Origins of Anesthetic Hysteresis

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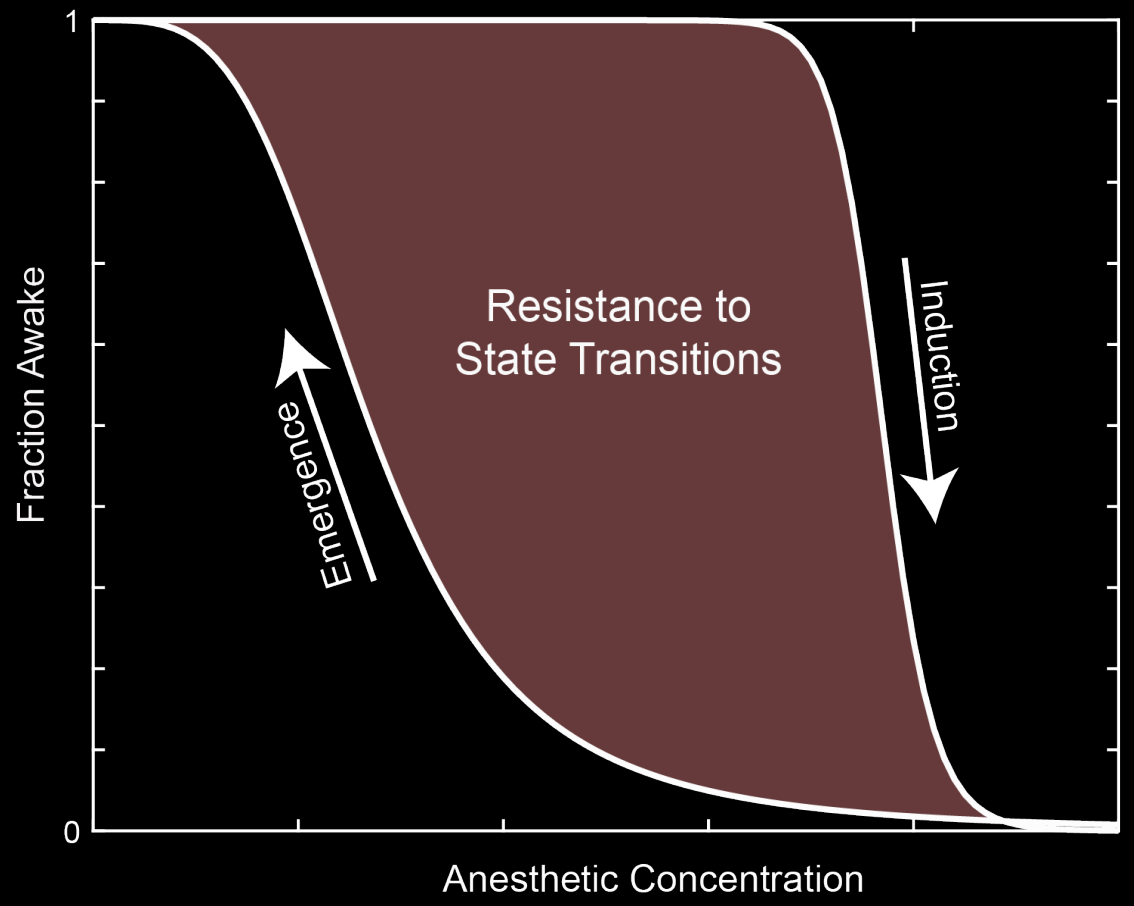
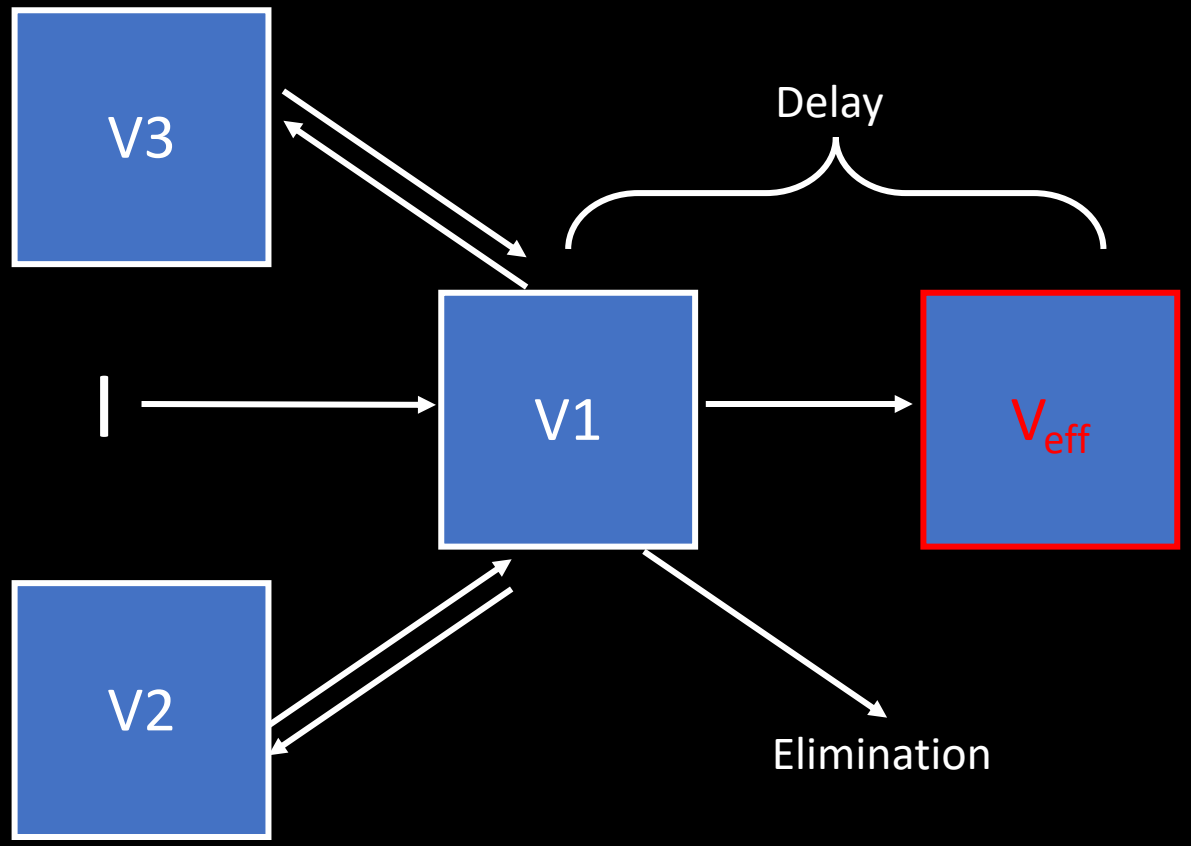
What is anesthetic hysteresis?

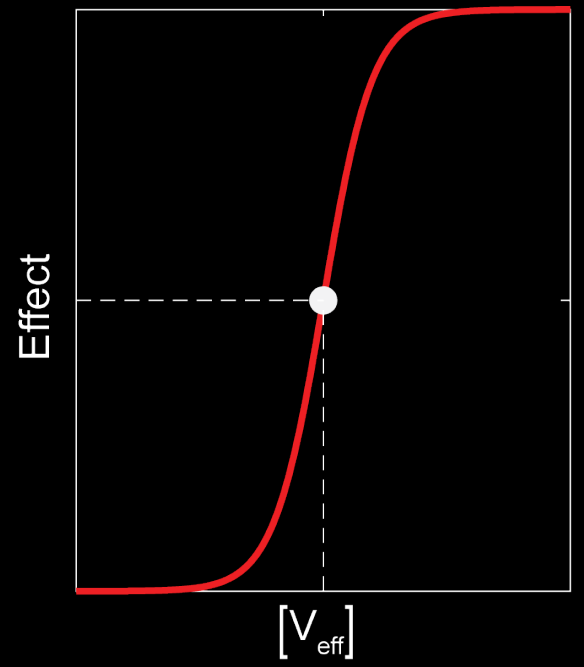


Kelz et al

Hysteresis is observed any time the output lags behind the input

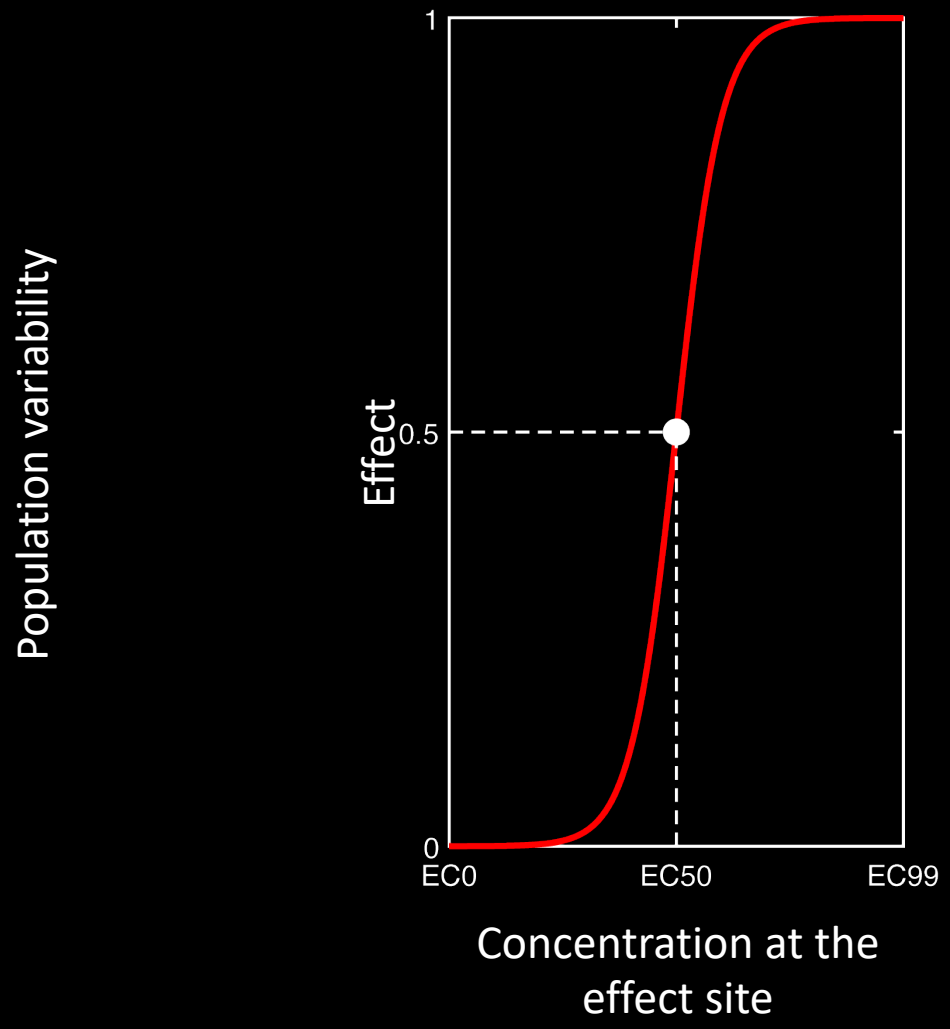
PK-PD explanation of anesthetic hysteresis



