Acta Biomed 2007; 78; Suppl 1: 67-83

Lecture

Computation and brain processes, with special reference to neuroendocrine systems

Roberto Toni[1, 4, 5, 6], Giulia Spaletta[2], Claudia Della Casa[1], Simone Ravera[1], Giorgio Sandri[3]

Departments of [1]Human Anatomy, [2]Mathematics, [3]Philosophy, Universities of [1]Parma and [2, 3]Bologna, [4]Academy of Sciences, Bologna, [5]Scientific Foundation and Clinic "G. B. Morgagni", Catania, Italy, [6]Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Tufts University School of Medicine, New England Medical Center, Boston, MA, USA

Abstract. The development of neural networks and brain automata has made neuroscientists aware that the performance limits of these brain-like devices lies, at least in part, in their computational power. The computational basis of a standard cybernetic design, in fact, refers to that of a discrete and finite state machine or Turing Machine (TM). In contrast, it has been suggested that a number of human cerebral activites, from feedback controls up to mental processes, rely on a mixing of both finitary, digital-like and infinitary, continuous-like procedures. Therefore, the central nervous system (CNS) of man would exploit a form of computation going beyond that of a TM. This "non conventional" computation has been called *hybrid computation*. Some basic structures for hybrid brain computation are believed to be the *brain computational maps*, in which both Turing-like (digital) computation and continuous (analog) forms of calculus might occur. The cerebral cortex and brain stem appears primary candidate for this processing. However, also neuroendocrine structures like the hypothalamus are believed to exhibit hybrid computional processes, and might give rise to computational maps. Current theories on neural activity, including *wiring and volume transmission*, *neuronal group selection* and *dynamic evolving models* of brain automata, bring fuel to the existence of natural hybrid computation, stressing a cooperation between discrete and continuous forms of communication in the CNS. In addition, the recent advent of *neuromorphic chips*, like those to restore activity in damaged retina and visual cortex, suggests that assumption of a *discrete-continuum* polarity in designing biocompatible neural circuitries is crucial for their ensuing performance. In these bionic structures, in fact, a correspondence exists between the original anatomical architecture and synthetic wiring of the chip, resulting in a correspondence between natural and cybernetic neural activity. Thus, chip "form" provides a *continuum* essential to chip "function". We conclude that it is reasonable to predict the existence of hybrid computational processes in the course of many human, brain integrating activities, urging development of cybernetic approaches based on this modelling for adequate reproduction of a variety of cerebral performances. (www.actabiomedica.it)

Key words: Neural network, brain automata, neural transmission, computational map, feedback, hypothalamus, neuroendocrine system

> *The mind and brain are inseparable. The brain is a complex organ of great computational capability […]. Looked at from this perspective mind is a set of operations carried out by the brain.*
> Eric R. Kandel
> In Search of Memory: the Emergence of a New Science of Mind, 2006

Introduction

In the first half of the XXth century a major problem concerning the notion of computation was to provide a general characterization of two elusive mathematical concepts, *computability* itself and *recursiveness*. The majority of investigators believed that this target could be reached by finding a general answer to the question "*what is a computable function?*". Differently, Alan Turing, a major scholar in the field of mechanical computation, suggested that the real question at issue was: "What are the *possible processes* which can be carried out in computing a number?" (1). Turing started with considering the actions of an abstract human being, called *computor*, making a calculation. Taking into account the limitations of this hypothetical mental and sensory apparatus, he set conditions or restrictions on the actions of the computor, *discreteness*, *locality* and *finiteness*. Specifically, he envisaged that the process of computation had to proceed in discrete steps *(discreteness)*, where at each step the action occured in a well defined physical space *(locality)*, and took the *computor* from a 'state of mind' to the next one, among a finite number of states *(finiteness)*.

On the basis of this conception, he was able to introduce a view of computation as a *process that can be broken down into the repetition or iteration of simple operations, following a set of rules, called program.* In particular, these operations comprise reading or writing a *symbol* (belonging to a finite set or alphabet), moving one cell (i.e. the position occupied by the symbol) to the left or to the right along a tape, eventually stopping the procedure on a specified cell. In this manner, at each step (i.e. at each movement of the symbol on the tape) the action is local and determined by a finite set of instructions (2). This ideal computing structure is called *finite automaton* that, when provided with a tape of infinite lenght, is known as a *Turing Machine* (TM), the "ancestor" of our modern computer (2).

By his logical construction Turing was then able to show that *the computor*'s *behavior* was thourougly simulated by a TM. In this way he "proved" a general theorem, known as the Turing Theorem (1):

> Any function which is effectively (mechanically) calculable by an abstract human being following a routine is computable by a Turing Machine.

First in the history of science, Turing had provided an abstract and general characterization of the notion of *computation* (as an effective procedure consisting in the repetition of simple operations, following a predetermined group of rules) that does not depend on the language used, i.e. is independent from conventional symbols or logical relations between these symbols, and purely operational (3). There have not been ways, at least up to now, to reduce such a notion to a simpler one. This major result was recognized already in 1946 by the great logician and mathematician Kurt Goedel (4).

Turing machines and neural networks

Structure of the Turing machine

Each TM computes the function for which it is programmed, through the set of rules that determine its behaviour. The TM accepts as *input* a string of symbols and performs a set of acts, according to the program, that end eventually (with the machine halting) on a string of symbols, constituting the *output*. The string-input is the *argument*, the string-output is the *value*, of the function being computed. The TM is thus *an input-output system* governed by a *black box*, corresponding to its program (Figure 1). Since TM inputs and outputs consist of digits (taken from a given, finite alphabet of symbols), the character of Turing computation is defined as *digital*. In addition, since "following a rule", as that set by the TM program, is an activity performed by a machine, *effective compu-*

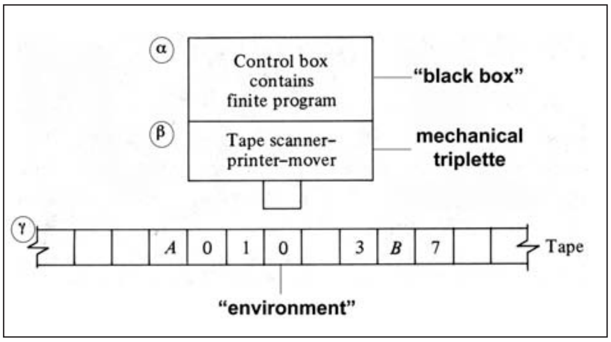

Figure 1. Simplified scheme of a Turing Machine. The machine consists of : α) a box containing a set of rules, i.e. the program; β) a device for scanning, printing and moving along a tape, one square at a time; and, γ) a tape of potentially infinite lenght, divided in squares or cells, where symbols (i.e. either single numbers or letters) can be written and/or read by the device, moving to the left or right and eventually stopping on a specified cell (from reference 2, partly modified)

tation can be characterized as a mechanical, digital input-output system. Finally, there is a general procedure, known as "goedelisation" (after Goedel's work) (2), that permits to associate a unique number to any formula, thus allowing for association of a unique number to each of the rules that control the machine, leading to a *code*. Based on the digital and mechanical character of computation and the possibility of creating codes (i.e goedelisation) for the TM activity, Turing described a further generalization of its computing system, known as the *Universal Turing Machine* (UTM) (5).

An UTM can: 1) employ as input the code of any specific TM; 2) use any input that the TM can take; 3) return the output the TM would compute (given that input). In other words, *the UTM performs any calculation that can be performed by using finite means and following a specific routine*. Therefore, the UTM is a digital input-output system that computes the set of *all computable functions*: since a function is Turing computable if and only if it is recursive (see chapter on Turing-Church Thesis for a definition of recursiveness), the UTM becomes a formal explication not only of "computability" but also of *general recursiveness* (5). Finally, as a stored-program machine, i.e. a machine having its program kept into a reservoir, called "memory", the UTM anticipated the structure of the EDVAC (Electronic Discrete Variable Automatic Computer), conceived in 1945 by one of the fathers of modern cybernetics, John von Neumann (6).

Early concepts on neural networks

In their 1943 seminal paper WS. McCulloch and WH Pitts (7), a neuroscientist and a logician, asserted that the control mechanism of the UTM could be simulated by a finite assembly of idealized neurons, related to each other by connections (synapses) incorporating delays. The fundamental hypothesis of the model was that all the relevant functioning of the Vertebrate *central nervous system* (CNS) was mediated by the passage of electrical impulses among neurons. In the model, a *module* (i.e a formal neuron) was an element with **n** inputs and **1** output, that fired impulses according to rules (Figure 2). A *modular net* was a collection of modules. The overall simplified structure was aimed at providing a *model of the brain,* and a functional correspondence (homomorphism) between the structure of the brain and the model was strictly assumed.

