Cellular Sentience – Downfall of Central Dogma and Atomism in Biology

Purushottama Jagannath Dasa, Ph.D.
Sri Chaitanya Saraswat Math

1.0 Introduction

All of us as sentient beings experience feelings and emotions. There is a sense of purpose and a desire to become happy. We have a very prominent sense of identity, a sense of volition and even our sense perceptions are something distinct from the analogue or digital sensors or devices used in machines and computers. Yet in the face of great technological advancements it is not very surprising that science is unable to determine exactly what actually makes a cognizant being. Darwin proposed the theory of evolution as a mechanical explanation for the appearance of cognitive entities based upon mutation, accumulation and natural selection. With the discovery of the DNA double helix molecular structure it was thought that the understanding of the cell could be reduced to the genome.

Lamarckism had already encountered several challenges. Weismann Barrier took an early step in the founding of genetics and proposed that information flows only from germline to the somatic cells and never in reverse thus giving Lamarckism its unceremonious burial. Even up to early 19th century, thoughtful men looked into different branches of knowledge such as art, philosophy, mechanics and biology in the search for a comprehensive concept of reality. In the end, however, it was the success Newton had in his use of mechanics and mathematics that had the greatest impact on the direction all science would take after him. Later, the synthesis of urea by Whoeler led to strengthening the faith, especially among biologists, that living organisms are nothing more than analyzable mechanisms (reductionism).

2.0 Central Dogma of Molecular Biology

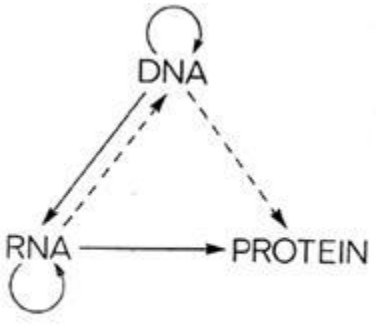

Fig. 1: Central Dogma of Molecular Biology

In search for an atomistic mechanism, the central dogma was proposed by Francis Crick in 1958. It is a hypothesis of genetic reductionism in molecular biology. Crick categorically stated that information does not flow from proteins to DNA. Even in 1992 Walter Gilbert stated, "You and I will one day hold up a CD containing our DNA sequence and say, "Here is a human being; it's me!" The central dogma was meant to be a formulation of general rules for the transfer of information from one polymer with a defined alphabet to another. It is represented in Fig. 1. The arrows indicate the directional flow of detailed, residue-by-residue sequence information from one polymer molecule to another. Crick divided all the transfer directions into three categories, (i) General transfers were those which occur in all cells, (ii) Special transfers are those which do not occur in all kinds of cells but only in some special

circumstances, and (iii) Unknown transfers were those that the central dogma postulated as those which never occur. General transfers were identified as DNA→DNA; DNA→RNA and RNA→Proteins; Special transfers were identified as RNA→RNA, RNA→DNA, and DNA→Proteins. The Unknown transfers were Proteins → Proteins, Proteins →DNA, and Proteins →RNA. The formulation of these rules was done at a time when according to Crick molecular biology was not so well developed. Crick conceded that if Special transfers were found to be general and occur widely it might indeed have profound implications for molecular biology. Further the discovery of just one type of present day cell which could carry out any of the three unknown transfers would shake the whole intellectual basis of molecular biology. He admitted however that our knowledge in molecular biology, even in one cell – let alone for all organisms in nature – is still far too incomplete to allow us to assert dogmatically that it is correct [1]. Nonetheless, the founders of molecular biology, despite lack of conclusive evidence believed that it would provide a firm physical and chemical foundation for the mechanistic views of heredity and cell function.

In the progress of experimental biology and genomics within the last five decades many new and surprising results have surfaced in cell biology, which have all challenged the central dogma. Epigenetics has emerged as being highly significant in cellular information processing. Biology is now firmly situated in the realm of information paradigm, complexity, redundancy, signal processing and decision making.

Science must have a guiding vision matched with appropriate technological advancement. The attempt to reduce all biology to the realm of the so called Holy-grail of biology (the genome) is turning out to be a limited concept [2]. The older concepts have lead to their logical end and the need is for newer, more comprehensive concepts in the light of the highly technological advancements in cellular biology.

