Stochastic gene expression in switching environments

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Abstract

We study a stochastic model proposed recently in the genetic literature to explain the heterogeneity of cell populations or of gene products. Cells are located in two colonies, whose sizes fluctuate as birth with migration processes in switching environment. We prove that there is a range of parameters where heterogeneity induces a larger mean fitness.

Keywords: Gene expression, recursive chain, ergodic, stationary measure

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1 Introduction

In [9], the authors introduce a model for stochastic gene expression to study the heterogeneity of cell populations. They assume that the cells, or for example the product of some gene, can be in two distinct states or colonies. Let $X(t)$ and $Y(t)$ be the sizes of these colonies, which are here considered as birth with migration processes. We assume that the birth rates are either γ_1 or γ_0 with $\triangle\gamma = \gamma_1 - \gamma_0 > 0$, and that the associated migration rates k_1 and k_0 are such that $k_0 \geqslant k_1$, that is cells located in the colony having the smaller birth rate migrate at a higher rate to the colony 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 colony (e.g. γ_0 and k_0 to X, and γ_1 and k_1 to Y), then the mean sizes $n_0(t) = \mathbb{E}(X(t))$ and $n_1(t) = \mathbb{E}(Y(t))$ satisfy the pair of differential equations (see [7] or [8])

$$\begin{aligned} \frac{\mathrm{d}n_0(t)}{\mathrm{d}t} &= (\gamma_0 - k_0)n_0(t) + k_1 n_1(t), \\ \frac{\mathrm{d}n_1(t)}{\mathrm{d}t} &= (\gamma_1 - k_1)n_1(t) + k_0 n_0(t). \end{aligned} \tag{1}$$

According to [9], we say that cells of the first colony represented by $X(t)$ are *unfit* (they have the lower birth rates), and conversely that cells of the second colony represented by $Y(t)$ are *fit*. The proportion of fit cells in the global population, $y(t) = n_1(t)/(n_1(t) + n_0(t))$, $t \geqslant 0$, satisfies the non-linear differential equation

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = k_0 + (\triangle\gamma - k_0 - k_1)y(t) - \triangle\gamma y(t)^2. \tag{2}$$

Then, as $t \to \infty$, $y(t) \longrightarrow y_1$, where $\frac{1}{2} \leqslant y_1 \leqslant 1$ follows directly from (2), see Section 2. This describes the equilibrium value of the proportion of fit cells in a non-changing environment. Fixing the values of the parameters k_0, γ_0 and γ_1, we can ask for the value of $0 \leqslant k_1 \leqslant k_0$ 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, $k_1 = 0$. This leads to $y_1 = 1$, and thus the optimal solution would be a homogeneous population.

Observations reveal however that most cell populations are not homogeneous; to explain this, the authors of [9] propose to introduce a small modification in the model by allowing environmental changes (for related questions in this context, see e.g. [8]), and show through Monte-Carlo simulations that the homogeneous solution $k_1 = 0$ is then not always optimal. The idea in their model is to allow the birth and migration rates to switch at random times from one colony to the other, so that cells in the fit colony 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 $f_1(t)$ 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 $f_1(t)$ is then switched to $f_1(T_1 + 0) = 1 - f_1(T_1)$. After T_1, the random process $\{f_1(t)\}_{t\geqslant 0}$ solves (2) with initial data $f_1(T_1 + 0)$ 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.

In [9], the fluctuations of the environment are modeled using a renewal process; the instants T_i, $i \geqslant 0$, are such that the sequence of random variables $\{t_i\}_{i\geqslant 1}$ given by $t_i \equiv T_i - T_{i-1}$, $i \geqslant 1$, 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 $f_1(t)$, of the form

$$S_N = \frac{1}{T_N} \int_0^{T_N} f_1(s)\,\mathrm{d}s.$$

This limiting average value is denoted by $\mathrm{Av}(f_1)_{k_1}$ to express its dependency on the migration rate $k_1 < k_0$, when all the remaining parameters are fixed. Their simulations indicate that there is a range of parameters (k_0 not too large) such that

$$\mathrm{Av}(f_1)_{k_1>0} > \mathrm{Av}(f_1)_{k_1=0},$$

which means that heterogeneous populations are more adapted than homogeneous ones in a switching environment.

In this paper, we study mathematically the limiting behavior of the stochastic process $f_1(t)$ and the associated time average S_N by giving its stationary measure, and we provide mathematical formulas and numerical solutions, which might be of interest in practical laboratory experiments (see e.g. [9]).

Our technique uses the process $X_k = f_1(T_k - 0)$, $X_0 = f_1(0)$, which is such that $X_{k+1} = \varphi_{t_{k+1}}(1 - X_k)$, for some mapping $\varphi_t(x)$ (see Definition 1). $(X_k)_{k\geqslant 0}$ is a stochastic recursive Markov chain, and S_N can be expressed as an additive functional of the trajectory of $(X_k)_{1\leqslant k\leqslant N}$. In Section 2, we recall a Theorem from [3] 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 3, we consider the case where μ is exponential of parameter $\kappa > 0$, and show that π has a $\mathcal{C}^\infty$ 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. In Section 5, we show numerical solutions, using the series expansions of Proposition 1 to start the numerical integration. We provide an example where $\mathrm{Av}(f_1)_{k_1>0} > \mathrm{Av}(f_1)_{k_1=0}$, which shows that it can be better to allow fit cells to migrate to the unfit state than to conserve all the fit cells in the fit state in such a switching environment. This is a regime where it is suitable for the colonies to anticipate bad hypothetical future events.

