The Balance between Excitation and inhibition in the Brain

Lin Xiaohan

11/17/23

Historical Note

- Rate Coding vs. Temporal Coding
  - **Rate coding**: information is conveyed via the average rate of spikes;
    - Neurons → integrator
  - **Temporal coding**: the precise timing of spikes conveys information.
    - Neurons → coincidence detector

Historical Note

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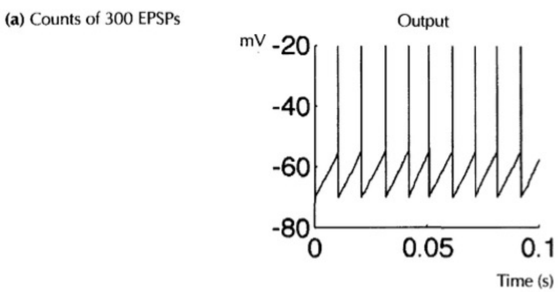
The Highly Irregular Firing of Cortical Cells Is Inconsistent with Temporal Integration of Random EPSPs

Softky & Koch 1993

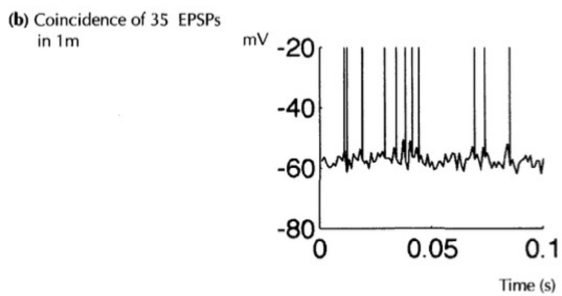
William R. Softky[1,2] and Christof Koch[2]

[1]Division of Physics, Mathematics, and Astronomy and [2]Computation and Neural Systems Program, California Institute of Technology, Pasadena, California 91125

Independent, random EPSPs induce highly regular firing patterns, inconsistent with experimental findings; Concluded neurons were coincidence detectors.



LIF neuron



Experimental data

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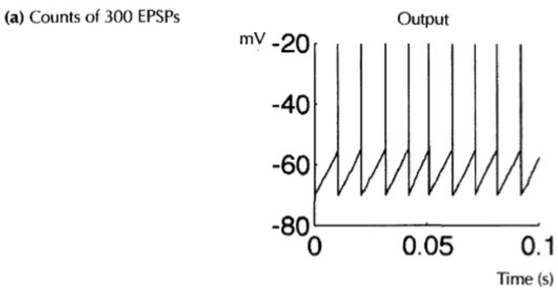

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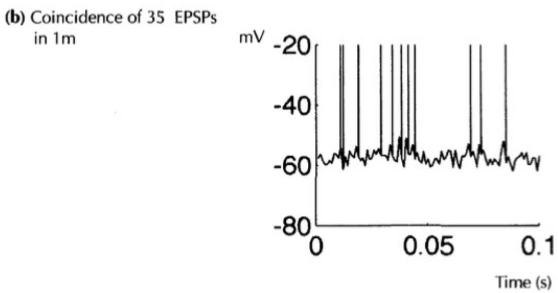

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LIF neurons (and all integrator models) are wrong!

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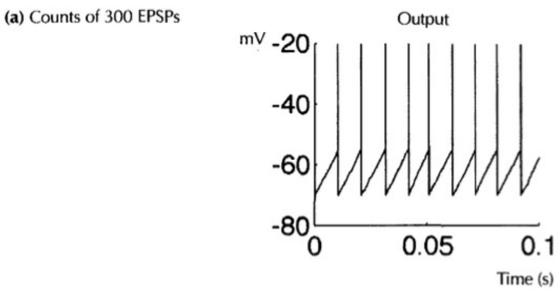

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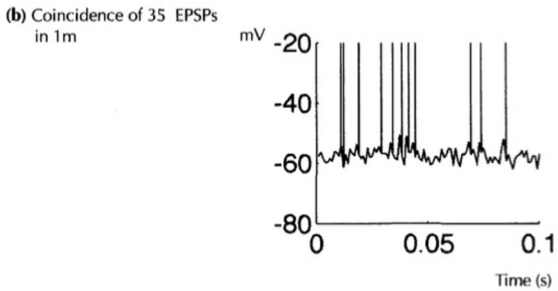

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Or are they?

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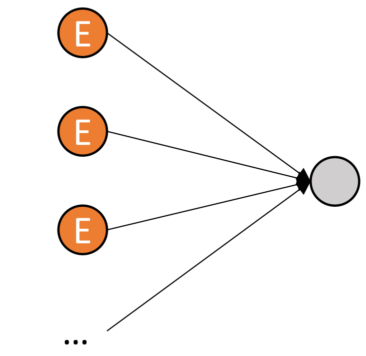
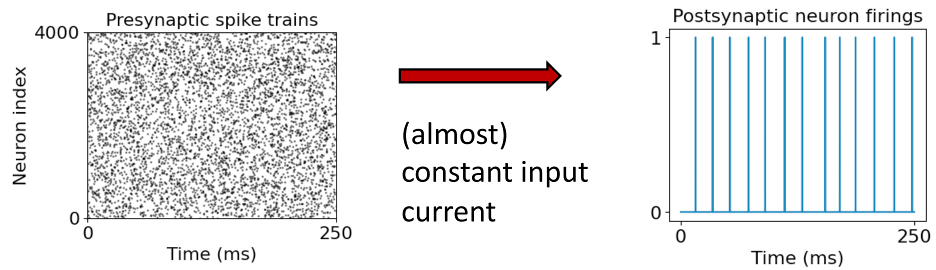


Centeral Limit Theorem



Historical Note

- We need to take inhibition into account.

Noise, neural codes and cortical organization

Michael N Shadlen and William T Newsome

Stanford University School of Medicine, Stanford, USA

(Shadlen & Newsome 1994)

Membrane potential undergoes a **random walk** under balanced EPSPs and IPSPs.

