Computational modelling at the cellular level

Cian O'Donnell
University of Bristol

cian.odonnell@bristol.ac.uk

@cian_neuro

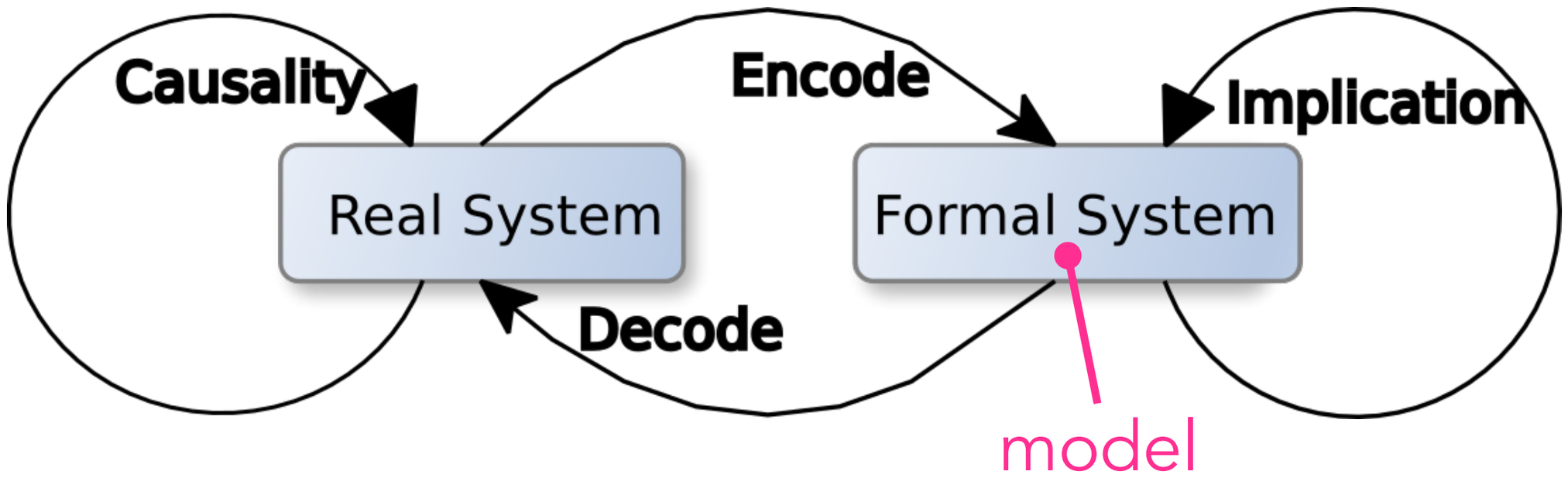
What we will cover

- What is a model?
- What is the purpose of computational modelling?
- Levels of abstraction (spatial, temporal, and conceptual)
- Test case: dendritic spine calcium signalling in plasticity.
- How do we choose the ‘correct’ model for our problem?
- What software should we use?

What is a model?

- A model is a simplified description of a real-world system.
- Models can be:
  - Physical (e.g. scale models of buildings)
  - Analogical (e.g. billiard-ball model of a gas)
  - Phenomenological (e.g. integrate-and-fire neuron)
- Models can be represented by:
  - A physical object
  - Words
  - Mathematical equations
- Overview of the philosophy of models in science: https://plato.stanford.edu/entries/models-science/

What is a model?



https://commons.wikimedia.org/wiki/File:MathModel.svg

What is a computational model?

- A computational model is just a mathematical model that is programmed and then solved or simulated using a computer.

- Technically speaking all computational models are phenomenological (Hodgkin & Huxley ignored quantum mechanics).

- However in practice in neuroscience, most people consider phenomenological models to be those which abstract away all laws of (bio)physics.

- More references: http://www.synapticlee.co.uk/blog/2018-08-05_references_on_simulation

What is the purpose of a computational model?

"All models are wrong, but some are useful."

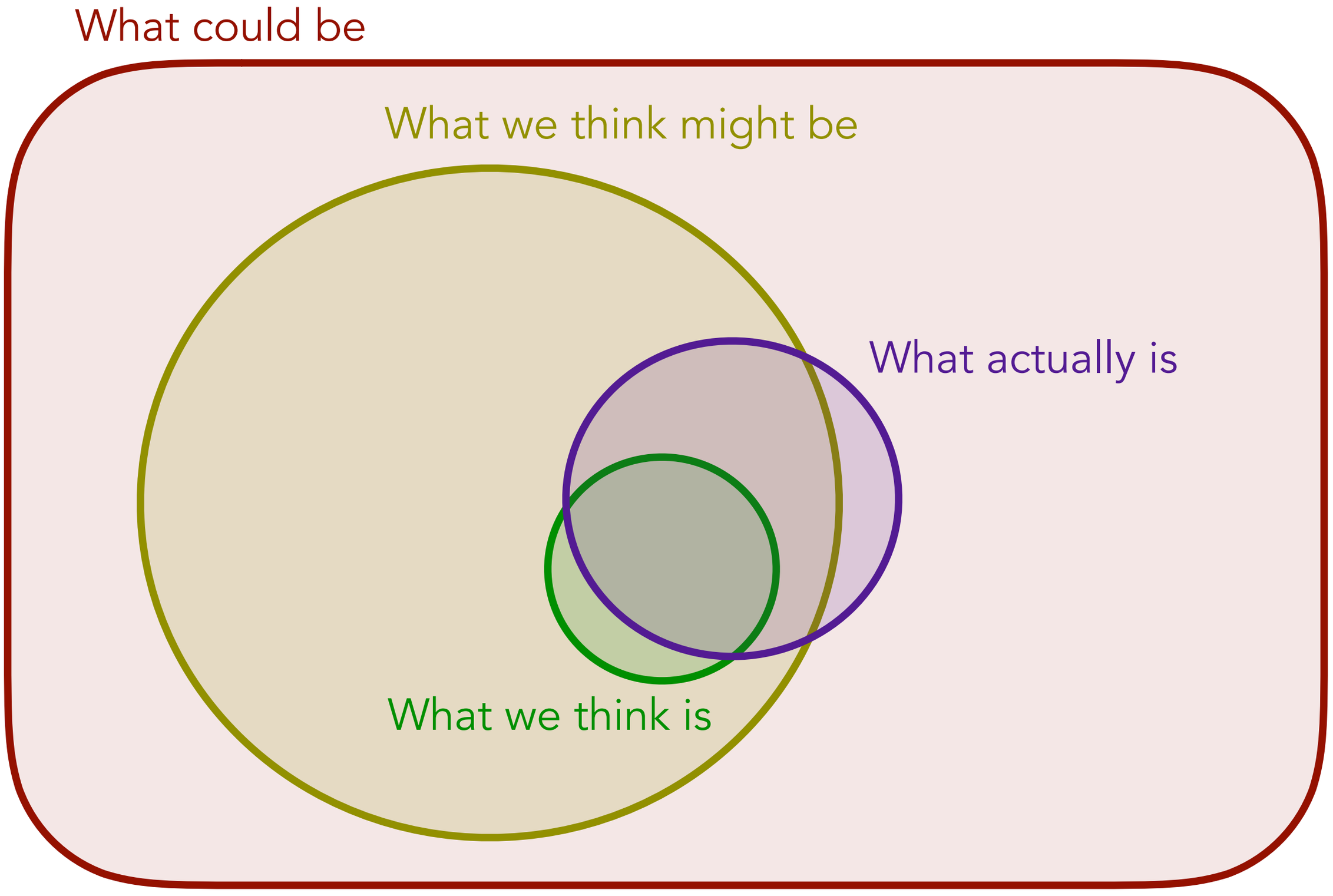
— George Box

What is the purpose of a computational model?

