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A comparison of stochastic and deterministic modelling using MesoRD on the Min-system in *E. coli*

Master’s degree project
# Abstract

A comparison of the mesoscopic and macroscopic reaction-diffusion modelling has been performed. The comparison has been done on a full 3D model using Monte Carlo simulation, solving the reaction-diffusion master equation, and deterministic simulation, solving partial differential equations. All simulations were done on the Min-system in *E. coli*. In many cases the stochastic and deterministic simulations has been observed to show similar results, in which the oscillations periods and spatial positioning of the involved proteins are equivalent in the two types of simulations. Differences between the stochastic and deterministic simulation has been observed for *E. coli* mutants with abnormal shape. In these cases the stochastic simulation will show a drift from the pattern observed from deterministic simulations. In the case of a mutant with spherical shape the stochastic simulation shows a behaviour that describes the experimental data better than the deterministic simulation.

# Keywords

Min proteins, macroscopic, mesoscopic, reaction-diffusion simulation

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**Sammanfattning**

När man med hjälp av en dator skall beskriva händelser som en utvald grupp av proteiner deltar i kan olika detaljnivåer i modellbeskrivningen användas. De två beskrivningsmodellerna som används i denna rapport är den makroskopiska och den mesoskopiska. I den mesoskopiska beskrivs alla händelser i systemet, reaktioner mellan molekyler och förflyttningar av molekyler, som slumpändelser där varje händelse har en väldefinierad sannolikhet att ske. I den makroskopiska beskrivningen beskrivs istället flödet av koncentrationen av molekyler i varje punkt i systemet med hjälp av ekvationer för kontinuerliga variabler.

I denna rapport har en jämförelse av dessa två beskrivningar utförts. Systemet som studerades var Min–systemet i den stavformade bakterien *E. coli*. Min–systemet är en av två föreslagna mekanismer för hur cellen hittar sin mittpunkt vid celldelning, i vilken involverade proteiner oscillerar över cellen. Oscillationen skapar en koncentrationsfördelning av involverade proteiner som har sitt minimum på mitten av cellen där celldelning då kan ske. Datorsimuleringar av både den makroskopiska och den mesoskopiska modellbeskrivningen visade att det kan finnas skillnader mellan de två beskrivningarna. Särskilt intressanta skillnader mellan beskrivningarna hittades för två *E. coli* stammar med abnorm cellform: sfäriska celler och långa celler.

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Contents

1 Introduction 3

2 Theory and background 3
  2.1 Reaction–Diffusion Theory 3
  2.2 MinCDE system 7

3 Methods 9
  3.1 Algorithms 9
    3.1.1 Stochastic Methods 9
    3.1.2 Deterministic Methods 13
  3.2 Model 17
    3.2.1 Reactions 17
    3.2.2 Geometries and Initial Conditions 19
  3.3 Software 21
    3.3.1 Deterministic extension of MesoRD 21

4 Results 23
  4.1 Short cylindrical cells 23
  4.2 Wildtype rounded cells 25
    4.2.1 Starting asymmetric 25
    4.2.2 Starting from the middle 25
    4.2.3 Starting symmetric 25
  4.3 Long cylindrical cells 26
    4.3.1 Starting from the middle 26
    4.3.2 Starting symmetric 27
    4.3.3Starting asymmetric 27
  4.4 Long rounded cells 29
  4.5 Spherical cells 30

5 Discussion 32

A Discrete representation of continuous data 37
1 Introduction

Modelling of a reaction–diffusion system can be done in many at different levels of detail. Assuming that the molecule is the smallest entity in the system, different levels of description can be used. On the lowest level, the microscopic level, molecular dynamics can be used to study the Newtonian mechanics of each molecule. Moving up one level of description the mesoscopic level will be entered. In the mesoscopic level there is a main assumption that reactive events for the molecules of interest in the system can be described as jump processes, defined by reaction probabilities, taking the system from one configuration to another. Moving even further to the macroscopic level of modelling the system can be described by concentrations and the change of the system is described by continuous and deterministic differential equations [2].

In this report a comparison between the macroscopic and the mesoscopic levels of modelling will be done for a full three dimensional system where molecules are both allowed to diffuse and react. The model used to do the comparison is the MinCDE system which is involved in the accuracy of the mid–cell division in *E. coli* [20]. The MinD system has been shown to have large spatial oscillations over the cell, making it a good system for comparison, since both the spatial diffusion of the system and the reaction plays vital roles in the overall dynamics of the system.

The comparisons are performed using the newly developed software, MesoRD, which is developed for stochastic reaction–diffusion modelling solving the master equation [17]. To allow for easy and convenient comparison with deterministic simulation MesoRD has been extended to allow for deterministic simulations to be done in the same framework.

2 Theory and background

2.1 Reaction–Diffusion Theory

In this report two different approaches to the reaction–diffusion problem have been used in simulations. The first one, the *mesoscopic* approach, is based on the assumption that the reactions occurs as *Markov* processes. The probability for each reaction can be setup based on the reaction rates for each reaction leading up to description of the time dependent probability distribu-
tion for each possible Markov state. The second approach, the *macroscopic*, is based on the differential equation for the change of concentrations of each molecule species in accordance to both reaction and diffusion. A theoretical layout of both the methods follows below.

**The mesoscopic approach**

Start by forming a state description that only includes the number of molecules of each molecular type represented by the set $X = \{x_i|i = 1\ldots N\}$ where $N$ is the number of different molecule species and $x_i$ is the number of molecules of species $i$. Define a set of reactions, $R = \{r_j|j = 1\ldots M\}$ where $M$ is the total number of reactions, in which each reaction can take the system from one state $X_k$ to a new state $X_l$. If it is assumed that the rate of each of the transition, $X_k \rightarrow X_l$, will depend only on the state $X_k$, known as a Markov property, an equation for the time-dependent probability of being in state $X_l$ can be stated. This equation is known as the *master equation* and states that

$$\frac{dP(X_k,t)}{dt} = \sum_{X_l} W(X_l \rightarrow X_k)P(X_l,t) - \sum_{X_l} W(X_k \rightarrow X_l)P(X_k,t) \quad (1)$$

where $W(X_l \rightarrow X_k)$ defines intensities going from the state $X_l$ to state $X_k$. Looking at the master equation it can be seen that the change in probability depends on the transition intensity jumping into the current state from any other state subtracted by the transition intensity jumping out of the current state. Both of the transitions are then multiplied with the probability of residing in the state from which the transition originated, giving the time dependent change in probability. The actual reactions $R$ will define both the intensity of each transition and also the set of allowed transition for each state [2, 5]. How the transition intensities depend on the reactions and the validity of the Markov property assumption on the transitions will be described in 3.1.1.