Historical Note

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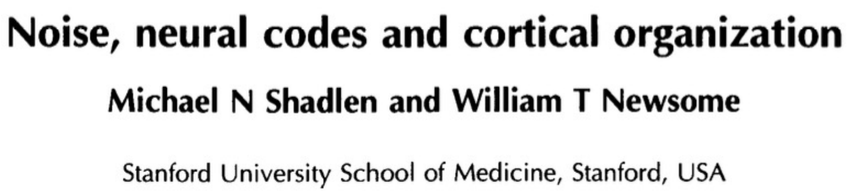
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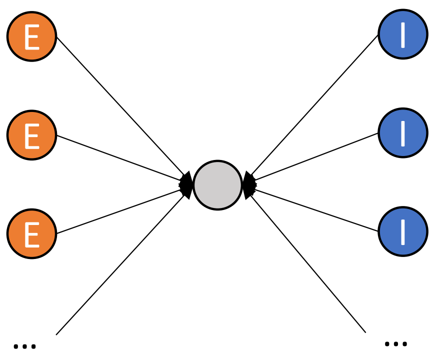
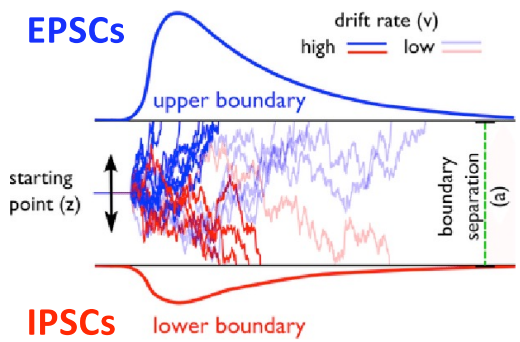
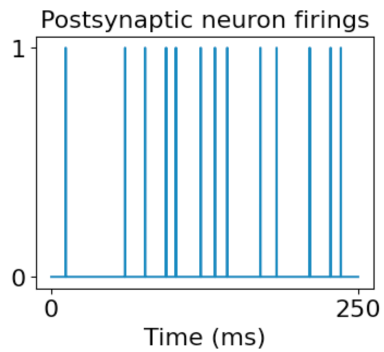






Sanity Check

Biological Constraints

Resting membrane potential	~ -70mV
Spike threshold	~ -55mV
Average EPSPs	~ -0.55mV

About 30 EPSPs can initiate an action potential.

Number of cortical neuron contacts	~ 4000
Excitatory synapses ratio	~ 85%
Spontaneous activity in cortex	~ 3 Hz
Neuron membrane time constant τ	~ 10 ms

A neuron receives about 100 EPSPs per τ on average.

Coincidence detector model would need $\tau \sim 1ms$ to avoid the accumulation of EPSP on membrane potential.

Random-walk model is more biologically plausible.

Simulation Time

irregular_inconsistent_integrator_Softky_Koch_1993.ipynb

random_walk_Shadlen_Newsome_1994.ipynb

Talk is cheap, what about experimental evidence?

Experimental Evidence

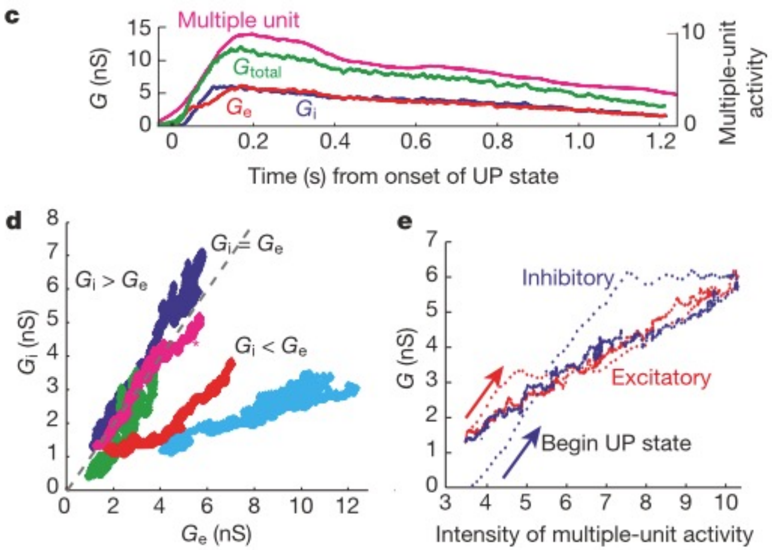
Turning on and off recurrent balanced cortical activity

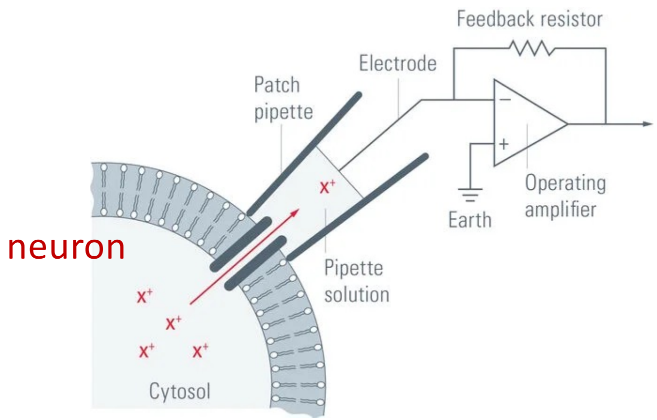
(Shu et al., 2003)

Yousheng Shu, Andrea Hasenstaub & David A. McCormick

Department of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, USA

Patch clamp





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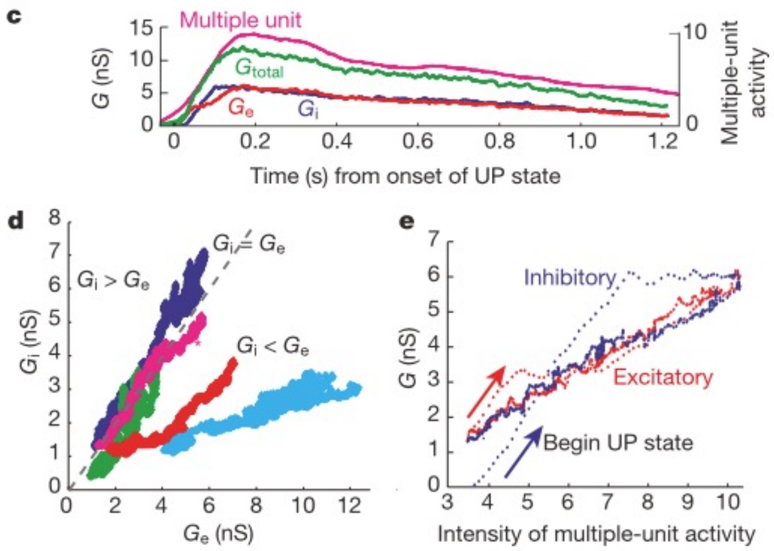
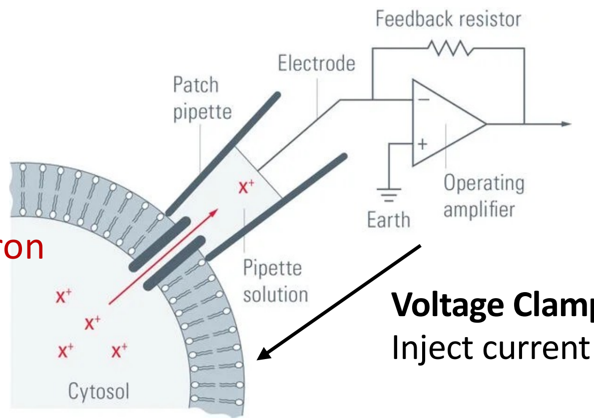


Patch clamp
- Voltage clamp
- Current clamp

neuron



Voltage Clamp
Inject current to maintain constant voltage.