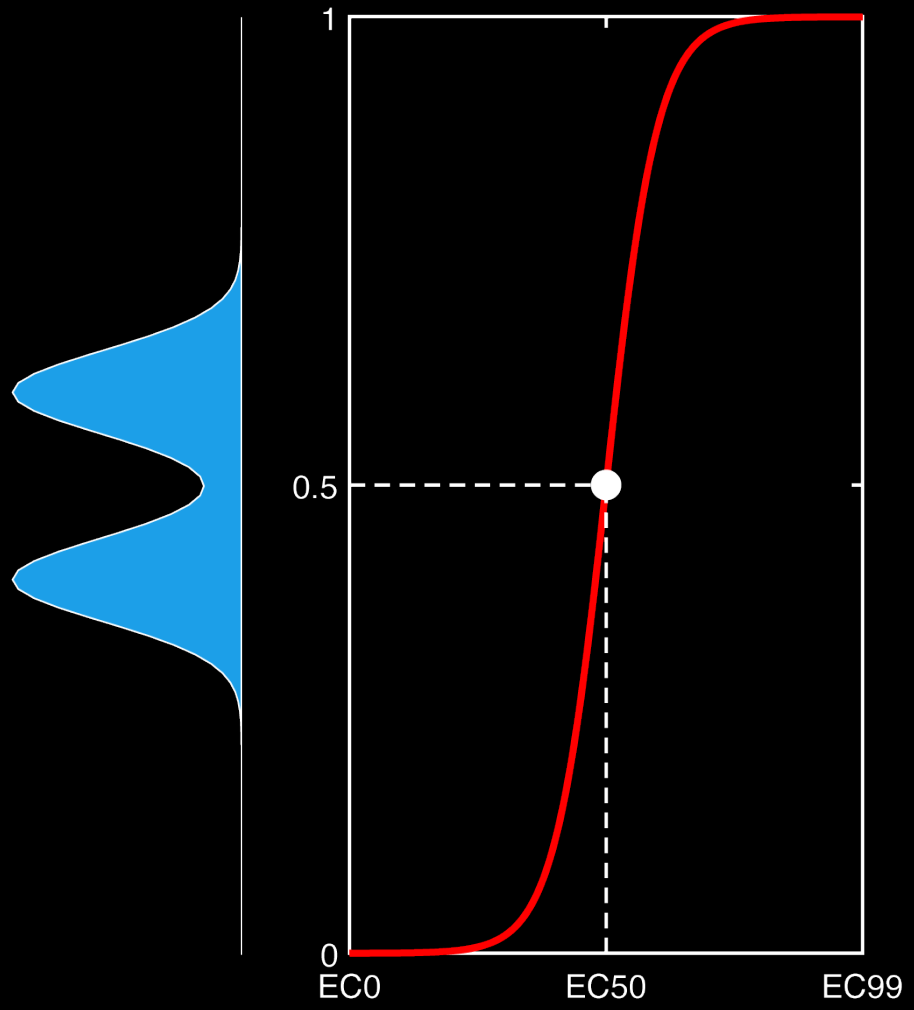


Key assumption : If I knew $[V_{eff}]$, I would know the effect

Testable predictions of the PK-PD framework



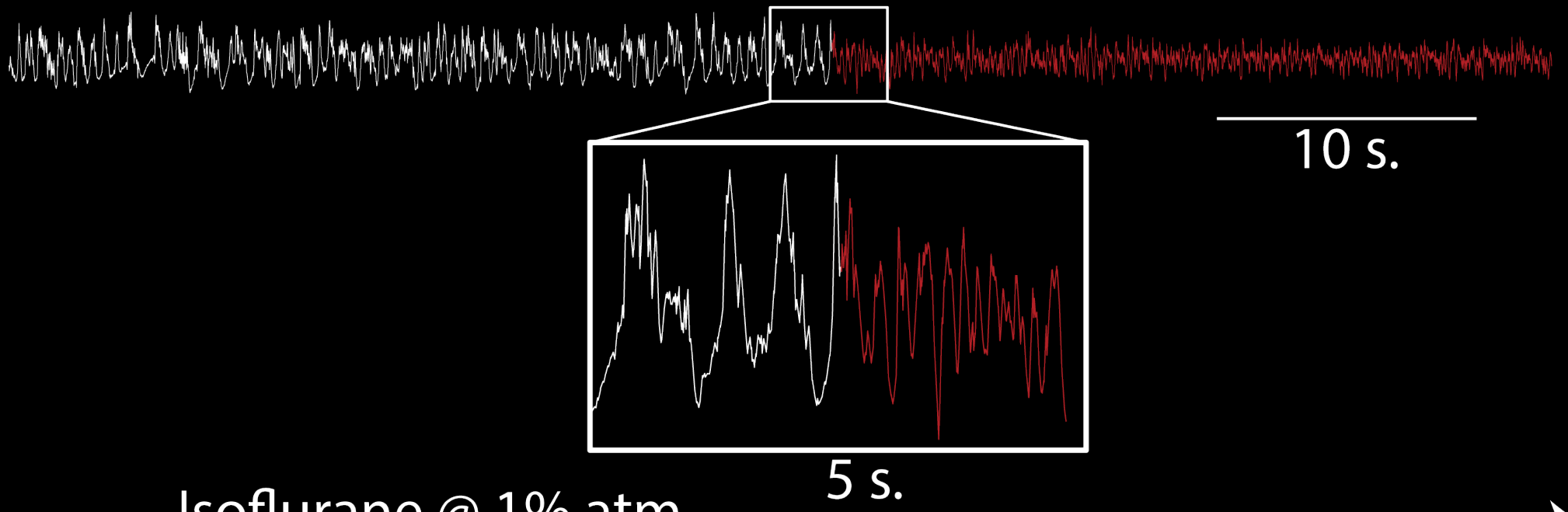
What I will try to prove



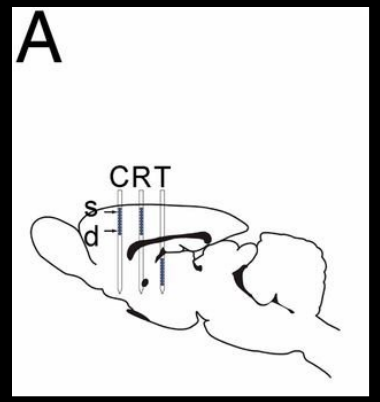
- At a fixed drug concentration, the system will stochastically fluctuate between several discrete states.
- The system will resist state transitions
- Resistance to state transitions is sufficient to give rise to hysteresis independently of effect site equilibration.
- **Characterization of these fluctuations reveals novel properties of anesthetics.**

Initial Observations:

cortical local field potential (recorded in V1)

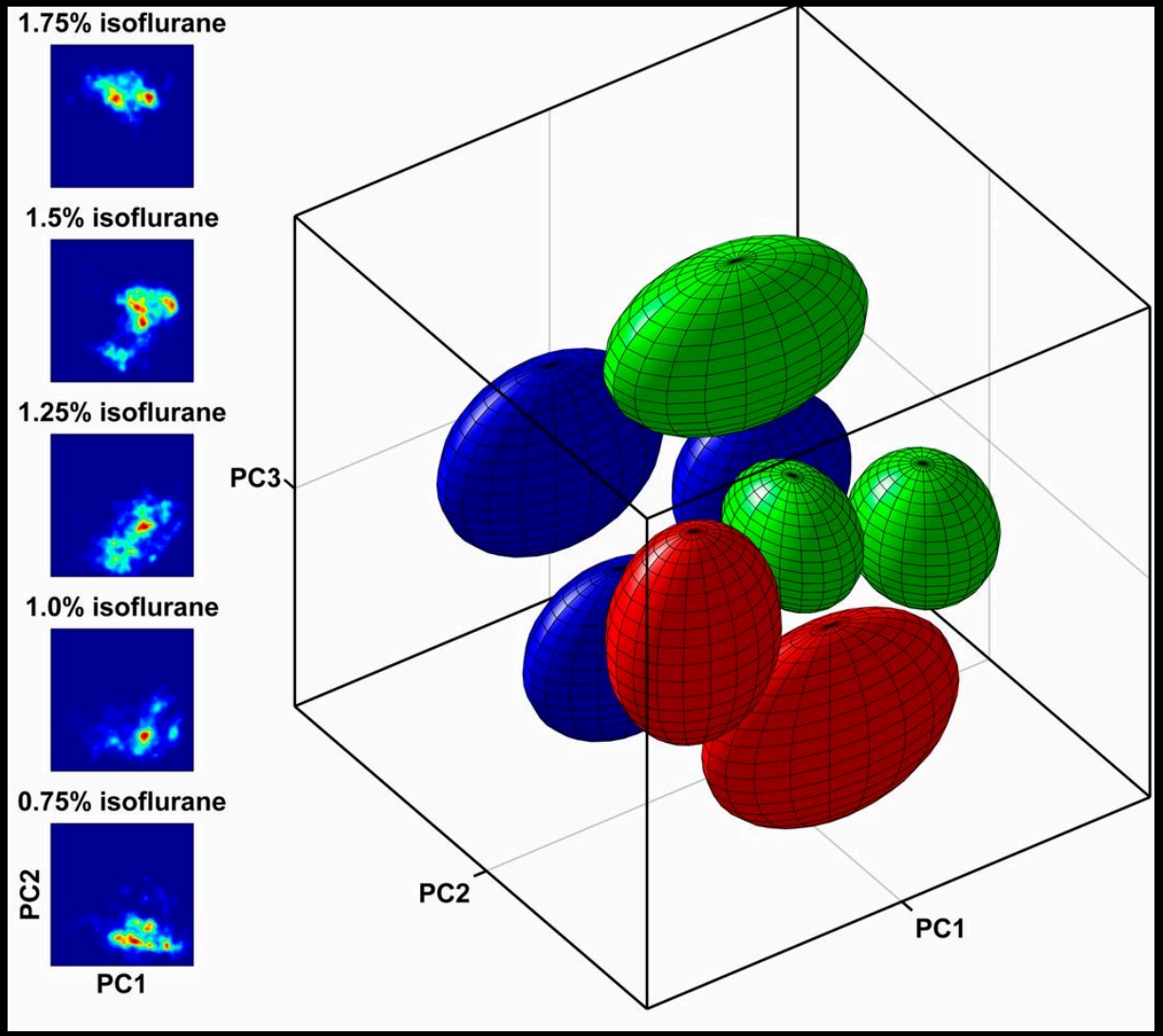


Discrete Fluctuations in Brain Activity under Fixed Anesthetic Concentration



Hudson et al, PNAS 2014

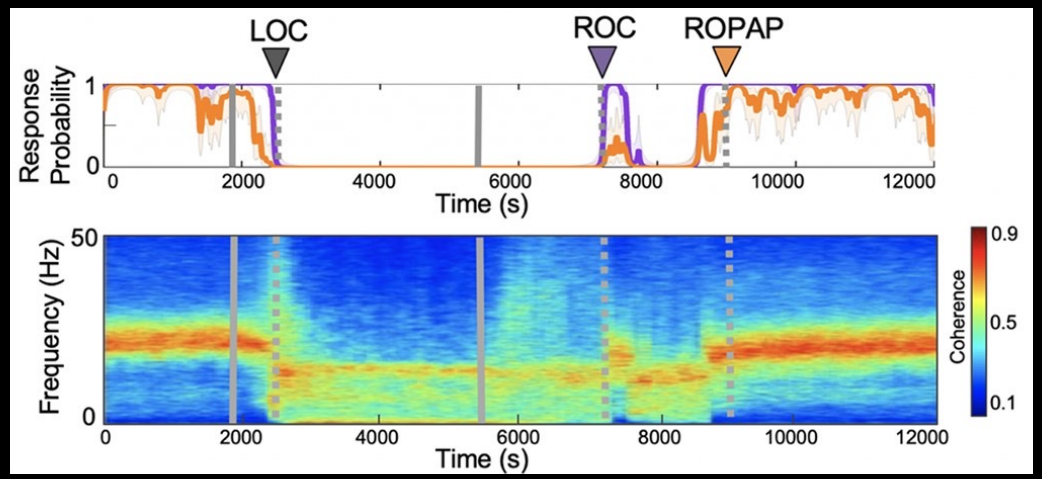
Distribution of Brain Activity Under Fixed Anesthetic Concentration is Confined to Discrete Clusters



