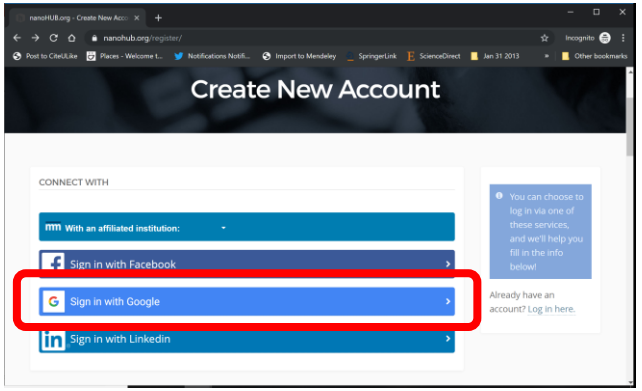
nanoHUB Account

- This talk's online PhysiCell models are cloud-hosted on nanoHUB.org.
- nanoHUB is **free**, but it requires a one-time registration.
- **Steps**:
  1. Visit https://nanohub.org/register
  2. Choose "Sign in with Google"
  3. Choose a Google account
  4. Click "No" (so it doesn't try to associate with some other nanoHIB account)
  5. Finish filling in details, and you're done!
  6. Use your google account to sign in in the future.

2



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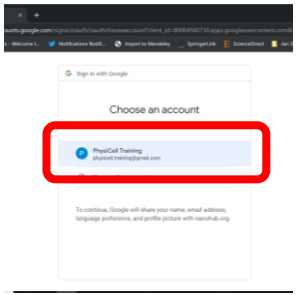

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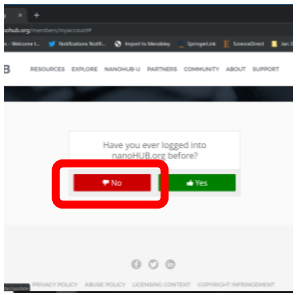

Biology of COVID-19 Attack on Epithelial Cells, understood from a Modeling and Simulation Perspective

Paul Macklin, Ph.D.

Intelligent Systems Engineering
Indiana University

January 19, 2021

Thank you to our coalition!

Multinational:
U.S.
Canada
United Kingdom

Federal partners:
Veterans Affairs
Argonne National Lab

Across Indiana:
Luddy School (lead)
UITS
IU Health
Purdue

Industry:
Pfizer
…

Rapid community-driven development of a SARS-CoV-2 tissue simulator

Michael Getz[1,**], Yafei Wang[1,**], Gary An[2,*], Andrew Becker[2,*], Chase Cockrell[2,*], Nicholson Collier[3,4,*], Morgan Craig[5,6*], Courtney L. Davis[7,*], James Faeder[8,*], Ashlee N. Ford Versypt[9,10,*],Juliano F. Gianlupi[1,*], James A. Glazier[1,*], Sara Hamis[11,*], Randy Heiland[1,*], Thomas Hillen[12,*], Dennis Hou[13,*], Mohammad Aminul Islam[9,*], Adrianne Jenner[5,6,*], Furkan Kurtoglu[1,*], Bing Liu[8,*,†], Fiona Macfarlane[11,*], Pablo Maygrundter[14,*], Penelope A Morel[15,*], Aarthi Narayanan[16,*], Jonathan Ozik[3,4,*], Elsje Pienaar[17,*], Padmini Rangamani[18,*], Jason Edward Shoemaker[19,*], Amber M. Smith[20,*], Paul Macklin[1,***]

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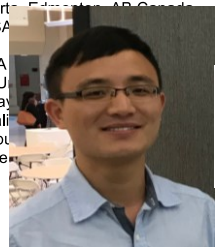
[15] Dep… …ersity of Pittsburgh. Pittsburgh, PA USA
… …d Infectious Disease, George Mason U…
… …gineering, Purdue University. West Lafay…
… …erospace Engineering, University of Cali…
… …oleum Engineering, University of Pittsbu…
… …ity of Tennessee Health Science Cente…
** equa…
† in me…
*** corresponding author: macklinp@iu.edu, @MathCancer

40+ regular contributors from 20+ institutions

Michael Getz
Indiana U.



Yafei Wang
Indiana U.

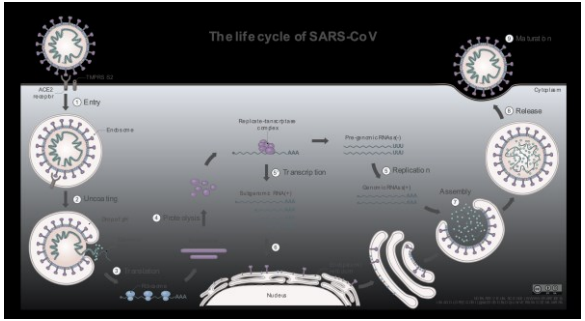
Note: This is a rapid prototyping project. For the very latest, see http://COVID-19.physicell.org

Also thank you to sponsors

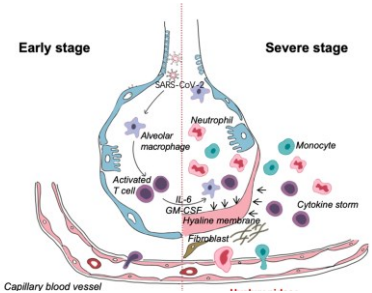
- This work is supported by:
  - **National Cancer Institute** & **Breast Cancer Research Foundation:**
    - Simulation methods were originally developed for cancer.
  - **National Science Foundation:**
    - Helped us automatically share complex simulation models on the cloud.
  - **Jayne Koskinas Ted Giovanis Foundation for Health and Policy**
    - A large emergency grant to jump-start a COVID-19 modeling coalition.
    - Funding for breast cancer research (jointly with Johns Hopkins and others).
  - Generous computing resources at Indiana University

COVID-19 is a multiscale problem

- At the **subcellular level:**
  - Viral binding and endocytosis (virus entry)
  - Viral replication and exocytosis (virus release)
  - ACE2 receptor trafficking
  - Signaling responses
- At the **cell level:**
  - Infected cells will die, but they can “warn” other cells (interferons)
  - Immune cells phagocytose dead cells
  - Immune cells attack infected cells
- At the **tissue level:**
  - Virus spreads through the tissue
  - The infected regions spreads
  - Tissue damage spreads
  - Immune cells coordinate with secreted factors
- At the **systems level** (a sampling):
  - Immune cells send signals to lymphatic system
  - Immune response ramps up (immune expansion, antibodies)
  - More immune cells arrive at site of infection



Source: wikimedia.org



Source DOI: 10.1038/s41418-020-0530-3

This is a complex system.

