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ORIGINAL PAPER

# Lithbea, a New Domain Outside the Tree of Life

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**Abstract**
At this time when the development of synthetic biology and artificial intelligence are changing the world around us, philosophers and scientists, first of all, must converge to analyze the present and predict the ethical-social consequences and biological dangers associated with new "living entities" that are not the result of the natural evolutionary process. As synthetic/artificial life forms (xenobots, robots, transgenic organisms, etc.) become more and more abundant and sophisticated, it seems first of all necessary to bring some order to all this new biodiversity, establishing what is alive and what is not, and analyzing the consequences of this incessant creative activity. Here I intend to organize all these human-made entities and clarify their status as living beings or artificial elements, leaving the door open to an uncertain future in which we will be able to see how "the artificial" and "the natural" could merge to originate something different from everything known. Accordingly, I propose the creation of a new domain, Lithbea, which includes all synthetic and artificial entities within a new kingdom called Humade (derived from human-made). I have also included viruses in a new realm, the Viral kingdom, because they were excluded from the classical three-domain tree of life despite playing a fundamental role in the evolution of biodiversity on Earth. Finally, I make a brief comment on the unpredictability of the unknown, the implications of this new landscape of biodiversity, and the uncertain future of all these advances.

**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 (hereafter *woesian* domains) as established by Woese et al. (1990). This classification has, in my opinion, two major drawbacks: (i) it separates

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prokaryotes into archaea and bacteria, making a molecular criterion such as the comparison of RNA sequences prevail over the absence of a cell nucleus, and (ii) it excludes viruses because they lack cellular structure and are not considered living beings by the scientific community (Moreira and López-García 2009). In addition to these natural life forms arising from the evolutionary process, more and more artificial life (hereafter A-life) forms and synthetic organisms, are being engineered. This new landscape, in which natural biodiversity, synthetic organisms and A-life entities are increasingly intermingled, raises some important questions for the present and future of the biodiversity in our planet with significant implications in science, biomedicine, economy and philosophy.

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 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). Wet A-life, unlike the two previous ones, is based on organic matter and therefore falls within the field of synthetic biology.

Synthetic Biology was defined as "the design and construction of new biological parts, devices, and systems and the redesign of existing, natural biological systems for useful purposes" (Calvert 2010). The advances in this branch of biology opens up new and uncertain biological possibilities with a wide range of applications and implications, generating significant scientific and philosophical debate (Ijäs and Koskinen 2021). In addition, synthetic biology expands the biodiversity of the planet by constructing new synthetic organisms with structural and/or functional elements that are different from natural ones and, therefore, are not the result of the evolutionary process (Fernau et al. 2020; Garner 2021).

As synthetic/artificial life forms become more abundant and ever more sophisticated, a growing number of bizarre organisms—xenobots, soft and hard A-life entities, genetically modified organisms, etc.—are beginning to populate laboratories, computers, natural spaces, etc. In this work, I intend to order all these human-made entities and clarify their status with reference to their consideration or not as living beings. In this new organization of the non-*woesian* biodiversity, I have also included the viruses because they straddle the line between living and non-living. In this sense, 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, but when they are outside the host, they 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 to include viruses within the living things that inhabit our cells, bodies, and ecosystems. Not forgetting that some viruses could also become part of the synthetic organisms world because they can be also created in the laboratory.

## 2 Life and Living Beings

Where is the borderline between the genuinely living and artificial or synthetic entities? Can viruses be considered as living beings? Is life the A-life? Are synthetic organisms new entities with their own individuality? 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". When we have a working definition of life, we will be able to establish more easily whether this or that entity is really a living being or not.

