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Editorial

Bacterial Communication and Human Communication: What Can We Learn From Quorum Sensing?☆

Comunicación bacteriana y comunicación humana: ¿qué podemos aprender del «quorum sensing»?

Hazael Jiménez Amador, Pere Casan Clarà*

Instituto Nacional de Silicosis, Hospital Universitario Central de Asturias, Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain

Communication is a phenomenon that is closely related with life, or better said, with life in society. The terms "communication" and "lack of communication" are part of the common terminology in diverse areas of study, such as the sciences, arts, philosophy, religion, and education. Humans even search for communication beyond our Earthly limits (existence of life on other planets) or in the period after physical death.

Communication is equivalent to living in social groups. Life in solitude was characteristic of biblical times, when some early Christians sought seclusion in deserts and even then found it difficult not to communicate with temptation. In the modern age, communication theory has impregnated social life to the extent that even politics are controlled by the media and communication professionals. Traditionally, the process of communication entails an element that emits, a receptor, codes, a medium for transmitting and a message. All these elements are equally important, but the role of the "medium" has reached such predominance that a phrase by Marshall McLuhan has become famous: "the medium is the message".[1] We could say that the message, what is actually being communicated, has lost its protagonism over how and where it is communicated.

The development of language in human beings was a key element in our evolution. The possibilities that communication provided enabled humans to overcome other larger, more agile or more numerous vertebrates and to be considered the "king of creation". This language, which is not a mere social contribution, but, according to the theories developed by Chomsky,[2] is instead preprogrammed in the human brain, arises at a certain phase in the maturation of the neuron connections and is able to be perfected and enable such lofty elements of communication as music or poetry.

As we have said, communication is a social fact, a necessity, something which we surely share with other species and which has developed to a greater or lesser extent. There is evident communication among animals, including warning signals, affection, hunting cues, and mating calls. Communication has also been seen among different members of the plant kingdom, based on the emission of chemical substances from leaves, flowers or fruits.[3]

And why not in the world of microscopic bacteria? In our zeal for putting names on things, several years ago the concept of "quorum sensing" was proposed in order to contemplate this variety of communication. Thus, this term would be defined as the phenomenon by which the accumulation of certain molecules with a signaling function would enable a certain bacteria to know the number of bacteria of the same species that are in its environment, and in this way initiate a response that is genetically predetermined. The response may vary: emit light, secrete mucus, create new radicals, etc. In any event, at a certain moment the bacteria acquire the "knowledge" that they are not alone and have reached a certain population density, after which time they react socially in a different way than they had before.[4]

The name used, quorum sensing, has been growing in popularity in the literature ever since a review by Fuqua et al.[5] It was one of these authors, Dr. Winans, who used the term proposed by his brother-in-law, a lawyer, who came up with the expression by comparing the bacterial situation with what happens in formal social meetings in which, once a minimum number is reached in order to formalize agreements, quorum is declared and the session is begun.[6] The concept has been the object of several studies and different names have been proposed. In a magnificent report,[7] the biologist Mercè Piqueras demonstrates this reality and calls attention to the fact that, despite several attempts, the name proposed by the mentioned authors has prevailed, and she proposes its Spanish translation as "*percepción de quórum*".

The term *quorum* comes from Latin, and it became popular in the political and social settings much before it came to be used in science or the media. Its use was based on the rules of a British tribunal, the "Justices of the Quorum", which required the mandatory presence of at least one of the members of the group in order to reach agreements. This presence was extended to the

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* Corresponding author.
E-mail address: pcasan@ins.es (P. Casan Clarà).

demand of a numerical majority or qualified minority prior to the start of sessions in order for any conclusions to be considered valid. Once the existence of quorum is accepted, the group behaves differently and there is a social process for developing certain actions. In the same way in bacteria, once a certain number of colonies is reached, these begin to behave "socially" and to defend themselves, attack the host, reproduce, emit a series of signals, etc. They perceive that they are sufficient in number and start to act in a way that is different from what they had done before.

How does quorum develop in the microscopic world? Let's see some examples.

Candida albicans is a commensal fungus that, in special situations, becomes a pathogen for humans. The first molecule associated with quorum sensing (farnesol) was described in eukaryotes, a fungus with dimorphic characteristics. The accumulation of farnesol prevents the change from yeast to the mycelia form, when the cell density is $\geq 10^6$ cells/ml in liquid culture. Both purified farnesol from *C. albicans* and commercial farnesol induce the change in micellar morphology toward the yeast phase of *C. albicans*, without inhibiting the growth of the yeast or the preexisting hyphae.[8] The formation of biofilm is also mediated by farnesol.[9] Therefore, the quorum sensing of *C. albicans* regulates the cell density, morphology and the formation of biofilm. The practical importance of farnesol is its capacity to induce apoptosis in other fungi or control the growth of hyphae, and it could therefore become a tool to combat fungal infections or become a drug treatment for candidiasis.[10,11]

