The Multiscale Modeling Consortium celebrates 20 years of IMAG:

Lessons from the past that guide the future

June 28 & 29 2023

Natcher Conference Center, NIH

Multiscale Modeling is Life

Denise Kirschner, University of Michigan Medical School

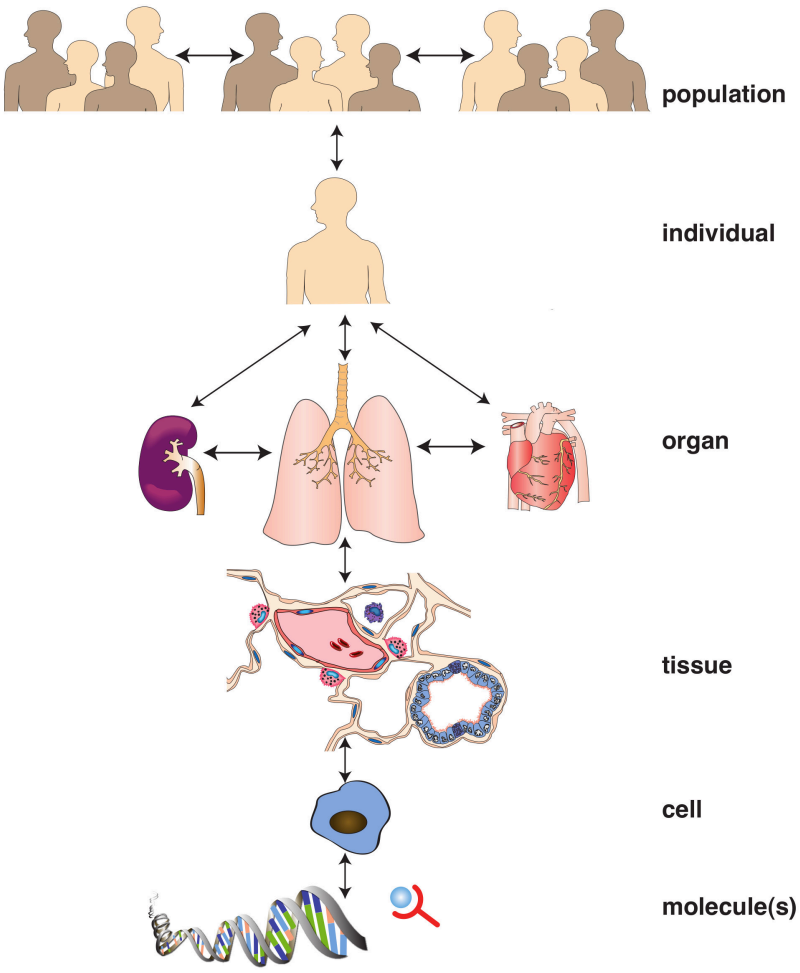
Paraphrased from Dani Rojas, Ted Lasso

Two cautionary tales that yield advice

Be prudent when offering comments/advice

Never miss a committee meeting

Multiscale models capture processes ranging over time & space (MSMs)



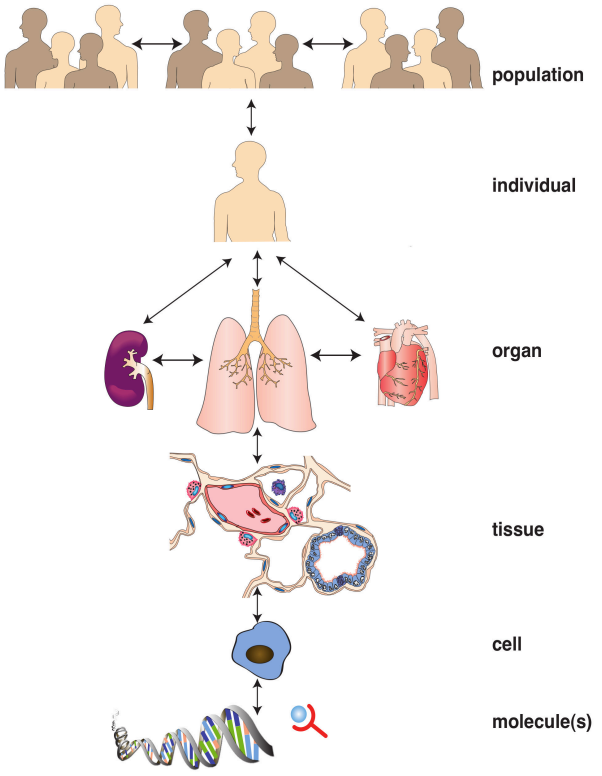
Questions for MSMs

- How do we build MSMs?
- How do we link scales?
- How do we calibrate MSMs?
- How do we simulate?
- How do we ensure MSMs are robust/credible?
- How do we analyze MSMs?
- How do we validate MSMs?
- How can MSMs be useful?
- Where do we go next?

How do we build MSMs?

1) What scale do you begin?

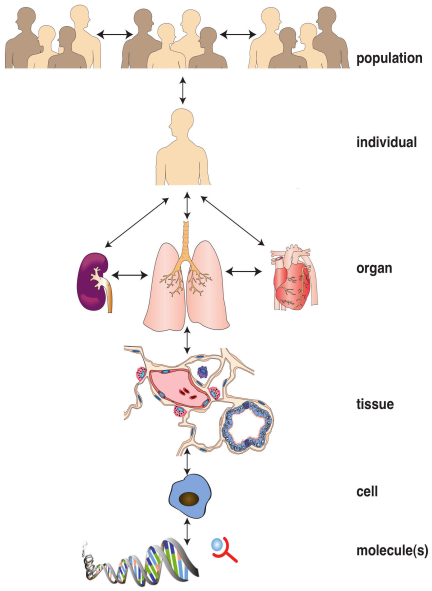
a. Top down
b. Bottom up
c. Meso-scale (in-out)



2) What modeling approach is most appropriate?

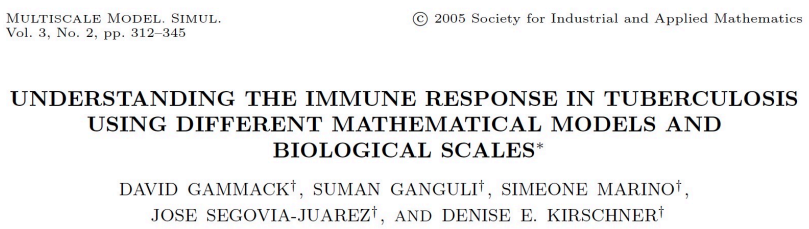
How do we build MSMs?

Biological Scale			Modeling Tool *David Gammack et al, *SIAM Journal of Multiscale Modeling and Simulation,* Vol 3(2), pp. 312-345, 2005	
	Time	***Length***	***Dynamics***	***Model Type***
Genetic/ Molecular	**10^{1}-10^{2} s**	**10^{-9}-10^{-8} m**	**Deterministic, continuous**	**Statistical**
Intracellular /Cellular	**10^{1}-10^{3} s**	**10^{-5} m**	**Deterministic, continuous**	**Mathematical: ODE**
Tissue	**10^{4} -10^{5} s**	**10^{-3}-10^{-2} m**	**Stochastic, discrete**	**Algorithmic: ABM**
Organ/ organism	**10^{5}-10^{6} s**	**10^{-2}-1 m**	**Deterministic**	**Hybrid: ODE+ABM**



Modeling Approaches example:

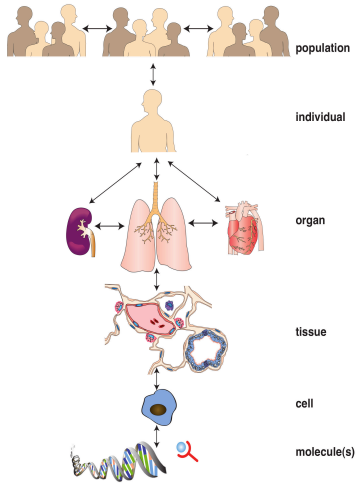
- **What is the most appropriate approach to model granulomas?**
- ODEs- Wigginton J and Kirschner D. **A Model to Predict Cell-Mediated Immune Regulatory Mechanisms During Human Infection with Mycobacterium tuberculosis** , J. Immunology 166: pp 1951-1976, 2001
- PDEs-- Gammack, C.R. Doering, D.E. Kirschner, **Macrophage response to Mycobacterium tuberculosis infection** Journal of Mathematical Biology. Published online: 20 August 2003, In print: Vol 48(2) February 2004
- Metapopulations- Suman Ganguli, David Gammack, Denise E. Kirschner, **A Metapopulation Model of Granuloma Formation in the Lung During Infection with Mycobacterium Tuberculosis** , Mathematical Biosciences and Engineering, Volume 2, Number 3, Aug 2005
- ABMs/IBMs--Jose L. Segovia-Juarez, Suman Ganguli, and Denise Kirschner, **Identifying control mechanism of granuloma formation during M. tuberculosis infection using an agent based model** , Journal of Theoretical Biology. 231, Issue 3, pp 357-376, 2004