Hudson et al, PNAS 2014

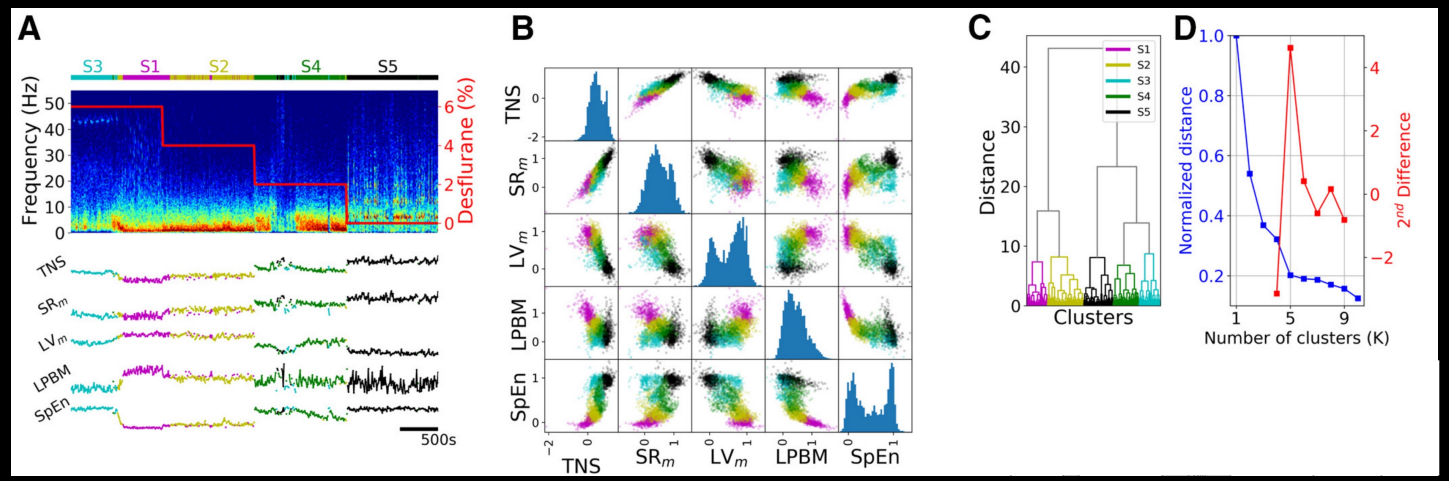
Abrupt state switches have been corroborated by others:

Non-human primate, recovery from propofol.
Measure: coherence



Patel et al, Brain, 2020

Rats, recovery from desflurane.
Measure: firing statistics



Lee et al, J. Neurosci. 2020

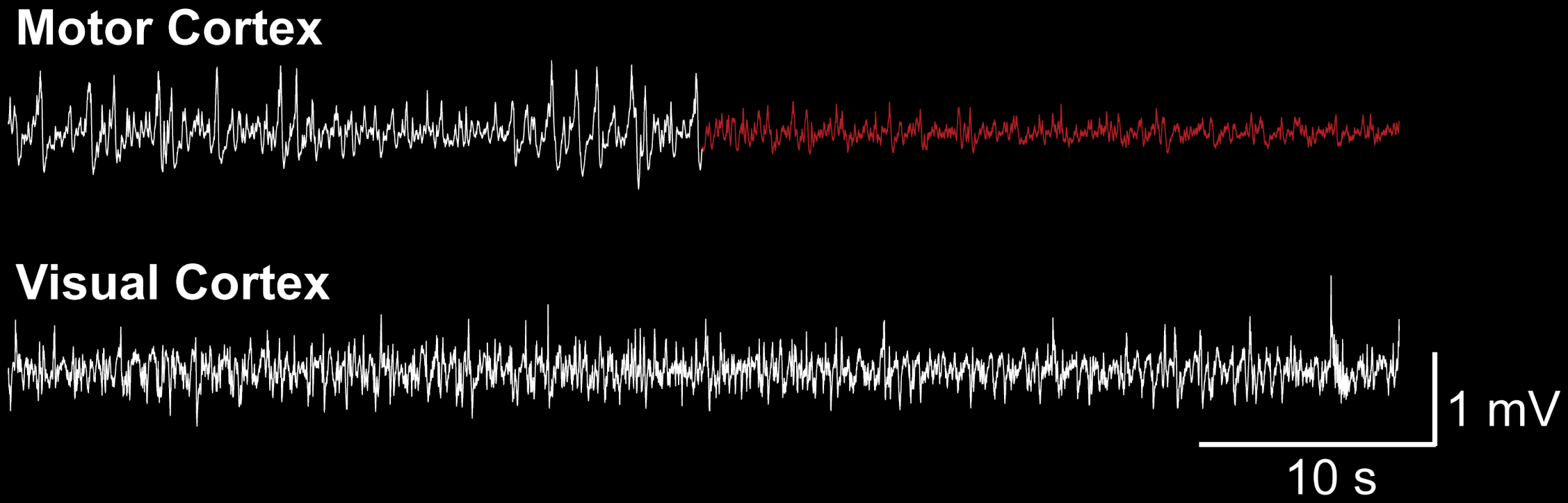
Abrupt transitions between discrete activity profiles are observed across species, are reflected in different measures of brain activity and are observed with mechanistically distinct anesthetics.

Objections to these experimental results:

- Could fluctuations in drug concentration be driving fluctuations in activity?
- Could an unaccounted-for stimuli be triggering state transition?

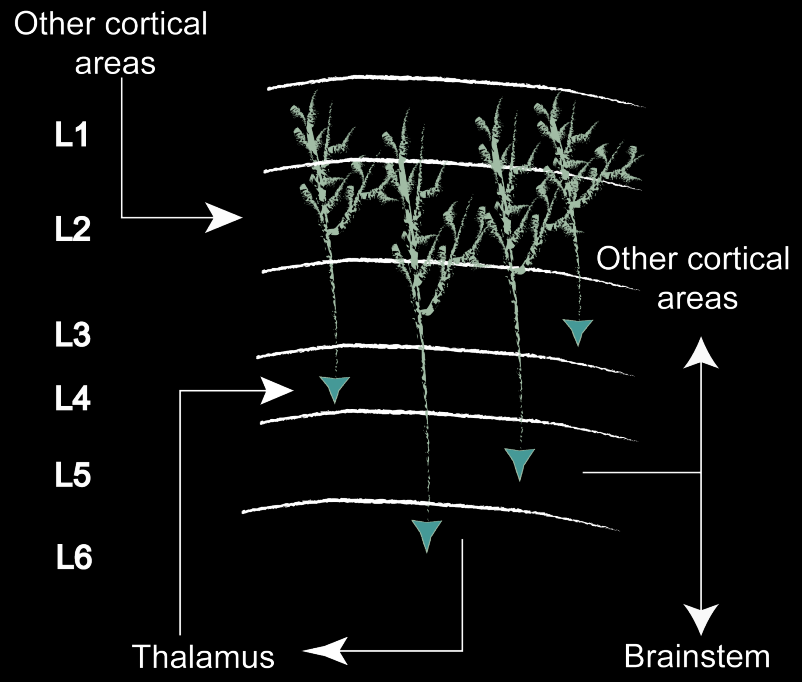
It is not possible to directly rule these out experimentally, but …..

If some external perturbation caused the switch in activity, then it should be observed simultaneously across the brain.

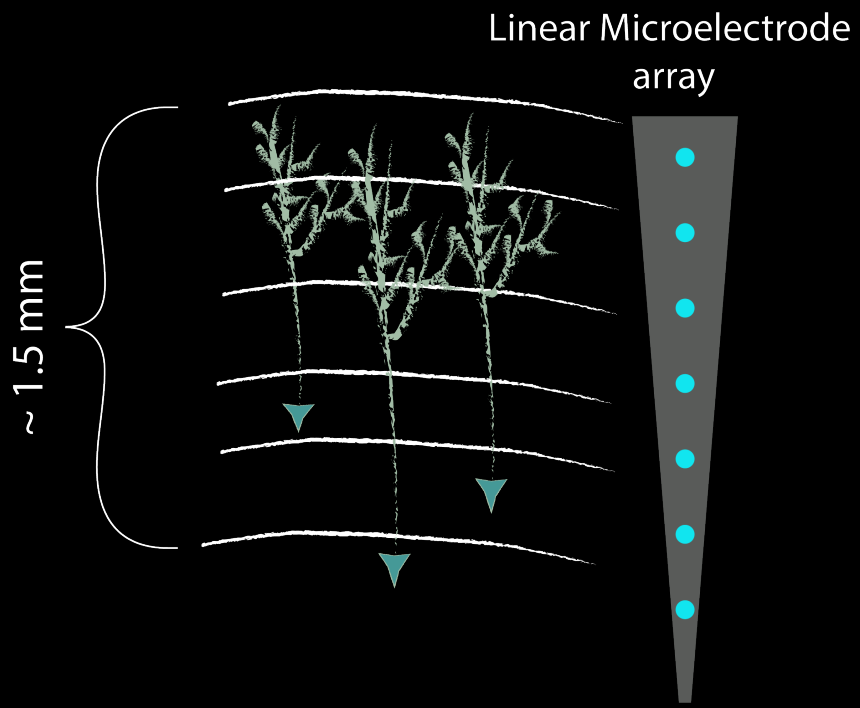


Blackwood et al, J. Neuroscience, 2022, *in press*

One slide review of cortical layer architecture and recordings

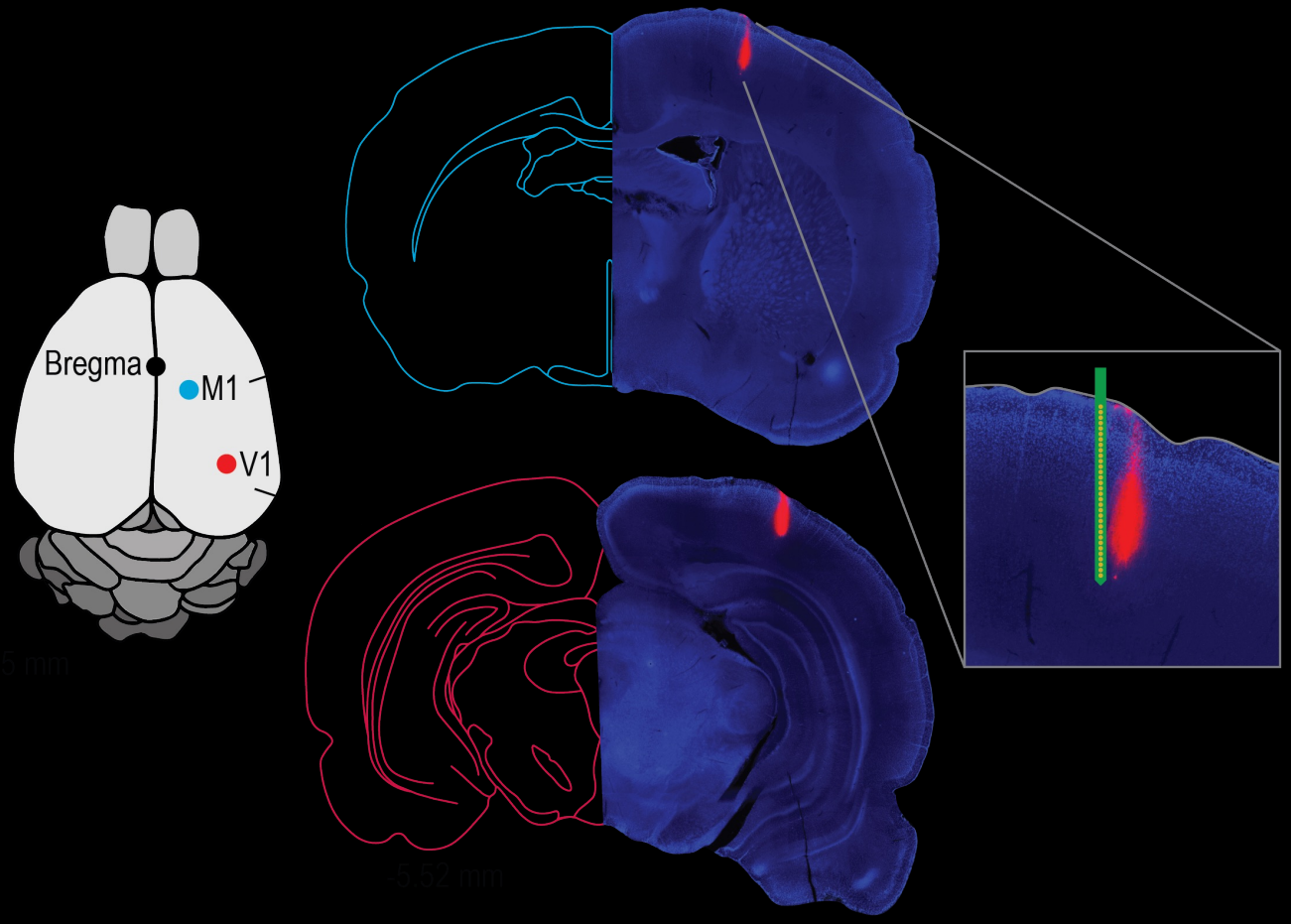


Neurons in different cortical layers have different properties and connectivity patterns

