A Multi-scale Dynamical Model for Neuro-Bio Systems. Application to Neural Processing and to Aging

by Andrée C. Ehresmann
*Université de Picardie Jules Verne
ehres@u-picardie.fr
http://ehres.pagesperso-orange.fr

(Work in collaboration with Jean-Paul Vanbremeersch)

Extended Abstract

Introduction

Can new technologies help increase the life quality of people by enhancing their capacities, or by compensating for more or less serious problems due to infirmities or old age? This problem becomes acute now that our societies become older and older, so that the risks of pathologies up to loss of autonomy and dependence increase.
One solution would be the development of Neuro-Bio-ICT systems that can adapt to the situation and perform high-level tasks. For this, we need to learn more about the way the organism and more particularly its neural system process information and can respond to ubiquitous complex events in an adequate way. In other words, we need analyzing the Neuro-Bio system consisting of the organism at its different levels (from atoms and molecules, to cells, organs and large systems), but also of the biological, neural, cognitive and mental processes which are at the basis of its dynamic.

Here we propose a dynamical multi-scale model NBS of such a Neuro-Bio System, as an application of the theory of *Memory Evolutive*

Systems (MES) which we have developed (for a general overview, cf. our book Ehresmann & Vanbremeersch, 2007).
MES give a mathematical model, based on a 'dynamic' Theory of Categories (Eilenberg and Mac Lane, 1945), for multi-scale systems with a tangled hierarchy of components varying over time; their dynamic is modulated by a network of internal agents with different rhythms, functions and logics, operating with the help of a flexible long-term 'memory'.
In ServiceWave 2010 (Ehresmann & Vanbremeersch, 2011), we have shown how ubiquitous complex events processing (U-CEP) can play an important role in such systems, thanks to two main features of a MES: the 'degeneracy' property (existence of multiform objects) that ensures the complexity and flexibility of the system, and the synchronicity laws which impose constraints on the operations of agents of different levels.

We give applications of NBS to neural processing and to an integrative Theory of Aging. Finally we propose some extensions of NBS in view of developing better strategies in neural processing and cognition, in particular to cope with biological, physiological or mental problems, such as loss of memory and neuro-degenerative diseases in aging.

1. The Neuro-Bio system NBS

A MES proposes a 'relational' view of a hierarchical system taking account of its components and of their interactions, as well as of their variation over time. In NBS the components will be components of the organism of various levels (e.g., molecules, cells, tissues,…), and also formal components acting as aggregates of more or less distributed neuronal assemblies (cf. Section 3).

1.1. NBS *an Evolutive System*

The states of the components of NBS at a time *t* are modeled by the nodes (or 'objects') of a (directed multi-)graph H_t whose arrows (or 'links') model channels carrying their interactions; this graph becomes a category*[1] by taking for composite of 2 successive links their combined effect.

[1] The words followed by * correspond to notions of Category Theory recalled at the end of the paper; however we have tried to make their 'concrete' meaning understandable. For more details, cf. the book (Ehresmann & Vanbremeersch 2007).

The system undergoes modifications over time through internal or external events. The global change from t to t' is measured by a *transition* functor* from a sub-category of H_t to the configuration category $H_{t'}$ at t': it maps a component at t on its new state at t' when the component still exists. This transition assesses the change but does not describe the dynamic leading to it. So the system is not represented by one category but by the family of categories H_t indexed by the life-time of the system, and the transitions between them. The transitions satisfy a transitivity condition so that a component C of NBS is represented by the family of its successive states during its existence.

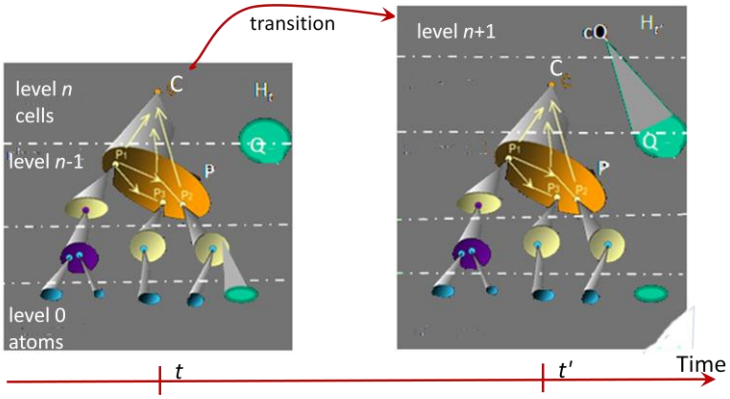

Figure 1. The transition between two successive configurations of NBS. A complex component C has a ramification down to the atomic level 0.