2 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 $-\triangle\gamma(y - y_0)(y - y_1)$, where $y_0 = (\triangle\gamma - k_0 - k_1) - \sqrt{d})/(2\triangle\gamma) < 0$, $y_1 = ((\triangle\gamma - k_0 - k_1) + \sqrt{d})/(2\triangle\gamma) > 0$, and $d = (\triangle\gamma - k_0 - k_1)^2 + 4k_0\triangle\gamma$. Then $k_0 > k_1$ implies that $0 < 1 - y_1 < \frac{1}{2} < y_1 < 1$, and that the derivative $\mathrm{d}f_1(t)/\mathrm{d}t$ is positive when $f_1(t)$ is in the interval $[0, y_1)$, negative in $(y_1, 1]$, and it vanishes for $f_1(t) = y_1$. It is not hard to check that any realization of the trajectory $\{f_1(t)\}_{t\geqslant 0}$, with initial data $f_1(0) \in I = (1 - y_1, y_1)$ 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, $f_1(0) = y_1$ implies $f_1(t) \equiv y_1$.) We thus restrict our study to the interval I.

Given $t \in \mathbb{R}^+$, we define the mapping $\varphi_t : I \longrightarrow I$ such that $\varphi_t(x)$ 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

$$\frac{\varphi_t(x) - y_0}{y_1 - \varphi_t(x)} = \frac{x - y_0}{y_1 - x}\exp(\beta t), \tag{3}$$

where we set $\beta = \triangle\gamma(y_1 - y_0)$. 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, $y \geqslant u$, when starting at time $t = 0$ at u. Then

$$\beta\delta t(u, y) = \ln\Big(\frac{(y - y_0)(y_1 - u)}{(y_1 - y)(u - y_0)}\Big). \tag{4}$$

Definition 1 *Given $X_0 = f_1(0) \in I$, consider the Markov chain with values in I defined by*

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

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 $f_1(T_k - 0)$, at the instants just before the switches, with $T_{k+1} - T_k = t_{k+1}$.

We first recall and adapt results of [3] on the convergence of such Markov chains, also called *stochastic recursive chains*, see e.g. [1]. 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 $f_\theta : S \longrightarrow S$, 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, $n \geqslant 1$, 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 (Theorem 1.1 of [3]). In what follows, $P^{(n)}(x, \mathrm{d}y)$ denotes the law of the Markov chain X_n and $\rho[P^{(n)}(x, \cdot), \pi]$ is the Prokhorov metric, see below.

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

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

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

$$\int K_\theta \mu(\mathrm{d}\theta) < \infty, \quad \int \rho(f_\theta(x_0), x_0) \mu(\mathrm{d}\theta) < \infty, \tag{5}$$

for some $x_0 \in S$, and that

$$\int \ln(K_\theta) \mu(\mathrm{d}\theta) < 0. \tag{6}$$

Then

- *The Markov chain has a unique stationary distribution π,*
- *$\rho[P^{(n)}(x, \cdot), \pi] \leqslant A_x r^n$, 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

$$P^{(n)}(X_0, C) < \pi(C_\delta) + \delta \quad \text{and} \quad \pi(C) < P^{(n)}(X_0, C_\delta) + \delta, \tag{7}$$

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 [3]). Condition (6) 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 $\varphi_t(u)$ is given explicitly by

$$\varphi_t(u) = \frac{y_0(y_1 - u) + y_1(u - y_0)\exp(\beta t)}{y_1 - u + (u - y_0)\exp(\beta t)}. \tag{8}$$

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

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

$$\frac{\mathrm{d}}{\mathrm{d}x} f_t(x) = -\frac{(y_1 - y_0)^2 \exp(\beta t)}{(y_1 - 1 + x + (1 - x - y_0)\exp(\beta t))^2},$$

$$K_t := \sup_{x \in I} |\frac{\mathrm{d}}{\mathrm{d}x} f_t(x)| = \frac{(y_1 - y_0)^2 \exp(\beta t)}{(2y_1 - 1 + (1 - y_1 - y_0)\exp(\beta t))^2}.$$

If μ is exponential of parameter $\kappa > 0$, and $\alpha = \kappa/\beta$, then the conditions given in (5) are satisfied, and

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

where we set $z = -(2y_1 - 1)/(1 - y_1 - y_0) < 0$. Condition (6) is thus satisfied if

$$-\alpha - 2z \int_0^\infty \frac{\exp(-(1+\alpha)t)}{1 - z\exp(-t)} \mathrm{d}t < 0. \tag{9}$$

Remark 1 *When $|z| \leqslant 1$, the integral $\int_0^\infty (\exp(-(1+\alpha)t))/(1 - z\exp(-t))\mathrm{d}t$ is the Lerch Phi function $\Phi(z, s, v) = \sum_{n \geqslant 0} (v+n)^{-s} z^n$, with $s = 1$ and $v = 1 + \alpha$, and is also equal to Gauss's Hypergeometric function ${}_2\mathrm{F}_1(1, 1+\alpha; 2+\alpha; z)/(1+\alpha)$ (see e.g. [4], chap. 1.11).*

