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3 **Research Report**

5 **THE USE OF REPRESENTATION AND FORMALISM**
 6 **IN A THEORETICAL APPROACH TO**
 7 **INTEGRATIVE NEUROSCIENCE**

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14 In the light of existing physical theories, it is shown that representation in terms of func-
 15 tional interactions and formalism (S-Propagators) should satisfy three physical and six
 16 biological constraints. Consequences are summarized for neurohormonal field, develop-
 17 mental phase, aging phase, functional hierarchy, Principle of Auto-Associative stability
 18 (PAAS), self-organization and neural selection, Darwinian evolution, and the intelligence
 19 of movement. Abstraction and complexity of the proposed theories are discussed relatively
 to their advantages for integrative neuroscience.

20 *Keywords:* Biological theory; mathematical model; integration; biological constraints;
 21 physical theory; hierarchy; time scales; space scales.

22 **1. Introduction**

23 Over the last several years, biologists have shown an increasing interest for integra-
 24 tive physiology in general and in specific integrative neuroscience. This way has been
 25 the consequence of the fantastic development of molecular biology and the design
 26 of sophisticated computational tools. Identification of the human genome led to the
 27 development of proteomic and new efficient experimental techniques. The main con-
 28 sequence of all this experimental research is the tremendous amount of data in all
 29 the fields of biology that may be handled with computers.

30 The present state of biology is then characterized by an immense amount of
 31 data and the difficulty in interpreting the data. The meaning given by biologists
 32 to the word “integration” corresponds to this state of biology. By “integration”,
 33 they understand the fact that experimental data are necessarily linked to some
 34 relationships yet to be discovered.

35 Specifically for many authors, “integration” is now related to novel tech-
 36 niques derived from informatics, which in neuroscience, constitute what is termed
 37

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1 “neuroinformatics”. As eloquently summarized by Evian Gordon in the editorial of
JIN dedicated to the Brain Resource International Database (BRID), “Integration
3 of such diverse information through models and databases is of course extremely
challenging, but is increasingly being encouraged at the highest levels Neuro-
5 science databases have, over the past decade, begun to be established as a part of
the emerging field of Neuroinformatics, which deals with information as diverse as
7 microanatomy, receptor distributions, single cell recordings, drug effects and com-
puter science driven interoperability among databases These databases have
9 mainly been established to acquire data in a flexible manner and to store the data
in a distributed fashion” [21].

11 The other aspect of integration associated with biologists concerns how gene
products integrate at the cellular, systems and whole-organism level [16, 13]. This
13 is obviously not an operational definition but it gives a good idea of what is integra-
tive physiology. In precise, these authors meant: “completion of the human genome
15 only serves to re-emphasise the significant knowledge gap between the basic parts
catalogues generated from powerful reductionist strategies and our understanding of
17 how gene products integrate at the cellular, systems and whole-organism level. Such
an integrative approach, bridging multiple organ systems, is beginning to reveal
19 novel mechanisms, fundamental physiological principles and therapeutic targets for
treatment of major human diseases.”

21 In this article, I shall introduce a new aspect of integration, i.e., the mathemati-
cal integration of physiological functions with its strict significance, and to show that
23 a general theory in biology should be of a mathematical nature leading implicitly to
integration. For this reason, I will recall in the next sections, (i) what are the basic
25 constraints for the construction of a theory in biology, (ii) what is a theory and what
could be a biological theory relative to a physical theory, and (iii) a summary of this
27 theory. Various consequences for development, aging, neuro-hormonal functions, evo-
lution of species, intelligence, consciousness, will also be developed in future issues.

29 **2. What are the Constraints for a Theory in (Neuro)physiology?**

There are two classes of constraints for a biological system: (i) something obvi-
31 ous: biological systems *are* physical systems, and (ii) constraints that are specific
to biological systems. Let us consider the first class of constraints. Evidently, bio-
33 logical systems constitute of molecules and they *satisfy to known physical law*. It is
important to remember this obvious fact. However, they are permanently *far from*
35 *thermodynamic equilibrium* state and are maintained in this state using energy from
environment. This is a basic fact that is seldom observed in the natural states of
37 non-animated matter. More specifically, in this class of physical constraints:

- (*Phys1*): *Biological systems are constituted of physical mechanisms*. The descrip-
39 tion of these mechanisms is the objective of mathematical modeling. An example
of such a description is given in Poznanski’s book [29].

- 1 • (*Phys2*): *Biological systems are hierarchically organized regarding their structure.*
 The structure being considered as the spatial, “physical” arrangement of the
 3 elements of the system, the structure will coincide with the histology and the
 anatomy of the system such that the structural hierarchy corresponds to the hier-
 5 archy of the material system observed. Thus, a first important character of living
 systems appears: the physical structures are arranged in the form of compartments
 7 within compartments, i.e., a hierarchical structural organization. The most simple
 vision of this particular structure is given by the image of the nucleus inside the
 9 cell, the cell inside the tissue, the tissue inside the organ, and the organ inside the
 organism. As we will see later, reality is much more complicated because of
 11 the relation of structural organizations with the physiological functions they have.
- 13 • (*Phys3*): *The behavior of biological systems results from dynamical process, i.e.,
 that are time- and space- continuously varying.* Any phenomenon considered in
 neuroscience such as opening of channels, changing in calcium concentration, mod-
 15 ification of potential at any point of the neural network, couplings between neurons
 and glial cells, depends continuously on space and time.

17 The second class of constraints addresses specific biological properties:

- 19 • (*Bio1*): *Biological systems are capable of action.* Biological systems are organized
 in a specific manner in order to accomplish a task. They are capable of action. This
 21 character makes them strongly different from a physical system, and in fact they
 are closer to engineering systems. This fundamental property of living systems is
 described by what are called “*physiological functions*”, more or less sophisticated
 23 according to living species. These functions exist at any level of the organization,
 and result from the working of organized structures. Many philosophers and biol-
 25 ologists have discussed about the relationship between structure and function. In
 the mathematical approach that I propose here, I will replace this ancient vision
 27 of the structure-function problem by another one more tractable regarding the
 relation between structural and functional organizations.
- 29 • (*Bio2*): *Biological systems are capable of auto-reproduction.* There is a fact, unique
 in the universe, that is the continuously reproduction of living species. The liv-
 31 ing world evolves thanks to the auto-reproduction of its members following the
 identical schema: birth, life, death. From a more biological point of view, we may
 33 extend this evident assertion as follows. Since each structure of the biological sys-
 tem has a fundamental gene level, it is capable of *self-reproduction*. Since all the
 35 structures contain identical genetic material, they have the fundamental property
 of *equipotentiality*. In other words, each structure normally possesses a potential of
 37 self-reproduction identical to that of all the others. This is often viewed with the
 word “stem cells”. Although equipotentiality is a general biological property, the
 39 mechanism of differentiation leads to the specific development of the structural
 units of an organism during its growth.
- 41 • (*Bio3*): *Biological systems are adaptive and self-organized.* Let us first consider
 the difference between *organized* and *self-organized* systems. We may say that a

