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Biological information systems: Evolution as cognition-based information management

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ABSTRACT

An alternative biological synthesis is presented that conceptualizes evolutionary biology as an epiphenomenon of integrated self-referential information management. Since all biological information has inherent ambiguity, the systematic assessment of information is required by living organisms to maintain self-identity and homeostatic equipoise in confrontation with environmental challenges. Through their self-referential attachment to information space, cells are the cornerstone of biological action. That individualized assessment of information space permits self-referential, self-organizing niche construction. That deployment of information and its subsequent selection enacted the dominant stable unicellular informational architectures whose biological expressions are the prokaryotic, archaeal, and eukaryotic unicellular forms. Multicellularity represents the collective appraisal of equivocal environmental information through a shared information space. This concerted action can be viewed as systematized information management to improve information quality for the maintenance of preferred homeostatic boundaries among the varied participants. When reiterated in successive scales, this same collaborative exchange of information yields macroscopic organisms as obligatory multicellular holobionts. Cognition-Based Evolution (CBE) upholds that assessment of information precedes biological action, and the deployment of information through integrative self-referential niche construction and natural cellular engineering antecedes selection. Therefore, evolutionary biology can be framed as a complex reciprocating interactome that consists of the assessment, communication, deployment and management of information by self-referential organisms at multiple scales in continuous confrontation with environmental stresses.

Contents

Abbreviations: CBE, cognition based evolution; PIF, pervasive information field; HGT, horizontal gene transfer; ERV, endogenous retrovirus; TE, transposable element; miRNA, micro RNA; ncRNA, non-coding RNA; piRNA, piwi-interacting RNA; RNAi, RNA interference; endo-siRNA, endogenous short interfering RNA; *EI*, effective information; viRNA, virus-derived, small-interfering RNA; mRNA, messenger RNA; HIV, human immunodeficiency virus; C. *elegans*, *Caenorhabditis elegans*; *E. coli*, *Echerichia coli*; LTR, long terminal repeat.

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1. Introduction

Developmental biology can be seen as the study of how information in the genome is translated into adult structure, and evolutionary biology of how the information came to be there in the first place

Maynard Smith

The traditional canonical Neodarwinian evolutionary narrative concentrates on the survival mechanisms of macroscopic organisms through random heritable variations and differential fitness (Bowler, 2003). The sources of those variations have been ascribed to random genetic mutations along fitness landscapes (Poelwijk et al., 2007). As a result, evolution has been typically framed as a direct product of changing gene frequencies (Koonin, 2009). Contemporary research has placed increasing emphasis on the evolutionary role of epigenetics which can further extend genetic expression from a flexible genome (Jablonka and Lamb, 2008; Laland et al., 2015). However, such alterations are typically considered within the framework of an already existing expansive genome upon which smaller modifications might act. An understanding of the mechanisms that permit the erasure of some epigenetic marks and the inheritance of others prior to arbitrating selection is still limited (Feng et al., 2010; Houri-Zeevi and Rechavi, 2016). The further mechanisms by which genomes accrete their widely variable sizes and ranges of biological expression and still retain effectiveness is not well understood (Eddy, 2012). Surprisingly, the question of why multicellular eukaryotes are obligatory holobionts or how that might affect levels of selection is little considered. (Miller, 2016a; Corning and Szathmáry, 2015; Theis et al., 2016). Most pertinently, although the mystery of cognition has been deeply weighed, there has been little regard for the role of universal basal cognition in biological development and a distinct disinclination to consider its evolutionary implications.

To further evaluate these issues, an exploration of evolutionary development is presented that focuses on the nature of biological information content, and its transfer and management, within the context of cellular faculties and constraints. This perspective is offered as a substantiating complement to previous arguments affirming the central role of self-referential cognition in evolutionary development (Miller, 2016a; Torday and Miller, 2016a, 2016b, 2017a; Miller and Torday, 2017).

2. The origin of biological information

2.1. Self-reference

That aspects of biology such as genes might be considered within an information framework is not new (Dodig-Crnkovic, 2014). Peter Medawar, the eminent British biologist, had addressed the concept decades ago, indicating that, "…… in speaking of genes and chromosomes, the language of information theory is often extremely apt. " (Kay, 1998). More recently, Griffiths (2017) argued that it is direct common sense to consider the development of evolved characteristics as the expression and transmission of information but laments the difficulty between theory and practice. For Walker and Davies (2013), that linkage is plain, declaring that information became the key to life by achieving " direct and context-dependent causal efficacy over the matter in which it is instantiated.".

It follows that an examination of biology should begin with the recognition that the boundary between the animate and inanimate lies within the capacity of living things to discriminate an individuated status such that physical states become biological information (Miller, 2016a). This can be regarded as a working definition of self-referential cognition in which the living condition is delineated by an awareness of status upon which adjustments might be made. That all living things have this capacity is not conjectural. It is now acknowledged that all living things exhibit basal cognition through such a fundamental awareness of status (Shapiro, 2011; Trewavas and Baluška, 2011; Miller, 2013, 2016a; Baluška and Mancuso, 2009; Dodig-Crnkovic, 2014). This is embodied within cells by negentropic boundary conditions, sustained by chemiosmosis, and maintained by homeostasis (Torday, 2015). The living state therefore extends from the physical environment through Schrödinger's "consumption of negative entropy" within boundary conditions by energy (ATP) transfers in a manner that information-based projections of status can be realized. (Jacob et al., 2006). Thus, intrinsic cellular properties that derive from the physical environment permit the self-referential reactions to environmental stresses that preserve preferred homeostatic flux boundaries. Plainly though, as such actions are achieved through the assessment and use of information and its pragmatic deployment, there is substantial justification for considering biology within an informational construct. (Miller, 2016a; Torday and Miller, 2016a, 2017a; Roederer, 2016; Ball, 2016; Cartwright et al., 2016).

Although the origin of self-reference is unknown, it has been attributed to a derivative of the thermodynamic scale as its own state function as a phase transition (Miller, 2016a; Eigen, 2013). Eigen (2013) considered that phase transition as a complexity threshold that had both entropic and semantic qualities that emerged from the reproduction and transmission of information. Proponents of complexity biology have suggested that this complexity threshold is a matrix of self-organized criticality. These are zones of instabilities that maximize information diversity in which the regulation of information processing might be optimized (Hankey, 2015). It has been proposed that it is within these zones of criticality that coherences can occur that enable the self-observing systems that underlie the integrated feedback loops that enable the living process (Hankey, 2015). Computational research has shown that the most favorable conditions for information storage and transmission can be identified as residing in the vicinity of such phase transition criticalities (Langton, 1990).

Others have considered the emergence of life as a first-order

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phase transition creating a gap between the animate and inanimate that occurred during a period of environmental shifts (Mathis et al., 2017). At that crucial period, it has been proposed that selection drove an explosive growth of replicators that altered the balance of the degree in which physical data as pre-biologic information was shared between the outer environment and primordial replicators. Therefore, the origin of life could be understood as the transition from physical data into pre-information that could replicate. Attempts have been made to place this within a mathematical context, wherein, entropy can be considered primordial information in probabilistic zones of preferential concentration of essential monomers, such as carboxylic acids, that could actuate potential candidates for biochemistry (Adami, 2016).

Placing all such theories aside, it is argued that the origin of life should be considered as coincident with the instantiation of self-reference. Furthermore, self-reference actualizes biological information as an ordered derivative of physical data. As an important codicil, 'self' should be seen as a process rather than any specific state (Hankey, 2015) and, further too, that process is the faculty that permits the awareness of information and its inherent limitations that can be flexibly deployed to maintain homeostatic equipoise.

Since self-reference defines the crucial aspect of the living state, then no matter the exact nature of its origins, it becomes the proper platform for the further consideration of its evolution. It deserves emphasis that this exploration of self-awareness within biology and evolution acknowledges it only as a property whose influences arise from preexisting physical states through which it might be measured. Its presence does not imply any evolutionary direction or teleological purpose beyond its own maintenance and survival. Thus, it is not different in kind than the Darwinian pre-condition of faithful DNA replication as its own relevant point of origin and whose origins also remain unknown. In effect, Dawkin's preservation of 'selfish genes' as a robotically disembodied program (Dawkins, 1981) is properly enlarged to encompass a 'selfish' living entity whose testable drive is to maintain individual homeostatic equipoise as a process and nothing more. Yet, admittedly, there is a crucial difference. Self-reference simultaneously enacts biological information that, unlike physical data, is predicated within ambiguity (Torday and Miller, 2017a).

As the living state uses information to assess individuated status, then the self-referential appraisal of information also characterizes cells of all types including individual eukaryotic cells (Shapiro, 2011; Trewavas and Baluška, 2011; Miller, 2013). Therefore, the capacity to use information unites the organizational structure that exists among all living organisms (Trewavas and Baluška, 2011; Gamow, 1955). Further, then, it becomes implicit that any organized use of information has the inherent requirement of systematic ordering which should be properly deemed as a form of systematic information management.

It has been previously advocated that communication of information characterizes all living organisms.

(De Loof, 2015a). At the cellular level, the direct purpose of that communication is the maintenance of self-referential homeostatic equipoise in confrontation with an often agitating external environment (Torday and Rehan, 2012). As all macrooganisms are dependent on such communication for their own survival, it can be advanced that the communication of information and its assessment are fundamental to the survival and well-being of all organisms across the unicellular and macroscopic scales (Torday and Rehan, 2012). From this perspective, several further assertions derive. First, attachment to an informational matrix is a definitional necessity for all living things as this represents the well-spring of information that might be communicated to sustain organismal-environmental complementarity (Miller, 2016a). Secondly, if the assessment and communication of information is a universal feature of living organisms to survive, then, all biological processes should be assumed to participate in some aspect of the acquisition, distribution, implementation or management of that information. It then follows that any comprehensive evolutionary narrative must concentrate on the means by which living entities acquire, assess, and deploy information.

2.2. A requisite attachment to information space

It has been previously advanced that all living entities assess information beyond their immediate environment and exist as part of a system of Pervasive Information Fields (PIFs) (Miller, 2016a). These fields of information are best modeled after the concept introduced by Lloyd (2002) as self-organizing, universal and scale free informational sets that can be appropriately applied to biological organisms. Within this frame, each living organism has its own unique information field within space-time as an attachment to an outward information space. This is composed by its physical environment and by the overlap of all the individualized information fields of each of the varied constituents with which it can communicate, both near and far (Fig. 1).

This unfamiliar frame of reference in the individual and collective use of systematized information can be illustrated in living systems. For example, bacteria of the symbiont genus *Spiroplasma* produce a series of ribosome-inactivating proteins that protect Drosophila *necotestacea* against attack by two of the three parasites wasps that can infect it (Ballinger and Perlman, 2017). The genomes of the Spiroplasma strains have determined how to target two of the three dissimilar parasites without apparent harm to the holobiont. The subtle intricacies of toxin diversity based on individual and collective sources of information has become encoded as information through genomic variations between *Spiroplasma* and D. *necoctestacea.* Each of the participants is attached to its own sources of information, directed towards individual goals, yet all become a part of the summary information field of the larger organism which, in turn, overlaps the outward environment.

The recent discovery of bacteria living in human pancreatic ductal adenocarcinoma associated with chemotherapy resistance serves as another example of how information fields intersect (Geller et al., 2017). Some of the Gammaproteobacteria that co-exist within the tumor can metabolize gemcitabine, contributing to chemotherapeutic resistance. Other bacterial strains within the tumor are exposed, yet unaffected, and continue to interact metabolically in other ways with tumor cells. Within that tumor ecology, environmental cues are experienced by normal cells, the tumor cells and the bacteria in a shared informational matrix, with each expressing independent but co-linked outcomes based on their individual PIFs.

Two issues of considerable significance directly extend from the concepts of information fields and underscore their conceptual utility. First, every self-referential organism is both observer and participant in its attachment to its own PIF and to the others that it overlaps. It is through this duality that an organism maintains its environmental correspondence and reciprocally communicates with other ecological participants (Miller, 2016a; Torday and Miller, 2016b). This places all living things within a complex informational interactome that becomes an informational architecture which can underscore communication and the complex cooperative behaviors that characterize multicellular life. Secondly, the same principles for the uses and management of information perseverates at all subsequent reiterating scales from unicell to holobiont. The epicenter of the assessment of information always remains at the level of the individual self-referential cell through its exclusive individualized PIF as it intersects all others.

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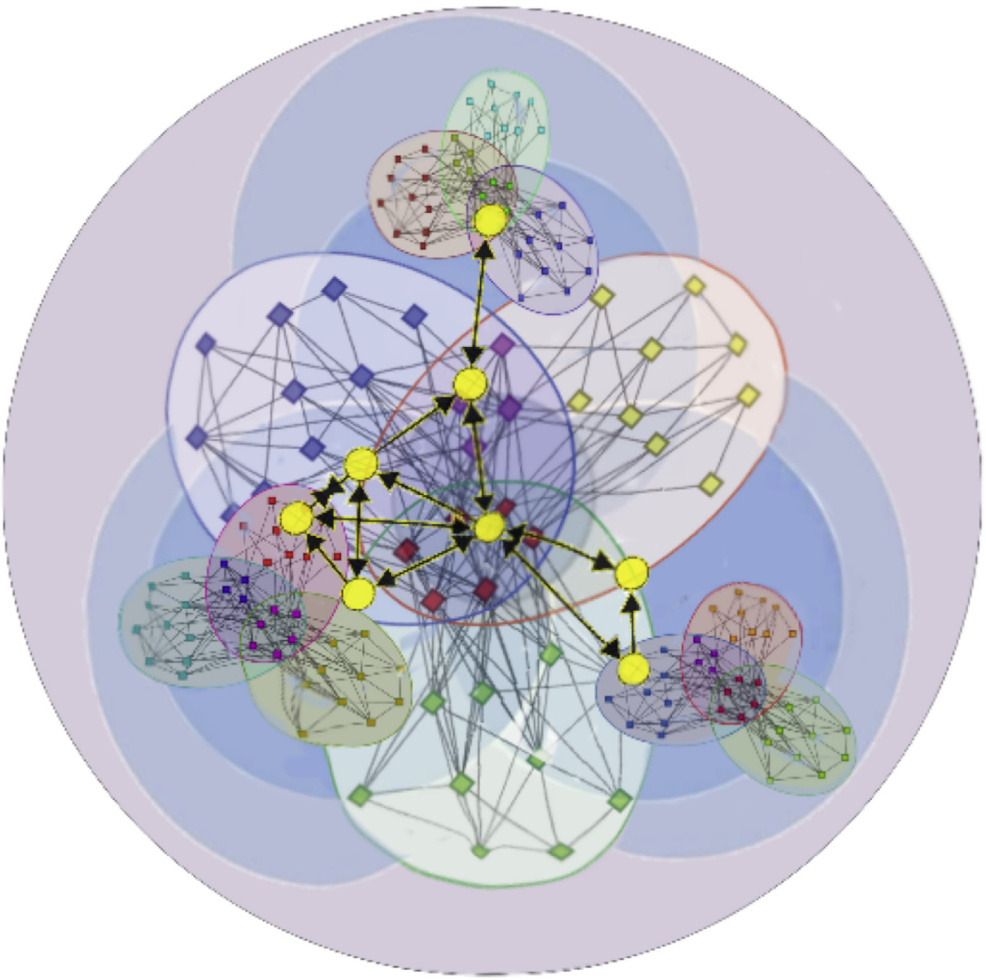

Fig. 1. Schematic overlap of biological and physical information fields. Single organisms with their own dimensional Pervasive Information Fields (connected circles) intersect other organisms and populations of organisms with their own individual fields (connected squares). Each have varied boundaries of local and distant biological activity (ovoid boundary lines) that exist within overlapping matrices of pertinent physical information fields (large circles).

