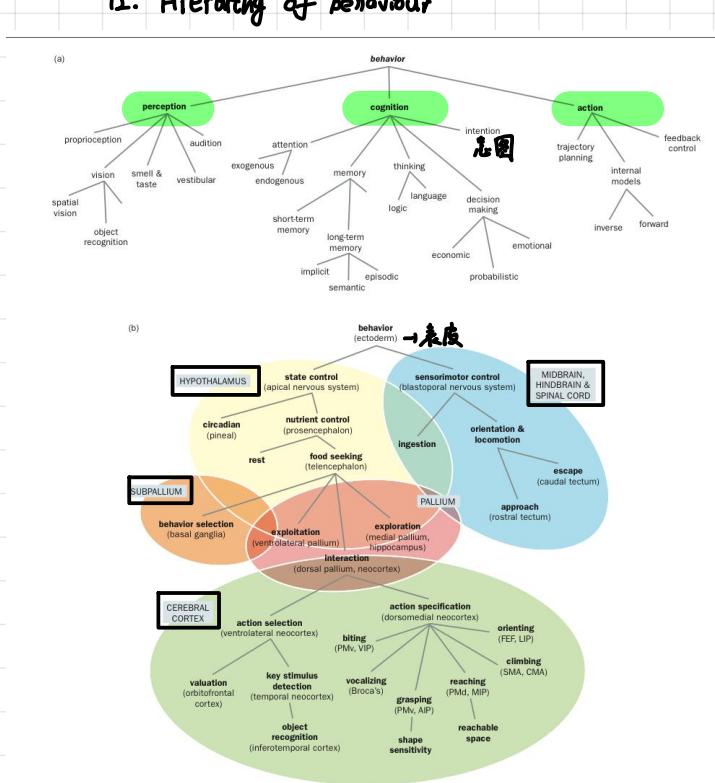
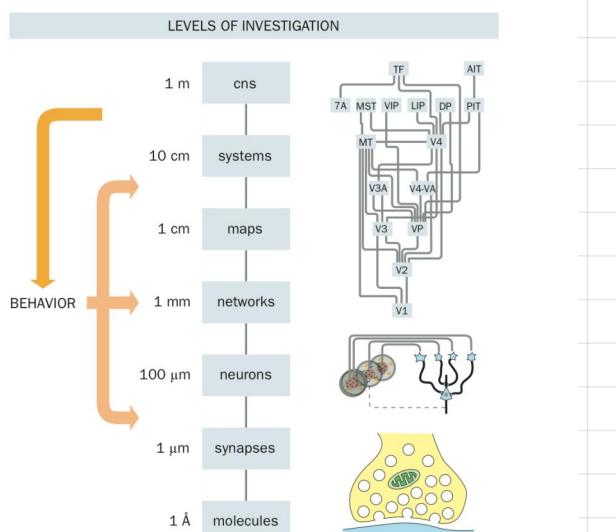


Chapter I : Understanding the Cognitive Brain

1. Two kinds of (basic) philosophical questions:
 - ① one aims at providing insights from a neuroscientific perspective into translating puzzles such as **consciousness**
 - ② the other address the field's **epistemology question** like what constitutes an explanation in brain science
2. **Epistemology questions:** what does it mean to understand the brain and its functions
how can we improve our philosophical methodologies in neuroscience.
3. A most important issue \Rightarrow the relationship between behaviour and neural circuit.
 - A popular guide to tackle the problem (by David Marr)** \Rightarrow
 - (1) formulate the problem and identify its **normative solution**
 - (2) search for computational algorithms that accomplish the optimal solution
 - (3) elucidate **hardware implementations** of such algorithm in the brain

↓
Marrian Framework
4. Unidirection function \rightarrow algorithm \rightarrow implementation
5. "From inside out approach" \rightarrow the brain is as active "at rest" in the absence of obvious external stimulation as during task
 - \hookleftarrow conceptualization of brain merely as an input (stimulus) - output (behaviour) information processing system seems quite limited
6. The viewpoint of behaviour primacy is linked to the traditional metaphor of brains as computers.
 - \hookleftarrow "multiple realizability" \rightarrow thoroughly criticized on epistemological grounds.
7. Limitation in "multiple realizability" \rightarrow we cannot limit ourselves to consider only one "target" function \rightarrow for PFC, we need to first identify a long list of various cognitive processes, then investigate how many ways they can actually all be realized in a single neural system
8. Brain functions are underpinned by neuroanatomy (connectome)
 - \hookleftarrow we need a profound knowledge about the inner workings of its biological components.
9. Behavior - to - brain \Rightarrow "Top - down"
10. CNS on multiple spatial scales



13. Neither the mind nor the brain can be assigned to a single level in a linear Mervian hierarchy

↳ each is a rich world with its own multi-level structure

14. The connections between the two societies are defined through a web of complex interactions across many levels of the two hierarchies of brain and behaviour.

15. The goal of neuroscience is to understand the biological brain mechanisms that causally explain behaviour and cognition

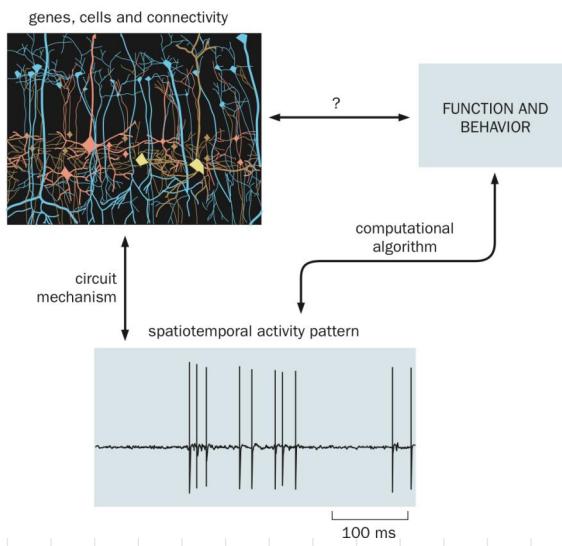
★ 全面

16. To understand the PFC, one would attempt an all-encompassing normative theory the must explain all PFC function



Theory and mathematical models in neuroscience should and eventually will play a similar role as theoretical physics does in physics

18. Theory is needed to: (a) identify computational algorithms carried out by a given empirically measured neural population activity and to assess whether it can explain behaviour;
(b) elucidate the underlying circuit mechanism, i.e. how the observed neural signals arise from genes, cells and connectivity



19. Cross-level mechanistic understanding

20. Brain \Rightarrow collective phenomena of interacting neurons described as a large and complex nonlinear dynamical system

21. Brain is plastic \rightarrow behaviour generated by the brain in turn alters the nervous system on multiple spatial scales from synapses and neurons to circuits

↳ Challenge: achieve understanding across levels for complex systems.

22. To meet this challenge, eschew the computer as a metaphor for the brain.
↓
Yet to be
defined

23. ★ Treating a neural circuit as a dynamic system (not just calculation)

→ The framework of dynamical systems provides a natural mathematical language for describing complex neural population spatiotemporal activity patterns.

24. A dynamic system describes \star how the current state of a system and interactions between constituent units predict the future evolution of the system over time.

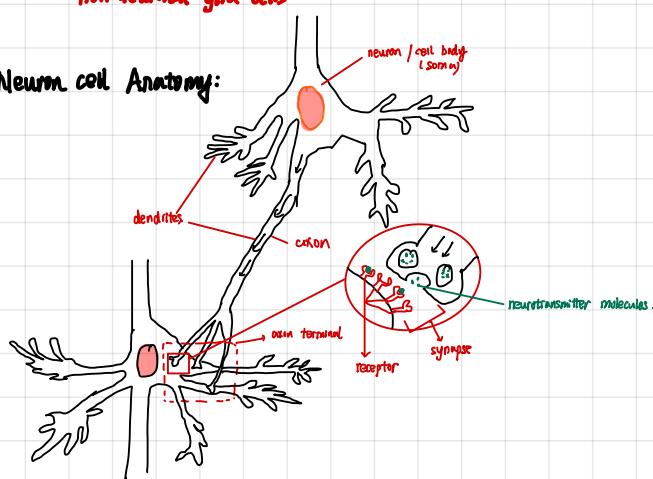
25. Dynamic system \Rightarrow  emergent phenomena
+
capture properties of constituent units \Rightarrow "cross-level understanding"

Chapter II: Neurons and Synapses

1. Brain

{ nerve cells
non-neuronal glia cells

2. Neuron cell Anatomy:



3. Primate Prefrontal Cortex (PFC) → "the CEO of the brain" in primates

4. A good starting point ⇒ consider microcircuits within a brain region dedicated to a specific function *

5. neocortex ⇒ plays a major role in higher brain functions.
↓

{ excitatory neurons increase the activity of target neurons (majority ⇒ pyramidal cells (pyramid-shaped soma))
inhibitory neurons ⇒ suppressing target neurons → interneurons → virtually all of them make connections locally within a cortical region

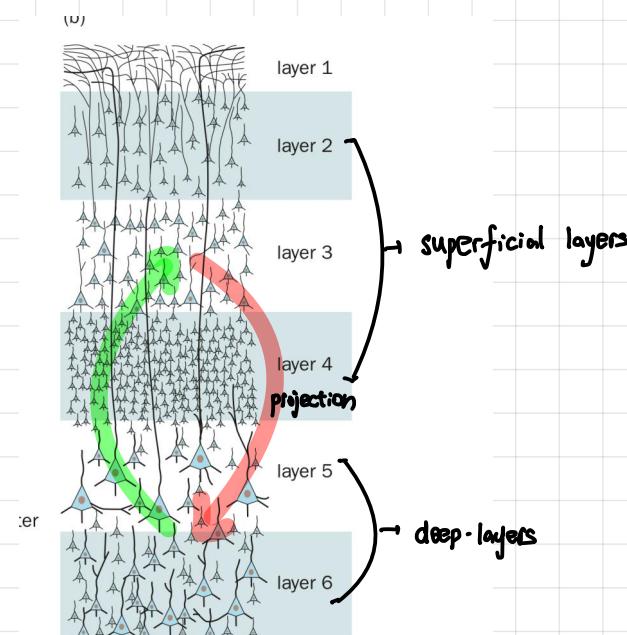
6. Excitatory : Inhibitory ratio varies significantly in different cortical regions.

7. In human, inhibitory neurons →

{ ~30% in PFC

{ ~15% in visual area (V1)

8. Cortical Microcircuit → Laminar Structure



9. LGN: lateral geniculate nucleus

10. Feedback loops within cortical microcircuit plays a role in explaining neural population dynamics and cognitive functions

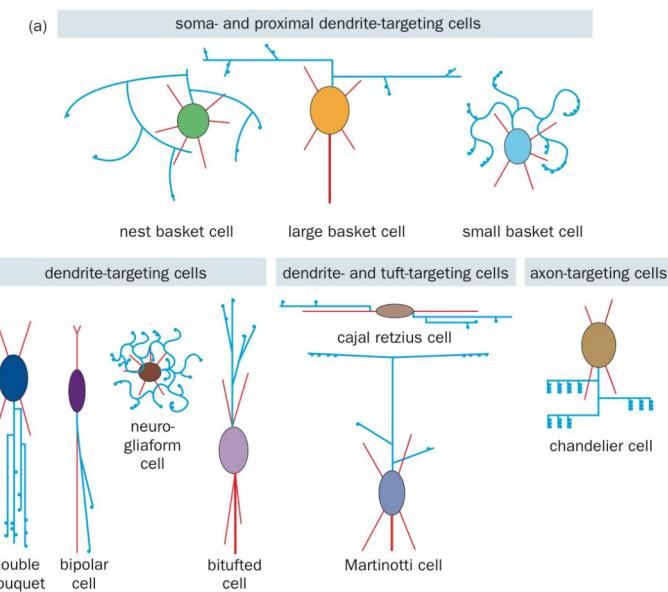
11. Main anatomical properties of inhibitory interneurons. →

12. Three distinct inhibitory neuron cell:
according to projections and protein expressions

PV
① target the perisomatic region of pyramidal cells and act to control spiking output of excitatory neurons
② Soma-targeting cells (STCs) express the calcium binding protein parvalbumin (PV)

SST (SST/CB)
① either express somatostatin (SST) or the calcium binding protein calbindin (CB)
② target pyramidal dendrites
③ control inputs onto excitatory neurons

VIP
① express either vasoactive intestinal peptide (VIP) or the calcium-binding protein calcitonin gene-related peptide (CGRP)
② target SST/CB inhibitory neurons



Form a disinhibitory motif → represent a general feature of cortical microcircuits.

The fourth major type of inhibitory neurons

① not express PV, SST or VIP
② constitute 90% of interneurons in layer 1 with various firing patterns
③ in other layers, either express neuropeptide Y and mediate GABA_A receptor-dependent slow inhibition, or express peptide CCK and underline the cannabinoid action in the brain.

13. Neuronal operations are shaped by chemical substances.

14. [idea] chemical process → describe single-neuron adaption mediated by intracellular calcium ions.

15. Four types of major cells to be modelled: excitatory pyramidal cells and 3 inhibitory subtypes

16. The electrical signaling of a neuron is determined by voltage difference across its membrane:

$$V = V_{in} - V_{out}$$

where V_{in} and V_{out} are voltages inside and outside the neurons.

The levels of V_{in} and V_{out} are determined by concentrations of ions (Cl^-, Na^+, K^+, Ca^{2+})

7. V related to spatial and temporal location

$$V(x, t)$$

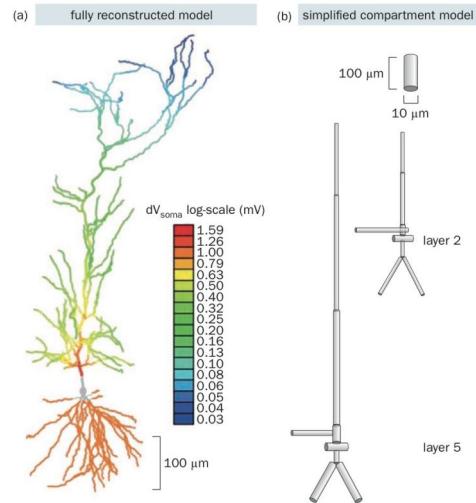
8. A morphologically fully reconstructed pyramidal neuron may be modeled with hundreds of compartments \rightarrow each assumed

to be **isopotential** \rightarrow simplified compartment model:

\hookrightarrow capture the basic spatial structure of a neuron with apical and basal dendrites, down to just three or two compartments

 **my inspiration** An important idea in computational neuroscience is to **simplify**. We need

to find a simplified (or the most simplified) model that is biologically plausible to use math and other method to capture the basic principals.