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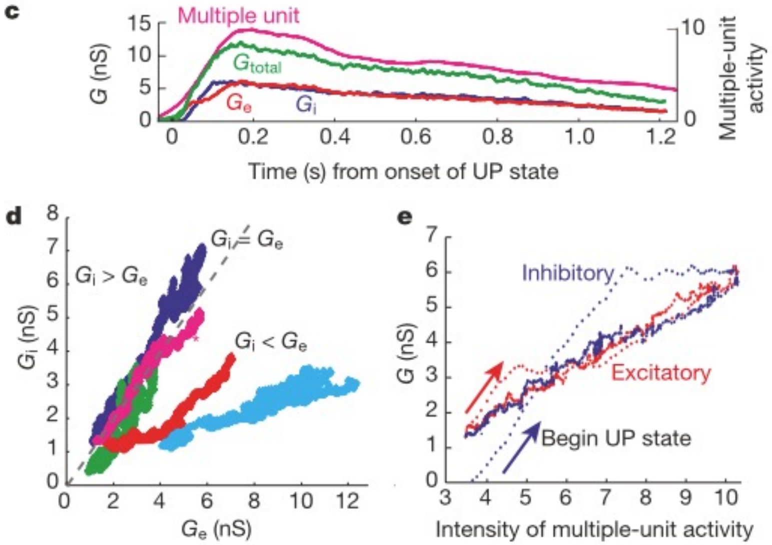
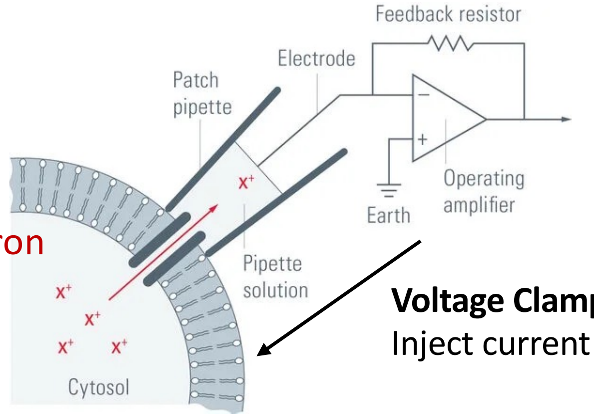


Patch clamp { Voltage clamp / Current clamp

neuron



Voltage Clamp
Inject current to maintain constant voltage.

PSCs: input currents from other neurons

Experimental Evidence

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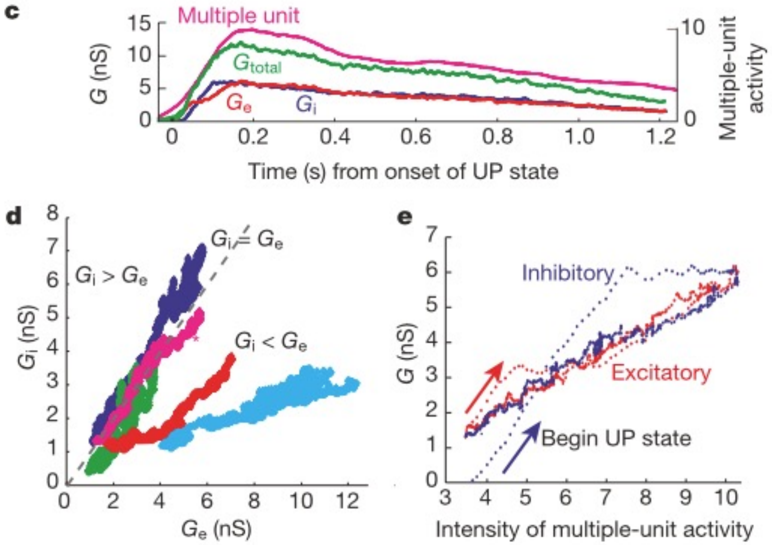
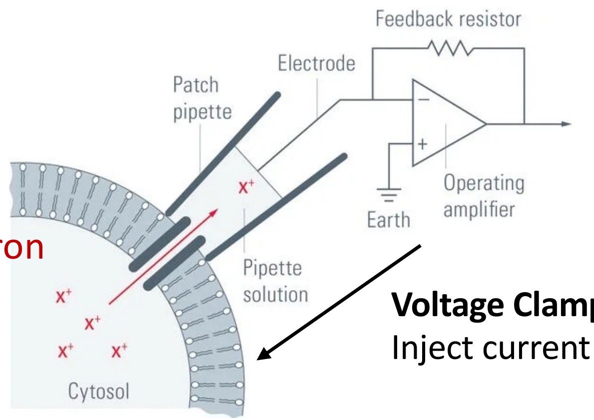


Patch clamp – Voltage clamp / Current clamp

neuron



Voltage Clamp
Inject current to maintain constant voltage.

$$R = V_{mem}/I_{inj} \qquad G = 1/R$$

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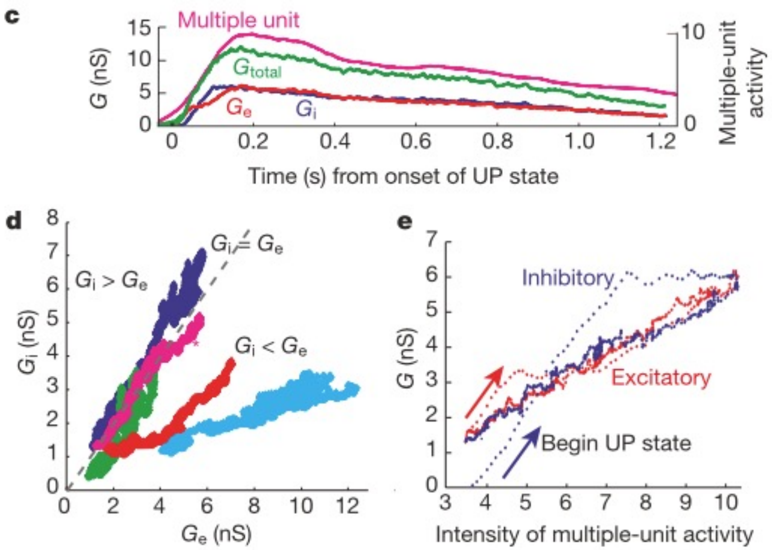

