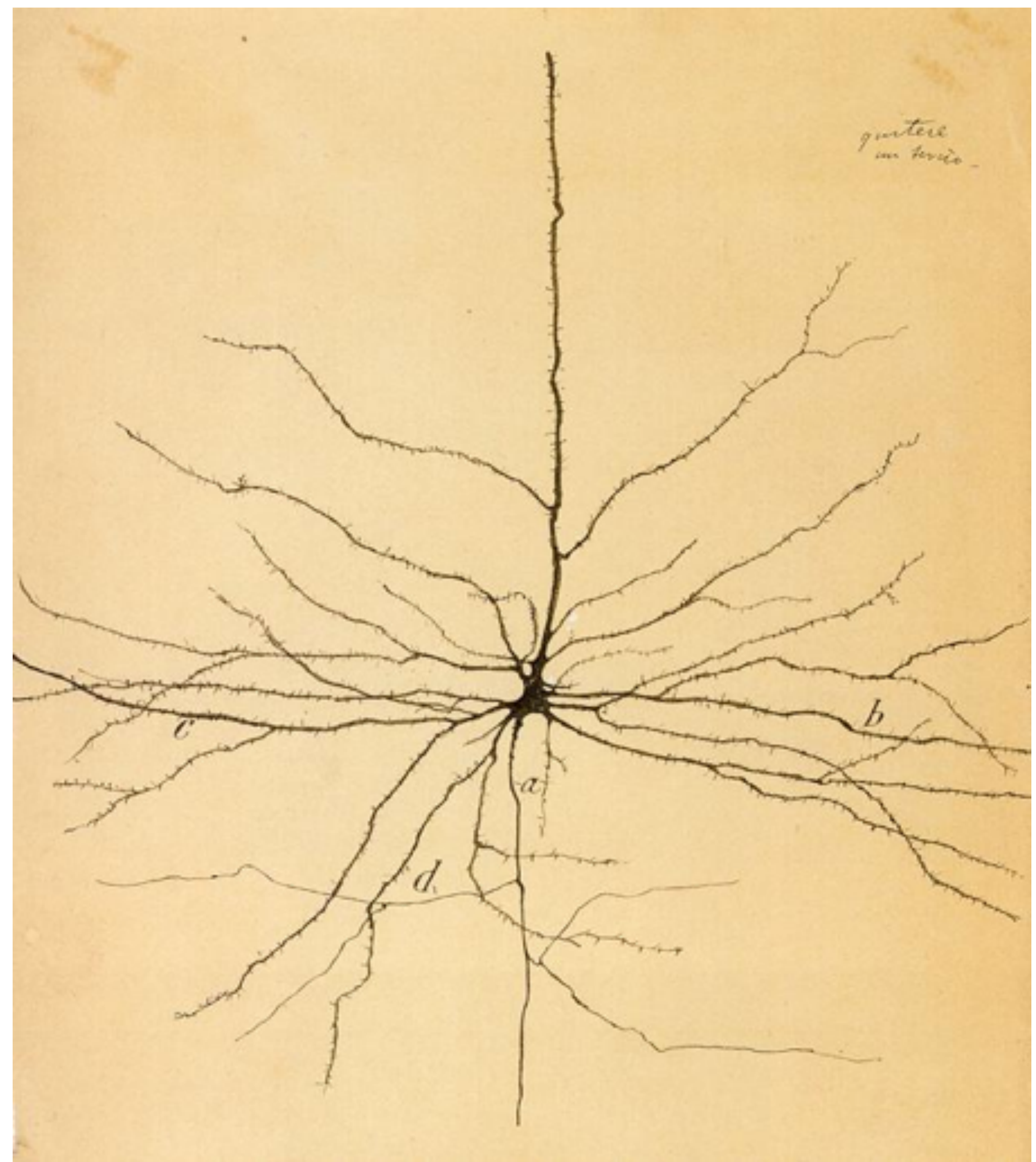
A speed-precision tradeoff for trafficking in dendrites

Alex Williams[1,2], Cian O'Donnell[2,3], Terrence Sejnowski[2], Timothy O'Leary[4]

1. Stanford University. Stanford, CA
2. Salk Institute for Biological Sciences. La Jolla, CA
3. University of Bristol. Bristol, UK
4. University of Cambridge. Cambridge, UK

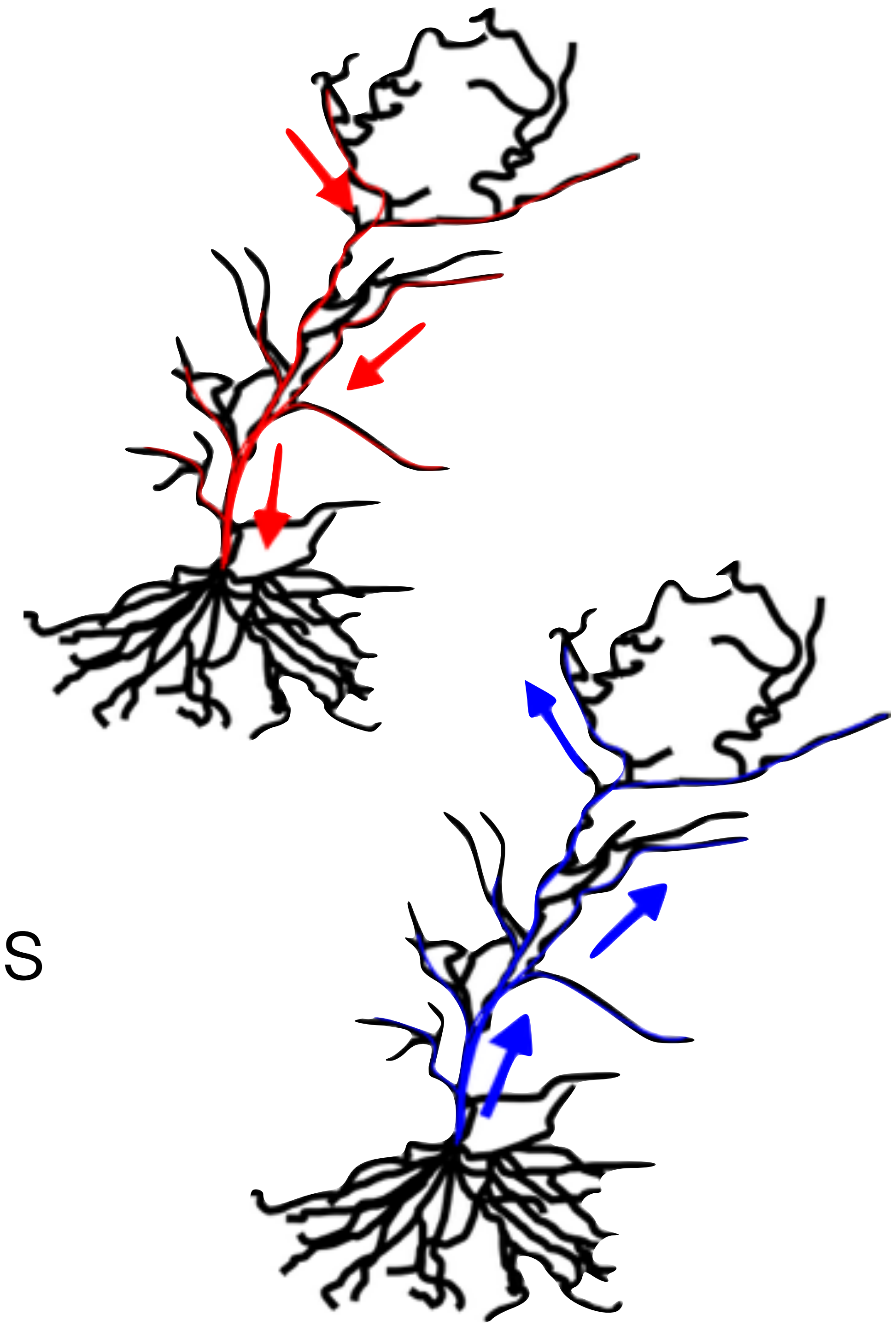
Neurons display incredibly complex and varied morphologies



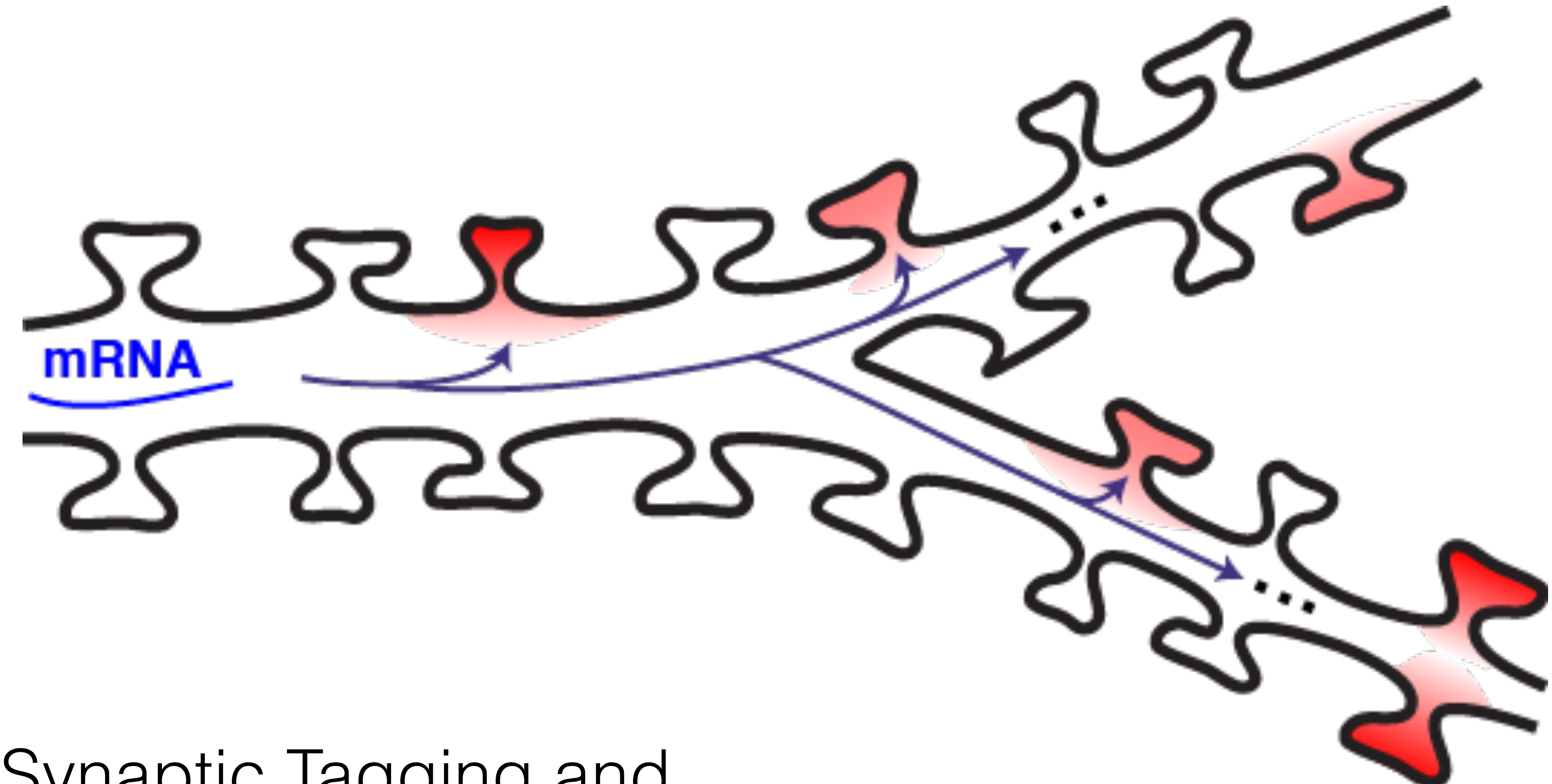
Transport of cargo within a single neuron is a critical cellular function

