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Cellular Information Processing & Artificial Neurons

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Abstract: In the present review we analyse the key features of cells, seen fundamentally as information processing machines. Even though the comparison between cells and machines or cells and computers provides a powerful tool for understanding how information is stored and processed by the cellular machinery, a series of misleading and simplistic assumptions are critically reviewed. Moreover, the seminal studies on understanding and artificially recreating the neuronal structure are analysed, both for exploiting its powerful computational abilities in information processing devices and for providing medical solutions to neurodegenerative diseases, neurological trauma and neuroprosthetics.

Contents

1. Introduction

From the chaotic and incredibly dense state of the primordial singularity, or the 'Big Bang', to the expected heat death, or 'Big Rip', life made its appearance in an entropic miracle where the ontologically identical components of reality assembled themselves in a meaningful and manyfold universe where complex systems could generate emergent properties and behaviour, adding new dimensions to the phase space of this reality. In the continuous increase of entropy dictated by — or which dictates — the arrow of time, living organisms fight against death and dissolution by constantly preserving their structures. While non-living things usually preserve their material, or substrate, as their shape or form gets modified throughout time — like stones on the shore being constantly eroded by the movement of the waves into fine granules of sand — living organisms are constantly replacing the matter sustaining them, willing to renounce to it in exchange for new matter, new atoms and molecules, while maintaining in the best possible way their form and structure. However, it is not the new particles replacing the old ones that keep an organism alive, in fact two electrons or two protons are fundamentally indistinguishable and ontologically identical. On the contrary, it is the process of exchanging energy and matter with the world while keeping the information on the structure and internal rules which keeps organisms alive — it is metabolism in its original meaning of metabàllein, to change while remaining the same. Using the words of Erwin Schrdinger, living matter 'feeds on negative entropy' and

> It is by avoiding the rapid decay into the inert state of 'equilibrium' that an organism appears so enigmatic; so much so, that from the earliest times of human thought some special non-physical or supernatural force (*vis viva*, entelechy) was claimed to be operative in the organism, and in some quarters is still claimed [1].

Entelechy literally means 'having the end (purpose) in itself' and represents an incredibly powerful intuition of the ancient thinkers (first Aristotle [2]) — comparable to Democritus theory of atoms — that of identifying an inner principle guiding the living organisms. That inner principle was identified in the DNA between the end of the 19th and the beginning of the 20th century and represents the only symbolic encoding of information (a four elements digital mechanism) which has been discovered in a natural system.

The present dissertation aims to analyse the key features of cells, seen fundamentally as information processing machines [3]. After briefly presenting the key components constituting the cellular structure in Section 2.1 and proposing five key features as the essential operational properties of living cells in Section 2.2, the comparison between cells and computers is analysed. Even though this comparison between cells and machines or cells and computers provides a powerful tool for understanding how information is stored and processed by the cellular machinery, a series of misleading and simplistic assumptions are critically reviewed in Section 3.

Of the hundreds of types of cells found in living systems, one type in particular has a distinct and powerful information processing ability: the neuron. While the neuronal structure itself — in particular that of pyramidal neurons, the primary excitation units of the mammalian prefrontal cortex and the corticospinal tract — allows the instantiation of a radically new analog-to-digital signal processing mechanism, the network configuration of these neuronal units with chemical-to-electrical-to-chemical signal transduction properties opens up a completely new reality sustained by the activity of these networks in animal brains. This reality of perception is mainly generated by the ability of the neural networks present in the brain to extrapolate patterns from the magmatic and undistinguished physical reality. This pattern recognition ability is what created a world of symbols and meaning which allowed in animals adaptive behaviour and communication systems up to the highest level of inner communication constituting the human self-consciousness.

In the last Section 4 of the present dissertation, the seminal studies on understanding and artificially recreating the neuronal structure are analysed, both for exploiting its powerful computational abilities in information processing devices that could lead the computational revolution required by the approaching realisation of the prophecy represented by Moore's law[1] impending end, and for providing medical solutions to neurodegenerative diseases, neurological trauma and neuroprosthetics.

2. Artificial Cells

2.1. What is a cell?

Cell theory (from *cellula*: 'small room') was developed in 1839 by Matthias Jakob Schleiden and Theodor Schwann. It states that all organisms are made of cells, which are their building blocks and smallest living

[1] Moore's law: prediction made by the American engineer Gordon Moore in 1965 that the number of transistors per silicon chip doubles every year[4].

units, and finally that all cells come from preexisting cells. In particular, cells appeared on Earth at least 3.5 billion years ago and all living organisms now living on earth share a genetic heritage from the same most recent common ancestor, also called *last universal commons ancestor* (LUCA).

Three things are common in all cells: the *semipermeable membrane*, which delimits the cell and selectively controls the transport of material inside and outside the cell; the *cytoplasm*, which is the collective denomination of the contents of the cell enclosed by the membrane; the *DNA*, which carries the genetic instructions for the cytoplasmic synthetic activity.

