The biosemiotic implications of 'bacterial wisdom'

Introduction

Eshel Ben-Jacob (1952-2015) was a brilliant physicist, and original and highly inquisitive thinker. He explored collective phenomena across scales, illuminating the dynamics and constraints giving rise to snowflakes and analogous *self-organizing* systems, bacterial colonies, neuronal networks, and the global stock market. In 1998, EBJ penned a paper, "Bacterial wisdom, Gödel's theorem and creative genomic webs" (BW) (Ben-Jacob 1998), wherein he called for a revision of the thinking still undergirding much of biology (especially molecular biology and biomedical science): that evolution proceeds exclusively from the interplay of 1) diversity arising via random mutations in the genes of organisms; and 2) differential reproduction (natural selection) among the resultant variable organisms. This is the logic of the modern synthesis, and the strength of EBJ's critique lies in the attention he paid to the adaptive feats of the world's simplest organisms – bacteria.

On Earth, bacteria are second to plants in total biomass, and exceed that of animals by more than two orders of magnitude (Bar-On et al. 2018). Bacteria live everywhere: on and in us and every multicellular organism, more than a mile into the Earth's crust, within radioactive water and under extreme desiccation, inside of alkaline or acidic hot springs, and at hydrothermal vents in the ocean floor (Hamilton et al. 2019; Karley et al. 2018; Knight et al. 2017; Makarova et al. 2001; Merino et al. 2019; Ramirez et al. 2019). Bacteria are highly evolvable and readily exchange genetic material, obtaining and discarding genes with shifting environmental pressures (Boto 2010). On the basis of adaptive mutagenesis and related phenomena in bacteria (described later) and the ongoing discovery of highly dynamic genomes, EBJ proposed biological evolution to be "based on the cybernetic capacity of the genome", describing genomes as adaptive cybernetic units capable of changing themselves and endowed with self-awareness. EBJ asserted that bacterial colonies are "genomic webs" that under stress

find solutions to problems that are insoluble paradoxes to genomes, and "exercise creativity on the genome level."

BW is brutally teleological and filled with engineering and tech-inspired terminology. Clearly bacterial genomes are not creative in the sense we know ourselves to be. Moreover, our tech-inspired models have infested our knowledge of life and living, are part of our wider disconnection and disenchantment (Kauffman 2016), and have led to a not uncommon belief in the fallacy of artificially intelligent machines (Braga and Logan 2017; Damer 2010). We believe that biosemiotics and related metaphysics furnish concepts needed for a more compelling and illuminating interpretation of the fascinating phenomena EBJ helped discover and made central to BW.

We will start by assessing EBJ's claim that genomes are self-aware, in order to 1) obtain a more compelling abstraction of a single bacterium and begin a semiotic analysis, and 2) avoid the kind of misleading and reductive synecdoche to which we often fall prey. We will then briefly describe adaptive mutagenesis and related phenomena, and begin a biosemiotic interpretation of experimental findings. From there, we will discuss biological stress and feeling, arguing the importance of seriously considering the latter and attempting to craft for it a metaphysical and scientific respectability. We will also consider the origins of self-hood, what separates the simplest extant selves (bacteria) from what we consider our clearest conceptual account of something approaching a living entity, and remark very briefly on the special nature of self-awareness. Finally, we will conclude with speculation on the semiotic abilities of bacteria.

Mistaken essence: the genome is not the cell

A single bacterium remains an unfathomed richness of structure and process. The bacterial genome and its constituent genes are essential constraints on the dynamics creating that richness. Furthermore, genomes are not static constraints; they have their own dynamical richness. Knowing this fact to be

underappreciated, EBJ emphasized it and further claimed that genomes are self-aware entities capable of changing themselves. But in proposing that genomes are self-aware and can change themselves, EBJ falls prey to a blinkered gene-centrism.