What is life? This is a question without a clear answer because life is a very difficult concept to define. In fact, there is a great controversy among scientists and philosophers of science on this question. There have been many attempts to define life from very different perspectives (obviously a comparative study of this enormous variety of definitions of life is beyond the scope of this article), yet none of the proposed definitions have been universally accepted (Benner 2010; Gómez-Márquez 2021; Mariscal 2021). 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). In this context, the comment that E. Koonin (2012) wrote about the complexity of defining life seems to me to be very appropriate: "… although life definitions are metaphysical rather than strictly scientific propositions, they are far from being pointless and have potential to yield genuine biological insights". On the other hand, we have general theories in physics and chemistry that help us understand the universe, but as far as biology is concerned, there are still no theories of our own that, together with the laws of science and philosophical thinking, help us explain nature. The lack of a general theory underpinning biological knowledge makes more difficult to understand life phenomena and to define what life is.

Reflecting on this, it was recently proposed a set of principles, named as the commandments of life, to explain the vital phenomena (Gómez-Márquez 2020). From this theoretical approach, it was proposed a definition of life based on the characteristics common to all living beings. Thus, life is defined as a process that takes place in highly organized organic structures that is characterized by being preprogrammed, interactive, adaptative and evolutionary (Gómez-Márquez 2021). Accordingly, living beings are the system where this vital process takes place. I want to highlight two important points because they are key to determining whether synthetic organisms or artificial life entities are something we can consider as living or not: (i) the consideration of life as a pre-programmed process, with adaptive capacity and the potential to evolve, and (ii) the realization that every living thing is a system of organic nature and, therefore, based on carbon chemistry (whether there is an alternative life form to carbon chemistry is not a fact, it is only a speculation).

## 3 Natural Versus Non-natural (Synthetic or Artificial) Life

Philosophers debate on the ontological differences between artifacts (an algorithm, a robot, or a genetically modified organism) and natural objects (a living organism). There is one obvious difference between them: their origin. Natural objects come into being without human intervention, whereas so-called artifacts are human-made. In addition, there are other differences between them related to their structure, functionality, and composition.

L. Baker defines artifact as “objects intentionally made to serve a given purpose” (Baker 2008) giving importance exclusively to the creator but ignoring something as important as the composition of the object and its structure. From that definition, a robot would be the same as a transgenic organism because both are “objects” constructed for a specific purpose. However, this is not true because a robot is an artificial entity and a transgenic organism is a living being.

Adding a different perspective, philosopher Symons (2010) asks if there is any difference between organisms and artifacts and concluded that there is a meaningful difference between both entities, and that this difference involves the character of their individuality. Moreover, he asks whether genetically engineered animals will have different persistence conditions than their wild cousins and concluded that genetically engineered animals are still individuals (Symons 2010). In my opinion, genetically modified organisms do not lose their vital essence, their character as a biological species (a transgenic mouse or tomato remains a mouse or a tomato) even if it has been modified in its genome. However, one fundamental question should be considered in this analysis: When does a genetically modified living being become a synthetic organism different from the one that was initially given its new identity by its creator? Symons examines the paradox of the Ship of Theseus, which raises the question of whether an object that has had all its components replaced remains fundamentally the same object, to resolve the problem of the individuality of artifacts and organisms (Symons 2010).

In my opinion, which is not that of a philosopher stricto sensu but that of a professor of Biochemistry and Molecular Biology, the solution to this metaphysical problem is that the artificial object will remain the same. Let us take a photographic camera as an example. When we change the batteries in a camera, it is still the same camera. When we change the memory card or even put in a different lens, it is still the same camera. With all these changes, the inanimate artifact known as a camera has not lost its identity as that camera. In the case of A-life entities such as, for example, a robot, this artifact will remain the same robot, even if all its components are changed, as long as the new components are the same: the robot will look the same (identical structure) and do the same functions; like Theseus’ Ship, the robot is just an inanimate object and does not lose its “artifactual individuality” as long as the replacements are identical. The entities belonging to A-life cannot lose their individuality, their vital essence, because they have never had it. They never were and never will be living beings because they lack all the necessary requirements for it. Any entity belonging to A-life (computer programs or robots) can be mass-produced. However, synthetic organisms, being organic in nature, with a functional genome, can mutate and generate individuals different from the original specimen. A robot can be an artificially organized, pre-programmed and interactive system, but it is not alive because it is neither organic, nor does it reproduce, adapt, or evolve on its own, without the intervention of its designer, it will always need to be built or programmed by an engineer to do so.