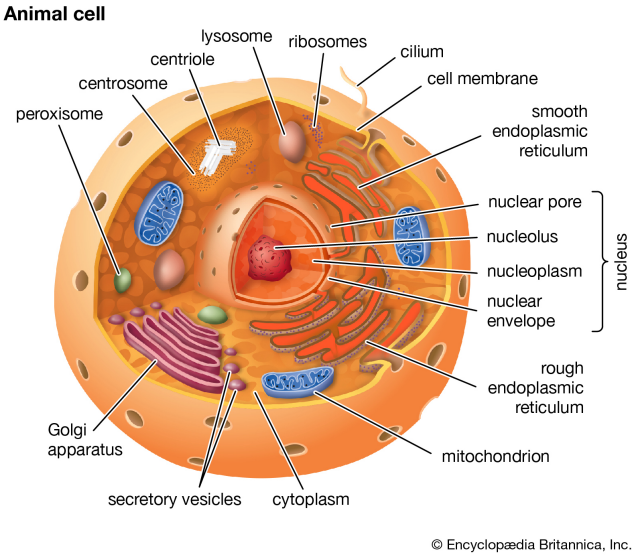

Figure 1: Cell structure of an Eukaryotic cell [5].

Cells can be divided into two main categories: *Eukaryotic* cells, which have organelles (e.g. the nucleus) and are in general more complex; *Prokaryotic* cells which constitute unicellular prokaryote organisms (e.g. bacteria), with no membrane-enclosed organelles and the genetic material not contained in the nucleus.

Organelles ('small organs') are specialised subunits of the cell. The *nucleus* contains the genetic material in the form of DNA, packaged in the chromatin, which dictates what the cell is going to do and how. The nucleus also contains the nucleolus, where ribosomes are made. *Ribosomes* synthesise proteins and they may travel freely through the cytoplasm or deposit on the surface of the endoplasmic reticulum. The *endoplasmic reticulum* (ER) with ribosomes on its surface is called *rough* (rER), while the one without ribosomes its called *smooth* (sER). The ER is a network of enclosed passages for transporting material (e.g. proteins).

Proteins emerge from the ER in small vesicles and are received by the *Golgi apparatus*. This customises the proteins in a form that the cell can use. Moreover, *vacuoles* are sack-like structures that store different materials. Found in many animal cells, *lysosomes* are comparable to garbage collectors, containing enzymes that can break down many types of biomolecules. The *mitochondrion* represents the power generator of both animal and plant cells, as it carries out cellular respiration and produces ATP molecules. In plants, the *chloroplast* is where the photosynthesis happens and the cell wall is a structural layer surrounding the cell membrane. Finally, the *cytoskeleton* is what maintains the shape of the cell and it is made of microfilaments (made of proteins) and microtubules (thin hollow tubes) [6].

2.2. Artificial Cells: five design concepts

The cell, being the simplest form of life and the fundamental unit of organisms, is nevertheless itself an incredibly complex machinery. Moreover, the name 'cell' is simply the label of a class of biological entities which can be quite different from each other, and that can radically change identity with time. However, this vast class of distinct entities shares a number of features that allow them to be collected and recognised under the general name of 'cells'. These common features are essential for the development and creation of artificial cells as they represent the necessary conditions for these artefacts to be considered cells and even to be considered alive. Five key features have been proposed as the essential operational properties of living cells [7] [8]:

- ⋆ **Compartmentalisation**: What can better define (from latin *de-*, 'completely' + *finis*, 'boundary') the cell, than the physical boundary separating it from the rest of the world: the cell membrane. The most

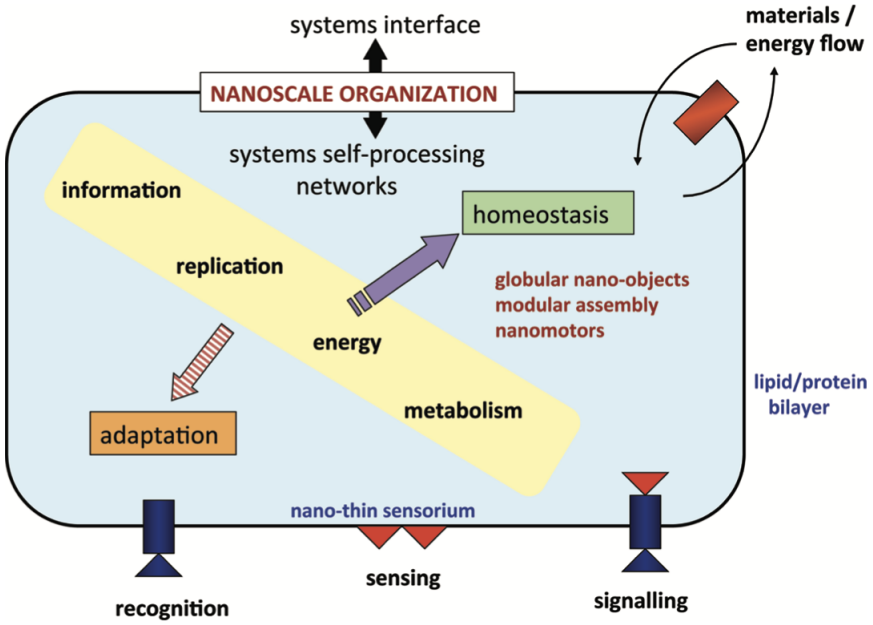

Figure 2: Systems of cellular life. Two are the main operative features of cells: an internal machinery for self-structuring and self-elaboration; an interface for communicating with the external environment [7].

important characteristic of the cell membrane, however, is that of being a semipermeable, selective barrier, instead of an impenetrable border. In fact, the semipermeable nature of the cell membrane allows the cell to interact with its environment by acquiring the exogenous components necessary for maintaining its activity and by expelling the endogenous products that constitute the intercellular messengers of the cellular network. Moreover, compartmentalisation of the intracellular components reduces the entropy of the cellular system, therefore making it an ordered machinery able to perform distinct and precise functions.

