Volume 86, No. 4 *THE QUARTERLY REVIEW OF BIOLOGY* December 2011

CENTRAL NERVOUS SYSTEM AND COMPUTATION

Diego Guidolin
Department of Human Anatomy and Physiology, University of Padova
Padova 35121, Italy
e-mail: diego.guidolin@unipd.it

Giovanna Albertin
Department of Human Anatomy and Physiology, University of Padova
Padova 35121, Italy
e-mail: giovanna.albertin@unipd.it

Michele Guescini
Department of Biomolecular Sciences, University of Urbino "Carlo Bo"
Urbino 61029, Italy
e-mail: michele.guescini@uniurb.it

Kjell Fuxe
Department of Neuroscience, Karolinska Institutet
Stockholm 17177, Sweden
e-mail: kjell.fuxe@ki.se

Luigi F. Agnati
IRCCS San Camillo
Lido Venezia 30126, Italy
e-mail: luigiagnati@tin.it

keywords
computation, computational modeling, computational explanation, plasticity

abstract
Computational systems are useful in neuroscience in many ways. For instance, they may be used to construct maps of brain structure and activation, or to describe brain processes mathematically.

The Quarterly Review of Biology, December 2011, Vol. 86, No. 4

0033-5770/2011/8604-0002$15.00

Furthermore, they inspired a powerful theory of brain function, in which the brain is viewed as a system characterized by intrinsic computational activities or as a "computational information processor." Although many neuroscientists believe that neural systems really perform computations, some are more cautious about computationalism or reject it. Thus, does the brain really compute? Answering this question requires getting clear on a definition of computation that is able to draw a line between physical systems that compute and systems that do not, so that we can discern on which side of the line the brain (or parts of it) could fall. In order to shed some light on the role of computational processes in brain function, available neurobiological data will be summarized from the standpoint of a recently proposed taxonomy of notions of computation, with the aim of identifying which brain processes can be considered computational. The emerging picture shows the brain as a very peculiar system, in which genuine computational features act in concert with noncomputational dynamical processes, leading to continuous self-organization and remodeling under the action of external stimuli from the environment and from the rest of the organism.

INTRODUCTION

WE ARE IN the midst of what is popularly called the *digital revolution*, a revolution that was born in the 1940s, leading to the development of the first electronic programmable computational systems (see Godfrey and Hendry 1993). In the last 30 years, a huge development of this technology occurred, with a significant impact on a great many aspects of everyday life and an unprecedented opportunity for scientists to devise new experimental and data analysis approaches. Brain imaging techniques (see Filler 2009) and computer-assisted image analysis methods (see Dragunow 2008) are examples of this advancement in neuroscience research. In addition, the *digital revolution* provided us with a new class of computer-based information technologies, in which informational contents of different types (including text, numbers, sounds, images, and video) are represented by discrete numerical values that can be easily stored, processed, and/or analyzed by numerical methods, combined and disseminated through local networks and the internet, allowing for a more efficient communication of resources and data. It has to be observed that these communication tools are also qualitatively new, since they support our natural multidimensional and multisensory approach to cognition (Leroi-Gourhan 1956; Lewkowicz and Ghazanfar 2009) more than any other technology in the past.

The relationship between computational systems and neuroscience is, however, more complex than the simple use of computers to construct maps of brain structure and activation, or to exploit new ways for sharing data and information. In fact, the rise of computational systems and the theoretical ground on which their development was based (see Cooper 2004) inspired a powerful theory of brain function, historically known as the "digital brain" (Werner 2001, 2007), and based on an analogy between the brain and machines computing a logical calculus of symbolically represented information. The landmark paper by McCulloch and Pitts (1943), which established that networks of abstract models of neurons as switching devices can represent all of propositional logic, can be considered the birthplace of this horizon for conceptualizing the central nervous system (CNS). Single neurons and nerve axons that deliver a sort of binary code seemed just ready made for computing and transmitting digital information in circuits and neural nets. These concepts found further development in a series of annual conferences sponsored by the Josiah Macy, Jr. Foundation, beginning 1943 and extending for the next ten years (see Heims 1991 for a historical review, and Werner 2007 for thoughtful analysis and discussion), leading to the view of the brain as a system characterized by intrinsic computational activities, or as a "computational information processor" (Marr 1982).

The claim that brains compute, therefore, was introduced in neuroscience as an empirical hypothesis to explain cognition by analogy with digital computers. Some neuroscientists were quite cautious about this view or rejected it (Perkel 1990; Edelman 1992; Free-

man 1997, 2001; Werner 2004, 2007), mainly objecting that it seeks to fit Nature into the idealized and unrealistic constraint of an algorithmic programmable machine (see Freeman 1997), and may obscure the proper task of neurophysiology, which is the study of the brain's inner workings in terms of its intrinsic biological and biophysical processes (Werner 2004). Others, on the contrary, believe that computations are genuinely part of CNS functions (Churchland et al. 1990). Thus, does the brain really compute? There are two ways to address such a question:

- Some authors argued that the brain is a computational system because everything is computational, since everything can be described that way (Churchland and Sejnowski 1992; Putnam 1999). This answer is not well founded and appears quite unsatisfactory. In fact, in general physical terms, each process in Nature occurs as a dynamical system moving (by the effect of the interactions between the system components and with the external environment) through a set of available states (the state space) from an initial to a final state. Starting from Galileo's and Newton's time, we also know that a physical description of the Nature can be associated with a mathematical one. The laws of physics are, however, generally formulated in terms of continuum mathematics, which is not materially executable, requiring unlimited sequences of operations (Landauer 1991, 1999). Thus, for practical purposes, continuous processes are mapped onto recursive, computational processes in order to calculate approximate estimates of the properties of the physical system under investigation and predict its evolution. Such a "convenient artifact" (Werner 2001) can lead to the misleading impression that every natural process is intrinsically computational. Thus, as well outlined by(Piccinini (2006, 2007a,b), being able to use a computational description to *model* the behavior of a system (such as meteorologists do to predict the weather using computers) does not necessary mean that the simulated behavior *is* a computation. This point will be developed in some more detail in the first part of the present review. Since they currently represent important tools in neuroscience research, the main strategies used to model and simulate brain processes will be also briefly reviewed.
- An answer to the question whether the brain could be *explained* computationally (such as when computer scientists explain what computers do) requires getting clear on a definition of computation that is able to draw a line between physical systems that compute and systems that do not, so that we can discern on which side of the line the brain (or part of it) could fall (see Piccinini 2006, 2007a,b). Thus, in the second part of the present review a very recently proposed taxonomy of notions of computations (Piccinini and Scarantino 2011) will be briefly illustrated and available neurobiological data will be summarized and discussed within this reference framework with the aim of shedding some light on the possible role of computational processes in brain function.

Computational Modeling

Models play many roles in science. They are used to make precise and accurate predictions and to summarize data. They are used as heuristic approaches for designing experiments or to demonstrate surprising and counterintuitive consequences of particular forms of systematic organization.

In *computational modeling* (Figure 1), the F1
outputs of a computing system are used to describe some behavior of a physical system under certain conditions. In the first type of computational modeling (see Piccinini 2007a for details), the computing system computes representations of the physical system's states at different times or for different values of an independent variable. To perform such a task, the computing system needs two types of inputs: (i) an input specifying some initial state, and (ii) an input specifying how the physical system's states change as a function of time or of some other variable. Usually, the latter input (i.e., the dynamical evolution of the modeled system) is given by a mathematical description, typically a set of differential equations, expressing what we know

tapraid5/qrb-qrb/qrb-qrb/qrb00411/qrb0073d11z | xppws | S=1 | 9/21/11 | Art: 2874

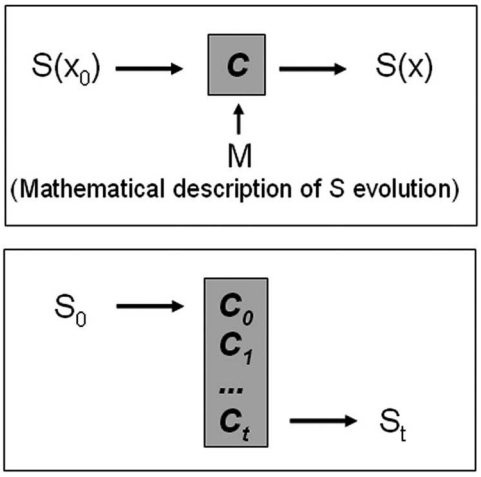

FIGURE 1. SCHEMATIC REPRESENTATION OF THE PROCEDURES TO *MODEL* A PHYSICAL SYSTEM

According to a first strategy (upper panel), the states of the system S for different values of a state variable x are calculated by a computational system C based on some initial state and a mathematical description M of S's dynamical evolution, expressing what is known about the properties of S. A second strategy (lower panel) involves the direct representation of the S's states by the discrete states of a suitable computing system C (such as a specific Turing machine or a cellular automaton). Such discrete computational models require the partitioning of S's states into a discrete set of states (see text).

about the system properties. If the solution of the equations is known, then the computing system can use it to estimate a representation of the physical system at any given condition. Most equations are, however, not solvable analytically, and this situation is where the present type of computational modeling proves most useful. In fact, mathematicians have devised numerical methods to approximate the solutions of these equations. Thus, they can be applied by a computing system to provide us with a representation of the physical system's states. The just described procedure is the most common type of computational modeling, which has become ubiquitous in many sciences (Rohrlich 1990; Humphreys 2004).

In a second type of computational modeling, the states of a physical system are represented directly by the discrete states of a suitable computing system. Thus, when the computing system goes into its internal states it generates outputs representing the states that the modeled system goes into. Obviously, not everything is describable with an approach of this type, since most things do not seem to have discrete internal states like ordinary computing systems do. Often, however, the possibility exists to apply an approximation, involving the partitioning of the states of the physical system of interest into a discrete number of representative states. This kind of approximation is behind the increasingly popular use of cellular automata as a modeling tool (Rohrlich 1990; Hughes 1999; Agnati et al. 2002, 2007a; Guidolin et al. 2011).

