Realistic modeling of neurons and networks: towards brain simulation

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Summary

Realistic modeling is a new advanced methodology for investigating brain functions. Realistic modeling is based on a detailed biophysical description of neurons and synapses, which can be integrated into microcircuits. The latter can, in turn, be further integrated to form large-scale brain networks and eventually to reconstruct complex brain systems. Here we provide a review of the realistic simulation strategy and use the cerebellar network as an example. This network has been carefully investigated at molecular and cellular level and has been the object of intense theoretical investigation. The cerebellum is thought to lie at the core of the forward controller operations of the brain and to implement timing and sensory prediction functions. The cerebellum is well described and provides a challenging field in which one of the most advanced realistic microcircuit models has been generated. We illustrate how these models can be elaborated and embedded into robotic control systems to gain insight into how the cellular properties of cerebellar neurons emerge in integrated behaviors. Realistic network modeling opens up new perspectives for the investigation of brain pathologies and for the neurorobotic field.

KEY WORDS: neuron models, computation, plasticity.

Introduction

Understanding brain functions is one of the greatest challenges in contemporary science (Markram, 2012; Abbott, 2013; Stix, 2013; Underwood, 2013; Wadman, 2013; Kandel et al., 2013). However, investigating brain functions presents special problems which are not common to other research fields. On the one hand, the brain exploits molecular and cellular mechanisms, which do not differ in principle from those of other cells and tissues. On the other hand, the brain is composed of networks connecting 10^{12} neurons through 10^{15} synapses capable of generating sensorimotor functions, cognition, emotion and, eventually, behavior and consciousness. So, what is the connection between the psychic and biological levels? Experimental evidence from physiology and neurology has taught us that the answer must be sought through the cellular principles of signal coding, communication, and plasticity (Fig. 1). While research in specific subfields is helping to clarify these mechanisms, an even more complex challenge is that of elucidating the details of neuronal connectivity and dynamics and their impact on brain functioning. Since it is impossible, in principle, to record all neurons simultaneously, we need new tools to address this issue. This problem is reflected in the duality between *reductionist* and *holistic* approaches, which are still incompatible in practice. The most important scientific agencies have taken up the challenge and launched three main projects addressing, together with the scientific issue, the development of new techniques and the benefits that society could derive from this research. These projects include: the *Human Brain Project* (HBP) (e.g. see D'Angelo, 2012; Markram, 2012; Stix, 2013), which is pioneering the development of realistic large-scale computational models, *Active Brain Mapping* (Alivisatos et al., 2013a,b), which is fostering the development of new recording techniques for cellular imaging, and the *Human Connectome Project* (McNab et al., 2013), which, based mainly on magnetic resonance imaging (MRI) technologies, is highlighting functional and structural brain connectivity. This complex enterprise has achieved considerable visibility in scientific and social media.

This review focuses on the HBP (Markram, 2013) and on *realistic computational modeling*. The cardinal elements of this technique can be summarized in the following considerations:

i) The models are constructed on the basis of solid biophysical principles, allowing the incorporation of relevant biological details (Koch, 1999; De Schutter, 2000).

This is a distinctive difference compared with theoretical models, in which the desired function is anticipated and the model is designed to generate it. In realistic modeling, the functions are the "emerging properties" of the system (be it a molecule, a neuron or a circuit). This difference can also be expressed by contrasting the *bottom-up* nature of realistic modeling with the *top-down* nature of theoretical modeling.

ii) Each modeling prediction has to be counter-tested and confirmed by biological observations. Therefore, biological assessment of brain function at different levels (molecular, cellular, circuit) is required.

iii) Importantly, an expansion towards whole-brain functions can now be envisaged thanks to the impressive advances obtained in the field of structural and functional brain imaging and stimulation. These non-invasive techniques (including MRI) can be used to analyze brain functions in living humans and animals and they make it possible to identify the circuits involved in complex behaviors. This, in turn, provides critical targets for brain modeling. It should also be noted that the generation of models on the dimensional and complexity scale required for investigating brain functioning is now within reach thanks to the advances achieved in supercomputing and modeling techniques. Supercomputers like *BlueGene* (Markram, 2006) have enough computational power to run brain models of unprecedented size and complexity.

The biophysical models of neurons and synapses will be used to generate realistic large-scale models of the brain, which are expected to help explain the principles of higher functions in cellular and molecular terms. This experimental process is not dissimilar in principle to that undertaken by physicists seeking to reconnect the properties of matter to those of constituent particles. However, the brain has a complex internal connectivity and is organized in multiple meta-levels, which precludes the identification of direct links between the molecular and behavioral processes. In this review we will elaborate on the case of the cerebellar network within the framework of the HBP. The modeling reconstruction of this network starting from biological observations and its incorporation into cerebro-cerebellar loops should make it possible to explain fundamental aspects of sensorimotor control and cognition on molecular and cellular grounds (D'Angelo and Casali, 2013). This may eventually lead to the provision of a powerful tool for elaborating pathophysiologi-