2.3. Biological information

Examination of genetically encoded biological information indicates that it is fundamentally unlike Shannon entropy. The crux of that difference is that information in a biological context must exist within 'meaning' (Koonin, 2016). For Shannon, information can be defined through entropy as a discrete set of probabilities to a receiver that reduces uncertainties. In biology, there is another dimensional aspect: information has both a probabilistic and linguistic contexts over an observable data set (Solomonoff, 1997). In biology then, meaning must relate to biological action through its measuring value as biological expression in space and time. That 'meaning' can be regarded as expression of biological information over time rather than having any strict relationship to the degree to which any specific biological sequence deviates from a set of random expectations. This relationship can be appreciated as the connection between a living thing and informational space-time in which the measuring value of time is achieved through its genetic evolutionary conservation (Koonin, 2016).

In some manner then, physical states must stand apart from biological information. Adami (2016) illuminates the difference concluding that information is, “that thing that which allows a living thing to make predictions with accuracy better than chance alone”. When placed in that perspective, any attempt at equivalence or linkage between entropy and information strictly rests on the availability of an information receptor. In sum, it becomes a function of measuring (Adami and LaBar, 2015). Such apportionment is precisely conditional on an observer/participant. As has been advanced, that stance is dependent upon its linkage with its own PIF. Since the amount of information that might be derived from any physical object is theoretically infinite, the entropy within a system as uncertainty must relate to the constraints that biological context imposes on information. No matter the scale then, such a delimitation connotes the assumption of being validated beyond simple stochastic variables. In biologic terms, this devolves into anticipation of outcomes beyond random occurrences. As any notion of anticipation naturally depends upon self-reference, the self-referential state can now be refined as a function of the restriction of sets of variables within boundary conditions. Necessarily then, stabilizing boundary conditions become a life requirement as a necessary self-organizing principle for the evolution of regulatory mechanisms (Yufik and Friston, 2016). Even more particularly, boundary conditions are the explicit biological circumstance in which the anticipation of outcomes becomes a conspicuously narrowed informational set and outcomes might thereby deviate from random. Importantly, the significance of

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boundaries ramifies beyond physical membranes or cellular compartmentalization. Sources of information require their own boundaries lest all inputs become chaotic overlaps. Therefore, the concept of a restricted informational set as a Pervasive Information Field receives validation as inherent to the living condition.

Furthermore, such boundary conditions are not restricted to cells. Recent research into the Human Immunodeficiency Virus-1 (HIV-1) capsid reveals a highly complex asymmetric structure with approximately 1300 proteins (Perilla, and Schulten, 2017). The virus is highly dependent on this capsid for its infective cycle. Different segments of the capsid oscillate at different frequencies through structural fluctuations with acoustic and mechanical properties. Thus, a viral capsid is much more than a protective coat, but a highly functioning boundary condition and integral aspect of its information system.

Boundary conditions for biological information also serve another purpose. All information in biological contexts is inherently noisy and ambiguous (Miller, 2016a; Torday and Miller, 2017a). The communication of biologic information is subject to degradation by distance, time delay between delivery and receipt, the uncertain origins of broadcast information, or distortion by the medium of transmission. The sources of error compound through its interpolation through the idiosyncratic Pervasive Information Fields that represent the information space-time boundaries of each organism. As each of these overlap others in an extended series, ambiguity is inextricably embedded within biological information through these interactions (Miller, 2016a; Torday and Miller, 2016b, 2016c, 2017a,b; Miller and Torday, 2017). The transfer of information from one individualized field to others which overlap incorporates inevitable degradation. In the terms of information, this can be best understood as sources of noise and error.

The circumstances in which information is imprecise among biological participants has been considered in the context of deviations from random variables in a probabilistic quantum system (Torday and Miller, 2017a). In that situation, it can be framed as incomplete information about the system (Khrennikov, 2007). However, in the self-referential frame it can be construed differently and viewed as an expression of anticipation or prediction based on quantum-like inferences (Miller, 2016a; Torday and Miller, 2017a). The biological expression that derives from any such information set would then involve a representational matrix of an upper and lower boundaries of expectational status. This can be properly considered as a set of implicates about any response to environmental stresses. Necessarily, any set of implicates requires boundary conditions of an otherwise infinite constellation if there is to be any settlement into biological expression. Therefore, the necessary boundaries through which all living things exist (membranes, PIFs) can now be understood as the only means by which uncertain information can be confronted within an actionable space-time information matrix (Miller, 2016a; Torday and Miller, 2017a). This accords with the assertion that the spatio-temporal patterns in organisms exist to support maximal predictability in space-time, which has been previously advanced as a 'principle of optimality' (Igamberdiev and Shklovskiy-Kordi, 2017).

When the constraints of biological information are appreciated, the self-referential assessment of ambiguous information and its requisite management to effect coherent deployment offers a reasoned platform for the further consideration of evolutionary development as a complex informational interactome (Fig. 2). From the instantiation of self-reference, an information cycle can be identified that builds the informational architectures that living things represent. Further collaborative linkages can then be understood to constitute the dominant informational motifs that characterize all of biology despite its wide variety of observable and vivid forms.

3. The information cycle

3.1. The communication and accumulation of genetic information

Although a large number of mechanisms for the transfer of information are now known to operate inside and among cells, any fruitful discussion of information in biology and evolution must appraise the crucial scope of genetic information content (Biémont and Vieira, 2006; Heinemann and Roughan, 2000; Koonin and Wolf, 2009). This must include a consideration of the means by which genomes accumulate a repository of information content and the varieties of genetic transfer mechanisms.

Epigenetic impacts are increasingly acknowledged as among those influences. Although initial studies had initially concentrated on the epigenetic effects of environmental exposures, a wide range of genetic transfers are now also considered epigenetic functions, some of which are deemed heritable over subsequent generations (Dolinoy et al., 2007; Champagne, 2008; Wild et al., 2013). Although epigenetic alterations can often be reversed, the heritable transmission of traits from DNA methylation or histone modification can be stable for generations (Oppermann, 2013; Mead and Sarkar, 2014). Stable inheritance patterns which can be identified in succeeding generations are acquired through transmissible non-coding RNAs of various types, including resistance to viral infection contributed as adaptive immunity. For example, Flock House virus in C. *elegans* produces virus-derived, small-interfering RNAS, (viRNAs) that demonstrate persistent trangenerational inheritance (Rechavi et al., 2011). Within an information context, such epigenetic impacts can be productively considered as a means of a continuous organismal-environmental match in which information about the environment is communicated to organisms for adaptative variations that do not require wholesale rearrangements of a central genome.

Genome-wide association studies of physiological traits, phenotype and some diseases indicate that intrinsic changes within a central genome including genetic mutation or allelic polymorphisms can only account for a small proportion of observed heritable variation (Trerotola et al., 2015). Epigenetic mechanisms appear to account for this evolutionary discrepancy through a wide range of influences including DNA methylation or its erasure, persisting histone and chromatin modifications based on environmental stresses, and the stable heritable transfer of a large range of RNA types (mRNA, miRNA, siRNA, piRNA, viRNA). The range of these effects can be surprisingly subtle. Blocking a specific miRNA in Drosophila prevents the fly from righting itself to a correct position if placed upside down (Picao-Osorio et al., 2015). Studies in monozygotic twins that share an identical genotype can demonstrate significant phenotypic discordance and disease susceptibilities (Fraga et al., 2005). Although twins share a nearly identical epigenome at birth and in early life, their genomic distribution of 5-methylcytosine DNA and histone acetylation, increasingly diverges over time. Therefore, environmental epigenomic adaptations may be nearly as critical as central DNA sequences to the long-term stability and success of organisms, conferring not only transmissible phenotypic but behavioral plasticity to organisms (LaFreniere and MacDonald, 2013).

The extent of the influence of small RNAs on DNA methylation and histone modification as contributing factors in gene expression is sufficient that the evolution of organic complexity might be heavily weighted towards their deployment (Costa, 2008). The cross-talk between long non-coding RNAs, coding RNAs, transcribed pseudogenes, and messenger RNAs that communicate through miRNAs can be framed as a form of structural 'language' that expands functional genetic information and acts as a large-scale regulatory network across the transciptome (Salmena et al.,

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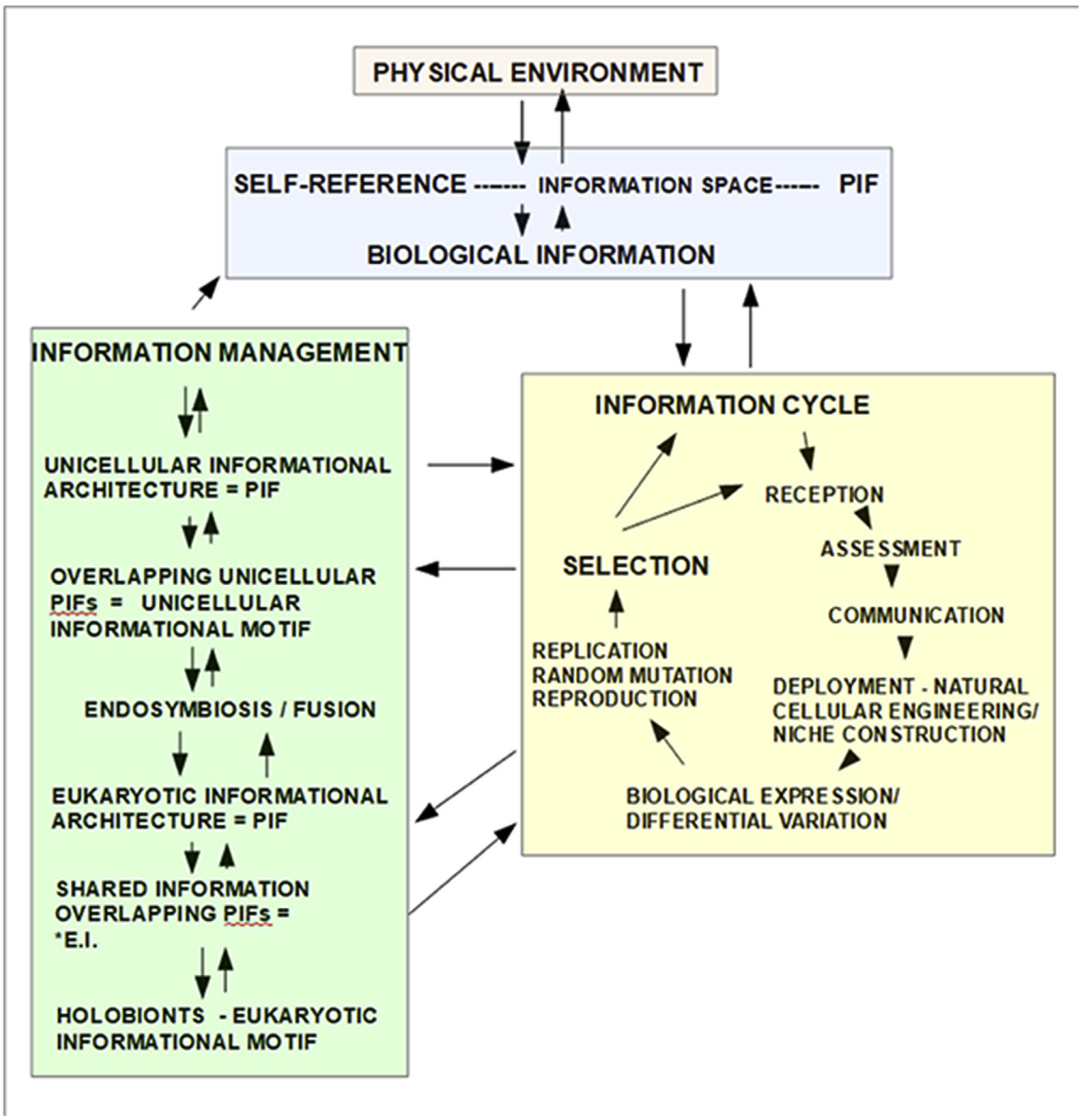

Fig. 2. The cognitive informational interactome reciprocates between the physical environment and self-referential attachment to information space-time through individualized Pervasive Information Fields. Self-reference creates biological information distinct from physical data based on the inherent ambiguities of the observer/participant status of living organisms. Biological information is received, assessed and deployed in a repetitive information cycle. This yields the unicellular and eukaryotic informational architectures and respective informational motifs that characterize systematized biological information as stabilized biological expression. Selection is a crucial post-facto filter of both niche construction and natural cellular engineering as problem-solving and random mutations, thereby helping to enforce continuous organismal-environmental complementarity.
*E.I = Effective Information.

2011). Importantly, it has been identified that there is reciprocal cross-talk at multiple levels. For example, miRNAs can regulate their targets, but it is now clear that the sequences that miRNAs target can reciprocally regulate the function of miRNAs themselves and govern their profusion (Pasquinelli, 2012). Such miRNAs have been identified as key regulators of gene expression at the post-translational level and their abundance suggests that they are critical to the evolution of biological complexity (Berezikov, 2011). Since these mechanisms are highly coordinated and permit trans-generational heritable transmission, this interaction should be considered a sophisticated transgenerational information system that affords a flexible set of adaptations to shifting environmental circumstances (Ho and Burggren, 2010; Lange and Schneider, 2010). Research has shown that similar epigenetic mechanisms even include prions as important aspects of heritable adaptive responses to environmental extremes (Halfmann and Lindquist, 2010).

It is a convention to consider cellular epigentic inheritance in a mechanistic framework that conceptually separates their effects on somatic cells from those that involve the germ line. This has led to categorizations that include direct germline induction, direct somatic induction, parallel induction involving both germline and soma, or non-parallel induction (the effects on the soma in one generation affects the germline but leads to dissimilar somatic effects in subsequent generations) (Jablonka and Raz, 2009). Yet, such traditional distinctions fail to encompass with accuracy the entire range of these interactions in complex multicellular organisms. It is now clear that some epigenetic impacts, no matter their initial target, are critical to organism-wide developmental processes. These can include either gene regulation or triggered genetic silencing dependent upon circumstances, such as can be illustrated

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by the range of effects of an inactive X-chromosome with its profound developmental ramifications (Weichenhan and Plass, 2013).

Therefore, external environmental conditions yield actionable epigenetic information with biological consequences across tissue types in complex patterns that can extend from soma to germ-line, or the reverse, and can have variable effects on immediate participants or successive generations. Such interactions are an essential aspect of vital organismal-environmental complementarity as fitness by which organisms demonstrate flexible adaptation to shifting conditions through their attachment to information space. An important aspect of this narrative is that current impacts may only yield latent epigenetic action which can pictured as an informational cue for a set of biological implicates. That encounter becomes pertinent information as memory to be put to eventual future use. Even if there is no immediate biological expression from them, they form part of the essential information field of any organism.

Transposable elements (TEs) are now considered to be an essential functioning component of organismal biology and a consistent form of epigenetic impact (Fedoroff, 2012). Once considered mere parasites, it is now acknowledged that TEs incorporate into genomes in a manner that can yield biological expression (Hedges and Belancio, 2011; Kidwell, 1992; Robertson and Lampe, 1995). Some remain dormant, yet other lineages are believed to actively proliferate and demonstrate horizontal transmission across species boundaries (Hedges and Belancio, 2011). Furthermore, they do not represent a recent evolutionary phenomenon. Their activity has deep ancestral roots. That breadth and longevity of action has been sufficient to permit a complex countervailing cellular apparatus to carefully regulate TE expression. Certainly, this can be viewed as part of a systemic regulatory information exchange.