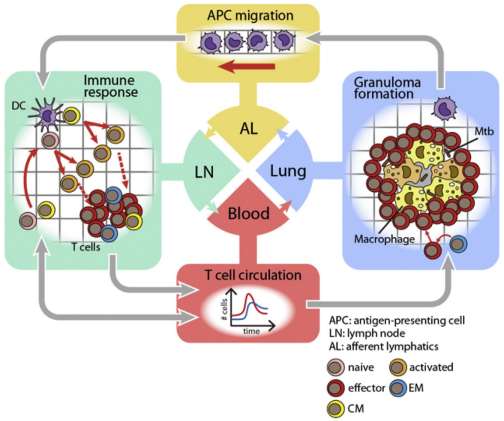

MULTISCALE MODEL. SIMUL.
Vol. 3, No. 2, pp. 312–345

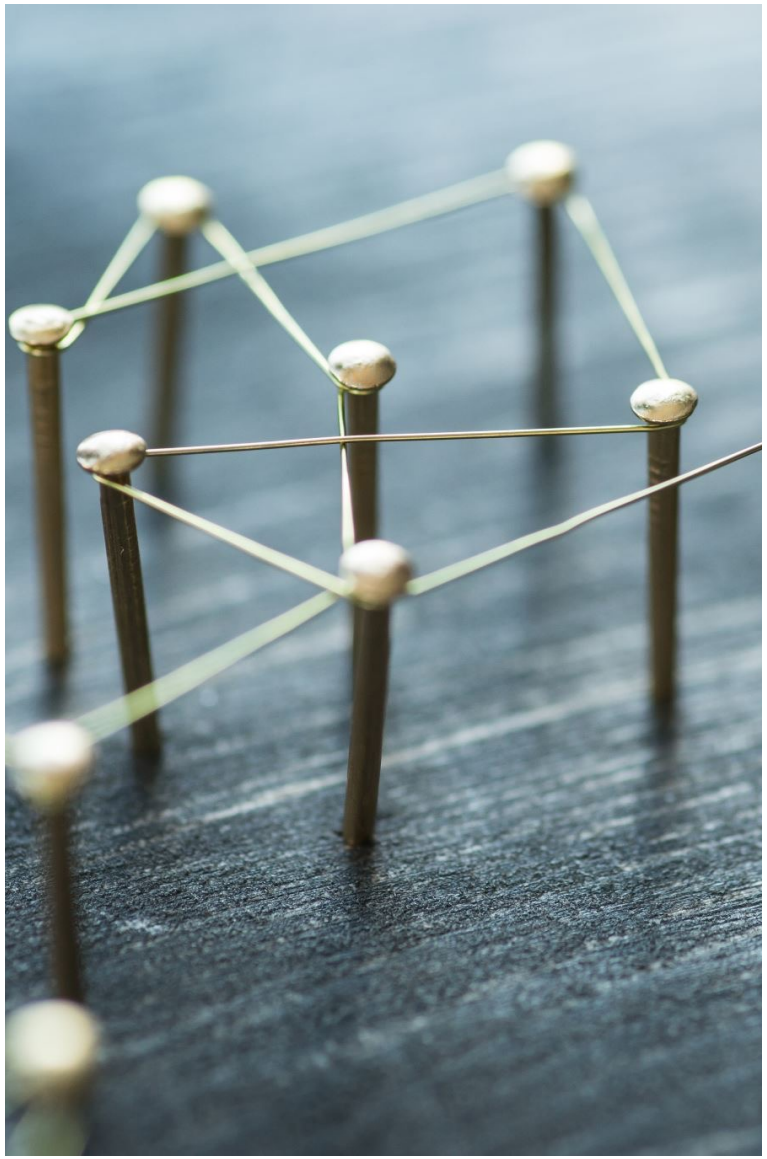
UNDERSTANDING THE IMMUNE RESPONSE IN TUBERCULOSIS USING DIFFERENT MATHEMATICAL MODELS AND BIOLOGICAL SCALES*

DAVID GAMMACK†, SUMAN GANGULI†, SIMEONE MARINO†, JOSE SEGOVIA-JUAREZ†, AND DENISE E. KIRSCHNER†

How do we link scales and compartments?







Linking issues

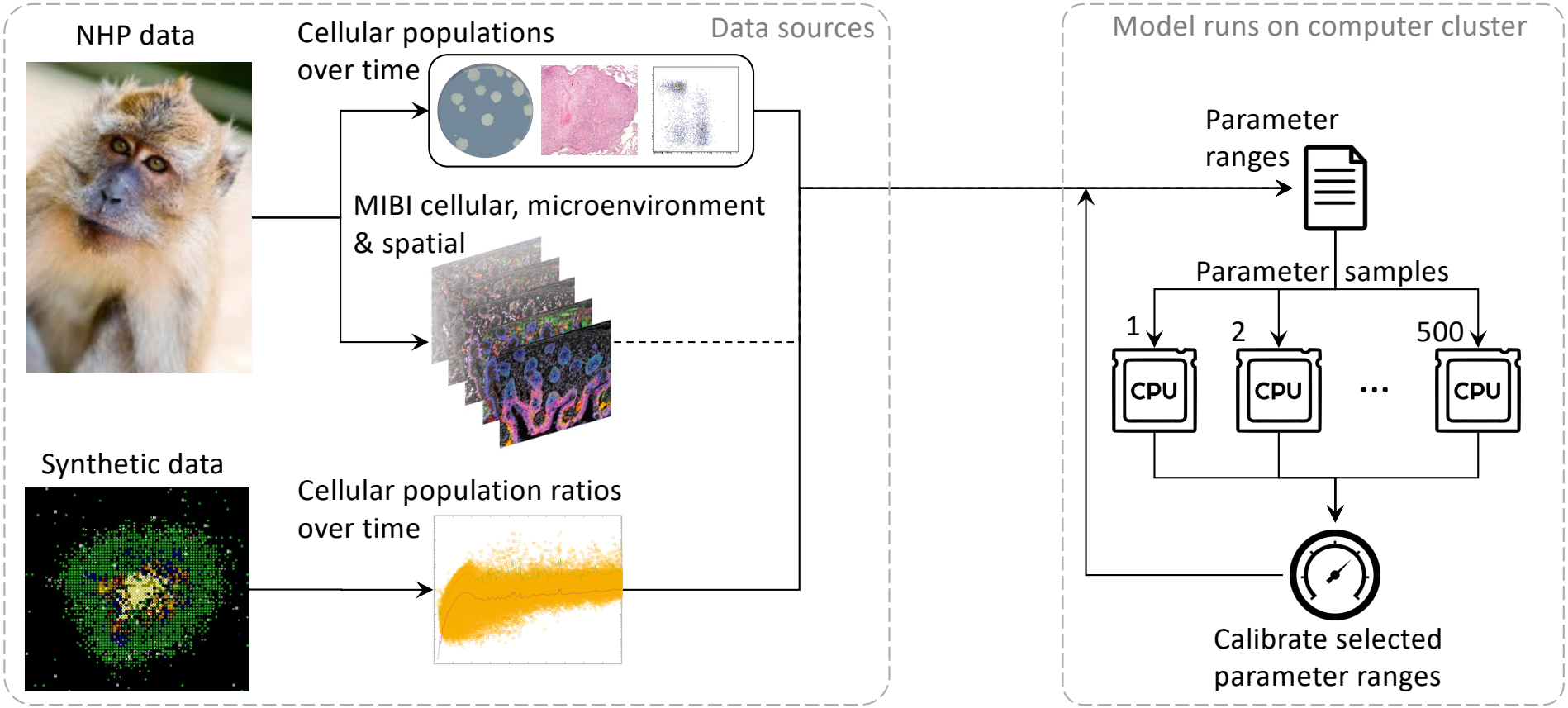
- There are no standard linking methods
- Interfacing or linking independent model components that:
  - operate at different temporal or spatial granularities
  - use different modes of computation (e.g., stochastic and continuous)
- Passing parameters can link model scales
- Volumetric scaling can link compartmental transfers
- Several groups developed frameworks to modularize models to improve model linking with an eye toward efficient modeling.
  - CompuCell 3D (www.compucell3d.org (ask James G!)

How do we calibrate MSMs?

By eye with data fitting or other regression methods

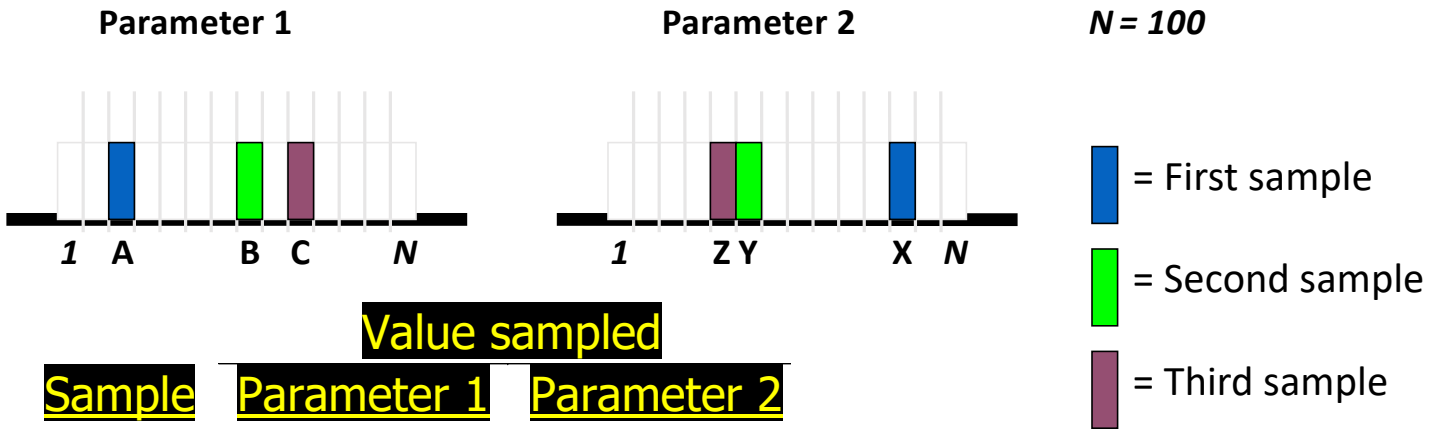
Multiple data types and space/time variations- need something else

calibration workflow to multiple types of data



Latin hybercube sampling (LHS) for stratified searches

Recent paper on Sampling schemes (To Sobol or not to Sobol)

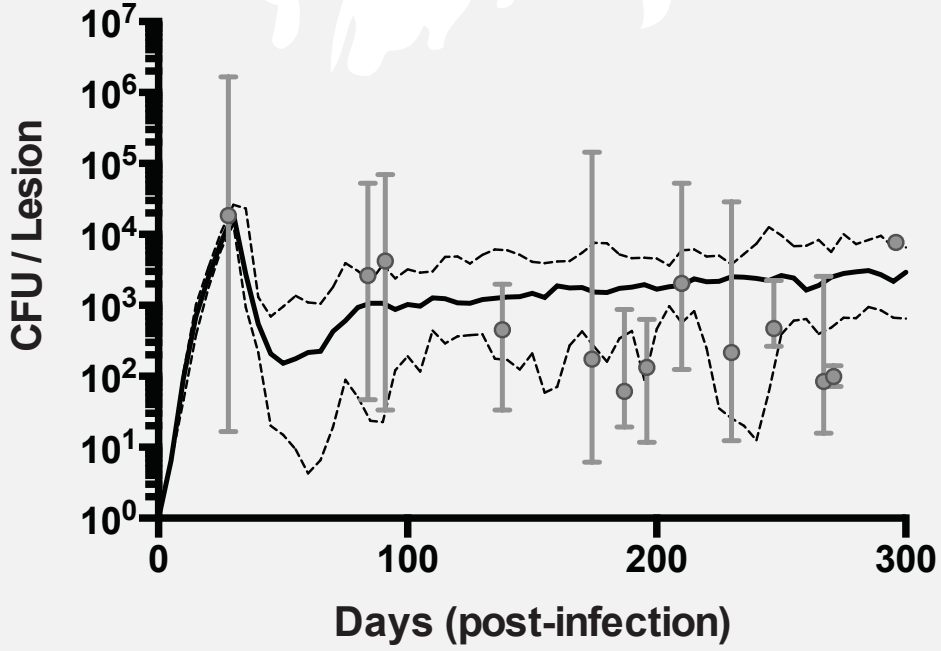


Sample	Value sampled: Parameter 1	Value sampled: Parameter 2
1	A	X
2	B	Y
3	C	Z
N	n_A	n_B

-Define f(x) to be the p.d.f. for parameter x, where the area under each equiprobable interval is equal to 1/N (i.e. =integral of f).

