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The problem of defining life: a case study using family resemblance

Jessica K. Abbott[1] ✉ & Erik Persson[2]

How to define 'life' is an unresolved question in the philosophy of biology, but has become more urgent as researchers around the world attempt to create synthetic cells in the laboratory, develop intelligent and autonomous robots, and search for signatures of life elsewhere in the galaxy. Here, we discuss the pros and cons of some of the current approaches to defining 'life', then propose an alternative approach based on family resemblance. Using a statistical modelling framework, we find that although living and non-living entities can be grouped according to overall similarity, it is difficult to find a single set of criteria that can both define known forms of life and be useful in identifying or characterizing novel forms of life. We hope that the family resemblance approach will prove to be a fruitful alternative to traditional approaches to defining 'life'.

Imagine that you are reading a book or article and come across an unfamiliar word. If it is not possible to determine the meaning of the word from the context, chances are that you would look up the definition of the word in a dictionary. A typical dictionary definition includes a description of the meaning of the word, a list of possible alternative usages with examples of each usage, and probably a list of synonyms. Even an apparently simple word such as 'chair' can be difficult to define if it has many possible uses depending on context. For example, the Oxford English Dictionary's entry for the word 'chair' is in fact over 5000 words long[1].

This stands in contrast to how children learn new words when acquiring language. All humans learn how to speak their first language through their interactions with other individuals, rather than by looking words up in a dictionary[2]. The child's mother might say "sit down on the chair", and use a gesture to help indicate her meaning. In this sort of situation, the child receives information not only about how a chair looks, but also what it's used for. Over time, the child will see many examples of different types of chair and learn what they all have in common[2]. Eventually, the child becomes able to recognize even rather unusual examples of chairs as chairs (Fig. 1).

This sort of learning process works well for words used in everyday situations, but what about more abstract concepts such as 'life'? Technical and scientific definitions of the word 'life' are necessary in various biological and chemical research fields, such as the origin of life[3] or production of synthetic cells, but how well do these definitions align with a layperson's definition of 'life' that builds on personal experiences of life and death? Does it even matter if the technical and layperson definitions don't align very well?

Although the question of how to define 'life' has been an important issue in the philosophy of biology at least since Aristotle[4], it is becoming increasingly relevant as a result of current technological developments. Researchers around the world are now engaged in attempts to create fully synthetic cells in a laboratory setting[5,6], and coordinated efforts are being made to try to detect signatures of life elsewhere in the galaxy[7]. Developments in these areas may end up overturning our current ideas about the distinction between life and non-life. It is therefore important to consider whether it is possible to develop a definition of 'life' that is useful in both technical and everyday contexts, while at the same time having the potential to be applied to as-yet unknown lifeforms. We will begin by briefly discussing pros and cons of some current approaches to defining 'life', then propose an alternative approach, and finally present preliminary data applying our new approach.

Types of definitions

The two examples of the definition of the word 'chair' discussed above – an adult who looks up an unknown word in the dictionary, and a child who learns new words through personal experience and interactions with other people – exemplify not only two different ways of acquiring information, but also two different approaches to defining words. In the first case, the dictionary definition, also known as a "lexical" definition, the usage of the word in different contexts is described, but not necessarily the essential features of what makes a chair a chair. Another common approach to definitions is to assume that an exhaustive list of criteria can be made, which must be fulfilled in order for an object to be considered a member of the category 'chair'. This is typically called a *de re definition*[8–12], and this is the sort of definition that is often found in textbooks. "De re" is Latin and can be translated as "about the thing"; it is often contrasted with "lexical", or "de dicto" (lat. "about what is said") definitions[13]. A de re definition, therefore, attempts to capture the essential properties of a phenomenon, while the de dicto reference aims to capture how a term is commonly used. De re definitions are common in technical definitions of objects and phenomena within the natural

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[1]Department of Biology, Lund University, Lund, Sweden. [2]Department of Philosophy, Lund University, Lund, Sweden. ✉e-mail: jessica.abbott@biol.lu.se

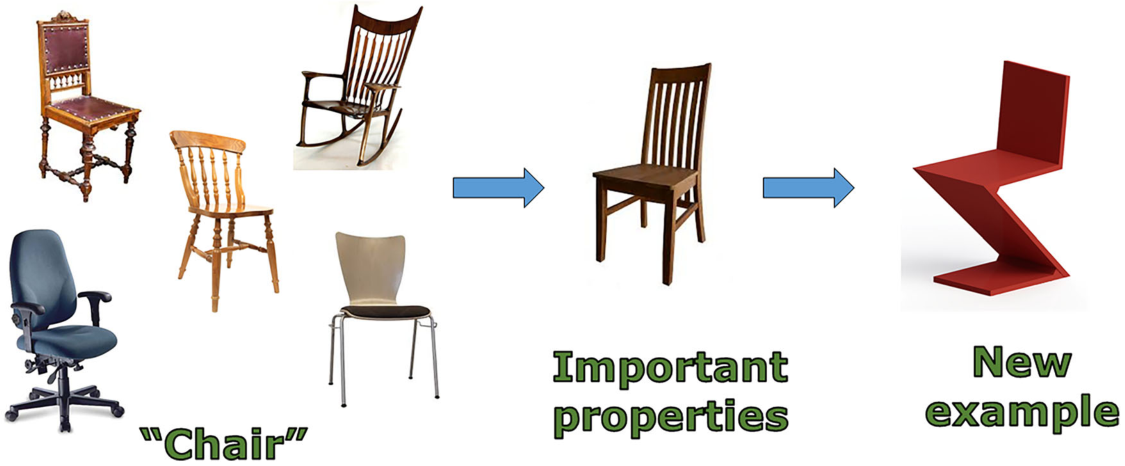

Fig. 1 | Spontaneous learning of the word "chair". After seeing multiple examples of a given type of object, we learn to identify the important properties associated with this type of object. This later allows us to recognize non-standard examples of chairs (all images obtained from Wikimedia Commons).

sciences (it is, for example, possible to unambiguously define an atom of gold based on the number of protons contained in the nucleus of the atom).

