 doi:10.20944/preprints202206.0094.v1

Concept Paper

Lithbea, A New Domain outside the Tree of Life

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Abstract: As synthetic/artificial life forms become more abundant and sophisticated, an increasing number of bizarre creatures - xenobots, robots, soft A-life entities, genetically engineered organisms, etc. - are invading our society. Therefore, we need to bring order to all this, to establish what is living and what is not. Here, I intend to classify all these non-natural entities and clarify their status with reference to their consideration or not as living beings, leaving the door open to an uncertain future in which perhaps we can see how "the artificial" and "the natural" merge to originate something new. To order all this "new biodiversity" and to also give entry to viruses (which are excluded of the three-domains tree of life), I propose the creation of a new domain, Lithbea (from the name: life-in-the-border entities), in which all these new human-made entities as well as the viruses will be included. Within this domain there would be two kingdoms, Virus and Humade (contraction of human-made), based on their origin, natural or human-made. A brief description of each component of Lithbea is included and the implications for society and biology of this “new biodiversity” is briefly discussed.

Keywords: viruses; synthetic organisms; artificial life; life domains; Lithbea

1. Introduction

The biodiversity that exists on our planet is grouped into three domains: Archaea, Bacteria and Eukarya (Woese et al., 1990). This classification has, in my opinion, two major drawbacks: i) it separates prokaryotes into archaea and bacteria, making a molecular criterion such as comparison of RNA sequences prevail over the absence of a cell nucleus, and ii) it excludes viruses because they lack cellular structure and because part of the scientific community does not consider them to be living beings (Moreira and López-García, 2009). In addition to these multiple nucleated life forms that exist in nature, an increasing number of new forms of artificial life (hereafter A-life) or synthetic organisms, generated primarily from a combination of biotechnological and artificial intelligence techniques, are emerging. This new landscape, in which natural biodiversity and A-life together with different forms of genetically modified organisms are increasingly intertwined, raises some important questions and issues for the future of biology.

Where is the borderline between the genuinely living and artificial or synthetic entities? Can viruses and synthetic organisms be considered as living beings? Is life the A-life? To find the answers to these and other questions, we first need to have an answer to the fundamental question of biology "what is life", and from that definition to deduce what a living thing is. There have been many attempts to answer this question from very different perspectives, yet none of the proposed definitions have been universally accepted (Benner, 2010). Some scientists and philosophers of science even argue that life cannot be defined (Cleland, 2019) or that seeking a definition is a futile task to understand the origin of life (Szostak, 2012). Recently, I have proposed my own definition of life based on the traits common to all living things (Gómez-Márquez, 2020) as well as in the principles that govern life (Gómez-Márquez, 2021). Thus, I defined life as a process that takes place in highly organized organic structures that is characterized by being preprogrammed, interactive, adaptative and evolutionary. Accordingly, living beings would be

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the system where this vital process takes place. I want to emphasize two important points: i) the consideration of life as a pre-programmed process with the potential to evolve by modifications of the genetic program, and ii) the understanding that every living thing is a system of organic nature and therefore based on carbon chemistry. There has been speculation that there may have been an alternative life form to carbon chemistry, but the only certainty is that everything we know is like this.

Whether or not one agrees with the classification of all cellular forms on our planet into the three *woesian* domains mentioned above, we must find a place on the tree of life where viruses can be located. Viruses straddle the line between living and non-living, and we could say that viruses are alive when they infect a cell, as they control the production of new viruses and fulfil the fundamental objective of all living beings, which is none other than to perpetuate the species, and when they are outside the host, viruses behave as infectious inert entities (Dupré and O'Malley, 2009; Gómez-Márquez, 2021). It is this dichotomy between living and inert that makes me think that we should consider a new category (domain or kingdom) of living entities to include viruses within the living things that inhabit our cells, bodies and ecosystems.

