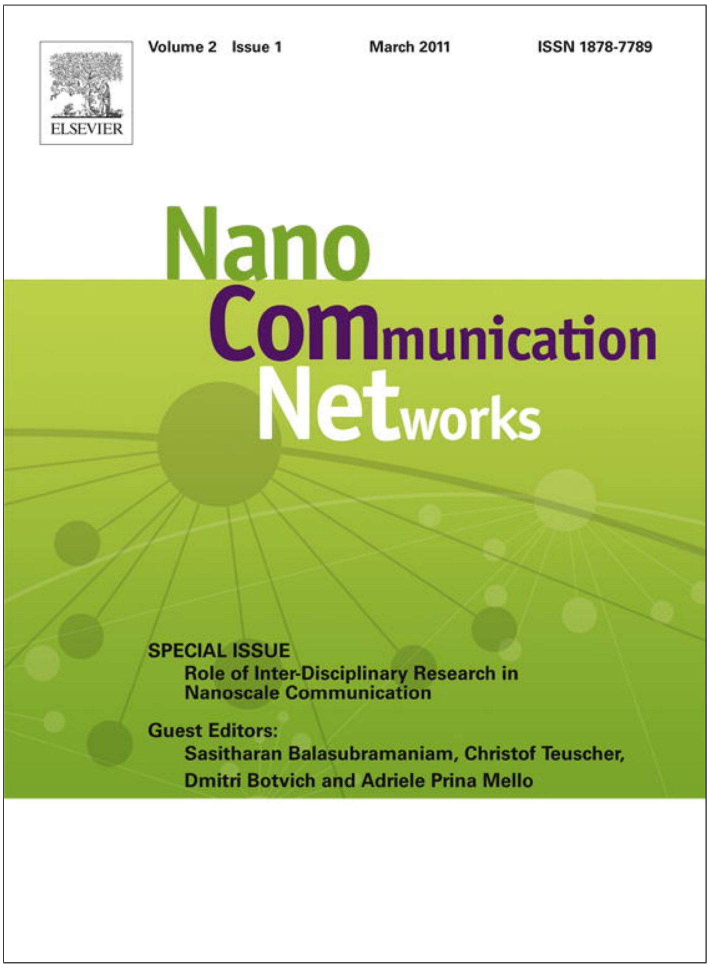
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# Automata modeling of Quorum Sensing for nanocommunication networks

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ABSTRACT

Nanotechnology is enabling the development of devices in a scale ranging from one to hundreds of nanometers. Communication between these devices underlying in the nanoscale greatly expands the possible applications, increasing the complexity and range of operation of the system. However, synchronization may be required to build a network architecture. In this work, we propose Quorum Sensing as a novel way to achieve synchronization between nodes of a nanonetwork. Quorum Sensing is a mechanism used by bacteria to sense their own population and coordinate their actions, through the emission and sensing of molecules called autoinducers. Here, the authors model the behavior of each bacterium as an individual finite state automaton, capturing its course of action. This model serves as the control unit of a "quorum nanomachine", which would be able to synchronize with its fellows in a distributed manner by means of molecular communication. Finally, this configuration is implemented and simulated, and the results are later discussed.



## 1. Introduction

Nanotechnology encompasses the development of structures and applications involving control of matter on an atomic and a molecular scale, ranging typically from 0.1 to 100 nanometers. Chemical and physical properties of particles at the nanoscale are also the object of study, results of which show great promise and are envisioned to provide novel solutions in a great range of fields. This is one of the reasons why nanotechnology is widely considered as a multidisciplinary discipline, comprising diverse areas of study such as chemistry, physics, molecular biology, computer science and telecommunications.

Being able to successfully arrange nanomachines stems from the major developments that occurred in nanotechnology. Nanomachines are "artificial or biological nanoscale devices that perform simple computation, sensing, or actuation" [20]. These devices are usually regarded as the most basic functional unit at this scale, and can be used as building blocks in order to construct more complex systems [1]. These new and more complex systems may not be strictly nano in size, but keep performing their tasks in the nanoscale, and taking advantage of the unique properties of nanomaterials or nanoparticles (e.g. quantum physics) to serve its purpose.

Communication between nanodevices greatly enhances and expands the capabilities of single nanodevices. The reach of nanodevices is extremely limited as is their size, and that is why networks of nanomachines (from now on, nanonetworks) allow application in larger scenarios [1]. Furthermore, nanonetworks can be used to coordinate tasks and realize them in a distributed manner, handling this way with complexity and low consumption of single entities. Specifically, molecular communication has re-

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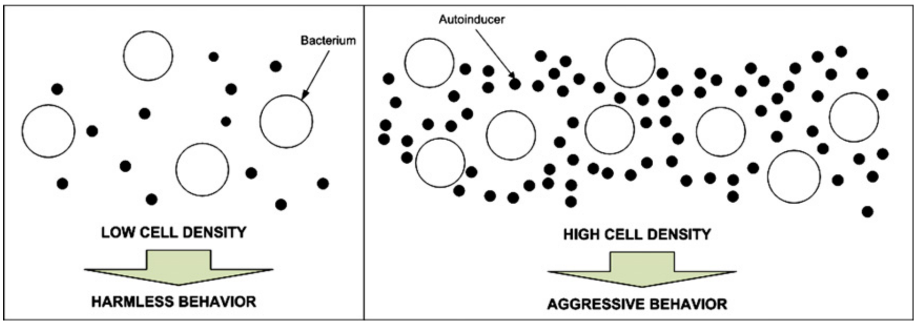


**Fig. 1.** Quorum Sensing unfavorable and favorable scenarios.

ceived the attention of the scientific community as a novel and promising way to achieve short-range communication between devices in the nanoscale [17]. It consists of the encoding of messages inside the molecules. Emitters release these molecules as a response to a certain command, and receivers have specific signal transducing mechanisms that react to specific particles. Other solutions have been proposed for medium-range [7] and long-range [15] nanonetworks.