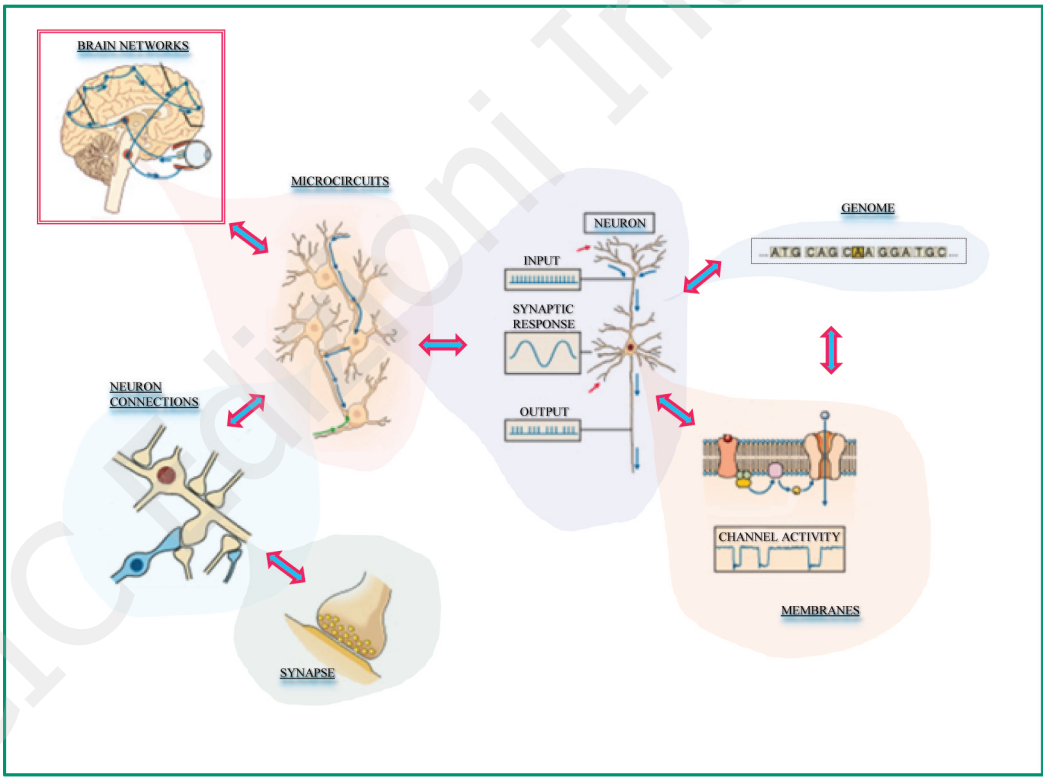


Figure 1 - Multilevel organization of brain structure and function (modified from D'Angelo and Peres, 2007).
Brain functions are the expression of a multilayered structure, ranging from ionic mechanisms to higher brain functions via neurons and neuronal assemblies forming circuits of varying complexity. The figure reproduces these levels starting with gene regulation of ion channel and synaptic receptor proteins, moving on to single neurons and microcircuits and finally reaching complex circuit connections forming the whole brain. The genome induces the synthesis of proteins (ion channels and receptors) that take part in the formation of cells, cell membranes and synapses. The cell membrane, governing the exchange of information, largely determines the chemical and electrical properties of neurons. Geometric organization of neuronal processes (dendrites and axons) determines the formation of subcellular microcircuits, taking advantage of interactions between synapses. Neurons aggregate in microcircuits that, in turn, constitute systems and neural pathways. The nervous system is a network of networks, and only at this level do highly abstracted functions emerge, giving rise to behavior.

cal hypotheses and for conceiving and developing an advanced generation of robotic control systems.

The biological basis of brain functioning: motivations for realistic modeling

Brain activity is based on a series of principles, which have been largely clarified over the last two centuries. The cellular elements of the brain, the *neurons*, interact at the level of the *synapses* and form neuronal *microcircuits* composed of thousands to millions of elements. These microcircuits are then organized into large-scale assemblies forming larger and larger networks and, eventually, the whole brain (Churchland and Sejnowski, 1993; Kandel et al., 2012) (Fig. 1).

Neurons are excitable elements, which can generate potential changes across their plasma membrane. Neurons are polarized at rest but can be depolarized by synaptic currents and generate action potentials when a certain threshold is reached. The core of neuronal functioning lies in the plasma membrane, in which are embedded several kinds of molecules including ion channels and pumps. Schematically, pumps actively generate electrochemical gradients for the main ions (Na^+, K^+, Cl^-, Ca^{2+}) through ATP hydrolysis and energy consumption. The balance of these gradients determines an electrical potential across the plasma membrane (approximated by the Goldman-Hodgkin-Katz equation). The opening of ion channels selective for specific ions allows current flow along the electrochemical gradients, thereby modifying the membrane potential. The fact that there are multiple molecular variants of the ion channels allows fine regulation of ion fluxes and membrane potential. The process of ion channel gating is complex and most commonly depends on sensitivity to membrane voltage and to chemical modulators such as neurotransmitters, calcium ions, cyclic nucleotides and G-proteins.

Neurons can organize spikes into specific patterns and use them to encode information and transmit it along the axons to other neurons (Rieke et al., 1997). At the synapses, neurotransmitters are released through a vesicle fusion mechanism activating receptors in the membrane of the receiving neurons. Different neurotransmitters and receptors can generate a large variety of electrical and metabolic effects on the postsynaptic neurons. The mechanisms regulating neurotransmitter release and receptor activation generate phenomena of short- and long-term plasticity, controlling the temporal dynamics of signal transmission and providing cellular mechanisms for learning and memory.

This brief summary raises specific motivations for generating and exploiting realistic models of the brain at different levels of complexity. First of all, the models will be fully explicit (as they are constructed by the researchers) and will therefore be able to provide answers regarding the intervention of low-level mechanisms in high-level brain processing. Second, the fundamental elements characterizing physical systems are their *structure, function* and *dynamics* (Arbib et al., 1998). While structure and function have been largely investigated using anatomical and neurophysiological tools, the complex *spatiotemporal dynamics* of brain activity remain largely unexplored (Buzsaki, 2006). Being endowed with the molecular mechanisms generating such dynamics, realistic modeling could help to provide answers in this regard.

Molecular and cellular modeling

Realistic modeling allows reconstruction of neuronal functions on a biological basis and through application of the principles of membrane biophysics (Fig.s 2, 3; see Box 1 for details). The primary role of these models is to integrate membrane and cytoplasmic mechanisms in order to explain membrane potential generation and intracellular regulation processes (Koch, 1999; De Schutter, 2000). Once validated, biophysical models can be used for predicting microcircuit functions. The basis of realistic modeling is the membrane equation, in which the first time derivative of membrane potential is related to the ionic conductances generated by the ion channels. These in turn are voltage- and time-dependent and are usually represented either through variants of the Hodgkin-Huxley formalism, through Markov chain reaction models, or using stochastic models (Hodgkin and Huxley, 1952; Connor and Stevens, 1971). All these mechanisms can be arranged into a system of ordinary differential equations, which are solved by numerical methods. The model can contain as many ion channel

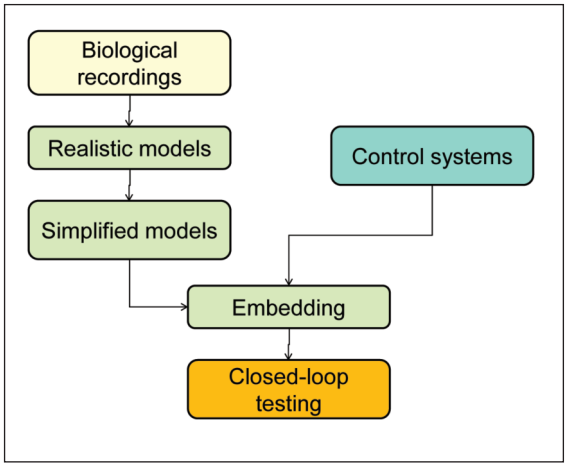
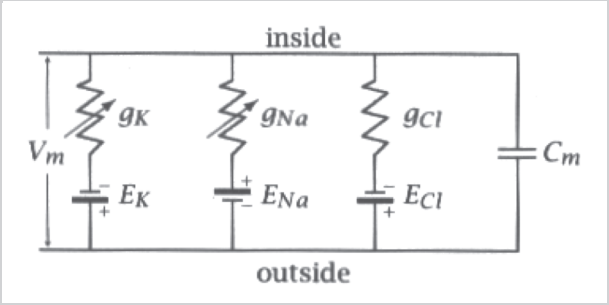


Figure 2 - Elaboration of neuronal and circuit models.
The construction of neuronal models is a complex procedure that requires a well-designed strategy. The process can be cross-validated by repeatedly matching modeling results with biological evidence. Once realistic models have been obtained, it is possible to abstract the fundamental neuronal functions by extracting the underlying dynamics to create computationally efficient simplified models. These latter can be embedded in control systems able to reproduce the neuronal context providing the model with input and output in a closed-loop circuit including sensory information, commands and feedback signals. The final step is the investigation of closed-loop circuits, interfacing the input and output of the neural network with the real world by means of anthropomorphic robotic devices.

BOX 1

The principles of neuronal modeling

Neuronal modeling is based on the "parallel electrical equivalent circuit" in which electrical branches connect the inside with the outside of the plasma membrane (Koch, 1999; De Schutter, 2000).