Synthetic biology and A-life are two branches of science that blend our knowledge of biology with engineering and artificial intelligence technologies. Scientists build hybrid entities, synthetic organisms and living machines, robots, or computer algorithms to better understand the process of life (Deplazes and Huppenbauer, 2009; Bongard and Levin, 2021). In this context, the terms "artificial" and "synthetic" have closely related meanings because both words refer to entities manufactured by humans and, consequently, are not the result of a natural evolutionary process. Sometimes they are even used interchangeably even though they are not exactly the same thing. A-life is more related to artificial intelligence, to the computer design of entities that pretend to imitate the living, such as, for example, some computer programs (software A-life or soft A-life) or physical robots (hardware A-life or hard A-life) (Gershenson et al., 2020). There is a third type of A-life (wet A-life) that aims to synthesize living systems from biochemical manipulations (Aguilar et al., 2014); we could say that wet A-life research, which, unlike the two previous ones that are not based on organic matter, also falls within the field of synthetic biology. Using the words of Aguilar et al. (2014) "Artificial life has studied living systems using a synthetic approach: build life in order to understand it better, be it means of software, hardware, or wetware".

In the creation of A-life, it is the engineer or the scientist who decides how this system, of a non-organic nature, imitator of the living, is going to be. However, in synthetic biology, what is often produced is a redesign of pre-existing organisms for medical, industrial, environmental, or nutritional purposes (Garner, 2021). In addition, synthetic biology is more focused on basic research into the life process and establishing what the minimum requirements are for making a cell from its basic components (Fernau et al., 2020). Anyway, the A-life and synthetic biology are becoming increasingly interrelated, making it difficult to clearly differentiate between them. What is important is to establish clear categories of "organisms or entities" generated by human intervention.

As synthetic/artificial life forms become more abundant and ever more sophisticated, a growing number of bizarre creatures – xenobots, soft and hard A-life entites, genetically modified organisms, etc. - are beginning to populate laboratories, computers, factories and, in some cases, natural spaces. In this work, I intend to order all these creatures or entities related to life and clarify their status with reference to their consideration or not as living beings, leaving the door open to an uncertain future in which perhaps we can see how "the artificial" and "the natural" merge to originate something new that we can imagine but we do not know for sure how it will be.

2. Life-in-the-border entities (Lithbes)

Lithbes, acronym of life-in-the-border entities, are beings, systems, or realities that we could place on the border between the living and the inert, between the natural and the artificial, between the organic and the inorganic, because they do not meet all the conditions necessary to be considered as truly living beings.

To identify and classify the lithbes, I take as the main criteria their origin (natural or synthetic/artificial), and the characteristics shared by all living beings (organic nature, high degree of organization, pre-programming, interaction, adaptation, reproduction, and evolution) as defined elsewhere (Gómez-Márquez, 2021). Naturally occurring lithbes are those entities that have arisen because of the evolutionary process and are not included within the three *woesian* domains. Artificial/synthetic lithbes are entities that have been manufactured, partially or totally, by humans and, therefore, they are not the consequence of a natural evolutionary process. Accordingly, there are four types of lithbes: those of natural origin, which are viruses, and those of synthetic/artificial (human-made) origin, which include synthetic organisms, with all their variants, physical robots or hard A-life, and soft A-life. It is important to emphasize that whereas natural viruses are the result of an unintentional evolutionary process, synthetic organisms, robots, and soft A-life are human-made, and this is a fundamental difference. Furthermore, the key distinction between synthetic organisms and A-life representatives is that the former are cellular and organic entities (fulfilling almost all the characteristics of living things except their non-natural origin), while the latter are non-organic or inorganic and do not involve metabolic processes and gene expression. We can find biochemistry and genetics in a synthetic organism, but never, at least for the time being, in a computer program or a robot.

