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Stochastic Modeling of Dynamical Processes in Biological Signaling and Cellular Transport

by

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ABSTRACT

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Successful cellular function and organ development rely on the effective transport of proteins and other biomolecules to specific positions. There are two basic mechanisms for biological transport: passive diffusion and motor-driven active transport. This thesis presents theoretical investigations of several biophysical problems in the context of active and passive transport.

In the matter of passive diffusion, we investigate fundamental processes of biological development that are governed by multiple signaling molecules that create non-uniform concentration profiles known as morphogen gradients. It is widely believed that the establishment of morphogen gradients is a result of complex processes that involve diffusion and degradation of locally produced signaling molecules. We have developed discrete-state stochastic and continuum mean field approaches to investigate the corresponding reaction-diffusion models.

In the case of active transport, we investigate the fundamental role of local interactions between molecular motors by analyzing a new class of totally asymmetric exclusion processes where interactions are accounted for in a thermodynamically consistent fashion. This allows us to explicitly connect microscopic features of motor proteins with their collective dynamic properties. Our theoretical analysis that
combines various mean-field calculations and computer simulations suggests that the dynamic properties of molecular motors strongly depend on the interactions, and that the correlations are stronger for interacting motor proteins.

Furthermore, we investigate all times dynamics of continuous-time random walks (CTRWs). The concept of continuous-time random walks (CTRW) is a generalization of ordinary random walk models, and it is a powerful tool for investigating a broad spectrum of phenomena in natural, engineering, social, and economic sciences. Recently, several theoretical approaches have been developed that allowed to analyze explicitly dynamics of CTRW at all times, which is critically important for understanding mechanisms of underlying phenomena. However, theoretical analysis has been done mostly for systems with a simple geometry. Here, we extend the original method based on generalized master equations to analyze all-time dynamics of CTRW models on complex networks.
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Chapter 1

Introduction

This thesis is composed of three parts: The first part deals with stochastic modeling of signaling mechanisms in biological development. The second part focuses on theoretical analysis of dynamical processes of interacting molecular motors. And, finally, the third part concentrates on the investigation of all-time dynamics of continuous-time random walks on complex networks.

1.1 Development of Morphogen Gradient

Development of various living organisms from initially very small group of identical embryo cells is one of the most fascinating and complex processes in biology [1, 2, 3, 4, 5]. A critical stage in biological development is a pattern formation during which the eventual fates of cells become determined at different times and different positions. Several classes of signaling molecules, known as morphogens, play the central role in tissue patterning and organ formation [1, 2, 3, 4, 5]. The term morphogen was first introduced by A. Turing in his seminal paper on mathematical modeling of biological pattern formation[36]. It is now widely accepted that the concentration gradient of morphogens provide cells with required positional information to activate or inhibit specific genes, probably utilizing the local concentration thresholds and/or other related mechanisms [1, 2, 3, 8, 9, 43]. In recent years, there has been a substantial progress in experimental and theoretical studies of the mech-
anisms of embryonic development stimulated by the various morphogen gradients [6, 8, 9, 10, 11, 12, 22, 23, 24, 35]. However, many features of the biological development processes still remain not well understood [9, 43].

Several mechanisms have been proposed for explaining how the morphogen gradients are established [9, 35, 43, 58]. The simplest and widely popular approach for the description of the signaling profiles formation is called a Synthesis-Diffusion-Degradation (SDD) model [9]. According to this model, morphogens are synthesized at specific locations, and from the source region they diffuse through a field of embryo cells where they eventually are degraded after binding to cell receptors [9]. As a result, exponentially decaying concentration profiles are developed at long times. Since qualitatively similar behavior is observed in many experimental systems, the SDD models have been widely utilized for understanding morphogen gradients [9, 11, 12, 13, 14, 22, 27, 37]. Recent investigations also point out to the importance of the degradation steps in the establishment of morphogen gradients [31, 38, 41, 49]. Without a constant removal of the morphogen molecules, non-uniform concentration profiles cannot be achieved, and thus the proper biological signals cannot be transferred downstream to genetic networks.

In this work, we develop discrete-state stochastic approaches for investigating corresponding reaction-diffusion models. For convenience, we adopt a single-molecule view of the process, in which the concentration of signaling molecules is equivalent to the probability of finding a single morphogen at given site. Since the balance between the synthesis, diffusion and degradation processes leads to the formation of concentration profiles of signaling molecules, we generalize our models to investigate roles of these processes on the dynamics of morphogen gradient formation. Specifically, we investigate the role of spatial dimensions, source delocalization, non-linear
degradation, and spatially varying degradation rates.

Biological signaling relies on efficient and fast transfer of information between different cells and tissues. It has been presumed for a long time that these long-distance communications in most systems can take place only indirectly via the diffusion of signaling molecules, also known as morphogens, through the extracellular fluid; however, recent experiments indicate that there is also an alternative direct delivery mechanism[35]. It utilizes dynamic tubular cellular extensions, called cytonemes, that directly connect cells, supporting the flux of morphogens to specific locations [35]. We present a first quantitative analysis of the cytoneme-mediated mechanism of biological signaling. Dynamics of the formation of signaling molecule profiles, which are also known as morphogen gradients, is discussed. It is found that the direct-delivery mechanism is more robust with respect to fluctuations in comparison with the passive diffusion mechanism.

1.2 Interacting Motors Proteins

Motor proteins or molecular motors are enzymatic molecules that actively participate in all major biological processes such as cellular transport, cell division, transfer of genetic information, synthesis of proteins, cell motility and signaling [63, 64, 65, 66, 67, 68]. They transform chemical energy from specific reactions that they catalyze (usually, hydrolysis or biopolymerization) into mechanical work to support their functions. For example, the directed motion along linear cytoskeleton filaments by kinesin, myosin and dynein motor proteins is fueled by the hydrolysis of adenosine triphosphate (ATP) [65]. Biological molecular motors have been intensively studied in recent years, and currently the single-molecule dynamics of motor proteins is well described [67, 68, 69]. Although the properties of individual molecules are very useful,
in biological systems motor proteins typically function in large teams. This underlines the importance of understanding the collective behavior of molecular motors [68, 70, 71].

Experimental studies of kinesin motor proteins moving along microtubules indicate that these molecular motors interact with each [72, 73, 74]. It was argued that these interactions most probably are short-range and relatively weak attractive \((1.6 \pm 0.5k_B T)\) [72]. It is reasonable to assume that many other motor proteins have similar properties. At microscopic level, molecular motors are involved in a variety of chemical transitions such as binding to the filament, chemical transformations during the hydrolysis, dissociation from the track [65]. Intermolecular interactions influence all these processes, suggesting an important role for interactions in the collective behavior of molecular motors. However, the underlying mechanisms are still not well clarified [68, 70]. Existing theoretical studies of cooperative dynamics in interacting molecular motors are mostly phenomenological without quantitative description of relevant chemical processes [75, 78, 79, 90].

We introduced a new theoretical approach for analyzing collective properties of interacting molecular motors [76, 77]. It is based on using a class of non-equilibrium models called totally asymmetric simple exclusion processes (TASEP), which are very powerful for studying multi-particle dynamic phenomena [80, 81, 82]. There are many processes in Chemistry, Physics and Biology that have been successfully analyzed by utilizing the asymmetric exclusion processes [81, 82, 83, 84, 85, 86, 88]. TASEPs were also employed before for investigating dynamic properties of motor proteins [71, 78, 81, 84, 87, 89, 90], including interacting molecular motors [78, 90, 91, 92]. But the main advantage of our method is a procedure that describes all chemical transitions at the single-molecule level using fundamental thermodynamic concepts
This allows us to properly couple microscopic properties of interacting molecular motors with their collective dynamic behavior.

1.3 Continuous Time Random Walks

Continuous-time random walks (CTRW) are stochastic lattice models that have been introduced by Montroll and Weiss in 1965 as a generalization of ordinary random walk processes [97, 98, 99]. In these models the motion of particles between different states is generally controlled by random waiting-time distribution functions. Simple random walks are recovered when the waiting-time distributions are exponential functions [97, 98, 99]. It turned out that CTRW is a powerful and efficient method for studying a wide distribution of complex dynamic processes in natural sciences, engineering, social sciences and in economics [100, 101, 102, 103, 104, 105, 106, 107, 108, 109]. It is natural to utilize CTRW for understanding transport phenomena that cannot be described within classical diffusion framework [97, 98, 103]. Recent experimental advances in single-molecule techniques that allowed to visualize various chemical and biological processes with high temporal and spatial resolution stimulated the application of CTRW for investigating biological and cellular transport phenomena with anomalous diffusion [110, 111, 112, 113, 114, 115, 116].

Theoretical studies of complex dynamic phenomena that utilize CTRW models mostly concentrate on long-time dynamics [97, 100]. While this might be a reasonable approach for systems where stationary states are well established and can be quickly reached, in many cases to fully understand mechanisms of complex processes one needs to have a description of dynamic behavior at all times. In addition, the situation is more complex for system that never reach the steady-state limit. The original work of Montroll and Weiss [97] suggested that all-time dynamics of CTRW
can be obtained by utilizing Laplace-Fourier transformations. Although this analysis is formally correct, it is practically impossible to apply for real dynamic processes. Recently, a new method of calculating dynamic properties of particles in the CTRW model at all times has been introduced[117]. It is based on analyzing a propagator and surviving probabilities to calculate analytically exactly Laplace transforms of all dynamic properties, which effectively provides an all-time description of the underlying processes. It was later extended to a CTRW model with branched states as a way of investigating biased diffusion in tubes with periodic dead ends[118]. However, it can be shown that this method could be utilized only for homogeneous CTRW with the same set of waiting time distributions at each site, limiting its application for more complex dynamic phenomena.

Recently, an alternative theoretical method of calculating all-time dynamic properties in CTRW models have been presented[119]. It utilizes a generalized master-equations approach[111, 120] that allows fast and efficient computation of all Laplace transforms of probability functions and all dynamic properties of the CTRW models. The advantage of the method is the ability to analyze some inhomogeneous CTRW models as well as more complex systems, as was shown explicitly for simple periodic CTRW models and for processes with irreversible detachments[119]. We generalize this method to analyze all-time dynamics of CTRW models on complex networks. Specific calculations are performed for models on lattices with branches and for models on coupled parallel chain lattices. Exact expressions for velocities and dispersions are obtained. Generalized fluctuations theorems for CTRW models on complex networks are discussed.
Chapter 2

Development of Morphogen Gradient: The Role of Dimension and Discreteness

2.1 Introduction

In most cases, theoretical analysis of the morphogen gradient formation employs one-dimensional continuum versions of the SDD model. A more realistic description of signaling processes that takes into account the structure of embryo requires the application of multi-dimensional models. The importance of dimensionality has been also pointed out in recent experiments on diffusion of morphogens in extracellular space where geometric obstacles strongly affect trajectories of signaling molecules. Recently, the spherically-symmetric continuum SDD model has been investigated for multi-dimensional situations. This elegant theoretical method analyzed the kinetics of formation of morphogen gradients, and it also provided analytical expressions for stationary concentration profiles and for local accumulation times (LAT), which are defined as average times to reach locally the steady-state concentrations. One of the most surprising observations of this work is a prediction that for two-dimensional and three-dimensional systems, in contrast to one-dimensional models, there are multiple time scales for dynamics of formation of signaling molecules concentration profiles for the spatial region near the source. It suggested that the dimensionality might play an important role in dynamics of these reaction-diffusion processes.
Analyzing the application of the results from continuum SDD models one has to remember that the continuum picture is an approximation which does not work for all set of parameters. The fundamental biological processes of morphogen gradients development are intrinsically discrete. The chemical reactions of degradation of signaling molecules are taking place at specific locations that are spatially separated from each other. Thus the comprehensive description of these complex phenomena must be based on a discrete-state stochastic approach. The continuum analysis is a special limiting case of more general discrete method which can only be applied when the characteristic length scales of the gradients are much larger than the average distance between receptors where the degradation is taking place. The discrete-state stochastic version of the SDD model on semi-infinite interval has been recently introduced.[49] It has been also shown that the local accumulation times can be well approximated via the corresponding mean first-passage times, and the degradation process can be viewed as an effective potential that drives morphogens away from the source.[49]

In this chapter, we present a discrete-state stochastic framework for description of SDD models with strongly localized sources in all spatial dimensions [38]. This analysis allows us to compute stationary-state density profiles for morphogens as well as transient dynamic properties such as local accumulations times, mean first-passage times and variance of the local accumulation times. It provides a direct way for measuring the effect of dimensionality in these reaction-diffusion processes. By comparing the obtained results with predictions from continuum models the role of discreteness is also investigated. The existence of multiple times scales in dynamics of morphogen gradients formation for two-dimensional and three-dimensional cases is critically tested, and it is found that there is only one time scale for all distances from the source.
2.2 A Discrete-State Stochastic SDD Model in General Dimensions

Let us consider a general discrete-state stochastic SDD model in $d$ spatial dimensions as illustrated in Fig. 2.1 for $d = 2$. Any lattice site in the $d$-dimensional space is characterized by $d$ coordinates, namely $\mathbf{n} = (n_1, n_2, ..., n_d)$. We assume that morphogens are produced at the origin $\mathbf{n}_0 = (0,0,...,0)$ with a time-independent rate $Q$. Then, from any lattice site $\mathbf{n} = (n_1, n_2, ..., n_d)$ they can jump to any nearest neighbor site with a diffusion rate $u$. The particle can also be degraded at any position with a rate $k$: see Fig. 2.1. The continuum limit is realized when $u \gg k$, i.e., when the diffusion rate is much larger than the degradation rate. For convenience, we adopt here a single-molecule view of the process, in which the concentration of signaling molecules is equivalent to the probability of finding a single morphogen particle at a given site.[49] We define a function $P(n_1, n_2, ..., n_d; t)$ as the probability to find the particle at the position $\mathbf{n} = (n_1, n_2, ..., n_d)$ at time $t$. The temporal evolution of these probabilities is governed by a set of master equations,

$$
\frac{dP(n_1, n_2, ..., n_d; t)}{dt} = u \sum_{nn} P(n_1, n_2, ..., n_d; t) - (2ud + k)P(n_1, n_2, ..., n_d; t), \quad (2.1)
$$

where $\sum_{nn}$ is an operator corresponding to summing over all nearest neighbors, namely:

$$
\sum_{nn} P(n_1, n_2, ..., n_d; t) = P(n_1 - 1, n_2, ..., n_d; t) + P(n_1 + 1, n_2, ..., n_d; t)
+ P(n_1, n_2 - 1, ..., n_d; t) + P(n_1, n_2 + 1, ..., n_d; t) + .... \quad (2.2)
$$

For the origin site we have a slightly different master equation,

$$
\frac{dP(0,0, ..., t)}{dt} = Q + u \sum_{nn} P(0,0, ..., t) - (2ud + k)P(0,0, ..., t) \quad (2.3)
$$
with
\[ \sum_{nn} P(0,0,...;t) = P(-1,0,...,0; t) + P(1,0,...,0; t) + P(0,-1,...,0; t) + P(0,1,...,0; t) + ... \] (2.4)

At large times, these equations can be solved exactly, producing the stationary density profiles,
\[ P^{(s)}(n_1,n_2,...,n_d) = \frac{2Qx^{|n_1|+|n_2|+...+|n_d|}}{\sqrt{k^2 + 4duk}} = \frac{2Q}{\sqrt{k^2 + 4duk}} \exp\left(-\frac{|n_1| - |n_2| - ... - |n_d|}{\lambda}\right), \] (2.5)

where
\[ x = \frac{(2du + k - \sqrt{k^2 + 4duk})}{(2du)}, \quad \lambda = -1/\ln x, \] (2.6)

and \( \lambda \) is a decay length. For \( d = 1 \) these expressions reduce, as expected, to already known results.[49]

Figure 2.1 : A schematic of the discrete-state SDD model for establishment of morphogen gradients in \( d \) dimensions. A specific case of \( d = 2 \) is presented. Signaling molecule are generated at the origin (shown in red) with a rate \( Q \). Particles can also diffuse along the lattice to the neighboring sites with a rate \( u \), or they might be degraded with a rate \( k \).
One can see that that in the steady-state the density profile is the exponentially decaying function with the decay length being independent of the source production rate $Q$. Similar behavior has been observed in multi-dimensional continuum SDD models\cite{20, 32}. In our approach, the continuum limit corresponds to the case when the diffusion rate is much larger than the degradation rate, $u \gg k$. In this case we have $\lambda \simeq \sqrt{du/k}$. At another limit, for fast degradation rates, $k \gg u$, the decay length is equal to $\lambda \simeq 1/\ln (k/2du)$. The analysis of Eqs. 2.5 and 2.6 suggests that increasing $d$ leads to lower probability to find the signaling molecules at the origin, while at the same time the decay in the density profile is also slower. There is an important difference between the predictions for the decay length in the continuum and discrete SDD models. We argue that $\lambda$ is generally larger ($\sim \sqrt{d}$ in the continuum limit), and it might be important for interpretation of experimental results in the formation of morphogen gradients.\cite{19}

### 2.2.1 Local Accumulation Times

An important dynamic property of morphogen gradients formation are local accumulation times. They are defined as average times at which the stationary density profile is achieved at given spatial position. Berezhkovskii and coworkers\cite{31} have introduced a method of calculating explicitly these quantities by using local relaxation functions $R(n_1, n_2, ..., n_d; t)$, which can be written as

$$R(n_1, n_2, ..., n_d; t) = \frac{P(n_1, n_2, ..., n_d; t) - P^{(s)}(n_1, n_2, ..., n_d)}{P(n_1, n_2, ..., n_d; t = 0) - P^{(s)}(n_1, n_2, ..., n_d)}$$

$$= 1 - \frac{P(n_1, n_2, ..., n_d; t)}{P^{(s)}(n_1, n_2, ..., n_d)} \quad (2.7)$$

for the discrete-state multi-dimensional SDD models. The physical meaning of the local relaxation function is that it gives a measure of how close the system to the
Figure 2.2: Local accumulation times in one dimension as a function of distance from the source $r$ for discrete-state and continuum SDD models. (a) Fast degradation rates, $k = 1$, $u = 0.01$; (b) Comparable diffusion and degradation rates, $k = u = 1$; and (c) Fast diffusion rates, $k = 1$, $u = 100$. The predictions for the continuum model are taken from Refs. [20, 32] - see Eq. 2.14. Insets show the same plots for larger length scales.

steady-state conditions. It ranges from $R = 1$ at $t = 0$ to $R = 0$ when the system reaches the stationary state at given location. Introducing the Laplace transform of this function, $\tilde{R}(n_1, n_2, ..., n_d; s) = \int_0^\infty R(n_1, n_2, ..., n_d; t)e^{-st}dt$, it can be shown that
Figure 2.3: Local accumulation times in two dimensions as a function of distance from the source \( r \) for discrete-state and continuum SDD models. (a) Fast degradation rates, \( k = 1, u = 0.01 \); (b) Comparable diffusion and degradation rates, \( k = u = 1 \); and (c) Fast diffusion rates, \( k = 1, u = 100 \). The predictions for the continuum model are taken from Ref. [20] - see Eq. 2.16. Insets show the same plots for larger length scales.

The LAT are given by[31]

\[
t(n_1, n_2, ..., n_d) = -\int_0^\infty t \frac{\partial R(n_1, n_2, ..., n_d; t)}{\partial t} dt = \int_0^\infty R(n_1, n_2, ..., n_d; t) dt = \tilde{R}(n_1, n_2, ..., n_d; s = 0). \tag{2.8}
\]

From this relation the explicit expressions for the local accumulation times can be found:

\[
t(n_1, n_2, ..., n_d) = \frac{2du + k}{k^2 + 4duk} + \frac{|n_1| + |n_2| + ... + |n_d|}{\sqrt{k^2 + 4duk}}. \tag{2.9}
\]

To compare our results with continuum SDD models (which were analyzed for
Figure 2.4: Local accumulation times in three dimensions as a function of distance from the source \( r \) for discrete-state and continuum SDD models. (a) Fast degradation rates, \( k = 1, u = 0.01 \); (b) Comparable diffusion and degradation rates, \( k = u = 1 \); and (c) Fast diffusion rates, \( k = 1, u = 100 \). The predictions for the continuum model are taken from Refs. [20, 32] - see Eq. 2.19. Insets show the same plots for larger length scales.

Spherically symmetric conditions),[20, 32] it is convenient to consider a specific direction in space along a radial vector \( \vec{r} = (n_1, n_2, ..., n_d) \) where \( |n_1| = |n_2| = ... = |n_d| \).

One can easily show that \( |n_1| = \frac{r}{\sqrt{d}} \) where \( r \) is the radius of hypersphere enclosing the hypercube of volume \( (2 |n_1|)^d \). This corresponds to a line of length \( 2 |n_1| \), a square of area \( 4 |n_1|^2 \) and a cube of volume \( 8 |n_1|^3 \) in one, two and three dimensions respectively. Therefore, the equivalent expression for the LAT at the distance \( r \) from the origin is equal to

\[
t(r) = \frac{(2du + k)}{(k^2 + 4duk)} + \left(\frac{\sqrt{d}}{\sqrt{k^2 + 4duk}}\right)r. \tag{2.10}
\]
In the fast degradation limit, \( k \gg u \), this equation simplifies into

\[
t(r) \simeq \frac{1}{k} + \frac{r\sqrt{d}}{k}.
\]  

(2.11)

In the fast diffusion case, \( u \gg k \), we obtain

\[
t(r) \simeq \frac{1}{2k} + \frac{r}{2\sqrt{uk}}.
\]  

(2.12)

The dependence of the LAT on the radial distance \( r \) for 1D, 2D and 3D systems for various sets of parameters is illustrated in Figs. 2.2-2.4. In one dimension, the expression for the local accumulation time derived in the discrete-state SDD model reads as

\[
t(r) \simeq \frac{2u + k}{k^2 + 4uk} + \frac{r}{\sqrt{k^2 + 4uk}},
\]  

(2.13)

while in the continuum SDD model it was shown that[32, 20]

\[
t(r) \simeq \frac{1}{2k} + \frac{r}{2\sqrt{uk}}.
\]  

(2.14)

The last expression could also be obtained in the limit of very large diffusion, \( u \gg k \), from Eq. 2.13. These results are plotted in Fig. 2.2. For fast diffusion rates the predictions from discrete and continuum calculations, as expected, fully agree (see Fig. 2.2c). The deviations between discrete and continuum models start to appear for comparable diffusion and degradation rates (Fig. 2.2b), and for fast degradation rates (Fig. 2.2a) the local accumulation times for discrete case is smaller for all range of distances except very close to the origin. In this regime the continuum model cannot be applied, but the discrete-state approach is valid for analyzing reaction-diffusion processes of morphogen gradients formation.

Similar calculations in two dimensions yield the following expression for the LAT,

\[
t(r) \simeq \frac{4u + k}{k^2 + 8uk} + \frac{\sqrt{2}r}{\sqrt{k^2 + 8uk}}.
\]  

(2.15)
The 2D continuum SDD model predicts the following result,[20]

\[ t(r) \simeq \frac{r}{2\sqrt{uk}} \frac{K_1(r\sqrt{k/u})}{K_0(r\sqrt{k/u})}, \]  

(2.16)

where \( K_m(x) \) is the \( m \)-th order modified Bessel function of the second kind. Note that taking the limit of \( u \gg k \) in our theoretical approach in Eq. 2.15, which supposed to be corresponding to the continuum limit, produces a different expression,

\[ t(r) \simeq \frac{1}{2k} + \frac{r}{2\sqrt{uk}}. \]  

(2.17)

Fig. 2.3 presents these functions for different sets of parameters. We can see that even for large diffusion rates (Fig. 2.3c) the predictions of discrete and continuum models do not fully agree, but for large distances from the source the differences are small. Again, as for 1D case, the deviations between two approaches start to build up with decreasing the diffusion rate (Fig. 2.3b), and for large degradation rates the LAT for the discrete-state model are significantly smaller for most distances, except for very small \( r \) (Fig. 2.3a).

For 3D systems the expressions for the local accumulation times in the discrete SDD model is given by

\[ t(r) \simeq \frac{6u + k}{k^2 + 12uk} + \frac{\sqrt{3}r}{\sqrt{k^2 + 12uk}}. \]  

(2.18)

The continuum description of the same reaction-diffusion processes yields,[32, 20]

\[ t(r) \simeq \frac{r}{2\sqrt{uk}}. \]  

(2.19)

For this case, the LAT are presented in Fig. 2.4. The observed trends are very similar to 2D systems, but with stronger deviations between discrete and continuum predictions.
Figure 2.5: Local accumulation times at the position $r = 10$ as a function of spatial dimensions. Upper curve corresponds to the fast degradation rates, $k = 1$, $u = 0.01$. The middle curve is for comparable diffusion and degradation rates, $k = u = 1$. The lower curve describes the fast diffusion regime, $k = 1$, $u = 100$.

Again, even in the continuum limit our theoretical predictions for the LAT do not agree with calculations from continuum SDD models,[20, 32] although for large $r$ the differences are not significant.

Comparing local accumulation times for discrete-state and continuum SDD models, the important observation can be made that for all regimes the continuum models in both 2D and 3D predict $t(r = 0) = 0$, while in the discrete-state analysis this time is always finite. Since at $t = 0$ there are no morphogens in the system and the LAT is associated with the time to reach the stationary density at given position, it is expected that this quantity to be finite even at the origin. It seems that predictions of the continuum models do not satisfy this requirement for $d > 1$, suggesting that
they cannot properly describe reaction-diffusion processes of formation of signaling molecules profiles close to the origin, even for conditions when the continuum approximation should hold. No such problems exist for the discrete-state approach. This is the main reason for predicting multiple time scales in the continuum description (for \( d > 1 \)) of the development of signaling molecules profiles. In the discrete model there is one time scale, given by the LAT, at all distances. The main reason for this discrepancy is that current continuum SDD models assume that there are spherically-symmetric solutions at all length scales\[20, 32\]. Obviously, very close to the source this is not working. Note that one could solve the problem in Cartesian coordinates in the continuum limit and it does show that solutions are not spherically symmetric near the source, in agreement with our arguments.

It is interesting also to investigate the role of dimensionality in the establishment of morphogen gradients. For fast degradation the discrete model predictions are given by Eq. 2.11, while in the fast diffusion limit they are given by Eq. 2.12. The dependencies of the local accumulation times on dimension \( d \) for the discrete and continuum SDD models are plotted in Fig. 2.5 for the sites that are far away from the source \((r \gg 0)\), and in Fig. 2.6 for the sites that are close to the origin \((r = 0)\). Surprisingly, the results are quite different. For fast degradation rates, the LAT is increasing with \( d \) for the sites not so close to the source, while at the origin and closest sites the LAT is slowly decreasing (compare upper plots in Figs. 2.5 and 2.6). A similar behavior is observed for comparable diffusion and degradation rates, although the effect is getting weaker (see middle plots in Figs. 2.5 and 2.6).

For continuum limit, \( u \gg k \), the LAT in both positions become independent of the dimension, as correctly predicted by Eq. 2.12. The following arguments can be given to understand this behavior in the discrete SDD model. At \( t = 0 \) the signaling
molecules start at the origin, $r = 0$. The local accumulation time is the average time to reach the steady-state density at a given position, so it depends on possible pathways connecting the origin and any site at $r > 0$. Increasing the dimensionality produces more pathways so it takes longer time if the diffusion is the rate limiting step. For this reason, the LAT depends on $d$ for diffusion rates comparable or smaller the degradation, while for $u \gg k$ there is no dependence on the dimension - the degradation is a rate-limiting step in this case. At sites close to the origin these diffusion pathways do not play any role. But the stationary density at these sites is also smaller for larger $d$, so it is faster to reach the steady-state concentration with increasing $d$ when the diffusion is rate limiting.
2.2.2 Mean First-Passage Times

It has been argued before that in order to understand mechanisms of formation of morphogen gradients it is useful to consider mean first-passage times (MFPT) to reach specific locations for molecules starting from the origin.\[49\] The reason for this is the fact that first-passage events are the dominating factors determining the local accumulation times at large distances, at least for one-dimensional systems,\[49\]; the explicit connections between these quantities have been recently studied for \( d = 1.\)\[16\] It is important to understand if first-passage processes describe the morphogen gradient formation in higher dimensions.

To compute MFPT we define \( f(n_1, n_2, ..., n_d; t) \) to be a first-passage probability to reach for the first time the site \( \vec{n} = (n_1, n_2, ..., n_d) \) at time \( t \) if at \( t = 0 \) the particle started at the origin. The temporal evolution of this function follows a backward master equation,\[133\]

\[
\frac{df(n_1, n_2, ..., n_d; t)}{dt} = u \sum_{nn} f(n_1, n_2, ..., n_d; t) - (2ud + k) f(n_1, n_2, ..., n_d; t), \quad (2.20)
\]

where \( \sum_{nn} \) is the operator that sums over all nearest neighbors. Utilizing the Laplace transformations, we obtain

\[
\tilde{f}(n_1, n_2, ..., n_d; s) = \frac{2\sqrt{a^2 - 4d^2u^2} y^{\sum|n_i|} - (a - 2du - \sqrt{a^2 - 4d^2u^2}) y^{\sum|n_i|}}{(a + \sqrt{a^2 - 4d^2u^2}) y^{\sum|n_i| + 2|n_d|}} - (a - 2du - \sqrt{a^2 - 4d^2u^2}), \quad (2.21)
\]

where

\[
a = s + 2du + k, \quad y = \left[ a + \sqrt{a^2 - 4d^2u^2} \right] / 2ud. \quad (2.22)
\]

The conditional mean first-passage time to reach the site \( \vec{n} = (n_1, n_2, ..., n_d) \) can be found from the following expression,

\[
\tau(n_1, n_2, ..., n_d) = - \frac{\frac{d\tilde{f}(n_1, n_2, ..., n_d; s)}{ds}}{\tilde{f}(n_1, n_2, ..., n_d; s)|_{s=0}} \quad (2.23)
\]
After some algebra, the corresponding expression for the MFPT is derived,

\[
\tau(n_1, n_2, \ldots, n_d) = \frac{1}{\sqrt{k^2 + 4duk}} \left[ -\frac{2du + k}{\sqrt{k^2 + 4duk}} \right. \\
+ \frac{(2du + k + \sqrt{k^2 + 4duk})z^{|n_1|+|n_2|+\ldots+|n_d|} - (2du + k - \sqrt{k^2 + 4duk})z^{-|n_1|-|n_2|\ldots-|n_d|}}{(k + \sqrt{k^2 + 4duk})z^{|n_1|+|n_2|+\ldots+|n_d|} - (k - \sqrt{k^2 + 4duk})z^{-|n_1|-|n_2|\ldots-|n_d|}} \\
+ \frac{|n_1| + |n_2| + \ldots + |n_d|)(2du + k - \sqrt{k^2 + 4duk})z^{-|n_1|+|n_2|+\ldots+|n_d|} - (k - \sqrt{k^2 + 4duk})z^{-|n_1|-|n_2|\ldots-|n_d|}}{(k + \sqrt{k^2 + 4duk})z^{|n_1|+|n_2|+\ldots+|n_d|} - (k - \sqrt{k^2 + 4duk})z^{-|n_1|-|n_2|\ldots-|n_d|}} \right].
\]

(2.24)

where \( z = \left[ 2du + k + \sqrt{k^2 + 4duk} \right] / 2du \). For fast degradation rate, \( k \gg u \), we obtain a much simpler expression,

\[
\tau(n_1, n_2, \ldots, n_d) \simeq \frac{|n_1| + |n_2| + \ldots + |n_d| + 1}{k},
\]

(2.25)

which for large radial distances, \( r \gg 1 \), can also be written as

\[
\tau(r) \simeq \frac{r\sqrt{d}}{k}.
\]

(2.26)

One can see that this expression agrees well with Eq. 2.11 at large \( r \). In the opposite limit of the fast diffusion rates (continuum limit), \( u \gg k \), one can show that the MFPT are equal to

\[
\tau(n_1, n_2, \ldots, n_d) \simeq \frac{|n_1| + |n_2| + \ldots + |n_d| + 1}{2\sqrt{kud}}.
\]

(2.27)

For \( r \gg 1 \) it modifies into

\[
\tau(r) \simeq \frac{r}{2\sqrt{uk}},
\]

(2.28)

which asymptotically agree with Eq. 2.12 at large distances.

These results again support the idea that main contribution to the LAT at large distances from the origin are due to the MFPT, extending the validity of this idea to
Figure 2.7: The ratio of MFPT over LAT as a function of distance from the source for different dimensions for the discrete-state SDD models. (a) Fast degradation rates, $k = 1, u = 0.01$; (b) Comparable diffusion and degradation rates, $k = u = 1$; and (c) Fast diffusion rates, $k = 1, u = 100$.

all dimensions. This is an important observation since the first-passage analysis is a well developed mathematical tool that was already successfully employed for analyzing multiple physical, chemical and biological processes.[133] To support arguments about the importance of the first-passage events in dynamics of the morphogen gradient development, the ratio of MFPT over LAT is plotted in Fig. 2.7 for different sets of parameters. One can see that this ratio is always approaching 1 for large distances. Larger degradation rates as well as higher dimensions lead to faster converging to unity, while in the continuum limit (fast diffusion rates) the effect of dimension disappears.
2.2.3 Effective Potentials

Analyzing mechanisms of morphogen gradient formation suggested a new idea that degradation can be viewed as an effective potential that drives the signaling molecules away from the source.[49] Thus morphogens are not simply diffusing with equal probability in each direction, but their motion is biased by this effective potential to move further away from the source. This concept can be extended and applied for the multi-dimensional SDD models of creating signaling molecules profiles.

The effective potential can be easily calculated from the stationary profile, leading to

\[
U_{\text{eff}}(n_1, n_2, ..., n_d) \simeq k_B T \ln P^{(s)}(n_1, n_2, ..., n_d) = k_B T | n_1 | + | n_2 | + ... + | n_d | \ln x, \quad (2.29)
\]

and it can be rewritten as follows (for \(i = 1, 2, ..., d\)),

\[
U_{\text{eff}}(n_1, n_2, ..., n_d) \simeq \sum_{i=1}^{d} U_{\text{eff}}(n_i), \quad U_{\text{eff}}(n_i) = k_B T | n_i | \ln x. \quad (2.30)
\]

This equation has an important physical meaning suggesting that the overall potential is a sum of potentials along each of the coordinate axes. Consequently, in higher dimensions the effective potential is stronger than one dimension. The reason for this is that in higher dimensions morphogens can diffuse in more directions and thus the probability of returning to the origin decreases as \(\sim 1/d\). It also suggests that there is a constant force component,

\[
F_i = -\frac{\partial U_{\text{eff}}}{\partial | n_i |} = -k_B T \ln x = k_B T / \lambda, \quad (2.31)
\]

along each axis that drives signaling molecules away from the source.

The importance of this concept can be seen in explaining most dynamic properties of morphogen reaction-diffusion systems. The linear dependence of the LAT on
distances from the sources [see Eq. 2.9] is the consequence of the effective potential that changes the unbiased diffusion of morphogen molecules into a driven motion. Similarly, the linear dependencies of the MFPT on distances have the origin: see Eq. 2.24. It also provides an alternative explanation for dependence of the LAT on dimension for sites near the source (Fig. 6): increasing \( d \) make this potential stronger so it drives particles faster to their destinations. The same reasoning can be used to understand why the MFPT approximate the LAT better at higher dimensions or at faster degradations (Fig. 2.7).

