Modelling Virus-Mediated Cell-Cell Fusion using a Probabilistic Agent-Based Model

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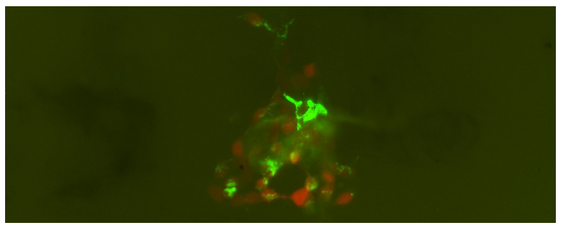
Background

- Some viruses form multi-nucleated cells due to viral protein expression on the surface of infected cells.
- These multi-nucleated cells are known as **syncytia**.
- Current models accurately represent the temporal increase in syncytia over time, but not the spatial effects syncytia have.
- We are interested in creating a model that can accurately represent the spatial dependence of syncytia.

Viral Cell-Cell Fusion

- Cell fusion occurs when a viral protein being expressed on a cell comes into contact with a cell expressing a receptor for that viral protein. This process is dependent on protein-receptor interaction can only occur if they are in contact with each other.
- This protein-receptor interaction limits syncytia formation. There is currently no method to model this spatial interaction.
- We can use an Agent-Based Model (ABM) to model each individual cell, and simulate a cell-cell fusion experiment.

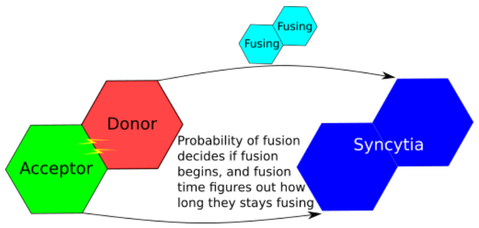


Model Development

- Development constraints like computational time and scale are problems to be addressed when creating an ABM.
- We will be using parallel processing to address both of these problems.
- Parallel processing will be done in the CUDA C++ coding language.
- CUDA C++ allows us to use the computational power found in graphics processing units (GPUs).
- GPUs have thousands of cores compared to a computers CPU, which will have 8-32 cores.
- By using the GPUs we solve both of the main problems with ABMs, but still have a limitation in the complexity of code being ran on the GPU.

Model Creation and Basics

- We will model each cell in our simulation as a hexagon. This allows for six edges for interaction of the cells around them.
- We will be simulating multiple different types of cells in the model:
  - ▷ Acceptor: cells expressing the receptor for the viral fusion protein
  - ▷ Donor: cells expressing the viral fusion protein
  - ▷ Fusing: two cells in the process of forming a syncytia
  - ▷ Syncytia: multi-nucleated cells that can continue to fuse with acceptor cells
- Each donor cell is put randomly throughout the tissue and is governed by a percentage of overall cells.
- Each cell type has specific code:
  - ▷ IF (cell = acceptor): no code is ran
  - ▷ IF (cell = dononr): probability of fusion is calculated for each side in contact with an acceptor
  - ▷ IF (cell = fusing): no code is ran
  - ▷ IF (cell = syncytia): probability of fusion is calculated for each side in contact with an acceptor

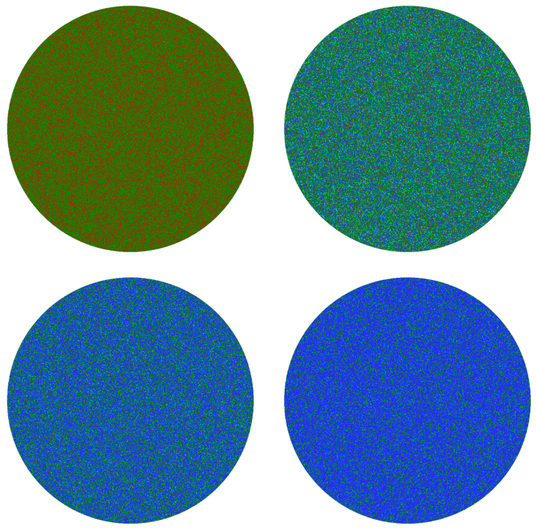


Probability and Syncytia Formation

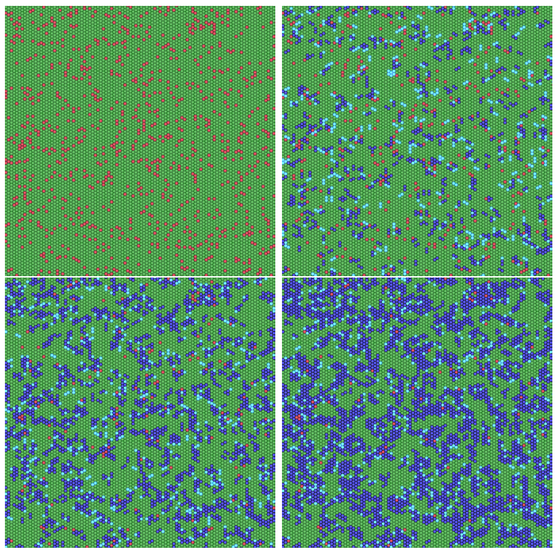
- Syncytia formation is governed by two parameters;
  - ▷ Syncytia Formation Rate: γ
  - ▷ Average Fusion Time: k
- The probability of fusion is taken from a uniform distribution, and the probability of fusion must be less than $P = 1 - e^{-\gamma t}$, where t is the time step.
- Fusion time determines how long a cell will stay in the fusing phase, before a syncytia is formed.
- The length of time for fusion time is taken from a gamma/Erlang distribution. The mean of this distribution is k.
- Two cells in the fusion process cannot do anything besides undergo the fusion process and become a syncytium.

Results

- The ABM runs a 480 hour simulation in 5 minutes on the GPUs, this allows for multiple simulated fusion experiment to be run quickly.



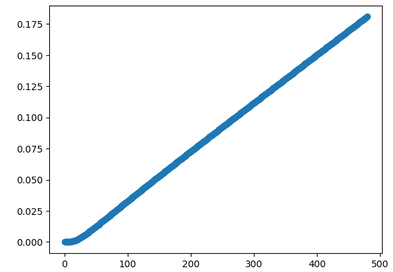
- The images seen above and below are simulate snapshots at 0 hours, 48 hours, 96 hours, and 144 hours.



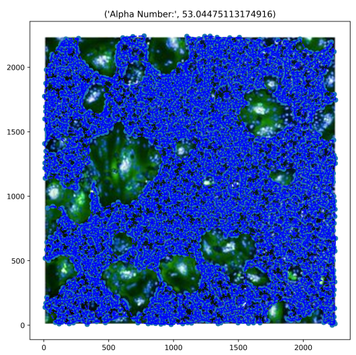
- Since the model is working, the next step is temporal and spatial validation using experimental cell-cell fusion data.

Model validation

- Two types of model validation must be done, temporal and spatial validation to ensure the syncytia formation in the model is realistic to experimental settings.
- Temporal validation was done through fitting syncytia over time to a surrogate data set made by the ABM.



- Spatial validation will be done through alpha shape filtration. This algorithm will need experimental data of cell-cell fusion in confluent layers to validate the model to.



- Spatial validation is currently underway as we are running cell-cell fusion experiments and implementing the alpha shape algorithm.

Conclusions/Future Plans

- Future plans include spatial validation, finalization of a cell-cell fusion experiment, and imaging of the experiment.
- We also wish to investigate cell-cell fusion as it occurs. This will be done with a homemade stage-top incubator we are currently working on. This allows for different temperatures and pH to be studied.
- We would also like to try different experimental fusion experiments with different viral proteins and cell lines.