We want to use mathematical modeling to understand this system and find better treatments.

Collaborative, Iterative Progress

Approach

- **Rapid prototyping**
  - Build, test, and refine
- **Multidisciplinary team**
  - Domain experts guide modelers
  - Subteams work in parallel
  - Integration team coordinates the work
- **Rapid communication**
  - Preprints (open science)
  - Cloud-hosted models for live demos to team experts
- **Open source** software

Progress

Phase I (community building)

- **v1 prototype** (March 2020) built in 12 hours
- **v2 model** (April) added ACE2 receptor trafficking

Phase II (community-driven) (current)

- **v3 model** (May-July) added tissue immune responses
- **v4 model** (August-October) is adding interferon signaling ● pyroptosis ● systems-scale immune model ● immune cell trafficking ● improved tissue immune model ● better receptor-virus binding ● better viral replication ● tissue fibrosis.

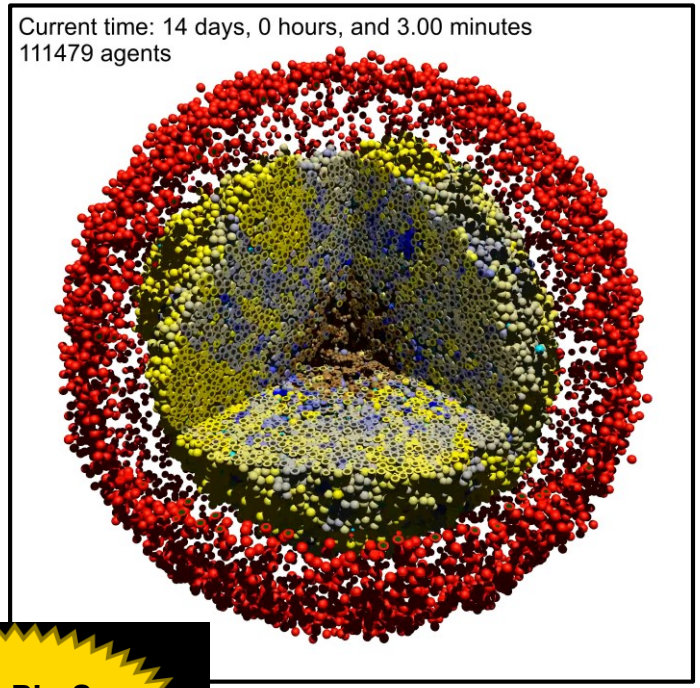
Agent-based models

- Simulate the **chemical microenvironment** of a tissue:
  - Movement of unbound virus particles
  - Diffusing signaling factors
  - Dead cell debris

- Simulate **individual cells** as software agents:
  - Individual states (member data)
  - Individual biological actions (divide, die, grow, move, secrete signals)

- Biological hypotheses become **agent rules**
  - Example:
    - Macrophages migrate randomly until they find and eat a dead cell.
    - Macrophages “activate” after eating a dead infected cell to recruit CD8 T cells
    - CD8 T cells seek and attack live infected cells.

- The cell agents are **multiscale** models. Each lung cell simulates:
  - ACE2 receptor binding and “trafficking”
  - Viral replication
  - Response to viral infection & signals (including behavioral changes)
  - Response to drugs (e.g., antivirals)



Sample PhysiCell model:
T cells attacking a tumor

2019 PLoS Computational Biology Research Prize *for* Public Impact

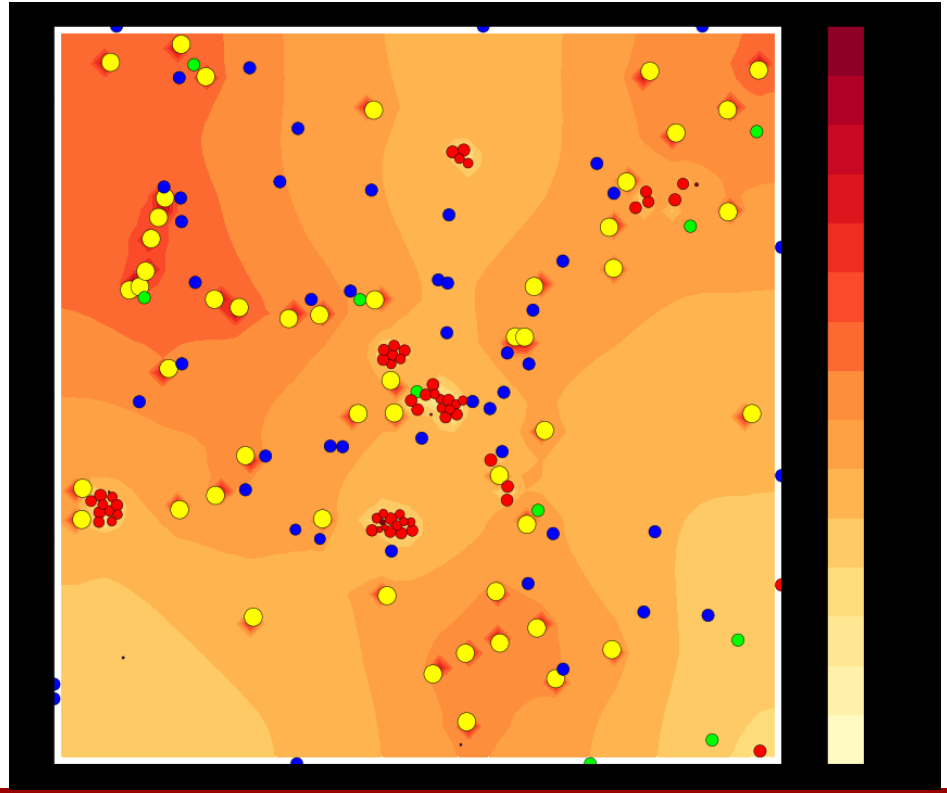
Let's run a motivating example

pcISA: an adversarial multicellular system

- What are the dynamics of an adversarial system?
- **suppliers (e.g., blood vessels)**
  - supply growth substrates
- **Invaders (e.g., bacteria)**
  - grow near vessels
  - avoid dead cells
  - avoid attackers
- **Scouts (e.g., macrophages)**
  - look for invaders, release signal
- **Attackers (e.g., T cells)**
  - Look for signal, attack invaders