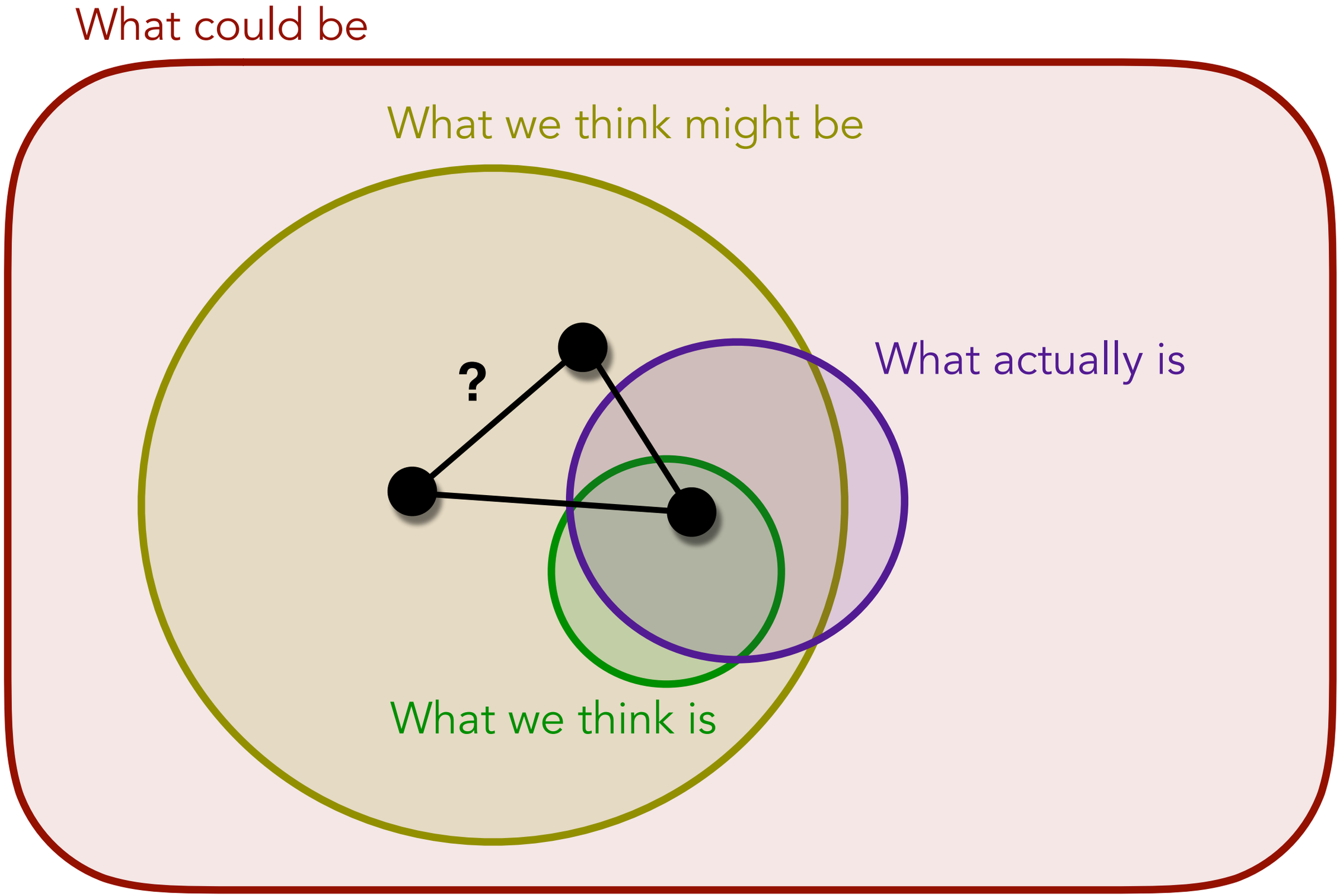
To gain an understanding of a system beyond what we could achieve via word models alone.

Computational models can be used to:

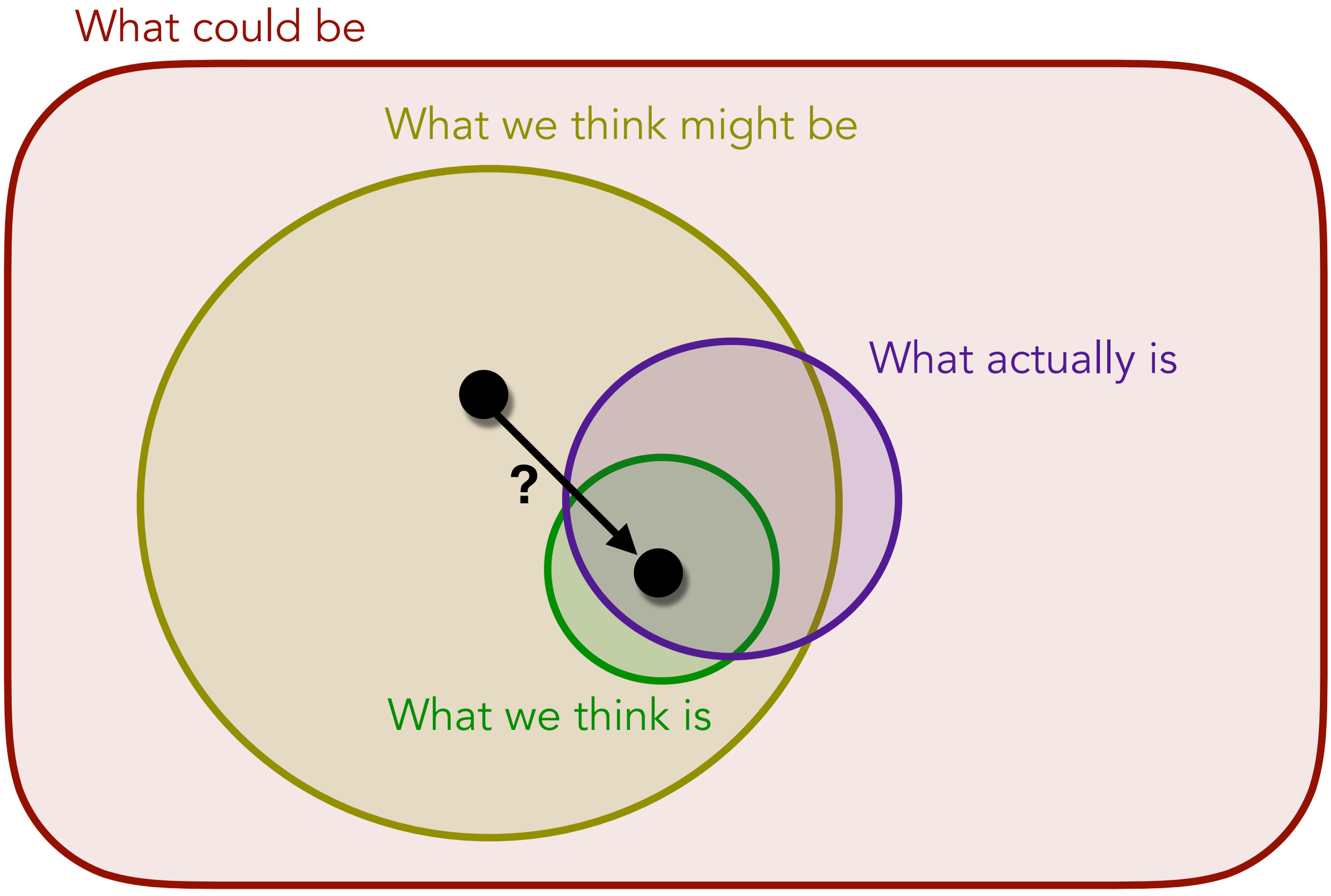
1. test if a set of concepts are mutually consistent. If not, why?
2. "link levels"; to ask if a mechanism at one level of description can account for a phenomenon at another level.
3. simulate experiments that are technically difficult or impossible to do in the lab.
4. explore "what if?" scenarios that may never occur in the nature.
5. validate a formal mathematical analysis.


