

In Search for the Definition of Life

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Abstract

Although many attempts have been made to explain what life is, the high diversity of behavioral and structural properties of living creatures makes it difficult to formulate a comprehensive definition of life. Among the many signs of life, the one which seems truly ubiquitous is effort expended on maintaining the internal environment in living constructs independent of its surroundings. Stability of the internal environment is based on automatic regulation, which, in turn, depends on negative feedback. Manifestation of features produced by this effort is taken as the most specific sign of life. Hence, automatism of regulation differentiates living creatures from inanimate objects. The paper explains why regulation needs to be automatic, and discusses those attributes of automatic regulation which are particularly relevant in the context of life.

Keywords: Criterion of life; Thermodynamics of life; Automatism and life; Homeostasis of living creatures; Independence of automatic regulation

Introduction

The phenomenon of life has intrigued mankind since the dawn of time. In ancient times it was studied, among others, by Aristotle and Socrates. In our own age, it represents a popular subject of research for philosophers and biologists alike. In approaching the subject, scholars have historically formed two camps, those, who asserted the existence of an unseen “life force” also referred to as *vis vitalis* (hence the term “vitalists”) and those, for whom life was an emanation of the laws of physics, chemistry and biology (also called “mechanists”).

The immense progress in genetics at the turn of the 20th century elevated this debate to an entirely new level-it now became possible to attempt to trace back life to specific genes. Such new concepts, however, necessitated enumeration of specific aspects of life for which individual genes would bear responsibility-or example, motility, fertility, metabolism, mutability and so on.

Unfortunately, it soon turned out that when the principles of life are defined in such broad terms, almost all genes turn out to contribute to one aspect or another. Consequently, the proposed paradigm does not really answer the basic question, i.e., “what is life?” Furthermore, not all of the proposed aspects seem equally important, for instance, plants are undoubtedly alive, yet incapable of locomotion. Many cells-such as neurons-endure, even though they lack the ability to multiply. Seeds, which are also commonly thought of as being alive, have no metabolism to speak of. Even evolution does not apply equally to all living things-some organisms are exceptionally well conserved while others undergo frequent mutations [1,2]. Note also that some cells fulfill special functions which are not usually thought of as being “essential for life”. The question therefore remains-what is the most basic, immanent feature of life? What process or mechanism can be thought of as the foundation of this phenomenon?

The famous philosopher Claude Bernard suggested that life requires autonomy, i.e., the capacity to make decisions. This criterion does indeed apply to all living biological constructs; however, autonomy is commonly associated with automatism, i.e., regulation, where decisions are undertaken by an internal regulatory system.

As a rule, dynamic systems reflect the properties of their regulatory mechanisms. Autonomy, understood as the capability of the regulatory

system to make decisions depending on environmental conditions, is essentially automatic in scope; hence it seems logical that living construct must base their processes on some forms of automatic control.

Automatic Regulation, Thermodynamic Background

From the point of view of thermodynamics, all living things are open systems, i.e., they never reach a state of thermodynamic equilibrium. While metabolism may produce a state of *quasi*-equilibrium, such a state differs markedly from chemical equilibrium. In biology, a set of mutually counterbalancing processes ensures constant, dynamic, balanced supply of substrates so as to maintain homeostasis. In thermodynamics, this is formally referred to as a steady state. Maintaining such a state in a cell, or an organism, is an obvious, critical prerequisite for the functioning of biological constructs commonly thought of as being “alive”. Such construct will actively counteract disruptive stimuli and attempt to revert to their steady state whenever possible. We can therefore assume that the existence of a steady state is a key property of all living things [3].

When a system is thermodynamically closed, its internal processes tend to a thermodynamic equilibrium, which effectively terminates those processes. A system in equilibrium has no spontaneity, and therefore no capacity for action. This lack of spontaneity precludes life (Figure 1) [3]. In contrast, in a thermodynamically open system (i.e., any biological system)-each process may be equilibrated at a certain, preset level, ensuring balance while also permitting certain spontaneity (Figure 2A and 2B). This condition can only be maintained when substrates are in supply while reaction products are removed at a set rate – aspects which fall in the scope of automatic regulation. The configuration of a detector (receptor) determines the system’s set point (Figure 2C and 2D).

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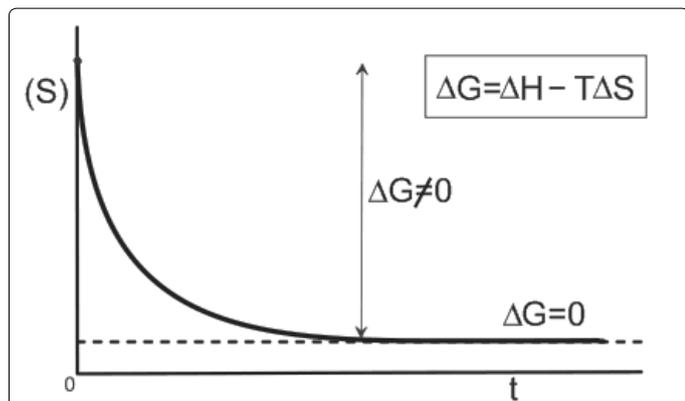


Figure 1: Standard kinetics of the chemical process (degradation) with marked area of spontaneity ($\Delta G \neq 0$) S-substrate, t-time, ΔG -change in free energy. ΔH -change in enthalpy, ΔS -change in entropy, K-temperature (in degrees Kelvin).

