Applications of global limit theorems for simulation of a cell population evolution

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Abstract

We discuss a spatio-temporal evolutionary model of a cell population. In modeling a cell population evolution, the key characteristics are the existence or the absence of sources where cells can die, after having produced or not produced offspring and having migrated or not migrated to different compartments. Based on such characteristics, we can apply continuous-time branching random walks on multidimensional lattices to study the evolution of a cell population with migration and division of cells. Consider particles living independently of each other and of their history. Each particle walks on the lattice until it reaches the source where its behavior is changed. The spatio-temporal modeling is implemented as a stochastic evolutionary system on a multidimensional lattice. At first, we present an approach to investigate the number of cells in the system and in every point of the lattice under fixation of the spatial coordinates in these models. Secondly, we examine the effect of one-point potential on the spatial dynamics on the lattice in the case when the spatial and temporal variables jointly tend to infinity. At last, we examine the effect of phase transitions on the behavior of a cell population. Based on the obtained results, we discuss possible strategies that may delay a cell population progression to some extent.
Keywords: branching random walks; non-homogeneous environments, spatio-temporal structure; phase transitions.

1. Introduction

We consider a model of stochastic lattice systems with the following key features: their elements can move on the lattice; they have a finite number of generation centers on the lattice, where the elements can produce new copies or disappear; the behaviour of all elements, being independent of each other, is covered by the same stochastic law. An important example of such stochastic multicomponent lattice systems is continuous-time branching processes with particles walking on the lattice $\mathbf{Z^d}$ which are usually called *branching random walks* (BRW). Recent investigations (Yarovaya, 2012a, 2013a) have demonstrated that continuous-time BRW on $\mathbf{Z^d}$ give an important example of stochastic processes whose evolution depend on the structure of the environment. It is convenient to describe such processes in terms of birth, death, and walks of particles on $\mathbf{Z^d}$. The structure of the environment is defined by the offspring reproduction law at a finite number of *branching sources* (generation centers) situated on $\mathbf{Z^d}$. The spatial dynamics of particles is considered under different assumptions about underlying random walks: symmetric or non-symmetric (Yarovaya, 2013b), with or without the finite variance of jumps (Yarovaya, 2013a).

Informal description of BRW on $\mathbf{Z}^d$ is follows: the population of individuals is initiated at time $t = 0$ by a single particle at a point $x \in \mathbf{Z^d}$. Being outside of the sources the particle performs a continuous time random walk on $\mathbf{Z^d}$ until reaching one of the sources. At a source it spends an exponentially distributed time and then either jumps to a point $y \in \mathbf{Z^d}$ (distinct from the source) or dies producing just before the death a random number of offsprings. The newborn particles behave independently and stochastically in the same way as the parent individual.

We will be mainly interested in describing the evolution of particles on $\mathbf{Z^d}$ in terms of the number of particles $n(t, x, y)$ at a point $y \in \mathbf{Z^d}$ and their moments $m_k(t, x, y) := E_x n^k(t, x, y)$, $k \in \mathbf{N}$, where E_x denotes the mathematical expectation under the condition $n(0, x, y) = \delta_y(x)$. Previous studies (see, for example, (Yarovaya, 2007) and the bibliography therein) were mainly concentrated on the analysis of the limit behavior of the process $n(t, x, y)$ on $\mathbf{Z^d}$ under fixed spatial coordinates. Investigation of the spatio-temporal evolution of a particle system, that is of the limit behavior of $n(t, x, y)$ when both coordinates, t and y, may vary, is undertaken in (Molchanov & Yarovaya, 2012a,b).

The presence of positive eigenvalues in the spectrum of the evolutionary operator implies the exponential growth of the number of particles in arbitrary lattice point and on the entire lattice (Yarovaya, 2010, 2012b), while the rate of grows is specified by the leading eigenvalue. Therefore, in the previous studies the authors were usually limited to finding only the leading eigenvalue. At the same time for the spatio-temporal analysis, the information about whether the positive eigenvalue is unique, or if it is not unique then how it is located with respect to other eigenvalues, can be significant in the analysis of the behavior of BRW. Below we will show that the number of positive eigenvalues of the discrete spectrum of the evolutionary operator and their multiplicity depend not only on the intensity of the sources but also on the spatial configuration of the sources.