In contrast, in the case of spontaneous learning of the word 'chair' discussed above, similarities in form and function can be used to create an internal list of properties that a chair *usually* fulfils. A list of properties or criteria of this type is more fluid than in a de re definition. Not all criteria need always be fulfilled, the list of criteria can be dynamically updated, and criteria can be weighted differently depending on their relative importance. This more fluid type of definition makes it possible for us to recognize non-standard examples of chairs as long as they have enough in common with other types of chair we have previously encountered (Fig. 1). This is an example of a *family resemblance* approach, where objects are understood based on their overall similarity rather than a list of necessary criteria[14]. Studies of language acquisition have shown that we generally use this type of approach when learning our native language[15]. The idea of family resemblance as a linguistic phenomenon was first developed by the philosopher Ludwig Wittgenstein (1889–1951) while working at the University of Cambridge after he moved there in 1929. He wanted to investigate how we describe and understand complex phenomena such as art or games. Following up on Wittgenstein's work, Rosch[16] later developed the prototype theory of categorization, and demonstrated that humans tend to determine membership in categories based on similarity to a learned prototype.

A game, one of Wittgenstein's primary examples[14], is a deceptively simple concept. Everyone knows what a game is, but to create a list of criteria shared by all games, while still excluding all non-game phenomena (i.e. a typical de re definition) is likely impossible. The diversity of different types of games is simply too large; there are board games, ball games, card games, video games, role-playing games, games that are played alone, games that are played as a group, cooperative games and competitive games, etc. The only things that all these different types of games could perhaps be said to have in common is that they are entertaining and include some sort of element of competition (it must be possible to "win" the game, either by defeating the other team, the other players, or the game itself). But the same could be said of other types of phenomena, such as a structured debate, and it is not clear whether these properties apply to all sorts of games. This makes it difficult and perhaps even impossible to define games as a group in the same way as we define an atom of gold.

Some writers have therefore suggested that we should instead use the family resemblance approach for constructing definitions[17,18], not simply considering it as an interesting linguistic phenomenon, and it has been applied to a variety of phenomena, including Feynman diagrams[19]. Using a family resemblance approach, one could use the properties of the majority of games to create a more intuitive definition (although we will not attempt this here). Under such a definition, not all criteria would need to be fulfilled, as long as the overall similarity is sufficiently high. For example, solitaire could be recognized as a game using a family resemblance approach based on its overall similarities with other types of card game, even though most games require multiple players.

"Fuzzy" definitions in biology

Biology encompasses many phenomena that are difficult to define. What is a gene, or a species? In both cases different definitions are used in different contexts, because it is difficult to develop a definition that works in all contexts[20,21]. Scientific definitions also change over time, as new knowledge is acquired and consolidated[22,23]. When it comes to defining species, there are a number of different widely-applied species concepts, and introductory textbooks in evolutionary biology typically include several different variants, each with its own pros and cons[24]. One of the most common is the so-called biological species concept, which states that individuals that can successfully mate and produce fertile offspring are members of the same species[20,24,25]. However, this definition is not useful for organisms that do not reproduce sexually, such as bacteria or parthenogenetic organisms (which reproduce clonally via unfertilized eggs)[21,25]. It also does not take into account the fact that there are many plants and animals that can hybridize with other closely related individuals when given the opportunity. For example, tigers (*Panthera tigris*) and lions (*Panthera leo*) can hybridize to produce partially fertile offspring (female hybrids are sometimes fertile but males are not), but this does not occur under natural conditions since the two species are normally found on different continents[26]. Although these two species could therefore potentially be classed as different populations of the same species according to the biological species concept, this solution is not embraced by biologists due to their divergent morphology, non-overlapping ranges (Asia versus Africa), adaptation to different habitats (mainly forest versus mainly savannah), and different social structure (solitary versus social)[27]. This simple example illustrates why many biologists embrace a pluralistic approach to defining species, where multiple possible definitions of what constitutes a species are acceptable, with different definitions being used in different contexts[20,28]. Developing different definitions where each one works best in a specific and well-identified context of course requires highly specialized knowledge of the field[25], and is intimately tied to what sort of scientific question one is trying to answer[22,23]. For example, for questions about the adaptative potential of lions and tigers to climate change, the biological species concept is not particularly helpful since hybridization between these species is essentially impossible in nature. However, the biological species concept would be highly relevant if one is interested in investigating the evolution of genetic incompatibilities between these species.

One reason why finding a single definition of a species is so challenging is because life is so diverse, and different groups of organisms can have completely different ways of living and reproducing. But this is not the whole story. Speciation is also a gradual process, which means that differences in morphology and behaviour can sometimes arise long before two populations become so genetically different that they can no longer hybridize[26]. This makes it very difficult to pinpoint any specific time when organisms cross the boundary from being two populations of the same species, to becoming two different species. There are, therefore, considerable similarities between the problem of defining species, and the problem of defining life. If anything, defining life is even more challenging since the origin of life is so difficult to study, and there are many entities which may in some sense be considered borderline between living and non-living, including viruses, intracellular parasites, or semi-autonomous components of organisms such as sperm. In addition, these problems will likely only increase as efforts intensify within synthetic biology to create artificial cells and self-replicators, and within artificial intelligence research to develop computational artificial life systems.