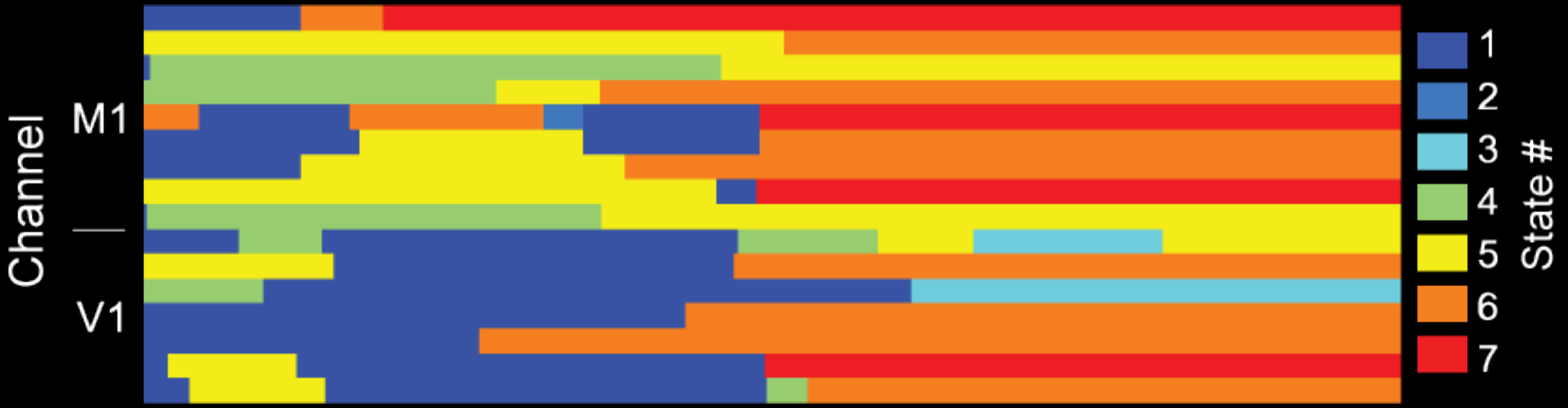


Linear electrode arrays allow simultaneous recordings across cortical layers

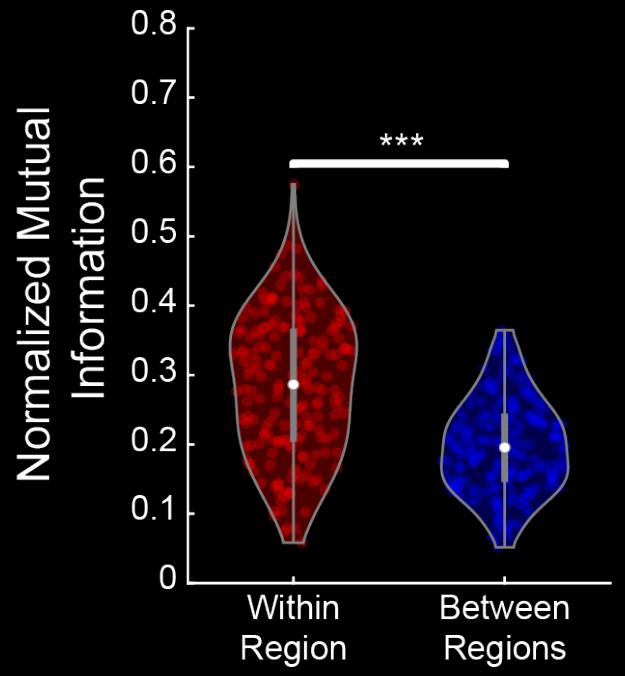
Histological confirmation of electrode locations



Clustering reveals that state fluctuations in different cortical sites are only loosely coupled



Coupling strength depends on distance, but also on cortical layer



Conclusions of Neurophysiology Work

- At a fixed drug concentration the state of the brain spontaneously fluctuates between several discrete states.
- These fluctuations are observed across different species, anesthetic agents, and measures used to define the state.
- State fluctuations are only loosely coupled between cortical regions and layers.
- There is no plausible mechanism through which drug concentration fluctuations or undetected stimuli are responsible for these state transitions.

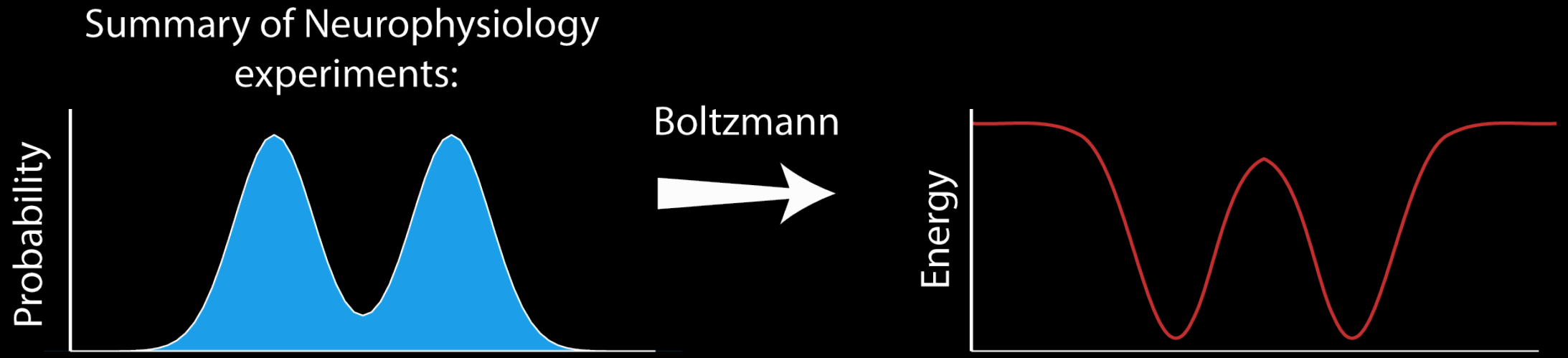
Thus, there is conclusive evidence that knowing the drug concentration is not enough.

How does this relate to hysteresis ?

$$p_i \propto e^{-E_i/(kT)}$$

The probability of observing a system in state *i* is related to the energy of the *i-th* state.

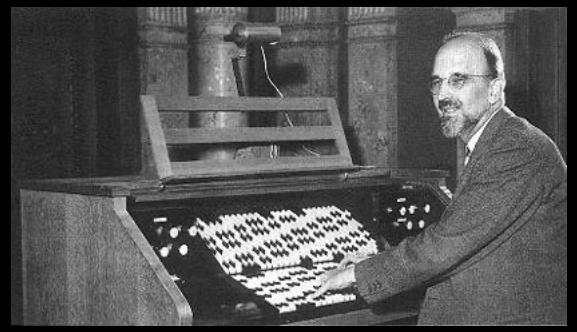
Neurophysiology experiments imply that the "energy" landscape has multiple wells at a constant drug concentration.



Boltzmann, equation only tells you about what happens in the steady state.

To get non-equilibrium behavior we need the Fokker-Planck Equation

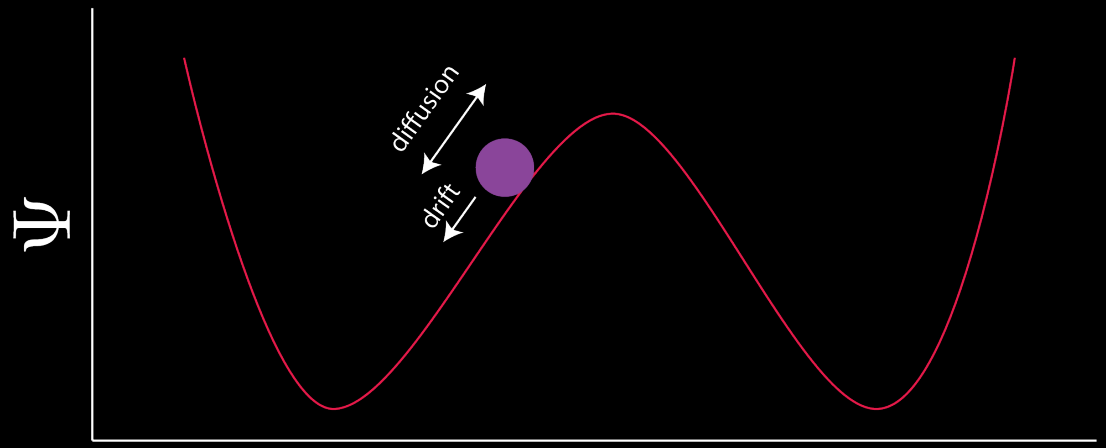
Adriaan Fokker



Max Planck

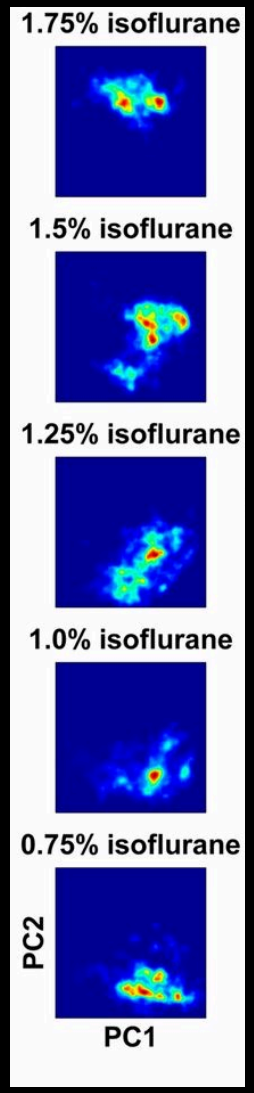
$$\frac{\partial p}{\partial t} = \underbrace{\nabla * (p_t \overbrace{\nabla \Psi}^{\text{energy gradient}})}_{\text{drift}} + \overbrace{D}^{\text{diffusion}} \Delta p_t$$

