Simulating a Germinal Center Notes

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Contents

1 Resources.

Research Paper: Robert, P., Rastogi, A., Binder, S. and Meyer-Hermann, M. (2017). How to Simulate a Germinal Center. Methods in Molecular Biology, pp.303-334.

2 Model Assumptions.

In this section, we highlight the assumptions made in the model we are following. This is primarily to refer to in future when making our own adjustments to the model.

- Only one antigen per Germinal Center.

3 Implementation Ideas

Assign each cell an ID from 0 to $m(=$ number of cells). Can then find each property by using ID as index for a list. >Using dictionaries instead

Generate $N \times N \times N$ spatial grid to place discrete sphere with radius $N/2$ within. Find and store the valid spatial points within this grid. At each time step, record where the discrete grid spot is free or contains a cell. Use dictionary, return None if empty, otherwise cell ID? If we want to find the position of a cell, we would need to work the dictionary backwards, likely to be computationally slow. Could have two dictionaries - one that gives position from cell ID and another that gives Cell ID / None from position. Is this likely to cause update issues?

The model given assigns cells an ID based on their position of each cell in its respective type list. This would allow for multiple cells to have the same ID and would require ID and type to be uniquely identified. Rather give each cell a unique ID regardless of type so always identifiable from ID alone.

Total number of initial cells can be calculated using totals for all types of cells. Use this to generate empty lists for each cell's parameters to be inserted into.

Don't need to have dictionary storing whether a point is within the sphere, can just re-apply the same calculation used to find original sphere co-ordinates.

4 Algorithms.

4.1 Parameters for each Cell

Property	Domain	Storage	Description?
Assigned ID	Integer starting at Zero	List?	
Location	(x, y, z) co-ordinates	List	
Type/Agent	String	List	
State	String	List	
BCR	4-digit integer	List	
pMutation	Float [0,1]	List	
responsiveToSignal[CXCL12]	Boolean	List	
responsiveToSignal[CXCL13]	Boolean	List	
Polarity	$(\hat{i}, \hat{j}, \hat{k})$ 3D Vector	List	
cycleStateTime	Float	List	
endOfThisPhase	Float	List	
numDivisionsToDo	Integer	List	
IAmHighAg	Boolean	List	
retainedAg	Float	List	
numFDCContacts	Integer	List	
selectedClock	Float?	List	
Selectable	Boolean	List	
Clock	Float	List	
tcClock	Float	List	
tcSignalDuration	Float	List	
individualDifDelay	Float	List	

4.2 General Parameters & Tracked Lists

- We keep two dictionaries, Grid_id and Grid_type. These dictionaries have a key of a tuple location within the sphere and return the cell and cell type located at that location, respectively. If that position is free, both dictionaries will contain 'None'.

- Dictionaries CXCL12 and CXCL12 will stores the amount of each located at a given location.

- We will use StormaList, FDCList, CBList, and TCList to store the IDs of cells in each of these respective states.

4.3 Algorithm 1 (Mutation)

Function: mutate()
   Notes: I believe all cells have an affinity? Need to examine reference 13 to determine what is meant by +/-1, do we do both or randomly choose from possibilities?
   Input: Cell, C; Probability of Mutation, pMutation.
   Accesses: BCR.
   Alterations: BCR.

4.4 Algorithm 2 (Dynamic Updating of Chemotaxis)

Function: initiateChemokineReceptors()
   Notes:
   Input: Cell, C (ID); Type of cell, T.
   Accesses: responsiveToSignal[CXCL12], responsiveToSignal[CXCL13].
   Alterations: responsiveToSignal[CXCL12], responsiveToSignal[CXCL13].

Function: updateChemokinesReceptors()
Notes:
Input: Cell, C (ID).
Accesses: responsiveToSignal[CXCL12], responsiveToSignal[CXCL13].
Alterations: responsiveToSignal[CXCL12], responsiveToSignal[CXCL13].

4.5 Algorithm 3 (Updating Position and Polarity of cells at each time-point)

Function: move()
Notes: With probability persistentLengthTime(Cell Type) do ..., looking at table of values, persistentLengthTime is greater than 1 for all but one type of cell.
Input: Cell, C (ID).
Accesses: Polarity, responsiveToSignal[CXCL12], responsiveToSignal[CXCL13].
Alterations: Cell Location; Cell Polarity
Function: updateChemokinesReceptors()
Notes: The inputs Θ and Φ are randomly generated in the function move(). The instructions for this function seem to be a bit confusing. Will need to draw this out to understand it better.
Input: Cell Polarity; Θ; Φ.
Accesses:
Alterations: Cell Polarity.