The master equation can either be solved analytically for systems including a very limited set of states or, when the state space has high dimension, a single trajectory through the dimensions of the *Markov* space is realised to give an estimate of the solution. The later is described in 3.1.1.

The above description, as already stated, is generally true for homogeneous systems where all reactions are equally probable to occur independent of their location, i.e. the system has to be well-stirred. Since the vast variety
of biologically interesting systems most definitely includes cases where the homogeneity of the system is altered, heterogeneities due to diffusion has to be included into the description.

One way of handling the diffusion problem is to divide the spatial extension of the systems into parts which are small enough to consider the systems to be homogeneous again. These smaller parts are generally called subvolumes (SV). The diffusion is in this case also treated as memoryless jumps, jumping from one subvolume to into the subvolumes next to it. To accommodate for the above described diffusion, the state in the master equation has to be extended in the following way [5]. The new state is described by $X = \{x_i^m | i = 1 \ldots N, m = 1 \ldots L\}$ where N is the number of molecule species and L is the number of subvolumes and where all reactions $i$ are included in every SV $m$. The total state will now include $M \times N$ entities. The state transitions intensities also have to be extended to include the new transitions. Even though the diffusion extension will not change the general description of the master equation, the set of possible transitions for each state in the Markov space will be increased including all possible reactions $N$ and all possible diffusion neighbours. In other words, leaving the well-stirred system increases the dimensionality of the problem quite dramatically.

The macroscopic approach

Reverting to the homogeneous case, the macroscopic approach defines the number an average concentration of each molecule species, $x_i$ over the system volume $\Omega$ as $c_i = x_i/\Omega$. Using the average yields an continuous description of the state. This is in comparison to the mesoscopic approach where each molecule is represented as an entity and the state vector therefore only includes integer numbers.

The macroscopic description rests on the chemical observation that the rate of a reaction is proportional to the concentration of each molecule species involved. This description naturally leads to a description of the change of each of the involved molecule species as continuous derivatives described in a general form below for the molecule species $i$

$$\frac{dc_i}{dt} = \sum_{j=1}^{M} \nu_{ij}k_jf_j(c)$$

(2)

where $M$ is the number of reactions, $\nu_{ij}$ is the stoichiometric coefficient for molecule species $i$ in reaction $j$, $i = 1 \ldots N$ — where $N$ is the number of
molecule species — and \( f_j \) is a function of the set of concentrations of the different molecule species participating in reaction \( j \).

To add diffusion to the macroscopic description, the flux of molecule \( i \) has to be added to the description. If the solution is dilute (that is, the diffusion of molecule \( i \) will not be affected by molecule \( j \)) the flux is proportional to the derivative of the concentration leading up to Fick’s first law that states

\[
  j_i = -D_i \nabla c_i \tag{3}
\]

where \( j_i \) is the flux of molecule species \( i \), \( c_i \) is the concentration of molecules species \( i \) and \( D_i \) is the diffusion constant.

In extending the description a total change of the system inside the volume \( \Omega \) can be written as

\[
  \left( \frac{dc_i}{dt} \right)_{\text{tot}} = \left( \frac{dc_i}{dt} \right)_{\text{reaction}} + \left( \frac{dc_i}{dt} \right)_{\text{diffusion}} \tag{4}
\]

where \( \left( \frac{dc_i}{dt} \right)_{\text{reaction}} \) describes the change of concentration due to reactions inside \( \Omega \) (described by equation 2) and \( \left( \frac{dc_i}{dt} \right)_{\text{diffusion}} \) is the change due to the flux of molecules over the surface bounding the volume \( \Omega \). Using Gauss divergence theorem the total flow over the boundary of the volume, as described by an surface integral of the flux, can be rewritten as a volume integral over the divergence of the flux. This leads to

\[
  \left( \frac{dc_i}{dt} \right)_{\text{tot}} = \left( \frac{dc_i}{dt} \right)_{\text{reaction}} - \text{div} \ j_i \tag{5}
\]

where \( j_i \) describes the flux in each point in the volume \( \Omega \).

Inserting 2 and 3 into 5 yields

\[
  \left( \frac{dc_i}{dt} \right)_{\text{tot}} = \sum_{j=1}^{M} \nu_{ij}k_j f_j(\{c\}) + D_i \nabla^2 c_i \tag{6}
\]

where the assumption that \( D_i \) is constant over the volume has been used, which allows the rewriting \( \text{div}D_i \nabla c_i = D_i \nabla^2 c_i \) [22].
Validity of the meso- and macroscopic approach

It has been shown by Baras et al. by comparing spatial correlation of molecule densities for simulation data from mesoscopic simulations — solving the master equation — and microscopic simulations— using molecular dynamics to follow the movement of each molecule — that the two simulations are in good agreement as long as the subvolume sizes are in the order of the reaction mean free path — the mean distance covered by a particle between two reactive events. The above thus states that the Markov property of the reactions is a good assumption as long as the cell sizes are in the range of the mean free path [2].

For homogeneous systems it has been shown by Kurtz that the mesoscopic approach will converge to the macroscopic approach in the limit of infinite volumes for a finite time, at least for reactions with linear dependency on the state variables, as long as the systems are started from the same initial conditions. [19].

The analysis by Kurtz has been extended to heterogeneous systems and it has been shown [1] that the above statement is true for the heterogeneous systems as long as the following conditions are fulfilled: The systems need to be started from the same initial conditions; both the size of the system, \( L \), and the size of the subvolume, \( l \), need to increase towards infinity keeping the relation \( L^2/l^{3d} \), where \( d \) is the dimensionality of the system; the diffusion transition intensity needs to fulfil the relation \( D'/2 = DN^2 \) where \( D' \) is the transition intensity for the stochastic system, \( D \) is the diffusion constant and \( N \) is the number of subvolumes defined as \( N = L/l \), i.e. \( D' \) needs to go fast to infinity with increasing system size. Stating the obvious: These restrictions are quite hard to fulfil in real biological systems.

2.2 MinCDE system

There are two major components that have been shown to affect the position of the middle in \( E. coli \) in cell division. The first is the nucleoid occlusion, which prevents cell division in the vicinity of the nucleoid and the second is the MinCDE system, which have three protein components: MinC, MinD and MinE [21]. A short description of the characteristics of the MinCDE systems is given below, trying to summarise the knowledge needed for the connection of simulation data to experimental data.

The position of the protein MinC has been shown to have direct effect on the formation of the FtsZ-ring. FtsZ is a protein which forms a polymer
structure, the FtsZ–ring, that is directly involved in the physical division the cell. In vitro it has been shown that MinC interacts with FtsZ and that it can decrease the polymerisation rate [12, 14]. Over expression of MinC in vivo has been shown to induce formation of long undivided cells [14] and mutation in the MinC protein has been shown to induce minicelling, cells that divide away from the middle causing the daughter cells to be unequal in size [13].