Genomes and their constituent genes are not causally independent of the myriad molecules and processes that support them. Thus, Crick's central dogma of molecular biology should not be depicted as a line but as a ring; reworded as Kantian quote (Kant 1790), "an organized product of nature [i.e., an individual organism] is that in which all the parts are mutually ends and means." The part-ness of genomes is valid to the extent that we see them properly, that we describe them to the best of our changing abilities. At its simplest, a single genome is a dynamic and heterogeneous macromolecular structure (enormous, containing on the order of at least 10^6 atoms) that, unlike almost all other intracellular macromolecules, which are far smaller (on the order of $10^{3\text{-}4}$ atoms), turns over or is reproduced with the cell. That the genome is, at its most basic structural level, an "aperiodic crystal" was predicted by Schrödinger at least one decade before the discovery of the double-helical structure of DNA (Schrödinger 1944). Across the domains of life, genomic DNA is an aperiodic and heterogeneous polymer of four chemicals (each monomer a nucleotide around 30 atoms in size). Genomic DNA can, with the appropriate enzymes and finite fidelity, catalyze the formation of a complementary macromolecule, which in turn can catalyze the formation of a molecule identical in sequence to the original. A sequence or length of genomic DNA is an intricate nanoscopic structure, or set of constraints on matter and energy, that has emerged and co-evolved in complex with tens to hundreds of other macromolecules (each also an intricate nanoscopic structure) to *encode* itself and these other macromolecules. It is a co-evolution that remains a total mystery. Nonetheless, understanding molecular structure as constraint(s) on the motion of matter and energy makes clear that genomes – and their co-dependent molecules – are constraints on energy release, essential to organizing the vast and intricate flows of matter and energy that go into the continual making, remaking, and reproduction

of a cell. Drawing on Stuart Kauffman's related insight linking constrained energy release and physical work (performed within or by an organism) to information (Kauffman 2000), it can be asserted that a genome is, or embodies, information for the cell of which it is a part. Thus, a genome is a sign nested within, interpreted by, and essential to a living cell.

Single living cells are Kantian wholes, but more open and less strongly individuated than Kant imagined. For instance, considering the bacteria *E. coli*, any single cell isolated from a laboratory or the wild can contain around 4,000 to 5,000 genes from a growing reservoir of more than 13,000 (can only speak in terms of an *E. coli* pangenome) (Brockhurst et al. 2019; Rasko et al. 2008); many of these genes are non-essential, where essentiality is ascertained by testing whether a cell without *gene x* can reproduce (under some set of conditions) (Hutchison et al. 2016; Yu et al. 2002). Thus, living cells have an openness that Kant's beautiful definition does not imply. Indeed, this openness makes evolution much less vertical than Darwin imagined, and means that a single bacterium can afford to maintain and reproduce parts that may not be essential to itself. In order to do so, living cells must accumulate constraint and the potential for energy release in excess of their immediate needs (Felipe A. Veloso, personal communication). It therefore seems productive to conceive of a living cell (and all living individuals including each of us) as an *open* Kantian whole. Further drawing on recent work by Terrence Deacon (2012; Sherman 2017), we can call each open Kantian whole *a self*.

Phenomena by the wayside: adaptive mutagenesis *et alia*

Two major modes of genetic change were long considered possible *a priori*: adaptive and random mutagenesis. By definition, adaptive or stress-induced mutagenesis is genetic mutation by and within an organism responding to stress. Adaptive mutagenesis is the opposite of (but not incompatible with) random or classical mutagenesis, which is independent of any adaptive action taken by the organism; and although most practicing biologists are unaware of the relevant findings and still smoldering debate,

it now seems well established that adaptive mutagenesis is a biological fact that we must accept (Fitzgerald et al. 2017; Foster 2007). Furthermore, adaptive mutagenesis does not require replication of genomic DNA, and the relevant kinds of stress are myriad: starvation, hypoxia, extreme pH, extreme temperature, sub-lethal dose of antibiotic, *etc.*

Some further history is in order: genetic mutation has been the subject of empirical study for over 150 years (at least since Mendel), since before the word *gene* was coined and before DNA was determined to be the linchpin of heredity. Salvador Luria and Max Delbrück began the empirical and analytical work necessary to distinguish between the major modes of mutation, and showed by statistical argument that mutations within *E. coli* conferring resistance to T1 phage (a virus of *E. coli*) pre-exist exposure (Luria and Delbruck 1943). These then likely arise randomly over the course of bacterial growth and reproduction. Although it has been repeatedly noted that an all-or-nothing stress (rapidly lethal to susceptible bacteria) like T1 phage should greatly reduce, if not completely eliminate, the possibility that the phenotype under selection by the experimenter (resistance to T1 phage) would emerge by adaptive mutagenesis, more than a few biologists were excited to project to the entire living world the most extreme implication of the results of Luria and Delbrück's now famous experiment – that *all* mutagenesis is random (i.e., independent of adaptive action taken by the organism itself). But starting a little over a decade later, several independent scientists began publishing data strongly suggesting the existence of adaptive mutagenesis (Cairns et al. 1988; Hall 1977; Ryan 1955; Ryan et al. 1955; Shapiro 1984). In the work of John Cairns *et al.*, strains of *E. coli* containing a defective version of a gene essential to lactose metabolism (*lacZ*) were challenged with growing on solid media containing lactose as the sole carbon source (Cairns et al. 1988). In at least one strain, colonies consistently emerged 1-2 days later than lactose-metabolizing colonies resulting from pre-existing mutations. Cairns interpreted the results of these and related experiments to indicate the existence of not only adaptive but potentially directed mutagenesis (i.e., somehow specific to the defective gene requiring the

