What the *Escherichia Coli* Tells Neurons about Learning

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Abstract. The Escherichia coli is a bacterium that comfortingly lives in the human gut and one of the best known living organisms. The sensitivity of this cell to environmental changes is reflected in two kind of movements that can be observed in a swimming bacterium: "run" towards an attractant, for example food, and "tumbling", in which a new direction is chosen randomly for the next "run".

This simple bimodal behavior of the *E. coli* constitutes in itself a paradigm of adaptation in which roboticists and cognitive psychologists have found inspiration. We present a new approach to synaptic plasticity in the nervous system by scrutinizing *Escherichia coli*'s motility and the signaling pathways that mediate its adaptive behavior. The formidable knowledge achieved in the last decade on bacterial chemotaxis, serve as the basis for a theory of a simple form of learning called habituation, that is applicable to biological and other systems. In this paper we try to establish a new framework that helps to explain what signals mean to the organisms, how these signals are integrated in patterns of behavior, and how they are sustained by an internal model of the world. The concepts of adaptation, synaptic plasticity and learning will be revisited within a new perspective, providing a quantitative basis for the understanding of how brains cope with a changing environment.

Keywords: chemotaxis, integral control, internal model principle, Escherichia coli, homeostatic synaptic plasticity, habituation learning, perfect adaptation.

1 Introduction

We are living times of dramatic technological improvements. High throughput techniques have produced an extraordinary data abundance that is now being complemented with new in vivo techniques.

Construction of complex cellular models, including detailed descriptions at molecular scale, is an ongoing process moving at a strong pace. The challenge is however, not merely technological, but conceptual [26]. The behavior of a biological system can be studied at multiple levels, in deciding the level of detail that each component is described, we are making a strong commitment that should not be neglected.

The question we are addressing here is, How much knowledge of itself the *E. coli* or a neuron for that matter, needs in order to adapt to a changing environment? This epistemic problem is tackled twofold. First, we need to explore what is the capability

of the *E. coli* of making new models of itself and the medium in which it moves; and second, how can we extrapolate the understanding on the organizational principles of the *E. coli* to the central nervous system of a mammal.

It must be said that by "knowledge of itself" we do not intend to tangle ourselves with speculative discussions about the introspective capacity of a single cell, rather our approach is in line with Fiorillo's neurocentric view, in which the information a neuron has about its world, may be quantified through biophysical parameters such as membrane potential [9], [10].

The paper is structured as follows. Section 2 emphasizes the necessity of realistic models grounded on empirical basis. Section 3 provides a basic understanding of *E. coli* adaptability at a molecular level. Behavioral aspects of the bacterium, and underlying mechanisms, such as homeostasis are sketched. Section 4 investigates adaptation in the *E. coli* within a quantitative framework, based on the computation of key properties like perfect adaptation. Furthermore, we introduce the idea that organisms are representational devices that subserve internal representations of the world [22].

The last part of the paper is devoted to expand concepts such as adaptation or internal model[15], to a more complex domain than bacterial chemotaxis i.e. nerve cells. Section 5 addresses, in a non speculative way, how much knowledge of itself has a biological system, by providing working definitions of knowledge as an internal model. In section 6 we borrow tools from Control Engineering. The Internal Model Principle, and in particular Integral Control, gives a mathematical basis for the study of *E. coli* adaptation, broading this result to synaptic plasticity in section 7. We conclude with conclusions and future works in 8.

2 Towards a New Approach in Modeling Adaptation

It is important to note that technical and biological systems differ in a fundamental way, while the former are built for a specific purpose the last is the product of thousand of years of evolution. The engineer is not (or should not be) a tinkerer [13], therefore technical systems, contrary to biological ones, are predominately linear, and this is because the mathematical tools accessible to the engineer are essentially linear. Furthermore, biological control systems may lack typical features present in engineering systems, such as the reference input, the error detector or the single input-single output architecture that makes amenable linear techniques like Laplace transforms [18].

E. coli is one of the simplest living things, and yet a complex system in the sense given by Trimmer in [24], where simple systems are formulated by a linear equation of second order or less, with constant coefficients. Those systems that do not meet these constraints are complex systems.

It is possible to model the movement of the *E. coli* as a control mechanism which drives the bacterium to one of the two possible set points or equilibria i.e. run and tumble. This approach subscribes a view of *E. coli* behavior as passively responding to a series of stimuli introduced in ideal laboratory conditions. The problem with this modeling strategy is that it does not inform us about the lengths of the run movements or the frequency of the tumblings.

A more realistic description of the bacterium should provide an analysis of the transients between the aforementioned run and tumble set points shown in figure 2. We need

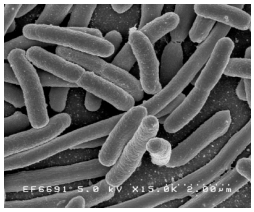


Fig. 1. *E. coli* microphotograph.