Proof: Taking the derivative of (8) with respect to u, we obtain

$$\frac{\mathrm{d}}{\mathrm{d}u} \varphi_t(u) = \frac{(y_1 - y_0)^2 \exp(\beta t)}{(y_1 - u + (u - y_0)\exp(\beta t))^2}$$

and thus

$$f_t'(x) = -\frac{\mathrm{d}}{\mathrm{d}u} \varphi_t(1 - x) = -\frac{(y_1 - y_0)^2 \exp(\beta t)}{(y_1 - 1 + x + (1 - x - y_0)\exp(\beta t))^2} < 0,$$

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

3 Convergence to stationarity in Poissonian environments

Assume that μ is exponential of parameter $\kappa > 0$. We will see in the sequel that the stationary measure π has, under some conditions, a density $P(y)$ such that with $Q(y) = ((y - y_0)/(y_1 - y))^\alpha$, where $\alpha = \kappa/\beta$, the function $G(y) = P(y)Q(y)(y - y_0)(y_1 - y)$ satisfies the differential equation

$$G''(y) + U(y)G'(y) + V(y)G(y) = 0, \tag{10}$$

where $\tilde{y}_0 = 1 - y_0$, $\tilde{y}_1 = 1 - y_1$,

$$U(y) = \frac{\alpha + 1}{y - \tilde{y}_0} - \frac{\alpha - 1}{y - \tilde{y}_1} + \frac{\alpha}{y - y_1} - \frac{\alpha}{y - y_0}, \tag{11}$$

and

$$V(y) = \frac{\alpha^2 (y_1 - y_0)^2}{(y - y_0)(y - y_1)(y - \tilde{y}_0)(y - \tilde{y}_1)}. \tag{12}$$

The following proposition will therefore be useful:

Proposition 1 *The solutions of the second order homogeneous linear differential equation (10) are analytic on the interval $I = (\tilde{y}_1, y_1)$. Two fundamental solutions $\tilde{G}_1(y)$, $\tilde{G}_2(y)$ are*

- $\tilde{G}_1(y) = (y - \tilde{y}_1)^\alpha \tilde{W}_1(y)$, *where* $\tilde{W}_1(y)$ *is analytic on* $(\tilde{y}_1 - \delta, y_1)$ *for some* $\delta > 0$ *and with* $\tilde{W}_1(\tilde{y}_1) = 1$.

- $\tilde{G}_2(y) = \begin{cases} \tilde{W}_2(y), & \text{if } \alpha \notin \mathbb{Z}, \\ \tilde{W}_2(y) + \tilde{C}\tilde{G}_1(y)\ln(y - \tilde{y}_1), & \text{if } \alpha \in \mathbb{Z}, \end{cases}$
with $\tilde{W}_2(y)$ *analytic on* $(\tilde{y}_1 - \delta, y_1)$ *for some* $\delta > 0$, $\tilde{W}_2(\tilde{y}_1) = 1$ *and* $\tilde{C} \in \mathbb{R}$.

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

- $G_1(y) = (y_1 - y)^{1-\alpha} W_1(y)$, *where* $W_1(y)$ *is analytic on* $(\tilde{y}_1, y_1 + \delta)$ *for some* $\delta > 0$ *and with* $W_1(y_1) = 1$.

- $G_2(y) = \begin{cases} W_2(y), & \text{if } \alpha \notin \mathbb{Z}, \\ W_2(y) + CG_1(y)\ln(y_1 - y), & \text{if } \alpha \in \mathbb{Z}, \end{cases}$
with $W_2(y)$ *analytic on* $(\tilde{y}_1, y_1 + \delta)$ *for some* $\delta > 0$, $W_2(y_1) = 1$ *and* $C \in \mathbb{R}$.

In the appendix, we show this result for completeness, and also how these fundamental solutions can be computed by series expansion about $\tilde{y}_1$ and y_1 respectively.

Theorem 2 *Assume that*

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

where $z = -(2y_1 - 1)/(1 - y_1 - y_0) < 0$. *Then the Markov chain* X_k *from Definition 1, with initial data* $X_0 \in I = (1 - y_1, y_1)$ *has a unique stationary distribution* π *of* $\mathcal{C}^\infty$ *density*

$$P(y) = \frac{Q(y)^{-1}(y - \tilde{y}_1)^\alpha \tilde{W}_1(y)/(y_1 - y)/(y - y_0)}{\int_I Q(z)^{-1}(z - \tilde{y}_1)^\alpha \tilde{W}_1(z)/(y_1 - y)/(y - y_0)\,\mathrm{d}z}.$$

Here, $Q(y) = \left(\frac{y - y_0}{y_1 - y}\right)^\alpha$, *where* $\alpha = \kappa/\beta$, $\tilde{W}_1(y)$ *is the analytic function on* $(\tilde{y}_1 - \delta, y_1)$ *with* $\tilde{W}(\tilde{y}_1) = 1$, *such that* $\tilde{G}_1(y) = (y - \tilde{y}_1)^\alpha \tilde{W}_1(y)$ *is a solution of the differential equation (10). In the neighborhood of* $y = y_1$, *this solution is such that* $0 < \lim_{y \to y_1} \tilde{W}_1(y) < +\infty$. *Finally, the behavior of the density* P *near* y_1 *is given by* $(y_1 - y)^{\alpha - 1}$, *and thus converges when* $\alpha \geqslant 1$ *and diverges toward* $+\infty$ *when* $\alpha < 1$. *Let* $f(x) = x$ *and* $g(x) = \ln((x - 1 + y_1)/(y_1 - x))$ *be defined on* I. *Then* $g \in \mathrm{L}^1(I, \mathbb{B}(I), \pi)$ *with*

$$\mathbb{E}_\pi(f) = y_0 + \frac{\kappa}{\Delta\gamma}\mathbb{E}_\pi(g). \tag{13}$$