diffusion constant

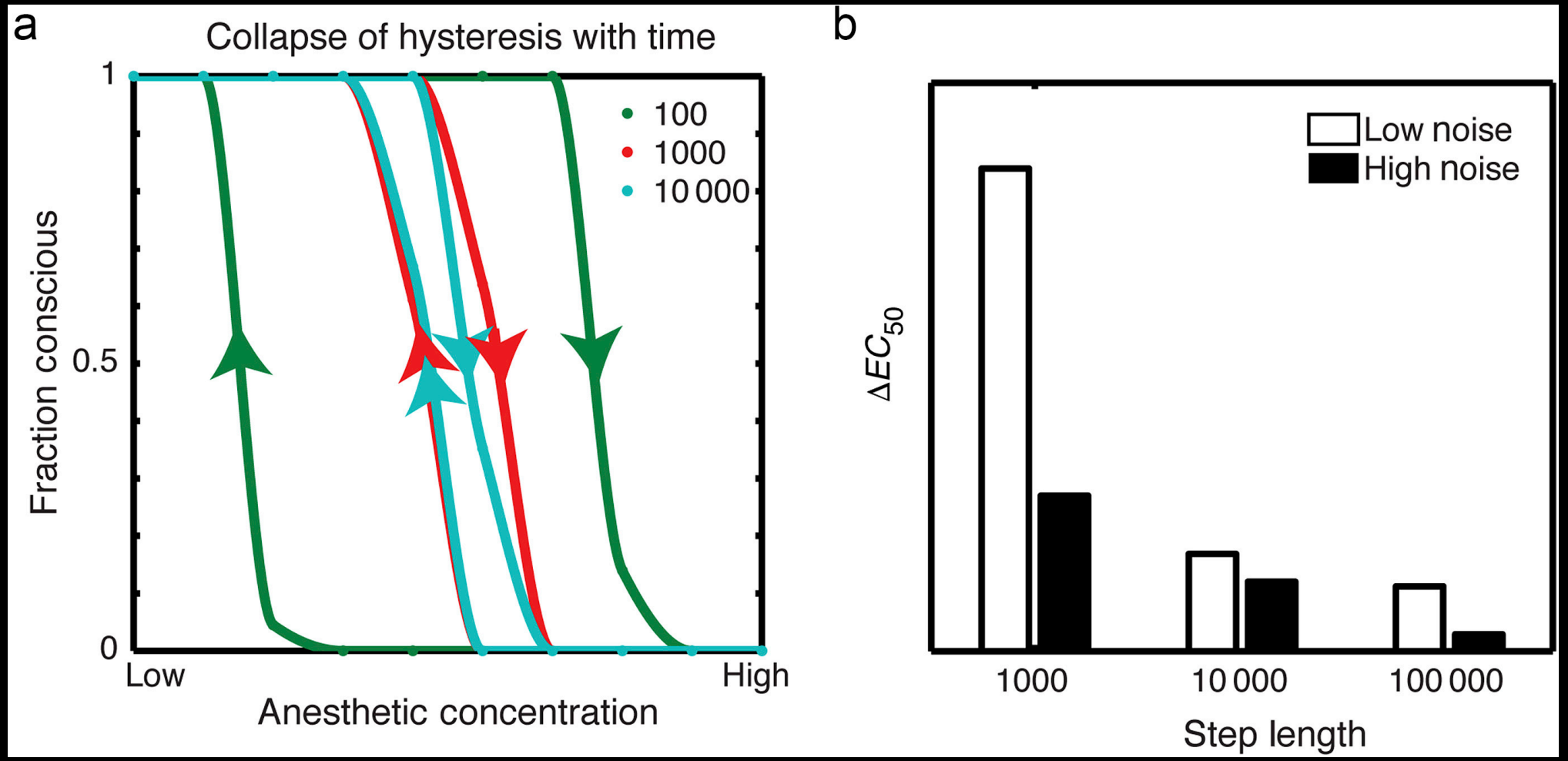


While the ultimate distribution is shaped by the energy landscape, the rate of approach to this steady state is depends on diffusion

Stochastic basis for hysteresis: anesthetic sets the energy landscape, but diffusion governs hysteresis



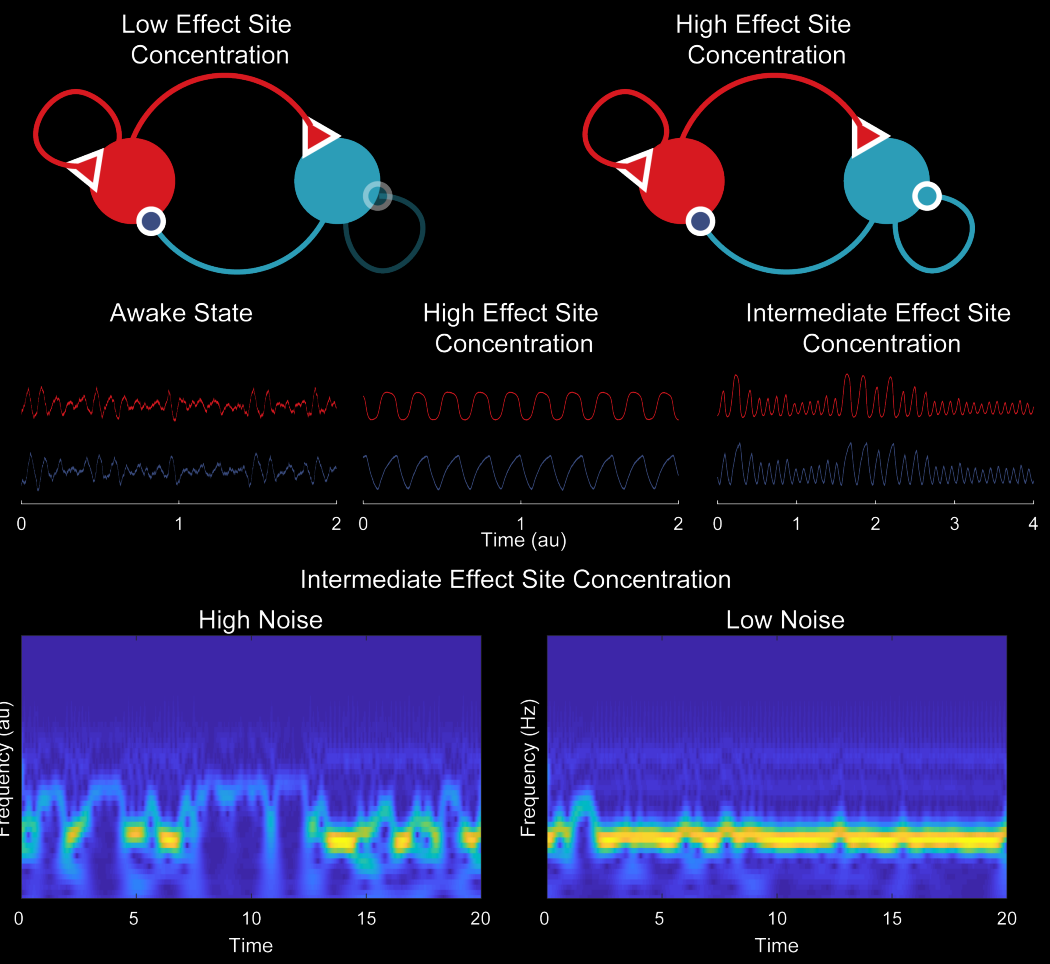
Proekt and Hudson, BJA, 2018



Proekt and Hudson, BJA, 2018.

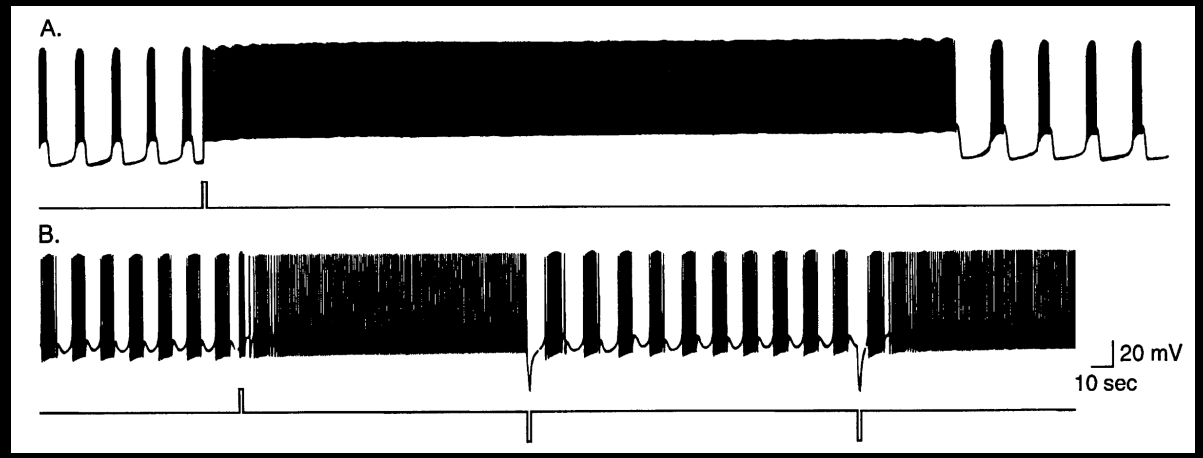
Its easy to get state transitions

Two model neurons do the trick.



Proekt and Kelz, BJA, 2021

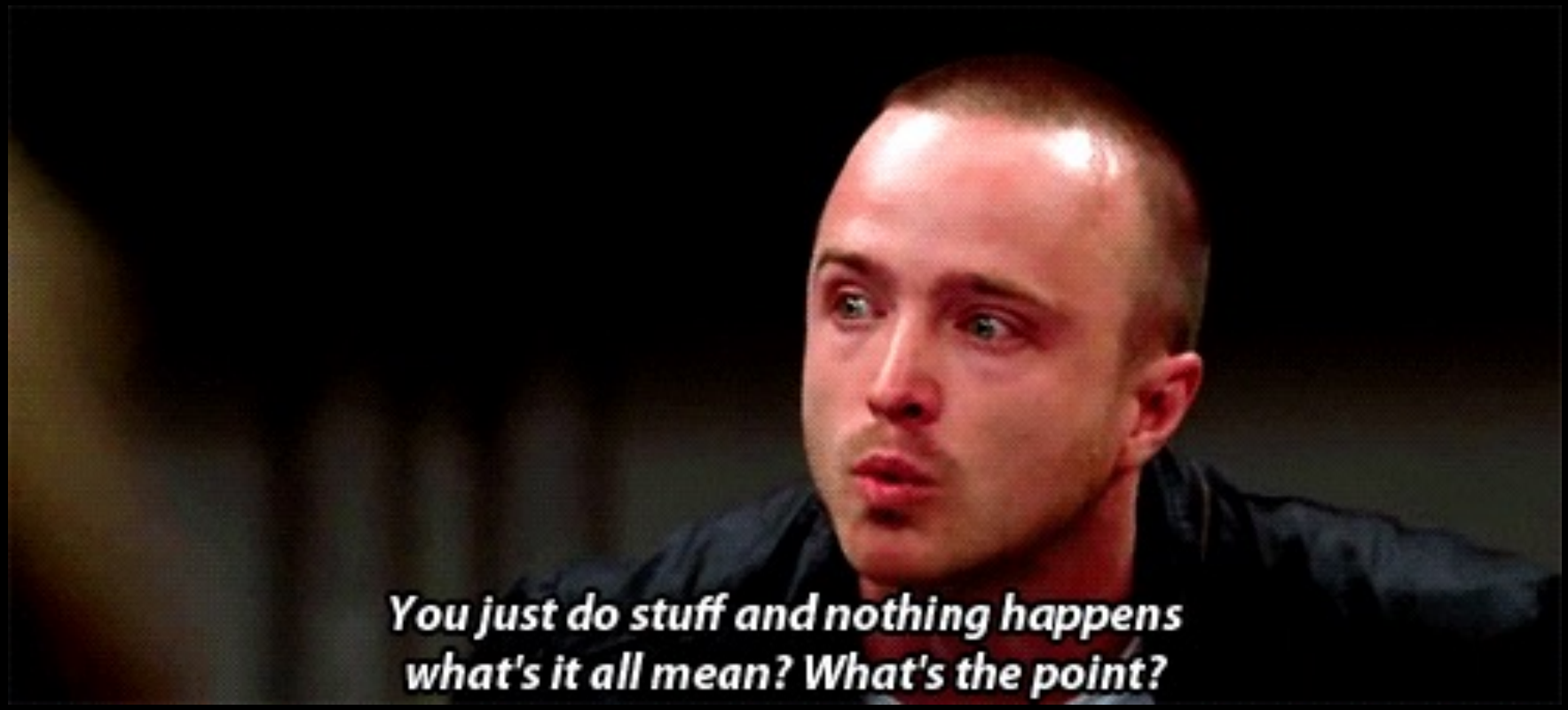
One real neuron can do it too



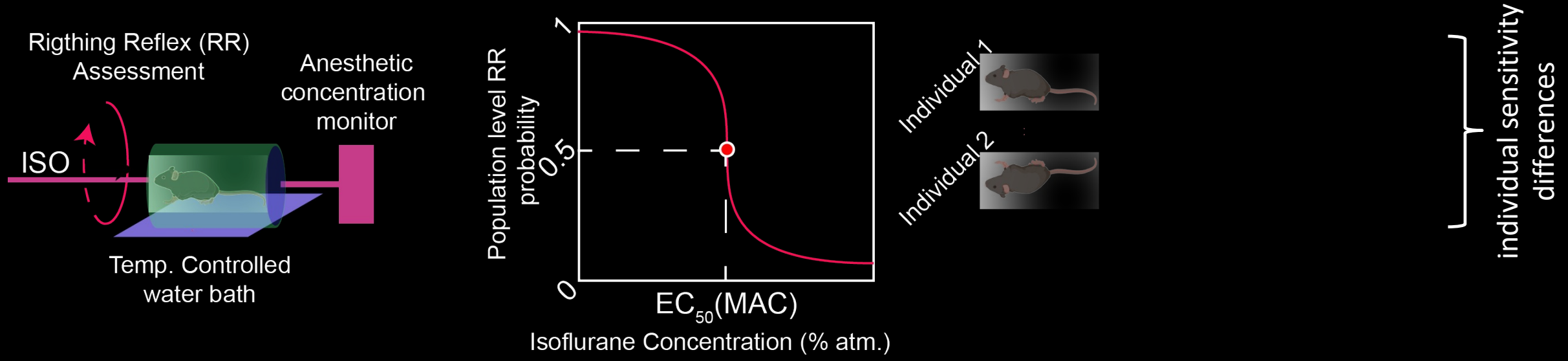
Lechner et al, J. Neurophys. 1996

Disclaimer:
I am not claiming that all you need is two neurons to understand the brain.
I am claiming that multi-stability is a generic property of nonlinear systems.

