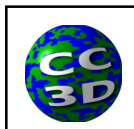
Understanding COVID-19 Infection, Immune Response, and Drug Therapy through Multiscale, Multicellular Modeling and Simulation

Please launch the nanoHUB tool:
https://nanohub.org/tools/cc3dcovid19

T.J. Sego, Ph.D.
Biocomplexity Institute
Indiana University Department of Intelligent Systems Engineering
tjsego@iu.edu

Support: **NIH R01 GM122424, U01 GM111243, U24 EB028887, NSF 1720625**



compucell3d.org

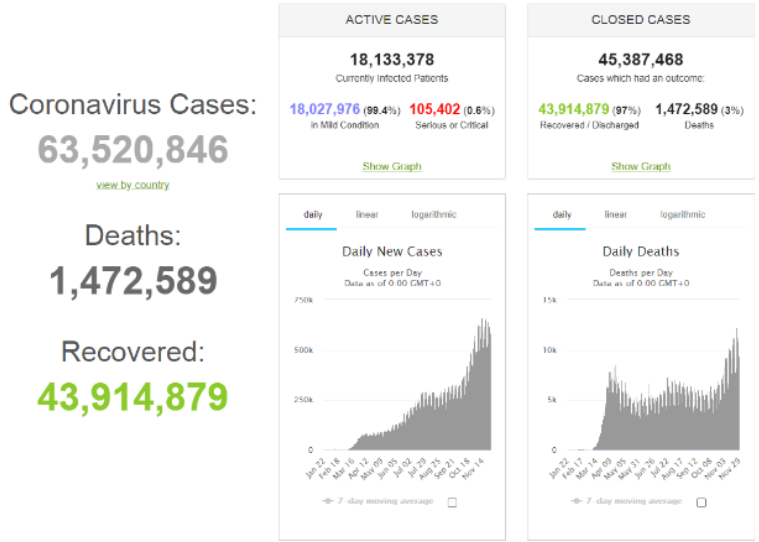
Itinerary

- Background: About SARS-CoV-2, COVID-19 and computational modeling
- Current simulation framework: Overview of the model and key results
- Basic framework manipulation: experiments with model parameters
- Q&A

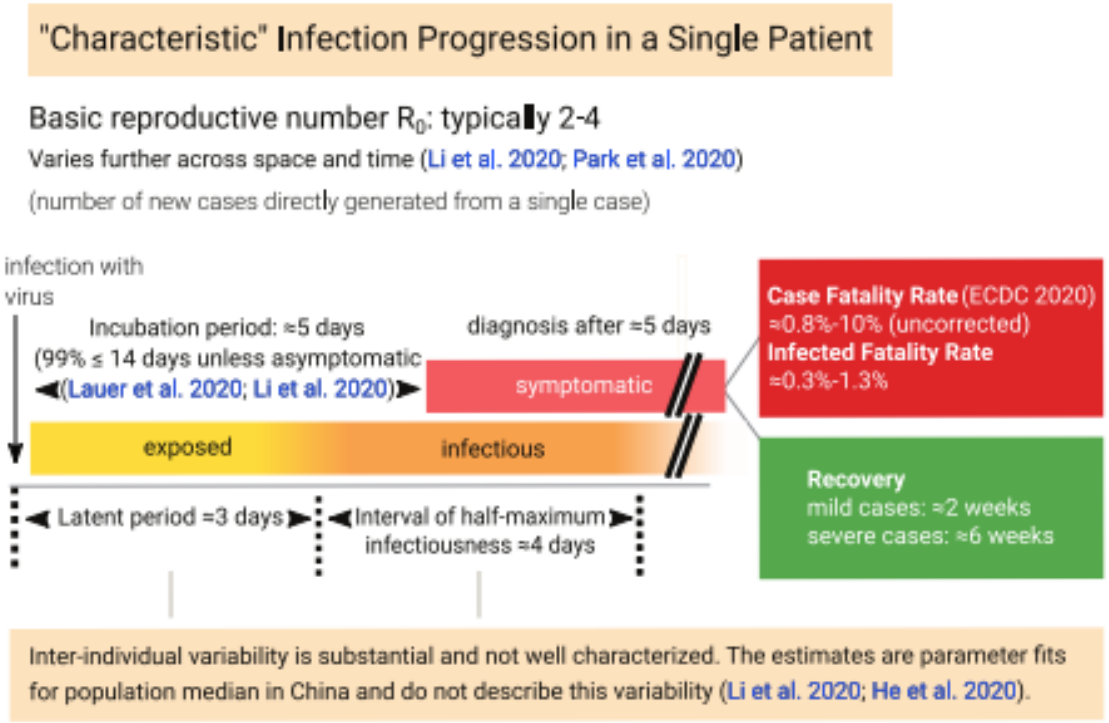
- Please submit questions/comments/concerns via Zoom chat

Sobering Times

- Infectious before symptomatic
- Outcomes are highly variable by patient and location
- Causes of death include refractory ARDS, septic shock, sudden cardiac arrest, hemorrhagic shock, acute myocardial infarction



https://www.worldometers.info/coronavirus/
Accessed 11/30/2020



Bar-On et al., eLife, 2020.

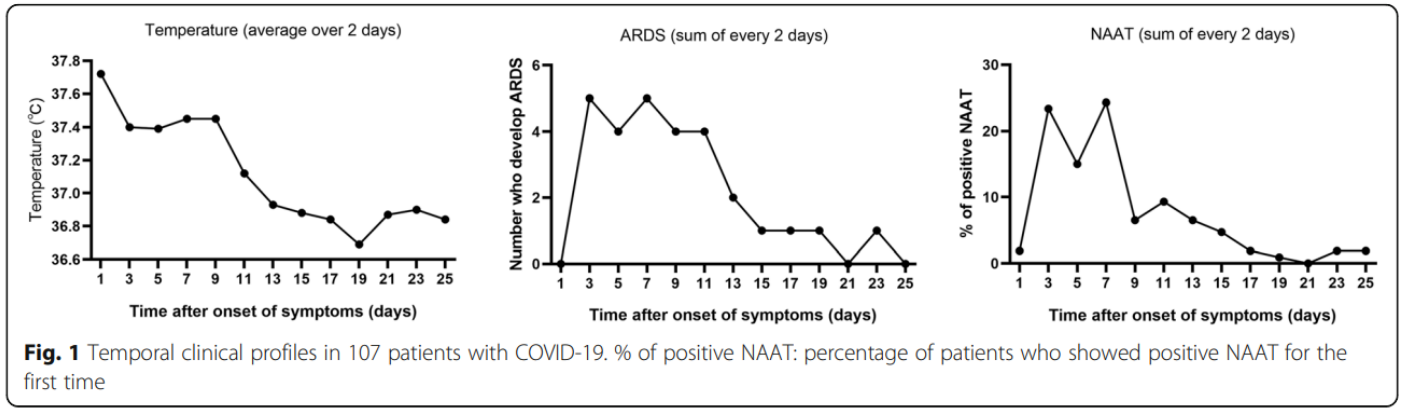


Fig. 1 Temporal clinical profiles in 107 patients with COVID-19. % of positive NAAT: percentage of patients who showed positive NAAT for the first time

Wang et al., Critical Care, 2020.

Motivating Questions of COVID-19 Modeling

So many questions:

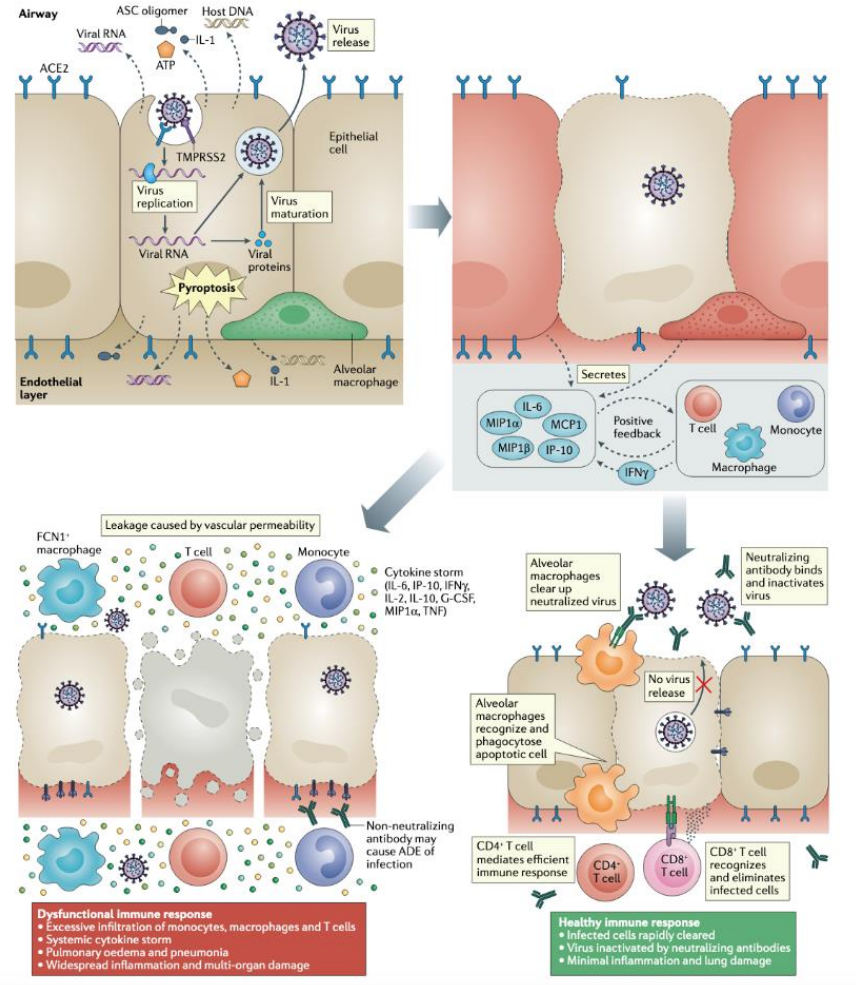
- Why do some people get sick, others not?
- Why is COVID-19 different from the flu?
- Why is there a delayed adverse response (recovery/relapse) in some individuals?
- What causes pneumonia, cytokine storms or other adverse effects?
- Why are there such strong age-related effects?
- What causes the differences in response to infection by the same virus in different tissues?

- Could we triage patients better?
- How could use of antiviral therapies be optimized?
- How could use of anti-inflammatory therapies be optimized?

Can we predict systems-level effects from molecular-level perturbations?