It is now estimated that as much as two-thirds of the human genome consists of transposable elements. These have contributed to genetic expansion and rearrangements that have shaped our genomes to a much larger degree than had been previously considered (De Koning et al., 2011; Ahmed and Liang, 2012; Pace et al., 2008). Importantly, the infectious origin of these mobile genetic elements is now considered likely. For example, a link between double-stranded DNA viruses and *Maverick/Polinton* eukarytoic DNA transposons has been found (Fischer and Suttle, 2011). Direct DNA and clustered regularly interspaced short palindromic repeats (CRISPER) have been demonstrated across a diverse range of prokaryotes and are believed to have been carried by HGT on megaplasmids (Godde and Bickerton, 2006).

An analysis of the prevalence of TEs in human and mouse mRNAs concluded that TEs affect the expression of many genes through the transfer of transcriptional regulatory signals involved in immunity and environmental responses to stress (Van de Lagemaat et al., 2003). Even though highly conserves genes are less affected, TEs can be considered essential aspects of the diversification and evolution of mammalian genomes. It is known that transposable elements carry an array of transcription factors with them (Wagner and Lynch, 2010). When integrated within a genome, they can enhance, promote or silence nearby genes. Their influence is sweeping. For example, mobile elements and their controllers significantly influence transcriptional networks in embryonic stem cells and a variety of adult tissues (Friedli and Trono, 2015; Mita and Boeke, 2016). Therefore, it is clear that TEs have a significant role in shaping gene regulation and genetic expression.

It is significant that TEs are consistently defined as intracellular parasites and can effect transfer from cell-to to-cell (Hua-Van et al., 2011). Several TEs have been found in eukaryotic viruses that appear to participate in horizontal dissemination to eukaryotes. The adaptive value of retrotransposon activation in the face of environmental stresses is frequent and is a contributing factor to the functional regulatory machinery of the cell (Shapiro, 2011). Retroelements can therefore be seen as residues of previous infection interchanges from which phenotypic variation can eventually emerge (Witzany, 2010). Hundreds of cases of documented horizontal transfer of transposable elements are now known and acknowledged as a propelling evolutionary force (Schaack et al., 2010; Bennetzen and Wang, 2014). In particular, they are known to be an important source of genetic variability and biological novelty either through direct non-homologous recombination at the insertion site or through indirect homologous recombination at adjacent genes (Brandt et al., 2005). This has been shown to be crucial for eukaryotic metabolic innovation and a factor in shaping the entire genomes of holobionts (Soucy et al., 2015).

Such transfers or not merely unilateral and can proceed by genetic acquisition by a phage to a cell, or from cell to a phage, or from phage to phage (Sullivan et al., 2006). Nor do the targets of viral or subviral infection need to stick to any specific species. The history of evolution is one of viruses evolving with their targets with cross species jumps a prominent feature of numerous virus families, especially those coded in RNA (Geoghegan et al., 2017). Such transfers can be substantial, involving entire metabolic pathways (Monier et al., 2009).

Even massive genetic transfers are now documented with a conspicuous example within bdelloid rotifers (Gladyshev et al., 2008). In fact, the extent of large-scale genetic transfers across evolution is great enough that genomes can be considered products of massive genetic bombardments and successful incursions by mobile genetic elements best conceptualized as symbiotic rather than parasitical (Brosius, 1999).

The extent of this activity and the range of its influences has previously been difficult to gauge with accuracy. In the inbred mouse genome, a very high incidence of de novo mutations could actually be linked to insertions of transposable elements which traces to ongoing activity of endogenous retroviral elements in the mouse genome (Maksakova et al., 2006). The levels of this insertional mutagenesis have been extensive enough that genomes can be considered to be under invasion. As humans, we are not spared. There is substantial evidence of overwhelming viral contributions to the human genome. It has been estimated that as much as 50% can be considered viral in origin with at least 9% of it counted as endogenous retroviruses (Ryan, 2009, 2010). Ryan (2009) emphasizes the importance of non-mutational epigenetic mechanisms, viral symbiogenesis and genomic hybridization events in evolution. As an example, evidence indicates a repertoire of Major Histocompatibility Complex class 1 genes has undergone significant reduction in chimpanzees but confers immunity to Simian immune deficiency virus. It can therefore be interpreted that modern chimp populations are the survivors of pandemic culling of ancestral chimpanzee population with the survivors being the product of specific genetic down regulations that offered a counterbalancing selective immunity (De Groot et al., 2002).

In 2016, Enard et al. analyzed adaptation from approximately 1300 virus-interacting proteins. They concluded that these proteins account for a high proportion of all protein adaptations in humans and other mammals, and are estimated to be a factor in close to 30% of all adaptive amino acid changes (Enard et al., 2016). Consequently, viruses can be seen as among the dominant drivers of evolutionary change across mammalian and human proteomes (Witzany, 2010; Witzany and Baluška, 2014). Furthermore, 30% of all human protein adaptations since the human divergence from chimpanzees have been driven by viruses. There is no requirement that such interactions need be random. It is known that the genes that are affected by viruses do not seem to conform to a simple

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stochastic distribution (Wilke and Sawyer, 2016). Goldenfeld and Woese (2011) cite evidence that both horizontal gene transfer and genetic mutations need not be random events. They note that the conjugative transfer of antibiotic resistance via the plasmid pCF10 to *Entercoccus faecalis* is controlled by cell–cell communication between plasmid-free recipient cells and plasmid-carrying donor cells (Goldenfeld and Woese, 2011).

Certainly, the importance of HGT is not confined to prokaryotes or animals. Gao et al. (2014) summarized ten mechanisms by which HGT has contributed to plant evolution. Importantly, they describe those mechanisms in terms common to infection, such as pathogenesis, parasitism, latency and symbiosis. Such direct genetic transfers may be accomplished as an exchange through a vector bridge, such as transposable elements. Gao et al. (2014) conclude that these agents are "a significant force propelling genomic variation and biological innovation, playing an important functional and evolutionary role in both eukaryotic and prokaryotic genomes." (p. 23). Bock (2010) emphasizes that plants are both donors and recipients of HGT whose partners extend across the domains, concluding that HGT must be considered a significant force in evolution that can drive both genomic and phenotypic changes.

This transfer is not confined to either viruses, or retroviruses. Significant non-retroviral RNA has invaded the genome of many mammalian species (Horie et al., 2010; Feschotte and Gilbert, 2012). Babić et al. (2008) indicate that they have actually witnessed the transfer of genes via a plasmid vector in vivo in the laboratory. It can be argued that horizontal gene transfer, that can then become vertical gene transfer, is a substantial force in evolution as a source of new genes, functions and evolutionary novelty that need not fit any conventional notion of a gradualistic process (Boto, 2010; Shapiro, 2017).

Furthermore, the transmission of heritable genetic agencies can proceed by any of the general means that are considered for the spread of any infectious pathogen. For example, it has been shown the oral administration of bacteriophage M13 DNA to mice can as be identified in fragmented form in the gastrointestinal tract and has been documented to penetrate the intestinal wall and incorporate into the nuclei of leukocytes, spleen and liver cells (Schubbert et al., 1998). Other investigations have demonstrated ingested plant DNA in samples of pig and sheep tissues (Reuter and Aulrich, 2003; Sharma et al., 2006). Nor is any body part sacrosanct. Studies have demonstrated DNA from intestinal bacteria in placental samples suggests that there is HGT of bacterial DNA between mother and fetus occurring within the placental niche (Satokari et al., 2009).

The origin of organelles such as mitochondria and plastids as the surviving products of episodes of infectious endocytosis is now fully accepted. Originally championed as Endosymbiotic Theory by Marguilis, there is a general consensus that endosymbiosis accounts for the origin of Eukaryota (Martin et al., 2015; Archibald, 2015). As an essential aspect of that process, it has been shown that genome reduction within the bacterial endosymbiont correlates with the horizontal acquisition into the host central genome (Nowack et al., 2016). A contemporary view of endocytosis with all of its various derivatives places it as a linchpin of eukaryotic cellular life.

Beyond episodes of endosymbiosis, endocytosis represents a significant aspect of routine cellular life that goes beyond the internalization and transport of molecules. It is central to the regulation of the plasma membrane and acts as an entire signaling apparatus within the communication infrastructure of the cell critical to the cellular integration of information (Sigismund et al., 2012). Thus, it occupies a cardinal aspect of cell logistics. That full range of endocytotic action has been termed an 'endocytic matrix ' to cover the entire spectrum of complex intersections between endocytosis and cellular signaling crucial to the information space of the cell.

Entosis is yet another means of information accumulation. Entosis represents the invasion of a living cell into another cell as a mechanism that is known to affect cytokinesis and induce aneuploidy (Janssen and Medema, 2011) The process is best understood as cellular invasion rather than the engulfment of one cell by another. Its yield is the incorporation of a vast signaling architecture from one cell to another without the need for individuating transport across the plasma membrane (Overholtzer et al., 2007). As such, it represents a form of extensive information exchange between cells. A recent experiment illustrates that information transfer is a significant aspect of cell mergers and fusions. Slime molds (Physarum *polycephalum*) learn behavioral patterns through habituation. If cell fusion occurs between habituated slime molds and others that are naive, the learned response is transferred to the fellow slime molds (Vogel and Dussutour, 2016).

Clearly then, there are abundant mechanisms for the transfer of information of all kinds both within and across the domains and, indeed, the exchange of genetic information crucially mediates intercellular communication (Mittelbrunn and Sánchez-Madrid, 2012). This genetic exchange is primarily accomplished by miRNAs through the absorption of secreted exosomes from a donor cell to recipient. This process has been shown to be crucial to neural pathways as part of the epigenetic landscape and represents an important element of the cell-cell communication at immune synapses (McNeill and Van Vactor, 2012; Gutiérrez-Vázquez et al., 2013). The surprising extent and importance of these means is still being elucidated. For example, it has only recently been found that bacteria have direct communication with mitochondria and alter the physiology of a holobiont (Lin and Wang, 2017). Such mutalistic crosstalk has been shown between Caenorhabditis *elegans (*C. elegans*)* and its resident gut *Echerichia coli (E. coli.).* Environmental stresses experienced by *E. coli* residing within *C. elegans* reciprocates with mitochondrial mediated C. *elegans* lipid metabolism. In turn, *E. coli* fusion-fission balance is constrained through the influence of shared proteins such as Patched and Sonic Hedgehog from C. *elegans* which serve as a common language between them.

3.2. Infectious interchange (HGT) as information transfer

There is substantial evidence that horizontal gene transfer (HGT) provides an important source of new genes and functions as a driving force of evolution (Hedges and Belancio, 2011; Kidwell, 1992; Shapiro, 2017; Woese and Goldenfeld, 2009; Baluška, 2009; Oliver and Greene, 2009; Witzany and Baluška, 2014). For example, although horizontal gene transfer (HGT) has been long acknowledged at the level of prokaryotes as an adaptive mechanism, HGT extends across eukaryotic development and has contributed more to adaptive evolution than previously supposed (Palenik et al., 2009; Soucy et al., 2015; Schönknecht et al., 2014). HGT in metazoans is acknowledged as an important aspect of evolution (Boto, 2014), contributing significantly to biochemical diversification during animal evolution (Crisp et al., 2015). Since many eukaryotic genes are bacterial in origin, it had been previously supposed that they largely derived from mitochondria or plastids. However, this does not seem to account for the majority of microbial genes in eukaryotes. There have been both ancient and recent HGT events in all eukaryotic groups (Huang, 2013). Therefore, HGT has been a regular occurrence in complex multicellular eukaryotes. (Pace et al., 2008; Monier et al., 2009; Gladyshev et al., 2008; Venner et al., 2009).

Both exogenous and endogenous HGT leads to heritable change

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with a wide range of biological expression (Crisp et al., 2015). For example, in eukaryotes, numerous cases of horizontal transfer of transposable elements have been reported (Loreto et al., 2008). Large numbers of tranposable elements are found in protein-coding genes (Nekrutenko and Wen-Hsiung, 2001). From such interactions, novel genes have routinely arisen from genomic parasites contributing functional changes to existing genomes as novel chimeric structures. These have led to the expression of novel cellular, physiological, morphological, reproductive and behavioral traits (Kaessmann, 2010). Although these mechanisms of genetic transfer are now readily acknowledged, it is often overlooked that these are actual infectious interchanges that occur among and between the domains.

Endogenous retroviruses (ERVs) are present in the genome of all vertebrates and are obviously infectious in origin. (Black et al., 2010). Such ERVs are recognized contributors to genome plasticity, phenotype and novelty. The development of the mammalian placenta is directly attributed to them (Chuong, 2013). A distant relative of HIV, Long Terminal Repeat (LTR) class I endogenous retrovirus (ERV) retroelements, have had a substantial impact on the transcriptional network of a primate master gene regulator, human tumor suppressor protein p53, which is crucial for primate differentiation (Wang et al., 2007). ERV endogenization has been ongoing for millions of years and are frequent enough to be observed in real-time during our extremely brief interval of informed observation through the recent endogenization of Koala retrovirus and recent attempts at endogenization by HIV (Tarlinton et al., 2006; Colson et al., 2014).

Beyond retroviruses, Villarreal and DeFilippis (2000) have identified DNA viruses that infect microalgae and filamentous brown algae with DNA polymerases essential to replication. Their findings indicate that *Pol* delta genes in eukaryotes derived from unicellular infection with an early viral DNA gene that is similar to the contemporary *Feldmania* virus. The persistence of this viral 'parasitic' DNA might be considered a viral strategy that permits the superimposition its own complex molecular genetic control onto its target. Many crucial eukaryotic regulatory genes are the consequences of prior DNA viral infection as the product of horizontal exchange. For example, the genetic material encoding *d*UTPases is a product of viral transfer between eukaryotes and archaea (Baldo and McClure, 1999). Indeed, phylogenetic analysis of the critical enzymes for DNA replication and synthesis of DNA precursors suggests an active reciprocating process of information interchange between viruses and their targets with bilateral genetic transfers that have continually contributed to evolutionary history and genetic novelty (Filée et al., 2003). Therefore, viruses or their subparticles are important facets of the mobilome as endogenous 'parasitical' elements transferring new information to new sites within a genome. DNA transposons that have shaped the genomes of eukaryotes for millions of years have been traced, at least in one instance, to a virophage that is considered a link between double-stranded DNA viruses and *Maverick/Polinton* eukaryotic DNA transposons (Fischer and Suttle, 2011).

Thus, viruses are not merely agents of pathogenesis but have played a crucial role in the evolution of genomes and their expression in biologic form (Forterre, 2006). Indeed, viruses can be viewed as operating as a collective archive of memory of community-wide genetic information (Goldenfeld and Woese, 2007). In that case, they should be regarded as crucial aspects of information space and then ultimately, a part of the information management systems of the cell.

Current research is revealing many other avenues for the transfer of information or its management in niches that were considered sacrosanct from exogenous influences. For example, it is now recognized that spermatozoa can take up exogenous DNA or RNA molecules into their nucleus in a manner that can be regarded as an infectious event (Sciamanna et al., 2009). Through such interactions, sperm endogenous reverse transcriptases, presumed to be LINE-1 retroelements, can be transcribed and delivered to oocytes during fertilization and expressed throughout embryogenesis and development (Spadafora, 2008). These reverse transcribed sequences have been likened to expressive extrachromosomal retrogenes that are part of the continuous flow of information that source novel epigenetic and phenotypic traits.

