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A Knowledge–Based Approach to Systematization of Life Processes

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ABSTRACT

A simple, nine–scale model of living systems consisting of five material scales, three knowledge scales, and one energy scale is introduced. It is shown that a systematic stratification of biological knowledge provides new insights into understanding of the material and energy flow processes. The model allows for an objective mapping of the knowledge–based genetic, epigenetic, and supragenetic spaces of different material scales that can also be approximated as an organizing principle.

Introduction

The purpose of this paper is to introduce a macrotheory for systematization of "knowledge" in biological processes. I do not characterize the proposed systematization of knowledge as a "philosophy" but as a "macrotheory." There are extensive writings on philosophy of knowledge, but as I will show in Sections II through VII, they all fall into one of the subsystems of the proposed methodology for systematization of biological knowledge. For those interested in philosophy of knowledge as it exists today I refer the reader to critical challenges by Kuhn and others to objectivity of scientific thought (Cole, et al. [1-8]), generic views and taxonomies of epistemological theories (Fuller, et al. [9-12]), knowledgebase and functional relevancy (Anderson, et al. [13-15]), representations of mental models and the flow of old knowledge into the new (Anderson, et al. [16-19]), biology as philosophy (Ayala, et al. [20,21]), the relationship between experts and knowledge (Bazerman, et al. [9,22-24]), and women's view of knowledge (Belenky, et al. [25-27]). As a subsystem of proposed systematization of knowledge in biological processes, the existing philosophies of knowledge are mainly concerned with how humans have produced knowledge and how humans have managed to do so in a short time. The intense homocentric preoccupation has rendered the scientific view of knowledge a human attribute embodied in linguistic and other practices (Fuller [10]).

Furthermore, the philosophies of knowledge possess an institutionally unaffiliated infrastructure with a large number of isolated disciplines that see their own local knowledge as core to any scientific debate, especially when facing a more general macrotheory (Bazerman, et al. [22,23]). As such, the philosophical arguments tend to constrain and discourage than support and construct a multidisciplinary macrotheory such as the one I propose for systematization of knowledge in biological processes. A macrotheory is handicapped from the point of view of past attempts at unification of biological sciences. Among unification theories we find creationism (Kitcher [28]), sociobiology (Kitcher, et al. [29,30]), natural selection (Brandon, et al. [31,32]), and others (Bechtel, et al. [33,34]). Despite their diversity, I will show in the following sections that all such efforts collectively encompass only one of the subsystems of the proposed methodology for systematization of knowledge in life processes. Thus, the starting point for systematization of knowledge is going to be neither philosophy nor unification but proven observations of the material processes

of biology. The traditional view of science sees life arising from infinite accidental mixing (intersecting material flows) of organic molecules in an environment where a myriad of energy flows such as light, heat, electrical discharges, etc. intersect. Such a paradigmatic view is epitomized in experiments of (Miller [35]).

As such, biological systems are often defined in terms of material boundaries drawn around blocks of activities that seem coherent and autonomous (Bastin [36,277]). I characterize such coherent and autonomous blocks of matter and energy as material–packets, distinct from knowledge–packets which I will define in Section II as autonomous and coherent "knowledge–carrying blocks of matter and energy." The majority of a living system's components exhibit the characteristics of both a knowledge–packet and a material–packet. I have defined material–packets and knowledge–packets as composites that integrate with energy flows. The various forms of energy flow that intersect at material and knowledge flows include radiant energies such as cosmic radiation and ultraviolet light, chemical energies of organic and inorganic compounds, and the heat energy as in dehydration and shock waves (Baltscheffsky, et al. [37,252]). As a dynamic configuration of material, energy, and knowledge flows, the material–packets retain substance, maintain structure, and exist continuously through some period of time (Hull [38,264]). In science, observations of relative stability of structures and properties of material–packets have engendered multi–scale, material–based classification schemes of life processes. The scales vary but singly or jointly cover the range from a single microorganism to the whole biosphere, though the analytical efforts usually focus on a singular phenomenon in one of the scales (O'Neill [39,269]).

These include structural properties such as branches of a universal phylogenetic tree (Woese, et al. [40,41]) or attributes such as "scaling laws" in which parameters like body size become a simplified representation of material flow (Calder, et al. [42-47]). At times the body size gets replaced with body mass which becomes a simple measure of phylogenetic history and a surrogate for material flow (Iskjaer, et al. [48]). In simple models, the material flow finds expression in power functions of the type $Y = aM^b$ where M is the body weight representing size, and a and b are constants and Y the property being scaled (LaBarbera [49]). Using these models, the traffic of material and energy—characterized as "metabolism"—can be analyzed using size. Organisms as seemingly different in size as animals, trees, eukaryotic unicells, and prokaryotes appear to have their energy flow characteristics (metabolic rate) superimposed on the material flow. The plot of metabolic rate as a function of body weight gives a straight line in logarithmic coordinates (LaBarbera, et al. [50,,268,51]). The traditional metabolic view of material and energy flows thus becomes a nested hierarchy of material–packets. The internal operations of every material–packet would consist of material and energy flows that emanate from a dynamic collection of internalized material–packets. Following (Fleischaker's terminology [257,52]), some of these material–packets establish a discrete material boundary (self–bounding). Others allow for material–packet transformations (self–generating).

In such processes, the material–packet dynamics is determined by relationships among material–packet properties (self–perpetuating). Collectively, these material–based operational criteria define the minimal features of a living autopoietic system (Maturana, et al. [53-55]). Autopoietic models see life the result of a complex system of molecular interactions whose material and energy flows manifest in concepts such as reproduction, compartmentalization, sexual dimorphism, patterns of nutrition, symbiosis, etc. (Luisi, et al. [56,257,57]). As such, the autopoietic system and its concepts of replication and reproduction are primarily "material flow" terms. Replication is thus a "phenomenon of individual system components and concerns multiplication of the molecules and molecular structures." Similarly, reproduction is "a phenomenon of the system as a whole and concerns the multiplication of the entire supramolecular assembly." These concepts collectively become the material processes of "generating one thing that closely resembles another" (Fleischaker [257,52]). At present, the material–focused autopoietic models search for elemental self–replicating systems (Luisi [58,273]). Most such efforts have so far culminated in replication of so–called "material shells" such as those of a liposome or a reverse micelle (Bachman, et al. [59,251,60-61,257]). The knowledge flow dynamics of these "shell production" processes, however, is totally overlooked.

In the absence of knowledge–based systematization of biological processes, one is forced to see life processes in terms of autopoietic dynamics. (Varela [54]) offers one such model consisting of

1) Relations of specifications,
2) Constitutive relations, and
3) Relations of order.

Using this model, the relations of specificity such as those among DNA, RNA, and proteins, constitutive relations such as those in production of lipids and proteins, and the relations of order in production of various components of a living system become surrogates for knowledge. The concept of knowledge in biological processes would thus become implicitly embedded in various relations of the material and energy flows, selectively determined as successive steps of external pressures and influences are exerted on the biological systems (Eigen, et al. [62]). In this paper I have discarded the view of knowledge as a spontaneously generated feature of the material and energy flows. I side with the observation that the key characteristic of living beings does not lie in their material and energy flows but in how they "retain, store, and utilize messages for thousands of millions of years" (Margulis, et al. [63,267]). I agree with (Oparin [64]) that the living system is not defined by overall metabolism and energy balance but also by the "flow of communications inwards and outwards, the flow of impressions received and actions performed." Without a knowledge–based view, the organic entity, individually or collectively,

cannot exhibit the operational unity characteristic of a living system (Luisi [58,273]).

The proposed systematization of biological knowledge in Sections II–VII will fully substantiate these points. As a supportive element of knowledge–based systematization of biological processes we observe that although the basic life processes do not emerge from any single molecule, the mainstream models of the origin of life often seek a resolution in terms of DNA, RNA, and protein molecules (Rowe [65]). From a knowledge–based point of view, these molecules are the primary knowledge–packets of life. The role of DNA as a knowledge-base is well–known. It is a knowledge storage molecule that along the path of evolution probably emerged from an earlier RNA–protein knowledge processing system (Alberts, et al. [66,67]). Prior to RNA–protein system, knowledge processing is assumed to have been conducted by simpler molecules capable of replication (Lazcano, et al. [68,265,69]). The hypothesis of an "RNA world," an intermediate step along the chain of knowledge–packets from prebiotic soup to today's DNA–protein world, has been a popular model (Gesteland, et al. [70]). It assumes that the storage and flow of biological knowledge could have been sustained by self–replicating RNA molecules in absence of proteins. Along the chain of knowledge–packets, the RNA molecules would have had to evolve from others that functioned as protogenetic knowledgebases (Joyce, et al. [71,72,260,73]).

The RNA world assumes the existence of "an informational macromolecule sufficiently similar to RNA" that either evolves directly or comes into existence from a "genetic takeover" of other self–replicating systems that had evolved independently (Joyce, et al. [70,74]). Where did these prebiotic knowledge–originating molecules come from? Rather than recognizing the possibility that "knowledge" can potentially be an inherent characteristic of organic molecules, the typical interpretation has tended towards material–based models of knowledge generation. The traditional models of the origin of biological knowledge fall into two categories of

1) Templates and

2) Aggregations.

The template models assume that biological knowledge originated from a "template," namely a polymer that can direct the synthesis of additional copies of itself (Goodwin, et al. [75,257,76,77]). A variation of the template model assumes that it is not the individual template molecule but an array of these molecules that forms a multi–molecule template that in turn acts as an "organizing center." It would bring the substrate molecules together and position them relative to the catalyst located within the organizing center (Gibson, et al. [78,79]). The aggregation models of the origin of biological knowledge simply assume that if a sufficient number of organic molecules come together, the random chemical interactions would generate a network whose properties would include "knowledge" (Kauffman, et al. [80-82]).

The aggregation models see knowledge as a material property that emerges at the intersection of a large number of material flows. I observe that, traditionally, knowledge flow has been either pushed towards obscure material–based "seeds" at origin of life as templates and catalytic aggregations, or it is treated as "appendages" to material and energy flows of today's biological processes, as in DNA. The fundamental deficiency of these material–based models is that the originating molecule "must have invented the relevant information, or received it from some template" (Eirich [83,267]). This corresponds to a never–ending cycle of search for a "seed of biological knowledge" that can be rectified only through recognition of knowledge flow as a complementary aspect of material and energy flows. This paper hypothesizes that knowledge is not the result of prebiotic templates and accidental aggregations of catalytic molecules in the distant past that today manifest as appendages to material processes of replication and reproduction. I propose and would demonstrate in the following sections that "knowledge flow" is as fundamental as material and energy flows and that it cannot be fully expressed in terms of the other two. Although my use of the word "knowledge" in biological processes is new, and I will define it in more detail in Section II, indications of the need for consideration of knowledge and knowledge flow in life processes has already appeared countless times in scientific literature under different names and in a variety of diverse arenas.

