Neural circuits for cognition

Neurobiology basics, single-neuron models, and simplification to rate-based models

MIT Course 9.49/9.490

Instructor: Professor Ila Fiete
Logistics

• Get on Piazza if you haven’t.
• New course website (linked from Stellar).
• Notes/slides not available for all lectures, but when available I’ll post (you’re still responsible for taking notes!)
• HW 1 will be assigned next week. (Out of ~6).
• A few journal club-like in-class presentations (6-8 times)
  • 2-3 people per presentation
  • Each person responsible for signing up (at least!) once
  • Part of HW grade
• General homework submission guidelines:
  • Type out derivations, turn in code, and turn in plots/numerical results.
  • Write your name
  • Write the names of your collaborators
  • Certify: “I wrote the submitted code.”
Basic facts and figures
The human brain

- 3 lbs
- 2-3% body weight 20% energy, oxygen use
- \( \sim 100 \) billion neurons \((10^{11})\) \((\sim 10^{10} \text{ in cerebral cortex, } \sim 10^{11} \text{ in cerebellum})\); 1 bit/neuron \(\rightarrow\) 0.1 terabits! (terabit = \(10^{12}\) bits)
- 10-100 trillion synapses \((10^{13} - 10^{14})\); 1 bit/synapse \(\rightarrow\) 10 terabits \(-\) 0.1 petabit (petabit = \(10^{15}\) bits)
- Synapses sparse: only 100-1000/cell (very far from all-to-all connectivity)
- Cell body size: 10 microns \((100^{th} \text{ of a millimeter or } 1/10 \text{ hair thickness})\)
- Axon/cell length up to 1 m (see Mouselight, Janelia Farms for highly detailed collateral projections of cells, showing highly specific, extensive across-brain axon projection of single neurons in mice)
Brain scaling across species


For more info on comparative brain scaling, see:
S. Herculano-Houzel. The human brain in numbers: a linearly scaled-up primate brain
[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776484/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776484/)
S.S. Wang. Functional tradeoffs in brain scaling: implications for brain function
Brain scaling across species

**Brain neurons (billions)**

- Elephant: 251
- Mammoth: 0.294
- Rhesus monkey: 6
- Gorilla: 38
- Chimpanzee: 22
- Human: 89

Sources: Suzana Herculano-Houzel, Marino, L. Brain Behav Evol 1998;51:238-238

**Cerebral cortex neurons (billions)**

- Elephant: 5.0
- Mammoth: 0.245
- Rhesus monkey: 1.7
- Gorilla: 9.1
- Chimpanzee: 6
- Human: 10.3

Sources: Suzana Herculano-Houzel, Marino, L. Brain Behav Evol 1998;51:238-238
Neurons
Neurons
~10000 cell types

Vast complexity in structure.
Could lead to rich spatial and spatio-temporal input interactions.
Simplify: parts of a neuron

- **Nucleus**
- **Cell Body**
- **Dendrite**
- **Schwann cell (Myelin Sheath)**
- **Axon**
- **Nodes of Ranvier**
- **Axon Terminals**

**Input end**

**where spikes are initiated**

**Output end**
Resting state: ionic segregation

- Membrane pumps use energy (ATP) to actively maintain chemical gradients across the membrane.
- Concentration gradients of various ions maintained across the cell:

<table>
<thead>
<tr>
<th>Ionic species</th>
<th>Pump direction</th>
<th>Outside (mM)</th>
<th>Inside (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+)</td>
<td>out</td>
<td>145</td>
<td>12</td>
</tr>
<tr>
<td>K(^+)</td>
<td>in</td>
<td>4</td>
<td>155</td>
</tr>
<tr>
<td>Ca(^{2+})</td>
<td>out</td>
<td>1.5</td>
<td>(10^{-4})</td>
</tr>
</tbody>
</table>
Resting state: ionic segregation and $V_m$

- Membrane pumps use energy (ATP) to maintain chemical gradients across the membrane.

