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A Mathematical Model of Complexity and Its Application to Chemotaxis

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Research Article

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Abstract

Important steps in our understanding of the bio–molecular mechanism of the bacterial chemotaxis allow for building an abstract informational–cybernetic model. The aim of this paper is to show that a mathematical model of complexity based on local (but not overall) shared information (soft assembly) allows for setting the appropriate constraints on both the connections among the bacterium's subystems as well as between the bacterium and the external environment (the case of *Escherichia coli* is considered here). The conclusion is that a necessary trade–off between intrinsic order and variability allows a good modelisation of the bacterium's behaviour.

Keywords: Soft assembly; information encapsulation; modularity; mutual information; adaptiveness
2010 Mathematics Subject Classification: 53C25; 83C05; 57N16

1 Introduction

The aim of this paper is to show that an appropriate formalization of complexity allows for a new understanding of bacterial chemotaxis. In the following I shall point out some general features of complexity (Sec. 2) and then introduce a general mathematical formulation (Sec. 3). In Sec. 4 I shall summarize the main bio–molecular aspects of chemotaxis. The information–cybernetic model (a particular connectionist network based on partly modular subsystems) of the *E. coli*'s behavior is introduced in Sec. 5. In Sec. 6 we shall deal with the way in which the network works. In Sec. 7 the previous treatment with weights is translated in a computation of probabilities. This shall allow us (in Sec. 8) the derivation of the involved entropies and mutual information and therefore of the computation of the complexity of the system. Discussion (Sec. 9) and conclusions (Sec. 10) shall follow.

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2 Complexity

Complex systems are a specific class of the wide class of self–organized systems (Auletta, 2010, 2011a, Sec. 6.3), and are characterized by four fundamental features (Ellis, 2005):

(1) Complex systems present hierarchical structures having (a) different levels of order and complexity, and (b) a relational web at each level of the structural hierarchy.

(2) They are top–down systems (upper–level variables and constraints influence or canalize the lower–level, efficient dynamics).

(3) They present recurrent basic structures at any level (called motifs in cellular networks).

(4) They show a certain plasticity and adaptive potentiality.

About Point (1), I also recall that the units themselves of a complex system may be structured or exist as complex systems as well. Here, a specification of a higher–level state determines a family of lower–level states, each of them able to give rise to the higher–level state. A higher–level state can influence a lower–level state (see Point (2)) in order to induce this to map to another lower–level state.

Complex systems show a characteristic soft assembly of the subsystems or parts: Subsystems are modularized but not totally shielded against external influences. They indeed show significantly more interconnections between their elements than with elements of other modules. Moreover, hierarchical structures are such that each level is partially shielded from the others. Since modularity applies also to (relative) independent elements at the same level of a hierarchy, it is better here to use the term *information encapsulation*, which is the hiding of certain lower level structures having informational value or content relative to a higher level of a hierarchy (Booch et al., 2007). A very common example of this is the way in which DNA is encapsulated. Modules and encapsulated unities have the specific advantage of representing discrete units. A clue to the reason why modules and information encapsulation are used by complex systems and evolve in biology can be found by looking at the way they are used in engineering (Alon, 2003). Modules in engineering convey an advantage in situations where the design specifications change in time: New devices or software can easily be constructed from existing, well–tested modules. A nonmodular device, in which every component is optimally linked to every other component, is effectively frozen and cannot evolve or adapt to meet new optimization conditions. Similarly, modular biological networks may have an advantage over nonmodular networks in real–life ecologies, which change over time: Modular networks can be readily reconfigured to adapt to new conditions. Furthermore, they are robust against impairment or the failing of components. The way in which they do this is by building degenerate structures and functional equivalence classes among different biochemical pathways.

So, organisms show a complementarity between modularity (discontinuity) and connectedness (continuity) (Ulanowicz, 2009), which allows for the integration of different levels of organization, (i.e. hierarchical organization). In this way, modularity and information encapsulation contribute to plasticity, typically in organisms (West-Eberhard, 2003 (pp. 12–13, 59–61, and 83–84)). I would like to summarize these results by pointing out the general conditions that determine the way in which networks show hubs and modularize. According to web theory (Barabási and Albert, 1999), non–random networks show two basic principles: Continuous addition of new nodes and preferred linkages (in the mean new nodes attach to nodes that are already best linked). This is the consequence of two more general principles (Bianconi and Barabási 2001): The continuous generation of variety (and therefore the intrinsic randomness of single events) and the establishment of preferred channels (channelization) due to the external conditions that generate regular patterns. As we shall see, this two aspects will turn out to be crucial also for our specific problem.

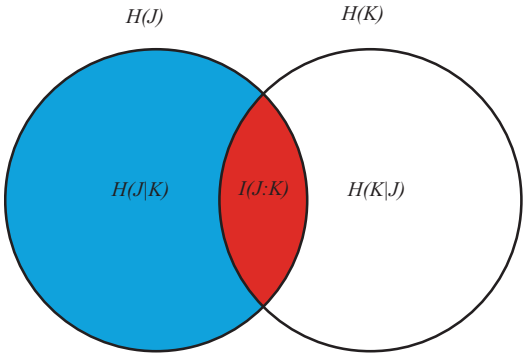

Figure 1: Graphic representation of mutual information: It is easy to verify that $I(J:K) = H(J) - H(J|K)$, where $H(J)$ is the whole set on the left (blue and red regions), $H(J|K)$ is the blue region, $I(J:K)$ the red region.

3 Mathematical Measure of Complexity

I recall that that, in the discrete case (the sole that I shall consider here), the entropy of the set of possible inputs i can be mathematically formulated as the negative of the mean value of the binary log function of the probabilities $p(i)$ with $i \in I$:

$$H(I) = -\left\langle \lg p(i) \right\rangle_I = -\sum_{i \in I} p(i) \lg p(i) \ . \tag{1}$$

Let us now consider the so-called Kullback–Leibler divergence D_{KL} (also known as relative entropy) that measures the distance of the probability distribution before the two vertical lines from another probability distribution $p(k)$. In the discrete case then, we have

$$\begin{aligned} D_{KL}\left(p'(k)||p(k)\right) &= \sum_k p'(k)\left(\lg p'(k) - \lg p(k)\right) \\ &= \sum_k p'(k) \lg \frac{p'(k)}{p(k)} \ . \end{aligned} \tag{2}$$

Let us now consider the total entropy $H(J,K)$ of a system composed of two subsystems with input sets J and K, having entropies $H(J)$ and $H(K)$, respectively:

$$H(J) = -\sum_j p(j) \lg p(j) \ , \quad H(K) = -\sum_k p(k) \lg p(k) \ , \quad H(J,K) = -\sum_{j,k} p(j,k) \lg p(j,k) \ , \tag{3}$$

Then, we can write down the Kullback–Leibler divergence between the joint probability and the product distribution of two involved parameters:

$$D_{KL}(p(j,k)||p(j)p(k)) = \sum_{j,k} p(j,k) \lg \frac{p(j,k)}{p(j)p(k)} = I(J:K) \ . \tag{4}$$

This quantity, which can be expressed as

$$\begin{aligned} I(J:K) &= H(J) + H(K) - H(J,K) \\ &= H(J) - H(J|K) \\ &= H(K) - H(K|J) \ , \end{aligned} \tag{5}$$

turns out to be the information that the two subsystems share (their mutual information) [Fig. 1] and is the principle of order in the system. This quantity is very interesting when dealing with organisms

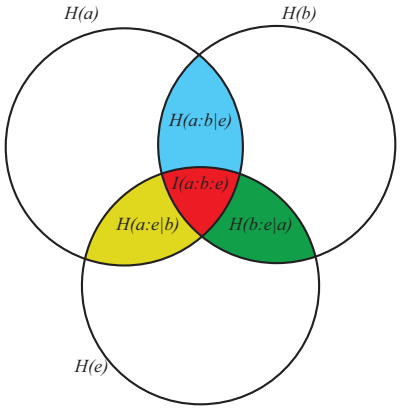

Figure 2: The *stored information* $I_s(a, b; e)$ of the system $a + b$ relative to e: It is represented by the yellow, red (taken two times), and green colored regions. *Complexity* of the system $a + b + e$: It is the whole colored region minus the red region [Eq. (16)].

(Auletta, 2011b, Sec. 6.4). I recall that the quantities $H(J|K)$ and $H(K|J)$ are conditional entropies. At a general level conditional entropy is given by:

$$H(J|K) = -\sum_j \sum_k p(j,k) \lg p(j|k) \ , \tag{6}$$

and means the incertitude that the set J of the output signals will occur if the set of the input signals K also occur, or, in other words, how much the disorder of the system described by the parameter set J depends on the disorder of the system described by the parameter set K.

