ServiceWave 2011 Conference
Poznan October 2011

An Aging Theory based on a cascade of U-CEP in organisms up to brain functioning

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Extended Abstract

What are the causes and effects of Aging? Organisms are subject to constraints imposed by the interplay between predetermined procedures with limited capacities for repair, and unpredictable external stochastic events. Accounting for this fact, numerous biological or physiological theories of aging have been proposed. Most of them approach the problem either in the evolutionary context, or in a local manner, stressing the role of a particular factor intervening at a certain level; and they do not allow for an integrative theory.

On the contrary, the theory described here proposes a global approach, based on a uniform process: ubiquitous complex events processing decreases the stability and flexibility of various components and slows their inter levels and intra-level communications, whence a loss of relative synchronicities between the operations of the organism at its different levels, up to brain functioning and mental processes. It is at the root of our theory of aging by a *cascade of re-synchronizations* at increasing levels (Ehresmann & Vanbremeersch, 1993).

The theory is developed in the frame of the *Memory Evolutive Systems* (Ehresmann & Vanbremeersch, 2007), a mathematical model (based on category theory) for multi-scale complex systems such as organisms of any nature and cognitive systems. These systems have a tangled hierarchy of components varying over time, and their dynamic is modulated by a network of internal co-regulators with different rhythms, functions and logics, operating with the help of a flexible long-term 'memory'. Their complexity and flexibility depends on a 'degeneracy property', called the *Multiplicity Principle*, which ensures the existence of *multiform* complex components which can operate under different modalities through structurally different and possibly non-connected lower level decompositions. In ServiceWave 2010 we have shown how U-CEP plays an important role in such systems (Ehresmann & Vanbremeersch, 2011).

1. An organism as a Memory Evolutive System

Though the theory could be applied to any kind of living or socio-economic system, the generic example we consider is the organism of a higher animal

1.1. *The hierarchy of components*

The organism has a hierarchy of components of various levels: atoms and molecules, macromolecules, infra-cellular structures, cells, tissues and organs, large systems (such as the immune or the neural system). The components at a time *t* are taken as the objects of a (directed multi-)graph

H_t whose arrows (or 'links') model channels carrying their interactions. H_t becomes a category*[1] by taking for composite of 2 successive arrows their combined effect.

To account for their hierarchy, the objects are distributed in a finite number of levels of increasing complexity, the objects of a certain level being homogeneous between them, but more 'complex' than those of lower levels. More precisely, each object C of level n+1 is 'complex' in the sense that it has some internal organization into a pattern* P of linked lower level components which it 'binds', so that P, operating as a whole, and C, by itself, have the same functional role. For instance, a tissue binds the pattern of its cells. In our model C is represented as the colimit* of P in H_t. Then C has a '*ramification*' down to the atom level 0, obtained by taking a lower level decomposition P of C, then lower level decompositions of the components of P, and so on down to level 0.

It is known (Edelman & Gally, 2001) that an organism satisfies a *degeneracy* property at its various levels, which we call the *Multiplicity Principle*: there are *multiform objects* C which admit several decompositions into structurally different and non-connected 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 at the basis of the emergence of higher complexity and of the flexibility of the organism (Ehresmann & Vanbremeersch, 2007).

1.2. *How the organism evolves; the complexification process*

The organism undergoes modifications over time through internal or external events. The global change from t to t' is modeled by a *transition* functor* from a sub-category of H_t to $H_{t'}$ which 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 organism will be represented not by one category but by the family H of categories H_t indexed by the life-time, and the transitions between them; these transitions satisfy a transitivity condition so that a component C of the organism is represented by the family of its successive states during its existence.

The changes result from events of the following kinds: suppression or decomposition of certain objects (catabolism, for example), absorption of external elements (endocytosis), formation of complex objects by gluing new patterns (biosynthesis of macromolecules), or strengthening of preexisting patterns in a more coherent and structured association (as during learning when there is the formation of synchronous 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* (Ehremann & Vanbremeersch 2007) explicitly describes the configuration of the organism after realization of a procedure of this sort.

1.3. *Stability span. Propagation delays*

The organism is subjected to material constraints which will play an essential role in aging. They are related to the stability of the components and the rapidity of their interactions.

A complex component maintains its identity and homeostasis despite the progressive modification in time of its internal lower level organization. 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 measured by their half-life which will be shortened when the population is unstable. To model this, we use the fact that several patterns may have the same colimit.

[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. our book (Ehresmann & Vanbremeersch 2007).