Figure 2.8: The ratio of variance over LAT as a function of distance from the source for different dimensions for the discrete-state SDD models. (a) Fast degradation rates, \( k = 1, u = 0.01 \); (b) Comparable diffusion and degradation rates, \( k = u = 1 \); and (c) Fast diffusion rates, \( k = 1, u = 100 \).
2.2.4 Variance of Local Accumulation Times

The advantage of presented theoretical method is that it allows us to calculate all dynamic properties of the morphogen gradient formation. To illustrate this, let consider higher moments of the local accumulation times. The LAT itself is the first moment as indicated in Eq. 2.8. The second moment, which is a mean-squared local accumulation time, can be also calculated from the local relaxation function,

$$<t^2(n_1, n_2, ..., n_d) >= - \int_0^\infty t^2 \frac{dR(n_1, n_2, ..., n_d; t)}{dt} dt = -2 \frac{d\tilde{R}(n_1, n_2, ..., n_d; s)}{ds} \bigg|_{s=0}. \quad (2.32)$$

Substituting the explicit expression for \( \tilde{R}(n_1, n_2, ..., n_d; s) \) we obtain,

$$<t^2(n_1, n_2, ..., n_d) >= \frac{2(|n_1| + |n_2| + ... + |n_d|)^2 - 2}{(k^2 + 4duk)} + \frac{4(2du + k)(|n_1| + |n_2| + ... + |n_d|)}{(k^2 + 4duk)^{3/2}} + \frac{6(2du + k)^2}{(k^2 + 4duk)^2}. \quad (2.33)$$

It can be shown that generally the \( m \)-th moment of the LAT is given by

$$<t^m(n_1, n_2, ..., n_d) >= (-1)^{m-1} m \frac{d^{m-1} \tilde{R}(n_1, n_2, ..., n_d; s)}{ds^{m-1}} \bigg|_{s=0}. \quad (2.34)$$

The explicit forms for the first and second moments of the LAT allow us to calculate a variance, which gives a measure of fluctuations in the local accumulation times. The variance of the local accumulation time is equal to

$$\sigma(n_1, n_2, ..., n_d) = \sqrt{<t^2> - <t>^2} = \left( \frac{|n_1| + |n_2| + ... + |n_d|}{(k^2 + 4duk)} \right)^2 - 2 + \frac{2(2du + k)(|n_1| + |n_2| + ... + |n_d|)}{(k^2 + 4duk)^{3/2}} + \frac{5(2du + k)^2}{(k^2 + 4duk)^2} \right)^{1/2}. \quad (2.35)$$

In terms of the radial distance \( r \) the variance can be written as

$$\sigma(r) = \left[ \frac{dr^2 - 2}{(k^2 + 4duk)} + \frac{2r \sqrt{d(2du + k)}}{(k^2 + 4duk)^{3/2}} + \frac{5(2du + k)^2}{(k^2 + 4duk)^2} \right]^{1/2}. \quad (2.36)$$
In the limit of fast diffusion rates (continuum limit) the expression for the variance is simpler,
\[ \sigma(r) \simeq \frac{\sqrt{5}}{2k} + \frac{r}{2\sqrt{5}uk}. \] (2.37)
This result implies that the variance becomes independent of the dimension for \( u \gg k \).

For the case of the fast degradation rates \( (k \gg u) \) the variance behavior is different,
\[ \sigma(r) \simeq \sqrt{dr^2 + 2r\sqrt{d} + 3}. \] (2.38)
In this limit the variance increases with \( d \) but becomes independent of the diffusion rate. The variances normalized with respect to the LAT are presented in Fig. 2.8. We can see that at large distance the ration \( \sigma(r)/t(r) \) is always approaching unity. The increase in the degradation rates lowers the variance, while increasing the diffusion rate make the system more noisy. At fast degradation rates, increasing the dimension lowers the variance (Fig. 2.8a), while for large diffusion rates there is no dependence on \( d \). The importance of these observations is that they suggest possible ways of how nature might control noise in morphogen gradient systems.

### 2.3 Summary and Conclusions

We developed a multi-dimensional discrete-state stochastic theoretical framework for understanding reaction-diffusion processes of morphogen gradients formation. The approach provides a full analytical description of stationary state and dynamic properties of complex systems where signaling molecules profiles are created. It allowed us to fully analyze the role of discreteness by comparing with current continuum theoretical models, as well as the effect of the dimensionality.

It is found that at large times the system will reach stationary exponential density profiles with the decay length that increases with the dimension, in contrast to the
continuum methods which predict the decay length to be independent of $d$. The differences between two approaches become larger in analyzing dynamic properties such as the local accumulation times that describe the relaxation to the stationary-state behavior. Continuum models predict that the LAT is approaching zero at the source, resulting in multiple time scales that control dynamics of the system. In contrast, our calculations suggest that the local accumulation times are always finite and they provide the only time scale to describe the kinetics of morphogen gradients formation. Thus, it is argued that current continuum models cannot be used in analyzing these complex reaction-diffusion dynamics at distances closer to the source, while our discrete approach does not have any problems.

From the presented discrete method an interesting dependence of dynamic properties on dimensions is observed. It is found that for sites close to the source, when the degradation is faster than the diffusion, the LAT times decrease with the dimension, while for regions far away from the source the dependence is reversed. At the same time, for large diffusion rates no effect is observed at any distance. It is explained by accounting for possible pathways connecting the source and the given location in the system. We also analyzed another dynamic property, mean first-passage times. It is shown that at large distances from the source the MFPT provide an excellent approximation for the LAT, and the approximation is better for higher dimensions and larger degradation rates, while at the continuum limit (fast diffusion) there is no dependence on $d$ and the approximation works not as well.

The concept that degradation processes can be viewed as an effective potential that pushes signaling molecules away from the source has been extended to multi-dimensional systems. It is found that increasing the dimension makes this potential stronger, and this simple idea was powerful enough to explain most trends in dynamic
properties, such as the linear dependence of the LAT and MFPT on the distances and the effect of dimensions. In addition, the method allowed us to compute higher moments of the local accumulation times, and specific calculations have been made for estimation of variances.

It was argued that the presented discrete-state stochastic approach allows to capture all relevant physical-chemical properties of the development of morphogen gradients. The main success of the method is a full analytical description of all involved processes at all times and distances. Another advantage is that other biochemical and biophysical processes can be consistently incorporated. In the following chapters the models are extended to take into account more complex phenomena such as non-uniform production rates, cooperative mechanisms of degradation and also spatially varying degradation rates. It will be also very important to test these theoretical ideas in experimental studies.
Chapter 3

The Role of Source Delocalization in the Development of Morphogen Gradients

3.1 Introduction

The majority of investigations of morphogen gradients formation that use the SDD models postulate that the signaling molecules are produced from a sharply localized source [15, 16, 17, 31, 32, 38, 49, 58]. However, experimental observations suggest that in many biological systems the production region of the morphogens is delocalized [9]. Morphogens are protein molecules that are synthesized from the corresponding RNA molecules. So the production of these signaling molecules to a large degree is determined by the distribution of the corresponding RNA molecules.

For one of the most intensely studied system, the formation of bicoid morphogen in early Drosophila embryo, it is known that the maternal RNA molecules are distributed over the region of size 30-50 $\mu$m, while the total length of the embryo is of order of 400 $\mu$m [9]. Obviously, in this case the production area cannot be defined as sharply localized. This raises many queries on the role of the source production in the developing morphogen gradients. Specific questions include: why the synthesis of signaling molecules is delocalized, why it is not produced over the whole embryo, and how the morphogen gradient depends on the spatial distribution of the source and on the synthesis rate? At the same time, although some of these issues were discussed, a comprehensive theoretical analysis of the delocalization of signaling
molecules synthesis is not available [15, 16, 17, 27, 28, 29, 31].

Experimental investigations suggest that specific distribution of maternal RNA molecules within cells controls the synthesis of morphogen molecules [52]. Three distinct mechanisms of RNA localization have been identified, including the protection from RNA degradation over the specific regions, diffusion of RNA molecules coupled with entrapment at specific locations and directed transport by motor proteins along cytoskeleton filaments [52]. The first mechanisms leads to mostly uniform production distribution of signaling molecules over finite regions, while the second and the third mechanisms produce mostly exponential source distributions.

In this chapter, we present a theoretical investigation on the role of source production in the development of morphogen gradients [44]. A theoretical approach for analyzing the formation of signaling molecules concentration profiles with arbitrary delocalization length and production rates is developed. Our method is based on discrete-state stochastic models that can be explicitly solved for arbitrary sets of parameters. We investigate several possible cases of the formation of signaling molecules concentration profiles to analyze the role of the synthesis of the signaling molecules. It is shown that the production might have a strong impact on the development of morphogen gradients.

3.2 Theoretical Method

We start our analysis by considering a general discrete-state stochastic SDD model in one dimension as illustrated in Fig. 3.1. Our system is semi-infinite. It is assumed that the synthesis of the morphogen particles is taking place only in the interval consisting of \( L \) sites: see Fig. 3.1. Inside the source region, signalling molecules are produced at any site \( m \) (0 \( \leq \) \( m \) \( \leq \) \( L \)) with a corresponding rate \( Q_m \), and the total
Figure 3.1: A schematic view of the one-dimensional discrete-state SDD model for the formation of the morphogen gradients. The production of morphogens is distributed over an interval of length $L$. Signalling molecule are produced at the sites $1 \leq m \leq L$ (shown in red) with a rate $Q_m$. Particles can also diffuse along the lattice to the neighboring sites with a rate $u$, or they might be degraded with a rate $k$.

production rate is equal to $Q = \sum_{m=0}^{L} Q_m$. From any site morphogens can jump to nearest neighbors left or right sites with a rate $u$. The particles might be degraded at any site with a rate $k$. One can define a function $P(n, t; m)$ as the probability to find the morphogen at the site $n$ at time $t$ if the particle can only be produced at the site $m$ ($0 \leq m \leq L$). The temporal evolution of this probability is governed by the following master equations:

$$\frac{dP(m, t; m)}{dt} = Q_m \delta_{m,n} + u[P(m-1, t; m) + P(m+1, t; m)] - (2u + k)P(m, t; m)$$

(3.1)

for $n > 0$, and

$$\frac{dP(0, t; m)}{dt} = Q_0 \delta_{m,0} + uP(1, t; m) - (u + k)P(0, t; m)$$

(3.2)

for $n = 0$. Here we use the fact that $\delta_{m,n} = 1$ for $m = n$, and it is zero otherwise. At long times we have $\frac{dP(n, t, m)}{dt} = 0$, and these equations can be solved analytically,
yielding the following stationary probability functions,

$$P_<(n; m) = \frac{Q_m[(k + \sqrt{k^2 + 4uk})x^{m-n} + (-k + \sqrt{k^2 + 4uk})x^{n+m}]}{(k + \sqrt{k^2 + 4uk})\sqrt{k^2 + 4uk}}$$

(3.3)

for $0 \leq n \leq m$, and

$$P_>(n; m) = \frac{Q_m[(k + \sqrt{k^2 + 4uk})x^{n-m} + (-k + \sqrt{k^2 + 4uk})x^{n+m}]}{(k + \sqrt{k^2 + 4uk})\sqrt{k^2 + 4uk}}$$

(3.4)

for $m \leq n$. In these expressions, the subscript $<$ ($>$) corresponds to the case of $n \leq m$ ($n > m$), and a parameter $x$ ($0 < x < 1$) is defined as

$$x = \frac{(2u + k - \sqrt{k^2 + 4uk})}{(2u)}.$$  

(3.5)

This approach is very useful since it allows us to obtain the total concentration profiles from all producing sites using a kind of a superposition principle. In other words, the total probability $P(n, t)$ of finding the particle at site $n \geq 0$ at time $t$ can be expressed as a sum of the probabilities $P(n, t; m)$ with production at the specific site $m$ ($0 \leq m \leq L$). This is because the synthesis processes at each site are independent of each other. The general equations for concentration profiles are given by

$$P(n, t) = \begin{cases} 
    \sum_{m=0}^{n} P_<(n, t; m) + \sum_{m=n+1}^{L} P_>(n, t; m), & \text{for } 0 \leq n \leq L; \\
    \sum_{m=0}^{L} P_>(n, t; m), & \text{for } L < n.
\end{cases}$$

(3.6)

The explicit expressions can be easily obtained by employing Eqs. 3.3 and 3.4. One of the main goals of morphogen gradients is to transfer the information. Most probably, it can be done well if the system is close to the stationary conditions. Then the important characteristics of morphogen gradients are times needed to achieve the steady state at specific spatial locations. These times are known as local accumulation
times (LAT), and a theoretical framework for computing these quantities has been developed recently [31]. It can be done utilizing local relaxation functions which are defined as

\[ R(n, t) = \frac{P(n, t) - P^{(s)}(n)}{P(n, t = 0) - P^{(s)}(n)} = 1 - \frac{P(n, t)}{P^{(s)}(n)}. \] (3.7)

The physical meaning of these functions is that they represent the relative distance to the stationary state: at \( t = 0 \) the distance is one, while at steady state it is equal to zero. The explicit formulas for the local accumulation time can be derived then via Laplace transformations of the local relaxation function, \( \tilde{R}(n, s) = \int_0^\infty R(n, t)e^{-st}dt \) [31],

\[ t(n) = -\int_0^\infty t \frac{\partial R(n, t)}{\partial t} e^{-st}dt = \tilde{R}(n, s = 0). \] (3.8)

### 3.3 Illustrative Examples

Our approach allows us to analyze the formation of morphogen gradients for arbitrary length of the production region and for arbitrary production rates. To explain it better, we illustrate the method by doing explicit calculations for four different production scenarios, which might be relevant for the morphogen gradients formation in real cellular conditions.

#### 3.3.1 Single Localized Source

As a first example, we start with the case when the source of signaling molecules is localized at the site \( m = m' \),

\[ Q_m = Q\delta(m - m'). \] (3.9)
Figure 3.2: Steady-state density profiles as a function of the distance from the origin. Red curves correspond to the single localized source at $m' = 0$. Green curves correspond to uniform production rates along the finite interval. Blue curves correspond to exponentially decaying production rates along the semi-infinite interval. $L = \lambda_s = 10\lambda$ is assumed for the single localized and uniform productions, while $\lambda_s = 10\lambda$ and $L \to \infty$ are assumed for the exponentially distributed productions. (a) Fast degradation rates with $k = 1, u = 0.01$; (b) Comparable diffusion and degradation rates with $k = u = 1$; and (c) Fast diffusion rates with $k = 1, u = 100$.

From equations (3.3) and (3.4) we directly obtain

$$P^{(s)}_<(n; m') = \frac{Q x^{m'}}{k + \sqrt{k^2 + 4uk}} \left[ (k + \sqrt{k^2 + 4uk})x^{-n} + (-k + \sqrt{k^2 + 4uk})x^n \right],$$

$$P^{(s)}_>(n; m') = \frac{Q x^n}{k + \sqrt{k^2 + 4uk}} \left[ (k + \sqrt{k^2 + 4uk})x^{-m'} + (-k + \sqrt{k^2 + 4uk})x^{m'} \right].$$
Figure 3.3: Steady-state density profiles as a function of the distance from the origin. Red curves correspond to the single localized source at $m' = 0$. Green curves correspond to uniform production rates along the finite interval. Blue curves correspond to exponentially decaying production rates along the semi-infinite interval. $L = \lambda s = 10\lambda$ is assumed for the single localized and uniform productions, while $\lambda s = \lambda$ and $L \rightarrow \infty$ are assumed for the exponentially distributed productions. (a) Fast degradation rates with $k = 1, u = 0.01$; (b) Comparable diffusion and degradation rates with $k = u = 1$; and (c) Fast diffusion rates with $k = 1, u = 100$. For $m' = 0$, as expected, we recover the results obtained earlier [49],

$$P^{(s)}(n; 0) = \frac{2Qx^n}{k + \sqrt{k^2 + 4uk}}.$$ \hfill (3.12)

These expressions indicate that the signaling molecules profiles are exponentially decaying functions of the distance from the source for $n > m'$, and the decay length,
\( \lambda = -1/\ln x \), is independent of the production rate \( Q \). The resulting morphogen gradients are presented in Figs. 3.2 and 3.3 for the case of \( m' = 0 \) with various diffusion and degradation rates. From relations (3.7) and (3.8) the explicit expressions for the local accumulation times can be evaluated. It is found that LAT are given by

\[
\begin{align*}
t_< (n; m') &= \frac{1}{\sqrt{k^2 + 4uk}} \left[ m' + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right] \\
&+ \frac{n}{\sqrt{k^2 + 4uk}} \left[ \frac{x^n(-k + \sqrt{k^2 + 4uk}) - x^{-n}(k + \sqrt{k^2 + 4uk})}{x^{-n}(k + \sqrt{k^2 + 4uk}) + x^n(-k + \sqrt{k^2 + 4uk})} \right] \\
&+ \frac{2uk}{k^2 + 4uk} \left[ \frac{(x^n - x^{-n})}{x^{-n}(k + \sqrt{k^2 + 4uk}) + x^n(-k + \sqrt{k^2 + 4uk})} \right],
\end{align*}
\]

(3.13)

\[
\begin{align*}
t_>(n; m') &= \frac{1}{\sqrt{k^2 + 4uk}} \left[ n + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right] \\
&+ \frac{m'}{\sqrt{k^2 + 4uk}} \left[ \frac{x^{m'}(-k + \sqrt{k^2 + 4uk}) - x^{-m'}(k + \sqrt{k^2 + 4uk})}{x^{-m'}(k + \sqrt{k^2 + 4uk}) + x^{m'}(-k + \sqrt{k^2 + 4uk})} \right] \\
&+ \frac{2uk}{k^2 + 4uk} \left[ \frac{(x^{m'} - x^{-m'})}{x^{-m'}(k + \sqrt{k^2 + 4uk}) + x^{m'}(-k + \sqrt{k^2 + 4uk})} \right].
\end{align*}
\]

(3.14)

Again, for the source localized at the origin, \( m' = 0 \), our results reproduce the already known expression [49],

\[
t(n) = \frac{1}{\sqrt{k^2 + 4uk}} \left[ n + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right].
\]

(3.15)

LAT for the formation of morphogen gradients with \( m' = 0 \) for various diffusion and degradation rates are presented in Figs 3.4 and 3.5. One can see that the local accumulation times for the sharply localized source linearly grow with the distance from the source. This can be explained by invoking the idea that the degradation acts as an effective potential that pushes the signaling molecules away from the source [49], leading to effectively driven diffusion of morphogens in the system.
Figure 3.4: Local accumulation times as a function of the distance from the origin. Red curves correspond to the single localized source at \( m' = 0 \). Green curves correspond to uniform production rates along the finite interval. Blue curves correspond to exponentially decaying production rates along the semi-infinite interval. \( L = \lambda_s = 10\lambda \) is assumed for the single localized and uniform productions, while \( \lambda_s = 10\lambda \) and \( L \to \infty \) are assumed for the exponentially distributed productions. (a) Fast degradation rates with \( k = 1, u = 0.01 \); (b) Comparable diffusion and degradation rates with \( k = u = 1 \); and (c) Fast diffusion rates with \( k = 1, u = 100 \).

### 3.3.2 Uniformly Distributed Production Over the Finite Interval

In another example, we consider uniformly distributed production of signaling molecules along a finite interval of length \( L \). This distribution can be represented as follows,

\[
Q_m = \begin{cases} 
\frac{Q}{L+1}, & 0 \leq m \leq L; \\
0, & m > L.
\end{cases}
\]  
(3.16)
In this case, the synthesis rates are the same for all production sites. Applying Eq. 3.6, one can obtain explicit expressions for the stationary profiles. They are different depending on the position of the lattice site with respect to the production region.

Inside the production area we have

$$P_s^{(s)} (n) = \frac{Q x^n}{(L + 1)(k + \sqrt{k^2 + 4uk})} \times \left[ \frac{(k + \sqrt{k^2 + 4uk})(x - x^{-n} - x^{1-n} + x^{L-2n+1}) + (-k + \sqrt{k^2 + 4uk})(-1 + x^{L+1})}{(x - 1)\sqrt{k^2 + 4uk}} \right],$$  \hspace{1cm} (3.17)

while outside it can be shown that

$$P_s^{(s)} (n) = \frac{Q x^n}{(L + 1)(k + \sqrt{k^2 + 4uk})} \times \left[ \frac{(k + \sqrt{k^2 + 4uk})(x - x^{-L}) + (-k + \sqrt{k^2 + 4uk})(-1 + x^{L+1})}{(x - 1)\sqrt{k^2 + 4uk}} \right].$$  \hspace{1cm} (3.18)

The maximal value of the concentration is achieved for \( n = 0 \),

$$P_s^{(s)} (n = 0) = \frac{2Q(-1 + x^{L+1})}{(x - 1)(k + \sqrt{k^2 + 4uk})(L + 1)}. $$  \hspace{1cm} (3.19)

The concentration profiles normalized by this maximal value are presented in Figs. 3.2 and 3.3. A stationary-state behavior of the morphogen gradients with the uniform production along the finite interval can be generally described in the following way. The concentration of signaling molecules is large and almost constant in the production region, and then it exponentially decays outside of the synthesis area. The transition between these two regimes depends on parameters of the system. Decreasing the diffusion and/or increasing the degradation rate makes this crossover sharper. In addition, the transition is more abrupt when the production length \( L \) is much larger than the decay length \( \lambda \) (see Fig. 3.2 where \( L = 10\lambda \) is utilized), while
Figure 3.5: Local accumulation times as a function of the distance from the origin. Red curves correspond to the single localized source at \( m' = 0 \). Green curves correspond to uniform production rates along the finite interval. Blue curves correspond to exponentially decaying production rates along the semi-infinite interval. \( L = \lambda_s = \lambda \) is assumed for the single localized and uniform productions, while \( \lambda_s = \lambda \) and \( L \to \infty \) are assumed for the exponentially distributed productions. (a) Fast degradation rates with \( k = 1, u = 0.01 \); (b) Comparable diffusion and degradation rates with \( k = u = 1 \); and (c) Fast diffusion rates with \( k = 1, u = 100 \).

for comparable \( L \) and \( \lambda \) (see Fig. 3.3 where \( L = \lambda \) is utilized) the concentration profile decays more smoothly.

It is interesting to analyze the behavior of the profiles in the asymptotic limit of very large production intervals, \( L \to \infty \),

\[
P^{(s)}(n, L \to \infty) \simeq \frac{Q(1 + x)}{L(1 - x)\sqrt{k^2 + 4uk}}. \tag{3.20}
\]
This corresponds to the case when the morphogens are synthesized all over the embryo with the same production rates. As expected, the concentration profile becomes uniform, and this is the reason why there is no dependence on the position $n$ in this equation. Obviously, the morphogen gradient cannot be established in such systems, and this is not a realistic situation for biological development. This might be the reason why the production region does not occupy the whole embryo. As was discussed above, the local accumulation times for uniform production along the finite intervals can be found from Eqs. 3.7 and 3.8. LAT for sites inside the production region are given by

$$ t_<(n) = \frac{1}{\sqrt{k^2 + 4uk}} \left[ n + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right] $$.  

while for the outside region we have

$$ t_<(n) = \frac{1}{\sqrt{k^2 + 4uk}} \left[ n + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right] $$.  

The results for local accumulation times are presented in Figs 3.4 and 3.5. For the uniform production along the finite interval the LAT usually consist of two parts.
Inside the production area LAT is almost constant as a function of the distance from the origin. At the same time, outside of the production area LAT is linearly growing. Again, arguments using the role of the degradation as an effective potential can be employed [49]. Outside of the synthesis region, the degradation creates the potential that moves particles away from the production area. This effective potential leads to strong biased diffusion and consequently linearly growing local accumulation times. This behavior is very similar to the case of the single localized source discussed above. Inside the synthesis region the dynamics is different. The degradation is compensated by synthesis and diffusion from neighboring cells, leading to mostly uniform accumulation times.

3.3.3 Exponentially Distributed Production Along the Semi-Infinite Interval

In this example, we consider the exponentially distributed production along the interval of length $L$. In this case, the synthesis rates can be written as

$$Q_m = \frac{Q(1-z)z^m}{1-z^{L+1}},$$

(3.23)

where $0 \leq m \leq L$ and a parameter $z$ ($0 < z < 1$) is introduced to characterize the exponential distribution of synthesis rates. One can see that the relation $\sum_{m=0}^{L} Q_m = Q$ is satisfied. We can also define a decay length $\lambda_s$ for this exponential distribution of the production rates,

$$\lambda_s = -1/\ln z.$$  

(3.24)

Detailed calculations of the stationary profiles for exponentially distributed production rates and for arbitrary length of the source region are given in the Appendix A. Here we report the final results for the case of the semi-infinite source interval,
i.e., in the limit of $L \to \infty$,

$$P^{(s)}(n) = \frac{Q(1-z)}{\sqrt{k^2 + 4uk}} \left[ \frac{(x^{n+1} - zx^{n+2} - z^{n+1} + x^2 z^{n+1})}{(x-z)(1-xz)} \right] \right] + \frac{Q(1-z)}{\sqrt{k^2 + 4uk}} \left[ \frac{(-k + \sqrt{k^2 + 4uk})x^n}{(k + \sqrt{k^2 + 4uk})(1-xz)} \right].$$

(3.25)

The maximal value of the concentration profile is achieved again for $n=0$,

$$P^{(s)}(n=0) = \frac{2Q(1-z)}{(1-xz)(k + \sqrt{k^2 + 4uk})}.$$ (3.26)

It is interesting to consider a special limiting case of this problem when the diffusion along the lattice cells is much faster than the degradation rate, $u \gg k$, while the decay length $\lambda_s$ for the exponential production rates is also large. This corresponds to a continuum limit of our problem, and it was already discussed in the literature [31, 15, 16, 17]. In this limit, we have the following asymptotic relations for important parameters $x$ and $z$,

$$x \simeq 1 - \frac{1}{\lambda},$$

(3.27)

$$z \simeq 1 - \frac{1}{\lambda_s}.$$ (3.28)

Using these results, one can easily show that the Eq. 3.25 reduces to the following form,

$$P(n) = \frac{Q\lambda^2}{u(\lambda^2 - \lambda_s^2)}(\lambda e^{-n/\lambda} - \lambda_s e^{-n/\lambda_s}).$$ (3.29)

This is exactly the concentration profile obtained previously in the continuum SDD model with the exponentially decaying distribution of the production rates [17].

The normalized concentration profiles for exponentially decaying production along the semi-indite interval ($L \gg 1$) are plotted in Figs. 3.2 and 3.3. For all sets of the parameters these profiles are monotonically decreasing functions of the distance.
from the origin, although the decay is slower for larger diffusion rates and/or for smaller degradation rates. This allows to increase significantly the range of morphogen action, as compared to systems with the sharply localized source, while still keeping the concentration profile of signaling molecules to be non-uniform. As expected, accelerating the exponential decay of production rates (lowering of $\lambda_s$) diminishes this effect as one can see by comparing Figs 3.2 and 3.3. As expected, for small $\lambda_s$ the concentration profiles of morphogen gradients with exponentially distributed productions become similar to the morphogen gradients with the single localized source.

The calculations for local accumulation times for exponentially decaying synthesis of signalling molecules and for arbitrary production lengths $L$ are also given in the Appendix A. We are interested in the large $L$ values that correspond to the semi-infinite interval. In this case, we obtain the following expression for LAT,

$$
t(n) = \frac{n}{\sqrt{k^2 + 4uk}} + \frac{2uk}{k^2 + 4uk} + \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{(-k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^n) + (k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^{n+2})}{(k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^{n+2} - z^n + x^2z^{n+1}) + (-k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^n)} \right]
$$

The results for LAT for the exponentially distributed production of the morphogens are illustrated in Figs. 3.4 and 3.5. In all cases the local accumulation times increase with the distance from the origin, as was found for other production scenarios of morphogen gradients considered in this work. The LAT growth is mostly linear since our arguments about the effective potential due to degradation still can be ap-
plied. But what is different from other production mechanisms is the fact that these times are usually much smaller, especially at large distances from the origin (larger than \( L \) or \( \lambda_s \)). This can be understood if we recall that main contribution to the local accumulation times at given spatial position is due to the first-passage (arrival) times to this location starting from the source region [49]. In the exponentially distributed production of signaling molecules along the semi-infinite interval the source is everywhere, so that the contribution of the arrival times is mostly negligible. This significantly lowers the time to reach the stationary-state concentration at the given spatial location.

3.3.4 Linearly Distributed Production Over the Finite Interval

In this final example, we consider linearly distributed production of morphogens along a finite interval of length \( L \). This distribution can be represented as follows

\[
Q_m = \frac{2Q_0}{(L + 1)(L + 2)}[-m + L + 1]
\]  

(3.31)

One can easily show that the relation \( \sum_{m=0}^{L} Q_m = Q \) is satisfied. Detailed calculations of the stationary profiles for linearly distributed production rates and for arbitrary length of the source region are given in the Appendix A. For the sites inside the production region we have

\[
\begin{align*}
P^{(s)}(n) &= \frac{2Qx^n}{(L + 2)(L + 1)(k + \sqrt{k^2 + 4uk})} \\
&\times \left[ \frac{(k + \sqrt{k^2 + 4uk})(x^{L+2-2n} + (L + 1)x^2 + (L - n + 1)x^{-n}) - (L + 2)x + (n - L - 1)x^{2-n}}{\sqrt{k^2 + 4uk}(x - 1)^2} \right] \\
&+ \frac{2Qx^n[(-k + \sqrt{k^2 + 4uk})(-L + 2)x + L + 1 + x^L+2]}{(L + 2)(L + 1)(k + \sqrt{k^2 + 4uk})(x - 1)^2\sqrt{k^2 + 4uk}} \\
&\times \left[ \frac{(k + \sqrt{k^2 + 4uk})(x^{L+2-2n} + (L + 1)x^2 + (L - n + 1)x^{-n}) - (L + 2)x + (n - L - 1)x^{2-n}}{\sqrt{k^2 + 4uk}(x - 1)^2} \right]
\end{align*}
\]  

(3.32)
Figure 3.6: Steady-state density profiles as a function of the distance from the origin. Red curves correspond to the single localized source at \( m' = 0 \). Blue curve correspond to linearly decaying production rates along the finite interval. \( L = \lambda \) is assumed. (a) Fast degradation rates with \( k = 1, u = 0.01 \); (b) Comparable diffusion and degradation rates with \( k = u = 1 \); and (c) Fast diffusion rates with \( k = 1, u = 100 \).

while for the outside of the production region we have

\[
P^{(s)}_>(n) = \frac{2Qx^n}{(L+2)(L+1)(k + \sqrt{k^2 + 4uk})} \times \frac{(k + \sqrt{k^2 + 4uk})(L+1)x^2 - (L + 2)x + x^L) + (-k + \sqrt{k^2 + 4uk})(-L+2)x + L + 1 + x^{L+2})}{(x-1)^2\sqrt{k^2 + 4uk}},
\]

(3.33)

The normalized density profiles for linearly decaying production along the finite
Figure 3.7: Steady-state density profiles as a function of the distance from the origin. Red curves correspond to the single localized source at $m' = 0$. Blue curve correspond to linearly decaying production rates along the finite interval. $L = 10\lambda$ is assumed. (a) Fast degradation rates with $k = 1$, $u = 0.01$; (b) Comparable diffusion and degradation rates with $k = u = 1$; and (c) Fast diffusion rates with $k = 1$, $u = 100$.

interval are presented in Figs. 3.6 and 3.7. These profiles are compared with the single localized source for all sets of parameters. One can see that for $L = \lambda$ the results are similar to the case of the single localized source (see Fig 3.6). In this case, at larger distances from the origin, a linearly decaying production along an interval acts as the single localized source. However, extending the size of the production interval ($L = 10\lambda$) increases the decay length of the resulting concentration profiles (Fig. 3.7).
Figure 3.8: Local accumulation times as a function of the distance from the origin. Red curves correspond to the single localized source at $m' = 0$. Red curves correspond to the single localized source at $m' = 0$. Blue curve correspond to linearly decaying production rates along the finite interval. $L = \lambda$ is assumed. (a) Fast degradation rates with $k = 1$, $u = 0.01$; (b) Comparable diffusion and degradation rates with $k = u = 1$; and (c) Fast diffusion rates with $k = 1$, $u = 100$.

The calculations for local accumulation times for linearly decaying synthesis of signalling molecules and for arbitrary production lengths $L$ are also given in the Appendix A. The results for LATs are presented in Figs. 3.8 and 3.9. Again, for $L = \lambda$ results are similar to the case of the single localized source. For larger intervals ($L = 10\lambda$), however, linear production increases the local accumulation times (see Fig. 3.9 (c)).
To explain this unexpected observation we can refer to the idea of effective potential due to degradation\cite{41, 49}. Let us consider 2 neighboring lattice cites, $n$ and $n + 1$. Because the morphogens are produced at the origin before diffusing along the interval, signaling molecules at the site $n + 1$ spend more time in the system than particles on the site $n$. Then they have higher probability to be removed from the system, the concentration of morphogens is generally smaller at the site $n + 1$. 

Figure 3.9 : Local accumulation times as a function of the distance from the origin. Red curves correspond to the single localized source at $m' = 0$. Red curves correspond to the single localized source at $m' = 0$. Blue curve correspond to linearly decaying production rates along the finite interval. $L = 10\lambda$ is assumed. (a) Fast degradation rates with $k = 1$, $u = 0.01$; (b) Comparable diffusion and degradation rates with $k = u = 1$; and (c) Fast diffusion rates with $k = 1$, $u = 100$. 

(a) $u=0.01$, $k=1$

(b) $u=1$, $k=1$

(c) $u=100$, $k=1$
Figure 3.10: Effective potential due to degradation as a function of the distance from the origin in units of $k_B T$. Red curves correspond to the single localized source at $m' = 0$. Red curves correspond to the single localized source at $m' = 0$. Blue curve correspond to linearly decaying production rates along the finite interval. $L = 10\lambda$ is assumed. (a) Fast degradation rates with $k = 1$, $u = 0.01$; (b) Comparable diffusion and degradation rates with $k = u = 1$; and (c) Fast diffusion rates with $k = 1$, $u = 100$.

Creating a gradient. Such concentration gradient can be also obtained as a result of the action of the potential in the system, acting in the direction of increasing $n$, but without degradations[41, 49]. This effective potential can be estimated in terms of the stationary concentrations,

$$U_{eff} \simeq k_B T \ln P_n.$$ (3.34)
Such potentials are plotted in Fig. 3.10. One can see that the effective potential is always linear and stronger for the system with a single localized source (red curves in Fig. 3.10). However, with increasing diffusion rate $u$ it becomes weaker for linearly distributed source. This observation is easy to explain: In the linearly distributed production of morphogens along the finite interval, there is a less tendency to remove signaling molecules in the source region, i.e., the degradation is required by production from neighboring cells, leading to a weaker potential. Outside of the production area, the degradation creates the potential that pushes morphogens away from the source region. This effective potential leads to strong biased diffusion and therefore linearly growing LATs. This behaviour is very similar to the case of the single localized source (Fig. 3.10(c)).

### 3.4 Time-Dependent Production Rate

In this section, we investigate the effects of a time-dependent production rate on the dynamics of morphogen gradient formation. We assume that the signaling molecules are produced at the origin, $n = 0$, with a time-dependent rate $Q(t)$. Then, they diffuse to the right $n \leq 0$ with a diffusion rate $u$. At any site, the morphogen might be degraded with a rate $k$. We define a function $P_n(t)$ as the probability to find the particle at the site $n$ at time $t$. Then, the temporal evolution of these probabilities is governed by a set of master equations,

$$
\frac{dP_n(t)}{dt} = u[P_{n+1}(t) + P_{n-1}(t)] - (2u + k)P_n(t) \quad (3.35)
$$

for $n > 0$, and

$$
\frac{dP_0(t)}{dt} = Q(t) + uP_1(t) - (u + k)P_0(t) \quad (3.36)
$$
for $n = 0$. Let us consider an exponentially varying production rate:

$$Q(t) = Q_0(1 - e^{-\gamma t}),$$  \hspace{1cm} (3.37)

At large times $Q(t) \to Q_0$, and these equations can be solved exactly, producing the steady-state density profiles,

$$P_n^{(s)} = \frac{2Q_0x^n}{k + \sqrt{k^2 + 4uk}},$$  \hspace{1cm} (3.38)

with $x = (2u + k - \sqrt{k^2 + 4uk})/(2u)$. From Eqs. 3.7 and 3.8 the local accumulation time can be determined

$$t(n) = \frac{1}{\sqrt{k^2 + 4uk}} \left[ n + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right] + \frac{1}{\gamma}.$$  \hspace{1cm} (3.39)

One can see that the local accumulation time at each site is increased by $1/\gamma$, the characteristic relaxation time of the source. Therefore, such a time-dependent source only delays transferring information to specific locations.