What could be
What we think might be
What actually is
What we think is

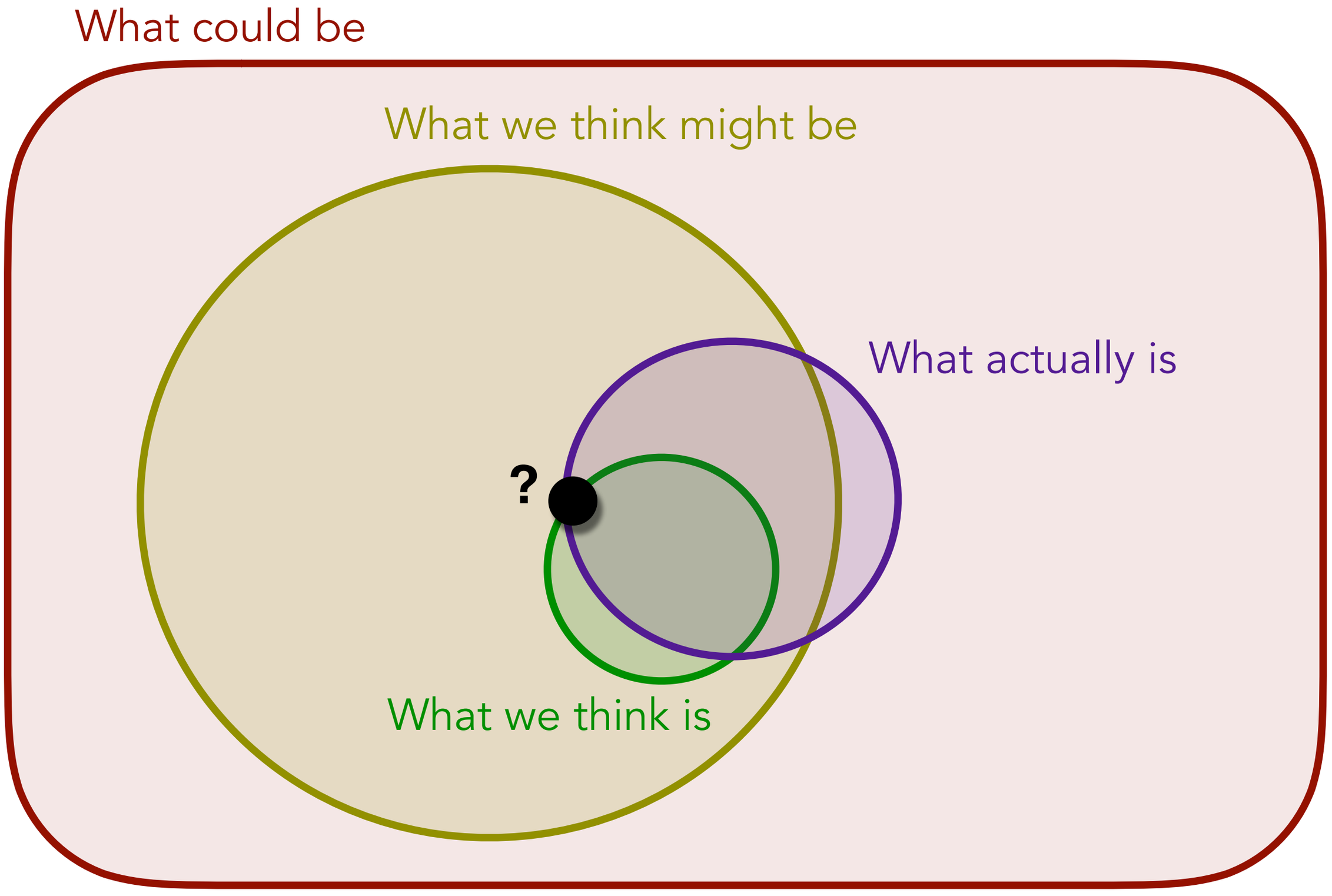
1. are these ideas mutually consistent?



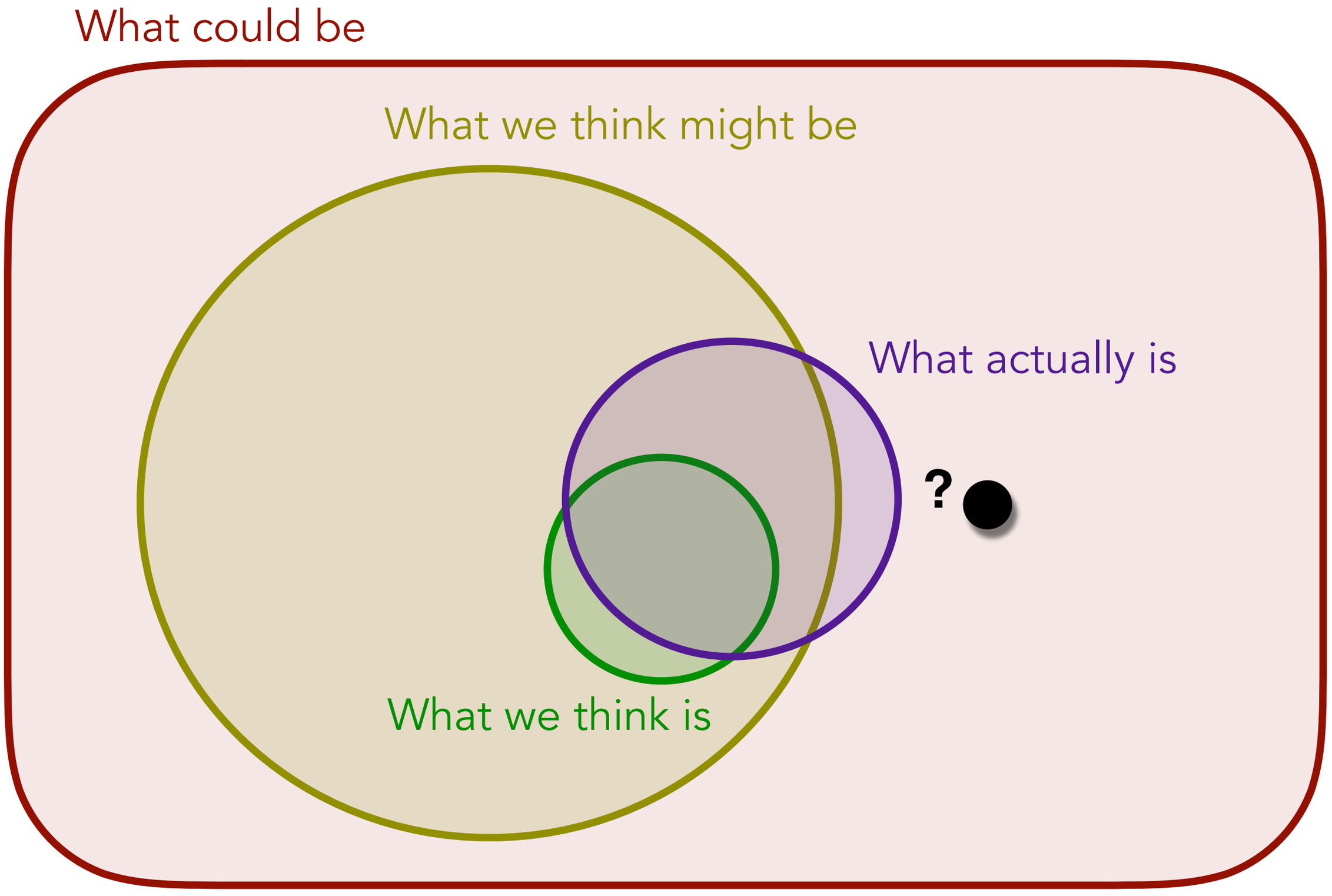
2. can ‘this’ explain ‘that’?



