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Using Mathematics to Gain Insights into Biology: An Application in Respiratory Mechanics

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research article

Using Mathematics to Gain Insights into Biology: An Application in Respiratory Mechanics

—William Matern (Editors: Stephen Dunn and Clia Goodwin)

Mathematical biologists try to describe biological phenomena quantitatively using mathematics. This is done by developing and analyzing mathematical models, which are sets of mathematical equations that describe the behavior of a biological system. Depending on their form, certain mathematical models are used to obtain very detailed and accurate predictions in biological phenomena, while others are employed to gain insights into the link between morphogenic (structural) form and biological function. Both types of models have numerous and important applications.

Mathematical biology is a very broad field. Anyone who has ever tried to use mathematics to predict how a population of humans or fish changes over time, the chances that a newborn will be color-blind if one of the parents is color-blind, or the concentrations of calcium and potassium ions in a neuron has engaged in mathematical biology.

The author working at his computer.

Mathematical biology is also a very old field, at least in some aspects. For example, population modeling has been performed for hundreds of years. Today, however, the field is rapidly growing, owing largely to the rise of computer power. With the advent of advanced computational capability afforded by modern computers, mathematical biologists can create and utilize sophisticated mathematical models that would be too complex to be amenable to hand calculations.

Understanding biology using mathematics provides an important complement to experimental approaches. Often, mathematical models can be used to model an experiment that cannot be realized in the lab. Whereas lab experiments are often done *in vivo* or *in vitro* (depending on whether the environment of the experiment is being controlled), experiments using only mathematical models (and a computer) are said to be done *in silico*. *In silico* experiments can be detailed and cheap alternatives to traditional lab experiments. However, it is crucial that any *in silico* experiment be validated via tests conducted *in vivo* or *in vitro*.

Since the fall of 2010, I've been involved in mathematical biology research being performed by Dr. Greg Chini of the Department of Mechanical Engineering and the College of Engineering and Physical Sciences (CEPS) Program in Integrated Applied Mathematics. Currently, I'm a senior majoring in mechanical engineering. The goal of our research is to create a mathematical model that can be used to study the mechanical behavior of wet, deformable lung tissue. Although solutions to our model must be obtained using appropriate computer algorithms, the modeling effort is directed toward gaining qualitative insights regarding robust behaviors rather than making detailed, quantitatively accurate predictions. I was awarded a Summer Undergraduate Research

Fellowship (SURF) to pursue this research on the UNH campus over summer 2011 and have continued this project in partial fulfillment of my senior thesis requirement. Our research is still ongoing.

The Role of Thin Liquid Films in Lung Mechanics

Lung mechanics research is often motivated by lung pathologies. According to the World Health Organization, diseases of the lower respiratory system constitute the fifth leading cause of human death. Many of these diseases impact the overall mechanical function of the lungs. For example, emphysema leads to a loss of elasticity and breakdown of connective tissue. Infant Respiratory Distress Syndrome (IRDS) is a condition in which a substance that reduces the energy required to expand the lungs is not produced, as often occurs in prematurely born infants. IRDS can be fatal. By gaining insights into the mechanics of lungs and how various diseases reduce lung function, we hope to inform clinicians and other medical specialists who might then be able to suggest treatments for restoring normal function.

Interestingly, it has been shown in numerous experiments that the (usually) thin layer of liquid that lines the lung airways and other tissues plays a primary role in how mammals breathe (Halliday). In particular, if the surface tension of these liquids is suppressed, then the lungs require far less energy to inflate. Conversely, if the surface tension of the fluid is high, then the mammal will not be able to expand its lungs properly. In the late 1950s researchers found that when a certain substance, called a surfactant, is absent from the lungs, surface tensions are much greater (Halliday). (Surfactants are also present in, for example, cleaning detergents.) In mammals, this surfactant, which reduces the surface tension of the liquid, is naturally produced by specialized cells in the lungs.