Biological Components of SARS-CoV-2 Infection

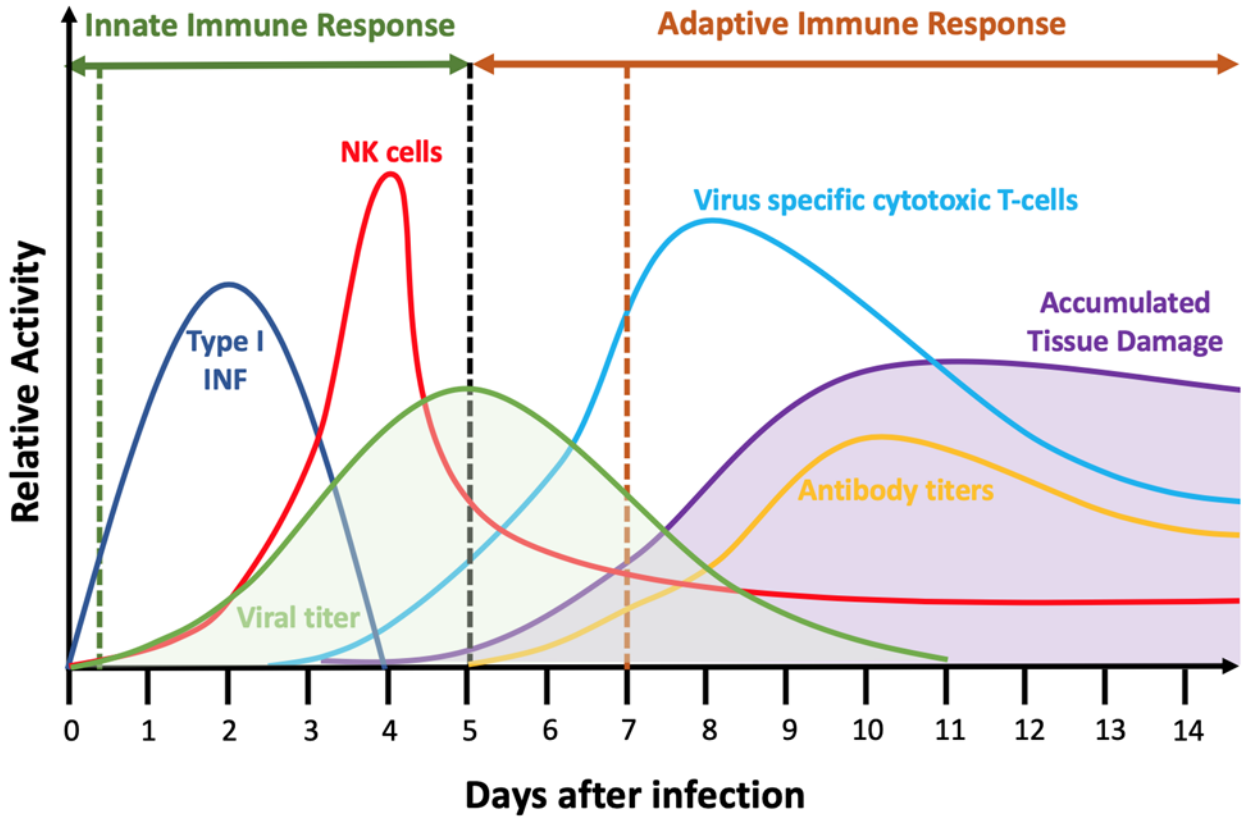
- Epithelial target tissue (nasal, throat, bronchial, alveolar)
  - Extracellular environment
  - Virus entry, replication, spread and removal
  - Immune cells (lots of them) and their recruitment and actions
  - Immune signals (lots of them)
  - Tissue damage and recovery
- Lymph nodes/systemic immune system
  - Immune signaling
  - Immune-cell proliferation
- Whole body transport (blood, lymph, air)
- Other non-target or secondary target organs (blood, heart, kidneys,…)
- Innate and adaptive immune responses



Tay et. al., Nat Rev Immunol, 2020

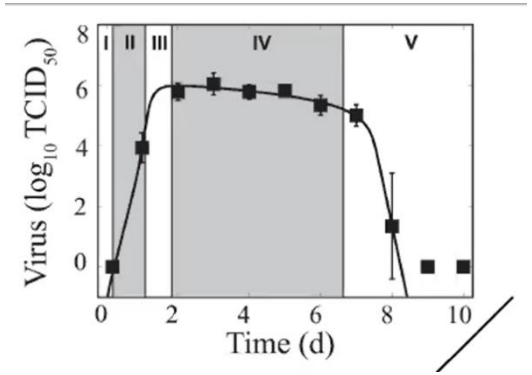
Immune Response Components

- Immune cell scavenging/phagocytosis of virus (peaks at 1 day, reduced after 2 days)
- IFN response, viral resistance and other non-cell-mediated responses (starts early, most important early)
- Systemic Cytokine signaling (starts around day 2 and goes on and is relayed and amplified by immune cells)
- Recruitment of NK cells (starts pretty fast and peaks as shown on diagram)
- Dendritic cells → Lymph node (day 4-6)
- Return of CD8+ and related immune cells to the tissue (days 7-14)
- B cells and antibodies (day 10 onward)
- Complications from infection like pneumonia (typically start around day 7 with beginning of adaptive immune response and positive feedback on cytokines)

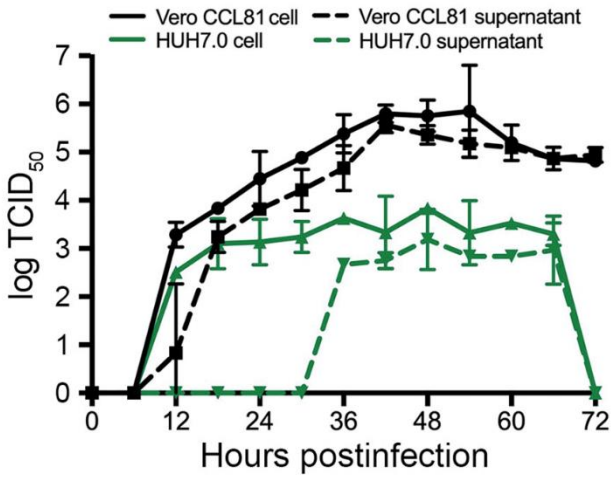


Viral Replication and Concentrations

- Eclipse Phase (6 h – slightly longer) before any cells start releasing virus
- Rapid exponential growth to maximum viral concentration (over 2 days for influenza)
- Saturation and mild decline (days 2-7 days for influenza)
- Rapid Viral Clearance (at 7-9 days for influenza)



Influenza in mice.
Smith et at. (2018) *Curr Opin Sys Biol*



SARS-CoV-2 in cultured kidney and liver cells.
https://wwwnc.cdc.gov/eid/article/26/6/20-0516_article

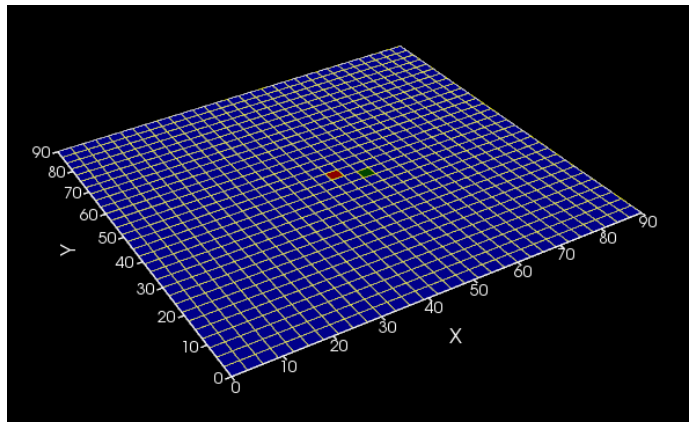
Multiscale Multicellular Modeling of Viral Infection and Immune Response

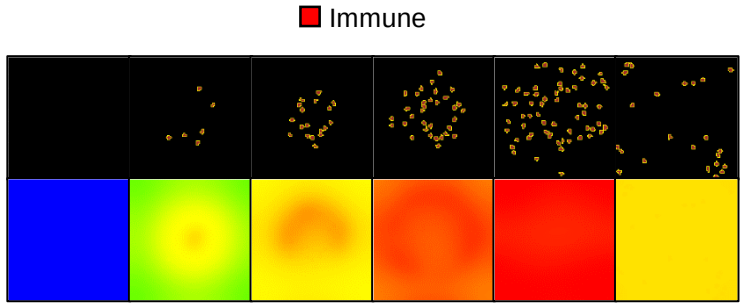
A modular framework for multiscale, multicellular, spatiotemporal modeling of acute primary viral infection and immune response in epithelial tissues and its application to drug therapy timing and effectiveness

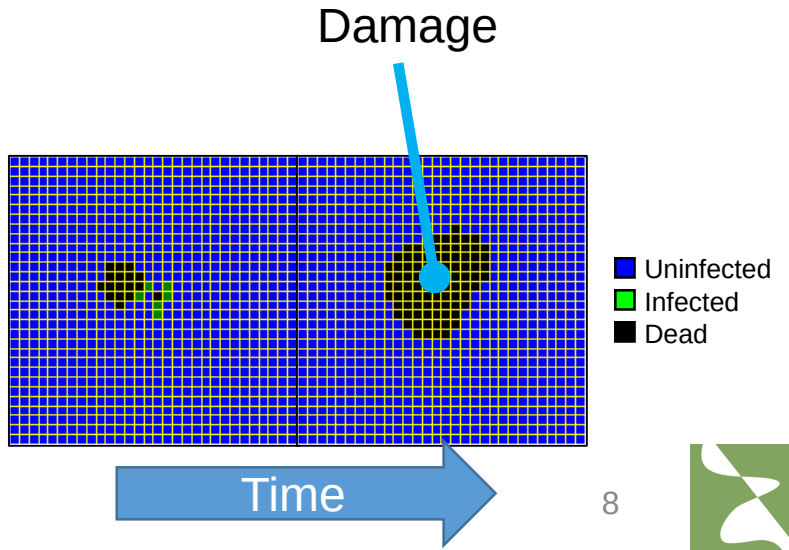
T.J. Sego, Josua O. Aponte-Serrano, Juliano Ferrari Gianlupi, Samuel R. Heaps, Kira Breithaupt, Lutz Brusch, Jessica Crawshaw, James M. Osborne, Ellen M. Quardokus, Richard K. Plemper, James A. Glazier

doi: https://doi.org/10.1101/2020.04.27.064139

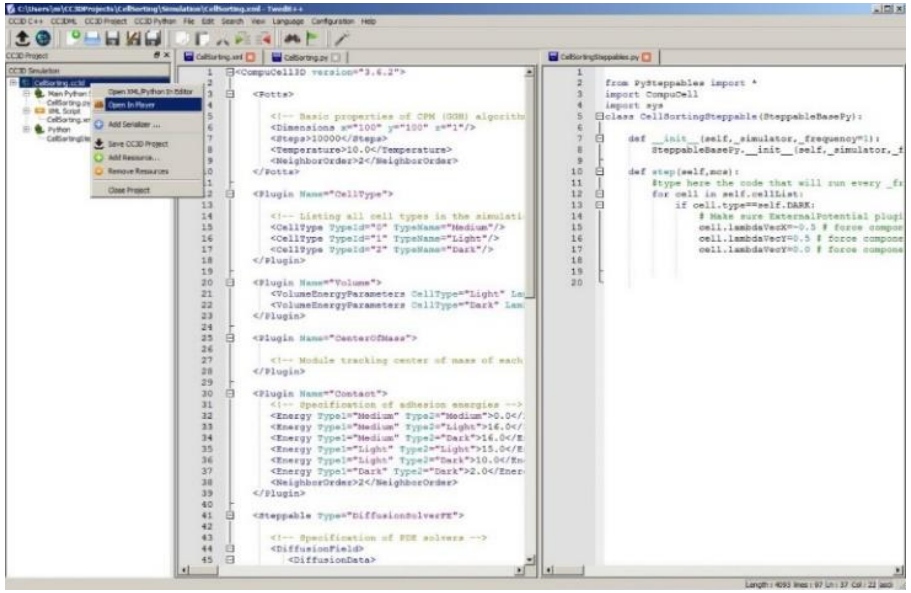
Accepted, PLoS Comp. Bio.





