Mathematical Models in Neuroscience
Lecture 2- From the Hodgkin-Huxley equations to neural fields and topological methods

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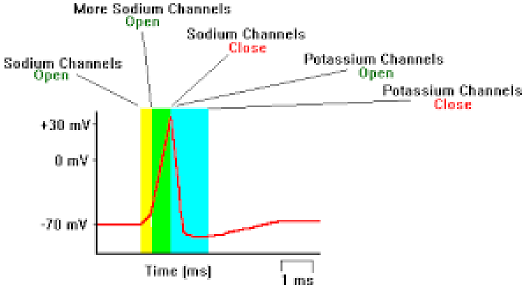
OUTLINE OF THE TALK

1. Hodgkin-Huxley equations
2. Fitzhugh-Nagumo equations
3. Leaky integrate and fire models
4. Neural fields
5. Representing neural networks by graphs
6. Using topological methods to evaluate the complexity of neuronal connections.
7. Mathematical tools of Neuroscience
8. Applications

1.HODGKIN-HUXLEYEQUATIONS

1.1 How is an action potential generated?

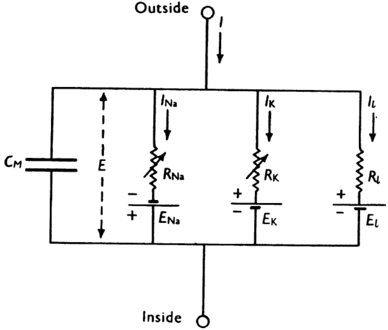


- The neuron membrane has a certain resting potential (about $-70Mv$).
- As a result of external stimulus, the membrane potential increases.
- When the membrane potential attains a certain threshold, the sodium channels open.
- As sodium ions flow into the neuron, the membrane potential increases (depolarization process).
- When the membrane potential attains a certain critical value, the sodium channels close and the potassium channels open.
- As potassium ions flow out of the neuron, the membrane potential decreases (repolarization process).

1.2 How can this process be described by a mathematical model?

In 1952 A.H. Hodgkin and A.F.Huxley introduced a mathematical model that describes the ionic mechanism underlying the iniciation and propagation of action potentials (nervous stimulus) in an axon.
The Hodgkin-Huxley model describes the ionic exchanges between the extracellular and intracellular medium, using the language of electric circuits (conductance, capacitance, current sources).
In 1963 A.H. Hodgkin and A.F.Huxley were awarded the Nobel Prize in Physiology or Medicine for this work.

1.3 HODGKIN-HUXLEY MODEL AND ELECTRIC CIRCUITS



Hodgkin and Huxley have described ion currents in the language of electric circuits.

The ion channels (sodium, potassium, leaky) are replaced by electrical resistances (R_{Na}, R_K, R_l).

The conductance in the leaky channel is constant (the channel is always open). The other channels may close or open when the membrane

1.4 EQUATION OF MEMBRANNE POTENTIAL

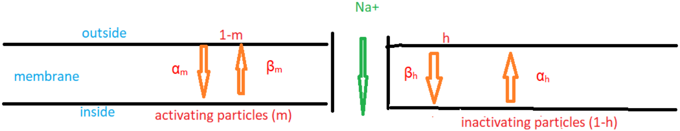
The main physical variables in the description of the ion currents are the membrane potential and the electrical conductances (sodium, potassium and leaky).
The equation for the membrane potential (V_m):

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

I- current; V_m - membrane potential;
g_k, g_{Na}, g_l- potassium, sodium, and leaky conductances;
V_k, V_{Na}, V_l - Potassium , sodium, and leaky reversal potentials.
The leaky conductance (conductance of the leaky channels) is constant.
The other conductances depend on the membrane potential.

1.5 How does the sodium conductance change?

There are particles that activate the sodium channels and particles that block them. These particles can move between inside and outside the membrane.



m- part of the activation particles which are inside the membrane.
h- part of the inactivation particles which are outside the membrane.

$$g_{Na} = \bar{g}_{Na} m^3 h,$$

$\bar{g}_{Na}$- maximal value of the sodium conductance.
α_m, β_m, (α_h, β_h) - transfer rates of the activation (inactivation) particles. Depend on the membrane potential, but not on the time.