3.0 Some salient developments in cell biology

The conventional and the widespread idea of molecular biology provides a mechanistic model of heredity and cell cycle, where the phenome is strictly genome directed. However, more and more it has become evident that such atomistic pre-DNA genome –> phenome concepts are inadequate. Now biology is encountering the deeper waters of complexity, signal transduction, redundancy, network and decision making or in short the information paradigm [3, 4]. Cells are immensely sophisticated systems and cell biology has undergone tremendous development within the last 50 years. The amount of data that biologists have generated is enormous. Certainly it takes time for all of this to trickle down to the ordinary scientist. But this cutting edge biology is forcing scientists to formulate newer concepts [3]. Older concepts like the central dogma or the atomistic pre-DNA concepts of genome activity and genotype-phenotype relations find very limited applications. Complexities in cellular informatics and cellular processing capabilities are quite bewildering. Millions and billions of biochemical operations are carried out dynamically with tremendous control and precision. There is involvement and management of hundreds of inputs – information on dynamic status of genome replication, the status of the cell

during the cell cycle, availability of nutrients, integrity of large bio-polymers, inter and intracellular informatics.

Thus some of the major turns in biology are:

- Limitations and conceptual bankruptcy encountered within conventional reductionist framework: Cell cannot be reduced to genome.
- The role of DNA in cellular informatics: how much of a role DNA plays in actual cell function
- Phenotype is not hard-wired in the Genome
- DNA is a multivalent and interactive storage system
- Cellular informatics has a distributed nature.
- Cellular activity is a whole cell activity and the conceptual significance of epigenetics and extra-genomic signaling is integral within cell dynamics.
- Recognition of natural genetic engineering tools. [3]
- Complexity of biological functionality and specificity.
- Need to relook at Genome informatics in Cognitive Context.
- Need for a new concept of biology and a non-mechanistic paradigm in biology.
- The consequences for evolutionary biology need to be addressed in the light of new biology.

In this paper we wish to review some of the work of Shapiro [3] to show how modern scientific developments in the study of biological organisms over the last few decades has led to the non-centrality of the DNA concept, completely overthrowing what is called the Central Dogma of biology following Crick's initial postulates.

Genome informatics is defined as the role that DNA plays in cellular computations. The conventional classical genetic concepts have limitations in that they do not assign any fundamental role to the so-called non-coding DNA sequences. Furthermore they do not consider the necessary role of multidirectional information transfer and systemic integration relevant in genome functioning.

3.1 Meaning and Nature of Genome Informatics in Cognitive Context

Cells have proved to be highly complex and sophisticated cognitive entities. All dimensions of study involving cell biology confirm this even from unicellular to the most complex multi-cellular entities like plants and animals. The contention that nervous systems are essential for the generation of cognitive behavior has been questioned in biology already [5 - 8], where it is argued that cognition already exists even within unicellular organisms. This means that basic cellular processes entail dynamics of immense complexity involving sensory events and processing of inputs within the identity and context of such cell dynamics. This has led to a need to address this cybernetic and cognitive challenge. We can no longer isolate individual biochemical processes from the whole cell in which such behavior takes place. The accuracy, robustness and control dynamics reveal the sophistication of these cellular moieties. Thus more and more we are led away from the reductionist camps and concepts of the past century and are ushered into the domain of whole cell approach or the “systemic approach.” The systemic

approach means that it includes all the three dimensions of (i) Genomic informatics, (ii) Epigenetic and extra-genomic informatics, which includes the environment and, (iii) computational informatics, which means the information domains related to the dynamic and transient states. Further the systemic approach implies that these realms are inseparably connected within a dynamic unity.

A major truth of the state of the art or the cutting edge of biology is that quite contrary to the assumptions of the central dogma, biology has shown that information is not hard-wired in the genome. The cellular networks access DNA as an information storage medium and the data is necessary for the execution of cellular tasks, but genomic information by itself is not sufficient. Rather the genomic information must be accessed in appropriate cellular context. On the other hand some tasks involving the genome can be executed by accessing alternative combinations of stored data. The distributed and natural network function is evident as cells are sometimes very robust despite many sites of mutational damage. Many mutational knockouts have no effect in the mutant phenotype [3].

