Coevolutionary Networks: a Novel Approach to Understanding the Relationships of Humans with the Infectious Agents

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Human organism is interpenetrated by the world of microorganisms, from the conception until the death. This interpenetration involves different levels of interactions between the partners including trophic exchanges, bi-directional cell signaling and gene activation, besides genetic and epigenetic phenomena, and tends towards mutual adaptation and coevolution. Since these processes are critical for the survival of individuals and species, they rely on the existence of a complex organization of adaptive systems aiming at two apparently conflicting purposes: the maintenance of the internal coherence of each partner, and a mutually advantageous coexistence and progressive adaptation between them. Humans possess three adaptive systems: the nervous, the endocrine and the immune system, each internally organized into subsystems functionally connected by intraconnections, to maintain the internal coherence of the system. The three adaptive systems aim at the maintenance of the internal coherence of the organism and are functionally linked by interconnections, in such way that what happens to one is immediately sensed by the others. The different communities of infectious agents that live within the organism are also organized into functional networks. The members of each community are linked by intraconnections, represented by the mutual trophic, metabolic and other influences, while the different infectious communities affect each other through interconnections. Furthermore, by means of its adaptive systems, the organism influences and is influenced by the microbial communities through the existence of transconnections. It is proposed that these highly complex and dynamic networks, involving gene exchange and epigenetic phenomena, represent major coevolutionary forces for humans and microorganisms.

Key words: coevolutionary networks - coevolution - gene exchange - infectron - microbial communities - immunoneuroendocrine system

It is increasingly becoming clear that every living being, from bacteria to mammals, is a consortium of living beings. Viruses are the most frequent component of this association and can be detected in animals and plants, as well as in bacteria, algae, fungi and protozoa (Lemke 1976, Wang & Wang 1991). In humans, the consortium comprises an heterogeneous array of species, including viruses, bacteria, fungi and protozoa, living temporally or permanently together. As Michael Oldstone once affirmed, we are continually bathed in a sea of microbes (Oldstone 1996). They are in our outer and inner surfaces, in our fluids, tissues and cells (Ambinder et al. 1985, Gradilone et al. 1996, Cassinotti et al. 1997, Srivastava et al. 2000). The human organism is considered to be composed of approximately 10^{13} cells, while the various body surfaces may be colonized by as many as 10^{14} indigenous prokaryotic and eukaryotic microbial cells, making a proportion of ten microbial cells per human cell (Savage 1977). These figures are further augmented if infectious agents present in the various cells and tissues of the human organism are considered. Microbes dwell the uppermost of our individuality: our genome. Indeed, it is now recognized that a proportion of the human genome is composed of complete genomes or DNA sequences derived from retroviruses, which are stably integrated into host genome and transmitted to progeny in a classical Mendelian fashion (Löwer et al. 1996, Kazazian & Moran 1998, Miki 1998).

Which are the consequences of such an extensive and prolonged association among humans and microbes? My proposal is that microbes and humans, in fact all living beings, are linked by functional networks, and that these networks act by promoting diversity, adaptation, and coevolution.

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THE MICROBES AND THEIR COMMUNITIES

A great deal of information has been recently gathered on the organization of microbes within the human organism. It is now recognized that several species of microorganisms live in communities, where they share a common niche, have similar metabolic features and trophic needs (Savage 1977). The degree of organization of certain microbial communities is such that they have been considered as multicellular organisms, since they display communication and decision-making capabilities that enable them to coordinate growth, movement and biochemical activities. Each individual cell of the community has the ability to receive, interpret, and respond to information from its neighbors. The benefits of multicellular cooperation include: (a) more efficient proliferation resulting from cellular division of labor; (b) access to resources and niches that cannot be utilized by isolated cells; (c) collective defense against antagonists that eliminate isolate cells; and (d) optimization of population survival by differentiation into distinct cell types by mutation, gene exchange, or sporulation and formation of dormant cells (Shapiro 1998).