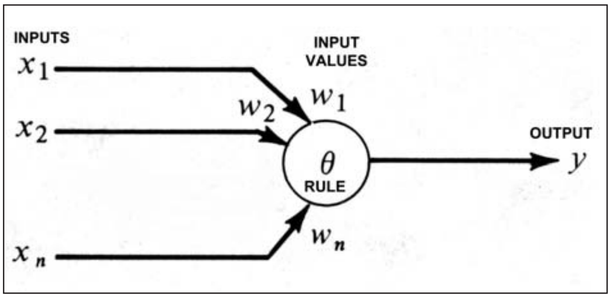

Figure 2. Schematic model of a threshold logic unit, after the piooneering work of WS. McCulloch and WH Pitts on neural networks, in the first half of the XXth century (7). The formal neuron or module (circle) is an element receiving inputs ($x_1 \ldots x_n$), each having a certain value or weight ($w_1 \ldots w_n$) and firing a single impulse or output (y) according to certain rules, like the threshold θ. (from reference 2, partly modified)

From a cybernetic viewpoint, every modular net can be considered as a finite automaton; conversely, the input-output behaviour of a finite automaton can be carried out by a suitably constructed modular net. *A finite automaton, therefore, is an input-output digital system that satisfies the discreteness, locality and finiteness restrictions required for a TM and also by its more general or universal version, a UTM*. In addition, since a TM is a finite automaton augmented with an infinite tape, the following statement can be proved (2):

> for any *finite automaton* **A** there is a *neural net* **N** such that, if in state S, input I of **A** yields output O of **A**, then in state S', input I' of **N** yields output O' of **N**.

As a consequence, it is possible to regard the correspondence between TMs and Neural Nets as a characterization of the concept of "effective" or "mechanical" applied to cerebral processes. Therefore, Turing's analysis of effective computation can be used to develop a concept of "mechanical brain activities", that sets theoretical standards for mechanistic theories of cerebral activities. However, it cannot be turned into a thesis about the mechanical character of brain activities in general. Any mechanical procedure, in fact, must satisfy specific restrictions (discreteness, locality and finiteness), that do not belong to the structure of what we call "high brain activities" in living beings. Indeed, Turing never aimed to show that high brain activities cannot go beyond mechanical procedures. He, instead, succeeded in proving that those brain activities that follow mechanical procedures must satisfy the restrictions mentioned above, whoever is the agent, human or mechanical.

Turing-Church Thesis

A generalization of the Turing Theorem has become a prevailing paradigm in theoretical computer science. It is known as the Turing-Church Thesis (2) and concerns the notion of an effective or mechanical method in logic and mathematics:

Any computable function is Turing computable

Although various equivalent formulations of the Turing-Church Thesis have been proposed, for our purposes a restricted formulation is acceptable (8):

Any effectively (mechanically) computable function is Turing computable

To better understand what a "computable function" is, recall the notion of c*omputable numbers*, i.e. numbers whose decimal representations can be generated by a TM. They include all numbers that would naturally be regarded as computable by a human being (most irrational numbers are not computable), as they can be yielded by a finite, terminating algorithm. Computable functions make our intuitive notion of algorithm more precise, as (Turing) computable functions are exactly those whose values can be obtained in a finite time, using a mechanical calculation device, following an effective procedure (i.e. an unambiguous prescription of rules).

Computable numbers can equivalently be defined using recursive functions, which take a positive integer as argument, return a positive integer and are built upon primitive operations as arguments, namely the primitive recursive functions. These form a building block (defined using rules of self-reference and composition) and can be yielded by machines that always halt, i.e. less powerful than TMs. In contrast, recursive functions require a UTM. As the set of recursive functions was shown to be equivalent to the set of Turing computable functions, the thesis by Turing and Church essentially says that *real-world computing models are equivalent to that of Turing and that a procedure is effective if it is executable by a TM* (2)

Kurt Goedel and mental processes

The Turing-Church Thesis does not rule out the possibility of forms of computation which are beyond the mechanical ones (3, 9). In contrast, in a famous critical note Goedel (4) remarked that a "philosophical error" was present in Turing's work. He asserted that Turing had provided an argument aimed at showing that procedures implied by high brain activities (i.e "mental" activities) could not go beyond mechanical procedures. Godel thought that this argument was inconclusive and stated: *"Turing disregards completely the fact that mind, in its use, is not static, but constantly developing"* (4).

In our opinion, the remark of "inconclusiveness" was philologically wrong. Turing, in fact, never forwarded any thesis concerning the general nature of high brain activities. He, instead, stated the conditions that any mechanical characterization of high brain activities had to satisfy, without taking a stand against the existence of non-mechanical mental procedures. Nevertheless, Goedel raised a major point: in our understanding of abstract terms, as we use them, more and more abstract terms enter the sphere of our understanding. Although at each stage the number of the abstract terms may be finite (and also the number of distinguishable states of mind), in the course of assuming them (i.e. in the application of the procedure), the tendency might be that of convergence towards infinity. More precisely Godel said: '*something like this seems to happen in the process of forming stronger and stronger axioms of infinity in set theory*' (4). In summary, Goedel introduced the idea that there are forms of mental processes that are not mechanical and, therefore, going beyond those of a TM, cannot be performed by a finite automaton.

Non mechanical and analog processes

In a 1939 paper (10) Turing himself put forth the idea of computational procedures going beyond the mechanical ones. He envisaged a computing system composed of two subsystems: one, named **T** (i.e. a sort of TM), was a discrete finite state machine behaving like a finite automaton. The other, called Oracle (**O**), was a non specified entity, able to solve in full generality problems of membership in a set of natural numbers. The reason why Turing envisaged this "mixed" type of computing system relates to the performance limitations intrinsic to any discrete and finite state machine, known as the unsatisfyability of the *halting problem for a finite automaton* or *Entscheidungsproblem* (2). Simply, there is no way for a finite automaton to decide whether, for any given input information, it will yield a specific output, on the basis of its mechanical procedures or algorithms, i.e. using a classic Turing computation. In other words, **T** is not able to decide, in a finite number of steps, whether a natural number **n** belongs or not to a specified set **K**, i.e. *to compute the characteristic function of the set*. In contrast, **O** is both able to compute the characteristic function of a non recursive set and to perform in its 'black box' (its logical core) calculations that go beyond the computational power of a TM. Therefore, although **O** works in an unspecified form, the **T-O** system conceives two different types of computation, a canonical and mechanical one and another one, non mechanical, called *analogical* (11).

The **T-O** system (or machine) has, thus, features of both mechanical and non mechanical computation. **T** is expected to use, in its own discrete and finite computing activity, the digital output of **O**: as a consequence, *input and output of the T-O system are discrete.* On the other hand, **O** carries out peculiar forms of calculus, the *analog* processess: as a consequence, communication and elaboration of information throughout **O** cannot correspond to that of a discrete state machine (11). Analog processes, in fact, employ physical entities, called *continuos variables*, whose values can be put in correspondence with *an interval of real numbers*. In contrast, mechanical processes use *discrete variable*, whose values are taken within mutually disjoint intervals that may be put in correspondence with the natural numbers. A way for practically isolating a mechanical but non recursive (i.e. non Turing computable) process, like that expected to occur in a **T-O** system, would be to assume a *continuous nature* for symbols (representing the variables) and for their elementary transformations. In this way, analog processes would become those that dynamically use symbolic information, interleaving at least one process in which continuous variables occur between two discrete processes (11).

Hybrid systems and feedback routines

The cooperation of a digital, discrete subsystem (as **T**) with an analog, continous subsystem (as **O**) yields a particular computing system, called *hybrid system* (11). Aspects of hybrid system may be already found in the classical work of J. von Neumann (6). von Neumann, in fact, describes the TM as a finite automaton, constituted by a hardware structure made by the triplet "scanner-printer-mover" and provided with a possibly infinite tape, the machine environment. The abstract, input-output system of strings is digital and discrete and is seen as *information*. This information moves back and forth along a tape, that is a *continuum*. As von Neumann underlined, the most relevant operative character of a TM lies in the description of *how it is taken to change state.* The change, in fact, is produced by interaction with the *external world* that, in the case of a TM, consists of a long tape. Therefore, this behavior recals that of an hybrid system, where *discrete* series of stimuli (inputs) and response (outputs) rise from and retun to a *source of continuum* (the "infinite" tape or environment).

On a similar line of thinking is also the work by Rosenblueth, Wiener, and Bigelow (12), describing various kinds of *goal-oriented* systems, whose most remarkable feature is what they called *negative feedback.* Negative feedback systems are those in which the input is altered by the output, in the direction necessary to reduce the discrepancy between the situation so far achieved and the goal situation. Similar to von Neumann's representation of the TM, Rosenblueth and his co-authors described the relation of a *source* of signals (either a mechanical or organic system) with a *target* (an "environment", to use von Neuwmann's terminology), external or internal to the source itself. In such a relation, the signal from the target (or target output) was used *to decrease* the input from the source that, otherwise, would have bypassed the expected target output. Even in the case of complex, teleologically goal-oriented performances, like the *extrapolative or predictive* behaviours of predators, they suggested that negative feedback would operate, by allowing for comparison between an actual performance (e.g. the position in space of a cat running towards a rat) with some tested performance (i.e. the continual correction of this position through a negative feedback routine, based on the position progressively aquired during running).