The main point of this section is whether there can be a quantitative measure for univocally distinguishing between more and less complex systems. In complexity an important role can by played by mutual information, especially when organisms are involved. However, as mentioned, mutual information alone only guarantees order, not complexity. When we get more complex systems out of the combination of less complex ones, the growing complexity of the system implies a further increase of the entropy but an even larger increase of the *maximal* entropy theoretically attainable by the system (since the number of different possible dispositions in which the compounding elements can be, grows much more than the elements' number). Indeed, when merging two systems the entropy of the resulting compound system cannot be smaller than the sum of the entropies of the two initially separated systems (Landsberg, 1984a; Landsberg, 1984b)

$$H(J,K) \leq H(J) + H(K) \ , \tag{7}$$

which does not necessarily imply that the entropy of the resulting system is the same as that of the two subsystems taken separatel. Therefore, the *gap* between the entropy in which the system is (which is not maximal, due to some interrelation between the subsystems) and its possible maximal entropy also grows. This allows for further order and complexity.

We must now find a measure of complexity that puts together two different aspects (Auletta, 2010):

(1) The differentiation of the system in relative independent parts (in some cases, information encapsulation between different levels and modularity at the same level) and

(2) A global order (coherence of the whole).

Let us consider the issue of stored information at an abstract level. Let us assume a system composed of two subsystems, say a and b (which could represent some string of information, that is, a sequence of 0 and 1s). For the sake of simplicity, both the systems a and b are assumed here to be in a state of maximal entropy $H(a)$ and $H(b)$, and $H(a, b)$ is the total entropy of a and b. Let us also consider an external environment with entropy $H(e)$, whose information our strings will store. Now, we can write

$$H(a|e) = H(a) - I(a:e) \quad \text{and} \quad H(b|e) = H(b) - I(b:e) \ . \tag{8}$$

Analogously, we can write a conditional entropy of both the systems a and b on e, that is,

$$\begin{aligned} H(a,b|e) &= H(a,b) - I(a,b:e) \\ &= H(a|e) + H(b|e) - H(a:b|e) \ , \end{aligned} \tag{9}$$

where an inspection of Fig. 2 can be very useful. The quantity $I(a,b:e)$ represents the information shared by a and b on the one hand and e on the other and is given by:

$$I(a,b:e) = I(a:e) + I(b:e) - I(a:e:b) \ , \tag{10}$$

where $I(a:e:b)$ (the red region in Fig. 2) is defined by

$$I(a:e:b) = I(a:e) - H(a:e|b) \ , \tag{11}$$

and represents the overall information shared by a, b, and e. Note that the quantity $I(a:e:b)$ is symmetric, as expected by a true mutual information. Indeed, we also have

$$I(a:e:b) = I(a:e) - H(a:e|b) \tag{12}$$

$$= I(b:e) - H(b:e|a) \ . \tag{13}$$

From a practical point of view, note that we have

$$\begin{aligned} H(a,b,e) &= H(a) + H(b) + H(e) - [I(a:b) + I(b:e) + I(e:a)] + I(a:b:e) \\ &= H(a|b) + H(b|e) + H(e|a) + I(a:b:e) \ , \end{aligned} \tag{14}$$

from which it easily follows that

$$I(a:b:e) = H(a,b,e) - [H(a|b) + H(b|e) + H(e|a)] \ . \tag{15}$$

Now, we can use the previous equations for defining the complexity of the system $a+b+e$ as (this can be considered to a certain extent to be a development of Kolmogorov's concept of complexity (Kolmogorov, 1963)) [Fig. 2]

$$\begin{aligned} C(a,b,e) &= [I(a:b) - I(a:b:e)] + [I(b:e) - I(a:b:e)] + [I(e:a) - I(a:b:e)] \\ &= I(a:b) + I(b:e) + I(e:a) - 3I(a:b:e) \\ &= H(a:e|b) + H(b:e|a) + H(a:b|e) \ . \end{aligned} \tag{16}$$

This measure of complexity is therefore the whole mutual information of the system $a+b+e$ minus their overall mutual information $I(a:b:e)$. It is interesting to note that the complexity of a system composed of two sole elements, say a and b, collapses into their mutual information. This shows that the concepts of complexity requires at least three elements Moreover, complexity is always relative to a certain environment or to a certain reference system. It is interesting to note that the difference between the maximal entropy attainable by a system and the entropy of its current state is due precisely to its structural order or, when there is codification, structural information. Indeed, by considering again Fig. 2, it becomes immediately evident that by increasing the colored region, the whole surface given by the combination of the three circles goes down. Finally, we can understand that by lowering more and more the overall mutual information present in the structural information (all the information shared locally and globally) we have a *natural transition to complex systems*.

The crucial point here is that mutual information, the quantity occurring several times in the second line of Eq. (16), *does not require* shared codified information but only that there is at least one local code on the one end and some combinatorics on the other. Indeed, as Eq. (5) already demonstrates, it is solely concerned with the interdependencies among systems and their components. This allows that, together with thermodynamic interdependencies, complex informational–entropic dependencies are established that can then result in new, unexpected informational features; indeed, patterns can still be combined to give rise to other patterns as well as complex systems can give rise

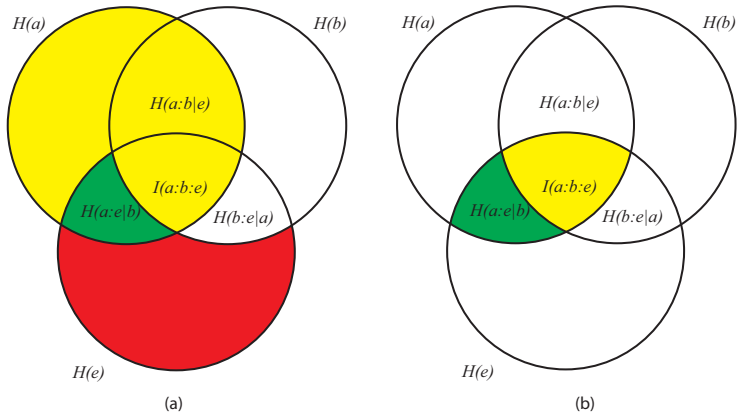

Figure 3: The powerfulness of the formalism shown in Eq. (16): Any of the mixed terms on the last line can be considered as a combination of order and disorder. If we take the term $H(a : e|b)$, in particular, (a) shows that it an be interpreted as $I(a : H(e|b))$ while (b) shows that it can be equivalently interpreted as $H(I(a : e)|b)$.

to other complex systems—this is evident when several organisms give rise to a whole ecosystem. As a matter of fact, only conditional entropies of a special kind are present in the last line of Eq. (16) that allow precisely for new forms of local information codification. Indeed, the case of organisms is such that there is always information nested somewhere. To understand this crucial point (that makes complexity far more interesting than molecular combinatorics), let us take a close look at the expressions of the form $H(a : e|b)$ occurring in the last line of Eq. (16). These quantities can be *equivalently* considered in two alternative ways:

- As the conditional entropy between the information shared by a and e, i.e. $I(a : e)$, on the one hand, and a third system b, on the other, that is, as $H(I(a : e)|b)$, or also
- As the information shared by a, on the one hand, and the conditional entropy $H(e|b)$ between e and b, on the other, that is, as $I(a : H(e|b))$.

It is easy to see that we have

$$H(I(a : e)|b) = I(a : e) - I(a : e : b) \ , \tag{17}$$

in accordance with Eq. (11). Instead, the expression

$$I(a : H(e|b)) = H(a) - H(a|H(e|b)) \tag{18}$$

is more puzzling and difficult to understand. A look at Fig. 3(a) shows, however, that this corresponds to take the red + green region first, i.e. $H(e|b)$, and then the conditional entropy $H(a|H(e|b))$ (the whole yellow region). Finally, we subtract this from $H(a)$, which gives precisely the searched green region. For expression (17), we first take the yellow + green region and then subtract the yellow region, as shown in Fig. 3(b). The relevance of this equivalence and of the relative expressions is that the latter show *both* conditional entropy and order as expressed by mutual information, and do so in accordance with an intuitive understanding of complexity as a mix of order and disorder.

There are therefore several advantages of the measure (16) of complexity:

(1) It displays both coherence (order: expressed by the dependencies of the subsystems a, b, and e) and autonomy of the parts (expressed by the lack of the mutual information $I(a : b : c)$). This means that the growth of complexity is not proportional to the growth of global order, as already anticipated.