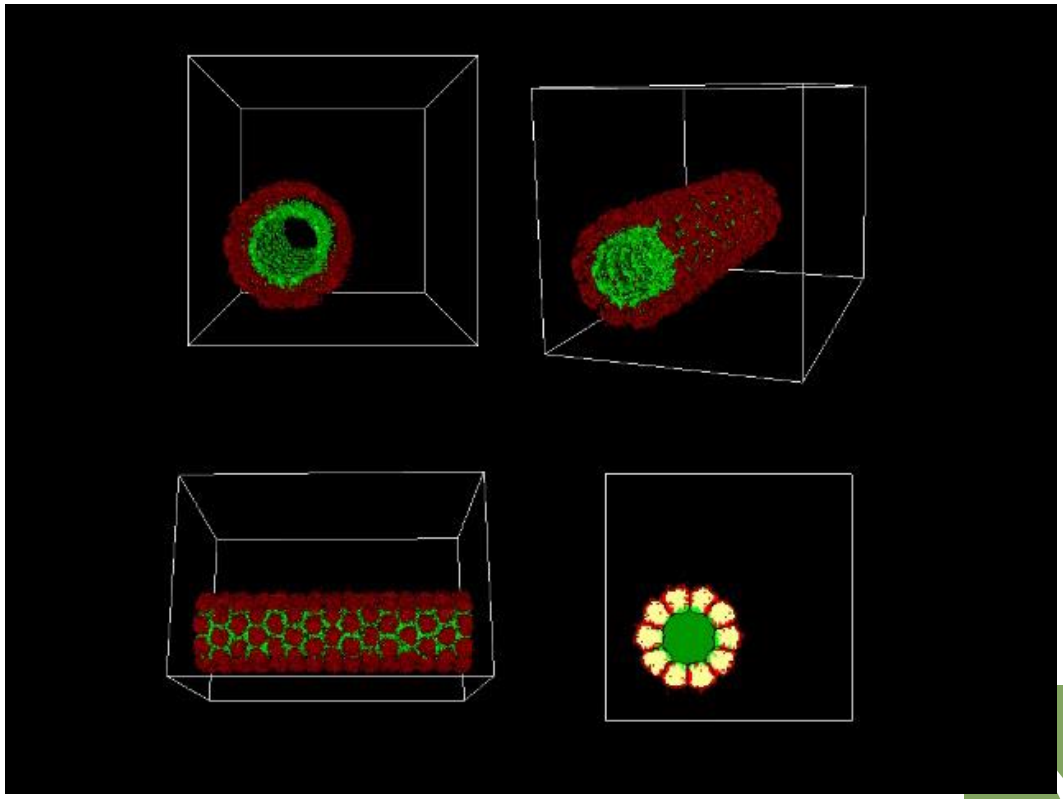


CompuCell3D Simulation Environment



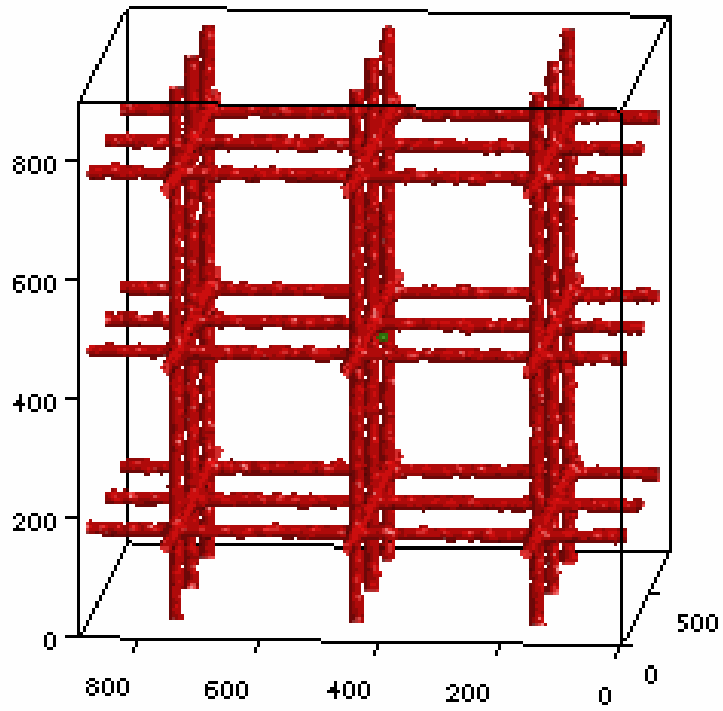
CompuCell3D: open-source, cross-platform software environment for virtual tissue modeling to make model specification and execution simple

- Framework is open source, simulations can be proprietary
- We provide training in these methods
- We aim to allow clinical and industrial researchers to develop models themselves without requiring excessive computational expertise
- See www.compucell3d.org



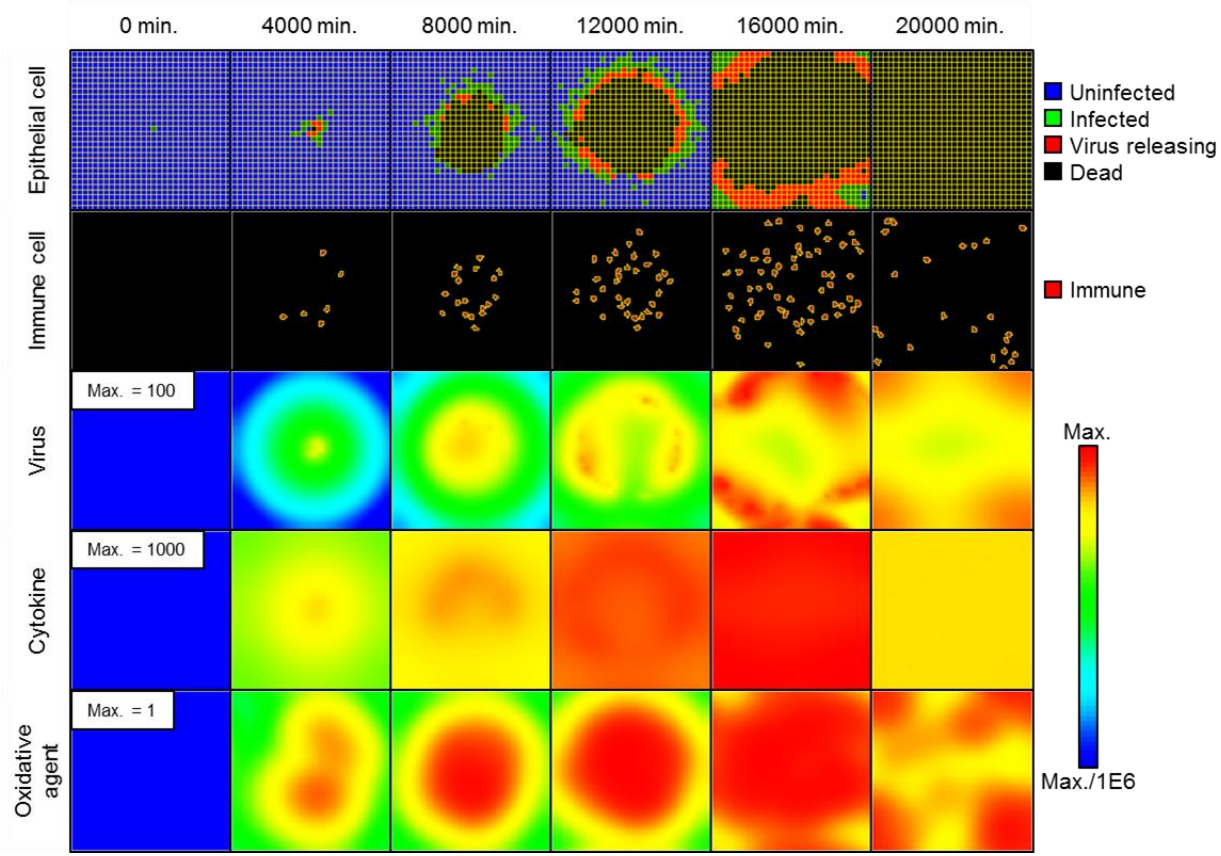
Select CompuCell3D Capabilities

- Computational performance + Rapid, intuitive, shareable model specification
  - Model specification: Python and XML
  - Computational backend: C++
  - Twedit++: model editor with built-in support tools for CC3D model development
- In-house PDE solver suite
  - String specification of field interactions
  - Uptake and release by cell
  - Diffusivity and decay by cell phenotype
  - Built-in stability and automatic time-stepping
- Concurrent ODE model simulation
  - Backed by libRoadRunner (fastest in class!)
  - Model specification with Antimony, CellML and SBML (BioNetGen coming soon!)
  - Supports attaching ODE models to individual cells (*e.g.*, intracellular processes) and simulation domains (*e.g.*, systemic processes)
- Advanced/integrated applications
  - Cluster execution
  - Built-in automated parameter sweeps
  - CC3D Python API (*e.g.*, model calibration using SciPy optimization or PyTorch)
- *Lots* of model plugins!
  - Cell volume, surface area, shape constraints
  - Phenotype- and molecule-specific adhesion (*e.g.*, modeling N-cadherin)
  - Compartmental cells (*e.g.*, modeling organelles)
  - Complete list: www.compucell3d.org



