Research report

I. On the mathematical integration of the nervous tissue based on the S-Propagator formalism. I. Theory.

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Abstract

Integration in neuroscience, and more generally in biology, is mainly of a theoretical nature, because the aim is to re-build a system able to work from its components. This task is very hard, if not impossible, out of a theoretical framework involving specific concepts, which leads to « simplifications ». Physiological function is an example of such concepts difficult to define in a general way. The present usual automaton approach for artificial neural networks is not easy to use in the case of real neural networks because of the problem of the traversing levels of organization, from the molecular to the tissue. This paper develops the derivation of neural field equations from a theoretical framework in terms of non-symmetry and non-local functional interactions (Chauvet, 1993c) (n-level field theory), recalled in the first section ; and from the S-propagator formalism (Chauvet, 1999) recalled in the second section. It is shown how levels of organization are crossed using local specific (and usual) models inside the global, non-local model. The complexity of the system is greatly reduced because of (i) the expression of the physiological function in terms of its time scales and space scales, and (ii) the non-locality of the functional interaction that is propagated at finite velocity in a continuous and hierarchical space. By integrating local specific models, this approach allows the systematic study of physiological functions in the same framework, and then increase in the complexity of biological systems.

Keywords: Modeling, physiological function, functional organization, non-locality, hierarchical graph, n-level field, theory, nervous tissue, real neural network, biological system, neural field equations, learning and Memory.

Contents

A. Introduction

A problem of first importance in neuroscience and, more generally in biology, is the integration of elementary physiological mechanisms discovered through experiments. Ultimately, these mechanisms are always described as a « black box ». For a set of input stimulations, evoked responses are measured which are the starting point for testing hypotheses. Because each part of a biological system is necessary for its working as a whole, taking account of several mechanisms in the same time becomes increasingly complicated. This is very different from physical systems (considered here as systems in the inert world). Such a feature makes specific integration, i.e., the re-construction of a biological system from its parts.. This is the reason of experimental difficulties that are considerable, and more and more difficult for large systems, and justifies, if not makes necessary, the understanding of these systems through a mathematical model. Mathematics allow integration because they are conceived to integrate repetitive mechanisms. At the end of the formalization, numerical simulations made under various hypotheses, and specifically hypotheses that could not be directly tested through experiments, provide the numerical solution of equations. Specific models describe more or less complex systems : (i) from an « analogical » point of view (Anderson & Rosenfeld, 1988), by considering an elementary model, e.g. RLC circuit to represent an element of membrane as an electric compartment, which is repeated a number of times in order to correspond to the geometry of the whole system. This approach is what is now called « computational neurosciences». The « compartment » is a physical subspace obtained by « discretization » of the continuous space, and not the strict definition of the compartment found in the framework of compartmental analysis, i.e. the set of the elements of the system in a given state (with no reference to the geometry of the system) (Jacquez, 1988). (ii) either from a mathematical point of view (MacGregor & Lewis, 1977) for which modern aspects are very developed (non-linearities, chaos (Amit, 1989), etc.). Large scale models (Traub & Miles, 1991) are based on analogical models.

The automata approach using finite number of states (Hopfield, 1982) has brought much to neurosciences, however even more in the field of formal (or artificial) neural networks (Looney, 1997). Relatively easy to use in modeling because their organization involves not more than two levels, the « neuron » defined as a mathematical object defined by two biological properties (space or space and time summation and synaptic modifiability, i.e. a given learning (Hebb, 1949)), and the level of the network of neurons (an ensemble of these objects interconnected). The large number of results discovered from the mathematical point of view and, mainly, numerically « proven », has shown the interest of this new discipline in computing and applied mathematics sciences, e.g. robotics (Omidvar & Van der Smagt, 1997).

The case of real neural networks presents a much more difficult problem, because of their complicated structural and functional organizations. For instance, although learning rule is imposed to the formal neural network from outside the system, the real neural network produces its own learning rule based on complicated biochemical machinery. Mathematical integration must take into account such biological constraints, e.g. the passage from the molecular level (channel-receptors and biochemical pathways) to the tissue level to mime the pharmacological effect on network activity. Another example is given by the sensorimotor system that involves at least six levels of structural organization (based on anatomical structures : cell nucleus, synapse, neuron, group of neurons, nervous tissue, ensemble of tissue nuclei). However, another organization exists, which is of a functional nature, superimposed to the structural organization, and which is much more difficult to recognize. This organization makes quite the difference with physical systems. More generally, there are strong limitations with the above recalled approaches. An important example could be the impossibility of defining isolate systems because interactions between subsystems cannot be identified, but also the absence of « operatorial » definition for a physiological function relatively to the physical structure, the increase in system complexity with the involved studied object. What is missing in these approaches ? Essentially, a theoretical framework that allows using specific formalism adapted to the study of complex systems.

I have shown that describing a biological system in terms of functional interactions may give an answer to the above questions, and lead to new properties (Chauvet, 1993d) with respect to physical systems. A great advantage of this kind of description is to take into account systematically interactions between the parts of the biological system. I will show that a specific formalism, the S-propagator formalism, (Chauvet, 1999), in the framework of an n-level field theory (Chauvet, 1993b) allows traversing levels of organization in a biological system. The proposed theory is based on new concepts, most often of a mathematical nature. The two first sections recall the foundations of the hierarchical n-level theory and S-propagator formalism. Neural field equations are developed in the third section, and integration of local models in the global non-local model is exposed in the fourth section. Discussion on advantages and limitations of this approach are given in the last section. In this paper, a "unit" will be either a neuron, a synapse or a channel. The formalism being totally general, we use generative terminology as "unit", level of organization, source and sink, and so on, which are determined by their functional properties.

B. Theoretical framework: Hierarchical representation for Unit-unit communication

1. Functional interaction and its basic properties

Whether we consider the processes of embryonic development, or those involved in memorization and learning, or in the regulation of physiological functions in higher organisms, the common point is the existence of molecules or *signals* emitted by one structural unit, the *source*, acting at a distance on another structural unit, the *sink*, in which a series of transformations occurs. This is illustrated by the propagation of an electric potential along a nerve, the action of a hormone operating at a distance from its site of synthesis after being carried in the bloodstream, and the change produced in the shape of a molecule after it binds to another molecule.

All these examples enable us to grasp a concept that is fundamental to the understanding of distinct biological phenomena – the concept of the *functional interaction*. In simple terms, this implies that *a product emanating from one entity acts on another at a distance.* Thus, a signal emitted by one cell acts on another, which in turn emits a new signal after transforming the signal received. This defines the functional interaction between two cells since the action operates from one cell to the other. It is called "*functional*" because the function of the first cell is to *act* on the second by means of the signal it emits, causing the second cell to *produce* a new signal at a distance.

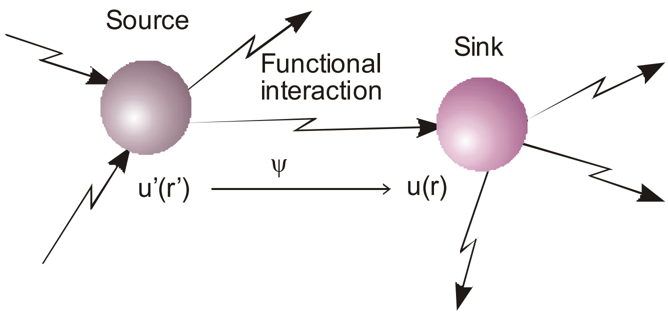


Figure 1: The functional interaction ψ is emitted by the neuron-source u' at r' and acts into the neuron-sink u at r.

Definition : Let us call u' the source at r' in an abstract space, the space of units $\mathcal{U}$ included in the physical space, u the sink in the same space at r, and ψ the interaction from u' to u. The functional interaction will be represented as (see Figure 1):

$$u'(r') \xrightarrow{\psi} u(r)$$

The functional interaction greatly resembles a mathematical function in that it consists of the application of one set on another, transforming an element of one set into an element of the other set. For this reason, we shall use the term "*functional interaction*" indifferently to describe the *action* of one biological structure on another as well as the *product* of this action, just as in mathematics we identify the function f: $x \rightarrow f(x)$ with its value $f(x)$.

2. Geometrical representation of the structural hierarchy: space of units and connectivity

However, structures are hierarchically organized. It is important to note the nature of the difference between the biological functional interaction and physical interactions, gravitational or electrical. The functional interaction exists at a given level of structural organization, as well as structural units u' and u and shows three properties described later. First, let us describe in more details the structural hierarchy of the nervous tissue (see Figure 2). We may consider *spaces of units* as abstract spaces included in the physical space. The action of one unit on another, which is the action of one neuron at r' (a volume) on another at r, is represented by ψ emitted by the axon hillock at r' (a point) to the other at r. This abstraction transforms Figure 2 into Figure 3 where the structural units "axon hillocks" represent the neurons-source *as concerns their function "nervous activity",* i.e. the propagation of action potentials. The physical extension of the structural units in the physical space may be projected onto the x-axis, then onto the r-space where they are represented by a point. This is shown on Figure 3.

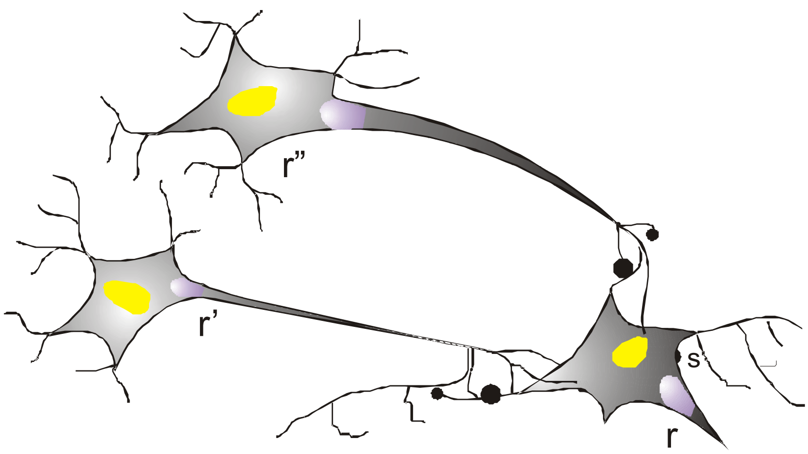


Figure 2: A set of three neurons interconnected. Axon hillocks are the structural units located at r, r', r" where action potentials are emitted. Black spots represent the synapses.

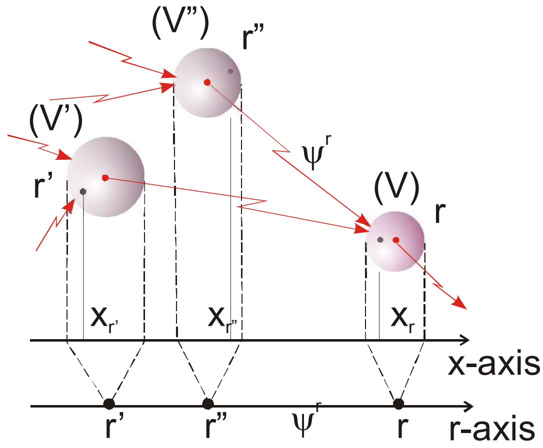


Figure 3: Extent of the structural units: the set of the three neurons in Figure 2 represented in the space of neurons (r-space), and "projected" on the r-axis and on the physical space (x-axis).