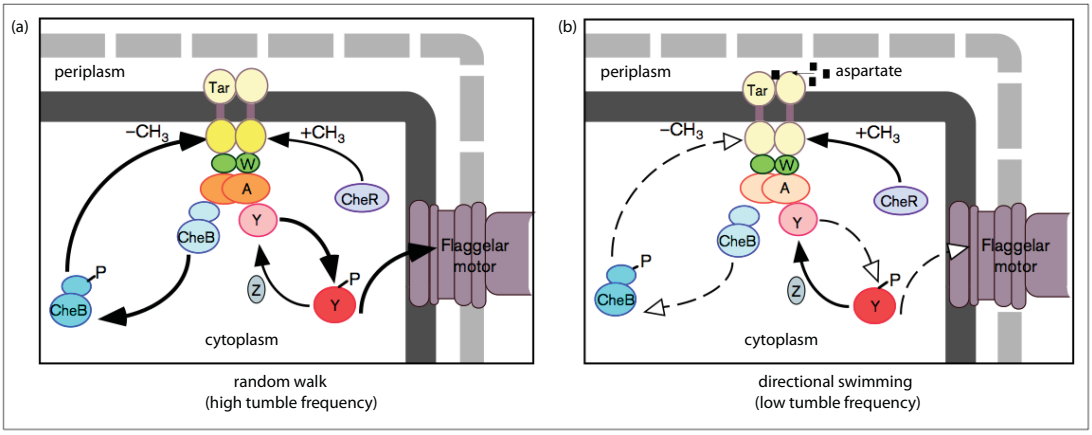

Figure 4: Activated forms of the proteins are shown in a darker colour and solid arrows are used for indicating activation. (a) The high level of phosphorylated CheY increases the frequency of switching to clockwise flagellar rotation and thus determines tumbling. (b) When a receptor binds ligand and/or is unmethylated, CheA is inactive. The levels of phosphorylated CheY are reduced, leading to more counterclockwise flagellar rotation and more running. With CheB inactive, the methyltransferase activity of CheR (purple) serves to decrease receptor sensitivity. Adapted from (Jurica and Stoddard, 1998).

(2) At a *global level*, it does not directly contain informational terms but only conditional–entropic ones. This means that complexity shows global patterns and functions that are independent of any explicit information coding, even if stemming from information codification.

(3) At a *local level* (the pairwise relations between the three subsystems) it does not require but allows for possible information exchange, sharing, and codification.

When the number of systems grows there are much more possibilities of partial interdependencies, which is the real quintessence of complexity. The quantities of the form $H(a:e|b)$ are very helpful for understanding such a process. I shall now show that complexity (and local shared information) sets specific constraints on the way in which an organism deals with the environment.

4 Chemotaxis

When a bacterium performs chemotaxis, chemical gradients are sensed through multiple transmembrane receptors, called methyl accepting chemotaxis proteins (MCPs), which vary in the type of molecules that they detect (Jurica and Stoddard, 1998; Bourret and Stock, 2002). These receptors may bind attractants or repellents directly or indirectly through interaction with proteins of the periplasmatic space between the exterior and the interior membranes (Rollins and Dahlquist, 1981) [Fig. 4]. The *E. coli* is attracted by various sugars and amino acids and repelled by fatty acids, alcohols, and other potentially noxious compounds. Attractants lower the activity of the receptors and so determine swimming, whilst repellents increase the activity of receptors determining tumbling (Kleene et al., 1979; Muskavitch et al., 1978). The signals from these receptors are transmitted across the plasma membrane into the cytosol, where Che proteins (CheA, CheB, CheR, CheW, CheY, and CheZ) are activated: they are able to alter the tumbling frequency according to the inputs [Fig. 4]. Signals are codified and passed from the transmitter module of one protein to the receiver module of a second

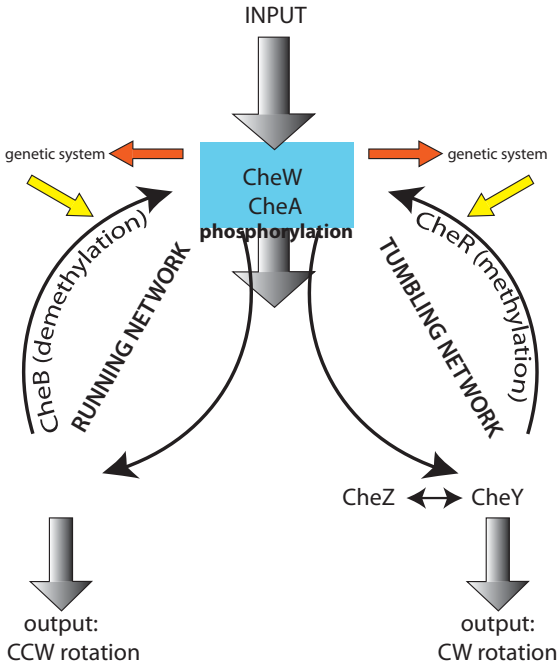

Figure 5: A schematic overview of the chemotaxis network system. Actually, it is a sort of module inside the organism relative to the genetic or metabolic modules. This shows that the organism is built as an organized and concerted cluster of subsystems (Auletta, 2010), in such a way that there are much more connections inside a single module than with other modules, although some connections always exist (in the figure schematic connections with the genetic system are shown).

protein via phosphotransfer. In the involved pathway, a family of related transmembrane receptors act as the input module by binding either small chemotactic molecules or their periplasmic binding proteins. Once these effectors are bound, the activity of a transmitter histidine kinase (CheA) that is associated with the cytosolic domain of the receptor(s) is rapidly modulated in cooperation with the scaffolding protein CheW. Increase (or decrease) in the activity of this kinase leads to transient increases (or decreases) in intracellular levels of phosphorylated CheY (the targeted *response regulator*) which directly affects flagellar rotation and the frequency of their reversal. The relative level of phosphorylated form of CheY (CheY-P) determines the bacterium's behavior: if high it will rotate CW and tumble. This means that the motors rotate CCW by default (inducing swimming), so that tumbling is induced as a sort of reaction to an external negative feedback. A very important element is reaction timing: Because Brownian motion of the fluid medium can randomly reorient the bacterium, this requires very short response latencies. It is here that genetic (instructional) factors play a role by enhancing and damping protein production. In order to account for the extraordinary stimulus sensitivity of the chemoreceptors, one must focus on CheZ, whose function is to accelerate the loss of phosphate from CheY.

Slower habituation (that is, the progressive adaptation to a constant stimulus) of the network response is induced by the reversible methylation and demethylation of a specific group of glutamate residues within predicted coiled–coil regions of the receptor cytosolic domains. These covalent modifications are catalyzed by an S–adenosylmethionine-dependent methyl–transferase (CheR) and a partner methyl–esterase (CheB) that act in order to respectively increase (methylase) or damp

(demethylase) the signal by adding or removing the methyl group CH_3, respectively (which also implies the rapid genetic expression or repression of CheR, CheB, and CheZ). When CheR is kept low, the bacterium swims; when CheB's activity is suppressed, the bacterium tumbles (Rao et al., 2004) [Fig. 5]. The steady–state level of the terminal protein–chain is determined by the balance between the production of CheY-P (catalyzed by CheA), and its destruction (catalyzed by CheZ). Now, in the presence of attractants the level of CheA-P, CheY-P and CheB-P remains low, allowing swimming. However, the absence of active Che-B will also raise the level of methylation with the consequence that the bacterium will tumble. On the contrary, in the presence of repellents, the level of CheY-P increases and the bacterium will tumble, but the level of both CheA-P and CheB-P will also rise, with the consequence that there will be less methylation and therefore swimming becomes possible.