- Dendritic proteins are ***retrogradely transported*** to the nucleus to act as transcription factors, and blocking this transport can impair plasticity [Ch'ng 2012, Ch'ng 2011].

- Synaptic learning relies on ***anterograde transport*** of mRNAs from the nucleus to the dendrites [Kandel 2001, Buxbaum 2014].



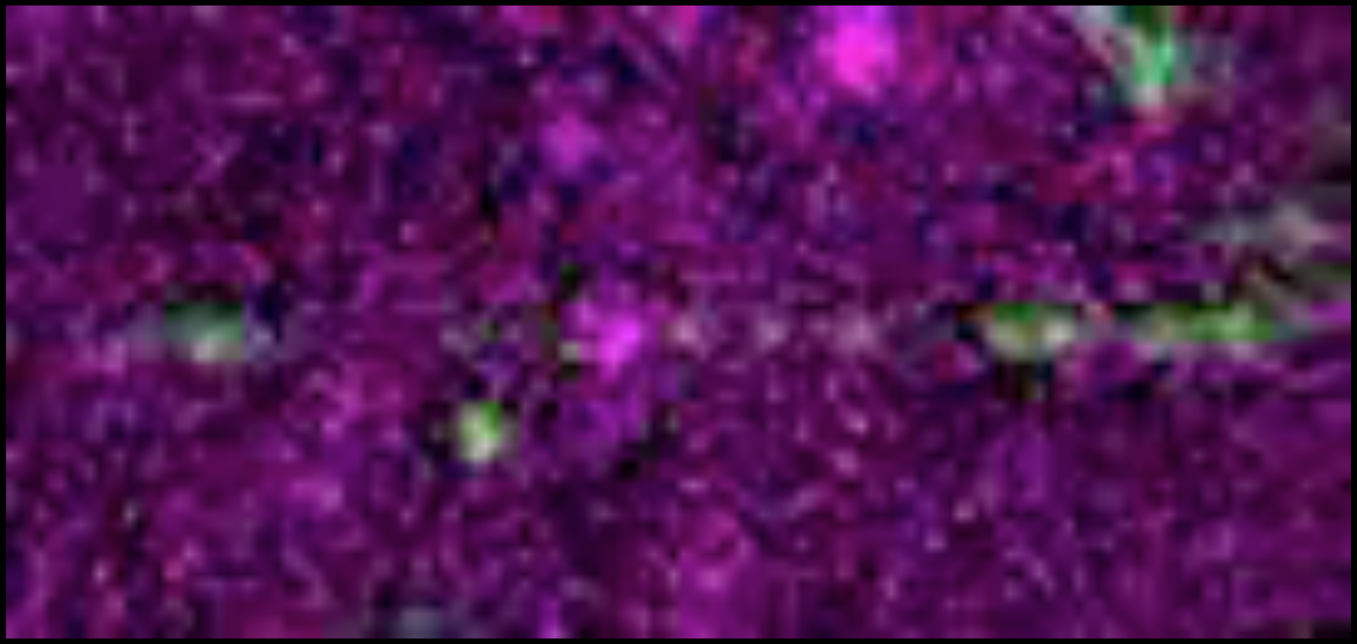
The Problem:



Synaptic Tagging and
Capture Hypothesis

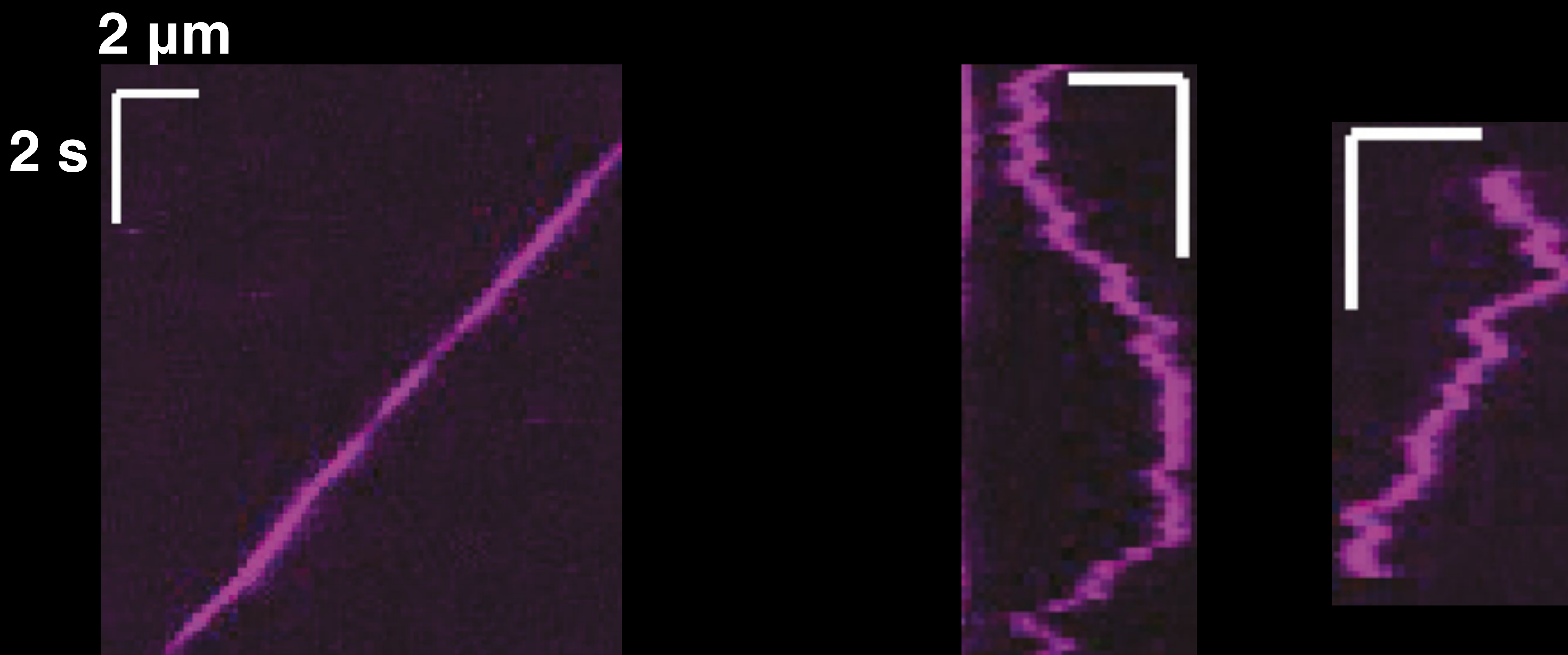
Redondo & Morris (2011)

Molecular cargoes exhibit bidirectional and unidirectional movements:



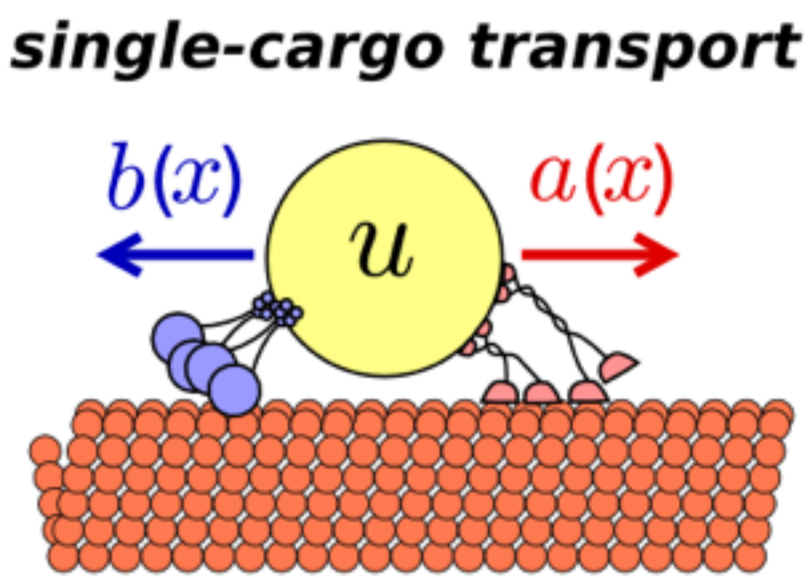
Harish Soundararajan & Simon Bullock (2014) *Elife.* 3:e01596