- ⋆ **Replication**: As each living entity is the result of reproduction, autonomous replication as continued growth and division, which relies only on the input of energy and small molecules, is a key feature of cells. In the process of replication, the genetic information of the parent cell is copied through template-directed polymerization. The genetic code, which guides the production of proteins and is carried in the form of DNA, is duplicated and divided in the two daughter cells.

- ⋆ **Metabolism**: Metabolism uses protein-based catalysts (enzymes) to accelerate life-sustaining and information processing chemical reactions. It can either use energy to synthesise compounds in anabolic processes or break down compounds and release energy in catabolic processes. Through the steps of metabolic pathways, a linked series of chemical reactions guided by enzymes, a chemical is gradually transformed into a different one.

- ⋆ **Energisation**: The cellular machinery is constantly in a state of non-equilibrium, requiring a continuous provision of energy from the environment which allows it to maintain its homeostasis. Homeostasis means a dynamic steady state arising from non-equilibrium conditions. In his *What is Life?* [1] Erwin Schrödinger affirmed that life subsists on *negative entropy* which he later corrected to *free energy* [2].

- ⋆ **Evolutionary capacity**: Through the evolutionary processes such as mutation and fitness or selection pressures and heredity, the cell, in term of population genetics, adapted to the changes in the terrestrial environment since their appearance, approximately 750 million years after the earth formation.

[2]The change in the free energy is defined as the maximum amount of work that can be performed by a thermodynamic system at constant pressure.

3. Information Processing in Cells: Cells as Computers

Information may be described as a force which produces organised structures and structured processes from chaos. It can also be described as the level of distinguishability from chaos. The genetic code represents the only symbolic encoding of information which has been discovered in a natural system. It represents the mechanisms which emerged through evolution in order to store the information encoding in digital form (with an alphabet comprising 4 symbols) its own structure and function. However, in order to communicate both internally and with the environment, the cell makes use of a wide range of languages [9].

3.0.1. The central dogma of molecular biology

The central dogma of molecular biology is a simplified model of the genetic code's information processing in a biological system. It first appeared in a paper by Francis Crick in 1958 as [10]:

> *The Central Dogma.* This states that once 'information' has passed into protein it cannot get out again. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the precise determination of a sequence, either of bases in the nucleic acid or of amino acid residues in the protein.

And then modified in a Nature paper in 1970 [11]:

> The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred back from protein to either protein or nucleic acid.

The cell represents an information processing machine whose structure is based on molecular technology. However, the types and modes of information it handles represent a wide spectrum which cannot be reduced to the central dogma model. In fact, the model only applies to less than 5% of the genome, i.e. the part encoding for proteins as opposed to non-coding DNA.

3.0.2. Cellular Computing

As Rafael Lahoz-Beltra highlights in his paper on *Cellular Computing: Towards an Artificial Cell* [12], those scientific disciplines attempting to create artificial biological entities believe in the Cybernetic assumption that most biological systems can be represented as machines. Two are the common misconceptions that should be considered in reviewing the analogy between 'cells & machines' or 'cells & computers':

- ⋆ The Cybernetic assumption which considers biological systems and entities as machines.
- ⋆ The ingenuous assumption of the 'hardware + software' dualism when considering biological information processes.

On the other hand, the proposed analogies between 'cells & computers' can be summarised as follows:

- ⋆ The linear topology of the program.
- ⋆ The execution of the program based on the code's translation.
- ⋆ The program's code is based on a limited number of symbols.
- ⋆ The susceptibility to virus infection.

The main conclusion stated in Beltra's paper is that while in computers the 'hardware + software dualism' allows its components to be considered separetly, in cells the 'biomolecule + function' dualism doesn't allow it as it is impossible to consider biomolecules without the biological function.

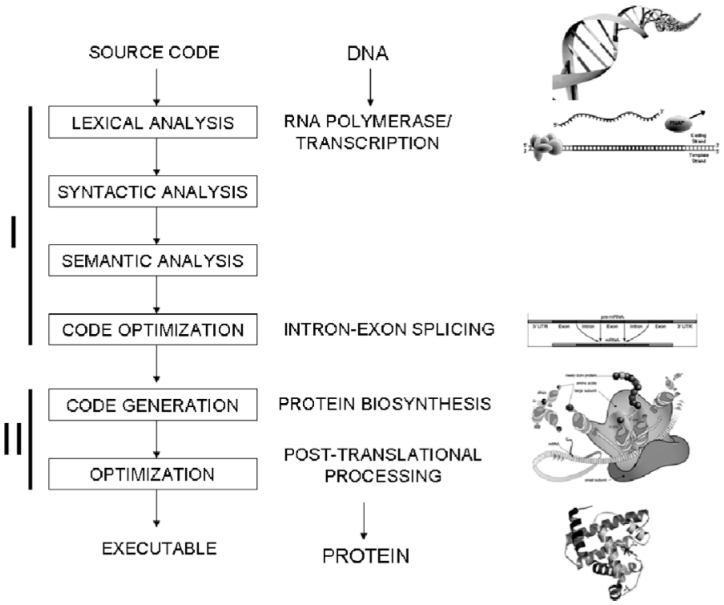

Figure 3: Analogy between cells and computers. The execution of the program is based on the translation of the code. (Left) Software compilation; (Right) Protein synthesis [12].