A major re-conceptualization is necessary from the assumption that DNA dictates phenotypes and determines the particular traits of individual genes. This view is incompatible with the now long standing reality that genome function is highly context dependent. In organisms with complex life cycles, different life forms share the same genome, for e.g. caterpillar and butterfly. In multi-cellular organisms there is genome conservation in the differentiated cells. The phenomenon of regulation and induction in response to experimental manipulations of animal development indicate that many steps in multicellular ontogeny are often dramatically dependent on non-genomic inputs [3, 9 - 10].

3.2 The role of DNA in cellular informatics

DNA's role in information storage is considerably more complex than being just a sequence of data bits. According to Shapiro DNA stores information in at least three different forms [3]:

(i) Genetic storage
(ii) Epigenetic Storage
(iii) Computational storage

Genetic storage is that which is stored in the nucleotide sequences over many cell generations. This includes the data files for the primary structures of proteins and RNA products. Other important classes of sequence information include the repetitive signals needed to direct cellular activity on the genome. The sequence information is the most widely recognized means by which genomes carry information. It is also thought to be the most stable form of information storage. However the interesting point is that in the conventional theory, DNA sequence information is implicitly considered as Read-Only-Memory (ROM) storage. It was considered to be hard wired and changed only by accidents or malfunctioning of the replication machinery. However subsequent evidence has indicated that it is truer to consider the DNA sequence information as data stored on a hard disk. which means this data is subject to modification and the cells have the biochemical machinery to rewrite DNA sequences. From this perspective, genetic storage can work as a Read-Write (RW) memory and also as providing epigenetic and computational storage work as well [11].

Epigenetic storage means information can be stored over multiple cell generations in the form of covalent modifications to specific residues, such as cytosine methylation. There are also chromatin complexes involving proteins and RNA which are heritable. This metastable form of storage is called 'epigenetic inheritance.' Although the covalent modification patterns and chromatin configurations can be maintained over many cell cycles, they are also subject to active and rapid change by "cellular chromatin remodeling machinery.' Specific regions of the genome can be independently remodeled. Evidence indicates that modification of the epigenetic storage has a major role during cellular differentiation during multicellular development. The role of epigenetic changes in forming differentiated adult cells has clarified much of the phenomenon associated with cloning by nuclear transplantation [3, 12].

Apart from epigenetics, even computational storage also becomes relevant. This provides information about recent conditions inside and outside the cell. These are maintained by the help of transient nucleoprotein complexes reflecting the internal and external signal responses. They represent the genomic nodes of signal transduction networks and can change rapidly as particular signals increase or decrease in intensity. Thus these are short term highly dynamic forms of information storage and analogous to RAM memory that reflects the current status of the physical, nutritional and biological environment and which in turn also represents internal processes such as cell growth and progress through the cell cycle [3].

3.3 DNA is a substrate for nucleoprotein complexes

Moreover DNA is also a substrate for the nucleoprotein complexes. DNA alone does very little in the living cells. All the major cellular activities involving genome processing like compaction, replication, transcription, transmission to daughter cells, repair and restructuring all involve complexes between DNA and other cell biomolecules. Thus it is of paramount importance to involve and align those concepts with the fundamental realities at the molecular level. Analyzing and understanding the formation and turnover of the nucleoprotein complexes is central to conceptualizing genome informatics [3].

RNA guided nucleoprotein complex as well as protein guided nucleoprotein complex formations are both of necessary importance in cellular dynamics. Protein binding to DNA is based upon the recognition of consensus sequence motifs. This was first determined for the binding of lac and lambda repressors to their respective operators. Protein determined specificity in nucleoprotein complex formation arises in several cases. For example, distributed binding sites for one protein are combined with binding sites for other proteins to generate organized substrates for the cooperative formation of complexes involving several different DNA binding factors [13].