Remark 2 *Relation (13) will be useful when considering time averages for Monte-Carlo simulations, see Section 4.*

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, $Y =_{\mathcal{L}} \varphi_T(1 - Y)$. Let $F(y) = P(Y < y)$. Then

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

where $\mathbb{I}(\cdot)$ denotes the indicator function. For given $y \in I$, the time variable t is restricted to the interval $0 \leqslant t < \delta t(\tilde{y}_1, y)$, see (4). Thus

$$F(y) = \int_0^{\delta t(1 - y_1, y)} \kappa\exp(-\kappa t) \int_I \pi(\mathrm{d}v)\mathbb{I}(\varphi_t(1 - v) < y)\mathrm{d}t.$$

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

$$\{v \in I;\ 1 - v < \frac{y_1(y-y_0) + \exp(\beta t)(y_1 - y)y_0}{y - y_0 + \exp(\beta t)(y_1 - y)}\}.$$

It follows that $\int_I \pi(\mathrm{d}v)\mathbb{I}(\varphi_t(1-v) < y) = 1 - F(1-u)$, where we set $u = (y_1(y-y_0)+\exp(\beta t)(y_1 - y)y_0)/(y - y_0 + \exp(\beta t)(y_1 - y))$, with $t = \delta t(u, y)$. We make the change of variable $t = \delta t(u, y)$ with

$$\frac{\mathrm{d}t}{\mathrm{d}u} = -\frac{y_1 - y_0}{\beta(y_1 - u)(u - y_0)}.$$

Then

$$F(y) = \alpha\Big(\frac{y_1 - y}{y - y_0}\Big)^{\alpha} \int_{1-y_1}^{y} \frac{y_1 - y_0}{(y_1 - u)(u - y_0)}\Big(\frac{u - y_0}{y_1 - u}\Big)^{\alpha}(1 - F(1-u))\mathrm{d}u.$$

This is a fixed point equation for the distribution function F. We use it for proving that the probability measure π has a $\mathcal{C}^\infty$ 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 $\mathcal{C}^\infty$ differentiability is obtained by iterating this argument. Let P be the $\mathcal{C}^\infty$ 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

$$0 \leqslant t \leqslant \delta t(u, y) = \ln((y - y_0)(y_1 - y)/(y_1 - y)(u - y_0))/\beta,$$

where $u = 1 - v$ (see 4). It follows that

$$F(y) = \int_{1-y}^{y_1} P(v)\mathrm{d}v \int_0^{\delta t(u,y)} \kappa \exp(-\kappa t)\mathrm{d}t,$$

with

$$\begin{aligned} P(y) = \frac{\mathrm{d}F(y)}{\mathrm{d}y} &= \int_{1-y}^{y_1} P(v)\mathrm{d}v\kappa\exp(-\kappa\delta t(u, y))\frac{\mathrm{d}\delta t(u, y)}{\mathrm{d}y} \\ &= \alpha\int_{1-y}^{y_1} \mathrm{d}v P(v)\frac{Q(u)}{Q(y)}\frac{(y_1 - y_0)}{(y - y_0)(y_1 - y)}, \end{aligned}$$

where we set $Q(y) = ((y - y_0)/(y_1 - y))^{\alpha}$. Using $u = 1 - v$ and setting $G(y) = P(y)Q(y)(y - y_0)(y_1 - y)$, one gets

$$G(y) = \int_{1-y_1}^{y} G(1-u)R(u)H(u)\,\mathrm{d}u, \tag{14}$$

where $R(u) = \alpha Q(u)Q(1-u)^{-1}$ is such that $R(1-u) = \alpha^2/R(u)$, and $H(u) = (y_1 - y_0)/(y_1 - 1 + u)/(1 - u - y_0)$. Taking the derivative gives

$$G'(y) = G(1-y)R(y)H(y), \tag{15}$$

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

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

and simplifying the terms leads to (10). We see that $R(u)H(u) \sim (u-1+y_1)^{\alpha-1}$, as $u \to 1-y_1$. The exponents associated with the fundamental solutions are $\rho = 0$ or α in the neighborhood of $y = 1-y_1$ and $\rho' = 0$ or $1-\alpha$ near $y = y_1$.

Assume first that $\alpha \notin \mathbb{N}^+$. We first check the behavior of G in a neighborhood of $y = \tilde{y}_1$. Set $y = \tilde{y}_1 + \varepsilon$, $\varepsilon > 0$, with $1-y = y_1 - \varepsilon$. 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 $\varepsilon \to 0$, the right hand side of (14) behaves like $\varepsilon^\alpha G(y_1-\varepsilon) \to 0$. Suppose that $\tilde{B} \neq 0$. Then $G(y) \sim \tilde{B}\tilde{W}_2(y) \neq 0$, and (14) can't be satisfied. One must thus have $\tilde{B} = 0$, so that $G(y) = \tilde{A}\varepsilon^\alpha \tilde{W}_1(y)$. When $\alpha > 1$, (14) implies that $A = 0$. It follows that, for arbitrary $\alpha > 0$, $\lim_{y\to y_1} G(y) = BW_2(y_1) \neq 0$, and that $G(\tilde{y}_1 + \varepsilon) \sim \tilde{A}\varepsilon^\alpha \tilde{W}_1(\tilde{y}_1)$, $\varepsilon \to 0$, as required. The corresponding result for P follows.