- Chemical gradient of ionic species A sets up voltage difference through Nernst Potential:

\[
V_m = \frac{k_B T}{z e} \ln \frac{[A]_{out}}{[A]_{in}}
\]

$e =$ electron charge
$z =$ charge of ionic species (Ca$^{2+}$: 2, Na$^+$: 1)
$T =$ temp in Kelvin
$k_B =$ Boltzmann const.

- Generalization to multiple ionic species/non-equilibrium: Goldman-Hodgkin-Huxley Potential (see Johnston & Wu textbook): $V_m \approx -55 - 60 \text{ mV}$
Activity in a neuron: electrical potential

Neurons have an electrical polarization between their insides and the outside world.

The polarization is maintained so that the cell’s resting voltage is negative; this is done through the expenditure of energy (ion channel pumps that maintain certain chemical gradients that induce electrical gradients).

An action potential is a brief, highly nonlinear, stereotyped and rapid voltage change in the cell’s state.

An action potential is how a neuron transmits a signal to other neurons or muscles.
First recording of AP by electrode inserted into axon: Hodgkin Huxley 1939; model: 1952; Nobel prize: 1963
Communication

The chemical synapse
The action potential is a signal that communicates a binarized version of the somatic state in a way that is regenerative and non-dissipative across short and long distances in the brain.
Chemical synapse

V(t)

C. Koch, Biophysics of Computation
The chemical synapse

1. Action potentials arrive at axon terminal.
2. Voltage-gated Ca^{2+} channels open.
3. Ca^{2+} enters the cell.
4. Ca^{2+} signals to vesicles.
5. Vesicles move to the membrane.
6. Docked vesicles release neurotransmitter by exocytosis.
7. Neurotransmitter diffuses across the synaptic cleft and binds to receptors.
The chemical synapse

Whether a neuron has an excitatory or inhibitory effect on its neighbors depends on the neurotransmitter it produces. **Dale’s law:** A neuron either excites all its synaptic contacts or inhibits all of them.
CNS neurotransmitters and timescales

• Key excitatory neurotransmitters:
  • Glutamate (amino acid); receptors: AMPA (fast; 5 ms), NMDA (slow; 50 ms)
  • Acetylcholine

• Key inhibitory neurotransmitters:
  • Gamma-aminobutyric acid (GABA) (amino acid); receptors GABA-A (fast; 5 ms); GABA-B (slow; ~100 ms)
  • Glycine (amino acid)

• Various others

Dale’s law: A neuron releases the same set of neurotransmitters from all its synapses. (Stated by Eccles in this form.)
Rough timescales

Neural membrane time-constant ~ 10 – 30 ms.
Action potential ~ 1 ms.
Postsynaptic potential decay time-constants ~ 5 - 100 ms.
Cross-brain conduction ~ 10-200 ms.
Protein degradation/turnover ~ 1 hour – 1 day.

Short-term memory ~1-100 s.
Long-term memory ~ 1 hour – 100 years.
Simple single-neuron models
Simple RC model for subthreshold voltage

Well below “AP threshold”, cell membrane dynamics well-modeled by a simple RC circuit.

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I \]

Equivalent RC circuit:

\[ V(t) = V_{in}(t) - V_{out} \]

With appropriate choice of I, this includes HH and other models.
Single voltage variable $V(t)$ in model: ignoring spatial dynamics

Simplest spatial models: multiple discrete equi-voltage compartments, resistively coupled.

Modeling software for biophysically detailed and spatially extended neurons: NEURON.
Simple RC model for subthreshold voltage

Well below “AP threshold”, neuron dynamics very well-modeled by a simple RC circuit

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I \]

At rest, the inside of neuron is maintained (with energy expenditure: setting up Nernst potential through chemical gradients) at a negative potential relative to the outside:

\[ V_m \approx -55 - 60 \text{ mV} \]

(Assuming \( I \) is small enough that cell is maintained below “AP threshold”; next slides.)
Simple RC model for subthreshold voltage

Equivalent RC circuit:

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I \]

Membrane capacitance \( C_m \)
Trans-membrane voltage drop \( g_m \)
Resting voltage \( V_m \)
Other currents

Equivalent RC circuit:

\[ V(t) = V_{in}(t) - V_{out} \]

\[ V_{in} \]
\[ C_m \]
\[ g_m \]
\[ I \]
\[ V_m \]
\[ V_{out} \]