4.6 Algorithm 4 (Updating events at the Centroblast Stage)

Function: initiateCycle()
Notes: getDuration(x) implies sampling guassian with mean x, standard deviation 1.
Input: Cell, C (ID); number of divisions to occur.
Accesses:
Alterations: C.state, C.cycleStartTime, C.endOfThisPhase, C.numDivisionsToDo.
Function: progressCycle()
Notes: 'Progress: ...' Implies that you move the cell to the next state available.
Input: Cell, C (ID).
Accesses: C.cycleStateTime, C.state.
Alterations: C.state, C.cycleStartTime, C.endOfThisPhase, C.numDivisionsToDo.
Function: divideAndMutate()
Notes: This function can create a new cell.
Input: Cell, C (ID).
Accesses: C.retainedAg
Alterations: New cell (Location and ID), IAmHighAg, retainedAg

4.7 Algorithm 5 (Antigen Collection from FDCs)

Function: progressFDCSelection()
Notes: Clock++ means increase clock by 1 right? If so, is it really an integer? F is an FDC, f is a fragment neighbouring C.
Input: Cell, C (ID).
Accesses:
Alterations: selectedClock, clock, selectable, numFDCContacts, F.antigenAmount[f].

4.8 Algorithm 6 (Screening for T cell help at the Centrocyte Stage)

Function: progressTCellSelection()
Notes: Calls functions in Algorithm individualDifDelay is Guassian.
Input: Cell, C (ID).
Accesses:
Alterations: state, tcClock, tcSignalDuration, individualDifDelay.

4.9 Algorithm 7 (Updating the T cells according to B cells Interactions)

Note: For the following two function, we introduce a list denoted 'ListInteractingB' to track the IDs of the B cells currently in interaction.

Function: updateTCell()
    Notes:
    Input: Cell, TC (ID); Cell, B (ID).
    Accesses:
    Alterations: TC.state, ListInteractingB

Function: liberateTCell()
    Notes:
    Input: Cell, TC (ID); Cell, B (ID).
    Accesses:
    Alterations: TC.state, ListInteractingB

4.10 Algorithm 8 (Transition between Centroblasts, centrocyctes, and output Cells)

Function: differToOut()
    Notes: We track Out cells using list 'outList', and number of using 'numOutCells'.
    Input: Cell, C (ID);
    Accesses:
    Alterations: numOutCells, outList

Function: differToCB()
    Notes: We track Centroblasts using list 'CBlist'.
    Input: Cell, C (ID).
    Accesses:
    Alterations: CBlist, pMutation, retainedAg, IAmHighAg

Function: differToCC()
    Notes: We track Centrocytes using list 'CClist'.
    Input: Cell, C (ID).
    Accesses: C.retainedAg
    Alterations: State, numFCDContacts.

4.11 Algorithm 9 (Initialisation)

Function: initialiseCells()
    Notes:
    Input: Various inputs such as number of Stromal cells.
    Accesses:
    Alterations: Generates cells, FCD Fragments, etc.

4.12 Algorithm 10 (Hyphasma: Simulation of Germinal Center)

Function: initialiseCells()
    Notes: Driver function.
    Input: Various inputs regarding simulation parameters.
    Accesses:
    Alterations:

5 Definitions & Terms.

- **Affinity Maturation**: The process by which Tfh cell-activated B cells produce antibodies with increase affinity for antigen during the course of an immune response.

- **Stromal Cells**: Connective tissue cells of any organ.

- **B Cells**: Type of white blood cell.

- **Centroblasts**: B cell that is enlarged and proliferating in the germinal center.

- **Clonal Expansion**: A large increase in the number of B cells and T cells in the presence of an infection.

- **Somatic Hypermutation (SHM)**: A cellular mechanism by which the immune system adapts to the new foreign elements that confront it. Allows B cells to mutate the genes that they use to produce antibodies.

- **B Cell Receptor (BCR)**:

- **VDJ Recombination Pattern**:

- **in vivo**: A study where the effects of various biological entities are tested on whole, living organisms or cells.

- **Centrocytes**: Nondividing B cells that endure a high apoptosis rate.

- **Follicular Dendritic Cells (FDCs)**: A type of cell in the immune system.

- **Fc Receptors**: A protein found on the surface of certain cells that contributes to the protective functions of the immune system.

- **MHC Class II**: A class of molecules normally found only on antigen presenting cells. Important in initiating immune responses.

- **Antigen Presenting Cell (APC)**: A cell that displays antigen complexed with major histocompatibility complexes (MHCs) on their surfaces.

- **T Helper Cells**: Cells that help the activity of other immune cells by releasing T cell cytokines (small proteins).

- **T Follicular Helper (Tfh)**: Within a Germinal Center they mediate the selection and survival of B cells that differentiate either into special plasma cells capable of producing high affinity antibodies against foreign antigen, or memory B cells capable of quick immune re-activation in the future if the same antigen is ever accounted again.

5.1 Questions for Julian

- For mutation, it says to apply +/-1 to a position, randomly choose + or -?

- Reference 16 is supposed to contain a distribution that requires sampling, unsure what this distribution is exactly. (Wrong reference was given in citation, correct citation in parameters table, reference 5. Still unable to find distribution.)

- Algorithm 3: "with probability persistentLengthTime(C.type)", in values, persistentLengthTime is greater than one for all but on Cell type. Maybe convert to hours and use that decimal?

- Algorithm 9: "get new BCR, randomly or from a predefined repertoire"

- Algorithm 1: Amount of CXCL12, CXCL13 at each position.

- pDif2Out(time) has a formula with a variable that's always zero.

- Algorithm 9: Do FDC branches have to remain in the light zone?

- variable++ means to add one?