Synchronization is a common requirement to build a network architecture. Concretely, synchronization between the elements of a nanonetwork is not easy to accomplish, due to the inherent characteristics of the nanodevices (i.e. issues involving complexity and energy needs). Individual clocks maintain nodes working continuously, which is not energy efficient. Whereas, a global clock [11] is not suitable in nanonetworks based on molecular communications, owing to the fact that information travels at low speeds. Also, a solution based on cellular automata and the classical "firing squad problem" [23,22] would be unfeasible because synchronization between neighboring nodes is needed in the first place.

In this work, Quorum Sensing is analyzed as a possible solution to the challenge of coordinating nodes in a nanonetwork using molecular communication. Quorum Sensing is a mechanism used by bacteria to sense their own population and coordinate or synchronize their behavior depending on the result of that sensing. This process is achieved by means of production, emission and reception of certain molecules, and enables bacteria to actuate *collectively*. We believe that Quorum Sensing can be applied to nanomachines with communication capabilities, in order to enable synchronization or coordination with the nodes in its close environment. Even though biological and mathematical models of Quorum Sensing have appeared over the years, a computational model that captures the course of action of bacteria that perform Quorum Sensing is still needed. Automata theory is a powerful tool that allows us to depict the behavior of these bacteria, identifying their different states, and the reaction to different inputs. Moreover, the resulting automata model can be later used as the control unit of a nanomachine that features Quorum Sensing.

The paper is organized as follows. First, the concept, principles and mechanisms of Quorum Sensing are introduced and explained. In Section 3, an application-independent automata model for the bacteria that participate in Quorum Sensing is presented, whereas the interaction between those bacteria is discussed in Section 4. These insights serve as the theoretical basis to develop a simulator, the results of which are introduced in Section 5. Finally, some conclusions are drawn.

## 2. Quorum Sensing: overview

Quorum Sensing is a biological process by which bacteria are able to communicate via signaling molecules called autoinducers. Precisely, by means of Quorum Sensing, bacteria are somewhat aware of their cell population density, and use that information to regulate their gene expression in a collective manner. Considering that the gene expression determines the behavior and functions of a living organism, we can explain how different groups of bacteria "exhibit cooperative behavioral patterns" [5]. The evolutionary reason behind the communication capabilities of bacteria is quite clear. Quorum Sensing enables the control of bacterial functions or processes that are unproductive when undertaken by an individual bacterium but become effective when undertaken by the group [8].

For instance, many bacteria species need to launch attacks in order to survive or spread. If a bacterium alone launches an attack, host's defenses will eliminate the threat immediately. Whereas if a large group of bacteria launches an attack, the success rate rises enormously (Fig. 1). Apart from virulence factors, several behaviors that are controlled by Quorum Sensing have been detected, namely motility, DNA processing, antibiotic biosynthesis, biofilm formation or bioluminescence [24], seen in diverse species such as the *Salmonella, Vibrio, Bacillus* and *Escherichia coli* families.

The phenomenon of Quorum Sensing has been observed to be rather ubiquitous in the bacterial world, and many examples can be found in the literature. This fact leads us to believe that Quorum Sensing is a powerful tool that could be used to coordinate the course of action of several nanomachines. As will be seen in the following sections, the Quorum Sensing mechanism can be seen as a distributed way to achieve synchronization by means of molecular communication. Moreover, bacteria follow a rather simple algorithm with no apparent need of configuration, two characteristics that might be critical if we take into account the intrinsic limitations of nanomachines. Finally, Quorum Sensing schemes can be combined to implement more complex interactions between groups of nanomachines, significantly expanding the possible applications of these systems.

### 2.1. Principles and mechanisms

Quorum Sensing is achieved through the production, release, and subsequent detection of and response to threshold concentrations of autoinducers [2]. Indeed, bacteria produce and emit a special kind of particles which diffuse in the medium. These particles, called autoinducers, have the ability of triggering the release of more of the same kind, when sensed. Hence, as the population of bacteria grows, the extracellular concentration of autoinducers increases as well. Changes in this extracellular concentration cause certain reactions in the behavior of each one of the members of the colony of bacteria. Specifically, if the concentration of particles reaches a critical threshold at a certain point, it means that a given population has been attained. That situation is sensed by the group, which responds to it with a population-wide regulation of the gene expression (Fig. 1).

#### 2.1.1. Autoinducers

As stated before, an autoinducer is a tiny molecule which triggers the emission of more particles of its kind. Which species are going to be able to bind and sense them is determined in its chemical composition. Actually, Quorum Sensing is a really common process between bacteria, and many different species use it for their purposes in a wide range of possibilities. Moreover, the type of autoinducer involved in the communication determines if two distinct species of bacteria are in the same conversation or not: there will be autoinducers that will enable *intraspecies cell to cell communication*, and others regarded as *interspecies cell to cell communication*. Interspecies communication allows the coexistence of different species in highly ordered communities, in which each of them carries out a specific subset of functions [2]. Some autoinducers, such as AI-2 and its synthase LuxS, even being extremely small (up to 4.5 Å), are to be considered as a kind of universal signal. The use of LuxS has been identified in more than 20 different species; a list can be found in [3].

Systems based on the principles of Quorum Sensing can be classified into three primary classes depending on the type of autoinducers involved and the internal reaction that is triggered when quorum is reached. Gram-negative bacteria use autoinducers of a family called AHL, which stands for Acylated Homoserine Lactone; Gram-negative bacteria rely on the use of oligopeptides as autoinducers, and there also exist Hybrid bacteria, which count on a system that is a mixture of the two previously stated options. Since it is not the objective of this paper to describe in detail these aspects, we will refer the reader to [3] for further biological details on the enzymes and reactions that are involved in each type of Quorum Sensing system.

#### 2.1.2. Thresholds

The behavior of Quorum Sensing bacteria is determined by the concentration of autoinducers that they sense in the environment. Changes in that behavior are consequences of variations in concentration, and several thresholds determine when these changes occur.