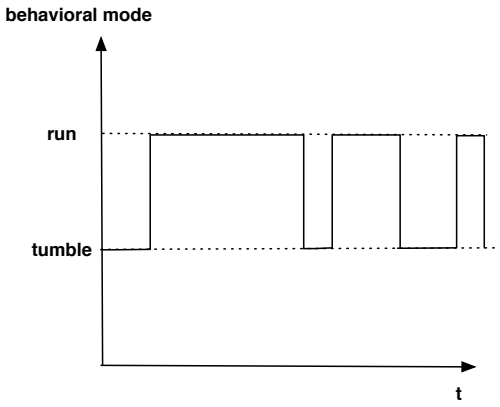


Fig. 2. The *E. coli* motility modeled as a system that alternates in its two possible states, *run mode* and *tumble* in the vertical axis, along time in the horizontal axis.

models able to explain how the extracellular signals are bounded to specific receptors in the cell's membrane and afterwards computed in the cellular milieu. The metabolic well-being of the cell, that is, its internal state, needs to be incorporated into our model.

In summary, we can say that in order to understand how the *E. coli*'s adaptation works, we need to acknowledge how the bacterium extracts information of the world, to encode it as signals that organize the system in a particular internal state.

3 *E. coli* Chemotaxis

In this section, we give a succinct description of the sensory and signaling machinery that direct the *E. coli* motion, for a more detailed account see [3], [21]. It may be worthy to start with a terminological remark. Molecular biologists use the term *pathway*, like in signaling pathway, as an abstraction to refer to a sequence of events involved in a specific process inside the cell, carried out by a network of molecules, mostly proteins, whose topology and dynamics have been explicitly described. Thus the *E. coli* chemosensory pathway is the basis of bacterial chemotaxis.

Pathways, in reality, are systems with complex network dynamics. Thus, the term pathway may be puzzling for the non specialist, because it entails a rather deterministic and linear vision, which is in direct opposition with the stochastic and non-linear nature of biochemical networks. Keeping this caveat in mind, we introduce the chemotaxis pathway which is one of the best well-known signaling pathways.

Bacterial chemotaxis is the movement towards or away from regions with concentrations of chemicals. For example, the bacterium *E. coli* swims toward substances such as amino acids (serine and aspartic acid), sugars (maltose, ribose, galactose, glucose), and away from potentially noxious chemicals, such as alcohols and fatty acids [4]. The chemotactic ability of the *E. coli* relies in its capacity to sense the rate of change of concentration of certain chemicals in its vicinity.

It is interesting to note that chemotaxis is an universal property of bacteria motility, which does not provide any evolutionary advantage per se, unless the movement is biased to produce a physiological response that is suited to a particular environment [27]. In order to acquire a real understanding of how the bacterium responds to a changing environment, we must capitalize the abundant empirical knowledge at single-cell level and, if possible, build predictive mathematical models grounded on quantitative data. The *E. coli* responds to the environment by a composition of two kinds of movements, *running* towards an attractant, and *tumbling*, in which a new direction is chosen randomly for the next running mode. In homogeneous environments, tumble events occur every second, so the *E. coli* moves randomly, while in environments with a non homogeneous concentration of chemicals, the frequency of tumbling is a function of the sensed gradients of attractants and repellents. There are two key mechanisms that underlie the movement of the bacterium; on the one hand, the binding ligand-receptor, and on the other hand, the homeostatic process by which the phosphorization of *CheA*[1] protein goes back to the pre-stimulus level. Let us see this in detail.

3.1 The Binding Ligand-Receptor

E. coli has five chemoreceptors, four of them are methyl-accepting proteins[2] (MCP) and the fifth is MCP-like protein. The receptors, in order to be effective, need to connect the cell with the environment, so the receptors are located through the membrane, having a periplasmatic section exposed to the environment, a thin section in the membrane, and a long tail immersed in the cytoplasm of the cell.

Ligands e.g: maltose, bind to the periplasmatic site, that is, the part of the receptor that is outside the cell. It might be said that the binding is not always 1:1 i.e. one kind of ligand to one kind of receptor, for example in the *E. coli*, one MCP (MCP *Tar*) can bind to two distinct ligands.

MCP receptors do not act in isolation but they form clusters. The clustering depends on the cytoplasmic proteins *CheA* and *CheB*. The clustering of MCP seems to play an important role in one of the most remarkable characteristics of the chemotaxis pathway, its high sensitivity: chemoreceptors are able to detect a change in a few molecules in simultaneity with a background concentration in the environment varying abruptly [23]. The binding of a ligand by a MCP cluster may affect other neighboring unbound receptors, thus the binding recognition process ligand-receptor, can not be understood as an isolated system with two matching parts, the ligand and the receptor [6].

[1] *Che* stands for chemotaxis.

[2] A methyl groups is a $-CH_3$ group.

The number of methyl groups ($-CH_3$) in the receptor cluster (Figure 3), informs the cell about the perturbations, that is to say, the number of methyl groups is a measure of the rate of change of attractants or repellents outside the bacterium. Methylation acts as a compensator of the external signals entering to the cell. Dennis Bray [5] suggests that the methyl groups works as a memory that allows to trace the recent conditions of the environment in terms of attracting or repulsive substances. The more attractants are sensed the more likely is to have methyl groups carried by the receptor in the cell cytoplasm. There are 8 slots in the receptor for methyl groups, the number increases with the attractant concentration, so 0 methyl groups may indicate a response to a repellent.