As is obvious from our own experiences, infectious disease can be identified as a binding aspect of our living circumstance. Until recently, our human appraisal of infection has been through the traditional host/pathogen model. Thus, it is no surprise that this same perspective has dominated prior examinations of any evolutionary impact of infection. It has always been presumed to operate within the confines of Darwinian competitive survival (Williams and Nesse, 1991). Yet, overt pathogenesis is only one aspect of a larger and more complex entirety. Infectious interchange represents a crucial facet of the continuous transfer of information within and among microbes and eukaryotic cells in continuous self-referential encounters with a shifting environment. Both the infectious agent and its target are observer/participants within that exchange of information, no matter the outward appearances of any pathogenic effect. A full range of outcomes can ensue that is dependent on the infecting agent, the target of opportunity and the amplitude of its interaction with that target. These variable manifestations include individual infectious pathogenesis, epidemic infection, symbiosis, parasitism, infectious latency, direct genetic transfers or epigenetic incursions that can yield evolutionary shifts (Miller, 2013). Yet, any of these encounters is information dependent insofar as both opportunist and target can now be viewed as the intersection of overlapping but still individualized information fields. Therefore, an enlarged biological perspective of the significance of infectious interchange can be proposed. Infectious interchange can be reappraised as a part of a complex language of information exchange among organisms that extends beyond competitive pathogenesis. It can be argued that the documented high levels of retroviral and viral sequences in modern genomes accumulating over evolutionary space-time attest to the universality of horizontal genetic incursion and assimilation as part of a process of continuous information exchange. As a cumulative result of these transfers and the widely varying effects of this information transfer, the infectious process can be reasonably assessed as a crucial driving force of evolution (Baluška, 2009; Witzany, 2010; Miller, 2013, 2016a). Since all self-referential entities have preferential states measured through the maintenance of homeostasis, all infectious genetic transfers can be understood as directed towards that aim, at least for the incurring agent, whether it is welcome or not. Their actions may be actively pathogenic or not, but either can be framed as niche construction by at least one party in the exchange. Therefore, infectious transfer can appropriately be appraised as an essential part of the totality of information exchange as part of the continuously reiterating information cycle which constitutes the common currency of biology and its evolution.

Recent evidence about the balance between lysis and lysogeny (a virus lies dormant within a host cell) in virus-bacteria population dynamics offers validating evidence. The previous assumption had been that lysogeny was rare and only occurred at low bacterial concentrations. Instead, a study of coral reefs has been demonstrated that lysogeny is prevalent and most common when bacteria are highly concentrated within an ecosystem (Knowles et al., 2017). As this is a considered a stressful condition, this phenomenon is exactly opposite to the lytic-lysogenic decision matrix that had been presumed to be operative. Some levels of cooperation and

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communication must induce bacterial phages to enter into symbiosis with a prokaryotic or eukaryotic cell according to deeply interconnecting parameters and information exchanges that are yet unclear.

As an example, transposable elements are not merely ubiquitous but have also been identified as critical aspects of episodic intervals of rapid speciation, adaptive radiations, and evolutionary transitions. The TE Thrust Hypothesis suggests that bursts of tranposable element activity and horizontal transfer of retroviral inclusions realize adaptive potential (Oliver and Greene, 2011). Therefore, in cyclical patterns, incurring infectious agents can be active promotors, repressors, or latent residents in nearly any cellular milieu and must be considered a significant aspect of the information set of any organism.

Perhaps the most powerful argument in support of the concept of infection as a primary means of effecting evolutionary change is the issue of the likelihood of fixation of a genetic point mutation arising in a solitary individual as the source of consequential heritable variation. In the context of populations, direct observation has indicated that any isolated mutation is diluted by the next reproductive cycle that necessarily includes another individual that is unaffected. Indeed, it can be considered that the meiotic requirement of sexual reproduction directly contradicts the primacy of that fixation mechanism. Meiotic division is an averaging mechanism that enforces a halving of genomic contributions as an effective means of assuring the immediate vitiation of any significant variation occurring in a single individual within the context of populations (Miller, 2013). This is merely ready observation. Müller and Newman (2005) directly point to this overwhelming barrier to the fixation of isolated point mutations. In evolution, it is always about numbers. The attempt to provide a redress mechanism through bottleneck theory is easily contradicted within its well-known problems of rapid inbreeding and its observable deleterious effects (Templeton, 1980).

3.3. Non-genic means of information reception and exchange

That all living organisms communicate in complex interacting skeins is now established (De Loof, 2017). For example, communication among prokaryotes is ubiquitous and enables the colonial biofilm form (Lyon, 2015). Aside from the now well-known classes of bioactive molecules that underscore communication between cells, or genetic transfers that are additional sources of information exchange, there are many other less often considered aspects of the cell that fully participate in cell-to cell-communication. For example, the primary cilia are an essential element of that communication process. These are slender projections from microbes or the cells of plants and animals that are both motile and non-motile organelles (Wheatley et al., 1996). They function as a sensory mechanism which analyzes mechanical and chemical signals as part of the cellular apparatus to assess and transfer information.

Each differentiated cell type within multicellular eukaryotes, including renal cells, intestinal epithelial cells, white blood cells, platelets, or skin cells have their own specialized and elaborate means of internal communication and intercourse among themselves (Donahue et al., 2000). For example, brain cells and neurons communicate abundantly by utilizing specialized neurotransmitters, calcium flux, and a large vocabulary of cytokines, other factors, and electrical signals (Laughlin and Sejnowski, 2003; Ghosh and Greenberg, 1995; Buzsáki and Draguhn, 2004). Among those cells, a wide array of physical mechanisms are regarded as assisting these well-known pathways. These include electromagnetic fields, actin cytoskeletal rearrangements, biophotons, atypical quantum mechanical biofields, non-classical energy fields and non-local entanglement (Fels, 2009; Fels et al., 2015; Volkmann and Baluška, 1999; Rein, 2004; Julsgaard et al., 2001).

Intercellular signaling system also exists through connexins (an assembly of protein subunits that forms one half of the cell-cell channel that spans plasma membranes) and gap junctions by which cells share ions and metabolites that permit coordinated cellular activity to maintain homeostasis during development (Bruzzone et al., 1996; Trosko et al., 2000).

Apoptopodia is a further example of the variety of forms of communication that are available to cells. In this mechanism, blebs form as cellular beading (Atkin-Smith and Poon, 2017). The plasma membrane ejects these blebs as exosomes from inside of dying cells in a string-of-beads formation that can be as great as eight times longer than the initiating cell (Minton, 2015). Eventually, these blebs break off from their cell of origin and circulate. Although previously assumed to be a stochastic phenomenon, it is now known to be a highly coordinated and regulated type of intercellular communication that serves as a molecular warning system among immunological cells to alert other cells to the presence of a pathogen.

Epithelial bridges are another universal means of cell-cell communication (Zani and Edelman, 2010). These are thin cytoplasmic channels, termed 'plasmodesmata' in plants and 'tunneling nanotubes' in animals, that permit the direct transfer of signaling molecules and even pathogens between cells as forms of information transfer. It is also known that they function in cell migration (Zani and Edelman, 2010). Recently too, it has been documented that all individual cells have their own circadian clock and that even this rhythm constitutes another form of intercellular communication (Westermark et al., 2009).

Therefore, all living things use a large variety of mechanisms to communicate, coordinate and attach to one another: contact, cytokines, epithelial bridges, exosomes, neurotransmitters, RNAs, peptides, genes, kinocidins, hormones, vesicles, photons, electricity, and nanotubes. Such communication extends extensively across the domains. For example, eukaryotes and bacteria engage in intimate mutualistic and competitive dialogues in highly evolved systems. The interactions of *E. coli* and C. *elegans* can again serve as an example. Altering the electron transport system in gut *E. coli* of C. *elegans* induces an oxidative stress reaction in the latter that excites transcription-related mediation of mitochondrial homeostasis (Govindan et al., 2015). C. *elegans* can not only react to the actual changes in electron transport in *E. coli* but can also anticipate it to preemptively meet any resulting potential challenge to its mitochondria. By interactions such as this, collective and coherent oscillations between molecules and molecular bridges that are mediated through discrete frequency bands yield an intra-cellular and inter-cellular set of resonances that help guide a living communicative network as a functioning and adaptable electrome of the cell. (Melkikh and Meijer, 2017).

3.4. Information reception and communication as problem-solving

The reception and communication of information is an omnipresent aspect of life extending across the domains. Cells are dependent upon these processes for the maintenance of their preferential state of homeostatic equipoise in the face of environmental shifts. Although the functional cell is clearly an anatomic unit, the concept of cellular life can be extended beyond its mechanistic context (Ford, 2009). It can be even better appreciated as a complex form of aggregated information. This information can be gathered in continuous reaction to environmental experiences through both genetic and non-genic means through both heritable

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and non-heritable transfers. Thus, the basic cellular form can be considered as constituting an embodiment of an informational set which is centered within its attachment to information-space as its constitutive PIF.

When information is considered the operative frame of reference for the basis of life, and the maintenance of preferred homeostasis and survival is assumed as the aim of the living condition, then the reception and communication of information directed towards its ultimate deployment can be considered it common currency. Sustaining homeostasis requires the reception of information, its assessment through an awareness of status, and its deployment to effect adjustments. Since information is ambiguous, organisms demonstrate anticipation and prediction at every cellular scale (Torday and Miller, 2017a) (Freddolino and Tavazoie, 2012). Within and among cells, this prescriptive linkage resolves as self-referential problem-solving (Miller, 2016a; Torday and Miller, 2016a, 2017a). Indeed, it has been previously suggested that life should be properly interpreted as both the summation of communication exhibited by any organism and its problem-solving (De Loof, 2014; Popper, 1999).

Such activities apply to all cells as it is now clear that the modes of communication among living things share certain aspects of universality. Along with the conservation of similar major metabolic biochemical pathway among animals and plants, their means of experiencing biological information and utilizing it are quite similar. The processes by which plants acquire immunity against pathogens, accumulate epigenetic marks, and process complex information through a large body of mechanisms bears remarkable similarity to animal neurobiology (Baluška et al., 2006). That such disparate morphologies use similar patterns of communication in response to stress is not surprising. Such actions are directed towards problem-solving in a context in which information is widely based and can be shared with similar cues available to many differing constituencies. As an example, many aspects of the plant cellular architecture, such as the actin cytoskeleton, participate in complex signaling systems similar to that seen in animals to utilize a common form information networking (Volkmann and Baluška, 1999).

Although traditionally viewed as passive, plants demonstrate robust aspects of embodied cognition and memory (Garzón and Keijzer, 2009). It is no surprise, then, that their activities should be consonant with the core cellular means of communication of information for problem-solving that have been shown to extend across all the domains. Recent findings have demonstrated that phage viruses communicate with one another with a small peptide molecule, *phi3T*, to coordinate a cooperative decision to choose a lysogenic pathway in cells (Erez et al., 2017). Viruses themselves use the machinery of the cell to communicate though toxins and antitoxins to coordinate or inject proteins as part of their own communications apparatus (Chapman et al., 2008; Lucas, 2006). Even prions can be appraised as communicating and information dependent. Prions are self-propagating clumps of misfolded protein produced by bacteria that lead to fatal neurodegenerative conditions in mammals that are both infectious and heritable (Yuan and Hochschild, 2017). Prion-identified proteins are a known part of the genetic regulatory system of bacteria through which they avoid immune surveillance within cells. Prions are now regarded as part of an organism's information content as they have a demonstrated capacity to make cooperative decisions to further effect adaptive changes within organisms (Derkatch et al., 2001). Since prions emerged prior to Eukaryota some billions of years ago and may have played a crucial role in the emergence of life (Lupi et al., 2006), it should not be surprising that they are part of the cellular informational architecture.

3.5. Problem-solving through natural cellular engineering and niche construction

The general concepts of niche construction and their applicability to evolution are now well accepted (Laland et al., 2014; Odling-Smee et al., 2003). Niche construction is a mechanism of mutual reciprocity between organisms and the outward environment through which reinforcing adaptive behaviors can contribute to phenotypic plasticity but are not exclusively related to survival. Heritable resources between generations can be both bioactive and behavioral with both leading to constructive development. Typically, niche construction had been considered within the framework of macroscopic organisms and populations, such as earthworms altering changing soil chemistry or the direct and indirect effects of beaver dams on local ecologies.

Niche construction in termite mounds have been modeled on the principles of stigmergy, as consensus networking that leads to indirect coordination (Heylighen, 2015). Traces left in the environment by an action stimulates the performance of a next action, by the same or a different agent in which its efficiency lies within the goals of the individual participants independent of the goal itself. In all instances, complexity builds in a collaborative manner in which conflicts are minimized since the origin of information among relevant senders and receivers is never clear within the shared information field. Each is its own observer/participant and each primarily operates through its own individualized PIF.

Clearly though, any range of niche construction activities must include the reception, communication and deployment of integrated information. This then proceeds in a coordinated, directional and systematic manner as part of a conjoined process of discrimination and adjustment towards environmental stresses. Therefore, niche construction can be identified as the reiterating process of the acquisition, communication and utilization of semantic and pragmatic information (Odling-Smee et al., 2003). Any coordinated adjustments in a genome that can be considered natural genetic engineering and natural genome editing can now be seen as specialized and localized aspects of that impulse towards niche construction.

Concepts of natural genetic engineering add significant explanatory power to an evolutionary narrative (Shapiro, 1993; Witzany, 2010,2011). This is certainly the case when DNA is conceptualized as data storage whose range includes specific DNA sequences within stabilizing chromosomal structures that adjust both within the single cell cycle through the action of nucleoprotein complexes and across multiple cell generations through epigenetic modifications. (Shapiro, 2005). The resulting modifications across these time scales is ascribed to DNA computation and decision-making within a genome that importantly has a systems architecture and a discrete signaling apparatus (Shapiro, 2005). The major architectural differences between genomes is generally ascribed as concentrated within repetitive elements, *cis*-acting regulatory elements and in the sub-set of genes that specify non-coding RNA's and their non-random introns. (Taft et al., 2007). Despite these clear indications of genome responsiveness, it has been argued that genomic DNA sequences function more as a background database on which the system periodically draws rather than as a logical systematic program. (Noble, 2010a). However, when genomes are placed within a self-referential frame as an acknowledged information architectural element of a cellular entirety, any discrepancies in the conceptualization of genomic interplay can be interpreted as coherently directed towards individualized self-referential cellular homeostasis as one aspect of reciprocating cell-wide systematized information management. The result of any genomic incursion of viruses or virus-like particles, the ramifications of transposable elements within a genome, and the entire

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complexity of their repression or promotion can then be seen as part of the information space of the cell tasked towards self-referential cellular problem solving to sustain homeostatic equipoise. Within a self-referential frame, the central genome is considered one of many architectural elements of the cell, each a product of niche construction whose inter-relationships within the cell is as a participant in a larger process of natural cellular engineering. Such intracellular action proceeds by many complex paths that have been assessed as combinatorial and context specific in such a manner as to be able to be characterized as resembling language-like text (Witzany, 2010).

