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Associations for the Reciprocal and Mutual Sharing of Advantages and DisAvantages (ARMSADA) - A Fruitful Predictive Paradigm

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Abstract: To survive the living systems must to eat and not to be eaten. But, soon or late, every one is eaten. The law of the strongest is not-at-all the best! The only way to escape for a moment from the struggle for life is to enter into an Association for the Reciprocal and Mutual Sharing of Advantages and DisAdvantages (ARMSADA http://armsada.eu). A lichen, which is both an organism and an ecosystem, a cell, which is both an ecosystem and an endosyncenosis (ceno: to meet and fuse, syn: into a system, endo: with a new internal structural and functional organization), both are ARMSADAs. A neuron emerges from the “unity through diversity“ between a population of Schwann's cells and a giant cell. The legumes' nodes emerge from the fusion of a population of Monera with an organism. The cell emerged with the help of a RNA virus from a microbial mat of Monera. In their new endophysiotope (endo: internal, tope: space, physio: of functioning), the parceners are absolutely dependent from each others. Every ARMSADA emerges when the partners lose simultaneously the capacity to kill the other one(s). In the new Whole, all that is an advantage for a partner is a disadvantage for the other one(s). The “parceners“ are linked together “for the best and for the worst”. Symbiosis is not at all a win-win association but an ARMSADA: the benefits are not for the partners but only for their Whole which expresses new “abilities”. But, through the iteration of the process of new ARMSADAs' emerging, the new -more and more complex- “system-of-systems” is, more and more, independent of its ecoexotope (exo: external, tope: space, eco: of inhabitation). The endophysiotope of a i level of organization is the ecoexotope of previous i-n levels. So the Whole is also less and more than the sum of its parts: because of the semi-autonomy of the parceners abilities of the previous levels are lost but new are gained. There are never advantages without disadvantages! To survive that is to turn disadvantages into advantages and to avoid advantages turning into disadvantages: the survival of the fittest is the survival of the best fitted mutual sharing association! The systemic disfunction of its ARMSADA explains the cell apoptosis as the result of the death of one endangered internal partner (the bacterial parts: the population of mitochondria or the nucleus) which results into the death of the whole endosyncenosis. Cancer also is a breaking of the cell's ARMSADA. Cells that should have to die, because of external dangers, “thanks” to the escape of internal dormant viruses do not. Through this metamorphosis their new endophysiotope survives but their previous ecoexotope, the organism, is altered and endangered. Into an ARMSADA each partner can survive only if the other ones survive first. Man is not an exception! AIDS and cancer curative vaccines that had been proposed using this ARMSADA paradigm are coming effectively in practice. Ecosystems management must take into account that paradigm before any change, economic and social managements should too.

Keywords: apoptosis; breakage; cancer; cell level; curative vaccines; ecosystem level; governance; lichen; limitations; limits; metamorphosis; Monera; mutualism; network; organism level; parceners; prisoners' dilemma; symbiosis; threshold; trans-disciplinary; virus; wholeness

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On the ice-bank of the Antarctic Continent Penguins are walking slowly. They have no need to run, there is no danger for them here. And that is a great advantage because the Penguins' body is not built for running! But there is nothing to eat on the ice-bank. That is a great disadvantage! As it is very cold an endotherm needs a great food amount to survive. ***There are never advantages without disadvantages!*** Into the Antarctic Ocean water, Penguins are swimming very fast. They have two reasons to do so. Firstly they must swim faster than the fishes. To survive they have to eat a lot of them. There is a lot of fishes there and the Penguins' body is built to swim very fast. That is a great advantage! Secondly they must swim faster than the Killer Whales that are eating Penguins to survive too. Wherever the Penguins are there are never advantages without disadvantages (Bricage, 1991, 1998). ***They will survive as long as they can transform disadvantages into advantages and prevent advantages from turning into disadvantages*** (Bricage, 2000). No difference between a Penguin, a multicellular macroscopic organism, and an Amoeba, a microscopic cell that is trillion times smaller in volume, both are predators and preys too, depending on the Beings' surrounding they are living with. An Amoeba is a predator that eats bacteria -its preys-, like a Penguin eats fishes. But sometimes certain bacteria that were engulfed by the Amoeba are predators too and they do eat the eater. The advantage to be able to catch bacteria sometimes turns into a great disadvantage too! There is ***only 1 simple rule: to survive that is 'to eat and not to be eaten'*.** Man is not an exception (Bricage, 2007, 2010b, 2014a). Every living system (a cell, a lichen, a forest) is a wholeness, made of actors with their interdependent links (Figure 1). The system stability and resiliency, while facing to changes of its internal medium -its endophysiotope: ENDO (from Greek: *endo* internal, *tope* space-time, *physio* of functioning)- and its external surrounding -its ecoexotope: EXO (from Greek: *exo* external, *tope* space- time, *eco* of inhabitation)-, is depending on the number of actors and the percolation process of their interactions (Bricage, 2014b).

1 What is an ARMSADA?

Ubiquitous widespread organisms, Lichens are able to colonize EXOs where no other life form can survive. Why? Monera are made of a one-membraned single compartment. How the exchanges controlling membrane does isolate the ENDO from the EXO? Outside the membrane, a wall determines the form. What for? Protoplasts, without a wall, are not resistant to osmotic shocks, what is a disadvantage, but they deform easily, what is an advantage. There are never advantages without disadvantages (Bricage, 1998).

1.1 Lichens: governance within a level of organization

A lichen is a box that is built with the body of a heterotrophic fungus species. In the box is encased a population of photoautotrophic plant cells of an algal species. The two are inseparable. They cannot be cultivated separately. And if one dies the other one dies too. It is an ARMSADA, ***an association in which all that is an advantage for a partner is a disadvantage for the other one, and reciprocally.*** The fungus offers the algal ENDO the mineral nourishment and its ENDO as a home. It is a great advantage for the alga that is then protected against predators and the usual variations of the EXO that would impair its survival if the alga would be free. That is a great disadvantage for the fungus who must consume a part of its matter and energy -of its ENDO- to allow the survival of the algal ENDO. ***But all that is an advantage must be paid with a disadvantage***. Soon or late, the fungus filaments eat the algal cells, like Man species eats domestic animals or cultivated plants (Bricage, 2010a). That is a great disadvantage for the alga and a great advantage for the fungus. All together are eating the matter and energy of the other one. Besides the **capacity of hosting** (HOSTING) of the EXO of the global Whole, each one is furnishing a HOSTING for the local ENDO of the other one. Its is a mutual and reciprocal predator-prey balanced relationship. Into the Whole, each one and the Whole may survive only if the other one does survive first. The Whole (the system) and the parts (the sub-systems) are both more and less than each sub-parts (Bricage, 2000, 2005b, 2009, 2010a; Zimmerman 2013). Sometimes a third partner, a bacterium, may enter the association. The Whole is an endosyncenosis (CENO: to meet and fuse, syn: into a system, ENDO: with a new internal structural and functional endophysiotope organization) (Bricage, 2005a).

