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Stochastic gene expression in switching environments

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Abstract Organisms are known to adapt to regularly varying environments. However, in most cases, the fluctuations of the environment are irregular and stochastic, alternating between favorable and unfavorable regimes, so that cells must cope with an uncertain future. A possible response is population diversification. We assume here that the cell population is divided into two groups, corresponding to two phenotypes, having distinct growth rates, and that cells can switch randomly their phenotypes. In static environments, the net growth rate is maximized when the population is homogeneously composed of cells having the largest growth rate. In random environments, growth rates fluctuate and observations reveal that sometimes heterogeneous populations have a larger net growth rate than homogeneous ones, a fact illustrated recently through Monte-Carlo simulations based on a birth and migration process in a random environment. We study this process mathematically by focusing on the proportion $f(t)$ of cells having the largest growth rate at time t , and give explicitly the related steady state distribution π . We also prove the convergence of empirical averages along trajectories to the first moment $\mathbb{E}_\pi(f)$, and provide efficient numerical methods for computing $\mathbb{E}_\pi(f)$.

Keywords Gene expression · fluctuating environment · steady state

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1 Introduction

Organisms are known to adapt to regularly varying environments, by regulating their intrinsic dynamics using circadian clocks. In most cases, the fluctuations of the environment are however irregular and stochastic, alternating between favorable and unfavorable regimes, so that cells must cope with an uncertain future, see e.g. [6], [19] or [20]. A possible response is population diversification: the cell population divides into several groups of various phenotypes, and cells can adapt their phenotypes to the changing environment [18]. In clonal populations, phenotypic diversity can be generated by stochastic phenotype-switching mechanisms. A cell can switch from a state where some gene is consistently expressed to a state in which it is silent. In what follows, we will consider an analytical study of a stochastic model of phenotype switching proposed in [20], which is similar to models proposed recently in [16] and [17].

When considering the time-evolution of phenotypes, the related switching rates can be deterministic or stochastic, and subordinated to or independent of the fluctuating environment. The above models are based on two main assumptions: cells can switch stochastically between various expression levels and the switching rates depend on the (random) environment. Some additional assumptions can be considered according to the specificity of the setting, as provided in [16] and [17] in the context of bacterial persistence. How do cells proceed to realize these transitions? Random phenotype-switching mechanisms have been observed in bacteria having a gene network structure leading to bistability (or multistability): such systems have two main states, corresponding typically to low and high gene expression levels, see e.g. [18]. This is the case for example in *Escherichia coli* for persister cells and in *Bacillus subtilis*, where cells can choose between three different genetic programs according to culture conditions, see e.g. [8] or [11]. The random switching mechanism is influenced by chemical gradients, and depends on the life-style of the bacteria (natural isolates or biofilms), see e.g. [14]. Bistability occurs when the regulatory network can switch between two different gene expression levels, through, for example, positive feedback loops (see e.g. [1], [3], or [18]). Bistable switches are epigenetic, that is, they are not mediated by genetic changes, mutations or DNA rearrangement. Finally, mechanisms possessing similar bistable structures are also found in eukaryotes, see e.g. [4] or [10].

The mathematical models presented in [16], [17] and [20] assume a division of the cell population into two or more sub-populations, corresponding to the various phenotypes. Cells can change their states stochastically, with rates depending on the environment. The environment itself can be deterministic and periodic as for example in [17], or random as in [16] and [20]. We will focus here on the model proposed in [20], which can be translated mathematically as a birth and migration process in a random environment (see below). We consider here a switching environment, which alternates between two regimes.

The mathematical study is instrumental for many reasons: such switching mechanisms occur in pathogenic bacteria (see e.g. [15]), so that this problem is clinically relevant. Moreover, the tight control of mathematical models

might be useful in practical laboratory experiments, as shown for example in the case of persistent bacteria in [17] or in [20], where it is shown that time-dependent conditions, as given by the various switching rates, ought to play a central role in the design and interpretation of laboratory experiments. We will derive the steady state of the stochastic system and verify mathematically that there are situations where cell populations can adapt their phenotype-switching rates to escape adverse conditions, should they arise, and increase the probability of being in a favorable regime. Simulations provided in [20] indicate that heterogeneity is however beneficial over only a small parameter range. A complete understanding of this phenomenon necessitates a tight control of the mathematical model.

2 The stochastic population model

Assume that the cells, or for example the product of some gene, can be in two distinct states or phenotypes. Let $X(t)$ and $Y(t)$ be the sizes of these populations. The phenotype-switching mechanism is viewed here as a migration process: cells of each group reproduce exponentially fast at some rates, and can switch their phenotypes, or equivalently, migrate to the other group. We assume that the birth rates are either γ_2 or γ_1 with $\Delta\gamma = \gamma_2 - \gamma_1 > 0$, and that the associated migration rates k_2 and k_1 are such that $k_1 \geq k_2$, which means that cells located in the group having the smaller birth rate migrate at a higher rate to the group with the higher birth rate than the other way round.

If the birth and migration rates are assigned once and for all to a corresponding group (e.g. γ_1 and k_1 to X , and γ_2 and k_2 to Y), then the mean sizes $n_1(t) = \mathbb{E}(X(t))$ and $n_2(t) = \mathbb{E}(Y(t))$ satisfy the pair of differential equations

$$\begin{aligned} \frac{dn_1(t)}{dt} &= (\gamma_1 - k_1)n_1(t) + k_2n_2(t), \\ \frac{dn_2(t)}{dt} &= (\gamma_2 - k_2)n_2(t) + k_1n_1(t). \end{aligned} \quad (1)$$

According to [20], we say that cells of the first group represented by $X(t)$ are *unfit* (they have the lower birth rates), and conversely that cells of the second group represented by $Y(t)$ are *fit*. The proportion of fit cells in the total population, $y(t) = n_2(t)/(n_2(t) + n_1(t))$, $t \geq 0$, satisfies the differential equation

$$\frac{dy(t)}{dt} = k_1 + (\Delta\gamma - k_1 - k_2)y(t) - (\Delta\gamma)y(t)^2. \quad (2)$$

Then, as $t \rightarrow \infty$, $y(t) \rightarrow y_2$, where $\frac{1}{2} \leq y_2 \leq 1$, which follows directly from (2), see Section 3. This describes the equilibrium value of the proportion of fit cells in a non-changing environment. Fixing the values of the parameters k_1 , γ_1 and γ_2 , we can ask for the value of $0 \leq k_2 \leq k_1$ which maximizes the proportion of fit cells, i.e. the equilibrium value of $y(t)$: the optimal strategy is to keep all the fit cells in the fit state, that is to set their migration rate

to zero, $k_2 = 0$. This leads to $y_2 = 1$, and thus the optimal solution would be a homogeneous population.

Observations reveal however that most cell populations are not homogeneous; to explain this, [16] and [20] propose to introduce a modification in the model by allowing environmental changes. In [20], the authors show through Monte-Carlo simulations that the homogeneous solution $k_2 = 0$ is then not always optimal. The idea is to allow the birth and migration rates to switch at random times from one group to the other, so that cells in the fit group become unfit and vice versa. If for example an environmental change occurs at some random time $T_1 > 0$ ($T_0 = 0$), then the function $f_2(t)$ representing the proportion of fit cells solves (2) up to time T_1 , and just after T_1 , say at time $T_1 + 0$, the fit cells corresponding to $Y(t)$ become unfit and vice versa. The proportion of fit cells $f_2(t)$ is then switched to $f_2(T_1 + 0) = 1 - f_2(T_1)$. After T_1 , the random process $\{f_2(t)\}_{t \geq 0}$ solves (2) with initial data $f_2(T_1 + 0)$ at time $T_1 + 0$, until a new environmental change occurs, say at time $T_2 > T_1$. There is a new switch, and the process is again solution of (2), until a new event occurs and so on. This model considers the evolution of the mean sizes $n_1(t)$ and $n_2(t)$ of the birth and migration process; stochasticity is the result of the random environment. This is of course a big simplification: the fully stochastic model, where no averaging is assumed for the birth and migration process, is out of reach mathematically at present time, and the model given in [20] is interesting since it permits a mathematical treatment while conserving the main features of the problem.