The *stability span* of a component C of level n+1 at time t is defined 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. Roughly the variation of P is progressive enough and it does not change 'too much' during the entire period δt. This period depends both on the object, its level and the date t.

The links represent informational messages (*e.g.* presence of an antigen) or energy transfers (command of effectors), whose transmission requires a certain latency delay. To model this, we associate to each link its *propagation delay* which may vary over time. A simple chemical message is sent more rapidly than a humoral response requiring the synthesis of various products.

2. The dynamic and its self-organization

The dynamic of the organism is modulated by a net of internal organs of regulation of different levels, called *co-regulators*, whose cooperation/competition assures a functional control and permits an adaptation of the state of the system to external and internal events. At each hierarchical level there are one or more co-regulators. Among them: protein networks, intracellular effectors, cell regulatory networks, cells, tissues, hormonal controls, large systems, .,. They operate with the help of a central long-term *memory* storing different innate or acquired inner processes and procedures at the basis of the functioning of the organism, as well as main past ubiquitous events.

2.1. *Dynamic of one co-regulator*

A co-regulator CR is a specialized sub-system of the organism which operates stepwise, 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 from t to t' consists of different phases:

(i) Reception and analysis of the partial information accessible to CR through the links arriving to it around t, leading to the formation of its *landscape* (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 memory of innate or acquired inner procedures in relation with the functions of CR; for instance replication of the DNA for a cell. Then its commands 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.

2.2. *The interplay among co-regulators*

Up to now 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'. 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 sent 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 some commands may be eliminated, 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.

2.3. *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. This rhythm is measured by the average duration of one of its steps around a 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 necessitating a *re-synchronization*.

Indeed, the period *d* of CR 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* of links allowing the formation of the landscape and the sending of commands. Moreover the components intervening in the landscape must keep their complex identity during the step so that their least stability span *s* must be much greater than *d*.

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 the SOS system for DNA repair, Radman 1975).

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*.

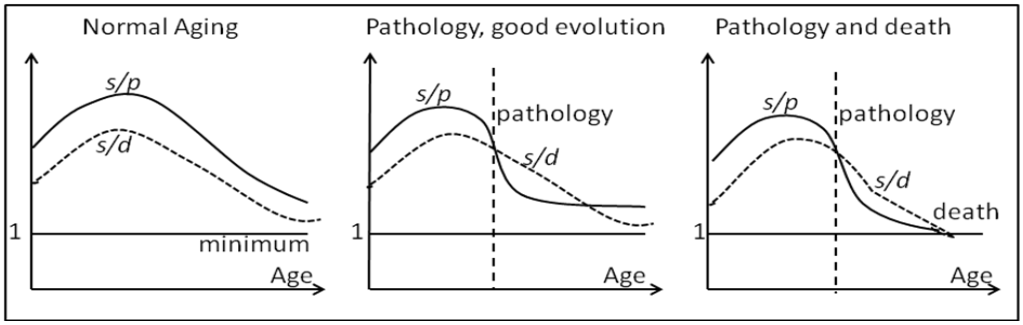
Deleterious events such as fractures, dyschronies and re-synchronizations can backfire through the co-regulators of various levels, possibly leading to a *cascade of re-synchronisations* to avoid a "dynamic disease".

2.4. *Consequence for aging*

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 *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). Let us note that 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.



In a pathological event implicating 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.

3. **Role of U-CEP in brain and mind aging**

The brain is a higher component of the organism, and the neural system with its neurons and synapses is an evolutive subsystem which plays a motor role in its functioning, hence also in aging. However this role also depends on the formation of mental objects and processes which are not 'physical' entities and thus are not components of the organism as such, though generated by it. To account for them, we extend the above theory in the frame of the integrative model MENS for the neuro-cognitive-mental system (Ehresmann & Vanbremeersch 2007).

3.1. *The model* MENS

MENS is a memory evolutive system based on the *Evolutive System of Neurons* NEUR which 'has' for components the neurons and for links between them synaptic paths. The higher levels of MENS are obtained by successive complexifications of NEUR, and its components, called *category-neurons*, represent mental objects looked at as the binding of more or less complex and distributed *synchronous (hyper-)assemblies of 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 is the colimit of P) in MENS**.** The "degeneracy of the neural code" (Edelman, 1989) implies that different assemblies of neurons may have the same functional role though not necessarily interconnected, and M will be the colimit of each of them. Thus M is a multiform object, with multiple

physical realizabilities by synchronous assemblies of neurons, and MENS satisfies the Multiplicity Principle. It allows constructing both simple and complex links (cf. Ehresmann &Vanbremeersch 2007) between category-neurons. We obtain MENS by iteration of such complexification processes.

