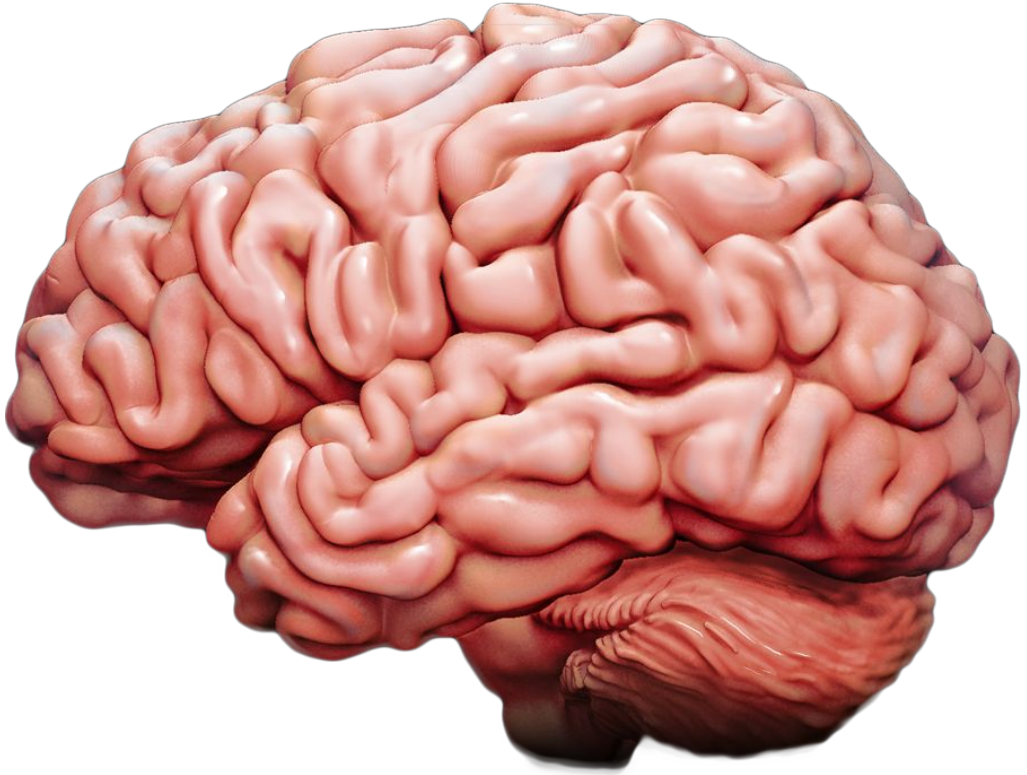
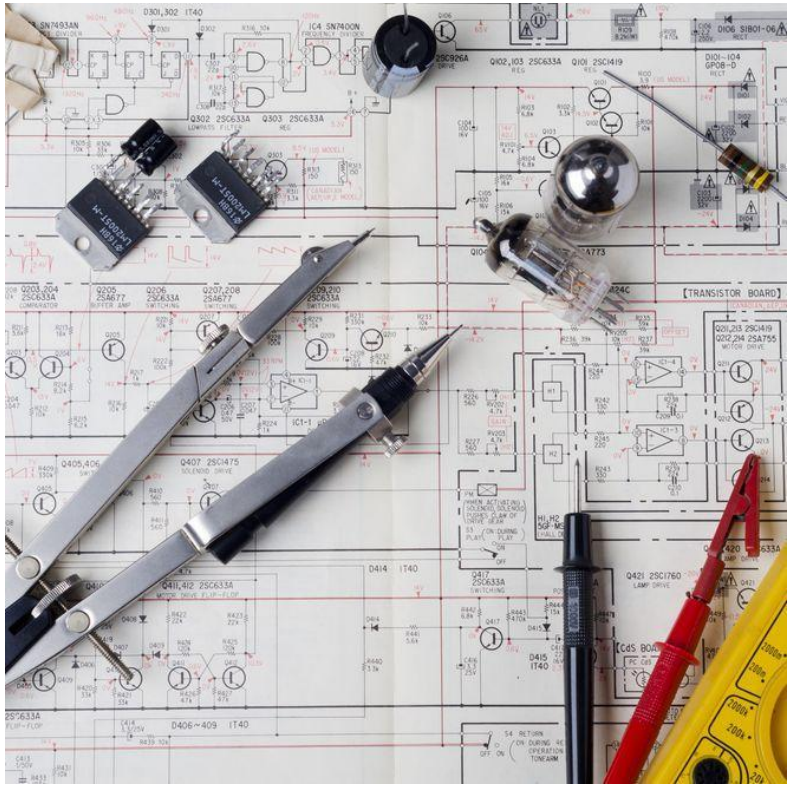
Studying the brain from the perspective of EE

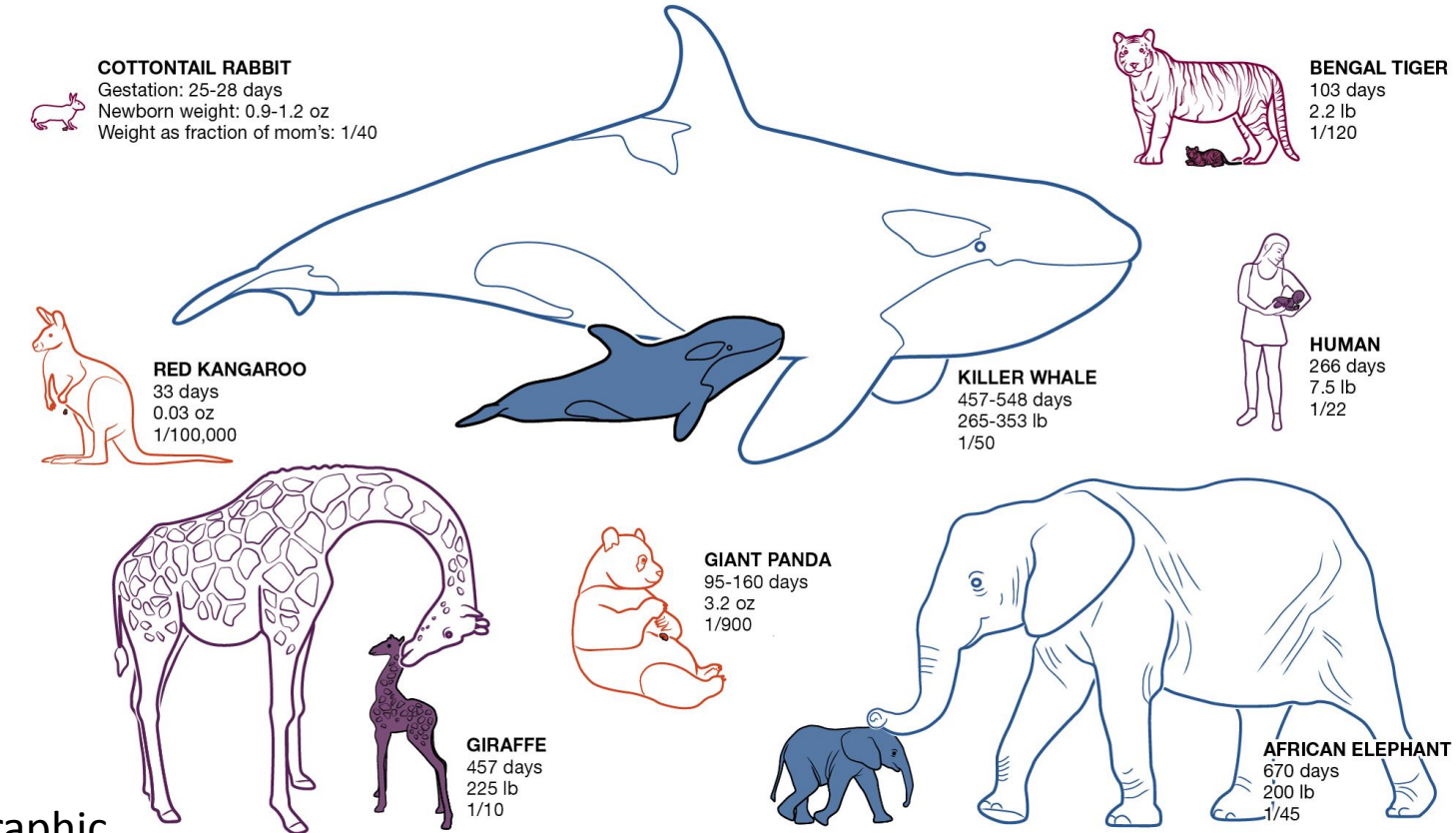


Lou Scheffer
Bonn
Germany
March 2026



Why study the brain?

- Many things the brain does better than our current EE tech
- Some are pure research - hard to copy, even if we understand how they work
  - Self wiring
  - Growth while operating
  - Recovery from injuries
- These are wonderful but will be hard to adopt into existing EE fabrication methods.



From National Geographic

Many areas where understanding the brain could help EE

- The brain does some operations MUCH better than our current EE techniques
- These are largely compatible with existing EE – if we understand these techniques we can adopt them
  - Power
    - Fruit fly does all computing, including optically stabilized flight with 125 nW, about 10^7 times better than a 1 watt drone chip
  - Learning
    - A child learns a language after few million (not billion) words
    - A teenager learns to drive with about 20 hours of experience
    - All on about 20 watts of power – a fraction of a single GPU
  - Algorithms
    - Brain learns, but not by back propagation. How?

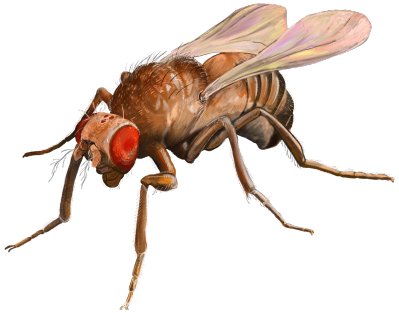


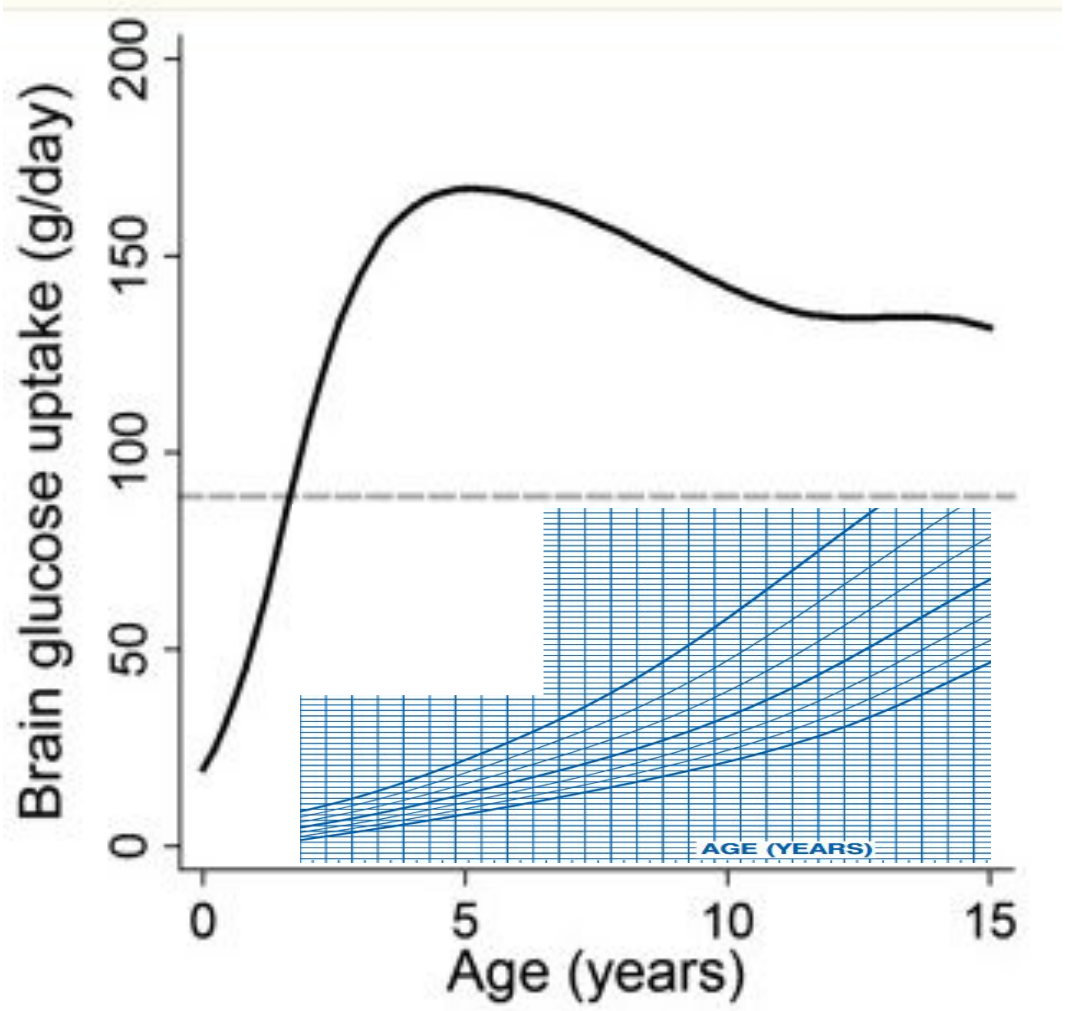
Photo credit: Wikipedia, Walmart, AAA

Power comparison especially stark

- Inference (using an already trained model)
  - Human driver 20 watts
  - Waymo CPU+GPU roughly 1000 watts
  - Human is 50x better
- Training/learning has even more spectacular ratios
  - Brain uses ~5% (1 watt) more when learning (adult)
    - Much more as a child, peaking at age 5
  - Incremental 20 watt-hours to add driving skill
  - Teenager's lifetime brain power usage ~ 3 MW-hours
  - Exact Waymo training energy unknown, but surely big
    - E.g., Llama 3.1-405B training took 21.6 GW-hours
  - Human brain somewhere between 1,000x and 50 MILLION times better!

Images: Amazon and Wikipedia

Human brain growth does not follow body mass

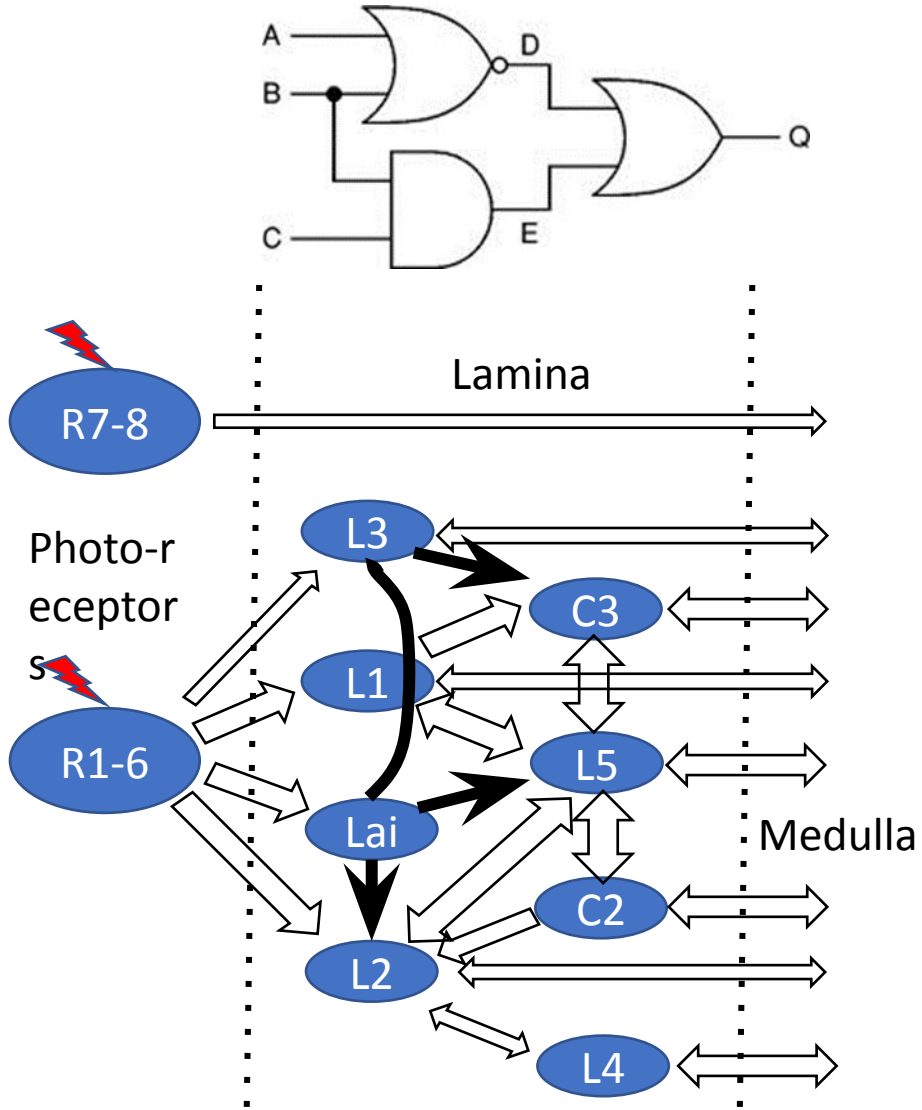


- Dotted line shows typical adult value
- Bottom curves are human weight
  - Curves are percentiles
  - Same curves you see in doctor's office
  - Grows monotonically as you expect
- Top curve is brain's sugar consumption (main source of power)
- Peaks at age 5.6, at more than 60% of the body's power consumption

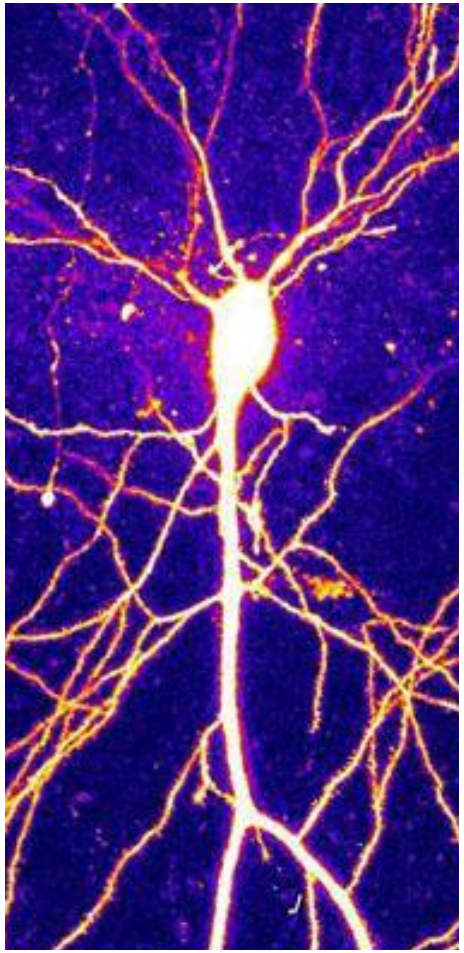
Brain curve from ""Metabolic costs and evolutionary implications of human brain development", weight curve from CDC

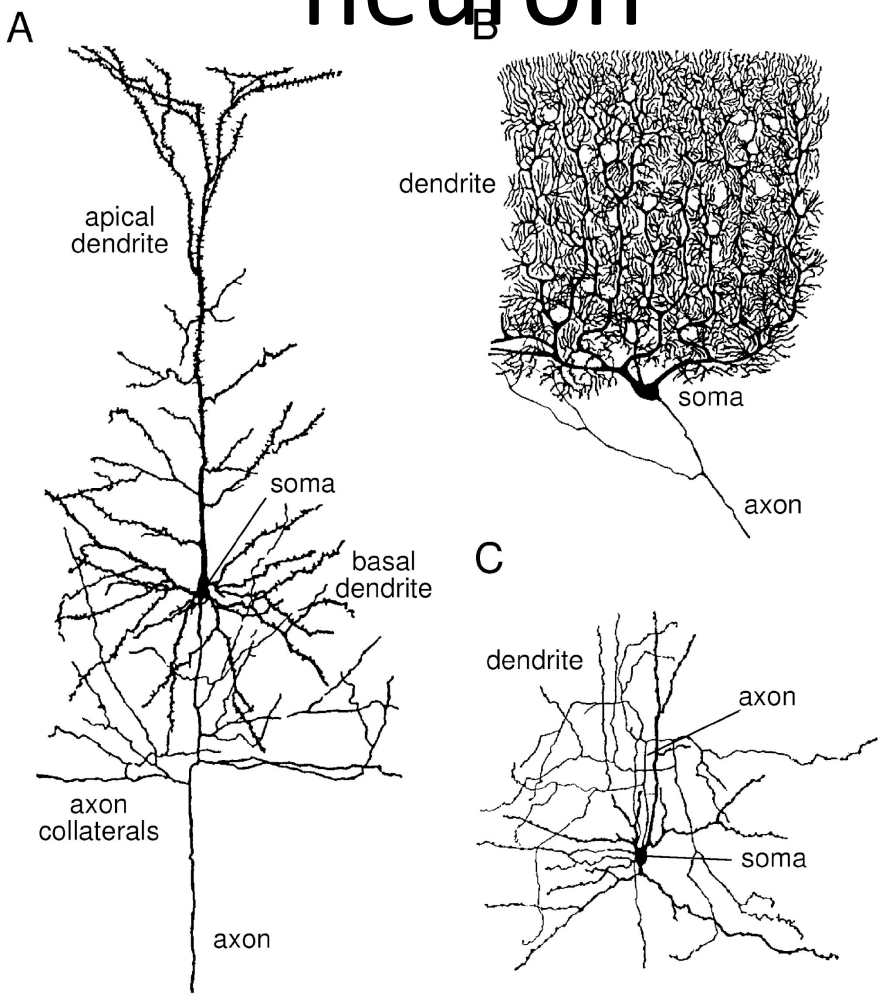
Many EE concepts apply directly to the brain

- Basic computation is electrical
- Computation as a network of elements
  - What engineers call a circuit diagram or netlist
  - Biologists call a “connectome”
- Algorithms (such as looming, walking, or flying)
- Stuck at faults
- Power
- Etc.



Fundamental biological computation unit is a neuron





Neurons come in many different sizes and shapes

Shape determines input/outputs, computation is similar

Just one type of non-linearity, trick is in the weights (as in ML)

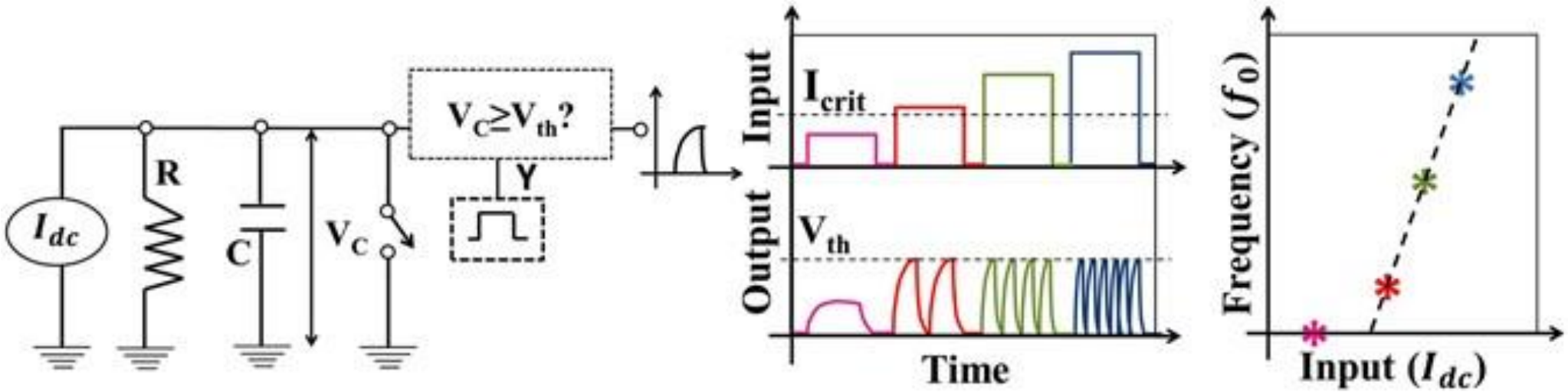
fly ~10^5 neurons; rodents ~10^9 neurons; human ~100×10^9 neurons

A neuron is the biological equivalent of a gate

- Basic architecture is a weighted threshold gate
- Synapses connect between neurons
- When the source cell fires, it turns on receptor which acts as a temporary current source (can be plus or minus)
- This acts against the capacitance of the cell membrane
- When the voltage rises enough, triggers a positive feedback loop (a spike)
- This in turn triggers a negative current channel, and cell resets
- This is called the “integrate and fire model”

Neuron logic operation

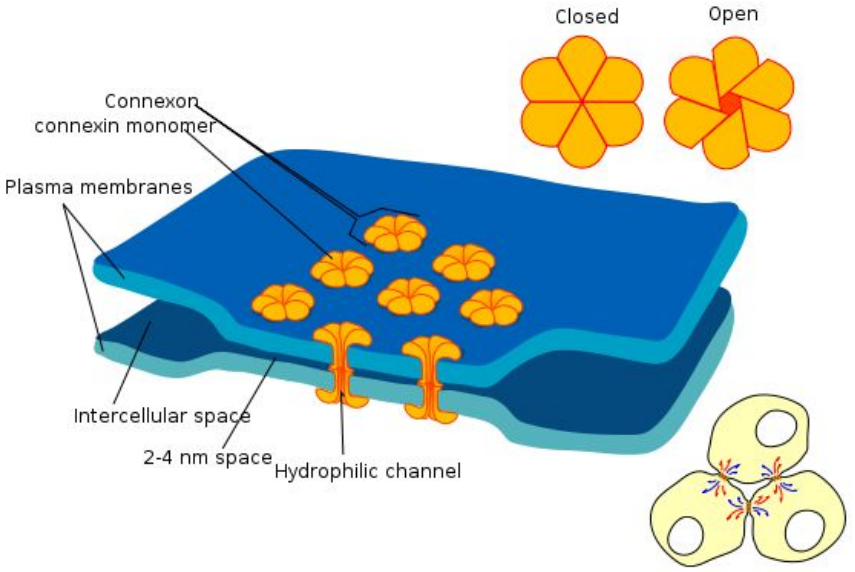
- Generic gate operation is “leaky integrate and fire”
  - Cell wall is very thin insulator, creating a capacitor
  - Quiescent neuron sits at resting potential (determined by leak currents)
  - Some synapses cause positive ions to come in (current source, voltage ramps up)
  - Some cause negative ions to come in (current source, voltage ramps down)
  - If voltage reaches a threshold, a strong positive ion channel turns on, leading to positive feedback and the cell ‘fires’
  - High positive voltage turns on a even stronger negative channel, and cell resets



From: Leaky Integrate and Fire Neuron by Charge-Discharge Dynamics in Floating-Body MOSFET

Also ‘gap’ junctions (resistors)