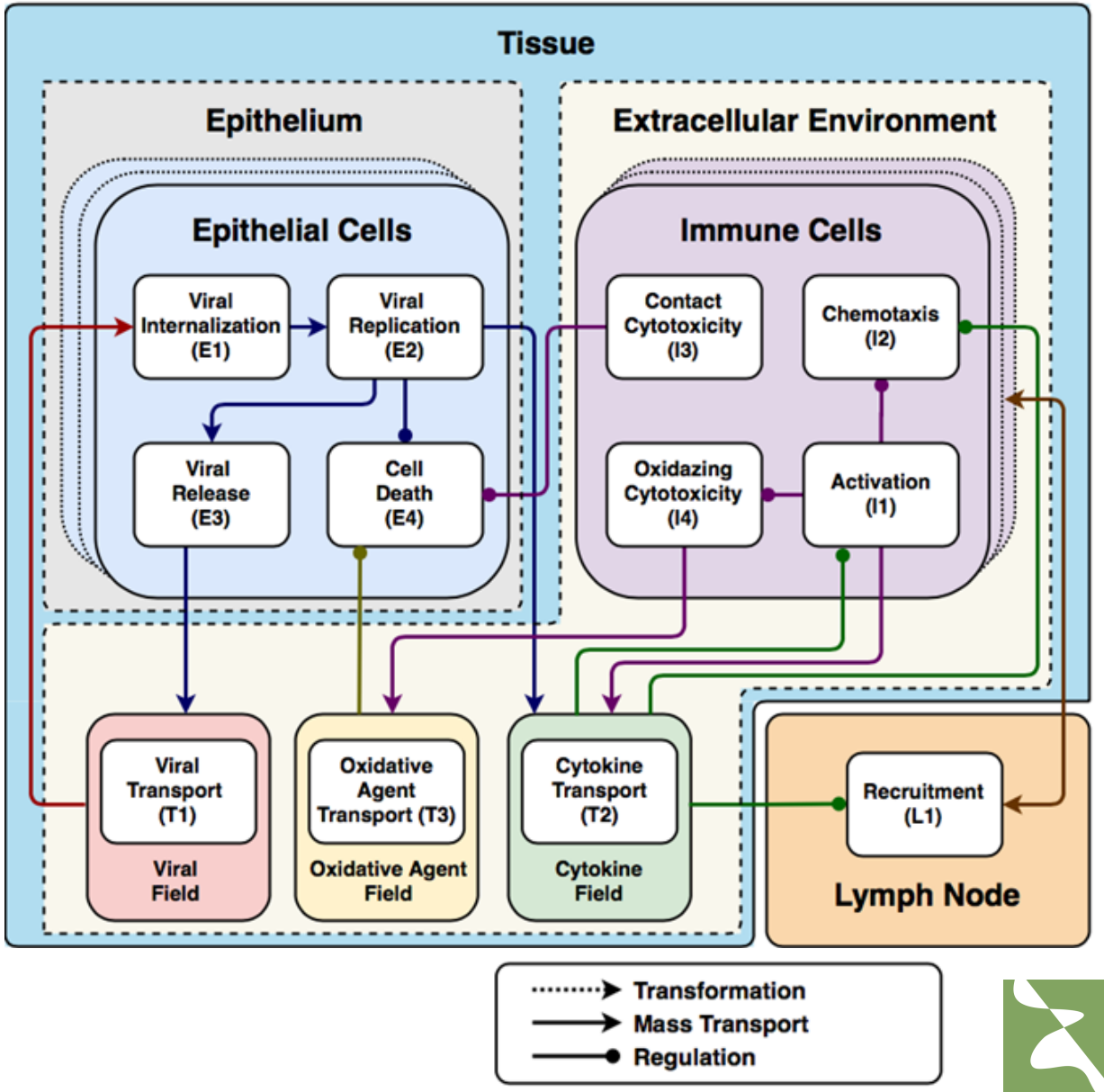
Premise: Primary Acute Local Infection and Innate Response in a Planar Milieu

- 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



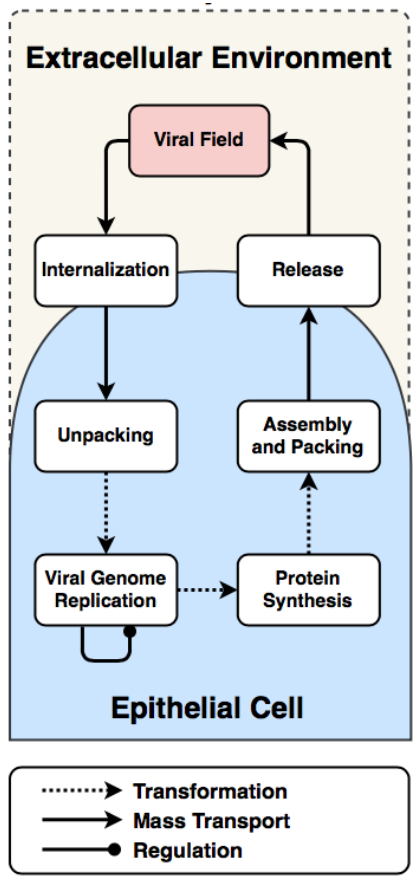
Overview of Model Components

- 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



Stages of Basic Viral Replication

- **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



$$\frac{dU}{dt} = Uptake - r_u U$$

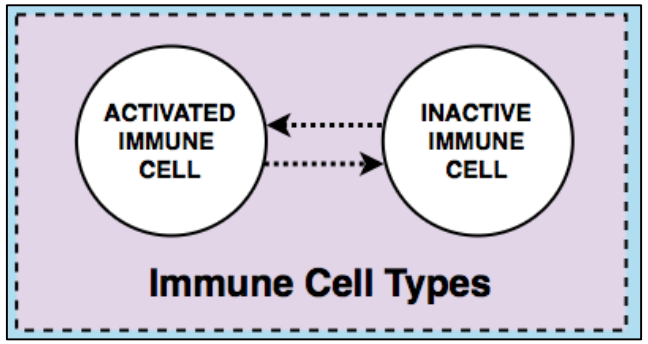
$$\frac{dR}{dt} = r_u U + r_{max} R \frac{r_{half}}{R + r_{half}} - r_t R$$

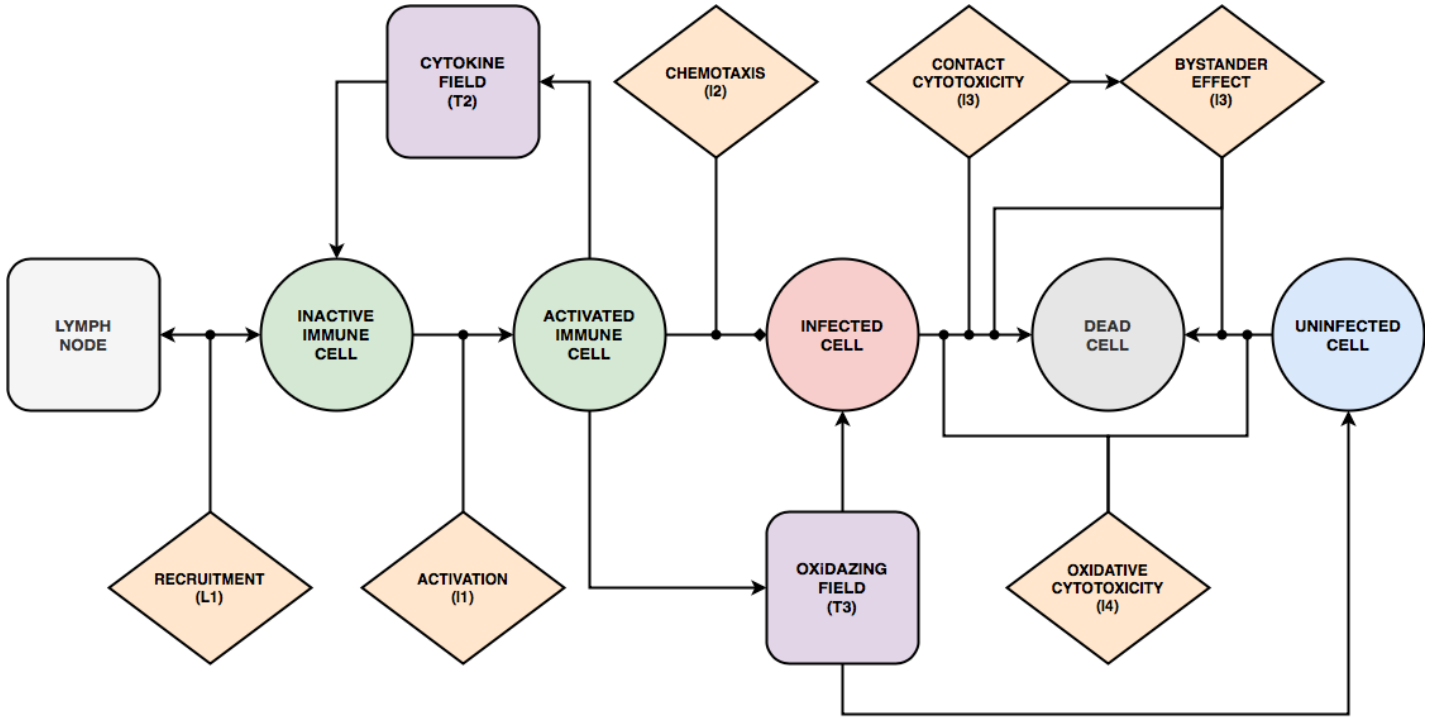
$$\frac{dP}{dt} = r_t R - r_p P$$

$$\frac{dA}{dt} = r_p P - Release$$

Immune cell models

- One generic immune cell type realized as 2 simulation cell types

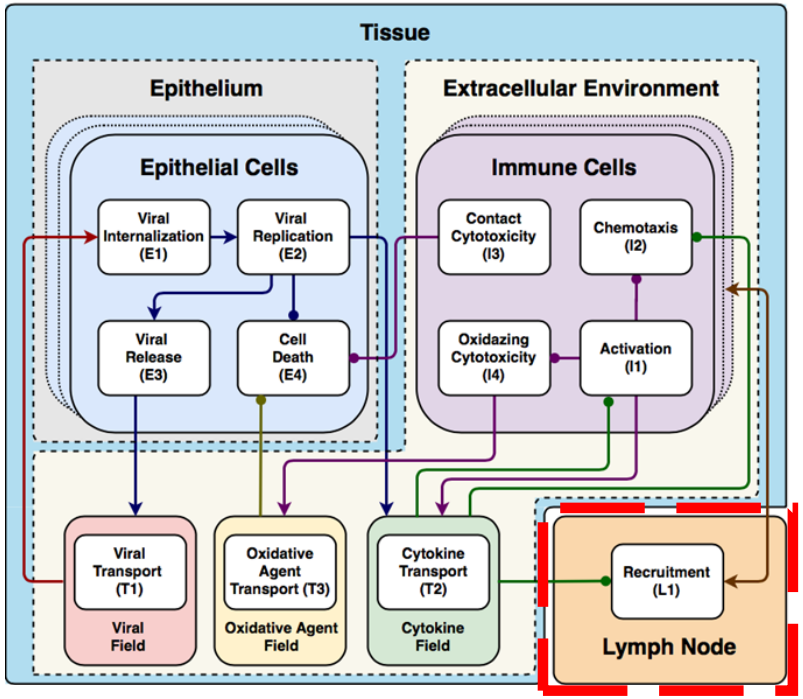




Type	Random Motility	Chemotax to Cytokine	Contact Kill	Release Cytokines	Activate in Response to Cytokine	Secrete Oxidative Chemical	Inactivate with time
Inactive	X		X		X		
Activated	X	X	X	X		X	X

Immune Recruitment Modeling

- A single variable S represents net inflammatory state (pro-inflammatory or anti-inflammatory) and controls immune cell recruitment
  - $S > 0$ add immune cells to tissue
  - $S < 0$ remove immune cells from tissue
- Signaling from the spatial domain due to infection affects S
  - S increases by the cytokine level in the tissue with a delay
  - S decreases when immune cells added



