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(Review Article)

Specificity of cellular communication, from signal to functional response

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Abstract

The specificity and complexity of molecular interaction is undoubtedly the characteristic trait shared by all universal matter. Quantum physics describes the nanometric particles that constitute it and the physically relevant properties that they express, by complex mathematical formulas, but it fails to identify the essence of the interactions that act within it.

He also adopted a dedicated nomenclature for their description, but in no way manages to materialize them in an easily intelligible form.

Even more difficult is trying to understand how communication between cells and living beings happens and how they can transfer a large variety of languages effectively. These communications use different identifiable codes within the same community even when issued simultaneously.

The solution adopted to make such a complex system of interactions effective is the result of the millennial evolution and selection of an infinite number of molecules, each able to transmit with its characteristic steric imprint, a unique and unmistakable message.

In this article we are going to describe how this mysterious communicative phenomenon takes place, even if we cannot grasp its intimate nature, which leaves us overwhelmed by so much complexity.

Keywords: Molecular evolution; Stimulus/receptor interaction; Specificity of intermolecular code; Cellular interactive systems

1. Introduction

Attraction is the force that "moves the sun and other stars"

In physics, force is the fundamental vector magnitude that expresses the reciprocal interaction between bodies and can produce a detectable effect. In the particles that make up matter, different forces act on their internal cohesion and their transformation.

The supreme Dante Alighieri (Florence 1265- Ravenna 1321) poetically compared love to a special force of attraction that moves things, the living and the universal matter, and described it thus: *"love that moves the sun and other stars"* (Paradise, XXXIII, v. 145, is the last verse of Paradise of the Divine Comedy).

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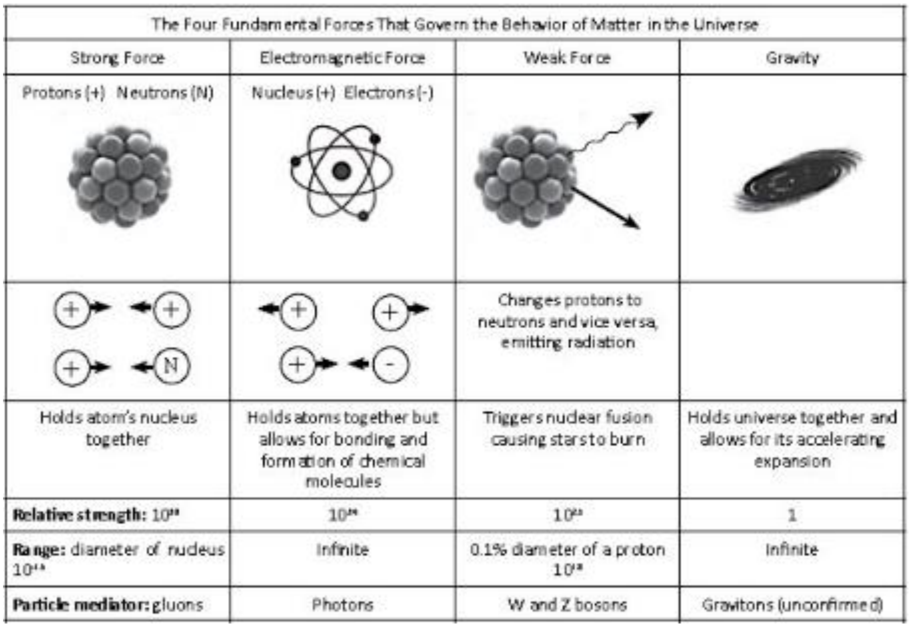
The power of love is for the Poet the most sublime concept between the forces and the only one able to overcome any other that opposes it, also able to cement in an indissoluble way the bond between lovers. By extension, the concept of love attraction can also be translated to the interpretation of the forces acting within the universal matter.

It is certainly an interpretation in a poetic key of the cohesive forces that form matter, but it makes the meaning of attraction intelligible, if it is related to a sentimental experience that each of us has experienced at least once in life.

The principle of the force of attraction, acting on all material bodies, was later taken up and described with the rigor of mathematical language by Newton's genius in his work "*Philosophiae Naturalis Principia Mathematica"* 1687 , where it enunciates the law of universal gravitation.

