THE MATHEMATICAL MODELING OF BRAIN

Pedro Miguel Lima

CENTRO DE MATEMÁTICA COMPUTACIONAL E ESTOCÁSTICA
INSTITUTO SUPERIOR TÉCNICO
UNIVERSIDADE DE LISBOA
PORTUGAL

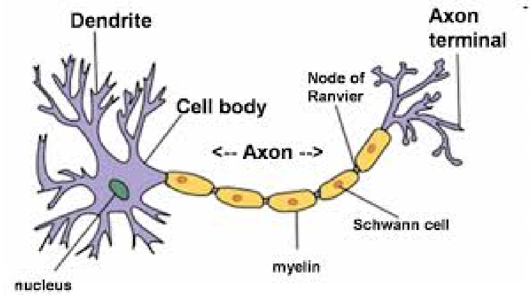
February 23, 2021

OUTLINE OF THE TALK

1. Introduction
2. Evolution of Mathematical Models
3. Mathematical Tools
4. Applications
5. Conclusion

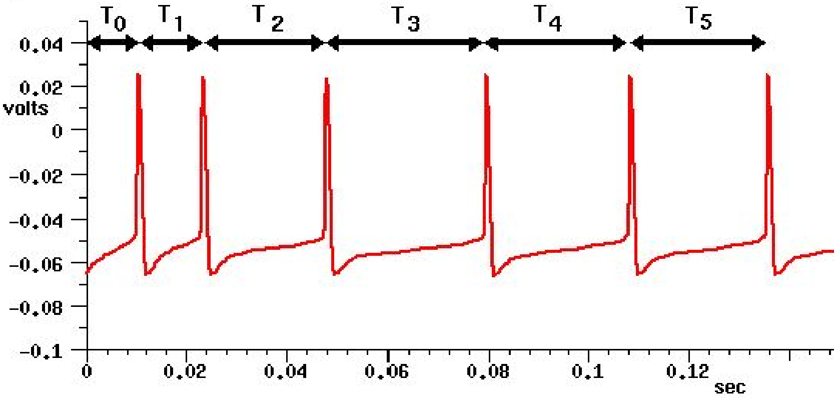
1. INTRODUCTION -THE HUMAN BRAIN

According to a lower estimate from 2009, the human nervous system contains 0.89×10^{11} neurons, which are connected by about 10^{15} synapses.



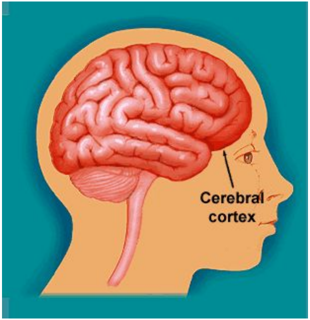
1.COMMUNICATION BETWEEN NEURONS

The change of voltage in the cell membrane of a neuron results in a voltage spike called an action potential, which triggers the release of other neurotransmitters. That is, neurons communicate with each other by firing.



1. THE CEREBRAL CORTEX

The cerebral cortex is the brain's outer layer of neural tissue in humans and other mammals. It plays a key role in controlling memory, attention, perception, awareness, thought, language and other important processes.

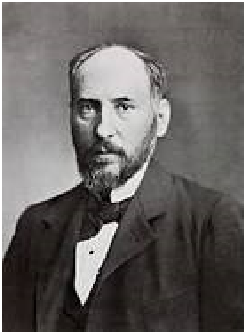


The cortex of a human is about 2-4 mm thick and contains about one fifth of all the neurons. According to recent estimates, the cortex can store up to
$100\,Tb$ (10^{14} bytes) of data!

1.DISCOVERY OF NEURON

In the middle of XIX century there were two theories about the structure of nervous cells:

- Reticularism: The nervous system consists of a large network of tissue (reticulum);
- Neuronism: The nervous systems consists of distinct cells (neurons).

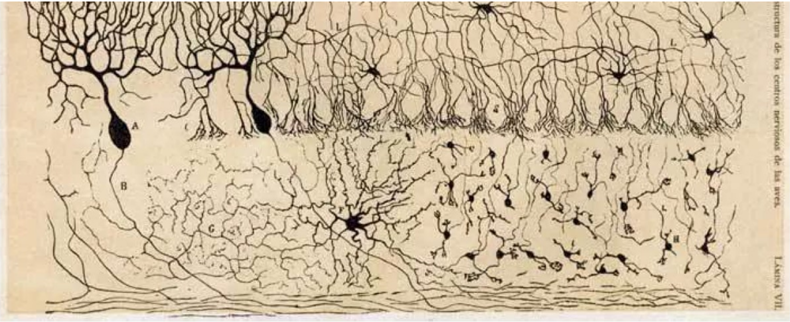


The second theory was defended by Ramon y Cajal (1852-1938) who was awarded the Nobel Prize in Physiology in 1906 (together with Colgi).