Microbes within each community communicate with each other by direct cell-cell physical and chemical interactions, or by the production of different signaling molecules that affect the growth or the chemotactic response to chemical agents produced by cells (Ben-Jacob et al. 1998). These *microbial intraconnections* form networks that keep the internal coherence of the microbial community by integrating and coordinating signals and other informations necessary for gene expression, and microbial growth and differentiation (Gottesman 1984, Shapiro 1998). The main instruments of communication between members of a microbial community are chemical signaling and gene exchange. By means of chemotactic signaling, a community of motile bacteria is kept organized in a particular niche, whereas 'quorum-sensing' signal molecules control its growth. Chemotaxis usually implies a response to an externally produced field such as attraction towards supplemented nutrients. However, self-generated bacterial chemotactic signaling by the excretion of amino acids and peptides has also been demonstrated (Ben-Jacob et al. 1998). Microbe cells sense the concentration of the chemoattractants (or chemorepellents) by measuring the fraction of receptors occupied by the signaling molecules. The chemotactic response vanishes when, at high concentrations of chemoattractants, receptor saturation is reached (Ben-Jacob et al. 1998).

To conduct a census of their population and control overgrowth, bacteria use 'quorum-sensing' signal molecules. This phenomenon was best characterized in the symbiotic marine bacterium *Vibrio fischeri*. This microorganism produces compound – *N*-3-(oxohexanoyl) homoserine lactone – that accumulates in the surrounding environment during growth. Since this molecule is freely diffusible through the bacterial membrane, it accumulates within the bacterium and, when a critical concentration is reached, growth-controlling genes are activated (Fuqua et al. 1996). Quorum-sensing systems have been recently identified in a wide variety of bacteria that infect humans (de Kievit & Iglewski 2000, de Saizieu et al. 2000, Parsek & Greenberg 2000, Rashid et al. 2000, Wu et al. 2000).

DNA exchange between bacteria of the same community occurs via plasmids, phages, and transposons, and play major roles in the spread of antibiotic resistance (Coffey et al. 1991, Archer & Niemeyer 1994, Coffey et al. 1995, Davison 1999), acquisition of pathogenicity determinants (Groisman et al. 1992, Gibbs & Meyer 1996, Kehoe et al. 1996, Bingen et al. 1998), development of new metabolic pathways (de la Cruz & Davies 2000), and overall evolution of the species (Medigue et al. 1991, Arber 2000). Efficient uptake of macromolecular DNA by bacteria occurs naturally and involves a genetic program encompassing different steps and enzymatic processes (Dubnau 1999). An interesting example of evolutionary transformation of a bacterium species mediated by DNA exchange has been described in *Helicobacter pylori*, a frequent inhabitant of human gastric mucosa that has been linked to the etiology of peptic ulcer and gastric cancer. This species shows a great deal of genetic polymorphism between isolates that has been attributed to gene transfer between members of the community (Suerbaum et al. 1998). It was found that between 6% and 7% of the coding capacity of each strain are genes that are absent from the other strain, whereas 20% of the total genome, comprising genes of unknown function, have analogues in other bacteria (Alm & Trust 1999). Viruses are also subjected to gene exchange between members of the same community. This is true particularly to RNA viruses that are known by their high degree of genetic polymorphism between different isolates (Steinhauer & Holland 1987, Strauss & Strauss 1988, Katz & Skalka 1990). The most common form of recombination among RNA viruses is the independent reassortment of different viral genome segments during a mixed infection to produce a progeny with characteristics from both parents, as occurs in infections by the influenza virus (Strauss & Strauss 1988). It has recently been recognized that gene exchange also occurs among retroviruses.

Multiple segmental gene exchanges between three HIV-1 strains (O, D, and IBNG) were detected in a patient presenting multiple infections (Takehisa et al. 1999). It is possible that mutation-induced variations in the biological features of retroviruses (Takeuchi et al. 1991) were due to recombination between individuals of the same microbial community (Steinhauer & Holland 1987).

Microbial communities do not live isolated from one another: they are interactively linked to other microbial communities by means of spatial, trophic, metabolic and genetic chains. The interactions between communities may produce beneficial or detrimental effects. Beneficial generally means adaptation or stimulation to growth, whereas the detrimental effects usually lead to new requirements for maintenance, inhibition of growth, or stimulation to death (Friedrickson 1977). The *interconnections* between different microbial communities include mutual signaling between microbes of different species, interference with gene expression, and gene exchange. Although communication between microbes of the same species has long been shown, the possibility of cross talk between different microbial species was only recently demonstrated. Hence, it is now recognized that individual bacterial cells possess the ability to sense, integrate and process informations derived not only from the members of their own community, but also those originated from other species of microorganisms that share the same ecosystem. The main instruments of communication are 'quorum-sensing' molecules, known as 'autoinducers' or 'pheromones'. They are highly diffusible molecules that monitor the density of bacterial population and regulate diverse physiological processes including bioluminescence, swarming, antibiotic biosynthesis, plasmid conjugal transfer and the production of virulence determinants (Hardman et al. 1998). The integration of 'quorum-sensing' signals with other global regulators can lead to very complex and sophisticated interactions that are not necessarily limited to the signal-producing species alone (Gray 1997). In spite of the fact that different bacteria produce chemically distinct signaling molecules (Shapiro 1998), a remarkable degree of trans-species or trans-genus effect has been demonstrated (Holden et al. 1999). Indeed, it has been shown that a pheromone of *Staphylococcus epidermidis* was capable to inhibit the virulence of *S. aureus* (Otto et al. 1999), whereas molecules produced by *Lactobacillus pentosus*, isolated from vaginal secretion, inhibited the growth of the same or different genera (Okkers et al. 1999). Communication between different species of viruses has been demonstrated among herpesviruses, usually leading to activation of gene expression and intensification of the replicative cycle (Flamand et al. 1993, Homer et al. 1999).

