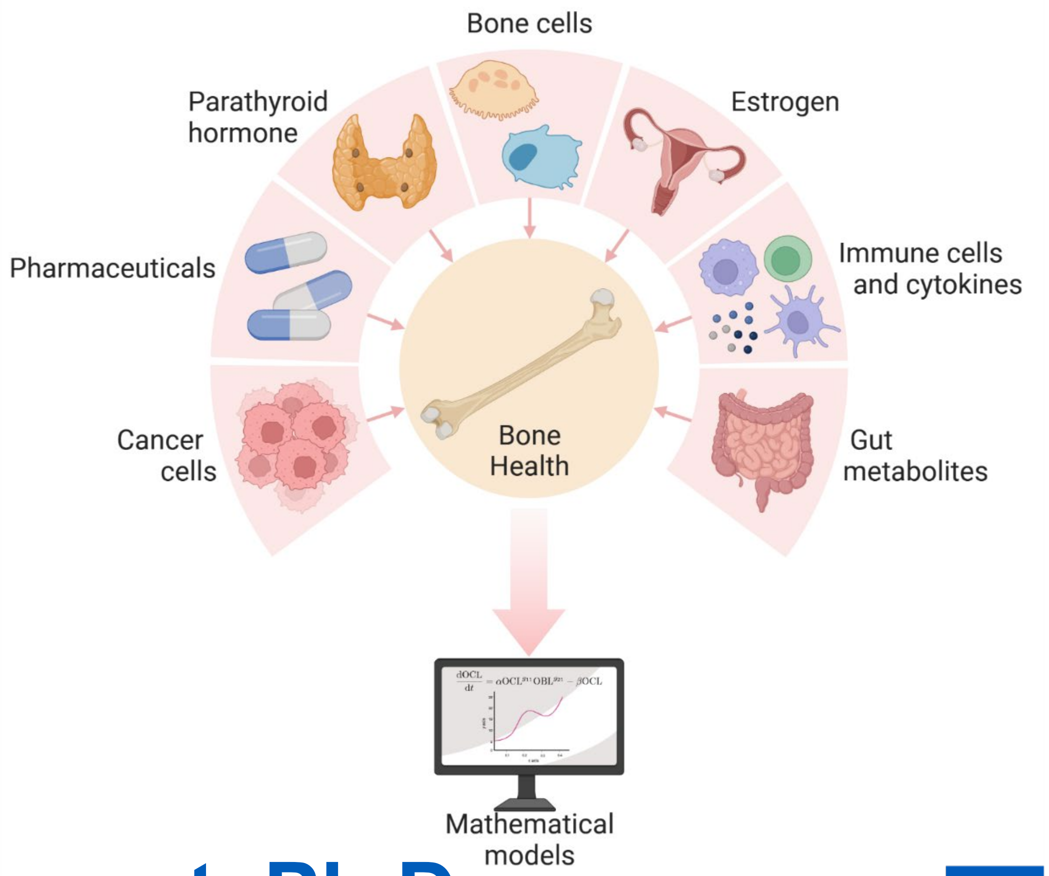
Systems Biology Challenges for Control of Human Diseases



Ashlee N. Ford Versypt, Ph.D.
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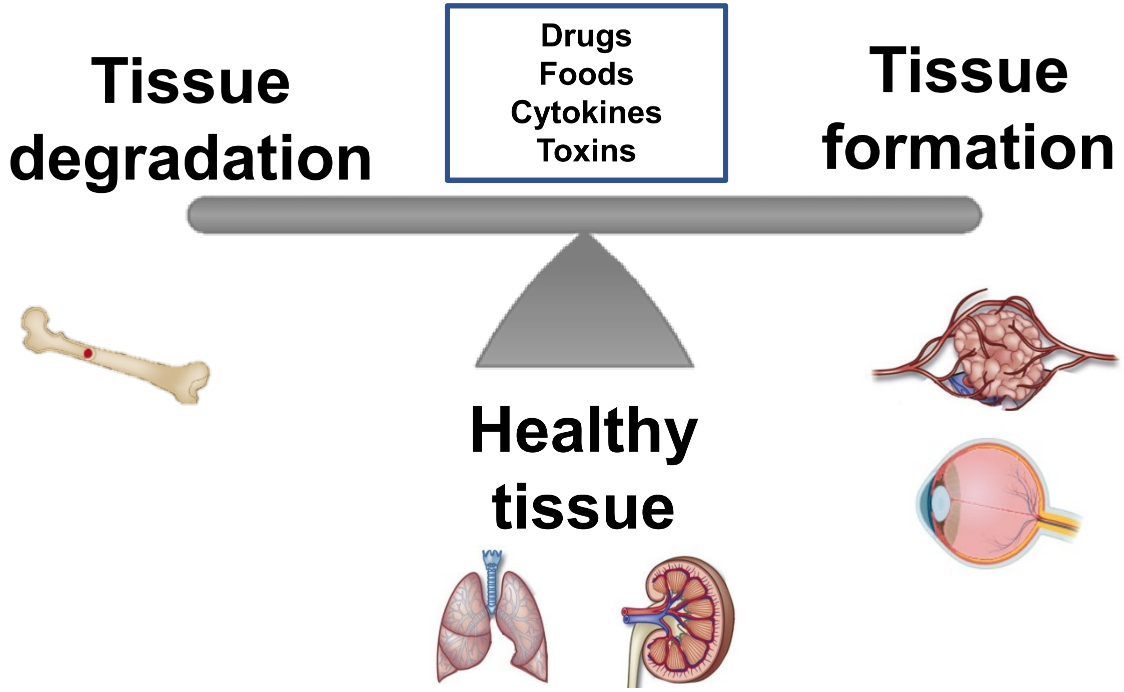
University at Buffalo
The State University of New York

Systems Biomedicine & Pharmaceutics

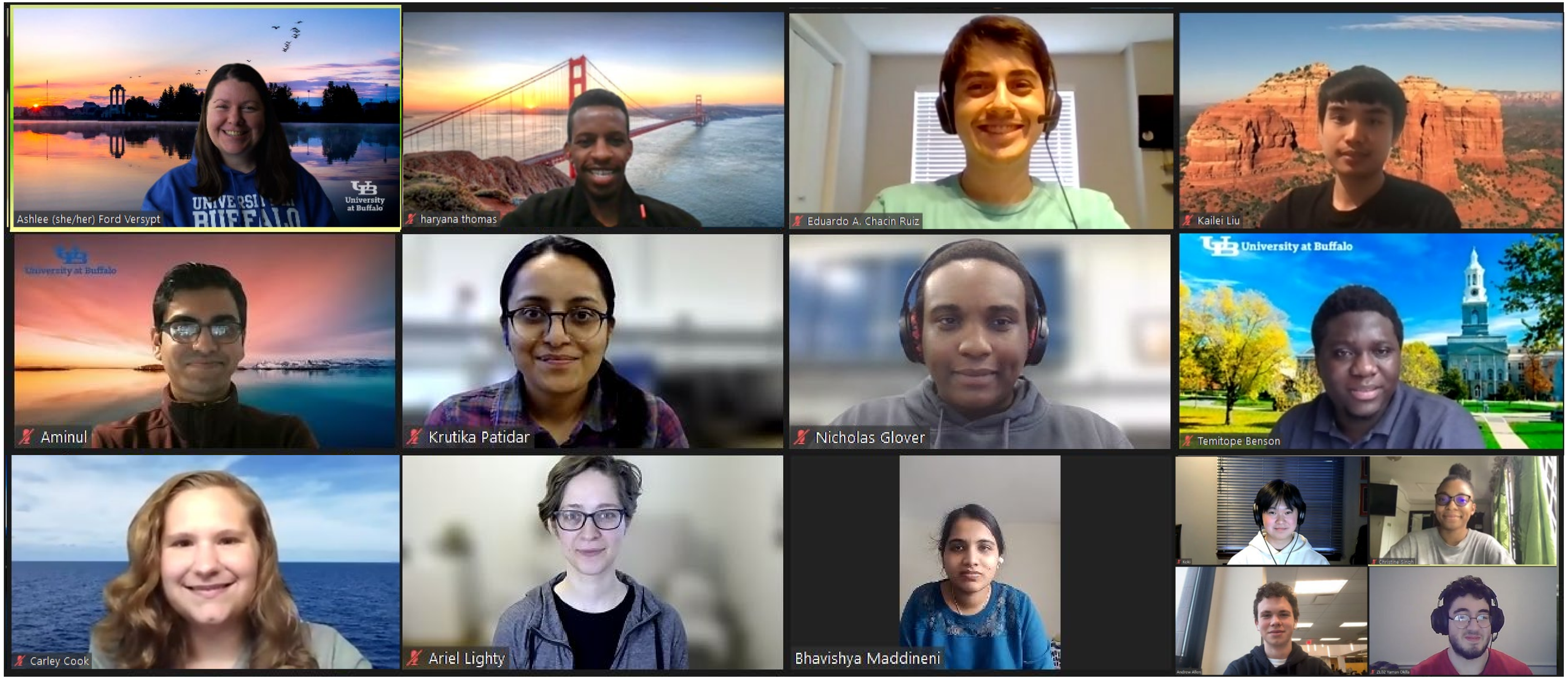
Multiscale Modeling of Tissue Remodeling, Damage, and Treatments



Ashlee N. Ford Versypt, Ph.D.
Chemical & Biological Engineering
Affiliate: Biomedical Engineering, Institute for Artificial Intelligence & Data Science

University at Buffalo
The State University of New York

Research team & sponsors



NIGMS R35 MIRA, NIBIB R01,
NIA R21, NICCH R15

NIH National Institutes of Health
Turning Discovery Into Health

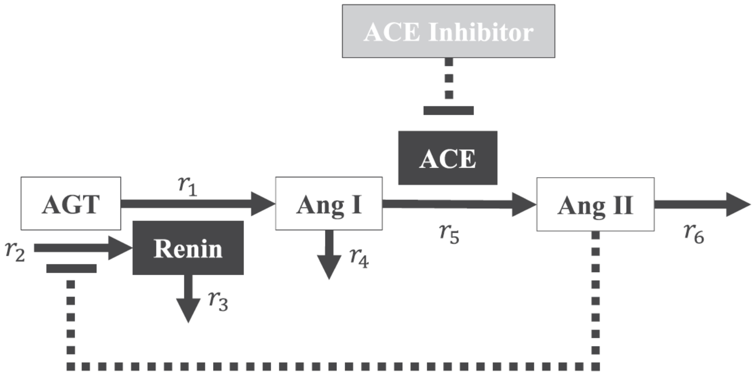
NSF
CAREER

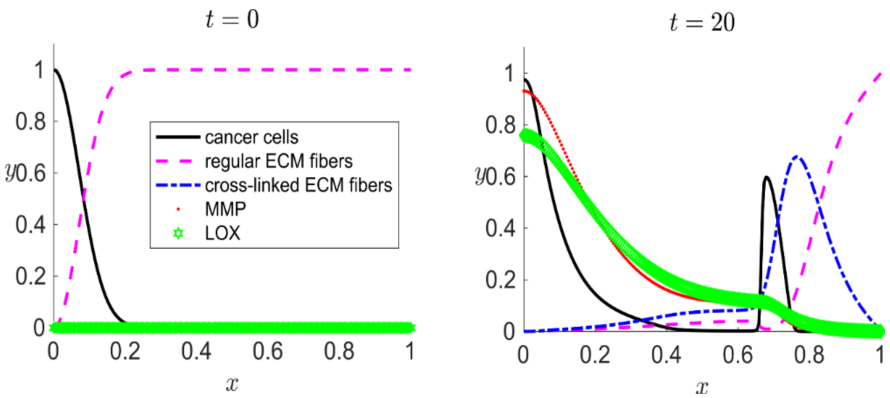
UB University at Buffalo

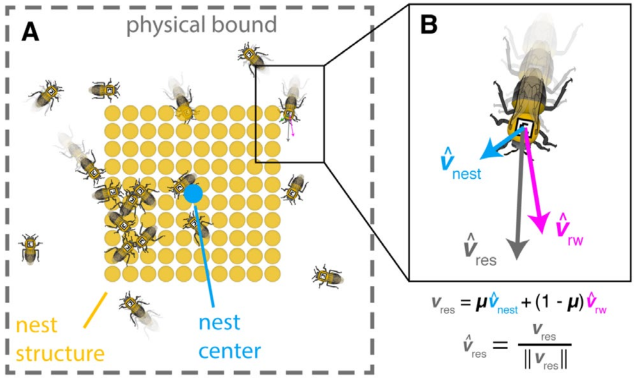
SUNY The State University of New York

My lab builds models for two types of problems

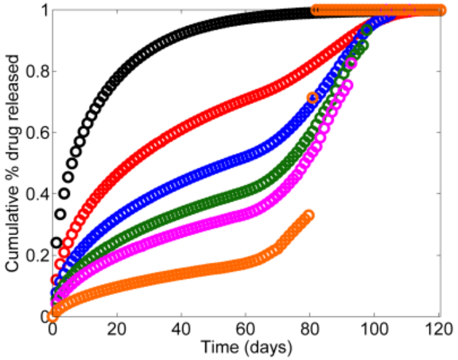
Kinetics modeling for biomolecules, cells, or organisms that react, interact, and/or change state in biochemical networks

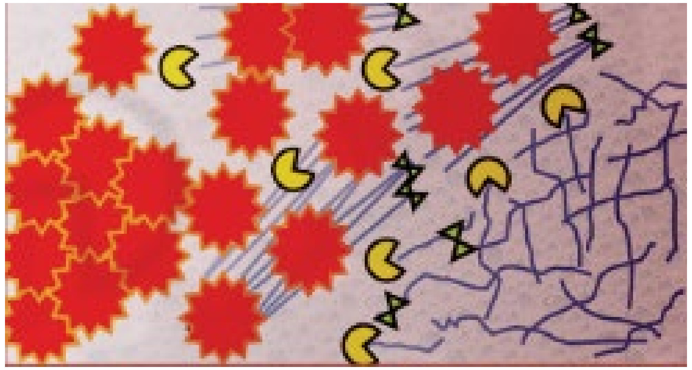


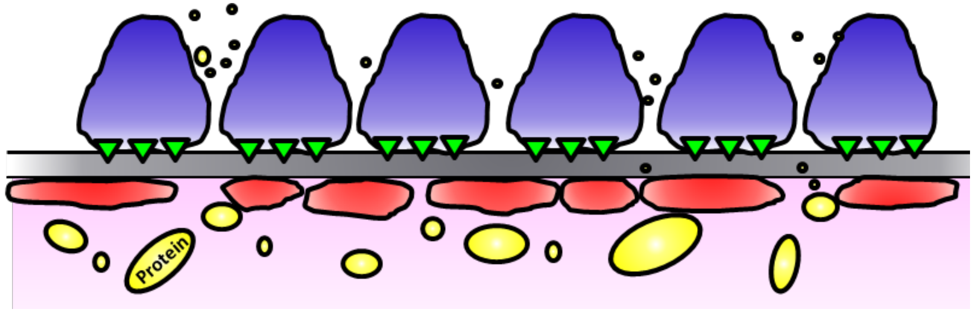




Mass transport of small molecules, macromolecules, and cells in reacting, heterogenous, porous biomaterials (engineered or natural)

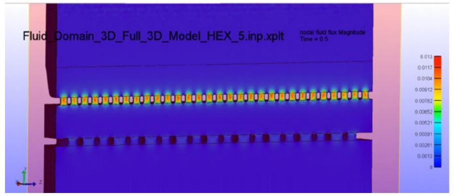






My lab uses a wide range of methods, all computational/mathematical

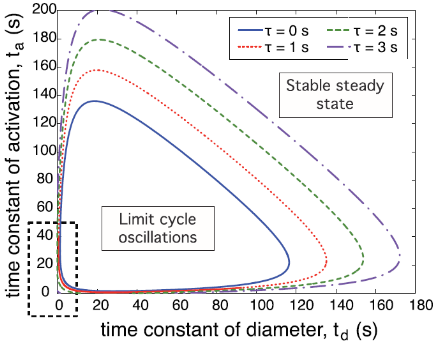
Finite element modeling: fluid dynamics & biomechanics



Differential equations (ordinary & partial) & numerical methods

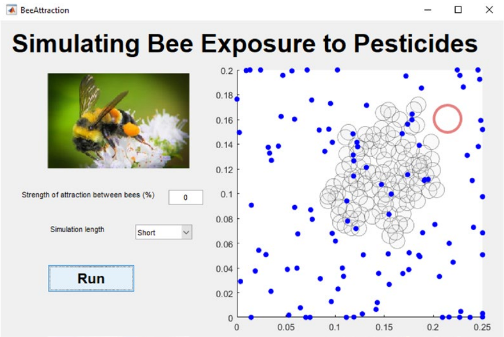
$$\frac{d[\mathrm{ANGI}]}{dt} = \mathrm{PRA} - (c_{\mathrm{ACE}} + c_{\mathrm{nonACE}})[\mathrm{ANGI}] - \frac{\ln(2)}{h_{\mathrm{ANGI}}}[\mathrm{ANGI}]$$

$$\frac{d[\mathrm{ANGII}]}{dt} = (c_{\mathrm{ACE}} + c_{\mathrm{nonACE}})[\mathrm{ANGI}] - (c_{\mathrm{ACE2}} + c_{\mathrm{APA}})[\mathrm{ANGII}]$$