appropriate mutation for growth to resume) (Cairns et al. 1988). His interpretation, especially concerning the potential directedness of adaptive mutagenesis, remains controversial for two very important reasons: 1) the bacterial challenge-experiments described hide enormous complexity (the observables are few relative to the multitude of factors – billions of cells, their dynamics and interactions), and some results seemingly consistent with adaptive mutagenesis can be explained without it (Ryan 1952; Roth and Andersson 2004); and 2) quite simply, adaptive mutagenesis rubs many a working biologist the wrong way – both through its apparent (but not actual) contradiction of random mutagenesis, and its inevitable suggestion of Lamarckism (a favorite punching bag, along with religion and spirituality, of certain card-carrying evolutionary biologists). Nevertheless, and as stated before, subsequent work has established that adaptive mutagenesis (by the basic definition given at the start of this section) does really occur, and may be universal to extant life (Fitzgerald et al. 2017; Foster 2007; Hall 1977; Hall 1998a; Hall 1998b; Hastings et al. 2004; Lombardo et al. 2004). Indeed, ample discovery has been made in the way of its molecular process and substance. For example, stress can induce a general transcriptional response resulting in the increased expression of low-fidelity and therefore error-prone polymerases (enzymes that synthesize DNA) leading to mutagenic repair of double-strand DNA breaks (Fitzgerald et al. 2017; Hastings et al. 2004). Genes encoding such polymerases are found throughout life; in bacteria as they are in humans. Thus, we now know that the nucleotide content of a genome within a living cell can depend, in part, on the environment as sensed. Uexküll, one of biosemiotic's fathers, would have concluded that the inner world of a bacterium (its *innenwelt*) becomes part of its world of action (its *umwelt*) under stress. This blurring of innenwelt and umwelt makes clear the fluid and indeterminate nature of even our most basic self-other distinction: that which traces a line around the visible boundaries of a single organism and severs it from the rest of its world.

Bacterial challenge experiments of the kind described above hide enormous complexity. Among other things, an experimenter is blind to interactions between cells (or sub-populations of cells) within

the population of bacteria being tested. Outside of laboratory test tubes and flasks, bacteria form colonies and biofilms: macroscopic structures containing billions of cells, and in the latter case a diversity of species, living alongside and interacting with each other. Inspired by the work of Hiroshi Fujikawa and Mitsugu Matsushita (1989) showing bacterial colonial morphologies reminiscent of the elegant structures of snowflakes and other self-organizing or azoic systems he so intensely studied, EBJ undertook work to explore how individual bacteria affect colonial structure, and how the colony affects individual bacteria (Ben-Jacob 1998; Ben-Jacob et al. 1992). To that end, EBJ *et al.* isolated a species of bacteria, *Paenibacillus dendritiformis*, which grows into colonies with distinct morphologies dependent on external conditions (hardness of substrate, nutrient density, temperature, humidity). EBJ recorded groups of individual cells within growing colonies by microscopy, and further studied the dynamics he observed by modelling the interactions among individual bacteria giving rise to colony formation. He also performed experiments to study the effects of a colony-level stress by abruptly changing growth conditions from those favoring one colonial morphology to another. EBJ reported a variety of stress-induced changes, from isolated bursts of morphological change to collective transitions spanning the entire border of a growing colony. His observations suggest that bacteria can coordinately adapt to stress in a variety of ways, and that the path taken resists facile predictability. These experiments further show, in ways at once more intimate and more global than typical bacterial challenge experiments, how adaptive bacteria are, and how, to borrow the physicist's phrase, non-trivial are their adaptive potentials.