Reviewed in: Marino et al, JTB, Vol 254, pp 178-196, 2008

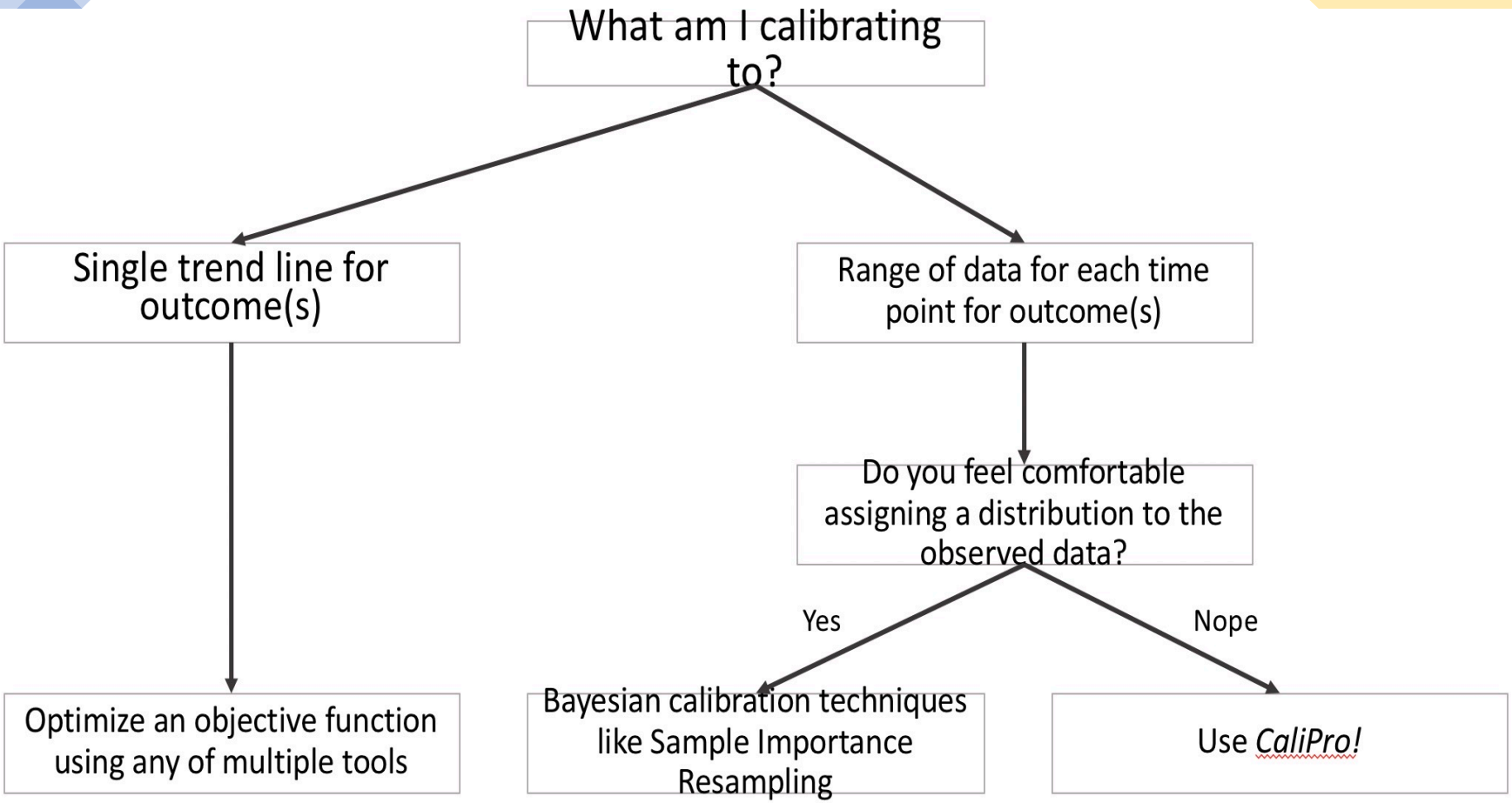
Model ‘calibration’: data versus model output



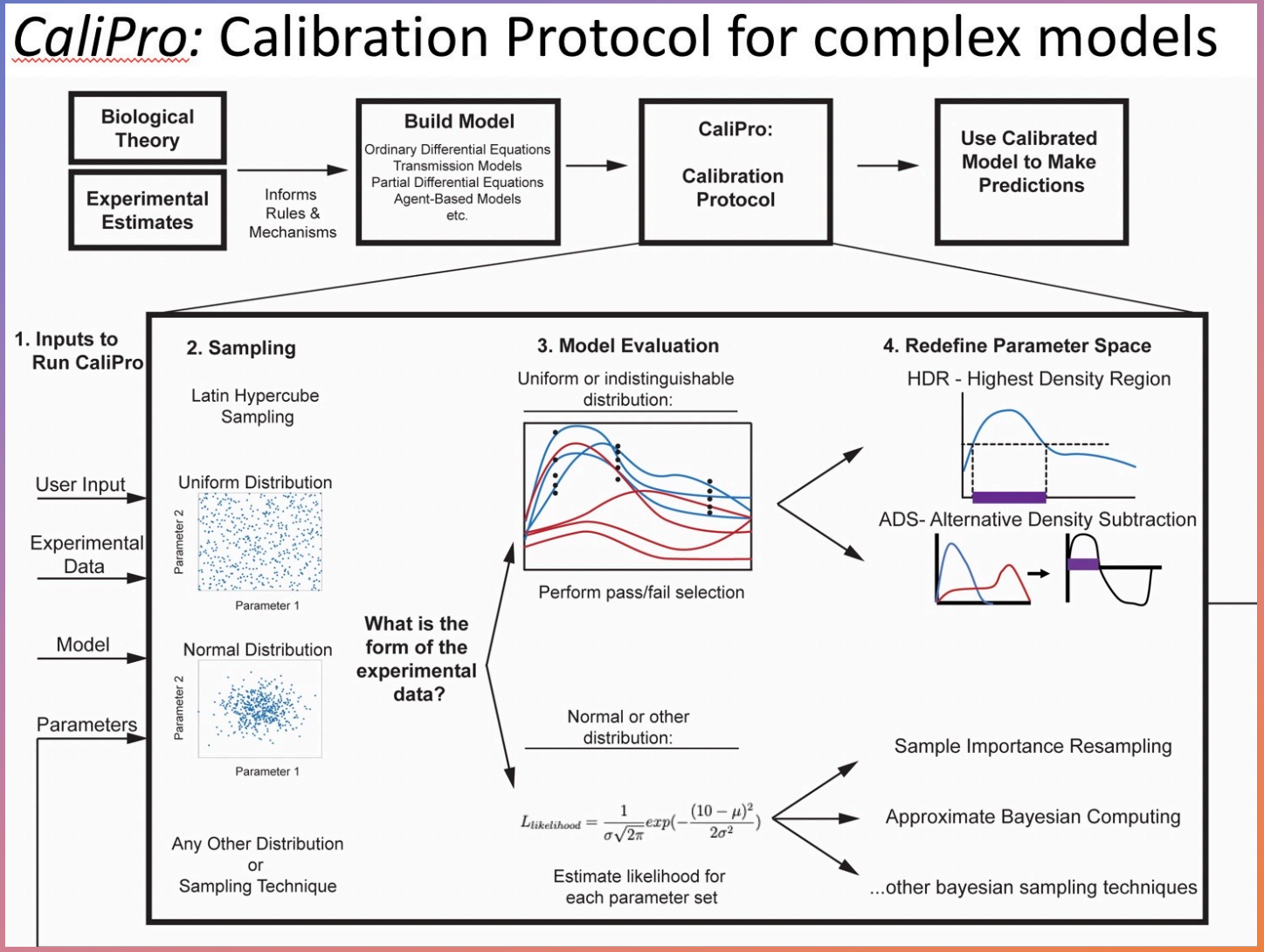
Model: curve, dashed lines (SEM)

NHP Data: Circles + SEM

(Data from Flynn Lab)


What am I calibrating to?
Single trend line for outcome(s)
Range of data for each time point for outcome(s)
Do you feel comfortable assigning a distribution to the observed data?
Yes
Nope
Optimize an objective function using any of multiple tools
Bayesian calibration techniques like Sample Importance Resampling
Use CaliPro!

