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EDITORIAL

Life is more than a computer running DNA software

František Baluška, Guenther Witzany

František Baluška, IZMB, University of Bonn, 53113 Bonn, Germany
Guenther Witzany, Telos-Philosophische Praxis, 5111 Buermoos, Austria
Author contributions: Both of the authors contributed to this paper.
Correspondence to: Guenther Witzany, PhD, Telos-Philosophische Praxis, Vogelsangstr. 18c, 5111 Buermoos, Austria. witzany@sbg.at
Telephone: +43-6274-6805 Fax: +43-6274-6805
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Abstract

In his recent interview for the Guardian Craig Venter is elaborating about a household appliance for the future, Digital Biological Converter (DBC). Current prototype, which can produce DNA, is a box attached to the computer which receives DNA sequences over the internet to synthesize DNA; later in future also viruses, proteins, and living cells. This would help the household members to produce, *e.g.*, insulin, virus vaccines or phages that fight antibiotic resistant bacteria. In more distant future, Craig Venter's hope is that the DBC will generate living cells *via* so-called "Universal Recipient Cell". This platform will allow digitally transformed genomes, downloaded from the internet, to form new cells fitted for the particular needs such as therapeutics, food, fuel or cleaning water. In contrast to this, the authors propose that DNA sequences of genomes do not represent 1:1 depictions of unequivocal coding structures such as genes. In light of the variety of epigenetic markings, DNA can store a multitude of further meanings hidden under the superficial grammar of nucleic acid sequences.

Key words: DNA; Genome; Information; Life; Non-coding RNA; Synthetic biology; Virus

Core tip: Craig Venter is elaborating a box attached to a computer that receives DNA sequences over the internet to synthesize DNA. As a leading expert in the field of synthetic biology, he is convinced that "life is a DNA software system", and all living things are reducible to DNA sequences. In contrast to this, the authors propose that DNA sequences of genomes do not represent 1:1 depictions of unequivocal coding structures such as genes. In light of the variety of epigenetic markings, DNA can store a multitude of further meanings hidden under the superficial grammar of nucleic acid sequences.

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INTRODUCTION

In his recent interview for the Guardian[1], Craig Venter is elaborating about a household appliance for the future, the Digital Biological Converter (DBC). The current prototype, which can produce DNA, is a box attached to a computer that receives DNA sequences over the internet to synthesize DNA; in future, it will be able to do the same for viruses, proteins and living cells. This would help the household members to produce, for example, insulin, virus vaccines or phages that fight antibiotic-resistant bacteria. Additionally, it could help future Martian colonists, giving them vaccines, antibiotics or personalized drugs that they would need on Mars. If there should be DNA-based life, a digital version could be transmitted to earth without danger of contaminating the home-planet's biosphere[1]. In the more distant future, Craig Venter' s hope is that the DBC will generate living cells *via* the so-called "Universal Recipient Cell". This platform will allow digitally transformed genomes, downloaded from the internet, to form new cells for particular needs (therapeutics, food, fuel or cleaning water)[1]. The final aim is to establish a "Digital Life Sending Unit" allowing biological teleportation. This unit will sample unknown organisms, perhaps on Mars, then analyse their sequences and generate digital DNA files that will be used by the receiving DBC to re-generate these organisms at new places, such as on Earth.

NOTHING ELSE THAN A SOFTWARE SYSTEM?

Some readers might be reminded of Goethe's Dr Faustus' pact with Mephisto and its goal to create a "homunculus" or similar dreams of living robots that would invade space and time, covered by an abundance of science fiction poetries. But Craig Venter is a leading expert in the field of synthetic biology, in which scientists design new biological systems, *i.e.*, synthetic life. He insists that his insertion of a synthetic bacterial (*Mycoplasma genitalium*) genome into a living recipient bacterium (*Mycoplasma capricolum*) represents the "world's first synthetic life" because the synthetic cell replicated itself into a colony of bacteria, containing only the synthetic DNA.

We do not want to enter here the debate of whether his indisputable achievements represent true creation of new life or represent just some kind of a copy-paste approach. We can also be pretty sure that he and his company will achieve several further technological breakthroughs in the near future. However, we would like to make very clear that his conclusions about the nature of Life are not justified. For example, Craig Venter is convinced that it would be possible, in principle, to synthetically create most complex organisms: "I can't explain consciousness yet, but like anything else it will be explainable at the molecular level, the cellular level and therefore the DNA coding level"[1]. In his view, the question of Erwin Schrödinger What is life? has been answered. "Life is a DNA software system", and all living things are reducible to DNA sequences[1]. The DNA-based software creates as well as directs the more visible "hardware" of life, such as proteins and cells[1-3].

This DNA-centric concept looks clear and straightforward. However, it can work only if the theoretical background on which Craig Venter makes his conclusions is correct. In his view[1-3], organisms are mechanistic apparatus-like molecular structures that work as computing machines according the algorithm-based programs encoded in the DNA storage medium. The syntax structure of DNA follows Francis Crick's central dogma of molecular biology "DNA-RNA-anything else". But is this view coherent with recent empirical knowledge? Are cellular organisms only robot-like computing machines that function strictly according to their algorithm-based programming? Or, rather, are they coordinated complex entities that share bio-communication properties that may vary according to different context-specific needs? Is DNA the unequivocal syntax for sequences out of which one can construct living cells, viruses and phages for a household appliance? Or is the superficial molecular syntax of DNA solely the result of evolution's long inserts and deletions of an abundance of various genetic parasites that shape host genomes? The most crucial questions are: do DNA sequences contain a hidden deep grammar structure that varies according to the meaning and context of environmental insults; do DNA sequences match with high fidelity environmental circumstances that led to epigenetic markings and memory? If yes, this would then mean that the identical DNA sequence may have various-even contradictory-meanings. In fact, this scenario is emerging as true[4-8].