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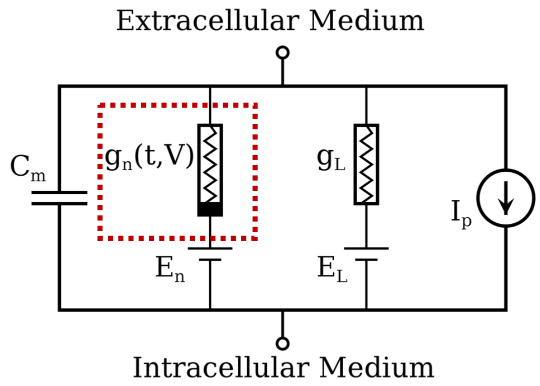

Equivalent circuit of a neuron

$$I = C_m \frac{dV_m}{dt} + \boxed{g_K}(V_m - V_K) + \boxed{g_{Na}}(V_m - V_{Na}) + g_l(V_m - V_l)$$

HH model

Experimental Evidence

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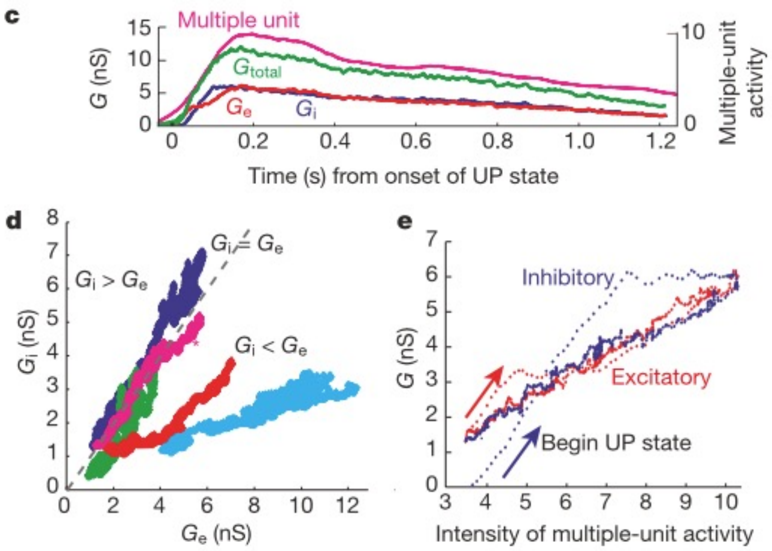

The conductance of excitatory channels (e.g. Na^+) and inhibitory channels (e.g. K^+, Cl^-) change together.

➡ **EPSCs and IPSCs are highly correlated, and thus balanced, in a single neuron.**

Experimental Evidence

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Turning on and off recurrent balanced cortical activity

(Shu et al., 2003)

In vitro conductance

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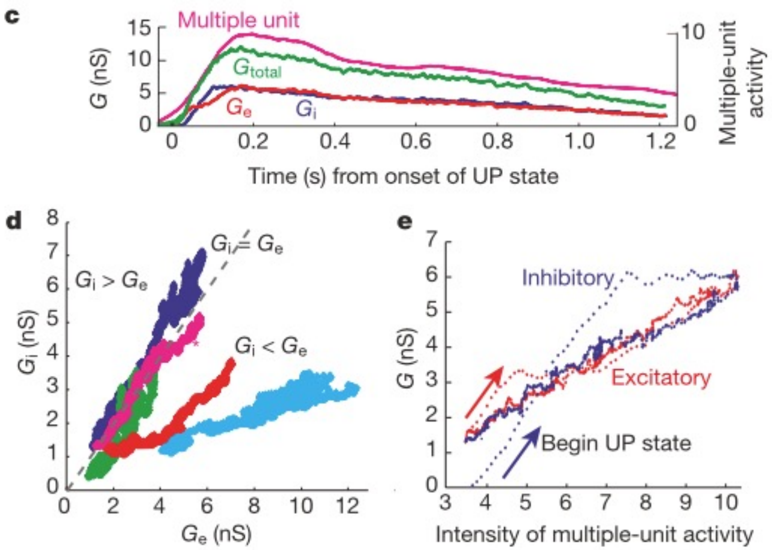


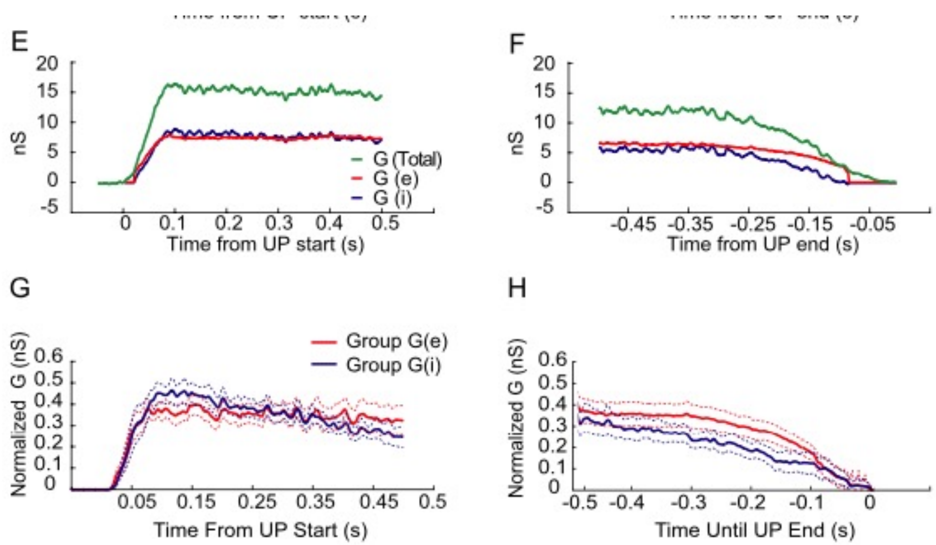
Neocortical Network Activity *In Vivo* Is Generated through a Dynamic Balance of Excitation and Inhibition

In vivo conductance

Bilal Haider, Alvaro Duque, Andrea R. Hasenstaub, and David A. McCormick

Department of Neurobiology, Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, Conne

(Haider et al., 2006)



