2005-07-08

A Mathematical Model of Adhesion Interactions between Living Cells

Casey P. Johnson
Brigham Young University - Provo

A MATHEMATICAL MODEL OF ADHESION INTERACTIONS BETWEEN LIVING CELLS

by

Casey Patrick Johnson

A thesis submitted to the faculty of

Brigham Young University

in partial fulfillment of the requirements for the degree of

Master of Science

Department of Mathematics

Brigham Young University

August 2005

BRIGHAM YOUNG UNIVERSITY

GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

Casey Patrick Johnson

This thesis has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

Date	John Dallon, Chair
Date	Christopher Grant
Date	Scott Glasgow

BRIGHAM YOUNG UNIVERSITY

As chair of the candidate's graduate committee, I have read the thesis of Casey Patrick Johnson in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

Date

John Dallon
Chair, Graduate Committee

Accepted for the Department

Tyler Jarvis
Graduate Coordinator

Accepted for the College

G. Rex Bryce, Associate Dean
College of Physical and Mathematical Sciences

ABSTRACT

A MATHEMATICAL MODEL OF ADHESION INTERACTIONS
BETWEEN LIVING CELLS

Casey Patrick Johnson
Department of Mathematics
Master of Science

This thesis presents a simple force-based model of moving and interacting cells that incorporates a realistic description of cell adhesion and applies it to a system of spherical cells. In addition, several results in matrix theory are proved with the end of showing that the equations produced by the model uniquely determine the motion of the system or cells.

ACKNOWLEDGMENTS

I would like to thank John Dallon for his enthusiasm and for encouragement throughout my academic career. I would also like to thank my parents for always encouraging my love of learning. Most importantly, I thank my wife, Kirsten, for her support and patience. The time I spent working on this thesis ultimately belonged to her.

Table of Contents

1 Introduction

1.1 Mathematics and Biology

The histories of mathematics and physics are closely intertwined. Indeed, a good deal of mathematics has been developed out of a desire to describe the earth and the heavens. Consequently, physicists have access to powerful mathematical theories when studying new phenomena. Even chemists have been able to take advantage of mathematics to model and quantify reactions. Some branches of biology, on the other hand, have not profited from the power of mathematics to the same extent.

Historically, a robust mathematical theory describing the behavior of biological systems has been impossible. To describe the behavior of a single cell is extremely complicated. To extend such a description to simultaneously describe the behavior of thousands, or even millions, of interacting cells is not only difficult in theory, but also very expensive computationally. However, modern computing and improvements in measuring devices have made it possible to produce and analyze various theories that describe biological phenomena, including various models of cellular movement and interaction.

For several years, biologists have been able to experimentally measure even the individual forces between pairs of interacting cells. This precision has made it possible to begin to mathematically describe biological systems at the cellular level. Such a mathematical description of cellular biology is essential, for a mathematical understanding at the cellular level will enable a more thorough study of macrobiological systems, such as tissues and organisms.

1.2 Adhesion

One of the hurdles that must be overcome in order to produce an adequate theoretical model for interacting cells is a more complete understanding of cell adhesion. Adhesion is the process by which cells are able to attach to other cells, as well as the substrate, in

order to move about.

A cell adheres to other objects via a family of specialized molecules, called integrins, which are attached to the cytoskeleton and pass through the bilipid layer of the cell membrane to lie mostly outside the cell. Integrins selectively attach to the substrate or to integrins belonging to other cells in order to form bonds. The bonds formed may be broken either by detaching the integrins from the attached object or by simply tearing the integrins from the cytoskeleton itself, leaving them behind.

The movement of an amoeboid cell is highly dependent on its ability to adhere to other objects. The motion of a cell toward a stimulus can be summarized in the following steps, described in [8], which may be repeated until the cell arrives at its destination:

1. **Morphological Polarization.** Before any motion is to occur, the cell must adopt an asymmetrical shape. This asymmetry may be manifest as a polarized morphology. That is, the cell creates a distinction between "front" and "rear". This transition may arise due to the sensing of spatial or stimulus gradients, and is often accompanied by a "forward redistribution of chemosensory signaling receptors, integrin adhesion receptors, and integrin-cytoskeleton linkages."

2. **Membrane Extension.** The cell adheres to the substrate near the tail and a region of the "front" of the cell membrane extends toward the movement stimulus, forming what is known, generally, as a pseudopod. This extension may be a lamellipod (a broad, flat structure) or a filopod, which is a "thin, cylindrical, needle-like projection."

3. **Formation and Stabilization of Attachments.** With the pseudopod extended, the cell forms adhesive attachments with nearby objects, such as other cells or the substrate. These attachments tend to be preferred along the leading edge of the pseudopod due to a forward redistribution of integrins.

4. **Contractile Forces and Traction.** Once attached, the cell retracts the pseudo-

pod, pulling against the object to which it is attached, thus propelling the main body of the cell forward.

5. **Rear Release.** As the cell moves forward, the adhesion bonds at the tail portion of the membrane gradually detach, allowing the tail to rejoin the main body of the cell. Experimental evidence shows that, in the case of fibroblasts, the majority of adhesion bonds are broken simply by ripping the integrins from the cell membrane and leaving them attached to the substrate. Integrins that remain concentrated at the rear may now be redistributed or concentrated forward to prepare for future adhesion bonds.

Throughout this process, it is essential that the strength of these adhesion bonds be carefully regulated. In stages 3 and 4, if the adhesion bond is of inadequate strength, the bond will simply break, leaving the cell unable to move, having nothing against which to exert force. In stage 5, the force holding the cell to the substrate must not be too strong. If adhesion receptors are over-expressed in the tail, the cell may require a great force to break the bond, which may retard the movement of the cell.

Movement on the substrate is but one aspect of the motion of which a cell is capable. Of more interest is the way large populations of cells interact and move with one another. When several cells selectively adhere to one another, the resulting system may behave as a single tissue whose movements are determined by the motions of its constituent cells relative to the fixed substrate, as well as relative to one another. How the individual connections between cells combine to produce this tissue-like movement is not well understood, and is therefore difficult to model mathematically.

In order to better understand the motive properties of amoeboid cells in general, biologists have focused their attention on *Dictyostelium discoideum* (Dd), a simple cellular slime mold that exhibits interesting motive behavior. Dd reacts to a nucleotide called cyclic Adenosine monophosphate (cAMP). Left to its own devices, Dd extends pseudopods

at random. In the presence of cAMP, however, Dd cells orient towards the source of the cAMP pulse. They initially travel independently, but eventually form streams of cells that move toward the cAMP stimulus. These streams of cells converge to a cigar-shaped mass called a slug. This slug of cells is able to detect stimuli and propogate these signals throughout. The cells are then able to respond in such a way that the result is concerted effort to move the slug, rather than random motions of individual cells. The mechanisms by which Dd cells adhere to one another and propogate stimulus signals continues to be actively studied.

In addition to Dd, there are other systems in which cell migration is important. Many cells, such as those found in embryonic tissues, move by a similar process. When many cells move inward at the same time, they slide past one another and line up in an alternating fashion, much like interlocking fingers. This process, called intercalation, results in narrowing (convergence) and lengthening (extension) of the tissue as a whole. By this mechanism, tissues are able to take the shape that is needed for appropriate embryonic development.

There are also many other physical processes in which cell migration is integral, as noted in [8]:

> Cell migration plays a central role in a wide variety of biological phenomena. In embryogenesis, cellular migrations are a recurring theme in important morphogenic processes ranging from gastrulation to development of the nervous system. Migration remains prominent in the adult organism, in normal physiology as well as pathology. In the inflammatory response, for example, leukocytes immigrate into areas of insult, where they mediate phagocytic and immune functions. Migration of fibroblasts and vascular endothelial cells is essential for wound healing. In metastasis, tumor cells migrate from the initial tumor mass into the circulatory system, which they subequently leave and migrate into a new site. Finally, cell migration is crucial to technological ap-

plications such as tissue engineering, playing an essential role in colonization of biomaterials scaffolding.

Since adhesion plays such an important part in these processes, it seems natural to study adhesion as a major component of cell motion. With this in mind, the intent of this thesis is to present a simple force-based model of moving and interacting cells that incorporates a realistic description of cell adhesion and applies it to a system of spherical cells. Rather than focusing on the geometry of the model and using *ad hoc* methods of treating adhesion, as is done in other models, we opt for a simple geometry so that we can focus our attention on implementing adhesion in the way it ought to behave. This model can be represented as a matrix equation where the velocities of the cells and the adhesion forces are unknowns that can be determined based on the spatial locations of the cells together with external forces acting on the system of cells. With the help of some matrix theory, we prove that this equation uniquely determines the motion of the system, but possibly not the adhesion forces.

2 Physical Principles

2.1 Aristotelian vs. Newtonian Mechanics

For centuries, the governing authority in physics seems to have been Aristotle. While time brought with it many advances in man's understanding of the physical world, it was not really until Newton that science was able to escape the mindset that had befuddled it for so long. From [4] we see that, at least as concerns our work here, there are four fundamental notions that distinguish the Aristotelian and Newtonian paradigms:

- The effect of force.
- The natural state of objects.
- Action at a distance.
- Infinite motion.

The Effect of Force

Aristotle believed that force was the sole cause of motion—that at a given moment an object is in motion if and only if some sufficient force is acting on it *at that moment*. Thus, the cause of acceleration is a change in the magnitude of the force causing the motion. Aristotle calculated velocity by the formula

$$\text{Velocity} = \frac{\text{Force (Motive power)}}{\text{Resistance}}.$$

This theory brought with it some difficulties. It is not hard to find examples where this simply doesn't work. For example, force can be applied to an object resting on a table without resulting in any sliding. For this reason, Archimedes stipulated that the motive force must be greater than the resistance force in order to achieve motion. Another

limitation to this formula is that it actually *requires* resistance to be nonzero, which makes travel in a vacuum a rather perplexing notion—a topic of much debate over the centuries.

Some of the limitations of this theory are evident in the problem of projectile motion. Under this theory, it is very difficult to explain the fact that the vertical motion of a projectile slows down until it attains its apex, and then speeds up again as it descends.

The Newtonian view, however, is simpler. Rather than causing movement *per se*, force causes *change* in motion. The problem of the object that resists sliding can be easily explained through the notions of static and kinetic friction. The fact that a projectile continues to move once it has left the hand of the thrower is due not to some mysterious force left in the projectile by the thrower. Rather, it is due to the inertia imbued by the thrower.

Natural State

Aristotle's idea of an object's natural state derives from his notion of its composition as some mixture of the four elements: earth, fire, wind, and water. For example, earth is believed to be absolutely heavy and, therefore, should fall to the center of the universe (the center of the earth). Fire, considered absolutely light, should rise to its natural place near the other extreme—a sphere within the lunar sphere. A mixture of fire and earth either rises or falls based on which of the two elements is dominant.

Thus, a composition of fire and earth tends to be at rest—either as near to the center of the universe as possible or as near to its natural sphere as possible, depending on which element dominates the composition. Many attempts were made over the ensuing centuries to explain this behavior.

Newton, on the other hand, was able to see past this idea. He understood that an object's natural tendency is not necessarily to be in any particular place, or even in any particular type of motion. Rather, he theorized that its natural tendency is for its behavior to remain unchanged—the principle of inertia. If in motion, it tended to maintain its velocity unless acted on by some external force. In short, whereas Aristotelian mechanics

favor lack of motion, Newtonian mechanics favor lack of acceleration.

Action at a distance

One of the underlying difficulties of Aristotelian mechanics was the idea that force could not be applied except upon physical contact between two entities. Enormous efforts were made during the Middle Ages to explain the motion of projectiles. Nobody could explain why a projectile continued to move once it had left the hand of the thrower. Avicenna (980-1037) wrote the following:

> There are some who hold that the cause lies in the tendency of the air which has been pushed to get behind the projectile and to unite there with a force which presses against that which is in front of it. There are others who say that the pusher pushes the air and the projectile together, but the air is more receptive to pushing and so it is pushed more swiftly and thus pulls that which has been placed in it. And there are those who hold that the cause is in that force which the moved acquires from the mover and which persists in it for a time until it is abolished by the opposing force of that which touches it and is displaced by it. ... But when we have verified the matter we have found the most valid opinion to be that of those who hold that the moved received an inclination from the mover. The inclination is that which is perceived by the senses to be resisting a forceful effort to bring the natural motion to rest or to change one violent motion into another.

Gravity, for example, was a great mystery to physicists before Newton. Even now, the nature and cause of gravity is mysterious, but Newton and physicists since have been much more successful at predicting its effects than Aristotle was.

Infinite motion

The idea that a projectile could continue to move forever without ever slowing down was completely alien to Aristotelian physicists. In fact, many physical arguments (such

as the possibility of motion in a vacuum) were rejected on the grounds that they would result in infinite motion.