### 3.5 Summary and Conclusions

We developed a theoretical framework for investigating the role of synthesis of signaling molecules in the formation of concentration profiles that are critically important in the biological development. Our analysis is based on discrete-state stochastic models for complex reaction-diffusion processes associated with the formation of morphogen gradients. It allows us to test the effect of the production in systems with arbitrary source lengths and synthesis rates by calculating stationary profiles and the times to achieve the stationary concentrations at specific locations. By analyzing several different systems we found that the spatial distributions of the sources and the production speeds have a strong effect in the development of morphogen gradients.
To understand the role of the production one might recall that there are two main requirements for successful function of the morphogen gradients in the biological systems [7]. The first one is to deliver the information to as many as possible embryo cells about their future fates. This can be done if observable concentrations of signaling molecules can be found as far as possible from the source. The second function is to ensure that different genes can be controllably turned on in the neighboring embryo cells. This can be accomplished by producing sharp boundaries in the concentration profiles of signaling molecules at specific locations. Our analysis suggests that the morphogen gradients produced with the single localized sources generally are not able to satisfy these requirements. At the same time, the morphogen gradients developed from the delocalized sources with various synthesis rates are capable to do all these tasks successfully.

Furthermore, the presented theoretical method provides a simple physical-chemical explanation on the role of delocalizations in the formation of signaling molecules concentration profiles. The delocalization effectively leads to faster diffusion along the productions regions, and it also shortens the arrival times to specific locations. As a result, the range of morphogen gradients with delocalized sources increases, while the times to reach the stationary states at specific locations become smaller. All of these properties make the morphogen gradients more efficient and robust. At the same, increasing the production area to the whole embryo is not reasonable since it will be difficult to sustain the non-uniform concentration profiles.
Chapter 4

Theoretical Analysis of Degradation Mechanisms in the Formation of Morphogen Gradients

4.1 Introduction

It is widely accepted that the process of degradation or removal of signaling molecules from the system is critically important for the development of morphogen gradients[9]. This allows the formation of the stationary profiles of signaling molecules, ensuring the robustness of the genetic information transfer in biological development. But specific details of how the degradation influences the formation of morphogen gradients are still not well clarified. There are many counter-intuitive observations that cannot be explained by current theoretical views. In the classical SDD model it is assumed that the degradation is linear, i.e., the particle flux leaving the system is proportional to the local concentration of morphogens. It was shown theoretically then that for this model the time to establish a stationary morphogen gradient at given location, which is also known as a local accumulation time (LAT), is a linear function of the distance from the source[31]. This observation is surprising since for the system with unbiased diffusion of particles much more slower quadratic scaling was expected[31, 49]. At the same time, several experiments suggested that in some cases the establishment of morphogen gradients is associated with nonlinear degradation mechanisms when the presence of signaling molecules self-enhances or self-catalyzes its removal from the system[39, 48, 50, 51]. Theoretical investigations of temporal evolution of the
morphogen gradients with nonlinear degradation suggested that in this case the local accumulation times, in contrast to linear degradation, scale quadratically with the distance from the source[39]. But the presented mathematical analysis was rather very complicated, and only bounds for LAT in several cases where obtained [39].

These observations raised several interesting and important questions concerning the role of the degradation in regulating the concentration profiles of signaling molecules. Why the degradation accelerates the relaxation to the stationary state for linear degradation? Why the actions of linear and nonlinear degradation processes are so different? What is the physical mechanism of degradation? Recently, it was suggested that the degradation acts as an effective potential that pushes signaling molecules away from the source region[49]. It means that the degradation will make the diffusion of morphogen molecules effectively biased. However, only qualitative arguments have been presented.

In this chapter, we extend and generalize the original idea that the removal of signaling molecules works as the effective potential[41]. A new quantitative approach that provides a microscopic view on the role of degradation in the formation of morphogen gradients is developed. It allows us to explain the differences between various degradation mechanisms. We argue that the linear degradation corresponds to a strong potential, leading to strongly biased motion of the signaling molecules. At the same time, the non-linear degradation creates a potential that is too weak to modify the underlying random-walk scaling behavior of the system, affecting only the magnitude of fluctuations.
4.2 Theoretical Method

Let us start the analysis of degradation mechanisms by introducing a discrete SDD model as presented in Fig. 4.1a. The cells in the embryo are represented as discrete sites \( n \geq 0 \) on this semi-infinite lattice. The signaling molecules are produced at the origin \( (n = 0) \) with a rate \( Q \). Then morphogens diffuse along the lattice with a diffusion constant \( D \). At each lattice site \( n \) the molecule can be degraded with a rate \( k_n \). It is convenient to adopt a single-molecule view of the process where the local concentration of signaling molecules is proportional to a probability to find the morphogen molecule at a given location [38, 49]. One can define then \( P_n(t) \) as a probability of finding the morphogen at the site \( n \) at time \( t \). These probabilities evolve with time as described by a set of master equations,

\[
\frac{dP_n(t)}{dt} = DP_{n+1}(t) + DP_{n-1}(t) - (2D + k_n)P_n(t), \tag{4.1}
\]

for \( n > 0 \); while at the origin \( (n = 0) \) we have

\[
\frac{dP_0(t)}{dt} = Q + DP_1(t) - (D + k_0)P_0(t). \tag{4.2}
\]

The situation when the degradation rate \( k_n \) is independent of the concentration of signaling molecules corresponds to linear degradation since the total flux that removes morphogens from the system \( [k_nP_n(t)] \) is proportional to the concentration. For the case of constant \( k_n = k \), this discrete SDD model with linear degradation was fully analyzed before [49]. In a more general scenario, the degradation rate might depend on the local concentration, \( k_n = kP_n^{m-1} \), where a parameter \( m \) specifies the degree of non-linearity, and this corresponds to non-linear degradation processes. However, it is not feasible generally to obtain full analytic solutions for these non-linear degradation models (with \( m > 1 \)).
The main idea of our approach is that degradation acts as an effective potential. This suggests that the original reaction-diffusion process with degradation is equivalent to a biased diffusion process in such potential but without degradation, as shown in Fig. 4.1b. To explain the origin of this potential, let us consider the system in the steady-state limit when a stationary non-uniform profile $P_n^{(s)}$ is achieved. The degradation leads to a concentration gradient between any two consecutive sites, and this gradient can be associated with a difference in the chemical potentials of the morphogens,

$$\mu_{n+1} - \mu_n = k_B T \ln P_{n+1}^{(s)} - k_B T \ln P_n^{(s)}. \quad (4.3)$$

This can also be viewed as an effective potential that influences particles that are not degraded. It follows then that this potential can be evaluated as

$$U_{n}^{\text{eff}} = k_B T \ln P_n^{s}. \quad (4.4)$$

The above arguments indicate that dynamics of the reaction-diffusion model (Fig. 4.1).
4.1a) can be mapped into the biased-diffusion model (see Fig. 4.1b), which is much simpler to analyze. For the equivalent biased diffusion model we define $\Pi_n(t)$ as the probability of finding a particle at position $n$ at time $t$. These probabilities are also governed by corresponding master equations,

$$\frac{d\Pi_n(t)}{dt} = r_{n+1}\Pi_{n+1}(t) + g_{n-1}\Pi_{n-1}(t) - (r_n + g_n)\Pi_n(t),$$  \hspace{1cm} (4.5)

for $0 < n < L$, while for $n = 0$ and $n = L$, we have

$$\frac{d\Pi_0(t)}{dt} = J + r_1\Pi_1(t) - g_0\Pi_0(t),$$ \hspace{1cm} (4.6)

$$\frac{d\Pi_L(t)}{dt} = g_{L-1}\Pi_{L-1}(t) - r_L\Pi_L(t) - J,$$ \hspace{1cm} (4.7)

where $J$ is the flux from the site $L$ back to the origin $n = 0$. At large times, the system reaches the stationary state with the constant flux $J$ across every site. One can also see the qualitative difference between two models. While the SDD model achieves the conservation of probability only at the stationary state, the biased-diffusion model always conserves the probability. Based on these observations, we expect that the mapping between two models should work better at large times, approaching the stationary state. The diffusion rates $g_n$ and $r_n$ are related to each other via the effective potential as can be shown using the detailed balance arguments [40]:

$$\frac{g_n}{r_{n+1}} = \exp \left( \frac{U_{n}^{\text{eff}} - U_{n+1}^{\text{eff}}}{k_B T} \right)$$ \hspace{1cm} (4.8)

This is an important result because it directly couples the original SDD model with degradation to the new biased-diffusion model without degradation.

One more step is needed in order to have comparable dynamic behaviors in both models. The average residence times for the particles at each site provide a measure of relevant time scales in the system. It seems reasonable to require that these quantities
to be the same in both models, leading to

\[ g_n + r_n = 2D + k_n. \]  

(4.9)

Note that Eqs. 4.8 and 4.9 uniquely define forward and backward rates in the biased-diffusion model.

To understand the mechanisms of formation of the morphogen gradients the relaxation dynamics to a stationary-state behavior needs to be investigated. This can be done by analyzing the local accumulation times \( t_n \), which are defined as times to reach the stationary state concentration at given position \( n \). The general approach for computing LAT is known [31], but analytical results can only be obtained for the linear degradation model \( (m = 1) \). We propose to use mean first-passage times \( \tau_n \) (MFPT), which are defined as times to reach a given site for the first time, as a measure of dynamics of the formation of morphogen gradients. It was shown before that MFPT approximate very well LAT at large distances from the source, i.e., for large \( n \) [49, 118]. In addition, the first-passage analysis provides more clear physical view of the underlying phenomena in the development of morphogen gradients.

Thus, our method of evaluating the formation of signaling molecules profiles consists of three steps. First, from the original SDD model with degradation the stationary-state profiles are obtained, from which the effective potentials are explicitly evaluated. In the second step, the transition rates in the equivalent biased-diffusion model without degradation are computed. Finally, these rates are utilized for calculating the first-passage dynamics in the system. It is important to note here that this procedure is not exact since it involves several approximations.
Figure 4.2: a) Ratio of the calculated mean first passage times and the exact analytical results from the SDD model with linear degradation as a function of the distance from the source. Different curves correspond to different values of the degradation and diffusion rates. b) The same ratio as a function of the ratio of the degradation rate over diffusion. Distance from the source is set to \( n = 10^4 \), which exceeds the decay lengths for all values of degradation rates.

### 4.3 Linear Degradation

To test our theoretical approach, we start with the simplest linear degradation model where all dynamic properties are analytically calculated for all sets of parameters.
The stationary-state profile for the SDD model can be easily evaluated [49],

$$P_n^{(s)} = \frac{2Qx^n}{k + \sqrt{k^2 + 4Dk}},$$

(4.10)

with $x = (2D + k - \sqrt{k^2 + 4kD})/2D$. This expression allows us to estimate the effective potential due to degradation for the equivalent biased-diffusion model,

$$\frac{U_{n}^{\text{eff}}}{k_B T} \simeq n \ln x.$$  

(4.11)

This potential is linear with a slope that depends on diffusion and degradation rates. It is also shown in Fig. 4.5. Employing these results in Eqs. 4.8 and 4.9, we obtain the following expressions for the forward and backward transition rates,

$$g_n = g = \frac{2D + k}{x + 1}, \quad r_{n+1} = r = x \frac{2D + k}{x + 1}.$$  

(4.12)

Note that these rates are independent of the position and the production rate $Q$.

In the final step, first-passage dynamics can be evaluated by using known expressions for MFPT [40],

$$\tau_n = \sum_{i=0}^{n-1} \sum_{j=0}^{i} \frac{r_ir_{i-1}...r_{j+1}}{g_i g_{i-1}...g_{j+1}g_j}$$

$$= \frac{(x + 1) [x(x^n - 1) - n(x - 1)]}{(2D + k) (x - 1)^2}.$$  

(4.13)

It can be easily checked that in the special case of no degradation in the original system, $k = 0$, this formula reduces to $\tau_n \simeq n^2/2D$ at large distances, as expected for a simple unbiased random walk.

It is possible to compare the obtained mean first-passage times from Eq. 4.13 with analytical expressions for LAT and for MFPT in the original SDD model which are available [49]. But it is more convenient first to do it in two different dynamic regimes. In the case when the degradation rate is much faster than diffusion, $k \gg D$, ...
it can be shown that \( x \simeq D/k \), which leads to \( \tau_n \simeq n/k \). It is in excellent agreement with exact results for LAT and MFPT for the original SDD model in this limit \([49]\),

\[
t_n = \tau_n^{SDD} \simeq (n + 1)/k.
\]

In the opposite limit of very fast diffusion \((D \gg k)\), we have \( x \simeq 1 - \sqrt{k/D} \) and Eq. 4.13 yields

\[
\tau_n \simeq n/\sqrt{kD}.
\]

(4.14)

Exact expressions for LAT and MFPT for the original SDD model give us \([49]\),

\[
t_n \simeq \frac{1}{2k} \left[ 1 + \frac{n + 1}{\sqrt{D/k}} \right], \quad \tau_n^{SDD} \simeq n/2\sqrt{Dk}.
\]

(4.15)

Thus, for large \( n \) our method still correctly reproduces the linear scaling in the local accumulation times, but the amplitude deviates in two times. The comparison between predicted MFPT for the biased-diffusion model and for LAT of the original SDD model for general sets of parameters is given in Fig. 4.2. One can see that our method approximates the dynamics of the formation of morphogen gradient reasonably well.

The agreement is better for larger degradation rates where the effective potentials are stronger. At the same time, for weaker degradation rates there are deviations, although the qualitative behavior is correctly captured. This is a remarkable result given how simple is the theory and that it involves several strong approximations. This also suggests that the method can be reliably applied to more complex systems with non-linear degradation.

### 4.4 Non-Linear Degradation

Here we apply our method for systems where the formation of signaling molecules profiles is accompanied by the non-linear degradation with \( k_n = kP_n^{m-1} \) for \( m = \)
Figure 4.3: Theoretically calculated mean first passage times as a function of the distance from the source for different degrees of non-linearity and for different values of the degradation rates: a) \( m = 2 \); b) \( m = 10 \).

2, 3, ... To evaluate the effective potential we need to estimate the stationary-state concentration profiles. However, it is not possible to calculate them analytically for general non-linear discrete SDD models. But we can use the fact that in the continuum limit \( (D \gg k_n) \) the original master Eqs. 4.1 and 4.2 can be written as the
corresponding non-linear reaction-diffusion equations,

\[
\frac{\partial P(n,t)}{\partial t} = D \frac{\partial^2 P(n,t)}{\partial n^2} - k P^m(n,t),
\]

(4.16)

with the boundary condition at the origin

\[
D \frac{\partial P}{\partial n} \big|_{n=0} = -Q.
\]

(4.17)

These equations can be solved in the steady-state limit, producing

\[
P_n^{(s)} \approx \frac{1}{(1 + n/\lambda)^{\frac{2}{m-1}}},
\]

(4.18)

where the parameter \( \lambda \) is given by

\[
\lambda = \frac{1}{m-1} \left[ \frac{(2D)^m(m+1)}{kQ^{m-1}} \right]^{\frac{1}{m+1}}.
\]

(4.19)
Figure 4.5: Effective potentials acting on morphogens due to degradation. Linear degradation corresponds to $m = 1$, while $m = 3$ and $m = 10$ describe different cases of non-linear degradation. For all calculations $k = D = Q = 1$ was assumed.

It can be shown that the continuum $P_n^{(s)}$ describes also quite well the stationary-state behavior of the general non-linear discrete SDD models at large distances from the source. This allows us to approximate the effective potentials for non-linear degradation as

$$\frac{U_n^{\text{eff}}}{k_BT} \simeq -\frac{2}{m-1} \ln(1+n/\lambda).$$  \hspace{1cm} (4.20)

This potential is logarithmic, and the degree of non-linearity determines its magnitude as illustrated in Fig. 4.5. It is important to note here that these potentials are always weaker than the potential for the linear degradation: see Fig. 4.5.

Now using Eqs. 4.8 and 4.9 one can obtain the expressions for transition rates in the biased-diffusion model,

$$g_n = D \left[ \frac{P_n^{(s)}}{P_{n+1}^{(s)}} \right]^{0.5}, \quad r_{n+1} = D \left[ \frac{P_n^{(s)}}{P_{n+1}^{(s)}} \right]^{-0.5}.$$  \hspace{1cm} (4.21)

In the final step, again utilizing the analytical framework for the first-passage pro-
cesses [40], we derive the explicit expressions for the mean first-passage times that approximate the formation of morphogen gradients with nonlinear degradation,

\[ \tau_n = \sum_{i=0}^{n-1} \sum_{j=0}^{i} \frac{r_i r_{i-1} \cdots r_{j+1}}{g_i g_{i-1} \cdots g_{j+1} g_j} = \frac{1}{D} \sum_{j=0}^{n-1} [j(j+1)]^{\frac{1}{m}} \sum_{l=0}^{j} l^{\frac{m-1}{2}}. \]  

(4.22)

It can be shown that this expression asymptotically at large distance approaches to

\[ \tau_n \approx \frac{(m - 1)}{(m + 1)} \frac{n^2}{2D}. \]  

(4.23)

This is an important result since it predicts a quadratic scaling for all non-linear degradation mechanisms with \( m > 1 \). Furthermore, as expected, for very large \( m \), which corresponds to effectively no degradation, this formula reduces to a simple random walk dependence.

Our theoretical estimates for the relaxation dynamics in the establishment of the morphogen gradients for various models with non-linear degradation are presented in Fig. 4.3. One can clearly see that the predicted local accumulation times approach the quadratic scaling for large \( n \) for all possible ranges of diffusion and degradation rates. The approach is faster for larger \( m \). The scaling is independent of the degradation mechanisms, and only the amplitude is determined by the degree of the non-linearity \( m \).

We also compared theoretical predictions with numerically exact values of LAT for different non-linear degradation models. The results are presented in Fig. 4.4. A remarkable agreement between predicted and exact relaxation times is found for \( m = 3 \). It can be seen that increasing the strength of the degradation (larger \( k \)) improves the agreement even for small distances from the sources. For \( m = 10 \) our theory also works qualitatively well, although there are bigger quantitative deviations. It correctly describes the scaling, and increasing the degradation rate \( k \) decreases the magnitude of these deviations.
Analyzing results given in Figs 4.3 and 4.4, we can make several conclusions about the applicability of the developed theoretical method for analyzing nonlinear degradation. Our approach correctly finds the quadratic scaling in the local accumulation times. It works better for large distances because it calculates only the arrival times which are always smaller than the correct LAT that also must include some local rearrangements. At large distances the contribution from MFPT to LAT becomes dominant[49]. One can also observe that our method works better for stronger degradation, which corresponds to small $m$ values and/or large degradation rates $k$. Most probably, this is due to the fact that our approach neglects particle fluctuations that are present even in the absence of degradation. For strong degradations these fluctuations become less relevant for dynamic properties of the signaling molecules.

It is interesting to discuss the physical origin of different qualitative dynamic behaviors for linear and non-linear degradation mechanisms. It might be related to a presence or absence of relevant length scales in the system. For linear degradation, there is the length scale $\lambda$ defined in such a way that the stationary concentration of signaling molecules reduces in $e$ times every $\lambda$ sites independent of the initial position and the production rate. This ensures that dynamics in the system is uniform everywhere. The situation is different for non-linear degradation mechanisms. They are characterized by scale-free power law concentration profiles, and there is no unique length scale to describe the system. As a result, all of them can be written in the logarithmic form. This leads to variable dynamics at different parts of the system. Near the origin, the degradations are very fast because of large amount of signaling molecules. But at large distances, the degradation is very weak since not many morphogens can be found there.
4.5 Summary and Conclusions

We developed a new theoretical approach to analyze mechanisms of degradation in the formation of signaling molecules profiles during the biological development. The method is quite simple, and it provides a full analytical description for all ranges of parameters. It is based on the idea that degradation is similar to the effective potential imposed to morphogen molecules. The potential pushes signaling molecules away from the source region. It allows us to map the original reaction-diffusion process into the biased-diffusion model without degradation, which is much easier to analyze. Finally, utilizing the first-passage approach, the dynamics of relaxation to stationary morphogen gradients can be fully described.

Despite the fact that our approach involves several strong approximations, it works remarkably well for different models with degradation. We correctly predict the scaling behavior for the local accumulation times in all cases. As we found for both linear and non-linear degradation processes, theoretical method is almost exact for large distances from the source and for faster degradation rates. At the same time, for close distances and for slower degradation rates the agreement is mostly qualitative, although the deviations are relatively small. The effect of the distance can be explained by recalling that in our method first arrival times are computed. The correct LAT involve local rearrangements which become less important for large distances. The strength and the speed of degradation influence our results because the theoretical method neglects the local particle fluctuations due to underlying random walk dynamics. These fluctuations are expected to contribute significantly to dynamic properties for weak and slow degradations, while they are much less important for strong and fast degradations.

The advantage of our method is not only the fact that it gives a fully analyti-
cal description of the complex processes during the development of the morphogen gradients. It also provides clear physical explanations for the observed phenomena. We can understand now why linear and non-linear degradation lead to very different dynamic behaviors. For linear degradation we predict that the effective potential is very strong (Fig. 4.5). The morphogens are strongly pushed away from the source region, and as a result a driven diffusion with the expected linear scaling is observed. For non-linear degradation processes the effective potentials are much weaker (logarithmic versus linear — see Fig. 4.5). The particles are moved preferentially in the direction away from the source region, but the underlying random-walk dynamics is not perturbed much. As a result, the quadratic scaling is predicted and the effect of the potential only shows up in the magnitude of fluctuations. These finding also suggest that the degradation might be an effective tool for tuning the complex biochemical and biophysical processes in biological development.

Although the presented method captures main features of the degradation processes during the formation of morphogen gradients, it is important to note that our approach is oversimplified and it involves many approximations. It will be important to test the proposed ideas with more advanced theoretical methods as well as in the extensive experimental studies.
Chapter 5

Development of Morphogen Gradients with Spatially Varying Degradation Rates

5.1 Introduction

So far, most theoretical studies of the formation of morphogen gradients assumed that the degradation rates are constant and uniform, i.e., independent of the spatial positions in the embryo [9, 31, 38, 41, 49]. However, this assumption probably is not very realistic since the density of the cell receptors might vary along the field of embryo cells[42]. Such spatial inhomogeneities might alter the morphogen fluxes absorbed by the cell receptors. But the effect of the spatial variations in degradation on the mechanisms of the formation of signaling profiles is not known.

In this chapter, we extend the existing theoretical methods to investigate the role of spatially varying degradation rates on dynamics of morphogen gradients formation. To illustrate our approach, we investigate in detail two examples of the discrete-state SDD model with spatially varying degradation rates for which full analytical solutions can be obtained. Our analysis shows that spatial inhomogeneity in degradation rates have dramatic effects on concentration profiles and on dynamics of their formation. These observations are explained using our original idea of degradation functioning as an effective potential [41].
5.2 Theoretical Method

Let us start the analysis by considering a general discrete-state stochastic SDD model in one dimension with position-dependent degradation rates as shown in Fig. 5.1. A system consisting of \( L+1 \) embryo cells distributed sequentially along one-dimensional interval will be investigated. We assume that signaling molecules are produced with a rate \( Q \) only at the site \( n = 0 \). From any site \( n \geq 0 \), they can diffuse in both directions with a diffusion rate \( u \). The particles might be degraded at any site \( 0 \leq n \leq L \) inside the finite interval with a corresponding rate \( k_n \). Generally, the values of these degradation rates are position-dependent. One can define a function \( P_n(t) \) as a probability to find the morphogen molecule at the site \( n \) at time \( t \). The temporal evolution of this probability function is governed by the following master equations:

\[
\frac{dP_0(t)}{dt} = Q + uP_1(t) - (u + k_0)P_0(t) \quad (5.1)
\]

for \( n = 0 \);\n
\[
\frac{dP_n(t)}{dt} = u[P_{n-1}(t) + P_{n+1}(t)] - (2u + k_n)P_n(t) \quad (5.2)
\]

for \( n > 0 \); and\n
\[
\frac{dP_L(t)}{dt} = uP_{L-1}(t) - (u + k_L)P_L(t) \quad (5.3)
\]

for \( n = L \). For the case of constant and uniform degradation rates, \( k_n = k \), this discrete-state SDD model with a linear degradation can be solved exactly [49]. In a more general scenario, the degradation rates on different spatial positions are not the same. It is difficult to obtain full analytical solutions for arbitrary spatial variations in the degradation rates. However, it is possible to solve the corresponding master equations for several simple cases. In the following sections, we will analyze
such two examples. First, we study a discrete-state stochastic SDD model with a local inhomogeneity, i.e., the degradation rate only at one site is different from other sites. In the second case, we consider a more complicated model in which a signaling domain is composed of two regions with different degradation rates. These inhomogeneous degradation models allow us to clarify many aspects of the mechanisms of the establishment of the signaling profiles.

One of the main functions of the morphogen gradients is to transfer biological information to embryo cells. It is still a debate on how it happens at the molecular level, and if the transfer of information is taking place in the stationary state or before reaching the steady-state conditions [43]. Let us assume for simplicity that the signaling profiles should reach the stationary state for transferring the information. However, our analysis can be also generalized for pre-steady-state coding possibilities.

Then the important characteristics of the dynamics of morphogen gradients formation are times needed to achieve the steady-state concentration levels at specific spatial locations. These times are known as local accumulation times (LAT), and a theoretical framework for computing these quantities has been developed recently [31]. It
can be done by utilizing local relaxation functions, which are defined as
\[ R(n, t) = \frac{P(n, t) - P(s)(n)}{P(n, t = 0) - P(s)(n)} = 1 - \frac{P(n, t)}{P(s)(n)}. \] (5.4)

The physical meaning of these functions is that they represent the relative distance to the stationary state: at \( t = 0 \) the distance is one, while at steady state it is equal to zero. The explicit formulas for the local accumulation time can be derived then via Laplace transformations of the local relaxation function, \( \tilde{R}(n, s) = \int_0^\infty R(n, t)e^{-st}dt \) [31],
\[ t(n) = -\int_0^\infty t\frac{\partial R(n, t)}{\partial t}e^{-st}dt = \tilde{R}(n, s = 0). \] (5.5)

This approach can be used to calculate essentially all dynamic properties of the morphogen gradients.

5.2.1 Finite Interval with a Local Inhomogeneity

We first consider the simplest situation with a local inhomogeneity in the degradation rates. In this case, the particles might be degraded at any site \( n \neq m \) inside the finite interval \( 0 \leq n \leq L \) with the rate \( k \). While the degradation rate at the special site \( m \) is different, \( k' \neq k \). We define again \( P_n(t) \) as the probability to find the signaling molecule at the site \( n \) at time \( t \). This probability function is controlled by the following master equations:
\[ \frac{dP_0(t)}{dt} = Q + uP_1(t) - (u + k)P_0(t) \] (5.6)
for \( n = 0 \);
\[ \frac{dP_n(t)}{dt} = u[P_{n-1}(t) + P_{n+1}(t)] - (2u + k)P_n(t) \] (5.7)
for \( n \neq m \);
\[ \frac{dP_m(t)}{dt} = u[P_{m-1}(t) + P_{m+1}(t)] - (2u + k')P_m(t) \] (5.8)
for \( n = m \); and
\[
\frac{dP_L(t)}{dt} = uP_{L-1}(t) - (u + k)P_L(t)
\]
for \( n = L \).

At large times, we have \( \frac{dP_L(t)}{dt} = 0 \), and these equations can be solved analytically. One can find the solution by using the following guess,

\[
P(s)_{n} = \begin{cases} 
A_1 x^n + B_1 x^{m-n}, & \text{for } 0 \leq n \leq m; \\
A_2 x^{n-m} + B_2 x^{L-n}, & \text{for } m < n \leq L.
\end{cases}
\]

with \( x = (2u + k - \sqrt{k^2 + 4uk})/2u \); and four unknown coefficients \( A_1, A_2, B_1 \text{ and } B_2 \) should be determined from the boundary conditions \( (n = 0, n = m \text{ and } n = L) \). Since there are four coefficients, we need four equations to find them. The corresponding master equation for \( n = m + 1 \) yields one more necessary equation:

\[
\frac{dP_{m+1}(t)}{dt} = u[P_m(t) + P_{m+2}(t)] - (2u + k)P_{m+1}(t)
\]

Now, using Eqs. 5.6, 5.8, 5.9, and 5.11, we can explicitly estimate the coefficients \( A_1, B_1, A_2, \text{ and } B_2 \).

The final expressions for the stationary density profiles have the following forms,

\[
P(s)_{n} = \begin{cases} 
x^{-n} \left[ c^2 x^{2L} (g x^{2m} - f x^{2n}) + c u x^{2L} (f x^{2n} - g x^{2m} + u x^{2m} - u x^{2n}) \right] \\
b^3 f x^{2m+2} + b^2 x^{2m+2} (c g x^{2m} + f u - u^2) - b c \eta - c^2 (c g + u(u - g)) x^{2(L+m)} \\
- \left[ b x^{2m-n+2} (b (g x^{2m} - f x^{2n}) + u (-f x^{2n} - g x^{2m} - u x^{2m} + u x^{2n})) \\
b^3 f x^{2m+2} + b^2 x^{2m+2} (c g x^{2m} + f u - u^2) - b c \eta - c^2 (c g + u(u - g)) x^{2(L+m)} \right]
\end{cases}
\]

for \( 0 \leq n \leq m \); and

\[
P(s)_{n} = \frac{u(f - g) (b x^{2n} + c x^{2L}) x^{2m-n+1}}{b^3 f x^{2m+2} + b^2 x^{2m+2} (c g x^{2m} + f u - u^2) - b c \eta - c^2 (c g + u(u - g)) x^{2(L+m)}}
\]

for \( m \leq n \). The auxiliary function \( \eta \) and the parameters \( f, g, b, \text{ and } c \) are given
Figure 5.2: Stationary state density profiles as a function of the distance from the source for the system with a local inhomogeneity in the degradation rates. Solid curves correspond to $k = 1; k' = 0.01$. Dashed curves correspond to $k = 0.01; k' = 1$. (a) $u = 0.01$; (b) $u = 1$; and (c) $u = 100$. For calculations $m = \frac{L}{2}$ was utilized.

below,

\[
g = 2u + k' - ux^{-1}, \quad f = 2u + k' - ux,
\]
\[
b = (k + \sqrt{k^2 + 4uk})/2, \quad c = (-k + \sqrt{k^2 + 4uk})/2,
\]
\[
\eta = -fx^{2L} - gx^{4m+2} + u \left(x^{2L} + x^{4m+2}\right).
\]

(5.14)

The resulting morphogen profiles are plotted in Fig. 5.2 for the inhomogeneity in the middle of the interval, $m = \frac{L}{2}$, and for various diffusion and degradation
Figure 5.3: Local accumulation times as a function of the distance from the source for the system with a local inhomogeneity in the degradation rates. Solid curves correspond to $k = 1$ and $k' = 0.01$. Dashed curves correspond to $k = 0.01$ and $k' = 1$. (a) $u = 0.01$; (b) $u = 1$; and (c) $u = 100$. For calculations $m = \frac{L}{2}$ was utilized.

From the Eqs. 5.4 and 5.5 the explicit expressions for the LATs can be calculated. They provide an important information on the dynamics of establishing the morphogen gradients. Since the corresponding formulas for LATs are very bulky, we present them in the Appendix B. LAT for the formation of morphogen gradients with $m = \frac{L}{2}$ for various diffusion and degradation rates are presented in Fig. 5.3. One can see that when the degradation rate at the special site is much smaller than at the other sites ($k' \ll k$), the effect of the inhomogeneity is local and relatively small. But the strong inhomogeneity ($k' \gg k$) has a more long-range effect by dividing the
interval into two parts with different dynamics and concentration profiles. This agrees well with the idea that degradation behaves like an effective potential\[41, 49\]. The small degradation rate modifies the system weakly, while the large degradation rate has a more global effect on the system.

### 5.2.2 Finite Interval with Two Different Degradation Regions

A more interesting behavior is observed in the system of two coupled degradation regimes. Here we consider a finite interval of length \( L \) composed of two degradation regions of length \( m \) and \( L - m \). Signaling molecules might be degraded at any site \( n \) inside the finite interval \( 0 \leq n \leq m \) with the rate \( k_1 \). While the degradation rate for any site \( m < n \leq L \) is equal to \( k_2 \). Employing again \( P_n(t) \) as the probability to find the morphogen at site \( n \) at \( t \), the temporal evolution of the system can be described as,

\[
\frac{dP_0(t)}{dt} = Q + uP_1(t) - (u + k_1)P_0(t) \tag{5.15}
\]

for \( n = 0 \);

\[
\frac{dP_n(t)}{dt} = u[P_{n-1}(t) + P_{n+1}(t)] - (2u + k_1)P_n(t) \tag{5.16}
\]

for \( 0 \leq n \leq m \);

\[
\frac{dP_n(t)}{dt} = u[P_{n-1}(t) + P_{n+1}(t)] - (2u + k_2)P_n(t) \tag{5.17}
\]

for \( m < n < L \); and

\[
\frac{dP_L(t)}{dt} = uP_{L-1}(t) - (u + k_2)P_L(t) \tag{5.18}
\]

for \( n = L \). In the stationary-state regime, we have \( \frac{dP_n(t)}{dt} = 0 \), and these equations can be solved analytically. The solution again can be written as

\[
P^{(s)}_n = \begin{cases} 
A_1 x_1^n + B_1 x_1^{m-n}, & \text{for } 0 \leq n \leq m; \\
A_2 x_2^{n-m} + B_2 x_2^{L-n}, & \text{for } m < n \leq L. 
\end{cases} \tag{5.19}
\]
Figure 5.4 : Stationary state density profile as a function of the distance from the origin for the system with two degradation regions. Solid curves correspond to \( k_1 = 1 \) and \( k_2 = 0.01 \). Dashed curves correspond to \( k_1 = 0.01 \) and \( k_2 = 1 \). (a) \( u = 0.01 \); (b) \( u = 1 \); and (c) \( u = 100 \). For calculations \( m = \frac{L}{2} \) was utilized.

with \( x_1 = (2u + k_1 - \sqrt{k_1^2 + 4uk_1})/2u \) and \( x_2 = (2u + k_2 - \sqrt{k_2^2 + 4uk_2})/2u \). To determine the unknown coefficients \( A_1, A_2, B_1, \) and \( B_2, \) we again need four equations. Two of them are given by master equations for \( n = 0 \) and \( n = L \). The additional two expressions are master equations for \( n = m \) and \( n = m + 1 \),

\[
\frac{dP_m(t)}{dt} = u[P_{m-1}(t) + P_{m+1}(t)] - (2u + k_1)P_m(t); \quad (5.20)
\]

\[
\frac{dP_{m+1}(t)}{dt} = u[P_m(t) + P_{m+2}(t)] - (2u + k_2)P_{m+1}(t). \quad (5.21)
\]
After some algebra, we finally obtain the following expressions for the stationary profiles,

\[
P^{(s)}(n \leq m) = \frac{Q[Bx_1^n + Ax_1^{m-n}]}{b_1 B - c_1 A x_1^m}; \quad (5.22)
\]

\[
P^{(s)}(n > m) = \frac{Q[(Bb_2(u - c_1)x_1^m + A(u + b_1)b_2)x_2^{n-m}]}{[ub_2x_2 + uc_2 x_2^{2L-2m-1}][b_1 B - c_1 A x_1^m]}
+ \frac{Q[(Bc_2(u - c_1)_1^m + Ac_2(u + b_1))x_2^{2L-n-m}]}{[ub_2x_2 + uc_2 x_2^{2L-2m-1}][b_1 B - c_1 A x_1^m]} \quad (5.23)
\]

where the auxiliary functions \(A\) and \(B\) are specified as

\[
A = x_1^m [x_2b_2^2(u-c_1)(u+b_2) - u^2b_2^2 x_2] + x_1^m x_2^{2L-2m-1} [b_2(u-c_2)(u-c_1)c_2 - u^2b_2c_2] \quad (5.24)
\]
Figure 5.6: Effective potential due to degradation as a function of the distance from the origin in units of $k_B T$ for the system with two degradation regions. Solid curves correspond to $k_1 = 1$ and $k_2 = 0.01$. Dashed curves correspond to $k_1 = 0.01$ and $k_2 = 1$. (a) $u = 0.01$; (b) $u = 1$; and (c) $u = 100$. For calculations $m = \frac{L}{2}$ was utilized.

\[ B = x_2 b_2^2 u^2 - x_2 b_2^2 (b_1 + u)(b_2 + u) + x_2^2 b_2^2 c_2 - b_2 (b_1 + u)(u - c_2) c_2, \]  

(5.25)

with constants $b_1, b_2, c_1, c_2, d_1, d_2, e_1,$ and $e_2$ given by

\[ b_1 = \frac{k_1 + \sqrt{k_1^2 + 4uk_1}}{2}, \quad b_2 = \frac{k_2 + \sqrt{k_2^2 + 4uk_2}}{2}, \]
\[ c_1 = \frac{-k_1 + \sqrt{k_1^2 + 4uk_1}}{2}, \quad c_2 = \frac{-k_2 + \sqrt{k_2^2 + 4uk_2}}{2}, \]
\[ d_1 = \frac{2u + k_1 + \sqrt{k_1^2 + 4uk_1}}{2\sqrt{k_1^2 + 4uk_1}}, \quad d_2 = \frac{2u + k_2 + \sqrt{k_2^2 + 4uk_2}}{2\sqrt{k_2^2 + 4uk_2}}, \]
\[ e_1 = \frac{2u + k_1 - \sqrt{k_1^2 + 4uk_1}}{2\sqrt{k_1^2 + 4uk_1}}, \quad e_2 = \frac{2u + k_2 - \sqrt{k_2^2 + 4uk_2}}{2\sqrt{k_2^2 + 4uk_2}}. \]  

(5.26)
The results of our calculations for density profiles for the system with two degradation regions are presented in Fig. 5.4. One can see that for slow diffusion (Fig. 5.4a) there is not much difference in the behavior independently of the order of degradation regions. The degradation is so strong that most morphogens are removed close to the origin. However, the difference becomes more pronounced with increasing the diffusion rate $u$. For the system with a strong degradation in the first region ($k_1 \gg k_2$) there is strong decay in the concentration profile, which is followed by essentially a constant density profile: see Fig 5.4c. This observation is easy to explain: there is a strong tendency to remove morphogens in the first region, and in the second one the dynamics is closer to a free diffusion. But for the system with the strong degradation in the second region ($k_1 \ll k_2$) there is a relatively weak linear decay in the region $0 \leq n \leq m$, and the fast exponential decay in the second region, $m \leq n \leq L$. The second region with strong decay serves as a sink for signaling molecules in the first part, yielding the expected in this case linear profile.