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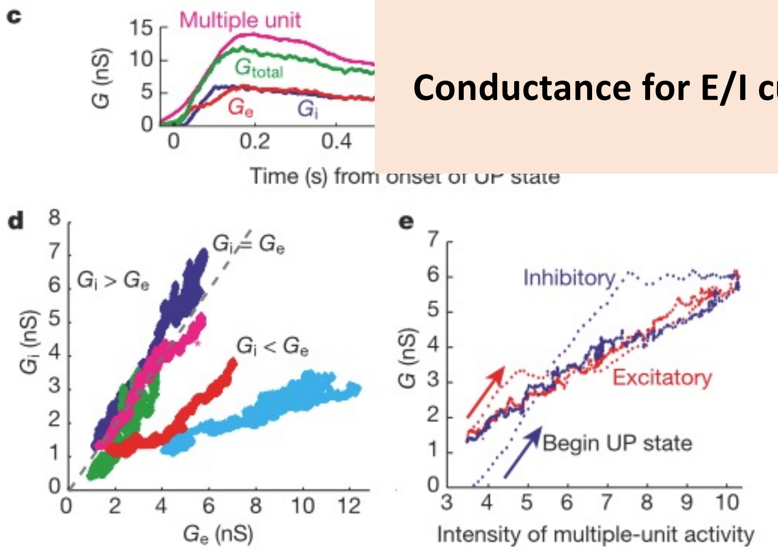
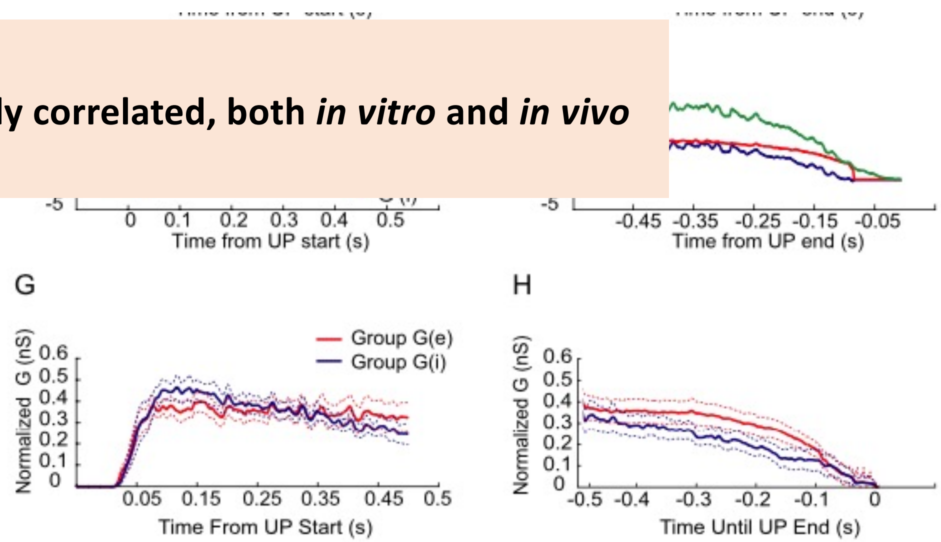




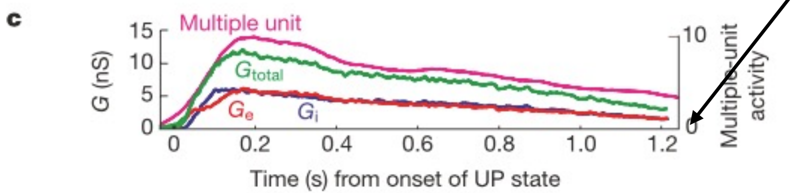
Conductance for E/I currents is strongly correlated, both *in vitro* and *in vivo*

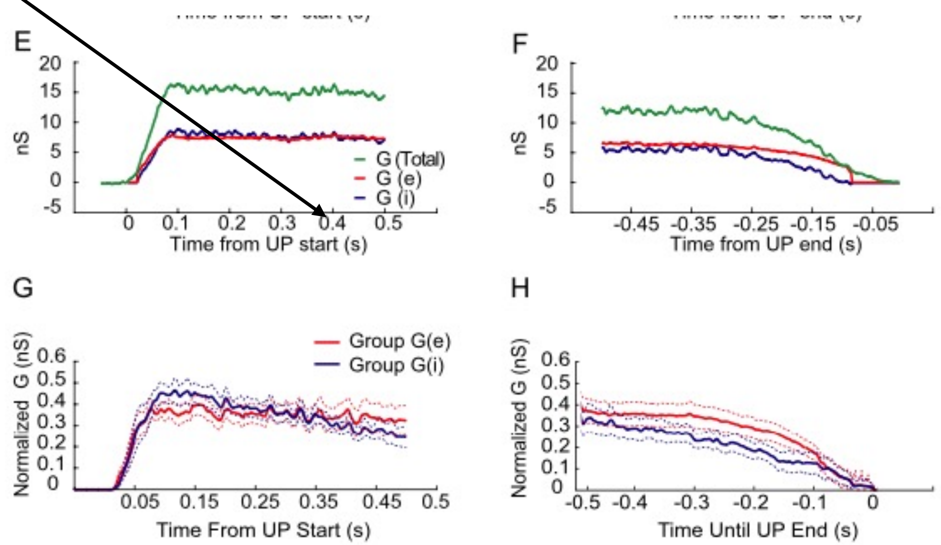
Experimental Evidence

Unit: Seconds

But neuronal dynamics operate at the time scale of ms.

Does the balance exist at finer time scales?





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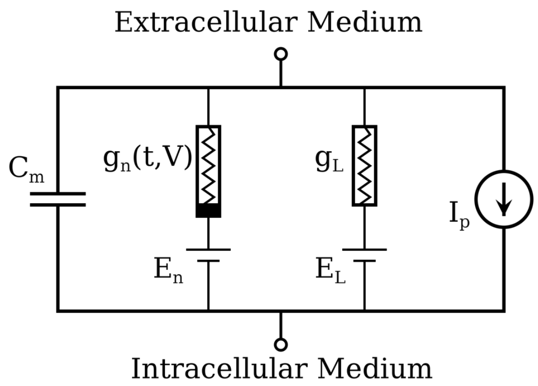


Equivalent circuit of a neuron

Experimental Evidence

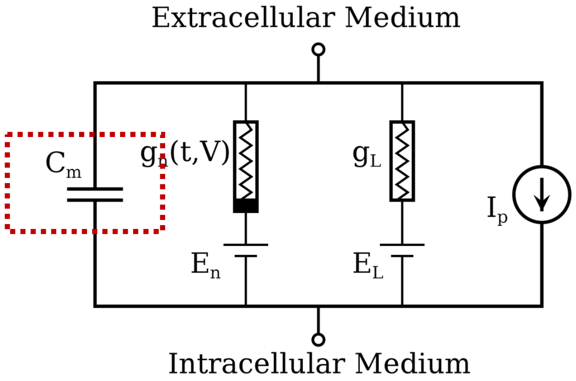
Unit: Seconds

But neuronal dynamics operate at the time scale of ms.

