Stochastic analysis of the motion of DNA nanomechanical bipeds

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Abstract

In this paper we formulate and analyze a Markov process modeling the motion of DNA nanomechanical walking devices. We consider a molecular biped restricted to a well-defined one-dimensional track and study its asymptotic behavior. Our analysis allows for the biped legs to be of different molecular composition and thus to contribute differently to the dynamics. Our main result is a functional central limit theorem for the biped with an explicit formula for the effective diffusivity coefficient in terms of the parameters of the model. A law of large numbers, a recurrence/transience characterization and large deviations estimates are also obtained. Our approach is applicable to a variety of other biological motors such as myosin and motor proteins on polymer filaments.

Keywords: DNA nanodevices, molecular spiders, controlled random walks, Markov additive processes, law of large numbers, recurrence-transience criteria, large deviations, central limit theorem, regeneration structure.

1 Introduction

Biological molecular motors are of fundamental importance for a variety of cell and tissue level processes. Nanomotors such as polymerases move along one-dimensional DNA templates in assembling messenger RNA macromolecules, while micromotors such as proteins of the myosin family are responsible for actin-based cell motility and the transport of cargo inside cells [7, 13]. Identifying the biochemical control mechanisms regulating such biological motor activities is the subject of current research activity in cellular and molecular biology [18], and different mathematical approaches have been recently employed in elucidating possible mechanisms at work [10, 17].

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Research in biological motors in conjunction with recent advances in DNA nanofabrication technology have spurred a lot of interest in biomimetic nanomotor design and DNA-based devices, such as nanomechanical switches and DNA templates for the growth of semiconductor nanocrystals to name a few [19]. Research activity in this area has been focused on designing and controlling dynamic DNA nanomachines that can be activated by and respond to specific chemical signals in their environment, thus expanding on the biochemical paradigm of eukaryotic and prokaryotic cells [14]. Potential applications of such synthetic molecular machinery include DNA-based computing and engineered DNA motors designed for intelligent drug delivery along other *in vivo* therapeutic applications [3, 12].

Currently, there exist two types of molecular designs implementing DNA-based walking devices. Both designs are based on control mechanisms that rely on nucleic acid hybridization, and the corresponding molecular constructs can be bipedal or multipedal with the latter sometimes referred to as molecular spiders [12]. In the first implementation approach, devised by Sherman & Seeman [15], the walking device consists of two double helical domains (the device legs) connected by flexible linker regions. The construct is held on a self-assembled, one-dimensional path by DNA set strands with nucleic acid domains complementary to molecular imprints on the device legs and the substrate. In this context, the detachment of a leg from the path during a walk cycle is mediated by the removal of the set strand through a hybridization reaction [14, 15].

A more recent molecular design by Pei *et al.* [12] does not require the presence of interface strands in that it allows for each device leg to be directly attached to the substrate through Watson-Crick base pair formation. Leg detachment during the walk cycle is controlled by the cleavase activity of nucleic acid domains imprinted on the leg. This latter attribute of the system leads to a random walk of the device on the substrate, dictated by the stochastic events of leg detachment and relocation. Specific aspects of the long-term dynamics of this random walk have been investigated mathematically by Antal *et al.* [2] and Antal & Krapivsky [1], who have derived explicitly the mean velocity and the diffusion coefficient of the walker under specific conditions on leg relocation rates. Another related work on a molecular spider random walk in a general setting is the recent paper by Gallesco, Müller and Popov [5].

In this paper we prove a strong law of large numbers and a functional central limit theorem for the location of the biped with explicit expressions for the asymptotic velocity and limiting variance. Our work focuses on the computation of the variance in the central limit theorem and generalizes the results of Antal *et al.* [2]. The latter is based on the existence of various symmetries in the definition of the underlying random walk, whereas our analysis relies on a different approach and is not restricted by such assumptions. The existence of a law of large numbers and a functional central limit theorem for the model follows from general theory of regenerative processes. Indeed, the model obeys a regenerative structure, which allows to represent it as a sum of independent and identically distributed parts or fragments, each such part corresponding to the restriction of the process to the time interval between two consecutive (random) regeneration times. However, the shortcoming of this purely probabilistic method lies in the quantitative analysis. Although it provides a theoretical expression for the variance in the central limit theorem, this expression is not useful for the actual computation or estimation of the variance, which is crucial for applications. Furthermore, a prominent feature in the regenerative setting is that the variance in the central limit theorem differs from the so-called "averaged variance" experienced by the process, a phenomenon known in the literature as effective diffusivity, and the regenerative approach does not provide the means to study it.

In this context, we employ an analytic framework presented recently by Ben-Ari and Neumann in [4], and which is based on the analysis of the generating function of additive functionals associated with an underlying finite Markov chain. It is well known that the formula for the limiting diffusivity appearing in CLT for mixing additive functionals of Markov chains contains a "generalized inverse" of the generator (see for instance a general result in Theorem 7.6 in Chapter 7 of [6]). In [4] the authors establish a link between the moment generating function and perturbations to the Perron eigenvalue for specific matrices and the generalized inverse. Furthermore, they provide an efficient method for computing these quantities in terms of expectations of hitting times. In our case, these ultimately lead to the desired results.

The remainder of the paper is organized as follows. The random walk formalism of the model is described in Section 2.1. In Section 2.2 we present the theoretical results obtained through the purely probabilistic regenerative approach. The analytic viewpoint is presented in Section 2.3, then followed by estimates on the variance, and an explicit formula for the variance, Sections 2.4 and 2.5, respectively. In Section 2.6 we present some examples.

2 Random walk analysis of the motion of DNA bipeds

2.1 Random walk formalism

We consider a continuous time random walk modeling the motion of a DNA biped on a one-dimensional walking path (see also [2] and [1, 5]). The legs of the biped are assumed to move on a discrete (integer) lattice representing the nucleic acid binding domains imprinted on the path. The waiting time for each leg follows an exponential distribution, with different legs being in general associated with different exponential clocks. The system is characterized by five parameters: (a) four parameters accounting for the transition rate probabilities corresponding to the relocation of each leg (two legs and two possible movement directions) and (b) the maximum possible distance between legs. The latter parameter represents a mechanical restriction imposed by the design of the molecular construct, whereas the transition rate probabilities for leg movements encode information on the interactions of the legs with the substrate path.