In [16] and [20], the fluctuations of the environment are modeled using a renewal process; the instants T_i , $i \geq 0$, are such that the sequence of random variables $\{t_i\}_{i \geq 1}$ given by $t_i \equiv T_i - T_{i-1}$, $i \geq 1$, is i.i.d. distributed according to some law μ on \mathbb{R}^+ . The authors then use Monte-Carlo simulations to estimate the limiting value of the time averages along trajectories of the process $f_2(t)$, of the form

$$S_N = \frac{1}{T_N} \int_0^{T_N} f_2(s) \, ds. \quad (3)$$

This limiting average value is denoted by $\text{Av}(f_2)_{k_2}$ to express its dependency on the migration rate $k_2 < k_1$, when all the remaining parameters are fixed. Their simulations indicate that there is a range of parameters (k_1 not too large) such that

$$\text{Av}(f_2)_{k_2 > 0} > \text{Av}(f_2)_{k_2 = 0},$$

which means that, for these parameters, heterogeneous populations are better adapted than homogeneous ones.

In this paper, we study mathematically the limiting behavior of the stochastic process $f_2(t)$ and the associated time average S_N by giving analytically the density of the stationary measure π . Our technique uses the process $X_k = f_2(T_k - 0)$, $X_0 = f_2(0)$, which is such that $X_{k+1} = \phi_{t_{k+1}}(1 - X_k)$, for some mapping $\phi_i(x)$ (see Definition 1). $(X_k)_{k \geq 0}$ is a stochastic recursive Markov chain, and S_N can be expressed as an additive functional of the trajectory of $(X_k)_{1 \leq k \leq N}$. In Section 3, we recall a Theorem from [7] on the convergence of stochastic recursive chains, which applies in this setting. We

give conditions ensuring the existence and uniqueness of a stationary measure π , as well as geometric ergodicity. In Section 4, we consider the case where μ is exponential of parameter $\kappa > 0$, and show that π has a C^∞ density P with respect to Lebesgue measure. We furthermore prove in Theorem 2 that a multiple G of P solves a second order differential equation with weak singularities. Proposition 1 provides series expansions for P , which are necessary to derive properties of P near the singularities. Section 5 considers time averages: It is proved that the empirical average S_N given in (3) converges to the steady state expectation $\mathbb{E}_\pi(f)$, where f is a random variable distributed according to π . In Section 6, we provide efficient numerical integration methods for computing the density associated to π , and therefore for computing the steady state average $\lim_{N \rightarrow \infty} S_N = \mathbb{E}_\pi(f)$. We then show numerical solutions, using the series expansions of Proposition 1 to start the numerical integration. The main results are summarized in Section 7.

3 Convergence of recursive chains

We first give some basic results for the differential equation (2). The right hand side of (2) can be factored into $-\Delta\gamma(y - y_1)(y - y_2)$, where $y_1 = (\Delta\gamma - k_1 - k_2) - \sqrt{d}/(2\Delta\gamma) < 0$, $y_2 = ((\Delta\gamma - k_1 - k_2) + \sqrt{d})/(2\Delta\gamma) > 0$, and $d = (\Delta\gamma - k_1 - k_2)^2 + 4k_1\Delta\gamma$. Then $k_1 > k_2$ implies that $0 < 1 - y_2 < \frac{1}{2} < y_2 < 1$, and that the derivative $df_2(t)/dt$ is positive when $f_2(t)$ is in the interval $[0, y_2)$, negative in $(y_2, 1]$, and it vanishes for $f_2(t) = y_2$. It is not hard to check that any realization of the trajectory $\{f_2(t)\}_{t \geq 0}$, with initial data $f_2(0) \in I = (1 - y_2, y_2)$ will remain forever in I , and that any trajectory starting in the interval $I^c = [0, 1] \setminus I$ will enter I after an almost surely finite time. (However, $f_2(0) = y_2$ implies $f_2(t) \equiv y_2$.) We thus restrict our study to the interval I .

Given $t \in \mathbb{R}^+$, we define the mapping $\phi_t : I \rightarrow I$ such that $\phi_t(x)$ is the value of the solution of (2) at time t when starting at $x \in I$ at time $t_0 = 0$. Using separation of variables for (2), we obtain the relation

$$\frac{\phi_t(x) - y_1}{y_2 - \phi_t(x)} = \frac{x - y_1}{y_2 - x} \exp(\beta t), \quad (4)$$

where we set $\beta = \Delta\gamma(y_2 - y_1)$. Given $u \in I$, let $\delta t(u, y)$ denote the time interval the orbit of the dynamical system (2) needs to join u and y , $y \geq u$, when starting at time $t = 0$ at u . Then

$$\beta \delta t(u, y) = \ln \left(\frac{(y - y_1)(y_2 - u)}{(y_2 - y)(u - y_1)} \right). \quad (5)$$

Definition 1 Given $X_0 = f_2(0) \in I$, consider the Markov chain with values in I defined by

$$X_{k+1} = \phi_{t_{k+1}}(1 - X_k),$$

where the sequence of random variables $\{t_k\}_{k \in \mathbb{N}^+}$ is i.i.d. distributed according to some law μ on \mathbb{R}^+ . This Markov chain describes the evolution of $f_2(T_k - 0)$, at the instants just before the switches, with $T_{k+1} - T_k = t_{k+1}$.

We first recall and adapt results of [7] on the convergence of such Markov chains, also called *stochastic recursive chains*. The general setting is described by a complete separable metric space (S, ρ) , the set of values taken by the Markov chain, a family of mappings $f_\theta : S \rightarrow S$, indexed by parameters θ living in some parameter space Θ , and a probability measure μ on Θ . Given an i.i.d. sequence of random elements θ_n , $n \geq 1$, of law μ , we can consider the Markov chain $(X_n)_{n \in \mathbb{N}}$ given by $X_{n+1} = f_{\theta_{n+1}}(X_n)$. The following Theorem gives conditions for the existence and uniqueness of a stationary measure. In what follows, $P^{(n)}(x, dy)$ denotes the law of the Markov chain X_n and $\rho[P^{(n)}(x, \cdot), \pi]$ is the Prokhorov metric, see below.

Theorem 1 [Theorem 1.1 of [7]] *Assume that the family of functions f_θ , $\theta \in \Theta$ is Lipschitz with*

$$\rho(f_\theta(x), f_\theta(y)) \leq K_\theta \rho(x, y), \quad x, y \in S,$$

$\forall \theta \in \Theta$. Assume furthermore that

$$\int K_\theta \mu(d\theta) < \infty, \quad \int \rho(f_\theta(x_0), x_0) \mu(d\theta) < \infty, \quad (6)$$

for some $x_0 \in S$, and that

$$\int \ln(K_\theta) \mu(d\theta) < 0. \quad (7)$$

Then

- The Markov chain has a unique stationary distribution π ,
- $\rho[P^{(n)}(x, \cdot), \pi] \leq A_x r^n$, for constants A_x and r with $0 < A_x < \infty$ and $0 < r < 1$; this bound holds for all times n and all starting positions x ,
- the constant r does not depend on n or x ; the constant A_x does not depend on n , and $A_x < a + b\rho(x, x_0)$, where $0 < a, b < \infty$.

