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DYNAMIC BEHAVIOR OF STOCHASTIC GENE EXPRESSION MODELS IN THE PRESENCE OF BURSTING

M. C. MACKEY[†], M. TYRAN-KAMIŃSKA[‡], AND R. YVINEC[§]

Abstract. This paper considers the behavior of discrete and continuous mathematical models for gene expression in the presence of transcriptional/translational bursting. We treat this problem in generality with respect to the distribution of the burst size as well as the frequency of bursting, and our results are applicable to both inducible and repressible expression patterns in prokaryotes and eukaryotes. We have given numerous examples of the applicability of our results, especially in the experimentally observed situation that burst size is geometrically or exponentially distributed.

Key words. analytical distributions, invariant density, piecewise deterministic Markov process

AMS subject classifications. 60J25, 60J28, 92C40

1. Introduction. Recent spectacular advances in the ability of experimentalists to monitor the temporal behavior of single molecules [4, 8, 18, 22, 23, 28, 33] inside cells has led to a quantum leap in our knowledge of their behavior as well as a plethora of data that challenge mathematicians. These techniques are so refined that they allow the single molecule quantification of the transcription of mRNA as well as the translation of the mRNA into protein. This visualization has shown that in many cases these transcription and translation processes occur in quantal bursts in which a few molecules are produced during a discrete period of time. An analysis of the data obtained from such experiments has given us many details of the nature of the bursting kinetics that are being used to guide mathematical modeling of these fascinating processes.

This paper utilizes the two main approaches that have been employed to model these bursting processes, i.e. a discrete formulation for the numbers of molecules [27] or a continuous one [6, 15] and illustrates the common features of both as well as the differences. Modeling (as opposed to simulation [7, 16] which we do *not* consider) of the details of gene expression as a discrete Markov process has an extensive literature (c.f. [9, 10, 20, 22, 25, 24, 27, 30]) that has recently seen a flurry of activity. The other approach that has received extensive attention is modeling of the process as a continuous one and [6, 13, 15, 17, 26] are representative of these efforts. The reader can consult [11] for an excellent expository account of the connection between these two approaches.

In the discrete Markov models, steady-state analytical solutions of the master equation can often be obtained using the moment generating function. For the continuous model formulations, one needs to solve the Fokker-Planck-like equations, sometimes using Laplace transforms. When solutions are not available, moment equations can be derived and usually solved [19, 29]. Though continuous models have many

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analytic advantages over discrete ones, it is also the case that information of potential importance may be lost in the continuous model formulation compared with the discrete formulation.

This paper presents a general one dimensional model for bursting gene expression in both a discrete Markov process formulation as well as a continuous situation. Section 2 presents some general background material while Section 3 presents the discrete version of the bursting model. Section 3.1 develops the general formulation of the discrete model while Section 3.2 deals with the special case in which the burst amplitudes are geometrically distributed. Section 4 develops the corresponding continuous model of the bursting expression, with a general development in Section 4.1 and Section 4.2 devoted to the situation where the burst amplitudes are exponentially distributed—a situation often found experimentally. Section 4.3 concludes with an examination of a generalization of the exponential distribution of burst amplitudes. The paper ends with some general observations in Section 5. Throughout the paper, our results are illustrated with numerous examples.

2. Notation and background. Let the triple $(E, \mathcal{E}, m)$ be a σ -finite measure space and let $L^1 = L^1(E, \mathcal{E}, m)$ with norm denoted by $\|\cdot\|_1$. A linear operator P on L^1 is called *substochastic* (*stochastic*) if $Pu \geq 0$ and $\|Pu\|_1 \leq \|u\|_1$ ($\|Pu\|_1 = \|u\|_1$) for all $u \geq 0$, $u \in L^1$. We denote by D the set of all *probability densities* on E , i.e.

$$D = \{u \in L^1 : u \geq 0, \|u\|_1 = 1\},$$

so that a stochastic operator transforms a density into a density. In the particular case of a countable set E with $\mathcal{E}$ being the family of all subsets of E and m the counting measure, the space L^1 will be denoted by ℓ^1 .

Let $\mathcal{P}: E \times \mathcal{E} \rightarrow [0, 1]$ be a *stochastic transition kernel*, i.e. $\mathcal{P}(x, \cdot)$ is a probability measure for each $x \in E$ and the function $x \mapsto \mathcal{P}(x, B)$ is measurable for each $B \in \mathcal{E}$, and let P be a stochastic operator on L^1 . If

$$\int_B Pu(x)m(dx) = \int_E \mathcal{P}(y, B)u(y)m(dy) \quad \text{for all } B \in \mathcal{E}, u \in D,$$

then P is called the *transition operator* corresponding to $\mathcal{P}$. A stochastic operator P on L^1 is called *partially integral* or *partially kernel* if there exists a measurable function $p: E \times E \rightarrow [0, \infty)$ such that

$$\int_E \int_E p(x, y) m(dy) m(dx) > 0 \quad \text{and} \quad Pu(x) \geq \int_E p(x, y)u(y) m(dy)$$

for every density u . If, additionally,

$$\int_E p(x, y) m(dx) = 1, \quad y \in E,$$

then P corresponds to the stochastic kernel

$$\mathcal{P}(y, B) = \int_B p(x, y) m(dx), \quad y \in E, B \in \mathcal{E},$$

and we simply say that P has *kernel* p . Note that each stochastic operator on ℓ^1 has a kernel.

We denote by $\mathcal{D}(A)$ the domain of a linear operator A . We say that $A \subseteq B$, or that B is an *extension* of A , if $\mathcal{D}(A) \subseteq \mathcal{D}(B)$ and $Bu = Au$ for $u \in \mathcal{D}(A)$. The

operator A is said to be *closable* if it has a closed extension. If A is closable, then the closure $\overline{A}$ of A is the minimal closed extension of A ; more specifically, it is the closed operator whose graph is the closure in $L^1 \times L^1$ of the graph of A . For an exposition of semigroup theory we refer to [5].

A semigroup $\{P(t)\}_{t \geq 0}$ of linear operators on L^1 is called *substochastic* (*stochastic*) if it is strongly continuous and for each $t > 0$ the operator $P(t)$ is substochastic (stochastic). A density u^* is called *invariant* or *stationary* for $\{P(t)\}_{t \geq 0}$ if u^* is a fixed point of each operator $P(t)$, $P(t)u^* = u^*$ for every $t \geq 0$.

THEOREM 1 ([21, Theorem 2]). *Let $\{P(t)\}_{t \geq 0}$ be a stochastic semigroup such that for some $t_0 > 0$ the operator $P(t_0)$ is partially integral. If the semigroup $\{P(t)\}_{t \geq 0}$ has only one invariant density u^* and $u^* > 0$ a.e. then*

$$\lim_{t \rightarrow \infty} \|P(t)u - u^*\|_1 = 0 \text{ for all } u \in D.$$

3. A discrete bursting model formulated as a Markov process. This section considers bursting gene expression as a Markov process.