1.DISCOVERY OF NEURON

The term neuron was introduced in 1891. Ramon y Cajal developped the so-called Neuron Doctrine:

- The neuron is the structural and functional unit of the nervous system;
- Each neuron is a distinct cell which is not fused with others;
- The neuron is composed by three parts: dendrites, axon and cell body;
- Information flow : dendrites $\rightarrow$ cell body $\rightarrow$ axon.

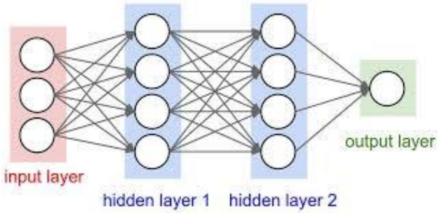


Drawing of the chicken cerebellum by S. Ramon y Cajal

2.NEURAL NETWORKS

The investigation of biological neuron networks in animal brains has inspired the mathematicians to create artifical neural networks (ANN).
In 1943 Warren McCulloch and Walter Pitts created a computational model for neural networks based on mathematics and algorithms. The original goal of the neural network approach was to solve problems in the same way that a human brain would. The ANN learns to do tasks by considering examples, generally without task-specific programming.
An ANN is based on a set of connected units called artificial neurons.Each connection(synapse) between neurons can transmit a signal to another neuron. The receiving neuron can process the signal and then send a new signal to neurons connected to it.

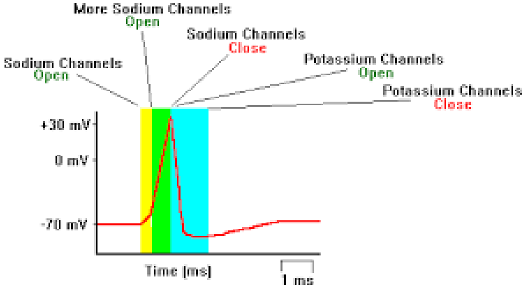
2.NEURAL NETWORKS



Neurons are organized in layers. Different layers may perform different kinds of transformations on their inputs. Signals travel from the first (input), to the last (output) layer.

Neural networks have been used on a variety of tasks, including computer vision, speech recognition, machine translation, social network filtering.

2.How is an action potential generated?

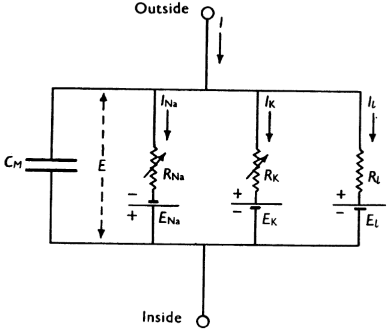


- The neuron membrane has a certain resting potential (about $-70Mv$).
- As a result of external stimulus, the membrane potential increases.
- When the membrane potential attains a certain threshold, the sodium channels open.
- As sodium ions flow into the neuron, the membrane potential increases (depolarization 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).

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.

2.HODGKIN-HUXLEY EQUATIONS



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 potential attains certain critical values.

2. HODGKIN-HUXLEY EQUATIONS

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;

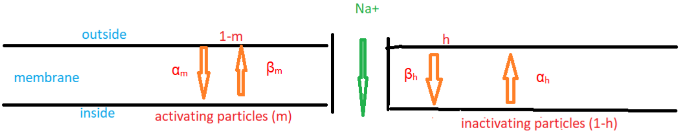
V_k, V_{Na}, V_l - Potassium , sodium, and leaky reversal potentials.

The leaky conductance (conductance of the leaky channels) is constant.

The other conductances depend on the membrane potential.

2. 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.

2. 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.

2. HODGKIN-HUXLEY 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:

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

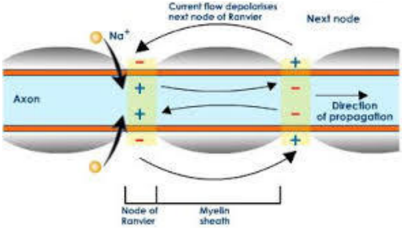
$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

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

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

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.

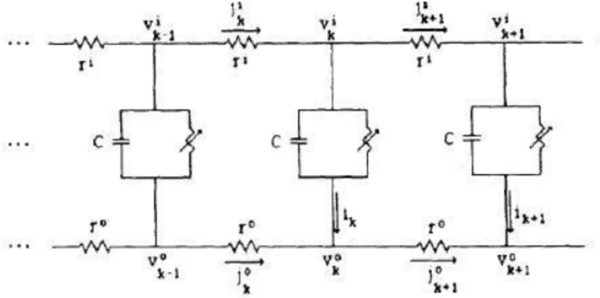


The myelin completely insulates the membrane, so that all the electric processes occur at the Ranvier nodes.