The survival of lichen organisms is based on ***a steady state of advantages and dis-advantages sharing between the partners***. As lodging host, the fungus partner pays a double cost: the cost of the accommodation of the alga, the cost of a growth limited by that of the alga. In order that the fungus survives it is ***necessary*** that the alga survives first (Bricage, 1998, 2000, 2010b). To survive, the algal partner, the lodged host, also pays a double cost: the cost of its growth limited by that of the fungus, the cost of the survival of its population of cells, through the non-survival of a part of it, which is eaten by the fungal filaments. ***To survive that is to eat and not to be eaten.*** The lichen organism is an ecosystem that contain a food chain. Soon or late it is impossible not to be eaten. The growth of each partner is ***limited*** by the growth of the other one. In order that one may survive, ***the other one must survive first****.* The fungus has to limit its growth demands with respect to the alga, ***reciprocally*** the hosted alga may develop only ***into the limit of the carrying capacity of the hosting*** fungus. ***Their mutual survival is depending on reciprocal limitations.*** But, the surviving is possible and the acquisition of new capacities is possible, even in conditions of global growth close to zero. But, if the one dies, the other dies too. The 2 totally interdependent partners form ***a wholeness, an ecosystem***. Together they can survive in ecoexotopes where there is no HOSTING for each partner separately. ***This symbiosis is not a win-win association, but a partnership of mutual sharing of profits and injuries***. The partners are not simply added but combined and inter-penetrated to form ***"an Association for the Reciprocal and Mutual Sharing of Advantages and DisAdvantages" (ARMSADA)***. They metamorphose themselves simultaneously in a new, unique, different, whole organism. Their autonomy is built on their interdependence (Bernard-Weil & Bricage, 2007).

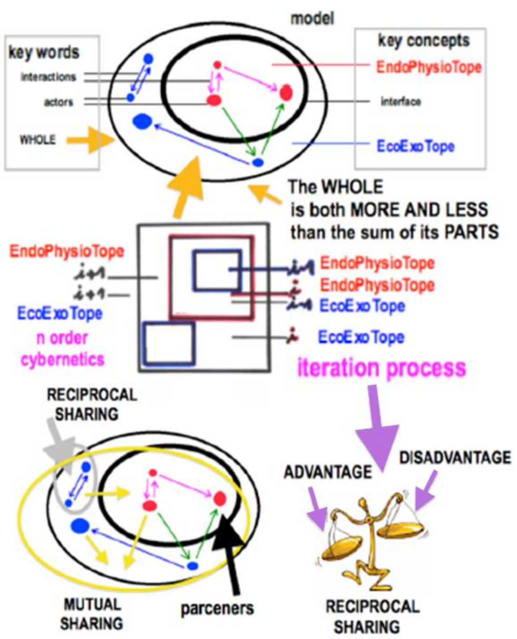

Figure 1: <u>What a system is</u>: ***ecoexotope and endophysiotope****.*

*-Top- A system is made of 3 kinds of entities: **the actors** (colored points), **their interactions** (blue, green and red arrows) & **their Whole** (the system) (Bricage, 1991, 2000).*

*-Middle- A system is always a system-of-systems: the endophysiotope **ENDO** of a level of organization **i** is the ecoexotope **EXO** of survival of previous **i-n** levels. Due to the actors semi-autonomy, abilities of previous levels are lost, new ones are gained. **"In space** (Bricage, 2000, 2002, 2014c), **time** (Bricage, 2013), **functionality** (Bricage, 1991) **and interactions** (Axelrod, 2006; Bernard-Weil & Bricage, 2007; Bricage, 1998), **the Whole is both less and more than the sum of its parts** (Bricage, 1991, 1998)."*

*-Down- Each living system is a guest of its hosting EXO, integrated into food chains it is undivided from all the other living forms. In order to survive it must first 'to eat'. Then, if it may 'not to be eaten', and if its ENDO can grow in mass, it must itself 'to survive its self', to generate an offspring, and eventually to grow in number (Bricage, 2000, 2002). **Food chains are juxtaposed and encased like times and spaces** (Bricage, 2009; Zimmerman, 2013). Systemic constructal law: networking Modeling. Every change of EXO or ENDO is feeding back, directly or indirectly, changes of ENDO and EXO themselves. Every actor is acting not only on itself but also on its adjacent superior and inferior levels of organization. Every local or global changes results, soon or late, directly or indirectly, on other global or local changes. You can look at Morin (2014), for a discussion about what a system is, and Zimmerman (2013), for the Universe as an emergent system (Bricage, 2009). There are never advantages without disadvantages: all that is an advantage for a sub-system is a disadvantage for another one. Partners are parceners only if they share advantages and disadvantages locally between them-selves and globally with their Whole, **for the best and for the worst**. Each one may survive only if all the others must survive first : UNUS PRO OMNIBUS OMNES PRO UNO.*

The ENDO organization level of a lichen is higher than the ENDO organization levels of each its sub-system (Figure 1). The lichens elaborate molecules that no other fungus or alga can elaborate. They are ecosystems that contain a food chain.

1.2 Decision-making in a community: the cell endosyncenosis

Into a green plant cell, as into a lichen, a compartment -the chloroplast- is specialized into the production of organic matter. Another one -the mitochondrion- is specialized into the consumption of that organic matter. The chloroplast is **the local compartment** that is specialized for the fixation of solar energy, carbon dioxide and water, into organic matter. Another local compartment, the mitochondrion is specialized into the production of energy from the consumption of organic matter. As in the lichen, it is also a local predator-prey like relationship, nevertheless it is ***a 'take, make, waste, but recycling association'.*** The mitochondrion eats the sugars that are synthesized by the chloroplast for the global cell use. But doing so it produces wastes, water and carbon dioxide, that are the raw materials for the chloroplast's metabolism. Inversely, the chloroplast's metabolism produces oxygen which is the raw material for the mitochondrion to use sugars. Another juxtaposed compartment, the peroxisome, recycles into water the toxic peroxide wastes the mitochondria and chloroplasts are producing together. The cell is made of local compartments of Monera origins, chloroplasts, mitochondria, peroxisomes that are juxtaposed to each other and encased into an other one, the hyaloplasm, also of Monera origin (Bricage, 2005a, 2008a). Their global whole is an endosyncenosis (ceno: to meet and fuse, syn: into a system, endo: with a new internal structural and functional organization), a global "E PLURIBUS UNUM" new System-of-Systems that has emerged step by step through ARMSADA "sprouting". ***All that is an advantage for a local partner is a disadvantage for all the other ones.*** All are mutually fused in a Whole, ***for the best and for the worst***. Each one may survive only if all the others must survive first : UNUS PRO OMNIBUS OMNES PRO UNO (Bricage, 2010a). What are wastes for some are aliments for others, and reciprocally. All products and by-products are mutually shared. It is through their **mutual (global) and reciprocal (local)** interactions that the parceners survive in a kind of half-autonomy that renders all more independent of the EXO that they would be if free, separately: IN VARIETATE CONCORDIA (Bricage, 2010a). All at once they are sharing internal dangers of their new EXO -the cell ENDO- and external dangers of their ancient EXO -the cell EXO- (Bricage, 2002).