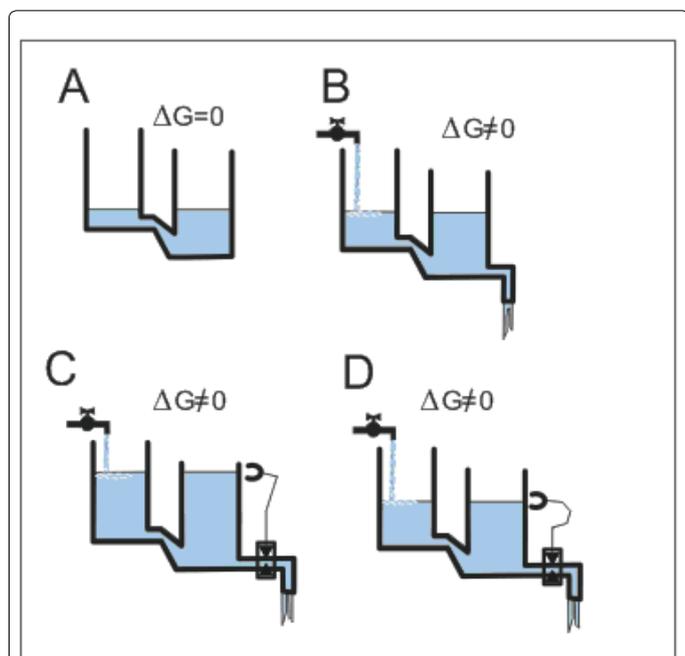


Figure 2: Model exposing the need for automatic regulation. The setting (affinity) of the detector (receptor) determines the desired quantity of water (product). A-closed system B-D-open systems.

Regulation may control processes in each individual cell, as well as within the organism as a whole-the latter condition is commonly referred to as homeostasis and concerns such issues as regulated supply of blood and other bodily fluids. As with most types of regulation, such mechanisms are based on negative feedback loops, a classic concept supplied by automation theory (Figure 3) [3].

Given the size and complexity of the organism, the necessary signaling may not follow the same principles as within each cell, and instead requires dedicated structures-hormonal and neural pathways. Here, the function of the organism is to coordinate the action of cell groups, while each cell is responsible for metabolism. The relation between the organism and the cell is necessarily hierarchical-signals sent by the organism to selected cells are treated as commands which must be obeyed to ensure homeostasis, even at a detriment to the cell itself [3]. In both systems, however, regulation remains automatic and

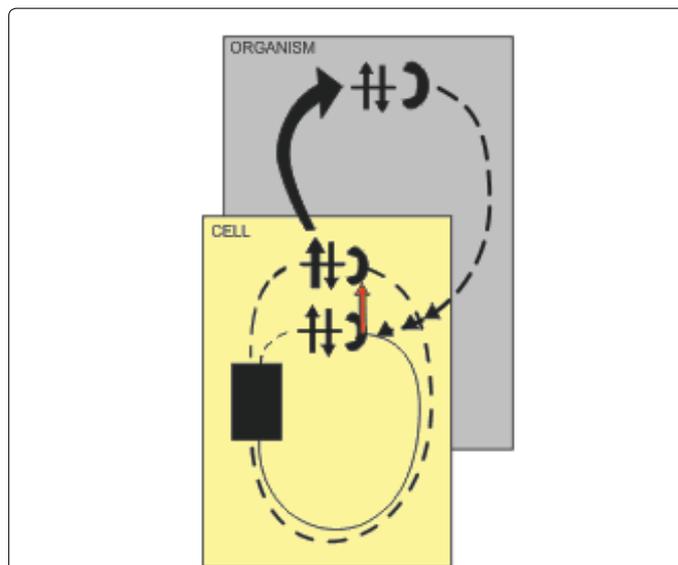


Figure 3: Hierarchical coupling of the organism and cell regulation (example). Organic signals (hormones) force the cell to increase its activity by changing the affinity of the corresponding receptor (red arrow), thus supplying extra products for the organism.

cells are only periodically engaged in meeting the demands of the organisms. The autonomy of this relation can be construed as another aspect of life, in any biologically active system; stability is produced by internal regulation. A cell forced to perform a task for the benefit of the organism will actively seek to counteract the “command signal”, for instance through using of G proteins.