On the contrary, in the case of a synthetic organism, when we alter its genetic material, we are altering the heart of its identity as a living being, which is its genome and, therefore, it will no longer be the same organism, although it will still be the same species or the same type of synthetic organism. In other words, a transgenic mouse or tomato will still be a mouse or tomato, but it will not be exactly the same as a wild mouse or tomato. Noteworthy, they will cease to be a mouse or a tomato when the modifications to their genome are so profound that they are unable to hybridize (reproduce) with their wild relatives. Then these organisms will seek a different individuality, giving rise to new species of synthetic organism. What happens to the individuality of organisms that have been modified without manipulating their genome? Nothing would happen, these organisms continue to maintain their individuality. Let's take the pacemaker as an example. I wear a pacemaker that keeps my heart in shape, but neither my genome nor my brain or other body parts have been altered; consequently, my individuality as a human being has not changed. Organisms that carry a pacemaker, contact lenses, a hip prosthesis, or any other inanimate object, cannot be considered synthetic organisms or members of the A-life world. They do not belong to the new Lithbea domain (see below).

The philosopher M. Bedau wrote: "So, to the extent that the essential properties of living systems involve processes like self-organization and evolution, suitably programmed computers will actually be novel realizations of life" (Bedau 2007). However, from my point of view, as I mentioned before, A-life cannot be considered life (at least in the biological sense of the term) because A-life does not meet all the requirements to be considered alive, just as a flight simulator is not a plane or a toy dog is not a dog. An A-life entity is not organic, nor does it have anything equivalent to genetic material with the capacity to express, replicate, adapt, mutate, and evolve in response to environmental stimuli. Furthermore, the structures and functioning of living things can be explained from their evolutionary history, but such explanations are not available for the creatures of A-life because they have no evolutionary history, they always depend on their designer. My conclusion is that A-life entities are artificial and cannot be considered as true living organisms, whereas synthetic organisms are living beings that are not the fruit of the tree of life but the result of the will of their creator.

## 4 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, synthetic, or 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* tree of life. Artificial and 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. Consequently, there are two types of lithbes: those of natural origin, which are represented by viruses, and those of synthetic/artificial origin, i.e. human-made, which include synthetic organisms, with all their variants, robots or hard A-life, and algorithms or soft A-life. It is important to note that, while viruses are the result of a natural, and therefore unintentional, evolutionary process, synthetic organisms and artificial life, robots and soft A-life are the total or partial result of the will of the creator who designs them according to a pre-established plan. In addition to their origin, the key distinction between synthetic organisms and representatives of A-life is that the former are cellular and organic entities, fulfilling almost all the characteristics of living beings, except their non-natural origin, while the latter are not organic and do not perform metabolic processes or gene expression, nor are they capable of evolving on their own, without the intervention of the designer. 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.

## 5 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, they are alive!

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. 2022) 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 also be created in the laboratory (artificial origin), and eventually be incorporated into any organism due to their infectious capacity. It is certainly a very high risk, with unforeseeable consequences, to release artificial viruses outside the laboratory.

Noteworthy, it has been recently reported that the flu virus and the respiratory syncytial virus can fuse together to create a new hybrid virus that can evade human immune system (Haney et al. 2022). This finding shows that viruses from completely different families can combine generating a new pathogen. Is it possible that natural viruses could also be combined with viruses created in the laboratory? The most likely answer is yes, viable viral chimeras could be created with unpredictable ecological and human health consequences.

## 6 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 (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. Here, 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 are organic in nature, highly ordered, have their own metabolism, their own genome, etc., but the fundamental difference with other living things is that they are human-made entities created by modifying other living things whose origin is in nature or by creating them from scratch.