A capacitive branch (representing the hydrophobic non-conductive lipidic bilayer) and resistive branches (representing ionic conductances) are arranged in parallel between the inside and outside of the membrane, across which a potential difference, *Vm*, is established. Different conductances g_k, g_{Na}, and g_{Cl}, are indicated for different permeant ions: Na^+, K^+, and Cl^- (others, such as Ca^{2+}, and leakage conductances, are not shown). E_k, E_{Na}, and E_{Cl} are the equilibrium potentials for the ions. The resistive branches, because they contain a battery, can effectively operate as current generators with tunable internal resistance. Thus, when a current i_m flows through the membrane, it divides over the capacitor C_m and the conductances g_k, g_{Na}, and g_{Cl} . In the electric equivalent scheme, it follows that the membrane equation is:

$$I = I_c + I_K + I_{Na} + I_{Cl}$$

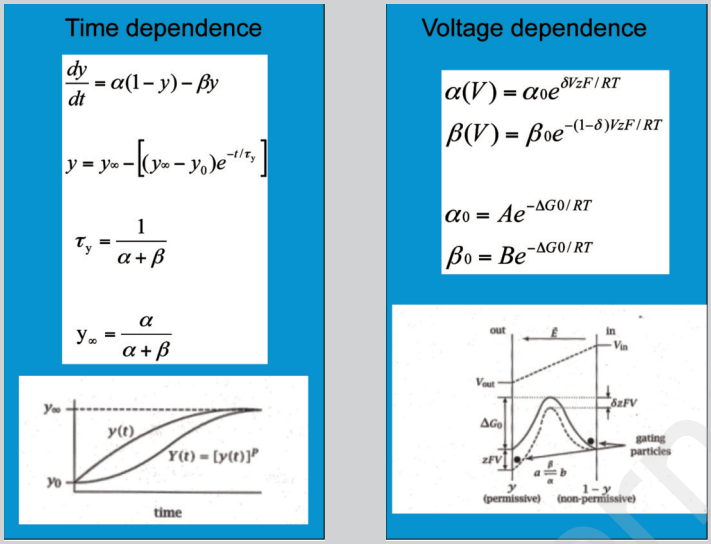
$$I = C\frac{dV_m}{dt} + g_k(V_m - E_K) + g_{Na}(V_m - E_{Na}) + g_{Cl}(V_m - E_{Cl})$$

where $(V_m - E_k)$, $(V_m - E_{Na})$, and $(V_m - E_{Cl})$ are the driving forces for the ions in each branch. This first order differential equation admits an exponential solution. The mathematical problem emerges because the conductances g_k, g_{Na}, and g_{Cl} are themselves a function of V_m and *t*. A standard description of these voltage- and time-dependent conductances is based on the Hodgkin-Huxley model (Hodgkin and Huxley, 1952; Connor and Stevens, 1971), in which each ionic conductance depends on the probability that gating particles are in the permissive state.

There can be multiple activation and inactivation particles in each ion channel, which can redistribute between the permissive state (*y*) and the non-permissive state (*1-y*). Thus, the ionic conductance depends on a maximum value g^{max} multiplied by the probability that the *m* activation or *n* inactivation particles are in the permissive state:

$$g_i = g_i^{\max} y_{i-act}^n y_{i-inact}^m$$

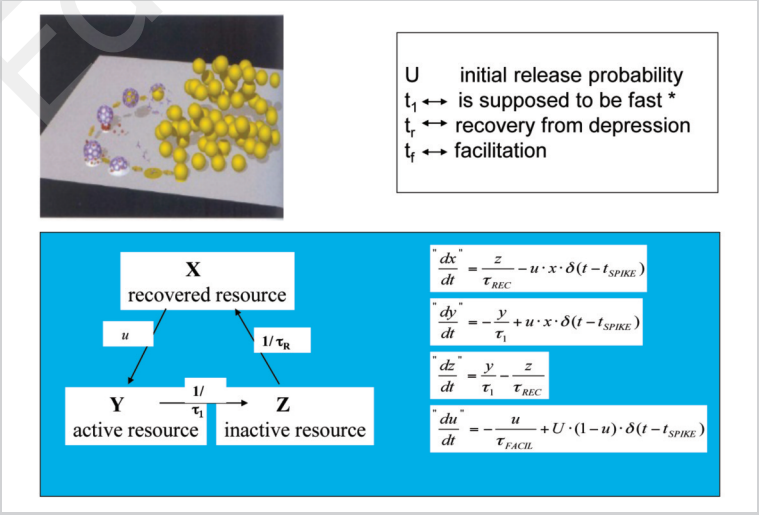
The interconversion between *y* and (*1-y*) occurs at a rate determined by the gating constants, α and β, following first order reaction kinetics and moving the reaction from the initial value y_0 to the final value y_∞.



The voltage dependence of the gating particles reflects the energetic properties of the underlying electrochemical conversions and can be approximated applying the Boltzmann and Arrhenius theories.
By considering each i^{th} gating particle for activation and inactivation, this entire description can be summarized in the following ordinary differential equation (ODE) system:

$$\begin{cases} \frac{dV}{dt} = \frac{1}{\tau_m}(V - \frac{\sum_i g_i(V - E_i)}{g_{tot}}) \quad ; \quad \tau_m = R_m / g_{tot} \\ \frac{dy_i}{dt} = \alpha_i - (\alpha_i + \beta_i) y_i \end{cases}$$

There can be as many as hundreds of gating particles describing the many ion channel types of a single neuron. This results in a very large ODE system, which is usually solved using numerical methods (Carnevale and Hines, 2009). Once implemented with all the different ion channels of a given cell, the solution of this ODE system gives the membrane potential time course reported, as an example, in figure 3 (D'Angelo et al., 2001; Solinas et al., 2010).
A variant of this approach can be applied to describe the synaptic vesicle cycle causing neurotransmitter release (Tsodyks and Markram, 1997).



Examples of how these theoretical aspects have been implemented are reported in several papers like those listed in table I.

species as are needed in order to match the experimental data (from a few to thousands). With these channels, neurons can generate the firing patterns observed in real cells, thereby providing a major validation criterion for the model itself. Models generated in this way collapse all neuronal properties and intracellular state memory and dynamics into a single equivalent electrical compartment. In several cases, the properties of a neuron cannot be explained by a single electrical compartment, and multiple compartments (representing soma, dendrites and axons) have to be included thus generating multicompartment models.

As well as membrane excitation mechanisms, synaptic transmission mechanisms can also be modeled. Differential equations are used to describe the vesicle cycle, neurotransmitter diffusion and receptor activation (Tsodyks and Markram, 1997). This last step consists of neurotransmitter binding to receptors, opening of connected ion channels or modulation of intracellular cascades and it is often accounted for by stochastic receptor models. The synapses can also be endowed with mechanisms generating various forms of short- and long-term plasticity (Migliore et al., 1995).