More information about the dynamics of formation of morphogen gradients with spatially varying degradation rates can be obtained from calculations of LAT. The explicit expressions are very bulky, and they are given in the Appendix B. The results of LAT for systems with two degradation regions are presented in Fig. 5.5. Different behavior at two regions is clearly observed. But one can also see that the system with the strong degradation in the first region (red curves in Fig. 5.5) always reaches the stationary profiles faster. The strongest effect is observed for slow diffusion (Fig. 5.5a), while for faster diffusion rates the difference is lower: see Figs. 5.5b and 5.5c. This is a surprising result. In our calculations we took $m = L/2$, i.e., two regions have the same length. The overall amount of degradation is the same in both systems, the difference is only in the order degradation regions. One would naively expect that
relaxation dynamics to the stationary state at the end of the interval \((n = L)\) should be the same in both systems. But this is not the case at all regimes. This leads us to an important conclusion that the dynamics of formation of morphogen gradients can be modified by changing the spatial distribution of degradation rates, even \textit{without} changing the amplitudes of the degradation rates.

To explain these surprising observations we can invoke the idea of effective potential due to degradation that was proposed earlier by us \cite{41, 49}. Let us consider 2 neighboring lattice cites, \(n\) and \(n + 1\). Because the morphogens are produced at the origin before diffusing along the interval, signaling molecules at the site \(n + 1\) spend more time in the system than particles on the site \(n\). Then they have higher probability to be removed from the system, the concentration of morphogens is generally smaller at the site \(n + 1\), creating a gradient. Such concentration gradient can be also obtained as a result of the action of the potential in the system, acting in the direction of increasing \(n\), but \textit{without} degradations\cite{41, 49}. This effective potential can be estimated in terms of the stationary concentrations,

\[
U_{\text{eff}} \simeq k_B T \ln P_n. \quad (5.27)
\]

We plot such effective potentials in Fig. 5.6. One can see that the effective potential is always stronger for the system with the strong degradation in the first region (red curves in Fig. 5.6) for weak diffusion. Increasing the diffusion rate \(u\) creates the region where the potential from the system with weaker degradations in the first region becomes stronger (blue curves in Fig. 5.6). But, \textit{on average} over the whole interval, the effective potential is stronger for the system with \(k_1 \gg k_2\). This nicely explains the dynamics of the relaxation to the stationary states as presented in Fig. 5.5. LAT is smaller when the effective potentials, that drive morphogens along the interval, are stronger.
5.3 Summary and Conclusions

We developed a theoretical framework for investigating the role of spatially varying degradation rates in the formation of morphogen gradients. Our analysis is based on the discrete-state stochastic models of the formation of signaling profiles. The approach provides a full analytical description for the stationary profiles and local accumulation times (LATs). We specifically analyzed two cases of systems with spatially varying degradations. First, a local inhomogeneity model, in which the degradation rate on a single cell differs from all other degradation rates, was considered. Second, we studied a system with two different regions of degradation. Our analysis shows that in both cases the inhomogeneity might lead to strong changes in dynamic behavior of the system. The effect is stronger for slow diffusion, while for the fast diffusion it becomes smaller. We also found a surprising result that the dynamics of morphogen gradient formation can be strongly influenced by varying the spatial distribution of degradation rates without changing the total amount of degradation. Using the idea of effective potential created by degradation, all obtained results are fully explained. Our theoretical method suggests that dynamics of signaling processes can be well tuned by modifying not only the strength of the degradation but also a spatial distribution of the receptors.

Although our approach provides a clear physical picture of the underlying processes during the development of morphogen gradients, it should be emphasized that the model is oversimplified and many important features are neglected, including temporal evolution of degradation rates, coupling of reaction-diffusion processes in signaling molecules with underlying mechanical changes in the embryo cells, and many others. It will be important to test our predictions in more advanced theoretical studies as well as directly in experiments.
Chapter 6

A New Mechanism of Biological Signaling: Direct Transport via Cytonemes

6.1 Introduction

Despite successful application of the SDD model for many biological systems, there is a growing number of experimental observations, suggesting that the indirect delivery of the morphogens via diffusion might not be the only mechanism in the transportation of biological signals [35, 46, 47]. It has been argued that the complex environment of the embryo systems might prevent free diffusion from establishing distinguishable morphogen gradients at different regions [35, 46]. An alternative direct delivery mechanism of signaling molecules that employs cytonemes has been proposed [35, 45, 53, 58]. Cytonemes are dynamic cellular extensions with the length varying from 1 to 100 µm and with the diameter of ~100 nm [46]. They have been observed in multiple biological systems [46, 47, 54, 55, 57, 59, 62]. These tubular objects are supported by actin networks, they can extend and retract quite fast, and their tips can attach to other cells [46]. The idea behind the indirect delivery mechanism is that the morphogens are moving inside the cytonemes, probably along the actin filaments with the help from motor proteins, starting from the source cell directly to the specific cell [35]. It is schematically shown in Fig. 6.1. The advantage of using cytonemes to deliver the biological signaling molecules is that they can easily adapt to a complex topography of embryo systems, providing a much more precise transfer
Figure 6.1: Schematic picture for the direct delivery of morphogens. Squares labeled as \( n = 0, 1, \ldots, N \) correspond to embryo cells. The red square \((n = 0)\) is a source cell, while green squares \((n > 0)\) are target cells. Signaling molecules, shown as small red circles, move along tube that starts in the source cell and ends at the target cells \( n \) with the rate \( w_n \). Morphogens are produced with the rate \( Q \) at the source cell. At the target cells they are degraded with the rate \( k \).

of information to underlying cells [35].

While various theoretical models have been proposed to describe the formation of the morphogen gradients via free extracellular diffusion[9, 32, 34, 38, 49], there is no theoretical framework for analyzing the direct delivery mechanism. In this chapter, we address this problem by developing a simple quantitative approach to explain the direct transportation of biological signals [61]. Our discrete-state stochastic model takes into account the most relevant chemical and physical processes in the system, and it predicts several important dynamic features that can be tested experimentally. Our calculations show that the morphogen gradients created by the direct delivery mechanism strongly depend on transportation rates along the cytonemes. We also find a surprising result that the stationary density profiles at all embryo cells are established at the same time, in contrast with the free extracellular diffusion route. This leads to an important conclusion that the direct delivery via cytonemes is more robust mechanism for the formation of signaling molecules profiles. But our analysis also suggests that the direct delivery route requires energy, and its efficiency might be lowered by intermolecular interactions.
6.2 Direct Transport Via Cytonemes

Our theoretical model is presented in Fig. 6.1. It is assumed that there are \( N + 1 \) embryo cells in the system (squares in Fig. 6.1). One of them (red square, \( n = 0 \)) is a source cell where morphogens are produced with a rate \( Q \). The source cell also generates \( N \) cytonemes that extend and attach to each of the target cell (green squares in Fig. 6.1). Morphogen molecules (small red circles in Fig. 6.1) are transported to the \( n \)-th cell with a rate \( w_n \) (\( n = 1, 2, ..., N \)). When the signaling molecules reach their target cells they are degraded with a rate \( k \). This is the simplest scheme that takes into account most relevant processes in the systems such as the production of morphogens in the specific cells, the transportation along the cytonemes to specific target cells and the removal of signaling at the targets.

To compute the dynamic properties of the direct delivery mechanism, it is convenient to adapt a single-molecule view here. We define then \( P_n(t) \) as a probability of finding a signaling molecule at the cell \( n \) at time \( t \). This can be viewed as proportional to a density or concentration of morphogens at given cell. The temporal evolution of this quantity is governed by a set of master equations:

\[
\frac{dP_0(t)}{dt} = Q - \sum_{n=1}^{N} w_n P_0(t) \quad (6.1)
\]

for \( n = 0 \), and

\[
\frac{dP_n(t)}{dt} = w_n P_0(t) - k P_n(t) \quad (6.2)
\]

for \( n > 0 \). Assuming that initially there were no morphogens in the system, \( P_n(t = 0) = 0 \) for all \( n \), these master equations can be solved exactly at all times, yielding

\[
P_o(t) = \frac{Q}{\eta} \left[ 1 - e^{-\eta t} \right] ; \quad (6.3)
\]

\[
P_n(t) = \left[ \frac{Q w_n}{\eta (\eta - k)} \right] e^{-\eta t} - \left[ \frac{Q w_n}{k (\eta - k)} \right] e^{-kt} + \frac{Q w_n}{\eta k}, \quad (6.4)
\]
where $\eta = \sum_{n=1}^{N} w_n$ is defined as a total transportation rate along all cytonemes. One can see that the concentration of signaling molecules at each cell is an exponentially decaying function of the time, and it is a result of balancing two opposing processes: the direct delivery with the rate $\eta$ and the removal with the rate $k$. For the special case of $k = \eta$ we obtain $P_n(t) = \frac{Q w_n}{k^2} \left[ 1 - e^{-kt} \right]$. At large times ($t \to \infty$), the density profiles reach stationary values,

$$P_n^{(s)} = \frac{Q}{k \eta} w_n, \quad P_0^{(s)} = \frac{Q}{\eta}.$$  \hspace{1cm} (6.5)

### 6.3 Local Relaxation Time

To understand the mechanisms of the direct delivery of signaling molecules, it is important to consider the approach to the stationary-state behavior. It can be quantified by calculating a local relaxation function $R_n(t) \equiv \frac{P_n(t) - P_n^{(s)}}{P_n(0) - P_n^{(s)}}$ \hspace{1cm} (31). This function can be viewed as a relative measure of how close is the system to the stationary state at the given location. Our calculations produce

$$R_n(t) = \frac{\eta e^{-kt} - ke^{-\eta t}}{\eta - k}, \quad R_0(t) = e^{-\eta t}.$$  \hspace{1cm} (6.6)

The local relaxation function can be used for evaluating a local accumulation time (LAT) $t_n = \int_0^\infty R_n(t) dt$ [31], which is defined as a time when the stationary concentration at the given location can be achieved for the first time. It can be easily shown that

$$< t_n > = \frac{1}{k} + \frac{1}{\eta}, \quad < t_0 > = \frac{1}{\eta}.$$  \hspace{1cm} (6.7)

Since there is no dependence on the target cell index $n$ these calculations lead to an important conclusion that the relaxation dynamics to the stationary behavior
is identical at all target cells. This is a surprising result, which also sharply contrasts with the position-dependent approach to the stationary phase in the indirect diffusional delivery of morphogens [31, 38, 49]. This can be understood using the following arguments. In the delivery of signaling molecules via cytonemes the behavior at each target cell is independent of other cells. In this case, the relaxation dynamics is governed by two processes: achieving the stationary state at the source cell \((n = 0)\) and the degradation of morphogens at the target cells \((n \geq 1)\), which is taking place with the same rate \(k\). For the free extracellular diffusion reaching by signaling molecules the specific locations for the first time is the most critical step [49]. Obviously, these first arrival processes are position dependent since the diffusional front moves sequentially from the source cell to the targets cells.

Analyzing the formation of biological signaling profiles, it is important to compare the robustness of direct and indirect delivery mechanisms. There are many ways to describe the robustness. Here we use the normalized variance as a quantitative measure of fluctuations and noise in the delivering of morphogen molecules to specific target cells. One expects that more robust system shows less fluctuations and noise. To perform such calculations, we need the second moment of LAT, which can be also obtained from the local relaxation function [31, 38],

\[
<t_n^2> = -\int_0^\infty t^2 \frac{dR_n(t)}{dt} dt,
\]

\[
<t_n^2> = \frac{2(\eta^2 + k\eta + k^2)}{k^2\eta^2}, \quad <t_0^2> = \frac{2}{\eta^2}.
\]  

\(6.8\)

The normalized variance is defined then as,

\[
\sigma_n = \left[ \frac{<t_n^2> - <t_n>^2}{<t_n>^2} \right]^{1/2},
\]

\(6.9\)

whiled yields for the direct delivery mechanism,

\[
\sigma_n = \left[ \frac{\eta^2 + k^2}{\eta^2 + 2k\eta + k^2} \right]^{1/2}, \quad \sigma_0 = 1.
\]

\(6.10\)
Figure 6.2: Normalized variance as a function of the distance from the source cell for direct and indirect delivery mechanisms. Solid lines correspond to the SDD model with a diffusion rate \( u \) [49]. Dashed lines correspond to the translocation of morphogens via cytonemes with the total transportation rate \( \eta \).

From this expression we find that the normalized variance is always less or equal to one for any target cell, and it reaches the minimum when \( \eta = k \), giving \( \sigma_n = 1/\sqrt{2} \). The largest variance, \( \sigma_n \approx 1 \), is achieved when one of the relevant rates dominates, i.e., for \( \eta \gg k \) or \( k \gg \eta \).

The normalized variances for the translocation of morphogens through cytonemes and via the free extracellular diffusion are presented in Fig. 6.2. One can see that there is always less fluctuations and noise in the direct delivery mechanism, and the largest difference is achieved when the degradation and the total transportation rates are comparable. This suggests that moving the morphogens across cytonemes provides a more robust mechanism of delivery biological signals. It can be explained
by noticing that the free diffusional mechanism is more stochastic because molecules can fluctuate spatially between different cells. In the direct delivery mechanism such option does not exist.

6.4 Transportation Rates

Our theoretical analysis indicates the importance of the transportation rates in the direct delivery of morphogens. To understand the mechanisms of the transport through cytonemes, a more microscopic description of \( w_n \) is needed. There are no quantitative measurements of these rates [35], but based on observations that the motion of motor proteins along the cytoskeleton might be involved [55], we propose the following two limiting models. Our first hypothesis is that the rate of moving along the cytoneme is given by a free-energy difference between finding the morphogen at the cell \( n \) and at the source cell,

\[
w_n = \exp \left[ -\frac{\Delta G(n)}{k_B T} \right] \tag{6.11}
\]

where \( \Delta G(n) \) is the energy required to displace the morphogen from the source to the target cell \( n \). Let us assume here that the length of the cytoneme that connects the source and the cell is, \( L_n \) is proportional to \( n \), i.e., \( L_n = An \). Furthermore, we assume that the motor proteins spend energy \( \varepsilon \) (in units of \( k_B T \)) by moving every signaling molecule a distance \( l \). The free energy difference can be written as

\[
\Delta G(n) = \frac{L_n \varepsilon k_B T}{l} = \frac{An \varepsilon k_B T}{l} = \frac{n k_B T}{a}, \tag{6.12}
\]

where \( a = l/A\varepsilon \). Then, the explicit expression for the transportation rate is given by \( w_n = \exp \left[ -\frac{n}{a} \right] \). This leads to the following stationary density profile of signaling molecules

\[
P_n^{(s)} = \frac{Q}{k\eta} \exp \left[ -\frac{n}{a} \right], \tag{6.13}
\]
where the total transportation rate $\eta$ is equal to

$$\eta = \sum_{n=1}^{N} \exp \left[ -\frac{n}{a} \right] = \frac{\exp \left[ -\frac{1}{a} \right] - \exp \left[ -\frac{(1+N)}{a} \right]}{1 - \exp \left[ -\frac{1}{a} \right]}.$$  \hspace{1cm} (6.14)

This model predicts the exponential decaying stationary-state density profile [see Eq. 6.13], and the decay length, specified by the parameter $a$, is larger for more efficient motor proteins that spend less energy in driving the morphogens along the cytonemes. The exponential morphogen gradients are also found for indirect free diffusion delivery of signaling molecules at large times [9, 35, 49]. However, in this case the decay length is determined by the ratio of diffusion and degradation rates [31, 49]. This underlies the importance of energy dissipation in the transportation of signaling molecules through cytonemes.

In the direct delivery route the morphogens are moved along effectively one-dimensional structures [35, 55], and this suggest that intermolecular interactions might strongly influence the translocation dynamics. From this point of view, our first model describes the transportation of morphogens that do not interact with each other inside of the cytonemes. In real systems, one expects that signaling molecules might interact with each other during the translocation. This is the basis for our second model of the transportation. Here we note that the motion of signaling molecules in each cytoneme can be viewed as 1D multi-particle biased transport. This can be well described by totally asymmetric simple exclusion processes (TASEP), which were successfully employed for analyzing many complex nonequilibrium phenomena in chemistry, physics and biology [81]. We assume that each cytoneme can be viewed as a lattice segment with $n$ sites: see Fig. 6.1. Signaling molecules are hoping only in the direction of the target cell from one site to the next one. To each lattice site $i$ ($1 \leq i \leq n$) we assign an occupation number $\tau_i$ which is zero if the site is empty or
\( \tau_i = 1 \) if the site is occupied. This means that only one molecule can be found at each site, and morphogens interact with each other via hard-core exclusions. The particle at site \( i \) can jump forward to the site \( i + 1 \) with the rate 1, provided that this site is empty. The particle can enter the lattice with a rate \( \alpha \) from the left boundary if the first site is empty, and it can also leave the lattice segment (cytoneme) from the last site with a rate \( \beta \). The steady-state properties for the TASEP on finite lattice segments with open boundaries have been calculated exactly [60, 81]. The particle flux through the segment of length \( n \) is given by [60],

\[
J(\alpha, \beta; n) = \frac{S_{n-1}(1/\beta) - S_{n-1}(1/\alpha)}{S_n(1/\beta) - S_n(1/\alpha)},
\]

(6.15)

where an auxiliary function \( S_n(y) \) is defined as,

\[
S_n(y) = \sum_{i=0}^{n-1} \frac{(n-i)(n+i-1)!}{n!i!} y^{n-i+1}.
\]

(6.16)

It is also possible to evaluate explicitly the occupation of every lattice site in all segments [60].

To connect TASEP with the transport through cytonemes with \( N \) target cells we can identify the effective entrance rate as \( \alpha = Q/N \) since \( Q \) is the total rate of production of signaling molecules in the source cell and we assume that they are split equally between all cytonemes going to \( N \) target cells. The exit rate can be associated with the degradation rate \( k \) that removes the particles from the cytonemes, i.e., \( \beta = k \).

It is also reasonable to connect the transportation rate \( w_n \) with the particle flux through the cytoneme to the \( n \)-th target cell, \( w_n = J(\frac{Q}{N}, k; n) \). At stationary-state conditions it leads us to explicit expression for the density profile,

\[
P_n^{(s)} = \frac{Q}{k\eta} J(\frac{Q}{N}, k; n) = \frac{Q}{k\eta} \left[ \frac{S_{n-1}(1/k) - S_{n-1}(N/Q)}{S_n(1/k) - S_n(N/Q)} \right],
\]

(6.17)
where the total transportation rate is given by

$$\eta = \sum_{n=1}^{N} \left[ \frac{S_{n-1}(1/k) - S_{n-1}(N/Q)}{S_n(1/k) - S_n(N/Q)} \right].$$  \hspace{1cm} (6.18)

The stationary-state density profiles obtained for the direct delivery mechanism for interacting and non-interacting morphogens are presented in Fig. 6.3. One can see that for target cells that are close to the source the behavior is similar in both cases, while for the cells located much further away there is a saturation behavior due to exclusion interactions between morphogens. Because the profiles are expected to be very non-uniform in order to efficiently transfer the information, this suggests that the direct delivery of interacting morphogens might not be the most efficient mechanism of transporting the biological signals on very long distances if exclusion interactions are important. However, it is important to mention that the presented model is rather oversimplified and some important biological phenomena might not be included here. The dynamics of the signaling transport might strongly deviate from these predictions.
6.5 Time-Dependent Production Rate

In this section, we investigate the effects of a time-dependent production rate on the dynamics of the direct delivery mechanism. We define, again, $P_n(t)$ as the probability to find the signaling molecule at the cell $n$ at time $t$. This probability function is controlled by the following master equations:

\[
\frac{dP_0(t)}{dt} = Q(t) - \sum_{n=1}^{N} w_n P_0(t) \quad (6.19)
\]

for $n = 0$, and

\[
\frac{dP_n(t)}{dt} = w_n P_0(t) - k P_n(t) \quad (6.20)
\]

for $n > 0$. It can be shown that the complete solutions for these equations at all times are

\[
P_0(t) = \int_0^t Q(t') e^{-\gamma(t'-t)} dt' + c_1 e^{-\eta t} \quad (6.21)
\]

\[
P_n(t) = \int_0^t P_0(t'') e^{-k(t-t'')} dt'' + c_2 e^{-k t} \quad (6.22)
\]

One can solve these equations for any integrable form of $Q(t)$. For $Q(t) = Q$, we recover results obtained in section 6.2. For simplicity, let us consider an exponentially varying production rate:

\[
Q(t) = Q_0(1 - e^{-\gamma t}) \quad (6.23)
\]

Substituting this equation into Eqn. (6.19), we find:

\[
P_0(t) = Q_0 \left[ \frac{1}{\eta} + \frac{\gamma e^{-\eta t}}{\eta (\eta - \gamma)} - \frac{e^{-\eta t}}{(\eta - \gamma)} \right] \quad (6.24)
\]

In addition, combination of Eqs. 6.24 and 6.22 yields:

\[
P_n(t) = \frac{w_n Q_0}{\eta k} + \left[ \frac{w_n \gamma Q_0}{\eta (\eta - \gamma)(k - \eta)} \right] e^{-\eta t} - \left[ \frac{w_n Q_0}{(\eta - \gamma)(k - \gamma)} \right] e^{-\gamma t}
\]

\[+ \quad w_n Q_0 \left[ \frac{1}{(\eta - \gamma)(k - \gamma)} - \frac{\gamma}{\eta (\eta - \gamma)(k - \eta)} - \frac{1}{k \eta} \right] e^{-k t} \quad (6.25)
\]
Again, the density profile of signaling molecules at each cell varies exponentially with time, and it is now a result of balancing the direct delivery with the rate \( \eta \), the degradation with rate \( k \), and source relaxation with characteristic time \( 1/\gamma \). At large times, the density profiles reach stationary values

\[
P_n^{(s)} = \frac{Q}{k\eta} w_n, \quad P_0^{(s)} = \frac{Q}{\eta}.
\]  

(6.26)

The local relaxation functions are given by

\[
R_0(t) = \frac{\eta e^{-\gamma t}}{(\eta - \gamma)} - \frac{\gamma e^{-\eta t}}{(\eta - \gamma)}
\]  

(6.27)

for \( n = 0 \), and

\[
R_n(t) = e^{-kt} - \left[ \frac{k\gamma}{(\eta - \gamma)(k - \eta)} \right] e^{-\eta t} + \left[ \frac{k\eta}{(\eta - \gamma)(k - \eta)} \right] e^{-\gamma t}
\]

\[
+ \left[ \frac{k\gamma}{(\eta - \gamma)(k - \eta)} - \frac{k\eta}{(\eta - \gamma)(k - \gamma)} \right] e^{-kt}
\]

(6.28)

for \( n > 0 \). The local accumulation time is given by \( t_n = \int_0^\infty R_n(t)dt \), and it yields

\[
< t_n > = \frac{1}{k} + \frac{1}{\eta} + \frac{1}{\gamma}, \quad < t_0 > = \frac{1}{\eta} + \frac{1}{\gamma}.
\]

(6.29)

One can show that for \( \lambda \to \infty \), we recover the results obtained in section 6.3. As we discussed in chapter 3, such a time-dependent source delays delivery of information to specific cells.

### 6.6 A Hypothetical Model of Direct Delivery in Classical Mechanics

In the last section of this chapter, we introduce a hypothetical model of direct delivery mechanism in the context of Newtonian mechanics. This model clearly indicates how energy dissipation is required for the direct delivery mechanism. The schematic of
Figure 6.4: A schematic picture for the hypothetical direct delivery mechanism. Objects are released from the reservoir (shown in red) located at the top of the platform of height $H$. Each route connects the source to a target site.

This model is shown in figure 6.4. A source is placed at the top of a platform of height $H$. Objects are released from rest and slide down on frictionless routes until they reach specific sites at distance $L_i$ from the base of the platform. They might exit the target sites at rate $k$. We define a function $N_i(t)$ as the number of objects at site $i$ at time $t$. The time evolution of this quantity is governed by a set of master equations,

\[
\frac{dN_0(t)}{dt} = Q - \sum_{i=1}^{M} w_i N_0(t) \tag{6.30}
\]

for $i = 0$, and

\[
\frac{dN_i(t)}{dt} = w_i N_0(t - t_i) - k N_i(t) \tag{6.31}
\]

for $i > 0$. Here $t_i = 1/w_i$ is the average arrival time to site $i$. Assuming that initially there were no objects in the system, $N_0(t = 0) = 0$ for all $i$, these equations can be solved exactly at all times, yielding

\[
N_0(t) = \frac{Q}{\eta} \left[ 1 - e^{-\eta t} \right] \tag{6.32}
\]

\[
N_i(t) = \left[ \frac{w_i Q}{\eta(\eta - k)} \right] e^{-\eta(t - \frac{1}{w_i})} - \left[ \frac{w_i Q}{k(\eta - k)} \right] e^{-kt} + \frac{w_n Q}{k\eta} \tag{6.33}
\]

where $\eta = \sum_{i=1}^{M} w_i$ is defined as a total transportation rate along all routes. One can see that the concentration profile of objects at each site varies exponentially with
time. At large times, the density profiles reach stationary values

\[ N_i^{(s)} = \frac{Q}{k\eta} w_n, \quad N_0^{(s)} = \frac{Q}{\eta}. \quad (6.34) \]

Similar to the analysis presented in Section 6.3, we define local relaxation function \( R_i(t) \) as

\[ R_i(t) = \frac{N_i(t) - N_i^{(s)}}{N_i(0) - N_i^{(s)}} = 1 - \frac{N_i(t)}{N_i^{(s)}}; \quad (6.35) \]

Substituting corresponding Eqs. 6.32 and 6.33, we obtain:

\[ R_i(t) = \frac{\eta e^{-kt}}{\eta - k} - \frac{k e^{-\eta(t - \frac{1}{w_i})}}{\eta - k}, \quad R_0(t) = e^{-\eta t} \quad (6.36) \]

The local accumulation time is given by \( t_i = \int_0^\infty R_i(t)dt \), and it yields

\[ <t_i> = \frac{\eta}{k(\eta - k)} + \frac{k e^{\eta/w_i}}{\eta(\eta - k)}, \quad <t_0> = \frac{1}{\eta}. \quad (6.37) \]

Since we take average arrival times into account, the resulting relation time becomes dependent on the target site index, \( i \). The exponential growth of LAT is controlled by the transportation rate, \( w_i \). To understand the mechanism of transport through routes, we need explicit forms of the transportation rates. For simplicity, we assume that no collision/interaction occurs between objects. Balancing forces along route \( i \) produces:

\[ ma_i = mg \sin(\theta_i) \quad (6.38) \]

where \( m \) is the mass of each object and \( \theta_i \) is the angle between the route \( i \) and the horizontal line. This equation results the acceleration of each object,

\[ a_i = g \sin(\theta_i) = \frac{gH}{\sqrt{H^2 + L_i^2}} \quad (6.39) \]
Having acceleration known, we can calculate the time required for objects to move from source to a target site \( i \), using this formula,

\[
t_i = \sqrt{\frac{2x_i}{a_i}} = \sqrt{\frac{2(H^2 + L_i^2)}{gH}}
\]  

(6.40)

Then the transportation rate \( w_i \), which is defined as the number of objects delivered in unit of time, is given by the inverse of \( t_i \),

\[
w_i = \frac{1}{t_i} = \sqrt{\frac{gH}{2(H^2 + L_i^2)}}
\]  

(6.41)

To simplify the calculations, we assume that \( L_i = iH \) where \( i \in [1, M] \). Furthermore, the explicit form for the transportation rate is given by

\[
w_i = \sqrt{\frac{g}{2H(1 + i^2)}}
\]  

(6.42)

This leads to the following stationary concentration profile of objects

\[
N_i^{(s)} = \left[ \frac{Q}{k\eta'} \right] \frac{1}{(1 + i^2)^{1/2}}
\]  

(6.43)

where the normalized total transportation rate \( \eta' \) is given by

\[
\eta' = \sum_{i=1}^{M} w_i = \sum_{i=1}^{M} \frac{1}{\sqrt{1 + i^2}}.
\]  

(6.44)

6.7 Summary and Conclusions

To summarize, we developed a comprehensive theoretical framework for analyzing a new mechanism of transferring biological signals that utilizes direct delivery of morphogens via the cellular extensions cytonemes. Recent experimental studies indicate that this mechanism might be important in the development of multi-cellular living systems. Our calculations predict that the transport through cytonemes simultaneously transfers the biological information to all target embryo cells. The critical
role in the direct delivery dynamics is played by the translocation rates along the cytonemes and degradation rates. It is shown that the transportation via cytonemes is more robust than the free extracellular diffusion for delivering the biological information. However, it requires energy dissipation for effective functioning. In addition, we found that intermolecular interactions between morphogens inside the cytonemes might limit the efficiency of this mechanism only target cells that are close to the source region. Although our theoretical analysis provides a fully quantitative description of the direct delivery mechanisms of signaling molecules and it explains its main characteristics, it should be noted that the presented method is still oversimplified with many important features not considered. For example, we assume that the cytonemes are static structures, while the experimental studies clearly indicate that the cytonemes might extend and retract dynamically [59]. It will be important to test the proposed theoretical ideas in experimental studies as well as in more advanced theoretical investigations.
Chapter 7

Theoretical Analysis of Dynamic Processes for Interacting Molecular Motors

7.1 Introduction

A central role in supporting many cellular processes is played by several classes of enzymatic molecules that are known as motor proteins or molecular motors [63, 64, 66, 67, 68]. They use the chemical energy released from hydrolysis of adenosine triphosphate (ATP) to drive cellular transport along cytoskeleton filaments. Single-molecule properties of various molecular motors are now well investigated both experimentally and theoretically [67, 68, 69]. However, cellular cargoes are often moved by groups of motor proteins, and microscopic mechanisms of collective motor behaviors remain not well understood [68, 70, 71]. Recent experiments on kinesin motor proteins indicate that motors bound to the microtubule filament interact with each other [72, 73, 74]. The evidences for this behavior are found from observations that kinesins on microtubules phase segregate into more dense and less dense patches, and from measurements of different times to be bound to the filament depending on the presence of neighbors [72, 73, 74]. It was estimated that these interactions are weakly attractive \((1.6 \pm 0.5k_B T)\) [72]. It raises a question on a fundamental role of this phenomenon in collective motion of motor proteins. Various chemical transitions such as bindings, unbindings, hydrolysis and steppings should be affected by this potentials, influencing the overall dynamics of motor proteins. However, the impact of
such interactions on transport of molecular motors is not fully explored [70]. There are several investigations addressing collective dynamics of interacting motor proteins [75, 78, 79, 90]. But the main limitation of these studies is a phenomenological description of interactions that does not provide a quantitative description for chemical transitions in motor proteins.

One of the most powerful tools in investigating multi-particle non-equilibrium systems is a class of models called totally asymmetric simple exclusion processes (TASEP) [80, 81, 82]. It is known that these models successfully capture essential properties of a large number of physical, chemical and biological systems [81, 82, 83, 84, 85, 86, 88]. Different versions of TASEP have been extensively employed in studies of various aspects of biological molecular motors [71, 84, 78, 81, 89, 90], providing an important microscopic insights on these complex processes. TASEP with interactions have been studied before, but only for the particles on the ring [78] or with phenomenologically defined interactions [90, 91, 92].

In this chapter, we investigate the effect of intermolecular interactions on collective dynamics of motor proteins by introducing a new TASEP model with interactions[76]. The most important advance of our method is that interactions are taken into account using a fundamental thermodynamical procedure. It provides a direct way of coupling microscopic properties of motor proteins with their collective dynamic features. To make the model more realistic we use open boundary conditions since the cytoskeleton filaments have finite length. Using various mean-field analytical methods and extensive Monte Carlo simulations we compute particle currents and density profiles for molecular motors. It provides us with a direct method to address the fundamental role of interactions. Our analysis suggests that there is an optimal interaction strength, corresponding to weak repulsions, that leads to the maximal particle flux.
It is also found that interactions introduce significant correlations in the system and modify phase diagrams. In addition, dynamic properties of molecular motors are influenced stronger by attractive interactions.