The Genetic Basis of Life-Fundamental Elements of the Process

In living organisms, each function is, necessarily, dependent on a variety of genes which condition the given regulatory (feedback) loop by describing its receptors and effectors (Figure 4). A feedback loop can even be thought of as a structural and functional unit in its own right; it carries full information regarding the given function and its structural underpinnings. More specifically, it answers the following questions, “what?”, “how?” and “how much?” (Figure 5), explaining which product is subject to control (“what?”), in what way it can be produced (“how?”) and what its required concentration should be (“how much?”). Feedback loops are building blocks for any animate matter, while each automatically regulated function has the property of being autonomous [3]. Structures associated with a given function represent an integral whole-they comprise a regulatory circuit based on a negative feedback loop.

When trying to determine the fundamental aspects of life, it is useful to consider properties and functions which remain constant and ubiquitous despite the structural and functional diversity of cells. Genes which condition these properties are sometimes called “housekeeping genes” they mainly concern metabolism, i.e., energy management, and the synthesis of basic structures, through transcription and translation of genetic material. Housekeeping genes are exceptionally well conserved, and usually found in central parts of chromosomes, where they are protected from meiotic recombination [4].

Another crucial set of genes concerns synthesis of components of the cellular membrane, which self-associate to form micellar sheets, owing to their neutral charge distribution (Figure 6). The cellular membrane

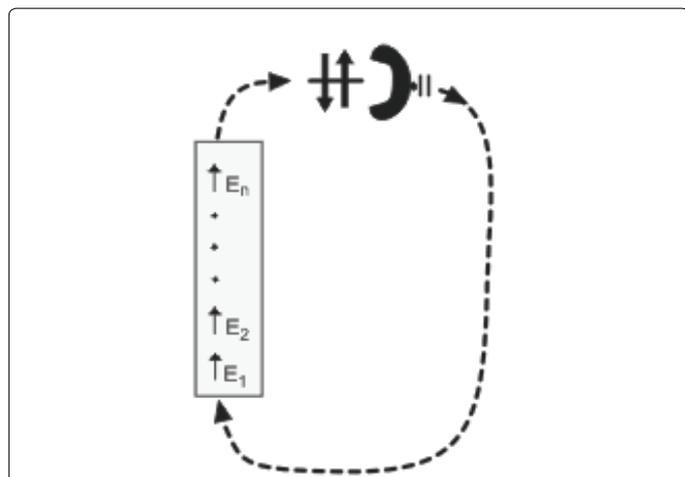


Figure 4: Schematic view (model) of the feedback inhibition with its main components, receptor and effector. Arrows in the effector indicate successive catalytic steps of the controlled process (e.g., synthesis of a desired product).

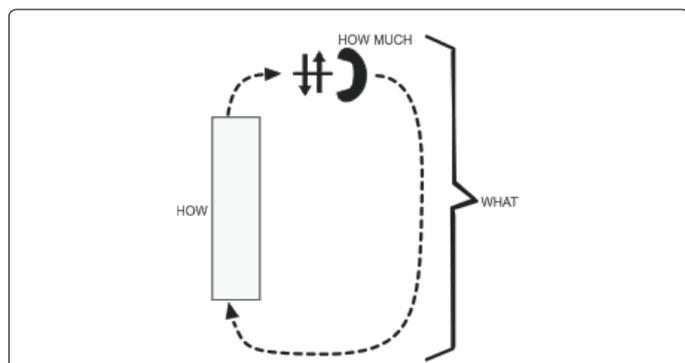


Figure 5: Schematic model of the feedback inhibition unit with indication of constituents which carry information ("What ?", "How ?" and "How much ?").

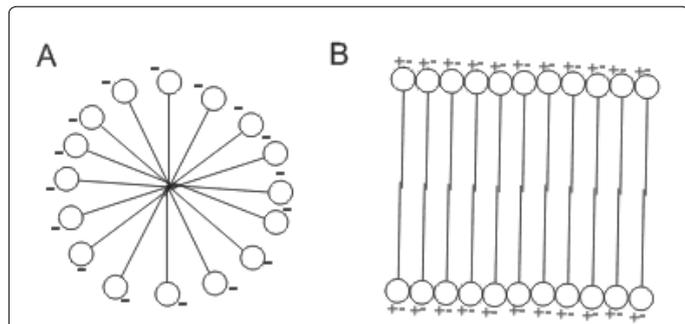


Figure 6: Synthesis of self-assembling phospholipid compounds. Neutralization of electrostatic repulsion is necessary for tight micellar packing and membrane formation.

is a fundamental requirement in any living system. By enclosing a small volume, it enables many other regulatory processes to function simply by measuring the concentrations of selected substances. Given the variety of intracellular processes, any other solution would be overly complex and unreliable. The simplicity of the presented system enables encapsulation of many critical processes within the cell itself. Changes in concentrations can be quickly detected and acted upon. Additionally, the cellular membrane creates favorable conditions for controlled

exchange metabolism products with the environment. Without it, no accurate control over the concentrations of substrates and products could be affected, the system would not be able to reach a steady state and life would not be possible.