The same intuition of force as primary morphogenetic greatness has been accepted by quantum physics which has codified it in the fundamental forces of interaction of matter: weak nuclear force, strong nuclear force, electromagnetic force and gravitational force, etc.) [1] Fig.1.



The Four Fundamental Forces That Govern the Behavior of Matter in the Universe			
Strong Force	Electromagnetic Force	Weak Force	Gravity
Protons (+) Neutrons (N)	Nucleus (+) Electrons (-)		
		Changes protons to neutrons and vice versa, emitting radiation	
Holds atom's nucleus together	Holds atoms together but allows for bonding and formation of chemical molecules	Triggers nuclear fusion causing stars to burn	Holds universe together and allows for its accelerating expansion
Relative strength: 10[illegible]	10[illegible]	10[illegible]	1
Range: diameter of nucleus 10[illegible]	Infinite	0.1% diameter of a proton 10[illegible]	Infinite
Particle mediator: gluons	Photons	W and Z bosons	Gravitons (unconfirmed)

Figure 1 The fundamental forces of quantum physics

The concept was then translated into the language of the equations of quantum mechanics, to describe a phenomenon otherwise incomprehensible and not reproducible with the inadequacy of natural language, for its extraordinary complexity.

1.1. The force of universal attraction

So the fundamental physical quantities are represented by the mysterious interactions that take place within matter, from the atomic nucleus to the galaxies of the universe, whose manifestations we can perceive, but we cannot understand and describe the origin and the elementary mechanism that guides them.

Therefore, to speak of weak nuclear force, strong nuclear force, gravitational force, and so on, is to identify the magnitudes that move the universe, with abstract immaterial entities like "the love that moves the sun and other stars" of Dante, and does not change their substantial cognitive elusiveness, unless we translate them into conventional mathematical formulas.

Examples from various demonstrations make what we have said more understandable.

The atomic nucleus is formed by several particles, today they describe a number that varies continuously FIG. 2, which are held together by the fundamental forces we have described [1].

But what is the nature of these forces and how do they interact within the atom and universe matter?

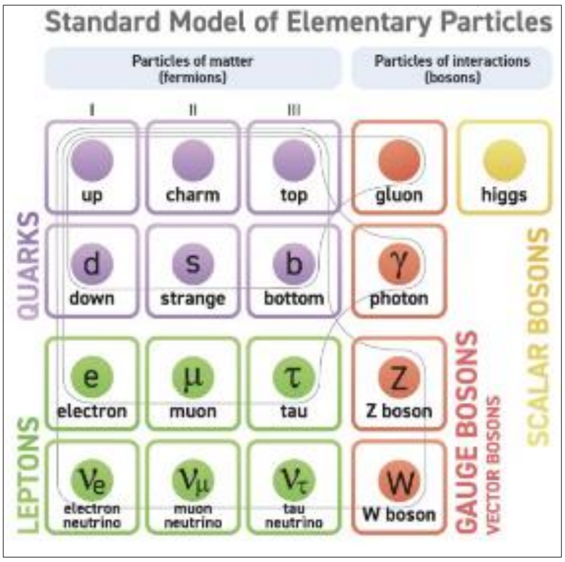


Figure 2 The elementary particles of the atomic nucleus

The same consideration also applies to these elementary particles described by quantum physics, they are abstract and arbitrary taxonomic entities, of pure nomenclature, adopted to describe elements such as protons, electrons, neutrons, etc. with definitions, that we cannot translate into knowable meanings.

How are Quarks and Leptons made, what happens when they are bombarded in the atomic nucleus with the powerful means of CERN synchrotron technology? Do they retain the same properties that they have in the nucleus intact or change completely because they are no longer subjected to the original forces of internal cohesion?

The only aspect of matter that we can grasp are the outer manifestations, two magnets that attract or reject, a light that strikes our eyes, two gametes that unite, and so on. But the question is why and how do these phenomena occur?

We give a description in terms of magnetic field, electromagnetic waves, chemotaxis and so on, but we cannot understand how and why they occur [2-3].

And the articulate descriptions of these phenomena that we find in the various sciences are worth nothing, it is only a lexical transfer that refers to other conventional definitions the inability to grasp them in their intimate essence.

However, what most affects our senses, and our imagination is the fundamental phenomenon of the interaction between the elementary particles that form matter.