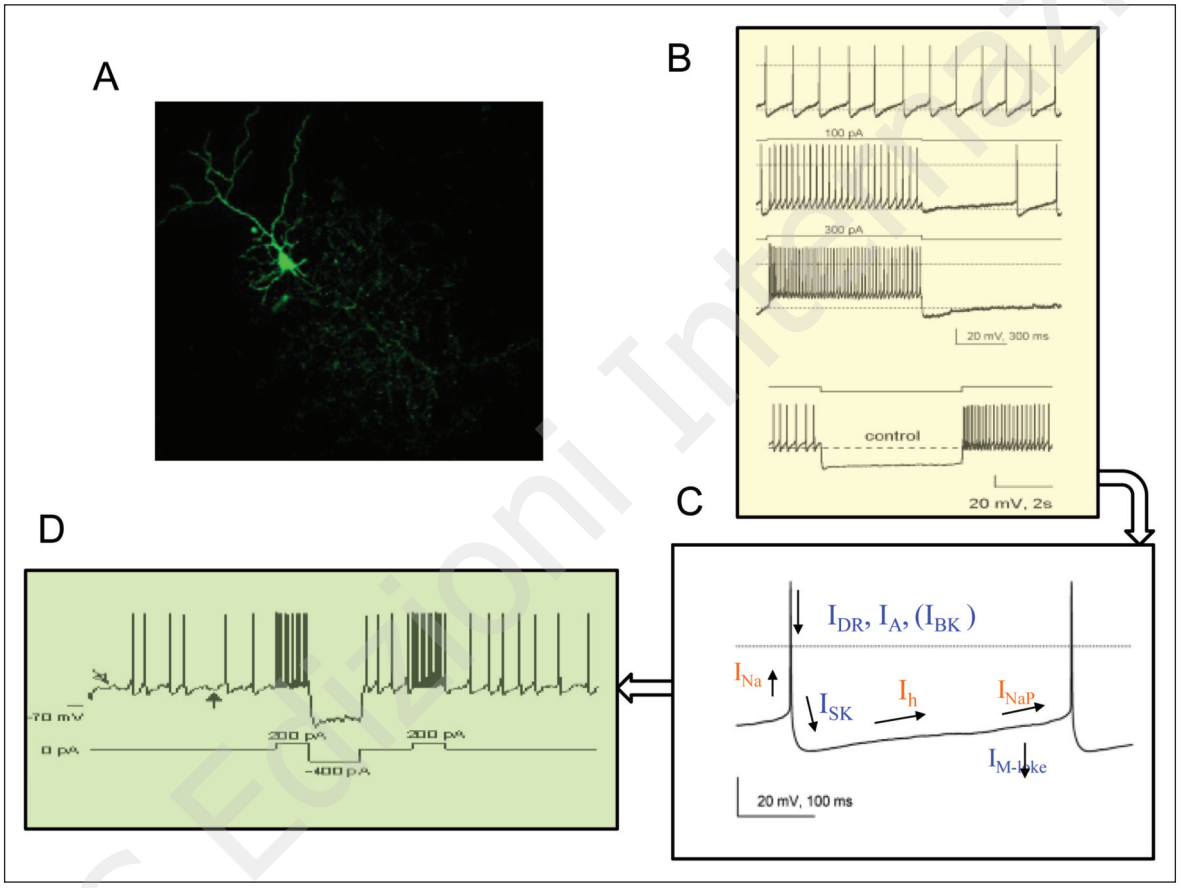


Figure 3 - Single cell modeling.
(A) Confocal image of a neuron loaded with neurobiotin (Golgi cell in a parasagittal brain slice; courtesy of B. Barbour). The dendritic arbor (upper left corner) starts from the soma and extends into the molecular layer. The axon originates from the soma opposite the dendrite and abundantly ramifies in the granular layer. (B) Whole-cell patch clamp recordings from a Golgi cell in current clamp mode (modified from Forti et al., 2006). Golgi cells show spontaneous auto-rhythmic firing in the absence of synaptic input (upper trace). When depolarized by step current injection, Golgi cells respond with sustained firing with slow adaptation, which is followed by a prolonged pause at the end of the current injection. In the lower trace, a negative current injection reveals the sagging profile caused by slow activation of the hyperpolarization-activated mixed cationic current (Ih). At the end of current injection, the rapid rise of membrane potential activates a low threshold Ca^{2+} current driving a rebound burst of spiking activity. (C) Golgi cell electrophysiological behavior was reconstructed in a conductance-based computational model (Lüthi and McCormick, 1998; Solinas et al., 2007a,b). In order to faithfully rebuild the richness of firing patterns the model was endowed with a total of 12 voltage-dependent and Ca^{2+}-concentration dependent ion channels. The panel shows the contribution of these ionic currents along the different phases of the action potential regenerative firing. IDr=non-inactivating delayed rectifier K^+ current; IA=A-type inactivating K^+ current; IBK=voltage-gated and Ca^{2+}-dependent K^+ current; ISK=Ca^{2+}-dependent K^+ current; Ih=hyperpolarization-activated mixed cation current; INaP=persistent Na^+ current; IM-like=slow non-inactivating M-like K^+ current. (D) The panel shows the response of the Golgi cell model inside the granular layer (modified from Solinas et al., 2010). In this configuration, the Golgi cell model was activated by mossy fibers (random activity at 3.9 Hz, Rancz et al., 2007) and inhibitory synapses from stellate cells (random activity at 10 Hz). During the simulation, the Golgi cell model was driven by current injections to enhance its firing rate (200 pA for 100 ms), to elicit sagging responses during hyperpolarization (-400 pA) and to elicit rebound. Ina=inactivating Na+ current

Circuit modeling

Once all neuronal and synaptic models are constructed and validated against a wide spectrum of experimental data, these same models can be used as building elements, which can be multiplied and connected to obtain functional microcircuits (Fig.s 2, 3) (Gerstner and Kistler, 2002). The connections can be reconstructed according to anatomical and physiological criteria. The construction and analysis of microcircuits is one of the most critical steps in the modeling process. Microcircuits can generate complex spatiotemporal dynamics making it possible to perform signal processing and recoding and to store information through long-term synaptic plasticity. As a result the microcircuits display a variety of emerging properties ranging from learning to pattern recognition, categorization and generalization, reflecting abstraction and the formation of the concept of objects. All these features have previously been reproduced using various ad hoc simplified neural networks, but none was able to perform all these tasks (Spitzer, 1998).[1] Clearly, validating these properties requires complex procedures and the parallel development of powerful experimental recoding techniques allowing local network investigation. Lastly, by passing from the single neuron to microcircuit level, the computational demand explodes and supercomputers are usually required.

The last step in the reconstruction of integrated brain subsystems is to connect microcircuits together in order to generate closed-loop models alimented by the senses and generating cognitive processing and movement (Fig.s 4-6). To do this, several different