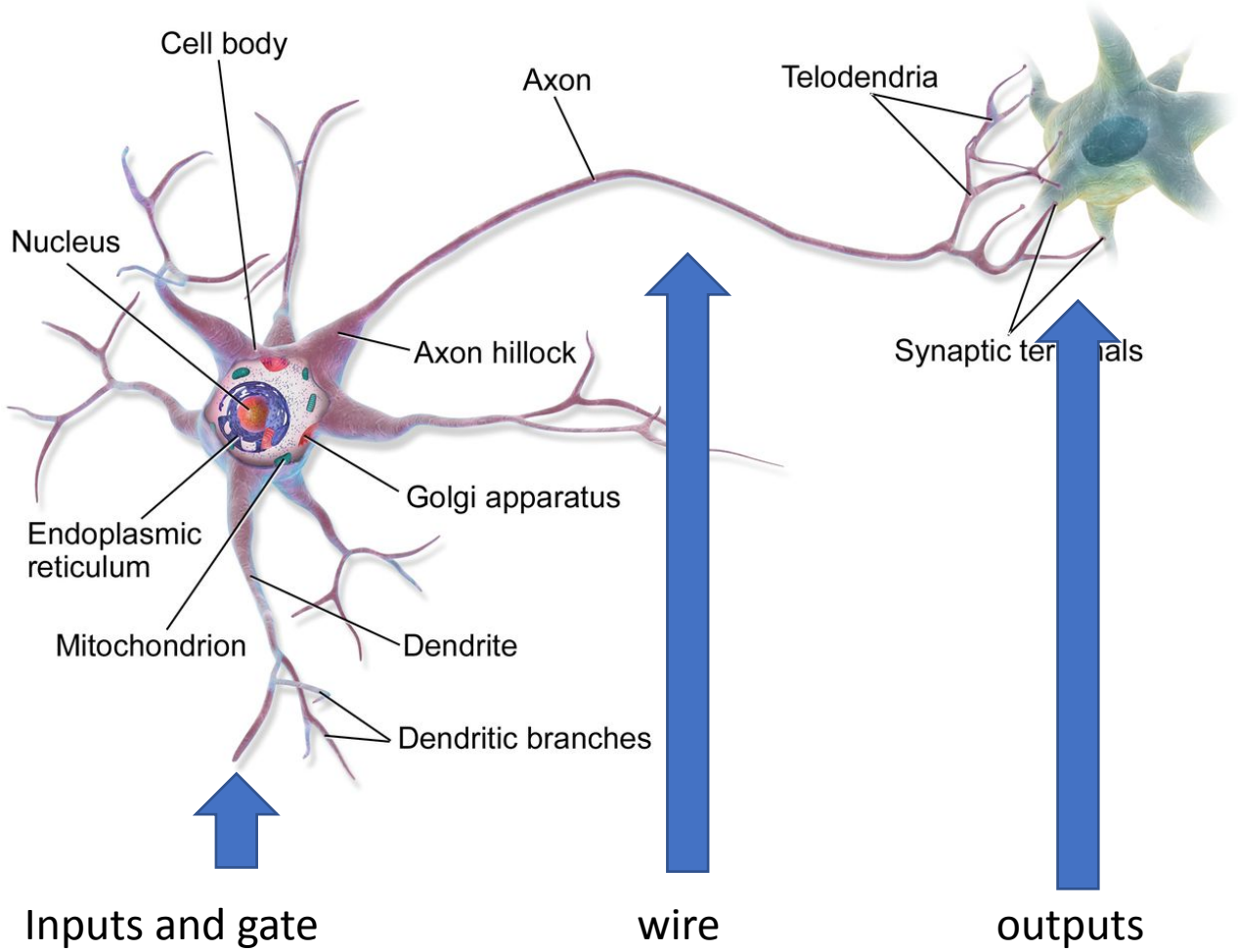
- Direct connection between cell interiors
  - Same sign
  - Gain < 1
  - Very fast
  - Used heavily in insect brains
  - Not used as much in mammalian brains
    - Except retina and visual system



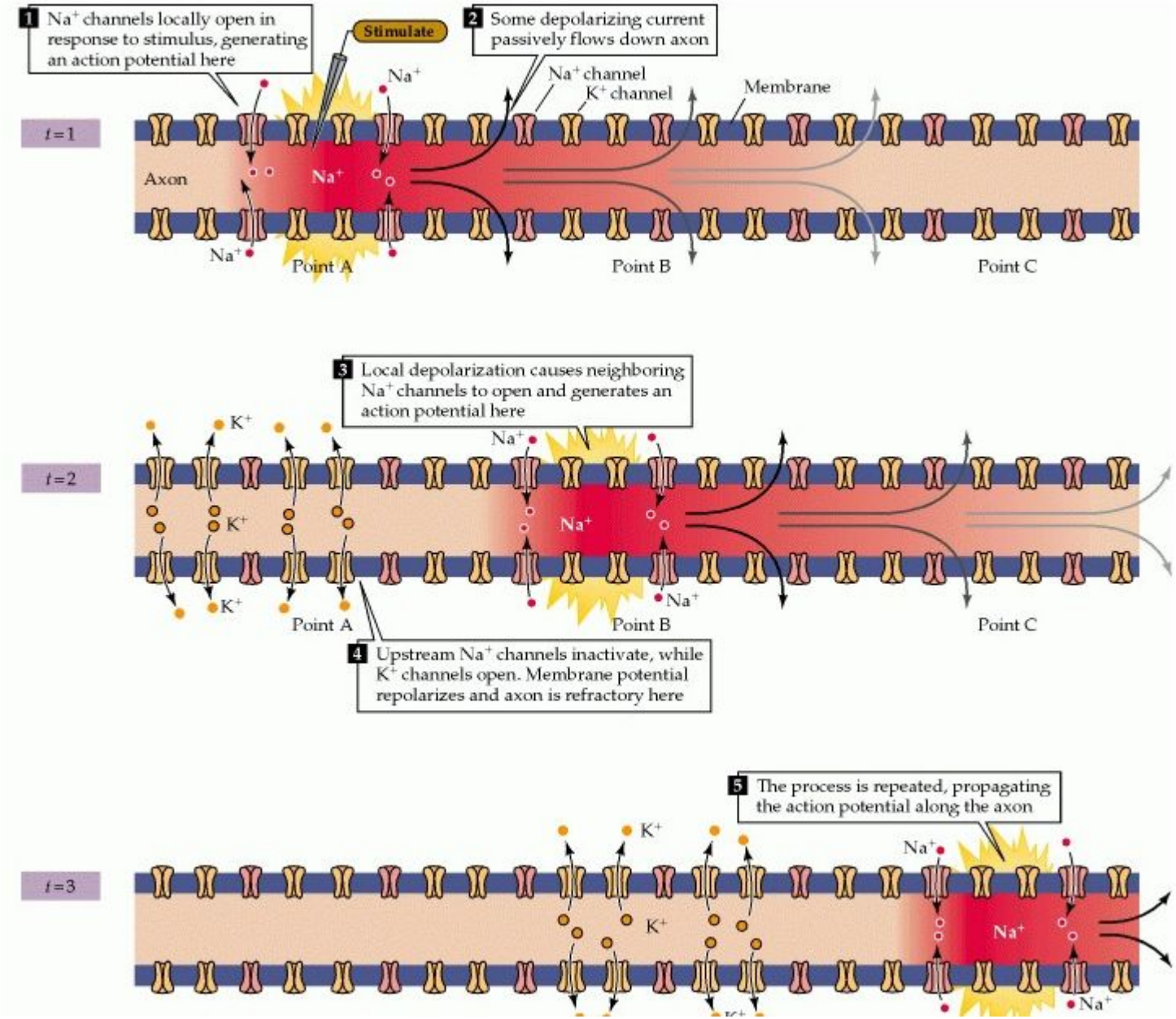
Wikipedia Gap cell junction en.svg 1 Nov 2009

Neurons are also the wires

- But quite bad wires by EE standards
  - Rho = 2.4 ohm-meter (10^8 worse than Cu)
  - C_0 = 0.01 F/m^2
- So for a 10 cm long, 1 μ diameter neuron, by RC only
  - R = Rho/(pi*r^2)*l = 3.06 Tohms/m = 306 Gohms
  - C = C_0 * pi*d*l = 3.1 nf
  - RC = 1000 seconds(!)
- Clearly this is not how neurons work



By BruceBlaus - Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=28761830



Signal regeneration

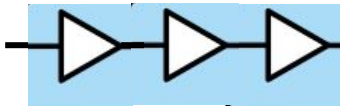
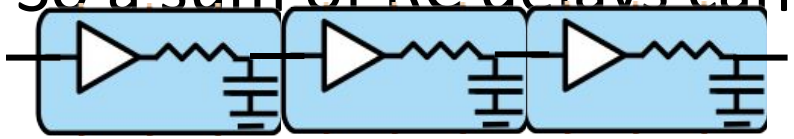
- A main success of Hodges/Huxley model
- Work done in 1952; Nobel prize in 1963
- Equivalent circuit 
- Delay is O(length)
- Constant speed of 1-10 meters/second
- For sufficiently big L, O(L) << $O(L^2)$

Figure 3.12 from "**Increased Conduction Velocity as a Result of Myelination**" in book "Neuroscience, 2nd ed".

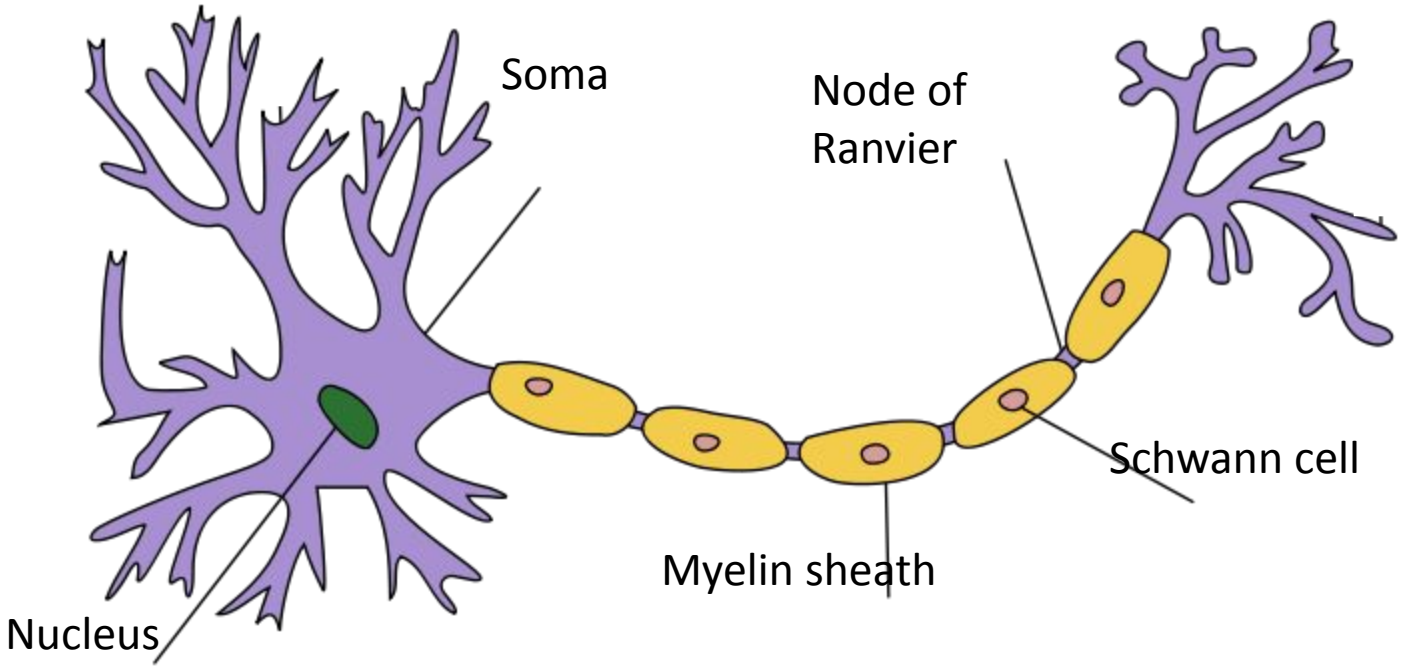
But as EEs, we know it's possible to do better

- But for a sufficiently short L, $O(L^2) << O(L)$
- So a sum of RC delays can do better yet



(with RC ~= gate delay)

- Biology also found this solution: myelinated nerves



Wikipedia: Neuron Hand-tuned.svg 1 Nov 2009

Closeup of myelinated axon

- Myelin is a good insulator
  - Isolates sections of line
  - Much less C (10-30x less) and less leakage
  - RC propagation to next node, where signal is regenerated
  - Gives speed O(length)
  - Exactly analogous to repeater insertion in VLSI
  - Speeds up to 150 m/s
- Myelin is white, which is why the brain is grey matter (no myelin) interconnected by white matter

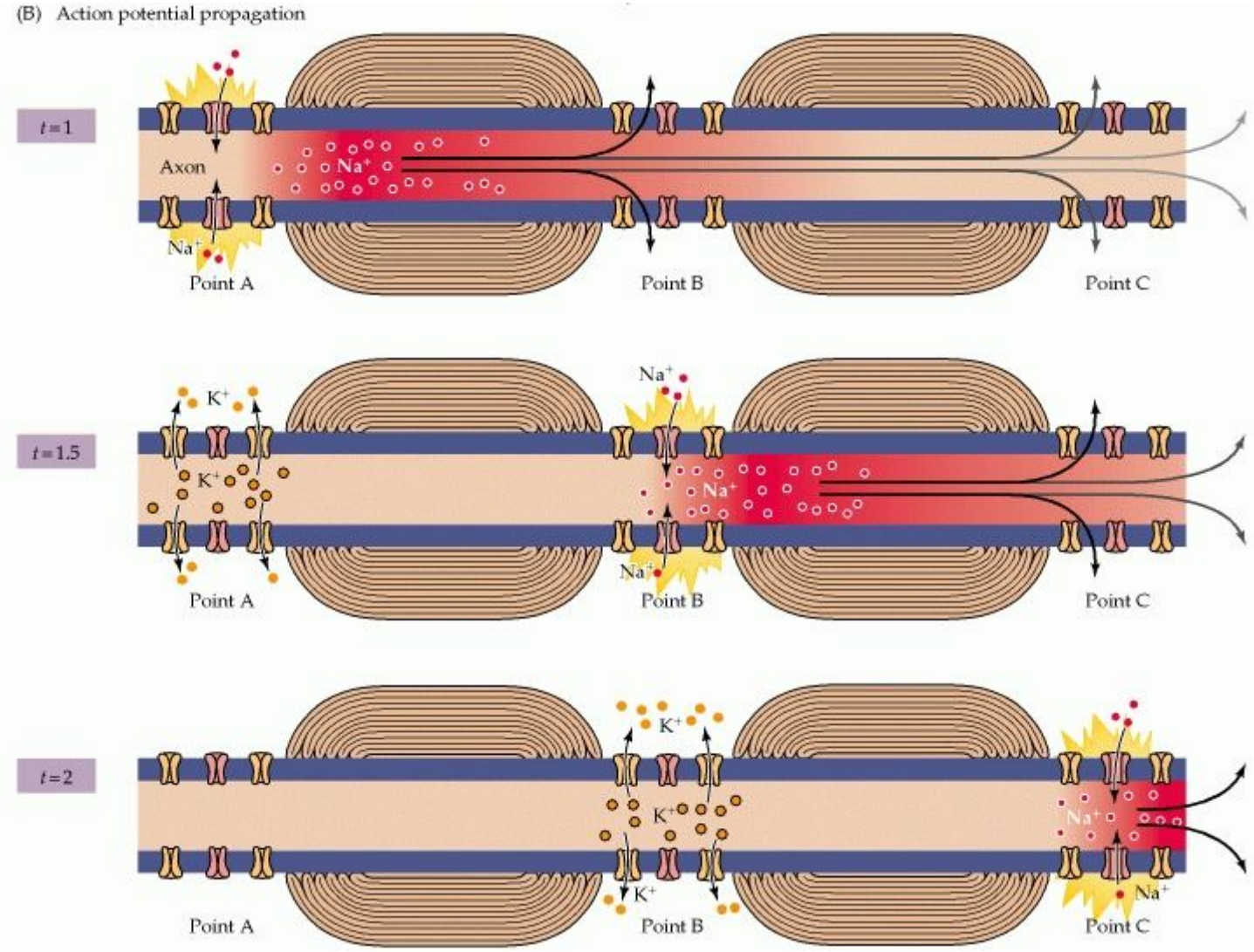


Figure 2-13 from "**Increased Conduction Velocity as a Result of Myelination**" in book "Neuroscience, 2nd ed". By Purves D, Augustine GJ, Fitzpatrick D

How does this help?

- Myelin is a good insulator
  - Isolates sections of line
  - Much less C (10-30x less) and less leakage
  - RC propagation to next node, where signal is regenerated
  - Gives speed O(length)
  - Exactly analogous to repeater insertion in VLSI
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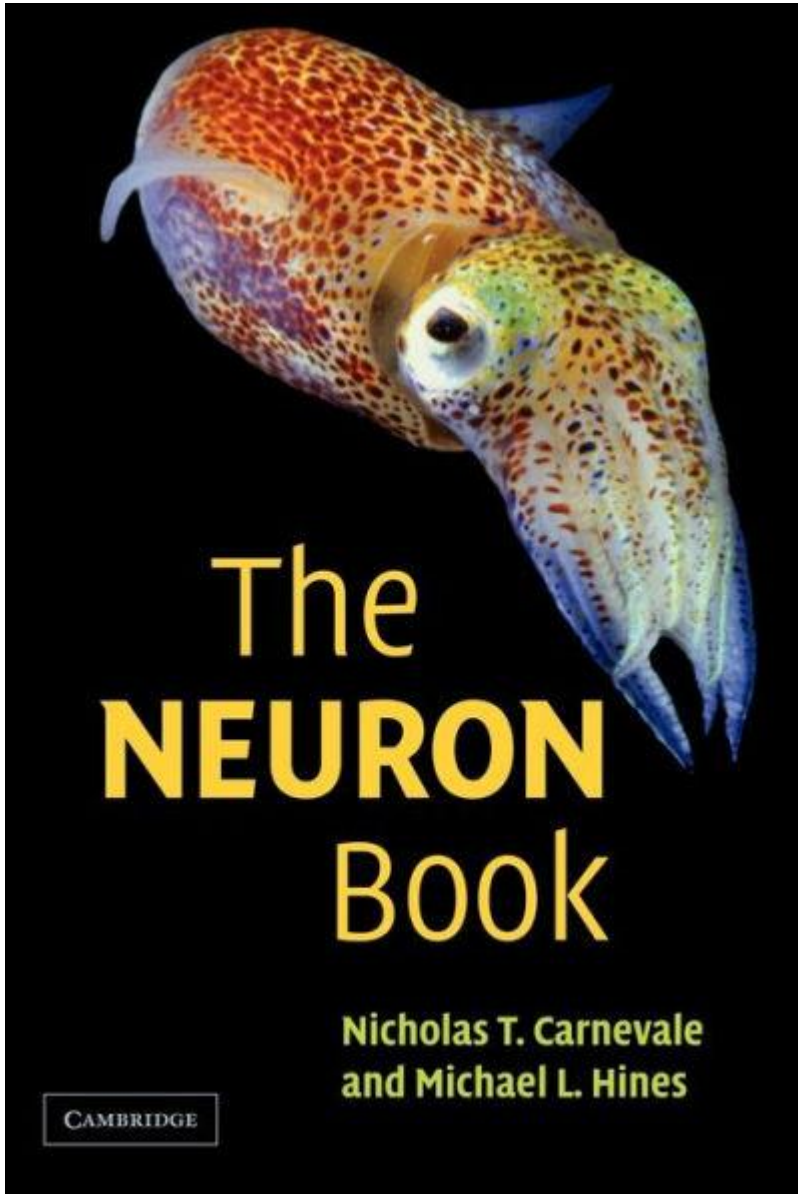
See section "**Increased Conduction Velocity as a Result of Myelination**" in book "Neuroscience, 2nd ed". By Purves D, Augustine GJ, Fitzpatrick D

Speed of Propagation

- As in EE, two regimes
  - Short neurons (<100 μ), neurons are isopotential and propagation delays are << gates
  - For long neurons, in large animals (mammals) transport delays dominate

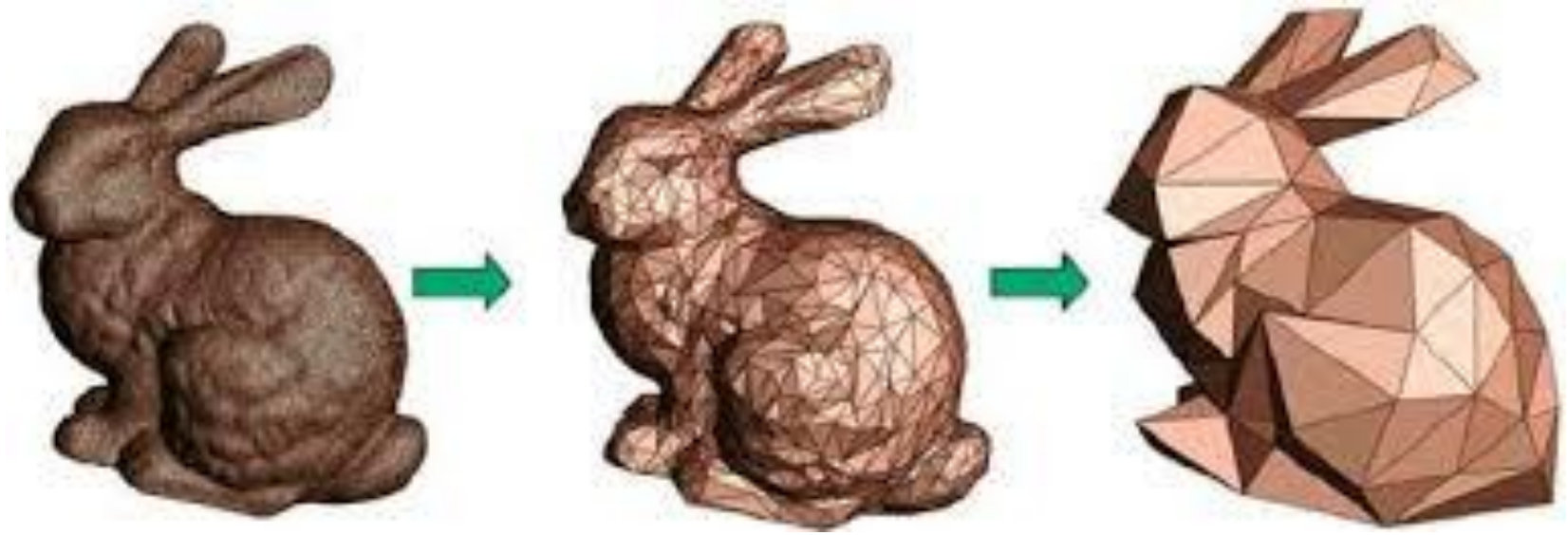
SPICE for neuroscience

- There is a program ‘NEURON’ that is the biological equivalent of SPICE
  - Considers all details, but quite slow
- Each neuron is a multi-compartment RC model determines response at all locations
- Each synapse is a small current source with a value and time constant
- Has exactly the same problems as SPICE with widely varying time constants
- Uses almost exactly the same numerical methods



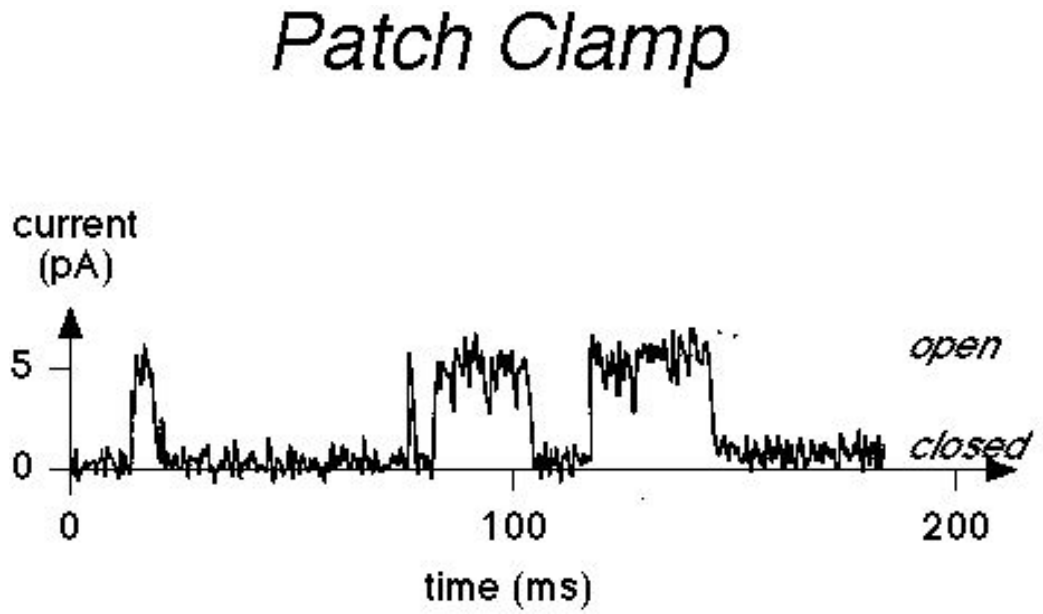
Model order reduction

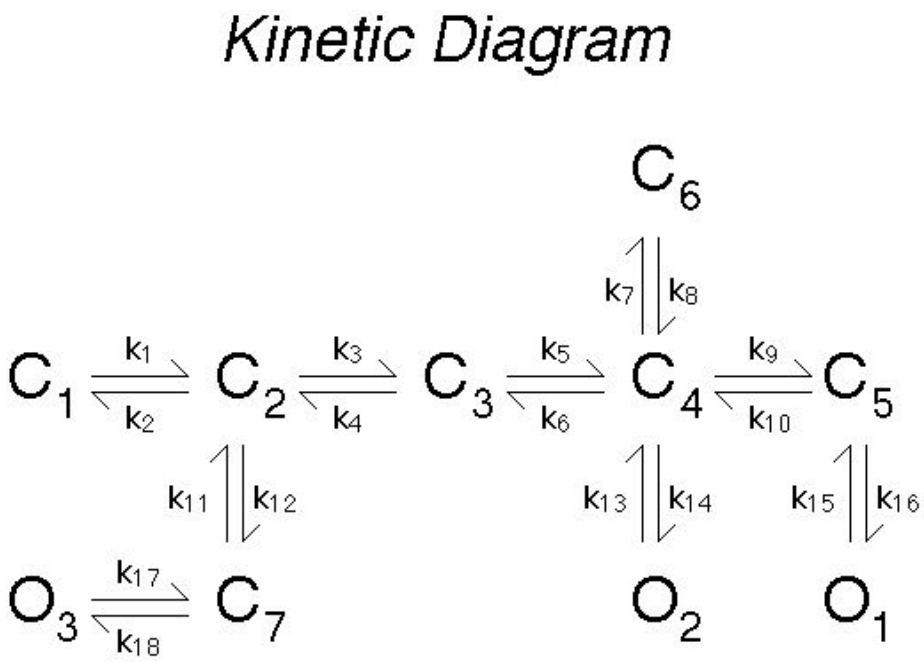
- As in EE, modeling geometric detail generates a many-element model which slows analog computation.
- Maybe we can replace a complex model with a simplified model that is “accurate enough”, as we do in EE? See, for example, “Model Order Reduction Techniques for Circuit Simulation” by Luis Miguel Silveira
- Being tried for brain modeling: “Model Order Reduction for Modeling the Brain”, by Mikko Lehtimäki



Statistical timing

- Every action in biological systems is statistical
- You can see this directly in detailed measurements
- And supported by theory





THE PHYSICAL BASIS OF ION CHANNEL KINETICS: THE IMPORTANCE OF DYNAMICS, Liebovitch and Krekora
http://www.ccs.fau.edu/~liebovitch/dyn.html

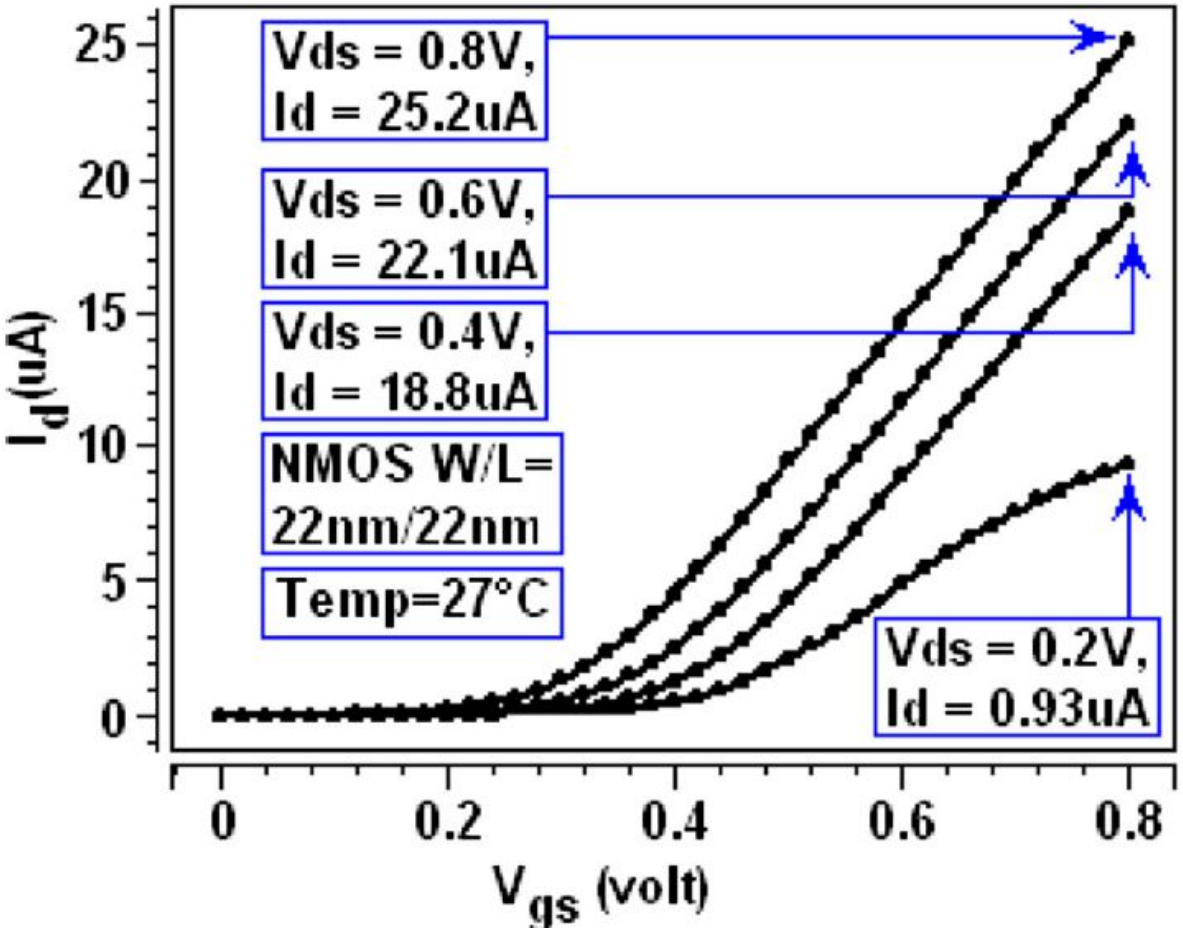
Statistical timing

- Almost all actions in nervous systems are statistical
- Small number (usually 1?) of vesicles released during an action potential
- Each has a small (~5000 molecules) so a ~70 molecule std deviation
- This triggers a few (1-10? Ion channels)
- That relax statistically…..
- EE has used this for years: “Statistical timing analysis: From basic principles to state of the art”, by D Blaauw, K Chopra, A Srivastava
- Seems like a great fit, but to my knowledge, statistical timing techniques from EE have not been applied to biological systems
  - A Ph.D. thesis just waiting to happen!

