Key Lessons from Multi-scale Modeling of Body, Tissue, Cell, and Sub-cellular Structures

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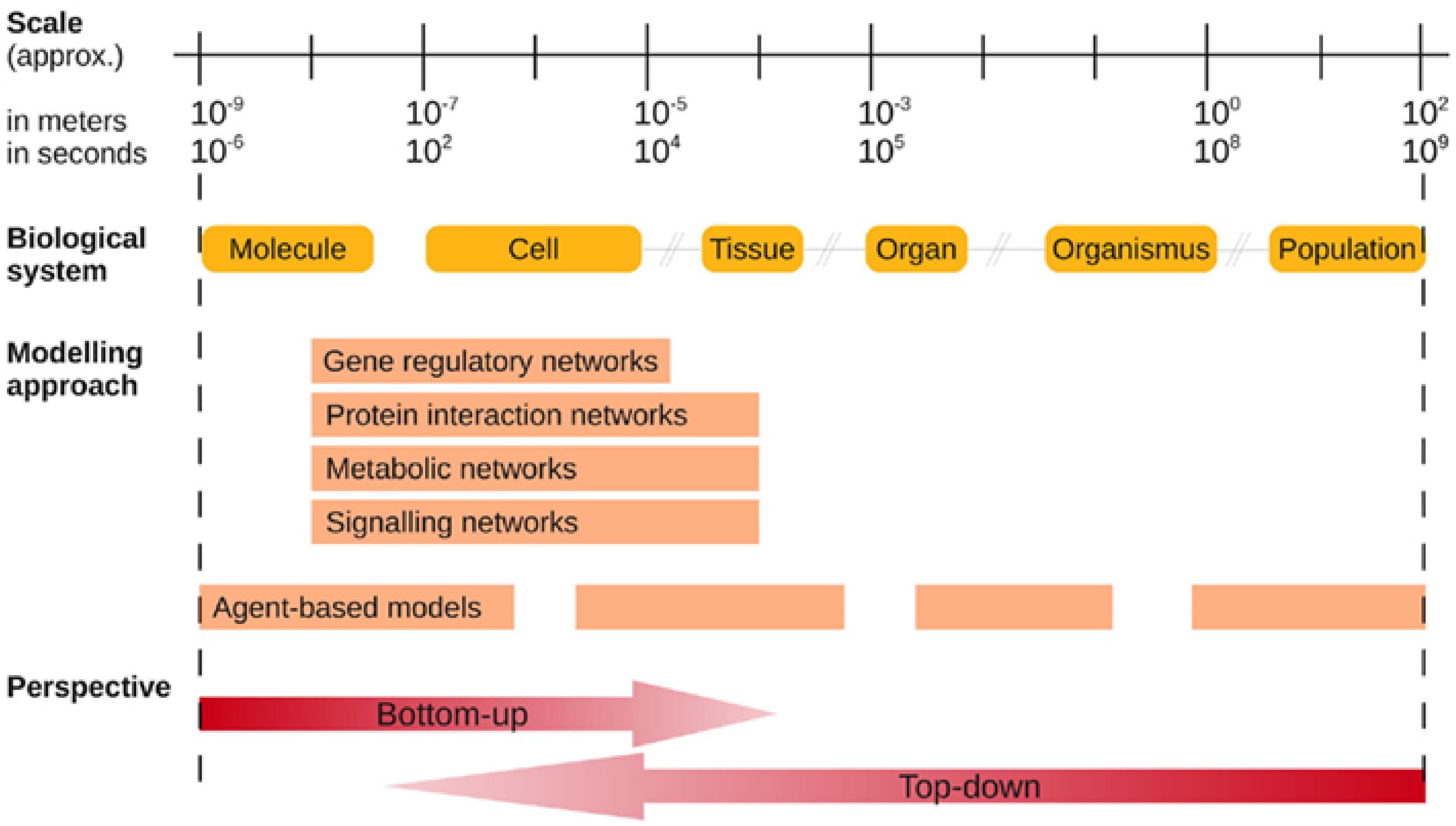
Benefits of Simulation in Biology

- Can model structures and processes that are inaccessible to experimentation
  - Surface of an axon
- Can make assumptions that are experimentally difficult or impossible
  - An in silico ‘lesion’ in a neural circuit, or stimulation of same
- Can simplify a system and its components at will
  - Model a microtubule as a 7-layer cylinder
- Can model at several hierarchical systems levels
- Scalable in ways that in vivo and in vitro studies are not
- Can generate large datasets and reduce statistical error