Volume integral of cytokine field decay

Total number of immune cells

$$\frac{dS}{dt} = \beta_{add} - \beta_{sub} N_{immune} + \frac{\alpha_{sig}}{\beta_{delay}} \delta - \beta_{decay} S$$

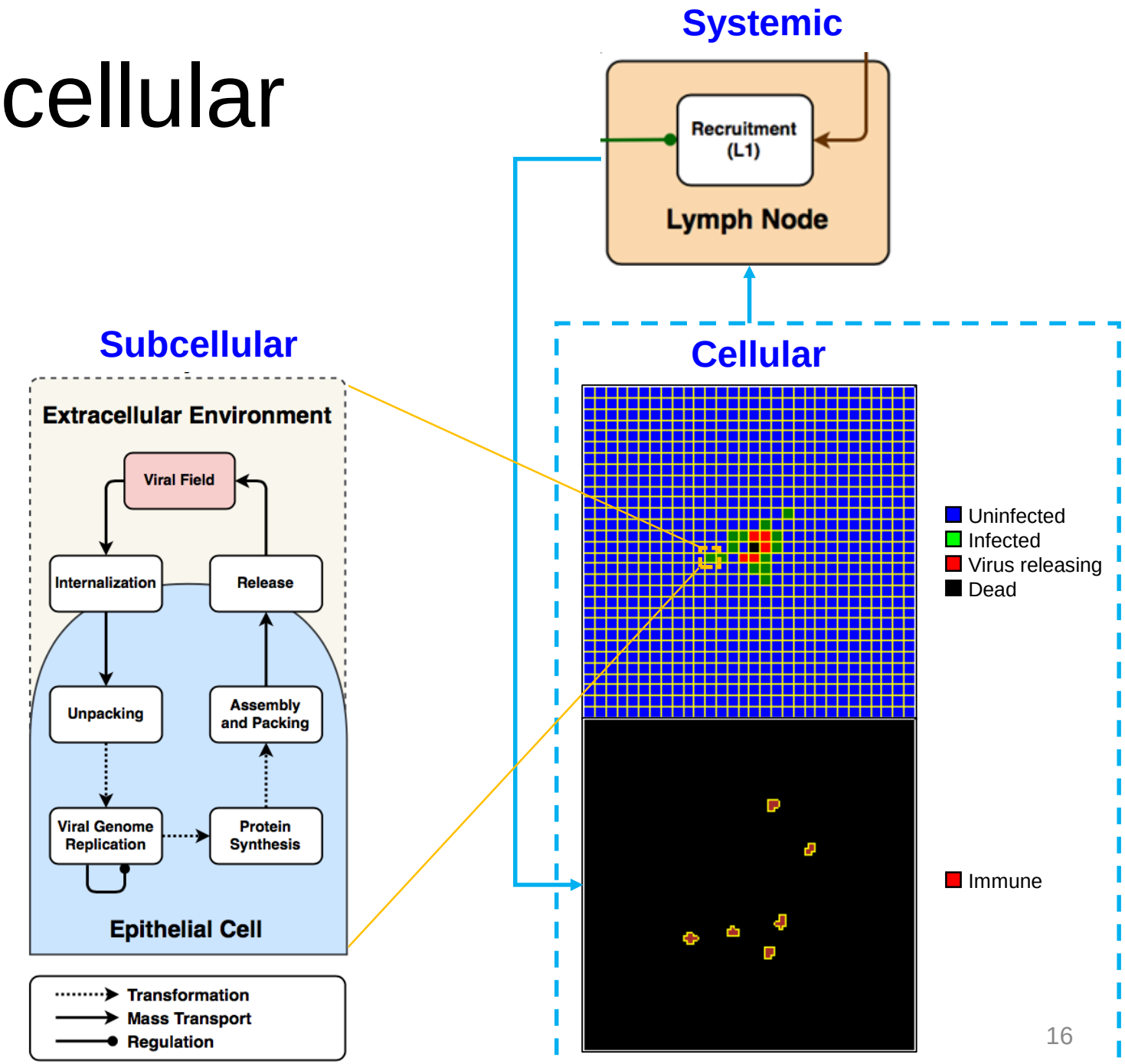
$$\Pr(\text{add immune cell}) = \text{erf}(\alpha_{immune} S), \quad S > 0$$

$$\Pr(\text{remove immune cell}) = \text{erf}(-\alpha_{immune} S), \quad S < 0$$

Systemic to Subcellular Interactions

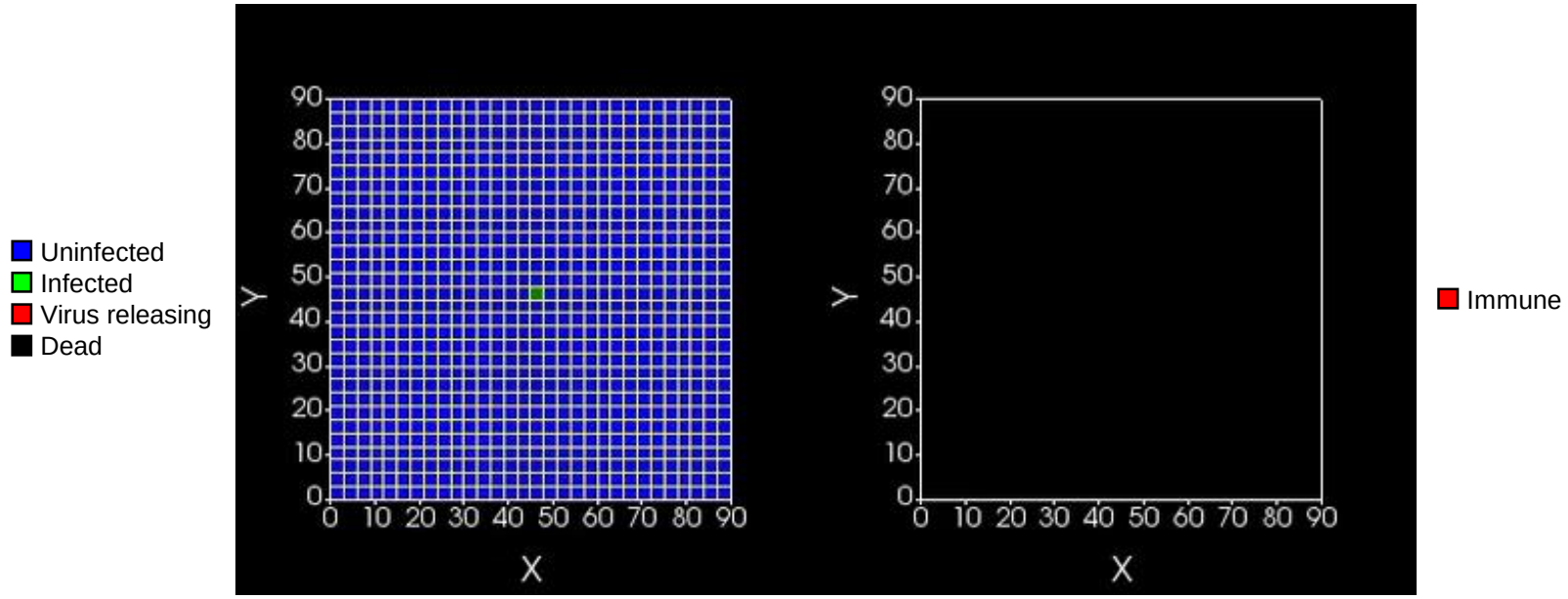
Basic mechanisms of infection and immune response range from subcellular to systemic

- Viral replication can occur in *each* cell
- Recruitment signaling can occur by *all* cells



Epithelial

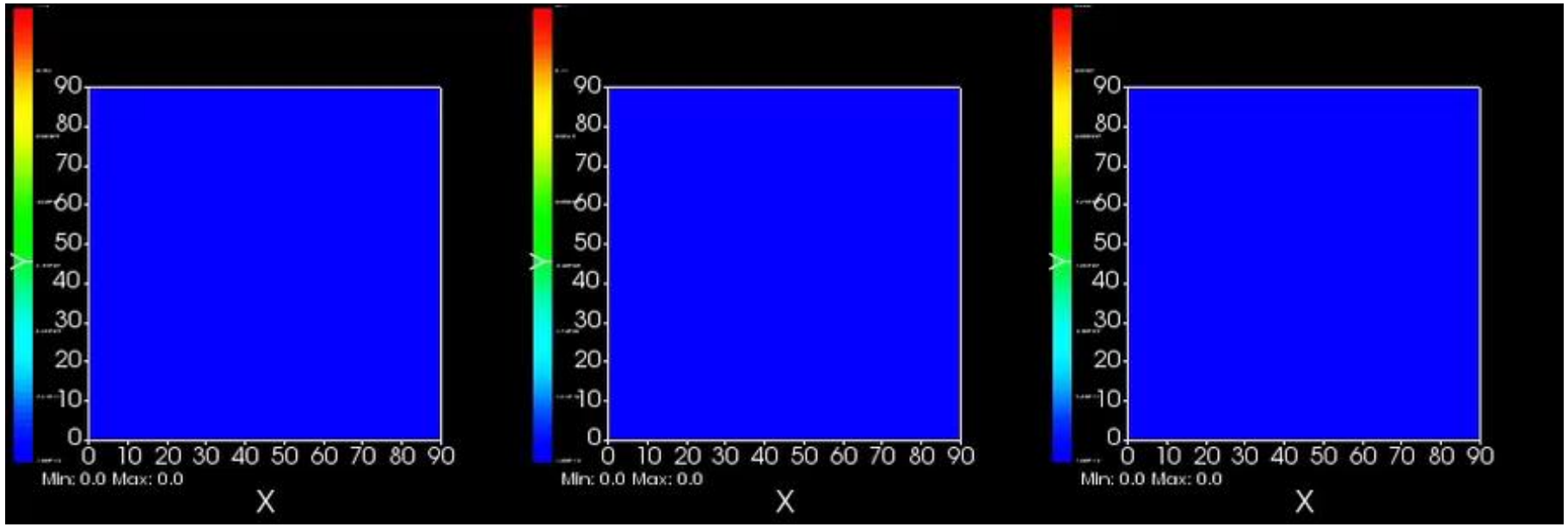
Immune



Virus

Cytokine

Oxidative Agent



Simulate Therapy with RNA-Synthesis Blocker

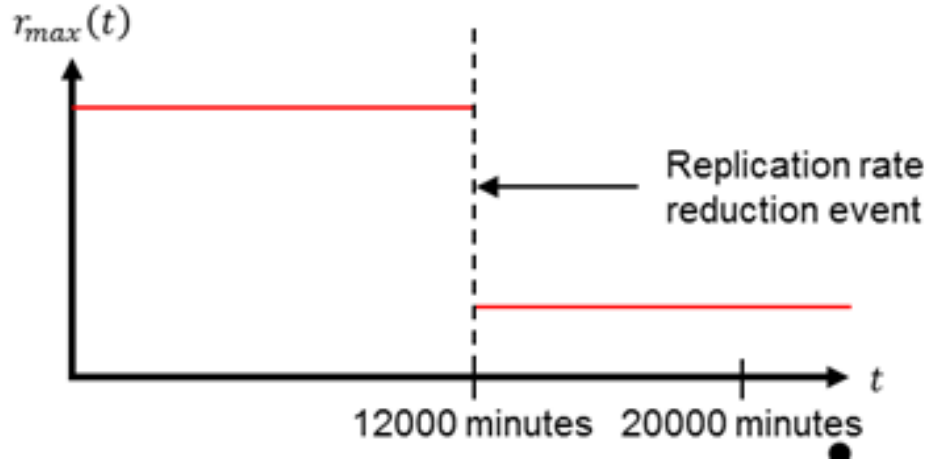
Drugs like Remdesivir inhibit RNA synthesis, the one exponential step in viral replication