It has been convincingly argued that the foundation of the cell was the first niche construction (Torday, 2016). In an informational frame, the cell as niche construction can then be equally understood as natural informational engineering. Indeed, every aspect of the cell can be equally so considered. That same process of natural informational engineering should be expected to underlie the informational architectural elements of the cell (mitochondria, ribosomes, plasma membrane, endoplasmic reticulum) are their own examples of internalized niche construction and natural cellular/informational engineering. Thus, the central genome represents just one such niche. The varieties of transposable elements that characterize the greater differences between genomes can then be framed as coordinating communities within a larger genomic ecosystem (niche) (Venner et al., 2009). The coordinating impulse for each of these informational elements of the cell is through the actualization of self-reference as linked problem-solving. Natural cellular engineering proceeds according to the community-wide assessment of variables and by communication among its participating elements. Therefore, biologic expression represents both integrated deterministic local organization as niche construction and stochastic reactions to environmental stresses (Caporale, 2003) (Caporale and Doyle, 2013).

Under these circumstances, it is argued that the dynamics of natural genetic engineering and niche construction activities can properly placed as part of a consistent informational cycle. That cycle is dependent upon the limitations of self-referential assessment of ambiguous information. Every aspect of the cell participates as a semi-autonomous intracellular informational architectural element. Through this means, biological entities of all types achieve or sustain preferential states through the reception, communication and deployment of information. This frame melds particularly well with the recent extension of niche construction theory beyond its typical environmental selection parameters towards a more comprehensive developmental niche construction concept. (Stotz, 2017). In developmental niche construction, a diverse range of mechanisms beyond the selective environment contribute to the transgenerational inheritance of developmental resources. This conceptualization enlarges niche construction into a more encompassing role in which the organism is a direct participant in its own developmental environmental repertoire that is akin to natural engineering at differing scales.

Biological action at the cellular level is contingent on the reception and assessment of information. Its deployment proceeds through reciprocal signaling, through the variable use of energy, the production of metabolic products, and immune response. These inter-relate to enable the variations of informational architecture that enable differing biological expression as novelty through local variations in niche construction as natural cellular engineering. This is the source of flexible and creative responses of cells to maintain homeostatic equipoise in response to continual environmental stresses of many kinds including HGT. It is argued that this coordinated deployment of information antecedes the reproductive cycle and selection (Fig. 2). Selection remains crucial as a post-facto phenomenon of the self-referential state. Its role is a rigorous filtering mechanism of the self-referential deployment of information by enforcing the essential organismal-environmental complementary that the living condition requires.

4. The structure of biological information management

4.1. Informational architecture and informational motifs

Any information system requires systematized management. At every scale, living organisms access self-referential information space as a delimiting range of potentials that can collapse into biological expression to sustain homeostatic equipoise. (Miller, 2016a). The self-referential frame itself, as a systematic matrix, can be construed as constituting an initiating level of information management through which cellular problem-solving can ultimately proceed. The varied architectural elements of the cell (nucleus, mitochondria, endoplasmic reticulum, endomembranes, etc) participate in the interrogation of that information space. Each of these sub-cellular informational architectural elements have their own varied capacities and limits as separable forms of internal sub-cellular niche constructions. Together, these conjoin into a primary unicellular informational architecture as a summary individualized PIF that overlaps the physical environment and any other living correspondents. By this means, the crowded, active cell subsumes its own distinct form of informational architecture through the melding of the multitude of sub-cellular informational architectural elements that comprise it. Through selection, this becomes the ancient, stable and enduring unicellular form. When considered in this manner, the central genome of a cell can now be properly regarded as a crucial participant among those diverse architectural elements that compose the entire cell.

It is known that sophisticated signaling mechanisms for the transfer of information underpin the mutualistic behaviors exhibited by cells (Lyon, 2015; Schauder and Bassler, 2001). This reciprocal signaling and the information that is exchanged form the basis for cooperative and self-organizing behaviors among cells. Although that information originates from observer/participant attachment to information space in a self-referential system, such collective behaviors should be considered a form of joint problem-solving to better cope with stressful environmental conditions (Eschel et al., 2000). When robust signaling and joint problem-solving effectively combine, the result is a unicellular (prokaryotic or archaeal) informational architectural motif which is the shared systematized information matrix that enables the multicellular experience among collaborating and competing unicells. This produces a summation overlap of the individualized PIFs of each the co-aligned participants. Thus, the informational architectures of the participating unicells combine in a successive level that represents its own form of collaborative and systematized information management through a now shared and reciprocal attachment to a resulting elaborated information-space (Fig. 2). That collaborative impulse is the selection driven requirement to maximize the assessment of ambiguous information through collective assessment. Together, this constitutes its own informational motif that represents collective networking, such as is seen with biofilm formation. Therefore, both the informational architecture of the primary unicell and its multicellular informational motif can be productively regarded as aspects of systematized information management.

The origins of Eukaryota has been substantially debated (Cavalier-Smith, 2002; Sogin, 1991; Rivera and Lake, 2004; Cox et al., 2008). There is a general belief that Eukaryota is the result of prokaryotic (or possibly Archaeal) genome fusions as a form of

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endosymbiosis (Williams et al., 2013; Spang et al., 2015). No matter the uncertainty of the origins of the basal cellular form of Eukaryota, it certainly can be interpreted as a product of intracellular niche construction through endosymbiotic mergers that enacted a stable cellular fusion. The resultant collaborative necessitated reciprocating information transfer between the prior separate elements that requires its own information management apparatus. In this manner, the nucleated and mitochondrial-enabled eukaryotic form is another iteration of natural cellular engineering and reciprocating niche construction (Fig. 2). This results in the eukaryotic basic cellular form becoming its own specific and separable informational architecture that can be distinguished from Prokaryota or Archaea through its particular range of attachment to information space.

The stabilized informational sets of the three primary informational architectures (Prokaryota, Archaea, Eukaryota) underscore a natural, self-organizing and reiterative form of cellular engineering to solve any further constellation of environmental problems through competition and collaboration. The improvement in the assessment of information quality through the multicellular experience represents that underlying impulse. Ultimately, this imperative towards the collective assessment of information becomes effective shared information through overlapped informational architectures. This yields the obligatory holobionic form that characterizes multicellular eukaryotes (Miller, 2016a). Therefore, a holobiont is the entanglement of these informational sets that includes the combination of the self-referential individual cellular informational architectures of the participants that becomes collective informational motifs. Together, they conjoin as a holobiont as the biological expression of a fully shared information space among the varied participants, whether eukaryote, prokaryote, archaea or viral. Evolutionary development can thus be appraised as continual self-organizing natural informational engineering and niche construction activities based on the systematized assessment and deployment of information at reiterating scales. This proceeds according to elemental cellular precepts of reiteration, cooperation, reciprocality, and competition. The virome can be considered either its own participating motif or as an intermediary.

Placing multicellular eukaryotic life in this frame has the advantage of coherently explaining a critical aspect of holobionic life. Despite any coordinating impulses within any holobiont, biological action is always realized at the level of the individual cell. Certainly, they work in concert to express bioactive molecules, but expression still emanates from individual cells. In Cognition-Based Evolution (CBE), this is no discrepancy. Biological action always progresses through individualized self-referential cellular interrogation and assessment of its information space and then proceeds through the continuous reiterative enactment of self-consistent mosaic formulation (Agnati et al., 2009). To put it plainly, cells attach but do not merge. They share information space, but retain self-referential integrity.

The existence of such a shared information space produces other necessary codicils. The existence of a coordinating information set as exemplified by multicellular life presumes mutualistic self-referential collaboration. In any system that can be demonstrated to have abundant shared communication, there must be rules of usage. Wittgenstein argued that such rules are not a matter of individual invention but must arise through the coordinated use of a system of communication among a community of participants (Wiley, 1983). Therefore, multicellular life can be understood as a non-stochastic informational response network based on shared information between stable informational motifs that is disciplined by both its own information management system and by selection.

4.2. The accumulation of information in the cell: the genome as a developmental organ

The concept that genomes can monitor themselves and initiate responses to environmental challenges was pioneered by McClintock over three decades ago (McClintock, 1993). Subsequent research has validated that perception as it is now established that accreted constituents of any genome, such as endogenous retroviruses (ERVs), are subject to regulation by the target genome. Evidence indicates that cells utilize histone modification machinery to silence some ERV subfamilies in embryonic stem cells and early embryos independent of DNA methylation (Lamm, 2014). Yet, the responsiveness proceeds in both directions. ERVs are not only regulated by genomic informational architecture but have co-opted some aspects of gene regulation and genomic information space by controlling a number of the processes that are necessary for embryonic development (Gifford et al., 2013).

In plants, LTR retrotransposons are essential genomic components that are particularly responsive to environmental stresses. Such sequences are highly plastic and exert a regulatory framework that permits plant genome diversification. That regulatory role governs LTR responses to stress as one aspect of coordinated genomic response. In this way, TEs and other insertional genetic elements alter genetic expression, play a substantial role in embryonic development and exert an active regulatory function that is crucial for multicellular eukaryotic evolutionary development.

It is now known that there are a substantial number of retrovirus transcriptional regulators that monitor their own insertion and amplification in cells. In embryonic stem cells, these not only control a regulatory apparatus but adjust the expression of native genes and the transcription of proviruses accumulated by infection (Schlesinger and Goff, 2015). Therefore, the coordinating pattern that emerges is one of a regulated mutual governance of both endowed genetic code but also of the incurring retroviral genes. Together these markers express embryonic cell pleuripotency (Robbez-Masson and Rowe, 2015). In effect, these viral sequences have been 'domesticated' towards to the needs of the target, yet, still have their own leverage. Therefore, this complex interaction reflects a systematic wide-ranging exploitation of any and all available genetic sequences within comprehensive, overlapping regulatory networks. Therefore, it is argued that such a coordination can only exist within a comprehensive information system. By default, a system of this responsiveness and complexity must have a balancing control mechanisms within any genome and its cellular surroundings (Robbez-Masson and Rowe, 2015). Indeed, the complexity of those regulatory mechanisms is quite deep. For example, if key regulatory miRNAs are targeted, such as *Dgcr8* and *Dicer* in mice, profound developmental defects result (Olive et al., 2015).

These levels of regulatory complexity do not merely relate to the operation of the central genome. The immune system has a similar set of regulatory modules that oversee the participating immune cells. In a pattern of constitutive reciprocation, as is evident within any genome, some aspects of the adaptive immune system are controlled by extracellular agencies, some of which are termed Virus-Like Particles originating from viral envelopes or capsid proteins (Grgacic and Anderson, 2006). Therefore, all parts of the cell are aspects of an integrated information apparatus with the genome as a crucial participant among many.

As the variety and complexity of interrelationships of this type have been steadily revealed, the extent of the influences of TEs, viruses, and virus-like particles is being thoroughly reexamined. Thus, there is a shift away from regarding TEs as epigenetic parasites that need to be down-regulated and suppressed by a native genome. Instead, a very differing viewpoint has been embraced. TEs

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and their derivative transponases are now considered to be essential elements of the evolvabililty of eukaryotes by creating and sculpting genes, and contributing to their programming and expression (Fedoroff, 2012). As these elements constitute a majority of eukaryotic genomes, these transposons are both controlled and reciprocally controlling. When the entire context is considered, it is plain that genomes can shape their own evolution to some limit in continuous responsiveness to external and internal stresses (Schrader et al., 2014; Oliver and Greene, 2009). Therefore, any genome can only be assessed at any particular moment of time as a 'snapshot' of a dynamic genetic mobilome (Mita and Boeke, 2016).

It is well-accepted that the nuclear genome of any organism represents a substantial incarnation of its total information content. Furthermore, it is known that this information is contained within a complex architecture that has its own high levels of internal communication (Fraser and Bickmore, 2007). Therefore, the means by which genomes accumulate as effective aspects of information management and biological complexity is worthy of exploration. Certainly, genetic duplications have been considered a significant mechanism for the establishment of genomic composition and genetic accumulation (Ohno, 1970; Zhang, 2003). It has been generally believed that genetic duplications permitted mutations to achieve expression with resulting novel proteins that would otherwise have been prevented or expunged. Some wholesale genomic duplications have occurred, with many instances of known polyploidy, most frequently occurring in plants (Blanc and Wolfe, 2004). Other instances of more restricted genetic duplication of only some aspects of a genome, individual chromosomes, or individual genes are well-documented (Gu et al., 2004). However, the overall incidence of genetic duplication is relatively infrequent and cannot itself account for our evolutionary narrative (Carroll, 2005). Carroll (2005) maintains that while evidence suggests that gene duplication has contributed to the evolution of form, the frequency of duplication events cannot account for the continuous diversification of lineages. The estimated rate of gene duplication is actually rare and the ancestry of genes casts doubt on whether evolutionary development is due to the appearance of de novo genes by duplication as much as it is due to new regulatory oversight of existing genes. For example, the crucial *Hox* genes have been essentially stable for 500 million years and the *Wnt* family of signaling ligands is also ancient (Van Amerongen and Nusse, 2009). The most relevant changes of these crucial genetic families seem to be confined to their regulation in which individual gene expression and the activity of transcription factors have differed over time (Davidson, 2001; Carroll et al., 2005). Therefore, although it is accepted that conserved proteins from de novo genetic mutations can contribute to novelty, there is an emerging contemporary narrative that regulatory sequence evolution is the dominating aspect of the diversification of gene function (Carroll, 2000).

As the nuances of genetic regulation are being more deeply explored, longstanding views are shifting. The power of gene frequency within populations to adequately explain a current standard of evolutionary development is now questioned (Lewontin, 1984; McCandlish and Stoltzfus, 2014; McCandlish et al., 2016). It is no longer assumed that the central genome of any organism exerts unyielding control. That prior attitude had been framed within the 'two spaces and a barrier' concept that was presumed to govern the separation between genotype and phenotype (Walsh, 2014). However, the dictum of the inviolable Weissman soma-germline barrier, and then, too, Crick's reinforcing central dogma of the unilateral direction of DNA transcription, are now both known to be incorrect (Shapiro, 2009). Instead, there must be a larger perspective of the role of genes and an acceptance that, in some circumstances, cellular expression is subordinate to consequential inputs and behaviors that are 'unmediated' by genes (Walsh, 2014). From this viewpoint, downstream effects, such as learning and behavior, become significant. It is becoming increasingly apparent that genes do not always do what the disciplinary matrix tells them to do. As Walsh (2014) aptly summarizes, "…… entire genomes, as adaptive, responsive systems, exploit, coordinate, and assimilate causal influences from genes, cells, tissues, physical, and social environments, in the production of robust, adaptive entities, organisms. Genomes reconcile, harmonize, and accommodate the demands of the various parts and subsystems of organisms, and ameliorate the vagaries of genes and environment. In this sense, organisms are not computed, or decoded; they are negotiated." (Walsh, 2014). Evolution is not exclusively within the province of the traditionally understood replicators and therefore, even after years of genetic research, the discrete causal relationships between genotype and phenotype remains unclear (Noble, 2010b; Diz et al., 2012).

With this as background, it would be productive to consider different participants in the evolutionary process beyond central genomes. Such an enlarged perspective lies within a thorough consideration of the information space of the cell, in which a large number of constituent cellular elements at the unicellular level and the totality of the collective individual participants in any holobiont together contribute to the relevant total information content. Certainly, consequential cellular genetic inputs beyond any central genome are now well-known. For example, it is now established that RNA is more than a passive mediary between DNA and proteins and is a crucial aspect of overall cellular genetic regulation and gene expression (Morris and Mattick, 2014). Messenger RNA (mRNAs) of many types function at multiple intersecting levels and are significant sources of potent epigenetic impacts that suggest their central role in evolution and ontogeny. Nor is there any simple overlap or mapping between mRNAs and proteins (Smalheiser, 2014). However, their summation yields an enormous increase in information capacity as compared with any single pattern of gene expression (Smalheiser, 2014).