Suppose that $\alpha \in \mathbb{N}^+$. The right hand side of (14) behaves like

$$F(\varepsilon) := \varepsilon^\alpha(A\varepsilon^{1-\alpha}W_1(y_1) + B(W_2(y_1) + C\varepsilon^{\alpha-1}W_1(y_1)\ln(\varepsilon))),$$

with $F(\varepsilon) \to 0$ as $\varepsilon \to 0$, and $G(\tilde{y}_1 + \varepsilon)$ behaves like

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

One has $\tilde{F}(\varepsilon) \sim \tilde{B}\tilde{W}_2(\tilde{y}_1)$, $\varepsilon \to 0$, when $\tilde{B} \neq 0$ and $\tilde{F}(\varepsilon) \sim \tilde{A}\varepsilon^\alpha \tilde{W}_1(\tilde{y}_1)$, when $\tilde{B} = 0$. (14) shows that necessarily $\tilde{B} = 0$. Suppose that $\alpha = 1$. Then one must have $BC = 0$, implying the existence of the limit $\lim_{y\to y_1} G(y) \neq 0$. When $\alpha > 1$, $A = 0$, $B \neq 0$, and $\lim_{y\to y_1} G(y) = BW_2(y_1)$, as required.

Finally, we check the identity (13). 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,

$$\mathbb{E}_\pi(g) = \int_I \ln(\frac{y-1+y_1}{y_1-y})P(y)\mathrm{d}y,$$

where $J := \int_I \ln(y-1+y_1)P(y)\mathrm{d}y$ is such that

$$\begin{aligned}
J &= \int_I \ln(y-1+y_1)G(y)Q(y)^{-1}\frac{H(1-y)}{y_1-y_0}\mathrm{d}y \\
&= \frac{1}{y_1-y_0}\int_I \ln(y_1-u)G(1-u)Q(1-u)^{-1}H(u)\mathrm{d}u \\
&= \frac{1}{\alpha(y_1-y_0)}\int_I \frac{\ln(y_1-u)}{Q(u)}G(1-u)R(u)H(u)\mathrm{d}u \\
&= \frac{1}{\alpha(y_1-y_0)}\int_I \frac{\ln(y_1-u)}{Q(u)}G'(u)\mathrm{d}u \\
&= \frac{1}{\alpha(y_1-y_0)}\Big(G(u)\frac{\ln(y_1-u)}{Q(u)}\Big|_{1-y_1}^{y_1} - \int_I G(u)\Big(\frac{\ln(y_1-u)}{Q(u)}\Big)'\mathrm{d}u\Big) \\
&= \frac{1}{\alpha(y_1-y_0)}\int_I \frac{G(u)}{Q(u)}\frac{(u-y_0)}{(y_1-u)(u-y_0)}\mathrm{d}u + \int_I \ln(y_1-u)P(u)\mathrm{d}u,
\end{aligned}$$

where we use (15). It follows that

$$\mathbb{E}_\pi(g) = \frac{1}{\alpha(y_1-y_0)}\mathbb{E}_\pi(f) - \frac{y_0}{\alpha(y_1-y_0)},$$

proving (13) since $\alpha = \kappa/(\triangle\gamma(y_1-y_0))$.

Corollary 1 *Assume that condition (9) holds. Then, as $t \to +\infty$, the law of the stochastic process $f_1(t)$, $t \geqslant 0$, $f_1(0) \in I$, 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 $f_1(t) =_{\mathcal{L}} \varphi_{S_*}(1 - X)$, where X is distributed according to π, and the result follows.

4 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. [2]). In [9], the authors use Monte-Carlo methods based on the process $f_1(t)$, $t \geqslant 0$, to estimate the mean fitness by considering the time average

$$S_N = \frac{1}{T_N} \int_0^{T_N} f_1(s)\,\mathrm{d}s, \tag{16}$$

where N is a fixed number of renewal periods.

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

$$\frac{1}{T_N} \int_0^{T_N} f_1(s)\,\mathrm{d}s = y_0 + \frac{(y_1 - y_0)}{\beta T_N} \ln\Big(\prod_{i=1}^{N} \frac{X_{i-1} - (1 - y_1)}{y_1 - X_i}\Big). \tag{17}$$

Proof: Consider the integrals

$$\int_{T_{i-1}}^{T_i} f_1(s)\,\mathrm{d}s,$$

where $f_1(T_{i-1} + 0) = 1 - X_{i-1}$ and $f_1(T_i - 0) = X_i$. The value of $y(s) = f_1(T_{i-1} + s)$, $s \in (0, T_i - T_{i-1})$ is given implicitly by (3); Therefore

$$y(s) = \frac{y_0(y_1 - u) + y_1(u - y_0)\exp(\beta s)}{y_1 - u + (u - y_0)\exp(\beta s)},$$

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

$$\int_{T_{i-1}}^{T_i} f_1(s)\,\mathrm{d}s = y_0(T_i - T_{i-1}) + \frac{y_1 - y_0}{\beta} \ln\left(\frac{y_1 - u + (u - y_0)\exp(\beta(T_i - T_{i-1}))}{y_1 - y_0}\right),$$

and the result follows, since

$$\begin{aligned} y_1 - u + (u - y_0)\exp(\beta(T_i - T_{i-1})) &= (y_1 - u)(1 + \frac{u - y_0}{y_1 - u}\exp(\beta t_i)) \\ &= \frac{(y_1 - (1 - X_{i-1}))(y_1 - y_0)}{y_1 - X_i}. \end{aligned}$$

