Simulation of Chemotaxis-based Sorting of Heterotypic Cell Populations

M. Eyiyurekli*, P.I. Lelkes** and D.E. Breen*

*Department of Computer Science
**School of Biomedical Engineering, Science and Health Systems

Conclusions & Future Work

- Model successfully simulates heterotypic cell sorting behavior
- Incorporates differential chemotaxis, adhesion and motility
- Parametric studies demonstrate influence of model components

Results

- Intermediate steps from an in silico cell sorting experiment
- Time increases from left to right
- Final result from a sorting simulation of a heterotypic mixture of two cell populations, T1 (blue) and T2 (red)

Parametric Studies

- Effect of detachment probability
- Parametric studies demonstrate influence of model components

Cell Model

- Two types of cells (blue T1, red T2)
- Each cell is defined by a collection of parameters and actions.
  - Number and the position of CTX receptors on the cell surface
  - Location of the cell
  - Age
  - Life cycle stage
  - Chemotactic vent rate (Rw)
  - Proliferation rate
  - Number of attached cells
  - Emission and sensing of chemotactic factors
  - Gradient following & Brownian motion
  - Proliferation
  - Collisions and adhesion
  - Attachments and separation
  - Aging and cell death

- ‘Proliferation and cell death are not included in the cell sorting model.’

System Structure for Cell Aggregation Model

- Cells live on a hexagonal grid
- Environment has toroidal topology
- Cells may attach to each other at six distinct sites
- Chemical diffusion approximated by a 1/r concentration field
- Assume chemical interaction stops beyond a certain distance
- Simulation time step is dynamically calculated for movements

CTX-based cell sorting

- Chemotaxis (CTX) is the phenomenon where cells detect chemical gradients and respond to the chemical stimulus by moving in the direction of these gradients, either towards (positive CTX) or away (negative CTX) from the source.

- Cell sorting is a fundamental process that is involved in early embryo development, tumorigenesis and morphogenesis.

- The sorting of heterotypic cell populations is produced by a variety of intercellular actions, e.g., differential adhesion and motility.

System Structure for Cell Sorting Model

- T1 (Flowchart above) cells respond to C1: they form aggregates.
- T2 (Flowchart below) cells respond to C2, as soon as they form aggregates
- They do not emit any chemotactic chemicals

- If PR2 is 10%, then blue T1 cells can cell sorting, left to right PR2 = 0.1, 0.2, 0.7, 1.0

- If the probability of gradient following is too low no aggregation is observed.

- As the probability increases blue T1 cells start forming a loose aggregate.
- All new neighbors attach (PAttach) when PR1 is 20% or more.

- Attachment is fixed and final; thus creating an asymmetric aggregate with heads.

- A tightly coupled aggregate is formed when PR1 is 20% or more.

- The final shape of the aggregate is desirable when this probability is between 40% − 70%.

- As the probability increases blue T1 cells start forming a loose aggregate.
- If the probability of gradient following is too low no aggregation is observed.

- Parametric studies demonstrate influence of model components

- Proliferation rate 
- Number of attached cells
- Diffusion radius (Rd)
- Life cycle stage
- Location of the cell on the cell surface
- *Proliferation and cell death are not included in the cell sorting model.

Cell Model

- Two types of cells (blue T1, red T2)
- Each cell is defined by a collection of parameters and actions.
  - Number and the position of CTX receptors on the cell surface
  - Location of the cell
  - Age
  - Life cycle stage
  - Chemotactic vent rate (Rw)
  - Proliferation rate
  - Number of attached cells
  - Emission and sensing of chemotactic factors
  - Gradient following & Brownian motion
  - Proliferation
  - Collisions and adhesion
  - Attachments and separation
  - Aging and cell death

- ‘Proliferation and cell death are not included in the cell sorting model.’

Parametric Studies

- Effect of detachment probability
- Parametric studies demonstrate influence of model components

System Structure for Cell Aggregation Model

- Cells live on a hexagonal grid
- Environment has toroidal topology
- Cells may attach to each other at six distinct sites
- Chemical diffusion approximated by a 1/r concentration field
- Assume chemical interaction stops beyond a certain distance
- Simulation time step is dynamically calculated for movements

Conclusion & Future Work

- Model successfully simulates heterotypic cell sorting behavior
- Incorporates differential chemotaxis, adhesion and motility
- Parametric studies demonstrate influence of model components

Intermediate steps from an in silico cell sorting experiment.
- Time increases from left to right.
- Final result from a sorting simulation of a heterotypic mixture of two cell populations, T1 (blue) and T2 (red).