Some Notes on the Interplay Between P Systems and Chemotaxis in Bacteria

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Summary. We describe some chemotactic behaviors of bacteria, that is, their movement response to changes in the environment, and the underlying molecular mechanisms. We outline how such processes could be linked to membrane computing, by taking inspiration from them for new type of rules or new features to be introduced in P systems, as well as by considering how the application of recent P system-based models can produce relevant results for the description and the analysis of chemotaxis processes.

1 Introduction

As living systems, bacteria perform deeply interconnected fluxes of matter, energy and information by means of sensing devices which can sense environmental factors such as nutrient concentration, light intensity, oxygen concentration, and so on [14, 8, 22, 21, 9]. These sensing devices elaborate signals that, for instance, in motile bacteria, are involved in changing the movement of the cell.

Chemotaxis, the movement of a bacterium (or other types of cells) toward a needed chemical (called attractant) or away from a dangerous chemical (called repellent) is one example of cell behavior involving fluxes of matter, energy and information, a behavior which is essential for bacterial survival. Chemotaxis allows the bacterium to move toward the needed substance (precisely, toward the increase in the gradient concentration of that substance); for example, oxygen respiring bacteria, which use molecular oxygen in respiration, move toward (optimal) oxygen concentrations. Chemotaxis also allows the bacterium to try and escape from a substance that is toxic for it; for example, bacteria which do not use molecular oxygen in respiration move away from molecular oxygen.

Chemotaxis machinery comprises two basic chemical parts (for more biochemical details we refer to [22, 21, 9]): (*i*) the *sensing device*, composed of a sensor and response regulator, and (*ii*) the *flagellum*, which is a nanostructure (in general, 10-20 nm in diameter and 500-2000 nm in length) acting as a molecular propeller for the cell body.

Chemotaxis is a "discrete" biological reality with respect to (at least) the chemical components sustaining chemotaxis and the molecular reactions in which these chemical components are involved.

Furthermore, many events involved in chemotaxis occur at the plasma membrane. Thus, such discrete molecular processes occurring (mainly) at the plasma membrane could be appropriately described by discrete mathematics, related to membranes, hence with the framework of P systems. This is one reason we try to focus some attention on the interplay between P systems and chemotaxis. This interplay would be (at least) in the following directions:

- chemotaxis as a natural source of inspiration for new types of evolutionary rules or, possibly, new features in P systems (e.g., the ability to sense abiotic signals from the environment and to "behave toward" these signals);
- P system-based mathematical models for a particular type of chemotaxis, in a given bacterium, to model the already known biological reality;
- the use of properly extended P system-based mathematical models to predict unknown biological realities related to chemotaxis.

2 Chemotaxis in Bacteria

One type of chemotaxis is *aerotaxis*, the active movement of bacteria along oxygen concentration gradients. For the bacterium *Escherichia coli* the fundamental basis of this behavior is the ability to regulate the frequency with which their flagella switch between clockwise (CW) and counterclockwise (CCW) rotations. CCW rotation results in "smooth swimming" of the bacterium in an approximately linear path, whereas the switch to CW rotation causes the bacterium to tumble, randomly reorienting it for the next smooth swimming run [19]. During a positive taxis, the flagella rotate CCW and the bacterium smoothly swims up a concentration gradient. When bacteria do not like the microenvironment where they are, the flagella starts to rotate CW and *one* tumble occurs, followed by another period of smooth swimming produced by CCW rotation. This behavior is essential for cell's life because oxygen is needed for respiration in aerobic bacteria, but it is a toxic compound for anaerobic bacteria. Moreover, in natural environments this behavior enables bacteria to actively and permanently respond to oxygen fluctuations.

The overall process of aerotaxis involves the following four integrates stages:

1. *Signal recognition and transduction* is performed by receptors and ligand binding proteins. Receptor proteins are usually transmembrane proteins, having the following domains: (*i*) a sensing domain at the exterior side of the plasma

membrane, (*ii*) a hydrophobic domain (so called TM helices) located within the plasma membrane, and (*iii*) an intracellular domain, containing the signalling region. The sensing domain interacts with the environmental signal (oxygen concentration, for example) and, through a series of chemo-physical changes, it induces changes in the signalling region (these changes will further enter the second stage of excitation). Interestingly, in *E.coli* as in other cells where the receptors have an extra-membrane domain, the localization of the receptors is around the poles of the cells, and not uniformly distributed over the whole cells surface. This clustering of receptors seems to be important in the possibility to achieve a given value of transduction, the so called *amplification* (more details in [21]).