However, inside units "neurons" exist other structures at the lower level, that we may call the "synapses" *as concerns the function of transfer between the two neurons*. The neural tissue is thus considered as an ensemble of axon hillocks and a neuron is abstracted as an ensemble of synapses. This is shown in Figure 4. As shown previously, neurons are condensed into the structural units $u(r)$ at r in the r-space, and synapses are condensed into the structural units $u(s)$ at s in the s-space. Thus:

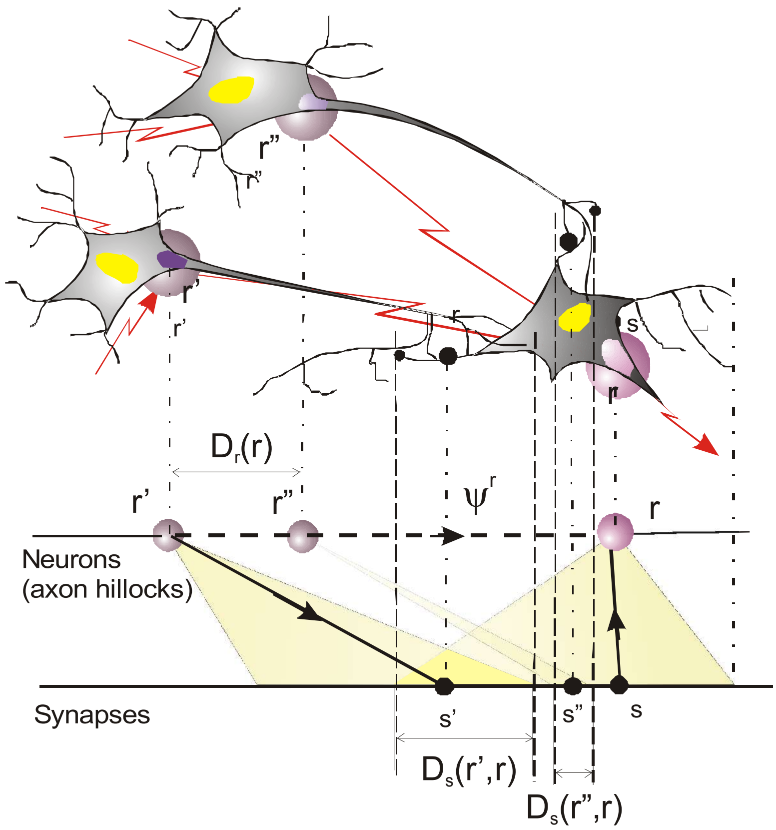


Figure 4: Up: The set of the three neurons shown in in terms of functional interactions. Bottom: the functional interaction goes from the neuron at r' in the ensemble $D_r(r)$ of the neurons

connected to r at the higher level of neurons, onto the neuron at r, through the synapses at the lower level. For instance, s' is a synapse that makes the communication between the neuron at r' and the current neuron at r, i.e. an element of the ensemble $D_s(r',r)$. They are structural discontinuities for the neurons. The local effect at r results from effects at r', r",..., i.e. effects located at a distance through s', s", ... This is non-locality.

Definition : *Space of units are abstract spaces in which defined physical structures capable of action may be considered as points.*

3. Properties of the functional interaction: non-symmetry and non-locality

a) Non-symmetry

In contrast to physical interactions, the functional biological interaction is *non-symmetrical.*

Definition : *The non-symmetry of biological functional interaction represents the action from one structural unit on another situated at a distance, i.e. from a source to a sink, although not directly from source to sink.*

This interaction is unidirectional since the molecule or signal, emitted at a given level of organization, will have no *direct* retroaction from sink to source, because of the transformation in the sink . Non-symmetry is thus related to the hierarchical structure of the sink.

b) Structural discontinuities

Regarding the dynamics in these two spaces, the space of neurons and the space of synapses, *physiological processes are different.* The existence of the two levels of structural organization (for the structural units called "neurons" and "synapses") is due to *structural discontinuities* between the structures at the higher level: synapses constitute structural discontinuity in the space of neurons, and clearly separate physiological processes in the two different media. In the same way, in the space of synapses are structural discontinuities represented by cytoplasmic structures. If these structural discontinuities are considered, then there is a functional interaction at this level, which means another lower level of organization (called the channels).

Definition: The r-space at level l is constituted by structural units $u^{(l)}$. Structural discontinuities represent portions of the physical space inside structural units $u^{(l)}$ in which physiological mechanisms differ from those that exist elsewhere in the r-space. These discontinuities constitute a lower level (l-1) of structural organization.

Structural discontinuities are essential to recognize because they are at the origin of the structural hierarchy. Spaces of units describe the propagation of functional interactions at different levels of the structural hierarchy. Each physiological process evolves in a certain hierarchical structural organization where each level is defined by the space scale, to which a given unit belongs depending on its real size.

They define a compartmentalization, i.e. a specific region of the space which is "homogeneous" for certain processes. They define a level of structural organization since, at a given level of the structural hierarchy, they constitute a structural unit for the lower level, for example: the membrane defines a level of structural organization for the cell, the synaptic junction for the neuron, the vascular tree for the respiratory system, and so on. Even when the limits are not well defined, we will see that a compartmentalization may exist, e.g. in the case of channeling for biochemical pathways.

c) Non-locality

The other important property of the functional biological interaction is that of *non-locality*, since the product emitted is transported at finite speed from source to sink. The property of non-locality is as fundamental to living organisms as that of the locality associated with physical systems. The two constraints of continuous representation of state variables and hierarchy of the system result in non-locality. The time course of any phenomenon at one level is based on processes at lower levels, the knowledge of which is therefore important. This is very apparent with the field approach. As will be shown, one problem comes from the fact that a local phenomenon in time and space at a given level is not local at lower levels. Representing the action of the unit by a global state variable leads to an important mathematical difficulty because of the hierarchy: local variables for a given unit, e.g. at *r* in Figure 4, depend not only on other local variables but also on global variables for the other units connected to it, through the sub-units included in units, e.g. at *s*', *s*''... Thus :

Definition : Non-locality is a space property according to which the system depends on mechanisms that are located elsewhere in the space.

4. *Diagrammatic representation of functional interaction. Physiological function*

a) A diagram to represent functional interaction

All the present knowledge on functional interaction may be brought together under the condensed form of a diagram as follows:

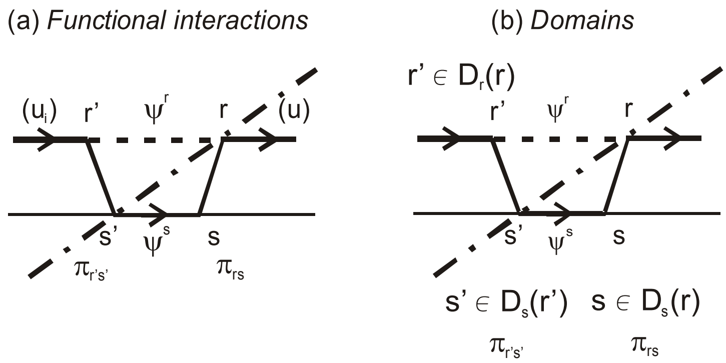


Figure 5:Diagram to represent functional interaction in the r-level through the s-level (left); domains $D_r(r)$ for neurons connected with neurons at r, $D_s(r)$ for synapses inside neurons at r; π_{rs} is the density-connectivity of synapses at s (s-level) with neurons at r. See this figure with respect to Figure 4 (bottom).

In Figure 5, the two horizontal lines represent the two levels of structural organization, the *r*-level and the *s*-level (*l* and *l*-1 for simplicity). The source at *r'* emits the functional interaction ψ^r onto the sink at *r* because there is a structural discontinuity between *r'* and *r.* The transformation occurs inside *r*, i.e. at the lower *s*-level of organization. From *s'* to *s* is another functional interaction if and only if there is a structural discontinuity between *s'* and *s.*

b) What is a physiological function?

Because the aim of the present approach is the mathematical modeling of the physiological function created by the physical structure, it is important to specify the relationship between the functional organization and the structural organization.

A *level of functional organization* corresponds to the activity of a set of structural units participating in the elaboration of a product on a certain time scale. It is represented by a mathematical graph in which the summits correspond to the structural units and the oriented arcs correspond to the functional interactions. The product is elaborated according to a given dynamics varying on a certain time scale, which defines the level of the functional organization. The *product*, which results from the dynamics of the structural units, may be assimilated to the corresponding *physiological function*. More precisely, in the mathematical sense, the product is the value of the physiological function.

An *elementary physiological function* is defined as the functional interaction between two structural units, i.e. the source and the sink. The product resulting from this interaction may, in a certain sense, be identified with the elementary function. Thus, the *physiological function* can be viewed as the final result of a set of functional interactions that are hierarchically and functionally organized. Finally, the physiological function may be identified with the global behavior of the hierarchical system. Thus :

Definitions :

- An elementary physiological function is the collective behavior (cooperation in some tasks, i.e. the dynamics) of at least one functional interaction.

- A physiological function (a biological system) is the collective product of a set of structural units which can be hierarchically classified according to their elementary interactions.

5. Combinatorics of functional interactions : (O-FBS) and (D-FBS)

Formal biological systems are defined on the basis of a small number of properties, which correspond to an idealization of real biological systems. Such systems may be built in terms of functional interactions, and the main question will thus be: What is the structure of a general biological law involving functional interactions?

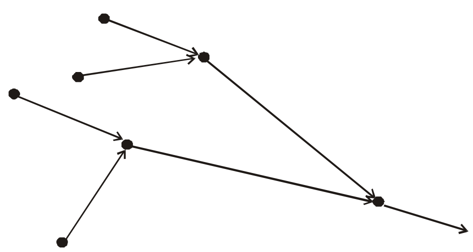


Figure 6 : The mathematical graph associated with the functional interactions of Figure 3.

a)The (O-FBS) describes the topology of the biological system

The first consequence concerns the combinatorial properties of the elementary functional interactions. The set of sources, sinks and their interactions can be conveniently represented by a *mathematical graph* (Figure 6). Two nodes correspond to the source and the sink of the functional interaction, and the interaction is the oriented arc joining the two nodes. Generalizing to any number of sources and sinks, gives a set of summits, the hierarchical structural units connected by oriented arcs, possessing mathematical properties. The number of summits corresponds to the "degree of organization" of the structure. This kind of *hierarchical graph* describes the functional organization of the biological system, denoted as (O-FBS), more generally of any organism, i.e. the *topology* of the biological system. Thus, the first objective of our work consists in the study of such systems and their topological properties.

b)The (D-FBS) describes the dynamics of the biological system

The second consequence of the existence of functional interactions concerns the formal expression of the dynamics of the process corresponding to the spatiotemporal fate of the product that, after being emitted by a source, will act at a distance on a sink. For example, a hormone is transported at a rate depending on the blood flow, a neurohormone migrates along the axon of hypothalamic neurons for several days before reaching its target, an action potential is propagated at a velocity of eighteen meters per second along the larger nerve fibers, and so on. Since the delay with which the signal from the source reaches the sink depends on the localization of the source and the sink, the geometry of the biological system influences the dynamics of the process and is therefore must be implicitly included in this representation.