It has been postulated that in *Pneumocystis* spp. there are quorum sensing systems that regulate the formation of biofilm, and interestingly farnesol inhibits its formation.[12] In *Staphylococcus aureus*, the accessory gene regulator (*agr*) has been described as the quorum sensing system. When the cell density is high, the expression of *agr* upregulates the pathogenicity factors that are secreted and downregulates those that are found in the cell wall, and depending on the characteristics of the environment in which it is located, it regulates the formation of biofilm. If *agr* is inhibited, there is an increased adherence to the surface and formation of biofilm, which makes the infection chronic. Therefore, pharmacologically inhibiting *agr* would be counterproductive.[13–15] *S. aureus* can disseminate from the biofilm, which seems to be regulated by *agr*, as there is an observed greater expression of *agr* in areas where the biofilm becomes detached.[15]

Pseudomonas aeruginosa is a pathogen associated with multiple infections in susceptible hosts. What is particularly important is that it causes respiratory infections in patients with cystic fibrosis, those with altered bronchial and lung structure (e.g. severe COPD, bronchiectasis), immunosuppressed and neutropenic patients and those on mechanical ventilation.[16,17] *P. aeruginosa* has factors of pathogenicity that it excretes in the surroundings or injects directly in the cells (e.g. ExoUa through the type III secretion system or injectisome) of the host, causing apoptosis in the epithelial cells and dysfunction of neutrophils and macrophages, the latter being very important in neutropenics.[18–20] On the other hand, *P. aeruginosa* has mechanisms to chronically remain in the host, mainly derived from the biosynthesis of exopolysaccharide alginate, Psl and Pel. Alginate is more widely studied and is made up of nonrepetitive subunits of selectively O-acetylated D-mannuronic acid and C5 epimer α-l-guluronic acid, which is a mucoid or gelatinous layer that is able to prevent opsonization and phagocytosis, in addition to providing refuge from its hostile surroundings. Psl and Pel have been described in environmental strains,[21,22] leading us to the concept of biofilm, which is microbiologically defined as: a sessile community characterized by cells connected to a substrate or interface, or joined together irreversibly, contained in a matrix of extracellular polymeric substances that have produced and exhibit an altered phenotype of the gene transcription and growth rate.[23] Biofilm is a source of bacteria dissemination[24] and its ultrastructure is characterized by being a thick, tridimensional layer made up of approximately 15% of cells and 85% of extracellular matrix that takes the form of setae or sessile with water canals between them that enable convective flow. Thus, the biofilm of *P. aeruginosa* protects it from the immune system, from antibiotics (by diminishing their diffusion, inactivating them in the matrix or due to a lack of effectiveness by being in a stationary growth phase), and it confers it a place to strengthen itself to later become disseminated.[23,24]

The *quorum sensing* system of *P. aeruginosa* regulates the production of various factors of extracellular pathogenicity and the previously mentioned formation and maturation of biofilm. This control is exerted through 3 autoinducer molecules expressed by the same number of quorum sensing systems. The molecules are: (a) N-3-oxododecanoyl homoserine lactone (3OC12-HSL); (b) n-butyryl homoserine lactone (C4-HSL); and (c) 2-heptil-3-hidroxil-4-quinolone, also known as *Pseudomonas* quinolone signal, o PQS.[25,26] In addition to being autoinducer molecules dependent on cell density for regulating pathogenicity factors, they also have direct effects on the cells of the host and its immune system. For example, 3OC12-HSL induces the secretion of proinflammatory cytokines such as IL-8 in human bronchial epithelial cells, and induces the production of COX-2. IL-8 induces cell apoptosis, and interestingly also appears to be high in COPD patients who smoke.[25,27] 3OC12-HSL directly induces apoptosis in macrophages and neutrophils, inhibits lymphocyte proliferation, downregulates the production of TNF-α, IL-12 and the stimulus that induces the transcription factor NF-κB to regulate the immune response is specifically repressed.[25,28,29] As for PQS, it is known to affect the formation of biofilm, regulate excreted pathogenicity factors (elastase, pyocyanin and lectin) and downregulate NF-κB in murine respiratory infection models.[30]

These genetic signals, chemical markers, biofilms, evidence of bacterial quorum sensing, etc. are all examples of an entire world of communication between these microorganisms, which lead us to contemplate the importance of their "social" actions. These factors are currently all receiving much scientific attention, and numerous publications have reported on these matters, especially those that come from a group of researchers from such diverse settings as engineering and mathematics, at the University of Tel-Aviv.[31,32]

In the 21st century, while the famous medical journal *The New England Journal of Medicine* celebrates its 200th anniversary and has dedicated a magnificent review to infectious diseases,[33] a commendable objective is to understand the keys to bacterial communication and to make sure that this uneven fight between humans and the microscopic world leans in favor of the former. After all, interfering with the communication systems of the enemy has been a war strategy since bygone days.[34] And in order to interfere, one must understand, and in order to understand, one must analyze. It is our hope that, in this instance, the systems created by man for analyzing social communication are also useful in this exciting bacterial world and, particularly, become part of the prevention and the cure of infectious diseases.

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