Although we will not discuss it in any further detail, it is worth mentioning here the issue of 'life' and 'living' as the opposite of 'death' and 'dead'. Defining 'living' versus 'dead' is a question of individual status as alive or not, and although the relationship between individual status as living and status as 'life' is certainly an interesting one, we do not feel that it is possible to delve into this issue in any depth here. We will therefore focus on being able to distinguish 'living' from 'non-living', i.e. all organisms that currently exist, have existed, or may exist in the future, compared to objects or entities that have never been alive and never will. All non-avian dinosaurs are currently extinct, but they were alive while they still existed on Earth. In contrast, a stone is not alive and never will be, so it would be nonsensical to call it 'dead'. Nevertheless, some of the criteria that are traditionally associated with defining 'life' versus 'non-life' are also associated with defining 'living' versus 'dead', making it difficult to discuss these issues completely independently of each other. For example, "metabolism" and "homeostasis" are criteria associated with 'life' that are also intimately associated with 'living' versus 'dead', while in contrast, "evolution" and "reproduction" are often closely associated with 'life' but of limited relevance to the question of individual life (since individuals cannot evolve, and sterile individuals such as mules are clearly living but cannot reproduce). Similar issues apply when considering components of organisms – a sperm cell or organ which is destined for transplant can be classified as living or dead (tissue), in that they can fulfil (or not) criteria related to individual life or death, such as metabolism and homeostasis. But can they be considered living in the full sense, given that they cannot fulfil other important criteria associated with 'life', such as reproduction and evolution? We believe that arguments can be made both for and against the idea that organismal components can be considered 'life'. For now, we must leave an analysis of these issues to future work.

How to define 'life'? Problems and potential solutions

Properties that are typically associated with life include, for instance, energy use, growth, reproduction, the ability to sense and react to the surrounding environment, and the ability to adapt to this environment[29,30]. There are a number of biological systems that have some but not all of these properties, of which viruses are likely the most familiar. However, other examples include transposable elements (DNA sequences that can copy themselves between different parts of the genome) or prions (proteins that can transform other proteins into the same configuration), both of which could be considered to carry out a form of reproduction. Apart from the difficulties arising from known cases such as this, the challenge of defining 'life' is multiplied when trying to develop a definition that could extend beyond the known forms of life. It might be only a matter of time before we will have to deal with practical problems associated with alternative lifeforms, such as autonomous robots, general artificial intelligences, or synthetic cells[31]. More speculative, but still within the realm of possibility, is the discovery of extra-terrestrial lifeforms, for example, microorganisms under the surface of Mars. We need to be able to recognize these alternative forms of life even if they may be very different from currently known lifeforms. This is unlikely to be possible using a de re approach. If we cannot agree on a set of criteria to define known lifeforms, how much more difficult will it be to find a unique set of criteria which unify robotic, synthetic, and extra-terrestrial life?

There are several potential ways to move forward given these difficulties. We might decide to simply try harder, under the assumption that at some point we will have gained enough knowledge to construct a correct and all-encompassing definition of 'life'. An obvious problem with this approach is that all currently known life has a single origin[3], which means that it may not be possible to determine which criteria are universal to all life and which are a contingent result of a common evolutionary history[32]. A second approach could therefore be to wait and see, i.e. put off trying to develop a single all-encompassing definition until we know what alternative forms of life it must include. Finally, we might decide to treat the definition of 'life' in the same way as the species concept, and simply accept that life is too diverse for a single definition to be adequate. In this case, different technical definitions of 'life' could be developed depending on the context, such as the origin of life. The earliest biological systems probably lacked some of the criteria typically associated with modern lifeforms, such as the ability to sense the external environment[3,33]. Definitions of 'life' that are used when researching the origin of life, therefore, tend to include broad criteria such as "energy use" and "dynamic equilibrium"[3], rather than narrow ones such as "composed of cells"[34] or "contains information encoded in DNA"[34–36]. Given the ongoing discussion in the literature of the problem of defining 'life'[31], none of these approaches seems to be particularly satisfying. We discuss why in more detail below.

Try harder

By "try harder", we mean gathering more knowledge about existing living organisms in the hope that this will uncover some sort of properties of life that have been previously unknown or overlooked. Although it may be valuable to continue searching for universal criteria for defining 'life' in this way, the question is how likely it is that this approach will succeed. Philosophers have attempted to define 'life' at least since Aristotle[4], and if anything, the difficulties have increased over time rather than diminished as our knowledge has increased[37]. For example, whether viruses should be considered living has been unclear since their discovery, and is still controversial among biologists today[38–45], even though most introductory textbooks state categorically that they are not living because they do not have a metabolism and cannot reproduce outside of a host cell[29,30]. Proponents of the view that viruses should be considered living tend to consider the ability to reproduce and adapt via evolution, as well as evidence of their relatedness to the rest of the tree of life, to be more important criteria[40,44]. An informal survey of 40 professional biologists of all career stages at Lund University revealed an almost exact 50–50 split on this issue (Abbott, unpublished data). Recent research has not helped to clarify the issue.

