Neuronal Integration of Synaptic Input in the Fluctuation Driven Regime

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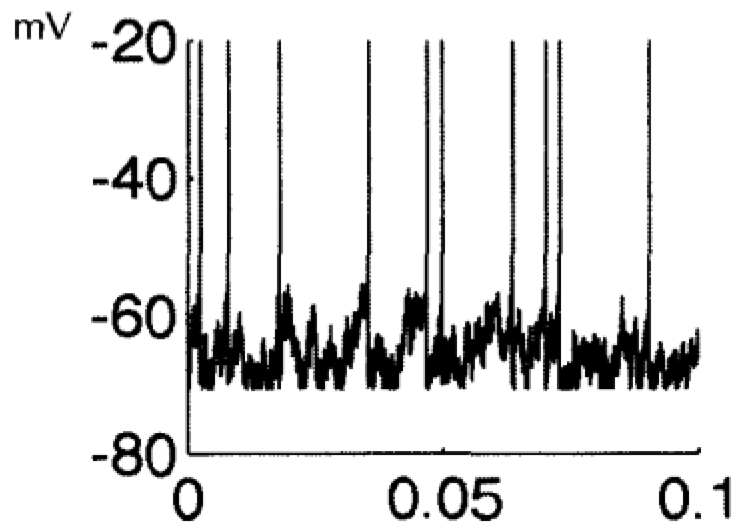
V_m

Cortical Activity in Sensory Processing

- Sensory specific cortical neurons are bombarded with synaptic input during sensory processing resulting in
  - A change in integrative properties of the neuron
  - Strong fluctuations in membrane potential (Vm) predominantly without Action Potentials due to balanced excitation and inhibition



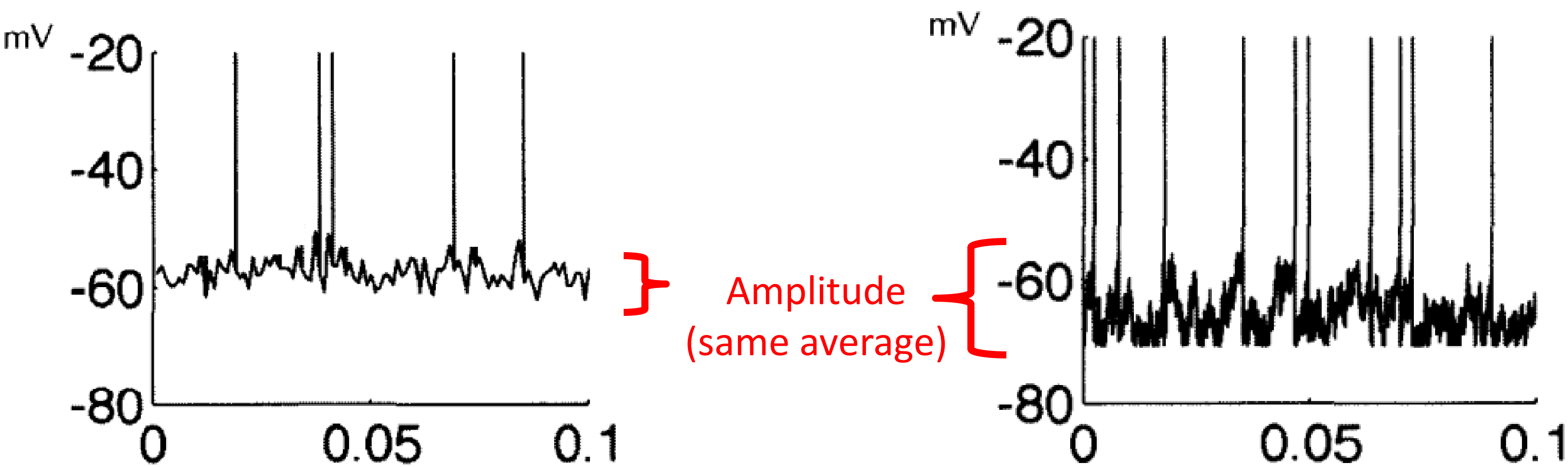
Non-monotonic Activity

- The membrane potential fluctuation and firing rate of sensory cortical neurons is driven by both inhibitory and excitatory inputs.
- At some point the relationship between co-occuring inhibitory and excitatory inputs, and membrane potential and firing rate changes direction (increase ➔ decreases) implying a non-monotonic relationship between input and output.