For example, the notion of "gene pool" has existed for some time (Adams [84]). Others have represented taxonomic classification as "gene flow" (Ehrlich, et al. [85]). Furthermore, the material and energy flows have implicitly, though generally, assumed the morphological continuity of living systems as a surrogate for knowledge flow (Roth [86]). It is presumed that the homology created by structural and functional resemblances will exemplify the knowledge flow from biological knowledgebases (Wagner [87]). There is also ample evidence that all organisms are open to inflow of information and "compute appropriate responses to that information" (Rothstein [267,88]). It is stated that the "multimolecular, interacting, cycling, and environmentally responsive processes can develop an 'instruction system'" (Eirich [89,267]). The living system can be represented as an "information source" (Rothstein [88]), it might have "ongoing cognitive activity" (Varela [257,57]), and evolution and learning require "acquisition and storage of order or information" (Pattee [90]). Despite the seemingly supportive statements above, it is important to recognize that almost all of them are constructed within the context of a material–based view that sees knowledge germinating from metabolic processes that take shape at the cross currents of material and energy flows (Morowitz [91]). Nevertheless, this paper is not the first to observe that as self–producing and self–improving systems, life processes should be viewed as manifestations of information–carrying and knowledge accumulating systems (Kuhn [92]).

I am also not the first to recognize that the flow of knowledge, as in continuity of genetic space, has precedence over homological resem-

blances (Van Valen [93]). Others have already supported distributed (multi–source) knowledgebases for understanding of development processes (Nijhout, et al. [94-95]). The knowledge utilized in an organism's development does not solely reside in the genetic space but also exists in a complex matrix of temporal and spatial interactions in the epigenetic space that brings the organism into existence (Hershey, et al. [94-95,96,97-98]). Knowledge can thus be viewed as a property that resides in molecules, cells, tissues, etc. "allowing these entities to recognize, select and instruct each other, to construct each other and themselves, to regulate, control, induce, direct and determine events of all kinds" (Oyama [95]). In the distributed view of knowledge, the membranes, proteins, etc. would supplement DNA as sources of storage, creation, and application of knowledge (Fox [99,259]). In more specific terms, it is well established that a molecule like DNA is a knowledge–packet that can flow across all scales through a number of mechanisms including duplication, phage or plasmid transfer, polyploidization, symbiosis, etc. Similar recognition is given to RNA as a knowledge–packet. Less well–known is the fact that "[a]ll biological catalysts are informational catalysts" (Joyce [76]) or that "topo genesis" is a knowledge flow term that describes the storage and processing of information required for routing proteins in intracellular processes (Blobel [100]).

The topogenetic knowledgebase is dynamic and can be a permanent or transitory part of the polypeptide chain. Even molecules such as lipids that have traditionally been viewed in material flow terms as structural components of a membrane that provides a physical barrier are now recognized for their knowledge–packet features as chemical mediators and messengers (Exton, et al. [101-103]). Recent developments in synthetic self–replicating molecules and observations in self–assembly of supramolecules have brought a new focus to the flow of knowledge at the lowest levels of biological processes. They depict supramolecules as carriers of both material and information, self–contained units for construction of complex structures and functions (Amabilino, et al. [104-110]). Whether the ability to replicate or self–assemble is labeled "complementarity," "programmed process," "instructed" or "recognition," its main features are

a) The ability to store knowledge, and

b) The flow of stored knowledge as information to direct selective molecular interactions (Gulik Krzywicki, et al. [108,111-113]).

The key aspect of the process is "a network formed by a population of active macromolecules—characterized by a very high degree of 'communication' between its members" (Hess, et al. [114]). The movement from the traditional material flow considerations towards incorporation of knowledge flow concepts is not confined to the arena of supramolecular replication and self–assembly. A similar phenomenon can be observed in "self–organization" properties of biological and other systems. Under certain conditions, complex systems give rise to expected, emergent, and collective properties characteristic of the living system (Kauffman, et al. [81,82]). Current view of self–organization is material–based and primarily structural. However, it is equally plausible to view the self–ordered properties of a complex system as signs of knowledge processing. (Grene [115]) observes that knowledge itself is "a form of constraint" on energy flow, material flow, and structure formation. Knowledge controls and directs the behavior of material and energy flows and the formation of corresponding structures. (Davies [116,258]) has reached similar conclusions from observations on computers as primitive knowledge–processors. Although the focus of majority of traditional models is on material and energy flows, a few models recognize a semblance of "knowledge flow" alongside the material and energy flows.

(Eldredge [117]), for example, describes the evolution of living systems in terms of "genealogical" and "ecological" flows. Genealogical flows consist of material–packets which transmit and transform information, such as genes, organism, species, etc. Ecological flows include all of the material and energy flows that take place in the form of proteins, organisms, populations, etc. This arrangement is similar to that of "replicators" and "interactors" proposed by (Hull [118]). Such dualistic, material–based models, however, are at best partial representations of knowledge flow. As observed by (Gayon [119]), genealogical entities are simply the providers of material players in the ecological arena. In offering a knowledge–based view of life processes, I must first emphasize that "knowledge flow" is built on a material foundation, the same as "energy flow" is built on a material foundation. Today it is well established that "energy" is not a pedagogical or explanatory property of matter that can be either ignored or described in purely structural terms. In this paper I will demonstrate that the weight of the accumulated scientific knowledge supports the hypothesis that "knowledge flow" is as distinct and as fundamental as "energy flow" and it has to be viewed and understood as a distinct property that cannot be represented in terms of material–packets alone. As such, the proposed systematization model will fully complement the currently accepted models of biological material and energy dynamics.

The proposed systematization model has a "nine–scale" configuration. Five of its scales define the material flow characteristics. Within each material scale, the flow of knowledge takes shape in three scales of genetic, epigenetic, and supragenetic spaces which collectively define the knowledge space. The ninth scale is "energy" which overlaps all other scales. Section II introduces the nine–scale knowledge flow model of life processes. Sections III through VI address the knowledge flow dynamics of material Scales 1 through 4. Sections VII and VIII focus on knowledge flow at inter–scale interfaces and the concluding remarks.

The Nine–Scale Knowledge Flow Model

What are the advantages of systematization of knowledge in biological processes? First, it allows for specific treatment of "knowledge flow," an aspect of life processes that has been largely overlooked.

Second, as I will show later, it forces simultaneous and systematic treatment of knowledge, material, and energy flows for understanding life processes. In presenting a model of systematization of knowledge in biological systems I need to emphasize that the proposed concepts would inevitably suffer from neologistic overtones (Allen, et al. [120,121]). It will include words such as knowledge, knowledge flow, knowledge–packet, knowledgebase, and knowledge processor. The introduction of such words can run afoul of science mainstream which in general does not recognize the existence of non–Homo sapien biological knowledge and moreover views even a terminology as seemingly innocuous as "biological information" as "employed in discourse, pedagogical and explanatory, about living systems," being "unnecessary for the definition of the living organization" (Varela [54]). Only minimal knowledge–processing is anthropomorphically attributed to higher organisms even though acts of knowledge–processing, as in gene replication, etc., take place in all scales (Rowe [65]). Any representation of biological knowledge has been traditionally embedded in material flow: Species are "information reservoirs" and "packages of information" (Eldredge [122]), living systems are "dynamics units" capable of taking into account and feeling the past and future possibilities (Birch [20,123]), and genes can survive better if carried by larger organisms (Bonner [124]).

These and similar statements focus on material–packets that perform life functions. They do not clarify how terms like "reservoir," "dynamic unit" or "package" could be systematically compared across the vast spectrum from bacteria to biosphere. There is also a scarcity of definitions for "biological knowledge." Only in a rare occasion has it been vaguely defined as a "quality of matter that becomes manifest with the emergence of the first self–producing and self–improving systems" (Kuhn [92]). Although the proposed nine–scale methodology for systematization of knowledge does not require a specific definition of biological knowledge and its units, I have tentatively chosen the general definition of biological knowledge as a "reservoir of experience."[1] This general definition is open to change as understanding of biological knowledge and its optimal systematization increases. For now, given this definition, I observe that at the core of the reservoir of experience sits the "ability to act." Restated, biological knowledge is a "dynamic reservoir of experience used in actions of life." From that point of view, "information" becomes a form of "flowing knowledge," a "stream of knowledge–packets" from a source knowledgebase transmitted to a destination knowledgebase. Information is thus a piece of knowledge transferred from a sender to a receiver. In this way, words like "message" and "signal" become subsets of information. Can definition of knowledge in biology be more specific?

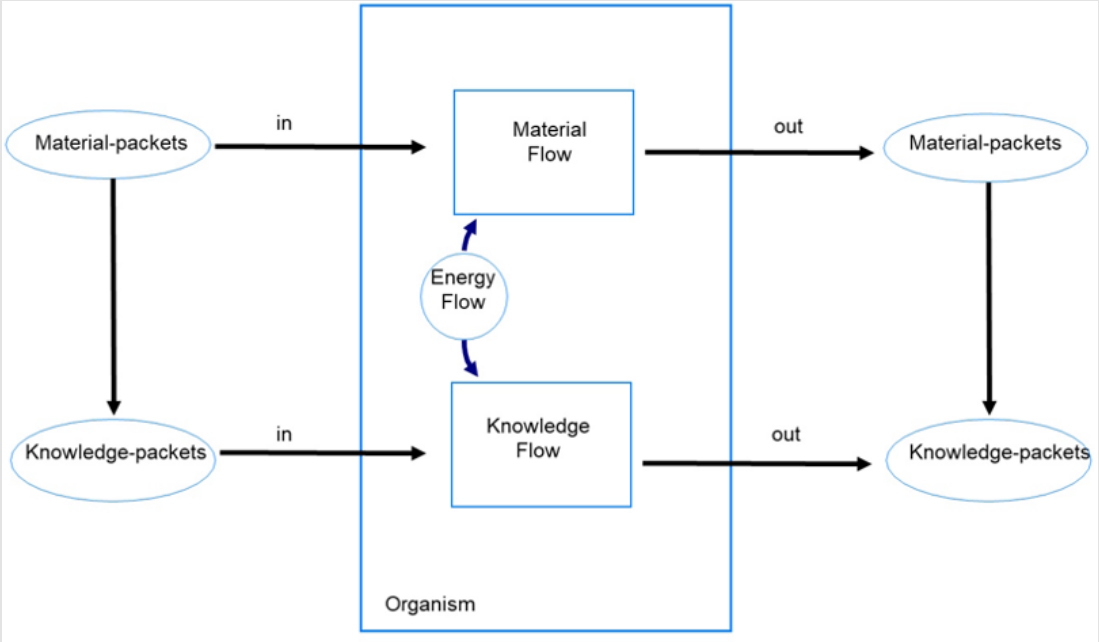

Figure 1: A simple integrated representation of material, energy and knowledge flows.

