An overview of single-cell and neural network models I

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Ribeirão Preto, SP, pop. ~620,000 (2012), alt. 547 m (1,791 ft)

Campus of the University of São Paulo at Ribeirão Preto. Notice the campus lake and the Clinics Hospital.
Part 1

Basic Concepts
# Spatial scales of the brain

<table>
<thead>
<tr>
<th>Scale</th>
<th>Level Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>~10cm</td>
<td>Whole brain</td>
</tr>
<tr>
<td>~1cm</td>
<td>Brain structure/cortical areas</td>
</tr>
<tr>
<td>100µm-1mm</td>
<td>Local network/‘column’/‘module’</td>
</tr>
<tr>
<td>10µm-1mm</td>
<td>Neuron</td>
</tr>
<tr>
<td>100nm-1µm</td>
<td>Sub-cellular compartments</td>
</tr>
<tr>
<td>~10nm</td>
<td>Channel, receptor, intracellular protein</td>
</tr>
</tbody>
</table>
Neuron

- The brain is made of isolated cells – neurons and glia –, which are structurally, metabolically and functionally independent.

- **Neuron doctrine** (Ramon y Cajal, 1894): The neuron is the **basic functional unit of the nervous system**

- Neurons are specialized for intercellular communication
A principal característica que distingue os neurônios das de mais células é que eles são especializados para comunicação intercelular.

Existem milhares de tipos diferentes de neurônios (veja a figura a seguir). Alguns neurônios não possuem dendritos, mas outros possuem arborizações dendríticas extremamente complexas. Alguns neurônios não possuem axônios, mas outros possuem axônios que podem atingir até 1 m de extensão.

Do ponto de vista anatômico, os neurônios podem ser diferenciados por tamanho e forma. As diferenças em tamanho e forma têm implicações sobre as maneiras como os neurônios processam e transmitem informação.

Os neurônios não são apenas unidades retransmissoras, isto é, que transmitem a mesma informação que recebem. Pelo contrário, um neurônio típico coleta sinais de várias fontes, integra e transforma esses sinais gerando complexos sinais de saída que são enviados para muitos outros neurônios.

Neurons have many and diverse shapes
Synapse

- Specialized region in which a **pre-synaptic** cell makes contact with a **post-synaptic** cell
- Synapses may be chemical or electrical
Neural circuits and networks

Alex Norton, EyeWire, Seung Lab, MIT

V.J. Wedeen e L.L. Wald, Martinos Center for Biomedical Imaging at Massachusetts General Hospital
Synaptic Plasticity

• Generic name given to any type of change (strengthening or weakening) in the efficacy of a synapse

• Synaptic plasticity can be of short or long duration

• Hypothetical mechanism underlying memory formation and learning

Kauer & Malenka (2007)
Neuronal Membrane

- Thin membrane (60-70 Å) that separates the cytoplasm from the extracellular space
- Made of a lipid bilayer in which proteins are immersed
- Some proteins cross the membrane forming ion channels

Ion channels

- Membrane proteins may undergo conformational changes under electrical and chemical control, thus regulating ionic flux
- The figure below illustrates a channel opening due to a protein-ligand binding
Membrane potential

• There is a difference of electrical potential between the two sides of the neuronal membrane

• Defining the zero of potential at the outside the inside is, in general, at a potential of −50 to −90 mV
Ionic concentrations

- Ion concentrations are different on the two sides of the neuronal membrane.

<table>
<thead>
<tr>
<th>Ion</th>
<th>In (mM)</th>
<th>Out (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frog muscle (20°C)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺</td>
<td>124</td>
<td>2,25</td>
</tr>
<tr>
<td>Na⁺</td>
<td>10,4</td>
<td>109</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>1,5</td>
<td>77,5</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>10⁻⁴</td>
<td>2,1</td>
</tr>
<tr>
<td><strong>Squid giant axon (20°C)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺</td>
<td>400</td>
<td>20</td>
</tr>
<tr>
<td>Na⁺</td>
<td>50</td>
<td>440</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>40-150</td>
<td>560</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>10⁻⁴</td>
<td>10</td>
</tr>
<tr>
<td><strong>Typical mammalian cell (37°C)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺</td>
<td>140</td>
<td>5</td>
</tr>
<tr>
<td>Na⁺</td>
<td>5-15</td>
<td>145</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>4</td>
<td>110</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>10⁻⁴</td>
<td>2,5 - 5</td>
</tr>
</tbody>
</table>
Origin of the membrane potential

- **Nernst potential**

\[
E = \frac{RT}{zF} \ln \frac{[C]_{\text{out}}}{[C]_{\text{in}}}
\]

