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Cell signaling as a probabilistic computer

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Abstract

Living organisms survive and multiply even though they have uncertain and incomplete information about their environment and imperfect models to predict the consequences of their actions. Bayesian models have been proposed to face this challenge. Indeed, Bayesian inference is a way to do optimal reasoning when only uncertain and incomplete information is available. Various perceptive, sensory-motor, and cognitive functions have been successfully modeled this way. However, the biological mechanisms allowing animals and humans to represent and to compute probability distributions are not known. It has been proposed that neurons and assemblies of neurons could be the appropriate scale to search for clues to probabilistic reasoning. In contrast, in this paper, we propose that interacting populations of macromolecules and diffusible messengers can perform probabilistic computation. This suggests that probabilistic reasoning, based on cellular signaling pathways, is a fundamental skill of living organisms available to the simplest unicellular organisms as well as the most complex brains.

1. Introduction

The information available to living organisms about their environment is uncertain, not only because biological sensors are imperfect, but more importantly because sensors inevitably provide an incomplete, partial description of the environment. Moreover, timing is a crucial constraint for biological systems. During a fight-or-flight dilemma, animals must quickly decide to fight or flee, and they can never be sure of the good or bad consequences of their decision. Incompleteness is therefore a key notion for an autonomous agent facing the complexity of the world. There is now growing evidence that probabilistic reasoning is a rigorous and efficient way to represent partial or incomplete knowledge and to answer optimally questions that have no uniquely defined solution [19].

Perception is a well-known example of ill-posed problems, because an indefinite number of object characteristics can theoretically give rise to the same set of sensory data. For instance, an indefinite number of objects with various shapes, sizes and movements can induce exactly the same retinal projection. A number of studies have shown that Bayesian models can accurately account for various aspects of perception [21, 42, 34, 29, 12, 26] and sensory-motor integration [24, 23, 6, 39].

Non-probabilistic models assume that the brain computes internal estimates of relevant state variables such as motion, object distance, and color. Each variable is supposed to have a unique estimate, on which no evaluation of uncertainty is performed. In contrast, Bayesian models assume that the brain evaluates the probability corresponding to each possible value of the relevant variables. Probability computation results from straightforward application of the Bayes (*i.e.*, multiplicative) and marginalization (*i.e.*, additive) rules, which can be seen as a generalization of logical inference to probability distributions [1, 2]. Following Pearl [33] and Jaynes [19], we define probabilistic reasoning as the ability to perform inference within a probabilistic knowledge base. In the following, we will call a subjective Bayesian model the specification of the variables of interest, their conditional dependencies, the parametric forms, and the way probability distributions can be inferred.

Acknowledging the efficiency of probabilistic reasoning in accounting for a large variety of perceptive reports or motor behaviors, one of the main scientific challenges is to explicitly demonstrate that the brain, and more generally bio-

logical systems, can effectively perform probabilistic computation. The problem is to show possible correspondences between subjective Bayesian models and descriptive models of biological systems and signal processing.

Most existing studies proposed assemblies of neuronal cells or single neurons as the appropriate level of analysis to explain how a brain could perform probabilistic inference. Several authors have proposed that the firing rate of a group of cells within a given temporal window [43, 9, 15? ?] could represent probability distributions over state variables. The mean firing rate might be well approximated by a graded value, to which a subjective probabilistic meaning can be attributed: for instance, the probability that a given proposal over a state variable is true, or its log-likelihood ratio. Other approaches are based on the Poisson-like variability of spike trains [28] or kernel convolution for encoding/decoding spike trains [8].

In contrast, we consider the molecular scale as an adequate framework to solve this matching problem between subjective Bayesian models and descriptive biological ones.

A common distinction is made between two classes of biochemical components that interact with one another. Simple molecules, called messengers, are available in large amount and/or diffusing rapidly across cellular compartments. Allosteric macromolecules, much more complex, have limited mobility and participate in the signaling pathway through changes in the spatial arrangement of their atoms. The messengers can bind to the allosteric macromolecules inducing their conformation changes. These conformation changes can, when in active states, modify the concentrations of the messengers either producing new ones or degrading existing ones. Enzymes are examples of macromolecules where these global changes in conformation are exposing parts of the molecules where reactants may bind to facilitate reactions producing or degrading messengers. Ionic channels belong to another class of macromolecules where the messengers' concentrations is controlled through opening or closing of the channel, letting ions flow across the membrane. Populations of macromolecules in their various conformational states and diffusible messenger concentrations are assumed to be the substrates used at sub-cellular level to represent and to compute probability distributions. Our proposal is that the biochemical processes involved in cell signaling can perform the elementary computations needed for subjective probabilistic reasoning, and that this biochemical computation is used extensively by the brain as an elementary component: a Bayesian "nano-gate." Specifically, we propose that macromolecular assemblies (receptors, ionic channels, and allosteric enzymes) coupled through several diffusible messengers (G-proteins, cytoplasmic calcium, cyclic nucleotides and other second messengers, membrane potentials, and neurotransmitters) are the biochemical substrates for subjective probability evaluation and updating. On the one hand, messenger concentrations play the role of parameters encoding probability distributions, on the other hand, allosteric conformational changes compute the probabilistic inferences. Diffusible messenger concentrations, including electric charge density, control the probability of conformational changes, which are in turn responsible for inflow and outflow rates of messengers and are then controlling their kinetics.

We started exploring these ideas in [17], where the kinetics of a rhodopsin channel were shown to converge to a posterior distribution of states in a hidden Markov model, the hidden state representing the presence or absence of light. A similar kinetic scheme derived from Bayesian formulation of receptor activations was compared with other common signaling schemes in [22] to emphasize its optimality. Rather than considering a binary (ON or OFF) hidden state, multiple activated states were considered in [36] (like self and nonself in the immune system) and they discussed how Koshland–Goldbeter could solve this decision problem. Napp and Adams proposed in a recent paper [31] a procedure to compile a probabilistic graphical model into a chemical reaction network.

In section 2 we present biochemical cascades, we exhibit elementary building blocks for which the concentration of the secondary messenger (output) is either the product, the sum or the ratio of the concentrations of the 2 primary messengers (inputs), we show that these building blocks can be combined into cascade and we demonstrate that these cascades are able to compute any Rational Function with Non-negative Coefficients (RFNC).

In section 3 we demonstrate that to solve any Bayesian inference problem it is necessary and sufficient to compute an RFNC. Consequently, we show that for any Bayesian inference problem it exists a theoretical biochemical cascade that solves it.