Newtonian mechanics, on the other hand, has no problems with infinite motion. In fact, infinite motion is precisely what Newtonian mechanics predicts in the absence of external force.

Thus, we see that there are several seemingly irreconcilable differences between the Aristotelian and Newtonian worldviews, and that the Newtonian model more accurately reflects reality. However, as we will see in the following subsections, there are circumstances under which the Aristotelian model is a very good approximation to the Newtonian model. We begin by introducing a fundamental concept from fluid dynamics.

2.2 Reynolds number

One of the most important quantities used in the study of the fluid dynamics of a system is a dimensionless quantity called the Reynolds number, Re. When a fluid flows through a conduit or around an obstacle, the Reynolds number measures the turbulence of the flow due to the cross-section of the conduit or obstacle. It is commonly defined by either of the formulas

$$Re = \frac{\rho v_s L}{\mu}, \tag{1}$$

$$Re = \frac{v_s L}{\nu} \tag{2}$$

where

- v_s - mean fluid velocity
- L - characteristic length of the cross-section. If the cross-section is circular, it is the diameter of the cross-section.

- μ - dynamic fluid viscosity
- ν - kinematic fluid viscosity ($\nu = \mu/\rho$)
- ρ - fluid density

A fluid flow can be visualized as parallel layers moving past one another. A low Reynolds number indicates that these layers are flowing freely and smoothly, with little friction between them. Large Reynolds numbers, on the other hand, indicate a great deal of interaction between the fluid layers, causing eddy currents that produce very turbulent flows.

Associated with a flow is a critical Reynolds number which represents the transition between laminar and turbulent flows. For example, water flowing through a circular pipe has a critical Reynolds number of approximately 2300. With a Reynolds number of 1000, the flow is laminar, while at 4000 the flow is quite turbulent. Near 2300, the flow may be rather unpredictable.

In practice it can be very useful to compare two flows with one another. Two flows are said to be similar if they have the same geometry and their Reynolds numbers are equal. This idea is essential in the use of wind tunnels for testing aerodynamic stability of aircraft, for example. Rather than subjecting a full-size model of the aircraft to a wind tunnel, a scaled-down version can be used. However, in order to use the model to deduce the behavior of the actual aircraft, the wind speed, air pressure and other parameters must be appropriately scaled so that the Reynolds number of the model matches the Reynolds number of the actual aircraft in flight.

In the case of our system of cells, it is instructive to calculate the Reynolds number for a cell in a fluid medium and compare it to a larger system that is similar (has the same Reynolds number).

In the case of the amoeboid *Dictyostelium discoideum*, we find the diameter of a large cell to be about 10 microns. The density and viscosity of water at 30 degrees Celsius are

995.7 kg/m^3 and 7.975×10^{-4}N $\cdot$ s/m^2, respectively. With a velocity of 10 microns per minute [1], we calculate the Reynolds number for the cell as

$$Re = \frac{\rho v_s L}{\mu} = \frac{995.7\,\mathrm{kg/m^3} \cdot 10\,\mu\mathrm{m/min} \cdot 10\,\mu\mathrm{m}}{7.975 \times 10^{-4}\,\mathrm{N \cdot s/m^2}} = 2.08 \times 10^{-6}.$$

If we were to produce a similar flow with a cell scaled to 1 m in diameter, we would find that

$$v_s = \frac{Re \cdot \mu}{\rho \cdot L} = \frac{2.08 \times 10^{-6} \cdot 7.975 \times 10^{-4}\,\mathrm{N \cdot s/m^2}}{995.7\,\mathrm{kg/m^3} \cdot 1\,\mathrm{m}} = 3.33 \times 10^{-12}\,\mathrm{m/s}.$$

So, to compare the flow of water around a cell of diameter 10 μm to the flow about one of diameter 1 m (both in water), we would require the 1-meter cell to travel at a miniscule speed of 3.33×10^{-12} m/s, or roughly 1.2×10^{-7} centimeters per hour. It would take such a cell roughly 9 500 years to travel a single meter!

It is unreasonable to believe that we could compare such flows in any precise way. The 5 orders of magnitude that separate a cell of diameter 10 microns from our hypothetical cell of 1 meter mean that our intuition of physics must be modified if we are to work with cells at the microscopic level when such a small Reynolds number governs the behavior of our system.

2.3 Low Reynolds number

If we manipulate equation (1), we find that

$$Re = \frac{\rho v_s L}{\mu} = \frac{\rho v_s}{\mu / L}.$$

That is, the Reynolds number can be thought of as the ratio between the effects of inertia (ρv_s) and the viscous forces (μ / L) of the system.

In the case, as above, where we have a low Reynolds number ($Re \ll 1$), this interpretation of Re indicates that inertial effects involved in our system are several orders of

magnitude smaller than the viscous forces present. Because of this, it is difficult, even in a system of double precision arithmetic, to distinguish between ρv_s and zero. In essence, this allows us to think of such a system as being without the inertial principle. As Purcell [10] says,

> For these animals inertia is totally irrelevant. *We* know that $F = ma$, but they could scarcely care less. ...In water where the kinematic viscosity is 10^{-2} cm/sec these things move around with a typical speed of $30\,\mu$m /sec. If I have to push that animal to move it, and suddenly I stop pushing, how far will it coast before it slows down? The answer is, about $0.1\mathring{A}$. And it takes it about 0.6μ sec to slow down. ...Inertia plays no role whatsoever. If you are at very low Reynolds number, what you are doing at the moment is entirely determined by the forces that are exerted on you *at that moment*, and by nothing in the past.

At this scale, things behave much as Aristotle and generations of scientists believed. That is, the only thing that can produce motion is force, and in the absence of force there is no motion. In particular, it is futile to discuss acceleration, for it is nearly instantaneous. As Purcell noted above, it takes one of these cells travelling at a normal speed only 0.6μsec to come to a full stop. Thus, it is not an unreasonable simplification to assume that a cell is either at rest or is in *uniform* motion and that there is no acceleration as a transition between the two.

This has some interesting consequences for Newton's Laws of Motion. Since we neglect acceleration, the familiar equation

$$\sum F_i = ma$$

becomes simply

$$\sum F_i = 0,$$

which will be extremely important to our calculations later on.

3 Current Research and Models

Before discussing the model that is the subject of this paper, we discuss some recent results in the study of adhesion and integrin behavior. This is followed by a discussion of two one-dimensional models of a cell moving on a substrate—the first dividing the cell into discrete subunits and the second treating the cells as a continuum. Finally, we present two related three-dimensional models of cell interaction.

3.1 Integrin Function

As mentioned earlier, the integrins are a variety of molecules that reside in the bilipid layer of the cell membrane. The main function of the integrins with which we are concerned here is their role in the formation of cell bonds, though they also serve as an essential means of signal transmission between the cell and its environment.

When two cells are in close proximity, their corresponding integrins bind to one another, attaching the cells together, thus creating a pathway through which forces may be transmitted between paired cells. That is, the bonds may be strong enough that cells can pull on one another with enough force to cause distortion of their shapes or even translocation of the cells themselves. The bond between integrins may even be strong enough that a cell will actually cause integrins to be ripped from the cell membrane rather than destroying the bond itself. Fibroblasts, for example, are known for this behavior.

Integrins have varying degrees of affinity for binding. It is not well known just how these different states are attained or what induces one integrin to adopt a greater affinity than another. However, as observed in [11], "Physical and biochemical data suggest altered integrin affinity states are due to conformational changes in the receptor itself rather than fluctuations in receptor number." The spatial density of integrins, then, doesn't seem to have an impact on how likely a given integrin is to bond. Rather, the integrin itself may change shape to encourage or inhibit bonding. Certain antibodies, peptides, and cations are known to induce a high-affinity conformation state in integrins.

It is also worthwhile to note that integrins are not restricted to any particular fixed location on the surface of a cell. Rather, a cell may concentrate them in a particular area to increase the number of bonding sites.

In addition to expressing various degrees of binding affinity, adhesion molecules may exhibit varying degrees of bond strength. In [3], Evans and Ritchie discuss how the strength of an individual adhesion bond can be measured, and how Brownian dynamics can be used to describe the strength of these molecular bonds over time under various force loads.

In addition to their role in adhesion, integrins "play a larger role in bidirectional signaling with the extracellular environment." They may signal the need to cluster integrins together or to increase gene transcription, or even regulate intracellular pH [11].

3.2 DiMilla, Barbee, and Lauffenburger Model

DiMilla, Barbee, and Lauffenburger [2] treat cells as one-dimenensional objects existing on a one-dimensional substrate. Thus, any angular properties exhibited by true cells are ignored. To describe the shape of the cells, each cell is divided into discrete subunits, each of which consists of a spring, a dashpot, and a contractile unit in parallel. All changes in shape, including the extension and contraction of pseudopodia, are modelled by these units. The subunits at the ends that represent pseudopodia each contain additional springs—one spring models the natural stiffness of the pseudopod and the others model changes in shape and transmission of force due to adhesion bonds.

This model treats cell movement in three distinct stages. In the first stage, the cell redistributes adhesion receptors asymmetrically on its surface, giving preference to the front, and extends a lamellipod forward. The model makes no account for the nature of the stimulus that might induce the cell to extend the pseudopod and ignores the biophysics of the lamellipod extension. It mainly accounts for the duration of such extensions.

During the second stage, the cytoskeleton of the cell contracts, exerting force on the

adhesion bonds that run the length of the cell. If the substrate is not fixed, the cell may cause substrate deformation. If, however, the substrate is fixed, the cell changes shape. In particular, if the force exerted by the lamellipod is greater than the force exerted by the uropod (tail) of the cell then the result is net forward motion of the main body of the cell while the lamellipod and uropod contract.

The third stage consists of cytoskeletal relaxation as the cell ceases to transmit force to the substrate through the adhesion bonds. The adhesion receptors are then redistributed over the surface of the cell, reducing the statistical asymmetry of adhesion receptor distribution.

In discussing the distribution of adhesion receptors, cells are treated, geometrically, as two rectangular sheets sewn together at the edges. This allows this distribution of receptors, on both top and bottom, to be described by a simple rectangular coordinate system.

The primary focus of this model is to predict the speed at which cells migrate on a substrate, based on rheological properties of the cell and the formation and destruction of adhesion bonds. An obvious limitation of the model, then, is that it provides no mechanism for cells to interact with one another—It only describes the motion of a single cell, being unable to model an interacting system. It is also limited in that it is one-dimensional and there does not appear to be a natural mechanism for extending this model to describe the motion of a cell in 3-space.

3.3 Gracheva and Othmer Model

Gracheva and Othmer [5] developed a one-dimensional cell on a viscous substrate. The cell consists of a set of points lying between the cell front $f(t)$ and rear $r(t)$. Changes in the shape of the cell are accounted for by the relative motion of the points in the interval.

The forces on the cell are the "internal active and passive stress, and the frictional force due to the repetitive formation and breaking of attachments to the substrate." They

treat the cytoplasm as being made of a "linear viscoelastic material that gives rise to a passive stress, an active protrusive stress due to actin polymerization concentrated at the leading edge, and an active stress generated by the interaction of myosin II motors with the cytoskeleton."

This model integrates the effects of the actin-myosin network on the viscoelastic properties of the cell, including how this contributes to the cell's contractile nature. In addition, discrete adhesion sites are assumed.

3.4 Palsson and Othmer Model

Palsson and Othmer [9] treat *Dictyostelium discoideum* cells as deformable ellipsoids of constant volume. That is, each cell is an ellipsoid with axes that are allowed to vary with time and force, with the constraint that the cell maintains its volume under all deformations. Each axis contains "a nonlinear spring in parallel with a Maxwell element [a dashpot and spring in series]" which regulate the deformation of the cell. Cells are allowed to be suspended in a fluid medium or in contact with a surface. When suspended, cells are assumed to be spherical, but may be deformed upon contact with other objects.

In addition to shape, each cell is given an orientation—a direction in which the cell tends to move. When not exposed to a chemotactic signal, the cell's orientation is chosen randomly. When exposed to a chemotactic signal, however, the cell moves so that it is aligned with the signal.

This model examines the forces that are present in the system of cells and calculates the motion of the cells over time from the force equations determined by Newton's second law of motion. The force equations are approximated by a system of first-order differential equations, and are solved iteratively, essentially using Euler's method.

The Palsson-Othmer model seems to be fairly successful at reproducing cell sorting and aggregation experiments. On the other hand, the mechanism by which they simulate adhesion is *ad hoc* and is not designed to be reflective of true adhesion behavior.

3.5 Dallon and Othmer Model

Dallon and Othmer [1] attempt to improve on the model from Palsson and Othmer by improving the mechanism by which *Dictyostelium discoideum* cells cling to one another and to refine how they interact in three dimensions. It is based on the Palsson and Othmer model, but "incorporating better descriptions of cell-cell and cell-substrate interactions." This model is then used to counter certain unexpected experimental results in how a *Dictyostelium discoideum* slug produces and transmits force.