7.2 Theoretical Description

7.2.1 Model

We consider a transport of molecular motors on the cytoskeleton filaments as a multi-particle motion along a lattice segment with $L$ sites as illustrated in Fig. 7.1. For each lattice site $i$ ($1 \leq i \leq L$) we assign an occupation number $\tau_i$, which is zero if the site is empty or $\tau_i = 1$ if the site is occupied. Each site cannot be occupied by more than one particle. It is assumed that each two particles sitting on neighboring sites interact with each other with an energy $E$ ($E > 0$ correspond to attractions and $E < 0$ describe repulsions). A single motor that is not a part of the particles cluster can move forward with the rate 1 if it moves to the site without neighbors (Fig. 7.1). There is no energy change in this case. However, if the particle hops into another cluster it moves with rate $q \neq 1$ because the energy of the system changed by creating a new pair of neighbors (see Fig. 7.1). Similarly, for the particle breaking from the cluster its forward rate is equal to $r \neq 1$ when the particle does not have neighbors in the new position. But for the case when one pair is broken and another one is created the stepping rate is equal to 1 since there is no overall energy change (Fig. 7.1). Creating and breaking the pair of particles can be viewed as opposite chemical transitions, so the detailed balance arguments can be applied,

$$\frac{q}{r} = \exp\left(\frac{E}{k_B T}\right).$$  \hspace{1cm} (7.1)
Figure 7.1: Schematic picture of TASEP model with interacting particles

To simplify analysis, we assume that the energy $E$ is equally split between creation and breaking processes, providing explicit expressions for the stepping rates $q$ and $r$,

$$q = \exp\left(\frac{E}{2k_B T}\right), \quad r = \frac{1}{q} = \exp\left(-\frac{E}{2k_B T}\right).$$

(7.2)

The splitting of the interaction potential between the rates $q$ and $r$ is not unique, but other possibilities can be easily explored in our method. In addition, it can be shown that particle dynamics is similar for all cases. Eqs. 8.2 have a clear physical meaning. For attractive interactions ($E > 0$) the particle moves faster ($q > 1$) to create a new pair since the energy of the system decreases by $E$. Breaking out of the cluster increases the energy by $E$ and the transition rate is slower ($r < 1$). Similar arguments can be given for repulsive interactions ($E < 0$). When there is no interactions ($E = 0$) we have $q = r = 1$ and the original TASEP with only hard-core exclusions is recovered.

This model is related to a class of lattice-gas models studied by Katz, Lebowitz and Spohn, which are known as KLS models [92, 93]. But the main difference is that our transition rates are determined from fundamental thermodynamic arguments, while KLS models are generally inconsistent with thermodynamics. Furthermore,
thermodynamics decrease the number of possible stationary phases in comparison with KLS models, as we show below. At the same time at weak interactions both approaches converge. It is also important to note that, in contrast to some previous studies, this is a thermodynamically consistent method that accounts for interactions in all transitions of the system. In addition, it differs from other TASEPs with interactions [78, 87, 90, 91, 95] because the stepping rates depend on the state of 4 consecutive lattice sites. Interactions also modify the boundary transitions as shown in Fig. 7.1. The entrance rate is equal to $\alpha$ if no particle pair created, while the rate is equal to $q\alpha$ when the pair creation is involved. Similarly, the exit rate of the single particle is given by the rate $\beta$, while exiting with breaking from the cluster changes the rate to $r\beta$.

7.2.2 Simple Mean-Field Theory

To analyze the system we start with the simplest mean-field (SMF) approach that neglects all correlations in the system. It assumes that for any two sites on the lattice their occupancies are independent of each other, i.e., $Prob(\tau_i, \tau_j) \approx Prob(\tau_i) \ast Prob(\tau_j)$ for $1 \leq i, j \leq L$. The particle density at every site is associated with an average occupancy, $\rho = \langle \tau \rangle$, and it reaches a constant value in the bulk of the system. It can be shown that, similarly to the classical TASEP without interactions, there are three stationary phases, low density (LD), high density (HD) and maximal current (MC), as illustrated in Fig. 7.2. When dynamics at the entrance is rate-limiting we have a low-density (LD phase). In this case the temporal evolution of the particle density $\rho$ can be described by

$$\frac{d\rho}{dt} = \alpha(1-\rho)^2 + q\alpha\rho(1-\rho) - \rho(1-\rho)^3 - r\rho^2(1-\rho)^2 - \rho^3(1-\rho) - q\rho^2(1-\rho)^2 \quad (7.3)$$
At the stationary state, we have $\frac{d\rho}{dt} = 0$, and this equation can be solved exactly, producing the following expression:

$$\rho_{LD} = \frac{q - \sqrt{q^2 - 4\alpha q(q - 1)}}{2(q - 1)}. \quad (7.4)$$

For $q = 1$ it reduces to $\rho_{LD} = \alpha$, as expected for the standard TASEP without interactions. From this equation and using Eq. 7.3 the expression for the current can be also derived,

$$J_{LD} = \alpha \frac{\alpha q(q - 1) - 1 + \sqrt{q^2 - 4\alpha q(q - 1)}}{q - 1}, \quad (7.5)$$

which in the limit $q \to 1$ produces $J_{LD} = \alpha(1 - \alpha)$.

For the case when the exiting becomes the rate-limiting step the system is in a high-density (HD) phase. In this case, the time evolution of the particle density is given by

$$\frac{d\rho}{dt} = \rho(1 - \rho)^3 + r\rho^2(1 - \rho)^2 + \rho^3(1 - \rho) + q\rho^2(1 - \rho)^2 - \beta\rho(1 - \rho) - r\beta\rho^2. \quad (7.6)$$

In the steady-state limit we obtain,

$$\rho_{HD} = \frac{q - 2 + \sqrt{q^2 - 4\beta(q - 1)}}{2(q - 1)}, \quad (7.7)$$

while for the current we have

$$J_{HD} = \beta \frac{\beta(q - 1) - 1 + \sqrt{q^2 - 4\beta(q - 1)}}{q(q - 1)}. \quad (7.8)$$

When there are no interactions in the system ($q = 1$) the particle density and the current reduce to the values for the standard TASEP, $\rho_{HD} = 1 - \beta$ and $J_{HD} = \beta(1 - \beta)$.

In the bulk of the system the steady-state particle current is independent of entry and exit rates. It can be expressed in terms of an average density $\rho$ in the following form,

$$J = \rho(1 - \rho)^3 + r\rho^2(1 - \rho)^2 + \rho^3(1 - \rho) + q\rho^2(1 - \rho)^2, \quad (7.9)$$
where \( q = \frac{1}{r} = \exp\left(\frac{E}{2k_B T}\right) \). In this situation, the current can reach its highest value and this phase is known as a maximal current (MC) phase. In the case of no interactions \( (E = 0 \text{ and } q = r = 1) \) we obtain the parabolic expression \( J = \rho(1-\rho) \) for the current as expected for the standard TASEP model without interactions. The MC phase is specified by a condition that \( \frac{\partial J}{\partial \rho} = 0 \), which leads to the following expression,

\[
(2\rho - 1)[-1 + \rho(4 - 2q - 2r) + \rho^2(2r + 2q - 4)] = 0.
\] (7.10)

This equation has only one real root, \( \rho = \frac{1}{2} \). Substituting \( \rho = \frac{1}{2} \) into Eq. 7.9, we obtain the following expression for the maximal current as a function of interaction energy,

\[
J_{MC} = \frac{1}{8} + \frac{r + q}{16} = \frac{1}{8} + \frac{\exp\left(\frac{E}{2k_B T}\right) + \exp\left(-\frac{E}{2k_B T}\right)}{16}.
\] (7.11)

For \( E = 0 \) (\( q = r = 1 \)) it yields \( J_{MC} = \frac{1}{4} \), as expected for the standard TASEP model. In the MC phase the bulk density reaches the maximal value of \( \rho_{MC} = 1/2 \), while the particle current can be written as

\[
J_{MC} = \frac{1}{8} + \frac{r + q}{16}.
\] (7.12)

As expected, for \( E = 0 \) (\( q = r = 1 \)) these equations yield the results for the standard TASEP with only hard-core exclusions. Our computer simulations indicate that LD-MC and HD-MC transitions are continuous. We use then the continuity of the stationary current at transition to determine the boundary lines separating LD and MC and HD and MC phases. The equality of the stationary current at the boundary \( J_{MC} = J_{LD} \) yields the following expression,
\[ \alpha(1 - \rho)^2 + q\alpha\rho(1 - \rho) = \rho(1 - \rho)^3 + r\rho^2(1 - \rho)^2 + \rho^3(1 - \rho) + q\rho^2(1 - \rho)^2. \] (7.13)

Since in the MC phase the density is equal to \( \rho = 1/2 \) the boundary in terms of the entrance rate is given by

\[ \alpha_b = \frac{1 + q}{4q}. \] (7.14)

Similarly, we can determine the boundary between the HD and MC phases,

\[ \beta_b = \frac{1 + q}{4}. \] (7.15)

However, the transition between LD and HD phases is discontinuous and it involves a density jump. Then from the condition of equal current at the phase line, \( J_{HD} = J_{LD} \), we derive

\[ \beta\rho_{HD}(1 - \rho_{HD}) + r\beta\rho_{HD}^2 = \alpha(1 - \rho_{LD})^2 + q\alpha\rho_{LD}(1 - \rho_{LD}), \] (7.16)

Using Eqs. 7.4 and 7.7 it can be shown that it leads to a simple relation for this phase boundary,

\[ \beta = q\alpha. \] (7.17)

### 7.2.3 Cluster Mean-Field Theory

The fact that SMF method neglects correlations is the main reason for not satisfactory description of TASEP with stronger intermolecular interactions. To develop a more reasonable analysis we propose to use a mean-field approach that takes into account some correlations. Our idea is to fully describe particle dynamics inside of a cluster of several lattice sites, but correlations between states of different clusters will be neglected. In our calculations clusters with 2 lattice sites are
utilized. In this approach, the occupation of four consecutive sites is written as

\[ \text{Prob}(\tau_{i-1}, \tau_i, \tau_{i+1}, \tau_{i+2}) \approx \text{Prob}(\tau_{i-1}, \tau_i) \ast \text{Prob}(\tau_{i+1}, \tau_{i+2}) \].

The method is called a cluster mean-field (CMF). There are four possible states for each two-site cluster depending on the occupancy of sites that can be labeled as (1,1), (1,0), (0,1) and (0,0).

We define \( P_{11} \), \( P_{10} \), \( P_{01} \) and \( P_{00} \) as probabilities to be found in one of these configurations, respectively. The normalization requires that \( P_{11} + P_{10} + P_{01} + P_{00} = 1 \). The average bulk density and the current can be expressed in terms of these functions,

\[
\rho_{\text{bulk}} = \frac{1}{2} \sum_{\tau_1} \sum_{\tau_2} \tau_1 P(\tau_1, \tau_2) + \frac{1}{2} \sum_{\tau_1} \sum_{\tau_2} \tau_2 P(\tau_1, \tau_2) = \frac{1}{2} \sum_{\tau_1} \sum_{\tau_2} \left[ \tau_1 P(\tau_1, \tau_2) + \tau_2 P(\tau_1, \tau_2) \right] = P_{11} + \frac{P_{01} + P_{10}}{2}. \tag{7.18}
\]

In CMF all dynamic properties for TASEP with interactions can be obtained from the temporal evolution of cluster probabilities, as presented in the followings. The temporal evolution of two-site probabilities in the bulk is governed by a set of Master equations:

\[
\frac{dP_{11}}{dt} = qP(0,1,0,1) + P(1,1,0,1) - rP(1,1,0,0) - P(1,1,0,1);
\]

\[
\frac{dP_{00}}{dt} = qP(0,1,0,1) + P(0,1,0,0) - rP(1,1,0,0) - P(0,1,0,0). \tag{7.19}
\]

In CMF all dynamic properties for TASEP with interactions can be obtained from the temporal evolution of cluster probabilities, as presented in the followings. The temporal evolution of two-site probabilities in the bulk is governed by a set of Master equations:

\[
\frac{dP_{11}}{dt} = qP(0,1,0,1) + P(1,1,0,1) - rP(1,1,0,0) - P(1,1,0,1);
\]

\[
\frac{dP_{00}}{dt} = qP(0,1,0,1) + P(0,1,0,0) - rP(1,1,0,0) - P(0,1,0,0). \tag{7.19}
\]
These expressions are exact. But utilizing the cluster mean-field assumptions the above master equations can be approximated by simpler expressions,

\[
\frac{dP_{10}}{dt} = r \{P(1, 1, 0, 0, 0) + P(1, 1, 0, 0, 1) + P(1, 1, 0, 1, 0) + P(1, 1, 0, 1, 1)\}
+ P(1, 0, 0, 0, 0) + P(1, 0, 0, 0, 1) + P(1, 0, 0, 1, 0) + P(1, 0, 0, 1, 1)
+ P(1, 0, 1, 0, 0) + P(1, 0, 1, 0, 1) + P(1, 0, 1, 1, 0) + P(1, 0, 1, 1, 1)
+ q \{P(0, 0, 0, 0, 0) + P(0, 0, 0, 0, 1) + P(0, 0, 0, 1, 0) + P(0, 0, 0, 1, 1)\}
- P(0, 0, 0, 0, 0) + P(0, 0, 0, 0, 1) + P(0, 0, 0, 1, 0) + P(0, 0, 0, 1, 1)
- q \{P(0, 0, 0, 0, 0) + P(0, 0, 0, 0, 1) + P(0, 0, 0, 1, 0) + P(0, 0, 0, 1, 1)\};
\quad (7.20)

\[
\frac{dP_{11}}{dt} = qP_{01}P_{01} + P_{11}P_{01} - rP_{11}P_{00} - P_{11}P_{01};
\quad (7.22)
\]
\[
\frac{dP_{00}}{dt} = qP_{01}P_{01} + P_{11}P_{00} - rP_{11}P_{00} - P_{11}P_{01}; \quad (7.23)
\]

\[
\frac{dP_{01}}{dt} = P_{10}[P_{10}P_{01} + P_{02} + P_{00}P_{10} + P_{00}P_{01}] + rP_{10}[P_{11}P_{00} + P_{01}^2 + P_{00}P_{01} + P_{01}P_{11}]
\]
\[
+ P_{10}[P_{11}P_{11} + P_{11}P_{10} + P_{01}P_{10}] + qP_{10}[P_{00}P_{10} + P_{10}^2 + P_{11}P_{10} + P_{00}P_{11}]
\]
\[
- P_{01}[qP_{00}P_{01} + P_{02} + P_{00}P_{10} + qP_{10}P_{01} + P_{00}P_{01} + qP_{01}^2 + P_{00}P_{11} + qP_{11}P_{01}]
\]
\[
- P_{01}[qP_{11}P_{01} + P_{11}P_{10} + qP_{10}P_{01} + qP_{01}^2 + P_{00}P_{11} + P_{11}P_{01} + qP_{00}P_{01}]; \quad (7.24)
\]

\[
\frac{dP_{10}}{dt} = 2rP_{11}P_{00} + P_{01}P_{00} + P_{10}P_{10} - P_{10}[P_{10}P_{01} + P_{02} + P_{00}P_{01} + P_{00}P_{10}]
\]
\[
- rP_{10}[P_{11}P_{00} + P_{02} + P_{00}P_{01} + P_{01}P_{11}] - P_{10}[P_{10}P_{11} + P_{11}^2 + P_{11}P_{01} + P_{01}P_{10}]
\]
\[
- qP_{10}[P_{00}P_{10} + P_{10}^2 + P_{11}P_{10} + P_{00}P_{11}]. \quad (7.25)
\]

From Eq. 7.22 at the stationary state we obtain,

\[
qP_{01}^2 = rP_{11}P_{00}; \quad (7.26)
\]

while equations Eqs. (7.24) and (7.25) yield,

\[
P_{10}[P_{01}(2 - r - q) + q] + P_{10}[P_{00} + P_{11} + rP_{01} + P_{00}P_{11}(q + r - 2)]
\]
\[
- 2qP_{01}^2 - P_{00}P_{01} - P_{11}P_{01} = 0. \quad (7.27)
\]

So far, we have three equations with four unknown two-site cluster probabilities and we need one more. The last equation can be derived from the expression for the current.

\[
J_{MC} = qP_{01}^2 + rP_{11}P_{00} + P_{11}P_{01} + P_{00}P_{01} = 2rP_{11}P_{00} + r\sqrt{P_{11}P_{00}(P_{00} + P_{11})}. \quad (7.28)
\]
where Eq. 7.26 was used to eliminate $P_{01}$. Using the normalization condition, the average density from Eq. 7.18 can be written as,

$$\rho = \frac{1}{2}(1 + P_{11} - P_{00}).$$

(7.29)

Now we can define a new variable $\eta$ such that

$$\eta = P_{11} + P_{00}.$$  

(7.30)

Then the particle current can be expressed as a function of $\rho$ and $\eta$. Then applying the condition of maximal current, $\nabla J(\rho, \eta) = 0$, it can be shown that $\rho = \frac{1}{2}$. It suggests that $P_{11} = P_{00} = qP_{01}$. Utilizing this condition together with the normalization, we obtain the following cubic equation for $P_{01},$

$$P_{01}^3[-1 - 2q + 2q^2 + 4q^3 - q^4 - 2q^5] + P_{01}^2[1 - 2q - 10q^2 + 2q^3 + 5q^4]$$

$$+ P_{01}[2q - q^2 - 4q^3] + q^2 = 0.$$  

(7.31)

The physically reasonable root ($0 < P_{01} < 1$) of this equation can be found, and it is used then to calculate the current via the relation $J = 4qP_{01}^2$. Various cluster probabilities can be interpreted as a measure of clustering in the lattice. For very strong repulsion, $P_{11} \to 0$ and no clusters form. As the interaction energy becomes more attractive $P_{11}$ and $P_{00}$ increase and the particles have larger tendency to form clusters.

At the entrance cluster probabilities satisfy the following master equations,

$$\frac{dP_{11}}{dt} = q\alpha \{ P(0,1,1,1) + P(0,1,1,0) + P(0,1,0,1) + P(0,1,0,0) \}$$

$$- P(1,1,0,1) - rP(1,1,0,0); \quad (7.32)$$

$$\frac{dP_{00}}{dt} = P(0,1,0,0) + qP(0,1,0,1)$$

$$- \alpha \{ P(0,0,1,1) + P(0,0,1,0) + P(0,0,0,1) + P(0,0,0,0) \}; \quad (7.33)$$
\[
\frac{dP_{10}}{dt} = \alpha \left\{ P(0, 0, 1, 1) + P(0, 0, 1, 0) + P(0, 0, 0, 1) + P(0, 0, 0, 0) \right\} \\
+ P(1, 1, 0, 1) + rP(1, 1, 0, 0) - P(1, 0, 0, 0) - P(1, 0, 0, 1) \\
- qP(1, 0, 1, 0) - qP(1, 0, 1, 1);
\]

(7.34)

\[
\frac{dP_{01}}{dt} = P(1, 0, 0, 0) + P(1, 0, 0, 1) + qP(1, 0, 1, 1) + qP(1, 0, 1, 0) \\
- q\alpha \left\{ P(0, 1, 1, 1) + P(0, 1, 1, 0) + P(0, 1, 0, 1) + P(0, 1, 0, 0) \right\} \\
- P(0, 1, 0, 0) - qP(0, 1, 0, 1).
\]

(7.35)

These equations can be simplified using the cluster mean-field approximation,

\[
\frac{dP_{11}}{dt} = q\alpha P_{01} - rP_{11}P_{00} - P_{11}P_{01};
\]

(7.36)

\[
\frac{dP_{00}}{dt} = P_{00}P_{01} + qP_{01}P_{01} - \alpha P_{00};
\]

(7.37)

\[
\frac{dP_{10}}{dt} = \alpha P_{00} + rP_{11}P_{00} + P_{11}P_{01} - P_{10}[P_{00} + P_{01} + qP_{11} + qP_{10}];
\]

(7.38)

\[
\frac{dP_{01}}{dt} = P_{10}[P_{00} + P_{01} + qP_{11} + qP_{10}] - q\alpha P_{01} - P_{00}P_{01} - qP_{01}P_{01}.
\]

(7.39)

At the stationary state it can be shown that

\[
P_{00} = \frac{qP_{01}^2}{\alpha - P_{01}};
\]

(7.40)

\[
P_{11} = q(\alpha - P_{01});
\]

(7.41)

\[
qP_{10}^2 + P_{10}(P_{00} + P_{01} + qP_{11}) - q\alpha P_{01} - \alpha P_{00} = 0.
\]

(7.42)

Using the normalization condition \(P_{10} = 1 - P_{00} - P_{11} - P_{01}\) we obtain,

\[
P_{01}^2(q - 1) + P_{00}^2(q - 1) - qP_{11} + P_{00}(1 - 2q) + P_{01}(1 - 2q) + P_{11}P_{00}(q - 1) \\
+ P_{11}P_{01}(q - 1) + 2P_{00}P_{01}(q - 1) + q - q\alpha P_{01} - \alpha P_{00} = 0.
\]

(7.43)
Using Eqs. 7.40 and 7.41 we derive the final equation for $P_{01}$.

\[
\begin{align*}
P_{01}^4 (2q^3 - 5q^2 + 4q - 1) \\
+ P_{01}^3 (-2\alpha q^3 + 7\alpha q^2 + 3q^2 - 7q\alpha - 3q + 2\alpha + 1) \\
+ P_{01}^2 (\alpha^2 q^3 - 4\alpha^2 q^2 - 5\alpha q^2 + 5q\alpha + q - \alpha^2 - 2\alpha) \\
+ P_{01} (\alpha^3 q^2 - 3\alpha q^2 - 2q\alpha^2 - 2q\alpha + \alpha^2) \\
+ q\alpha^2 - q^2\alpha^3 = 0.
\end{align*}
\]  

(7.44)

It can be solved numerically, which leads to calculating all other properties in the LD phase.

In the HD phase the exit controlling the dynamics, and cluster probabilities evolve as given by

\[
\frac{dP_{11}}{dt} = P(1, 1, 0, 1) + qP(0, 1, 0, 1) \\
- r\beta \left\{ P(0, 0, 1, 1) + P(1, 0, 1, 1) + P(0, 1, 1, 1) + P(1, 1, 1, 1) \right\}; \quad (7.45)
\]

\[
\frac{dP_{00}}{dt} = \beta \left\{ P(0, 0, 0, 1) + P(1, 0, 0, 1) + P(0, 1, 0, 1) + P(1, 1, 0, 1) \right\} \\
- P(0, 1, 0, 0) - rP(1, 1, 0, 0); \quad (7.46)
\]

\[
\frac{dP_{01}}{dt} = P(0, 0, 1, 0) + rP(0, 1, 1, 0) + rP(1, 1, 1, 0) \\
+ P(1, 0, 1, 0) - P(1, 1, 0, 1) - qP(0, 1, 0, 1) \\
- \beta \left\{ P(1, 1, 0, 1) + P(0, 0, 0, 1) + P(1, 0, 0, 1) + P(0, 1, 0, 1) \right\}; \quad (7.47)
\]

\[
\frac{dP_{10}}{dt} = P(0, 1, 0, 0) + rP(1, 1, 0, 0) \\
+ r\beta \left\{ P(1, 1, 1, 1) + P(0, 0, 1, 1) + P(1, 0, 1, 1) + P(0, 1, 1, 1) \right\} \\
- P(0, 0, 1, 0) - rP(1, 1, 1, 0) - rP(0, 1, 1, 0) - P(1, 0, 1, 0). \quad (7.48)
\]
Applying the cluster approximation leads to simpler equations,

\[ \frac{dP_{11}}{dt} = qP_{01}P_{01} + P_{11}P_{01} - r\beta P_{11}; \quad (7.49) \]

\[ \frac{dP_{00}}{dt} = \beta P_{01} - r P_{11}P_{00} - P_{00}P_{01}; \quad (7.50) \]

\[ \frac{dP_{01}}{dt} = P_{10}[P_{00} + P_{10} + rP_{11} + rP_{01}] - P_{11}P_{01} - qP_{01}P_{01} - \beta P_{01}; \quad (7.51) \]

\[ \frac{dP_{10}}{dt} = P_{01}P_{00} + rP_{11}P_{00} + r\beta P_{11} - P_{10}[P_{00} + P_{10} + rP_{11} + rP_{01}]. \quad (7.52) \]

At the steady state we obtain:

\[ P_{11} = \frac{qP_{01}^2}{r\beta - P_{01}}; \quad (7.53) \]

\[ P_{00} = \beta - qP_{01}; \quad (7.54) \]

\[ P_{10}^2 + P_{10}[P_{00} + rP_{11} + rP_{01}] - \beta rP_{11} - \beta P_{01} = 0. \quad (7.55) \]

Again using the normalization condition one can calculate,

\[ P_{01}^2(1-r) + P_{00}^2(1-r) + P_{11}(r-2) - P_{00} + P_{01}(r-2) + P_{11}P_{00}(1-r) \]

\[ + P_{00}P_{01}(1-r) + 2P_{11}P_{01}(1-r) + 1 - \beta P_{01} - r\beta P_{11} = 0. \quad (7.56) \]

Eliminating \( P_{00} \) and \( P_{11} \) from this expression yields

\[ +P_{01}^4(2q^5 - 5q^4 + 4q^3 - q^2) \]

\[ +P_{01}^3(3q^4 - 3q^3 + q^2 + 2q\beta - 7q^2\beta + 7\beta q^3 - 2\beta q^4) \]

\[ +P_{01}^2(q^3 - \beta^2 + q^3\beta^2 - 5q^3\beta^3 - 3q^2\beta^2 + 5\beta q^2 + 4q^2\beta^2 - 2q\beta) \]

\[ +P_{01}(\beta^2 - \beta^3 - 2q\beta^2 - 2q^2\beta^2 + 3\beta^2q^2) \]

\[ +q\beta^2 - q^3\beta^3 = 0. \quad (7.57) \]
This equation can be solve numerically exactly for \( P_{01} \), and all other properties can be obtained as explained above. Phase diagram for the CMF method can be obtained using the same approach as was explained for SMF. We apply the condition \( J_{LD} = J_{MC} \) to determine the boundary between \( LD \) and \( MC \) phases

\[
\alpha P_{00} + q\alpha P_{01} = qP_{01}P_{01} + rP_{11}P_{00} + P_{11}P_{01} + P_{00}P_{01}. \tag{7.58}
\]

In the MC phase we have \( \rho_{\text{bulk}} = 0.5 \), and it leads to \( P_{11} = P_{00} \). Combining this equality with Eqs. 7.40 and 7.41 the following quadratic equation is derived,

\[
\alpha^2 - 4\alpha P_{01} + 4P_{01}^2 = 0. \tag{7.59}
\]

It has only one solution at \( \alpha_b = 2P_{01} \) where \( P_{01} \) is solution of the Eq. 7.31. Similarly, for the boundary between HD and MC phases we obtain \( \beta_b = 2qP_{01} \). To determine the phase boundary between LD and HL phases we must solve the equation \( J_{LD} = J_{HD} \), producing

\[
\alpha P_{00} + q\alpha P_{01} = \beta P_{01} + r\beta P_{11}. \tag{7.60}
\]

It can be further simplified into

\[
\beta^2(P_{01} - \alpha) + q\alpha^2\beta - q^2\alpha^2P_{01} = 0. \tag{7.61}
\]

Solving this equation for \( \beta \) leads us to

\[
\beta = \frac{q\alpha P_{01}}{\alpha - P_{01}}. \tag{7.62}
\]

From Eq. 7.62 it can be shown that \( P_{01} = \frac{\alpha^3}{q\alpha + \beta} \). After substituting it into Eq. 7.44 we obtain the following relation for the boundary between LD and HD phases,

\[
\beta^4(1 - q) + \beta^3(-1 + 3\alpha + 2q - 2q\alpha) + \beta^2(-\alpha + \alpha^2 - q + q\alpha + q\alpha^2 + 2q^2\alpha + q^2\alpha^2 - q^3\alpha^2)
+ \beta(-q\alpha^2 - 2q^2\alpha + 2q^2\alpha^2 + 2q^2\alpha^3 + q^3\alpha^2 - q^3\alpha^3) - q^3\alpha^2 + q^4\alpha^3 = 0.
\tag{7.63}
\]
Figure 7.2: Stationary phase diagram for TASEP with intermolecular interactions. The case of weakly repulsive interactions, \( E = -1.2 \ k_B T \), is shown.

Figure 7.3: Density profiles TASEP with intermolecular interactions for \( E = -1.2 \ k_B T \). (a) LD phase with \( \alpha = 0.4 \) and \( \beta = 0.8 \); (b) HD phase with \( \alpha = 0.8 \) and \( \beta = 0.2 \).
7.3 Monte Carlo Simulations and Discussions

We performed extensive Monte Carlo simulations to test our theoretical approaches. Our chosen lattice size \( L = 1000 \), is large enough to avoid finite size and boundary effects. The particle current and density profiles were averaged over \( 10^8 \) Monte Carlo steps and the first \( \%20 \) were discarded to ensure the system had reached the steady state. Comparing theoretical predictions of SMF approach with Monte Carlo computer simulations (Figs. 7.2 and 7.3) we can see that it is a reasonable approximation for very weak interactions \((E \approx 0)\), while for stronger attractions or repulsions the simple mean-field method does not work well. The calculated density profiles in SMF deviate from computer simulations results (see Fig. 7.3). But the strongest argument against using SMF for TASEP with interactions comes from the analysis of Eq. 7.12 for the current in the MC phase. It predicts that for \(|E| \gg 1\) the current is increasing without a bound, which is clearly an unphysical result. In the case of strong attractions particles will tend to stay in one big cluster that cannot move because particle breaking from the cluster is not possible. In this case the current is expected to go to zero. For strong repulsions the situation is different. In this case any particle cannot have neighbors so that the system behaves like TASEP with particles that cover 2 sites, for which precise estimates for the current are known, \( J = 1/(\sqrt{2} + 1)^2 \approx 0.17[94] \). Our computer simulations agree with these predictions (see Fig. 7.4).

Theoretical framework of the CMF method along with computer simulations allows us to investigate the fundamental effect of interactions on multi-particle dynamics in the TASEP model. It has been argued above that particle currents should diminish for strong attractions and repulsions. It suggests that there is an intermediate strength of interactions where the maximal flux might be achieved. Our calcula-
tions support these arguments as illustrated in Fig. 7.4. We found that this optimal strength corresponds to weak repulsions with $E^* \approx -3k_B T$ in CMF, while the simulations indicate $E^* \approx -1.2k_B T$. The surprising observation is that optimal conditions do not correspond to the case of no interactions, as one would expect from naive symmetry arguments. In addition, the optimal particle flux can be larger than the current for the system with only hard-core exclusions. The computer simulations predict $J_{max} \approx 0.29$, which is 16% more than the maximal current for TASEP without interactions $J_{max} = 0.25$. Thus, intermolecular interactions might significantly modify particle fluxes.

It could be also observed that the effect of interactions on particle dynamics in TASEP is not symmetric with respect to $E = 0$. The results of the CMF calculations and Monte Carlo computer simulations suggest that there is more sensitivity for attractive interactions. The phase diagram also depends on the sign and strength of interactions. Fig. 7.5 shows the position of the triple point (that connects LD,
HD and MC phases) at different values of $E$. One can see that increasing repulsions shrinks the MC and HD phases, and the LD phase occupies the largest fraction of the parameters space. For strong attractions the result is opposite. The HD phase dominates, while the LD and MC phase significantly diminish. These observations can be easily explained. Repulsions decrease the effective entrance rate into the system, making it a rate-limiting step for a larger range of parameters. This corresponds to expanding the LD phase. For attractions the exit rate slows down significantly because particles leaving the system sometimes should break from the clusters. This is not favorable from the energetic point of view. In this case, the HD phase dominates the system.

It is interesting to apply our theoretical analysis for real motor proteins. Experimental studies show that kinesins molecular motors bound to cytoskeleton filaments experience a short-range attractive interactions of order $E = 1.6 \pm 0.5 k_B T$ [72]. Comparing this with plots in Fig. 7.4 we conclude that kinesins probably do not function at the most optimal regime with the maximal particle current. However, they operate at conditions where small changes in interactions might lead to large modifications in dynamic properties. It suggests that kinesins might be optimized not for the maximal flux but for supporting robust cellular transport via tuning its intermolecular interactions. It allows molecular motors to compensate for fluctuations due to collisions with other molecules and from external loads. We hypothesize that this collective dynamic behavior of kinesins might be the most efficient from energetic point of view. This picture agrees with current views on mechanisms of cooperativity in multiple kinesins [68, 70]. However, we should notice that our model of motor protein dynamics is oversimplified. It ignores many important processes such as back steppings, bindings to the filaments and unbindings from them, and hydrolysis. It is not clear what ef-
Figure 7.5 : Coordinates of the triple point as a function of interaction strength. Lines correspond to predictions from mean-field calculations. Computer simulations results are close to CMF predictions.

fect the intermolecular interactions will have if all relevant chemical transitions are included.

7.4 Summary and Conclusions

In conclusion, we developed a new theoretical approach to investigate the effect of intermolecular interactions on dynamics of cellular molecular motors that move along cytoskeleton filaments. Our method is based on employing totally asymmetric simple exclusion processes that are known to be successful for analysis of non-equilibrium multi-particle phenomena. The important part of the method is a thermodynamically consistent procedure that allowed us to quantitatively describe the effect of intermolecular interactions. Theoretical calculations indicate that interactions bring significant spatial correlations in the system that could be partially captured by con-
sidering dynamics of clusters. It is found that there is an optimal strength of interactions at which the particle current reaches the maximum, while for large attractions or repulsions the fluxes disappear. For TASEP these optimal conditions correspond to weak repulsions. This observation is unexpected since from naive symmetry arguments the case of no interactions seems to be optimal. Interactions also modify stationary phase diagrams. For repulsions the LD phase becomes the most important, while for attractions the HD phase dominates. Our analysis also show that dynamic properties are more sensitive to attractive interactions. The implications of these observations for kinesins motor proteins are discussed. It is argued that kinesins might be functioning under conditions to support the robustness of the cellular transport instead of the maximal fluxes. At the same time, it was noticed that our theoretical analysis does not account for several important transitions in motor proteins that might limit its applicability in the current form. It will be important to extend our method to include these features and to test our theoretical predictions for other classes of motor proteins.
Chapter 8

Correlations and Symmetry of Interactions
Influence Collective Dynamics of Molecular Motors

8.1 Introduction

In chapter 7, we introduced a new theoretical approach for analyzing the collective characteristics of interacting molecular motors[76]. Analyzing this theoretical approach, it was found that there is an optimal interaction strength (weakly repulsive) that can maximize the current through the system [76]. In addition, the calculations suggested that correlations play important role in dynamics of interacting molecular motors. However, the progress in understanding the cooperativity in motor proteins in this model was limited by the following issues. Two mean-field analytical treatments were proposed. But the first one, a simple mean-field approach (SMF), failed completely, as compared with extensive Monte Carlo computer simulations, producing unphysical trends in dynamic properties for strong interactions. The second approach, a cluster mean-field (CMF), worked better, but it involved very heavy numerical calculations. At the end, CMF was able to reproduce only qualitatively dynamics of interacting molecular motors and not even for all ranges of parameters. Furthermore, only symmetric splitting of interactions on hopping rates was considered. In addition, it was not possible to extend CMF to take into account more realistic features of motor protein’s transport such as backward steps, bindings and
unbindings from the filament, and more general symmetries of the interactions. To understand the mechanisms of cooperativity, it is important to have an analytical method that can successfully capture main features of interacting molecular motors, and which can be also extended to more complex situations.

In this chapter, a new theoretical framework for analyzing complex dynamics of interacting molecular motors via TASEP is presented[77]. We develop a modified cluster mean-field (MCMF) approach that accounts for some correlations in the system. This provides a direct way of analytically calculating all dynamic properties in the system, and the results agree quite well with computer simulations. The method allows us to explicitly analyze the role of interactions in dynamics of interacting molecular motors. More specifically, it is found that correlations are weaker and more short-range for repulsive interactions while for attractions they are stronger and more long-range. We also investigate the role of the symmetry of interactions and show that it might dramatically modify the dynamic behavior. But most importantly, the developed framework allows us to understand the microscopic origin of dynamic phenomena in motor proteins and it can be easily generalized to account for more complex processes associated with molecular motors.

\section{Theoretical Description}

\subsection{Model}

In our model, the transport of molecular motors along linear filaments is viewed as a motion of multiple particles on a lattice with $L$ ($L \gg 1$) sites, as shown in Fig. 8.1. The state of occupancy for each lattice site $i$ ($1 \leq i \leq L$) is characterized by an occupation number $\tau_i$. If the site $i$ is occupied then $\tau_i = 1$, if it is empty then $\tau_i = 0$. 
Each lattice site can accommodate only one particle.