Let α denote the transition rate for the left leg moving to the left and β be the corresponding transition rate for the left leg moving to the right. Similarly, let λ and μ be the transition rate probabilities for the right leg moving to the left/right, respectively. The mechanical constraint is that the right leg is always between 0 and S units to the right of the left leg, where $S \in \mathbb{N}$ is some fixed parameter. Whenever a clock ticks, an attempt to move is made by the corresponding leg in the corresponding direction. The attempt succeeds if the new leg configuration satisfies the mechanical constraint. We denote the position of the left and right legs of the spider at time $t \in \mathbb{R}_+$ by $X^{(1)}(t)$ and $X^{(2)}(t)$, respectively. Note that neither $X^{(1)}$ nor $X^{(2)}$ is a Markov chain. However, the pair $(X^{(1)}, X^{(2)})$ is a Markov chain. Figure 1 shows the transition rates and the state space for the Markov chain $(X^{(1)}, X^{(2)})$,

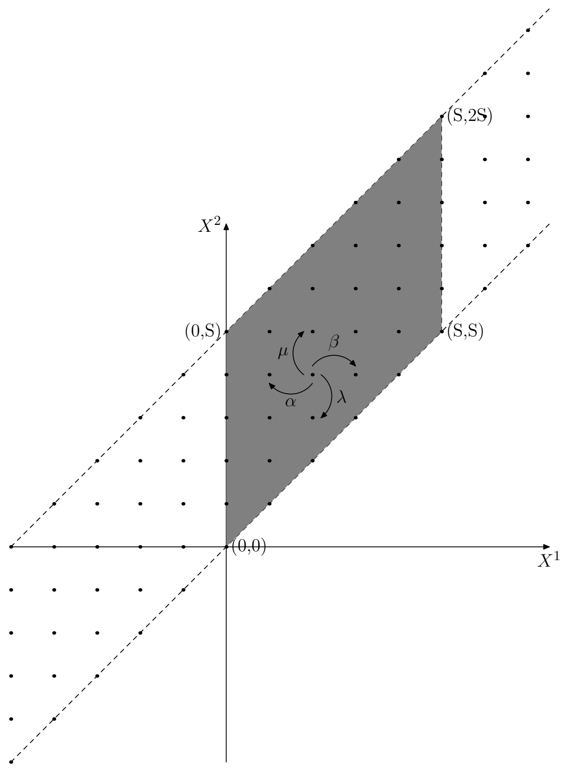

Figure 1: State space for the Markov chain $(X^{(1)}, X^{(2)})$

consisting of all points in $\mathbb{Z}^2$ between the two dashed diagonal lines. For each state, the horizontal coordinate describes $X^{(1)}$ (left leg) and the vertical coordinate describes $X^{(2)}$ (right leg). Note that the transition rates at each site to each of the allowed directions depend only on the direction.

2.2 The regenerative viewpoint

Let $Y(t) = X^{(2)}(t) - X^{(1)}(t)$ denote the process corresponding to the distance between the left and the right leg. Then Y is a pure birth and death Markov chain on $\{0, \ldots, S\}$ with rates $x = \alpha + \mu$ to the right and $y = \beta + \lambda$ to the left. A significant amount of information for the asymptotic behavior of $X^{(2)}(t)$ can be derived using a renewal structure induced by Y, defined by successful return times of this chain to a distinguished state, say S. More precisely, let $\tau_0 = 0$ and $\tau_k = \inf\{t > \tau_{k-1} : Y(t) = S\}$ for $k \in \mathbb{N}$. Let $N_t = \sup\{k \in \mathbb{N} : \tau_k < t\}$ be the number of returns to S prior time $t > 0$.

The following lemma and the corollary to this lemma are standard, and their proof is thus omitted (see for instance [16] in the context of random walks in a random environment and [8] in the context of excited random walks in dimension one).

Lemma 2.1. *We have:*

(i) Time intervals $(\tau_n - \tau_{n-1})_{n\geq 1}$ are independent random variables, moreover all of them besides maybe $\tau_1 - \tau_0$ are identically distributed.

(ii) Path fragments $(X_t^{(2)} : \tau_{n-1} \le t < \tau_n)_{n\ge 1}$ *are independent, moreover all of them except maybe the first one* $(X_t^{(2)} : t < \tau_1)$ *are identically distributed.*

Let $D(\mathbb{R}_+;\mathbb{R})$ denote the set of real-valued functions on $\mathbb{R}_+$, which are right-continuous and possess left limits. We endow this set with the Skorokhod topology and its Borel σ-field.

Corollary 2.2.

(i) (strong law of large numbers)

$$\mathrm{v} = \lim_{t\to\infty} \frac{X_t^{(2)}}{t} = \frac{E(X_{\tau_2}^{(2)} - X_{\tau_1}^{(2)})}{E(\tau_2 - \tau_1)} \in (-\infty, \infty), \ \ a.s.$$

(ii) (recurrence/transience dichotomy)

(a) If $\mathrm{v} > 0$, *then* $\lim_{t\to\infty} X^{(2)}(t) = \infty$, *a.s.*

(b) If $\mathrm{v} = 0$, *then* $\liminf_{t\to\infty} X^{(2)}(t) = -\infty$ *and* $\limsup_{t\to\infty} X^{(2)}(t) = \infty$, *a.s.*

(c) If $\mathrm{v} < 0$, *then* $\lim_{t\to\infty} X^{(2)}(t) = -\infty$, *a.s.*

(iii) (functional central limit theorem) For $t \ge 0$, *define a process* $W^{(t)}$ *in* $D(\mathbb{R}_+, \mathbb{R})$ *by setting*

$$W^{(t)}(s) = \frac{\big(X_{ts}^{(2)} - ts\mathrm{v}\big)}{\sqrt{t}}, \qquad s \ge 0.$$

Then $W^{(t)}$ *converges in law in the space* $D(\mathbb{R}_+, \mathbb{R})$, *as* $t \to \infty$, *to Brownian motion with diffusivity coefficient* $\sigma_{eff}^2 \in (0, \infty)$ *given by*

$$\sigma_{eff}^2 = \frac{E\big([X_{\tau_2}^{(2)} - X_{\tau_1}^{(2)} - \mathrm{v}(\tau_2 - \tau_1)]^2\big)}{E(\tau_2 - \tau_1)}.$$

The subscript eff stands for "effective", and the reason for using this term is explained in the next section, immediately below Theorem 2.4. The law of large numbers is complemented by a large deviation principle (see for instance [9] or Remark (ii) in [11, p. 594]).

