



# A paradigm for viewing biologic systems as scale-free networks based on energy efficiency: Implications for present therapies and the future of evolution

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**Summary** A network constitutes an abstract description of the relationships among entities, respectively termed links and nodes. If a power law describes the probability distribution of the number of links per node, the network is said to be scale-free. Scale-free networks feature link clustering around certain hubs based on preferential attachments that emerge due either to merit or legacy. Biologic systems ranging from sub-atomic to ecosystems represent scale-free networks in which energy efficiency forms the basis of preferential attachments. This paradigm engenders a novel scale-free network theory of evolution based on energy efficiency. As environmental flux induces fitness dislocations and compels a new meritocracy, new merit-based hubs emerge, previously merit-based hubs become legacy hubs, and network recalibration occurs to achieve system optimization. To date, Darwinian evolution, characterized by innovation sampling, variation, and selection through filtered termination, has enabled biologic progress through optimization of energy efficiency. However, as humans remodel their environment, increasing the level of unanticipated fitness dislocations and inducing evolutionary stress, the tendency of networks to exhibit inertia and retain legacy hubs engender maladaptations. Many modern diseases may fundamentally derive from these evolutionary displacements. Death itself may constitute a programmed adaptation, terminating individuals who represent legacy hubs and recalibrating the network. As memes replace genes as the basis of innovation, death itself has become a legacy hub. Post-Darwinian evolution may favor indefinite persistence to optimize energy efficiency. We describe strategies to reprogram or decommission legacy hubs that participate in human disease and death.

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## Hypothesis

We propose a framework for understanding the physical world as an emergent property of a scale-free network in which energy efficiency is the basis of preferential attachment. Implications

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for understanding the nature of diseases and their potential solutions are discussed.

## Theoretical framework

### Structure of scale-free networks

We often think of a network as an interconnected system of individuals. However, a network also represents a means by which to conceptualize the relationships between otherwise unrelated entities. A network is made up of units called nodes, which form links, or connections, to each other.

A node can be a functional entity, but it also can be merely conceptual – for instance, an idea. In similar fashion, the links formed by the nodes can be functional, where the nodes exchange physical material or information to effect change, or they can also be conceptual, where a link merely represents validation or subscription to the scheme or program of action espoused by a particular node. Memes and conceptual nodes are essentially interchangeable paradigms. Adoption of a meme is akin to linking to a conceptual node. Much as a meme gains its significance as it becomes incorporated into other behaviors and philosophies, which represent memes onto themselves, conceptual nodes can become functional if sufficient “buy-in” occurs from other nodes so as to alter the behavior of the network. If a power law can be used to describe the probability distribution of the number of links per node, the network is described as being “scale-free” [1–3]. Biological and other real complex networks typically exhibit this property.

In scale-free networks, regions of the network often exhibit a behavior called clustering [4], where nodes in a vicinity tend to link to a particular node, referred to as the hub. Two principal mechanisms appear to drive formation of a hub. While the opportunity to form links may be fundamentally a stochastic process [5] driven by probabilistic considerations [6], once initiated, consolidation of links into more durable attachments frequently depends on other factors. As demonstrated both in reality and in simulations, in some systems, the number of links already possessed by a node encourages subsequent link formation. Those nodes that already have links are more likely to acquire additional links. This phenomenon is known as preferential attachment [4,7]. Thus when the network first forms, nodes that are present at that time tend to possess a “first mover” advantage over those nodes, and are more likely to become hubs. Such nodes by definition have a function in that they aggregate links, but they may or may

not have conceptual appeal. Other than their role as aggregators of links, they may not offer any other compelling reason to link to them. Alternatively, some intrinsic property of a particular node may encourage other nodes to link to it. The existence of such a property would enable nodes that emerge well after the origin of the network to offset the first mover advantages possessed by incumbents. Such nodes have conceptual appeal in addition to functionality: they provide a compelling value proposition unto themselves independent of the links they possess. Consequently, a scale-free network emerges when preferential attachment constitutes an organizing property of the system.

Moreover, preferential attachment can be a multivariate function. A simple network model can be considered with two variables, such as the number of links to a node and the intrinsic property of the node itself. In such a case, preferential attachment is given to the node exhibiting the highest energy efficiency as a result of its endowment through both links and intrinsic merit. However, real systems are more complex, where variables such as distance between nodes and resource constraints become cost factors in the determination of preferential attachment. Nevertheless, it is useful to consider corner cases to understand the boundary conditions of the general problem. Consider for example, one pattern of development where a node attracts links based solely on the number of links that it already possesses. Such a scheme tends to give rise to hierarchical organizations with a central hub. Lesser nodes are compelled to link to this hub, which only further reinforces its dominant status. As an example, industries in which monopolies exist represent economic networks where legacy holds forth.