The MinC has been observed to oscillate over a E. coli cells showing high resemblance to the oscillation also observed for MinD. The oscillation of MinC is dependent on both MinD and MinE [25]. Lack of MinD protein will cause the MinC to occupy the entire membrane giving rise to long cells which are unable to divide [11], a result in agreement with the result above for MinC interaction with FtsZ polymerisation.

The oscillation of MinD is dependent on MinE, in which MinE induces ATP hydrolysis of ATP bound to MinD in the presence of phospholipids in vitro [13, 15]. Lack of MinE will cease the oscillation of MinD causing the MinD to be distributed over the entire membrane. MinD assembles on the membrane in the absence of MinE and MinC in vivo [25] and has in vitro been shown to bind to phospholipids in the presence of of ATP[15]. The pattern of the MinD oscillation has been observed as follows: First a polar zone of MinD molecules will appear. This zone stretch from the end of the cell to somewhere close to the middle of the cell. After the polar zone appear it will start to shrink towards the end of the cell. The shrinking leads to a high concentration of MinD at the pole and while this pole zone is disappearing a new zone will form on the opposite side of the cell and the pattern will start over again [13, 25]. The MinD/E oscillation is summarised in Figure 1.

The initial polar zone has been observed to be altered in some mutants, giving MinD zones that stretches beyond the middle of the cell [26].

MinE has been observed to form rings which appear adjacent to the MinD polar zone. In wildtype cells the MinE ring will appear close to the cell middle. The MinE ring follows the rim of the MinD zone of the MinD oscillation as the zone shrinks towards the end of the cell. [27].

As stated above, mutations in the FtsZ gene will produce phenotype in which the cells grow very long since they are unable to divide. The oscillation of MinE and MinD has been shown to sustain in these longer cells [24, 23]. The oscillation will show a different characteristic though, which has not been observed in wildtype. The oscillation will be divided into several oscillating segments within the long cell, showing a zebra pattern in MinD concentration.
on the membrane. The zebra pattern will oscillate in accordance with the oscillation for wildtype cells, where the zone of MinD and the MinE ring will appear at different locations in the cell.

For *E. coli* cells with a mutation leading to a spherical shape the MinD oscillation pattern has been shown to change. The oscillation will not have a natural long–axis to follow instead the oscillation will move in a more random way picking new zones without following any distinct pattern [3].

### 3 Methods

#### 3.1 Algorithms

As stated in section 2.1 there are (at least) two ways to solve Reaction–Diffusion systems in time. The first method, the mesoscopic approach, will in most algorithms use a Monte–Carlo method to find one possible trajectory of the system. The second method, the macroscopic approach, solves the differential equations numerically. Given the fact that the macroscopic approach gives the same result in every run (as compared to the stochastic methods) it is here called a deterministic method.

##### 3.1.1 Stochastic Methods

Returning the attention to the homogeneous master equation defined in section 2.1 and especially how the set of reactions, $R$, affect the transition intensities $W$. This section will start by describing Monte Carlo algorithms for sampling of the Markov process described by the homogeneous master equation. The transition intensities defines the probability per time unit that
the state $X_l$ will change into some other state. Using the macroscopic description, which defines reaction rates stating the fraction of collisions that are reactive, the actual number of state transitions is known given that the concentration is known. Since the master equation is restrained to Markov processes the transitions intensities are set to time independent constants in the calculations below.

As stated in section 2.1 the main idea behind the Monte–Carlo method is to follow one trajectory through the Markov state space. The result of this is that the master equation defined in equation 1 is reduced to

$$\frac{dP(X_k, t)}{dt} = -\sum_{X_l} W(X_k \rightarrow X_l) P(X_k, t)$$

(7)

where the probability of being in any other state then $X_k$ is zero, since only one trajectory is followed. The expression in equation (7) can be solved as an ordinary differential equation, giving the probability of still being in $X_k$ at time $t = \tau$ if it was in $X_k$ at time $t = 0$

$$P(X_k, \tau) = \exp \left[ -\sum_{X_l} W(X_k \rightarrow X_l) \tau \right]$$

(8)

The cumulative distribution function for reaction times, describing the probability that the reaction has occurred for time less than $\tau$, then becomes

$$F(\tau) = 1 - P(X_k, \tau)$$

(9)

this gives the probability function for reaction times as

$$f(\tau) = \sum_{X_l} W(X_k \rightarrow X_l) \exp \left[ -\sum_{X_l} W(X_k \rightarrow X_l) \tau \right]$$

(10)

The joint probability for reaction $X_k \rightarrow X_l$ will occur at time $\tau$ is given by

$$P(X_k \rightarrow X_l, \tau) = W(X_k \rightarrow X_l) P(X_k, \tau)$$

(11)

According to the rules of total probability the joint probability for reaction $W(X_k \rightarrow X_l)$ at time $\tau$ can be rewritten as

10
\[ P(X_k \rightarrow X_l, \tau) = P(X_k \rightarrow X_l|\tau)P(\tau) \] (12)

where the probability distribution function in equation 10 is used to calculate an expression for the conditional probability for reaction \( X_k \rightarrow X_l \) at time \( \tau \).

Based on the probabilities above there are two commonly used algorithms to sample the time evolution in the Markov space.

**Direct Method**

This method will first find at what time the next reaction will occur and then find the reaction which occurred. This is realised in the following steps [7].

- Sample a transition time from equation 9 according to 
  \[ t = -(\ln \text{rand})/\sum_{X_l} W(X_k \rightarrow X_l). \]
- Sample the reaction according to the probability 
  \[ P(X_k \rightarrow X_m|t) = W(X_k \rightarrow X_m)/\sum_{X_l} W(X_k \rightarrow X_l) \]
  according to equation 12.
- Update the time and the state according to the two steps above and restart.

**First–Reaction Method**

This method calculates the time until each reaction assuming that no other reaction occurred first. Thereafter the reaction that has the lowest next transition time is selected for transition[7].

Under the assumption that it is known which reaction that occurs first the probability of being in state \( X_k \) will only depend on the known transposition \( X_k \rightarrow X_m \). Under the above assumption the probability of being in state \( X_k \) can be stated as

\[ P(X_k, \tau) = \exp [-W(X_k \rightarrow X_m)] \] (13)

leading the a cumulative distribution function for the reaction time as

\[ F(\tau) = 1 - \exp [-W(X_k \rightarrow X_l)\tau] \] (14)

since the probability that no reaction has occurred until time \( \tau \) will have to include that the known reaction \( X_k \rightarrow X_m \) has not occurred.
The algorithm states the following. In each step, sample the reaction time for each possible reaction according to

\[
    t_m = -\frac{\ln(rand)}{W(X_k \rightarrow X_m)} \tag{15}
\]

where \( m = 1 \ldots M \) and \( M \) is the number of reactions. Thereafter pick the reaction that will occur first. Perform the selected reaction. Update the time and the state according to the selected reaction. Restart the algorithm.