Being more and more dependent for their collective sharing of dangers of the cell's ENDO -through inter-recycling-, they become more and more independent of their ancient EXO which is still the EXO of their new Whole: the cell. The internal compartment of mitochondria or chloroplasts is sequestered outside the hyaloplasm: 2 membranes are building a limiting interfaces between the ENDO of mitochondria or chloroplasts and the ENDO -the hyaloplasm- of the cell (Bricage, 2005a). The cell is a resilient system that is sustainable for all the partners because it is sustained by each one (Bricage, 2010a). The cellular organization level is higher (more recent) than the organization levels of the organelles (mitochondria and chloroplasts) that constitute the cellular self. The cell is a new mode of integration, a new blueprint, with **a new ENDO into a new EXO** (Figure 1). The hyaloplasm, compartment of hosting, protection, trades and communication, includes all organelles. As water tanks, vacuoles are close to both mitochondria and chloroplasts, because mitochondria produce water, a respiratory waste, and chloroplasts consume water as raw material for photosynthesis. Foods for ones are waste products for other ones. Mitochondria that consume oxygen and sugars (foods for the respiratory process) are close to chloroplasts that release sugars and oxygen (waste product of photosynthesis). Waste products of ones are foods for other ones. Mitochondria emerged from ancient bacteria. Formerly free-living they invaded the hyaloplasm of the ancient **welcome system** from which the cell originated, so emerged an **ARMSADA** in which mitochondria eliminate oxygen, a toxic for the cell! In counterpart the cytoplasm lodges and feeds mitochondria. This disadvantage for **'the resided', inhabited or lodging host** is the cost of the advantage of its protection by **'its residents', inhabitants or lodged guests**. An ecosystem like a cell is **an endosyncenosis (CENO)**, it has emerged by juxtaposition and encasement of a variety of previous pre-existing antagonist life forms (Figures 1 & 2). Like a forest, with preys and predators (Bricage & al., 1989), a cell is **an ecosystem of organisms** (Bricage, 2005a).

1.3 EcoSystems are Not 'Win-Win' Associations

A CENO is a resilient system that is ***sustainable for all the partners because it is sustained by each one*****.** The survival of a lichen or a cell depends on a steady state for the sharing of advantages and of disadvantages: benefits for the host ENDO are damages for the guest ENDO and reciprocally. The symbiosis is ***an association for the mutual sharing of profits and losses but not an association 'for mutual benefits'!*** The growth of each is limited by the growth of the other(s). This ***'unity through diversity' long-term partnership*** for the mutual sharing of profits and injuries has been allowing for billions of years the survival organisms who, for supporting EXO changes, have joined together into wholenesses, which have allowed the increase of the HOSTING only through the increase of their **capacity to be hosted** (HOSTED). The ENDO development is not durable, if it is not sustainable for the EXO (Bricage & al., 1989). The ENDO survival is durable if it is sustainable for the EXO, namely if it does not impair the durable survivals of the other organisms that are sharing this EXO. With time, the epigenetic heritage of the parental generations is integrated into the genetic heritage of the offsprings (Bricage, 2002). ***'To convert disadvantages into advantages and to prevent conversions of advantages into disadvantages.'*** is the natural survival's rule (Bricage, 1998; 2008b).

2 How will an ARMSADA emerge?

To eat, an Amoeba (a predator) captures and digests bacteria (preys). Its capacity of phagocytosis is **an advantage** for the Amoeba survival. But some bacteria are able to survive to ingestion by elaborating a wall. Captured bacteria can digest the Amoeba, the phagocytosis **advantage has become a dis-advantage** for the Amoeba! Invaded by bacteria, few amoebas are able to survive to their resident living bacteria. After a metabolic depression, they grow again, and live on, as at the same time bacteria grow and live on. **A steady state** has been established between the inhabitants (the 'residing' hosts) and the inhabited (the 'resided' host)! The capture **dis-advantage has become an advantage** for the 'aliens', the residing hosts, and, simultaneously, the disadvantage of the initial invasion by aliens has become an advantage for the resided host! ***The local disadvantage of the loss by each ones of the capacities to kill the other one has become a reciprocal global advantage for the survival of the two***. The two inseparable co-partners, form a new biological system, an organism of a higher organization level (Bricage, 2009).

How and why appeared (Bricage, 2005a, 2005b) such symbiotic associations?

2.1 Struggle for life: cooperation and modularity

The comparison of the cell's organelles with Monera and the study of the apoptotic, necrotic and cancerous cells, make possible to resume the paradigm of the cell's phylogeny (Bricage, 2005a, 2008a, 2009). Monera aggregation or fusion is triggered by a high pH, an osmotic shock or a virus. Agglomerated their ENDO are able to resist to a hard EXO. Osmotic stresses can induce their ENDO acidification and sporulation. An amalgamation of a population of side by side aggregated Monera, but without membranes coalescing, had made their ENDO to become continuous, and was at the origin of both the nuclear envelope and endoplasmic reticulum of the cell (Bricage, 2005a). These new internal spaces were delimiting thus a continuous intermediary lumen, an EXO, which has played the role of a buffer between the ancient ENDO and the previous EXO. It allowed a new network, the Golgi apparatus, to emerge with a new HOSTED. The first metamorphosis resulted from a nutriments depletion and an accumulation of waste products. The singled-membrane lysosomes and peroxisomes originated from the fusion of Monera with the same type of membrane interface. The hyaloplasm with its ancient anaerobic metabolism of sugars is not specialized. The peroxisome is an ubiquitous and pluripotent compartment. The nucleus is an emergent compartment that is specialized in nucleic acids synthesis and storage. The endoplasmic reticulum and Golgi apparatus are specialized in proteins metabolism.