Complexes formed on a DNA segment comprising multiple binding sites can change their structures as the concentrations of the different protein factors go up and down or as individual components are degraded or chemically modified. This resulting plasticity in the nucleoprotein complex structure endows these manifold combinatorial binding regions with the ability to participate in nonlinear responses to changing conditions during complex biological processes [3].

Thus the current opinion in biology is rapidly changing in that the dynamics of nucleoprotein complex formations and breakdown provides a key basis to cellular phenomenon involving the genome. That DNA is not just a carrier of information is abundantly evident. DNA cannot be treated like a tape utilizing the Turing's distinction between a tape and a machine. Several considerations have shown us that DNA is more than a passive coded tape in genomic computations. In addition DNA has a functional role within cellular behavior and context. The structural role of DNA in nucleoprotein complex formation endows it with allosteric properties and therefore with the ability to operate as a communication molecule [14].

3.5 DNA Formatting and Genome system architecture

DNA, as an information storage medium is thus only a part of the living system. Consequently it has many functional requirements to fulfill. Some of the features may be likened to that of an electronic data storage system and there is also a vast aspect in which it is quite different. The functions that DNA provides within a living system (cellular context) are: DNA condensation within the spatial confines of the nucleus or the nucleoid, transcription access to particular RNA and protein data files under appropriate circumstances, maintenance of differentiated cellular states, genome replication, accurate transmission of genome copies to daughter cells, proofreading and damage repair, DNA restructuring during normal life cycle and during crisis.

Thus the genome's function requires that it must be formatted or conform to the specific interactions of the particular cellular components comprised of other molecules and super-molecular structures. Great specificity is necessary in regulating the functioning and expression of the thousands of data files in complex ways throughout the cell and its life cycle. The specificity relates to the structure, function and the cooperative interaction between the different formatting signals. The network of cellular components, formatting signals and repetitive motifs forming the structure and combinatorial complexity is very intricate [9, 15 - 16].

The lesson learned in molecular genetics is that genomes are organized structures. They carry out higher levels of regulation of data expression. These are all coordinated activities. Epigenetic control via chromatin formatting thus becomes a higher order form of regulation [17].

A 'genome system architecture' is defined as the genomes that are formatted and organized hierarchically for replication, transmission, regulated data file access, repair and restructuring. Computer information storage and retrieval systems have system architectures independent of the data file content. Both in computers and genome systems different architectures can achieve the same function in different ways. Genome architecture can influence the data files without altering the data files themselves. Thus there are position effects or chromosome rearrangements or transpositions of intact genetic loci that alter regulation and phenotype [19 - 20].

4. Genome is integrated into Distributed Cellular Information Processing

Conventional concepts postulate a kind of Cartesian duality between genome information stored in nucleic acids and the executive functions housed largely in proteins. However, from research

over the last five decades on the control of protein synthesis and signal transduction networks in regulating all aspects of the genome function this dualistic view has become invalidated. There are major cellular information processing realms that do involve the genome directly, e.g. control of bacterial swimming by the chemotaxic control circuit is a basic paradigm for these extra-genomic networks [22]. Other examples include rapid control of catabolism and biosynthetic aggregation of surface receptors in response to ligands, protein and vesicle targeting to distinct compartments and cytoskeletal organization. Thus quite evidently cellular activities can occur and guide important processes without accessing the DNA data files.

4.1 Involvement of whole cell in computations involving the Genome

Moreover in the model systems that have been investigated beginning from lac operon and bacteriophage λ, even up to the multicellular development of drosophila and sea urchins, everywhere there is communication between nuclear or the DNA binding transcription factors and molecules in other compartments of the cell. In the case of the *lac* operon, *lac* depression only occurs with the participation of cytoplasmic enzymes and membrane transport proteins. One cannot make a basic distinction between functional metabolism and information processing nor can one model *lac* operon control be considered as a function solely of transcription factors. Similarly there is analogous involvement of extra-genomic processes in eukaryotic signal transduction. Control of genome transcription by environmental conditions, nutrition, physiology, pheromones, hormones, intercellular signaling, cell injury or checkpoints is invariably subject to extra-genomic inputs. For example, transcription factors can be modified by protein kinases and phosphatases, which are often linked to the cell-surface receptors, receptor-activated C proteins, or second messengers. In other words transcriptional control circuitry of every cell is in continuous communication with the rest of the cell [3].