Although at this time I have chosen not to give a more specific definition of knowledge and its units, definitions such as accumulation of DNA instructions (Kimura [125]), replicators (Dawkins [126]), or composites of interactors and replicators (Eldredge [117]) have attempted to incorporate more specific aspects of biological knowledge into the material flow. Knowledge–units such as DNA, gene, or replicators provide a restricted view of knowledge space. For example, from this article's point of view, DNA and gene would be instrumental in defining the "genetic space," a subsystem of the proposed systematization of knowledge, but would say little about other subsystems

such as epigenetic and supragenetic spaces to be defined later in this section. As stated above, the proposed systematization of biological knowledge does not require specification of a knowledge unit. Therefore, I will defer the determination of a knowledge unit to future studies as understanding of biological knowledge space progresses. The flow of knowledge takes shape through "knowledge–packets." A knowledge–packet's physical contour can be defined according to its corresponding material–packet. Thus, in biological systems, a knowledge–packet can be defined similar to a material–packet as a spatio-temporally localized knowledge–processor that exists for a specific time period (Hull [118]). The material, energy, and knowledge flows are integrated spaces as shown in the simple model in (Figure 1). The systematization of material flow is primarily expressed in terms of the existing phylogenetic models.

The five–scale representation of material flow consists of

1) Prokaryotes,
2) Eukaryotes,
3) Multicellulars (including animals and plants),
4) Humans, and
5) The environment.

The word "scale" should be taken as a relatively rough and somewhat static representation of material flows. Despite its simplicity, the proposed five–scale systematization of material flow has universality (Kadanoff [127]). Any redefinition of the scale boundaries would not alter the conclusions drawn from the proposed systematization of knowledge. The "knowledge space" is an aggregation of genetic, epigenetic, and supragenetic spaces. In this stratification, the definition of "genetic space" is relatively straightforward because of the specificity that can be assigned to points of DNA concentration. The "epigenetic space," however has been traditionally characterized as a "chain of past events" (Cowley, et al. [128]) and this has led to different definitions of the word "epigenetic" in different contexts (Atchley, et al. [129]). Such diversity derives from the multiplicity of choices available for the boundary between genetic and epigenetic spaces. For the systematization of biological knowledge model, the "epigenetic space" will be defined to start at the gene–protein or gene–enzyme boundary, and extend all the way to the external material boundary of a knowledge processor. This in effect makes the "epigenetic space" a distributed source of knowledge. The epigenetic space is a knowledge–packet's "distributed network of internal knowledge flows." It differs from genetic space primarily in the distributed character of its knowledgebase.

The distributed character of knowledge in the epigenetic space can be visualized in terms of the "epigenetic landscape" model which represents the genetic space as guy ropes that shape and hold the surface—the epigenetic space—on which the life processes such as the developmental system take place (Waddington [130]). It is important to recognize that the epigenetic landscape model converts "knowledge flow" into "channels of flow." The channels are a rough complex of valleys in the landscape within which life processes take place. The changes in length and location of guy wires (caused by influences such as mutations) act as a surrogate for production and flow of knowledge from a centralized knowledgebase. The epigenetic landscape model has a number of shortcomings (Saunders, et al. [131]). The weakest feature is the conversion of knowledge flow into material flow through a two–dimensional material channel. Such conversion carries the comfort of visualizing knowledge as material flow but the disadvantage of knowledge flow becoming largely masked. The epigenetic space interfaces with the "supragenetic space" which is the domain of externalized knowledge–packets of a living system. In general terms, using the terminology of (Jonesburg, et al. [132,133]), the supragenetic space is the "world of artifacts" created externally by knowledge processors (the living systems). The "artifacts" would correspond to externalized material–packets and knowledge–packets produced by the living systems.

The five material scales, the three knowledge scales, and the energy scale which underlies all other scales create the nine–scale knowledge flow model shown graphically in (Figure 2). Each scale can be visualized as a "space," thus the words scale and space would be used interchangeably. The boundaries between genetic, epigenetic, and supragenetic spaces are relatively diffuse and depend on definition. The supragenetic space begins at the material boundaries that have traditionally defined the "organism." From this article's point of view, "organism" is equivalent to "knowledge–processor." The boundaries between genetic and epigenetic spaces can be defined anywhere within the spectrum that starts at points of DNA concentration and ends at the organism's material boundaries. However defined, the epigenetic space remains a domain of substantial distributed knowledge while genetic space is characterized by its high–density, centralized knowledgebases. The main feature of the supragenetic space will be its externalization relative to the knowledge processors that created it. "Environment" is the material and energy space external to the genetic, epigenetic, and supragenetic spaces of a living system. The supragenetic system and environment overlap. While the definition of environment can be further refined into subspaces (Brandon [134,264]), that refinement is not included, focusing primarily on the knowledge flow dynamics in the nine–scale view of material and energy flows. (Figure 3) shows the organism–environment interactions within the context of flowing knowledge.

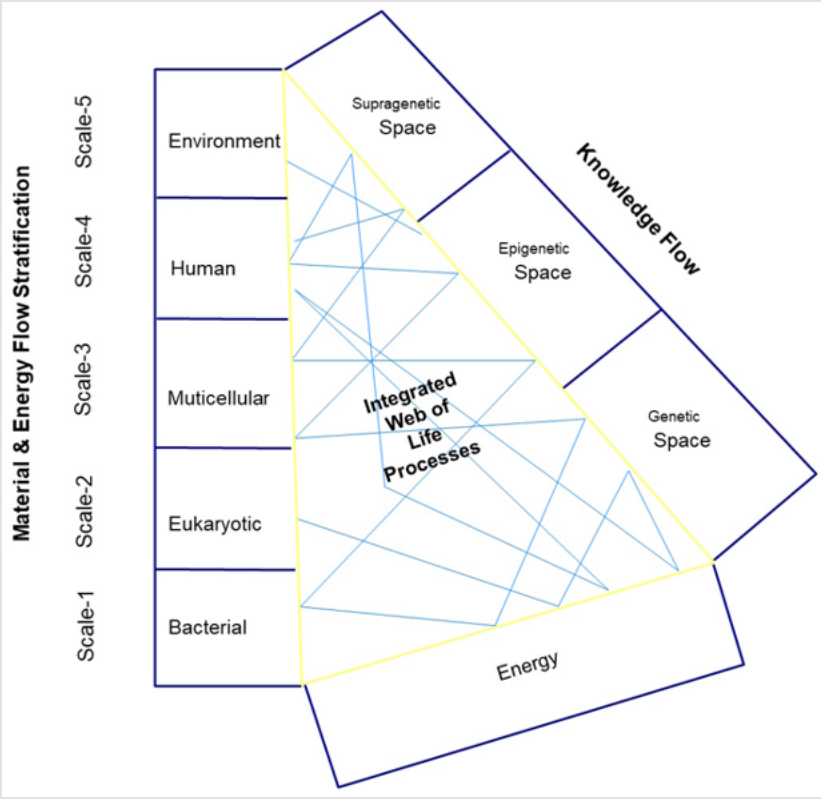

Figure 2: The nine–scale knowledge flow model of life processes.

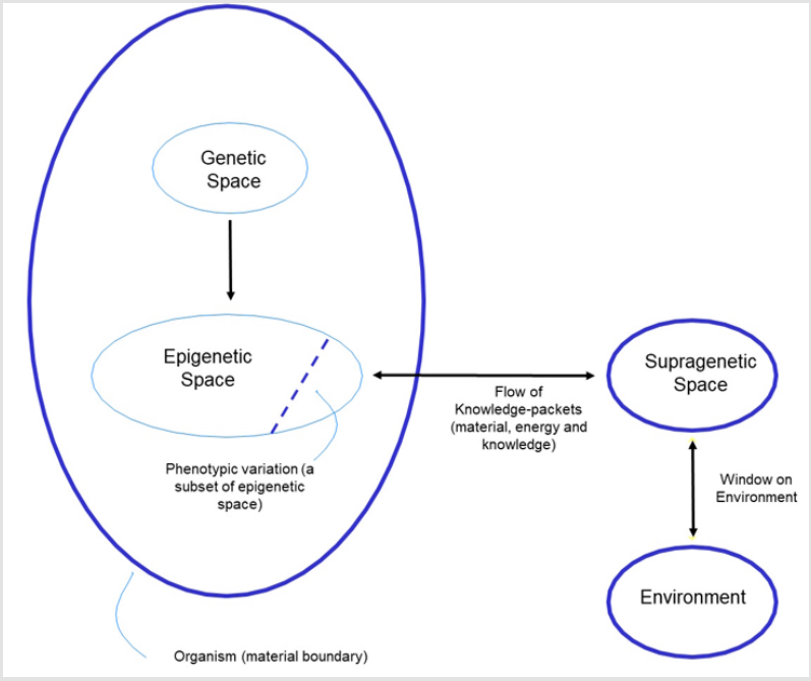

Figure 3: An illustrative view of the knowledge–flow model of organism and environment.

In all scales and in every domain of knowledge space, a "knowledgebase" is a specific, centralized or distributed, material–packet used for storage of knowledge. Except for the genetic space, other knowledgebases of the five material scales are not necessarily centralized but exist as "distributed" knowledgebases. The distinction between centralized and distributed knowledgebases, in general, can be best observed in embryological development. The centralized knowledgebase, as in genetic space, provides a portion of knowledge needs of embryological events through knowledge stored in the genes. In contrast, the remainder of the knowledge needs of the embryological events comes from the distributed knowledgebase that is an outcome of the knowledge dispersed in the epigenetic space, as in local morphogenetic factors. From the point of view of systematization of knowledge, the centralized and distributed sources of knowledge are complementary knowledgebases of the genetic and epigenetic spaces. They manifest as needed by the living system. As an example, "maternal effects" take place in a composite subspace of epigenetic and supragenetic spaces (Atchley, et al. [128,135-137]). The prenatal (uterine) events take place in the epigenetic space while the postnatal (nursing) activities are resident in the supragenetic space. More specifically, mitochondria and egg cytoplasm contributed by mother comprise subspaces of mother's epigenetic space. This classification, however, is not absolute because epigenetic space can also be defined at the uterine wall.