Try this model yourself!

https://nanohub.org/tools/pcisa



pcISA exercises

1. **Suppliers and invaders only**
   - Set # of scouts and # of attackers to 0
   - Set max time to 2400 minutes.
   - Click run. What happens?
   - Plot the resource. How does this explain the behavior?
2. **Add scouts**
   - Set # of scouts to 10
   - Click run. What happens? Does plotting the "signal" help explain their behavior?
3. **Add attackers (full model)**
   - Set # of attackers to 50
   - Set max time to 7200 minutes.
   - Click run. What happens?
4. **Modify invaders**
   - Set invader quorum weight to 0.01
   - Click run. What happens?
   - Plot the death signal. How does this explain the behavior of invaders after an attack?
5. **Modify invaders and scouts (on your own)**
   - Set invader quorum weight to 1
   - Set scout migration bias to 1
   - Increase invader max death rate to 0.01
   - Click run. What happens?

Iterative modeling progress

v1: Proof of concept model

- **Agents:**
  - **lung epithelium**

in each cell →

$$\frac{dV}{dt} = -r_U V + \{\text{ uptake from PDE }\}$$
$$\frac{dU}{dt} = r_U V - r_P U$$
$$\frac{dR}{dt} = r_P U$$
$$\frac{dP}{dt} = r_S R - r_A P$$
$$\frac{dA}{dt} = r_A P \ - \{\text{ export to PDE }\}$$

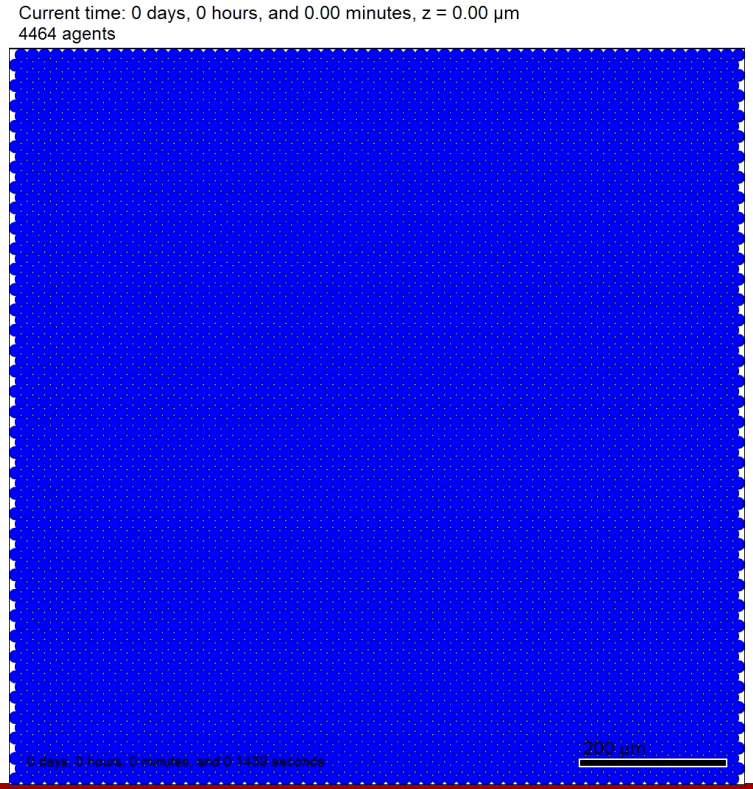
- **Submodels:**
  - Viral replication
    - system of 5 ODEs
    - constitutive relations to connect with virus PDE
  - Cell death response
    - Hill pharmacodynamics function

in each cell →

$$r_{death} = r_{max} \frac{A^n}{A_{half}^n + A^n}$$

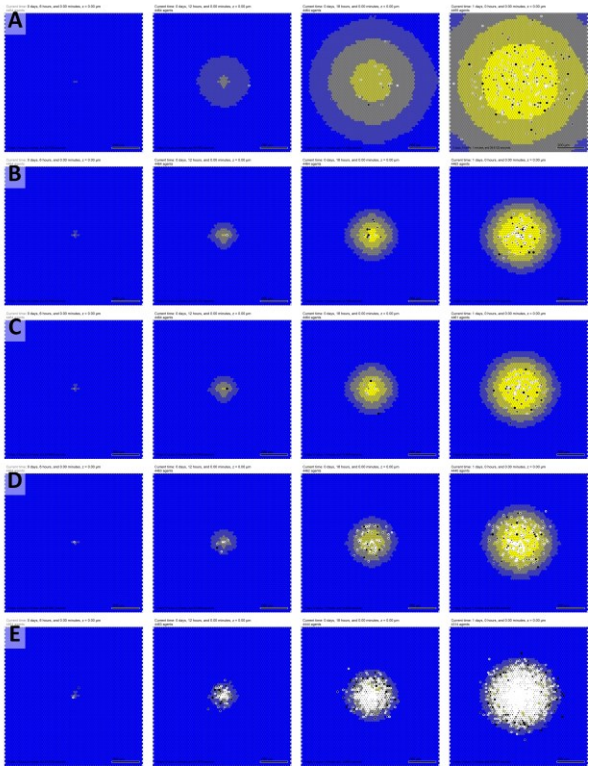
- **Microenvironment:**
  - Virus spread
    - reaction-diffusion PDE

$$\frac{\partial \rho}{\partial t} = D\nabla^2 \rho + \sum_{cells} \delta(x - x_i)(-U_i \rho + E_i)$$