5.0 The conceptual significance of the communication paradigm

The overall conceptual significance is that communication with extra-genomic signal transduction involving cytoplasmic, organelle and surface compartments establishes that (1) organismal phenotypes are not hard wired in the genome, (2) attempts to portray cell regulatory systems as direct ‘gene to gene’ circuits are not realistically feasible, and (3) the control regimes are distributed. Thus cells can adjust to normal function and phenotype despite genetic deficiencies, developmental errors or experimental disruptions [3].

5.1 Genome as a Read – Write and not merely a Read-Only Information Storage System

There is thus short term and mid-term information written into the genome in addition to the sequence residue by residue information. This is the information stored in the nucleoprotein complexes, chromatin domains, and chemical modifications of the DNA executed by the cellular functions, and these serve as a basis for further cellular activities. Changes in chromatin configurations that do not alter DNA sequence content can be perpetuated over cell or organismal generations. Somatically heritable chromatin structures appear to serve as one aspect by which there is maintenance of the differentiated cell states. Accordingly basic cellular

processes indicate that epigenetic storage and computational storage could be regarded as a RW (Read-Write) memory. However the RW aspect of the information stored in the DNA is more difficult to see due to the very old assumption [neo-synthesis] that this information changes only accidentally and randomly. But it is a fact that cellular biochemical activities have the capacity to change the sequence information in DNA molecules [3].

It means there is now considerable knowledge of how the biochemical cellular machinery of cells has the ability to write new information. The molecules and complexes that generate novel DNA structures are subject to control by signal transduction networks and are activated in response to particular stimuli. There is also what is called 'natural genetic engineering' (NGE) tools that can be targeted to regions, sites or specific inter-nucleotide bonds in the genome. These natural genetic engineering tools include the nucleases, ligases, polymerases, homologous recombination proteins, non-homologous end-joining systems, site specific recombination systems, DNA transposons, reverse transcriptases and retrotransposons, and combinations of all the above [3, 22, 23].

Thus in many organisms, controlled DNA rearrangement is a part of the normal life cycle. Examples include bacterial phase variation and cell differentiation, yeast mating type interconversion, macronuclear development in ciliated protozoa, chromatin diminution in invertebrate somatic development etc. Thus organisms utilizing DNA restructuring are taxonomically very diverse. These DNA rearrangements fulfill specific purposes in the life cycle. And thus they serve as counterexamples to the widespread belief or the conventional ideas stemming from Central Dogma that genome changes must occur only stochastically and cannot be targeted in any functional way. Although the belief is widespread that the insertions of mobile genetic elements and sites of action of other DNA rearrangement systems are random in the genome, on the contrary evidence for targeting is quite extensive. These include sequence recognition by proteins, protein – protein interactions, sequence recognition by RNA, transcriptional activation, telomere targeting of certain LINE elements in insects and Pfactor homing directed by internal transcription factor sites and chromatin signals [24 – 27].

Thus when we speak of an evolutionary hypothesis, the new focus takes us to a radically new stance than what was offered until now. Thus it is a growing conviction among many scientists that we must turn our thoughts in the direction of a whole cell approach instead of thinking about it from a random or a mutational approach. Additionally here there is a role of diverse components within the cell like the NGE systems. And for a proof they cite similarities in the genome sequences between species which are taxonomically diverse. Thus Shapiro postulates that the NGE functions have provided informatics/ computational inputs in influencing the novel configurations that were tested and selected. Thus in the face all these developments within the context of cellular cognizant behavior, evolution can no longer be taken as a blind walk. Organic development needs to be re-conceptualized as a systemic and guided process. Furthermore the guided process or targeting involves facilitating the fine tuning of the individual components. Some suggest that fine tuning occurs when exon joining and clonal selection are followed by somatic hypermutation targeted to exons encoding antigen-binding domains. And the suggestion is also that NGE tools leads to the accumulation of dispersed repeats.