CaliPro: Calibration Protocol for complex models

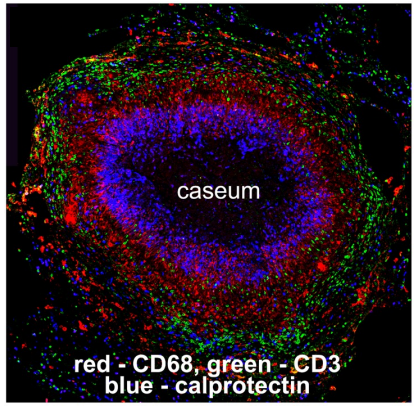


Louis R. Joslyn et al
CaliPro,
Cellular and Molecular Bio
15 September 2020

Simulations simultaneously match non-human primate data in both space and time

Spatial analysis

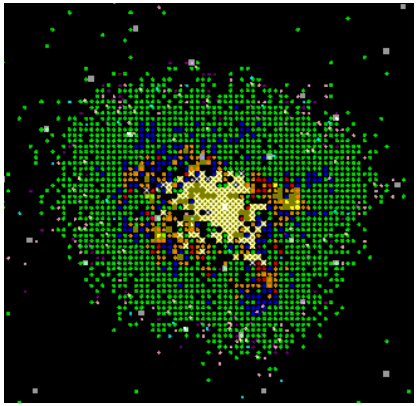
NHP data



Data from Flynn lab

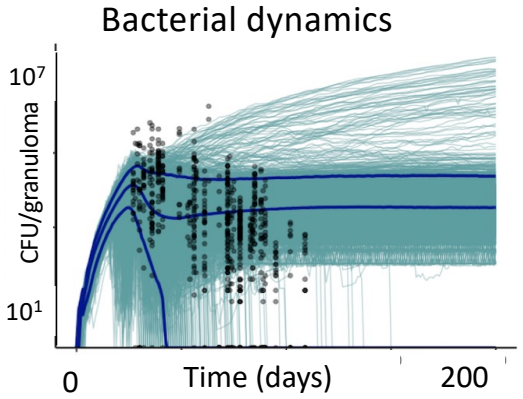
Macrophages
T-cells
Neutrophils

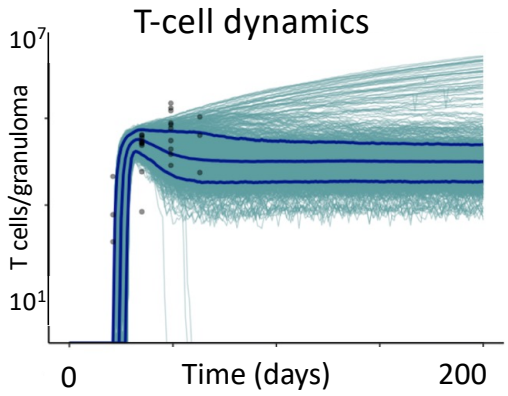
GranSim

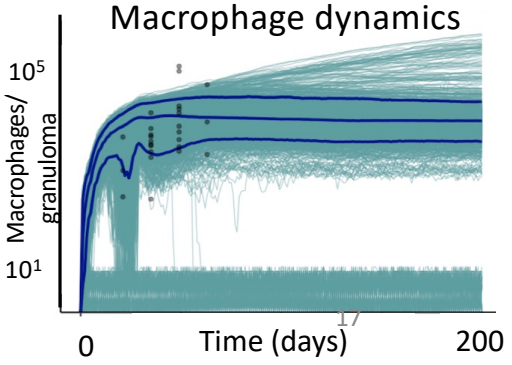


Simulation

Temporal analysis





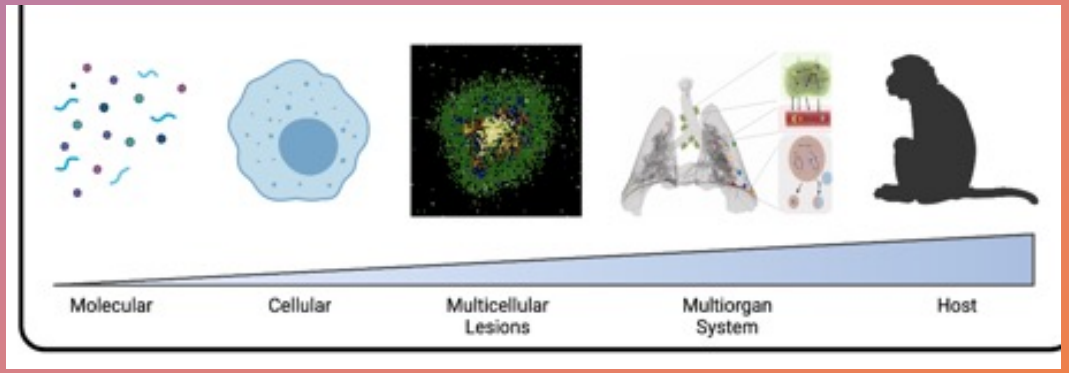


GranSim simulations
NHP data from Flynn lab

What about Bayesian approaches?

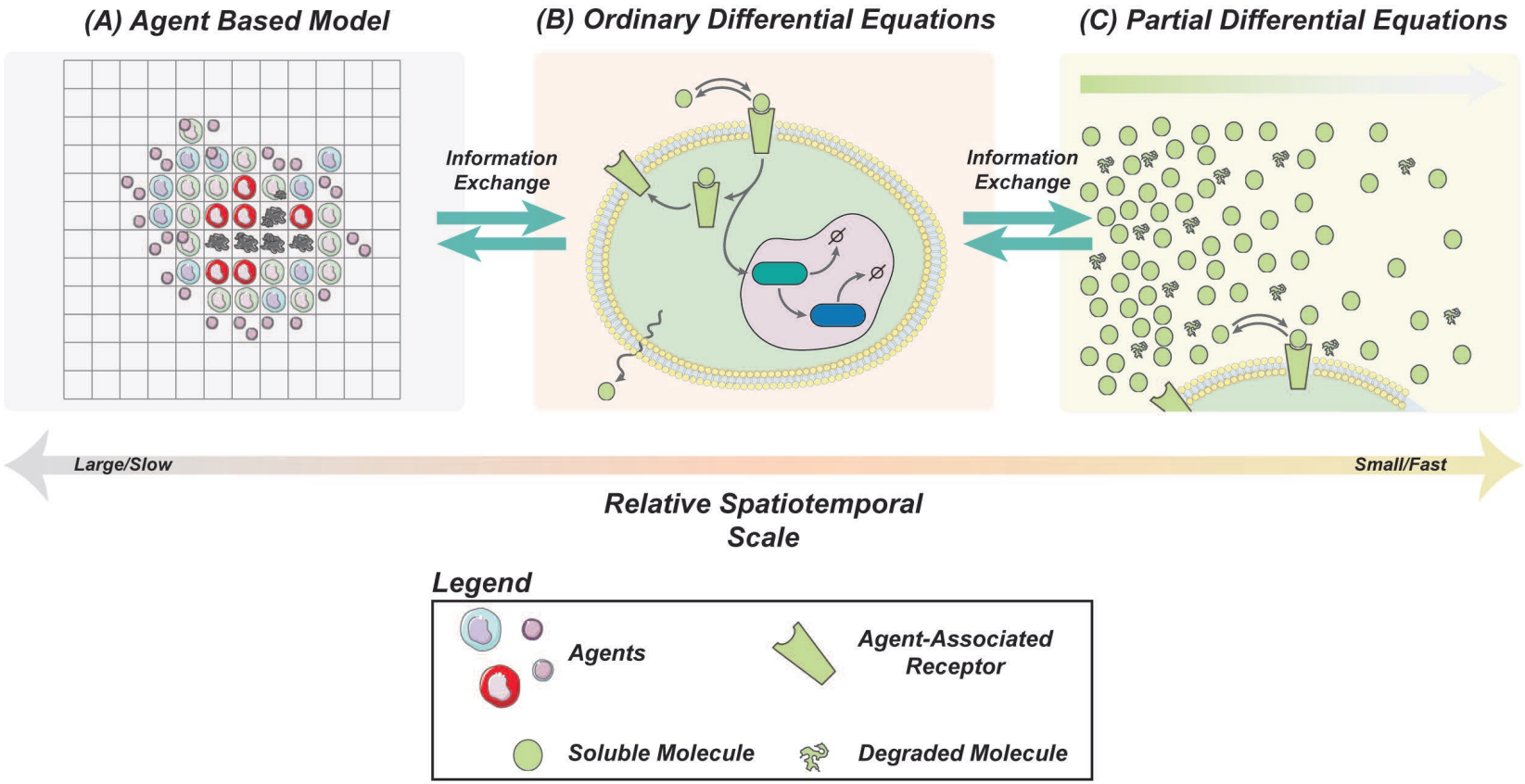
-See poster by Dr. Pariksheet Nanda here at MSM….