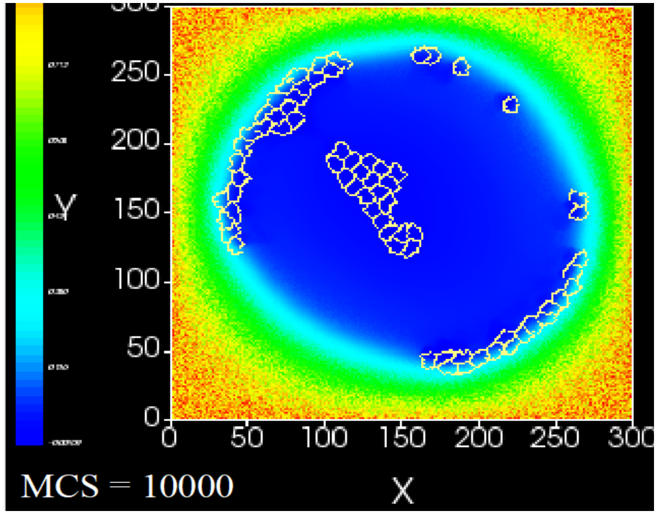


Dynamic systems, PSE, & data analysis

Programming & GUI development in Python, MATLAB



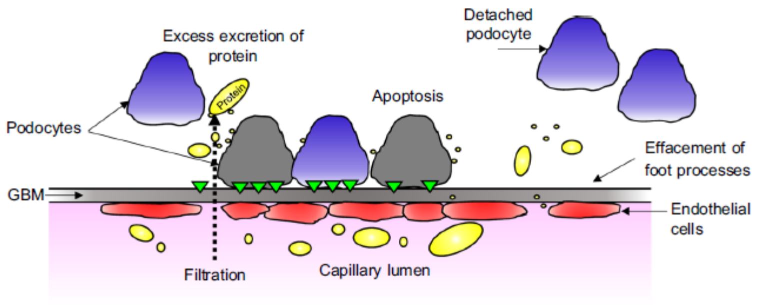
Agent-based modeling



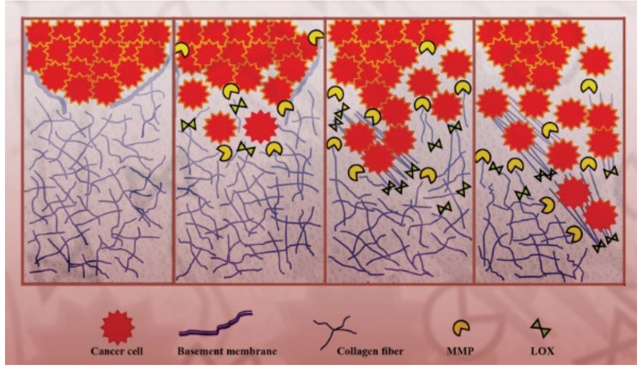
Systems Biomedicine & Pharmaceutics Lab

Multiscale Modeling of Tissues, Treatments, & Toxicology

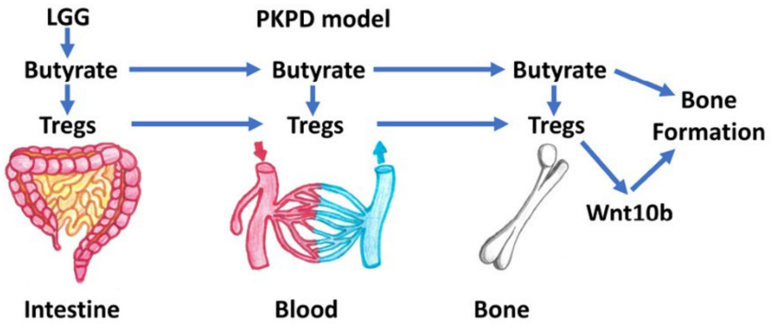
Diabetic Kidney Disease



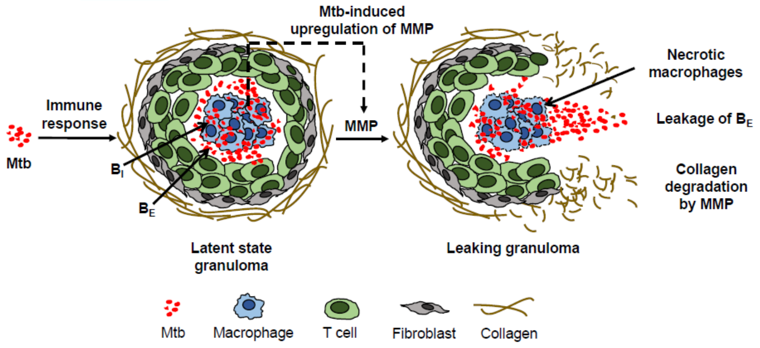
Cancer Metastasis & Cell Migration



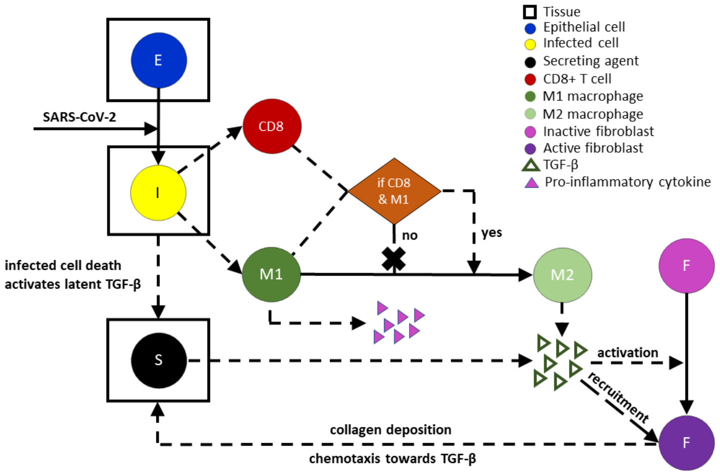
Gut-Immune-Bone Axis



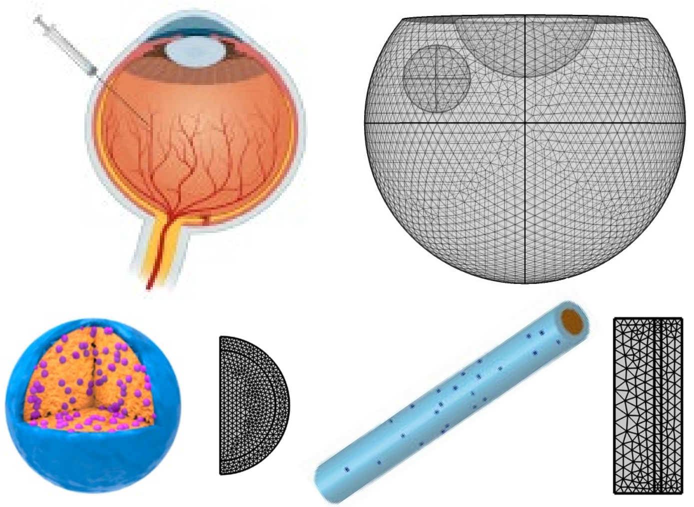
Immunology & Immunotherapy



Lung Infection & Fibrosis



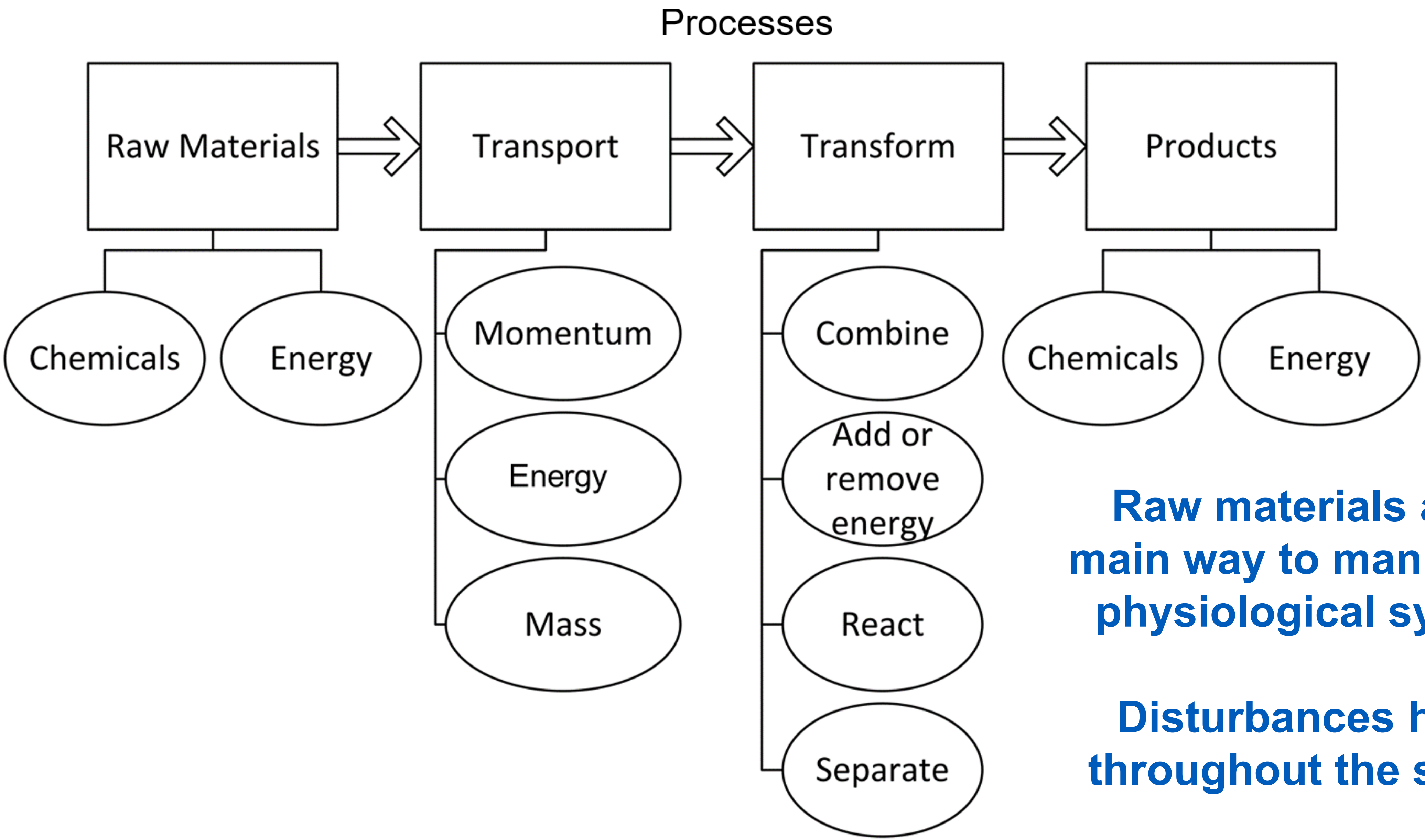
Eye Drug Delivery



Challenges for control of human diseases

- **Limited manipulated variables**

Limited manipulated variables in physiological processes



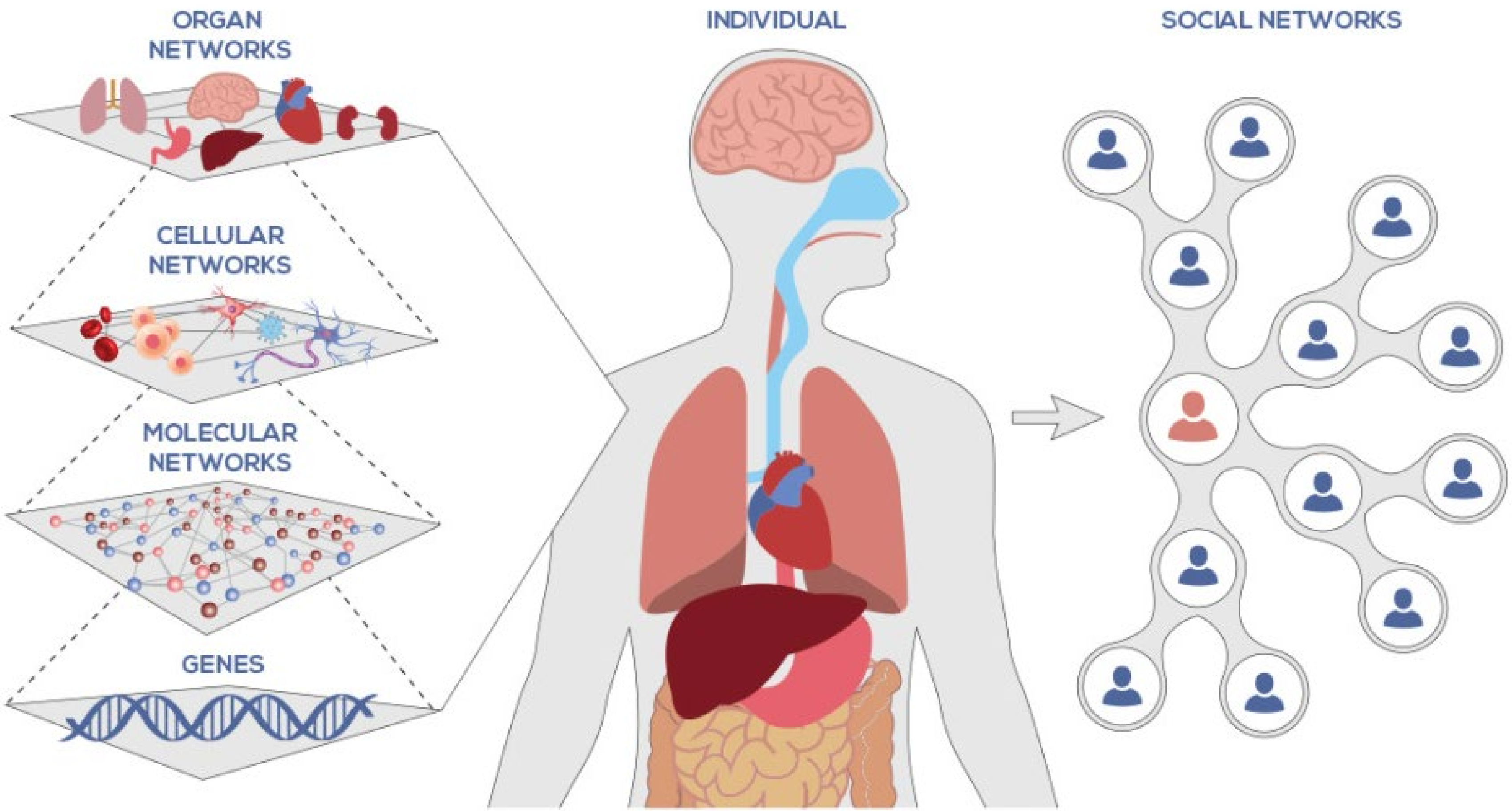
Raw materials are the main way to manipulate physiological systems

Disturbances happen throughout the system

Challenges for control of human diseases

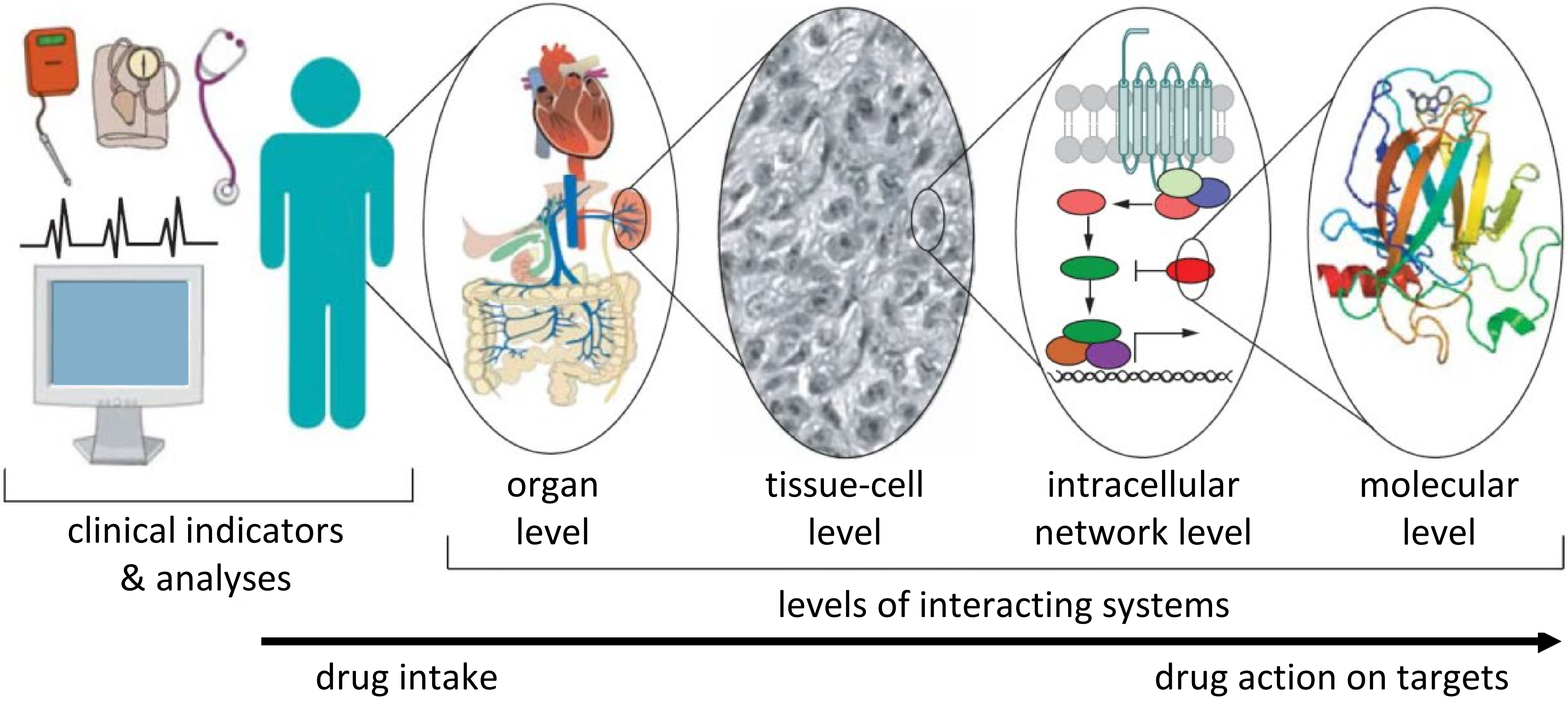
- **Limited manipulated variables**
- **Multiscale (space and time) interacting systems**

Multiscale systems biomedicine considers network interactions across length & time scales



Institute for Systems Biology
https://systemsbiology.org/about/what-is-systems-biology/

Multiscale systems biomedicine is the translational counterpart to systems biology



Wist et al., *Genome Med*, 2009

Time scales can be quite separated in chronic diseases

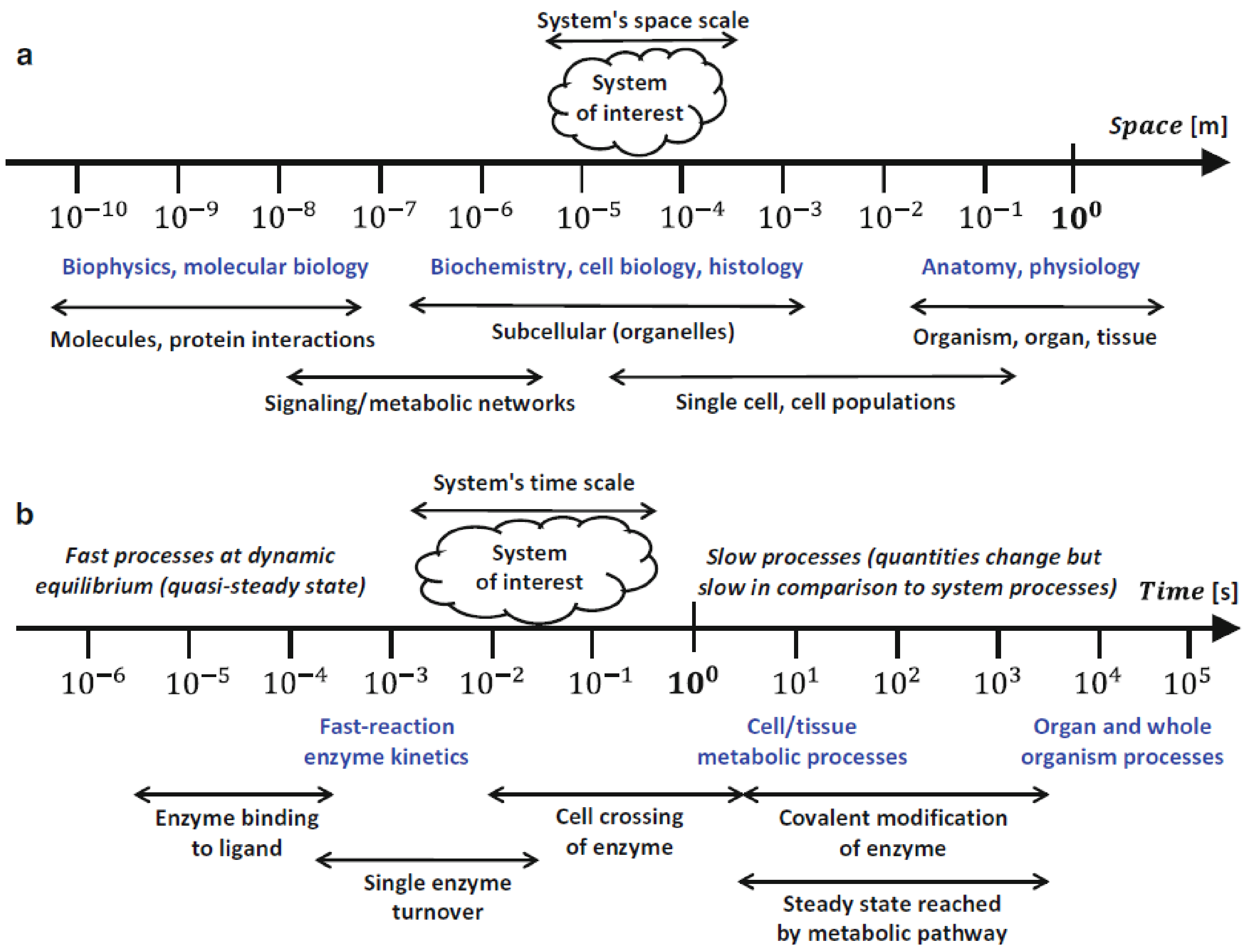


Fig. 1 Conceptualization of a biomedical system (cloud shape) and its associated spatiotemporal (part (**a**) shows space and (**b**) time scales) and organizational scales [8]