2. FITZHUGH-NAGUMO EQUATIONS

Circuit Model

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



2. FITZHUGH-NAGUMO EQUATIONS

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. FITZHUGH-NAGUMO EQUATIONS

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

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

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. FITZHUGH-NAGUMO EQUATIONS

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

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

In many applications this function is taken as

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

where $b > 0$.

2. FITZHUGH-NAGUMO EQUATIONS

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

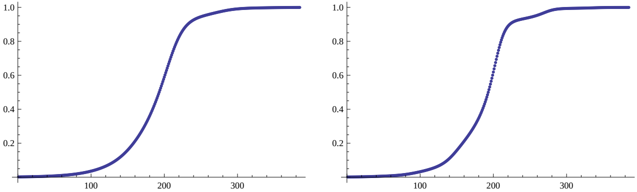
$$v_{k+1}(t) = v_k(t-\tau),$$

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:

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

2. FITZHUGH-NAGUMO EQUATIONS

Conditions for the existence of solution: $0 < a < 1/2$.
The solution cannot be solved by analytical methods.
Numerical solutions a)with $a = 0.1$; b) with $a = 0.3$.



2. POPULATION MODELS

How to describe the activity of a large population of N connected neurons ($N \to \infty$)?

Asumptions (See Gerstner and Kistler, 2001):

- The total number of neurons N remains constant.
- The state of neuron i depends explicitely only on the most recent firing time (t_i) and on the input from other neurons (but not on firing times of earlier spikes).
- The number of spikes that a network emits on a short time window is the sum of N independent random variables, and therefore converges to its expectation value. Hence in a large network we consider expectation values

2. NEURAL FIELDS

A new approach to the modeling of neuron populations 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 $\bar{x} \in \Omega$;
$V(\bar{x}, t)$ represents the spatiotemporal structure of the neuronal population:
- spatial distribution of potential;
- time evolution;

2. NEURAL FIELDS

Neural Field Equation (NFE):

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

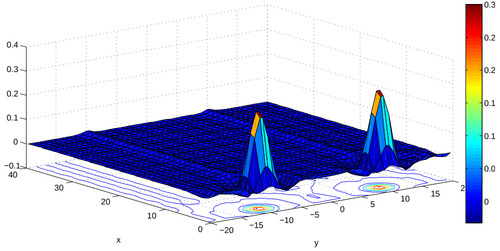
$$t \in [0,T], \bar{x} \in \Omega \subset \mathbb{R}^2;$$

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 $\bar{y}$.

2. NEURAL FIELDS

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).



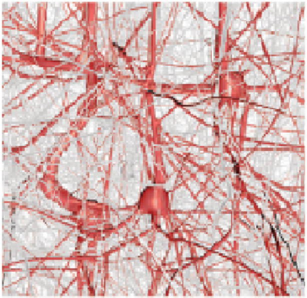
2.ALGEBRAIC TOPOLOGY METHODS

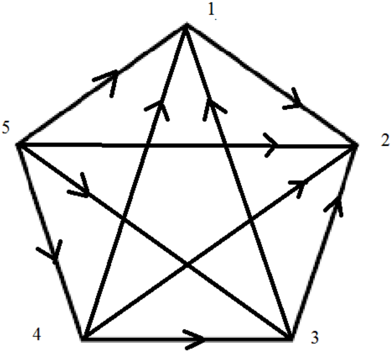
Blue Brain Project

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.

2. ALGEBRAIC TOPOLOGY METHODS





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)

2. ALGEBRAIC TOPOLOGY METHODS

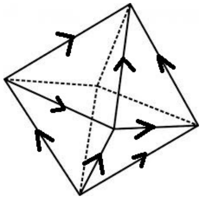
directed simplex of dimension $n-1$ - clique of n all-to-all connected neurons.
Each neuron belongs to many directed simplices of various dimensions.
A collection of simplices 'glued' together along common faces forms a simplicial complex.
The space enclosed by directed graphs forming a simplicial complex is called a cavity. The dimension of a cavity is the dimension of the simplices that enclose it.

Measures of Topological Complexity of a Simplicial Complex S

Betti number -β_n- number of cavities of dimension n enclosed in S.
Euler characteristic - $\chi(S) = \sum_{n \geq 0} (-1)^n |S_n|$, where S_n is the number of n-dimensional simplices contained in S.

2. ALGEBRAIC TOPOLOGY METHODS

EXAMPLE



Betti number - $\beta_2 = 1$ (one 2-dimensional cavity);
$S_0 = 6$ - 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: $\chi(S) = 6 - 12 + 8 = 2.$

2. ALGEBRAIC TOPOLOGY METHODS

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

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

2. ALGEBRAIC TOPOLOGY METHODS

"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".