2. *Excitation.* The main protein of this stage is CheA kinase. The chemical coupling between signalling region and excitation occurs via a protein called CheW. In *E.coli*, CheW is required for the activation of CheA, but not for its inhibition. The activation of CheA is achieved by phosphorylation, the chemical additions of a phosphate group to the protein (the phosphorylated CheA is indicated as CheA-P). This activated form, CheA-P, serves as substrate, reservoir of phosphate, for another essential protein, CheY. When CheY brings the phosphate from CheA-P, it becomes phosphorylated as well. In the phosphorylated form, as CheY-P, this protein binds to an assembly of proteins called the "switch", at the base of the flagellar motor, thus controlling the direction of the flagellar rotation: when CheY-P is bound to the flagellum, the flagellum rotates CCW in *Bacillus subtilis* and CW in *E.coli*. When this protein is not phosphorylated, it does not bind to the flagellum and the flagellum rotates CW in *B.subtilis* and CCW in *E.coli*.
3. *Adaptation* is very important for bacterial taxis because it requires the ability to recognize when the bacterium is moving in the wrong direction, i.e., away from the higher attractant concentration [21]. To do that, a "memory" is required that is able to indicate whether higher or lower concentrations are being reached [16]. Adaptation is achieved by the chemical addition of a methyl group to one ore more type of proteins, which directly or indirectly affects the function of CheA and, afterwards, the status of CheY (for more details see [21]). The detailed study of what was called, around 30 years ago, a "memory" [16], could add not only essential information and knowledge about biological processes on their material and energetic sides, but also on their informational aspects.
4. *Signal removal* means the biochemical removing of phosphate from CheY-P; the resulting dephosphorylated form (CheY) binds no more to the flagellum. Signal removal is achieved by two (known so far) mechanisms:
   a) CheY-P actively catalyzes autodephosphorylation. As a consequence, this protein has a half time shorter than 1 minute. However, this short half time for a protein is still too long as compared with the needs for a quick response, on a time scale of seconds, to ever changing environments [21]. Thus a second mechanism for signal removal is necessary.

b) The second mechanism involves in *E.coli* a protein, CheZ, which destabilizes CheY-P because it has phosphatase activity, thus removing the phosphate group from CheY-P.

In short, membrane-spanning receptors are coupled to an intracellular sensor kinase (CheA), which autophosphorylate, and the phosphoryl group is subsequently transferred from CheA to CheY. The phosphorylated Che-Y (CheY-P) diffuses through the cytoplasm and binds to an assembly of proteins called the "switch" at the base of the flagellar motor [19].

2.1 Examples of chemotaxis

Positive aerotaxis in *E.coli*. Aerotaxis is the response in changes to respiratory electron flow that results from an increase or decrease in oxygen concentration. In *E.coli* there are two types of receptors involved in aerotaxis:

- Aer, the sensor/signal transducer named for aerotaxis and energy response, senses the electron transport system, more precisely the ratio between the reduced forms and oxidized forms of electron transporters . Aer sensors contains a cofactor (flavin adenine dinucleotide) which seems to be able to accept or donate electrons for the electron transport system [20].
- Tsr, which has no cofactor and is not a likely candidate for sensing redox potential or oxygen per se. There is evidence [22, 21] that Tsr senses changes in proton motive force (generated by the respiratory electron transport). Tsr is a multi-functional (and multidomain) protein which is involved in response to other stimuli such as: serine (the first discovered function for Trs was that of serine receptor), external pH (by its periplasmic domain), cytoplasmic pH (by its cytoplasmic domain), temperature, hydrophobic aminoacids, and indole ([22] and references herein).

The occurrence of two types of sensors active in aerotaxis in the same bacterium, as well as the multi-functionality of one of them, is an example of parallelism in Microbiology that could receive some attention for P systems which copiously use the concept (and power of) parallelism [18]. Furthermore, chemotaxis already received some attention in systems biology area [9].

Positive chemotaxis for aspartate in *E.coli*. When no aspartate is present in the extracellular medium, the flagellum of *E.coli* rotates CW which results in a high tumble frequency and the consecutive random walk to different directions. When some aspartate molecules are detected within a given direction, then the flagellum changes to CCW rotation which results in mono directional swimming toward the source of the aspartate [15]. The mechanism is similar to that presented above for aerotaxis in the bacterium *E.coli*, the receptor protein being noted Tar.

Magneto-aerotaxis mechanisms. *Axial magneto-aerotaxis*: some strains (e.g., *Magnetobacterium magnetotacticum*) in a capillary tube (CT) placed in a static magnetic field (few gauss) oriented along the CT, migrate toward both ends of the

CT, where the oxygen concentration is higher, thus forming two visible bands at each end of the CT. The two bands remain intact when the magnetic field rotates 180° and, within each band, the cells themselves also rotate 180°. The distinction between north seeking and south seeking does not apply to magnetotactic bacteria with axial magneto-aerotaxis (see [10] for more details).

Polar magneto-aerotaxis: other strains (e.g., *Marine coccus* strain MC-1) migrate toward only one end of the CT following the direction where the magnetic field and the oxygen concentration gradient are oriented opposite to each other, forming one band. The band is dispersed by rotating the magnetic field by 180°, because the cells not only rotate themselves 180°, but afterwards they dissipate something (for more details see [10]). The difference between north seeking and south seeking does apply to magnetotactic bacteria with polar magneto-aerotaxis.

See also [13] for further details on magneto-aerotaxis mechanisms.