\( C_m = 1 \mu F/cm^2 \)
\( 1/g_m \approx 10000 \Omega \ cm^2 \)
\( \Rightarrow \tau_m = C_m/g_m \approx 10 \ m.s \)

Take note of the short single-neuron time-constant (memory of single cells).
Simple RC model for subthreshold voltage

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I \]

Steady-state with \( I = I_{app} \ll g_m(V_{th} - V_m) \)

\[ \bar{V} = V_m + \frac{I_{app}}{g_m} \]
Numerical integration

\[ \frac{dx}{dt} = f(x, t) \]

1st order (nonlinear) differential equation

\[
\lim_{\Delta t \to 0} \frac{x(t + \Delta t) - x(t)}{\Delta t} = f(x, t)
\]

Euler method: discretize time in steps of \( \Delta t \) and approximate differential by finite difference:

\[
\frac{x(t + \Delta t) - x(t)}{\Delta t} \approx f(x, t) \quad \text{for sufficiently small } \Delta t
\]

\[
x(t + \Delta t) \approx x(t) + \Delta t \times f(x, t)
\]

Here, \( x \) is a single point in each time-bin, replacing the continuously varying \( x \) in the original. The discrete-time is a time-a-
Numerical integration

\[ \frac{dx}{dt} = f(x, t) \quad \text{1st order (nonlinear) differential equation} \]

\[ x(t + \Delta t) \approx x(t) + \Delta t \cdot f(x, t) \quad \text{for sufficiently small } \Delta t \]

Here, \( x(t) \) takes single value across one time-bin, replacing the continuously varying \( x(t) \) in the original.

The discrete-time \( x(t) \) can be viewed as a time-average of the continuous \( x(t) \) over the bin.
Numerical integration

• For first order differential equation with no delay, given $x(0)$, can obtain all subsequent $x(t)$.

• Euler method is very simple, but slow (have to choose $\Delta t$ small to get reasonable accuracy; “small” depends on dynamics).

• Other, more efficient methods for matched accuracy: Runge-Kutta; adaptive step-size; etc.
Numerical integration of subthreshold voltage

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{\text{app}} \]

Membrane capacitance
Membrane conductance
Trans-membrane voltage drop
Resting voltage
Input currents

\[ \dot{V} = V_m + \frac{I_{\text{app}}}{g_m} \]

\[ \tau_m = C_m/g_m \sim 10 \text{ ms} \]
Add spike mechanism

Hodgkin-Huxley model for both subthreshold voltage and AP generation

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} + I_{spk}(V(t), t) \]

Equivalent RC circuit:

Complex, nonlinear voltage-dependent currents for AP generation (see Hodgkin-Huxley model for details)
Leaky integrate-and-fire (LIF) model

Replace complex, detailed AP currents with a simple reset condition

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} \]

When \( V \gtrsim V_{th} \), then reset \( V \rightarrow V_{reset} \) and consider that the cell has spiked

+ spike-and-reset condition
Leaky integrate-and-fire (LIF) model

Replace complex, detailed AP currents with a simple reset condition

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} \]

When \( V/V_{th} \) then reset \( V \rightarrow V_{reset} \) and consider that the cell has spiked

As \( I_{app} \) increases, firing rate will increase \( \text{(HW: derive this).} \)
Synaptic activation model

Each synapse is a linear, low-pass filter of the presynaptic neuron's spikes; activation is a dimensionless variable than can be thought of as “fractional activity”

\[
\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_{\alpha} \delta(t - t_{spk, \alpha})
\]

Simple exponential decay

Upward increment whenever there is a spike (when \( t = t_{spk, \alpha} \))
Aside: Dirac delta function

\[ \int_{-\epsilon}^{\epsilon} \delta(x) \, dx = 1 \quad \rightarrow \text{has units of the inverse of its argument} \]

\[ \int_{-1}^1 f(x) \delta(x - a) \, dx = f(a) \quad \text{if } a \in I \]

\[ \int_{-1}^1 f(x) \delta(x - a) \, dx = 0 \quad \text{if } a \notin I \]
Aside: Kronecker delta

\[ \delta_{ij} = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases} \]
Synaptic activation model