2.2 To survive, that is 'to eat and not to be eaten'

Ancient Monera survived from eating early organic compounds but were eaten by viruses. Bacteria and viruses that are eating them (bacteriophages), cells (that descend of bacteria) and viruses that are eating them (cytophages), are engaged in a never-ending predator-prey struggle (Figure 2), an arms defenses race, with an escalade of violence. The nude centrosome, which its structure of 2 nude empty viral capsids, is the fossil of the RNA virus that ensured the melting of Monera within the same common membrane (Bricage, 2005a). ***An early constrained danger, when discharged, becomes a KeyStone Actor*.** Each organelle has its specific phages that descend from previous free-living Monera phages. The mitochondria and plastids, which are delimited by two membranes, originated from the merging of antagonistic preys and predators into an ARMSADA. The cell is a 'Matryoshka' box (Figure 1)! The inhabitant organelles are protected from ancient viruses by the hyaloplasm, their inhabited compartment of welcome in which the abundance of water favors the hydrolysis, not the dehydrating syntheses. Phagocytosis is an emergent process. Regularly, protagonists reply to an attack by a defense and to a stronger defense by a stronger attack. The no-resolution of the conflict, 'cause and consequence of the natural selection' (systemic constructal law), starts an escalation of ripostes with a cost always greater. The mitochondrion integration into the cell is an escalation end giving a cheap stable steady state which is imperative to optimize the local partners and global whole survivals. The mitochondrion is an hostage trapped into the hyaloplasm. Its outer membrane is a trace of the attack/defense balance system (Figure 2) during the sequestration process (Bricage, 2005a; 2005b; Kerr & al., 2006).

2.3 *A preventive deal...* : a 'unity through diversity' partnership for mutual sharing of profits and injuries, for local and global production, consumption, growth sharing and survival

The ENDO phenotype is changing with the EXO changes. *With time, the common becomes particular and the rare common* (Kerr & al., 2006). The metabolic pathways are juxtaposed and encased in the same manner the compartments that contain them are. The mitochondrion is specialized into the conversion of lipids and sugars in energy. As the mitochondrion, the chloroplast owns its nucleotides, proteins and lipids metabolisms, and a genome. The endoplasmic reticulum and Golgi apparatus are specialized in proteins metabolism. A cell is a mosaic of juxtaposed and encased organelles, with limited lifetimes. They are continuously recycled and renewed. In the hyaloplasm EXO there is a competition between the compartments ENDOs for nucleotides, fatty acids and amino-acids. The local competition between the parts is avoided through the global assistance for their Whole's survival. ***Exaptation results from modularity, recycling and pleiotropy***. Mitochondria eat waste products from the hyaloplasm and provide back useful products for chloroplasts and peroxisomes. Mitochondria and chloroplasts are ***working in constrained reverse ways***. Mitochondria stocks Ca2+, which content has to be maintained very low into the hyaloplasm. 'The survival of one, or of the Whole, has a prerequisite that all the other ones survive first, and reciprocally.' A mitochondrion hyperactivity provokes the cell ENDO apoptosis. The nucleus and mitochondria, foreigner ENDOs hosted by the hyaloplasm ENDO, are killed by its proteases. The no-self is rejected. 'In order the Whole (the symbiont) survives, it is necessary that each parcener (the endosymbionts) survives first.' All what is an advantage for a parcener is a disadvantage for the other ones and reciprocally. The peroxisomes and microsomes emerged from pluripotent, ubiquitous Monera whose pleiotropy permitted both their integration and the cell exaptation. Mitochondria and peroxisomes activities **mutually** control the cell's fate and are controlled **reciprocally** (Bricage, 2005a; Leng & al., 2014).

3 Why will an ARMSADA emerge?

One century ago was identified the first virus at the origin of a cancer (a leukemia of chicken). Others retroviruses, and the AIDS/HIV, were identified as to be also at the origin of cancers. In **AIDS** (**A**cquired **I**mmuno**D**eficiency **S**yndrome), with the invading of **HIV** (**H**uman **I**mmuno-deficiency **V**irus), like in cancers, cells display uncontrolled growth, destruction of tissues and spread. **H**uman **T-L**ymphotropic **V**iruses (**HTLV**) are associated with human cancers, as Human Papilloma, Hepatitis or Epstein-Barr Viruses. De-controlled genes cause over-expression of viral invading genomes (Bricage, 2008a). A link was evidenced between HIV infection and infectious diseases. AIDS linked cancer is increasing. Disseminated infections caused by Mycobacteria, which multiply in macrophages, are common in AIDS patients. Paradoxically **the predator is also a prey**: HIV is eaten by Langerhans cells, which derived from the same cell precursors that monocytes, that are eaten by HIV.

3.1 Life Dangers and Risks: Prevention and Curation

Whatever the level of organisation, the emergence of new living blueprints runs through the juxtapositions and nesting of few previous systems. The new Whole, which is more and less than the sum of its parts, emerges through simultaneous metamorphoses of the parts into the whole. But each host or guest maintains its identity into that new whole.

3.1.1 Advantages/Disadvantages balance: The Metamorphoses of the Living Systems

The partial autonomy of each partner is allowed through maintenance of individual and collective interfaces into the ENDO of the whole and of the whole into its EXO (Figure 1). The transition from one level of organization to an adjacent superior one is the result of the building of a new space-time network, an ARMSADA (Table 1). In a no-change EXO this allows the maintenance of the partners diversity and the unity of the whole. If the ENDOs or the EXOs are changing, this is the only way to make a new networking mode of integration. ARMSADAs emerge through an interactive fitness between parceners' EXO HOSTING and ENDO HOSTED, with the simultaneous losses by all of the capacity to kill the other ones.

The genome of any organism is hosting viral sequences. Genes of fly were identified in the Man's genome in 1992! Several hundreds of 'jumping' genes are hosted in our genome. At least 20 % of our genes are of viral origin. These endogenous **'constrained'** viruses are still active. They never express viruses, but confer a resistance against similar viruses or against other dangers. In the case of AIDS, a protein, APOBEC3G, prevents the liberation of the endogenous HIV by blocking replication. It also introduces mutations into the genomes that make the retrovirus unable to reproduce. Many genes can be controlled by viral promoters or activated by viral transcription factors. Many genes (like RNA coding genes) that are nowadays indispensable for the survival of a cell or the reproduction of an organism have originated from ancient viral lytic genes, particularly from retroviruses (Bricage, 2008a). Endogenous retroviral sequences are required for genes' tissue specific expression. Our retroviral heritage is a guarantee of our survival. But if bad located, sometimes in growth controlling genes, expressions may result in cancerization. Some opportunistic infections are specific of interactions between the HIV and other viruses like the Epstein-Barr Virus.