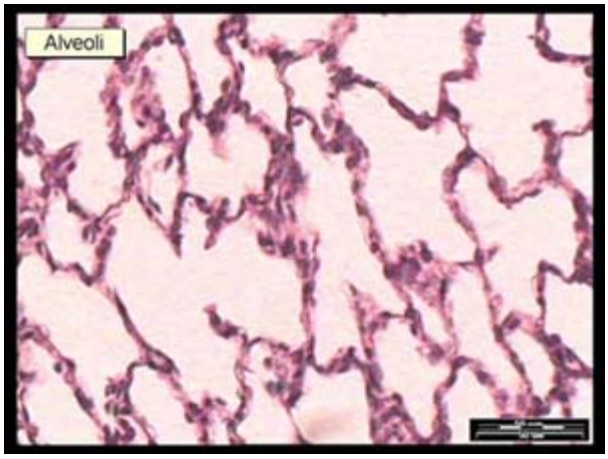
In humans, these cells usually become active by week 24 of pregnancy, but a normal level of surfactant is not reached until around week 34 (Bissinger). Thus, the earlier a human infant is born, the less surfactant will have been produced; and the chance that breathing complications will develop and result in IRDS is increased.

Fortunately, methods have been developed to treat infants with breathing difficulties. Often, a human-made surfactant, usually derived from bovine lung surfactant, is added to the infant's lungs (Bissinger). In many cases this eliminates the danger to the infant. Though these methods are empirically effective, a well-founded theory to explain in detail how the mechanics of the lungs are affected by the addition of surfactant is lacking. Some open questions include: How much surfactant should medical staff add? Which of the numerous proposed surfactants is best to use? How does the surfactant flow through the bifurcating airways into regions in which the air sacs are collapsed? How is airway re-opening achieved? Theoretical investigation of lung mechanics aims to shed light on these and other related questions.

Creating the Mathematical Model

Mathematical modeling cannot be completely reduced to a recipe or algorithm but remains, at least in part, an art. The formulation of an appropriate model depends heavily on the nature of the information being sought, e.g., qualitative versus quantitative or mechanistic understanding versus statistical description, and requires the retention of certain elements, the omission of others, and the approximation of still others.

In developing a mathematical model of the lung mechanics, Dr. Chini and I were motivated by the desire to address a fundamental question concerning human respiratory mechanics: how is the overall behavior of the lung, as would be manifested on machines in a clinician's office, connected to the mechanical behavior of the lung microstructure, which is on scales less than the thickness of a human hair? We were particularly interested in retaining key ingredients relating to geometrical, elastic, and liquid film (surface tension) properties of the lung.



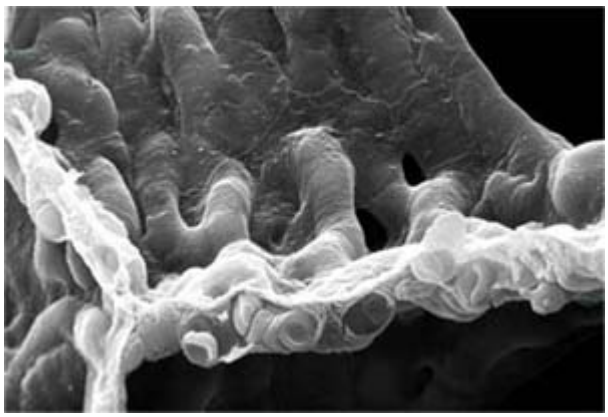


Figure 1 (top): A cross-section of a real mammalian lung.
(www.technion.ac.il/~mdcourse/274203/lect13.html)

Figure 2 (bottom): The connective tissue of the alveoli as seen with an electron microscope. Note that the tissue is far from smooth and therefore difficult to describe mathematically. (European Lung Foundation)

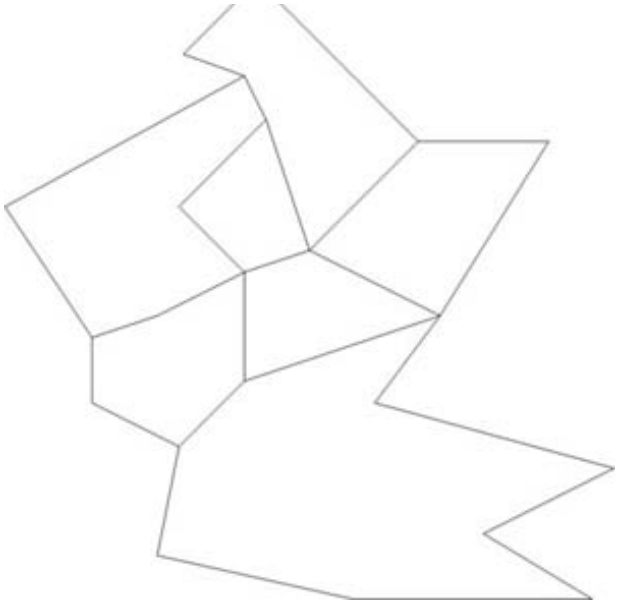


Figure 3: A mathematical diagram of a two-dimensional network of alveoli, which simplifies the real geometry of figure 1.