The most compelling evidence of communication between different microbial communities comes from the demonstration of trans-species gene exchange. DNA translocation across bacterial membranes occurs during the processes of infection by bacteriophages, conjugative transfer of plasmids, or foreign DNA transfer, by mechanisms not completely understood (Heinemann 1999). Several examples of horizontal transfer of gene sequences between bacterial species have been described, including that of *Streptococcus pneumoniae* (Muñoz et al. 1998) or *Yersinia pestis* (Schubert et al. 1998) to *Escherichia coli*, of *S. mitis* or *S. oralis* to *S. pneumoniae* (Whatmore et al. 1999), and of *Enterococcus faecalis* to *Lactococcus lactis* (Hirt et al. 2000). Populations of *Bacillus subtilis* can develop subpopulations competent for DNA uptake from any source and thereby incorporate novel proliferation and survival abilities (Solomon & Grossman 1996). The complete genome sequence of bacteria such as *B. subtilis* (Kunst et al. 1997) and *E. coli* (Blattner et al. 1997) has showed that they contain insertion sequence elements, phage remnants, and many other patches of unusual composition indicating genome plasticity through horizontal transfer. Horizontal trans-species gene transfer has also been described among retroviruses (Takehisa et al. 1998, 1999), exogenous and endogenous retroviruses (Yang et al. 1999), retrovirus and bacteria (Temin 1989, Varmus 1989), and herpesvirus and mycoplasma (Turk & Hutt-Fletcher 1994).

THE HUMAN ORGANISM AND ITS ADAPTIVE SYSTEMS

The human organism reckons on three adaptive systems to allow a profitable conviviality with microbes: the immune, the nervous, and the endocrine systems. The adaptive systems are critical for the maintenance of the equilibrium of the organism – the homeostasis – and, to carry out efficiently their role, they need to be kept under strict control. Thus, each adaptive system is organized into cellular and molecular networks, or *intraconnections*, aiming at the maintenance of its internal coherence.

The prototype cell of the immune system is the lymphocyte, which differently from all other cells of the organism, is endowed with surface receptors capable to specifically recognize molecules. The contact of these antigenic molecules with cell receptors triggers a signaling cascade that lead to gene expression, proliferation, and acquisition of new phenotypic and functional characteristics. This differentiated lymphocyte produces *antibodies*, molecules capable to react specifically with the

antigen that induced its differentiation, or *cytokines*, a heterogeneous family of regulatory, inflammatory and cell-growth promoting molecules. The ultimate aim of the immune system is the maintenance of the molecular individuality of the organism. It carries out this task by comparing the new molecular pattern it comes across with those that are part of the normal constituent of the organism, and reacts when this is found different. To maintain its own internal coherence, the immune system is organized in complex regulatory networks: the idiotypic network, which links antibodies and lymphocyte receptors through their specificity (Varela & Coutinho 1991, Coutinho 1995), and the cytokine network, which defines how the system will react, and the intensity of the response (Chaplin & Fu 1998, Mellstedt et al. 1999). The second adaptive system – the nervous system – has much in common with the immune system: both act by sensing stimuli through cell receptors, and both learn from experience. The prototype cell is the neuron, comprising, as the lymphocytes, about 10^{12} cells, which form about 10^{15} synaptic connections. This vast network of synapses, together with the molecules neurons produce, act as regulatory connections, responsible for maintaining the internal coherence of the nervous system. As the immune system, the nervous system possesses a high degree of functional plasticity (Rapoport 1999), and is sensitive to patterns, rather than to individual representations (Sanes & Donoghue 2000). Cells of the nervous system produce hormone-releasing factors that stimulate the production of hormones by the cells of the other adaptive system, the endocrine system. The endocrine system relies on the production of hormones to keep the organism metabolically controlled. The different hormones are produced and their concentration controlled through an intricate network of stimulating and inhibitory products (Nystrom & Quon 1999, Herbison et al. 2000).