In section 4 we give a simple example of theoretical biochemical cascade to implement a phototaxis behavior for a unicellular organism.

Finally, in section 5 we discuss the different hypothesis and simplifications made in the paper and we propose different directions to extend this work.

2. Biochemical cascades

The biochemical processes in a cell form very complex networks of reactions that insures the survival of the cell for unicellular organisms or participate to the survival of the multi-cellular organism they belong to. These reactions are organized into pathways either metabolic that provide homeostasis (for instance, energy regulation) or sensory-motor that elaborate appropriate responses to given stimuli (for instance, phototaxis and chemotaxis behaviors or transduction of light in the retina). Some common messengers encountered in biochemical pathways include charged elements (electrons, calcium ions), cyclic AMP, phosphate or methyl groups. Two examples of biochemical cascades are presented (i) the detection of high nutrient areas during bacterial chemotaxis (Figure 1) and (ii) the conversion of light impinging the retina into biochemical signals (Figure 2).

The biochemical components participating in these pathways are subject to various dynamics and there are two common ways for allosteric macromolecules and messengers to interact:

1. Ligand (messenger) binding to macromolecules and activation.
2. Enzymatic action of messengers on the production and degradation of messengers.

The aim of this section is to study the dynamics of biochemical cascades in an abstract manner. This will provide us with a general description of the computations which it can implement.

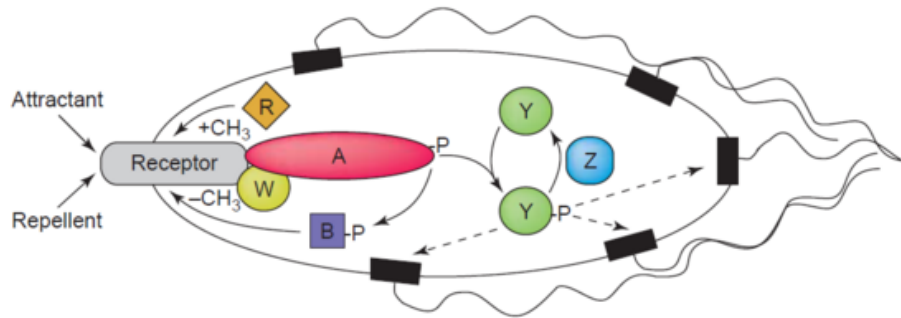


Figure 1: *Bacterial chemotaxis*: Bacteria are unicellular organism often able of chemotaxis either moving toward attractant chemical components or away from repellent ones. The detection of these components by specific receptors initiate a cascade of biochemical reactions which *in fine* change the movement of flagella and the motion of the bacteria. In this example [37] attractant or repellent ligands binding to the specific receptors favors auto-phosphorylation of the histidine kinase (A - macromolecules) and the production of phosphoryl groups (messengers) which are then transferred to regulator (Y - macromolecules) which in turn modulate the flagellar motor activity. The allosteric macromolecule Y is itself controlled by the phosphatase activity of Z. Other allosteric macromolecules (R and W) modulate the receptor sensitivities through methyl messengers (CH₃), while negative feedback is provided by a third macromolecule (B) through phosphoryl group messengers (P). Apart from specific receptors and flagella motors, six allosteric macromolecules (A, B, R, W, Y, Z) and 2 messengers (CH₃ and P) are involved in bacterial chemotaxis.

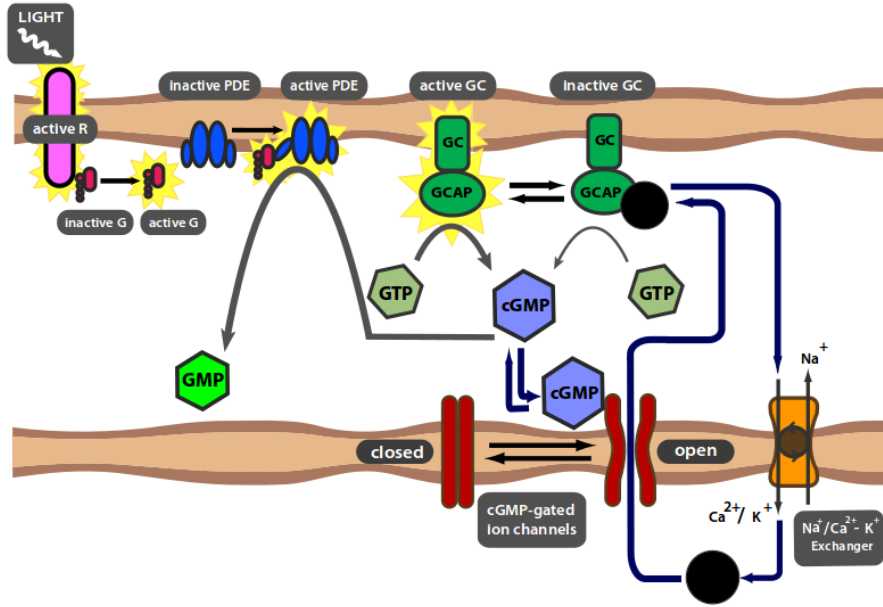


Figure 2: *Retina photo-transduction*: When photons hit the retina, it changes the conformation of retinal which turns the rhodopsine in an active state, releasing the active G-protein (an example of macromolecule acting as a messenger). The G-protein activates the next macromolecule in the cascade; the phosphodiesterase (PDE) which in turn degrades the messenger cyclic GMP (cGMP) which is produced by the enzyme guanyl cyclase (GC). cGMP is the main messenger acting on the ionic channel. The light-induced decrease of cGMP concentration increases the probability for the channel to be closed. Adapted from [17].

2.1. Allosteric macromolecules and messengers

In this section we will demonstrate that the interaction between messengers and allosteric macromolecules result in concentration of active macromolecules or in secondary messengers that are Rational Function with Non-negative Coefficients (RFNC) of the concentration of the primary messengers.

Formally, a RFNC is defined as follow:

RFNC: Given a vector $x = (x_1, x_2, \dots, x_N)$ of N entries, $h(x)$ is an RFNC of x if one of the following conditions is satisfied:

1. $h(x)$ is a non-negative constant;
2. $h(x) = x_n$;
3. $h(x) = h_1(x)h_2(x)$ where $h_1(x)$ and $h_2(x)$ are RFNC of x ;
4. $h(x) = h_1(x) + h_2(x)$ where $h_1(x)$ and $h_2(x)$ are RFNC of x ;
5. $h(x) = h_1(x)/h_2(x)$ where $h_1(x)$ and $h_2(x)$ are RFNC of x .