Theorem 3 *Suppose that μ is exponential of parameter $\kappa > 0$, and assume (9). Let $f(x) = x$ and $g(x) = \ln((x - 1 + y_1)/(y_1 - x))$ be defined on I. Then*

$$\lim_{N\to\infty} \frac{1}{T_N} \int_0^{T_N} f_1(s)\,\mathrm{d}s = y_0 + \frac{\kappa}{\triangle\gamma}\mathbb{E}_\pi(g) = \mathbb{E}_\pi(f), \quad a.s.$$

Proof: From equation (17), we obtain

$$\frac{1}{T_N}\int_0^{T_N} f_1(s)\,\mathrm{d}s = y_0 + \frac{(y_1-y_0)}{\beta T_N}\ln(\frac{X_0-1+y_1}{y_1-X_N}) + \frac{(y_1-y_0)}{\beta T_N}\sum_{i=1}^{N-1} g(X_i).$$

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 $y = 1-y_1$ is given by $(y-1+y_1)^{\rho_1}$ where $\rho_1 = \alpha$ and by $(y_1-y)^{\rho_2+\alpha-1}$ in the neighborhood of $y = y_1$, where $\rho_2 = 0$. The Markov chain X_k is geometrically ergodic, and thus the last term converges a.s. toward $(\kappa/(\triangle\gamma))\mathbb{E}_\pi(g)$. We finally check that $\ln(y_1-X_N)/N$ converges a.s. toward 0. Given $\epsilon > 0$, consider the probability

$$\begin{aligned} P(|\ln(y_1-X_N)| > N\epsilon) &= P(\ln(y_1-X_N) < -N\epsilon) \\ &= P(X_N > y_1 - \exp(-N\epsilon)) = P^{(N)}(X_0, A_N), \end{aligned}$$

where $A_N = \{x > y_1 - \exp(-N\epsilon)\}$. Using the behavior of P in the neighborhood of $y = y_1$, one gets that $\pi(A_N) \leqslant M(\exp(-\epsilon N))^{\rho_2+\alpha}$, 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 (7). If $\pi(A_N) \geqslant P^{(N)}(X_0,A_N)$, then $\gamma_N \leqslant \pi(A_N)$. If $\pi(A_N) \leqslant P^{(N)}(X_0,A_N)$, one has $P^{(N)}(X_0,A_N) \leqslant \pi((A_N)_{d_N}) + d_N$, and it follows that

$$\begin{aligned} \gamma_N = P^{(N)}(X_0,A_N) - \pi(A_N) &\leqslant \pi((A_N)_{d_N}) - \pi(A_N) + d_N \\ &= \int_{y_1-\exp(-\epsilon N)-d_N}^{y_1-\exp(-\epsilon N)} P(y)\mathrm{d}y + d_N \\ &\leqslant d_N + D(\exp(-\epsilon N)^{\rho_2+\alpha} - (d_N + \exp(-\epsilon N))^{\rho_2+\alpha}), \end{aligned}$$

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

$$P(|\ln(y_1-X_N)| > \epsilon N) \leqslant |P^{(N)}(X_0,A_N) - \pi(A_N)| + \pi(A_N) \leqslant h(X_0)\lambda^N,$$

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 (13) of Theorem 2.

5 Numerical Examples

We now compute the density P given in Theorem 2 numerically. To do so, we solve the differential equation (10) numerically, starting in the neighborhood of the singular point $y = \tilde{y}_1 = 1 - y_1$. Proposition 1 and Theorem 2 show that $\lim_{y\to\tilde{y}_1} P(y) = 0$, and that the first derivative of P behaves like $(y-\tilde{y}_1)^{\alpha-1}$, which goes to $+\infty$ when $\alpha < 1$. We start the numerical solution at the point $y = \tilde{y}_1 + \varepsilon$, where $\varepsilon > 0$ is small, and use the initial conditions $G(\tilde{y}_1+\varepsilon)$ and $G'(\tilde{y}_1+\varepsilon)$ from the series expansions given in Proposition 1. In addition, we use the numerical integration procedure to compute the integral to scale the density P, by adding an additional ordinary differential equation to (10).

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 (10) 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_1 increases the overall fitness