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1 system is organized if its internal state varies under the influence of an external
2 cause, and ceases to do so when the cause is suppressed. For example, the struc-
3 ture of a metal rod corresponds to an arrangement of elements that are completely
4 stabilized by physical interactions. If the rod is twisted, the set of forces acting
5 between its elements will be perturbed, leading to a modification of its structure.
6 Again, if the forces acting between the elements are modified, the rod will change
7 its shape. This type of definition, which expresses the relationship between exter-
8 nal causes and internal effects, can be readily expressed in mathematical terms.
9 It may also be extended to a self-organizing system *when the organizing forces*
10 *are internal with respect to the system*. Obviously, the mathematical formulation
11 of self-organizational processes will then be identical to that of an organizational
12 process, the only difference lying in the nature of the applied forces, which are
13 internal in the former and external in the latter. It is equally obvious that the inter-
14 nal forces change with the system such that there is a reciprocal action between
15 cause and effect. Thus, it is easy to see how a material system subjected to inter-
16 nal forces, such as shear forces, may be deformed and change from one state to
17 another with a different molecular configuration.

18 • (*Bio4*): *Biological systems are composed of specialized functions*. A fundamental
19 property of living organisms is that of *functional specialization*, as observed for
20 example in the organs of a body. During the development and growth of an organ-
21 ism, sets of cells associate in the body to form tissues with specific functions. Then,
22 the various tissues are regrouped step by step to form a structured organ with a
23 well-defined physiological function. For example, the ventilatory function of the
24 lungs requires the association of lungs, thoracic and abdominal muscles, as well
25 as the system of respiratory regulation. The process that leads to the formation
26 of the elastic walls of the lungs by the association of tissues made up of cells, all
27 having the same structural properties, may be considered as that of *functional*
28 *specialization*.

29 • (*Bio5*): *Biological systems are highly integrated based on elementary mechanisms*.
30 This is certainly the most important property of biological systems, which repre-
31 sents a unique complexity and thus the mystery of the living world [9]. How and
32 why so complicated systems may work, given the immense number of intricate
33 elementary mechanisms? This is the case for the nervous system with its several
34 billions of interconnected neurons, not only from the point of view of its cogni-
35 tive functions, but also for its working. Indeed the brain, the noble organ of the
36 body, poses a major environmental problem in the organism. It consumes large
37 amount of glucose and burns up enormous quantities of oxygen (25% of the total
38 body consumption whereas it represents only about 2% of the mass), producing
39 a high level of acidity. The brain is as well-protected against mechanical shocks
40 by the skull and its meningeal structures as it is against bacterial attack by the
41 blood-brain barrier. However, it also needs to be protected against the excess
42 acidity produced by the metabolic activity of cerebral tissue. The by-products of

1 metabolism, hydrogen ions and carbon dioxide, diffuse into the cerebrospinal fluid
 (CSF) that may be truly qualified as the “internal sea”. The CSF, a medium that
 3 has still to reveal all its secrets, contains neuronal endings that act as the chemore-
 ceptors of a highly efficient regulatory system designed to eliminate wastes.

5 • (*Bio6*): *Biological systems evolve in time according to two different phases: the*
phase of development and the phase adult.

7 All these constraints, largely accepted by biologists, will now be compared with
 the theory and its consequences. They will be recalled as (constraint *Physx*) or
 9 (constraint *Bioy*) in the text.

3. The Mathematical Theory of Integrative Physiology (MTIP)

11 In physics, a theoretical framework is very well known, accepted and needed. There
 are some decisive advantages to work within a theoretical framework. The most
 13 important is certainly the ability of scientists to discuss on the same bases, i.e., to
 speak using the same language, leading to the improvement of common and accepted
 15 scientific knowledge. Before presenting my own vision of physiology, I will recall what
 are representation and formalism in physics, which would be useful to understanding
 17 the notion of operator.

3.1. An example of representation and formalism in physics

19 Reality in physics may be described and its processes predicted using *mathematical*
representations. For example, the dynamics of a physical system expressed in terms
 21 of forces acting on particles and their positions is obtained inside a mathemati-
 cal representation, in which forces and positions are mathematical objects (Landau
 23 and Lifchitz 1969). In this representation, there are relations that govern the vari-
 ation in space and time of the object. These relations constitute the physical law.
 25 Mathematical representation joined with hypotheses and laws constitute a *theory*.
 In physics, there are many related theories, derived from one of them. They are
 27 valid in specific conditions, one of them being the limit of another. This is the case
 of Newtonian mechanics which is the limit of relativity when velocities of particles
 29 are small relative to light velocity.

More specifically, let us consider a system of N interacting particles. Its position is
 31 completely determined by $3N$ Cartesian coordinates. The minimum number of inde-
 pendent coordinates is the number of degree of freedom. Then, it is possible to chose
 33 s coordinates called $q_1, q_2, \dots, q_s \equiv q$, also known as the *generalized coordinates*. The
 time variation of this system is given by the principle of Maupertuis-Hamilton, i.e.,
 35 a principle of least action as follows: Between the two positions $q^{(1)}$ and $q^{(2)}$ at times
 t_1 and t_2 respectively the system moves in space such that the integral:

$$I = \int_{t_1}^{t_2} L(q, \dot{q}, t) dt \quad (3.1)$$

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1 is minimum, i.e., $\delta I = 0$, where \dot{q} is the time derivative of q . $L(q, \dot{q}, t)$ is the Lagrange
 2 function that contains only coordinates and velocities because in a mechanical sys-
 3 tem these data are sufficient to completely determine the state of the system. Devel-
 4 oping $\delta I = 0$, the Lagrange equations for the system of particles, are equivalent to
 5 the Newton equations between accelerations, velocities and positions:

$$\frac{d}{dt} \frac{\partial L}{\partial \dot{q}_i} - \frac{\partial L}{\partial q_i} = 0 \quad i = 1, 2, \dots, s$$

7 We may say that the system is described in terms of \dot{q} and q in a Lagrangian
 8 representation. A new formalism, the Hamiltonian formalism, may be deduced from
 9 the Lagrangian formalism. In this case, Lagrange equations are replaced by Hamilton
 10 equations. Lagrange equations are written in terms of generalized coordinates and
 11 velocities. Considering momentum rather than velocity leads to the new formulation
 that implies:

$$\begin{cases} \dot{p}_i = -\frac{\partial H}{\partial q_i} \\ \dot{q}_i = \frac{\partial H}{\partial p_i} \end{cases} \quad i = 1, 2, \dots, s \quad (3.2)$$

12 These Hamilton equations are the $2s$ first order movement equations and they
 13 replace the s second order equations deduced from Lagrange equations. We may say
 14 that the system is described in terms of \dot{q} and \dot{p} in a Hamiltonian representation.

