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Overview on possible causes of COVID-19

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Abstract

Background: The infection with the new coronavirus SARS-CoV-2 has caused a large number of cases of disease and death worldwide. Identifying the source of COVID-19 is an important issue though still unresolved. The analysis of the literature on highlighting possible sources of the SARS-CoV-2 virus was carried out.

Conclusions: The COVID-19 pandemic is occurring on the underlying imminent global ecological catastrophe as a result of the anthropogenic activity. Therefore, it can be stated that *Homo Sapiens* in the context of the interaction with the biosphere is a maladaptive species. According to the literature, the species' adaptive responses to environmental changes are due to endogenous retroviruses. The latter act as evolutionary factors. Possible pandemic COVID-19 is not a separate epidemic process caused by the penetration of a new virus into human populations, but rather is one of the manifestations of a more complex natural phenomenon – an evolutionary process under the guise of an infectious one. In terms of evolution, COVID-19 plays the role of a biosphere factor that seeks to help a relatively new species to adapt to the general conditions of survival in a symbiotic relationship with other living organisms.

Key words: COVID-19, lateral gene transfer, viruses, microbiota.

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"People usually blame fate, circumstances, other people for their own misfortunes, but not the main culprit of their misfortunes – themselves" - Plato.

Introduction

More than two years after the first documented cases in Wuhan, the origin of SARS-CoV-2 has not yet been established. In-depth researches do not indicate that Chiroptera is a direct zoonotic agent. At the same time, genomic analysis showed that SARS-CoV-2 has many specific characteristics not found in other Sarbecoviruses [1]. According to Boni et al., SARS-CoV-2 is not a recombinant of any sarbecovirus detected so far [2].

According to researchers, human activities can trigger various interactions between animal species and their viruses, sometimes causing the emergence of new viral pathogens with unknown pathogenic properties [1]. They, in turn, could quickly adapt to a new host organism (human) and acquire a stable intraspecific contagion.

Examples of this scenario are SARS-CoV and perhaps SARS-CoV-2.

The unique mechanism of CoV replication provides high-frequency genetic recombination in their RNA and subsequent mutations, thus enabling an extreme adaptability to new hosts and ecological niches [3].

Xiao K. et al., suggested that stray dogs in Hubei province may be natural reservoirs of the SARS-CoV-2 precursor and that high levels of antiviral protein in their intestinal tissue could trigger the development of a potential antecedent virus [4].

The above listed reflections of the authors, complemented by literature research, may outline a credible hypothesis for the origin of SARS-CoV-2. For a clearer understanding and explanation of possible plausible events, a bibliographic foray into some properties of microorganisms and particularly of viruses is necessary to be carried out.

Typically, the history of humankind communication with viruses is portrayed as a permanent conflict. This pattern is as follows – the emergence of infection, its generalization and, ultimately, its control or eradication. All stages are associated with fear, suffering and death. This picture shows the darkest virus image.

Retroviruses and retroelements found in the genome of modern humans have their own evolutionary history that began in the Mesozoic era (according to the chronology,

not less than 100 million years ago) [5]. Almost half of the human genome is made up of various transposable elements as HIV-like structures, collectively referred as retroelements [6].

Examples of different virus hypostasis refer to how the Arc neuron gene was obtained (retrotransposons, which are the ancestors of retroviruses). According to scientists, the Arc is necessary for synaptic plasticity viz. the ability of nerve cells to form and strengthen new nerve connections [7].

With a seemingly very simple structure, the virus contains vast genetic information. The discrepancy between the amount of information and the insignificant molecular weight of RNA and viral DNA is explained by special mechanisms that allow replicating to the same genetic sequence in different ways [8].

Virus persistence in a cell is possible due to a specific property called lysogeny [9]. Lysogeny (from the Greek *lysis* means decomposition, degradation and *geneia* – origin, creation) is a genetically determined ability of bacteria to lysis with the release of a bacteriophage several generations after the direct infection with it. Lysogenic state is associated with the presence of a potentially infectious structure of bacteria in cells, namely a prophage. Thus, the virus that has entered the cell does not betray its presence. Therefore, an infected cell is similar outwardly to a normal cell.

