Simulation of Chemotaxis-based Sorting of Heterotypic Cell Populations

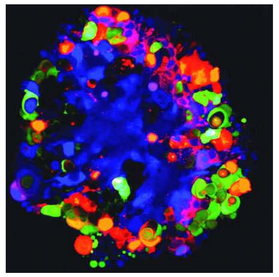
M. Eyiyurekli*, P.I. Lelkes** and D.E. Breen*

*Department of Computer Science College of Engineering

**School of Biomedical Engineering, Science and Health Systems

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, tumerogenesis and morphogenesis.

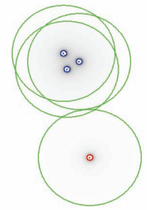


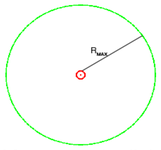
- The sorting of heterotypic cell populations is produced by a variety inter-cellular actions, e.g. differential adhesion and motility.

Cell Model

- Two types of cells (blue T_1 and red T_2)
- 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
- Chemoattractant emission rate
- Diffusion radius (R_{MAX})
- Proliferation rate*
- Number of attached cells

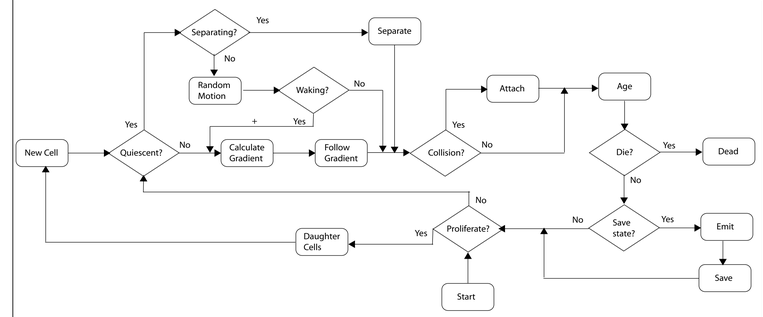




- Emission and sensing of chemoattractors
- Gradient following & Brownian motion
- Proliferation
- Collisions and adhesion
- Detachments and separation
- Aging and cell death*

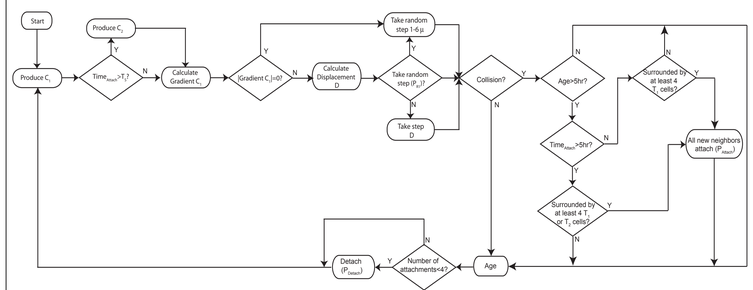
- *Proliferation and cell death are not included in the cell sorting model.

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

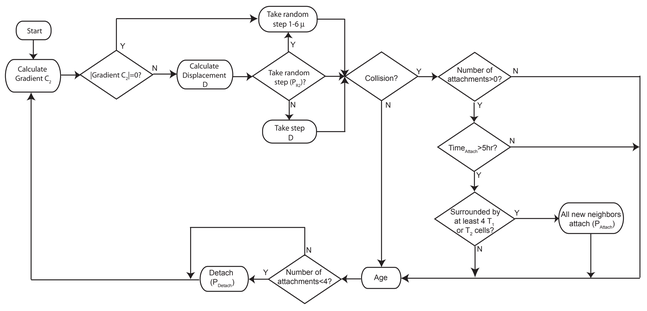
System Structure for Cell Sorting Model



- T_1 (flowchart above) cells respond to C_1
- Produce C_1 throughout the simulation and C_2 T_s (9 hours) after they form aggregates
- Can attach to both types of cells

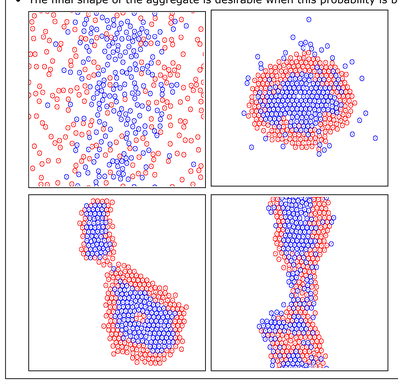
- T_2 (flowchart below) cells respond to C_2 as soon as T_1s start producing C_2
- They do not emit any chemoattractant chemicals