In our setting, S is given by I and the parameter set Θ is just \mathbb{R}^+ . The Prokhorov distance $d_n := \rho[P^{(n)}(X_0, \cdot), \pi]$ is the infimum of the $\delta > 0$ such that

$$P^{(n)}(X_0, C) < \pi(C_\delta) + \delta \quad \text{and} \quad \pi(C) < P^{(n)}(X_0, C_\delta) + \delta, \quad (8)$$

where C runs over the Borel sets of I and, for given $C \in \mathbb{B}(I)$, C_δ denotes the set of points of I whose distance from C is less than δ (see Section 5.1 of [7]). Condition (7) means that the functions f_θ are contractions in the average. We first express this condition in our setting: for $t \in \Theta = \mathbb{R}^+$ and $u \in I = S$, the mapping $\phi_t(u)$ is given explicitly by

$$\phi_t(u) = \frac{y_1(y_2 - u) + y_2(u - y_1) \exp(\beta t)}{y_2 - u + (u - y_1) \exp(\beta t)}. \quad (9)$$

Setting $f_t(x) = \phi_t(1 - x)$, we obtain

Lemma 1 For all $t \in \mathbb{R}^+$,

$$\frac{d}{dx} f_t(x) = -\frac{(y_2 - y_1)^2 \exp(\beta t)}{(y_2 - 1 + x + (1 - x - y_1) \exp(\beta t))^2},$$

$$K_t := \sup_{x \in I} \left| \frac{d}{dx} f_t(x) \right| = \frac{(y_2 - y_1)^2 \exp(\beta t)}{(2y_2 - 1 + (1 - y_2 - y_1) \exp(\beta t))^2}.$$

If μ is exponential of parameter $\kappa > 0$, and $\alpha = \kappa/\beta$, then the conditions given in (6) are satisfied, and

$$\int_{\mathbb{R}^+} \kappa \exp(-\kappa t) \ln(K_t) dt = -\alpha - 2z \int_0^\infty \frac{\exp(-(1+\alpha)t)}{1 - z \exp(-t)} dt,$$

where we set $z = -(2y_2 - 1)/(1 - y_2 - y_1) < 0$. Condition (7) is thus satisfied if

$$-\alpha - 2z \int_0^\infty \frac{\exp(-(1+\alpha)t)}{1 - z \exp(-t)} dt < 0. \quad (10)$$

Remark 1 When $|z| \leq 1$, the integral $\int_0^\infty (\exp(-(1+\alpha)t))/(1 - z \exp(-t)) dt$ is the Lerch Phi function $\Phi(z, s, v) = \sum_{n \geq 0} (v+n)^{-s} z^n$, with $s = 1$ and $v = 1 + \alpha$, and is also equal to Gauss's Hypergeometric function ${}_2F_1(1, 1 + \alpha; 2 + \alpha; z)/(1 + \alpha)$ (see e.g. [9], chap. 1.11).

Proof: Taking the derivative of (9) with respect to u , we obtain

$$\frac{d}{du} \phi_t(u) = \frac{(y_2 - y_1)^2 \exp(\beta t)}{(y_2 - u + (u - y_1) \exp(\beta t))^2}$$

and thus

$$f'_t(x) = -\frac{d}{du} \phi_t(1-x) = -\frac{(y_2 - y_1)^2 \exp(\beta t)}{(y_2 - 1 + x + (1 - x - y_1) \exp(\beta t))^2} < 0,$$

as required. The expression for K_t follows from direct computation.

4 Convergence to stationarity in Poissonian environments

Assume that μ is exponential of parameter $\kappa > 0$. We will see in what follows that the stationary measure π has, under some conditions, a density $P(y)$ such that with $Q(y) = ((y - y_1)/(y_2 - y))^\alpha$, where $\alpha = \kappa/\beta$, the function $G(y) = P(y)Q(y)(y - y_1)(y_2 - y)$ satisfies the differential equation

$$G''(y) + U(y)G'(y) + V(y)G(y) = 0, \quad (11)$$

where $\tilde{y}_1 = 1 - y_1$, $\tilde{y}_2 = 1 - y_2$,

$$U(y) = \frac{\alpha + 1}{y - \tilde{y}_1} - \frac{\alpha - 1}{y - \tilde{y}_2} + \frac{\alpha}{y - y_2} - \frac{\alpha}{y - y_1}, \quad (12)$$

and

$$V(y) = \frac{\alpha^2 (y_2 - y_1)^2}{(y - y_1)(y - y_2)(y - \tilde{y}_2)(y - \tilde{y}_1)}. \quad (13)$$

The following proposition will therefore be useful:

Proposition 1 *The solutions of the second order homogeneous linear differential equation (11) are analytic on the interval $I = (\tilde{y}_2, y_2)$. Two fundamental solutions $\tilde{G}_1(y)$, $\tilde{G}_2(y)$ are*

- $\tilde{G}_1(y) = (y - \tilde{y}_2)^\alpha \tilde{W}_1(y)$, where $\tilde{W}_1(y)$ is analytic on $(\tilde{y}_2 - \delta, y_2)$ for some $\delta > 0$ and with $\tilde{W}_1(\tilde{y}_2) = 1$.
- $\tilde{G}_2(y) = \begin{cases} \tilde{W}_2(y), & \text{if } \alpha \notin \mathbb{R}, \\ \tilde{W}_2(y) + \tilde{C}\tilde{G}_1(y) \ln(y - \tilde{y}_2), & \text{if } \alpha \in \mathbb{R}, \end{cases}$
with $\tilde{W}_2(y)$ analytic on $(\tilde{y}_2 - \delta, y_2)$ for some $\delta > 0$, $\tilde{W}_2(\tilde{y}_2) = 1$ and $\tilde{C} \in \mathbb{R}$.

Another set of two fundamental solutions $G_1(y)$, $G_2(y)$ is

- $G_1(y) = (y_2 - y)^{1-\alpha} W_1(y)$, where $W_1(y)$ is analytic on $(\tilde{y}_2, y_2 + \delta)$ for some $\delta > 0$ and with $W_1(y_2) = 1$.
- $G_2(y) = \begin{cases} W_2(y), & \text{if } \alpha \notin \mathbb{R}, \\ W_2(y) + C G_1(y) \ln(y_2 - y), & \text{if } \alpha \in \mathbb{R}, \end{cases}$
with $W_2(y)$ analytic on $(\tilde{y}_2, y_2 + \delta)$ for some $\delta > 0$, $W_2(y_2) = 1$ and $C \in \mathbb{R}$.

In the appendix, we prove this result for completeness, and also show how these fundamental solutions can be computed by series expansion about \tilde{y}_2 and y_2 respectively.