There are three main hypotheses about the origin of viruses[46]. One of the earliest hypotheses was that viruses are remnants of the most ancient lifeforms on earth, a transitional form between non-living organic molecules and living cells. Support for this hypothesis has decreased over time since it is hard to see how an entity that is completely dependent on living cells for reproduction could arise before the existence of such cells[46]. A second hypothesis is that viruses arose from transposable elements that acquired the ability to transmit themselves horizontally (i.e. between unrelated individuals, rather than exclusively from parent to offspring). This hypothesis is fairly widely accepted since there are a number of structural and biochemical similarities between retroviruses and transposable elements[46,47]. A third hypothesis is that viruses arose from bacteria or other intracellular parasites that lost more and more of their genetic material and independent functions as they became more dependent on their hosts[46]. If this hypothesis is true, then this implies that viruses have evolved from living to non-living over time, which may be problematic for definitions of 'life' that consider metabolism to be an essential criterion[34,35,48]. Recent work suggests that all three processes may have contributed to the origin of viruses[46,49]. Although the status of viruses as either living or non-living today need not be related to their evolutionary origin, this example serves to illustrate that gathering more information about ambiguous cases doesn't necessarily provide any solution. Similar issues apply to mitochondria and chloroplasts, which are cell organelles with a bacterial origin – when does a symbiont transition from autonomous lifeform to cell component[50]? (As with other organismal components such as cells or organs discussed above, we feel that it is currently unclear whether cell components should be considered living in their own right or not.) We are therefore sceptical that the problem of defining 'life' will be resolved if we simply collect more data.

Wait and see

By this, we mean wait to even try to formulate a definition until completely new forms of life have been discovered, or until we have created a "unified theory" of life (as suggested by Cleland and Chyba[51–54]). As mentioned above, one of the reasons why it is difficult to define 'life' is because we currently only have information about life on Earth. We therefore cannot conclusively distinguish between properties that are truly essential or universal from those that are specific to our kind of life. For example, some definitions of 'life' include the criterion that individuals should encode information in DNA[29], or be composed of cells[30]. It is relatively easy to imagine that another type of molecule could be used to encode information rather than DNA[55], but less clear whether it is possible for lifeforms to exist that are not composed of cells. Experiments with synthetic lifeforms may be useful in helping to investigate these questions, but these synthetic lifeforms will likely be highly influenced by existing life, partly because it is most convenient if they can be kept under ordinary lab conditions, but also because existing lifeforms are often used as templates for synthetic organisms[56]. For example, *Syn-3.0*, a synthetic bacterium created by Hutchinson et al.[5], is a highly modified version of the bacterium *Mycoplasma mycoides*, an intracellular parasite of cattle and goats. Synthetic biology is a fast-developing field, yet it is currently unclear how long it will take to develop synthetic lifeforms that are radically different from known life.

Because of this, it would actually be much more valuable if extra-terrestrial life with a completely independent origin is eventually detected, as has been noted by e.g. Cleland and Chyba[51,54]. But whether this is even feasible is currently unclear. Although it might be technologically feasible to bring back samples from Mars, either now or in near future, there is a history of traffic between the Earth and Mars both through natural and artificial means (via meteorites and probes, respectively), which means that should life be detected there, then there is no guarantee that it will have an independent origin[57]. It is also conceivable that lifeforms based on different chemistries could exist in other parts of the solar system, and be accessible for direct study at some point in the future[57,58]. But here we end up in a catch-22 of sorts. Without a definition of 'life' that goes beyond currently known types of life, how are we supposed to recognize these novel lifeforms? Although Cleland has argued that this is not a problem if we focus on identifying and studying anomalies rather than constructing definitions[52], we are less convinced since, as argued by Brigandt, definitions are tightly coupled to the direction of scientific inquiry[22,23]. We can therefore conclude that although we will surely learn much if and when we create or discover completely new types of life, we cannot wait until then to develop a better definition of 'life'.

Accept that there cannot be a single definition

Another option is to abandon the search for a single all-encompassing definition of 'life'[59–61], similar to the plurality of species concepts that was discussed above. Such an approach would result in the development or refinement of multiple technical definitions of 'life', each of which would be most useful within a specific context. Different criteria could be included depending on whether the definition was to be relevant for the transition from pre-biotic chemistry to living organism during the origin of life or synthetic biology applications, when an autonomous robot or artificial intelligence could be considered alive, or what minimal properties a potential extra-terrestrial lifeform might need in order to qualify as such. The advantage of this approach is that it reflects the fact that life is a dynamic process, which is difficult to capture using a limited set of criteria.

However, there are also disadvantages with this approach. For one thing, a single common definition of 'life' would be very useful when discussing the challenges associated with novel forms of life. A definition of 'life' which is broadly applicable and understandable for laypersons and policymakers, not only experts, would be an advantage during public debate of issues related to novel forms of life. This does not mean that a broad definition would necessarily replace the various technical definitions within a given field, but it might make interdisciplinary communication more successful. The ”working definition” of life adopted by the National Aeronautics and Space Administration (NASA) – "a self-sustaining chemical system capable of Darwinian evolution“[62] – is a welcome step in this direction, but unfortunately it is simultaneously too broad (almost anything could be considered a chemical system) and too narrow (constructed organisms such as artificial cells are unlikely to have undergone Darwinian evolution, i.e. evolution via natural selection).

Another potential problem with existing technical de re definitions of 'life' is that many of these definitions include criteria at different hierarchical levels of organization. For example, a typical textbook definition of life might include the criteria "energy use", "growth and development", "reproduction", "homeostasis" (the ability to maintain a consistent internal state), and "evolutionary adaptation"[63]. Of these criteria, the first four can be applied to the individual organism, but the last one can only be applied to a population of organisms[64]. A population cannot undergo development from embryo to adult (other than via its component organisms), while a single individual cannot undergo evolutionary adaptation. This leads to an odd situation where this definition cannot sensibly be applied in its entirety to *either* a specific individual *or* to a specific population of individuals, calling its general utility into question.