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.

$$\frac{dU}{dt} = Uptake - r_u U$$

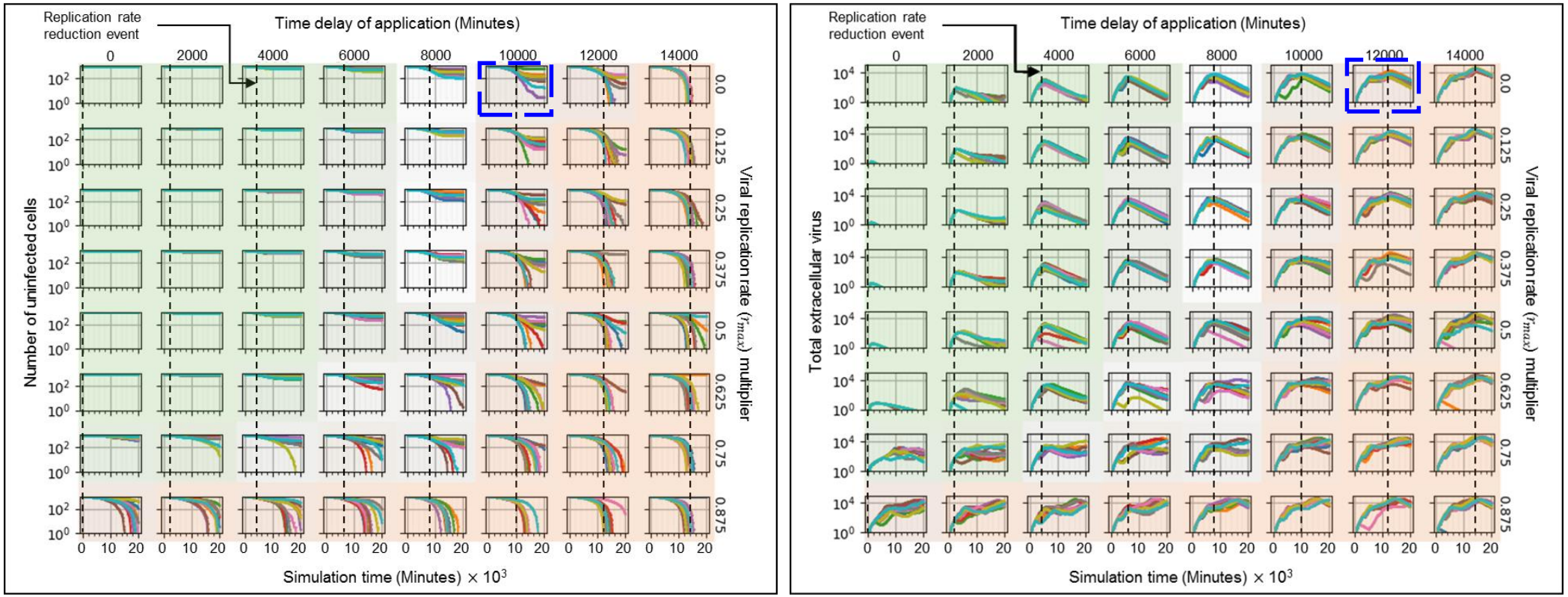
$$\frac{dR}{dt} = r_u U + r_{max} R \frac{r_{half}}{R + r_{half}} - r_t R$$

$$\frac{dP}{dt} = r_t R - r_p P$$

$$\frac{dA}{dt} = r_p P - Release$$

Time vs Potency Tradeoffs for an RNA-Synthesis Blocker

Later Treatment



Higher Potency

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

Viral Infection Model on nanoHUB

- https://nanohub.org/tools/cc3dcovid19

compucell3d.org

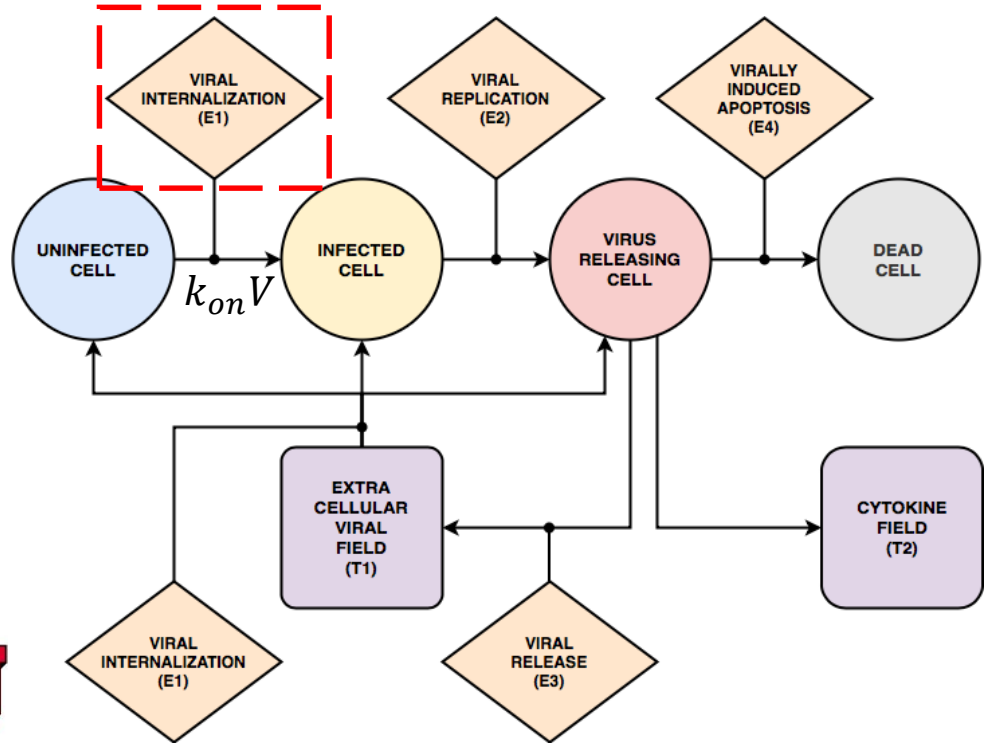

Watch/Star/Fork this project on GitHub: https://github.com/covid-tissue-models/covid-tissue-response-models

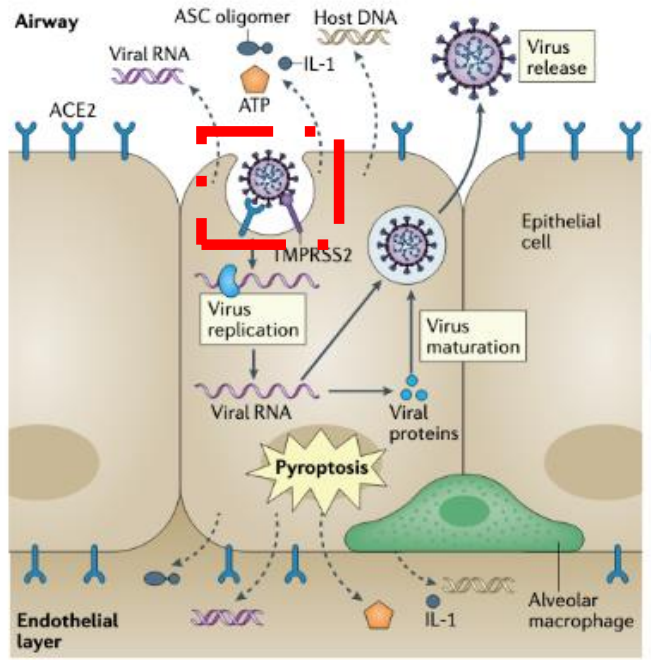
Rate of Infection

- Critical parameter: virus-receptor association affinity coefficient k_{on}
- Increasing k_{on} increases the rate of internalization

$$\Pr(Uptake(\sigma) > 0) = \frac{\Delta t}{\alpha_{upt}} \frac{\left(c_{vir}(\sigma)\right)^{h_{upt}}}{\left(c_{vir}(\sigma)\right)^{h_{upt}} + {V_{upt}}^{h_{upt}}}$$

$$V_{upt} = \frac{R_o k_{off}}{2k_{on} v(\sigma) SR(\sigma)}$$





Tay et. al., Nat Rev Immunol, 2020

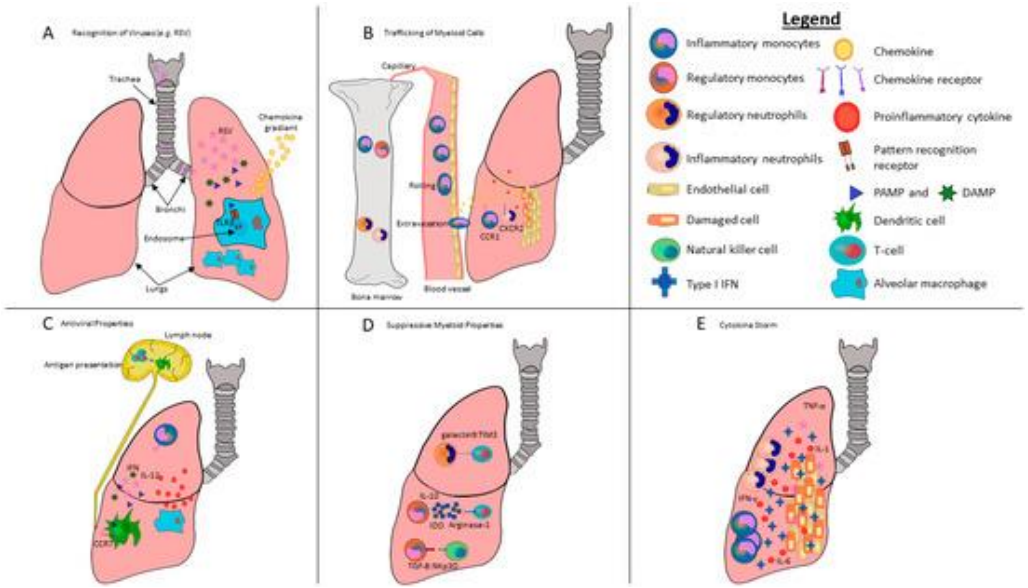
Recruitment Delay

- Critical parameter: immune recruitment delay coefficient β_{delay}
- Increasing β_{delay} increases the delay of immune cell recruitment by cytokine