Summarizing, the whole network combines two completely different molecular–chemical mechanisms: a phosphorylation mechanism (expressed by the path from CheA to CheY) and a methylation–demythilation balance induced by the opposite actions of CheR and CheB. The cybernetic–informational value of this molecular–chemical network is further displayed when considering two aspects:

- Attractant and repellent compounds are sensed by means of the relative specific chemoreceptors and not through their beneficial or harmful physiological effects, as it would be the case for a mechanical engine. It is exactly this that gives to this step the significance of an informational step and not of a metabolic one (a chemoattractant need not be a substance that the bacterium can metabolize in any way): When the transmitter binds to the input signal, autophosphorylation and docking (i.e. the binding of the signaling molecule with its partner) are not the sole possible reaction. Alternatively, the transmitter can "choose" undocking (Parkinson, 1993).
- Temporal comparison is effected between a stimulus experienced during the past second with that experienced during the previous 3 seconds, which implies that the cell recovers from a small step stimulus (a pulse in the concentration of attractants or repellents) within 4 seconds (Block et al., 1982; Segall et al., 1986). It is very important to understand that any signal is always mixed with noise and there is therefore always the possibility of an error. The length of time over which the signal is averaged is inversely proportional to the filter cut–off frequency (that separates signal from noise) and determines the adaptation time of a differentiating system to step inputs (Berg and Purcell, 1977; Strong et al, 1998; Andrews et al, 2006). This averaging time may also be thought of as a memory length because the cell must remember previous values of the input in order to compute the average. If the averaging or adaptation time is too short, then the noise is not filtered out; alternatively, if the time is too long, then the bacteria cannot detect real changes in the gradient. There is an optimal adaptation time that allows cells to chemotax the farthest and to reach this is the business of the adaptive mechanism.

The further aspects of the model to be developed below will show that the system works thanks to constraints that are of informational nature and not determined by the chemical interactions that are rather vehicles and channels for those constraints to become active.

5 A Model

I wish to introduce now a very simplified model of how the whole *E. coli*'s network (with its sensory, regulatory, genetic and motor sub-networks) may work. Many of the following assumptions should be considered as hyper–simplifications. Nevertheless, one of the advantages of the following model is that it may be modified in a relative simple way by introducing increasing levels of sophistication, although the basic form I present here is able to simulate some general behaviors of the *E. coli*. However, it is also important to consider that the mathematical formulation I shall provide is not a

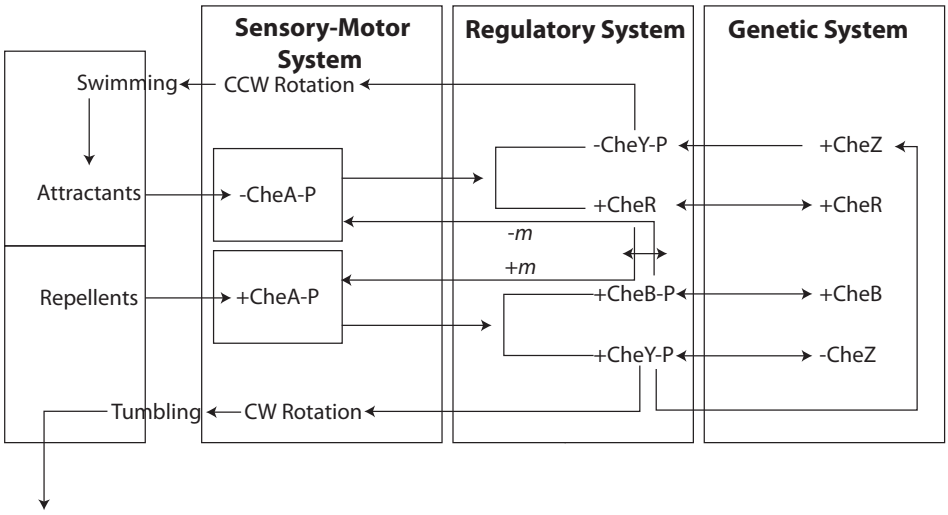

Figure 6: Scheme of the E. coli's basic network. We can see that low activity of CheA (in presence of attractants) will keep the level of CheY-P low but also favour a relative increase in activity of CheR that will help the CheA phosphorylation. On the other hand, when the activity of the CheA is increased (through repellents) it will also contribute to the phosphorylation of the CheB which results in a reduction of the CheA activity.

mirror image of how things work in reality. Further studies will probably correct or precise in one way or the other some of my basic assumptions.

The network I wish to introduce can be understood as a connectionist net. Therefore, I shall make use of weights in connecting the different unities. The first step for building this network can be of the kind whown in Fig. 6. However, the different weights will not be given by positive or negative number according to whether the connection is improving or damping, respectively. For practical purposes, I shall assume that there are deterministic connections that have weight 1.0, which turn out to be the maximal positive contribution that an unit can give to another unit, and smoothing–damping effects given by numbers < 1.0. This will simplify the task to translate weights into (conditional) probabilities, which are necessary if we wish to make use of the formalism of the mutual information. In particular, let us consider the reformulation of the network as in Fig. 7. I have assumed that:

- The sensory system can be in two alternative states that for practical purposes I have indicated as two different units: s1 meaning plus CheA-P (more activity of Che-A) whilst s2 means minus CheA-P. The interesting point with this model is that it allows different weights (and probabilities) of s1 and s2 in a continuous way, imitating the mixture between attractants and repellents that it is likely to be found in a real environment (with its gradient effects). For the sake of simplicity I have considered the initial weights to inputs i1 and i2 as 0.50 in both cases (while the weights connecting i1 with s1 and i2 with s2 are equal to 1.0 and therefore deterministic.
- I have further assumed four regulatory elements: r1 and r2 are directly competitive, since they represent high and low phosphorylation of CheY, respectively. The connections of s1 with r1 and of s2 with r2 are again equal to 1.0 and therefore deterministic. We know that there is a second couple of circuits dealing with methylation. In particular, the CheB (represented here by r4) decreases the level of methylation, while the CheR (represented by r3) has the opposite effect. Therefore, although deriving from an increasing in the activity of the CheA, the indirect effect of the CheB is to favour the CCW rotation of the flagella and therefore swimming, while

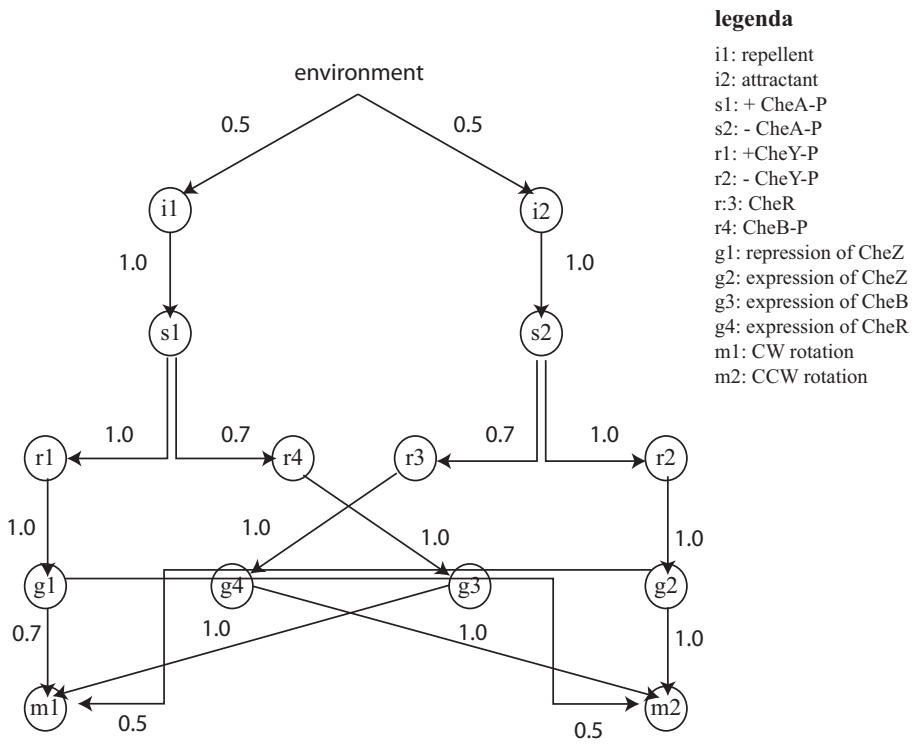

Figure 7: The proposed network with weights connecting the various units. The legenda provides their meaning.

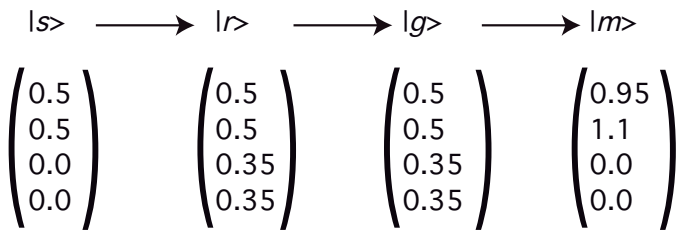

Figure 8: The vectors are expanded vertically. The first row of vector $|s\rangle$ represents s1 whilst the second row s2. Instead, s3 and s4 are empty. Similar conventions for the other vectors.

the activity of CheR, although proprtional to a decreased level of activity of the CheA, favours the CW rotation. I have introduced here relative damping weights: 0.7 for both the connection from s1 to r4 and from s2 to r3. These weights, as many other aspects of the proposed network may be changed, and these values are to be taken only as indicative and tentative. It is obviously well likely that there are some complicated cross–effects among all regulatory elements, but here I shall limit my study to the essential.