This conception leads to a functional hypothesis. Since the dispersed repeats influence both the coding sequence expression and also the physical organization of the genome, it is reasonable to entertain the functional hypothesis that repeat accumulation represents the establishment of a system architecture required for effecting genome functioning. Thus the significant outcome from these observations is that complexity of cellular sentient phenomena necessitates the search for a higher order concept than what has been given within Darwinian and reductionistic paradigms.

6.0 What is fundamentally new?

Classical molecular genetics has not proved particularly helpful in formulating a conceptual framework for interpreting the ever widening catalogue of genes, proteins, RNAs, pathways and networks that molecular cell biology and genome sequencing has uncovered. Thus Shapiro's approach is to focus on a non-reductionistic computational basis for a whole cell dynamics [3]. These are the natural consequences of the failure of all reductionist frameworks like Central Dogma.

Further, cellular life in the systemic context cannot be reduced to genomic units. Genomes are not indivisible. However by emphasizing the systemic nature of the genome function, Shapiro suggests that genomic informatics avoids the reductionist fallacy of claiming that a given segment of the genome determines a particular trait. In this view, each data file or repetitive signal may contribute a necessary component to phenotypic expression, but individual sequence elements can never be sufficient to encode a trait by themselves. Thus we require a more intrinsically systemic view. Furthermore even the so called non-coding genomic information is essential and there are major functional roles for these repetitive DNA sequence elements that format and organize the genome and its data files during the multiple tasks and organismal life cycle within the cellular context [3].

All these development have brought revolutionary consequences for the evolution theory. Central dogma does not provide any basis for the molecular evolution of life. It has proved utterly fallacious in its assumptions. All these years of research in searching for a so called ancestor molecule have also failed. RNA world theory and all other concepts have proven limited and infeasible. Within a cellular context, genome function involves an intrinsically complex series of molecular interactions. These are more complex than any non-living complex phenomenon. The living context prevents the system from relapsing into attractor states in the sense of a non-living complex state [3]. Thus life is a demonstration of an existing contradiction between variability and invariability. These interactions or the systemic interaction involves the information contributed from genome, the extra-genomic substance, computational information relating to the transient complexes and that from the environment.

Moreover these complex interactions produce outputs with remarkable accuracy and coordination. Unbalanced growth, chromosome non-disjunction, inappropriate cell differentiation, and unprogrammed cell death are rarely observed. The cellular context is greatly geared for conservation and stability within its own cellular identity and context. This is its

survival principle. All of these considerations indicate a need for systemic guidance coordinating the huge numbers of biochemical and biomechanical operations necessary for every cell cycle. Now scientists and especially biologists are beginning to acquire knowledge of how these guiding computations occur, at least in a very abstract sense of the term, say in the form of checkpoints. But elucidating the underlying general principles will be the key goal of the twenty first century. And within an evolutionary concept, the task has just become more complex than the mere attempt to synthesize a biomolecule, as ultimately that is not life. Life must be re-conceptualized at the systemic level to be precise within a cognitive context and that calls for a deeper search for a more comprehensive reality. The blind walk of the Darwinian paradigm does not seem to provide the necessary and sufficient criteria for the diversity of living forms in the light of the information paradigm which is proving to be a basis for the search for new biology of genome informatics within the cellular context.

The picture that is emerging from the complex processes that are going on within the simplest cells is that DNA has a more participatory role in a dynamic system that maintains a stable integrity and control over its own content of interacting constituents that form an utterly restless dynamical milieu. All moieties within the cell participate in a constant process of construction, maintenance and destruction (metabolism) that is a pervasive characteristic at both the local (biomolecular) and global (cellular) levels, not to mention the vital ecological level essential to its very being and survival.