3.2 Homeostasis in the *E. coli*

The other interesting phenomenon in bacterium motility is homeostasis by which the rate of phosphorilation in *CheA*, returns to the pre-stimulus state. As *CheB* is also phosphorylated by *CheA-P*, an increase in demethylation of the MCPs is produced, reducing *CheA* auto-phosphorization (even for low concentration of attractants). As a consequence, the rate of auto-phosphorization, together with the rate of direction changing in the motor flagella also decreases, returns to pre-stimulus level (Figure 3).

3.3 The Tumbling Mode

The tumbling mode is triggered by a decrease in the concentration of attractants, which produces a reduction in attractant binding to the MCPs, that in turn, elicits an increase in the auto-phosphorization rate of *CheA* protein, now called *CheA-P*. The phosphates are then transferred to the *CheY* protein, which regulates the way in which the bacterial motors turn. The phosphorylated form of *CheY*, *CheY-P*, binds to the flagellar motor, switching the rotation motor to clockwise so as to cause the bacterium to tumble.

3.4 The Running Mode

The run mode is symmetric to the tumble mode. As the concentration of attractants increase, the *CheA* auto-phosphorization is inhibited, which reduces the concentration of *CheY-P*, as a result, the frequency of motor switching is reduced. The bacterium swims towards a favorable region in the direction of a positive gradient, by rotating counterclockwise all the motor flagella.

In synthesis, the strategy followed by the *E. coli* may be easily stated as "if things are getting better do not change what you are doing, else change direction". It is interesting to note that *E. coli*'s behavior is fundamentally stochastic. The rationale for this must be found in the frequency of the tumbles i.e. the probability of a tumble decreases with the presence of chemoattractants, thus the bacterium moves in a favorable direction. When the environment is homogeneous, no privilege movement direction is observed in the *E. coli* since no beneficial nor detrimental chemical exists in the vicinity of the cell. Thus *E. coli*'s tumbling is produced by frequent aleatory changes in the direction of movement.

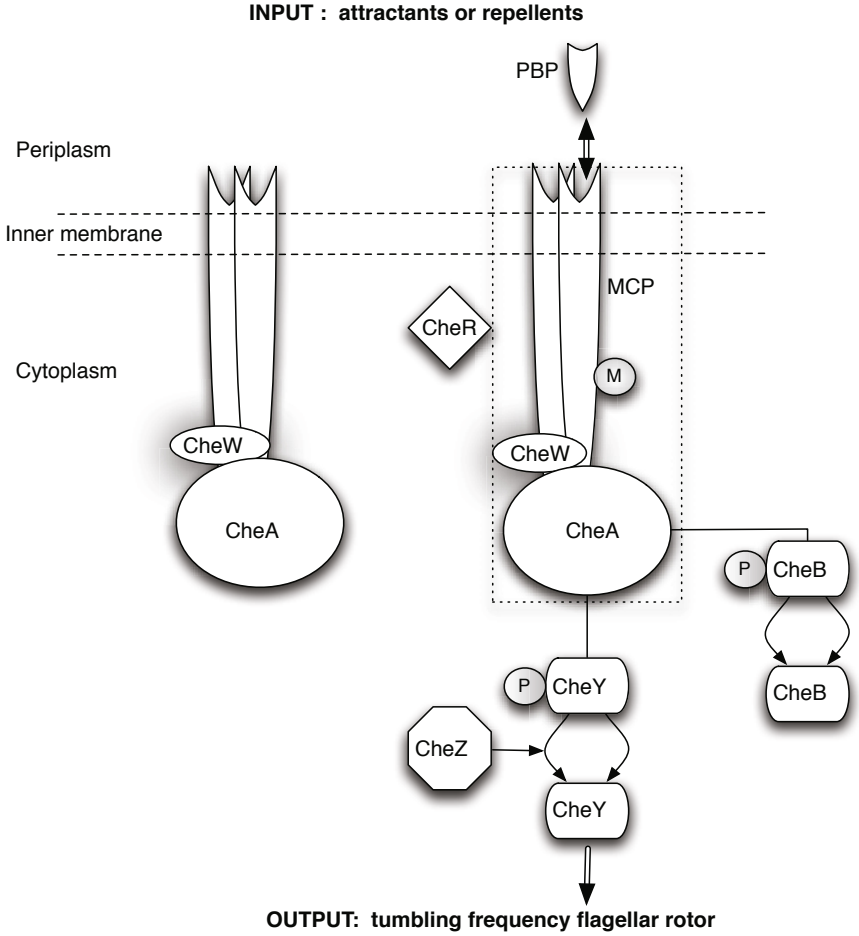


Fig. 3. Model system of *E. coli* chemotaxis. The figure shows two methyl-accepting proteins (MCP), one of which is interacting with one periplasmic binding protein (PBP), phosphoryl groups P, methyl groups M ($-CH_3$) and chemotaxis proteins CheA, CheB, CheR, CheW, CheY and CheZ. The receptor (dashed box) which is the system modeled in [2], is a protein complex composed of MCP, CheA and CheW. The kinetics inside the receptor is modeled by a set of coupled differential equations. The input is the ligand concentration and the output is the activity in the receptor, which is finally translated into bacterial movement through changes in the tumbling frequency in the flagellar rotor. A decrease in attractant concentration induces trans-autophosphorylation of CheA, which phosphorylates CheY, *CheY-P*, to bind to the flagellar motor to bring about a change in direction. Phosphorylated CheA also phosphorylates CheB which competes with CheR to control the number of methyl groups in the MCPs. As concentration of attractants increase, the *CheA* auto-phosphorization is inhibited, which together with phosphatase CheZ, reduce the concentration of *CheY-P*, as a result, the frequency of motor switching is reduced.