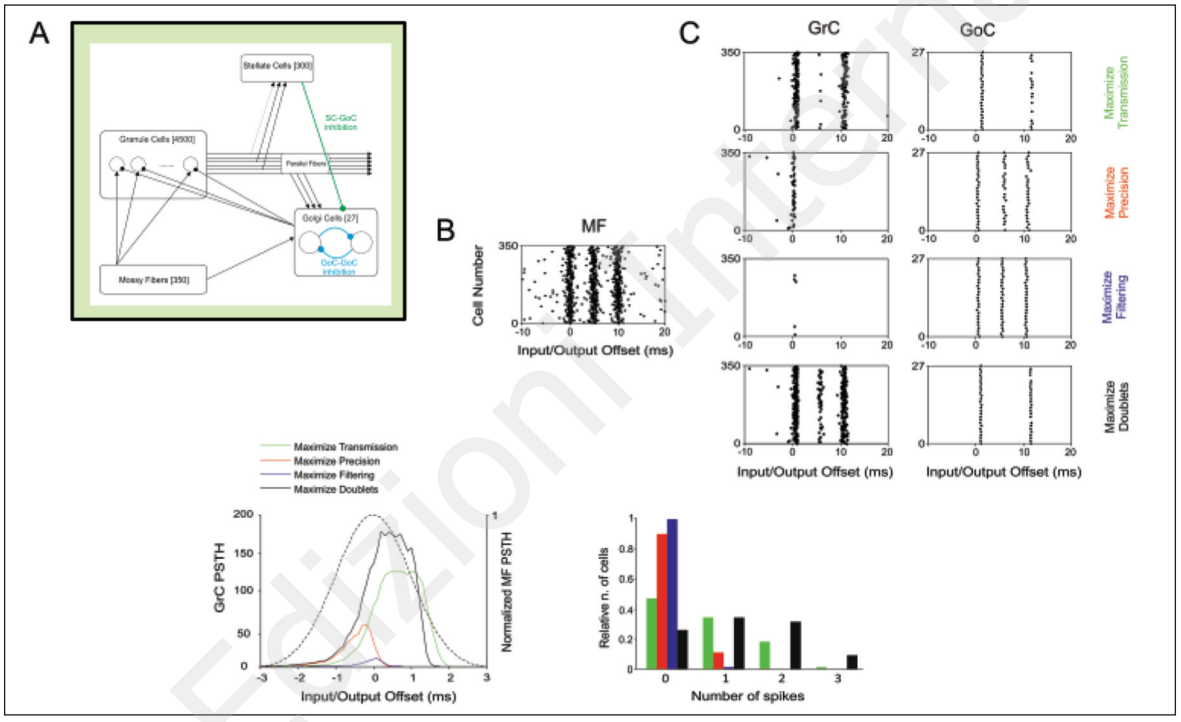


Figure 4 - Simplified real-time spiking model of the granular layer network.
(A) Schematic representation of the cerebellar granular layer model. The network includes 350 mossy fibers (MF), 4500 granule cells (GrC) and parallel fibers, 300 stellate cells, and 27 Golgi cells (GoCs). The basic network (black lines) includes the excitatory pathway (MF-GrC), feedforward inhibitory loop (MF-GoC-GrC) and the feedback inhibitory loop (GrC-GoC-GrC). Additional extended versions studied the influence of the GrC-SC-GoC-GrC loop (green line) and the GoC-GoC inhibitory connection (blue lines). (B) Effect of different weight configurations in the GrC response. In these simulations, synaptic weights were set according to four arbitrary configurations determining the following effects: increasing transmission (green), filtering (blue), maximization of time precision (red) and maximization of bursting (black). (top) Raster plots of the network responses to the same MF stimulation (left) with each weight configuration. Raster plots of activity recorded in the GrC (center) and GoC (right) populations with the hypothesized weight configurations (one per row), respectively. (bottom left) Peristimulus time histogram (PSTH) of the GrC response to the first spike in the burst. (bottom right) Relative number of GrCs generating 0, 1, 2, or 3 spikes in response to the stimulation burst. (Modified with permission from Garrido et al., 2013). (C) Probability of output burst responses composed of 1, 2, 3, 4 spikes in the different network weight configurations.

[1] In classical artificial networks, neurons are represented as mathematical functions (probabilistic functions generating an all-or-none output), synapses are simply "weights" (i.e. represent the strength of connections), and connectivity is stereotyped and usually far from real microcircuit structures. Artificial networks are based on layers connected according to various rules, forming simple perceptrons, recurrent networks (Hopfield), self-organizing networks (Kohonen), hidden-layer networks (Sejinowski) and context-layer networks (Elman). The artificial network can be described by a matrix product (actually the output matrix is the product of the input matrix by the weight matrix) and can usually be treated analytically. Clearly, these networks are non-spiking and do not contain any of the biological properties of neurons and synapses but rather implement abstract computational principles. These abstract networks have been useful for proving basic principles of circuit functioning (for references see Spitzer, 1998).

microcircuits need to be available and interconnected. The biological results used as targets for validation are the emerging behaviors and the functional imaging data obtained with MRI and other advanced imaging techniques.

The cerebellum as a prototype of realistic network simulation

Due to its stereotyped and regular structure, the limited number of neuronal types, and the extensive experimental investigations carried out on it at several levels, the cerebellum lends itself perfectly to implementation of the realistic modeling process. Recent years have seen the generation of highly precise biophysical models of neurons and synapses, followed by the connecting and testing of microcircuits. Most remarkably, these sub-networks have been precisely validated against experimental data and are now almost ready to be assembled into the first realistic whole-cerebellum model (Fig.s 2, 3). This approach, pioneered by two European projects led by the University of Pavia, namely REALNET (http://www.realnet-fp7.eu/) and CEREBNET (http://www.cerebnet.eu/), have provided a prototype for the multilevel modeling of the rat/mouse brain, which is now being applied on a larger and more integrated scale in the HBP ("brain simulation platform", http://www.humanbrainproject.eu/).

Table I lists the main neuronal models of the cerebellar network. These models present certain differences and raise specific scientific issues. The granule cell model is among the most characterized and best reconstructed models in the whole brain. A pivotal point was the discovery and description of all the critical ion channels and their characterization; this indeed led to a highly detailed model characterized by accurate description of the spike-generating mechanisms down to axonal transmission and dendritic integration (D'Angelo et al., 2001; Nieus et al., 2006; Diwakar et al., 2009). This model has allowed field potential reconstruction, explaining the granular layer function *in vivo* (Diwakar et al., 2011). Furthermore, it has allowed precise calculation of the information transferred through the synaptic relay and has been implemented with stochastic neurotransmission mechanisms (Arleo et al., 2010). Another of the best characterized neurons is the Golgi cell (Solinas et al., 2007a,b), which has subsequently been implemented with gap junctions to form an oscillating interneuron network. The Purkinje cell is outstanding for its complexity and it is one of the best characterized prototypes of multicompartment neurons in the brain (De Schutter and Bower, 1994a,b). These neurons have been embedded into the first realistic cerebellar network (Solinas et al., 2010) and integrated into high-performance computing schemes (Garrido et al., 2013).