Do any of these brain fluctuations mean anything?

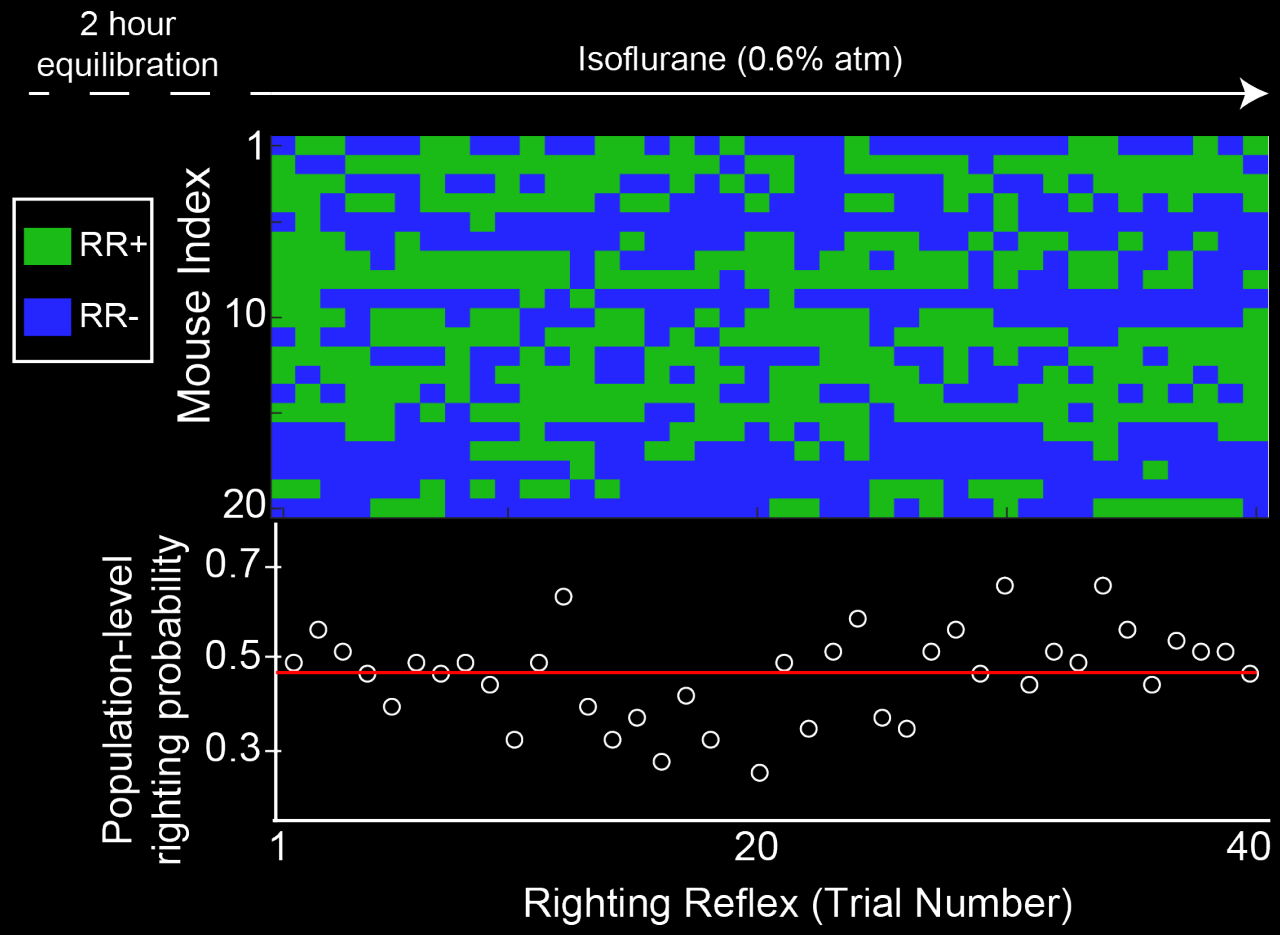


Behavioral responses fluctuate at fixed anesthetic concentration.



Traditional interpretation of the discrepancy between binary responses in individuals and graded responses in a population is *individual differences* in anesthetic sensitivity.

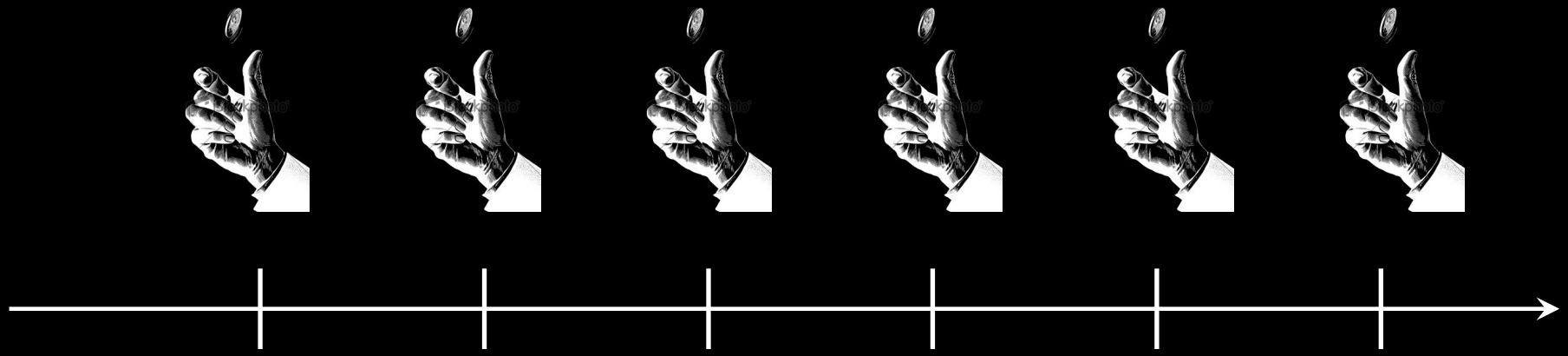
Each animal fluctuates between being responsive and unresponsive



Wasilczuk and McKinstry-Wu et al, Elife 2019

The response of each mouse fluctuates from trial to trial while at the level of population the response probability remains constant

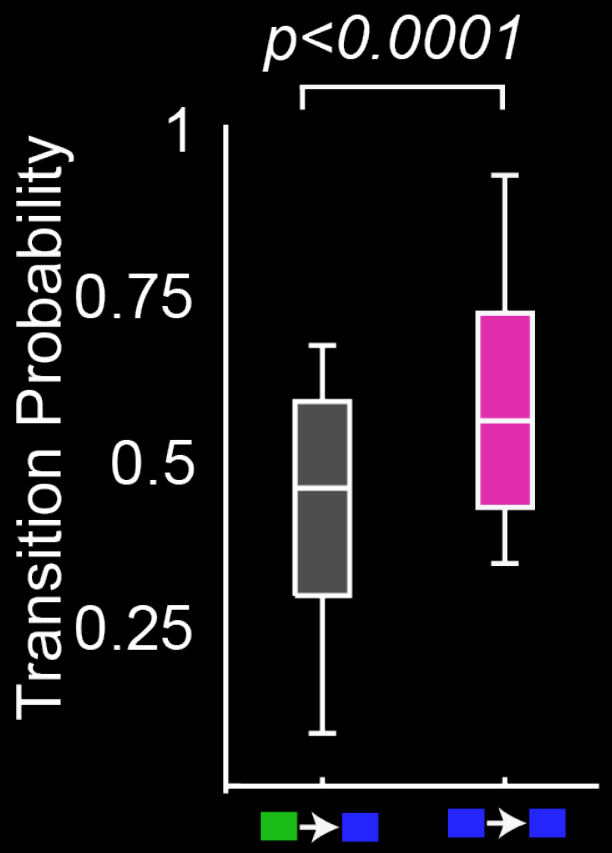
The simplest model of fluctuations in RR.



Righting Reflex (trial number)

If this were true, then the response probability should be the same on every trial

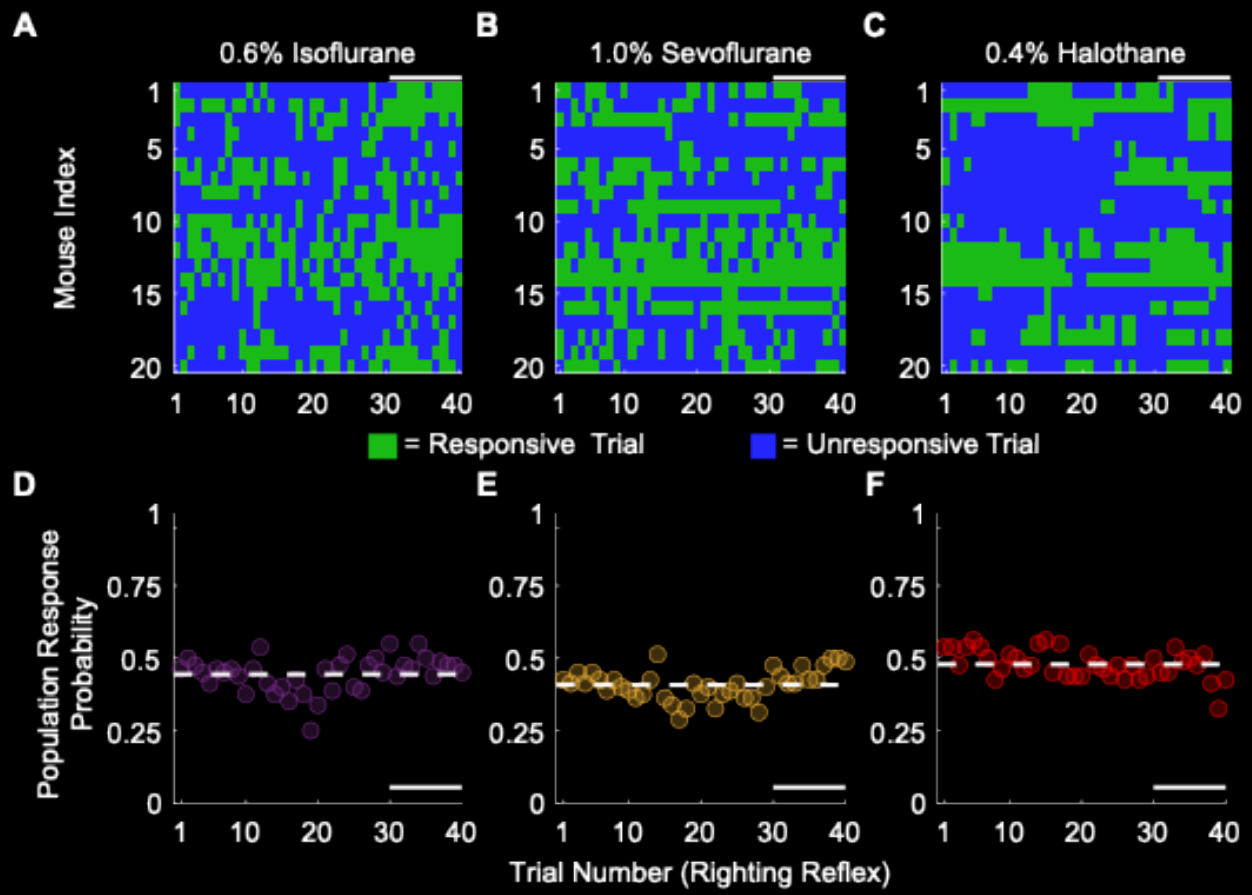
Probability of successful righting depends on the previous history