As a result of lysogenization, some properties of the bacterial cell can change (the so-called lysogenic conversion) that allows the bacteria to acquire new genetic information [10].

The authors reported that a viral infection is not only an infectious process, but also ultimately acts as an important evolutionary trigger [11, 12]. The researchers noticed that when the virus-induced lytic cycle develops, the host chromosome degrades. Subsequently, the bacterial chromosome fragments of the corresponding size are packed into phage bodies and, strictly according to the canonical rules of viral transfer (adsorption on receptors, injection of DNA contained in the cell body), are introduced into other cells, thus causing their transformation. At the same time, in a cell with formed bodies containing host's DNA fragments, the viral genome is also replicated and packed to a certain extent, thus causing it to multiply. Therefore, most viral bodies perform completely different functions, such as being a packing material for cellular genes without viral admixture.

Gene transfer for species perpetuation has also been reported between viruses. The symbiosis between mimivirus and the tiny Sputnik virophage is an example of that. Both infect amoeba, however, the virophage cannot reproduce in the absence of mimivirus [13]. Of the 13 virophage genes, 3 are similar to mimivirus and mammavirus genes, which can be introduced into the virophage genome during particle formation. It can be assumed that the Sputnik virus could transfer genes between viruses similarly to how bacteriophages transfer genes between bacteria [14].

The above-mentioned evolutionary changes are possible due to a unique property of microorganisms called *lateral gene transfer* (LGT). This phenomenon is a process in which an organism transfers genetic material to a non-descendant organism [15, 16], unlike vertical gene transfer, when an organism receives its genetic material from an ancestor [17]. Lateral gene transfer is the main mechanism in the evolution, maintenance and transmission of virulence [18]. The researcher Peter Gogarten points to horizontal (lateral) gene transfer as a "new paradigm for Biology" [19].

The long-term survival of the host bacteria is actually necessary for the phage (virus) [20]. The best way is to make sure that their hosts adapt to the rapidly changing environments and challenges. Some cases have reported that phages remove antibiotic resistance genes from neighboring cells competing for host bacteria in a process called autotransduction [21]. According to the researchers, viruses play an extremely important role in microbial evolution, thus creating an extensive biological network, which connects all the genomes in the bacterial universe [20].

Recent in-depth researches show that viruses can communicate with each other. Scientists noticed that during a host cell infection, temperate phages infecting *Bacillus subtilis* release a signaling peptide that shape the lysis-lysogeny decision in subsequent infections [22]. Thus, the phages produce new virions and then lyse their host when the signal concentration is low, but favor the latent infection when the signal concentration is high by lysogenizing the host cell. They found via a mathematical model, that a communication strategy in which phages use a lytic cycle at the onset of an outbreak (when susceptible host cells are abundant), shifting to a lysogenic cycle later (when the susceptible cells become scarce) is more appropriate than a strategy in which cells lysogenized with constant probability.

According to Stanciugelu I. et al., communication is the perfected result of thinking, the ascending process from the specific sphere to the abstract one [23]. According to Vladutescu S., communication is a structure in itself, through which we think about reality [24].

How is this possible that a non-living organism thinks? Perhaps, there is a mathematical model that allows this possibility and namely, the theory of integrated information, developed in 2004 by the Italian scientist Giulio Tononi [25]. He considers consciousness as the ratio between the quantity and quality of information, which is determined by a special measurement unit – φ (phi). The idea is that there is an upward series of transition states between the completely unconscious matter (0 - φ) and the conscious human brain (maximum - φ). Any object capable of receiving, processing, and generating information has a minimum level of φ, including inanimate objects, such as tonometer or LED, since they can convert blood pressure and light into data. Consciousness is the highest level of data processing. The scientist G. Tononi called this phenomenon integration. Integrated information is something that qualitatively surpasses the simple amount of collected data: not just a set of individual characteristics of an object, such as the yellow light, round shape and heat, but rather a full image of a lighted lamp consisting of all these characteristics.