15 However, this notion of representation is even more crucial in quantum mechan-
 16 ics. We may derive the dynamics of the N -particles quantum system using the
 17 Hamiltonian formalism for the N -particles classical system. The *Schrödinger rep-*
 18 *resentation* is obtained when correspondence rules are applied to the classical
 19 Hamiltonian H :
 20

$$H \equiv H(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N, \mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_N) \quad (3.3)$$

21 where $\mathbf{r}_i(x_i, y_i, z_i)$, $i = 1, N$, is the position in rectangular Cartesian coordinates and
 22 $\mathbf{p}_i(p_{xi}, p_{yi}, p_{zi})$, $i = 1, N$, are momentum components. Thus, we get the quantum-
 23 mechanical Hamiltonian operator:
 24

$$H \equiv H\left(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N, -i\hbar \frac{\partial}{\partial \mathbf{r}_1}, -i\hbar \frac{\partial}{\partial \mathbf{r}_2}, \dots, -i\hbar \frac{\partial}{\partial \mathbf{r}_N}\right) \quad (3.4)$$

25 For a system of N particles with potential energy $V(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N)$, the classi-
 26 cal Hamiltonian is $H = \sum_{i=1}^N \frac{\mathbf{p}_i^2}{2m_i} + V(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N)$ and the quantum-mechanical
 27 Hamiltonian operator is:
 28

$$H = -\sum_{i=1}^N \frac{\hbar^2}{2m_i} \nabla_i^2 + V(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N) \quad (3.5)$$

1 The Schrödinger equation will then be $H\psi = E\psi$ where $\psi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N, t)$ is the
 2 wave function, i.e., a function of the Cartesian coordinates of all the particles in the
 3 system. E being replaced by the operator $i\hbar\frac{\partial}{\partial t}$, the Schrödinger equation is:

$$i\hbar\frac{\partial}{\partial t}\psi = -\sum_{i=1}^N \frac{\hbar^2}{2m_i} \nabla_i^2 \psi + V(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N)\psi \quad (3.6)$$

5 Thus, from the classical energy equation in Hamiltonian form: $H(\mathbf{r}, \mathbf{p}) = E$ where
 6 E is the total energy ($\mathbf{p}^2/2m + V(\mathbf{r})$), the Hamiltonian has been transformed into
 7 an operator that acts on a function of positions $\psi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N)$, giving rise to the
 8 time variation of the wave function or, in the stationary state, the discrete values of
 9 energy that are the eigenvalues of the Hamiltonian. The determination of the wave
 10 function provides the probability of the presence of the particles at a given point in
 11 the physical space.

12 In specific, $|\psi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N)|^2 d\mathbf{r}_1 d\mathbf{r}_2 \dots d\mathbf{r}_N$ is interpreted as the probability
 13 that particle 1 (the particle with position vector \mathbf{r}_1) be found in the small vol-
 14 ume element $d\mathbf{r}_1$ at point \mathbf{r}_1 , and simultaneously that particle 2 be found in the
 15 small volume element $d\mathbf{r}_2$ at point \mathbf{r}_2 , and so forth. The quantum interpretation
 16 is therefore radically different from the classical one. It is also primarily important
 17 to note that the general quantum theory is based on Hilbert spaces that make all
 18 representations equivalent to the Schrödinger representation (all derived through
 19 linear transformations), which is the case of the Heisenberg representation.

21 **3.2. A representation and a formalism for Formal Biological 22 Systems (FBS) in the framework of the MTIP**

23 To describe the dynamical states of a formal biological system, i.e., an idealized
 24 biological system, I propose a representation in terms of *functional interactions*
 25 (Chauvet 1993), i.e., mathematical objects denoted as $\psi^{(l)}(\mathbf{r}, t)$, defined at time t
 26 and at \mathbf{r} in a hierarchical continuous space, the space of structural units, at level l .
 27 They represent anything that is propagated from one structure to another (con-
 28 straint *Bio1*), such as action potential, molecules crossing membrane, the effect of
 29 an abstract parameter, and so forth.

30 This means that an organism is hierarchically structured (the hierarchy being
 31 defined by *space scales*) and that functional interactions exist between physical struc-
 32 tures in this space (providing a mathematical definition of a *physiological function*).
 33 There are at least two reasons for this choice: (1) Most often, biological properties
 34 result from couplings at lower levels of the functional organization, giving rise to
 35 “emergent” properties; (2) There is certainly a principle of organization based on
 36 the increasing number of coupled functional interactions in developing biological
 37 systems, something that is different from physical systems. This component is of a
 topological nature, independent of the physical geometrical space. The representa-
 tion in terms of functional interactions allows us to build such a rigorous theoretical

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1 framework, topological and geometrical, i.e., to mathematically define what we call
 2 “functional organization”, “physiological function”, “emergent” property, “hierar-
 3 chical space”, “structure”, and so forth.

3.2.1. *Topological definition of physiological functions: the (O-FBS)*

5 First, we define a *structural unit* as an *anatomic physical structure capable of action*,
 6 e.g., receptors, subcellular organites, synapses, neurons, groups of neurons, glial cells,
 7 neural networks, groups of neural networks. Because these structures correspond to
 8 given space volumes, we define structural units by the related space scale.

9 Second, we define the *spaces of units* as *abstract spaces in which defined structural*
 10 *units may be considered as points*. The inclusion of space of units inside the other,
 11 e.g., synapses inside neurons themselves inside groups of neurons, leads to *structural*
 12 *hierarchy* defined by the space scales (constraint *Phys2*).

13 Third, we define the *functional interaction* as the action of a structural unit,
 14 the source (say u_i in a given space of units and at a given level of this space) on
 15 another, the sink, say u_j , in the same space (given these preliminary definitions, see
 16 the appendix for a more precise definition).