The simplicity by which signals are transmitted inside the cell is fundamentally important and facilitated by the small volume of the cell itself. This is why cells are uniformly small, regardless of whether they make up a mouse or an elephant.

Allosteric Structures-Fundamental Components of Life

Automatic regulation calls for protein- or RNA-based structures which possess allosteric properties, i.e., can undergo conformational changes affecting two separate active groups. Usually, this effect is obtained through association of separate proteins and formation of oligomers with distinct subunits, exhibiting varying degrees of affinity for their respective ligands [5-13].

Evolutionarily conditioned association of enzymes involved in successive steps of complex reactions was probably the "blueprint" for allosteric structures, where components of regulatory systems bind together, radically simplifying their internal communication (Figure 7). Such proteins often act as receptors, consisting of regulatory and catalytic subunits and ensuring the operation of negative feedback loops. Thus, genetically encoded allosteric effects can be proposed as another immanent property of life.

The Biological Clock-An Important Component of Life

Another noteworthy phenomenon irrevocably associated with life involves biological structures whose purpose it is to measure time [14-18]. Their function drives cyclical processes, both within the cell and the organism as a whole. Many types of biological clocks have been described. The most commonly referenced one-the circadian cycle-does not appear strictly necessary, however its ubiquitous nature betrays its importance. Special cellular structures have been described, providing a constant time base (Figure 8).

These structures take on many different forms. For example, cyanobacteria and erythrocytes are capable of recognizing the circadian cycle; however they employ different structures than those used by organisms and eukaryotic cells [19-21]. The multitude of ways by which evolution has come up with ways to measure time further underscores

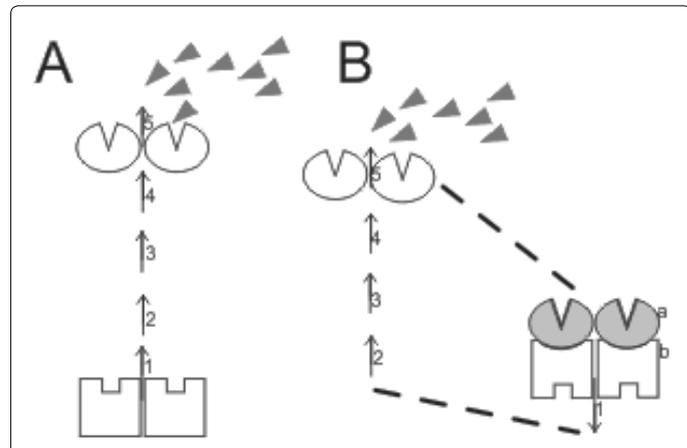


Figure 7: Hypothetical mechanism of formation of cell-regulatory enzymes, constructed from genetically modified distal enzymatic components of a multi-step processes.

the fundamental nature of this mechanism. The circadian cycle is an important determinant of metabolic processes [22-26], but it also appears to play another critical role-it encourages cells and organisms to remain active. Systems based on negative feedback naturally tend to minimize fluctuations. In the context of life, this phenomenon is undesirable, since it results in quiescence. Cyclical changes counteract this trend by promoting activity; hence oscillatory mechanisms appear beneficial for living constructs.

All of the abovementioned properties can be explained on the basis of current knowledge. It is, however, possible that the presented set will undergo further expansion.

In Search for a Minimal Set of Genes

Recent developments in genetics have led to attempts to reduce the observed genome to a “minimal” set of genes necessary to support life. Analyses of bacterial genomes have singled out life forms in which only several hundred genes exist. One example is *Mycoplasma genitalium*-a bacterium, which is capable of functioning while expressing only 477 genes [27-32]. Attempts to further prune this-already quite small-pool of genes or to design synthetic “minimal genomes” have been made [27-32]. Nevertheless, it is difficult to establish a strict lower limit, as the presented criterion appears somewhat fuzzy. The search for minimal genomes which still support some aspects of life may reveal deeper correlations between both concepts. In attempting to define life, we can also refer to natural biological systems with limited complexity, based on automatic regulation. An interesting example is the erythrocyte-an incomplete cell, lacking a nucleus and incapable of reproduction. In spite of these properties, the erythrocyte has a stable metabolism, subject to automatic control, as well as a definite lifespan [33-35]. Erythrocyte metabolism involves mostly glycolysis and the pentose cycle. Metabolic processes supply energy in the form of ATP and reduced nucleotides (NADH, NADPH)-compounds, which protect the erythrocyte against oxidative stress. Erythrocytes play an important role in the organism, they deliver oxygen to tissues. As they circulate in the bloodstream, they encounter a variety of conditions which they must adapt to. They

are also subject to structural stress as they squeeze through capillary vessels. While they are deeply involved in gas and ion exchange, they must maintain a stable internal environment, and for this purpose they are equipped with automatic control mechanisms. The erythrocyte is therefore a living construct, and nature treats it as such-it has a finite lifespan and a mechanism by which it undergoes controlled death (a process known as eryptosis (Figure 9).