More v1 results

default parameters



"baseline" results

slower virus diffusion

sharper plaque boundaries

apoptotic cells release virions at lysis

little impact on overall dynamics

infected cells less tolerant of viral load

somewhat slowed spread

lower infected cell survival time

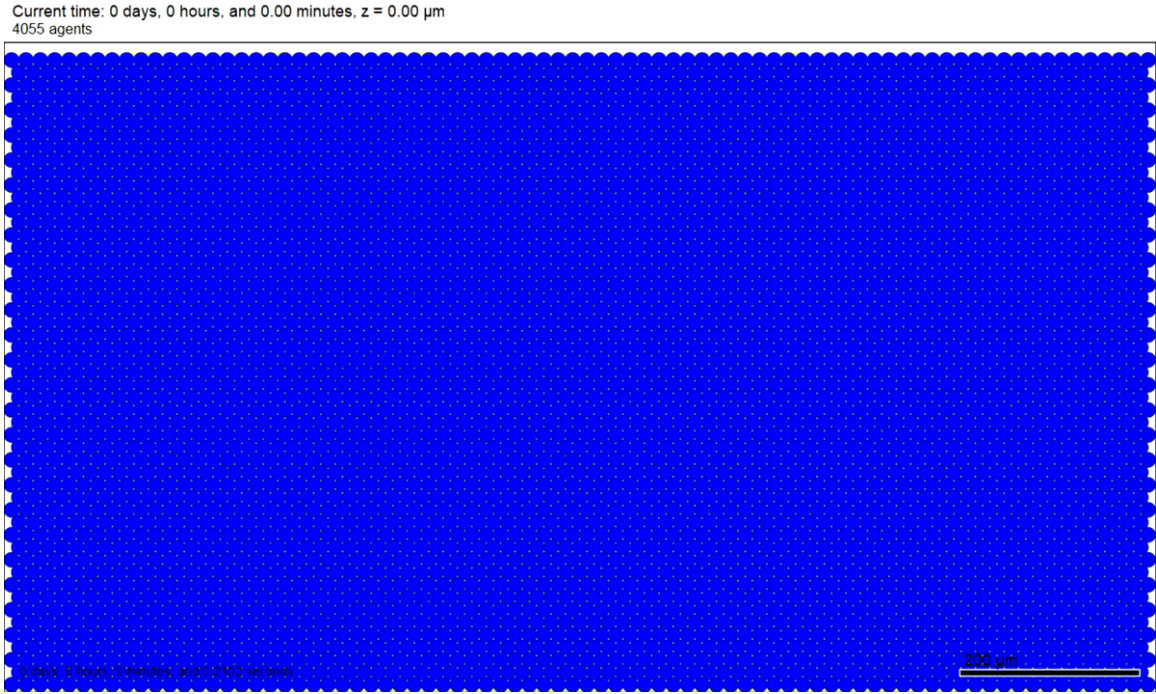
much more tissue damage,
but plaque spreads at same speed

Prototype 2

(April 1-May 9, 2020)

v2: Add ACE2 receptor dynamics

- **Agents:**
  - **lung epithelium**
- **Submodels:**
  - ACE2 receptor binding & trafficking
    - mass-matching with virus PDE in virus binding
    - system of 4 ODEs
  - Viral replication
    - system of 5 ODEs
    - constitutive relation to connect with ACE2 trafficking
    - constitutive relation to connect with virus PDE
  - Cell death response
    - Hill pharmacodynamics function
- **Microenvironment:**
  - Virus spread
    - reaction-diffusion PDE



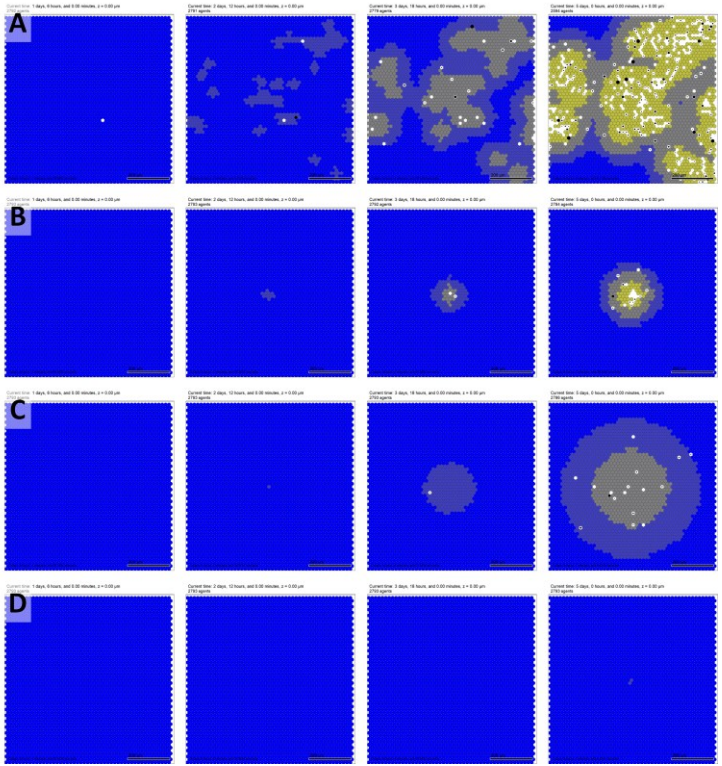
More v2 results

MOI-based initialization

slower viral diffusion

fewer ACE2 receptors

slower viral exocytosis



better approximation of *in vivo*

slower spread, sharper interface

less multiple infection, but faster plaque growth

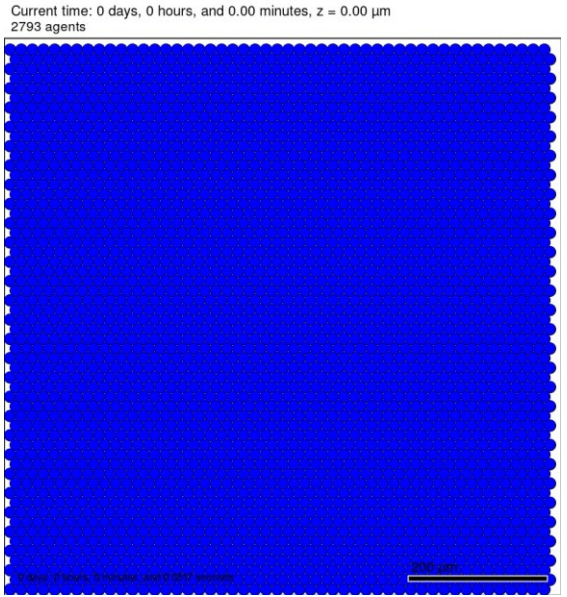
significant inhibition of plaque growth

Prototype 3

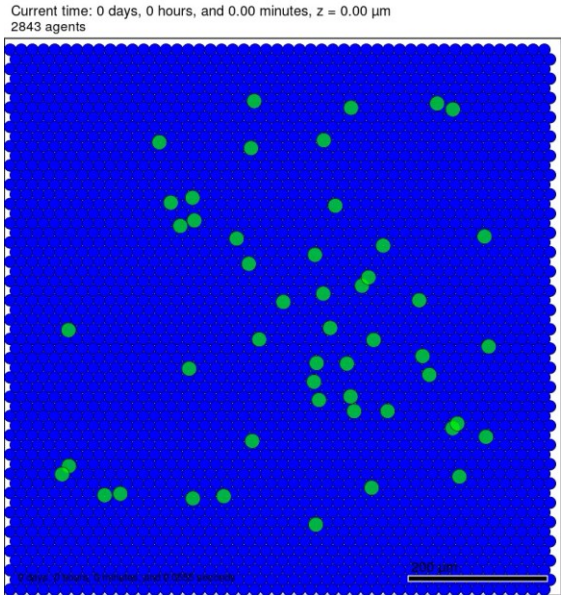
(May 10-July 27, 2020)

