**Simulation in Biology Project Abstract**

**Group:** Cellular Biology

**Project name:** Systemic Lupus Erythematosus (SLE) & Anifrolumab

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**Project description:**

The immune system relies on several cells signaling to one another and passing information, but when distorted, this signaling can result in unintuitive processes. Systemic Lupus Erythematosus (SLE), which tricks antibodies and T-cells into attacking healthy cells. From an unknown cause, healthy cells go under some form of cell death (apoptosis/necrosis) and nucleic antigens become present in the system. When cleaned up through phagocytosis, dendritic cells (D-cells) recognize the DNA as a foreign invader and go through the normal immune pathway. This involves D-cell to T-cell interaction in which type 1 interferons (T1IFN) are transferred between D-cells and T-cells along with the nucleic antigen. This coupled transition of the antigen and T1IFN allow the spread of information that a foreign invader has effected the host. This leads to T-cell to B-cell interactions, using the same mechanism as D to T cell interactions. When B-cells have information on an antigen it in tern produces antigen specific antibodies. These antibodies then bind to the nucleic antigens induced by apoptosis to form an antibody-antigen complex. The antibody-antigen complex can be destroyed by phagocytes such as D-cells. When D-cells consume the antibody-antigen complex, D-cells then increase their potency of T1IFN. Such that when in contact, D-cells alter T-cells to become autoreactive cell that attacks the hosts’ own healthy cells and B-cells can then become corrupted again to produce autoreactive antibodies which attack the host cells.

This simulation will look at what would happen across several positions in the SLE pathway and hope to add preventative measures to parts of the pathway in hope to model a potential solutions. The preventative measure, Anifrolumab, attaches to type 1 interferon receptors blocking the passage of antigen presentation signals between T-cells and B-cells therefore preventing them from going autoreactive. Due to the coupled nature of transferring the antigen and cytokines, blocking the cytokines would prevent the transport of antigens, thereby preventing the autoreactive response.

**Agents and rules:**

*Healthy Cells:*

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1) Agents in simulation representing healthy tissue

2) Is destroyed when attacked by corrupted Autoreactive cells

3) Have a chance of becoming Apoptotic dictated by a slider



4) If apoptotic, has a chance of releasing a number of Nucleic Antigens dictated by a slider

5) Signals “Eat me” to Phagocyte (D – cells) while being apoptotic

6) Can spawn a new cell if there are no cells in the patch directly next to it

*Nuclear Antigens:*

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1. Nucleic bits that signal “danger” to APC (D-cell) based on a chance of external factors
2. Can be discovered by APC, B-cells and antibodies
3. Will degrade overtime

*Dendritic Cell (dcell):*

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1. Can eat Antigens and pass on it’s info to helper T-cells this info is denoted by a ring around the D-cell



1. Can search for Apoptotic cells
2. Can “eat” antibody-antigen complex to mature (denoted by the M)



1. Mature D-cells are not phagocytes
2. Will die after so much time given dictated by a slider
3. Will spawn every so many ticks dictated by a slider plus dynamically by how many antigens are present to simulate the inflammation response.

*Bcells:*

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1. Agents that recognize nucleic antigens if so it is denoted



1. Can recognize the same info from T-cells which causes a antibody production
2. Produces autoreactive antibodies in response of the detection of the antigens (in production of antibodies the B-Cell darkens in color)
3. Can obtain info from Mature D-cells to produce autoreactive antigens
4. Will die after so much time given dictated by a slider
5. Able to be “vaccinated” to prevent the transfer of auto-antigens



*Tcells:*

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1. Transfers info between D-cells and B-cells
2. Will die after so much time given dictated by a slider
3. Able to be “vaccinated” to prevent the transfer of auto-antigens



1. If in contact with Mature D-cells they become autoreactive cells



*Antibodies:*

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1. Can bind to nucleic antigens to form a Antigen-Antibody complex
2. Will die after so much time given dictated by a slider

*Antigen-Antibodies:*

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1. Attacks all other cells with the same dna (which in this case is the healthy tissue)
2. Will die after so much time given dictated by a slider (same slider as normal antibodies)
3. If made in reaction to a mature d cell then Autoantigens attack healthy cells.
4. After killing the healthy cell they will die (they commit suicide with the cell)



*Anifrolumab:*



1. Attaches to T-cells & B-cells and prevents them from transferring info from the Dendritic Cells
2. Will die after so much time given dictated by a slider

*Autoreactive Cell:*



1. When in contact with healthy body cells it takes time destroying them.
2. The time it takes to destroy cells is dictated by a slider
3. Will die after so much time given dictated by a slider

**Reactions Cheat Sheet (Reactions in terms of mathematical equations):**

D Cell + Apoptotic Cell = No Antigens

Time + Apoptotic Cell = Antigens

Antigens + B Cell = Activated B Cell

Antigens + D Cell = Activated D Cell

Activated D Cell + T Cell = Activated T Cell + Activated D Cell

Activated T Cell + Activated B Cell = T Cell + Activated B Cell + Antibodies

Antibodies + Antigens = Antibody-antigen

Antibody-antigen + D Cell = Mature D Cell

Mature D Cell + T Cell = Autoreactive Cell + Mature D Cell

Mature D Cell + Activated B Cell = Mature D Cell + Activated B Cell + Autoreactive Antibody