By equipping biological systems with a “death clock” nature itself determines what is alive and what isn’t. Under this criterion viruses should not be considered alive, since the metabolism associated with their activity is supplied by the cell, not the virus itself. They also do not create their own environment (which would require automatic control), and do not possess any evolutionarily conditioned death mechanism. Consequently, they are not regarded as living constructs-rather, they represent parasitic information packets.

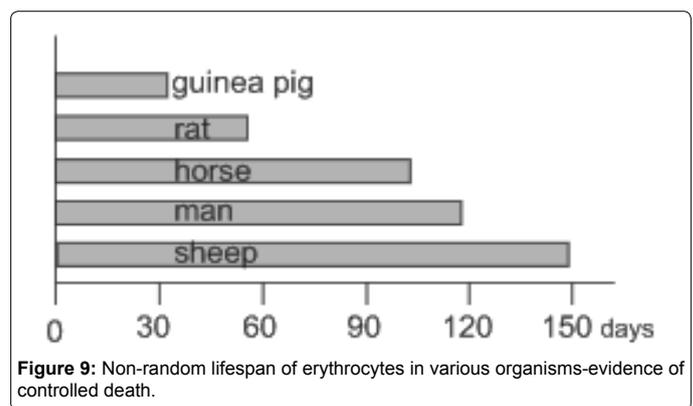
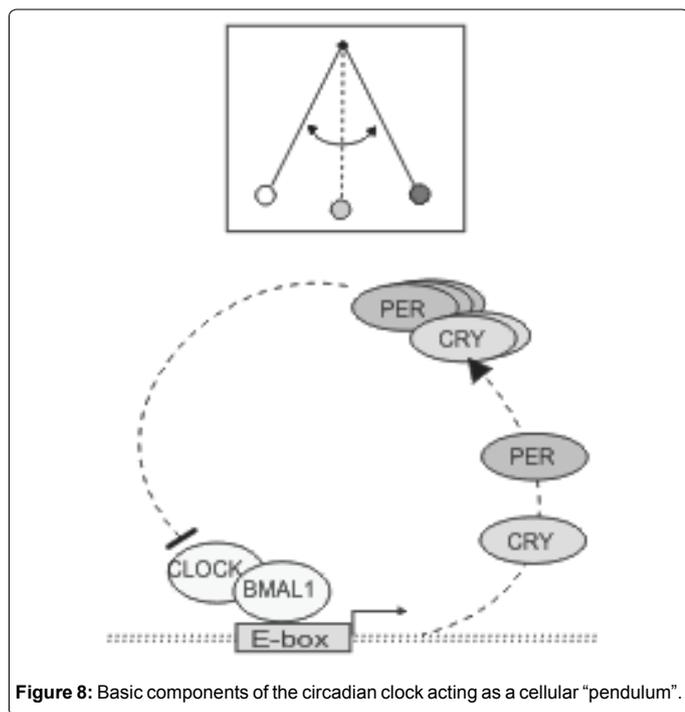
The death of living construct is an integral component of nature [36]. Cancer cells, while functionally immortal, eventually suffer a catastrophic death together with their host organism.

Autocatalysis and Its Involvement in Creating Life

Some theories regarding life invoke the phenomenon of autocatalysis, described as a cyclical process, a hypercycle, a chemoton or an ACS (collectively auto-catalytic set) [37-42]. The model possesses interesting dynamics; however its nature does not reflect the mechanisms which produce a stationary state in a living cell. The classical definition of autocatalysis involves amplification and is therefore more akin to positive feedback, which organisms (or cells) occasionally employ to strongly amplify and/or modify a given signal. Amplification does not, however, promote stability and must be subject to regulation, which reflects the main type of automatism present in a cell (following over three billion years of evolution) [43]. Note that autocatalysis may have played an important part in the prebiotic era, enabling rapid acceleration of the synthesis of organic compounds, and promoting processes which eventually produced organic matter. While there is some evidence regarding the role of autocatalytic processes, their involvement in the formation of life remains hypothetical?

The Origin of Life on Earth - A Hypothetical Path towards Automatic Regulation

Life most likely emerged in the vicinity of volcanic vents situated on the seabed [44-46]. Its creation was promoted by temperature gradients and high levels of sulfur, phosphorus and various metals. Under these conditions catalysis processes must have been widespread [47-64], eventually leading to synthesis of hydrocarbons and polar compounds. This, in turn, engendered self-organization, including creation of



micellar membranes [65-71]. Energy would have been supplied in the form of polyphosphates, and later-nucleoside triphosphates [72]. Catalytic synthesis of polymers became possible [73,74], and when enclosed in liposomal bubbles-provided a starting point for regulatory mechanisms, particularly the synthesis and replication of polymeric forms of RNA occurring in enclosed spaces [75-78]. The consequent product-based inhibition of such processes led to negative feedback loops, which, in time, became the dominant controlling factor, ensuring environmental stability.