3 An Interplay Between P Systems and Chemotaxis

Chemotaxis is a biological process whose chemical components are discrete nanostructures, and the molecular reactions in which these chemical components are involved are also of a discrete type. Chemotaxis investigation is under tremendous development, the plethora of experimental data needing mathematical modeling as well. Moreover, biochemical and biophysical progresses in the deeper understanding of how protein modifications (e.g., phosphorylation and methylation) and protein-protein interactions work together in chemotaxis could offer detailed information to obtain discrete mathematical models of these biochemical, biophysical and biological realities. Here we will focus mainly on the above presented data, stressing on their possible relevance to P systems.

1. Tar receptor, in the absence of dissolved aspartate is not methylated; in this molecular form lacking the methyl (CH3) group, Tar receptor is a detector of warmth and *E.coli* swims toward a distant source of (moderate) heat. In the presence of the dissolved aspartate, Tar receptor becomes highly methylated; in this molecular form Tar receptor is also a detector of cold and the bacterium swims away from heat. The capability of Tar protein to be a warmth detector in the non methylated form and a cold detector in the methylated form is an example of how an addition of a chemical group changes the properties of that molecule. This reality is very common in (micro)biology and it was already formalized in signal-based P systems, where the symbol objects cannot be moved, and the evolution rules can be activated/inactivated using a finite number of signals (signal-promoters) moved or not across the membranes [7]. This type of formalism could be further developed to describe other biological processes where covalent protein modification (by addition/removal of phosphate, methyl, etc.) plays an important role in vivo: intermediary metabolism, enzymatic cascades, chemotaxis, the concentration and activity of transcription factors regulated by either external-sensing, internal sensing and hybrid

sensing devices [17].
Furthermore, experimental search and mathematical modelling on Tar receptor would be fruitful for a healthy interplay between (Micro)biology and P systems.

2. Bacterial chemotaxis belongs to a larger family of regulatory systems that share the same fundamental strategy of information transmission, based on signal recognition and transduction [19]. This larger family comprises specific systems that govern a wide range of processes, some of them already discussed in the framework of P systems: regulation of enzyme synthesis and activity [3], quorum sensing [3, 11] and long term adaptation to environmental factors (temperature, pH, osmotic pressure, etc.) [1, 5, 4, 6]. Thus, it is expected that chemotaxis should be a natural source for new type of evolutionary rules which could be used to develop P system-based mathematical models for a particular type of chemotaxis, in order to fit the already known biological reality or to predict unknown biological realities.
3. The interaction between different types of taxis is also an emerging topic for microbiology. For example, in *E.coli* the chemotaxis signal transducing pathways involves the following sensors: Tar (for aspartate), Trg (for ribose), Tap (for dipeptides) and Trs (for serine). All of these should interact in vivo, under real conditions, to generate bacterial taxis behaviors. The situation is further complicated because in the cell there are also other types of receptors mediating other type of taxis. It seems, however, that P systems could be of help in understanding this reality by defining, e.g., separate models for the different types of taxis, and then joining them together for the investigation of the role played by each one of them in a parallel scenario.
4. In the absence of oxygen, in *E.coli* alternative electron acceptors, such as fumarate or nitrate, support electron flow, and this is the basis for electron acceptor taxis. In the presence of oxygen, the thermodynamically preferred electron acceptor, the bacteria have a positive aerotaxis whereas alternative electron acceptors, nitrate or fumarate - if present in the medium - do not elicit any behavioral response (any taxis). However, if the oxygen concentration become the limiting growing factor, then bacteria start positive electron acceptor taxis toward the present alternative electron acceptor (nitrate or fumarate). A model comprising the different responses to environmental and/or internal biochemical conditions would indeed help in clarifying the various mechanisms adopted by bacteria to react in the best possible way for their survival.
Interestingly, *E.coli* for example, when are in good energetic shape (that is, fully energized cells), preferentially navigate by chemotaxis to aminoacids and other constituents for cell building. The energy taxis (aero, or carbon, etc.) has priority in bacterial behavior only/mainly in the case of cells in which the energy levels are threatened [22]. The Microbiology is only at the beginning with topics like that, so mathematical models could contribute to understand the mechanism of this “decision”, and its significance for living cells as information-processing devices.

5. As for receptor clustering, it started to be shown that the protein acting as receptors in bacterial chemotaxis are not distributed uniformly at the surface of the *E.coli* cell, the main localization being at one pole of the cell [12]. It should be reminded here that *E.coli* is an almost cylindrical cell; nothing is known so far about the specialized - if any - distribution of protein receptors at the surface of a spherical cell. This polarized distribution of receptors in space is an on growing topic in Microbiology and it could be interesting for P systems at least as a new type of communication rules, in which the position, the density of the interacting symbols is essential for the rule to occur. This could be a challenge for P systems to develop their application in those domains where spatial distribution of objects is very important, for instance, collective sports, military strategy, games (chess, GO, etc.).
6. Chemotaxis is a very robust process. Following [9], the CheA-CheY phosphorrely mechanism, used for a wide range of different signal transduction systems, and its underlying kinetically controlled switching mechanism, appear to provide a robust strategy for linking a sensory input to an output response (for more details see [9, 2, 23]). Biological properties such as adaptation, memory, robustness, are all relevant aspects to be achieved as emergent behaviors in mathematical models of the underlying biological system.

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