Dissertation Proposal: A Multi-Scale, Physics Engine-Based Simulation of Cellular Migration

Terri A. Grosso

CUNY Graduate Center

December 5, 2014
To model the molecular interactions between cells and their environment, in order to study macro-level emergent behaviors.
Research Motivation

Research Scope

Design of the Tool
  The Physics Engine
  Modeling the Cell
  Modeling the Bonds
  Modeling Trafficking and Protein Interactions
  Modeling the Environment

Research Schedule
Biological Motivation - Cellular Migration

- Embryogenesis
- Wound-Healing
- Immune responses
- Cancer metastasis
Importance of Simulation

- System is very complex
- Experiments are time-consuming
- Supplies are expensive
- Difficult to isolate variables
## Research Issues

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple moving objects</td>
<td>Physics Engine</td>
</tr>
<tr>
<td>Physical bonds and constraints</td>
<td>Physics Engine</td>
</tr>
<tr>
<td>Complex shapes</td>
<td>Triangular Mesh</td>
</tr>
<tr>
<td>Heterogenous cell surface</td>
<td>Triangular Mesh</td>
</tr>
<tr>
<td>Surface protein trafficking</td>
<td>Differential equations</td>
</tr>
<tr>
<td>Developing concentration gradients</td>
<td>Partial differential equations</td>
</tr>
<tr>
<td>Visualization</td>
<td>Rendering Engine</td>
</tr>
<tr>
<td>Extensibility</td>
<td>User-defined parameters</td>
</tr>
</tbody>
</table>
Research Scope
Specific Goals

- Clearly represent the interactions between the cell and its environment
- Interactions happen at the cell membrane
- Demonstrate how ligand binding affects the trafficking of surface proteins
- Show how that trafficking leads to cells moving
Research Scope

▶ Building around work with Retinal Progenitor Cell migration in Microfluidic Channels at the Redenti Lab at Lehman College
▶ Mouse RPG cells
▶ Long, closed, narrow channel (13mm by 95µ diameter) with laminin-coated walls
▶ Generates a stable gradient of ligand across the channel
▶ Can take pictures of cells and track them as they migrate
The Microfluidic Channel

Figure: Microfluidic Channel Design [1]
Designing the Tool

- The Physics and Rendering Engines
- Modeling the Cells
- Modeling Protein Interactions
- Modeling Surface Protein Trafficking and Protein Interactions
- Modeling the Environment
The Use of the Physics Engine

Advantages:

- Designed for video games
- Supplies motion, forces, collision detection and constraint resolution
- Works in real time
- Using the JBullet Physics Engine
- Binds to OpenGL for rendering
Rendering the Channel
Migrating Cells Have Complex Shapes

Figure: Mesenchymal and Amoeboid Migration[2]
Modeling with a Triangular Mesh

- Data structure composed of a set of triangles in 3D space that share edges and vertices
- Used frequently to represent very complex shapes in video games
- Use is optimized in physics and rendering engines
- Allows characteristics of an object to be represented at finer granularities
Different Levels of Granularity
The Heterogenous Cell Membrane

- Distribution of surface proteins and internal proteins differ from one triangle segment of the cell to another
- How that distribution changes over time also differs across the cell
- Can use the triangular mesh to represent these distributions at a fine granularity
- Can visualize these differences with different shades of color
Visualizing Variability Across the Cell
Binding to a Surface

- Surface binding is necessary for cell migration
- Binding happens between receptors and surface proteins
- Do not model each individual molecular bond - too many of them
- Each constraint represents a group of molecular bonds (100 molecules here)
The Lifetime of a Bond

- Bonds break probabilistically based on:
  - age
  - the force being applied
- When first formed, they can easily break.
- Over time bonds become focal adhesions - large, stable, hard to break.
- Eventually focal adhesions are degraded.
- Forces applied to bonds help to break them.
- Bond flexibility also age-dependent.
Change in Concentration of Surface Proteins

- Receptors are secreted to the surface at a specific rate
- Some receptors bind to ligand in the environment
- Empty receptors are internalized at a different rate
- Bound receptors are internalized at still another rate
- Movement of membrane proteins in and out of cell called trafficking
Schematic Representation of Trafficking
Mathematical Description of Surface Membrane Turnover

Differential equations describing the changes in membrane proteins over time:

Changes in the number of unbound receptors:

$$\frac{dR}{dt} = -k_{on} RL + k_{off} C - k_t R + Q_R$$

Changes in the number of bound receptors:

$$\frac{dC}{dt} = k_{on} RL - k_{off} C - k_e C \ [3]$$
Localized Turnover of Surface Proteins

- Each triangle membrane segment has its own rates for each represented protein
  - Rate of secretion to the surface
  - Rate at which unbound receptor is internalized
  - Rate at which bound receptor is internalized

- Changes to these rates affect the number of receptors on the membrane surface
Proteins Affect Each Other

Defining Protein Interactions

- Receptor and Target
- Number of bound Receptor molecules determines affect on the Target protein
- Binding of Receptor can affect any of the trafficking rates of the Target protein
- Receptor of one Interaction can be the Target of another
Walls

- Can simply use a set of rigid boxes
- Represent the surface concentration of a protein with a single value if we assume it is constant
- Can represent a wall as a triangular mesh to represent varying amounts of surface ligands
- Can set them to be invisible for visualization
Ligand Gradients

- Ligand concentration modeled continuously using partial differential equations
- Dependent on the experimental set-up
- Visualized on screen
Walls and Gradients - Example

Viewing Protein: Integrin (Unbound)

Experimental Time: 00:00:30:001
Distance From Source Reservoir: 0.0

Sink Conc: 0.0 nM
Source Conc: 5.6 nM
Some Example Videos

Here are some example videos.
## Current Progress

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple moving objects</td>
<td>Implemented</td>
</tr>
<tr>
<td>Physical bonds and constraints</td>
<td>Partially implemented</td>
</tr>
<tr>
<td>Complex shapes</td>
<td></td>
</tr>
<tr>
<td>Heterogenous cell surface</td>
<td>Implemented</td>
</tr>
<tr>
<td>Surface protein trafficking</td>
<td>Implemented</td>
</tr>
<tr>
<td>Developing concentration gradients</td>
<td>Implemented</td>
</tr>
<tr>
<td>Visualization</td>
<td>Implemented</td>
</tr>
<tr>
<td>Extensibility</td>
<td>Partially implemented</td>
</tr>
</tbody>
</table>
Next Steps - Changing Cell Shape

- Shapes of the cells need to change in response to the environment
- Vertices should move relative to each other
- New vertices form at bond positions
- Vertices may also be removed if no longer necessary
Next Steps - Simulation Analysis

- Computational Efficiency - how does changing number of cells, triangles and proteins affect the speed of computation?
- Parameter Estimation - which parameters give results similar to those found in the lab?
- Sensitivity Analysis - how do parameter ranges affect the output?
Future Research

- An XML interface for user-defined objects and parameters
- Implement other assays and compare to published research
References


The End

Thank you for your time and support! Questions?