Finally, we believe it is worth mentioning the results of experiments by Erez Braun *et al.* challenging yeast (a eukaryotic microbe) to adapt to a stress to which they already had the necessary solution (a certain fully functional gene) but placed by the experimenter in an unusual context (under a different promoter), making the gene inactive precisely when needed (Stern et al. 2007). In short, and for those more familiar with molecular biology, the experimenters placed *his3* (an essential gene) under

a galactose-inducible promoter; grew the modified cells in a bioreactor (a high-tech vessel for culturing microbes), then switched from growth media containing galactose to media containing glucose; thus, rendering the *his3* gene inactive. Unlike the bacterial challenge experiments of Cairns *et al.*, here the experimenters could not foresee a particular solution to the challenge posed. Growth of the yeast cells was monitored and periodic measurements of transcription (gene expression/activity) were made in sub-populations extracted from the well-mixed total. In duplicate experiments, the populations crashed shortly after yeast were switched to glucose, but completely recovered after approximately 20 generations. In each experiment, the population crash correlated with transient changes in the expression of hundreds of genes, followed by the resumption of growth and relaxation into a new and stable pattern of gene expression. Two results seem crucial: 1) yeast in both experiments adapt to the applied stress on the same time-scale; and 2) from both experiments, the sets of hundreds of genes undergoing a change in expression hardly overlap (around 15%). Furthermore, the hundreds of genes involved account for roughly one quarter of the genome and represent a diversity of functions; and many genes within any particular functional module showed opposing responses, either increasing or decreasing in response to the stress. Thus, the form of the adaptive response described here is both global and multifarious. Indeed, it suggests a spontaneity of feeling.

Your simplest self: feeling and the dynamics supporting it

As biologists, we are comfortable thinking and writing about stress to organisms, but we never concede the obvious: that biological stress requires biological feeling. Biological stress is legitimate, feeling is taboo; but the latter logically subsumes the former. We are comfortable with stress because the term suggests measurability; indeed, mechanical stress is measurable, but biological stress is not mechanical stress (although it can originate there). Simply, biological stress is acknowledged when we notice that something has perturbed an organism. We have a harder time noticing feeling, but there can be no such thing as biological stress without feeling. The bacterial and yeast challenge experiments described in the

previous section help force the logical realization that single cells (bacterial and eukaryotic) have a level of causal freedom that we as biologists have been trained to ignore. Single cells are living and therefore feeling creatures.

We wish to continue a speculative analysis of feeling partly in order to better define biological self-hood. So far, we have established that living individuals (a bacterium or a person, both *selves*) can be thought of as open Kantian wholes – an abstraction that is reductive (like all abstractions) but productive (in that it seems to mirror the world). Open Kantian wholes can experience stress and can therefore feel, but is feeling exclusive to selves? CS Peirce would say no, it is not. Nevertheless, biological feeling is clearly distinct in that it is part of the dazzling causal powers of living beings. To achieve a better understanding and attempt a consistent semiotic description, we believe a detour into what separates animate from inanimate process is necessary.

Life emerged billions of years ago on Earth from non-living substance and process. Although we do not (and perhaps cannot) know exactly how, we can marshal our full understanding of non-living phenomena to produce general and potentially illuminating models. The birth and ongoing development of complexity science from experimental and theoretical non-equilibrium physics have made the dynamical richness of the non-living world impossible to ignore, and greatly increased our understanding. At least a few compelling models relevant to the origins of life on Earth draw heavily from an understanding of self-organization (Bagley and Farmer 1991; Lerman 2010; Woese 1979); but almost all fail to offer a formal distinction between living and non-living systems (between Bateson's *Creatura* and *Pleroma*). Terrence Deacon's emergent dynamics is a clear exception (2012). Emergent dynamics is a metaphysical framework, and a qualitative generalization of thermodynamics to non-equilibrium conditions. Deacon recognizes three distinct dynamical regimes at play in the world: homeo- (or thermo-), morpho-, and teleo-dynamics. Homeodynamic or thermodynamic change is observed as a decrease in constraint within a system; where constraint is roughly equivalent to order, and is therefore

the inverse of entropy. Morphodynamic change (i.e., that characteristic of abiotic *self-organizing* phenomena) is observed as an increase in constraint within a system. Finally, teleodynamic change is observed as the preservation of constraint within a system and/or the reproduction of the whole system of constraints into more such systems of constraints. Like Peirce's icon, index, and symbol, teleodynamics depends on (emerges from) morphodynamics, which depends on homedynamics. Following this logic, we, and all other living things exclusively, are teleodynamic beings; our defining modes of change result from special relationships among morphodynamic systems, which result from special relationships among homeodynamic systems.

