A Mathematical Model of Cytokineti

ic Morphogenesis

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By

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Abstract

Cytokinesis occurs through coordinated biochemical processes that result in biophysical stresses that act on the cytoskeleton. In order to uncover the physical mechanisms responsible for the cytokinetic behavioral differences between normal and abnormal cells, we use computational methods to simulate the effects of varying these physical mechanisms; our methods are applied to both deterministic and stochastic models. Particularly in non-adhesive conditions, it has been observed that Myosin II Contractile Force is the major driving force of furrow ingression. Modification of the maximum myosin stress parameter, the myosin distribution and cell elasticity achieved results that coincide with other findings and biological inferences about cell behavior. The model presented in this report provides a preliminary basis for future quantitative identification of abnormal cells, and the identification of possible cancer therapeutic targets. Via this model we are able to gain further understanding of the bio-mechanical properties of cells and their effects on cytokinesis.
Dedicated to my mother, Karen Anderson, and my Undergraduate Advisor,

Dr. Michael Marsalli.
Acknowledgments

I would like to thank Yanli Wang for her work in the construction and development of the code, and her assistance in my further understanding of the numerical method.
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# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>ii</td>
</tr>
<tr>
<td>Dedication</td>
<td>iii</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>iv</td>
</tr>
<tr>
<td>Vita</td>
<td>v</td>
</tr>
<tr>
<td>List of Figures</td>
<td>viii</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>2. Recreation of the Model</td>
<td>5</td>
</tr>
<tr>
<td>2.1 Model Construction</td>
<td>5</td>
</tr>
<tr>
<td>2.2 Summary of Subsystems</td>
<td>7</td>
</tr>
<tr>
<td>2.2.1 Myosin II Contractile Force</td>
<td>7</td>
</tr>
<tr>
<td>2.2.2 Adhesive Stress</td>
<td>8</td>
</tr>
<tr>
<td>2.2.3 Protrusion Force</td>
<td>8</td>
</tr>
<tr>
<td>2.2.4 Surface Tension</td>
<td>9</td>
</tr>
<tr>
<td>2.2.5 Strain Stiffening</td>
<td>10</td>
</tr>
<tr>
<td>2.2.6 Volume Conservation</td>
<td>11</td>
</tr>
<tr>
<td>2.3 Numerical Method: Level Set Method</td>
<td>11</td>
</tr>
<tr>
<td>2.4 Inferences and Modifications</td>
<td>13</td>
</tr>
<tr>
<td>2.5 Types of Models</td>
<td>14</td>
</tr>
<tr>
<td>3. Implementation and Results</td>
<td>16</td>
</tr>
<tr>
<td>3.1 Variation of the Myosin Stress: Deterministic Model</td>
<td>16</td>
</tr>
<tr>
<td>3.1.1 Constant Variance</td>
<td>16</td>
</tr>
</tbody>
</table>
3.1.2 Non-Constant Variance ........................................... 18
3.2 Variation of the Myosin Stress: Stochastic Model ................. 18
3.3 Variation of Elasticity ............................................... 22

4. Discussion ....................................................................... 24
   4.1 Limitations of the Model ........................................... 24
   4.2 Discussion and Biological Interpretation ....................... 25

5. Goals and Future Contributions ....................................... 27

Bibliography ................................................................. 29
### List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Molecular Mechanisms of the Contractile ring: The localized activation of the small GTPase Rho at the cell equator controls the position of the contractile ring. When Rho is specifically activated at the equatorial cortex, it promotes actin polymerization and myosin-2 activation via Rho effector proteins. The ATPase activity of myosin II is required for F-actin disassembly [2].</td>
<td>2</td>
</tr>
<tr>
<td>1.2 Cell behaviors during MCF-10A, MCF-7 and MDA-MB-231 cell division [9].</td>
<td>4</td>
</tr>
<tr>
<td>2.1 A: Assumed 2-D Cylindrical Symmetry B: Voigt Model illustrating visco-elastic connection [6].</td>
<td>6</td>
</tr>
<tr>
<td>2.2 Myosin Force Action: The myosin contractile force is assumed to act tangentially to the cortex, as the stress acts radially inward reducing the circumference of the furrow [6].</td>
<td>7</td>
</tr>
<tr>
<td>2.3 A (Adhesive Stress): Area density maps (Dr(z) and Dz(r)), obtained by summing the cell area (in the z-r plane) one axis at a time. The resultant adhesion map, shown overlaid on the cell shape, is obtained by a product of the two. B (Protrusive Stress): Protrusive stress is assume to work in the z-direction away from the furrow but only the component normal to the boundary is used [6].</td>
<td>9</td>
</tr>
<tr>
<td>2.4 Level Set Method Boundary: A: Diagram of a cell indicating membrane velocity direction. B: Illustration of ( \Gamma(t) ) as the zero level set. C: Illustration of the signed distance function ( \phi(x, y, t) ) [B,C [10]].</td>
<td>13</td>
</tr>
</tbody>
</table>
2.5 **Original Myosin Profiles:** Spatial distribution of myosin II motors along the division axis (z) at different time points. During the simulation, the myosin II forces were distributed according to these profiles indexed by the furrow diameter [6].