A simple example of the application of the two abovementioned modeling schemes is illustrated in Figure 2. It concerns the binding properties of a tetrameric receptor. According to the first approach to modeling, the theoretical binding curve of this structure was derived (see Agnati et al. 2010a) from the thermodynamics of the system in the framework of a sequential scheme for the binding of a ligand to a multisubunit protein, where the free energy changes involved depend on the binding of the ligand, on subunit conformation changes, and on subunit-subunit interactions. The result is a typical sigmoid dose-response curve expressing the cooperativity existing in the modeled system. A consistent result can also be obtained by following the second modeling scheme. In this case, however, the set of the possible conformations a receptor subunit can assume is organized in two broad classes: (i) inactive conformations, characterized by a "low affinity" for the macromolecular effectors, and (ii) active conformations, characterized by a "high affinity" for the macromolecular effectors. Thus, as a first approximation, the state of each subunit can be simply described by a binary variable and the behavior of the system estimated by using a suitable Boolean network (see Agnati et al. 2007a). F2

As far as computational modeling is concerned, it is important to emphasize (Craver 2006; Piccinini 2007a) that what explains the behavior of the modeled physical system has to do with the properties of the system and

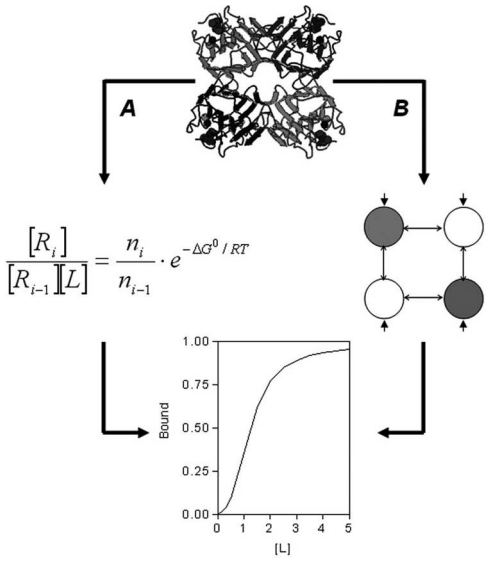

Figure 2. Modeling the Binding Properties of a Trameric Receptor

A first strategy (path A) involves the use of thermodynamic concepts. The model, for instance, can be based on a sequential scheme for the binding to a multisubunit protein (see Agnati et al. 2010a). For each binding step we have an equilibrium condition of the illustrated form, where L denotes the ligand, R_i the protein complex with i occupied sites and ΔG^0 is the change in free energy involved in the process. The multiplicity factor n_i accounts for the number of ways to achieve i occupied sites. From such a condition the theoretical binding curve can be derived. It estimates the amount of bound sites as a function of the ligand concentration. A consistent result can be obtained with a second modeling strategy (path B), in which the possible conformational states of each subunit are partitioned into two broad classes, "active" and "inactive" with respect to the macromolecular effectors (see text). With such an approximation the system corresponds to a network of interacting binary elements, and a suitable "boolean network" (see Kauffman 1993) can be used to estimate its properties (Agnati et al. 2007a). As illustrated, each element of this computing system receives inputs from itself and from the two nearest neighbors. Furthermore, the state of each unit can change according to a binary rule derived from a Hamiltonian taking into account the action of the ligand and the interactions between the network elements (see Agnati et al. 2007a for details).

the whole theory about it used to build the simulation, not with the computation performed by the model. In other words, none of the computations used to predict what a system would do under specified conditions of necessity constitute computations performed by the modeled system. As a matter of fact, the same system can be described by many different computational models (as in the example illustrated in Figure 2), some of which approximating its behavior and estimating its properties better than others.

modeling the cns

Almost all of the physical systems are amenable to computational modeling and simulation. Computational modeling applies equally well to paradigmatic computing systems (e.g., digital computers can be approximated by other computers) and to paradigmatic noncomputing systems (e.g., the dynamics of atmosphere can be approximated by meteorological computer programs). In this sense, the CNS, just like any other physical system, can be modeled and its functions simulated computationally. The modern approach to modeling the brain and its intricate, interrelated network of subsystems is carried out through the mathematical computational field of "*complex system science*" (Sporns et al. 2000; Siegelmann 2010), which, following Siegelmann (2010), is the combination of two ingredients:

- *Complex architectures* that are the basis for computational simulations aimed at describing the emergent behavior of interacting elements. In this context, neural networks (see Churchland et al. 1990; Elman 1999) and cellular automata (see Chopard and Droz 1998; Elman 1999) are the two most followed modeling strategies. Quite a large number of neural networks-based models and simulations of brain functions were proposed (see Arbib 2003). Examples include the representation and processing of visual (Marr 1982; Piepenbrock 2002) and of other (see Mountain and Hubbard 2001) sensory information, the coding of force for movements (Lukashin et al. 1996), memory storage and retrieval (McNaughton and Morris 1987; Blumenfeld et al. 2006), the mechanisms of rewarding (Montague et al. 1996; Agnati et al. 2007b), and correlation learning (Gally et al. 1990). On the

tapraid5/qrb-qrb/qrb-qrb/qrb00411/qrb0073d11z | xppws | S=1 | 9/21/11 | Art: 2874

other end, examples of the use of cellular automata-based modeling include the simulation of the cooperative dynamics of interacting receptor systems (Shi and Duke 1998; Duke and Bray 1999; Agnati et al. 2007a), and the engram formation (Zoli et al. 1996; Guidolin et al. 2007).

- *Systems of equations* governing the temporal evolution of values of interacting sets of variables and parameters (Alligood et al. 1997). In biology, this fundamental mathematical tool proved useful to model complex phenomena such as physiological processes and diseases (Rapatski et al. 2005; Villanueva et al. 2008).

Complex system science is a rapidly maturing approach, probably allowing us to describe connections between lower-level brain functions and the higher-level of perception and behavior. In fact, this strategy is at the basis of sophisticated and realistic modeling efforts (see Markram 2006), such as simulations of networks of spiking neurons (see Brette et al. 2007 for a review), large-scale models of thalamocortical systems (Izhikevich and Edelman 2008) and of their dynamics in sleep and wakefulness (Hill and Tononi 2005; Olcese et al. 2010), circadian intersystem synchronization (Leise and Siegelmann 2006), memory reconsolidation (Siegelmann 2008), and cerebellar motor control (McKinstry et al. 2006).

Thus, modern computational neuroscience is providing us with growing possibilities and tools to integrate what we know about the properties of the nervous system and its components in order to explore its complex dynamics and functions. As discussed previously, however, being able to computationally model a system does not mean that the modeled system computes. If the CNS computes, this needs to be established by more than the existence of computational neuroscience.

Computational Explanation

Addressing the question whether the brain computes or not obviously depends on a suitable definition of "*computation*." Computational processes may be defined both abstractly (i.e., based on a mathematical theory) and concretely. Here, we are interested primarily in concrete or physical processes of computation. In this respect, a useful taxonomy of notions of computation was very recently proposed by Piccinini and Scarantino (2011) and will be briefly summarized in the section that follows.

on computation

The most restrictive notion of computation that we will consider here is "*digital computation*." Since it is well established from the mathematical point of view (Davis et al. 1994) and inspired the "digital brain" theory of cerebral function, it is a particularly relevant notion for present purposes. As schematically illustrated in Figure 3A, a physical system is a digital computing system when the laws of physics governing it allow the generation of internal objects (also called "*vehicles*" in the specialized literature) having the structure of a "string of digits," i.e., realized as an ordered (concatenated) set of system's components, each in a specific state from a finite and discrete set of states, which can be transformed by the system into a new "string of digits" in accordance with a general rule, which depends on the input string (and perhaps internal state of the system) for its application, and which is implemented in the system by exploiting specific properties and an appropriate functional organization of its parts (see Piccinini 2007b for a discussion). Examples of physical systems fitting the provided definition of "digital computation" include digital computers and related devices, calculators, and machines realizing finite state automata (Piccinini 2008), cellular automata (Wang and Lieberman 2004), or artificial neural networks (see Cabestany et al. 2005).

F3

The definition of "digital computation" can be generalized by allowing for a broader range of vehicles (e.g., continuous variables as well as discrete digits). Thus, the term "*generic computation*" (Piccinini and Scarantino 2011) was proposed to designate processes in which a generic vehicle is transformed into another vehicle of the same type by rules that are specifically sensitive to differences between different portions of the vehicle.

An important characteristic of this definition of a concrete computational process is

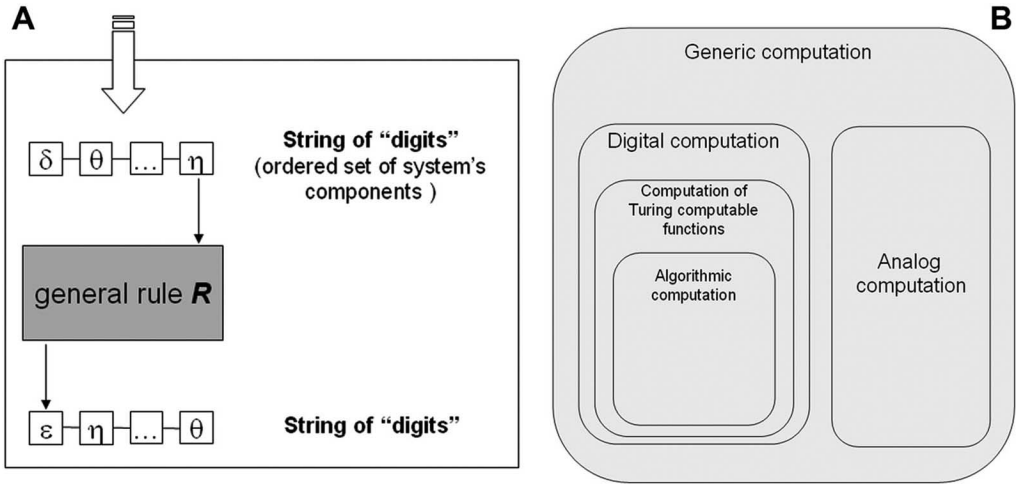

Figure 3. Types of Computation

A. Schematic representation of a digital computing system. It is designed in a way that allows for the manipulation of special types of inputs, which are called *string of digits*. A "digit" is any state (from a finite and discrete set of states) of some system's component (such as a memory cell in digital computers), and a "string of digits" is realized as a concatenated set of system's components, each in a specific state (Greek letter in the figure). Thus, it is individuated by the digits that compose it, and the format according to which they are assembled. Among systems that manipulate "strings of digits," some of them do so in a special way (i.e., following a general rule R, implemented by properly designing the organization of the system's parts, and which apply to any string entering the system, and depends on such an input for its application). **B.** Types of computation and their relations of class inclusion (simplified from Piccinini and Scarantino (2011)). The more restrictive notion of "digital computation" shown is "algorithmic computation." Any algorithmic computation, in turn, is "Turing computable," but the computation of Turing computable functions need not be carried out by following an algorithm. For instance, it can be performed by a suitable neuronal network.

that the rules (i.e., the input-output maps) defining a computation are sensitive only to the general structure (i.e., to the relationship between different portions) of the vehicle they manipulate, not to its specific physical nature. This feature, also called "*medium independence*" (see Piccinini and Scarantino 2011 for more details) implies that a concrete computational process can be implemented in multiple physical media. For instance, it is well known that a digital computation (manipulating "strings of digits") can be equally implemented in electronic, electromechanical, or mechanical devices.