Neither the Direct Method nor the First–Reaction Method will scale very well for large systems leading the unrealistic simulation times for systems that either includes a lot of reactions or needs to be defined to include diffusion. A new algorithm presented by Gibson and Bruck [6] can handle a larger amount of reactions efficiently but is still restricted to homogeneous systems\(^1\).

Here an algorithm called the Next–SubVolume Method is used[4]. This algorithm efficiently handles inhomogeneous systems allowing both diffusion and reactions to occur. The method divides the spatial dimensions into subvolumes and uses data structures and algorithms highlighted in the Gibson and Bruck paper [6] to quickly find the appropriate subvolume. The algorithm is described below.

**The Next–SubVolume Method(NSM)**

Define a set of subvolumes \( \{SV_m | m = 1 \ldots L \} \) \(^2\) where \( L \) is the number of subvolumes. In each subvolume two things can occur: a reaction event or a diffusion event. Define a set of reaction intensities \( \{a_q^m(\{x_r^m\})\} \) where all \( a_q^m \) and \( x_q^m \) belong to \( SV_m \) and \( q = 1 \ldots Q(m) \) and \( Q(m) \) is the number of reactions available in \( SV_m \). Every subvolume also has a set of diffusion intensities in the direction of each neighbour subvolume \( \{d_r^m(\{x_r^m\})\} \), \( r = 1 \ldots P(m) \) where \( P(m) \) is the number of neighbours to \( SV_m \). Define the total reaction rate and the total diffusion rate for each \( SV_m \) as

\[
    A_m = \sum_q a_q^m(\{x_r^m\})
\]

\(^1\) Or more correct, it was optimised to handle large amount of reactions.
\(^2\) With properties as described in section 2.1.
\( D_m = \sum_r d_r^m(\{x_r^m\}) \)

Using the ideas developed for the First–Reaction–Method the reaction time for each subvolume can be sampled by

\[ t_m = -\frac{\ln(\text{rand})}{D_m + R_m} + t_{\text{current}} \]

where the addition of \( t_{\text{current}} \) represents the current time for the system. Switching from relative time (between reactions) to absolute time will obviate recalculation of reaction times for subvolumes where no reaction occurred [6].

Using one of the efficient data structures highlighted by Gibson and Bruck [6] the subvolumes are stored in a binary tree sorted by the \( t_m \) for each subvolume. Here follows the necessary steps in each iteration.

1. Pick the subvolume where the next event will occur, i.e., the subvolume with the lowest \( t_m \).
2. Decide if the next event is a reaction or a diffusion event. Using the methods outlined for the Direct Method, the probability for a reaction event can be sampled from the probability function \( P(\text{reaction}) = \frac{R_m}{R_m + D_m} \).
3. If a reaction occurred choose which reaction according to \( P(q) = \frac{a_q^m}{R_m} \). If a diffusion occurred choose a diffusion direction according to \( P(r) = \frac{d_r}{D_m} \).
4. Recalculate the event times for the involved subvolume(s).
5. Restart.

### 3.1.2 Deterministic Methods

Before reading this section it should be noted that the set of partial differential equations (PDE) resulting from the macroscopic reaction–diffusion equation has been rewritten as ordinary differential equations (ODE) using the method of lines [8]. All the time integration is therefore performed using ODE:s. See section 3.3.1 for details.

There are many different methods for solving ordinary differential equations. Here I will present the methods that are used in the extension to the MesoRD
software. The numerical methods used can be found in books on the subject\textsuperscript{3}[8]. The notation is made to coincide with the notation used in section 2.1 for the first two sections, thereafter a shorter notation is used.

**Euler Forward**

The simplest of methods for solving ODE:s numerically is the Euler Forward methods, which states

\[ x_i^{k+1} = x_i^k + \frac{dx_i^k}{dt} \Delta t \] (16)

where \( \Delta t \) is the timestep used, \( x_i^k \) is the state of the molecule \( i \) in step \( k \) and \( \frac{dx_i^k}{dt} \) is the derivate for the state in step \( k \) of the algorithm.

The Euler Forward method is easy to both understand and implement but the usefulness is limited by the fact that the method has a small stability region and that the accuracy only improves linear with decreasing step size.

**Euler Backward**

The Euler Backwards method states that

\[ x_i^{k+1} = x_i^k + \frac{dx_i^{k+1}}{dt} \Delta t \] (17)

where the parameters are the same as for Euler Forward. The new state \( x_i^{k+1} \) depends not only on the state \( x_i^k \) but also on the state \( x_i^{k+1} \). Methods sharing this feature are called *implicit methods*, while methods that do not depend on information from the \( k + 1 \) step are called *explicit methods*. For implicit methods an equation has to be solved to determine the new state or if the number of molecule species are more than one, a systems of equations.

The Euler Backwards is stable for all choices of stepsize. The accuracy is only improved linearly with decreasing stepsize, but can be improved to second order using the Trapezoid Rule giving the following scheme

\[ x_i^{k+1} = x_i^k + \frac{1}{2} \left( \frac{dx_i^k}{dt} + \frac{dx_i^{k+1}}{dt} \right) \Delta t \] (18)

\textsuperscript{3}The proper choice of methods are not given in books. Great help has been given by Prof. Per L"otstedt in this subject.
For the more complicated methods the notation is switched to a shorter style in which \( y_k \) represents the current state, \( y_k' \) the time derivative for state \( k \) and the timestep is represented by \( h \).

**Runge–Kutta (the 4th order)**

The classical Runge–Kutta method uses first derivatives at points in between the current and the next timestep. The Runge–Kutta methods of 4th order is implemented in the deterministic extension and therefore included in the report. One step of the method is defined by

\[
y_{k+1} = y_k + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)
\]  

(19)

where

\[
\begin{align*}
k_1 &= y_k' h_k \\
k_2 &= y_{k+\frac{1}{2}}' h_k \\
k_3 &= y_{k+\frac{3}{2}}' h_k \\
k_4 &= y_{k+1}' h_k
\end{align*}
\]

**Backward Differentiation Formula**

There is a family of methods called linear multi-step methods. The linear multi-step methods use information from earlier time points when the next state in the new time point is calculated.