1.2. *The hierarchy of components at a given time t*

The components of NBS are the components of the organism of various levels: atoms, molecules, macromolecules, infra-cellular structures, cells, tissues and organs, …; it has also more formal components, called *category-neurons*, coding information under the form of synchronous neuronal (hyper-)assemblies as we'll explain in Section 3.

The links represent channels through which informational messages (*e.g.* presence of an antigen) or energy transfers (command of effectors) can be transmitted. A link from C to D can be active or passive at time *t*, and it has a *propagation delay* measuring the delay necessary for transmitting information from C to D; a simple chemical message is sent more rapidly than a humoral response requiring the synthesis of various products. The *propagation delay* of a link may vary over time.

To account for their hierarchy, the components are distributed in a finite number of levels of increasing complexity so that the components of a given level be homogeneous between them, but more 'complex' than those of lower levels: a molecule acts as the aggregate of the pattern formed by its atoms and their chemical interactions.
Formally, a component C of level n+1 acts as the aggregate (or 'binding') of a pattern* P of linked lower level components, so that P, operating as a whole, and C, by itself, have the same functional role; in the other direction, we can look at P as a decomposition (or internal organization) of C. For instance, a tissue binds the pattern of its cells and interacts through them. In the categorical model C is represented as the colimit* of P.
It follows that a complex component C admits at least one '*ramification*' down to the atom level 0, obtained by taking a lower level decomposition P of C, then lower level decompositions of the components P_i of P, and so on down to level 0. The *complexity order* of C is the smallest length of such a ramification.

1.3. *Flexibility as a result of degeneracy/multiplicity*

The degeneracy of the genetic code is well known: the same amino acid can be coded by several codons. By correlation Edelman (1989) has spoken of the 'degeneracy of the neural code'. Later he realized that a same kind of degeneracy, or 'flexible redundancy' is present at other levels:

> "Degeneracy, the ability of elements that are structurally different to perform the same function or yield the same output, is [….] a ubiquitous biological property […] a feature of complexity […], both necessary for, and an inevitable outcome of, natural selection." (Edelman & Gally, 2001)

In a MES, and in particular in NBS, we formalize this degeneracy property into the *Multiplicity Principle*: there are objects C, said to be *multiform*, which admit several decompositions into structurally different and non well-interconnected patterns of lower levels, and C can operate through one or the other, and even *switch* between them depending on the context. We have proved that this property is necessary for the emergence of components of higher complexity order and that it gives flexibility and robustness to the system (Ehresmann & Vanbremeersch, 2007).

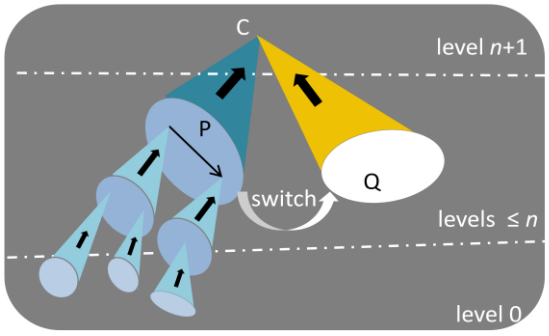

Figure 2. C is a *multiform object* if it admits two decompositions into patterns P and Q of levels ≤ *n* which are not isomorphic and not even well-interconnected.

1.4. *How the system varies over time: the complexification process*

We have said that the transition from *t* to *t'* models the changes of configuration. These changes result from events of the following kinds: suppression or decomposition of certain components (catabolism, for example), absorption of external elements (endocytosis), formation of complex components by binding or strengthening some pre-existing patterns to form a more coherent and structured association (biosynthesis of macromolecules; learning of a new procedure through the synchronization of neural assemblies); or, conversely, reduction of the coherence of a pattern by addition or loss of objects and/or modifications of links (result of the action of alkylating agents or radiation on DNA).

The *complexification process* (Ehresmann & Vanbremeersch 2007) explicitly describes the configuration of the system after realization of a procedure with objectives of this sort.

Over time, a complex component C maintains its identity and homeostasis despite the progressive modification of its internal lower level organizations. For instance the components of a cell are continuously renewed even though the cell as such is conserved; the turnover of a population of proteins is shortened when the population is unstable.

To model the rapidity of the changes, we define the *stability span* of a component C of level *n*+1 at time *t* as the largest period δt during which there is a decomposition of C in a pattern P of linked lower level components at *t* whose successive states still admit C as their colimit up to $t+\delta t$ (not included). Roughly the variation of P is progressive enough and it does not change 'too

much' during the entire period δt. This span depends both on the object, its level and the date t.