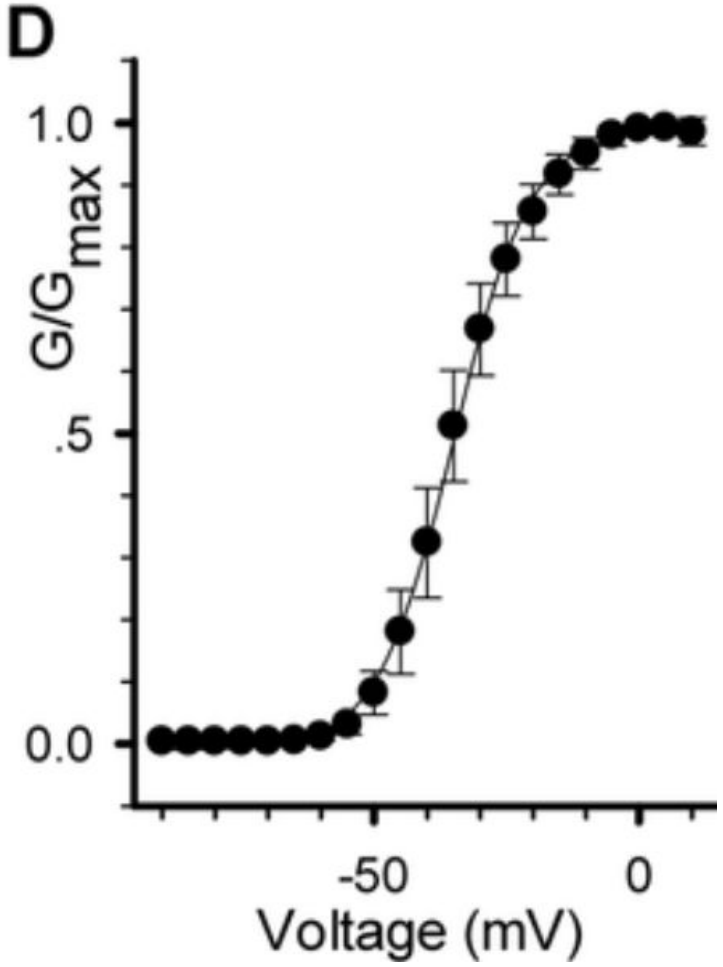
Power

- How does biology achieve such low power?
- Two components – hardware and software
- First consider hardware
  - Power goes like V^2
  - How low can voltage get and still work?
  - Using MOSFET gates, a 1,000,000:1 on/off ratio needs 14 Vthermal (kt/Q), or at least 0.4 volts
- But biology does 50 mv (see next slide)
- How does it do this??

MOSFET compared to ion channel

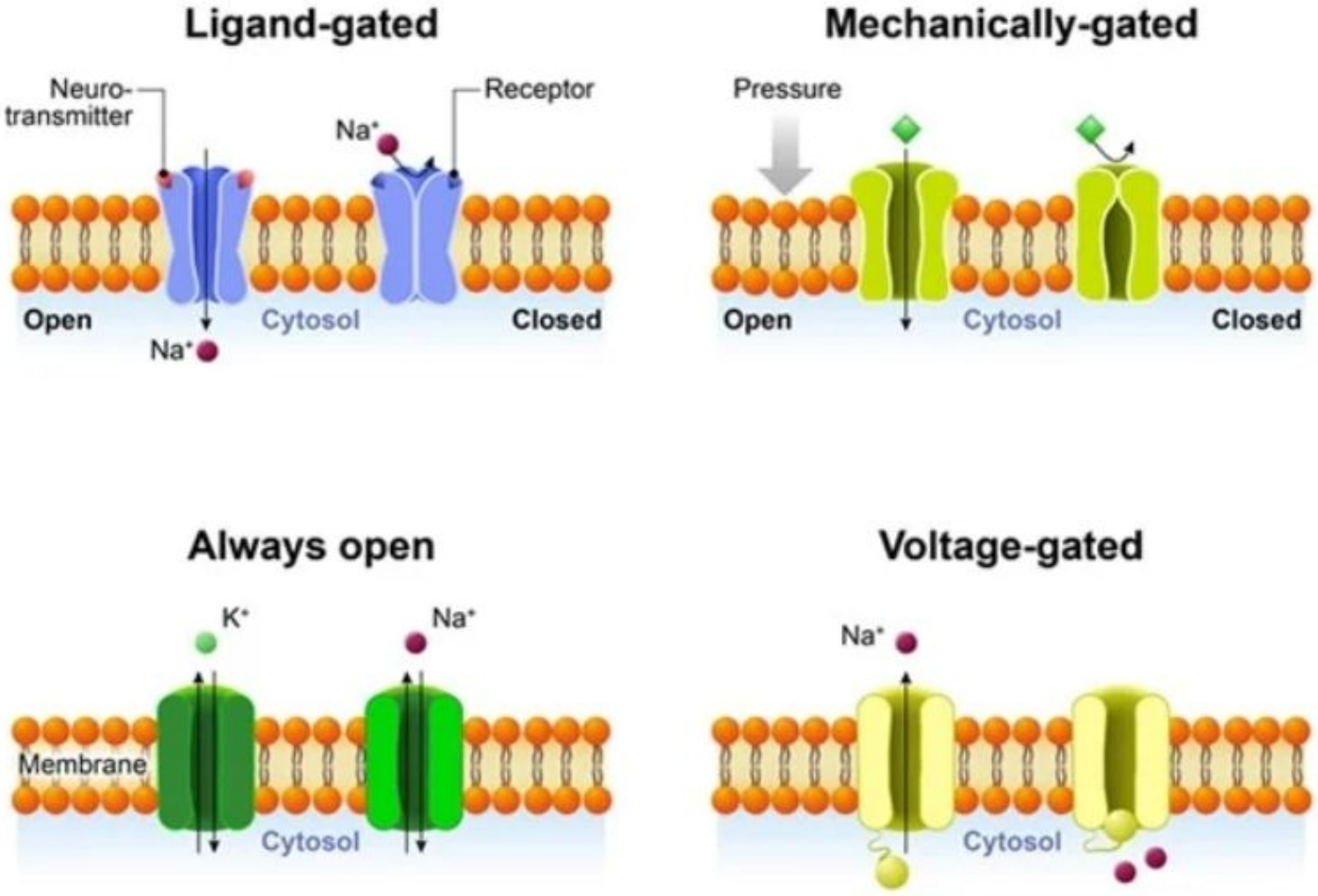


- From "Characterization of single-ended 9T SRAM cell"



From: "Kinetic Model of Nav1.5 Channel Provides a Subtle Insight into Slow Inactivation Associated Excitability in Cardiac Cells"

Ion channels provide inputs to neurons

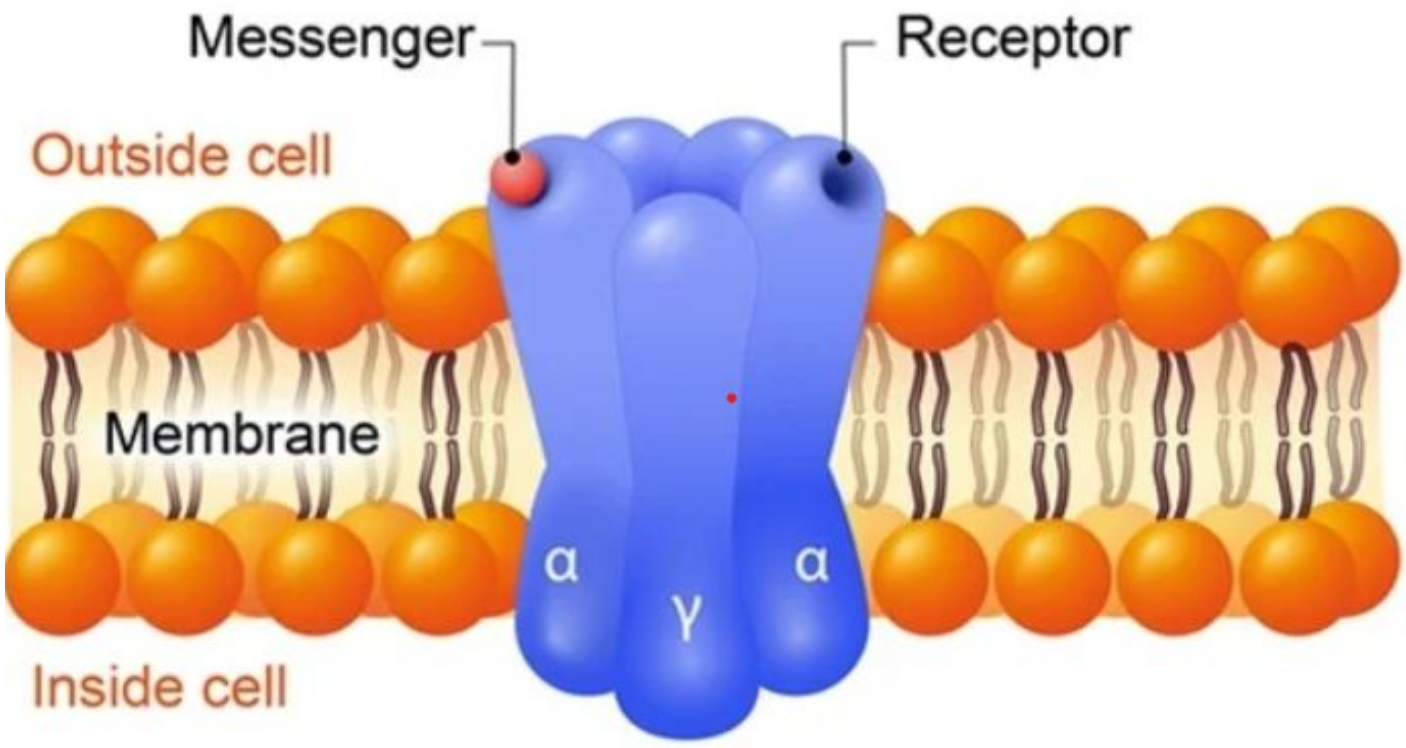


Types of ion channel. Classification by gating. mechanism of action. Voltage-Gated, Ligand-gated, Mechanically-gated and Always open ion channels. Image Credit: Designua / Shutterstock

Change shape upon binding or voltage change

All subunits need to change to open channel

Picture of ion channel



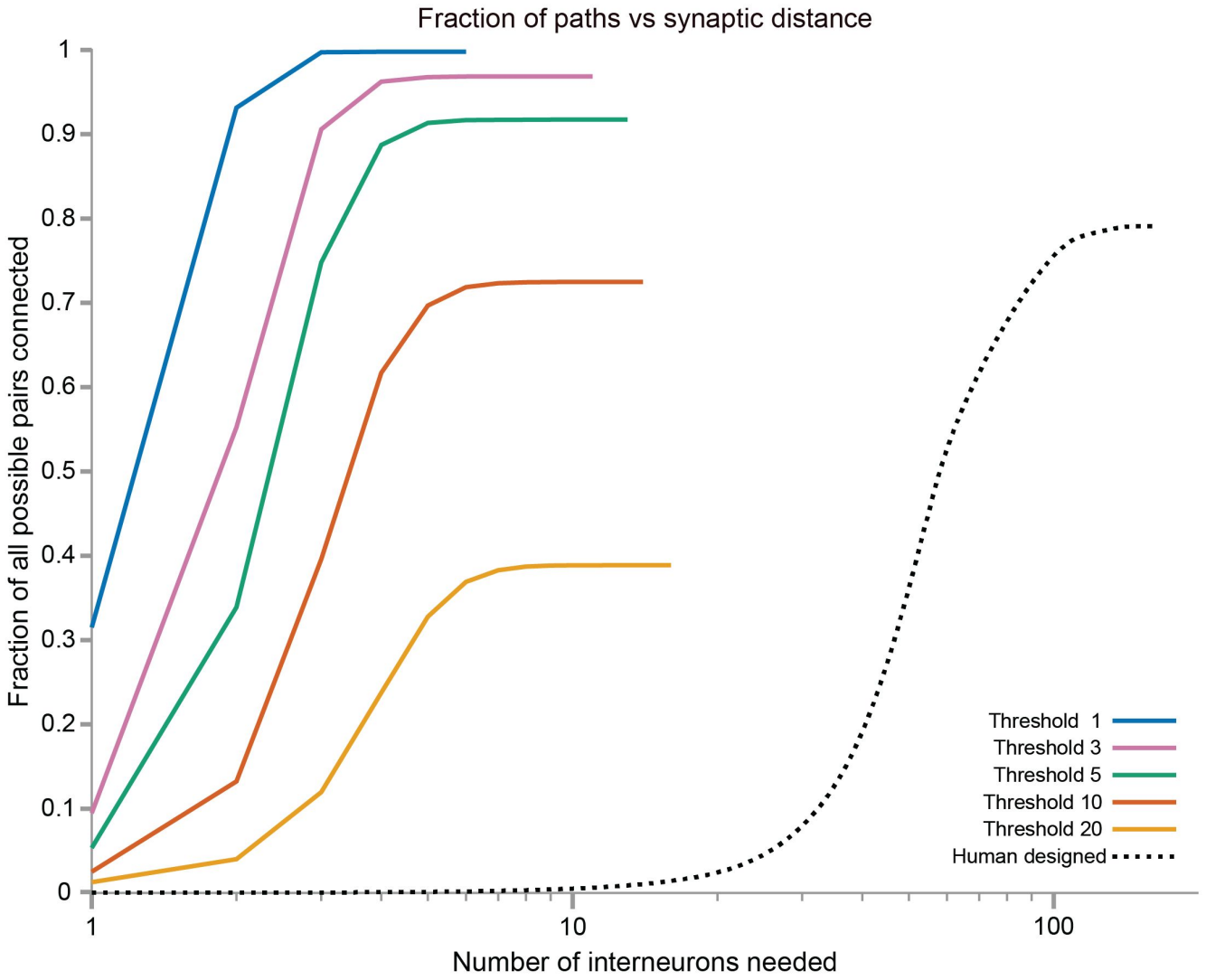
Ion channel. Structure of the channel. Image Credit: Designua / Shutterstock

- 5 fold symmetry is critical
- From thermo, probability site is occupied goes like $e^{-kt/Q}$
- So slope is e-fold change for 27 mv
- But if all 5 sites must be occupied, odds $e^{-5*kt/Q}$
- e^5 = 148 fold change in probability for 27 mv change
- No Vt variation

But this hardware change is not solely responsible

- 10x smaller swing results in 100x less power
  - This part will be hard to copy, at least in the short term
- Much of the rest is from lower speed (ms vs ns)
  - Real time response (ie. driving a car) with KHz rates!
- Biology uses architecture and parallelism to recover real time response
  - This is the part we can understand and use

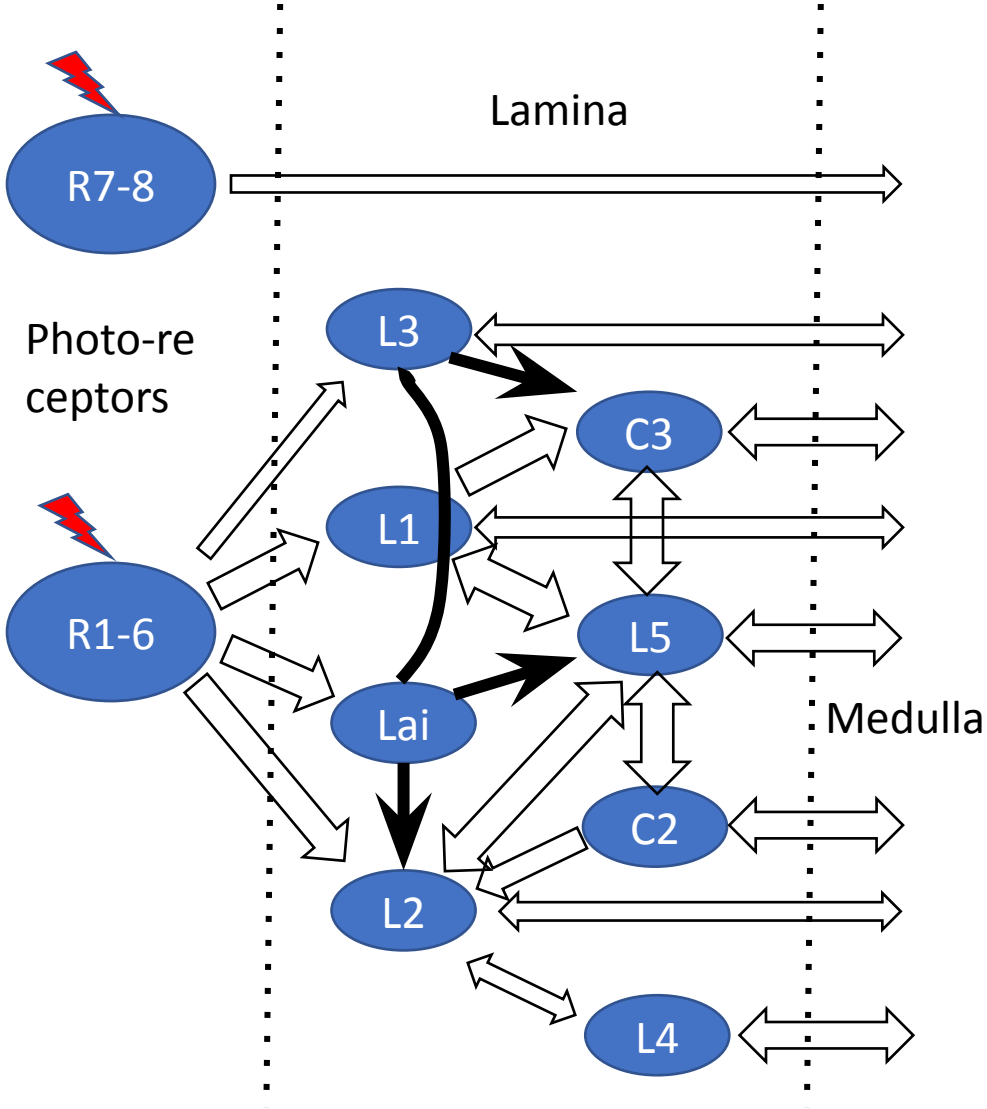
Neural circuits are quite different



- Very short path lengths
  - 2-3 neurons to get anywhere in the brain
- Very large fanouts
  - For fruit fly, average fanin/fanout is 143
- No clocks – fully asynchronous
- Not feedforward only – lots of loops w/o clocked elements
- Many different cell (gate) types

Human design is S38584 from Brglez et al., 1989

Biological Neural Net



- Relatively few layers
- Not neatly organized
- Lots of lateral and feedback connections
- No clocks
- Designed by evolution. Trained by ???

Understanding these networks likely the key to huge power savings

- How are they connected?
  - We have examples, but designed by evolution
- How do they work?
  - Similar to the problem understanding operation of general neural networks
  - For specific hardwired responses we know
- How are the weights determined?
- Can these circuits be synthesized?

Large number of cell types

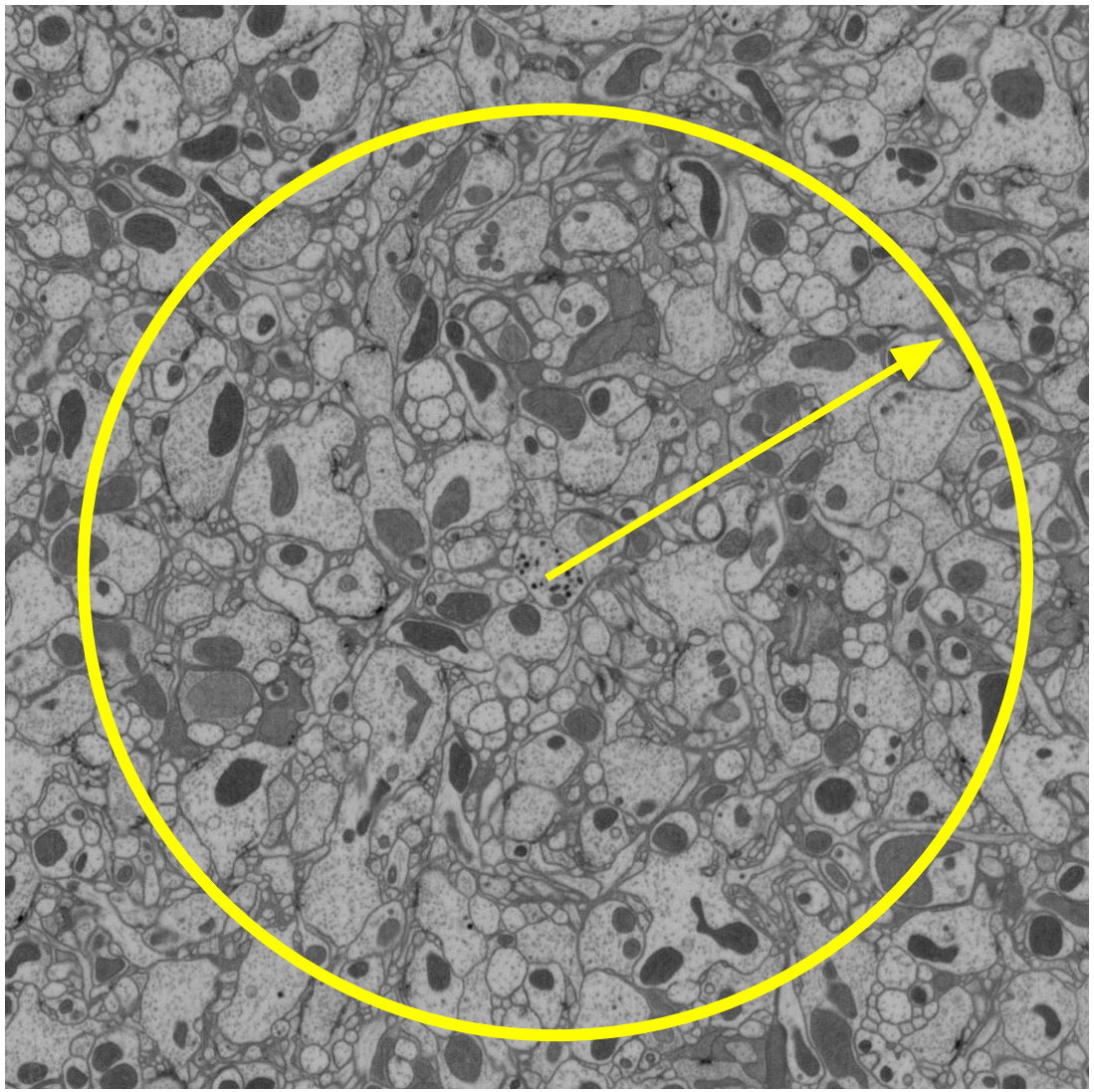
- Drosophila brain has 150K neurons, but more than 5K types
  - Mostly due to need for cells to implement wiring, not differing computation.
- Leads to another direct analogy with EE – “stuck-at” faults
- Can insert special (genetic) ‘code’ in a cell type to change behavior
  - Permanently silence the cell type (stuck-at off).
  - Conditionally activate or deactivate cell based on conditions such as light, temperature, or food
  - Only works in animals where detailed genetics are known (fly, mouse).
- As in EE, a huge help in decoding how the circuit works

In this talk so far, every element has a direct analog to EE circuit design

- Neurons <-> gates and wires
- Ion Channel <-> Voltage controlled current source
- Capacitance (same)
- Thresholds <-> Schmidt trigger
- Biological signal propagation <-> Wire delay and repeaters
- Gap junctions <-> resistive coupling

- But one signaling mechanism does not
  - Understanding this will be more like device modelling