Modern robotics exploits the similarities between mechanical constructs and living organisms, by providing such constructs with ever greater autonomy [79]. This increase in autonomy is achieved by integrating additional regulatory circuitry in a manner similar to the evolution of the nervous system [80]. Linking distinct circuits in such a way that the signal generated by one circuit acts upon the receptor of another circuit fosters a qualitative leap [2], which may be reinforced by increasing the complexity of the resulting regulatory network.

The French philosopher and cybernetician Pierre de Latile rated the progressive independence of biological systems by referring to the notion of freedom, which involved two aspects, "What?" and "How?". According to this view, the basic regulatory systems present in the cell and leading to a stable state have limited freedom in both respects—they serve to implement a predetermined program. With their advanced nervous system, capable of reasoning and logic, organisms have limited freedom in the scope of "What?", but relatively extensive freedom in the scope of "How?" For example, cats must hunt mice to survive, but they may come up with a variety of ways to snare their prey. At some point, continuing evolution of neural networks produces freedom related to the "What?" aspect. On this level, the human being can make its own plans of action and remains fully autonomous in their implementation.

Conclusions

Both machines and living creatures must be regulated in order to operate properly. The behavior of these entities reflects the properties of their regulation. In terms of regulation modes, dynamic entities can be divided into automata and non-automatic mechanisms. Living creatures and mechanical automata are similar in behavior, but differ with respect to the materials they are built from. Automatic regulation of living creatures is—according to the presented interpretation—designed to stabilize their internal environment. Elements of independence derived from the automatic nature (character) of biological regulatory systems differentiate living creatures from inanimate objects.

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References

1. Woolston C (2013) 'Living fossil' genome unlocked. *Nature* 496: 283.
2. Sussman MR, Phillips GN Jr (2009) How plant cells go to sleep for a long, long time. *Science* 326: 1356-1357.
3. Konieczny L, Roterman I, Spolnik P (2016) *Systems Biology*. Springer.
4. Keller B, Krattinger SG (2017) Genomic compartments in barley. *Nature* 544: 424-425.
5. Gunasekaran K, Ma B, Nussinov R (2004) Is allostery an intrinsic property of all dynamic proteins?. *Proteins* 57: 433-443.
6. Hilser VJ, Thompson EB (2007) Intrinsic disorder as a mechanism to optimize allosteric coupling in proteins. *Proc Natl Acad Sci* 104: 8311-8315.