To test whether inanimate objects can adapt and develop

experience, G. Tononi and his colleagues designed a virtual model [26]. The subjects were "animated" units with basic artificial intelligence. Each received randomly generated instructions for the body parts, being placed in a virtual maze. From time to time, researchers selected and copied animations that showed the best coordination. The next generation inherited the same code from the "parents". Its size did not change, but random digital "mutations" were introduced to strengthen, weaken, or supplement the connections between the "brain" and "limbs". Therefore, over 60000 generations, natural selection increased the efficiency of passing the maze in animates from 6% to 95%.

In this sense, the virus is far superior to many inanimate objects, since it carries (genetic) information itself. Viruses are more likely to increase the φ – level as viral generations succeed much faster. For example, the picornavirus genome is amplified by up to 50000 copies of each host cell in its active phase [27, 28], thus, in the active phase, hepatitis A viruses are also found in blood, reaching a concentration of up to 10^5 virus particles per milliliter [29].

There is another condition to integrate information at the level of consciousness, which requires a complex system. Similar to a computer program compressed by a file archiver, a virus does not need the entire control algorithm of the host cell. A short viral code is quite enough to make the entire operating system of the cell work properly for the virus itself.

According to recent experiments, while integrated in the organism, viruses can share and control the metabolic processes of the cell and the whole organism [30]. According to Raftery et al., and Delgado-Rizo et al., several viruses, including Hantaan virus (HTNV), H1N1 influenza virus (IV), human immunodeficiency virus (HIV-1) and the respiratory syncytial virus (RSV) directly stimulates immunocompetent cells to release neutrophil extracellular traps (NETs) [31, 32]. Therefore, in a complex system (like our body) viruses can use additional options to increase information processing which, according to G. Tononi's model, is assumed as intelligent life.

Viral interference with a macroorganism

Scientists describe amazing examples of the various impacts of viruses on the survival of host microorganisms [33]. The studies on the interaction of phytoplankton showed that marine viruses are able to change the way algae cells receive nutrients from the environment, while concomitantly harming and destroying the algae hosts. The viral genome often encodes genes derived from their host. These genes may allow the virus to manipulate the host's metabolism to improve its adaptive properties. Thus, a host-derived ammonium transporter has been identified in the genome of the phytoplankton virus infecting the small green algae *Ostreococcus tauri*.

This gene is transcribed during infection and keeps algae growing when cultured with ammonium as the only nitrogen source. Viral infection also changes the way the host cells absorb the nitrogen compound, allowing the host to access various sources of nitrogen. This is important since nitrogen availability often limits phytoplankton growth. Collectively, these data show that a virus can acquire genes encoding nutrient transporters from a host genome and that viral gene expression can alter the nutrient uptake behavior of host cells. These results show how viruses affect the physiology and ecology of phytoplankton, influence marine nutrient cycles and act as vectors for horizontal (lateral) gene transfer.

The researchers have reported a similar phenomenon [34]. The study of the complete 668 kilobase genome of a mimivirid infecting the green algae *Tetraselmis* (Chlorodendrophyceae) described viral genes that have never been observed before. These genes are represented by the enzymes for mannitol metabolism viz. *mannitol 1-phosphate dehydrogenase*, the saccharide-degrading enzyme, *alpha-galactosidase* and the key fermentation genes – *pyruvate formate-lyase.* These genes indicate complex mechanisms by which viruses can manipulate the host metabolism.

Another recent study revealed genes-encoding enzymes that play a potential role in photosynthesis, various substrate transport processes, light-activated proton pumps, and retinal pigments [35]. This diversity of virus-encoded genes, which play a role in energy production and nutrient supply, points to a large-scale impact of viruses on ecosystem dynamics.

Microbiota – the "second genome" of a macroorganism

One of the largest microbial communities, accounting for about 10^{14} microorganisms of more than 500 species from nine bacterial divisions, which inhabit the human gastrointestinal tract, include *Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Fusobacteria, Proteobacteria, Spirochaeates, Verrucomicrobia* [36-38]. The enormous bacterial density and physical protection create an ideal environment for horizontal gene transfer [39, 40]. The environmental physical and chemical conditions allow natural transformation, conjugation and transduction. According to the researchers, the importance of natural transformation in this environment is underestimated [39, 40].