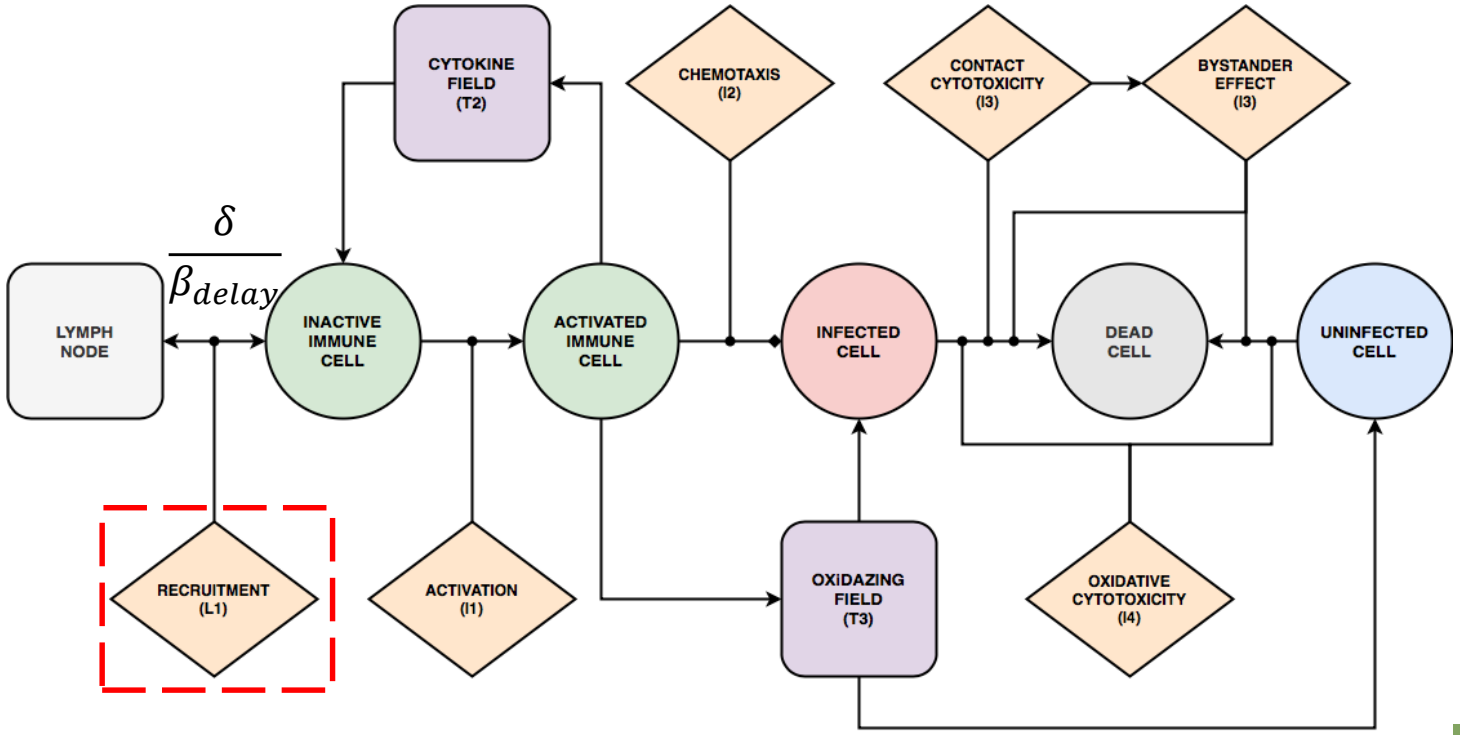
$$\frac{dS}{dt} = \beta_{add} - \beta_{sub} N_{immune} + \frac{\alpha_{sig}}{\beta_{delay}} \delta - \beta_{decay} S$$

$$\Pr(add\ immune\ cell) = \mathrm{erf}(\alpha_{immune} S), \quad S > 0$$

$$\Pr(remove\ immune\ cell) = \mathrm{erf}(-\alpha_{immune} S), \quad S < 0$$



Stegelmeier, Viruses, 2019

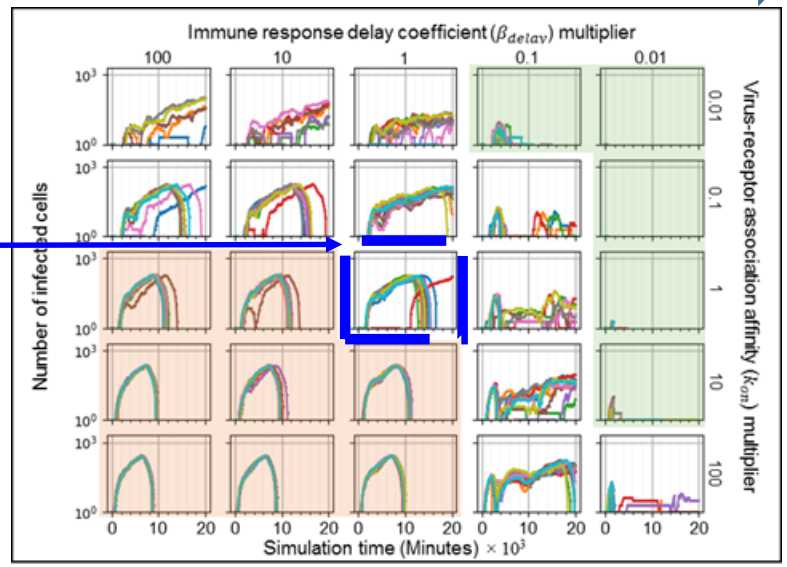


Parameter Sensitivity for Immune Response and Viral Internalization

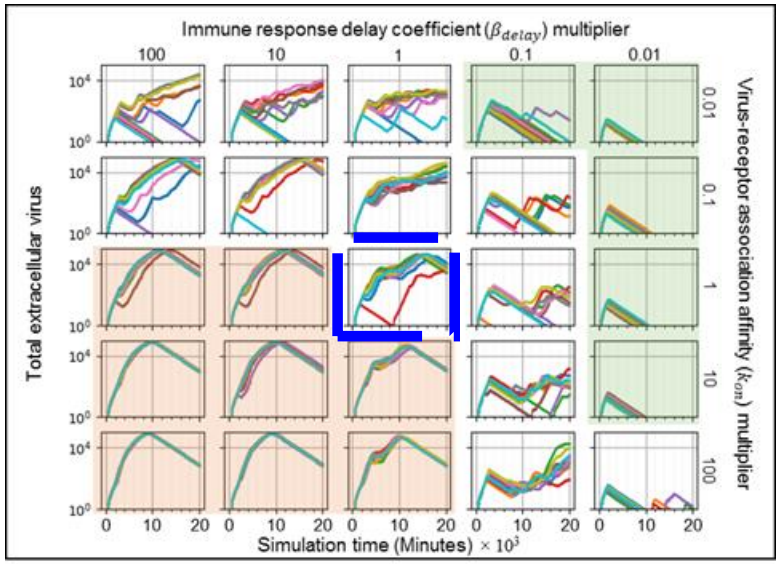
- Parameter variations: immune response delay and viral internalization rate
- Regions of certain outcomes, with variability in between
  - Green: at end of simulation, no infected or virus releasing cells, and some uninfected cells
  - Red: at end of simulation, no uninfected cells

Stronger Immune Response

Baseline parameter set



Number of Infected Cells



Extracellular Virus

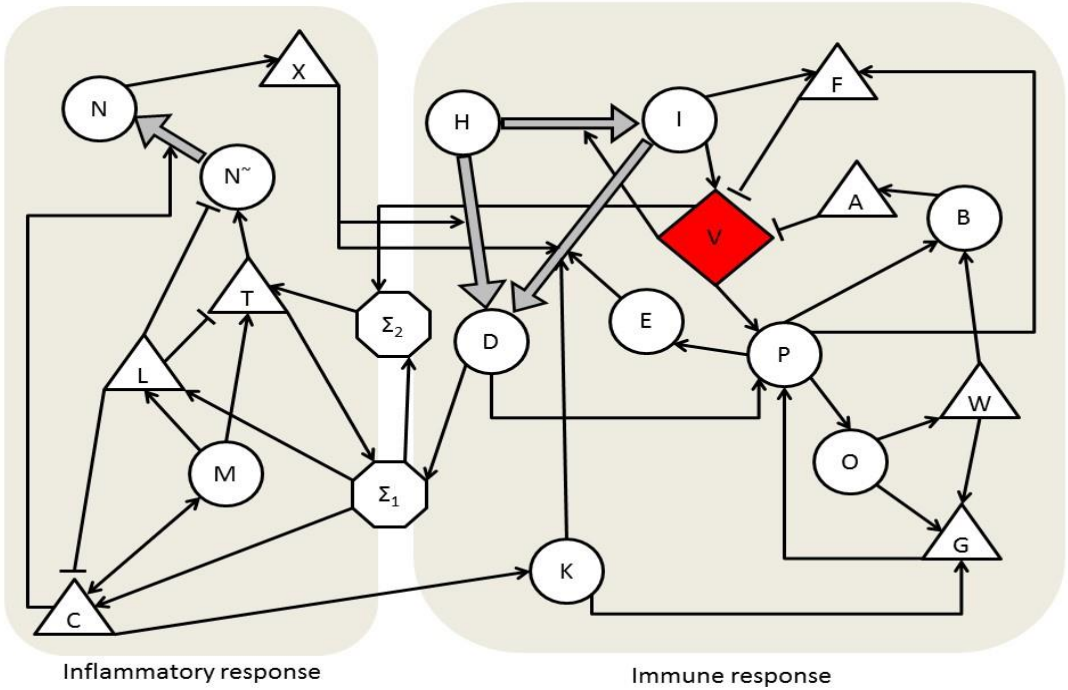
Faster Viral Internalization

Influenza Infection Modeling in Space!