Theorem 2 *Assume that*

$$-\alpha - 2z \int_0^\infty \frac{\exp(-(1+\alpha)t)}{1 - z \exp(-t)} dt < 0,$$

where $z = -(2y_2 - 1)/(1 - y_2 - y_1) < 0$. Then the Markov chain X_k from Definition 1, with initial data $X_0 \in I = (1 - y_2, y_2)$ has a unique stationary distribution π of C^∞ density

$$P(y) = \frac{Q(y)^{-1} (y - \tilde{y}_2)^\alpha \tilde{W}_1(y) / (y_2 - y) / (y - y_1)}{\int_I Q(z)^{-1} (z - \tilde{y}_2)^\alpha \tilde{W}_1(z) / (y_2 - y) / (y - y_1) dz}.$$

Here, $Q(y) = \left(\frac{y-y_1}{y_2-y}\right)^\alpha$, where $\alpha = \kappa/\beta$, $\tilde{W}_1(y)$ is the analytic function on $(\tilde{y}_2 - \delta, y_2)$ with $\tilde{W}_1(\tilde{y}_2) = 1$, such that $\tilde{G}_1(y) = (y - \tilde{y}_2)^\alpha \tilde{W}_1(y)$ is a solution of the differential equation (11). In the neighborhood of $y = y_2$, this solution is such that $0 < \lim_{y \rightarrow y_2} \tilde{W}_1(y) < +\infty$. Finally, the behavior of the density P near y_2 is given by $(y_2 - y)^{\alpha-1}$, and thus converges when $\alpha \geq 1$ and diverges toward $+\infty$ when $\alpha < 1$. Let $f(x) = x$ and $g(x) = \ln((x - 1 + y_2)/(y_2 - x))$ be defined on I . Then $g \in L^1(I, \mathbb{B}(I), \pi)$ with

$$\mathbb{E}_\pi(f) = y_1 + \frac{\kappa}{\Delta\gamma} \mathbb{E}_\pi(g). \quad (14)$$

Remark 2 (14) will be useful when considering time averages for Monte-Carlo simulations, see Section 5.

Proof: The existence and uniqueness of the stationary measure follows from Theorem 1 and Lemma 1. Let Y be a random variable of law π , and let T be exponential of parameter $\kappa > 0$, independent of Y . In the stationary regime, $Y =_{\mathcal{L}} \phi_T(1 - Y)$. Let $F(y) = P(Y < y)$. Then

$$F(y) = \int_{I \times \mathbb{R}^+} \pi(dv) \kappa \exp(-\kappa t) \mathbb{I}(\phi_t(1 - v) < y) dt,$$

where $\mathbb{I}(\cdot)$ denotes the indicator function. For given $y \in I$, the time variable t is restricted to the interval $0 \leq t < \delta t(\tilde{y}_2, y)$, see (5). Thus

$$F(y) = \int_0^{\delta t(1-y_2, y)} \kappa \exp(-\kappa t) \int_I \pi(dv) \mathbb{I}(\phi_t(1 - v) < y) dt.$$

For given t in this interval, the set of $v \in I$ with $\phi_t(1 - v) < y$ is given by

$$\left\{ v \in I; 1 - v < \frac{y_2(y - y_1) + \exp(\beta t)(y_2 - y)y_1}{y - y_1 + \exp(\beta t)(y_2 - y)} \right\}.$$

It follows that $\int_I \pi(dv) \mathbb{I}(\phi_t(1 - v) < y) = 1 - F(1 - u)$, where we set $u = (y_2(y - y_1) + \exp(\beta t)(y_2 - y)y_1) / (y - y_1 + \exp(\beta t)(y_2 - y))$, with $t = \delta t(u, y)$. We make the change of variable $t = \delta t(u, y)$ with

$$\frac{dt}{du} = -\frac{y_2 - y_1}{\beta(y_2 - u)(u - y_1)}.$$

Then

$$F(y) = \alpha \left(\frac{y_2 - y}{y - y_1} \right)^\alpha \int_{1-y_2}^y \frac{y_2 - y_1}{(y_2 - u)(u - y_1)} \left(\frac{u - y_1}{y_2 - u} \right)^\alpha (1 - F(1 - u)) du.$$

This is a fixed point equation for the distribution function F . We use it for proving that the probability measure π has a \mathcal{C}^∞ density on the interval I . First notice that F is monotonically increasing and integrable on I . The above relation then shows that F is continuous on I . Using again this argument recursively, one sees that F is the integral of a continuous function and is therefore differentiable, with a continuous derivative. The \mathcal{C}^∞ differentiability is obtained by iterating this argument. Let P be the \mathcal{C}^∞ density of π with respect to Lebesgue measure. Our strategy runs as follows: We use the fixed point relation to show that a multiple G of P satisfies a second order differential equation, which has only weak singularities, and then deduce properties of P with the help of Proposition 1.

For given $v \in I$, the time variable t is restricted to the interval

$$0 \leq t \leq \delta t(u, y) = \ln((y - y_1)(y_2 - y) / (y_2 - y)(u - y_1)) / \beta,$$

where $u = 1 - v$ (see 5). It follows that

$$F(y) = \int_{1-y}^{y_2} P(v) dv \int_0^{\delta t(u, y)} \kappa \exp(-\kappa t) dt,$$

with

$$\begin{aligned} P(y) &= \frac{dF(y)}{dy} = \int_{1-y}^{y_2} P(v) dv \kappa \exp(-\kappa \delta t(u, y)) \frac{d\delta t(u, y)}{dy} \\ &= \alpha \int_{1-y}^{y_2} dv P(v) \frac{Q(u)}{Q(y)} \frac{(y_2 - y_1)}{(y - y_1)(y_2 - y)}, \end{aligned}$$

where we set $Q(y) = ((y - y_1)/(y_2 - y))^\alpha$. Using $u = 1 - v$ and setting $G(y) = P(y)Q(y)(y - y_1)(y_2 - y)$, one gets

$$G(y) = \int_{1-y_2}^y G(1-u)R(u)H(u) du, \quad (15)$$

where $R(u) = \alpha Q(u)Q(1-u)^{-1}$ is such that $R(1-u) = \alpha^2/R(u)$, and $H(u) = (y_2 - y_1)/(y_2 - 1 + u)/(1 - u - y_1)$. Taking the derivative gives

$$G'(y) = G(1-y)R(y)H(y), \quad (16)$$

or

$$G(1-y) = G'(y)R(y)^{-1}H(y)^{-1} = \alpha^{-2}G'(y)R(1-y)/H(y).$$

Taking a second derivative then gives

$$G''(y) + \frac{d}{dy} \ln\left(\frac{R(1-y)}{H(y)}\right)G'(y) + \alpha^2 H(y)H(1-y)G(y) = 0.$$

and simplifying the terms leads to (11). We see that $R(u)H(u) \sim (u - 1 + y_2)^{\alpha-1}$, as $u \rightarrow 1 - y_2$. The exponents associated with the fundamental solutions are $\rho = 0$ or α in the neighborhood of $y = 1 - y_2$ and $\rho' = 0$ or $1 - \alpha$ near $y = y_2$.

Assume first that $\alpha \notin \mathbb{N}^+$. We first check the behavior of G in a neighborhood of $y = \tilde{y}_2$. Set $y = \tilde{y}_2 + \varepsilon$, $\varepsilon > 0$, with $1 - y = y_2 - \varepsilon$. Proposition 1 shows that G is a linear combination $G(y) = \tilde{A}\varepsilon^\alpha \tilde{W}_1(y) + \tilde{B}\tilde{W}_2(y)$, for constants $\tilde{A}, \tilde{B} \in \mathbb{R}$. Similarly, $G(1-y) = A\varepsilon^{1-\alpha}W_1(1-y) + BW_2(1-y)$, for real constants A and B . As $\varepsilon \rightarrow 0$, the right hand side of (15) behaves like $\varepsilon^\alpha G(y_2 - \varepsilon) \rightarrow 0$. Suppose that $\tilde{B} \neq 0$. Then $G(y) \sim \tilde{B}\tilde{W}_2(y) \neq 0$, and (15) can't be satisfied. One must thus have $\tilde{B} = 0$, so that $G(y) = \tilde{A}\varepsilon^\alpha \tilde{W}_1(y)$. When $\alpha > 1$, (15) implies that $A = 0$. It follows that, for arbitrary $\alpha > 0$, $\lim_{y \rightarrow y_2} G(y) = BW_2(y_2) \neq 0$, and that $G(\tilde{y}_2 + \varepsilon) \sim \tilde{A}\varepsilon^\alpha \tilde{W}_1(\tilde{y}_2)$, $\varepsilon \rightarrow 0$, as required. The corresponding result for P follows.