3.0.3. Biological information processing

In a 2015 paper Stumpf et al. [13] analysed the flowing and processing of information in biological organisms at the molecular level through the lens of Claude Shannon's *Information Theory* [14]. Shannon's Theory describes information — not to be confused with meaning — through the use of probability and, in particular, entropy. The role of information in biological organisms is here considered in particular for the crucial role of adaptive behaviour and response to environmental stimuli and therefore the study focuses on the efficiency of information transmission. The key concept here is 'mutual information' (the mutual dependence of two random variables), which is a measure of the uncertainty reduction of the output of an information channel by knowing the state of the input. By considering the random variables[3] X and Y (representing the input and the output, respectively) the mutual information $I(X|Y)$, is

$$I(X|Y) = H(Y) - H(Y|X) = H(X) - H(X|Y)$$

Where the entropies $H(X)$ and $H(Y)$ are used to represent the uncertainty of X and Y. $H(X|Y)$ is the *conditional entropy* of Y, which describes the quantity of information required to represent the outcome of Y given X. In the absence of noise, a perfect information transmission yields $H(Y|X) = 0$ and therefore $I(X|Y) = H(Y)$, or the mutual information between X and Y is equal to the entropy of Y. Two interesting differences are proposed in the paper that distinguish classical information theory from its biological applications:

- ⋆ At the molecular level, transduction pathways map the input signal X, to a corresponding cellular reaction Y. However, the cellular mechanism processes and, therefore, alters the incoming signal, instead of simply replicating it.
- ⋆ In traditional applications of information theory to physical systems it is possible to distinguish the message from the means of transmission or processing of the message and the energy required to support the process. An example can be represented by an antenna receiving electric current and radiating electromagnetic waves. In biomolecular systems, these elements are all represented by molecules which form a deeply interconnected complex mechanisms.

Moreover, the paper analyses the role of *noise* in affecting signal transduction during molecular information processing. In particular, two types of noise are considered: 'intrinsic noise', or signal distortions due to the stochastic nature of molecular dynamics; 'extrinsic noise', or variability between different cells (e.g. different

[3] *Random variable.* Given a sample space S, a random variable is a function from the space S to the real numbers . Thus, a random variable X assigns a numerical value $X(s)$ to each possible $s \in S$ [15].

amounts of specific elements). Through the use of linear noise approximations to approximate the chemical master equation [4], by representing the system through a deterministic and a stochastic component and the use of stochastic differential equation, Stumpf et al. found that while extrinsic noise causes an apparent increment in the mutual information, intrinsic noise causes an evident decrease. Extrinsic noise can cause groups and units of a population of cells to exhibit qualitatively divergent behaviour, e.g. oscillation vs stable equilibrium. On the other hand, intrinsic noise usually leads to a broader deterministic solution.

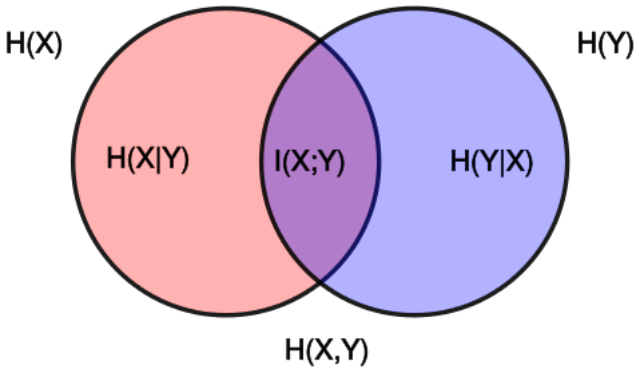

Figure 4: Venn diagram showing the additive and subtractive relationships between mutual information $I(X;Y)$, conditional entropies $H(X|Y)$ and $H(Y|X)$, uncertainties $H(X)$ and $H(Y)$, joint entropy $H(X,Y)$[6]. Public domain image by Konrad Voelkel.

4. Artificial Neurons

4.1. What is a Neuron?

Two types of cell constitute the nervous system: neurons and glia. While glia, or neuroglia, serves as support and protection to neurons, nerve cells are distinguished form other types of cells by their characteristic ability to communicate rapidly and precisely with other cells, even at great distances in the body. The neuron is composed of what can be described as an input region, the dendrites, a signal processing (metabolic) unit, the cell body or soma, and an output region, the axon, which connects to the other neurons dendrites through the presynaptic terminals. The axon of a neuron can range from 0.1 mm to 2 m. A typical neuron in the mammalian central nervous system receives thousands of inputs distributed along the dendritic tree and dendritic spines, where the neuron is postsynaptic to its presynaptic partners. Inputs are collected in the form of synaptic potentials, which travel toward the cell body and are integrated at the initial segment of the axon to produce action potentials. Action potentials propagate to the axon terminals and trigger neurotransmitter release that conveys information to many of its postsynaptic partner neurons. The action potentials are electrical signals generated near the cell body and optimally conveyed by the axon at speeds ranging from 1 to 100 m/s. The action potential produced by a neuron is digital in nature as the voltage amplitude is kept constant at 100 mV.
Two are the main features that characterise neurons [16]:

- ⋆ **Morphological and functional asymmetry:** Neurons are structured with a receptive end made of dendrites and a transmitting axon at the other end. This highly asymmetric structure provides the basis for the unidirectional signalling system of nerve cells.
- ⋆ **Electrical and chemical excitability:** The plasma membrane of neurons is the key of their excitability and signalling ability. The cell membrane of neurons, in fact, is a lipid bilayer which constitutes a powerful electrical insulator. However, embedded in the membrane are specialised protein structures, e.g. ion channels and receptors, which are electrically active and allow the flow of specific organic ions. This controlled flow of ions modifies the voltage across the membrane, which can be compared to both a resistor and a capacitor in an electrical circuit [17].

[4]The chemical master equation describes intracellular processes comprising the reactants mean concentration and deviation from it

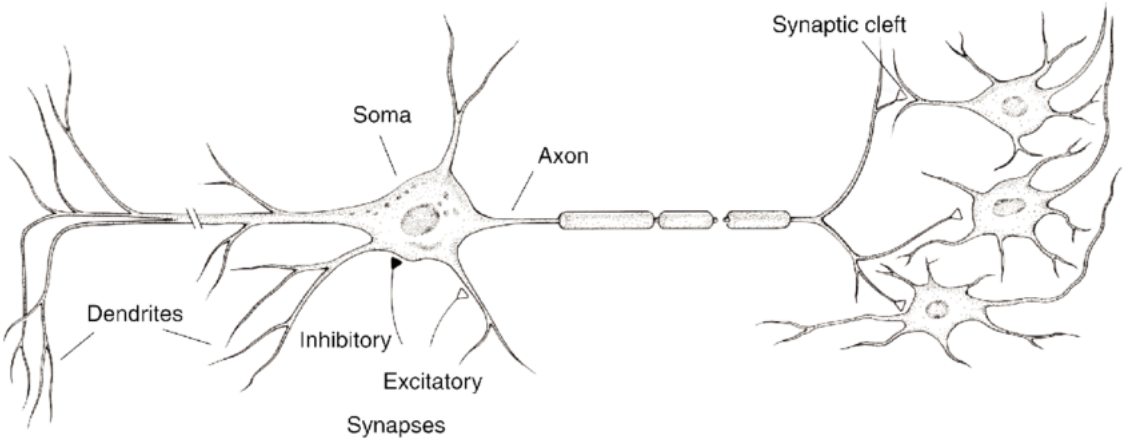

Figure 5: The structure of a neuron. Here are represented the main features of neurons of the vertebrate nervous system. The neuron receives inputs distributed along the dendritic tree and dendritic spines which are then collected in the form of synaptic potentials and intefgrated at the initial segment of the axon to produce action potentials. Action potentials propagate to the axon terminals and trigger neurotransmitter release that conveys information to many of its postsynaptic partner neurons. Modified from Kandel et al. (2000) [16].

4.1.1. Neuron linear threshold models

In a 2000 Nature review on *The role of single neurons in information processing*, Christoph Koch and Idan Segev analyse the major models for the neurons activity as information processing units. Following the fundamental and foundational work by McCullough and Pitts in 1943 on the point neuron as a threshold logic gate [18] (more on this in Section 4.2.1), a wide range of *linear threshold models* were proposed in the following years.

- ⋆ **integrate-and-fire neuron**: simulating the biophysical phenomenon of action potentials, where the dendritic inputs modify the voltage across the membrane until the threshold is reached, the neuron fires and the voltage returns to its initial state.
- ⋆ **leaky integrate-and-fire neuron**: were the synaptic charge is allowed to 'leak' through the addition of an ohmic resistance parallel to the capacitance. This causes the synaptic input to decay.
- ⋆ **rate neuron**: instead of producing discrete pulses the output is represented by a continuous activation function. The strength of the excitatory incoming signals determines the neuron's firing rate.

McCullough and Pitts proved that these units theoretically allow universal computation through the non-linear nature of the threshold mechanism as it can be adapted to compute the logical conjunction AND.

In addition to these single unit models, it is interesting to note a new trend, influenced by recent multi-neuronal recording methods, which considers groups of neurons as physiological units that can generate emergent properties [19].

4.2. Artificial Neurons: Organic, Electronic, Digital

Under the general name of *Neuromorphic Engineering*, many are the types of artificial creations trying to mimic some or all of the characteristic features of nerve cells. Three are the main types of artificial neurons (or synapses) that have been studied and explored up until now: *organic*, *electronic* and *digital neurons*. These three classes of artificial neurons range from the more arduous purely organic artificial neurons to the potentially revolutionary electronic neurons — which might represent an alternative to quantum computing in overcoming Moore's law impending end — and finally to the digital (mathematical) neurons, as those implemented in machine learning.