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

## 7 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

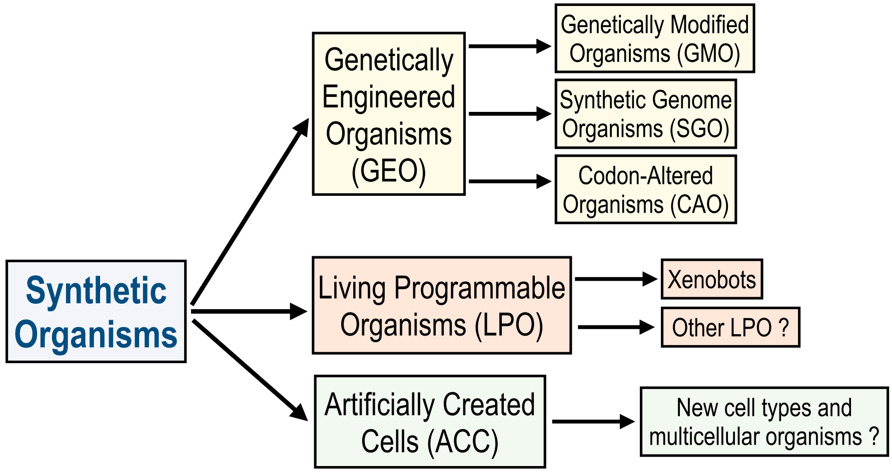


**Fig. 1** Classification of synthetic organisms. If we consider the procedure for constructing synthetic organisms in the laboratory, we can distinguish three different types: (i) Genetically Engineered Organisms (GEO) have altered their natural genome or they have a new genome synthesized in the laboratory. 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. The CAO 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. (ii) 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 a frog. Other LPO includes all LPO that have not yet been born but are very likely to start being produced in the future. (iii) 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

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 Isaacs 2021). Discoveries like this one, besides showing us once again that nature is full of surprises, expand the possibilities of synthetic biology to design new organisms with modifications in their genetic code.

## 8 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). They are not entities belonging to A-life, as stated elsewhere (Popa 2020), and they are not mainly because of their organic nature and cellular structure which gives them a certain autonomy in their behavior. 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.

The Cooperating Thrust, one of the commandments of life (Gómez-Márquez 2020), is about the need for cooperation as a survival and reproductive strategy. There is cooperation everywhere in nature from the molecular level to symbiotic and social interactions, and in the past, it was involved in two of the most important transformations on the history of life: eukaryogenesis and multicellularity. Xenobots are a good example of cooperation between cells to become a primitive pluricelular organisms, a good example of the existence of an imperative force that compels cells to associate to survive and reproduce. Surely, with the passage of time and genomic mutations, xenobots could evolve into more refined and efficient forms of cellular cooperation.

## 9 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). A major breakthrough in this field was made by Xu et al. (2022), who introduced two types of bacteria into membrane-free droplets and this bacterial mixture resulted in the formation of an artificial cell with functional and compositional complexity reminiscent of living ones.

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. The creation of life from the minimal vital components of cells will be of great help in solving the great mystery of life, which is none other than its origin.

## 10 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 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.

## 11 The Lithbea Domain

The term "domain" was introduced by Woese et al. (1990) to classify all living cellular forms found on this planet, excluding, as I mentioned before, viruses because they are not cells. Now the question is how to group all the lithbes, which represent a new biodiversity that can no longer be ignored when we talk about living beings and relate them to the three *woesian* domains. In this sense, I would like to propose here the creation of a fourth domain called Lithbea (this name derives from the term lithbes), which would include viruses, synthetic organisms and artificial life forms (Fig. 2). This new domain would have two kingdoms: Viral and Humade (derived from the human-made contraction). A fundamental difference of Lithbea with the three Woesian domains is that the latter most likely share a common ancestor (Theobald 2010), whereas evidently there can be no common ancestor for the panoply of heterogeneous entities included in the Lithbea domain.