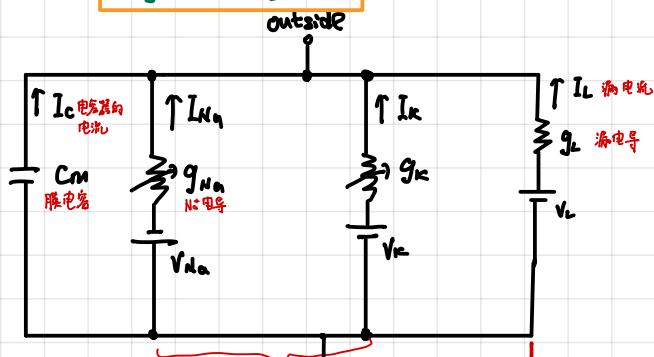
When distinct dendritic versus somatic signaling is not the main focus



\hookrightarrow "point neuron" with a single compartment

\hookrightarrow the Hodgkin-Huxley conductance-based model (integrate-and-fire model)

Hodgkin-Huxley model



20. Neuronal Membrane as an RC circuit.

• Neuronal Membrane \rightarrow a fatty lipid bilayer \rightarrow not permeable to charged molecules \rightarrow capacitor with a capacitance C

• Charge stored in capacitor $Q = CV$

• Capacitive current: $\frac{dQ}{dt} = C \frac{dV}{dt}$

• Opening an ion channel leads to a current: $I = g(V - V_{\text{rev}})$ (unit: $\mu\text{A}/\text{cm}^2$)

when g is a conductance ($\frac{1}{\Omega}$) per unit area cm^2 (MS/cm^2)

V_{rev} is a reversal potential

"driving force"

• Given a membrane with area $A \Rightarrow G = gA$, $I = G(V - V_{\text{rev}})$ (unit: nA)

quantifies the strength of an ion current

• V_{rev} depends on the selective permeability of an ion channel and the intracellular and extracellular concentrations of ions that can pass through the channel.

• When a channel is permeable for a single type of ions \Rightarrow Nernst equation: $V_{\text{rev}} = \left(\frac{RT}{F}\right) \ln([C_{\text{ext}}]/[C_{\text{in}}])$

$\hookrightarrow R$: the universal gas constant F : Faraday constant

T : temperature

(Equ 2.2)

Z : the charge of an ion

- K^+ : inside \rightarrow outside $\Rightarrow V_K < 0$ ($\approx -80\text{mV}$)

Ca^{2+}, Na^+ : inside $<$ outside $\Rightarrow V_{Na} > 0$ $\cdot V_{Ca} > 0$
 ($\approx +50\text{mV}$) ($\approx +120\text{mV}$)

- The combined effects of various ion types yield a net reversal potential given by:

Goldman-Hodgkin-Katz Equation: $V_m = \frac{RT}{F} \ln \left[\frac{\sum P_{ion} \cdot C_{ion,out}}{\sum P_{ion} \cdot C_{ion,in}} \right] \Rightarrow G \cdot \ln \frac{P_K \cdot C_{K^+,out} + P_{Na^+} \cdot C_{Na^+,out}}{P_K \cdot C_{K^+,in} + P_{Na^+} \cdot C_{Na^+,in}}$

(Eqn 2.3)

p: permeability

- a neuron is "at rest" \Rightarrow voltage: inside $<$ outside $\Rightarrow V \approx -70\text{mV}$

\hookrightarrow modeled by a "leak" current $I_L = G_L(V - V_L)$ \star (Eqn 2.4)

G_L : constant $V_L: -70\text{mV}$

21. A minimal model for a passive neuronal membrane \Rightarrow described by an RC circuit with $R = \frac{1}{G_L}$, and C associated

with the membrane's lipid bilayer. If I_{app} represents an external current injected into the membrane, then:

$C_m \frac{dV}{dt} = -G_L(V - V_L) + I_{app}$ (Eqn 2.5)

can
be
rewritten as

$\frac{dV}{dt} = \frac{V_{ss} - V}{T_m}$ (Eqn 2.6)

$\hookrightarrow V_{ss} = V_L + \frac{I_{app}}{G_L}$ \rightarrow steady-state

~~eg: $C_m = 0.2\text{nF}$, $G_L = 0.02\text{MS}$, $T_m = 10\text{ms}$~~

$\hookrightarrow S: \text{membrane} : IS = \frac{1}{T_m}$

$F = \Omega \cdot S \quad S = FS = \Omega \cdot S \cdot \frac{1}{T_m} = S \star$

?

In a given "state" (a particular V), the right-hand side determines the slope (dV/dt) of its change into future.

A "steady state" V_{ss} is determined by V and not change with time $\Rightarrow \frac{dV}{dt} = 0 \Rightarrow V = V_{ss}$, which is in the absence of input I_{app} = 0.

When given a I_{app}, V_{ss} increase linearly with I_{app}, and inversely proportional to the G_L.

This steady state is stable: if V is transiently depolarized or hyperpolarized by a current pulse, after the input offset it will evolve back to V_{ss} exponentially with a time constant T_m.

an example of:
Attractor State

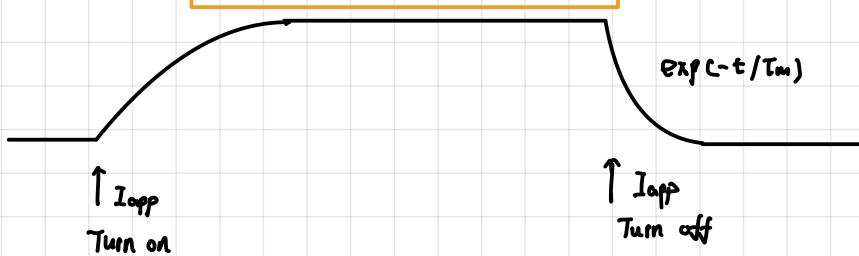
really important

\hookrightarrow A mathematical term to describe a state of a dynamical system that is stable under perturbation if it

22. For an initial condition $V(t=0) = V_0$, the general solution for Eqn 2.5 is:

$$V(t) = V_{ss} + (V_0 - V_{ss}) \exp(-t/T_m)$$
Eqn 2.7

23. "Forget":



24. Neurons have many active channels \Rightarrow conductances are not fixed

a general version of Kirchhoff's circuit equation:

$$C_m \frac{dV}{dt} = -\sum_j I_{ion,j} + I_{opp}$$
Eqn 2.8

$$I_{ion,j} = g_j (V - V_{rev,j})$$
Eqn 2.9

Review:

$$V = V_{in} - V_{out}$$

25. Negative current \Rightarrow "inward" \rightarrow increase or depolarize V

Positive current \Rightarrow "outward" \rightarrow decrease or hyperpolarize V

26. Neuronal communication is conveyed by action potentials, or spikes. \rightarrow brief pulses of electrical signals

27. The more spikes are emitted per unit time (s), the more active is a neuron.

28. Leaky integrate-and-fire (LIF) model \Rightarrow built on the simplification that spikes are stereotypical and brief events

striker

- it describes a passive neuron that incorporates spikes into an RC circuit in a simplified way
- assume the generation of a spike as a "point event" in time whenever V exceeds a preset voltage threshold V_{th} .
- if V reaches V_{th} at time $t \Rightarrow$ a spike is discharged with the spike time t
- V is instantaneously reset to V_{rest} and stays there for a refractory period of time T_{ref} . ★
- $V_{th}, V_{rest}, T_{ref}$ can be determined by physiological measurements for a particular type of neurons

the behaviour of LIF depends on the intensity of I_{opp} \rightarrow small $I_{opp} \rightarrow V_{ss}$ below V_{th}

large $I_{opp} \rightarrow V_{ss}$ exceeds V_{th} \rightarrow (exceed a threshold I_c)

when V crosses V_{th} .

V will be reset to V_{rest}

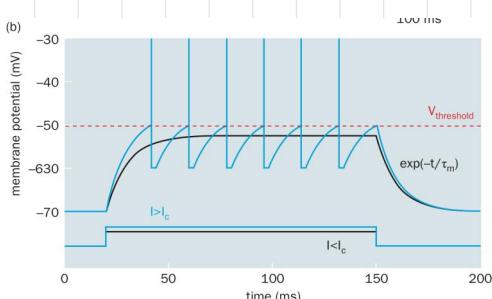
$$I_c = G_L (V_{th} - V_L)$$

where, $V_{ss} = V_{th}$

Eqn 2.10

V_{rise} and reaches V_{th} again

repetitive firing of spikes



With a fixed I_{app} the firing is **regular** in time, characterized by a constant period T or inter-spike interval (ISI) and firing rate $r = \frac{1}{T}$

What and why is "firing rate"

29. ISI: V : from V_{reset} to V_{th}

According to eqn 2.7, V will reach V_{th} at $t = T - T_{ref}$

Solve the eqn 2.7

$$r = \begin{cases} \frac{1}{T_{ref} + \frac{C_m}{G_L} \ln \left[1 + \frac{G_L \Delta V}{I_{app} - I_c} \right]} & \text{if } I_{app} > I_c \\ 0 & \text{otherwise} \end{cases}$$

Specially
→ When $V_L = V_{reset}$ $r = \frac{1}{T_{ref} + \frac{C_m}{G_L} \ln \left[1 + \frac{I_c}{I_{app} - I_c} \right]}$

Eqn 2.11

$$\Delta V = V_{th} - V_{reset}$$

Try to solve the eqn 2.7

$$V(t) = V_{ss} + (V_{reset} - V_{ss}) \exp(-t/T_m)$$

When $V = V_{reset}$ $t=0$

When $V = V_{th}$ $t = T - T_{ref}$

$$V_{th} = V_{ss} + (V_{reset} - V_{ss}) \exp\left(-\frac{T - T_{ref}}{T_m}\right)$$

$$\ln \frac{V_{th} - V_{ss}}{V_{reset} - V_{ss}} = -\frac{T - T_{ref}}{T_m}$$

$$T = -T_m \ln \frac{V_{th} - V_{ss}}{V_{reset} - V_{ss}} + T_{ref}$$

$$= -T_m \ln \frac{V_{th} - V_L - \frac{I_{app}}{G_L}}{V_{reset} - V_L - \frac{I_{app}}{G_L}} + T_{ref}$$

$$= -\frac{C_m}{G_L} \ln \frac{G_L(V_{th} - V_L) - I_{app}}{G_L(V_{reset} - V_L) - I_{app}} + T_{ref} = \frac{C_m}{G_L} \ln \frac{G_L(V_{reset} - V_L + V_{th} - V_{reset}) - I_{app}}{G_L(V_{reset} - V_L) - I_{app}} + T_{ref}$$

$$= \frac{C_m}{G_L} \ln \left(1 + \frac{G_L(V_{th} - V_{reset})}{I_{app} - I_c} \right) + T_{ref}$$

$$r = \frac{1}{T} = \frac{1}{T_{ref} + \frac{C_m}{G_L} \ln \left[1 + \frac{G_L \Delta V}{I_{app} - I_c} \right]}$$

30: Neuronal input-output transfer function \Rightarrow the frequency-current relationship (f - I curve) \Rightarrow fundamental concept

describing a neuron's mapping from an input current into an output firing rate

$$\xrightarrow{\text{Input}} \frac{I_{app}}{I_{app}} \xrightarrow{\text{output}} \text{firing rate } r$$

31. Well above I_c ($I_{app} \gg I_c$) $\Rightarrow r$ is approximately linear with I_{app} , with a slope given by $\frac{1}{G_{mV}}$

When I_{app} is extremely large $I_{app} \rightarrow \infty$. $r \rightarrow \frac{1}{I_{app}}$ \Rightarrow plateaus $\frac{1}{I_{app}}$

Try to prove

$$1. \text{ When } I_{app} \gg I_c, r = \frac{1}{T_{ref} + \frac{C_m}{G_m} \ln\left(1 + \frac{G_m V}{I_{app}}\right)}$$

$$\text{* Taylor: } \ln(1+x) = x - \frac{x^2}{2} + \frac{x^3}{3} - \dots$$

$$\text{For } x \ll 1 \quad \ln(1+x) \approx x$$

$$\text{For } \frac{G_m V}{I_{app} - I_c} \ll 1, \quad \ln\left(1 + \frac{G_m V}{I_{app} - I_c}\right) \approx \frac{G_m V}{I_{app} - I_c}$$

$$r = \frac{1}{T_{ref} + \frac{C_m \cdot G_m V}{I_{app}}} \xrightarrow{\substack{\text{approx} \\ \text{linear to}}} \frac{1}{C_m \cdot G_m} \cdot I_{app}$$

$$2. \text{ When } I_{app} \rightarrow \infty \quad r \rightarrow \frac{1}{T_{ref} + T_m \ln(1+0)} = \frac{1}{T_{ref}}$$

$$\text{for } T_{ref} = 2 \text{ ms} \quad f_{max} = \frac{1}{T_{ref}} = 500 \text{ Hz}$$

波动

↑

32. In an intact brain *in vivo*, synaptic inputs to a neuron fluctuate considerably in time
 \Downarrow 随机的

neuronal firing of a spike train is **highly irregular**

33. For a periodic spike train $\rightarrow ISI$ is constant \Rightarrow review: ISI: Interspike interval $\Rightarrow T$