MicroRNAs and other non-coding RNAs (ncRNAs, endo-siRNAs, piRNAs, antisense and long ncRNAs, transposable elements) are all part of a complex regulatory apparatus that affects protein translation and mRNA transcription as significant genetic and epigenetic mechanisms. This is a system that functions at multiple levels governing the activation, repression, or level of transcription of entire classes of cellular RNAs (Filipowicz et al., 2008). Even at this regulatory level, there is no one to one correlation between the pattern of mRNA, pre-mRNA, and ncRNA activation and gene expression (Smalheiser, 2014). Indeed, post-genomic studies now indicate that ncRNAs are the dominant form of RNA (Ponting et al., 2009).

Smalheiser (2014) indicates that such ncRNAs are crucial participants in the regulation of gene expression through activation or suppression of specific genes and through chromatin based epigenetic modifications. It is now known that RNA interference (RNAi), a small RNA that forms a complex with an Argonaute family homologue, has been implicated in learning, can self-amplify and self-propagate (Takahashi et al., 2009). Their influences can spread from tissue to tissue in a pattern that has been likened to infectious spread.

Although it had been supposed that the non-conservation of ncRNAs reflects a generalized absence of function, that is not the case. Instead it has been proposed that they change too quickly to be traced according to standard homologies (Smalheiser, 2014). Smalheiser (2014) notes that ncRNAs, although diverse, demonstrate a common general principle. Their mode of influence seems to be beyond intrinsic function. Instead, their actions lie within a form of complement to other existing genetic sequences. They exert specific local modifying effects on genes thereby minimizing the

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chances of deleterious 'off-target' consequences (Qureshi and Mehler, 2012). Essentially then, ncRNAs permit the rapid acquisition of information flux from the environment (Laurent and Wahlestedt, 2007).

In that case, it can be considered that the transposable elements (TEs) and TE transcripts that derives from small RNAs can be considered as computational elements from which other RNAs, such as miRNAs, endo-siRNAs and piRNAs represent further 'specializations' (Schratt, 2009). Nor are mRNAs the only type of extrachromosomal genetic material. Abundant extrachromosomal circular DNA has been identified in yeast (Møller et al., 2015). Some of these function as retrotransposons, abundant in plant and animal genomes, as part of a repertoire of a significant mobilome that has epigenetic effects, particularly in plants (Lanciano et al., 2017). These are non-genomic circular DNA rings ranging in size up to sixteen thousand base pairs. Their role is not completely clear but appear to participate in cell specialization, such as in the production of the protein, *titin,* in heart muscle (Pennisi, 2017). Accumulating evidence suggests that this functional circular DNA is part of the distant communication apparatus of the cell that can be mobilized via extracellular vesicles, along with proteins, mRNAs, and miRNAs (Kumar et al., 2017; Cai et al., 2016).

It is clear that non-genetic aspects of the cell, such as the cellular matrix, are also essential to cellular maintenance, and its development and specializations through the active transfer of information within the cell. It is has been shown experimentally that the inner cellular environment is itself a crucial aspect of genetic function. Recent studies on DNA biomechanics indicate that physical processes operate in the regulation of gene expression (Milstein and Meiners, 2011). Moreover, it appears that the cellular matrix components and the crowded, active environment of the cell are necessary for proper genetic function. For example, the transduction elements of the cell that mobilize the conversion of mechanical stimuli are necessary components for activation of various transcription factors and other regulatory functions. These effects have widespread consequences across cellular networks. These have been evaluated by studying the cumulative effects on mammalian and amphibian embryogenesis in microgravity that demonstrate substantial distortions in reaction-diffusion processes, changes in ion channels, and molecular organization (Crawford-Young, 2003).

The summation of these influences of so many types underscore an increasing awareness of genomes as products of a stream of complex and differing inputs whose influences need not be direct and may be subject to changes that are not necessarily gradual. Genomes are continuously active products of insertions and deletions, duplications and rearrangements, some of which can be large events (Merhej and Raoult, 2012). Merhej and Raoult (2012) note that, " Genomes are collections of genes with different evolutionary histories that cannot be represented by a single tree of life (TOL). A forest, a network or a rhizome of life may be more accurate to represent evolutionary relationships among species." Moreover, central genomes are not nearly the exclusive hereditary players that were once supposed. Instead, a vast array of constituencies comprise any cellular information network. As this complexity reveals, such networks need management.

When all the foregoing is considered within the context of biology as an information system, then the central genome of any organism might be best conceptualized as a developmental organ that is dependent upon serial accretions, exaptations, and deletions (Lamm, 2014). It is certainly not a static store of information, but can be considered " a highly organized subsystem, both physically and logically, with well-ordered if highly context-sensitive and localized developmental processes that are tied to cellular and organism function." (Lamm, 2014). In this case, the virome can be considered a crucial participant in that development over evolutionary space-time through the fluid communication of information that crosses the domains. This effects a general common narrative based on cellular translational characteristics mediated through HGT (Goldenfeld and Woese, 2007). All this becomes a versatile pathway towards genetic novelty and complexity that actualizes in continuous responsiveness to the outward environment through self-referential requirements. Any genome is no longer perceived as an isolated island of genetic information. Instead, it is a part of an extensive and highly connected and continuously developing 'interactome' that together enacts phenotype through successive layers over time (Dreze et al., 2009). Stencel and Crespi (2013) view a genome as a set of genetic material in a lineage that has 'common interests' that tend to favor the same or similar phenotypes as a cooperative program. Since this is a mechanism based on implicit cooperation, it extends beyond passive selection. If viewed in this manner, then a genome is a product of many non-stochastic inputs and outputs that are matched to sensed environmental hazards.

In consequence, our conceptualization of the nature of the substantial integrity of a genome requires adjustment away from any concept of permanency towards one of continuous adjustment in response to information. At all times, self-referential cells direct their entire toolkit including their genome towards purposeful solutions to cellular problems. That path might be through co-option, transferred genetic elements, the rearrangement of already existing functional circuits, molecular pathways, or adjustment of lipid membranes. As these biological combinations reverberate throughout the cell, the central genome is both observer and engineering participant. Sources of variation as natural genetic and cellular engineering as part of collaborative niche constructions can be explored as wellsprings of cellular creativity counterbalancing a churning external environment. However, when information and its usage is understood to have primacy in cellular systems, then genes, despite whatever level of autonomy which they might possess, must still be regarded as informational tools of self-aware cells that are used to solve problems at their scope and scale (Miller, 2016a; Miller and Torday, 2017). Implicitly then, natural genetic engineering, as the coordination of genetic responsiveness to environmental demands, becomes subordinate to the entire cellular environment. The genome and the transposable elements and sub-viral particles of diverse origin that contribute to genomic editing must be regarded as occupying their own niche within the broader context of the entire cellular compartment and its myriad connections. Thus, natural genetic engineering is an articulated expression of underlying cellular self-reference directed towards the maintenance of homeostatic imperatives within preferential boundaries. Natural genetic engineering is an aspect of internal cellular niche construction among the large variety of overlapping niches and compartments that constitute the complex internal cellular milieu. In sum, genes are not an exclusive set of privileged entities within the active, crowded environment of the eukaryotic cell.

By many processes, all living entities converge as a networked informational interactome in which information can be assessed as having four dimensions: first, as a function of space-time, then, by extension across the domains in modes of lateral dissemination that can spread to populations, further through vertical inheritance from individual to individual, and then ultimately, in reciprocal extension back into the external environment to become part of the information system of other overlapping biological entities. Together, these intersect, conjoin and ultimately spread across the planet as interdigitating skeins of information. Therefore, the consideration of an overarching informational system architecture as an enfolding regulatory apparatus is justified, epitomizing the

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entire panoply of all cellular attributes that can be directed towards cellular problem solving. Holobionts are those concatenated cellular solutions to prokaryotic/eukaryotic cellular stresses (Miller, 2016a).

4.3. Biological information management systems

When genes are considered symbolic code, something else must operate that might in some way quantify information density within genomic sequences. Koonin (2016) proposes that this is best estimated through homologues that most contribute to biological function over evolutionary space-time. In this frame, sites of evolutionary conservation are the most 'meaningful' sites that have persisted through 'purifying selection'. However, a paradox ensues. As genome size increases, so does its conventionally considered entropic status. It can be calculated that configurational possibilities and expressive outputs multiply at an even faster rate than base genetic code. In consequence, information density within a larger genome necessarily decreases. Therefore, even though the genomes of 'complex' organisms such as plants and animals have the highest total information content, they are burdened with low information density. In contrast, primitive organisms such as bacteria have smaller genomes with higher information density that might be considered more biologically efficient.

However, that seeming inconsistency can be effectively resolved through centering biology as an information management system which always resides at the cellular level. In such terms, the entropic status of a genome and, more importantly, its information density remains in essential conformation with its cellular genome with respect to information density with an information size that is the yield of its entire multicellular informational motif. Information content becomes a function of the total complement of the connected interfacing of the biological players that permit any resulting macroscopic holobionic form. Since all holobionts are an enactment of a complex ecological partnership between specialized innate cells and microbes, the decentralized nature of that life form becomes an effective compromise between efficient local information density, which is actualized at the level of each of the myriad participants, and leveraged total information content that is required to sustain the macroorganic whole against its macroscopic scale of environmental threats.

This reconciliation through an effective information management apparatus offers further explanatory power. The obligatory recapitulation of all multicellular eukaryotes through the unicellular phase has been rationalized as the critical phase for the adjudication of epigenetic marks.(Torday and Miller, 2016b, 2016c, 2017a; Miller, 2016a,b; Miller and Torday, 2017). These have been acquired through phenotype during the macrooganic elaboration response to both long and short-term environmental perturbations (Torday and Miller, 2016c). In an information context, this can now be viewed as the critical stage of assessment of information quality that is needed to maintain long-term organismal-environmental complementarity. Passage through the high information density environment of the zygotic unicell provides the means by which the entire bauplan for the macroscopic elaboration remains adherent to conserved principles of cellular life that support self-reference at the unicellular level. In this manner, there is a consistent re-centering towards the deepest cellular homologies and, importantly, epigenetic marks are adjudicated towards that prerequisite. Thus, the unicellular form in eukaryotic life is an obligatory measurement phase in which the range of epigentic stresses that have impacted phenotype in the macroscopic elaborated form is moderated against the necessary bandwidth for perpetual survival of the essential eukaryotic unicellular form. This can now be regarded as the centrality of the information management system from which the next macroorganic elaboration will emanate and thereby constitutes the inner reality of eukaryotic life. Importantly though, the unicellular zygote is a measurement phase of information quality rather than a specific further method of selection. Selection determines what choices get delivered to the unicellular zygote as implicates. The perpetual unicell then adjudicates the result of filtering selection according to its long-term needs and short-term requirements. The holobionic form can then be understood as a combination of complex co-linked mixed microbial and innate cellular ecologies in which entropy is highest, through its variety of participants and decentralization, yet whose information density is maximized through its unicellular recapitulation. Despite appearances then, the centrality of problem-solving for eukaryotic life is permanently endowed within the cellular frame, anchored by the unicellular zygotic recapitulation rather than its more complex appearing macroscopic assembly.

It has also been acutely proposed that segments of the genome, though not 'junk' are zones of 'fuzzy' meaning (Koonin, 2016). However, insofar as bioactive molecules and their precise interactions are concerned, it can instead be considered that biology is firm its but circumstances can be vague. For any living entity, which is by definition self-referential, information quality is always equivocal and the utility of any information or code is always dependent on the explicit set of biological circumstances. When viewed in that frame, any arbitrary definition between 'meaningful' genetic code or meaningless 'parasitical' coding elements cannot be sustained. Usefulness in these situations becomes a function of time and context. Thus, the status of all existing sequences fluctuates as serviceable memory to be employed as needed to solve cellular problems dependent on a range of stresses that can extend over many life spans and a multiplicity of environmental viscissitudes. The sequences themselves can express or not, either fully or partially, but are indefinite in their responses only to the extent that it is the nature of some information to be equivocal and dependent upon explicit environmental stresses and contexts. There is, then, no need for 'fuzzy' to be considered as any embedded logic of the system of the expression of bioactive molecules. Instead, issues of indistinct meaning in cellular terms or with respect to genetic code are better understood as a variable set of tools that might be intermittently deployed to problem-solve when information is imperfect and the full necessary range of response is unpredictable. If prediction and the value of anticipation are limited, the deployment of information may be variable and incomplete.

It is clear that 'meaning' cannot be fully ascertained from analysis of any isolated genome. Any such objectified status must be assessed as a response system juxtaposed towards external variables based on an entire information space of which any specific genome is only a participle. The meaning of biologic information is intensely related to both sender and receiver. Among those sequences that have been considered as simply parasitical or of low information density, context is all. In a flexible genome that has situational preparedness, any such sequences are 'on call' for the exact circumstance in which they are needed to solve cellular problems (Miller, 2013). In evolution, the hurly-burly of invasive elements and their endogenization within any genome can be refined away from any connotation of 'junk' or indeterminacy into a common narrative of self-referential problem-solving in which heritable genomic meaning is not biologically fuzzy at the molecular level but the information upon which it must act always is (Miller, 2016a; Torday and Miller, 2017a). Furthermore, mechanisms for genomic deletions or epigenetic silencing are known to be commonplace (Moran, 2002). It should therefore be concluded that genomes, as cellular constituents, act to retain useful segments that are needed now or are aspects of cellular memory of prior

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environmental stresses and seek to actively discard or silence those mobile elements that have been imposed but do not pertain. By default, the retention of others aspects of memory that do not seem to conform to current environmental exigencies becomes a necessary element of a long-range environmental forecast. Griffiths (2017) argues that development is expression of accumulated information over evolutionary space-time and that might be judged according to a concept of precise determination derived from Crick's central dogma. Yet, in biological context, information is inherently ambiguous (Torday and Miller, 2017a). Thus, any concept of precise information must yield to the living circumstance in which the reliability of biological information is always precarious.

Since cognition is information-dependent, then the cell can be seen as an information management system of its own as an embodiment of information content. As it has been previously asserted that the cell is a primary initiating niche construction, it can be considered that its structured informational architecture provides a robust means of sustaining self-referential identity despite outward noise and ambiguous cues. Thus, it must be granted, that all aspects of the cell, including genes or lipids, are informational tools in support of that informational architecture. The active cellular context is its overlap with other self-same information systems wherein information is pervasive and is context mostly ambiguous. Though information fields overlap, the primary level of cellular activity remains centered at the level of the individual cell. Its contextual use of information ultimately depends upon its explicit biological circumstances in which the received information is noisy and unclear. Therefore, information that is meaningful and understandable knowledge is not objective but must be 'relativized' in relationship to the receiver's knowledge and limitations. (Brier, 2015). It reasonably follows that any improvement in information quality necessarily includes the recruitment of a collective assessment, which even if only an averaging in space-time, which it need not be, represents an improvement in the reliability of the assessment of information when environmental cues are ambiguous. Thus, although cellular problems are personalized, its best solutions are through the multicellular form that ultimately reiterates into holobionts. This is the form that achieves the higher effective information content and quality upon which relevant individualized decisions can be made in juxtaposition to the outside environment.