<table>
<thead>
<tr>
<th>Ion</th>
<th>Inside (mM)</th>
<th>Outside (mM)</th>
<th>Equilibrium potential (Nernst)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>400</td>
<td>20</td>
<td>-75 mV</td>
</tr>
<tr>
<td>Na⁺</td>
<td>50</td>
<td>440</td>
<td>+55 mV</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>40-150</td>
<td>560</td>
<td>-66 to -33 mV</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>10⁻⁴</td>
<td>10</td>
<td>+145 mV</td>
</tr>
<tr>
<td>A⁻ (organic ions)</td>
<td>385</td>
<td>—</td>
<td>Squid giant axon at 20°C</td>
</tr>
</tbody>
</table>
Depolarization and hyperpolarization

Graded variation

Action potential
Action potential

- Shape (width and amplitude) characteristic of each neuron
- Threshold phenomenon (all or none)
- Propagates unchanged while subthreshold voltage fluctuations are strongly attenuated
- Used by neurons to code and transfer information
Refractory periods

- **Absolute**: period during which a second stimulus (no matter how strong) will not lead to a second spike. It is as if the spike threshold were infinite.
- **Relative**: period during which a second spike can be generated by a second stimulus stronger than the first. The strength of the second stimulus decays with time.

![Graph showing refractory periods](image)
F-I Curve

- Firing rate (F) of a neuron as a function of its input current (I)
- Each I value corresponds to a constant step current applied for a given time
- Describes the input-output transfer function of the neuron
- In general, F-I curves are nonlinear with saturation for high input values
Different types of neurons produce different spike train patterns in response to the same input current.

The different patterns are grouped in **electrophysiological classes** (four examples of cortical classes are shown below).

Steriade (2004)
Spike train measures

Spike train

\[ S(t) = \sum_{i=1}^{n} \delta(t - t_i), \]

Spike count

\[ r = \frac{n}{T} = \frac{1}{T} \int_{0}^{T} S(\tau) d\tau, \]

Time-dependent firing rate

\[ r_1(t) = \frac{n(t; t + \Delta t)}{\Delta t} \]

\[ r_2(t) = \int_{-\infty}^{+\infty} w(\tau) S(t - \tau) d\tau \]

\[ w(t) = \begin{cases} 
1/\Delta t & \text{se } -\Delta t/2 \leq t \leq \Delta t/2 \\
0 & \text{caso contrário.}
\end{cases} \]

\[ w(t) = \frac{1}{\sqrt{2\pi\sigma_w^2}} e^{-\frac{t^2}{2\sigma_w^2}} \]

Dayan & Abbott (2001)
Raster plot and PSTH

Used to represent neuronal response because of neuronal variability

Each dot represents an action potential

Each line corresponds to a repetition of the same stimulus

PSTH (spikes/sec)

PSTH: Peristimulus time histogram

rate = average over several runs (single neuron, repeated runs)

input

1st run

2nd

3rd

\[
\rho = \frac{1}{\Delta t} \frac{1}{K} \sum_{t} n_K(t, t+\Delta t)
\]

Gerstner & Kistler (2002)
Interspike Intervals (ISIs)

Another way to measure neuronal variability

\[ CV_{\text{ISI}} = \frac{\sigma_{\text{ISI}}}{\mu_{\text{ISI}}} \]
The graphs show two ways to quantify the responses of four types of cortical neurons: by the F-I curve and the histogram of ISIs.

Postsynaptic potentials

EPSP: excitatory postsynaptic potential

IPSP: inhibitory postsynaptic potential
The membrane equation (passive)

\[ I_C = C \frac{dV_m}{dt} \]

\[ I_r = \frac{(V - E_N)}{r} = g(V - E_N) \quad (1 \text{ open channel}) \]

\[ I_R = Ng(V - E_N) = G(V - E_N) \quad (N \text{ open channels}) \]

\[ \tau_m \frac{dV_m(t)}{dt} = -V_m(t) + E + RI_{inj}(t) \]

\[ \tau_m = RC \]
3D representation of a network model
Part 2

Single neuron models
What to model in a neuron model?