3.1. The general case. In this section we model the number of gene products as a pure-jump Markov process $X = \{X(t)\}_{t \geq 0}$ in the state space $E = \{0, 1, 2, \dots\}$. Thus a master equation governs the dynamics evolution of probabilities. A general one-dimensional bursting gene expression model [11] may be constructed as follows. Let n be the number of gene products and $P_n(t) = \Pr(X(t) = n)$ denote the probability of finding n gene products inside the cell at a given time t . We shall include a loss ($n \rightarrow n-1$) and gain ($n \rightarrow n+k$) of functional processes in terms of the general rates γ_n and λ_n , respectively. The step size assumes the values $k = 1, 2, \dots$ and is a random variable (independent of the actual number of gene products) with probability density function h , so that $\sum_{k=1}^{+\infty} h_k = 1$. Therefore, our general master equation describing the time evolution of the probabilities P_n to have n gene products in a cell is an infinite set of differential equations

$$(3.1) \quad \frac{dP_n}{dt} = \gamma_{n+1}P_{n+1} - \gamma_n P_n + \sum_{k=1}^n h_k \lambda_{n-k} P_{n-k} - \lambda_n P_n, \quad n = 0, 1, \dots,$$

where we use the convention that $\sum_{k=1}^0 = 0$. We supplement (3.1) with the initial condition $P_n(0) = v_n$, $n = 0, 1, \dots$, where $v = (v_n)_{n \geq 0} \in \ell^1$ is a probability density function of the initial amount $X(0)$ of the gene product. In the following paragraphs, we consider the existence and uniqueness of solutions of (3.1) together with convergence to a stationary distribution and then summarize our results in Theorem 2.

Assume that

$$(3.2) \quad \lambda_0 > 0, \quad \gamma_0 = 0, \quad \gamma_n > 0, \quad \lambda_n, h_n \geq 0, \quad n = 1, 2, \dots, \quad \sum_{n=1}^{+\infty} h_n = 1.$$

The process X is the minimal pure jump Markov process with the jump rate function $\varphi(n) = \lambda_n + \gamma_n$, $n \geq 0$, and the jump transition kernel $\mathcal{K}$ given by

$$(3.3) \quad \mathcal{K}(n, \{n+j\}) = \begin{cases} q_n, & \text{if } j = -1, n \geq 1, \\ (1 - q_n)h_j, & \text{if } j \geq 1, n \geq 0, \\ 0, & \text{otherwise,} \end{cases} \quad q_n = \frac{\gamma_n}{\lambda_n + \gamma_n}.$$

First, we recall the construction of X . Let $\{\xi_k\}_{k \geq 0}$, be a discrete time Markov chain in the state space $E = \mathbb{Z}_+ = \{0, 1, \dots\}$ with transition kernel $\mathcal{K}$ and let $\{\varepsilon_k\}_{k \geq 1}$ be a sequence of independent random variables, exponentially distributed with mean 1. Set $T_0 = 0$ and define recursively the times of jumps of X as

$$T_k = T_{k-1} + \frac{\varepsilon_k}{\varphi(\xi_{k-1})}, \quad k = 1, 2, \dots$$

Starting from $X(0) = \xi_0$ we have

$$X(t) = \xi_k, \quad T_k \leq t < T_{k+1}, \quad k = 0, 1, 2, \dots,$$

so that the process is uniquely determined for all $t < T_\infty$, where

$$T_\infty = \lim_{k \rightarrow \infty} T_k$$

is called the explosion time. If the explosion time is finite, we can add the point -1 to the state space and we can set $X(t) = -1$ for $t \geq T_\infty$. The process X is called *nonexplosive* if $\mathbb{P}_i(T_\infty = \infty) = 1$ for all $i \in E$, where $\mathbb{P}_i$ is the law of the process starting from $X(0) = i$. In particular, if the chain $\{\xi_k\}_{k \geq 0}$ is recurrent, then X is nonexplosive.

We now rewrite equation (3.1) as an abstract Cauchy problem in the space ℓ^1 . We make use of the results from [32]. Let K be the transition operator on ℓ^1 corresponding to $\mathcal{K}$ defined as in (3.3). For $v = (v_n)_{n \geq 0} \in \ell^1$ we have $(Kv)_0 = q_1 v_1$ and

$$(Kv)_n = q_{n+1} v_{n+1} + \sum_{k=1}^n h_k (1 - q_{n-k}) v_{n-k}, \quad n = 1, 2, \dots$$

Define the operator

$$Gu = -\varphi u + K(\varphi u) \quad \text{for } u \in \ell_\varphi^1 = \{u \in \ell^1 : \sum_{n=0}^{\infty} \varphi_n |u_n| < \infty\}.$$

There is a substochastic semigroup $\{P(t)\}_{t \geq 0}$ on ℓ^1 such that for each initial probability density function $v \in \ell_\varphi^1$ the equation

$$(3.4) \quad \frac{du}{dt} = G(u), \quad t > 0, \quad u(0) = v,$$

has a nonnegative solution $u(t)$ which is given by $u(t) = P(t)v$ for $t \geq 0$ and

$$(P(t)v)_n = \sum_{j=0}^{\infty} \mathbb{P}_j(X(t) = n, t < T_\infty) v_j, \quad n = 0, 1, \dots$$

The process X is nonexplosive if and only if the semigroup $\{P(t)\}_{t \geq 0}$ is stochastic. Equivalently, the generator of the semigroup $\{P(t)\}_{t \geq 0}$ is the closure of (G, ℓ_φ^1) . In that case the solution $u(t)$ of (3.4) is unique and it is a probability density function for each t , if v has these properties.

The equation for the steady state $p^* = (p_n^*)_{n \geq 0}$ of (3.1) is of the form

$$(3.5) \quad \gamma_{n+1} p_{n+1}^* - \gamma_n p_n^* + \sum_{k=1}^n h_k \lambda_{n-k} p_{n-k}^* - \lambda_n p_n^* = 0, \quad n = 0, 1, \dots$$

Observe that $\gamma_1 p_1^* = \lambda_0 p_0^*$ and that we can rewrite (3.5) as

$$\gamma_{n+1} p_{n+1}^* - \gamma_n p_n^* = \lambda_n p_n^* - \sum_{k=0}^{n-1} h_{n-k} \lambda_k p_k^*, \quad n = 1, 2, \dots$$

Hence

$$\gamma_{n+1} p_{n+1}^* = \sum_{j=0}^n \lambda_j p_j^* - \sum_{j=1}^n \sum_{k=0}^{j-1} h_{j-k} \lambda_k p_k^*$$

and changing the order of summation, we obtain

$$(3.6) \quad p_{n+1}^* = \frac{1}{\gamma_{n+1}} \sum_{k=0}^n \bar{h}_{n-k} \lambda_k p_k^*, \quad n = 0, 1, \dots,$$

where

$$\bar{h}_l = \sum_{j=l+1}^{\infty} h_j, \quad l \geq 0.$$

Thus given p_0^* , equation (3.6) uniquely determines p^* . Consequently, there is one, and up to a multiplicative constant only one, solution of equation (3.5). If $p_0^* > 0$ and either $\bar{h}_l > 0$ for all $l \geq 0$ or $\lambda_l > 0$ for all $l \geq 1$, then $p_n^* > 0$ for all $n \geq 1$. Now, if

$$(3.7) \quad \sum_{n=0}^{\infty} p_n^* = 1 \quad \text{and} \quad \sum_{n=0}^{\infty} (\lambda_n + \gamma_n) p_n^* < \infty,$$

then $p^* \in \ell_\varphi^1$, $G(p^*) = 0$, and $K(\varphi p^*) = \varphi p^*$, which implies that the semigroup $\{P(t)\}_{t \geq 0}$ is stochastic. We have thus proved the following result, which is an analog of Theorem 1 for the discrete bursting model.