2. BRW with a few branching sources

Let $A = (a(x,y))_{x,y\in\mathbf{Z^d}}$ be the matrix of transition intensities of a random walk: $a(x,y) \geq 0$ for $x \neq y$, $a(x,x) < 0$; $a(x,y) = a(y,x) = a(0, y-x) = a(y-x)$ and $\sum\limits_z a(z) = 0$. Let us also suppose that the random walk is irreducible, i.e. for every $z \in \mathbf{Z^d}$ there exists a set of vectors $z_1, z_2, \dots, z_k \in \mathbf{Z^d}$ such that $z = \sum_{i=1}^k z_i$ and $a(z_i) \neq 0$ for $i = 1, 2, \dots, k$. We assume also that branching in every source is described by the infinitesimal generating function $f(u) := \sum\limits_{n=0}^{\infty} b_n u^n$, where $b_n \geq 0$ for $n \neq 1$, $b_1 < 0$ and $\sum\limits_n b_n = 0$, where $\beta_r := f^{(r)}(1) < \infty$, $r \in \mathbf{N}$, and $\beta := \beta_1$.

In the BRW models with finitely many sources, there arise multipoint perturbations (Yarovaya, 2012b) of the symmetric random walk generator $\mathscr{A}$, which have the form

$$\mathscr{H}_\beta = \mathscr{A} + \beta \sum_{i=1}^{N} \Delta_{x_i},$$

where $x_i \in \mathbb{Z}^d$, $\mathscr{A} : l^p(\mathbb{Z}^d) \to l^p(\mathbb{Z}^d)$, $p \in [1, \infty]$, is a symmetric operator acting by formula

$$(\mathscr{A}u)(z) := \sum_{z'\in\mathbf{Z^d}} a(z - z')u(z'),$$

where $\Delta_x = \delta_x \delta_x^T$ and $\delta_x = \delta_x(\cdot)$ denotes the column vector on the lattice which is equal to 1 at the point x and to zero otherwise.

The perturbation $\beta \sum_{i=1}^N \Delta_{x_i}$ of the operator $\mathscr{A}$ can result in the appearance of positive eigenvalues of the operator $\mathscr{H}_\beta$, besides the multiplicity of each eigenvalue does not exceed the number of terms in the last sum. That is in this case the discrete spectrum σ_d consists of no more than N nonnegative eigenvalues provided that there are N sources of the branching on the lattice (Yarovaya, 2012b).

The structure of the eigenvalues and eigenfunctions of $\mathscr{H}_\beta$ are closely related to the transition probabilities $p(t,x,y) = p(t,0,y-x) = p(t,0,x-y)$ of the underlying random walk which satisfy the Kolmogorov backward equation

$$\partial_t p = \mathscr{A}p, \quad p(0,x,y) = \delta_y(x).$$

The Green's function for them is as follows:

$$G_\lambda(x,y) := \int_0^\infty e^{-\lambda t} p(t,x,y)\, dt = \frac{1}{(2\pi)^d} \int_{[-\pi,\pi]^d} \frac{e^{i(\theta, x-y)}}{\lambda - \widehat{\mathscr{A}}(\theta)} d\theta, \quad \lambda \geq 0,$$

where $\widehat{\mathscr{A}}$ is the Fourier transform of the operator $\mathscr{A}$.

Analysis of BRW depends on whether the value of $G_0 = G_0(0,0)$ is finite or infinite.

Definition 1 *A random walk is* transient *if* $G_0(0,0) < \infty$ *and* recurrent *if* $G_0(0,0) = \infty$.

In what follows we will consider $a(\cdot)$ under two different assumptions:

1. $\sum\limits_z |z|^2 a(z) < \infty$, where $|z|$ is Euclidean norm of a vector z.

2. $a(z) \sim \frac{H\left(\frac{z}{|z|}\right)}{|z|^{d+\alpha}}$, as $z \to \infty$, $\alpha \in (0,2)$, where $H(\cdot)$ is continuous positive and symmetric on the sphere $\mathbb{S}^{d-1} = \{z \in \mathbb{R}^d : |z| = 1\}$ function.

In the first case $G_0 = \infty$ for $d = 1, 2$ and $G_0 < \infty$ for $d \geq 3$. In the second case $\sum_z |z|^2 a(z) = \infty$ which implies infinite variance of jumps. In this case $G_0 = \infty$ for $d = 1$ and $\alpha \in [1, 2)$, while $G_0 < \infty$ for $d = 1$ and $\alpha \in (0, 1)$ or $d \geq 2$ and $\alpha \in (0, 2)$ (Yarovaya, 2013a).

3. Configuration of the sources

Let β_c denotes the minimal value of the source intensity β such that for $\beta > \beta_c$ the spectrum of $\mathscr{H}_\beta$ has positive eigenvalues.