For a stochastic point process $\rightarrow ISI$ is a random variable

34. The **stochasticity** of a spike train can qualified in two ways:

1. the Coefficient of Variation (CV) of ISIs

$$CV = \frac{\text{Std}(ISI)}{\text{Mean}(ISI)} = \frac{\langle (ISI - \langle ISI \rangle)^2 \rangle^{1/2}}{\langle ISI \rangle} \quad \text{Eqn 2.12}$$

where $\langle x \rangle = \int p(x) dx \Rightarrow$ average of x

2. Fano factor of spike count $N(T)$ (number of spikes in a time window T):

$$F(T) = \frac{\text{Variance}(N(T))}{\text{Mean}(N(T))} \quad \text{Eqn 2.13}$$

35. For a regular periodic spike train $\Rightarrow \begin{cases} CV=0 \\ F(T)=0 \end{cases}$

$$\text{Std} = N \cdot \sigma = 0$$

$$P(ISI) = \lambda e^{-\lambda ISI}$$

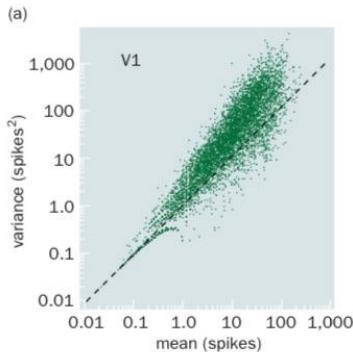
If a spike train is Poisson $\Rightarrow \begin{cases} CV=1 \\ F(T)=1 \end{cases}$

36. High variability represents a salient characteristic of spike train \rightarrow typically the spike-count variance exceeds the mean.
显著的

Inspiration

Draw variance-mean plot to find the characteristic of spike train

e.g.:



37. CV is typically larger than 1 for neural activity in the prefrontal cortex of a behaving macaque monkey

38. To capture stochastic spike firing in an integrate-and-fire model



Introduce a noise $\eta(t)$ into I_{app} :

$$C \frac{dV}{dT} = -G_L(V - V_L) + I_{app} + \delta \eta(t) \quad \text{Equ 2-14}$$

I_{app} is the mean of I_{app} , δ is the noise level

39. The simplest kind of noise \rightarrow no temporal correlation and a Gaussian probability density of η of zero mean and unit variance:

$$P(\eta) = \frac{1}{\sqrt{2\pi}} e^{-\frac{\eta^2}{2}} \quad \text{Equ 2-15}$$

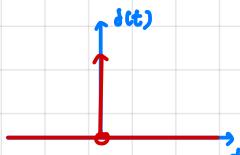


"White Noise" \rightarrow because its power spectrum is constant and therefore completely devoid of dependence on frequencies

40. The absence of temporal correlation in math is described by:

$$\langle \eta(t) \eta(t') \rangle = \delta(t-t') \quad \text{Equ 2-16}$$

where the delta function $\delta(t)$ is infinity when $t=0$ and zero otherwise



41: Equ 2-14

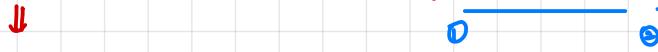
$$C \frac{dV}{dT} = -G_L(V - V_L) + I_{app} + \delta \eta(t) \quad \text{Equ 2-14}$$

with a leak and white noise \Rightarrow Ornstein-Uhlenbeck process *

42. When μ is below $I_c \Rightarrow$ the deterministic steady-state V_{ss} is below $V_{th} \Rightarrow$ but V is driven by noise and may still reach V_{th} through fluctuations

43: ISIs are statistically independent of each other, since each time a spike is fired, V is reset to V_{reset} and memory about the past is lost

44. Starting at $V_{reset} \Rightarrow$ the time it takes for V to reach V_{th} for the first time is mathematically called "first passage time"



an ISI is the first passage time + T_{ref}

$$\text{ISI: } T = T_{\text{first-passage}} + T_{\text{ref}}$$

Eqn 2.17

The statistics of ISIs can be analysed by the theory of first passage times of an Ornstein-Uhlenbeck process

In particular, the average $\langle \text{ISI} \rangle \propto \frac{1}{f}$, the input-output function is:

$$\frac{1}{f} = T_{\text{ref}} + T_m \sqrt{\pi} \int_{\frac{C_m(V_{th}-V_{ss})}{\sqrt{T_m}\delta}}^{\frac{C_m(V_{th}-V_{ss})}{\sqrt{T_m}\delta}} e^{x^2} (1 + \text{erf}(x)) dx$$

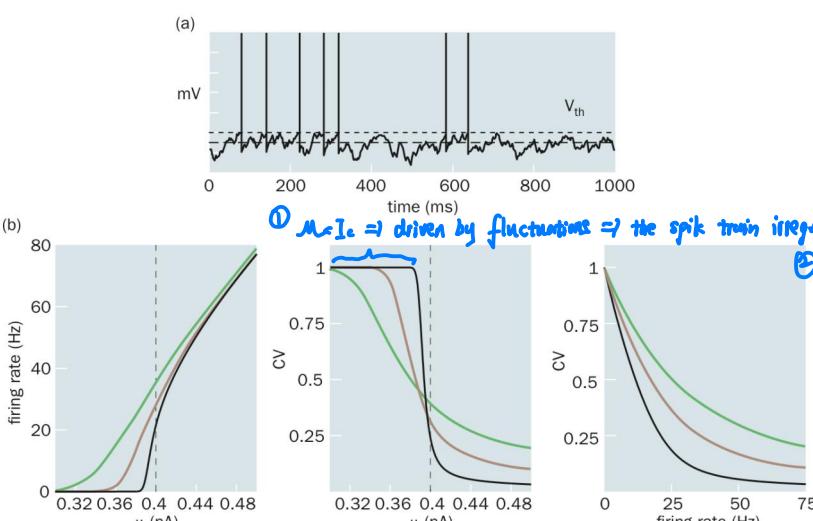
Eqn 2.18

where. $\text{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x \exp(-x'^2) dx' \Rightarrow$ error function

CV is given by:

$$CV^2 = 2\pi f^2 \int_{\frac{C_m(V_{th}-V_{ss})}{\sqrt{T_m}\delta}}^{\frac{C_m(V_{th}-V_{ss})}{\sqrt{T_m}\delta}} e^{x^2} \left[\int_{-\infty}^x e^{y^2} (1 + \text{erf}(y)) dy \right] dx$$

Eqn 2.19



\Rightarrow line \Rightarrow different δ

(Unit: $\delta: nA\sqrt{nA}$; $\delta: nN$)

① $\mu = I_c \Rightarrow$ driven by fluctuations \Rightarrow the spiketrain irregular $\Rightarrow CV$ close to 1

② when $(\mu - I_c)$ is much larger than $\delta = \frac{\delta}{\sqrt{T_m}}$ the firing becomes increasingly regular

③ With large μ , CV decays to zero and spiking becomes regular

↳ sharpness of this transition depends on δ

↳ when the fluctuations are small, { the transition is very sharp the large value of δ , the transition is smooth

45. A more basic physiological question: how a high variability of neural spike firing can be explained mechanistically
 ↓
the total input to a single cortical cell must operate near the firing threshold, regardless of the firing rate level.

Conductance-based Models of Single Neurons

46. Hodgkin-Huxley model, an action potential is produced by an interplay of voltage-gated Na^+ and K^+ ion currents (I_{Na} and I_{K})

$\begin{cases} I_{\text{Na}}: \text{inward} \cdot \text{depolarize} \\ I_{\text{K}}: \text{outward} \cdot \text{hyperpolarized} \end{cases}$

$$I_{\text{Na}} = g_{\text{Na}}(V - V_{\text{Na}})$$

Eqn 2.20

$$I_{\text{K}} = g_{\text{K}}(V - V_{\text{K}})$$

with reversal potentials V_{Na} and V_{K}

Unlike passive leak conductance, the conductances g_{Na} and g_{K} are not constant but "gated" by membrane potential V

?

K 通常由 4 个独立相同的电门控制

47. Specifically, the K^+ conductance g_{K} becomes $g_{\text{K}}n^4$, where n is the action gating variable

The idea is that n represents the 'fraction' of "gates" in an open state, and $1-n$ is the fraction of gates in a closed state

The gating variable n obeys a dynamical equation according to a first-order chemical kinetics:

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n \quad \text{Eqn 2.21}$$

rewritten
 $\begin{cases} \alpha_n: \text{opening rates} \\ \beta_n: \text{closing rates} \end{cases} \rightarrow *$ dependent on V

$$\frac{dn}{dt} = \frac{n_{\infty} - n}{T_n} \quad \text{Eqn 2.22}$$

with the steady-state $n_{\infty} = \frac{\alpha_n}{\alpha_n + \beta_n}$

and constant $T_n = \frac{1}{\alpha_n + \beta_n}$

Try to prove 2.21 \Leftrightarrow 2.22

$$\frac{dn}{dt} = \frac{n_{\infty} - n}{T_n} = \frac{\frac{dn}{dt + \beta_n} - n}{\frac{1}{\beta_n}} = \Delta n - n(\alpha_n + \beta_n) = (1-n)\Delta n - \beta_n n$$

48. g_{Na} has
- (1) an activation gating variable m
 - (2) an inactivation gating variable h

\rightarrow Na 通道由 \uparrow activation 电门 + \uparrow inactivation 电门控制
 $\rightarrow g_{Na}$ becomes $g_{Na} m^3 h$

supplied knowledge

chemical kinetic equation

Reaction order

zero

first

second

Differential Rate Law

$$\frac{-d[A]}{dt} = k$$

$$\frac{-d[A]}{dt} = k[A]$$

$$\frac{-d[A]}{dt} = k[A]^2$$

Integrated Rate Law

$$[A] = [A_0] - kt \quad [A_0] - [A] = kt$$

$$[A] = [A_0] e^{-kt} \quad \ln([A_0]) - \ln([A]) = kt$$

$$[A] = \frac{[A_0]}{1 + kt[A_0]} \quad \frac{1}{[A]} - \frac{1}{[A_0]} = kt$$

49.

Four differential equations in Hodgkin-Huxley model:

$$C_m \frac{dv}{dt} = -g_L(v - V_L) - g_{Na} m^3 h (v - V_{Na}) - g_K n^4 (v - V_K) + I_{app} \quad \text{Eqn 2.23}$$

$$\frac{dm}{dt} = \Phi_m (\alpha_m(v)(1-m) - \beta_m(v)m) = \frac{(M_{\infty}(v) - m)}{T_m(v)} \quad \text{Eqn 2.24}$$

$$\frac{dh}{dt} = \Phi_h (\alpha_h(v)(1-h) - \beta_h(v)h) = \frac{(h_{\infty}(v) - h)}{T_h(v)} \quad \text{Eqn 2.25}$$

$$\frac{dn}{dt} = \Phi_n (\alpha_n(v)(1-n) - \beta_n(v)n) = \frac{(n_{\infty}(v) - n)}{T_n(v)} \quad \text{Eqn 2.26}$$

where I_{app} is the injected current (unit: $\mu A/cm^2$).

Φ_x are the temperature factors (equals to 1 in the original Hodgkin-Huxley model $\Rightarrow 6-7^\circ C$)

↓
Temperature T Φ_T

small $g \Rightarrow$ specific conductance (per cm^2)

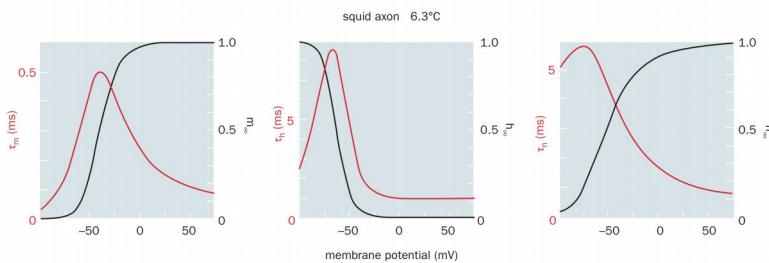
large $G \Rightarrow$ total conductance

50. Hodgkin-Huxley model is a highly nonlinear coupled system \Rightarrow as the V equation depends on all four variables

[the rates α and β in the equations for the gating variables are complex function of V .]

★ Iden

51. "voltage-clamp" \rightarrow hold V at a constant level in time $\rightarrow \alpha$ and β are mere numbers \rightarrow measure I_{Na} and $I_K \rightarrow$ calculate conductance $\frac{1}{V - V_{Na}}$ $\frac{I}{V - V_K}$ with a fixed $V \Rightarrow$ deduce α and β values for each V



→ Review:

$$n_{\infty} = \frac{d_n}{d_n + p_n}$$

$$T_n = \frac{1}{d_n + p_n}$$

If we know n_{∞} & T_n

$$d_n = \frac{n_{\infty}}{T_n}$$

$$d_n + p_n = \frac{1}{T_n}$$

$$p_n = \frac{1}{T_n} - d_n = \frac{1 - n_{\infty}}{T_n}$$

$$\left\{ \begin{array}{l} d_n = \frac{n_{\infty}}{T_n} \\ p_n = \frac{1 - n_{\infty}}{T_n} \end{array} \right.$$

52. Quantitative Dependence of the rates on V :

Relationship between
 d_n
 p_n
 d_m
 p_m
 d_h
 p_h
and V

$$d_m(V) = -0.1(V+40) / (\exp(-0.1(V+40)) - 1)$$

Equ 2.27

$$p_m(V) = 4 \exp(-(V+65)/18)$$

Equ 2.28

$$d_h(V) = 0.07 \exp(-0.05(V+65))$$

Equ 2.29

$$p_h(V) = 1 / (1 + \exp(-0.1(V+35)))$$

Equ 2.30

$$d_n(V) = -0.01(V+55) / (\exp(-0.1(V+55)) - 1)$$

Equ 2.31

$$p_n(V) = 0.125 \exp(-(V+65)/80)$$

Equ 2.32

53. Other parameter values of classic Hodgkin-Huxley model:

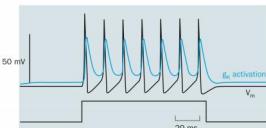
$$C_m = 1 \mu F/cm^2$$

the maximum conductance: $g_{Na} = 120$, $g_K = 36$, $g_L = 0.3$ (unit: MS/cm^2)

the reversal potentials: $V_{Na} = +50$, $V_K = -77$, $V_L = -54.4$ (unit: mV)

the passive time constant $T_m = C_m / g_L \approx 33$ ms

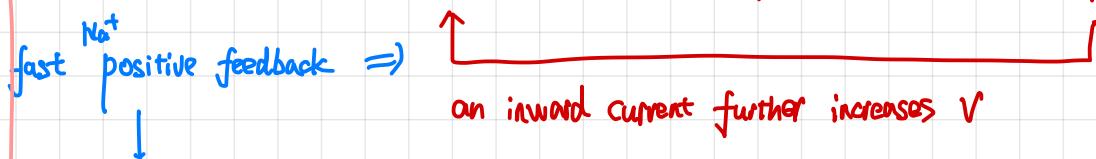
54.