In a news article published in New York Times [28], it was reported that, “In a startling discovery, geneticists at Purdue University say they have found plants that possess a corrected version of a defective gene inherited from both their parents, as if some handy backup copy with the right version had been made in the grandparents' generation or earlier. The finding implies that some organisms may contain a cryptic backup copy of their genome that bypasses the usual mechanisms of heredity. If confirmed, it would represent an unprecedented exception to the laws of inheritance discovered by Gregor Mendel in the 19th century. Equally surprising, the cryptic genome appears not to be made of DNA, the standard hereditary material. The discovery also raises interesting biological questions - including whether it gets in the way of evolution, which depends on mutations changing an organism rather than being put right by a backup system. "It looks like a marvelous discovery," said Dr. Elliott Meyerowitz, a plant geneticist at the California Institute of Technology. Dr. David Haig, an evolutionary biologist at Harvard, described the finding as "a really strange and unexpected result," which would be important if the observation holds up and applies widely in nature. … The finding poses a puzzle for evolutionary theory because it corrects mutations, which evolution depends on as generators of novelty. … Dr. Pruitt said it was not yet known if other organisms besides arabidopsis could possess the backup system. Colleagues had been quite receptive to the idea because "biologists have gotten used to the unexpected," he said, referring to a spate of novel mechanisms that have recently come to light, several involving RNA.”

Take the example of axial rotation. In the axial rotation of a sphere we can find a metaphor for the fixity of the dimensionless linear axis (or self-identity) in the midst of an otherwise wholly dynamic content (or body). Life exhibits this type of fixity of its integral identity within a milieu of ubiquitous internal and external flux. In other words, the scientific understanding of life must embrace an appropriately complex description that is truly worthy of this idea, if people are to

give genuine consent to it and avoid the constant and unresolved debate that the lesser/reductionist concept has perennially produced. Shapiro represents the new biologists who eloquently try to capture this idea in all its scientific detail. He summarizes the direction his work has taken him in the following abstract from his paper "Bacteria are small but not stupid" [27]:

"Analysis of cellular processes such as metabolism, regulation of protein synthesis, and DNA repair established that bacteria continually monitor their external and internal environments and compute functional outputs based on information provided by their sensory apparatus. Studies of genetic recombination, lysogeny, antibiotic resistance and my own work on transposable elements revealed multiple widespread bacterial systems for mobilizing and engineering DNA molecules. Examination of colony development and organization led me to appreciate how extensive multicellular collaboration is among the majority of bacterial species. Contemporary research in many laboratories on cell–cell signaling, symbiosis and pathogenesis show that bacteria utilise sophisticated mechanisms for intercellular communication and even have the ability to commandeer the basic cell biology of 'higher' plants and animals to meet their own needs. This remarkable series of observations requires us to revise basic ideas about biological information processing and recognise that even the smallest cells are sentient beings."

7.0 Conclusions

To abstractly isolate an organism from the whole matrix in which it derives and sustains its vitality is to reduce the fullness of life to a subjective ideality that is useful only to a finite anthropomorphic mind but neither expressive nor descriptive of natural reality as it is in and for itself. In other words, simplified models developed in the physics and chemistry of matter cannot naively be applied at the more complex biological level of life.

Thus content as well as concept must be considered. There is a limit placed on the randomness of the system. It allows adaption but at the same time the cell maintains its integrity. The identity or the integrity of the organism is that which is constraining the cell. Continuance of the identity is necessary for its survival. This identity is constraining the structure and functionality. Laws of physics and chemistry create order. But a cellular organization (to which the idea of organism is related) requires that certain functions are to be fulfilled. Structural order is not the same as functional organization, and the former does not encompass the latter. Prigogine's idea of ordering systems has not proven sufficient since it does not explain organization. Organization implies that certain functional requirements are met. Function creates order but on the other hand order does not create functionality. Thus a biological system has a concept of self that is organizing itself. It has its sentience as many contemporary publications are beginning to recognize. Integral individuality and its maintenance, is called its survival principle. Every living entity has that principle – as a unit, as self-preservation or as a self.

References

[1] Francis Crick, "Central Dogma of Molecular Biology", Nature, Vol. 227, 1970, pp. 561-563.

[2] Carl R. Woese, "A New Biology for a New Century", MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS, June 2004, pp. 173–186.