It has also to be observed that the inputs and outputs may be interpreted (i.e., assigned semantic content). If they are interpreted, they may be called *representations* (or "symbols") of such a content. Computations, however, can be defined independently of any semantic interpretation of the computational inputs and outputs (Machtey and Young 1978; Piccinini 2006). In fact, there are plenty of paradigmatic computations that lack representational content. Examples include parsers, compilers, and assemblers.

The provided broader definition of computation includes as a special case not only the above described "digital computation," but also the so called "*analog computation*" (Pour-El 1974), in which the vehicles are continuous variables instead of discrete strings of digits. Analog computers can be physically implemented and since some authors claimed that neural processes may be more similar to analog computations (see Rubel 1985), this type of computational process is also relevant for our purposes. The

tapraid5/qrb-qrb/qrb-qrb/qrb00411/qrb0073d11z | xppws | S=1 | 9/21/11 | Art: 2874

relationship between the different types of generic computation is schematically illustrated in Figure 3B.

Physical systems implementing computational processes in some of the abovementioned sense and performing this kind of activity can, therefore, be considered computing systems properly so called, whose function is to perform that computation. It follows that they can be not only computationally modeled, but also computationally explained. Thus, computational explanation is a special form of mechanistic explanation (i.e., an explanation in terms of a system's components, functions, and organization), which applies only to systems with peculiar structural and functional characteristics. They include a format out of which internal objects can be constructed, a set of components that are functionally organized to manipulate these objects, and a rule specifying which output objects are generated. It should go without saying that when we employ computational explanation in the present sense, a great many natural systems are not computing systems (see Piccinini 2007b for a detailed discussion). For example, planetary systems and the weather are not collections of functional components organized to exhibit specific capacities. Furthermore, they do not translate the inputs from an external environment into formatted internal objects, process them, and return outputs distinct from themselves. Other systems (e.g., digestive systems) operate according to a rule, and yet they do not perform computations, because they perform the same operations regardless the properties of the inputs they process, and the outputs are in general of a kind so different from the inputs that they cannot be fed back into the system for further computational processing. Thus, whether the brain (or part of it) behaves as a computing system according to some of the provided definitions remains an empirical question open to research and analysis: to find out whether some computational process is operating within the brain, the only effective way is to look at all levels of organization of the CNS and find out how they operate. In the next section, neurobiological data will be reviewed from this specific standpoint.

COMPUTATIONAL EXPLANATION IN NEUROSCIENCE

According to the criteria described in the foregoing section, genuine computational properties of the CNS are possible only in the presence of peculiar morphofunctional features. In particular, it has to be assessed whether brain anatomy and physiology would allow:

- the generation, as a consequence of the interaction with the external world, of internal objects in a suitable format (and eventually of "representations") and
- their transformation by the system according to rules (i.e., input-output maps).

Computational Processes in the Brain

A striking morphofunctional characteristic of the CNS is its hierarchical organization as a complex system of "networks of networks" (Csete and Doyle 2002; see also Werner 2009, 2010) nested within each other. This view has been put forward already by Agnati and Fuxe (1984), who suggested that the "Russian doll" analogy proposed by Jacob (1970) for living beings could be extended to the CNS as a single organ. In particular, it has been suggested (Varela et al. 2001; Agnati et al. 2004) that at least macro-, meso- and micro-scale levels can be recognized in the CNS (see Figure 4): F4

- The macro-scale level, in which it is possible to recognize neuronal networks and complex cellular networks (Agnati and Fuxe 2000).
- The meso-scale level is the level of single neurons and synaptic aggregates (see Golding et al. 2002) in which multiple synapses act cooperatively to modulate their strength.
- At the micro-scale level are the molecular networks, made by molecules that function as a metabolic and/or regulatory signaling pathway in a cell (Bhalla and Iyengar 1999). Of particular interest are the "receptor mosaics" (RM), i.e., macromolecular complexes formed at the membrane level by G protein-coupled receptors (see Fuxe et al. 2010 for a

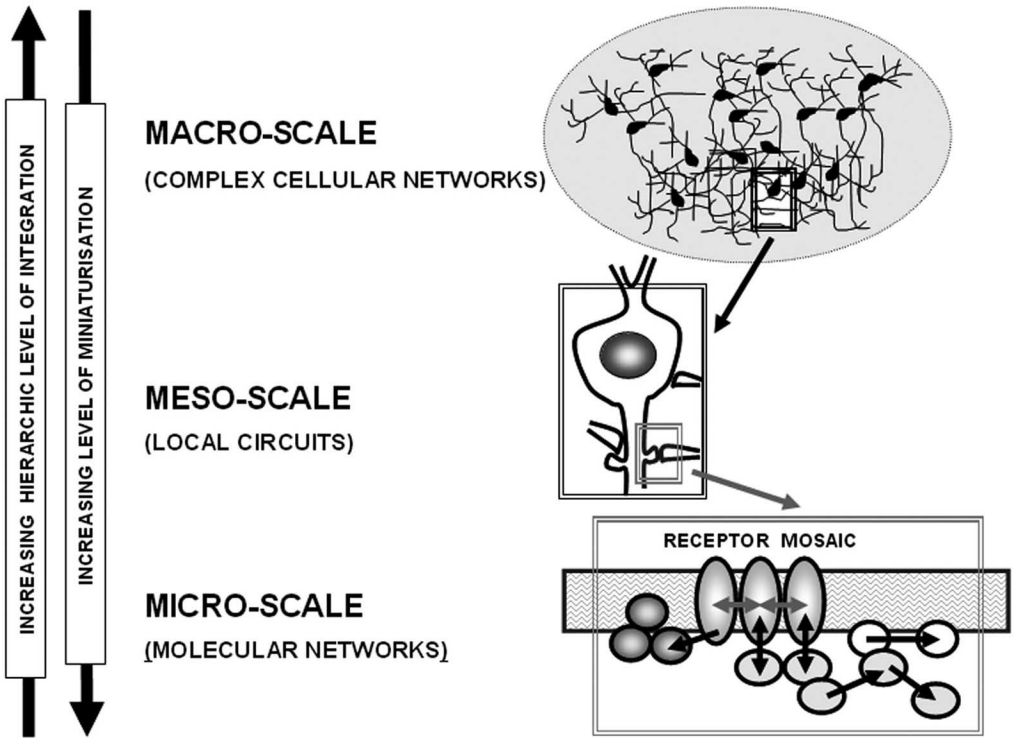

Figure 4. Schematic View of the CNS as an Organized System Where Networks of Networks can be Described

These can be nested within each other according to some hierarchical principle (Agnati et al. 2007b).

review) as a consequence of direct allosteric receptor-receptor interactions (Fuxe et al. 1983; Kenakin et al. 2010).

This morphofunctional feature is of particular relevance for our discussion since, as demonstrated by the connectionist paradigm to computation (Hebb 1949; Rosenblatt 1958; Rumelhart et al. 1986a), networks of interacting elements can implement rules and computable functions in their own structure (see Figure 5). The class of architectures falling under the connectionist umbrella is very large and diverse, but almost all of them share certain characteristics. Processing is carried out by a usually large number of simple processing elements (called nodes or units), having a nonlinear response function (Hopfield 1984). Each node receives input (excitatory or inhibitory) from some number of other nodes, responds to that input according to the response function, and in turn excites or inhibits other nodes to which it is connected. There are some key characteristics worth noting. First, what the system "knows" is essentially captured by the pattern of connections and the efficiency associated with each of them (Knoblauch et al. 2010). Second, rather than using symbolic representations, the "vocabulary" of a connectionist system consists of patterns of activation across different units. Furthermore, what made connectionism so attractive to many was the possibility to develop "learning algorithms" (Rumelhart et al. 1986b), by which the network would adjust the connection efficiencies in small incremental steps (for instance, based on examples of a target behavior) in such a way that over time the network's response accuracy would improve. Thus, the structural similarity between connectionist systems and the networks in the CNS legitimates the hypothesis of a computational interpretation in the form of executing rules on some distributed architecture.

tapraid5/qrb-qrb/qrb-qrb/qrb00411/qrb0073d11z | xppws | S=1 | 9/21/11 | Art: 2874

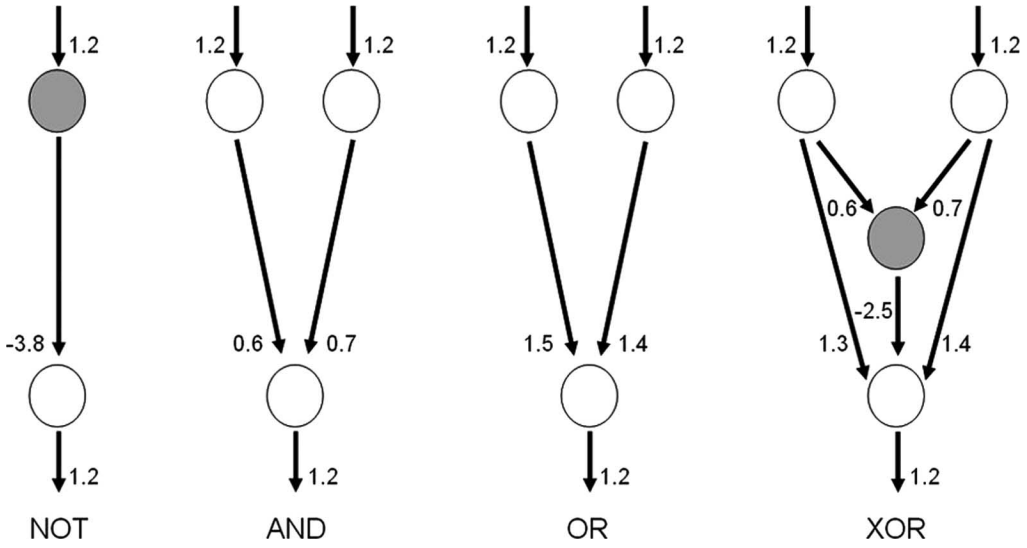

FIGURE 5. THE CORE LOGIC FUNCTIONS THAT CAN BE REALIZED BY A CONNECTIONIST NETWORK (SEE PENROSE AND GARDNER 1989)

In the illustrated schemes each "neuron" is assumed to have activation threshold of 1.0 and each "synapse" has some degree of excitatory or inhibitory effect on the target "neuron" (inhibitory units are highlighted in grey). Combining these kinds of circuits all of the functions necessary for any definable logical operation can be realized.