Proposition 2.1. *There exists a convex lower semi-continuous rate function* $J : \mathbb{R} \to \mathbb{R}$ *such that*

(i) $J(\mathrm{v}) = 0$, *and* $J(u) > 0$ *for* $u \ne \mathrm{v}$.

(ii) $\lim_{t\to\infty} \frac{1}{t} \log P\big(X_t \ge tu\big) = -J(u)$ *for all* $u > \mathrm{v}$.

(iii) $\lim_{t\to\infty} \frac{1}{t} \log P\big(X_t \le tu\big) = -J(u)$ *for all* $u < \mathrm{v}$.

2.3 The analytic viewpoint

Our analysis is based on the observation that $X^{(2)}$ is an additive functional of a process on a finite state space, the reduction of $(X^{(1)}, X^{(2)})$ to some appropriately defined torus. To illustrate this idea, consider a Markov chain on the vertices of a triangle with jump rates 1 from each vertex to any other vertex. If one counts the number of jumps in the clockwise direction minus the number of jumps in the counterclockwise direction up to time t, then the resulting process is an additive functional, which has the same distribution as the nearest neighbor random walk on $\mathbb{Z}$ with jump rates 1 between two neighbors. Here the triangle serves as the torus and the random walk is the additive functional.

Let D be the parallelogram in $\mathbb{Z}^2$ whose vertices are $(0,0)$, (S,S), $(S,2S)$ and $(0,S)$. The shaded region in Figure 1 represents D. Let Z be the Markov chain $(X^{(1)}, X^{(2)})$ modulo D. That is, $Z = (Z^1, Z^2)$ is the nearest neighbor Markov chain on D with rates to the left and right equal to α and β, respectively, and rates for moving downwards and upwards equal to λ and μ, respectively. Additionally, we allow jumps to the left from $(0,i)$, $i \leq S-1$ to $(S, i+S+1)$ at rate α, and we allow jumps to the right from $(S, i+S+1)$ to $(0,i)$ at rate β. We observe then that the difference process $Z^2(t) - Z^1(t)$ coincides with $Y(t)$.

We further observe that the displacement $X^{(2)}(t) - X^{(2)}(0)$ has the same distribution as the number of jumps Z upwards minus the number of jumps downwards, until time t (or the difference between the number of jumps Z^2 performs to the right and the number of jumps it performs to the left, up to time t). This is an additive functional of Z, which we denote here by $I(t)$. Fix $\eta \in \mathbb{R}$ define the family of linear operators $\mathcal{T}^\eta = \{\mathcal{T}^\eta_t : t \in \mathbb{R}_+\}$ on $\mathbb{R}^{S+1}$ by letting

$$\mathcal{T}^\eta_t f(u) = E_u e^{\eta I(t)} f(Z(t)).$$

By setting $f = \delta_{u'}$ for some $u' \in D$, it follows that $\mathcal{T}^\eta$ has an infinitesimal generator $\mathcal{L}^\eta$, defined by $\mathcal{L}^\eta f(u) = \sum_{u'} \eta(u,u') f(u')$, where the rates $\eta(u,u')$ are non zero only if $u = u'$ or u' is one step away from u and then $\eta(u,u')$ is given by the following table:

u' relative to u	-1	+1
horizontal	α	β
vertical	$\lambda e^{-\eta}$	μe^{η}

Note that $\eta(u,u) = \lim_{t\to 0} \frac{1}{t}[E_u \delta_u(Z(t)) - 1] = \frac{d}{dt} P_u(X(t) = u)|_{t=0}$, and is then equal to $-(\alpha+\mu)$ when $u = (i,i)$, to $-(\beta+\lambda)$ if $u = (i, i+S)$ and is equal to $-(\alpha+\beta+\lambda+\mu)$ otherwise. As a result, $\eta((i,j),(i',j')) = \eta(i'-i, j'-j)$, which in turn implies that if $\varphi(i,j) = \varphi(j-i)$ then $(\mathcal{L}^\eta \varphi)(i,j)$ is also a function of $j-i$. In particular, it follows that for all $t \in \mathbb{R}_+$, $\mathcal{T}^\eta_t \mathbf{1}(i,j) = E_{(i,j)} e^{\eta I(t)}$ is a function of $j-i$. Let then $\varphi_t(s) = E_{(i,i+s)} e^{\eta I(t)}$ for some arbitrary i. It follows that $\frac{d}{dt}\varphi_t(s) = A(\eta)\varphi_t(s)$, where $A(\eta)$ is the following matrix, whose rows and columns are indexed from 0 to S:

$$A(\eta) = \begin{pmatrix} -x & x(\eta) & & & & \\ y(\eta) & -(x+y) & x(\eta) & & & \\ & \ddots & \ddots & \ddots & & \\ & & & & & \\ & & & \ddots & \ddots & \\ & & & y(\eta) & -(x+y) & x(\eta) \\ & & & & y(\eta) & -y \end{pmatrix}.$$

Here $x(\eta) = \alpha + \mu e^{\eta}$ and $y(\eta) = \beta + \lambda e^{-\eta}$. Clearly, $x = x(0),\ y = y(0)$. In what follows we write A, A', and A'' for $A(0), A'(0)$, and $A''(0)$, respectively. Now that A is the generator of Y. Let π denote its invariant distribution. Then $A^t\pi = 0$. Equivalently, π satisfies the detailed balance condition

$$y\pi_{i+1} = x\pi_i, \quad i = 0, \ldots, S-1. \tag{1}$$

Let $\Lambda(\eta)$ denote the Perron eigenvalue of $A(\eta)$. It follows from [4, Theorem 5] that

Proposition 2.2. *For all θ in some neighborhood of* 0*,*

$$\lim_{t\to\infty} E\exp\left(\theta\frac{X^{(2)}(t) - \Lambda'(0)t}{\sqrt{t}}\right) = e^{\frac{1}{2}\Lambda''(0)\theta^2}.$$

This implies

Corollary 2.3.