- Both T_1 and T_2 cells
  - Can attach to both type of cells
  - May detach if they are on the outer layers of an aggregate (P_{Detach})
  - Do random motion
- T_1 cells are an order of magnitude faster than T_2 cells
- T_1 cells have a higher probability of attaching, i.e. more adhesive
- T_1 cells follow the gradient most of the time while T_2 cells have a higher probability of taking random steps

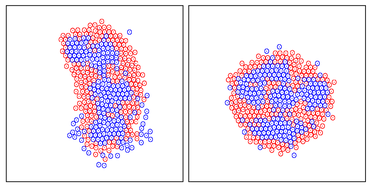


Parametric Studies

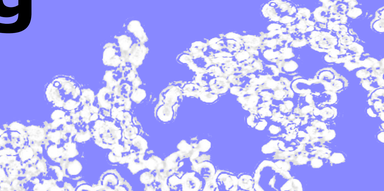
- Effect of P_{R1} for blue T_1 cells on cell sorting. Left to right P_{R1} = 0.1, 0.2, 0.7, 1.0.
- If the probability of gradient following is too low no aggregation is observed.
- As the probability increases blue T_1 cells start forming a loose aggregate.
- A tightly coupled aggregate is formed when P_{R1} is 20% or more.
- The final shape of the aggregate is desirable when this probability is between 40% – 70%.



- Effect of chemoattractant gradient response on sorting and aggregation.
- Slower cells (λ_1 = 1.0 for T_1 cells) cannot form into one aggregate within 24 hours.



- Effect of T_s on cell sorting.
- A premature aggregation of red T_2 cells is observed when the response time is 6 hours.

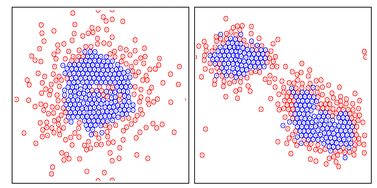


- Left: Effect of probability of attaching on cell sorting.
- Probability of attaching for two blue T_1 cells is zero.
- No aggregates are formed, therefore blue T_1 cells never produce the chemical to attract red T_2 cells.

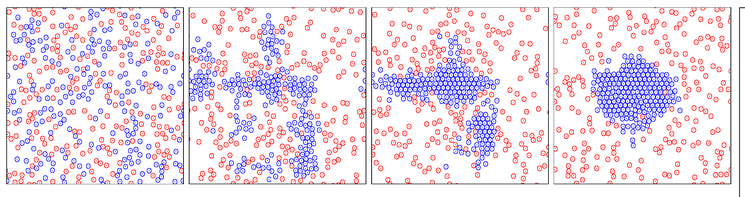
- Right: Effect of probability of detachment on cell sorting.
- If we eliminate detachments, P_{Detach} = 0, all the attachments are fixed and final; thus creating an asymmetric aggregate with holes.

- Left: Modifying T_2 's probability of responding to chemoattractant C_2
- T_2 cells show little sign of aggregating when P_{R2} = 10% Red cells create a cloud around blue

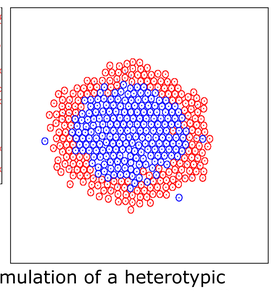
- Right: Increasing P_{R2} to 30% results in several smaller aggregates partially sorted
- Once the T_2 cells spread over the T_1 cells, the T_1 cells are prevented from aggregating further



Results



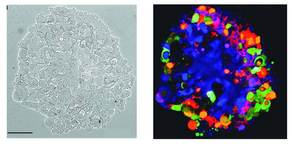
- Intermediate steps from an in silico cell sorting experiment. Time increases from left to right.



- Final result from a sorting simulation of a heterotypic mixture of two cell populations, T_1 (blue) and T_2 (red).

Conclusion & Future Work

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



- Extend model to 3D
- Simulate early tissue and tumor formation