- I have further assumed that all connections between regulatory elements and genetic factors are linear, unidirectional, deterministic and isomorphic. It is quite likely that this is not the case. We can at most say that a high presence of CheR is correlated with the expression of the gene that codifies it but it is not clear (to me, at least) which are the sub-networks allowing the crucial passages of signals. The feedback effects here and in the following will manifest themselves when the new sensory input to the network is combined with the previous motor output, as we shall see below. The only remarkable aspect here is that r4 contributes to g3 (expression of CheB) and r3 to g4 (expression of CheR), allowing some cross-effects. Finally, note that g1 and g2 are directly in competition, since g1 means repression of CheZ whilst g2 means its expression.
- The relation between the genetic factors and the motor outputs is a little more complicated. Only g1 (with a partly damping effect), g2 (with a damping effect), and g3 contribute to m1 (standing for CW rotation of the flagella, i.e. tumbling), whilst only g1 (with damping effects), g2, and g4 contribute to m2 (standing for CCW rotation of the flagella, i.e. swimming).

We expect from the network that it will slightly prefer the CCW rotation (the default swimming) so that it will spontaneously bring back to this situation, but nevertheless be sensitive to changes in the environment.

6 The Networking

We may represent the whole network as a sequence of operations mathematically described by matrices that act on vectors. The matrices are three:

$$\hat{W}_{rs} = \begin{bmatrix} 1.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 1.0 & 0.0 & 0.0 \\ 0.0 & 0.7 & 0.0 & 0.0 \\ 0.7 & 0.0 & 0.0 & 0.0 \end{bmatrix}, \quad \hat{W}_{gr} = \begin{bmatrix} 1.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 1.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 1.0 \\ 0.0 & 0.0 & 1.0 & 0.0 \end{bmatrix}, \quad \hat{W}_{mg} = \begin{bmatrix} 0.7 & 0.5 & 1.0 & 0.0 \\ 0.5 & 1.0 & 0.0 & 1.0 \\ 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 \end{bmatrix}. \tag{19}$$

The matrix $\hat{W}_{rs}$ (the r's are rows whilst the the s's are columns) will act on the input vector $|s\rangle$ and produce the output regulative (the first hidden) vector $|r\rangle$, the matrix $\hat{W}_{gr}$ (the g's are rows whilst the

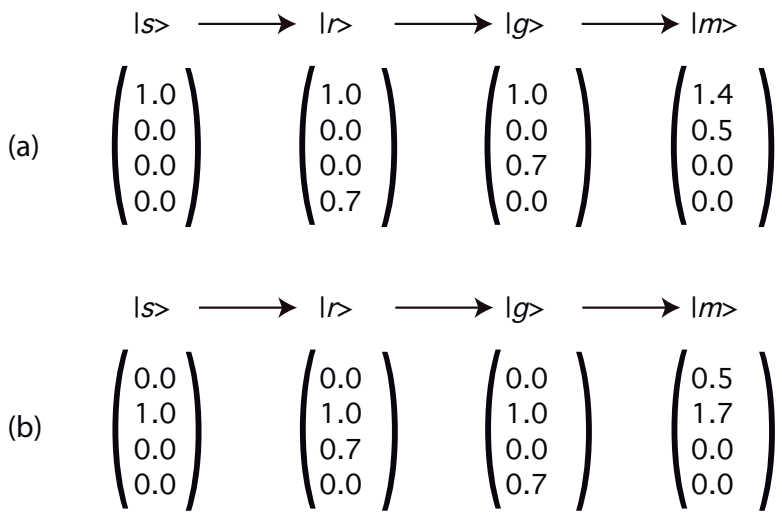

Figure 9: Two limit situations: (a) only repellents are present in the environment, whist (b) shows the presence of sole attractants.

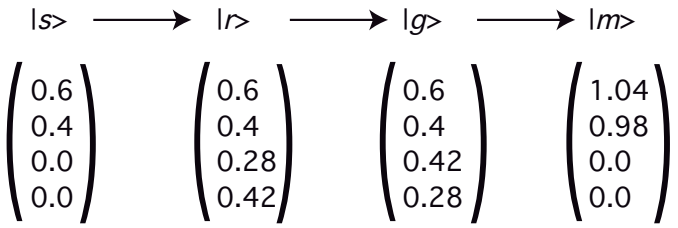

Figure 10: The mixture 0.60 repellents and 0.40 attractants represents the threshold effect.

r's are columns) will act on the latter vector and produce the genetic-activity (the second hidden) vector $|g\rangle$, whilst the matrix $\hat{W}_{mg}$ (the m's are rows whilst the g's are columns) will act on the latter vector and produce the output (motor) vector $|m\rangle$. Summarizing,

$$\hat{W}_{rs}|s\rangle = |r\rangle \ , \ \ \hat{W}_{gr}|r\rangle = |g\rangle \ , \ \ \hat{W}_{mg}|g\rangle = |m\rangle \ . \tag{20}$$

Let us consider now some concrete examples. Let us take as a start that s1=s2=0.5, when attractants and repellents are present in the same quantity in the environment. In this case we have the situation shown in Fig. 8. We may see that the output m2 is slightly enhanced relative to m1, as expected. We may think here of a switch mechanism that for certain thresholds activates either CCW or CW rotation.

Consider now a completely different situation, one in which we only have repellents in the environment. Our net gives the result shown in Fig. 9(a). The net excess of CW rotation (represented by m1) is what we expect. On the contrary, when only attractants are present, we have the situation shown in Fig. 9(b). It may be seen that in this case the prevalence of the CCW rotation is slightly bigger than the prevalence of he CW was in the case (a).

It is interesting to consider that about 60% (40%) of concentration of repellents (attractants) represents a sort of threshold effect: above (below) that concentration repellents predominate, above

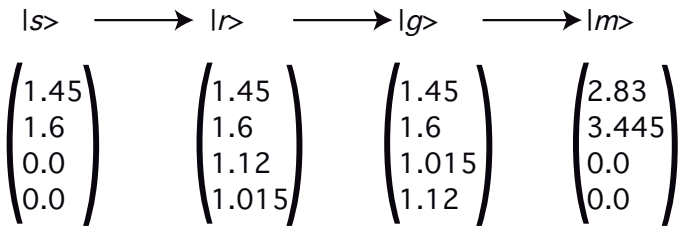

Figure 11: This figure represents the case in which the bacterium undergoes again the inputs shown in Fig. 8.

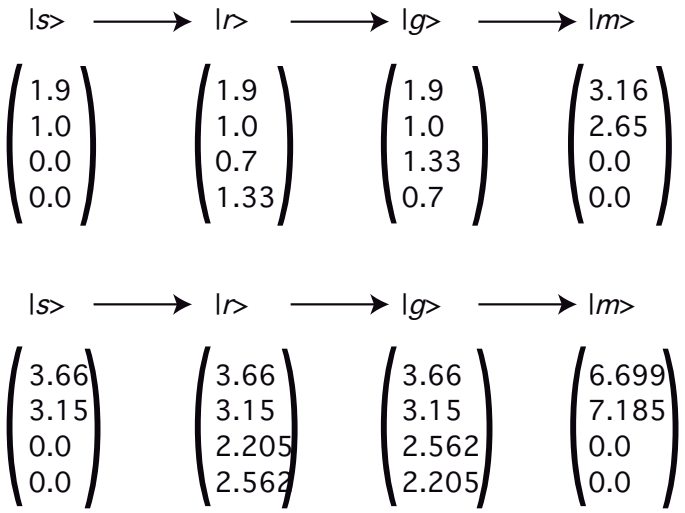

Figure 12: Having started with the inputs displayed in Fig. 9(a), we let the network run two times in conditions of parity. After the second cycle it comes back to its default state, CCW rotation.

(below) it is repellents (attractants) to predominate, as shown in Fig. 10. This threshold should be appropriately corrected according to empirical data.