1.6 How does the potassium conductance change?

In the case of potassium, there are only activation particles
n- part of the activation particles which are inside the membrane.

$$g_k = \bar{g}_k n^4,$$

$\bar{g}_k$- maximal value of the potassium conductance.
n satisfies the differential equation:

$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n.$$

α_n, β_n - transfer rates of the activation particles of the potassium channel.
m and h satisfy similar equations.

1.7 FULL SYSTEM OF EQUATIONS

By coupling the equation for the membrane potential with the equations for n, m,h, we finally obtain a system of 4 nonlinear ordinary differential equations, known as Hodgkin-Huxley equations:

$$I = C_m \frac{dV_m}{dt} + \bar{g}_k n^4 (V_m - V_k) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + g_l (V_m - V_l)$$

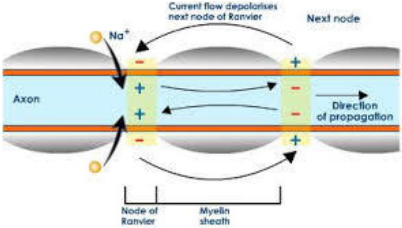
$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m) n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m) m$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m) h$$

2. FITZHUGH-NAGUMO EQUATIONS

Further investigation of the propagation of nervous stimulus has lead to the FitzHugh-Nagumo equations (1962), which describe the propagation of signals in myelinated axons.

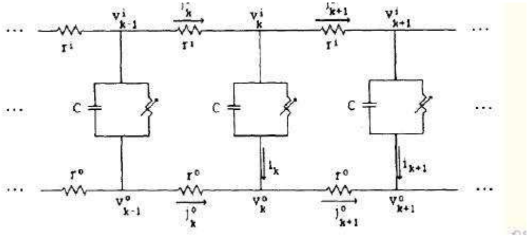


The myelin completely insulates the membrane, so that all the electric processes occur at the Ranvier nodes.

2.1 AXONS AND ELECTRIC CIRCUITS

Circuit Model

Impulse conduction in a myelinated axon can be simulated using a circuit model: the nodes of Ranvier correspond to capacitors and the space between them, to resistances.



2.2.Assumptions of the Nerve Conduction Model

- the nodes are uniformly spaced and electrically identical,
- the axon is infinite in extent,
- the cross-sectional variations in potential are negligible,
- a supra-threshold stimulus begins a signal which travels down the axon from node to node.

2.3.DISCRETE FITZHUGH-NAGUMO EQUATIONS

The propagation of nervous stimulus can be modeled by the following system of difference equations:

$$\left\{ \begin{array}{c} \frac{1}{R}(v_{k+1} - 2v_k + v_{k-1}) = C\frac{dv_k}{dt} - f(v_k) + w_k \\ \sigma v_k - \gamma w_k = \frac{dw_k}{dt} \end{array} \right. , \ k \in Z, \qquad (1)$$

where v_k represents the membrane potential at the k-th node , w_k is the so-called recovery variable, σ and γ are non-negative rate constants, R and C are the axoplasmical resistance and the nodal membrane capacitance. Equations (1) are known as the discrete FitzHugh-Nagumo equations.

2.4 ACTIVATION FUNCTION

The nonlinear function f in discrete FitzHugh-Nagumo equations represents a current-voltage relation (activation function) and is supposed to satisfy the following conditions:

$$\begin{gathered} f \in C^1([0,1]), \; f(0) = f(a) = f(1) = 0, \\ f(v) < 0, \; if \; 0 < v < a; \\ f(v) > 0, \; if \; a < v < 1. \end{gathered} \tag{2}$$

In many applications this function is taken as

$$f(v) = bv(v-a)(1-v), \tag{3}$$

where $b > 0$.