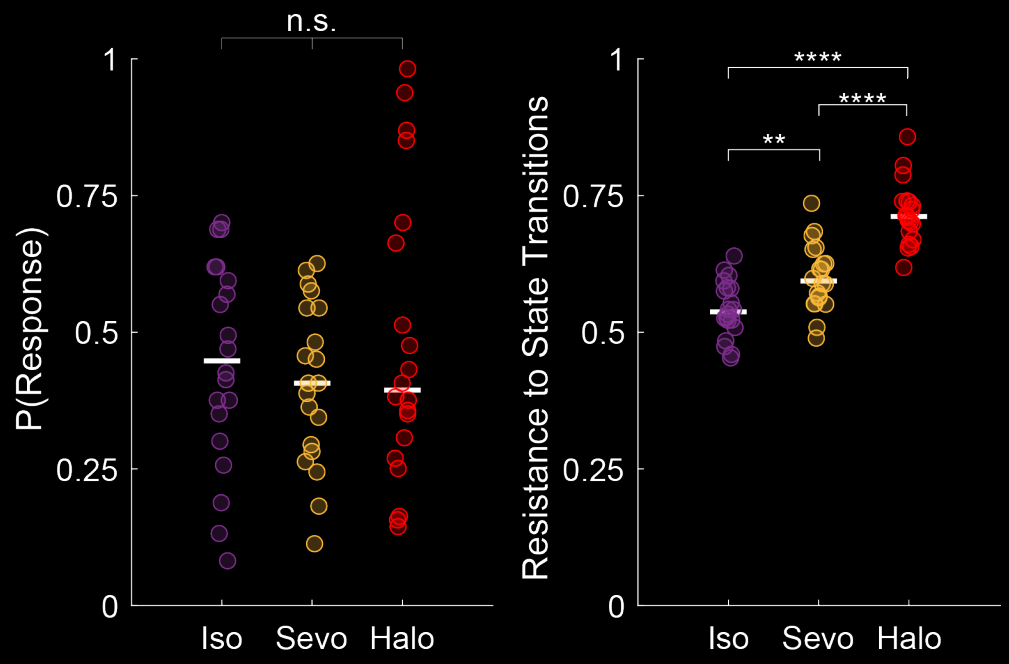


The animal is much more likely to stay unresponsive if it was found to be unresponsive on the previous trial

Wasilczuk and McKinstry-Wu et al, Elife 2019

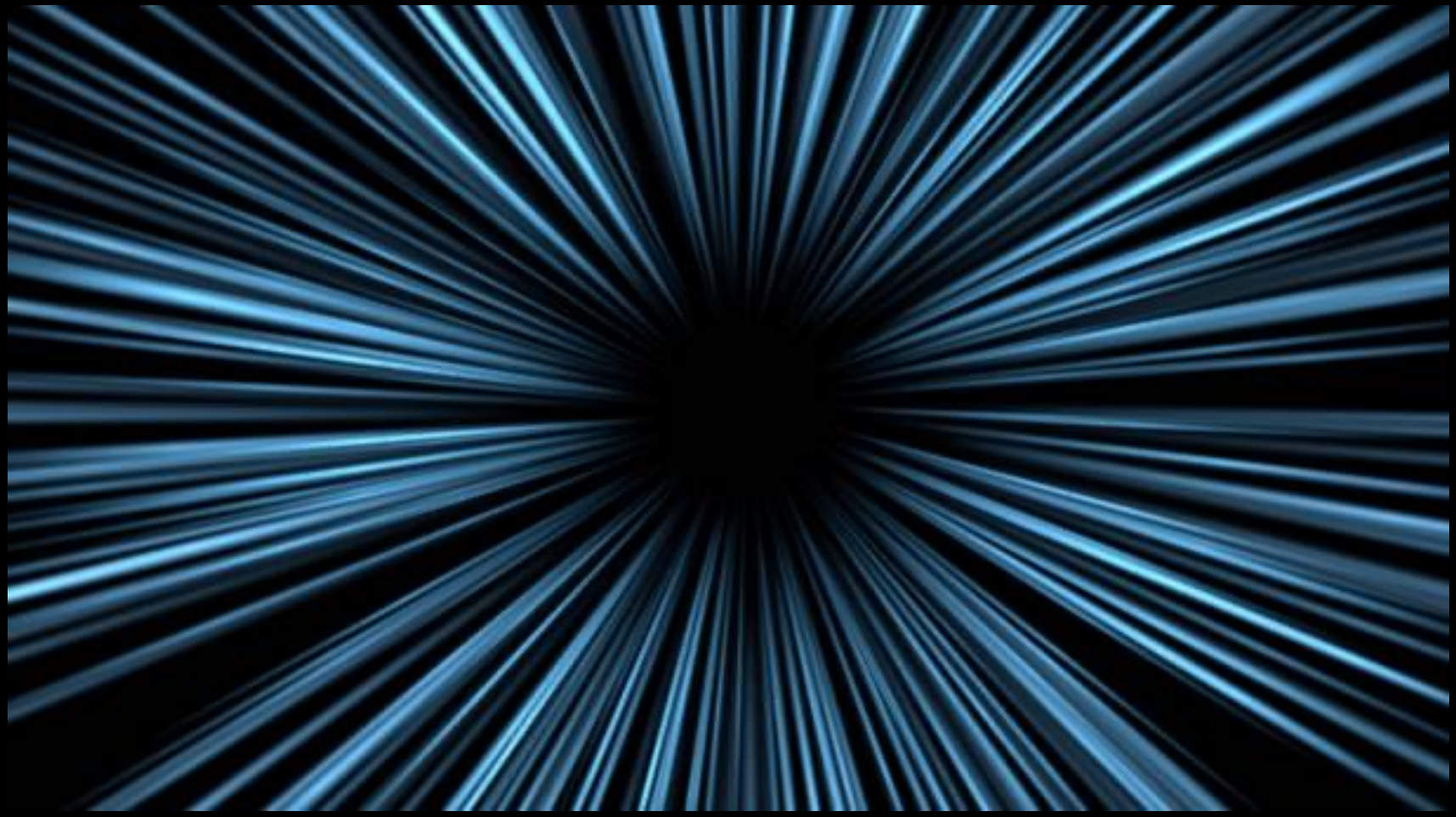
Resistance to state change be modulated independently of potency.



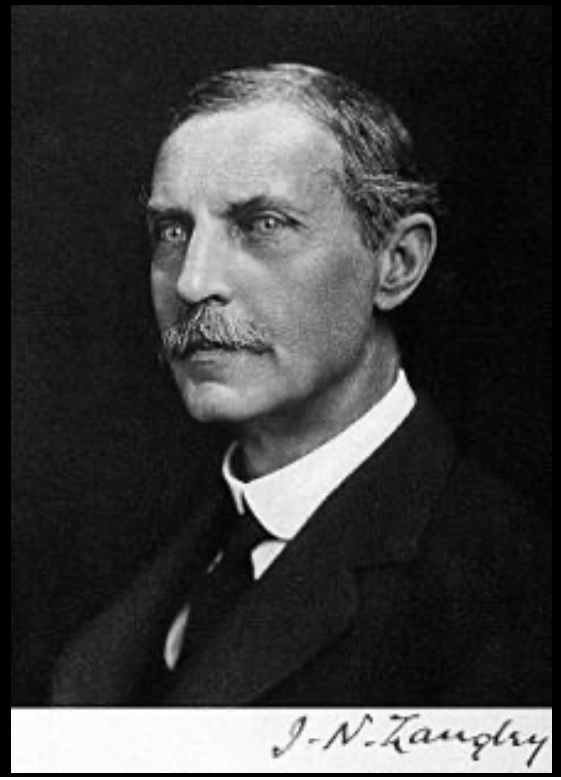


Wasilczuk, et al. *BJA* 2020

Let's zoom out



Pharmacology then was abstract



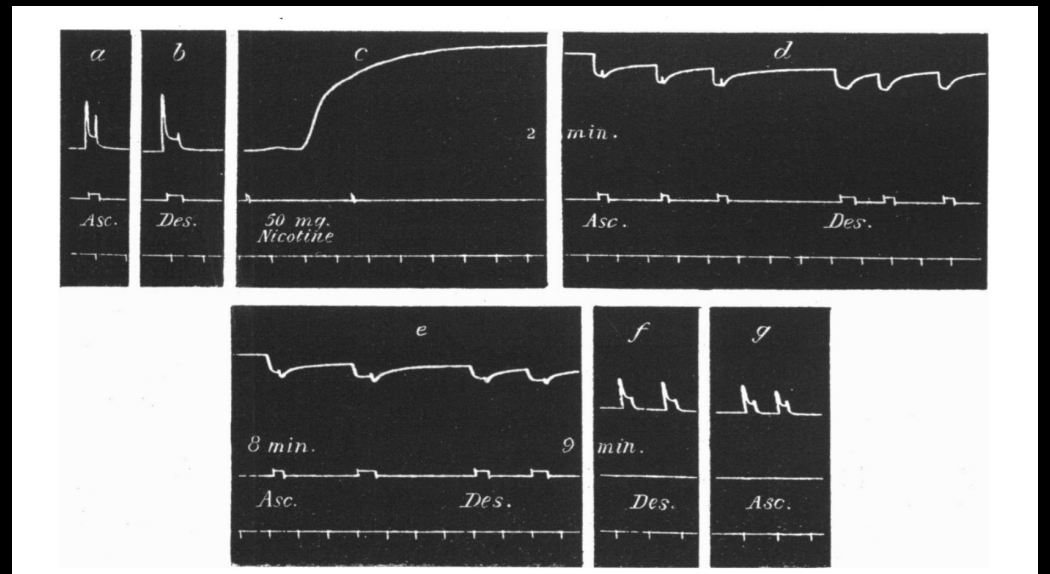
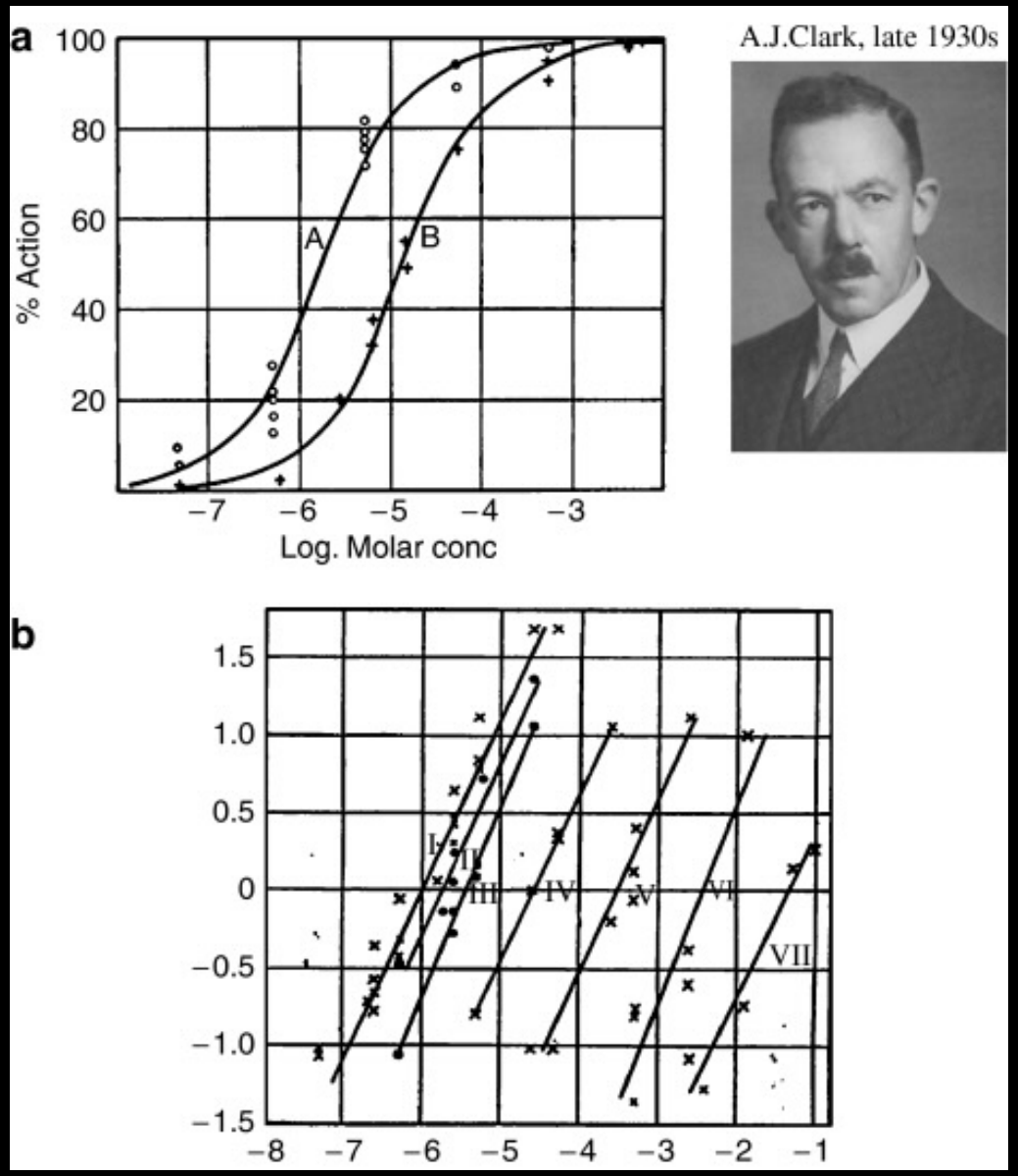