As I have mentioned, feedback effect have been considered only after a cycle is completed. They involve the different levels of methylation as well as the action of the CheZ on the phosphorylation of the CheY. They obviously depend on the homeostatic necessity of the organism to come back to its default state given by the CCW rotation of the flagella. Although it is likely that some feedback effects already act during a single cycle, the reason for this choice is that this makes the computation far easier. It is also clear that the bacterium performs comparisons between different inputs by preserving for about 4 seconds the older input. In this way, such a model should mirror to a certain extent a real behavior. Again, empirical data can help to adjust some parameters. Let us first consider the case in which we rerun the same input as in Fig. 8 (parity of attractants and repellents concentrations). In this case, the prevalence of CCW rotation (represented by the output m2) is very clear and fulfills our expectations, as shown in Fig. 11. However, what happens when we have a previous computation with a pure–repellent input—the situation shown in Fig. 9(a)—and we make a second computation with a parity of attractants and repellents concentrations? This situation is shown in the upper part of Fig. 12. We have still a significant prevalence of CW rotation (m1). However, if we rerun a third time

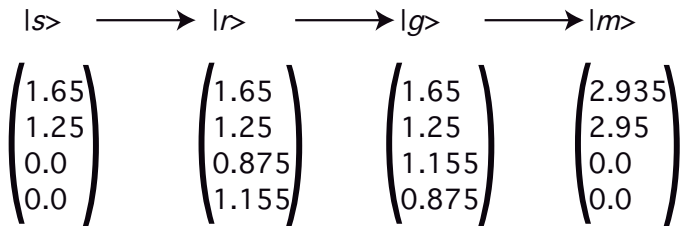

Figure 13: Starting again with a situation like that displayed in Fig. 9(a), we assume now that the environment shows a current concentration of 75% 75% attractants and 25% repellents. In this case, the bacterium comes back to its default (CCW) state after a single cycle.

the network always in parity conditions between attractants and repellent concentrations, we have a clear prevalence of CCW rotation (m2), as shown in the lower part of Fig. 12. In this way, we have simulated the effects of information erasure in absence of negative stimuli inducing further tumbling. The fact that this effect is delayed of a cycle is probably not so bad, considered that the chosen environment does not show a clear prevalence of attractants. In any case, with a similar previous cycle (started with a pure–repellent input) but with a current concentration of 75% attractants and 25% repellents, the result in a single cycle already shows a slightly prevalence of CCW rotation (as displayed in Fig. 13), that is obviously increased with an increased percentage of attractants. It is quite obvious that when attractants have already prevailed (as in Fig. 9(b)), their prevalence is maintained in parity conditions.

7 Probabilities

Let us now try to translate the previous figures in a probability calculus. I stress that these probabilities should only be understood as displaying the abstract potentialities of the model and not as depicting the real behavior of the *E. coli*. For doing that we need to refine the model and to collect sufficient statistical data for supporting an appropriate probability calculus.

Let s start with a parity situation: this is the only specific assumption that I shall do. Moreover, the initial probabilities may be arbitrarily changed without appreciably affecting what I shall say in the following. The probabilities of s1 and s2 are then both 0.5. The conditional probabilities of the rj ($j = 1, 2, 3, 4$) are then calculated by making use of the matrix $\hat{W}_{rs}$ (see Fig. 14):

$$p(r1|s1) = 0.588235294\ , \qquad p(r4|s1) = 0.411764706\ , \tag{21}$$

$$p(r2|s2) = 0.588235294\ , \qquad p(r3|s2) = 0.411764706\ , \tag{22}$$

whilst the absolute probabilties of the regulatory system's units are:

$$p(r1) = p(r1|s1)p(s1) = 0.294117647\ , \qquad p(r2) = p(r2|s2)p(s2) = 0.294117647\ , \tag{23}$$

$$p(r3) = p(r3|s2)p(s2) = 0.205882353\ , \qquad p(r4) = p(r4|s1)p(s1) = 0.205882353\ . \tag{24}$$

It can be easily seen that

$$\sum_{j=1}^{4} p(rj) = 1\ . \tag{25}$$

Since the regulatory system's units are univocally dependent on the sensory units s1 or s2, it is also clear that we have $p(r1, s1) = p(r1)$ ad similarly for the other units. It is also clear that we have:

$$p(g1|r1) = p(g2|r2) = p(g3|4) = p(g4|r3) = 1\ , \tag{26}$$

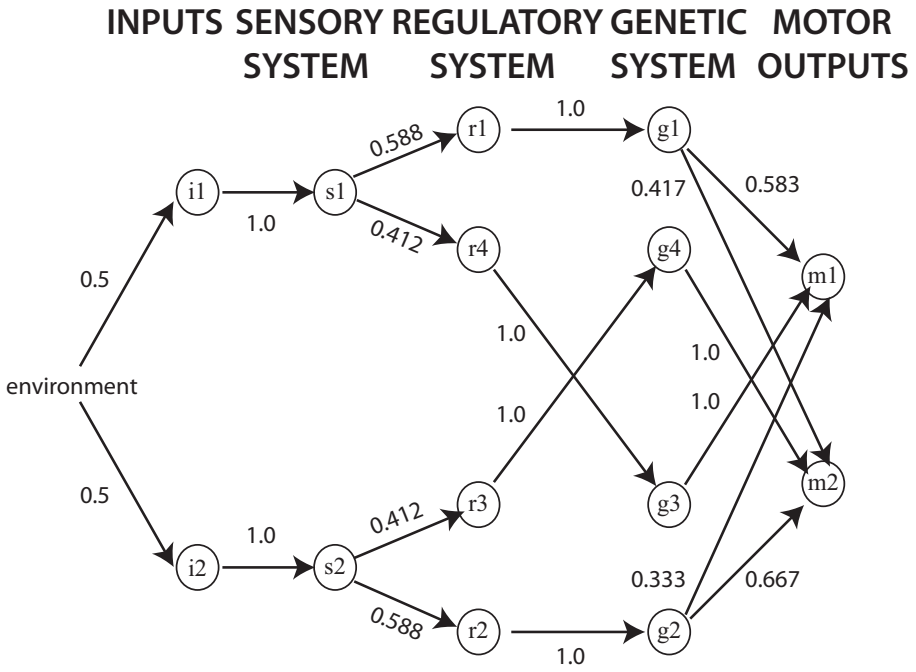

Figure 14: The conditional and absolute probabilities according to the chosen model.

whilst all other conditional probabilities are zero acording to the matrix $\hat{W}_{gr}$. Then, the absolute probabilities $p(gj)$ (with $j = 1, 2, 3, 4$) coincide with the respective absolute probabilties of the regulatory system's units (but with interchange of indexes 3 and 4, which in this case does not change the result). For instance,

$$p(g1) = p(g1|r1)p(r1) = 0.294117647\ . \tag{27}$$

Since the probability of any genetic unit is always conditioned on the regulatory units, these probabilities also coincide with the joint probabilities of genetic and regulatory units. For instance,

$$p(g1, r1) = p(g1|r1)p(r1) = 0.294117647\ . \tag{28}$$

A little bit more engaging is the computation of the conditional and absolute probabilities of the motor outputs. In this case, we take advantage of the matrix $\hat{W}_{mg}$. Then, we have:

$$\begin{aligned} &p(m1|g1) = 0.5833\ , \quad p(m1|g2) = 0.3333\ , \quad p(m1|g3) = 1.0\ , \\ &p(m2|g1) = 0.4167\ , \quad p(m2|g2) = 0.6667\ , \quad p(m2|g4) = 1.0\,, \end{aligned} \tag{29}$$

whilst $p(m1|g4) = p(m2|g3) = 0.0$. Taking into account only probabilities different from zero, the

absolute probabilities of m1 and m2 are finally given by:

$$\begin{aligned} p(m1) &= \frac{1}{2}[p(m1|g1)p(g1|r1)p(r1|s1) + p(m1|g2)p(g2|r2)p(r2|s2) + p(m1|g3)p(g3|r4)p(r4|s1)] \\ &= \frac{1}{2}(0.5833 \cdot 1.0 \cdot 0.58823529 + 0.3333 \cdot 1.0.58823529 + 1.0 \cdot 1.0 \cdot 0.411764706) \\ &= 0.475490 \ , \end{aligned} \tag{30}$$

$$\begin{aligned} p(m2) &= \frac{1}{2}[p(m2|g1)p(g1|r1)p(r1|s1) + p(m2|g2)p(g2|r2)p(r2|s2) + p(m2|g4)p(g4|r3)p(r3|s2)] \\ &= \frac{1}{2}(0.4167 \cdot 1.0 \cdot 0.58823529 + 0.6667 \cdot 1.0 \cdot 0.58823529 + 1.0 \cdot 1.0 \cdot 0.411764706) \\ &= 0.524510 \ . \end{aligned} \tag{31}$$