In addition to exclusions, molecular motors can interact with each other via a short-range potential. Here we assume that any two neighboring particles interact with each other with an energy $E$. The case of positive $E$ defines attractive interactions, while $E < 0$ corresponds to repulsions. In other words, any bond connecting two neighboring particles on the lattice is associated with the energy $E$. In our system transition rates depend if these bonds are broken or created. Any forward motion of the individual molecular motor that does not change the number of bonds is taking place with the rate 1. It can be done by a single molecule that do not have any neighbors (see Fig. 8.1), or it can involve breaking one bond and creating another one (Fig. 8.1). In both cases, there is no energy change in the system. However, the forward transition associated with creating a new bond has a rate $q \neq 1$. In this case, the molecular motor joins an existing cluster of particles: see Fig. 8.1. Similarly, the transition that is coupled with breaking the bond has a rate $r \neq 1$. Here the particle dissociates from the cluster but simultaneously it does not bind to another cluster (Fig. 8.1). The transition rates $q$ and $r$ are associated with changes in energy.

It has been argued that creating and breaking such bonds (or pairs of particles) can be viewed as opposing chemical transitions, which justifies the application of the detailed balance arguments [76]. This leads to the following relation between the transitions rates,

$$\frac{q}{r} = \exp\left(\frac{E}{k_B T}\right).$$  \hfill (8.1)

To evaluate dynamic properties of molecular motors we need to know the explicit values for rates $q$ and $r$. The interaction energy can be split in the following way,

$$q = \exp\left(\frac{\theta E}{k_B T}\right), \quad r = \exp\left(\frac{(\theta - 1)E}{k_B T}\right).$$ \hfill (8.2)
where a dimensionless parameter $\theta$ ($0 \leq \theta \leq 1$) specifies how the energy affects these transition rates. Previously, only a symmetric splitting of interactions ($\theta = 1/2$) has been considered [76].

It is easy to understand the physical meaning of Eq. 8.2 [76]. When the interactions between molecular motors are attractive ($E > 0$), the rate of creating the bond is larger ($q > 1$), while the rate of breaking the bond is smaller ($r < 1$). For repulsive interactions ($E < 0$) the trend is opposite — it is faster to break the particle cluster ($r > 1$) than to increase the cluster size ($q < 1$). In the case of no interactions ($E = 0$) these transitions rates are the same ($q = r = 1$) and the model reduces to standard TASEP with only hard-core exclusions.

In our model, particles enter the system from the left side of the lattice and they leave the system from the right side of the lattice: see Fig. 8.1. Interactions are also modifying the entrance and exit rates in comparison with the original TASEP model. When entering the system does not lead to creating a pair of particles the rate for this process is $\alpha$ (Fig. 8.1). However, entering with creating the bond has a rate $q\alpha$. Similarly, the exit rate for the case when no bond breaking is involved is equal to $\beta$, while the dissociating from the cluster is taking place with the rate $r\beta$ (Fig. 8.1).
Figure 8.2: Four-sites bulk lattice segments that are utilized for calculating the particle currents in the system.

Previous theoretical studies indicated that correlations are important for the system with multiple particles [76]. Neglecting correlations leads to unphysical behavior for strong interactions between molecular motors [76]. This indicates that any successful theoretical treatment must take correlations into account. This is the main idea of our approach that we call a modified cluster mean-field.

To account for correlations we analyze bulk clusters of two neighboring sites on the lattice. Each cluster can be found in one of four possible states. We label a configuration with 2 empty sites as $(0, 0)$, with two occupied sites as $(1, 1)$, and two half-occupied clusters are labeled as $(1, 0)$ and $(0, 1)$. Next, we introduce functions $P_{11}$, $P_{10}$, $P_{01}$ and $P_{00}$ as probabilities of finding the configurations $(1, 1)$, $(1, 0)$, $(0, 1)$ and $(0, 0)$, respectively. The conservation of probability for these functions requires that

$$P_{11} + P_{10} + P_{01} + P_{00} = 1. \quad (8.3)$$

In addition, we have

$$P_{10} + P_{11} = \rho, \quad P_{01} + P_{11} = \rho, \quad (8.4)$$
where $\rho$ is the bulk density (or the probability to find the particle at given site). Here it was assumed also that the bulk density is uniform and independent of the position on the lattice if the two-site cluster is far away from the boundaries. Combining Eqs. 8.3 and 8.4 leads to $P_{10} = P_{01}$ and

$$P_{10} + P_{00} + \rho = 1. \quad (8.5)$$

Let us consider a particle flux in the bulk of the system at large times when stationary conditions are achieved. We can concentrate on the segment of 4 consecutive sites as shown in Fig. 8.2. To measure the current, only transitions between the second and the third sites of the segment are counted. Then there are four possible configurations that support the particle current, as illustrated in Fig. 8.2. Correspondingly, the total flux have 4 contributions from each configurations, $J_{bulk} = J_1 + J_2 + J_3 + J_4$. The first contribution from configuration 1 (Fig. 2) can be written as

$$J_1 = \gamma P_{10} \left( \frac{P_{00}}{\rho + P_{00}} \right), \quad (8.6)$$

where $\gamma = \frac{1}{1 + \exp \left( \frac{E}{kT} \right)}$. This expression is an approximation and it can be understood in the following way. The second factor ($P_{10}$) gives the probability that the cluster consisting of the second and third sites (see Fig. 8.2) is in the state $(1, 0)$. The first factor ($\gamma$) gives a probability that the first site is empty, i.e., it is just a Boltzmann’s factor. The third factor ($\frac{P_{00}}{\rho + P_{00}}$) is a probability to have the last site empty. If we have the configuration $(1, 0)$ in the middle cluster then the last site can be found in one of two states: it can be occupied with the probability $\rho$ or it can be empty with the probability $P_{00}$. This is because in this case the cluster consisting of the sites 3 and 4 can only be found in configurations $(0, 0)$ or $(0, 1)$. Then the particle current from the second configuration (Fig. 8.2) is equal to

$$J_2 = (1 - \gamma) r P_{10} \left( \frac{P_{00}}{\rho + P_{00}} \right). \quad (8.7)$$
Here \((1 - \gamma) = \frac{\exp \left( \frac{E}{k_B T} \right)}{1 + \exp \left( \frac{E}{k_B T} \right)}\) is a probability to have the first site occupied, and \(r\) is the transition rate for this configuration. Similar arguments can be presented for contributions from configurations 3 and 4, yielding

\[ J_3 = \gamma q P_{10} \left( \frac{\rho}{\rho + P_{00}} \right), \]  

(8.8)

and

\[ J_4 = (1 - \gamma) P_{10} \left( \frac{\rho}{\rho + P_{00}} \right). \]  

(8.9)

Combining together Eqs. 8.6, 8.7, 8.8 and 8.9 we obtain the expression for the total bulk current,

\[ J_{bulk} = \gamma \left( \frac{P_{10} P_{00}}{\rho + P_{00}} \right) + (1 - \gamma) r \left( \frac{P_{10} P_{00}}{\rho + P_{00}} \right) + q \gamma \left( \frac{\rho P_{10}}{\rho + P_{00}} \right) + (1 - \gamma) \left( \frac{\rho P_{10}}{\rho + P_{00}} \right). \]  

(8.10)

This equation can be also written in the following form,

\[ J_{bulk} = A \left( \frac{P_{10} P_{00}}{1 - P_{10}} \right) + B \left( \frac{\rho P_{10}}{1 - P_{10}} \right), \]  

(8.11)

where auxiliary functions \(A\) and \(B\) are defined as

\[ A = \frac{1 + r \exp \left( \frac{E}{k_B T} \right)}{1 + \exp \left( \frac{E}{k_B T} \right)}, \quad B = \frac{q + \exp \left( \frac{E}{k_B T} \right)}{1 + \exp \left( \frac{E}{k_B T} \right)}. \]  

(8.12)

To calculate explicitly dynamic properties in the system we have to express everything in terms of the bulk density \(\rho\) and the interaction energy \(E\). Eq. 8.5 gives the connection between \(P_{10}, P_{00}\) and \(\rho\), and one more additional relation is needed in order to have all equations only in terms of \(\rho\) and \(E\). We can approximate the function \(P_{10}\) as

\[ P_{10} \approx \frac{\rho(1 - \rho)}{1 - \rho + \rho \exp \left( \frac{E}{k_B T} \right)}. \]  

(8.13)
The physical meaning of this approximation can be explained if we note that $P_{10}$ is the probability to have the two-site cluster in the configuration $(1, 0)$. This probability is equal to the product of two terms: one is the probability to have the first site occupied ($\rho$) and the second term is the probability that the second site is empty \textit{given} that the first one is not $((1 - \rho)/[1 - \rho + \rho \exp \left(\frac{E}{k_B T}\right)])$. It can be argued that the situation when two sites in the cluster are occupied is affected by the interactions between them, and we approximate it via the usual Boltzmann’s factor. One can see that this equation leads to a very reasonable behavior at the limiting cases. When there is no interactions ($E = 0$) it predicts that $P_{10} = \rho(1 - \rho)$, as expected. For very strong repulsions ($E \to -\infty$) it gives $P_{10} = \rho$, which is a correct result since in this limit our problem is identical to the motion of non-interacting dimers on the lattice [76, 94]. For very large attractions ($E \to \infty$) the prediction is that $P_{10} \to 0$. This is again seems to be a reasonable result because in this case one is expecting to have the whole system fully occupied without any vacancies.

Finally, taking into account all approximations we obtain the general expression for the bulk current only in terms of the particle density $\rho$ and the interaction $E$,

\[
J_{\text{bulk}} = \frac{A \rho(1 - \rho)^2 \left[1 - 2\rho + \rho \exp \left(\frac{E}{k_B T}\right)\right]}{(1 - \rho)^2 + \rho \exp \left(\frac{E}{k_B T}\right) \left[1 - \rho + \rho \exp \left(\frac{E}{k_B T}\right)\right]} + \frac{B \rho^2 (1 - \rho)}{(1 - \rho)^2 + \rho \exp \left(\frac{E}{k_B T}\right)}
\]

(8.14)

For the case of zero interactions this equation suggests that $J_{\text{bulk}} = \rho(1 - \rho)$, the known result form the original TASEP model [80, 81]. For strong repulsions ($E \to -\infty$) we predict that

\[
J_{\text{bulk}} = \frac{\rho(1 - 2\rho)}{1 - \rho}.
\]

(8.15)

This is identical to the expression that was derived earlier for TASEP of dimers [94].
For large attractions ($E \to \infty$) it predicts that the bulk current vanishes, $J_{bulk} = 0$, and this is expected because particles will not be able to move since they will be stuck together in one large cluster.

At boundaries the dynamics in the system is governed by exit and entrance rates. Using the same approximations as explained above for the bulk fluxes it can be shown that the expressions for entrance current is given by

$$J_{entr} = \frac{\alpha(1 - \rho)\left[1 - 2\rho + \rho \exp\left(\frac{E}{k_B T}\right)\right] + \alpha q \rho (1 - \rho)}{1 - \rho + \rho \exp\left(\frac{E}{k_B T}\right)}. \quad (8.16)$$

For $E = 0$ this equation reduces to $J_{entr} = \alpha(1 - \rho)$, which is expected for this situation. For $E \to -\infty$ it predicts that $J_{entr} = \alpha(1 - 2\rho)$, in agreement with known results on TASEP of extended objects [94]. For strong attractions ($E \to \infty$) the current disappears, $J_{entr} \to 0$. Similarly, for the exit current we obtain

$$J_{exit} = \frac{\beta \rho \left[1 - \rho + r \rho \exp\left(\frac{E}{k_B T}\right)\right]}{1 - \rho + \rho \exp\left(\frac{E}{k_B T}\right)}. \quad (8.17)$$

Again, for $E = 0$ and for $E \to -\infty$ it produces the expected result, $J_{exit} = \beta \rho$, while for strong attractions it leads to $J_{exit} \to 0$.

**8.2.2 Phase Diagrams**

Similarly to the original TASEP, it can be argued that in the system of interacting molecular motors there are three dynamic phases at stationary conditions. When the rate limiting step is the entrance into the system we have a low-density (LD) phase. For the case of exiting being small a high-density (HD) phase will be realized. Finally, when bulk processes are the most important, the system is in a maximal-current (MC) phase.
Our analytical theory can calculate explicitly the phase boundaries. The MC phase is characterized by a condition that \( \frac{\partial J_{\text{bulk}}}{\partial \rho} = 0 \), which leads to the following expression:

\[
(2\rho^2 - 4\rho + 1) (\rho - 1)^4 - \rho^4 \exp \left( (\theta + 3) \frac{E}{k_B T} \right) - \rho^2 (2\rho - 1)(\rho - 1)^2 \exp \left( (\theta + 2) \frac{E}{k_B T} \right) \\
+ (\rho - 1)^6 \exp \left( \theta \frac{E}{k_B T} \right) - (\rho - 2)\rho(\rho - 1)^4 \exp \left( (\theta + 1) \frac{E}{k_B T} \right) + (\rho^4 - 2\rho^5) \exp \left( 4 \frac{E}{k_B T} \right) \\
- \rho (4\rho^3 - 16\rho^2 + 15\rho - 4) (\rho - 1)^2 \exp \left( \frac{E}{k_B T} \right) - \rho^3 (\rho^3 - 10\rho^2 + 13\rho - 4) \exp \left( 3 \frac{E}{k_B T} \right) \\
+ \rho^2 (3\rho^4 - 22\rho^3 + 39\rho^2 - 26\rho + 6) \exp \left( 2 \frac{E}{k_B T} \right) = 0.
\]

For \( E = 0 \) this complicated expression reduces to the following formula,

\[
-4\rho^5 + 10\rho^4 - 16\rho^3 + 14\rho^2 - 8\rho + 2 = 0,
\]

which has only one real root, \( \rho = \frac{1}{2} \). For very large repulsions (\( E \to -\infty \)) one can obtain from Eq. 8.18,

\[
(2\rho^2 - 4\rho + 1) (\rho - 1)^4 = 0.
\]

This equation has three roots but only one of them is physically reasonable, \( \rho = 1 - 1/\sqrt{2} \), which leads to a nonzero flux in the system. (The root \( \rho = 1 \) does not support the nonzero flux through the system and it can be neglected.) Substituting this density into Eq. 8.15 leads to a prediction that the particle flux in this case is equal to \( J = 3 - 2\sqrt{2} \approx 0.17 \). For large attractions (\( E \to \infty \)) Eq.8.18 predicts that \( \rho = 1/2 \), but the current here is approaching zero, as was discussed above. For general conditions, this equation can be always solved numerically and after choosing the physically relevant root for the density in the MC phase, \( \rho_{\text{MC}} \), the particle fluxes can be calculated using Eq. 8.14. The phase diagrams calculated via this method are presented in Fig. 8.3 for various sets of parameters.
To determine the density of molecular motors in the LD phase and the boundary lines separating the low-density and the maximal-current phases, we use the continuity of the stationary currents at the transition line, $J_{\text{bulk}} = J_{\text{entr}}$. Combining Eqs. 8.14 and 8.16 yields the following expression for the entrance rate $\alpha$,

$$\alpha = \frac{A\rho(1-\rho)\left[1 - 2\rho + \rho \exp \left( \frac{E}{k_B T} \right) \right] + B\rho^2 \left[1 - \rho + \rho \exp \left( \frac{E}{k_B T} \right) \right]}{\left[1 - 2\rho + \rho \exp \left( \frac{E}{k_B T} \right) + q\rho \right] \left[ (1-\rho)^2 + \rho \exp \left( \frac{E}{k_B T} \right) \right]}.$$  \hspace{1cm} (8.20)

Solving this equation for $\rho$ provides an estimate for the particle density in the bulk of the system in the LD phase. Increasing the entrance rate $\alpha$ leads to large bulk densities, and the phase boundary between LD and MC phase is achieved when $\rho = \rho_{MC}$. For example, for zero interactions, $E = 0$, from Eq. 8.20 it follows that
\[ \rho_{LD} = \alpha, \text{ and the phase boundary corresponds to } \alpha = 0.5. \] These estimates fully agree with results from the original TASEP with non-interacting particles [80, 81]. For the case of very strong repulsions, \( E \to -\infty \), we derive from Eq. 8.20 that \( \rho_{LD} = \alpha/(1 + \alpha) \), and the phase boundary between LD and MC phase corresponds to \( \alpha = \sqrt{2} - 1 \approx 0.41 \). This again agrees with known results on TASEP of extended objects [94]. In the opposite limit of very large attractions, \( E \to \infty \), the low-density phase cannot be realized for any nonzero values of \( \alpha \).

Similar calculations can be performed for obtaining properties of the HD phase and the boundaries between high-density and maximal-current phase. The exit rate \( \beta \) is coupled with the density \( \rho \) via

\[
\beta = \frac{A(1 - \rho)^2 \left[ 1 - 2\rho + \rho \exp \left( \frac{E}{k_B T} \right) \right] + B\rho(1 - \rho) \left[ 1 - \rho + \rho \exp \left( \frac{E}{k_B T} \right) \right]}{(1 - \rho)^2 + \rho \exp \left( \frac{E}{k_B T} \right) \left[ 1 - \rho + r\rho \exp \left( \frac{E}{k_B T} \right) \right]}.
\] (8.21)

This expressions allows us to calculate the bulk particle density in the HD phase. One can see that increasing the exit rate \( \beta \) lowers the bulk density until the phase boundary with the MC phase is reached at \( \rho = \rho_{MC} \). This can be illustrated by again considering the limiting cases. When motor proteins do not interact with each other \( (E = 0) \) Eq. 8.21 yields \( \rho_{HD} = 1 - \beta \) and the phase boundary between HD and MC phase can be found at \( \beta = 0.5 \). This is fully consistent with known results for TASEP of non-interacting particles [80, 81]. For strong repulsions we predict that \( \rho_{HD} = (1 - \beta)/(2 - \beta) \), and the phase boundary between HD and MC phases is observed at \( \beta = 2 - \sqrt{2} \approx 0.59 \). Note that these results slightly differ from calculations for TASEP of dimers because of the different exiting rules [94]. For strong attractions the flux through the system is vanishing and the high-density is always observed. The phase boundary between LD and HD phases can be estimated from the condition that at this line the particle currents from both phases become equal, \( J_{LD} = J_{HD} \). It can
be shown from Eqs. 8.16 and 8.17 that

$$
\frac{\beta}{\alpha} = \left[ \frac{q\rho_{LD}(1 - \rho_{LD}) + (1 - \rho_{LD})(1 - 2\rho_{LD} + \rho_{LD} \exp\left(\frac{E}{k_B T}\right))}{\rho_{HD}(1 - \rho_{HD} + r\rho_{HD} \exp\left(\frac{E}{k_B T}\right))} \right] \\
\times \left[ \frac{1 - \rho_{HD} + \rho_{LD} \exp\left(\frac{E}{k_B T}\right)}{1 - \rho_{LD} + \rho_{LD} \exp\left(\frac{E}{k_B T}\right)} \right].
$$

(8.22)

In this expression, densities $\rho_{HD}$ and $\rho_{LD}$ are obtained by solving Eqs. 8.20 and 8.21, respectively, for specific values of $E$ and $\theta$. For $E = 0$ we find that the LD-HD phase boundry is given by $\beta = \alpha$, and the triple point (where LD, HD and MC phases meet together) is found at $\beta_c = \alpha_c = 0.5$, as expected for the standard TASEP [80, 81].
8.3 Monte Carlo Simulations and Discussions

Because of the approximate nature of our method, it is important to test these theoretical predictions. It was done in this work by running extensive computer Monte Carlo simulations. We utilized the Monte Carlo algorithm known as a random sequential update. In our simulations we used a lattice of size $L = 1000$ to minimize any finite size and boundary effects. The particle current and density profiles of molecular motors were averaged over $10^8$ Monte Carlo steps. To ensure that the system is at the stationary-state conditions, the first 20% of events were discarded. We have used a precision of 0.01 when comparing density profiles to construct accurate phase diagrams. The error in calculating the phase boundaries by our method was estimated to be less than 1%.

In Fig. 8.3 we compare theoretically calculated phase diagrams with results obtained in Monte Carlo computer simulations. One can see that for relatively weak interactions theory agrees quite well with computer simulations (Fig. 8.3c), while for stronger interactions (attractive or repulsive) the agreement is mostly qualitative (although still better for repulsions): see Figs. 8.3a, 8.3b and 8.3d. Comparing phase behavior at different interactions, one can notice that the LD phase is dominating at repulsions, but the HD phase is more prevalent for attractions. These observations are consistent with expectations that repulsions lead to smaller particle clusters and lower density while attractions stimulate the formation of large clusters, which corresponds to higher density.

However, our method works much better for predicting particle fluxes in the MC phase, as illustrated in Fig. 8.4. The theory correctly describes the fluxes for repulsive interactions for all ranges of parameters (with the exception of the special case corresponding to $\theta = 0$). But for attractions the good agreement is found only for
small $\theta$. For larger values of the energy splittings ($\theta > 0.25$) there is only a qualitative agreement on the overall trends: the fluxes decrease to zero with increasing the interaction strength (with the exception of the special case corresponding to $\theta = 1$).

These observations suggest that correlations are important for understanding dynamic properties of interacting molecular motors. To quantify this effect, we investigated a correlation function $C_i$ defined as

$$C = \langle \tau_i \tau_{i+1} \rangle - \langle \tau_i \rangle \langle \tau_{i+1} \rangle, \quad i = 1, \ldots, L - 1$$  \hspace{1cm} (8.23)

where two-point and one-point density functions are given by

$$\langle \tau_i \tau_{i+1} \rangle = \sum_{\tau_i} \sum_{\tau_{i+1}} \tau_i \tau_{i+1} P(\tau_i, \tau_{i+1}) = P_{11},$$  \hspace{1cm} (8.24)

$$\langle \tau_i \rangle = \sum_{\tau_i} \tau_i P(\tau_i) = \rho.$$  \hspace{1cm} (8.25)

The physical meaning of the correlation function $C_i$ is that it gives a measure of how the presence of the particle at site $i$ affects the occupation of the neighboring site $i + 1$. Using the definition together with the normalization condition and Eq. 8.13, we obtain the following analytical expression for $C$,

$$C(E) = \frac{\rho^2 (1 - \rho) \left[ \exp \left( \frac{E}{k_B T} \right) - 1 \right]}{1 + \rho \left[ \exp \left( \frac{E}{k_B T} \right) - 1 \right]}.$$  \hspace{1cm} (8.26)

Note that $C$ is uniform in the bulk of the system. For the case of zero interactions ($E = 0$) it predicts that $C = 0$. This fully agrees with what we know about TASEP for noninteracting particles. Here a simple mean-field theory, that completely neglects any correlations, works quantitatively well and it correctly describes the majority of dynamic properties of the system [80, 81]. For strong repulsions ($E \rightarrow -\infty$) it gives $C = -\rho^2$, while for strong attractions ($E \rightarrow \infty$) we have $C = \rho(1 - \rho)$. The correlation functions predicted in our method and obtained from computer simulations are
Figure 8.5: Correlations as a function of the interaction energy for: (a) $\theta = 0.25$, (b) $\theta = 0.5$, (c) $\theta = 0.75$. In simulations $\alpha = \beta = 1$ was utilized.

The physical meaning of the correlation function $C_i$ is that it gives a measure of how the presence of the particle at site $i$ affects the occupation of the neighboring site $i + 1$. When there are no correlations we have $C = 0$. Negative correlation functions ($C < 0$) indicate that there is a less probability to find the particle next to the already occupied site. This is the case for repulsive interactions. In contrary, positive values for $C$ suggest that the presence of the particle at given site enhances the probability to find the particle at the neighboring site. It is clear that this situation can be realized for attractive interactions. Comparing theoretical predictions with Monte Carlo simulations (Fig. 8.5) again indicates that our theory works very well for repulsive interactions, while for attractions, although the trends are correctly picked up, there are deviations.
The analysis of results presented in Figs. 8.3, 8.4 and 8.5 strongly indicates that correlations are important for understanding the mechanisms of interacting molecular motors. However, it also raises a question of why our theoretical approach, that explicitly takes into account some correlations, is able to correctly describe the stationary properties only for repulsive interactions and for weak attractions. To answer this question we note that the dynamic behavior strongly depends on the sign of the interactions. For $E < 0$, the presence of the particle at the site $i$ leads to a lower probability of finding another particle at the site $i + 1$. Then if there is nothing at the site $i + 1$ the occupancy of the site $i + 2$ will be independent of the fact that there is the particle at the site $i$. These arguments suggest that correlations for repulsive interactions are short-range and relatively weak. For $E > 0$ the situation is very different. Here the presence of the particle at the site $i$ stimulates the occupancy of the site $i + 1$, and consequently the occupation state of the site $i + 2$ depends on the state of the site $i$. This is consistent with long-range and strong correlations. By construction (see Sec. 2.2), our theory accounts only for short-range correlations because the evolution of two-site clusters is monitored. This is the main reason why our approach is so successful for repulsive interactions, while providing mostly a qualitative description for attractive interactions. One of the main advantages of our theoretical method is the fact that it can be easily extended to account for more realistic features of the motor proteins transport. To illustrate this we analyze the effect of varying the splitting coefficient $\theta$ on multi-particle dynamics of interacting molecular motors. The results are presented in Figs. 8.4 and 8.6. One can see that dynamics is different for small and large values of the interaction splittings. It can be concluded from Eq. 8.2 that small $\theta$ describe the situation when the formation of the particle clusters is weakly affected by the interactions. At the same time, the breaking of the particle
Figure 8.6: Maximal particle currents as a function of the interaction energy for large energy splittings. Lines are theoretical predictions, symbols are from computer simulations.

bonds is strongly influenced by interactions. For $\theta \approx 1$ the trend is opposite: the particle cluster formation depends strongly on interactions, while the bond breaking is not. The particle current (in the MC phase) is generally a non-monotonic function of interactions. At large repulsions the current saturates, while for large attractions the fluxes are going to zero. The maximal particle current is achieved for relatively weak repulsive interactions ($E \simeq -(1-2) k_B T$). The monotonic decrease in the particle current is only observed for the special case of $\theta = 0$. Similar dynamics is observed for large $\theta > 0.9$ (see Fig. 8.6), but here the most optimal conditions are reached now for positive interactions. The case of $\theta = 1$ is again a
special one, and the monotonic increase in the current is observed for all range of interactions.

In light of these findings, it is important to discuss the effect of intermolecular interactions for real motor proteins. These interactions have been measured experimentally for kinesins, indicating weak attractions of order of $E = (1.6 \pm 0.5) \, k_B T$ [72]. Previous theoretical studies suggested that kinesins function at the conditions that do support the maximal current, but the analysis was based on the symmetric splitting of interactions for transitions rates ($\theta = 0.5$) [76]. Our new results presented in Figs. 8.4 and 8.6 indicate that this is probably a reasonable description of multi-particle dynamics of kinesins for for most interaction splittings ($\theta < 0.9$). In this case the kinesin might operate at the conditions where small changes in interactions lead to large modification in the particle dynamics. It has been argued that this might be important for maintaining robust cellular transport [68, 70, 76]. However, our results (Fig. 8.6) also suggest another intriguing possibility that the kinesin fluxes might be optimized if the splitting affects more the formation of particle clusters ($\theta > 0.9$). The parameter $\theta$ is a microscopic property that cannot be obtained from our mesoscopic theoretical method. To test this idea it will be important to measure and calculate this quantity in more advanced experimental and theoretical investigations.

8.4 Summary and Conclusions

We developed a new theoretical approach to analyze the role of intermolecular interactions in the collective dynamics of molecular motors that move along linear filaments. Our method is based on utilizing totally asymmetric exclusion processes, which have been successfully applied for studying various processes in Chemistry, Physics and Biology. It modifies the transition rates by interactions via fundamental
thermodynamic arguments. A simple theoretical framework, that we call the modified cluster mean-field and that takes into account some correlations, is presented and fully discussed. It allows us to calculate analytically or numerically exactly all dynamic properties of interacting molecular motors. We find that interactions induce correlations in the system of collectively moving motor proteins, and the strength of correlations depends on the sign of the interactions. It was argued that for repulsions the correlations are short-range and relatively weak, while for attractions the range and amplitude of correlations are larger. This also leads to different dynamic behavior of interacting molecular motors. For repulsions the dynamics is weakly affected by the strength of interactions, however for attractions the dynamics is modified much stronger. We also investigated the effect of the symmetry of interaction by analyzing splittings between different transitions. It was found that when the formation of particle clusters is weakly affected by interactions the most optimal fluxes can be realized for weakly repulsive interaction. But when breaking of bonds between neighboring particles is strongly influenced, the maximal current can be achieved for attractive interactions. Furthermore, the importance of these results for kinesin motor proteins has been discussed.

The most important advantage of our method is that it can be easily extended to investigate additional more realistic features of molecular motors transport such as backward steps, binding and unbinding of motor proteins at all sites, multiple parallel pathways and limited resources of motor proteins in the surrounding solution. It will be very interesting to generalize our approach to study these phenomena if we want to understand better mechanisms of cellular transport processes. However, despite its simplicity and the successful application for the interacting molecular motors, it should be noted that our method is still approximate and many important features
are not well described. For example, for a large range of parameters the effect of attractive interactions is given only qualitatively. Thus it will be important to test our theory in experiments and in more advanced theoretical models.
Chapter 9

All-Time Dynamics in Complex Continuous-Time Random Walk Models

9.1 Introduction

Theoretical studies of complex dynamic phenomena that utilize CTRW models mostly concentrate on large-time dynamics\[97, 100\]. While this might be a reasonable approach for systems where stationary states are well established and can be quickly reached, in many cases to fully understand mechanisms of complex processes one needs to have a description of dynamic behavior at all times. In addition, the situation is more complex for systems that never reach the steady-state limit. The original work of Montroll and Weiss\[97\] suggested that all-time dynamics of CTRW can be obtained by utilizing Laplace-Fourier transformations. Although this analysis is formally correct, it is practically impossible to apply for real dynamic processes. Recently, a new method of calculating dynamic properties of particles in the CTRW model at all times has been introduced\[117\]. It is based on analyzing a propagator and surviving probabilities to calculate analytically exactly Laplace transforms of all dynamic properties, which effectively provides all-time description of the underlying processes. It was later extended to a CTRW model with branched states as a way of investigating biased diffusion in tubes with periodic dead ends\[118\]. However, it can be shown that this method could be utilized only for homogeneous CTRW with the same set of waiting time distributions at each site, limiting its application for
more complex dynamic phenomena. An alternative theoretical method of calculating all-time dynamic properties in CTRW models have been presented by one of the authors[119]. It utilizes a generalized master-equations approach[111, 120] that allows fast and efficient computation of all Laplace transforms of probability functions and all dynamic properties of the CTRW models. The advantage of the method is the ability to analyze some inhomogeneous CTRW models as well as more complex systems, as was shown explicitly for simple periodic CTRW models and for processes with irreversible detachments[119].

Most of chemical and biological processes can be viewed as complex networks of states that are connected by dynamic transitions. The application of CTRW method for understanding mechanisms of these systems require a theoretical analysis that is valid at all time scales. In this chapter, we extend the generalized master-equations method to analyze all-time dynamics of CTRW models on complex networks[132]. It is interesting to note that closely related method has been proposed recently for temporal fully-connected networks[121]. Here, stationary networks will be investigated. Specifically, dynamic properties for the CTRW models with branched states and the coupled parallel-chain CTRW models are obtained and analyzed. In addition, generalized fluctuations theorems for these systems are discussed. Our approach can also be viewed as an extension of stochastic studies of multi-state diffusion processes on lattices where only exponential waiting-time distribution functions have been used[122, 123].

### 9.2 Homogeneous CTRW

To start, let us first consider the sequential CTRW kinetic model as shown in Fig. 9.1. The dynamics of the system is governed by the waiting-time distribution functions
ψ_i^+(t)$ and $ψ_i^-(t)$. The random walker at the site $i$ on the chain can jump one step forward and backward with the corresponding probabilities $ψ_i^+(t)dt$ and $ψ_i^-(t)dt$, respectively. One can define $P_n(t)$ as a probability of finding the random walker at the site $n$ at time $t$. This probability is governed by corresponding generalized master equation,

$$\frac{dP_n(t)}{dt} = \int_0^t [φ_i^+(τ)P_{n-1}(t-τ) + φ_i^-(τ)P_{n+1}(t-τ)]dτ - \int_0^t [φ_i^+(τ) + φ_i^-(τ)]P_n(t-τ)dτ,$$  

(9.1)

where $φ_i^±(t)$ are waiting-time rate distributions. In Ref. [99] it is shown that they are related to waiting-time distribution functions via Laplace transforms,

$$\tilde{φ}^±(s) = \frac{ψ^±(s)}{1 - ψ(s)},$$  

(9.2)

with $ψ(s) = ψ^+(s) + ψ^-(s)$.