Does the balance exist at finer time scales?

$$R = V_{mem}/I_{inj} \qquad G = 1/R$$

- Capacitors (of the membrane) prevent measuring conductances at finer time scales.



Equivalent circuit of a neuron

Experimental Evidence

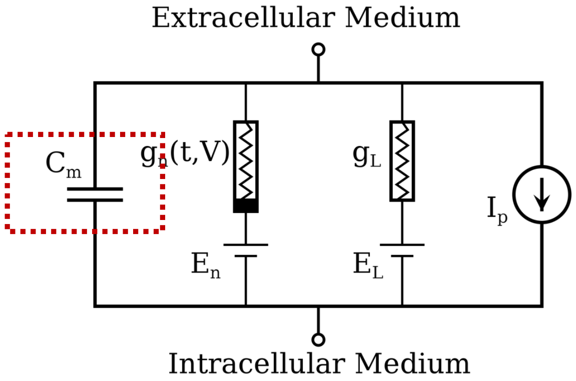
Unit: Seconds

But neuronal dynamics operate at the time scale of ms.

Does the balance exist at finer time scales?

- Capacitors (of the membrane) prevent measuring conductances at finer time scales.
- Cannot simualtaneously measure EPSCs and IPSCs.

$$R = V_{mem}/I_{inj} \qquad G = 1/R$$



Equivalent circuit of a neuron

Experimental Evidence

Published: 30 March 2008

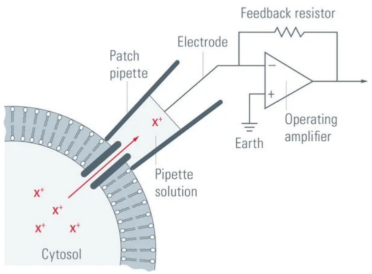
Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked activities

Michael Okun & Ilan Lampl

Nature Neuroscience **11**, 535–537 (2008) | Cite this article

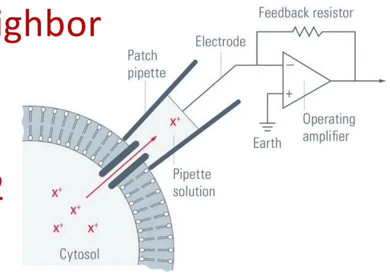
in vivo
Paired patch clamp recording

Neuron 1



neighbor

Neuron 2



Neighboring neurons receive similar inputs.

	Neuron 1	**Neuron 2**
Exp. 1	EPSCs	IPSCs
Exp. 2	IPSCs	EPSCs

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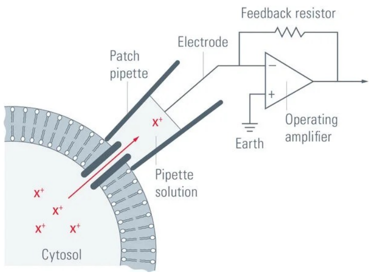

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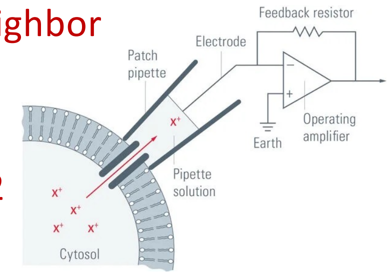
Neuron 2



	Neuron 1	**Neuron 2**
Clamp Voltage	reversal potential of inhibition $\sim -75mV$	reversal potential of depolarization QX-314 added to prevent firing
Membrane potential	Increase reflect EPSCs	Decrease reflect IPSCs

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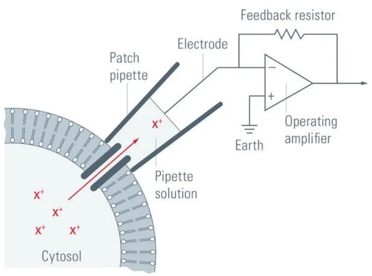
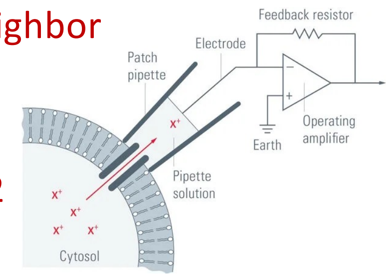


neighbor

Neuron 2



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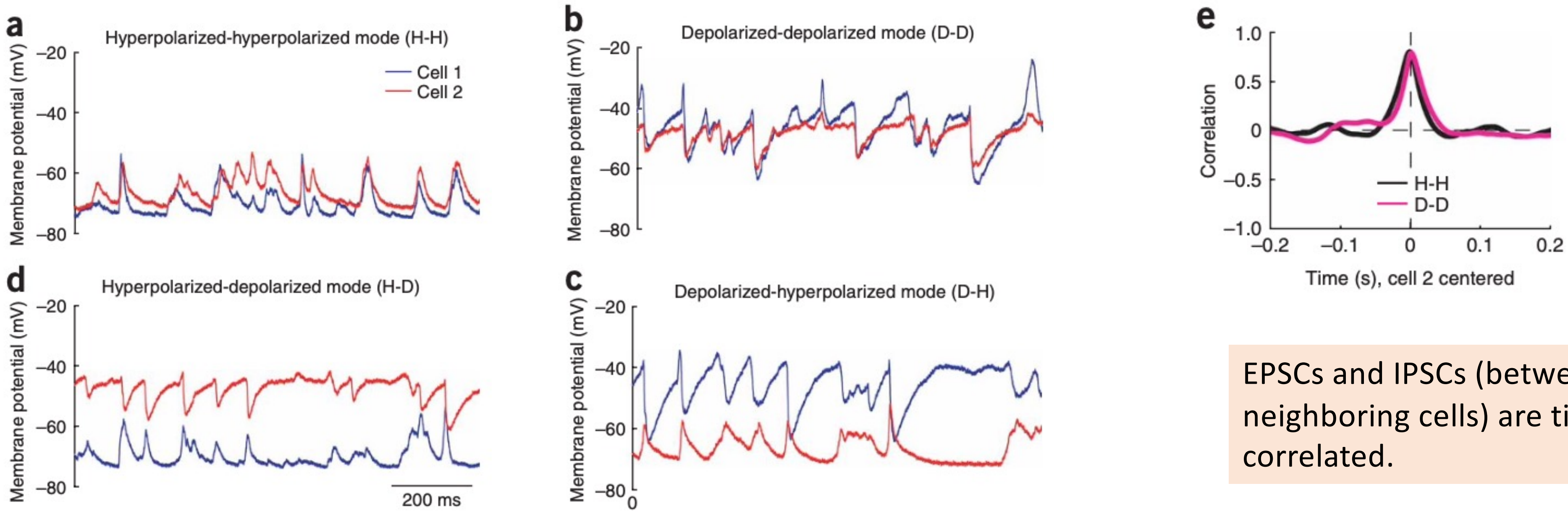

EPSCs and IPSCs (between neighboring cells) are tightly correlated.