Theorem 1 *If $G_0 = \infty$ then $\beta_c = 0$ for $N \geq 1$. If $G_0 < \infty$ then $\beta_c = G_0^{-1}$ for $N = 1$, and $0 < \beta_c < G_0^{-1}$ for $N \geq 2$.*

When $G_0 < \infty$ and $N = 2$ the quantity β_c is computed, for example, in (Yarovaya, 2012b):

$$\beta_c = (G_0 + \widetilde{G}_0)^{-1},$$

where $\widetilde{G}_0 = G_0(x_1, x_2)$.
The next theorem gives an additional information about the structure of the spectrum of the operator $\mathscr{H}_\beta$.

Theorem 2 *Let $N \geq 2$. Then for $\beta > \beta_c$ the operator $\mathscr{H}_\beta$ may have no more than N positive eigenvalues of finite multiplicity*

$$\lambda_0(\beta) > \lambda_1(\beta) \geq \cdots \geq \lambda_{N-1}(\beta) > 0,$$

besides the eigenvalue $\lambda_0(\beta)$ has multiplicity one. In addition, there exists a value $\beta_{c_1} > \beta_c$ such that for $\beta \in (\beta_c, \beta_{c_1})$ the operator has no other eigenvalues except $\lambda_0(\beta)$.

In general, the problem of finding the eigenvalues of a linear operator is rather complicated. To help solving it, one may use the following assertion proved in (Yarovaya, 2012b) for a more general case of different types of branching sources.

Theorem 3 *An eigenvalue λ belongs to the discrete spectrum of the operator $\mathscr{H}_\beta$ if and only if the following system of linear equations*

$$V_i - \beta \sum_{j=1}^{N} G_\lambda(x_i, x_j) V_j = 0, \quad i = 1, \ldots, N,$$

with respect to variables $\{V_i\}_{i=1}^N$ has at least one nontrivial solution.

Let, for example,

$$(\mathscr{A} u)(z) = \varkappa \sum_{|z-z'|=1} a(z - z') u(z'), \quad \varkappa > 0, \quad z' \in \mathbf{Z^d}, \tag{1}$$

be the lattice Laplacian, and the points $x_1, \ldots, x_N$, $N \geq 2$, at which sources of equal intensities are disposed, form the vertices of a regular simplex. Such a kind of simplices in $\mathbb{Z}^d$ can be obtained, for example, as an arbitrary combination of the standard basis vectors. Then, using Theorem 3, the critical values β_c and β_{c_1} can be computed explicitly:

$$\beta_c = (G_0 + (N-1)\widetilde{G}_0)^{-1}, \quad \beta_{c_1} = (G_0 - \widetilde{G}_0)^{-1},$$

where $\widetilde{G}_0 = G_0(x_i, x_j)$ for $i \neq j$ (in our case all the values $G_0(x_i, x_j)$ for different $i \neq j$ coincide with each other and then the value $\widetilde{G}_0$ does not depend on i and j).

Remark 1 The operator $\mathscr{A}$ should not necessarily be the lattice Laplacian. In order that the assertion of the example remained to be valid, it suffices to require that the values of the Fourier transform $\widehat{\mathscr{A}}(\theta)$ of the intensity function $a(z)$ do not change under any permutation of coordinates of the vector $\theta = \{\theta_1, \theta_2, \ldots, \theta_d\}$. The latter property will take place, for example, if the function $a(z)$ does not change its values under any permutation of coordinates of the vector $z = \{z_1, z_2, \ldots, z_d\}$.

4. Weakly supercritical BRW

Definition 2 *Let there exist $\varepsilon_0 > 0$ such that for $\beta \in (\beta_c, \beta_c + \varepsilon_0)$ the operator $\mathscr{H}_\beta$ has only one (accounting multiplicity) positive eigenvalue $\lambda(\beta)$ satisfying $\lambda(\beta) \to 0$ for $\beta \downarrow \beta_c$. Then the supercritical BRW will be called* weakly supercritical for β close to β_c.

There is naturally arises the question: whether any supercritical BRW for $\beta > \beta_c$ sufficiently close to β_c is weakly supercritical?