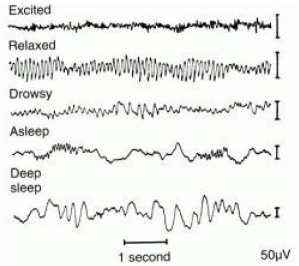
Michael Reinmann et al., 2017

3. MATHEMATICAL TOOLS

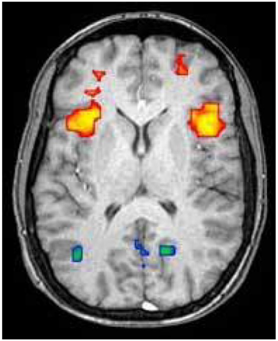
- Differential equations
- Dynamical systems
- Bifurcation theory
- Algebraic topology
- Stochastic processes (essential to take into account the influence of random factors)
- Computational methods (most of the considered equations cannot be solved analytically)

4. APPLICATIONS

INTERPRETATION OF MEDICAL DATA



Output from EEG



Output from fMRI

Neural field models provide a framework for unifying data from different imaging modalities , for example, EEG (good temporal resolution) and fMRI (good spatial resolution).

S. Coombes, 2010

4. APPLICATIONS

NEURAL FIELDS IN 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.

Conclusion

There is a very strong interaction between Mathematics, Neuroscience and Informatics.

- Along the XX century, Mathematics has created many powerful tools which gave an important contribution to the investigation of brain and simulation of brain functions.
- Neuroscience has contributed to the development of Mathematics with experimental data that have given rise to new mathematical models.
- Mathematics has also benefited from the development of Informatics, which allowed the creation of powerful computers and software tools.
- With all these advances the simulation of brain functions by artificial devices became a reality and is developing very fast.

Conclusion

Signifficant progress obtained in the second decade of XXI century:

- Large amounts of data, generated by devices;
- High-performance computers;
- Improved machine learning algorithms.

This all resulted in powerfull artificial intelligence systems.
(Arlindo Oliveira, Former President of IST,expert on artificial intelligence).
It is nowadays possible to replace human by artificial intelligence, but only for very specific tasks, which do not require creativity, flexibility of adaptativity. Of course the artificial intelligence will be further developed and improved.
Open question: Will it be possible sometime that artificial intelligence can replace the human brain?

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.
- Mo Constandi, The Discovery of Neuron, posted on 29/8/2006, https://neurophilosophy.wordpress.com/2006/08/29the-discovery-of-the-neuron
- Video *The Action Potentials*, Neural Academy, Youtube, 2018.

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. Cosner, 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.
- H. Chi, J. Bell and B. Hassard, Numerical solution of a nonlinear advance-delay-differential equation from nerve conduction theory,J. Math. Biol., 24 (1986), 583-601.
- Mo Constandi, The Discovery of Neuron, posted on 29/8/2006, https://neurophilosophy.wordpress.com/2006/08/29the-discovery-of-the-neuron
- S.Coombes, Large-scale neural dynamics: Simple and complex, NeuroImage 52, (2010), 731–739.

BIBLIOGRAPHY

- Coombes S., beim Graben P., Potthast R., and Wright J., Neural Fields. Springer Berlin, Heidelberg, 2014 .
- 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
- W.Erlhagen, E.Bicho, The dynamic neural field approach to cognitive robotics, J. Neural Eng. 3, (2006), R36-R54.
- G. Faye and O. Faugeras, Some theoretical and numerical results for delayed neural field equations, Physica D 239 (2010) 561–578.
- 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

- W.M.Gerstner and W. Kistler, Spiking Neurons, Cambridge University Press, 2002.
- 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 .
- A. Hutt and N. Rougier, Activity spread and breathers induced by finite transmission speeds in two-dimensional neuronal fields, Physical Review,E 82 (2010) 055701.
- A. Hutt and N. Rougier, Numerical Simulations of One- and Two-dimensional Neural Fields Involving Space-Dependent Delays, in S. Coombes et al., Eds., Neural Fields Theory and Applications, Springer, 2014.
- J.P. Keener, Propagation and its failure in coupled systems of discrete excitable cells, SIAM J. Appl. Math. , 47 (1987), 556-572.

BIBLIOGRAPHY

- J. Nagumo, S.Arimoto and S. Yoshizawa, An active pulse transmission line simulating nerve axon, Proceedings of the IRE, 50 (1962), 2061–2070.
- A. Oliveira, Inteligência Artificial, Fundação Francisco Manuel dos Santos, Lisboa, 2019.
- R. Potthast and P. beim Graben, Existence and properties of solutions for neural field equations, Math. Meth. Appl. Sci., 33 (2010) 935-949.
- 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.
- H.R. Wilson and J.D. Cowan, Excitatory and inhibitory interactions in localized populations of model neurons, Bipophys. J., 12 (1972) 1-24.