THEOREM 2. *Assume condition (3.2) and suppose that a strictly positive $p^* = (p_n^*)_{n \geq 0}$ given by (3.6) satisfies (3.7). Then for each initial probability density function $v = (v_n)_{n \geq 0} \in \ell_\varphi^1$ equation (3.1) has a unique solution which is a probability density function for each $t > 0$ and satisfies*

$$\lim_{t \rightarrow \infty} \sum_{n=0}^{\infty} |(P(t)v)_n - p_n^*| = 0.$$

Remark 1. From (3.6) it follows that

$$\sum_{n=0}^{\infty} \gamma_{n+1} p_{n+1}^* = \sum_{n=0}^{\infty} \sum_{k=0}^n \left(\sum_{j=n-k+1}^{\infty} h_j \right) \lambda_k p_k^* = \sum_{k=0}^{\infty} \sum_{n=k}^{\infty} \left(\sum_{j=n-k+1}^{\infty} h_j \right) \lambda_k p_k^*.$$

The mean value $\mathbb{E}(h)$ of the distribution h can be represented as

$$\mathbb{E}(h) = \sum_{j=0}^{\infty} j h_j = \sum_{n=0}^{\infty} \sum_{j=n+1}^{\infty} h_j.$$

We thus obtain

$$\mathbb{E}(h) = \sum_{n=k}^{\infty} \sum_{j=n-k+1}^{\infty} h_j$$

for each $k \geq 0$. Combining these leads to

$$\sum_{n=0}^{\infty} \gamma_{n+1} p_{n+1}^* = \mathbb{E}(h) \sum_{k=0}^{\infty} \lambda_k p_k^*.$$

3.2. Bursting with a geometric distribution. Next, we give sufficient conditions for (3.7) in the case when h is geometric

$$(3.8) \quad h_k = (1-b)b^{k-1}, \quad k = 1, 2, \dots,$$

with $b \in (0, 1)$. Since

$$\sum_{j=n-k+1}^{\infty} h_j = b^{n-k},$$

we obtain the following equation for $p^* = (p_n^*)_{n \geq 0}$

$$(3.9) \quad \frac{p_{n+1}^*}{p_n^*} = \frac{\lambda_n + b\gamma_n}{\gamma_{n+1}}, \quad n = 0, 1, \dots$$

Explicit stationary solutions in this case were recently obtained in [1]. However, for h geometric, we can go further and prove convergence to this stationary state with the following result which follows from Theorem 2 and Remark 1.

COROLLARY 3. *Assume that condition (3.2) holds. Suppose that h is geometric as in (3.8). Then $p^* = (p_n^*)_{n \geq 0}$ is given by*

$$(3.10) \quad p_n^* = p_0^* \prod_{k=1}^n \frac{\lambda_{k-1} + b\gamma_{k-1}}{\gamma_k} = \frac{p_0^* \lambda_0}{\gamma_n} \prod_{k=1}^{n-1} \frac{\lambda_k + b\gamma_k}{\gamma_k}, \quad n = 1, 2, \dots$$

In particular, if

$$(3.11) \quad \limsup_{n \rightarrow \infty} \frac{\lambda_n}{\gamma_n} < 1 - b \quad \text{and} \quad \liminf_{n \rightarrow \infty} \gamma_n > 0,$$

then the conclusions of Theorem 2 hold.

Example 1. Consider λ_n to be a Hill function of the form

$$(3.12) \quad \lambda_n = \lambda \frac{1 + \Theta n^N}{\Lambda + \Delta n^N}$$

where $\Lambda, \Delta, N > 0$ and $\Theta \geq 0$. If h is geometric and

$$\liminf_{n \rightarrow \infty} \gamma_n > \frac{\lambda \Theta}{\Delta(1-b)},$$

then condition (3.11) holds.

Remark 2 (Bifurcation in the discrete case). Equation 3.9 can be used to examine the bifurcations in the stationary density, defined as changes in the number of maxima,

as a function of the model parameters. The number of maxima are linked to the number of sign changes of

$$(3.13) \quad n \mapsto \lambda_n + b\gamma_n - \gamma_{n+1}.$$

In particular, p^* has a maximum at 0 if $\lambda_0 < \gamma_1$, and each successive sign change of (3.13) gives a maximum/minimum of p^* .

We now provide examples for which the stationary distribution can be identified explicitly. In the following examples we assume that h is geometric with parameter b as in (3.8) and that $\gamma_n = \gamma n$, $n \geq 1$, with $\gamma > 0$.

Example 2 (Negative binomial). Suppose that $\lambda_n = \lambda_0 + \lambda n$ with $\lambda_0 > 0, \lambda \geq 0$. We have $\lambda_n \geq 0$ for each n . Substituting γ_k and λ_k into (3.10) gives

$$p_n^* = \frac{p_0^*}{n!} \prod_{k=0}^{n-1} \left(\frac{\lambda_0}{b\gamma + \lambda} + k \right) \left(\frac{\lambda + b\gamma}{\gamma} \right)^n, \quad n = 0, 1, \dots$$

Thus $p^* \in \ell^1$ if and only if

$$\lambda + b\gamma < \gamma.$$

In that case we obtain the negative binomial distribution

$$p_n^* = \frac{(a)_n}{n!} p^n (1-p)^a, \quad n = 0, 1, \dots,$$

where

$$p = \frac{\lambda + b\gamma}{\gamma}, \quad a = \frac{\lambda_0}{b\gamma + \lambda},$$

and $(a)_n$ is the Pochhammer symbol defined by

$$(a)_n = \frac{\Gamma(a+n)}{\Gamma(a)} = a(a+1)(a+2) \dots (a+n-1), \quad (a)_0 = 1.$$

This was previously obtained in [27].

Example 3 (Mixture of logarithmic distribution). Suppose that $\lambda_0 > 0$ and $\lambda_n = 0$ for $n \geq 1$. Then

$$p_n^* = p_0^* \frac{\lambda_0}{\gamma} \frac{b^{n-1}}{n}, \quad n = 1, 2, \dots,$$

which can be rewritten as

$$p_n^* = -\frac{b^n}{n \ln(1-b)} (1-p_0^*), \quad n = 1, 2, \dots, \quad p_0^* = \frac{b\gamma}{b\gamma - \lambda_0 \ln(1-b)}.$$

The distribution

$$\tilde{p}_0 = 0, \quad \tilde{p}_n = -\frac{b^n}{n \ln(1-b)}, \quad n = 1, 2, \dots,$$

is called a logarithmic distribution.

If we assume that $\lambda_n = 0$ for $n > m$, then we obtain the following distribution

$$p_n^* = p_0^* \frac{b^n}{n!} \prod_{k=0}^{n-1} \left(\frac{\lambda_k}{b\gamma} + k \right), \quad n = 0, \dots, m,$$

and

$$p_n^* = \frac{b^n}{cn} \left(1 - \sum_{j=0}^m p_j^* \right), \quad n > m,$$

where c and p_0^* are such that

$$c = \sum_{j=m+1}^{\infty} \frac{b^j}{j} \quad \text{and} \quad \sum_{j=0}^m p_j^* + p_m^* \frac{mc}{b^m} = 1.$$

In particular, this type of distribution will be obtained if we take $\lambda_0 > 0$, $\lambda < 0$, and

$$\lambda_n = \begin{cases} \lambda_0 + \lambda n, & \text{if } n \leq -\lambda_0/\lambda, \\ 0, & \text{otherwise.} \end{cases}$$

Example 4 (Hypergeometric distributions). We now take

$$(3.14) \quad \lambda_n = \lambda \frac{1 + \Theta n}{\Lambda + \Delta n}$$

where $\lambda > 0$, $\Lambda \geq 1$, $\Theta \geq \Delta$. We find that, for each n ,

$$\frac{\lambda_n + b\gamma n}{\gamma} = \frac{b(n + a_1)(n + a_2)}{n + b_1},$$

where

$$b_1 = \frac{\Lambda}{\Delta}, \quad a_1 = \frac{1}{2}(\alpha - \beta), \quad a_2 = \frac{1}{2}(\alpha + \beta),$$

and

$$\alpha = \frac{\Lambda}{\Delta} + \frac{\lambda\Theta}{b\gamma\Delta}, \quad \beta^2 = \alpha^2 - \frac{4\lambda}{b\gamma\Delta}.$$