Arle, J. E., & Carlson, K. W. (2016). The use of dynamic computational models of neural circuitry to streamline new drug development. Drug Discovery Today: Disease Models, 19, 69-75. doi:https://doi.org/10.1016/j.ddmod.2017.01.002

Carlson, K. W., Shils, J. L., Mei, L., & Arle, J. E. Functional Requirements of Small- and Large-Scale Neural Circuitry Connectome Models. In S. Makarov, G. Noetscher & A. Nummenmaa (Eds.), Brain and Human Body Modeling 2020: Computational Human Models Presented at IEEE EMBC 2019 (Cham CH: Springer Nature (2020). 249-260.

Schroll, H., and Hamker, F.. Basal Ganglia Dysfunctions in Movement Disorders: What Can Be Learned from Computational Simulations. *Mov Disord 31(11)* (2016) 1591-1601. doi: 10.1002/mds.26719.



Horn, F., et al. Systems biology of fungal infection. *Front Microbiol (2012), 3, p 108 (after Forst, 2006)*

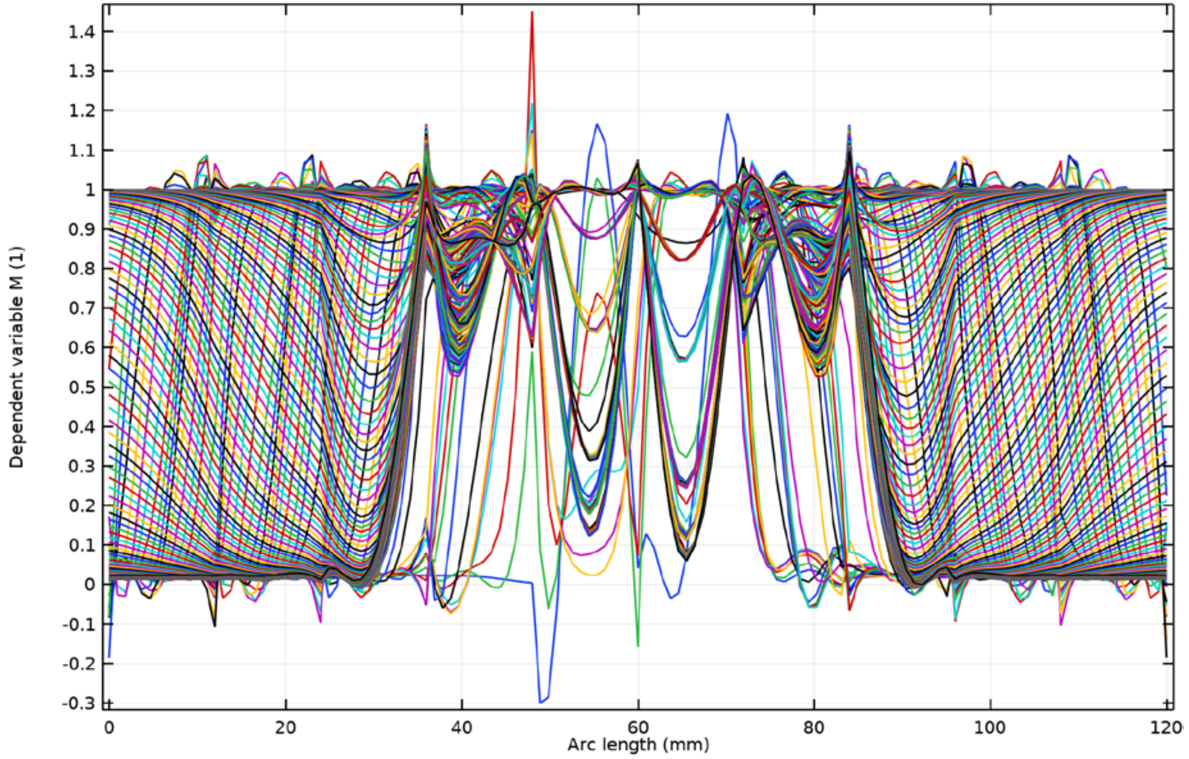
Multi-scale modeling in biology

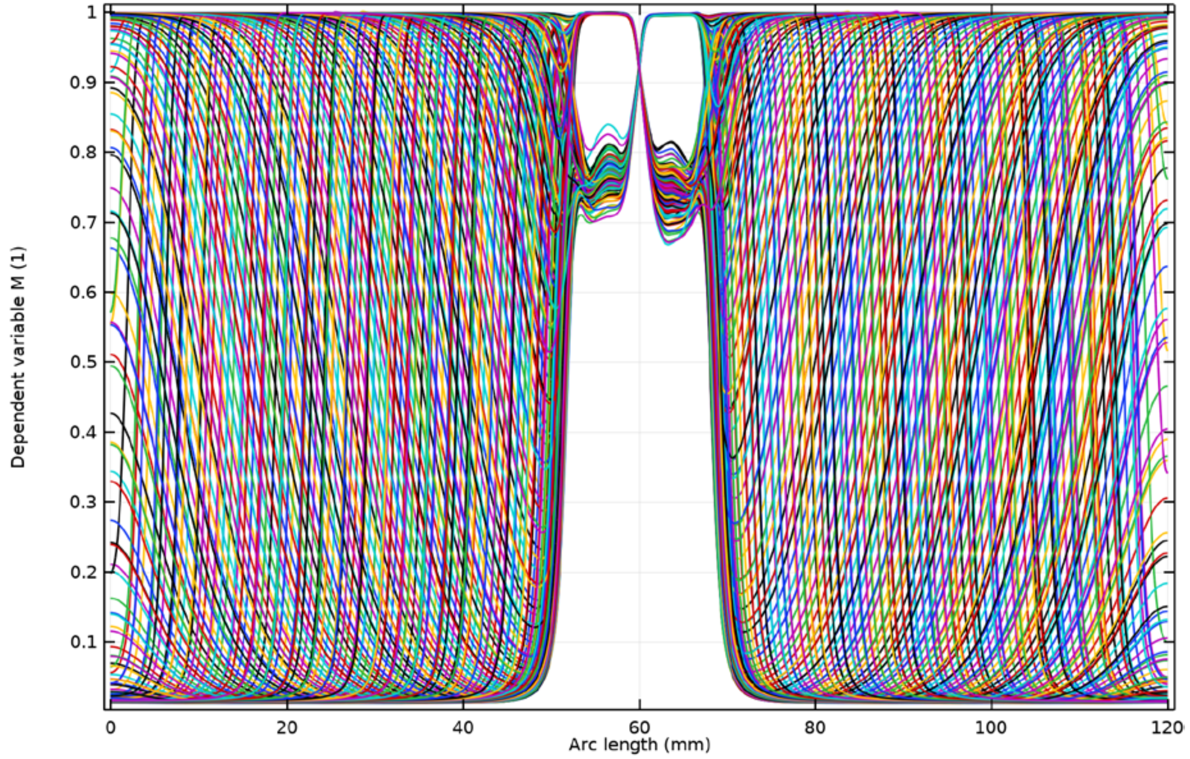
- **LESSON ONE**
- Finite element dimensional scales must approximate the smallest physical component, the shortest time constant, or the most sensitive component

  - Space scale: Nanometers to meters
  - Time scale: Nanoseconds to seconds
  - Force scale: Piconewtons (10^{-12})
  - Energy scale: 10^{-21} joules
- John Howard: Learn to think on the scale of your model
  - 1 pN = weight of a red blood cell, or the pressure of a laser pointer on a screen

COMSOL, Resolving Time Dependent Waves, https://www.comsol.com/support/knowledgebase/1118.
Howard, *Mechanics of Motor Proteins and the Cytoskeleton.* Oxford Univ/Sinauer Associates (2001)

Example: Numerical overshoot





Left: Numerical overshoot. Y-coordinate is a probability, which must be between 0 and 1.

Right: Solved with a finer spatial mesh.

Interweave analytic and empirical approaches with finite element modeling

- **LESSON TWO**
- Biological models tend to be under-calibrated and therefore under-constrained.
- Calibrate to one or more analytic results, and to multiple empirical datasets that are orthogonal in some sense.
- Large error bars are typical in biology
  - Solution: parameter sweeps, sensitivity analysis
  - Provide a simple path for new empirical results to be incorporated into the model
  - Testable predictions are the ultimate validation

Dokos, *Modelling Organs, Tissues, Cells and Devices: Using MATLAB and COMSOL Multiphysics.* Springer (2017).