2. The dynamic of NBS and its self-organization

NBS has a multi-temporality self-organization. Its dynamic is modulated by the cooperation/competition between a net of internal agents, called *co-regulators*, which act as local organs of regulation and permit an adaptation of the state of the system to external and internal events.

2. 1. *Co-regulators and Memory*

A co-regulator is a specialized evolutive sub-system of NBS, for instance: protein networks, intracellular effectors, cell regulatory networks, cells, tissues, more or less extended specialized brain modules... It has its own complexity level, a specific discrete timescale and a differential access to a central long term memory, in particular to retrieve the *admissible procedures* which characterize its function.

The *memory* is modeled by an evolutive sub-system Mem of NBS which develops over time. Its components store information concerning innate or acquired inner processes at the basis of the functioning of the organism, features of the environment, as well as main past ubiquitous events. As they are multiform, they can be retrieved under different decompositions, (with possible switches between them), so that the memory is robust though flexible, and it has enough plasticity for adaptation to changes.
Mem has a sub-system, the procedural memory, whose components, called *procedures*, relate to processes and behaviours for responding in an adapted way to some external or internal events. A procedure S is associated to a pattern OS of interacting effectors which can be activated through links from S to OS, called *commands* of S.

2.2. *Dynamic of one co-regulator*

A co-regulator CR acts stepwise as a hybrid system, at its own rhythm depending on its function and its complexity. For instance, a step of a cell coincides with the cell cycle.
A step of CR from t to t' extends between two successive instants of its discrete timescale. It consists of different phases:

(i) Reception and analysis of the partial information transmitted to CR through the active links arriving to its components around *t*, leading to the formation of the *landscape* of CR at *t* (modeled by a category). For a cell this landscape is determined by a few biochemical events affecting its components and triggered by the binding to the membrane of a cellular mediator (for example, hormonal), by changes in the concentration of some oligo-element, and so on.

(ii) Selection of an admissible procedure to respond, by recall from the procedural memory of innate or acquired inner procedures in relation with the function of CR; for instance replication of DNA for a cell. Then the commands of the selected procedure are sent to effectors.

(iii) At the beginning *t'* of the next step, evaluation of the result.

In the event the result is not adequate (e.g., DNA is not replicated), we speak of a *fracture* for CR.

2.3. *The interplay among co-regulators*

Above we have described the regulation at the level of a single co-regulator. However there are several co-regulators, each operating at its own rhythm and level, with its own 'logic' (depending on their function). The system can function as long as the commands sent by all of them at a given time to the effectors are more or less coordinated, and at least not conflicting, so that they can be synchronously realized.

Otherwise, an equilibrium process, called the *interplay among the co-regulators*, will be necessary; it amounts to a kind of Darwinian selection among the various commands that the procedures selected by the co-regulators send to effectors. It is made flexible enough by the fact that each complex command can be realized through any of its lower level decompositions, with possibility of switches between them for selecting the ones the most adapted to the context. However the operative procedure finally realized may eliminate some commands, causing a deleterious event for the corresponding co-regulators; it might be a fracture quickly repaired, or a longer term *dyschrony* if it persists during several steps or cannot be repaired.

For instance, because of the propagation delays, small events for a lower co-regulator CR cannot be observed in real time by a higher co-regulator CR', but their accumulation during the longer step of CR' may cause a fracture to CR'; the following repair can later backfire by also causing a fracture for CR.

Whence a *dialectics between co-regulators* with different rhythms and complexities, corresponding to loops of retroactions between levels.

2.4. *Synchronicity laws*

An important cause of deleterious events such as fractures and dyschronies comes from the structural temporal constraints that a co-regulator CR must respect, in relation with its rhythm and the propagation delays of the links. The rhythm is measured by the average duration of one of its steps around the time *t*, called its *period*. The period depends on the co-regulator: a step at the molecular level (pair two bases) is shorter than a step at the cellular level (duplicate the cell). It may slowly vary, or be drastically changed in case of a long-term dyschrony (fracture not repaired in a few step), necessitating a *re-synchronization*.