We can make vaccines against many viruses, but HIV research has not designed a AIDS preventive one. Viruses like phages are alternatives for drugs, a remedy for a viral infection or cancer (Bricage, 2008a). The defense against provirus excision and virus expression is in an infection with an other virus that restores apoptosis through the reversion of infected-cells to normal sick cells or kills the infected cells before the first hosted virus has been reproduced: HIV sick cell assassination through a sooner viral lysis or curative vaccine (Bricage, 2005b). More than 50 species of Mycobacteria have more than 10 plasmids (that easily transfer resistance genes) but also phages that killed them all 'specifically'. All were detected in AIDS patients! But 'domesticated' viral lysis can lead either to the lysis of tumors (or bacteria) or to growth of cancer or AIDS. Lymphocytes that express HIV antigenes do exist. HIV induced apoptosis of neurons is evidenced in the cerebral cortex. But in HIV induced apoptosis of lymphocytes much more cells die than infected ones.

3.1.2 How to turn disadvantages into advantages: a HIV curative vaccine strategy

A patented HIV-like retrovirus was evidenced in multiple sclerosis. Integrated into the genome, viruses induce changes that interact with non-coding genes expression. This can change the cell's fate in all ways (apoptosis, cancer) and the fate of the organism. The HIV genes that encodes for proteins show a great variability in sequences due to high number of errors made in the reverse transcription. That is **an advantage for the virus** because every new mutant can escape the previous neutralizing antibodies and new HIV strains become more abundant within their host before being eventually recognized and suppressed. To survive that is not only '*not to be eaten'* or '*not to be killed'*, but also ***'to turn disadvantages into advantages' and 'to avoid advantages turn to disadvantages',*** in order to reproduce. It is just what cancer or AIDS viruses are doing (Bricage, 2005b; 2008a). Even if a sharp decline in mortality due to AIDS has followed the introduction of antiretroviral tri-therapy, although the prevalence of HIV infection has not increased, in the USA the amount of cancers linked to AIDS or other viral sources is continuously increasing. High copy number of endogenous retrovirus families are hosted in the human genome. Mammals genomes contain a great array of repetitive viral sequences. These dangers, which are constrained, do not cause diseases and even are indispensable for the cell's and organism's survival. AIDS is the result of the non-control of a non-constrained danger. Foreign genes can be integrated like viruses. Silencing of these potential dangers (repression of their expression: 'constraining') is assumed with widespread translation inhibition mechanisms. Massive gene transfers are associated with endosymbiosis.

Why would HIV not be constrained as other invaders are? Endogenous para-retroviruses (derived from free DNA viruses) are inserted into plant chromosomes and not only they are silent but they also provide immunity against related viruses, with no sign of infection under a variety of growth conditions. Once silenced in an host, ancient free but hosted viruses will no more be freed, but remain active in non-host species. HIV is active in *Homo sapiens* but not in chimpanzee, which is hosting SIV from which HIV is derived.

3.1.3 How to turn disadvantages into advantages: a cancer curative vaccine strategy

The first found cancerous agents were viruses. Cancer may affect people at all ages, even fetuses, and risk tends to increase with age. A group of cells displays the traits of 'uncontrolled growth, division beyond the normal limits', invasion and destruction of adjacent tissues and spreading to other locations. Cancer is the result of the failure of the HOSTED of cells ENDO, in response to the failure of the HOSTING of their EXO, the organism (Bricage, 2008a). When the EXO is changing, a disadvantage can turn to an advantage and conversely. For stressed endangered cells, cancer is the way not to die. Cancer is a survival response for damaged cells! But with advantages and disadvantages that are unequally balanced between cells (Figure 2).

A good virus is not a dead one, but a quite alive one, whose ENDO is integrated into a cell, as the mitochondrial genome is integrated into that of the cell nucleus, or as the sheep organism needs a retrovirus to reproduce its self, ***like did 'natural selection' for 'constrained' dangers that are lodged in all genomes***. Thus the cost of breaking 'selected' gene associations is a slippage of an advantage to a dis-advantage, that we need to evaluate at all organization levels (Banks-Leite, 2014). Due to the robustness of the gene regulation processes, ARMSADAs are favored by natural selection both *in vivo* and *in vitro*. Expression of foreign genes in genetically modified cells with plasmid vectors is easy.

Hundred of phages, cancer-cell phages or virus-infected cells phages exist. Advances have been made in the way to seek them. A recombinant replication-defective chimpanzee adenovirus is used as a novel rabies virus vaccine. Non-pathogenic, targeting tumor cells anti-oncogenes and efficient recombinant vector productive, single-stranded DNA Parvoviruses are used for gene therapy. Recombinant derived vectors have been tested in many clinical models of human diseases, including cancer. They can be used to develop a cancer curative vaccine (Bricage, 2008a). The use of 'domesticated' viruses, 'harmless for our cells' and lodged within (Figure 2), is an alternative to drug treatments that generate resistances. HIV was eliminated with the transfusion to patients of hematopoietic stem cells at the origin of HIV resistant immune cells (Leng & et al., 2014), as previously proposed (Bricage, 2005b). This solution is not only curative for AIDS, but also preventive and curative for cancers. Homing into an ARMSADA protects against viruses attacks. The cell is an CENO within which a niche partitioning process increases the fitness of the Whole, the coexistence of the consumer parceners is 'fostered' by their resource-use differences.

Our ENDO owns and inherits both a HOSTING (as EXO of survival for other living organisms) and a 'to be welcome' capacity (into an EXO which is shared with other organisms). At the same time, normal events of the cellular metabolism activate both the expression of healthy genes, oncogenes or viral constrained dangers. ***The 'balance' advantages versus disadvantages is depending on the considered level of organization, into the space and through the time***. A transformation of a cell can result from a variety of metamorphoses depending '**the place of integration of the danger'** and **'the moment of its expression'** or not...

The stability of the association is in the key fact that *the virus does not kill the cell* and *reciprocally the cell does protect the virus of the killing by other cells*. Infectious particles are not liberated following the fusion of some transformed cells with non-transformed permissive ones. Preys or hosts and predators or parasites (like immune cells and HIV) struggle each other ***in a war neither with mercy nor with end***. Each defensive innovation of a prey causes an aggressive one of its predators. 'To attack is never the best defense', but 'to change' of food network (Figure 2)! Only the ENDO metamorphosis allows **to contain** dangers. The cancer cell fate, as that of a phage infected bacterium, depends on percolation interactions with invading viruses (Bricage, 2008b). As the previously proposed AIDS curative vaccine, built with HIV engineered stem cells (Bricage, 2005b), the application of the ARMSADA paradigm will allow to design new curative vaccines against cancers and HIV.