3. simulate difficult experiments

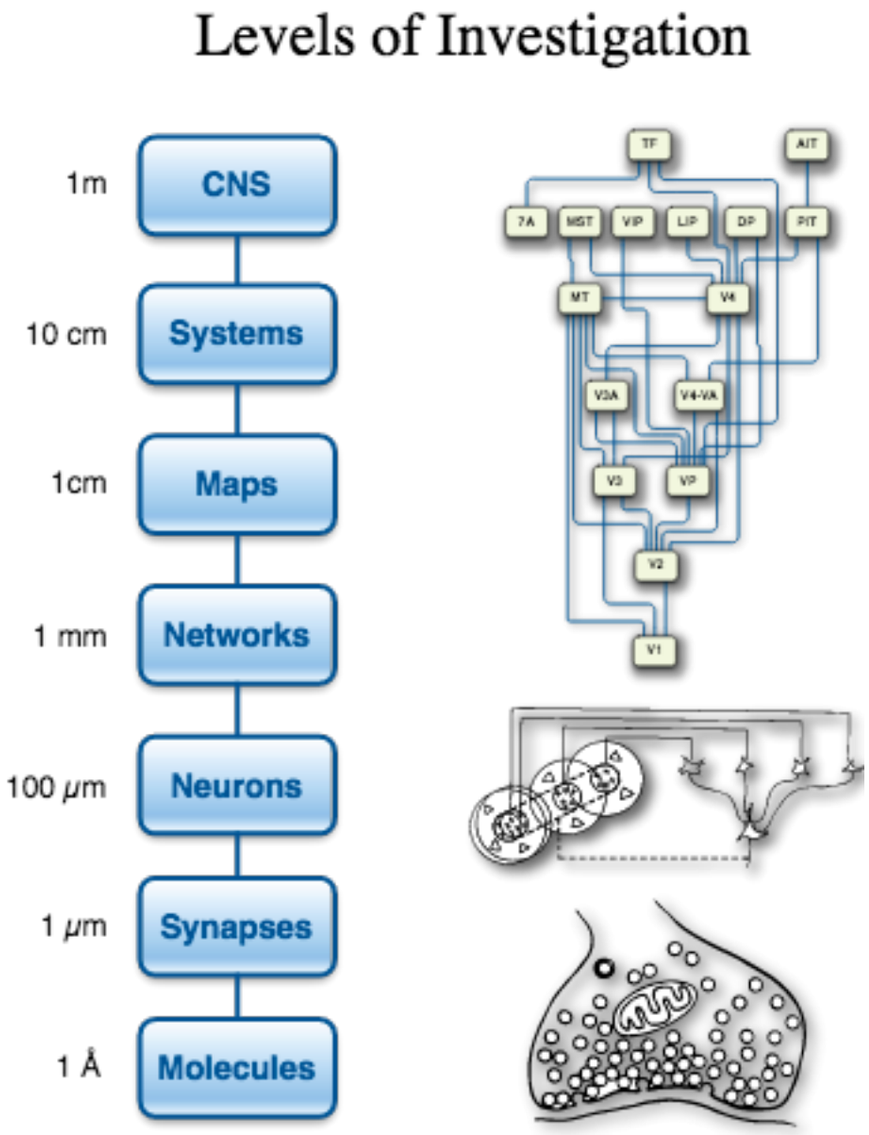


4. simulate 'what if?' scenarios



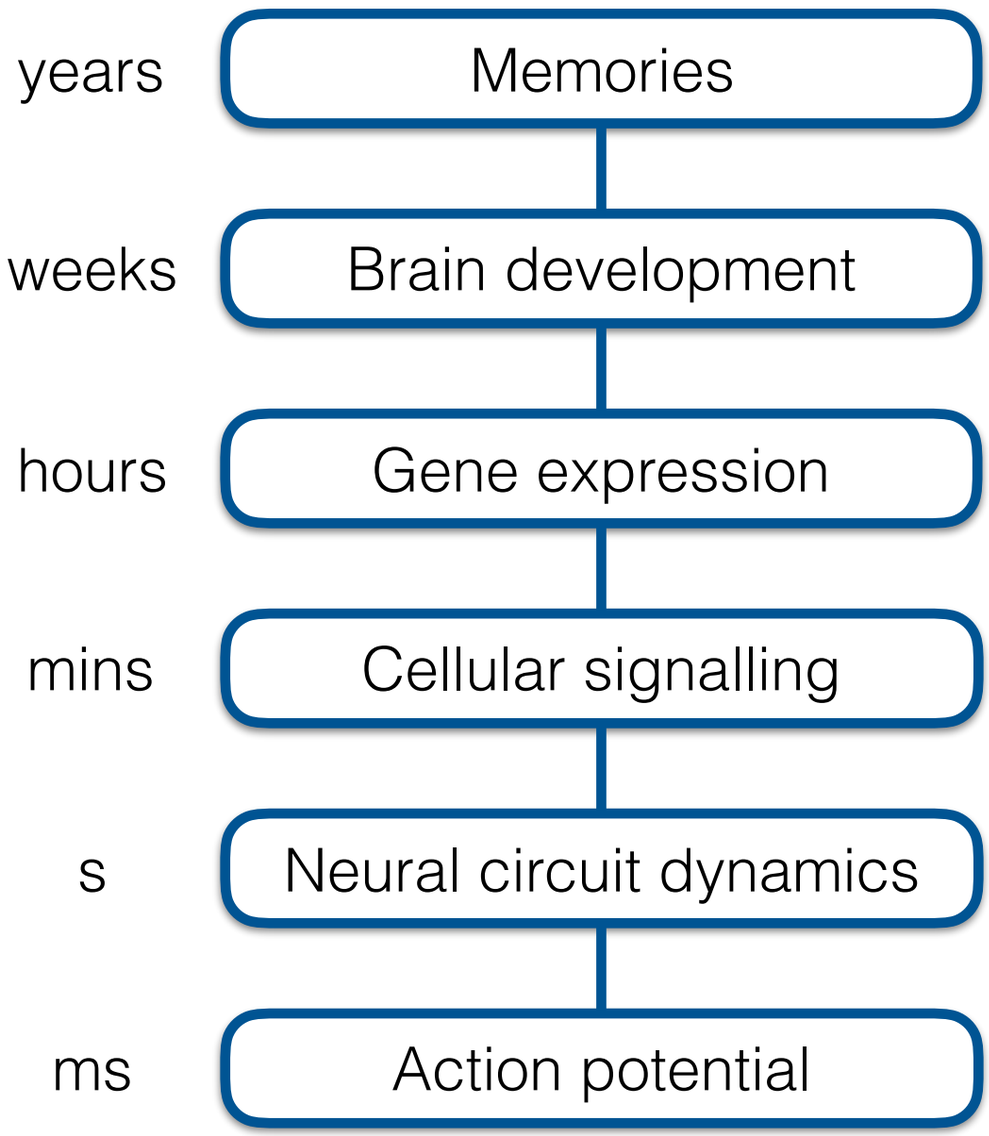
Levels of abstraction

Spatial

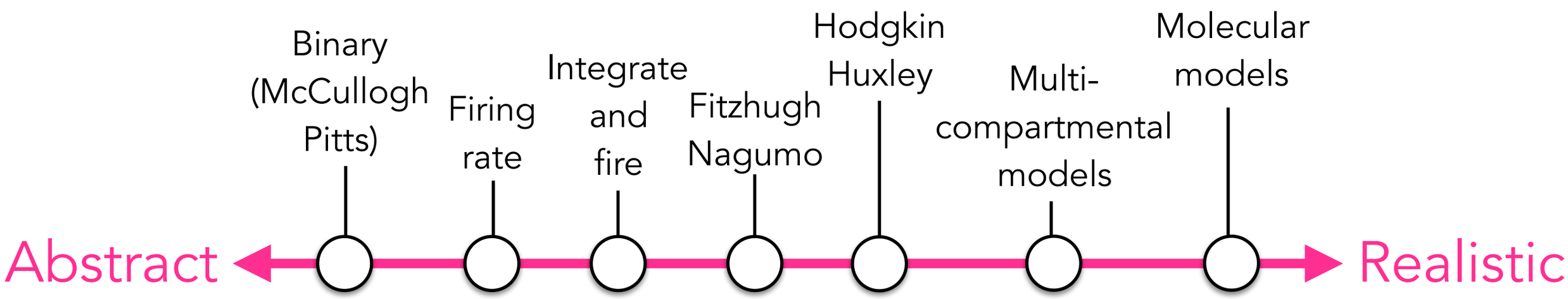


T. Sejnowski
http://cnl.salk.edu/

Temporal



Models of single neurons



Abstract models		**Realistic models**
Simple	vs	Detailed
Hard to relate to biology	vs	Contains stuff you could measure
Few parameters	vs	Lots of parameters
Fast simulation	vs	Slow simulation
Mathematical analysis	vs	Intractable
Generic	vs	Specific

Case study: calcium dynamics in a dendritic spine.

16142 • The Journal of Neuroscience, November 9, 2011 • 31(45):16142–16156

Development/Plasticity/Repair

Dendritic Spine Dynamics Regulate the I… rm Stability of Synaptic Plasticity

Cian O'Donnell,[1,2] **Matthew F. Nolan**[3]

[1]Institute for Adaptive and Neural Com… Informatics, University of Edinburgh, Edinburgh EH8 9AB, United Ki… urgh, Edinburgh EH8 9XD, United Kingdom

4 different models!

Long-term synap… Ca^{2+} and is accompanied by changes in dendritic spine size. Unless Ca^{2+} influx mechanism… tionally, changes in spine size will modify spine Ca^{2+} concentrations during subsequent synaptic activ… elationship between Ca^{2+} influx and spine volume is a fundamental determinant of synaptic stability. If Ca^{2+} in… mpensated for increases in spine size, then strong synapses are stabilized and synaptic strength distributions have a s… peak. In contrast, overcompensation of Ca^{2+} influx leads to binary, persistent synaptic strengths with double-peaked distributions. Biophysical simulations predict that CA1 pyramidal neuron spines are undercompensating. This unifies experimental findings that weak synapses are more plastic than strong synapses, that synaptic strengths are unimodally distributed, and that potentiation saturates for a given stimulus strength. We conclude that structural plasticity provides a simple, local, and general mechanism that allows dendritic spines to foster both rapid memory formation and persistent memory storage.