Since $\Lambda \geq 1$ and $\Theta \geq \Delta$, we can find a nonnegative β , thus $a_2 \geq a_1 > 0$. Consequently, the stationary distribution is of the form

$$(3.15) \quad p_n^* = \frac{1}{{}_2F_1(a_1, a_2; b_1; b)} \frac{(a_1)_n (a_2)_n}{(b_1)_n} \frac{b^n}{n!}, \quad n = 0, 1, \dots,$$

where ${}_2F_1$ is Gauss' hypergeometric function

$${}_2F_1(a_1, a_2; b_1; x) = \sum_{n=0}^{\infty} \frac{(a_1)_n (a_2)_n}{(b_1)_n} \frac{x^n}{n!}.$$

Example 5 (Generalized hypergeometric distributions). The generalized hypergeometric function ${}_pF_q$ is defined to be the real analytic function on $\mathbb{R}$ given by the series expansion

$${}_pF_q(a_1, \dots, a_p; b_1, \dots, b_q; x) = \sum_{n=0}^{\infty} \frac{(a_1)_n \dots (a_p)_n}{(b_1)_n \dots (b_q)_n} \frac{x^n}{n!}.$$

The negative binomial distribution in Example 2 for the case of $\lambda = 0$ has the probability generating function $s \mapsto {}_1F_0(a_1; bs)/{}_1F_0(a_1; b)$ with $a_1 = \lambda_0/b\gamma$. The distribution obtained in Example 4 has the probability generating function

$$s \mapsto \frac{{}_2F_1(a_1, a_2; b_1; bs)}{{}_2F_1(a_1, a_2; b_1; b)}.$$

Extending both of these examples we suppose that $\lambda_n \geq 0$ is a rational function of n satisfying

$$\frac{\lambda_n + b\gamma n}{\gamma} = \frac{(n + a_1) \dots (n + a_{q+1})b}{(n + b_1) \dots (n + b_q)}, \quad n = 0, 1, 2, \dots$$

Then $p^* = (p_n^*)_{n \geq 0}$ has the probability generating function

$$\frac{{}_{q+1}F_q(a_1, \dots, a_{q+1}; b_1, \dots, b_q; bs)}{{}_{q+1}F_q(a_1, \dots, a_{q+1}; b_1, \dots, b_q; b)}.$$

4. Continuous bursting model.

4.1. The general case. In this section we consider a continuous state space version of the model presented in Section 3, which is a piecewise deterministic Markov process (PDMP) $Y = \{Y(t)\}_{t \geq 0}$ with values in $E = (0, \infty)$ where $Y(t)$ denotes the amount of the gene product in a cell at time t , $t \geq 0$. We assume that protein molecules undergo degradation at a rate γ that is interrupted by production at random times

$$t_1 < t_2 < \dots$$

occurring with intensity φ , and that both φ and γ depend on the current number of molecules. At each t_k a random amount of protein molecules is produced, so that the process changes from $Y(t_k-)$ to $Y(t_k) = Y(t_k-) + e_k$, $k = 1, 2, \dots$, where $\{e_k\}_{k \geq 1}$ is a sequence of random variables such that

$$\Pr(e_k \in B | Y(t_k-) = y) = \int_B h(x, y) dx,$$

where h is a nonnegative measurable function satisfying

$$(4.1) \quad \int_0^\infty h(x, y) dx = 1, \quad y > 0.$$

The time-dependent probability density function $u(t, x)$ is described by the continuous analog of the master equation [14, 15]

$$(4.2) \quad \frac{\partial u(t, x)}{\partial t} = \frac{\partial(\gamma(x)u(t, x))}{\partial x} - \varphi(x)u(t, x) + \int_0^x \varphi(y)u(t, y)h(x - y, y)dy$$

with the initial probability density $u(0, x) = v(x)$, $x > 0$.

We assume that γ is a continuous function such that

$$(4.3) \quad \gamma(x) > 0 \quad \text{for } x > 0, \quad \int_0^\delta \frac{dx}{\gamma(x)} = +\infty,$$

for some $\delta > 0$ and that φ is a nonnegative measurable function with φ/γ being locally integrable on $(0, \infty)$ and satisfying

$$(4.4) \quad \int_0^\delta \frac{\varphi(x)}{\gamma(x)} dx = +\infty.$$

From (4.3) it follows that the differential equation

$$(4.5) \quad x'(t) = -\gamma(x(t)), \quad x(0) = x > 0,$$

has a unique solution which we denote by $\pi_t x$, $t \geq 0$, $x > 0$. For each $x > 0$ we have $\pi_t x > 0$ for all $t > 0$ and $\pi_t x \rightarrow 0$ as $t \rightarrow \infty$. This and condition (4.4) give

$$\int_0^t \varphi(\pi_s x) ds = \int_{\pi_t x}^x \frac{\varphi(y)}{\gamma(y)} dy \rightarrow \infty, \quad \text{as } t \rightarrow \infty,$$

which implies that the function

$$t \mapsto 1 - e^{-\int_0^t \varphi(\pi_s x) ds}$$

is a distribution function of a positive and finite random variable for every $x > 0$.

We now recall the construction of the minimal piecewise deterministic Markov process Y (see e.g. [2, 3] or [32] for details). Let $\{\varepsilon_k\}_{k \geq 1}$ be a sequence of independent random variables exponentially distributed with mean 1, which is also independent of $\{e_k\}_{k \geq 1}$. Set $t_0 = 0$. For each $k = 1, 2, \dots$ and given $Y(t_{k-1})$ the process evolves as

$$(4.6) \quad Y(t) = \begin{cases} \pi_{t-t_{k-1}} Y(t_{k-1}), & t_{k-1} \leq t < t_k, \\ Y(t_{k-}) + e_k, & t = t_k, \end{cases}$$

where $t_k = t_{k-1} + \Delta t_k$ and Δt_k is a random variable such that

$$\Pr(\Delta t_k \leq t | Y(t_{k-1}) = x) = 1 - e^{-\int_0^t \varphi(\pi_s x) ds}, \quad t, x > 0.$$

The random variable Δt_k can be defined with the help of the exponentially distributed random variable ε_k through the equality in distribution

$$\varepsilon_k = \int_0^{\Delta t_k} \varphi(\pi_s Y(t_{k-1})) ds,$$

which can be rewritten as

$$\varepsilon_k = Q(\pi_{\Delta t_k} Y(t_{k-1})) - Q(Y(t_{k-1})),$$

where the non-increasing function Q is given by

$$(4.7) \quad Q(x) = \int_x^{\bar{x}} \frac{\varphi(y)}{\gamma(y)} dy,$$

and $\bar{x} = +\infty$, when the integral is finite or any $\bar{x} > 0$ otherwise. Since $Y(t_k-) = \pi_{\Delta t_k} Y(t_{k-1})$, we obtain the following stochastic recurrence equation for $\{Y(t_k)\}_{k \geq 0}$

$$(4.8) \quad Y(t_k) = Q^{-1}(Q(Y(t_{k-1})) + \varepsilon_k) + e_k, \quad k = 1, 2, \dots,$$

where Q^{-1} is the generalized inverse of Q , $Q^{-1}(r) = \sup\{x : Q(x) \geq r\}$. Consequently, $Y(t)$ is defined by (4.6) for all $t < t_\infty$, where $t_\infty = \lim_{k \rightarrow \infty} t_k$ is the explosion time. As in the discrete state space we can extend the state space E by adding the point -1 and define $Y(t) = -1$ for $t \geq t_\infty$. Let $\mathbb{P}_x$ be the law of the process Y starting at $Y(0) = x$ and denote by $\mathbb{E}_x$ the expectation with respect to $\mathbb{P}_x$.