3.2 Ecoexotope & endophysiotope: integration governance

A swarm of bees is an organism. Into the Whole (the swarm system), the actors (the bees) are in interaction but only the swarm owns the characteristics of a living system. A single bee does not. But the bee is an actor of the survival of the ENDO of the swarm, which in return protects the bee(s), but between some limits, structural and functional limits of the ENDO and ecological ones of the EXO. A blood cell is a living system that is hosted into the living hosting system of our organism. The ENDO of the cell will survive as long as it can preserve its gauge invariance whatever are the changes of its EXO of survival. Into our organism all cells, like the swarm itself, are functionally defined both by their ENDO and EXO. They both define the system as a whole and the interface of exchange between ENDO and EXO. Each system is a local actor. It is spatially, temporally and functionally integrated into its whole of survival, the global actor, the multi-meta-system organism. To make models we need basic axioms and solid definitions, we need the design of new key words to represent new key concepts (Table 1). The EXO furnishes the ENDO a limited **HOSTING**. And the ENDO expresses a limited **HOSTED** by an EXO of hosting. The system is simultaneously: -the ENDO with its actors, -the EXO with other actors, -the network of interactions inside the ENDO, -the network of interactions outside into the EXO, -the network of interactions from inside to outside and back (the network of the networks), and -the whole. The cell is the adjacent inferior level of organization of that of the organism. And the ENDO of the organism is the EXO of survival of the cells. The organism, a System-of-Systems, is integrated into a superior adjacent level of organization, an ecosystem, which he/it shares with other organisms. When the EXO is changing, the ENDO must change too, in order to allow the survival of the Whole. Both together, EXO & ENDO are changing or not-at-all.

A harmless human tumor killing virus may be loaded into a cell type that houses to tumors. It infects all cells, but multiply only in cancer cells which it destroys rapidly, 1 cell producing 500 viral particles in 48 hours. Like the interaction between a predator and its prey, that between a virus and its host cell, is an arms race, a rapid escalation with each new viral attack parried by the host and each new host defense one-upped by the virus. A cancer is a disease of an **ARMSADA breakage** usually leading to apoptosis or sometimes to cancer. On the short duration, the cell lysis (Figure 2) is **an advantage for the virus** and **a disadvantage not only for the permissive cells but the whole organism too**. Virus coded proteins are usually expressed on the host cell surface, making the cell a target for destruction by the immune system. Thus, at the long duration, the hosted cells are killed by the virus, it is **a disadvantage for the virus** and **an advantage for the organism as a whole** if now 'vaccinated' against the virus and its relatives. But, if the cells' deaths result in the organism's death without reproduction, it is **a disadvantage for both**.

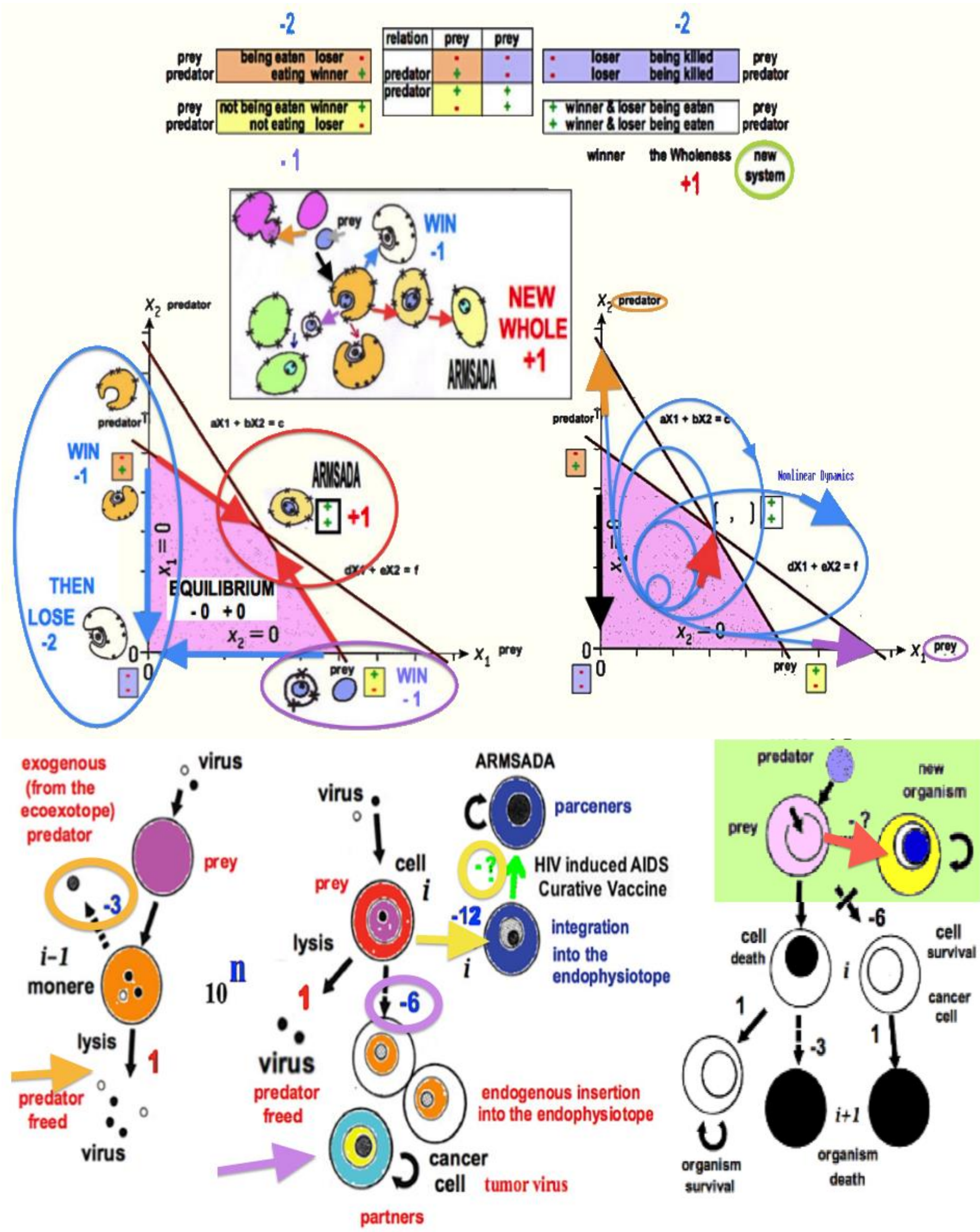

Figure 2. ARMSADA emergence: Why?, When?, How?, What for?