3. Viruses

Viruses are acellular infectious agents, intracellular parasites, formed by a macromolecular complex of proteins and nucleic acids. They do not metabolize substances, nor can they reproduce by themselves, grow, or breathe. Outside the cell, viruses do not satisfy the seven characteristics of living things because they are inert particles without any vital activity. In contrast, when viruses infect a cell, they become a sort of living entity because they meet the characteristics common to all living things: in addition to being organic, highly organized and possessing a genetic program, they interact with the host, they reproduce, and they can adapt and evolve because they can mutate. We could say that they are alive (Gómez-Márquez, 2021).

Some authors include viruses within the biological entities called biological replicators along with plasmids, organellar DNA, transposons, etc. (Koonin and Starokadomskyy, 2016) whereas other scientists classify them as capsid-encoding organisms (Raoult and Forterre, 2008). However, viruses differ from all these DNA elements in their ability to infect cells on their own, to interact with the host cellular machinery and to evolve. Their exclusion from the tree of life, even though they played a key role in the history of life most likely from its origins, should be somehow reevaluated. Today virtually no one questions the importance of the virosphere in the evolution of species and ecosystems (Agnati et al., 2021) as well as in shaping the tree of life (Villarreal and Witzany, 2010).

The reason for including viruses as lithbes lies in their live-inert duality and in the fact that they lack cellular structure and are therefore excluded from the woesian domains. They are the only lithbes of natural origin although they could be created in the laboratory (artificial origin), and eventually be incorporated into any ecosystem due to their infectious capacity. It is certainly a very high risk, with unforeseeable consequences, to release artificial viruses outside the laboratory.

4. Synthetic Organisms

There is no single definition of what a synthetic organism is and very different definitions can be found on the web. Three examples: i) organisms for which a substantial portion of the genome or the entire genome has been designed or engineered (seen in "Nature portfolio"); ii) organisms that produce a substance, such as a medicine or fuel, or gain a new ability, such as sensing something in the environment (NHGRI, National Institutes of Health); iii) an organism that has been synthesized by the human beings

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(Deplazes and Huppenbauer, 2009). They are probably all correct, even if they emphasize different nuances (the genome, industrial application, or the fact that they were created by us). We could add another definition for synthetic organisms: living entities that are not the result of a natural evolutionary process.

In this paper, by synthetic organisms I mean human-made living entities that are based on carbon chemistry. Consequently, physical robots or computer programs are not synthetic organisms, they are entities that belong to A-life (see below). All types of synthetic organisms meet (or will meet) the seven traits common to all living things (see above) and are human-made entities created from the knowledge or use of real living things.

According to my proposal (Figure 1), synthetic organisms can be divided into three different types: 1) Genetically Engineered Organisms (GEO), 2) Living Programmable Organisms (LPO), and 3) Artificial Created Cells (ACC).