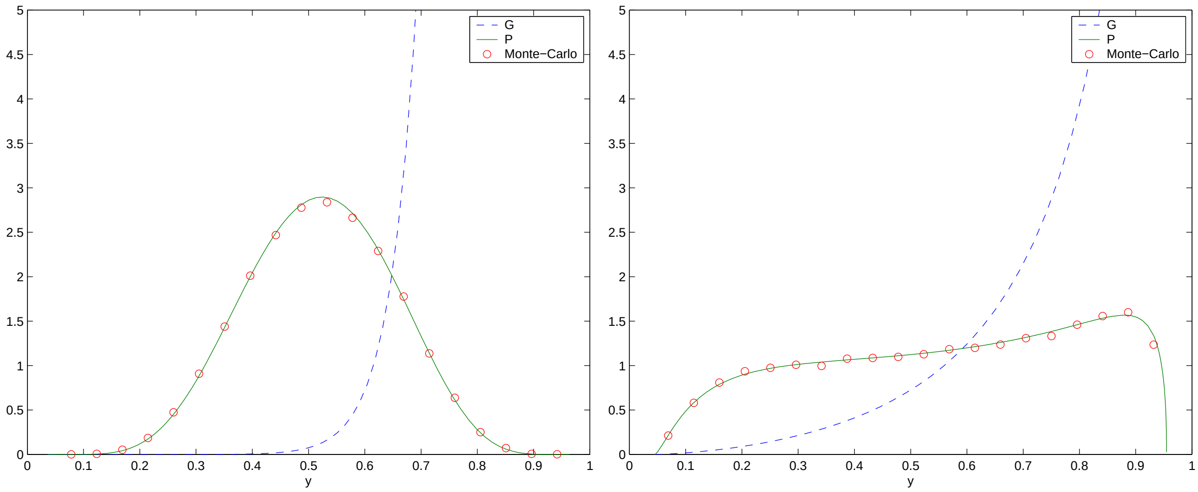

Figure 1: Density P on the left when $\kappa = 10$, $\triangle\gamma = 1$, $k_0 = 0.4$, $k_1 = 0.05$, and on the right when $\kappa = 1.5$, $\triangle\gamma = 1$, $k_0 = 0.1$, $k_1 = 0.05$.

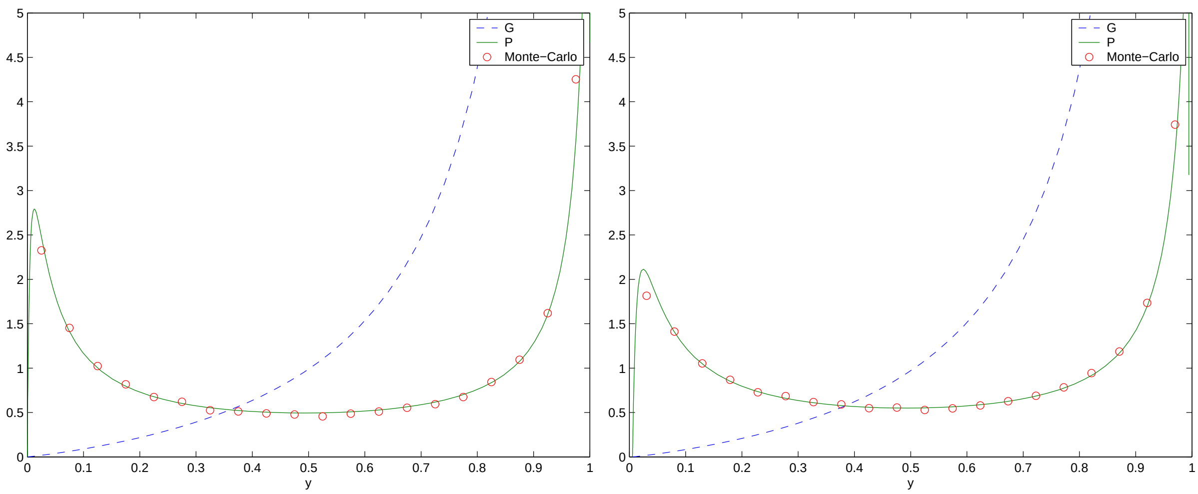

Figure 2: Density P on the left when $\kappa = 10$, $\triangle\gamma = 9$, $k_0 = 0.1$, $k_1 = 0$. $Av(f_1)_{k_1=0} = 0.553274111$, and on the right when $\kappa = 10$, $\triangle\gamma = 9$, $k_0 = 0.1$, $k_1 = 0.05$. $Av(f_1)_{k_1=0.05} = 0.55672212$. Clearly the average fitness is larger when $k_1 = 0.05$ than when $k_1 = 0$.

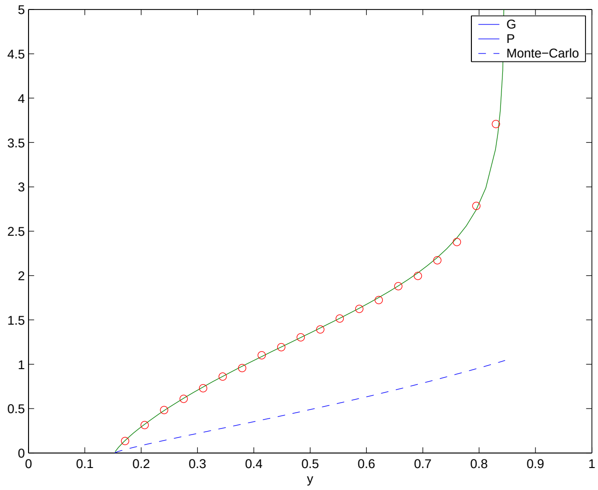

Figure 3: Density P when $\kappa = 5$, $\triangle\gamma = 3$, $k_0 = 3$, $k_1 = 1$, a case where $\alpha < 1$.

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 [5].