Some authors have attempted to resolve this problem by developing definitions of 'life' in terms of systems rather than individuals, circumventing the issue of criteria that are applicable at different hierarchical levels[3,65,66]. Since evolutionary adaptation is usually considered one of the most important properties of life compared to other dynamically stable non-living systems (such as a self-driving car, or the earth's system of ocean currents), this means in practice that the system must be defined at the population level or higher. The advantage of such a definition is that it is more internally consistent, but this usually comes at the expense of being more complicated, imprecise, or unintuitive[3,65,66]. The question is whether the problems discussed above are because defining 'life' is impossible, or are they a result of the traditional fixation on a de re definition?

A case study of a family resemblance approach

We would like to suggest that continuing to search for a broadly applicable de re definition of 'life' is unlikely to be fruitful, and that it would be better to try a new type of approach that can accommodate the complexity of life as we know it. In our view, a family resemblance-based approach has better potential to achieve the aim of producing a broadly applicable and intuitive definition of 'life', since such a definition would be based on overall similarities across lifeforms and allow for occasional exceptions from specific criteria. A family resemblance approach could also allow for different weighting of criteria, for example, if metabolism is considered to be a more important property of life than evolutionary adaptation (or vice versa). It is worth noting here that although we do can do this without taking any stance on whether life is a natural kind or not[21], we do assume below that it is possible to develop a definition of life that somehow captures true differences between living and non-living things; this is not an assumption that all philosophers of science endorse[67].

A potential weakness of the family resemblance approach to definitions is that it is not sufficiently objective. What if we cannot all agree on what or how much two entities need have in common, in order for both to be classified as alive? This is of course a problem, but not, we would argue, an insurmountable one. We have attempted to use statistical modelling to determine which criteria are most useful for describing life as we know it, while excluding criteria that are uninformative. Using this information, it may be possible to develop a cluster definition of 'life' that builds on specific

Table 1 | List of criteria defining for defining life obtained from the literature and from introductory textbooks in biology

Criterion	Source
Adapt to the environment	30,63,79,80
Autocatalytic cycles	81–83
Boundary	18,83–85
Can die	86
Cells	30,82,84,87
Chromosomes	79
Decrease in entropy	18,79,81,82,88
Development	30,63,80,89,90
DNA	29,82,84
Enzymes	82,91,92
Evolves	18,29,30,63,79,82,85,87,89,92
Feeding	85
Genes	87,89,92,93
Genetic control of development	18
Genetic material isolated from the environment	18
Growth	18,29,30,63,68,79,82,85,90,91,93
Homeostasis	29,30,63,68,87
Metabolism	18,30,79,81,84,85,87,89,91,93
Movement	30
Mutation	18
Natural selection	85
Nucleic acids	91
Order	63,79,80,88–90,92
Organic molecules	18,29,82
Protoplasm	79,92
Purposiveness	18
Regulatory mechanisms	18,83,90,94
Related	87
Replicate chemical information	18,82,88
Reproduction by self or non-self (not specified)	18,30,63,68,80,82,85,88–91,93
Reproduction by self-replication	29,79,81,83,87
Stimulus response	18,29,30,63,79–81,85,90,91
Use external substances	29,63,68,80,82,85,87,91

Table 2 | List of entities included in the analysis of life

Entities	Classified as living?
Arabidopsis thaliana (thale cress)	Yes
Caenorhabditis elegans (nematode)	Yes
Chlamydomonas reinhardtii (single-celled alga)	Yes
Clay crystals	No
Colloids	No
Danio rerio (zebrafish)	Yes
DNA virus (e.g. herpes simplex)	Yes/No
Drosophila melanogaster (common vinegar fly)	Yes
Escherichia coli (intestinal bacterium)	Yes
Gallus gallus (domestic chicken)	Yes
Homo sapiens (human)	Yes
Hydra vulgaris (freshwater polyp)	Yes
Liposome (phospholipid bilayer vesicle)	No
Macrostomum lignano (flatworm)	Yes
Memes	No
Mus musculus (house mouse)	Yes
Plastids (cell organelle, e.g. chloroplast)	Yes/No
Poecilia formosa (Amazon molly)	Yes
Prion (e.g. CJD-causing)	No
Red blood cell	Yes/No
Ribozyme (catalytic RNA)	No
Rickettsia typhi (intracellular parasitic bacterium)	Yes
RNA virus (e.g. HIV)	Yes/No
Saccharomyces cerevisiae (brewer’s yeast)	Yes
Snowflake	No
Sperm	Yes/No
Synechocystis sp. PCC 6803 (cyanobacterium)	Yes
Transposon	No
Viroid (e.g. tomato chlorotic dwarf viroid)	Yes/No
Virophage (viral parasite on other viruses)	Yes/No
Wolbachia (intracellular parasitic bacterium)	Yes
Xenopus tropicalis (western clawed frog)	Yes

Entities indicated as “Yes/No” were considered ambiguous, and analysed separately as both living and non-living in order to see how this influenced the outcome of the analysis.

combinations of criteria, rather than a single exhaustive list. Here we present preliminary results from a case study illustrating how this type of approach might work.