According to the scientists, viruses, plasmids, conjugative transposons and integrons play an essential role in adaptation, virulence maintenance and antibiotic resistance of the human microbiome due to the mechanism of lateral gene transfer (LGT) [41-43].

The researchers provide living evidence of the viral involvement in protecting the integrity of the microbiota [44]. When analyzing the intestinal microflora, it was observed that bacteria are exposed to stress conditions under antibiotic administration (ciprofloxacin and ampicillin), generating a SOS-inducing signal. In response to this signal, the concentration of antibiotic resistance genes in phage particles increases. Subsequent bacteriophage infection allows transduction of resistant genes to intestinal bacteria. Thus, phages maintain the functional integrity of the intestinal microflora. The following study reflects the enormous value of lateral gene transfer (LGT) between microorganisms for adaptation and maintenance of the

functionality of the human microbiota in various conditions [45]. Thus, the use of unique dietary components will also facilitate the selection of appropriate additional genes. For example, the gene for the enzyme porphyrinase appears to have been successfully transferred from the *Bacteroides marin* to *Bacteroides plebeius* in the microbiota of the Japanese population. This enzyme helps digest seaweed, a common element in the Japanese diet [46].

Gut microbes are significantly influenced by many factors such as host genetics, lifestyle (urbanization and global mobility), medical interventions (antibiotic use, vaccination and hygiene), and overall health [47]. Moreover, food is delivered by modern intensive farming systems, characterized by an extensive use of herbicides, insecticides, fungicides, fumigants, desiccants, crop agents, antimicrobials, growth regulators and many other chemical substances. Similarly, the modern human microbiota is affected by genetically engineered microorganisms, plants and animals, as well as new nutrients, new food technologies, engineered microbial delivery systems, and various food additives [48].

In this context, it is worth mentioning the researchers, who could point to particularly high loads on the microbiota of modern humans [49]. Thus, the study showed that lateral gene transfer (LGT) is 25 times more intense among human-associated bacteria than among non-human isolates. Ecology is the most important factor that drives a global network of gene exchange.

Some researchers stated that human microbiota is a reservoir of a diverse and a dense mass of species, as well as multiple antibiotic resistance genes with functional systems for horizontal gene transfer [50]. The ability of new pathogens to develop in this environment is exceptional.

Amoeba – "single cell engineer"

In the context of the interaction of living beings, the lateral transfer of genes and, finally, the mystery of the emergence of new microbial properties, adjusting to the dynamic environmental conditions, amoeba is worth mentioning as a supercomplex organism, and considered as "*a single cell engineer*".

Amoebas are phagocytic protists, which can be considered wild macrophages [51]. Some amoeba have the largest genome size currently known on Earth. For example, dubia amoeba has a genome of 670000 Mb (200 times larger than human at 2900 Mb) and has the largest known genome of any living organism [52].

Amoebas are very sensitive to environmental changes, including increased pollution, climate changes and conditions of water bodies [53]. According to the researchers, the morphological and functional characteristics of the tested amoeba, due to its pronounced susceptibility, can reflect important information about the functioning of ecosystems [54, 55]. Amoebas phagocytize any inert particles larger than 0.5 μm [56]. A phagocytic amoeba can simultaneously contain various bacteria, fungi and viruses without harming them. Additionally, there are evidences on lateral gene transfer between amoebas and their hosts [57]. For example, *Marseillevirus*, a giant virus, has recently been identified in amoebas. Its analysis showed the chimeric nature of its genome with genes derived not only from mimiviruses, but also from archaea and eukaryotic bacteria [58]. A similar phenomenon is also observed in intracellular amoeba symbionts, such as *Legionella drancourtii*, containing an amoebic-derived sterol reductase [59, 60].

The important role of amoebas in the spread of *Legionella spp*. among people was assumed by T. Rowbotham as early as 1980 [61]. The scientist admitted that human infection occurs not by direct inhalation of free bacteria, but rather by inhalation of vesicles or amoebae containing *Legionella spp.* Later studies confirmed that free-living amoebae are needed to multiply Legionella in water biofilms, although bacteria can survive dormant in amoeba-free biofilms [62]. This phenomenon may explain the onset of the disease after an increased exposure of people to aerosol water due to the use of new devices such as air conditioning systems, spas, showers, etc. [63].