If so, the cytoplasmic material would be in the epigenetic space of a newly formed knowledge–packet, namely the egg itself. The egg, in turn, would be in the mother's supragenetic space. In this paper I have chosen to view the egg as one of the distributed knowledgebases of mother's epigenetic space. It would become a distinct knowledge–packet in mother's supragenetic space when it is externalized (born). The distinct advantage of the nine–scale knowledge flow model thus lies in its systematic and integrated treatment of life processes. Another example of significance of systematization of knowledge can be observed in the supragenetic space of Scale–4 which can be characterized as "macrosupragenetic" space of Scale–4. The macrosupragenetic space of Scale–4 is most familiar because humans have created it. The human macrosupragenetic space has been called the "world of artifacts" (Jonesburg, et al. [132,133]). It comprises the collection of everything that humans make: crops, livestock, machines, buildings, transport and communication systems, hospitals, nuclear–tipped rockets, etc. It contrasts the macroepigenetic space of Scale–4 where the knowledge–packets commonly known as thoughts, feelings, emotions, etc. reside. Once the knowledge–packets of the macroepigenetic space of Scale–4 are externalized, they move from Scale–4 macroepigenetic space into Scale–4 macrosupragenetic space. They become knowledge–packets such as spoken or written words, machines, etc. The three–scale knowledge space proposed in this paper has already appeared in various combined forms in material Scale–4.

For example, the supragenetic, epigenetic, and genetic spaces of Scale–4 have been combined in the tenuous concept of "metaman"—a man–machine global superorganism (Cornish [138-140]). Metaman differs from concepts such as Gaia (Lovelock, et al. [141,142,276,143,275]) and noosphere (Teilhard de Chardin [144]). The model proposed in this article allows for systematic comparison of other models. Gaia and noosphere represent the sum of all knowledge and material spaces in Scales 1–4 plus environment. In comparison, metaman is only the sum of knowledge spaces of Scale–4. Such objective systematization capabilities do not exist in other holistic models of life processes (Allen, et al. [141,142,276,143,275,145,146 ,253,147]). Additionally, in the supragenetic space, the word "knowledge–packet" is more versatile than names such as meme (Dawkins [148]), culturgen (Lumsden, et al. [149]) or culture (Cavalli Sforza, et al. [150]). Such terms are not only confined to Scale–4 events but mask the externalized flow of knowledge from other scales so essential to creation and maintenance of the supragenetic space. The "knowledge–packet" is a description that readily spans all domains of knowledge space and reveals essential similarities in all of them. Words, rules of conduct, automobile, computer, domesticated animals, managed farms, etc. are all knowledge–packets in the macrosupragenetic space of Scale–4 as are plasmids and phages in microsupragenetic space of Scale–1.

To enhance clear understanding of features of the proposed nine–scale knowledge flow model, this introductory section concludes with a comparative summary of the proposed systematization with foundational features of biological processes as delineated by (Varela [274,151]):

1) At the core of every living system—a knowledge processor—would reside a producer and processor of microknowledge (the cellular unity of the living system). "Microknowledge" is the molecular form of biological knowledge, most exemplified by DNA.

2) In every living system, an internal process and structure would check the suitability of external material–packets and knowledge–packets for internal use (the immunological foundation). Not all material–packets and knowledge–packets constructively interface with all other material–packets and knowledge–packets, thus the need for screening.

3) There exists an internal mechanism based on microknowledge (Scales 1 and 2) and macroknowledge (Scales 3 and 4) that manages the events in the supragenetic space (the cognitive, perceptomotor behavior). "Macroknowledge" is the multicellular form of biological knowledge, most exemplified by the nervous system of higher animals[2].

4) Knowledge processing takes place in the appropriate microknowledge or macroknowledge languages (socio–linguistic identity and link).

5) All genetic–epigenetic spaces produce an external supragenetic space (the collective, social, multi–individual totality).

In summary, the proposed stratification of life processes into five material, three knowledge spaces, and one energy space would function as a representational device for the knowledge flow that, as I will

demonstrate later in Section VII, can also approximate as a microknowledge to macroknowledge transformation of life processes. Within this framework, the most significant aspect of the proposed model is its systematic and integrated treatment of knowledge, material, and energy flows. It allows for objective mapping, namely understanding the events of one scale in terms of knowledge flow dynamics observed at another scale. I will further expand on these points in specific treatments of each scale's knowledge flow in the following sections.

Knowledge Flow Dynamics of Material Scale–1

Material Scale–1 is designated for prokaryotes. What are the already–established points of view about Scale–1 that would oppose that characterization? The first already–established point of view is that the microorganisms of Scale–1 are immaterial to the processes of Scale–4 (Margulis [152]). This view is widespread even though the Scale–1 microorganisms exhibit a strong presence in the material and energy flows of all scales. They provide food and mutualist interfaces for almost all life forms, demonstrate an extensive capacity to adjust to environmental factors, and maintain the basic links of terrestrial food web (Price [153]). From a material and energy flow point of view, plants and animals largely exist because microorganisms support and sustain them. "Big organisms are very dependent upon small organisms, without the reverse being true" (Price [153]). The second already–established point of view is that the biological knowledgebase solely resides in higher organisms because the Scale–4's knowledge space corresponds to the tip of the evolutionary ladder (Ritvo, et al. [65,174,272]). Along this line of thought, the recognition that life processes have originated from a Scale–1 bacterial source is a recent development (Sonea, et al. [40,155]). Until a few decades ago, the scientific consensus viewed the Scale–1 bacteria as mainly parasitic and lacking a genetic system like that of the higher organisms (Megasanik, et al. [156,157]). Today, science still remains reluctant to characterize bacteria with a chromosome–like genetic system and to recognize Scale–1 as a legitimate knowledge link in life processes (Brock [158]).

The bacterial chromosome continues to be named "nucleoid." The implied notion remains strong that only the chromosome is a foundational representation of the genetic system, and that it is a sole feature of the Scale–2 eukaryotic cell. It is true that the bacterial chromosome is not the same as the eukaryotic chromosome in design and operational structure (Drlica, et al. [159,256]). But the structural dissimilarities of bacteria and eukaryotes are not confined to only chromosomes. The listing of structural contrasts is in fact quite long (Cavalier Smith, et al. [160,255,161]). All those differences reflect the variation in material flows of different scales. Nonetheless, the perceived material flow differences have led to another already–established view, namely that because Scale–1 material flow can be classified differently from that of Scales 2–4, then any Scale–1 knowledgebase must be inferior to those of Scales 2–4 (Brock, et al. [156-158]). Such already–established tendencies would counter the discourse of the proposed knowledge flow model. They have already undermined the knowledge–based observations about Scale–1 as in multiplicity of bacterial replication forks (Drlica, et al. [159,256]), inhomogeneous distribution of bacterial DNA in a ribosome–free area of the cell (Kellenberger [162,256]), mitotic equivalents for segregation process of bacterial chromosome (Schaechter [163,256]), and the seemingly directed mutation as demonstrated by Escherichia coli (Cairns, et al. [164,165,274,166-169]). Any knowledge–based model of Scale–1 would thus face arguments for and against it.

The already–established points of view, like those briefly described above, would deny that Scale–1 possesses any knowledgebase or knowledge processing capabilities relevant to Scale–4, and may most likely assert that Scale–1 is at best a residuum of the evolutionary processes that have passed that scale by billions of years. On the other side, support for a knowledge–based point of view of Scale–1 would come from diverse sources such as preliminary indications of the possibility of directed flow of knowledge (Davis, et al. [170-173]), examples of distributed flow of knowledge in biological systems (Nijhout, et al. [94-96]), and the observations of knowledge flow dynamics that elicits complex and far from random responses from a Scale–1 knowledgebase (Ornston, et al. [174,256]). The supragenetic space and environment of Scale–1 include viruses and bacteriophages (phages). They are traditionally depicted as agents of illness and have never been characterized as knowledge–packets. Yet, the nine–scale knowledge flow model would label them as Scale–1 knowledge–packets—"messengers" that transfer DNA (knowledge) from one organism to another. The Scale–1 has to overcome the homocentric bias. provide An example of anthropomorphic bias toward knowledge flow in microsupragenetic space of Scale–1 characterizes the possibility of directed flow of knowledge in Scale–1 as "intriguing (and frightening)," reflecting the fear of losing human centrality of knowledge (Condit, et al. [175]). Returning to Scale–1's knowledge flow dynamics, phages and plasmids are indispensable as message–transmission elements of Scale–1's epigenetic and supragenetic spaces.

Both phages and plasmids are carriers of double–stranded pieces of DNA and capable of self–replication. These knowledge–packets of the bacterial knowledgebase are further complemented by smaller pieces of non–self–replicating plasmids. Such knowledge transfer mechanisms are traditionally viewed as flow of parasitic entities by infectious transfer (Campbell, et al [176,177]). Studies such as those performed by (Condit, et al. [178]) have managed to only partially vindicate the knowledge–packets such as transposons because they contribute to the prokaryotic host's fitness by offering information on antibiotic resistance. Scale–1 accentuates extensive interactions of knowledge processors with the supragenetic space. As a knowledge processor, each bacterium possesses hundreds of receptors on its cell wall awaiting the arrival of phages or plasmids. Such structure discernibly corresponds to an open, communal pool of knowledge—a large supragenetic space—in which extensive flow of knowledge is a permanent feature (Davey, et al. [155,179,262,180]). The Scale–1's

communal pattern of flow of knowledge has been characterized as a "global gene pool" and a "complex, dispersed, single global organism" (Sonea [181,245]). Such characterizations of Scale–1's supragenetic space can improve substantially when the knowledge space is systematically described in terms of genetic, epigenetic, and supragenetic spaces that define and direct the material and energy flows.

The knowledgebase of Scale–1 consists of centralized and distributed components. The chromosome of the individual bacteria can be viewed as either the largest of the distributed knowledgebases in the bacterial epigenetic space, or a centralized knowledgebase at each bacterial node of Scale–1's genetic space. I have chosen to refer to the bacterial chromosome as a centralized knowledgebase of the genetic space while classifying all other Scale–1 knowledge–packets as distributed knowledgebases of epigenetic and supragenetic spaces. As an example of prominence of Scale–1's epigenetic and supragenetic spaces, the bacterial multiple resistance to antibiotics does not come from alternation of the affected bacterium's existing genetic space but from DNA additions that have their origin at the bacterial supragenetic space. The intensity of knowledge flow in Scale–1 supragenetic space is impressive and can be gauged from observations of antibiotic resistance. For example, within a 10–year period, a bacterium's resistance to four antibiotics rose from 0% to 74%, merely by information that was somehow asked for by the bacteria facing the antibiotics and received from the supragenetic space that transmitted the needed piece of information (Davey, et al. [262,179]). The knowledge–packets of Scale–1 such as plasmids, phages, and chromosomes, are not static. They span a dynamic range of interactions as illustrated in (Figure 4). Plasmids and phages contain insertion sequences (IS) which can transpose from one genetic locus to another. IS units are the shortest representatives of transposable elements—transposons.