4 Adaptation in *E. coli*

Adaptation means different things depending on the context. For an ecologist, adaptation means the possession of forms and functions that help to explain how well an organism does what it does in a changing environment. In this paper, we are interested on a study of adaptation that does not rely on *survival* as the sole criteria of fitness. We need to provide a quantitative criteria of fitness, different to the anthropomorphic vision that assumes the idea of the system as a prosecutor of an "optimal fit" which has been established a priori by an external observer. Note the ressemblance with Expected Utility Theory in economics [20].

Definition 1. *Adaptation is the adjustment of a set of parameter values that permits continuing stability in the face of environmental changes.*

Adaptation in the *E. coli* is understood in relation to adaptation of a stimulus e.g. a chemoattractant, where methylation works as a force that compensates for the change in the tumbling frequency induced by the stimulus.

The addition of attractants causes a transient decrease in the activity of the cell, as a consequence, the methylation of receptors increase to compensate this activity reduction. It might be noted that methylation is a reversible process, therefore a removal of attractants will cause an increase in system activity, and consequently methylation will compensate for this effect.

Alon et al. [1] and Barkai and Leibler [2] have developed a quantified theory of bacterial adaptation based on the computation of a set of key parameters i.e. steady state tumbling frequency, perfect adaptation degree and adaptation time. When the membrane receptor is perturbed by an external ligand, methylation is triggered to retrieve the previous receptor activity value. This capacity of the system to compensate for external stimulation, in order to be ready for the next stimulus is adaptation at work.

Formally, the chemotactic behavior of the bacterium is adaptive when the output is equal to the pre stimulus state:

$$A(\delta) = A^{st}$$

where $A(\delta)$ is the activity function of the stimulus δ, and A^{st} is the steady state activity. For example, in a model of the *E. coli* chemotaxis, the output is the tumbling frequency and the input is the concentration of the ligand. We say that the bacterium has adapted in the face of a perturbation or external input, when the tumbling frequency returns to the pre stimulus value. Hence, $A(\delta) = A^{st}$, because the activity function A is independent of the external input δ.

4.1 Perfect Adaptation

By sensing and processing certain chemicals in the environment, the *E. coli* changes direction and position. This seemingly intentional movement is in reality a process of adaptation, that strives to maintain certain physiological conditions within acceptable limits. Hence, bacterium's adaptation pertains mainly to the homeostatic mechanisms by which the effect of the stimulus is gradually not taken into account despite is presence. The adaptation or homeostatic property in the *E. coli* refers to the adjustment of

an output (tumbling frequency) to an external stimulus (the ligand, an attractant or a repellent).

Adaptation can be measured by its precision, which is ideally 1 (perfect adaptation).

$$precision = \frac{unstimulated\ tumbling\ frequency}{stimulated\ tumbling\ frequency}$$

Hence, perfect adaptation is a precise return to the activity level existing before the stimulus.

Terminology again may be confusing. For biologists, perfect adaptation occurs when the value of the steady state activity is independent of the ligand concentration. In dynamical systems theory, for a given linear system with a state vector state $q = (q_1, q_1, \ldots, q_n)$, an external stimulus u and output y, the equations of its dynamics are given by:

$$\begin{aligned} \frac{dq_1}{dt} &= A_{11}q_1 + \ldots + A_{1n}q_n + b_1u \\ . &= .. \\ \frac{dq_n}{dt} &= A_{n1}q_1 + \ldots + A_{nn}q_n + b_nu \end{aligned}$$

This system has perfect adaptation when y is independent of the external stimulus u at steady state:

$$y = c_1q_1 + \ldots + c_nq_n$$

4.2 Internal Models of the *E. coli*

Two sorts of mathematical models have been produced to model the adaptation property in the *E. coli*: models based on fine-tuning of parameters[16], and models of adaptation as an intrinsic property of the network[1]. While these two kinds models differ in the approach; both share a very fundamental characteristic, the internal structure of the system i.e. network of protein complexes, is precisely known.

However, the mere assumption of a wise parametric adjusting does not guarantee that the prediction of future states of the system is attained. This is mainly because in an unpredictable environment, the structure is not always valid; as a matter of fact, it may be drastically modified by the environment. This limitation in biological systems modeling becomes conspicuous with the use of metaphors.

For example, the key-and-lock metaphor still prevails to explain the selective binding between an extracellular molecule i.e. ligand, and the receptor site in a cell's membrane which targets the ligand specifically. Biologists call to this matching binding recognition.