v3: Add the initial immune response

- **Agents:**
  - lung epithelium
  - macrophages (magenta when activated)
  - neutrophils
  - CD8+ T cells
- **Submodels:**
  - ACE2 receptor binding & trafficking
    - mass-matching with virus PDE in virus binding
    - system of 4 ODEs
  - Viral replication
    - system of 5 ODEs
    - constitutive relation to connect with ACE2 trafficking
    - constitutive relation to connect with virus PDE
  - Cell death response
    - Hill pharmacodynamics function
  - Immune cell rules
  - Immune cell recruitment
- **Microenvironment:**
  - Virus spread
  - Chemokine secreted by infected cells
  - Pro-inflammatory cytokine released by activated macrophages

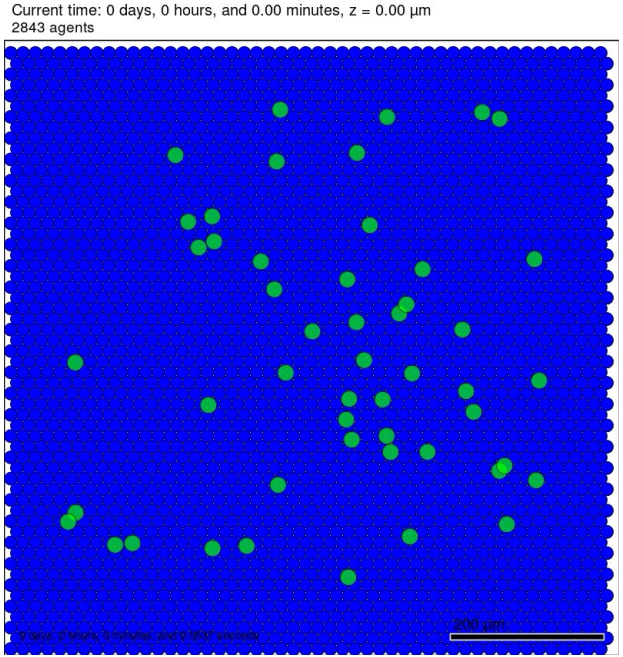


no immune response

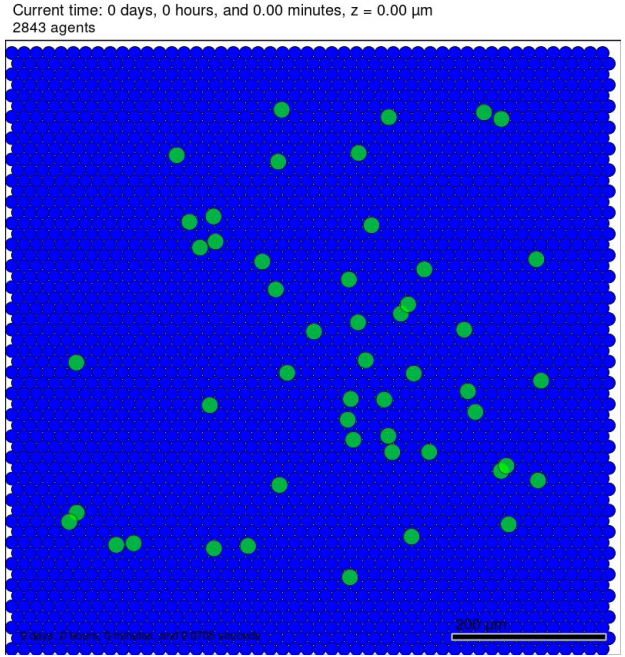


with immune response

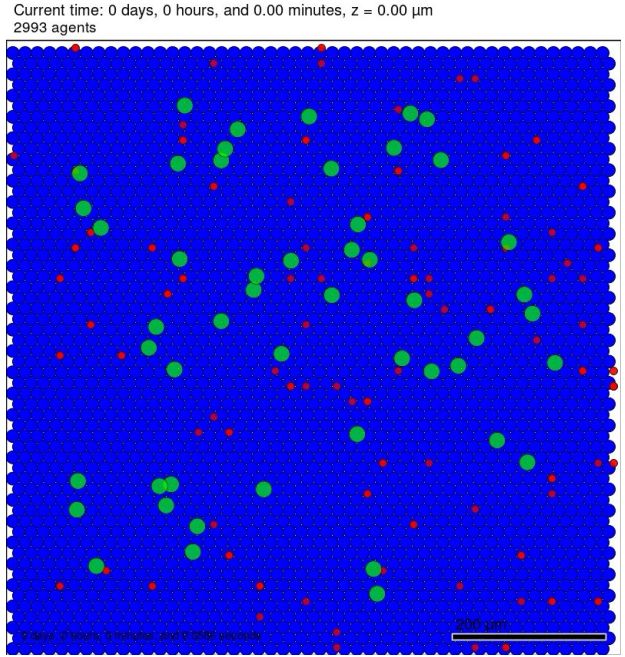
We can explore T cell strategies



faster T cell recruitment



faster T cell killing



resident T cells

Version 4

(ongoing)

Try this model yourself!

https://nanohub.org/tools/pc4covid19

multiscale immune model advances

Improved macrophages:
- Macrophages exhaustion & death
- Phenotype changes from CD8+ T cell contact
  - Stop secreting pro-inflammatory cytokine
- Enable phagocytosis of live infected cells

Dendritic cells:
- Resident DCs activated by virus or infected cells
- DCs traffick to lymph node to drive T cell expansion