1. *(Strong law of Large Numbers)* $\frac{X^{(2)}(t)}{t} \underset{t\to\infty}{\to} \Lambda'(0)$ *almost surely.*

2. *(Central Limit Theorem)* $\frac{X^{(2)}(t)-\Lambda'(0)t}{\sqrt{t}} \underset{t\to\infty}{\to} \mathcal{N}\big(\Lambda''(0)\big)$ *in distribution, where $\mathcal{N}(\sigma^2)$ denotes the centered normal distribution with variance σ^2.*

Thus, comparing Corollary 2.3 with Corollary 2.2, we conclude that $\mathrm{v} = \Lambda'(0)$ and $\sigma^2_{eff} = \Lambda''(0)$. We comment that the analytical approach also leads to an expression for the rate function J of Proposition 2.1, in the form $J(u) = \Lambda(\theta_u) - \theta_u u$, where θ_u is the unique solution to $\Lambda'(\theta_u) = u$. However, since this expression is not local and therefore does not fall into the realm of perturbative study of Λ, we will not discuss it further here.

Next we obtain explicit expressions for $\Lambda'(0)$ and $\Lambda''(0)$. We need to recall the notion of the group inverse, also known as the generalized inverse of the non-invertible matrix A. The Euclidean space $\mathbb{R}^{S+1}$ can be represented as the following direct sum of two A-invariant subspaces: $\mathbb{R}^{S+1} = \mathrm{Span}\{\mathbf{1}\} \oplus V_0$, where $V_0 = \{f : \langle f, \pi\rangle = 0\}$, and A is one-to-one on V_0. Let $A^{\#}$ denote the inverse of $-A$ on V_0 and extend it to $\mathbb{R}^{S+1}$ by letting $A^{\#}\mathbf{1} = 0$. Then $A^{\#}$ is the group inverse of $-A$ and for each $f \in \mathbb{R}^{S+1}$, $A^{\#}f$ is the unique solution $u \in V_0$ to $Au = -f_\perp$, where $f_\perp$ is the projection on V_0 defined through

$$f_\perp = f - \langle f, \pi\rangle, f \in \mathbb{R}^{S+1}. \tag{2}$$

We have:

Theorem 2.4.

1. *$\Lambda'(0) = \mu(1-\pi_S) - \lambda(1-\pi_0)$.*
2. *Let $\rho = \frac{y}{x}$ and*

$$Q = \begin{pmatrix} \rho\pi_0 A^{\#}_{0S} & -\frac{1}{2}(\rho\pi_0 A^{\#}_{00} + \rho^{-1}\pi_S A^{\#}_{SS}) \\ -\frac{1}{2}(\rho\pi_0 A^{\#}_{00} + \rho^{-1}\pi_S A^{\#}_{SS}) & \rho^{-1}\pi_S A^{\#}_{S0} \end{pmatrix}.$$

Then

$$\Lambda''(0) = \mu(1-\pi_S) + \lambda(1-\pi_0) + 2\Big\langle Q\begin{pmatrix}\mu\\ \lambda\end{pmatrix}, \begin{pmatrix}\mu\\ \lambda\end{pmatrix}\Big\rangle.$$

A probabilistic interpretation of this result can be obtained as follows. Recall that π is the invariant distribution for the birth-death process $Y = X^{(2)} - X^{(1)}$. At each site of this process (distance between biped legs), the right leg experiences a local drift. The drift is equal to μ at 0, to $-\lambda$ at S, and to $\mu - \lambda$ at any other state of Y. It follows that the average local drift is

$$\mathrm{v} = (\mu-\lambda)(1-\pi_0-\pi_S) + \pi_0\mu - \pi_S\lambda,$$

which coincides with the expression for $\Lambda'(0)$ given in the statement of Theorem 2.4. Similarly, at each site the right-leg experiences a "local variance" or diffusivity, equal to μ at 0, λ at S, and to $\mu+\lambda$ at all other states of Y. Thus, the "average variance" is given by

$$\sigma^2_{ave} := (\mu+\lambda)(1-\pi_0-\pi_S) + \mu\pi_0 + \lambda\pi_S = \mu(1-\pi_S) + \lambda(1-\pi_0).$$

This is the first term in the expression for $\Lambda''(0)$. We show in Theorem 2.5 that the entries of Q are strictly negative, hence the real, effective variance, $\sigma^2_{eff} = \Lambda''(0)$ is strictly less than σ^2_{ave}. The reason for this inequality is the restrictions imposed on the motion of the biped when the configuration process $Y(t)$ is at one of the two extremal states, 0 or S. The appearance of the term containing Q in the formula for limiting variance is a general phenomenon which is due to an interaction (dependence through the configurations) between successive displacement of the process $X^{(2)}(t)$ (see for instance Chapter 7 in [6] for general results of this type).

Proof of Theorem 2.4. Let $\varphi(\eta)(\cdot)$ denote the eigenvector for $A(\eta)$ corresponding to the Perron eigenvalue $\Lambda(\eta)$, normalized to satisfy

$$\langle\varphi(\eta), \pi\rangle = 1. \tag{3}$$

Note that $\varphi(0) = \mathbf{1}$. Then

$$\Lambda(\eta) = \langle A(\eta)\varphi(\eta), \pi\rangle.$$

Differentiating both sides yields

$$\Lambda'(\eta) = \langle A'(\eta)\varphi(\eta), \pi\rangle + \langle A(\eta)\varphi'(\eta), \pi\rangle. \tag{4}$$

Set $\eta = 0$. Then the second term on the left-hand side is equal to $\langle \varphi'(0), A^T\pi\rangle = 0$. Therefore,

$$\Lambda'(0) = \langle A'\mathbf{1}, \pi\rangle.$$

Let $e_0, e_1, \ldots, e_S$ denote the standard unit vectors in $\mathbb{R}^{S+1}$, and let $e_j = 0$ for $j < 0$ or $j > S$. Define the left and right shift operators on $\mathbb{R}^{S+1}$ by letting $\Theta_l e_j = e_{j+1}$, $\Theta_r e_j = e_{j-1}$, and then expanding the definitions to the whole $\mathbb{R}^{S+1}$ by using the linearity. Observe then that $A' = \mu\Theta_l - \lambda\Theta_r$. In particular, $A'\mathbf{1} = \mu(1-\delta_S) - \lambda(1-\delta_0)$. It follows that