We must acknowledge that these are toy models that make assumptions that are not completely realistic. If we want to build models as realistic as possible, we should account for the individual "character" of genetically identical cells. Furthermore, non linear characteristics, such as the crosstalk between receptors or the interaction between chemotactic and other signal systems, would introduce undesirable effects related to non computability.

But it is indeed possible and advisable to understand how the *E. coli* behaves and adapts, without being in possession of a complete description of the organism. This may be achieved by investigating which are the organizational principles that our model implements.

For it to be an engineering biology (or synthetic biology as vogue dictates today), it is necessary to be able to study the environment as signals that are mapped onto the organism's receptors, configuring a network where information is efficiently integrated and transmitted.

It is extremely important to emphasize that the *E. coli* is a representational device that subserves the formation of internal representation of the world through networks of proteins, notably *CheA* which informs the concentration of attractants in the neighboring of the cell, and *CheP*, which instructs the movement of the cell. Thus, the study of *E. coli* chemotaxis provides a solid step in this direction, because it is possible to map the concentration of attractants outside the cell onto the concentration of key signaling molecules such as *CheA*, *CheP* or *CheY* inside the cell.

5 How Much Knowledge of Itself Has a Biological System?

Before in this paper, in section 4.2, we addressed the important issue of how much knowledge of itself possesses the *E. coli*. According to Bray, [5], the internal representation of the bacterium is encoded in its networks of proteins.

Since our ultimate concern is to set the basis for a general theory of adaptation and learning, it is pertient to provide some working definitions of key concepts, such as knowledge and internal representation. Following Dudai in [8]:

Definition 2. *Knowledge is structured bodies of information that the* organism *has about the* world*, and capable of setting the organism's reactions to the* world*.*

It is important to precise that in this definition, *world* is both the environment and the internal state of the *organism*.

Definition 3. *Internal representation is a version of the world encoded in biological basis, typically a neural system. Internal representations are constituent of knowledge, they influence in the organism's behavior, and therefore are able to change the* world*.*

At least at conceptual level, it is easy to draw similarities in the way the *E. coli* and nerve cells adapt and process information. Both systems have internal models of their surrounding, built from networks of protein molecules. What is still to be shown is the precise way in which that connection can be materialized in a common framework. This will be discussed in section 6.

In order to understand the representational properties of neurons we need to unravel how they transduce, compute and transmit information. Neurons receive information from other neurons and/or the environment, integrate this information, and transmit it to other neurons or effector cells, for example in a muscle. Neurons signal to each other through specialized junctions called synapses.

Two kind of signals cohabit in neuronal information processing, electrical signals and chemical signals. Electrical signals are measured by the membrane potential produced by ionic currents across the membrane. The neuron's membrane receptors are

gated ion channels. Based on the gating mechanisms, ion channels can be classified in voltage-gated or chemically-gated channels.

Local potential is a graded electrical signal that propagates passively in an attenuated way. Depending on its neuronal input, local potentials are called receptor potential or synaptic potential. The former is a local potential generated in sensory neurons and the last is generated in synapses. Local potentials are integrated by the cell, and when the summation depolarizes the neuron's membrane over a threshold, an action potential is elicited. Contrary to local potential, action potential is all-or-none signal, transmitted in a unattenuated way and maintained by voltage gated channels. The terms neural fire and neural spike mean both that the neuron generated an action potential.

An action potential conveys information as follows: it enters into a presynaptic terminal of a chemical synapse generating a release of neurotransmitters, which invade the synaptic cleft and bind to specific receptors in the postsynaptic terminal, which elicit a synaptic potential that eventually may trigger an action potential. Thus, a chemical synapse can be seen as a signal transduction system from chemical to electrical signals.

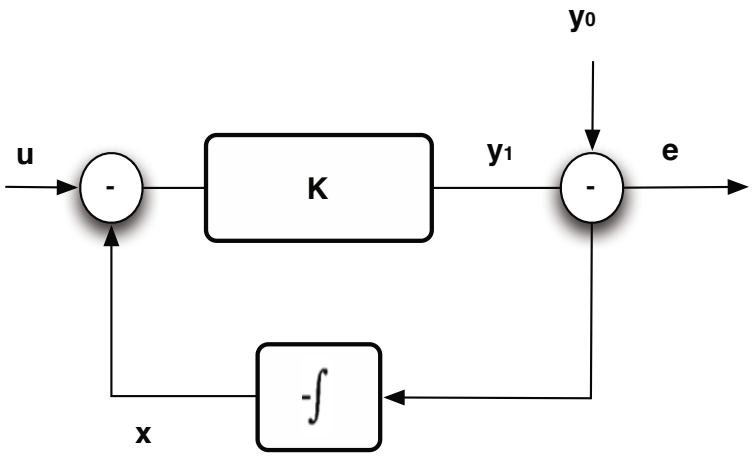
6 The Internal Model Principle

The aforementioned work of Barkai et al. [2] and Alon et al.[1], stated the robustness of perfect adaptation in bacterial chemotaxis. Yi et al.[28] generalized that result demonstrating that Barakai and Alon's model is a particular case of integral feedback control.