2.1.1. Ligand binding to macromolecules and activation

The first reaction network motif describes the binding of messengers to a receptor, with deactivating messengers S_d favoring its transitions to inactive states M and activating messengers S_a favoring activations to states M^* according to the reaction:



The full reaction mechanism is illustrated in the transition diagram of Figure 3 for a receptor having two binding sites and four active states.

In this general form, the model implies that the various events (binding of messengers, activation) occur in a random order [27]. The probability of the macromolecule to change its conformation state towards an activate state is modulated by one or several messengers. The transition among states is often reduced to a Markov network dynamics

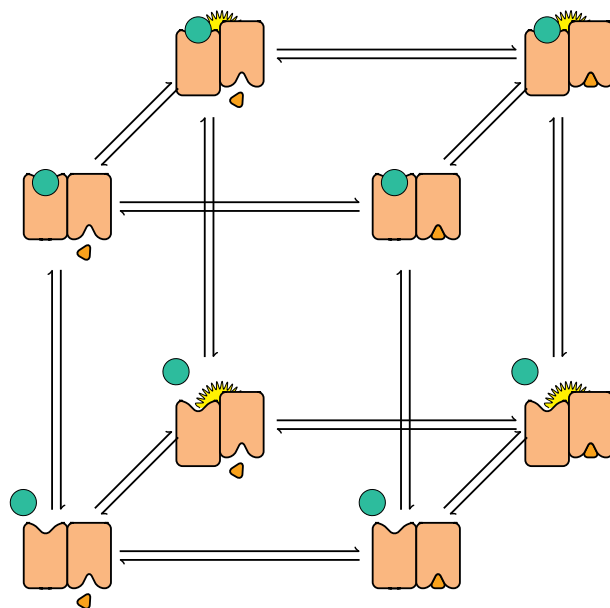


Figure 3: According to the Monod–Wyman–Changeux (MWC) model [30, 4], the activity of a macromolecule depends on its tridimensional tertiary or quaternary structure, which can be in a discrete number of states, typically two, named “tensed” and “relaxed” in the original formulation of the model. The transition probability between these allosteric conformations depends on the status (free or not) of the receptor sites, and the affinity for specific messengers depends on the allosteric conformation. An example is given here, for a macromolecule with 8 states and 2 binding sites for primary messenger (represented as green circles and orange triangles). Four of these states are considered as “active”: able to change the concentration of a secondary messenger (marked by a yellow star denoting their relaxed conformation). The dynamic of the configuration changes may be specified by the 24 propensities of the possible changes (corresponding to the 24 arrows). At equilibrium, the probability to be in any of the 8 configuration can be obtained as a RFNC of the concentrations of the primary messengers (see text for demonstration). The non-negative coefficient of the RFNC are the propensities. The probability to be active, as the sum of the probabilities of the four active states, is itself an RFNC of the concentrations of the messengers.

and the binding rates are supposed to be proportional to the messengers' concentrations. For macromolecules with total concentration M_t spread among n states, $\mathbf{M} = \{M_k\}_{k \in \{0, n\}}$, each with concentration M_k evolves according to the law of mass action for unimolecular reaction under the constrain $M_t = \sum_{k=0}^n M_k$ which leads to k differential equations:

$$\tau_k \frac{dM_k}{dt} = -M_k + \mathbf{R}_k \mathbf{M} \quad (2)$$

where \mathbf{R}_k gathers the rescaled reaction rates for transitions towards state k and the time constant τ_k gathers the ones for its degradation, R_{ki} is the propensity of the reaction from state i to k . Moreover, due to conservation law, we have $\sum_l R_{lm} = 1$ so that all of the molecules departing from a state m are spread among other states.

The stationary concentrations are in the eigenvector of $(\mathbf{I} - \mathbf{R})$, with the matrix \mathbf{R} lines composed of \mathbf{R}_k , for eigenvalue 1 which for this matrix is:

$$M_k = \frac{\det(\mathbf{I} - \mathbf{R})^{(k)}}{\sum_{j=1}^n [\det(\mathbf{I} - \mathbf{R})^{(j)}]} \quad (3)$$

where the super index $\{k\}$ on a matrix, $M^{(k)}$, denotes the matrix M from which column and row of index k have been removed.

The concentration for each macromolecule state, in particular for the active ones, is thus a Rational Function with Non-negative Coefficient (RFNC as defines in the box **RFNC**) of the input concentrations of the messengers (see [10] for a detailed demonstration). The coefficients are the propensities of each of the reaction corresponding to the different possible change of configuration of the macromolecule.

2.1.2. Enzymatic action of macromolecules on the production and degradation of messengers

The second reaction network motif describes how two antagonist macromolecules regulate the production of a secondary messenger. M_p^* is the equilibrium concentration of active allosteric macromolecules producing the secondary messenger S , when M_r^* is the analogous for the macromolecules reducing S (see Figure 4). It is a very common motif in both signaling and metabolic pathways:

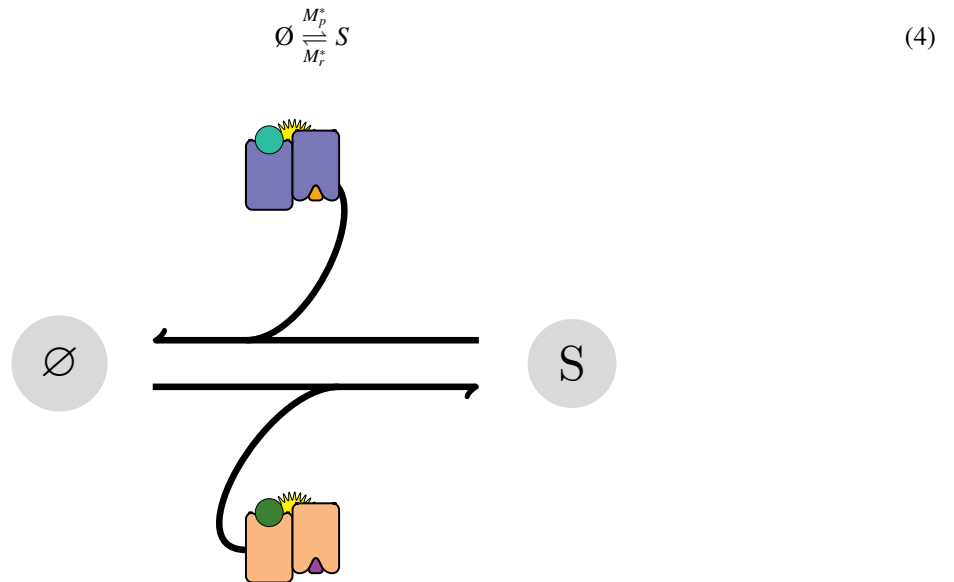


Figure 4: Two antagonist allosteric macromolecules producing and reducing a secondary messenger S . The purple macromolecule (top), when active, reduces the secondary messenger S . The orange macromolecule (bottom), when active, produces S .