Indeed, the period *d(t)* of the co-regulator CR at *t* must be sufficient for realizing the various operations occurring during the present step. So *d* should be much greater than the average propagation delay *p(t)* of links allowing the formation of the landscape and the sending of commands to effectors. Moreover the components intervening in the landscape and the realization of the procedure must keep their complex identity during the step so that their least stability span *s(t)* must be much greater than *d(t)*.
Finally each co-regulator CR must satisfy the following '*synchronicity laws*':

$$s >> d >> p \qquad \text{or} \qquad s/p >> s/d >> 1$$

(where >> means of a greater magnitude order). It suffices that these inequalities be satisfied 'on the average': if one of them is not respected at a certain instant, for example following a fracture, it can be fixed at the next step by the in-built repair mechanisms of CR, or, if they are overrun, by higher level repair processes. For instance, during the replication of DNA in a cell, specific self-repair mechanisms intervene to ensure a strict pairing of the bases; however if too many errors occur, they are overrun, and a higher co-regulator, the SOS system for DNA repair (Radman 1975), intervenes making the replication complex tolerant to errors; however later it can lead to a mutation.

If a fracture persists during several steps, there is a dyschrony which may lead to a sequence of events decreasing the stability spans and/or increasing the

propagation delays. To respect its temporal constraints, CR might be forced to re-synchronize by modification of its period *d*.
Deleterious events such as fractures, dyschronies and re-synchronizations can backfire through the co-regulators of various levels, possibly leading to inter level loops backfiring between co-regulators:

fracture → repair → fracture …

perhaps even forcing a *cascade of re-synchronisations* to avoid a systemic failure or death.

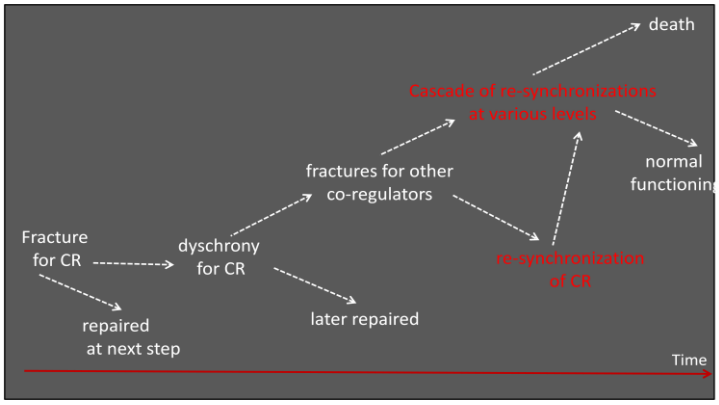

Figure 3. Backfiring of fractures between co-regulators with different rhythms leading to a cascade of re-synchronizations

3. A comprehensive theory of neural processing and cognition

The neural system, consisting of neurons and synapses between them, is an evolutive sub-system Neur of NBS which plays a motor role in processing and coding information. It is at the basis of the formation of more and more complex components, called *category-neurons*, representing cognitive and mental objects and processes of increasing complexity.

3.1. *The sub-system* MENS of NBS

Category-neurons have been introduced as higher levels components of an integrative model MENS for a neuro-cognitive-mental system (Ehresmann & Vanbremeersch 2007, 2009). MENS is a hierarchical evolutive system which

is obtained by successive complexifications of Neur. Here we include the whole of MENS as an evolutive sub-system of NBS.

The construction of MENS relies on the fact that, though various brain areas are heterogeneous both anatomically and functionally, there is a common process in brain dynamics, namely the 'synchronous' activation of more or less complex and distributed *neuronal assemblies*. This process (already noted by Hebb, 1949), as well as its *degeneracy property* (emphasized by Edelman, 1989), are at the root of the construction of an 'algebra of mental objects' (Changeux, 1983) through iterative binding of more and more complex assemblies, leading to flexible mental objects and cognitive processes of increasing complexity.

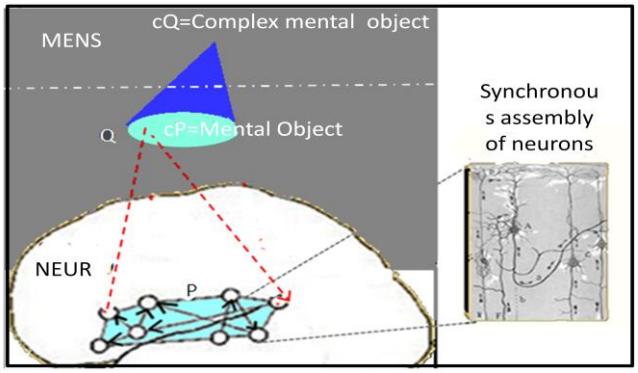

Figure 4. A mental object activates a synchronous assembly of neurons P; it is modeled in NBS by the category-neuron binding P. More complex category-neurons, such as cQ, bind synchronous assemblies Q of category-neurons