Integral control (IC) is used ubiquitously in engineering systems, ranging from simple thermostats, to the control of speed, altitude and heading in sophisticated airplanes. IC is a particular case of the Internal Model Principle (IMP) proposed by Francis and Wonham in 1976 [11]. IMP establishes that for asymptotic tracking of a signal, the controller must contain a model of that signal. This model of the exogenous input is called an internal model.

The *E. coli* adaptation is properly understood under the Internal Model Principle. Figure 4 shows a feedback loop that successfully implements a zero tracking error for a constant input. The integral control action is in the integral of the error that is feed back into the system. The input stimulus u is the concentration of chemoattractant, the output y is the concentration of active receptor complex. The reference signal y_0 is the pre-stimulus concentration of active receptor complex. The error is given by the difference between the actual output y_1 and the reference value, $e = y_1 - y_0$.

At steady state we have $e = 0$ for all input u. Thus, at steady state the *E. coli* activity i.e. tumbling frequency, is independent of the input i.e. ligand concentration. Therefore, the perfect adaptation is achieved when we have a zero tracking error in integral control action, that is to say, the output is independent of the input level in steady state. Feedback control theory is pertinent in the biological context if we acknowledge that "the physiology of biological systems can be reduced almost entirely to their homeostasis [12]". Homeostasis, the maintenance of constant physiological conditions, can not be fully understood without control system theory. The constancy of the internal state is achieved by negative feedback, and the internal state of the system is a representation of the *world* at a particular instant.



$$x(t) = \int_0^t e(t)dt, then$$
$$\dot{x} = e\,, where$$
$$e = y_1 - y_0\,, \; being\; y_0\; constant$$

Fig. 4. At steady state $\dot{x} = e = 0$ for all input u. In the *E. coli* case this means that the tumbling frequency of the bacterium is independent of the sensed attractants in its surroundings. In habituation learning in sensory neurons, the membrane potential is independent of the concentration of glutamate. For the *E coli*, the control signal u is the concentration of attractants in the bacterium's surrounding, y_1 is the tumbling frequency, y_0 is the tumbling frequency previous pre-stimulus and e is the difference between the actual tumbling frequency and the desired one. In habituation learning, u is concentration of glutamate in the synaptic cleft prompted to be binded in the membrane's receptors, y_1 is the membrane potential V_m, y_0 is the membrane potential pre-stimulus and e is the difference between the actual membrane potential and the desired one, y_0.

By no means should be this result undervalued or enclosed for the particular case of the *E. coli*. Integral control is both a necessary and sufficient condition for robust tracking of a specific steady-state value. One of the rationale of this paper is to bring this important result into physiological systems more complex than bacteria. In particular, we use it for modeling habituation learning in the nervous system.

7 Habituation Learning

Thanks to Kandel's work in the Aplysia, a mollusc with about 400 neurons, some of them visible to the naked eye, it is possible to distinguish three kinds of learning in this animal: habituation, sensitization and classical conditioning.

Habituation is the decrease in the behavioral response for a stimulus when the organism is exposed repeatedly to the same stimulus. At a cellular level, habituation leads to a reduction in effectiveness of synaptic transmission by sensory neurons.

Sensitization is characterized by an increase in the response when the animal is exposed to continual harmful stimulus, as a result, the animal learns to respond more vigorously to the coming harmful and also harmless stimulations.

Put in behavioral terms, both habituation and sensitization are an enhancement of reflex responses. Habituation tends to an unique equilibrium state of non response, while sensitization is a more complex behavior because it produces responses that do not converge to an equilibrium point. We focus here on the most basic form of implicit learning i.e. habituation.

In habituation learning, the organism learns to ignore a repetition of stimulus that is harmless. The effectiveness of synaptic transmission by sensory neurons that perceive the stimulus, is reduced by lowering the release of glutamate neurotransmitters. Thus, habitation is caused by a reduction in the release of glutamate from presynaptic neurons. It might be remarked that sensitivity of receptors in the postsynaptic terminal is not modified with habituation [14], which relies on glutamate concentration at the postsynaptic gates.

Figure 4 can be interpreted as the integral control scheme for habituation learning, which is the simplest type of implicit learning. The stimulus u is given by the synaptic input and the output is the membrane potential V_m. In the *E. coli* case, the internal model of the external signal ligand is the chemoattractant concentration; while in the neural case, the internal model is the concentration of glutamate that binds with specific receptors, eliciting the depolarization of the cell. Thus, depolarization is a deviation from the neuron's resting membrane potential towards its threshold potential.

The membrane potential at steady state V_m^{st} is independent of the input signal u (glutamate concentration), this result can be obtained because the neuron has a replicated model of the external signal, glutamate concentration. We say that the habituation learning capacity found in neurons is adaptive when

$$V_m^{st} = V_m$$

7.1 Homeostatic Synaptic Plasticity

Although all living cells have a difference of voltage across the membrane, in nerve cells, the membrane potential acts as an integrator of the neuronal input i.e. local potential. Synaptic potential depends on the release of neurotransmitters, for example glutamate in sensory neurons.