If we can observe the phenomena, they produce it in precisely way because they interact, and even before interacting they communicate with each other and communicate to our senses their existence and the properties that characterize and distinguish them.

So, we could conclude that if the universe exists, it's because some entities, which we call elementary particles, have formed (how?) because they had found a way to communicate and interact with each other.

Thus the necessary condition of the existence of the universe is the presence of elemental matter, but it is not sufficient alone, the sufficient and efficient cause is its ability to communicate before and interact after. They are two distinct events because communication is the manifestation of the existence of a phenomenon, interaction is the reciprocal action of substances on each other.

Let's try to describe the phenomenon of communication-interaction starting from the elementary matter to arrive at the most complex forms of aggregation.

We neglect what happens in the atomic nucleus (nucleosynthesis) and in atoms, I have devoted another article to this topic [4], and we start directly from the simplest organisms and then consider the most complex forms.

1.2. Communicating is an unavoidable necessity.

The main property that distinguishes living systems and matter in general, as stated earlier, is the innate need to communicate.

Communication is the most characteristic and intrinsic phenomenon that expresses the morpho-functional state of the animate and inanimate matter of the universe and is the phenomenon through which material things manifest their properties to us.

And it is this intrinsic property that allows them to exist and evolve, each with distinctive unique properties.

Over the course of billions of years, molecular complexes have been evolving into infinitely different forms, such as we observe them in their current state, which in any case is not definitive but destined to change seamlessly.

In living systems, which represent the most complex form of molecular aggregation, the ability to communicate has reached maximum expression.

I repeat the fundamental concept that isolated elementary entities don't have reason to exist, and the ability to interact is the fundamental presupposition of material evolution.

Even the molecular aggregates and especially the living are never isolated but in constant interaction with each other and with the environment in which they live, in search of new existential modes.

In the living, the ability to interact and communicate within and between species allows to perform all the essential functions for their survival.

For this they have developed multiple receptor systems and transmitters, which have evolved into complementary and specific structures to ensure their effective contact.

The interaction takes place through contact, using some kind of stimulus-receptor recognition system, which can be direct or indirect, of a chemical, mechanical or electromagnetic nature [5].

Roger Sperry (Hartford 1913- 1994) defined the connection between nerve fibers by means of chemical signals as "chemoaffinity", a definition later extrapolated to the chemical attraction of substances.

But the chemoaffinity does not mean other than that the molecular structures are similar, that is able to recognize by conformational coupling or complementary energy, like what happens between two chemical forms enantiomer specular, or between the key and the lock.

But immediately a question arises, how do the stimulus-receptor systems are guided to mutual recognition distinguishing themselves among the infinitives that populate the environment?

There may be some sort of preferential path that guides them to their contact. Quantum mechanics hypothesizes that they are guided by the electromagnetic forces emitted by the two molecular systems that interact, an alternative hypothesis calls into question the different chemical gradients that trace the path to follow.

This second hypothesis has been brilliantly demonstrated by studying the specific tropism of the retinal axons towards their targets of the cerebral visual areas, in this mechanism the proteins of the *Efrine* group play an important role. But the question remains open for other reception systems.

In any case, the most relevant aspect to highlight is that isolated molecular complexes do not survive if they cannot communicate and interact. It's their reason for existing.

1.3. Specificity of communicative properties

As mentioned above, communication interactions are differentiated into specific receptor and stimulus systems and highly selective for the type of communication to be reported. Recognizable signals are in the form of particles (atomic or molecular) or in the form of electromagnetic waves.

And they can be transmitted by direct or indirect contact-interaction, in this case by exploiting the environmental medium or substrate within which the interaction takes place. Quantum physicists define the perturbations of the environment produced by material "field" entities, which is the equivalent of the ecosystem of biologists. Both are not the passive place of events, but the result of mutual interaction with the elements that populate them.

We know signals at a distance of various types, able to use the environment, such as light signals (electromagnetic), sound (mechanical), molecular stimuli acting at a distance (hormones), and molecular signals that act by direct contact, neurotransmitters, enzymes, antigens, etc.

In all cases, the effect they produce is a structural or conformational change specific to the receptor, through the effective molecular signature phenomenon [5].