-Also he will show you our Multi-scale Tissue Time Machine

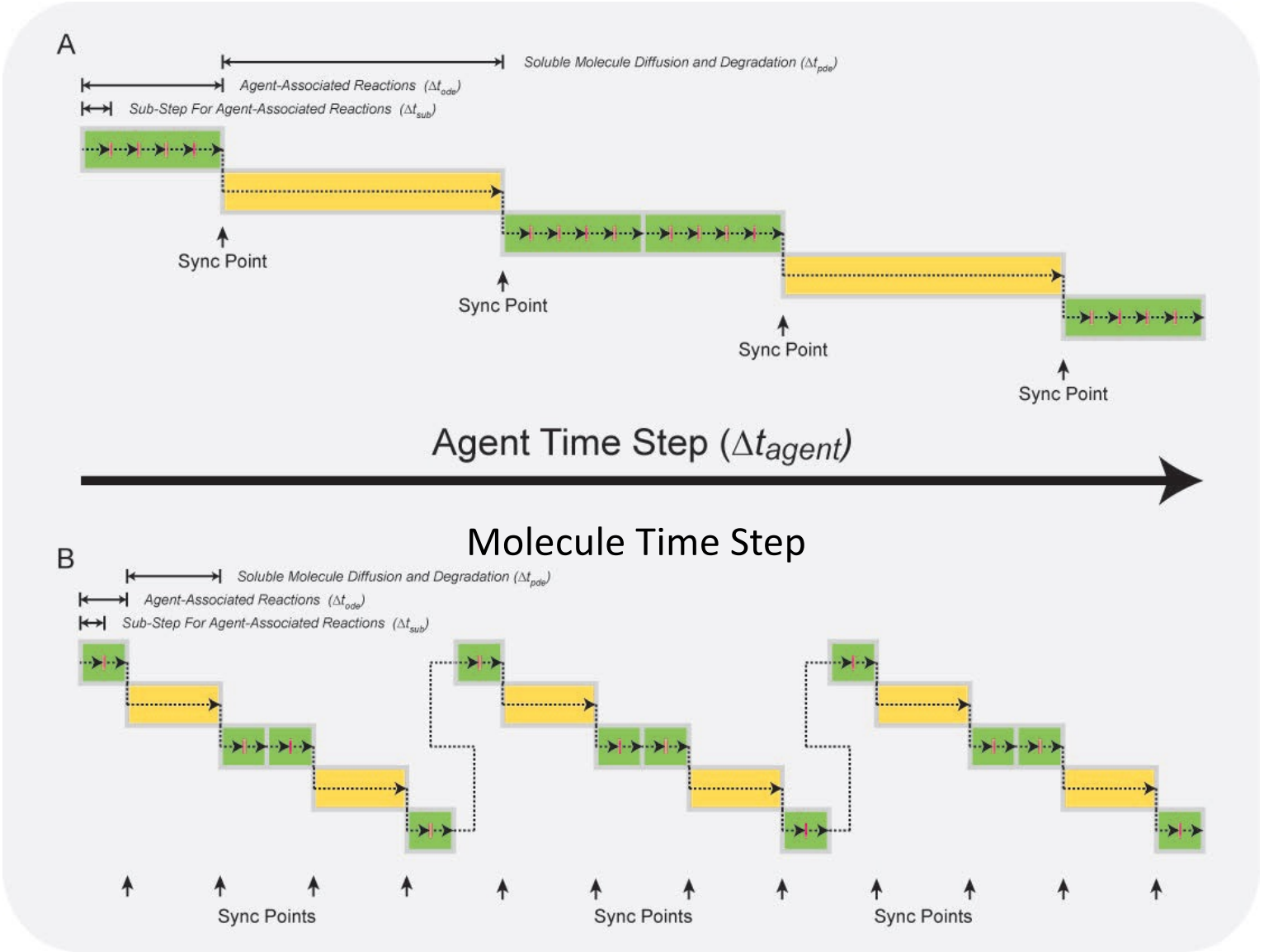



How do we simulate MSMs?

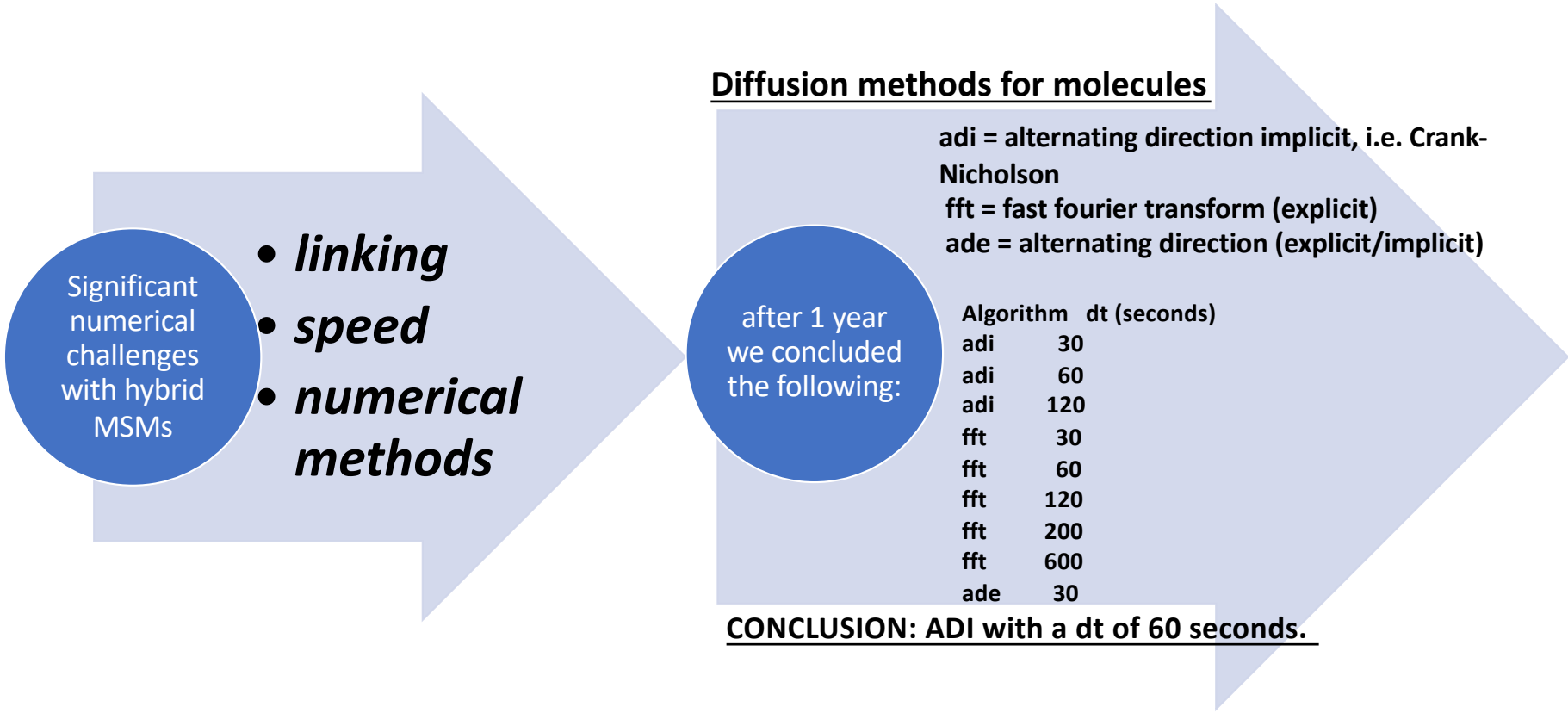
How do we simulate MSMs that are usually hybrid?



Cilfone, N, Kirschner, D and Linderman, JJ. Efficient numerical implementation of hybrid multi-scale agent-based models to describe biological systems *Cellular and Molecular Bioengineering, 2014*

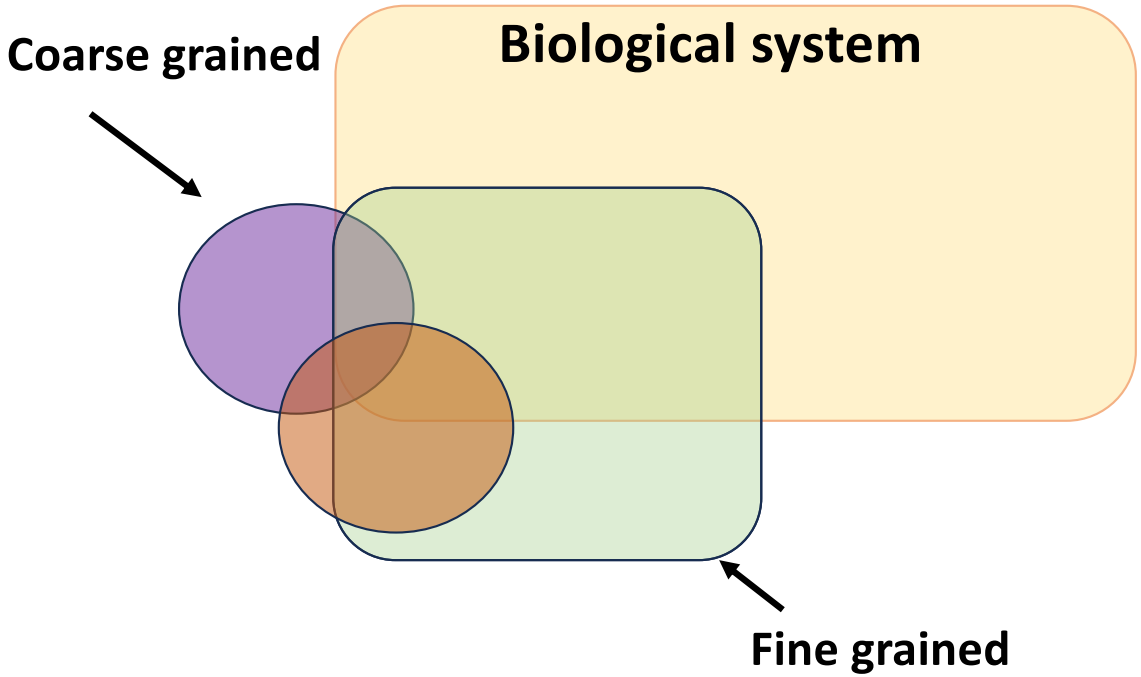

A
Soluble Molecule Diffusion and Degradation (Δt_{pde})
Agent-Associated Reactions (Δt_{ode})
Sub-Step For Agent-Associated Reactions (Δt_{sub})
Sync Point
Sync Point
Sync Point
Sync Point
Agent Time Step (Δt_{agent})
Molecule Time Step
B
Soluble Molecule Diffusion and Degradation (Δt_{pde})
Agent-Associated Reactions (Δt_{ode})
Sub-Step For Agent-Associated Reactions (Δt_{sub})
Sync Points
Sync Points
Sync Points