- Activation threshold: as explained earlier in this section, when the concentration of autoinducers reaches a certain threshold, the colony performs a population-wide regulation of the gene expression. Therefore, all the bacteria of the colony change their behavior at once. From now on, we will refer to this critical value as "activation threshold".
- Autocatalytic threshold: related to the emission of autoinducers, or particles that trigger the release of more of the same kind. By default, the autoinducers are synthesized at a basal or nominal rate. With increasing cell density, the extracellular concentration of autoinducers also increases. When this concentration reaches a certain threshold, referred to as "autocatalytic threshold", the rate of emission of autoinducers rises dramatically. This is due to the fact that after surpassing this threshold, the autoinducers are synthesized by means of autocatalysis.

Autocatalysis is a chemical reaction widely known and studied. In this case, the reaction product is itself the catalyst for that reaction, thus creating a positive feedback loop. This serves as an explanation of how an autoinducer triggers the synthesis and emission of more particles of the same kind, and how the rate of emission in the autocatalytic phase is much higher than the nominal rate.

### 2.2. Combination of Quorum Sensing systems

There have been cases reported about bacteria containing several, oftentimes overlapping, Quorum Sensing systems. That is, some bacteria are able to react to different autoinducers sequentially or in parallel, constructively or destructively. For instance, the species *Pseudomonas aeruginosa* makes use of two overlapping systems [9]. Moreover, these systems act in series to regulate two overlapping subsets of genes, which ensures a sequential activation of the two groups [19]. Hence, supposing that a non-activation of one of the systems does not affect any genes, the overlapping set of genes will respond to the equivalent of an OR gate between the two systems.

On the other hand, there exist at least two documented cases in which Quorum Sensing works in parallel: *Vibrio harveyi* and *Bacillus subtilis*. The Quorum systems present in *V. Harveyi* converge to regulate a common set of target genes [13], by reacting to two different types of autoinducers. The change of behavior will only occur when both autoinducer types are present, because they are complementary in terms of the reaction that triggers the regulation of the gene expression. In the case of *B. subtilis*, bacteria use parallel systems to respond to different autoinducers. In this species, the competence behavior is controlled by the level of autoinducers "A" only if the other autoinducer, "B", is not sensed [10]. This is due to the fact that both autoinducers have inverse chemical consequences inside the cell, meaning that one is able to cancel the other.

In conclusion, these cases make us think that the embedding of complex systems based on Quorum Sensing in nanomachines is possible. Moreover, the series or parallel configurations are perfect for the engineering or assembly of some kind of logic circuitry for systems based on the principles of Quorum Sensing. For instance, if the levels of autoinducers A and B are seen as digital 'high' and 'low' levels, the systems described above would both act as AND gates of the two levels (AB for the *V. harveyi* case and $A\overline{B}$ for *B. subtilis*).

## 3. Automata modeling of Quorum Sensing bacteria

The objective of this section is to formally model the process of Quorum Sensing, thus enabling the abstraction from the biologic phenomenon. Quorum Sensing is a particular communication process in which, considering the intraspecies case, all the agents are identical. The strategy followed is to model the bacteria from the emitter and receiver perspective, which are also connected. Once this is done, a big part of the global model is achieved. Automata theory gives the necessary tools to characterize the bacterium as a Finite State Machine (FSM), which in the future can be used to program nanodevices with communication capabilities. This approach has been chosen mainly because it enables the *Information and Communications Technology* community to understand the biological processes that occur in nature, and its dynamics. After that, modeling of the environment and the interaction between bacteria has to be addressed, since communication is the basis of the Quorum Sensing phenomenon.

Let us follow an inductive development. A first simple model, often named as "gene expression switch" will be introduced and will serve to explain the basic behavior of Quorum Sensing. After that, the two states of this initial model will be further explained and decomposed in several states, in what we called the pre-Quorum and post-Quorum sections. Finally, the complete model is stated as the juxtaposition of these two sections.

### 3.1. Gene expression switch

Overall, the course of action of bacteria performing Quorum Sensing can be regarded as an ON–OFF switch. In fact, Quorum Sensing has been named "gene expression switch" in numerous occasions [4,6,21]. This is a good starting point to develop the model, due to the fact that the finite state machine representation of an ON–OFF switch is widely known. Basically, a bacterium in a colony which has not reached quorum has the following simplified routine.

First, the bacterium senses the autoinducers concentration in its close environment. This result is processed and compared with the activation threshold. Hence, a decision is to be made.

- If the concentration is below the threshold, the bacterium will release a given amount of autoinducers, which will depend on the intracellular concentration as well.
- On the other hand, if the concentration is above the threshold, the gene regulation is performed, thus changing the behavior of the bacterium.

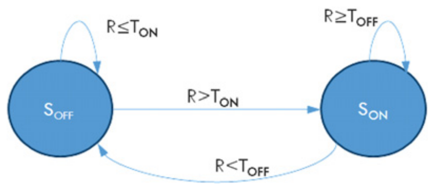


**Fig. 2.** States diagram for an ON–OFF switch.

This cycle is continuous, meaning that bacteria will sense the environment and release autoinducers in an infinite loop (low density state, $S_{OFF}$) as long as the concentration sensed is below the activation threshold $T_{ON}$. Once the concentration exceeds this limit, the loop breaks and the gene regulation will follow in state $S_{ON}$.

After the change of behavior, the bacterium will again control the concentration of autoinducers to sense the population of the colony. The purpose of this new loop is to ensure that the concentration is still over a certain different threshold. Thus, the bacterium keeps in this state until the density of the cluster falls below a certain level ($T_{OFF}$), moment in which will return to the initial state. Finally, it is important to remark that the two thresholds introduced do not have to be the same. In fact, it is believed that they inherently ensure a hysteretic behavior in the switch ($T_{ON} > T_{OFF}$), thus avoiding easy reversal of each change of state. The state diagram of this finite state machine is shown in Fig. 2.

### 3.2. Pre-Quorum and post-Quorum

From now on, the initial or OFF state shown in the previous lines will be called *pre-Quorum* section, as the critical population or quorum has not been reached. In the same fashion, the ON state will be referred to as the *post-Quorum* section.

#### 3.2.1. Pre-Quorum section

While being in this part of the automaton model, the cluster of bacteria has not reached the critical density of population to activate, meaning that the amount of autoinducers in the environment is too low. Here, the bacterium senses the environment periodically and depending on the result of the perception, the chemical reactions inside the cell will cause (or not) the gene regulation. After the checking the bacterium will emit a certain production of autoinducers that also depends on the amount sensed (as seen in Section 2.1.2).