17 In the specific case of the nervous tissue, the action of one unit on another, which
 18 is the action of one neuron on another, is represented by ψ emitted by the axon
 19 hillock which is propagated to the other. This abstraction transforms the space of
 20 neurons into the space of structural units “axon hillocks” *as concerns their function*
 21 *“nervous activity”*, i.e., the propagation of action potentials. The neuron is reduced
 22 into a point (located at the axon hillock), allowing us to use mathematical tools: a
 23 function of the neuron therefore is a function of point, although these points contain
 24 other structural units as synapses.

25 3.2.2. *Geometrical definition of functional interaction, operators* 26 *and fields: the (D-FBS)*

27 Let us consider now the positions of the structural units, i.e., we introduce the
 28 geometry of the system. Due to of the hierarchy and the definition of the space of
 29 units at a given level, structural units are continuously distributed at this level, in
 30 which they may be identified by their position, e.g., $u'(\mathbf{r}')$ for the source and $u(\mathbf{r})$
 31 for the sink. These notations correspond to the above u_i and u_j respectively. The
 32 functional interaction from $u'(\mathbf{r}')$ to $u(\mathbf{r})$ is represented as:

$$33 \quad u'(\mathbf{r}') \xrightarrow{\psi} u(\mathbf{r}) \quad (3.7)$$

34 and because the value of the functional interaction inside the sink at \mathbf{r}' and at time
 35 t' is $\psi(\mathbf{r}', t')$, we may interpret the functional interaction as a field variable that is
 36 transported from a source at \mathbf{r}' , represented by Γ , to a sink at \mathbf{r} (at a later time
 37 $t = t' + d(\mathbf{r}', \mathbf{r})/v$ where v is the velocity of interaction) under the action of a field
 38 operator H . This field approach is a natural way to represent the time and space

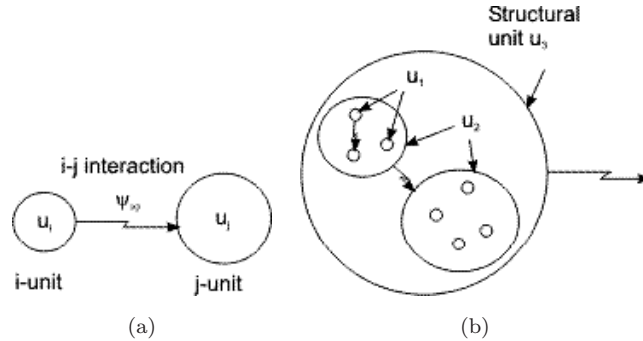


Fig. 1. (a) The basic element (left); and (b) the hierarchical biological system resulting from a combination of functional interactions with different levels of structures: u_1 are synapses, u_2 are the neurons, u_3 is a group of neurons.

1 continuous dynamics of the functional interaction (constraint *Phys3*):

$$\psi(\mathbf{r}', t') \xrightarrow{H} \psi(\mathbf{r}, t) \quad (3.8)$$

3 The formal field equation at a given level may be written:

$$[H(\psi, \psi^{(n)}, n = 1, 2, \dots)\psi](\mathbf{r}, t) = \Gamma(\mathbf{r}, t) \quad (3.9)$$

5 where Γ is the source term, and H depends on ψ and on its successive deriva-
 7 tives $\psi^{(n)}$ with respect to time and space coordinates. Geometry is involved in this
 9 equation since the operator which acts from one point of space to another, takes
 11 into account the distance between these two points. The dynamical processes that
 13 express the behavior of the related functional interactions occur continuously in
 15 space and time with a finite velocity. The velocity v has a finite value because
 it represents the transport of molecules, potentials, currents, or parameter effects
 depending on the elementary physiological function. Consequently, there is a *delay*
 in the response between units at different times of their production. These effects
 are included directly in the field interaction operator. The aim is to determine the
 operator that specifically describes a physiological function.

17 The basic equation (3.9) has obviously a different meaning from equations of
 physics (3.4) to (3.6) because the representation is quite distinct. Specifically, in
 19 contrast to the equation (3.9): (i) describes the propagation of the field variable ψ
 from \mathbf{r}' to \mathbf{r} in the hierarchical space of structural units at a given level, (ii) includes
 the local transformation in \mathbf{r} represented by $\Gamma(\mathbf{r}, t)$, and (iii) describes the diffusion
 21 in the extra-structural units. However, a new formalism is now necessary to traverse
 the levels of structural organization and to satisfy physical constraints such as the
 23 law of conservation of mass and ions. I have called it the *S-Propagator formalism* that
 works with specific *trans*-level operators [see Eq. (A.5)] identified with mathematical
 25 models of the processes (constraint *Phys1*).

27 This formalism [b] has been summed up in the Appendix, showing the main prob-
 lem, as the need to describe the dynamics through the levels of organization. Some

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1 methods had been proposed for one level of organization by Beurle [2], Griffith [22],
 2 Fischer [30] Wilson and Cowan [31], Ermentrout and Cowan [19]. At present, be
 3 as several levels of organization are taken into account, new concepts are involved,
 especially, the concept of *non-locality*.

5 **4. Developing the MTIP in the ψ -Representation with the S-Propagator Formalism**

7 The Mathematical Theory of Integrative Physiology (MTIP) is a theory of *functional
 organization* with some consequences that may be summarized as follows.

9 **4.1. *Two immediate consequences of the ψ -representation: non-symmetry and non-locality***

11 The functional interaction has two important properties: firstly, *non-symmetry* is
 12 directly derived from its definition because there is necessarily a transformation in
 13 the sink due to the structures existing *inside* the sink (hierarchy). Secondly, *non-
 14 locality* is due to the structural hierarchy. For this reason, the field operator H is
 15 non local as the infinitesimal distance between two points at a level, corresponds
 16 to a finite distance at the lower level. These two properties are the bases for the
 17 development of the topologic and geometric aspects of MTIP.

4.2. *Why a functional interaction? The PAAS*

19 We know that before reaching adulthood, the organism passes through a devel-
 20 opmental phase during which structural and functional organizations are modified
 21 under the control of a genetic program. Why does this program actually work as
 22 it is observed to do? To answer this question, we proposed the *Principle of Auto-
 23 Associative stability* (PAAS), which may be stated as follows: *The functional inter-
 24 action is created, in other words it exists so that the domain of stability of the
 25 physiological functioning increases, or is at least maintained, in spite of the increase
 26 in complexity due to the increase in the number of interactions.* In other words,
 27 the observed functional interaction is the one that increases the stability of the
 unit composed of the two units interacting through this functional interaction. This
 29 hypothesis is the basis for the MTIP [5].