- Morphology (shape, axonal target, smooth or spiny);
- Electrophysiology (spike shape, pattern of spike train);
- Neurochemistry (neurotransmitter released at synapses);
Neuron model

• Deterministic vs. Stochastic
• Firing rate vs. Spiking
• High-dimensional vs. Low dimensional
• More vs. Less Biologically Faithful
Deterministic

Stochastic

Probability of firing

A still larger probability of firing

oops, neuron fired!
• Stochastic neuron models may fire in the presence of **subthreshold** inputs

• Firing of stochastic neuron models is **not reproducible**, i.e. repetitions of the previous simulation with the same order of synaptic inputs produce firing patterns with different spike times
Response variability of a neuron recorded from area MT of an alert monkey. A. Raster and PSTH depict responses for 210 presentations of an identical random dot motion stimulus. The motion stimulus was shown for 2 sec. The PSTH plots the spike rate, averaged in 2 msec bins, as a function of time from the onset of the visual stimulus. Vertical lines delineate a period in which spike rate was fairly constant. The gray region shows 50 trials from this epoch, which were used to construct B and C. D. Variance of spike count vs. mean no. of spikes obtained from randomly chosen rectangular regions like the gray one in A. The dashed line is the expected relationship for a Poisson point process.
The firing rate neuron

\[ u = w_1 x_1 + w_2 x_2 + \ldots + w_n x_n + b = \sum_{i=1}^{n} w_i x_i + b \]

or

\[ u = \sum_{i=0}^{n} w_i x_i, \quad x_0 = 1 \quad \text{and} \quad w_0 = b \]
Transfer functions

Step function:

\[ S = f(u) = \begin{cases} f_{\text{max}} & \text{se } u \geq 0 \\ 0 & \text{se } u < 0 \end{cases} \]

Piecewise linear:

\[ S = f(u) = \begin{cases} f_{\text{max}} & \text{se } u \geq u_{\text{max}} \\ \alpha u + \beta & \text{se } u_{\text{min}} < u < u_{\text{max}} \\ 0 & \text{se } u \leq u_{\text{min}} \end{cases} \]

Sigmoid
(e.g. logistic):

\[ S = f(u) = \frac{f_{\text{max}}}{1 + \exp(-\alpha u)} \]
Comments

• Firing rate models are among the earliest forms of neuron modeling (late 1930s)
• They are the default neuron model used by Artificial Neural Networks (ANNs)
• In brain modeling, firing rate models are supposed to mimic not single cells but the “average” firing behavior of cell populations
Population rate model

• Suppose a population of neurons so close together that they can be considered as ‘equivalent’, i.e. they have similar properties and connectivity and receive the same input. Due to noise, which is assumed to be independent for each neuron, their response to the input can be different.

• The firing rate, or activity $A(t)$, of the population is given by

$$A(t) = \lim_{\Delta t \to 0} \lim_{N \to \infty} \frac{1}{\Delta t} \frac{n_{\text{spikes}}(t; t + \Delta t)}{N}$$

where $n_{\text{spikes}}$ is the number of spikes of the population in the short time $\Delta t$
• Assume there are many groups of neurons. Each group \( i \) contains a large number of neurons and is described by its activity \( A_i(t) \).

• The interaction between the different groups can be modeled by

\[
A_j = f\left( \sum_i J_{ji} A_i \right)
\]

where \( A_j \) is the population activity of group \( j \) which receives input from other groups \( i \).

• In this equation, \( J_{ij} \) are no longer the weights of synapses between two neurons but an effective interaction strength between two groups of neurons.
Model dimension

• The dimension of a model is the number of variables used by the model: 1, 2, 3, 4, etc

• In general, the higher the number of dimensions of a model, the more difficult to understand its behavior

• Each variable has an equation associated to it, so high dimensional models are more computationally expensive
Criteria for biological faithfulness

- Explicitness: model variables can be mapped to measured quantities;
- Number of details included: dendritic morphologies, ionic channel types, inhomogeneities in ion channel distributions, intracellular and biochemical mechanisms (calcium buffering, diffusion, second messengers pathways), extracellular potential
- How is a spike generated? By hand or naturally from the equations
Hodgkin-Huxley model

- 4D, single compartment, explicit (based on ionic conductances), spikes naturally generated
Hodgkin-Huxley model
Mathematical fitting of experimental conductances

\[ C \frac{dV_m(t)}{dt} + G(V, t)(V_m - E_{rev}) = I_{inj}(t) \]

\[ dV_m/dt = 0 \]

\[ I_{inj}(t) = G(t)(V_m - E_{rev}) \]

\[ g_K(V, t) = \bar{g}_K n^4(V, t) \]

\[ n(V, t) = n_\infty(V) \left( 1 - e^{-t/\tau_n(V)} \right) \]

\[ g_{Na}(V, t) = \bar{g}_{Na} m^3(V, t) h(V, t) \]
Hodgkin-Huxley formalism

Opening and closing of Individual channels is a stochastic process

\[ I = \bar{g} \cdot p \cdot (V - E) \]