Model of Irregular Firing in Cortical Neurons

Fluctuation Driven Firing

- Shadlen and Newsome (1994, 1998) propose that *increasing* balanced excitatory and inhibitory input results in a constant average membrane potential, but with higher amplitude fluctuations and therefore a greater rate of firing due to membrane potential more regularly crossing threshold.



Unaccounted for Shunting Effects

- The previous model does not account for observed changes in membrane properties resulting from synaptic events, most importantly for this paper's purposes, the effects of shunting do to increased membrane conductance.
- Assuming a fluctuation-driven regime, this study explores integration of synaptic events, membrane potential fluctuation, and firing rate (FR) in response to
  - Balanced excitatory and inhibitory Input modeled as *current*; based on previously explored models
  - Balanced excitatory and inhibitory Input modeled as *conductance*
  - *Semi-independently varying* excitatory and inhibitory Input modeled as *conductance*

Modeling Synaptic Inputs as *Current* Sources

$U(t)$: free membrane potential

U_r :resting membrane potential

G_l : membrane leak conductance

$\tau_{\mathrm{m}} = C/G_l$

$\lambda_e \ \lambda_i$:Event (current) input rate (excitatory, inhibitory); following poison statistics.

t_k :time of occurrence of *excitatory* input

t_j : time of occurrence of *inhibitory* input

$A_e > 0,\ A_i < 0$:peak synaptic current (excit,inihib)

$$H(x) = \begin{cases} 0 & \text{for } x < 0 \\ 1 & \text{for } x \geq 0. \end{cases}$$

(Linear differential equation with constant coefficients)

This equation includes all membrane parameters needed to describe current flowing across the membrane

$$\tau_{\mathrm{m}} \frac{d}{dt} U(t) = -[U(t) - U_r] + \frac{I(t)}{G_l}$$

I_t is induced by both excitatory and inhibitory synaptic events

$$I(t) = I_e(t) + I_i(t) = \sum_j \mathrm{EPSC}(t - t_j) + \sum_k \mathrm{IPSC}(t - t_k),$$

$$\mathrm{EPSC}(t) = A_e \frac{t}{\tau_e} e^{1 - t/\tau_e} H(t) \qquad \mathrm{IPSC}(t) = A_i \frac{t}{\tau_i} e^{1 - t/\tau_i} H(t)$$

Membrane response to single PSC

$$\tau_{\mathrm{m}} \frac{d}{dt} U(t) = -[U(t) - U_r] + \frac{\mathrm{PSC}(t)}{G_l} \quad \text{with } U(0) = U_r$$

Time course of PSP

$$\mathrm{PSP}(t) = \frac{A_s e}{C \tau_s} \left[\frac{-t e^{-t/\tau_s}}{1/\tau_s - 1/\tau_{\mathrm{m}}} + \frac{e^{-t/\tau_{\mathrm{m}}} - e^{-t/\tau_s}}{(1/\tau_s - 1/\tau_{\mathrm{m}})^2} \right] H(t)$$

$$\mu(U) = U_r + \lambda_e \int \mathrm{EPSP}(t) dt + \lambda_i \int \mathrm{IPSP}(t) dt$$

$$\sigma^2(U) = \lambda_e \int \mathrm{EPSP}(t)^2 dt + \lambda_i \int \mathrm{IPSP}(t)^2 dt.$$

Membrane Parameters:

C = 250 pF, G_l = 1/60 uS, U_r = -70 mV, $U_\theta = -50$ mV

Synaptic Parameters*:

$A_e > 0,\ A_i < 0$ = 390.5 pA, -74 pA,

$\tau_e = 0.2$ msec, $\tau_i = 2$ msec

*Tarczy-Hornoch et al. (1998, 1999)

