**Example: Model Development Workflow for the Changes of Shape of Epithelial Cells due to Cell Cycle Progression**

Working from the published article:

Nematbakhsh, Ali, Wenzhao Sun, Pavel A. Brodskiy, Aboutaleb Amiri, Cody Narciso, Zhiliang Xu, Jeremiah J. Zartman, and Mark Alber. "Multi-scale computational study of the mechanical regulation of cell mitotic rounding in epithelia." *PLOS Computational Biology* 13, no. 5 (2017): e1005533.

**Biological Observations**



Apical surface of epithelial sheet in the wing disc of Drosophila with some cells undergoing mitosis. Fluorescent tag is GFP associated with E-cadherin, a protein responsible for forming impermeable connections between cells.

 

 (<http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1005533>)

**Initial Questions**

**Observables:**

 From the images can determine cell’s shape, *i.e* **PERIMETER** and **SURFACE AREA** and nature of **ADHESION** values. We infer the **CELL CYCLE STATE** of the Cell from the configuration, but we can’t measure it directly.

**General Questions:**

All cells are not undergoing mitosis at the same time. But when they are, cells increase their apical surface area and become more round. They also seem to lose their adhesivity to neighbouring cells.

What is going on at the level of each individual cell?

**Defining Questions and Hypotheses**

**Problem**: Why do Epithelial Cells entering mitosis become rounder and also decrease their adhesion to other cells?

**Governing Hypothesis:** Increase in the cortical stiffness of the underlying actomyosin ring from the increased mass during mitosis results in the adjustment of shape. This also leads to reduced intracellular pressure reducing adhesion strengths.

The changes in stiffness can be connected to an internal clock which cells use to keep track of time and division.

**Defining Qualitative Verbal Model**

**Objects: Cells** (Representing apical domains in Epithelia)

What are the **Properties** of our cells?

Shape

[Mass]—not observed but inferred from

Perimeter Length

Surface Area

Cell Cycle Progression State {Interphase, Mitosis}

What are the **Behaviors** of our cells?

Cells vary their cortical stiffness depending on their Cell Cycle Progression State, specifically cells increase their cortical stiffness when their Cell Cycle Progression State reaches mitosis.

Cells’ Mass **increases** as their Cell Cycle Progression State increases

Cells **divide** when their Cell Cycle Progression State reaches mitosis

After Division, Cell Cycle Progression resets to Interphase

What are the **Interactions** between our cells?

Cells adhere to neighboring cells by forming adhesive junctions, cells reduce their adherence when their Cell Cycle Progression State reaches mitosis

What are the **Initial/Boundary Conditions** and **Tweaks**?

**Initial Conditions:**

A fixed number of cells adjacent to each other, all with Cell Cycle Progression State set to Interphase

**Boundary:**

An infinite universe

**Tweaks:**

None

What are the **Dynamics** of the cells?

The Cell Cycle Progression State increases stochastically in time

Cells adjust their shapes in response to the forces acting on them internally and externally

Cells change their cortical stiffness and adhesivity when their Cell Cycle Progression State reaches mitosis

Express Qualitative Verbal Model as tables



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Object | Properties | Property Type | Annotation on Terminology | Source Reference |
| Universe(Medium) |  |  | MESH:D004777 | <https://link.springer.com/protocol/10.1007/978-1-59745-525-1_13> | New Concept but could be related to source in link |
|  | X-extent | Parameter | SIO:000400PATO:0001708 | <https://link.springer.com/protocol/10.1007/978-1-59745-525-1_13> | New Concept but could be related to source in link |
|  | Y-extent | Parameter | SIO:000401PATO:0001708 | <https://link.springer.com/protocol/10.1007/978-1-59745-525-1_13> | New Concept but could be related to source in link |
|  | Z-extent | Parameter | SIO:000402PATO:0001708 | <https://link.springer.com/protocol/10.1007/978-1-59745-525-1_13> | New Concept but could be related to source in link |
| Cell |  |  | CL:0000000 | <http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1005533><https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3612985/> |
|  | Perimeter(*L*) | Variable | SIO:000046 | <https://link.springer.com/protocol/10.1007/978-1-59745-525-1_13> | New Concept but could be related to source in link |
|  | Surface Area(*SA*) | Variable | MESH:D001830 | <https://link.springer.com/protocol/10.1007/978-1-59745-525-1_13> | New Concept but could be related to source in link |
|  | Cell Cycle Progression(*CP*) | Variable | MESH:D002453Thesaurus:C25630 | <http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1005533> |

|  |  |  |
| --- | --- | --- |
| Behavior | Participant Object | Properties |
| Cell Growth | Cell | Surface Area(*SA*) |
| Cell Division | Cell | Surface Area(*SA*) |
| Cortical Stiffness($C\_{t}$) | Cell | Perimeter(*L*) |

|  |  |  |  |
| --- | --- | --- | --- |
| Interaction | Participant Objects | Properties | Property Type |
| Formation of Adhesive Junctions | Cell 1 with Cell 2 if neighbours | Adhesion Strength(*S*) | Parameter |

|  |  |  |  |
| --- | --- | --- | --- |
| Dynamics | Participant Objects | Participant Behavior/Interactions | Property Affected |
| Stochastic Transition from Interphase to Mitosis | Cells | Cortical Stiffness,Growth,Division | Cell Cycle Progression(*CP*),Surface Area(*SA*) |
| Dynamics of Cortical Stiffness | Cells | Adhesion Between Cells | Perimeter(*L*), Adhesion Strength(*S*) |

**Define Quantitative Model Template**

Cell Cycle Progression as a function of random growth :

 $CP\rightarrow CP+η$

Surface Area Changes:

 $S\rightarrow \left(CP+1\right)S\_{initial}$

Cortical Stiffness Changes:

 $C\_{t}\rightarrow \left(1-CP\right)C\_{t}$

This affects perimeter:

 $L\rightarrow {C\_{t}}/{\left(2λ\right)}+L$