It is easy to verify that $p(m1) + p(m2) = 1$. Finally, the relevant joint probabilities of genetic and motor units are:

$$p(m1, g1) = 0.1715686 \ , \quad p(m1, g2) = 0.0980392 \ , \quad p(m1, g3) = 0.2058824 \ , \tag{32}$$

$$p(m2, g1) = 0.1225490 \ , \quad p(m2, g2) = 0.1960784 \ , \quad p(m2, g4) = 0.2058824 \ . \tag{33}$$

8 Entropies and Mutual Information

The above probabilities allow us to easily compute their binary logarithms and relative probabilities times these logarithms. The entropy of the sensory subsystem is easily calculated by making use of binary logarithms:

$$H(S) = -[p(s1) \lg p(s1) + p(s2) \lg p(s2)] = 0.5 \cdot (-1.0) + 0.5 \cdot (-1.0)] = 1.0 \ . \tag{34}$$

For the absolute probabilities of the regulatory units, we have:

$$\lg p(r1) = -1.765534746 \ , \qquad \lg p(r2) = -1.765534746 \ , \tag{35}$$

$$\lg p(r3) = -2.280107919 \ , \qquad \lg p(r4) = -2.280107919 \ , \tag{36}$$

from which, taking into account Eqs. (23), we obtain:

$$p(r1) \lg p(r1) = p(r2) \lg p(r2) = -0.519274925 \ , p(r3) \lg p(r3) = p(r4) \lg p(r4) = -0.469433983 \ . \tag{37}$$

For the conditional probabilities of the regulatory units we obtain:

$$\lg p(r1|s1) = \lg p(r2|s2) = -0.765534746 \ , \qquad \lg p(r4|s1) = \lg p(r3|s2) = -1.280107919 \ , \tag{38}$$

which, taking into account Eq. (28) and similar results, gives:

$$p(r1, s1) \lg p(r1|s1) = p(r2, s2) \lg p(r2|s2) = -0.225157278 \ , \tag{39}$$

$$p(r4, s1) \lg p(r4|s1) = p(r3, s2) \lg p(r3|s2) = -0.26355163 \ . \tag{40}$$

Since

$$H(R) = -[p(r1) \lg p(r1) + p(r2) \lg p(r2) + p(r3) \lg p(r3) + p(r4) \lg p(r4)] = 1.977417818 \ , \tag{41}$$

$$\begin{aligned} H(R|S) &= -[p(r1, s1) \lg p(r1|s1) + p(r2, s2) \lg p(r2|s2) + p(r4, s1) \lg p(r4|s1) + p(r3, s2) \lg p(r3|s2)] \\ &= 0.977417818 \ , \end{aligned} \tag{42}$$

we have

$$I(R : S) = H(R) - H(R|S) = 1.0 \ . \tag{43}$$

Note that $H(R)$ approximates quite well the binary logarithm of 4, which is what we expect since the sensory system can be understood as a combination of r1/r2 and r3/r4 as well as of r1/r4 and r2/r3, depending on whether we consider the opposite effects on these units on the network or their derivation from the sensory inputs. Another remarkable point is the following: the information that the sensory and regulatory systems share [Eq. (43)] is precisely identical to the entropy of the sensory system alone, given by Eq. (34). We may arrive to this result also by making use of the formula:

$$H(S) = H(S|R) + I(S:R) \ . \tag{44}$$

In other words, there is no entropy of S that lays outside R, i.e. the whole entropy of S is included in the entropy of R. I also remark that this expression is interesting in so far it splits the entropy of the system in two parts: a disordered part given here by $H(S|R)$ (which expresses the variability of S relative to R) and and ordered part, given by $I(S:R)$ (which express the information that S shares with R). The previous conclusion is confirmed by explicit calculation. Indeed:

$$p(s1|r1) = p(r1|s1)\frac{s1}{r1} = 1 \ , \qquad p(s1|r4) = p(r4|s1)\frac{s1}{r4} = 1 \ , \tag{45}$$

$$p(s2|r2) = p(r2|s2)\frac{s2}{r2} = 1 \ , \qquad p(s2|r3) = p(r3|s2)\frac{s2}{r3} = 1 \ , \tag{46}$$

which implies that all the logarithms of these probabilities are zero and therefore the conditional entropy $H(S|R)$ is also zero. This is not a big worry, since in the proposed model all the information received by the sensory system is faithfully transmitted to the regulatory system. So, we expect a certain additional variability of the regulatory system on the sensory one (expressed by the fact that $H(R|S) = 0.977417818$) but not vice versa.

The computation of the mutual information between regulatory and genetic system is even simpler: since all conditional probabilities of the form (26) are 1, their logarithms are all zero (this is due to the deterministic connections between the two systems). The logarithm of the absolute probabilities of the genetic system's units are instead:

$$\lg p(g1) = \lg p(g2) = -1.765534746 \ , \qquad \lg p(g3) = \lg p(g4) = -2.280107919 \ , \tag{47}$$

which together with the probability (27) and similar gives:

$$p(g1)\lg p(g1) = p(g2)\lg p(g2) = -0.519274925 \ , p(g3)\lg p(g3) = p(g4)\lg p(g4) = -0.469433983 \ . \tag{48}$$

Since we have now

$$H(G) = -[p(g1)\lg p(g1) + p(g2)\lg p(g2) + p(g3)\lg p(g3) + p(g4)\lg p(g4)] = 1.977417818 \ , \tag{49}$$

$$H(G|R) = 0.0 \ , \tag{50}$$

we also have

$$I(G:R) = H(G) - H(G|R) = 1.977417818 \ . \tag{51}$$

This result means that the entropies of the regulatory and genetic system fully overlap (it consist only in the information that they share). This is again not a surprise, since there is no variability of the genetic system relative to the regulatory system, neither vice versa, due to the fact that all their connections are deterministic (all the conditional probabilities connecting elements of one system with an element of another system are either 0 or 1). Such an assumption may be always changed.

Again, a little more cumbersome is the calculation of the mutual information between motor and genetic systems. The logarithms of the absolute probabilities of m1 and m2 are given by:

$$\lg p(m1) = -1.0725125 \quad \text{and} \quad \lg p(m2) = -0.930958356 \ , \tag{52}$$

which together with probabilities (30) give:

$$p(m1)\lg p(m1) = -0.509969179 \quad \text{and} \quad p(m2)\lg p(m2) = -0.488296785 \ . \tag{53}$$

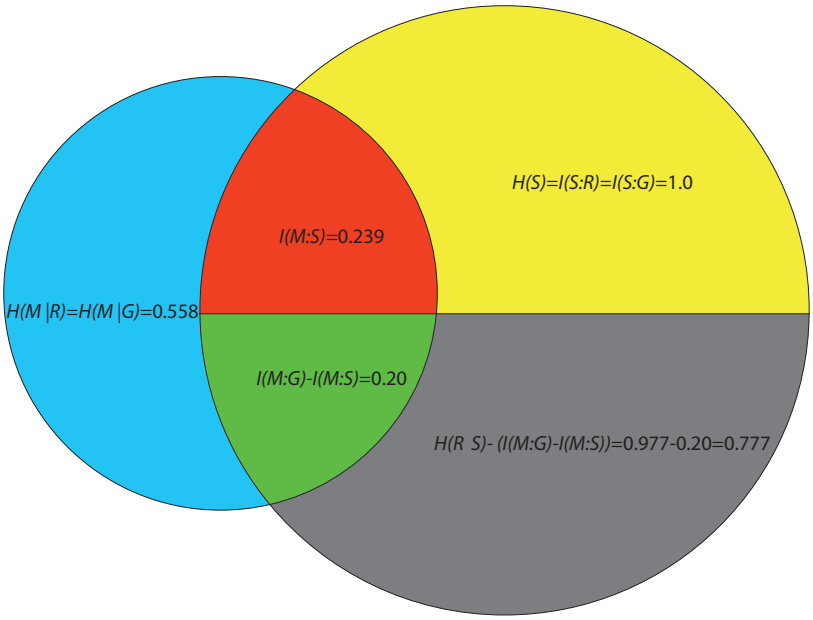

Figure 15: I have artificially divided the sensorimotor system in two parts. Note that the red zone is the mutual information between the motor system and the sensory system that coincides with the overall mutual information, that is, the information shared by the motor, the regulatory (genetic) system, and the sensory system. The green are is the information shared by the motor and the regulatory (genetic) system when to this the overall information has been subtracted. The yellow area represents the information shared by the sensory and the regulatory (genetic) systems. The grey area is the entropy of the regulatory (genetic system) that remains after removal of the information that it shares with the other systems. Therefore, the whole entropy of the regulatory (genetic) systems ($H(G) = H(R)$) is given by the sum of the red, the green, the yellow and the grey areas. The blue are is the entropy of the conditional entropy of the motor system on the regulatory (genetic) one. Then, the whole entropy of the motor system ($H(M)$) is given by the sum of the blue, green and red areas.