Neuromodulators

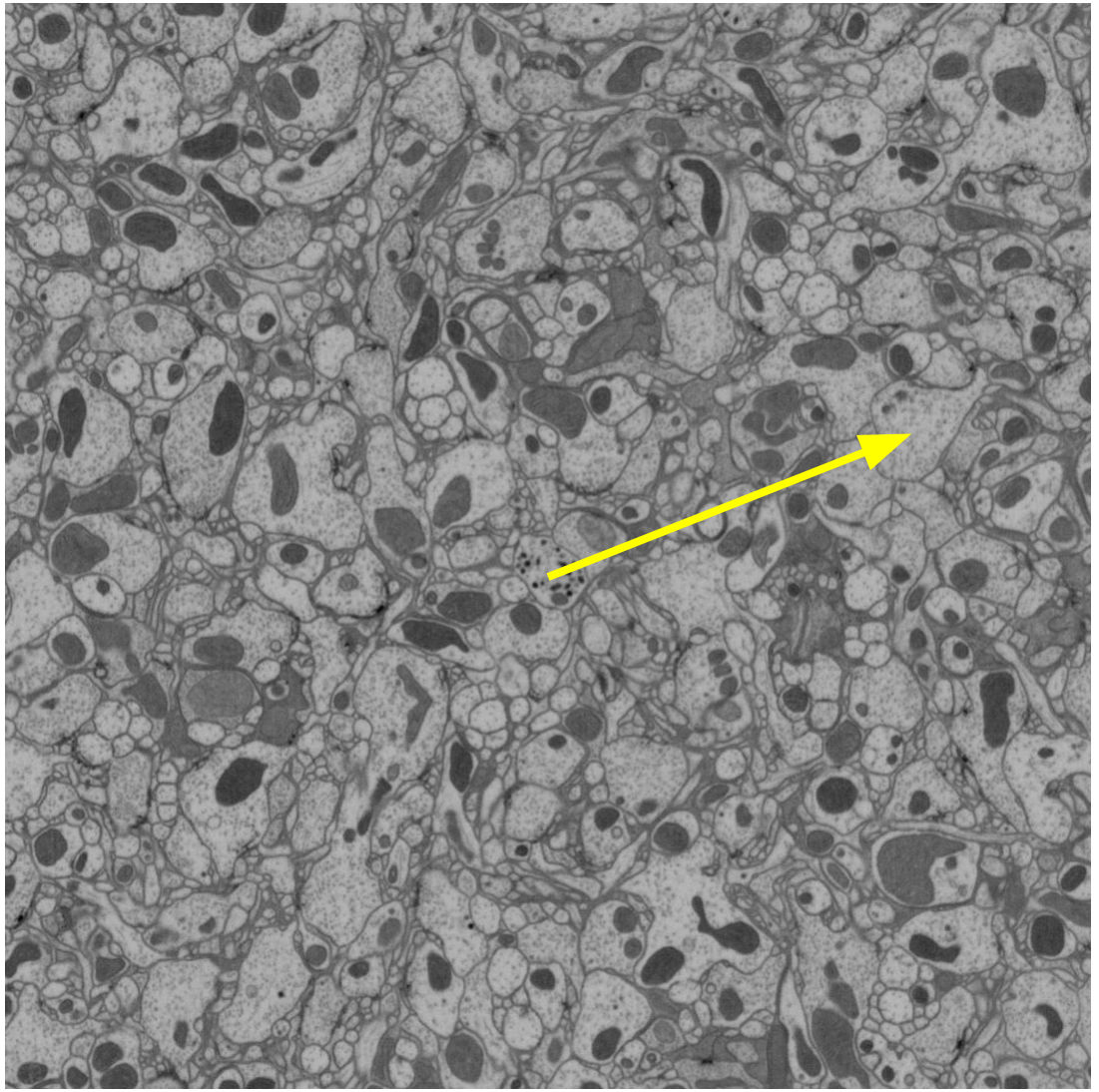


Not just adjacent signaling, unlike synapses or gap junctions

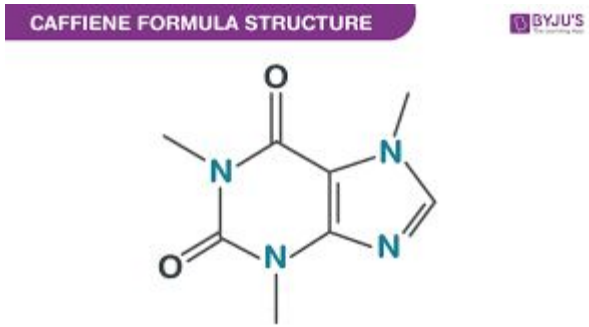
- Works by diffusion through the tissue
- Action ranges between a local and global variable
- Hundreds of independent signals
- Slow compared to synapses, but very large reach

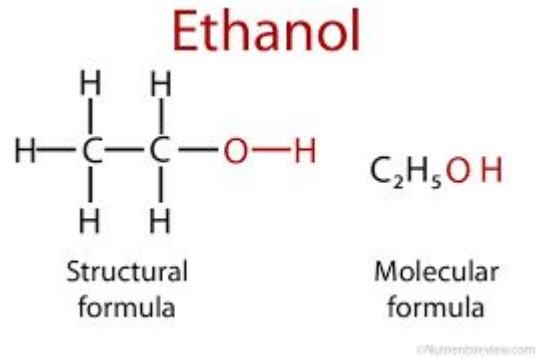
Neuromodulators: Building a (more) complete model of computation

- Adjacent cell communicate through **synapses** and **gap junctions**.
- But cells also communicate by expressing **neuromodulators**, which diffuse through tissue and activate channels on distant cells (volume transmission).
- This is known to (sometimes dramatically) affect their behavior

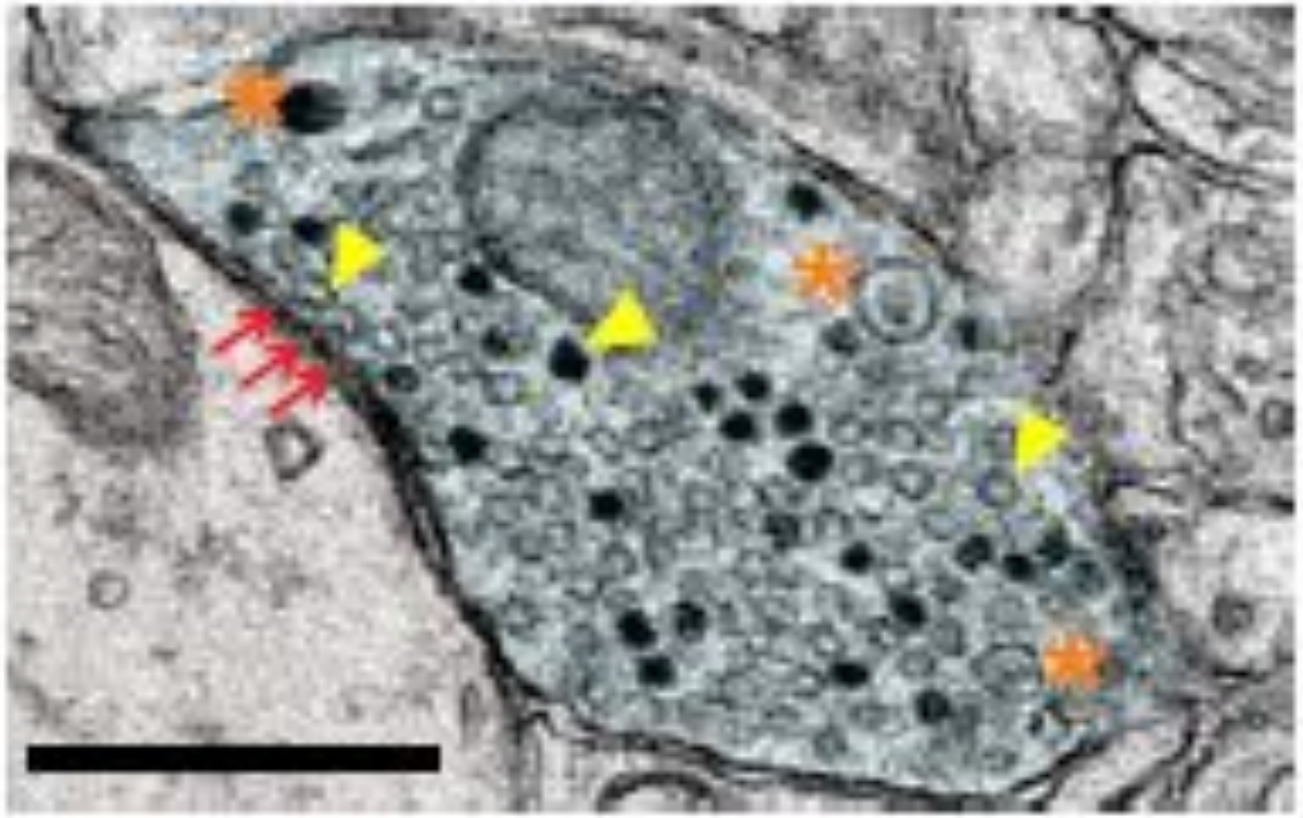


Some neuromodulators with global effect are well known





Neuromodulators are a common circuit element



Deniz Atasoy, J. Nicholas Betley, Wei-Ping Li, Helen H. Su, Louis K. Scheffer, Julie H. Simpson, Richard D. Fetter, Scott M. Sternson

Estimates show about 20% of neurons express both mechanisms – synapses and neuromodulators

Can sometimes see evidence in EM: different sizes of vesicles (yellow and orange), synapses in red.

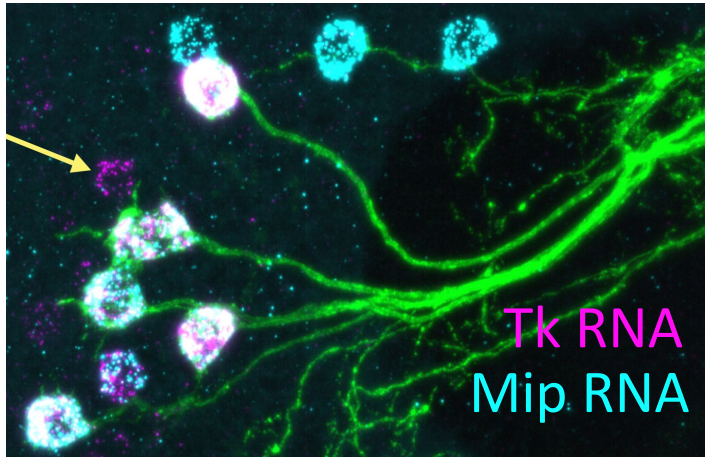
A few are known through specific experiments

But, in general, we don't know what these modulators are, or who receives these signals.

Many modulators are neuropeptides, and tools to find them are in progress

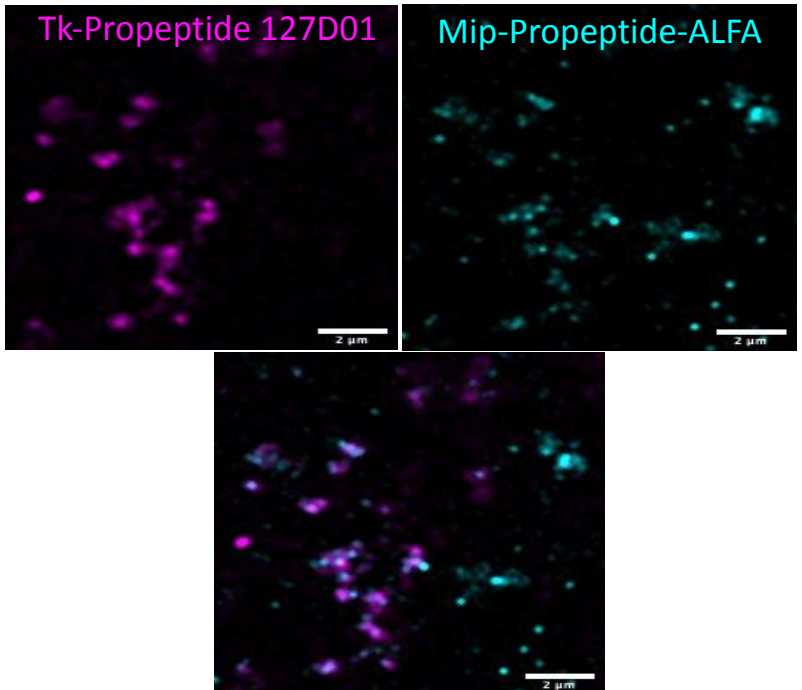
Gene Expression

EASI-FISH probes against neuropeptides identifies where neuropeptides expressed



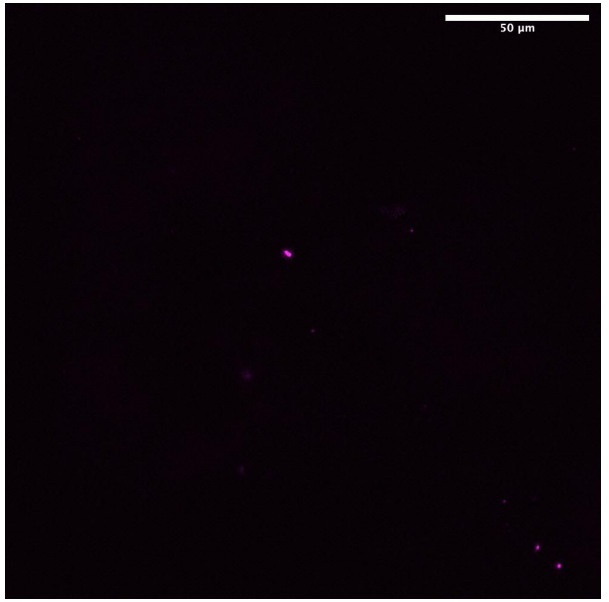
Neuropeptide Tagging

Using Nanotags, we can visualize the vesicles neuropeptides are packaged into.



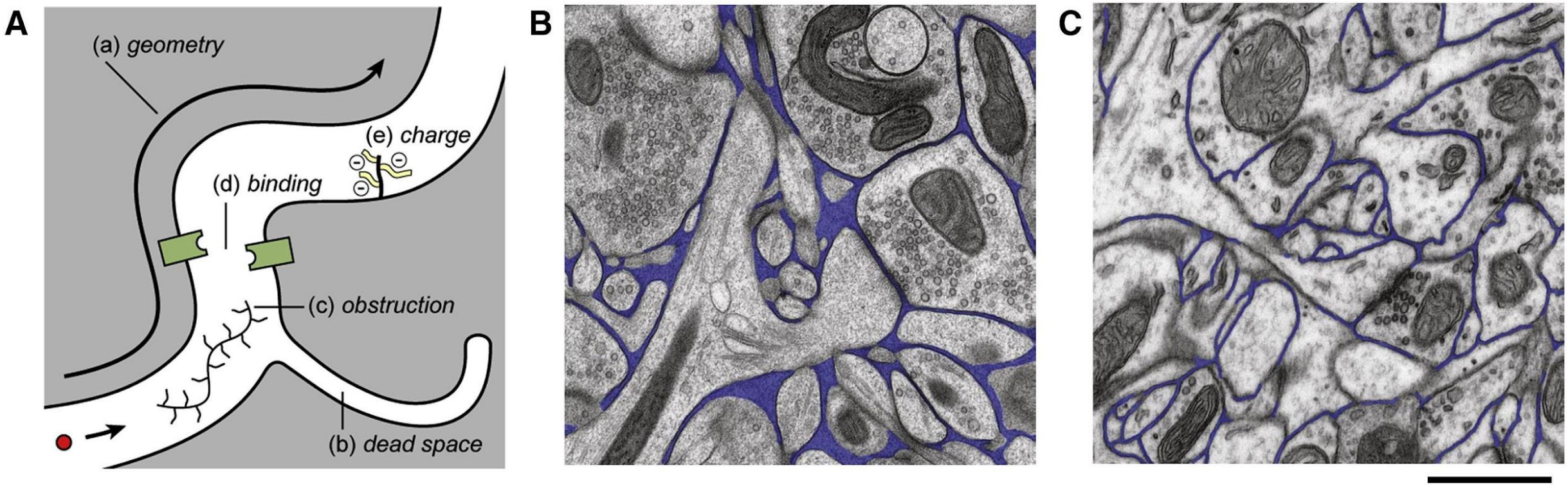
Neuropeptide Receptor Tagging

We are currently testing candidate regions in neuropeptide receptors to see where neuropeptides bind.



sNPFR-ALFA

Neuromodulators propagate through extracellular space



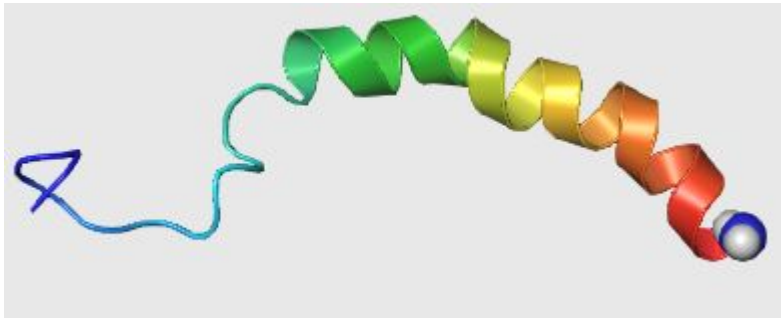
- Extracellular space (ECM) is a sizeable and complex environment
  - Typical value is 21% by volume in live animals
- It is hard to see in electron microscope images made for connectomics – it gets squeezed out during sample prep.

Brain Extracellular Space: The Final Frontier of Neuroscience; Charles Nicholson, Sabina Hrabětová[2,3]

Most neuromodulators are neuropeptides

"The *C. elegans* genome contains more than 120 genes that encode neuropeptide precursor proteins, and these proteins are processed to more than 250 neuropeptides."

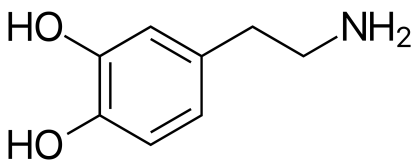
From: "Neuromodulators: an essential part of survival, Joy Alcedo and Veena Prahlad"



Neuropeptide Y (From Wikipedia, By 3bitcoins - Own work, CC BY-SA 4.0

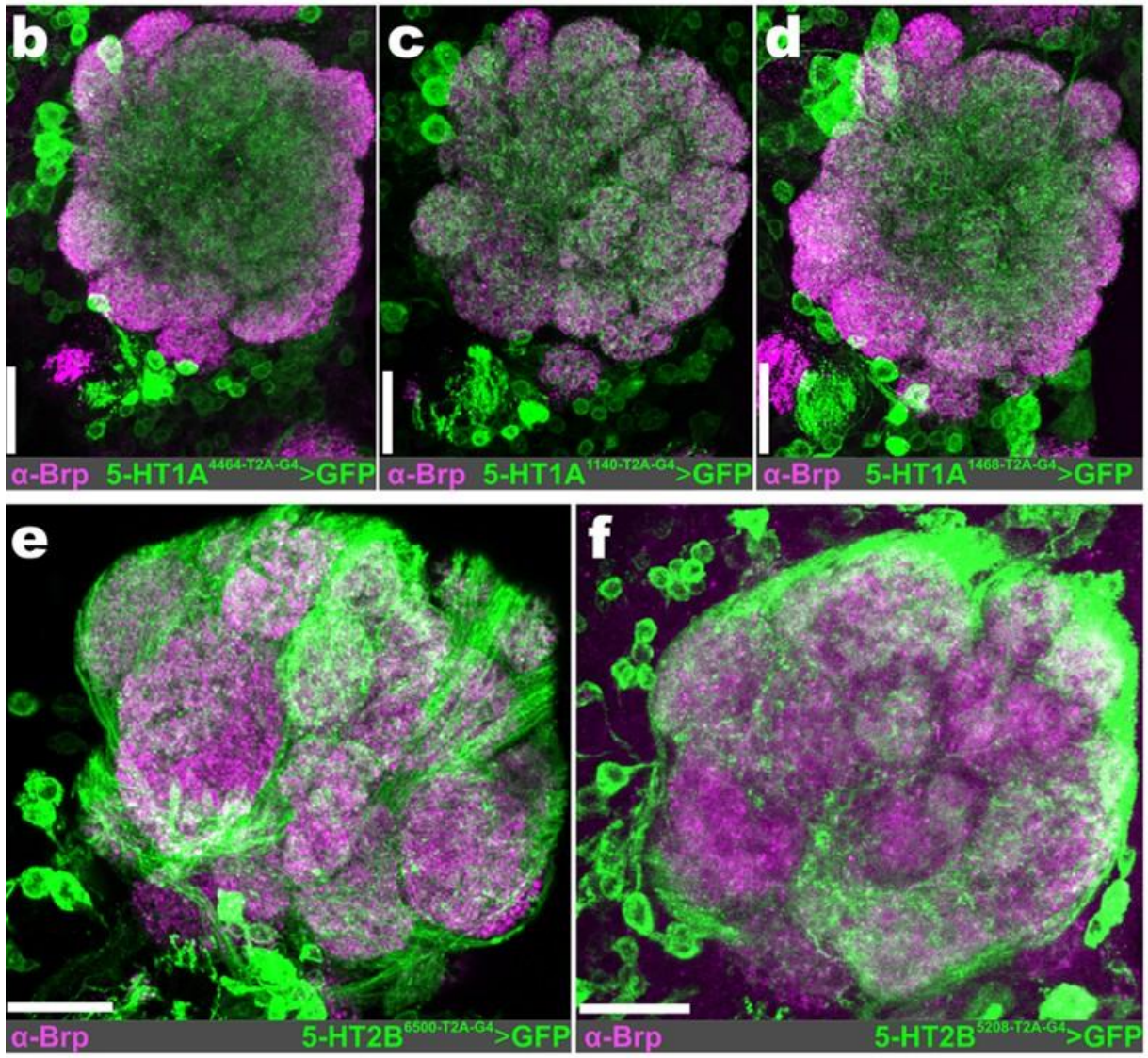
- "Overview of neuropeptides: awakening the senses?"
  - Andrew F Russo; PMCID: PMC5424629; PMID: 28485842
- Some classic small neurotransmitters (such as dopamine) also act as neuromodulators

Neuropeptides are typically 3-100 amino acids long



So what do we do with this data??

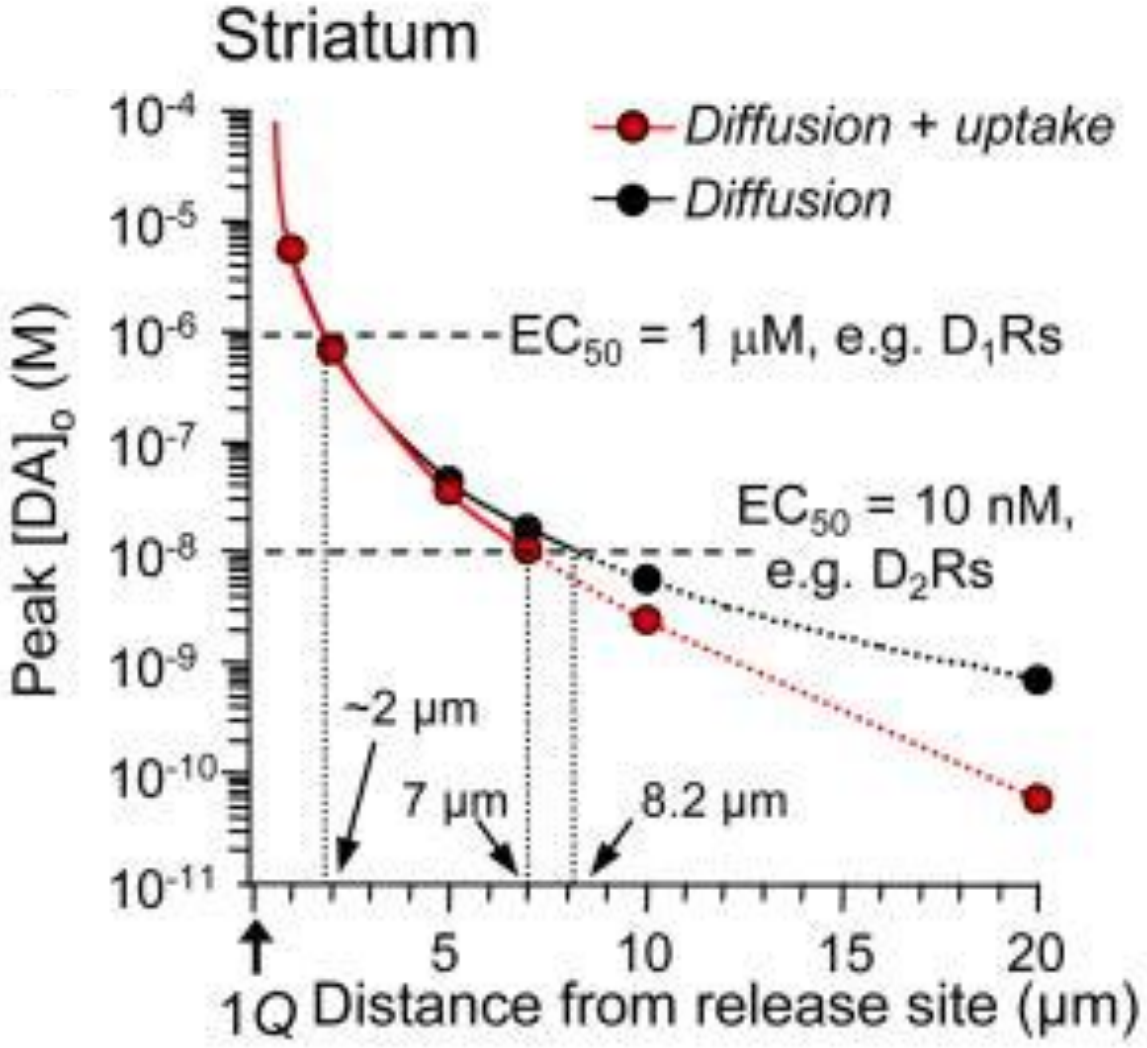
- Assuming we know the release sites and receptors for neuromodulators.
- How will these be incorporate into modelling and the connectome?
- Start with how these modulators behave



Serotonergic Modulation Differentially Targets Distinct Network Elements within the Antennal Lobe of *Drosophila melanogaster*

Tyler R. Sizemore & Andrew M. Dacks

Neuro-modulators behave differently than fast, local neurotransmitters



- Range is much larger
- Transport is dominated by diffusion
- Neurotransmitter, uptake is rapid, only neighbor sees
- Neuromodulator, uptake is slow, many cells see.

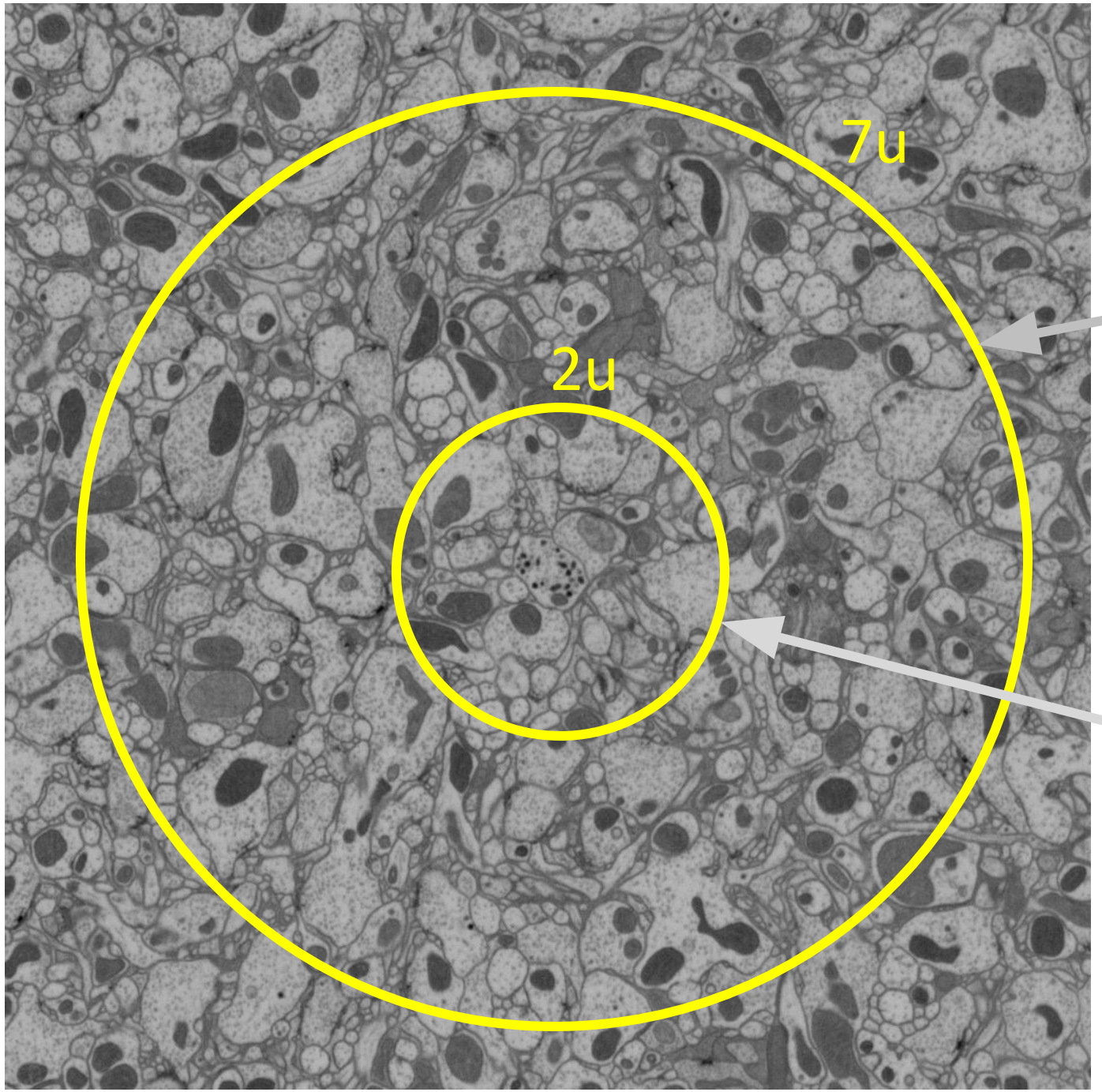
Rice, Patel, and Cragg, Dopamine Release in the Basal Ganglia, Neuroscience 198:112-137, 2011

Neuro-modulators

Cross-section of medulla of fruit fly

Range of influence may include hundreds to thousands of cells

Data from Zhi-Yuan Lu, Shan Xu, Harald Hess.