For information about the geometry of the lungs, we referred to anatomy journals and texts. For the behavior of the tissue, we relied on models supplied by researchers based on laboratory experiments. We idealized the aqueous liquid film as a "Newtonian" incompressible fluid, as commonly assumed for watery liquids. Finally, given these assumptions about tissue, liquid film, and geometrical properties, we expressed in mathematical form the fundamental laws of nature— specifically, Newton's second law of conservation of mass and momentum— to obtain a mathematical model describing the response of the system to imposed external forces.

The structure of mammalian lungs has been described in detail by physiologists, providing an accurate picture of how the lungs look, down to a microscopic level. Figure 1 shows a picture of an actual cross-section of lung tissue in a mammal. The lungs consist of a system of flexible tubes, or airways, that repeatedly branch out from one large tube (the trachea) to form smaller and smaller tubes The openings formed by the connecting tissue, which in three-dimension look like tiny balloons of air, are called alveoli. Eventually each of these tiny tubes is capped by a raspberry-like cluster of alveoli. During inspiration, the alveoli stretch out like a million tiny balloons and then deflate during exhalation. (Figure 2)

Although commonly described as balloons, alveoli are more accurately represented as interconnected polyhedrons. In fact, the detailed topology of the alveolar surface is exceedingly complex and difficult to describe mathematically. Including every detail in a mathematical model is neither feasible nor desirable, and some simplifications must be made. Therefore, for our model, we simplified the geometry of the alveoli into a two-dimensional system of hexagonal air sacs defined by simple straight connective tissue. (Figure 3) This simplification is a reasonable approximation of the cross-section of lung tissue and consequently can still capture many of the details of the inflating alveoli.

Researchers have used a variety of "constitutive" equations to describe the mechanical, i.e., stress/deformation, properties of alveolar tissue. We are comparing how these different representations of alveolar elasticity affect the results of our model of alveolar mechanics. To model the liquid that lines the alveolar tissue, we referred to a special branch of fluid mechanics called lubrication theory, according to which the governing equations of mass and momentum conservation can be combined and greatly simplified. Lubrication theory is apt for thin liquid films, and we used it to describe the flow of alveolar liquid driven by motion of the lung tissue and by surface tension-induced, or capillary, pressure gradients within the film.

Dr. Chini and I proceeded with the analysis by focusing on a single wall, or septum, of an alveolus. The diagram in Figure 4 shows a simplified system of the wall of an alveolus and its liquid film as the lung expands and contracts. By understanding how a single alveolar septum behaves, we can then begin to investigate how a large network of septa and alveoli responds to forces or displacements imposed at the boundaries of the network. Of prime importance is finding the conditions under which the alveoli will fully collapse. Under these conditions, termed *atelectasis*, the alveoli are difficult to re-inflate and respiratory distress can ensue. If the conditions for onset of atelectasis can be found theoretically, then this may help chemists and medical researchers design improved surfactant treatments.

As noted previously, it is important to validate the mathematical model with experimental results. A common experiment performed on mammalian lungs is to monitor how the pressure (P) and volume (V) of air within the lungs change on inspiration and exhalation. This data is often conveniently expressed as a graph depicting P-V curves, and they are specific to a lung. We hope that in its final form the mathematical model we develop can be used to predict — and understand—these curves based only on the geometry of the lungs and measureable properties of the connective tissue and surfactant. If the results of the mathematical model are sufficiently similar to the results from experimental data, then this will confirm our analysis.