Thus, two considerations are to be taken into account when defining the states of this part. First of all, the aforementioned causality between sensing and emission. Even though bacteria count on systems that can perform both actions concurrently, we will separate sensing states from emission states. The second consideration has to do with the variability of the rate of emission. In Section 2.1.2, the concept of "autocatalytic threshold" was defined as the concentration of autoinducers beyond which the autocatalytic reaction is turned on. This means that, when the concentration sensed is higher than this threshold, the bacterium will emit autoinducers in a much higher rate. On

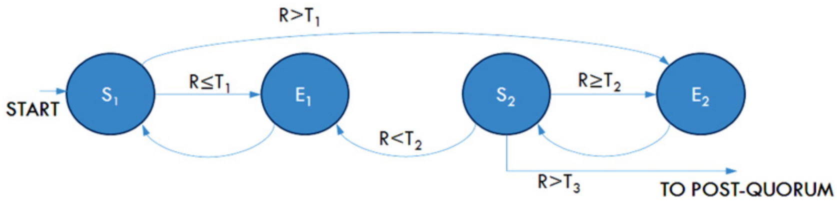


**Fig. 3.** States diagram proposed for the pre-Quorum part.

the other hand, a change from high to low density of population also affects the emission of autoinducers the other way around. If the population falls below a certain level, the same will happen with the concentration of autoinducers, thus turning off the autocatalysis and returning to the initial or nominal levels. Again, the thresholds for activation or deactivation of the autocatalytic reaction are naturally set to ensure hysteresis [4,14].

The state diagram shown in Fig. 3 represents a first approximation of the pre-Quorum part, and tries to accommodate the two conditions exposed above. $S_1$ and $S_2$ states are those in which the cell senses the environment. The next state will be chosen between the emission states $E_1$ and $E_2$, depending on the concentration received (R): thresholds $T_1$ and $T_2$ are the limits for switching from initial to autocatalytic production rate, and vice versa. The distinction between emission states is done because the output will be different in each case (basal rate for $E_1$ and autocatalytic rate for $E_1$), whereas sensing states will have null output. In the end, the bacterium will only advance to the post-Quorum states if the activation threshold, defined by $T_3$, is surpassed. It is easy to see that this transition is the passing from the OFF state to the ON state, in the switch model that served as starting point (see Fig. 2). Therefore, $T_3 = T_{ON}$.

In conclusion, this part of the automaton model can be summarized as follows. At a starting point, in which we suppose null presence of autoinducers, the bacterium is in state $S_1$. After sensing the environment, the bacterium will jump to state $E_1$ in which it will emit autoinducers at a rate "by default" (basal rate). If the concentration of autoinducers remains low, the bacterium will stay in the $S_1 - E_1$ loop. However, if the population of bacteria grows, the concentration of autoinducers will increase accordingly. If that concentration surpasses the autocatalytic threshold, the bacterium will jump to state $E_3$ and it will produce and emit autoinducers at a much higher rate, due to the process of autocatalysis.

### 3.2.2. *Post-Quorum section*

The states of the post-Quorum section capture the behavior of the bacteria after having reached quorum, meaning that the concentration of autoinducers has surpassed the activation threshold. As stated before, there are different behaviors depending on the species, and they are controlled by the gene expression, which is regulated in this phase of Quorum Sensing. Moreover, in this part, the bacterium keeps sensing the environment. It checks if the concentration of autoinducers keeps above a certain threshold, to maintain the post-Quorum behavior activated. If the concentration of autoinducers falls below a

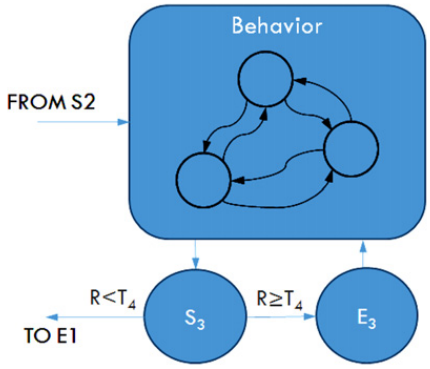


**Fig. 4.** States diagram proposed for the post-Quorum section.

certain level, the post-Quorum function is reversed, getting back to the pre-Quorum states. We can also assume that, at the same time, the bacterium will return to the initial state, thus emitting autoinducers at the basal rate again.

As there exists a vast variety of bacteria, a lot of different post-Quorum behaviors can be observed. To give a unique model for each and every case is impossible, since each species controls its own subset of behaviors, and in the end, its own gene expression regulation. Our proposal is based on modeling the behavior that the bacterium acquires after the regulation of the gene expression. This way, the model is generic for different species that present same types of post-Quorum behavior, regardless of their genetic material. Therefore, there will be a different set of states for each concrete behavior that, in turn, is potentially usable for several applications. For instance, there exist some species of bacteria that regulate motility through Quorum Sensing and a unique behavioral model would be generic for all of them, whereas motility can be the key for the development of applications such as transport of information or targeted killing.

Fig. 4 shows a general scheme of the behavioral post-Quorum model, in which the states corresponding to the concrete behavior are placed in a black box. On the other hand, two states corresponding to sensing and emission are maintained, as the behavior should be turned off as soon as the concentration of autoinducers falls below the threshold $T_4$. It is easy to see that $T_4$ corresponds to $T_{OFF}$ of the "gene expression switch" model.