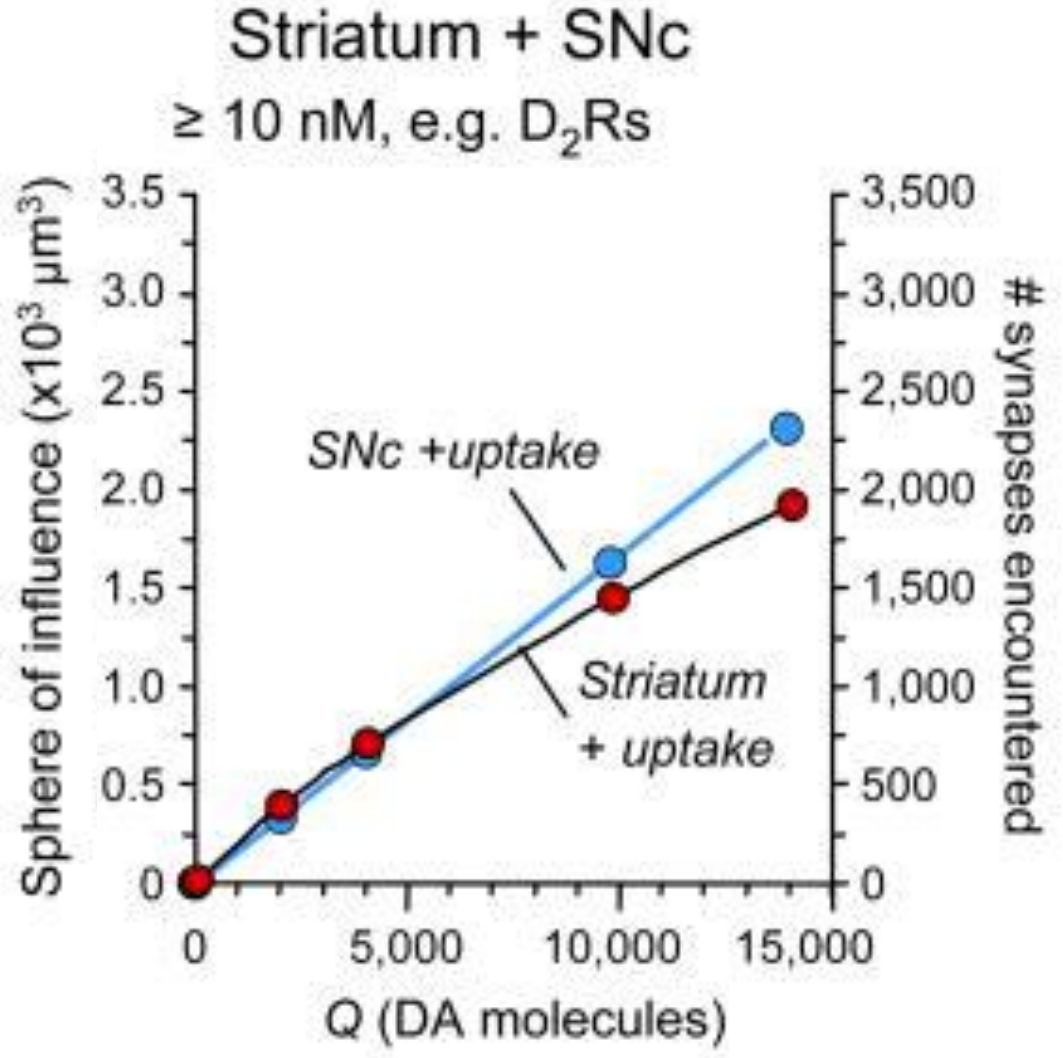


Range of influence with receptor of sensitivity 10 nM (for a single vesicle release!)

Range of influence with receptor of sensitivity 1 uM

Influence depends on release strength

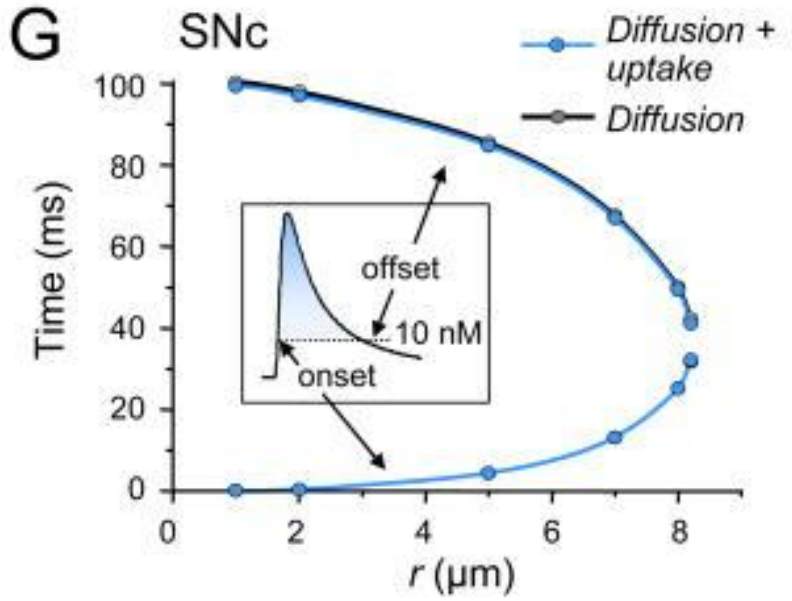
- Concentration at a given distance is linear in release strength
- Plot of volume (left) and number of synapses (right) vs. number of molecules released.



Rice, Patel, and Cragg, Dopamine Release in the Basal Ganglia, Neuroscience 198:112-137, 2011

Active time depends on distance

- Plot below shows on and offset times vs distance away
- Quite a bit slower than classic transmitters
  - Could explain why connectomes have been successfully without NM
  - Vision, escape response, navigation need to be fast, so use synapses not NM



Rice, Patel, and Cragg, Dopamine Release in the Basal Ganglia, Neuroscience 198:112-137, 2011

Timing and range depend on how many vesicles are released

- From “Overview of neuropeptides: awakening the senses?” by Andrew F Russo; PMCID: PMC5424629; PMID: 28485842
  - “a conservative estimate is that at least hundreds of vesicles will be released from a neuron over a time scale of seconds.”

Vesicles released	Max distance (10 nM receptor)	Approx time near max distance[1]
1	8 u	66-172 ms
10	17 u	280-820 ms
100	37 u	1.4-3.7 sec
1,000	80 u	6.6-16 sec
10,000	170 u	29-68 sec

- Upper range estimates might be low since sizes are comparable to boundary conditions (some have degradation times of hours)

[1]Computed with 10K molecules/vesicle and diffusion constant of a 4000 Dalton neuropeptide

Neuropeptides can cover much of a small brain

- Cells can release hundreds of vesicles
- Can result in ranges > 100 μ, and times > 10 seconds
  - 100 micron radius circle superimposed on fly brain

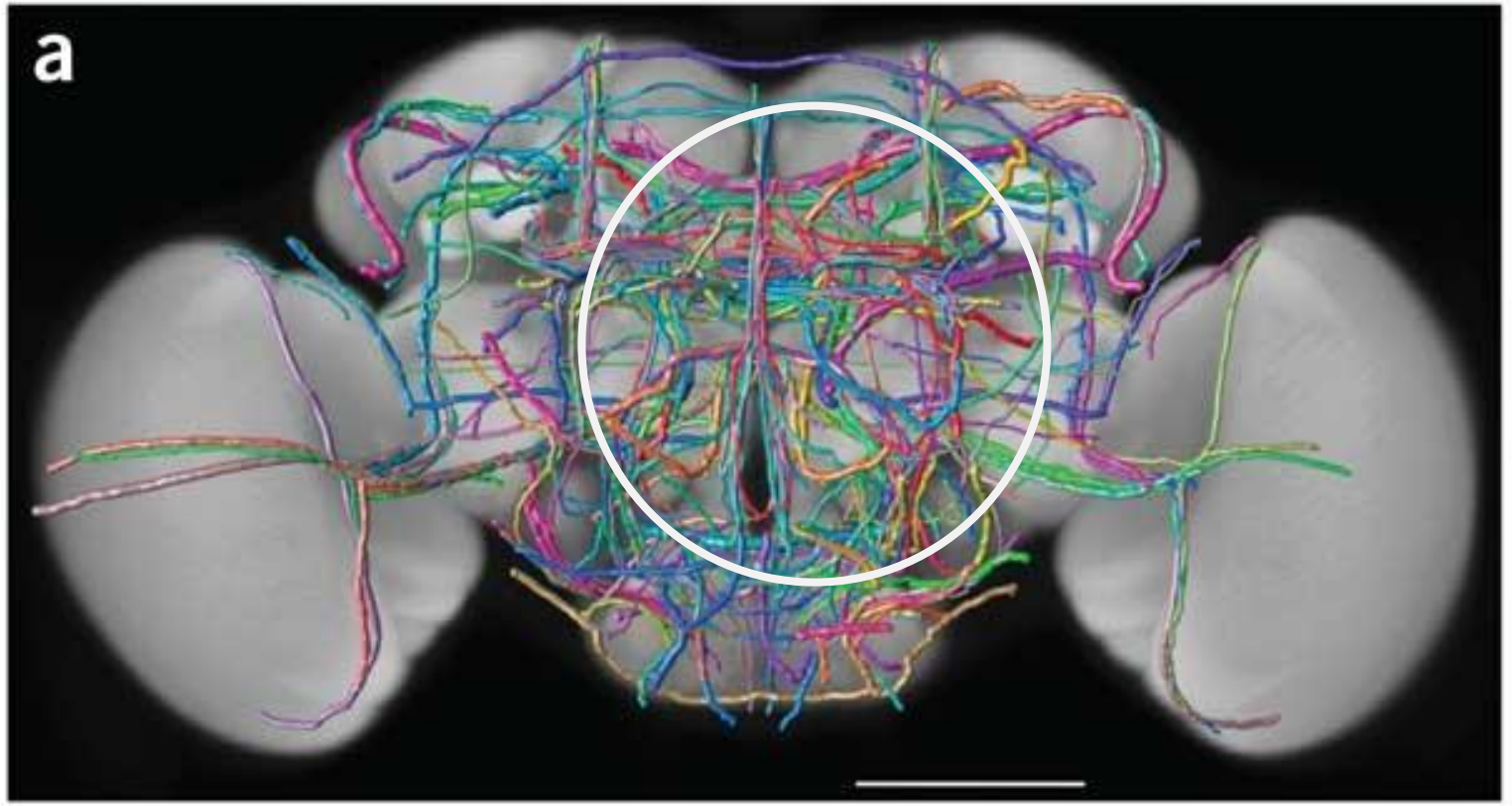


Image from:
BrainAligner: 3D registration atlases of *Drosophila* brains
- Hanchuan Peng,
- Phuong Chung,
- Fuhui Long,
- Lei Qu,
- Arnim Jenett,
- Andrew M Seeds,
- Eugene W Myers &
- Julie H Simpson

Lots of receptors with different properties

- "Given that a FLP receptor can bind to multiple peptides encoded by different genes and a single peptide can bind to multiple receptors, the potential complexity of peptide actions in *C. elegans* is astounding."
- "A FLP receptor can also bind to a diverse group of peptides with a range of activities. The Y59H11AL.1 receptor binds to 15 peptides encoded by 6 *flp* genes with EC_{50} values ranging from 25 nM to 5 μM (Mertens et al., 2006).
- WormBook, Chapter "Neuropeptides", C. Li and K. Kim

What we need to know to model neuromodulators

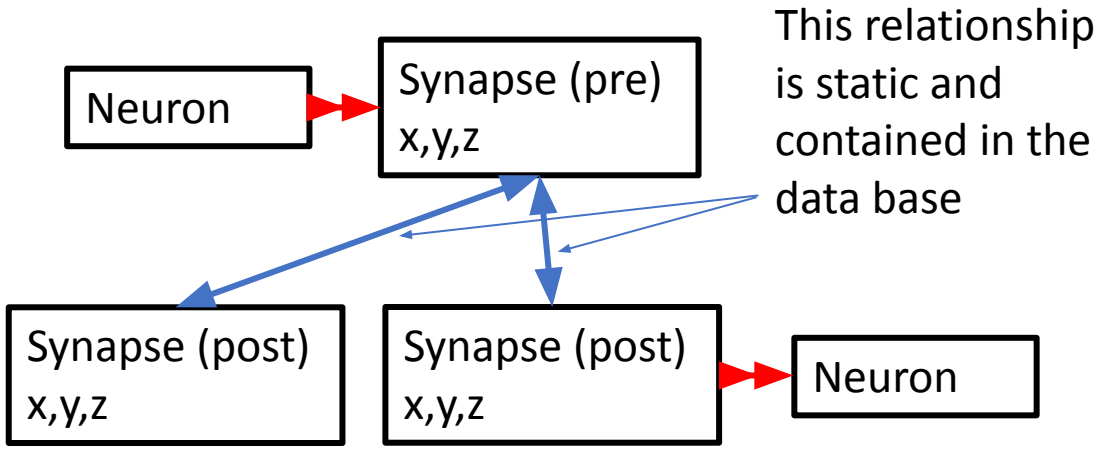
- The locations, and cell types, of sources and receptors
- A way to add them to the connectome (circuit graph)
- Amount of release
- How the modulator diffuses and degrades as it traverses the ECM
- Sensitivity of receptors
  - Many NMs have multiple receptors with different properties
  - A single receptor can respond to multiple different NMs

Add neuromodulators to the connectome

- Release sites registered as ‘pre’ synaptic sites
- Receptor sites as ‘post’ sites
- No direct link (unlike neurotransmitters) since range depends on superposition
  - A single release will need evaluation at a different set of receptors from a release coincident with a nearby release.
  - In theory, any receptor in whole nervous system could be triggered.
- Receptor sites, in particular, will likely need to be estimated because:
  - They may not be co-located with visible features such as synapses
  - They will be measured in different animals than used for connectome.

Different data structures required

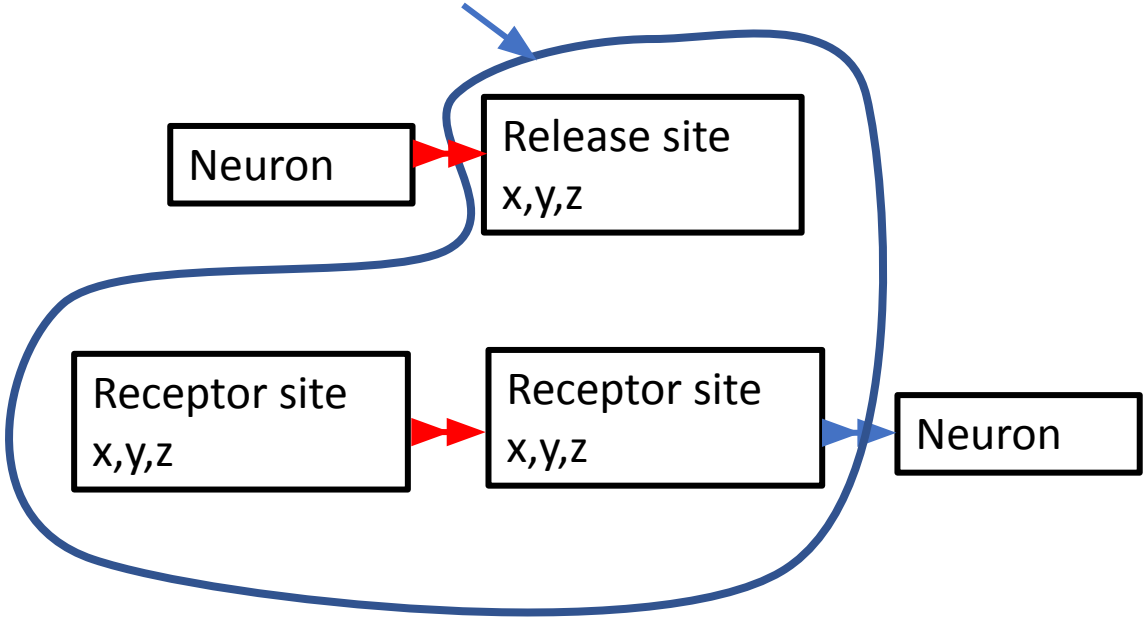
- Classical Neurotransmitter
  - Also gap junctions
- Represented as a graph (netlist)



1:1 (PSD->Tbar), or 1:(small) N (Tbar->PSD)

- Neuromodulator
- KD tree or similar

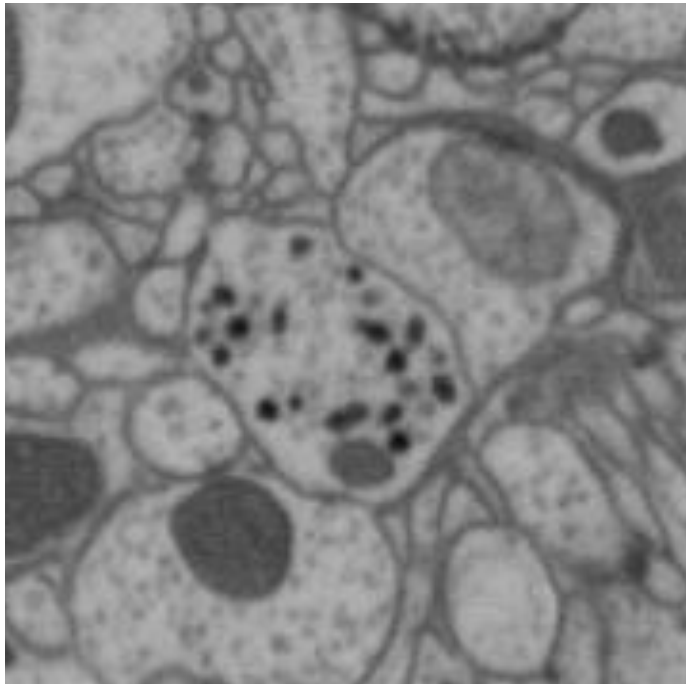
Too many edges to store; this relationship must be computed



Many to Many

Release amounts

- Release amounts can be estimated from vesicle sizes
- Need to correct for occupancy fraction α of the ECM
- Typical numbers
  - About 10,000 molecules released
  - Occupancy fraction α of ECM about 0.21
    - Doesn't look like this from classic EM because preparation techniques reduce ECM volume



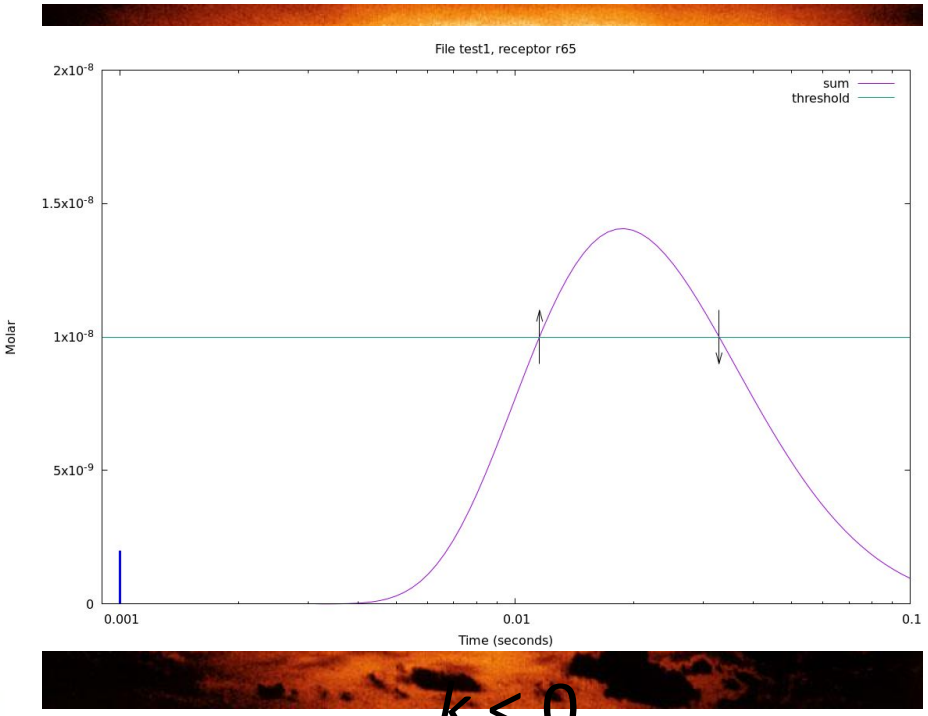
Propagation

- Common approximation is diffusion + proportional

$$\frac{dC}{dt} = D\nabla^2 C + kC$$

- So the solution to a point release at t=0 in 3D is

- C(r,t) = $$C(r,t) = \left(\frac{1}{\sqrt{4\pi Dt}}\right)^3 e^{-\frac{r^2}{4Dt}} e^{kt}$$



$k < 0$

$k > 0$

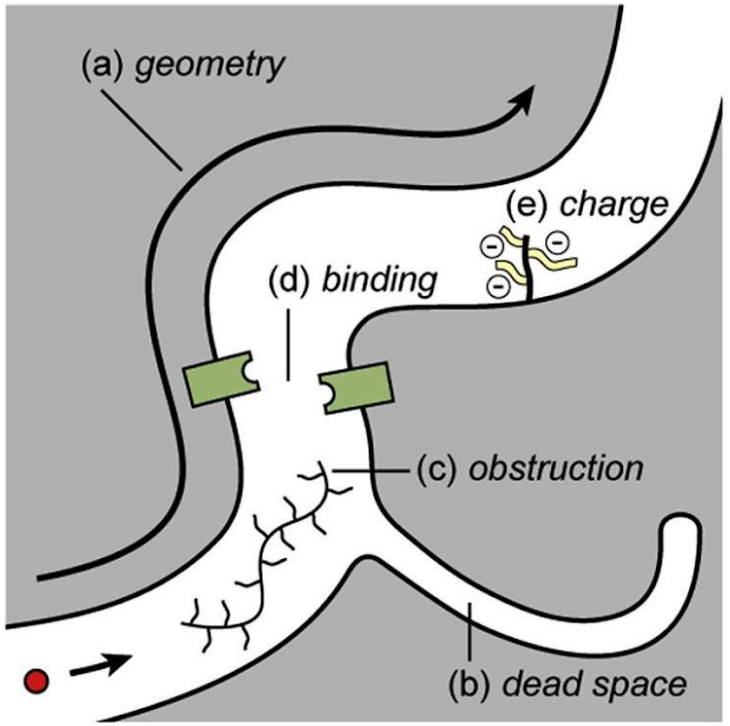
- Known limitations of this approximation
  - Does not take into account detailed obstructions/occupancy in the ECM (local)
  - Assumes linearity
  - Some enzymes degrade neuropeptide A and turn it into neuropeptide B. Then source of B depends on A and is not a point source.

Brain Extracellular Space: The Final Frontier of Neuroscience, Charles Nicholson, Sabina Hrabětová

Rice, Patel, and Cragg, Dopamine Release in the Basal Ganglia, Neuroscience 198:112-137, 2011

Propagation

- Parameters are not raw physical values, but adjusted:
  - Equation uses D*, which is the effective constant. Can be measured or estimated from free space diffusion constant D and the tortuosity of the ECM (typically 1.5).
  - Receptor concentration per molecule released depends on the ECM fraction (typically about 21%)
  - k (decay constant) is hard to figure out from first principles (determined by receptors and enzymes)
    - Big range of values, from 1/25 of a second to >10 minutes
    - Measure directly? Work backwards from radius of action?
- Spherical propagation not super accurate close-in (a micron or so, where it depends on detailed obstruction in ECM) but good further away

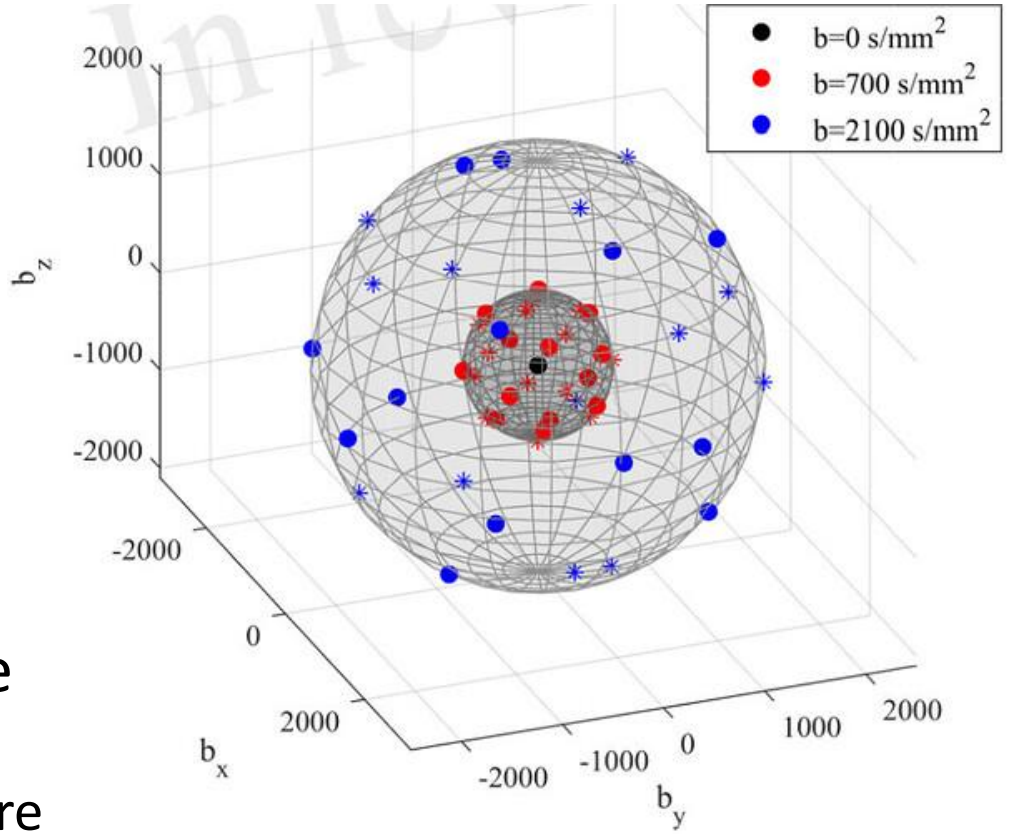


Diffusion and related transport mechanisms in brain tissue, Charles Nicholson

Measurements of neuromodulators and the ECM

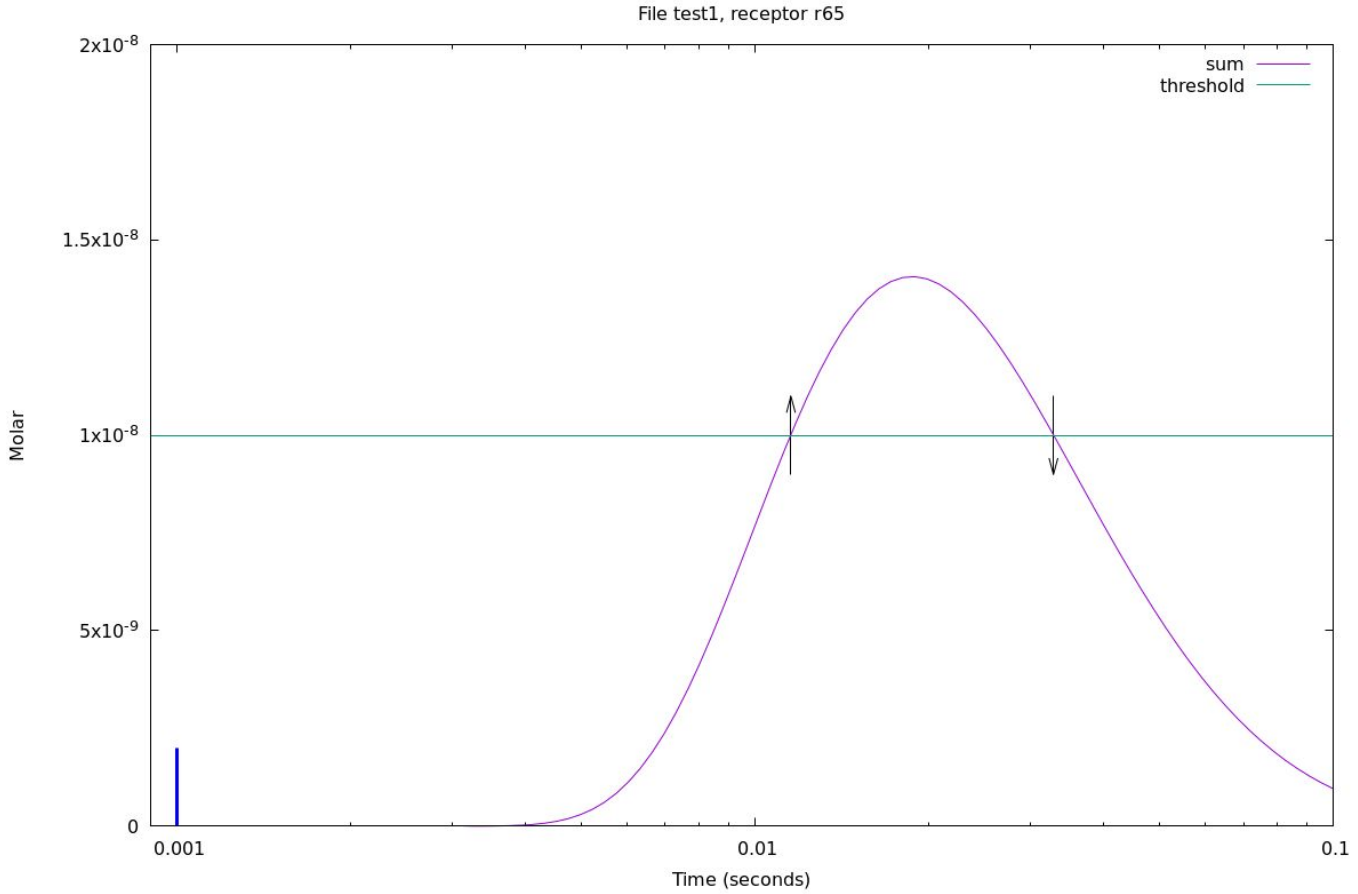
- Constants known to differ in different regions of the (mammal) brain
- Extracellular volume fraction (typically called α), affects concentration
- Tortuosity (typically called λ), affects D*, the effective diffusion constant
- Decay constant *k*

- All can be computed from measured values, if we have them
  - We need sensors and indicators for each, but there are a lot of neuropeptides. (See Yulong Li work)
  - Extra wrinkle in cold blooded animals such as flies – need temperature dependence.