4 The Adhesion Model

4.1 Adhesion and Potentials

Due to the changes in shape of which a living cell is capable, a pair of cells may interact with one another over a range of distances. That is, there is an interval in which the distance between their centers of mass may lie. If cells are interacting and too close together, their cytoplasms and membranes deform, storing a rheological force that tends to push the cells apart. On the other hand, if the cells are interacting from a large distance, the cells tend to pull toward each other. Thus, there is a natural distance at which interacting cells are at rest with respect to one another and toward which they tend.

This tendency is reminiscent of the behavior of interacting atoms. When certain types of atoms are distant (but not too distant) from one another, their tendency is attraction. When they approach one another too closely, however, a repulsive force dominates, pushing the atoms apart. As with the cells, there is an optimal separation between pairs of atoms toward which they tend. It seems natural, then, to use interacting atoms as a model for interacting cells.

An advantage to this approach is that there is a wealth of theory in place to describe the behavior of interacting atoms. For example, the motion of atoms acting under electromagnetic forces, as above, is often described using functions known as potentials. If $F : \mathbb{R}^3 \to \mathbb{R}^3$ is a vector field such that $\nabla \times F \equiv 0$ then there exists a twice-continuously differentiable function $f : \mathbb{R}^3 \to \mathbb{R}$ such that $\nabla f = F$. The function f, unique up to an additive constant, is called a potential function for the vector field F. Potentials have been studied for centuries and there is much that is known about them.

However, interacting atoms are not entirely analogous to interacting cells. In both systems, interacting objects repel when too close and attract when too distant, and tend toward some distance of minimum potential energy. However, the mechanisms by which

they do this are completely different. While it is tempting to employ potentials to study interacting cells, in analogy with atoms, this should be avoided. The similarities do not justify the use of potentials to model the behavior of interacting cells. This would be mathematically simple, but in section 6.2 we will see that this is not reflective of the true behavior of cells.

4.2 Holonomic Constraints

In examining the constraints on a system, we find that some constraints are much easier to study than others. One type of constraint that is usually easier to work with than others is called *holonomic*. A constraint is said to be holonomic if it can be expressed in the form

$$f(x^1, \ldots, x^n) = 0 \tag{3}$$

where $x^1, \ldots, x^n$ are the variables manifest in the system.

A holonomic constraint reduces the number of degrees of freedom of a system. For example, if $x, y \in \mathbb{R}$ are the variables of a system and can be chosen independently then there are 2 degrees of freedom. If we add the constraint $x - y = 3$, then y is completely determined by x (and vice versa) so there is only one degree of freedom. We have reduced the input space by one degree from $\mathbb{R}^2$ to a one-dimensional topological subspace of $\mathbb{R}^2$. Thus, a holonomic constraint, by reducing the input space to, perhaps, a lower-dimensional manifold, may be applied by (explicitly or implicitly) solving for one of the variables in terms of the others. The method of Lagrange multipliers can also be used to impose many holonomic constraints.

A constraint that cannot be expressed in the form (3) is said to be *nonholonomic*. An example of a nonholonomic constraint is

$$|x| + |y| < 2.$$

While this constraint reduces the size of the input space from a measure theory standpoint,

it does not reduce its dimension. It is still a two-dimensional topological subspace of $\mathbb{R}^2$.

In describing adhesion, one might assume that if two cells are interacting then their centers of mass x and y must satisfy

$$0 < d_{\min} < |x - y| < d_{\max} < \infty$$

where $d_{\min}$ and $d_{\max}$ are minimum and maximum allowable distances between interacting cells. This spatial constraint is clearly nonholonomic. Numerically, this constraint significantly reduces the search space for a solution. However, x and y lie in $\mathbb{R}^3$ so that, mathematically, the input space is still a 3-dimensional submanifold of $\mathbb{R}^3$—a ball whose core has been removed.

In our model, however, we introduce a different sort of constraint. Rather than considering the allowable distances to vary, we require the distance between the two cells to be zero. However, this is not the distance between the centers of mass. Rather, we think of two cells as closed topological balls. As such, the distance we use is a standard one for measuring the separation of subsets of $\mathbb{R}^n$. That is,

$$d(A, B) = \inf \{\|x - y\|_2 \mid x \in A, y \in B\}$$

where $\|x\|_2 = \sqrt{x^T x}$.

With this idea in mind, we can phrase our constraint thus: If adhesion is acting between cells A and B then $d(A, B) = 0$. This constraint is clearly holonomic. Intuitively, we can think of this constraint as forcing the two cells A and B to be tangent at some point. Thus, if we think of one of the cells as being fixed in space then the other must move about on the surface of the first. In this way, we have reduced the space in which a cell can move from three dimensions to two. It is now a topological sphere (the boundary of a topological ball).

An important effect of this adhesion constraint is that the difficulty is no longer in calculating the magnitude of the adhesion force. Rather, the difficulty lies in describing the shape of the surface (membrane) of the cells—especially in calculating the *changes*

the shape of a cell undergoes when in contact with other cells. In order to examine the system of equations that governs the motion of a system of cells, we will be making some assumptions that, though unrealistic, allow us to reduce the complexity of the system so that we are able to study it.

4.3 Simplifying Assumptions

Since great difficulty lies in describing the shape of cells over time, the first assumption that we will make is that our cells are rigid spheres, each of the same radius r. We will not account for any variation in the size of specimens, nor will we account for the rheological properties of the cells. That is, the cell membrane and cytoplasm do not change shape, nor do they absorb force—they simply transmit it. In particular, the formation of pseudopodia and lamellipodia is completely ignored.

In the general model, we think of cells as being in contact when their membranes are tangent to one another. Since we are here fixing the shape of the cell membrane as a sphere, and the cells may not overlap, the natural assumption is that cells are in contact with one another if and only if their spherical shells are tangent to one another. Specifically, if x^i and x^j represent the centers of the two spherical cells that are in contact then $\left\|x^i - x^j\right\|_2 = 2r$.

The system we will work with consists of n of these rigid spherical cells. We arbitrarily number the cells from 1 to n and, as suggested above, we denote the position in $\mathbb{R}^3$, relative to a fixed orthonormal basis, of cell i by x^i. We may refer to the kth component of the position vector x^i by x^i_k. It should be noted that, since no two cells can occupy the same position, $x^j - x^i = 0$ if and only of $j = i$. The following notation will be helpful as we proceed to examine the forces acting on each cell, in order to produce the system of differential equations that governs the motion of the cells.

Notation 1. In addition to $\|\cdot\|_2$, we will use the following notational conventions:

1. $\|x\|_\infty$ denotes the infinity norm of the vector x. That is, if $x \in \mathbb{R}^n$ then $\|x\|_\infty =$

$\max\left\{|x_k| \,\middle|\, k = 1, \ldots n\right\}$

2. $\widehat{x} = \dfrac{x}{\|x\|_2}$, if x is not the zero vector.

3. $\dot{x}$ denotes the componentwise derivative of the vector function x with respect to the time variable t. That is, $\dot{x} = \dfrac{dx}{dt} = \begin{pmatrix} \frac{dx_1}{dt} \\ \vdots \\ \frac{dx_n}{dt} \end{pmatrix}$.

4.4 The Force Equations

We consider the following forces that affect the motion of cell i:

1. *Motive Force.* This is the force produced when cell i pushes or pulls against an object external to the system of cells, such as the substrate. It accounts for the reactive force when the cell exerts force in the substrate in response to a stimulus. It is this reactive force that results in motion of the cell. It also includes the reactive force when the cell is pushed against the substrate by another cell. This component is what prevents the cell from passing through the substrate rather than crawling on the surface. A more sophisticated treatment of the model would distinguish between these two forces, but we will combine their effects and denote this composite force M_i. Due to the variety of possible interactions with non-cell objects, the motive force may be of arbitrary magnitude and direction.

2. *Adhesion.* This force is active between a pair i, j of cells only when the two cells are in close proximity (i.e., the spherical shells are tangent). This force represents the tendency of cells to resist being separated once they are near to one another. It arises between a pair of cells when the net force acting on each would separate them. The magnitude of the adhesion force is equal to the magnitude of the net force pulling the two cells apart. If, however, the net force pulling them apart is larger than the maximum adhesion force that the cell can maintain, then the adhesion breaks and

the cells are pulled apart. Numerically, then, there is a Heaviside function to break the bond if the force is too great, but we will not explicitly include the Heaviside function in our calculations here.

The adhesion force acting on cell i due to contact with cell j is orthogonal to the surface of cell i at the point of tangency. Thus, this force is in the direction of $(x^j - x^i)$, and is denoted $\mathcal{A}_{ij}$ so that $\mathcal{A}_{ij} = \|\mathcal{A}_{ij}\|_2 \widehat{x^j - x^i}$. Since forces occur in action/reaction pairs, we have $\mathcal{A}_{ij} = -\mathcal{A}_{ji}$.

3. *Repulsion.* This force, too, is active between a pair i, j of cells only when the two cells are very close. It arises when the net force acting on each cell would push the pair closer together. Since the cells are considered to be rigid spheres, they cannot be made to be closer than twice the radius of the cell (within numerical tolerance). It is always exactly equal in magnitude to the net force pulling the two cells together. This constraint prevents the cells from overlapping.

   The repulsive force acting on cell i due to interaction with cell j occurs in the direction $(x^i - x^j)$, and is denoted $\mathcal{P}_{ij} = \|\mathcal{P}_{ij}\|_2 \widehat{x^i - x^j}$. As above, since forces exist in action/reaction pairs, we have $\mathcal{P}_{ij} = -\mathcal{P}_{ji}$.

   Clearly, adhesion and repulsion are mutually exclusive. That is, a pair of cells cannot be simultaneously pulling and pushing on one another. At a given instant, therefore, no more than one (perhaps neither) of $\|\mathcal{P}_{ij}\|_2$ and $\|\mathcal{A}_{ij}\|_2$ is nonzero.

   As discussed above, adhesive and repulsive forces preserve the distance between cell membranes at zero, providing our holonomic constraint. Since our cells are spheres, this is equivalent to $\left\|x^j - x^i\right\|_2 = 2r$, where x^i and x^j are the centers of the cells. Differentiating, we obtain the equivalent condition

$$(x^i - x^j)^T(\dot{x}^i - \dot{x}^j) = 0. \tag{4}$$

4. *Friction.*

(a) *Substrate/Fluid.* As cell i travels, it has an area A_{if} of its surface (membrane) in contact with the fluid medium. It is possible that $A_{if} = 0$. A cell that is entirely surrounded by other cells satisfies this condition, for example. The viscous forces of the fluid resist the translation of the cell through the fluid. We take this resistance to be jointly proportional to A_{if} and to $\left\|\dot{x}^i\right\|_2$, with constant of propotionality μ_f, and in the direction $-\dot{x}^i$. Thus, the viscous force can be written $-\mu_f A_{if}\dot{x}^i$.

Similarly, a cell may have an area A_{is} in contact with the substrate. As above, it is possible that $A_{is} = 0$. Similarly, we assume that the substrate in contact with the cell produces a frictional force $-\mu_s A_{is}\dot{x}^i$.

Since densely packed spheres can have as many as 12 neighbors, we assume that each cell in contact with cell i occupies $\frac{1}{12}$ the surface area of cell i. That is, we assume that fluid directly between interacting cells, occupying $\frac{1}{12}$ the surface area of the cell, moves *with* the cells so that it does not resist the motion of the cells. Therefore, we take the total surface area in contact with the fluid and substrate to be

$$A_{if} + A_{is} = 4\pi r^2 \left(1 - \frac{n_i}{12}\right)$$

where n_i is the number of cells in surface contact with cell i.

Since both of these forces are in the same direction, we can consider them together as a single frictional force $-\mu_i\dot{x}^i$ where $\mu_i = \mu_s A_{is} + \mu_f A_{if}$. It should be emphasized that μ_i is not a constant. While we assume homogeneity of the fluid medium and substrate so that μ_f and μ_s are constant, the two areas involved depend upon the number of cells in contact with cell i, and thus upon the positions of all the other cells relative to cell i. Therefore, μ_i is really a function of the positions of all cells in the system. However, for ease of calculation this dependence will be suppressed in the notation.

(b) *Intercellular.* Since we are assuming that our cells are rigid spheres, equation (4) requires that whenever our cells adhere to (or repel) one another, their relative velocity is tangential to both spheres at the point where they are in contact. Thus, in this circumstance, the two cells can be thought of as "sliding" past one another.

This produces a friction-like force between the cells in the direction opposite their relative velocity. Its magnitude is proportional to the magnitude of the relative velocity, with proportionality μ_{ij}. So, we denote this force by $-\mu_{ij}(\dot{x}^i - \dot{x}^j)$. Note that $\mu_{ij} = \mu_{ji}$ since these forces exist in action/reaction pairs. If cells i and j are not in contact then, naturally, $\mu_{ij} = 0$. In the physical system, μ_{ij} might be thought of as a function of the distance between cells i and j.

