Simulating a Germinal Center Notes

November 30, 2018

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 Implementation Notes

- Note that the size of the GC is constant. This gives us an upper bound on the number of cells. We generate a list of integers with as many unique entries as the size of the GC. When a new cell is created, we assign it an ID from this list. When a cell leaves the simulation, we add its ID back into the list. We use this unique ID as a key for each cells properties in respective cell types dictionaries.
- Since the sphere is shifted to be in the first octant, we can create a 3D numpy array where each element corresponds to a position in the GC. We set points outside the GC to -1 and empty points within the GC to None. In the filled positions we store the ID of the cell in that position. This allows for O(1) checks for where a position is free or inside the GC.
- We set the surface layer points of the GC to be those that have a neighbour outside of the GC.
- The following was followed to generate random unit vectors for initial polarity: https://codereview.stackexchange.com/q random-unit-vectors-around-circle Summary: Can sample three $\mathcal{N}(0,1)$ variables and normalise to obtain a vector on unit sphere.
- Rotating Polarity: Instructions were ambiguous, here is the implemented interpretation. We find a vector $\boldsymbol{v}$ that is perpendicular to the polarity vector. We first rotate the polarity θ degrees towards the vector $\boldsymbol{v}$. θ is sampled from a distribution not given, replaced with Normal distribution. Next, we rotate the resulting vector by ϕ degrees around the original polarity vector. Here, ϕ is sampled from uniform$(0, 2\pi)$. Since $\boldsymbol{v}$ is chosen randomly and ϕ is chosen uniformly at random, these actions are equivalent to rotating the original polarity vector by θ degrees around a randomly generated perpendicular vector $\boldsymbol{v}$. We can generate $\boldsymbol{v}$ using

$$\boldsymbol{v} = \boldsymbol{r} - (\boldsymbol{r} \cdot \boldsymbol{n})\boldsymbol{n}, \tag{1}$$

  where $\boldsymbol{r}$ is a random unit vector, and $\boldsymbol{n}$ is the polarity vector. We can then use the rotation matrix

$$\begin{bmatrix} \cos(\theta) + v_x^2\,(1-\cos(\theta)) & v_x v_y\,(1-\cos(\theta)) - v_z \sin(\theta) & v_x v_z\,(1-\cos(\theta)) + v_y \sin(\theta) \\ v_y v_x\,(1-\cos(\theta)) + v_z \sin(\theta) & \cos(\theta) + v_y^2\,(1-\cos(\theta)) & v_y v_z\,(1-\cos(\theta)) - v_x \sin(\theta) \\ v_z v_x\,(1-\cos(\theta)) - v_y \sin(\theta) & v_z v_y\,(1-\cos(\theta)) + v_x \sin(\theta) & \cos(\theta) + v_z^2\,(1-\cos(\theta)) \end{bmatrix}, \tag{2}$$

  to rotate the polarity around $\boldsymbol{v} = (v_x, v_y, v_z)$.
- Diffusion of CXCL12 and CXCL13:
- Secrete CXCL12 and CXCL13:

3 Parameters for each Cell

3.1 Stromal cell

Property	Data Type	Description
Type	Enumeration	The type of cell.
Position	Tuple	Position within GC.

3.2 F-Cell

Property	Data Type	Description
Type	Enumeration	The type of cell.
Position	Tuple	Position within GC.
antigenAmount	Float	Amount of Antigen Retained by the Fragment.
icAmount	Float	
Fragments	List of IDs(int)	List of IDs for each fragment of given F-cell.

3.3 Fragment

Property	Data Type	Description
Type	Enumeration	The type of cell.
Position	Tuple	Position within GC.
antigenAmount	Float	Amount of Antigen Retained by the Fragment.
icAmount	Float	
Parent	Integer	ID for center of F cell.

3.4 Centroblast

Property	Data Type	Description
Type	Enumeration	The type of cell.
Position	Tuple	Position within GC.
State	Enumeration	Current state of the cell.
BCR	4 Digit integer	BCR value for cell.
Polarity	3D Numpy Array / Vector	Polarity of cell.
responsiveToCXCL12	Boolean	Records whether cell is responsive to signal CXCL12.
responsiveToCXCL13	Boolean	Records whether cell is responsive to signal CXCL13.
numDivisionsToDo	Integer	The number of divisions the cell is yet to do.
pMutation	Float	Probability of the cell mutating.
IAmHighAg	Boolean	
retainedAg	Float	Amount of antigen retained by the cell.
cycleStartTime	Float	Amount of time spent in current state.
endOfThisPhase	Float	Time at which the cell will finish being in this state.

3.5 Centrocyte

Property	Data Type	Description
Type	Enumeration	The type of cell.
Position	Tuple	Position within GC.
State	Enumeration	Current state of the cell.
BCR	4 Digit integer	BCR value for cell.
Polarity	3D Numpy Array / Vector	Polarity of cell.
responsiveToCXCL12	Boolean	Records whether cell is responsive to signal CXCL12.
responsiveToCXCL13	Boolean	Records whether cell is responsive to signal CXCL13.
selectedClock	Float	
Clock	Float	
selectable	Boolean	
FragContact	None or Integer	
numFDCcontacts	Integer	
tcClock	Float	
tcSignalDuration	Float	
individualDifDelay	Float	
TCell_Contact	None or Integer	If in contact with T cell, this stores the ID of said T cell.

3.6 T cell

Property	Data Type	Description
Type	Enumeration	The type of cell.
Position	Tuple	Position within GC.
State	Enumeration	Current state of the cell.
Polarity	3D Numpy Array / Vector	Polarity of cell.
BCell_Contacts	List of integers	List of IDs of B cells (Centrocytes) in contact with T cell.

3.7 Outcell

Property	Data Type	Description
Type	Enumeration	The type of cell.
Position	Tuple	Position within GC.
Polarity	3D Numpy Array / Vector	Polarity of cell.
responsiveToCXCL12	Boolean	Records whether cell is responsive to signal CXCL12.
responsiveToCXCL13	Boolean	Records whether cell is responsive to signal CXCL13.

4 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.