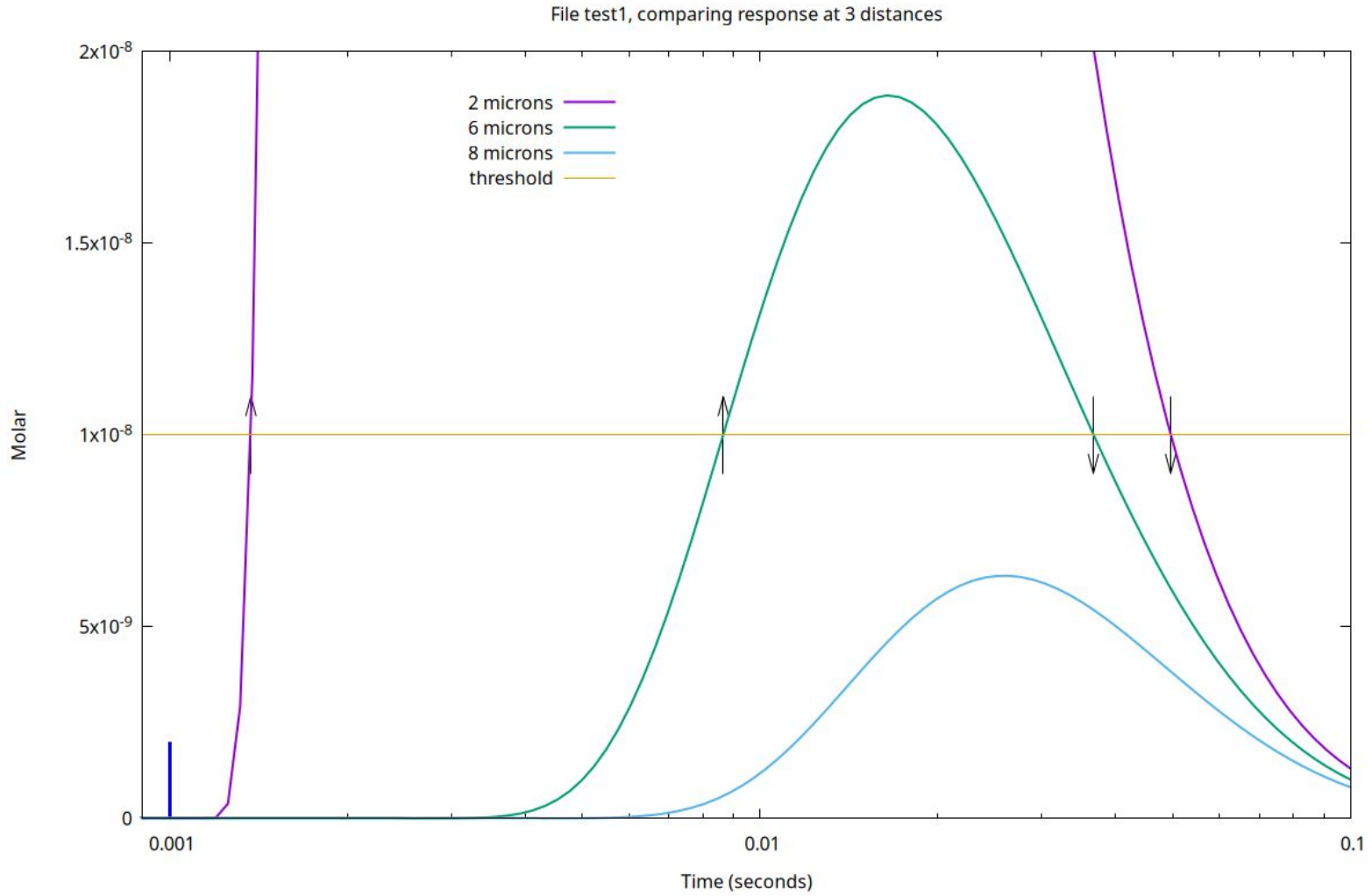


Analysis: response to a single release

- 10,000 molecules released
- D* typical for small molecule in tissue
- Volume fraction 0.21
- Tortuosity 1.5
- Receptor 6.5 u away
- Receptor threshold 10 nM.

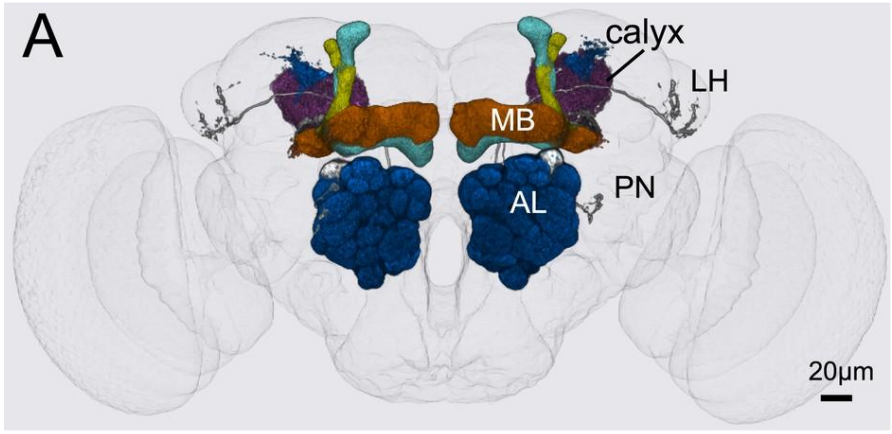


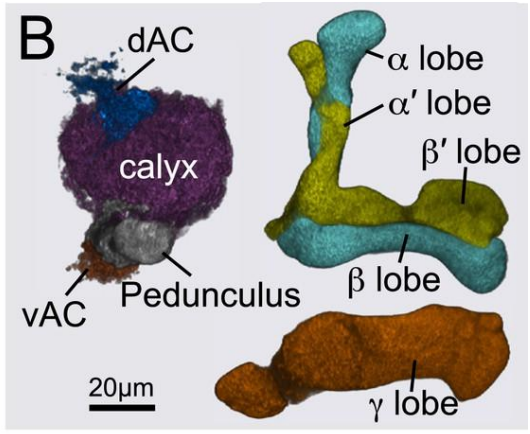
Solutions to these equations for a single vesicle (10K molecules) release, threshold 10 nM

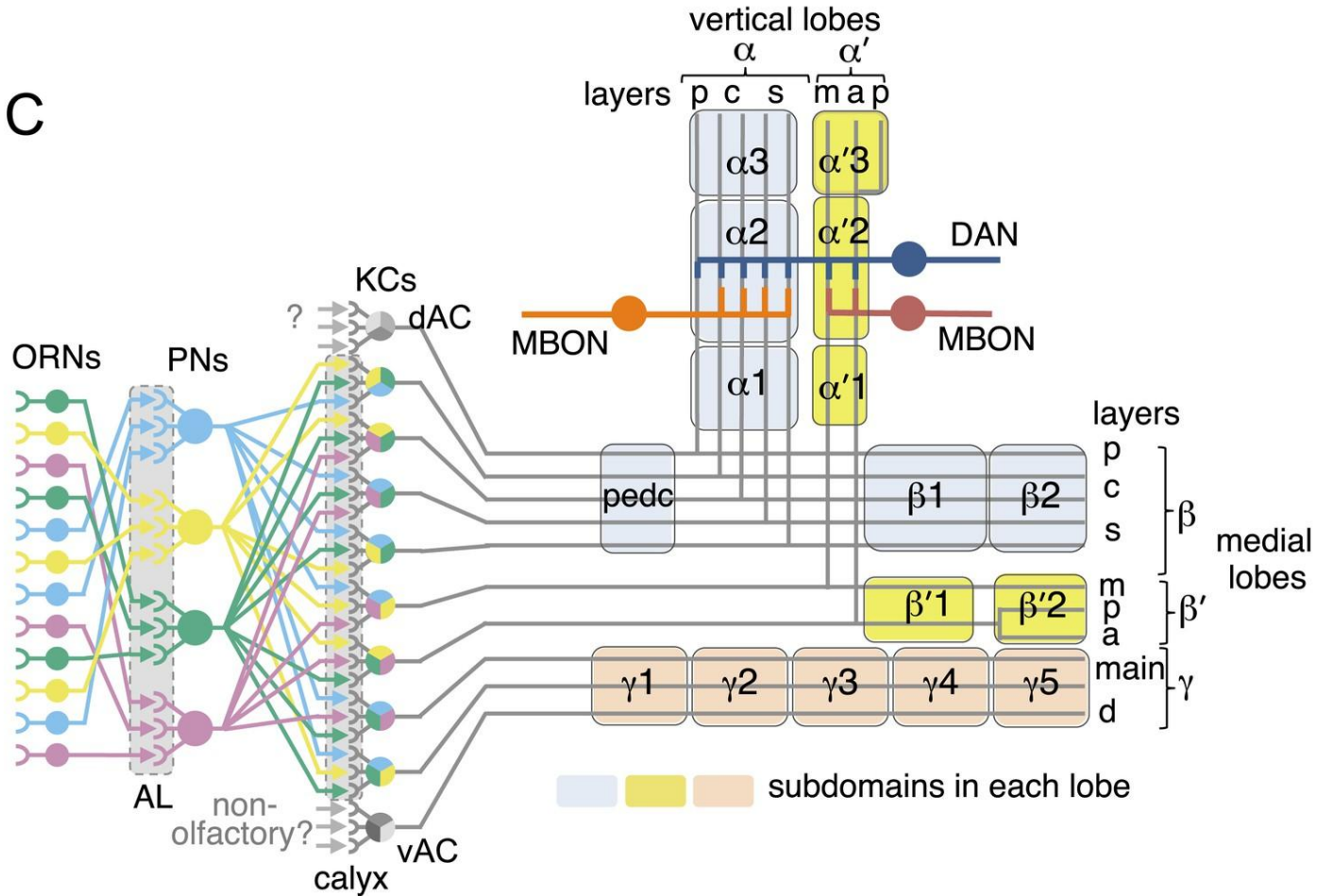


Static analysis example

- Mushroom body of *Drosophila*
- Well studied and architecture is known
- Operation depends on diffusion to non-adjacent synapses
- Multiple connectomes of both sexes available



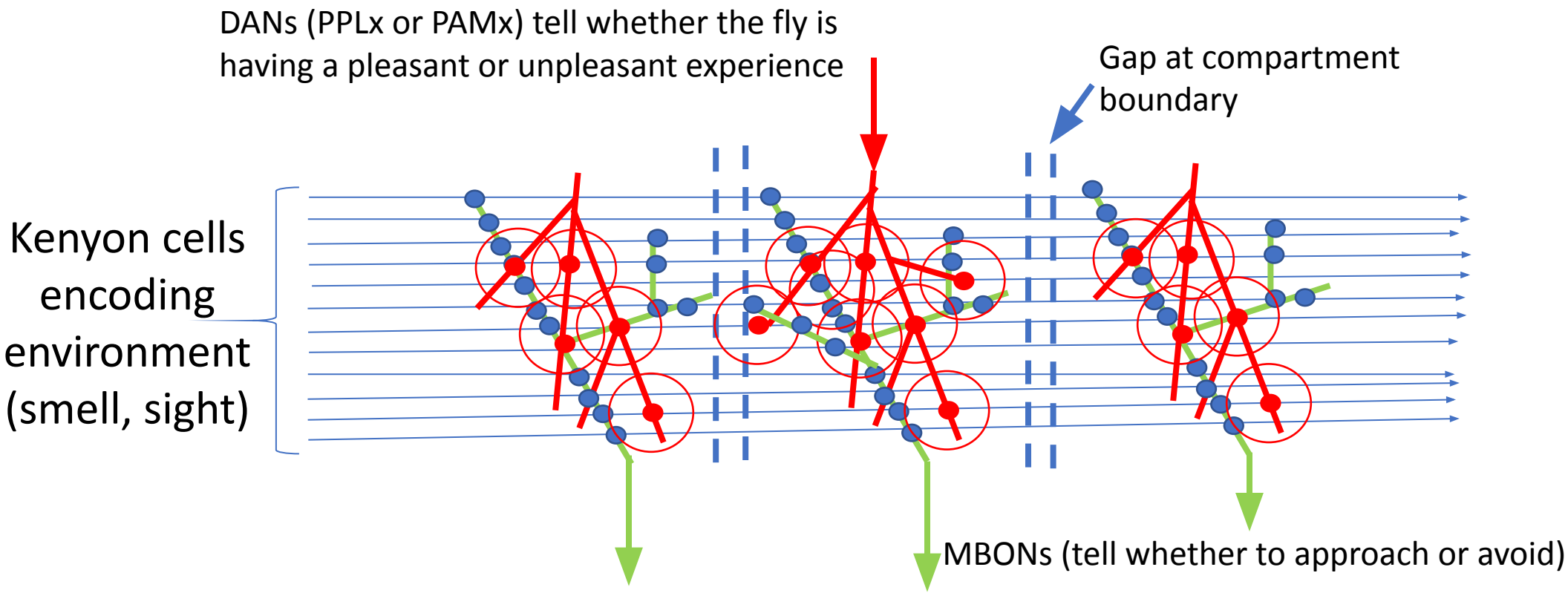




The neuronal architecture of the mushroom body provides a logic for

Rough sketch of operation

- Blue dots are KC->MBON adjustable synapses
- Red dots are pre-synapse of DANs (Dopamine expressing neurons)
- Circles represent spread of dopamine

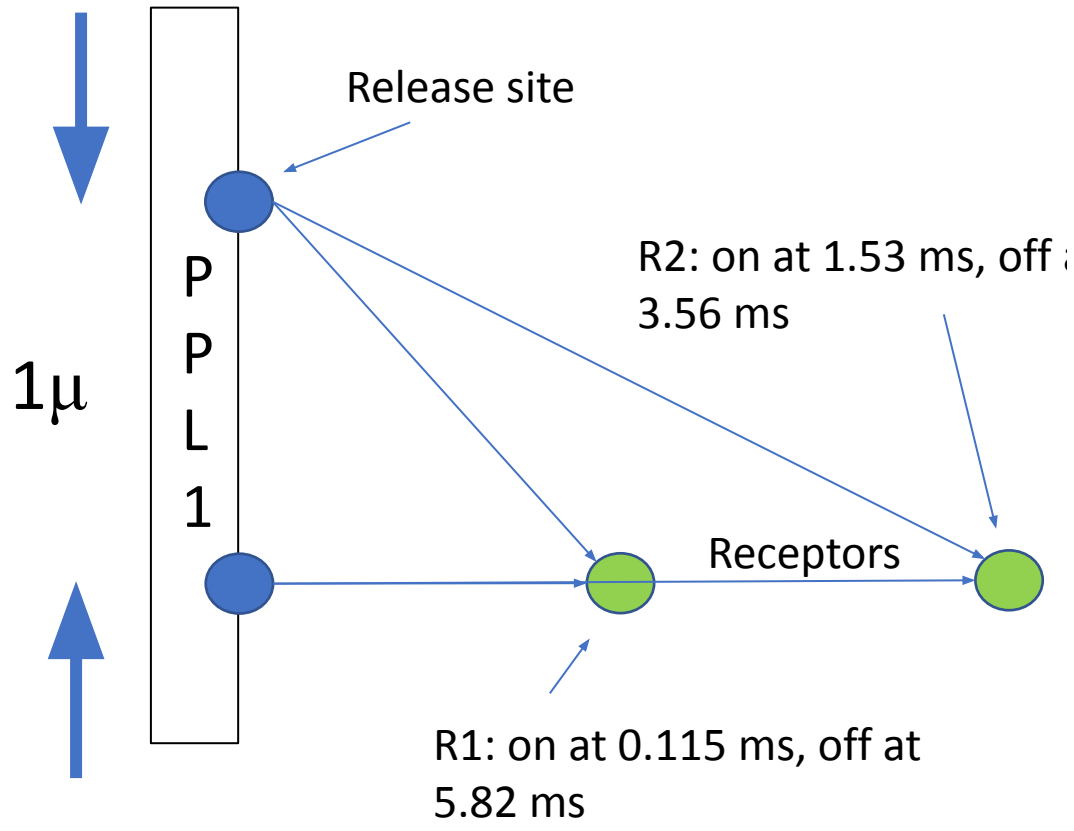


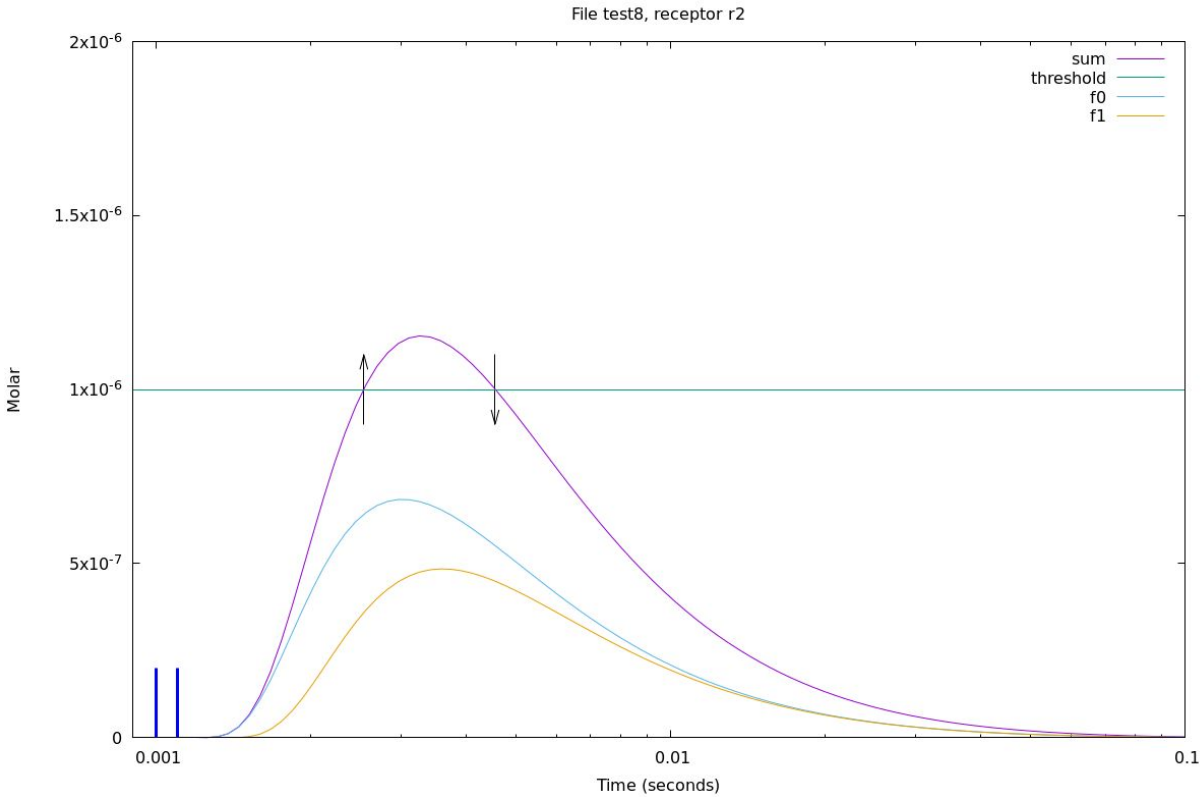
To model, need to make assumptions

- Assume compartments are activated one at a time
- Source is only 1-2 neurons (PPL/PAM teaching neurons) and from the pre-synaptic sites
- Assume all TBARs of these neurons release at the same time
- Assume receptor locations are same as KC->MBON synapses
- For each receptor location, sum all sources to compute on and off times
- Assume activation times are far enough apart for concentration to return to near zero
- Lots of assumptions about propagation (ECM space, diff constant, etc.)
  - Obtained from the literature from a wide variety of animals

Static analysis

- Real compartments of MB have thousands of sources, tens of thousand receptors
- Tiny example shown – dopamine, receptor sensitivity 1 uM molar (D1 receptor)





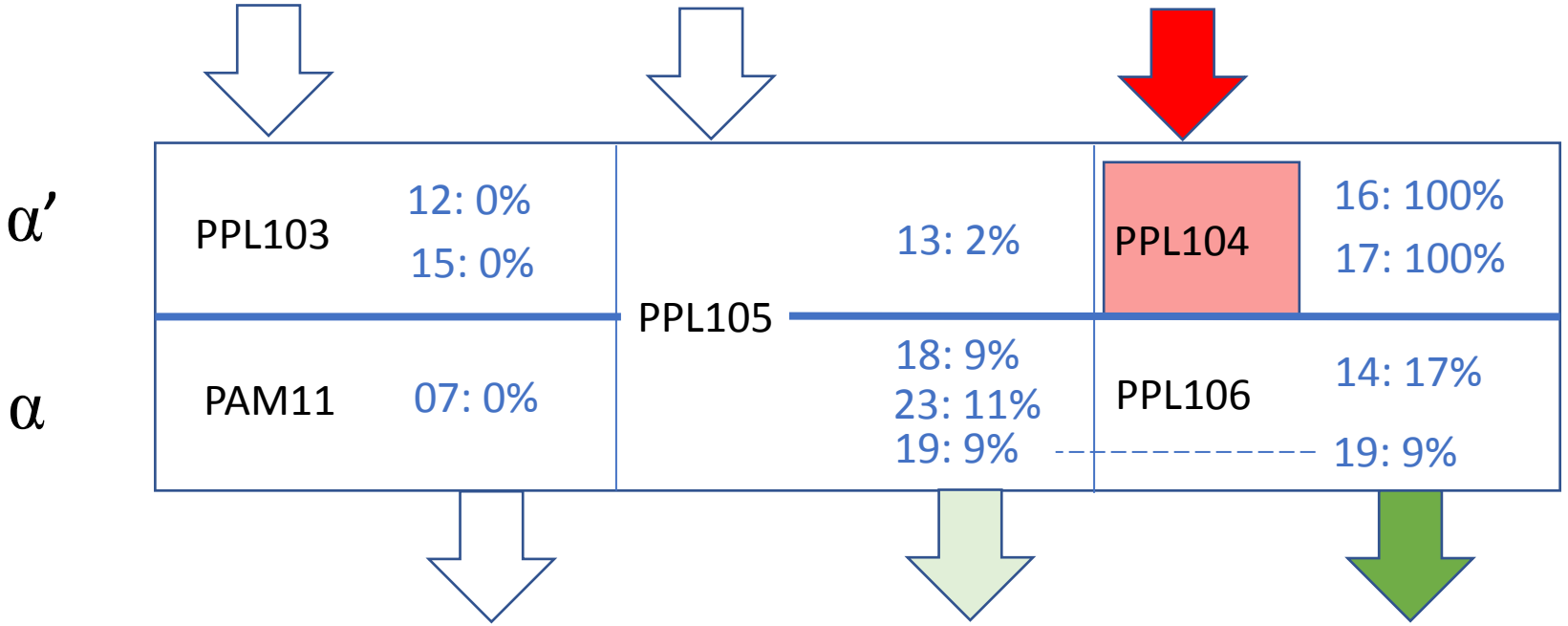
Modelling assumptions

- Dopamine is the transmitter
- Dopamine is released at PPL or PAM pre-synaptic sites
- Receptors located at or near MBON post-synaptic sites
- Diffusion constants are (from mammal data, “DAncing past the synapse”)
  - Free diffusion of 7.63e-10, modified by tortuosity factor 1.54
  - 1/e lifetime in extracellular medium 50 ms
- Extracellular space is 21%
- Dopamine receptor threshold is 1 μM
- 10K dopamine molecules released per event.
- Model is linear, so many combinations give equal results

What we compute using our model

- What percentage of KC->MBON synapses in the target compartment reach threshold?
  - Should be near 100%
- What percentage of such synapses in adjacent compartments reach threshold?
  - Should be small
- What is the time course of activation in compartments?
  - Ground truth unknown – existing imaging not fast enough
- Is result consistent across data from 3 animals, two sexes?
  - Hemibrain(F), 2014 Alpha lobe (M), Male CNS (2 MBs, left and right) (M)

Example response: All PPL104 activated



Percent activated agrees on all 4 samples from 3 animals (PPL-105 response shown)