Significant numerical challenges with hybrid MSMs

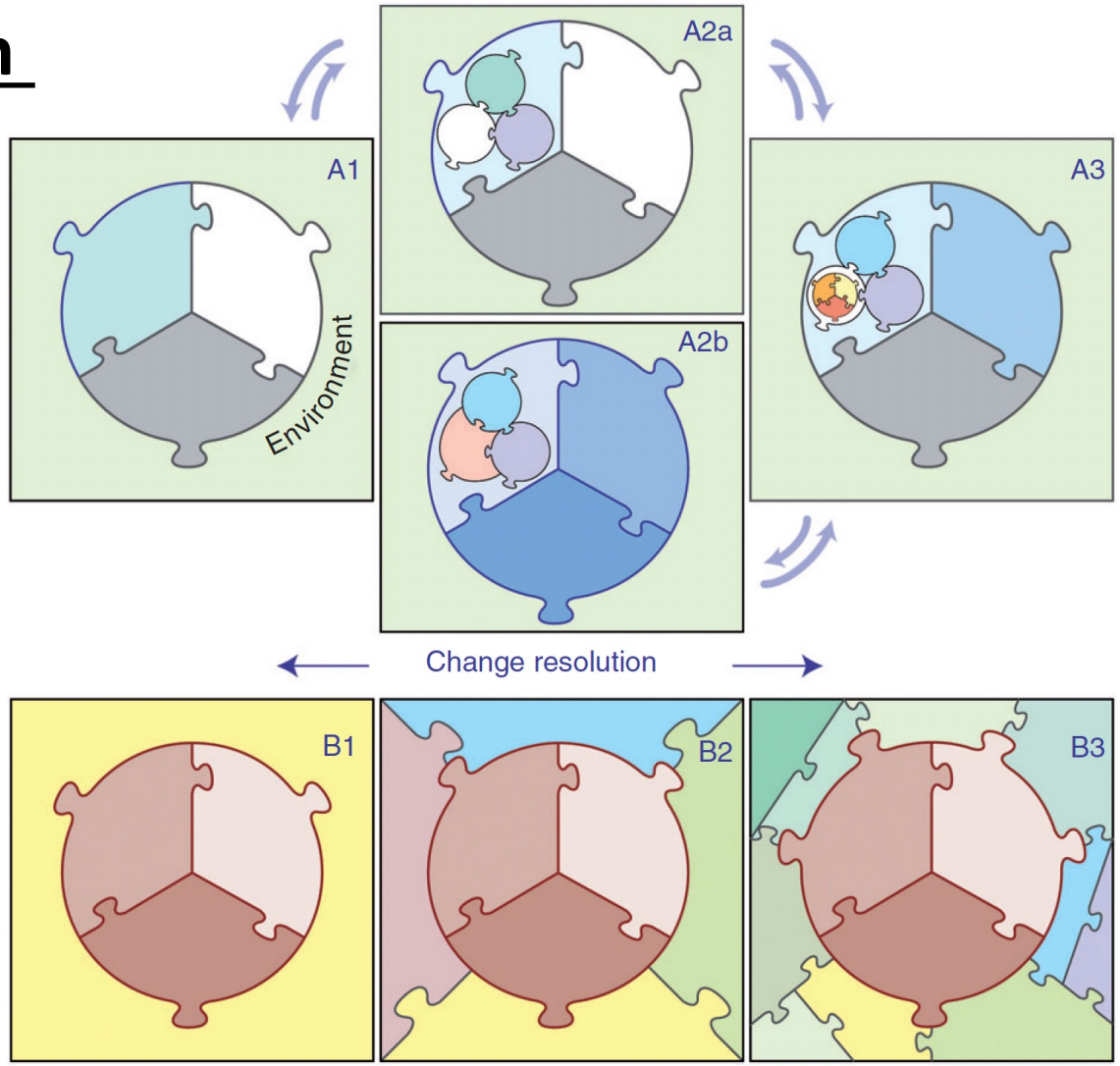


Coarse-grain versus Fine-grain Modeling

can help with computation

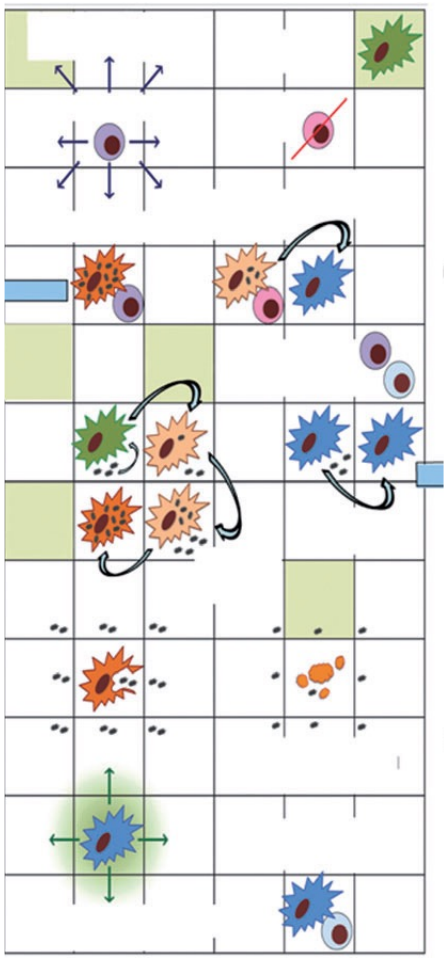


Tuneable resolution



Kirschner et al, **Tuneable resolution**
WIREs Syst Biol Med 2014, 6:289-309

Tuneable resolution- how does it work?



Complex ABM

-grid
-agents
-rules
-timescales

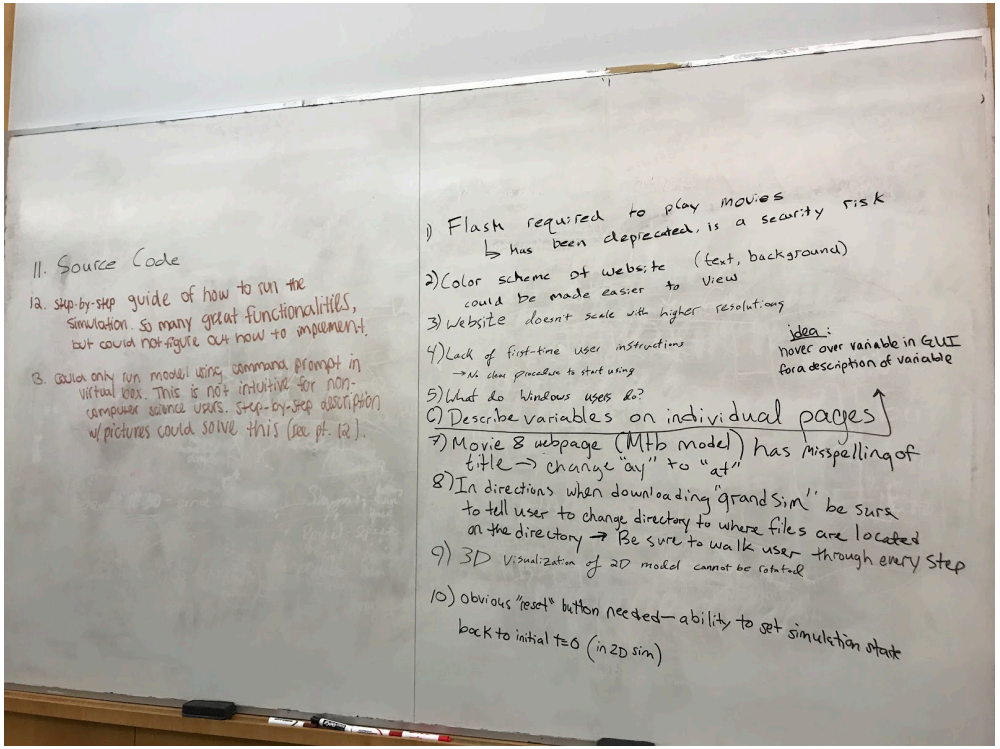
How do we ensure MSMs are robust/credible?

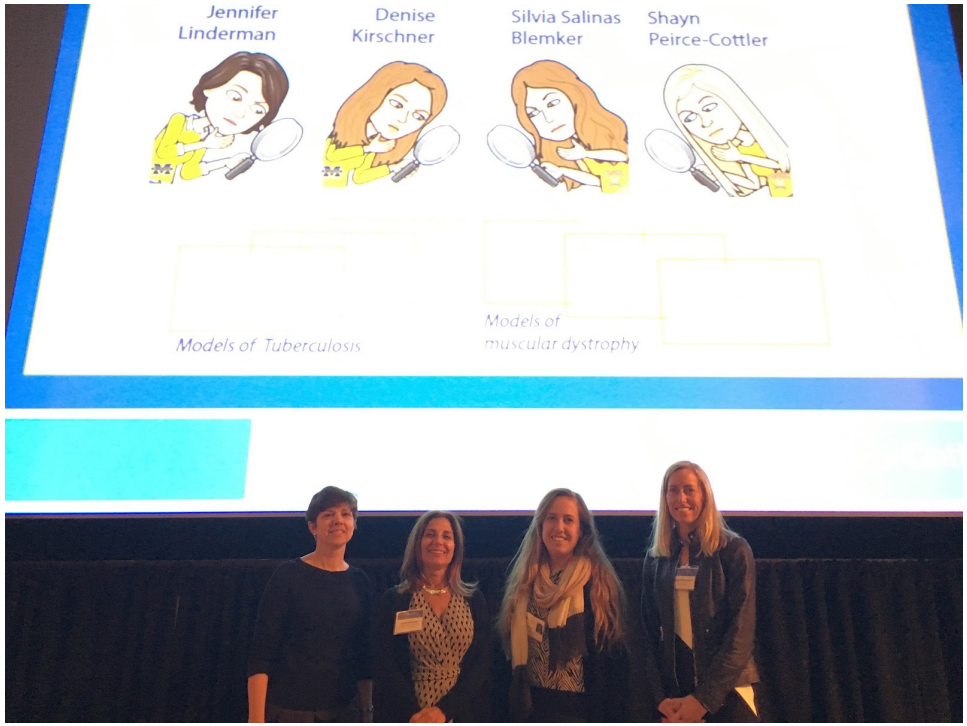
- **See Session 1.2 today after the coffee break!**

  Ahmet Erdemir, Jerry Myer, Lealem Mulugeta, Herbert Sauro

- **Created a team in Fall 2017 toward satisfying the 10 requirements of credibility:**

  -myself, Jennifer Linderman (UM) w/ Shayne Peirce-Cottler and Silvia Blemker (UVA)


11. Source Code
12. step-by-step guide of how to run the simulation. So many great functionalities, but could not figure out how to implement.
13. Could only run models using command prompt in virtual box. This is not intuitive for non-computer science users. Step-by-step description w/pictures could solve this (see pt. 12).
1) Flash required to play movies
→ has been depreciated, is a security risk
2) Color scheme of website (text, background) could be made easier to view
3) Website doesn't scale with higher resolutions
4) Lack of first-time user instructions
→ No clear procedure to start using
idea: hover over variable in GUI for a description of variable
5) What do Windows users do?
6) Describe variables on individual pages
7) Movie & webpage (Mtb model) has misspelling of title → change "ay" to "at"
8) In directions when downloading "grandSim" be sure to tell user to change directory to where files are located on the directory → Be sure to walk user through every step
9) 3D visualization of 2D model cannot be rotated
10) obvious "reset" button needed—ability to set simulation back to initial t=0 (in 2D sim)


Jennifer Linderman
Denise Kirschner
Silvia Salinas Blemker
Shayn Peirce-Cottler
Models of Tuberculosis
Models of muscular dystrophy

How do we analyze MSMs?