4.2.1. Threshold Logic Gate

The first mathematical model of *threshold logic gate* (TLG) was proposed in 1943 by Mc Culloch and Pitts [18], inspired by the biological neuron threshold mechanism. The model computes the sign of the weighted sum of inputs in order to check weather the threshold is overcome:

$$f(x_1, x_2, ..., x_n) = sgn(\sum_{i=1}^{n} w_i x_i - T)$$

$$sgn(x) := \begin{cases} 0, & if \quad x < 0 \\ 1, & if \quad x \geq 0 \end{cases}$$

where x_i are the input values, w_i are their relative weights and T is the threshold value that needs to be overcome in order for the TLG to fire. This simple model will later evolve in the *perceptron* — as developed by Frank Rosenblatt and implemented in one of the first pioneering artificial neural networks — and in the *sigmoidal artificial neuron*, to name the main examples.

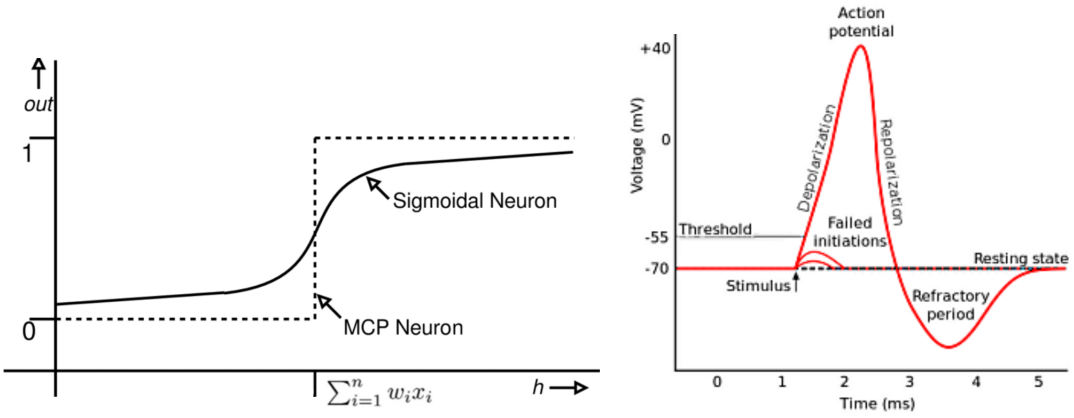

Figure 6: (Left) All-or-nothing step function of the McCulloch and Pitts (MCP) neuron compared to the smooth Sigmoidal neuron [20]. (Right) Integrate-and-fire model for the generation of action potentials [21].

4.2.2. Memristive threshold logic

The technology most diffused in creating artificial electronic neurons is that of *memristive threshold logic* (MTL) circuits [22]. A *memristor* (MEMory ResISTOR) is a non-linear two-terminal passive circuit element characterised by a relationship between the electric charge and the magnetic flux linkage (equivalent to the magnetic flux, for a typical inductance). The MTL circuits reproduce the biological synaptic activity due to the flow of neurotransmitter. In particular, it mimics the combined effect of excitatory signals on a neuron. When the total weight of the synapses receiving excitatory (or inhibitory) signals exceeds a threshold, in a short period of latent summation, the neuron is prompted to fire. The weight corresponds to the device's *memristance* which is defined as $M = d\phi_m/dq$ where ϕ_m is the magnetic flux linkage and q is the charge. The use of threshold logic in memristive devices therefore provides:

- ⋆ A synaptic-like function enabling the incremental modification of the weight, or memristance, by controlling the electric charge or the magnetic flux.
- ⋆ A thresholding system regulating the firing mechanism in order to produce the output.

4.2.3. Silicon neuron model

A 1991 Nature paper by Misha Mahowald and Rodney Douglas represents the seminal paper for purely electronic neuromorphic engineering as it introduces the first model for an analog integrated circuit mimicking the electrical properties of biological neurons [23]. This silicon device represents a complete revolution with respect to previous *in silico* neural models as the neuron's functional characteristics are not simply reproduced trough mathematical simulations on classical computing machines, but the actual physics of the silicon device's conductivity is similar to that of nerve cells' biological membranes. The different ion currents determining the voltage of the cell membrane are implemented in the device through combinations of *complementary metal-oxide-semiconductor* (CMOS) circuits which represent the combinations of cell conductances sensitive to ions, voltage or neurotransmitter controlling these ion currents. Each type of membrane conductance is represented by individual circuits comprising 'conductance' transistors for specific ions. While the cell membrane is represented

by a fixed capacitor and a variable leak conductance, the activation of membrane conductances is implemented with time- and voltage- dependent output currents of differential pairs[7]. The *conduction transistor* then controls the flux of the 'ionic' currents descending the gradient originating from the 'membrane' voltage and the ionic 'equilibrium potential'. When testing the device behaviour by injecting current steps, the silicon neuron reacted in the same way of a biological neocortical neuron where the threshold discriminated between current stimuli triggering a discharging impulse or not.