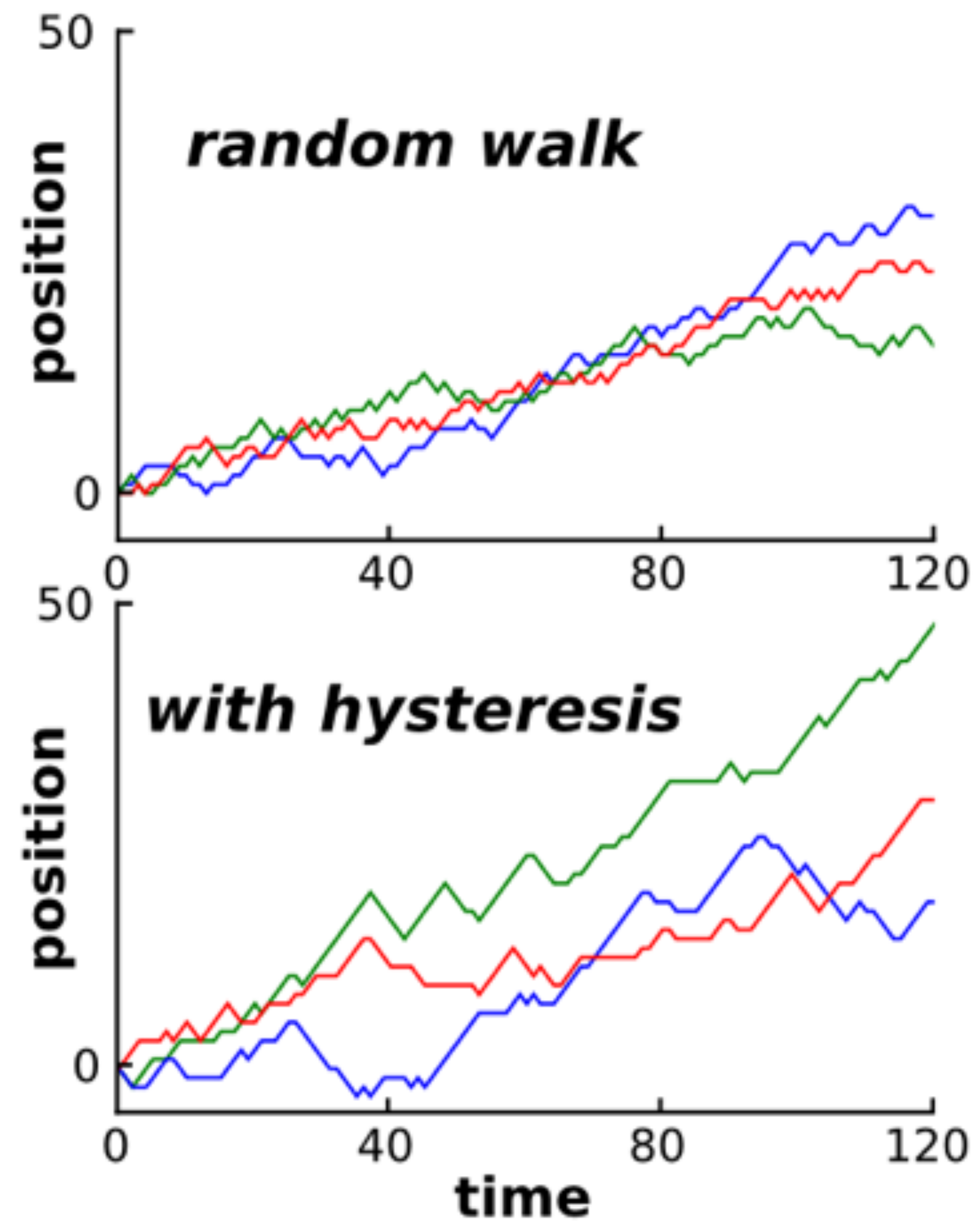
Molecular cargoes exhibit bidirectional and unidirectional movements:



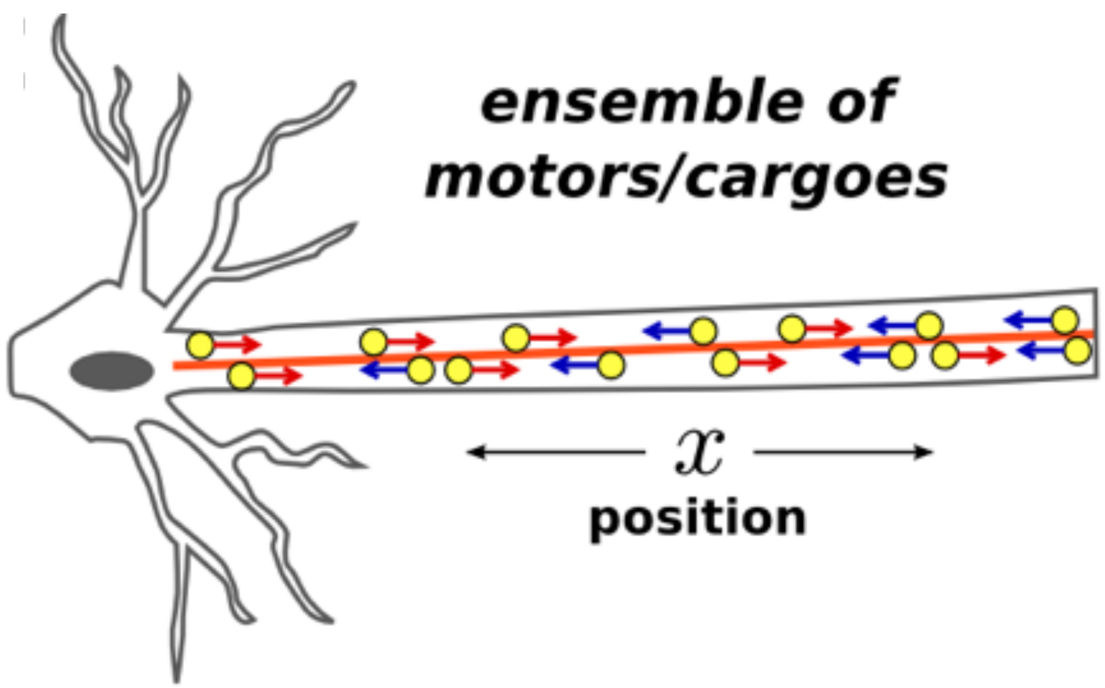
Harish Soundararajan & Simon Bullock (2014) *Elife.* 3:e01596

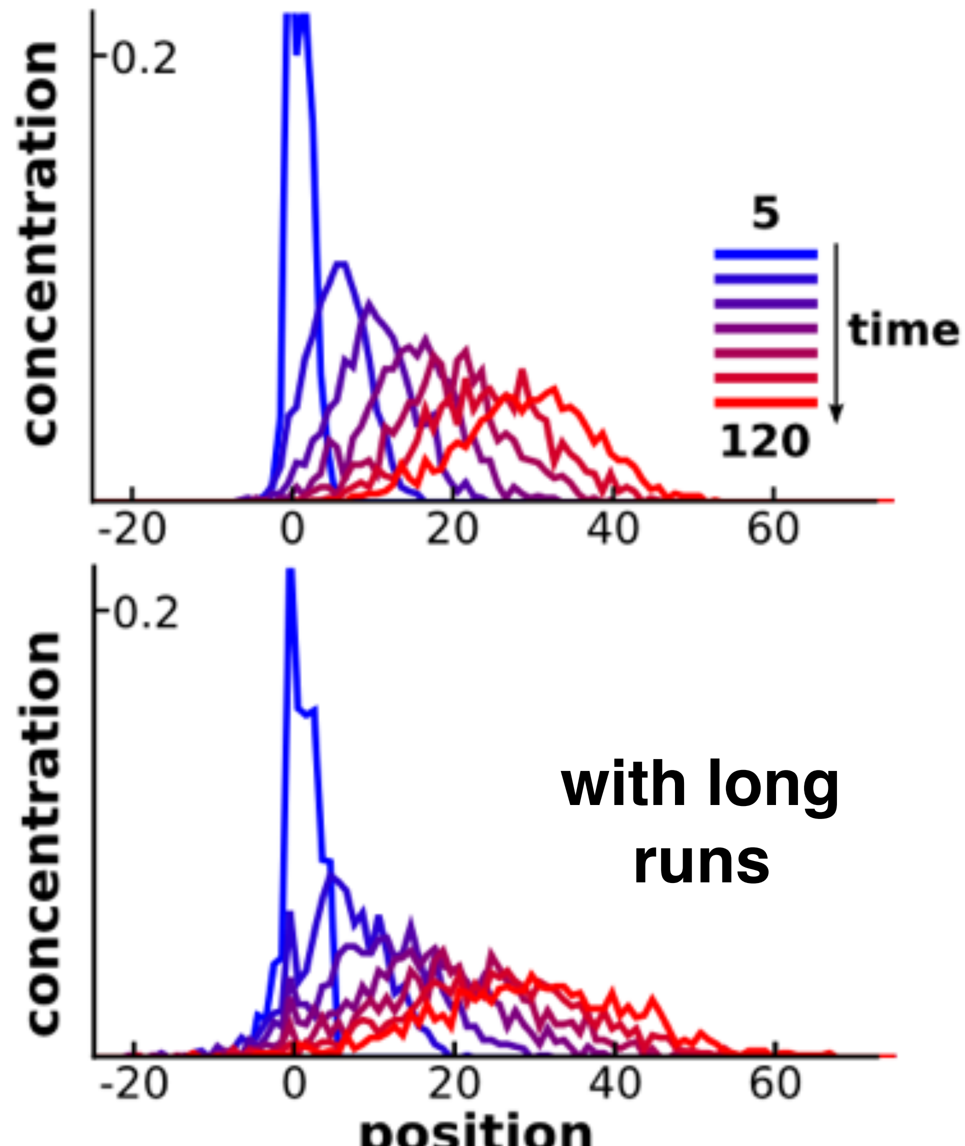
We approximate single-particle movements as a biased random walk.





Assume there are large numbers of particles. Each follows an independent random walk.