The functional interaction being determined by its three elements, i.e. the source, the sink and the transformation of a product in the sink, the propagation of the signal and its action at a distance represent the dynamics of the process, describing *how* the interaction takes place (Figure 1). The second objective of our work is the determination of the *dynamics of the formal biological system* (D-FBS), in other words, in a given system, the dynamics of the action in space and in time of a structural unit on another. The field approach is useful to reach at this objective (see section D) .

c)Functional and structural organizations

Functional organization

Although it may appear easy to think of a biological system in terms of structural levels, because of its anatomical description and organization (from the cellular to the organismal levels), it is considerably more difficult to describe an organism in terms of its functional levels of organization. This is an answer to the question: what are the structures involved in this function? As we will see along the course of this book, it appears to be necessary to distinguish between the *structural association* of the units involved in a given structure, and the *functional association* of the units involved in a given physiological function. In terms of functional interactions, an organism may be identified with a set of parallel hierarchical systems, one for each physiological function, which could be modeled using a parallel computer. This would allow us to investigate the laws of conservation applicable to a given interaction and to a set of interactions, i.e. a *physiological function*, so as to determine which aspects of the related organization of an organism are maintained invariant.

How to define the functional organization? Because the above definition of the physiological function involves implicitly the hierarchy of the "collective behavior of the involved structural units", and because given dynamics evolve on a defined time scale, we have:

Definition : *The level of the functional organization for a given function is defined by the time scale of the dynamics of the structural units involved in the function.*

This definition has a practical advantage. The order relation between time scales correspond to time loop included one in the other, and explains why physiological functions are hierarchically organized. This is apparent and useful in computer programming.

Structural organization: space scales

Let us consider a structural unit u, which may be a source and/or a sink for a functional interaction involved in the dynamics at a given level. Since this structural unit is made up physical matter, it is also an element of the biological structural organization. Thus, for the same structural unit, there exist two organizations, the structural and the functional organizations, which may be characterized by their dynamical space and time properties:

Definition : For a given time scale, there exists a structural organization distributed according to the space scales, consisting of macromolecules, intracellular organelles, cells, tissues, organs and organisms; and for a given space scale, the functional organization is distributed according to the time scales of its dynamics.

The structural and the functional organizations are represented by hierarchical systems, the levels of organization being defined by the time scale of the dynamics and the space scales of the structure to which these dynamics apply. The coupling between the structural and functional organizations is carried out through the time and space properties corresponding to the physiological function.

d) Consequence: Uniqueness and 3D representation of a biological system

Uniqueness

Uniqueness is an important constraint for a theoretical approach. It means that the procedure of construction of an FBS must provide a unique system. With the above definition of the physiological function in terms of functional interactions, we obtain an abstract construction –

distinct from the real anatomical construction – represented by a set of parallel hierarchical functional systems. The hierarchy of the structural units, i.e. the "anatomical" hierarchy that is well known in terms of molecules, organelles, cells, tissues, organs and organ systems, is linked to the existence of structural discontinuities. Our definition of the physiological function introduces a *functional hierarchy* based on structural units organized within hierarchical systems that do not generally coincide with the "anatomical" hierarchy. In practice, these systems are determined first by isolating a particular function, which is identified by the dynamics of the corresponding process and its time scale, and then by seeking the anatomical structures subtending this function. The same method will be applied to each subsystem obtained so as to determine the corresponding subfunctions, which will lead to the isolation of sub-subfunctions, and so on. The identification of the levels of functional organization results from the identification of the physiological subfunctions of which the spatiotemporal dynamics corresponds to the global behavior of the structural units at this level. Since this dynamics involves relationships between variables, the subfunction itself will be identified by these variables. We then deduce the following properties:

The abstract construction of the physiological function leads to a unique definition of the biological system. At the lowest level of the structural organization, or the fundamental level at which auto-replicating molecules exist, the association of structural units leads to the production of complex molecules, i.e. proteins. These proteins constitute the essential elements of metabolic pathways that form interconnected networks. A given organ may produce several different types of molecule, for example specialized cells in the pancreas produce glucagon and insulin. In contrast, the activity of an operon will lead to the biosynthesis of only one type of molecule. Thus, the specificity at the fundamental level will, by construction, lead to the uniqueness of the physiological function as a hierarchical functional system.

<u>Equivalence class of structural units</u>

Each structural unit is itself a hierarchical system organized at several levels, including the fundamental level. Structural units that are similar according to certain histological and anatomical criteria constitute a class of structural equivalence. In mathematical terms, an equivalence class is a set of elements satisfying given equivalence relationships (reflexivity, symmetry and transitivity). The equivalence class can then be considered as an element of a set on which algebraic operations may be performed. In the case of biological structures, the equivalence class corresponds to the *geometrical identity* of its elements. For example, the nephrons, which are identical anatomical and functional units of the kidneys, may be grouped into a single "nephron unit", the alveoli of the lungs may be grouped into a single "alveolar unit", and so on. This is different from neurons that are not functionally identical because of the specific properties of efficacy at the synaptic level.

Consequence: 3D representation, the basic relation between the structural and the functional organizations

We may represent the relation between the structural and the functional organizations as follows. A physiological process, i.e. a physiological function, evolves in a given hierarchical structure. This is represented in Figure 7 using a 3-D diagram: each function ψ is represented along the *y*-axis defined by the time scales, its hierarchical structural organization is represented in terms of the space of units along the *z*-axis, thus defined by the space scales, and the distribution of the units is represented along the *x*-axis. The lowest *z*-level is the physical space.

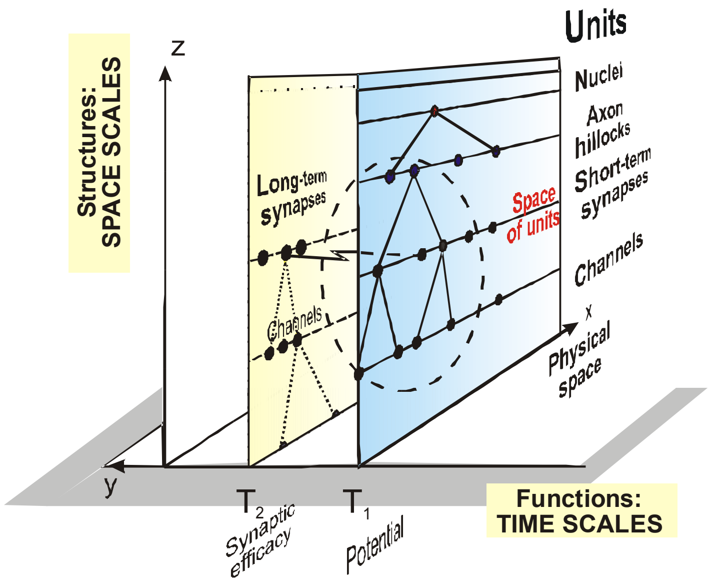


Figure 7 : Schema of the nervous tissue in terms of functional interactions

The space scales κ^l determine the different levels l of structural organization (*z*-axis in the 3D-representation of the FBS) for a given physiological function ψ. These scales have an influence on the propagation delays because of the finiteness of the velocity of the functional interaction involved in ψ. The resulting dynamics, i.e. ψ, varies on a certain time scale, defining the level of functional organization. Thus, it is clear that the time scale of the dynamics is coupled to the delays of propagation related to space scales. *This coupling between time scales and space scales is another feature of this type of hierarchical system*. Essentially, the properties of the (D-FBS) are based on the concept of *non-locality* of functional interactions, that is apparent on Figure 7 through the *z*-axis for a given function ψ, and which is mathematically described by "*non-local*" field operators. The geometrical constraint is at the origin of the present description of a biological system in terms of functional interactions.

C. A specific formalism, The S-propagator, to traverse levels of structural organization

1. Fields And Functional Interactions

The continuous approach, and thus fields, have been used in neural modeling by, e.g. (Beurle, 1956; Feldman & Cowan, 1975a; Feldman & Cowan, 1975b; Griffith, 1965; Griffith, 1968; Freeman, 1975; Wilson & Cowan, 1973). Concepts and theory recalled in the previous section allowed us to conceive the physiological processes expressed by functional interactions related to the geometry of the structure, as *the transport of a field variable submitted to the action of a field operator* (Chauvet, 1993c). Let $\psi(r,t)$ be the field variable defined in the r-space, and let $\mathscr{H}$ be the field operator which depends on ψ and on successive derivatives $\psi^{(n)}$ with respect to time and space coordinates. The field equation may be written in a general form as follows:

$$(\mathscr{H}(\psi,\psi^{(n)},n=1,2,\ldots)\psi)(r,t)=\Gamma(r,t)$$

where Γ is the source term. In this equation, $\mathscr{H}$ describes the propagation of the field variable ψ from r' to r, and the local transformation in r is represented by $\Gamma(r,t)$. Since the operator acts from one point of space to another, it must take into account the distance between these two points, and thus includes an *interaction operator*. More generally, the influence of the location of the points, i.e. the role of geometry on the dynamical processes, may be studied by means of a field theory. The dynamical processes that express the behavior of the related functional interactions occur continuously in space and time with a finite velocity. Thus, what is observed at point (r,t) results from what was emitted at point (r',t'), where $t=t'+\left\|r'-r\right\|/v_\psi$ and v_ψ is the velocity of the interaction.

The finite value of the velocity v_ψ of the transport of the interaction, which is the transport of molecules, potentials, currents, or parameter effects depending on the elementary physiological function, has an important role on the behavior of the biological system, because of the *delay* in the response between units at different times of their production. These effects are included directly in the field interaction operator. The aim now is to determine the specific operator that describes a physiological operator.

In the most general case, for a given physiological function, i.e. activity or synaptic efficacy, the biological system is assumed to have:

- (i) n levels of structural organization denoted as r, s, c … from the highest to the lowest (equivalent to: n, n-1, …1) standing for r-space, s-space, etc.;

- (ii) Each level, except the lowest, represents a structural discontinuity;
- (iii) Only one time scale for all the levels.

Phenomena are observed at the highest level, which means:

- The functional interaction ψ^r traverses levels successively from the highest to the lowest ;
- At each level, the interaction cannot go directly from one point to another without traversing the lower levels because of (ii) ; thus, at each level, except the lowest, the field equation is non-local;
- At the lowest level (molecular level), the field equation is local (reaction-diffusion type).