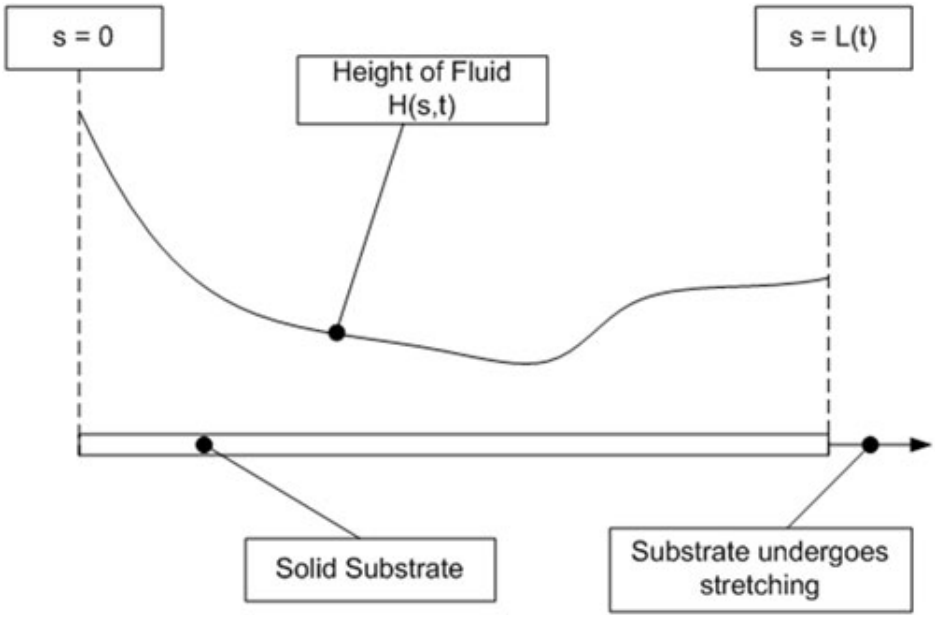


Figure 4: A diagram of the wall of an alveolus. A liquid film rests on the wall. The film is described by a height (H), and the position along the wall (substrate) is described by the length variable (s). (t) represents the time elapsed during expansion and contraction of the wall.

However, at present, we are far from being able to obtain *in silico* results that are comparable to those from an *in vivo* experiment.

Research Challenges

It is the rule rather than the exception that research investigations are fraught with unforeseen obstacles. In our project, we were able to write down a mathematical model describing how the liquid surfactant and a single wall of an alveolus move and deform when these components interact. However, the resulting equations were very complicated and could not be solved exactly analytically. Therefore, as has become common in various science and engineering disciplines, we sought approximate solutions to the equations. Owing to the number of calculations required to find the approximate solutions, we programmed a computer to automate the computations. There are numerous methods for finding numerical approximations to the solutions of various equations; the entire field of numerical analysis was developed to create and analyze these methods. Nevertheless, despite implementing five different numerical algorithms, we have not been able to obtain reasonable approximate solutions to our mathematical model. While the computer program operates properly, the approximations that it outputs are not close to the true solution.

An obvious question is: How can we judge a numerical approximation to be incorrect without knowing what the "true" solution is? The answer is that the computer-generated solution lacks some of the properties we expect to see in the true solution. Specifically, we expect the surface of the liquid film to be relatively smooth, but we observe that in the approximate solutions, it is jagged. Some of the difficulties seem to stem from the disparate

response times of the solid tissue and liquid film to imposed displacements as well as to the strongly nonlinear dynamics of the hybrid solid/liquid system. We are hopeful that our present attempts to find an approximate solution will be successful.

Future Directions

Once we have a working method for obtaining numerical solutions to our mathematical model, we aim to extend the model to encompass a network of walls connected to each other as shown in Figure 3. This network model should exhibit many similar mechanical phenomena as are expected to occur in actual lungs. With the appropriate choice of parameters, such as the length of the alveolar septa and the viscosity of the liquid film, as informed by experimental results, we hope that by investigating different scenarios in our model we can predict—at least qualitatively—what would happen in the real lungs under those same conditions.

For example, we plan to consider the impact of different surfactants on surface tension levels. We will run our computer program to estimate how much the tissue network dynamics change when surfactants of different strengths are used. From these results, we will seek a relationship between surface tension and the probability of atelectasis. We are also interested in understanding how the mechanics of the lungs change in diseased states. For example, we plan to modify by adjusting the parameter value controlling the tissue stiffness to mimic the effects of an emphysematic lung. A related change can be implemented to model the effects of cystic fibrosis. The goal of producing these "diseased state" models is to understand in detail how the mechanics of diseased lungs differ from those of healthy lungs and to identify potential ways to restore normal behavior.