Unit: miliseconds

Experimental Evidence

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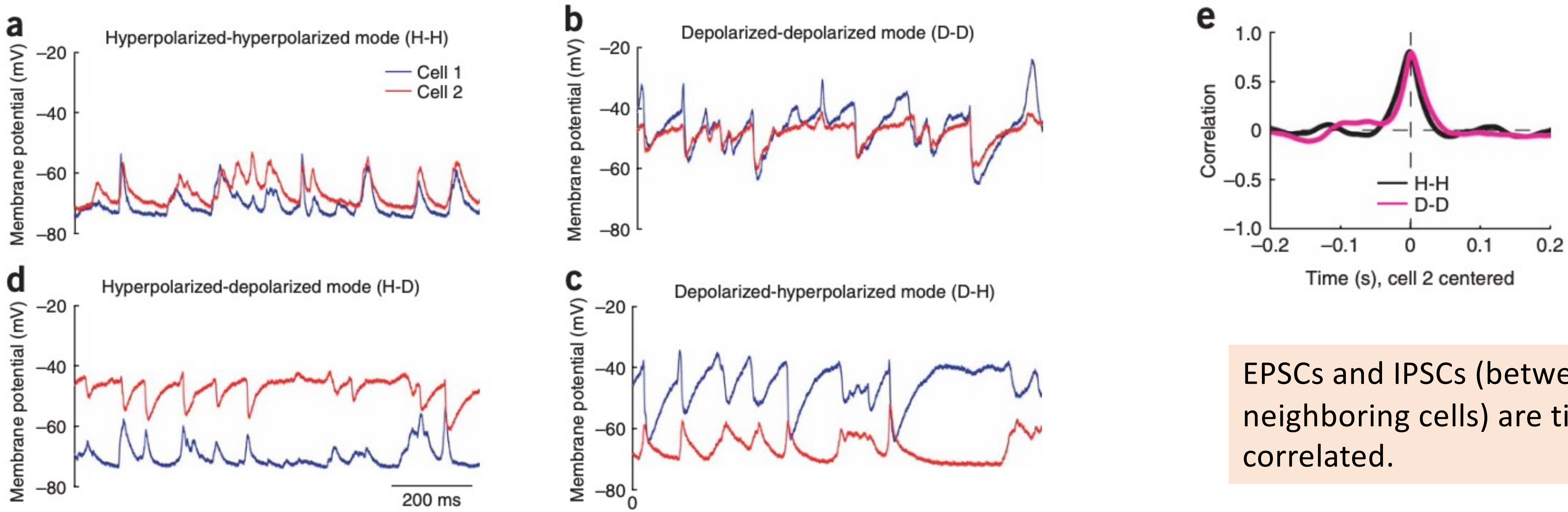
E/I currents are tightly correlated with short delay.

→ **Tight balance**



EPSCs and IPSCs (between neighboring cells) are tightly correlated.

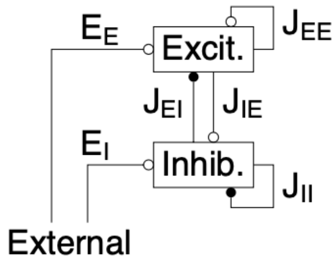
Unit: miliseconds

Take a break.

E-I Balance Model

Chaos in Neuronal Networks with Balanced Excitatory and Inhibitory Activity

C. van Vreeswijk and H. Sompolinsky (Science, 1996)

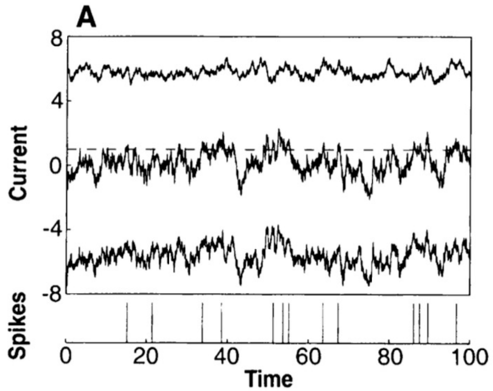


Sparse connectivity $1 \ll K/N \ll 1$

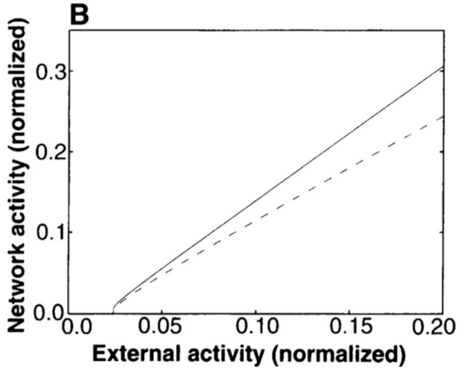
Strong connection strength $J_{kl}^{ij} \sim O(1)$

Threshold $\sim O(\sqrt{K})$

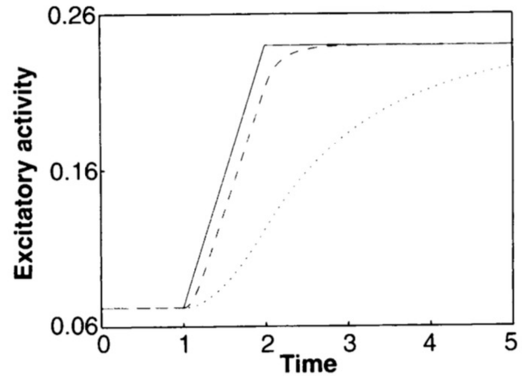
Irregular spike



Linear encoding



Fast response



EI Balance Model

Linear Encoding

北京大學 PEKING UNIVERSITY

Chaotic Balanced State in a Model of Cortical Circuits

C. van Vreeswijk
H. Sompolinsky
Racah Institute of Physics and Center for Neural Computation, Hebrew University, Jerusalem, 91904 Israel

(neural comp., 1998)

Neuron dynamics

$\sigma_k^i(t) = \Theta\left(u_k^i(t)\right)$ $\Theta(.)$ Heaviside function

$\mathrm{u}_k^i(t) = \sum_{l=1}^{2} \sum_{j=1}^{N_l} J_{kl}^{ij}\sigma_l^j(t) + u_k^0 - \theta_k, \quad k = E, I$