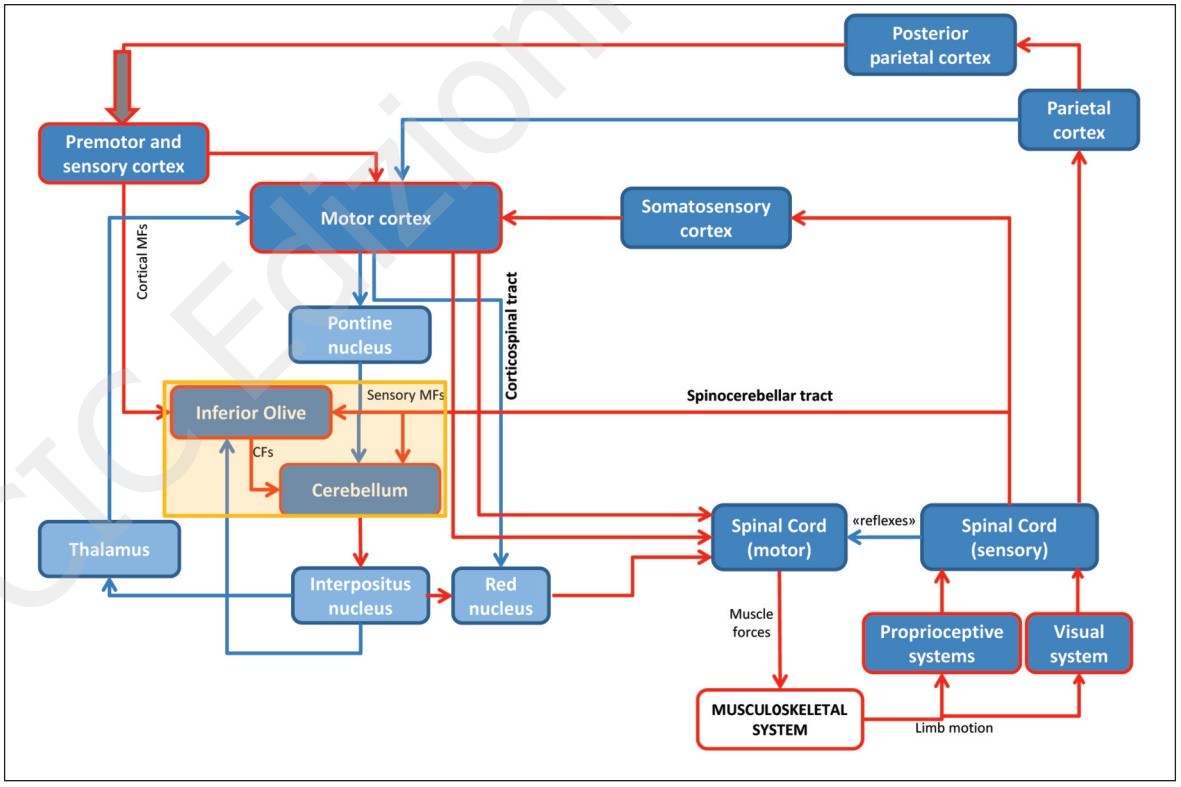


Figure 5 - Distributed neuromotor control system embedding the cerebellum model.
The scheme includes the main neural structures and functional interconnections taken into account for the brain-inspired controller. This scheme couples internal models and an adaptive cerebellar neural network, in order to obtain human-like behavior with learning skills in closed-loop sensorimotor tasks (modified from Casellato et al., 2012).

It is important to note that the cerebellum plays a key role in timing, learning and sensory prediction (Ivry and Baldo, 1992; Ivry et al., 2002; Ivry and Spencer, 2004) (see Box 2 for details). Simulating all these functions requires a closed-loop circuit integrating the motor cortex, several motor nuclei and motor structures. In order to proceed in this direction, simplified models have been generated and adapted from the realistic models (Fig. 4). These simplified models can be either analogical or spiking and can run in real time. They are suitable for integration into a robotic simulator or into a real robot (Fig.s 5, 6), and can

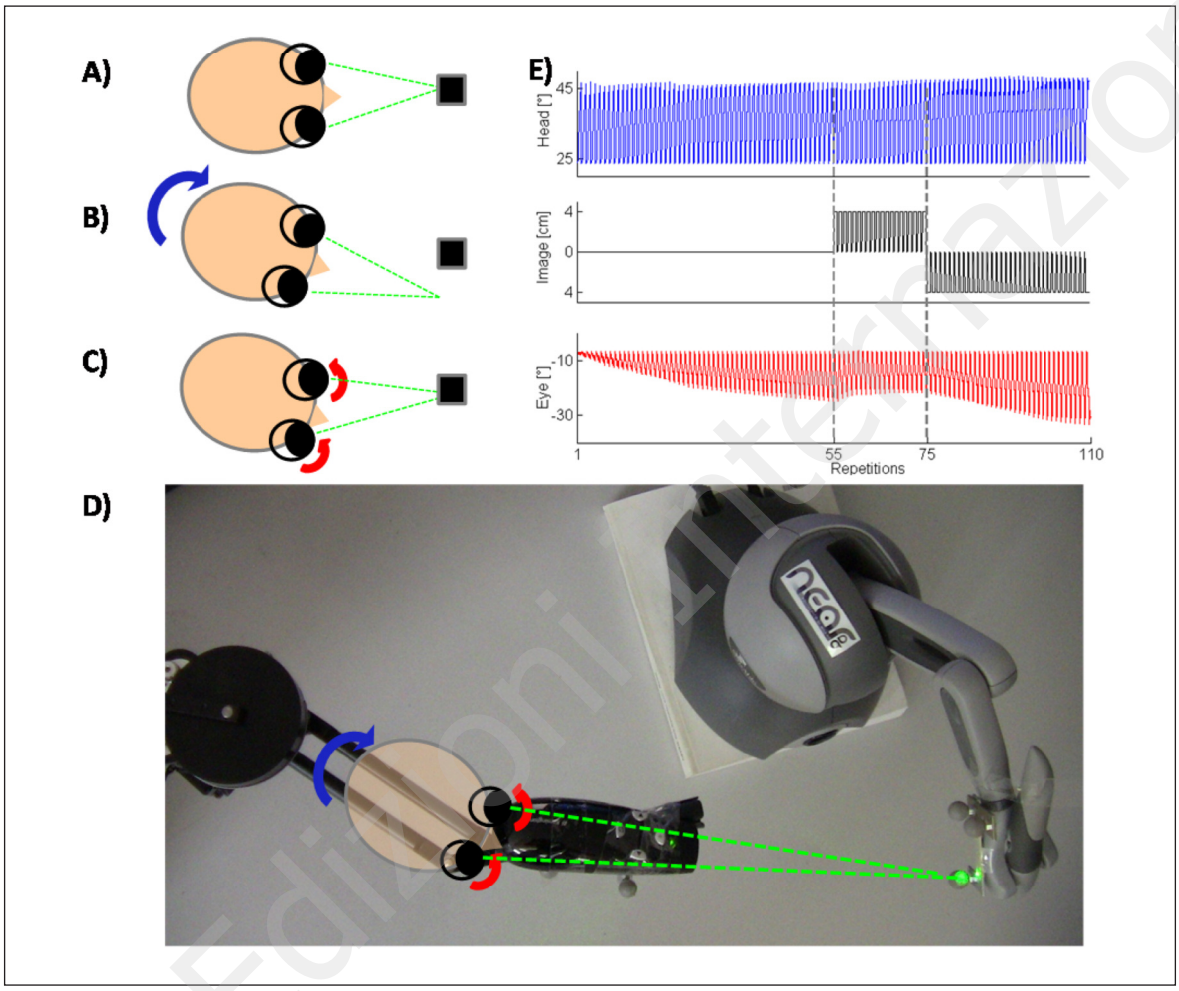
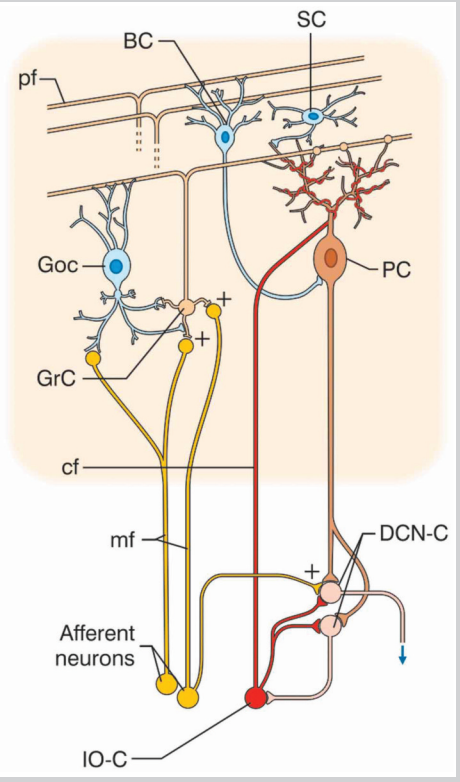