Mizeranschi et al. in *Systems Medicine,* Springer, 2016

…chronic conditions 10^9

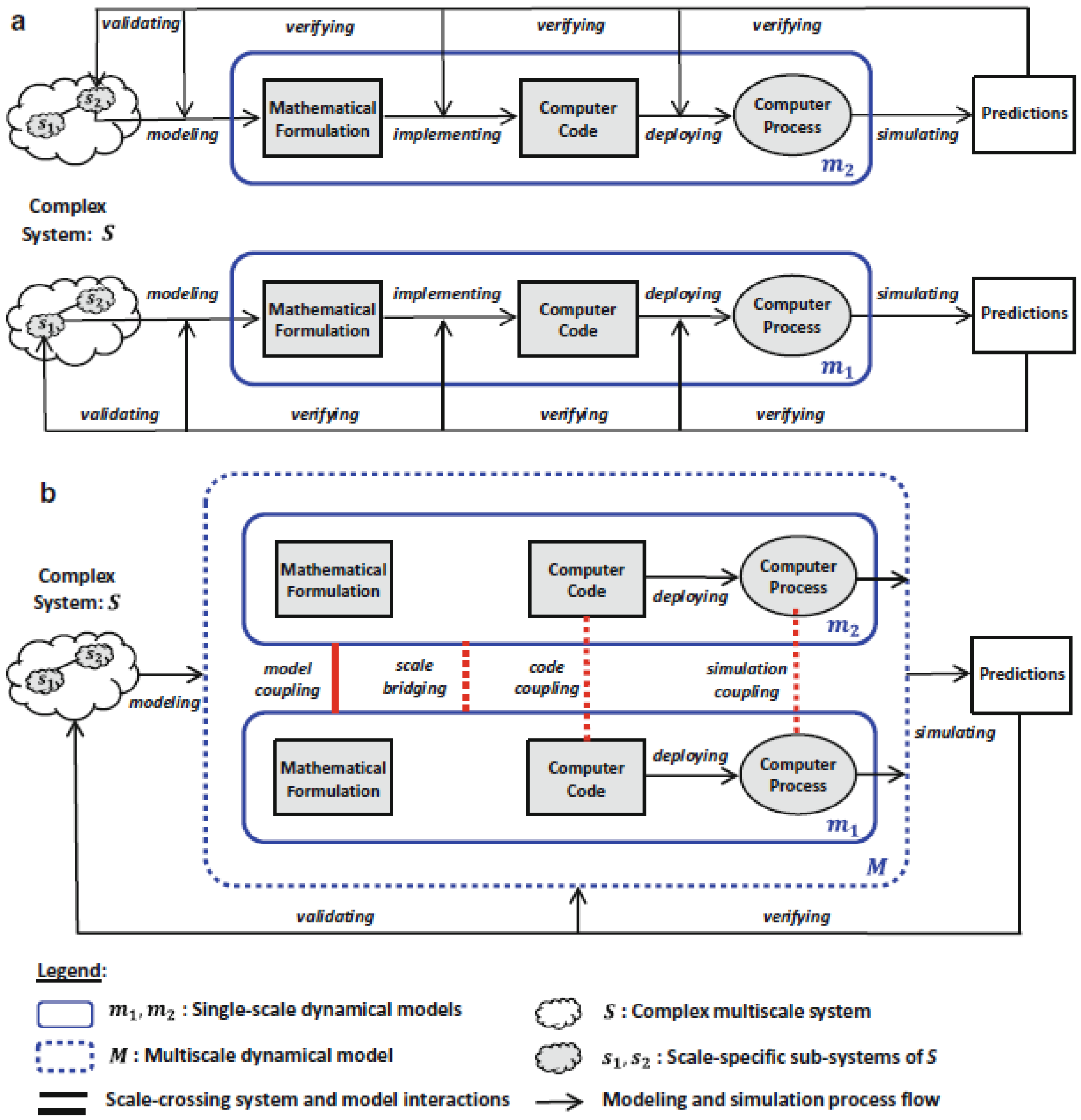


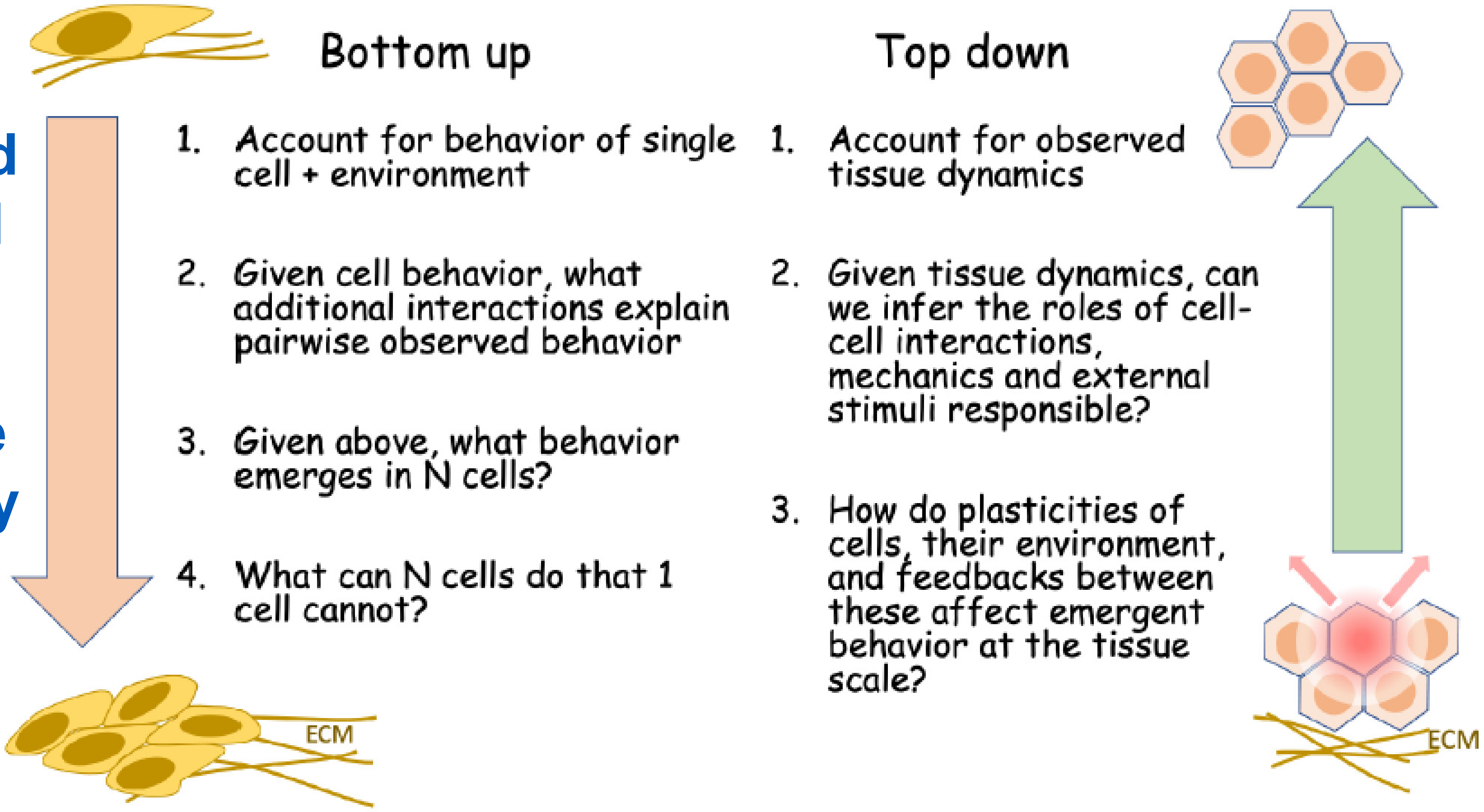
Fig. 3 Components and processes of multiscale modeling and simulation approaches. (**a**) Development of multiple (two in this case) single-scale dynamical models. (**b**) Coupling of multiple (two in this case) single-scale models to form a multiscale dynamical model

Mizeranschi et al. in *Systems Medicine,* Springer, 2016

Modeling approaches are often selected based on the questions of interest—must make simplifications somewhere

Agent-based models and biophysics

Can include stochasticity



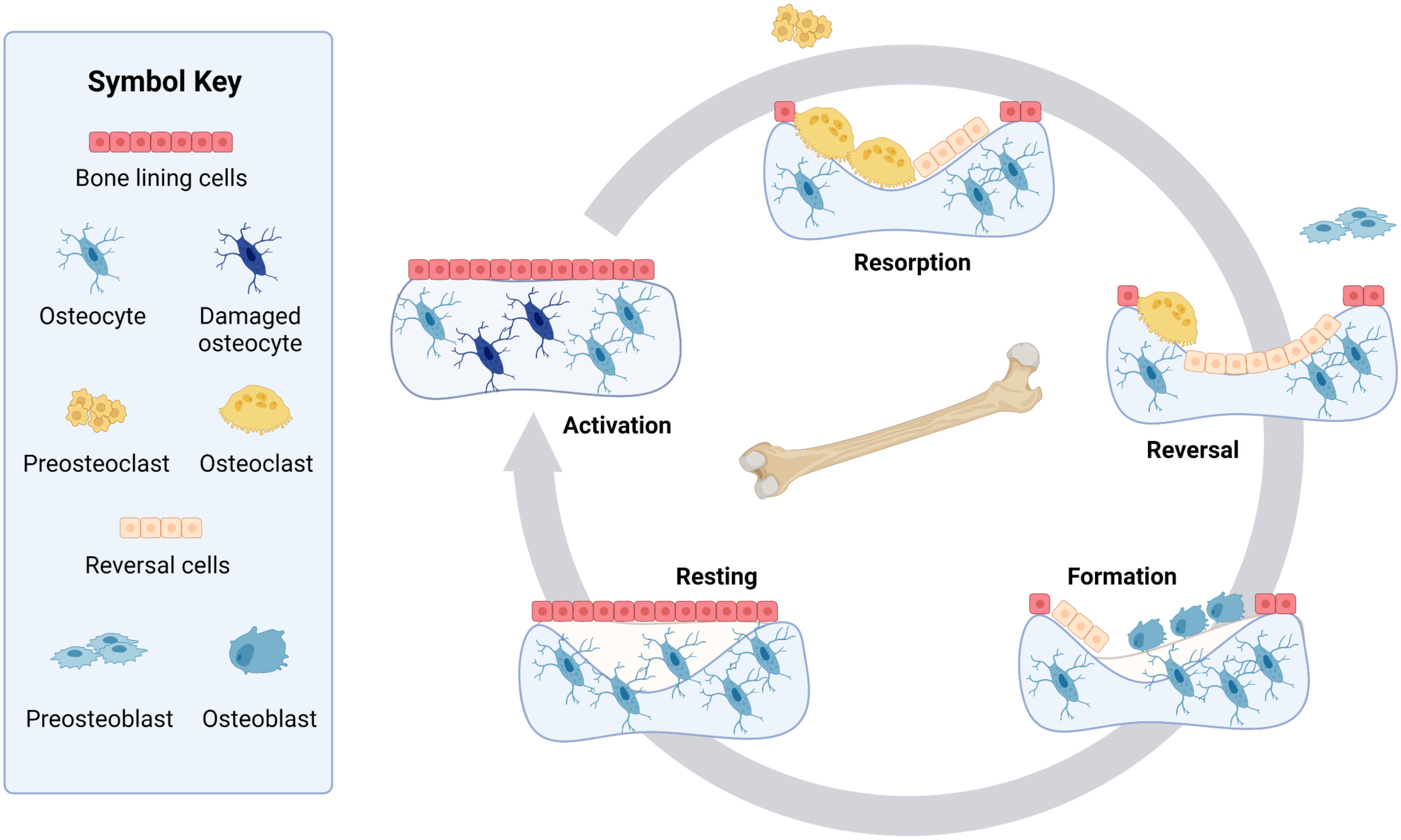
Generally ODEs, PDEs, or data-driven models

Often deterministic approaches are used

Fig 3. Modeling goals can be classified into broad categories that span levels of hierarchy. Some models attempt to span knowledge of single cell behavior plus interactions to predict emergent multicellular behavior (bottom up, left), whereas others start with observations of tissue dynamics and seek to infer underlying rules, feedbacks, and cell-cell (c-c) interactions that lead to those observations (top down, right).

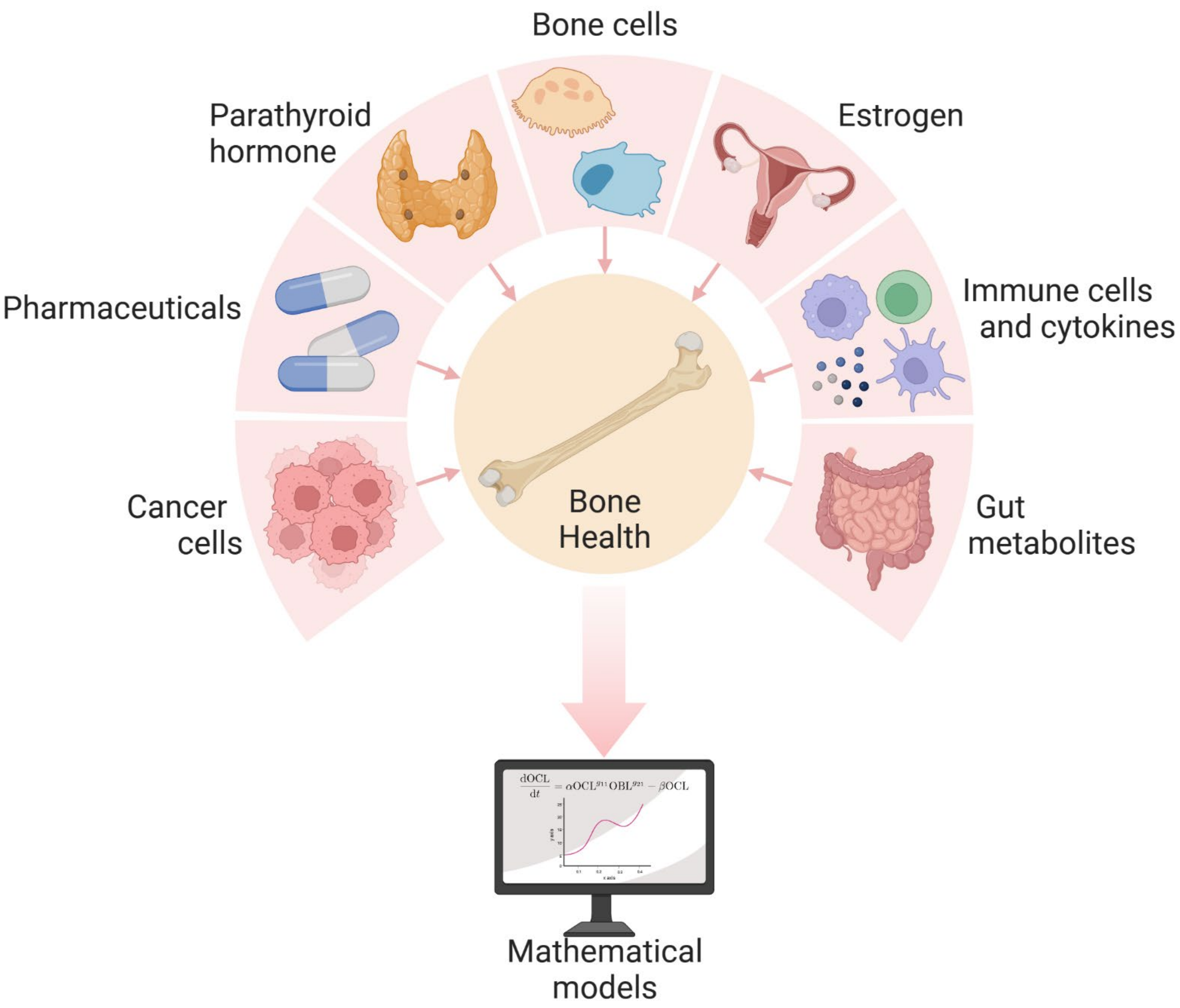
Buttenschon & Edelstein-Keshet, *PLOS Comp Biol*, 2020

We study disturbances to the bone remodeling cycle & dietary stimuli to restore homeostasis



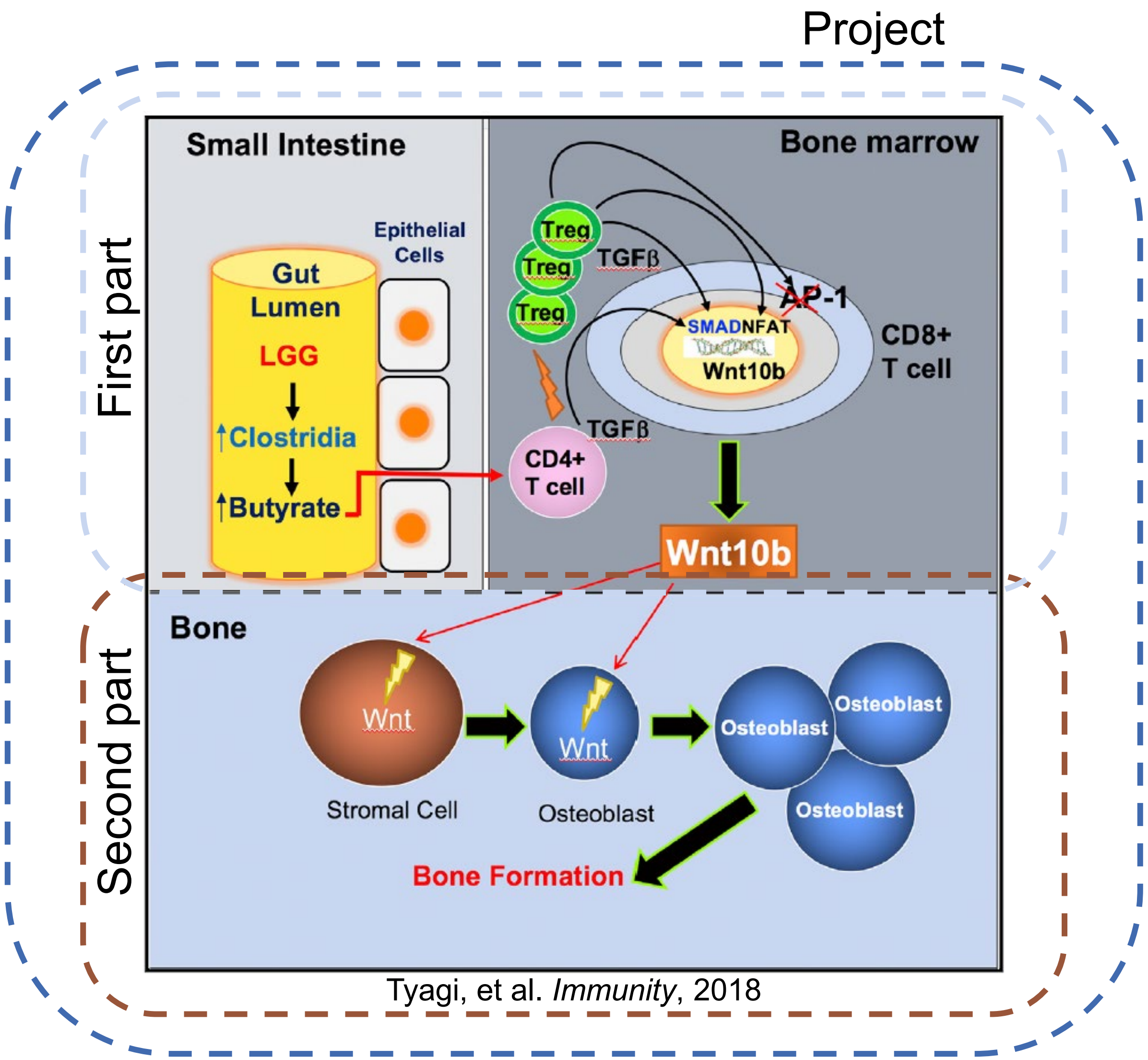
Cook, Lighty, Smith, Ford Versypt, *Front Syst Biol*, 2024

Many systemic factors can influence the bone remodeling cycle



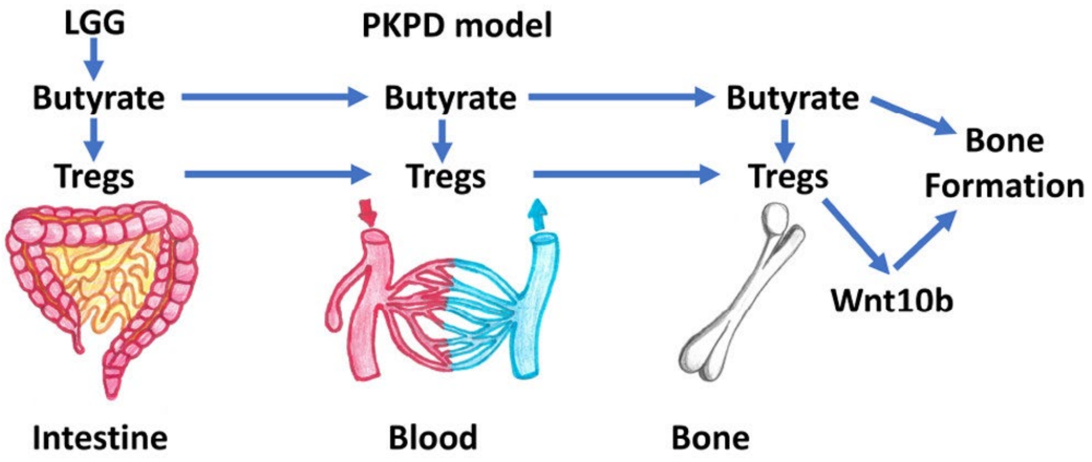
Cook, Lighty, Smith, Ford Versypt, *Front Syst Biol*, 2024

First objective: Mathematical modeling of gut-bone axis and implications of butyrate treatment on bone



Tyagi, et al. *Immunity*, 2018

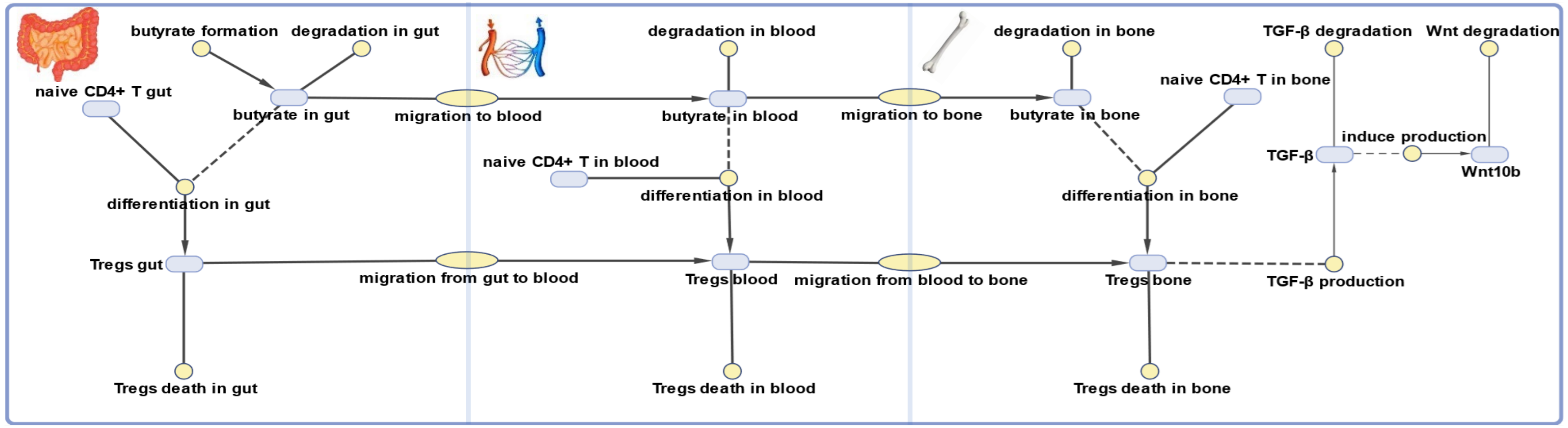
- **Create a multi-compartment PBPK model to track and quantify effects of butyrate on Tregs in gut, blood, and bone**
- **Connect Wnt10b expression enhanced by Tregs to bone remodeling**
- **Validate the model with experimental observations**