$J_{EE} = J_{IE} = 1 \qquad J_E \equiv -J_{EI}; J_I \equiv -J_{II}$

Mean activity $\boldsymbol{m_k^i(t)}$

$m_k^i(t) \equiv < \sigma_k^i(t) >$

Mean-field analysis

$$u_E = (Em_0 + m_E - J_E m_I)\sqrt{K} - \theta_E$$
$$u_I = (Im_0 + m_E - J_I m_I)\sqrt{K} - \theta_I$$

EI Balance Model

Linear Encoding

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Mean-field results

$$u_E = (Em_0 + m_E - J_E m_I)\sqrt{K} - \theta_E$$

$$u_I = (Im_0 + m_E - J_I m_I)\sqrt{K} - \theta_I$$

Balanced state **necessary** condition: $0 < m < 1$ even when K is large

$$\begin{aligned} Em_0 + m_E - J_E m_I &= O\left(1/\sqrt{K}\right) \\ Im_0 + m_E - J_I m_I &= O\left(1/\sqrt{K}\right) \end{aligned} \xrightarrow[K \to \infty]{} \begin{aligned} m_E &= \frac{J_I E - J_E I}{J_E - J_I} m_0 \equiv A_E m_0 \\ m_I &= \frac{E - I}{J_E - J_I} m_0 \equiv A_I m_0 \end{aligned}$$

Linear encoding

<u>Linear encoding property</u> resulted from **linear** summation of E&I current,
regardless of channel and activation non-linearity. (i.e. works for Hodgkin–Huxley model as well)

EI Balance Model

Linear Encoding

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Mean-field results

$$u_E = (Em_0 + m_E - J_E m_I)\sqrt{K} - \theta_E$$

$$u_I = (Im_0 + m_E - J_I m_I)\sqrt{K} - \theta_I$$

Balanced state **necessary** condition: $0 < m < 1$ even when K is large

$$Em_0 + m_E - J_E m_I = O\left(1/\sqrt{K}\right)$$
$$Im_0 + m_E - J_I m_I = O\left(1/\sqrt{K}\right)$$

$\xrightarrow{K \to \infty}$

$$m_E = \frac{J_I E - J_E I}{J_E - J_I} m_0 \equiv A_E m_0$$
$$m_I = \frac{E - I}{J_E - J_I} m_0 \equiv A_I m_0$$

s.t. $m_E > 0, m_I > 0$ $\Rightarrow$

$$\frac{E}{I} > \frac{J_E}{J_I} > 1.$$
$$J_E > 1$$

Necessary condition for EI balance

EI Balance Model

Fast Response

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Dynamics of $m_k^i(t)$ (Ginzhurg & Sompolinsky, 1994)

$$\tau_k \frac{d}{dt} m_k^i(t) = -m_k^i(t) + \Theta\left(u_k^i(t)\right)$$

Rewriting $\boldsymbol{u_k^i(t)}$

$$\Theta\left(u_k^i(t)\right) = F_k(m_E, m_I) = \sum_{n_E, n_I = 0}^{\infty} p_E(n_E) p_I(n_I) \Theta\left(\underbrace{\boxed{\sqrt{K} J_{k0} m_0}}_{\mathcal{O}(\sqrt{K})} + \underbrace{\boxed{\sum_l \frac{J_{kl}}{\sqrt{K}} n_l}}_{\mathcal{O}(\sqrt{K})} - \theta_k\right)$$

$p_l(n_l)$ the prob. of receiving n_l spikes from population l.

$$p_l(n) = \sum_{s=n}^{\infty} \underbrace{\frac{K^s}{s!} e^{-K}}_{\text{The prob. of } s \text{ contacts with pop. } l} \underbrace{\binom{s}{n} m_l^n (1 - m_l)^{s-n}}_{\text{Out of } s \text{ contacts, only } n \text{ are active}} = \frac{(m_l K)^n}{n!} e^{-m_l K}$$

The prob. of s contacts with pop. l

Out of s contacts, only n are active

Poisson distribution with rate $m_l K$

$\Downarrow$

Gaussian distribution $\mathcal{N}(m_l K; m_l K)$

EI Balance Model

Fast Response

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Perturbation analysis

Linearize around the fixed point m_k

$$\delta m_k(t) = m_k(t) - m_k$$

$$\tau_k \frac{d}{dt}\delta m_k(t) = -\delta m_k(t) + \sqrt{K}\sum_{l=1,2} f_{kl}\delta m_l(t)$$

Sol. $\delta m_k(t) = \delta m_{k,1}\exp(\lambda_1 t) + \delta m_{k,2}\exp(\lambda_2 t)$ $\lambda_1, \lambda_2 \sim \mathcal{O}(\sqrt{K})$

Setting $Re(\lambda_1) < 0, Re(\lambda_2) < 0$

Gives $\tau_k < \tau$ The precise value of τ has a complicated dependence on the system parameters.

When $\boldsymbol{\tau_k < \tau}$, perturbation will decay extremely fast on the order of $\boldsymbol{\mathcal{O}(1/\sqrt{K})}$

EI Balance Model

Fast Response

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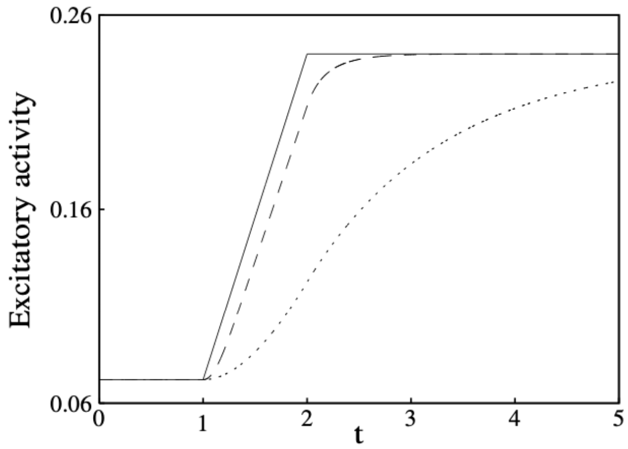
Perturbation analysis

$\tau_k < \tau$ The precise value of τ has a complicated dependence on the system parameters.

When $\tau_k < \tau$, perturbation will decay extremely fast on the time scale of $\mathcal{O}(1/\sqrt{K})$

Fast response to external changing stimulus



Summary

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- The historical background of the EI balance model.
  - Rate coding vs. temporal coding;
  - Neurons as integrator vs. as coincidence detector.

- Experimental evidence
  - Patch clamp experiments, both *in vitro* and *in vivo*.
  - Paired patch clamp → tight balance

- Theorectical EI balance model
  - Irregular spike pattern
  - Linear encoding
  - Fast response