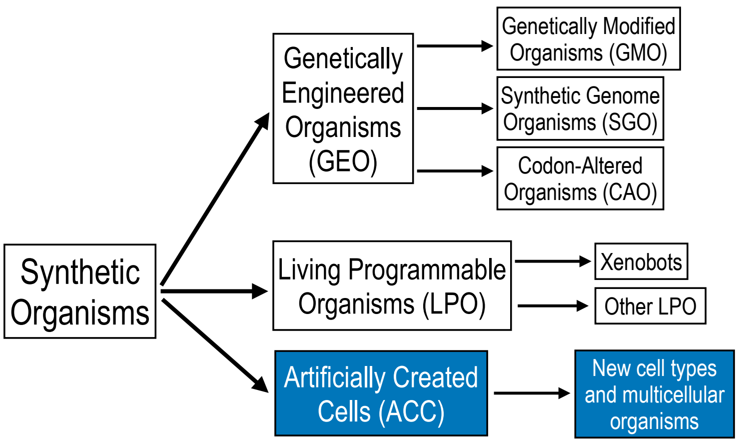

Figure 1. Classification of synthetic organisms. There are three classes of synthetic organisms which differ in the procedure employed to built them. Genetically Engineered Organisms (GEO) have their genome partially or totally modified. There are three kinds of GEO: GMO, SGO, and CAO. The GMO have incorporated a gene (or genes) from other species becoming a transgenic organism. Other GMO consist in organisms with the genome edited either by knock-in (insertion of a sequence in a specific region of the genome) or knock-out (delete or inactivate a specific sequence of the genome). The SGO includes all organisms with a synthetic complete genome, i.e. designed and constructed in the laboratory. CAOs have their genetic code altered either because the number of triplets has been modified (taking advantage of the redundancy of the genetic code) or because new triplets have been introduced. Living Programmable Organisms (LPO) are new forms of life designed by the combination between biology techniques, robotics and artificial intelligence. The first member of this bizarre group of synthetic creatures are the xenobots designed by a special algorithm and constructed from embryonic cells of X. laevis. Other LPO includes all LPO that have not yet been born but are very likely to start being produced in the near future. Finally, Artificial Created Cells (ACC) will include all cells and multicellular organisms synthesized in the laboratory following essentially a bottom-up approach. No cell has yet been made using this strategy, but it is very likely that in the not-too-distant future the goal of making a cell from its components will become a reality.

4.1. The GEO

GEO are organisms whose genome or genetic code has been intentionally altered (engineered) in the laboratory to achieve a specific result. These genomic changes may be aimed at causing a physiological change, producing a specific substance, or altering the genome to investigate its function or to open up new genomic possibilities. Depending on the type of manipulation carried out to create the synthetic organism, I find three main types of GEO: i) Genetically Modified Organisms (GMO), ii) Synthetic Genome Organisms (SGO), and iii) Codon-Altered Organisms (CAO).

GMO are organisms whose genome has been manipulated in the laboratory using recombinant DNA techniques either by the introduction of a foreign DNA from another species (transgenic organisms) or by genome editing (gene-edited organisms). Animals, plants, and bacteria have been used to generate transgenic organisms for purposes related to basic research, food or the production of substances of therapeutic interest (Cartwright, 2009). Gene editing may involve deletions, insertions (gene knock-in), silencing (gene knock-out) or repression of specific genes (Khalil, 2020). Key among gene-editing technologies is a molecular tool known as CRISPR-Cas9 that allows to remove and insert DNA in the desired locations (Anzalone et al., 2020). It should be noted that the difference between the knock-in organism and the transgenic organism is that in the former, the insertion is directed to a specific locus in the genome, whereas in the transgenic organism, the insertion of the transgene is random.

SGO are organisms that have a genome entirely synthesized in the laboratory. In 2010, researchers from the J. Craig Venter Institute (JCVI) announced the first self-replicating synthetic cell known as JCVI-syn1.0 (Gibson et al., 2010). For that purpose, they digitized the genome of the bacterium *Mycoplasma mycoides* and then synthesized and assembled it in vitro. Later on, the JCVI team created the smallest synthetic cell up to that time, *M. mycoides* JCVI-syn3.0, a minimized version of JCVI-syn1.0 with only 473 genes (Hutchison III et al., 2016). However, this weird bacterium behaved strangely as it grew and divided producing cells with very different shapes and sizes. Interestingly, it was found that when they were added seven genes to JCVI-syn3.0, normal growth and cell division were restored (Pelletier et al., 2021). On the other hand, it was recently reported the creation of the first bacterial genome designed entirely by a computer from the essential genome of *C. crescentus* (Venetz et al., 2019), although a viable engineered bacterium, named as *Caulobacter ethensis-2.0*, does not yet exist. Basic research on minimal cells and synthetic genomes should be very useful to understand the evolutionary history of life as well as to bring about new biotechnological applications.