Suppose that $\alpha \in \mathbb{N}^+$. The right hand side of (15) behaves like

$$F(\varepsilon) := \varepsilon^\alpha (A\varepsilon^{1-\alpha}W_1(y_2) + B(W_2(y_2) + C\varepsilon^{\alpha-1}W_1(y_2)\ln(\varepsilon))),$$

with $F(\varepsilon) \rightarrow 0$ as $\varepsilon \rightarrow 0$, and $G(\tilde{y}_2 + \varepsilon)$ behaves like

$$\tilde{F}(\varepsilon) := \tilde{A}\varepsilon^\alpha \tilde{W}_1(\tilde{y}_2) + \tilde{B}(\tilde{W}_2(\tilde{y}_2) + \tilde{C}\varepsilon^\alpha \tilde{W}_1(\tilde{y}_2)\ln(\varepsilon)).$$

One has $\tilde{F}(\varepsilon) \sim \tilde{B}\tilde{W}_2(\tilde{y}_2)$, $\varepsilon \rightarrow 0$, when $\tilde{B} \neq 0$ and $\tilde{F}(\varepsilon) \sim \tilde{A}\varepsilon^\alpha \tilde{W}_1(\tilde{y}_2)$, when $\tilde{B} = 0$. (15) shows that necessarily $\tilde{B} = 0$. Suppose that $\alpha = 1$. Then one

must have $BC = 0$, implying the existence of the limit $\lim_{y \rightarrow y_2} G(y) \neq 0$. When $\alpha > 1$, $A = 0$, $B \neq 0$, and $\lim_{y \rightarrow y_2} G(y) = BW_2(y_2)$, as required.

Finally, we check the identity (14). First $g \in L^1(I, \mathbb{B}(I), \pi)$ follows from the behavior of the density P at the boundaries of I , as described above. Next,

$$\mathbb{E}_\pi(g) = \int_I \ln\left(\frac{y-1+y_2}{y_2-y}\right) P(y) dy,$$

where $J := \int_I \ln(y-1+y_2) P(y) dy$ is such that

$$\begin{aligned} J &= \int_I \ln(y-1+y_2) G(y) Q(y)^{-1} \frac{H(1-y)}{y_2-y_1} dy \\ &= \frac{1}{y_2-y_1} \int_I \ln(y_2-u) G(1-u) Q(1-u)^{-1} H(u) du \\ &= \frac{1}{\alpha(y_2-y_1)} \int_I \frac{\ln(y_2-u)}{Q(u)} G(1-u) R(u) H(u) du \\ &= \frac{1}{\alpha(y_2-y_1)} \int_I \frac{\ln(y_2-u)}{Q(u)} G'(u) du \\ &= \frac{1}{\alpha(y_2-y_1)} \left(G(u) \frac{\ln(y_2-u)}{Q(u)} \Big|_{1-y_2}^{y_2} - \int_I G(u) \left(\frac{\ln(y_2-u)}{Q(u)} \right)' du \right) \\ &= \frac{1}{\alpha(y_2-y_1)} \int_I \frac{G(u)}{Q(u)} \frac{(u-y_1)}{(y_2-u)(u-y_1)} du + \int_I \ln(y_2-u) P(u) du, \end{aligned}$$

where we use (16). It follows that

$$\mathbb{E}_\pi(g) = \frac{1}{\alpha(y_2-y_1)} \mathbb{E}_\pi(f) - \frac{y_1}{\alpha(y_2-y_1)},$$

proving (14) since $\alpha = \kappa / (\Delta\gamma(y_2 - y_1))$.

Corollary 1 *Assume that condition (10) holds. Then, as $t \rightarrow +\infty$, the law of the stochastic process $f_2(t)$, $t \geq 0$, $f_2(0) \in I$, converges toward the stationary measure π of density P of the Markov Chain X_k .*

Proof: Given $t \in \mathbb{R}^+$, let t_* be the last renewal time before t , and set $S_* = t - t_*$. When the length of the overlapping random interval is exponential, S_* is also exponential. In the stationary regime, or equivalently for large t , one has the identity in law $f_2(t) =_{\mathcal{L}} \phi_{S_*}(1 - X)$, where X is distributed according to π , and the result follows.

5 Time averages

When the conclusions of Theorem 1 hold, the chain X_k has a unique stationary probability measure π , and $\sum_{k=1}^n g(X_k)/n$ converges a.s. toward the expectation of g under π , for any function g in $L^1(I, \mathbb{B}(I), \pi)$, (see e.g. [5]). In

[20], the authors use Monte-Carlo methods based on the process $f_2(t)$, $t \geq 0$, to estimate the mean fitness by considering the time average

$$S_N = \frac{1}{T_N} \int_0^{T_N} f_2(s) \, ds, \quad (17)$$

where N is a fixed number of renewal periods.

Lemma 2 *Let $N \in \mathbb{N}^+$. Given a realization $0 = T_0 < T_1 < \dots < T_N$ of the renewal process, we have*

$$\frac{1}{T_N} \int_0^{T_N} f_2(s) \, ds = y_1 + \frac{(y_2 - y_1)}{\beta T_N} \ln \left(\prod_{i=1}^N \frac{X_{i-1} - (1 - y_2)}{y_2 - X_i} \right). \quad (18)$$

Proof: Consider the integrals

$$\int_{T_{i-1}}^{T_i} f_2(s) \, ds,$$

where $f_2(T_{i-1} + 0) = 1 - X_{i-1}$ and $f_2(T_i - 0) = X_i$. The value of $y(s) = f_2(T_{i-1} + s)$, $s \in (0, T_i - T_{i-1})$ is given implicitly by (4); Therefore

$$y(s) = \frac{y_1(y_2 - u) + y_2(u - y_1) \exp(\beta s)}{y_2 - u + (u - y_1) \exp(\beta s)},$$

where we set $u = 1 - X_{i-1}$, and thus, after a longer but not difficult computation, one obtains

$$\begin{aligned} \int_{T_{i-1}}^{T_i} f_2(s) \, ds &= y_1(T_i - T_{i-1}) \\ &+ \frac{y_2 - y_1}{\beta} \ln \left(\frac{y_2 - u + (u - y_1) \exp(\beta(T_i - T_{i-1}))}{y_2 - y_1} \right), \end{aligned}$$

and the result follows, since

$$\begin{aligned} y_2 - u + (u - y_1) \exp(\beta(T_i - T_{i-1})) &= (y_2 - u) \left(1 + \frac{u - y_1}{y_2 - u} \exp(\beta t_i) \right) \\ &= \frac{(y_2 - (1 - X_{i-1}))(y_2 - y_1)}{y_2 - X_i}. \end{aligned}$$

Theorem 3 *Suppose that μ is exponential of parameter $\kappa > 0$, and assume (10). Let $f(x) = x$ and $g(x) = \ln((x - 1 + y_2)/(y_2 - x))$ be defined on I . Then*

$$\lim_{N \rightarrow \infty} \frac{1}{T_N} \int_0^{T_N} f_2(s) \, ds = y_1 + \frac{\kappa}{\Delta \gamma} \mathbb{E}_\pi(g) = \mathbb{E}_\pi(f), \quad a.s.$$

Proof: From equation (18), we obtain

$$\frac{1}{T_N} \int_0^{T_N} f_2(s) ds = y_1 + \frac{(y_2 - y_1)}{\beta T_N} \ln\left(\frac{X_0 - 1 + y_2}{y_2 - X_N}\right) + \frac{(y_2 - y_1)}{\beta T_N} \sum_{i=1}^{N-1} g(X_i).$$

