Creating a Computer Model to Study Wound Healing

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Abstract

Understanding how cells move in large groups is important to understanding how wounds heal and cancer progresses. Although we can perform biological experiments in the lab to study cell movement, computer modeling allows us to analyze this behavior much faster to determine the underlying forces that govern cell movement. In this article, I will summarize how I constructed a computer model to study the cellular movement behind wound healing. My model is much simpler than existing models and can still describe all of the complex behavior that happens in the cell from many different types of forces. I will also describe how I got interested in this project and bioengineering in general.

1 Discovering Science

1.1 My Scientific Passion

When I was little, I always wondered why my parents worked late every day. While my friends went home after preschool, I would stay at my parents labs, waiting for them to finish their research. What was so interesting about science?

One day, I begged my dad to show me his experiments. Smiling at my enthusiasm, he scraped off some of my cheek cells and put them under the microscope. As he pointed out the nucleus and organelles of each cell, I watched in awe at the hidden complexity within my own body. At that moment, I knew that I wanted to be like my dad: to be able to look into the microscope and understand how the world works. Once I started elementary school, I pursued math and science relentlessly. By high school, my desire to learn more outpaced the normal school curriculum, so I started independent research projects in mathematics, biology and bioengineering.

Although I work in fields that are different from my parents, I share their passion for science. The many fields of science, math and engineering may seem incredibly disparate, but they actually all share one common starting point: an open-ended, significant question. It does not matter if this question is Does this mutation increase the likelihood of Parkinsons disease? or Can we make a computational model of wound healing? or even How do we make the best basketball-playing robot?. What matters is that each of these questions requires an innovative approach to solve. I love scientific exploration because it gives me the opportunity to both pose these hard questions and answer them creatively. With each question that I answer, I further my knowledge just far enough to pose additional questions, continuing the happy investigative cycle.

Now, I completely understand why my parents kept late hours in the lab. Unless my parents remind me to go to bed, I would spend every waking hour testing my code or running literature searches. There is just too much in the world to explore. Like Isaac Newton felt over four hundred years ago, I feel like a young girl playing on the sea-shore, and diverting myself now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me. As I continue my scientific career and try to chart that ocean of truth, I know that the fascination and wonder I felt from those cheek cells will always remain.

1.2 Finding a Mentor

I started research on my Intel project when I was at a personal crossroads. Although I enjoyed biological research, I also wanted to incorporate my love for engineering. Through Stanford's Education Program for Gifted Youth and the Canada / USA Mathcamp, I found I had a deep passionate love for programming and building. I loved being a lead coder for my school's robotics team, creating robots heavier than me that could play basketball or ultimate frisbee. I found that code was not just abstract algorithms on a computer, but a pragmatic way to solve real-world problems. How could I reconcile my love for scientific research and engineering?

Bioengineering was the solution to my quandary. When I found out that scientists were applying engineering principles to push the biomedical field into unexplored directions, I knew that this was my field. I could combine my two loves innovatively, constructing mechanical substitutes for organic parts or creating technology to interpret biologic processes. The field truly captured my imagination. So, when my school's science chair introduced me to Dr. Leamy, a Georgia Tech mechanical engineering professor interested in biology, I immediately accepted the research opportunity

I met with Dr. Leamy every week at Georgia Tech for half an hour over two years, doing most of the work at home independently. Dr. Leamy's guidance helped me throughout the entire process, making suggestions regarding possible mechanical forces to consider, discussing possible causes of instabilities, and making wording suggestions to my paper. I independently researched the biological behavior that I would like to capture by combing through the literature and hypothesizing what would cause the cell behavior that I saw in the videos. I decided which rule sets to include and built the entire model by myself. I implemented rule sets into the code and performed all debugging and code stability tests.

2 Performing Science

2.1 Introduction

Group cell movement is an important part for many biological processes, from cancer progression to embryo formation. We can study this behavior in the lab with biological experiments, but these can often be time-consuming or unable to tell what is responsible for the behavior. Computer models are the perfect solution - we can run many tests very quickly and we can find and control the exact causes for the cells' movement. So, my goal is to create a computer model that can accurately study how groups of cells move during wound healing. I will need to make sure that this model is biologically accurate so that I can find what forces are really behind wound healing.

2.2 Approach

To create an accurate model, I first took videos of cells healing a wound in the lab. With these videos, I could observe how the cells behaved and hypothesize what was causing the behavior. I then programmed these hypotheses into my model and ran simulations with it. By controlling which forces were active, I could see precisely which forces caused the cellular movement.