A complex system of interactions so distinctive and selective interactions is the basis of the evolution of living systems, which manifest them in the most surprising forms. And this happens at every stage of the individual’s development process or metabolic activity.

1.4. Signal-receptor molecular system

The receptors are specific for each type and chemical-physical properties of the signal to be recognized. In addition, they are specialized for the mechanisms they must activate within the structure in which they reside, to produce a particular effect on the final target.

In living, receptors are molecular complexes capable of transmitting (transduce) the signal emitted from outside the biological system in a form decipherable inside.

The intracellular response, in turn, can be represented by:

- Regulation of the rate of enzymatic reactions;
- Regulation of the transport of molecules through membranes;
- Modulation of gene expression.

The receptors can be membrane or intracellular. In any case they are formed by complex protein molecules.

The receptors can be classified into four large families:

- Type 1 receptors or connected to ion or ionotropic channels;
- Type 2 receptors or coupled to G proteins or metabolotropes;
- Type 3 receptors or coupled to Tirosinchinase (enzymes);
- Type 4 or cytoplasmic receptors, nuclear.

Remember that the receptor is neither a channel nor an enzyme, but it is the sensitive part capable of modulating an ion channel or an enzyme.

Table 1 Types of receptors

Receptor	Localization	Effector	Coupling	Action time
TYPE 1	Membrane	Ion Channel	Direct	Very Fast
TYPE 2	Membrane	Enzyme o channel	Protein G	Seconds
TIPE 3	Membrane	--------------	Kinase	Hours/Day
TYPE 4	Intracellular	--------------	At various receptors and transport proteins	Very long

1.5. Morphogenesis of receptor systems

The complex mechanisms underlying the transformations that lead to the development and differentiation of cells, in the form of tissues, organs, individuals, are driven by the interactions between signal molecules and specific receptor.

Molecular biology has clarified an infinite number of guiding mechanisms of this kind that occur, for example in movement or selective tropism, which leads to migration by attraction of cells, or specific morphogenetic and tissue transformation during development and metamorphosis.

They are the typical mechanisms, for example, of cell differentiation during embryonic development.

As embryonic development increases the complexity and number of cells and tissues, we are witnessing an equal evolution of the transmission-which become increasingly specific and mutually selective and act as driving forces of the morphogenetic process. But while being specific and selective, they must necessarily maintain a constant feed-back contact with the system for the maintenance of functional homeostatic.

Today we know an infinite series of specific molecular stimulatory-receptor complexes that drive tropism and cellular differentiation and can select among the countless stimuli suitable for the function to be performed.

And even more fundamental is the selective ability in the interaction that takes place in the complex and intricate metabolism of evolved organisms, where the molecules involved are many and each with an intrinsic ability to communicate.

Not only that, but everything must also happen in a perfectly ordered and synchronized way both reciprocally and chronologically to have a harmonious operation.

The same phenomena also occur in the numerous colonies and forms of animal aggregation, where everyone, whether parent or child, can recognize in the most complete and noisy confusion of sound calls and olfactory stimuli produced by the community, the specific one that maintains and guides close parental relationships.

1.6. Cellular interactive systems

In 1965, Zuckerkandle and Pauling published in the Journal of Theoretical Biology (1965) an article that later became famous,[7] in which they introduced the concept of information molecules or semantides. He expressed the idea that molecules can store and transmit conformational (steric) information and that, by virtue of this, living organisms carry their own historical matrix inscribed in themselves. I expressed the same concept in the article by introducing the idea of specificity and molecular imprint [5].

We have said that the interaction between substances is the most typical phenomenon of universal matter and is particularly developed in cellular systems and in organisms from these formats.

Depending on the type of signal and the level of organization, the interaction must ensure small, medium and long-range communications, between different compartments of the organism itself and within the same compartment: the signal must therefore be able to 'travel' and be able to be translated (transduction) from one code to another (sensory, chemical, electrical, etc.). The purpose of these communications is the maintenance of contact between the various organisms and the ability to adapt in homeostatic mode to the stimuli of the environment for survival.

According to the type of interaction we must distinguish between intercellular communication (which takes place between separate and distinct cellular complexes) and intracellular communication (which takes place within the same cell).