Linear multi step methods have the form

\[
y_{k+1} = \sum_{i=1}^{n} \alpha_i y_{k+1-i} + h \sum_{i=0}^{n} \beta_i f(t_{k+1-i}, y_{k+1-i})
\]  

(20)

Using \( \alpha_1, \alpha_2 \) and \( \beta_0 \) you will get a Backward Differentiation Formula (BDF) of the second order (BDF2), which has the form

\[
y_{k+1} = \frac{4}{3}y_k - \frac{1}{3}y_{k-1} + \frac{2}{3}y_{k+1}' h
\]  

(21)

**Iterative Methods, especially Conjugate Gradient (CG)**

A common way of solving large systems of equations — for example the systems of equations resulting from the implicit methods — is to use an iterative method instead of solving the systems of equations directly.
Define a system of equations on a general form, $Ax = b$. The heart of the iterative methods is to first make an initial guess of the solution, $x_0$, and then refine the solution iteratively by applying transformations, which make the solution more and more accurate. The iteration is terminated when appropriate convergence is reached.

Since the method used in this report is the conjugate gradient method it will be described below. Begin by assuming that $A$ is a symmetric positive definite matrix$^4$. If $A$ is symmetric positive definite then the function

$$F(x) = \frac{1}{2}x^T Ax - x^T b$$

will attain a minimum at $Ax = b$. The resulting optimisation problem can be solved by doing a iterative line search in one dimension, minimising the function $F$. Stated more mathematically: Define a search along a line $x_{k+1} = x_k + \alpha s_k$ where $\alpha$ is chosen to minimise $F(x_{k+1})$. Using the knowledge of the function $F$ it is possible to derive an optimal $\alpha$ in one step and obviate the need for iterations. Optimal $\alpha$ is chosen such that

$$0 = \frac{d}{d\alpha} F(x_{k+1})$$
$$= \nabla F(x_{k+1}) \frac{d}{d\alpha} x_{k+1}$$
$$= (Ax_{k+1} - b)^T \left[ \frac{d}{d\alpha} (x_k + \alpha s_k) \right]$$
$$= -r_{k+1}^T s_k$$

where the chain rule has been used in the second equality, the fact that $-\nabla F(x) = b - Ax$ in the third and $r = b - Ax$ in the fourth. An expression for $\alpha$ can now be derived using the relation that

$$r_{k+1} = r_k - \alpha As_k.$$  

Inserting equation (24) into equation (23) yields an expression for $\alpha$

$$\alpha = \frac{r_k^T s_k}{s_k^T As_k}$$

$^4$In section 3.3.1 it will be shown that this is a good assumption.
Now all the tools to make the iterative equation solver work are at hand.

1. Calculate $\alpha_k$ according to equation (25).

2. Calculate $x_{k+1}$ according to equation (22).

3. Calculate $x_{r+1}$ according to equation (24).

4. Rescale the search direction according to $s_{k+1} = r_{k+1} + \beta_{k+1}s_k$ where $\beta_{k+1} = (r_{k+1}^Tr_{k+1})(r_{k}^Tr_k)$.

5. Goto 1.

### 3.2 Model

#### 3.2.1 Reactions

Many different models have been suggested to describe the oscillating behaviour of the MinCDE-system\cite{9, 10, 18}. The model presented below is a model suggested by Huang et al. \cite{16}.

Most models describing the MinCDE oscillations will exclude the MinC molecules, since they have been shown co-oscillate with the MinD proteins and do not seem to have any effect on the oscillatory behaviour of the MinD and MinE proteins. \cite{11, 24} The model described below makes no exception to this rule.

The model is described by reactions R1–R6 seen in Table 1, where $d$ and $de$ are concentrations of MinD and MinD-MinE complex on the membrane and $D_{ATP}$, $D_{ADP}$ and $E$ are MinD in ATP-form, MinD in ADP-form and MinE in the cytoplasm.

| R1: $D_{ATP} \xrightarrow{\sigma_D} d$ | R2: $E + d \xrightarrow{\sigma_E} de$ |
| R3: $de \xrightarrow{\sigma_{de}} E + D_{ADP}$ | R4: $D_{ADP} \xrightarrow{\sigma_{DADP\rightarrow ATP}} D_{ATP}$ |
| R5: $de + D_{ATP} \xrightarrow{\sigma_{dD}} d + de$ | R6: $d + D_{ATP} \xrightarrow{\sigma_{dD}} 2d$ |

Table 1: Reaction used in simulations.
R1 describes the association of MinD molecules to the membrane. R2 is the forming of the complex between MinD and MinE on the membrane. R3 is the hydrolysis of the MinD in ATP form to ADP form on the membrane resulting in the release of MinD and MinE into the cytoplasm. R4 is the regeneration of the MinD ATP form in the cytoplasm through nucleotide exchange. R5 describes the fact that free MinD molecules can bind to MinD-MinE complexes on the membrane. R6 states that MinD molecules seem to be able to bind free MinD molecules cooperatively to already existing MinD molecules on the membrane. The reactions are summarised in Figure 2.

\[
\begin{align*}
&D\rightarrow\text{ATP} \quad \text{R1} \\
&D\text{--ATP}\rightarrow\text{ADP} \quad \text{R2} \\
&D\text{ATP} \quad \text{R3} \\
&D\text{ATP} \quad \text{R4} \\
&D\text{ATP} \quad \text{R5} \\
&D\text{ATP} \quad \text{R6}
\end{align*}
\]

Figure 2: Overview of Reactions 1 to 6.

The reaction rate constants used, unless otherwise stated, can be seen in Table 2. These reaction rates are the same as the reaction rates used by Huang et al. [16].

<table>
<thead>
<tr>
<th>Constant</th>
<th>Value (unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\sigma_D)</td>
<td>(0.5 \text{ (s}^{-1})</td>
</tr>
<tr>
<td>(\sigma_E)</td>
<td>(5.58 \times 10^7 \text{ (M}^{-1}\text{s}^{-1}))</td>
</tr>
<tr>
<td>(\sigma_{de})</td>
<td>(0.7 \text{ (s}^{-1})</td>
</tr>
<tr>
<td>(\sigma_{ADP\rightarrow ATP})</td>
<td>(1.01 \text{ (s}^{-1})</td>
</tr>
<tr>
<td>(\sigma_{dD})</td>
<td>(9 \times 10^5 \text{ (M}^{-1}\text{s}^{-1}))</td>
</tr>
</tbody>
</table>

Table 2: Reaction constants used in simulations.

The model also allows the molecules to diffuse inside the cell, but not when bound to the membrane. The diffusion constants used in simulations are \(D_{\text{cytosole}} = 2.5 \times 10^{-8} \text{cm}^2\text{s}^{-1}\) and \(D_{\text{membrane}} = 0.01 \times 10^{-8} \text{cm}^2\text{s}^{-1}\), where \(D_{\text{membrane}}\) is the diffusion constant for all molecules that are membrane bound and \(D_{\text{cytosole}}\) is the diffusion constant for all molecules not bound to the membrane.