Remark 3. Note that if condition (4.4) holds (equivalently $Q(0) = \infty$) then the amount of the gene product $\{Y(t_k)\}_{k \geq 0}$ at the jump times is a discrete time Markov process with transition probability function given by

$$\mathcal{K}(y, B) = \int_B k(x, y) dx, \quad B \in \mathcal{B}((0, \infty)),$$

where

$$(4.9) \quad k(x, y) = e^{Q(y)} \int_0^y 1_{(0, x)}(z) h(x - z, z) \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} dz, \quad x, y > 0.$$

If $Q(0) < \infty$ then the random variable Δt_1 is infinite with positive probability, since we have for any $x > 0$

$$\Pr(\Delta t_1 = \infty | Y(0) = x) = \lim_{t \rightarrow \infty} \Pr(\Delta t_1 > t | Y(0) = x) = e^{Q(x) - Q(0)} > 0,$$

which then forces the process $Y(t, \omega)$ starting from $Y(0, \omega) = x$ to be $\pi_t(x)$ for all t , if ω is such that $\Delta t_1(\omega) = \infty$.

In what follows we assume that (4.3) and (4.4) hold. We rewrite equation (4.2) as an abstract Cauchy problem in L^1

$$(4.10) \quad \frac{du}{dt} = \mathcal{C}u, \quad u(0) = v,$$

where the operator

$$(4.11) \quad \mathcal{C}u(x) = \frac{d(\gamma(x)u(x))}{dx} - \varphi(x)u(x) + \int_0^x \varphi(y)u(t, y)h(x - y, y)dy$$

is defined on the domain

$$(4.12) \quad \mathcal{D}(\mathcal{C}) = \{u \in L^1 : \gamma u \in \text{AC}, (\gamma u)' \in L^1, \lim_{x \uparrow \infty} (\gamma(x)u(x)) = 0, \varphi u \in L^1\},$$

and $\gamma u \in \text{AC}$ means that the function $x \mapsto \gamma(x)u(x)$ is absolutely continuous. From [14, 32] it follows that there is a substochastic semigroup $\{P(t)\}_{t \geq 0}$ on L^1 such that for each initial density $v \in \mathcal{D}(\mathcal{C})$ equation (4.10) has a nonnegative solution $u(t)$ which is given by $u(t) = P(t)v$ for $t \geq 0$ and

$$(4.13) \quad \int_0^\infty \mathbb{P}_x(Y(t) \in B, t < t_\infty) v(x) dx = \int_B P(t)v(x) dx$$

for all Borel subsets B of $(0, \infty)$. The semigroup $\{P(t)\}_{t \geq 0}$ is stochastic if and only if its generator $(\mathcal{C}, \mathcal{D}(\mathcal{C}))$ is the closure of the operator $(\mathcal{C}, \mathcal{D}(\mathcal{C}))$.

We first study the fixed points of the semigroup, showing that $\{P(t)\}_{t \geq 0}$ has no more than one invariant density through

PROPOSITION 4. *The substochastic semigroup $\{P(t)\}_{t \geq 0}$ can have at most one invariant density.*

Proof. Recall that u^* is an invariant density for the semigroup $\{P(t)\}_{t \geq 0}$ if and only if it is an invariant density for the resolvent operator

$$Rv := R(1, C)v = \int_0^\infty e^{-t} P(t)v dt.$$

The operator R is substochastic and it satisfies $Rv \geq R_1 v$ for any nonnegative $v \in L^1$ (see [14]), where

$$R_1 v(x) = \frac{1}{\gamma(x)} \int_x^\infty v(y) e^{Q(y)-Q(x)+\int_x^y \frac{1}{\gamma(z)} dz} dy, \quad x > 0.$$

Note that R_1 is the resolvent operator $R(1, A)$ of a substochastic semigroup $\{S(t)\}_{t \geq 0}$ with generator

$$Au(x) = \frac{d(\gamma(x)u(x))}{dx} - \varphi(x)u(x), \quad u \in \mathcal{D}(\mathcal{C}).$$

Since for any two nonnegative and nonzero $v_1, v_2 \in L^1$ we can find $c(v_i) > 0$ such that

$$\int_{c(v_i)}^\infty v_i(y) dy > 0, \quad i = 1, 2,$$

we obtain $Rv_i(x) > 0$ for all $x < \min\{c(v_1), c(v_2)\}$, $i = 1, 2$. Now suppose that u_1, u_2 are densities such that $u = u_1 - u_2$ is nonzero. Then both $u^+ = \max\{0, u\}$ and $u^- = \max\{0, -u\}$ are nonnegative and nonzero. Thus, $R(u^+)(x) > 0$ and $R(u^-)(x) > 0$ for $x < c$ and some $c > 0$. We have

$$|Ru(x)| = |R(u^+)(x) - R(u^-)(x)| \leq R(u^+)(x) + R(u^-)(x) = R(|u|)(x),$$

thus the inequality is strict on a set of positive measure, which implies that if $u_1 - u_2 \neq 0$ then

$$\|Ru_1 - Ru_2\|_1 < \|R|u_1 - u_2|\|_1 \leq \|u_1 - u_2\|_1.$$

Consequently, the operator R can have at most one invariant density. $\square$

Let K be the transition operator on L^1 given by

$$(4.14) \quad Kv(x) = \int_0^\infty k(x, y)v(y)dy, \quad v \in L^1,$$

where the kernel k is as in (4.9). Observe that

$$(4.15) \quad Kv(x) = \int_0^x h(x-z, z) \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} \int_z^\infty v(y) e^{Q(y)} dy dz.$$

A mild condition on the transition operator K , in conjunction with Theorems 3.6 and 5.2 of [32], has interesting consequences for $\{P(t)\}_{t \geq 0}$ as contained in the following result.

PROPOSITION 5. *If the transition operator K is mean ergodic, i.e. for any $v \in L^1$, $v \geq 0$ the sequence*

$$\frac{1}{n} \sum_{j=0}^{n-1} K^j v$$

is convergent in L^1 , then the semigroup $\{P(t)\}_{t \geq 0}$ is stochastic.

In particular, if K has a strictly positive fixed point, i.e. there is v^* such that $Kv^* = v^*$ and $v^* > 0$ a.e., then K is mean ergodic [12]. Note that a mean ergodic stochastic operator has a nonzero fixed point.

We now describe invariant densities for the semigroup $\{P(t)\}_{t \geq 0}$ with the help of fixed points of the operator K .