The repetitive firing can be intuitively understood as a result of interplay between fast positive feedback mediated by I_{Na} and slower negative feedback by I_K

{ I_{Na} : fast positive feedback
 I_K : slow negative feedback

55: the activation variable m increases with $V \Rightarrow$ depolarization leads to the opening of I_{Na}



occur like a chain reaction very quickly. underlying the rapid upstroke of an action potential

56. the inactivation variable h decreases with $V \rightarrow$ the K^+ conductance decreases on a slower timescale

the outward current produces the downstroke \leftarrow the activation variable n of I_K grows with depolarization of an action potential

FIT/FIT

↓

During a refractory period,

the membrane potential is hyperpolarized $\rightarrow n$ (thus I_K) to decay away \rightarrow the inactivation variable h for I_K recovered to a high value

slow K^+ negative feedback

a periodic train of action potentials.

My Insights

Idea to design an experiment in computational neuroscience: Firstly: simplify the problem (i.e.: use mathematical language to describe the problem)

{ From neuron-to-behaviour aspect to build a model

From behavior-to-neuron aspect to acquisit data and evaluation.

(neuron - to - behaviour)
In Computational Neuroscience

① From a basic principle

(e.g: LIF or H-H model)

to build a net of neurons.

↓

② Use computational neuroscience

method to calculate what would be the

keypoints that most related to the behaviour

(e.g.: some parameters like: m, n, h

or attractor states)

↓

③ After modeling using ML/DL, analyse the

latent space and connect all the parameters in the

ML/DL to our computational framework (interpretability analysis)

↓

① Engineering-related application

② New finding in neuroscience

In ML/DL (Engineering)

① According to the computational

↓

framework. build a biological

plausible model (silicone twin of neuron)

↓

② According to our prediction via computation

and/or hypothesis, train our model with a

specific task \Rightarrow i.e.: the simplified problem

↓

③ After interpretability analysis, using

real data (e.g: from human or animals)

for validation

↓

① Engineering-related application

② New finding in neuroscience

~~truth~~

57. Oscillation underlying repetitive firing of action potential, result from:

- 1. fast positive feedback (N_f)
- 2. slow negative feedback (K_f)

★ Adversarial Relationship

*: Indeed, if the negative feedback by activation of g_K was as fast as. or faster than, the positive feedback by N_f .

rhythmic action potential would be impossible.

↓
Instead, the membrane potential would reach a steady-state ★ regardless of the injected current I_{app}

58. I_{app} increase gradually across I_c , the behaviour undergoes a qualitative change from steady-state to repetitive firing

↳ a bifurcation phenomenon
↳ ↗

★ bifurcation can just occur in non-linear dynamic system



Mathematically, a stable state is called an

Attractor



↓
simply means that when the system deviates slightly away from the state, it will evolve

back to that state over time.

60: { RC circuit: steady-state \Rightarrow a stationary attractor

Hodgkin-Huxley model: a regular train of action potentials \rightarrow an oscillatory type of attractor behaviour



"Limit Cycle"

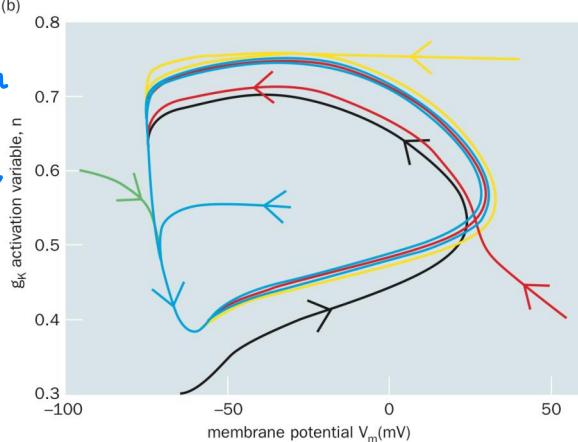
→ regardless of the initial states, the model always converges to the same periodic attractor state

If the system is perturbed by a transient stimulus, it would

evolve over time and eventually resume the same firing pattern

after the stimulus offset, except for a shift of spiking time,

or the phase of the periodic attractor state

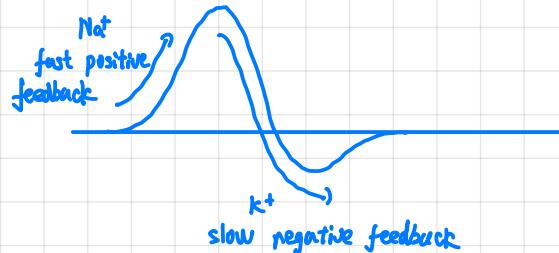


↓
Thus, a periodic attractor is robust

the phase can be shifted by an external stimulation, hence the clock can be readily reset

My Insight

An example of attractor: Action potential



rest state \Rightarrow attractor

Type II neuron: ① contrary to LIF, the Hodgkin-Huxley model the firing rate of action potentials is not zero but finite ($\approx 45\text{Hz}$)

at the threshold input current

② the range of possible firing rates is rather limited

③ A finite minimum firing rate at the onset of repetitive spike firing

(a characteristic of the current-frequency curve of type II neurons)

④ the minimum firing rates $\approx 45\text{Hz} \Rightarrow$ reflects an intrinsic oscillatory freq even when V is subthreshold

⑤ when the input current I_{app} is near the firing threshold \Rightarrow the membrane potential displays damped oscillations

temporal oscillations around its steady-state ($V_{ss} \approx -60\text{mV}$)

⑥ The damped oscillation is ^{"again"} produced by the interplay between fast positive fb and slow negative fb

⑦ when the input current is not sufficiently strong to drive V above the threshold, oscillations are subthreshold and occur on a small scale of membrane potential variations around $\approx -60\text{mV}$

⑧ the "gap" in frequency-current curve \Rightarrow the time

constants of the activation of I_Na and inactivation of

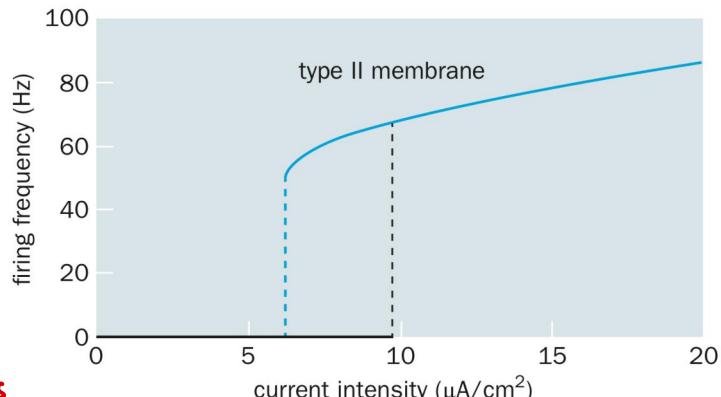
I_{Na} are $\approx 5-10\text{ms}$, yielding a periodicity of $\approx 20\text{ms}$

in agreement with a frequency of 4Hz

L this intrinsic frequency sets a minimum for firing

rate of action potentials when the input current exceeds

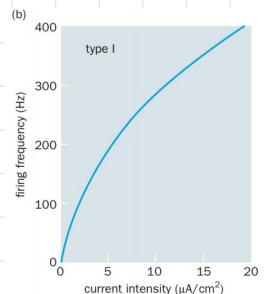
the spiking threshold.



"Type I" neuron: ① a continuous frequency-current curve

② starting from zero firing rate

③ the firing rate can be as high as a few hundred Hz (not damped)



62.

Quantitative changes of parameters from original H-H model gives rise to Type I neuron:

① shift the activation and inactivation curves of I_{Na} and I_K to more depolarized membrane potential
(a few mV for I_{Na} and I_{Ks} and ≥ 20 mV for I_{Na})

↳

② As a result, the voltage-dependent conductances are no longer significant at ~ -60 mV

- ③ because the activation of I_K requires a lot more depolarization compared to I_{Na} , activated the fast positive feedback (mediated by I_{Na}) inevitably produces sufficient depolarization for the generation of an action potential
- ④ therefore, subthreshold oscillation is no longer possible
- ⑤ spike firing starts at 0 Hz
- ⑥ the gating kinetics of I_{Na} and I_K speed up \Rightarrow a broad range of firing rate

63.

The ion channel model of type I neuron can be captured by a modified integrate-and-fire model

An exponential term into the LIT equation that describes the positive feedback underlying action potential.

The Exponential Integrate-and-Fire (EIF) model obey:

$$C_m \frac{dV}{dt} = -g_L(V - V_L) + \Delta \cdot \exp((V - V_{th}) / \Delta) + I_{app}$$

Eqn 2.33

where: V_{th} : the voltage firing threshold

Δ : measures the sharpness of the action potential upstroke

→ when V approaches V_{th} , the inward current grows exponentially with $V \rightarrow$ providing a rapid and powerful positive feedback

→ when V reaches V_{th} , a spike is triggered. V is reset to V_{reset} for a time $T_{spike} + T_{ref}$

↓
duration of an action potential

14. In absence of noise, for input current near firing threshold value I_c :

→ the firing rate is predicted to behave as

$$r = \sqrt{\beta} (I_{app} - I_c)$$

Eqn 2.34

with $\beta = 38 \text{ Hz}/(\text{pA})^2/\text{cm}^2$

Time-dependent Neural Firing Pattern

65. Synchronous network rhythm \Rightarrow reflect as frequency f .

↓

Consider an input

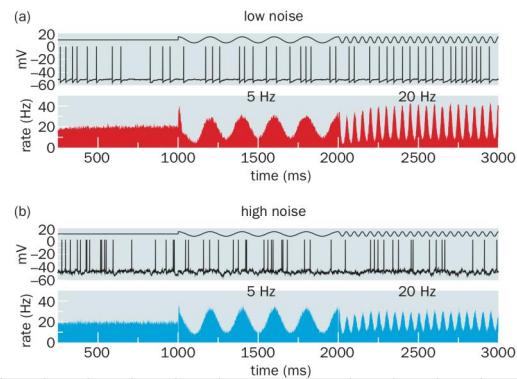
$$I_{app} = I_0 + I_s \cos(2\pi f t) + I_{noise}$$

Eqn 2.35

I_0 : overall firing rate above 0

I_s : amplitude of the sinusoidal input

I_{noise} : white noise



16: PSTH: Post-stimulus time histogram \Rightarrow trial-averaged firing rate $r(t)$

$$r(t) = \frac{\text{the number of spikes within a time window}}{\text{the time window size}}$$

Eqn 2.36

67. Under the condition: $I_s \ll I_0$

↓

$$r(t) = r_0 + r_s(f) \cos(2\pi f t) + \Phi(t)$$

Eqn 2.37

↓

$\Phi(t)$: phase shift relative to the input current

68. At low f : the neuronal response can "keep up" with input oscillation

$r_s(f)$ is roughly independent with f

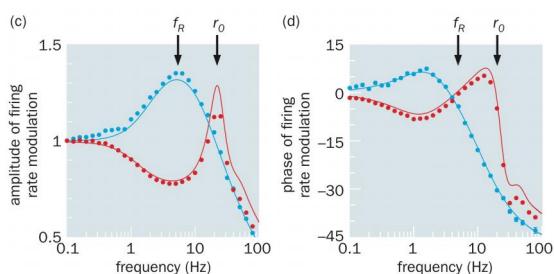
$f > f_c$ (f_c : "cutoff" value): $r_s(f)$ decrease with f

↓

reflect that neuron dynamics cannot follow effectively more rapid changes in input

- Both the type I and its reduced EIF model \rightarrow predict:
- 1. $r(f)$ decays with f as $f^{-\frac{1}{2}}$
 - 2. the phase shift $\Phi(f)$ reaches an asymptotic level of 90 degrees at high frequency
- \Downarrow
- Qualitatively Different
- \Updownarrow
- For classic LIF model driven by a sinusoidal input and white noise:
- 1. $r(f) \sim \frac{1}{f}$
 - 2. $\Phi(f)$ plateaus at 45°

70. Some types of neurons show a resonance phenomenon $\Rightarrow r(f)$ shows a peak at "preferred" f



At Low noise, the resonance frequency = the mean firing rate r_0

At high noise, the resonance frequency is determined by damped oscillations of subthreshold membrane potential

71. At resonance frequency \Rightarrow shows a phase advance $\Phi(f) > 0$

72. Spike Rate Adaptation: commonly observed in a majority of excitatory pyramidal cells and some inhibitory cells in mammalian cortex



Definition: a phenomenon of gradual decrease of spiking discharges of a neuron in response to a long-lasting stimulus, as a form
of neuronal dynamics that renders a single neuron to be more sensitive to changes in the input rather than
steady-state \Rightarrow in order to achieve efficient coding of inputs

73: Both in vitro and in vivo:

$$r(t) = r_{ss} + (r_0 - r_{ss}) \exp(-t/T_{adapt})$$

Eqn 2.38

The degree of adaptation:

$$F_{adapt} = \frac{r_0 - r_{ss}}{r_0}$$

Eqn 2.39

Without adaption: $F_{adapt} = 0$

Maximum adaption (in case that $r_{ss}=0$) $F_{adapt} = 1$

74: SRA can be fully described with $\begin{cases} F_{adapt} \\ z \\ T_{adapt} \end{cases}$

75: In cortical pyramidal neurons \Rightarrow SRA is primarily mediated by a calcium-activated potassium ion current