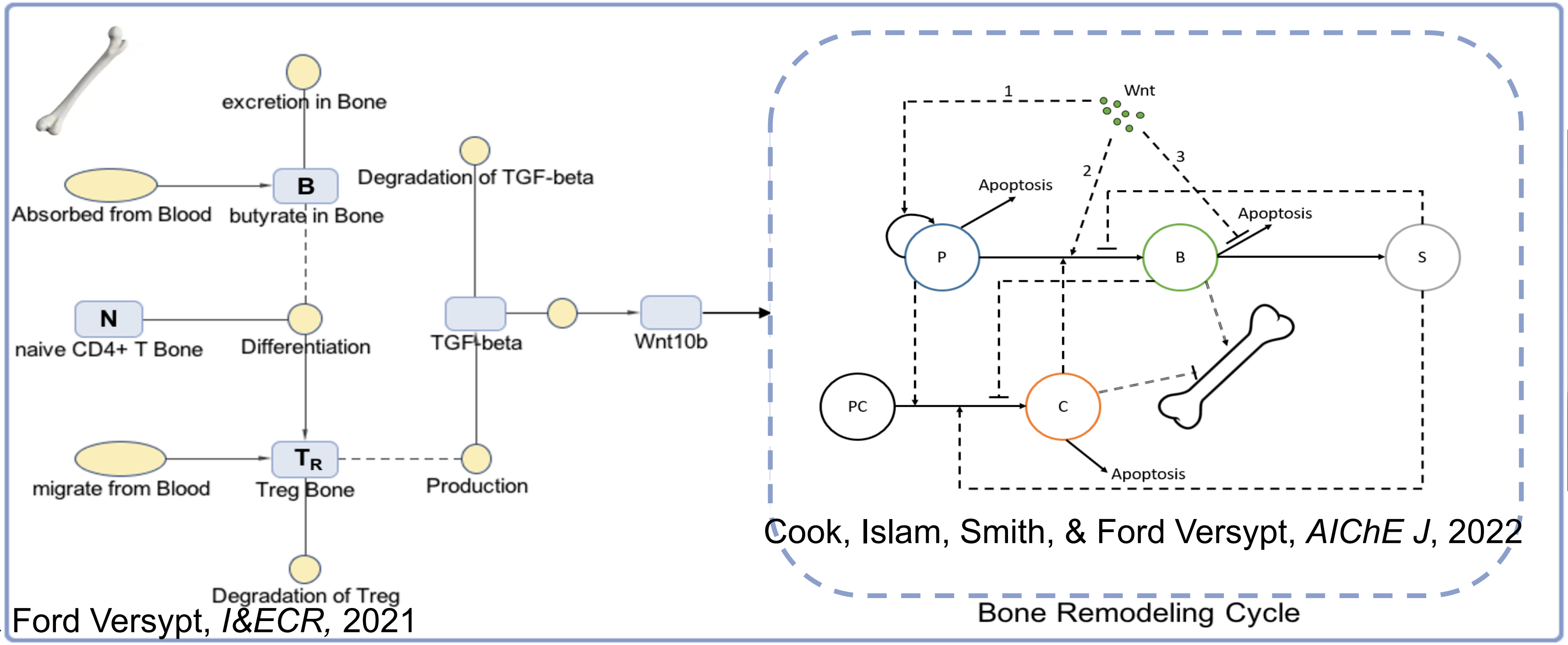


Islam, Cook, Smith, & Ford Versypt, *I&ECR,* 2021

We connected 3 compartment gut-immune system response to bone remodeling

Mohammad Aminul Islam



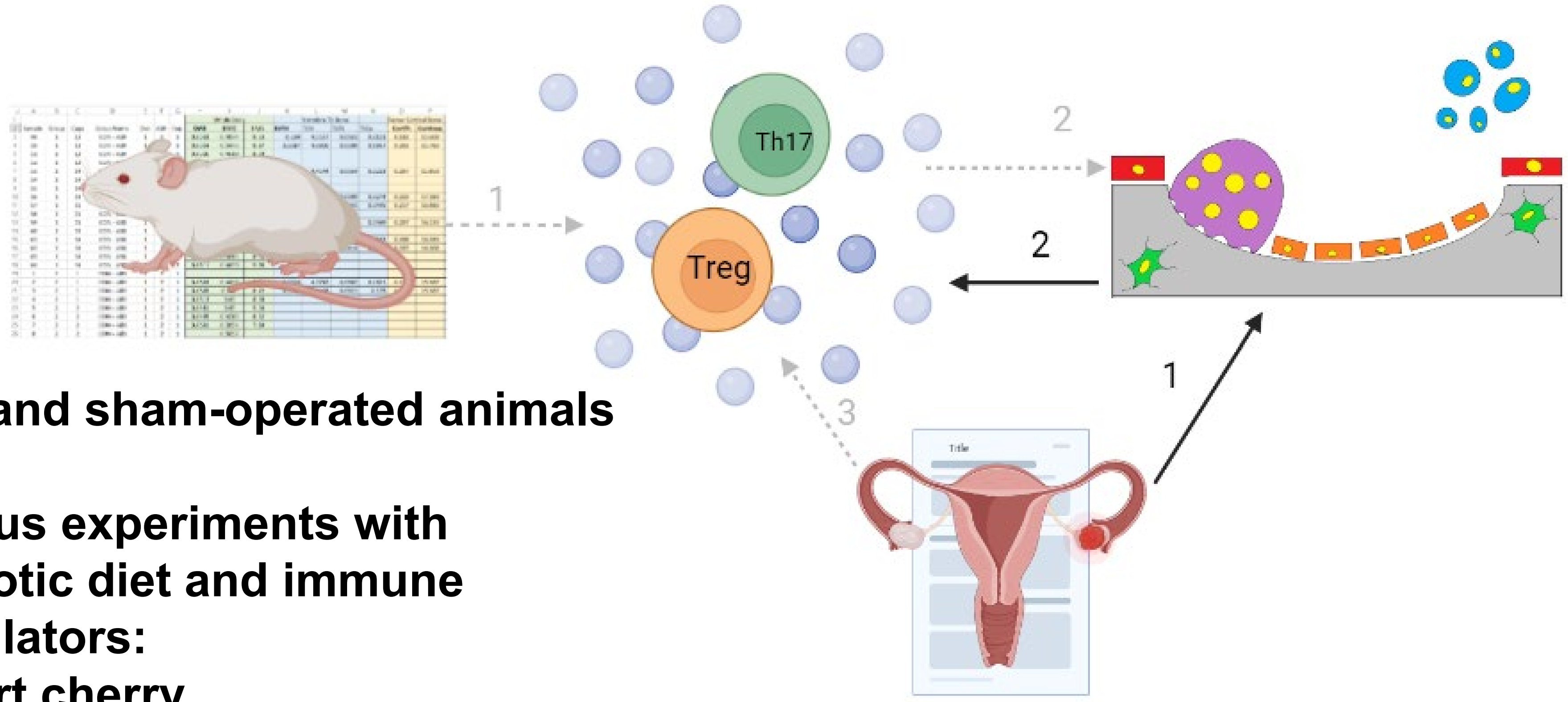


Carley Cook

Islam, Cook, Smith, & Ford Versypt, *I&ECR*, 2021

R21 grant exploring prebiotic benefits in the bone

Short chain fatty acid influence on normal and estrogen deficient bone remodeling



Carley Cook

OVX and sham-operated animals

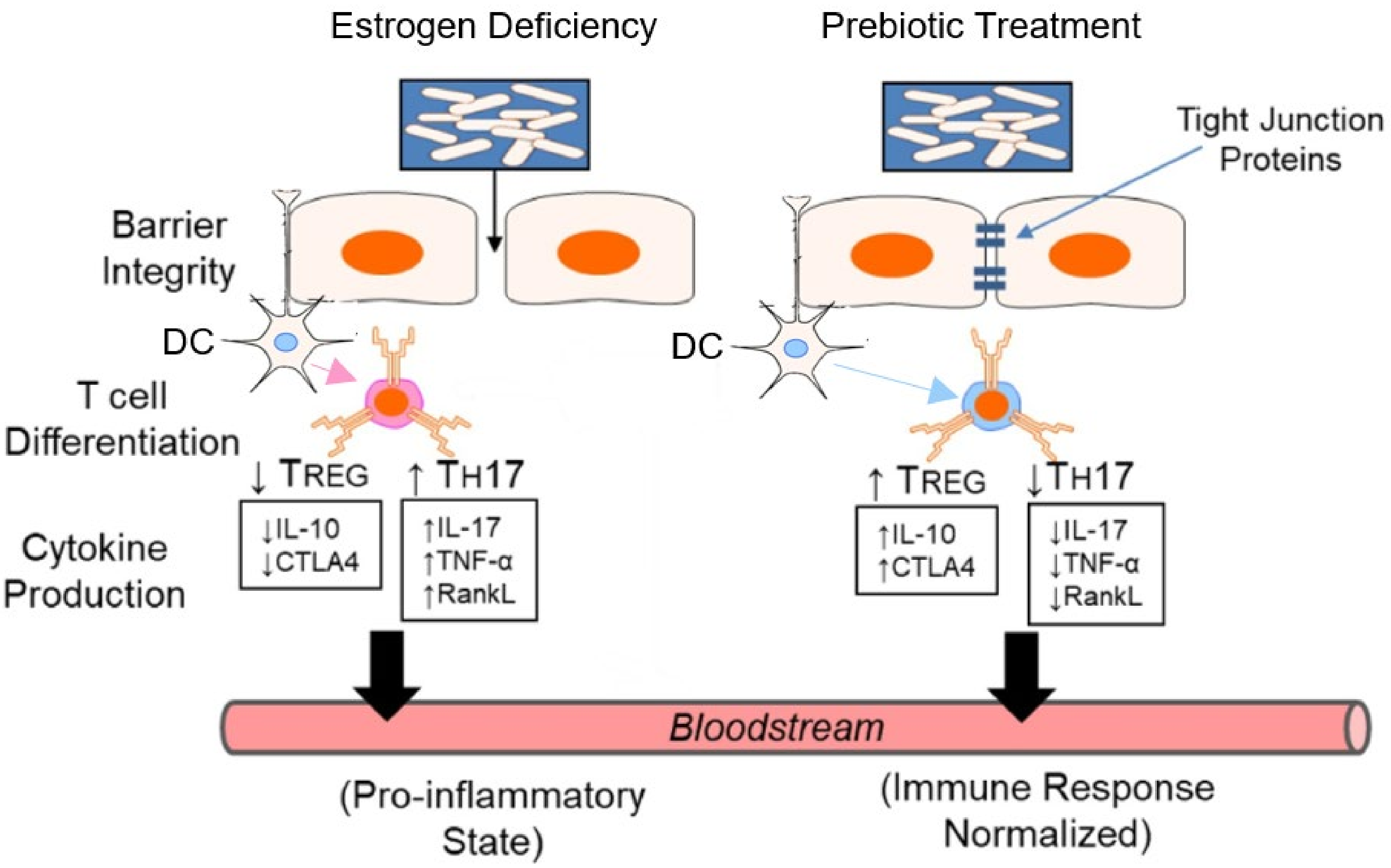
Various experiments with prebiotic diet and immune modulators:

- **Tart cherry**
- **Fructooligosaccharides**
- **Galactooligosaccharides**

P Islam, …, Ford Versypt, …, Smith, *JBMR Plus,* 2024

R21 grant exploring prebiotic benefits in the gut

Short chain fatty acid and estrogen influence on gut inflammation and immune signaling



Ford Versypt & Smith, unpublished
adapted from Keirns, Lucas & Smith, *Nutrition Res*, 2020

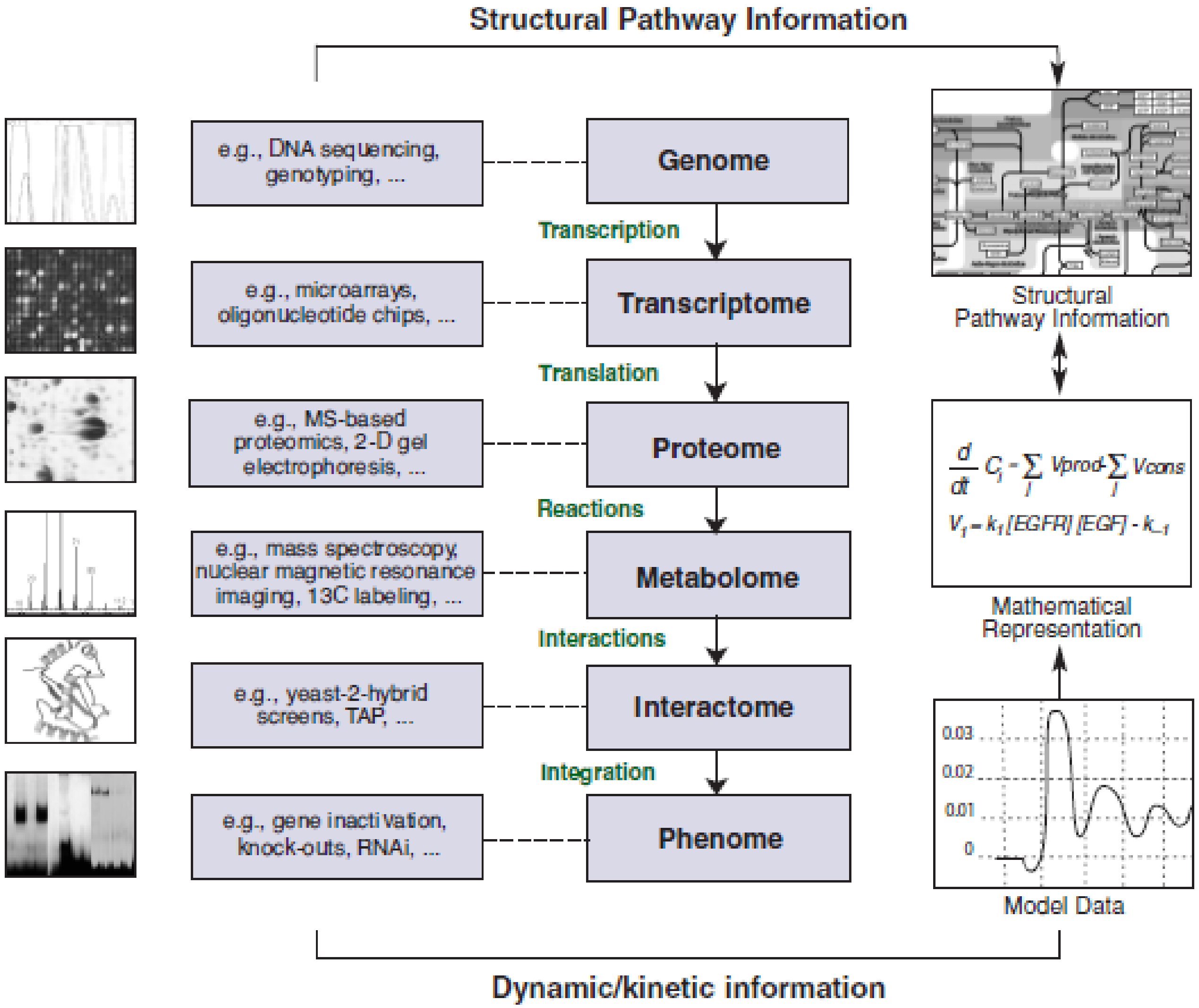
Ariel Lighty

Challenges for control of human diseases

- **Limited manipulated variables**
- **Multiscale (space and time) interacting systems**
- **Big AND small data issues and limited dynamic measurements**

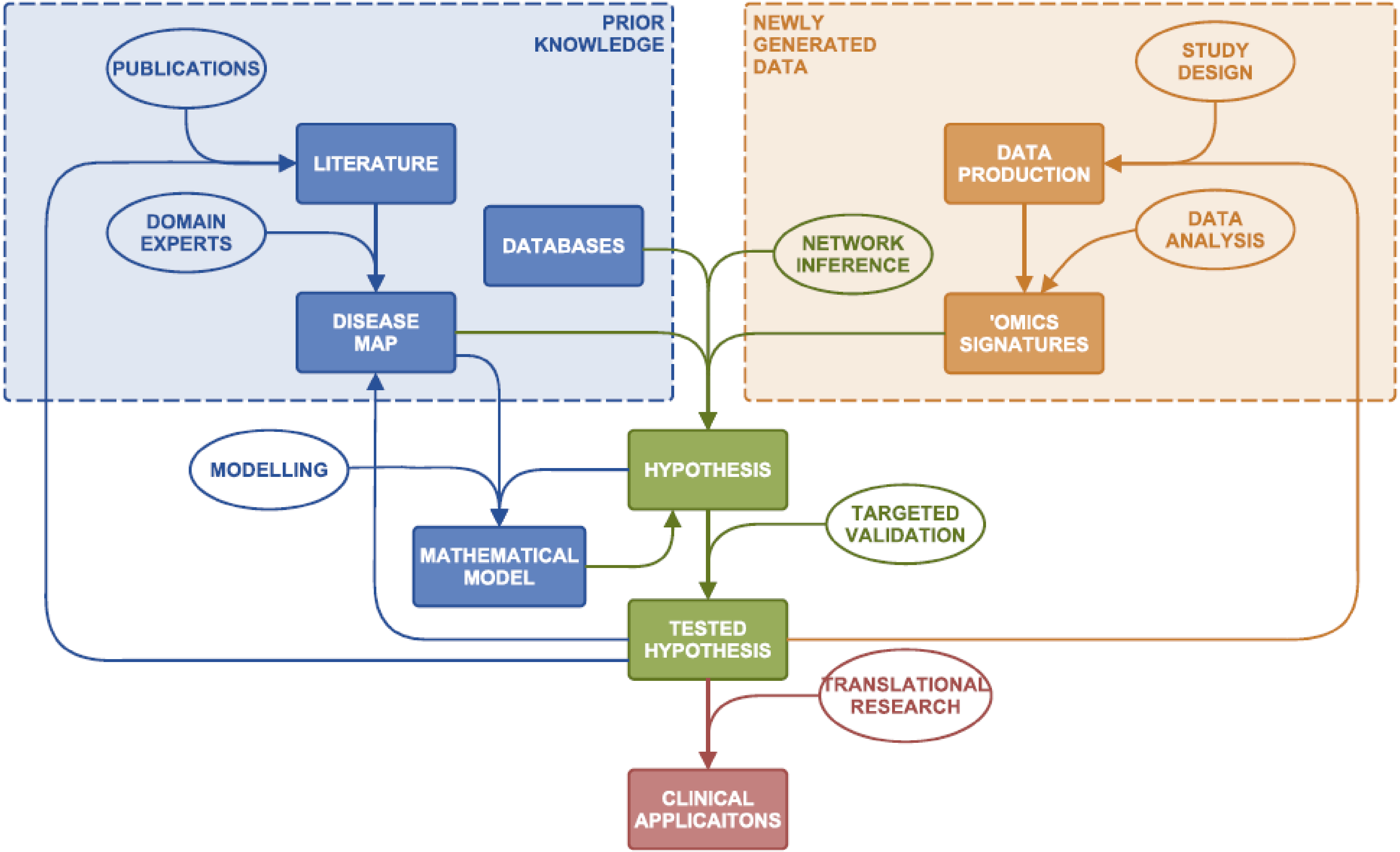
In theory we can relate omics up to phenotype. In practice…

- Integrating large volumes of disparate types of data
- Sparsity of data connecting diverse patient phenotypes or disease conditions to dynamic molecular markers of disease
- Even more limited dynamic data or spatially resolved data



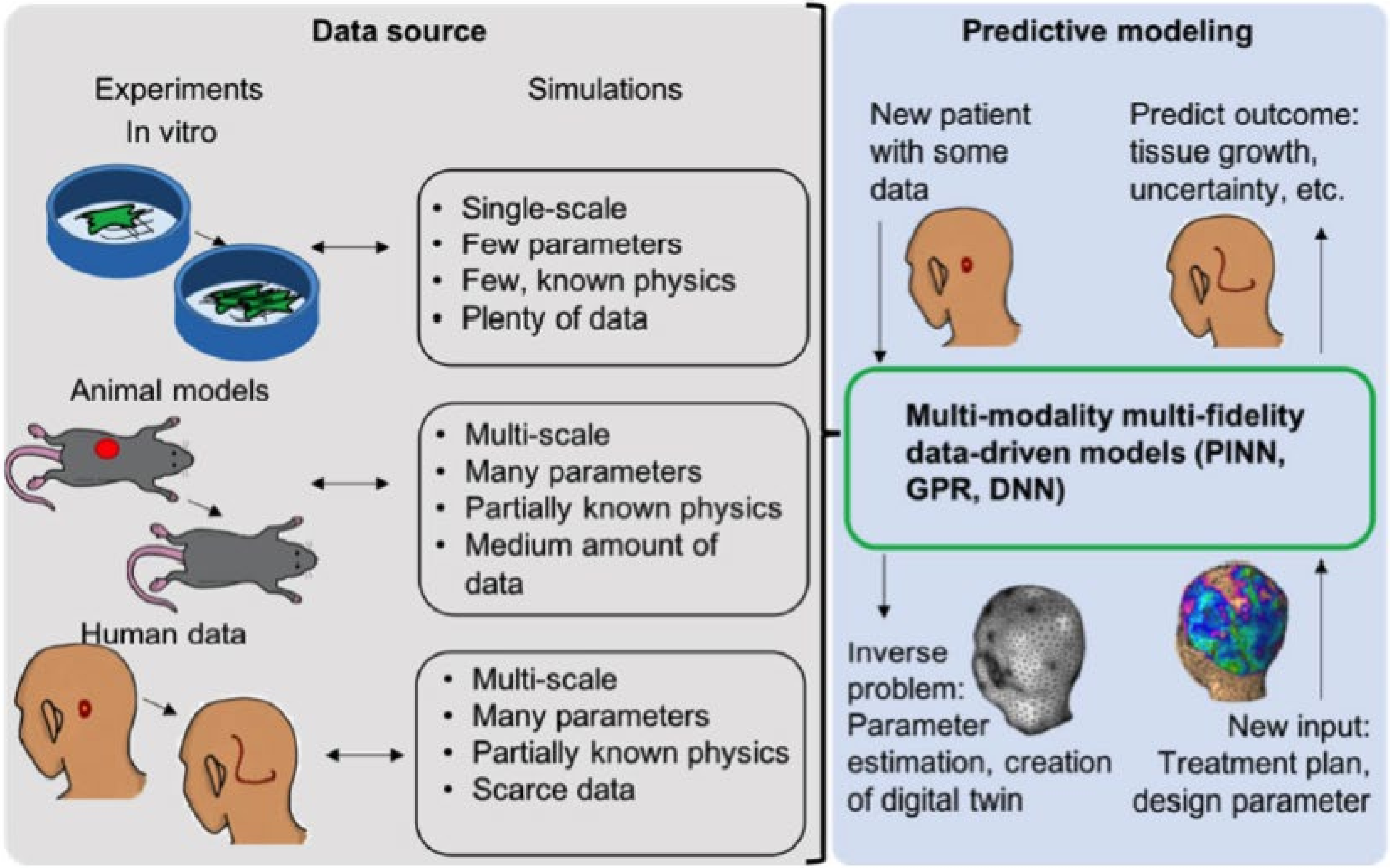
Fischer, *Alcohol Res Health*, 2008

Systems biomedicine workflow



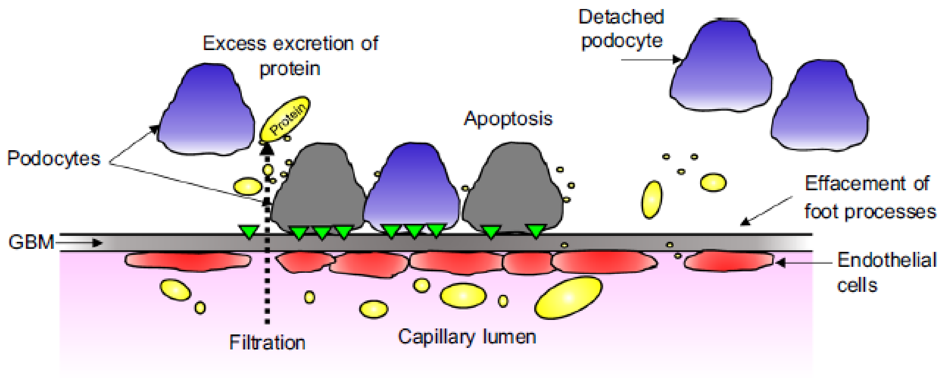
Mazein et al., *NPJ Sys Biol Appl*, 2018