$$\Lambda'(0) = \mu(1-\pi_S) - \lambda(1-\pi_0).$$

Next, differentiate both sides of the equation $A(\eta)\varphi(\eta) = \Lambda(\eta)\varphi(\eta)$ at $\eta = 0$ to obtain $A'\mathbf{1} + A\varphi'(0) = \Lambda'(0)\mathbf{1}$. Therefore $A\varphi' = -A'\mathbf{1} + \Lambda'(0)\mathbf{1} = -(A'\mathbf{1} - \langle A'\mathbf{1}, \pi\rangle) = -(A'\mathbf{1})_\perp$, where the projector operator $\perp$ is defined in (2). Furthermore, it follows from (3) that $\varphi' \in V_0$. Thus,

$$\varphi' = A^\# A'\mathbf{1}.$$

Returning to the computation of $\Lambda''(0)$, differentiate (4) to obtain

$$\Lambda''(\eta) = \langle A''(\eta)\varphi(\eta), \pi\rangle + 2\langle A'(\eta)\varphi'(\eta), \pi\rangle + \langle A(\eta)\varphi''(\eta), \pi\rangle.$$

Evaluate this expression at $\eta = 0$. Then the second term on the left-hand side is equal to $\langle \varphi''(0), A^T\pi\rangle = 0$, and so we obtain

$$\Lambda''(0) = \langle A''\mathbf{1}, \pi\rangle + 2\langle A' A^\# A'\mathbf{1}, \pi\rangle.$$

Next, observe that $A'' = \mu\Theta_l + \lambda\Theta_r$, therefore $A''\mathbf{1} = \mu(1-\delta_S) + \lambda(1-\delta_0)$. This gives

$$\langle A''\mathbf{1}, \pi\rangle = \mu(1-\pi_S) + \lambda(1-\pi_0).$$

Using again the equality $A' = \mu\Theta_l - \lambda\Theta_r$, we obtain $A'\mathbf{1} = \mu(1-\delta_S) - \lambda(1-\delta_0)$. Thus, we obtain

$$\begin{aligned} A' A^\# A'\mathbf{1} &= A'(\lambda A^\#\delta_0 - \mu A^\#\delta_S) \\ &= \mu\lambda\Theta_l A^\#\delta_0 - \mu^2\Theta_l A^\#\delta_S - \lambda^2\Theta_r A^\#\delta_0 + \mu\lambda\Theta_r A^\#\delta_S. \end{aligned} \tag{5}$$

Next, observe that

$$\langle \Theta_l v, \pi\rangle = \sum_{j=0}^{S} v_{j+1}\pi_j = \rho\sum_{j=0}^{S} v_{j+1}\pi_{j+1} = \rho(\langle v, \pi\rangle - v_0\pi_0),$$

and similarly

$$\langle \Theta_r v, \pi \rangle = \sum_{j=0}^{S} v_{j-1}\pi_j = \rho^{-1} \sum_{j=0}^{S} v_{j-1}\pi_{j-1} = \rho^{-1}(\langle v, \pi\rangle - v_S \pi_S).$$

Now since $A^{\#}u \in V_0$ for all u, it follows that

$$\langle \Theta_l A^{\#} u, \pi \rangle = -\rho (A^{\#}u)_0 \pi_0, \quad \langle \Theta_r A^{\#} u, \pi \rangle = -\rho^{-1} (A^{\#}u)_S \pi_S.$$

Plugging this into (5) we obtain

$$\langle A' A^{\#} A' \mathbf{1}, \pi \rangle = -\mu\lambda\rho\pi_0 A^{\#}_{00} + \mu^2 \rho \pi_0 A^{\#}_{0S} + \lambda^2 \rho^{-1} \pi_S A^{\#}_{S0} - \mu\lambda\rho^{-1}\pi_S A^{\#}_{SS}, \tag{6}$$

completing the proof of Theorem 2.4 □

2.4 Bounds on variance in CLT

Theorem 2.5.

1. *The entries of Q are strictly negative.*
   In particular, $\Lambda''(0) < \mu(1-\pi_S) + \lambda(1-\pi_0)$.
2. $\Lambda''(0) \geq \frac{\mu\alpha}{\mu+\alpha}(1-\pi_S) + \frac{\lambda\beta}{\lambda+\beta}(1-\pi_0)$.

We note that the lower bound is attained when $\alpha = \beta = \lambda = \mu$, see Section 2.6.1.

Proof of Theorem 2.5. From [4, Corollary 1] we have

$$A^{\#}_{ij} = \pi_j \Big(\sum_{k \neq j} \pi_k E_k \sigma_j - \delta_{i\neq j} E_i \sigma_j\Big),$$

where E_k denotes the expectation with respect to Y starting from site k and σ_j denotes the first time Y enters the site j (or re-enters if starts at j). In particular,

$$A^{\#}_{SS} = \pi_S \sum_{k=0}^{S-1} \pi_k E_k \sigma_S > 0.$$

Since $E_k\sigma_S < E_0 \sigma_S$ for all $k > 0$, it follows that

$$A^{\#}_{SS} \leq \pi_S (1-\pi_S) E_0 \sigma_S.$$

This implies

$$A^{\#}_{0S} = A^{\#}_{SS} - \pi_S E_0 \sigma_S < -\pi_S^2 E_0 \sigma_S < 0.$$

Similarly,

$$A^{\#}_{00} = \pi_0 \sum_{k=1}^{S} \pi_k E_k \sigma_0 > 0,$$

and then

$$A^{\#}_{00} < \pi_0(1-\pi_0)E_S\sigma_0, \qquad A^{\#}_{0S} < -\pi_S^2 E_S\sigma_0 < 0.$$

In particular, all entries of Q are strictly negative, and so the inner product in Theorem 2.4 is strictly negative. This provides an upper bound on the variance. We turn to proving a lower bound.