For instance a simple stimulus S activates an assembly of neurons P (or pattern in Neur); if S is repeated or persists, the distinguished links of P are strengthened (via *Hebb rule*, Hebb 1949) so that P can act synchronously; the *long-term memory* of S is recorded by a category-neuron M binding P (that is, M becomes the colimit of P) in NBS. This M can also act as the aggregate of the other assemblies of neurons which may be activated by S in other contexts. Thus M is a formal object, acting as a multiform component of NBS; though not a 'physical' object, it has multiple physical realizabilities obtained by unfolding one of its ramifications down to synchronous assemblies of the neuron level,

3.2. *The Archetypal Core and its role in information processing*

Higher mental and cognitive processes depend on the development over time of the *Archetypal Core* AC. It is a sub-system of the memory of NBS based on an integrative part of the brain that Hagmann & al. (2008) have called its *structural core*; they write (PLoS Biology, VoL 6, Issue 7):

> " Our data provide evidence for the existence of a structural core in human cerebral cortex. This complex of densely connected regions in posterior medial cortex is both spatially and topologically central within the brain. Its anatomical correspondence with regions of high metabolic activity and with some elements of the human default network suggests that the core may be an important structural basis for shaping large-scale brain dynamics. "

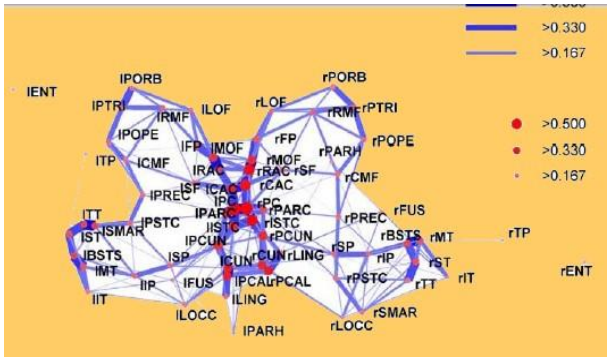

Figure 5. The structural core of the brain (from Hagmann & al. 2008)

The components of AC are higher order category-neurons with long ramifications going down to this structural core. They integrate significant memories of various modalities (sensorial, motor, affective,…). Their frequent recall strengthens their links in AC (via Hebb rule), leading to the formation of *archetypal loops* consisting of strong and fast links; these loops propagate very quickly the activation of an archetypal component A back to itself, thus maintaining it for a long time.

Thanks to its numerous links to the different parts of the system, AC plays a central role in the functioning of the system, embodying its complex identity ('Self'). It acts as a *flexible internal model*, taking part of the diffusion and processing of information and allowing a better handling of U-CEP.

3.3. *Development of higher cognitive processes*

An increase of activation of some cat-neurons in AC triggers, through archetypal loops, a self-maintained recollection of a large domain of AC, which propagates first to a decomposition P of some cat-neuron A, then, via a complex switch, to another non-interconnected decomposition Q of A and to ramifications of their components.

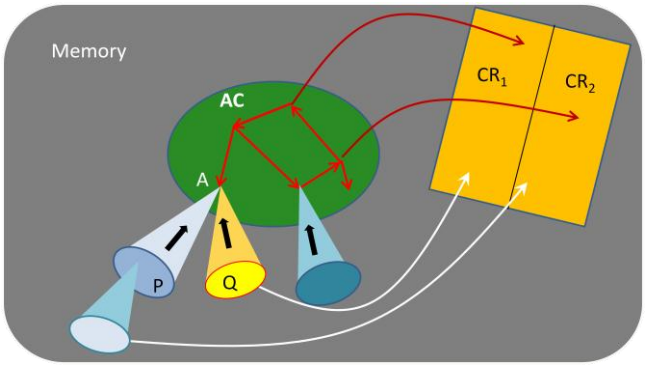

Figure 6. How AC allows the diffusion of information and its preservation thanks to the formation of a global landscape

An unexpected event (possibly causing a fracture to a higher co-regulator) increases the attention, thus activating part of AC. This activation diffuses through self-maintained archetypal loops, and then propagates to lower levels as above. Thus the information is transmitted to a large domain of NBS which remains activated for some time. Received by higher level co-regulators CR_i directly linked to AC, it allows the formation of a *global landscape* GL uniting and extending their landscapes and with a longer span time (cf. the "theater" of Baars, 1997).

Higher cognitive and mental processes (up to conscious processes) can develop in the global landscape GL, thanks to a two-steps integration of the time dimension:

(i) A *retrospection proces*s (toward the past) in GL allows recollecting the recent past, "sensemaking" of the present information, and diagnosing new trends.