This motif (often call “enzymatic futile cycle”) following the Koshland-Goldbeter kinetics has been shown to act as a signal amplifier [16] or insulator depending on the relative time scales of complex formation and messenger

production [41]. We assume in our model that the catalysis is a first process in the law of mass action so that the rates of production and degradation of messengers is proportional to the corresponding enzymes concentrations.

Macromolecules with concentrations in active states M_d^* , M_r^* are acting with first order kinetics:

$$\frac{dS}{dt} = K_p M_p^* - K_r M_r^* S \quad (5)$$

so that at steady state: $S = \frac{k_p M_p^*}{k_r M_r^*}$. Alternatively, we can consider the stochastic Poisson kinetics for this reaction which result in a Poisson distribution of mean $\frac{k_p M_p^*}{k_r M_r^*}$. Note that it is assumed that precursors messengers to be in large amount so that it is not limiting the production of messengers. As M_p^* and M_r^* are both RFNC of the concentrations of the primary messengers, S is also an RFNC of these concentrations.

2.2. Artificial biochemical cascades

In this section, we will demonstrate that for any RFNC it exists an artificial biochemical cascade to compute this RFNC. We will first propose an elementary module made of the 2 motifs just presented for which the concentration of the secondary messenger (output of the module) is an RFNC of the concentrations of the 2 primary messengers (inputs of the module). We will then show, that by adequate choice of the propensities, we may obtained the output concentration to be either the product, the sum or the ratio of the inputs concentrations. In a third step, we will demonstrate that it is possible for any RFNC to combine these elementary operator modules into cascade to obtain the desired computation. The obtained biochemical cascade is “artificial” because we do not pretend that the chosen propensities for the operators have any kind of biological plausibilities and also because the way the cascade is build is only a proof of existence and in no way an arrangement pretending to any optimality criteria or biological plausibility.

2.2.1. Elementary module

As an elementary module, we propose to consider two populations of primary messengers x and y , a population of secondary messengers S and two populations of macromolecules with state vectors $\mathbf{M}_p, \mathbf{M}_r$ (see Figure 5).

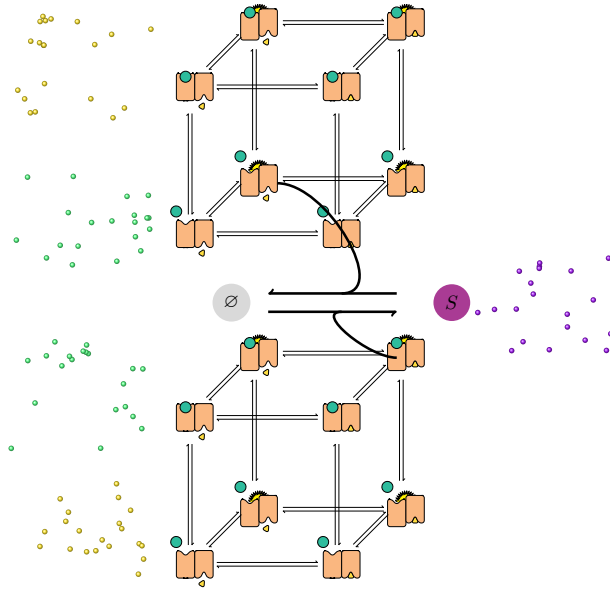


Figure 5: Two populations of antagonist macromolecules combined to form an elementary module to regulate the production of a secondary messenger S . The 2 populations change their configuration influenced by the 2 same species of primary messengers (x in yellow and y in green). The 2 populations when active influence the production or degradation of a secondary messenger S (in purple).

The two types of messengers both bind and modulate the activations of enzymes. The concentrations in active states are thus $M_p^* = RFNC_p(x, y)$ and $M_r^* = RFNC_r(x, y)$ and the output messenger concentration is itself an RFNC of the concentrations of the primary messengers:

$$S = \frac{k_p * M_p^*}{k_r * M_r^*} = \frac{k_p * RFNC_p(x, y)}{k_r * RFNC_r(x, y)} \quad (6)$$

2.2.2. Product, sum and division modules

For an elementary building block as just described we have 50 parameters available to design the RFNC: $S = RFNC(x, y)$. These 50 parameters are the 24 propensities of the macromolecule producing S , the 24 propensities of the macromolecule reducing S , k_p and k_r . For a theoretical biochemical cascade, we can chose these parameters as we wish¹.

In this section we will show how to choose these coefficients in order to obtain 3 elementary building blocks for which the concentrations of secondary messengers are respectively the product, the sum and the ratio of the concentrations of primary messengers.

Product:. The product may be obtain by the propensities choice shown in Table 1. Only 4 states among the 8 possibles are necessary for both the producing macromolecules and the reducing ones. For the chosen propensities, using Equation 3, we get:

$$RFNC_r(x, y) = \frac{1}{2(1+x+xy)} \quad (7)$$

and :

$$RFNC_p(x, y) = \frac{xy}{2(1+x+xy)} \quad (8)$$

and finally, choosing $k_r = k_p = 1$, we obtain:

$$S = x \times y \quad (9)$$

Transition matrix for reduction				
	● ▲ ✨	● ▲ ✨	● ▲ ✨	● ▲ ✨
● ▲ ✨	*	1	0	1
● ▲ ✨	2x	*	1	0
● ▲ ✨	0	y	*	0
● ▲ ✨	1	0	0	*

$$RFNC_r(x, y) = \frac{1}{2(1+x+xy)}$$

Production matrix				
	● ▲ ✨	● ▲ ✨	● ▲ ✨	● ▲ ✨
● ▲ ✨	*	1	0	0
● ▲ ✨	x	*	2	0
● ▲ ✨	0	y	*	1
● ▲ ✨	0	0	1	*

$$RFNC_p(x, y) = \frac{xy}{2(1+x+xy)}$$

Table 1: Propensities for product. Only the non-null propensities are represented.

¹Of course, biochemistry imposes for real biochemical cascades numerous constraints on the value of these parameters that we do not consider here.