4.3. *Functional hierarchy*

31 The FBS has been described in terms of functional interactions that propagate in
 32 the structural organization, i.e., in terms of space scales. However, we may also
 33 consider the nature of dynamical processes, i.e., the velocity of propagation of the
 functional interactions, in order to classify them in terms of their time scales. As
 35 the physiological function is a process, we get a set of functions that are organized
 according to the speed of the process. For example, action potential varies in time

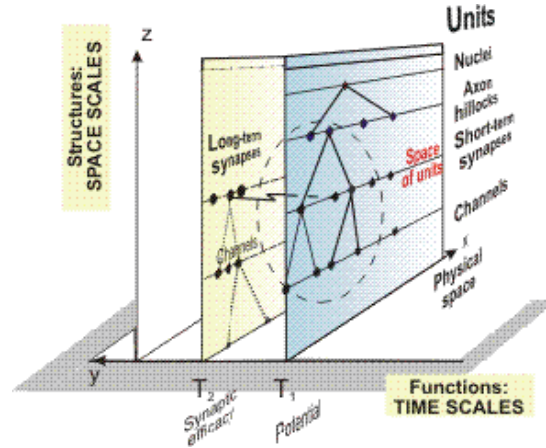


Fig. 2. The 3D representation of the neuron. Planes correspond to functions in two different time scales, activity and synaptic efficacy modification. Each plane contains the hierarchical structural organization (levels are indicated on the figure) to which the S-Propagator formalism applies. Functions are coupled through a given relation.

1 in the scale of msec, whereas synaptic efficacy varies in the scale of sec or min. This
 2 provides a means to separate physiological functions and to minimize the number
 3 of couplings between them in a highly organized and integrated biological system
 4 (constraint *Bio5*). As a consequence, a function described in a hierarchical structural
 5 organization, in terms of space scales, corresponds to a given time scale. Several
 6 coupled functions correspond to different time scales (e.g., for the neuron, see Fig. 2)
 7 as well.

4.4. Neurohormonal field theory of the brain: cerebral activity 9 and emotions derived from non-locality

10 We may wonder whether it is possible to construct a formal theory of neurohormonal
 11 interactions on the basis of the MTIP, which extends the phenomena of propagation
 12 and synaptic transmission, the binding of intra- and extracellular neuromediators
 13 with activatory or inhibitory receptors, i.e., which generalizes the problem of the
 14 description of cerebral activity by means of a neural field theory. The extraordinary
 15 structural and functional complexity of the brain are to be emphasized. Moreover,
 16 current research favors investigation of the chemistry of the brain, i.e., the neuro-
 17 chemistry of interneuronal communication, rather than that of the physical aspects
 18 involved in the propagation of electrical potentials along nervous fibres [28, 3]. How-
 19 ever, it is in fact the neurotransmitter-receptor or neuromodulator-receptor relation-
 20 ships, which directly or indirectly modify membrane permeability and thereby the
 21 neuronal activity. A neurohormonal field theory should integrate the two aspects of
 22 biochemical and electrophysiological of the cerebral function, and show how a varia-
 23 tion in the chemical composition of the intra- and extracellular media may produce

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1 a variation in neuronal activity and a coded language of intercellular communication
[14, 15, 1, 27].

3 It is clear that if a substance is known to have opposite effects on activatory and
inhibitory receptors, the sensitivity of which may be modified, as we shall see below,
5 by the surrounding medium. If these receptors in turn can induce an action at a
distance, thereby modifying the medium, then it appears reasonable to attempt to
7 describe these interactions by means of a field theory. The major issue here is due to
the current lack of knowledge of the topography of the effects at a molecular level in
9 a given functional “volume”. Although the spatial complexity of the cerebral nuclei
and their interconnections seem to favor the use of a field theory, the complexity
11 of the functional chemistry of the brain makes it rather difficult to go from theory
to experiment. For example, neuropeptides take on multiple roles since they act as
13 local hormones or mediators in the digestive tract, as well as global mediators in
the brain.

15 **4.5. *The developmental phase: how does the functional hierarchy vary in time?***

17 We may examine a property of the “variation” of the functional hierarchy during the
development of an organism (constraint *Bio6*). How does the functional organization
19 of an organism satisfying the principle of invariance behave, when it is subjected
to internal or external perturbations? Why do we observe a particular organization
21 among the many that may be possible? Such questions lead to two fundamental
problems:
23

(1) *How does a biological system grow and reproduce, restructuring itself by
25 increasing the number of levels of organization and functional relationships, while
conserving, the stability of its functional organization, i.e., the O-FBS, and that of
27 the dynamics of its functional interactions, i.e., the D-FBS?*

(2) *Is the time-variation of the functional organization of the biological system
29 governed by an extremum principle? In other words, is there a functional equivalent
31 of the second law of thermodynamics that might apply to living organisms?*

33 I recall here the main results [6–7, 4]. A similar problem encountered in physical
systems has been resolved by the principle of least action which imposes a pathway,
35 which is in fact the pathway actually observed among a set of possible pathways.
The fundamental reason for this compulsory “choice” lies in the geometry of the
37 space in which the movement occurs. In the case of biological systems in which
the functional organization is represented by a graph of the interactions, we show
39 that the problem may be stated in terms of the stability of the graph. Why, during
the development of the organism, does a certain structural unit become a source,
41 and in another a sink? For purposes of reasoning, we may separate two processes
which are in fact closely dependent. On one hand, we have the modification of