Methods

First, we compiled a list of suggested criteria for defining life from the primary literature, as well as from introductory textbooks in biology (see Table 1). Descriptions of a phenomenon were considered to be equivalent to specific terms with the same meaning, such that “maintenance of their functional systems”[68] was considered equivalent to “homeostasis”[63] (at least within the context of this particular dataset – it could be interesting to disentangle them in future work). This resulted in approximately 30 individual criteria, some of which were variants on a similar theme; e.g. “evolves”, “adapt to environment”, and “natural selection” were considered separate criteria since evolution can occur through purely neutral processes and does not necessarily require adaptation to the environment or natural selection[24]. We then selected a number of living organisms and other entities (including objects, processes, and organismal components) which were intended to span the boundary between living and non-living (see Table 2). This process of initial selection was inevitably somewhat arbitrary since the number of potential organisms and non-organisms is immense, so we deliberately included cases that we expected could be considered exceptional in some way (e.g. living organisms that might not fulfil all criteria, and non-living entities that could fulfil several of the criteria). However, it is worth noting that if our approach is applied in an iterative way, future selections of criteria and entities need not be arbitrary (see Discussion for more details). Next, we attempted to determine whether these entities fulfilled the criteria in Table 1 or not. This resulted in the production of a data matrix where 1 indicated that the criterion was fulfilled for that entity, and zero indicated that it was not (see Supplementary data 1). Note that it was not always obvious how a given criterion should be applied to a specific entity (e.g. does a bacterium have purposiveness?), but we discussed these cases thoroughly and attempted to use our best judgement. We also scored each entity according to whether it is usually considered to be living or not (see Table 2). This classification as “living” or “non-living” is of course also open to interpretation, so in the cases where the answer was ambiguous (e.g. plastids

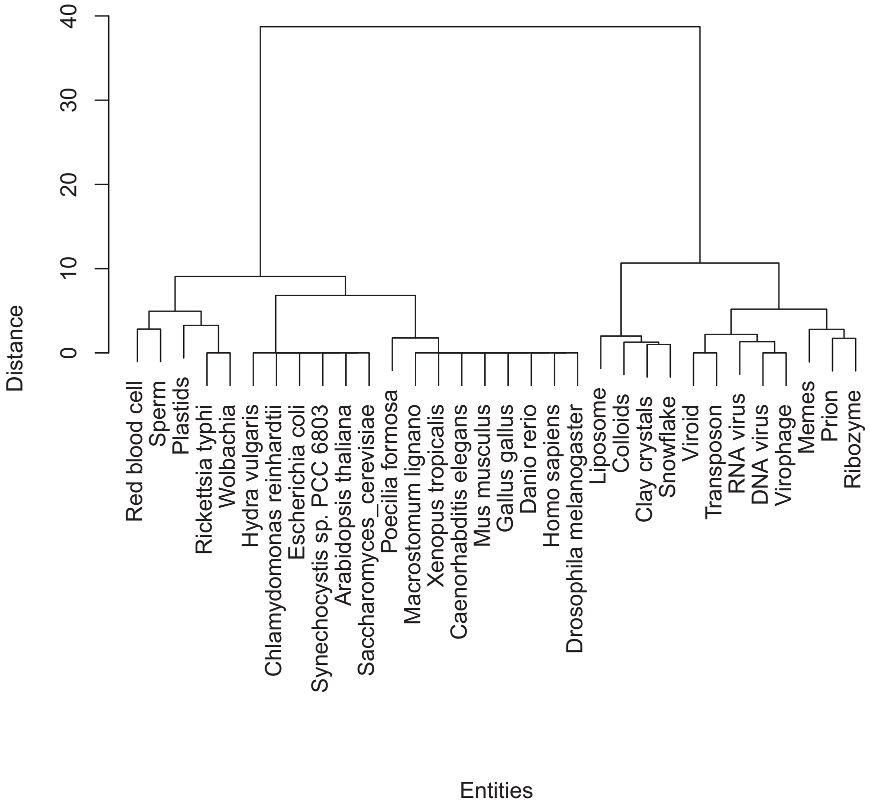

Fig. 2 | Results of cluster analysis. Non-living entities generally cluster together at the right-hand side of the plot, and living entities at the left-hand side of the plot. However, both main clusters include some ambiguous cases; red blood cells and sperm cluster together with intracellular parasite species on the left-hand side of the plot, and viruses cluster together with non-living entities on the right-hand side of the plot. This is presumably because the red blood cells and sperm fulfil slightly more criteria than the viruses do.

or viruses), we carried out two sets of analyses – one more inclusive analysis where all ambiguous cases were classified as "living", and one more conservative analysis where all ambiguous cases were classified as "non-living".

Once the data matrix was complete, we analysed it in various ways. All analyses were carried out in the R Statistical Programming environment[69] (see Supplementary data 2 for the R script). First, we checked whether our evaluation of all criteria produced a useful descriptive result by carrying out a cluster analysis using the *hclust* function[69,70]. Results presented below are from an analysis using the Ward's d clustering method, but results were qualitatively similar using unweighted pair group method with arithmetic mean (UPGMA), and complete linkage methods (see supplementary information). Hierarchical clustering was selected rather than e.g. k-means since we did not want to impose a predetermined number of clusters. We expected that successful scoring would result in living organisms clustering separately from other entities. We also investigated multivariate similarity using principal components analysis (PCA)[71] with the function *princomp()*[69]. Next, we carried out linear discriminant analysis using the *lda()* function in the MASS package[72] to determine if it was possible to accurately assign entities to the classes "living" and "non-living" using the full set of criteria. If so, this might suggest that a de re definition is feasible after all. Finally, we checked which criteria were most highly correlated with classification as "living" using Spearman rank correlation using the *cor.test()* function[69,73], in order to determine which criteria may be most useful in constructing future definitions of 'life'.