CAO are synthetic entities in which the genetic code has been altered, either by changing the number of triplets or by introducing new codons that do not exist in nature. The generation of organisms with a reduced genetic code, avoiding redundancies without losing information, or the introduction of new variants from synthetic nucleotides, is one of the most important challenges for researchers in synthetic biology (Rennekamp, 2019). Researchers at the MRC Laboratory of Molecular Biology (Cambridge), redesigned the DNA of *Escherichia coli*, creating an artificial genome that has an altered genetic code with 61 codons instead of 64 (Fredens et al., 2019), demonstrating that life can operate with a reduced number of synonymous sense codons. Scientists are now creating synthetic organisms with an expanded nucleotide alphabet by making DNA with unnatural nucleotides (Duffy et al., 2020; Nie et al., 2020); these modified DNAs are also called xeno nucleic acids. Remarkably, Romesberg and coworkers have been able to engineer *E. coli* and create a semisynthetic organism with an expanded genetic code (Zhang et al., 2017). Subsequently, Hoshika et al. (2019) presented the *hachimoji* DNA and RNA, an eight (hachi-) letter (-moji) genetic system, demonstrating the power of synthetic biology research for developing new synthetic organisms and biotechnological applications alongside understanding how fundamental biological systems work.

Researchers are aware of the enormous applications of modifying or expanding the genetic alphabet, although this is not without risk, especially if these organisms were to "escape" from the laboratory. Nature also experiments with variants of the ACGT alphabet. This is the case of the genome of certain phages in which adenine (A) has been replaced by 2-aminoadenine or diaminopurine (Z) generating a DNA with an alternative alphabet (ZTGC) that evades the attack of restriction enzymes (reviewed by Grome and

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Isaacs, 2021). Discoveries like this expand the possibilities of synthetic biology for designing new organisms with modifications to their genetic code.

4.2. The LPO

LPO are living programmable organisms or living robots, i.e. synthetic organisms which are the result of combining molecular and cell biology technology with artificial intelligence. The first designed LPO were the xenobots, so-called because they were made from cells of the African frog *Xenopus laevis*. They are synthetic life forms designed using an evolutionary algorithm, and built from *X. laevis* embryonic stem cells (Kriegman et al., 2020). The first xenobots grew from the combination of skin (working as an architectural component) and heart cells (giving motion to the whole). Xenobots exhibit coordinated locomotion, push a payload, can work together in groups, and heal themselves if damaged (Blackiston et al., 2021). Interestingly, these artificial multicellular aggregates show a new form of self-replication by pushing loose cells together (Kriegman et al., 2021). The term LPO is taken from J. Bongard, one of the researchers who invented the xenobots, who said: "They're neither a traditional robot nor a known species of animal. It's a new class of artifact: a living, programmable organism."

Xenobots have many potential applications, from the removal of pollutants from the oceans to the treatment of diseases. Unlike robots made of plastic and metal, xenobots are biodegradable and therefore their disposal, in case of massive use, would not pose major problems. Over the next few years, we can reasonably expect to have improved xenobots and new creatures to enrich the LPO world.

4.3. The ACC

As we have mentioned above, scientists working in the field of synthetic biology are seeking ways of altering living organisms with different purposes, but the main goal of synthetic biology is to build from its essential components a fully synthetic or artificial cell that can grow and divide (Powell, 2018). This would be a milestone in biological research and would also bring us much closer to understanding how cellular life originated on our planet.

Bottom-up synthetic biology uses both biological and artificial chemical building blocks to create artificial cells. Researchers have been trying to create cells for several decades using a bottom-up approach, putting together the essential components of any cell: a membrane, a metabolism that allows energy to be obtained and new components to be synthesized, a cytoskeleton, and genetic information that ensures the continuity of the cell (Jia and Schwille, 2019; Frischmon et al., 2021; Wang et al., 2021). At the moment, the development of "proto-cells" that mimic real cells as well as the development of networks of communicating synthetic protocells, are the main goals of bottom-up research in synthetic biology (Lyu et al., 2020; Grimes et al., 2021).

Although the goal of creating a cell from scratch has not yet been achieved, there is no doubt that it will be achieved sooner or later. For this reason, I have included in the classification of "Synthetic Organisms" this section on "Artificially Created Cells", even though we cannot include any elements for the time being.

