin{array}{c} P_1(\phi) \left( (k(1|1)\phi + k(2|1)(1 - \phi) - \lambda \right) \\ + P_2(\phi) \left( k(1|2)\phi + k(2|2)(1 - \phi) - \lambda \right) \end{array} \right\}
\]

As in Theorem 2.1, we let \( \delta f_{\text{growth}} = f_{\text{growth}} - \lambda \), where \( \lambda \) is the average growth rate. We introduce the convenient bracket notation \( \langle f, g \rangle(\phi) := \sum_{s=1,2} \int f_s(\phi)g_s(\phi) \) for functions \( f = (f_s(\phi))_{s\in S}, g = (g_s(\phi))_{s\in S} \).

**Solving for extremum.** We find the supremum of the concave functional of Theorem 2.2 by solving a Euler-Lagrange equation in \( a_1 \); namely, the two terms

\[
\frac{\delta}{\delta a_1} \langle P, \delta f_{\text{growth}} \rangle = \langle P, \delta f_{\text{growth}} \rangle = P_1(f_{\text{growth},1} - \lambda) + P_2(f_{\text{growth},2} - \lambda)
\]

and

\[
\frac{\delta}{\delta a_1} \left( \frac{1}{2}((-L_{\text{sym}})^{-1}L^\dagger a, L^\dagger a)_p \right) = -2\left( \frac{(v_1P_1)^2}{\kappa_1 P_1 + \kappa_2 P_2} a_1' \right)'
\]

coming from (29) must be equal. Postulating equality of the right-hand sides of (55) and (56) yields \( a_1 \) by explicit integration. Formally, by direct computation from (29), \( f = \kappa a \), with \( \kappa = L((-L)^{-1}f, f)_p = \frac{1}{2}((\kappa a, a) = \frac{1}{2}(a, a)_p \). Instead of this computation based on variational calculus, we can simply check, assuming equality of (55) and (56), and using (52), that

\[
\langle \delta f_{\text{growth}}, a \rangle_p - \frac{1}{2}((-L_{\text{sym}})^{-1}L^\dagger a, L^\dagger a)_p = \int a_1 \langle P, \delta f_{\text{growth}} \rangle - \int \frac{(v_1P_1 a_1')^2}{\kappa_1 P_1 + \kappa_2 P_2}
\]

\[
= -2 \int a_1 \left( \frac{(v_1P_1 a_1')^2}{\kappa_1 P_1 + \kappa_2 P_2} a_1' \right)' - \int \frac{(v_1P_1 a_1')^2}{\kappa_1 P_1 + \kappa_2 P_2}
\]

\[
= \int \frac{(v_1P_1 a_1')^2}{\kappa_1 P_1 + \kappa_2 P_2}
\]
(by integration by parts). Letting \( q := \frac{(v_1 P_1)^2}{k_1 P_1 + k_2 P_2} \), equality of (55) and (56) is tantamount to 
\[ \langle \mathbb{P}, \delta f_{\text{growth}} \rangle = -2(qa')' \], whence
\[
\frac{1}{2}((-\mathbb{I})^{-1}\delta f_{\text{growth}}, \delta f_{\text{growth}}) = \int d\phi \, q(\phi)(a'_1(\phi))^2 = \frac{1}{4} \int d\phi \, q^{-1}(\phi) \left( \int_{\phi_1^+}^{\phi_2^+} d\phi' \langle \mathbb{P}, \delta f_{\text{growth}} \rangle(\phi') \right)^2
\]
(58)
since \( q(\phi_2^+) = 0 \). Finally, multiplying by 4 (compare Theorem 2.1 to Theorem 2.2), we get our explicit formula for the variance, in terms of the parameters \( (\pi_x)_{x=1,2}, (\kappa_x)_{x=1,2}, (k(x|s))_{x,s=1,2} \) and of the Hufton-Lin-Galla-McKane stationary distribution (40), (42), (43) only:

**Theorem 3.1 (asymptotic growth-rate variance for two states)** Let
\[
\hat{\lambda} = \sum_{s=1,2} \int_{\phi_1^+}^{\phi_2^+} d\phi \, \mathbb{P}_s(\phi) \delta f_{\text{growth}}(\phi; s)
\]
(59)
be the average growth rate (see (32)), \( I(\phi) := \int_{-\phi_1^+}^{\phi_2^+} d\phi' \, (\mathbb{P}_{1,1} \delta f_{\text{growth,1}} + \mathbb{P}_{2,2} \delta f_{\text{growth,2}})(\phi') \), and \( q(\phi) := \frac{(v_1 P_1)^2(\phi)}{k_1 P_1(\phi) + k_2 P_2(\phi)} \) (see (33)). Then the asymptotic growth-rate variance (12) is
\[
\text{var}(\hat{\lambda}) = \int_{\phi_1^+}^{\phi_2^+} d\phi \, q^{-1}(\phi) \, I^2(\phi).
\]
(60)

## 4 Conclusion

We have presented in this work a derivation of the variance of the growth rate of a general class of mutation-selection models. Our general formula, Theorem 2.2, is based on the piecewise deterministic Markov process (PDMP) reformulation of the model used by Hufton-Lin-Galla-McKane. The analytic formula found by these authors for the stationary measure of the PDMP in the simplest non-trivial case (two phenotypes, two environments) makes it possible to derive an analytic formula both for the average growth-rate \( \hat{\lambda} \) (which was done previously by Hufton et al.), and then for its variance \( \text{var}(\hat{\lambda}) \) (see our Theorem 3.1, as a consequence of Theorem 2.2).

The particular case \(|X| = |S| = 2\) already exhibits many interesting features studied in [10], notably, the nature of the ‘optimal’ phenotypic switching strategy (as characterized by the mutation rates \( \pi_1, \pi_2 \)), i.e. that leading to the largest growth-rate. It has been found that a ‘bet-hedging’ strategy (with \( \pi_1, \pi_2 \neq 0 \)) is favored when environmental switching rates \( \kappa_1, \kappa_2 \) are not too large, whereas a homogeneous phase, characterized by the presence of a single phenotype, is favored in the contrary case.

In the companion preprint [6], following the strategy of [5], we optimize instead of \( \hat{\lambda} \) alone various positive linear combinations of \( \hat{\lambda} \) and of \( -\text{var}(\hat{\lambda}) \). It will be interesting to see how this changes the previous observations, in particular, the phase diagrams.
It seems impossible to obtain analytic formulas for the stationary measure of the PDMP beyond the case $|\mathcal{X}| = |S| = 2$, hence Theorem 3.1 cannot be extended. However, our rather abstract variational formula, Theorem 2.2, which depends on the unknown measure $\mathbb{P}$, allows a priori various lower bounds for the variance. One may hope to obtain from it uncertainty relations such as that obtained in [8], yielding a lower bound for the variance in terms of the (squared) growth-rate and some $\mathbb{P}$-dependent function playing the rôle of an entropy dissipation. However, we have not been able to prove such a formula for the moment.

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