MBON	Percent activated					Time activated (ms)			
	Hemi	2014	CNS-R	CNS-L		Hemi	2014	CNS-R	CNS-L
7	8	5	6	8		49	19	36	43
12	16		38	43		63		41	46
13	98		100	100		87		68	70
14	1	3	0	2		16	51		17
15	39		50	52		60		44	47
16	4		0	3		25			3
17	9		7	7		22		14	27
18	99	100	98	98		88	67	68	74
19	97	99	97	98		96	64	68	80
23	99	96	97	97		90	66	67	77

Timing of responses agrees in all 4 samples

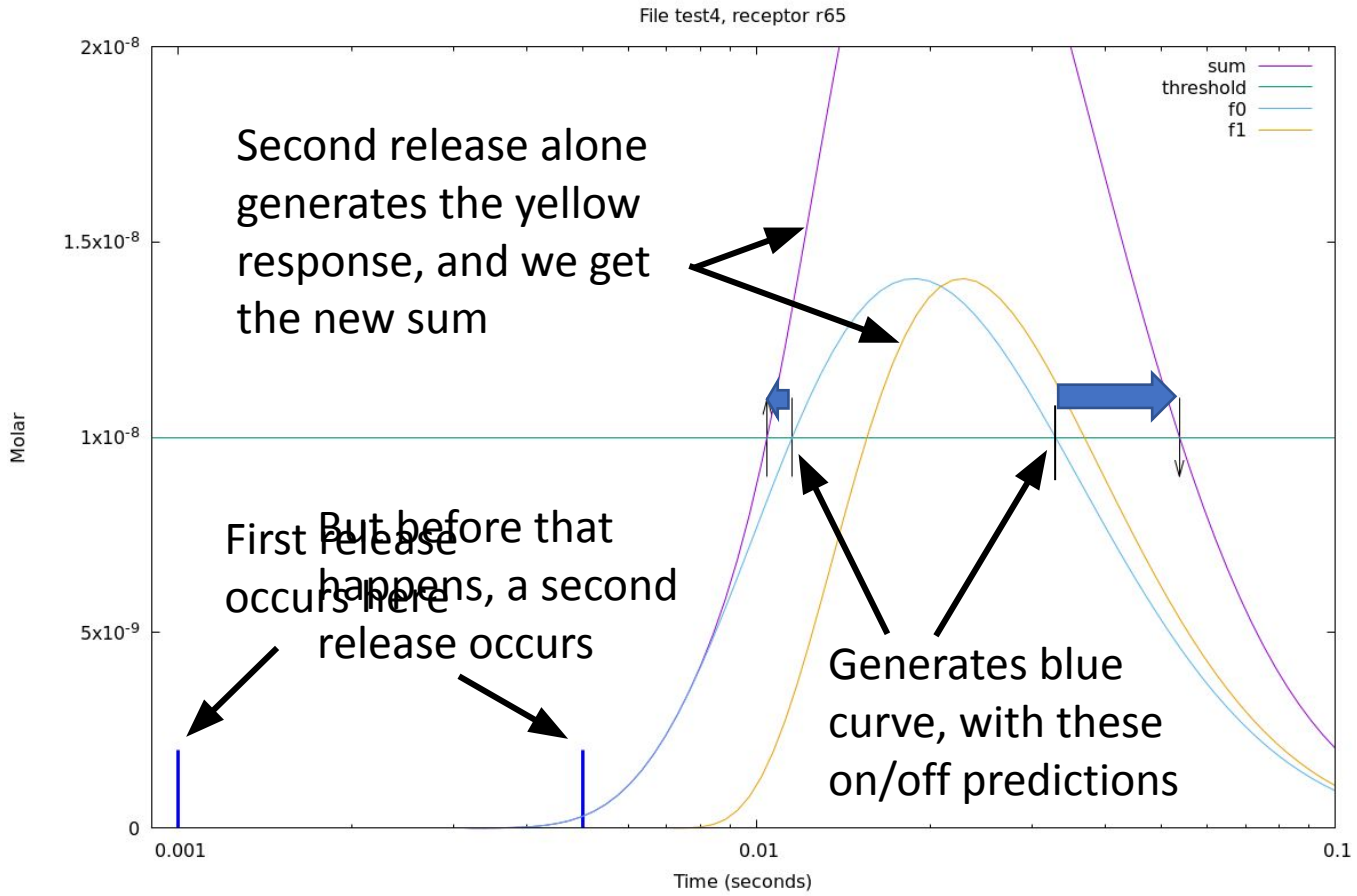
MBON	Percent activated					Time activated (ms)			
	Hemi	2014	CNS-R	CNS-L		Hemi	2014	CNS-R	CNS-L
7	8	5	6	8		49	19	36	43
12	16		38	43		63		41	46
13	98		100	100		87		68	70
14	1	3	0	2		16	51		17
15	39		50	52		60		44	47
16	4		0	3		25			3
17	9		7	7		22		14	27
18	99	100	98	98		88	67	68	74
19	97	99	97	98		96	64	68	80
23	99	96	97	97		90	66	67	77

Response to this one DAN shown; others also agree (data not shown)

No sign of sexual dimorphism

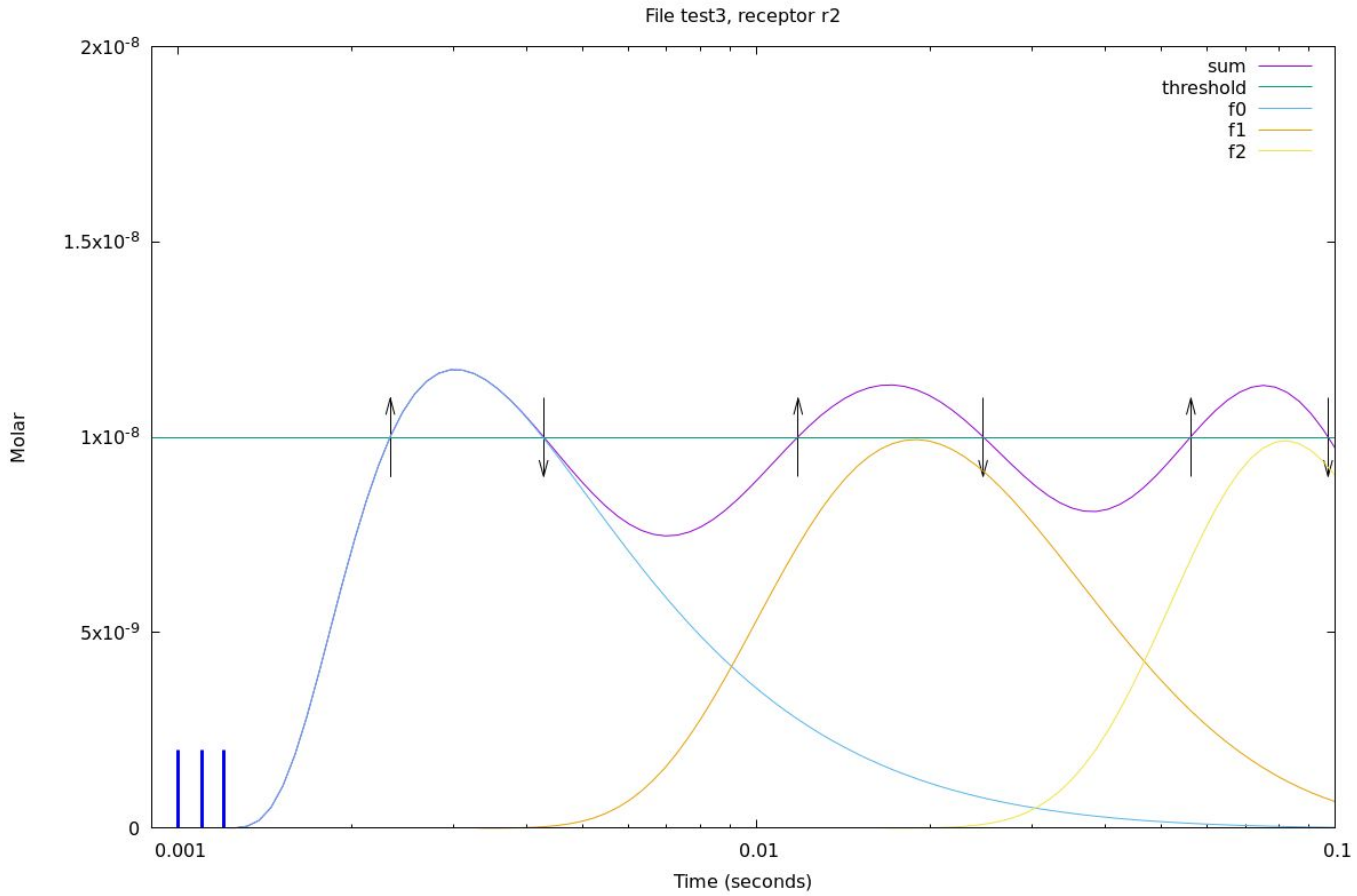
Simulation has additional challenges

- Changing your mind after events have already been scheduled

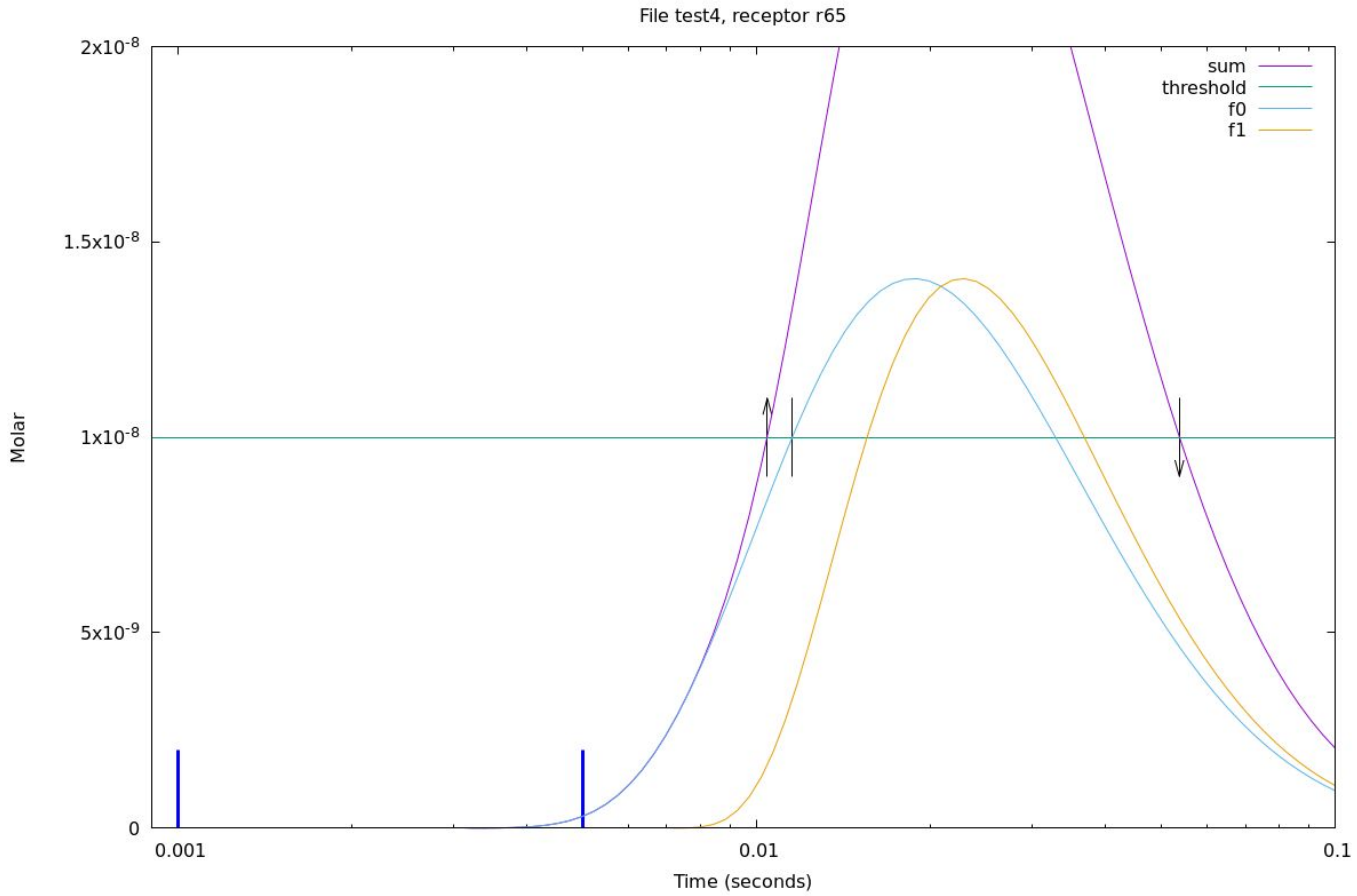


Need to unschedule and move future events

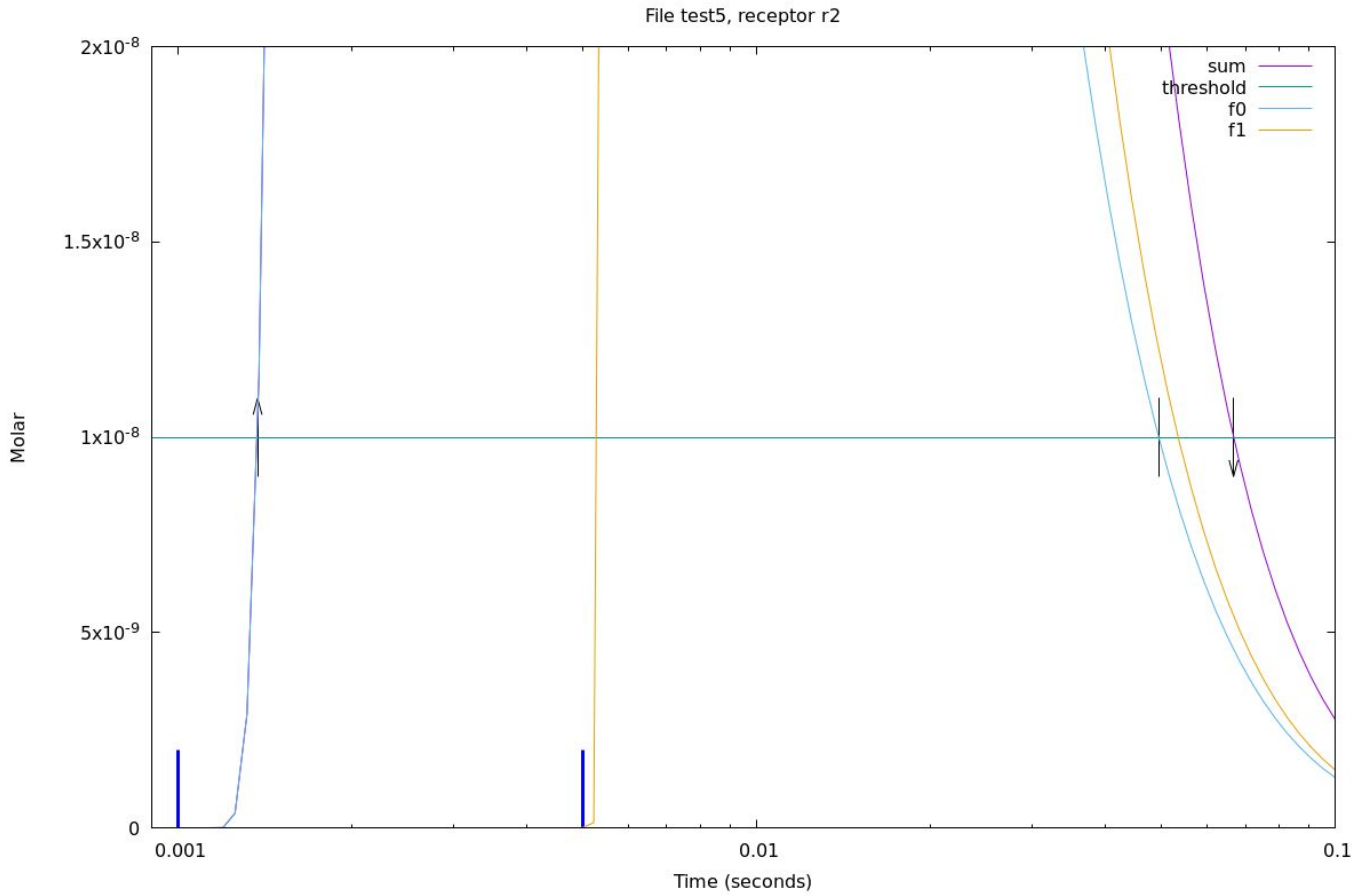
Example: Three sources at different distances



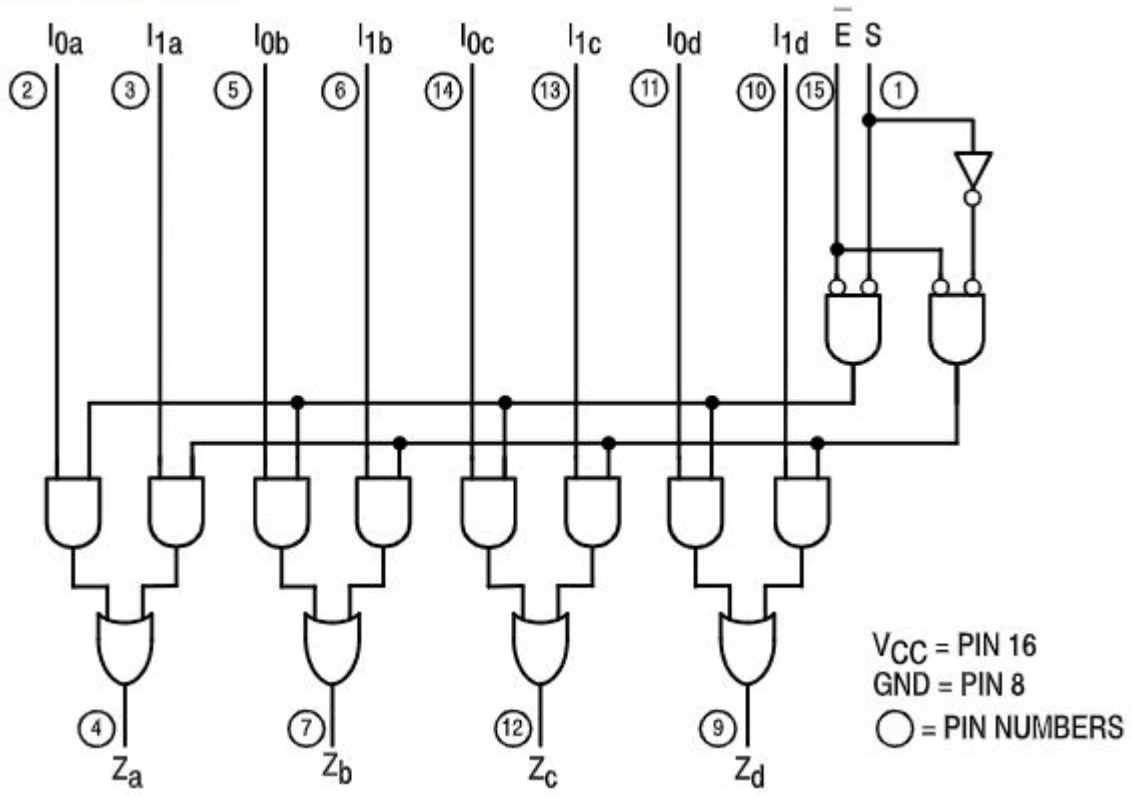
Example: new release can reschedule on and off times



Example: release during on-time can reschedule off time.



LOGIC DIAGRAM



AC CHARACTERISTICS (T_A = 25°C)

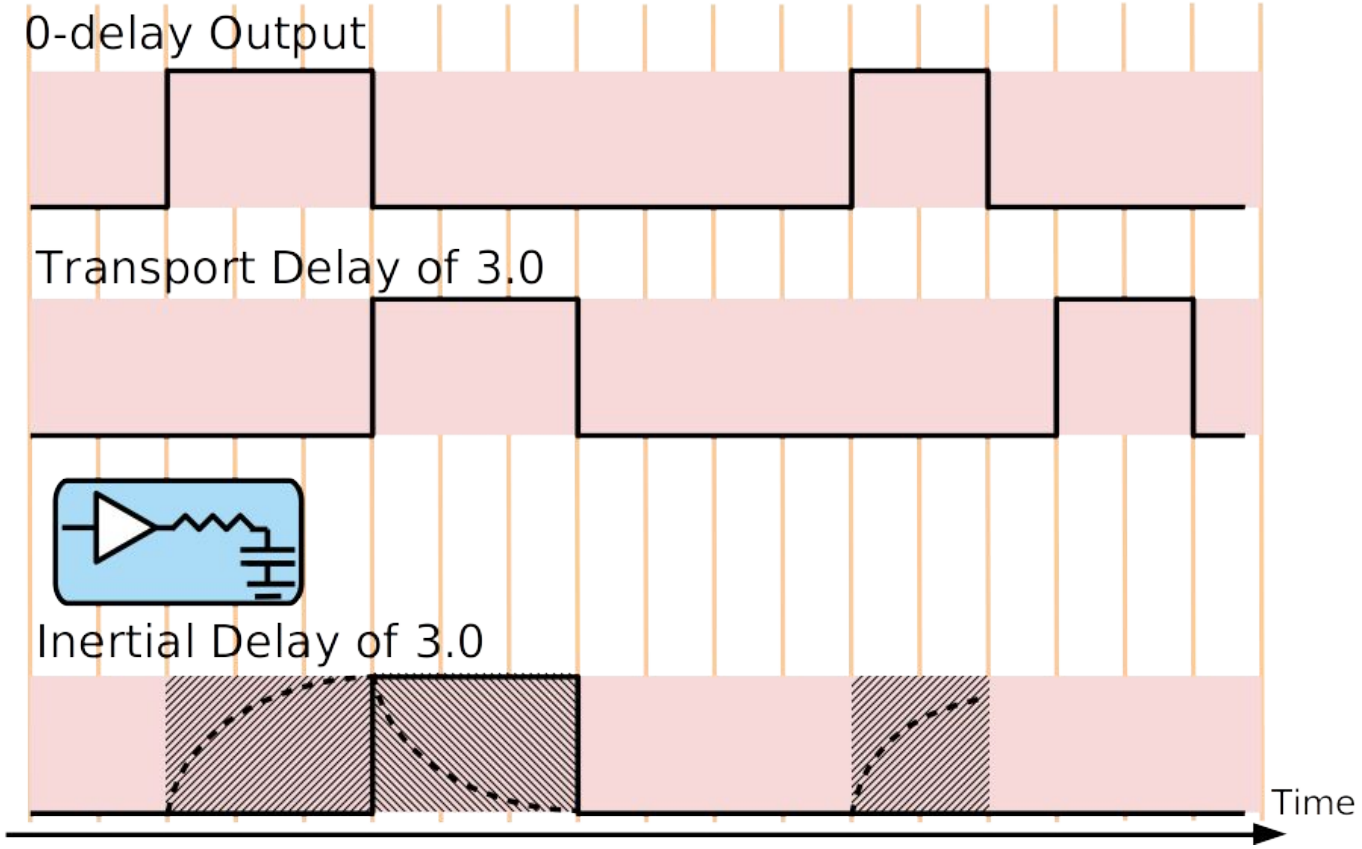
Symbol	Parameter	Limits			Unit
		Min	Typ	Max	
t_{PLH} t_{PHL}	Propagation Delay Data to Output		9.0 9.0	14 14	ns
t_{PLH} t_{PHL}	Propagation Delay Enable to Output		13 14	20 21	ns
t_{PLH} t_{PHL}	Propagation Delay Select to Output		15 18	23 27	ns

The same problems occur in digital logic simulation

- Example part: 74LS157
- Example – a Select change occurs at t0
- Output change scheduled for t0+20
- But then the data changes
- May need to retract events, change event timing, etc.
- Biologists can steal EE techniques to deal with this

Logic simulators already deal with this, so biologists can use this technology

- Extensive, formal descriptions of dealing with delays
- Implemented with queues and heaps



This example from Verilog

"Lecture 02 – Verilog Events, Timing, and Testbenches" by Ryan Robucci

We can (and I did) use these EE techniques in neuromodulator timing

Logic simulators already deal with this, so biologists can use this technology

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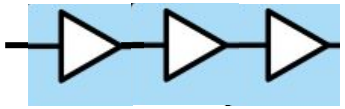

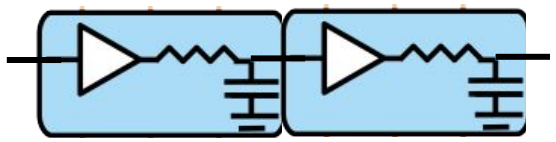

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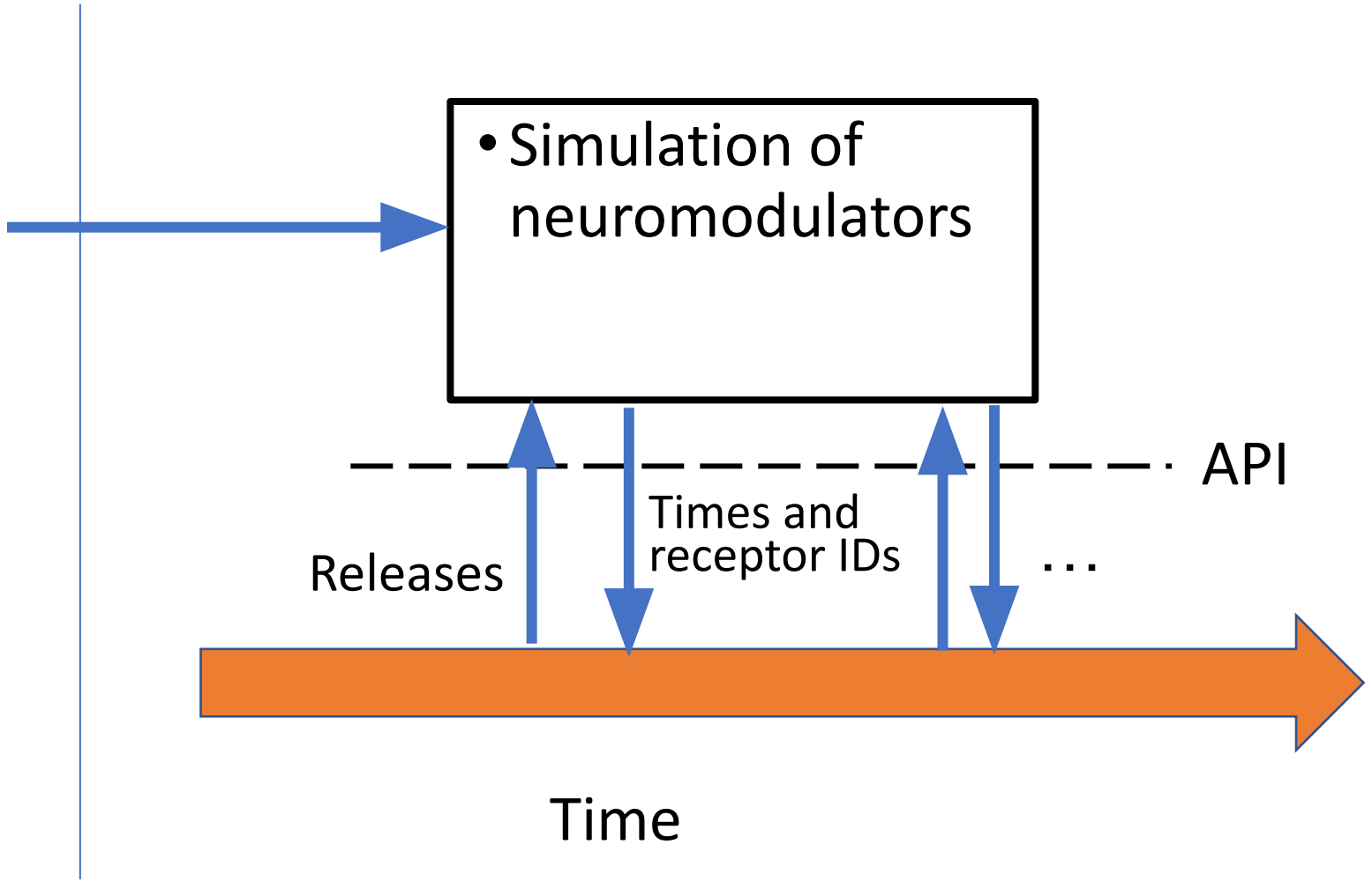
We can (and I did) use these EE techniques in neuromodulator timing