Autoreactive Antibody + Antigen = Autoreactive Antibody-Antigen

Autoreactive Antibody-Antigen + Healthy Cell = Dead Cell + Antigens

Autoreactive Cell + Healthy Cell = Autoreactive Cell + Dead Cell + Antigens

Anifrolumab + T Cell = Inhibited T Cell

Anifrolumab + B Cell = Inhibited B Cell

Inhibited T Cell + Mature D Cell = Inhibited T Cell + Mature D Cell

Inhibited B Cell + Mature D Cell = Inhibited B Cell + Mature D Cell

**Model validation:**

1. The Autoreactive cells are able to destroy healthy cells
2. Cells replicate
3. Simulation stops if no more healthy cells the
4. Cells die over time

**Hypotheses / Predictions:**

1. By inhibiting the Type 1 interferon (T1IFN) receptor for the coupled reaction of antigen and T1IFN on T and B cells it is possible to slow down or completely stop the inflammation/damage of healthy cells

**Evaluation (graphs, statistics):**

1. Amount of Autoreactive Antibodies & Autoreactive Cells
2. Number of Inhibited T & B Cells
3. Number of Dead Cells
4. Number of Mature Dendritic Cells & Nucleic Antigens

**User Interaction (sliders, buttons):**

1. Setup: sets the scene for the simulation
2. Go: runs the simulation
3. Inject Anifrolumab: after every determined ticks N amount of Anifrolumab will spawn
4. Predisposition?: button that effects the rate of apoptosis by increasing it by 10 times
5. Initial conditions sliders for D,T,B cells
6. Spawn rates for T, B, D, and body cells
7. Growth rate of cells in apoptosis
8. Number of antigens a dead cell will produce
9. Amount of time anti-production time
10. Lifetime slider for all agents
11. Amount of time required to kill a healthy cell by a Autoantibody or autoreactive cell

**Simplifications:**

* No Memory Cells
* Rate of Apoptosis is over exaggerated
* CD4 and CD8 T cells are represented as 1 T cell
* T1IFN is not expressed as it is coupled with antigens
* T1IFN is passed trough contact only
* Healthy Cells can be any group of cells in the body
* Lifetime rates are over simplified to the point where it is impossible to direct it to a point of actual time. But for the sake of argument 10 ticks are set as 1 day
* D cells serve as APC and Phagocytes (this allows the removal of Macrophages as phagocytes)

**Testing:**

All tests are done with the following constants:

* Num-tcell = 1
* Num-bcells = 1
* Num-dcells = 1
* T Cell spawn rate = 32
* B Cell Spawn rate = 32
* D cell Spawn Rate = 32
* Antibody-Production time = 1
* Cell growth rate = 21
* Body-cell-spawn-rate = 3
* Base cell death rate = 27
* Nucleic-antigen-per-cell = 3
* Autoreactive-eating-time = 4
* Has predisposition = on
* Autoantibody eating-time = 5
* T cell lifetime = 100
* B cell lifetime = 100
* D cell lifetime = 100
* Anifrolumab lifetime = 100
* Antibody lifetime = 50
* Antigen lifetime 50
* Runtime = 10,000 ticks
* Anifrolumab amount = 100

Control:

Run the simulation without Anifrolumab for 10,000 ticks or when all cells die

Tests:

Anifrolumab on from start

Run for 10,000 ticks or all cells die

Variable Cycle length (administration length) = 10 (1 day), 100 (10 days), 300 (1 month)

In the figures below you are able to see a direct comparison between the effects of Anifrolumab and autoreactive cells and the effects over different administration periods. Comparing figures 1 and 2 reveal that a high delay of admission (figure 2) of Anifrolumab results in almost the same data and patterns with no Anifrolumab (figure 1).

As this is not the result I would have hoped, I tested again with 2 other admission rates; every 10 days and everyday. Figure 3 denotes the every 10 days administration period. This proved much better results in the fact that within the 10,000 ticks (1000 days) there was a point on tick 8534 where there were no autoreactive cells or antibodies in the host. In addition, overall there was a decrease of autoreactive cells in compared to the control group. This data shows enlightenment on the aspect of hopes for a cure SLE but as seen in figure 4 this is not the case.

In figure 4, Anifrolumab was administered every day. This test resulted in autoreactive cells & antibodies continuously drop to zero but seem to come back. This disproves the hypothesis that Anifrolumab would be able to cure SLE however, it does nullify and slow the autoimmune and inflammation down.

Figure1:

This graph models the base rate for autoreactive cell & antibody production for individuals with SLE

Figure 2:

This graph models the rate for autoreactive cell & antibody production for individuals with SLE with a monthly injection for Anifrolumab

Figure 3:

This graph models the rate for autoreactive cell & antibody production for individuals with SLE with an injection for Anifrolumab every 10 days

Figure 4:

This graph models the rate for autoreactive cell & antibody production for individuals with SLE with a daily injection for Anifrolumab

**References:**

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