3.1 The Effect of Variance on Cell Elongation

3.2 Non-Constant Variance: Division at different $\sigma_{\text{myo-max}}$ values.

3.3 Juxtaposition of Deterministic and Stochastic Simulations

3.4 **Furrow Diameter Trajectories.** A Deterministic: Initial parameters with $\sigma_{\text{myo-max}} = 1.45nN/\mu m^2$. B Stochastic: Initial parameters with $\sigma_{\text{myo-max}} = 2.05nN/\mu m^2$.

3.5 Variation of Elasticity
Chapter 1: Introduction

Cytokinesis is the process occurring in the sixth stage of Mitosis that results in the separation of the mother cell into two daughter cells. This process occurs through the coordinated action of biochemically-mediated stresses acting on the cytoskeleton [6] [Fig. 1.1]. The structure that generates the force to accomplish cytokinesis is the contractile ring. The contractile ring is a dynamic structure which forms beneath the plasma membrane during cytokinesis and constricts to pinch the two daughter cells apart. The contractile ring is composed of actin filaments, myosin II filaments and many other structural and regulatory proteins [1].

Contractile ring constriction is no longer believed to operate according to the traditional ‘purse string’ model [1]. The ‘purse string’ model suggests that constriction is caused by many myosin II bipolar filaments using motor activity to move along anti-parallel actin filaments. This activity causes the actin filaments to slide past each other [2]. However, with an increase in experimental data, the exact mechanisms of this constriction are believed to be more sophisticated. As the ring constricts, it maintains a constant thickness and cross-sectional area suggesting that total ring volume and the number of filaments decrease steadily. More specifically, F-actin disassembly must balance F-actin polymerization [1, 2].

The dynamic nature of the contractile ring differs among species. Studies in mammalian cells and yeast have shown that ring dynamics are attributed to the continuous assembly and turnover of F-actin and myosin II. However, recent studies in *C. elegans* show that the ring is disassembled over time, and the rate of constriction is proportional to the ring’s initial circumference [2].

![Diagram](current_biology.png)

**Figure 1.1: Molecular Mechanisms of the Contractile ring:** The localized activation of the small GTPase Rho at the cell equator controls the position of the contractile ring. When Rho is specifically activated at the equatorial cortex, it promotes actin polymerization and myosin-2 activation via Rho effector proteins. The ATPase activity of myosin II is required for F-actin disassembly [2].
The major mechanical subsystems of cytokinesis are adhesive stress, protrusive forces, Laplace-like pressures (surface tension) and myosin contractile force. Simulations done by Poirier et al [6] demonstrate that initial furrow ingestion is achieved either through the combination of adhesive and protrusive forces or, in the absence of adhesion, from the myosin contractile force [6].

Normal and abnormal cells exhibit different behaviors during and after cytokinesis. For example, normal cells completely separate after cyokinesis whereas abnormal cells may remain bounded or rapidly move away from each other [9]. According to Wang et al [9], cell characteristics such as geometry and motion are reflections of intracellular tension dynamics.

Although abnormal cells are not necessarily cancerous [3] some characteristics of abnormal cells, such as faster division time, asymmetric division and irregular geometry, are particular characteristics of cancerous cells [9]. Other characteristics of cancerous cells include vertical and overlapping division [Fig. 1.2], wider distribution of cell area and axis ratio, and small cytoplasmic volume and an irregularly shaped nucleus.