The Future Promises of Mathematical Biology

The potential positive impacts of mathematical biology research are immense. One goal is to create models that can be widely used. A famous example of a mathematical model based on experimentation is the one derived by Hodgkin-Huxley for which Hodgkin and Huxley won the Nobel Prize in physiology in 1963. It is widely used to predict how electric current travels through the membranes of nerve cells. The model was developed by doing numerous experiments on large nerve cells found in squids. The large size of these nerve cells was the key to the development of the model because the two researchers could connect measurement instruments directly to the individual cells. From the data they collected, they were able to develop a mathematical model that could accurately predict the electrical properties of these nerve cells. Due to the similarity between the squid nerve cells and the nerve cells of other organisms, this model is often applied to the study of nerve cells in many species.

The Hodgkin-Huxley model illustrates a particular mathematical model widely used by biologists and biomedical researchers. This model was derived from experimental data and is thus an accurate representation of real life. Many other mathematical models for phenomena in biology have been created similarly. These include models for the chemical reactions occurring within cells (systems biology), electrical models of cells in the heart for studying defibrillation, and models for diabetes (Yi et al.; Boutayeb and Chetouani). In our research, we combine a number of already developed mathematical models to make predictions about data. Each of these models is derived by a researcher from experimental data.

The reach of mathematical biology has grown tremendously owing to the rise in readily available high-performance computational resources. Many mathematical models (including our own) require that a huge number of equations be solved repeatedly, which was impossible to do with early computers. However, improvements in both computer hardware and numerical algorithms have enabled solutions to many mathematical models to be obtained that would not have been possible even five years ago. Indeed, having powerful computers available allows for more accurate predictions, and many problems that were once too hard for the previous generation of computers can now be solved.

Accurate mathematical models allow for a precise understanding of biological phenomena. This precision opens the door to a new kind of bioengineering where prototype designs can be evaluated in detail before the prototypes are manufactured. These prototypes could be of artificial organs, new pharmaceuticals, or even completely novel organisms. The ability to design effectively these prototypes would constitute a major scientific advance and perhaps lead to breakthroughs in industrial processes, biofuel production, and the treatment of disease. It's exciting to think ahead to what might be accomplished in the next fifty years.

I would like to thank my mentor, Dr. Greg Chini, for getting me involved in this research and providing advice throughout the project. Thank you to the Hamel Center for Undergraduate Research for funding me over summer 2011 to pursue this project.

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Author Bio

William Matern*, from Kingston, New Hampshire, is a University Honors Program student who will graduate in May 2012 with a Bachelor of Science in mechanical engineering. Will began his research in biomechanics in Dr. Gregory Chini's Fluid Mechanics class and has continued it through a Summer Undergraduate Research Fellowship (SURF) in 2011 and for his senior honors thesis. Will said that he found keeping up to date in the sciences is crucial to conducting research, and he had to pick up a lot of physiology and some biology to understand his research subject. The result is that he has learned that it "takes a lot of thinking, reading, and writing to push human knowledge forward." What has been most satisfying to him in this experience is the confidence his studies have given him and how well prepared he was to approach new problems. Only the repeated failures and lack of results that occur in research have been frustrating.*

He chose to write for Inquiry rather than for a scientific journal because it is accessible to readers of many different backgrounds, and he is glad to have the opportunity to share what he and his team have learned. Will plans to go to graduate school because of his "great research experience," which showed him how much

interesting research is going on in biology. He plans to pursue a doctoral degree in one of several related fields in bioengineering and mathematical biology.

Mentor Bio

*Dr. **Gregory Chini**, an associate professor in the Department of Mechanical Engineering and co-director of the CEPS Program in Integrated Applied Mathematics, has worked at the University of New Hampshire for 12 years. His research and teaching interests are in the allied fields of applied mathematics and fluid dynamics, with a particular focus on environmental and biological flows. Dr. Chini frequently mentors undergraduate researchers, but this is his first experience mentoring an Inquiry author. He began working with Will Matern almost two years ago, and said that he has rarely seen an undergraduate who combines genuine creativity and intellectual independence with a true command of the fundamentals of mechanics, mathematics, and numerics as capably as Will does. According to Chini, writing for a broad audience has been a rewarding obligation that comes with the privilege of performing scientific and engineering research.*