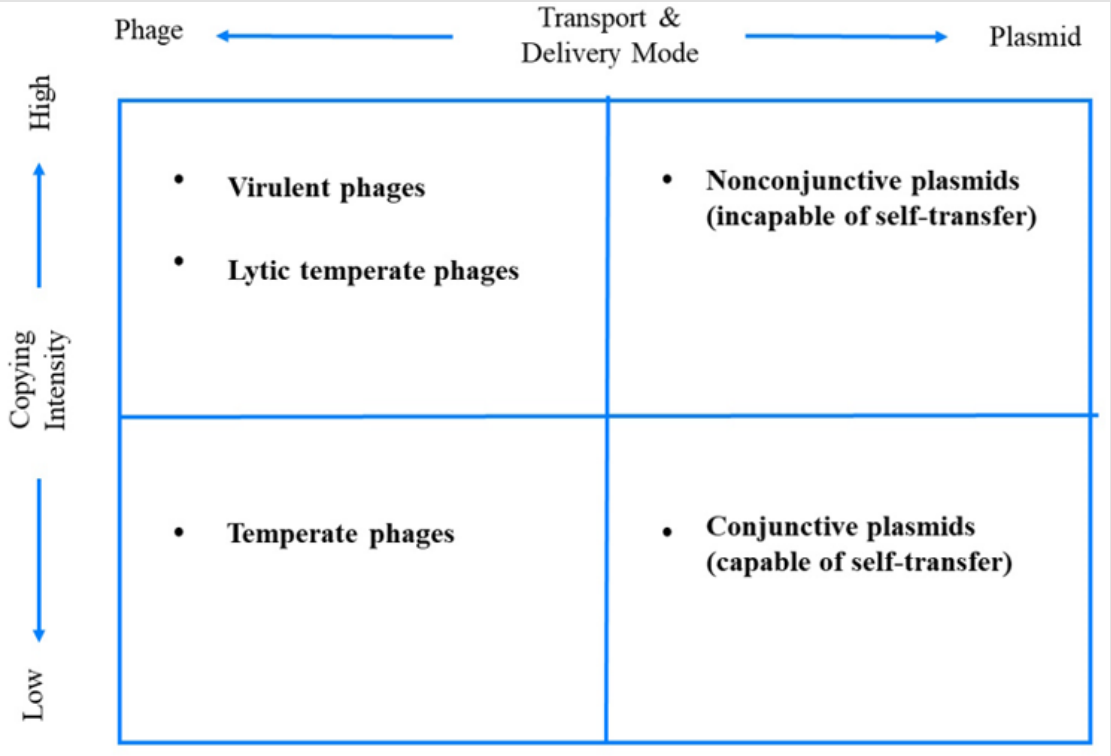

Figure 4: An illustrative representation of channels of knowledge flow in Scale–1 (partly adopted from Davey and Reanney 1980, pp. 118-120). [179,262]

They can move from one locus to another, creating new gene combinations and juxtapositions, thus giving rise to many plasmid–plasmid, plasmid–phage, and plasmid–chromosome interactions (Davey, et al. [262,179]). Complementing such diverse flows of genetic, epigenetic, and supragenetic knowledge is "conjugation," a direct transfer of DNA from one bacteria to another. One cell is the receptor and the other the donor. The DNA comes from a variety of plasmids that the donor cell carries. The transfer takes place without mixing cellular contents (Silverman [182,263]). In the operational sense, the control of knowledge flow in Scale–1 is more intricate. Notwithstanding the complexity of supragenetic knowledge flow from a variety of messengers, internally, the bacterium's genetic space is dispersed in the cytoplasmic epigenetic space. As a knowledge processor, the cell has to keep the bulk of its genetic space free from ribosomes of the epigenetic space, allowing only the genome's active parts (areas relevant to needed knowledge applications) to come in contact with the

ribosomes—knowledge–packets of the epigenetic space (Kellenberger [256,162]). Similar multi–control processes can be observed in the mitotic apparatus (Schaechter [163,256]). Scale–1 possesses the potential for unrestricted flow of microknowledge. From a material flow point of view, the observed nodes, as in distinct bacteria, exhibit somewhat individualistic features that may limit the flow and processing of microknowledge. It is also possible that certain inherent constraints, as on chromosomes, can limit and control certain flows of knowledge.

These features conform to the observation that, in general, knowledge has a self–constraining character (Grene [115]). This kind of operational constraint would also correspond to specializations that may over a long period of time give rise to localized divergences in the supragenetic space (Campbell [254,183]). However, such dynamic variations would remain strongly linked via a variety of knowledge flow channels. Nonetheless, in Scale–1's extensive supragenetic space, localization would not imply isolation. The recognition of knowledge flow in Scale–1 has been traditionally undermined by the anthropomorphic perception of seemingly "higher" structural form of eukaryotic cell. Bacteria consist of a single–enclosure structure, though morphologically they are capable of performing feats traditionally presumed to be an exclusive of the eukaryotic cell's multiple–enclosure structure. Membrane–bounding of DNA is characterized as a unique feature of eukaryotes even though bacteria can form DNA–carrying, membrane–bounded vesicles called "blebs." Blebs are intercellular carriers of plasmid, linear DNA, and RNA (Dorward, et al. [184]). Among Gram–negative bacteria, packaging of DNA in membranous vesicles is commonplace (Dorward, et al. [185]). It can be argued that blebs are "externalized" membrane–bounded DNA packages in the supragenetic space. They are not internal DNA–carrying vesicles in the epigenetic space of bacteria. That argument is now facing the discovery of Gemata oscuriglobus, a bacterium that carries its genes in an internal membrane–bounded structure (Dayton, et al. [186,187]).

Similarly, the DNA of G. obscuriglobus is bounded within a two–membrane envelope. From material and energy flow point of view, bacteria are localized, solitary and somewhat disjointed from other organisms. The material flow primarily sees bacteria in terms of individual bacterium's body plan, having an extremely small size, and being dependent on diffusion for survival (Beveridge [188,266]). Such perspective does not allow seeing the bacteria's knowledge space as dynamic units of a gigantic microsupragenetic space with global dimensions that interface with all other knowledge flows in all energy and material scales. The traditional material and energy flow paradigms value the small size of the prokaryotic chromosome in terms of "economy of packaging" within a small–sized bacterium (Woolley [189,261]). However, the Scale–1 supragenetic knowledge flow amplifies the bacterial chromosome to a much larger effective size through microsupragenetic linkages of Scale–1's knowledge flow processes. The knowledge–based view reveals the fundamental property of Scale–1 as "intense and open" supragenetic space where the flow of knowledge is profuse among various knowledge–storing and knowledge–processing units as shown in (Figure 5). One measure of extensiveness of Scale–1's size of "microknowledge" can be gleaned from the fact that not only knowledge flows of other scales originated from it but are still sustained by it. The relatively uniform morphology of bacteria reveals other fundamentals of microknowledge flow.

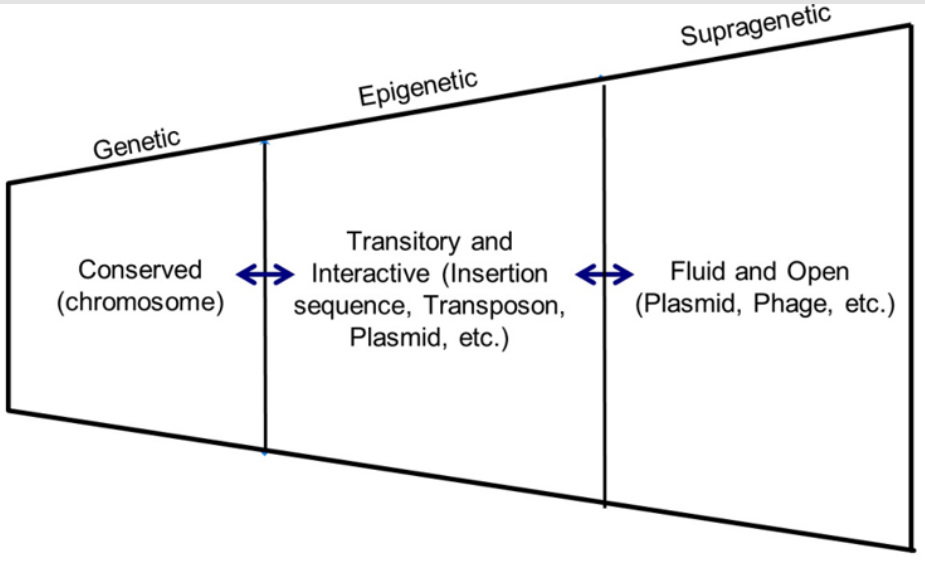

Figure 5: An illustrative representation of dynamic stratification in Scale–1's knowledge space.

Scale–1 does not emphasize either differentiation or multicellularity. Instead, the focus is on development of a large and highly flexible supragenetic knowledge space. The large number of knowledge receptors on bacterial surface, the ability to multiply rapidly and exponentially, and the capability to react very rapidly to environmental influences and pressures are all indicators and measures of Scale–1's relatively free–flowing supragenetic knowledge space. Another measure of diversity and flexibility of Scale–1's knowledge space lies in its extensive multiplicity of metabolic pathways. Such diversity is far greater than that found in other scales. Nevertheless, in absence of knowledge–based models, the norm of today's evolutionary studies of bacteria remains entrenched in body structure (Cavalier Smith, et al. [40,160,255,190,271]). Moreover, eukaryotes have remained the anthropomorphic norm of structural classification of bacteria. Bacterial "species" are defined structurally despite strong evidence for interspecies transfers of genes via microsupragenetic space (Woese [271,190]). Along the same vein, because of material–based models, the tendency to devise phylogenetic relations among bacteria based on molecular homologies remains strong (Wagner, et al. [87,190,271]). Such analyses seek a delineation of lines of descent and characterization of structural radiations via morphological similarities and contrasts (Campbell, et al. [40,183]).

While structural representation of life processes is valuable, the material flow alone remains an incomplete and deficient tool for representation of Scale–1 which is founded on large–scale amplification of knowledge flow in the supragenetic space. Our attempt to establish knowledge flow and knowledgebases as key features of the bacterial life is not new. The notion that Scale–1's extended gene flow makes it a unified whole has existed for some years. The fluidity of exchange of genetic material among bacteria has already led to characterizations such as "world–wide bacterial clone," "bacterial planetary organism" (Sonea [191]), "a community of interacting members," and "Gaian sort of entity" (Margulis, et al. [276,192]). My approach, however, is different. Previous observations primarily confined themselves to Scale–1. Only occasionally did they use the gene flow arguments to propose models such as formation of the eukaryotic nucleus from assembly and confinement of pre–existing plasmids and small replicons (Sonea [193]). Otherwise, they only promoted a "unified view of the bacterial world." They did not dwell on a systematic definition of the knowledge space that would link Scale–1's microsupragenetic space to other scales of life processes. The systematic stratification of knowledge and material spaces, as offered by the nine–scale knowledge flow model allows simple but profound observations on how one scale may give rise to another. For example, using the nine–scale knowledge flow model, what can be said about conditions that a Scale–1 knowledge–packet must satisfy if it is to leave Scale–1 and establish itself in Scale–2?