Introduction

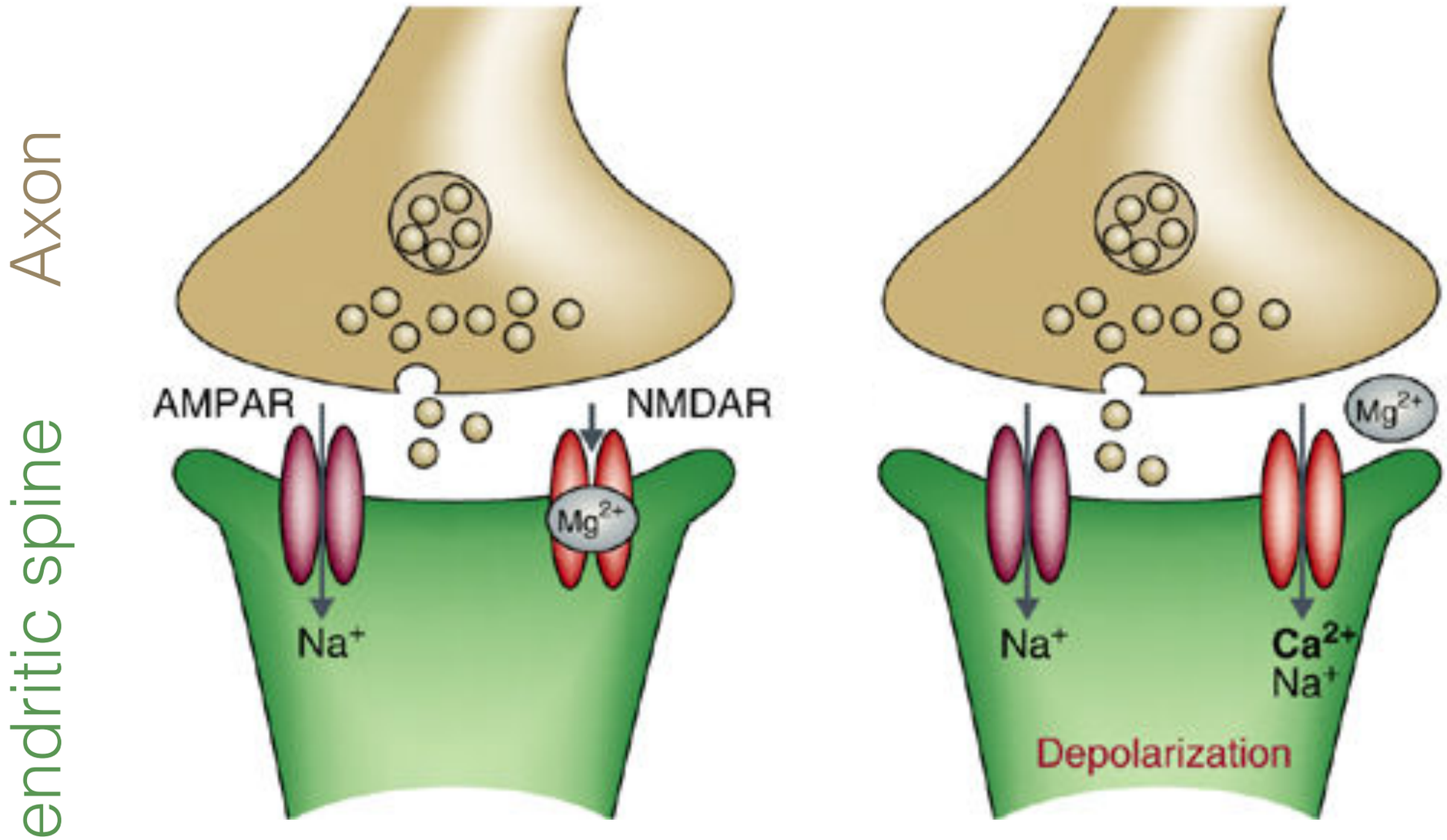
Long-term synaptic plasticity is believed to underlie learning in the brain (Milner et al., 1998; Morris et al., 2003). Synaptic plas-

because of their differences in volume, small spines exhibit greater $[Ca^{2+}]$ changes during synaptic activation than large spines (Nimchinsky et al., 2004; Noguchi et al., 2005; Sobczyk et al., 2005); and (4) large spines are more persistent *in vivo* than

Our question:

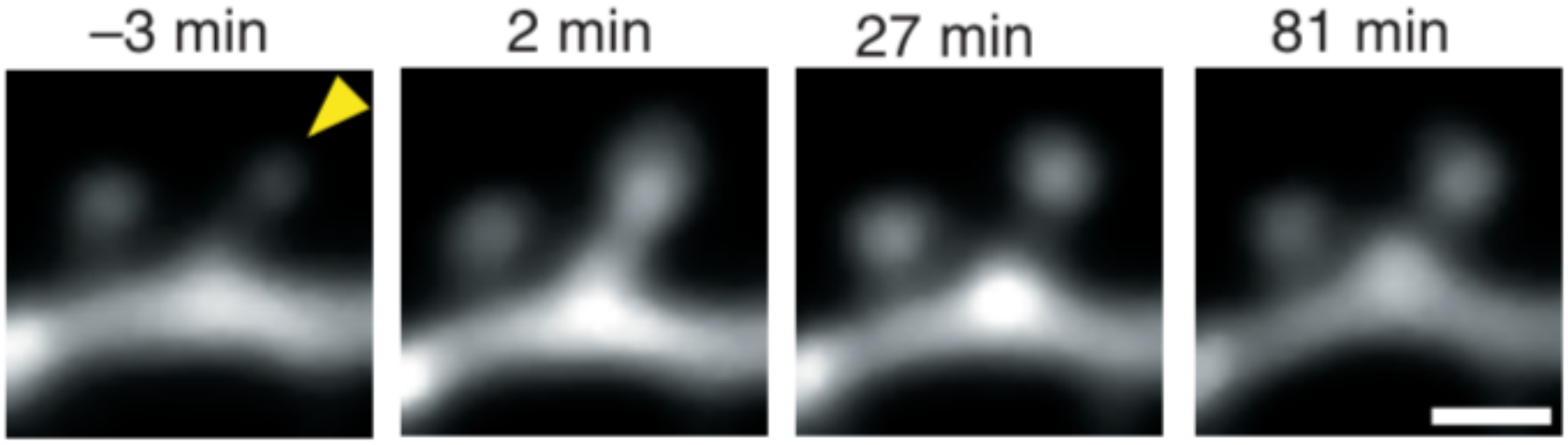
What does dendritic spine structural plasticity do to the rules of synaptic plasticity?

Background



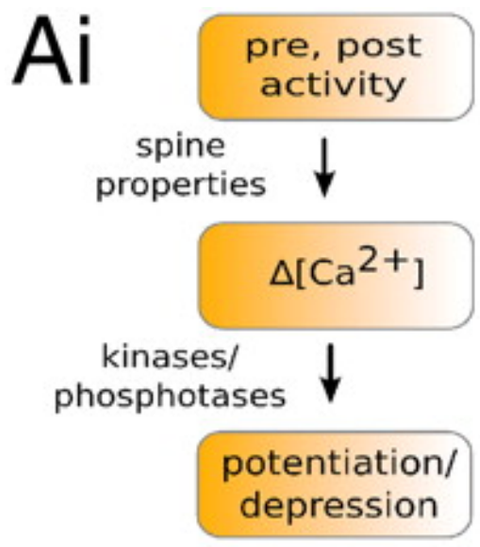
Citri and Malenka, *Neuropsychopharmacology* (2007)