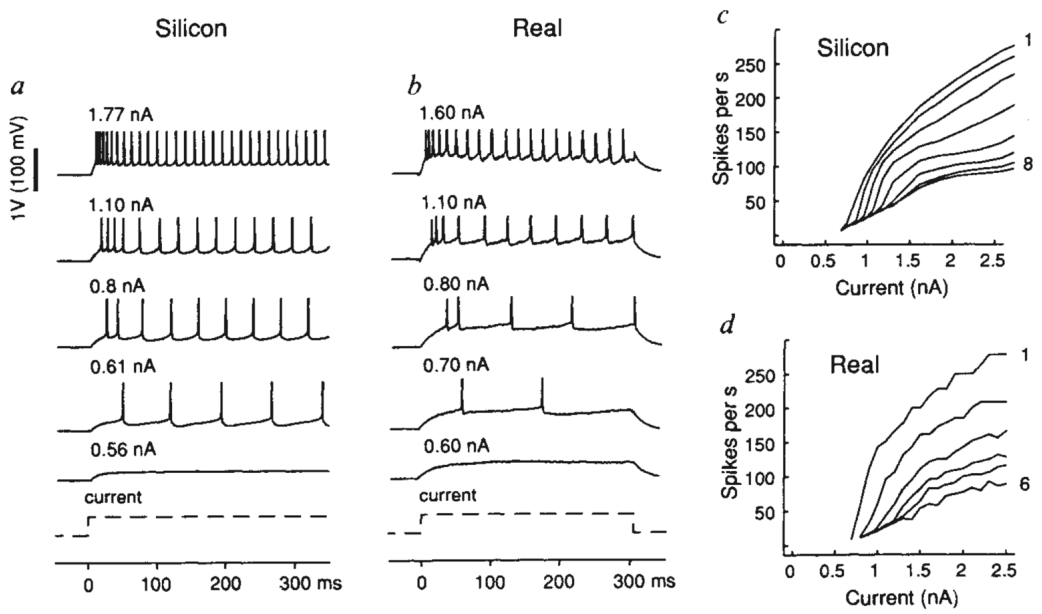

Figure 7: Comparison of response to intrasomatic current injection of the silicon neuron (a-c) and a neocortical neuron (b-d). Voltage scale represents 1V for the silicon neuron and 100mV for the neocortical neuron [23].

4.2.4. Stochastic phase-change neurons

The first example of an artificial electronic neuron implementing stochastic behaviour at the physical level is provided by IBM's *stochastic phase-change neurons* [25]. Tuma et al. created randomly spiking neurons that imitate the functionality of biological neurons. Electronic circuitry is highly deterministic: equal inputs will always produce equal outputs. Nerve cells, on the other hand, exhibit what is know as stochastic behaviour. By the implementation of a phase-change material, specifically chalcogenide, the IBM researchers have been able to reproduce the stochastic nature of the nerve cells dynamics. Each neuron-mimicking phase-change device comprises dendrites-like inputs, a central body called soma, and an axon-like output. The central body acts as a processing unit receiving the inputs from the dendrites and then producing an output on the axon. Similarly to real neurons, the artificial neuron integrates the potentials received through the dendrites using the patented phase-change device. Every incoming signal heats and slightly melts the phase-change device determining a transformation in the original physical condition, while gradually incrementing the electrical conductance. The total conductance of the device is increased in this way until finally reaching the required threshold. At this point, the phase-change device produces a spike. Moreover, after firing, the device is reset to a non-conductive state. The nature of the phase change material is the main aspect of this device, as every time the neuron is reset, it configures itself in an always different state. This feature is what allows the instantiation of an inherent stochastic behaviour in the activity of the artificial neuron, which is a key property of real nerve cells.

4.2.5. Organic electronic biomimetic neuron

While the development of purely organic artificial neurons has not been attempted yet, hybrid implementations have been developed as in the case of the organic electronic biomimetic neuron created by Agneta Richter-Dahlfors et al. at the Karolinska Institutet in Sweden [26]. They identify the *chemical-to-electrical-to-chemical*

[7]instead of responding to the difference between the wire and the ground, as in the so called 'single ended' mode, a circuit implementing differential signalling reacts to the electrical variance between two incoming signals. [24]

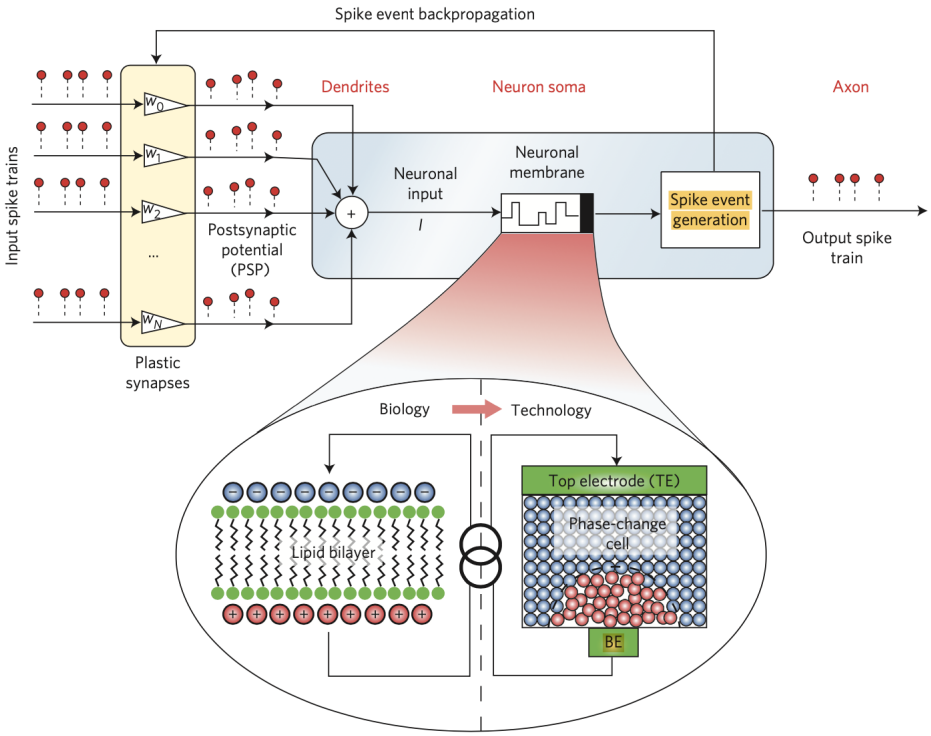

Figure 8: Artificial neuron based on a phase-change device, with an array of plastic synapses at its input. Schematic of an artificial neuron that consists of the input (dendrites), the soma (which comprises the neuronal membrane and the spike event generation mechanism) and the output (axon) [25].