2.5.REDUCTION TO A SINGLE EQUATION

The discrete FitzHugh-Nagumo equations can be simplified by neglecting the recovery process (that is, it is assumed that the constants σ and γ are so small that the recovery process has no influence in propagation). Let us assume that

$$v_{k+1}(t) = v_k(t-\tau),$$

where τ is is a certain delay, which is proportional to the space between nodes and to the reciprocal of propagation speed. Then we obtain a mixed-type functional differential equation:

$$\frac{1}{R}(v(t-\tau) - 2v(t) + v(t+\tau)) + f(v(t)) = C\frac{dv(t)}{dt}, \qquad (4)$$

3. LEAKY INTEGRATE AND FIRE MODELS

In the LIF (Leaky Integrate and Fire) model, each neuron i can be fully described in terms of a single internal variable, namely the depolarization potential $V_i(t)$ of the neural membrane.

$$\tau \frac{dV_i}{dt} = -\left(V_i(t) - V_L\right) + RI_i(t),$$

where V_L -leaky (resting) potential;RI_i- total synaptic current (the sum of the action of all the synapses):

$$RI_i(t) = J \sum_{j=1}^{N} K_{ij} \sum_k \delta(t - t_j^{(k)}),$$

N - number of neurons connected with i; K_{ij} -efficacy of the connection between i and j; $t_j^{(k)}$ -time of the k_{th} spike of the j_{th} neuron;J -constant. When V_i reaches a certain threshold θ, the i-th neuron fires and the system is reset: V_i is set to the resting value V_L.

4. NEURAL FIELDS

A new approach was introduced in the years 70:
Wilson and Cowan, 1972 and Amari, 77
Consider a region Ω of the *n*-dimensional space and a function $V(\bar{x}, t)$, with $\bar{x} \in \Omega$.
We assume that the neurons are very densely distributed, so that we can assign a certain electric potential V to each point of Ω.
This approach is realistic when considering regions of the cortex.

$V(\bar{x}, t)$ represents the spatiotemporal structure of the neuronal population:
- spatial distribution of potential;
- time evolution.

4.1 NEURAL FIELD EQUATION

Neural Field Equation (NFE):

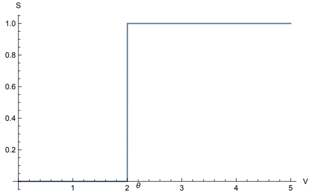
$$c\frac{\partial}{\partial t}V(\bar{x},t) = I(\bar{x},t) - V(\bar{x},t) + \int_{\Omega} K(\|\bar{x}-\bar{y}\|_2)S(V(\bar{y},t))d\bar{y}, \quad (5)$$

$$t \in [0, T], \bar{x} \in \Omega \subset \mathbb{R}^2;$$

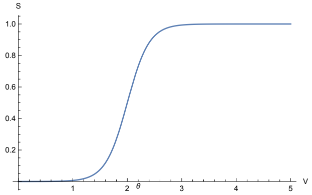
Initial Condition: $V(\bar{x},0) = V_0(\bar{x}), \qquad \bar{x} \in \Omega.$

- $V(\bar{x},t)$ - the membrane potential in point $\bar{x}$ at time t;
- $I(\bar{x},t)$ - external sources of excitation;
- $S(V)$ - dependence between the firing rate of the neurons and their membrane potentials (sigmoidal or Heaviside function);
- $K(\|\bar{x}-\bar{y}\|_2)$ - connectivity between neurons at $\bar{x}$ and $\bar{y}$.

4.2 EXAMPLES OF FIRING RATE FUNCTIONS

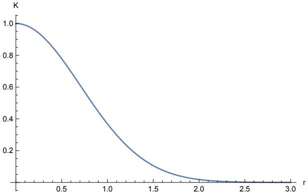


Heaviside function - the neuron is inactive ($S = 0$) while the potential does not reach the threshold value θ and then becomes fully activated ($S = 1$) .

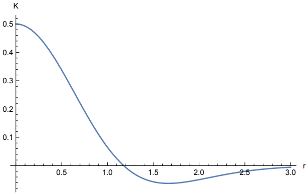


Sigmoidal function - as the potential increases the activation (S) varies continuously from 0 to 1.

4.3 EXAMPLES OF CONNECTIVITY FUNCTIONS



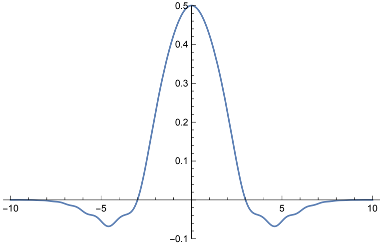
Gaussian function - the connectivity is positive everywhere (excitatory) and decreases with distance.