\( \bar{g} \) = maximal conductance

\( p \) = probability of open channel

\( p = m^a h^b \)
Comment

• Hodgkin and Huxley (1952) developed their model to describe action potential generation in the **squid giant axon**

• It is hugely different from mammalian cortical neurons

• But ionic currents in cortical neurons can be described in a similar way, hence “Hodgkin-Huxley-type models”
Detailed compartmental models

- \( D = q(m+1); \) \( q = \) number of compartments; \( m = \) number of conductances
- Used mostly for **single-neuron** modeling

Model of a cerebellar Purkinje cell (De Schutter and Bower, 1994): 4550 compartments.
Comment

• The addition of more and more compartments to a neuron model seems to be a good strategy to get closer to the “real thing”

• However, increased complexity not necessarily always lead to better models:
  – Each new compartment requires the modeler to decide which conductances to put in it and with what parameters, and there are few cases in which these are known (so the modeler has to “guess”)
  – As the number of parameters increase so does the number of parameter combinations that produce similar behavior (how unique is a model?)
Reduced compartmental models

- Few compartments (e.g. ball-and-stick model)
- Used in “realistic” network models
Reduced HH models

- Single compartment models with only 2 or 3 variables (one being $V$
- Can replicate a number of properties of the HH model, including the genesis of an action potential
- Can be analyzed in the phase plane using dynamical systems tools: equilibrium points, limit cycles, bifurcations
Reduced HH models

V, m: fast variables  
N, h: slow variables

\[ m(t) \rightarrow m_{\infty} \]

\[ n(t) = 0.84 - h(t) \]

Model with 2 variables: V(t) and n(t)

Reduced models can be analyzed in the phase plane using dynamical systems tools: equilibrium points, limit cycles, bifurcations
Fast variables \((V, m)\)

\[
C_m \frac{dV}{dt} = -\bar{g}_K h_0^4 (V - E_K) - \bar{g}_{Na} m^3 h_0 (V - E_{Na}) - \bar{g}_V (V - E_V) + J_{\text{inj}}
\]

\[
\tau_m \frac{dm}{dt} = m_\infty - m.
\]

nullclines

\(J_{\text{inj}} = 0\)

\(J_{\text{inj}} > 0\)
$V$ and $n$ (fast and slow variables)

$$\frac{dV}{dt} = C_m \left( -g_K n^4 (V - E_K) - g_{Na} m^3 (V)(0.8 - n)(V - E_{Na}) - g_V (V - E_V) + J_{inj} \right)$$

$$\tau_n \frac{dn}{dt} = n_\infty - n,$$

$V$, $m$: fast variables

$n$, $h$: slow variables

$m(t) \rightarrow m_\infty$

$n(t) = 0.84 - h(t)$
Fitzhugh-Nagumo Model

2-D system that has the same qualitative characteristics of the fast-slow phase plane

\[
\frac{dv}{dt} = f(v) - w + I_{app}
\]
\[
\frac{dw}{dt} = \epsilon(v - \gamma w).
\]

\(v\) = voltage;
\(w\) = recovery variable

Cubic

Stable branches

Unstable branch

Keener & Sneyd (1998)

System has a stable resting state and is excitable

The resting state is unstable and there is a periodic orbit
Fitzhugh-Nagumo model
(Bifurcation diagram)

Keener & Sneyd (1998)
Simple spiking neuron models

• 1D or 2D, non-HH type models (not explicit)
• Emphasis on neuronal response (spike trains)
• Spikes generated by hand
• Examples:
  – Leaky integrate-and-fire (LIF) model (Lapicque 1907)
  – Non-linear LIF models (quadratic, exponential)
  – Izhikevich model
  – Adaptive exponential integrate-and-fire (AdEx) model
The LIF model

- Subthreshold dynamics ($V < V_{\text{th}}$):
  \[
  \tau \frac{dV}{dt} = -(V - V_{\text{rest}}) + R \cdot I
  \]

- Spike emitted (by hand) at $t = t_{\text{sp}}$ when $V = V_{\text{th}}$

- Then voltage reset to $V = V_{\text{reset}}$

- (Optional) refractory period:
  \[
  V(t) = V_{\text{reset}} \text{ for } t_{\text{sp}} < t < t_{\text{sp}} + \tau_{\text{ref}}
  \]

Response to noisy input $I(t)$

\[
I_{\text{th}} = \frac{V_{\text{th}} - V_{\text{rest}}}{R}
\]
Dynamics of the LIF model