Note also that a cell is always in contact with some combination of the substrate, the fluid medium, and other cells, so that at least one of $\mu_i, \mu_{i1}, \mu_{i2}, \ldots, \mu_{in}$ is positive, and so the sum $\mu_i + \sum_{j \neq i} \mu_{ij}$ is also positive.

From Newton's second law of motion, we know that the motion of cell i obeys the vector differential equation

$$m_i \ddot{x}_i = \sum_j F_{ij}$$

where the vectors F_{ij} are the forces acting on cell i. However, from our discussion of the low Reynolds number of the system, we have $m_i \ddot{x}_i \approx 0$, so that we may neglect the left-hand side of the equation and approximate the equation as

$$\sum_j F_{ij} = 0.$$

Thus, the motion of cell i is approximated by the first-order vector differential equation

$$\begin{aligned} &-\mu_i \dot{x}^i - \mu_{i1}(\dot{x}^i - \dot{x}^1) - \cdots - \mu_{in}(\dot{x}^i - \dot{x}^n) \\ &+\mathcal{A}_{i1} + \cdots + \mathcal{A}_{in} + \mathcal{P}_{i1} + \cdots + \mathcal{P}_{in} + M_i = 0. \end{aligned} \tag{5}$$

The entire system, then, is:

$$\begin{aligned}
\mu_1\dot{x}^1 + \sum_{j\neq 1}\mu_{1j}(\dot{x}^1 - \dot{x}^j) &= \sum_{j\neq 1}(\mathcal{A}_{1j} + \mathcal{P}_{1j}) + M_1, \\
&\vdots \\
\mu_n\dot{x}^n + \sum_{j\neq n}\mu_{nj}(\dot{x}^n - \dot{x}^j) &= \sum_{j\neq n}(\mathcal{A}_{nj} + \mathcal{P}_{nj}) + M_n.
\end{aligned} \tag{6}$$

4.5 The Matrix Equation

System (6) will now be expressed as a matrix equation, rather than as a system of equations. In order to simplify the form of the matrix equation, however, we will rearrange the terms in equation (5) as follows:

$$\begin{aligned}
M_i &= \mu_i\dot{x}^i + \sum_{j\neq i}\mu_{ij}(\dot{x}^i - \dot{x}^j) - \sum_{j\neq i}\mathcal{A}_{ij} - \sum_{j\neq i}\mathcal{P}_{ij} \\
&= \left(\mu_i + \sum_{j\neq i}\mu_{ij}\right)\dot{x}^i - \sum_{j\neq i}\mu_{ij}\,\dot{x}^j - \sum_{j\neq i}(\|\mathcal{A}_{ij}\|_2 - \|\mathcal{P}_{ij}\|_2)\,\widehat{x^j - x^i}.
\end{aligned} \tag{7}$$

In order to facilitate calculations and since $\widehat{x^j - x^i} = \dfrac{x^j - x^i}{\|x^j - x^i\|_2}$, we define

$$a_{ij} = \frac{\|\mathcal{A}_{ij}\|_2 - \|\mathcal{P}_{ij}\|_2}{\|x^j - x^i\|_2} \tag{8}$$

and find that

$$(\|\mathcal{A}_{ij}\|_2 - \|\mathcal{P}_{ij}\|_2)\,\widehat{x^j - x^i} = a_{ij}\,(x^j - x^i).$$

Note that $a_{ij} = a_{ji}$ so that $a_{ij}(x^i - x^j) = a_{ji}(x^j - x^i)$. Since adhesion and repulsion are mutually exclusive, we find that $a_{ij} > 0$ if and only if cells i and j are adhering, while $a_{ij} < 0$ if and only if the two cells are repelling one another. The values of the coefficients a_{ij} are unknowns in this system, and are to be calculated as a step in determining the motion of the cells. Once these coefficients are calculated, the magnitudes of the adhesive/repulsive forces can be found by calculating each quantity $|a_{ij}|\,\left\|x^i - x^j\right\|_2$. Substituting equation (8) into equation (7), we have a much simpler representation of the system:

$$M_i = \left(\mu_i + \sum_{j\neq i}\mu_{ij}\right)\dot{x}^i - \sum_{j\neq i}\mu_{ij}\,\dot{x}^j + \sum_{j\neq i}a_{ij}\,(x^i - x^j). \tag{9}$$

We now construct a matrix equation that is equivalent to the system (9) of equations governing the motion of the system of cells. Observe that if, for each i, we define the $3n \times 1$ vector $\dot{x}$ and the $3 \times 3n$ matrix V_i by

$$\dot{x} = \begin{pmatrix} \dot{x}^1 \\ \vdots \\ \dot{x}^i \\ \vdots \\ \dot{x}^n \end{pmatrix},$$

$$V_i = \left(-\mu_{i1} I, \ldots, -\mu_{i(i-1)} I, \left(\mu_i + \sum_{j \neq i} \mu_{ij} \right) I, -\mu_{i(i+1)} I, \ldots, -\mu_{in} I \right),$$

where I is the identity matrix in $\mathbb{R}^3$, then equation (9) becomes

$$\left(\mu_i + \sum_{j \neq i} \mu_{ij} \right) \dot{x}^i - \sum_{j \neq i} \mu_{ij} \, \dot{x}^j = V_i \dot{x}. \tag{10}$$

In order to facilitate calculations later, we now need a systematic way of ordering the numbers a_{ij}. Though the order is irrelevant, it seems convenient to order them as follows:

$$a_{12}, \quad a_{13}, a_{23}, \quad a_{14}, a_{24}, a_{34}, \quad \ldots, \quad a_{1n}, \ldots, a_{(n-1)n}.$$

Observe that the terms appear in $(n-1)$ clusters, the first cluster containing one element and each successive cluster incremented in size by one, for a total of $\frac{1}{2}n(n-1)$ elements.

Now we would like to be able to determine, under this ordering, the location of a_{hk} for given h, k. Similarly, it is useful to be able to caculate, for given j, the integers h, k if a_{hk} is the jth term in the sequence. With this in mind, observe that if l is a positive integer then the total number of elements in the first l clusters is

$$1 + 2 + 3 + \cdots + l = \frac{1}{2} l(l+1).$$

Let $a_{h_j k_j}$ be the jth term in the sequence. Notice that this term lies in the $(k_j - 1)th$ cluster. Therefore, exactly $(k_j - 2)$ complete clusters precede the jth term, so that

$$\frac{1}{2}(k_j - 2)(k_j - 1) < j \leq \frac{1}{2}(k_j - 1)(k_j).$$

Considering these two inequalities independently, we find that

$$\left| k_j - \frac{3}{2} \right| < \frac{1}{2}\sqrt{8j+1},$$

$$\left| k_j - \frac{1}{2} \right| \geq \frac{1}{2}\sqrt{8j+1}.$$

Putting them together and observing that $k \geq 2$, we find that

$$0 \leq k_j - \frac{1}{2}\left(1 + \sqrt{8j+1}\right) < 1.$$

Thus,

$$k_j = \left\lceil \frac{1}{2}\left(1 + \sqrt{8j+1}\right) \right\rceil$$

where $\lceil \cdot \rceil$ denotes the *least integer*, or *ceiling*, function. Finally, a quick observation shows that

$$h_j = j - \frac{1}{2}(k_j - 2)(k_j - 1).$$

By reordering this equation, we see that if a_{hk} is in the sequence then a_{hk} is the jth term, where $j = j(h,k)$ may be calculated as

$$j = h + \frac{1}{2}(k-2)(k-1).$$

We now construct the $3n \times \frac{1}{2}n(n-1)$ block matrix A and the $\frac{1}{2}n(n-1) \times 1$ block vector a as follows: For each $1 \leq h < k \leq n$, if cells h and k are close enough to interact then set $A_{hj} = x^h - x^k, A_{kj} = x^k - x^j$ and $a_j = a_{hk}$. Otherwise, set $A_{hj} = 0, A_{kj} = 0$ and $a_j = a_{hk} = 0$. In the matrix equation, A controls the direction of each adhesion force, while a encodes the magnitudes of the adhesion vectors. We will see later that the holonomic constraint discussed earlier can be phrased in terms of A. Note that, since a cell can only have as many as 12 neighbors, and a nonzero column accounts for a single interacting pair, A has no more than $6n$ non-zero columns and the corresponding entries of a are the only entries of a that can possibly be non-zero. With A_i denoting the ith row of blocks of A, we find that

$$A_i a = \sum_{j \neq i}^{n} a_{ij}(x^i - x^j). \tag{11}$$

We now substitute equations (10) and (11) into equation (9) to see that

$$M_i = V_i\dot{x} + A_i a. \tag{12}$$

Thus, if we rewrite the entire system in this way, we have the matrix equation

$$M = V\dot{x} + Aa, \tag{13}$$

where

$$V = \begin{pmatrix} V_1 \\ \vdots \\ V_n \end{pmatrix}$$

tracks the friction interactions and

$$M = \begin{pmatrix} M_1 \\ \vdots \\ M_n \end{pmatrix}.$$

represents the motive forces of the collection of cells.

It is easy to see that V is a block matrix of the form

$$V = \begin{pmatrix} \left(\mu_1 + \sum_{k\neq 1}\mu_{1k}\right) I & -\mu_{12}I & \dots & -\mu_{1n}I \\ -\mu_{12}I & \left(\mu_2 + \sum_{k\neq 2}\mu_{2k}\right) I & \dots & -\mu_{2n}I \\ \vdots & \vdots & \ddots & \vdots \\ -\mu_{1n}I & -\mu_{2n}I & \dots & \left(\mu_n + \sum_{k\neq n}\mu_{nk}\right) I \end{pmatrix}.$$

So, V can be represented as

$$V = W \otimes I,$$

where $\otimes$ denotes the Kronecker (direct) product and

$$W = \begin{pmatrix} \mu_1 + \sum_{k \neq 1} \mu_{1k} & -\mu_{12} & \cdots & -\mu_{1n} \\ -\mu_{12} & \mu_2 + \sum_{k \neq 2} \mu_{2k} & \cdots & -\mu_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -\mu_{1n} & -\mu_{2n} & \cdots & \mu_n + \sum_{k \neq n} \mu_{nk} \end{pmatrix}.$$

The matrix W is clearly symmetric, so its eigenvalues are real. Furthermore, since μ_i and μ_{ij} are non-negative real numbers for each i and j, we clearly have the inequality

$$w_{ii} = |w_{ii}| \geq \sum_{j \neq i} |w_{ij}|.$$

The Geršgorin disk theorem, therefore, tells us that the eigenvalues of W lie in the right closed half-plane. That is, the eigenvalues of W are all non-negative real numbers. We conclude that W is positive semi-definite and, therefore, so is V. To complete the analysis of the matrix system, we need to show that V is positive definite. If W is invertible, then $V = W \otimes I$ is also invertible and, therefore, positive definite with inverse $V^{-1} = W^{-1} \otimes I$. If it is the case that $\mu_i \neq 0$ for each i then the Geršgorin theorem guarantees that W is invertible. However, if cell i is completely enclosed by other cells then $\mu_i = 0$. Therefore, we pause our discussion of this matrix system so that we can construct the tools we need in order to conclude that W is nonsingular.

5 Matrix Analysis

We begin this section by defining some notation and a vector product that we will employ throughout the section. Throughout this section, the symbols i, j, k, l, m, and n will always denote positive integers.

Notation 2. Let $M_{m,n}$ denote the set of $m \times n$ matrices whose entries lie in the field $\mathbb{C}$ of complex numbers. Let $A \in M_{m,n}$ be a matrix. We will denote by a_{ij} the entry of A lying in the ith row and jth column. We will denote the ith row vector of A by A_i. That is,

$$A = \begin{pmatrix} a_{11} & \dots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{m1} & \dots & a_{mn} \end{pmatrix}$$

and

$$A_i = \begin{pmatrix} a_{i1} & \dots & a_{in} \end{pmatrix}.$$

Also, we will denote by A^* the Hermitian transpose of A.

Definition 1. Let $x, y \in \mathbb{R}^n$. We define the product $\langle x, y \rangle$ by the formula

$$\langle x, y \rangle = \sum_{j=1}^{n} |x_j y_j|.$$

Note that here we make no distinction between row vectors and column vectors. In general, we will consider row vectors and when referring to columns of A we will actually treat them as rows of A^*. Before proceeding further, we demonstrate some basic facts about the product $\langle \cdot, \cdot \rangle$.

Lemma 1. *Let $x, y, z \in \mathbb{C}^n$ and $\alpha \in \mathbb{C}$. Then:*

(a) $\langle x, y \rangle \geq 0$.

(b) $\langle x, x \rangle = 0 \iff x = 0$.

(c) $\langle y, x \rangle = \langle x, y \rangle$.

(d) $\langle \alpha x, y \rangle = |\alpha| \langle x, y \rangle$.