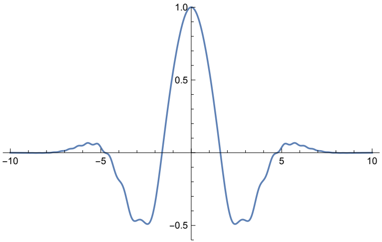
Mexican hat - the connectivity is positive (excitatoty) at short distances and negative (inhibitory) at long ones.

4.4 MULTIBUMP SOLUTIONS

Activation Domain : subset of Ω where the potential is higher than the threshold. In this domain there is a strong connection between neurons. The stationary solutions of NFE often have one or several activation domains (multibump solutions).



one-bump solution

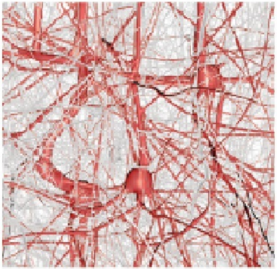


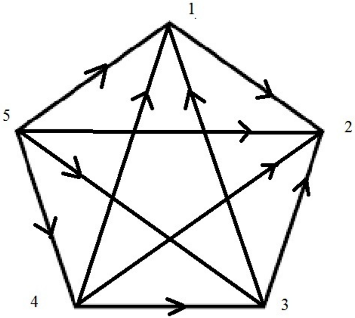
three-bump solution

5.ALGEBRAIC TOPOLOGY METHODS

Blue Brain Project
M. Reimann et al., Cliques of Neurons Bound into Cavities Provide a Missing Link between Structure and Function, Frontiers of Mathematical Neuroscience, June 2017.
Construct graphs of a network that reflect the direction of information flow and analyse these directed graphs using algebraic topology.

5.1 CLIQUES OF NEURONS AND GRAPHS





clique of neurons	directed graph
neuron	node
synapsis	directed edge
number of connected neurons	dimension

source: node that is source of all edges (5);
sink: node that is target of all edges (2)

5.3 DIRECTED SIMPLICES AND SIMPLICIAL COMPLEXES

directed simplex of dimension $n-1$ - clique of n all-to-all connected neurons.

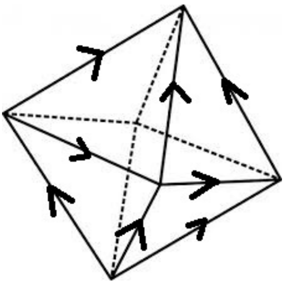
Each neuron belongs to many directed simplices of various dimensions. A neural network contains in general many simplices.

Definition. A simplicial complex K is a set of simplices that satisfy:

- Every face (subset) of a simplex from K is also in K.
- The intersection of two simplices S_1, S_2 of K is a face of S_1 and S_2.

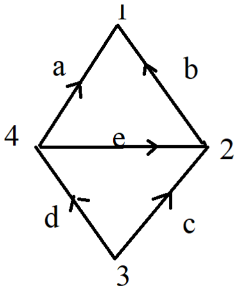
The dimension of a simplicial complex is the maximal dimension of the simplices that compose it.

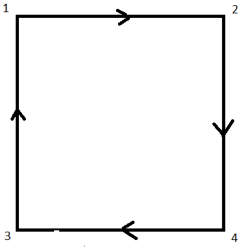
5.4 EXAMPLES OF A SIMPLICIAL COMPLEX



The octahedron is a simplicial complex because it is composed of 2D-simplices (triangles) and the intersection of these triangles is a 1D-simplex (an edge). The dimension of the octahedron is 2 (dimension of the faces).

5.4 MORE EXAMPLES





The lozenge (left-hand side) is a simplicial complex: each face of the complex is a triangle and the intersection of the two triangles is the edge e (a 1D-simplex). The dimension of this complex is 2 (dimension of the faces).

The square (right-hand side) is also a simplicial complex: it is a set of edges and the intersection of two edges is a vertice (a 0D-simplex). The dimension of this complex is 1 (dimension of the edges).