signal transduction as the fundamental function of neurons, which they reproduce through the connection of enzyme-based amperometric biosensors and organic electronic ion pumps. The *organic electronic biomimetic neuron* (OEBN) produced by Richter-Dahlfors et al. is an example of iontronics, or organic electronic electrophoretic transport devices, and in particular it is composed of an *organic electronic ion pump* (OEIP) connected to an amperometric biosensor. The OEIP is made of an organic bioelectronic polymer which can transmit both electronic and ionic signals, without liquid flow, which is exactly what a neuron can do. The device can then sense signals at one end and very rapidly transmit that signal to the fore end in order to relay the signal in the neuronal system, by actually releasing neurotransmitter. This unique combination of electronic and ionic properties is what allows the transduction between biochemical signals and electronic impulses, and vice versa. In its current format physical synaptic integration cannot be obtained due to limitations yet to be overcome, e.g. the size and time of the response. However, future applications include therapies requiring signal translation, long-distance communication (artificial projection neurons) and potentially connecting prosthetics through the implementation of wireless communication.

5. Conclusion

Understanding the mechanisms underlying the cellular machinery means understanding how life originates from non-living matter. However, the boundary between the living and the inanimate world is still a blurred line. Here we reviewed a series of works attributing to the unique information processing ability of the cell the role of watershed between these two worlds. We proposed a comparison between cells and computers which can drive powerful insights on the former given the much better understanding of the latter. However, this comparison also bears the risk of misleading a proper understanding of the cellular mechanism due to common simplistic assumptions. Moreover, we provided a framework for understanding the cellular information processing mechanism in terms of entropy, by borrowing some tools from Shannons Theory of Information, adapted to the unique features of the biological domain. Finally, we reviewed the seminal works on modelling and artificially replicating neurons, as they represent a radically different and incredibly powerful information processing structure. These models started being developed in the first half of the 20th century as purely mathematical frameworks for understanding the neuronal analog-to-digital signal processing mechanism. This models

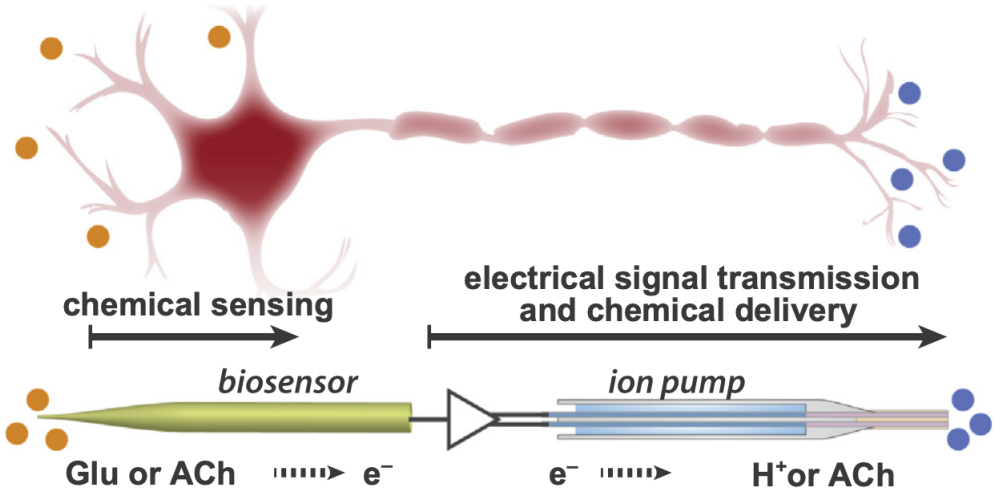

Figure 9: Chemical-to-electrical-to-chemical signal transmission of a neuron [26].

were then implemented first into artificial *in silico* neural network implementations (e.g. machine learning algorithms) and later drove the development of electrical silicon hardware mimicking the neuronal mechanism at the physical level. Finally, while studies on purely organic artificial neurons have not been conducted yet, important results are being obtained in the field of hybrid organic electronic biomimetic neurons, which might lead to great advancements in neurological diseases or trauma rehabilitation medicine and neuroprosthetics.

Life and consciousness represent the two greatest leaps and mysteries in terms of emergent properties from complex systems since the beginning of the universe as we know it. While solving the former mystery requires the understanding the cellular machinery, unraveling the latter requires the comprehension of the neurons unique signalling mechanism. Unimaginable achievements have been obtained in both fields in less than a century, and we believe that while the understanding of both problems requires a radical rethinking of fundamental yet elementary axioms of the scientific method, the solution might be in the reach of a lifetime.

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