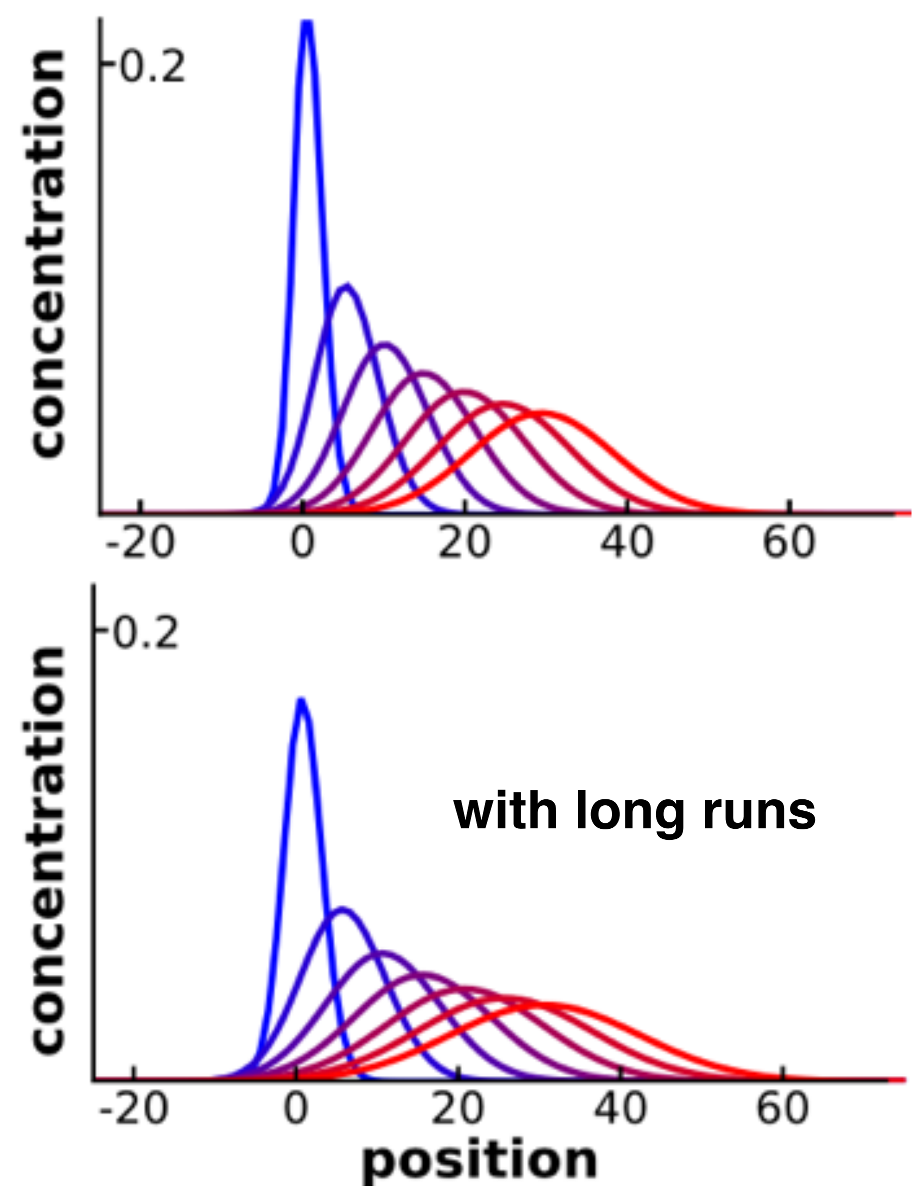




The ensemble behavior* is well-approximated by the drift-diffusion equation:

** Equivalently, the probability distribution for position of a single particle*

$$\frac{\partial u}{\partial t} = \left(\frac{a+b}{2}\right)\frac{\partial^2 u}{\partial x^2} + (b-a)\frac{\partial u}{\partial x}$$



Discretized Drift-Diffusion ("mass-action model"):

$$u_1 \underset{b_1}{\overset{a_1}{\rightleftharpoons}} u_2 \underset{b_2}{\overset{a_2}{\rightleftharpoons}} u_3 \underset{b_3}{\overset{a_3}{\rightleftharpoons}} u_4 \underset{b_4}{\overset{a_4}{\rightleftharpoons}} u_5$$

$\mathbf{u_i}$ amount of mRNA in compartment i

$\mathbf{a_i}$ anterograde transport rate constant

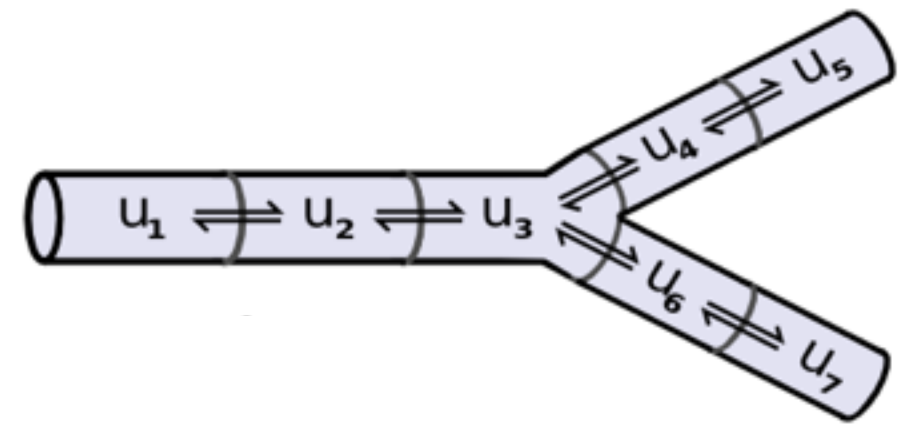
$\mathbf{b_i}$ retrograde transport rate constant

Discretized Drift-Diffusion ("mass-action model"):

$$u_1 \underset{b_1}{\overset{a_1}{\rightleftharpoons}} u_2 \underset{b_2}{\overset{a_2}{\rightleftharpoons}} u_3 \underset{b_3}{\overset{a_3}{\rightleftharpoons}} u_4 \underset{b_4}{\overset{a_4}{\rightleftharpoons}} u_5$$

$$\frac{du_i}{dt} = a_{i-1}u_{i-1} + b_i u_{i+1} - (a_i + b_{i-1})u_i$$

Three reasons for using the mass-action model:

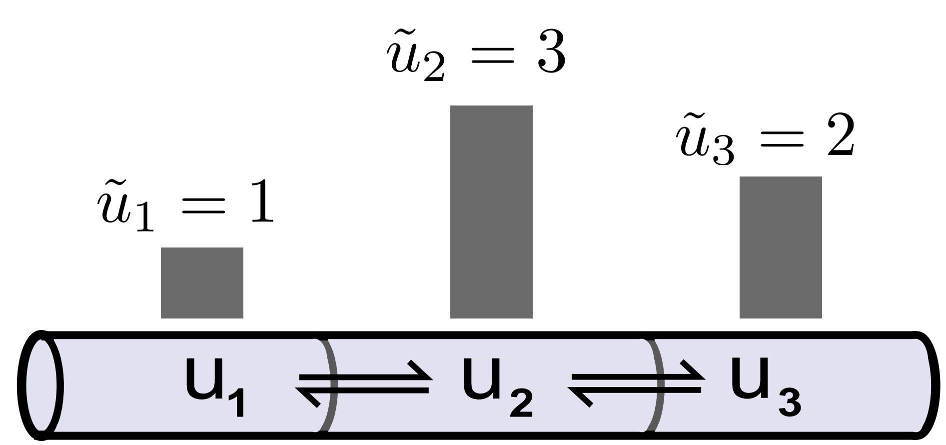


- Easy to extend to branched morphologies *(top)*
- Allows non-uniform drift/diffusion coefficients across morphology
- Steady-state distribution is unique* and defined analytically *(bottom)*

** Up to scaling the overall amount of cargo in the neuron.*

Steady-state distribution of cargo:

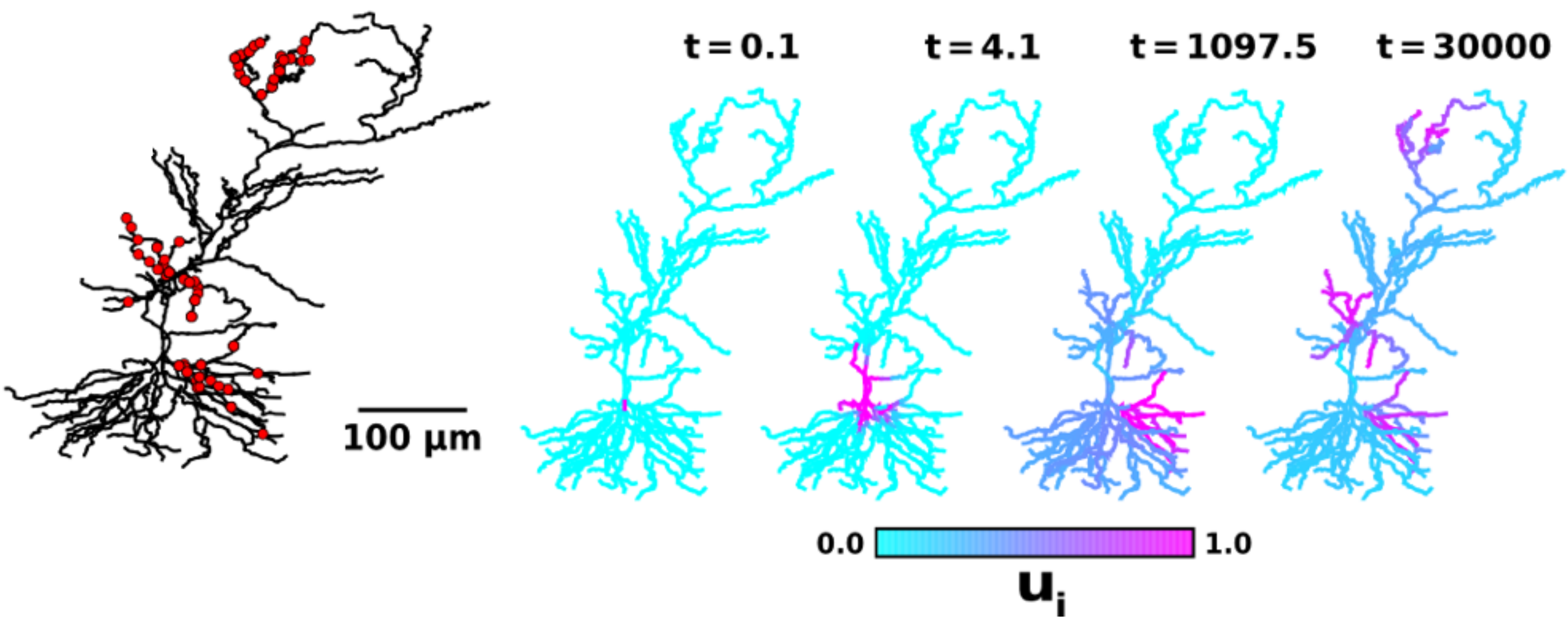
$$\left.\frac{u_p}{u_c}\right|_{ss} = \frac{b}{a}$$