The other pattern of development is based on merit. For example, industries characterized by the ongoing development of disruptive, innovative technologies represent scale free networks where merit rules. Here a node attracts links based on some unique feature that provides benefits to other nodes or to the system as a whole. In biological networks, this feature constitutes the ability to utilize energy efficiently and, perhaps more importantly, to enable other nodes that link to this node to do the same. The greater the efficiency advantage that it confers, the more likely the node is to become a hub. However, the threat of a new entrant is always present: the arrival of a new node which confers better energy efficiency will drive nodes to link to it, rather than to the extant but less efficient node.

## Biological systems as scale-free networks

Both of these processes can and do operate within the context of biological networks [8]. For example, within the cell, adenosine triphosphate (ATP), an efficient carrier of energy, plays a critical role in many biochemical processes. It thus effectively forms a functional node to which the other participants in such processes become inextricably linked. ATP ultimately becomes a hub [9]. Moreover, since ATP has yet to be supplanted by a more efficient molecule for the transport and exchange of energy, its position remains merit-based, though an argument can be made for legacy considerations given its ubiquity.

Conversely, the concept of the cell itself represents a hub that likely originally arose because of its relative merits [10–12], but now persists due to legacy effects. A cell defines a conceptual hub whereby molecules aggregate in such a fashion so as to create one or more independent chemical contexts within a tightly defined vicinity. A cell provides a relatively stable biochemical environment in which chemical reactions can occur without significant perturbation from external forces. It also enables efficient utilization of the energy generated through those chemical reactions. Hence cellular organization offered to biochemical molecules floating in the primordial soup an opportunity to facilitate energy use. As functional nodes, these biochemical molecules then formed links to a conceptual node – that of the cell. As more molecules linked to this conceptual node, the cell became a functional node, and eventually a hub. This property of self-organization constitutes a function of thermodynamics – a path of energy efficiency among interconnected nodes. An emergent property of a thermodynamically governed network, this principle of self-organization gives rise to life.

As the notion of specialization to achieve greater efficiency became refined, a novel conceptual node arose which proposed further promotion of energy efficiency by creating a more specialized entity, the organ, which had a cellular substructure. The organ extends the concept of the cell to another order of magnitude, in this case promoting sustained association so as to mobilize an assembly of formerly independent units towards a particular biologic function. Here the unit is that of the cell, channeling its efforts in manipulating molecules towards a higher order purpose. Recognizing the merits of this idea, the functional nodes of cells linked to the conceptual node of the organ, until it became transformed into a functional node and ultimately a hub.

However, biochemical molecules may not have necessarily regarded linkage to the conceptual node of an organ with a cellular substructure with similar zeal. Although sequestering function within individual cells may confer certain advantages, biochemical molecules may function more effectively when freed from the constraints imposed by the cell, so as to enable more efficient redistribution of resources within the organ. The barriers imposed by the physical structures of the cell, which previously provided an advantage in protecting against the outside environment, now serve to impede both physical and informational communication required to coordinate the activities of multiple cells in the context of the organ.

Indeed, these biochemical molecules would be more likely to favor linkage to a different conceptual node, one where the idea of an organ remains, but with an underlying substructure not bound by the legacy of the cell. However, because these molecules have linked to the functional node of the cell, dissolution of these existing connections and linking *de novo* to a novel conceptual node for the organ, without invoking the functional node of the cell, may involve greater risk for these molecules, specifically the loss of energy efficiency in effecting a new set of links, as opposed to merely allowing the existing functional node of the cell to function as their proxy.

With respect to these molecules, the cell thus retains its functional status as a node, but loses some of its conceptual validation as necessarily representing a mechanism for enhancing energy efficiency. It remains a hub, but becomes subjugated in concept to that of the organ. The cell effectively becomes a proxy, a meta-node whose linkage actions impact but do not necessarily reflect the best interests of the nodes that link to it. Consequently its persistence and linkage to higher order structures becomes a function of the links that it already possesses, rather than any merit that it necessarily possesses over an alternative. The cell thus becomes an artifact of legacy rather than persisting on the basis of its own merits. A hierarchy is created, one where the needs of the biochemical molecules effectively become subjugated to the needs of the cell.