Signals can also be diversified to:

- type (mechanical, thermal, luminous, sound, chemical, etc.), that is, transmitted by separate codes;
- Dimensional scale (macroscopic, cellular, microscopic - molecular).

1.7. Intracellular communication.

To describe this phenomenon, we start from an interesting article in which Bastian C. and colleagues have developed an experimental system engineered to examine the molecules involved in the mechanism of molecular communication [8].

Such systems mimic the mechanisms observed in cells and have provided important clues as to how communication takes place.

The general mechanism of transmission and transduction between signal and receptor molecule is given in Fig.3:

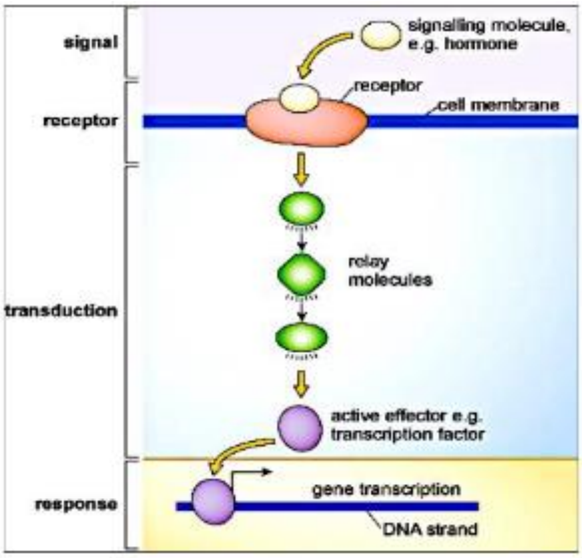


Figure 3 Mechanism of transmission receptor stimulus effector

Receptors have ligand binding specificity and effector interaction specificity:

The cellular response induced by a given extracellular signal molecule depends on its binding to a particular receptor protein located on the surface, nucleus or cytoplasm of the target cell (Specific molecular recognition, complementary steric coupling)

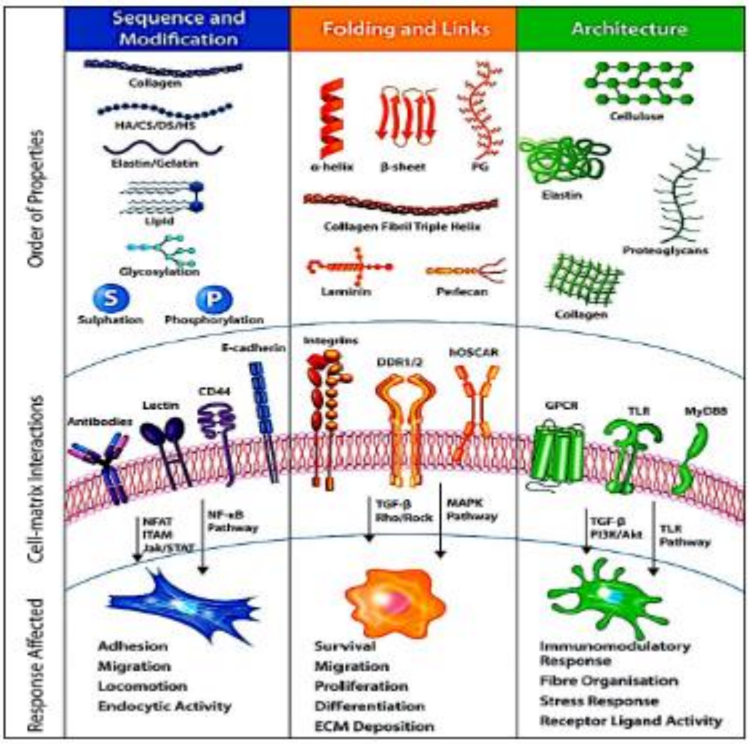


Figure 4 Schematic representation of the molecular mechanism stimulus response in different biological structures

Binding of the ligand to the receptor causes a conformational change of the receptor, which initiates a sequence of reactions leading to a specific cellular response;

A receptor protein is characterized by a binding specificity for a particular ligand, and the ligand-receptor complex has an effector selectivity that produces a particular cellular response.

As we have said before, there is a specificity of stimulus-receptor binding and effector (final molecular target), so in cells the response to a stimulus depends on the type of receptor present in the cell, on the cellular reactions produced by the binding of the stimulus on the receptor [9].