Theorem 4 *Every supercritical BRW for $\beta \downarrow \beta_c$ is weakly supercritical.*

Using the asymptotic behavior for $p(t, 0, 0) \sim \gamma_d t^{-\frac{d}{2}}$, as $t \to \infty$, we can describe the asymptotic behavior of G_λ under assumption 1 in more details (Yarovaya, 2012b). If $\lambda \to 0$ then

$$G_\lambda = \begin{cases} \widetilde{\gamma}_1(\sqrt{\lambda})^{-1} \cdot (1 + o(1)), & d = 1, \\ -\widetilde{\gamma}_2 \ln \lambda \cdot (1 + o(1)), & d = 2, \\ G_0 - \widetilde{\gamma}_3 \sqrt{\lambda} \cdot (1 + o(1)), & d = 3, \\ G_0 + \widetilde{\gamma}_4 \lambda \ln \lambda \cdot (1 + o(1)), & d = 4, \\ G_0 - \widetilde{\gamma}_d \lambda \cdot (1 + o(1)), & d \geq 5, \end{cases}$$

where $\widetilde{\gamma}_d$ is a positive constant. From these representations we get the asymptotic behavior of $\lambda_0(\beta)$ (Molchanov & Yarovaya, 2012a). The eigenvalue $\lambda_0(\beta)$ of the operator $\mathscr{H}_\beta$ has the following asymptotic behavior as $\beta \downarrow \beta_c$:

$$\begin{aligned} &\lambda_0(\beta) \sim c_1 \beta^2, && d = 1, \\ &\lambda_0(\beta) \sim e^{-c_2/\beta}, && d = 2, \\ &\lambda_0(\beta) \sim c_3(\beta - \beta_c)^2, && d = 3, \\ &\lambda_0(\beta) \sim c_4(\beta - \beta_c) \ln^{-1}((\beta - \beta_c)^{-1}), && d = 4, \\ &\lambda_0(\beta) \sim c_d(\beta - \beta_c), && d \geq 5, \end{aligned}$$

where c_i, $i \in \mathbf{N}$, is a positive constant.
Under appropriate regularity conditions on the tails of the jump distributions, asymptotic behavior of the transition probability $p(t, 0, x)$ uniformly when $|x| + t \to \infty$ is investigated in (Agbor et al., 2014). From these results for fixed spatial coordinates, the next asymptotic relation immediately follows:

$$p(t, x, y) \sim \gamma_{d,\alpha} t^{-\frac{d}{\alpha}}, \quad t \to \infty, \quad 0 < \alpha < 2. \tag{2}$$

The local limit theorem for $p(t, x, y)$ in the absence of any regularity conditions was obtained by using the multidimensional analog of the known Watson's Lemma. From the asymptotic representation (2) we obtain asymptotic behavior of G_λ under Assumption 2.

Theorem 5 *If $\lambda \to 0$ then*

$$G_\lambda = \begin{cases} \breve{\gamma}_{1,\alpha} \lambda^{\frac{1-\alpha}{\alpha}} \cdot (1 + o(1)), & d = 1, \quad 1 < \alpha < 2, \\ -\breve{\gamma}_{1,\alpha} \ln \lambda \cdot (1 + o(1)), & d = 1, \quad \alpha = 1, \\ G_0 - \breve{\gamma}_{1,\alpha} \sqrt{\lambda} \cdot (1 + o(1)), & d = 1, \quad 0 < \alpha < 1, \\ G_0 - \breve{\gamma}_{d,\alpha} \lambda \cdot (1 + o(1)), & d \geq 2, \quad 0 < \alpha < 2, \end{cases}$$

where $\breve{\gamma}_{i,\alpha}$, $i \in \mathbf{N}$, is a positive constant for every α.

From this theorem we get the asymptotic behavior of $\lambda_0(\beta)$, as $\beta \downarrow \beta_c$, for BRW under Assumption 2.

Theorem 6 *The eigenvalue $\lambda_0(\beta)$ of the operator $\mathscr{H}_\beta$ has the following asymptotic behavior as $\beta \downarrow \beta_c$:*

$$\begin{aligned}
&\lambda_0(\beta) \sim c_{1,\alpha}\beta^{\frac{\alpha}{\alpha-1}}, && d=1, \quad 1<\alpha<2,\\
&\lambda_0(\beta) \sim e^{-c_{1,1}/\beta}, && d=1, \quad \alpha=1,\\
&\lambda_0(\beta) \sim c_{1,\alpha}(\beta-\beta_c), && d=1, \quad 0<\alpha<1,\\
&\lambda_0(\beta) \sim c_{d,\alpha}(\beta-\beta_c), && d\ge 2, \quad 0<\alpha<2.
\end{aligned}$$

where $c_{i,\alpha}$, $i \in \mathbf{N}$, is a positive constant for every α.