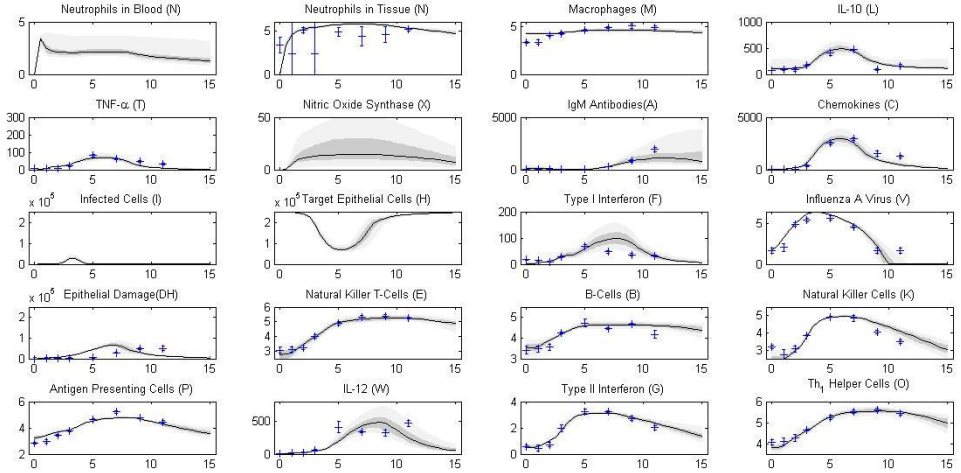
- The immune response is *very* complicated
  - Innate and adaptive immune response
  - Lots of involved phenotypes (*e.g.*, macrophages, T cells, B cells, neutrophils) and chemical species (*e.g.*, interleukins, IFNs, antibodies)
  - Lots of local events interacting over long distances via cellular/signal transport (*e.g.*, local infection, lymph nodes, thymus)
- Ericka Mochan (Carlow U.), G. Bard Ermentrout and colleagues developed a host-pathogen ODE model of influenza with innate and adaptive immune response and calibrated it to mouse model data of lethal and non-lethal infection
- This work: spatialize Ericka and Bard's model

Influenza Model Overview

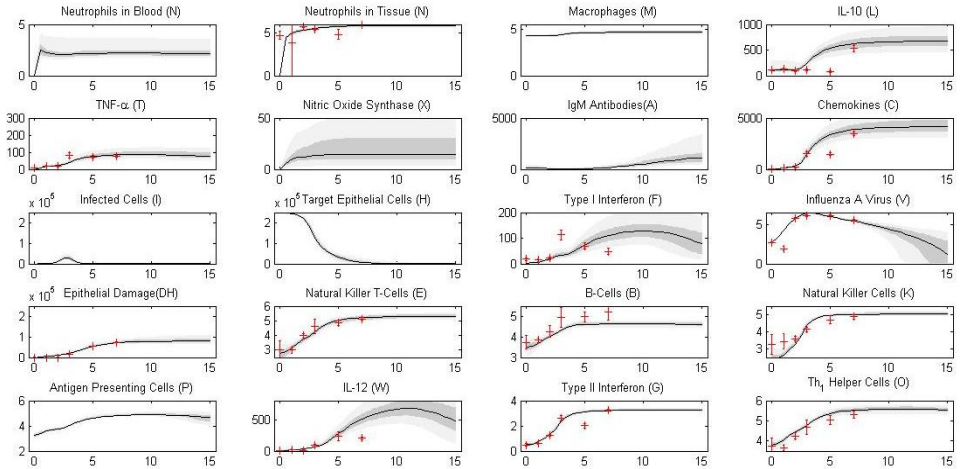
Label	Variable
TNF	T
IL-10	L
Chemokines	C
Macrophages	M
Blood neutrophils	Ñ
Tissue neutrophils	N
Reactive oxygen species	X
Target epithelial cells	H
Infected epithelial cells	I
Damaged epithelial cells	D_H
Virus	V
Type I interferon	F
Type II interferon	G
Natural killer cells	K
Antigen presenting cells	P
B cells	B
CD8+T cells	E
IL-12	W
CD4+T cells	O
Antibodies	A



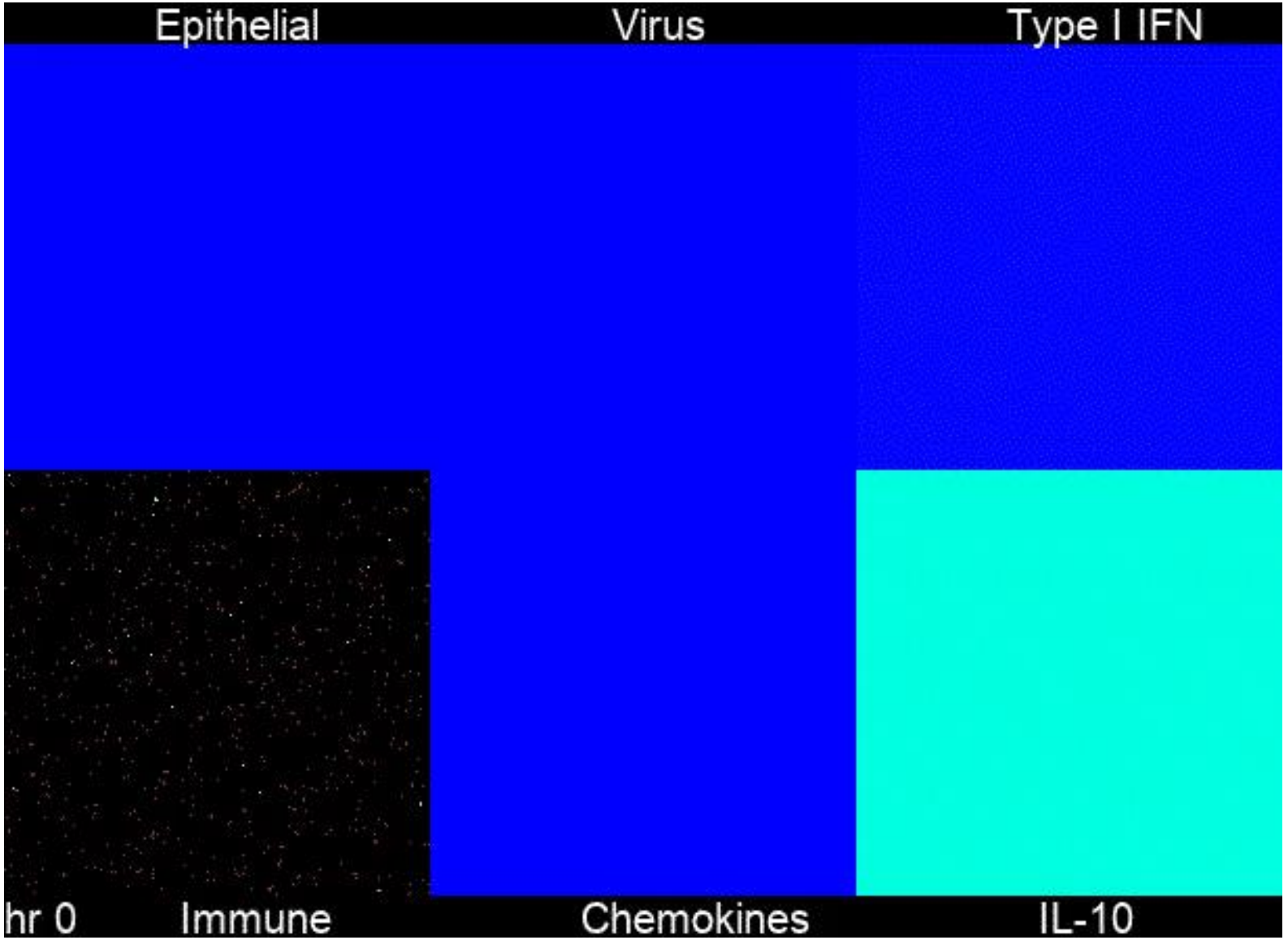
Nonlethal scenario



Lethal scenario

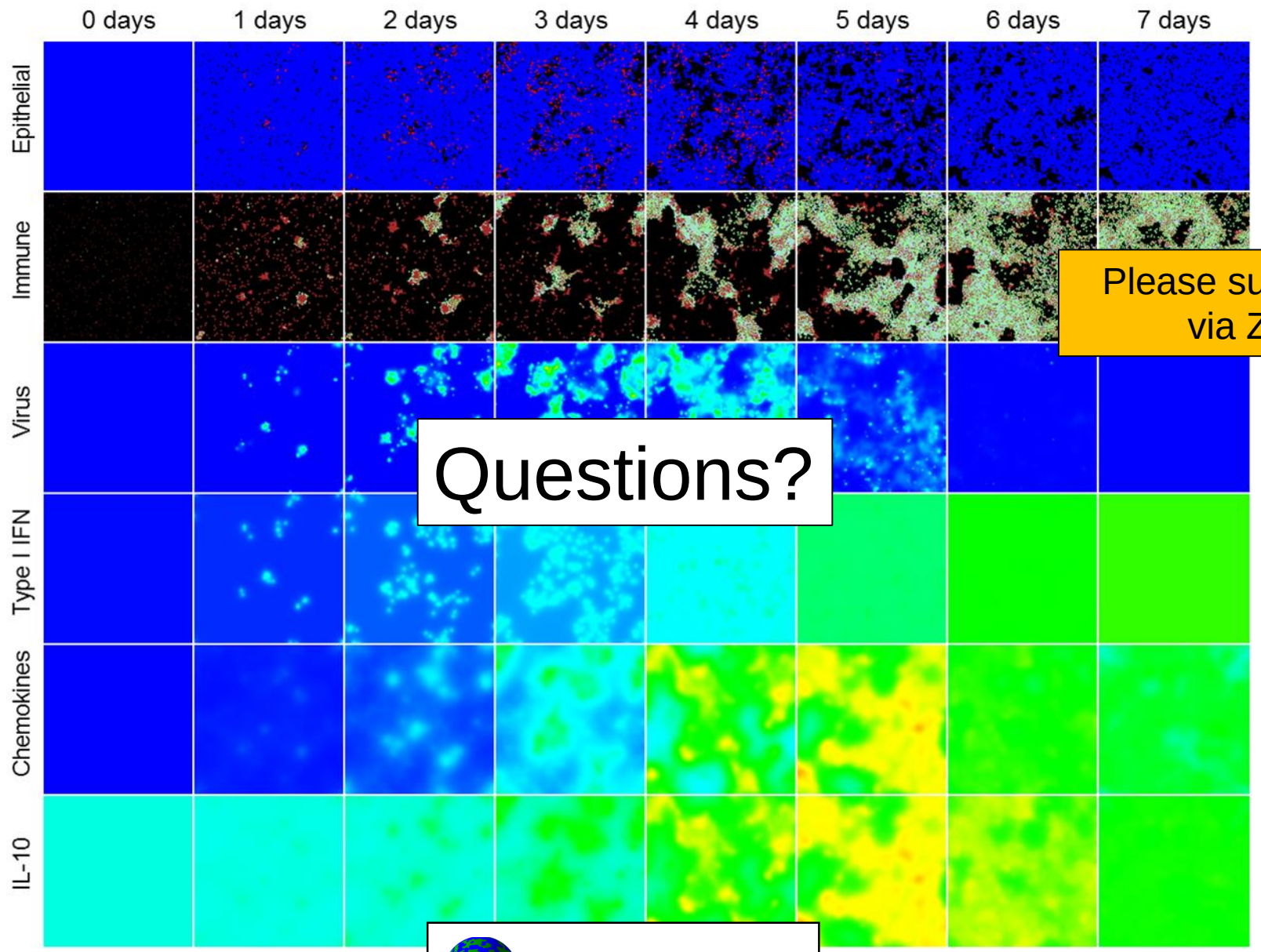


Price, Mochan et. al, J Theor. Biol., 2015


Epithelial
Virus
Type I IFN
hr 0
Immune
Chemokines
IL-10

Next week’s workshop

- Prof. Geoffrey Fox
- Deep Learning for Time Series Illustrated by COVID-19 Infection Studies



Please submit questions via Zoom chat

Questions?

compucell3d.org

tjsego@iu.edu