Via automated cell tracking, our collaborators Jhiang et al [9], were able to quantitatively characterize variations in cell geometry and cell motion. They found that non-transformed breast cells (MCF-10A) divide horizontally with smooth separation after division [Fig. 1.2A]. In contrast, non metastatic breast cancer cells (MCF-7) divide vertically and remain overlapping for a while before the cell on top slides down and attaches to the substrate [Fig. 1.2B]. Finally, metastatic breast cancer cells (MDA-MB-231) are unique in that they often undergo rapid motion and irregular geometric changes [Fig. 1.2C].
Figure 1.2: Cell behaviors during MCF-10A, MCF-7 and MDA-MB-231 cell division [9].

Furrow ingression dynamics of the social amoeba *Dictyostelium discoideum* are well characterized for various strains and thus a large number of experimentally measured parameter values is available. The initial parameters used in the development of our model were obtained from micropipette aspiration of *Dictyostelium*. Using these parameters, a mathematical model and computational techniques we simulate cytokinetic morphogenesis in order to better understand the incidences that lead to abnormal cytokinetic developments. We will then infer the biological meaning and implications of the changes based on the results.
Chapter 2: Recreation of the Model

2.1 Model Construction

The model developed in this report is based on the information presented in Poirier, Ng, et al’s *Deconvolution of the Cellular Force-Generating Subsystems* [6]. The model assumes 2D cylindrical symmetry about the division axis [Fig. 2.1A]. The model also assumes that cell deformation obeys \( v = \dot{x}_m \) where \( v \) is the velocity of the level set that describes the cell membrane protrusion and reaction velocities. (We will go more into the Level Set Method in the section on numerical methods.) The velocities can be driven by either external forces, such as micropipette aspiration, or internal forces, such as actin polymerization and myosin II retraction, or both. As such, determining how these forces translate to membrane velocities requires a mechanical model of the cell [10]. The total membrane displacement is the sum of the displacement of the cortex (\( x_{cor} \)) and the cytoplasm (\( x_{cyt} \)). The Voigt model [Fig. 2.1B], which consists of a parallel connection of elastic (\( K \)) and viscous (\( D, B \)) elements, describes how the stresses affects these velocities. We are tracking membrane and cortex displacement as represented by the following system of equations:

\[
v = \dot{x}_m = -\left(\frac{K}{D}\right)x_{cor} + \left(\frac{1}{D} + \frac{1}{B}\right)\sigma_{tot}
\]  (2.1)
\[ \dot{x}_{\text{cor}} = -\left( \frac{K}{D} \right) x_{\text{cor}} + \left( \frac{1}{D} \right) \sigma_{\text{tot}} \]

with \( \sigma_{\text{tot}} \) (Eqn. 2.2) being the total net stress acting on the cell during cytokinesis (9).

\[ \sigma_{\text{tot}} = \sigma_{\text{adh}} + \sigma_{\text{pro}} + \sigma_{\text{myo}} + \sigma_{\text{ten}} + \sigma_{\text{vol}} = D\dot{x}_{\text{cor}} + Kx_{\text{cor}} = B\dot{x}_{\text{cyt}} \quad (2.2) \]

Each component is described in detail in the next section.

Figure 2.1: **A:** Assumed 2-D Cylindrical Symmetry **B:** Voigt Model illustrating visco-elastic connection [6].

Our model initially utilizes the parameter values obtained in Poirier et al’s paper [6]. These values, the quantitative characterization of the biophysical characteristics of the cell, were obtained using micropipette aspiration [6]. A few parameters were later modified for the purposes of behavior analysis.
2.2 Summary of Subsystems

2.2.1 Myosin II Contractile Force

Myosin contractile force is produced from the work of myosin II against the cytoskeleton [6]. This force acts tangentially to the cortex as the contractile stress works radially inward [Fig. 2.2]. This results in the reduction of the circumference with the net effect of reducing the furrow diameter. The magnitude of this force depends on the maximum stress generated by myosin II $\sigma_{myo-max}$ and the local distribution of myosin II. The total stress of the Myosin Contractile Force is represented by the following:

$$\sigma_{myo}(z, r) = -\sigma_{myo-max}myo(r, z)n$$  \hspace{1cm} (2.3)

where $myo(r, z)$ describes the distribution of myosin in the $r$ and $z$ directions and $n$ being the outward normal unit vector.