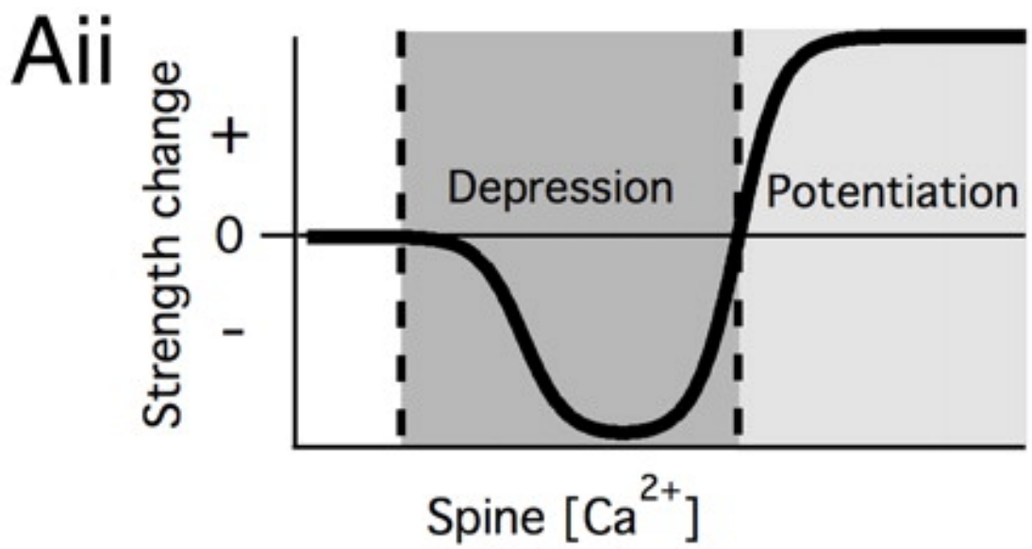
Background



[Matsuzaki et al., Nature, 2004]

Dendritic spines change size during synaptic plasticity.



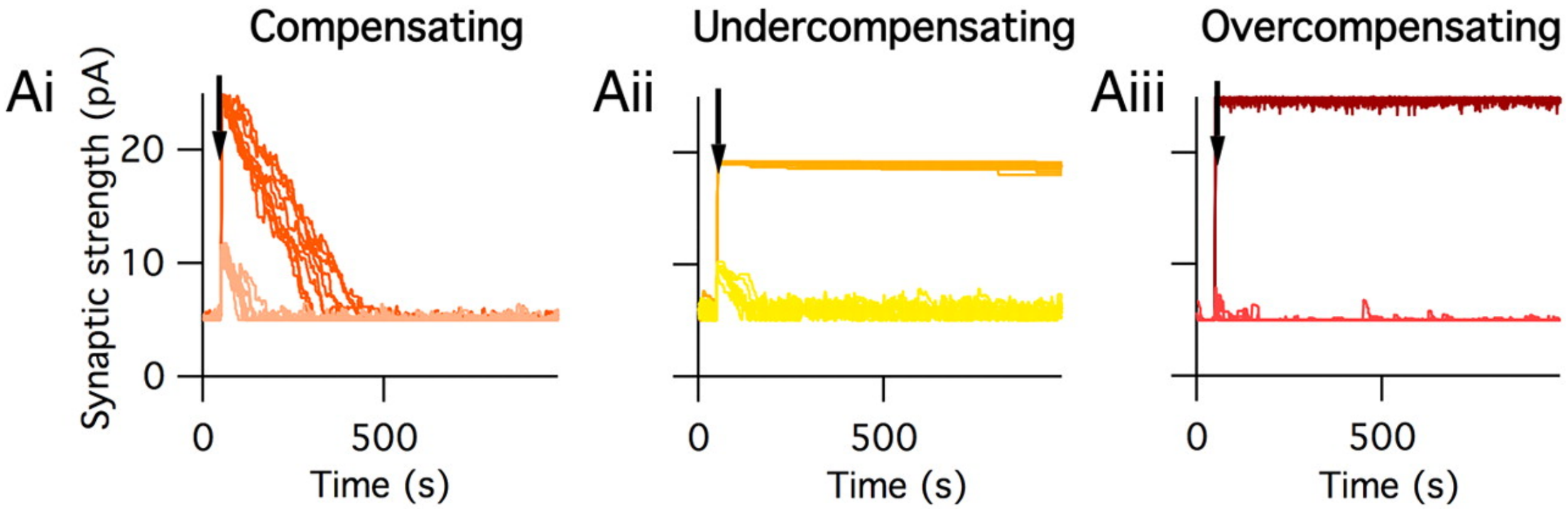


[O'Donnell et al., J Neurosci 2011]

4 models for 4 questions

	Figure 3	Figures 4+5	Figure 6	Figure 7
Mathematical form of model	Small set of ODEs	Fokker-Planck equation	Biophysical model (large set of ODEs)	Particle-based reaction-diffusion
Level of detail	Medium	Low	High	Crazy high
Question	“Can spine plasticity stabilise synaptic strength dynamics?”	“What happens the distribution of synaptic strengths in the long-term?”	“Are rodent hippocampal CA3-CA1 synapses stable or unstable?”	“Does this idea hold up if calcium nanodomains are important?”

Model 1: Integrate and fire



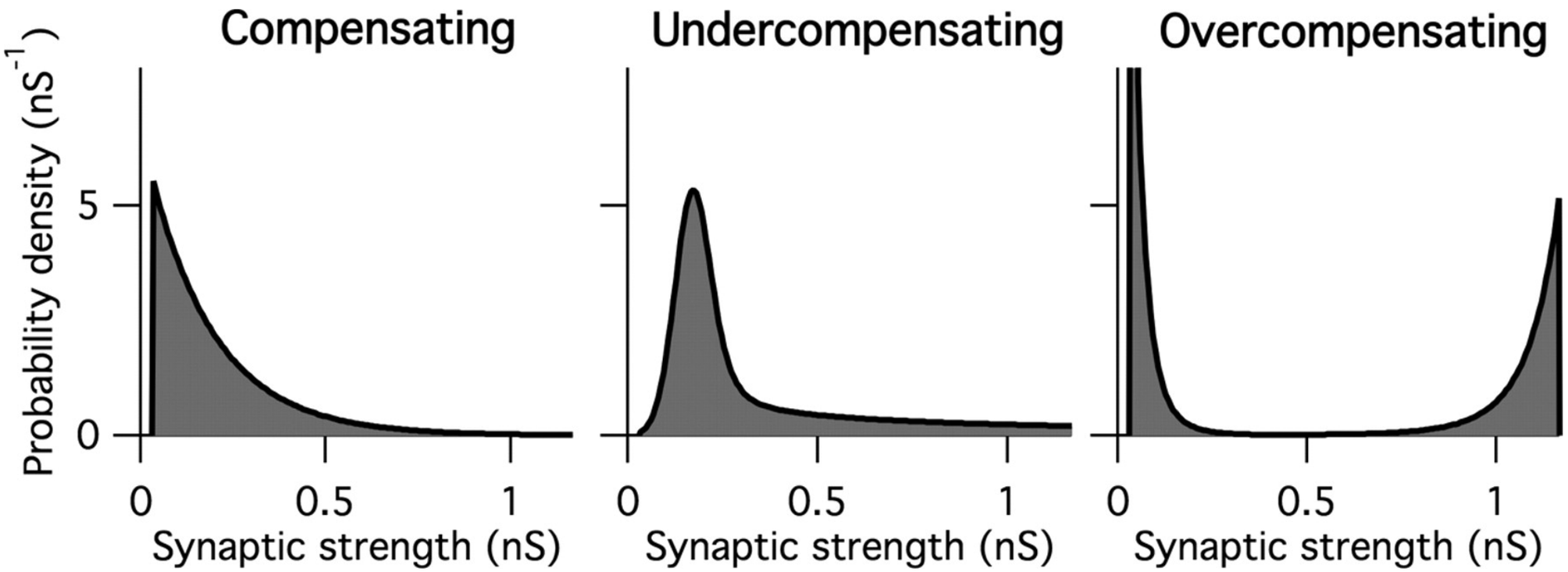
Voltage:

$$\frac{dV}{dt} = (-V + R_{\text{in}} I_{\text{syn}})/\tau_m$$

Calcium in spine:

$$\frac{dCa_{\text{sp}}}{dt} = J_{\text{NMDA}} - Ca_{\text{sp}}/\tau_{\text{Ca}}$$