6 Appendix

In this appendix we show for completeness the proof of Proposition 1 and describe a method how to solve the differential equation (10) (see also [6], 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 $y_0 < \tilde{y}_1 := 1 - y_1 < y_1 < \tilde{y}_0 := 1 - y_0$. The solutions are therefore analytic in the open disc of radius $(y_1 - \tilde{y}_1)/2$ centered at $1/2$. We look for real solutions in the interval $I = (\tilde{y}_1, y_1)$. In order to simplify calculations, we use the variable transformation

$$y = \tilde{y}_1 + (y_1 - \tilde{y}_1)z, \qquad z = \frac{y - \tilde{y}_1}{y_1 - \tilde{y}_1} \tag{18}$$

and set $g(z) := G(y)$. With this transformation, the differential equation (10) becomes

$$g''(z) + u(z)g'(z) + v(z)g(z) = 0, \tag{19}$$

where u and v have four poles of order one at the points $-b < 0 < 1 < 1 + b$ with $b = (\tilde{y}_1 - y_0)/(y_1 - \tilde{y}_1)$:

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

We can therefore rewrite this equation as

$$g''(z) + \frac{h(z)}{z}g'(z) + \frac{k(z)}{z^2}g(z) = 0, \tag{20}$$

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

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

Multiplying the equation (20) by z^2 we get an equivalent equation which can be written as

$$\mathrm{L}(g) := ({\mu_z}^2\mathrm{D}^2 + \mu_h\mu_z\mathrm{D} + \mu_k)(g) = 0, \tag{21}$$

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

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

we may identify the function $g(z)$ with the infinite row $[w] = [1, w_1, w_2, w_3, \ldots]$ and write (21) in matrix form:

$$[\mathrm{L}^\rho][w]^\mathrm{T} = 0. \tag{22}$$

If we write L as $\mathrm{L} = (\mu_z\mathrm{D} + \mu_{h-1})\mu_z\mathrm{D} + \mu_k$, we get the lower triangular matrix

$$[\mathrm{L}^\rho] = \begin{bmatrix} \rho(\rho+\alpha_0-1)+\beta_0 & 0 & \cdots & & \\ \rho\alpha_1+\beta_1 & (\rho+1)(\rho+\alpha_0)+\beta_0 & 0 & \cdots & \\ \rho\alpha_2+\beta_2 & (\rho+1)\alpha_1+\beta_1 & (\rho+2)(\rho+1+\alpha_0)+\beta_0 & 0 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{bmatrix}.$$

A solution $[w] = [1, w_1, w_2, \ldots]$ of the linear system (22) exists if and only if $L^{\rho}_{00} = 0$. 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 (19). 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^{ν}_{ij} instead of $L^{\rho_\nu}_{ij}$.

For $\rho = \rho_1$, the solution $[w^{(1)}] = [1, w^{(1)}_1, w^{(1)}_2, \ldots]$ may be calculated by the recursion scheme

$$w^{(1)}_0 = 1, \quad w^{(1)}_n = \frac{-1}{L^1_{nn}} \left(\sum_{j=0}^{n-1} L^1_{nj} w^{(1)}_j \right) \quad \text{for } n \geqslant 1.$$

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

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

is a solution of (19). From the general theory of linear differential equations in the complex plane it follows that g_1 is analytic in the disc 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 $\mathrm{L}^2_{nn} = 0$ for $n = \alpha$, and we look in this case for a solution $g_2(z)$ of the form $g_2(z) = 1 + \sum_{n \geqslant 1} w^{(2)}_n z^n + C g_1(z) \ln z$. As g_1 is a solution, the terms in $\mathrm{L}(g_2)$ containing $\ln z$ cancel and the function $w^{(2)}(z) = 1 + \sum_{n \geqslant 1} w^{(2)}_n z^n$ must satisfy the equation

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

Identifying $w^{(2)}(z)$ with the infinite row $[w^{(2)}] = [1, w^{(2)}_1, w^{(2)}_2, \ldots]$, we can write this in matrix form

$$[\mathrm{L}^2][w^{(2)}]^{\mathrm{T}} = -C[v_1, v_2, \ldots]^{\mathrm{T}}. \tag{23}$$

For the right-hand side one checks easily that $v_j = 0$ for $j = 0, \ldots, \alpha - 1$ and $v_\alpha = \alpha$. Therefore we can resolve the inhomogeneous linear system (23) in the following way:

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

2. We set $w^{(2)}_\alpha := 0$ and determine the constant C by the equation $\sum_{j=0}^{\alpha-1} L^{(2)}_{\alpha,j} w_j(2) = -C v_\alpha$.

3. We determine the coefficients $w^{(2)}_n$ for $n > \alpha$ by the recursion formula

$$w^{(2)}_n = \frac{-1}{L^2_{nn}} \left(C v_n + \sum_{j=0}^{n-1} L^2_{nj} w^{(2)}_j \right) \quad \text{for } n \geqslant \alpha + 1.$$

We shall not go into further details, for example present concrete formulas expressing the v_n by the $w^{(1)}_n$, because we don't really need the solution g_2 of (20) in our case, as we have shown in the proof of Theorem 2.

Using the variable transformation (18) we get the solutions $\tilde{G}_j(y)$ of the original differential equation (10), in particular

$$\tilde{G}_1(y) = (y_1 - \tilde{y}_1)^\alpha g_1 \left(\frac{y - \tilde{y}_1}{y_1 - \tilde{y}_1} \right) = (y - \tilde{y}_1)^\alpha \tilde{W}_1(y) = (y - \tilde{y}_1)^\alpha \left(1 + \sum_{n=1}^{\infty} \frac{w^{(1)}_n}{(y_1 - \tilde{y}_1)^n} \right).$$

In order to find fundamental solutions near the singularity y_1, we can apply the same method once more, but using the variable transformation

$$y = y_1 - (y_1 - \tilde{y}_1)z, \qquad z = \frac{y_1 - y}{y_1 - \tilde{y}_1}.$$

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_1 are $\rho'_1 = 1 - \alpha$ and $\rho'_2 = 0$. We obtain thus the second fundamental system of solutions $G_1(y)$ and $G_2(y)$.

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