Figure 2.2: **Myosin Force Action:** The myosin contractile force is assumed to act tangentially to the cortex, as the stress acts radially inward reducing the circumference of the furrow [6].
2.2.2 Adhesive Stress

Adhesion is applied spatially as a restrictive stress element counteracting the net effect of other stresses. Rather than use the cylindrical symmetry assumed by the model, Poirier et. al considered the cross sectional area in the \((z,r)\) plane which more closely corresponds to the cell-substrate contact area [Fig. 2.3A][6]. The area densities are computed as follows:

\[ D_z(r) = \frac{1}{A} \sum_i 1(z_i,r) \]  \hspace{1cm} (2.4)
\[ D_r(z) = \frac{1}{A} \sum_j 1(z,r_j) \]
\[ A = \sum_{ij} 1(z_i,r_j) \]

1 \((z_i,r)\) is the indicator function that equals one when the point \((z,r)\) is inside the cell and zero otherwise. The spatial adhesion map is the product of these densities and the maximum adhesive stress \(\sigma_{adh-max}\):

\[ \sigma_{adh}(z,r) = \sigma_{adh-max} D_z(r) D_r(z) \]  \hspace{1cm} (2.5)

2.2.3 Protrusion Force

We assume the protrusive force acts at both ends of the cell to pull the cell apart [Fig. 2.3B]. This local force depends on the contact area \(D_r(z)\) and is scaled by the linear function \(l(z)\). This force increases as you move away from the cleavage furrow, thus the protrusive stress acts along the \(z\) axis. The force decreases over time with the magnitude given by:

\[ \sigma_{pro}(z,r) = \sigma_{pro-max} e^{-5(w_f(0) - w_f(t))/w_f(0)} D_z(r) l(z) \]  \hspace{1cm} (2.6)
where the furrow diameter is defined by \( w_f(t) \) and \( \sigma_{\text{pro-max}} \) is the maximum protrusive stress applied. Though the stress is assumed to act along the \( z \) axis, only the component normal to the surface is used in the simulations. Poirier notes that though the model of protrusive forces is phenomenological, it does capture the net movement of the membrane [6].

![Diagram of Adhesive Stress and Protrusive Stress](image)

Figure 2.3: **A (Adhesive Stress):** Area density maps (\( D_r(z) \) and \( D_z(r) \)), obtained by summing the cell area (in the \( z-r \) plane) one axis at a time. The resultant adhesion map, shown overlaid on the cell shape, is obtained by a product of the two. **B (Protrusive Stress):** Protrusive stress is assumed to work in the \( z \)-direction away from the furrow but only the component normal to the boundary is used [6].

### 2.2.4 Surface Tension

Surface tension, or Laplace-like pressures, is a function of mean curvature, \( \kappa_{\text{mean}} \), and cortical tension, \( \gamma \):

\[
\sigma_{\text{ten}}(z, r) = -\gamma(z)\kappa_{\text{mean}}(z)n
\]

(2.7)

where \( n \) is a normal unit vector.
κ\text{mean} is the arithmetic mean of two curvatures: The first, κ_{2D}(x, y), is computed using Lagrangian formulation based on the cellular boundary [6].

\[ \kappa_{2D}(x, y) = \frac{(x'y'' - y'x'')}{(x'^2 + y'^2)^{3/2}} \]  

(2.8)

The second, κ_P, takes advantage of the cell’s assumed cylindrical symmetry.

\[ \kappa_P = \frac{\mathcal{N}_r(r)}{r} \]  

(2.9)

where \( \mathcal{N}_r(r) \) is the normal at the radial direction at a given point and \( r \) is the radius of the cell at that point.

For cells in interphase, it is assumed that the cortical tension is homogeneous around the cell with the nominal value 1.0 nN/\( \mu \)m. For mitotic myosin II null cells, Poirier et al also assumes a spatially heterogeneous \( \gamma \) with values of 0.5 and 1.0 nN/\( \mu \)m at the pole and furrow, respectively [6]. The values are interpolated using the Gaussian profile:

\[ \gamma(z) = \gamma_{pole} + (\gamma_{furrow} - \gamma_{pole}) \exp\left(-\frac{1}{2} \left(\frac{4z}{R_0}\right)^2\right) \]  

(2.10)

where \( R_0 \) is the initial radius of the cell, and \( z \) is the position between the pole and the furrow. This profile is used as a means of marking intracellular changes in the material properties of the cell during division [6].