5.5 EULER HARACTERISTIC OF A SIMPLICIAL COMPLEX

Euler characteristic - $\chi(S) = \sum_{n=0}^{n_{max}} (-1)^n |S_n|$,
where S_n is the number of n-dimensional simplices contained in S.

EXAMPLES

In the case of the lozenge:
$S_0 = 4$ - number of 0-dimensional simplices (vertices);
$S_1 = 5$ - number of 1-dimensional simplices (edges);
$S_2 = 2$ - number of 2-dimensional simplices (faces);
Euler characteristic: $\chi(S) = 4 - 5 + 2 = 1$.

In the case of the octahedron:
$S_0 = 6$ - number of 0-dimensional simplices (vertices);
$S_1 = 12$ - number of 1-dimensional simplices (edges);
$S_2 = 8$ - number of 2-dimensional simplices (faces);
Euler characteristic: $\chi(S) = 6 - 12 + 8 = 2$.

5.5 EULER CHARACTERISTIC OF POLYHEDRA

The Euler characteristic was first introduced for polyhedra and defined as

$$\chi(P) = V - E + F,$$

where F is the number of faces, E is the number of *edges* and V is the number of vertices. In this context, Euler has stated the well-known polyhedron formula:

If P is a convex polyhedron, then

$$\chi(P) = 2.$$

For example, in the case of a cube:

$$V = 8, E = 12, F = 6,$$

then

$$\chi(P) = 8 - 12 + 6 = 2.$$

5.6 BETTI NUMBERS OF SIMPLICIAL COMPLEXES

- β_0- number of connected parts.
- β_1- number of one-dimensional circular holes (regions surrounded by one-dimensional simplices)
- β_2-number of two-dimensional cavities (regions surrounded by two-dimensional simplices)

5.7 EXAMPLES

Consider the lozenge: There is

- one connected component in this figure - $\beta_0 = 1$;
- two holes -$\beta_1 = 2$;
- no two-dimensional cavities- $\beta_2 = 0$.

Consider the octaedr: There is

- one connected component in this figure -$\beta_0 = 1$;
- eight holes - $\beta_1 = 8$;
- one two-dimensional cavity (the interior of the octaedr) - $\beta_2 = 1$.

5.9 LOCAL AND GLOBAL MEASURES OF INFORMATION

How do the topologic measures of geometrical objects reflect the properties of neural networks?

- Local flow of information is well described by directed graphs, identifying sources and sinks.
- Global measures of information are given by Betti numbers and Euler characteristic.

5.10 TOPOLOGICAL MEASURES AND NEURAL ACTIVITY

"The variation in Betti numbers and Euler characteristic over time (in response to stimulus) indicates that neurons become bound into cliques and cavities by correlated activity."

"A stimulus may be processed by binding neurons into cliques of increasingly higher dimension, as a specific class of cell assemblies, possibly to represent features of the stimulus."

"'The presence of high-dimensional topological structures is a general phenomenon across nervous systems".

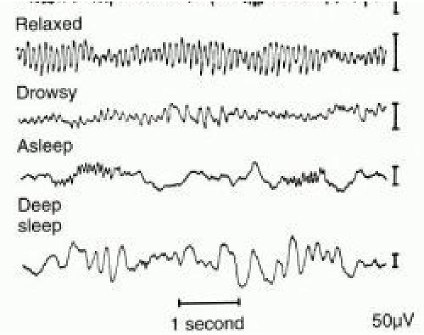
Michael Reinmann et al., 2017

6. MATHEMATICAL TOOLS IN NEUROSCIENCE

- Differential equations
- Dynamical systems
- Bifurcation theory
- Algebraic topology
- Stochastic processes (essential to take into account the influence of random factors)
- Computational methods (most of the considered equations cannot be solved analytically)

7. APPLICATIONS

INTERPRETATION OF MEDICAL DATA



Output of a Electroencephalogram (EEG). The EEG registrates neuronal activty with a good time resolution.