7. Motlagh HN, Wrabl JO, Li J, Hilser VJ (2014) The ensemble nature of allostery. *Nature* 508: 331-339.
8. Elber R (2011) Simulations of allosteric transitions. *Curr Opin Struct Biol* 21: 167-172.
9. Ferreon AC, Ferreon JC, Wright PE, Deniz AA (2013) Modulation of allostery by protein intrinsic disorder. *Nature* 498: 390-394.
10. Flock T, Ravarani CNJ, Sun D, Venkatakrisnan AJ, Kayikci M (2015) Universal allosteric mechanism for Gα activation by GPCRs. *Nature* 524: 173-179.
11. Perica T, Kondo Y, Tiwari SP, McLaughlin SH, Kemplen KR (2014) Evolution of oligomeric state through allosteric pathways that mimic ligand binding. *Science* 346: 1254346
12. Fenton AW (2008) Allostery, an illustrated definition for the 'second secret of life'. *Trends Biochem Sci* 33: 420-425.
13. Hilser VJ (2013) Signalling from disordered proteins. *Nature* 498: 308-310.
14. Gao XJ, Elowitz MB (2016) Precision timing in a cell. *Nature* 538: 462-463.
15. Bass J, Takahashi JS (2010) Circadian integration of metabolism and energetics. *Science* 330: 1349-1354.
16. Rey G, Reddy AB (2013) Rhythmic respiration. *Science* 342: 570-571.
17. Hurley JM, Dunlap JC (2013) A fable of too much too fast. *Nature* 495: 57-58.
18. Kaiser TS, Poehn B, Szkiba D, Preussner M, Sedlazeck FJ, et al. (2016) The genomic basis of circadian and circalunar timing adaptations in a midge. *Nature* 540: 69-73.
19. Vogel G (2011) Telling time without turning on genes. *Science* 331: 391.
20. Mihalcescu I, Hsing W, Leibler S (2004) Resilient circadian oscillator revealed in individual cyanobacteria. *Nature* 430: 81-85.
21. Kramer A (2015) When the circadian clock becomes blind. *Science* 347: 476-477.
22. Zhang Y, Fang B, Emmett MJ, Damle M, Sun Z, et al. (2015) Discrete functions of nuclear receptor Rev-erba couple metabolism to the clock. *Science* 348: 1488-1492.
23. Peek CB, Affinati AH, Ramsey KM, Kuo HY, Yu W, et al. (2013) Circadian clock NAD⁺ cycle drives mitochondrial oxidative metabolism in mice. *Science* 342: 1243417.
24. Xu Y, Ma P, Shah P, Rokas A, Liu Y, et al. (2013) Non-optimal codon usage is a mechanism to achieve circadian clock conditionality. *Nature* 495: 116-120.
25. Zhou M, Guo J, Cha J, Chae M, Chen S, et al. (2013) Non-optimal codon usage affects expression, structure and function of clock protein FRQ. *Nature* 495: 111-115.
26. Panda S (2016) Circadian physiology of metabolism. *Science* 354: 1008-1015.
27. Bartley BA, Kim K, Medley JK, Sauro HM (2017) *Synthetic Biology, Engineering Living Systems from Biophysical Principles*. *Biophys J* 112: 1050-1058.
28. Maxmen A (2017) Synthetic yeast chromosomes help probe mysteries of evolution. *Nature* 543: 298-299.
29. Service RF (2016) Synthetic microbe has fewest genes, but many mysteries. *Science* 351: 1380-1381.
30. Callaway E (2016) 'Minimal' cell raises stakes in race to harness synthetic life. *Nature* 531: 557-558.
31. Hutchison CA III, Chuang RY, Noskov VN, Assad-Garcia N, Deerinck TJ, et al. (2016) Design and synthesis of a minimal bacterial genome. *Science* 351: aad6253.
32. Kannan K, Gibson DG (2017) Yeast genome, by design. *Science* 355: 1024-1025.
33. Bosman GJ, Willekens FL, Werre JM (2005) Erythrocyte aging, a more than superficial resemblance to apoptosis?. *Cell Physiol Biochem* 16: 1-8.
34. Föller M, Huber SM, Lang F (2008) Erythrocyte programmed cell death. *IUBMB Life* 60: 661-668.
35. Lang KS, Lang PA, Bauer C, Duranton C, Wieder T, et al. (2015). Mechanisms of suicidal erythrocyte death. *Cell Physiol Biochem* 15: 195-202.
36. Dong X, Milholland B, Vijg J (2016) Evidence for a limit to human lifespan. *Nature* 538: 257-259.