Since Scale–1 consists of a highly cohesive, practically infinite microsupragenetic space, no participant can leave it on its own without first bundling an adequate supply of knowledge. As a result, the formation of any new scale out of a strongly communal scale must include the following root features:

1) Bundling an adequate base of knowledge.

2) Individualizing the bundled knowledge.

Only then can an organism develop the type of form and function that would allow it to exist relatively independent of the communal microsupragenetic space of Scale–1 from which it has emerged. The delineation of these conditions, based on observations of the properties of the microsupragenetic space of Scale–1, is an important contribution of the knowledge flow model to understanding of inter–scale transformations in life processes. These observations are relatively independent of the actual mechanisms through which a communal form of knowledge, as in microsupragenetic space of Scale–1, gives rise to a bundled, individualized knowledge–packet. Whether eukaryotes get their knowledge primarily from archaeobacteria (Doolittle, et al. [194,271,195]) or whether all eukaryotes and bacteria are independent radiations originating at the knowledge reservoir of "progenotes"—entities simpler and more rudimentary than modern prokaryotes (Woese, et al. [40,196]), the Scale–1's essence of communal exchange of knowledge, which gives rise to the next scale, remains unchanged. This fundamental observation remains unchanged whether eukaryotes come about as a result of small autogenous changes in a bacteria (Raff, et al. [197-199]), or serial endosymbiosis of all organelles (Margulis, et al. [200,201]), or selective symbiosis scenarios (Cavalier Smith, et al. [202,203]). The knowledge–based view of material and energy flows yields foundational insights on scale transformations of life processes.

Knowledge Flow Dynamics of Material Scale–2

Using Scale–1's knowledge flow dynamics and recognizing that knowledge flow would be the common thread for a new scale forming out of Scale–1, features of Scale–2 we have are characterized as individualized and bundled microknowledge. Otherwise, any new knowledge–packet would have remained captive in the communal microsupragenetic space of Scale–1. Although a resident of Scale–2 would lose the advantages of access to a large supragenetic knowledgebase, it would gain new advantages through an individualized, bundled knowledgebase in its genetic and epigenetic spaces. In Scale–2, the supragenetic space appears to be small. The main flow of knowledge takes place via reproduction or sharing (sex) of individualized knowledgebases. This type of flow is primarily confined to the epigenetic and genetic spaces. The knowledge flow in the Scale–2 epigenetic space has distributed components in addition to the centralized knowledgebases. One of such flows is characterized as promiscuous flow of DNA among organelles (Ellis [204]). The other is in the form of extrachromosomal circular DNA (eccDNA) which varies in size, sequence complexity and copy number. Some eccDNAs can be viewed as analogous to Scale–1 plasmids. In general, the eccDNAs are a regular phenomenon among eukaryotes, though the diversity of

types of chromosomal sequences of eccDNAs make their isolation and study more difficult (Gaubatz [205]). What is the apparent purpose of knowledge flow in Scale–2? Scale–2's knowledge flow is intensely focused on construction of a knowledgebase about internal and external "body–parts."

The diversity is so immense that Scale–2 has precluded the development of a coherent phylogeny (Bode, et al. [206-213]). To focus on Scale–2's specifics, consider protozoa which constitute a major grouping of Scale–2's organisms. In Scale–2, the diversity of external body parts—elements of the epigenetic space that interface with the supragenetic space and environment—far outnumbers the diversity of internal body parts—the internal elements of epigenetic space (Anderson, et al. [214,215]). A myriad of external body parts are created using a limited number of internal body parts. The key internal body part is the individualized, bundled knowledgebase in the genetic space, namely the nucleus. Within the context of Scale–2's epigenetic–supragenetic interface, "[m]embers of the same clone of protozoa, or even the same individual at different times, may have different forms, varying from minor modifications to extreme alternatives in the type of cell–parts" (Tartar [216]). I hypothesize that such material–flow features indicate intense knowledge flows essential for development and accumulation of the knowledgebase needed by Scale–3 for tissue formation. The dynamic character of knowledge flow in creation of Scale–2 body parts can be observed in many protozoan processes. For example, many protozoa can resorb and then renew all their internal organelles (except for nuclei) (Tartar [216]). Similarly, they can regenerate body parts that are lost (Tartar [216]) or quickly transform their external shape from ameboid to swimming flagellate form (Tartar [216]).

The key for such material flow capabilities resides in the knowledgebase that molds the material and energy flows into novel forms and functions. While many of Scale–2's material flow capabilities have been studied, some unique organelles such as costa, pelta, and axostyle in zooflagellates (Farmer [215]) remain to be explored as examples of Scale–2 body–part specialization and thus novel aspects of Scale–2 knowledge space. In analogy with Scale–1's supragenetic space, the extent and depth represented by protozoan diversity in form and function can only be a partial manifestation of potential applications inherent in Scale–2's knowledge accumulated in genetic and epigenetic spaces (Farmer, et al. [215,217,218]). Depending on how protozoa are characterized in Scale–4's macrosupragenetic terms, they can be plant–like, animal–like, or exhibit mixed characteristics (Farmer [215]). In general, protozoa classification as "unicellular animals" is based on the reasoning that (Farmer, et al. [215,219]):

1) Protozoa ingest food by "food vacuole" formation.

2) They "drink" by using pinocytotic vesicles.

3) They use cilia, flagella and pseudopodia for locomotion.

4) They coordinate locomotion with ingestion.

5) They exhibit a variety of food–gathering structures including:

   a. Pseudopodia,

   b. Tentacular Feeding Tubes, and

   c. Mouths.

Protozoa exhibit a dynamic, and seemingly inexhaustible portfolio of possible material flows in the form of body parts. A realistic appreciation of the knowledgebase giving rise to such diversity can only come from taxa defined within the patterns of structural similarities (Anderson, et al. [214,215]). Accentuating the significance of the myriad of Scale–2 body parts is the observation that protozoa contain most if not all of the life processes of Scale–3 within a single cell, and in absence of tissues and organs (Anderson [214]). Furthermore, the extent of presence of Scale–2 organisms in terrestrial and aquatic environments is as prevalent and widespread as that of Scale–1's bacteria (Anderson [214]). In colonies such as those formed by Volvox, protozoa demonstrate differentiation into reproductive and vegetative groups thus representing the division of labor that would generate other components of the knowledgebase needed for creation of Scale–3 (Farmer [215]). Collectively, Scale–2 organisms represent a pattern of knowledge flow that would accumulate the knowledgebase needed to launch the Scale–3 organisms. Scale–2 patterns of substantial diversity must be seen emanating from a focused knowledgebase. The Scale–2's intensive portfolio of body–part generation is a direct reflection of the potential to create, store, and propagate the corresponding knowledge. Taxonomic and phylogenetic schemes of classification only represent certain static aspects and thus a subset of the material flow features that the Scale–2 knowledgebase can bring into existence (Anderson, et al. [214,215]).

What do we know about the modes of knowledge transfer in Scale–2? The most important is that the bundling and individualizing of knowledge is not singular. In ameboid forms there can be many nuclei per cell and as a rule, the large amebas are multinucleate (Hanson [219]). In acantharians, all adult forms are multinucleate (Hanson [219]). In ciliates there is a mix of macronucleus and micronucleus in varying numbers (Hanson [219]). For cilliates, the cell always contains two types of nuclei: one or more macronuclei regulating the metabolism, and many small micronuclei controlling sexuality and reproduction (Anderson, et al. [214,217]). Both macronuclei and micronuclei vary in size, spatial proximity, and chromatin organization (Anderson [214]). While multinuclearity is prevalent in Scale–2, it does not mean an absence of single–nucleus cells. For example, all protozoa, except for cilliates, can have cells with a single nucleus. Given the multiplicity of the modes of storage and bundling of knowledge, protozoan modes of propagation of knowledge include (Farmer, et al. [215,217,220]):

a) Binary fission where the individual replicates itself.

b) Multiple fission where rapid and repeated division of the cell occurs without cytoplasmic differentiation, producing a multinucleate mass that may possess thousands of nuclei. From this mass, individual cells form around specific nuclei that then break away.

c) Fusion of free–swimming gametes to form a zygote.

d) Conjugation (only in ciliates) where micronuclei are exchanged across a cytoplasmic bridge.

e) Budding where fission is asymmetric.

What is the significance of such diverse forms of multiplicity of bundling and individualizing of knowledgebases in Scale–2? Traditionally, such foundational features of Scale–2 are eclipsed by the homocentric focus on multicellularity of Scale–3 which is perceived as an alternative to multinuclearity. The traditional view would declare the Scale–2 multinuclearity as an evolutionary dead end (Hanson [219]). From the knowledge flow perspective, however, the Scale–2 multinuclearity is an operational aspect of creation, bundling, and individualizing knowledge in a diverse arena of genetic, epigenetic, and supragenetic spaces. In the knowledge space of body–part building, there is little operational advantage in limiting the number of knowledgebases to one per organism. Yet, once the accumulated knowledgebase is large enough to launch an organism out of Scale–2 into Scale–3, the singularity of the central knowledgebase has operational advantages. Thus, the appearance of a single nucleus in the Scale–3 that emerges out of Scale–2 should not be taken as a sign of deficiency of multinuclearity in Scale–2 but a sign of Scale–2's efficiency in producing and packaging a knowledgebase of body parts whose sole mission would be to create Scale–3 multicelluarity. Furthermore, from a knowledge–based point of view, the Scale–2 bundling and individualizing of microknowledge seems focused on creation of "macroknowledge" which makes its first appearance in Scale–3. Macroknowledge and its features are described in the next section.

Knowledge Flow Dynamics of Material Scale–3

Scale–3 makes its first appearance relatively abruptly about 700 million years ago (Cloud, et al. [210,221]). This mode of appearance is similar to Scale–2's eukaryotes arriving swiftly at about 1.3 billion years ago (Cloud [221]). Scale–3 knowledge processors such as burrows with hydrostatic skeletons and soft–bodied floaters are deemed as first multicelled animals (Valentine [222]). Because of this article's space limitations, I will not include the delineation of arrival of terrestrial animals (Little, et al. [223,224,252]) or plants (Delevoryas, et al. [225-227]) and only state that they are temporal progressions of Scale–3's knowledgebase. Such patterns of knowledge flow in Scale–3 are traditionally recognized within structural classifications called "speciation" (McNamara [228]). The traditional material flow models seek the origin of Scale–3's multicellularity in possibilities such as association of free–swimming flagellates into a colony, suppression after cell division, cellularization of a multinucleate cytoplasm, or fusion of ameboid protozoans (Hanson [219]). Such postulates attempt to link the structural features of one scale to the next. From a knowledge flow perspective, one does not need to start from unidirectional lines of structural change from a distant and structurally–specific ancestor. Instead, the key premise becomes the availability of the knowledgebase in Scale–2 that flows to form the next scale, Scale–3. In principle, the knowledge of multicellularity gathered by Myxobacteria (Shapiro [229]) or the knowledge of membrane–bounded nucleus as exhibited by G. obscuriglobus (Fuerst, et al. [186,187]) pose as knowledge potentially available to all members of the bacterial Scale–1.