The Viral kingdom includes all viruses and represents the most diverse kingdom on our planet with many members of this club 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

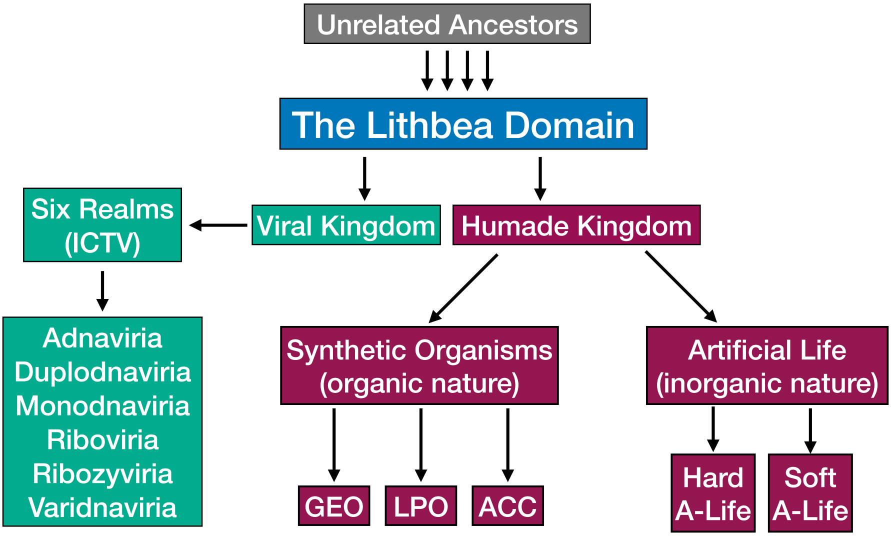


**Fig. 2** The Lithbea domain. Because of the heterogeneous nature of the members of the Lithbea domain, there is no common ancestor for all of them, there are several unrelated ancestors. Lithbea is divided into two kingdoms: Viral and Humade. Organisms belonging to the Viral kingdom are organic in nature and have a natural origin (a consequence of the evolutionary process). In this kingdom there are six realms as established by the ICTV. 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. See main text for detailed description of all lithbes

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). Accordingly, the Viral 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? We do not know, and the origin of viruses is still a mystery although 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). In any case, the emergence and evolution of viruses is closely linked to the emergence and evolution of their cellular hosts, and vice versa (Irwin et al. 2022). This is the only way to explain the presence of huge amounts of viral traces in the genomes of many species. For example, scientists have learned that a protein called Hemo, made by a fetus and the placenta, is produced from viral DNA that entered our ancestors' genomes 100 million years ago (Heidmann et al 2017).