(e) $\langle x+z, y\rangle \leq \langle x, y\rangle + \langle z, y\rangle$.

(f) $\langle x, y\rangle \neq 0$ *if and only of there is an index* k *such that* x_k *and* y_k *are both nonzero.*

Proof.

(a) This is immediate, since $\langle x, y\rangle$ is the sum of non-negative terms.

(b) $$\begin{aligned}\langle x, x\rangle = 0 &\iff \sum_{j=1}^{n} |x_j^2| = 0 \\ &\iff |x_j|^2 = 0 \text{ for each index } j \\ &\iff x_j = 0 \text{ for each } j \\ &\iff x = 0.\end{aligned}$$

(c) $$\langle y, x\rangle = \sum_{j=1}^{n} |y_j x_j| = \sum_{j=1}^{n} |x_j y_j| = \langle x, y\rangle.$$

(d) $$\begin{aligned}\langle \alpha x, y\rangle &= \sum_{j=1}^{n} |\alpha x_j y_j| \\ &= \sum_{j=1}^{n} |\alpha||x_j y_j| \\ &= |\alpha| \sum_{j=1}^{n} |x_j y_j| \\ &= |\alpha|\langle x, y\rangle.\end{aligned}$$

(e) $$\begin{aligned}\langle x+z, y\rangle &= \sum_{j=1}^{n} |(x+z)_j y_j| \\ &= \sum_{j=1}^{n} |(x_j y_j + z_j y_j| \\ &\leq \sum_{j=1}^{n} |x_j y_j| + \sum_{j=1}^{n} |z_j y_j| \\ &= \langle x, y\rangle + \langle z, y\rangle.\end{aligned}$$

(f) $$\begin{aligned}\langle x, y\rangle \neq 0 &\iff \sum_{j=1}^{n} |x_j y_j| \neq 0 \\ &\iff |x_k y_k| \neq 0 \text{ for some } k \\ &\iff x_k \neq 0 \text{ and } y_k \neq 0 \text{ for some } k.\end{aligned}$$

□

Corollary 1. *Let $A \in M_{m,n}$ and let $D \in M_{m,m}$ and $D' \in M_{n,n}$ be diagonal matrices, with D' invertible. Then*

$$\langle (DA)_i, (DA)_j \rangle = |d_{ii}||d_{jj}| \langle A_i, A_j \rangle$$

and

$$\langle (AD')_i, (AD')_j \rangle = 0 \iff \langle A_i, A_j \rangle = 0.$$

Proof. Since D is diagonal, then $(DA)_i = d_{ii}A_i$ for each i. Therefore,

$$\begin{aligned} \langle (DA)_i, (DA)_j \rangle &= \langle d_{ii}A_i, d_{jj}A_j \rangle \\ &= |d_{ii}||d_{jj}| \langle A_i, A_j \rangle. \end{aligned}$$

Since D' is invertible, $d'_{ii} \neq 0$ for each i. Therefore,

$$\begin{aligned} \langle (AD')_i, (AD')_j \rangle = 0 &\iff \sum_{k=1}^{n} |a_{ik}d_{kk}a_{jk}d_{kk}| = 0 \\ &\iff |a_{ik}d_{kk}a_{jk}d_{kk}| = 0 \text{ for each } k \\ &\iff |a_{ik}a_{jk}| = 0 \text{ for each } k \\ &\iff \sum_{k=1}^{n} |a_{ik}a_{jk}| = 0 \\ &\iff \langle A_i, A_j \rangle = 0. \end{aligned}$$

□

Notation 3. Let σ be a permutation on n letters. Then we define the permutation matrix S_σ by $s_{ij} = \delta_{i\sigma(j)}$, where δ_{ij} denotes the Kronecker delta function.

Lemma 2. *The product $\langle \cdot, \cdot \rangle$ is invariant under the permutation of rows and columns of a matrix in the following sense: If $S = S_\sigma \in M_{m,m}$ and $T = S_\tau \in M_{n,n}$ are permutation matrices, and $A \in M_{m,n}$ then*

$$\langle (SAT)_{\sigma(i)}, (SAT)_{\sigma(j)} \rangle = \langle A_i, A_j \rangle$$

Proof. Since $S = S_\sigma$ and $T = S_\tau$ are permutation matrices, we have $s_{ij} = \delta_{i\sigma(j)}$ and $t_{ij} = \delta_{i\tau(j)}$. Therefore, we calculate the entries of SA and AT as follows:

$$(SA)_{\sigma(i)j} = \sum_{k=1}^{n} s_{\sigma(i)k} a_{kj} = \sum_{k=1}^{n} \delta_{\sigma(i)\sigma(k)} a_{kj} = a_{ij}, \tag{14}$$

$$(AT)_{ij} = \sum_{k=1}^{n} a_{ik} t_{kj} = \sum_{k=1}^{n} a_{ik} \delta_{k\tau(j)} = a_{i\tau(j)}. \tag{15}$$

From (14) we have the following:

$$\begin{aligned} \langle (SA)_{\sigma(i)}, (SA)_{\sigma(j)} \rangle &= \sum_{k=1}^{n} |(SA)_{\sigma(i)k} (SA)_{\sigma(j)k}| \\ &= \sum_{k=1}^{n} |a_{ik} a_{jk}| \\ &= \langle A_i, A_j \rangle. \end{aligned} \tag{16}$$

Similarly, from (15) we have:

$$\begin{aligned} \langle (AT)_i, (AT)_j \rangle &= \sum_{k=1}^{n} |(AT)_{ik} (AT)_{jk}| \\ &= \sum_{k=1}^{n} |a_{i\tau(k)} a_{j\tau(k)}| \\ &= \sum_{k=1}^{n} |a_{ik} a_{jk}| \\ &= \langle A_i, A_j \rangle. \end{aligned} \tag{17}$$

The second and third sums in this previous step are equal because the third sum is merely a reordering of the terms of the second. We now combine the previous two results to obtain the desired conclusion:

$$\begin{aligned} \langle (SAT)_{\sigma(i)}, (SAT)_{\sigma(j)} \rangle &= \langle ((SA)T)_{\sigma(i)}, ((SA)T)_{\sigma(j)} \rangle \\ &= \langle (SA)_{\sigma(i)}, (SA)_{\sigma(j)} \rangle \\ &= \langle A_i, A_j \rangle. \end{aligned} \tag{18}$$

□

Observe that right permutation (permutation of columns) has no effect on the product $\langle \cdot, \cdot \rangle$.

Definition 2. Let $A \in M_{m,n}$ be a matrix. A finite sequence $(p_1, p_2, \ldots, p_k)$ of positive integers is called a *chain of rows of* A if $\{p_1, \ldots, p_k\} \subset \{1, \ldots, m\}$ and for $i \in \{1, \ldots, k-1\}$ we have $\langle A_{p_i}, A_{p_{i+1}} \rangle > 0$. That is, for each consecutive pair (p_i, p_{i+1}) of integers in the sequence there is at least one integer j such that the jth component is nonzero in both rows p_i and p_{i+1}. A *chain of columns of* A is a chain of rows of A^*.

With this definition in place, we observe that if S and T are permutation matrices and $(i_1, \ldots, i_r)$ is a chain of rows of A, then $(\sigma(i_1), \ldots, \sigma(i_r))$ is a chain of rows of SAT. This follows quickly from Lemma 2 because if $1 \leq k < r$, then

$$\langle (SAT)_{\sigma(i_k)}, (SAT)_{\sigma(i_{k+1})} \rangle = \langle A_{i_k}, A_{i_{k+1}} \rangle \neq 0.$$

Thus, we may reorder the rows and columns of a matrix without destroying its chains of rows and columns. That is, reordering rows simply *moves* chains of rows and has no effect on chains of columns, while reordering columns has similar effects on the chains rows of A^*. We also observe that the effect of Lemma 1 is that multiplication (on the left or right) of a matrix A by an invertible diagonal matrix has no impact on the chain structures of A and A^*.

We also note that it follows immediately from Lemma 2 and from the symmetry of $\langle \cdot, \cdot \rangle$ that if $(p_1, p_2, \ldots, p_k)$ is a chain of rows of A, then the sequence $(p_k, p_{k-1}, \ldots, p_1)$ is also a chain of rows of A.

Definition 3. A chain of rows $(p_1, \ldots, p_k)$ of A will be called *diagonal* if for each $i \in \{1, \ldots, k-1\}$ we have $|a_{p_i p_{i+1}} a_{p_{i+1} p_{i+1}}| > 0$.

Notation 4. We write $i \overset{A}{\sim} j$ if $i = j$ or if there exists a chain $(p_1, p_2, \ldots, p_k)$ of rows of A with $p_1 = i$ and $p_k = j$. If there exists a diagonal chain $(p_1, \ldots, p_k)$ of rows of A such that $p_1 = i$ and $p_k = j$, then we write $i \overset{A}{\to} j$.

We will find in this section that there are several proofs in which the crucial idea is to show that some particular property is transitive with one of the relations $\overset{A}{\sim}$ and $\overset{A}{\to}$. That

is, any property (in general, any logical statement that evaluates to TRUE) that is passed from row i to row j whenever $\langle A_i, A_j \rangle \neq 0$ or when $|a_{ij}a_{jj}| > 0$ is then passed along to every element to which there is a chain (or diagonal chain) from j. The most natural example of this is the logical condition $P_i(k) = i \overset{A}{\sim} k$ itself. That is, for a fixed number i, $P_i(k)$ evaluates to TRUE if $i \overset{A}{\sim} k$ and to FALSE otherwise. Because $\langle A_j, A_k \rangle \neq 0$ is the condition that allows us to move between elements j and k of a chain, we conclude that if $i \overset{A}{\sim} k$ and $\langle A_j, A_k \rangle \neq 0$ then $i \overset{A}{\sim} j$ because we have a natural way to construct a chain from i to j. So, the property P_i is passed from connect to connect. We would like to conclude, then, that P_i is passed to the entire chain. For this purpose, we introduce the following lemma:

Lemma 3. *Let $A \in M_{m,n}$. Let P and R be logical statements that satisfy the following conditions for every pair of integers k, i:*

(a) $P(i)$ whenever $\langle A_k, A_i \rangle \neq 0$ and $P(k)$.

(b) $R(i)$ whenever $|a_{ki}a_{ii}| > 0$ and $R(k)$.

Then

(a) $P(i)$ whenever $k \overset{A}{\sim} i$ and $P(k)$.

(b) $R(i)$ whenever $k \overset{A}{\rightarrow} i$ and $R(k)$.

Proof. The proofs of (a) and (b) are exactly symmetric to one another, so we omit the proof of (b) and we prove (a). Let $(p_1, \ldots, p_n)$ be a chain of rows of A. We induct on n:

The case $n = 1$ is trivial, since the chain has a single element p_1 and if $P(p_1)$ then certainly $P(p_1)$.

For the inductive step, assume that the result holds for $n = k - 1$ and assume that $P(p_1)$. Then, by the inductive hypothesis, $P(p_{k-1})$. But since $(p_1, \ldots, p_k)$ is a chain we have $\langle A_{p_{k-1}}, A_{p_k} \rangle \neq 0$. By condition (a), then, we have $P(p_k)$.

By induction, then, claim (a) holds. □

Lemma 4. *The relation $\overset{A}{\sim}$ is an equivalence relation and the relation $\overset{A}{\to}$ is transitive.*

Proof. 1. **Reflexivity.** Since for each i we have $i = i$, then $i \overset{A}{\sim} i$ by definition.

2. **Symmetry.** Let $i \overset{A}{\sim} j$. If $i = j$ then clearly $j \overset{A}{\sim} i$. Otherwise, there is a chain $(p_1, p_2, \ldots, p_k)$ of rows of A with $p_1 = i$ and $p_k = j$. Then $(p_k, p_{k-1}, \ldots, p_2, p_1)$ is a chain starting with row j and ending at row i, so $j \overset{A}{\sim} i$.

   $\therefore i \overset{A}{\sim} j \Rightarrow j \overset{A}{\sim} i$.

3. **Transitivity.** Consider the logical statements $P(n) =$ "$i \overset{A}{\sim} n$" and $R(n) =$ "$i \overset{A}{\to} n$." By definition, both $\overset{A}{\sim}$ and $\overset{A}{\to}$ satisfy the conditions of Lemma 3, so that both relations are transitive, which completes the proof.

□

Definition 4. If $i \overset{A}{\sim} j$ then we say that i and j are *connected in* A. If A is a matrix such that each pair of rows is connected, then A will be called *connected*. If i and j are not connected in A, then we will say that i and j are *disjoint in* A. If $i \overset{A}{\to} j$ then we will now say that i is *diagonally connected to* j *in* A. If A is a matrix such that $i \overset{A}{\to} j$ for each pair i, j then A is called *diagonally connected*.