In order to better understand the nature of extant life (including biological feeling), let us compare the simplest conceivable teleodynamic system, Deacon's autogen model, to a bacterium, the simplest extant self. The autogen is the model of a molecular system/process resulting from two co-dependent and complementary morphodynamic (or *self-organizing*) processes. First, each member of a particular set of molecules catalyzes the formation of at least one other member from food (substrate), forming an autocatalytic set; and second, at least one member molecule also catalyzes the formation of a polymerizing molecule that self-assembles, above some threshold concentration, into a container that can enclose and partition members of the autocatalytic set *away* from food. In principle, the autogen can persist as an inert (but poised) virus-like structure before somehow rupturing and reproducing in the presence of food. Thus, the autogen appears to be a Kantian whole (a proto-self) that cycles into and out of equilibrium. While a bacterium is an *open* Kantian whole (a self as defined earlier) that is persistently out of equilibrium – sensing, feeling, and acting its way through its umwelt. The distance between the autogen and the simplest extant self is vast. Indeed, a single bacterium remains an unfathomed richness of structure and process.

The above was necessary to illustrate what separates (and joins) living and non-living process, and to begin concluding our preliminary discussion of feeling. Following Peirce's logic of the continuity

of mind, feeling is immanent in the universe; but the biological or organismic forms of it must be as radically distinctive from non-living forms as the dynamics of life are from those of non-living process. We believe that biological feeling requires and issues uniquely from the occurrence of pure potential within teleodynamic process. By pure potential, we mean the *res potentia* of Kauffman *et al.'s* interpretation of quantum mechanics (Kastner et al. 2018). Only the ontological freedom afforded by quantum coherence (and decoherence and recoherence) occurring within teleodynamic constraints can enable what we mean by biological feeling: a greatly varying *freedom-to* in service of survival and reproduction. In Peircian terms, we would argue that biological feeling is pre-iconic. It is the semiotic firstness of life, and the ground for further biosemiosis.

The feeling experienced by a single bacterium is nothing like (i.e., it is incomprehensibly remotely like) our feeling. Indeed, we are unquantifiably more complex than bacterial selves (our ancient ancestors and endosymbionts), being separated from them and their interiority by an untold hierarchy of teleodynamic process (Deacon and Koutroufinis 2014). Regarding self-awareness, we can say only that from our own limited conscious experience, self-awareness is not always achieved in the life of a human being; and when it is found, it waxes and wanes, sometimes disappearing. But feeling is different. Feel bacteria do, like me and you.

Bacterial learning

Having established that bacteria and all living selves feel, and having begun a characterization of biological feeling and its origins, we now wish to conjecture on the semiotic abilities of bacteria. Kalevi Kull describes four types (or mechanisms) of learning (Kull 2018). He relates them to Peircian categories of sign and also explores their Uexküllian dimensions. Does adaptive mutagenesis fit any of these? A fully undirected adaptive mutagenesis seems iconic or pre-iconic; but we cannot adequately answer this question here. We will instead assume that individual bacteria, living selves with myriad sensing and

adaptive abilities, readily interpret features of their umwelt iconically. The question that succeeds this assumption is interesting and can be answered empirically: can a bacterium link two icons into an index? Kull calls the process underlying the formation of an index from icons (two or more), conditioning. All mammals do this, and it is not unlikely that all multicellular selves do too. Indeed, pea seedlings are able to associate the direction of air flow from a fan (the *conditioned stimulus*) with the likely direction of blue light (the *unconditioned stimulus*) (Gagliano et al. 2016). But can a bacterium interpret indexically? We propose and roughly outline a doable experiment. A single bacterium can be confined to a microfabricated chamber and kept alive for days (Yang et al. 2019). Two such chambers connected via a long and narrow channel (dimensions with respect to the size of the bacterium will be important) could be made and used to house a single bacterium (a flagellated *E. coli*, say), with the bacterium free to swim between chambers. A different stimulus (or sign) can be applied at one end of each chamber periodically: for example, a pulse of coherent red or blue light (a conditioned stimulus) can be applied every 15 minutes at one end of one chamber, followed several minutes later by a small amount of glucose (a *yummy* unconditioned stimulus) at one end of the opposite chamber. Along with many replicate experiments, and the appropriate control experiments, the statistics of movement of individual bacteria could then be analyzed for behavior consistent with conditioning. Similar experiments with a different readout could also be performed to test bacterial colonies for their ability to form indices.