By deconstructing a holobiont to the level of its various cellular constituencies, including its microbial partners, it becomes evident that there might be differing values for any information content at one scale or for a particular participant that need not be the same at another. What is obscure at one level of problem-solving implicates might yield decisive biological expression at another. The cell identifies a problem, uses its tools to solve its problems, and learns through experience and communication to eliminate unsuccessful solutions. In holobionic entities, in which tissue ecologies unite towards a whole, all aspects of cellular life are still directed towards self-referential local solutions to solve limited independent problems while upholding essential self-identity. Importantly, this is being achieved through a shared collaborative information space at multiple intersecting levels. In a life form that is both decentralized and connected, the participants can separably evaluate information, maintaining some forms of local autonomy within an integrated whole. They sustain themselves by assessing their own self-referential information field which is gained through a shared organism-wide information space. As a crucial part of that evolutionary solution set, selection and survival have their crucial post-facto influences.

In complex organisms with a large number of interacting subsystems at multiple temporal and spatial scales, there would be an impulse to assume high levels of control over the individual participants so that all might thrive. However, one manner in which the emergence of self-organization can occur in the absence of any absolute superintendency is to approach collective action as a function of effective information (*EI*) (Hall, 2005). *EI* content is higher when there is constraint of any system's range of possible alternative states, either past or future. In such a system, any associated cell or microbe has accepted a limitation of possible states in the furtherance of achieving its most desirable one. In that context, the holobionic form can be seen as maximizing the utilization of *EI* through its unique information architecture in a confederated form that is simultaneously a vast array of constituencies and an entirety. In this circumstance, the global flow of information is fluid across the whole and importantly, can be compared to Ulanowicz's ecological networks. (Ulanowicz, 2017). Such ecological networks do not progress to the most efficient (ordered) configuration, but to a level that is balanced between constraints and reliability. In informational terms, this can be considered within the general frame of the robustness of the available information, that is, the most consistently reliable information within a range of external stresses.

It has been presented that a living organism depends on the continuous aggregation of information from a multitude of sources for its relationship with the outward physical environment. As a derivative of those physical states, it can be advanced that the cognitive assessment of biological information is rooted within quantum inferences and their limitations (Miller, 2016a). This is the means by which equivocal cues can be placed within their context in circumstances of informational insecurity (Gunji et al., 2016). When placed in a frame of information assessment, multicellular biology becomes a simple matter of greater safety in numbers as a form of quantum summation. The multicellular form, either among prokaryotes or eukaryotes, is purposed towards improving the quality of ambiguous information that is either derived from the outward environment or shared as transferred information among ecological participants. That cooperation can be justified as an impulse towards a collaborative assessment of equivocal information in which a mixed microbial/eukaryotic multicellular ecology represents the specific compromise circumstance in which information quality is optimized for all of the participants. By working together, networked living entities can better evaluate ambiguous information and stressful environmental cues in their directed search to sustain their individual states of preference and homeostatic equipoise. Self-referential identity initializes the use of that information towards that purpose. Therefore, in an active biological sense, self-referential cognition permits the purposive use of information and communication at reiterating scales. It is pertinent that this is not a specific genetic phenomenon. Anesthetic states can be produced within a time frame in which genetic action cannot supervene (Baluška and Levin, 2016). This same non-volitional state can be sustained so that other bodily functions continue unabated. As a direct derivative, it can be surmised that the entirety of the cell must participate in a cognitive process that extends beyond genes. Therefore, a concept of cells as a comprehensive informational architecture that extends well-beyond genes is justified.

It is now well accepted that free-living cells and complex microbial communities are dependent on communication as exchanged information (Ben-Jacob, 2009). De Loof has represented that cells should be seen as the summation of their communicative capacities as sender/receiver units (De Loof, 2015b). According to their scale, individual cells send, receive and interpret information to maintain homeostatic preferences based on both local and global inputs (Ingber, 2003). As sender/receiver units, cells of all types register and convert information as part of their inherent information systems. Therefore, the need to maximize information can

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be assessed as the impulse towards the self-organizing colonial form, such as biofilms, in which cells exhibit specialized behaviors. Such actions have been attributed to problem-solving via collective sensing and the use of information based upon shared environmental experiences and stored information as memory (Ben-Jacob, 2009). Bacteria utilize information through quorum sensing, chemotactic signaling and horizontal transfer of information through plasmid exchange to support their collaborative communities (Ben-Jacob and Levine, 2006). Research has corroborated that bacteria make predictions, remember, learn and engage in intelligent behaviors that must be assessed as cognitive complexity (Ford, 2009; Pinto and Mascher, 2016).

All cells communicate and employ information towards collaborative goals. Prokaryotic biofilms and multicellular eukaryotic organisms marshal these skills which can be considered a form of natural informational engineering at the cellular level. It is through this latter process that complexity builds in the macroorganic cellular realm. It has been advanced that this reiterating pattern is of sufficient sophistication as to be analogous to the manner in which humans engineer within their own sphere (Shapiro, 2011; Miller, 2013). Since all information dwells in ambiguity with respect to any biological entity, the coordination that emerges within these tissue ecologies is coordinated problem solving through the highest obtainable information quality. In such contexts, cell-cell communication becomes a deeply reciprocal and entangled means of information sharing by all participants in any common information space towards the settling of those uncertainties (Torday and Miller, 2017a). With proper collaborative networking, even noise within a system can be used to advantage. Stochastic resonance has been shown to be a feature of biological information processing wherein random noise can enhance the detection of weak information signals among co-aligned participants (Hänggi, 2002; McDonnell and Ward, 2011). Among cellular ecologies, this entanglement principle can be best understood as overlapping information fields that involve all phases of life from the unicellular zygotic phase, across post-zygotic embryonic development, and throughout the entire adult macro form (Miller, 2016a). It is therefore clear that in all biological instances, information undergirds reproduction, development, and all elaborating macroorganic survival characteristics.

This complex intersection has been typically explained in a Darwinian selection-centered macroorganic frame including that of holobionts (Chiu and Gilbert, 2015). Instead, no matter the scale, it is now plain that it is a cellular world (McFall-Ngai et al., 2013). All cells and living entities should be properly regarded as base cognitive agencies making decisions in the furtherance of their own aims towards goals that are achieved through the use of information as interpreted through their own faculties and limitations, no matter their specific circumstances within a conjoined informational matrix (Bai et al., 2016). Each is its own informational architecture which derives it particular information set from its local and distant sources. With all the foregoing as prelude, it is defended that cellular life is best considered as a unique type of information management system.

Recent trends in management and economics have led to the development of models based on cellular organizational structure (Daft and Lengel, 1986). The intent has been to imitate certain perceived aspects of biological systems, particularly those that concentrate on nodal architecture that retain some semi-autonomous functions. Such systems are recognized as being capable of achieving common collective problem-solving goals through the extensive exchange of information. The effectiveness of this communication has been defined through concepts of conveyance and convergence that are meant to define a reciprocating match between a sender and a receptor. These models find that the most robust informational level concentrates closest to that of the individual participant as opposed to ever higher levels of aggregated participants (Dennis and Valacich, 1999). This structure is a direct contradiction to the typical hierarchical relationships in traditional management systems and suggests that the highest levels of efficiency are achieved through the maintenance of high levels of local control as exemplified in biological systems.

It is generally considered that there are three forms of semiotic information: semantic (the information content or meaning of communication), syntactic (the degree of probability of an event that relates to frequency of communication and its structure) and pragmatic (awareness of the situational context of the communication) (Ferran and Koussa, 2012). In information systems, knowledge can be considered pragmatically tested information. (Baluška and Levin, 2016). Even bacteria have highly sophisticated communication systems to cooperate and self-organize based on the use of semiotic information as a form of linguistic communication and social intelligence (Jacob et al., 2004). Therefore, all living things exist within the architecture of an information management system whose existence is as important as any biological materiality and can be demonstrated at every scale.

Any information based system that has cognition at its center within the cellular domain is likely to meet resistance with respect to the limits of that cognitive ability and the intentional capacity of cells to support its coordination. However, this putative injunction is far from any negative. Instead, it is asserted that these cellular limitations are their explicit advantage when they act within any information system that exercises cooperation to enact solutions. That specific cognitive cellular advantage is that cells are not seeking ideas but only solutions. It can be reasonably assumed that cellular self referential limits do not include emotions and biases that affect more complex organisms as they confront ambiguous information. Therefore, these limits encourage the free flow of solutions. Since cellular communication is a general broadcast in nearly all circumstances, including HGT, cellular information system can be best understood as an open source network that reinforces opportunities for collaboration. Therefore through their limitations and constraints, cells are more efficient in finding aggregate and consensual solutions than humans are in constructing their own cities.

This principle can be directly illustrated through stigmergy. A stigmergic feedback loop occurs when one action that leaves a trace in a medium triggers a further action by another individual (Heylighen, 2015). This represents an indirect method of coordination and is typically applied to self-organization in the macro sphere, such as termite mounds. Importantly, the intentionality of the participants can be minimal and directed towards an individual organism coping with environmental conditions without the necessity of any explicit goal. The only actual requirement is a self-referential ability to send and receive information. As Heylighen (2015) notes, there is no need for anticipation, intentional communication, any imposed division of labor, central control or supervision.

These same stigmergic feedback loops are a self-organizing principle that can apply to the cellular sphere as well as macroganic life (Miller, 2016a; Miller and Torday, 2017). Any cell or other living entity that is biased towards maintaining individual homeostasis according to its own self-directed goals can participate in a reciprocating feedback loop in any mixed cellular ecology. Having individuals with differing goals would represent a natural division of labor upon which complexity could build. Within the shared ecological information space, neither the sender nor receiver of information is necessarily clear, so potential conflicts are minimized. Hence, there is no organized resistance towards any particular solution since there is no central authority and no actual

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errors are being made. At each moment, individuals are engaged in solutions to epiphenomena that can be communicated by a vast arsenal of means to other participants. Therefore, natural self-organization emerges from local actions (Heylighen, 2001). Collaboration in the use and deployment of information becomes an emergent phenomenon as the most efficient means for any individual organism to evaluate the equivocal information that characterizes any biologic system in all its forms. Thus, biology can be securely placed within a narrative of recursive levels of information management, from the first self-reinforcing intracellular feedback loops that led to stabilized unicellular informational architectures, and then, to multicellular informational motifs. All are manifestations of a perpetual self-referential information cycle.

5. Discussion: a separation from the past

"No self is of itself alone. […] The 'I' is chained to ancestry by many factors[…]. This is not mere allegory, but an eternal memory."

Erwin Schrödinger, 1918

Conventional precepts commend that evolutionary change is gradual and progresses via cumulative random genomic mutations. Those resulting variations permit selection that determines an evolutionary direction that leads to complexity and phenotypes (Raoult and Koonin, 2012). From that base, evolutionary history has been generally conceptualized as a Tree of Life. Contemporary research and opinion now indicate that each of these governing principles are insufficient and that the standard synthesis requires adjustment (Merhej and Raoult, 2012; Koonin and Wolf, 2012; Müller, 2017).

It is currently accepted that gene expression is dependent on a range of epigenetic factors that are both chemical and genetic and are both reversible and heritable (Davies, 2012). Davies (2012) points out that the genome can be specified as a location within a cell, but the epigenome is non-centralized and systemic. Further, information can be stored in genes but is often not. Information space for an organism is not merely stored as genetic code but is continuously adjusted as an emergent self-organized phenomenon as part of complex cellular systems. In biological instances, these interchanges yield individual bioactive consequences and interconnecting feedback loops as reciprocating aspects of information space based upon individual self-referential PIFs (Miller, 2016a). Those PIFs are the sum of the overlap with the physical environment and its intersection among all living participants within any ecology (Fig. 1). Necessarily, in an information system that is defined by such conjunctions, there is no absolute hierarchy among the participants. All elements interlace and merge to greater and lesser degrees dependent on circumstances. In terms of causality, this form of life complies with the assertion that top-down causation intermingles (Davies, 2012). In evolutionary terms then, there can be no privileged level of causation (Noble, 2012). In eukaryotic life, all of the individual participants are self-referential agents, and each is seeking its most efficient means of obtaining and utilizing information. When this is the objective biological narrative, concepts of hierarchical selection are depleted. Further yet, Davies (2012) wonders whether there is sufficient indeterminacy in the system to insist that any simple reductionist view of biology is unrealistic. Instead, it might be that biology fundamentally changes the nature of causality akin to the distance between quantum and classical physics and therefore, must be approached in a different manner than prior.

Villarreal and Witzany (2013) have found that single hairpin RNA stem-loops essential to RNA function operate independently without selection, but in combination. These act together as a.

"self-litigating" consortia in which the influence of selection is only derivative (Villarreal and Witzany, 2013). Such local actions illustrate the larger terms through which individuals partially subordinate to an essentially non-hierarchical collaborative constituency. This same phenomenon reiterates at all scales. Among RNA stem-loops, it has been noted that behavioral motifs relevant to variation arise through this concerted action (Villarreal and Witzany, 2013). The final repercussions of these consortia is not based on their errors but through their 'natural competence' in which their actions are analogous to 'social groups'. Each consortia forms a subdivision and together, they collectively enable aspects of a total organism-wide informational system yielding effects that extend beyond the individual limits of the base constituencies. It is of further interest that stem-loop RNA hairpins have aspects of common ancestry that link them, through various RNA particles and metabolites, to 'parasitic' RNAs including ribosomal viroids, giant viruses, Rickettsia repeated palindrom in elements, domesticated viruses and retroviral sequences (Seligmann and Raoult, 2016). All of these are characterized as 'infection derived agents' that can communicate and, in combination, originate genetic innovation (Villarreal and Witzany, 2013; Seligmann and Raoult, 2016). Interactions of these types, among these genetic constituents, illustrate the linkages between infectious interchange, DNA transfers and eventual biological expression in which the participants both utilize and become the formative elements of an organism-wide information management system directed to local problem-solving. Crucially though, the terms of this engagement within any macroscopic organism is through linked constituencies of self-referential participants.

When organisms are properly conceptualized as aggregates of semi-autonomous participants linked by both individual and shared information spaces, they assume the form of 'super-system— system— sub-system' that Bohm described in his attempt to reconcile the physics of quantum non-locality and time (Bohm and Hiley, 1975). As he envisioned, although individual participants make the whole, they cannot be properly understood or evaluated outside of the context of the entirety. Their meaning is lost outside of the whole, so a reduction to the level of the participants loses its integrity. Even the relevant time order for any subsystem within such a larger inter-related system depends on the "over-all state of movement of the whole system, and is not (as implied in classical and commonsense notions of time) fixed in a way that is independent of the state of the whole system." (Bohm and Hiley, 1975, p. 15) This Bohmian conceptualization can be well applied to a holobionic super-system in the context of informational architecture. Co-linked participants comprise a fully functioning holobionic whole in which all participants continue to connect to their individual self-referential information space (PIF). Together, they complete an intertwined organismal informational architecture as a summary informational motif that is both semi-autonomous and co-dependent. Once a self-referential participant is part of a whole, any reductive dissection to the level of that participant can only be understood in its context as part of that entirety.