In Figure 6 we present a simulation of the behavior of such an elementary product building block.

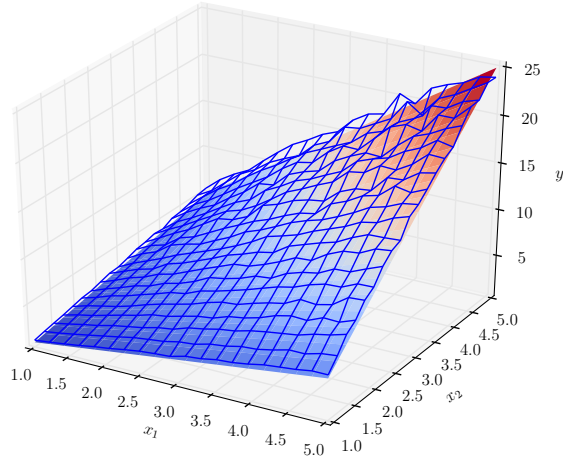


Figure 6: Result of the simulations where macromolecule transitions are updated using stochastic simulation and S production is computed using Euler integration. The surface shows the product of ligand concentrations $x \times y$ and the wireframe shows the scaled simulated concentration in S.

Sum.: For the sum, a possible choice for the propensities is given in Table 2. Note that we use 5 states for the producing macromolecules. Choosing $k_p = 1$ and $k_r = 2$, we get:

$$S = x + y \quad (10)$$

Reduction matrix					
	○ △ *	● △ *	○ △ *	○ △ *	○ △ *
○ △ *	*	1	1	1	1
● △ *	4x	*	0	0	0
○ △ *	4y	0	*	0	0
○ △ *	1	0	0	0	*

$$RFNC_r(x, y) = \frac{1}{2(1+2(x+y))}$$

Production matrix					
	○ △ *	● △ *	○ △ *	○ △ *	○ △ *
○ △ *	*	1	1	0	0
● △ *	x	*	0	1	0
○ △ *	y	0	*	0	1
○ △ *	0	1	0	*	0
○ △ *	0	0	1	0	*

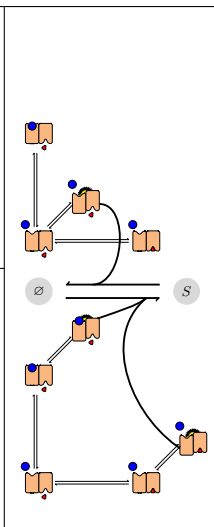
$$RFNC_p(x, y) = \frac{x+y}{1+2(x+y)}$$


Table 2: Propensities for sum. Only the non-null propensities are represented.

Ratio:. For the ratio, a possible choice for the propensities is given in Table 3. Choosing $k_p = k_r = 1$, we get:

$$S = x/y \quad (11)$$

Reduction matrix				
	● ▲ *	● ▲ *	● ▲ *	● ▲ *
● ▲ *	*	1	1	0
● ▲ *	x	*	0	1
● ▲ *	0.5y	0	*	0
● ▲ *	0	1	0	*

$$RFNC_r(x, y) = \frac{0.5x}{1+x+y}$$

Production matrix				
	● ▲ *	● ▲ *	● ▲ *	● ▲ *
● ▲ *	*	1	1	0
● ▲ *	0.5x	*	0	0
● ▲ *	y	0	*	1
● ▲ *	0	0	1	*

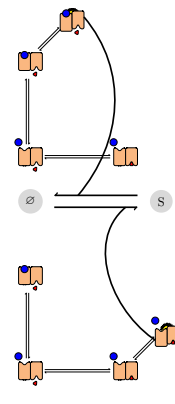
$$RFNC_p(x, y) = \frac{0.5y}{1+x+y}$$


Table 3: Propensities for ratio. Only the non-null propensities are represented.

2.2.3. Any RFNC can be computed by an artificial biochemical cascade

Given any RFNC of the concentration of some input messengers, it is always possible, by definition of an RFNC, to considered it as an arborescent cascade of application of the 3 basic operators: product, sum and division.

As we just demonstrated that these basic operators may be implemented by the proposed elementary modules, it is always possible to build the arborescent artificial biochemical cascade that exactly correspond to the required computation.

Due to the ability of the enzymatic futile cycle (motif 2) to act as an insulator, the concentrations in messengers at a given depth in the tree only depends on messengers' concentrations at the depth below. However, all the intermediary messengers encoding different quantities used in some branch or at some depth of this tree should be different from one another in order to insure that there is no possible confusion.

3. Subjective probabilistic inferences

Subjective probabilistic models (often called Bayesian models) include variables describing states of the world highly relevant for the organism, such as the presence of food or predators. The values taken by these variables cannot be known with certainty by the organism. However, according to the Bayesian approach, the organism can evaluate the probability distribution over these variables on the basis of specific observations, such as the detection of light or the detection of an odorant molecule. Furthermore, they can infer the probability for their actions according to the probabilities of these state variables and *in fine* decide what to do.

More formally, subjective probabilistic model and inference may be algebraically defined as follow (see [2] for thorough definitions and discussions and review of numerous examples):

Subjective probabilistic model:^a A subjective probabilistic model is defined by a set $X = \{X_1, X_2, \dots, X_N\}$ of relevant variables and by a decomposition which states the joint distribution as a product of simpler ones assuming some conditional independencies between variables:

$$P(X_1, X_2, \dots, X_N) = \prod_{m=0}^M [P(L_m | R_m)] \quad (12)$$

where L_m and R_m are subsets of X verifying the following conditions which simply impose that each variable is appearing once and only once left of the conditional sign in the decomposition:

1. Sets L_m are a partition of set X : $\cup_{m=0}^M [L_m] = X$ and $\forall i, j \leq M, i \neq j, L_i \cap L_j = \emptyset$
2. Any variable appearing left of the conditional sign previously appeared right: $R_0 = \emptyset$ and $R_m \subseteq \cup_{i=0}^{m-1} [L_i]$

^aThis definition is, in algebraic terms, equivalent to the definition of probabilistic factor graphs ([?]) and consequently a generalization of Bayesian nets ([33]).