### 2.2.5 Strain Stiffening

Though nonlinearities in cellular response to deformations have been observed [6], no precise model of strain stiffening is currently available. Strain stiffening is a nonlinear effect whereby materials harden when sufficiently deformed. This force acts to
slow down division. The elastic component of the cell $K(x,t)$ is assumed to undergo strain stiffening likely due to stalling of myosin II motors. Poirier et al posits the following phenomenological model of strain stiffening [6]:

$$K(x,t) = K_0 \left(1 + \text{myo}(r, z) \left(1 + \frac{w_f(0) - w_f(t)}{w_f(0)}\right)^2\right)$$

(2.11)

where $K_0$ is the nominal elasticity.

### 2.2.6 Volume Conservation

It is assumed that the cellular volume remains constant with the following stress contribution:

$$\sigma_{vol} = K_{vol} (V_{\text{resting}} - V_{\text{actual}}) n$$

(2.12)

where $V_{\text{resting}}$ is constant while $V_{\text{actual}}$ is dependent on the change in cell radius. The volume conservation constant, $K_{vol}$, acts to maintain volume stability and is set at $0.1nN/\mu m$. Considering radial symmetry the volume is calculated as follows:

$$V_{\text{actual}} = \pi \int_{\text{cell length}} r^2(z) dz$$

(2.13)

### 2.3 Numerical Method: Level Set Method

Level Set Method (LSM) is a versatile numerical technique developed by Sethian and Osher for tracking interfaces and shapes [10, 5]. Considering the membrane cortex structure as the boundary of the cell, we employ Level Set Method to simulate the movement of this interface. This method, via an Eulerian approach, tracks a moving...
boundary deformed by a continuing stress field on a static Cartesian grid [4]. LSM relies on a continuum description of the material properties of the cell, rather than the traditional discretization of the boundary [10].

Imagine a region bounded by a closed contour $\Gamma(t)$, the cell membrane [Fig. 2.4 A]. $\Gamma(t)$ is implicitly embedded in a potential function $\phi(t)$, and is related to $\phi(x,t)$ via the following [Fig. 2.4 B, C][10]:

$$\Gamma(t) = \{ x | \phi(x,t) = 0 \}$$  \hspace{1cm} (2.14)

Thus $\Gamma(t)$ is the zero level set of $\phi(x,t)$ [Fig 2.4 B, C].

A good candidate for the potential function, $\phi(x,t)$ is the signed distance function defined as:

$$\text{sign}(x, \Gamma) = \begin{cases} 
-d(x, \Gamma), & \text{if } x \in S \\
0, & \text{if } x \not\in S \\
d(x, \Gamma), & \text{if } x \in \Gamma 
\end{cases}$$  \hspace{1cm} (2.15)

where $S$ is the area occupied by the cell and $d(x, \Gamma)$ is the shortest distance from a point $x \in \mathbb{R}^2$ to the curve $\Gamma(t)$.

As $\phi(x,t)$ evolves in time, $\Gamma(t)$ is manipulated implicitly according to the convection equation:

$$\frac{\partial \phi(x,t)}{\partial t} + v(x,t) \cdot \nabla \phi(x,t) = 0$$  \hspace{1cm} (2.16)

where $v(x,t)$ is the velocity of the level set moving in the outward normal direction.

As the potential function evolves, it can become quite steep or flat leading to numerical errors [6, 10]. These errors can be minimized by periodically reinitializing $\phi$ according to the following:

$$\frac{\partial \phi(x,t)}{\partial t} = S(\phi(x,0))(\| \nabla \phi(x,t) \| - 1)$$  \hspace{1cm} (2.17)
2.4 Inferences and Modifications

Though there is no extensive micropipette aspiration data available for mammalian cells, the biophysical dynamics in *Dictyostelium discoideum* are well documented. For the purposes of this model we assume that the division dynamics of *Dictyostelium* and mammalian cells are sufficiently similar. That is, *Dictyostelium*...
and mammalian cell cultures have exhibited similar division behaviors in adhesive and non-adhesive environments [6].