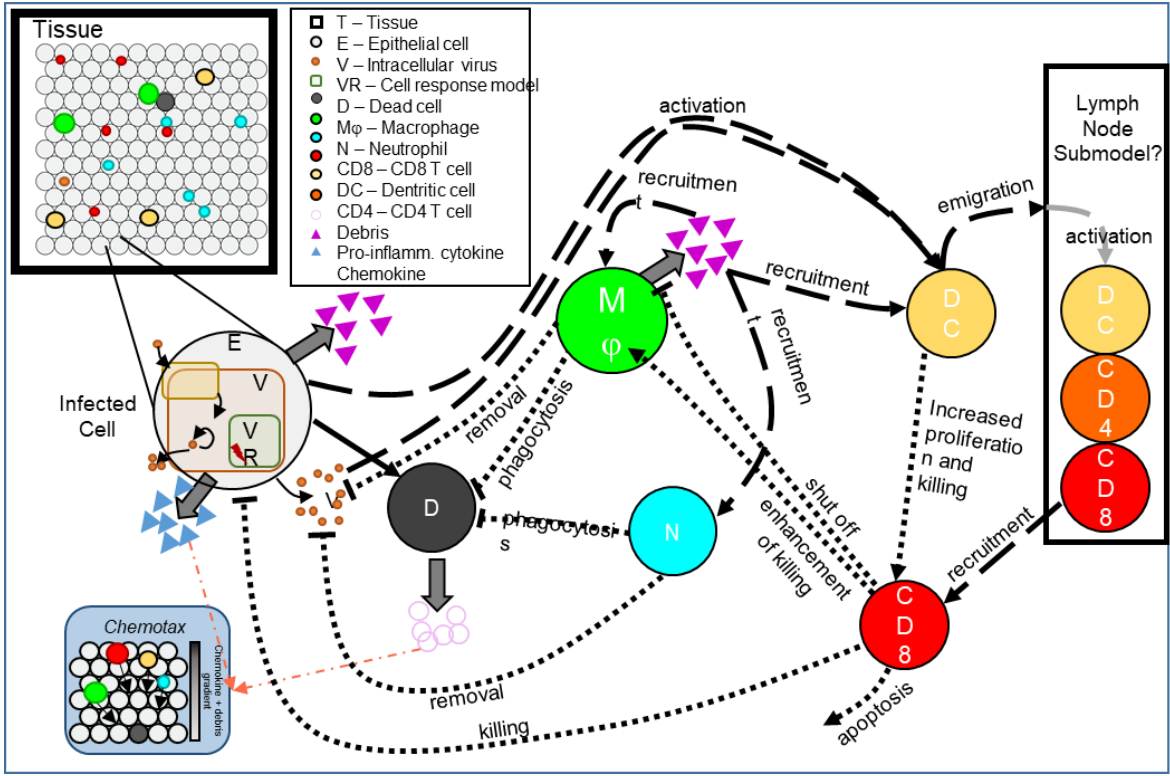
More T cell types

Epithelial cells present antigens

Systems-scale model of immune activation

systems scale:
Tarunendu Mapder
IUPUI

tissue scale:
Adrianne Jenner
U. Montreal

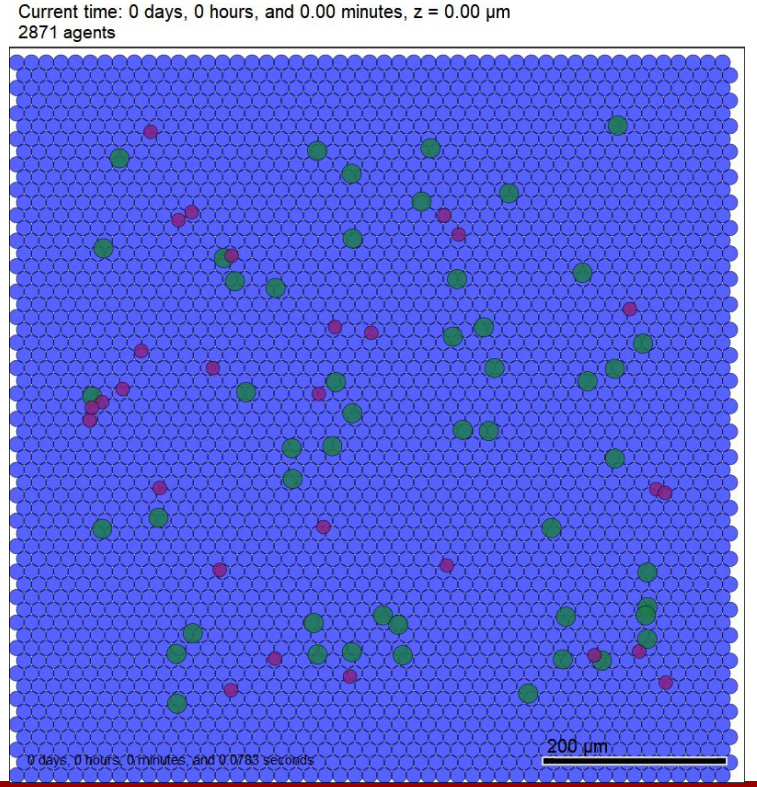


Fully integrated model (v4)

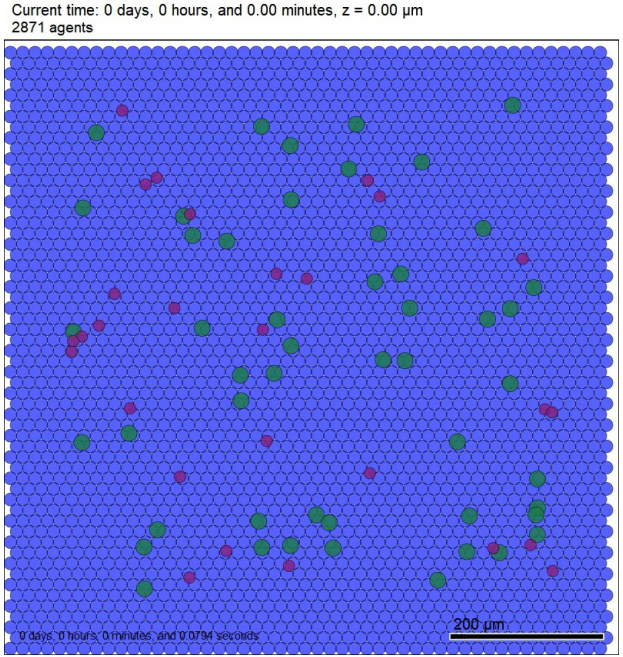
- Tissue-scale immune activation
- Systems-scale immune expansion
- Immune cell trafficking between local and systems scales
- Interferon slows down replication
- Paracrine secretion of interferons further slows

Try this model yourself!