5. A-Life entities

The aim of A-life is to build life to understand it better, be it by means of software, hardware, or wetware (Aguilar et al., 2014). Three types of A-life are usually mentioned in the specialized literature: i) soft A-life (short from software), which refers to computational modeling and simulation of lifelike behaviors, ii) hard A-life (short for hardware), which encompasses physical robots or, more simply put, life-like artefacts made of metal and plastic, capable of sensing their physical environment and acting in response, iii) wet A-life which is basically the same as what in synthetic biology refers to the creation of artificial cells from their fundamental components (what I have included in ACC synthetic

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organisms). Consequently, in the universe of A-life I only include those "creatures" related to software and non-organic robots.

In many respects, the study of A-life has borrowed from concepts and tools related to the self-organization defined as the ability of a system (the living being or the lithbe) to display ordered spatiotemporal patterns solely as the result of the interactions among the system components (Trianni et al., 2020). This is because in the life process there are many behaviors in which self-organization is present, such as self-replication, physiological homeostasis or self-assembly (Aguilar et al., 2014).

The purpose of most research on soft and hard A-life is not to create life, but to gain a better understanding of the processes of life (genetic, metabolic, and behavioral) and the structure and functioning of living beings (anatomy and physiology) by simulating them on computers or modeling them with robots. Soft A-life creates simulations that claim to show life-like behavior whereas hard A-life produces hardware also trying to imitate nature (Bedau, 2003). Both approaches generate "creatures" that are not based on the chemistry of life and, therefore, can hardly be considered as living: they imitate or simulate the living but are far removed from it, even if it might seem otherwise (as I mentioned above wet A-life is very different because it works with organic matter). If I consider the attributes common to all living things (Gómez-Márquez, 2021), I must conclude that both soft and hard A-life entities are not living things at all. They are not organic, and they cannot adapt, reproduce, and evolve by themselves.

Cellular automata were one of the first modelling frameworks employed in the soft A-life research. This model encompasses a grid of cells, each of which takes a discrete state (Peña and Sayama, 2021). The use of computer simulations or modelling, although not strictly a biological process and therefore not directly linked to life, offers the possibility of practical applications and it also can help us to better understand the nature of biological systems (Komosinski and Adamatzky, 2009; Aguilar et al., 2014).

Mechanical or physical robots can imitate living organisms, but they are not living machines or living systems because inside them there is no life. Robots are made of metal and plastic, they are predictable because they do not mutate and evolve by themselves; these machines are totally dependent on the computer program that controls their behavior, whereas living beings, in addition to having a genetic program written in their DNA, interact with their environment and with other organisms of the same or other species. Evolutionary robotics is a very active field of research and is a useful tool to generate and test new hypotheses in biology and cognitive science, as well as to support us in education, industrial processes, and biomedicine (Eiben, 2021). However, I believe that we are a long way from a metal and plastic machine having the ability to mutate, reproduce and pass on these mutations to its robotic progeny; only then will it be able to evolve, at least from a Darwinian point of view.

6. The Lithbea domain

The term "domain" was introduced by C. R. Woese et al. (1990) together with a new system for classifying prokaryotic and eukaryotic organisms into three major domains. Now the question is how to group all lithbes and relate them to the three *woesian* domains. I propose to create a fourth domain called Lithbea, separate from the three previous ones, which would include viruses, synthetic organisms, and artificial life forms (Figure 2). The name Lithbea derives from what I have called life-in-the-border entities. This new domain would have two kingdoms: Virus and Humade (derived from the human-made contraction of words). It is very likely that the cellular life forms share a universal common ancestry (Theobald, 2010) but, in contrast, there can be no common ancestor for the panoply of heterogeneous entities included in the Lithbea domain.