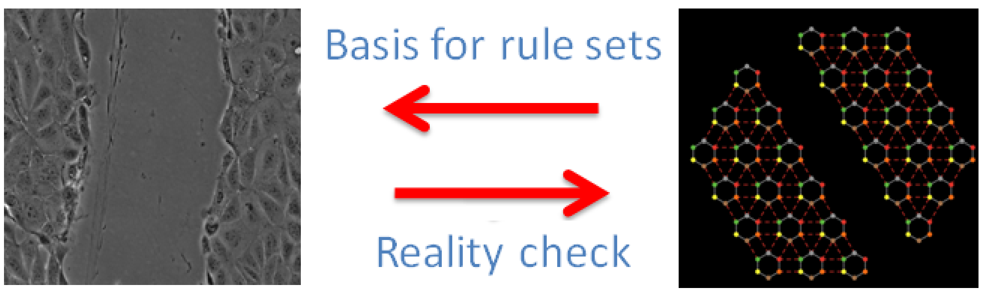

Figure 1: Research approach - Take actual wound healing videos (left), derive what rules I want to implement in my model (right) and double check that they represent accurate behavior.

2.2.1 Videos

To take videos of wound healing, I first grew a sheet of cells on a Petri dish in the lap. Then, I scratched the surface of the cells to create a "wound". I then placed the dish underneath a microscope which was configured to take a picture every 10 minutes for 15 hours, which I could then stitch together to form a video. With this video, I could see what rules I should include in my model.

2.2.2 Model

I used NetLogo to create my model as an agent-based model. Agent-based modeling works by taking a set of agents that each follow their own set of instructions. From these small-scale interactions, complex behavior appears on the larger scale. The best way to think about this is to imagine a flock of bird, flying in a V formation. Each bird is an "agent", and it makes decisions on how and where to fly. Based on each individual bird's decisions, the complex behavior of a V emerges without explicitly telling the birds what to do.

So, in my model, each cell was represented as a hexagon, with each vertex an agent. Each agent would calculate the forces that acted on it and then compute what its new position should be. By repeating this process over time, I could see each cell move. This movement could be then compared back to the original wound healing videos, letting me verify the accuracy of the modeled behavior.

2.3 Results and Discussion

After calibrating the basic model according to the videos and constants found in other scientific papers, I could then test the impact of different cellular foot forces on the overall rate of wound healing. I tested the effects of mechanical and chemical forces on the cell and found that mechanical forces alone could close a wound. If mechanical and chemical forces worked together, the wound would close at a much faster rate.

Overall, I have created a model that can give a complete picture of cell movement during wound healing. The model is kept accurate by its close ties with reality, based on observation from actual wound healing videos. Agent-based modeling allows me to explicitly write the local causes of this overarching behavior, allowing me and future scientists to focus on specific forces for future biological study.

2.4 Advice

I am really grateful to have been selected as an Intel Science Talent Search Finalist. After two years of hard work, it has been an incredibly rewarding experience for me, not only allowing me to strengthen my programming knowledge and analytical ability, but also showing me the power of applying engineering principles to biological questions. I have loved every second I have spent coding up new rule sets for my model or analyzing videos of wound-healing. To see my hard work be honored by Intel is extremely gratifying and awe-inspiring for me at the same time.

I highly encourage all high school students to do some sort of scientific research. The thrill of discovering something fundamental and true about the world is worth the long years of hard work. The question does not have to be big - just being able to say "I taught myself something that I did not know before" is worth it. I encourage girls in particular to do science and math. As the only female member on my school's robotics programming and build teams, I know how hard it can be to be the only female in a male-dominated field. But do not give up! Persevere! Never let anyone else's preconceptions prevent you from realizing your scientific dreams.

If you want to get involved in research, I recommend emailing professors at your local university in your field of interest. The more informed you are about the work that they do and what work you are interested in, the better they will be able to give you a project or recommend someone who is a better fit. If there are no local mentors who can take you in, try to network online with other professors or do a project on your own. While these are difficult to pull off, they are still very possible if you have sufficient drive and motivation. Regardless, be prepared to invest a large amount of time into your project. Good work does not come easily, and while there are times that you may want to just give up, always push through, keeping in mind the larger goal of what you want to create.

Most importantly, spread the message of science through outreach to younger kids. Start a math and science club or a robotics team at your local elementary school. Have a model rocket day or a toothpick bridge competition. Get out there and show everyone that math and science is not just doing problems in a textbook. It is about discovery and investigation - pure and simple fun.