

July 2018 (via Social Media)

“I will periodically repost this on till hopefully some intelligent comments are made by people in power. drbob”

Evolution: a Dynamic Fractal

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It is a well-established paradigm that the genetic transfer of information occurs from DNA to RNA, its subsequent translation into proteins integrate into life's concert of homeostatically regulated enzymatic activities. A broadly accepted thought in the scientific community is that life and evolution are the result of an accumulation of improbable accidental events miraculously retained by evolution. This line thinking is a natural consequence of foundational physics that is based on a logical mathematical formalism of timeless equilibrium (maximum entropy, minimum free energy). A logical extension naturally leads to the conclusion time that is reversible. Essentially, the appearance of irreversibility in our everyday world 1 occurs in a time-biased fashion at any instant for unknown reasons. There is a discrepancy between these conclusions and the everyday experiences of living organisms that are guided by of the arrow of time. Random, time independent statistics cannot explain life that is too improbable to exist.

Before new biological concepts can be examined, the physical underpinnings of life must be considered. The life's work of Nobel laureate Ilya Prigogine provides a novel foundation that can be developed into an understanding of physics and life. In his last book “The End of Certainty 2,” he fully embraces his earlier work “From Being to Becoming 3,” and concludes that flowing energy has a creative organizing capacity fully consistent with the Second Law of Thermodynamics, in far from equilibrium open systems 4. His perspective is extended to living systems to create the “Physics of Life”, the physical basis for a biological systems perspective 5.

Surprisingly, it appears that the scientific establishment has missed understanding the genetic consequences of life's most fundamental property, adaptability. Currently, the physical foundations of life are ironically embedded in a dead, equilibrium perspective of random statistics. The ability of flowing electrons to create a statistically impossible molecular distribution, as seen in the Belousov–Zhabotinsky reaction 6, provides a clear parallel with the metabolic redox processes of living systems.

Life and evolution are driven by the creative nature of nature. Creativity, solutions of systemic complexity that degrade potential, emerge when far from equilibrium systems

are pushed to a flow dependent critical point whereby the system spontaneously undergoes a far from equilibrium phase change to a higher level of spatiotemporal organization (negative entropy). Conceptually, it is easy to understand a network of localized inorganic flow dependent reactions interacting, feeding and being fed by each other, ultimately leading to sufficient distance from equilibrium to create the far from equilibrium phase change of life as repeated throughout evolution of species.

Environmental conditions, both sub-cellular and planetary, create flow dependent structures that are in turn will be affected by the systemic interactions resulting from their own creation (dynamic fractal). Consequently, a complex landscape of evolving, selective pressures maintains ongoing homeostatic ability with constant dynamic adaptability. Evolution of all systems, across scales of time and space, are driven by excess energy potential that is maintained by appropriate cellular prevention (antioxidant) and recycling (autophagy) efforts that are in constant engagement to overcome the consequences of the friction of life, free radicals. Life and evolution must occur, driven by the flow of energy, but shaped by free radicals. Consequently, below is a metabolic perspective on the evolution of species and cancers.

Life's main energy sources, carbohydrates and lipids, are not functionally equivalent sources. Carbohydrates preferentially feed the efficient but dangerous electron transport system that promotes and supports differentiated cellular functions including nerve transmission, muscle contraction, hormone production. In contrast, enhanced antioxidant activity, coupled with cellular recycling allows a state of health to emerge from a living system (mathematically speaking an attractor). There is a balance between CB1/electron transport driven ATP production and resources production by recycling free radical damaged cellular components driven by CB2 activity. CB2 promotes symmetrical stem cell expansion, whereas CB1 activity promotes stem cell differentiation. In essence what we as a species will explore is the heart of our regenerative capacity, the endocannabinoid system. We are just beginning the journey out of ignorance.

The underlying concept is that survival of the fittest means survival of the most adaptable. Consequently, the initial selection for a systemic state occurs at the metabolic, not the genetic level. Metabolic imbalances promote excess free radical production that focuses epigenetic modifications that are followed by focused genetic change on the genes and their controlling regions that are responsible for survival. Hence, evolution for the most part occurs by metabolically focusing needed evolutionary change, in a multi-

gene fashion that promotes the systemic metabolic survival state.