Conclusions

Bacteria are open Kantian wholes endowed with feeling. The smallest and simplest selves known, they remain far removed from the world of abiotic morphodynamic phenomena – indeed, though clearly of the universe, like us and everything else, their multifarious paths of emergence within it remain profoundly mysterious. It remains to be seen whether bacterial selves possess semiotic abilities more readily associated with far more complex multicellular selves; perhaps they, and every individuated locus of organismic feeling (every living being), are capable of forming indices among the many iconic

signs of their umwelt. Indeed, a micro-biosemiotics is just beginning; and a single bacterium remains an unfathomed richness of structure and process.

Bibliography

BAGLEY, Richard J., and J. Doyne FARMER.

1991 "Spontaneous Emergence of a Metabolism". in *Artificial Life II*, ed. Christopher Langton, C. Taylor, J. Farmer and S. Rasmussen (Redwood City, CA: Addison-Wesley), 93-140.

BAR-ON, Yinon M., Rob PHILLIPS, and Ron MILO.

2018 "The biomass distribution on Earth", *Proceedings of the National Academy of Sciences of the United States of America* 115.25, 6506-11. https://doi.org/10.1073/pnas.1711842115

BEN-JACOB, Eshel.

1998 "Bacterial wisdom, Gödel's theorem and creative genomic webs", *Physica A: Statistical Mechanics and its Applications* 248.1-2, 57-76. https://doi.org/10.1016/S0378-4371(97)00529-3

BEN-JACOB, Eshel, Haim SHMUELI, Ofer SHOCHET, and Adam TENENBAUM.

1992 "Adaptive self-organization during growth of bacterial colonies", *Physica A: Statistical Mechanics and its Applications* 187.3-4, 378-424. https://doi.org/10.1016/0378-4371(92)90002-8

BOTO, Luis.

2010 "Horizontal gene transfer in evolution: facts and challenges", *Proceedings of the Royal Society B: Biological Sciences* 277.1683, 819-27. https://doi.org/10.1098/rspb.2009.1679

BRAGA, Adriana, and Robert K. LOGAN.

2017 "The Emperor of Strong AI Has No Clothes: Limits to Artificial Intelligence", *Information* 8.4, 156. https://doi.org/10.3390/info8040156

BROCKHURST, Michael A., Ellie HARRISON, James P.J. HALL, Thomas RICHARDS, Alan MCNALLY, and Craig MACLEAN.

2019 "The Ecology and Evolution of Pangenomes", *Current Biology* 29.20, 1094-103. https://doi.org/10.1016/j.cub.2019.08.012

CAIRNS, John, Julie OVERBAUGH, and Stephan MILLER.

1988 "The origin of mutants", *Nature* 335.6186, 142-5. https://doi.org/10.1038/335142a0

DAMER, Bruce.

2010 "The Singularity is Far", presentation given by Bruce Damer at the Singularity University, slides accessed from *https://www.slideshare.net/bdamer/the-singularity-is-far-singularity-u-presentation-by-bruce-damer-aug-2010*, on 25 November 2019.

DEACON, Terrence, and Spyridon KOUTROUFINIS.

2014 "Complexity and Dynamical Depth", *Information* 5.3, 404-23. https://doi.org/10.3390/info5030404

DEACON, Terrence.

2012 Incomplete Nature: How mind emerged from matter. (New York: W.W. Norton & Co.).

FITZGERALD, Devon M., P.J. HASTINGS, and Susan M. ROSENBERG.

2017 "Stress-Induced Mutagenesis: Implications in Cancer and Drug Resistance", *Annual Review of Cancer Biology* 1, 119-40. https://doi.org/10.1146/annurev-cancerbio-050216-121919

FOSTER, Patricia L.

2007 "Stress-Induced Mutagenesis in Bacteria", *Critical Reviews in Biochemistry and Molecular Biology* 42.5, 373-97. https://doi.org/10.1080/10409230701648494

FUJIKAWA, Hiroshi, and Mitsugu MATSUSHITA.

1989 "Fractal Growth of *Bacillus subtilis* on Agar Plates", *Journal of the Physical Society of Japan* 58.11, 3875-78. https://doi.org/10.1143/JPSJ.60.88

GAGLIANO, Monica, Vladyslav V. VYAZOVSKIY, Alexander A. BORBÉLY, Mavra GRIMONPREZ, and Martial DEPCZYNSKI.

2016 "Learning by Association in Plants", *Scientific Reports* 6.38427. https://doi.org/10.1038/srep38427

HALL, Barry G.