2. *The S-Propagator formalism*

Let us recall here the main concepts that may be found elsewhere (Chauvet, 1999). In terms of operators, the local time-variation may be expressed as:

$$\mathscr{H}\ \psi^r = \Gamma \qquad \text{with} \qquad \mathscr{H} = \frac{\partial}{\partial\, t} - D\nabla^2 - \mathscr{H}_I$$

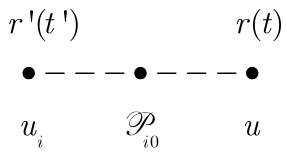
The discontinuity between spatial structures u_i at *r'* and u at r is taken into account by considering a discrete non-local operator:

$$\mathscr{P}_i : \psi^r\left(t - \frac{d(r',r)}{v}\right) \quad \rightarrow \quad \psi^r(r,t)$$

which, *in the linear case*, leads to:

$$(\mathscr{H}_I \psi^r)(r,t) = \sum_{u_i \in D_r} \mathscr{P}_i\, \psi^r\left(r',t - \frac{d(r',r)}{v}\right)$$

where D_r is the set of r'-units connected with the r-unit. This corresponds to the diagram in a:



d(*r'*,*r*) is the distance between *r'* and *r*. We have called $\mathscr{P}_i[\psi^s]$ the *structural propagator* (*S-propagator*) since the propagation of the functional interaction occurs in the structural organization for the space of units *u*, including the structural discontinuities at level *s* with the field variable ψ^s . Now, using the continuous notation for *r'*, the propagation of the field from *r'* to *r* occurs, at the lower level, along $\boldsymbol{d}_i(r')$ from *r'* in u_i to the border of the structural discontinuity denoted as *s'*, then along $\boldsymbol{d}(s)$ inside *s*, and finally from *s* to *r* along $\boldsymbol{d}(r)$ inside the unit *u*. This propagation corresponds to the mathematical operation *per unit time*:

$$\mathscr{P}_i[\psi^s] = \mathrm{P}\Phi\,\mathrm{P}_i \equiv \mathrm{P}\Phi(r)\mathrm{P}(r')$$

which is the product of the trans-level propagator $\mathbf{P}_i$ in u_i, i.e. $\mathbf{P}$(r'), the in-level propagator Φ for field variable ψ^s at the level s, which represents the transport through the structural discontinuity, and the trans-level propagator P in u, i.e. P(r), as shown by the diagrams ( ) in which the dotted line shows that s', s belong to the unit at r. Note that the product in must be understood as:

$$P\Phi(r)P(r') = [P(r,s)\Phi(s,s';r)]P(r',s')$$

i.e. an operator $[P(r,s)\Phi(s,s';r)]$ that acts on the result of the operation $P(r',s')\psi^r$. It is sometimes convenient (however confusing) to note in the same way the operator and the field variable, as well as to suppress the second argument *s*' for the clarity. If there is no discontinuity in the *s*-space, then: $\Phi(s,s';r) = \delta(s-s')$ where δ is the Dirac function. Thus, the passage from r' to r through s' gives:

$$[P(r,s')P(r',s')] \equiv [P(r)P(r')]$$

This is the case studied in section D.

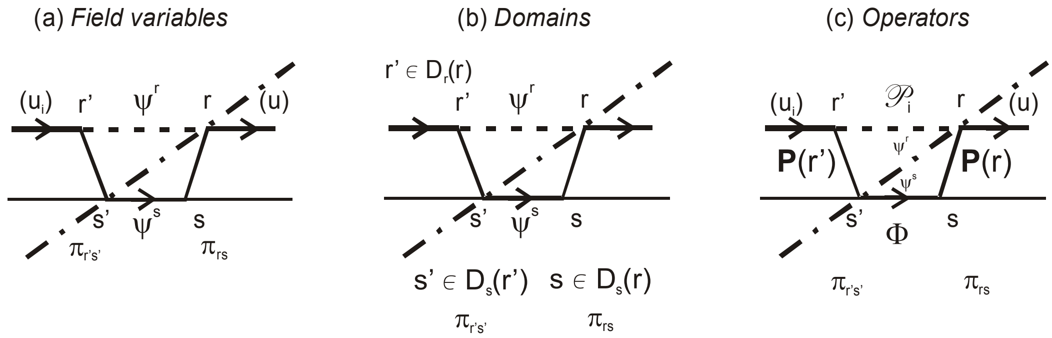


Figure 8 : a) and b) Diagram for operators viewed as in Figure 5. c) Field variables as operators are denoted as Greek symbols at the two r- and s-levels. At the lower s-level, the corresponding functional interaction Φ *associated (necessarily) with* $P(r)$ *is called the in-operator,* $P(r)$ *and* $P(r')$ *are the trans-operators.*

This relationship includes the density of units and their connectivity (a continuous expression using a density-connectivity function π_{rs}, i.e. the product of the density and the probability of connection for the specific units, see Figure 8b). The pathways in the above diagram represent the action of the operators. Thus, the non-local term becomes:

$$(\mathscr{H}_I\psi^r)(r,t) = \sum_{u_i \in D_r} [P\Phi(r)]P(r')\,\psi^r(r',t-\frac{d(r',r)}{v})$$

With the density of the r'-units denoted as $\rho^r(r')$, this non-local term, which describes the action from *r'* to *r* , through s' and s, may be written in continuous notation:

$$(\mathscr{H}_I\psi^r)(r,t) = \int_{D_r(r)} \rho^r(r')[P\Phi(r)]P(r')\,\psi^r(r',t-\frac{d(r',r)}{v^r})\,dr'$$

According to this definition, the *S*-propagator represents the operation of the processes *inside* the units of the hierarchical structural organization from *t'* to *t*, and includes all the processes *integrated* at the lower level. It gives the global representation of the operation of the processes at each level of the hierarchy. The *S*-propagator is a non-local field operator that transports the field variable ψ^r from point *r'* in the space of units at time *t'* to point *r* at time *t*. This represents the transport in three sequential steps:

(i) a *propagation* of the functional interaction ψ^r inside the source (in this emitting unit, the process is represented by operator $\mathrm{P}(r')$;

(ii) a *transformation* due to the structural discontinuity that provides a propagation at the lower level due to the functional interaction ψ^s at this lower level (the process is represented by operator Φ, i.e. the solution of the field equation for ψ^s at this level); and

(iii) a *propagation* of ψ^r at the higher level in the sink (in this receiving unit, the process is represented by the operator $\mathrm{P}(r)$).

3. Field equations in the non-linear and the linear cases

To sum up, it is crucial to note that the *S*-propagator represents the operation of the processes *inside* the units of the space of units. In some cases, transport is possible through *extra-unit* space, *inside the physical space*. The non-local term inserted into gives the *hierarchical field equation that describes the dynamics at the highest level of structural organization:*

a) In the non-linear case

$$\frac{\partial \psi^r}{\partial t}(r,t) = \nabla_r (D^r \nabla_r \psi^r (r,t)) \; + \int_{D_r(r)} \rho^r(r') \, \mathrm{P}\Phi(r) \; \mathrm{P}(r') \, \psi^r(r', t - \frac{d(r',r)}{v^r}) \, dr' \; + \; \Gamma_r(r,t)$$

The non-local term is also a "source" term, because it provides the contribution to the current compartment of a virtual compartment (i.e. from other levels of organization). The "factor" represented by the operator and the integral represents the quantity of ψ brought *per unit time* into the current compartment. Because operators are generally non-linear, the operator which applied to the input function ψ represents the specific local model, i.e. mechanisms that occur during a unit time interval (see section E).

b) In the linear case

In this (not usual) case, the operator may be replaced by a kernel. The result of each operator, taking into account the inter-level connectivities, is:

$$\psi^s(s',t') = \mathrm{P}(r')\ \psi^r(r',t') = \int_{D_r(r)} \pi_{r',s'} B(r',s')\psi^r(r',t')\,dr'$$

$$\psi^r(r,t) = \mathrm{P}\Phi(r)\ \psi^s(s',t') = \int_{D_s(r')} \int_{D_s(r)} \pi_{rs} \mathscr{P}_{s',s}[\psi^c] A(s,r)\,ds\,ds'$$

where A and B are specific space-time functions that depend on the local physiological mechanisms. The second equation involves the functional interaction at the lower c-level, through the S-Propagator $\mathscr{P}_{s',s}[\psi^c]$. In the same way, the given s is connected (abstractly) to all c, each being connected (abstractly) to all s', and each of these being connected (abstractly) to all r' in the corresponding spaces. Equation then becomes:

$$\frac{\partial \psi^r}{\partial t}(r,t) = \nabla_r \left(D^r \nabla_r \psi^r(r,t)\right) \quad +$$

$$\int_{D_r(r)} \int_{D_s(r)} \int_{D_s(r')} \rho^r(r')\, \pi_{rs} \pi_{r's'} \mathscr{P}_{s',s}[\psi^c]\, A(s,r)\, B(r',s') \psi^r(r', t - \frac{d(r',r)}{v^r})\, dr'\, ds\, ds'$$

$$+\ \Gamma_r(r,t)$$

where the three levels and their connected units appear through the units at c, s', r'. The local mechanisms associated with the propagators are clearly represented for the s'-unit by the functions $B(r',s')$, and for the s-unit by $A(s,r)$. However, development down to the c-level would require a non-local field equation for ψ^s in the same functional organization, i.e. in the same time scale. Most often the field only exists at the highest level.

D. Neural field equations

1. *Functional organization of the nervous tissue*

Let us first consider the nervous system relatively to its function, i.e. propagation of activity through the nervous tissue modulated by the variation of synaptic efficacy in the long-term. For this function, the structure is uniquely determined. The nervous system is represented on Figure 9, as shown in Figure 7 in the 3D representation.

Thus, there are two time scales, one for *activity* (msec), the other for *synaptic efficacy* (sec, min). For each of them, the structures involved are distributed according to their space scales. According to the theory, there are two field equations, one per level of functional organization, i.e. corresponding to each plane of Figure 9. Operators that constitute the S-propagator correspond to the processes at the lower level of the structural organization in this time scale. More specifically, let us consider :

1) The dynamics of *activity* (action potential frequency), represented in the front plane defined by the "instantaneous" time scale, involves two levels of structural organization :

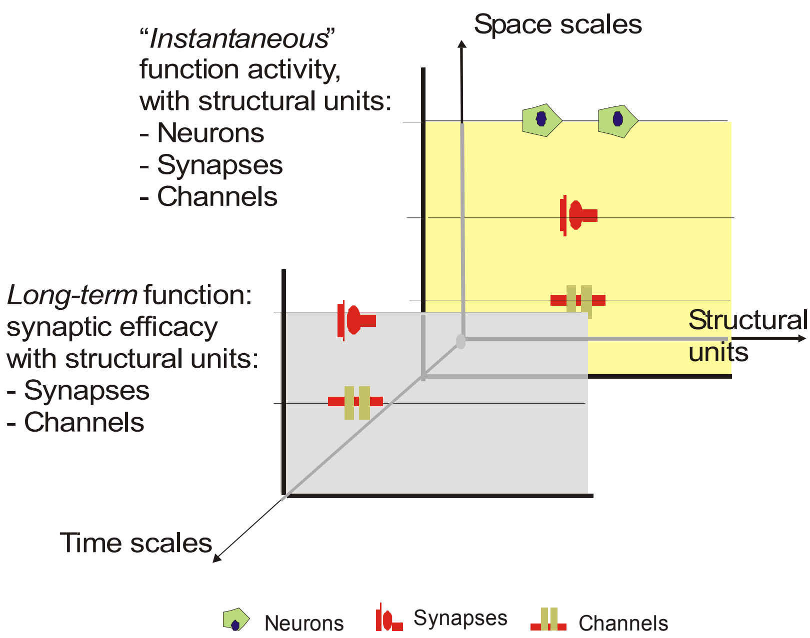


Figure 9 : After Figure 7, the FBS for activity propagation (back plane) modulated by synaptic efficacy (front plane)

- The highest level is composed of the "neurons". I have already specified that neurons are the structural units, sources and sinks, which emit and receive membrane potentials. They are identified with *axon hillocks*, i.e. this area of the real neuron that initiates the action potential before its propagation. The field equation at this level governs the state variable *membrane potential*.
- The lower level is composed of the *synapses*, which involve the AMPA receptors (AMPARs), for which the dynamics are given by several local models. They will be described in section (a. We may assume that there is no discontinuity at this level, and thus operators satisfy equation .