The brain, of course, can generate algorithms (i.e., ordered sequences of operations) and classic examples include the process of speaking (Fodor 1975) and the voluntary control of movements (Fan et al. 2008). It has also been proposed that algorithms could be generated in the cerebellum (see Yeo 2004) and the visual system (Schyns et al. 2009). However, it is widely acknowledged that the main way the brain can exploit to implement computational rules is in the form of suitable network architectures.

As discussed before, the possibility to execute computational rules is only one feature of physical computational systems. To fully characterize whether computational processes are in operation within the brain we also need to identify if vehicles of computation are generated and their characteristics. To this end we have to explore in some more detail the abovementioned main levels of the hierarchical organization of the CNS:

- *The cellular networks.* In the late 1980s, Wolf Singer and colleagues (Gray et al. 1989, 1990) found specific, phase-synchronized EEG in the visual cortex of cats that was strongly correlated to a particular visual stimulation. The phase synchrony they found in the gamma frequency band (from 30 to 90 Hz) of the EEG became known as "coherent 40 Hz," and has been regarded as the electrophysiological marker of a highly specific coordinating link among distributed neurons leading to the formation of a dynamically assembled pattern of neuronal activity as a response to the applied stimulus. This finding, together with the increasing evidence of a high structural plasticity of synapses and neuron connections (see Bennett et al. 1964; Holtmaat and Svoboda 2009), indicated in dynamically self-organized aggregates of neurons the basic vehicle for computation in neural networks. The "Darwinian brain" by Edelman (1987) and the "dynamical cell assembly hypothesis" (Fujii et al. 1996) are outstanding examples of this concept. Possible mechanisms responsible for the formation of these neuron assemblies were also recently investigated and discussed by Buzsáki (2010). Since these neuronal populations

are a discrete set of system components, each in a firing or notfiring state, it has been suggested (Pereira and Furlan 2010) that processes of digital computation are realized by the neuronal networks.

A broadened view on the cellular networks in the CNS came with the proposal (Agnati et al. 1986) of the existence in the brain of two main modes of intercellular communication, called wiring transmission (WT) and volume transmission (VT), respectively (see Agnati et al. 2010b for a detailed review). WT is characterized by a structurally well-defined channel (a "wire," i.e., a private communication channel), connecting a source with its targets. The synaptic transmission between neurons is the most important example of WT in the CNS. VT, on the other side, takes place by using the extracellular space as a nonprivate communication channel, and represents the three-dimensional diffusion of signals for a distance greater than the synaptic cleft (see also Fuxe et al. 2007a). Nicholson's (1988) work provided strong experimental support for VT in the brain and also characterized the physical features of the process (Nicholson 2001). Different classes of VT signals have been identified and include chemicals (see Table 3 in Agnati et al. 2010b), such as neurotransmitters, ions, gases, and enzymes, as well as physical signals such as electrotonic currents (Holt and Koch 1999; Kamermans and Fahrenfort 2004), temperature gradients (Yablonskiy et al. 2000; Fuxe et al. 2005; Rivera et al. 2006), and pressure waves generated by arterial pulses (Agnati et al. 2005a). VT is also characterized by a very high divergence, since one source usually gives signals to a great many targets, including not only neurons, but also other types of cells in the CNS, such as astrocytes (Syková and Chvátal 2000) and microglial cells (Färber and Kettenmann 2005). This leads to the formation of "complex cellular networks," exchanging signals in a certain volume of brain tissue and, due to this cross-talk, integrating their activity (Agnati and Fuxe 2000).

In this context, the relationship between neurons and astrocytes is the best studied (see Fellin and Carmignoto 2004) and recent findings highlighted the involvement of "neuron-astroglial interactions" in the higher brain functions. Astrocytes can play an important role in the functional organization of the cerebral cortex from specific interactions with single synaptic contacts to modulatory interactions with entire neuronal networks (Schipke et al. 2008; Pereira and Furlan 2010). As a matter of fact, it has been introduced the concept of *tripartite synapse*, since in most glutamatergic central synapses, the extremity of a protoplasmic astrocyte process wraps the synaptic cleft. It should be noted that astrocytes express membrane receptors to neurotransmitters and can release their own chemical messengers (gliotransmitters). Thus, they establish a cross-talk with both pre- and postsynaptic neurons. What is of particular importance for our discussion is that several astrocytes participate in this functional organization, coupled with each other by gap junctions to form a network (see Carmignoto 2000). Gap junction channels are regulated by extra- and intracellular signals, suggesting that also in astrocyte networks computational rules could be implemented (Giaume 2010). As discussed by Pereira and Furlan (2010), however, astrocytic networks seem to differ from neuronal networks for what it concerns the vehicle of computation they use, namely "calcium waves," suggesting that analog-like computational processes are realized by this type of cellular network. Thus, neuroastroglial networks do exist controlling not only dynamic glucose delivery (Rouach et al. 2008), but also participating in cognitive functions (Robertson 2002). It follows that such a complex network appears to integrate and exploit both "digital" and "analog" computational processes.

- *The single neuron.* Current evidence indicates that the vehicles of neural processes are neuronal spikes and the processing of neural spike trains by neurons is often called "*neural computation*." Many neuroscientists see in the sequence of spikes a sort of binary string (see Rieke et al. 1997 for a detailed review), others (see Churchland and Sejnowski 1992) argue that the input to a neuron is analog (continuous values between 0 and 1). Thus, whether neural computation is best regarded as a form of digital computation, analog computation,

or something else is a debated question. However, since the functionally relevant aspects of neural process are medium-independent aspects of the spikes (see Piccinini and Scarantino 2011 for a discussion), primarily spike rates, spike trains appear as proper vehicles for computation. It follows that we can certainly consider the single neuron as performing computation in the generic sense. Furthermore, as suggested by some authors (Koch and Segev 2000; Cook 2011), spatially distributed physical variables (such as calcium distribution throughout the dendritic tree and the cell body) also play an important role in the function of single neurons, indicating that neurons are likely sophisticated processors in which the abovementioned "neural computation" could act in concert with some form of analog computation.

- *The receptor mosaics.* In recent years, increasing experimental evidence supported the hypothesis (put forward in Agnati et al. 1980) that G protein-coupled receptors (GPCRs) can form high-order receptor oligomers at the cell membrane. In particular, by using sequential resonance energy transfer (SRET) approaches it has been possible to demonstrate the existence of trivalent GPCR complexes in living cells. For instance, the existence of higher-order A_{2A}-CB_1-D_2 (Carriba et al. 2008) and A_{2A}-D_2-$mGlu_5$ (Cabello et al. 2009) heteromers has been shown. Recently, another set of studies supported the existence of higher-order receptor oligomers. In the case of the β_2-adrenergic receptor (β_2-AR), the research by Kobilka and colleagues has demonstrated that the receptor is predominantly tetrameric following reconstitution into phospholipid vesicles (Fung et al. 2009). The existence of these supramolecular complexes is considered of particular importance because it allows the emergence of integrative functions performed by a protein aggregate as a whole. In fact, owing to receptor–receptor interactions a configuration change of a given receptor will transform the probability of changing the configuration for the adjacent receptors in the RM and the effect will propagate throughout the cluster, leading to a complex collective behavior and to an integrated regulation of multiple effectors (see Fuxe et al. 2007b for a review). It was suggested that this molecular mechanism may also lead to a transient and/or permanent change of the synaptic efficacy and then contribute to memory storage and engram formation (see Guidolin et al. 2007 for a review). Some authors (Agnati et al. 2002) argued that the RMs could be considered computational devices and their behavior could be explained as a computation. In this respect, it is worth noting that when formed a RM is a system manipulating sets of protein conformations. In fact, the conformational state each component unit assumes is conditioned by the conformations of the other receptors in the mosaic according to a rule defined by the topology of the interactions (i.e., by the spatial arrangement of the receptors forming the assembly) and by the efficacy of the allosteric receptor-receptor interactions interconnecting the receptors with each other (Agnati et al. 2010a). Since this mechanism also appears to be medium-independent (see Conrad and Zauner 1997), RM can be considered to perform computations at least in the generic sense.