Current Source Model

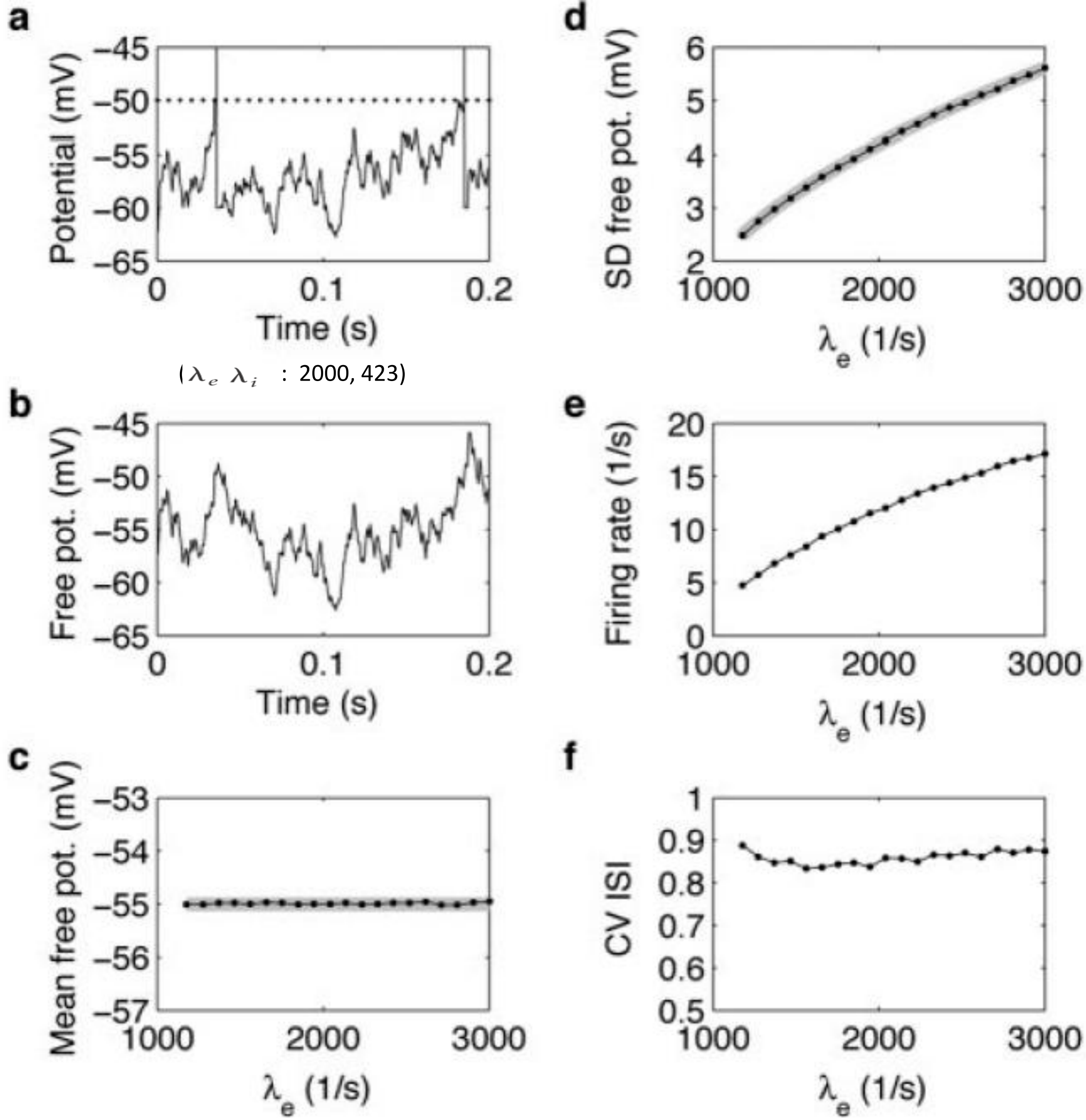


Figure 1. Free membrane potential fluctuations and firing rate of the model neuron with current input increase monotonically with the balanced increase of excitation and inhibition. *a*,

Modeling Synaptic Inputs as *Transient Conductances*

This equation includes all membrane parameters needed to describe current flowing across the membrane, in the case of conductance based synapses

$$\tau_{\text{eff}}(t)\frac{d}{dt}U(t) = -U(t) + \frac{U_r G_l + U_e G_e(t) + U_i G_i(t)}{G_{\text{tot}}(t)}$$

$g_e(t)$ and $g_i(t)$: represent membrane conductance changes elicited by a single excitatory or inhibitory synaptic event

$$g_e(t) = B_e\frac{t}{\tau_e}e^{1-t/\tau_e}H(t),\ G_e(t) = \sum_j g_e(t - t_j).$$

$$g_i(t) = B_i\frac{t}{\tau_i}e^{1-t/\tau_i}H(t),\ G_i(t) = \sum_k g_i(t - t_k)$$

$$\mu(G_e) = \lambda_e\int g_e(t)dt = \lambda_e B_e \tau_e e$$

$$\mu(U) \approx \frac{U_r G_l + U_e\mu(G_e) + U_i\mu(G_i)}{\mu(G_{\text{tot}})},$$

$$\mu(G_i) = \lambda_i\int g_i(t)dt = \lambda_i B_i \tau_i e.$$

with $\mu(G_{\text{tot}}) = G_l + \mu(G_e) + \mu(G_i)$.