## 3.3. *Complete model of Quorum Sensing bacteria*

After having explained how the bacterium works in both pre-Quorum and post-Quorum Sensing, and having introduced the states for each part, a formal statement of the automaton model has to be build. This model is a Moore machine $A = \{Q, \Sigma, \Lambda, \delta, \tau, q_0\}$ the inputs of which are

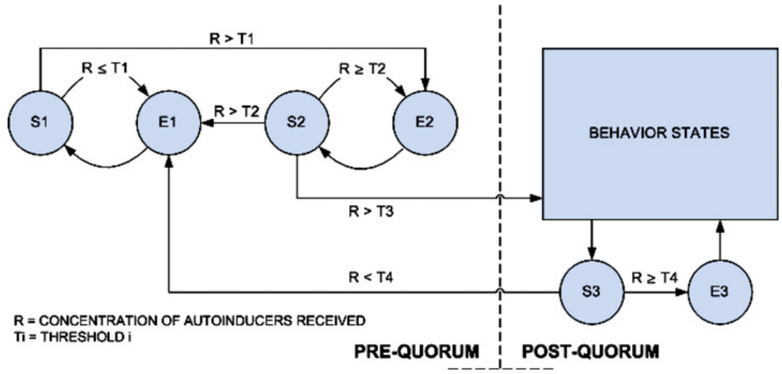


**Fig. 5.** State diagram proposed for the Quorum Sensing bacteria.

discrete levels of particles, and the outputs are signals that trigger the emission of a certain amount of autoinducers. The elements that define the automata are the following.

*States (Q)*

The states that form the automaton for the Quorum Sensing bacterium are

$$Q = \{S_1, E_1, S_2, E_2, S_3, E_3, B\}$$

where $B = \{b_1, b_2, b_3, \ldots, b_n\}$ is the subset of states that represent the model of the behavior that the bacteria show after reaching Quorum. Each behavior (motility, antibiotic release or bioluminescence, to name a few) determines the model that will lead to a certain subset $B$ of states, and the cardinality of it ($n$) is subject to that. As for the rest of the automaton, the sensing states $S_1$, $S_2$ and $S_3$ dictate the emission to be done (state $E_1$, $E_2$ or $E_3$), as well as the future state, indirectly.

*Input alphabet ($\Sigma$)*

The alphabet of possible inputs of the automaton will be

$$\Sigma = \{d_1, d_2, d_3, d_4, X\},$$

where $X = \{x_1, x_2, x_3, \ldots, x_n\}$ are the inputs that might be needed to model the transitions between the states that represent the post-Quorum behavior of the bacterium.

The rest of the symbols of the input alphabet serve to model how the input of the cell $R$ affects its behavior, taking into account the different thresholds that have been introduced. In our case, $d_1 = R > T_1$, $d_2 = R < T_2$, $d_3 = R > T_3$ and $d_4 = R < T_4$. Symbols $d_1$ and $d_3$ activate when the received concentration surpasses the basal to autocatalytic threshold and the Quorum threshold, respectively. On the other hand, $d_2$ and $d_4$ activate when the concentration is lower than the autocatalytic to basal thresholds.

*Output alphabet ($\Lambda$)*

In this case, it is formed by symbols that will trigger the production of autoinducers. The alphabet of outputs proposed in the Quorum Sensing bacteria model is

$$\Lambda = \{l_1, l_2, Y\},$$

where $Y = \{y_1, y_2, y_3, \ldots, y_m\}$ are the outputs that might be needed to complete the model of the post-Quorum behavior of the bacterium. The rest of the symbols of the output alphabet serve to model the quantity of autoinducers that the cell will emit. In fact, $l_1$ represents a nominal or initial level of emission, and $l_2$ indicates that an emission in autocatalytic levels is to be done. Although the quantity of autoinducers emitted by Quorum Sensing bacteria varies within those two levels, for the sake of simplicity, only the emission in these two extremes is considered.

*Transition function ($\delta$)*

The easiest way to describe the transition between states is by means of the state diagram, that is represented in Fig. 5.

Regarding the set of states which represent the post-Quorum behavior ($B$), the internal transitions between their states is determined solely by the inputs defined for it ($X$). The transitions that mark the entrance to that set of states $B$ are known, but those that mean the exit of $B$ are also determined by the set of inputs $X$. Remember that both $B$ and $X$ are subsets that depend on the post-Quorum behavior to model.

*Output function ($\tau$)*

Here, the symbols of the output alphabet are mapped with the states. $l_1$ indicates that an emission at a basal rate is to be performed, whereas $l_2$ indicates an autocatalytic emission. Then, these symbols will be assigned to each emission state: basal emission for $E_1$ in the pre-Quorum section, and autocatalytic for the other two states. Regarding the sensing states, when the environment is being perceived, there will be no output. This is represented with the symbol $\epsilon$. In the case of the post-Quorum behavior states, $B$, the output depends on the behavior that is being modeled and that is defined by the set of outputs $Y$.

*Initial state ($q_0$)*

Simply,

$$q_0 = S_1.$$

## 4. Interaction between bacteria in Quorum Sensing

Quorum Sensing is a process that can be considered as collective. It needs a certain number of specimens interacting globally using signaling molecules called autoinducers. These molecules have to travel from one transmitting bacterium to another unspecified cell that will be the receiver. This receiver can be the cell that is closer to the emitter, or

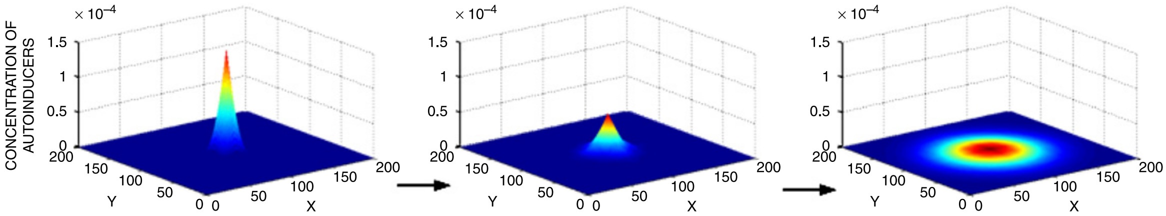


**Fig. 6.** Propagation by means of diffusion of a punctual emission.

simply the one that intercepts the autoinducer in its erratic path through the environment. Hence, to fully explain and model the Quorum Sensing phenomenon, let us make a description of the environment and the laws that govern the movement of the particles involved.

### 4.1. Background: diffusion basics

Some assumptions about the environment in which bacteria live and perform Quorum Sensing, are needed in order to simplify the simulations. We will consider that the autoinducers emitted by bacteria will move in a homogeneous low Reynolds number [18], finite and discrete space, following a process called molecular diffusion.