The motivation for this terminology comes from the system of cells that we are studying. Two cells i and j are connected if they are in contact, or if there is a sequence of cells beginning and ending with cells i and j, respectively, such that every consecutive pair is in contact. Thus, we may draw an analogy between a collection of cells and a graph, with cells as vertices and undirected edges between vertices representing contact between the two cells. A collection of cells is connected if the corresponding graph is connected.

Each row of the matrix W produced by the cell system represents the contact between a fixed cell and with all other cells and with the substrate and fluid. For example, if two cells are in contact then there is a column in which both corresponding rows are nonzero. The diagonal entries represent the sum of all contact of the cell with other cells and with

the substrate or fluid. In this context, it is impossible to have all entries for a cell (an entire row) be zero, since the cell is always in contact with some combination of cells, substrate, and fluid. So, in the matrix representing the physical system, a row of zeros has no meaning and will, therefore, never appear. The use of the word "connected" in connection with zero rows is merely to simplify the terminology and extend it to matrices that are more general than those that really concern us in this paper.

In terms of the system of cells, the use of the term "diagonally connected" carries with it no particular meaning. Rather, it derives from the fact that these connections are passed on the diagonal entries themselves. It is this structure, though, that will guarantee us invertibility of W. In the case of cells, when two cells are in contact, each has the same amount of contact with the other. This results in a matrix that is symmetric, so we are aided by the lemmas that follow.

Before we come to them, however, it is important to recognize that not all cells in a system need be connected to one another. Some cells may be in contact with no other cell. There may be several clusters of cells that are connected within the cluster but the clusters themselves are not connected. The following lemma allows us to decompose the system of cells into connected clusters so that each cluster can be considered individually.

Since we may permute rows or columns of zeros down and to the right, and then consider the submatrix without the rows and columns of zeros, we will lose no generality in assuming that there are no rows or columns of zeros in the following:

Lemma 5. *If $A \in M_{m,n}$ has no rows or columns consisting entirely of zeros then there exist permutation matrices S and T such that SAT^* is a block matrix of the form*

$$SAT^* = \begin{pmatrix} B^1 & & & \\ & B^2 & & \\ & & \ddots & \\ & & & B^k \end{pmatrix}$$

where B^i and $(B^i)^T$ are connected matrices for each i (The superscripts are to be interpreted as indices rather than exponents). In particular, if A is Hermitian then S and T

may be chosen so that $T = S^*$ and B^i is Hermitian for each i.

Proof. This proof provides an inductive construction for the matrices S and T.

Let $a_{i\hat{j}}$ be a nonzero entry of A. Let $r_1 = \hat{\imath}, r_2, \ldots, r_k$ be the integers that satisfy $\hat{\imath} \overset{A}{\sim} r_i$ and $s_1 = \hat{\jmath}, s_2, \ldots, s_l$ be those that satisfy $\hat{\jmath} \overset{A^*}{\sim} s_i$.

Let σ and τ be any permutations on n letters that map as follows:

$$\sigma : \begin{cases} r_1 & \mapsto & 1 \\ r_2 & \mapsto & 2 \\ & \vdots & \\ r_k & \mapsto & k \end{cases}, \qquad \tau : \begin{cases} s_1 & \mapsto & 1 \\ s_2 & \mapsto & 2 \\ & \vdots & \\ s_l & \mapsto & l \end{cases}.$$

Note that if A is Hermitian then $1 \overset{A}{\sim} i$ if and only if $1 \overset{A^*}{\sim} i$, so that in this case we can choose $\sigma = \tau$.

Let $L_1 = S_\sigma$ and $R_1 = S_\tau$.

Claim: The matrix $H = L_1 A R_1^*$ is of the form

$$H = \begin{pmatrix} B & 0 \\ 0 & A^1 \end{pmatrix}.$$

where $B_1 \in M_{k,l}$ and $A_1 \in M_{m-k,n-l}$ and B_1 and B_1^* are both connected.

Proof of claim: By Lemma 2 we have

$$i \overset{H}{\sim} 1 \iff 1 \leq i \leq k, \tag{19}$$

$$j \overset{H^*}{\sim} 1 \iff 1 \leq j \leq l. \tag{20}$$

Suppose, by way of contradiction, that $a_{ij} \neq 0$ for some $i > k$ and $1 \leq j \leq l$. Since $i > k$, we do not have $r \overset{H}{\sim} i$ if $r \leq k$. This means that if $r \leq k$ then $\langle H_r, H_i \rangle = 0$ so that in particular $h_{rj} = 0$ (since $h_{ij} \neq 0$). Since $H_j^* \neq 0$ and $j \overset{H^*}{\sim} 1$, there is some integer s such that $\langle H_j^*, H_s^* \rangle > 0$. Therefore, $|h_{l,s} h_{l,j}| > 0$ for some l. By the above argument,

this forces $h_{rs} = 0$ whenever $1 \leq r \leq k$. By Lemma 3, then, $h_{rs} = 0$ for each r whenever $j \overset{H^*}{\sim} s$. Since $j \overset{H^*}{\sim} 1$, $h_{r1} = 0$ for $1 \leq r \leq k$. But this contradicts the fact that $h_{11} \neq 0$.

Thus, our supposition was false and so $a_{ij} = 0$ if $i > k$ and $1 \leq j \leq l$. Performing the same steps on H^* shows that $a_{ij} = 0$ if $1 \leq i \leq k$ and $j > l$. So, H has the block structure as claimed. It only remains to show that B and B^* are connected. This follows quickly, for

$$\begin{aligned}
\langle B_i, B_j \rangle &= \sum_{s=1}^{l} |b_{is} b_{js}| \\
&= \sum_{s=1}^{l} |b_{is} b_{js}| + \sum_{s=l+1}^{n} 0 \\
&= \sum_{s=1}^{l} |h_{is} h_{js}| + \sum_{s=l+1}^{n} |h_{is} h_{js}| \\
&= \sum_{s=1}^{n} |h_{is} h_{js}| \\
&= \langle H_i, H_j \rangle
\end{aligned}$$

so that connections in B are inherited from H. Similar calculations work for B^*. Thus, B and B^* are both connected as claimed.

Let $B^1 = B$. The previous steps are repeated inductively on A^1. The process will terminate when the construction leaves a null block in the lower right. This is because the process is shown to create a diagonal block structure and by hypothesis if there are entries left in the lower right then at least one of them is non-zero.

Note if A is Hermitian then each iteration of this process allows us to preserve the Hermitian nature of A so that each block in the decomposition is Hermitian.

□

Definition 5. The matrices $B^1, \ldots, B^k$ produced by Lemma 5 are called the *connected components of* A.

Thus, A is invertible if and only if each connected component of A is a square invertible matrix. In addition, the construction provides us with the following corollary.

Corollary 2. *If A has no rows or columns consisting entirely of zeros, then A and A^T each have the same number of connected components.*

Lemma 6. *Let $A \in M_{n,n}$ be a Hermitian matrix whose diagonal entries are nonzero. Then $i \overset{A}{\sim} j \iff i \overset{A}{\to} j$. In particular, if A is connected then A is diagonally connected.*

Proof. That $r \overset{A}{\to} s$ implies $r \overset{A}{\sim} s$ follows by definition.

To show the reverse implication, assume that $r \overset{A}{\to} k$ and $\langle A_k, A_i \rangle \neq 0$. Since $\langle A_k, A_i \rangle > 0$ there is an index j such that $|a_{k,j} a_{i,j}| > 0$, which forces $a_{k,j} \neq 0$ and $a_{j,i} = a_{i,j} \neq 0$. Since $a_{j,j}$ and $a_{i,i}$ are both nonzero, we have $|a_{k,j} a_{j,j}| > 0$ and $|a_{j,i} a_{i,i}| > 0$ so that $r \overset{A}{\to} k \overset{A}{\to} j \overset{A}{\to} i$ and by transitivity we have $r \overset{A}{\to} i$.

Thus, the logical statement P defined by $P(k) =$ "$r \overset{A}{\to} k$" satisfies condition (a) of Lemma 3 so that, whenever $r \overset{A}{\to} k$ and $k \overset{A}{\sim} i$, we have $r \overset{A}{\to} i$. But $r \overset{A}{\to} r$ since the diagonal entries A are all nonzero. Therefore, $r \overset{A}{\to} i$ whenever $r \overset{A}{\sim} i$, completing the claim. That A is diagonally connected if A is connected follows immediately.

□

It is worth noting that requiring A to be Hermitian was actually a stronger condition than what we needed. All we really relied on was that the non-zero entries of A appear symmetrically with respect to the diagonal of A.

Definition 6. We say that a row i of a matrix $A \in M_{m,n}$ is *diagonally dominant* if its entries satisfy the inequality

$$|a_{ii}| \geq \sum_{j \neq i} |a_{ij}|.$$

If this inequality is not an equality, then we say that row i is *strictly diagonally dominant.* If each row of A is (strictly) diagonally dominant then we will say that A is (strictly) diagonally dominant.

Lemma 7. *Let $D \in M_{m,m}$ be an invertible diagonal matrix and let $A \in M_{m,n}$. Then A_i is (strictly) diagonally dominant if and only of $(DA)_i$ is (strictly) diagonally dominant.*

Proof. Consider the matrix $A' = DA$. A quick calculation shows that $a'_{ij} = d_{ii}a_{ij}$. This means that

$$|a'_{ii}| = |d_{ii}||a_{ii}|,$$

$$\sum_{j\neq i} |a'_{ij}| = \sum_{j\neq i} |d_{ii}||a_{ij}| = |d_{ii}| \sum_{j\neq i} |a_{ij}|,$$

$$|a'_{ii}| \geq \sum_{j\neq i} |a'_{ij}| \iff |d_{ii}||a_{ii}| \geq |d_{ii}| \sum_{j\neq i} |a_{ij}|$$

as claimed. Furthermore, each of the two inequalities is strict if and only if the other is also strict.

□

Theorem 1. *Let $A \in M_{n,n}(\mathbb{C})$ be a diagonally connected, diagonally dominant matrix and let $D = diag(a_{11}, \ldots, a_{nn})$. Then A is singular if and only of A can be factored as $A = DBCB^*$, where B is a unitary diagonal matrix and C is a diagonally connected real matrix that satisfies the following:*

1. *$c_{ii} = 1$ for each i.*
2. *$c_{ij} \leq 0$ whenever $j \neq i$.*
3. *$\sum_{j=1}^{n} c_{ij} = 0$ for each $i \in \{1, \ldots, n\}$.*

Moreover, this factorization is unique in the sense that if $A = DB'C'B'^*$ is another such decomposition then $C' = C$ and $B' = \alpha B$ for some scalar α such that $|\alpha| = 1$.

Proof. The "if" implication is trivial. We assume that A admits such a factorization and let $b \in \mathbb{R}^n$ be defined by $b = (1, 1, \ldots, 1)^T$. We calculate Cb, taking advantage of equality 3:

$$Cb = C \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix} = \begin{pmatrix} c_{11} + \cdots + c_{1n} \\ \vdots \\ c_{n1} + \cdots + c_{nn} \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix} = 0.$$

So, the null space of C is non-trivial, making C singular. Therefore, A is also singular.