I_{KCa} *

76. SRA in the LIF model

↓

$$\text{assuming } I_{KCa} = G_{KCa} [Ca^{2+}] (V - V_K)$$

↓ where $V_K = -80 \text{ mV}$ is the reversal potential

The modified LIF:

$$C_m \frac{dV}{dt} = -G_L(V - V_L) - G_{KCa} [Ca^{2+}] (V - V_K) + I_{app} \quad \text{Eqn 2.40}$$

$$\frac{d[Ca^{2+}]}{dt} = 2 \sum_j \delta(t - t_j) - \frac{[Ca^{2+}]}{\tau_{Ca}} \quad \text{Eqn 2.41}$$

↓ where: $\{t_j\}$: presynaptic spike train

I_{Ca-L} : mediated calcium influx per spike \Rightarrow described by a delta-function
 Δ : the amount of calcium influx per spike ($\sim 200 \text{ nM}$)
 τ_{Ca} : decay time constant ($\sim 100 \text{ ms}$)

Derivation

$$\text{LIF: } C_m \frac{dV}{dt} = -G_L(V - V_L) - \underline{I_{KCa}} + I_{app} \quad (1)$$

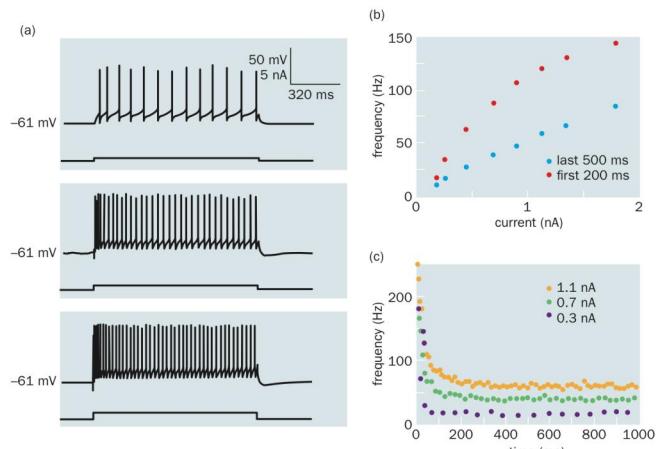
$$I_{KCa} = G_{KCa} [Ca^{2+}] (V - V_K) \quad (2)$$

$$(1) + (2) \Rightarrow C_m \frac{dV}{dt} = -G_L(V - V_L) - G_{KCa} [Ca^{2+}] (V - V_K) + I_{app}$$

71. SRA can be quantified by: $r(t) = \frac{1}{ISI(t)}$ Eqn 2.42

Inter-spike interval

Figure 2.12 Spike frequency adaptation of an excitatory pyramidal neuron from the human cortex recorded in *in vitro* slices. (a) Membrane potential in response to a current injection at three intensity values. (b) The initial firing rate and steady-state firing rate as a function of input current intensity. (c) The instantaneous firing rate (defined as the inverse of an interspike interval) as a function of time for the three examples from (a), each can be fitted with an exponential function of time. Reproduced from Lorenzon and Foehring (1992). Lorenzon, N. M., & Foehring, R. C. (1992). Relationship between repetitive firing and afterhyperpolarizations in human neocortical neurons. *Journal of Neurophysiology*, 67(2), 350–363.



A theoretical analysis framework for SRA:

Step 1: assume that the firing rate:

$$r(t) = f(I_{tot}) \approx \beta I_{tot}$$

Eqn 2.43

is approximately linear with the total current

$$I_{tot} = I_{app} - I_{KCa} \quad . \text{ above the firing threshold}$$

Step 2: replace V by a constant average $\langle V \rangle$ in I_{KCa} :

$$r(t) \approx \beta (I_{app} - G_{KCa} [Ca^{2+}] (\langle V \rangle - V_K)) \approx r_0 - J_{KCa} [Ca^{2+}] \quad \text{Eqn 2.44}$$

where: $r_0 = \beta I_{app}$ initial firing rate

$$J_{KCa} = \beta G_{KCa} (\langle V \rangle - V_K)$$

↓
quantify the effective strength of the adaption current

Derivation

$$I_{tot} = I_{app} - I_{KCa} \quad (1)$$

$$I_{KCa} = G_{KCa} [Ca^{2+}] (V - V_K) \quad (2)$$

$$r(t) \approx \beta I_{tot} = \beta [I_{app} - I_{KCa}]$$

$$\begin{aligned}
 &= \frac{\beta (I_{app} - G_{KCa}[Ca^{2+}] (\langle V \rangle - V_f))}{\tau} \\
 &= \beta I_{app} - \beta G_{KCa}[Ca^{2+}] (\langle V \rangle - V_f) \\
 &= r_o - J_{KCa}[Ca^{2+}]
 \end{aligned}$$

Step 3: assume that electrical activity is faster than calcium signal

which thus averages spikes over time
 \downarrow

so the the spike train in $[Ca^{2+}]$ equation can be approximately replaced by firing rate r :

$$\frac{d[Ca^{2+}]}{dt} = \alpha \sum_j \delta(t-t_j) - \frac{[Ca^{2+}]}{\tau_{Ca}} \simeq \alpha r - \frac{[Ca^{2+}]}{\tau_{Ca}} = \alpha r_o - \frac{[Ca^{2+}]}{\tau_{adapt}} \quad \text{Eqn 2.45}$$

Eqn 2.45

$$\frac{1}{\tau_{adapt}} = \alpha J_{KCa} + \frac{1}{\tau_{Ca}} \quad \text{Eqn 2.46}$$

Derivation

$$\alpha r - \frac{[Ca^{2+}]}{\tau_{Ca}} = \alpha(r_o - J_{KCa}[Ca^{2+}]) - \frac{[Ca^{2+}]}{\tau_{Ca}}$$

$$\begin{aligned}
 &= \alpha r_o - [Ca^{2+}] \left(\frac{1}{\tau_{Ca}} + \alpha J_{KCa} \right) \\
 &= \alpha r_o - [Ca^{2+}] \left| \frac{1}{\tau_{adapt}} \right|
 \end{aligned}$$

$$\frac{1}{\tau_{adapt}} = \alpha J_{KCa} + \frac{1}{\tau_{Ca}}$$

 solving Eqn 2.45: $\alpha r - \frac{[Ca^{2+}]}{\tau_{Ca}} = \alpha r_o - \frac{[Ca^{2+}]}{\tau_{adapt}}$

$$\alpha(r - r_o) = [Ca^{2+}] \left(\frac{1}{\tau_{Ca}} - \frac{1}{\tau_{adapt}} \right)$$

$$[Ca^{2+}] = \frac{\alpha(r - r_o)}{\frac{1}{\tau_{Ca}} - \frac{1}{\tau_{adapt}}}$$

 73: Both in vitro and in vivo:

$$r(t) = r_{ss} + (r_o - r_{ss}) \exp(-t/\tau_{adapt}) \quad \text{Eqn 2.38}$$

$$\frac{d[Ca^{2+}]}{dt} = 2\Gamma_0 - \frac{[Ca^{2+}]}{\tau_{adapt}}$$

$$\frac{d[Ca^{2+}]}{dt} + \frac{[Ca^{2+}]}{\tau_{adapt}} = 2\Gamma_0$$

$$M(t) = \exp\left(\int \frac{1}{\tau_{adapt}} dt\right) = e^{\frac{t}{\tau_{adapt}}}$$

$$\underbrace{\frac{d[Ca^{2+}]}{dt} \cdot e^{\frac{t}{\tau_{adapt}}} + \frac{e^{\frac{t}{\tau_{adapt}}}}{\tau_{adapt}} [Ca^{2+}]}_{\text{cancel terms}} = e^{\frac{t}{\tau_{adapt}}} d\Gamma_0$$

$$\star \quad \frac{d}{dt} \left(e^{\frac{t}{\tau_{adapt}}} [Ca^{2+}] \right) = e^{\frac{t}{\tau_{adapt}}} \Gamma_0$$

$$e^{\frac{t}{\tau_{adapt}}} [Ca^{2+}](t) = \int e^{\frac{t}{\tau_{adapt}}} \Gamma_0 dt$$

$$= 2\tau_{adapt} \Gamma_0 e^{\frac{t}{\tau_{adapt}}} + C$$

$$[Ca^{2+}](t) = 2\tau_{adapt} \Gamma_0 + C e^{-\frac{t}{\tau_{adapt}}}$$

$$t=0 \quad [Ca^{2+}](t)=0 \Rightarrow C = -2\tau_{adapt} \Gamma_0$$

↓

$$[Ca^{2+}](t) = 2\tau_{adapt} \Gamma_0 (1 - e^{-\frac{t}{\tau_{adapt}}})$$

★

$$[Ca^{2+}](t) = [Ca^{2+}]_{ss} (1 - \exp(-t/\tau_{adapt}))$$

Equ 2.47

$$[Ca^{2+}]_{ss} = 2\tau_{adapt} \Gamma_0$$

Equ 2.48

↓

combine with equ 2.44:

$$\Gamma(t) = \Gamma_{ss} + (\Gamma_0 - \Gamma_{ss}) \exp(-t/\tau_{adapt})$$

Equ 2.49

↳ with $\Gamma_{ss} = \Gamma_0 - J_{KCa} [Ca^{2+}]_{ss}$

↳ predict a linear relationship between Γ_{adapt} and τ_{adapt}

Step 4: write $[Ca^{2+}]_{ss}$ in two ways:

$$\Delta r_{ss} - \frac{[Ca^{2+}]_{ss}}{T_{Ca}} = \Delta r_0 - \frac{[Ca^{2+}]_{ss}}{T_{adapt}} = 0$$

Eqn 2.50

↓ $[Ca^{2+}]_{ss}$ from each equation must be the same



$$F_{adapt} = 1 - \frac{T_{adapt}}{T_{Ca}}$$

Eqn 2.51

Derivation

$$\Delta r_{ss} - \frac{[Ca^{2+}]_{ss}}{T_{Ca}} = 0$$

$$[Ca^{2+}]_{ss} = 2T_{Ca}r_{ss}$$

$$\Delta r_0 - \frac{[Ca^{2+}]_{ss}}{T_{adapt}} = 0$$

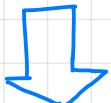
$$[Ca^{2+}]_{ss} = 2T_{adapt}r_0$$

Hence: $2T_{Ca}r_{ss} = 2T_{adapt}r_0$

$$F_{adapt} = \frac{r_0 - r_{ss}}{r_0} = 1 - \frac{r_{ss}}{r_0} = 1 - \frac{T_{adapt}}{T_{Ca}}$$

79. A slower form of adaptation \Rightarrow realised by a potassium current activated by the intracellular sodium

level: single cells



$[Na^+]$ concentration rather than $[Ca^{2+}]$

↓

Prolonged firing of action potentials leads to a graduate Na^+ influx into the cell

through the opening of Na^+ channels.



eventually activates a K^+ current $\Rightarrow I_{KNa}$



- ① hyperpolarization of the neuronal membrane
- ② a reduced responsiveness of the cell

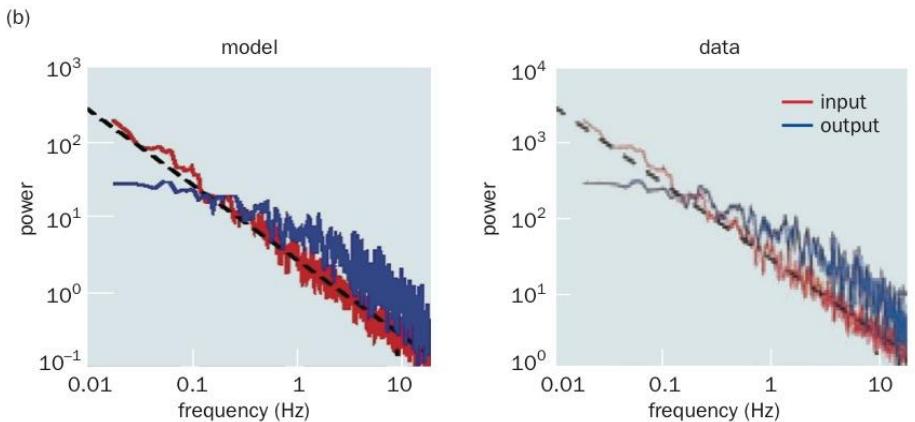
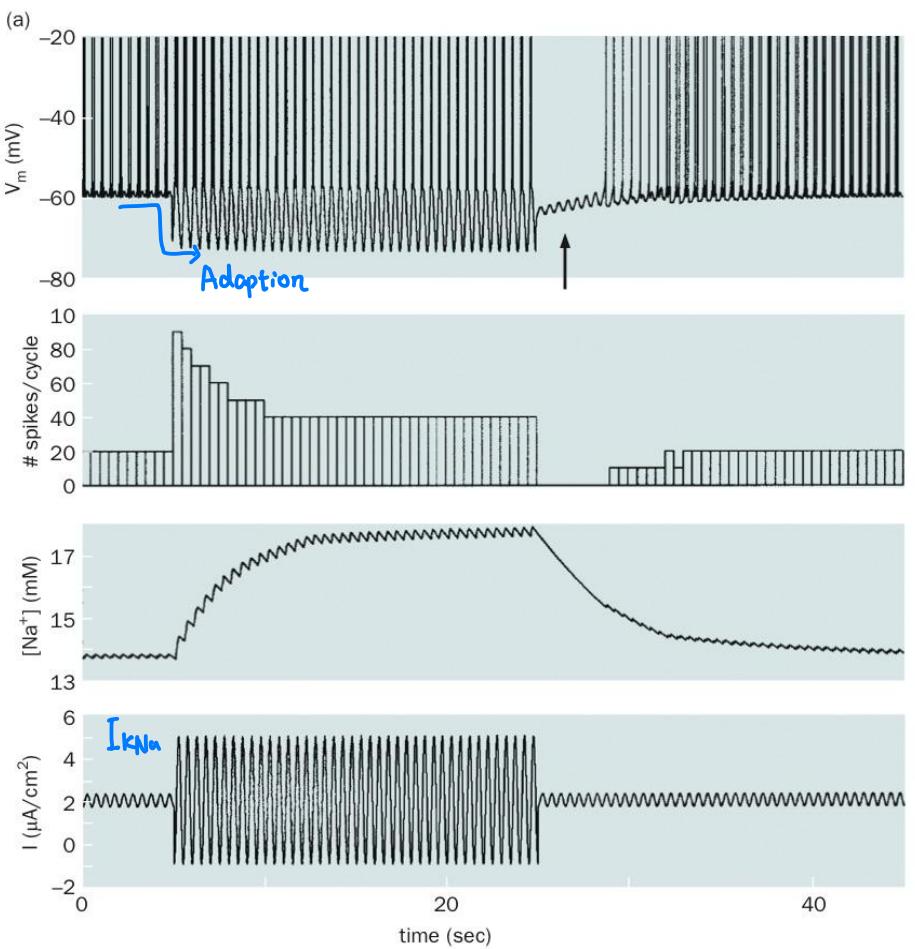


recovery of neuronal responsiveness: Na^+/K^+ ionic pump
(with a time constant of $\sim 10s$)

contrast adaptation

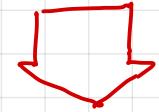


I_{KNa}

*Bg/3*

81: Removal of redundancy \Rightarrow enhance the efficiency of neural coding of sensory stimuli