Figure 6 - Control system with the cerebellar model running on a real-time robotic platform.
Tests on a vestibular-ocular reflex (VOR) protocol. A head turn is imposed moving the robotic platform (joint 2). The eye movement (joint 3) is controlled through the cerebellar model output. (A) stable condition. (B) Head turn leading to an image slip. (C) Head turn and compensatory eye movement. (D) The set-up: Phantom Premium (SensaAble™)with the optical tool on the end-effector; Phantom Omni with the object-tool. The green laser is attached parallel to the second link, to highlight the gaze point on the environmental scene. (E) An example of the VOR protocol implementation, with 110 task repetitions. First, only the head turn is imposed. Then, in the other two conditions, object motion is added, for 20 repetitions in the same direction as the head turn, then, in the opposite direction to the head turn. The first row reports the head angle (from encoder of joint 2); the second row depicts the object motion, and the third row represents the eye compensatory motion (joint 3 angle). The cerebellar network provides eye-movement compensation (modified from Casellato et al., 2013).

Table I - The state of the art in cerebellar single cell models: publications dealing with cerebellum-related neuronal models

Neuron	References
Granule cell	D'Angelo et al., 2001; Roggeri et al., 2008; Diwakar et al., 2009; Dover et al., 2010
Golgi cell	Solinas et al., 2007a,b
Purkinje cell	De Schutter and Bower, 1994a,b; Miyasho et al., 2001
Deep cerebellar nucleus cell	Steuber et al., 2011
Inferior olive cell	Jacobson et al., 2008
Granular layer	Maex and De Schutter, 1998; Medina and Mauk, 2000; Solinas et al., 2010
Inferior olive	Jacobson et al., 2009

BOX 2
The cerebellum: circuit properties and system integration

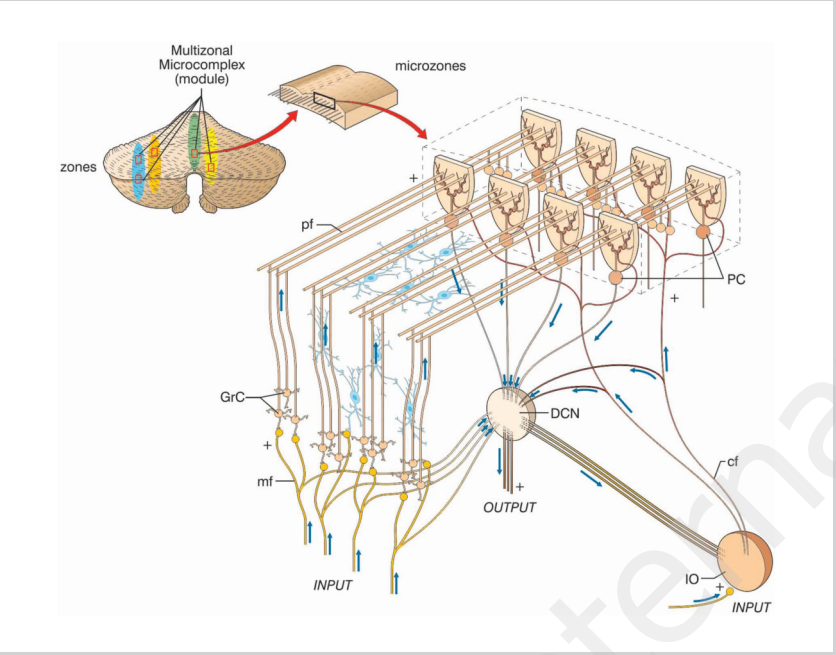


Schematic representation of the cerebellar circuit. The cerebellar circuit consists of cortical and subcortical sections. At subcortical level, the afferent fibers activate deep cerebellar nucleus cells (DCN-C) and inferior olive cells (IO-C). The deep cerebellar nucleus emits the output and at the same time inhibits the inferior olive. In the cerebellar cortex, there are different types of neurons including granule cells (GrC), Golgi cells (GoC), Purkinje cells (PC), stellate and basket cells (SC, BC), Lugaro cells, and unipolar brush cells (not shown). The two main inputs are represented by mossy fibers (mf) originating in various brain stem and spinal cord nuclei, and by climbing fibers (cf) originating from the inferior olive. Signals conveyed through the mf diverge to deep cerebellar nuclei and activate the granular layer (containing GrC and GoC). The ascending axon of the GrC bifurcates in the molecular layer (containing PC, SC, and BC) forming the parallel fibers (pf). The cerebellar cortical circuit is organized as a feedforward excitatory chain assisted by inhibitory loops: mf excite GrC, which activate all the other cortical elements. In the granular layer, inhibition is provided by GoC, in the molecular layer by SC and BC. Finally, PC inhibit deep cerebellar nuclei. The inferior olive, which is also activated by brain stem and spinal cord nuclei, controls PC activity though a single powerful synapse. Thus, the whole system can be seen as a complex mechanism controlling deep cerebellar nucleus output. (From D'Angelo and Casali, 2013).

The cerebellar circuit is organized into modules (zones), microzones and multizonal microcomplexes. A microzone is defined as a group of the order of 1000 PC all having the same somatotopic receptive field. These PC are arranged in a long, narrow strip, oriented perpendicular to the cortical folds and are crossed by pf. The branches of the cf (about 10) usually innervate PC belonging to the same microzone and the olivary neurons generating such cf tend to be coupled by gap junctions. All the PC belonging to a microzone send their axons to the same small cluster of output cells within the deep cerebellar nuclei. Finally, the axons of BC are much longer in the longitudinal direction than in the mediolateral direction. Thus, cellular interactions within a microzone are much stronger than those between different microzones (From D'Angelo and Casali, 2013).

The cerebellum is classically thought to control movement coordination (Flourens, 1824; Luciani, 1891) and motor learning (Marr, 1969; Albus, 1971) but recent experimental evidence suggests that it may also play a key role in cognition and emotion (Schmahmann, 2004; Schmahmann and Caplan, 2006; Ito, 2008). This clearly raises broader questions: how can the same circuit cope with so many different tasks? Is signal processing in the cerebellar circuits always based on the same computational scheme? Is it conceivable that what underlies the different roles of the cerebellum is the specific connectivity of cerebellar modules, rather than specific microcircuit properties? In order to address these questions, a "meta-levels hypothesis" operating over four levels was proposed: 1) cellular/molecular, 2) network, primitives of circuit processing, 3) high-level cognitive/emotional processing, and 4) mental processing (D'Angelo and Casali, 2013).