37. Bissette AJ, Fletcher SP (2013) Mechanisms of autocatalysis. *Angew Chem Int Ed Engl* 52: 12800-12826.
38. Semenov SN, Kraft LJ, Ainla A, Zhao M, Baghbanzadeh M, et al. (2016) Autocatalytic, bistable, oscillatory networks of biologically relevant organic reactions. *Nature* 537: 656-660.
39. Ganti T (1971) *The principle of life*. Oxford University Press, USA.
40. Kauffman SA (1986) Autocatalytic sets of proteins. *J Theor Biol* 119: 1-24.
41. Eigen M (1971) Self-organisation of matter and the evolution of biological macromolecules. *Naturwissenschaften* 58: 465-523.
42. Hordijk W, Hein J, Steel M (2010) Autocatalytic sets and the origin of life. *Entropy* 12: 1733-1742.
43. Nutman AP, Bennett VC, Friend CR, Van Kranendonk MJ, Chivas AR (2016) Rapid emergence of life shown by discovery of 3,700-million-year-old microbial structures. *Nature* 537: 535-538.
44. Dodd MS, Papineau D, Grenne T, Slack JF, Rittner M, et al. (2017) Evidence for early life in Earth's oldest hydrothermal vent precipitates. *Nature* 543: 60-64.
45. Gollihar J, Levy M, Ellington AD (2014) Many paths to the origin of life. *Science* 343: 259-260.
46. Popkin G (2016) The physics of life. *Nature* 529: 16-18.
47. Jeschek M, Reuter R, Heinisch T, Trindler C, Klehr J, et al. (2016) Directed evolution of artificial metalloenzymes for in vivo metathesis. *Nature* 537: 661-665.
48. Juliá-Hernández F, Moragas T, Cornella J, Martin R (2017) Remote carboxylation of halogenated aliphatic hydrocarbons with carbon dioxide. *Nature* 545: 84-88.
49. Welin ER, Le C, Arias-Rotondo DM, McCusker JK, MacMillan DW (2017) Photosensitized, energy transfer-mediated organometallic catalysis through electronically excited nickel(II). *Science* 355: 380-385.
50. Schmidt J, Choi J, Liu AT, Slusarczyk M, Fu GC (2016) A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters. *Science* 354: 1265-1269.
51. Lin S, Diercks CS, Zhang YB, Kornienko N, Nichols EM, et al. (2015) Covalent organic frameworks comprising cobalt porphyrins for catalytic CO₂ reduction in water. *Science* 349: 1208-1213.
52. Begley TP (2017) Biochemistry Origin of a key player in methane biosynthesis. *Nature* 543: 49-50.
53. Chemler SR (2013) Copper's contribution to amination catalysis. *Science* 341: 624-626.
54. Edwards JT, Merchant RR, McClymont KS, Knouse KW, Qin T, et al. (2017) Decarboxylative alkenylation. *Nature* 545: 213-218.
55. Furukawa H, Cordova KE, O'Keeffe M, Yaghi OM (2013) The chemistry and applications of metal-organic frameworks. *Science* 341: 1230-1234.
56. Choi J, Fu GC (2017) Transition metal-catalyzed alkyl-alkyl bond formation, Another dimension in cross-coupling chemistry. *Science* 356: 633-634.
57. Zhang Z, Tanaka K, Yu JQ (2017) Remote site-selective C-H activation directed by a catalytic bifunctional template. *Nature* 543: 538-554.
58. Paudyal MP, Adebisin AM, Burt SR, Ess DH, Ma Z (2016) Dirhodium-catalyzed C-H arene amination using hydroxylamines. *Science* 353: 1144-1147.
59. Korstanje TJ, van der Vlugt JI, Elsevier CJ, de Bruin B (2015) Hydrogenation of carboxylic acids with a homogeneous cobalt catalyst. *Science* 350: 298-330.
60. Kattel S, Ramirez PJ, Chen JG, Rodriguez JA, Liu P (2017) Active sites for CO₂ hydrogenation to methanol on Cu/ZnO catalysts. *Science* 355: 1296-1329.
61. Vinogradova EV, Zhang C, Spokoyny AM, Pentelute BL, Buchwald SL (2015) Organometallic palladium reagents for cysteine bioconjugation. *Nature* 526: 687-691.
62. Dydio P, Key HM, Nazarenko A, Rha JY, Seyedkazemi V, et al. (2016) An artificial metalloenzyme with the kinetics of native enzymes. *Science* 354: 102-106.
63. Meng F, Li X, Torker S, Shi Y, Shen X, et al. (2016) Catalytic enantioselective 1,6-conjugate additions of propargyl and allyl groups. *Nature* 537: 387-393.
64. Xia Y, Lu G, Liu P, Dong G (2016) Catalytic activation of carbon-carbon bonds in cyclopentanones. *Nature* 539: 546-550.
65. van der Zwaag D, Meijer EW (2015) Fueling connections between chemistry and biology. *Science* 349: 1056-1057.
66. Zeng C, Chen Y, Kirschbaum K, Lambright KJ, Jin R (2016) Emergence of hierarchical structural complexities in nanoparticles and their assembly. *Science* 354: 1580-1584.
67. Villar G, Graham AD, Bayley H (2018) A tissue-like printed material. *Science* 340: 48-52.
68. Sacanna S, Irvine WT, Chaikin PM, Pine DJ (2010) Lock and key colloids. *Nature* 464: 575-578.
69. Evers CH, Luiken JA, Bolhuis PG, Kegel WK (2016) Self-assembly of microcapsules via colloidal bond hybridization and anisotropy. *Nature* 534: 364-368.
70. Aida T, Meijer EW, Stupp SI (2012) Functional supramolecular polymers. *Science* 335: 813-817.
71. Benitez-Nelson C (2015) Ocean chemistry. The missing link in oceanic phosphorus cycling? *Science* 348: 759-760.
72. Shelke SA, Piccirilli JA (2014) Origins of life, RNA made in its own mirror image. *Nature* 515: 347-348.
73. Cech TR (2009) Evolution of biological catalysis, ribozyme to RNP enzyme. *Cold Spring Harb Symp Quant Biol* 74: 11-16.
74. Matsumura S, Kun Á, Ryckelynck M, Coldren F, Szilágyi A, et al. (2016) Transient compartmentalization of RNA replicators prevents extinction due to parasites. *Science* 354: 1293-1296.
75. Vaidya N, Manapat ML, Chen IA, Xulvi-Brunet R, Hayden EJ (2012) Spontaneous network formation among cooperative RNA replicators. *Nature* 491: 72-77.
76. Leontis NB, Westhof E (2014) Self-assembled RNA nanostructures. *Science* 345: 732-733.
77. Rubenstein M, Cornejo A, Nagpal R (2014) Programmable self-assembly in a thousand-robot swarm. *Science* 345: 795-799.
78. Shen H (2016) Meet the soft, cuddly robots of the future. *Nature* 530: 24-26.
79. David SV (2017) Cognition, Neurons couple up to make decisions. *Nature* 548: 35-36.
80. de Latil P (1953) *La pensée artificielle*. In: Gallimard G (ed.).