For $e = (i, i+1)$ or $(i, i-1)$ let $\alpha_e(\eta) = \ln A_e(\eta)$. By [4, Theorem 5], Λ is an increasing and convex function of the variables of $\{\alpha_e\}$, and for $i \neq j$,

$$\frac{\partial \Lambda}{\partial \alpha_e} = \pi_i A_{ij}. \tag{7}$$

Next,

$$\Lambda'(\eta) = \sum_e \frac{\partial \Lambda}{\partial \alpha_e}\frac{d\alpha_e}{d\eta},$$

and so

$$\Lambda''(\eta) = \sum_{e,e'} \frac{\partial^2 \Lambda}{\partial \alpha_e \partial \alpha_{e'}}\frac{d\alpha_e}{d\eta}\frac{d\alpha_{e'}}{d\eta} + \sum_e \frac{\partial \Lambda}{\partial \alpha_e}\frac{d^2\alpha_e}{d\eta^2} \geq \sum_e \frac{\partial \Lambda}{\partial \alpha_e}\frac{d^2\alpha_e}{d\eta^2},$$

where the inequality follows from the above mentioned convexity of Λ. We now compute the right-hand side at $\eta = 0$. We have $\alpha_e'(\eta) = \frac{A_e'(\eta)}{A_e(\eta)}$. Therefore

$$\alpha_e''(\eta) = \frac{A_e''(\eta)A_e(\eta) - (A_e'(\eta))^2}{A_e(\eta)^2} = \frac{A_e''(\eta)}{A_e(\eta)} - \alpha_e'(\eta)^2.$$

Letting $\eta = 0$, we obtain

$$\alpha'_{i,i+1}(0) = \frac{\mu}{x}, \qquad \alpha'_{i,i-1}(0) = -\frac{\lambda}{y}.$$

The second derivatives are then given by

$$\alpha''_{i,i+1}(0) = \frac{\mu}{x}\Big(1 - \frac{\mu}{x}\Big), \qquad \alpha''_{i,i-1}(0) = \frac{\lambda}{y}\Big(1 - \frac{\lambda}{y}\Big).$$

Equivalently,

$$\alpha''_{i,i+1}(0) = \frac{\mu\alpha}{(\mu+\alpha)^2}, \qquad \alpha''_{i,i-1}(0) = \frac{\lambda\beta}{(\lambda+\beta)^2}.$$

Using this along with (7) and (8), we obtain

$$\begin{aligned}\Lambda''(0) &\geq \frac{\mu\alpha}{(\mu+\alpha)^2}\sum_{i=0}^{S-1}\pi_i(\alpha+\mu) + \frac{\lambda\beta}{(\lambda+\beta)^2}\sum_{i=1}^{S}\pi_i(\beta+\lambda) \\ &= \frac{\mu\alpha}{\mu+\alpha}(1-\pi_S) + \frac{\lambda\beta}{\lambda+\beta}(1-\pi_0),\end{aligned}$$

completing the proof of Theorem 2.5 $\square$

2.5 Explicit Formula for σ^2_{eff}

In this section we assume $\rho \neq 1$. The case $\rho = 1$ will be dealt in Section 2.6.1.

Proposition 2.3. *Let $H(\rho) = \pi_0\pi_S E_0\sigma_S$, and write $H(\rho^{-1})$ for $\pi_0\pi_S E_S\sigma_0$. Then*

$$\begin{aligned} H(\rho) &= \frac{\pi_0\pi_S}{x(\rho-1)}\sum_{j=0}^{S-1}(\rho^{j+1}-1) = \frac{(1-\rho)(\rho^S-1) - S(1-\rho)(1-\rho^{-1})}{(y-x)(1-\rho^{-(S+1)})(1-\rho^{S+1})} \\ &= \frac{y^{S+1}(y^S-x^S) - Sx^Sy^S(y-x)}{(y^{S+1}-x^{S+1})^2}, \end{aligned}$$

and a similar expression for $H(\rho^{-1})$ is obtained from the one above by replacing ρ with ρ^{-1} and exchanging between x and y.

Theorem 2.6.

1. *Let*

$$\begin{aligned} &\Delta = H(\rho) - H(\rho^{-1}), \\ &\Sigma = H(\rho) + H(\rho^{-1}), \ \textit{and} \\ &\kappa = \frac{1}{\rho^{S+1}-1} - \frac{1}{\rho^{-(S+1)}-1}. \end{aligned}$$

Then

$$Q = \frac{1}{2}\begin{pmatrix} \rho(\kappa\Delta - \Sigma) & -\kappa\Delta \\ -\kappa\Delta & \rho^{-1}(\kappa\Delta - \Sigma) \end{pmatrix}.$$

2. *Furthermore, we have:*

$$\begin{aligned} \kappa\Delta &= \frac{(\rho^{-(S+1)} - \rho^{S+1})\left((1-\rho)(\rho^S-1) + (1-\rho^{-1})(\rho^{-S}-1) - 2S(1-\rho)(1-\rho^{-1})\right)}{(y-x)(1-\rho^{-(S+1)})^2(1-\rho^{S+1})^2} \\ &= \frac{(y^{S+1}+x^{S+1})^2}{(y^{S+1}-x^{S+1})^2}\Sigma - \frac{2Sx^Sy^S(y^{S+1}+x^{S+1})(y-x)}{(y^{S+1}-x^{S+1})^3}. \end{aligned}$$

and

$$\Sigma = \frac{(1-\rho)(\rho^S-1) - (1-\rho^{-1})(\rho^{-S}-1)}{(y-x)(1-\rho^{-(S+1)})(1-\rho^{S+1})} = \frac{y^S - x^S}{y^{S+1}-x^{S+1}}.$$

The second term in the right-hand side of the expression for $\kappa\Delta$ can be rewritten as

$$\frac{2Sx^Sy^S(y^{S+1}+x^{S+1})(y-x)}{(y^{S+1}-x^{S+1})^3} = \frac{(y^{S+1}+x^{S+1})^2}{(y^{S+1}-x^{S+1})^2}\underbrace{\frac{2Sx^Sy^S(y-x)}{(y^{S+1}+x^{S+1})(y^S-x^S)}}_{(*)}\Sigma.$$

Since all entries of Q are strictly negative, $(*) > 1$. This can be easily verified by using the identity $y^S - x^S = (y-x)\sum_{k=0}^{S-1} y^k x^{S-1-k}$.