Noncomputational Processes in the Brain

In addition to the above described computational processes, at each scale of the morpho-functional organization of the brain other processes also important for the higher brain functions have to be considered. They are summarized in Table 1 and will be briefly discussed here: T1

- A number of global signals (originating from the rest of the body and from the metabolism) significantly influence the activity of the complex cellular networks. They include signals of a chemical, such as circulating hormones (McEwen et al. 1968; Gillies and McArthur 2010; McEwen 2010), and/or physical nature, such as the abovementioned pressure waves (Agnati et al. 2005a; Linninger et al. 2009), thermal gradients (Yablonskiy

TABLE 1
Noncomputational processes at different levels of the hierarchical organization of the brain

Level	Process	References
Complex cellular networks (macro-scale)	Systemic chemical signaling	McEwen et al. 1968
		Gillies and McArthur 2010
		McEwen 2010
		Russo et al. 2010
	Pressure waves	Greitz 1993, 2006
		Agnati et al. 2005a
		Ostrow and Sachs 2005
		Linninger et al. 2009
	Temperature macrogradients	Yablonskyi et al. 2000
		Kiyatkin 2010
	Glial cell proliferation	Bennett et al. 1964
	Neurogenesis	Stranahan et al. 2006
		Onténiente 2009
Local circuits (meso-scale)	Changes in dendtritic branches	Bennett et al. 1964
	Structural synaptic plasticity	Adams et al. 2006
		Kerchner and Nicoll 2008
		Stevens 2008
		Theodosis et al. 2008
		Holtmaat and Svoboda 2009
	Extracellular matrix changes	Dityatev and Fellin 2008
	Temperature microgradients via uncoupling protein	Fuxe et al. 2005
		Rivera et al. 2006
	Mitochondrial biogenesis	Gutsaeva et al. 2008
Molecular networks (micro-scale)	Changes in membrane lipids	Botelho et al. 2006
	Electric fields	Frölich 1968
		Rochlin and Peng 1989
		Vos et al. 1993
		Agnati et al. 2005b
	Intracellular signaling pathways	Bhalla and Iyengar 1999

et al. 2000; Kiyatkin 2010), and field potentials (Shepherd 1998). It is noteworthy that some of these VT signals, such as thermal gradients and pressure waves, are "pervasive signals" (see Agnati et al. 2007b) that affect quite large brain areas and possibly make their activity coherent with (or at least informed of) the activity of other brain areas. In the case of pressure waves generated by arterial pulses, for instance, they may globally inform the CNS on the state of the cardiovascular system. As a consequence, the orchestration of activity among cell pools can change according to the situational context (also involving the organism in which the brain is embedded). The structure of the cell networks can also be remodeled in an experience-based way by processes of glial cell proliferation (Bennett et al. 1964) and, in particular conditions, neuron replacement by neurogenesis (Stranahan et al. 2006).

- Processes of adaptive structural remodeling are well known at the level of neurons and local circuits. Examples include changes in dendritic branches (Bennett et al. 1964), in synaptic connectivity (Adams et al. 2006; Kerchner and Nicoll 2008; Holtmaat and Svoboda 2009), and mitochondrial biogenesis as an adaptive mechanism that protects brain metabolism during hypoxia (Gutsaeva et al. 2008). Emerging evidence also indicates that the cross-talk between perisynaptic astrocytes and neurons mediates synaptogenesis, synapse elimination, and structural plasticity through a variety of secreted and contact-dependent signals (Stevens 2008; Theodosis et al. 2008). It is noteworthy that by expressing several

forms of synaptic plasticity, a single neuron can convey an array of different signals to the neural circuit in which it operates (Abbott and Regehr 2004).

- As far as receptor mosaics are concerned, it is important to underline that each receptor molecule can span three distinct microenvironments: the extracellular fluid, the membrane, and the intracellular fluid. Thus, the relevant chemical–physical characteristics of the three microenvironments in which it is embedded can significantly influence its conformation as well as the possibility to form macromolecular complexes and their topology (Agnati et al. 2002, 2005b). Experimental data (see Botelho et al. 2006) indicate, for instance, that changes in the composition of the lipid environment in which receptors are embedded (and in particular lipid rafts) may modulate the conformational state of receptor heteromers and homomers, likely leading to altered receptor–receptor interactions and thus altered integrative signaling. Other mechanisms for the rapid reshuffling of protein interactions at the membrane levels involve changes in the electric field across the membrane (see Fröhlich 1968; Vos et al. 1993) and the action of the abovementioned field potentials (Shepherd 1998). Extracellular field potentials result from the activity in a large number of nearby cells and have an action at molecular level (Rochlin and Peng 1989). In fact, field potentials even at distances of many microns from the sources still have an intensity of some tens of μV (Bédard et al. 2004). Therefore, they can affect electrostatic interactions within and between membrane molecules.

Finally, it should always to be remembered that RMs work as specialized input units (Agnati et al. 2008) for the intracellular signal transduction pathways. These biochemical processes (see Bhalla and Iyengar 1999) are interacting chains of chemical reactions involving low-molecular weight G proteins, effector enzymes, second messenger mechanisms, and ion channels. It is such a complex biochemical machinery that allows the cell to process and respond to external signals.

The just outlined processes can hardly be considered as computational. In fact, they do not appear to occur by organizing specific functional components into formatted internal vehicles that are manipulated according to a rule. Nevertheless, they play a significant part in the higher functions of the brain. As discussed above, many of them carry information on the overall activity of the brain and/or on the body in which the brain is embedded. Moreover, the brain networks, seat of genuine computational functions, are constantly reshaped and their activity modulated by most of the mechanisms here considered.

Concluding Remarks

The rise of the computational paradigm to conceptualize the CNS deeply influenced neuroscience and notions such us *computation*, *representation*, and *information* appeared as key concepts to characterize and describe CNS functions. For example, Sejnowski et al. (1988) introduced "computational neuroscience" with the explicit agenda of explaining "how electrical and chemical signals are used in the brain to represent and process information" (Sejnowski et al. 1988:1299). This view supported and encouraged the development of an increasing number of computational approaches to model and simulate neurophysiological phenomena, which today allow us to integrate what we know about the CNS and to explore its complex behavior and properties. As pointed out by Grush (2001), however, a question remained unanswered. Is computation in neuroscience just a tool for building models, playing a role analogous to the role it plays in other disciplines, or is there something more to it? In other words, is being computational a genuine property of nervous systems?

In this respect, John Searle, for one, maintained that computation is observer-dependent in the strong sense that we can ascribe any computation to any process as we please and there is no fact of the matter as to whether our ascriptions are correct (Searle 1992). Under this view, being computational is not so much false as vacuous. On the other side, many authors rejected this contention and have argued that computation may be seen

as a way of capturing some aspects of the causal structure of the world (Chalmers 1996; Copeland 1996; Smith 2002). This raises a further question: which physical processes deserve to be described as computational?

In the present paper, the general account of *computation* recently proposed by Piccinini and Scarantino (2011) was assumed (see above under the heading Computational Explanation in Neuroscience), which allows a classification of different forms of concrete (physical) computational processes, from the "generic computation" to the more restrictive notion of "digital computation." It is a mechanistic explanation that can be applied only to systems able to generate internal objects with a specific format and manipulate them according to a general rule, defined over the inputs for producing outputs of the same type. Thus, it is independent of any semantic interpretation of the computational vehicles (inputs and outputs), and allows for discrimination between physical systems that do not compute and physical systems that can be considered computational systems (at least in the more generic sense) properly so called.

Looking at available neurobiological data from this standpoint, the CNS appears characterized by genuine computational possibilities. In fact, its basic architecture as a hierarchical system of networks of interacting elements (Agnati et al. 2004, 2007b) allows the physical realization of different forms of computational processes at different levels of its morphofunctional organization. In general they can be classified as "generic computations," but in some cases (as, for instance, in the neuroastroglial networks), both "digital" and "analog" computational processes seem to contribute to the brain higher functions by acting in concert (Pereira and Furlan 2010). An often emphasized point of difference between ordinary computational systems (such as the electronic computers) and the CNS emerges when the timing of the system's activities is taken into consideration: every computational mechanism properly so called (including connectionist systems) assumes, either explicitly or implicitly, that there are finite time intervals during which it can be determined what counts as a system's inputs and outputs. However, when the overall brain activity is considered it is unclear whether any fixed time interval of unambiguous physiological significance could be defined. Although this aspect would need deeper and more specific experimental investigations, some insight on this topic was recently proposed by Buzsáki (2010), providing a thoughtful discussion on possible mechanisms that allow for an ordered evolution in time of cell assemblies that lead to a sort of "neuronal syntax."

In this respect, however, it has to be observed that the overall brain activity also includes many noncomputational processes (occurring at all the hierarchical levels of the morphofunctional organization of the CNS) in addition to the computational ones. They play significant physiological roles, the most important being the global delivery of information about the external world and, in particular, the organism in which the brain is embedded, and the experience based reshaping of the brain structures (Bennett et al. 1964; McEwen 2010), including those involved in computational processes. The brain, therefore, appears characterized by a peculiar combination of computational and noncomputational processes, and could be defined as a dynamically morphing system with computational capabilities of different types, undergoing genetically and environmentally driven self-organization (and, as a consequence, a sort of "reprogramming" of its computational properties) in response to the external context. For this reason, some authors (Varela et al. 2001; Werner 2004) suggested that relevant conceptual frameworks provided by physics, such as statistical mechanics (Baszó et al. 1999; Sirovich et al. 2000) and nonlinear dynamics (Abarbanel and Rabinovich 2001; Haken 2002), could represent for theoretical neuroscience particularly suitable tools, likely more helpful than the simple use of concepts from computability theory. In this respect it is noteworthy that, from a mathematical point of view, the models employed by modern theoretical neuroscientists (see above under the heading Modeling the CNS)

mainly involve mathematical biophysics instead of concepts and techniques from computability theory.

Thus, the view of the brain as a pure computational system or as a computational information processor (as in the "digital brain" theory based on an analogy between brain and computers) does not appear to fully fit with the morphofunctional characteristics of the CNS as we know them today. As with any successful analogy, however, it canalized thought in some directions, foreclosing others (Werner 2004). In particular, it emphasized the idea of the brain as a machine storing and manipulating symbols and the knowledge as a system of logical relationships between them (see Freeman 1997 for a critical discussion), but sidestepped the brain as an embodied (Damasio 1999; Carlson et al. 2010), situated (see Dreyfus 1972) agent, continuously responding to and shaped by the external world (Noe 2004).

REFERENCES

Abarbanel H. D. I., Rabinovich M. I. 2001. Neurodynamics: nonlinear dynamics and neurobiology. *Current Opinion in Neurobiology* 11:423–430.

Abbott L. F., Regehr W. G. 2004. Synaptic computation. *Nature* 431:796–803.

Adams V. L., Goodman R. L., Salm A. K., Coolen L. M., Karsch F. J., Lehman M. N. 2006. Morphological plasticity in the neural circuitry responsible for seasonal breeding in the ewe. *Endocrinology* 147:4843–4851.