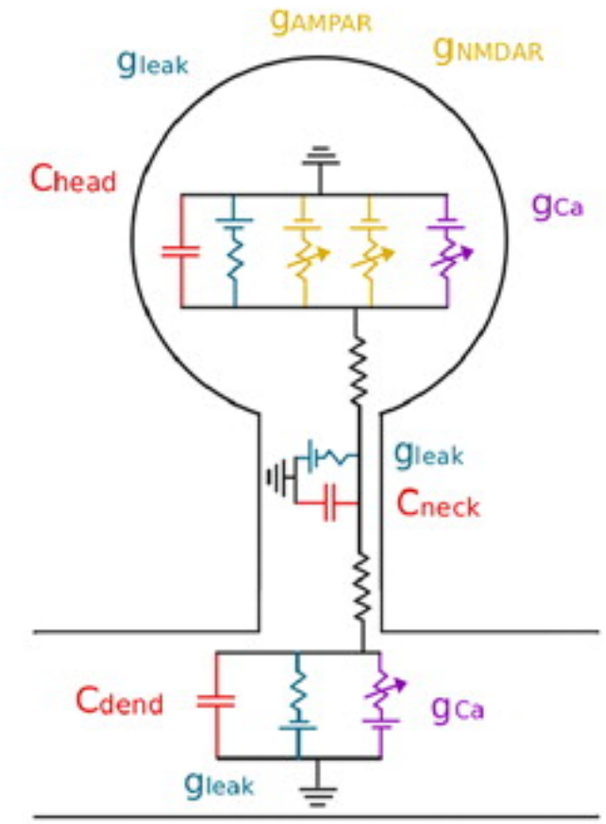
Model 2: Fokker-Planck

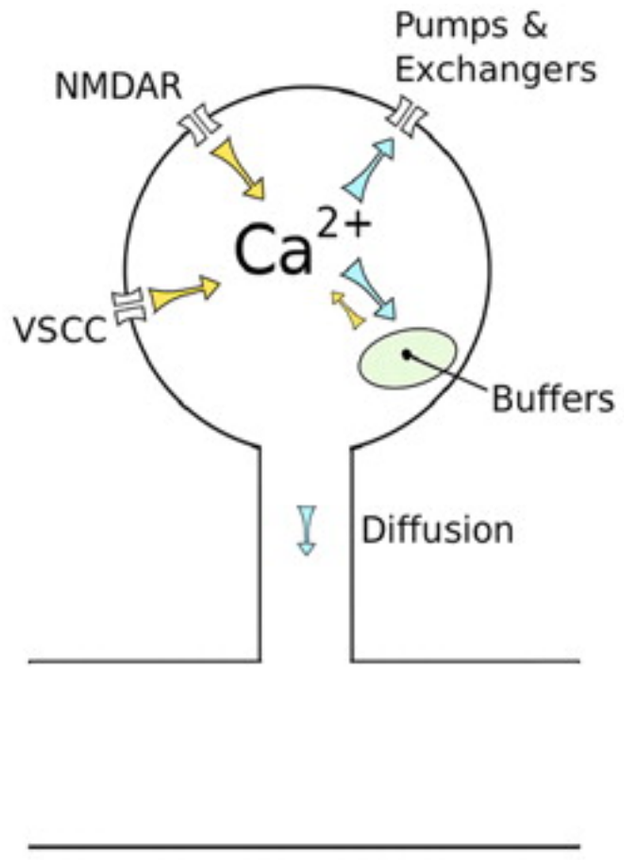


Dynamics of distribution of spine sizes:

$$\frac{\partial P(V_{sp},t)}{\partial t} = -\frac{\partial}{\partial V_{sp}}[A(V_{sp})\,P(V_{sp},t)] + \frac{1}{2}\frac{\partial^2}{\partial V_{sp}^2}[B'(V_{sp})\,P(V_{sp},t)]$$

Model 3: Biophysical

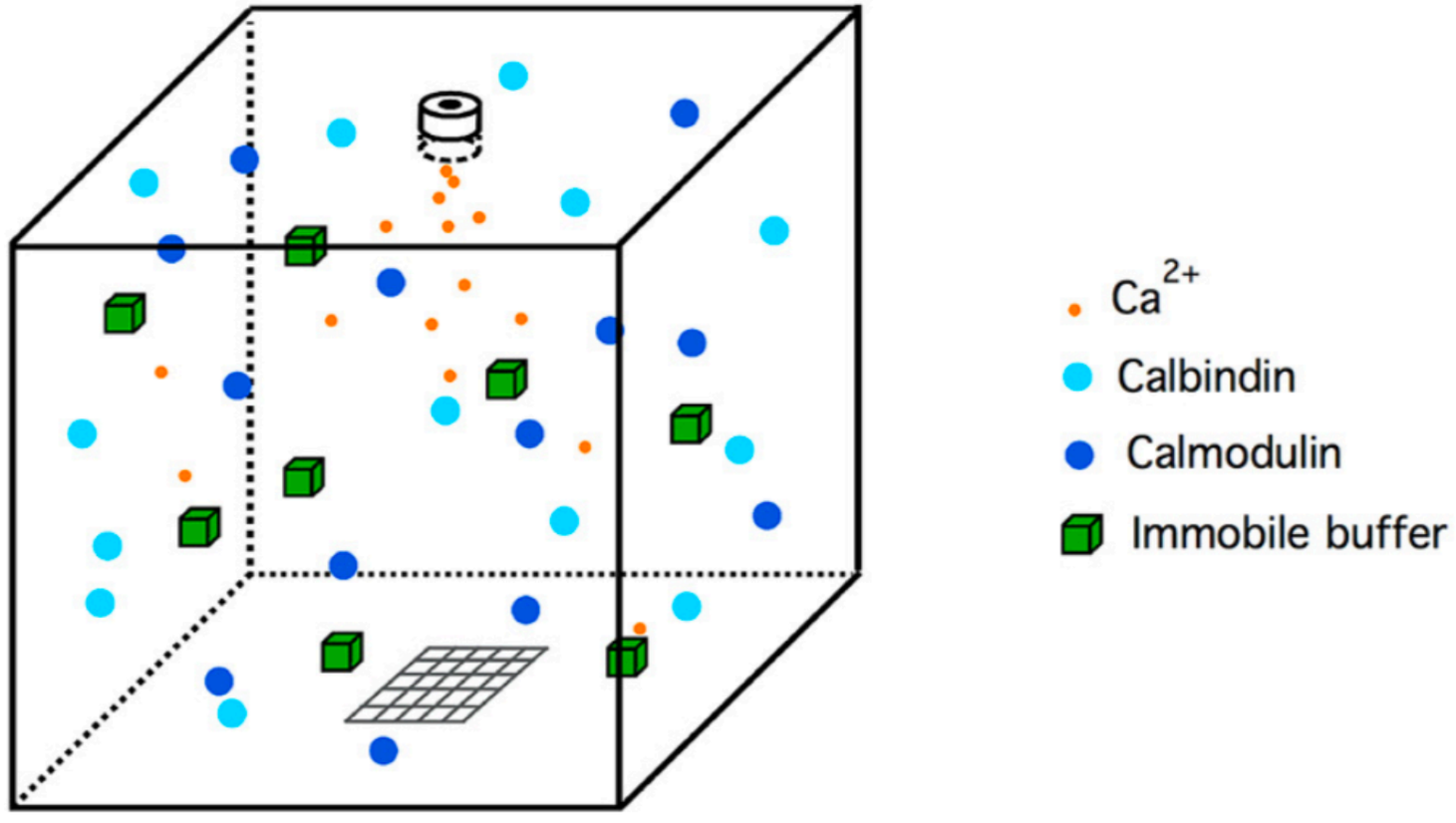




Spine calcium concentration:

$$\frac{d[\mathrm{Ca}^{2+}]_{sp}(t)}{dt} = \frac{-I_{Ca}}{zFV_{sp}} - ([\mathrm{Ca}^{2+}]_{sp}(t) - [\mathrm{Ca}^{2+}]_0)\frac{\beta_{sp}S_{sp}}{V_{sp}} - D\frac{([\mathrm{Ca}^{2+}]_{sp}(t) - [\mathrm{Ca}^{2+}]_{neck}(t))A_{neck}}{l_{neck}V_{sp}} - k_f([B]_{sp}(t)[\mathrm{Ca}^{2+}]_{sp}(t)) + k_b([B]_{Tsp} - [B]_{sp}(t))$$