Plasticity is an experience-dependent modification of neuronal properties such as synaptic strength. It is widely believed that plasticity is at the core of learning and memory. Learning is a word with many different interpretations as it conveys a complex phenomenon that encompasses multiple of levels of analysis.

The neuron's stimulus is given by glutamate molecules that bind the membrane's receptor depolarizing the neuron. The concentration of glutamate constitutes an internal representation of the external stimulus. The output is the membrane potential generated by the integration of information in the neuron. The view of the brain as a decision making device is typically related with Helmholtz's motto "the brain is an inferential

machine". In the beginnings of modern neurobiology, Sherrington perceived integration as the quintessential action of nervous system, which values consequences of different types of information to choose a proper response [19].

Homeostatic synaptic plasticity is a relatively young area of research that is dedicated to unveil the mechanisms that allow neurons and assemblies of neurons, to maintain a stable way of functioning in the face of perturbations and changes in synaptic strength [7],[17].

As it may be expected, homeostatic synaptic plasticity is sustained by negative feedback action that compensate for activity-dependent changes in synaptic strength through, for example, learning.

Habituation learning is indeed a form of homeostatic plasticity. For an extended review on the typology homeostatic plasticity see [25]. It is important to point out that given a change of synaptic properties, the identification of the plasticity mechanisms that underlie such modification are not straightforward. In summary, we propose here the internal model principle implemented in an integral control as the plasticity mechanism for the simplest form of implicit learning, habituation. A quantitative theory of learning and memory is a long way goal (Figure 5). More complex forms of learning such as explicit learning would require hierarchical structures of control that still need to be elucidated. However, the formulation of a common theoretical basis for adaptation in prokaryotic cells and plasticity in the neuronal system represents a solid milestone in this direction.

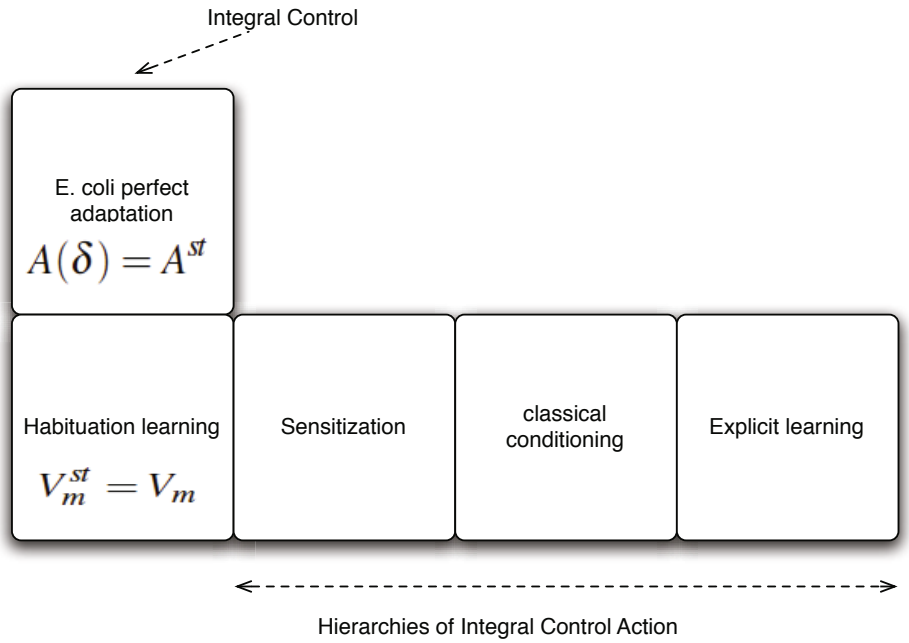


Fig. 5. Both *E. coli* and habituation learning can be modeled using Integral control. For more complex types of memory, the Integral Model Principle does not directly apply, perturbations are not necessarily constant control signals, though it is valid in the homeostasic mechanisms that characterized *E. coli* adaptation and habituation learning in neurons.

8 Discussion

Here we present, for the first time, an application of the Internal Model Principle used in control engineering to habituation learning in neuronal systems. By focusing on the domain of bacterial chemotaxis, we intend to translate quantitative models that are relevant in the domain of synaptic plasticity. We do this by capturing the general principles that apply to both domains. Our approach -i.e. going small in order to escalate to more complex domains through the formulation of general principles expressed in quantitative terms- is similar to Sidney Brenner's *middle-out* alternative to the customary rhetoric of bottom-up versus top-down.

Integral feedback control has been postulated as the strategy by which bacterial chemotaxis achieves robust adaptation, and in a more general way, underlies homeostatic mechanisms [28]. The integral control is one of the simplest controllers defined under the Internal Model Principle. We demonstrate that the IMP applies to habituation learning in neuronal systems. The membrane potential of a neuron integrates the world's stimuli received by the neuron through its ion channels. The knowledge that the neuron has of itself is gathered in the membrane voltage.

The control strategy proposed here has as regulated variable, the error, expressed as the neuron's output (membrane potential) *minus* the reference input (pre stimulus membrane potential), and as input the glutamate concentration. By feeding back into the system the time integral of the error which contains an internal model of the external stimuli, we are able to provide mathematical formulation of the homeostatic plasticity that mediates in habituation.