Each synapse is a linear, low-pass filter of the presynaptic neuron’s spikes; activation is a dimensionless variable than can be thought of as “fractional activity”

\[
\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_{\alpha} \delta(t - t_{spk,\alpha})
\]

Discretize equation in time

\[
\frac{s(t + \Delta t) - s(t)}{\Delta t} = -\frac{s(t)}{\tau_{syn}} + \beta \int_{t}^{t+\Delta t} dt' \sum_{\alpha} \delta(t' - t_{spk,\alpha})
\]

\[
= -\frac{s(t)}{\tau_{syn}} + \beta \sum_{\alpha} \delta_{t,t_{spk,\alpha}^b}
\]

where the b superscript in \(t_{spk,\alpha}^b\) indicates the spike time bin in place of the precise spike time.
Synaptic activation model

Each synapse is a linear, low-pass filter of the presynaptic neuron’s spikes; activation is a dimensionless variable than can be thought of as “fractional activity”

\[
\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_\alpha \delta(t - t_{spk,\alpha})
\]
Synaptic activation model

Each synapse is a linear, low-pass filter of the presynaptic neuron’s spikes; activation is a dimensionless variable than can be thought of as “fractional activity”

\[
\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_{\alpha} \delta(t - t_{spk,\alpha})
\]

\[
\tau_{syn} = 20 \text{ ms}
\]

Compare: neural recording

\[
\tau_{syn} \sim 5 - 100 \text{ ms}
\]
From single neurons to interacting groups: networks
Closing the loop from output to input: spiking network equations

**Current-based model**

\[ I_{i,app} = \sum_j W_{ij} s_j(t) \]

OR, can use:

\[ I_{i,app} = \sum_{j \in E} W_{ij} s_j(t)(V_i(t) - V_E) + \sum_{j \in I} W_{ij} s_j(t)(V_i(t) - V_I) \]

**Conductance-based model:**
Effectiveness of synaptic input depends on voltage of target neuron.
From spike-based to rate-based models
From spike-based to rate-based neural models

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} + I_{spk} \]

\[ \frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_\alpha \delta(t - t_{spk,\alpha}) \]

input \( I_{app} \) → voltage → voltage spikes  

voltage spikes → output \( s \)

Can we model input \( I_{app} \) → output \( s \) and bypass \( V \)?
From spike-based to rate-based neural models

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} + I_{spk} \]

\[ \frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_{\alpha} \delta(t - t_{spk,\alpha}) \]

- Replace sum of fast-varying delta function input in (ii) by an average over one one inter-spike-interval, \( T_{isi} \)
- Reasonable if \( T_{isi} \ll \tau_{syn} \)

input (\( I_{app} \)) ➞ voltage

voltage (spikes) ➞ output (s)
From spike-based to rate-based neural models

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} + I_{spk} \]
\[ \frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_{\alpha} \delta(t - t_{spk,\alpha}) \]

- Replace sum of fast-varying delta function input in (ii) by an average over one inter-spike-interval, \( T_{isi} \)
- Reasonable if \( T_{isi} \ll \tau_{syn} \)
- Now:
  \[ \frac{1}{T_{isi}} \int_{t}^{t+T_{isi}} dt \sum_{\alpha} \delta(t - t_{spk,\alpha}) = \frac{1}{T_{isi}} \equiv r \]
  Instantaneous firing rate of cell
From spike-based to rate-based neural models

\[ C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} + I_{spk} \]
\[ \frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_\alpha \delta(t - t_{spk,\alpha}) \]

input (I_{app}) \rightarrow voltage

voltage (spikes) \rightarrow output (s)