From a modelling point of view, thus, negative feedback signals include: a) an input of quantity **K**, released by a *source* to a *circuitry S*, defined as the *black box* of the system, that links the source to a *target*. In particular, **K** is supposed to set the measure of the output desired from the target; b) the target, that in turn *continually* sends back to the circuitry *S* an output of quantity **K'**, whose value is close to that of **K**. Thus, **K'** is *continually* **fed back** to *S*. Since *S* contains an *error detector*, it calculates the *error signal* **E = K - K'**. Therefore, it is **E** that controls the behavior (i.e. the performance) of the entire system, and so determines its output. As a consequence, the ideal condition of activity of the system occurs when E tends to zero, i.e. when K and K' are equal (13) (Figure 3A).

The computational capacity of S might be based on continuous rather than discrete variables. S, in fact, is an input-output system in which information concerning the difference between the goal and the actual output is *continually* fed back into the input. Since continuous variables are those employed in analogous computation (see Analog Computation), it seems possible to envisage *S as an hybrid system*, consisting of a *discrete computation* (like a TM) that processes information computed by a subsystem of *analog computation*. *In other words, systems with negative feedback are*

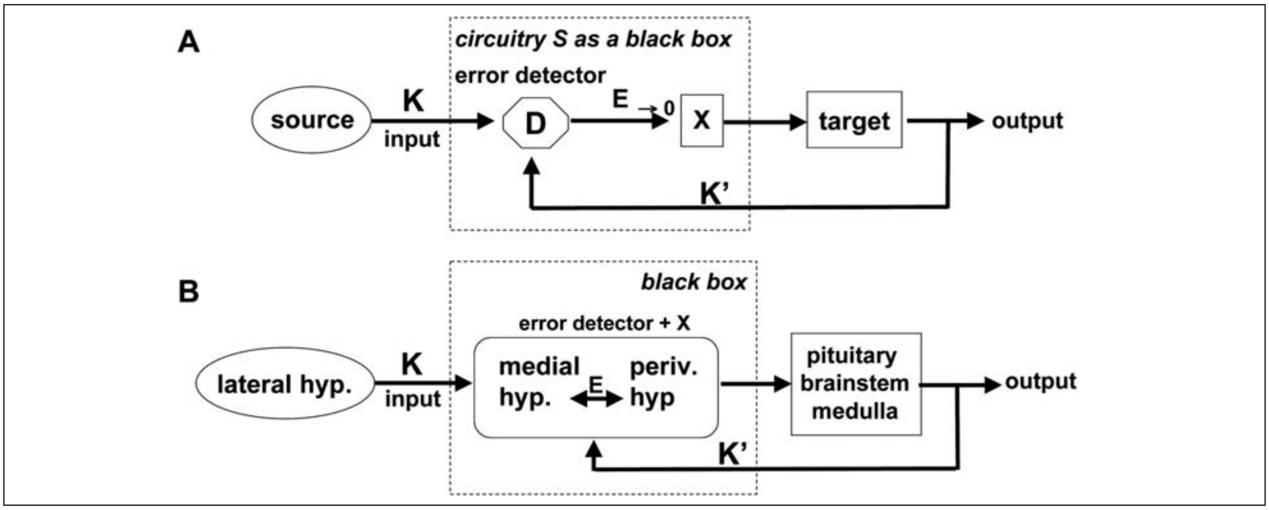

Figure 3. (A) Schematic representation of a negative feedback system, after the pioneering studies of N. Wiener on cybernetic mechanisms, in the first half of the XXth century (13). A source feeds into the circuitry S (large dotted rectangle) an input K, supposed to correspond to the output relased by the target. However, the actual target output is fed back into the circuitry S as a quantity K', that is recorded by an error detector D (octagon). D calculates a difference, called the error signal or E, between the original source input K and the resulting target output K'. In the best performance possible of S (whose unknown organization, called "black box", includes the structure X) E would go towards value 0, i.e. input and output signals would be identical. (B) Schematic representation of a possible negative feedback routine acting in the Mammalian hypothalamus. The lateral hypothalamic zone sends an input K to the medial and periventricular hypothalamic zones, expected to be proportional to the outputs released by their neural targets, i.e the pituitary gland, brainstem and medulla. However, the real target outputs are fed back into both medial and periventricular hypothalamic zones, that represent the natural "black box" and act as a complex of error detector + unknown modulating structure X. The resulting error signal E triggers an emerging information, directed onto the targets (pituitary, brainstem and medulla), that is the real determinant for their response. hyp = hypothalamus, periv = periventricular. (from ref. 14, with permission, partly modified)

likely to be hybrid systems, where the feedback routine might be interpreted as a routine that processes continuous variables (14).

Natural and bionic hybrid systems

Neural feedback systems

Premonitory to the current view on hybrid computational systems, more than 40 years ago the British anatomist and physiologist, John Young, in his seminal work on Octopus behavior, suggested that the basic scheme for the CNS of both invertebrates and vertebrates had necessarily to be a mixed digital and analogic, computing device (15). Indeed, the Vertebrates CNS contains a number of anatomical structures functioning as feedback systems, not only negative but also positive, thus possibily exploiting an hybrid computational power. The hypothalamus represents an example of natural feedback structure, with continuous (neural and humoral) signals feeding back to a black box, responding with either decremental (if negative feedback) or incremental (if positive feedback), discrete (neural) output (Figure 3B). Recently, then, a proposal has been raised by K. Fuxe and LF. Agnati that, besides discrete packages of signals released during conventional, synaptic transmission (called wiring transmission) an additional form of non synaptic transmission exists, based on a graded and constant flow of signals, electrotonic and autocrine/paracrine-like, called volume transmission (16, 17). We have, therefore, suggested that in the human hypothalamus wiring transmission might imply discrete/digital computational procedures, whereas volume transmission might be associated to a continuous/analog computational process (18), rendering it a center naturally exploiting an hybrid computational capacity

Brain computational maps

Beyond feedback systems, it has been suggested that a definition of computation occuring in the brain of higher mammals and man might be that of "transformation in the representation of an information" (19). Part of communication signals in the CNS travel as predetermined, genetic stimuli (20, 21). Nevertheless, during development and in adult life the bulk of incoming "information" is never equivalent to "instruction". The CNS, in fact, *continually* analyzes complex events in a *continually changing* environment, where emerging stimuli are deprived of any preset "label" or category (20, 22). This approach overrules the idea of a brain computing only as a "programmable" structure, that is believed a weaknesses of the Strong Hypothesis of Artificial Intelligence in its classical formulation (23)

The idea of "information", then, leads to that of "reduction in uncertainty" about the state of a given environmental signal or group of signals (24). The concept of "uncertainty", though, implies an *a priori* capacity of the CNS to develop the "meaning" of this language term; indeed, it has been authoritatively argued the unlikeliness of the existence of environmental signals as "certain" or "uncertain" *per se* (25). Nevertheless, it remains the need for the CNS to represent, in a simple and systematic form, the large amount of inputs, even contradictory, originating from a given "state" of the environment and directed towards the body. One possibility is that strengthening of intercellular, synaptic and non synaptic, contacts belonging to the neuronal population that repeatedly receives a stimulus during time acts as a selectionist force for that given stimulus (22), thus rendering it "less uncertain".

On these premises it seems acceptable the proposal for the existence of *computational maps,* providing an intermediate step in information processing (19), after reception and sorting of incoming environmental signals. *In a brain computational map, a systematic variation in the value of the incoming physiological parameter occurs across at least one linear dimension of the neural structure.* In fact, neurons constituting a map act as an array of preset processors (or filters), each tuned slightly differently in terms of cellular responsiveness to the stimulus and collectively operating *in parallel* on the afferent signal. The result is to transform (i.e. compute) the environmental input into a place-coded, probability distribution of their activation states. This distribution, therefore, comprises sets of values for that physiological parameter, yielding a real topography of neuronal responses, i.e. a map that exploit a *parallel computation* (19).

The idea of parallel computation is already sufficient in itself to forecast a computational efficiency higher than that of a TM. Indeed, Robin Gandy has recently described a system with a new definition of "mechanism" and "locality", called Gandy machine, capable of *coping with parallel information and computation*, while satisfying the conditions of finiteness and locality of a TM (26). As a consequence Gandy-type computation (i.e. a sort of Turing-like, parallel computation) would exploit a type of calculus of an higher order of efficiency than that of a standard, discrete-digital machine. Therefore, existence of parallel computation in brain computational maps would render these structures able to perfom more efficiently than a TM.

Auditory, visual and global computational maps

An example of parallel computation in the CNS of mammals seems to occur in the brain stem and auditory cortex during evaluation of the *auditory space* (19). Neurons are tuned to sounds arriving from specific regions of the environment and, since auditory cues are numerous, these can be collected as sound features (e.g. frequency-specific interaural delays and intensity differences). By progressively distributing the value variation of each parameter (e.g. delays and intensity) along (*i.e in parallel to)* specific neuronal groups, a map of the sound cues is obtained. Then, using patterns of parameter convergence and gradients of neuronal projection these cues are combined in a sort of "topography" of sound frequency, delay and amplitude, resulting in formation of a presumptive sound source location (Figure 4). The processes is similar to that used to estimate the ship course, where some parameters (e.g. longitude, latitude, hight from horizon) are combined to predict its location.