Similarly, Scale–2 is an accumulator of many if not all features of Scales–1's knowledgebase. Moreover, Scale–2 is the creator of new structural and functional features that may not exist anywhere within the knowledge space of the preceding scale. I emphasize that the structural features observed in Scales 1 and 2 are not necessarily the complete portfolio of material flow features that can be produced from these scales' existing knowledgebases. The apparent material flow features can be prudently taken to be a subset of the material flow features that potentially can be produced by each knowledgebase. From the knowledge flow perspective, multicellularity arises when Scale–2 accumulates the knowledgebase for formation of macroscopic (multicelled) entities. The appearance of metazoa about 700 million years ago marks the start of tissue formation as focus of material flow in Scale–3 organisms. Thus, the knowledge flow would shape material flow into function–specific differentiations where tight assemblies of differentiated cells (organs) would provide particular services such as digestion, locomotion, etc. for the organism. It is important to recall that in Scale–2 such functions are concentrated at a single cell. Specifically, in Scale–2 the ingestive organelles of a cell are complete. Yet the tissue cells in Scale–3 have no such counterparts (Tartar [216]). The knowledge flow model identifies the difference between the two scales not in functions performed but in microscopic to macroscopic transition of functions. Scale–3 is the macrospace version of the functions performed in Scale–2's microspace.

The Scale–2 flow of knowledge primarily consists of bundled microknowledge that flows through

a. Reproduction, where the cell replicates itself, thus enhancing the flow of its bundled knowledge, and

b. Sex, which results in sharing of bundled knowledge.

In Scale–3 these two processes combine to maintain a flow of microknowledge primarily based on sexual (sharing) processes. As such, the channels for flow of microknowledge have strong resemblances to those of Scale–2. However, Scale–3's total flow of knowledge differs radically from that of Scale–2 in that the Scale–3's flow of microknowledge gets complemented with macroknowledge. How is macroknowledge produced? What does it consist of? Scale–3's macroknowledge production is the outcome of collections of knowledge processors that become capable of communicating, storing, and

processing macroknowledge. In animals we recognize the most vivid example of the aggregate knowledge processors as the "nervous system." Because of the anthropomorphic focus, limited work is done as to the mode of creation, storage, and processing of macroknowledge in plants. Though it is demonstrated that plants are capable of creating macroknowledge in the process of detecting and reacting to events in their external environment (Braam, et al. [230]). In Scales 1 and 2, microknowledge can flow in any of the genetic, epigenetic or supragenetic spaces.

In Scale–3, for the first time, epigenetic space becomes capable of sustaining the flow of both microknowledge and macroknowledge while the supragenetic space becomes the domain of macroknowledge flow. The externalized macroknowledge forms the macrosupragenetic space while the internalized macroknowledge resides in the epigenetic space complementing the microknowledge flow. Thus, the epigenetic space of Scale–3 radically differs from the epigenetic spaces of Scales 1 and 2 because of macroknowledge flow. The Scale–3 flow of macroknowledge is highly internalized. It resides fully in the epigenetic space. There is little externalization of macroknowledge, thus a small macrosupragenetic space. In Scale–3's macrosupragenetic space a major component of the externalized macroknowledge consists of communication signals. Examples of such externalization are alarm signals differentiated according to the type of danger (Griffin [231]) and the sound and dance to communicate information about the location of food (Wolfgang, et al. [232]). The externalization of Scale–3 macroknowledge also manifests itself in construction of shelters, nests, and structures that capture prey or attract mates (Griffin, et al. [231,233]). Does the flow of macroknowledge in Scale–3 have parallels with Scale–1's flow of microknowledge? Is Scale–3 engaging in the same mode of accumulation of macroknowledge that Scale–1 performed with microknowledge?

Would there be some sort of packaging of internalized macroknowledge that would then be offered to certain knowledge processor (organism) being launched into Scale–4? While I have not developed detailed answers to these questions, it seems plausible that the flow of Scale–3 macroknowledge, while confined to the epigenetic space, does have the potential to accumulate substantial internalized macroknowledge. I thus postulate that from a knowledge flow perspective, one of the Scale–3's potentialities is the accumulation of internalized macroknowledge for application in Scale–4 where macroknowledge is extensively externalized.

Knowledge Flow Dynamics in Material Scale–4

Scale–4 is the domain of substantial externalized flow of macroknowledge, especially as characterized by knowledge–packets such as words and language as medium of creation, storage, and transmission of macroknowledge. The key feature of Scale–4 is the intensity of macroknowledge flow into a macrosupragenetic space potentially shared by all Scale–4 participants. In Scale–3, the flow of externalized macroknowledge is primarily in the form of nonverbal (body or vocal) communication (Papousek, et al. [234]) and simple structures like nests, etc. (Griffin, et al. [231,233]). That forms a relatively shallow and somewhat localized Scale–3 macrosupragenetic space. In Scale–4, however, the macrosupragenetic space is potentially worldwide and can remain essentially bottomless in terms of knowledge–packets it creates. In this sense, Scale–4 is the macro equivalent of Scale–1. The traditional view of human evolution recognizes the brain as the differentiating organ (Washburn [235]). Yet, from a knowledge flow point of view, the uniqueness of the human brain compared to brains of Scale–3 residents lies in its intensity of externalization of macroknowledge, a process that continually builds up the communal pool of macroknowledge in Scale–4's macrosupragenetic space. We have thus arrived at a dynamic model of continuation of knowledge flow in life processes that can be described as:

1. Scale–3: Focused on internalized flow of macroknowledge emerging from a foundation of microknowledge in Scales 1 and 2.

2. Scale–4: Focused on externalized flow of macroknowledge out of a foundation defined by microknowledge and macroknowledge of Scales 1–3.

As a comprehensive view of the nine–scale model of knowledge flow, I have summarized the key features and characteristics of all scales in (Figure 6). The majority of (Figure 6) statements are novel, knowledge–based observations that provide new insights into traditional material and energy flow observations.

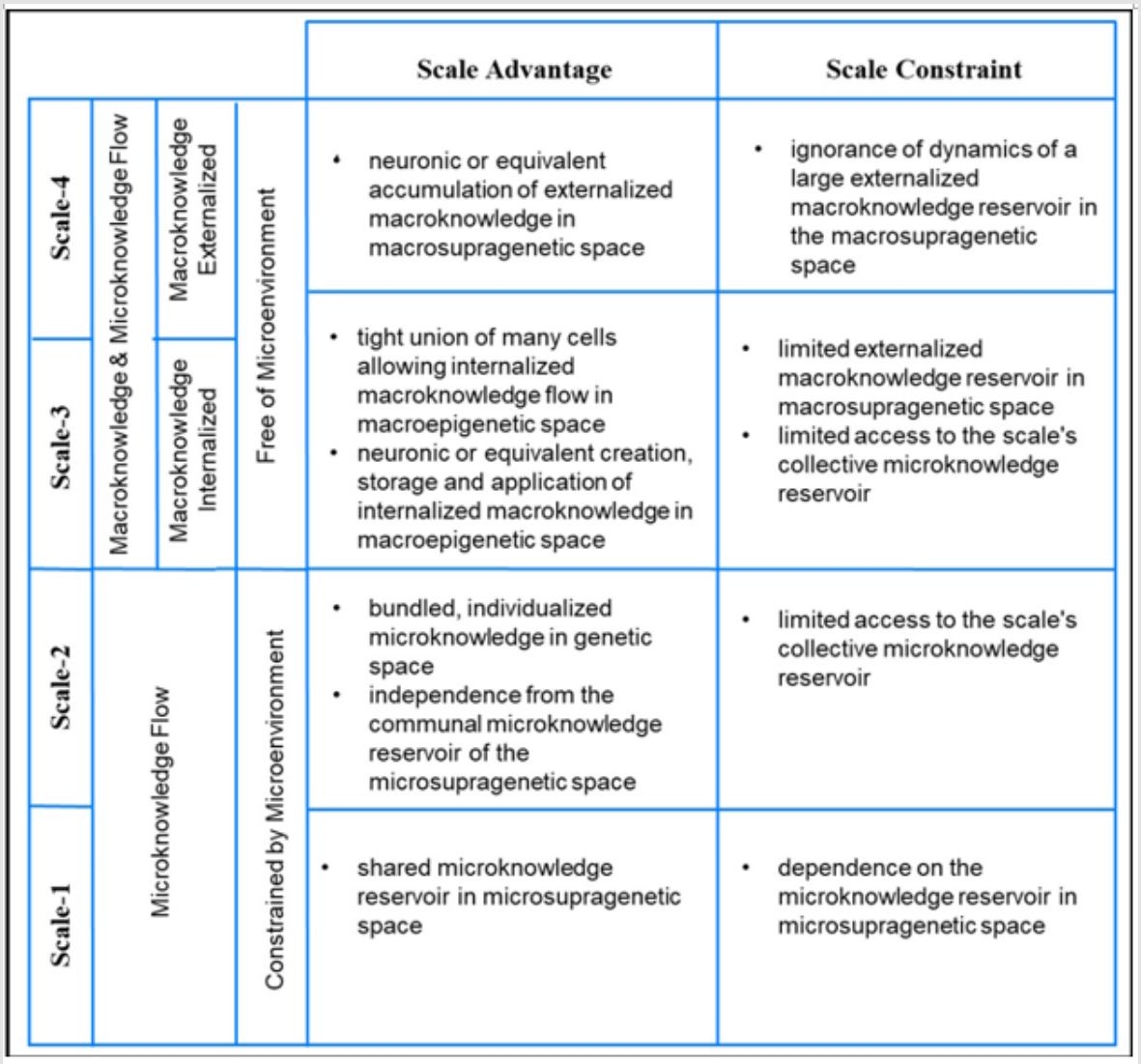

Figure 6: A holistic, knowledge–based view of integrated scales in life processes, based on the nine–scale knowledge flow model.

Inter–Scale Interfaces

The nine–scale model of knowledge flow presented in this article has a stratified structure. The scales, however, are not isolated domains. Each scale is nested within a supportive knowledgebase formed by the previous scales. It is plausible to assume that the knowledge flow is multi–dimensional and that there are many possibilities for inter–scale flow of knowledge through a variety of interfaces. Given the multi–billion–year stability and foundational character of Scale–1, it is further plausible that Scale–1 may function as the main broker of global knowledge exchange. This postulate is contrary to the anthropomorphic perception of superiority of Scale–4's macrosupragenetic space in the global knowledge space. The Scales 1 through 4 are defined not as lines of absolute demarcation but as bands of transition where a new balance of communal and individual knowledge, material, and energy flows takes shape. (Figure 7) characterizes the scales interlinked at various boundaries. The scale interfaces require appropriate knowledge flow, namely mechanisms for signaling and transfer of information, if they are to be effective (Clarke, et al. [236-238,270]). The interfaces would exhibit different degrees of knowledge–packet specificity. Not all knowledge flows can be assumed to be mutually reinforcing or mutually constructive. Nor all material features of knowledge–packets can be assumed to match and fit positively and coherently with other material–packets. Numerous examples of such discongruities can be most vividly observed among knowledge–packets created by humans in Scale–4 macrosupragenetic space.