Several of the criteria were found to produce exactly the same result when evaluated across all entities. For example, entities that fulfilled the criterion "metabolism" invariably also fulfilled the criteria "growth" and "stimulus response" (at least within this particular dataset). We therefore collapsed perfectly correlated criteria into single variables in order to reduce the dimensionality of the dataset for the PCA, linear discriminant, and correlation analyses. The full (unreduced) dataset was used for the cluster analysis, in order to preserve complete information about relative similarity. However, results were qualitatively similar when carried out on the reduced dataset (data not shown).

Results

The cluster analysis revealed that non-living entities generally did not cluster with living entities (see Fig. 2 and Supplementary Fig. S1). However, both main clusters included some ambiguous cases; for example, red blood cells and sperm clustered together with living intracellular parasite species, and viruses clustered together with non-living entities. This likely reflects the fact that red blood cells and sperm fulfilled slightly more of the criteria in total than viruses did (14–15 vs. 12–13 criteria, respectively). This means that even using a more conservative classification of viruses as non-living, it is still difficult to clearly separate (more or less) autonomous living organisms from their component parts.

The PCA and linear discriminant analysis confirmed this. In the PCA, the first component accounted for 55% of the total variation and was positively correlated with all criteria, suggesting that this is a measure of how many criteria were fulfilled in total (Supplementary Table S1). The second component accounted for 14% of the total variation, and seemed to capture some sort of trade-off between different criteria that was not easy to interpret, but which could reflect criteria associated with reproduction and evolution compared to metabolism and homeostasis (Supplementary Table S1 and Supplementary Fig. S2). For the linear discriminant analysis of the inclusive classification dataset, entities were correctly classified as "living" only 44% of the time (14/32 cases – 4 correctly predicted as "non-living" and 10 correctly predicted as "living"). Entities which were classified as "living" in this dataset tended to be misclassified as "non-living" in the analysis more often than the reverse (14 living organisms incorrectly predicted as "non-living" compared to 4 non-living entities incorrectly predicted as "living"). For the conservative classification dataset, the criteria "feed" and "homeostasis" correctly predicted all cases.

The criteria that were most and least highly correlated with our classification as "living" are presented in Tables 3 and 4. Results were somewhat different for the inclusive and conservative classification datasets. The only criteria that were among the top 5 best predictors in both datasets were "autocatalytic cycles" and "enzymes". Poorly-performing criteria across both datasets were more consistent, and included "mutation",

Table 3 | Criteria that are most (rank 1-5) and least (rank 18-22) strongly associated with a priori classification as living versus non-living, when ambiguous cases are classified as "living"

Criteria	Rank	Correlation coefficient	*P*-value
Autocatalytic cycles Chromosomes Genes	1	0.833	**3.23×10^{-9}**
Enzymes	2	0.832	**3.59×10^{-9}**
Movement	3	0.762	**3.95×10^{-7}**
Nucleic acids DNA	4	0.745	**9.87×10^{-7}**
Reproduction by self-replication	5	0.698	**8.96×10^{-6}**
Mutation	18	0.494	**0.00417**
Reproduction by self or non-self (not specified)	19	0.462	**0.00773**
Purposiveness	20	0.361	**0.0423**
Order	21	0.149	0.415
Adapt to the environment natural selection	22	−0.149	0.415

Criteria with equal correlation coefficients are presented on the same row. Significant correlations are indicated in bold.

Table 4 | Criteria that are most (rank 1-5) and least (rank 18-22) strongly associated with a priori classification as living versus non-living, when ambiguous cases are classified as "non-living"

Criteria	Rank	Correlation coefficient	*P*-value
Feeding Homeostasis	1	1.00	**0**
Movement Protoplasm	2	0.939	**1.96×10^{-15}**
Cells	3	0.881	**3.03×10^{-11}**
Growth Metabolism Simulus response Regulatory mechanisms Genetic material isolated from the environment	4	0.825	**6.52×10^{-9}**
Autocatalytic cycles Enzymes	5	0.770	**2.50×10^{-7}**
Nucleic acids Evolves Replicate chemical information	18	0.511	**0.00278**
Mutation Can die Related	19	0.458	**0.00837**
Organic molecules Adapt to the environment Natural selection	20	0.402	**0.0224**
Order	21	0.342	0.0551
Reproduction by self or non-self (not specified)	22	0.275	0.128

Criteria with equal correlation coefficients are presented on the same row. Significant correlations are indicated in bold.

"reproduction by self or non-self", "order", "adapt to environment", and "natural selection". These results suggest (1) that exactly which criteria are best for defining life depend on the specific set of phenomena we wish to define, and (2) that criteria which are likely to be most useful for identifying novel forms of life (e.g. "reproduction by self or non-self", "order" or "adapt to environment") are unlikely to be sufficient for classifying known forms of life, since they were rather poorly correlated with status as "living" within this dataset.

Conclusions

Consistent with our initial speculations, living organisms tended to cluster separately from non-living objects and entities in our proof-of-concept analysis. This is perhaps more surprising than it might appear at first glance; although the results fit well with our a priori intuitions, we attempted to avoid bias in our selection of criteria and entities as much as possible, and so we did not know for sure whether our analysis would provide evidence for a clear-cut distinction between clusters of living and non-living organisms or not. Given that the total number of criteria that were fulfilled for e.g. sperm and red blood cells (14–15) was not much higher than for viruses (12–13), it was also not at all obvious that our dataset would produce two such well-delineated clusters. Interestingly, the distinction between cell components and intracellular parasites was not particularly clear, consistent with our initial evaluation that the status of organismal components as living is ambiguous. This is also in line with our expectation that defining life based on a single set of criteria is not easy (Fig. 2). In addition, the poor classification results in the linear discriminant analysis of the inclusive dataset suggest, as discussed above, that simply adding more information does not necessarily help to resolve problems with separating life from non-life. There also seems to be a trade-off between accuracy and broad applicability when attempting to define 'life' that was recaptured in our analysis. Very general criteria such as "adapt to environment" or "order", which are expected to be most useful in the context of the origin of life, synthetic biology, or extraterrestrial life, were poorly correlated with classification as "living" or "non-living" in this dataset (Tables 3 and 4). This suggests that although it might be possible to develop a de re definition of life that encompasses all currently living organisms on earth, such a definition is unlikely to be useful in the context of understanding and characterizing novel lifeforms.