2) The dynamics of *synaptic efficacy*, represented in the rear plane defined by the long time scale, involves two levels of structural organization:

- The highest level is composed of the anatomical part of the synapses, called the "*synapson*" composed of AMPARs, NMDA receptors (NMDARs) and cytoplasmic biochemical pathways. The collective behavior, i.e. the physiological function, of these structures is the long-term function modification of synaptic strength. The dynamics of these synapsons are given by the field equation for the functional interaction in the space of synapsons. The field variable is the synaptic efficacy or, better, the postsynaptic potential (PSP) relatively to its initial value.

- The lower level is composed of the channels that are involved in the long-term dynamics of synapsons.

3) *The coupling between the above dynamics*, represented by the functional interactions between the two planes (see Figure 9), expresses the modulation of basal activity by long-term synaptic efficacy. This coupling is not yet well known. However, since the synaptic neuron-to-neuron instantaneous transfer seems to be modulated by another function in the long-term, let us assume that ϕ, the PSP value in the instantaneous time scale, is added to the PSP baseline value φ^0 which evolves in the long time scale, to provide the observed PSP denoted as φ:

$$\varphi = \phi + \varphi^0$$

More generally, the resulting PSP φ would be a certain mathematical function of φ^0 and ϕ.

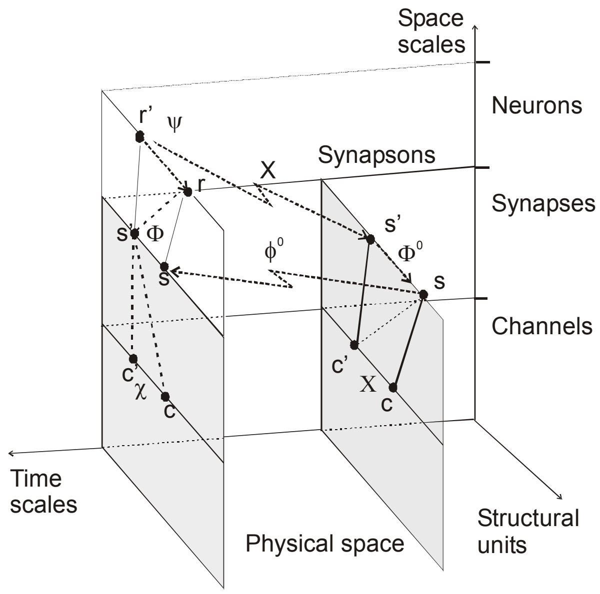


Figure 10: Functional organization for neural activity and LTP in the nervous tissue. Couplings between the two functions, i.e. the two planes, are indicated: X is the input for LTP, and postsynaptic potential φ^0 *is the output of this system.*

Initially, the LTP process starts when postsynaptic potential φ^0 reaches a threshold due to the strong repetitive activity of the connected neurons. This relationship between equations and , which is the input from the ψ-plane to the φ-plane (see Figure 10) may be written:

$$\varphi^0(s, t_0; r) = f(X(r, t_0))$$

where $X(r, t_0)$ is the firing frequency (activity) at r and at time t_0.

2. *Dynamics in the short-term (instantaneous): Field equation and S-propagator for membrane potential*

In the field continuous description, the neuron is a point that is identified with the axon hillock, the part of the neuron where the action potential is initiated. This means that, at each point $(x,y) \equiv r$ of the nervous tissue, exists a neuron for which the membrane potential is given by :

$$\frac{\partial \psi}{\partial t}(r,t) = \nabla_r (D^r \nabla_r \psi(r,t)) + \int_{D_r(r)} \rho^r(r')\left[\mathrm{P}\Phi(r)\right]\mathrm{P}(r')\,\psi\left(r', t - \frac{d(r',r)}{v^r}\right) dr'$$
$$+\ \Gamma_r(\psi,t)$$
$$\psi(r,t) = \psi^{AP} \quad \text{if} \quad \psi(r,t) \geq \psi^s \quad \text{for} \quad t \geq t^s \quad \text{and} \quad t < t^s + t_{ref}$$

where ψ^s is the threshold, t^s, t_{ref} are respectively the time at which the neuron fires and the refractory period. Because no structural discontinuity is assumed at this level for this function, $[\mathrm{P}\Phi(r)]\mathrm{P}(r') = [\mathrm{P}(r,s)\Phi(s,s';r)]\mathrm{P}(r',s') = \mathrm{P}(r)\mathrm{P}(r')$ from and . In the following, we determine operators $\mathrm{P}(r')$ and $\mathrm{P}(r)$, which represent the passage from the neuronal level to the synaptic level (Figure 11) for the neuron located at *r*, and Γ that is the source of the field.

a) Diffusion term

The diffusion term may generally be neglected, but in some situations depending on the density and the geometry of neurons, e.g. in the Hippocampus, ions can flow through the interstitial medium, adding current to the normal synaptic transfer. Such a current due to ion diffusion *between* neurons may be studied relatively to the propagation from neuron to neuron using the present field equations.

b) Expression of the non-local term (input to the axon hillock)

As shown in Figure 11, the *trans*-operator $\mathrm{P}(r')$ is the product of operators $\mathrm{P}_i \ (i = 1,3)$, and the *trans*-operator $\mathrm{P}(r)$ is the product of $\mathrm{P}_i \ (i = 4,5)$. Each of these operators is now calculated.

1. *The postsynaptic current* is obtained by applying the product of operators $\mathrm{P}_i \ (i = 1,3)$ to the action potential emitted by the structural unit "source" at *r'* and at time *t'*, i.e.:

$$\psi^{AP}(s'^-,t) \rightarrow i_s(s'^+,t) = \mathrm{P}_3(r',s'^-,s'^-)\mathrm{P}_2(r',s'^-,s'^+)\mathrm{P}_1(r',s'^+,s'^+)\psi^{AP}(s'^-,t)$$

where operators are non linear and represent the transport through the synapse from s' to s'^+:

- P_1 for the emission of the neurotransmitter;
- P_2 for diffusion through the synaptic cleft;
- P_3 for transmitter-receptor binding.

From the physiological point of view, applying the product of these three operators to the action potential at *r'* results in the postsynaptic current : $i_s(s'^+,t) = g_s\phi_s(s'^+,t)$, where g_s is the membrane conductance and ϕ_s the postsynaptic potential:

$$i_s(s'^{+},t) = \mathrm{P}(r')\ \psi(r',t')$$

where *s*' depends on *r*, because it belongs to the neurons at *r*'. This is the *non-linear contribution* of the membrane potential ψ^{AP} at r' to the synaptic current $i_s(s'^{+},t)$, thus to the postsynaptic potential ϕ_s at $s'^{+}(r')$.

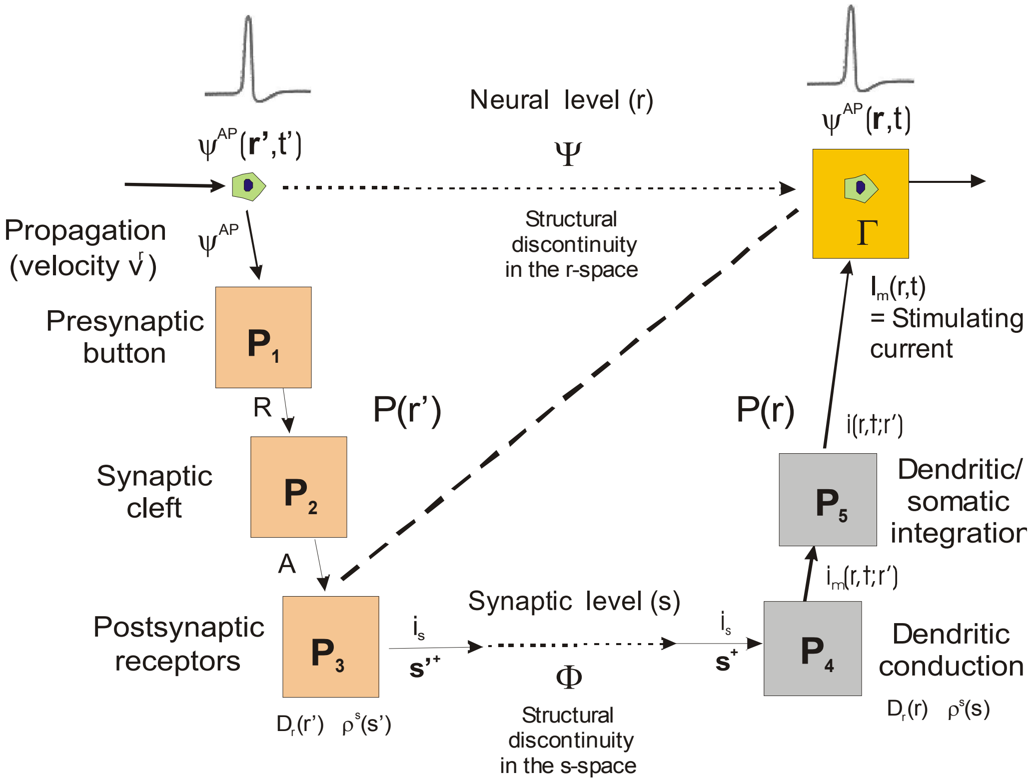


Figure 11 : corresponds to the general abstract diagram presented in in which the structures have been explicated. Functional interaction Ψ represents the global process of propagation from one axon hillock to another, introducing a delay, and the local processes represented by operators $\mathrm{P}_i, i = 1,4$

2. *The postsynaptic current* $i_s(s'^{+},t)$, obtained for one given synapse at s'^{+}, is carried on passively at a distance before integration at the axon hillock with the other PSCs. Let $i_m(s',t;r)$ the *partial* membrane current at the axon hillock that originates from the *individual* synaptic current $i_s(s'^{+},t)$:

$$i_m(r,t;s') = \mathrm{P}_4(r)\ i_s(s',t)$$

where operator $\mathrm{P}_4(r)$ represents the dendritic conduction between synapses at *s*' and the axon hillock at *r*.

