Using an agent-based model to explore the impact of inoculum dose and transmission mode on viral infection

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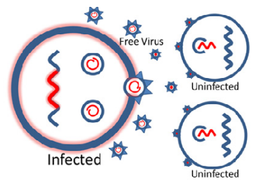
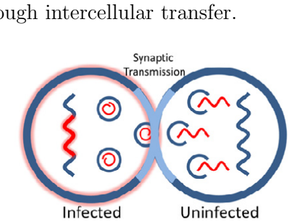
Motivation

- A virus spreads through a body in two known ways, cell free transmission and cell to cell transmission.
  - In cell free transmission, cells produce and release viruses that diffuse throughout the body which may cause any cell that the virus touches to become infected.



  - In cell to cell transmission, virus spreads through intercellular transfer.



- In cell to cell transmission, virus spreads through intercellular transfer.
- The two transmission modes allow viruses to spread at different speeds.
- Cell to cell transmission also protects the virus from dangers outside the cell such as antivirals and components of the immune response.
- We would like to understand how different transmission modes alter the time course of the disease.

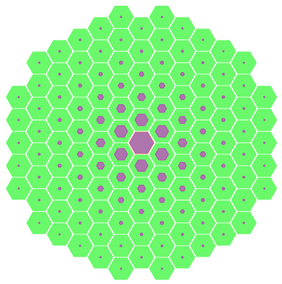
Our Approach

- We will construct a hybrid agent-based and partial differential equation (PDE) model to simulate the spread of virus.
- An agent-based model represents each cell independently and allows us to examine the collective behavior.

Virus Spread

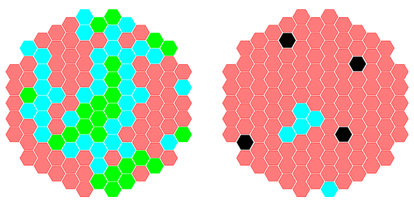
- The virus produced by free cell transmission diffuses over the top of the cell layer.
- Virus spreads according to the following partial differential equation,

$$\frac{\partial V}{\partial t} = D\nabla^2 V + pI - cV$$



Modeling Cell States

The cells can be in one of four states.

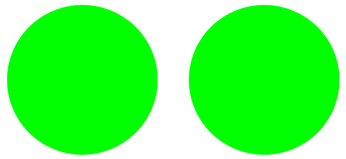


- Green - Healthy cells
- Blue - Infected cells not producing virus (Eclipse cells)
- Red - Virus-producing infected cells
- Black - Dead cells
- Cells become infected either from virus above them or from virus transferred from neighboring cells.
- Cells transition from eclipse to infectious and infectious to dead after periods of time drawn from a gamma distribution.

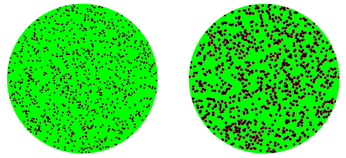
Modeling Infections

- A million cells in a hexagonal grid were simulated.
- For the images below a Multiplicity of Infection (MOI) of 10^{-3} was used. MOI determines the initial amount of virus.
- We compared infections using only cell-free transmission and only cell-to-cell transmission.
- Below the first 4 days for cell-to-cell (left) and cell-free (right) transmission are shown.

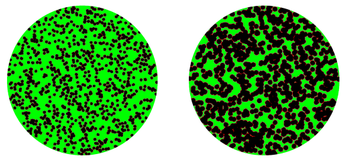
Day 0:



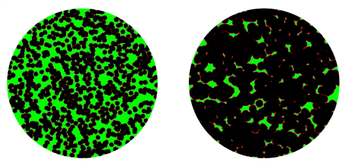
Day 2:



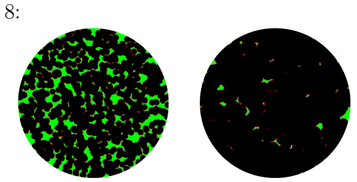
Day 4:



Day 6:

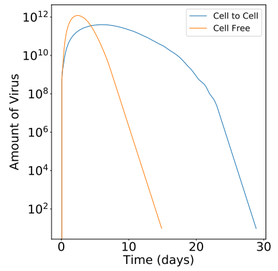


Day 8:



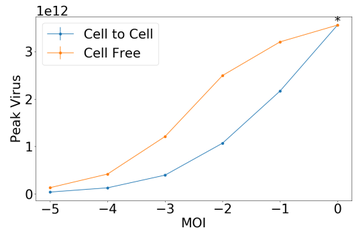
Viral Time Course

A simulation is performed for a number of MOIs and a virus vs. time graph is recorded for each.



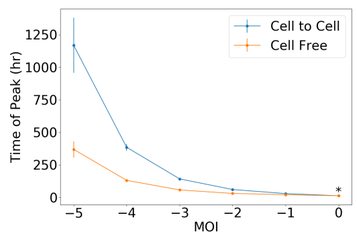
We use different features of the viral time course to assess how transmission mode changes the infection.

Peak Viral Titer



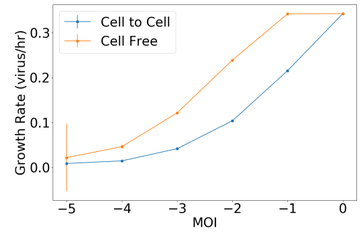
At low and high MOIs, both transmission modes lead to similar peak viral titers, but cell-free transmission has higher viral peaks at the middle MOIs.

Time of Viral Peak



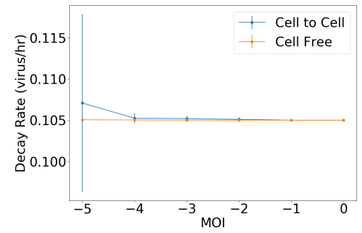
Time of peak differs at low MOIs.

Growth Rate



Cell to cell transmission has a lower growth rate particularly at low MOI.

Decay Rate



Cell free transmission has a slightly higher decay rate at low MOI.

Conclusions

- In general, the infection spreads quicker with cell-free transmission.
- For high MOI, there is little difference in infections transmitted by either mode.
- At lower MOI, there are distinct dif-ferences in several measures of infection.

Future Work

- Simulate infections with both modes of transmission.
- Examine the effect of antivirals.
- Incorporate cell regeneration.