Subjective probabilistic inference: Let us consider a partition of the set X of relevant variables in 3 subsets: S the set of searched variables, K the set of known variables and F the set of free variables. A subjective probabilistic inference is defined as the computation of the probability of $P(S | [K = k])$

To compute the probability distribution on the searched variables S knowing the known variables K we must marginalize out the variables F , the variables which are neither in the search variables S nor in the known variables, and normalize the result:

$$P([S = s] | [K = k]) = \frac{\sum_F [P([S = s], [K = k], F)]}{\sum_S \sum_F [P(S, [K = k], F)]} \quad (13)$$

This is the general formula for Bayesian inference. The involved computation is very simple as it supposes only to compute sums and quotients of probabilities. However, the exact computations is most of the time intractable as the number of operations grows exponentially with the number of elementary variables in F and S . The joint probability distribution may be replaced by the decomposition defined in the model:

$$P([S = s] | [K = k]) = \frac{\sum_F \left[\prod_{m=0}^M [P(L_m | R_m)] \right]_{[S=s][K=k]}}{\sum_S \sum_F \left[\prod_{m=0}^M [P(L_m | R_m)] \right]_{[K=k]}} \quad (14)$$

where we see that, now, the necessary computations suppose only product, sums and quotients of probabilities. The decomposition is a great help as the joint distribution is broken in smaller pieces of lower dimensionality. Rearranging the order in which the sums and products are done allows, most of the time, for drastic simplifications in the number of necessary computations (see [2], Chapter 14). After these simplification and given the chosen order, $P([S = s] | [K = k])$ can be computed by an arborescent structure (a calculus tree) of products, sums and ratios of positive quantities: an RFNC.

Finally, for any subjective probabilistic inference, it exists numerous calculus tree that can be mapped to an artificial biochemical cascade.

4. A simple example of biochemical cascade for phototaxis

Many unicellular algae, like *Chlamydomonas reinhardtii*, are able to do photosynthesis to produce the energy they need. Consequently, many of them are also able to detect and measure the quantity and eventually the rough direction of light in order to do phototactic or photophobic movements to get the adequate illumination (see Figure 7).

As an example of what was described before we propose in this section a very simple instance of a phototaxis model and its possible implementation as a theoretical biochemical cascade made of 4 elementary building blocks.

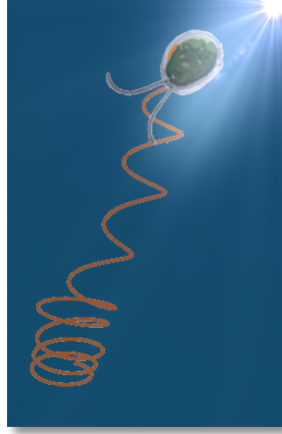


Figure 7: Chlamydomonas has an “eye spot” (the red dot on the figure) sensible to illumination and 2 flagella to swim toward or away from light. It swims following an helicoidal trajectory. Consequently, the eye spot scans different directions during a rotation of an alga. According to the successive light measurements coming from the eye spots, the algae either swim straight (synchronized motion of flagella) or makes random changes of direction (desynchronized motion of the flagella). This behavior, even very simple, appears to be very efficient to drive the algae toward the adequately illuminated places where their production of photosynthetic energy is optimal.

Let’s consider a model made of 3 binary variables:

1. L_1 a binary variable taking the value 1 if there is light in direction 1
2. L_2 a binary variable taking the value 1 if there is light in direction 2
3. G a binary variable taking the value 1 when the algae have to swim straight and 0 when it should change direction.

The considered decomposition of the joint probability distribution on these 3 variables is:

$$P(L_1, L_2, G) = P(L_1) P(L_2) P(G|L_1, L_2) \quad (15)$$

where $P(G|L_1, L_2)$ is defined as follow:

L_1	L_2	$P([G = 1] L_1, L_2)$
0	0	0
0	1	0
1	0	0
1	1	1

which specifies that the algae should go straight ($G = 1$) only when both light measurements are positive ($L_1 = 1, L_2 = 1$).

The phototaxis behavior, has to decide of going straight or not ($P(G)$) according to probabilistic evaluations of the enlightenment ($P(L_1), P(L_2)$), which is obtained by:

$$P(G) = \sum_{L_1, L_2} [P(L_1) P(L_2) P(G|L_1, L_2)] \quad (16)$$

This formula can be restated using the odds of the 3 variables defined by $O(X) = \frac{P(X=1)}{P(X=0)}$:

$$= \frac{O(G)}{P([G=0]|00)+P([G=0]|01)O(L_2)+P([G=0]|10)O(L_1)+P([G=0]|11)O(L_1)O(L_2)} \quad (17)$$

Replacing the terms $P(G|L_1, L_2)$ by their values, we finally obtain:

$$O(G) = \frac{O(L_1)O(L_2)}{1 + O(L_2) + O(L_1)} \quad (18)$$

Using the 3 building blocks described in Section 2.2.2, it is very easy to build the theoretical biochemical cascade that implement the calculus corresponding to Equation 18 (see Figure 8). The stationary concentrations of the messengers encode for the initial odds ($O(L_1)$ and $O(L_2)$), the intermediary results ($O(L_1)O(L_2)$, $O(L_1) + O(L_2)$ and $1 + O(L_1) + O(L_2)$) and the final result ($O(G)$).