In summary, the original sound information (i.e. collectives of signal frequencies, delays, intensities) becomes represented (i.e. physically recorded) as sets of neural activations dependent on parallel and progressive, parametric values within appropriate CNS areas (brain stem and cortex) and this representation transformed (i.e.computed) into a *place-coded, probability distributio*n. This distribution can eventually be transferred to secondary and tertiary CNS sites as well as readily integrated with other, sorrounding topographic maps of sensory space, based on existing neural projections and morphology of the glial-neuron spaces, as proposed by cable-like and volume-like, transmission modalities (16, 17).

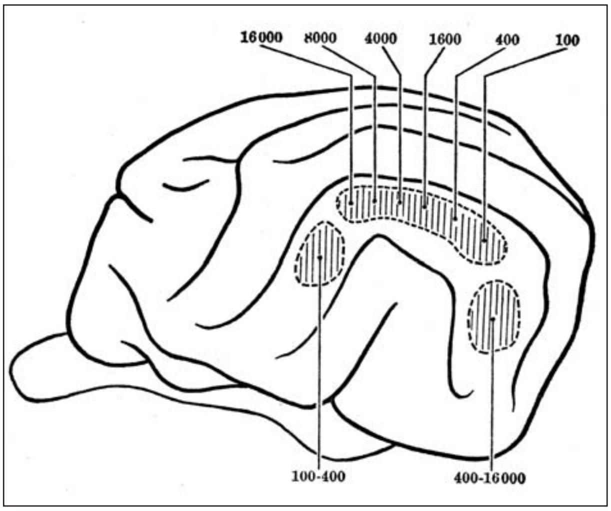

Figure 4. Auditory map of the dog brain, after the the pioneering studies of the Nobel Laureate E.D. Adrian on perception, at the beginning of the XXth century (56). In the mammalian brain sounds are "represented" as states of neural activation in response to their physical features (e.g. frequency). These states are "progressively distributed" along (*i.e in parallel to)* an array of neurons located in specific brain regions (brainstem and cortex). These frequency-dependent, neural activations are "transformed" (i.e. *computed*) into a *place-coded, probability distributio*n of their response values. This distribution constitutes the *computational map*. In the upper part of the figure is depicted the anatomical area selectively responding to those sound frequencies (indicated by numbers as cycles/s) that produce maximal variation in neuronal electrical potential (i.e the place-coded, probability distribution of response values or *fine-grain computational map*). Similarly, in the lower part are shown the anatomical areas reponding only to gross intervals of sound frequency (so called *coarse-grain computational map*). Through a peculiar anatomical connectivity linking upper with lower areas as well as with other somatic and sensory areas, particular sets of frequency values may eventually be associated with time- and amplitude-dependent sound cues, to yield an estimate of sound location in space. This latter process is similar to that used in a sailing map, where geodetic variables (e.g. longitude and latitude) are combined to establish the presumptive ship course (from reference 56, with permission, partly modified).

Similar considerations can be applied also to the evaluation of the visual space by the primary visual cortex, where neurons assembled in peculiar arrays, called *hypercolumns* (27), progressively *map* in parallel all the values of a line orientation and ocular dominance (the parameters to be computed) (Figure 5). In

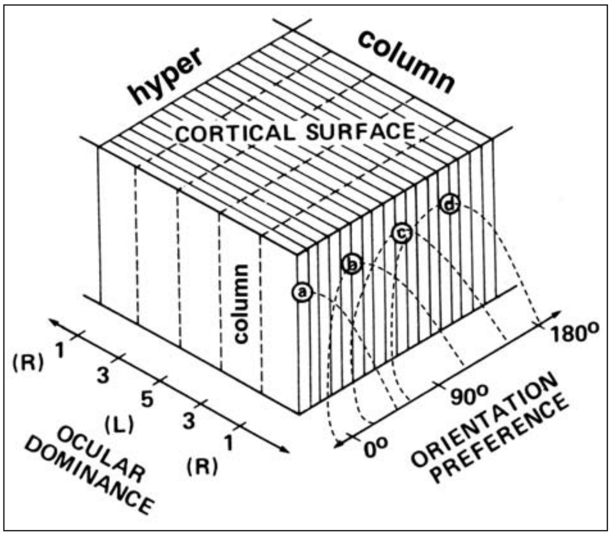

Figure 5. Simplified, schematic three-dimensional image of a neuronal *hypercolumn* in the primate visual cortex, as determined after the pioneering studies of the Nobel Laureates D.H. Hubel and T.N. Wisel, in the second half of the XXth century (27). Each hypercolumn is made up of single neural columns, containing neurons that electively respond to a given visual parameter (e.g vertical, horizontal or oblique orientation of a line in the space, ocular dominance). The parameter input is distributed in parallel to all neurons of the hypercolumn, but the different "receptivity" of each neuron (or collective of neurons in single columns) induces a *place-coded, probability distribution* of the visual signal. Circled letters, infact, identify columns containing neurons that respond to specific degree intervals of line orientaton (angles from 0° to 180°), whose "receptivity" distribution is depicted by the related dotted curves. Thus, the parameter input is recorded as anatomical topography (i.e. *mapped* as neural receptivity) and "transformed" (i.e. *computed*) into a probability distribution of the neuronal response. R = right eye; L = left eye (from reference 19, with permission, partly modified)

addition, since these maps can be activated in the course of behavioral responses to images (19), one of us (G. Sandri) has raised the hypothesis that, at least in humans, *high order computational maps* might be involved in yielding abstract expressions related to vision, like creative painting (14). This idea is close to that of J.P. Changeaux (28) about the seminal observation of Rizzolatti's group (29) on "mirrow neurons" in the primate motor cortex (for mirror neurons see also G. Giorello and C. Sinigaglia, this issue). These cells are interpreted as contributing to a neural network aimed at integrating different somato-motor and somato-sensory data, as in a finitary, parallel sampling of signals, into the perception of intentions and feelings, believed to be based on infinitary cues.

Parallel information processing, then, has been recently assumed as a basic requirement for global map formation in Gerald Edelman's, Extended Theory of Neuronal Group Selection (25). In this theory, specific regions and layers of the cortical mantle (called classification couples or classification n-ple), simultaneoulsy and *in parallel*, sample two (or more) physical features from the environment. Each set of signals related to a given feature *re-enters* from a receiving neuronal repertory (i.e. from a *map* in a given CNS site) onto a *reciprocal* neuronal repertory (i.e. onto another *map* in another CNS site), both neuronal repertories being part of the classification couple. In this manner a *recursive integration* of the two (or more) environmental signals occurs (30), *continually* providing spatial and temporal correlation of at least two (or more) different physical features. It has been proposed that primary motor and cerebellar cortexes might act as a classification n-ple for categorization of volontary movements in primates and man (25), thus exploiting parallel information processing. More widely, networks of classification couples or n-ples, when interconnected by wide recursive integration, could give rise to a *global map* for brain abstraction and mentation, called *high order consciousness* in Edelman's terminology (25).

In summary, a brain computational map and in particular, a global map results based on parallel processing of incoming signals (due to the anatomical organization of the map itself), their recursive handling (i.e. treatement of signals as functions "computable" through primitive operations) and inclusion into a continuous state space (i.e. with infinitary parameter values), like in hybrid computational systems.

Neuroendocrine computational maps

Recently, we have suggested that the hypothalamus and limbic system might act as a classification n-ple for motivated behaviors in man (18), by simultaneoulsy and *in parallel* sampling visceral/metabolic and emotional/compulsive features arising in the course of body adaptation to enviromental challange and stress. In addition, preliminary observations of our group suggest that a modular organization exists in the periventricular zone of the rodent hypothalamus, based on neurons that operate *in parallel* on chemically-specified, afferent signals (31, 32) (Figure 6). Such a processing array might explain the ability of particular sets of neuroendocrine cells, like those synthesizing the neuropeptides somatostatin (SRIF) and thyrotropin-releasing hormone, to give rise to