THEOREM 6. *Let*

$$\overline{H}(x, y) = \int_x^\infty h(z, y) dz, \quad x > 0.$$

Suppose that there is a nonnegative solution u^ of the equation*

$$(4.16) \quad \gamma(x)u^*(x) = \int_0^x \overline{H}(x-y, y)\varphi(y)u^*(y)dy$$

such that $\varphi u^ \in L^1$. Then the function*

$$(4.17) \quad v^*(x) = \int_0^x h(x-y, y)\varphi(y)u^*(y)dy$$

is a fixed point of the operator K in L^1 , where K is as in (4.15). Moreover, if $u^ \in L^1$ then $u^* \in \mathcal{D}(\mathcal{C})$ and $\mathcal{C}(u^*) = 0$, where $\mathcal{C}$ is as in (4.11).*

Conversely, if the operator K has a nonnegative fixed point $v^ \in L^1$ then the function*

$$(4.18) \quad u^*(x) := \frac{1}{\gamma(x)} \int_x^\infty e^{Q(y)-Q(x)} v^*(y) dy$$

is a solution of (4.16) and $\varphi u^ \in L^1$.*

Proof. Let u^* be a solution of (4.16) such that $\varphi u^* \in L^1$. Since

$$\lim_{x \rightarrow \infty} 1_{[y, \infty)}(x) \overline{H}(x-y, y) = 0$$

for each y and $0 \leq 1_{[y, \infty)}(x) \overline{H}(x-y, y) \leq 1$ for all x, y , we obtain

$$\lim_{x \rightarrow \infty} \gamma(x)u^*(x) = \lim_{x \rightarrow \infty} \int_0^x 1_{[y, \infty)}(x) \overline{H}(x-y, y)\varphi(y)u^*(y)dy = 0,$$

by the Lebesgue's dominated convergence theorem. Similarly, we conclude that

$$\lim_{x \rightarrow 0} \gamma(x)u^*(x) = 0.$$

We have

$$\int_0^x \overline{H}(x-y, y)\varphi(y)u^*(y)dy = \int_0^x \varphi(y)u^*(y)dy - \int_0^x \int_0^{x-y} h(z, y)dz\varphi(y)u^*(y)dy.$$

Thus, $\gamma u^* \in \text{AC}$ and

$$(4.19) \quad \frac{d}{dx}(\gamma(x)u^*(x)) = \varphi(x)u^*(x) - \int_0^x h(x-y, y)\varphi(y)u^*(y)dy.$$

The functions φu^* and v^* are integrable. Consequently, if $u^* \in L^1$ then $u^* \in \mathcal{D}(\mathcal{C})$ and $\mathcal{C}(u^*) = 0$. Since

$$v^*(x) = \varphi(x)u^*(x) - \frac{d}{dx}(\gamma(x)u^*(x)) = -e^{-Q(x)} \frac{d}{dx}(e^{Q(x)}\gamma(x)u^*(x)),$$

we obtain

$$\int_z^\infty v^*(x)e^{Q(x)}dx = - \int_z^\infty \frac{d}{dx}(e^{Q(x)}\gamma(x)u^*(x))dx = e^{Q(z)}\gamma(z)u^*(z),$$

which shows that $Kv^*(y) = v^*(y)$, by (4.15).

We now turn to the converse part. Suppose that u^* is as in (4.18), where v^* is a fixed point of K . Since Q is non-increasing and v^* is integrable, we see that

$$\lim_{x \rightarrow \infty} \gamma(x)u^*(x) = 0$$

and that $\varphi u^* \in L^1$. It is easily seen that u^* satisfies equation (4.19). Integrating equation (4.19) with respect to x from z to ∞ leads to

$$\int_z^\infty \frac{d}{dx}(\gamma(x)u^*(x))dx = \int_z^\infty \varphi(x)u^*(x)dx - \int_z^\infty \int_0^x h(x-y, y)\varphi(y)u^*(y)dydx$$

and changing the order of integration in the last integral gives

$$\begin{aligned} \int_z^\infty \int_0^x h(x-y, y)\varphi(y)u^*(y)dydx &= \int_0^z \int_z^\infty h(x-y, y)\varphi(y)u^*(y)dx dy \\ &+ \int_z^\infty \int_y^\infty h(x-y, y)\varphi(y)u^*(y)dx dy. \end{aligned}$$

We have

$$\int_0^z \int_z^\infty h(x-y, y)\varphi(y)u^*(y)dx dy = \int_0^z \bar{H}(z-y, y)\varphi(y)u^*(y)dy$$

and

$$\int_z^\infty \int_y^\infty h(x-y, y)\varphi(y)u^*(y)dx dy = \int_z^\infty \varphi(y)u^*(y)dy.$$

Combining these we conclude that u^* satisfies (4.16). $\square$

The following theorem guarantees that $\{P(t)\}_{t \geq 0}$ is stochastic and its strong convergence to a unique stationary density u^* that is given explicitly.

THEOREM 7. *Suppose that the operator K as in (4.15) has an invariant density $v^* > 0$ a.e. and let*

$$c := \int_0^\infty \frac{1}{\gamma(x)} \int_x^\infty e^{Q(y)-Q(x)} v^*(y) dy dx < \infty.$$

Then the semigroup $\{P(t)\}_{t \geq 0}$ is stochastic and for each initial density v we have

$$\lim_{t \rightarrow \infty} \|P(t)v - u^*\|_1 = 0,$$

where

$$u^*(x) = \frac{1}{c\gamma(x)} \int_x^\infty e^{Q(y)-Q(x)} v^*(y) dy$$

is the unique stationary density of $\{P(t)\}_{t \geq 0}$.

Proof. By Proposition 5, the semigroup $\{P(t)\}_{t \geq 0}$ is stochastic. From Theorem 6 it follows that $u^* \in \mathcal{D}(\mathcal{C})$ and $\mathcal{C}(u^*) = 0$. Thus, u^* is an invariant density for the stochastic semigroup $\{P(t)\}_{t \geq 0}$ and it is unique, by Proposition 4. Since $v^*(x) > 0$ for a.e. $x > 0$, we conclude that $u^*(x) > 0$ for all $x > 0$. From assumptions (4.3) and (4.4) it follows that there is a δ_0 such that $\varphi(y) > 0$ for $y \in (0, \delta_0)$. This and (4.17) imply that

$$\int_0^\infty \int_0^\infty p(x, y) \varphi(y) dy dx > 0, \quad \text{where } p(x, y) = 1_{(0, x)}(y) h(x - y, y).$$

Consequently, we can find $t > 0$ such that the operator $P(t)$ is partially integral [14] and the result follows from Theorem 1. $\square$

We conclude this section with sufficient conditions for mean ergodicity of the transition operator K .

PROPOSITION 8. *Let K be a transition operator K with a bounded kernel k . Suppose that there exist a nonnegative measurable function $V: (0, \infty) \rightarrow [0, \infty)$ which is bounded on bounded subsets of $(0, \infty)$ and constants $a, d > 0$ such that*

$$(4.20) \quad \int_0^\infty V(x) k(x, y) dx \leq V(y) - 1 + a 1_{(0, d)}(y), \quad y > 0.$$

Then the operator K is mean ergodic on L^1 .

Proof. Let $Z_n, n \geq 0$, be a Markov chain with stochastic kernel $\mathcal{K}$ given by

$$\mathcal{K}(y, B) = \int_B k(x, y) dx, \quad y > 0, B \in \mathcal{B}((0, \infty)).$$

Recall that a probability measure μ is invariant for the chain if and only if the measure μ satisfies the equation

$$\mu(B) = \int_0^\infty \mathcal{K}(y, B) \mu(dy)$$

for all Borel measurable sets B . We have

$$\mu(B) = \int_B \int_0^\infty k(x, y) \mu(dy) dx.$$

Thus each invariant probability measure is absolutely continuous with respect to the Lebesgue measure on $(0, \infty)$. Since K is the transition operator corresponding to $\mathcal{K}$, we have

$$\int_B K^j v(x) dx = \int_0^\infty \mathcal{K}^j(y, B) v(y) dy, \quad B \in \mathcal{B}((0, \infty)),$$

where $\mathcal{K}^1(y, B) = \mathcal{K}(y, B)$ and

$$\mathcal{K}^j(y, B) = \int_0^\infty \mathcal{K}^{j-1}(z, B) \mathcal{K}(y, dz), \quad y > 0, j \geq 2.$$

From Theorem 1 and Lemma 1 of [31] it follows that there exist a finite number of invariant probability measures $\mu_1, \dots, \mu_N$ and a finite number of nonnegative functions $L_1, \dots, L_N$ such that $\sum_{i=1}^N L_i(y) = 1$ and

$$(4.21) \quad \frac{1}{n} \sum_{j=1}^n \mathcal{K}^j(y, B) \rightarrow \sum_{i=1}^N L_i(y) \mu_i(B)$$

for all y and all Borel sets B . Let $v_1, \dots, v_N$ be the densities of the invariant measures $\mu_1, \dots, \mu_N$. Now let $v \in L^1$. From (4.21) and the Lebesgue dominated convergence theorem it follows that

$$\lim_{n \rightarrow \infty} \int_B \frac{1}{n} \sum_{j=1}^n K^j v(x) dx = \int_B \sum_{i=1}^N \int_0^\infty L_i(y) v(y) dy v_i(x) dx,$$

for all Borel B . Moreover, the sequence $\frac{1}{n} \sum_{j=1}^n K^j v$ is bounded in L^1 . Thus, it is weakly convergent in L^1 and, by the mean ergodic theorem, it converges in L^1 . $\square$

We now apply the last result to our transition operator K .