Neural Adaptation \Leftrightarrow decorrelation operation \Leftrightarrow reduce input redundancy in time



Negative Feedback mediated by I_{KNa}

Burst Firing

82. Ping-pong interplay between Soma and Dendrite

isopotential

Compartmental modelling of dendrite \Rightarrow a spatially continuous dendrites into a number of discrete components

Key components : (Interaction between components j & k)



depends on the physical properties
(e.g.: the radius and length of each cylinder-shaped compartment)

- Dendrites
 - ① not passive
 - ② endowed with various types of active ion channels
 - ③ show a rich repertoire of electroresponsiveness

• Voltage-dependent ion channels at dendrite sites \Rightarrow activated \Rightarrow plateau potential \Rightarrow a depolarizing drive during a burst firing

Hodgkin-Huxley-type Na^+ and K^+ currents on the dendrite \Rightarrow action potential (initiated at the initial segment of axon, near the soma)

\rightarrow propagate back into the dendrite



a soma-dendrite "ping pong" interplay : an action potential backpropagates and depolarizes

dendritic membrane potential, activates dendritic voltage-gated channels and prolongs dendritic depolarization \rightarrow in turn produces more spikes

Simplified model of burst firing



Current-balance Equations:

The somatic voltage V_s obeys:

Eqn 2.52

$$C_m A_s \frac{dV_s}{dt} = -A_s (I_L + I_{Na} + I_K + I_s) - \frac{1}{R_C} (V_s - V_d)$$

Dendritic Voltage V_d obeys:

$$C_m A_d \frac{dV_d}{dt} = -A_d (I_L + I_{Ca-L} + I_{K-c} + I_{KCa} + I_a) - \frac{1}{R_c} (V_d - V_s)$$

Eqn 2.53

$\hookrightarrow: C_m = 1\text{ M}\Omega/\text{cm}^2$

A_s, A_d : Membrane surface areas (mm^2)

R_c : axial resistance (resistive coupling) ($\text{M}\Omega$)

I_{Na}, I_K : H-H-type spike-generating currents

I_{Ca-L} : voltage-gated L-type calcium current I_{Ca-L}

I_{KCa} : calcium-activated K^+ current

I_{K-c} : another K^+ current → depends on both dendrite voltage and intracellular Ca^{2+} concentration

I_s, I_a : the injected currents to the perisomatic and dendritic compartments

Total membrane area: $A_{tot} = A_s + A_d$

The fractional area for the perisomatic membrane:

$$p = \frac{A_s}{A_{tot}}$$

Rewrite

$$C_m \frac{dV_s}{dt} = - (I_L + I_{Na} + I_K + I_s) - \frac{g_c}{p} (V_s - V_d)$$

Eqn 2.54

$$C_m \frac{dV_d}{dt} = - (I_L + I_{Ca-L} + I_{K-c} + I_{KCa} + I_a) - \frac{g_c}{1-p} (V_d - V_s)$$

Eqn 2.55

where $g_c = \frac{1}{R_c \cdot A_{tot}}$ (in mS/cm^2)

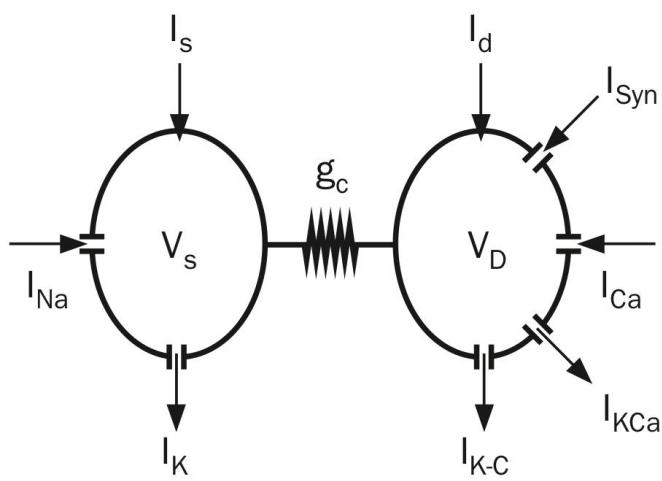
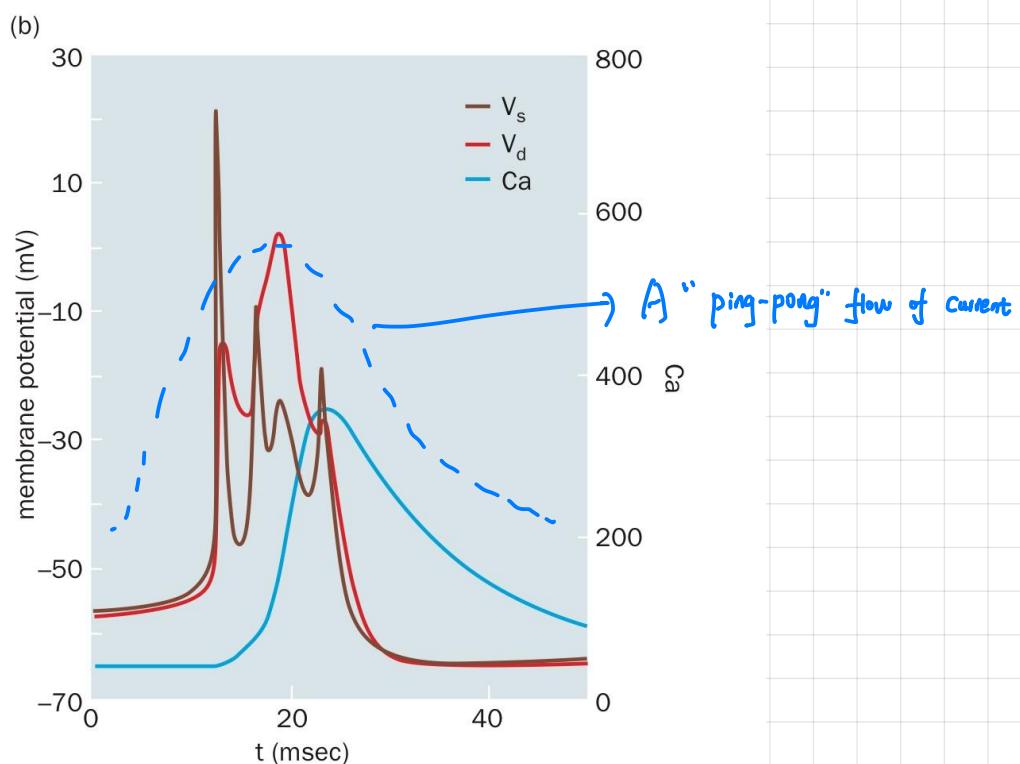
- The resistive coupling acts to equalize V_s and V_d
- The soma-dendrite interaction is not symmetrical: if dendritic compartment is larger than somatic compartment

$$p < 0.5 \quad \frac{g_c}{p} > \frac{g_c}{1-p}$$

reflect the intuition that: there is a stronger influence of the larger dendritic compartments to smaller somatic compartment than in the opposite direction.

★

(a)

 pA_{tot} $(1-p)A_{tot}$ 

→ A "ping-pong" flow of current

- Besides two-compartment model, multiple mechanisms contributing to bursting, especially the voltage-gated synaptic conductance mediated by the N-methyl-D-aspartate (NMDA) receptors



Potential Research Topic

Modelling of dendrites

Postinhibitory Rebound

- Another kind of burst firing \Rightarrow rely on a low-threshold (T-type) Ca^{2+} current $I_{\text{Ca-T}}$, rather than a high-threshold Ca^{2+} current $I_{\text{Ca-L}}$ \square thus can be activated at membrane potentials below the spiking threshold.

- $I_{\text{Ca-T}}$ is conditioned on a prolonged membrane hyperpolarization

its activation variable

Steady state: virtually zero near or above the resting membrane potential

when V is hyperpolarized with a time constant $\sim 100\text{ms}$: $h \uparrow$

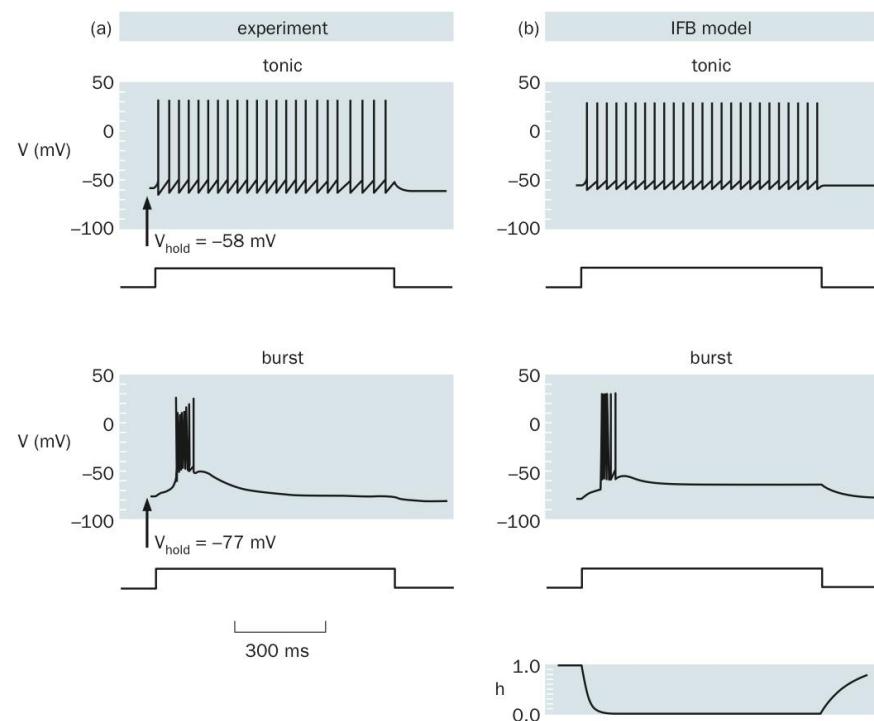
with moderate depolarization: become significant



- when a neuron is endowed with a large $I_{\text{Ca-T}}$ \rightarrow depolarization from resting-state leads to repetitive spikes (tonic mode)

upon release from a sufficiently long hyperpolarization, $I_{\text{Ca-T}}$ is activated to underlie a "depolarization wave" (postinhibitory rebound) with a burst of spikes riding on top of it (burst mode)

- Examples of the phenomenon:
 - ① thalamic neurons (relay information)
 - ② thalamus (pacemaker of synchronous brain oscillations)
 - ③ wakefulness



An extension of LIF model to incorporate postinhibitory rebound:

$$C_m \frac{dV}{dt} = -g_L(V-V_L) - g_{Ca-T} M_\infty(V) h(V-V_{Ca}) + I_{app}$$

Eqn 2.56

The dynamics of its slow inactivation:

$$\frac{dh}{dt} = \begin{cases} -\frac{h}{T_h}, & \text{if } V > V_h \\ \frac{(1-h)}{T_h}, & \text{if } V < V_h \end{cases}$$

Eqn 2.57

$V_{Ca} = 120 \text{ mV}$: reversal potential

$V_h = -60 \text{ mV}$: activation threshold

For simplifying: the fast activation variable m is replaced by its steady-state (M_∞)

$$\text{A } M_\infty = \begin{cases} 0, & V < V_h \quad (\text{h is the same}) \\ 1, & V > V_h \quad \text{inactivation variable} \end{cases}$$

$T_h = 100 \text{ ms}$: time constant controls the timescale of hyperpolarization needed for postinhibitory rebound

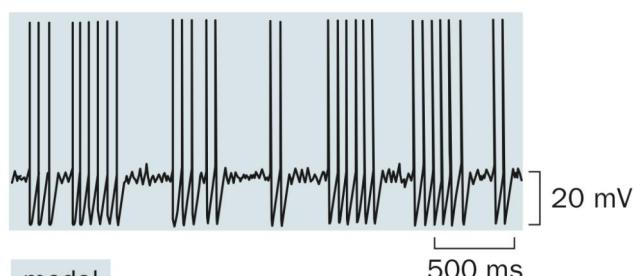
$T_h = 20 \text{ ms}$: determines the duration of depolarization underlying rebound burst

→ Produce the salient tonic and burst mode
突出的

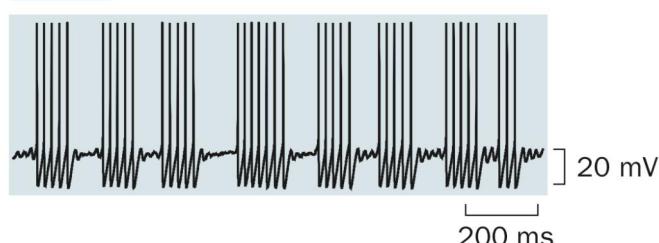
84. Clustered and Irregular Spiking

• An example of clusters of spikes inter-nested in time with episodes of subthreshold membrane fluctuations:

(a) data



model



- The regular repetition of spiking clusters is in range of theta oscillations

↓

a prominent rhythm in the hippocampus

\circlearrowleft an animal's spatial navigation
 \circlearrowleft depends on inputs from the medial septum

- the medial septum contains two major cell types
 - \circlearrowleft Cholinergic cells \Rightarrow release acetylcholine \Rightarrow regulate excitability
 - \circlearrowleft GABAergic cells \Rightarrow act on a faster timescale \Rightarrow entrain hippocampal neurons at theta oscillations.