5Cooperative binding to a (presumably) short lived complex seems unlikely and no evidence for it has been found in literature. It can be that the model will produce oscillations without R5.

18
Subvolume discretization is done by dividing the cell into cubic subvolumes of side length $0.05\mu m$ using regular Cartesian coordinates in 3 dimensions.

In deterministic simulations the BDF2 method is used together with the CG method. The convergence criteria used for CG is that the difference of the 2-norm of the residual between two steps must be less than $10^{-6}$. The stepsize in BDF2 is $2 \times 10^{-3}$ seconds. These conditions apply unless otherwise stated.

Simulations done by Huang et al. [16] have shown oscillations for MinD and MinE molecules using the model described above. All simulations done by Huang et al. are for cylinder shaped cells (see section 3.2.2 for definitions of different cell shapes). The oscillations frequency has been shown to match with experimental results [24] with period time of around 40 seconds for cell of length 4 $\mu m$, starting with 4000 MinD molecules and 1400 MinE molecules. The oscillation period was shown to be proportional to the initial MinD concentration and inverse proportional to the MinE concentration. The simulations also showed the doubled pattern (the pattern is doubled in comparison to the regular oscillations in wildtype cells, three zebra stripes in the terminology from section 2.2) described in section 2.2 for cells of length 10 $\mu m$.

3.2.2 Geometries and Initial Conditions

Below follows a list of the geometries used in simulations. All cells are divided into two compartments, one compartment is the cytosole and the other is the membrane. Intersections with a plane in the middle of the cell is shown in Figure 3.

Short Cylindrical Cells Cell shaped as a cylinder, with length 4.1 $\mu m$ and radius 0.5 $\mu m$. The cytosole is of length 4.0 $\mu m$ and radius 0.45 $\mu m$. The rest of the cell is the membrane. The initial amount of MinD and MinE is 4000 and 1400 respectively. The number of subvolumes after discretization was 25912. (Figure 3(a), $L=4.1 \mu m$, $d=1.0 \mu m$).

Long Cylindrical Cells The configuration is the same as for the Short Cylindrical cell, except that the cell is of length 10.1 $\mu m$. The cytosole is of length 10.0 $\mu m$. The rest of the cell is the membrane. The initial amount of MinD and MinE is 10000 and 3500 respectively. The number of subvolumes after discretization was 63832. (Figure 3(a), $L=10.1 \mu m$, $d=1.0 \mu m$).

Wt Rounded Cells Consists of a cylinder of length 3.5 $\mu m$ and radius 5
$\mu m$ and two half spheres with radius $5\, \mu m$ attached to either side of the cylinder. The cytosole is a cylinder of length $3.5\, \mu m$ with radius $4.5\, \mu m$ with half spheres with radius $4.5\, \mu m$. The rest of the cell is the membrane. The initial amount of MinD and MinE is 4000 and 1400 respectively. The number of subvolumes after discretization was 26344. (Figure 3(b), $L=4.1\, \mu m$, $d=1.0\, \mu m$).

**Long Rounded Cells** The configuration is the same as for the small rounded cell except that the cylinder is of length $9.5\, \mu m$. The initial amount of MinD and MinE is 10000 and 3500 respectively. The number of subvolumes after discretization was 64264. (Figure 3(a), $L=10.1\, \mu m$, $d=1.0\, \mu m$)

**Spherical Cells** Cells that are spheres with a radius of $0.95\, \mu m$. The cytosole is a sphere with radius $0.85\, \mu m$. The rest of the cell is the membrane. The initial amount of MinD and MinE is 5000 and 1250 respectively. (Figure 3(c), $r=0.95\, \mu m$). For spherical cells reaction 5 has not been used, due to the fact that the simulation would not show any oscillations with the original setup of reaction and reaction constants. Removing reaction 5 and tweaking the initial concentrations produced oscillations in both spherical and wildtype rounded cells (no results are shown for the later case). The number of subvolumes after discretization was 28768.

Here is also a list of the initial conditions used in the simulation.

**Asymmetric** For all geometries except the spherical one the MinE molecules are located in a box with side lengths $0.4\, \mu m$ positioned at $0.5\, \mu m$ deviation from the middle along the long–axis of the cell and in the middle in the other two dimensions. For spherical geometries the MinE molecules are located in a sphere with radius $0.25\, \mu m$ positioned at $0.3\, \mu m$ deviation from the middle along one of the axis in the 3D space and in the middle in the other two dimensions.

**Symmetric** MinE molecules are located uniformly throughout the entire cytosole.

**Middle** As the asymmetric case with the exception that the box and the sphere are positioned at the middle of the cell in all dimensions.

The MinD molecules are always distributed uniformly in the membrane.

---

6Uniform in the stochastic case is defined as randomly chosen subvolumes during distribution of molecules in the geometry.
Figure 3: Overview of the different cell shapes. Shapes are presented as plane intersection through the middle.

### 3.3 Software

The software used in all simulations is MesoRD [17], which has been extended to include the possibility to do deterministic simulations.

MesoRD can parse model description files written in SBML with extension to handle geometries. In SBML reactions and molecules can be defined and in the geometric extension compartments with diffusion can be defined. MesoRD will make discretization of the compartments into cubic subvolumes as defined by the NSM (see section 3.1.1).

#### 3.3.1 Deterministic extension of MesoRD

The deterministic extension uses the existing model–parsing system of MesoRD to extract the current state of the system when the simulation is started. The state is stored in a vector $Y$, which includes all elements in the set $\{x_i^m\}$, $i = 1 \ldots N$, $m = 1 \ldots L$ where $N$ defines the number of molecule species in each subvolume and $L$ is the number of SV:s in the system. Note that $N$ does not necessary need to be the same for all SV:s but it is so in the software, due to ease of implementation.
Since the NSM defines the diffusion intensities for each subvolume, this information can be extracted from the model description. Resting on the fact that the state is defined as a vector where each element represents a certain molecule species in a certain subvolume, a matrix containing the diffusion rates can be extracted, $D$. Multiplying the diffusion rate matrix with the current state will yield a vector containing the change of state in accordance to the diffusion. It can be noted that the random walk approximation of diffusion done in the NSM will result in the Laplacian discretization often used for approximation of the spatial second derivatives. Note further that the above precalculation of the second order spatial derivatives will transform the reaction–diffusion PDE into an ODE, since no spatial dependency is left in the problem. This method is known as the method of lines [8].