3. The sum of all the postsynaptic currents $i_s(s'^{+},t)$ due to the action potential stimulation at (*r*',*t*'), i.e. the sum of all the partial membrane currents in gives rise to the current $i(r,t;r')$ by

integrating on all the synapses connected with the neurons at *r*' (domain $D_s(r')$), and described by the density-connectivity function $\pi_{r's'}$:

$$i(r,t;r') = \int_{D_s(r')} \pi_{r's'}(s') i_m(r,t;s'(r'))\, ds' = \mathrm{P}_5(r)\, i_m(s'(r'),t;r)$$

where operator $\mathrm{P}_5(r)$ represents the synaptic summation. Then the total current for all the neurons (density $\rho^r(r)$) connected with the neurons at *r* (Domain $D_s(r')$):

$$I_m(r,t) = \int_{D_r(r)} \rho^r(r') i(r,t;r')\, dr'$$

Finally, from and :

$$I_m(r,t) = \int_{D_r(r)} \int_{D_s(r')} \rho^r(r') \pi_{r's'}(s') i_m(s'(r'),t;r) \quad ds'dr'$$

and from and :

$$I_m(r,t) = \int_{D_r(r)} \int_{D_s(r')} \rho^r(r') \pi_{r's'}(s') \mathrm{P}_4(r) \mathrm{P}(r')\, \psi(r',t') \quad ds'dr'$$

or:

$$I_m(r,t) = \int_{D_r(r)} \rho^r(r') \mathrm{P}(r) \mathrm{P}(r')\, \psi(r',t')\, dr'$$

where $\mathrm{P}(r) = \mathrm{P}_5 \mathrm{P}_4$. Because *the contribution per time unit of the membrane current to the partial membrane potential* at *r* is $\dfrac{i_m(r,t;s')}{c_m}$ where c_m is the membrane capacitance (at the axon hillock), the following contribution to the membrane potential is derived from :

$$\left(\frac{\partial \psi}{\partial t}\right)_m = \frac{1}{c_m} I_m(r,t) = \frac{1}{c_m} \int_{D_r(r')} \rho^r(r') \mathrm{P}(r) \mathrm{P}(r') \psi(r',t') dr'$$

This expression gives the non-local term of the neural field equation .

c) Calculation of the source term Γ

The source of the field produces the action potential ψ^{AP} in the axon hillock after depolarization of this segment due to the stimulation current $I(r,t)$. The source of the field is given by the Hodgkin-Huxley model :

$$\Gamma(\psi,t;r) = \frac{1}{r_m c_m} \psi(r,t) + \sum_{ions} \frac{\Delta g}{c_m} \left(\psi_{e,ion} - \psi(r,t)\right)$$

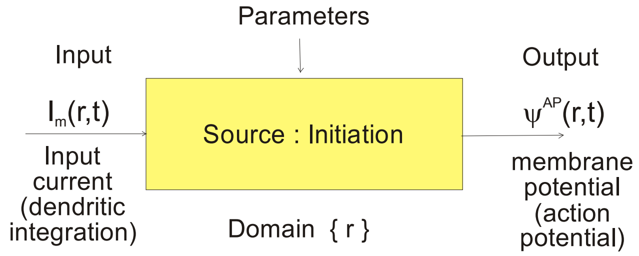


Figure 12 : Block simulating the source at the axon hillock r for the initiation of action potential.

where $\psi_{e,ion}$ is the Nernst potential for a given ion, and Δg is the increase in conductance relative to its resting level. From and placed in , we may derive the neural field equation for membrane potential:

$$\frac{\partial\psi}{\partial t}(r,t) = \nabla_r(D^r\nabla_r\psi(r,t)) + \frac{1}{c_m}\int_{D_r(r')}\rho^r(r')\mathrm{P}(r)\mathrm{P}(r')\,\psi(r',t')\,dr' \; + \\ + \left(\frac{1}{r_m c_m}\psi + \sum_{ions}\frac{\Delta g}{c_m}\left(\psi_{e,ion} - \psi(t)\right)\right)$$

where $\mathrm{P}(r) = \mathrm{P}_5(r)\mathrm{P}_4(r)$ and $\mathrm{P}(r') = \mathrm{P}_3(r')\mathrm{P}_2(r')\mathrm{P}_1(r')$. We may note that the mathematical structure of this equation is the same as the well-known Hodgkin-Huxley equation (see, e.g. (Chauvet, 1996), p.114):

$$c_m\frac{\partial\psi}{\partial t}(t) = \frac{1}{r_m}\psi + \sum_{ions}\Delta g\left(\psi_{e,ion} - \psi(t)\right) + I$$

that does not depend on space. In contrast to , the neural field equation may be interpreted as a “cable” equation in the nervous tissue. This aspect of the approach will be discussed in conclusion.

3. Dynamics in the long-term : Field equation and S-Propagator for synaptic efficacy

a) Elementary mechanisms

First, let us briefly describe the present knowledge about the modulating function of nervous activity. Referring to review paper from (Malenka & Nicoll, 1999), there is now evidence for the role of increased calcium in the expression of long-term potentiation (LTP) in the dendritic spine. LTP is the long-lasting synaptic enhancement under the repetitive activation of excitatory synapses in the hippocampus. It is now well admitted that STP (short-term potentiation) and LTD (long-term depression) are different expressions (under other certain conditions) of the same biological system. Triggering mechanisms followed by signal transduction then expression mechanisms result in LTP. Two different subtypes of the glutamate receptor are (often) colocalized on a dendritic spine: (i) the AMPA receptor (AMPAR) has a channel permeable to

Na^+ and K^+ cations, responsible of inward postsynaptic current (basal synaptic response) when the cell is close to its resting membrane potential; (ii) the NMDA receptor (NMDAR) depending profoundly on voltage because of the blocking of its channel by extracellular Mg^{++}. Thus, NMDAR contributes very little to basal synaptic current, but high frequency stimulation depolarizes the postsynaptic cell and consequently induces LTP. Depolarization provokes the dissociation of Mg^{++} from its binding site, which allows Ca^{++} (and Na^{++}) to enter the dendritic spine.

Triggering mechanism of LTP is the consequence of the rise of intracellular Ca^{++} within dendritic spines when it reaches the threshold. It is remarkable that a reversal of these mechanisms occurs when this threshold is not reached. In this case, either a short-term potentiation (STP) or long-term depression (LTD) can be generated. This means that the same biological system originates in LTP, STP or LTD according to the initial conditions.

Signal transduction is the second step, i.e. the set of mechanisms that translate the increase in Ca^{++} into an increase in synaptic efficacy. Strong evidence implicates α-calcium-calmodulin-dependent proteinkinase II (CaMKII) as the key component of the molecular machinery of LTP. In conjunction with calmodulin (CaM), calcium activates CaMKII that undergoes autophosphorylation. When autophosphorylated, activity of CaMKII is no longer dependent on CaM, thus maintaining its activity after Ca^{++} returns to basal levels. Several other protein kinases could have a role in LTP, as well as postulated retrograde messengers (which must be released by the postsynaptic cell to modify presynaptic function), but evidences are not so strong for their absolute requirement.

Expression mechanisms are the third step, i.e. the mechanisms inside the synapse that cause the increase in synaptic efficacy as soon as CaMKII is autophosphorylated. There are three candidates for postsynaptic modification to cause LTP: AMPA receptor function, AMPA receptor number, and probability of neurotransmitter release. It is clear now that the mechanism of change in AMPAR responsiveness is the increase in AMPA receptor *single-channel conductance*, due to the phosphorylation of the AMPA receptor subunit GluR1 mediated by CaMKII (a dephosphorylation of this receptor provokes LTD). It has also been shown that there is a differential redistribution of synaptic AMPARs and NMDARs after prolonged increases or decreases in neuronal activity. These receptors can therefore be *independently* regulated by activity at individual synapses. The phosphorylation of the AMPAR itself influences the subsynaptic localization of the AMPARs such that more AMPARs are delivered to the synaptic plasma membrane. This would also explains LTD because of their dephosphorylation and their movement away from the synaptic plasma membrane. "Reserve" AMPARs are the most probably localized in the dendritic shaft at the base of the spine, although this is not yet clear.

b)Functional organization and dynamics of the LTP system

Because of the generality of the formalism, we may follow the same reasoning as for the activity-organization level. The main structure involved in the modification of synaptic efficacy is the synapson, i.e. the structure in the dendritic spine composed of NMDARs inside the subsynaptic membrane on one hand, biochemical pathways and "reserve" AMPARs inside the cytoplasm of the dendritic spine on the other hand. In the field continuous description, the functional interaction φ^0 is propagated in the space of synapsons from one point to another. At any point s in this space, the source of the field is identified with AMPARs activity, and contains expression mechanisms of LTP, because the conductance of the channel is increased as well as the number of AMPARs.

The main property that leads to learning and memory in the brain is that a strong activation of one set of synapses depolarizes adjacent regions of the dendritic tree. What are the mechanisms for this effect? There are two possibilities: either through non-local functional interactions in the space of synapsons, at the origin of associativity between two sets of synapsons corresponding to two ensembles of connected presynaptic neurons; or following local diffusion through the extracellular space.

More specifically, let us consider equation for φ^0 in the space of synapsons:

$$\frac{\partial \varphi^0}{\partial t}(s,t) = \nabla_s (D^s \nabla_s \varphi^0\ (s,t)) \ +$$

$$\int_{D_s(s)} \rho^s(s')\ \mathrm{P}\Phi(s)\ \mathrm{P}(s')\ \varphi^0\ (s',t - \frac{d(s',s)}{v^s})\ ds' \ + \ \Gamma_s(s,t)$$

The first diffusion term describes the local influence through the extraneuronal space, e.g. the ability of molecules emitted postsynaptically, that diffuse in the extracellular space to act presynaptically on other neighboring synapses.

The second non-local term describes the effect of synaptic current flowing through the cytoplasm from one synapson to act upon other "connected" synapsons. Operator $\mathrm{P}(s')$ includes the decremential propagation of potential φ^0 along the dendrite, and operator $\mathrm{P}(s)$ describes triggering and transduction mechanisms that start when the increase in potential due to the summation of potentials has reached the threshold at s. Specify the latter requires knowing in which part of the synapsons these mechanisms are localized. We do not know yet enough about these mechanisms to go further. However, because chemical reactions for CaMKII are localized in the cytoplasm and AMPARs are partly in the subsynaptic membrane, non-local interactions exist certainly between them at this lower *c*-level. We will consider here a simpler model for the set of channels-biochemical pathways, applying equations and . This means that they are localized at one point *s* in the continuous space of synapsons, where the local dynamics of the system are evolving. The diagram of Figure 13 as well as for activity sums up the location of these mechanisms, i.e. in what space operators apply. Figure 14 is an extension of this diagram. As we have shown in another paper (Chauvet, 1993b), Hebbian learning rules may come from the mathematical structure of the non-local term.