Marking the entry of the mitotic stage, the cell becomes rounded with decreased cell surface area [9], thus cell-substrate contact area is minimal. In order to create a model consistent with these conditions, the adhesive stress parameter is neglected. Thus this model is representative of a cell in suspension, with the myosin contractile force being the major force driving furrow ingression [6].

Poirier et al’s paper [6], on which our models are based, did not provide a function for the myosin distribution \( \text{myo}(r, z) \). Instead we were provided with five myosin profiles illustrating the distribution at specific times [Fig. 2.5]. Our code then extracted the appropriate time data from the distribution profiles. However, there were restrictions with this profile: The myosin profiles were limited to an observed maximum z-direction range of about -8 to 8 \( \mu \text{m} \). During the simulation, however, the cell attempts to extend pass the maximum range but the code is unable to extract data for further extension. To remedy this restriction the individual myosin profiles were replaced with the Gaussian distribution. This change is justified by Stachowiak et al’s findings showing myosin and formin to follow such a distribution around the furrow.[8]

\[ \text{myo}(r, z) \]

2.5 Types of Models

Two models were considered in the analysis: a deterministic model which was held as the standard for comparison, and a stochastic model which simulates abnormal morphology.
Figure 2.5: **Original Myosin Profiles:** Spatial distribution of myosin II motors along the division axis (z) at different time points. During the simulation, the myosin II forces were distributed according to these profiles indexed by the furrow diameter [6].
Chapter 3: Implementation and Results

3.1 Variation of the Myosin Stress: Deterministic Model

As previously mentioned, the myosin profile obtained from the literature was replaced by the Gaussian distribution. Using the deterministic model, the variance was modified indirectly by changing the $x^2d$ coefficient in the exponent of the myosin distribution below:

$$\text{pdf} = \text{maxs}_\text{myo} \times \exp(-0.5 \times (4 \times x^2d/R_{tmp})^2)$$

(A larger coefficient corresponds to a smaller variance.) At various coefficient values the maximum myosin stress ($\sigma_{myo-max}$) values were also held at various constant values throughout the simulation.

3.1.1 Constant Variance

The variances were held constant throughout each simulation, varying the $x^2d$ coefficient among the values 0.5, 1, 2, 4 and 6. At each of these values simulations was run with constant $\sigma_{myo-max}$ values of 0.1, 0.5, 1.05, 1.55 and 2.05$nN/\mu m^2$ and observed the results.
Regardless of the variance level, no division was observed at small $\sigma_{\text{myo-max}}$ values, particularly values $0.1 nN/\mu m^2$ and $0.5 nN/\mu m^2$. For the majority of these simulations the cell exhibits virtually no shape change or furrow ingression [Fig. 3.1 High Variance: $t=0.05$]. Only at a coefficient of 1 does the cell elongate for $\sigma_{\text{myo-max}} 0.5$. At a coefficient of 0.5, no $\sigma_{\text{myo-max}}$ level produces furrow ingression, only elongation [Fig. 3.1 High Variance: $t=0.3$] at $\sigma_{\text{myo-max}} =1.55 nN/\mu m^2$ and $2.05 nN/\mu m^2$ [Fig. 3.2 High Variance: $t=0.3$]. The simulations exhibit division for coefficients 1 through 6 at $\sigma_{\text{myo-max}}$ values greater than $0.5 nN/\mu m^2$. From these simulations we were able to conclude that changing the variance affects the cell shape: The smaller the variance, the less elongated the cell [Fig. 3.1]. Also, changing the $\sigma_{\text{myo-max}}$ level affects the division time: The larger the $\sigma_{\text{myo-max}}$, the lower the division time [Fig. 3.2].

Figure 3.1: The Effect of Variance on Cell Elongation
3.1.2 Non-Constant Variance

Experimental data has shown that during cytokinesis the myosin II distribution around the furrow varies as the cell shape evolves in time during cytokinesis [6]. Therefore, to more appropriately reflect realistic cell behavior, the myosin profile was modified to depend on the furrow diameter. As before, the $\sigma_{\text{myo-max}}$ values were varied among $1.45$, $1.55$, $2.05$ and $2.15 nN/\mu m^2$, and held constant throughout each simulation.