$$\sigma^2(U) \approx \lambda_e\int \text{EPSP}(t)^2 dt + \lambda_i\int \text{IPSP}(t)^2 dt.$$

Membrane response to single PSC
(in the presents of synaptic bombardment)

$$\tilde{\tau}_{\text{eff}}\frac{d}{dt}U(t) = -[U(t) - \mu(U)] - \frac{[U(t) - U_s]g_s(t)}{\mu(G_{\text{tot}})} \text{ with } U(0) = \mu(U),$$

Time course of PSP

$$\text{PSP}(t) \approx [U_s - \mu(U)]\frac{B_s e}{C\tau_s}\left[\frac{-te^{-t/\tau_s}}{1/\tau_s - 1/\tilde{\tau}_{\text{eff}}} + \frac{e^{-t/\tilde{\tau}_{\text{eff}}} - e^{-t/\tau_s}}{(1/\tau_s - 1/\tilde{\tau}_{\text{eff}})^2}\right]H(t).$$

$U(t)$: free membrane potential

U_r :resting membrane potential

G_l : membrane leak conductance

$\tilde{\tau}_{\text{eff}} = C/\mu(G_{\text{tot}})$ (effective membrane time constant)

$G_e(t)$ and $G_i(t)$: synaptic conductances *Input* (excit., inhib.)

$\lambda_e\ \lambda_i$: Event (conductance) input rate

U_e and U_i : synaptic reversal potentials (excit., inhib.)

$$G_{\text{tot}}(t) = G_l + G_e(t) + G_i(t)$$

t_k :time of occurrence of *excitatory* input

t_j : time of occurrence of *inhibitory* input

B_e and B_i : peak synaptic *conductance* (excit,inhib)

Membrane Parameters:
C = 250 pF, G_l = 1/60 uS, U_r = -70 mV, $U_\theta = -50\,\text{mV}$ $\quad H(x) = \begin{cases} 0 & \text{for } x < 0 \\ 1 & \text{for } x \geq 0. \end{cases}$

Synaptic Parameters:
B_e and B_i = 7.1 nS, 3.7 nS,
U_e and U_i = 0 mV, -75mV
$\tau_e = 0.2$ msec, $\tau_i = 2$ msec.

Modeling Synaptic Inputs Cont.

The previous equations can also be used to infer current or conductance input rates from post synaptic membrane parameters. The same equations are used to derive balanced inhibitory inputs.

Current Input

$$\lambda_i = -\frac{\int \mathrm{EPSP}(t)dt}{\int \mathrm{IPSP}(t)dt}\lambda_e - \frac{U_r - \mu(U)}{\int \mathrm{IPSP}(t)dt}.$$

Conductance Input (slope determination depends on membrane potential level)

$$\lambda_i \approx -\frac{[U_e - \mu(U)]\int g_e(t)dt}{[U_i - \mu(U)]\int g_i(t)dt}\lambda_e - \frac{[U_r - \mu(U)]G_l}{[U_i - \mu(U)]\int g_i(t)dt}$$

Complete Spiking Model (Troyer & Miller 1997)

A spike was generated any time the membrane potential hit threshold: $U_\theta = -50\,\mathrm{mV}$
To simulate refractory period, the potential was held at -60 mV for 2ms

Firing Rate Model (Conductance)

$$r \approx \frac{1}{\tilde{\tau}_{\mathrm{eff}}}\int_{U_\theta}^{\infty} P(U)dU, \qquad r \approx \frac{1}{2\tilde{\tau}_{\mathrm{eff}}}\mathrm{erfc}\left[\frac{U_\theta - \mu(U)}{\sqrt{2}\sigma(U)}\right]$$