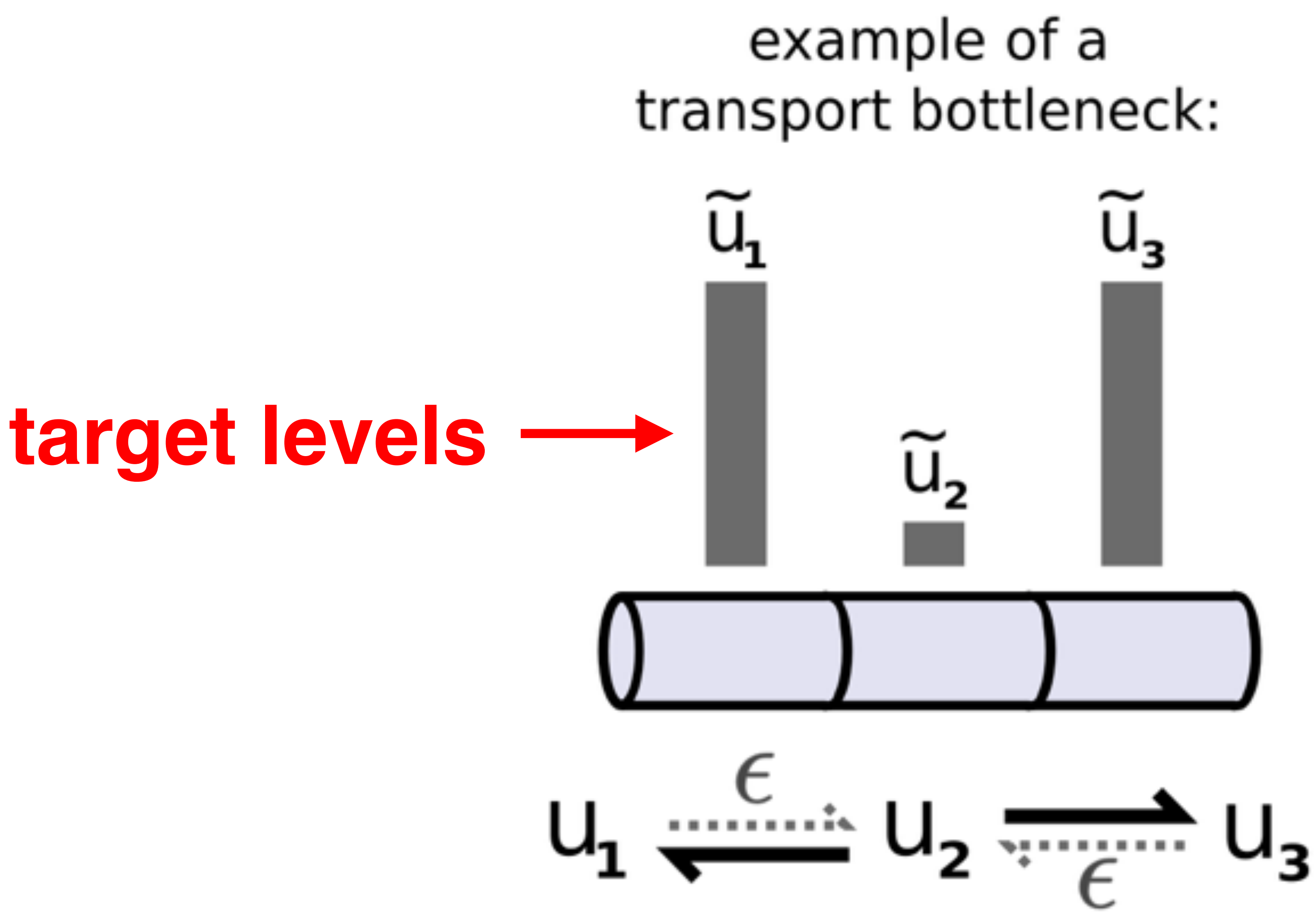
$$\frac{b_1}{a_1} = \frac{\tilde{u}_1}{\tilde{u}_2} = \frac{1}{3} \longrightarrow b_1 = \frac{1}{4} \quad a_1 = \frac{3}{4}$$

$$\frac{b_2}{a_2} = \frac{\tilde{u}_2}{\tilde{u}_3} = \frac{3}{2} \longrightarrow b_2 = \frac{3}{5} \quad a_2 = \frac{2}{5}$$

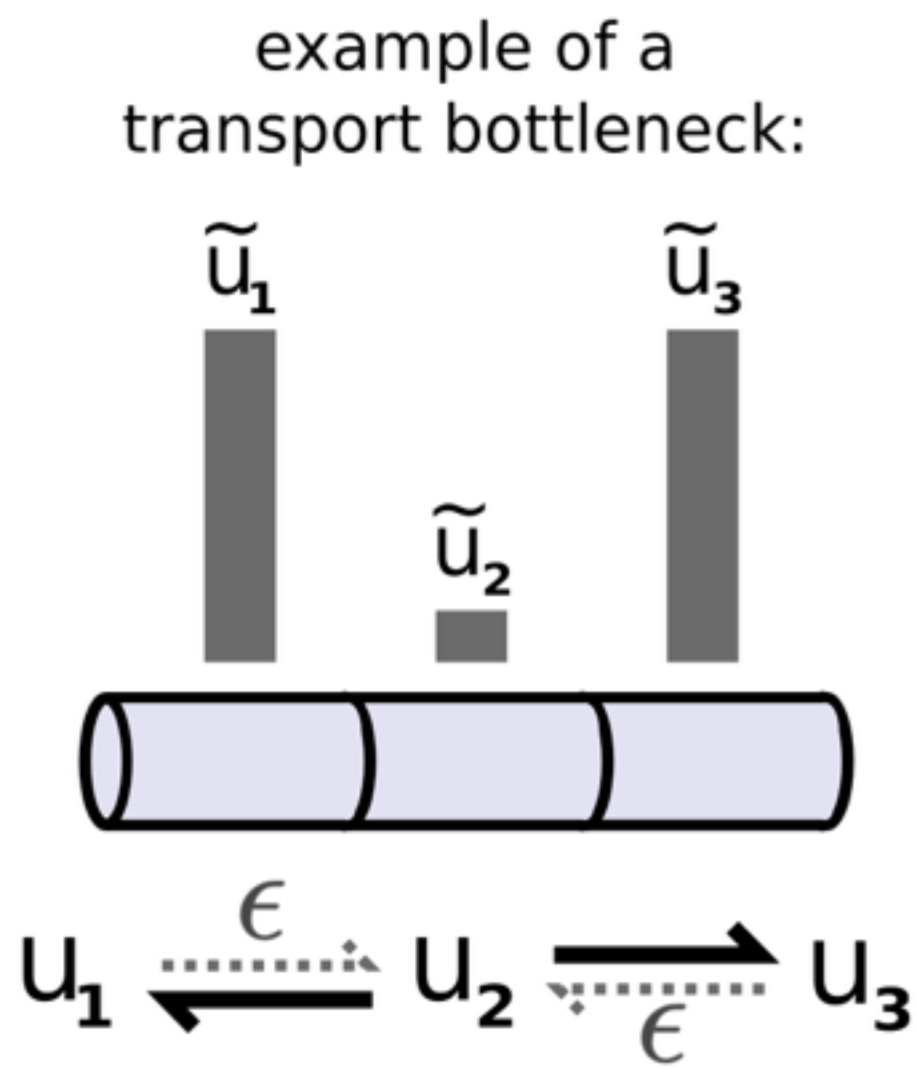
Proof of principle: cargo trafficked to stimulated synapses (red dots) in a multi-compartment CA1 pyramdial cell.