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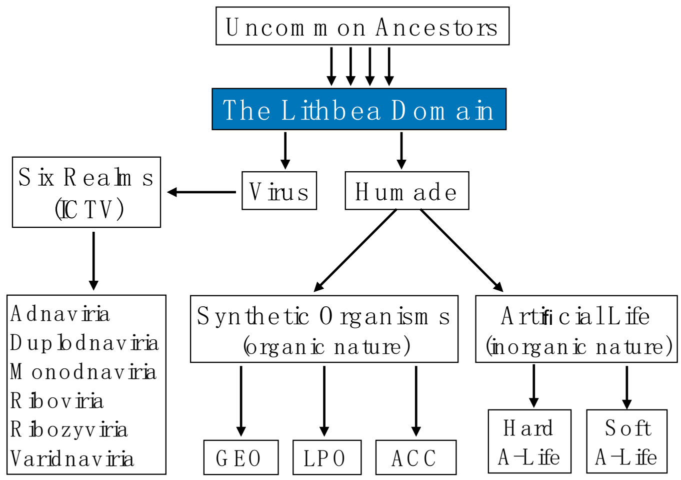

Figure 2. The Lithbea domain. Because of the heterogeneous nature of the members of the Lithbea domain, there is no common ancestor for all of them. Lithbea is divided into two kingdoms: Virus and Humade. Organisms belonging to Virus are organic in nature and have a natural origin (a consequence of the evolutionary process). In the kingdom Virus there are six realms as established by the ICTV. This kingdom initially excludes viruses that could be created in the laboratory. Humade is a kingdom that includes human-made lithbes: synthetic organisms (their chemical composition is equivalent to that of any cell) and members belonging to A-life (soft-A life and robots) that are inorganic.

The Virus kingdom includes all viruses and represents the most diverse kingdom on our planet with many species yet to be discovered (Dance, 2021; Harris and Hill, 2021). For example, the recent identification of thousands of marine RNA viruses enabled the development of more robust phylogenetic trees regarding the evolution of RNA viruses (Zayed et al., 2022), showing the tight evolutionary connections between viral and cellular worlds. According to the International Committee on Taxonomy of Viruses (ICTV), the "Realm" is the highest taxonomic rank established for viruses (ICTV, 2020; Dance, 2021). Consequently, the Virus kingdom has six realms: Adnaviria, Duplodnaviria, Monodnaviria, Riboviria, Ribozyviria and Varidnaviria.

Do viruses have a common ancestor or have they arisen n-times throughout the history of life from different ancestors? The origin of viruses is still a mystery and there are several hypotheses to explain it. Thus, they may have arisen from mobile genetic elements, from descendants of previously free-living organisms, or perhaps they existed before, and led to the evolution of cellular life (Wessner, 2010). Other authors believe that viruses emerged in a "chimeric" scenario in which different types of replicons recruited host proteins to form virions, and that the emergence of new groups of viruses occurred at all stages of the evolution of life (Krupovic et al., 2019).

The Humade kingdom incorporates all entities that have been created by humans. This is the only common nexus of all lithbes belonging to this kingdom. There is no common ancestor for all Humade members, but several unrelated ancestors, so it is illogical to establish evolutionary relationships between the individuals of this kingdom. What unites all Humade members is not their evolutionary origin but their composition and creation system. The lithbes in this kingdom can be either organic (synthetic organisms) or inorganic (computer programs and robots).

Synthetic organisms are divided into three different types based on the way in which they have been created in the laboratory. We can consider them living organisms because they are organic, highly organized, have a genetic program, can interact with their

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environment and could adapt, reproduce and evolve. However, they have a fundamental shortcoming compared to natural living beings: they are not the result of an evolutionary process because they have been artificially manipulated and, therefore, have not participated in the history of life.

A-life includes all kinds of lithbes that are not of organic nature. This is a very important point because life is a process that takes place in chemical systems based on carbon chemistry. That makes it possible for living things to metabolize, adapt, interact with their environment and evolve. It is clear that lithbes lacking proteins and nucleic acids, cellular structure, metabolism, etc., are far removed from the systems we call living things and the process we call life. There are two main classes of A-life: soft A-life (computer algorithms) and hard A-life (mechanical robots or machines equipped with an artificial intelligence program). In both cases, we find some features equivalent to those we can observe in living beings, such as the existence of a program that controls them, a high degree of organization or even the capacity to interact with their environment but, in addition to being inorganic in nature (plastic and metal as main components) and human-made, they lack the ability to adapt, reproduce and evolve on their own and therefore cannot be considered as living beings.