Transient Conductance Model

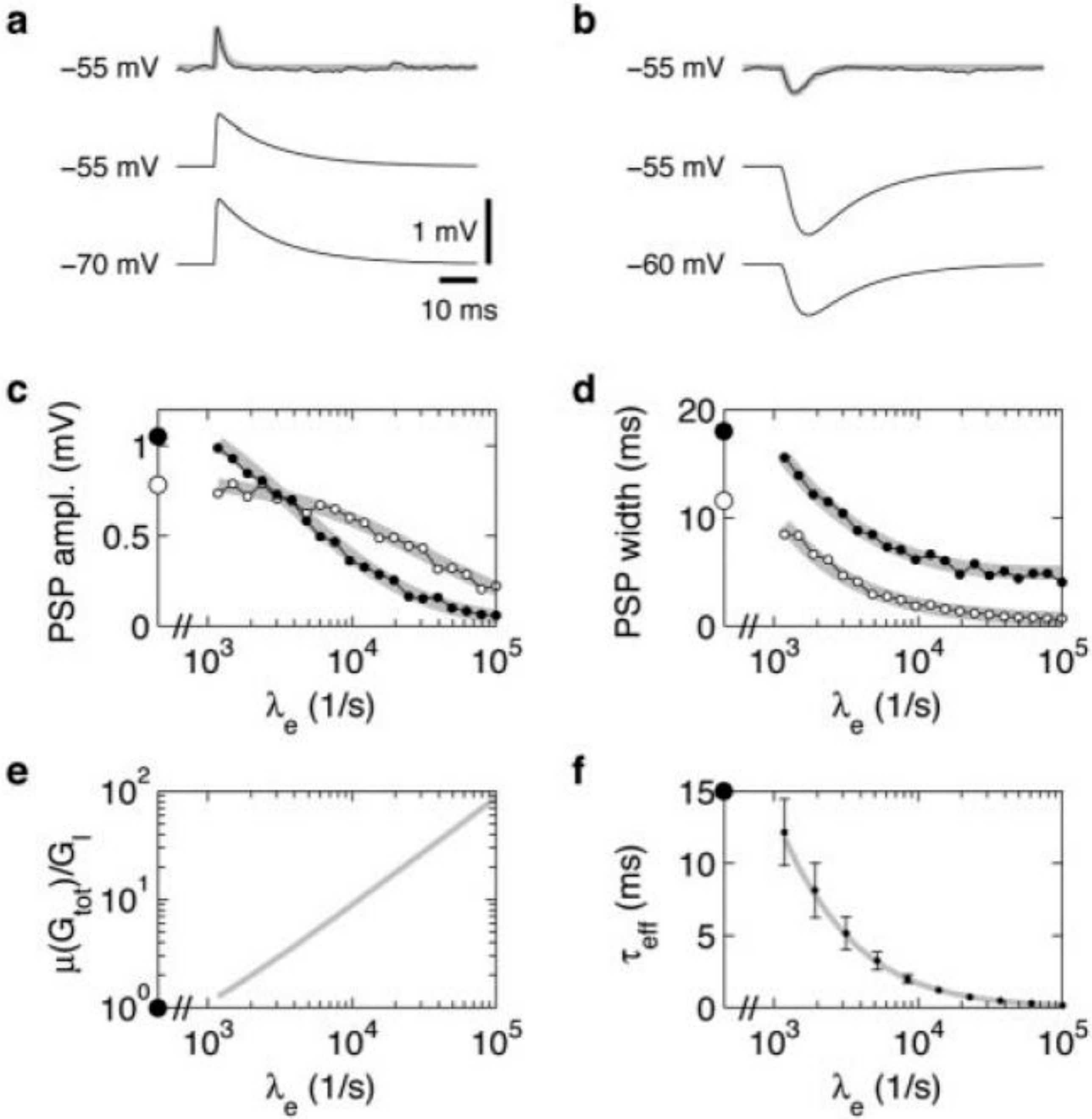


Figure 2. Amplitude and width of PSPs decrease with increasing synaptic bombardment