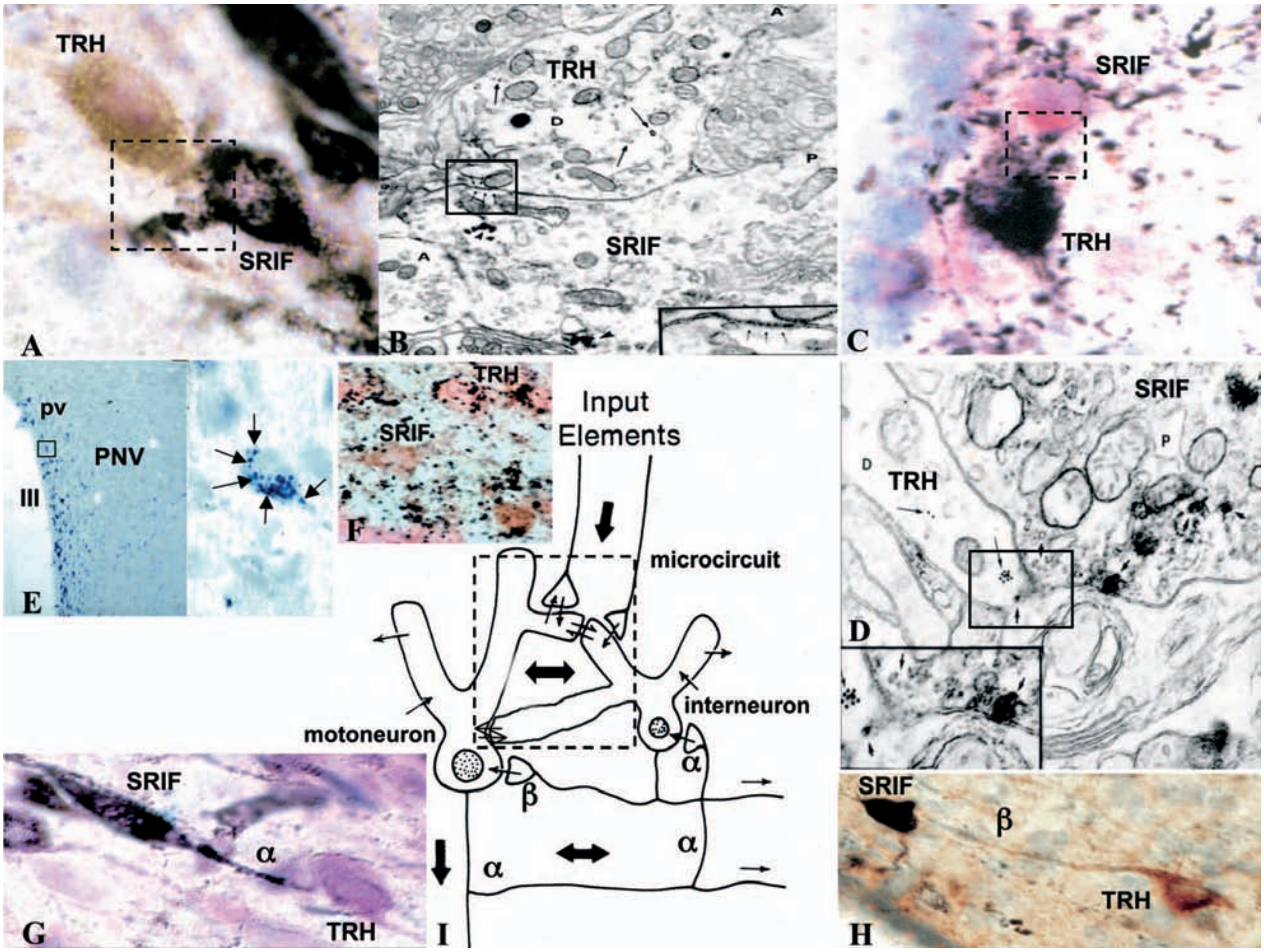

Figure 6. Morphofunctional evidence for microcircuits and local circuits between somatostatin (SRIF) and thyrotropin-releasing hormone (TRH) neurons, in the periventicular subdivision (pv) of the hypothalamic paraventricular nucleus (PVNpv) of the adult male rat. A) Light microscopic, double labeling immunocytochemical evidence for juxtaposition (frame) between the main dendritic trunk of a TRH-immunoreactive (IR) neuron (brown color) and a proximal dendrite of a SRIF-IR neuron (black color), as in the case of interacting dendrites in a *microcircuit*; B) double labeling, ultrastructural evidence of a dendro-dendritic interaction, mediated by a tight junctional specialization (frame and inset), between a SRIF-IR (containing coarse, electrondense material, pointed by arrowheads) and a TRH-IR (containing fine electrondense, 15 nm gold particles, pointed by arrows) neuron. Note that both dendrites establish symmetric (likely inhibitory), axo-dendritic synaptic contacts with unlabeld axon terminals, as that occurring in the afferent pole, or *microcircuit*, of a *local circuit*; C) light microscopic, double labeling immunocytochemical evidence for a somato-dendritic interaction (frame), between a SRIF-IR perikaryon (pink color) and TRH-IR dendrite (black color), as that occuring in a local circuit between a *tuberoinfundibular motoneuron* and a *interneuron*; D) double labeling, ultrastructural evidence of a functional, somato-dendritic interaction (frame) between a SRIF-IR perikaryon (containing coarse, electrondense material in secretory granules, indicated by small arrows) and a TRH-IR dendrite (containing fine electrondense, 15 nm gold particles, indicated by long arrows). Note in the inset the presence of a SRIF-IR vescicle (short arrow) in exocytoses from the perikaryon to the dendrite, as that expected to occur by non-synaptic release between a *tuberoinfundibular motoneuron* and an *interneuron* in a microcircuit; E) light microscopic, single labeling immunocytochemical distribution of nerve endings in the PNVpv (left side of the image), after electrophoretic injection of the anterogradely-transported lectin, PHA-L in the neuropeptide Y (NPY)-rich, adrenergic C2 region of the dorsal brain stem (nucleus of the tractus solitarius, rostral part). Note that axonal boutons (small arrows) are concentrated on the perikaryon and main dendritic trunk of PVNpv neurons

(right side of the image), suggesting that brain stem, NPY/adrenergic inputs are involved in the establishment of microcircuits in the PVNpv; F) Light microscopic, triple labeling immunocytochemical evidence for NPY-IR (black color) innervation of SRIF-IR (brown color) and TRH-IR (pink color) neurons in the PVNpv, supporting the possibility for simultaneous regulation by NPY afferents of microcircuits between SRIF-IR and TRH-IR neurons; G) light microscopic, double labeling immunocytochemical evidence for axonal projections of a SRIF-IR (black color) onto a TRH-IR (pink color) neuron and, H) of a TRH-IR (brown color) onto a SRIF-IR (black color) neuron, as those expected to occur in a "feedback" interaction between a tuberoinfundibular motoneuron and an interneuron of a local circuit (letters α and β identify the type of axonal projection, as shown in I); I) simplified version of a local circuit in the PVNpv, as derived from the anatomical evidence presented above (adapted from ref. 57). Note the afferent integrating pole, or *microcircuit*, represented by axo-dendritic contacts, primarily conventional synapses, between dendrites of both the tuberoinfundibular motoneuron (or relay neuron) and the interneuron (or intrinsic neuron), and afferent axon terminals. Both the motoneuron and the interneuron may also interact through non-synaptic contacts between dendrites (dendro-dendritic interactions) or dendrites and perikarya (somatodendritic juxtapositions), likely mediating slow-release, electrotonic and/or autocrine/paracrine signals, as well as via a "feedback" system, mediated by short, reciprocal axonal projections (α and β type). III = third ventricle; A = axon; D = dendrite; P = perikarionn

graded and coordinated responses in the presence of changing levels of circulating metabolites and hormones, like glucose and leptin (Figure 7). In this manner, parallel processing of continuous variables, collected in a feeding back routine, would occur as in the case of hybrid computation. Finally, we raise the possibility that a sort of place-coded, probability distribution of neural signals reaching the hypothalamus occurs through a *parallel regulation* of their access, similar to afferent signal regulation within the cerebellar cortex