As T_N is a renewal process with exponential inter arrival times of parameter κ , it follows that T_N/N converges a.s. toward $1/\kappa$. Next, $g \in L^1(I, \mathbb{B}(I), \pi)$ follows from the behavior of the density P at the boundaries of I , as described in Theorem 2. From Proposition 1 and Theorem 2, the behavior of P in the neighborhood of $y = 1 - y_2$ is given by $(y - 1 + y_2)^{\rho_1}$ where $\rho_1 = \alpha$ and by $(y_2 - y)^{\rho_2 + \alpha - 1}$ in the neighborhood of $y = y_2$, where $\rho_2 = 0$. The Markov chain X_k is geometrically ergodic, and thus the last term converges a.s. toward $(\kappa/(\Delta\gamma))\mathbb{E}_\pi(g)$. We finally check that $\ln(y_2 - X_N)/N$ converges a.s. toward 0. Given $\varepsilon > 0$, consider the probability

$$\begin{aligned} P(|\ln(y_2 - X_N)| > N\varepsilon) &= P(\ln(y_2 - X_N) < -N\varepsilon) \\ &= P(X_N > y_2 - \exp(-N\varepsilon)) = P^{(N)}(X_0, A_N), \end{aligned}$$

where $A_N = \{x > y_2 - \exp(-N\varepsilon)\}$. Using the behavior of P in the neighborhood of $y = y_2$, one gets that $\pi(A_N) \leq M(\exp(-\varepsilon N))^{\rho_2 + \alpha}$, for some positive constant M . Let $\gamma_N := |P^{(N)}(X_0, A_N) - \pi(A_N)|$, and let d_N be the Prokhorov distance defined in (8). If $\pi(A_N) \geq P^{(N)}(X_0, A_N)$, then $\gamma_N \leq \pi(A_N)$. If $\pi(A_N) \leq P^{(N)}(X_0, A_N)$, one has $P^{(N)}(X_0, A_N) \leq \pi((A_N)_{d_N}) + d_N$, and it follows that

$$\begin{aligned} \gamma_N = P^{(N)}(X_0, A_N) - \pi(A_N) &\leq \pi((A_N)_{d_N}) - \pi(A_N) + d_N \\ &= \int_{y_2 - \exp(-\varepsilon N) - d_N}^{y_2 - \exp(-\varepsilon N)} P(y) dy + d_N \\ &\leq d_N + D(\exp(-\varepsilon N))^{\rho_2 + \alpha} \\ &\quad - (d_N + \exp(-\varepsilon N))^{\rho_2 + \alpha}, \end{aligned}$$

for some positive constant $D > 0$. Theorem 1 gives that

$$P(|\ln(y_2 - X_N)| > \varepsilon N) \leq |P^{(N)}(X_0, A_N) - \pi(A_N)| + \pi(A_N) \leq h(X_0)\lambda^N,$$

for some bounded function h and a positive number $0 < \lambda < 1$. The result then follows from the Borel-Cantelli Lemma. The last identity is (14) of Theorem 2.

6 Numerical Examples

We now compute the density P given in Theorem 2 numerically. To do so, we solve the differential equation (11) numerically, starting in the neighborhood of the singular point $y = \tilde{y}_2 = 1 - y_2$. Proposition 1 and Theorem 2 show that $\lim_{y \rightarrow \tilde{y}_2} P(y) = 0$, and that the first derivative of P behaves like $(y - \tilde{y}_2)^{\alpha - 1}$, which goes to $+\infty$ when $\alpha < 1$. We start the numerical solution at the point $y = \tilde{y}_2 + \varepsilon$, where $\varepsilon > 0$ is small, and use the initial conditions $G(\tilde{y}_2 + \varepsilon)$

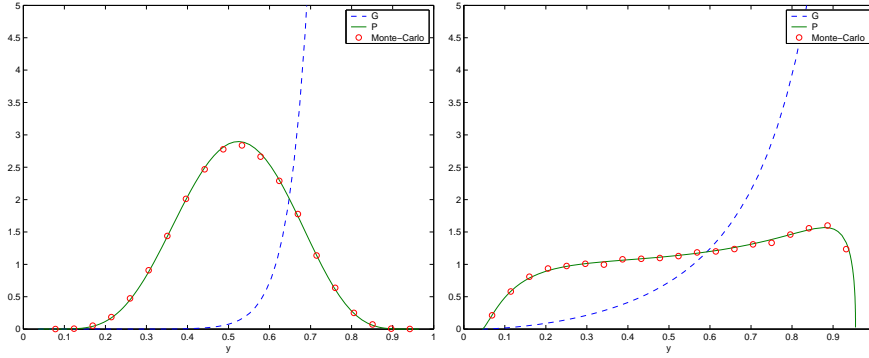


Fig. 1 Density P on the left when $\kappa = 10$, $\Delta\gamma = 1$, $k_1 = 0.4$, $k_2 = 0.05$, and on the right when $\kappa = 1.5$, $\Delta\gamma = 1$, $k_1 = 0.1$, $k_2 = 0.05$.

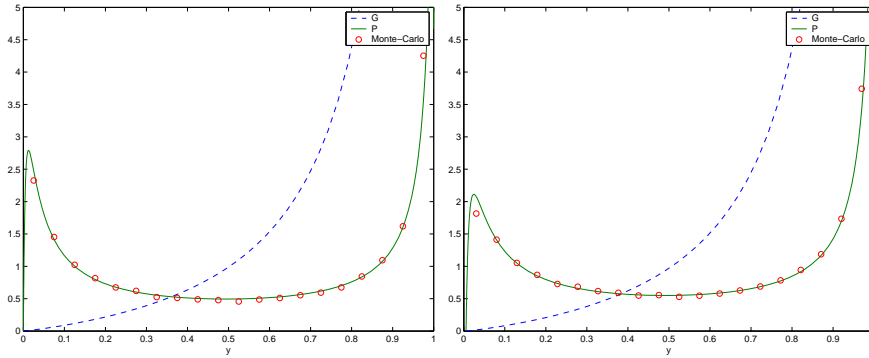


Fig. 2 Density P on the left when $\kappa = 10$, $\Delta\gamma = 9$, $k_1 = 0.1$, $k_2 = 0$. $Av(f_2)_{k_2=0} = 0.553274111$, and on the right when $\kappa = 10$, $\Delta\gamma = 9$, $k_1 = 0.1$, $k_2 = 0.05$. $Av(f_2)_{k_2=0.05} = 0.55672212$. Clearly the average fitness is larger when $k_2 = 0.05$ than when $k_2 = 0$.

and $G'(\tilde{y}_2 + \varepsilon)$ from the series expansions given in Proposition 1. In addition, we use numerical integration procedure to compute the integral to scale the density P , by adding an additional ordinary differential equation to (11).

We show in Figures 1 to 3 the results obtained for five different sets of parameters. In all the figures, we show the computed solution G of the differential equation (11) in dashed, the computed density P as a solid line, and the results of a Monte-Carlo simulation with 100'000 samples as circles. The density from the theory and the Monte-Carlo simulations agree very well. It is interesting to see in Figures 1 and 2 the variety of densities that can be generated by this simple model. Figure 2 contains a case where increasing k_2 increases the overall fitness of the population. Figure 3 finally shows a case where $\alpha < 1$. We note that the numerical integration out of the singularity can be challenging. In particular, for the first case in Figure 1, the standard ode45 from Matlab needed very small absolute tolerances to succeed with the integration for $\varepsilon < 1e - 2$. A more robust method turned out to be DOPRI853, see [12].