This struggle between meritocracy and legacy continues at the level of the organism, the ecosystem, communities and societies and ultimately to the level of ideas where the hubs that form may energetically benefit a specific set of nodes, but not necessarily those nodes whose links are even once removed from the critical point of interaction. That which is favored only serves to energetically support those who have the direct means to

influence it. Much has been made regarding the “small world” phenomenon in many complex networks, whereby any two nodes can be readily connected by a very small number of links [1]. However, what has not been carefully examined is the value of a particular link to a particular node depending on the number of intervening nodes. In any network, a true meritocracy may only be able to occur if one degree of separation exists between all nodes. Otherwise, a network is constrained in its development by its legacy. Consequently, biological networks tend towards relative sufficiency rather than absolute perfection, and even then only with respect to a certain set of controls. Even with the mere insertion of an additional degree of separation, hierarchical considerations encroach [13], and the law of preferential attachment begins to pervade.

The Darwinian principle of natural selection becomes reinterpreted in the context of networks as a principle of sustenance through preferential attachment. If each organism in a given environment constitutes a node, the resultant network represents an ecosystem. The links formed between these nodes would then indicate the degree to which a given node can form a symbiotic relationship with another node – effectively, a lifeline. The significance of a symbiotic relationship is conservation of energy, that is, improved energy efficiency. Organisms that possessed a feature beneficial to other organisms would become hubs within this network ecosystem, as preferential attachment would drive those other organisms to form symbiotic relationships with organisms that harbored such desirable traits. Organisms that had less suitability for a given environment would experience difficulty establishing symbiotic relationships with other organisms, effectively becoming nodes isolated but for one or two links. Such isolated nodes would have greater susceptibility to any event that caused loss of one of their existing links, compared with a hub that would have other organisms present to support it. In similar fashion, the loss of a node with minimal linkages would have less consequence on a networked ecosystem than would the loss of a hub organism. Even with the loss of a single hub organism, the network should be able to withstand such extinctions because of the abundance of other linkages present. Only loss of multiple hub organisms in a concerted fashion would then lead to collapse of the network ecosystem.

## Implications

Whether nodes are seen to represent biochemical molecules, cells, organs, organisms, or systems,

understanding biology in terms of scale-free networks and energy efficiency carries significant implications.

## Environmental flux drives network recalibration

We previously posited that energy efficiency represents the fundamental basis of evolution [14]. The pursuit of energy efficiency characterizes not only the history of evolution to date, but also its future. The conflict between merit and legacy-based attachments related to energy efficiency comprises the principal challenge of evolution. As conditions change, a new meritocracy arises, displacing the old meritocracy. Attachments that previously arose due to merit become relationships based on legacy. Novel attachments based on the new meritocracy emerge compelling the network to recalibrate. The degree of recalibration can range from subtle, where legacy hubs persist and continue to dominate, to drastic, where the topography of the network may entirely transform to achieve a new optimum, with replacement of legacy hubs by novel ones.

To what degree recalibration occurs depends on the external constraints that define the incumbent network as well as how these constraints change – a concept that we refer to as environmental flux. Use of ATP as the energy currency and cells as the units of construction represent examples of legacy hubs that will likely persist until a cataclysmic environmental change occurs. However, the tendency of networks to exhibit inertia and retain legacy hubs becomes increasingly counterproductive as the degree of evolutionary displacement increases. As the existing network becomes less suited for new conditions, evolutionary stress occurs. As sufficient stress accumulates, so does the incentive for non-linear, non-incremental rearrangement of the network topography, until recalibration occurs – that is, the configuration of the network adjusts to fit the new constraints imposed upon the network, thereby decompressing the accumulated evolutionary stress [15]. Nodes attain and lose hub status, and links are both formed and lost. Evolutionary stress and incentive represent two sides of the same coin, much as the “fight-or-flight” and “fear-and-greed” dualities that exist in other scientific parlance. These forces compel genetic and epigenetic risk-taking to induce adaptations to changing environmental conditions [16].

## Examples of evolutionary displacement

The modern human condition is characterized by rapid environmental flux associated with the col-

lective endeavor to remodel our own environment, producing both anticipated and unanticipated changes. The long-term impact of these evolutionary displacements is often hard to measure and remains unknown in many cases. We argue that much of what humans perceive as disease fundamentally derives from evolutionary displacements. The recent evolutionary dislocation of the prehistoric trauma response represents the archetypal example of this concept [17,18].

One might extend this concept to the behavioral component of the trauma response – the fear response. In the past, coupled to fitness-altering situations, the fear response was adaptive. Modern history has seen the emergence of new behavioral stressors that bear little to no relation to adaptive benefits and may even link directly to maladaptive harm. Increasing incentives for illegitimate signals due to dissolution of kin networks and cheapening distribution costs of illegitimate signals due to technical innovations have bolstered the emergence of maladaptive triggers of the fear response, which in turn have contributed to the development of various physiologic and behavioral ailments.