Using Laplace transformation, Eq. 9.1 can be transformed to the following recurrence relation,

$$[s + \tilde{φ}^+(s) + \tilde{φ}^-(s)] P_n(s) = δ_{n,0} + \tilde{φ}^+(s)P_{n-1}(s) + \tilde{φ}^-(s)P_{n+1}(s).$$  

(9.3)

After introducing new auxiliary variables: $a ≡ s + \tilde{φ}^+(s) + \tilde{φ}^-(s)$, $b ≡ \tilde{φ}^+(s)$, $c ≡ \tilde{φ}^-(s)$, this equation can be written as,
\[ a\tilde{P}_n(s) = \delta_{n,0} + b\tilde{P}_{n-1}(s) + c\tilde{P}_{n+1}(s). \] (9.4)

To solve this equation we use Fourier transform. This approach was originally presented in Ref. [117]. To start, let us introduce the Fourier transform,

\[ \tilde{P}_\phi(s) = \sum_{n=-\infty}^{\infty} \tilde{P}_n(s)e^{-i\phi n}. \] (9.5)

Using Fourier transform, Eq. 9.4 can be converted to the following form:

\[ \tilde{P}_\phi(s) = \frac{1}{a - be^{-i\phi} - ce^{i\phi}}. \] (9.6)

Inverting the Fourier transform we obtain

\[ \tilde{P}_n(s) = \frac{1}{2\pi} \int_{-\pi}^{\pi} \tilde{P}_\phi(s) = \frac{1}{2\pi} \int_{-\pi}^{\pi} \frac{e^{i\phi n} d\phi}{a - be^{-i\phi} - ce^{i\phi}}. \] (9.7)

To proceed further, we define a new variable \( z = e^{i\phi} \). Therefore, the integral takes the form:

\[ \tilde{P}_n(s) = -\frac{1}{2\pi i c} \int_{-\pi}^{\pi} \frac{z^{n|} dz}{(z - z_+)(z - z_-)}. \] (9.8)

The integrand has two well-separated poles at \( z_\pm = \frac{-a \pm \sqrt{a^2 - 4bc}}{2c} \). If we consider \( e^{i\phi z|} \), then \( z_+ \) lies inside the region bounded by this contour. Using the residue theorem, this integral can be written as

\[ \int_{-\pi}^{\pi} \frac{z^{n|} dz}{(z - z_+)(z - z_-)} = 2\pi i \cdot \text{Res} \left( \frac{z^{n|}}{(z - z_+)(z - z_-)} ; z_+ \right) = \frac{z^{n|}_+}{z_+ - z_-} \] (9.9)

Combining Eqs. 9.8 and 9.9, one can show that the final expression for the Laplace transformation of the probability function is given by

\[ \tilde{P}_n(s) = \left( \frac{b}{c} \right)^{n/2} \left( \frac{a - \sqrt{a^2 - 4bc}}{2\sqrt{bc}} \right)^{|n|} \frac{1}{\sqrt{a^2 - 4bc}}, \] (9.10)
or

\[ \tilde{P}_n(s) = \left( \frac{\tilde{\varphi}^+(s)}{\tilde{\varphi}^-(s)} \right)^{n/2} \left( \frac{s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s) - \sqrt{[s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s)]^2 - 4 \tilde{\varphi}^+(s) \tilde{\varphi}^-(s)} \right)^{|n|} \times \frac{1}{\sqrt{[s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s)]^2 - 4 \tilde{\varphi}^+(s) \tilde{\varphi}^-(s)}} \]. \tag{9.11} \]

It can also be written in terms of the original waiting-time distribution functions with the help of Eq. 9.2,

\[ \tilde{P}_n(s) = \left( \frac{\tilde{\psi}^+(s)}{\tilde{\psi}^-(s)} \right)^{n/2} \left( \frac{2 \sqrt{\tilde{\psi}^+(s) \tilde{\psi}^-(s)}}{1 + \sqrt{1 - 4 \tilde{\psi}^+(s) \tilde{\psi}^-(s)}} \right)^{|n|} \frac{(1 - \tilde{\psi}(s))/s}{\sqrt{1 - 4 \tilde{\psi}^+(s) \tilde{\psi}^-(s)}} \] \tag{9.12} \]

This is exactly the expression for the Laplace transform of the probability distribution function obtained in Ref. [119] by a different method. These equations allow us to calculate first three moments of the motion. Defining \( \langle n(t) \rangle \) as the mean position of the particle at time \( t \), the following expression for the corresponding Laplace transform can be found:

\[ \langle \tilde{n}(s) \rangle = \sum_{-\infty}^{\infty} n \tilde{P}_n(s) = \frac{b - c}{(a - b - c)^2} = \frac{\tilde{\varphi}^+(s) - \tilde{\varphi}^-(s)}{s^2} \] \tag{9.13} \]

Similar calculations produce following expression for the Laplace transform of the second moment:

\[ \langle \tilde{n}^2(s) \rangle = \sum_{-\infty}^{\infty} n^2 \tilde{P}_n(s) = \frac{(b - c)(a + b + c) - 8bc}{(a - b - c)^3} = \frac{[\tilde{\varphi}^+(s) - \tilde{\varphi}^-(s)][s + 2 \tilde{\varphi}^+(s) + 2 \tilde{\varphi}^-(s)] - 8 \tilde{\varphi}^+(s) \tilde{\varphi}^-(s)]}{s^3} \] \tag{9.14} \]

And, for the Laplace transform of the third moment we obtain:

\[ \langle \tilde{n}^3(s) \rangle = \sum_{-\infty}^{\infty} n^3 \tilde{P}_n(s) = \frac{(b-c)[a(4a+4c+a)+(b+c)^2-24bc]}{(a-b-c)^4} = \frac{[\tilde{\varphi}^+(s)-\tilde{\varphi}^-(s)][(s+\tilde{\varphi}^+(s)\tilde{\varphi}^-(s))(s+5 \tilde{\varphi}^+(s)+5 \tilde{\varphi}^-(s))+(\tilde{\varphi}^+(s)+\tilde{\varphi}^-(s))^2-24 \tilde{\varphi}^+(s) \tilde{\varphi}^-(s)]}{s^4} \]
Expanding Laplace transforms of waiting-time rate distributions at the stationary-state \((t \to \infty)\), it can be shown that

\[
\tilde{\varphi}^+(s) \simeq u + g^+ s + \cdots, \quad \tilde{\varphi}^-(s) \simeq w + g^- s + \cdots,
\]

(9.15)

where \(u = \tilde{\varphi}^+(s = 0)\) and \(w = \tilde{\varphi}^-(s = 0)\) are effective transition rates, and \(g^\pm = \frac{d\tilde{\varphi}^\pm}{ds}|_{s=0}[111]\). After substituting these expressions into Eqs. 9.13, 9.14 and 9.15, we obtain

\[
\langle n(t) \rangle \simeq (u - w)t + (g^+ - g^-),
\]

(9.16)

\[
\langle n^2(t) \rangle \simeq (u - w)^2 t^2 + [(u + w) + 4(u - w)(g^+ - g^-)]t + 2(g^+ - g^-)^2 + (g^+ + g^-),
\]

(9.17)

\[
\langle n^3(t) \rangle \simeq (u - w)^3 t^3 + [3(u - w)(u + w) + 6(u - w)^2(g^+ - g^-)]t^2 + (u - w) + 6(u - w)(g^+ - g^-) + 6(u + w)(g^+ - g^-) + 13(u - w)(g^+ - g^-)^2]t + (g^+ - g^-)^3 + 6(g^+ - g^-)^2 + (g^+ - g^-).
\]

(9.18)

From stationary-state form of the moments we could calculate important dynamic characteristics such as the effective drift velocity \(V\) and the effective diffusion constant \(D\). The drift velocity is given by

\[
V = \lim_{t \to \infty} \frac{d\langle n(t) \rangle}{dt} = u - w.
\]

(9.19)

The corresponding expression for the diffusion constant is given by

\[
D = \frac{1}{2} \lim_{t \to \infty} \frac{d\langle n^2(t) \rangle - \langle n(t) \rangle^2}{dt} = \frac{1}{2} (u + w) + (u - w)(g^+ - g^-).
\]

(9.20)

### 9.3 CTRW on Lattices with Branches

There are many different type of geometries in complex networks that might characterize various dynamic processes. In this chapter, we specifically consider 2 types of
geometries: a model with branched states and a parallel-chain lattice model as shown in Fig. 9.2; but the analysis can also be straightforwardly extended to other network topologies.

First, we consider the CTRW model on the lattice with branched states, as illustrated in Fig. 9.2a. The dynamics of the random walker in this system is governed by a set of waiting-time distribution functions. The particle at the site \( i \) on the main lattice can jump one step forward with the probability \( \psi_+^i(t)dt \), while the step backward can take place with the probability \( \psi_-^i(t)dt \). The particle could also move into the branched state with the probability \( \psi_\beta^i(t)dt \), and the motion back to the main lattice is controlled by the probability \( \psi_\gamma^i(t)dt \) (see Fig. 9.2a). It is assumed that the system is homogeneous, i.e., waiting-time distribution function are independent of the state \( i \): \( \psi_+^i(t) = \psi_+^j(t) \); \( \psi_\beta^i(t) = \psi_\beta^j(t) \) and \( \psi_\gamma^i(t) = \psi_\gamma^j(t) \). Since detachments into the branched state are reversible the probability to find the particle in the system is conserved.

Our method of calculating all-time dynamic properties in CTRW models is based on the important result obtained by Landman, Montroll and Shlesinger in 1977. They showed that the dynamics of the particle in any CTRW model can be fully described by a generalized master equation. For the system with branched states we define \( P_{n,j}(t) \) as the probability of finding the random walker at the site \( n \) at time \( t \). Here, the label \( j = 0 \) corresponds to the site on the main lattice, while \( j = 1 \) represents the branched state. It is assumed that at \( t = 0 \) the particle starts at the origin (\( n = 0 \)) on the main lattice. Then the corresponding generalized master
equations can be written as

\[
\frac{dP_{n,0}(t)}{dt} = \int_0^t [\varphi^+(\tau)P_{n-1,0}(t-\tau) + \varphi^-(\tau)P_{n+1,0}(t-\tau) + \varphi^\gamma(\tau)P_{n,1}(t-\tau)]d\tau - \int_0^t [\varphi^+(\tau) + \varphi^-(\tau) + \varphi^\beta(\tau)]P_{n,0}(t-\tau)d\tau; \quad (9.21)
\]

\[
\frac{dP_{n,1}(t)}{dt} = \int_0^t \left\{ \varphi^\beta(\tau)P_{n,0}(t-\tau) - \varphi^\gamma(\tau)P_{n,1}(t-\tau) \right\}d\tau. \quad (9.22)
\]

Here we used waiting-time rate distributions \(\varphi^\pm(t), \varphi^\beta(t)\) and \(\varphi^\gamma(t)\), and it can be shown that they are related to waiting-time distribution functions via Laplace
transforms,\cite{111,119}

\[
\tilde{\varphi}^\pm(s) = \frac{s\tilde{\psi}^\pm(s)}{1-\tilde{\psi}(s)}, \quad \tilde{\varphi}^\beta(s) = \frac{s\tilde{\psi}^\beta(s)}{1-\tilde{\psi}(s)}, \quad \tilde{\varphi}^\gamma(s) = \frac{s\tilde{\psi}^\gamma(s)}{1-\tilde{\psi}(s)},
\]

(9.23)

with \(\tilde{\psi}(s) = \tilde{\psi}^+(s) + \tilde{\psi}^-(s) + \tilde{\psi}^\beta(s)\).

After performing Laplace transformations the generalized master equations are modified into

\[
\left[s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s) + \tilde{\varphi}^\beta(s)\right] \tilde{P}_{n,0}(s) = \delta_{n,0} + \tilde{\varphi}^+(s)\tilde{P}_{n-1,0}(s) + \tilde{\varphi}^-(s)\tilde{P}_{n+1,0}(s) + \tilde{\varphi}^\beta(s)\tilde{P}_{n,1}(s);
\]

(9.24)

\[
[s + \tilde{\varphi}^\gamma(s)] \tilde{P}_{n,1}(s) = \tilde{\varphi}^\beta(s)\tilde{P}_{n,0}(s).
\]

(9.25)

It is convenient to introduce new auxiliary variables: \(a \equiv s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s) + \frac{s\tilde{\varphi}^\beta(s)}{s + \tilde{\varphi}^\gamma(s)}\), \(b \equiv \tilde{\varphi}^+(s)\), \(c \equiv \tilde{\varphi}^-(s)\) and \(d \equiv \frac{\tilde{\varphi}^\beta(s)}{s + \tilde{\varphi}^\gamma(s)}\). Combining Eqs. 9.24 and 9.25 and utilizing these variables leads to a simpler expression,

\[
a\tilde{P}_{n,0}(s) = \delta_{n,0} + b\tilde{P}_{n-1,0}(s) + c\tilde{P}_{n+1,0}(s).
\]

(9.26)

This recursion relation can be solved exactly,\cite{119} and the solution is given by:

\[
\tilde{P}_{n,0}(s) = \left(\frac{b}{c}\right)^{n/2} \left(\frac{a - \sqrt{a^2 - 4bc}}{2\sqrt{bc}}\right)^{|n|} \frac{1}{\sqrt{a^2 - 4bc}},
\]

(9.27)

or more explicitly,

\[
\tilde{P}_{n,0}(s) = \left(\frac{\tilde{\varphi}^+(s)}{\tilde{\varphi}^-(s)}\right)^{n/2} \left(\frac{s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s) + \frac{s\tilde{\varphi}^\beta(s)}{s + \tilde{\varphi}^\gamma(s)}}{2\sqrt{\tilde{\varphi}^+(s)\tilde{\varphi}^-(s)}} - \sqrt{\frac{(s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s) + \frac{s\tilde{\varphi}^\beta(s)}{s + \tilde{\varphi}^\gamma(s)})^2 - 4\tilde{\varphi}^+(s)\tilde{\varphi}^-(s)}}\right)^{|n|} \times
\]

\[
\frac{1}{\sqrt{(s + \tilde{\varphi}^+(s) + \tilde{\varphi}^-(s) + \frac{s\tilde{\varphi}^\beta(s)}{s + \tilde{\varphi}^\gamma(s)})^2 - 4\tilde{\varphi}^+(s)\tilde{\varphi}^-(s)}}.
\]

(9.28)

It can also be written in terms of the original waiting-time distribution functions with
the help of Eqs. 9.23,
\[
\tilde{P}_{n,0}(s) = \left(\frac{\tilde{\psi}^+(s)}{\tilde{\psi}^-(s)}\right)^{n/2} \left(\frac{2\sqrt{\tilde{\psi}^+(s)\tilde{\psi}^-(s)}}{1 - \tilde{\psi}^\beta(s)\tilde{\psi}^\gamma(s) + \sqrt{(1 - \tilde{\psi}^\beta(s)\tilde{\psi}^\gamma(s))^2 - 4\tilde{\psi}^+(s)\tilde{\psi}^-(s)}}\right) \times \frac{(1 - \tilde{\psi}(s))/s}{\sqrt{(1 - \tilde{\psi}^\beta(s)\tilde{\psi}^\gamma(s))^2 - 4\tilde{\psi}^+(s)\tilde{\psi}^-(s)}} \right)^{\left| n \right|}.
\]
(9.29)

Similar formulas for \(\tilde{P}_{n,1}(s)\) are easily obtained directly from Eq. 9.25.

Exact analytical expressions for Laplace transforms of probability distribution functions [Eqs. 9.29] provide a convenient method of analyzing dynamics of CTRW model on the lattice with branched states at all times. To illustrate this, let us calculate first two moments of the motion for the system. We define \(\langle n(t) \rangle\) as the average position of the random walker at time \(t\), and the corresponding Laplace transform is given by
\[
\langle \tilde{n}(s) \rangle = \sum_{n=-\infty}^{\infty} n(\tilde{P}_{n,0}(s) + \tilde{P}_{n,1}(s)) = (1 + d) \sum_{n=-\infty}^{\infty} n\tilde{P}_{n,0}(s),
\]
(9.30)
which yields[119]
\[
\langle \tilde{n}(s) \rangle = (1 + d) \frac{(b-c)}{(a-b-c)^2} = \frac{1}{1 + \frac{\varphi^\beta(s)}{s+\varphi^\gamma(s)}} \left[ \frac{\tilde{\varphi}^+(s) - \tilde{\varphi}^-(s)}{s^2} \right].
\]
(9.31)

Similar analysis of the Laplace transform for the second moment produces,
\[
\langle \tilde{n}^2(s) \rangle = \sum_{n=-\infty}^{\infty} n^2(\tilde{P}_{n,0}(s) + \tilde{P}_{n,1}(s)) = (1 + d) \sum_{n=-\infty}^{\infty} n^2\tilde{P}_{n,0}(s)
= (1 + d) \frac{(b+c)(a+b+c) - 8bc}{(a-b-c)^3}
= \frac{[\tilde{\varphi}^+(s) + \tilde{\varphi}^-(s)][s + 2\tilde{\varphi}^+(s) + 2\tilde{\varphi}^-(s) + \frac{s\varphi^\beta(s)}{s+\varphi^\gamma(s)}] - 8\tilde{\varphi}^+(s)\tilde{\varphi}^-(s)}{s^3(1 + \frac{\varphi^\beta(s)}{s+\varphi^\gamma(s)})^2}.
\]
(9.32)

The steady-state dynamic behavior of the first and second moments \((t \to \infty)\) can be found by considering the limit of \(s \to 0\). Expanding Laplace transforms of
waiting-time rate distributions for small $s$, one could write\[111\]
\[
\tilde{\varphi}^+(s) \simeq u + g^+ s + \cdots, \quad \tilde{\varphi}^-(s) \simeq w + g^- s + \cdots,
\]
\[
\tilde{\varphi}^\beta(s) \simeq \beta + g^\beta s + \cdots, \quad \tilde{\varphi}^\gamma(s) \simeq \gamma + g^\gamma s + \cdots,
\] (9.33)

where $u = \tilde{\varphi}^+(s = 0)$, $w = \tilde{\varphi}^-(s = 0)$, $\beta = \tilde{\varphi}^\beta(s = 0)$ and $\gamma = \tilde{\varphi}^\gamma(s = 0)$ are effective transition rates;\[111\] while $g^\pm = \frac{d\tilde{\varphi}^\pm}{ds}|_{s=0}$, $g^\beta = \frac{d\tilde{\varphi}^\beta}{ds}|_{s=0}$ and $g^\gamma = \frac{d\tilde{\varphi}^\gamma}{ds}|_{s=0}$. To proceed further, we substitute these expansions into Eqs. 9.31 and (9.32), leading to

\[
\langle n(t) \rangle \simeq \frac{(u - w)}{1 + \frac{\beta}{\gamma}} t + \frac{(g^+ - g^-)}{1 + \frac{\beta}{\gamma}} + \frac{(u - w)}{(1 + \frac{\beta}{\gamma})^2} \left( \frac{1 + g^\gamma}{\gamma} - \frac{g^\beta}{\beta} \right) \frac{\beta}{\gamma},
\] (9.34)

\[
\langle n^2(t) \rangle \simeq \frac{(u - w)^2}{(1 + \frac{\beta}{\gamma})^2} t^2 + \frac{4(u - w)(g^+ - g^-)}{(1 + \frac{\beta}{\gamma})^2} + \frac{(u + w)}{(1 + \frac{\beta}{\gamma})^3} + \frac{4(u - w)^2}{(1 + \frac{\beta}{\gamma})^3} \left( \frac{1 + g^\gamma}{\gamma} - \frac{g^\beta}{\beta} \right) \frac{\beta}{\gamma} t.
\] (9.35)

The large-time behavior of the moments allows us to compute important dynamic properties such as the effective drift velocity $V$ and the effective diffusion constant $D$. The velocity is found from

\[
V = \lim_{t \to \infty} \frac{d\langle n(t) \rangle}{dt} = \frac{(u - w)}{1 + \frac{\beta}{\gamma}}.
\] (9.36)

The corresponding expression for the diffusion constant is given by

\[
D = \frac{1}{2} \lim_{t \to \infty} \frac{d\langle n^2(t) \rangle - \langle n(t) \rangle^2}{dt} = \frac{(u + w)}{(1 + \frac{\beta}{\gamma})^2} + \frac{(u - w)(g^+ - g^-)}{(1 + \frac{\beta}{\gamma})^2} + \frac{(u - w)^2}{(1 + \frac{\beta}{\gamma})^3} \left( \frac{1 + g^\gamma}{\gamma} - \frac{g^\beta}{\beta} \right) \frac{\beta}{\gamma}.
\] (9.37)

### 9.3.1 Calculation of Velocity and Dispersion Using Derrida’s Approach

It is important to note that these equations reproduce expressions for stationary-state dynamic properties of the CTRW model with branched states, as was obtained earlier by Derrida’s approach\[111\]. In this section, we prove that both methods yield same result.
For sequential kinetic models with branches of finite length, the drift velocity is given by

\[ V_\beta(\beta, \gamma) = d(1 - \Pi_1^N) / R_N^\beta \]  \hspace{1cm} (9.38)

where

\[ R_N^\beta = \sum_{j=0}^{N-1} r_j^\beta, \quad r_j^\beta = r_j \left[ 1 + \sum_{k=1}^L \Pi_j^{\beta,k} \right] \]  \hspace{1cm} (9.39)

and

\[ \Pi_j^k = \prod_{i=j}^k w_i, \quad \Pi_j^{\beta,k} = \prod_{i=1}^k \frac{\beta_{j+i-1}}{\gamma_{j+i}} \]  \hspace{1cm} (9.40)

For \( L = 1 \) and \( N = 1 \), we obtain

\[ \Pi_1^1 = \frac{w}{u} \]  \hspace{1cm} (9.41)
\[ r = \frac{1}{u} \]  \hspace{1cm} (9.42)
\[ R_1^\beta = r_1^\beta = \frac{1}{u} \left[ 1 + \frac{\beta}{\gamma} \right] \]  \hspace{1cm} (9.43)

and from this expression we can calculate the drift velocity as

\[ V = \frac{u - w}{1 + \frac{\beta}{\gamma}} \]  \hspace{1cm} (9.44)

The diffusion constant can be written as:

\[ D_\beta = D_{0,\beta} + D_{1,\beta} + D_{2,\beta} \]  \hspace{1cm} (9.45)

The first two terms are given by

\[ D_{0,\beta} = (d/N)[V_\beta S_N^\beta + dU_N^\beta]/(R_N^\beta)^2 - \frac{1}{2}(N + 2)V_\beta, \]  \hspace{1cm} (9.46)

\[ D_{1,\beta} = (d/N)[NV_\beta/(R_N^\beta)^2] \sum_{j=0}^{N-1} s_j^\beta (g_j^+ r_j - g_{j+1}^- r_{j+1}), \]  \hspace{1cm} (9.47)
where auxiliary functions $S_N$ and $U_N$ are defined by

\[ S_N^\beta = \sum_{j=0}^{N-1} s_j \sum_{k=0}^{N-1} (k+1)r_{k+j+1}^\beta, \quad U_N^\beta = \sum_{j=0}^{N-1} u_j r_j s_j^\beta \]  \hfill (9.48)

\[ s_j^\beta = u_j^{-1} \left[ 1 + \sum_{l=1}^{L} \Pi_j^{\beta,l} + \sum_{k=1}^{N-1} \left( 1 + \sum_{l=1}^{L} \Pi_j^{\beta,l} \right) \Pi_{j-k}^{\beta,j-1} \right]. \]  \hfill (9.49)

From these expressions for $N = 1$ and $L = 1$ we obtain

\[ s^\beta = \frac{1}{u} \left[ 1 + \frac{\beta}{\alpha} \right], \quad S_1^\beta = \frac{1}{u^2} \left[ 1 + \frac{\beta}{\alpha} \right]^2, \quad U_1^\beta = \frac{1}{u} \left[ 1 + \frac{\beta}{\alpha} \right] \]  \hfill (9.50)

Substituting into Eqs. 9.46 and 9.47, we obtain

\[ D_{0,\beta} = \frac{1}{2} \left[ \frac{u + w}{1 + \frac{\beta}{\gamma}} \right] \]  \hfill (9.51)

\[ D_{1,\beta} = \frac{(u - w)(g^+ - g^-)}{(1 + \frac{\beta}{\gamma})^2} \]  \hfill (9.52)

$D_{2,\beta}$ is a contribution due to the presence of side branches, given by

\[ D_{2,\beta} = V_\beta^2 \sum_{j=0}^{N-1} \sum_{k=1}^{L} W_j^{\beta,k} \]  \hfill (9.53)

where coefficient $W_j^{\beta,k}$ is given by

\[ W_j^{\beta,k} = \frac{r_j}{R_N^\beta \gamma_{j,k}} \left[ \sum_{l=k}^{L} \Pi_j^{\beta,l} - g_{j,k-1}^\beta \Pi_j^{\beta,k-1} + g_{j,k}^\gamma \Pi_j^{\gamma,k} \right] + \frac{r_j}{R_N^\beta \gamma_{j,k}} \left[ \sum_{i=1}^{k-1} \Pi_j^{\beta,i} \left( \sum_{l=k-i-1}^{L} g_{j,k-i-1}^\beta \Pi_j^{\beta,k-i-1} + g_{j,k-i}^\gamma \Pi_j^{\gamma,k-i} \right) \right]. \]  \hfill (9.54)

and after some algebra, we obtain

\[ D_{2,\beta} = \left( \frac{u - w}{(1 + \frac{\beta}{\gamma})^2} \right) \left[ \frac{g^\gamma + 1}{\gamma} - \frac{g^\beta}{\beta} \right] \frac{\beta}{\gamma} \]  \hfill (9.55)

Adding three expressions yields

\[ \frac{1}{2} \left[ \frac{u + w}{1 + \frac{\beta}{\gamma}} \right] + \frac{(u - w)(g^+ - g^-)}{(1 + \frac{\beta}{\gamma})^2} + \left( \frac{u - w}{(1 + \frac{\beta}{\gamma})^2} \right) \left[ \frac{g^\gamma + 1}{\gamma} - \frac{g^\beta}{\beta} \right] \frac{\beta}{\gamma} \]  \hfill (9.56)
9.4 CTRW on Coupled Parallel-Chain Lattices

In this section, a CTRW model on more complex network that consists of coupled parallel chains (see Fig. 9.2b) is investigated. The random walker can be found in one of two lattices. On the lattice 1, the waiting time distributions to move forward or backward along the same chain are given by probabilities $\psi_1^+(t)dt$ and $\psi_1^-(t)dt$, respectively. Similarly, $\psi_2^\pm(t)dt$ are the probabilities to hop along the lattice 2: see Fig. 9.2b. The particle from the lattice 1 can jump to the same site on another channel with the probability $\psi_\gamma(t)dt$, while the reversed motion has the probability $\psi_\delta(t)dt$. Since only the homogeneous CTRW model is analyzed here these probabilities do not depend on the site position. Again, we introduce a function $P_{n,i}(t)$ as the probability to find the particle on the site $n$ on the channel $i$ ($i = 1, 2$) at time $t$. For initial conditions we assume that the particle at $t = 0$ starts in the first channel at the site $n = 0$. Then the temporal evolution of the system is governed by a set of generalized master equations:

$$\frac{dP_{n,1}(t)}{dt} = \int_0^t [\varphi_1^+(\tau)P_{n-1,1}(t-\tau) + \varphi_1^-(\tau)P_{n+1,1}(t-\tau) + \varphi_\delta(\tau)P_{n,2}(t-\tau)]d\tau,$$

$$- \int_0^t [\varphi_1^+(\tau) + \varphi_1^-(\tau) + \varphi_\gamma(\tau)]P_{n,1}(t-\tau)d\tau \quad (9.57)$$

$$\frac{dP_{n,2}(t)}{dt} = \int_0^t [\varphi_2^+(\tau)P_{n-1,2}(t-\tau) + \varphi_2^-(\tau)P_{n+1,2}(t-\tau) + \varphi_\gamma(\tau)P_{n,1}(t-\tau)]d\tau$$

$$- \int_0^t [\varphi_2^+(\tau) + \varphi_2^-(\tau) + \varphi_\delta(\tau)]P_{n,2}(t-\tau)d\tau. \quad (9.58)$$

In these equations rate-distribution functions are related to waiting-time distributions as follows:

$$\widetilde{\varphi}_1^\pm(s) = \frac{s\psi_1^\pm(s)}{1 - \psi_1(s)}; \quad \widetilde{\varphi}_\gamma(s) = \frac{s\psi_\gamma(s)}{1 - \psi_1(s)};$$

$$\widetilde{\varphi}_2^\pm(s) = \frac{s\psi_2^\pm(s)}{1 - \psi_2(s)}; \quad \widetilde{\varphi}_\delta(s) = \frac{s\psi_\delta(s)}{1 - \psi_2(s)}; \quad (9.59)$$
with \( \tilde{\psi}_1(s) = \tilde{\psi}_1^+(s) + \tilde{\psi}_1^-(s) + \tilde{\psi}_1^\gamma(s) \) and \( \tilde{\psi}_2(s) = \tilde{\psi}_2^+(s) + \tilde{\psi}_2^-(s) + \tilde{\psi}_2^\gamma(s) \).

Applying the Laplace transformation to generalized master equations, we obtain,

\[
[s + \tilde{\varphi}_1^+(s) + \tilde{\varphi}_1^-(s) + \tilde{\varphi}_1^\gamma(s)] \tilde{P}_{n,1}(s) = \delta_{n,0} + \tilde{\varphi}_1^+(s)\tilde{P}_{n-1,1}(s) + \tilde{\varphi}_1^-(s)\tilde{P}_{n+1,1}(s) + \tilde{\varphi}_1^\gamma(s)\tilde{P}_{n,1}(s). \tag{9.60}
\]

\[
[s + \tilde{\varphi}_2^+(s) + \tilde{\varphi}_2^-(s) + \tilde{\varphi}_2^\gamma(s)] \tilde{P}_{n,2}(s) = \tilde{\varphi}_2^+(s)\tilde{P}_{n-1,2}(s) + \tilde{\varphi}_2^-(s)\tilde{P}_{n+1,2}(s) + \tilde{\varphi}_2^\gamma(s)\tilde{P}_{n,1}(s). \tag{9.61}
\]

The conservation of probability in this system, \( \sum_{n=-\infty}^{\infty} [P_{n,1}(t) + P_{n,2}(t)] = 1 \), leads to the following expression in the Laplace space,

\[
\sum_{n=-\infty}^{\infty} \left[ \tilde{P}_{n,1}(s) + \tilde{P}_{n,2}(s) \right] = \frac{1}{s} \tag{9.62}
\]

For convenience, we define new parameters: \( d_1 \equiv \tilde{\varphi}_1^\gamma(s) \), \( d_2 \equiv \tilde{\varphi}_2^\gamma(s) \), \( b_1 \equiv \tilde{\varphi}_1^+(s) \), \( c_1 \equiv \tilde{\varphi}_1^-(s) \), \( b_2 \equiv \tilde{\varphi}_2^+(s) \) and \( c_2 \equiv \tilde{\varphi}_2^-(s) \). Then summing over Eqs. 9.60 and 9.61 produces

\[
\sum_{n=-\infty}^{\infty} \tilde{P}_{n,1}(s) = \frac{d_2}{s + d_1} \sum_{n=-\infty}^{\infty} \tilde{P}_{n,2}(s), \tag{9.63}
\]

\[
\sum_{n=-\infty}^{\infty} \tilde{P}_{n,1}(s) = \frac{s + d_2}{d_1} \sum_{n=-\infty}^{\infty} \tilde{P}_{n,2}(s), \tag{9.64}
\]

which suggests that the following relation holds:

\[
\frac{d_1}{s + d_2} = \frac{s + d_1}{d_2}. \tag{9.65}
\]

Then using the normalization condition, Eqs. 9.63 and 9.64 one can show that

\[
\sum_{n=-\infty}^{\infty} \tilde{P}_{n,1}(s) = \frac{s + d_2}{s(s + d_1 + d_2)} \tag{9.66}
\]

\[
\sum_{n=-\infty}^{\infty} \tilde{P}_{n,2}(s) = \frac{d_1}{s(s + d_1 + d_2)}. \tag{9.67}
\]
Next we make an assumption that

\[ \tilde{P}_{n,2}(s) = K \tilde{P}_{n,1}(s) \] (9.68)

and from Eqs. 9.66 and 9.67 the unknown parameter \( K \) can be easily determined,

\[ K = \frac{d_1}{s + d_2} = \frac{s + d_1}{d_2}. \] (9.69)

In terms of waiting-time distributions this expression can be rewritten as

\[ \frac{\tilde{\psi}^\gamma(s)}{1 - \tilde{\psi}_1^+(s) - \tilde{\psi}_1^-(s)} = \frac{\tilde{\psi}^\delta(s)}{1 - \tilde{\psi}_2^+(s) - \tilde{\psi}_2^-(s)}. \] (9.70)

This is an important result since it sets a constraint on possible waiting-time distribution functions that describe homogeneous CTRW on the coupled parallel lattices.

Combining Eqs. 9.60 and 9.61 with 9.69, we obtain:

\[ A \tilde{P}_{n,1}(s) = \delta_{n,0} + B \tilde{P}_{n-1,1}(s) + C \tilde{P}_{n+1,1}(s), \] (9.71)

where new auxiliary functions are defined as

\[ A \equiv s + b_1 + c_1 + \frac{d_1(s + b_2 + c_2)}{s + d_2}, \]

\[ B \equiv s + b_1 + \frac{d_1 b_2}{s + d_2}, \]

\[ C \equiv s + c_1 + \frac{d_1 c_2}{s + d_2}. \] (9.72)

The recursion relation 9.71 is similar to Eq. 9.26, and the solution again can be found in the following form,[119]

\[ \tilde{P}_{n,1}(s) = \left( \frac{B}{C} \right)^{n/2} \left( \frac{A - \sqrt{A^2 - 4BC}}{2\sqrt{BC}} \right)^{|n|} \frac{1}{\sqrt{A^2 - 4BC}}. \] (9.73)

Similar expression for \( P_{n,2}(s) \) can be easily obtained from Eqs. 9.68 and 9.69.

The Eq. 9.73 provides a full description of the CTRW dynamics on the coupled parallel channels at all times. It will be illustrated by looking at first two moments.
of motion. It can be shown that the Laplace transform of the first moment is equal to
\[
\langle \tilde{n}(s) \rangle = \sum_{n=-\infty}^{\infty} n(\tilde{P}_{n,1}(s) + \tilde{P}_{n,2}(s)) = (1 + \frac{d_1}{s + d_2}) \sum_{n=-\infty}^{\infty} n\tilde{P}_{n,1}(s),
\]
(9.74)
which can also be written as
\[
\langle \tilde{n}(s) \rangle = \frac{(b_1 - c_1)(s + d_2) + (b_2 - c_2)(s + d_1)}{s^2(s + d_1 + d_2)}.
\]
(9.75)
Utilizing waiting-time distributions it can be shown that,
\[
\langle \tilde{n}(s) \rangle = \frac{(\tilde{\varphi}_1^+(s) - \tilde{\varphi}_1^-(s))(s + \tilde{\varphi}_2^\delta(s)) + (\tilde{\varphi}_2^+(s) - \tilde{\varphi}_2^-(s))(s + \tilde{\varphi}_3^\gamma(s))}{s^2(s + \tilde{\varphi}_2^\gamma(s) + \tilde{\varphi}_2^\delta(s))}.
\]
(9.76)
Similar calculations for the Laplace transform of the second moment produce
\[
\langle \tilde{n}^2(s) \rangle = \frac{[s + \tilde{\varphi}_1^+(s)]^2(s + \tilde{\varphi}_1^-(s)] + 2[s\tilde{\varphi}_1^+(s) - \tilde{\varphi}_1^{-}(s)]^2}{s^4(s + \tilde{\varphi}_2^{-}(s) + \tilde{\varphi}_3^{-}(s))^2} + \frac{\tilde{\varphi}_2^{-}(s)\tilde{\varphi}_3^{-}(s)}{s^4(s + \tilde{\varphi}_2^{-}(s) + \tilde{\varphi}_3^{-}(s))^2}
\]
\[
+ \frac{\tilde{\varphi}_3^{-}(s)\tilde{\varphi}_4^{-}(s)\tilde{\varphi}_5^{-}(s)\tilde{\varphi}_6^{-}(s)}{s^4(s + \tilde{\varphi}_2^{-}(s) + \tilde{\varphi}_3^{-}(s))^2}.
\]
(9.77)
The stationary-state behavior \((t \to \infty)\) of the first and second moments of the motion can be found by using expansions of waiting-time rate distribution functions at \(s \to 0\),
\[
\tilde{\varphi}_1^+(s) \simeq u_1 + g_1^+ s + \cdots, \quad \tilde{\varphi}_2^-(s) \simeq w_2 + g_2^- s + \cdots,
\]
\[
\tilde{\varphi}_1^-(s) \simeq w_1 + g_1^- s + \cdots, \quad \tilde{\varphi}_2^+(s) \simeq u_2 + g_2^+ s + \cdots,
\]
\[
\tilde{\varphi}_2^\delta(s) \simeq \delta + g^\delta s + \cdots, \quad \tilde{\varphi}_3^\gamma(s) \simeq \gamma + g^\gamma s + \cdots,
\]
(9.78)
where \(u_i = \tilde{\varphi}_i^+(s = 0), \quad w_i = \tilde{\varphi}_i^-(s = 0)\) for \(i = 1, 2; \quad \delta = \tilde{\varphi}_2^\delta(s = 0)\) and \(\gamma = \tilde{\varphi}_3^\gamma(s = 0)\) are effective transition rates.[111] Other coefficients are given by \(g_i^\pm = \frac{d\tilde{\varphi}_i^\pm}{ds}|_{s=0}\) for \(i = 1, 2, \quad g^\delta = \frac{d\tilde{\varphi}_2^\delta}{ds}|_{s=0}\) and \(g^\gamma = \frac{d\tilde{\varphi}_3^\gamma}{ds}|_{s=0}\). The asymptotic calculations then produce
the following results for the average position of the random walker,

$$\langle n(t) \rangle \simeq \left[ \frac{(u_1 - w_1)\delta + (u_2 - w_2)\gamma}{\delta + \gamma} \right] t$$

$$+ \frac{1}{\gamma + \delta} \left[ (u_1 - w_1)(1 + g^\delta) + \delta(g_1^+ - g_1^-) + (u_2 - w_2)(1 + g^\gamma) + \gamma(g_2^+ - g_2^-) \right]$$

$$- \frac{(1 + g^\delta + g^\gamma)\delta(u_1 - w_1) + \gamma(u_2 - w_2)}{(\gamma + \delta)^2}. \quad (9.79)$$

The expression for mean-squared position of the particle is more complex,

$$\langle n^2(t) \rangle \simeq \left[ \frac{(u_1 - w_1)\delta + (u_2 - w_2)\gamma}{\delta + \gamma} \right] 2t^2$$

$$+ \left\{ \frac{(u_1 + w_1)\delta + (u_2 + w_2)\gamma}{2(\gamma + \delta)^2} \right\} \right.$$ 

$$+ \frac{\left[ \delta^2(u_1 - w_1)(g_1^+ - g_1^-) + \gamma^2(u_2 - w_2)(g_2^+ - g_2^-) + \gamma\delta(u_1 - w_1)(g_2^+ - g_2^-) + \delta\gamma(u_2 - w_2)(g_1^+ - g_1^-) \right]}{(\gamma + \delta)^2}$$

$$+ \frac{\left[ 4\delta^2(u_1 - w_1)^2(1 + g^\delta) + 4\gamma^2(u_2 - w_2)^2(1 + g^\gamma) + 4\delta\gamma(u_1 - w_1)(u_2 - w_2)(\gamma g^\delta + \delta g^\gamma) \right]}{(\gamma + \delta)^2} \left\} t. \quad (9.80)$$

These expressions allow us to derive the stationary drift velocity,

$$V \simeq \frac{(u_1 - w_1)\delta + (u_2 - w_2)\gamma}{\delta + \gamma}; \quad (9.81)$$

and the effective diffusion constant,

$$D = \left[ \frac{(u_1 + w_1)\delta + (u_2 + w_2)\gamma}{2(\gamma + \delta)^2} \right]$$

$$+ \left[ \frac{\delta^2(u_1 - w_1)(g_1^+ - g_1^-) + \gamma^2(u_2 - w_2)(g_2^+ - g_2^-) + \gamma\delta(u_1 - w_1)(g_2^+ - g_2^-) + \delta\gamma(u_2 - w_2)(g_1^+ - g_1^-)}{(\delta + \gamma)^2} \right]$$

$$+ \frac{\gamma\delta(u_1 - w_1)^2(\gamma g^\delta + \delta g^\gamma) + \gamma^2g^\delta(u_2 - w_2)^2}{(\delta + \gamma)^3}$$

$$- \frac{(u_1 - w_1)(u_2 - w_2)(\gamma g^\delta + \delta g^\gamma)}{(\delta + \gamma)^4}. \quad (9.82)$$

When the waiting-time distribution functions are exponential all transitions in the system become Poissonian and CTRW models are reduced to simple random walk processes. In this case we have \( g_1^+ = g_1^- = g_2^+ = g_2^- = g^\gamma = g^\delta = 0 \), and the expression for dispersion is much simpler:

$$D = \frac{[(u_1 + w_1)\delta + (u_2 + w_2)\gamma]}{2(\delta + \gamma)} + \frac{[(u_1 - w_1)^2 - (u_2 - w_2)^2]}{(\delta + \gamma)^3}. \quad (9.83)$$
It agrees exactly with the formula obtained earlier for stationary properties of ordinary random walks on coupled parallel-chain lattices.[124]

To test the validity of our approach, one could notice that the CTRW model with the branched states can be viewed as a special case of the CTRW on coupled parallel channels if the motion along one of the lattice is disabled, i.e., $\psi_1^\pm(t) = 0$ or $\psi_2^\pm(t) = 0$. Then one can show that in this case the Laplace transform for the probability function to find the particle at the site $n$, Eq. 9.73, reduces to the main result of Section 2, Eq. 9.28, as expected.