Top table: <u>The prisoners' dilemma game of predator-prey's food chain relationship</u>. When the prey wins (+) and the predator loses (-) biodiversity is reduced: -1. When the two lose (- and -) biodiversity is reduced: -2. The same when the predator wins (+) and the prey loses (-), it is a "who wins is a loser" game, no more prey means no more food. To survive that is first to eat! It is a "lose-lose" situation! Only ARMSADA emergence increases biodiversity, with a new blueprint +1, in which all partners (the fungus, the alga, in the case of a lichen) are losers and winners, the only Winner is the Whole (the lichen).
Top schema: <u>From predator-prey's interactive escalade of violence to ARMSADA emergence: from emergency to emergence!</u> There is no win-win situation but ARMSADA (Bricage, 2005a, 2007, 2009). Only ARMSADA allows the end of the violence escalade, for a while, with a new blueprint (+1).

Middle left: <u>Simplex graph representation of the previous table and schema</u>. Usually the predator wins and eats the prey (The strongest is the fittest...) but not too much! Because if there is no more prey, nothing else to eat for the predator, it will disappear too! And the biodiversity will be reduced -2. Sometimes but rarely, the prey wins and maybe eats the predator (The biter is bitten!), the biodiversity is reduced -1. Sometimes also, the two lose and die (and they are eaten, dead of alive, by an other life's form) and the biodiversity is reduced too -2. Exceptionally (in term of probability), but certain (that will always arrive, soon or late, at the scale of the geological times), the two win and lose simultaneously (it is not a "win-win" situation!) and a new Whole, an ARMSADA, emerges (Bricage, 2000). That is the way *the living systems, to be resilient and sustainable, do run trough (Bricage, 2010a). That is the only way for increasing biodiversity +1 (Bricage, 2009).*

Middle right: ARMSADA emergence is an attractor of a Lotka-Volterra equilibrium (same simplex graph). The agoantagonistic relations balance (Bernard-Weil & Bricage, 2007), within any ecoexotope, ends soon or late with the predators' disappearance and a reduction of biodiversity. The merging into an ARMSADA allows the emergence of a new biodiversity. "It is a rare wind that blows everyone some good but not without some ill." An ARMSADA emerges only when all the partners lose simultaneously the capacity to kill the other ones! (Bricage, 2005a, 2010b, 2014a).

Down left: Bacteriophages. The most frequent predator (virus)-prey (bacterium) food chain. Usually 1 (minimal probability 0.999), the predator wins, eats the prey and survives with an offspring (bacterium lysis). Rarely -3 (maximal probability 0.001), a new blueprint emerges with the integration (Bricage, 2002) of the viral genome into the bacterial ENDO as EXO of survival (Bricage, 2005b).

Down center: Virus diseases and cell cancerization. Usually 1 (minimal probability 0.999999), the predator (like HIV for example) wins, eats the prey and survives with an offspring (cell lysis). Rarely -6 (maximal probability 0.000001), a new blueprint, a cancer cell, emerges with a hazardous integration (Bricage, 2002) of the hosted viral genome into the hosting tumorous cell ENDO as EXO of survival (Bricage, 2005b). Even if the event of an ARMSADA emergence is totally improbable -12 (probability 0.000000000001), soon or late it happens, because of selection pressure (Kerr & al., 2006). It is the basic paradigm (Table 1) of emergence of a HIV induced curative vaccine, which probability (?) is higher (Bricage, 2005b). And, soon or late, with elite controllers for example, it works (Leng & al., 2014).

*Down right: Agoantagonism between levels of organization. Whatever the level of organization (i-1 bacterium, i cell, i+1 multi-cell organism), what is an advantage at a level i is a disadvantage for the adjacent inferior i-1 or superior i+1 levels. But for the one i to survive the other ones i-1, i+1 must mutually survive first and reciprocally. Usually 1 (minimal probability 0.999), cells (i) viral infections lead to cells death with the survival of the organism (i+1). Rarely -3 (maximal probability 0.001), the no-death of infected cell leads to viral progenies and the death of the organism. Rarely -6 (maximal probability 0.000001), but surely **1** ... the no-death of cancer cells leads soon or late to the death of the organism. Based on ARMSADA paradigm (Bricage, 2008b) and using exogenous and endogenous de-constrained viruses we can get the killing of cancer cells and a cancer curative vaccine (Bricage, 2008a).*

CURATIVE VACCINES

2 NEW WORDS: ECOEXOTOPE & ENDOPHYSIOTOPE

2 "TRIVIAL" CONCEPTS:
* **TO SURVIVE IT IS "TO EAT" & "NOT TO BE EATEN"**
* **THERE ARE NEVER ADVANTAGES WITHOUT DISADVANTAGES**

1 NEW PARADIGM:
ALL THE LIVING SYSTEMS MERGED FROM AN ARMSADA
ASSOCIATION for the RECIPROCAL and MUTUAL SHARING OF ADVANTAGES and DISADVANTAGES

2 "EVIDENT" FACTS: MODULARITY & ERGODICITY

2 NEW IDEAS:
* **DANGERS HOSTED IN CELLS, ARE NECESSARY FOR THE SURVIVAL**
* **VIRUSES ARE REGULATORS & PROTECTORS OF LIFE THROUGH THEIR CONTROL OF THE CAPACITY OF HOSTING OF THE ECOEXOTOPES & OF THE CAPACITY OF TO BE HOSTED OF THE ENDOPHYSIOTOPES.**

Table 1. ARMSADA : words and concepts, axioms for a new fruitful paradigm.

An endosyncenosis (CENO) is a ***'E PLURIBUS UNUM'*** *new System that emerged step by step through the sprouting of an ARMSADA. All that is an advantage for a partner is a disadvantage for all the other ones, they all are mutually fused* ***'for the best and for the worst'****. For a Whole to survive, each one of its parts MUST survive first:* ***UNUS PRO OMNIBUS OMNES PRO UNO****.*

All that is an advantage at a ***i*** *organization level is a disadvantage at the adjacent inferior* ***i-1*** *and superior* ***i+1*** *levels (Figure 1). So, soon or late, due to selective pressures, an ARMSADA will emerge because this is the only way for complementary ENDOs to share locally and mutually costs and benefits for growth and to become globally more and more independent of their EXO for development and survival (Bricage, 2000; 2009; 2010b).*

4 Conclusion

To survive that is to eat and not to be eaten (Figure 2). Sooner or later it is impossible not to be eaten! Any living system belongs to a food chain. Any living system is organised in a hierarchy of juxtaposed and embedded sub-systems. The endophysiotope (ENDO) of a i level of organisation is the ecoexotope of survival (EXO) of i-1 levels of organisation which are juxtaposed and embedded in it (Figure 1). At every level of organisation what is an advantage for a sub-system is a disadvantage for other juxtaposed local ones, and reciprocally. The local survival of a sub-system is antagonistic the survival of its global Whole (neighbouring upper level system) in which it is embedded (imbrication) and all other local sub-systems with which it is sharing the same ecoexotope of survival (juxtaposition). All that is an advantage at a level of organisation is a disadvantage at the upper and lower neighbouring levels and reciprocally (Table 1).