5. Spatio-temporial analysis of BRW

For spatio-temporial analysis of particle systems we apply the methods of the spectral theory of operators with multipoint perturbations. We use resolvent analysis of a bounded symmetric operator with multipoint perturbations to study the distribution of population inside the front of propagation of the weakly supercritical BRW on $\mathbf{Z}^d$. In (Cranston et al., 2009) an approach based on the resolvent analysis of evolutionary operators has been proposed to study a continuous model of homopolymers on $\mathbf{R}^d$ with path large deviations for the Brownian motion, but this model does not cover the case of BRW on $\mathbf{Z}^d$.

We consider the case which is the most important for simulation of a cell population evolution: the operator $\mathscr{A}$ has the form (1) that implies validity of Assumption 1, and at the moment τ_1 of the first reaction, the particle is duplicated $P \to P+P$ and both copies independently start moving from the point $x(\tau_1)$ with the same law. In the frame of BRW models, the exponential growth of the cellular population may occur when β surpass the critical value β_c, so we are interested in the situation of weakly supercritical BRW for which $\beta \downarrow \beta_c$.

Assume that $n(0,0,y)=\delta_0(y)$ and $\beta_c<\beta<\beta_{c_1}$. Then

$$m_1(t,0,y)=e^{\lambda_0(\beta)t}\psi_0(y)\psi_0(0)+O(1),$$

where $\psi_0(y,\beta)$ is the eigenfunction corresponding to the eigenvalue λ_0 of the evolutionary operator $\mathscr{H}_\beta$. If $\beta \downarrow \beta_c$ then $\lambda_0(\beta)\to 0$, and $\psi_0(y,\beta)$ may be represented in the explicit form:

$$\psi_0(y,\beta) \asymp G_{\lambda_0(\beta)}(0,y) \asymp e^{-\sqrt{\lambda_0(\beta)}|y|(1+o(1))},$$

where we write $f(y) \asymp g(y)$ for $0<c\le \frac{f}{g} \le C<\infty$.

Let us call $\Gamma_t=\{y : m_1(t,0,y)\le C\}$ *the population front.* The definition of the front depends on the constant C, but with the logarithmical accuracy it will not depend on C, and instead of C one can consider any function $o(e^{\varepsilon t})$.

Let us note that in general

$$G_\lambda(0,y) \asymp \frac{e^{-|y|h_\lambda\left(\frac{y}{|y|}\right)}}{|y|^{\frac{d-1}{2}}}$$

for any $\lambda>0$, where the representation $h_\lambda(y/|y|)=h_\lambda(\theta)$ has been obtained in (Molchanov & Yarovaya, 2012a). In this case $\ln G_\lambda(0,y) \sim -|y|h_\lambda\left(\frac{y}{|y|}\right)$, as $|y|\to\infty$. Then

$$\Gamma_t=\left\{y : \frac{|y|}{t}h_1\left(\lambda_0(\beta),\frac{y}{|y|}\right) \ge \lambda_0(\beta)+o(1)\right\},$$

where $o(1)$ is a function tending to zero under the joint unbounded growth of $|y|$ and t subjected to the condition $|y|=O(t)$. For $\beta \downarrow \beta_c$ the front has approximately spherical form: $\Gamma_t \approx \left\{y : |y| \ge t\sqrt{\lambda_0(\beta)}\right\}$.

As in the classical Kolmogorov-Petrovskii-Piskunov model, the population is spreading linearly in time.

6. Applications

One of potential areas of application is the investigation of limit distributions of the cell population with migration of cells. The division of cells at the source is described by a birth-and-death process. For example,

the tumor cell proliferation at the source can be represented as a branching process (Fedotov & Iomin, 2008; Thalhauser et al., 2010), where the environment for the transport of cells is a multidimensional lattice, and compartments are treated as the points of the lattice. Then, the migration of cancer tumor cells is described by a random walk on the lattice whereas the processes of metastasis may be roughly described by BRW with a few sources of branching. Self-reproducibility of the cancer cells is a specific feature of such systems. The evolution of such systems may be studied under the assumption that the cancer cells may be found at every compartment, but the proliferation processes are exhibited only at the sources. Thus the models described in terms of birth, death and walk of particles may be useful in the study of the long-time behavior of a cell population. An important aspect of the study is to obtain the threshold value β_c of a parameter β which characterizes the process of cell proliferation at the sources. For example, active growth of the cancer cellular population in the frame of BRW models may be explained by the excess of the threshold value.
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