- Traditional equation-based analyses are not always available to us with hybrid MSMs
    - Stability
    - Bifurcation
    - Correlations
    - Ro
    - Existence/uniqueness
    - etc

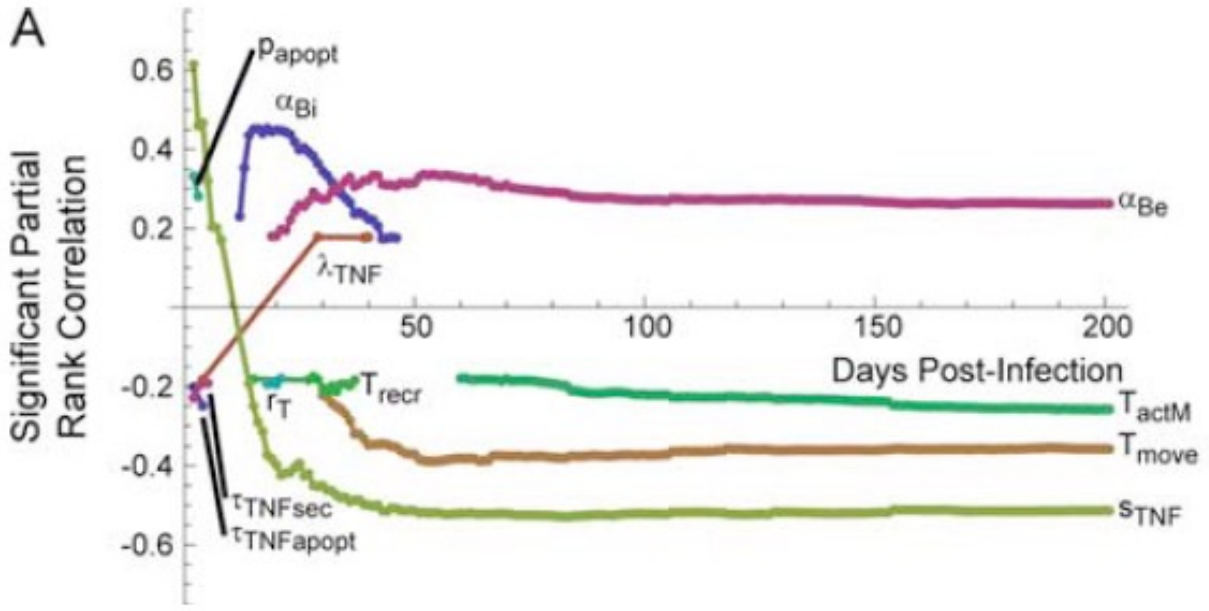
Key Analysis Tools

- **Uncertainty Analysis - determines how much variability in outcome is induced by variability in parameter values**
  Latin Hypercube Sampling (LHS) or Sobol
- **Sensitivity Analysis– measures which parameters induce this variability and ranks the correlations** ***Partial Rank Correlation (PRCC) and eFAST***
- ***KEY FEATURE - can quantify relationships over time***

- ***Simeone Marino, Ian B. Hogue, Christian J. Ray, Denise E. Kirschner. A Methodology For Performing Global Uncertainty and Sensitivity Analysis in Systems Biology Journal of Theoretical Biology, Vol 254, pp 178-196, 2008***

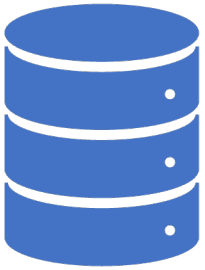
programs available on our website in MATLAB and R

Results of Sensitivity Analysis: Significant PRCCs
What factors distinguish different outcomes (CFU)?



How do we validate MSMs?

Part of credibility process



Ties to types of data available

Ex: Validation to Pharmacokinetic data for a drug Bedaquiline

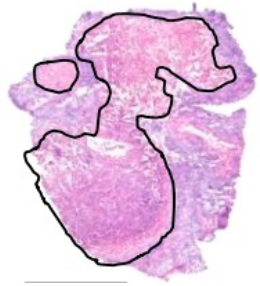
Spatial analysis

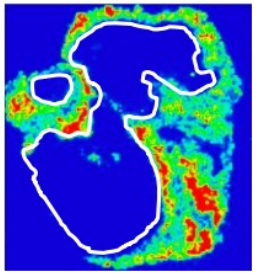
Granuloma
(white outline: caseum)

Drug distribution within granuloma

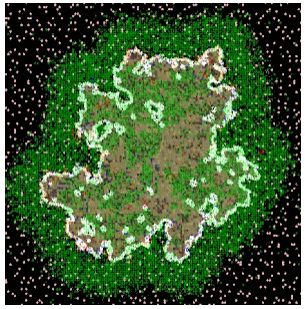
Human data

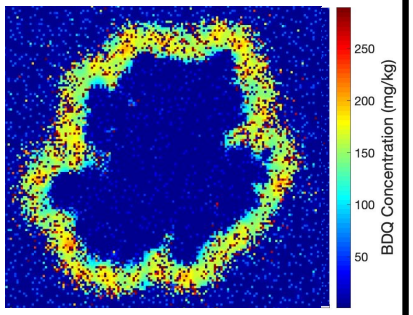
Prideaux *et al*. *Nat. Med.* (2015)



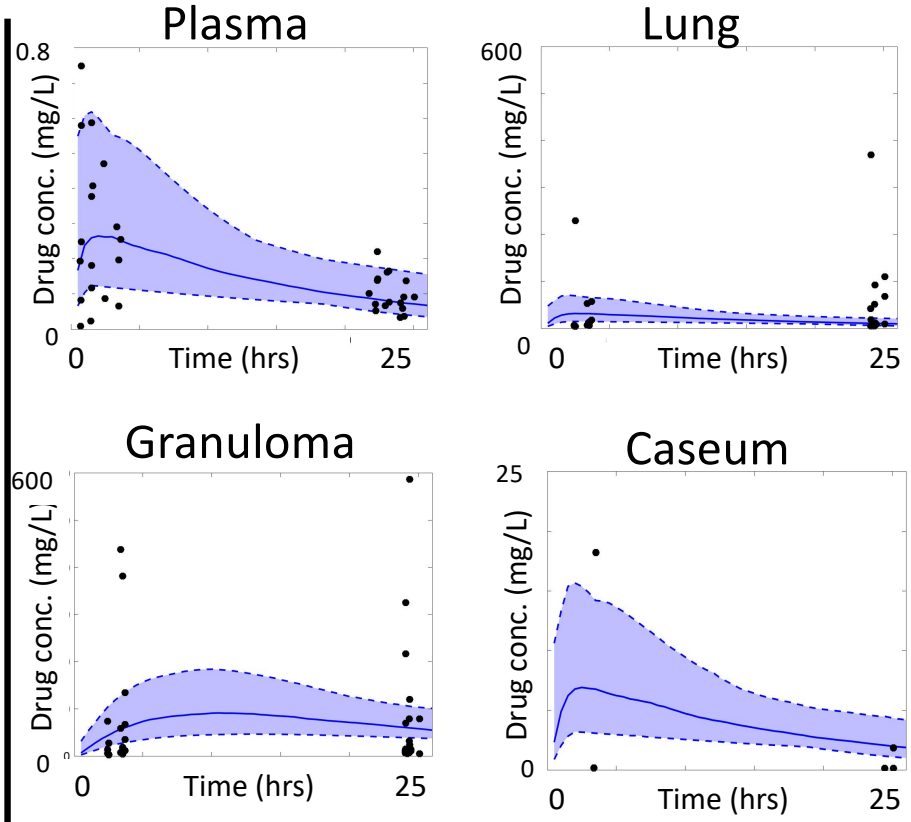


GranSim data



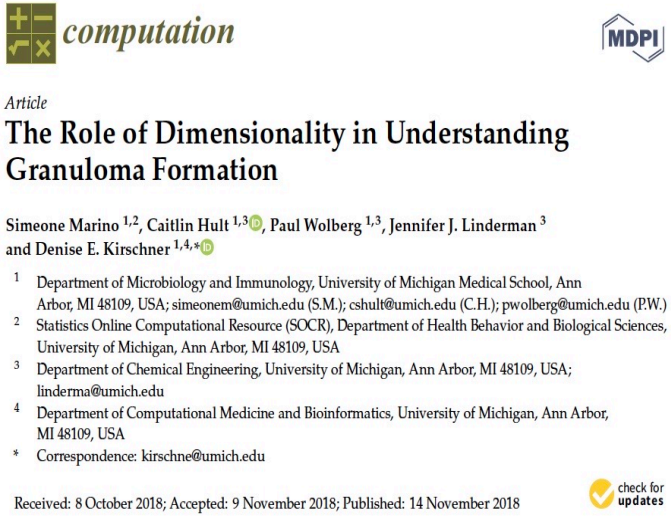


Temporal analysis



2D vs. 3D issues in multi-scale modeling

- Most of biology is 3 dimensional
- Most people model in 2 dimensions
- HOW WRONG/OK IS THAT? In other words:
  1) When are we safe using a 2D model?
  2) We propose a methodology for scaling 2D model outputs to compare with 3D experimental datasets



computation

MDPI

Article

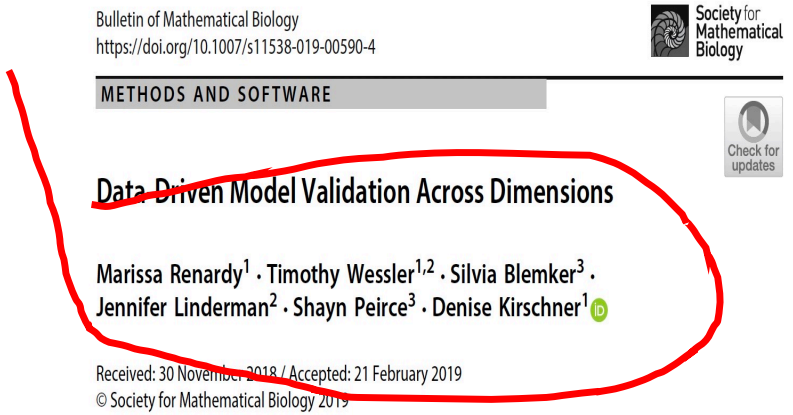
The Role of Dimensionality in Understanding Granuloma Formation

Simeone Marino [1,2], Caitlin Hult [1,3], Paul Wolberg [1,3], Jennifer J. Linderman [3] and Denise E. Kirschner [1,4,*]

1 Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI 48109, USA; simeonem@umich.edu (S.M.); cshult@umich.edu (C.H.); pwolberg@umich.edu (P.W.)
2 Statistics Online Computational Resource (SOCR), Department of Health Behavior and Biological Sciences, University of Michigan, Ann Arbor, MI 48109, USA
3 Department of Chemical Engineering, University of Michigan, Ann Arbor, MI 48109, USA; linderma@umich.edu
4 Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA
* Correspondence: kirschne@umich.edu