### 9.5 Generalized Fluctuation Theorem

Fluctuation theorems are important for understanding fundamental mechanisms of complex phenomena[125, 126, 127]. Generalized fluctuation theorems, which reduce to the original formulation under some condition, have been introduced and studied for several CTRW models.[117, 119] The analysis is performed by considering the ratio of $\overline{P}_{n,0}(s) / \overline{P}_{n,0}(s)$. Theoretical results obtained in this paper allows us to investigate explicitly generalized fluctuation theorems for CTRW on complex networks.

For CTRW model with branches it can be shown that

$$\frac{\overline{P}_{n,0}(s)}{\overline{P}_{n,0}(s)} = \frac{\overline{P}_{n,1}(s)}{\overline{P}_{n,1}(s)} = \left[ \frac{\tilde{\psi}^+(s)}{\tilde{\psi}^-(s)} \right]^n = \left[ \frac{\tilde{\phi}^+(s)}{\tilde{\phi}^-(s)} \right]^n. \quad (9.84)$$

It is the same formula as for the homogeneous CTRW on lattices without branched states,[117, 119] suggesting that reversible detachments do not affect the ratio of probabilities for forward and backward steps of the random walker. Consequently, branched states do not change statistics for occurrence of different fluctuations. It leads to the original fluctuation theorem result when $\frac{\psi^+(t)}{\psi^-(t)}$ is time-independent.
For the CTRW model on coupled parallel channels the results are more complex,

\[ \frac{\tilde{P}_{n,1}(s)}{\tilde{P}_{n,2}(s)} = \frac{\tilde{P}_{n,2}(s)}{\tilde{P}_{n,1}(s)} = \left[ \frac{\tilde{\varphi}_1^+(s) + \tilde{\varphi}_2^+(s) + \tilde{\varphi}_1^-(s) + \tilde{\varphi}_2^-(s)}{\tilde{\varphi}_2^+(s) + \tilde{\varphi}_1^+(s) + \tilde{\varphi}_2^-(s) + \tilde{\varphi}_1^-(s)} \right]^n. \]  

(9.85)

In terms of the waiting-time distribution functions the generalized fluctuations theorem has the following form,

\[ \frac{\tilde{P}_{n,1}(s)}{\tilde{P}_{n,2}(s)} = \frac{\tilde{P}_{n,2}(s)}{\tilde{P}_{n,1}(s)} = \left[ \frac{\tilde{\psi}_1^+(s) + \tilde{\psi}_2^+(s) + \tilde{\psi}_1^-(s) + \tilde{\psi}_2^-(s)}{\tilde{\psi}_2^+(s) + \tilde{\psi}_1^+(s) + \tilde{\psi}_2^-(s) + \tilde{\psi}_1^-(s)} \right]^n. \]  

(9.86)

This result can be understood physically using the following arguments. The numerator can be viewed as an effective waiting-time distribution function to move forward, which is averaged over finding the particle on the lattice 1 and 2. The denominator has the meaning for effective waiting-time distribution function to move backward. It also shows the importance of transitions between channels on individual trajectories and on statistics of fluctuations.

### 9.6 Summary and Conclusions

A theoretical method of calculating all-time dynamics of continuous-time random walks is extended to processes that take place on complex networks. Specifically, dynamic properties of CTRW models on the lattices with branched states and CTRW models on the coupled parallel channels are analyzed at all times. The theoretical approach is flexible and robust to deal with complex CTRW models since it is based on the construction of the generalized master equations which are solved exactly in the Laplace space. It suggests that homogeneous CTRW processes on any networks can be analyzed in the similar way.
Our calculations yielded stationary-state dynamic properties for processes that can reach the steady states. All derived results for drift velocities and dispersions of CTRW models on complex networks at stationary conditions agree with available large-time expressions obtained by different methods. In addition, generalized fluctuation theorems are discussed. It is shown that the presence of branched states do not affect fluctuation dynamics of particles, while in the model with coupled parallel lattices transitions between channels are important. It will be interesting to extend this method to more complex inhomogeneous CTRW models on networks\[128, 129\] that will help to understand better fundamental mechanisms of various complex dynamic phenomena. It has been suggested recently that in this case one could utilize the fractional Fokker-Planck approach\[130, 131\].
Appendix A

In this appendix, we present detailed calculations of the stationary profiles and LATs for the exponential and linear distribution of production rates discussed in chapter 3.

A.1 Calculation of stationary density profiles and local accumulation times for exponentially distributed production

Using a superposition principle, the total stationary profile can be written as

\[
P_{\text{s}}(s) = \frac{x^n}{\sqrt{k^2 + 4uk(k + \sqrt{k^2 + 4uk})}} \left[ (k + \sqrt{k^2 + 4uk}) \sum_{m=0}^{n} Q_m x^{-m} + (-k + \sqrt{k^2 + 4uk}) \sum_{m=0}^{n} Q_m x^m \right] 
\]

\[
+ \left[ (k + \sqrt{k^2 + 4uk})x^{-n} + (-k + \sqrt{k^2 + 4uk})x^n \right] \frac{\sqrt{k^2 + 4uk(k + \sqrt{k^2 + 4uk})}}{L} \sum_{m=n+1}^{L} Q_m x_m \right] (A.1)
\]

for the sites inside the production area. For the sites outside of the production we have

\[
P_{\text{s}}(s) = \frac{x^n}{\sqrt{k^2 + 4uk(k + \sqrt{k^2 + 4uk})}} \left[ (k + \sqrt{k^2 + 4uk}) \sum_{m=0}^{L} Q_m x^{-m} + (-k + \sqrt{k^2 + 4uk}) \sum_{m=0}^{L} Q_m x^m \right].
\]

(A.2)

The summations over \( m \) for different intervals can be performed in the following way,

\[
\sum_{m=0}^{L} Q_m x_m = \frac{Q(1-z)}{1-z^{L+1}} \left[ \frac{1-(xz)^{L+1}}{1-xz} \right]; \quad (A.3)
\]

\[
\sum_{m=0}^{L} Q_m x^{-m} = \frac{Q(1-z)}{1-z^{L+1}} \left[ \frac{x-z(z/x)^L}{x-z} \right]; \quad (A.4)
\]

\[
\sum_{m=0}^{n} Q_m x^{-m} = \frac{Q(1-z)}{1-z^{L+1}} \left[ \frac{x-z(z/x)^n}{x-z} \right]; \quad (A.5)
\]
\[
\sum_{m=n+1}^{L} Q_{m} x^{m} = \frac{Q(1-z)}{1-z^{L+1}} \left[ \frac{(xz)^{n+1} - (xz)^{L+1}}{1-xz} \right]. \tag{A.6}
\]

Substituting these expressions into Eqs. (A.1) and (A.2), we obtain for the sites inside the source region,

\[
P_{<}(n) = \frac{Q(1-z)}{\sqrt{k^2 + 4uk(1-z^{L+1})}} \left[ \frac{(x^{n+1} - zx^{n+2} - zL^{+1}x_{L+2-n} + zL^{+2}x_{L+1-n} - z^{n+1} + x^{2}z^{n+1})}{(x-z)(1-xz)} \right]
\]
\[+ \frac{Q(1-z)}{\sqrt{k^2 + 4uk(1-z^{L+1})}} \left[ \frac{(-k + \sqrt{k^2 + 4uk})(1 - (xz)^{L+1})(x^{n+1} - zx^{n})}{(k + \sqrt{k^2 + 4uk})(x-z)(1-xz)} \right]. \tag{A.7}
\]

while for the outside region we have

\[
P_{>}(n) = \frac{Q(1-z)}{\sqrt{k^2 + 4uk(1-z^{L+1})}} \left[ \frac{(x^{n+1} - zx^{n+2} - zL^{+1}x_{L+2-n} + zL^{+2}x_{L+1-n} + z^{n+1} - x^{2}z^{n+1})}{(x-z)(1-xz)} \right]
\]
\[+ \frac{Q(1-z)}{\sqrt{k^2 + 4uk(1-z^{L+1})}} \left[ \frac{(-k + \sqrt{k^2 + 4uk})(1 - (xz)^{L+1})(x^{n+1} - zx^{n})}{(k + \sqrt{k^2 + 4uk})(x-z)(1-xz)} \right]. \tag{A.8}
\]

The corresponding expressions for LATs for the source region can be written as

\[
t_{<}(n) = \frac{n}{\sqrt{k^2 + 4uk}} \left[ \frac{(-k + \sqrt{k^2 + 4uk})(1 - (xz)^{L+1})(x^{n+1} - zx^{n}) + (k + \sqrt{k^2 + 4uk})\Psi_{<}(n)}{\Delta_{<}(n)} \right]
\]
\[+ \frac{2uk}{k^2 + 4uk} \left[ \frac{(1 - (xz)^{L+1})(x^{n+1} - zx^{n}) - x^{n+1} + zx^{n+2} + zL^{+1}x_{L-n+2} - zL^{+2}x_{L-n+1} + z^{n+1} - x^{2}z^{n+1}}{\Delta_{<}(n)} \right]
\]
\[+ \frac{L}{\sqrt{k^2 + 4uk}} \left[ \frac{(k + \sqrt{k^2 + 4uk})(zL^{+2}x_{L-n+1} - zL^{+1}x_{L-n+2}) - (-k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^{n})(xz)^{L+1}}{\Delta_{<}(n)} \right]
\]
\[+ \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{(k + \sqrt{k^2 + 4uk})\Phi_{<}(n) + (-k + \sqrt{k^2 + 4uk})(x^{n+1}(1 - (xz)^{L+1}) - (x^{n+1} - zx^{n})(xz)^{L+1})}{\Delta_{<}(n)} \right]
\]
\[+ \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} + \frac{xz}{1-xz} - \frac{x}{x-z} \right]. \tag{A.9}
\]

where we defined new auxiliary functions

\[
\Delta_{<}(n) = (k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^{n+2} - zL^{+1}x_{L+2-n} + zL^{+2}x_{L+1-n} - z^{n+1} + x^{2}z^{n+1})
\]
\[+ (-k + \sqrt{k^2 + 4uk})(1 - (xz)^{L+1})(x^{n+1} - zx^{n}) \tag{A.10}
\]

and

\[
\Psi_{<}(n) = x^{n+1} - zx^{n+2} + zL^{+1}x_{L+2-n} - zL^{+2}x_{L+1-n}, \tag{A.11}
\]
$$\Phi_<(n) = x^{n+1} - 2zx^{n+2} - 2z^{L+1}x^{L+2-n} + 2x^2z^{n+1} + z^{L+2}x^{L+1-n}. \quad (A.12)$$

Similar calculations for LAT for the region outside of the source area produce

$$t_>(n) = \frac{n}{\sqrt{k^2 + 4uk}} \left[ \frac{(-k + \sqrt{k^2 + 4uk})(1 - (xz)^{L+1})(x^{n+1} - zx^n) + (k + \sqrt{k^2 + 4uk})\Psi_>(n)}{\Delta_>(n)} \right]$$

$$+ \frac{2uk}{k^2 + 4uk} \left[ \frac{(1 - (xz)^{L+1})(x^{n+1} - zx^n) - x^{n+1} + zx^{n+2} + z^{L+1}x^{L+2-n} - z^{L+2}x^{L+1-n} + z^{n+1} - x^2z^{n+1}}{\Delta_>(n)} \right]$$

$$+ \frac{L}{\sqrt{k^2 + 4uk}} \left[ \frac{(k + \sqrt{k^2 + 4uk})(z^{L+1}x^{L-n} - z^{L+2}x^{L-n+1}) - (-k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^n)(xz)^{L+1}}{\Delta_>(n)} \right]$$

$$+ \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} + \frac{xz}{1 - xz} - \frac{x}{x - z} \right] \quad (A.13)$$

where another set of auxiliary functions is introduced,

$$\Delta_>(n) = (k + \sqrt{k^2 + 4uk})(x^{n+1} - zx^{n+2} - z^{L+1}x^{-L+n} + z^{L+2}x^{-L+1+n})$$

$$+ (-k + \sqrt{k^2 + 4uk})(1 - (xz)^{L+1})(x^{n+1} - zx^n); \quad (A.14)$$

and

$$\Psi_>(n) = x^{n+1} - zx^{n+2} - z^{L+1}x^{-L} + z^{L+2}x^{-n+1}, \quad (A.15)$$

$$\Phi_>(n) = x^{n+1} - 2zx^{n+2} + z^{L+2}x^{-n+1}. \quad (A.16)$$

Taking the limit of $L \to \infty$ in equations (A.7) and (A.9) we obtain the expressions for the stationary-state profiles and the local accumulation times used in the main text of the paper.
A.2 Calculation of stationary density profiles and local accumulation times for linearly distributed production

From Eq. 3.6 we can obtain explicit expressions for stationary density profiles. For the sites inside the production region we have

\[
P_{\leq}^{(s)}(n) = \frac{x^n \left[ (k + \sqrt{k^2 + 4uk}) \sum_{m=0}^{n} Q_m x^m - m + (\sqrt{k^2 + 4uk}) \sum_{m=0}^{n} Q_m x^m \right]}{\sqrt{k^2 + 4uk}(k + \sqrt{k^2 + 4uk})} \]

\[
+ \frac{[k + \sqrt{k^2 + 4uk}x^{-n} + (-k + \sqrt{k^2 + 4uk})x^n]}{\sqrt{k^2 + 4uk}(k + \sqrt{k^2 + 4uk})} \left[ \sum_{m=n+1}^{L} Q_m x^m \right], \tag{A.17}
\]

while for the sites outside the production area we have

\[
P_{>}^{(s)}(n) = \frac{x^n \left[ (k + \sqrt{k^2 + 4uk}) \sum_{m=0}^{L} Q_m x^m - m + (\sqrt{k^2 + 4uk}) \sum_{m=0}^{L} Q_m x^m \right]}{\sqrt{k^2 + 4uk}(k + \sqrt{k^2 + 4uk})}. \tag{A.18}
\]

The summations over \( m \) can be performed in the following way,

\[
\sum_{m=0}^{L} x^m = \frac{1 - x^{L+1}}{1 - x}; \tag{A.19}
\]

\[
\sum_{m=0}^{L} x^{-m} = \frac{x - x^{-L}}{x - 1}; \tag{A.20}
\]

\[
\sum_{m=0}^{L} m x^m = \frac{x}{d/dx} \sum_{m=0}^{L} x^m = \frac{x - (L + 1)x^{L+1} + Lx^{L+2}}{(1 - x)^2}; \tag{A.21}
\]

\[
\sum_{m=0}^{L} m x^{-m} = -\frac{d}{d/x} \sum_{m=0}^{L} x^{-m} = \frac{-x + (L + 1)x^{-L+1} - Lx^{-L}}{(x - 1)^2}; \tag{A.22}
\]

\[
\sum_{m=0}^{n} x^m = \frac{1 - x^{n+1}}{1 - x}; \tag{A.23}
\]

\[
\sum_{m=n+1}^{L} x^m = \frac{x^{n+1} - x^{L+1}}{1 - x}; \tag{A.24}
\]
Substituting these expressions into Eqs. A.17 and A.18, we obtain for the sites inside the production area,

$$P_{<}^{(s)}(n) = \frac{2Qx^n}{(L+2)(L+1)(k + \sqrt{k^2 + 4uk})} \times \left[ \frac{(k + \sqrt{k^2 + 4uk})(L+2-2n) + (L+1)x^2 + (L - n + 1)x^{-n} - (L + 2)x + (n - L - 1)x^{-n}}{\sqrt{k^2 + 4uk}(x - 1)^2} - (L + 2)x + (n - L - 1)x^{-n} + 2Qx^n[(-k + \sqrt{k^2 + 4uk})(-L+2)x + L + 1 + x^{L+2}]}{(L+2)(L+1)(k + \sqrt{k^2 + 4uk})(x - 1)^2\sqrt{k^2 + 4uk}} \right],$$

(A.29)

while for the outside of the production region we have

$$P_{>}^{(s)}(n) = \frac{2Qx^n}{(L+2)(L+1)(k + \sqrt{k^2 + 4uk})} \times \left[ \frac{(k + \sqrt{k^2 + 4uk})(L+1)x^2 - (L + 2)x + x^L) + (-k + \sqrt{k^2 + 4uk})(-L+2)x + L + 1 + x^{L+2}]}{(x - 1)^2\sqrt{k^2 + 4uk}} \right],$$

(A.30)
The corresponding expressions for local accumulation times for the sites inside the production area can be written as

\[ t_<(n) = \frac{1}{\sqrt{k^2 + 4uk}} \left[ n + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right] \]

\[ + \frac{2uk}{\sqrt{k^2 + 4uk}} \left[ \frac{x^{-L} + (L + 1)x - L - 1 - x^{L+2}}{(k + \sqrt{k^2 + 4uk})\psi + (-k + \sqrt{k^2 + 4uk})\zeta} \right] \]

\[ + \frac{L}{\sqrt{k^2 + 4uk}} \left[ \frac{(x + x^{-L} - 2x^2)(k + \sqrt{k^2 + 4uk}) + (x - x^{L+2})(-k + \sqrt{k^2 + 4uk})}{(k + \sqrt{k^2 + 4uk})\psi + (-k + \sqrt{k^2 + 4uk})\zeta} \right] \]

\[ + \frac{x}{(x - 1)\sqrt{k^2 + 4uk}} \left[ \frac{\xi(k + \sqrt{k^2 + 4uk}) + \chi(-k + \sqrt{k^2 + 4uk})}{(k + \sqrt{k^2 + 4uk})\psi + (-k + \sqrt{k^2 + 4uk})\zeta} \right] \] (A.31)

where we defined new auxiliary functions

\[ \psi = (L + 1)x^2 - (L + 2)x + x^L, \quad \zeta = -(L + 2)x + L + 1 + x^{L+2}, \]

\[ \chi = (2Lx + 2x^{L+2} - 2Lx^2 - 2x^2), \quad \xi = (2Lx^3 - 2Lx^2 + 2x^{-L+1} - 2x). \] (A.32)

Similar calculations for local accumulation time for the region outside of the production area produce

\[ t_>(n) = \frac{1}{\sqrt{k^2 + 4uk}} \left[ n + \frac{2u + k + \sqrt{k^2 + 4uk}}{k + \sqrt{k^2 + 4uk}} \right] \]

\[ + \frac{2uk}{\sqrt{k^2 + 4uk}} \left[ \frac{x^{L+2-2n} + (L + 1)x^2 + (L - n + 1)x^{-n} + (n - L - 1)x^{2-n} - x^{L+2} - L - 1}{(k + \sqrt{k^2 + 4uk})\Omega(n) + (-k + \sqrt{k^2 + 4uk})\zeta} \right] \]

\[ + \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{(k + \sqrt{k^2 + 4uk})\Lambda(n) + (Lx - Lx^{L+2})(-k + \sqrt{k^2 + 4uk})\zeta}{(k + \sqrt{k^2 + 4uk})\Omega(n) + (-k + \sqrt{k^2 + 4uk})\zeta} \right] \]

\[ + \frac{x}{(x - 1)\sqrt{k^2 + 4uk}} \left[ \frac{(k + \sqrt{k^2 + 4uk})\Gamma(n) + (-k + \sqrt{k^2 + 4uk})(2xL - 2x^2(L + 1) + 2x^{L+2})}{(k + \sqrt{k^2 + 4uk})\Omega(n) + (-k + \sqrt{k^2 + 4uk})\zeta} \right], \] (A.33)

where another set of auxiliary function is introduced

\[ \Omega(n) = x^{L+2-2n} + (L + 1)x^2 + (L - n + 1)x^{-n} - (L + 2)x + (n - L - 1)x^{2-n}, \]

\[ \Lambda(n) = Lx + x^{2-n}(n - L - 1)(n - 2) - (L + 2 - 2n)x^{L+2-2n} + n(L - n + 1)x^{-n} - 2Lx^2, \]

\[ \Gamma(n) = 2x^{L+3-2n} + 2(n - L - 1)x^{3-n} + 2Lx^3 + 2(L - n + 1)x^{-n+1} - 2Lx^2 - 2. \] (A.34)
Appendix B

This appendix consists of two sections with explicit formulas for the local accumulation times discussed in chapter 5.

B.1 Local accumulation times for finite interval with local inhomogeneity

The final formulas for LATs have the following forms,

\[
\begin{align*}
t(n) &= T_0 + \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{-2b(m+1)x^{2m+2}(\xi + u\psi) - 2cL\psi x^{2L} + 2Lc^2\xi x^{2L}}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} - n \right] \\
&\quad + \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{c^2x^{2L}(k' - \frac{n}{2} + 2u) - 2nx^{2n}(k' + u(-x) + 2u) + ux^{2m} + ux^{2n+1}}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} \right] \\
&\quad - \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{cux^{2L-1}(2k'mx^{2m+1} - 2k'nx^{2n+1} - 2mux^{2m} + uux^{2m+1})}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} \right] \\
&\quad - \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{bux^{2m+1}(2k'mx^{2m+1} - 2k'nx^{2n+1} - 2mux^{2m} + uux^{2m+1})}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} \right] \\
&\quad - \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{bux^{2m+1}(2mux^{2m+1} - 2ux^{2n+1} + 2ux^{2n+2} + uux^{2n+2})}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} \right] \\
&\quad + \frac{1}{\sqrt{k(k+4u)}} \left[ b^2x^{2m+2}(-2mxx^{2m}(k' - \frac{n}{2} + 2u) + nx^{2n}(k' + u(-x) + 2u) - ux^{2m+1} - uux^{2n+1}) \right] \\
&\quad - \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{cux^{2L-1}(-4kux^{2m+1} - k^2x^{2m+1} + 4kux^{2n+1} + k^2x^{2n+1})}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} \right] \\
&\quad - \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{bux^{2m+2}(-4kux^{2m+1} - k^2x^{2m+1} + 4kux^{2n+1} + k^2x^{2n+1})}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} \right] \\
&\quad - \frac{1}{\sqrt{k(k+4u)}} \left[ \frac{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}}{-bx^{2m+2}(\xi + u\psi) + c^2\xi x^{2L} - cu\psi x^{2L}} \right]
\end{align*}
\]

(B.1)
for \(0 \leq m \leq n\); and

\[
t(n) = T_0 - \frac{1}{\sqrt{k(k + 4u)}} \left[ \frac{(u - ux) u x^{2m-n+1} x^{n-2m} \left(2bnu^2 + 2cLx^{2L}\right)}{u^2 (x^2 - 1) \left(bx^2n + cx^{2L}\right)} \right]
+ \frac{1}{\sqrt{k(k + 4u)}} \left[ \frac{x^{n-2m} \left((-2m + n - 1) \left(\frac{u}{x} - ux\right) x^{2m-n+1} + u \left(x^2 + 1\right) u^{2m-n}\right)}{u (x^2 - 1)} \right]
+ \frac{1}{\sqrt{k(k + 4u)}} \left[ \frac{x \left(\frac{u}{x} - ux\right) \left(dx^{2n} + ex^{2L}\right)}{u (x^2 - 1) \left(bx^2n + cx^{2L}\right)} \right]
\]

(B.2)

for \(m \leq n\); The auxiliary function \(T_0\) is given by,

\[
T_0 = \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{c^2 \left(\mu - u^2\right) x^{2L+m-1} - 2b^2 (m + 1) \chi x^{2m+2}}{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}} \right]
+ \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{-2b^3 (m + 1) x^{2m+2} \left(k' + u(-x) + 2u\right) + b^3 u x^{2m+3} + 2c^2 \mu (L + m) x^{2L+m}}{b^3 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}} \right]
- \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{b^2 x^{2m+2} \left(-2cux^2m \left(k' - \frac{u}{x} + 2u\right) - cu x^{2m-1} + u^2 x\right)}{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}} \right]
- \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}}{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}} \right]
+ \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}}{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}} \right]
\]

\[
+ \frac{1}{\sqrt{k^2 + 4uk}} \left[ \frac{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}}{b^2 x^{2m+2} \left(k' + u(-x) + 2u\right) + b^2 \chi x^{2m+2} - bc \Psi - c^2 \mu x^{2L+m}} \right]
\]

(B.3)

with auxiliary functions \(\Psi, \psi, \xi, \mu, \) and \(\chi\) given by

\[
\Psi = u \left[ x^{2L} \left(-(k' - ux + 2u)\right) + x^{4m+2} \left(-k' + \frac{u}{x} - 2u\right) + u \left(x^{2L} + x^{4m+2}\right) \right]
+ c x^{2L} (k' - ux + 2u)
\]

(B.4)
\[ \psi = k'x^{2m} - k'x^{2n} + ux^{2m} - ux^{2n} - u \] \[ \xi = x^{2m} \left( k' - \frac{u}{x} + 2u \right) - x^{2n}(k' - ux + 2u) \] \[ \mu = ck' - \frac{cu}{x} + 2cu - k'u + \frac{u^2}{x} - u^2 \] \[ \chi = cx^{2m} \left( k' - \frac{u}{x} + 2u \right) + k'u - u^2x + u^2 \]

The constants \( d \) and \( e \) are given below,

\[ d = \frac{2u + k + \sqrt{k^2 + 4uk}}{2\sqrt{k^2 + 4uk}} \]
\[ e = \frac{2u + k - \sqrt{k^2 + 4uk}}{2\sqrt{k^2 + 4uk}} \] (B.9)

**B.2 LATs for finite interval with two different degradation regions**

We obtain following formulas for the local accumulation times,

\[ t(n) = \tau_0 + \frac{1}{\sqrt{k_1^2 + 4uk_1}} \left[ \frac{(m-n)\Delta x_1^{2m-n} + n\Phi x_1^n + m\gamma x_1^{2m-n}x_2^{L-2m-1} + m\delta x_1^{2m-n}}{\Delta x_1^{2m-n} + \Phi x_1^n} \right] 
+ \frac{x_1^n}{\sqrt{k_2^2 + 4uk_2}} \left[ \frac{b_2^{m-n}x_2 - b_2^m(u + b_1)(u + b_2)x_2 + (2L - 2m - 1)\gamma x_2^{2L-2m-1}}{\Delta x_1^{2m-n} + \Phi x_1^n} \right] 
+ \frac{1}{\sqrt{k_2^2 + 4uk_2}} \left[ \frac{(2L - 2m - 1)\gamma x_1^{2m-n}x_2^{L-2m-1} + \delta x_1^{2m-n}}{\Delta x_1^{2m-n} + \Phi x_1^n} \right] 
- \left[ \frac{2x_1^n b_2 d_2 u^2 x_2 - x_1^n x_2 b_2 d_2 (u + b_1) - x_1^n x_2 (u + b_2) (b_2^2 d_1 + 2b_2 d_2 (u + b_1))}{\Delta x_1^{2m-n} + \Phi x_1^n} \right] 
- \left[ \frac{x_1^{2m-n} x_2^{L-2m-1} \Lambda + x_1^{2m-n} \Gamma + x_1^n x_2^{L-2m-1} \Omega}{\Delta x_1^{2m-n} + \Phi x_1^n} \right] \] (B.10)

for \( 0 \leq m \leq n \); and
$$t_>(n) = \tau_0 - \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ x_1 \frac{m_{x_2}}{x_2^{3m+n+1}} \left( m\Phi_c (u - c_1) x_1^{m} x_2^{2L-m-n} + m\Phi_b (u - c_1) x_1^{m} x_2^{n-m} \right) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$- \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ c_2 (b_1 + u) x_1^{m} x_2^{2L+2m+1} \left( \gamma_m x_1^{m} x_2^{2L-2m-1} + \delta_m x_1^{m} \right) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$- \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ (b_1 + u) x_1^{m} x_2^{m+2m+1} \left( \gamma_m x_1^{m} x_2^{2L-2m-1} + \delta_m x_1^{m} \right) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$- \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ \Delta_c (b_1 + u) (2L - m - n) x_1^{m} x_2^{L-m-n} + c_2 \Phi (u - c_1) x_1^{m} x_2^{L-m-n} \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$+ \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ x_1^{m} x_2^{m+2m+1} \left( \Delta_b (b_1 + u) (m - n) x_1^{n-m} + \Phi_b (u - c_1) (m - n) x_1^{n-m} \right) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$+ \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ c_2 (u - c_1) x_2^{2L+2m+1} \left( 2b_2 d_2 u^2 x_2 + x_2 (b_2 d_2 (-b_2 + u)) - (b_2 + u) (2b_2 d_2 (b_1 + u) + b_2 d_1) \right) + \Omega e_{2L-2m-1} \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$+ \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ (u - c_1) x_2^{2m+2m+1} \left( 2b_2 d_2 u^2 x_2 + x_2 (b_2 d_2 (-b_2 + u)) - (b_2 + u) (2b_2 d_2 (b_1 + u) + b_2 d_1) \right) + \Omega e_{2L-2m-1} \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$+ \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ x_1^{m} x_2^{m+2m+1} \left( \Delta_b x_2^{2L-m-n} (c_2 (b_1 + u) + c_2 d_1) + \Phi x_2^{m} (c_2 (u - c_1) - c_2 e_1) x_2^{2L-m-n} \right) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$+ \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ x_1^{m} x_2^{m+2m+1} \left( \Delta_b x_2^{2L-m-n} (c_2 (b_1 + u) + c_2 d_1) + \Phi x_2^{m} (c_2 (u - c_1) - c_2 e_1) x_2^{2L-m-n} \right) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$+ \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ x_1^{m} x_2^{m+2m+1} \left( c_2 (b_1 + u) x_2^{2L-m-n} (\Delta_x^{m} x_2^{2L-2m-1} + \Gamma_x^{m}) + b_2 (b_1 + u) x_2^{n-m} (\Delta_x^{m} x_2^{2L-2m-1} + \Gamma_x^{m}) \right) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$

$$+ \frac{1}{\sqrt{k_1^2 + 4u_k^2}} \left[ (u - 2c_2 L + 2c_2 m + c_2 x_2^{2L-2m-1} - b_2 x_2 + d_2 u x_2 + u e x_2 x_2^{2L-2m-1}) \right] \frac{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}{b_2 u^2 (b_1 + c_1) \left( b_2 x_2^{2m+2} + c_2 x_2^{2L} \right) \left( b_2 x_2^{2n} + c_2 x_2^{2L} \right)}$$
for $m \leq n$; The auxiliary function $\tau_0$ is given by,

$$
\tau_0 = \frac{1}{\sqrt{k_2^2 + 4uk_1}} \left[ \frac{c_1 x_1^m \left( \gamma mx_1^m x_2^{2L-2m-1} + \delta mx_1^m \right) + \Delta c_1 x_1^m}{b_1 \Phi - c_1 \Delta x_1^m} \right]
+ \frac{1}{\sqrt{k_2^2 + 4uk_2}} \left[ \frac{c_1 x_1^m \left( \gamma(2L - 2m - 1)x_1^m x_2^{2L-2m-1} + \delta x_1^m \right)}{b_1 \Phi - c_1 \Delta x_1^m} \right]
+ \left[ \frac{b_1 \Omega x_2^{2L-2m-1} - c_1 x_1^m \left( \Delta x_1^m x_2^{2L-2m-1} + \Gamma x_1^m \right) + d_1 \Phi - \Delta e_1 x_1^m}{b_1 \Phi - c_1 \Delta x_1^m} \right]
+ \left[ \frac{b_1 \left( 2b_2 d_2 u^2 x_2 + x_2 \left( b_2^2 d_2 (- (b_1 + u)) - (b_2 + u) (2b_2 d_2 (b_1 + u) + b_2 d_1) \right) \right)}{b_1 \Phi - c_1 \Delta x_1^m} \right]
$$

(B.12)

with auxiliary functions $\Phi$, $\Delta$, $\Lambda$, $\Omega$, $\gamma$, $\delta$, and $\epsilon$ defined by,

$$
\Phi = b_2 c_2 \left( b_1 c_2 + b_1(-u) + c_2 u \right) x_2^{2L-2m-1} + b_2^2 u^2 x_2 - b_2^2 x_2 (b_1 + u) (b_2 + u)
$$

(B.13)

$$
\Delta = b_2 c_2 \left( c_1(-u) - c_2 u + c_2 c_1 \right) x_1^m x_2^{2L-2m-1} - b_2^2 x_2 x_1^m \left( b_2 c_1 + b_2(-u) + c_1 u \right)
$$

(B.14)

$$
\Lambda = -b_2 c_2 e_1 u - 2b_2 c_2 e_2 u - b_2 c_1 e_2 u + b_2 c_2^2 e_1 + 2b_2 c_1 c_2 e_2 + c_2^2 d_2(-u) - c_1 c_2 d_2 u + c_1 c_2^2 d_2
$$

(B.15)

$$
\Gamma = -2b_2 c_1 d_2 u x_2 - 3b_2^2 c_1 d_2 x_2 + 3b_2^2 d_2 u x_2 - b_2^2 e_1 u x_2 + b_2^3 (-e_1) x_2
$$

(B.16)

$$
\Omega = -b_2 c_2 d_1 u - b_1 c_2 d_2 u + b_2 c_2^2 d_1 + b_1 c_2^2 d_2 + 2b_2 c_2 e_2 u + 2b_1 b_2 c_2 e_2 - b_1 b_2 c_2 u + c_2^2 d_2 u
$$

(B.17)

$$
\gamma = b_2 c_2^2 (-u) - b_2 c_1 c_2 u + b_2 c_1 c_2^2
$$

(B.18)

$$
\delta = -b_2^2 c_1 u x_2 - b_2^3 c_1 x_2 + b_2^3 u x_2
$$

(B.19)

$$
\epsilon = b_2 c_2^2 u - b_1 b_2 c_2 u + b_1 b_2 c_2^2
$$

(B.20)
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