This is a well-established molecular mechanism that has been handed down from the most elementary living forms, the prokaryotes, up to the complex ones of the pluricellular eukaryotes Fig.4.

General characteristics common to all signal transduction routes are:

- Transmembrane communication of effector signals via receptor proteins;
- Grouping of membrane receptors and their ligands into large clusters called *signalosomes;*
- Reversible covalent modifications that regulate the function of certain proteins and lipids (phosphorylation, methylation, acetylation, ubiquitination, hydroxylation, limited proteolysis);
- Protein interaction domains that selectively recognize selected structural patterns and bind with high affinity and specificity;
- Second messengers who bind to particular targets, changing their activity and behavior;
- Intracellular signaling pathways that often involve a cascade of enzymes (e.g. protein-kinases), which connect receptors to their downstream functional targets.

Membrane receptors and intracellular receptors:

Receptors for signal molecules can be bound to the cell membrane or be present inside the cell (in the cytoplasm or nucleus) depending on the ability of the signal to cross the membrane.

Membrane receptors: bind protein-type messengers, peptides, and polar molecules that are unable to cross the double layer of the cell membrane Fig.5.

Intracellular receptors: bind lipophilic messengers that can cross the plasma membrane (e.g. steroid hormones).

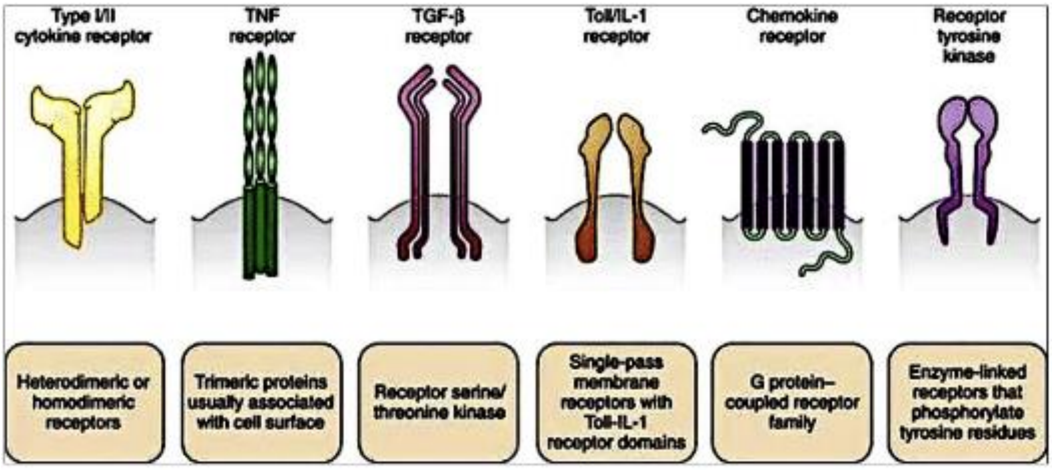


Figure 5 Drawings of some membrane receptors

1.8. Intercellular communication

Intercellular communication also plays a very important role because it interacts cellular individuals who share the same environment, must compete for the nutrients present in it, and compete for environmental adaptation and cellular evolution [10].

During the evolution the cellular specialization has produced functional cellular complexes, differentiated in a somatic line, representative of the phenotype, and a germinal line destined to the production of the reproductive elements, the gametes.

For evolutionary purposes this step was crucial, as it allowed the maximum assortment and recombination of genes, through the crossing of gametes, with an exponential possibility of biodiversity.

To achieve this goal, in the organisms that reproduce sexually, the male and female gametes must merge, and here comes back in action the mechanism of communication, that must guide the two gametes and encourage their encounter and their fusion.

The mechanism of intercellular communication is of an extraordinary complexity, and even today there are many dark points to clarify.

The primitive description of the mechanisms of intercellular attraction was made by T.W. Engelmann (1881), by Pfeffer (1884) on bacteria and by H.S. Jennings (1906) on ciliate protozoa.