Agnati L. F., Fuxe K. 1984. New concepts on the structure of the neuronal networks: the miniaturization and hierarchical organization of the central nervous system. *Bioscience Reports* 4:93–98.

Agnati L. F., Fuxe K. 2000. Volume transmission as a key feature of information handling in the central nervous system: possible new interpretative value of the Turing's B-type machine. *Progress in Brain Research* 125:3–19.

Agnati L. F., Fuxe K., Zini I., Lenzi P., Hökfelt T. 1980. Aspects on receptor regulation and isoreceptor identification. *Medical Biology* 58:182–187.

Agnati L. F., Fuxe K., Zoli M., Ozini I., Toffano G., Ferraguti F. 1986. A correlation analysis of the regional distribution of central enkephalin and β-endorphin immunoreactive terminals and of opiate receptors in adult and old male rats. Evidence for the existence of two main types of communication in the central nervous system: the volume transmission and the wiring transmission. *Acta Physiologica Scandinavica* 128:201–207.

Agnati L. F., Santarossa L. M., Benfenati F., Ferri M., Morpurgo A., Apolloni B., Fuxe K. 2002. Molecular basis of learning and memory: modelling based on receptor mosaics. Pages 165–196 in *From Synapses to Rules: Discovering Symbolic Rules from Neural Processed Data*, edited by B. Apolloni and F. Kurfess. New York: Kluwer Academic/Plenum Publishers.

Agnati L. F., Santarossa L., Genedani S., Canela E. I., Leo G., Franco R., Woods A., Lluís C., Ferré S., Fuxe K. 2004. On the nested hierarchical organization of CNS: basic characteristics of neuronal molecular networks. Pages 24–54 in *Computational Neuroscience: Cortical Dynamics*, edited by P. Érdi, A. Esposito, M. Marinaro, and S. Scarpetta. Berlin (Germany): Springer.

Agnati L. F., Genedani S., Lenzi P. L., Leo G., Mora F., Ferré S., Fuxe K. 2005a. Energy gradients for the homeostatic control of brain ECF composition and for VT signal migration: introduction of the tide hypothesis. *Journal of Neural Transmission* 112:45–63.

Agnati L. F., Guidolin D., Genedani S., Ferré S., Bigiani A., Woods A. S., Fuxe K. 2005b. How proteins come together in the plasma membrane and function in macromolecular assemblies. *Journal of Molecular Neuroscience* 26:133–153.

Agnati L. F., Guidolin D., Leo G., Fuxe K. 2007a. A boolean network modelling of receptor mosaics: relevance of topology and cooperativity. *Journal of Neural Transmission* 114:77–92.

Agnati L. F., Guidolin D., Fuxe K. 2007b. The brain as a system of nested but partially overlapping networks. Heuristic relevance of the model for brain physiology and pathology. *Journal of Neural Transmission* 114:3–19.

Agnati L. F., Guidolin D., Carone C., Dam M., Genedani S., Fuxe K. 2008. Understanding neuronal molecular networks builds on neuronal cellular network architecture. *Brain Research Reviews* 58:379–399.

Agnati L. F., Guidolin D., Vilardaga J. P., Ciruela F., Fuxe K. 2010a. On the expanding terminology in the GPCR field: the meaning of receptor mosaics and receptor heteromers. *Journal of Receptors and Signal Transduction* 30:287–303.

Agnati L. F., Guidolin D., Guescini M., Genedani S., Fuxe K. 2010b. Understanding wiring and volume transmission. *Brain Research Reviews* 64:137–159.

Alligood K. T., Sauer T. D., Yorke J. A. 1997. *Chaos: An Introduction to Dynamical Systems*. New York: Springer-Verlag.

Arbib M. A. 2003. A guided tour of brain theory and neural networks. Pages 25–80 in *The Handbook of Brain Theory and Neural Networks*, edited by M. A.

Arbib. Second Edition. Cambridge (MA): MIT Press.

Baszó F., Szalisznyó K., Payrits S., Érdi P. 1999. A statistical approach to neural population dynamics: theory, algorithms, simulations. *Neurocomputing* 26/27: 329–334.

Bédard C., Kröger H., Destexhe A. 2004. Modeling extracellular field potentials and the frequency-filtering properties of extracellular space. *Biophysical Journal* 86:1829–1842.

Bennett E. L., Diamond M. C., Krech D., Rosenzweig M. R. 1964. Chemical and anatomical plasticity of brain. *Science* 146:610–619.

Bhalla U. S., Iyengar R. 1999. Emergent properties of networks of biological signaling pathways. *Science* 283:381–387.

Blumenfeld B., Preminger S., Sagi D., Tsodyks M. 2006. Dynamics of memory representations in networks with novelty-facilitated synaptic plasticity. *Neuron* 52: 383–394.

Botelho A. V., Huber T., Sakmar T. P., Brown M. F. 2006. Curvature and hydrophobic forces drive oligomerization and modulate activity of rhodopsin in membranes. *Biophysical Journal* 91:4464–4477.

Brette R., Rudolph M., Carnevale T., Hines M., Beeman D., Bower J. M., Diesmann M., Morrison A., Goodman P. H., Harris F. C., Zirpe M., Natschläger T., Pecevski D., Ermentrout B., Djurfeldt M., Lansner A., Rochel O., Vieville T., Muller E., Davison A. P., El Boustani S., Destexhe A. 2007. Simulation of networks of spiking neurons: a review of tools and strategies. *Journal of Computational Neuroscience* 23:349–398.

Buzsáki G. 2010. Neural syntax: cell assemblies, synapsembles, and readers. *Neuron* 68:362–385.

Cabello N., Gandía J., Bertarelli D. C. G., Watanabe M., Lluís C., Franco R., Ferré S., Luján R., Ciruela F. 2009. Metabotropic glutamate type 5, dopamine D_2 and adenosine A_{2a} receptors form higher-order oligomers in living cells. *Journal of Neurochemistry* 109: 1497–1507.

Cabestany J., Prieto A., Sandoval F. 2005. *Computational Intelligence and Bioinspired Systems*. Berlin (Germany): Springer-Verlag.

Carlson T. A., Alvarez G., Wu D.-A., Verstraten F. A. J. 2010. Rapid assimilation of external objects into the body schema. *Psychological Science* 21:1000–1005.

Carmignoto G. 2000. Reciprocal communication systems between astrocytes and neurones. *Progress in Neurobiology* 62:561–581.

Carriba P., Navarro G., Ciruela F., Ferré S., Casadó V., Agnati L. F., Cortés A., Mallol J., Fuxe K., Canela E. I., Lluís C., Franco R. 2008. Detection of heteromerization of more than two proteins by sequential BRET-FRET. *Nature Methods* 5:727–733.

Chalmers D. J. 1996. Does a rock implement any finite-state automaton? *Synthese* 108:309–333.

Chopard B., Droz M. 1998. *Cellular Automata Modeling of Physical Systems*. Cambridge (UK): Cambridge University Press.

Churchland P. S., Sejnowski T. 1992. *The Computational Brain*. Cambridge (MA): MIT Press.

Churchland P. S., Koch C., Sejnowski T. J. 1990. What is computational neuroscience? Pages 46–55 in *Computational Neuroscience*, edited by E. L. Schwartz. Cambridge (MA): MIT Press.

Conrad M., Zauner K. P. 1997. Molecular computing: from conformational pattern recognition to complex processing networks. *Lecture Notes in Computer Science* 1278:1–10.

Cook N. D. 2011. *Harmony, Perspective and Triadic Cognition*. New York: Cambridge University Press.

Cooper S. B. 2004. *Computability Theory*. Boca Raton (FL): Chapman & Hall/CRC.

Copeland B. J. 1996. What is computation? *Synthese* 108: 335–359.

Craver C. F. 2006. When mechanistic models explain. *Synthese* 153:355–376.

Csete M. E., Doyle J. C. 2002. Reverse engineering of biological complexity. *Science* 295:1664–1669.

Damasio A. R. 1999. *The Feeling of What Happens: Body and Emotions in the Making of Consciousness*. New York: Harcourt Brace.

Davis M., Sigal R., Weyuker E. J. 1994. *Computability, Complexity, and Languages: Fundamentals of Theoretical Computer Science*. Boston (MA): Academic Press.

Dityatev A., Fellin T. 2008. Extracellular matrix in plasticity and epileptogenesis. *Neuron Glia Biology* 4:235–247.

Dragunow M. 2008. High-content analysis in neuroscience. *Nature Reviews Neuroscience* 9:779–788.

Dreyfus H. L. 1972. *What Computers Can't Do: A Critique of Artificial Reason*. New York: Harper and Row.

Duke T. A. J. Bray D. 1999. Heightened sensitivity of a lattice of membrane receptors. *Proceedings of the National Academy of Sciences of the United States of America* 96:10104–10108.

Edelman G. M. 1987. *Neural Darwinism: The Theory of Neural Group Selection*. New York: Basic Books.

Edelman G. M. 1992. *Bright Air, Brilliant Fire: On the Matter of the Mind*. New York: Basic Books.

Elman J. L. 1999. Connectionism, artificial life, and dynamical systems. Pages 488–505 in *A Companion to Cognitive Science*, edited by W. Bechtel and G. Graham. Malden (MA): Blackwell Publishing.

Fan J., Guise K. G., Liu X., Wang H. 2008. Searching for the majority: algorithms of voluntary control. *PLoS One* 3:e3522. doi:10.1371/journal.pone.0003522.

Färber K., Kettenmann H. 2005. Physiology of microglial cells. *Brain Research Reviews* 48:133–143.

Fellin T., Carmignoto G. 2004. Neurone-to-astrocyte signalling in the brain represents a distinct multifunctional unit. *Journal of Physiology* 559:3–15.

Filler A. G. 2009. The history, development, and impact of computed imaging in neurological diagnosis and

neurosurgery: CT, MRI, DTI. *Nature Precedings* http://dx.doi.org/10.1038/npre.2009.3267.5.

Fodor J. A. 1975. *The Language of Thought.* New York: Crowell.