Received: 8 October 2018; Accepted: 9 November 2018; Published: 14 November 2018

check for updates



Bulletin of Mathematical Biology
https://doi.org/10.1007/s11538-019-00590-4

Society for Mathematical Biology

METHODS AND SOFTWARE

Check for updates

Data-Driven Model Validation Across Dimensions

Marissa Renardy[1] · Timothy Wessler[1,2] · Silvia Blemker[3] · Jennifer Linderman[2] · Shayn Peirce[3] · Denise Kirschner[1]

Received: 30 November 2018 / Accepted: 21 February 2019

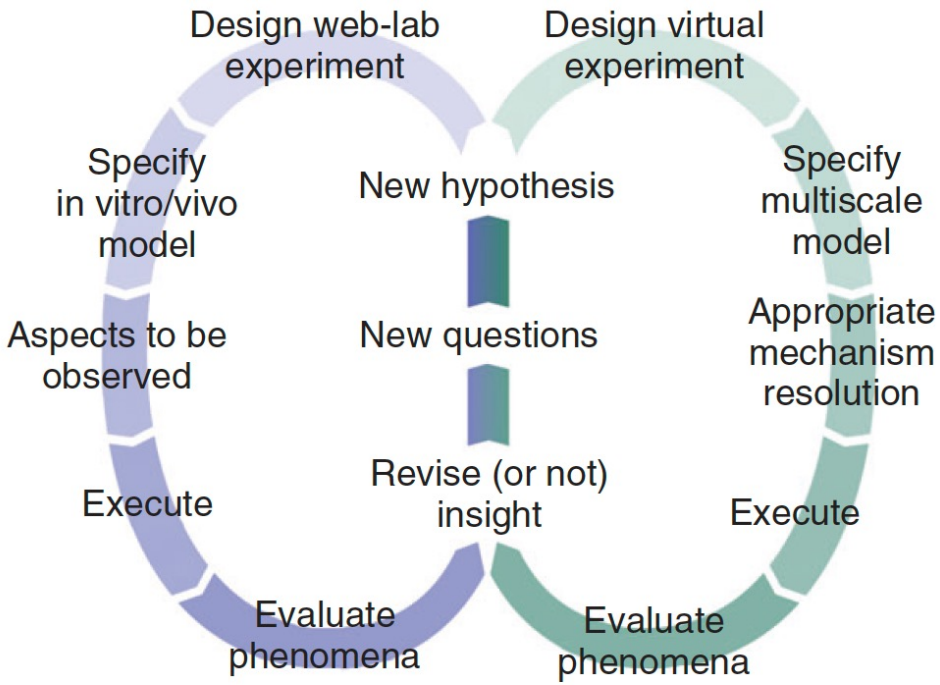
How can MSMs be useful?

- ***Past and current applications from just our work-***
  - Tuberculosis immune response in lungs
  - Inner workings of the lymph nodes during health and infection
  - Blood as a reflective compartment of lungs
  - TB Drug regimens
  - Vaccine efficacy
  - Epidemiology of TB
  - COVID-19 spin off
  - Tumor modeling spin off
  - Modeling tools for building and studying MSMs
- ***Future applications of our work-***
  - Creation of a Digital partner/twin
  - Virtual City
  - Other?

Yin and Yang of biological modeling

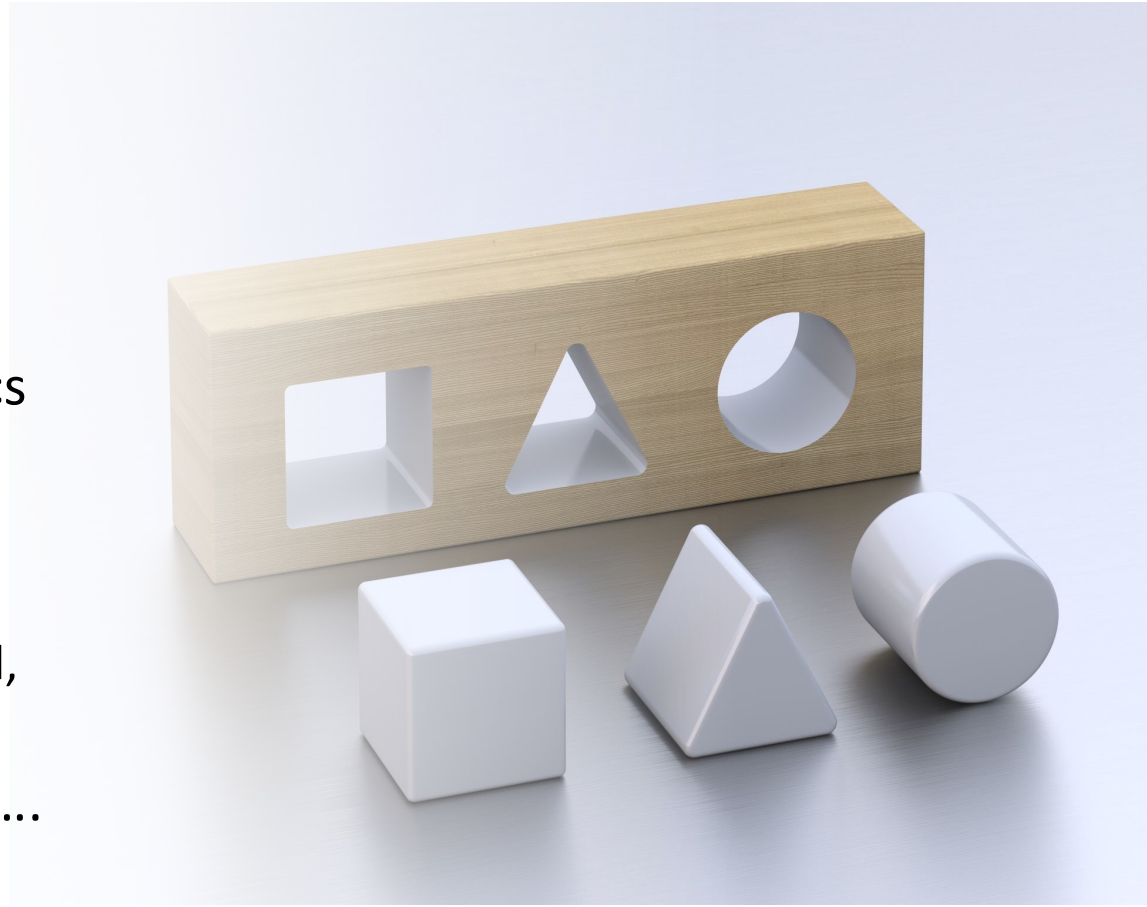
Coupled wet-lab and in silico studies for validation and prediction:

- Two cycles intersect to:
- *generate hypotheses*
- *pose new questions*
- *iteration is key!*



Where to go from here?? Now that we have tackled MSMs…

- Crosstalk with other projects to share ideas/models?
- Could be a big project consortium be next (e.g. digital twins) ?
- As a math person..are mathematics still interesting/needed?
- More advanced applications?
  - ..COVID-19, flu, HIV, TB, malaria, cancer, politics, climate, justice, food, antibiotic resistance, heart disease…
- Mechanistic modeling soap box…….
  - *Is AI/ML the next answer??…….*



PERSPECTIVE
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Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead

Cynthia Rudin

Black box machine learning models are currently being used for high-stakes decision making throughout society, causing problems in healthcare, criminal justice and other domains. Some people hope that creating methods for explaining these black box models will alleviate some of the problems, but trying to explain black box models, rather than creating models that are interpretable in the first place, is likely to perpetuate bad practice and can potentially cause great harm to society. The way forward is to design models that are inherently interpretable. This Perspective clarifies the chasm between explaining black boxes and using inherently interpretable models, outlines several key reasons why explainable black boxes should be avoided in high-stakes decisions, identifies challenges to interpretable machine learning, and provides several example applications where interpretable models could potentially replace black box models in criminal justice, healthcare and computer vision.

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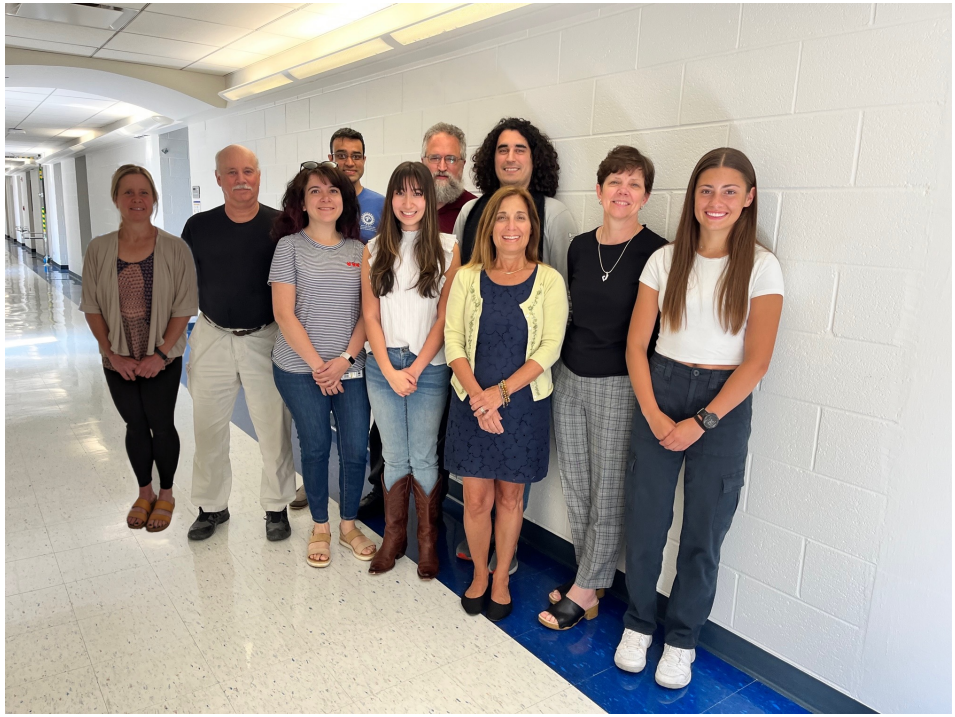

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