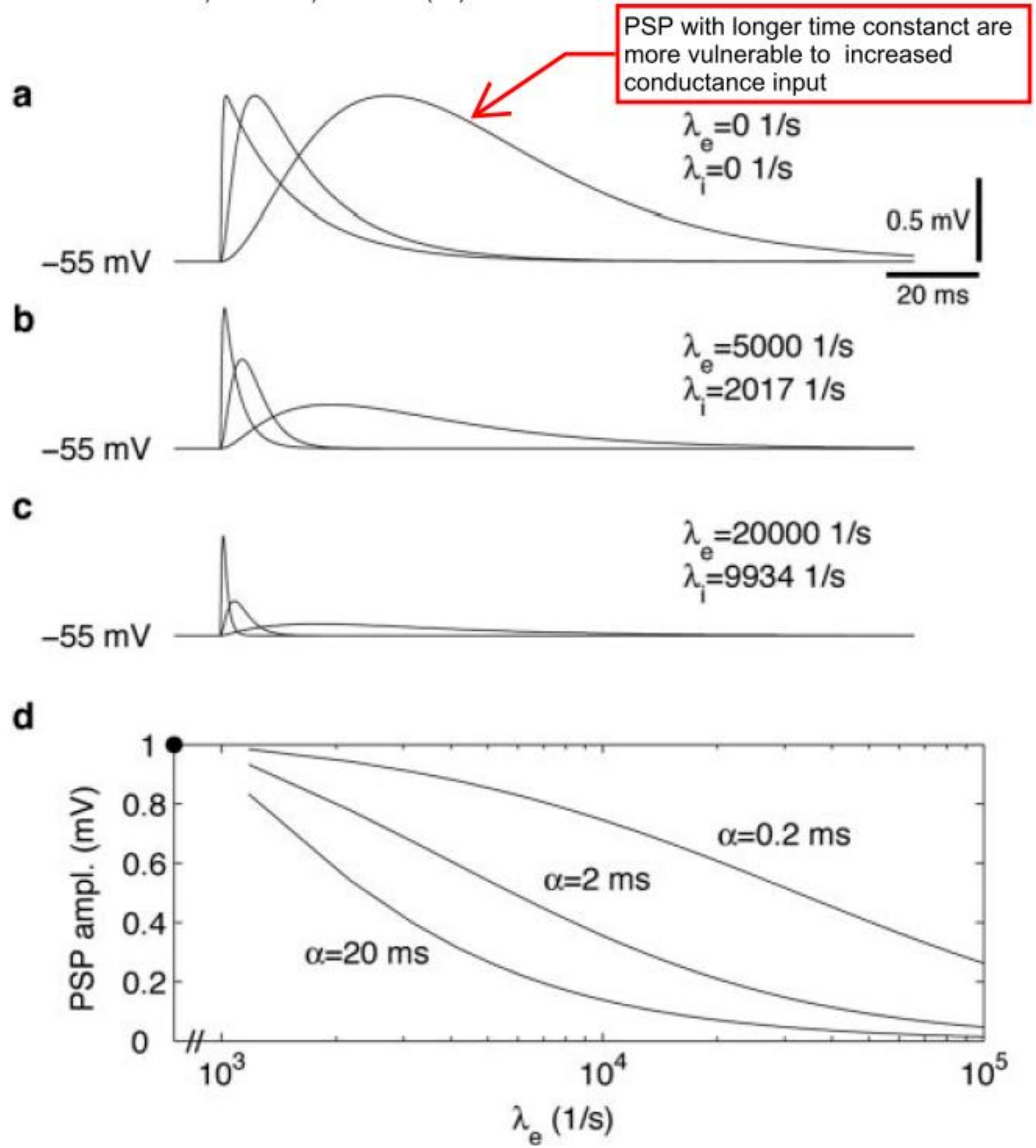


Figure 3. Amplitude of fast PSPs is less vulnerable to synaptic bombardment.