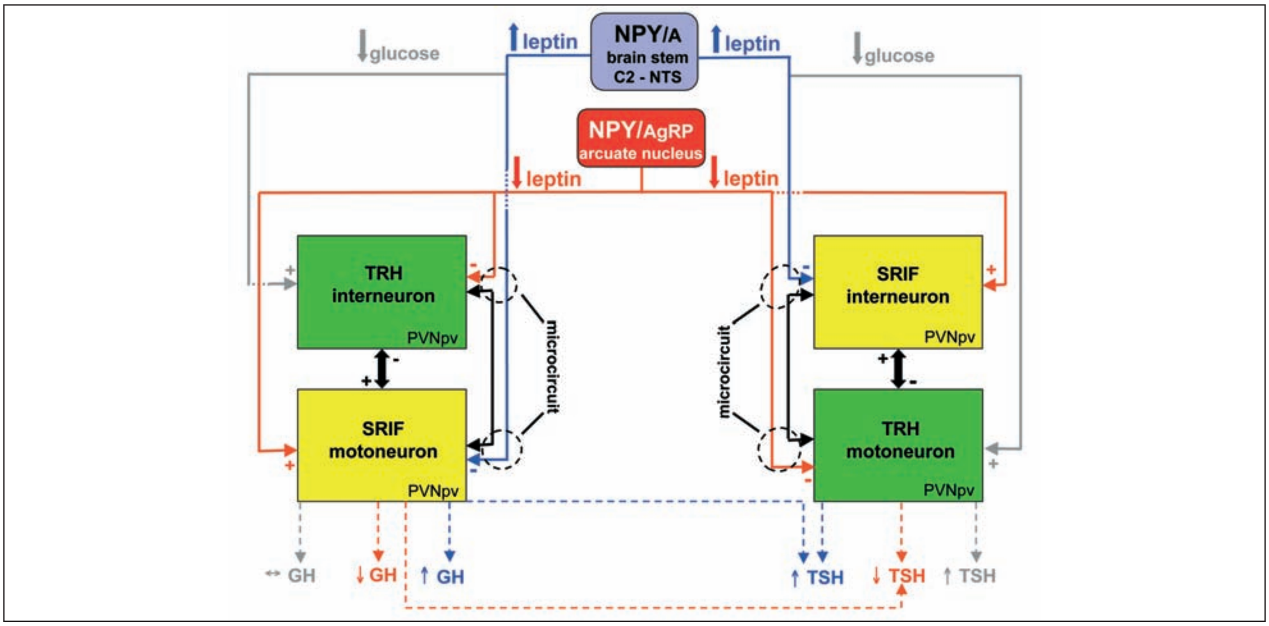

Figure 7. Schematic representation of a hypothetical module (i.e. repetion of a given architecture as individual morphofunctional units) in the periventicular subdivision (pv) of the hypothalamic paraventricular nucleus (PVNpv) of the adult male rat, as derived from the anatomical data presented in figure 6. Note that somatostatin (SRIF) and thyrotropin-releasing hormone (TRH) neurons may respond *in parallel* to two different neuropeptide Y (NPY) afferent signals, as expected to occur during a *parallel computation*. We raise the possibility that both brain stem and arcuate NPY-containing afferents participate to the formation of microcircuits in the PVNpv involved in body energy regulation, likely exploiting the action of co-contained neuromodulators, like adrenaline (58) and Agouti-gene related peptide (AgRP) (59). This would allow for mapping (i.e. a place-coded, probability distribution) of their inputs to SRIF (60) and TRH neurons (61, 62) involved in local circuits coordinating pituitary, growth-hormone (GH) and thyroid-stimulating hormone (TSH) secretions in response to *continually* changing levels of glucose (63, 64) and the adipose hormone leptin (65, 66), during starvation and refeeding. This combined circuitry might also shed light on recent observations on the lack of effect of glucose administration to fasted animals in restoring (if not worsening) TRH biosynthesis (67) ↑ = increase; ↓ = decrease; ↔ = no change

(33, 34). Both structures, in fact, show similarities in the geometry of afferent signals and internal circuits. In particular sagittally-oriented, cellular zones (hypothalamic nuclear zones, cerebrellar granular and Purkinje cells, respectively) and afferent inputs (periventricular system, stria terminals-fornix, medial forebrain bundle in the hypothalamus; rampicant and muscoid fibers in the cerebellum) contrast with orthogonally-directed outputs (interzonal connections, in the hypothalamus; parallel granular fibers, in the cerebellum). Analysis of dendritic and axonal arborizations in nuclei of the rodent hypothalamus supports this geometrical assumption (35, 36). Therefore, the effect of sagittally-oriented, incoming signals *continually* reaching the hypothalamus could be influenced *in parallell* by orthogonally-oriented outputs (Figure 8). As a consequence, a parallel computational processing might occur.

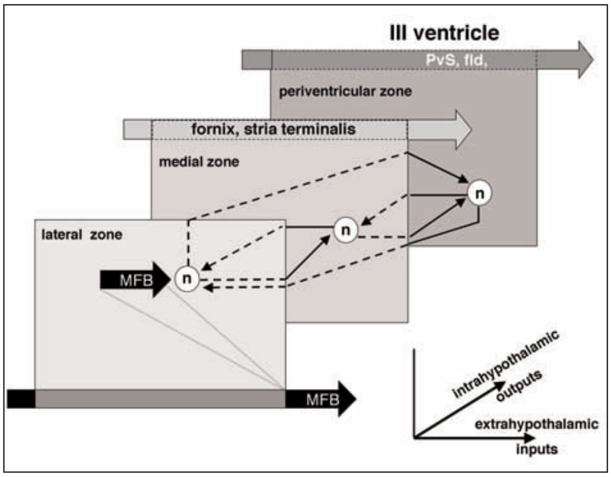

Figure 8. Simplified overview of the geometry linking afferent inputs and inner outputs in the Rodent hypothalamus. Extrahypothalamic stimuli reach the three, sagittally-oriented nuclear zones of the hypothalamus (lateral, medial, periventricular), entering each zone parallel to intrinsic nuclei. Large arrows depict the course of the main afferent tracts in each zone, whereas their shaded areas indicate penetration of signals into nuclei along the same direction of bundles (e.g the MBF, innervating nuclei in the lateral hypothalamic zone). In contrast, outputs from hypothalamic nuclei (thin arrows) run perpendicular to afferent fibers, from one zone to the other two. In this manner orthogonally-oriented, intrahypothalamic outputs can influence *in parallel* sagittally-oriented, extrahypothalamic inputs, realizing parallel regulation of signal access. It results a sort of place-coded, probability distribution of signals reaching the hypothalamus, like in parallel processing of continuous variables. MBF = medial forebrain bundle; PvS = periventricular system; fld = fasciculus longitudinalis dorsalis, n = nucleus

High cerebral processes

Theoretical arguments raise the possibility that the human mind possesses a computational capacity well beyond that of a finite and discrete state machine. The philosopher James Lucas and the physicist Roger Penrose have proposed one of these argument, against an algorithmic theory of mind (37, 38). Recall Goedel's *Incompleteness Theorems* (2, 39):

"Whithin any given branch of mathematics, there would always be some propositions that could not be proven nor disproved using the rules and axioms of that mathematical branch itself. You might be able to prove every conceivable statement about numbers within a system by going *outside* the system, in order to come up with new rules and axioms. By doing so, though, you will only create a larger system with its own unprovable statements. […] The implication is that all logical systems of some complexity are, by definition, *incomplete*. Each of them contains, at any given time, more true statements than it can possibly prove according to its own defining set of rules." In other words, Goedel demonstrated that it is impossible, *for any possible algorithmic system*, to yield an algorithm able to solve any possible problem.

In contrast to a TM, that is an algorithmic system, a typical problem solved by the human mind would be, according to the thesis, to *prove the truth of propositions*, i.e. language statements, *even when these propositions imply a semantical procedure*, i.e. a procedure that takes into account their *meaning*. Therefore, it is argued that *is the association of the notion of "prove" with that of "meaning" that makes a difference between the TM and the human mind*. In accepting a truth-conditional theory of meaning (40), there are formulas (i.e. propositions of system language) that, either the formula or its negation, is *true*: but, in light of Goedel's *Incompleteness Theoremes*, none of these formulas (or propositions) *can be proved*. In contrast, the human mind is able to activate procedures, defined *semantical*, through which the notion of "meaning" (as condition of truth) becomes *provable.* Therefore, the computational power of a TM would, anyway, remain below the power of human mind and, as consequence, Lucas and Penrose have interpreted Goedel's results as an indication that high cerebral processes cannot be reduced to those of a TM.

In spite of some authoritative criticism has been raised to this and similar arguments (2, 41), it is in keeping with what expressed by Godel when he noted that some human brain processes do not satisfy the finiteness and determinacy conditions required by a TM (4). Therefore, we conclude that complex brain activities, like abstraction and mentation, to use the terminology introduced by Paul D. McLean (42), include functions that are not Turing computable, but that might be worked out through a more "elastic" form of computation (2), as that offered by hybrid systems.

Dinamically evolving models of brain automata and neuromorphic bionic structures

In the past the reliability of classical neural networks has been seriously challanged by the evidence that excess of discreteness exists in their information processing with respect to living brains (43), even for those using a sort of intrinsic feedback or re-entering routines, called back propagation algorithms, that has some similarities with natural, re-entering neural wiring and recursive integration. Recently, however, HT. Siegelmann (44) has developed a neural network model with a greater amount of continuum, being based on *real values* for interactions (i.e. neural weights) among a finite number of components. This implicates the possibility to design devices working with analog computation; however, if it will be feasible to physically built this machine remains a problem. Some authors deny this possibility (45), while others suggest that not necessarily an analog computer should have architectural features similar to a TM (46). Nevetheless, also in devices possibly containing internal continuous values, discreteness of the output could be dictated by limits intrinsic to the precision of the detector measuring the continuous phase state. Therefore, a sole analogical strategy does not appear sufficient to reach in a synthetic structure a living brain-like power of information processing. Support to this possibility is offered by the *dynamically evolving machines*, characterized by autonomous sampling of environmental signals. Their capacity to recognize the continuous nature of incoming stimuli is, though, poor. The iterative presentation of the same signals, however, *select and reinforce* specific groups of circuits, and the ensuing performance can be interpreted as *learning capability* for signal recognition over time. Automata of the Darwin Project (47) remarkably fulfill these requirements.

These last achievements have been reached by mimicking some natural processes occuring in the living brain, as those of neuronal group selection after environmental challange (better known as Neural Darwinism) and parallel sampling of stimuli, leading to global map formation (22, 25). Therefore, in designing neural circuits to reproduce brain activities it might be fruitful to choose theoretical assumptions even more basic than those implied by a digital versus analog computational approach. The *discrete versus continuum polarity* seems promising (11). A cybernetic example of such a theoretical perspective may be envisaged in the recently realized *neuromorphic chips* for damaged retinas and visual cortex (48). In these bionic devices a correspondence exists between the anatomical architecture of the original brain region and the synthetic wiring of the chip, the latter aimed at physically reproducing the natural organization. The result is a surprising similarity between the living and cybernetic neural activity. Apparently, the *shape* of chip circuits provides the *continuum phase state*, as that associated to recognition of "form" (11), essential to obtain a chip performance reproducing that observed in the living brain. The surmised concept, then, is that in the living brain *the hardware makes the software* (30, 49), as opposed to the standard idea in computer science that the two entities can work independently. Indeed, in living systems, efficiency of a given physiological activity, even throughout evolution and development, relies upon constancy of topological constraints in the morphology of many brain regions, as in the case of nuclear assembly in the mammalian hypothalamus (50) (Figure 9). Therefore, it is likely that a concordance between topological constraints in both natural and synthetic wiring is pivotal to the chip computational capacity. In summary, a computational continuum appears the ideal target for reproducing complex neural functions, being able to range from a finite, TM-like process (no learning) to hybrid / neuromorphic performances (high level learning).