- Replace sum of fast-varying delta function input in (ii) by an average over one inter-spike interval, \( T_{isi} \)
- Reasonable if \( T_{isi} \ll \tau_{syn} \)
- Since:
  \[ \frac{1}{T_{isi}} \int_t^{t+T_{isi}} dt \sum_\alpha \delta(t - t_{spk,\alpha}) = \frac{1}{T_{isi}} \equiv r \]  
  Instantaneous firing rate of cell
- Thus:
  \[ \frac{ds}{dt} \approx -\frac{s}{\tau_{syn}} + \beta r \]
From spike-based to rate-based neural models

\[
C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} + I_{spk}
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  \[
  \frac{1}{T_{isi}} \int_t^{t+T_{isi}} dt \sum_\alpha \delta(t - t_{spk,\alpha}) = \frac{1}{T_{isi}} \equiv r
  \]
- Instantaneous firing rate of cell

- Thus:
  \[
  \frac{ds}{dt} \approx -\frac{s}{\tau_{syn}} + \beta r
  \]

- Finally, note that: \( r = f(I_{app}) \) (\( f \) depends on neuron model; IF model for homework)
From spike-based to rate-based neural models

\[
C_m \frac{dV}{dt} = -g_m(V(t) - V_m) + I_{app} + I_{spk}
\]

\[
\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta \sum_{\alpha} \delta(t - t_{spk,\alpha})
\]

*input (I_{app}) \rightarrow voltage*

*Voltage (spikes) \rightarrow output (s)*

• Replace sum of fast-varying delta function input in (ii) by an average over one inter-spike-interval, \( T_{isi} \)

• Reasonable if \( T_{isi} \ll \tau_{syn} \)

• Since:

\[
\frac{1}{T_{isi}} \int_{t}^{t+T_{isi}} dt \sum_{\alpha} \delta(t - t_{spk,\alpha}) = \frac{1}{T_{isi}} \equiv r
\]

• Thus:

\[
\frac{ds}{dt} \approx -\frac{s}{\tau_{syn}} + \beta r
\]

• Finally, note that: \( r = f(I_{app}) \) (\( f \) depends on neuron model; IF model for homework)

• Thus:

\[
\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta f(I_{app})
\]

This equation relates neural \textbf{input} (I_{app}) to \textbf{output} (s) without intervening voltage: \textbf{rate-based equation.}
The rate-based equation

\[ \frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta f(I_{app}) \]

Common transfer functions (approximations to forms observed in neurons):

- **F-I curve**
- **Neural transfer function**
- **Neural nonlinearity**

- **Hodgkin-Huxley neuron**
- **sigmoid**
- **LIF neuron**
- **threshold-linear or ReLu (rectified linear unit)**

\[
\begin{align*}
\text{Hodgkin-Huxley neuron:} & \quad 1 + \tanh(I) \\
\text{sigmoid:} & \quad \frac{e^I}{1 + e^I} \\
\text{LIF neuron (homework):} & \quad \max(0, I - b)
\end{align*}
\]
Many simplifications in our model

“Point” neuron: space-clamped cell held at equipotential so it can be described by single voltage variable (vs actual branched structure; spatial coincidence detection)

That there is a “threshold” for activation (LIF models, not in HH); actually depends on timecourse of deporalizing response (HH models capture this).

All synapses emanating from a neuron have the same dynamics (vs stochastic transmission and separate history dependence at each synapse).

Neuron input-output can be described by firing rates not spikes. This ignores possible non-linear effects of coincident spiking/temporal coincidence detection, etc.
The rate-based network equation: Wilson-Cowan

\[
\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + \beta f(I_{\text{app}})
\]

In network, each neuron, \(i\), has a synaptic output: \(s_i(t)\)

The input to the neuron \(i\) is the sum of the outputs of all its connections: \(I_{\text{app},i}(t) = \sum_j W_{ij}s_j(t)\)

It might also receive some input from outside the network: \(b_i(t)\)

\[
\frac{ds_i}{dt} + \frac{s_i}{\tau} = f(\sum_j W_{ij}s_i + b_i(t)) \equiv r_i
\]
Interpretation of terms

\[ \frac{d s_i}{d t} + \frac{s_i}{\tau} = f(\sum_j W_{ij} s_i + b_i(t)) \equiv r_i \]

- Synaptic activation: output
- Total input ($g_i$) or input conductance
- Firing rate
- Biophysical time-constant (cell or synapse, depending on which is slow for method of averaging)
- Network input
- External input