Generally, use small, simple, specialized models

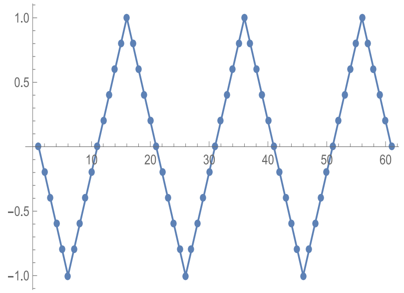
- **LESSON THREE: The Freddie Hansen approach**
- Hansen has built 300 models in 6 years
- Most are small, simple, and specialized
- Designed to answer carefully-defined specific questions

“With simple models I use COMSOL Multiphysics like a pocket calculator. I build one in a few hours, run it and get an answer.”

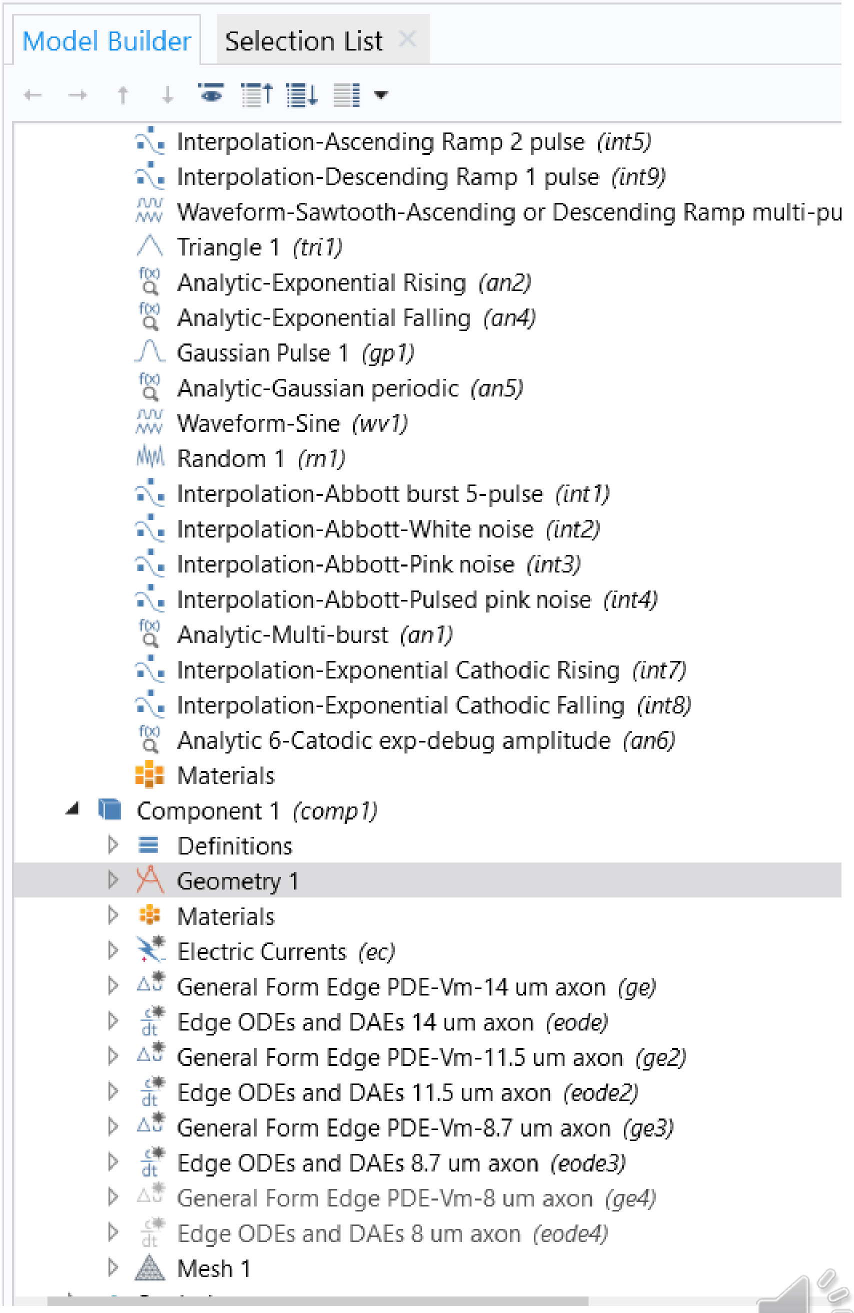
“Others are sophisticated. I work with complex models for months before I get the information I want from them.”