It has been recognized that the adaptive systems are functionally linked by *interconnections* in such way that what happens to one is immediately sensed by the others (Besedovsky & del Rey 1992, Straub et al. 1998, Downing & Miyan 2000). This extremely fluent flow of communication among the three adaptive systems occurs because they share ligands and receptors. Indeed, it has been demonstrated that lymphocytes express surface receptors for virtually every hormone, neuro-hormone, neuropeptide, and neurotransmitters, apart from producing several of these substances (Blalock 1994, Johnson et al. 1997), while the cells of the nervous system synthesize a number of cytokines, so far considered typical products of lymphocytes (Fabry et al. 1994). An example of this intertwined function is the effect of corticotropin-releasing hormone, produced either by cells of the hypothalamus or by lymphocytes, on macrophages. It triggers the release of a cytokine, interleukin-1, which acts on B-lymphocytes and induces the synthesis of beta-endorphin. This neuropeptide have pleiotropic effects that include the ability to enhance the cytotoxicity of NK cells towards tumors cells, and to cause analgesia by acting on neurons (Blalock 1994).

TRANSCONNECTIONS: ADAPTATION AND EVOLUTION THROUGH DIVERSITY

Although the immune, the nervous and the endocrine systems share receptors among them, which allow their intercommunication, the cells of each system express specific receptors that make them targets of different infectious agents. Thus, certain microorganisms as the human immunodeficiency virus and the Epstein-Barr virus infect the cells of the immune system, the herpes simplex virus and the poliovirus virus prefer the cells of the nervous system, while the mumps virus infects preferentially the cells of secretory glands. However, neither each microbial community act isolately, since they are linked to other communities by *microbial interconnections*, nor does each adaptive system, linked one to the others by *adaptive interconnections*. As a result, the presence of a microbial community in the organism can mobilize not only other microbial communities, but also the adaptive systems as a whole, even when they are not the primary targets of infection, since they are able to sense modifications in cells and tissues throughout the organism. The bi-directional communication between the microbial communities and the adaptive systems – the *transconnections* – involves mutual gene activation, as well as gene exchange between host and microbe.

Microbes activate host cell genes by acting as antigens or superantigens, by producing immunomodulatory molecules, or by interfering with the apoptosis of the cell. Superantigens are proteins originated from bacteria or viruses that form complexes with MHC class II molecules on antigen-presenting cells by binding to the outside of the antigen-binding cleft. This complex subsequently binds to certain sequences of the antigen receptor and CD4 molecules of T lymphocytes, which triggers signaling and gene activation, and leads to polyclonal activation of as many as 20% of the helper T lymphocyte repertoire (Torres & Johnson 1998). The possibility that B-lymphocytes undergo superantigen-induced polyclonal activation has recently been demonstrated (Silverman 1998). The intense production of cytokines that accompanies lymphocyte activation causes a cascade effect of

gene activation in a vast array of cells, which may lead to dysfunction of the immune system, manifested by immunodeficiency or autoimmune diseases. Several human infectious agents act as superantigens, including *Staphylococcus aureus* (Krakauer 1999), *Streptococcus pyogenes* (Eriksson & Norgren 1999), *Mycoplasma arthritidis* (Hodtsev et al. 1998), *Mycobacterium tuberculosis* (Ohmen & Modlin 1996), *Yersinia pestis* (Yagi et al. 1999), rabies virus (Lafon & Galleli 1996), HIV (Vingerhoets et al. 1998), Epstein-Barr virus (Sutkowski et al. 1996), cytomegalovirus (Dobrescu et al. 1995), and parvovirus (Lunardi et al. 1998). The possibility that IDDMK(1,2)22, a human endogenous retrovirus of the family HTDV/HERV-K, could act as a superantigen and lead to autoimmune diabetes (Conrad et al. 1997) has recently been disputed (Löwer et al. 1998, Jaeckel et al. 1999, Lapatschek et al. 2000).