7. Connections between Lithbea and the cellular domains

There are several connections between the entities belonging to the Lithbea domain with the organisms included in the three domains of cellular life (Figure 3). In all these interactions, the virus kingdom plays a central role because the branches of the viral tree (represented by the six realms) and the three cellular domains touch each other from the beginning of evolution (Harris and Hill, 2021). Viruses infect all kinds of cells, affecting to all domains of life, and they have participated in the evolution of species and ecosystems for millions of years exchanging DNA between hosts (horizontal gene transfer), regulating the population of microbial communities, or participating in global geochemical cycles and nutrient recycling (Jover et al., 2014). It should also be noted that natural viruses could infect some synthetic organisms and interfere with their life cycle.

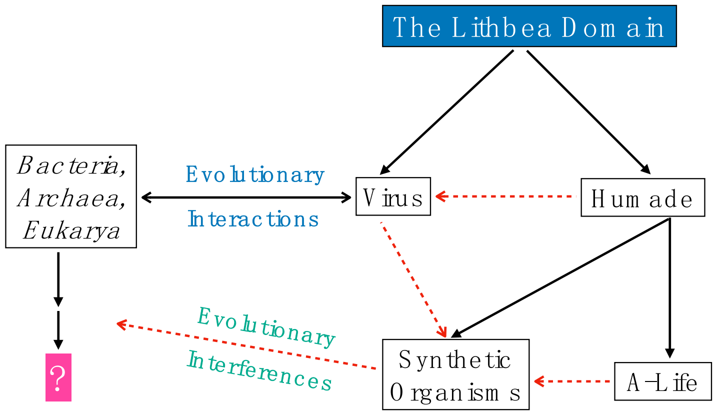

Figure 3. Interactions between the four domains. Here it is shown the interactions between the diverse kinds of lithbes with the domains of cellular life. The double-headed arrow indicates the existence of real reciprocal evolutionary interactions between the elements of the virus kingdom and the organisms belonging to the three *woesian* domains. The unidirectional arrow with dashed line indicates possible interactions between the lithbes themselves and between the lithbes and the three *woesian* domains. The question mark signifies an uncertain future for biodiversity on our planet caused by both the destruction of nature and the increasingly frequent interactions between "synthetic/artificial" and "natural" to create something unknown.

As a responsible society, we should consider that new viruses, like known species or completely new ones, can be produced in specialized laboratories and legally regulate such biotechnological practices. These new viruses could infect any type of living thing, synthetic or not, and pose a danger to humanity in the form of a pandemic or by disrupting the biological balance.

The organic nature and cellular structure of synthetic organisms makes it possible, but undesirable, that they interact, accidentally or unintentionally, with wild organisms. If this were to happen, it could seriously interfere with the normal course of evolution in nature, something that is already happening due to human intervention in ecosystems. An example of this is the massive cultivation of GM plants, which has been shown to produce ecologically dangerous alterations to the environment (Tsatsakis et al., 2017). We should do our utmost to ensure that the cultivation of transgenic plants for food purposes does not lead to irreparable ecological disturbances. There are also interactions (and in the future there will be more) between artificial life and synthetic organisms. A clear example of this are the xenobots (discussed above) which are born from the combination of biotechnology and artificial intelligence. In conclusion, the enormous advances in the field of synthetic biology, together with the development of new technologies, pose a future that will be both exciting from a scientific point of view and uncertain from a social and ecological perspective.

Acknowledgments: I want to thank Dr. Miguel López (CIMUS-USC) for his support and dedicate this work to my students to whom I have always tried to transmit my passion for biology.

Conflicts of Interest: The authors declare no conflict of interest.

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