Proof of Proposition 2.3. Let $L_i = E_i\sigma_S$. Then $L_i = \sum_{k=i}^{S-1} K_k$, where $K_k = E_k\sigma_{k+1}$. By conditioning on the time of the first jump from i, we observe that

$$K_i = E_i(\text{Jump time}) + P(\text{Jumped Left})(K_{i-1} + K_i).$$

Therefore

$$K_i = \frac{E_i(\text{Jump Time})}{P(\text{Jumped Right})} + \frac{P(\text{Jumped Left})}{P(\text{Jumped Right})}K_{i-1} = \frac{1}{\text{Rate Right}} + \frac{\text{Rate Left}}{\text{Rate Right}}K_{i-1}.$$

Returning to our case, the rate to the right is $x = \alpha + \mu$ whereas the rate to the left is $y = \beta + \lambda$. Therefore

$$K_i = x^{-1}(1 + \cdots + \rho^i) = \frac{\rho^{i+1} - 1}{x(\rho - 1)}.$$

Thus,

$$\begin{aligned} E_i\sigma_S &= \frac{1}{x(\rho-1)}\sum_{j=i}^{S-1}\big(\rho^{j+1} - 1\big) = \frac{1}{x(\rho-1)}\Big(\rho^{i+1}\sum_{j=0}^{S-i-1}\rho^j - (S-i)\Big) \\ &= \frac{1}{x(\rho-1)}\Big(\frac{\rho^{S+1} - \rho^{i+1}}{\rho - 1} - (S-i)\Big). \end{aligned}$$

In particular

$$E_0\sigma_S = \frac{1}{x(\rho-1)}\Big(\rho\frac{\rho^S - 1}{\rho - 1} - S\Big) = \frac{1}{y - x}\Big(\frac{\rho^S - 1}{1 - \rho^{-1}} - S\Big).$$

In virtue of (1),

$$\pi_0 = \frac{1 - \rho^{-1}}{1 - \rho^{-(S+1)}}, \qquad \pi_S = \frac{1 - \rho}{1 - \rho^{S+1}},$$

completing the proof of Proposition 2.3. □

Proof of Theorem 2.6. We have

$$\begin{aligned} A^{\#}_{SS} = \pi_S\sum_{j=0}^{S-1}\pi_j E_j\sigma_S = \pi_0\pi_S\sum_{j=0}^{S-1}\rho^{-j}\sum_{k=j}^{S-1}K_k &= \pi_0\sum_{k=0}^{S-1}\sum_{j=0}^{k}\rho^{-j}K_k \\ &= \frac{\pi_0\pi_S}{x(\rho-1)(\rho^{-1}-1)}\sum_{k=0}^{S-1}(\rho^{-(k+1)} - 1)(\rho^{k+1} - 1) \\ &= \frac{\pi_0\pi_S}{x(\rho-1)(\rho^{-1}-1)}\Big(S - \rho\frac{\rho^S - 1}{\rho - 1} + S - \rho^{-1}\frac{\rho^{-S} - 1}{\rho^{-1} - 1}\Big) \\ &= \pi_0\pi_S\Big(-\frac{E_0\sigma_S}{\rho^{-1} - 1} - \frac{\rho E_S\sigma_0}{\rho - 1}\Big) = \frac{\pi_0\pi_S}{1 - \rho^{-1}}(E_0\sigma_S - E_S\sigma_0) = \frac{\Delta}{1 - \rho^{-1}}. \end{aligned}$$

Similarly, $A^{\#}_{00} = \frac{-\Delta}{1-\rho} = \frac{\Delta}{\rho-1}$. A straightforward calculation shows then that

$$Q_{01} = Q_{10} = -\frac{1}{2}(\rho\pi_0 A^{\#}_{00} + \rho^{-1}\pi_S A^{\#}_{SS}) = -\frac{1}{2}\kappa\Delta.$$

Finally, by the detailed balance condition (1), $\pi_i A_{ij} = \pi_j A_{ji}$. That is, A is self-adjoint with respect to the reference measure π. By the spectral theorem (or a direct computation), $A^{\#}$ is also self adjoint with respect to π. In particular, $\pi_0 A^{\#}_{0S} = \pi_S A^{\#}_{S0}$. We have

$$\pi_0 A^{\#}_{0S} = \pi_0(A^{\#}_{SS} - \pi_S E_0\sigma_S),\ \pi_S A^{\#}_{S0} = \pi_S(A^{\#}_{00} - \pi_0 E_S\sigma_0).$$

But

$$\pi_0 A^{\#}_{0S} = \frac{\pi_0\Delta}{1-\rho^{-1}} - H(\rho)$$

and

$$\pi_S A^{\#}_{S0} = \frac{\pi_S\Delta}{\rho-1} - H(\rho^{-1}).$$

Thus,

$$\pi_0 A^{\#}_{0S} = \pi_S A^{\#}_{S0} = \frac{1}{2}(\kappa\Delta - \Sigma),$$

completing the proof of Theorem 2.6. □

2.6 Examples

2.6.1 $\rho = 1$

Here $\pi_j = \frac{1}{S+1}$, and hence

$$\Lambda'(0) = (\mu - \lambda)\frac{S}{S+1}.$$

Let K_k be defined as in the proof of Proposition 2.3. Then $K_k = \frac{1}{x}(1+k)$. Therefore,

$$\pi_0 E_S\sigma_0 = \pi_S E_0\sigma_S = \frac{1}{x(S+1)}(1+2+\cdots+S) = \frac{S}{2x}.$$

We also have

$$\begin{aligned} A^{\#}_{SS} &= \pi_S\pi_0\sum_{k=0}^{S-1}\sum_{j=0}^{k}K_k = \frac{1}{x(S+1)}\sum_{k=0}^{S-1}(1+k)^2 = \frac{1}{x(S+1)^2}\frac{S(S+1)(2S+1)}{6} \\ &= \frac{S(2S+1)}{6x(S+1)}. \end{aligned}$$

Therefore,

$$\pi_0 A^{\#}_{00} = \pi_0 A^{\#}_{SS} = \frac{S(2S+1)}{6x(S+1)^2}$$

and

$$\begin{aligned}\pi_0 A^{\#}_{0S} &= \frac{1}{x(S+1)}\Big(\frac{S(2S+1)}{6(S+1)} - \frac{S}{2}\Big) = \frac{1}{6x(S+1)^2}\big(S(2S+1) - 3S(S+1)\big) \\ &= -\frac{S(S+2)}{6x(S+1)^2}.\end{aligned}$$

Therefore

$$Q = -\frac{S}{6x(S+1)^2}\begin{pmatrix} S+2 & 2S+1 \\ 2S+1 & S+2 \end{pmatrix}.$$