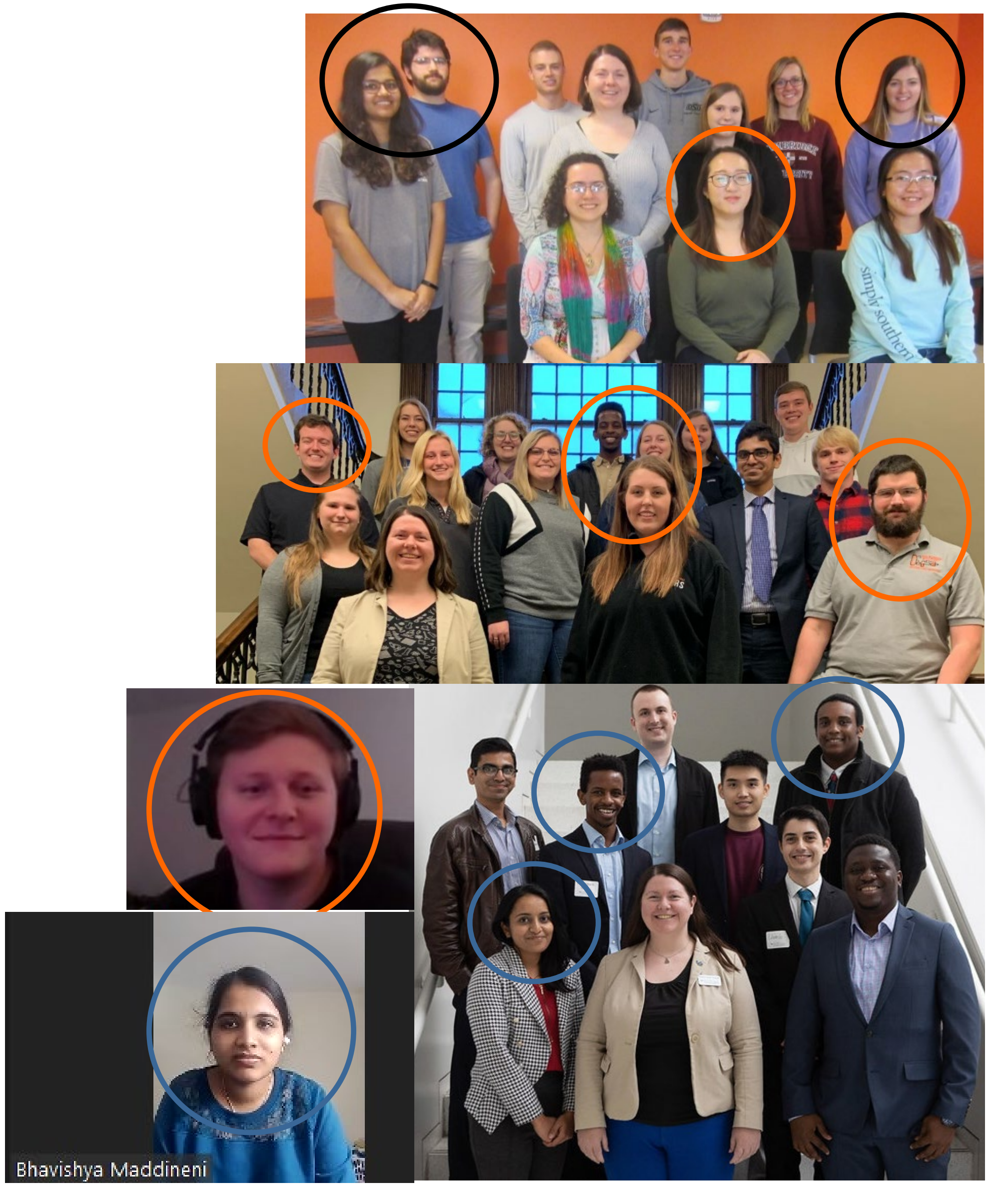
Fig. 4 Multi-modality and multi-fidelity modeling of biomedical systems. Data from both experiments and computational models can be combined through machine learning to create predictive models. The underlying assumption is that, for a system of interest, data from different sources is correlated and can be fused. Parameter estimation, system identification, and function discovery result in inverse problems, for example, the creation of a digital twin, and forward problems, for example, treatment planning



Peng et al., *Archiv Computat Methods Eng,* 2020

Diabetic kidney disease modeling is a long-standing team effort in the lab supported by NSF CAREER





Patidar & **Ford Versypt**, *Int J Molec Sci*, 2024
Thomas & **Ford Versypt**, *J Biol Engr*, 2022
Thomas & **Ford Versypt**, *Proc FOSBE*, 2022
Ford Versypt, *Curr Opin Sys Biol*, 2021
Ruggiero & **Ford Versypt**, *J Open Source Software*, 2019
Pilvankar, Yong, & **Ford Versypt**, *Processes*, 2019
Eastep, Harrell, McPeak, & **Ford Versypt,** *Chem Engr Educ*, 2019
Pilvankar, Higgins, & **Ford Versypt,** *Bull Math Bio,* 2018
Ford Versypt, Harrell, & McPeak, *Computers Chem Engr,* 2017
Ford Versypt, Harrell, & McPeak, *J Open Source Software*, 2017
Arciero, Ellwein, **Ford Versypt**, et al, *Appl Dynamical Sys Biol Med*, 2015
Ford Versypt, et al., *Math Biosci*, 2015

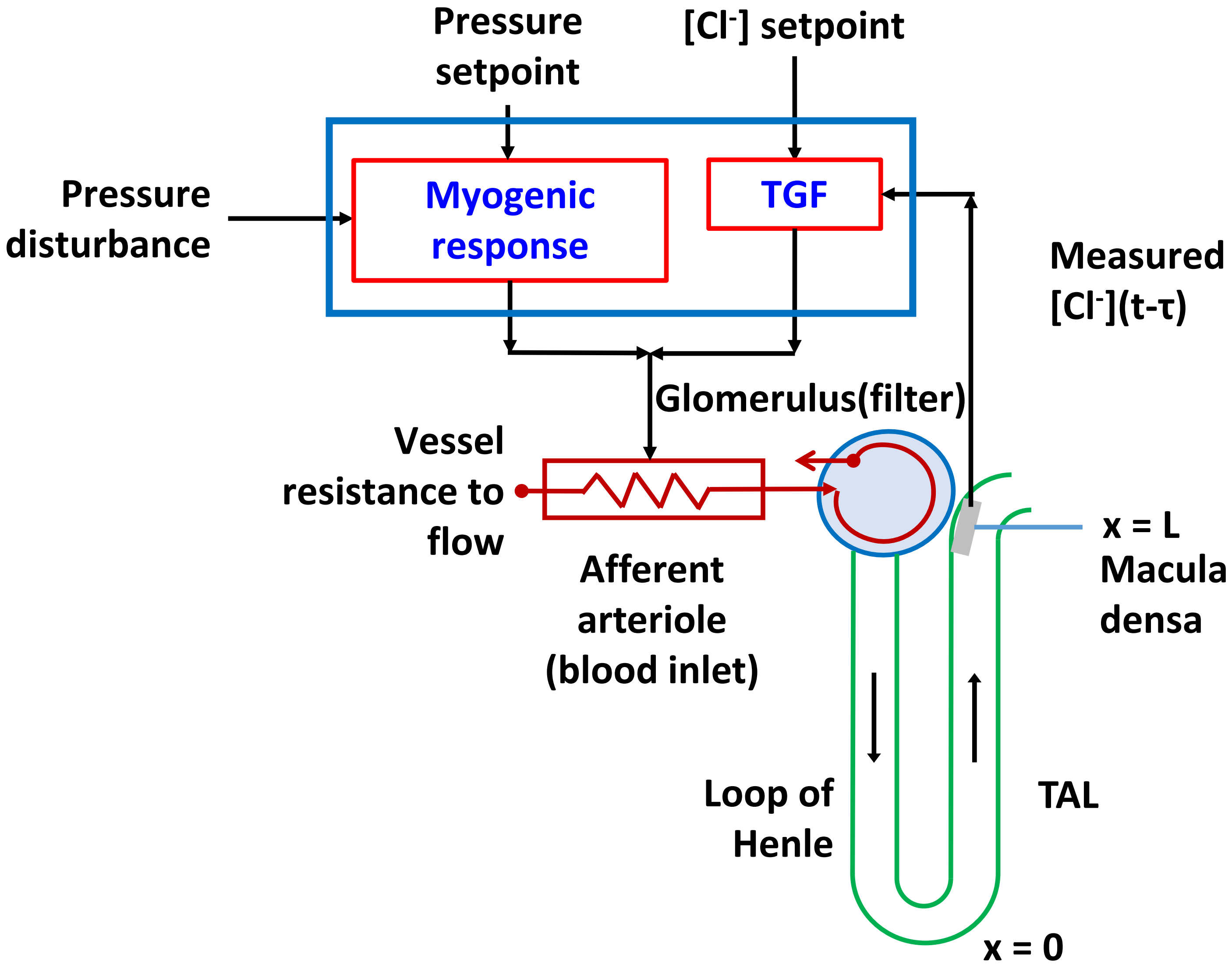
Our work in the kidney started from biological control of blood pressure

Fluid dynamics and mass transport

Two mechanisms regulate blood flow

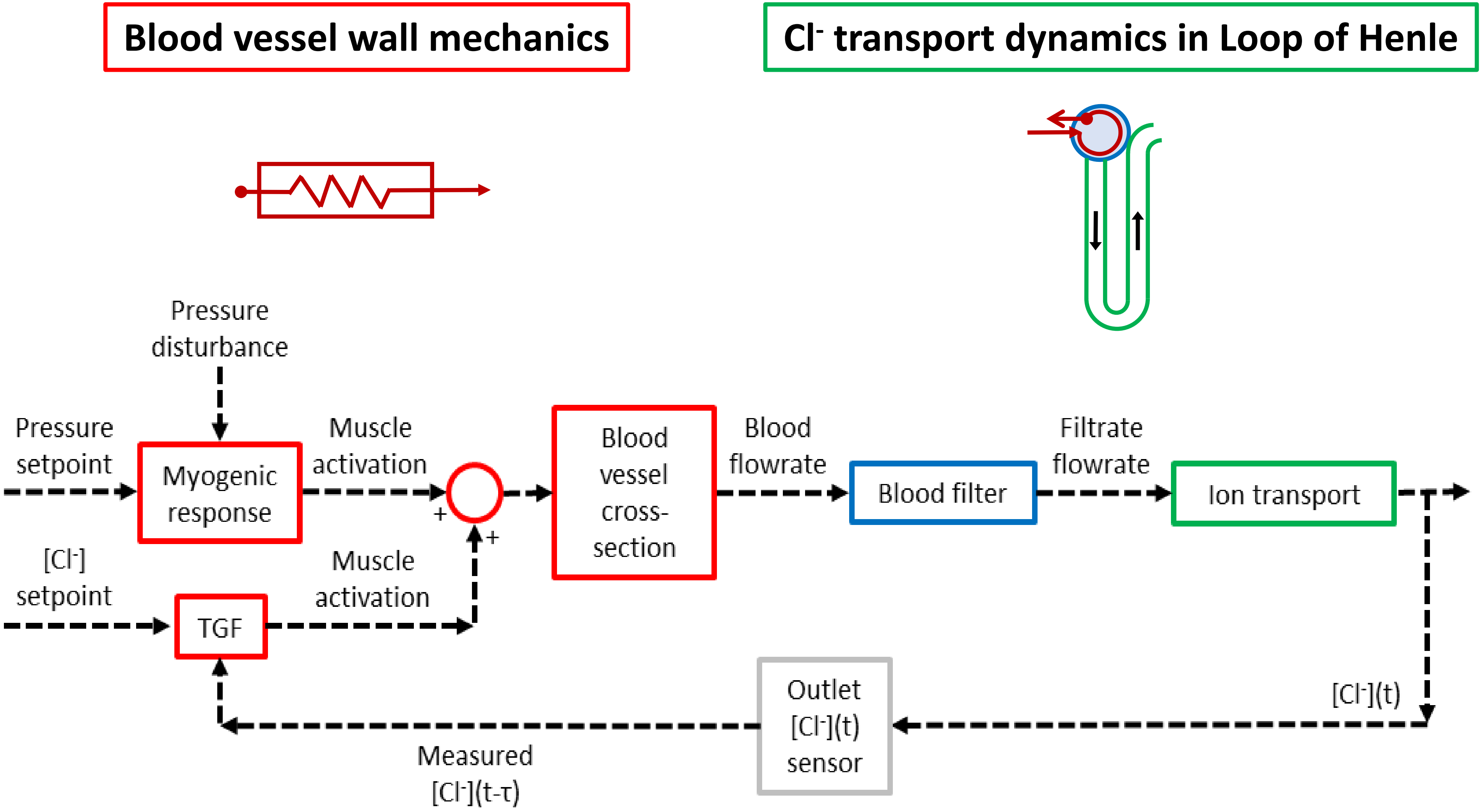
- Myogenic mechanism
- Tubuloglomerular feedback (TGF)

Autoregulation is the mechanism that keeps blood flow and filtration rate relatively constant despite fluctuations in systemic blood pressure

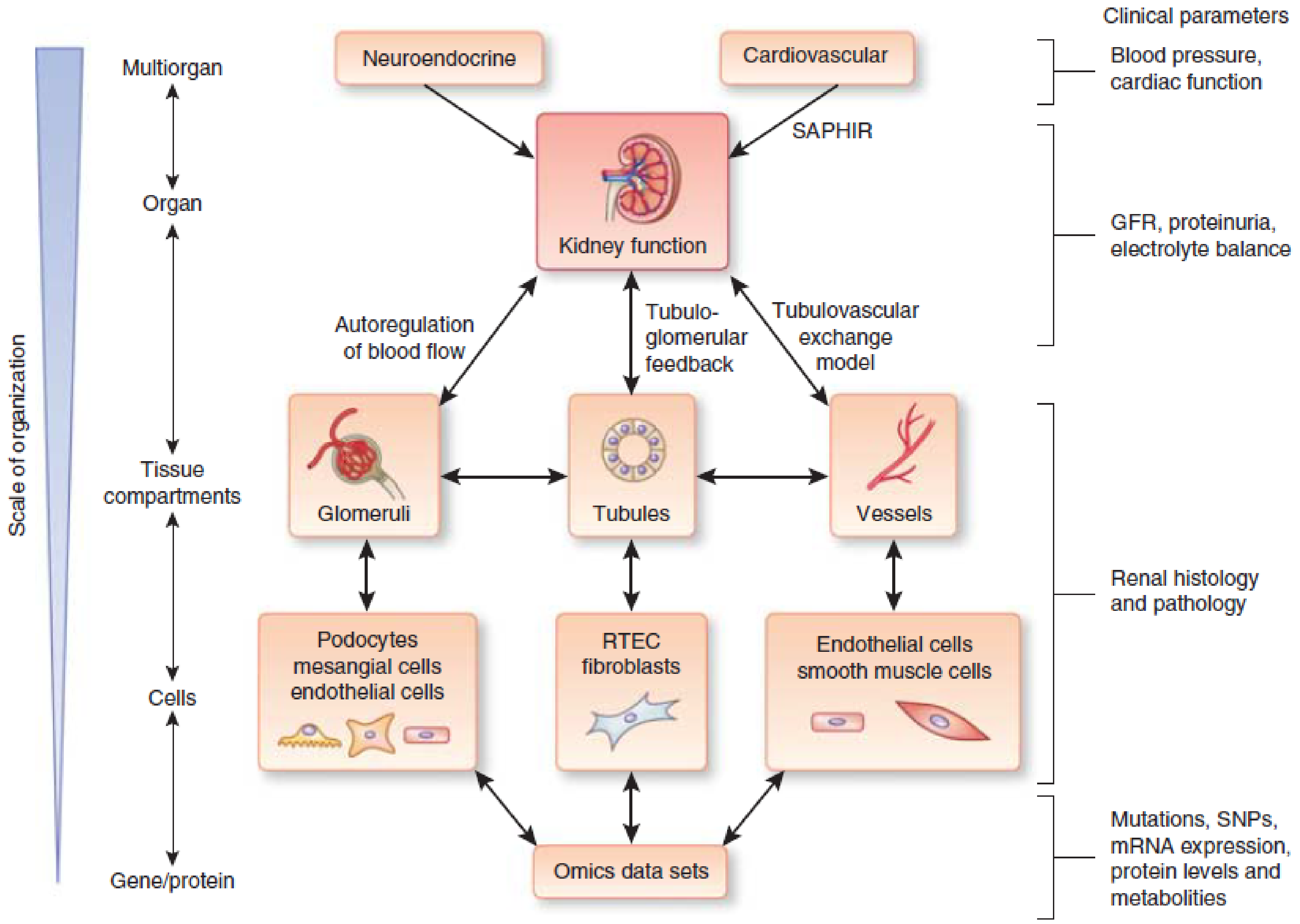


Ford Versypt et al., *Math. Biosci.* 2015

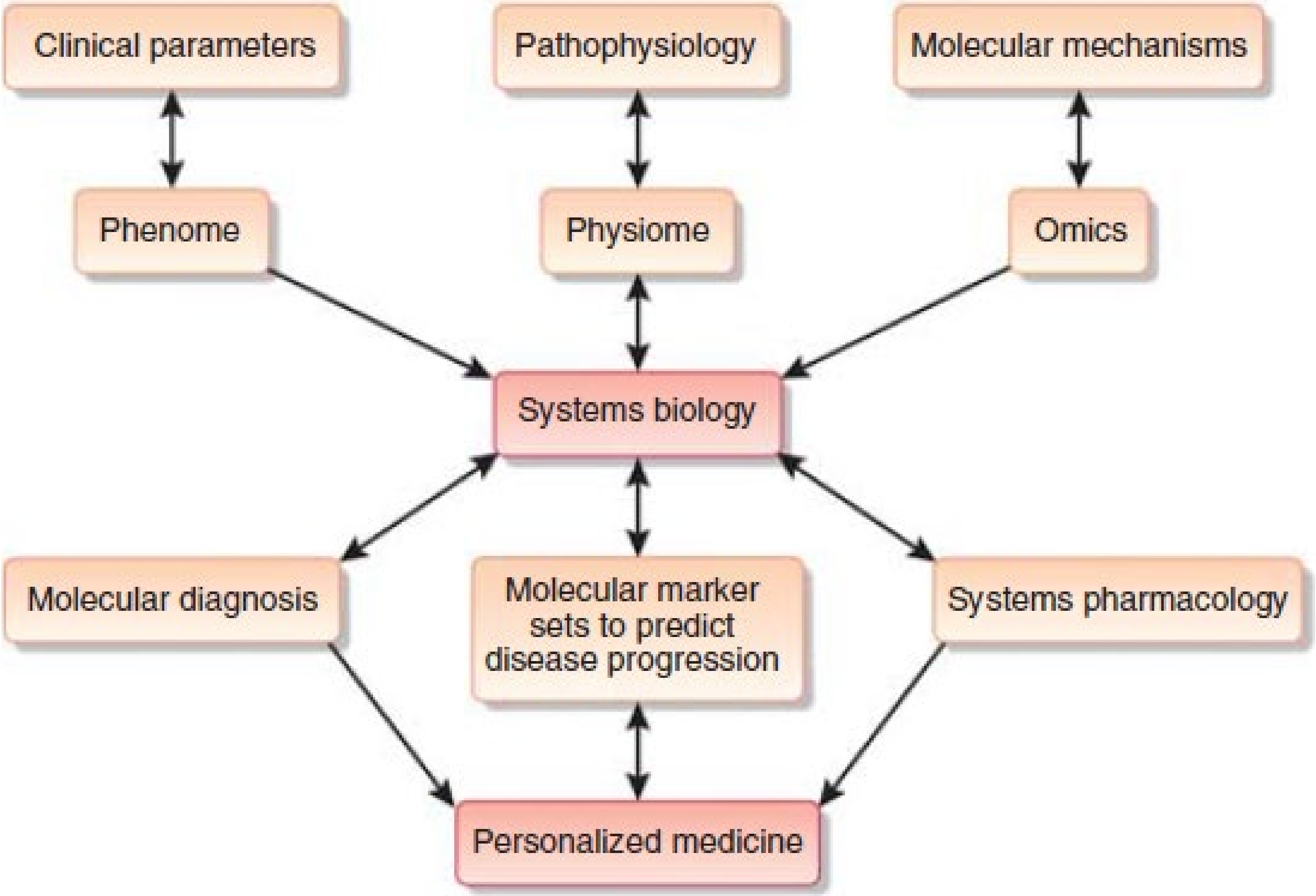
The model includes two processes coupled by feedback from the Cl^- ion concentration sensor



Kidney disorders include multiple cell types and tissue segments across different scales