From this, the difference between physical systems and biological ones can be discerned. Goldenfeld and Woese specify that cusp: " Self-reference is a specific feature of biological systems and not physical systems……" (Goldenfeld and Woese, 2011, p. 9). As cells are affirmed as self-aware and thereby self-organizing problem-solving entities, then, cellular constituents including genes from all sources are inescapably used as tools in service to that purpose. It is an important matter that the general narrative about genes tends to ascribe active agency to them, for example, by 'turning on' or 'turning off'. However, as R. C. Lewontin points out in

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Oyama's *The Ontogeny of Information: Developmental Systems and Evolution,* genes do not 'do' anything on their own (Oyama, 2000). If that were the case, then recovered DNA from a crime scene could remake the victim or perpetrator on its own. Instead, Lewontin says, “DNA becomes 'information' about the organism only in the actual process of cell function.” (Oyama, 2000, p. xiii). The cell is directly using DNA for its larger purposes as an informational and ontogenetic agency and reciprocally, is participating in determining the scope of information storage from environmental informational cues. Within the complexity of our biologic system, genes serve the cell, serve themselves, and then, reciprocally are being served by other aspects of the cellular apparatus.

There is room, then, to at least tentatively approach the consideration of the instantiation of self-reference as a primary level of biological causation (Pattee and Rączaszek-Leonardi, 2012). From that moment forward, no privileged level of causation can be assigned within the networks that enact levels of higher biological complexity. Once self-reference supervened, it defined the living state through its attachment to information space. All living things share that essential co-equality. Through that imperative transition, always rooted within an individualized assessment of information space, evolution becomes a collective phenomenon that must be assessed through a systematized network (Goldenfeld and Woese, 2011). Indeed, it has been considered that there are only two types of organisms in the biosphere: capsid-encoding organisms (the virome) and ribosome-encoding organisms (cells) (Koonin and Dolja, 2014). However, all are a linked interactome. Homologous capsids have been found in a large sample of iscosahedral viruses that are known infectious agents of the three cellular domains. In turn, analysis of their genomes suggests a mosaic of genes that have been derived from a variety of susceptible microbial and eukaryotic targets during evolution.

A highly relevant question about the limits of information has been previously posed concerning evolution. Can a low-informational state that modifies through a rapid succession of dissipative structures self-order into organization? (Yan et al., 2009). Within Cognition-Based Evolution (CBE) as systematized networking based on self-reference, an answer in the affirmative is offered (Miller, 2016a; Miller and Torday, 2017). In such a network, genes are not a linear program. Instead, they form an informational aspect of an information management network as they interchange and respond to internal cues and external environmental stresses. In this manner, the information content of biology resides within the dynamics of the system (Davies, 2012). It is process over form. Each self-referential entity extends into information space and experiences the outward environment through an exchange of bioactive molecules, genetic transfers and other environmental epigenetic impacts. Since the cell is a highly integrated functional unity, all aspects of the cell must participate in the information set that the cell represents as both observer and participant (Torday and Miller, 2016b). All aspects of the cellular domain must be regarded as contributing including lipids, membranes, bioactive minerals and genetic material. Therefore, although genes are crucial aspects of the interconnected informational set that becomes all living entities, they are only one aspect, albeit crucial, of the cellular toolkit. It is the entire toolkit that integrates the cellular information set and governs its range of responses to epiphenomena. Therefore, many phenomena that have typically been regarded as descriptively separable, such as epistasis, pleiotropy, or exaptation are differing expressions of the cellular usage of its toolkit. When viewed within this necessary frame, the reception, assessment, and deployment information and its communication supersede any concentration on material forms (Witzany, 2016).

It will certainly be insisted that compelling models of evolutionary development can be developed that do not depend upon the centrality of cognition as the foundation of an information management system. The Darwinian narrative and its successor adjustments are testimony to those efforts and beliefs. However, it is evident that self-reference defines living things as a practical biological identity (all living things have that measurable faculty and inanimate things do not). Then, no matter its cause, self-referential awareness must be regarded as the essential living state. It follows that this must be regarded as the relevant platform from which any cohesive biological narrative ensues. This loose syllogism stands akin to the NeoDarwinian reliance on its originating presumption of an extraordinary level of replicative fidelity from which intermittent variations might arise. However, replication is surely more than mere chemical bonding. It has been asserted that the 'self' in self-replication and its microstates can only be assessed through observer status. (England, 2013). Thus, it can argued that replication likely depends on self-reference to assure replicative fidelity and therefore may have preceded Darwinian selection. In that case, selection would always have been a vital post-facto epiphenomenon. As Deacon (2011)asserts, “ Although natural selection is not a teleological process itself, it depends on the intrinsic end-directed and informational properties of organisms: their self-maintenant, self-generative, and self-reproducing dynamics. Without these generative processes that are prerequisites of evolution, and require certain supports for their environment, there is no basis for selection.” (Deacon, 2011).

The particular advantage of a cognitive approach to evolution is that fitness can now have definitions that are testable and refutable. Fitness can be evaluated as the capacity to discriminate information towards problem-solving in the most efficient, reliable and robust manner at varying scales under differing environmental stresses. Although this measure of fitness surely relates to reproductive success, it is not its only outcome, nor is it an explicit function of raw genetic frequencies. Research becomes an exploration of the precise ways in which biological information is deployed, shared, and managed at any and successive scales. This approach integrates well with the growing field of integrative biomathics in its attempt to derive mathematical and computational models. These explore a full range of dynamic biological multilevel complex systems and the mathematics of replication and self-reference that underlie them. (Simeonov and Ehresmann, 2017; Kauffman, 2015).

It is well accepted that constraint is a requirement for evolution (Shakhnovich and Koonin, 2006; Murren et al., 2015; Futuyma, 2010). In CBE, immunology rules as a primary biological expression of that damper (Miller, 2016a; Miller and Torday, 2017). It is both governing guidepost and restraint. It controls significant aspects of the accessibility and quality of exchanged information. In biological terms, immunology provides many constraining guideposts. Genetic interchanges occur and reciprocate within immunological limits. The compact between cells and microbes is maintained and enforced through immunological rules. Self-referential status thereby has its means of protection, even if information is transferred and shared. Cooperation is enabled, but separation is enforced. In this manner, evolution becomes sustainable ecological continuity instead of ever larger cells. Evolution is accomplished by the fluid transfer of information and its management within and among self-referential living things whose integrity can be preserved. When information is utilized in this manner, information systems can self-modify towards greater complexity (Kampis, 2013). In biological circumstances, in which the deployment of information is requisite and the reliability of such information must be prioritized, the sharing of that information permits problem-solving solutions towards the sustenance of homeostasis in the face of environmental stress. This advantage energizes cooperation and collaboration that can become self-referential pragmatic cellular knowledge. Bacteria know this and

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act accordingly. Separate *Bacillus subtilis* biofilm communities use coupling electrical signals through in-phase and out-of-phase oscillations to time-share nutrients under stress and diminish conflict (Liu et al., 2017). Clearly, this is a directed self-referential engineering solution in which biologic outcomes become consensual endpoints. It is precisely upon this crest that the Darwinian narratives of the primacy of selection and stochasticity erodes. As it can be asserted as axiomatic that any biological context is the systematized use of information, then no matter any chaotic inputs, outputs are no longer a series of stochastic events. At respective limits and at each scope and scale, biology 'knows' what it is doing. Its necessary direction is always towards self-directed problem-solving that is continuously centered at the individual cellular level to maintain homeostasis and self-identity in the face of environmental stresses. If it were otherwise, there would be no organizational impulses and biology would have remained organic chemistry.

Placing evolutionary development within the specific frame of information content and its handling permits a coherent context for all biological processes. Within this dynamic, infectious interchange extends beyond pathogenesis and can be seen as a primary mechanism for both genetic transfer and a crucial aspect of the information management system upon which organisms depend. The obligatory recapitulation of eukaryotes through the zygotic unicell no longer confounds. That passage is in service to the regulation of all sources of information to maintain the long-term cellular equipoise of the perpetual eukaryotic unicellular informational architectural form in the face of temporary environmental dislocations. The fact that the gene-phenotype relationship is reciprocating but never discretely one-to-one is reconciled. Macroorganic phenotypic expression elaborates for the exploration of information space to better assesses a stream of ambiguous informational cues as an expression of a cellular problem-solving information apparatus. Further yet, the multicellular eukaryotic form, as an obligatory holobiont, is rationalized. It is the most efficient cellular means of sorting ambiguous informational cues amidst troublesome environmental shifts.

Within this narrative, cellular creativity has latitude as local and connected problem-solving. Creativity is ever and always the agitating cusp between cellular drive towards continuous homeostatic balance and the ambiguous information upon which it depends. Creative cellular solutions are achieved through a combination of random events and the deliberate cellular utilization of information to solve self-referential problems in steady incremental responsiveness to environmental stresses and their attendant uncertainties (Table 1).

It will be argued that there is no need for cognition to properly frame an evolutionary narrative when selection based gene frequencies might the alternative consideration. The counterarguments are direct. The placement of evolution within the lattice of gene frequencies was conceived at a time when the modern complexities of the genome were unknown and the contribution of a myriad of other non-genomic genetic contributions was not yet explored. That was also an era in which macroscopic organisms were considered unitary beings and their inherently collaborative and cellular holobionic character that includes an obligatory and influential microbial fraction was not even imagined. Further yet, until relatively recently, the concept of cellular intelligence was unknown. However, in a contemporary frame in which self-referential cellular faculties have been conclusively demonstrated, the proper examination of biology and its evolution must be conducted through a frame in which the use of physical and biological information to problem-solve is given primacy. Therefore, constructing an evolutionary narrative without cognition at its center requires any who might dismiss its position, or regard it as less than indispensable, to offer an explanation of its role as a universal property exhibited by all living things. It is either epicenter or mere epiphenomenon. If only the latter, then exceptions ought to be identified and presented for research. If it is alternately insisted that natural selection established self-reference through the selection of replicators, and therefore, cognition is only derivative, the status of the argument with respect to our evolutionary course does not change. Once self-reference is instantiated, it becomes the substantive evolutionary driver and natural selection subsumes a post-facto role. The analysis must take one of two sides. Either random variation and resulting natural selection present us with ourselves, or a universal property of self-reference enables the directed networked complexities upon which filtering selection might then act to make us what we are. Thus, a principle of parsimony can be applied to the entire construct of Cognition-based Evolution that can stand in equal apposition to the satisfying simplicity of selection: self-referential cognition is life's basal condition (Miller, 2013, 2016a; Shapiro, 2011; Trewavas and Baluška, 2011; Baluška and Mancuso, 2009; Dodig-Crnkovic, 2014) That cognition underscores all cellular activity. Its direction is ever, always, and only towards its own self-referential homeostatic equipoise. Importantly, such action is information dependent.

6. Conclusion

Contemporary evolutionary theory has liberty to move beyond genes and their selection to accommodate a counter focus based upon self-referential cognition as the universal living condition. Living things are set apart from the inanimate by their self-referential attachment to informational space-time. This obligatory union is a connection to physical space as current status and to time as an historical memory of an immediately prior status. The fundamental difference between an abiotic predecessor and its ensuing biotic ensemble can be specifically identified as residing in the use of information as a self-referential awareness of its limitations. It is the predicament of living things that any attempted resolution of environmental stresses must advance through the deployment of ambiguous information. This attachment to uncertain information defines the living condition. In attempting to maintain self-referential homeostatic equipoise, cells simply make the best of it within the disciplining confines of selection. Within that self-referential context, genes and all other cellular components are implements to be actively deployed. Still, chance plays its part. Everything new and unexpected establishes a fresh space of possibilities that might be realized (Coffman, 2014).

It is apparent that cells are aware of their environment as a function of basal cognition. It can be also argued that viruses, subviral particles and prions are similarly capable. Yet, whatever the exact living threshold based on contingent and collaborating responses, all are surely information dependent within any cellular environment. By default then, the highly organized cellular ability to confront stress must exist within the context of an information management structure that organizes that coexistence. Therefore, cells can be considered biomolecular realizations of an informational architecture that reflects a systematic and orderly use of information. That management structure can now be understood as embodied biological forms. These are expressed through the interactions of stable reiterating unicellular informational architectures of Prokaryota, Archaea, and unicellular Eukaryota. The combined multicellular form among unicells or multicellular eukaryotes become the underlying informational motifs from which all the variables of multicellular life are comprised. The distinctions between those essential unicellular and eukaryotic motifs arises from their differential assessment and deployment of uncertain information. One realm remains perpetually confined to the

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Table 1
Differential features between Cognition-Based Evolution and NeoDarwinian selection.

Cognition-based evolution	NeoDarwinian selection model
Self-referential cognition undergirds evolution	Selection determined gene frequencies drive evolution
Proceeds by information assessment, communication and management	Proceeds through random replication errors/differential survival
Self-referential homeostasis guides resource utilization	Random mutations precede the use of resources
Niche construction/natural cellular engineering and mutations yield variations prior to selection	Mutations yield variation during reproduction
Phenotype as self-referential environmental exploration	Phenotype is driven by selection
Natural selection is a post-facto filter	Natural selection defines evolution
Genes as informational tools - a flexible response system for environmental stress	Random genetic mutations vary a passive code
Integrated proteomics/transcriptomics link to self-referential problem-solving	Transcription is selection dependent
Primacy of immunology to sustain self-reference	Immunology as a selection driven secondary phenomenon
Deterministic cellular creativity solves problems relating to ambiguous environmental cues	Fitness/selection; stochastic variables
Infection is a primary evolutionary driver as an important means of inter-domain communication	Host/pathogen model
Holobionts as integrated problem-solving collaboration between innate cells and microbes to deal with ambiguous information	Microbes as colonizers
The eukaryotic zygotic recapitulation is a requirement for cellular information management and epigenetic modulation	Meiosis serves genetic variation
Macroorganisms remain permanently anchored to unicellular roots	Macroscopic existence independent from unicellular requirements

unicellular form and the other can further elaborate through the multicellular eukaryotic informational motif as an obligatory co-adapting holobiont. That latter structure is the means by which self-referential agents organize in collective response towards their advantaged means of using information to problem-solve.

As a reiterating underlayment, the perpetual information cycle permits the self-referential collaboration that extends across the entire macroorganic biologic spectrum as self-directed niche construction and natural cellular engineering. Within this overarching narrative, infectious interchanges as HGT are an efficient means of information transfer in the furtherance of self-referential imperatives among all participants. Thus, traits as fitness achieve measurable and testable definitions. Traits are representations of the effective utilization of information towards sustaining cellular requisites. It is this effective self-organizing assessment and deployment of information that enables the cell itself and then, further, the aggregations of mixed ecologies that constitute holobionts as a collaborating cellular constituencies (Gilbert et al., 2012; Miller, 2016b). Ford has championed the recognition of individual cells as perceptive and intelligent and has exactly placed these faculties in their proper perspective: “ Once we consider multicellular living organisms as communities of coordinated-but inherently autonomous entities, the nature of life is more meaningfully revealed.” (Ford, 2009, p.351).

At every scale and within its limits, cognitive ability discriminates the use of information from a proscribed range of uncertainties that can settle into biologic action. The zone of separation between the animate and the inanimate thereby lies upon the threshold of physical data becoming biological information. Its crux is the condition of knowing that this information has constraints. As any awareness of situation is information dependent, evolutionary development is the perpetual entanglement of living entities in their use of information to resolve environmental ambiguities into explicate self-referential biological solutions to meet environmental stresses. The compulsory gap between information and its reliability is the exact rationale towards assessing the scope of life at every scale as systematized information management. Simply put, perfect information needs no management. Thus, evolutionary development can be appraised as centered within the systematic management of information to sustain cellular homeostatic equipoise. At a consequence, and at all reiterating scales, the survival of any living organism is granted only through the self-referential scrutiny of its incertitude.

Competing interests/conflicts

None.

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None.

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