The genus *Entamoeba* (order *Amoebida*, family *Endamoebidae*) lives in the human gastrointestinal tract. Some of them are commensal, others are of uncertain pathogenicity, and *D. fragilis* and *E. histolytica* are confirmed human pathogens [64].

The researchers believe that protists constantly generate new species with a chimeric repertoire, which can subsequently be viable after adapting to environmental conditions and may occupy a specific niche [65].

Results and discussion

Amazing observations of the symbiosis of algae with viruses in the marine phytoplankton ecosystem were made at the beginning of the article. The described phenomena show eloquently that the microbial world is able to finely perceive the fluctuations of the environment and even the metabolic deficiencies of the host organism. Under hostile environmental conditions, through the unique mechanism of lateral gene transfer (LGT) microorganisms correct the host's exchange of substances, ensuring its adaptation to new conditions and ultimately to its survival.

According to researchers, microorganisms are the "invisible majority" living on Earth that plays a critical role in human and animal health, agriculture, world food network, and industry [66]. Although invisible to the naked eye, the microbial abundance (about 10^{30} of bacteria and archaea) and diversity underlie a healthy global ecosystem, which actually provide support for the biosphere life [67]. At the same time, only 1% to 10% of microbes have been classified, cultured in the laboratory, and further studied [68].

The oldest known traces of bacterial colonies (filamentous cyanobacteria) are 3.7 billion years old. Retroviruses found in the genome of modern humans existed even before the emergence of the mammalian class [5].

According to V. Kordyum, viruses as infectious agents that cause pathological processes are a small part of some general principles in nature [70]. These general principles

are non-cellular information transmitters. Thus, viruses are considered primarily as factors for genetic material transferring. A viral epidemic twice mobilizes an explosive transmission of information, viz. at first, by damaging the cell and transmitting the information contained in it, and secondly, by acting environmentally friendly. An "instant" epidemic will shortly cover the entire population (or even several populations) at once, providing an explosive information transfer to the entire population instantaneously. Thus, what we perceive as a virus-induced disease is nothing but our perception of a side effect of the main event, which is a minor and by no means the main manifestation of the basic and universal process, vital for the whole biosphere.

The article continued on the example of another ecosystem, perhaps one of the most specific and complex on Earth – the human ecosystem. On the one hand, the system involves the host or the human being that is the "crown of creation" endowed with higher consciousness, and microbiota, on the other hand, whose bacterial cells exceed the number of human eukaryotic cells in a ratio of ten to one [71]. Similarly, the genes encoded by the gut microbiome outnumber the human genome by 100 to 1 [72].

The complexity and specificity of the human ecosystem is evidenced by the fact that lateral gene transfer (LGT) is 25 times more intense among human-associated bacteria than among non-human isolates [49].

Historically, it is believed that the phylogenetic line associated with the origin of modern humans (*Homo sapiens*), separated from other hominids 6-7 million years ago (in the Miocene) [73, 74].

Thus, if the above data are true, then *Homo sapiens,* as a separate factor and being still a component or a product of the biosphere, is a relatively recent link of the balanced world ecosystem for over billions of years. At the same time, the 2005 Millennium Ecosystem Assessment concluded that changes in ecosystems due to human activity occurring in the last 50 years have been faster occurring than at any time in history [75]. Human activity disrupts both the structure and functions of ecosystems and natural biodiversity. These disturbances reduce the abundance of some organisms, increase the populations of others, alter the interactions between organisms, and alter the interactions between organisms and their physical and chemical environments.

According to experts, the rapidly mutating viruses as well as the occurrence and recurrence of epidemics will continue and intensify increasingly [76].

Summing up the observations of scientists outlined above, it could be mentioned that our global ecosystem has evolved over approximately 4 billion years. An ecosystem that includes a huge variety of unicellular and multicellular organisms. A microcosm is characterized by a surprising plasticity of adaptive mechanisms to the environment. Despite all the latest technical advances, our environment has little been studied [68]. Over the past 50 years, the Earth biosphere has been subjected to more unprecedented challenges than throughout the whole history, resulting in the loss of many species and habitats, brought to the edge of a planetary catastrophe as a result of human activities. As a product of the biosphere, the human being is actually a very "young" member among the various surrounding organisms. In the current situation (considering the evidence listed above), it can be stated that *Homo Sapiens,* in terms of interaction with the biosphere, is a maladaptive species.