Microbes can also interfere with host cell genes by acting as antigens, by producing immunomodulatory molecules such as lipopolysaccharide, exotoxins, cytokines, and chemokines (DiMaio et al. 1998, Lalani et al. 2000), or by affecting cell apoptosis. Apoptosis is a genetically controlled process by which every cell is programmed to die. It is a crucial phenomenon for the maintenance of homeostasis, the organogenesis, and the development of lymphocyte repertoires in lymphoid tissues. The phenomenon is centered in special enzymes called caspases, present in cells as inactive proenzymes, that are coordinately activated through complex pathways leading to inhibition of DNA synthesis, repair and splicing, to degradation of DNA, and finally the disintegration of the entire cell contents into apoptotic bodies. A vast variety of microbes, both bacteria and viruses, influences host cell apoptosis, either by inducing or suppressing it (Roulston et al. 1999, Weinrauch & Zychlinsky 1999). Apoptosis can be advantageous or detrimental for microbes, depending on the features of the relationship the infectious agent maintain with host cell. Thus, during certain phases of the life cycle of viruses, viral proteins perturb normal cell physiology and provide signals that trigger cell death. During apoptosis, the entire cellular contents, including progeny virions, are packed into membrane-bound apoptotic bodies that are taken up by surrounding cells. This process limits the inflammatory response, protects the infectious agent from the action of antibodies and proteases, and allows the infection to spread undetected by the host organism. When apoptosis is detrimental for the microorganism, it uses different strategies to suppress cell death, including the inhibition of 'death receptors' on the cell surface (for tumor necrosis factor and Fas ligand), inhibition of the proapoptotic interferon response, inhibition of caspases, and production of homologs of the antiapoptotic Bcl-2 molecules or inhibitors of transcriptional regulators of apoptosis (Roulston et al. 1999). The fate of an infected cell towards lysis or apoptosis depends on an exquisite balance between host and viral proapoptotic and antiapoptotic factors. In this regard, it was found that early in the infection of HeLa cells with poliovirus, a predominantly proapoptotic viral function was expressed, rendering the cells committed to apoptosis, whereas with the onset of fast generation of viral progeny, the implementation of the viral apoptotic program was abruptly interrupted, and the cells become committed to lysis by cytotoxicity. This changing was due to overexpression of the antiapoptotic Bcl-2 protein within the cell (Agol et al. 2000).

Transconnections through gene activation are bi-directional, that means, either the infectious agent activates host genes, as the host activates microbial genes. This occurs by different mechanisms including the action of hormones, cytokines, and neuropeptides produced by the immunoneuroendocrine system. Indeed, it has been demonstrated that microbes can express receptors for these molecules, and are responsible to them. Some examples include the expression of thyrotrophin binding sites on *Yersinia enterocolitica* (Heyma et al. 1986), the modulatory effect of hormones of the hypothalamic-pituitary-axis on Epstein-Barr virus (Glaser et al. 1995), the growth-stimulating effect of gastrin on *H. pylori* (Chowers et al. 1999), the antimicrobial effect of alpha-melanocyte-stimulating hormone on *Candida albicans* and *S. aureus* (Cutuli et al. 2000), the stimulating effect of corticosteroids on the replication of hepatitis C virus (Magy et al. 1999), and of thyroid hormone on HIV-1 long terminal repeats (Desai-Yajnik et al. 1995).

Another category of transconnections among human host and microbial communities encompasses bi-directional gene exchanges. Horizontal gene transfer has long been recognized to naturally occur between individuals of different species, genus, families or kingdoms (Syvanen 1985, 1994, Kidwell 1993, Thompson 1999), and is considered to contribute to diversity, adaptation and coevolution.

It has been shown that about of one-third of human genome is constituted by gene sequences originated from retroviruses, collectively known as retroelements, some of them integrated for millions of years (Miki 1998, Kim et al. 1999). Although most of these retroelements are degenerate and inactive sequences resulting from ancient integration, *de novo* insertion has been described

(Kazazian et al. 1988), and it has been recognized that a proportion of the integrated infectious DNA retain the potential to retrotranspose and thus to change genomic structure and function (Panning & Smiley 1995, Esnault et al. 2000, Pickeral et al. 2000). Retroelements have been found in association with MHC (Dawkins et al. 1999), or exerting genome regulatory functions (Mager et al. 1999), thus influencing human genome organization and expression; while others have been associated to inherited human diseases such as muscular dystrophy (Holmes et al. 1994), or peripheral neuropathies (Kennerson et al. 1997). Exogenous retroviral sequences continue to enter germline cells (Katz & Skalka 1990), and therefore become endogenized, and vertically transferred to the progeny. On the basis of the phylogenetic congruency test, the possibility of horizontal transfer of retroelements in some taxa has been considered (Syvanen 1994).