(ii) A *prospection* process (toward the future) can be developed in the longer term GL, still using the motor role of AC, to iteratively construct virtual landscapes in which sequences of strategies are tried with evaluation of

their risk of dysfunction. Thus various long term 'scenarios' can be built and their effects compared. Once a scenario is selected, the retrospection process allows back-casting to find sequences of procedures able to realize it.

A better understanding of the role of U-CEP in NBS, in particular in the neural processing leading to the development of AC, might allow developing new methods for increasing mental and learning capacities, possibly with the addition of external devices to cope with mental deficits. For instance in education, it could help overcoming learning deficiencies, such as dyslexia. It could also be helpful in impairments due to neuro-degenerative pathologies, such as Alzheimer or Parkinson.

4. The Aging Problem

In our societies, the number of aged people increases each year, multiplying the risks of pathologies and loss of autonomy. Can new technologies help preserve the life quality of these persons without too much a burden for the society? To approach this problem, first we must ask what are the causes and effects of aging, to be able to develop adequate processes for responding.

4.1. *Different theories of aging*

Numerous evolutionary, biological or physiological theories of aging have been proposed (cf. Table 1, extracted from Weiner and Timiras, 2003).
The evolutionary theories relate to the question: are aging and death genetically programmed? For the "error theories" of aging (the most usual) organisms are subject to constraints imposed by the interplay between predetermined procedures with limited capacities for repair, and unpredictable external stochastic events.

Most of the theories take account of local events, stressing the role of a particular factor intervening at a certain level; and they do not allow for an integrative theory. The difficulty is that aging has not well-defined symptoms but presents multiple facets which interact and backfire at higher and higher levels from molecules, cells, organs to the whole system, and these local theories do not allow for a unified treatment.

On the opposite we propose a global approach in NBS, based on a uniform process: U-CEP decreases the stability and flexibility of various components of the organism and slows their inter levels and intra-level communications, with a loss of relative synchronicities between the operations of the system at its different levels, from the molecular, protein, cell and organ levels up to brain functioning and mental processes. It is at the root of the *theory of aging by a cascade of re-synchronizations* (Ehresmann & Vanbremeersch, 1993).

4.2. *An integrative theory of aging*

In Section 2, we have explained how U-CEP can cause fractures or dyschronies to various co-regulators, possibly forcing their re-synchronization (by change of their period).

Aging will be defined as a progressive decrease of the average ratios s/*d* and s/*p* relative to different co-regulators, which forces a *cascade of re-synchronizations* to higher and higher levels. It can result from an instability decreasing the stability spans *s* (proteins become denatured more rapidly, cells die, skeletal muscle mass and strength decrease,…), or from an extension of the propagation delays *p* (the communications slow down) and of the duration of the steps *d* (consequence of the propagation delays).

The instability can also result from the loss of lower level decompositions of a component, leaving less possibility of switches between them, hence less flexibility for the interplay among co-regulators.

This hypothesis appears to unify the different physiological theories of aging that have been proposed, each starting at a different level, or on a general instability and loss of flexibility of components. (For a review on these theories, cf. *Handbook of Theories of Aging*, 2008.)

Graphically, we can represent the curves of s/*d* and s/*p* for a given co-regulator CR as a function of time. In normal senescence, the minimum threshold of 1 for s/*d* is continuously approached, on a more or less long duration.

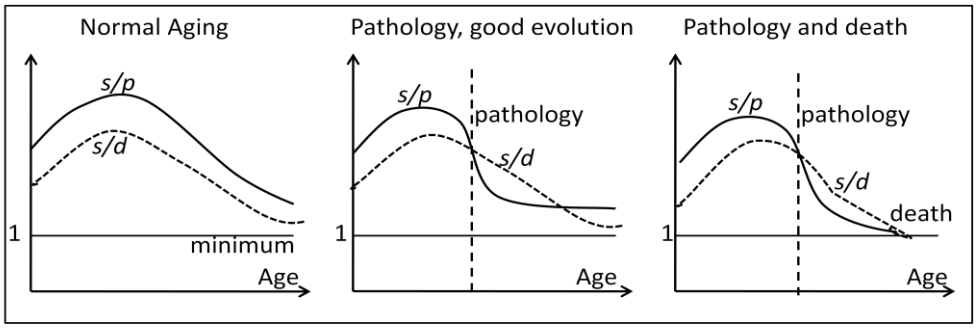

Figure 7. The curve of *s/d* as a function of time slowly approaches 1 during senescence, while the curve of s*/p* also approaches 1, but remains above the first curve. The increasing regions of the curves correspond to growth of the organism.