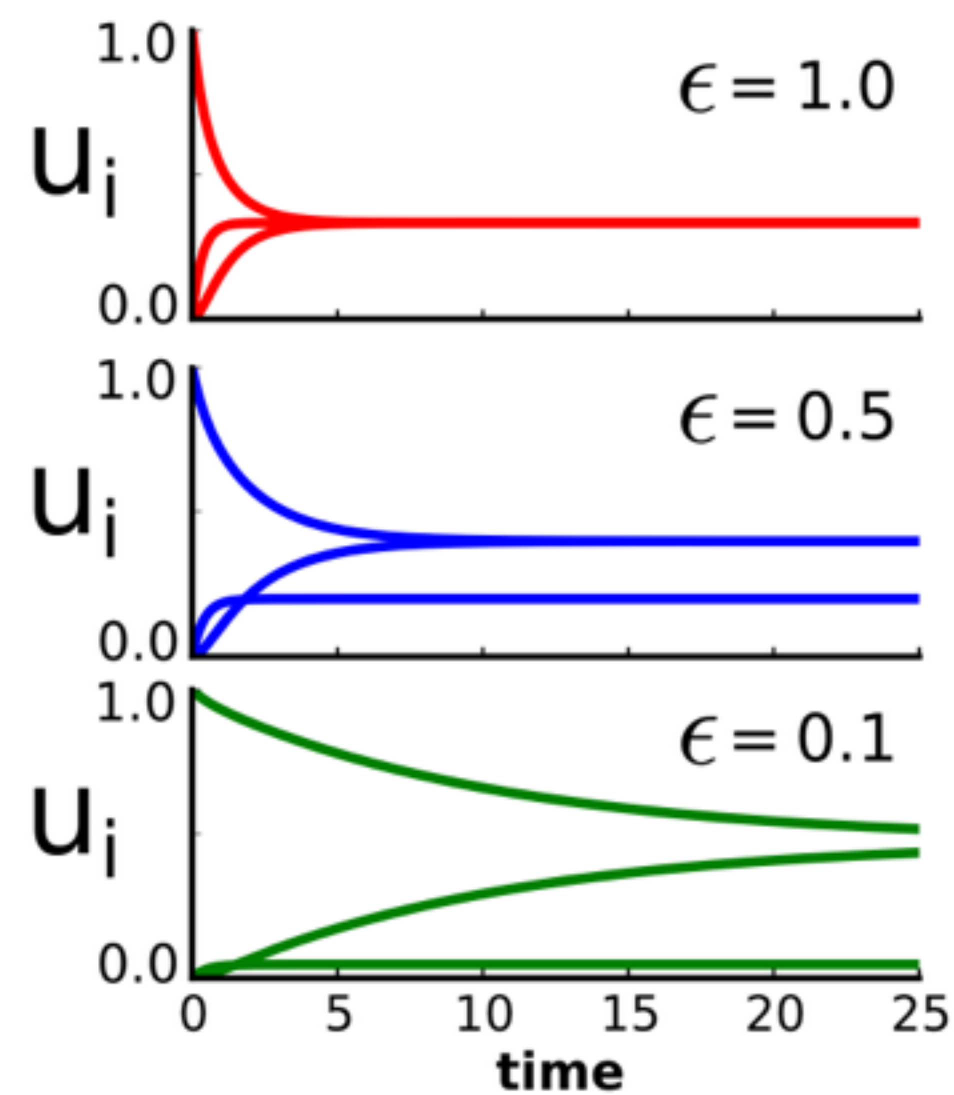


Pinches in the target profile produce bottlenecks

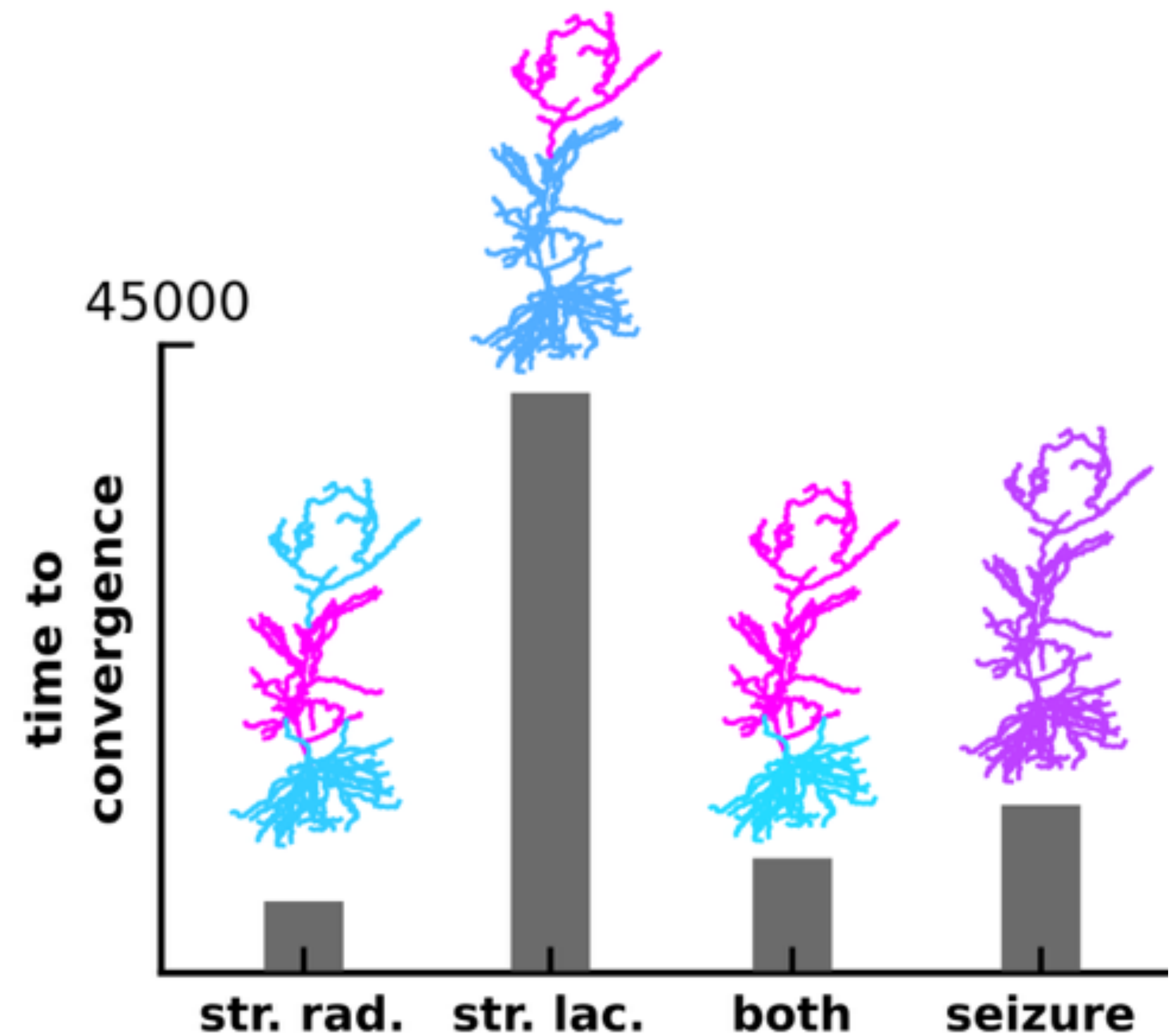


Pinches in the target profile produce bottlenecks

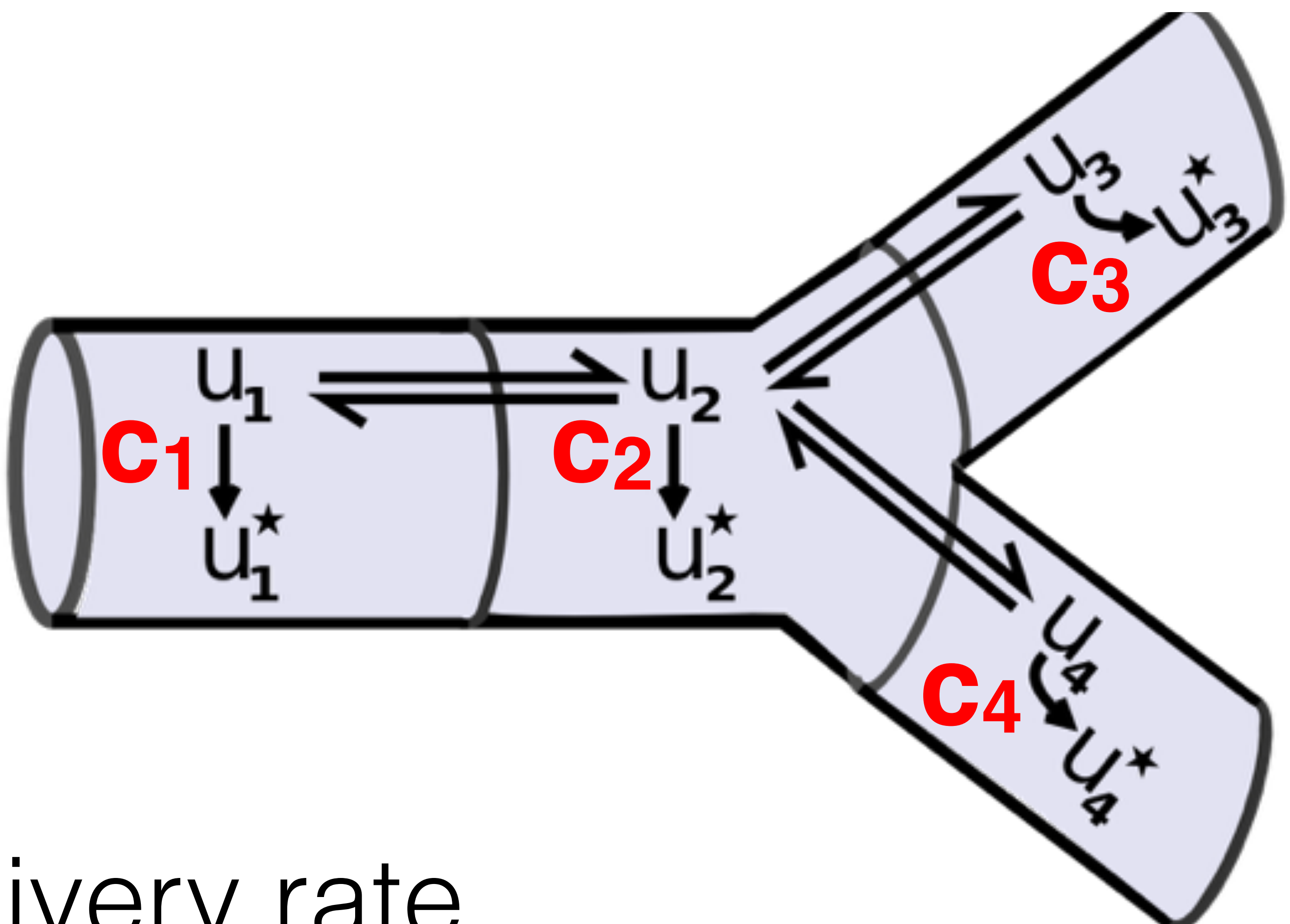




A proposed experiment to test bottlenecks in hippocampus