[3] James A. Shapiro, “Genome Informatics: The Role of DNA in Cellular Computations”, Biological Theory 1(3) 2006, 288–301.
[4] Attila Grandpierre, Biological Extension of the Action Principle, NeuroQuantology, Dec 2007, 4, pp. 346-362.
[5] Bitboll, M., & Luigi, P. L. (*in preparation*). *Autopoiesis with or without Cognition: Defining Life at its Edge*.
[6] Lyon, P. (*in press*). Realization of the *Knowing*: Reflections on Maturana’s Biogenic Explanation of Cognition. *Cybernetics & Human Knowing*.
[7] Müller, B. S., di Primio, F., & Lengeler, J. W. (2001). Contributions of Minimal Cognition to Flexibility. In N. Callaos, W. Badawy & S. Bozinovski (Eds.), SCI 2001 *Proceedings of the5th*
[8] Taylor, B. L. (2004). An Alternative Strategy for Adaptation in Bacterial Behavior. *Journal of Bacteriology*, *186*, 3671 - 3673.
[9] Spemann H (1938) Embryonic Development and Induction. New Haven, CT:Yale University Press.
[10] Spemann H, Mangold H (1924) U ber Induktion von Embryonanlagen durch Implantation artfremder Organisatoren. Roux’ Archiv fur Entwicklungsmechanik 100: 599–638.
[11] Shapiro JA, von Sternberg R (2005) Why repetitive DNA is essential for genome function. Biological Review 80: 227–250.
[12] Muller C, Leutz A (2001) Chromatin remodeling in development and differentiation. Current Opinion in Genetics and Development 11: 167–174.
[13] Lippman Z, Gendrel AV, Black M, Vaughn MW, Dedhia N, McCombie WR, Lavine K, Mittal V, May B, Kasschau KD, Carrington JC, Doerge RW, Colot V, Martienssen R (2004) Role of transposable elements in heterochromatin and epigenetic control. Nature 430: 471–476.
[14] Cases I, de Lorenzo V (1998) Expression systems and physiological control of promoter activity in bacteria. Current Opinion in Microbiology 1: 303–310.
[15] von Neumann J, Burks AW (1966) Theory of Self-Reproducing Automata.Urbana: University of Illinois Press.
[16] Marino-Ramirez L, Lewis KC, Landsman D, Jordan IK (2005) Transposable elements donate lineage-specific regulatory sequences to host genomes. Cytogenetic and Genome Research 110: 333–341.
[17] Van Driel R, Fransz PF, Verschure PJ (2003) The eukaryotic genome: A system regulated at different hierarchical levels. Journal of Cell Science 116: 4067–4075.
[18] Kosak ST, Groudine M (2004) Gene order and dynamic domains. Science 306: 644–647.
[19] Hazelrigg T, Levis R, RubinGM(1984) Transformation of white locus DNA in drosophila: Dosage compensation, zeste interaction, and position effects. Cell 36: 469–481.
[20] Schotta G, Ebert A, Dorn R, Reuter G (2003) Position effect variegation and the genetic dissection of chromatin regulation in Drosophila. Seminars in Cell and Developmental Biology 14: 67–75.
[21] Armitage JP, Holland IB, Jenal U, Kenny B (2005) “Neural networks” in bacteria: Making connections. Journal of Bacteriology 187: 26–36.

[22] McClintock B (1984) Significance of responses of the genome to challenge. Science 226: 792–801.
[23] Wessler SR (1996) Plant retrotransposons: Turned on by stress. Current Biology 6: 959–961.
[24] Haber JE (1998) Mating-type gene switching in Saccharomyces cerevisiae. Annual Review of Genetics 32: 561–599.
[25] Muller F, Bernard V, Tobler H (1996) Chromatin diminution in nematodes. Bioessays 18: 133–138.
[26] Prescott DM (2000) Genome gymnastics: Unique modes of DNA evolution and processing in ciliates. Nature Reviews Genetics 1: 191–198.
[27] Goday C, EstebanMR(2001) Chromosome elimination in sciarid flies. Bioessays 23: 242–250.
[28] Nicholas Wade, New York Times, March 23, 2005.
[29] JA Shapiro, Bacteria are small but not stupid: cognition, natural genetic engineering and socio-bacteriology, Stud. Hist. Phil. Biol. & Biomed. Sci. 38 (2007) 807–819.