1977 "Number of Mutations Required to Evolve a New Lactase Function in *Escherichia coli*", *Journal of Bacteriology* 129.1, 540-3.

1998a "Adaptive Mutagenesis at *ebgR* Is Regulated by PhoPQ", *Journal of Bacteriology* 180.11, 2862-5.

1998b "Adaptive mutagenesis: a process that generates almost exclusively beneficial mutations", *Genetica* 102.0, 109-25. https://doi.org/10.1023/A:1017015815643

HAMILTON, Trinity L., Annastacia C. BENNETT, Senthil K. MURUGAPIRAN, and Jeff R. HAVIG.

2019 "Anoxygenic Phototrophs Span Geochemical Gradients and Diverse Morphologies in Terrestrial Geothermal Springs", *mSystems* 4.6. https://doi.org/10.1128/mSystems.00498-19

HASTINGS, P.J., Andres SLACK, Joseph F. PETROSINO, and Susan M. ROSENBERG.

2004 "Adaptive Amplification and Point Mutation Are Independent Mechanisms: Evidence for Various Stress-Inducible Mutation Mechanisms", *PLOS Biology* 2.12. https://doi.org/10.1371/journal.pbio.0020399

HUTCHISON III, Clyde A., Ray-Yuan CHUANG, Vladimir N. NOSKOV, Nacyra ASSAD-GARCIA, Thomas J. DEERINCK, Mark H. ELLISMAN, John GILL, Krishna KANNAN, Bogumil J. KARAS, Li MA, James F. PELLETIER, Zhi-Qing QI, R. Alexander RICHTER, Elizabeth A. STRYCHALSKI, Lijie SUN, Yo SUZUKI, Billyana TSVETANOVA, Kim S. WISE, Hamilton O. SMITH, John I. GLASS, Chuck MERRYMAN, Daniel G. GIBSON, and J. Craig VENTER.

2016 "Design and synthesis of a minimal bacterial genome", *Science* 351.6280. https://doi.org/10.1126/science.aad6253

KANT, Immanuel.

1790 Critic der Urteilskraft. English trans. by J.H. Bernard as Kant's Critique of Judgement. (London, 1914).

KARLEY, Dugeshwar, Sudhir K. SHUKLA, and Toleti Subba RAO.

2018 "Isolation and characterization of culturable bacteria present in the spent nuclear fuel pool water", *Environmental Science and Pollution Research* 25.11, 20518-26. https://doi.org/10.1007/s11356-017-0376-5

KASTNER, R.E., Stuart KAUFFMAN, and Michael EPPERSON.

2018 "Taking Heisenberg's Potentia Seriously", *arXiv.* https://arxiv.org/abs/1709.03595

KAUFFMAN, Stuart.

2000 Investigations. (New York: Oxford University Press, Inc.).

2016 Humanity in a Creative Universe. (New York: Oxford University Press, Inc.).

KNIGHT, Rob, Chris CALLEWAERT, Clarisse MAROTZ, Embriette R. HYDE, Justine W. DEBELIUS, Daniel MCDONALD, and Mitchell L. SOGIN.

2017 "The Microbiome and Human Biology", *Annual Review of Genomics and Human Genetics* 18, 65-86. https://doi.org/10.1146/annurev-genom-083115-022438

KULL, Kalevi.

2018 "On the Logic of Animal Umwelten: The Animal Subjective Present and Zoosemiotics of Choice and Learning". in *Semiotics of Animals in Culture*, ed. Gianfranco Marrone and D. Mangano (Springer International Publishing), 135-48. https://doi.org/10.1007/978-3-319-72992-3_10

LERMAN, Louis.

2010 "The Primordial Bubble: Water, Symmetry Breaking, and the Origin of Life". in *Water and Life: The Unique Properties of H_2O*, ed. Ruth M. Lynden-Bell, S.C. Morris, J.D. Barrow, J.L. Finney, and C.L. Harper, Jr. (Boca Raton, FL: CRC PRESS/Taylor & Francis Group), 259-90.

LOMBARDO, Mary-Jane, Ildiko APONYI, and Susan M. ROSENBERG.

2004 "General Stress Response Regulator RpoS in Adaptive Mutation and Amplification in *Escherichia coli*", *Genetics* 166.2, 669-80. https://doi.org/10.1534/genetics.166.2.669

LURIA, S.E., and M. DELBRÜCK.

1943 "Mutations of Bacteria from Virus Sensitivity to Virus Resistance", *Genetics* 28.6, 491-511.