Before we consider the "only if" implication, we first observe that, since A is diagonally connected, each diagonal entry of A is nonzero. So, D is invertible and we may consider the matrix $A' = D^{-1}A$. From basic linear algebra, Corollary 1, and Lemma 7 we see that A' satisfies the hypotheses of this theorem exactly when A satisfies them. Furthermore, we see that

$$a'_{ii} = \frac{1}{d_{ii}} a_{ii} = \frac{1}{a_{ii}} a_{ii} = 1.$$

Thus, we lose no generality in assuming that $D = I$, the identity matrix. Now, the "only if" implication will follow from a proof [6] of the Geršgorin Disk Theorem:

Assume that A is singular. Then we may select a nonzero vector x such that $Ax = 0$. We may assume that $\|x\|_\infty = 1$ so that $|x_k| = \|x\|_\infty = 1$ for some integer k. Since $Ax = 0$, then $A_k x = 0$, so that $\sum_{j=1}^{n} a_{kj} x_j = 0$. Therefore:

$$\begin{aligned}
|a_{kk}| &= |a_{kk}||x_k| \\
&= |a_{kk} x_k| \\
&= \left| -\sum_{j \neq k} a_{kj} x_j \right| \\
&\leq \sum_{j \neq k} |a_{kj} x_j| && (21) \\
&\leq \sum_{j \neq k} |a_{kj}| \, |x_j| \\
&\leq \sum_{j \neq k} |a_{kj}| \, \|x\|_\infty && (22) \\
&= \sum_{j \neq k} |a_{kj}| \\
&\leq |a_{kk}| && (23)
\end{aligned}$$

Since the first and last terms in the chain of inequalities are equal, the intermediate terms must also be equal. The inequalities (21), (22) and (23) must, therefore, be equalities. Equality in (22) follows if and only if $|x_j| = 1$ whenever $a_{kj} \neq 0$. We conclude

that if $a_{kj} \neq 0$ and $|x_k| = 1$ then $|x_j| = 1$. Since $a_{jj} \neq 0$, we have $a_{kj} \neq 0$ if and only if $|a_{kj}a_{jj}| > 0$. Thus, the logical statement '$|x_j| = 1$' satisfies condition (b) of Lemma 3. Therefore, $|x_j| = 1$ whenever $k \xrightarrow{A} j$. But A is diagonally connected, so $k \xrightarrow{A} j$ for each j. Therefore, $|x_j| = 1$ for each j. So, from (21), (22) and (23) we have, for each $k \in \{1, \ldots, n\}$:

1. $|x_k| = 1$
2. $|a_{kk}| = \sum_{j \neq k} |a_{kj}|$.
3. $\left| \sum_{j \neq i} a_{ij}x_j \right| = \sum_{j \neq i} |a_{ij}x_j|$

We will now use these facts to show that A can be factored as $A = BCB^*$ as claimed. By the triangle inequality for complex numbers, $\left| \sum_{j \neq i} a_{ij}x_j \right| = \sum_{j \neq i} |a_{ij}x_j|$ if and only if there is a single (nonzero) complex number z_i such that for each $j \neq i$ there is a non-negative real number α_{ij} such that $a_{ij}x_j = \alpha_{ij}z_i$. We may assume, with no loss of generality, that $|z_i| = 1$ for each i. Define the diagonal matrices B and H by $b_{ii} = -z_i$ and $h_{ii} = x_i$ and let $C = B^*AH$. We here note that by their definitions B and H are clearly unitary. We calculate:

$$\alpha_{ij} = |\alpha_{ij}| = \frac{|a_{ij}||x_j|}{|z_i|} = |a_{ij}|$$

So, whenever $j \neq i$, we have $a_{ij} = \alpha_{ij}\frac{z_i}{x_j} = |a_{ij}|\frac{z_i}{x_j}$. Therefore:

$$c_{ij} = (B^*AH)_{ij} = \overline{b_{ii}}a_{ij}h_{jj} = -\overline{z_i}a_{ij}x_j = -\overline{z_i}|a_{ij}|\frac{z_i}{x_j}x_j = -|a_{ij}| \leq 0$$

So, the off-diagonal entries of C are all non-positive real numbers, proving claim 2. In fact, this shows that the off-diagonal entries of C are completely determined by A. We calculate the diagonal entries of C as follows:

$$c_{ii} = \overline{b_{ii}}a_{ii}h_{ii} = -\overline{z_i}x_i$$

Since $A = BCH^*$, we have $BCH^*x = 0$. Since B is invertible, we have $(CH^*)x = 0$. But

$$(H^*x)_i = \overline{h_{ii}}x_i = \overline{x_i}x_i = 1$$

So we have $H^*x = (1, \ldots, 1)^T$. Therefore, $C(1, \ldots, 1)^T = 0$. This gives us

$$0 = (C_i(1, \ldots, 1)^T) = \sum_{j=1}^{n} c_{ij} = c_{ii} + \sum_{j \neq i}(-|a_{ij}|) = c_{ii} - \sum_{j \neq i} |a_{ij}|$$

which proves claim 3, as well as showing that $c_{ii} = \sum_{j \neq i} |a_{ij}| \geq 0$, completing the proof that C is real. In addition, since $c_{ii} = -\bar{z}_i x_i$, we have $|c_{ii}| = |z_i||x_i| = 1$ so that $c_{ii} = 1$, proving claim 1. This also completes the proof that C is uniquely determined by A. Furthermore, observe that C has nonzero entries in exactly the same places as A so that C is diagonally connected. We now notice that

$$-\overline{z_i}x_i = c_{ii} = 1$$

so that $z_i = -x_i$ for each $i \in \{1, \ldots, n\}$. In particular, $b_{ii} = -z_i = x_i = h_{ii}$, so that $H = B$ and we have the factorization $A = BCH^* = BCB^*$ as claimed.

To complete the uniqueness claim, let us assume that $A = B'CB'^*$ is another such factorization. Define $F = B^*B'$. Then

$$C = B^*AB = B^*B'CB'^*B = (B^*B')C(B^*B')^* = FCF^*$$

Therefore, $c_{ij} = f_{ii}c_{ij}\bar{f_{jj}}$ so that $f_{ii} = f_{jj}$ whenever $c_{ij} \neq 0$. More generally, by Lemma 3 we have $f_{ii} = f_{jj}$ whenever $i \xrightarrow{C} j$. But, C is diagonally connected, so $i \xrightarrow{C} j$ for each i, j, forcing $f_{ii} = f_{jj}$ for each i, j. Therefore, $F = \alpha I$ for some scalar α such that $|\alpha| = 1$, forcing $B^*B' = \alpha I$ and, therefore, $B' = \alpha B$ as claimed.

□

Corollary 3. *If A satisfies the conditions of Theorem 1 and is singular, then for each $i \in \{1, \ldots, n\}$ we have*

$$|a_{ii}| = \sum_{i=1}^{n} |a_{ij}|$$

Proof. Since $A = DBCB^*$ as the theorem concludes, we find that

$$\begin{aligned}
|a_{ii}| &= |d_{ii}b_{ii}c_{ii}\bar{b_{ii}}| \\
&= |d_{ii}||c_{ii}| \\
&= |d_{ii}|\sum_{j=1}^{n}|c_{ij}| \\
&= \sum_{j=1}^{n}|d_{ii}||c_{ij}||b_{ii}||b_{jj}| \\
&= \sum_{j=1}^{n}|d_{ii}c_{ij}b_{ii}b_{jj}| \\
&= \sum_{j=1}^{n}|a_{ij}|
\end{aligned}$$

□

Corollary 4. *If every connected component of A satisfies the conditions of Theorem 1 and has at least one row that is strictly diagonally dominant, then A is invertible.*

Proof. By Corollary 3 every connected component of A is a square, invertible matrix. □

6 Analysis of the Model

We begin this section by pointing out that W is invertible by Corollary 4. That is, each cell of the system is either in contact with the fluid or substrate (i.e., not entirely surrounded by other cells) or else is connected to a cell that is not entirely surrounded by cells. Therefore, $\mu_i > 0$ for at least one i in each connected component of W, giving us at least one row in each component that is *strictly* diagonally dominant. Since W is invertible, we can conclude that V is positive definite as claimed earlier. This gives us the information that we need to proceed with our analysis.

The system (13) of vector equations is clearly equivalent to the matrix equation

$$\begin{pmatrix} V & A \end{pmatrix} \begin{pmatrix} \dot{x} \\ a \end{pmatrix} = M. \tag{24}$$

Note that $A^T\dot{x}$ is a vector of length $\frac{1}{2}n(n-1)$ and that if cells h and k are interacting, with $h < k$ and $j = j(h,k)$, then

$$\begin{aligned} (A^T\dot{x})_j &= \sum_{i=1}^{n} (A_{ij})^T \dot{x}^i \\ &= (x^h - x^k)\cdot\dot{x}^h + (x^k - x^h)\cdot\dot{x}^k \\ &= (x^h - x^k)\cdot(\dot{x}^h - \dot{x}^k). \end{aligned} \tag{25}$$

If, on the other hand, cells h and k are not interacting then $(A^T\dot{x})_j = 0$. Thus, the condition (4) can be phrased as

$$A^T\dot{x} = 0.$$

This is, in turn, equivalent to the matrix equation

$$\begin{pmatrix} A^T & 0 \end{pmatrix} \begin{pmatrix} \dot{x} \\ a \end{pmatrix} = 0. \tag{26}$$

Combining (24) and (26), we find that the matrix equation that determines the motion of our cell system is:

$$\begin{pmatrix} V & A \\ A^T & 0 \end{pmatrix} \begin{pmatrix} \dot{x} \\ a \end{pmatrix} = \begin{pmatrix} M \\ 0 \end{pmatrix}. \tag{27}$$

This system is intended to be solved in a time-stepping manner. That is, from an initial configuration, the coefficients μ_{ij} and μ_i are known, as are the positions x^i and the motive forces M_i. Therefore, once we show that there is a solution, the system can be solved for $\dot{x}$ and a. The positions of the cells are then updated by moving x^i in the direction of $\dot{x}^i$ for a small time increment and the process is repeated.

6.1 Analyzing the Matrix

Setting $B = \begin{pmatrix} V & A \\ A^T & 0 \end{pmatrix}$, the system of force equations (27) is equivalent to the matrix system:

$$B \begin{pmatrix} \dot{x} \\ a \end{pmatrix} = \begin{pmatrix} M \\ 0 \end{pmatrix}. \tag{28}$$

In general, as we shall see, B is singular so that equation (28) has infinitely many solutions $\begin{pmatrix} \dot{x} \\ a \end{pmatrix}$. Since the end we seek is to solve for $\dot{x}$, we will show that $\dot{x}$ is well-defined and independent of the value of a. That is, different combinations of adhesion and repulsion forces may be possible, but all yield the same motion for the system.

Suppose that two vectors $\begin{pmatrix} \dot{x} \\ a \end{pmatrix}$ and $\begin{pmatrix} \dot{y} \\ b \end{pmatrix}$ satisfy equation (28). Then

$$\begin{aligned} B \begin{pmatrix} \dot{x} - \dot{y} \\ a - b \end{pmatrix} &= B \left[\begin{pmatrix} \dot{x} \\ a \end{pmatrix} - \begin{pmatrix} \dot{y} \\ b \end{pmatrix} \right] \\ &= B \begin{pmatrix} \dot{x} \\ a \end{pmatrix} - B \begin{pmatrix} \dot{y} \\ b \end{pmatrix} \\ &= \begin{pmatrix} M \\ 0 \end{pmatrix} - \begin{pmatrix} M \\ 0 \end{pmatrix} \\ &= 0 \end{aligned}$$

So, the vector $\begin{pmatrix} \dot{x} - \dot{y} \\ a - b \end{pmatrix}$ lies in the null space of B. It behooves us, then, to examine the null space of B. Let $\begin{pmatrix} \dot{x} \\ a \end{pmatrix} \in \text{null}\,(B)$. Then

$$\begin{pmatrix} V & A \\ A^T & 0 \end{pmatrix} \begin{pmatrix} \dot{x} \\ a \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

We multiply this system on the left by the invertible matrix $\begin{pmatrix} V^{-1} & 0 \\ A^T V^{-1} & -I \end{pmatrix}$ to get the equivalent equation:

$$\begin{pmatrix} I & V^{-1} A \\ 0 & A^T V^{-1} A \end{pmatrix} \begin{pmatrix} \dot{x} \\ a \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \tag{29}$$

Decoupling equation (29), we have the system

$$\begin{aligned} \dot{x} + V^{-1} A\, a &= 0 \\ A^T V^{-1} A\, a &= 0 \end{aligned} \tag{30}$$

This means that if $\begin{pmatrix} \dot{x} \\ a \end{pmatrix}$ is any vector that satisfies (29), then $A^T V^{-1} A\, a = 0$, so that

$$\begin{aligned} (A\, a)^T V^{-1} (A\, a) &= a^T A^T V^{-1} A\, a \\ &= a^T (A^T V^{-1} A\, a) \\ &= a^T\, 0 \\ &= 0 \end{aligned}$$

Since V^{-1} is positive definite, it must be the case that $Aa = 0$, so that a is in the null space of A. Thus, we see that all vectors in $\text{null}\,(B)$ are of the form $\begin{pmatrix} 0 \\ a \end{pmatrix}$, where $a \in \text{null}\,(A)$. Conversely, if $a \in \text{null}\,(A)$ then $B \begin{pmatrix} 0 \\ a \end{pmatrix} = 0$. We conclude, therefore, that $\text{null}\,(B) = \left\{ \begin{pmatrix} 0 \\ a \end{pmatrix} \,\middle|\, a \in \text{null}\,(A) \right\}$.

We now return to the question of the uniqueness of solutions to (28). Since $\begin{pmatrix} \dot{x} - \dot{y} \\ a - b \end{pmatrix} \in \text{null}(B)$, we conclude that $\dot{x} - \dot{y} = 0$ and, therefore, $\dot{x} = \dot{y}$. Therefore, though equation (28) generally has multiple solutions, the derivative portion of the solution vector is unique. Therefore, the motion of the system of cells is uniquely determined by the equation (27).