Freeman W. J. 1997. Three centuries of category errors in studies of the neural basis of consciousness and intentionality. *Neural Networks* 10:1175–1183.

Freeman W. J. 2001. *How Brains Make Up Their Minds.* New York: Columbia University Press.

Fröhlich H. 1968. Long-range coherence and energy storage in biological systems. *International Journal of Quantum Chemistry* 2:641–649.

Fujii H., Ito H., Ahiara K., Ichinose N., Tsukada M. 1996. Dynamical cell assembly hypothesis—theoretical possibility of spatio-temporal coding in the cortex. *Neural Networks* 9:1303–1350.

Fung J. J., Deupi X., Pardo L., Yao X. J., Velez-Ruiz G. A., DeVree B. T., Sunahara R. K., Kobilka B. K. 2009. Ligand-regulated oligomerization of β_2-adrenoceptors in a model lipid bilayer. *EMBO Journal* 28:3315–3328.

Fuxe K., Agnati L. F., Benfenati F., Celani M., Zini I., Zoli M., Mutt V. 1983. Evidence for the existence of receptor–receptor interactions in the central nervous system. Studies on the regulation of monoamine receptors by neuropeptides. *Journal of Neural Transmission* S18:165–179.

Fuxe K., Rivera A., Jacobsen K. X., Höistad M., Leo G., Horvath T. L., Staines W., De la Calle A., Agnati L. F. 2005. Dynamics of volume transmission in the brain. Focus on catecholamine and opioid peptide communication and the role of uncoupling protein 2. *Journal of Neural Transmission* 112:65–76.

Fuxe K., Dahlström A., Höistad M., Marcellino D., Jansson A., Rivera A., Diaz-Cabiale Z., Jacobsen K., Tinner-Staines B., Hagman B., Leo G., Staines W., Guidolin D., Kehr J., Genedani S., Belluardo N., Agnati L. F. 2007a. From the Golgi-Cajal mapping to the transmitter-based characterization of the neuronal networks leading to two modes of brain communication: wiring and volume transmission. *Brain Research Reviews* 55:17–54.

Fuxe K., Canals M., Torvinen M., Marcellino D., Terasmaa A., Genedani S., Leo G., Guidolin D., Diaz-Cabiale Z., Rivera A., Lundstrom L., Langel U., Narvaez J., Tanganelli S., Lluís C., Ferré S., Woods A., Franco R., Agnati L. F. 2007b. Intramembrane receptor–receptor interactions: a novel principle in molecular medicine. *Journal of Neural Transmission* 114:49–75.

Fuxe K., Marcellino D., Borroto-Escuela D. O., Frankowska M., Ferraro L., Guidolin D., Ciruela F., Agnati L. F. 2010. The changing world of G protein-coupled receptors: from monomers to dimers and receptor mosaics with allosteric receptor-receptor interactions. *Journal of Receptors and Signal Transduction Research* 30:272–283.

Gally J. A., Montague P. R., Reeke G. N., Edelman G. M. 1990. The NO hypothesis: possible effects of a short-lived, rapidly diffusible signal in the development and function of the nervous system. *Proceedings of the National Academy of Sciences of the United States of America* 87:3547–3551.

Giaume C. 2010. Astroglial wiring is adding complexity to neuroglial networking. *Frontiers in Neuroenergetics* 2:129.

Gillies G. E., McArthur S. 2010. Independent influences of sex steroids of systemic and central origin in a rat model of Parkinson's disease: a contribution to sex-specific neuroprotection by estrogens. *Hormones and Behavior* 57:23–34.

Godfrey M. D., Hendry D. F. 1993. The computer as von Neumann planned it. *IEEE Annals of the History of Computing* 15:11–21.

Golding N. L., Staff N. P., Spruston N. 2002. Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature* 418:326–331.

Gray C. M., König P., Engel A. K., Singer W. 1989. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* 338:334–337.

Gray C. M., Engel A. K., König P., Singer W. 1990. Stimulus-dependent neuronal oscillations in cat visual cortex: receptive field properties and feature dependence. *European Journal of Neuroscience* 2:607–619.

Greitz D. 1993. Cerebrovascular fluid circulation and associated intracranial dynamics. A radiographic investigation using MR imaging and radionucleide cisternography. *Acta Radiologica Supplementum* 386: 1–23.

Greitz D. 2006. Unraveling the riddle of syringomyelia. *Neurosurgical Review* 29:251–264.

Grush R. 2001. The semantic challenge to computational neuroscience. Pages 155–172 in *Theory and Method in the Neurosciences,* edited by P. K. Machamer, R. Grush, and P. McLaughlin. Pittsburgh (PA): University of Pittsburgh Press.

Guidolin D., Fuxe K., Neri G., Nussdorfer G. G., Agnati L. F. 2007. On the role of receptor-receptor interactions and volume transmission in learning and memory. *Brain Research Reviews* 55:119–133.

Guidolin D., Ciruela F., Genedani S., Guescini M., Tortorella C., Albertin G., Fuxe K., Agnati L. F. 2011. Bioinformatics and mathematical modelling in the study of receptor-receptor interactions and receptor oligomerization. Focus on adenosine receptors. *Biochimica et Biophysica Acta-Membranes* 1808:1267–1283.

Gutsaeva D. R., Carraway M. S., Suliman H. B., Demchenko I. T., Shitara H., Yonekawa H., Piantadosi C. A. 2008. Transient hypoxia stimulates mitochondrial biogenesis in brain subcortex by a neuronal nitric oxide synthase-dependent mechanism. *Journal of Neuroscience* 28:2015–2024.

Haken H. 2002. *Brain Dynamics: Synchronization and Activity Patterns in Pulse-Coupled Neural Nets with Delays and Noise.* Berlin (Germany): Springer-Verlag.

Hebb D. O. 1949. *The Organization of Behavior: A Neuropsychological Theory.* New York: Wiley.

Heims S. J. 1991. *The Cybernetics Group.* Cambridge (MA): MIT Press.

Hill S., Tononi G. 2005. Modeling sleep and wakefulness in the thalamocortical system. *Journal of Neurophysiology* 93:1671–1698.

Holt G. R., Koch C. 1999. Electrical interactions via the extracellular potential near cell bodies. *Journal of Computational Neuroscience* 6:169–184.

Holtmaat A., Svoboda K. 2009. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nature Reviews Neuroscience* 10:647–658.

Hopfield J. J. 1984. Neurons with graded response have collective computational properties like those of two-state neurons. *Proceedings of the National Academy of Sciences of the United States of America* 81:3088–3092.

Hughes R. I. G. 1999. The Ising model, computer simulation, and universal physics. Pages 97–145 in *Models as Mediators: Perspectives on Natural and Social Sciences,* edited by M. S. Morgan and M. Morrison. Cambridge (UK): Cambridge University Press.

Humphreys P. 2004. *Extending Ourselves: Computational Science, Empiricism, and Scientific Method.* New York: Oxford University Press.

Izhikevich E. M., Edelman G. M. 2008. Large-scale model of thalamocortical systems. *Proceedings of the National Academy of Sciences of the United States of America* 105:3593–3598.

Jacob F. 1970. *La logique du Vivant. Une Histoire de l'Hérédité.* Paris (France): Ed. Gallimard.

Kamermans M., Fahrenfort I. 2004. Ephaptic interactions within a chemical synapse: hemichannel-mediated ephaptic inhibition in the retina. *Current Opinion in Neurobiology* 14:531–541.

Kauffman S. A. 1993. *The Origins of Order: Self-Organization and Selection in Evolution.* Oxford (UK): Oxford University Press.

Kenakin T., Agnati L. F., Caron M., Fredholm B., Guidolin D., Kobilka B., Lefkowitz R. W., Lohse M., Woods A., Fuxe K. 2010. International workshop at the Nobel Forum, Karolinska Institutet on G protein-coupled receptors: finding the words to describe monomers, oligomers, and their molecular mechanisms and defining their meaning. Can a consensus be reached? *Journal of Receptors and Signal Transduction Research* 30:284–286.

Kerchner G. A., Nicoll R. A. 2008. Silent synapses and the emergence of a postsynaptic mechanism for LTP. *Nature Reviews Neuroscience* 9:813–825.

Kiyatkin E. A. 2010. Brain temperature homeostasis: physiological fluctuations and pathological shifts. *Frontiers in Bioscience* 15:73–92.

Knoblauch A., Palm G., Sommer F. T. 2010. Memory capacities for synaptic and structural plasticity. *Neural Computation* 22:289–341.

Koch C., Segev I. 2000. The role of single neurons in information processing. *Nature Neuroscience* 3:1171–1177.

Landauer R. 1991. Information is physical. *Physics Today* 44:23–29.

Landauer R. 1999. Information is inevitably physical. Pages 77–92 in *Feynman and Computation: Exploring the Limits of Computers,* edited by A. J. G. Hey. Cambridge (MA): Perseus Books.

Leise T., Siegelmann H. 2006. Dynamics of a multistage circadian system. *Journal of Biological Rhythms* 21:314–323.

Leroi-Gourhan A. 1956. L'homme, races et moeurs. In *Encyclopédie Clartés,*Volume 4. Paris (France): Editions Clartés.

Lewkowicz D. J., Ghazanfar A. A. 2009. The emergence of multisensory systems through perceptual narrowing. *Trends in Cognitive Sciences* 13:470–478.

Linninger A. A., Xenos M., Sweetman B., Ponkshe S., Guo X., Penn R. 2009. A mathematical model of blood, cerebrospinal fluid and brain dynamics. *Journal of Mathematical Biology* 59:729–759.

Lukashin A. V., Amirikian B. R., Georgopoulos A. P. 1996. Neural computations underlying the exertion of force: a model. *Biological Cybernetics* 74:469–478.

Machtey M., Young P. 1978. *An Introduction to the General Theory of Algorithms.* New York: North-Holland.

Markram H. 2006. The blue brain project. *Nature Reviews Neuroscience* 7:153–160.

Marr D. 1982. *Vision: A Computational Investigation into the Human Representation and Processing of Visual Information.* San Francisco (CA): W. H. Freeman.

McCulloch W. S., Pitts W. H. 1943. A logical calculus of the ideas immanent in nervous activity. *Bulletin of Mathematical Biophysics* 5:115–133.