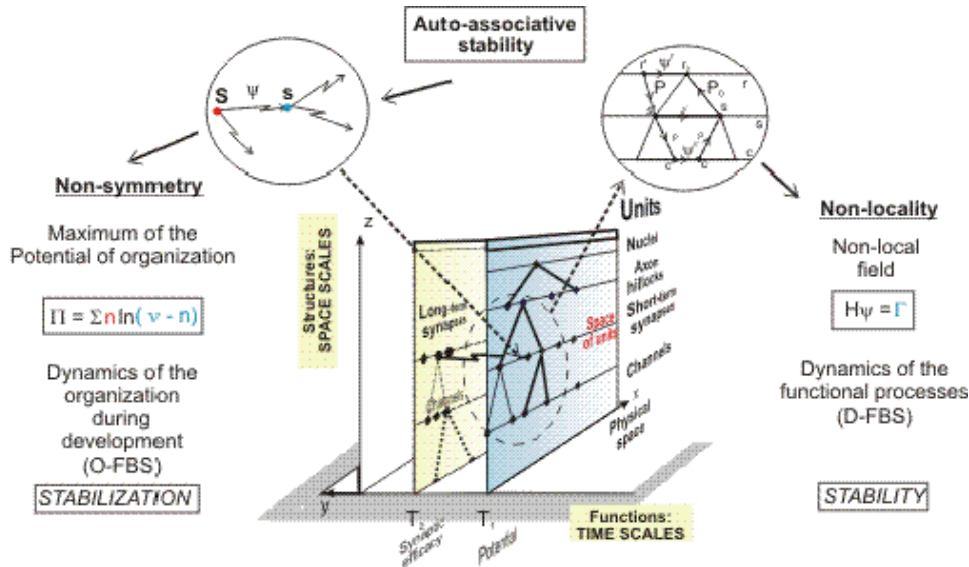


Fig. 3. A visual summary of the MTIP. The Principle of Auto-Associative stability gives rise to functional interaction “source-sink”. On the left: the property of non-symmetry determines the dynamics of the organization (the topology) during the developmental phase (the potential of organization remains at its maximum), which imposes stabilization of the function. On the right: the property of non-locality results in a non-local field equation for the functional process, which insures its stability.

1 the number of receptor units of the products (the sinks of the graph), and on the
 2 other, the modification of the total number of units (the summits of the graph).
 3 We have analyzed the consequences of these two variations with time and since the
 4 results are of considerable importance, let us now present them briefly (see also
 5 Fig. 3).

7 *Potential of functional organization.* When the number of structures receiving the
 8 product (the sinks) varies during development, the fact that a particular functional
 9 organization is observed among several possible organizations means that there
 10 exists a *potential of organization*, i.e., a range of potentialities for the organization
 11 of the system, and that there must also exist a cause leading to the organization
 12 observed. The presence of the genetic blueprint in all the self-reproducing elements
 13 of an organism as well as the non-symmetry has led us to formulate such a potential
 14 of functional organization, defined from their property of auto-reproduction (con-
 15 straint *Bio2*).

17 *Principle of vital coherence.* This approach is based on a *principle of invariance* of
 18 the physiological function and on the consequences that may be observed in a given
 19 species. For example, an aerobic organism needs oxygen in order to survive; it has
 to self-replicate to perpetuate the species and so forth. This invariance can only be
 expressed if the physiological function can be mathematically defined.

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1 *Principle of optimality.* The apparent number of the structures, e.g., organelles, cells
 2 and tissues, evidently varies (cell division), but so does the *quality* (source or sink) of
 3 the units of functional organization (cell differentiation). However, as the quality is
 4 less apparent, the variation is far less evident. We have shown that biological systems
 5 possessing the property of self-replication, and in which the functional interactions are
 6 created according to the PAAS, have a maximum potential of organization. Clearly,
 7 only the experimental verification of the mathematical consequences of this property,
 8 i.e., the monotonic variation of the number of units, validates the theory.

9 *Specialization (constraint Bio4):* When the number of structural units varies during
 10 the course of development, two cases may arise according to whether or not the units
 11 are reorganized. This reasoning is useful for understanding and demonstrating the
 12 mathematical property of the variation of functional hierarchy. Let us suppose that
 13 the system does not undergo reorganization, i.e., that the sources remain sources,
 14 and the sinks remain sinks, so that the quality of the units is not modified. In this
 15 case, the system is governed by what we have called an *orgatropic* function, the time-
 16 variation of which is always positive. In reality, the system undergoes simultaneous
 17 reorganization that corresponds to functional specialization.

18 *Functional order.* We have demonstrated the existence of a function, the *functional*
 19 *order*, which describes the time-variation of the biological system through the emer-
 20 gence of various levels of organization with time. The hierarchy of the organization,
 21 i.e., the hierarchy of the graph, develops in such a way that the physiological function
 22 remains invariant during the successive transformations of the functional organiza-
 23 tion. Since the functional order varies positively with time, it indicates the direction
 24 of the evolution of the biological system. In addition, the functional order may be
 25 used as a criterion of comparison between biological and physical systems.

26
 27 Let us consider the theoretical aspects of the two distinct functional processes
 28 involved in the development of nervous tissue. The first process concerns cell pro-
 29 liferation, during which there is an increase in the number of neurons accompanied
 30 by the increase in the orgatropy of the system from its initial value to a maximum,
 31 without any reorganization of its structural units. The second process concerns the
 32 reorganization of synapses. During this process, there is a decrease in the number
 33 of target neurons accompanied by a reorganization, of synapses, such that there is a
 34 decrease in the number of sinks accompanied by a decrease in the orgatropy of the
 35 system. These theoretical findings are in keeping with results of observations [23].

36 **4.6. Self-organization: a relation between structural and functional** 37 **organizations (constraint Bio3)**

38 All this is of course a consequence of the expression of the genetic program of the
 39 living organism. Thus, the *density-connectivity* of the structural units of a biolog-
 40 ical system, which determines the propagation of *biological fields*, varies during its

1 development. However, the O-FBS may also vary under other circumstances. For
 2 example, in the nervous system, the process of learning will obviously modify the
 3 system [26]. It can be theoretically shown that a biological system, subjected to a
 4 condition of constant global organization, such as that of having a constant number
 5 of structural units, will undergo a redistribution of structural units between its dif-
 6 ferent levels of structural organization, property that has been found by Edelman
 7 as the “selection of neuronal groups” [17, 18]. This will evidently affect the D-FBS
 8 and modify the propagation of biological fields. Furthermore, in the adult organism,
 9 there are also constraints of stability in the regulation of the physiological functions.
 10 We have seen that the *self-organization* of the biological system corresponds to the
 11 maintenance of the stability of the D-FBS when the O-FBS is modified. Thus, *the*
 12 *self-organization of a biological system is a consequence of the relationship between*
 13 *the topology and the dynamics of the system, i.e., between its structural and func-*
tional organizations.