Hansen, Multiphysics modeling of heart pumps. https://www.youtube.com/watch?v=Vahz_lVgrFc

When to use large, complicated models



- Large, complicated models
  - Take months or years to build
  - Can be difficult to validate
  - Can be difficult to understand
- Build when the coupled interaction of their parts must be studied
- Restrict models to one biological systems level
  - Systems level coupling
    - Result of a lower systems models is assumption in higher-level models
    - Result of higher-level systems model is a constraint or calibrations or validation of lower-systems level model



von Neumann, The general and logical theory of automata, in Newman, *The World of Mathematics*. Dover (2000).

Use ‘dimensionless’ modeling

LESSON FOUR:

- A powerful tool when modeling the microcosm
- Steps:
  1. Simplify the differential equations as much as possible.
  2. Re-scale constants to the desired order of magnitude
     Imagine a simple problem on that scale
  3. Divide each model dimension by its re-scaled constant
  4. Solve with these variables
  5. Invert Step 3 to convert back to original scale

$$\text{Length scale: } L_0 = L = 1.8\times10^{-8}\ \text{m}$$

$$\text{Time scale: } t_0 = \frac{1}{\omega} = 5\times10^{-6}\ \text{s}$$

$$\text{Electric field scale: } E_0 = E_i = 200\ \text{Volts/m}$$

$$\text{Potential scale: } V_0 = E_0 L_0 = E_i L = 4\times10^{-6}\ \text{Volts}$$

$$\text{Current density scale: } J_0 = \sigma_c E_0 = \sigma_c E_i = 20\ \text{A/m}^2$$

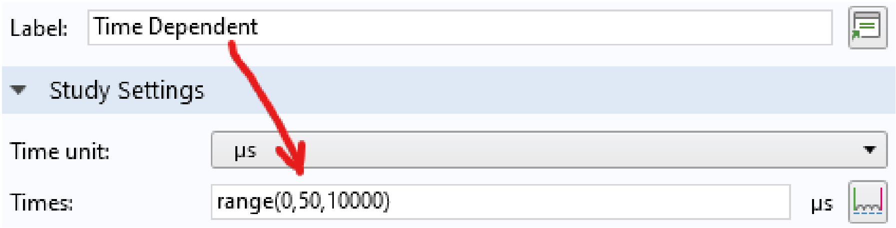
$$\text{Charge density scale: } \rho_0 = \frac{\varepsilon_0 V_0}{L_0^2} = \frac{\varepsilon_0 E_i}{L} = 0.0854\ \text{C/m}^3$$

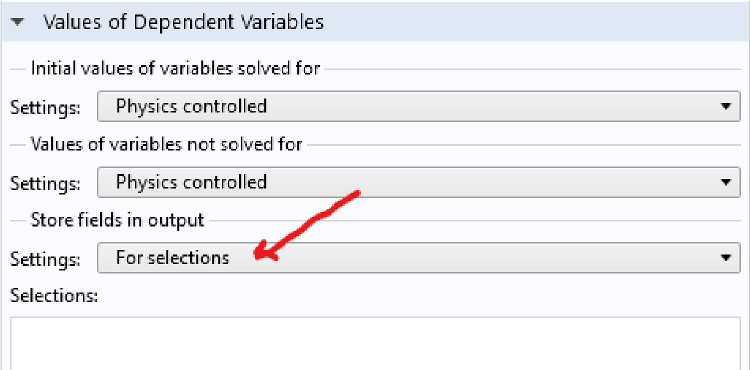
$$\text{Electrical conductivity scale: } \sigma_0 = \sigma_c = 0.1\ 1/(\Omega\text{m})$$

Detailed example:
Dreeben, An Example of Dimensionless Modeling of the Biomedical Microcosm.
https://comsol-finite-element-analysis.blogspot.com/2020/09/an-example-of-dimensionless-modeling-of.html

COMSOL Techniques for Large Models

- Use Time-Dependent Solver as Steady-State Solver
  - Why? More control, e.g. over timesteps
  - How to implement? Only store last time step, no intermediate time steps
- Reduce run time and model size by storing selections, not entire geometry
  - Solver (e.g. Time Dependent)
    - Values of Dependent Variables
      - Store fields in output, Settings: For selections





Thank you!

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  - Tom Dreeben
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  - Ze’ev Bomzon

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