Multiscale Multicellular Spatiotemporal Modeling of Viral Infection and Immune Response

A Modular, Extensible Agent-Based Framework

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Try the nanoHUB tool at https://nanohub.org/tools/cc3dcovid19

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About Me

• Postdoctoral Fellow
  • Biocomplexity Institute, Prof. James Glazier
  • Intelligent Systems Engineering
  • Lead developer: CompuCell3D
• Ph.D. (Mech. Eng.): Purdue University, August 2019
  • Engineering Design Research Lab, Prof. Andres Tovar
• Research
  • Theoretical/computational modeling in cellular/tissue dynamics and tissue engineering applications
  • Bone biomechanics and implant design
  • Biofabrication processes and bioreactor design
  • Immunology and viral infection
Multiscale Multicellular Modeling of Viral Infection and Immune Response

A modular framework for multiscale, multicellular, spatiotemporal modeling of acute primary viral infection and immune response in epithelial tissues and its application to drug therapy timing and effectiveness


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Premise: Primary Acute Local Infection and Innate Response in a Planar Milieu

- Infection in a small quasi-2D patch of susceptible tissue
- Assume primary infection
  - no pre-existing adaptive immune response
  - no specific antibodies, memory T-cells or targeted B cells
- Assume acute infection
  - consider a short time where the immune system either clears the virus, the virus spreads over the entire tissue patch, or something in between
Overview of Model Components

• Two cell classes
  • Epithelial cell: the susceptible cells
  • Immune cell: the infection fighters

• Three diffusive fields
  • (Extracellular) Viral Field: extracellular virus transport
  • Cytokine Field: local and global signaling
  • Oxidative Agent Field: epithelial cell killing by immune cells

• Lymph node
  • Compartmental model
  • Regulates local immune cell population
• **Viral Internalization**: how virus gets into a cell
  • Virus is taken from the environment and transferred into a cell
  • Binding to receptors determines rate of internalization vs. extracellular viral concentration

• **Viral Replication**: how virus replicates inside a cell
  • Four basic stages of replication: Unpacking, Genome Replication, Protein Synthesis, and Assembly and Packing
  • Exponential amplification phase: Genome Replication

• **Viral Release**: how virus is released into the environment
  • Virus is taken from the cell and transferred into the environment
  • Rate of release is proportional to internal amount of Assembled and Packaged genomic material

\[
\frac{dU}{dt} = \text{Uptake} - r_u U
\]
\[
\frac{dR}{dt} = r_u U + r_{\text{max}} R \frac{r_{\text{half}}}{R + r_{\text{half}}} - r_t R
\]
\[
\frac{dP}{dt} = r_t R - r_p P
\]
\[
\frac{dA}{dt} = r_p P - \text{Release}
\]
Drugs like Remdesivir inhibit RNA synthesis, the one exponential step in viral replication.

Issues:
- Effectiveness decreases rapidly as the time of first treatment increases.
- Optimal treatment: lowest effective dose.

Easy to model and simulate:
- Treatment corresponds to reducing replication rate in viral replication model.
- Treatment can be applied at various times after initial infection in simulation.

Example simulated therapy. $r_{max}$ is the replication rate of all cells in simulation time.

\[
\frac{dU}{dt} = Uptake - r_u U \\
\frac{dR}{dt} = r_u U + \frac{r_{max} R}{R + r_{half}} - r_t R \\
\frac{dP}{dt} = r_t R - r_p P \\
\frac{dA}{dt} = r_p P - \text{Release}
\]
Time vs Potency Tradeoffs for an RNA-Synthesis Blocker

Green: virus controlled and most cells left uninfected
Red: most cells infected, virus not controlled
In between: high stochasticity, uncertain outcome
Framework Deployment

• CompuCell3D: a widely used software environment for virtual tissue modeling
  • Open source
  • PDE solver suite, ODE solver (libRoadrunner)
  • Real-time GUI-based interactive simulations
  • Code editor supporting easy model specification
  • HPC deployment (e.g., Carbonate at IU)
• Modular model specification using XML and Python
Collaborative, Concurrent Model Development

- Simulation framework is designed with *interchangeable, shareable, and extensible* model modules (architecture like the Python programming language)
- Simulation specification: load a set of model modules
- Built-in support for seamlessly downloading, adding, using and uploading add-on model modules
- Architecture prevents collision during concurrent development
- Framework and library are maintained on GitHub: collaborative public development

```python
CompuCellSetup.register_steppable(stephable=NeighborRecoveryDataSteppable(frequency=1))
CompuCellSetup.run()
```
Group A recovery model: RecoverySimple
Dead cells resurrect with a fixed probability

Group B recovery model: RecoveryNeighbor
Extend recovery model by Group A with neighbor-dependent recovery probability

Main simulation script

Import model parameters defined in a different script
Copy the recovery model by Group A
Overwrite recovery criterion

Get CompuCell3D’s model specification features
Test for recovery at each step
Define a recovery criterion
Define what recovery means

Load from main framework
Load from add-on library
Building a Better Simulation Framework Together

- Continuous development of framework to better support community development
- Default framework is particular to SARS-CoV-2, but supports modeling other viruses

Integrated Compartmental HCV subcellular model
(Dahari, Ribeiro, Rice, Perelson, J Virol, 2007)

Revised viral replication model

\[
\frac{dR_p}{dt} = k_2 T_c + k_{Pout} R_p - k_1 R_{abo} R_p^{cyt} - k_{Pin} R_p^{cyt} - \mu_P R_p^{cyt} + n_{HCV} \tau_u U
\]

\[
\frac{dT_c}{dt} = k_1 R_{abo} R_p^{cyt} - k_2 T_c - \mu_T T_c
\]

\[
\frac{dP^{cyt}}{dt} = k_2 T_c - k_P P^{cyt}
\]

\[
\frac{dE^{cyt}}{dt} = k_P P^{cyt} - k_{Ein} E^{cyt} - \mu_E E^{cyt}
\]

\[
\frac{dR_p}{dt} = -k_3 R_p E + k_4 P_{ds}\]

\[
\frac{dR_{ds}}{dt} = k_4 m R_{ip} + k_5 R_{ds} E - \mu_{ds} R_{ds}
\]

\[
\frac{dE}{dt} = k_{Ein} E^{cyt} + k_m R_{ip} + k_4 P_{ds} - k_3 R_p E - k_5 R_{ds} E - \mu_E E
\]

\[
\frac{dR_{ip}}{dt} = k_3 R_p E - k_4 m R_{ip} - \mu_{ip} R_{ip}
\]

\[
\frac{dR_{ids}}{dt} = k_5 R_{ds} E - k_4 P_{ids} - \mu_{ids} R_{ids}
\]
Extending the Framework: Enhanced Immune Response Modeling

- Collaboration with Profs. Ericka Mochan (Carlow U.) and G. Bard Ermentrout (U. Pittsburgh)
- Approach: generate a spatial model analogue of their calibrated ODE model of influenza and immune (innate and adaptive) response

Inflammatary response

Nonlethal scenario

Lethal scenario

Immune response

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**Questions?**

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