COROLLARY 9. *Let K be the transition operator as in (4.15) with bounded h . Suppose that the function*

$$m_1(y) = \int_0^\infty x h(x, y) dx, \quad y > 0,$$

is bounded on bounded subsets of $(0, \infty)$. If

$$(4.22) \quad \limsup_{y \rightarrow \infty} e^{Q(y)} \int_0^y \left(m_1(z) \frac{\varphi(z)}{\gamma(z)} - 1 \right) e^{-Q(z)} dz < 0,$$

then the operator K is mean ergodic.

Proof. Since K has kernel k given by (4.9), we obtain

$$k(x, y) \leq c_1 e^{Q(y)} \int_0^y \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} dz = c_1, \quad x, y > 0,$$

where c_1 is the upper bound for h . By Proposition 8 it is sufficient to check that the function $V(x) = x$, up to a multiplicative constant, satisfies condition (4.20). We have

$$\int_z^\infty V(x) h(x - z, z) dx = m_1(z) + z, \quad z > 0.$$

Thus

$$\int_0^\infty V(x) k(x, y) dx = e^{Q(y)} \int_0^y (m_1(z) + z) \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} dz$$

for all $y > 0$. Since

$$y = e^{Q(y)} \int_0^y z \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} dz + e^{Q(y)} \int_0^y e^{-Q(z)} dz,$$

we obtain

$$\int_0^\infty V(x) k(x, y) dx - V(y) = e^{Q(y)} \int_0^y \left(m_1(z) \frac{\varphi(z)}{\gamma(z)} - 1 \right) e^{-Q(z)} dz,$$

which is a bounded function on sets of the form $(0, d)$. $\square$

Remark 4. Observe that if $Q(\infty) = 0$ and

$$\limsup_{z \rightarrow \infty} \frac{m_1(z) \varphi(z)}{\gamma(z)} < 1$$

then condition (4.22) holds, since we can find $z_0 > 0$ and $\delta > 0$ such that

$$m_1(z) \frac{\varphi(z)}{\gamma(z)} - 1 \leq -\delta \quad \text{for } z \geq z_0,$$

which implies that

$$e^{Q(y)} \int_{y_0}^y \left(m_1(z) \frac{\varphi(z)}{\gamma(z)} - 1 \right) e^{-Q(z)} dz \leq -a e^{Q(y)-Q(y_0)} (y - y_0)$$

for all $y \geq y_0 \geq z_0$ with the right-hand side going to $-\infty$.

If $Q(\infty) = -\infty$ and

$$\limsup_{z \rightarrow \infty} \left(m_1(z) - \frac{\gamma(z)}{\varphi(z)} \right) < 0$$

then condition (4.22) holds as well by d'Hospital's rule.

4.2. Exponentially distributed bursts. Experimental findings in populations of cells indicate that the burst size is often exponentially distributed [33] so we now consider

$$(4.23) \quad h(x, y) = \frac{1}{b} e^{-x/b}, \quad x, y > 0,$$

where $b > 0$. The operator K as defined in (4.15) then takes the form

$$Kv(x) = \int_0^x \frac{1}{b} e^{-(x-z)/b} \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} \int_z^\infty v^*(y) e^{Q(y)} dy dz.$$

Note that the integrable function

$$v^*(x) = e^{-x/b-Q(x)}$$

is a fixed point of the operator K , since

$$Kv^*(x) = e^{-x/b} \int_0^x \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} dz = e^{-x/b-Q(x)}.$$

Again, an explicit stationary solution was recently obtained in [1], and we establish convergence to this stationary state with the following result.

COROLLARY 10. *Assume that conditions (4.3) and (4.4) hold and that h is exponential as in (4.23) with $b > 0$. Suppose that*

$$(4.24) \quad c := \int_0^\infty \frac{1}{\gamma(x)} e^{-x/b-Q(x)} dx < \infty, \quad \int_0^\infty e^{-x/b-Q(x)} dx < \infty.$$

Then the semigroup $\{P(t)\}_{t \geq 0}$ is stochastic and for each initial density v we have

$$\lim_{t \rightarrow \infty} \|P(t)v - u^*\|_1 = 0,$$

where

$$(4.25) \quad u_*(x) = \frac{1}{c\gamma(x)} e^{-x/b-Q(x)}$$

is the unique stationary density of $\{P(t)\}_{t \geq 0}$.

Remark 5. Note that if $Q(0) = \infty$ and

$$\lim_{x \rightarrow \infty} \frac{\varphi(x)}{\gamma(x)} < \frac{1}{b},$$

then the function $x \mapsto e^{-x/b-Q(x)}$ is integrable on $(0, \infty)$. If, additionally,

$$\liminf_{x \rightarrow \infty} \gamma(x) > 0, \quad \lim_{x \rightarrow 0} \frac{e^{-Q(x)}}{\gamma(x)^r} < \infty, \quad \text{and} \quad \int_0^\delta \gamma(x)^{r-1} dx < \infty$$

for some $\delta, r > 0$, then condition (4.24) holds. Furthermore, if it should happen that $b, \gamma(x)$ and $u^*(x)$ are known or can be approximated from data, then it is possible to estimate $\varphi(x)$ from

$$(4.26) \quad \varphi(x) = \frac{1}{b}\gamma(x) + \frac{(\gamma(x)u^*(x))'}{u^*(x)}.$$

Finally, note that if φ is assumed to be bounded, then u^* has an exponential tail, from which we can deduce the parameter b .

Remark 6 (Bifurcation in the continuous case). As in the discrete formulation of the model we can use relation (4.26) to derive bifurcation properties of the stationary density as a function of the relevant parameters. Namely, the number of extrema are linked to the number of solutions of

$$\varphi(x) = \frac{\gamma(x)}{b} + \gamma'(x).$$

In all examples below, we consider a linear degradation function, $\gamma(x) = \gamma x$ with $\gamma > 0$.

Example 6. Consider the function φ of the form

$$(4.27) \quad \varphi(x) = \lambda \frac{1 + \Theta x^N}{\Lambda + \Delta x^N} = \frac{\lambda}{\Delta} + \lambda \left(1 - \frac{\Lambda}{\Delta}\right) \frac{1}{\Lambda + \Delta x^N},$$

where $\lambda, \Lambda, \Delta, N$ are positive constants and $\Theta \geq 0$. Then

$$Q(x) = c_1 - \frac{\lambda}{\gamma\Lambda} \log(x) + \frac{\lambda}{N\Delta\gamma} \left(\frac{\Delta}{\Lambda} - \Theta\right) \log(\Lambda + \Delta x^N),$$

where c_1 is a constant. The stationary density is given by

$$(4.28) \quad u^*(x) = (c\gamma)^{-1} e^{-x/b} x^{\lambda(\gamma\Lambda)^{-1}-1} (\Lambda + \Delta x^N)^\theta,$$

where

$$(4.29) \quad \theta = \frac{\lambda}{N\Delta\gamma} \left(\Theta - \frac{\Delta}{\Lambda}\right).$$

This solution has been extensively studied in terms of numbers of maxima (P-bifurcation) in [15] when $\Theta = 1$. When $\Theta = \Delta = \Lambda = 1$ the density u^* is that of a gamma distribution, as obtained in [6].