Finite because the process is rather local, meaning that events taking place at several centimeters of distance will not affect it. Also, we consider the space discrete in order to make the simulations feasible. On the other hand, let us assume that the space is homogeneous, so that the degree of complexity is kept relatively low. Finally, in the scenario we are considering, normally particles are subject to viscous forces rather than inertial forces. This ratio of forces is usually expressed with the Reynolds Number, which is said to be 'low' in this case.

*Fick's laws of diffusion*

Molecular diffusion, or otherwise simply referred to as diffusion, is the thermal motion of all molecules at temperatures above the absolute zero. Following this principle, when in a certain environment exists a non-uniform distribution of particles, these tend to diffuse away in order to reach an uniform concentration through all the space [16]. Molecular diffusion can be also considered as a specific case of random walk or Brownian motion, which models the random movement of particles suspended in a fluid, and also some other phenomena in diverse fields.

The emission and propagation of the autoinducers are subject to these physical rules. When a bacterium emits a certain amount of autoinducers, a peak of concentration appears in a point in space. Then, the autoinducers will diffuse away as explained before, following the gradient of the concentration, therefore going away from the source (Fig. 6).

Hence, there is a need to model mathematically this phenomenon and implement this model into the simulator. Molecular diffusion is typically described mathematically using Fick's laws of diffusion [16], mathematical expressions derived by the German physiologist Adolf Fick that describe the diffusion phenomenon. Concretely, we will use the second Fick's law in its finite differences form, relating the spatial and temporal variations of the concentration of autoinducers $\phi(\overline{x}, t)$, using the diffusion coefficient $D$ as parameter:

$$\frac{\phi(\overline{x}, t+\Delta t) - \phi(\overline{x}, t)}{\Delta t} = D \sum_{i=0}^{n} \frac{\phi(\overline{x} - \Delta\overline{x_i}, t) - 2\phi(\overline{x}, t) + \phi(\overline{x} + \Delta\overline{x_i}, t)}{(\Delta\overline{x_i})^2}, \quad (1)$$

the solutions of which are stable if (limiting the spatial resolution):

$$\Delta t \leq \frac{(\Delta\overline{x})^2}{2D}. \quad (2)$$

This equation allows us to know the future concentration of autoinducers in one point provided the concentration in one point and its vicinities in the present, also depending on the diffusion coefficient. The diffusion coefficient or diffusivity, gives the "speed" at which the particles move to the positions with less concentration, and is characteristic for each medium. In this case, the diffusion coefficient for spherical particles moving low Reynolds number fluids is [18]:

$$D = \frac{K_B T}{6\pi \eta R}, \quad (3)$$

where $K_B$ is the Boltzmann constant, $R$ the radius of the particle, and $T$ and $\eta$ are the temperature and the viscosity of the environment, respectively.

### 4.2. Transmission and reception of autoinducers

The Quorum Sensing phenomenon can be reduced to the emission, propagation and reception (sensing) of autoinducers. In the emission process, bacteria raise the concentration of autoinducers in its area of influence by means of secretion. The resultant concentration due to this emission will diffuse away following the laws described before, seeking uniform distribution of the autoinducers in all the space. The mean distance traveled by the diffusing particles over time is $x = \sqrt{2Dt}$. When the autoinducers enter the area of influence of another bacterium, that cell might end up sensing it through its chemoreceptors. Hence, the internal concentration of autoinducers of that bacterium increases, and some chemical reactions are triggered depending on this level.

This process can be also seen from the point of view of the automata. To do that, the evolution of the states of different bacteria represented by automata will be shown in two cases. In the first one, there will not be enough

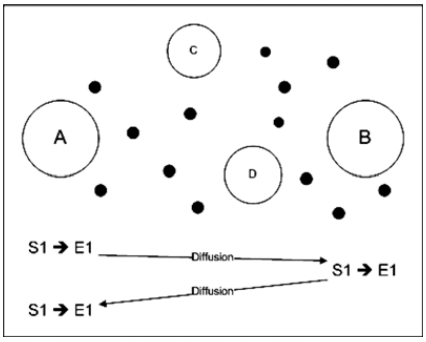


**Fig. 7.** Interaction between automata in unfavorable conditions.

population to activate the post-Quorum behavior. In the second one, the bacterial concentration will be enough to reach the post-Quorum states. As there is not any kind of synchronization between bacteria, we will assume that different individuals sense and emit at different moments in time, but they do it in a certain and equal rate. The model used is the one described in Section 3.3.

#### 4.2.1. *Low bacteria concentration*

In the case there is only a few bacteria, far below the number needed to reach quorum, the evolution is as follows (represented in Fig. 7):

(1) Starting from scratch, in the case where there is not enough bacteria to reach quorum, let the environment be free of autoinducers. Then, initially, the bacterium A is in state $S_1$ and therefore will sense its close surroundings and will detect no autoinducers. As zero is below the first threshold, the next state will be $E_1$ and the emission burst will correspond to the basal rate. These autoinducers will diffuse away in all directions.
(2) On its turn, bacterium B is also in the initial state $S_1$ and will sense the portion of the emission of A (and maybe other bacteria) that arrives to its surroundings. Let the amount sensed be below the first threshold. Then, the emission will be done in the basal rate (state $E_1$).
(3) Bacterium A senses the environment some time after the action of B, still in state $S_1$. As there are just a few bacteria, this new sensing will be also below the first threshold and the emission will keep being in the basal rate.
(4) The same happens for bacterium B, and the system arrives to a loop in where all the bacteria emit at a basal rate, and the accumulation of autoinducers is not enough to trigger any other reaction in the colony.

#### 4.2.2. *High bacteria concentration*

On the other hand, there is the case in where the bacteria grow and divide and the colony reaches the required number to activate the post-Quorum behavior. The evolution is represented in Fig. 8, and can be explained as follows:

(1) The first steps are like in the previous context. The bacteria A and B emit in a basal rate ($S_1 \rightarrow E_1$).