MAKAROVA, Kira S., L. ARAVIND, Yuri I. WOLF, Roman L. TATUSOV, Kenneth W. MINTON, Eugene V. KOONIN, and Michael J. DALY.

2001 "Genome of the Extremely Radiation-Resistant Bacterium *Deinococcus radiodurans* Viewed from the Perspective of Comparative Genomics", *Microbiology and Molecular Biology Reviews* 65.1, 44-79. https://doi.org/10.1128/MMBR.65.1.44-79.2001

MERINO, Nancy, Heidi S. ARONSON, Diana P. BOJANOVA, Jayme FEYHL-BUSKA, Michael L. WONG, Shu ZHANG, and Donato GIOVANNELLI.

2019 "Living at the Extremes: Extremophiles and the Limits of Life in a Planetary Context", *Frontiers in Microbiology* 10.780. https://doi.org/10.3389/fmicb.2019.00780

RAMIREZ, Gustavo A., Arkadiy I. GARBER, Aurélien LECOEUVRE, Timothy D'ANGELO, C. Geoffrey WHEAT, and Beth N. ORCUTT.

2019 "Ecology of Subseafloor Crustal Biofilms", *Frontiers in Microbiology* 10.1983. https://doi.org/10.3389/fmicb.2019.01983

RASKO, David A., M.J. ROSOVITZ, Garry S.A. MYERS, Emmanuel F. MONGODIN, W. Florian FRICKE, Pawel GAJER, Jonathan CRABTREE, Mohammed SEBAIHIA, Nicholas R. THOMSON, Roy CHAUDHURI, Ian R. HENDERSON, Vanessa SPERANDIO, and Jacques RAVEL.

2008 "The Pangenome Structure of *Escherichia coli*: Comparative Genomic Analysis of *E. coli* Commensal and Pathogenic Isolates", *Journal of Bacteriology* 190.20, 6881-93. https://doi.org/10.1128/JB.00619-08

ROTH, John R., and Dan I. ANDERSSON.

2004 "Adaptive Mutation: How Growth under Selection Stimulates Lac^+ Reversion by Increasing Target Copy Number", *Journal of Bacteriology* 186.15, 4855-60. https://doi.org/10.1128/JB.186.15.4855-4860.2004

RYAN, Francis J.

1952 "Distribution of Numbers of Mutant Bacteria in Replicate Cultures", *Nature* 169.4308, 882-3. https://doi.org/10.1038/169882b0

1955 "Spontaneous Mutation in Non-Dividing Bacteria", *Genetics* 40.5, 726-38.

RYAN, Francis J., Miriam SCHWARTZ, and Phyllis FRIED.

1955 "The Direct Enumeration of Spontaneous and Induced Mutations in Bacteria", *Journal of Bacteriology* 69.5, 552-7.

SCHRÖDINGER, Erwin.

1944 What is Life? (New York: Cambridge University Press, 2018).

SHAPIRO, James A.

1984 "Observations on the formation of clones containing *araB-lacZ* cistron fusions", *Molecular and General Genetics* 194.1-2, 79-90. https://doi.org/10.1007/BF00383501

SHERMAN, Jeremy.

2017 Neither Ghost nor Machine: The Emergence and Nature of Selves. (New York: Columbia University Press).

STERN, Shay, Tali DROR, Elad STOLOVICKI, Naama BRENNER, and Erez BRAUN.

2007 "Genome-wide transcriptional plasticity underlies cellular adaptation to novel challenge", *Molecular Systems Biology* 3.106. https://doi.org/10.1038/msb4100147

WOESE, C.R.

1979 "A Proposal Concerning the Origin of Life on the Planet Earth", *Journal of Molecular Evolution* 13.2, 95-101. https://doi.org/10.1007/BF01732865

YANG, Yifan, Ana L. SANTOS, Luping XU, Chantal LOTTON, Francois TADDEI, and Ariel B. LINDNER.

2019 "Temporal scaling of aging as an adaptive strategy of *Escherichia coli*", *Science Advances* 5.5. https://doi.org/10.1126/sciadv.aaw2069

YU, Byung Jo, Bong Hyun SUNG, Michael D. KOOB, Choong Hoon LEE, Jun Hyoung LEE, Won Sik LEE, Mi Sun KIM, and Sun Chang KIM.

2002 "Minimization of the *Escherichia coli* genome using a Tn5-targeted Cre/loxP excision system", *Nature Biotechnology* 20.10, 1018-23. https://doi.org/10.1038/nbt740