The recognition that microbial DNAs circulate freely in the blood (Stroun et al. 2000), and that these molecules can cross both the cellular (Hefeneider et al. 1992, Ivanova et al. 1999), and nuclear membranes (Gerace 1992), gain access to host genome (Doerfler et al. 1995), and eventually become integrated (Schubbert et al. 1994, Doerfler 1996), has open up intriguing new avenues on the possibility of interference of infectious agents with human genome. Since association of DNA with proteins involves processes that take place on a femtosecond (10^{-15}s) or picosecond (10^{-12}s) time scale (Anfinrud et al. 1999, Wan et al. 1999), it is possible that even a short stay of the foreign DNA in host genome can lead to some functional alterations. Insertion of DNA into the host genome brings about different outcomes: the foreign sequence is either rejected, silenced, or retained. Eukaryotic genomes possess surveillance systems that protect them from foreign DNA invasion, which lead to deletion of the alien sequence (Scrable & Stambrook 1999), or to cytosine methylation and consequent silencing of the exogenous gene (Doerfler et al. 1995, Lorincz et al. 2000). However, the success of DNA vaccines (Gurunathan et al. 2000), and gene therapy (Cavazzana-Calvo et al. 2000, Giuliano et al. 2000) proves that the cell surveillance systems can be surpassed.

An increasing number of viral proteins, particularly from large DNA viruses, such as herpesviruses and poxviruses, have been described that present homology with those of the host cell (Lalani et al. 2000). Viruses use this molecular mimicry, also known as molecular piracy, as part of their survival strategy, since it involves important factors of antiviral defense, such as complement factors, cytokines, chemokines and their receptors, presently known as virokines and viroceptors (Kotwal 2000, McFadden & Murphy 2000). Molecular mimicry has been interpreted as due do the capture of host genes by the virus (Murphy 1994, Cohen 1999). However, the possibility that homologous proteins coded by host genome result from the capture of viral genes cannot be ruled out.

INFECTRONS AS INSTRUMENTS OF COEVOLUTION

To encompass the broad array of exogenous DNAs that invade a genome and interfere with its organization or function the term *infectron* was coined. The main characteristics of infectrons are: (1) an entire genome or part of it; (2) from any source to any target; (3) horizontal or vertical transfer; (4) short or lifelong action; (5) natural or artificial transfer; (6) causes structural or functional alterations of host genome. Infectrons are not novel elements but a novel way to interpret the relationships of these elements with a host genome, and to connect them through the recognition of common mechanisms of interference with this genome and hence, with its functions and fate.

It is considered that all connections within or between microbial communities, or among these communities and the host that involve gene exchange are *infectronic connections*. Differently from *noninfectronic connections*, infectronic connections lead to diversity and, hence, to adaptability. Since they have usually a bi-directional nature, they bring about coevolution. The concept of infectron reminds us that genomes are not close structures: they are crucial parts of the individual that is interchanging with the environment and, therefore, is adapting and evolving. The adaptability starts in the genome and is the result of its ability to diversify and, therefore, to increase the probability of survival of the individual and its descendants. The recognition that genomes are dynamic structures that learn as they move through time and generations, and can take up, from the outside, information that transform their behavior in a heritable way (Caporale 1999) is one of the most important achievements of modern biology. To attain this degree of plasticity the genome uses different strategies, including gene shuffling, genome rearrangements, base bias composition, and horizontal gene transfer of DNA across species barriers (Bellgard et al. 1999), besides some epigenetic control phenomena such as homology-depending gene-silencing (Wolffe & Matzke 1999). The ability of the genome to take advantage of such multiple and complex array of strategies of adaptation presupposes a high degree of organization. Indeed, it is becoming clear that, by means of combinatorial joining of DNA sequences, the genome is ca-

pable of integrating signals from different regulatory and signaling pathways, and thus to create regulatory networks (Caporale 1999).

The organization in regulatory networks is an efficient way the genome has to preserve its 'internal coherence'. However, confrontation with an unpredictable challenge may force the genome to reorganize itself (McClintock 1984, Kidwell & Lisch 1997) and therefore, to create new patterns. In other words: to evolve. My proposition is that infectrons are major constituents of networks that act bilaterally as unpredictable challenges, influence genome plasticity by increasing its diversity, and hence, contribute to coadaptability, and may function as coevolutionary forces.

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