6.2 Adhesion as a Potential

We conclude this section by showing that our assumptions and calculations do not admit the use of potentials to model adhesion. We consider the case of two cells that are

adhering. This gives us the following equations

$$\mu_1 \dot{x}^1 + \mu_{12}(\dot{x}^1 - \dot{x}^2) = \mathcal{A}_{12} + M_1, \tag{31}$$

$$\mu_2 \dot{x}^2 + \mu_{21}(\dot{x}^2 - \dot{x}^1) = \mathcal{A}_{21} + M_2. \tag{32}$$

$$\left(x^1 - x^2\right)\left(\dot{x}^1 - \dot{x}^2\right) = 0.$$

Subtracting μ_1 times (32) from μ_2 times (31) and since $\mathcal{A}_{12} = -\mathcal{A}_{21}$ and $\mu_{12} = \mu_{21}$ we find that

$$\mathcal{A}_{12} = \frac{1}{\mu_1 + \mu_2}((\mu_1\mu_2 + \mu_{12}(\mu_1 + \mu_2))(\dot{x}^1 - \dot{x}^2) - \mu_2 M_1 + \mu_1 M_2).$$

Taking the inner product of each side of this equation with $\widehat{x^2 - x^1}$ and using the fact that $(x^1 - x^2) \cdot (\dot{x}^1 - \dot{x}^2) = 0$, we find that

$$|\mathcal{A}_{12}| = \frac{1}{\mu_1 + \mu_2}(\mu_1 M_2 - \mu_2 M_1) \cdot \widehat{x^2 - x^1}.$$

In order to simplify the following calculations, we now assume that cell 1 is fixed in space. More precisely, we adopt a (possibly) moving coordinate system, so that all measurements are made with respect to an orthonormal basis with x^1 at the origin. This being done, we also assume that $M_1 = 0$. For simplicity of notation in the following calculations, we will here define $M = M_2$ and $x = x^2$ and let subscripts on x and M denote vector components, with superscripts being exponents. So, we have

$$\begin{aligned}
A_{12} &= \left(\frac{1}{\mu_1 + \mu_2}(\mu_1 M) \cdot \hat{x}\right)\hat{x} \\
&= \left(\frac{\mu_1}{\mu_1 + \mu_2}\right)\left(\frac{M \cdot x}{||x||^2}\right)x \\
&= \left(\frac{\mu_1}{\mu_1 + \mu_2}\right)\left(\frac{M_1 x_1 + M_2 x_2 + M_3 x_3}{x_1^2 + x_2^2 + x_3^2}\right)x \\
&= R\,x \\
&= (R\,x_1, R\,x_2, R\,x_3)
\end{aligned}$$

where $R(x) = \left(\frac{\mu_1}{\mu_1 + \mu_2}\right)\left(\frac{M_1 x_1 + M_2 x_2 + M_3 x_3}{x_1^2 + x_2^2 + x_3^2}\right)$.

Therefore, if A_{12} is the gradient of a potential, then for $i, j = 1, 2, 3$ we have

$$\frac{\partial}{\partial x_j}(R\, x_i) = \frac{\partial}{\partial x_i}(R\, x_j)$$

or, equivalently,

$$x_i \frac{\partial R}{\partial x_j} - x_j \frac{\partial R}{\partial x_i} = 0.$$

However,

$$\frac{\partial R}{\partial x_i} = \left(\frac{\mu_1}{\mu_1 + \mu_2}\right) \frac{(x_1^2 + x_2^2 + x_3^2)\, M_i - 2\, x_i (M_1 x_1 + M_2 x_2 + M_3 x_3)}{(x_1^2 + x_2^2 + x_3^2)^2},$$

so that

$$\begin{aligned} x_i \frac{\partial R}{\partial x_j} - x_j \frac{\partial R}{\partial x_i} &= x_i \left(\frac{\mu_1}{\mu_1 + \mu_2}\right) \frac{(x_1^2 + x_2^2 + x_3^2)\, M_j - 2\, x_j (M_1 x_1 + M_2 x_2 + M_3 x_3)}{(x_1^2 + x_2^2 + x_3^2)^2} \\ &\quad - x_j \left(\frac{\mu_1}{\mu_1 + \mu_2}\right) \frac{(x_1^2 + x_2^2 + x_3^2)\, M_i - 2\, x_i (M_1 x_1 + M_2 x_2 + M_3 x_3)}{(x_1^2 + x_2^2 + x_3^2)^2} \\ &= \left(\frac{\mu_1}{\mu_1 + \mu_2}\right) \frac{M_j x_i - M_i x_j}{x_1^2 + x_2^2 + x_3^2}. \end{aligned}$$

This quantity is zero for every pair i, j if and only if M is a scalar multiple of x. But M can be arbitrary so that, in general, A_{12} is not the gradient of a potential. Therefore, in the more general n-cell case, potentials do not accurately model the affects of adhesion.

7 Future Work

There are several avenues of further research which can be explored from where this paper ends.

7.1 Numerical

The first task is to begin a numerical study of the model. Several questions are of interest. The problem is to solve, in an efficient manner, the matrix equation

$$\begin{pmatrix} V & A \\ A^T & 0 \end{pmatrix} \begin{pmatrix} \dot{x} \\ a \end{pmatrix} = \begin{pmatrix} M \\ 0 \end{pmatrix} \tag{33}$$

One observation that may be helpful in studying the system numerically is that, as discussed earlier, each cell may have no more than 12 neighbors. Therefore, A has no more than $6n$ columns that are non-zero. Since some cells must be in contact with the substrate and/or fluid, as well as any neighbors they may have, there are clearly fewer than $6n$ such pairs. Thus, A has *more than* $\frac{1}{2}n(n-1) - 6n = \frac{1}{2}n(n-13)$ columns of zeros.

Since no more than 6 entries of each column of A may be non-zero, A has fewer than $36n$ nonzero entries. For similar reasons, each row of V can have no more than 13 nonzero entries. Therefore, the total number of nonzero entries of $B = \begin{pmatrix} V & A \\ A^T & 0 \end{pmatrix}$ is fewer than

$$2(36n) + 13(3n) = 111n$$

By contrast, the total number of entries of B is

$$\left(3n + \frac{1}{2}n(n-1)\right)^2 = \left(\frac{1}{2}n(n+5)\right)^2 = \frac{1}{4}n^2(n+5)^2$$

Thus, as n gets large, the percentage of the entries of the matrix that are nonzero decreases to zero very rapidly (order n^3). Therefore, one possibility for solving the system is through an iterative solver that is capable of taking advantage of the sparseness of the matrix B.

Of course, since most of the rows and columns of B are known to be zero, a great deal of the sparseness may be eliminated by simply constructing from A the matrix $\hat{A}$ with all

columns of zeros removed. Then, rather than solving the full system (33), we solve the system

$$\begin{pmatrix} V & \hat{A} \\ \hat{A}^T & 0 \end{pmatrix} \begin{pmatrix} \dot{x} \\ \hat{a} \end{pmatrix} = \begin{pmatrix} M \\ 0 \end{pmatrix} \tag{34}$$

where $\hat{a}$ is the vector a with the appropriate entries deleted. This new system has the same number of nonzero entries as system (33). However, the total number of entries is now less than

$$(3n + 6n)^2 = (9n)^2 = 81n^2$$

Thus, system (34) is still sparse, but the total number of entries grows quadratically with n, rather than the quartic growth of system (33).

Alternatively, Hu and Zou [7] have presented an iterative scheme for solving equations of the form

$$\begin{pmatrix} A & B \\ B^T & 0 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} f \\ g \end{pmatrix} \tag{35}$$

where $A \in M_{q,q}$ is symmetric and positive definite, and $B \in M_{q,p}$, with $p \leq q$. Problems of this form are common to fluid dynamics.

This is very nearly of the form we need to solve our problem. We know V to be positive definite, but the dimensions of our matrix A do not, in general, satisfy the requirement $p \leq q$. As discussed above, A has $3n$ rows and $\frac{1}{2}n(n-1)$ columns. Thus, A is only guaranteed to satisfy the dimension requirement if $n \leq 7$. However, this is not very helpful if we wish to model a system of $n = 10,000$ cells. We can eliminate columns of zeros as above, but that only guarantees that we have fewer than $6n$ columns—still not a sufficient improvement to employ the method of Hu and Zao. However, perhaps a modified version of their algorithm could be employed for our problem.

Another consideration in preparing a numerical solution is that the structure of V and A may allow the system to be efficiently reduced to smaller problems. For example, observe that if the blocks A_{ij} and A_{sj} are both nonzero then cells i and j are both in contact with cell k_j. Therefore, cells i and j are linked. From our results in matrix theory, this allows us to renumber the cells so that equation (33) takes the form

$$\begin{pmatrix} \begin{pmatrix} V_1 & A_1 \\ A_1^T & 0 \end{pmatrix} & & & \\ & \begin{pmatrix} V_2 & A_2 \\ A_2^T & 0 \end{pmatrix} & & \\ & & \ddots & \\ & & & \begin{pmatrix} V_r & A_r \\ A_r^T & 0 \end{pmatrix} \end{pmatrix} \begin{pmatrix} \begin{pmatrix} \dot{x}^1 \\ a^1 \end{pmatrix} \\ \begin{pmatrix} \dot{x}^2 \\ a^2 \end{pmatrix} \\ \vdots \\ \begin{pmatrix} \dot{x}^r \\ a^r \end{pmatrix} \end{pmatrix} = \begin{pmatrix} \begin{pmatrix} M^1 \\ 0 \end{pmatrix} \\ \begin{pmatrix} M^2 \\ 0 \end{pmatrix} \\ \vdots \\ \begin{pmatrix} M^r \\ 0 \end{pmatrix} \end{pmatrix} \tag{36}$$

Therefore, the system can be fully decoupled into r equations of the form

$$\begin{pmatrix} V_i & A_i \\ A_i^T & 0 \end{pmatrix} \begin{pmatrix} \dot{x}^i \\ a^i \end{pmatrix} = \begin{pmatrix} M^i \\ 0 \end{pmatrix}$$

where each is the portion of equation (33) that corresponds to a cluster of linked cells. Perhaps this approach could be employed to produce more efficient results.

7.2 Structure of A

Another question of interest is in the structure of A. We showed that the null space of B corresponds in a nice way to the null space of A—that $a \in null(A)$ if and only if $\begin{pmatrix} 0 \\ a \end{pmatrix} \in null(B)$. This means that the adhesive forces are determined by the initial conditions only up to elements of the null space of A. Thus, the adhesive forces are unique if and only of the null space of A is trivial. It is not currently known if the construction of B admits a configuration which causes A to have a non-trivial null space. If such a configuration exists, it is worthwhile to consider what significance this has in the physical system, but to date no such effort has been undertaken.

7.3 Relaxing constraints

In order to produce more realistic results, it is necessary to relax the constraints on the shape of a cell, as spheres do not very well describe the shape of many cells. Initially, deformable ellipsoids could be used. Eventually, perhaps, more general shapes could be allowed. With these more general situations, the form of the equations of motion will be different, and it would be interesting to see just how they are affected, and how they are to be solved.

In addition, there is an additional assumption that needs to be made but is not included in the model as yet. There is a limit to how strong the adhesive force between cells may be. If two cells pull on one another with too great a force, the bond will be broken and the cells will move apart, so that the adhesive force is zero. Therefore, in constructing the matrix, there is really a heaviside function, or something similar to break the bond when the force is too great. This may require that the matrix system be solved in multiple passes—each time dissolving any adhesions which have been broken.

7.4 Comparison with other models

Perhaps the most important aspect of a numerical analysis of the model is to compare the results with other current models, particularly those which bear a resemblance to this one. The Palsson-Othmer and Dallon-Othmer models would be of particular interest in comparing models numerically.

References

[1] J. C. Dallon and Hans G Othmer. How cellular movement determines the collective force generated by the *Dictyostelium discoideum* slug. *J Theor Biol*, 231:203–222, 2004.

[2] P. A. DiMilla, K. Barbee, and D. A. Lauffenburger. Mathematical model for the effects of adhesion and mechanics on cell migration speed. *Biophys J*, 60(1):15–37, 1991.

[3] E Evans and K Ritchie. Dynamic strength of molecular adhesion bonds. *Biophys. J.*, 72(4):1541–1555, 1997.

[4] Allan Franklin. Principle of inertia in the middle ages. *Am. J. Phys.*, 1976.

[5] M. E. Gracheva and Hans G. Othmer. A continuum model of motility in amoeboid cells. *Bull. Math. Biol.*, 66:167–193, 2003.

[6] Roger A. Horn and Charles R. Johnson. *Matrix Analysis*. Cambridge University Press, 1999.

[7] Qiya Hu and Jun Zou. An iterative method with variable relaxation parameters for saddle-point problems. *SIAM J. Matrix Anal. Appl.*, 2001.

[8] Douglas A. Lauffenburger and Alan F. Horwitz. Cell migration: A physically integrated molecular process. *Cell*, 84:359–369, 1996.

[9] Eirikur Palsson and Hans G. Othmer. A model for individual and collective cell movement in Dictyostelium discoideum. *PNAS*, 97(19):10448–10453, 2000.

[10] E. M. Purcell. Life at low Reynolds number. *Am. J. Phys.*, 45:3–11, 1977.

[11] I Stuiver and TE O'Toole. Regulation of integrin function and cellular adhesion. *Stem Cells*, 13(3):250–262, 1995.