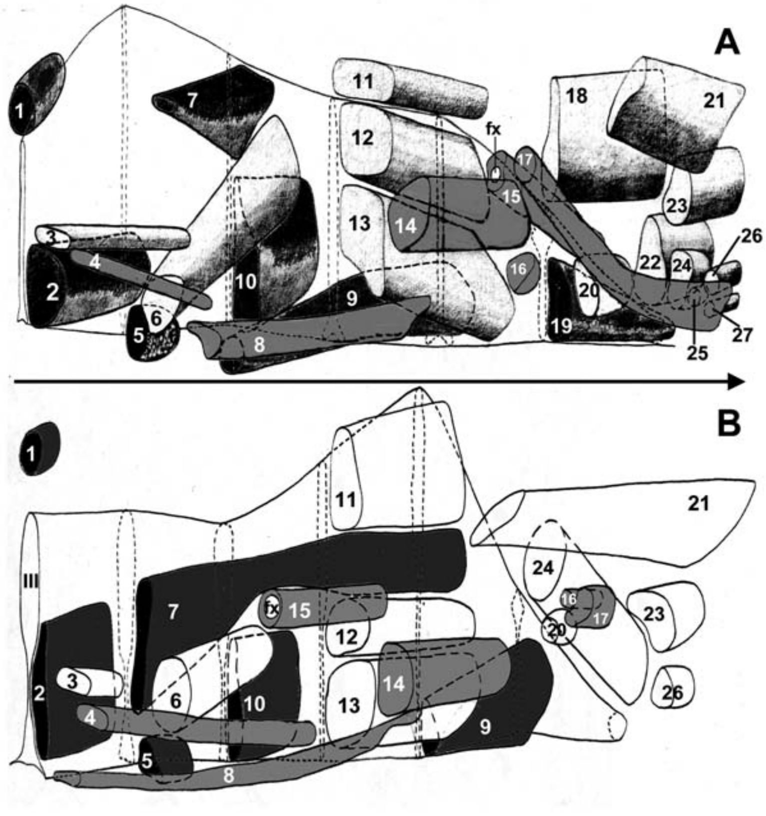

Figure 9. Stereological reconstruction of the nuclear distribution of the adult (A) rat and (B) monkey hypothalamus, obtained using serial sections at approximately corresponding levels along the cranial-caudal extent of the third ventricle. Nuclei of the hypothalamic periventricular zone are in black, medial zone in white and lateral zone in grey. Note that a fundamental topological nuclear pattern is preserved from Rodents to higher Primates. This suggests that size and positional distorsions observed in hypothalamic nuclei from one mammalian species to another are transformations keeping constant their geometrical relations, i.e bearing an invariance in topological connectedness. On these bases it is expected that also in human beings anatomical relations between hypothalamic nuclei, zones and fiber systems be very similar to that of other Mammals, in order to keep constat basic hypothalamic physiological responses. 1 = median preoptic nucleus, 2 = preoptic periventricular nucleus, 3 = medial preoptic nucleus, 4 = lateral preoptic nucleus, 5 = suprachiasmatic nucleus, 6 = anterior hypothalamic area; 7 = paraventricular nucleus, 8 = supraoptic nucleus, 9 = arcuate or infundibular nucleus, 10 = anterior periventricular nucleus, 11 = dorsal hypothalamic nucleus, 12 = dorsomedial hypothalamic nucleus, 13 = ventromedial hypothalamic nucleus, 14 = lateral hypothalamic area, 15 = perifornical nucleus, 16 = lateral tuberal nucleus, 17 = tuberomammillary nucleus, 18 = dorsocaudal hypothalamic area, 19 = posterior periventricular nucleus, 20 = premammillary nucleus, 21 = subthalamic nucleus, 22 = median mammillary nucleus, 23 = supramammillary nucleus, 24 = medial mammillary nucleus, 25 = nucleus mammillaris cinereus, 26 = lateral mammillary nucleus, 27 = intercalate nucleus Arrow indicates the cranial to caudal extension of the ventricle. III = third ventricle (from ref 50, with permission)

Conclusions

The presence of "non conventional" computability has been theorized since computer science origins, and appears now philosophically consistent with the depth of abstract and significant, natural brain processes especially when confronted to the discreteness and limitation of conventional, logical and mathematical processes. It is compatible with many cerebral activities, including circuitries devoted to neuroendocrine regulation, and hybrid systems represent an example of this computation, in which digital and analog processes would coexist. However, in accepting the idea of hybrid systems, both in Nature and as physically producible devices, the dichotomy of effective Turing-like versus analog calculus is bypassed, to end up in a deeper and less palpable operational polarity, that of discrete versus continuum. This allows for recognition that the more abstract is the structure of a reasoning, the higher is the need for combinatorial, infinitary procedures (28). A similar requirement emerges also from recent modelling of global CNS computational capacity (16, 51). Miniaturization of cerebral circuits, their expansion as local circuits and their widening as networks of neural membrane domains, including homeostatic and heterostatic regulation of synaptic transmission (52) are, in fact, coupled to divergence of computed inputs within each of the above mentioned architectural levels. As a consequence, a *vertical information processing* is associated to an *horizontal information processing*, impling a sort of "continuum" in signal handling. In addition, the evidence that the "material form" (53) may influence the performance of a cybernetic circuit, as in neuromorphic chips, stresses the importance of the physical "continuum" for the operational potency of these designs, urging to widen the horizon of mathematical/informatic tools able to mimik it. A mathematical treatment of environmental signals with *mother structure theory* (54) might help to simulate aspects of natural perception, believed to be based on "family resemblances" (to use Wittegenstein's terminology) or "polymorphic sets of stimuli" (to use Edelman's terminology) (22). Similarly, *fuzzy logic* could represent another theoretical reservoir where to get elements of "continuum" for future designs of brain-like, computational capacity (55). The challenge to dig out the hidden logic structure of brain processes is on stage and promises unexpected clues for the just started, XXIst century neuroscience.

Aknowledgements

This work has been possible by Grants MIUR FIRB RBAU01CHZ4_001, PRIN2004064523_003, FIL05, FIL06

References

1. Turing AM: On computable numbers with an application to the Entscheidungsproblem. *Proc London Math Soc* 1936; 42 (2): 230-65.
2. Arbib MA. Brains, Machines and Mathematichs, 2nd ed. New York, Springer-Verlag, 1987.
3. Gandy R. The confluence of ideas in 1936. In: Herken R, ed: The Universal Turing Machine. Oxford University Press, Oxford, 1988: 55-111.
4. Goedel K. Collected Works, vol 1. In Feferman S, ed. Oxford University Press, New York, 1986.
5. Herken R. The Universal Turing Machine: a half-century survey. Oxford, Oxford University Press, 1988.
6. von Neumann J. The general and logical theory of automata. In Cerebral Mechanisms in Behaviour. The Hixon Symposium, Wiley, New York, 1951.
7. McCulloch WS, Pitts WH: A logical calculus of the ideas immanent in nervous activity. *Bull Mathem Biophys* 1943; 5: 115-33.
8. Lupacchini R, Tamburrini G. Grounding effective processes in empirical laws: introductory remarks. In Lupacchini R, Tamburrini G, eds: Grounding effective processes in empirical laws. Bulzoni, Roma, 1999: 7-21.
9. Sieg W. Mechanical procedures and mathematical experience. In George A, ed: Mathematics and Mind. Oxford University Press, Oxford, 1994.
10. Turing AM: System of logic based on ordinals. *Proc Lon Math Soc* 1939: 45 (2nd series): 161-228.
11. Tratteur G. Analog computation and the continuum-discrete conundrum. In Lupacchini R, Tamburrini G, eds: Grounding effective processes in empirical laws. Bulzoni, Roma, 1999: 23-42.
12. Rosenblueth A, Wiener N, Bigelow J: Behaviour, purpose, and teleology. *Philosophy of Science* 1943; 10: 18-24.
13. Wiener N. Cybernetics: or control and communication in the animal and the machine, 2nd ed. Boston, The MIT Press, 1961.
14. Sandri S: Does computation provide a model for creativity? An epistemological perspective in neuroscience. *J Endocrinol Invest* 2004; 27 (suppl 6): 9-22
15. Young JZ. A Model of the Brain. Oxford; Oxford University Press, 1964.
16. Fuxe K, Agnati LF, Zoli M, Bjelke B, Zini I. Some aspects of the communicational and computational organization of the brain. *Acta Physiol Scand* 1989; 135: 203-16.
17. Fuxe K, Agnati LF, eds. Volume Transmission in the Brain. Novel Mechanisms for Neural Transmission. Advances in Neuroscience, New York, Raven Press, 1991, vol 1.
18. Toni R, Malaguti A, Benfenati F, Martini L. The human hypothalamus: a morpho-functional perspective. *J Endocrinol Invest* 2004; 27 (suppl 6): 73-94.
19. Knudsen EI, du Lac S, Esterly SD. Computational maps in the brain. *Ann Rev Neurosci* 1987; 10: 41-65.
20. Popper KR, Eccles JC. The Self and its Brain: an Argument for Interactionism, vol 1. Berlin-Heidelberg; Springer-Verlag, 1977.
21. Toni R. The neuroendocrine system: organization and homeostatic role. *J Endocrinol Invest* 2004; 27 (suppl 6): 35-47.
22. Edelman GM. Neural Darwinism: The Theory of Neuronal Group Selection. New York; Basic Books, 1987.