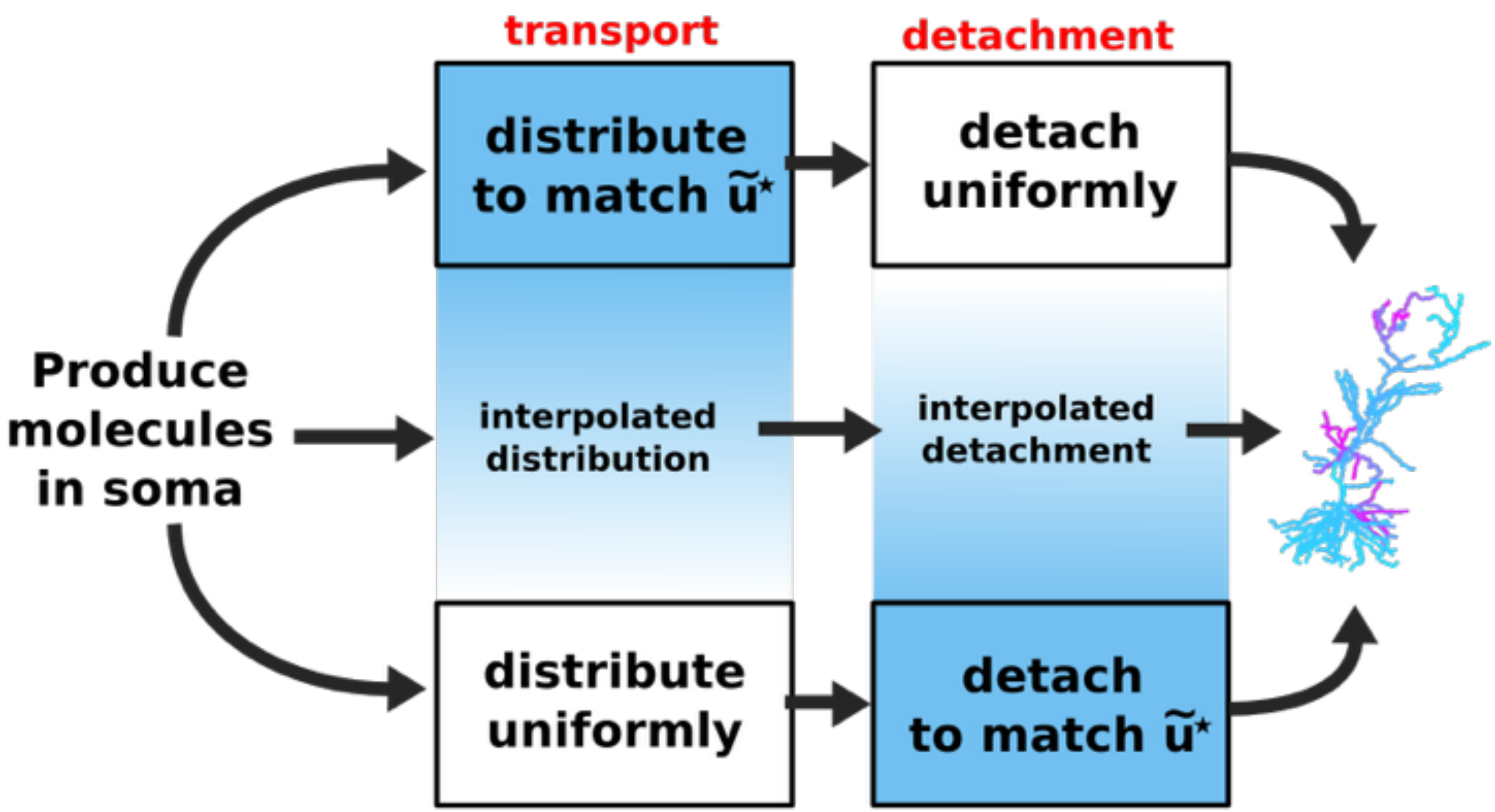
We then studied a model containing both cargo trafficking and detachment



c_i delivery rate constants

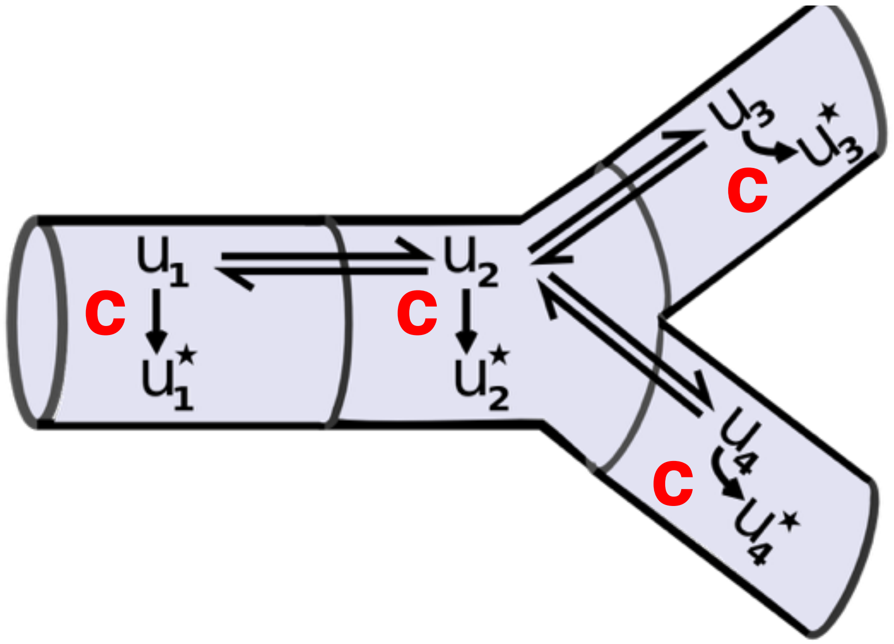
"The Sushi-Belt Model"
(Doyle & Keibler, 2012)

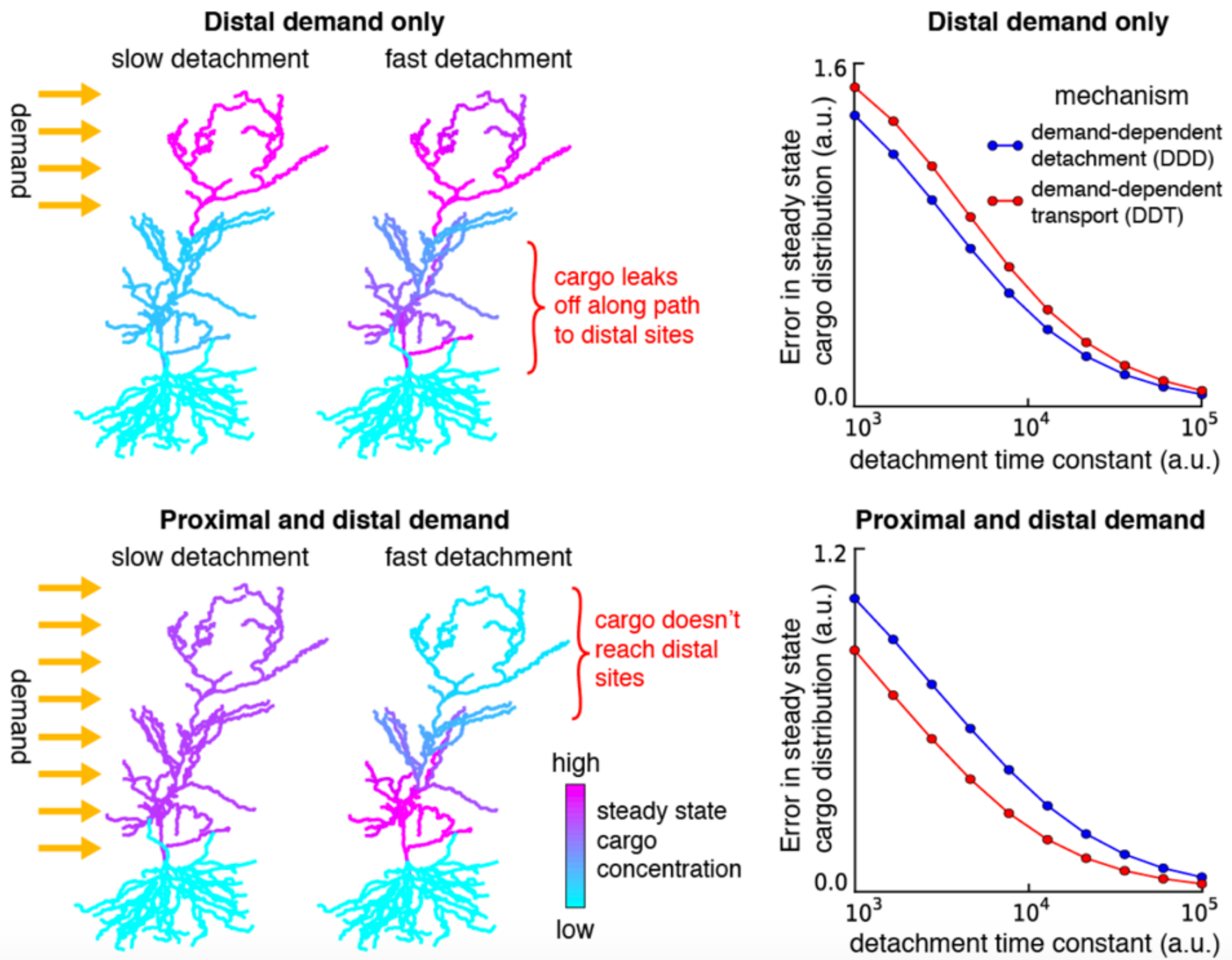
This model enables a broader spectrum of solutions