A key observation is that the cerebellum carries out basic computational functions, timing and learning, applicable in different cases. The cerebellum has been reported to assist brain operations by providing accurate timing of multiple series of signals coming from the cerebral cortex and the sensory systems [reviewed in (Bower, 1997, 2002; Jacobson et al., 2008, 2009; D'Angelo and De Zeeuw, 2009; D'Angelo et al., 2009; D'Angelo, 2010a,b; D'Angelo et al., 2011; De Zeeuw et al., 2011)]. This could underlie the implementation of processes like sensory prediction, novelty detection, error detection, time matching, and sequence ordering (Ivry and Baldo, 1992; Ivry et al., 2002; Ghajar and Ivry, 2009). This multidimensional computation would allow the same circuit to contribute to functions as diverse as voluntary movement (a cognitive process, after all) and thought, provided that appropriate connections with different cortical and subcortical centers were established and that communication between these centers occurred over the appropriate frequency bands and using compatible codes (Ito, 1993, 2008; D'Angelo, 2011). Therefore, the cerebellum may operate as a general coprocessor, whose effect depends on the centers to which different modules are connected, affecting cognitive functions as well as sensorimotor processing.



In system theory terms, the cerebellum is thought to lie at the core of the *forward controller operation* set up by cerebello-cerebrocortical loops. It is well documented that motor planning means predicting the sensory consequences of a motor act: a motor plan is coded in terms of an anticipated sensory state (Blakemore et al., 1998). This is akin to the general hypothesis of the "prediction imperative" that needs to be satisfied in order to allow brain processing (Llinás and Roy, 2009). Prediction processes are normally performed by "forward controllers," which use internal memory to represent the system state (Diedrichsen et al., 2010; Shadmehr and Mussa-Ivaldi, 2012). On the basis of studies of the vestibulo-ocular reflex, eye-blink conditioning, and saccadic eye movements, and the fundamental theoretical concepts of motor learning (Marr, 1969), the cerebellum has been suggested to provide forward models of the motor system. These forward models can predict the posture or motion of body parts following a motor command and, by a further transformation, predict the sensory consequences of actions (Miall and Reckess, 2002). More precisely, a copy of motor commands generated by the motor cortex (efference copy) is sent to the cerebellum, which uses its internal forward model to predict their sensory consequences (corollary discharge). The sensory predictions are then compared to actual sensory feedback (Wolpert et al., 1998): in the presence of errors (or novelty, i.e., deviations from prediction), the cerebellum emits corrective signals. A fully characterized example of generation of predictions by cerebellar circuits is provided by electro-perception in weakly electric fishes, in which a cerebellar-like structure compares the expected electric field generated by the fish with the actual electric field sensed by the electroreceptors, thus gaining information on the structure of the environment through the changes that this latter has caused in the field itself (Bell et al., 2008).

In the presence of persistent deviations from prediction the cerebellum learns to modify the forward model itself. Learning appears to occur through two distinct processes, one faster and more labile, involving the cerebellar forward controller, the other, which may at least partly reside outside the cerebellum, slower and consolidated (Shadmehr and Mussa-Ivaldi, 2012). In fact, the cerebellar cortex is thought to process the faster component of memory, while the deep cerebellar nuclei may elaborate its slower component (Medina and Mauk, 2000). Given the anatomical connections of the cerebellum with associative areas and the similarity of motor planning and cognitive processing, it seems logical to generalize the forward controller role of the cerebellum to cognition. Indeed, Ito (2008) hypothesized that the cerebellum could operate as a generalized forward controller regulating cognition as well as sensorimotor control.

There are thus four open questions about cerebellar functioning, and it is here that computational modeling could come into its own:

1) How does the cerebellar network process incoming signals?
2) How does the cerebellum perform the forward controller operation?
3) How does the cerebellum contribute to sensory prediction and timing?
4) How might the cerebellum contribute to different aspects of motion and cognition?

Clearly, a realistic cerebellar network model embedded into an appropriate system control loop, and eventually into a simulated brain, could help to answer these questions.

therefore allow the cerebellar network to be studied in closed-loop conditions. In this manner, the impact of the salient network parameters (including ion channels, synaptic receptors, network connections, neuronal types and plasticity rules) on network computations and behavior can be tested.

Concluding remarks

Realistic modeling is a new methodology for investigating brain functions. Being based on biology, realistic models:
- are not constrained into a rigid scheme but can be updated as new biological information becomes available;
- can embed multilevel information ranging from molecular properties to system organization;
- can be expanded, in ever greater detail, toward specific properties, considered relevant for function;
- do not reflect a predetermined design but rather account for the many evolutionary stratifications, progressions and regressions that have caused a specific brain to reach its present state;
- can be adapted to generate brains of different species and different ontogenetic stages;
- can be modified in order to mimic pathological states;
- provide the substrate for a new wave of theoretical analysis, in which not only neuronal outputs but also a wealth of low-level functional parameters are accessible.

Clearly, one drawback is that realistic models do not provide an immediate intuition or any synthetic description of brain functioning, which were the objectives (probably impossible) of classical efforts to understand the brain. In addition, possible weaknesses could derive from missing mechanisms, lack of appropriate connectivity rules, or inaccurate representations of neuronal and synaptic processes. Therefore, realistic modeling requires step-by-step validation through experimental assessment.

Beyond what a single laboratory can provide, brain-scale realistic models require a huge interactive effort and computational infrastructures like those provided by worldwide enterprises such as the HBP. Just as single molecule or single neuron modeling requires specialized techniques and laboratories, network connectivity at different levels requires the development of precise and detailed structural and functional maps through highly specialized techniques (a field called "connectomics"; Silvestri et al., 2013). In turn, the multiscale nature of realistic modeling provides a powerful new tool for investigating brain diseases through the so-called hyper-models of pathogenetic mechanisms, reflecting the fact that multifactorial diseases with distributed lesions like Alzheimer's disease or multiple sclerosis reflect the recursive and interactive nature of brain functioning (Redolfi et al., 2013). Thus, realistic modeling, avoiding the temptation to simplify nature, tackles complexity and allows us to consider the multiparametric distributed nature of brain diseases. Finally, realistic modeling has profound implications for the robotic sectors, as it allows the brain's computational mechanism to be not only simulated through software, but also emulated in new electronic devices (a field called "neuromorphic computing"; Calimera et al., 2013).

In the case of the cerebellum, the process of signal coding and learning is particularly relevant and could be investigated at the mechanistic level. Moreover, motor dysfunctions (ataxia) and procedural learning deficits could be investigated by generating specific alterations in the molecular and cellular mechanisms of the cerebellar network model. Likewise, pathologies involving the cerebellum could be simulated in order to understand how different processes of dysfunction and compensation take place. These include various ischemic and neoplastic conditions, multiple sclerosis, paraneoplastic cerebellar degeneration, alcoholism, and pathologies like autism and dyslexia, to mention just a few (D'Angelo and Casali, 2013). A wealth of applications in terms of pathophysiology, diagnosis and therapy of brain diseases can be envisaged, ranging from simulations of the impact of molecular/cellular damage on network functioning to the identification of new therapeutic tools. Finally, realistic models could be developed in 3D and used to interpret the hemodynamic signals of functional MRI or to simulate the effect of the transcranial magnetic stimulation pulse on the underlying circuits. On the robotic side, embedding a realistic cerebellum model into a sensorimotor control system could make it possible not only to investigate neuronal functioning in closed-loop conditions, but also to extend the adaptive and flexible control capabilities of robots and potentially to link their activity to cognitive functions.

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