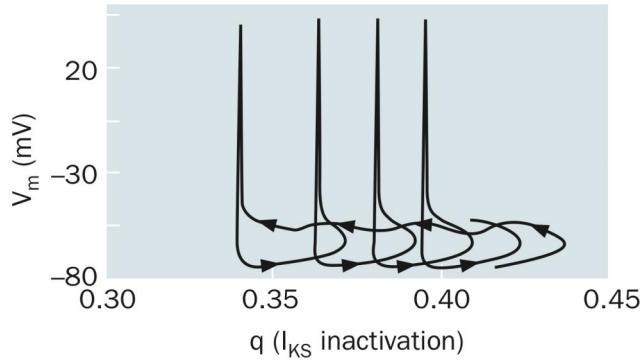
such pacemaker activity of single neurons is captured by a H-H-type model endowed with a slowly inactivating potassium current I_{KS}

The mechanism relies on two assumptions:

- \circlearrowleft a low-threshold K^+ current I_{KS} should be transient and inactivate slowly during depolarization
- \circlearrowleft the neuronal spike afterhyperpolarization is strong \Rightarrow the averaged membrane potential is lower during spikes than during sub-threshold epochs.

When the neuron fires a cluster of spikes, the de-inactivation of I_{KS} slowly builds up during spike afterhyperpolarization, so the amplitude of I_{KS} increases gradually and eventually becomes large enough to terminate a spiking episode

• (b)



→ When the cell does not fire spikes in a subsequent subthreshold epoch

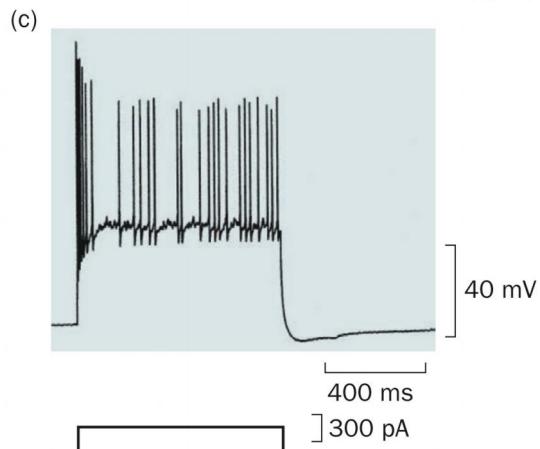


the membrane potential is relatively depolarized

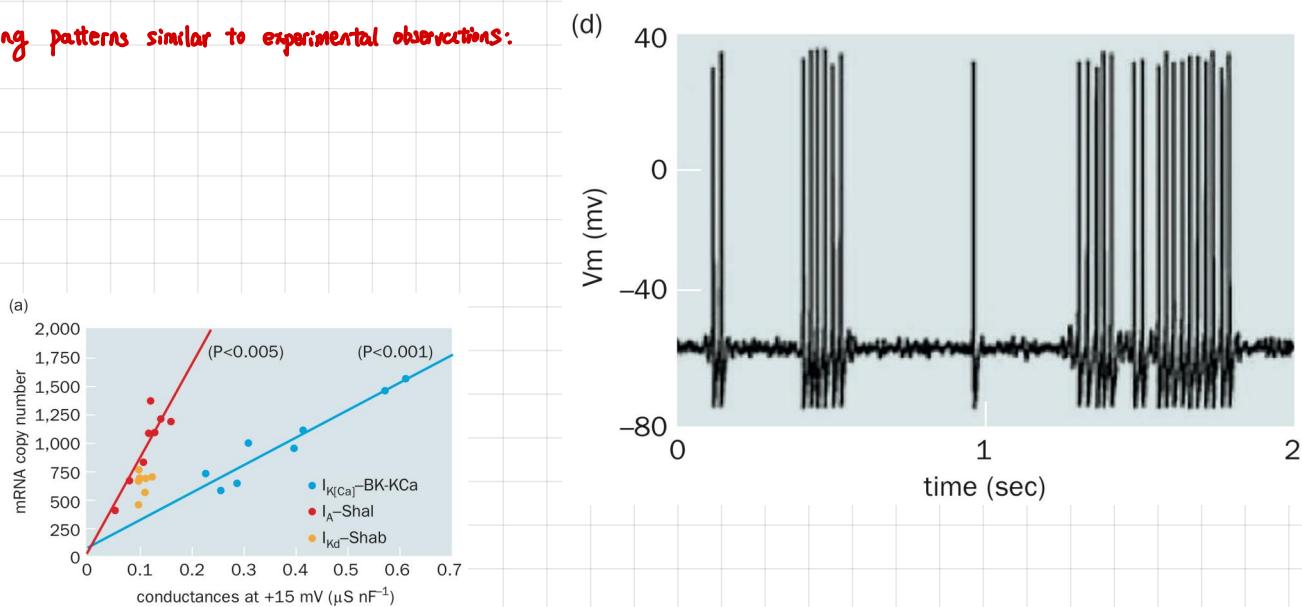


I_{KS} slowly decreases due to inactivation, until the cell is sufficiently recovered and can start to fire again.

- In VIP/CR type of inhibitory neurons in the neocortex \Rightarrow spike clusters interspersed with subthreshold epochs takes place irregularly.



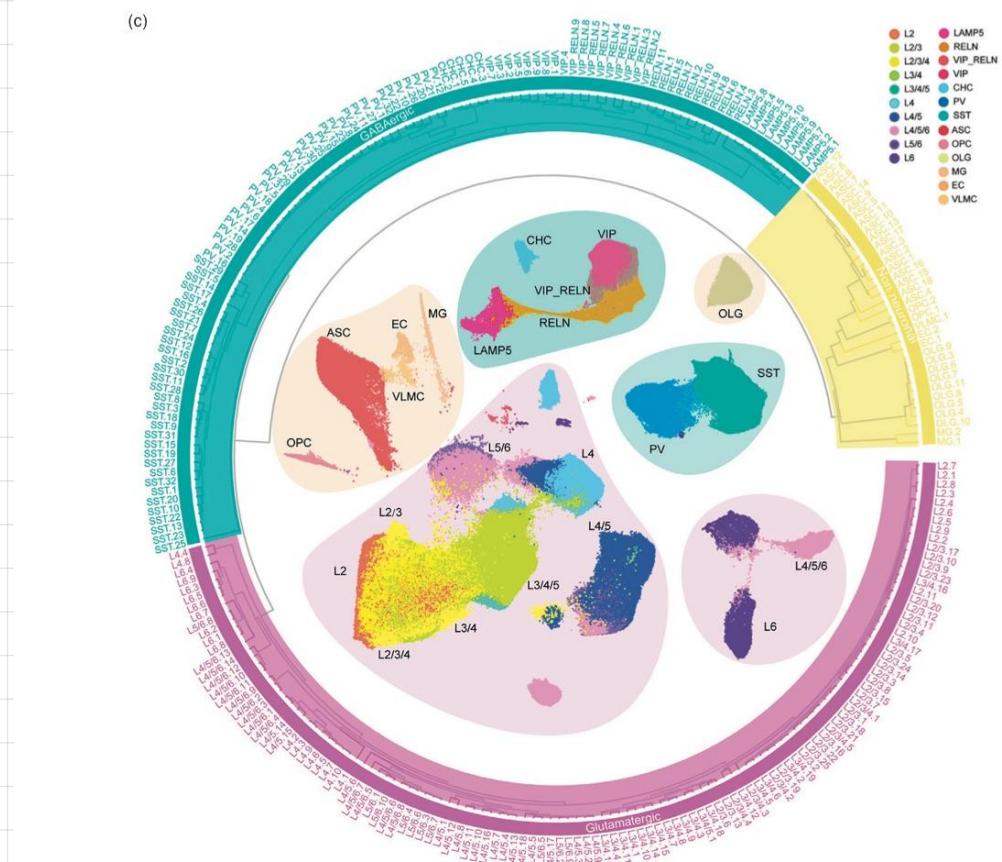
- A conductance-based model with a low-threshold potassium current, driven by a noisy input current \rightarrow produces irregular firing patterns similar to experimental observations:



- Three types of ion channels:
 - non-inactivating potassium current I_{Kd} \Rightarrow described in H-H-model \rightarrow determine the width of an action potential
 - an inactivation potassium current I_A
 - a voltage- and calcium-activated potassium current I_{BK-KCa}

- use single-cell transcriptomic data for cell-type classification:

Identify transcriptomic clusters:



- hierarchical clustering of three major cell types
 - 1. glutamatergic
 - 2. GABAergic
 - 3. non-neuronal cells
- 23 cell subclasses

My Insight

Modeling different cell types to fully mimick the firing patterns of the brain



only major cell types have now been modelled.

Single Synapse Models

85. neuronal communication requires a combination of **electrical signals** (spikes) and **chemical substances** (e.g.: neurotransmitters)

86. In CNN, a given neuron only synthesizes either glutamate or GABA



its action on all its connected postsynaptic neurons is uniformly **dopolarizing** or **hyperpolarizing**

"Dale's law"

a neuron is either "excitatory" or "inhibitory". not both

87. the focus of synapse Model: the impact of a presynapse spike onto a postsynaptic neural membrane.



88. "transmission latency" $\Delta t \Rightarrow$ the time taken by all the intermediate step of synapse transmission

89. Two major respects differentiate various models of single synapses:

1. A distinction must be made between "current-based" and "conductance-based" synapse models



describe a synaptic current similarly to any other ionic current:
 $I_{syn} = g_{syn} s(V - V_{syn})$

Eqn 2.58

$\hookrightarrow g_{syn}$: the maximum conductance

s : a synaptic gating variable that is not activated unless a presynaptic spike

V_{syn} : the reversal potential determines whether a current is depolarizing or hyperpolarizing

$V_E = 0 \text{ mV}$ for synaptic excitatory mediated by AMPA and NMDA receptors of the transmitter glutamate

$V_I = -70 \text{ mV}$ and -80 mV for synaptic inhibition mediated by the GABA_A and GABA_B receptors of the transmitter GABA

- For a neuron that receives synaptic inputs from M presynaptic neurons, each with a weight w_i and gating variable s_i

the summated synaptic current:

$$I_{\text{syn}} = \sum_{i=1}^M w_i s_i (V - V_{\text{syn}})$$

Eqn 2.59

- A current-based model neglects the dependence on the postsynaptic voltage:

$$I_{\text{syn}} = \sum_{i=1}^M j_i s_i$$

Eqn 2.60

$\hookrightarrow j_i$: synaptic weight
(with a different unit from w_i)

2. choose how to model the synaptic gating variable s_i involves a tradeoff between the desire for mathematical simplicity

and the need for details to capture the synaptic dynamics

90. Kick Synapses

start from the simplest description of synaptic interaction

\hookrightarrow assumption: each presynaptic spike causes an instantaneous change ("a kick") in the postsynaptic neurons.

A presynaptic neuron with a train of spikes at time t_j , $j=1, 2, 3, \dots$. then:

the synaptic current: $I_{\text{syn}} = J_s$

Eqn 2.61

$$s = \sum_j \delta(t - t_j)$$

Eqn 2.62

unit of $J \Rightarrow$ electric charge

Current-based

If an LIF neuron is initially at rest, and a presynaptic cell fires a single spike at time $t=0$:

$$V(t) = V_L + \frac{J}{C_m} \exp\left(-\frac{t}{T_m}\right) H(t)$$

Eqn 2.63

↓ where $H(t)$: Heaviside function $H(t) = \begin{cases} 0 & t < 0 \\ 1 & t \geq 0 \end{cases}$

$$\bar{J} = \frac{J}{C_m} : \text{an instantaneous kick's size}$$

* the impacts of M neuron synapses are additive:

$$I_{syn} = \sum_{i=1}^M J_i S_i$$

Eqn 2.64.

$$S_i = \sum_j \delta(t - t_j)$$

Conductance-based

$$I_{syn} = \sum_{i=1}^M w_i s_i (V - V_{syn})$$

Eqn 2.65

If synaptic inputs have an average conductance G_{syn}

$$\text{average } I_{syn} \sim G_{syn} (V - V_{syn})$$

Eqn 2.66

$$\text{effective time constant } T_{m, \text{eff}} = \frac{C_m}{G_L + G_{syn}}$$

Eqn 2.67

much shorter than $T_m = \frac{C_m}{G_L}$ without synaptic inputs

- with increased synaptic inputs, the neuron becomes leakier → less capable of temporal integration
- its firing is determined by the coincidence of multiple synaptic inputs within a very brief period of time \rightarrow behave as a "coincidence detector"

rather than an "integrator".