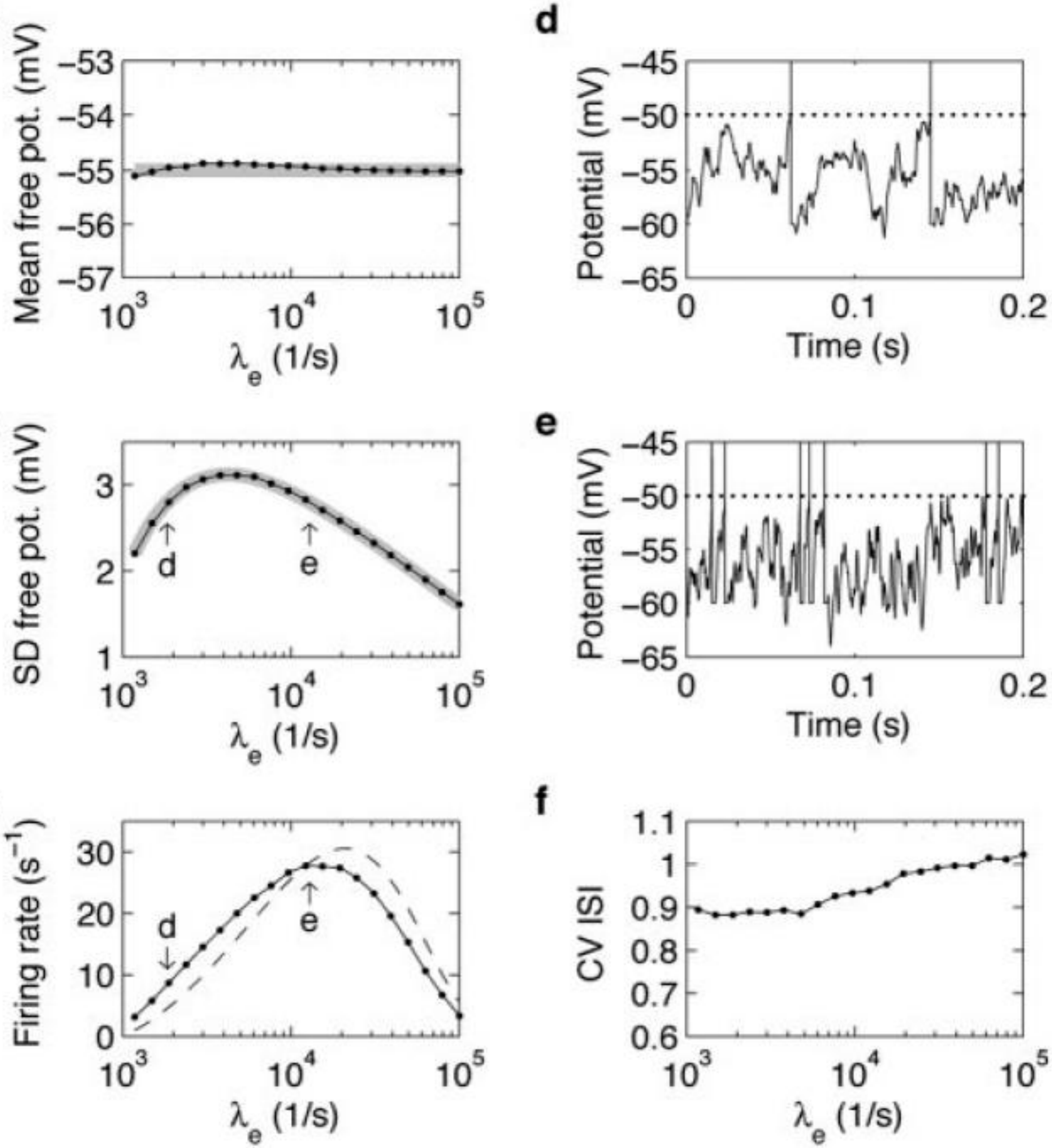


Figure 4. Free membrane potential and firing rate of the model neuron with conductance input are non-monotonic functions of the balanced increase of excitation and inhibition.

Model vs In Vivo Cortical Data

- Amplitude of membrane fluctuation and input rate(λ_e λ_i)
  - Assuming between 10^3 and 10^4 active synapses per cortical neuron, the maximal membrane potential fluctuation was achieved with an input rate of 1 spike per second per synapse. Similar to what is found in ongoing cortical activity
- Amplitude of membrane fluctuation and conductance
  - The conductance required to achieve maximal membrane fluctuation was five fold greater than the leak conductance. This is in the lower range of what has been reported (i.e. 3-70 fold increase)