Taking into account the logarithms of the conditional probabiliites that count:

$$\lg p(m1|g1) = -0.777607579\ , \qquad \lg p(m1|g2) = -1.584962501\ , \tag{54}$$

$$\lg p(m2|g1) = -1.263034406\ , \qquad \lg p(m2|g2) = -0.584962501\ , \tag{55}$$

thanks to probabiliities (32), we obtain

$$p(m1, g1) \lg p(m1|g1) = -0.133413065\ , \qquad p(m1, g2) \lg p(m1|g2) = -0.15538848\ , \tag{56}$$

$$p(m2, g1) \lg p(m2|g1) = -0.154783628\ , \qquad p(m2, g2) \lg p(m2|g2) = -0.11469853\ . \tag{57}$$

Therefore,

$$H(M) = -[p(m1) \lg p(m1) + p(m2) \lg p(m2)] = 0.998265963\ , \tag{58}$$

$$\begin{aligned} H(M|G) &= -[p(m1, g1) \lg p(m1|g1) + p(m1, g2) \lg p(m1|g2) + p(m2, g1) \lg p(m2|g1) + p(m2, g2) \lg p(m2|g2)] \\ &= 0.558283703\ , \end{aligned} \tag{59}$$

from which it follows:

$$I(M : G) = H(M) - H(M|G) = 0.43998226\ . \tag{60}$$

We also have that

$$H(M) = H(M|G) + I(M:G) = 0.558283703 + 0.43998226 = 0.998265963 \,, \tag{61}$$

in full accordance with the derivation of Eq. (58). It is interesting to note that a similar result could be found by explicit calculations of $H(M|S)$ and $I(M:S)$, which will show that:

$$H(M|S) = 0.758715564 \quad \text{and} \quad H(M:S) = 0.239550399 \,, \tag{62}$$

which imply

$$H(M|S) + H(M:S) = 0.758715564 + 0.239550399 = 0.998265963 \,, \tag{63}$$

again in accordance with the derivation of Eq. (58). This particular result is due t the fact that $H(S)$ is part of $H(R)$ or $H(G)$.

I recall that I have artificially factorized the sensorimotor system in two subsystems: the sensory and the motor parts. This assumption can obviously be corrected with more sophisticated models if this results necessary. Moreover, the conditional entropies are here very strong. What seems more important here is that if we take the sum of the whole entropies of the three main (sensorimotor, regulatory and genetic) subsystems [Eqs. (34), (41)-(42), (49) (58)], we obtain:

$$H(S) + H(R) + H(M) \quad = \quad 1.0 + 1.977417818 + 0.998265963 = 3.975683781 \,, \tag{64}$$

which approximates quite well the sum of the maximal entropies of two systems that can be in 4 different configurations each (I recall that $H(G) = H(R)$). The joint entropy of the whole system is easily calculated by taking into account that amounts to the entropy of R (or G), which also includes the entropy of S, plus the part of M that is outside G, that is, $H(M|G)$ [see also Eqs. (41) and (59); see also Fig. 15]

$$H(S,M,R,G) = H(R) + H(M|G) = 1.977417818 + 0.558283703 = 2.535701521 \,. \tag{65}$$

The difference between the quantity (64) and the quantity (65) will give the sum of the whole mutual information of the system (we obviously do not consider the fact that $H(G) = H(R)$, since from an entropic point of view they behave like a single system). This can be also be calculated by summing the information shared by S and R, on the oner hand, and the information shared by M and G, on the other [Eqs. (43) and (60)], that is,

$$I(R:S) + I(M:G) = 1.0 + 0.43998226 \quad = \quad 1.43998226 \,, \tag{66}$$

$$H(S) + H(R) + H(M) - H(S,M,R,G) = 3.975683781 - 2.535701521 \quad = \quad 1.43998226 \,. \tag{67}$$

On the other hand, the overall information shared by all subsystems is given by

$$I(M:S:R:G:S) = I(M:S) = 0.239550399 \,, \tag{68}$$

so that the complexity of the system is finally given by

$$I(R:S) + I(M:G) - I(M:S:R:G:S) = 1.43998226 - 0.239550399 = 1.200431861 \,, \tag{69}$$

in accordance with formula (16). It is also interesting to note that the overall mutual information represents a small part (about 16%) of the whole mutual information:

$$\frac{I(M:S:R:G:S)}{I(R:S) + I(M:G)} = 0.166356493 \,, \tag{70}$$

and even a smaller part (less than 10%) of the whole entropy:

$$\frac{I(M:S:R:G:S)}{H(S,M,R,G)} = 0.094471056 \,. \tag{71}$$

9 Discussion

In one of my recent papers (Auletta, 2011b) I have underlined how a system like the bacterial control of environmental information can ensure also a certain mutual information between the bacterium and the environment. This does not obviously imply that the bacterium is able to learn in any sense (indeed its space of freedom is relative tiny). However, the model I have presented as a refinement of the precedent study can throw some light on this mechanism.

What is most interesting and peculiar in the bacterial chemotaxis is both sensitivity to the external environment and a certain autarchy (the *E. coli* tries always to come back to its default state) (Auletta, 2011b). The first property is necessary, otherwise chemotaxis could not be adaptive. The second aspect is also necessary, otherwise the bacterium would be driven and finally enslaved by the external environment. However, this would turn out in a rapid dead since (due to thermodynamic constraints) the number of environment's configurations that would promote the survival of the bacterium is so tiny to be practical zero. So, the bacterium must find a trade–off between these two opposite exigencies. It must favour certain ordered connections between itself and the environment as well as among the different subsystems that constitute it. However, these connections cannot be too rigid, and a certain amount of variability is necessary (soft assembly). If we take the mutual information as a measure of order while conditional entropies (strongly dependent on modularity and information encapsulation) represent disorder, the bacterium needs a certain balance between the two, that is, a balance between intrinsic but autarchic order (the basis of the organism's homeostasis) and variability allowing its ability to respond to changes of the environment and to display and adaptive behaviour. I recall here the two general principles formulated in Sec. 2:

- The establishment of preferred channels (channelization) with the external conditions that in conditions of relative stability generates regular patterns and
- The continuous generation of variety (and therefore the intrinsic randomness of single events).

In the quoted previous study I have focused on the mutual information between bacterium and environment. Here, I focus on the mutual information between internal subsystems. Ideally, the balance between order and disorder could be parity, that is, $50\% - 50\%$. Actually, my guess is that an organism needs to keep a higher level of variability (Fisher, 1930), since a parity would very easily determine an excessive rigidity in certain conditions. Therefore, my estimate is that an optimal trade off is 60% disorder and 40% order, which is approximately expressed by the relation

$$\frac{I(R:S)+I(M:G)}{H(S)+H(R)+H(M)} = \frac{1.43998226}{3.975683781} = 0.362197383\ . \tag{72}$$

In other words, the amount of order relative the sum of the entropies of the system considered as separated (full disorder) is about 36%. My estimate is that it can be a bit higher but not go much further than this value. The quantity (72) may be called relative complexity of the system and may turn out to be very important when examining the shifts in order and disorder at evolutionary scale. I have indeed said that adding more subsystems generates a maximal entropy attainable by the system but that in most cases it is not currently attained, according to the inequality (7).

10 Conclusions

- What I have shown is that chemotaxis displays a new kind of "mechanics": the mechanics of information, which obeys to other rules and mechanism relative to the old mechanics that was centered on local exchanges of dynamical quantities like energy and momentum.
- Chemical reactions are obviously fundamental (everything occurs through them). However, they are "enslaved" by a system for controlling information which uses acquiring of free energy to maintain its intrinsic order, i.e. to aliment itself (Auletta, 2011a, Ch. 8).

- Often, there is a certain confusion on these matters when it is said that organisms preserve their state as any other physical system of the world. The fact is that abiotic physical systems preserve their state only against *external* forces or perturbations. On the contrary, they change spontaneously their state since they show an intrinsic tendency to disorder (according to the second law of thermodynamic). The situation of living systems is totally different. Although they do not violate the second law (they discharge into the environment sufficient entropy to compensate their acquiring of free energy), they are able, thanks to the mechanism of information control, to keep their state invariant also relative to the intrinsic tendency to disorder, at least for a sufficient time window allowing not only the survival of the individual through diverse cycles of self–production but also the possibility of transmit the core of the intrinsic program (the genome) to further generations.

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