Model 4: Molecular

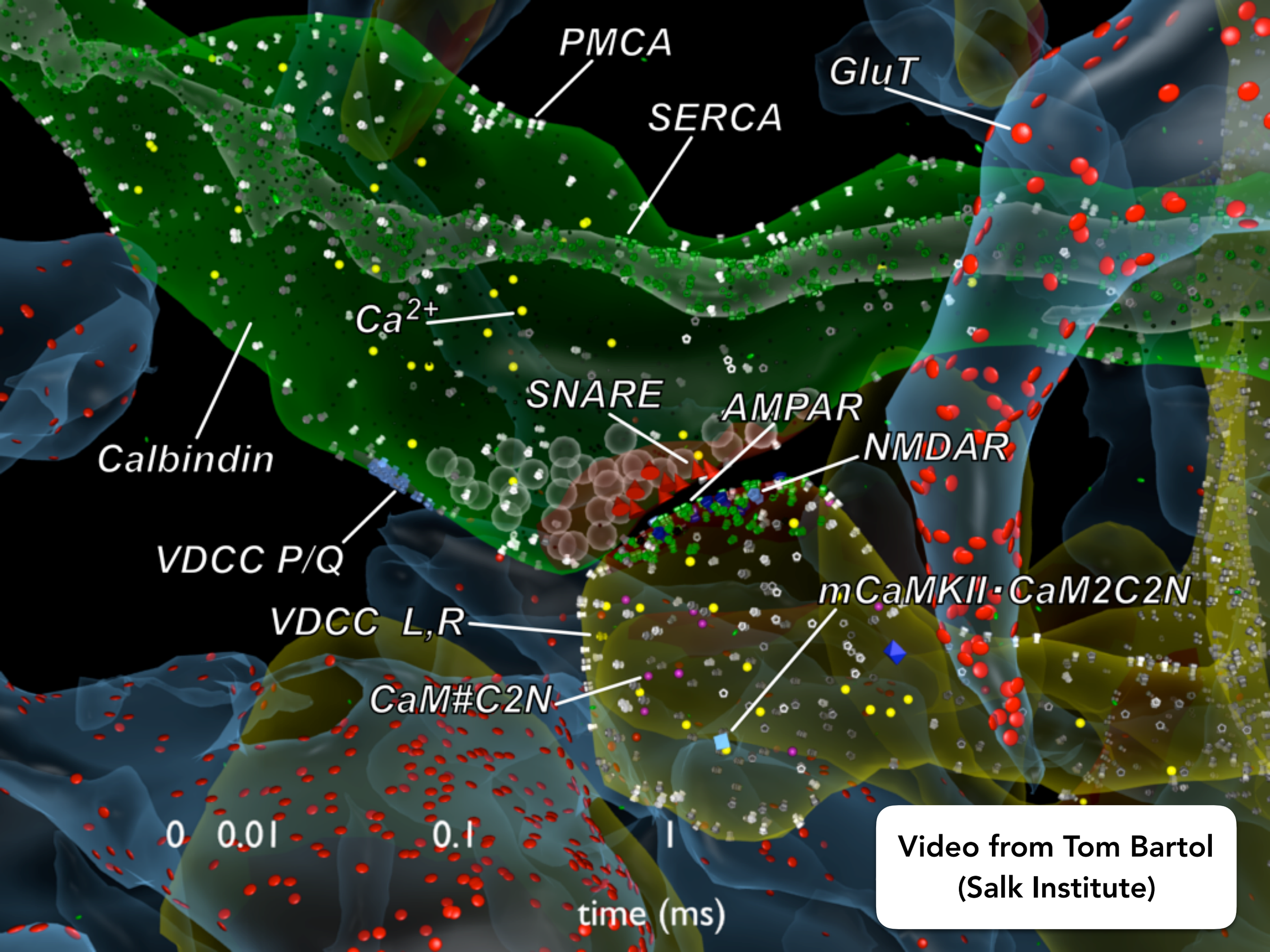


Diffusion

$$\rho(r,t) = \frac{1}{(4\pi Dt)^{3/2}} e^{-r^2/4Dt}$$

Reaction

$$p = k \frac{\sqrt{\pi\,\Delta t}}{4A_{\text{int}}\left(\sqrt{D_1} + \sqrt{D_2}\right)}$$



Video from Tom Bartol (Salk Institute)

Which model is best for my problem?

- Choose the form of the model that best matches the granularity of your scientific question.

- *"A model should be as simple as possible, but no simpler"*
  — Albert Einstein

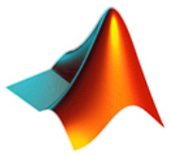
- Often this choice is dictated by:
  - the data you have to constrain the model
  - the phenomenon you wish to explain
  - the computational resources you have available
  - how much maths/programming you know
  - ~~what someone else did previously~~

Which computational tool should I use for my project?

- **Single synapses:** MCell, VirtualCell, STEPS
- **Single neurons:** NEURON, Genesis
- **Networks of neurons:** Brian, NEST
- **Whole-brain models:** someone later today will tell you

D.I.Y. modeling

C

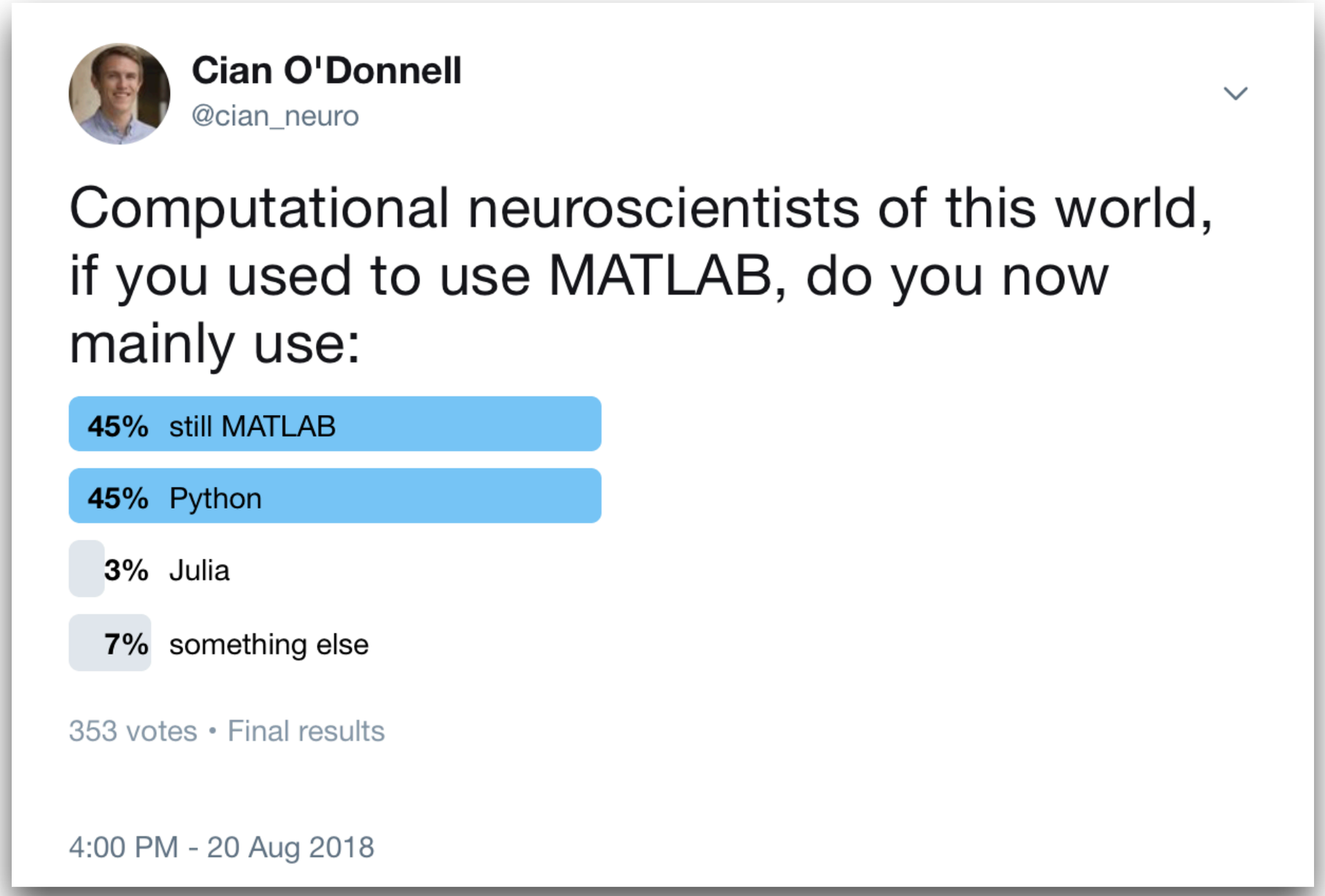


MATLAB

python

julia

Which computational tool should I use for my project?



Excellent reference textbook for cellular models.

Tells you how to make computational models of the brain, as opposed to other books which explore theories about how the brain works, or analyse mathematical models.