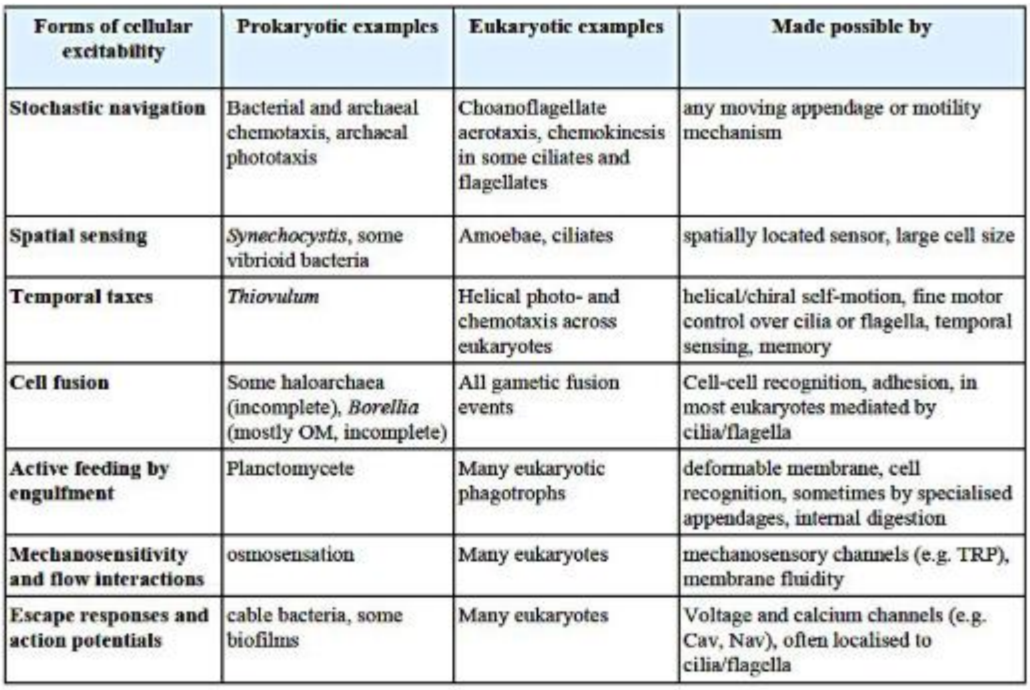
The Authors defined this special attraction between chemotaxis cells because they considered that the phenomenon was produced by special chemicals that selectively moved the cells towards each other [11].

Early experiments on bacteria and protozoa provided important clues to the molecular mechanism involved in this process.

From the general point of view, interspecific and intercellular communication manifests itself in two different modalities :

Stimuli exerted by the environment on living beings that play a fundamental role in the adaptive process, and intercellular communications within the same organism useful to ensure the functional homeostasis of the general well-being or pathological conditions.

Communication between individuals belonging to the same species, useful to inform the events that take place in the surrounding environment and have an adaptive value.



Forms of cellular excitability	Prokaryotic examples	Eukaryotic examples	Made possible by
Stochastic navigation	Bacterial and archaeal chemotaxis, archaeal phototaxis	Choanoflagellate aerotaxis, chemokinesis in some ciliates and flagellates	any moving appendage or motility mechanism
Spatial sensing	*Synechocystis*, some vibrioid bacteria	Amoebae, ciliates	spatially located sensor, large cell size
Temporal taxes	*Thiovulum*	Helical photo- and chemotaxis across eukaryotes	helical/chiral self-motion, fine motor control over cilia or flagella, temporal sensing, memory
Cell fusion	Some haloarchaea (incomplete), *Borellia* (mostly OM, incomplete)	All gametic fusion events	Cell-cell recognition, adhesion, in most eukaryotes mediated by cilia/flagella
Active feeding by engulfment	Planctomycete	Many eukaryotic phagotrophs	deformable membrane, cell recognition, sometimes by specialised appendages, internal digestion
Mechanosensitivity and flow interactions	osmosensation	Many eukaryotes	mechanosensory channels (e.g. TRP), membrane fluidity
Escape responses and action potentials	cable bacteria, some biofilms	Many eukaryotes	Voltage and calcium channels (e.g. Cav, Nav), often localised to cilia/flagella

Figure 6 Forms of cellular excitability in eukaryotes and prokaryotes

From , Kirsty Y. Wan and Gáspár Jékely; Origins of eukaryotic excitability.

Intercellular communication is a highly intraspecific selective mechanism confined within the same species, to avoid contamination of alien species.