Example 7. Consider the case of linear regulation with the function φ of the form

$$\varphi(x) = \lambda_0 + \lambda x,$$

where λ_0, λ are nonnegative constants. If

$$(4.30) \quad \frac{1}{b} > \frac{\lambda}{\gamma} \quad \text{and} \quad \lambda_0 > 0,$$

then u^* is integrable and is given by the gamma distribution

$$(4.31) \quad u^*(x) = \frac{1}{\Gamma(\lambda_0/\gamma)} \left(\frac{1}{b} - \frac{\lambda}{\gamma} \right)^{\lambda_0/\gamma} x^{\frac{\lambda_0}{\gamma}-1} e^{-(\frac{1}{b}-\frac{\lambda}{\gamma})x},$$

which is a continuous approximation of the negative binomial distribution previously obtained, as in [27].

4.3. Other examples. In this subsection we consider some more exactly solvable examples. The class of examples we provide generalizes the exponentially distributed case of h . Let $\nu(y)$ be a positive, decreasing, and absolutely continuous function on $(0, \infty)$ such that $\nu(y) \rightarrow 0$ as $y \rightarrow \infty$. Consider the function

$$(4.32) \quad h(x, y) = -\frac{\nu'(x+y)}{\nu(y)}, \quad y, z > 0.$$

Then for each y the function $x \mapsto h(x, y)$ is a density and

$$h(x-y, y) = -\frac{\nu'(x)}{\nu(y)}, \quad x > y.$$

The operator K can be thus rewritten as

$$Kv(x) = -\int_0^x \frac{\nu'(x)}{\nu(z)} \frac{\varphi(z)}{\gamma(z)} e^{-Q(z)} \int_z^\infty v(y) e^{Q(y)} dy dz.$$

It is easily seen that if the function

$$v^*(x) = -\nu'(x) e^{-Q(x)}$$

is integrable then $Kv^*(x) = v^*(x)$, thus we obtain the following.

COROLLARY 11. *Let h be as in (4.32). Suppose that*

$$c := \int_0^\infty \frac{\nu(x)}{\gamma(x)} e^{-Q(x)} dx < \infty \quad \text{and} \quad -\int_0^\infty \nu'(x) e^{-Q(x)} dx < \infty.$$

Then the semigroup $\{P(t)\}_{t \geq 0}$ is stochastic and for each initial density v we have

$$\lim_{t \rightarrow \infty} \|P(t)v - u^*\|_1 = 0,$$

where

$$u_*(x) = \frac{\nu(x)}{c\gamma(x)} e^{-Q(x)}$$

is the unique stationary density of $\{P(t)\}_{t \geq 0}$.

Remark 7 (Bifurcation in the continuous case—again). As before (see Remark 6), the number of extrema are linked to the number of solutions of

$$\varphi(x) = -\frac{\nu'(x)}{\nu(x)} + \gamma'(x).$$

Note that if it should happen that $\nu(x)$, $\gamma(x)$ and $u^*(x)$ are known or can be approximated from data, then it is possible to estimate $\varphi(x)$ from

$$\varphi(x) = -\frac{\nu'(x)}{\nu(x)}\gamma(x) + \frac{(\gamma(x)u^*(x))'}{u^*(x)}.$$

If $m_1(x) = \int_0^\infty zh(z, x)dz < \infty$, then only the knowledge of $m_1(x)$ is sufficient as

$$-\frac{\nu'(x)}{\nu(x)} = \frac{1 + m_1'(x)}{m_1(x)}.$$

In the examples below, we take a linear degradation function $\gamma(x) = \gamma x$, with $\gamma > 0$.

Example 8. Suppose that the function ν is of the form

$$\nu(x) = (\alpha + x)^{-\beta}$$

where $\alpha, \beta > 0$ and that the function φ is of the form (4.27). If

$$\beta > \frac{\lambda\Theta}{\gamma\Delta} + 1$$

then the assumptions of Corollary 11 are satisfied and the stationary density u^* is given by

$$u^*(x) = \frac{1}{c\gamma}(\alpha + x)^{-\beta}x^{\lambda(\gamma\Delta)^{-1}-1}(\Lambda + \Delta x^N)^\theta,$$

where θ is as in (4.29).

Example 9. Suppose that the function ν is of the form

$$\nu(x) = e^{-(\alpha x + \beta x^2)},$$

where $\alpha, \beta > 0$. Consider the case of linear regulation with the function φ of the form

$$\varphi(x) = \lambda_0 + \lambda_1 x,$$

where λ_0, λ_1 are nonnegative constants. If

$$\lambda_0 > 0,$$

then u^* is integrable and is given by

$$u^*(x) = \frac{1}{c\gamma}x^{\frac{\lambda_0}{\gamma}-1}e^{-(\alpha-\frac{\lambda_1}{\gamma})x-\beta x^2}.$$

Consider the case of quadratic regulation with the function φ of the form

$$\varphi(x) = \lambda_0 + \lambda_1 x + \lambda_2 x^2,$$

where $\lambda_0, \lambda_1, \lambda_2$ are nonnegative constants. If

$$\beta > \frac{\lambda_2}{2\gamma} \quad \text{and} \quad \lambda_0 > 0,$$

then u^* is integrable and is given by

$$u^*(x) = \frac{1}{c\gamma} x^{\frac{\lambda_0}{\gamma}-1} e^{-(\alpha-\frac{\lambda_1}{\gamma})x-(\beta-\frac{\lambda_2}{2\gamma})x^2}.$$

Example 10. Suppose that the function ν is of the form

$$\nu(x) = (\alpha - x)^\beta,$$

where $\alpha, \beta > 0$, for all $x < \alpha$, and $\nu(x) = 0$ for $x \geq \alpha$. Suppose the function φ is given by (4.27) where $\lambda, \Lambda, \Delta, N$ are positive constants and $\Theta \geq 0$. Then the stationary density u^* is integrable and is given by, for all $x < \alpha$,

$$u^*(x) = \frac{1}{c\gamma} (\alpha - x)^\beta x^{\lambda(\gamma\Lambda)^{-1}-1} (\Lambda + \Delta x^N)^\theta,$$

where θ is as in (4.29). Convergence is obtained in the state space $(0, \alpha)$.

5. Conclusions and summary. In this paper we have presented both a discrete Markov process formulation as well as a continuous model formulation for bursting gene expression. Our development of the discrete model formulation in Section 3.1 allowed us to prove a very general convergence result in Theorem 2 and then to use that result to explore a variety of examples in Section 3.2 when the burst amplitude is geometrically distributed. In Section 4 we developed the analogous continuous model for bursting expression. Section 4.1 contains the general development with Proposition 4 limiting the number of invariant densities of the semigroup $\{P(t)\}_{t \geq 0}$, while Proposition 5 uses mean ergodicity of the transition operator K to show that $\{P(t)\}_{t \geq 0}$ is stochastic. Theorems 6 and 7 give criteria for a unique stationary density u^* of $\{P(t)\}_{t \geq 0}$ and for convergence to that stationary density. In Section 4.2 we have used these results in a number of specific examples when the burst amplitudes are exponentially distributed—a situation often noted experimentally. Section 4.3 concludes with an examination of a generalization of the exponential distribution of burst amplitudes.

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