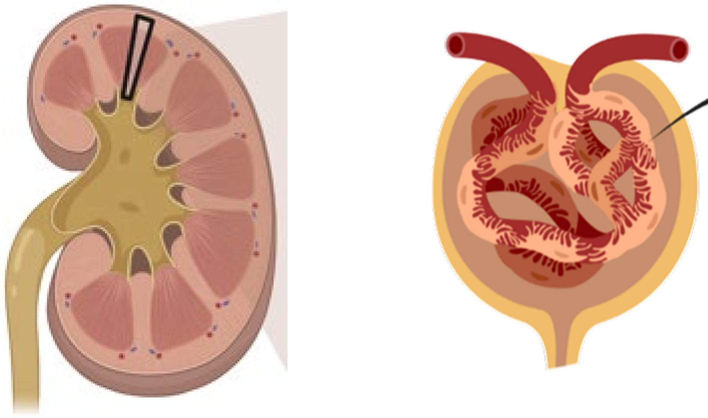


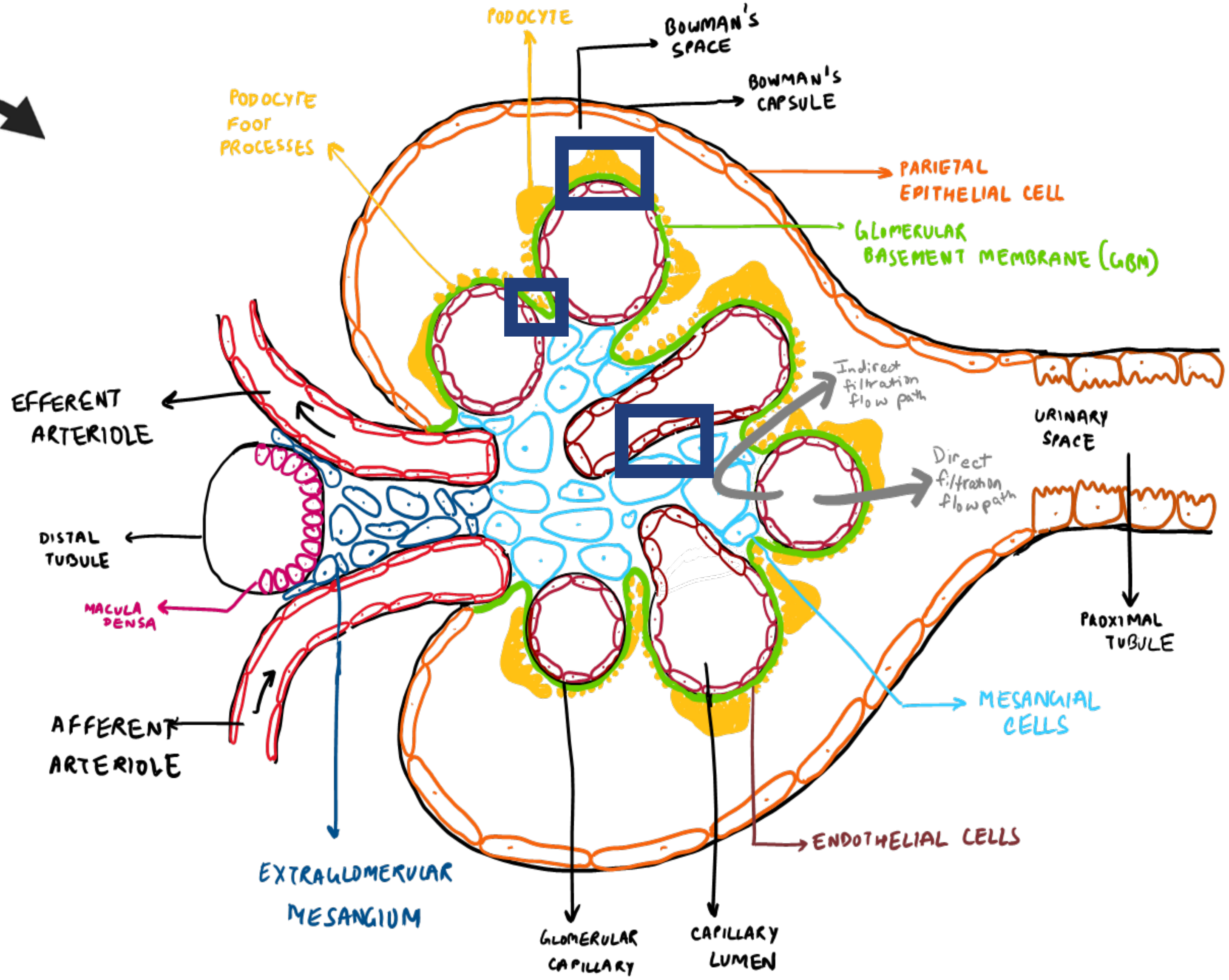
He et al., *Kidney Int*, 2012



He et al., *Kidney Int*, 2012

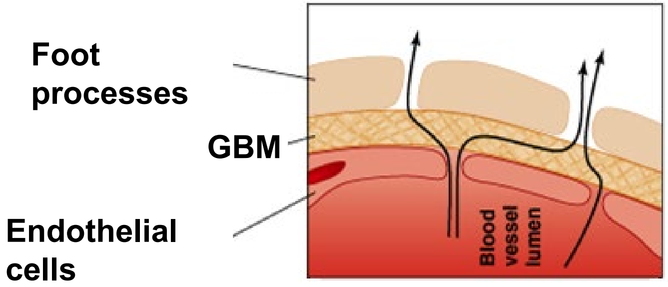
We consider multiple glomerular (kidney) cell types damaged in DKD & how they interact





Pilvankar & Ford Versypt, https://doi.org/10.6084/m9.figshare.10269434.v3 (2019)

Hyperglycemia damages the glomerular filtration barrier primarily via podocytes



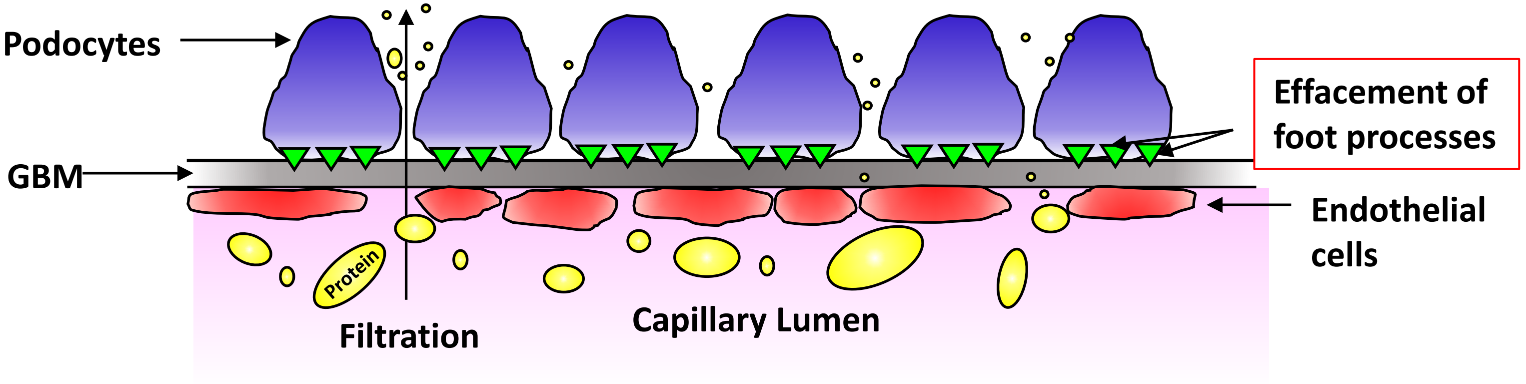
Moyes & Schulte, *Principles of Animal Physiology*, 2006

High Glucose (HG)

Excess excretion of protein

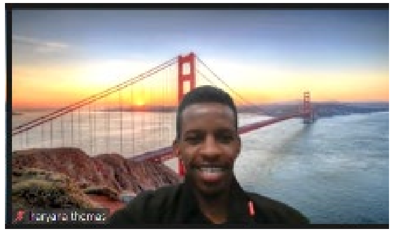
Podocyte Detachment

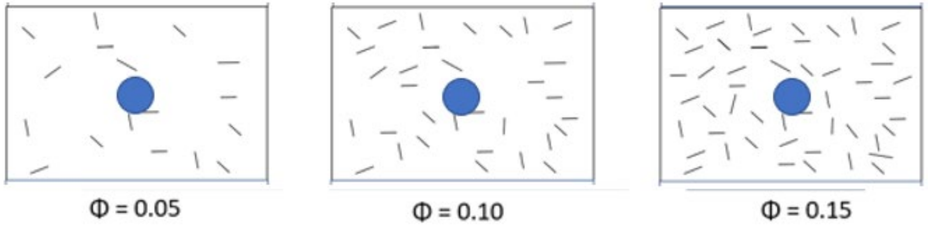
Apoptosis

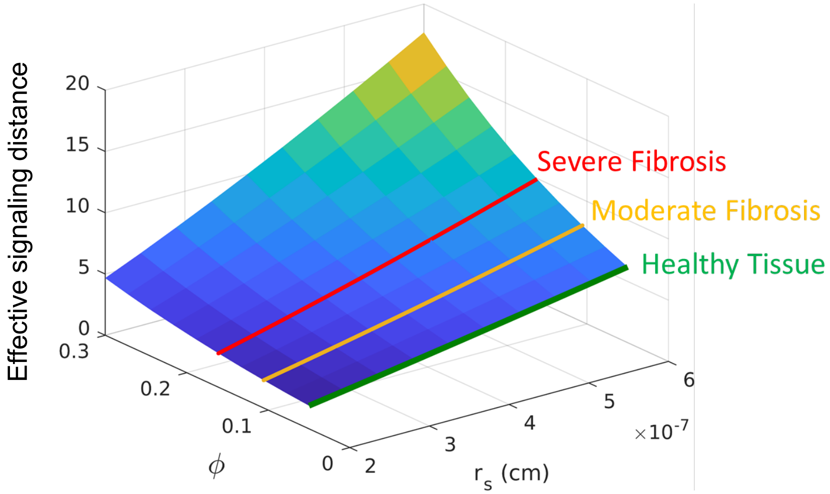


Pilvankar, Higgins, & Ford Versypt, *Bull Math Biol*, 2018

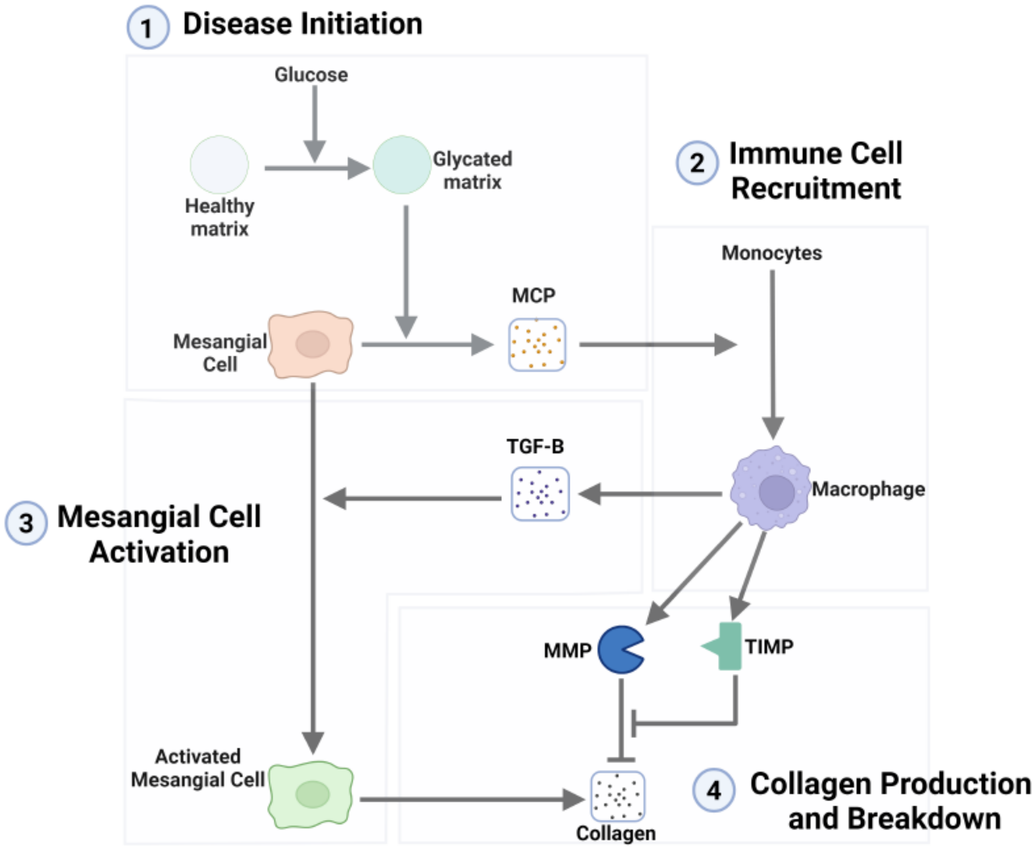
We are modeling the effects of renal fibrosis

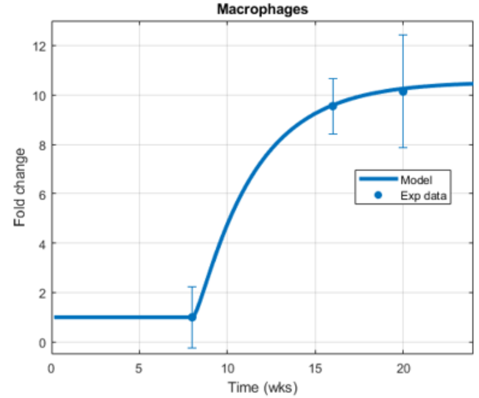


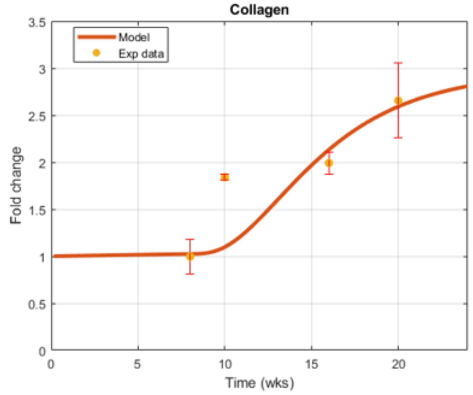




Thomas & Ford Versypt,
Proc FOSBE, IFAC Papers Online, 2022

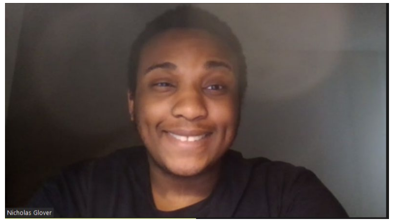




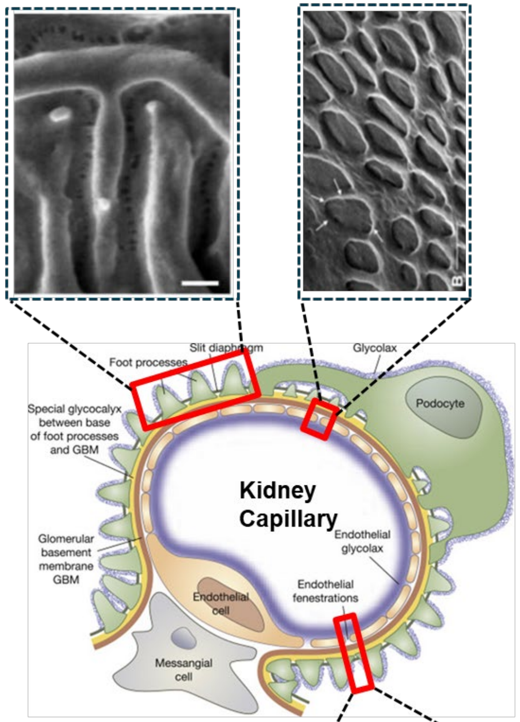


Thomas & Ford Versypt,
BioRxiv, 2023

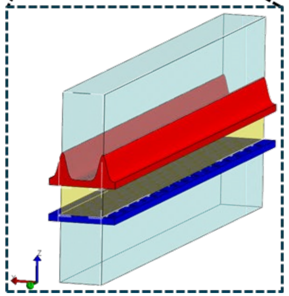
We are connecting the submodels for the damage to each tissue layer into a finite element model

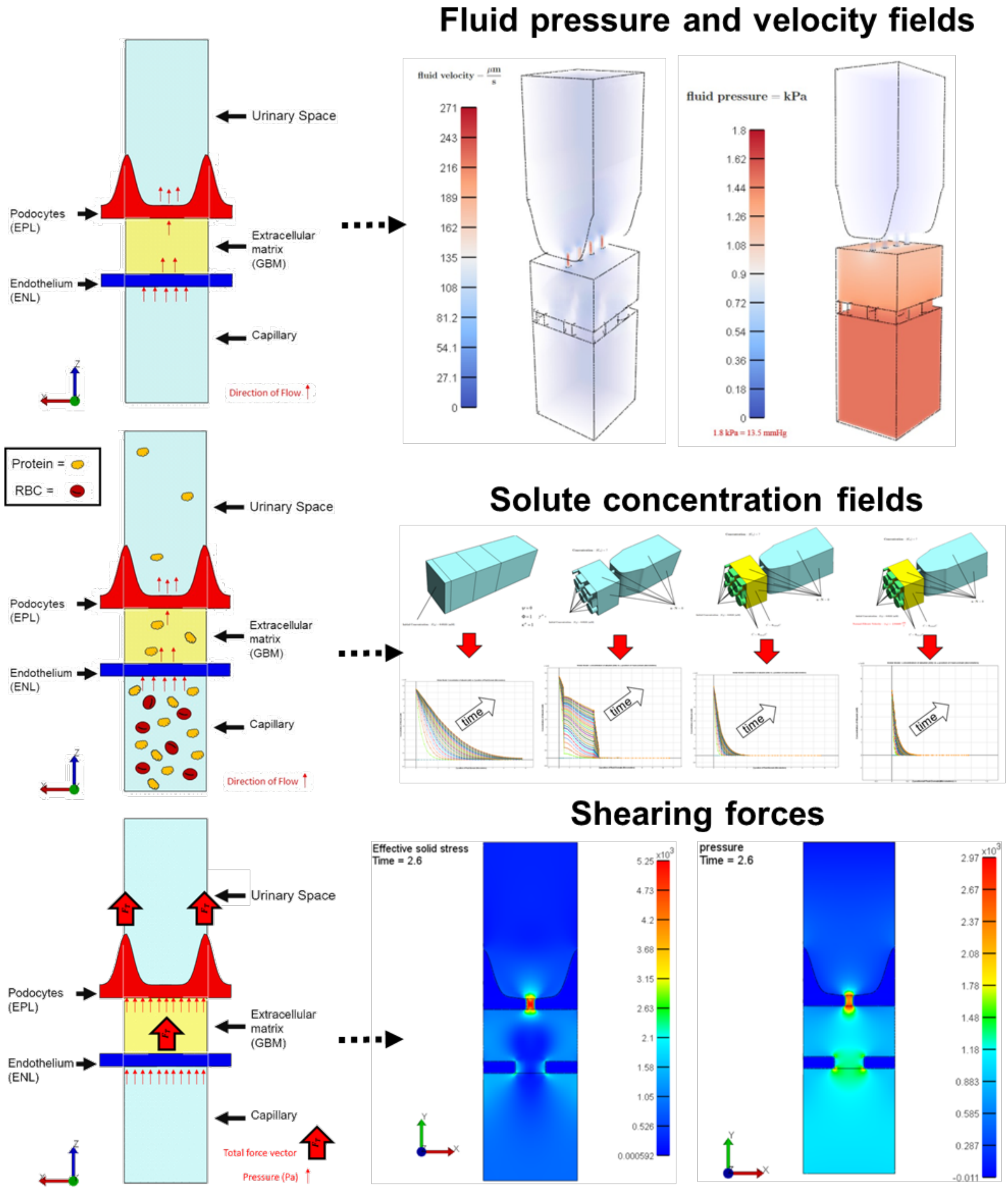


Glover & Ford Versypt, *in prep*, 2024

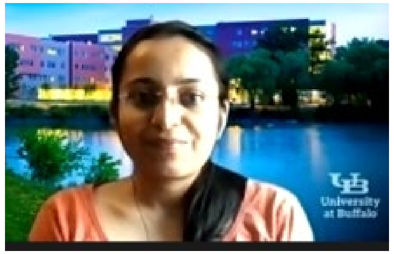


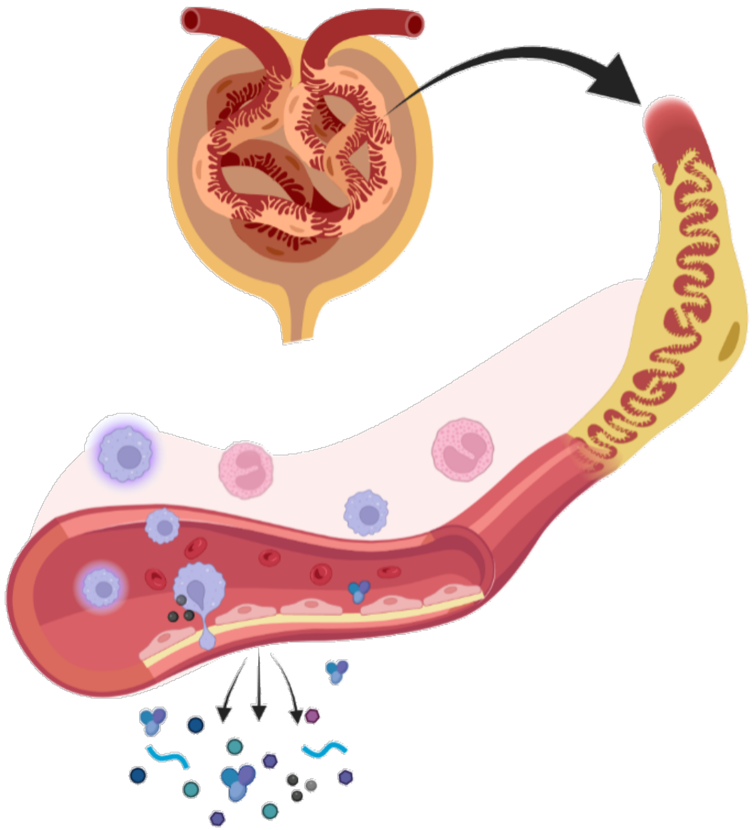
Schlondorff et al, Kidney Int, 2017

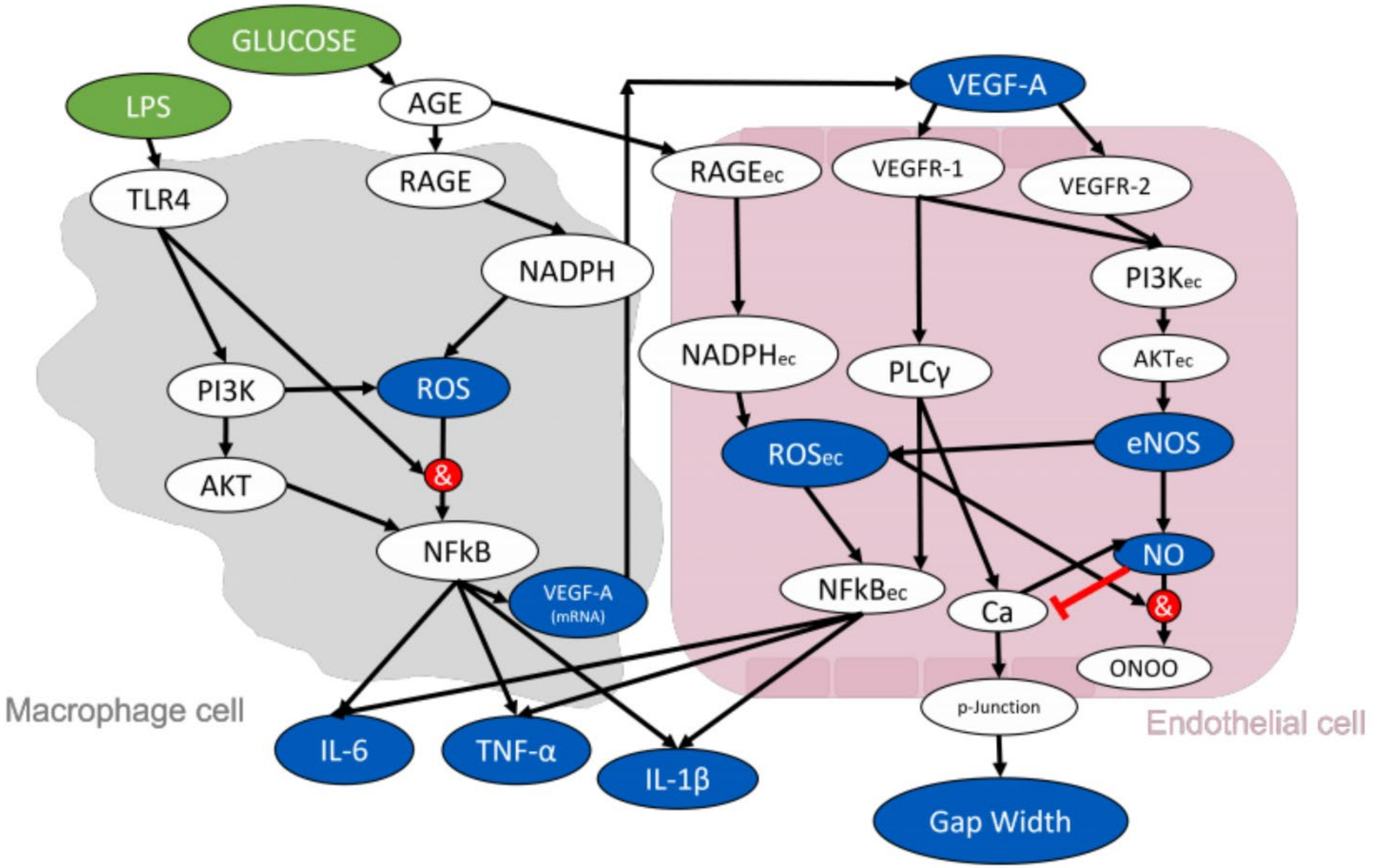




We are building a logic-based model for signaling between endothelial cells and immune macrophages—All manual curation of prior knowledge