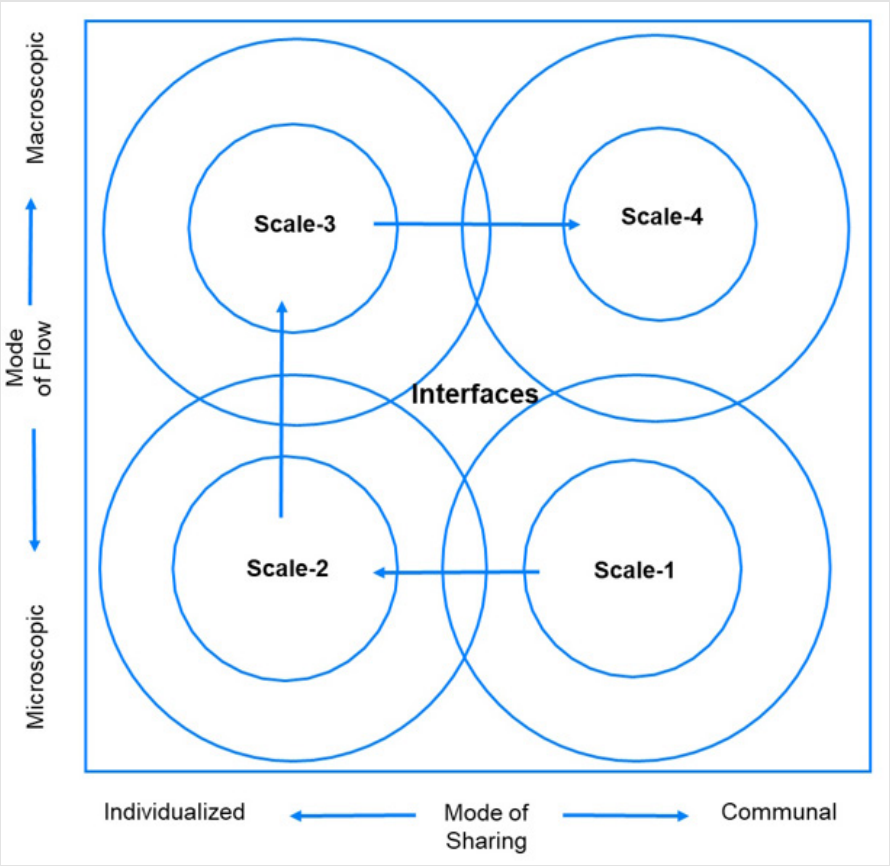

Figure 7: The holistic unity (microknowledge to macroknowledge transformation) of life processes through knowledge flow, trophic flux, symbiosis and other interfaces and support boundaries.

It is logical to assume that there exists the potential for a similar pattern in every other scale of the knowledge space. Thus, bacteria will form nodules with some host plants and not others (Long, et al. [239]). In general, Scale–1 (bacteria) and Scale–4 (humans) are most adept in changing their interfaces in order to enhance their effectiveness in flow of knowledge–packets (Cherfas [240]). Because of the traditional anthropomorphic focus, the human interfaces with Scales 1 and 2 have remained largely invisible even though, at absolute minimum, billions of bacteria, protozoa, and fungi reside within each human. These interfaces manufacture nutrients, stimulate the immune system into recognition of adverse interfaces (diseases) and keep out knowledge and material flows capable of forming dysfunctional (disease–causing) interfaces (Lewis [241]). Within the context of knowledge flow, inter–scale boundaries are also diffuse, dynamic, and quite active in transport of trophic materials and knowledge–packets. Such features are most vivid in symbiotic interfaces. At present, symbiosis is primarily viewed in individualistic terms, focused on the concept of "individuals living together" (Margulis [245,242]). Within the traditional framework, symbiotic phenomena are primarily seen as

a. Intimate living together of two or more organisms, or

b. Host and guest relationships in which the guest eventually becomes an organelle of a new kind of a cell (Margulis [243,275]).

While the localized and individualized view of symbiosis is valuable, it would not reveal the role that symbiosis plays at scale interfaces. From a knowledge–flow perspective, symbiotic arrangements are forms of scale interfaces where one scale supports or nurtures another. The Rhizobium–legume symbiosis (Beringer, et al. [244,245]) is an essential interface between the bacterial Scale–1 and multicellular Scale–3. The bacteria (Scale–1)–yeast (Scale–2) DNA transfer is another example of inter–scale interface (Heinemann, et al. [246]). An example of a tri–scale interface is termite, a Scale–3 organism that within its hindgut carries a Scale–2 protist which in turn carries or is associated with a number of Scale–1 bacteria. The interface has been so tightly interwoven that neither the termite nor the protist can survive without each other (Margulis, et al. [276,192]). While such configurations can be characterized as individual symbiosis, they should be more appropriately viewed as scale interfaces that sustain one scale with elements from another. In Scale–4, the commonality of interfaces is exemplified by 10% of human dry–weight being made of microbes, or in Scale–3 all of the cellular digestion of a cow being entirely of microbial origin (Margulis, et al. [276,192]). The dynamics

of the nine–scale knowledge flow model can also be approximated by a simple model of transformation of microknowledge to macroknowledge. This, as shown in (Figure 7), would provide a holistic view of how various scales are interlinked through a knowledge–based "organizing principle."

The microknowledge to macroknowledge transformation in life processes can provide new insights. For example, it deflates the materialist notions of life as cutthroat competition for survival of the fittest. It would instead embody life as a pattern of flowing knowledge where the myriad of interfaces have a dynamic and not static design. The so–called "savage acts" of predator inflicted on the prey become dynamic interfaces for material flow needed to sustain the knowledge flow. Without such changes, there will be a static and non–interacting environment in which minimal knowledge would flow. More importantly, the manifestation of dynamic interfaces is not limited to predator–prey interactions but finds expression in a myriad of cooperative arrangements where life–forms of one scale are highly supportive of existence of the life–forms of the same or other scales. As a prevalent example, the vast threadlike underground networks of fungi play a foundational role in the uptake of nutrients to trees, grasses, and other plants (Fausto Sterling [247]). The microknowledge to macroknowledge transformation of the nine–scale knowledge flow model also puts into a new perspective the homocentric acts of tinkering with various interfaces. For example, the use of chemical nitrogen fertilizers or the search for creation of nitrogen–fixing plants (Postgate [248]) are all potential alterations in the knowledge–flow processes that sustain life.

Thus the scientific search for immediate means of increasing the food supply of human societies, an act within macrosupragenetic space of Scale–4, needs to consider the long–term implications for altering the global knowledge space. A Scale–4 macroknowledge flow not in balance with flows of other scales can potentially give rise to various biological waste streams that could radically alter Scale–4's flow of knowledge–packets, thus altering its organisms, namely humans (Jonesburg [132]). The nine–scale knowledge flow model sees a one–to–one correspondence between organism (knowledge processor) and knowledge flow. Change the knowledge flow and the organism as a node of accumulation, processing, and application of knowledge will change.

Concluding Observations

In this paper I have introduced a macrotheory for systematization of knowledge in biological processes. The proposed model is a nine–scale knowledge flow model. There are five material scales of prokaryotes, eukaryotes, multicellulars (including animals and plants), humans, and the environment. The three knowledge scales consist of genetic, epigenetic, and supragenetic spaces. The ninth scale is energy. The knowledge scales are described in new terminology that includes: knowledge flow, knowledge–packet, material–packet, knowledgebase, knowledge processor, and others. The introduction of these new terms enhances insightful observations that will be described below. The nine–scale knowledge flow model provides a number of insightful and previously unknown views of life processes. It shows that from a knowledge flow point of view, the prokaryotic Scale–1 is a highly cohesive, practically infinite microsupragenetic space. No organism can leave this communal knowledge space without first bundling an adequate supply of knowledge. The emergence of the eukaryotic Scale–2 with organisms that possess bundled, individualized knowledgebases thus becomes an intrinsic outcome of the knowledge structure in Scale–1. This is a new knowledge–based view of the prokaryote–eukaryote scale transformation. The knowledge–based view of eukaryotic Scale–2 portrays it as a knowledge space of "body–part building." The key characteristic of Scale–2 knowledgebases is that a knowledgebase is not singular to the organism.

Almost all Scale–2 organisms have many nuclei and engage in a dynamic, seemingly inexhaustible portfolio of material flows to produce a multitude of body parts. The knowledge–based model provides the insight that the multi–nuclearity of Scale–2 is an effective operational device for creation, aggregation, bundling and individualizing of knowledgebases that collectively accumulate the Scale–2's immense knowledgebase of internal and external body parts. I have hypothesized that the myriad of Scale–2 body parts corresponds to a knowledge–driven process of preparing for the needs of the Scale–3 epigenetic space's interface with its supragenetic space and environment. The systematization of biological knowledge as proposed in the nine–scale knowledge flow model distinguishes microknowledge from macroknowledge. "Macroknowledge" is the type of knowledgebase and knowledge–processing associated with multicellular aggregations of knowledge processors. Scale–3 is primarily a domain of internalized macroknowledge manifesting in a diverse variety of multicellular material forms. With humans and Scale–4, for the first time we observe intense externalization of macroknowledge. In a process similar to the supragenetic space of Scale–1, the supragenetic space of Scale–4 is evolving as a communal, bottomless pool of externalized knowledge–packets. The final insight from the proposed model is that knowledge flow has the potential to approximate as an "organizing principle" for life processes.

As depicted graphically in (Figure 7), the flow of knowledge has a distinct pattern of microknowledge to macroknowledge transformation. This is a dynamic indicator of connectedness of life forms and complements the historic (static, fossil) indicators of evolutionary linkages.

Notes

1) I define "reservoir of experience," and its manifestations as knowledge–packets and knowledge processing within the context of natural selection, the central dogma of biology which contemplates only an outward, unidirectional flow of knowledge from central knowledgebases, specifically, the nuclei (Crick, et al. [169,174,256,249-250]). Therefore, the centralized components

of the reservoir of experience, namely the nuclei are not modified by living systems' interactions with the environment. They can change only through selective pressures exerted on phylogenetically different knowledge–packets.

2) "Microknowledge" and "macroknowledge" are more specific characterizations of biological knowledge that will be defined respectively in Sections III and VIII.

Statements and Declarations

Declaration of Competing Interests

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Data Availability

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