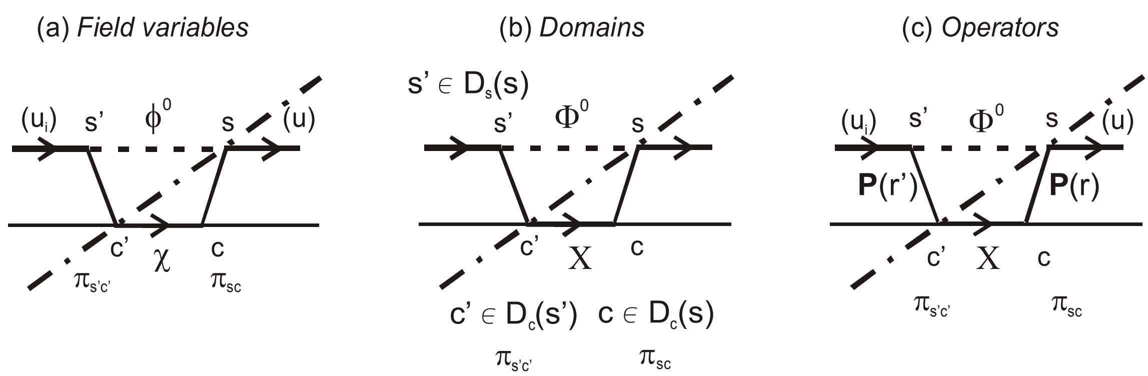


Figure 13 : Diagram for synaptic efficacy (to compare with for activity).

The third term, the source $\Gamma_s(s,t)$, contains expression mechanisms, i.e. the mechanism of increase in AMPA receptor *single-channel conductance*, due to the phosphorylation of the AMPA receptor mediated by CaMKII.

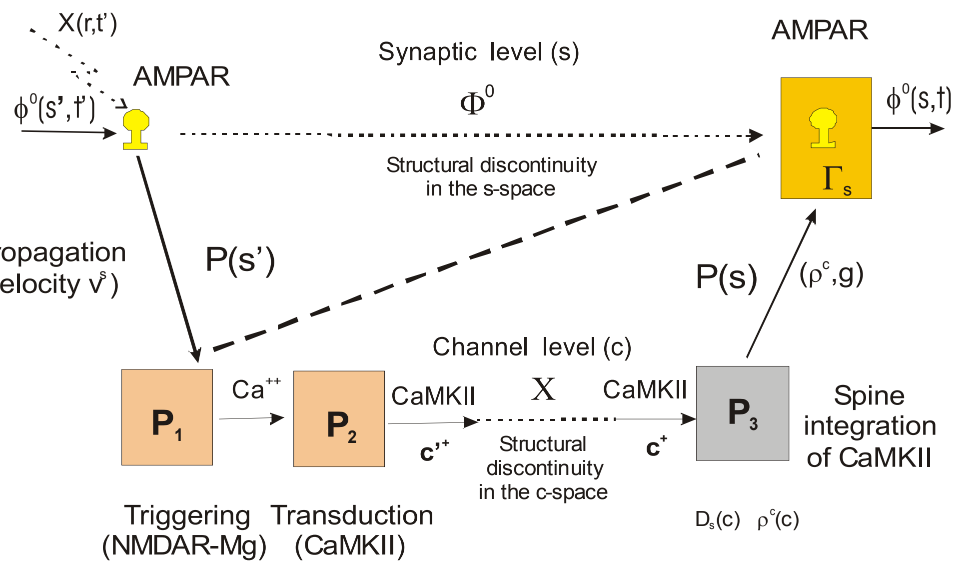


Figure 14: A possible schema for LTP, similar to Figure 11 for activity.

A succinct presentation will now be given for illustrating the integration of local models in the n-level field formalism.

E. Local dynamics : specific usual models for *trans*-operators

For illustration, I show in this section how operators $(\mathrm{P}_i)_{i=1,5}$ may be calculated in the short-term using usual mathematical models. The choice of the model regarding, e.g. its complexity, depends on assumptions for the given problem. Only the principle of the method is exposed in the following, the companion paper (Chauvet P. & Chauvet G.A., submitted) will present the detailed modeling as well as the techniques of resolution.

1. Neurotransmitter release : Operator P_1

In the terminal, complicated calcium dynamics provide for the diffusion of neurotransmitter in the synaptic cleft, as a consequence of the action potential ψ^{AP} (Chaudhuri & Bhaumik, 1996; Giovannucci & Stuenkel, 1997; Littleton & Bellen, 1995; Thomas & Elferink, 1998). Let us consider the model of the presynaptic bouton (Figure 15) described in the s-space, the internal coordinates being denoted as $s_0, s_1, s_2, \cdots$. In this model, calcium diffuses from the boundary at s_0 to the terminal at s_1, the neurotransmitter is released at s_1, diffuses from s_1 to s_2, and binds to the receptor at s_2. Thus, the space coordinate is $s \in [s_0, s_1]$ and $s \in [s_1, s_2]$. Processes occur in these two compartments, the bouton and the cleft. Free calcium concentration $c(s,t)$ is given by the approximated system:

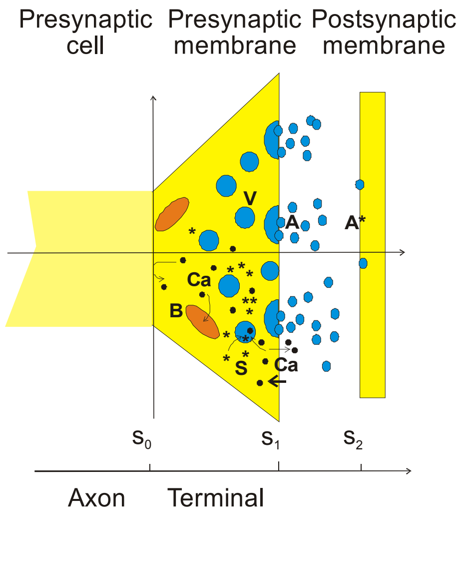


Figure 15: Model of the terminal bouton (left), mathematical geometry notations (right).

$$\frac{\partial c}{\partial t}(s,t) = D\nabla^2 c(s,t) + I_{Ca}(s,t)$$

where D is the calcium diffusion coefficient and I_{Ca} is the calcium current, depending on the chemical mechanisms as follows:

- *Buffering process inside the core of the bouton* ($s \in]s_0, s_1[$). Calcium complexes with the buffering protein B to provide the complex Ca-B (Ca-buffering protein) in concentration, giving rise to the current:
$$I_{Ca}(s,t) = I_{Buf}(s,t)$$
- *Calcium current I_{Bd} at the absorbing interface* ($s = s_0$). At s_0 in the absorbing interface, the function I_{Bd} represents absorbed calcium at a certain rate measured by q:
$$I_{Ca}(s,t) = I_{Bd}(s,t)$$
- *Calcium current at the terminal membrane* ($s = s_1$). This current is due to ATP pumps (I_{Pump}), entrance of calcium through the calcium channels giving rise to current I_{in} (following action potential $\psi^{AP}(t)$), and exit of calcium I_{out} on the boundary. Thus:
$$I_{Ca}(s,t) = -I_{Pump}(t) + I_{in}(t) - I_{out}(t)$$
- Dynamics of vesicles, free calcium and synaptotagmin at the membrane of the terminal ($s = s_1$). Free calcium ions (not fixed by buffer B) react with synaptotagmin S following the chemical reactions where R is the chemical complex that attach to the vesicles. The corresponding dynamic system may be written (in simplified notations, because all molecules are located at s_1):
$$\frac{dS_1(t)}{dt} = k_{+1}(c_1(t))^2 S_0(t) - k_{-1}S_1(t) - \frac{dS_2(t)}{dt}$$
$$\frac{dS_2(t)}{dt} = k_{+2}c_1(t)(S_1(t))^2 - k_{-2}S_2(t) - \frac{dR(t)}{dt}$$
$$\frac{dR(t)}{dt} = k_3[S_2(t)]^m - \frac{dI(t)}{dt}$$
$$\frac{dI(t)}{dt} = k_{+4}R(t) - k_{-4}I(t)$$

This first model, expression of the operator $\mathrm{P}_1 \equiv \mathrm{P}(r)$ may be summed up by the diagram shown in Figure 16.

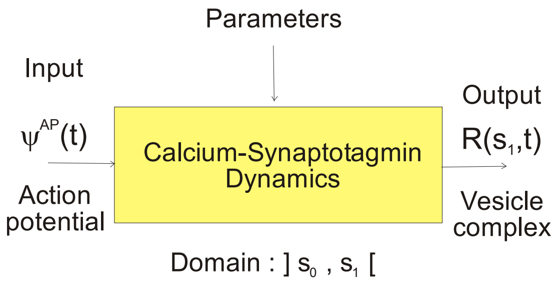


Figure 16 : Input-output model for the calcium-synaptotagmin dynamics that causes release of the neurotransmitter

2. *Neurotransmitter diffusion in the synaptic cleft : Operator* P_2

The second process represented by operator P_2 is the release of the neurotransmitter A and its diffusion in the synaptic cleft. When the number of complexes per vesicle is higher than a certain level R^{th}, vesicles are opening and they release their content in the synaptic cleft. Neurotransmitter diffuses in the cleft following the (local) equation:

$$\frac{\partial A}{\partial t}(s,t) = D_c \nabla^2 A(s,t) - P(s,t)$$

This second model, expression of the operator P_2 may be summed up by the diagram shown in Figure 17.

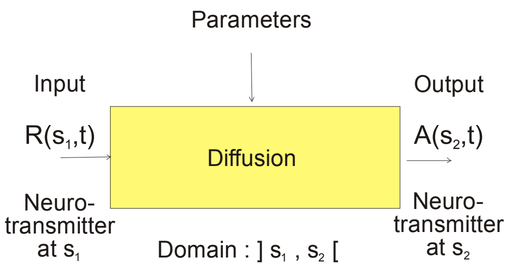


Figure 17 : Input-output model for the dynamics in the synaptic cleft (only diffusion here without recaptation).