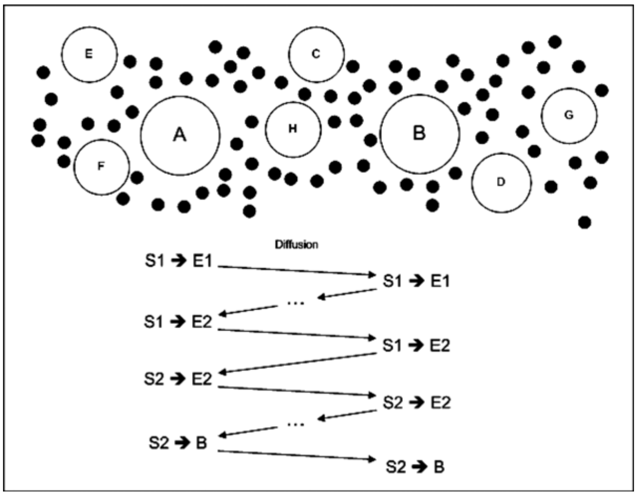


**Fig. 8.** Interaction between automata, and quorum achievement.

(2) At some point, the population reaches certain conditions of number and positions. Bacterium A senses the environment, and this time the accumulated concentration is above the first threshold. Hence, there are enough autoinducers to trigger an autocatalytic reaction and emit at a higher rate ($E_2$). The automaton reaches the autocatalytic state.
(3) Bacterium B senses the environment after the emission of A. The increase of the emission rate in A makes the difference for B to surpass the first threshold and to switch the state to autocatalytic ($E_2$).
(4) After some cycles, the change has spread and a big part of the bacteria reaches autocatalytic situations, in which the emission of autoinducers is much higher than the beginning. Then, at some point bacteria A and B will do the periodical sensing of the environment ($S_2$) to find that the concentration of autoinducers is above the activation threshold. Eventually, they change their behavior to post-Quorum (state *B*), and Quorum Sensing is achieved as the change of state occurs at almost all the bacteria.

## 5. Simulation results

Taking into account all the considerations made through the previous sections, we built a simulator that helped us to validate the model proposed. This simulator, coded in C, implements a finite, concrete and homogeneous space in which some bacteria live. The course of action of these bacteria is defined by the automata model proposed in Section 3.3. On its turn, the concentration of autoinducers is calculated for each point in space, depending on several factors such as the autoinducer emission of the different bacteria or the diffusion coefficient of the medium. The calculation is performed by using the laws of diffusion presented before.

This section is devoted to show that the model implemented exhibits the expected behavior. Later, a connection between the activation threshold and the number of activating bacteria is pointed out.

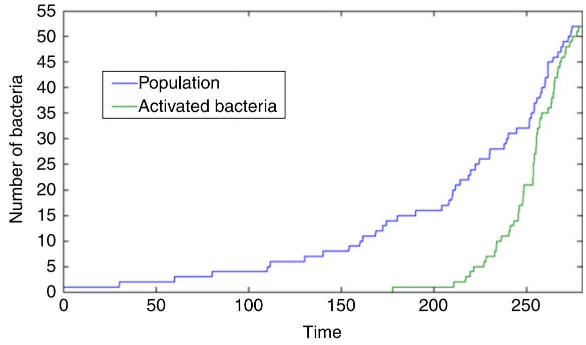


**Fig. 9.** Number of activated and total bacteria as a function of time.

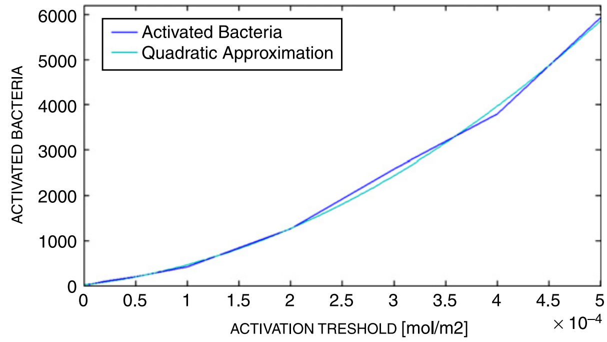


**Fig. 10.** Number of activating bacteria as a function of the threshold.

### *5.1. Validation*

In this case, the simulation starts with a bacterium in the center of the simulated space. That bacterium and its descendants reproduce themselves again and again, so that the population doubles with a certain frequency. Meanwhile, these bacteria keep sensing the environment and emitting autoinducers. There must be a certain point in which a great part of the colony will change of state. At each time step, the list of the states of the bacteria is constantly updated, and a count of bacteria in post-Quorum states is performed. The results for a certain set of parameters can be seen in Fig. 9: the population grows in a steady basis until reaching a point in which almost all the bacteria activate simultaneously. The rest activates shortly after, reaching a 100% of activation when the bacteria are clustered, not spread.

Nevertheless, for simulations in which a high population of bacteria is required to achieve Quorum Sensing, 100% of activation is not attainable. Bacteria located on the limits of the cluster do not sense enough concentration of autoinducers and consequently, do not activate. Those individuals keep reproducing until they are not on the limit anymore. Then, they sense a raise in the concentration of autoinducers and eventually they activate the post-Quorum behavior. But again, new bacteria are on the edge of the cluster and they will not activate. This way, the percentage of activation reaches a value of around the 95%.

### *5.2. Number of activating bacteria*

It seems clear that one of the key parameters in the overall process is the concentration threshold beyond which the bacteria activate, because it has influence upon the minimum population needed to change their status. These simulations are very important, because we envision that the first applications of Quorum Sensing will require the deployment of a given number of agents. The election of a reasonable value for this threshold is the key for the proper activation of these agents that perform Quorum Sensing.

To check if there is a connection between the minimum number of activating bacteria and the activation threshold, we carried out a series of simulations in which the activation threshold was taken as a parameter. For each iteration, the threshold is modified and the final number of activating bacteria (with a percentage of over 95%) is taken.

Fig. 10 shows the result of the simulations and points out a certain relation. In this case, the number of activating bacteria is quadratically dependent with the activation threshold used. The blue plot represents the number of quorated bacteria as a function of the activation threshold, and the green plot is the quadratic approximation, which fits the original plot almost without error.

## 6. Conclusions

Communication among devices in the nanoscale is needed in order to expand the possibilities of single nanomachines, increasing the complexity and range of operation of the system. Molecular communication is considered as the most promising option for this matter.