In all simulations little elongation of the cell was observed. According to the previous variance study, this is indicative of a small variance (large $x2d$ coefficient) in the Gaussian Myosin Profile. Further calculation revealed that the variance value, in this case, did not exceed a magnitude of 1. The simulation achieves division at all $\sigma_{\text{myo-max}}$ levels and, as hypothesized, the time to separate decreases with increasing $\sigma_{\text{myo-max}}$ values [Fig. 3.2].

3.2 Variation of the Myosin Stress: Stochastic Model

Irregular geometry is a characteristic of abnormal and cancerous cells [9]. It has been shown through the previous $\sigma_{\text{myo-max}}$ varying simulations and experimental data [6] that varying Myosin II Contractile Force has a significant effect on cytokinetic behavior. Therefore, we hypothesized that perturbations in the myosin profile will result in irregular geometries.

Uniform random noise, from the interval $[-1,1]$, was added to the myosin profile of the non-constant variance model. The $\sigma_{\text{myo-max}}$ values were varied as before. After periods of 51 iterations, noise was reintroduced to the profile as to prevent significant decimation due to reinitialization:
Figure 3.2: Non-Constant Variance: Division at different $\sigma_{myo-max}$ values.

\[
\text{if } \text{mod(iter,51)} == 1; \\
\text{uniform random noise on } [-1,1] \\
\text{noise} = 1 - 2 \times \text{rand(nx)}; \\
\text{end} \\
\text{random noise} \\
\text{if } \text{mod(iter,51)} < 10 \\
\text{tmp\_sig\_myo1} = \text{pdf} + 3 \times \text{noise}; \\
\text{tmp\_sig\_myo} = \text{conv2(tmp\_sig\_myo1,weight,'same')};
\]
As hypothesized, this did produce irregular membrane geometry. Due to the random nature of the noise, however, division is not guaranteed. So, although all simulations achieved furrow ingression, not all simulations achieved division. More often, though not consistently, division was achieved at relatively higher $\sigma_{\text{myo-max}}$ values. Figure 3.3 B and D illustrate division achieved at $\sigma_{\text{myo-max}}$ values of $2.05 \, \text{nN/\mu m}^2$ and $2.55 \, \text{nN/\mu m}^2$ respectively.

Figure 3.3: Juxtaposition of Deterministic and Stochastic Simulations
Due to the limited number of successful divided simulations obtained from the random noise analysis, the results had not provided enough information to draw appropriate conclusions about the effects of noise. That is, no patterns of irregular cell behavior in response to this particular study were able to be determined. However, general trajectories of the change in furrow diameter $w_f(t)$ were obtained for each model [Fig. 3.4]. A non-linear change is observed for both models. Interestingly, although oscillations in the furrow diameter were visually observed in the stochastic simulations, the deterministic trajectory illustrates rapid oscillatory behavior closer to $t = 1$.

![Figure 3.4: Furrow Diameter Trajectories. A Deterministic: Initial parameters with $\sigma_{myo-max} = 1.45nN/\mu m^2$. B Stochastic: Initial parameters with $\sigma_{myo-max} = 2.05nN/\mu m^2.$](image-url)
3.3 Variation of Elasticity

From the interactions of global and regional proteins, genetic modules have been proposed to control cytokinesis [7]. The first module consists of regional actin-binding proteins myosin II and cortexillin I. The second module is a global pathway controlled by the RacE small GTPase and includes dynacortin and the actin-bundling protein coronin. RacE, myosin II and cortexillin I have been shown to contribute to the bending modulus, surface tension, and in-plane elasticity of cells [7]. Using the deterministic model with $\sigma_{myo-max}$ held at a constant 1.45$nN/\mu m^2$, the nominal cortical elasticity constant, $K_0$, was changed for each simulation. The current model, was unable to achieve division with values greater than the initial parameter value $K_0 = 0.098nN/\mu m^3$. However, division was obtained at values less than the initial parameter value. This finding was consistent with that of Poirier et al. [6]: Decreasing the elasticity resulted in a shorter division time [Fig. 3.5].
Figure 3.5: Variation of Elasticity
4.1 Limitations of the Model

Our model visually simulates what we intended, division and irregular morphology, but the development of the model relied on assumptions, inferences and non-mammalian cell data. Though we were justified in assuming sufficient similarity between the mechanical dynamics of *Dictyostelium discoideum* and mammalian cells, we may have inadvertently neglected important organismal mechanical differences. This may be remedied when micropipette aspiration data for normal, abnormal or cancerous mammalian cells become available.