3. *Postsynaptic side, binding to the receptor : Operator* P_3

Activation of AMPA receptors by glutamate starts when neurotransmitter binds to the receptors present in the postsynaptic membrane. The AMPA receptor-channel complex is one of the simplest glutamate activated ion permeable channels to be found in the postsynaptic membrane. It is permeable to both sodium and potassium ions, but unlike some other types of channel (e.g. the NMDA) it is impermeable to calcium. Once activated, the postsynaptic membrane potential changes due to desequilibrium between ion concentrations (Na and K) apart the membrane. We can use, e.g. the model of (Patneau & Mayer, 1991) also considered by (Ambros-Ingerson & Lynch, 1993):

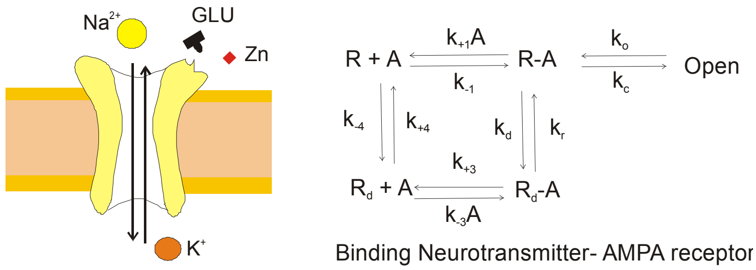


Figure 18 : Left: the AMPA receptor -channel in the postsynaptic membrane. The channel is permeable to sodium and potassium. Two types of receptor control the channel, one which binds with the glutamate and the other which binds with zinc ions.Right: Kinetic schema for binding between neurotransmitter and AMPA receptor

The AMPAR has 3 states, sensitised, desensitised and open. Whilst the AMPA is sensitised its receptor can either be bound with glutamate (state RA) or unbound (state R), similarly the unbound and bound desensitised states are R_d and R_dA respectively (Figure 18b). The kinetics corresponding to the model given in this figure may be obtained using a general method (Chrétien & Chauvet, 1998). Finally, operator P_3 corresponds to the diagram shown in Figure 19: the postsynaptic current is determined from the known amount of neurotransmitter released.

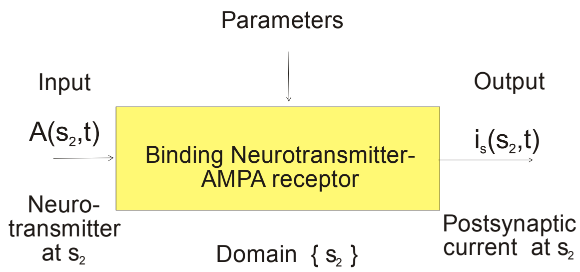


Figure 19 : Input-output model for the postsynaptic side.

4. Conduction of the postsynaptic currents: Operator P_4

There are numerous works using more and more sophisticated methods that accounts for conduction of the postsynaptic currents towards axon hillocks. All are based on cable theory. The difficulty of the problem is related to the geometry of the dendritic tree. Most often it is assumed that a cable equation can be applied to each segment of each dendritic tree between branch points:

$$r_m c_m \frac{\partial \psi}{\partial t} = \frac{r_m}{r_i} \frac{\partial^2 \psi}{\partial z^2} - \psi + r_m i_s$$

where r_m, r_i, i_s are respectively the membrane resistance of unit length times unit length, the internal resistance per unit length, and the postsynaptic current density per unit length. Coordinate z measures the position along the dendrite axis (equivalent cylinder). Rigorously, if no assumption is made on the geometry of the dendritic tree and the input-current density, one cable equation must be solved for each of segment. Moreover, the biophysics of the dendrites becomes more and more complicated given the existence of "weakly" active synapses (see, e.g.,(Poznanski, 2002)).

Under certain highly restrictive symmetry requirements on the input-current density and boundary conditions, the dendritic tree can be transformed to an equivalent cylinder. In this case, only one cable equation needs to be solved. However, in real physiological situations, input currents do not satisfy the symmetry requirements. (Walsh & Tuckwell, 1978) have proven a mapping theorem giving a method of determining the potential over the soma-dendritic surface when the input-current density is arbitrary. The method is based on the transformation from tree to nonequivalent cylinder. The time-dependent solution of the cable equation for this cylinder gives the potential at the soma, and the Green's function allows analytical resolution (Tuckwell, 1988). Another theorem applies to neurons with several dendritic tree originating from a common soma. In any case, the local conduction model provides the membrane potential at the axon hillock, thus the current for a given input-current synaptic density.

With these assumptions, operators P_4 and P_5 may be defined as follows. Equation is replaced by:

$$i(r,t;r') = \mathrm{P}_5(r)\ i_s(s'(r'),t)$$

and equation by:

$$\begin{cases} r_m c_m \dfrac{\partial \psi_m(z,t)}{\partial t} = \dfrac{r_m}{r_i}\dfrac{\partial^2 \psi}{\partial z^2} - \psi + r_m i(r,t;s') \quad z \in [0,l] \\ \psi_m(r,t) = \psi_m(0,t) = P_4\, i(r,t;r') \end{cases}$$

where z is the coordinate in the s-space for neurons at r, which runs from 0 (origin corresponding to the axon hillock at r) to l (terminal of the dendritic equivalent cylinder) in the physical space. Operatorial equations and mean: first that the total postsynaptic current is calculated for the equivalent cylinder using P_5; second that the cable equation is solved using P_4, and the source current, created by neurons at r', at the axon hillock is derived as : $I_m(r,t) = \psi_m(r,t)/r_m$. Then equations with $\mathrm{P}(r) = \mathrm{P}_4\mathrm{P}_5$ and apply.

It is important to note that, in this approach, even highly complicated local models are input-output models, the mathematical solution may be placed in the non-local field equation . The mathematical structure is the same for any given biological system, so that whenever the functional interaction is identified, existing local models may be used for the *trans*-operators, their degree of complexity depending on the problem to solve.

F. Discussion and conclusion

In this approach of a biological system in terms of functional interactions, there is a theory (n-level field theory of functional organization) and a formalism (S-propagator). These two parts are now discussed.

The theory is based on an ensemble of abstract concepts that make an idealization of the biological system with a given approximation. What is this approximation ? It must be justified from a general property, and I have shown that the dynamical stability of the system justifies the existence *a posteriori* of the functional interaction in two cases, either simple (associates biochemical pathways) or more complex (functional units of the cerebellar cortex). For this reason, I have chosen the representation in terms of functional interactions. The basic idea is that a certain quantity is emitted by a structure (structural unit "source"), propagated at finite velocity, and acts onto another structure localized at a distance (structural unit "sink"). This is the most elementary definition of a physiological function. Thus, the biological functional system is a combination of such interactions, and this combination defines the functional organization of the system. Each structural unit being organized according to space scales, it may be deduced that the resulting organization is double, structural according to the space scales and functional according to the time scales. This second organization comes from the time hierarchy of the dynamical processes, which means that physiological functions are included one into the other. It may be seen from two equivalent ways. From the mathematical point of view, it means that the state variables of the dynamical system at a level are parameters for the dynamical system at the higher level. From the computing point of view, the computation is driven by time units that evolve inside imbricated time loops. In the nervous tissue, activity evolves in one millisecond time scale, although LTP evolves in one minute (or more) time scale. These two dynamical processes, which run in two different time scales, are two different physiological functions, the second function controlling the first one. Therefore, the structural units that are involved in a physiological function are hierarchically and lead to the 3D representation (Figure 7).

The principle of the method has its core in this continuous and hierarchical representation. Each structural unit in the hierarchical system contains dynamics that are space-dependent on other structures located elsewhere. In other words, two neurons infinitesimally close located at r and $r+dr$ in the space of neurons are at a finite distance at the lower level that is defined as the space of synapses. Therefore, the interaction runs on a finite distance in the space of synapses although infinitesimally close in the space of neurons. This property is called *non-locality* of the functional interaction. An equivalent way to see this problem is as follows. Because of the continuity, the neuron at *r'* is a point (because mathematically its dimension is null) in the space of neurons. The value of the potential at this point is $\psi(r')$. This neuron provokes another neuron to fire at *r'* where the potential will be $\psi(r')=\psi^{AP}$. Non-locality just expresses the following fact: Points *r* and *r'* are not points, but have an extension in the physical space (they are volumes, i.e. objects with dimension higher than zero) which contain the structures needed for the processes that make the potential to have the value ψ^{AP}. Continuous representation and spatial hierarchy are at the origin of non-locality.

To replace a neuron by a point that acts onto another point is therefore an idealization that describes a non-local transport (propagation) with velocity *v*. The great advantage of this method comes from this non-local property. Of course, in the extended physical space, there are only local processes since the transport of matter satisfies to physical laws, e.g. the Naviers-Stokes for blood, the Hodgkin-Huxley equation for action potential. Instead of this transport, the propagation of functional interaction is considered *as an action that introduces a delay* at the highest level of the structure for the given function, which is most often sufficient for the study of the complex system. Only the case of the local transport itself could need a specific analysis. But this case could be studied out of the global study, and the corresponding results introduced in the field equation as parameters. For example, the velocity of action potential propagation in the space of neurons, or the study of the dendritic propagation for the postsynaptic potential in the space of synapses, may depend on parameters the influence of which would be preliminary studied. Thus, it is made a certain simplification that make possible the study of the complex system on rigorous bases, and specifically that leads to the representation of the system by a hierarchical graph. Of course, physical laws of conservation must be satisfied in this new representation. The structure of the non-local equation has been derived from this law of conservation (Chauvet, 1993a).

The continuity of the space of units, neurons or synapses, bring other advantages. Specifically, continuity imposes new continuous functions, the so-called *density* and *density-connectivity functions for* structural units neurons or synapses, often easier to handle and closer to reality because what is observed is often expressed in terms of optical density. Continuity allows more sophisticated mathematical formalization, and the use of mathematical tools of classical analysis. The computing treatment appears only at the end to solve the equations numerically, such that in the continuous space of neurons, the number of neurons is described by neuronal volume density, and the numerical resolution calls for standard techniques whatever these numbers. In contrast to computational analysis that requires the number of processors (or objects) depending on the size of the network.

The second aspect of the theory concerns the S-propagator formalism. Using this formalism, functional interaction may traverse levels of structural organization. Why? Basically, the breakdown of the physiological function along space scales and time scales allows the functional interactions to traverse levels of organization, using mathematical operators. The difficulty is in the definition of the functional interaction for the given problem. Any functional interaction, more or less complex, or non-elementary, with the level of structural organization, must traverse levels of structure. Rigorously, this crossing would have to be non-local, but due to mathematical constraints related to the interpretation of processes, it is necessary to chose which processes are local and which ones are non-local. In the example of action potential propagation, because the axon hillock is chosen as the source (and thus the sink), the functional interaction must go from the source to the sink, i.e. must pass through the axon in r', the synapse in $s'(r)$, the cell body from $s'(r)$ to the axon hillock at r. The summation of currents would be at r. Propagation would occur from r' to r such that mechanisms in the neuron (synaptic transfer, dendritic transport) would be coarsely replaced by a propagation with a delay depending on velocity. It is thus more acceptable to consider the neuron as the sink and the axon hillock as the source of the interaction to avoid too important simplification. Operators provide easily such a separation between local and non-local processes. The S-propagator is the mathematical operator that allows the interaction to pass from r' to r. It is the product of three operators called respectively: (i) the *trans*-operator that acts at r' and makes the interaction to go from the observed level down to the lower level; (ii) the *in*-operator that propagates the interaction from r' to r at the lower level, and (iii) the *trans*-operator that acts at r and makes the interaction to go from the lower level up to the observed level.

The usefulness of the S-propagator formalism comes from the ability of choosing between non-local and local processes depending on the existence of specific local models to describe elementary biophysical mechanisms (Poznanski, 2001). Indeed, the great advantage of this formalism in the framework of the n-level field theory is the ability of integrating specific models existing in scientific literature. Any *trans*-operator corresponds to one or several mathematical models adapted to the general, global model. This has been shown in section 5.

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