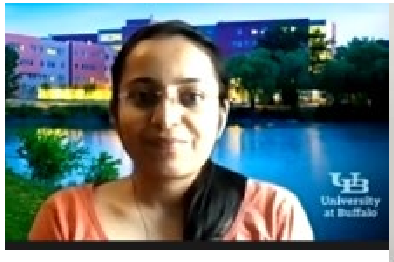


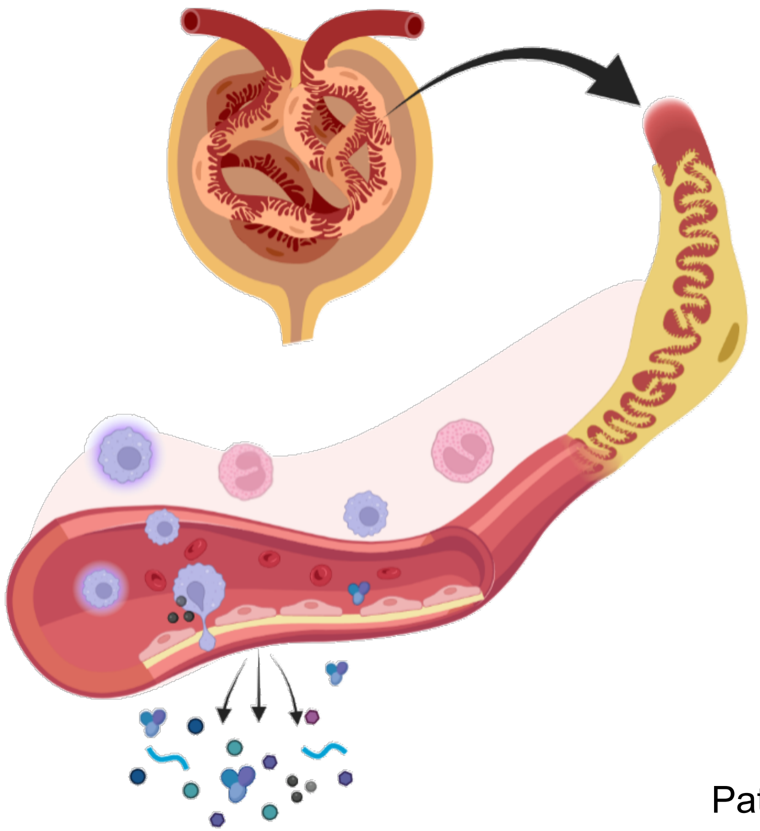


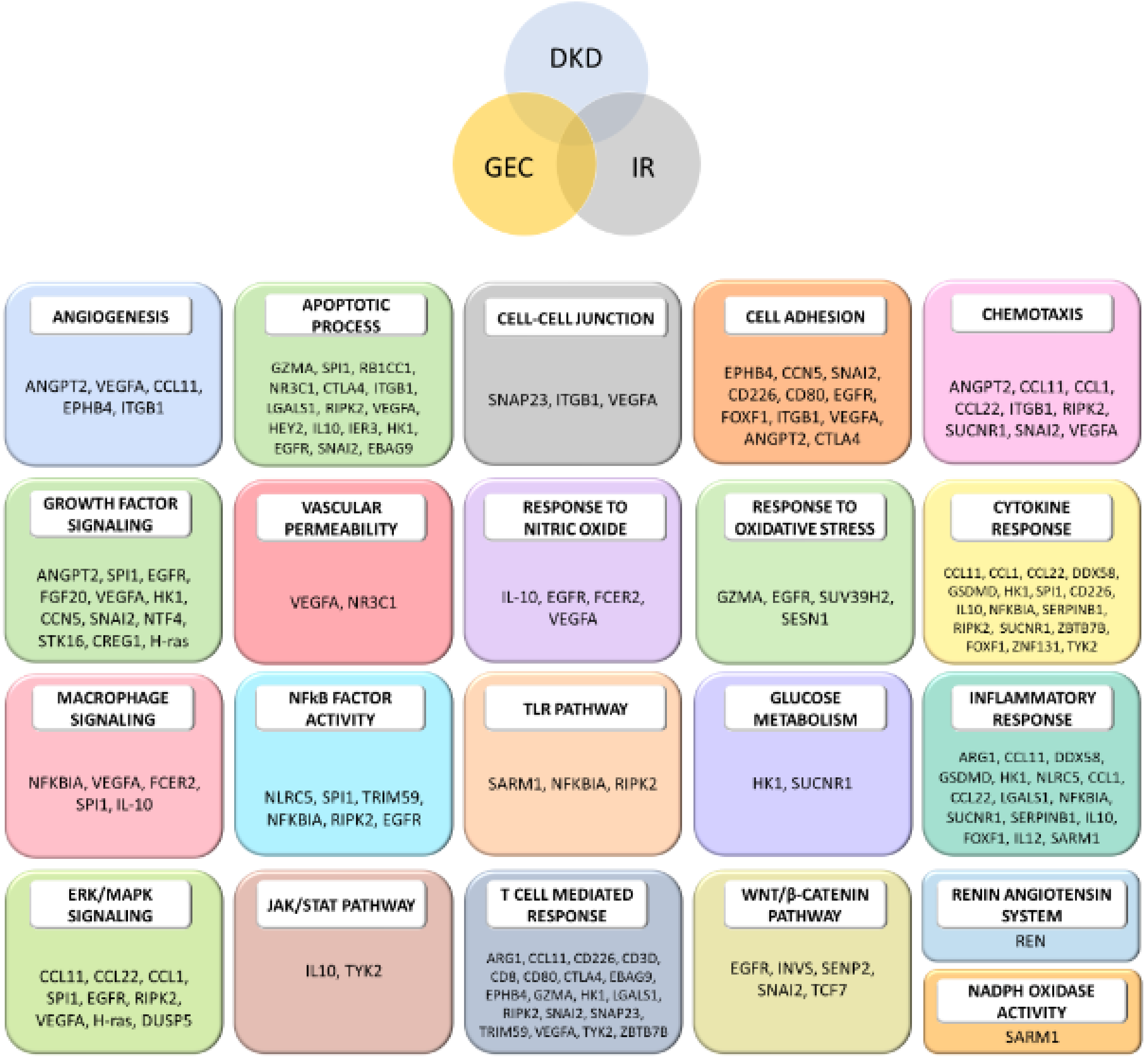


Patidar & Ford Versypt, *BioRxiv*, 2023

We also extended the work to use SemNet 2.0 to text-mine 33 million+ PubMed articles to enhance our network

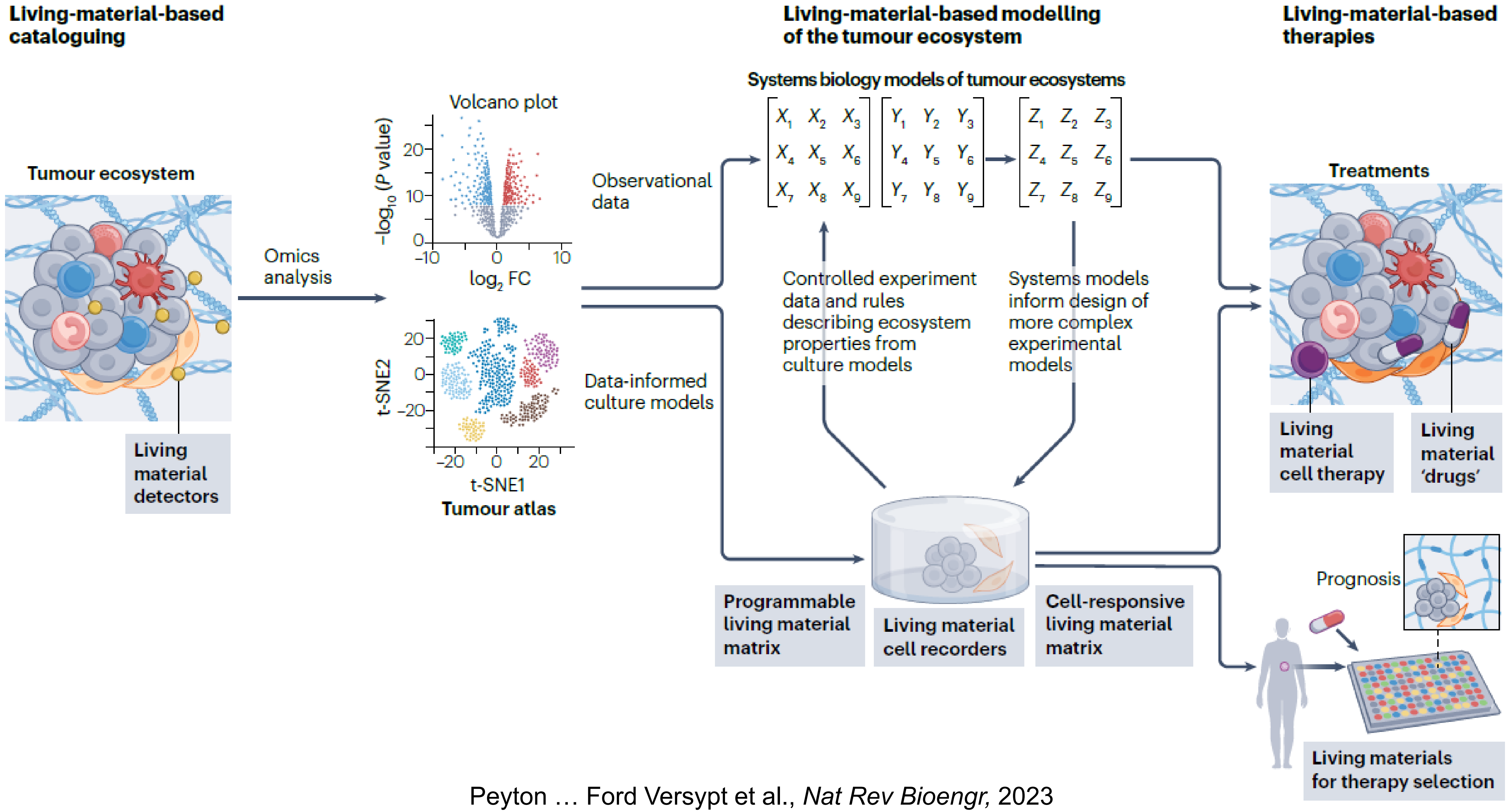






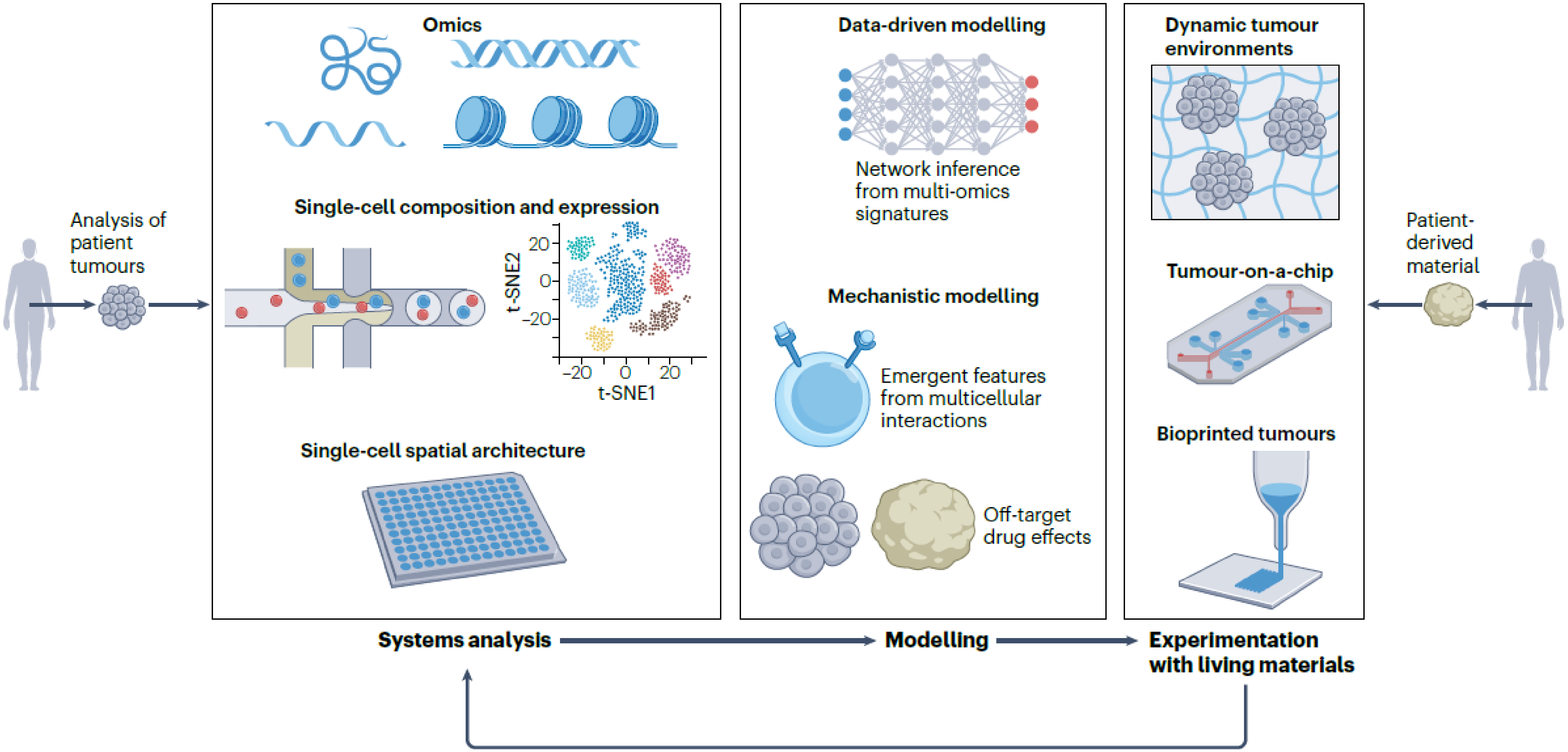
Patidar, Deng, Mitchell, & Ford Versypt, *Int J Molec Sci*, 2024

Close integration between experimentalists and systems biology



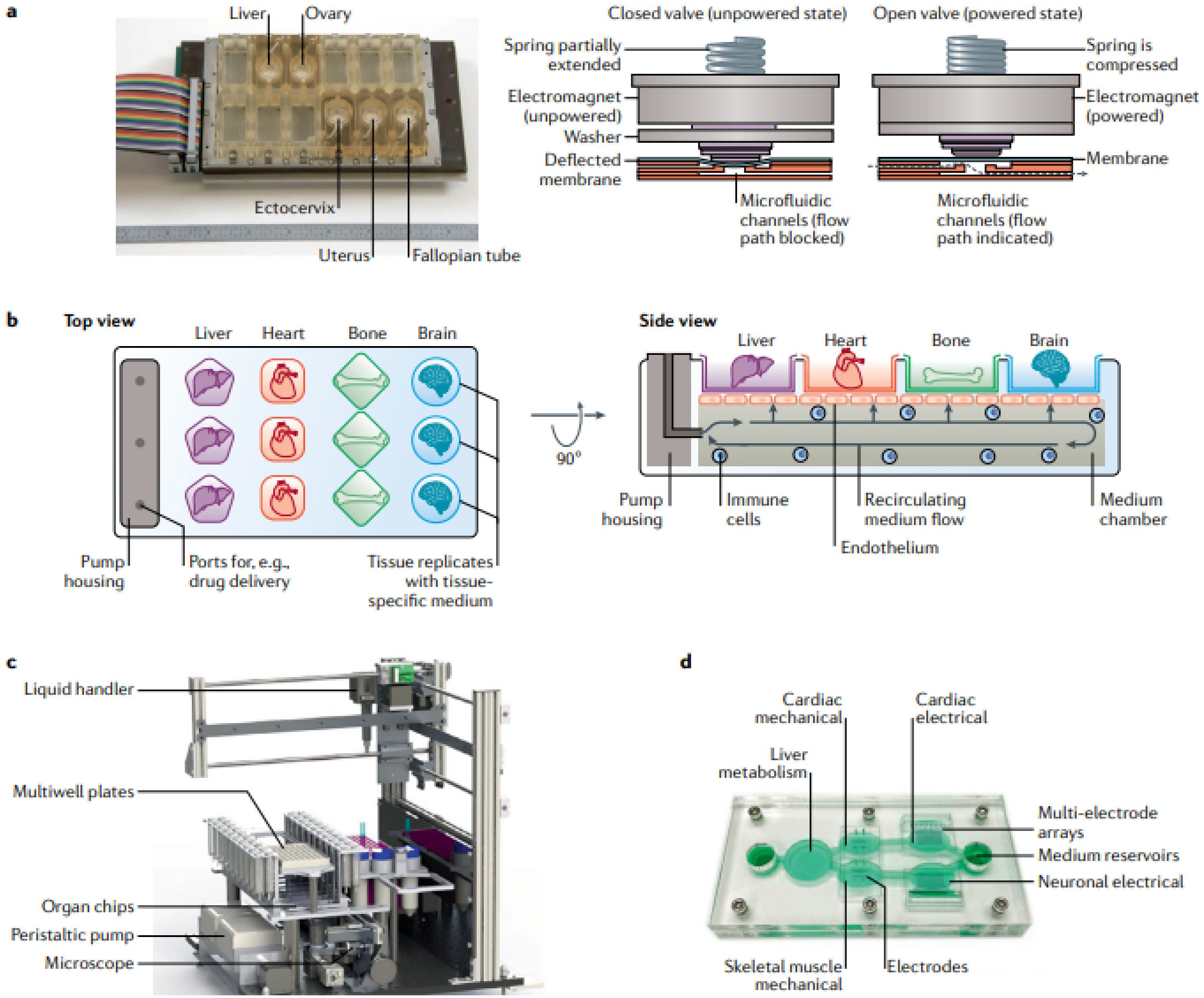
Peyton … Ford Versypt et al., *Nat Rev Bioengr,* 2023

Close integration between experimentalists and systems biology



Peyton … Ford Versypt et al., *Nat Rev Bioengr,* 2023

Biomaterials/tissue-engineered organ-on-a-chip provide rich opportunities for PSE and systems biomedicine