A wolf will share (even inequitably) its food with other members of its group. The altruism of an individual is reducing its survival compared with that of selfish individuals, but favours that of its group, it is a disadvantage for the individual but an advantage for the group (Axelrod, 2006; Trivers, 1971). As the variability INTRA (variance between individuals, inside a species) is higher than the variability INTER (between species), the selection INTRA (between individuals) is higher than the selection INTER (between groups). Any adaptation of a sub-system that is favourable whatever the level of hierarchy it is, tends to be prevented by natural selection at the neighbouring inferior level (the sub-sub-systems which it contains) and superior one (the hyper-system of systems in which it is contained), and conversely. Any sorts of selection act simultaneously at every level of organisation (Bricage, 2008b). The features, which benefit to the whole system are usually not advantageous for its sub-systems. It is an inevitable event in the survival of every species!

The system dynamics of human societies change shift, from breakdown to breakthrough path (Laszlo, 2014), is not an exception. ARMSADA emergence is the keystone process for that breakage (Bricage, 2002; 2005b). But the adaptations for a group (the Whole, the global system) are always working against some individuals (the parts, the local sub-systems) facing others (Bricage, 2000). The only way of evolving is to share and counterbalance advantages and disadvantages. No system can be a privileged level of the biological hierarchy (Bricage, 2009; 2014c)! The harmony and coordination can exist at any level of organisation. Only that is bearable (sustainable) and supported (sustained) is long-lasting! 'To survive that is to turn disadvantages into advantages and to avoid advantages turning to disadvantages.' *We need to evaluate the costs (disadvantages) and benefits (advantages) of set-asides in ecosystems, in terms of biodiversity hotspot (Banks-Leite & al., 2014).* The survival of the fittest is a survival of the best fitted Association for the Reciprocal and Mutual Sharing of Advantages and DisAdvantages (Figure 2). The evolutionary transitions are both causes and effects (systemic constructal law) of a change in the balance between 'within the system' (INTRA) and 'between systems' (INTER). An advantage for a i level is acceptable for all entangled i-1 levels only if the disadvantages which they undergo are bearable for them. And the survival of the i level is long-lasting only if it is supported by the of all the i-1 levels. The fittest is not the strongest or the best. Within a community of bacterial host preys (Escherichia coli) and viral predators (T4 coliphage) distributed across a network of subpopulations, the migration pattern affects coexistence and evolution. Different patterns of migration select for distinct predator strategies. Rapacious phages displace prudent variants for shared host resources, but a weak virus strain can survive longer and better than more aggressive ones.

Due to embedded levels of emergence, evolutive changes involve mosaic transformations, and ***'instability, emergency, is an opportunity for emergence'***. But, only ***a sufficient pre-requisite' variety*** of species and levels of organization can generate, soon or late, more and more post-potential varieties of structures of the ARMSADA type. The (transient) stability is limited in time. It is born from the instability, more and more, and it generates, more and more, the instability. At all organization levels of the Universe, the growth and development of every living system are durable ***only if they are sustainable for their local partners and sustained by their local and global actions*** (Bricage, 2009). All local parts are in interaction with other inferior adjacent local ones and other superior adjacent local ones and with their wholes too (Figure 1). An ecosystem as a cell, a lichen, an atom, a galaxy, or the whole Universe all are CENOs that emerged by juxtapositions and encasements of initially free ago-antagonist actors (Table 1). A lichen, a cell, an atom, or a galaxy, all are equally alive... and the Universe too. This is true at all levels of organization of living systems. An atom or a stellar system has the same functional behavior (Bricage, 2002) as a bacterium or a cell. These are living systems but **at another scale** of space, time and action. A pebble on the soil is not alive, but it contains living atomic systems, and pebbles in the sky are parts of a stellar living system (Bricage, 2009; 2010a; 2013; 2014c). But to understand their structures and functionalities we need a new global knowledge through a new mode of education for complexity thinking (Bricage, 2010b; Morin, 2014).

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About the Author

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Born in 1947 (Paris, France, Europe), graduated in biochemistry, embryology and genetics from Paris 6 University (the first French University in ARWU, in the top 15 in Natural Sciences and 5 in Mathematics), as ENS Alumnus he passed the aggregation of biology. He learned American Civilization in CalTech, California (ranking 5). Now retired, he edited or published more than 250 pedagogic or scientific works in more than 20 countries http://web.univ-pau.fr/~bricage. During 8 years at the University of Dakar (Senegal, Africa), the biological rhythms of biochemical, ecological, physiological & genetical markers of plant enzymes & pigments were his research interests for sustainable management of natural resources and environmental education. As head of the biology department at the University of Pau, France, he founded a centre for Agricultural Research. During 40 years, as researcher in biochemistry, enzymology, genetics, microbiology, animal or plant physiology, and systems analysis, he taught Systems Theories & Micro-Informatics applied to Quality Control, Health and Social Sciences (Societal Engineering and Man's Societal Environmental Responsibility). Pointing to Fundamentals in Biology, with On Line "Creative Commons" works (http://hal.archives-ouvertes.fr/hal-00130218/fr) he has been developing new Key concepts (endophysiotope, ecoexotope, gauge invariance of Life, phylotagmotaphology http://hal.archives-ouvertes.fr/hal-00423730/fr), through the paradigm of ARMSADA "Associations for the Reciprocal and Mutual Sharing of Advantages and DisAdvantages" http://www.armsada.eu, with applications in curative vaccines (cancer, AIDS). As a researcher in environmental, health and education sciences Pierre is Vice-President of the French Association for Systemics and Cybernetics AFSCET (http://www.afscet.asso.fr), Deputy Secretary General of the European Union for Systemics UES-EUS (http://ues-eus.eu/), Member of the Directorate of the World Organisation of Systems and Cybernetics WOSC (http://www.wosc.co/) and Secretary General of the International Academy for Systems and Cybernetic Sciences IASCYS (http://www.iascys.org). As an educator in societal and environmental responsibility he is treasurer of the PELLEAS and President of the ALBA not-for-profit Associations (http://www.abbayeslaiques.asso.fr).