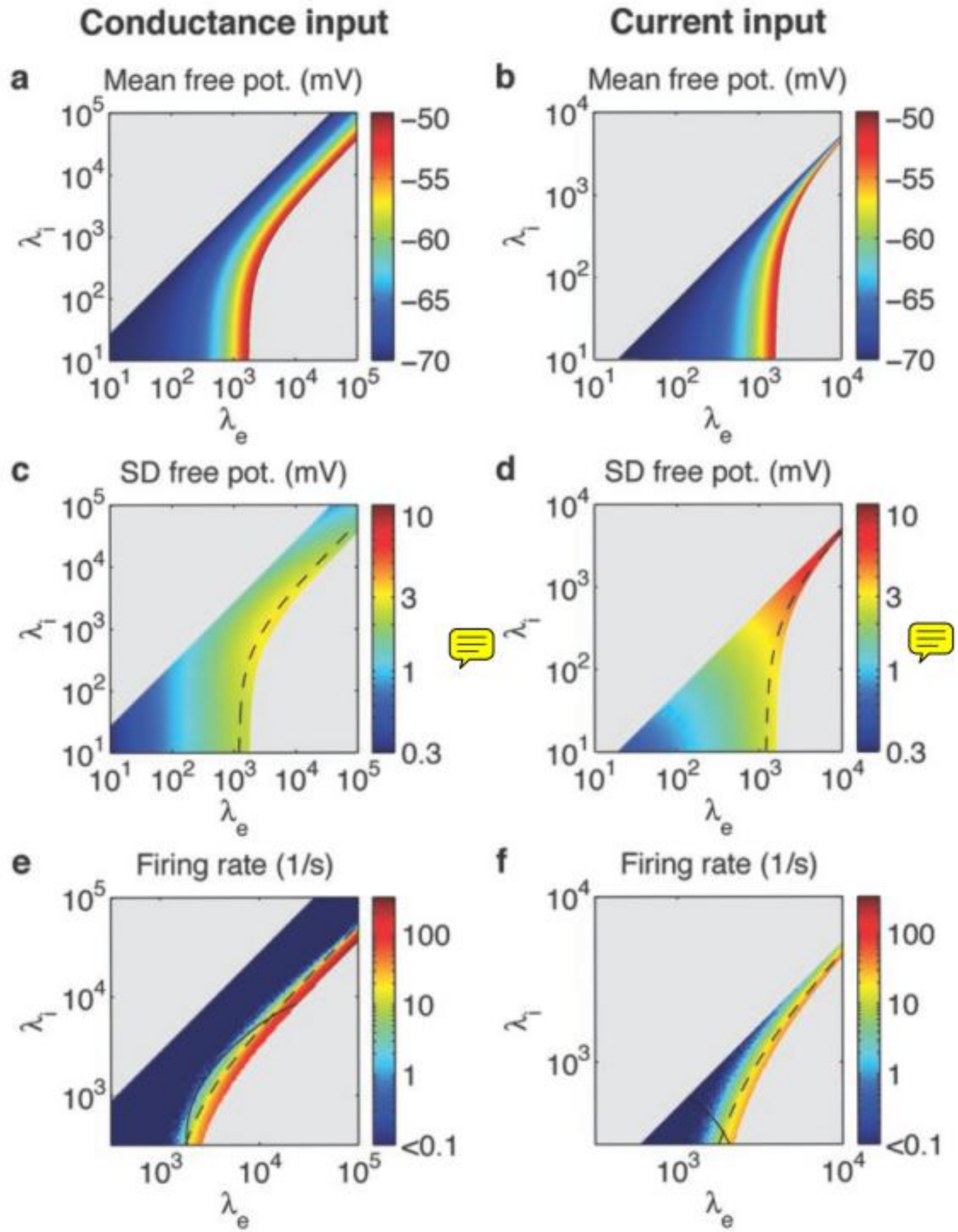


Figure 5. Free membrane potential and firing rate as a function of excitatory (λ_e) and inhibitory (λ_i) input rates, for the model neuron with conductance input (left) and with current input (right)

Physiological Relevance

- V1 neurons where found to have membrane potential amplitude fluctuations (SD) of 3-4 mV varying with object contrast and orientation. Model fluctuations where maximal at ~3 mV
- The same study also showed that the mean amplitude of fluctuations (averaged across trials) did not “change much” with varying stimuli.
- Two independent studies found that visual neurons only produce spikes at mean membrane potentials less than 10 mV from threshold. This was the same cutoff found for the conductance model regardless of the absolute level of synaptic bombardment.
- However other studies have suggested that conductance input has a subtractive or divisive affect on post synaptic output

Conclusion

Membrane fluctuation rate and firing rate activity in response to *balanced* excitatory and inhibitory conductance input

- Increase Membrane fluctuation rates are overpowered by increased membrane conductance at higher input rates
- Membrane fluctuation amplitude (SD) do not increase with increasing (balanced) excitatory and inhibitory input rates monotonically, but instead decrease for higher input rates
- Firing rate also has a non-monotonic relationship to input rates but continues to increases with higher input rates beyond the point that membrane fluctuation rate begins to decline
  - This increased firing continues due to the reduced effective time constant increasing the likelihood of fluctuations crossing threshold; this occurs in spite of membrane fluctuation beginning to decrease at higher input rates

$\lambda_e \lambda_i$ $\lambda_e \lambda_i$ $\lambda_e \lambda_i$