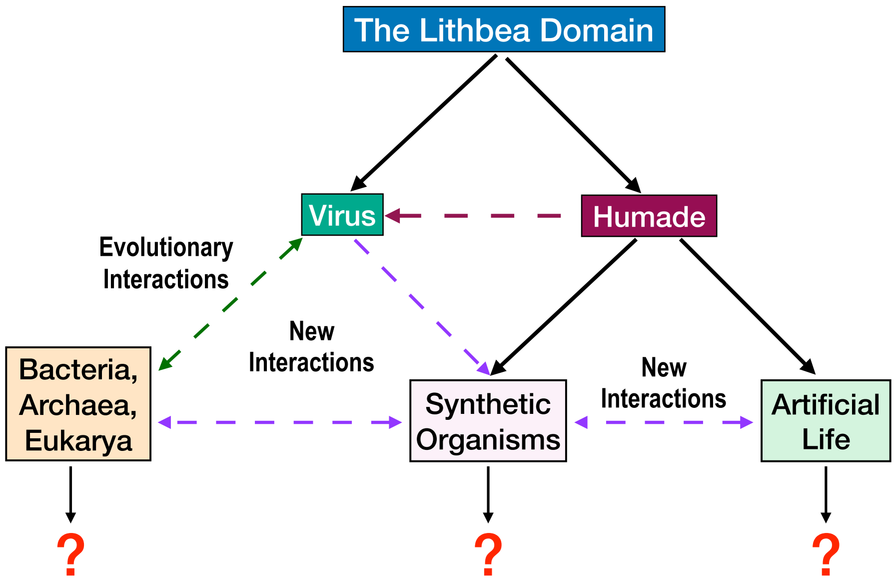


**Fig. 3** Interactions between the four domains. All the interactions between the various types of lithbes with each other and with the domains of cellular life are shown schematically here. Viruses have been interacting with the three *woesian* domains since their appearance on Earth. These evolutionary interactions have been reciprocal, and genomes are good evidence of this continuous flow of information. Viruses are also related to the Humade kingdom because they can also infect synthetic organisms and because new viruses can be engineered by us. Synthetic organisms may also interact (voluntarily or accidentally) with bacteria and eukaryotic organisms through processes related to competing for biotope or food, reproducing, or even cooperating. The double-headed arrow indicates the existence of reciprocal interactions between different lithbes and with organisms belonging to the three *woesian* domains. Interactions between synthetic organisms, natural organisms and artificial life are also possible and an example of this would be xenobots. The question mark signifies an uncertain future for our planet's biodiversity, caused both by the destruction of nature and by the increasingly frequent interactions between the "synthetic/artificial" and the "natural" to create something unknown

There are several connections between the entities belonging to the Lithbea domain with the organisms included in the three domains of cellular life (Fig. 3). In all these interactions, the viral kingdom plays a central role because viruses and the three cellular domains have been interacting with each other probably since the beginning of evolution (Harris and Hill 2021). Viruses infect all kinds of cells and they have participated in the evolution of species 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). Viruses are also related to the Humade kingdom because they can infect synthetic organisms and interfere with their life, and because they can be created in laboratories as variants of known viruses or as a completely new virus. In relation to the latter, we should bear in mind that lab-made 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 natural biological balance. Therefore, we need social responsibility and legal regulation of these biotechnology practices (Li et al. 2021).

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 (see above). We can consider them living organisms because they fulfill all the characteristics of a living being of cellular nature, but 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. They lack proteins and nucleic acids, cell structure, metabolism, etc., and 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 and human-made, they lack the ability to adapt, reproduce and evolve on their own and therefore cannot be considered as living beings.

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 genetically modified 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.

## 12 The Unpredictability of the Unknown

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. The unpredictability of the unknown means that when we create a synthetic organism in the laboratory, there is always a point of uncertainty, of partial knowledge of what it will be. We can reasonably imagine what the result of the creation will be like because we have an ever-deepening understanding of biology and biotechnological tools are becoming more and more precise. However, we cannot be completely sure what the new organism will be like and, above all, how it will behave. The explanation for this uncertainty lies in the fact that we are creating something new, something that is neither a machine nor the consequence of the evolutionary process, something that while subject to the laws of nature is also subject to the unpredictability of chance or randomness.

An example of this unpredictability is the case of xenobots. As I mentioned before, xenobots are very special creatures because they are living machines produced by the combination of artificial intelligence with cellular techniques without genomic manipulation. They can self-assemble, move in groups and sense their environment, etc. and this behaviour was designed to happen more or less like this. What was a big surprise was to see that xenobots could reproduce in a completely new and different way to any animal or plant known to biological science (Kriegman et al. 2021).

What would happen if organisms with an altered genetic code were released into the wild? What would happen if a pathogenic virus or bacterium made in a laboratory could infect human populations? Could a pandemic occur with millions of deaths? Could the massive cultivation of GM crops eventually displace wild species or have negative consequences for the environment? What would happen if xenobots or other similar organic entities with the ability to reproduce were to invade our environment? and so on and so forth. We do not really know the answer to these and other questions and therefore we have to balance scientific progress with safety and prudence, without forgetting the ethical aspects that we as civilized societies should never forget.

The research and analyses of the new advances related to synthetic biology and artificial life offers a new perspective on life, poses intriguing new challenges, and opens new avenues of thought with important philosophical implications. For the first time we are playing God, creating new species, and altering the natural course of the evolutionary process. Beyond generating new organisms in the laboratory for purposes related to industry, health or basic research, there is no overarching goal in this whole biological revolution. Perhaps we should reflect on where we want to go and whether we should set limits that prevent us from making abnormal organisms or go beyond the limits of more traditional ethics. The unpredictability of the unknown should make us cautious about making new synthetic organism, especially if these new entities are released (or "escape") into the outside world.

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