We have reported other significant examples of evolutionary displacements that contribute to ailments. Remodeling of the environment has undermined many oscillating natural cues, upon which our legacy physiology has relied to train its response mechanisms [19]. The resultant deconditioning of our response pathways induces biologic complacency and may play a role in the derangement of many systems that participate in disease. The modern paradigm of medicine that relies on correcting errors may act as an environmental stressor through additional deconditioning – a phenomenon often referred to as tachyphylaxis. We have previously explored the possibility that modern medicine may participate in the progression of many diseases such as myopia, diabetes, Parkinson's disease, and hypertension [19]. Paradoxical medicine may represent a novel way to address human ailments by reconditioning pre-existing pathways [20].

The decline of cognitive plasticity during the teenage years previously served an adaptive function in enabling humans to apply memes more efficiently during adulthood after acquiring them during development. However, it has become a maladaptive feature in the modern world where lifespan has increased and environmental change occurs far more rapidly [21]. Overconsumption of food and information constitute other examples of evolutionary displacements related to modern innovations that inadvertently produce disease [22].

## Death as an evolutionary displacement

The most profound evolutionary displacement may be death itself [23]. A living system can be understood as a mass-based phenotype that samples for information about environmental conditions as well as potential innovations that enable adaptation to those conditions. These demands help explain the rapid evolution of sensory systems, cognitive systems, reproductive systems, and super-organismal mating systems. Improvements through reproduction, combined with recycling of mass-based components enabled by pre-programmed death, permitted reasonably efficient accumulation of hard-wired adaptive traits over time and reduced competition with legacy predecessors. However, in the post-Darwinian era, where memes have overtaken hard-wired mass-based traits as the most efficient form of adaptive innovation, death has become counterproductive. Due to low costs of acquisition, assimilation, and distribution of memes, a single intact life span of indefinite persistence would represent a more efficient evolutionary strategy than the legacy strategy of life-death recycling. In essence, the rise of the meme has transformed death from a merit-based hub to a legacy-based hub, rendering it inefficient. The present human endeavor can be viewed as the struggle to transfer adaptive memes through the sequential generation of death-trapped legacy embodiments. Ironically, scientific solutions to the evolutionary inefficiencies that will one day enable indefinite life spans themselves represent memes that we are inefficiently transferring horizontally amongst ourselves and vertically across generations.

The recognition that death represents a pre-programmed process of self-termination, termed phenoptosis, [24,25] rather than a progressive, passive dilapidation, constitutes a meme of first-order significance. Death may have held enough adaptive value that it itself was once a merit-based hub. This recognition compels a search for the hubs – once merit-based and efficient, now legacy-based and inefficient – that enabled organisms to self-terminate under certain conditions such as sepsis and post-reproductive aging [23]. Identifying and eliminating these hubs represent exciting opportunities to reprogram human biology and meet the new challenges of indefinite persistence. Cancer may represent a model system that has successfully reprogrammed itself to eliminate pre-existing pathways of self-termination, e.g. apoptosis. Although cancer cells often lack functional differentiation, this phenomenon may reflect an attempt

to gain plasticity so as to better contend with a variety of potential futures. Indeed, if not for the induction of host collapse, cancer could persist indefinitely. The example of cancer may show us the resilience of life once the mechanisms of self-termination have become decommissioned.

Only recently have humans begun to discover how to control and reprogram such systems previously thought inexorable. One such pathway, the autonomic nervous system, may represent a legacy hub that produces programmed death through acute and chronic derangements such as renal failure, cardiac arrhythmias, inflammation, and other diseases of aging [26–29]. We believe that one solution to the progressive emergence of central and peripheral autonomic dysfunction involves reclaiming hegemony over the end-organs and restoring proper function. One embodiment of a potential solution involves an array of programmable neuromodulation micro-implants distributed at all dysfunctional target organs, centrally integrated and coordinated by an intelligent circuit. Such a solution may eliminate one of the legacy hubs of death. Opportunities to reprogram or decommission other legacy hubs of self-termination may become increasingly apparent over time.

Energy efficiency serves as a point of departure for a network theory of evolution. It also serves as a potential point of convergence for many disparate theories of life ranging from the theological to the existential, by incorporating both the notion of the origin of life in the form of light and the idea of progression through sequential incarnations to achieve improvement. It may also provide suggestions as to the direction ultimately assumed by evolution. All extant networks that utilize mass to store energy may lack the flexibility to prevent merit-based hubs from eventually becoming relegated to the status of legacy hubs. The ideal biologic system may reflect a scale-free network comprising a hegemony of ideas and complexity over mass-based structures — a system of hubs which will more likely remain merit-based rather than fall prey to legacy effects.

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