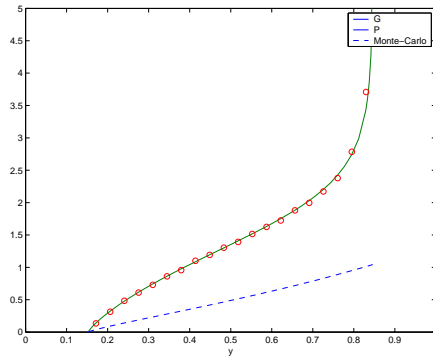


Fig. 3 Density P when $\kappa = 5$, $\Delta\gamma = 3$, $k_1 = 3$, $k_2 = 1$, a case where $\alpha < 1$.

7 Concluding remarks

We have analyzed a stochastic population model presented in [20], which is similar to models considered in [16] and [17]. The biological setting introduced in Section 1 shows that the stochastic model given in Section 2 might be relevant for the design of laboratory experiments involving time-dependent conditions or various time-scales. We now discuss the obtained results for non-specialists in probability and statistics. Our main object of study is the proportion $f_2(t)$ of fit cells at time t , that is in the cells having the largest growth rate. Denoting by T_i the instants where environmental changes occur, we consider the process $X_k = f_2(T_k - 0)$, giving the proportion of fit cells just before the occurrence of the k th environmental change. We assume in Section 4 a Poisson environment, that is, we suppose that the collection of random variables $\Delta_i = T_i - T_{i-1}$, giving the length of the time intervals separating two environmental changes, are independent with the same exponential density of the form $P(\Delta_i \in [t, t + dt]) \approx \kappa \exp(-\kappa t) dt$, for small dt . A related process is given by N_t , which gives the number of environmental changes before t . When the random variables Δ_i are independent with the same exponential distribution, the law of N_t is Poisson of parameter κt , that is, $P(N_t = j) = (\kappa t)^j / j! \exp(-\kappa t)$, hence the terminology *Poissonian environment*. We proved that the process X_k admits a steady state distribution π of density P , as given in Theorem 2. The statistical meaning of this statement is simply that for a given interval $J = [a, b]$, $\pi(J) = \int_a^b P(x) dx$ gives the probability of observing X_k in J when k is large. We next proved that the limiting law of $f_2(t)$ is also given by π for t large, hence $P(f_2(t) \in J) \approx \pi(J)$, $t \gg 1$.

Typical problems considered in [20] consist in finding the maximum value of the average steady state fitness $\mathbb{E}_\pi(f_2) = \int x P(x) dx$ as a function of k_2 , when all the other parameters are fixed. Heterogeneity is beneficial when this maximum is realized for some positive value $k_2^* > 0$ (homogeneous populations are obtained when $k_2 = 0$). The authors of [20] showed that heterogeneity is beneficial for a small range of the parameter space, namely when k_1 is not too large. They used Monte-Carlo simulations, which are roughly de-

scribed as follows: pick some realization of the process $f_2(t)$ for $0 \leq t \leq T_N$, and compute the empirical average $S_N = \int_0^{T_N} f_2(s) ds / T_N$. Of course, one must repeat this procedure several times to get statistically significant estimates. S_N gives a time-averaged fitness, and we expect that S_N converges to some limiting value as N is large. The above optimization problem can thus be approximatively solved by repeating Monte-Carlo simulations for many values of the parameter k_2 , and then looking for the maximum. We however proved in Theorem 3 that S_N converges to $\mathbb{E}_\pi(f_2)$, giving thus the limiting average proportion of the cell population having the largest growth rate, which corresponds to our basic notion of fitness. Our analytical results permit thus to avoid the computation of thousands of Monte-Carlo simulations by computing exactly the density P . These computations can be efficiently performed using optimized integration schemes, as given in Section 6. Furthermore, closed analytical formulas of this kind will be essential for a complete understanding of the properties of the model.

8 Appendix

In this appendix we show for completeness the proof of Proposition 1 and describe a method how to solve the differential equation (11) (see also [13], pp. 317-321). This equation is of the form

$$G''(y) + U(y)G'(y) + V(y)G(y) = 0,$$

where the functions $U(y)$ and $V(y)$ are meromorphic in the complex plane with four poles of order one at $y_1 < \tilde{y}_2 := 1 - y_2 < y_2 < \tilde{y}_1 := 1 - y_1$. The solutions are therefore analytic in the open disk of radius $(y_2 - \tilde{y}_2)/2$ centered at $1/2$. We look for real solutions in the interval $I = (\tilde{y}_2, y_2)$. In order to simplify calculations, we use the variable transformation

$$y = \tilde{y}_2 + (y_2 - \tilde{y}_2)z, \quad z = \frac{y - \tilde{y}_2}{y_2 - \tilde{y}_2} \quad (19)$$

and set $g(z) := G(y)$. With this transformation, the differential equation (11) becomes

$$g''(z) + u(z)g'(z) + v(z)g(z) = 0, \quad (20)$$

where u and v have four poles of order one at the points $-b < 0 < 1 < 1 + b$ with $b = (\tilde{y}_2 - y_1)/(y_2 - \tilde{y}_2)$:

$$u(z) = \frac{1 - \alpha}{z} + \frac{\alpha}{z - 1} - \frac{\alpha}{z + b} + \frac{\alpha + 1}{z - (1 + b)}, \quad v(z) = \frac{\alpha(1 + b)^2}{z(1 - z)(z + b)(1 + b - z)}.$$

We can therefore rewrite this equation as

$$g''(z) + \frac{h(z)}{z}g'(z) + \frac{k(z)}{z^2}g(z) = 0, \quad (21)$$

where $h(z)$ and $k(z)$ are analytic in the disk of radius $\min\{1, b\}$ centered at 0:

$$h(z) = \sum_{n=0}^{\infty} \alpha_n z^n, \quad k(z) = \sum_{n=0}^{\infty} \beta_n z^n.$$

Multiplying the equation (21) by z^2 we get an equivalent equation which can be written as

$$L(g) := (\mu_z^2 D^2 + \mu_h \mu_z D + \mu_k)(g) = 0, \quad (22)$$

where D denotes differentiation and μ_f multiplication by a function $f(z)$. Looking for solutions of the form

$$g(z) = z^\rho w(z), \quad w(z) = 1 + \sum_{n=1}^{\infty} w_n z^n,$$

we may identify the function $g(z)$ with the infinite row $[w] = [1, w_1, w_2, w_3, \dots]$ and write (22) in matrix form:

$$[L^\rho][w]^T = 0. \quad (23)$$

If we write L as $L = (\mu_z D + \mu_{h-1})\mu_z D + \mu_k$, we get the lower triangular matrix $[L^\rho]$ given by

$$\begin{bmatrix} \rho(\rho + \alpha_0 - 1) + \beta_0 & 0 & \dots & & \\ \rho\alpha_1 + \beta_1 & (\rho + 1)(\rho + \alpha_0) + \beta_0 & 0 & \dots & \\ \rho\alpha_2 + \beta_2 & (\rho + 1)\alpha_1 + \beta_1 & (\rho + 2)(\rho + 1 + \alpha_0) + \beta_0 & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{bmatrix}.$$

A solution $[w] = [1, w_1, w_2, \dots]$ of the linear system (23) exists if and only if $L_{00}^\rho = 0$. This is the so-called indicial equation for ρ . From now on we shall no longer treat the general case but only the case corresponding to our differential equation (20). In this case $\alpha_0 = 1 - \alpha$ and $\beta_0 = 0$. So the indicial equation is $\rho(\rho - \alpha) = 0$ and yields the two characteristic exponents $\rho_1 = \alpha$ and $\rho_2 = 0$. We shall write L_{ij}^ν instead of L_{ij}^ρ .