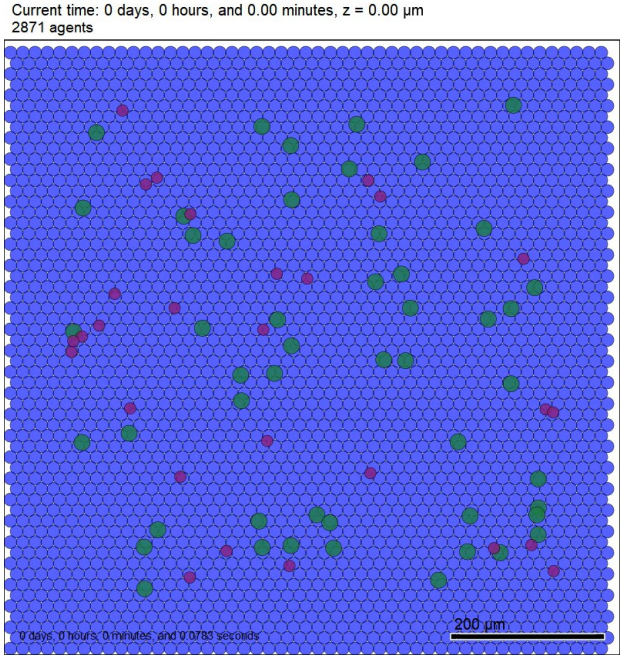
https://nanohub.org/tools/pc4covid19



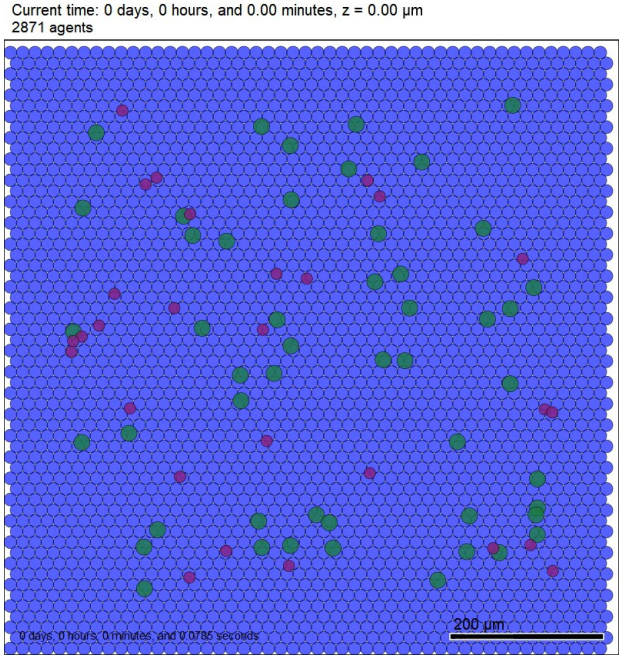
Type I interferon signaling slow progression



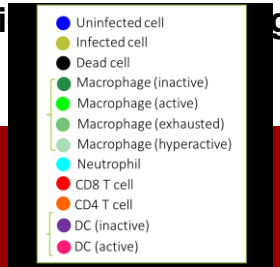
no paracrine secretion



moderate paracrine secreti



gh paracrine secretion

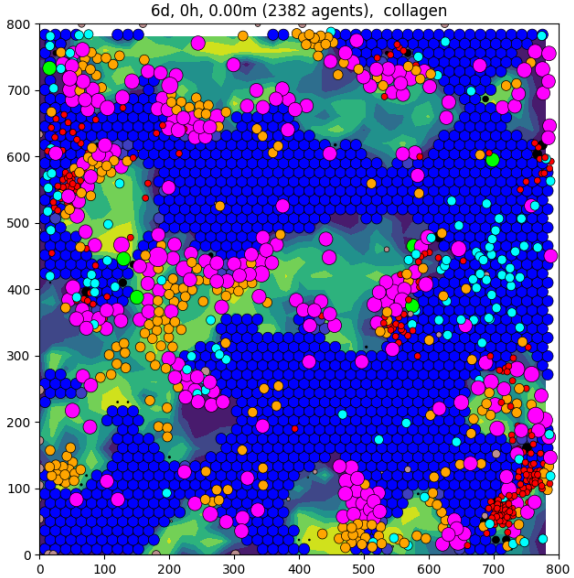


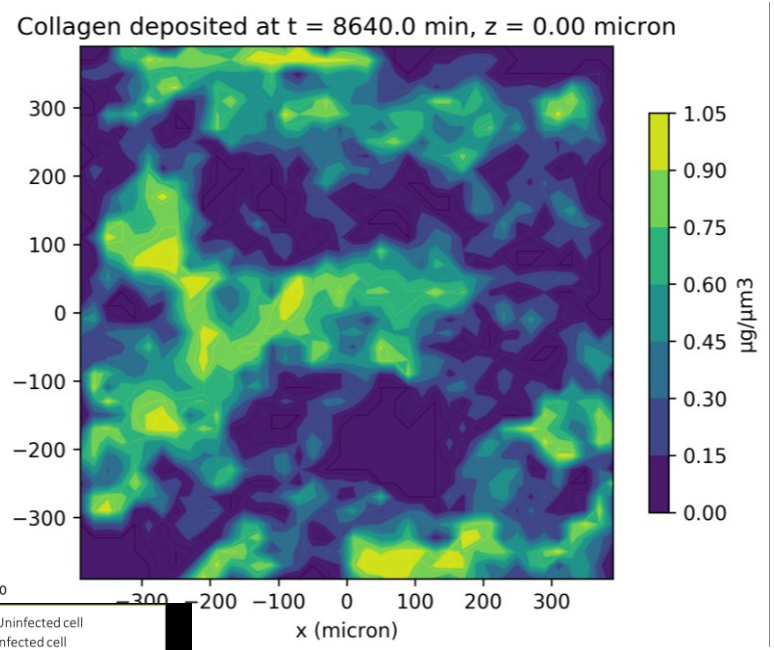
Preliminary work: coupled fibrosis

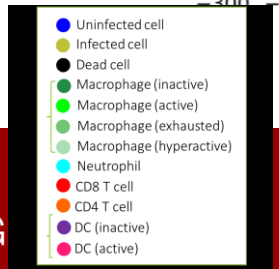
- Recruited fibroblasts re=seek damage from CD8+ T cells
- Fibroblasts deposit collagen

Hohammad Aminul Islam
Oklahoma State

Ashlee N. Ford-Versypt
Oklahoma State







Other ongoing work in v4

- Improved viral binding and replication models
  - Stochastic events for better continuum-discrete "conversion"
- Detailed infected cell pyroptosis model
- PKPD for current antiviral drugs

So what are we learning?