7.1 APPLICATIONS TO MEDICINE

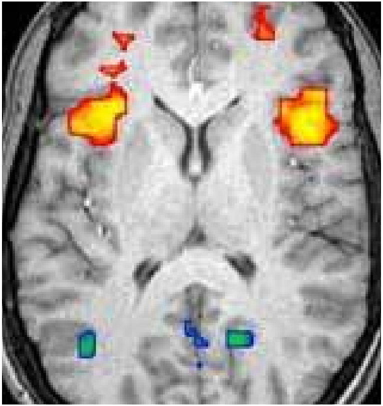


Image obtained by means of Magnetic Resonance (FMRI), showing the neural activity during the perception of a visual signal.
Neural field models provide a framework for unifying data from different imaging modalities, for example, EEG (which has a good time resolution) and FMRI (good spatial resolution).

7.2 APPLICATIONS TO ROBOTICS

"To efficiently interact with another agent in solving a mutual task, a robot should be endowed with cognitive skills such as memory, decision making, action understanding and prediction. The proposed architecture is strongly inspired by our current understanding of the processing principles and the neuronal circuitry underlying these functionalities in the primate brain."
W. Erlhagen and E. Bicho, The dynamic neural field approach to cognitive robotics, J. Neural Eng. 3 (2006) R36 – R54

Neural fields are a good tool to simulate working memory.
They simulate how a population of neurons can encode in its firing pattern the features of an external stimulus.

CREDITS

Michael W. Reimann, Max Nolte, Martina Scolamiero, Katharine Turner, Rodrigo Perin, Giuseppe Chindemi, Pawel Dlotko, Ran Levi , Kathryn Hess and Henry Markram, Cliques of Neurons Bound into Cavities Provide a Missing Link between Structure and Function, Frontiers in Computational Neuroscience, 2017, doi: 10.3389/fncom.2017.00048.

BIBLIOGRAPHY

- S.L. Amari, Dynamics of pattern formation in lateral-inhibition type neural fields, Biol. Cybernet. 27 (2) (1977) 77–87.
- J. Bell, Behaviour of some models of myelinated axons, IMA Journal of Mathematics Applied in Medicine and Biology, 1 (1984), 149–167.
- J. Bell and C. Costner, Threshold conditions for a diffusive model of a myelinated axon,J. Math. Biology , 18 (1983), 39-52.
- I. Bojak, D.T.J. Lily, Axonal Velocity Distributions in Neural Field Equations, Comput. Biol. 6(1), (2010), e1000653.
- S.Coombes, Large-scale neural dynamics: Simple and complex, NeuroImage 52, (2010), 731–739.

BIBLIOGRAPHY

- S.Coombes, N.A.Venkov, L.Shiau, I.Bojak, D.T.J.Liley, C.R.Laing, Modeling electrocortical activity through improved local approximations of integral neural field equations, Phys. Rev. E , 76, (2007), 051901.
- Gustavo Deco, Viktor K. Jirsa, Peter A. Robinson, Michael Breakspear, and Karl Friston, The Dynamic Brain: From Spiking Neurons to Neural Masses and Cortical Fields, Comput Biol. 2008 Aug; 4(8): e1000092
- R. FitzHugh, Impulses and physiological states in theoretical models of nerve membrane, Biophysical J., 1(1961), 445-466.
- R. FitzHugh, Computation of impulse initiation and saltatory condition in a myelinated nerve fiber, Biophysical J. , 2 (1962), 11-21.

BIBLIOGRAPHY

- A. Hodgkin and A. Huxley, A qualitative description of nerve current and its application to conduction and excitation in nerve, J. Physiology, 117 (1952), 500-544 .
- J.P. Keener, Propagation and its failure in coupled systems of discrete excitable cells, SIAM J. Appl. Math. , 47 (1987), 556-572.
- J. Nagumo, S.Arimoto and S. Yoshizawa, An active pulse transmission line simulating nerve axon, Proceedings of the IRE, 50 (1962), 2061–2070.
- R. Potthast and P. beim Graben, Existence and properties of solutions for neural field equations, Math. Meth. Appl. Sci., 33 (2010) 935-949.
- H.R. Wilson and J.D. Cowan, Excitatory and inhibitory interactions in localized populations of model neurons, Bipophys. J., 12 (1972) 1-24.