EPIGENETICS: HIDDEN DEEP GRAMMAR

Interestingly, in complex genomes like humans, the coding genes are about 1.5% of the total genome whereas the abundance of non-coding RNAs are about 98.5%. This means Craig Venter's household appliance box could focus only on the 1.5% coding sequences. The DNA sequences of genomes do not represent 1:1 depictions of unequivocal coding structures such as genes, but in light of the variety of epigenetic markings-with its executives RNA editing and alternative splicing-can store a multitude of further meanings[4-8].

This means epigenetic marking saves energy costs like in human language. A limited repertoire of signs, and a limited number of rules to combine these signs correctly, enables signs using agents to generate an unlimited number of sentences with a superficial grammar in the visible text and an abundance of connotations by marking through gestures and other conscious and unconscious bodily expressions such as the movements of three hundred different eye muscles[9].

Are organisms computing machines that fulfil what the DNA program determines? The machine metaphor in molecular biology is an old-fashioned narrative[9] that would like to reduce life to physics and chemistry. Manfred Eigen and Sydney Brenner expanded the concept by adding also information: "Life = physics + chemistry + information"[10,11]. But they defined information according to the mathematical theory of language as used by John von Neumann and Alan Turing in their concept of self-reproducing automata, a chimera that has remained for the last 80 years at a conceptual stage without any functional realization[9,12].

Similar to the algorithm-based computing machines of Turing and von Neumann, Venter's concept of DNA as a software system relies on these computation models. However, these models cannot explain: (1) *de novo* generation of new functional nucleic acid sequences; (2) their context-dependent recombination; and (3) the abundance of mobile regulatory elements being active in all essential processes of life such as replication, transcription, translation, repair and immune defence, all of which are organized by an abundance of small and large RNAs[4-8].

Today, we know that these RNAs predated the emergence of DNA and many of these RNA-world descendants-even RNA viruses-remain as defective parts of genetic parasites in host cellular genomes as exapted and endogenized tools to regulate gene functions[13-17].

RNA-WORLD AGENT ACTIVITIES

Endogenous viruses, transposons, retrotransposons, long terminal repeats, non-long terminal repeats, long interspersed nuclear elements, short interspersed nuclear elements, group Ⅰ introns, group Ⅱ introns, phages and plasmids are currently investigated examples that use genomic DNA as their preferred live habitat. This means that DNA is not solely a genetic storage medium that serves as a read and write medium as an evolutionary protocol, but it is also a (quasi-)species-specific ecological niche[4,17]. A great variety of such mobile genetic elements infect, insert, delete, cut and paste, copy and paste and spread within the genome. They change host genetic identities either by insertion, recombination or the epigenetic regulation of genetic content, and co-evolve with the host and interact in a module-like manner. In this respect, they play vital roles in evolutionary and developmental processes. In contrast to accidental point mutations, integration at various preferred sites is not a randomly occurring process but is coherent with the genetic content of the host; otherwise, important protein-coding regions would be damaged, causing disease or even lethal consequences for the host organism[17].

Therefore, DNA organized in chromatin is far more complex than the human-made "software system", except that we are confusing the algorithm-based simulation of real-life storage with the real life, the computer machines with the living cells and organisms, and the self-reproducing automatons with the real-life organisms that can replicate since the origins of life[5,9,14].

Although various complex attempts to simulate early evolution and emergence of life have been accomplished, no complete living cell with all of its components (cell membranes, organelles, microtubules, chromosomes, *etc*.) has yet been engineered. Although hundreds of announcements have been made within the last 60 years, not one of them has been successfully completed.

BIOCOMMUNICATION AND NATURAL GENOME EDITING

The logical alternatives to the concepts of synthetic biology are not "guilty of a kind of modern day vitalism" as suggested by Craig Venter[1,2]. The alternative is the full range of nucleic acid sequence-based life and the agents that are competent to arrange and rearrange DNA information according to their real-life needs. Communication between cells, tissues, organs and organisms cannot be predicted or simulated by computing machines, because biocommunication does not function mechanistically and is not algorithm dependent[18]. The genome itself, *via* natural genome editing[19], generates large amounts of coherent new sequences and inserts these into DNA genomes without damaging essential protein-coding regions. This is not possible for any human-made software. Therefore, despite the bold visions of Craig Venter, it will not be possible to create digital life in the future. The 20th century DNA-based models and concept cannot integrate current empirical data into a coherent picture of how the real life functions. We need new concepts that will be able to integrate all the currently available empirical data on viruses, mobile genetic elements and the abundance of non-coding RNAs most relevant for genome shaping, regulation and evolution[20-26].

CONCLUSION

Despite the theoretical concepts of Turing and von Neumann, and the abundance of announcements of self-reproducing machines, the vision of digital life files that can be used as modules for generating life units will remain on the theoretical stage. The main reason is that the 20th century DNA-based models cannot integrate current empirical data into a coherent picture of how the real life functions: nucleic acid sequences do not represent unequivocal meanings that can be expressed in protein bodies, but depend on context, *i.e.*, epigenetic markings, RNA-editing and alternative splicing that vary according to environmental circumstances, even though the DNA remains identical.

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