According to some scientists, the adaptive reactions of the species to environmental changes are due to endogenous retroviruses [6]. The latter ones develop the genome of the host species by evolving and producing new descendants of their own, as well as due to the genetic changes via the formation of new exons from introns and/or an increase in the number of genes undergoing alternative splicing. Due to the abundance of genetic material created by endogenous retroelements and under the pressure of natural selection, the species become more complex, thus, adapting to the environment and ultimately surviving. The original species, which have become maladaptive to changing environmental conditions, gradually disappear.

At this point, it is appropriate to develop the above data in terms of the self-similarity principle. This concept assumes that an object is exactly or approximately similar to a part of itself. Self-similarity can be widely found in nature as well. Examples include the blood and lung vascular system, cauliflower or broccoli, crystals, mountain ranges, lightning bolts, river networks, etc. [77].

As previously reported, the possibility of the impact of terrestrial environment through microorganisms on the species is truly astonishing. An example worth mentioning is the relatively simple ecosystem, such as phytoplankton, which can survive under harmful conditions, being influenced by virus. Another different ecosystem or the humans are also constantly exposed to the environment. The environment is represented by the biosphere, which has evolved over billions of years, being on the verge of catastrophe for the last 5 decades due to human activity – a relatively recent species.

The human microbiome always interacts with the global pangenoma (the sum of all genes in the biosphere) through environmental exposure and lateral gene transfer (LGT) [78.] Thus, why it cannot be assumed that the adaptive deficiencies of the human beings, as well as of the other ecosystems cannot be perceived by the microbial consortium that inhabits it. The community is actually a biosphere continuum. The microbiota can potentially acquire any gene from the external environment through lateral gene transfer [79]. This assumption has been supported by a number of scientists, who observed that bacteria can perceive and react to signals from the host microorganism [80-83].

The microbial high-density and biofilm communities of the human microbiota are a good environment for gene exchange and the emergence of microorganisms with novel properties [50]. Moreover, the presence of "single-cell engineers" sensitive to environmental fluctuations, such as amoebae, are likely to generate chimeric forms of viruses.

Thus, it is quite interesting to note some COVID-19 fingerprints. According to the scientists, the SARS-CoV-2 genome contains a unique insert – the Y674QTQTNSPRRAR685 motif, homologous to the neurotoxins of highly venomous snakes of the genera *Ophiophagus* (cobra) and *Bungarus*, as well as the neurotoxin-like sequences from three RABV strains [84]. On the other hand, the study of 236379 medical records of patients diagnosed with COVID-19 showed a development of neurological or psychiatric disorders over the next 6 months following the disease in 33.62% of cases [85]. Therefore, a logical question arises, like what long-term consequences may possibly occur in case of an eventual endogenization in the human genome of viruses with such properties.

According to the bibliographic data, human life on Earth can face the most terrible diseases that can be imagined, due to the man-made environmental disasters [76]. The repeated waves of the COVID-19 pandemic compel us to abandon the idea of human superiority over other species, and rather care for and protect the Earth's ecosystem, plant and animal diversity for a sustainable future on this planet.

Conclusions

Perhaps the COVID-19 pandemic has not emerged as a separate epidemic process, caused by a new virus penetration into the human population, but rather a manifestation of a more complex natural phenomenon – an evolutionary process disguised as an infectious one. From an evolutionary perspective, COVID-19 plays the role of a biospheric factor, trying to help a relatively new species adapt to general conditions for symbiotic survival with other living organisms. The COVID-19 pandemic may be somewhat an exam for non-adaptive species and for our existence as human individuals.

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ID conceptualized the idea, conducted literature review, collected the data, interpreted the data, and wrote the manuscript.

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Ethics approval and consent to participate
No approval was required for this study.

Conflict of interests
The author has no conflict of interests to declare.