We are cognizant that the complexity of the brain will require of more powerful mathematical tools than those used here, to address other forms learning, like conditional learning or explicit learning. Nevertheless, this approach provides a quantitative framework that may open new and relevant insights for researchers in learning and memory.

Both adaptation in the *E. coli* and learning in neuronal systems are studied here as experience-dependent mechanisms of generation and modification of internal representations. We expect that important concepts in either technological and natural systems, such as adaptation or learning, which are used with multifarious connotations, will benefit from the quantitative stance developed here.

What is needed now is to design the tools and fabricate the concepts that account for the process of adaptation itself, that is, from the point of view of the organism.

References

1. Alon, U., Surette, M.G., Barkai, N., Leibler, S.: Robustness in bacterial chemotaxis. Nature 397(6715), 168–171 (1999)
2. Barkai, N., Leibler, S.: Robustness in simple biochemical networks. Nature 387(6636), 913–917 (1997)
3. Berg, H.C.: E. coli in Motion. Springer, New York (2004)
4. Blair, D.F.: How bacteria sense and swim. Annual Review of Microbiology 49(1), 489–520 (1995)
5. Bray, D.: Wetware: A Computer in Every Living Cell. Yale University Press (2009)

6. Bray, D., Levin, M.D., Morton-Firth, C.J.: Receptor clustering as a cellular mechanism to control sensitivity. Nature 393(6680), 85–88 (1998)
7. Davis, G.W.: Homeostatic control of neural activity: from phenomenology to molecular design. Annual Review of Neuroscience 29, 307–323 (2006)
8. Dudai, Y.: The Neurobiology of Memory: Concepts, Findings, Trends, 1st edn. Oxford University Press, USA (1989)
9. Fiorillo, C.D.: Towards a general theory of neural computation based on prediction by single neurons. PLoS ONE 3(10), e3298 (2008)
10. Fiorillo, C.D.: Towards a general theory of neural computation based on prediction by single neurons. In: Simeonov, P.L., Smith, L.S., Ehresmann, A.C. (eds.) Integral Biomathics: Tracing the Road to Reality. Springer, Heidelberg (2011)
11. Francis, B.A., Wonham, W.M.: The internal model principle of control theory. Automatica 12, 457–465 (1976)
12. Friston, K.: The free-energy principle: a unified brain theory? Nature Reviews Neuroscience 11, 127–138 (2010)
13. Jacob, F.: Evolution and tinkering. Science 196(4295), 1161–1166 (1977)
14. Kandel, E.R., Schwatz, J., Jessell, T.M.: Principles of Neural Science. McGraw-Hill, New York (2000)
15. Kawato, M.: Internal models for motor control and trajectory planning. Current Opinion in Neurobiology 9(6), 718–727 (1999)
16. Knox, B., Devreotes, P., Goldbeter, A., Segel, L.: A molecular mechanism for sensory adaptation based on ligand-induced receptor modification. Proc. Natl. Acad. Sci. 83, 2345–2349 (1986)
17. Marder, E., Goaillard, J.-M.: Variability, compensation and homeostasis in neuron and network function. Nat. Rev. Neurosci. 7(7), 563–574 (2006)
18. Milhorn, H.T.: The Application of Control Theory to Physiological systems. W.B. Saunders Company, Philadelphia (1966)
19. Molnar, Z., Brown, R.E.: Insights into the life and work of sir charles sherrington. Nature Reviews. Neuroscience 11(6), 429–436 (2010)
20. Morgenstern, O., von Neumann, J.: Theory of Games and Economic Behavior, 3rd edn. Princeton University Press (1980)
21. Neidhardt, F.C., et al.: Escherichia Coli and Salmonella Typhimurium: Vols 1-2: Cellular and Molecular Biology, 2 volume set edn. American Society for Microbiology (1987)
22. Sanz, R., López, I., Rodríguez, M., Hernández, C.: Principles for consciousness in integrated cognitive control. Neural Networks: The Official Journal of the International Neural Network Society 20(9), 938–946 (2007)
23. Sourjik, V., Berg, H.C.: Receptor sensitivity in bacterial chemotaxis. Proceedings of the National Academy of Sciences of the United States of America 99(1), 123–127 (2002)
24. Trimmer, J.D.: Response of physical systems. John Wiley & Sons Inc. (1956)
25. Turrigiano, G.G., Nelson, S.B.: Homeostatic plasticity in the developing nervous system. Nat. Rev. Neurosci. 5(2), 97–107 (2004)
26. Vilar, J.M.G., Guet, C., Leibler, S.: Modeling network dynamics: the lac operon, a case study. The Journal of Cell Biology (3), 471–476 (2003)
27. Wadhams, G.H., Armitage, J.P.: Making sense of it all: bacterial chemotaxis. Nature Reviews. Molecular Cell Biology 5(12), 1024–1037 (2004)
28. Yi, T.-M., Huang, Y., Simon, M.I., Doyle, J.: Robust perfect adaptation in bacterial chemotaxis through integral feedback control. Proceedings of the National Academy of Sciences 97(9), 4649–4653 (2000)