Vertical division and overlapping are characteristics of breast cancer cells observed by Wang et al [9]. Our current model, however, is not able to simulate such division. This will be addressed as part of the development of this model, perhaps through usage of a 3-dimensional model.

The time scale in our model is representative of a general unit of time and is thus used to measure general differences in division time and furrow ingression rather than actual time. Actual time is necessary to fully understand the dynamics of real cell behavior.
The degree and accuracy of the relationship between the quantitative parameters and the biology of the cell are unknown. Recall that the models for strain stiffening and protrusion were phenomenological, and also, the volume constant $K_{vol}$ served merely as a stabilizer. Biological interpretation of these parameters is unclear.

Cell shape may change in response to external or internal changes, however these shape changes are not reflected about the division axis, E.g. cell protrusion during chemotaxis occurs in the direction of the chemoattractant. Therefore, perhaps the most important limitation of the model is the assumption of 2D cylindrical symmetry. This assumption implies that a deformation in one location of the cell is rotated around the cell. This is not consistent with realistic cell behavior.

4.2 Discussion and Biological Interpretation

Modification of the parameters is essentially the changing the properties of the cell cortex. The extent of cell elongation is affected when the variance of the myosin distribution is manually changed. Statistically, increasing the variance (decreasing the $x2d$ coefficient) decreases the maximum value of the distribution. Biomechanically, increasing the variance decreases the myosin stress around the furrow. This could be indicative of a change in protein recruitment during contractile ring formation. Therefore at larger variances it requires more time for the cell to achieve the myosin stress value necessary for furrow ingression and cleavage. This extended time allows other forces more time to impose their stresses. Most evident is the extended effect of the protrusive stress (elongation).

When the variance is dependent on the furrow diameter, similar behavior is observed. Varying the maximum myosin stress values could be interpreted as varying
the concentration of myosin II or other significant contractile ring proteins in the location of the furrow. This could also imply changes in protein recruitment dynamics. It is also possible that this may be representative of abnormal protein function or interaction.

As the appropriate assembly and disassembly of contractile ring components is necessary for proper division [1], the noise introduced to the myosin profile may be representative of a disruption in myosin distribution and reorganization during cytokinesis. Varying the elasticity may be indicative of irregularities in global or regional proteins or their interactions. Non-division could, in one sense, represent cellular abnormalities, perhaps a characteristic of non-cancerous but abnormal cells.

Finally, it is possible that in modifying parameters we are in fact changing the type of cells being observed. There are naturally occurring differences among cells of different types. Cells varying in function, among organisms and among age groups etc. have varying characteristics including shape, symmetry, means of division and process rates [1]. For example, non-division could also indicate that a change in certain parameters results in a quantitative characterization of a cell which does not undergo cytokinesis such as brain or nerve cells. More data and research is imperative to the development of the model and thus the analysis of the aforementioned hypotheses.
Chapter 5: Goals and Future Contributions

Many developed mathematical models of cytokinesis are based on the interactions of biochemical signaling pathways. Biomechanical models are still in development as experimental data for the biomechanical properties of mammalian cells is limited. It is hoped that this preliminary model will contribute to the development of more accurate models for mammalian cells. A model such as the one presented in this report holds the potential of obtaining threshold and maximum parameter values which mark specific stages in cytokinesis. These values may be used in the development of future models. As experimental data is acquired in the future, this information can be incorporated into the model thus improving accuracy and specificity to mammalian cells.

Future studies involve varying noise levels and analyzing adhesive properties as adhesion is an important difference between normal and cancerous cells [9]. Also, as the rate of constriction is proportional to the initial size of the contractile ring [2], it may be fruitful to vary the cell size and analyze not only division rates, but parameter agreement.

An important application of our research is cancer therapeutics. In identifying the major biophysical subsystems responsible for the cancer phenotype, we may be able to identify therapeutic targets. These targets may range from a specific gene
to a specific protein, or a specific pathway. To fully understand the mechanisms that regulate these cell shapes and behaviors requires detailed knowledge of signaling pathways as well as their effects on the mechanical properties of the cell.