McEwen B. S. 2010. Stress, sex, and neural adaptation to a changing environment: mechanisms of neural remodeling. *Annals of the New York Academy of Sciences* 1204:38–59.

McEwen B. S., Weiss J. M., Schwartz L. S. 1968. Selective retention of corticosterone by limbic structures in rat brain. *Nature* 220:911–912.

McKinstry J. L., Edelman G. M., Krichmar J. L. 2006. A cerebellar model for predictive motor control tested in a brain-based device. *Proceedings of the National Academy of Sciences of the United States of America* 103:3387–3392.

McNaughton B. L., Morris R. G. M. 1987. Hippocampal synaptic enhancement and information storage within a distributed memory system. *Trends in Neurosciences* 10:408–415.

Montague P. R., Dayan P., Sejnowski T. J. 1996. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *Journal of Neuroscience* 16:1936–1947.

Mountain D. C., Hubbard A. E. 2001. Sensing scenes with silicon. *The Biological Bulletin* 200:227–234.

Nicholson C. 1988. Issues involved in the transmission of chemical signals through the brain extracellular space. *Acta Morphologica Neerlando-Scandinavica* 26: 69–80.

Nicholson C. 2001. Diffusion and related transport mechanisms in brain tissue. *Reports on Progress in Physics* 64:815–884.

Noë A. 2004. *Action in Perception*. Cambridge (MA): MIT Press.

Olcese U., Esser S. K., Tononi G. 2010. Sleep and synaptic renormalization: a computational study. *Journal of Neurophysiology* 104:3476–3493.

Onténiente B. 2009. Neuroplasticity: from physiological adaptation to the concept of therapeutic plasticity. *Journal de la Société de Biologie* 203:107–111.

Ostrow L. W., Sachs F. 2005. Mechanosensation and endothelin in astrocytes—hypothetical roles in CNS pathophysiology. *Brain Research Reviews* 48:488–508.

Penrose R., Gardner M. 1989. *The Emperor's New Mind: Concerning Computers, Minds and the Laws of Physics*. Oxford (UK): Oxford University Press.

Pereira A., Furlan F. A. 2010. Astrocytes and human cognition: modeling information integration and modulation of neuronal activity. *Progress in Neurobiology* 92:405–420.

Perkel D. H. 1990. Computational neuroscience: scope and structure. Pages 38–45 in *Computational Neuroscience,* edited by E. L. Schwartz. Cambridge (MA): MIT Press.

Piccinini G. 2006. Computational explanation in neuroscience. *Synthese* 153:343–353.

Piccinini G. 2007a. Computational modelling vs. computational explanation: is everything a Turing machine, and does it matter to the philosophy of mind? *Australasian Journal of Philosophy* 85:93–115.

Piccinini G. 2007b. Computing mechanisms. *Philosophy of Science* 74:501–526.

Piccinini G. 2008. Computers. *Pacific Philosophical Quarterly* 89:32–73.

Piccinini G., Scarantino A. 2011. Information processing, computation, and cognition. *Journal of Biological Physics* 37:1–38.

Piepenbrock C. 2002. Natural image statistics for cortical orientation map development. Pages 181–202 in *Probabilistic Models of the Brain: Perception and Neural Function,* edited by R. P. N. Rao, B. A. Olshausen, and M. S. Lewicki. Cambridge (MA): MIT Press.

Pour-El M. B. 1974. Abstract computability and its relation to the general purpose analog computer (some connections between logic, differential equations and analog computers). *Transactions of the American Mathematical Society* 199:1–28.

Putnam H. 1999. The nature of mental states. Pages 27–34 in *Mind and Cognition: An Anthology,* Second Edition, edited by W. G. Lycan. Malden (MA): Blackwell Publishers.

Rapatski B. L., Suppe F., Yorke J. A. 2005. HIV epidemics driven by late disease stage transmission. *Journal of Acquired Immune Deficiency Syndromes* 38:241–253.

Rieke F., Warland D., de Ruyter van Steveninck R., Bialek W. 1997. *Spikes: Exploring the Neural Code*. Cambridge (MA): MIT Press.

Rivera A., Agnati L. F., Horvath T. L., Valderrama J. J., de La Calle A., Fuxe K. 2006. Uncoupling protein 2/3 immunoreactivity and the ascending dopaminergic and noradrenergic neuronal systems: relevance for volume transmission. *Neuroscience* 137: 1447–1461.

Robertson J. M. 2002. The astrocentric hypothesis: proposed role of astrocytes in consciousness and memory formation. *Journal of Physiology—Paris* 96:251–255.

Rochlin M. W., Peng H. B. 1989. Localization of intracellular proteins at acetylcholine receptor clusters induced by electric fields in *Xenopus* muscle cells. *Journal of Cell Science* 94:73–83.

Rohrlich F. 1990. Computer simulation in the physical sciences. *PSA: Proceedings of the Biennial Meeting of the Philosophy of Science Association* 2:507–518.

Rosenblatt F. 1958. The perceptron: a probabilistic model for information storage and organization in the brain. *Psychological Review* 65:386–408.

Rouach N., Koulakoff A., Abudara V., Willecke K., Glaume C. 2008. Astroglial metabolic networks sustain hippocampal synaptic transmission. *Science* 322: 1551–1555.

Rubel L. A. 1985. The brain as an analog computer. *Journal of Theoretical Neurobiology* 4:73–81.

Rumelhart D. E., McClelland J. L., PDP Research Group. 1986a. *Parallel Distributed Processing: Explorations in the Microstructure of Cognition, Volume 1: Foundations*. Cambridge (MA): MIT Press.

Rumelhart D. E., Hinton G. E., Williams R. J. 1986b. Learning representations by back-propagating errors. *Nature* 323:533–536.

Russo S. J., Dietz D. M., Dumitriu D., Morrison J. H., Malenka R. C., Nestler E. J. 2010. The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens. *Trends in Neuroscience* 33:267–276.

Schipke C. G., Haas B., Kettenmann H. 2008. Astrocytes discriminate and selectively respond to the activity of a subpopulation of neurons within the barrel cortex. *Cerebral Cortex* 18:2450–2459.

Schyns P. G., Gosselin F., Smith M. L. 2009. Information processing algorithms in the brain. *Trends in Cognitive Sciences* 13:20–26.

Searle J. R. 1992. *The Rediscovery of the Mind*. Cambridge (MA): MIT Press.

Sejnowski T. J., Koch C., Churchland P. S. 1988. Computational neuroscience. *Science* 241:1299–1306.

Shepherd G. M. 1998. *The Synaptic Organization of the Brain.* New York: Oxford University Press.

Shi Y., Duke T. 1998. Cooperative model of bacterial sensing. *Physical Review E* 58:6399–6406.

Siegelmann H. T. 2008. Analog-symbolic memory that tracks via reconsolidation. *Physica D: Nonlinear Phenomena* 237:1207–1214.

Siegelmann H. T. 2010. Complex systems science and brain dynamics. *Frontiers in Computational Neuroscience* 4:7.

Sirovich L., Ormutag A., Knight B. W. 2000. Dynamics of neural populations: the equilibrium solution. *SIAM Journal on Applied Mathematics* 60:2009–2028.

Smith B. C. 2002. The foundations of computing. Pages 23–58 in *Computationalism: New Directions,* edited by M. Scheutz. Cambridge (MA): MIT Press.

Sporns O., Tononi G., Edelman G. M. 2000. Connectivity and complexity: the relationship between neuroanatomy and brain dynamics. *Neural Networks* 13: 909–922.

Stevens B. 2008. Neuron-astrocyte signaling in the development and plasticity of neural circuits. *Neurosignals* 16:278–288.

Stranahan A. M., Khalil D., Gould E. 2006. Social isolation delays the positive effects of running on adult neurogenesis. *Nature Neuroscience* 9:526–533.

Syková E., Chvátal A. 2000. Glial cells and volume transmission in the CNS. *Neurochemistry International* 36: 397–409.

Theodosis D. T., Poulain D. A., Oliet S. H. R. 2008. Activity-dependent structural and functional plasticity of astrocyte-neuron interactions. *Physiological Reviews* 88:983–1008.

Varela F., Lachaux J.-P., Rodriguez E., Martinerie J. 2001. The brainweb: phase synchronization and large-scale integration. *Nature Reviews Neuroscience* 2:229–239.

Villanueva R. J., Arenas A. J., González-Parra G. 2008. A nonstandard dynamically consistent numerical scheme applied to obesity dynamics. *Journal of Applied Mathematics* doi:10.1155/2008/640154.

Vos M. H., Rappaport F., Lambry J.-C., Breton J., Martin J.-L. 1993. Visualization of coherent nuclear motion in a membrane protein by femtosecond spectroscopy. *Nature* 363:320–325.

Wang Y., Lieberman M. 2004. Thermodynamic behavior of molecular-scale quantum-dot cellular automata (QCA) wires and logic devices. *IEEE Transactions on Nanotechnology* 3:368–376.

Werner G. 2001. Computation in nervous systems. http://users.ece.utexas.edu/~werner/Neural_computation.html. (Accessed 23 November 2010).

Werner G. 2004. Siren call of metaphor: subverting the proper task of neuroscience. *Journal of Integrative Neuroscience* 3:245–252.

Werner G. 2007. Perspectives on the neuroscience of cognition and consciousness. *BioSystems* 87:82–95.

Werner G. 2009. On critical state transitions between different levels in neural systems. *New Mathematics and Natural Computation* 5:185–196.

Werner G. 2010. Fractals in the nervous system: conceptual implications for theoretical neuroscience. *Frontiers in Physiology* 1:15.

Yablonskiy D. A., Ackerman J. J. H., Raichle M. E. 2000. Coupling between changes in human brain temperature and oxidative metabolism during prolonged visual stimulation. *Proceedings of the National Academy of Sciences of the United States of America* 97:7603–7608.

Yeo C. H. 2004. Memory and the cerebellum. *Current Neurology and Neuroscience Reports* 4:87–89.

Zoli M., Guidolin D., Fuxe K., Agnati L. F. 1996. The receptor mosaic hypothesis of the engram: possible relevance of boolean network modeling. *International Journal of Neural Systems* 7:363–368.

Handling Editor: Daniel Dykhuizen