The extension also extracts a vector describing the state change due to reactions, $R(Y)$. The total change to the system in each timestep can therefore be described by

$$\Delta(Y) = D \times Y + R(Y)$$  \hspace{1cm} (26)

The division of the state–change vector into a diffusion and a reaction part is used in the implicit methods, where a system of equations has to be solved in each step. If the problem is not divided the system of equations needed to perform time stepping in implicit methods will be nonlinear, due to the unknown change of the reaction part $R(Y)$. To avoid solving nonlinear systems of equations, either the reaction and diffusion can be done in separate steps in or in one step estimating the reaction derivatives.

In the one step approach the reaction derivatives in the next coming step is extrapolated using earlier reaction derivatives.

Using the separation of the two terms of the derivative, the algorithm used for BDF can be extracted as follows

$$y_{k+1} = \frac{4}{3} y_k - \frac{1}{3} y_{k-1} + \frac{2}{3} (y_{k+1})h$$  \hspace{1cm} (27)

$$y_{k+1} - \frac{2}{3} D y_{k+1} h = \frac{4}{3} y_k - \frac{1}{3} y_{k-1} + \frac{2}{3} R(y_{k+1})h$$  \hspace{1cm} (28)

$$\frac{3}{2} (1 - Dh) y_{k+1} = 2 y_k - \frac{1}{2} y_{k-1} + 2R(y_k)h - R(y_{k-1})$$  \hspace{1cm} (29)
In the last step the value in the point $R(y_{k+1})$ has been extrapolated by $2R(y_k) - R(y_{k-1})$.

In the two step approach the change due to diffusion is applied to the system first using an implicit method and afterwards the system is updated due to reactions using an explicit method giving the following algorithm for the BDF:

$$\frac{3}{2}(1 - Dh)y_{k+1}^{diff} = 2y_k - \frac{1}{2}y_{k-1}$$  \hspace{1cm} (30)

$$y_{k+1} = y_{k+1}^{diff} + R(y_k)h$$  \hspace{1cm} (31)

where $y_{k+1}^{diff}$ is updated value due to diffusion and Euler Forward has been used as the explicit method for the reaction step.

The one step approach with extrapolation of the reaction derivatives has been used in all simulations.

4 Results

4.1 Short cylindrical cells

Simulations of short cylindrical cells can be seen in Figure 4 where 2D projections of the different molecules involved are shown for a subset of simulated time points. For short cylindrical cells both the stochastic and the deterministic simulations show regular oscillations of both the MinD polar zone and a following zone of membrane (complex) bound MinE molecules. Both the deterministic and the stochastic simulation have the same period and have tight gathering of the membrane bound MinD molecules on the end-disc of the cylinder. The MinE molecules are following the zone of the MinD molecules as it shrinks towards the pole. The MinE molecules are almost totally bound into complex with MinD on the membrane (Figure 4(e) and Figure 4(j)). Both MinD in ATP form and MinD in ADP form have a high presence in the cytosole ( Figure 4(c), 4(h), 4(d) and 4(i)).
Figure 4: 2D projection of MinD (membrane bound (a) and (f) in ATP-form (c) and (h) in ADP-form (d) and (i)) and MinE (free ((e) and (j), complex bound (b) and (g)) in cells of 4 µm and with cylindrical shape. (a) - (e) show stochastic simulations and (f) - (j) show deterministic simulations. In Figures (f) - (j) the continuous distribution of molecules has been represented by a discrete distribution (see Appendix A). The time is incremented with 5 seconds between each picture.
4.2 Wildtype rounded cells

4.2.1 Starting asymmetric

Simulations with the wt rounded cells (Figure 5) gives oscillations much like the oscillations for the cylinders described in section 4.1. The oscillation has a somewhat shorter period then the cylindrical counterpart. The rounded cell also has more spatially extended polar zones of MinD molecules than the cylindrical simulations.

4.2.2 Starting from the middle

If the stochastic simulation is started from the middle it will have a short period of doubled pattern (see section 2.2 for experimental observations on oscillation patterns) and then, after about 100 seconds it will have fallen back into a stable undoubled oscillation pattern. The undoubled oscillation from pole to pole is stable for the rest of the simulation (600 seconds).

When starting the deterministic simulation from the middle, the general behaviour is the same as for the stochastic case, there is a short period of double pattern and then the oscillations fall into the undoubled oscillation pattern. The difference between stochastic and the deterministic simulation is that the latency time for the stochastic simulation is much smaller. The deterministic will start the undoubled oscillations after about 200 seconds while the stochastic simulation will find this solution in about 100 seconds.

4.2.3 Starting symmetric

When starting the stochastic simulation from a symmetric initial condition there will be a 100 second latency before the oscillations start. The oscillation show the same behaviour as described above.

Starting the deterministic simulation from symmetric initial conditions gives the same overall behaviour as the stochastic simulation. The difference is that the latency period before the oscillations start is longer, as in the middle starting case.
Figure 5: 2D projection of membrane bound MinD ((a) and (c)) and MinE ((b) and (d)) in cells of 4 µm and with rounded shape. In Figure (c) and (d) the continuous distribution of molecules has been represented by a discrete distribution (see Appendix A). (a) and (b) are stochastic simulations starting at 65 seconds and each picture shows a 5 second increment in time. (c) and (d) are stochastic starting at 65 seconds and each picture shows a 5 second increment in time.

4.3 Long cylindrical cells

4.3.1 Starting from the middle

Simulation of long cylindrical cells with the “middle initial condition” can be seen in Figure 6. In deterministic simulation the MinD molecules will oscillate over the cell, starting at the two cell ends and then meeting at the middle, then dividing and moving back towards the poles as seen in Figure 6(b). No deviations have been observed in this pattern in the deterministic simulations for 200 seconds.

In the stochastic simulation there will be a drift in the MinD zone position.
The MinD zones will gather away from the middle with deviation varying in size up to $\frac{1}{3}$ of a cell length Figure 6(a) and Figure 6(c). The deviation will change side in each oscillation.

4.3.2 Starting symmetric

When the MinE molecules are distributed in the entire cytosole in a uniform manner the oscillations of the membrane bound MinD molecules will show similar dynamics as the ones described for the stochastic simulation in the middle–starting case, that is, a double oscillation pattern which is drifting away from the middle. Looking at two different simulations with the same choice of parameters it is clear that the solution may choose different trajectories in different simulations as the deviation from the middle were very different in two subsequent simulations. The first simulation shows large deviations from the middle and the second shows small to no deviation from the middle. In deterministic simulation, no deviations from the doubled pattern have been seen during a simulation of 250 seconds (5 oscillations).