In a pathological event implicating the co-regulator CR, the slope of s*/p* presents a sudden change in direction that makes its curve go under that of s*/d*, even though the latter also decreases. Depending to the intensity of this change in direction, it will be possible to recover the initial position after repair, or the slope of s*/d* will also decrease suddenly, and go beyond the minimum threshold; it corresponds to the case the system cannot recover its equilibrium, and thus dies.

The analysis of these relations can also explain the quasi-absence of aging if a system has a restricted number of hierarchical levels and few external functional relations, leaving s*/d* almost invariant. That could be the case of cancer cells and certain isolated cells such as spermatogonia.

4.2. Strategies to cope with aging problems.

Let us note that the above curves concern each co-regulator; some of them can 'age' more quickly, while others begin to age only under stressing U-CEP.

In particular in the aging brain, the transmissions are longer and the loss of many neurons causes an instability which also decreases the flexibility because of less possible switches. The senses are less acute and the perceptuo-motor integration decreases, reducing mobility because of stability and performance problems (cf. Erwin de Vugt and Carel Meskers, 2011).
It is more difficult to maintain the attention, so that the activation of AC is less strong and diffuses to a smaller lower level domain. The global landscape is less extended and of a shorter duration. Thus, the retrospection process is

less efficient, and the prospection process leads to shorter term and less adapted strategies, affecting the anticipation and decision processes.

The preceding theory reveals some of the main mechanisms which can go wrong during aging, at the different levels of the organism. Can we use it for preventing deleterious events and helping aged people to keep a quality of life in spite of their deficiencies? One possibility is to use modern transmission devices for continuously assessing the state of some main physiological functions and monitoring important causes of immediate or future problems. It is what is proposed in Table 2, due to Jean-Paul Vanbremeersch, in view of his experience as a geriatric physician, medical coordinator of an old people's home.

Conclusion. Extensions of NBS

This paper describes the multi-scale dynamical model NBS for a neuro-bio system, integrating its different complexity levels up to a comprehensive theory of neural processing and development of higher cognitive processes. It stresses the role of U-CEP in its functioning and gives an application to an integrative theory of aging.

NBS has been introduced as a model for a living organism and its neural and mental processing. However the main part of what has been said could be applied to an artificial system with enough components, in particular with a sufficient net of co-regulators and a sub-system emulating the archetypal core. The problem would be to make computable the different operations we have described. It seems that the complexification process is computable (for instance in terms of λ-calculus). The question which remains is whether the interplay among co-regulators can be made computable; the difficulty comes from the flexibility due to the multiform components, and from the need to simultaneously take account of the different temporalities of the co-regulators.

Another possibility is to enrich NBS (in its initial configuration) by developing neuro-bio-ICT systems, obtained by adding to NBS some 'artificial' components, for instance to replace defective components (of any level) or to allow for new capacities (such as new sensory organs). The idea is to develop new brain-computer interface technologies so that the multi-scale

dynamic of NBS analyzed here would extend to such a system. Among the applications: increasing mental and learning capacities; coping with learning deficiencies and with the various deficiencies caused by aging, such as cognitive impairments due to neuro-degenerative pathologies.

***Definitions**

Category = graph with a composition law associating to a path (*f, g*) from A to B a unique arrow *fg* from A to B, this composition being associative and each object having an identity.
Pattern P in a category = family of objects P_i with some distinguished arrows between them.
Collective link from P to A = family of arrows a_i: $P_i \rightarrow A$ such that $a_i = fa_j$ for each distinguished link f: $P_i \rightarrow P_j$.
Colimit of P = object C such that there is a collective link from P to C through which any other collective link from P to A factors.
Functor from a category K to K' = map from K to K' preserving the identities and the composition law.

References

Baars, B.J., 1997, *In the theatre of consciousness: The workspace of the mind*, Oxford University Press. Oxford.
Changeux, J.-P., 1983, *L'homme neuronal*, Fayard, Paris.
Edelman G.M., 1989, *The Remembered Present*, Basic Books, New York.
Edelman, G.M. & Gally, J.A., 2001, Degeneracy and complexity in biological systems, *Proc. Natl. Acad. Sci. USA* 98, 13763-13768.
Ehresmann & Vanbremeersch, 1993, Memory Evolutive Systems: An application to an aging theory, in *Cybernetics and Systems*, Tata McGraw Hill Pub., New Delhi, 190-192.
Ehresmann & Vanbremeersch, 2007, *Memory Evolutive Systems: Hierarchy, Emergence, Cognition*, Elsevier.
Ehresmann & Vanbremeersch, 2009, MENS, a mathematical model for cognitive systems, *Journal of Mind Theory* 0-2, 129-180.
Ehresmann & Vanbremeersch, 2011, Analysis of complex events in Memory Evolutive Systems, In: Cezon, M., Wolfsthal, Y. (eds.) ServiceWave 2011 Workshops. *Lecture Notes in Computer Science* 6569, Springer, pp. 153–159.