23. Newell A, Simon H. Computer science as empirical enquiry. *Communicaton of the ACM* 1976; 19: 113-26.
24. Pines S. Emerging Synthesis in Science. New York; Santa Fè Institute Publications, Addison Wesley, 1987.
25. Edelman GM. The Rememberd Presence. A Biological Theory of Consciuousness. New York; Basic Books, 1989.
26. Gandy R. Church's thesis and the principles for mechanism. In Barwise J, ed. The Kleene Symposium. Amsterdam, North-Holland, 1980: 123-148.
27. Hubel DH, Wiesel TN. Functional architecture of Macaque monkey visual cortex. *Proc R Soc London* 1977; 198 (Ser B): 1-59.
28. Changeux JP, Ricoeur P. La Nature et la Règle. Paris; Editions Odile Jacob, 1998.
29. Rizzolatti G, Craighero L. The mirror neuron system. *Ann Rev Neurosci* 2004; 27: 169-92.
30. Edelman GM. Bright Air, Brilliant Fire. On the Matter of Mind. New York Basic Books, 1992.
31. Toni R., Lechan RM. Hypophysiotropic neuroendocrine circuitries between thyrotropin-releasing hormone-, somatostatin- and neuropeptide Y-immunoreactive neurons in the rat hypothalamic paraventricular nucleus (PVN). XXLIV National Congress of the Italian Society of Anatomy, Bologna, Italy, 24-27 Settembre, 1990, 163 (Abstract).
32. Toni R, Briganti F, Lechan RM. Modular organization of the TRH-and SRIF-immunoreactive (ir) neurons and NPY-ir fibers in the paraventricular nucleus of the rat hypothalamus. *It J Anat Embriol* 1996; suppl 101: 97 (Abstract).
33. Oscarsson O. Functional units of the cerebellum-sagittal zones and microzones. *Trends Neurosci* 1979; 2: 143-5.
34. Kassel J, Shambes GM, Welker W. Fractured cutaneous projections in the granule cell layer of the posterior cerebellar hemisphere of the domestic cat. *J Comp Neurol* 1984; 225: 458-68.
35. Swanson LW, Sawchenco PE. Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. *Ann Rev Neurosci* 1983; 6: 269-24.
36. Swanson LW. The Hypothalamus. In Bjorklund A, Hokfelt T, Swanson LW, eds: Handbook of Chemical Neuroanatomy, Integrated Systems of the CNS, vol 5, part 1. Elsevier Science Publishers, Amsterdam, 1987: 1-124.
37. Penrose RE. The Emperor's New Mind. Oxford, Oxford University Press, 1998.
38. Penrose RE. Precis of the emperor's new mind. *Behav Brain Sci* 1990; 13: 643-705.
39. Goedel KG. Uber formal unentscheidbare Satze der Principia Mathematica und verwandter Systeme. *I Monats Math Phys* 1931; 38: 173-98.
40. Glymour C. Thinking Things Through. Boston; the MIT Press, 1992.
41. H. Putnam. Review of E. Nagel and J.R. Newman "Goedel's proof." In Anderson AR,ed: Mind and Machines. Englewood Cliffs, Prentice Hall, 1964: 43-59.
42. MacLean PD. The Triune Brain in Evolution. Role in Paleocerebral Functions. New York; Plenum Press, 1990.
43. Crick F. The recent excitement about neural networks. *Nature* 1989; 337: 129-32.
44. Siegelmann HT. Neural Networks and Analog Computation. Beyond the Turing Limit. Boston; Birkhauser, 1999.
45. Deutsch D. Quantum theory, the Church-Turing principle, and the universal quantum computer. *Proc Royal Soc Lond* 1985; A-400: 97-117.
46. Kreisel G. A notion of mechanistic theory. *Synthèse* 1974; 29: 11-26.
47. Edelman GM, Reeke GN jr. Selective networks capable of representative trasformations, limited generalizations, and associative memory. *Proc Natl Acad Sci USA* 1982; 79: 2091-5.
48. Boahen K. Neuromorphic chips. *Sci Am* 2005; May: 57-63.
49. Searle J. Minds, brain and program. *Behav Brain Sci* 1980; 3: 417-57.
50. Toni R, Malaguti A, Benfenati F, Martini L. The human hypothalamus: a morpho-functional perspective. *J Endocrinol Invest* 2004; 27 (suppl 6): 73-94.
51. Agnati LF, Fuxe K. New concepts on the structure of the neuronal networks: the miniaturization and hierarchical organization of the central nervous system. *Bioscience Rep* 1984; 4; 93-8.
52. Agnati LF, Ferrè S, Lluis C, Franco R, Fuxe K. Molecular mechanisms and therapeutical implications of intramembrane receptor/receptor interactions among heptahelical receptors with examples from the striatopallidal GABA neurons. *Pharmachol Rev* 2003; 55: 509-50.
53. Toni R. Ontic conception and scientific explanation in biomedicine: the case of the anatomical doctrine. *Epistemologia* 2003; 26: 285-316.
54. Epstein RL. Degress of Unsolvability: Structure and Theory. Berlin; Springer-Verlag, 1979.
55. Lopez F, Jobe TH, Helgason C. A fuzzy theory of cortical computation: neuropoietic engrams, fuzzy hypercubes, and the nature of consciousness. *Medical Hyp* 2006; 66: 121-32.
56. Adrian ED. The Physical Background of Perception. Oxford; Clarendon Press, 1947.
57. Shepherd GM. Neurobiology 2nd ed: New York; Oxford University Press, 1988.
58. Sahu A. Dube MG, Kalra SP, Kalra PS. Bilateral transection at the level of the mesencephalon increases food intake and reduces latency to onset of feeding in response to neuropeptide Y. *Peptides* 1988; 9: 1269-73
59. Fekete Cs, Sarkar S, Rand WM, et al. Agouti-related protein (AGRP) has a central inhibitory action on the hypothalamic-pituitary-thyroid (HPT) axis; comparison between the effect of AGRP and neuropeptide Y on energy homeostasis and the HPT axis. *Endocrinology* 2002; 143: 3846-33.
60. Hisano S, Tsuruo Y, Kagotani Y, Daikoku S, Chihara K. Immunohistochemical evidence for synaptic connections between neurpeptide Y-containing axons and periventricular somatostatin neurons in the anterior hypothalamus in rats. *Brain Res* 1990; 520: 170-7.
61. Legradi G, Lechan RM. The arcuate nucleus is the major source for neuropeptide Y-innervation of thyrotropin-relea-

sing hormone neurons in the hypothalamic paraventricular nucleus. *Endocrinology* 1998; 139: 3262-70.
62. Diano S, Naftolin F, Goglia F, Horvath R. Segregation of the intra- and extrahypothalamic neuropeptide Y and catecholaminergic inputs on paraventricular neurons, including those producing thyrotropin-releasing hormone. *Regul Pept* 1998; 75-76: 117-26.
63. Rondeel JMM, de Greef WJ, Heide R, Visser TJ. Hypothalamo-hypophysial-thyroid axis in streptozotocin-induced diabetes. *Endocrinology* 1992; 130: 216-20.
64. Williams G, Bing C, Cai XJ, Harrold JA, King PJ, Liu XH. The hypothalamus and the control of energy homeostasis. Different circuits, different purposes. *Physiol Behav* 2001; 74: 683-701.
65. Watanobe H, Habu S. Leptin regulates growth hormone-releasing hormone, somatostatin and a-melanocyte-stimulating hormone but not neuropeptide Y release in the rat hypothalamus *in vivo*: relation with growth hormone secretion. *J Neurosci* 2002; 22: 6265-71.
66. Fekete C, Kelly J, Mihaly E, et al. Neuropeptide Y has central inhibitory action on the hypothalamic-pituitary-thyroid axis. *Endocrinology* 2001; 142: 2606-13.
67. Fekete Cs, Singru PS, Sanchez E, et al Differential effects of central leptin, insulin, or glucose administration during fasting on the hypothalamic-pituitary-thyroid axis and feeding-related neurons in the arcuate nucleus. *Endocrinology* 2006; 147: 520-9.

Correspondence: Roberto Toni MD PhD,
Dipartimento di Scienze Anatomiche Umane e
Fisiopatologia dell'Apparato Locomotore
Via Irnerio 48
40126, Bologna, Italy
Tel. 051 242218
Fax 051 251735
E-mail: rtoni@biocfarm.unibo.it