Fig. 2. Inhibition of contraction by the constant current. Nerves paralysed by 15 mgs. curari. Make and break stimulation with 4 Daniell's cells. (*a*) Ascending. (*b*) Descending. (*c*) Injection of 50 mgs. nicotine. Interval of 2 mins. (*d*) Ascending current three times, and descending current three times. Interval of 8 mins. (*e*) Ascending twice, descending twice. Interval of 9 mins. (*f*) Descending twice. (*g*) Ascending twice. Reduced ½.

Since this accessory substance is the recipient of stimuli which it transfers to the contractile material, we may speak of it as the *receptive substance* of the muscle.

Langley, Journal of Physiology, 1905



A.J.Clark, late 1930s

"The hypothesis that the concentration-action curve of acetylcholine expresses an adsorption process of the type described by Langmuir appears to involve fewer improbable assumptions than any alternative hypothesis"

A.J. Clark, 1933

Adapted from Rang, H. P. *British journal of pharmacology* (2006)

The idea that the activity of acetylcholine-like drugs is due to two separate properties—affinity for the receptors, and efficacy—thus seems to explain most of the observed facts ; and, assuming its correctness, it becomes interesting to attempt to separate the contributions of the two factors to the total effect.

R.P. 'Steve' Stephenson

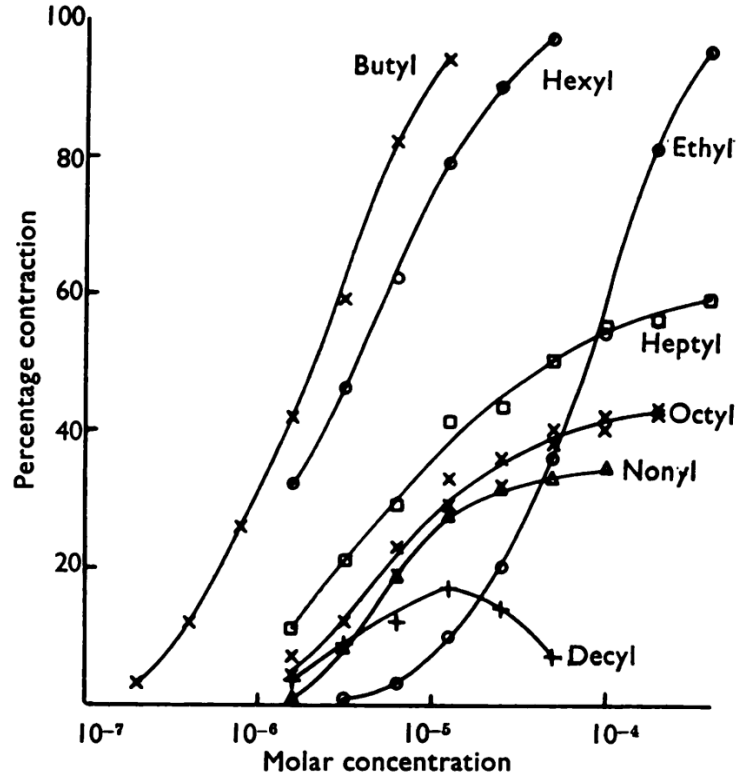
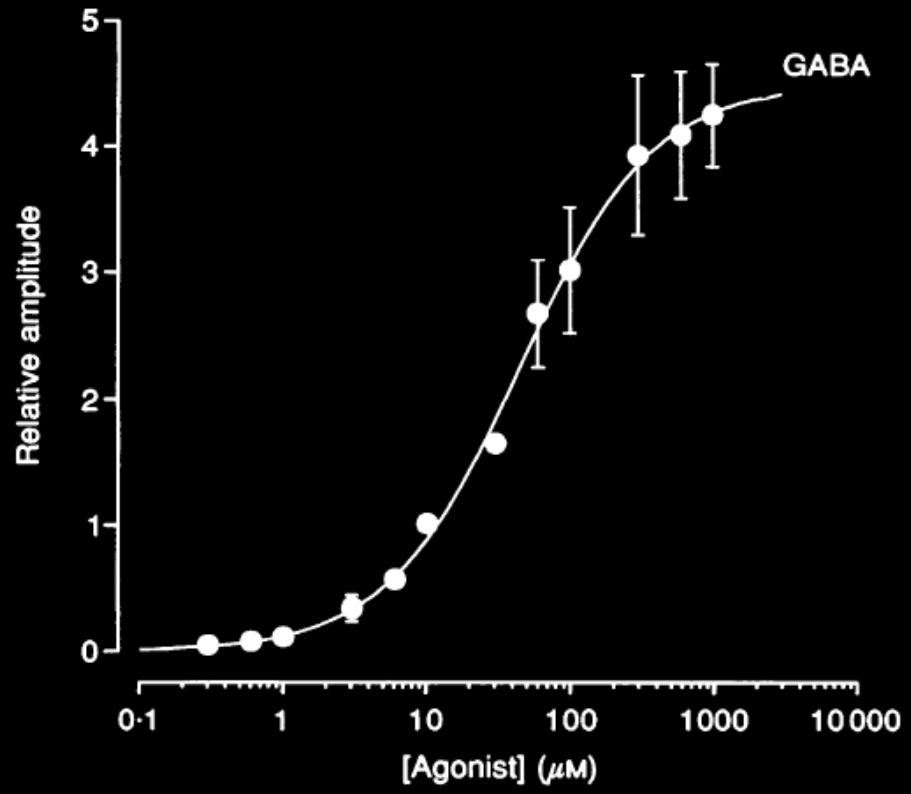


FIG. 1.—Concentration-effect curves for some alkyl-TMA ions on guinea-pig ileum. The contractions were produced by additions to the bath to give the final concentrations indicated; each concentration was left in contact with the ileum for about 15 sec. and then washed away. All the points for a given substance were obtained in consecutive contractions, starting with a low dose which was progressively doubled until the response range was covered. This was done twice with octyl-TMA and both sets of points are plotted.

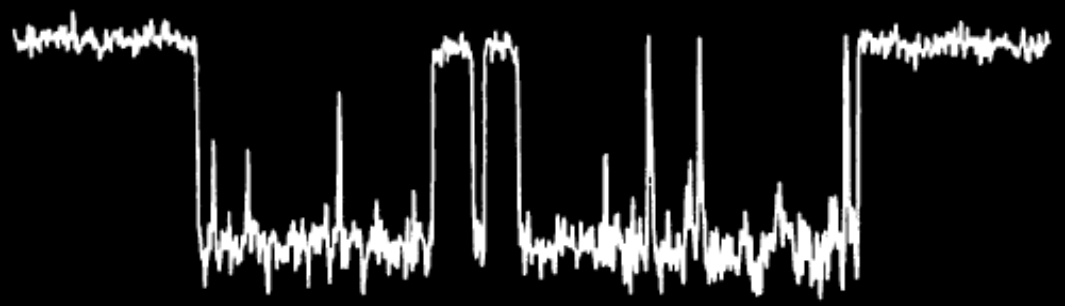
Stephenon, British Journal of Pharmacology, 1956

Pharmacology Now – receptors are biological macromolecules with their own intrinsic dynamics

Whole cell currents mediated by many GABA-A receptors



Single GABA-A receptor molecule exposed to 10 μM GABA



Kaneda et al, J. Physiol., 1995

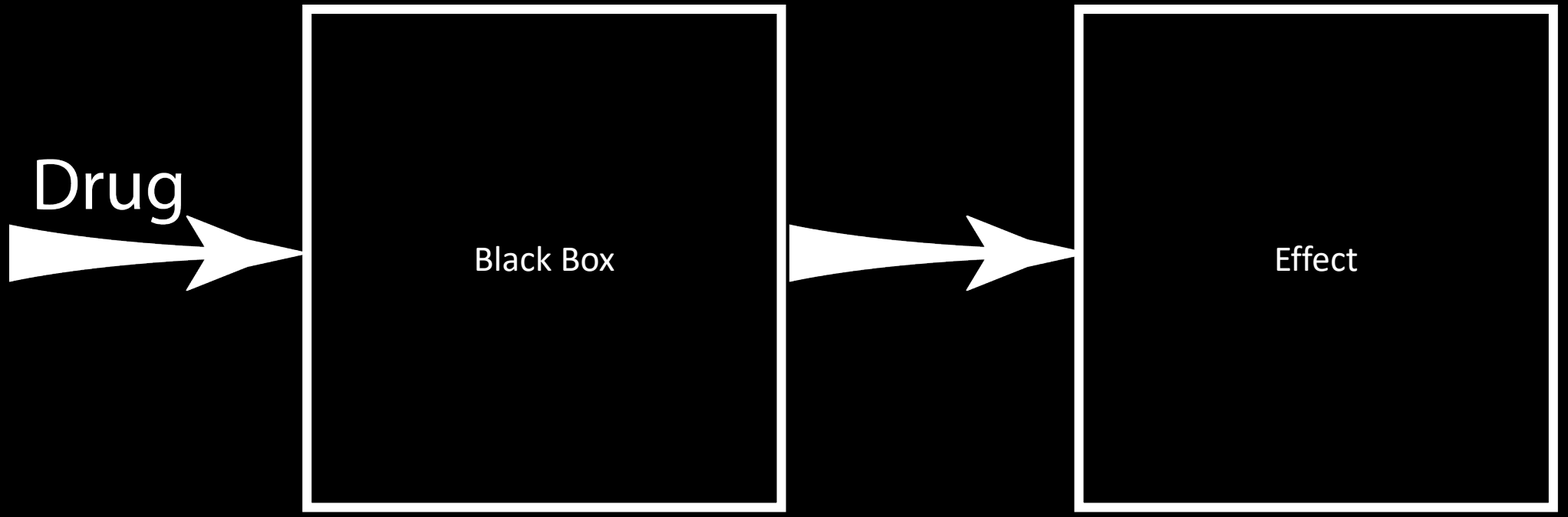
The actual microscopic constants tell us about what is going on. In contrast, concentration response curve defines a macroscopic constant; it describes what we see, but does not tell us what is going on underneath.

David Colquhoun (UCL)

Grand Conclusion

The study of how macroscopic phenomena (e.g. concentration response curves) arise from more primitive microscopic ones, reveals qualitatively new and wholly unexpected features.

Multi-stability and the consequent resistance to state transitions that gives rise to anesthetic hysteresis is one such feature of anesthetic pharmacology



It’s not different from what happens when we see a distant forest as a uniform green and then get closer and start seeing the trees, the branches, the insects.... we learn more about the world, and in this process our previous pictures are challenged.

Carlo Rovelli talking about conceptual revolution brought about by quantum mechanics