4.3.3 Starting asymmetric

When starting the simulations asymmetrically both the stochastic and deterministic simulations will show an undoubled oscillation pattern, oscillating from one pole off the cell over to the other. The oscillation of the membrane bound MinD molecules will not be gathered in a pole at the end of the cell as in the wt cell case instead the zone of MinD molecules appears close to the old polar zone and moves along the cell membrane over to the opposite end of the cell.
Figure 6: 2D projection of membrane bound MinD in cells of 10 µm and with cylindrical shape. (a) and (b) are stochastic and deterministic simulations starting at 65 seconds and each picture shows a 5 second increment in time. (c) is a stochastic simulation starting at 150 seconds with a 5 second increment in time. In Figure (b) the continuous distribution of molecules has been represented by a discrete distribution (see Appendix A).
4.4 Long rounded cells

When using rounded cells and starting with asymmetric initial conditions the stochastic simulations will show oscillations similar to the ones described in section 4.3.2 and section 4.3.1 where the oscillations starting in the doubled pattern have two different oscillations—periods in one cell and and after time drift from a symmetric oscillation to an asymmetric doubled oscillations where the MinD zone accumulates away from the middle. This simulation also leaves the doubled oscillation pattern completely, after approximately 500 seconds, and falls into the “regular” oscillation pattern shown by wt cells and also with the initial conditions used in section 4.3.3. The transition from double to single oscillation pattern is exemplified in Figure 7.

![Figure 7: 2D projection of membrane bound MinD in cells of 10 µm and with a rounded cylindrical shape. (a) and (b) are stochastic simulations showing increments in time with ten seconds starting at 130 seconds and 410 seconds respectively.](image-url)
4.5 Spherical cells

Simulating the model in a cell with spherical shape gives large differences between the stochastic and deterministic simulations. The deterministic will oscillate over the cell in much the same way as described for the cylindrical and rounded cells, moving from one end of the cell to the opposite end. The direction of the oscillation will depend on how the system is started in such a way as the oscillation will never break the initial conditions set on the system. In other words, if the system is started with an inhomogeneous distribution along the y-axis the oscillation will continue in this direction showing no deviation from the pattern at all, at least in the time frame of our observations (175 seconds, 3 oscillations). Figure 8(c) and Figure 8(d).

Starting the deterministic simulation from an even distribution of MinE molecules in the cytosole no oscillations will occur. Both MinD and MinE will be uniformly distributed over the membrane over the entire simulation.

When a stochastic simulation is run in a spherical cell the oscillations will show a different pattern compared to the oscillation obtained with deterministic simulation. The direction of oscillations will continuously change during the simulation causing the MinD and MinD membrane bound zones to move over the cell leaving the oscillation direction set up by the initial conditions. Figure 8(a) and Figure 8(b). The centre of mass of membrane bound MinD molecules can be seen in Figure 9 showing deviations from the middle of the cell in all three dimensions.

The stochastic simulation will also start to oscillate when the MinE molecules are distributed uniformly in the cytosole leading to an oscillation pattern which is very similar to the one observed with asymmetric initial conditions.

The MinE molecules will show a broadened distribution over the cell compared to the case in the cylindrical and rounded cells in both the stochastic and deterministic case. The MinE molecules will have the same general behaviour following the MinD oscillations as in the case of cylindrical and rounded cells.
Figure 8: 2D projection of membrane bound MinD and MinE molecules in spherical cells of size 0.85 µm. (a) and (b) are stochastic simulations of MinD and MinE on the membrane showing increments in time with ten seconds starting at 150 seconds. (c) and (d) are deterministic simulations of MinD and MinE on the membrane showing increments in time with ten seconds starting at 50 seconds. In Figure (c) and (d) the continuous distribution of molecules has been represented by a discrete distribution (see Appendix A).
5 Discussion

For the cylindrical cells, short and long, the deterministic simulations are in good agreement with the simulations by Huang et al. [16] for the same initial conditions and cell shapes. These results are in good qualitative agreement with experimental data showing the oscillations with a correct frequency [25]. The stochastic simulations of the wildtype cylindrical cells show good agreement with the deterministic counterpart.

Both deterministic and stochastic simulations of wildtype rounded cells show a general behaviour that is in good agreement with the cylindrical cells. The frequency of the oscillations is somewhat shorter, but can possibly be explained by the change in shape, since the rounded cells have a smaller total volume than the cylindrical cells. The rounded cells have a larger MinD polar zone which is in better agreement with experimental data [27].

When studying long cells, both rounded and cylindrical, it can be seen that the middle of MinD molecules is drifting away from the middle. In the rounded cells the drift has been observed to fall back into an undoubled pattern. It is believed by the author that the cylindrical cells will also fall into the undoubled pattern if the simulations are run for longer times, though no lengthy simulations were done to prove this point. The drift of the middle has not been found reported in any experimental results leading to the conclusion
that either the model is lacking stability features to sustain the doubled pattern or the result has not been reported due to deviation from the general behaviour of the oscillations.

It can be seen from the results of both the spherical cell and the longer cylindrical cells that the initial conditions play a role in which solution the simulation will converge to. This high dependency on the initial conditions is not of equal importance in stochastic simulations since these simulations continuously probe the solution space for other possible solutions during the simulation. For the longer cylindrical cell the deterministic simulation will stay in the double oscillation state if it is released from a symmetrical state. On the other hand if the deterministic simulation is released from an asymmetrical initial state it will fall back into a undoubled state much like the one observed for short cells. The stochastic simulation will find the undoubled state independently, or so it seems, of initial conditions.

It can also be seen from the result that the stochastic simulation can gain new insights into problems that the deterministic simulations will fail to highlight. This has been seen in the case of round cell where the deterministic simulation did not explain the experimental results in which the MinD zone is seen to change position over the cell [3]. The stochastic simulation has better agreement with the experimental data and also has the capacity to initiate oscillations from a wider range of initial conditions.

As a general conclusion is can be said that there is a detectable difference in the results from stochastic and deterministic models, which not only includes the expected fluctuation around the deterministic path but also larger deviations where the deterministic solution to the problem gives an incomplete description of the spatial dynamics of the system.

References


[14] Z Hu, A Mukherjee, S Pichoff, and J Lutkenhaus. The MinC component of the division site selection system in Escherichia coli interacts with


A Discrete representation of continuous data

To make the continuous distribution — resulting from the deterministic simulations — easier to plot and more comparable to stochastic data the following algorithm was used to transform the continuous data:

- Define the continuous number that is to be plotted as $C$.
- Truncate the continuous number $C$ into $T$.
- Draw a random number, $rand = (0\ldots1)$.
- If $(C - T) \geq rand$, plot $T + 1$ in the same way as the discrete plot. Else, plot $T$.

**Example1:** The number 2.72 will be plotted as 2 with probability 0.28 and 3 with probability 0.72.

**Example2:** The number 3.14 will be plotted as 3 with probability 0.86 and 4 with probability 0.14.