The most archaic forms of chemotaxis are found in prokaryotes, bacteria that use special locomotor apparatuses, piles or flagella sensitive to environmental stimuli, used for general motility. These same scourges, we find them still today in the male gametes, spermatozoa, which allow the movement driven by the strong chemical attraction towards the egg that must fertilize.

Thus flagella are an important means of locomotion universally shared by many animal species.

It is not by chance that these structures contain protein substances, flagellines, particularly sensitive to the chemical calls exerted by the egg, both in external fertilization, and in internal fertilization.

The egg plays a primary role both in the production of active chemicals for attraction and in the selection of male gametes to fertilise them [12] Fig.6.

1.9. Communication according to quantum mechanics

The basis of the communicative phenomenon is the wave movement capable of producing waves of different nature and energetic consistency (movement is the manifestation of energy) in the environment in which they are immersed.

So the physical Substrate of communication, that is, the interaction between two or more distinct entities, is made up of matter that produces and transmits waves .

Waves in turn are formed by vibrations that possess peculiar characteristics and properties:

They have an energy content;

They transmit (transfer) only energy (sound waves, gravitational waves) or even particles with an energetic content (electromagnetic waves, wave-particle dualism).

The characteristic physical properties of waves are represented by their high informational content.

In fact, the various types of waves are distinguished by the following physical parameters :

The mechanical waves have Wavelength, frequency and wave amplitude (they are all space-temporal vector quantities) characteristics.

Electromagnetic waves, in addition to the quantities of mechanical waves, also contain a charge of an electric nature, which during the motion produces an environmental modification of a magnetic type [13] Fig.7.

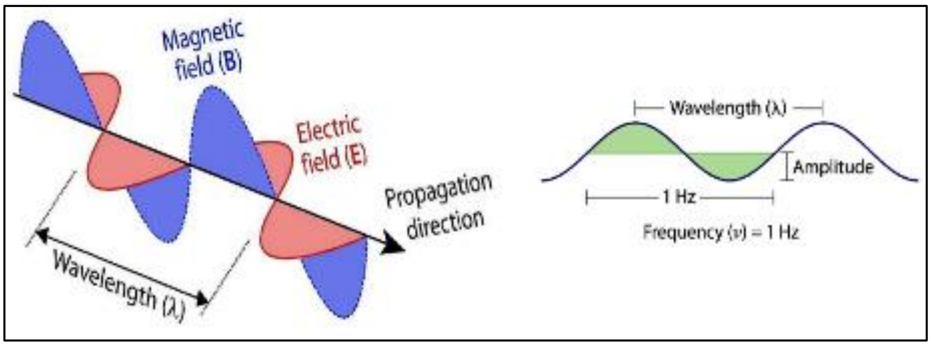


Figure 7 Design of electromagnetic waves

So that in their transfer carry up to four information simultaneously: amplitude, length, frequency and electromagnetic charge, and represent the most effective and universally adopted communication system in nature.

2. Conclusion

As we have seen, every material entity, atoms, molecules, molecular aggregates emits its own unique, distinctive, unrepeatable electromagnetic wave, with which it transfers this information to the surrounding environment.

With our technologies, which are nothing more than improved and enhanced sensory systems, we only might collect and measure the quantities and properties of individual material entities.

Returning to the interaction between living systems, the ability they possess of attraction is mediated by the emission of frequencies with amplitude and energy characteristic intra and interspecific.

This quantum interpretation explains how the phenomena of selective tropism occur between signal molecules and cellular receptors.

According to this principle, each cell or organism communicates to its complementary target the information necessary to achieve a functional result.

Quantum physics expresses this concept in terms of resonance systems.

The descriptions provided to explain the biological phenomena connected to the interactions between living beings are suggestive and plausible, but they still do not tell us what are and how the constituent elements of the matter that "moves the sun and other stars" work.

If from the point of view gnoseological/ epistemological communication is still veiled by an aura of mystery, there remains the certainty that it performs a fundamental task for the evolution of universal matter and the human species.

Thanks to it we have acquired the opportunity to exchange experiences, information and emotions, both in oral form and in written form and for representing them and transferring them to indelible witness for future generations.

Compliance with ethical standards

Disclosure of conflict of interest

The author report no conflicts of interest in this work.

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