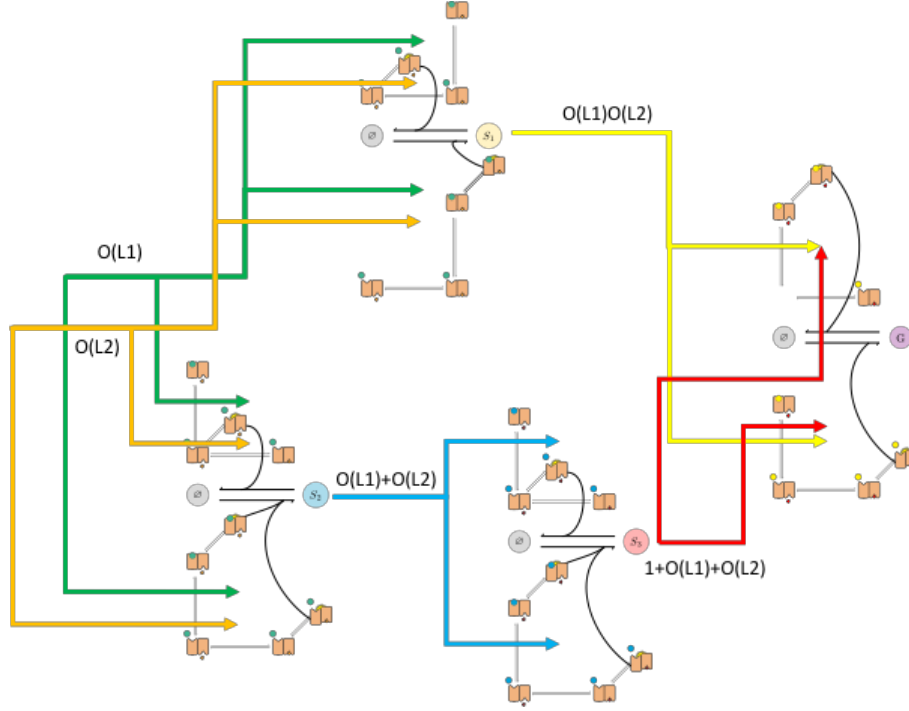


Figure 8: A 4 building blocks cascade to solve a phototaxis problem. The cascade takes as inputs 2 messengers with concentrations $O(L_1)$ (green) and $O(L_2)$ (orange). The top building block produces a secondary messenger S_1 (yellow) with stationary concentration $O(L_1)O(L_2)$. The bottom left building block produces a secondary messenger S_2 (blue) with stationary concentration $O(L_1) + O(L_2)$. The bottom middle building block produces a secondary messenger S_3 (red) with concentration $1 + O(L_1) + O(L_2)$. Finally, the right building block is activated by messengers S_1 and S_3 and produce as output the messenger G (purple) with concentration $O(G) = \frac{O(L_1)O(L_2)}{1+O(L_2)+O(L_1)}$.

5. Discussion

We proposed to look at an aspect of cell signaling and biochemistry from a new viewpoint, assuming that these processes may be seen as performing probabilistic inference.

This proposition is supported by the demonstration that any subjective probabilistic inference may be computed by an RFNC which in turned may be mapped to artificial biochemical cascade.

The main necessary hypotheses may be summarized as follows.

1. We consider a small volume (order of magnitude: $1\mu m^3$) of cell cytoplasm in which thermal diffusion ensures homogeneous concentrations of messengers at the considered time scale (in the range $1ms$ to $1s$).
2. We consider one or several populations of allosteric macromolecules with a fixed concentration but variable conformations.
3. We consider one or several messengers with a single conformation but varying concentrations.
4. We consider the conformational changes of the macromolecules, which control the concentrations of the messengers and reciprocally, the concentrations of the messengers, which control the conformational changes of the macromolecules.

Assuming these four hypotheses, we have demonstrated that descriptive models of biochemical systems might be seen as performing probabilistic inference of some subjective models. Although the validity of these four hypotheses remains to be discussed, the propositions made in this paper open new perspectives for future directions of study, for instance: can we propose subjective interpretations of descriptive models of other types of biochemical interactions? At the same time and space scale? At different time and space scales?

5.1. *Validity of the hypotheses?*

A critical issue for designing descriptive model is to specify the space and time range in which processes are analyzed.

In the spatial domain, molecular assemblies of nanometer size govern the behavior of organisms that are several meters long. In this paper, we have restrained our analysis to small compartments of a single cell, typically a portion of a dendrite or axon. The order of magnitude of the size of such a compartment is $1\mu m^3 = 10^{-18}m^3$.

Biological events range from about $10^{-12}s$ [20, 11] for the fastest observed conformational changes to millions of years for gene evolution. We have restrained our analysis to time windows of $1ms$ to $1s$, which is long enough to insure homogeneous concentrations of messengers in the considered compartments.

Our description of biochemical system is still too schematic for several reasons.

- The distinction between macromolecules and diffusible messengers is not sharp. Macromolecules also diffuse within membranes [40] and their spatial distribution, for instance, between cytoplasmic and nuclear compartments, is also controlled by specific biochemical mechanisms [38]. However, at the space and time scale we are considering, this mobility of macromolecules may be neglected as a first approximation.
- A number of macromolecules directly act on other macromolecules without intermediate messengers. A clear example in cell signaling is given by the interplay of kinases and phosphatases. This was also discarded from our study for the moment.
- Detailed models of biochemical processes should also take into account the particular geometry of the cell. This includes (3D) phenomena arising in homogeneous volumes (such as the concentration of diffusible messengers), (2D) phenomena arising on a membrane area (such as the distribution of channels), and (1D) phenomena arising mainly along a symmetry axis (such as the propagation of potential along dendrite or axon branches). At present, we have only considered homogeneous concentrations of messengers and fixed distributions of channels, and we have neglected the effect of membrane potentials.
- We have only considered biochemical systems at equilibrium. Clearly, the temporal evolution of concentrations and macromolecular configurations must be further developed, in particular to account for slow reaction and diffusion processes, and for the various roles of biochemical feedback pathways. These dynamic processes could be related to time-evolving probabilistic reasoning, for instance hidden Markov models and Bayesian filters. However, the wide diversity of time scales encountered in biological systems contrasts with the somewhat schematic and oversimplified view of time representation in the usual subjective models. In future work, promising ideas could be the development of a more complex temporal hierarchy, and a subtler view of the respective roles of memory and temporal reasoning in subjective models.

5.2. *Subjective interpretation of other biochemical interactions?*

Obviously, the above detailed hypotheses are too restrictive. Furthermore, in this work, we have only considered a few possible biochemical interactions among the huge variety of possible ones. An important task in the near future will be to relax these hypotheses and look for subjective models that could be associated with other kinds of biochemical interactions. Some instances of such perspectives are discussed in the sequel to this section.

5.2.1. At the same time and space scale

Macromolecules with more allosteric states:. The allosteric theory [30], initially developed to account for regulatory enzyme kinetics, postulated that proteins undergo fast, reversible transitions between a discrete number of conformational states. Transitions occur spontaneously, but some are favored by fixation of ligand to specific receptor sites. This model has been successfully applied to a large number of fundamental macromolecular assemblies, such as hemoglobin, ionic channels, and nuclear or membrane receptors (see [4] for a review).

The number of conformational states and the variety of controlled mechanisms for conformational changes can be relatively high. As an example, DARPP-32, a key macromolecule in the integration of dopamine and glutamate inputs to the striatal GABAergic neurons, exhibits four phosphorylation sites, thus 16 conformational states, and each phosphorylation is controlled by a different chemical messenger pathway [14]. Inactivation of rhodopsin in vertebrate photoreceptors involves up to 12 phosphorylation sites, which are all controlled by the intracellular calcium concentration. In [17] we described a first application of our approach to the vertebrate photo-transduction biochemical cascade. Augmenting the number of conformational states opens very exciting perspectives on the complexity of the computation that a single population of macromolecules could perform, but the corresponding subjective models are still to be proposed.