What we have said about the self-organization of an organism can also be applied to MENS. Its co-regulators are based on more or less extended specialized brain modules, and they help developing a robust though flexible memory, with enough plasticity for adaptation to changes. The dynamic is modulated by their interplay, and the synchronicity laws are still valid for them, with the possibility of cascades of re-synchronizations due to more instability and longer propagation delays. The above aging theory for an organism extends to the neural, mental, cognitive and psychic domains. Let us see what are its effects on higher mental processes.

3.2. *Evolution of higher mental and cognitive processes*

These processes depend on the development over time of the *Archetypal Core* AC, which is a subsystem of the memory formed by higher order category-neurons integrating significant memories, with many lower level decompositions and possibility of switches between them. Their strong and fast links form *archetypal loops* self-maintaining their activation. AC embodies the complex identity of the system ('Self'), and acts as a *flexible internal model* It is based on the neural core (Hagmann & al, 2008) which participates in the main mental functions.

An unexpected event, such as a fracture to a higher co-regulator, increases the attention, thus activating part of AC**.** The activation diffuses through self-maintained archetypal loops, and then propagates to lower levels through decompositions and switches between them. Thus a large domain of MENS is activated and its activation maintained for some time. Transmitted back to higher level co-regulators directly linked to AC, it allows the formation of a *global landscape* GL uniting and extending their landscapes and with a longer span time (cp. the "theater" of Baars, 1997).

Higher mental processes will develop in GL, in particular conscious processes by a two-steps integration of the time dimension:

(i) A *retrospection proces*s (toward the past) in the global landscape GL allows recollecting the recent past, "sensemaking" of the present, 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 'scenarios' are built. Once a scenario is selected, the retrospection process allows back-casting to find sequences of strategies able to realize it.

In aging, 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. 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.

Practical conclusion

In this paper, we have shown how complex event processing plays an important role in aging, and we have proposed a theory of aging for an organism (up to the mental) by cascades of re-

synchronizations and loss of flexibility. It reveals some of the main mechanisms which can go wrong during aging.

Can we use it for preventing deleterious events and helping aged people to keep a quality of life in spite of their deficiencies? This is an important social problem in our aging populations. 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 the following table, due to one of the authors, Jean-Paul Vanbremeersch, in view of his experience as a geriatric physician, medical coordinator of an old people's home.

<table>
<tr><th colspan="5">Internal monitoring project of some physiological functions and current aging pathologies,
with real time data integration for prevention and start of repair strategies</th></tr>
<tr><td colspan="4">Physiology</td><td></td></tr>
<tr><td></td><td>Internal interfaces</td><td>Internal automatic measures</td><td>Internal strategies</td><td>External Strategies</td></tr>
<tr><td>Muscles</td><td>Multiple nanometric sensors and 1 specific chip integrating all the muscular data</td><td>Electromyography
Enzymatic measure of rhabdo-myolysis. Differential measures of sarcopenia by constant measure of muscle mass near the sensors</td><td>Muscle electrostimula-tions depending on the results of the data on the chip by activation of double action sensors</td><td></td></tr>
<tr><td>Vision</td><td>Glass-analysis during reading, manual or physical activity, twice a month during 2 hours</td><td>Analysis of convergence, keenness and reactivity abilities to change of position, reading (oculo-motricity)</td><td rowspan="2">Data sent from the chip to the external terminal</td><td rowspan="2">Adapted training and re-education sessions (from the external terminal to adapted peripherals)</td></tr>
<tr><td>Audition</td><td>Subcutaneous sensors</td><td>Measure of the vestibular action potentials</td></tr>
<tr><td colspan="4">Pathology</td><td></td></tr>
<tr><td>Lungs</td><td rowspan="6">Multi-sensor monitoring</td><td>Enzyme assays of lung inflam-mation, blood gases test</td><td rowspan="6">Specific alarms generated by the chip and sent to the external terminal</td><td rowspan="6">Diagnosis and treatment worked out by the external terminal</td></tr>
<tr><td>Arteries</td><td rowspan="2">Sensors of embolism, thrombosis, artery inflammation</td></tr>
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<tr><td>Metabolism</td><td>Metabolic balance</td></tr>
<tr><td>Kidney</td><td>Kidney functions</td></tr>
</table>

***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: $P_i \to A$ such that $a_i = fa_j$ for each distinguished link f: $P_i \to P_j$.
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.

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