Eilenberg, S. & Mac Lane, S., 1945, General theory of natural equivalences, *Trans. Am. Math. Soc*. 58, 231-294. 1945

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Van J. Wedeen and Sporns, O., 2008, Mapping the Structural Core of Human Cerebral Cortex, *PLoS Biology* 6, Issue 7, 1479-1493. Online: www.plosbiology.org

Handbook of Theories of Aging, Second Edition (Ed**.** Vern L. Bengtson, Daphna Gans, Norella Putney, Merril Silverstein, Springer, 2008

Hebb, D. O., 1949, *The organization of behaviour*, Wiley, New York.

Radman, M, 1975, SOS repair hypothesis: phenomenology of an inducible DNA repair which is accompanied by mutagenesis, in *Molecular mechanisms for repair of DNA* (Ed. Hanawalt and Setlow), Plenum Press, 355-367.

de Vugt, E. & Meskers, C., Draft 2011

Weinert B.T. and Timiras P.S., 2003, Invited Review: Theories of aging, *Journal of Applied Physiology, vol. 95 no. 4 1706-1716* Online:

http://jap.physiology.org/content/95/4/1706.full

**

Table 1. Classification and brief description of main theories of aging
(From "Invited Review: Theories of aging", Weinert and Timiras, 2003)

Biological Level	Description
Evolutionary	
Mutation accumulation	Mutations that affect health at older ages are not selected against.
Disposable soma	Somatic cells are maintained only to ensure continued reproductive success; after reproduction, soma becomes disposable.
Antagonistic pleiotropy	Genes beneficial at younger age become deleterious at older ages.
Molecular	
Gene regulation	Aging is caused by changes in the expression of genes regulating both development and aging.
Codon restriction	Fidelity/accuracy of mRNA translation is impaired due to inability to decode codons in mRNA.
Error catastrophe	Decline in fidelity of gene expression with aging results in increased fraction of abnormal proteins.
Somatic mutation	Molecular damage accumulates, primarily to DNA/genetic material.
Dysdifferentiation	Gradual accumulation of random molecular damage impairs regulation of gene expression.
Cellular	
Cellular senescence-Telomere theory	Phenotypes of aging are caused by an increase in frequency of senescent cells. Senescence may result from telomere loss (replicative senescence) or cell stress (cellular senescence).
Free radical	Oxidative metabolism produces highly reactive free radicals that subsequently damage lipids, protein and DNA.
Wear-and-tear	Accumulation of normal injury.
Apoptosis	Programmed cell death from genetic events or genome crisis.
System	
Neuroendocrine	Alterations in neuroendocrine control of homeostasis results in aging-related physiological changes.
Immunologic	Decline of immune function with aging results in decreased incidence of infectious diseases but increased incidence of autoimmunity.
Rate-of-living	Assumes a fixed amount of metabolic potential for every living organism (live fast, die young).

Table 2. Internal monitoring project of some physiological functions and aging pathologies, with real time data integration for prevention and start of repair

Physiology				
	Internal interfaces	Internal automatic measures	Internal strategies	External Strategies
Muscles	Multiple nanometric sensors and 1 specific chip integrating all the muscular data	Electromyography Enzymatic measure of rhabdo-myolysis. Differential measures of sarcopenia by constant measure of muscle mass near the sensors	Muscle electrostim-ulations depending on the results of the data on the chip by activation of double action sensors	
Vision	Glass-analysis during reading, manual or physical activity, twice a month during 2 hours	Analysis of convergence, keenness and reactivity abilities to change of position, reading (oculo-motricity)	Data sent from the chip to the external terminal	Adapted training and re-education sessions (from the external terminal to adapted peripherals)
Audition	Subcutaneous sensors	Measure of the vestibular action potentials		
Pathology				
Lungs	Multi-sensor monitoring	Enzyme assays of lung inflammation, blood gases test	Specific alarms generated by the chip and sent to the external terminal	Diagnosis and treatment worked out by the external terminal
Arteries		Sensors of embolism, thrombosis, artery inflammation		
Veins				
Heart		Enzyme assays of ischemia, cardiac decompensation, embolism		
Metabolism		Metabolic balance		
Kidney		Kidney function		