Macromolecules with several receptor sites for the same messenger:. Macromolecules with several receptor sites for the same messenger are very frequent in biochemistry. A number of allosteric macromolecules, including ionic channels, are composed of several subunits, and some of them are identical. The presence of a receptor site for a specific messenger on each subunit makes the whole macromolecule controlled by the second, third, or fourth power of the concentration. As a consequence, the catalytic activity is a highly nonlinear function of the messenger concentration, and may exhibit very sharp sensitivity.

In terms of subjective models, this means that similar observations, converted into likelihood ratios, are performed several times to infer the posterior distribution. This might be a simple and elegant way to enrich the computational complexity performed by macromolecules without requiring high dynamic ranges of messenger concentration. In the present work, we have assumed a simple proportional relationship between likelihood ratios and messenger concentrations. The presence of multiple receptor sites for the same messenger, and more generally the multimeric structure of some macromolecules can be interpreted as a nonlinear coding of the likelihood ratio, which could be better adapted to the biological constraints. For instance, a tenfold increase in messenger concentration could correspond to a likelihood ratio multiplied by 10^4 for a tetrameric receptor.

Allosteric changes governed by other events instead of chemical messengers:. Allosteric changes may be caused by other types of events besides chemical messengers such as electrical or mechanical ones. These events are not considered in the present model and should be studied in future.

Single-channel voltage clamp recordings [32, 35] have revealed several important characteristics of channels: (i) currents through isolated channels, and thus channel conductance, alternate between discrete values; (ii) transitions between current/conductance values are random brisk events; (iii) the transition probabilities can be modulated by pharmacological and biological agents (neurotransmitters, second messengers), ions (calcium), or membrane potentials. In agreement with the allosteric theory, the current descriptive model of ion channels [7, 25, 5] is that of a finite state Markov model, similar to the one we used in this paper. Some transitions depend on the presence of a specific messenger in the vicinity of receptor sites, either in the extracellular domain (ionotropic receptor-channels) or in the intracellular domain, where receptor sites are specific to second messengers or calcium transporters. In voltage-dependent channels, transition probabilities are controlled by the membrane potential.

Local cascades and feedbacks:. Metabotropic receptors are transmembrane macromolecular assemblies with a receptor site in the extracellular domain and an activatable site in the intracellular domain. Chemical binding of the neurotransmitter with the extracellular receptor site induces allosteric conformational change of the macromolecule, which activates the intracellular site (an activatable enzyme site such as protein kinase, protein phosphatase, or G-protein release). More generally, macromolecules can be activated by various events like mechanical strength, photoisomerization, pheromones, or odor detection. The intracellular activity results in the release of a primary messenger (*e.g.*, the G_α subunit in the G-protein-dependent signaling), which triggers the production or elimination of a diffusible second messenger (cyclic nucleotides, inositol triphosphate, \dots), which in turn acts on ionic channels.

In the complex molecular chain from the primary receptor to the set of ionic channels, several allosteric macromolecules intervene. Most of them have receptor sites for calcium, or are calcium transporters like calmodulin, thus allowing feedback regulation. As discussed above, the role of feedback should be understood in terms of the dynamics of the systems, including long-term adaptation.

5.2.2. At different time and space scales

Different dynamics to store information.: In the core of our model, we postulate that the existence of well-separated fast rates (10^4 to $10^5 s^{-1}$) and relatively slow rates (10 to $10^3 s^{-1}$) of biochemical reactions is fundamental. It allows the Markov processes of molecular collision and configuration changes generated by thermal agitation to converge to quasi-stationary states that approximate probabilistic inference of subjective models. We have not yet considered the very slow dynamics of some allosteric changes (like desensitization) or the diffusion of large molecules in membranes, among many other slow biochemical events. These mechanisms can clearly be used for accumulating and storing information over long periods, which is a key computational capacity for adaptation and learning.

The role of membrane potential at cell scale.: The overall effect of all ionic fluxes can be summed up in the membrane potential kinetics. Though it is rather unusual to include membrane potentials in the set of messengers, it seems appropriate because the kinetic equations of membrane potential are similar to those for chemical messenger concentrations. Moreover, the membrane potential controls macromolecule conformational transition in a similar way, although constrained to a particular, but important, class of macromolecules, namely the voltage-gated channels [3]. In turn, ionic channels change the membrane potential similarly to the way that activatable enzymes control chemical messenger concentration. Membrane potentials propagate much faster than messengers diffuse and can transmit the result of a given local computation to the whole cell. Consequently, including membrane potentials into our proposed framework would extend the space scale from a compartment to the whole cell.

Unicellular organisms.: At this molecular description level, our proposal applies not only to brain-controlled complex organisms and not only to small neuron networks, but also to unicellular organisms. Simple organisms like *Paramecium* or *Euglena gracilis* have limited numbers of sensors, and a greatly reduced repertoire of actions, but they must nevertheless adapt their behavior to an even more unpredictable environment. The efficiency of probabilistic reasoning with an incomplete model of the world applies equally to these simple organisms. Furthermore, the biochemical mechanisms that we propose for implementing probabilistic computation are already effective in controlling the behavior of eukaryotes. Among many other examples, it has been shown [18] that the photo-avoidance behavior of the micro-algae (*E. gracilis*) is mediated by concentration changes of cyclic adenosine monophosphate, a second messenger known to be involved in olfaction and many neuronal signaling pathways of multicellular animals.

Information transmission in multicellular organisms.: Excitable cells, particularly neurons, differentiate from other cells in complex multicellular organisms, from cnidarians to all bilaterians. These excitable cells provide a distant and discrete mode of messenger flux control: both chemical or ionic diffusion and passive electrical propagation become very ineffective at long distances. Note, however, that slow, but distant, signal propagation through active biochemical processes without action potentials has been recently discovered [13]. On the contrary, active regeneration of action potential thanks to voltage-gated channels allows the message to be transmitted unchanged at high speed along axonal branches up to the presynaptic terminals, where it is converted into chemical signals. Distant interactions between macromolecular assemblies by action potential propagation allow multicellular organisms to reach sizes and speeds far greater than the limit imposed by passive diffusion process. This constitutes an obvious gain for long-distance communication. However as opposed to membrane potential and messengers' concentrations which are graded and local signals, the action potentials are all-or-none signals. Therefore long distance communication is achieved at the cost of signal impoverishment. According to our view, fast-spike propagation must be completed by local and graded signal processing involving complex biochemical interactions that constitute a fundamental mechanism for probability computation.

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