This case study only includes a limited number of entities and criteria, and this will of course affect the outcome of the analyses to some extent. For example, correlations among criteria, or between criteria and classification as living, will likely change depending on exactly which combinations of criteria and entities are included in the analysis. The differences in outcome between the inclusive and conservative classification datasets reflect this. Similarly, how each criterion should be interpreted with respect to a given entity is not always straightforward. For example, does a red blood cell have genetic control of development? Yes, in the sense that our genes control the development of our red blood cells, and that the maturing cell itself must actively express these genes in order to develop normally[74]. But it would also be reasonable to argue that the answer should be no, in the sense that the red blood cell does not itself contain any genes when it is mature, and therefore cannot produce any new red blood cells via genetic control of development[74]. The specific results presented here should therefore be considered preliminary, and we feel that the most useful application of the approach will be to use it iteratively, so that previous analyses inform future ones, both in terms of which criteria and entities are included, as well as how the criteria are interpreted in each case. In this way, we hope that it will be possible to reach some sort of consensus with respect to the evaluation of the criteria and thereby obtain robust results.

We therefore feel that this approach has considerable promise, especially when used iteratively. Although it is mainly descriptive, it is based on actual properties of living and non-living entities. This is in contrast to recent work, which has used similar methods of multivariate analysis to instead describe how we talk about life versus non-life[75]. Any useful definition must be able to reflect our intuitions about life, so understanding what terms we choose when discussing life is of course valuable. But this assumes that we know which terms are the best ones to use. We feel that it is an advantage that the family resemblance approach is agnostic to which specific formulation of a criterion is best. For example, we found various formulations of a criterion related to reproduction in the literature, which we summarized as "replicate chemical information", "reproduction by self or non-self (not specified)", and "reproduction by self-replication". It is not necessarily obvious which formulation is most useful for drawing a distinction between living and non-living, so it is likely that we can capture more nuances by including multiple similar criteria within our approach. It may also be possible to detect cryptic patterns of similarity between different types of entities that would not be initially obvious by using a family resemblance approach. Brigandt has argued that phenomena which are difficult to define may be made more amenable to definition if the theoretical context and scientific aim of the definition is clarified[22,23]. We therefore hope that by trying out various combinations of criteria and entities with specific aims in mind, we may obtain new knowledge about what sort of dimensions of similarity exist among various types of lifeforms (and non-life).

Another advantage of this approach is that it can be dynamically updated as new information is obtained. This means that new advances in synthetic biology or artificial intelligence research could be incorporated as they arise within a family resemblance approach. In fact, we feel that the family resemblance approach is likely to be most useful in contexts where the boundaries between living and non-living are being pushed in one way or another. Not only in terms of describing these boundaries, but also in guiding future research. For example, Cleland and Chyba have argued that a general definition of 'life' will be impossible before we have developed a "unified theory" of life[53,54]. Cleland, therefore, advocates focusing on anomalies rather than definitions in order to hasten the development of this "unified theory"[52]. We agree with the importance of focusing on anomalies (e.g. contexts where the boundaries between living and non-living are being pushed in one way or another, as mentioned above), but otherwise would argue the opposite; that the search for a definition can in itself be useful in developing our understanding of life. We therefore believe that our method can potentially be helpful in guiding the search for a "unified theory". By applying a family resemblance approach to abiotic chemical systems compared to living biochemical systems, we may be able to identify which properties are more closely associated with living systems, and then design experiments aimed at determining how these properties can be stimulated to arise from abiotic systems. Or in the context of synthetic biology, of guiding progress toward making more complex and "life-like" entities from simpler organic systems. Both of these research programs could conceivably move us closer to being able to develop a "unified theory" of 'life'.

We therefore propose that the family resemblance approach has the potential to be useful as more than just a descriptive method, if it is used iteratively to inform future research. Maybe we will eventually conclude that different types of life are fundamentally different, and that life is not a natural kind[21], so that no "unified theory" of life[52,54] is really possible. Maybe we will determine that it is in fact possible to develop a coherent de re definition, if we use the best possible formulations of criteria in the right combination. And maybe the family resemblance approach will prove to be a powerful tool to help us develop a "unified theory" of life[52,54]. Any of these outcomes would arguably be a step forward relative to the current state of knowledge.

But there are also a number of interesting questions that the family resemblance method raises that can be addressed in the short term. For example, which combinations of criteria best describe each cluster within Fig. 2? What happens if we include hypothetical examples of novel forms of life? Some authors have suggested that life might be a matter of degree, rather than a binary property[34,76–78]. Would it then be more useful to include additional levels of classification than simply "living" versus "non-living"? How well does the clustering of different entities reflect our general "feeling" about their overall similarity? There are many outstanding questions and possible directions to explore. Nevertheless, we hope that this case study of a cluster-based family resemblance approach to defining 'life' shows the potential that this approach provides, especially within the context of experimental evolution, synthetic biology, and artificial life.

Data availability

Data and analysis scripts are included in the Supplementary Material.

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Correspondence and requests for materials should be addressed to Jessica K. Abbott.