Energy driving evolutionary change provides an easy to understand explanation for the evolution of life, species and similarly, cancer drug resistance and the genetic diversity of tumors. Potential important beneficial health consequences, especially with respect to cancer need to be considered. The existing scientific/medical framework has been unsuccessful in creating the desired health outcomes. An extreme example that demonstrates the utility of a cannabis-driven metabolic approach to treat multiple cancers that resulted from a genetic defect in the cell's ability to repair ultraviolet light induced mutagenic DNA damages. The patient below shows a multi-phenotypic reversal of the genetic deficiency (xeroderma pigmentosum) of ultraviolet light induced cancers including: elimination of pain, ending depression, healing melanoma, tongue and lip cancers, restoration of sight (personal communication B. Radisic).

Is there a connection between the lack of nucleotide excision repair seen in xeroderma some and the potential for cannabinoids to regulate free radical production and potentially associated base excision repair? It's important to remember that when we are dealing with open systems we are focusing on dynamics not static processes. Consequently small perturbations can be amplified into macroscopic systemic changes (the well-known butterfly effect). The human body has approximately 15 trillion cells that every day receive at least 30,000 oxidative base damages where one damage; in the wrong gene, one time; could kill a person as it amplifies through the system to create a lethal cancer. Common sense dictates that an extensive amount of life's organization must be devoted to protecting life from excess free radical damage and the organizational

disruption that free radical impose on cellular biochemical harmony. When flow dependent organization decreases to a thermodynamic critical point it leads to the systemic collapse, commonly known as apoptosis.

One of the most dramatic examples of metabolic adaptability in response to potential free radical damage is seen during s-phase cell of the cycle. The electron transport system efficiently provided the needed energy to build up a cells negentropic flow during G1 of the cell cycle. Consequently free radical damages, to all cell constituents, form part of the homeostatic feedback loop that directs cells to shut off the excess free radical production, coming from the electron transport system, and turn on the safe, inefficient aerobic glycolysis process, a.k.a. the Warburg effect 7. Glutaminolysis provides an additional ATP source that maintains the carbohydrate driven differentiated state by supporting Krebs cycle intermediates. In contrast, glutaminolysis activity

and AMPK activity seem mutually exclusive, again separating synthetic and differentiated pathways from those responsible for recycling of free radical damage to cellular components.

First a unique biochemical state is selected that is typically maintained by epigenetics after initial metabolic adaptation resulting from countless post-translational modifications. Consequently, excess free radical damages, due to maintaining and expanding the original metabolic imbalance, are focused on transcriptionally active genes that promote survival. Consequently, the damages themselves, the DNA nicks and single-stranded regions that are undergoing repair, promote recombinational events, gene duplications, and mutations, providing new material for evolution. For example, stalled DNA and RNA polymerase molecules can generate a variety of novel DNA outcomes^{9 10 11}. The significance of DNA architecture is emphasized by the fact there exists both global DNA repair as well as transcription-coupled repair^{12 13}.

The above proposal clearly challenges conventional modern interpretations of molecular genetics and its role in evolutionary change. The evolution of species, and cancers for the most part is not the randomly created mutations on a genome wide level, but focus of mutational change where it's needed, the genes that are responsible for survival in any metabolic state. Add to that intellectual perturbation of corroborated, unpublished studies (personal communication YW Kow, Z Hatahet) that demonstrated the fat burning, drug/radiation resistant HL60 monocytic cells do not express base excision repair enzymes. In contrast, these repair enzymes were expressed in the drug sensitive parent cell line. (Melamede and Stubbs, unpublished results).

The medical cannabis community has been successfully using a cannabis-based metabolic approach not only to control HIV and associated illnesses including dementia, dyslipidemia, Kaposi sarcoma, autoimmune diseases, pain etc. numerous age-related inflammatory and fibrotic illnesses affecting all body systems

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Before



After