9.1. Filter and Kinetic Models

9.1.1 Understand the temporal synaptic dynamics:

1. assume a temporal filter $h(t)$

the synaptic variable $s(t)$ is given by:

$$s(t) = \sum_j h(t - t_j)$$

→ the kick synapse model is a special case with $h(t - t_j) = \delta(t - t_j)$

Eqn 2.68

• A commonly used filter $h(t) = (t/2) \exp(-dt)$

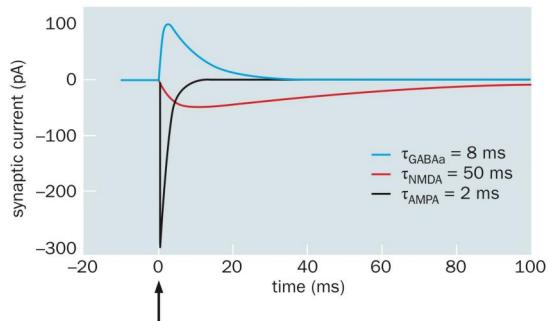
↓

this "alpha-function" } rise from 0
 reach a maximum at time $t_{peak} = \frac{1}{2}$
 decays exponentially with a time constant $T_{syn} = \frac{1}{2}$

→ to describe the rise time and decay time

$$h(t) = A(\exp(-t/\tau_1) - \exp(-t/\tau_2)) \quad \text{Eqn 2.69}$$

↳ $\tau_1 > \tau_2 \Rightarrow h(t) > 0$
 $t_{peak} = \ln(\tau_1 / \tau_2) / (1/\tau_1 - 1/\tau_2)$
 decays as $\propto \exp(-t/\tau_1)$



2. describe synapses by a kinetic equation:

assuming channels obey first-order chemical reaction

For a presynaptic spike train $\{t_j\}$:

$$\frac{ds}{dt} = \alpha_s \sum_j \delta(t-t_j)(1-s) - \beta_s s \quad \text{Eqn 2.70}$$

where: $(\alpha_s \sum_j \delta(t-t_j))$: opening rate ($=0$ except when there is presynaptic spiking activity)

β_s : the rate of "unbinding" with the receptor leading to "channel closing"

$s(t)$ decays exponentially with a time constant $T_s = \frac{1}{\beta_s}$

$s \rightarrow 1, s=1 \rightarrow 0 \Rightarrow s$ cannot exceed 1

can be extended to two or more chemical reactions

Saturation properties

reflecting that there is only a finite amount of receptor-channel complex available at a synapse

91.2: understand synaptic saturation

approximate the pre-synaptic spike train by its average rate

$$r = (1/T) \int_0^T \sum_j \delta(t - t_j)$$

Eqn 2.71

$$\frac{ds}{dt} = \alpha_s r(1-s) - \beta_s s$$

Eqn 2.72

with repetitive simulation, $s \uparrow$ and eventually reaches a steady-state:

$$S_{ss} = \frac{\alpha_s T_s r}{\alpha_s T_s r + 1}$$

Eqn 2.73

$\alpha_s T_s r \ll 1 \rightarrow$ the level of synaptic activation increases roughly linearly with presynaptic firing rate

consider $ds \approx 1 \Rightarrow r \ll 1/T_s \rightarrow$ when firing rate is tens of Hz

we often can neglect the factor $(1-s)$



$$\frac{ds}{dt} = \alpha_s \sum_j \delta(t - t_j) - \beta_s s$$

Eqn 2.74

for AMPA and GABA_A receptor-mediated synaptic current

equivalent to a linear filter with the time constant T_s

$$\text{the summated inputs: } S_{tot} = \sum_{j=0}^M S_j$$

Eqn 2.75

$$\frac{dS_{tot}}{dt} = \alpha_s \sum_j \sum_i \delta(t - t_j^i) - \beta_s S_{tot}$$

Eqn 2.76

the approximation $(1-s) \approx 1$ is no longer valid for NMDA ($T_s \approx 50-100 \text{ ms}$)

92. NMDA receptor-mediated synaptic excitation

A distinguishing feature of the NMDA synaptic conductance \Rightarrow nonlinear dependence on the postsynaptic voltage:

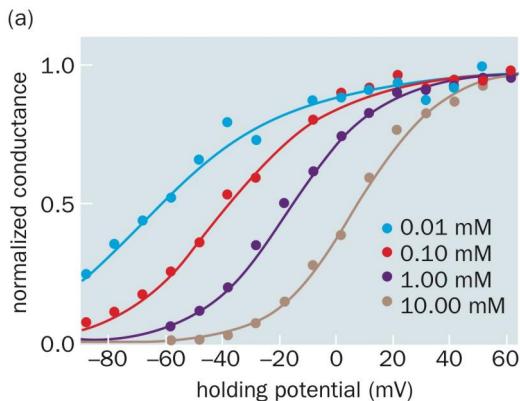
the current:

$$I_{NMDA} = g_{NMDA} F(V) s(V - V_E)$$

Eqn 2.77

$$F(V) = 1 / (1 + [Mg^{2+}] \exp(-0.062V) / 3.57)$$

$[Mg^{2+}]$: extracellular Mg^{2+} concentration



→ Sigmoid-shaped dependence on the postsynaptic membrane potential

↳ the NMDA channel opening is negligible if the membrane potential is close to the resting state (-70 mV) and becomes large only when depolarization

↳ NMDA conductance activation requires a coincidence of pre- and post-synaptic activity

↳ NMDARs have a crucial role in Hebbian synaptic plasticity that relies on pre- and post-synaptic co-activation.

- NMDARs play an important role in online neural computations,

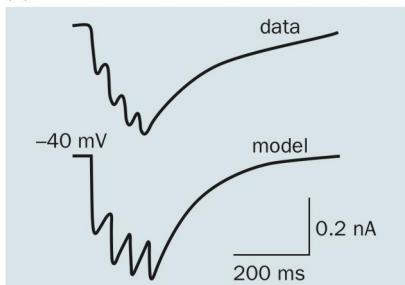
especially in brain structures of importance to higher cognition

↳ NMDA-mediated excitation is much slower than AMPA



saturation cannot be neglected even for firing rates within common observed physiological range (10-50 Hz)

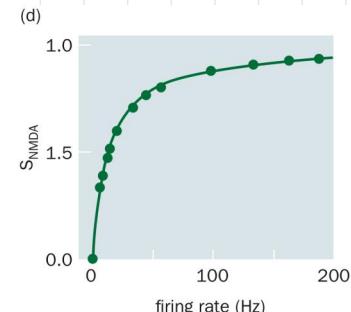
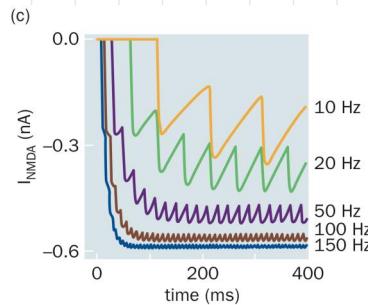
(b)



Potential Topic

My Insight

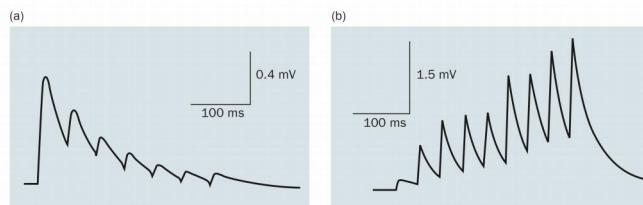
compare neural signal from real data and simulated signal from models.



93. Short-term Synaptic Plasticity

↳ refer to the phenomenon that synaptic transmission between two neurons is not static, but can either decrease or increase

depending on the history of the presynaptic neuron's firing activity



97.1

short-term synaptic depression

素還り

 N : readily releasable vesicles of neurotransmitters N_0 : total releasable vesicles of neurotransmitters

sensitive to input but not its steady-state

$$\text{Let } D = \frac{N}{N_0} \xrightarrow{\text{after each release in average}} (1 - P_{\text{rel}})D$$

release probability ↑

$$\frac{dD}{dt} = -P_{\text{rel}} D \sum_j \delta(t - t_j) + \frac{(1-D)}{T_0}$$

Eqn 2.78

where D multiplying $\delta(t - t_j)$ → take the value D^- evaluated immediately before the spikes, at t_j

$$\text{the update by a spike: } D^+ - D^- = -P_{\text{rel}} D^-$$

or

$$D^+ = (1 - P_{\text{rel}})D^-$$

Eqn 2.79

For a Poisson spike train at rate r → approximate the presynaptic spike train $\sum_j \delta(t - t_j)$ by its rate r :

$$\frac{dD}{dt} = -P_{\text{rel}} r D + \frac{1-D}{T_0}$$

Eqn 2.80

$$\text{The steady-state } \Rightarrow \frac{dD}{dt} = 0 \rightarrow D_{\text{ss}} = \frac{1}{1 + P_{\text{rel}} r T_0}$$

Eqn 2.81

$$-P_{\text{rel}} r D + \frac{1-D}{T_0} = 0$$

$$1 = (T_0 P_{\text{rel}} r + 1) D_{\text{ss}}$$

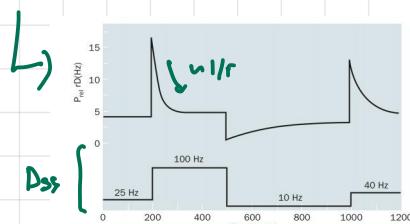
$$D_{\text{ss}} = \frac{1}{1 + r P_{\text{rel}} T_0}$$

$$\cdot \text{ For } r \gg \frac{1}{P_{\text{rel}} T_0} \Rightarrow r P_{\text{rel}} T_0 \gg 1 \Rightarrow D_{\text{ss}} \cong \frac{1}{r P_{\text{rel}} T_0} \propto \frac{1}{r} \quad \hookrightarrow r \uparrow \rightarrow \text{saturation (independent of } r)$$

means that the impact on the postsynaptic cell is not sensitive to the steady-state level of presynaptic activity

when there is a sudden change in the input \uparrow the synapse can detect it by a transient response after

transient response after



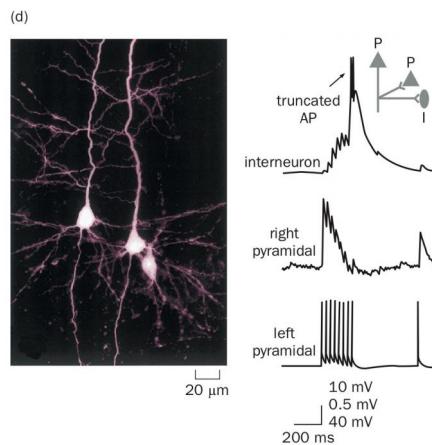
→ the time constant governing the decay process toward a steady-state

$$T_{\text{decay}} = \frac{T_0}{1 + P_{\text{rel}} r T_0}$$

Eqn 2.82

9.2. Short-term synaptic facilitation

a presynaptic pyramidal cell connects to another pyramidal cell with short-time depression or an inhibitory neuron with short-term facilitation



An important rule

whether an excitatory synaptic connection displays predominantly short-term depression or facilitation is determined by the postsynaptic (excitatory or inhibitory) cell types.

↓
short-term dynamics of an inhibitory connection depends on the presynaptic cell subclass



{ excitatory \Rightarrow postsynaptic
inhibitory \Leftrightarrow presynaptic

- Pres depends on the intracellular calcium concentration at a presynaptic terminal.

\curvearrowleft may accumulate over repetitive stimulation due to slow residual calcium

\downarrow
(on average of Pres)
Pres increases in time \Leftrightarrow gradually larger synaptic response

Computational model:

- assume $\text{Pres} = u(t)$ is activity-dependent and obeys:

$$\frac{du}{dt} = U \sum_j \delta(t-t_j) (1-u) + (U-u)/T_F \quad \text{Eqn 2.83}$$

\hookrightarrow where: U (less than one): the baseline value of u or release probability

$U(1-u) \delta(t-t_j) \Leftrightarrow U(1-u^-) \Leftrightarrow$ evaluated immediately before the delta functions at t_j

the update from before to after a spike: $U^+ - U^- = U(1-u^-)$

$$\text{or} \\ U^+ = U^- + U(1-u^-)$$

Eqn 2.84

- When absence of presynaptic firing $\Rightarrow U \sum_j \delta(t-t_j)(1-u) = 0 \Rightarrow \frac{du}{dt} = (U-u)/T_F$

U decays exponentially towards U with a time constant T_F

Derivation when steady-state: $\frac{du}{dt} = 0 \quad \frac{U-u}{T_F} = 0 \quad U_{ss} = U$

$$\frac{du}{dt} = \frac{U}{T_F} - \frac{1}{T_F} \cdot u \quad \frac{du}{U-u} = \frac{dt}{T_F} \quad \int \frac{1}{U-u} du = \int \frac{1}{T_F} dt$$

!

$$-\ln(U-u) = \frac{t}{T_F}$$

$$U-u = e^{-t/T_F}$$

$$u(t) = U - e^{-t/T_F}$$

- Replace $\sum_j \delta(t-t_j)$ by firing rate r :

$$U_{ss} \approx \frac{U(1+rT_F)}{1+UrT_F}$$

Eqn 2.85

Derivation

$$\frac{du}{dt} = U(1-u)r + \frac{U-u}{T_F} = 0$$

$$Ur + \frac{U}{T_F} = U(Ur + \frac{1}{T_F})$$

$$U = \frac{Ur + \frac{U}{T_F}}{Ur + \frac{1}{T_F}} = \frac{U(1+rT_F)}{1+UrT_F}$$

At low firing rates $r \leq \frac{1}{UrT_F} \Rightarrow UrT_F \ll 1 \Rightarrow U_{ss}$ increases linearly with r

$$r \gg \frac{1}{UrT_F}, \quad U_{ss} \rightarrow 1$$

- For a synapse can display both short-term depression and facilitation:

$$\frac{du}{dt} = U \sum_j \delta(t-t_j)(1-u) + \frac{U-u}{T_F} \quad \text{Eqn 2.85}$$

$$\frac{dD}{dt} = -uD \sum_j \delta(t-t_j) + \frac{1-D}{T_D} \quad \text{Eqn 2.86}$$

the change of synaptic variable D induced by a presynaptic spike \underline{ds} is $\underline{d}uD$.

and more precisely $u^+D^- \rightarrow$ subtlety in differentiating a variable before and after a spike

• by a spike input $u^+ = u^- + U(1-u^-)$

$$D^+ = (1-u^+)D^-$$

recall: $\frac{ds}{dt} = \lambda s \sum_j \delta(t-t_j)(1-s) - \beta_s s$

→ the synaptic variable s is updated using

$$\Delta s = \alpha u^+ D^-$$



• replay by r :

Idea! replace $\sum_j \delta(t-t_j)$ with firing rate r

$$\frac{du}{dt} = Ur(1-u) + \frac{u-u}{T_f}$$

Eqn 2.87

$$\frac{dD}{dt} = -uD r + \frac{1-D}{T_p}$$

Eqn 2.88

$$\frac{ds}{dt} = \alpha u D r (1-s) - \frac{s}{T_s}$$

Eqn 2.89

↓

Computational model for short-term synaptic plasticity