Low et al., *Nat Rev Drug Discovery*, 2021

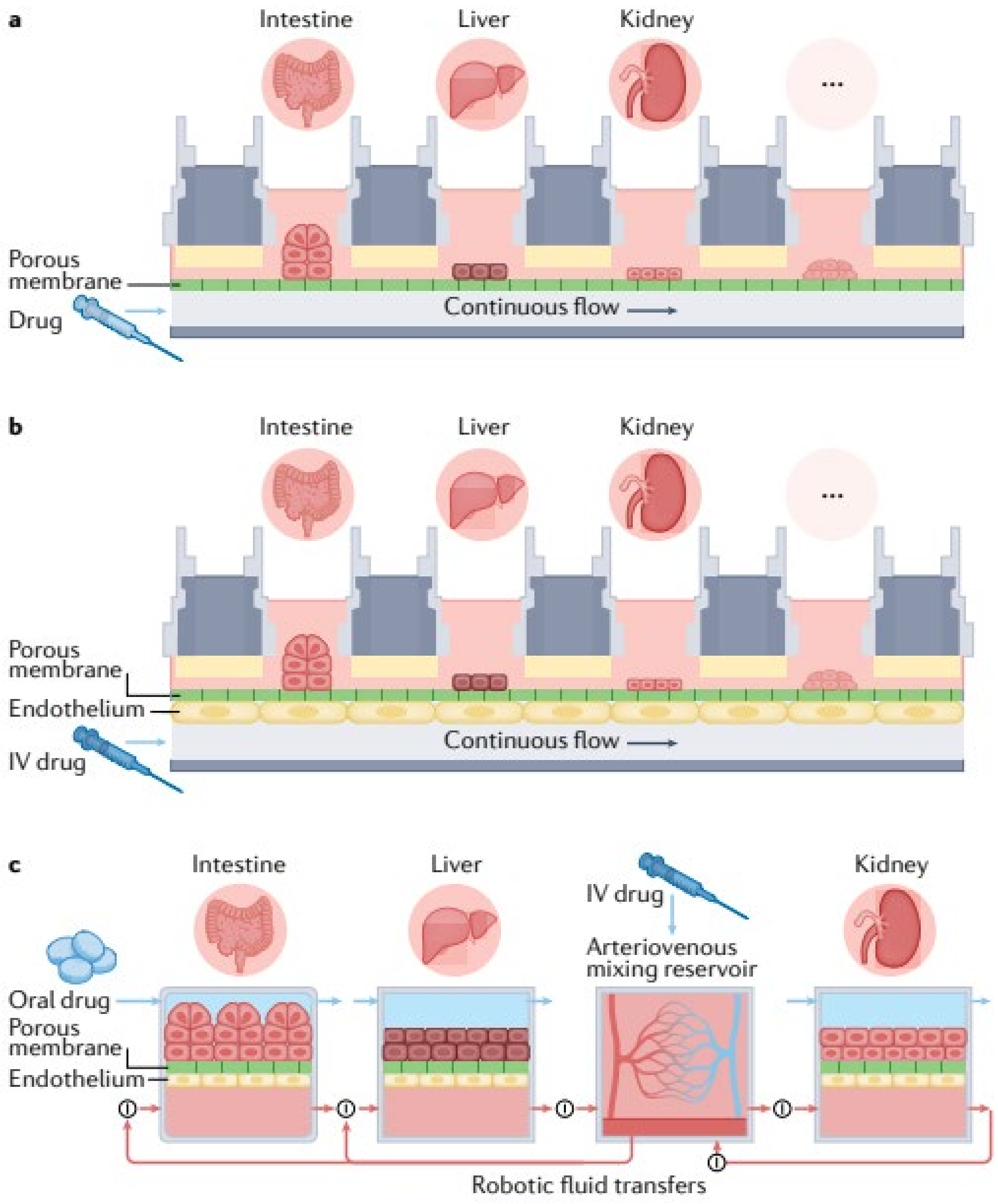


Fig. 2 | **Schematics showing different multi-organ human body-on-chips formats.**

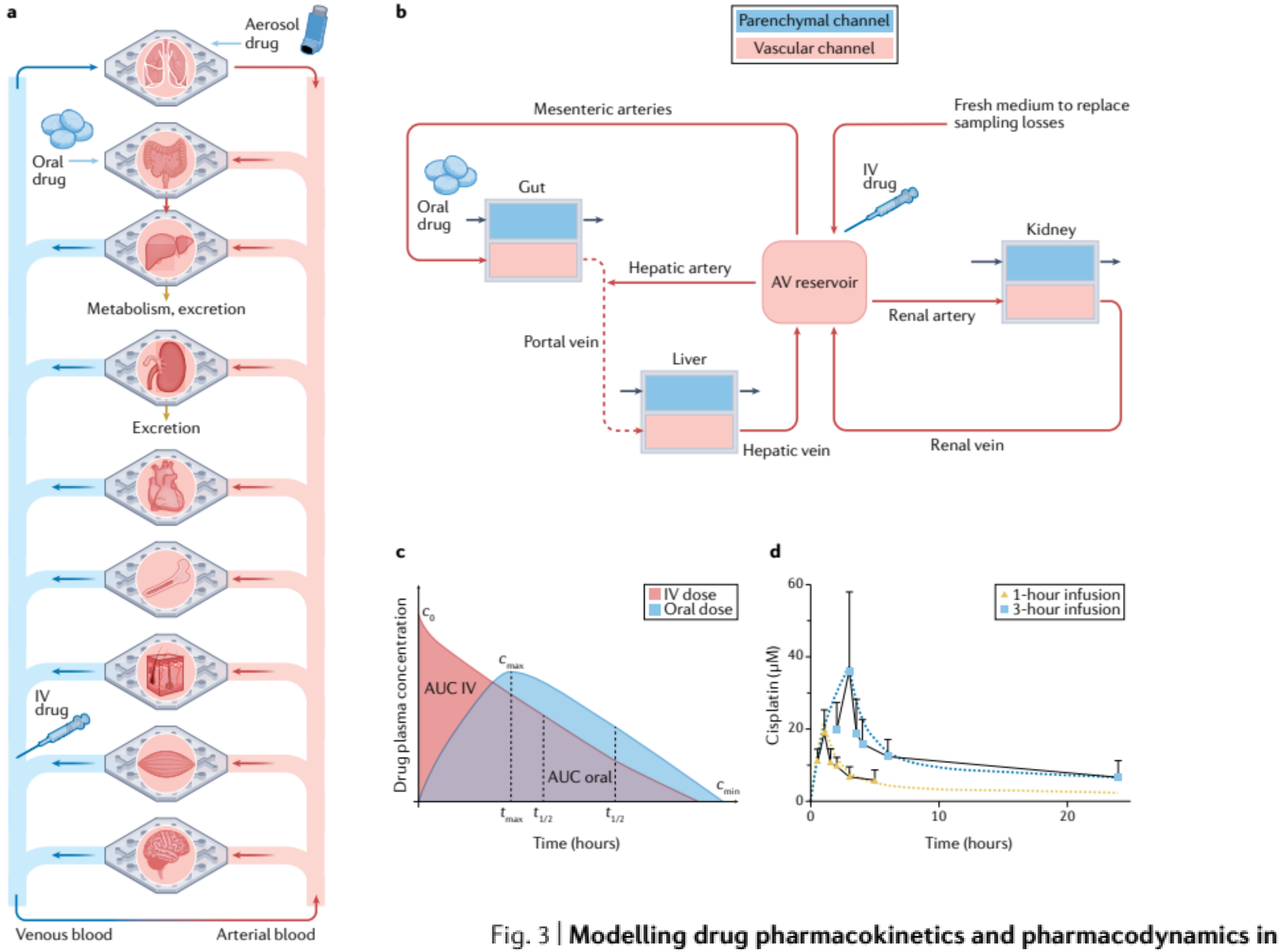


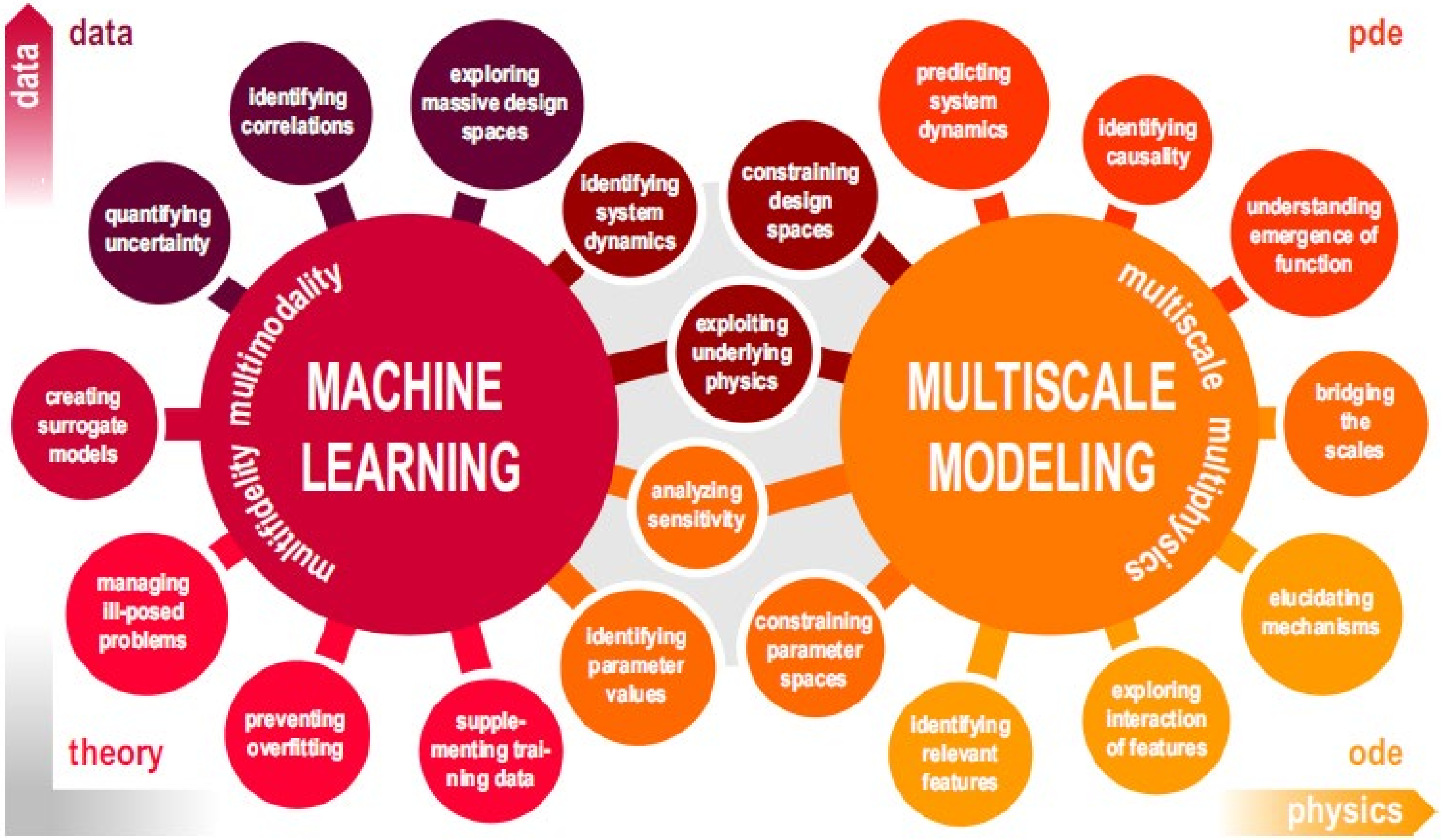
Fig. 3 | **Modelling drug pharmacokinetics and pharmacodynamics in human body-on-chips. a** | Multi-organ chip systems linked by common flow channels can mimic the physiological linking of organs in our bodies, and hence drug absorption, distribution, metabolism and excretion (ADME) that occurs in the human body as a result of whole body-level physiology can be modelled using this approach. Aerosolized, oral and intravenous (IV)

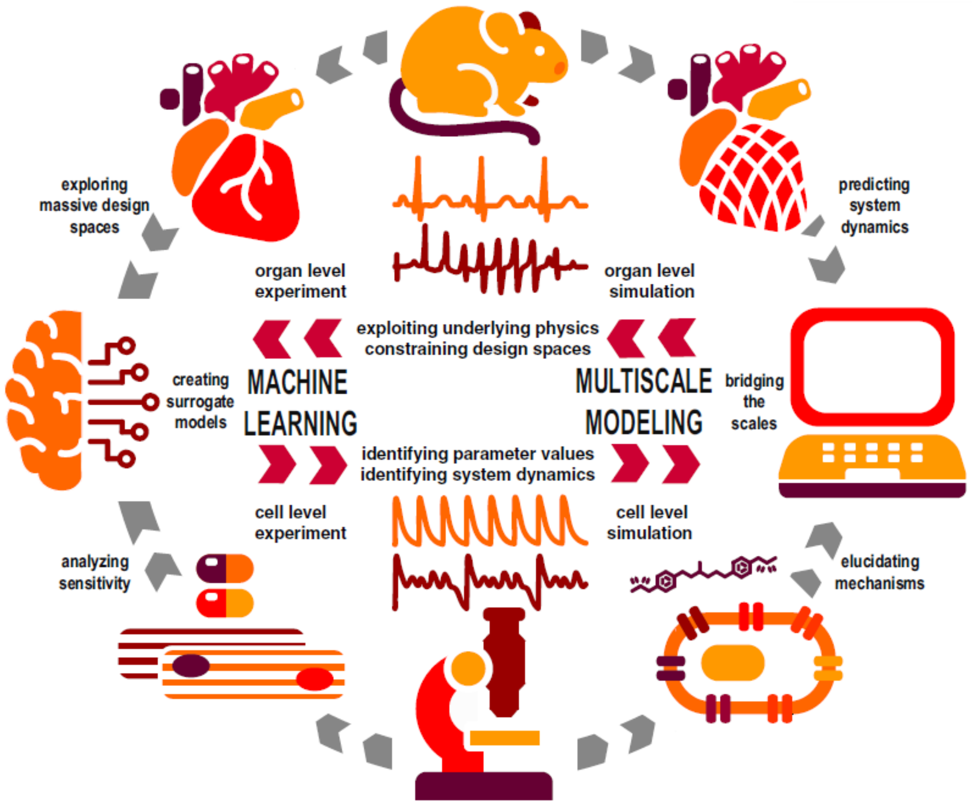
Ingber, *Nat Rev Genetics*, 2022

Challenges for control of human diseases

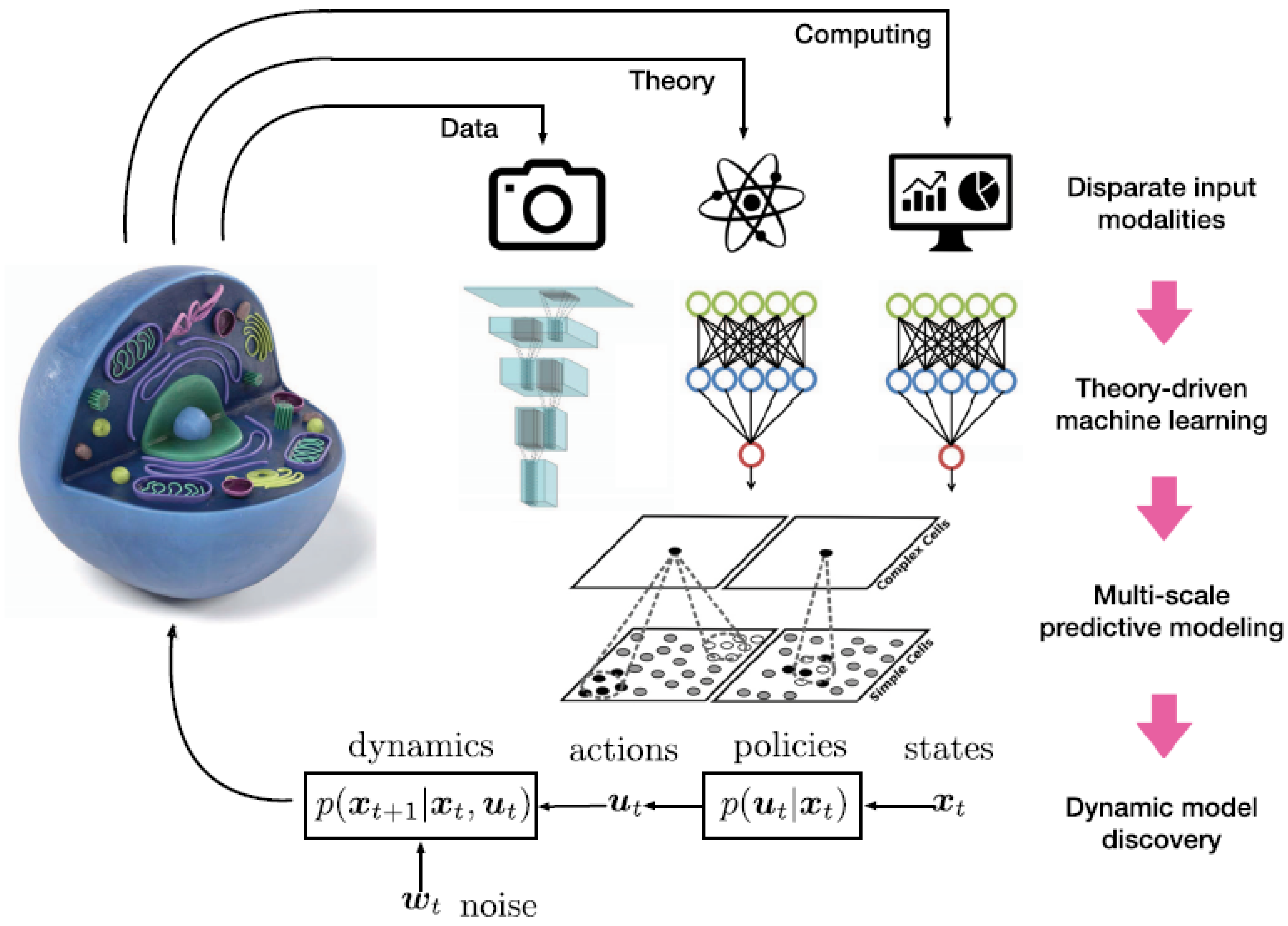
- Limited manipulated variables
- Multiscale (space and time) interacting systems
- Big AND small data issues
- Leveraging AI/ML for biomedical applications

IMAG white paper on ML & MSM in biosystems

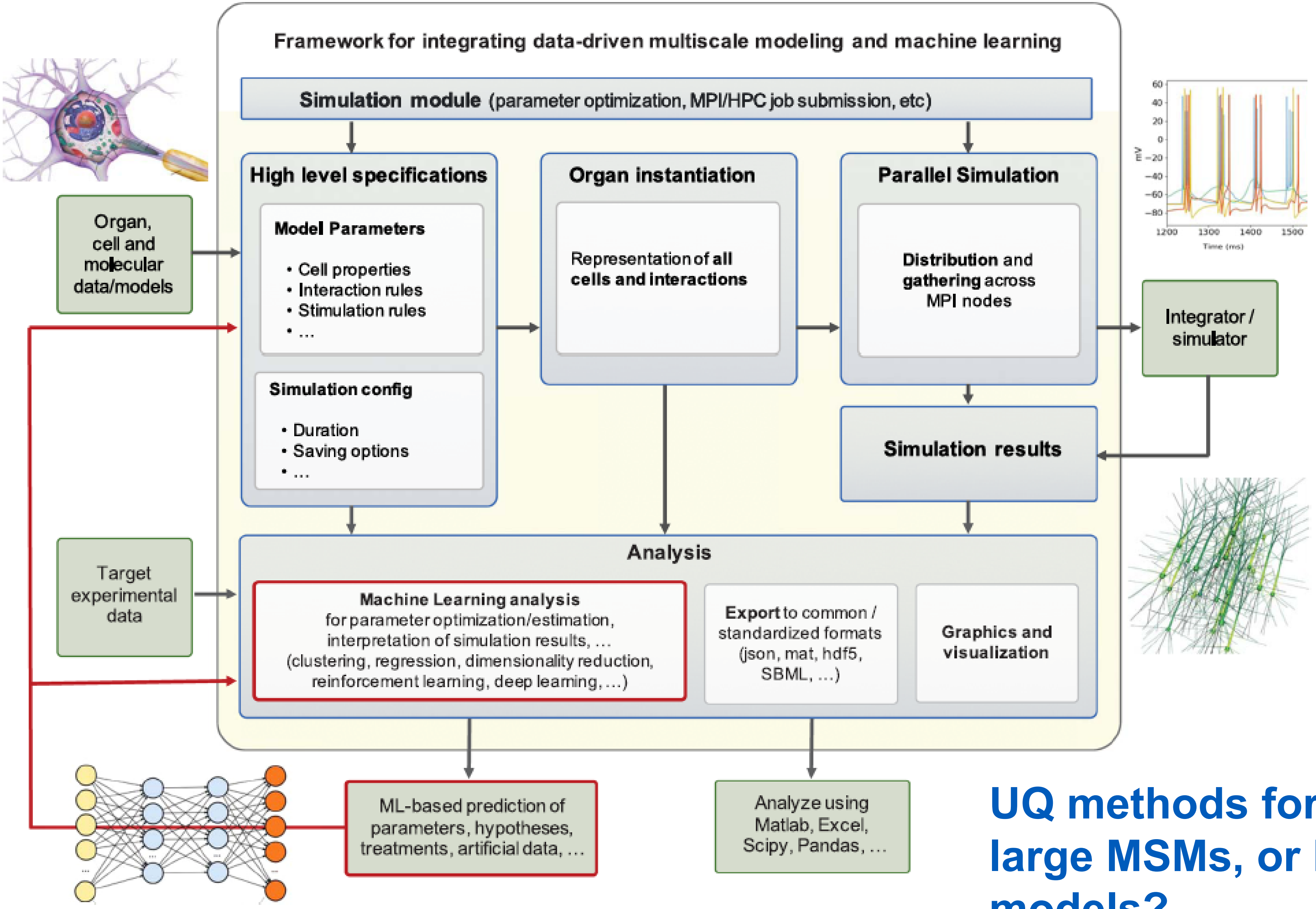




Alber et al., *npj Dig Med,* 2020



Alber et al., *npj Dig Med,* 2020



UQ methods for ABMs, large MSMs, or hybrid models?

Alber et al., *npj Dig Med*, 2020

IMAG white paper on ML & MSM in biosystems: open challenges and opportunities

- Managing ill-posed problems
- Identifying missing information
- Creating surrogate models
- Discretizing space and time
- Bridging the scales
- Supplementing training data
- Quantifying uncertainty
- Exploring massive design spaces
- Elucidating mechanisms
- Understanding emergence of function
- Harnessing biologically inspired learning
- Preventing overfitting
- Minimizing data bias
- Increasing rigor and reproducibility

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REVIEW ARTICLE OPEN

Integrating machine learning and multiscale modeling—perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences

Mark Alber[1], Adrian Buganza Tepole[2], William R. Cannon[3], Suvranu De[4], Salvador Dura-Bernal[5], Krishna Garikipati[6], George Karniadakis[7], William W. Lytton[5], Paris Perdikaris[8], Linda Petzold[9] and Ellen Kuhl[10*]

Alber et al., *npj Dig Med,* 2020

Challenges for control of human diseases

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- **Multiscale (space and time) interacting systems**
- **Big AND small data issues**
- **Leveraging AI/ML for biomedical applications**

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