15 **4.7. An interpretation of aging**

16 What happens when a perturbation of this relationship leads to modifications in the
 17 structure of a biological organism? The present approach of aging is another con-
 18 sequence of the MTIP (inspired by Prigogine’s approach for physical systems [30],
 19 i.e., the effect of small perturbations, called *fluctuations*, of the physical structure of
 20 units on the dynamics of the biological system during its adult life. Even with specific
 21 genes controlling aging, the time-irreversibility of the system can be shown to be due
 22 to the degradation of physiological functions. For example, in the case of structural
 23 modifications produced at the lowest molecular level of an organism through errors
 24 of transcription of the genetic message, the optimum regulation with respect to time
 25 between the different levels of structural organization can be determined by Hamil-
 26 tonian dynamics [9]. Structural modifications that occur during the functioning of
 27 the system may affect regulatory mechanisms, thus altering the functional organi-
 28 zation, i.e., the topology of the system, and consequently, the associated biological
 29 fields. If the fluctuations produced have random effects at the lowest structural level,
 30 which also contains the largest number of structural units, then non-Hamiltonian
 31 dynamics, rather than Hamiltonian dynamics, will have to be used. In this case,
 32 the time-variation of the biological system is *irreversible*, as is clearly shown by the
 33 phenomenon of *aging* in a living organism. This is obviously a manifestation of *bio-*
 34 *logical time*, i.e., the internal time of the individual organism [32] on the time scale
 35 of its physiological processes.

36 The example concerning learning and memory is a good illustration of the idea
 37 contained in the functional approach: as stated above, each physiological function
 38 has a specific age which depends on the structural fluctuations occurring in the
 39 epigenetic-metabolic system. Thus, neural network activity depends closely on this
 40 age, and what we actually observe and feel is the expression of this activity. It is
 41 common knowledge that there is a variation in an individual’s *psychological age*,

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1 expressed by an acceleration of time during the course of life. The present theory supports the existence of this *physiological age*, since it may be interpreted
3 as resulting from the numerous structural fluctuations that occur randomly in the epigenetic and metabolic nervous system; as well as according to the present formulation, the dynamics of synaptic plasticity may be expressed in terms of its weak
5 stability. We believe that, although it is difficult to determine the conditions of weak stability in real biological systems, this approach could suggest new experiments to define the role of biological time in the functional organization of living
7 systems.
9

4.8. *A product of Darwinian evolution*

11 One of the most fascinating aspects of life in nonliving matter is, the *evolution of the species*. The question therefore arises concerning the coherence of the principles
13 of our MTIP with those of evolution [5]. In other words, is the time-variation of the organization of physiological functions compatible with intra-species and trans-species modifications? The time-variation of the phenomena of life at the level of an
15 individual organism expresses the coupling of its topology and its dynamics on the time scale of its physiological processes. Similarly, the evolution of the species can be viewed as the consequence of a perturbation of the coupling of the topology and
17 the dynamics of specific groups of biological organisms on the time scale of the living universe. Such a perturbation may be either an internal transformation compatible with the survival of the species, such that the physiological function is conserved,
19 or else a reaction to the persistent influence of some particular property of the environment. In the former case, the biological system will undergo self-organization by means of successive adaptations the biological system evolves without losing
21 any of its physiological functions in the following generation (in keeping with the *restricted* principle of vital coherence), thus ensuring the conservation of the species. In the latter case, the evolution of the biological system involves the loss of some of
23 its functions in the following generation through the modification of its genetic sex characteristics (according to the *general* principle of vital coherence), thus leading to trans-speciation. In both cases, however, the physiological processes will be modified,
25 from the point of view of the construction of the structural hierarchy, by the self-association of structural units during the development of living organisms. Then,
27 if our theory is valid, the living universe, just like the individual organism, may be considered to operate on a specific time scale corresponding to its own aging process.
29
31
33
35

37 In the case of the evolution of the species, the field theory provides an interpretation of the existence of evolutionary jumps as a consequence of reciprocal effects between the dynamics of physiological processes, and the variable number
39 of structural units involved taking into account the condition of the invariance of the physiological function.

1 **4.9. The intelligence of movement**

3 The Purkinje unit, which is the repeating unit of the cerebellar cortex, is the basic
 5 element of a hierarchical network. It is divided into two subsystems, the granular
 7 cell subsystem (GCS), i.e., the neural network composed of granular cells, and the
 Purkinje cell subsystem (PCS). The Purkinje unit associated with the deep cerebellar
 nuclei, i.e., the local circuit composed of one Purkinje cell and its associated cells,
 can be considered as the functional unit of the cerebellar cortex. This is supported
 by the following arguments:

- 9 • The definition of a Purkinje unit is *geometrical* as well as *functional*. A set of
 11 Purkinje units corresponds to a *micro-zone* [24], although it should be noted that
 the definition of the micro-zone is not based on mathematical criteria.
- 13 • The *stability* of the function, which takes into account the internal dynamics due
 to the time-lag in the propagation within the unit and between two units [11],
 determines the conditions for the definition of the structural unit.
- 15 • *Variational learning rules* (VLRs) [8], deduced from neural learning rules, apply to
 17 Purkinje units and govern the coordination of movement through excitatory and
 inhibitory interactions between the units. The hypothesis of synaptic plasticity,
 applied to granular cells, reveals a wide range of learning behavior. The same
 19 learning rules probably apply during the developmental period as well as in adult
 life to ensure the convergence of signals carried by the climbing fibers of the
 21 cerebellar cortex.
- 23 • *The coupling between units increases the overall stability of the system* in agree-
 ment with the general theory.

Figure 3 shows a visual summary of the MTIP.

25 **5. Conclusion**

27 The proposed representation in terms of functional interactions emphasizes two
 29 types of hierarchical organization on which the functioning of a living organism is
 based. The first is the structural organization corresponding to the ordered spatial
 distribution of the various structural units of the organism, such as cells, tissues and
 organs. The second is the functional organization, resulting from the coordination
 31 of a set of time ordered interactions between the structural units. A convenient way
 of studying the relations between the structural and the functional organizations is
 33 by means of a graphical representation (Fig. 2). The points of the graph represent
 the structural units and the directed arcs represent the elementary physiological
 35 functions, i.e., the relations between the structural units.

37 Two properties are basic for this representation: the non-symmetry of interac-
 tions used for the concept of potential of organization and the topological system,
 and the non-locality due to hierarchy used for the non-local field formalism. The

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1 graphs may be used in at least two ways. The first, which scarcely calls for the math-
 2 ematical properties of graph theory, depends on a computer program to organize
 3 the physiological functions between the structural units so that the functional hier-
 4 archy is automatically displayed. The second, however, fully exploits graph theory
 5 to search for specific sub-structures, such as cyclic sub-graphs, the best path in the
 6 graph for a given constraint, and so on. Just as there exists a structural or anatomical
 7 hierarchy, i.e., a group of more or less similar units at different levels of organization,
 8 there also exists a functional hierarchy. Indeed, it is precisely the existence of inter-
 9 linked functional hierarchies that complicates the representation of the functional
 10 organization of living organisms. Moreover, in most cases, the functional hierarchy
 11 does not coincide with the structural hierarchy. The non-local field formalism, called
 12 S-Propagator formalism, allows traversing levels in the structural organization, and
 13 thus results in the quantitative description of space and time dynamical processes.
 14 As they are expressed in terms of lower levels, they totally integrate mechanisms at
 15 lower levels. Operators in the formalism correspond to adapted known mathematical
 16 models of the identified mechanisms. An example has been proposed for real neural
 17 networks [10].