Summarizing the above computation, it follows that

$$\begin{aligned}\Lambda''(0) &= (\lambda+\mu)\frac{S}{S+1} - \frac{S}{3x(S+1)^2}\big((S+2)(\mu^2+\lambda^2) + 2(2S+1)\lambda\mu\big) \\ &= (\lambda+\mu)\frac{S}{S+1} - \frac{S}{3x(S+1)^2}\big((S+2)(\mu+\lambda)^2 - 2(S+2)\mu\lambda + 2(2S+1)\mu\lambda\big) \\ &= (\lambda+\mu)\frac{S}{S+1} - \frac{S}{3x(S+1)^2}\big((S+2)(\mu+\lambda)^2 + 2(S-1)\lambda\mu\big) \\ &= (\lambda+\mu)\frac{S}{S+1}\Big[1 - \frac{1}{3x(S+1)}\Big((S+2)(\lambda+\mu) + 2(S-1)\frac{\mu\lambda}{\mu+\lambda}\Big)\Big].\end{aligned}$$

To get a lower bound, observe that

$$\begin{aligned}(S+2)(\mu+\lambda) + 2(S-1)\frac{\mu\lambda}{\mu+\lambda} &\le (S+2)2x - (S+2)(\alpha+\beta) + (S-1)(x-\alpha) \\ &= 3(S+1)x - (S+2)(\alpha+\beta) - (S-1)\alpha.\end{aligned}$$

Therefore

$$\Lambda''(0) \ge (\lambda+\mu)\frac{S}{S+1}\frac{(S+2)(\alpha+\beta) + (S-1)\alpha}{3x(S+1)}.$$

The same argument then shows that

$$\Lambda''(0) \ge (\lambda+\mu)\frac{S}{S+1}\frac{(S+2)(\alpha+\beta) + \frac{1}{2}(S-1)(\alpha+\beta)}{3x(S+1)} = \frac{S}{S+1}\frac{(\lambda+\mu)(\alpha+\beta)}{2x}.$$

The equality holds if and only if $\lambda = \mu$, in which case

$$\Lambda''(0) = \frac{S}{S+1}\frac{2\mu\alpha}{\alpha+\mu}.$$

In particular, for the fully symmetric case $\alpha = \beta = \lambda = \mu$, we obtain

$$\Lambda''(0) = \frac{S}{S+1}\mu.$$

2.6.2 $S = 1$

Then $\pi_1 = \frac{1}{1+\rho} = \frac{x}{x+y}$ and then $\pi_0 = \frac{y}{x+y}$. We have

$$\Lambda'(0) = \frac{\mu y - \lambda x}{x+y}.$$

Now, $E_0\sigma_1 = \frac{1}{x}$ and hence $A^\#_{11} = \frac{\pi_0\pi_1}{x} = \frac{y}{(x+y)^2}$ and $A^\#_{00} = \frac{x}{(x+y)^2}$. Since $A^\#$ has zero row sum, it follows that

$$A^\# = \frac{1}{(x+y)^2}\begin{pmatrix} x & -x \\ -y & y \end{pmatrix}.$$

Hence $\pi_1 A^\#_{11} = \frac{xy}{(x+y)^3}$ and $\pi_1 A^\#_{10} = -\frac{xy}{(x+y)^3}$. Similarly, $\pi_0 A^\#_{00} = \frac{xy}{(x+y)^3}$ and $\pi_0 A^\#_{01} = -\frac{xy}{(x+y)^3}$. Thus, recalling that $\rho = \frac{y}{x}$, we obtain

$$Q = -\frac{1}{(x+y)^3}\begin{pmatrix} y^2 & \frac{1}{2}(x^2+y^2) \\ \frac{1}{2}(x^2+y^2) & x^2 \end{pmatrix}.$$

Summarizing, we obtain

$$\begin{aligned}\Lambda''(0) &= \frac{\mu y + \lambda x}{x+y} - \frac{2}{(x+y)^3}\big(\mu^2 y^2 + \lambda^2 x^2 + (y^2+x^2)\mu\lambda\big) \\ &= \frac{\mu y + \lambda x}{x+y} - \frac{2}{(x+y)^3}\big((\mu y + x\lambda)^2 + (x-y)^2\lambda\mu\big).\end{aligned}$$

The positivity of $\Lambda''(0)$ can be seen directly by writing

$$\Lambda''(0) = \frac{\mu y + \lambda x}{x+y}\Big[1 - 2\Big(\frac{\mu y + \lambda x}{(x+y)^2} + \frac{(x-y)^2\mu\lambda}{(x+y)^2(\mu y + \lambda x)}\Big)\Big],$$

and using the inequalities $\mu < \alpha + \mu = x$, $\lambda < \beta + \lambda = y$.

2.6.3 $S = \infty,\ \rho \geq 1$

We take $S \to \infty$ while fixing the other parameters of the model. Because of the fact that the resulting limiting birth-and-death process is recurrent (null recurrent when $\rho = 1$ and positive recurrent when $\rho > 1$), it is not hard to show that a law of large number and functional central limit theorem hold, and the corresponding velocity and variance are obtained as the limits of the finite-state counterparts. Being somewhat of digression from our main theme, we only present the limiting quantities. When $\rho = 1$, these are easily attainable from the results of Section 2.6.1. We move to the case $\rho > 1$. We have $\lim_{S\to\infty} \pi_S = 0$ and $\lim_{S\to\infty} \pi_0 = 1 - \rho^{-1} = \frac{y-x}{y}$. Thus,

$$\Lambda'(0) = \mu - \lambda\rho^{-1} = \mu - \lambda\frac{\alpha+\mu}{\beta+\lambda}.$$

This means that there is no mechanical constraint to move to the right, but moving to the left is possible only a proportion of ρ^{-1} of the time, namely whenever the birth and death process Y is not at 0. To compute $\Lambda''(0)$, we first compute the matrix Q, using the formulas provided by Theorem 2.6. We have

$$\kappa\Delta = \Sigma = \frac{1-\rho^{-1}}{y-x} = \frac{1}{y}.$$

Therefore,

$$Q = -\frac{1}{2y}\begin{pmatrix} 0 & -1 \\ -1 & 0 \end{pmatrix}.$$

It follows that

$$\Lambda''(0) = \mu + \lambda\rho^{-1} - \frac{\lambda\mu}{y} = \mu + \lambda\frac{\alpha}{\lambda+\beta}.$$

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