For $\rho = \rho_1$, the solution $[w^{(1)}] = [1, w_1^{(1)}, w_2^{(1)}, \dots]$ may be calculated by the recursion scheme

$$w_0^{(1)} = 1, \quad w_n^{(1)} = \frac{-1}{L_{nn}^1} \left(\sum_{j=0}^{n-1} L_{nj}^1 w_j^{(1)} \right) \quad \text{for } n \geq 1.$$

With these coefficients $w_n^{(1)}$, the function

$$g_1(z) = z^{\rho_1} \left(1 + \sum_{n=1}^{\infty} w_n^{(1)} z^n \right)$$

is a solution of (20). From the general theory of linear differential equations in the complex plane it follows that g_1 is analytic in the disk of radius $1/2$ centered at $1/2$, but the power series for $w_1(z)$ might have a convergence radius $0 < \delta < 1$.

If α is not an integer, another solution $g_2(z)$, linearly independent of $g_1(z)$, can be obtained in the same way from $\rho = \rho_2 = 0$. If, however, α is an integer, the corresponding matrix has the entry $L_{nn}^2 = 0$ for $n = \alpha$, and we look in this case for a solution $g_2(z)$ of the form $g_2(z) = 1 + \sum_{n \geq 1} w_n^{(2)} z^n + C g_1(z) \ln z$. As g_1 is a solution, the terms in $L(g_2)$ containing $\ln z$ cancel and the function $w^{(2)}(z) = 1 + \sum_{n \geq 1} w_n^{(2)} z^n$ must satisfy the equation

$$L(w^{(2)}) = -C(2\mu_z D + \mu_{h-1})(g_1).$$

Identifying $w^{(2)}(z)$ with the infinite row $[w^{(2)}] = [1, w_1^{(2)}, w_2^{(2)}, \dots]$, we can write this in matrix form

$$[L^2][w^{(2)}]^T = -C[v_1, v_2, \dots]^T. \quad (24)$$

For the right-hand side one checks easily that $v_j = 0$ for $j = 0, \dots, \alpha - 1$ and $v_\alpha = \alpha$. Therefore we can resolve the inhomogeneous linear system (24) in the following way:

1. We determine $w_j^{(2)}$ for $j \leq \alpha$ in the same way as $w_j^{(1)}$.

2. We set $w_\alpha^{(2)} := 0$ and determine the constant C by the equation $\sum_{j=0}^{\alpha-1} L_{\alpha,j}^{(2)} w_j^{(2)} = -Cv_\alpha$.
3. We determine the coefficients $w_n^{(2)}$ for $n > \alpha$ by the recursion formula

$$w_n^{(2)} = \frac{-1}{L_{nn}^{(2)}} \left(Cv_n + \sum_{j=0}^{n-1} L_{nj}^{(2)} w_j^{(2)} \right) \text{ for } n \geq \alpha + 1.$$

We shall not go into further details, for example present concrete formulas expressing the v_n by the $w_n^{(1)}$, because we don't really need the solution g_2 of (21) in our case, as we have shown in the proof of Theorem 2.

Using the variable transformation (19) we get the solutions $\tilde{G}_j(y)$ of the original differential equation (11), in particular

$$\begin{aligned} \tilde{G}_1(y) &= (y_2 - \tilde{y}_2)^\alpha g_1 \left(\frac{y - \tilde{y}_1}{y_2 - \tilde{y}_2} \right) = (y - \tilde{y}_2)^\alpha \tilde{W}_1(y) \\ &= (y - \tilde{y}_2)^\alpha \left(1 + \sum_{n=1}^{\infty} \frac{w_n^{(1)}}{(y_2 - \tilde{y}_2)^n} \right) \end{aligned}$$

In order to find fundamental solutions near the singularity y_2 , we can apply the same method once more, but using the variable transformation

$$y = y_2 - (y_2 - \tilde{y}_2)z, \quad z = \frac{y_2 - y}{y_2 - \tilde{y}_2}.$$

One easily checks that in this case the indicial equation is $\rho(\rho + \alpha - 1) = 0$ and that therefore the two characteristic exponents at y_2 are $\rho'_1 = 1 - \alpha$ and $\rho'_2 = 0$. We obtain thus the second fundamental system of solutions $G_1(y)$ and $G_2(y)$.

References

1. Arkin, A., Ross J. and McAdams H. (1998) Stochastic Kinetics Analysis of Developmental Pathway Bifurcation in Phage λ -Infected *Escherichia coli* Cells. *Genetics*, **149**, 1633–1648.
2. Balaban, N., Merrin J., Chait R., Kowalik L. and Leibler S. (2004). Bacterial Persistence as a Phenotypic Switch. *Science*, **305**, 1622–1625.
3. Biggar S. and Crabtree G. (2001) Cell signaling can direct either binary or graded transcriptional responses. *The EMBO Journal*, **20**, 3167–3176.
4. Blake W., Kaern M., Cantor C. and Collins J. (2003) Noise in eukaryotic gene expression. *Nature*, **422**, 633–637.
5. Breiman, L. (1960). The strong law of large numbers for a class of Markov chains. *Ann. Math. Stat.*, **31**, 801–803.
6. Bürger R. (1999) Evolution of Genetic Variability and the Advantage of Sex and Recombination in Changing Environments. *Genetics*, **153**, 1055–1069.
7. Diaconis, P. and Freedman, D. Iterated Random Functions. *Siam Review*, **41**, 45–76.
8. Dubnau D. and Losick R. (2006). Bistability in bacteria. *Molec. Microbio.* **61**, 564–572.
9. Erdelyi, A. Higher Transcendental Functions. (1953). Bateman Manuscript Project. Vol.1. McGraw-Hill

10. Ferrell, J. (2002). Self-perpetuating states in signal transduction: positive feedback, double-negative feedback and bistability. *Curr. Opin. Cell Biol.*, 140–148.
11. Graumann, P. (2006). Different genetic programs within identical bacteria under identical conditions: the phenomenon of bistability greatly modifies our view on bacterial populations. *Molec. Microbiol.* **61**, 560–563.
12. Hairer, H., Nørsett, S. and Wanner, G. (2000) *Solving Ordinary Differential Equations I, Nonstiff Problems*, Springer Series in Computational Mathematics. Springer. Second Edition.
13. Jänich, K. (2001). *Analysis für Physiker und Ingenieure*, Springer Verlag.
14. Kearns, D and Losick R. (2005) Cell population heterogeneity during growth of *Bacillus subtilis*. *Genes Dev.*, **19**: 3083–3094.
15. Keren, I., Shah D., Spoering A., Kaldalu N. and Lewis K. (2004). Specialized persister cells and the mechanism of multidrug tolerance in *Escherichia coli*, *J. Bacteriol.* **186**: 8172–8180.
16. Kussell, E. and Leibler, S. (2005). Phenotypic Diversity, Population Growth, and Information in Fluctuating Environments. *Science*. **309**, 2075–2078.
17. Kussell, E., Kishony R., Balaban N. and Leibler S. (2005). Bacterial Persistence: A Model of Survival in Changing Environments. *Genetics*. **169**, 1807–1814.
18. Smits, W, Kuipers O. and Veening, J. (2006). Phenotypic variation in bacteria: the role of feedback regulation. *Nat. Rev. Microbiol.* **4**, 259–271.
19. Tanaka, M., Bergstrom C. and Levin B. (2003). The evolution of mutator genes in bacterial populations: the roles of environmental change and timing. *Genetics*. **164**: 843–854.
20. Thattai, M. and van Oudenaarden, A. (2004) Stochastic Gene Expression in Fluctuating Environments. *Genetics*, **167**, 523–530.

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