- The immune response is multi-pronged
  - "Scouting" cells (macrophages, dendritic cells) kick of increased immune activity
  - Interferon response helps slow replication in infected cells
  - Interferon responses by infected cells help "warn" nearby cells
  - Interferon responses by uninfected cells help spread the warning signal faster
  - T cell expansion in lymph node drives a more robust longer-term response
  - Interferon response appears to "bridge" the gap between initial infection and later immune response
    - Too early for immune detection, but early enough to cause trouble.

- Some unanswered questions:
  - Can an infected cell infect itself (thus speeding replication)?
    - If not, why/how not?
  - What about damage to nearby uninfected cells? (v5 question)
    - Can this be protective?
  - How do neutralizing antibodies change the dynamic in a naïve response?
  - How do neutralizing antibodies change the dynamics in an immunized individual?

Let's try it!

Some investigations

- Base model parameters
- Reducer MOI (multiplicity of infection) to 0.01
  - parameters tab
    - multiplicity_of_infection = 0.01
- Increase interferon secretion (autocrine and paracrine) by 10×
  - cell types tab for lung epithelial cells
    - interferon_secretion_rate_via_infection = 0.5
    - interferon_secretion_rate_via_paracrine = 5
- Increase interferon inhibition to 0.99
  - cell types tab for lung epithelial cells
    - interferon_max_virus_inhibition = 0.99

Try this model yourself!

https://nanohub.org/tools/pc4covid19

Next steps

- **v5 model**
  - Negative feedbacks (anti-inflammation signals)
  - Antibodies
  - "bystander" effects (collateral damage to uninfected cells)

- **v6 model (final release candidate)**
  - Fine tuning parameters
  - Parameter space exploration on HPC, ML-guided analysis
  - Prototype 3D tissue geometry
  - Pivot to Phase III
    - Documentation and training materials
    - Long-term support
    - Data & results clearinghouse

Learning from other domains

- **Key shared biology across many problems**
  - Inflammation
  - Tissue damage
  - Innate and adaptive immune responses
- **Mixing expertise from many fields**
  - Software tools & HPC from math oncology
  - Domain experts in immunology and microbiology
  - Domain experts in tissue mechanics and damage
- **Reusable open source software modules** can be used beyond COVID-19
- **Future cancer advances**
  - Tumor-associated macrophage and fibroblasts
  - Cancer inflammation
  - viral carcinogenesis, oncolytic virus therapies
  - CAR T cell therapies, other immunotherapies

We've learned how to coordinate big teams to rapidly build multiscale models.
We should do this for other problems!

COVID-19 Links

***bioRxiv* preprint:**
https://doi.org/10.1101/2020.04.02.019075

online model:
https://nanohub.org/tools/pc4covid19

Further reading (1)

- **BioFVM method paper (3-D diffusion)**
  A. Ghaffarizadeh, S.H. Friedman, and P. Macklin. BioFVM: an efficient, parallelized diffusive transport solver for 3-D biological simulations. *Bioinformatics* 32(8):1256-8, 2016. DOI: 10.1093/bioinformatics/btv730.

- **PhysiCell method paper (agent-based model)**
  A. Ghaffarizadeh, R. Heiland, S.H. Friedman, S.M. Mumenthaler, and P. Macklin. PhysiCell: an open source physics-based cell simulator for 3-D multicellular systems. *PLoS Comput. Biol.* 14(2):e1005991, 2018. DOI: 10.1371/journal.pcbi.1005991.

- **PhysiBoSS (PhysiCell + MaBoSS for Boolean networks)**
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- **xml2jupyter paper (create GUIs for cloud-hosted models)**
  R. Heiland, D. Mishler, T. Zhang, E. Bower, and P. Macklin. xml2jupyter: Mapping parameters between XML and Jupyter widgets. *Journal of Open Source Software* 4(39):1408, 2019. DOI: 10.21105/joss.01408.

- **PhysiCell+EMEWS (high-throughput 3D PhysiCell investigation)**
  J. Ozik, N. Collier, J. Wozniak, C. Macal, C. Cockrell, S.H. Friedman, A. Ghaffarizadeh, R. Heiland, G. An, and P. Macklin. High-throughput cancer hypothesis testing with an integrated PhysiCell-EMEWS workflow. *BMC Bioinformatics* 19:483, 2018. DOI: 10.1186/s12859-018-2510-x.

- **PhysiCell+EMEWS 2 (HPC accelerated by machine learning)**
  J. Ozik, N. Collier, R. Heiland, G. An, and P. Macklin. Learning-accelerated Discovery of Immune-Tumour Interactions. *Molec. Syst. Design Eng.* 4:747-60, 2019. DOI: 10.1039/c9me00036d.

Further reading (2)

- **A review of cell-based modeling (in cancer):**

  J. Metzcar, Y. Wang, R. Heiland, and P. Macklin. A review of cell-based computational modeling in cancer biology. *JCO Clinical Cancer Informatics* 3:1-13, 2019 (invited review). DOI: 10.1200/CCI.18.00069.

- **Progress on multicellular systems biology:**

  P. Macklin, H.B. Frieboes, J.L. Sparks, A. Ghaffarizadeh, S.H. Friedman, E.F. Juarez, E. Jockheere, and S.M. Mumenthaler. "Progress Towards Computational 3-D Multicellular Systems Biology". In: . Rejniak (ed.), *Systems Biology of Tumor Microenvironment*, chap. 12, pp. 225-46, Springer, 2016. ISBN: 978-3-319-42021-9. (invited author: P. Macklin). DOI: 10.1007/978-3-319-42023-3_12.

- **Challenges for data-driven multicellular systems biology**

  P. Macklin. Key challenges facing data-driven multicellular systems biology. *GigaScience* 8(10):giz127, 2019. DOI: 10.1093/gigascience/giz127