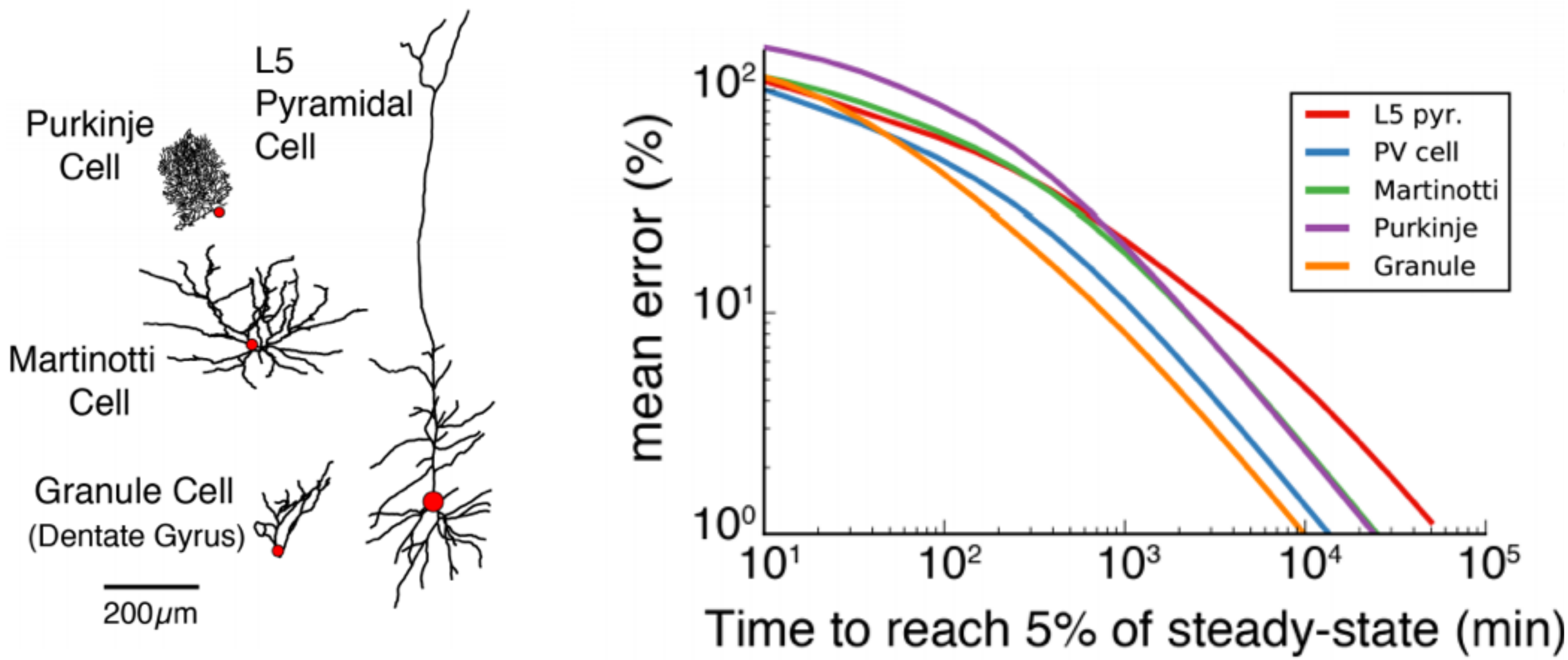
Take home message:
There is a tradeoff in this class of models between accuracy and speed of delivery

For the steady-state analysis to approximately hold, the c_i must be small (slow detachment)

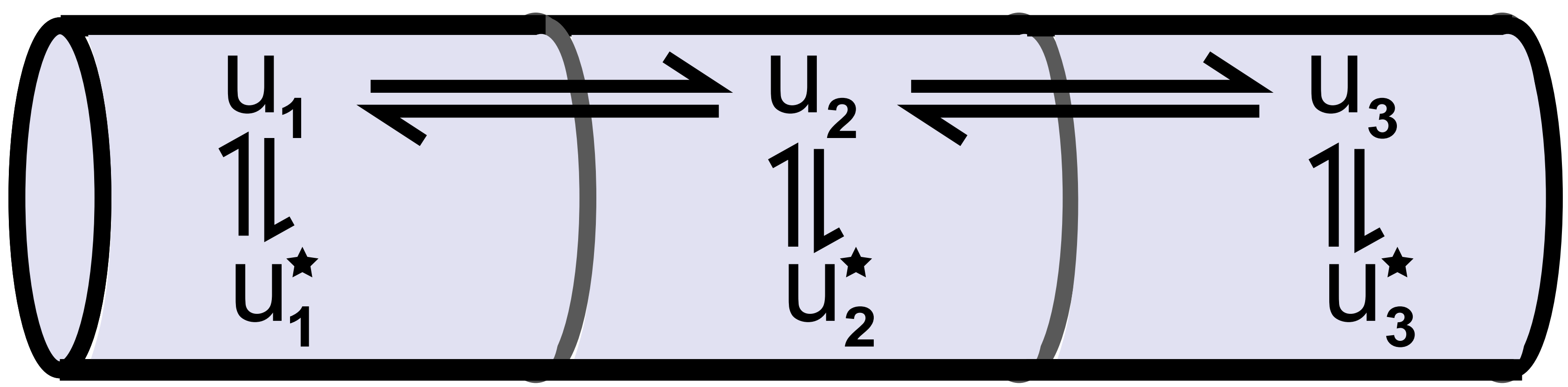



Distal demand only
slow detachment
fast detachment
demand
cargo leaks off along path to distal sites
Distal demand only
1.6
0.0
Error in steady state cargo distribution (a.u.)
mechanism
demand-dependent detachment (DDD)
demand-dependent transport (DDT)
10^3
10^4
10^5
detachment time constant (a.u.)
Proximal and distal demand
slow detachment
fast detachment
demand
cargo doesn't reach distal sites
high
steady state cargo concentration
low
Proximal and distal demand
1.2
0.0
Error in steady state cargo distribution (a.u.)
10^3
10^4
10^5
detachment time constant (a.u.)

Severity of the tradeoff depends on morphology



Adding reattachment of cargo does not circumvent tradeoffs

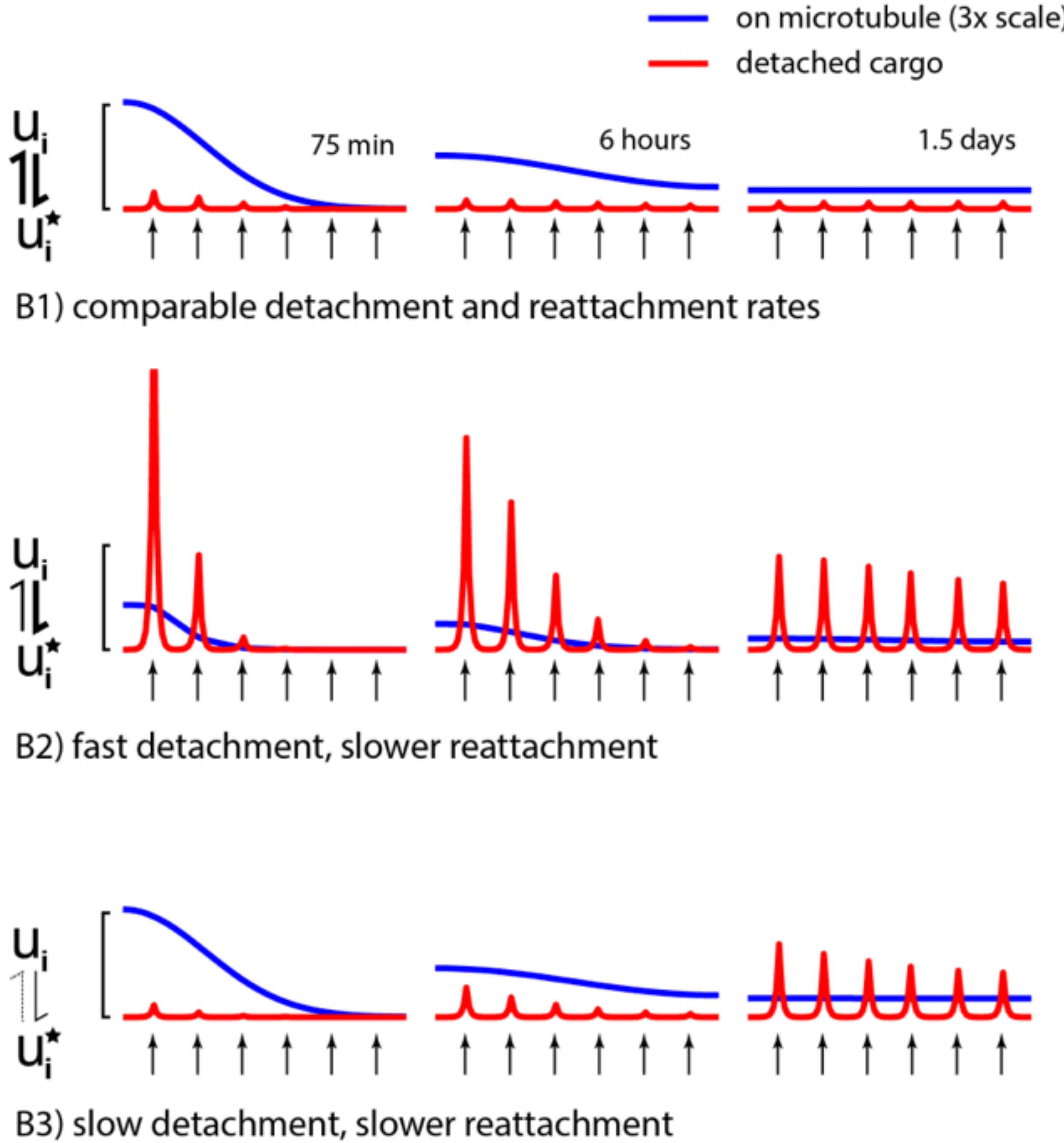


u_i = cargo on microtubule (in transit)

$u_i^\star$ = detached/delivered cargo

Fast convergence, large excess of undelivered cargo

Efficient models with little excess take longer to converge



Summary

- We constructed a family of rationally designed models that solve the transport problem in a biologically plausible manner.

- These models face a severe tradeoff in the speed vs. accuracy of cargo delivery

- Fine-tuned models can produce moderately fast and accurate delivery. However, these models are fragile to changes in the profile of cargo demand.

How do cells deal with these problems/tradeoffs?

- Some cargoes may not need to be accurately distributed
- Other cargoes may not require fast transport
- Fine-tuning might work for neurons with stereotyped morphology and demand profiles
- More complex local computations/models could circumvent the speed/accuracy tradeoff.

Co-authors:




Cian O'Donnell
Terry Sejnowski
Eve Marder
Tim O'Leary

Special Thanks to:

Ben Regner (Sejnowski Lab)

Surya Ganguli (Stanford)

Subhaneil Lahiri
Friedemann Zenke
Madhu Advani
Kiah Hardcastle
Niru Maheswaranathan
Ben Poole
Lane Mcintosh
Chris Stock

Funding and Support:

DOE CSGF

contact // alex.h.willia@gmail.com

preprint on my website:

alexhwilliams.info/

and also on biorxiv:

10.1101/037374