Quorum Sensing is a natural phenomenon that uses molecular communication to coordinate the action of a group of bacteria, depending on the population of that group. In this work, this process has been studied and modeled in order to capture the course of action of the bacteria that perform Quorum Sensing. In a more broad view, we are giving a new example of how biologically inspired research offers great solutions to networking issues [12].

The model presented in Section 3.3 reproduces the behavior of an individual that builds, senses and emits molecules in order to reach Quorum Sensing. The use of automata theory enables an easy, yet accurate, implementation in a simulator, from which some results are extracted in terms of validation of the model and threshold values. They all depend on the reproductive process of the bacteria.

We consider that the automata model introduced in this work can be also used as the control unit of a nanomachine. Slight modifications of the original automata proposed for bacteria could lead to the creation of control units for other types of nanomachines with different applications. Synchronizing several nanomachines would increase the effectiveness and reach of targeted killing, for intelligent drug delivery, or tissue repairing. Also, we could think about a global response of a localized sensing: if our nanomachines start Quorum Sensing when they sense a certain chemical, the whole swarm of nanomachines will activate at the same time to send an external signal or to actuate properly.

We conclude that Quorum Sensing is a valid technique that enables the coordination or synchronization of a group of entities at the nanoscale by means of molecular communication, and we envision that the application of this feature in nanomachines will be feasible in the near future, allowing them to synchronize in a novel and distributed manner.

Nonetheless, many biological aspects regarding Quorum Sensing are still relatively unknown and have to be studied in detail to fully understand this phenomenon. A detailed study of those aspects will enable the improvement of the existing models, and the creation of a 3D simulator will help us to obtain more reliable results.

## References

[1] I. Akyildiz, F. Brunetti, C. Blazquez, Nanonetworks: a new communication paradigm, Computer Networks 52 (12) (2008) 2260–2279.
[2] B. Bassler, Small talk: cell-to-cell communication in bacteria, Cell 109 (2002) 421–424.
[3] B. Bassler, How bacteria talk to each other: regulation of gene expression by quorum sensing, Current Opinion in Microbiology 2 (6) (1999) 582–587.
[4] J.D. Dockery, J.P. Keener, A mathematical model for quorum sensing in Pseudomonas aeruginosa, Bulletin of Mathematical Biology 63 (1) (2001) 95–116.
[5] C. Fuqua, S. Winans, P. Greenberg, Quorum sensing in bacteria: the LuxR-LuxI Family of cell density-responsive transcriptional regulatorst, Journal of Bacteriology 176 (2) (1994) 269–275.
[6] A.B. Goryachev, D.J. Toh, K.B. Wee, T. Lee, H.B. Zhang, L.H. Zhang, Transition to quorum sensing in an agrobacterium population: a stochastic model, PLoS Computational Biology 1 (4) (2005) 265–275.
[7] M. Gregori, I. Akyildiz, A new nanonetwork architecture using flagellated bacteria and catalytic nanomotors, Journal of Selected Topics in Communications (JSAC) 28 (4) (2010) 612–619.
[8] J. Henke, B. Bassler, Bacterial social engagements, Trends in Cell Biology 14 (11) (2004) 648–656.
[9] N. Krasnogor, M. Gheorghe, G. Terrazas, S. Diggle, P. Williams, M. Camara, An appealing computational mechanism drawn from bacterial quorum sensing, Bulletin of the EATCS 85 (2005) 135–148.
[10] B. Lazazzera, The intracellular function of extracellular signaling peptides, Peptides 22 (10) (2001) 1519–1527.
[11] Q. Li, D. Rus, Global clock synchronization in sensor networks, IEEE Transactions on Computers 55 (2) (2006) 214–226.
[12] M. Meisel, V. Pappas, L. Zhang, A taxonomy of biologically inspired research in computer networking, Computer Networks 54 (6) (2010) 901–916.
[13] K.C. Mok, N.S. Wingreen, B. Bassler, Vibrio harveyi quorum sensing: a coincidence detector for two autoinducers controls gene expression, The EMBO Journal 22 (4) (2003) 870–881.
[14] J. Müller, C. Kuttler, B.A. Hense, M. Rothballer, A. Hartmann, Cell–cell communication by quorum sensing and dimension-reduction, Journal of Mathematical Biology 53 (2006) 672–702.
[15] L. Parcerisa, I. Akyildiz, Molecular communication options for long range nanonetworks, Computer Networks 53 (16) (2009) 2753–2766.
[16] J. Philibert, One and a half century of diffusion: Fick, Einstein, before and beyond, Diffusion Fundamentals 4 (6) (2006) 1–19.
[17] M. Pierobon, I. Akyildiz, A physical end-to-end model for molecular communication in nanonetworks, IEEE Journal on Selected Areas in Communications (JSAC) 28 (4) (2010) 602–611.
[18] E. Purcell, Life at low reynolds number, American Journal of Physics 45 (1977) 3–11.
[19] R. Smith, B. Iglewski, P. aeruginosa quorum-sensing systems and virulence, Current Opinion in Microbiology 6 (1) (2003) 56–60.
[20] T. Suda, M. Moore, T. Nakano, R. Egashira, A. Enomoto, Exploratory research on molecular communication between nanomachines, in: Genetic and Evolutionary Computation Conference, GECCO, Late Breaking Papers, June, 2005.
[21] W.J. Tang, Q.H. Wu, J.R. Saunders, Individual-based modeling of bacterial foraging with quorum sensing in a time-varying environment, Lecture Notes in Computer Science 4447 (2007) 280–290.
[22] H. Umeo, K. Michisaka, N. Kamikawa, A Synchronization Problem on 1-Bit Communication Cellular Automata, vol. 2657, Springer, Berlin, Heidelberg, 2003, p. 650.
[23] A. Waksman, An optimum solution to the firing squad synchronization problem, Information and Control 9 (1) (1966) 66–78.
[24] K. Xavier, B. Bassler, LuxS quorum sensing: more than just a numbers game, Current Opinion in Microbiology 6 (2) (2003) 191–197.

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