Software architecture

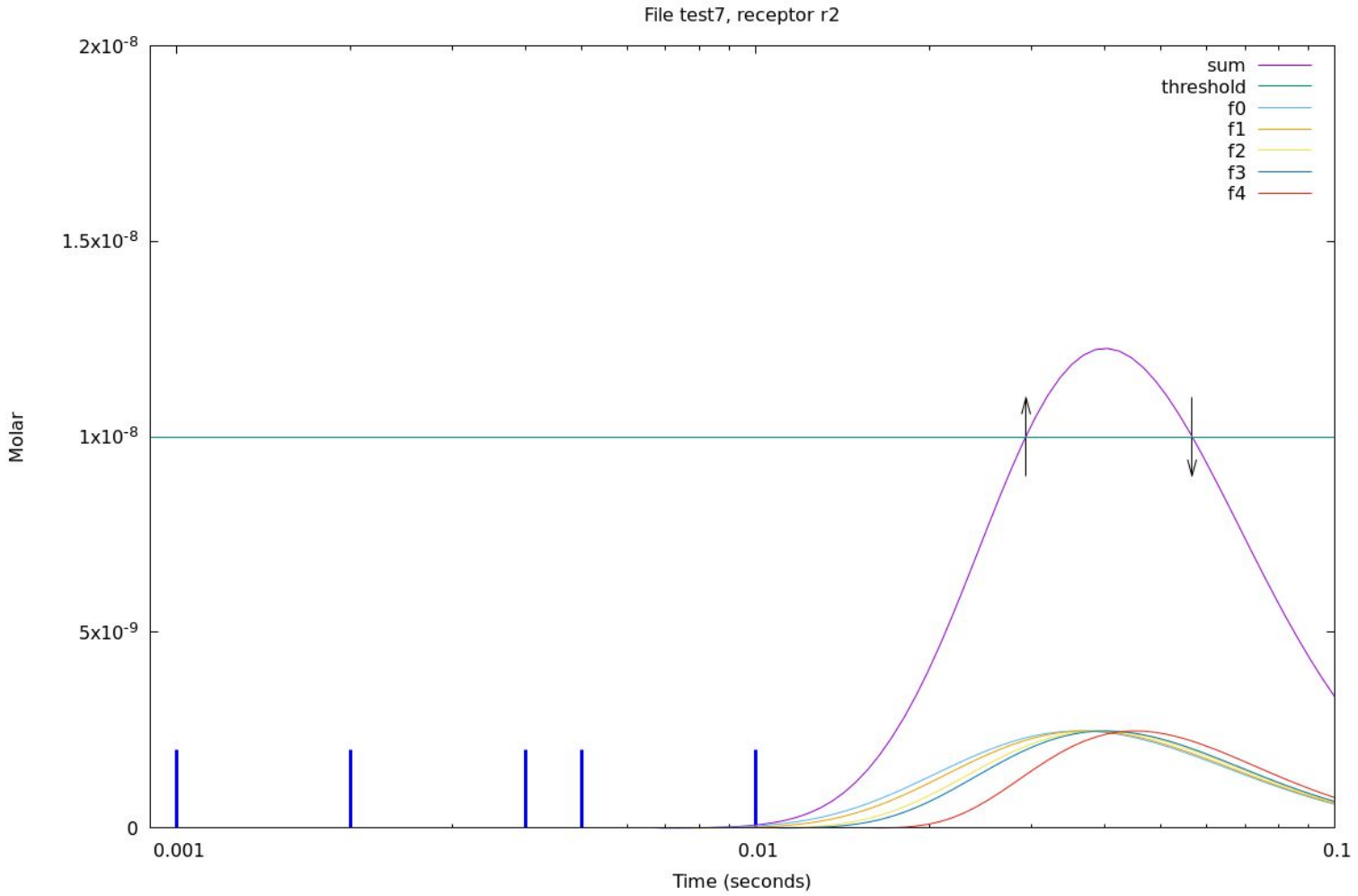
<u>Initialization</u>

Locations, neuromodulator types, constants



• Simulator (such as Brian2)

But some calculations are still analog: Many small releases, each too small themselves, can add up.



Need additional heuristics

- In theory, each event influences all receptors at every distance for all time after the event
- But keeping all previous events around is impractical
- So need to prune (heuristics)
  - Don’t record event where peak < some limit (say 1% of threshold)
  - Similarly drop event once it falls too low
  - When deciding if a new event causes a threshold crossing, look near the peak
  - If a single event releases many vesicles, combine
- You can find cases where these heuristics fail, but they seem contrived

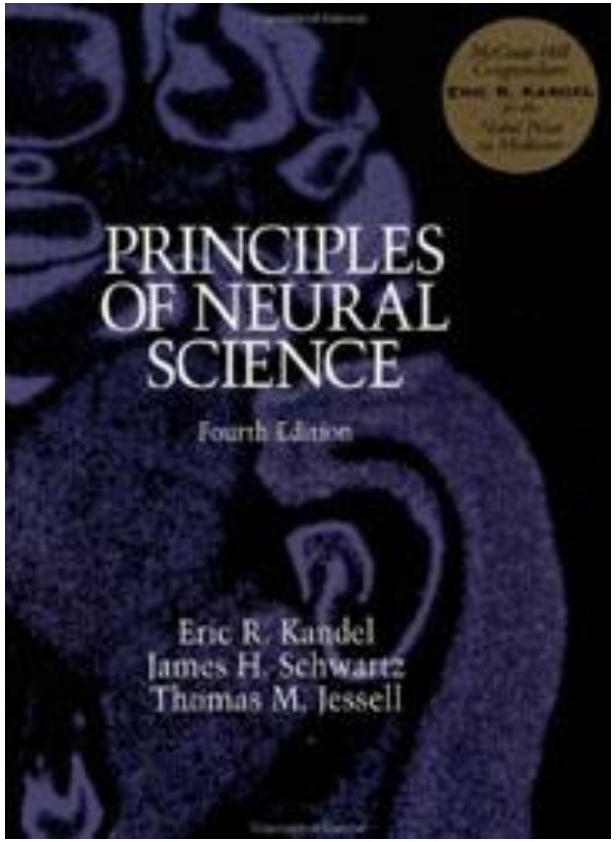
Conclusions for neuromodulators

- Modelling effects and timing of neuromodulators seems feasible
  - Various techniques are known from other fields such as EE
- We have a prototype that matches known measured results, at least in some cases (not shown)
- Need new experimental data
  - Sources, receptors, decay constants, ECM constants, new sensors
- Need new models; diffusion model is only a first approximation
  - Some are understood but not modelled: Interconversion
  - Some are not understood: Superposition at receptors sensitive to multiple modulators
- Both static and dynamic analysis may be needed
- Comments, suggestions, and help from EEs welcome!

Where to find out more?

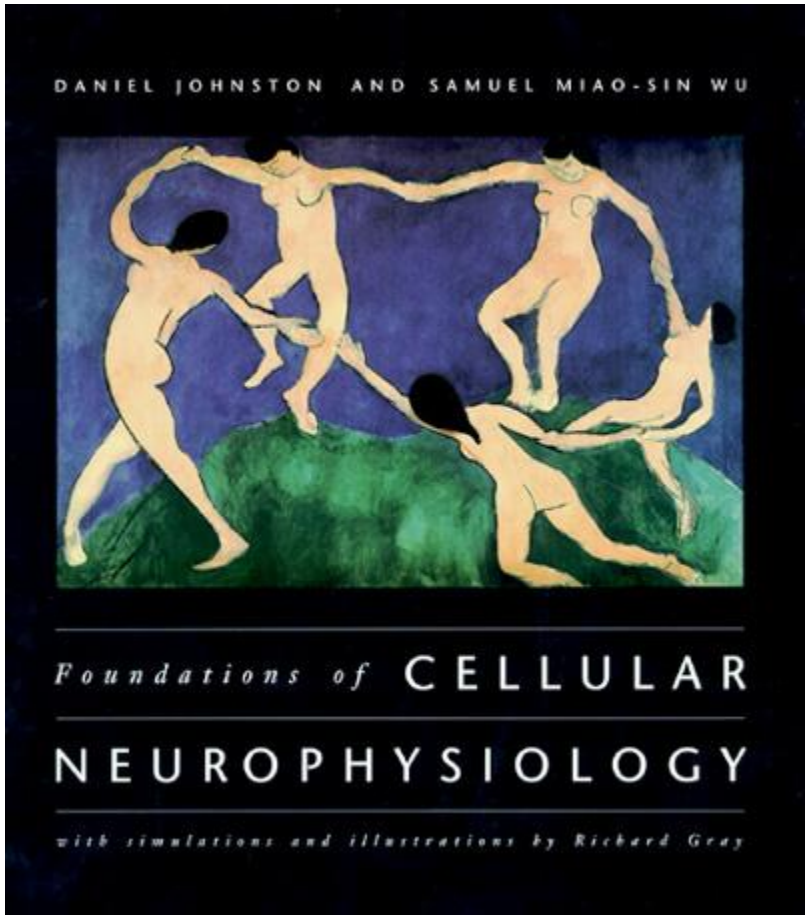
- Papers
  - Hodgkin-Huxley, 1952
- Books
  - Principles of Neural Science by Kandel, Schwartz, and Jessell
  - Foundations of Cellular Neurophysiology by Johnston and Wu
- Web
  - http://sfn.org – Society for Neuroscience

Principles of Neural Science



- Basic text of the field
- Size grows almost linearly with edition number
  - 468 pages in v1, 1981
  - 1414 pages in v4, 2001
  - 1696 pages in v6, 2021

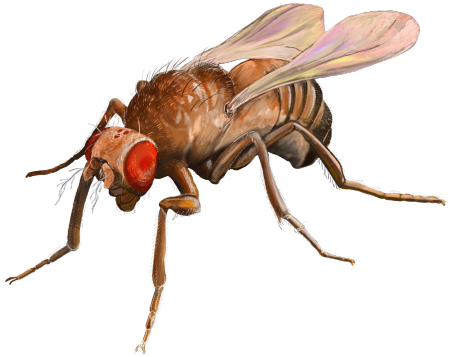
Foundations of Cellular Neurophysiology



- Very EEish text
- Lots of equations, of spherical cow variety
- Discussion of limitations of models
- Good discussion of stochastic behavior

So where are we now?

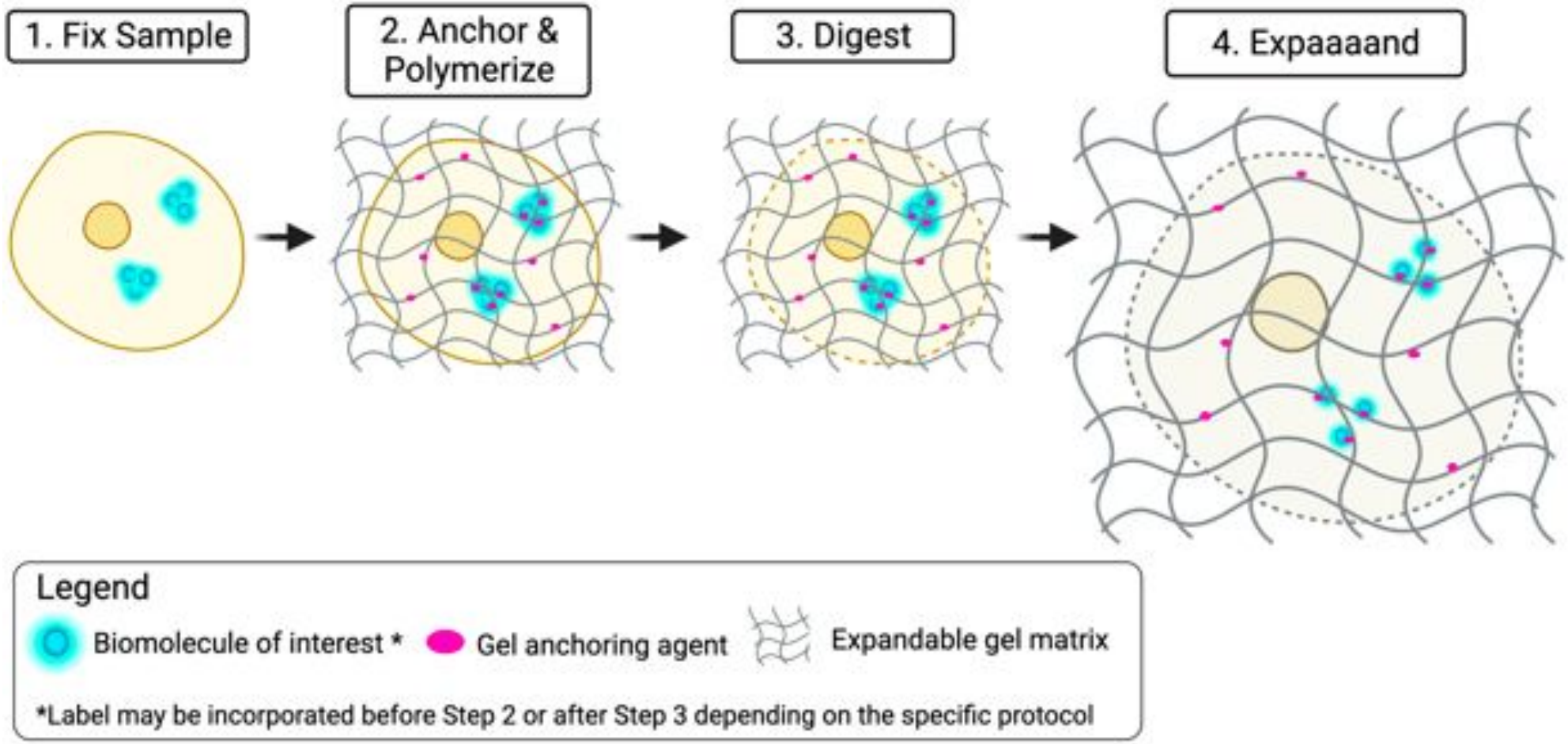
- Complete synaptic circuit known for a few small animals
  - Two different larva (few hundred neurons)
  - Fruit fly (Drosophila), about 150K neurons, 300M synapses
    - Have both brain and VNC (spinal cord)
    - Existing models include 1 male and 1 female
    - Have built combined neural/physical models
    - Can create and control stuck-at faults to aid understanding
  - With such small numbers, hard to tell individual variation from systematic



- All connectomes so far obtained via electron microscopy (EM)
  - Even these small animals took many years and 10s of millions of $ each

- Mouse brain is 10,000 times bigger, and human brain 100x more yet
  - Far out of reach of existing technology
  - Maybe in a decade or two if we can get Moore's law like progress

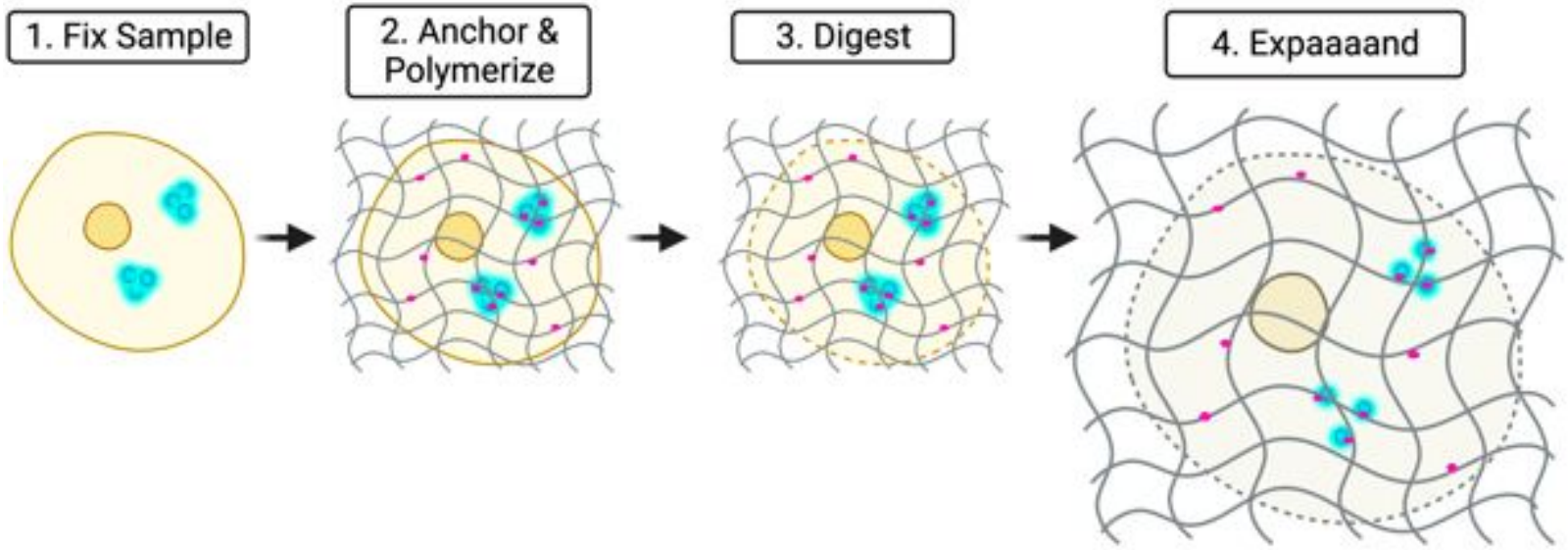
A new technology: expansion microscopy



From: https://blog.addgene.org/getting-to-know-expansion-microscopy

If expansion microscopy can be made to work reliably, it's poised to take over

- Can do in two stages to get 25x (map 10 nm -> 250 nm)
- Then you can use optical microscopes instead of EM
  - Much cheaper ($250K for confocal, $5M for multi-beam EM)
  - Much faster (no need for physical sectioning)
  - Multi-color (can tell cellular components apart)



Expansion with LOTS of colors (potentially hundreds)

Step 1: Bind hundred of special antibodies. Pick three to image.

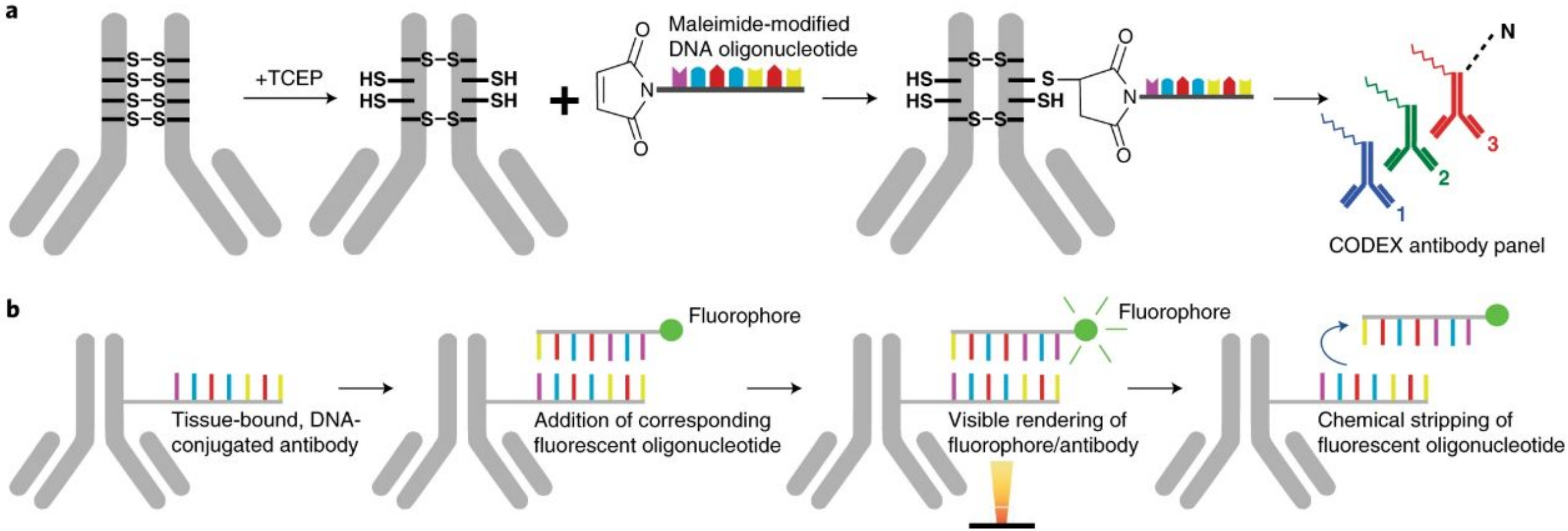


Image from paper "**CODEX multiplexed tissue imaging with DNA-conjugated antibodies**"

Step 2: Repeat N/3 or N/2 times

- After imaging, strip off the dies. Works because DNA binding is looser than antibody binding.
- Add three new dyes with corresponding antibodies. Re-image.
- Images aligned and combined for data analysis

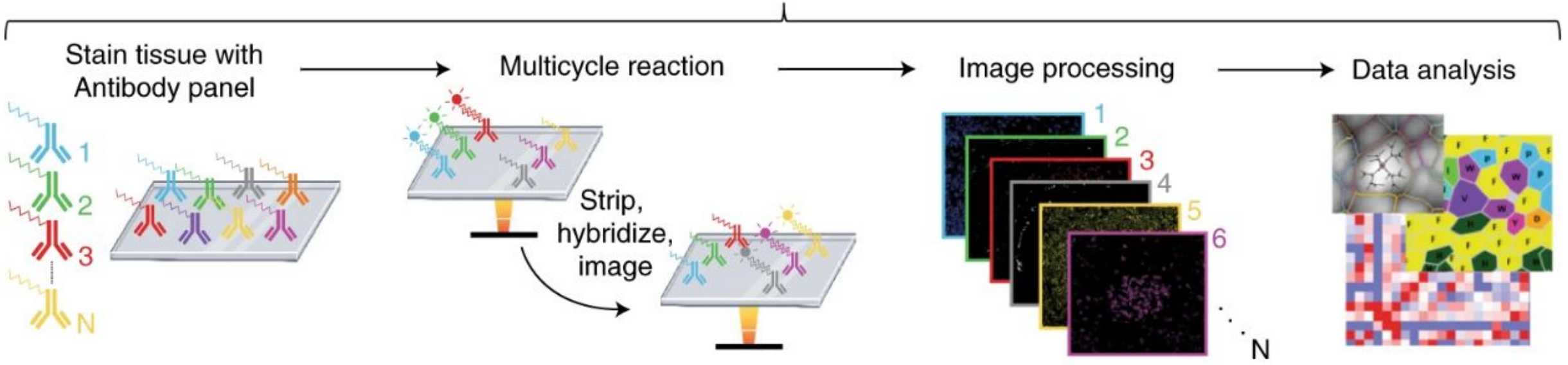
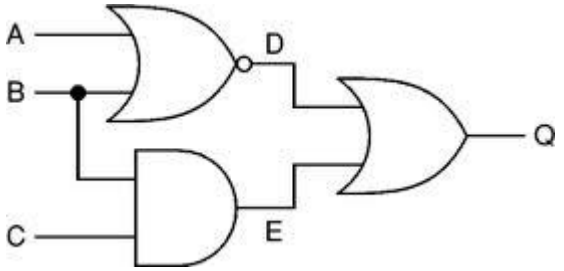
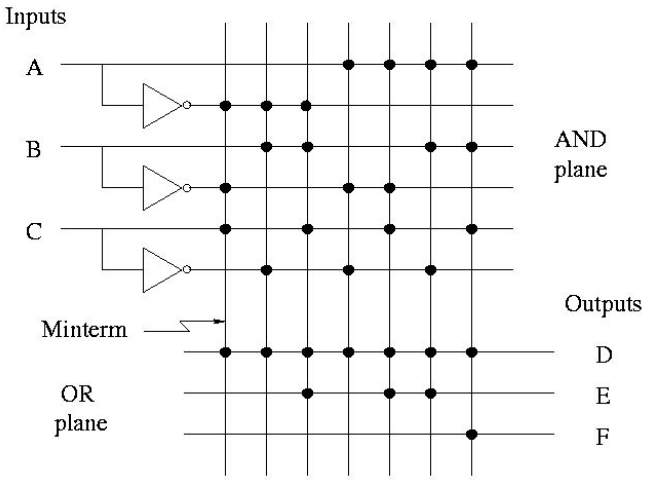


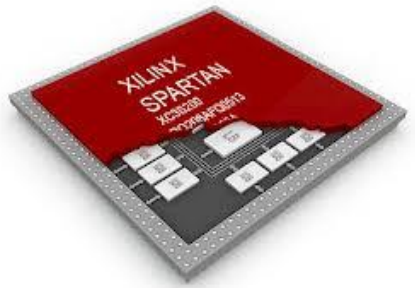
Image from paper "**CODEX multiplexed tissue imaging with DNA-conjugated antibodies**"

Where are we in understanding the brain?

- Some circuits are hardwired (vision, escape response, other reflexes) and understood
  - These must be fast, and use synapses which we can see
- We understand some conditioned learning in flies (2D, change the weights, as in a PLA)
  - Learning simple aversive/attractive smells, for example
- We do not understand circuits that use neuromodulators
  - Hunger, fright, sex drive, etc., and their interactions
  - Don't yet have the technology to detect their use
  - Don't have good modeling tools
- We do not understand more sophisticated learning
  - But we know it's not straight back-propagation as in LLMs.

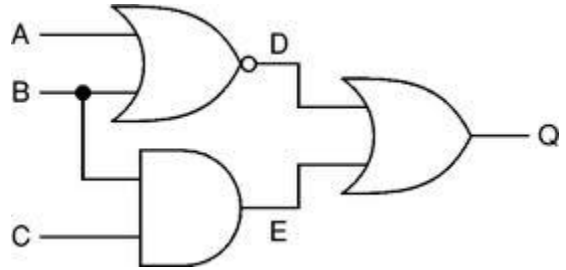


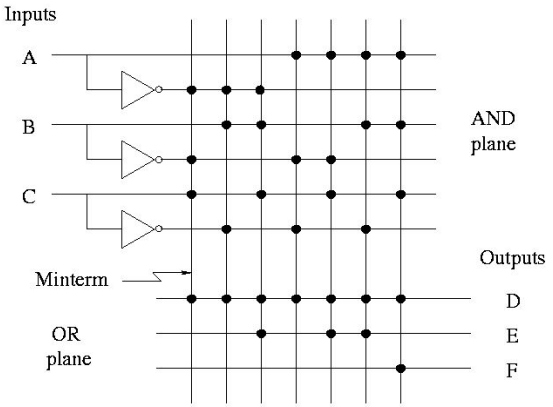


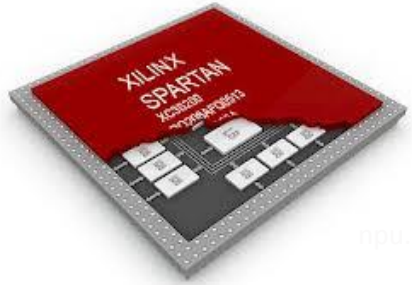


Circuit types and status

- Hardwired circuits (vision system)
  - Same from animal to animal
  - Making good progress
- PLA like systems (olfactory)
  - Every animal different, but in standard ways
  - Harder, but technical advances should suffice
- Fully programmable and time varying, use neuromodulators (cortex)
  - New ideas are needed







What does the future hold?

- Neuroscience, the study of the brain, is extremely promising
- Electrical engineering is a key to this problem, in both directions
  - EEs can help understand the brain
  - Use understanding of the brain to improve EE
- We know some small brains (worms and flies), and are working up!
- We will need better techniques, and many more analysts and theorists to understand the brain and learning
- Potential benefits are huge
  - Huge power savings
  - Better learning (both methods and results)
- Come and help us decipher the brain!