• Rescaling \( \tau \frac{dV}{dt} = -(V - V_{\text{rest}}) + R \cdot I \):

\[
v \equiv \frac{V - V_{\text{rest}}}{V_{\text{th}} - V_{\text{rest}}}; \quad i \equiv \frac{RI}{V_{\text{th}} - V_{\text{rest}}}; \quad t' \equiv t / \tau \quad \Rightarrow
\]

\[
\Rightarrow \frac{dv}{dt'} = -v(t') + i
\]

with threshold at \( v = 1 \)

• Stable fixed point at \( v = i \)

• For \( i < 1 \) the membrane potential goes to the fixed point and stays there (no spikes)

• For \( i > 1 \) the membrane potential gets to the threshold and a spike occurs

• After the spike the membrane potential is reset to 0 and the process starts again

• The neuron keeps firing regularly while the above threshold stimulus is on
Non-linear I&F models

• Extensions of the LIF model given by

\[ \tau \frac{dv}{dt} = \phi(v) + i \]

with

\[ \phi(v) = a(v - b)^2 \] (quadratic IF model, QIF)
\[ \phi(v) = -v + ae^{v-b} \] (exponential IF model, EIF)

• The black dot in the top graph is a stable fixed point and the white dot is an unstable fixed point
• The voltage value of the white dot is the critical voltage for spike initiation by a short current pulse
• The bottom graph shows the case for a constant super-threshold current: the result is repetitive firing
• Notice that a strong inhibitory current can push the curve below the dv/dt = 0 line and disrupt the repetitive firing
Firing behavior of IF models

Voltage traces of IF models for the same noisy input current. B shows a higher resolution for a short time interval in which a spike has been generated in all models.

Fourcaud-Trocmé et al. (2003)
LIF with adaptive variable

$g_a$ is incremented after each spike so that the stronger $I_a$ current forces the voltage to $V_r$, thus making it more difficult for the voltage to reach threshold.
Izhikevich model

Quadratic integrate-and-fire with recovery variable (v and u).

v nullcline: quadratic
u nullcline: linear

\[ \begin{align*}
  v' &= 0.04v^2 + 5v + 140 - u + I \\
  u' &= a(bv - u)
\end{align*} \]

If \( v \geq 30 \text{ mV} \), then \( \begin{cases} v &\leftarrow c \\ u &\leftarrow u + d \end{cases} \)

v can escape to infinity (modeling spike initiation) but the voltage is reset when it reaches the peak value (defined by hand).

In the Izhikevich model the voltage reset occurs not at the threshold but at the peak of the spike

Izhikevich, 2007
Izhikevich model

By adjusting the four parameters \((a, b, c, d)\) of the model to experimental data, Izhikevich was able to mimic the firing behavior of a large number of cell types.
Adaptive EIF model (AdEx)

Exponential integrate-and-fire with recovery variable \((v \text{ and } u)\)

\[
\tau_v \frac{dV}{dt} = -(V - V_r) + \Delta_L \exp\left(\frac{V - V_L}{\Delta_L}\right) - Ru + RI
\]

\[
\tau_u \frac{du}{dt} = a(V - V_r) - u
\]

se \(V \geq V_{\text{pico}}\), então \(\{\begin{array}{l}
V \leftarrow V_{\text{reset}} \\
u \leftarrow u + b.
\end{array}\)
AdEx vs Izhikevich

The main differences of the Izhikevich model and the AdEx model are:
- quadratic voltage dependence in the voltage equation of the Izhikevich model versus exponential dependence in the AdEx model;
- upswing of the action potential is too slow in the Izhikevich model (Izhikevich 2007) compared to real neurons and more realistic in the AdEx model because of the exponential voltage dependence (Badel et al. 2008);
- the Izhikevich model shows unrealistic nonlinearities in the subthreshold regime, whereas the AdEx model is linear in agreement with experiments (Badel et al. 2008);
- attenuation of high frequency inputs as $1/f^2$ for a model with quadratic voltage dependence like in the Izhikevich model vs. $1/f$ for models with exponential voltage dependence (Fourcaud et al, 2003);
- the choice of the voltage cut-off value for spikes is critical in the Izhikevich model but less so in the AdEx model (In the absence of a cut-off the adaptation variable $w$ diverges in the Izhikevich model during the upswing of the action potential but does not diverge in the AdEx model.);
- extraction of the voltage dependence from experiments suggests a combination of linear and exponential terms as in the AdEx model (Badel et al. 2008), rather than a quadratic dependence as in the Izhikevich model;
- while qualitative fits to firing patterns are possible with both models, the AdEx model allows better quantitative fits to voltage traces (Naud et al. 2008).

http://www.scholarpedia.org/article/Adaptive_exponential_integrate-and-fire_model
What Is the Most Realistic Single-Compartment Model of Spike Initiation?

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Kink at onset