18 There are of course difficulties to apply the MTIP, due to theoretical complexity
 19 and mathematical tools yet to be fully developed. Phenomena are to be described
 20 in the theoretical framework in terms of biophysical mechanisms and should thus be
 21 described in terms of functional interactions. However, the mathematical complexity
 22 is highly compensated by the systematic use of known numerical tools (e.g., solver
 23 for partial differential equations), the identical mathematical structure of equations
 24 at each level of the hierarchy, the ability of fast update in case of novel knowledge,
 25 the use of a unique computing system. This has been clearly shown by P. Chauvet,
 26 using his own sophisticated computing system [12]. Even through we do not know
 27 a lot about hierarchical systems due to the lack of mathematical knowledge in this
 28 field, it is hoped that mathematicians and theoreticians will be inspired to discover
 29 new tools, properties and theorems. As shown here, the MTIP within the chosen
 30 representation and the using of the specific formalism satisfy the main physical and
 31 biological constraints accepted by biologists. This is certainly a great advantage for
 using this framework in integrative neuroscience.

33 **Appendix**

Representation

34 The functional interaction is mathematically defined as follows (notations are Latin
 35 subscripts i, j, \dots for units u_i, u_j, \dots , and Greek subscripts for products: $P_{\alpha, i} \equiv$
 36 P_{α, u_i} denotes an α -product synthesized in the i -unit u_i ; a level of organization is
 37 represented by a Latin superscript):

The Use of Representation and Formalism in a Theoretical Approach to Integrative 19

1 The functional interaction from the i - to the j -unit is denoted as ψ_{ij} and is an elementary digraph (Fig. 1):

3 (i) Each element u_i or u_j (nodes i and j) represents a structural unit with an elementary function ψ_{ij} from u_i (the source) to u_j (the sink).

5 (ii) The result of this interaction is a product which may be either the direct value of the elementary function from the source to the sink or the transformed value in
7 the sink:

$$P_i \xrightarrow[\psi_{ij}(P_i) \phi_j]{\phi_{ij}} P_j = \phi_j \circ \psi_{ij}(P_i) \quad (\text{A.1})$$

9 The variables P_i or P_j are identified as elementary physiological functions.

11 (iii) A physiological function will result from a set of elements that are hierarchically organized and functionally interacting. The physiological function will be identified with the collective behaviour of the elements whose product is denoted by F :

$$13 \quad F = f(F^1, F^2, \dots, F^n) \quad (\text{A.2})$$

where $F^l (l = 1, \dots, n)$ is an elementary physiological function at level l .

15 More generally, there exist μ products $P_{\alpha,i}$, $\alpha = 1, \mu$ emitted by the i -unit that occur during the execution of the elementary physiological function F .

17 **S-Propagator formalism**

19 In the linear case, operator H in Eq. (3.9) is written:

$$(H\psi)(\mathbf{r}, t) = \sum_{u(r') \in D_r(r)} P\psi^r \left(r', t - \frac{d(r', r)}{v} \right) \quad (\text{A.3})$$

21 where $D_r(r)$ is the set of r' -units in the r -space connected with the r -unit (Fig. 4b). $P_i[\psi^s]$ is the *structural propagator* (*S-Propagator*), which propagates the field variable from r' to r along the distance $d(r', r)$ (see Fig. 4a). It may be represented by
23 the diagram:

$$\begin{array}{ccc} (r', t) & P_i & (r, t) \\ \bullet & \text{---} & \bullet \\ u_i & & u \end{array} \quad (\text{A.4})$$

25 which can be developed as in Fig. 4c, showing the propagation as the mathematical
27 operation *per unit time*:

$$P_i[\psi^s] = P\Phi P_i \equiv P\Phi(r)P(r') \quad (\text{A.5})$$

29 It is the product of three operators:

1. The propagator P_i in u_i , i.e., $P(r')$ that we may call the *trans-level propagator*,

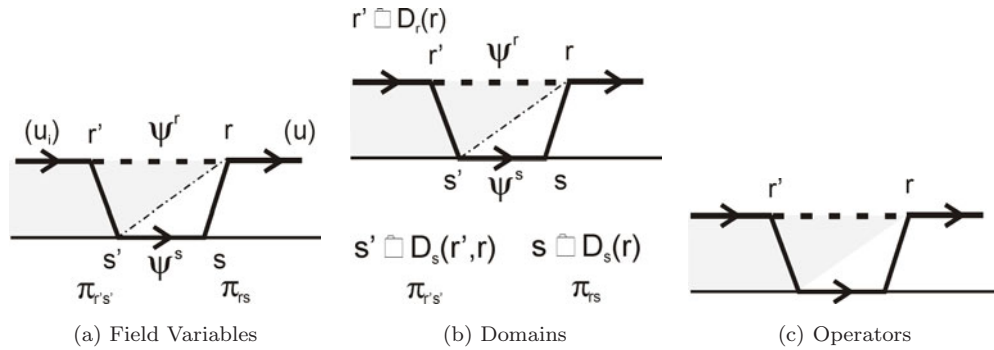
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Fig. 4. Three diagrams that illustrate: (a) Field variables, (b) Domains of definition for connectivity between the two levels, (c) Operators. $\mathbf{P}(r)$ and $\mathbf{P}(r')$ are the mathematical models that correspond to mechanisms. The functional interaction propagates along the extent $d(r')$, from r' in u_i [under the action of operator $P(r')$] to the border of the structural discontinuity denoted as s , then $d(s)$ inside s (if and only if, functional interaction y^s exists at level s , operator F), and finally form s to r along the extent $d(r)$ in the unit [under the action of operator $P(r)$]. The units r' that correspond to a unit r through units s are given by the relationship that includes the density of units $r(r)$ and the density-connectivity at the lower s -level, i.e., the density-connectivity function $P_{r,s}$, product of the density of the s -units times the probability of connection between the r' - and the s -units.

- 1 2. the *in*-level operator Φ corresponding to the functional interaction (field variable)
- 2 ψ^s at the level s , and which represents the transport through the structural
- 3 discontinuity, and
3. the propagator P in u , i.e., $P(r)$.

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