The imitation game—a computational chemical approach to recognizing life

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When is an artificial cell alive? A Turing test–like method may provide the answer.

The definition of 'life' has invoked innumerable vigorous discussions, ranging from the religious to the scientific, philosophical and metaphysical, and still today no universally acceptable definition is available. This controversy is inescapable because of the absence of a theory of the nature of living systems[1]. There is, however, an urgent practical need for a universally acceptable way of recognizing life or the potential for life. The absence of any agreed-upon guiding definitions of what it is to be alive, and more generally of what is life, makes it difficult for researchers in a variety of communities to objectively recognize success. For example, it remains far from trivial within the exobiology and astrobiology communities to objectively assess whether a new form of extraterrestrial life has been discovered; for researchers studying the origins of life, it is difficult to demonstrate whether life's beginnings have been successfully explained; and in the synthetic biology and artificial chemistry communities, demonstrating the creation of a wholly synthetic life form is a daunting process.

Here, we propose an approach to the recognition of 'living' artificial chemical systems based on chemical cells (chells) as a *Gedankenexperiment* that exploits a cellular imitation game. The conceptual implications of this Turing test–like method are discussed as a procedure for deciding whether an artificially constructed chemical system is or is not alive.

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First principles

Although we might chauvinistically assume that all life in the Universe is based upon our own biomolecules[2,3], such as RNA, DNA and proteins, this clearly prejudges the primary chemical routes to a cellular or 'living' system and excludes many avenues of research without justification[4]. In addition, the origin of life on Earth may be just one function of such cellularity—just the tip of a functional iceberg—and, as has been recently suggested[5], might have followed a very convoluted and complicated sequence of events where RNA, DNA and proteins were indeed latecomers. Moreover, it has been argued[6] that "…the [nucleic acid or protein] sequences of living systems may have been determined in part by chance occurrences at origins. Any extrapolation linking sequences (as opposed to functions) obtained in the laboratory to what may have occurred *ca.* 4 billion years ago are tenuous at best."

Living systems exhibit a plethora of qualities that fundamentally distinguish them from inorganic or 'dead' matter. Life is a complex phenomenon requiring not only individual self-replicating (autopoiesis[7]) and self-sustaining systems, but also a mechanism that allows

Table 1 Comparison of Turing tests for intelligence and life

	Turing test for intelligence	Turing test for life
Imitated emergent property	Thought	Cellular functions (e.g., metabolism, evolution and containment)
Embodiment of property	Computational digital machine	Chemical system (e.g., artificial cell or 'chell')
Probing mechanism	Questions/answers mediated by natural language	Questions/answers mediated by (natural) physico-chemical language (e.g., interconversion of chemical potentials, mechanical transduction, signaling)

spatio-temporally resolved organization of information within these systems, which brings about characteristic evolutionary and metabolic dynamics. Previous proposals[8–10] that consider bottom-up engineering of artificial cells have drawn inspiration from certain functions that are present in natural living cells, albeit not necessarily following their implementation. These structural functions are thought to be a prerequisite for realizing a living system. Most researchers focus on the 'components' or physical embodiment of life and often cite three key functional structural units: container, metabolism and genes (information units). To implement these functional units, some researchers approach this challenge using biomimicry or cell-free extracts[11], whereas others[8–10] aim to design and construct fully synthetic, or non-natural, implementations.

In either case, from a chemical point of view, it is helpful to insist that all such systems must have a semi-permeable active boundary or membrane (container) that might be recursively structured, a metabolism to generate and channel energy (from an universal energy currency) and that can process both raw and waste materials, along with an information storage system (genes) that has high fidelity, but can cope with imperfect copies and introduction of random mutations. This approach, however, already starts to outline notions of life and cells that are somewhat restrictive, especially if taken together with a focus on existing building blocks of current life. We believe that a broader definition and clearer conceptual goals are needed.

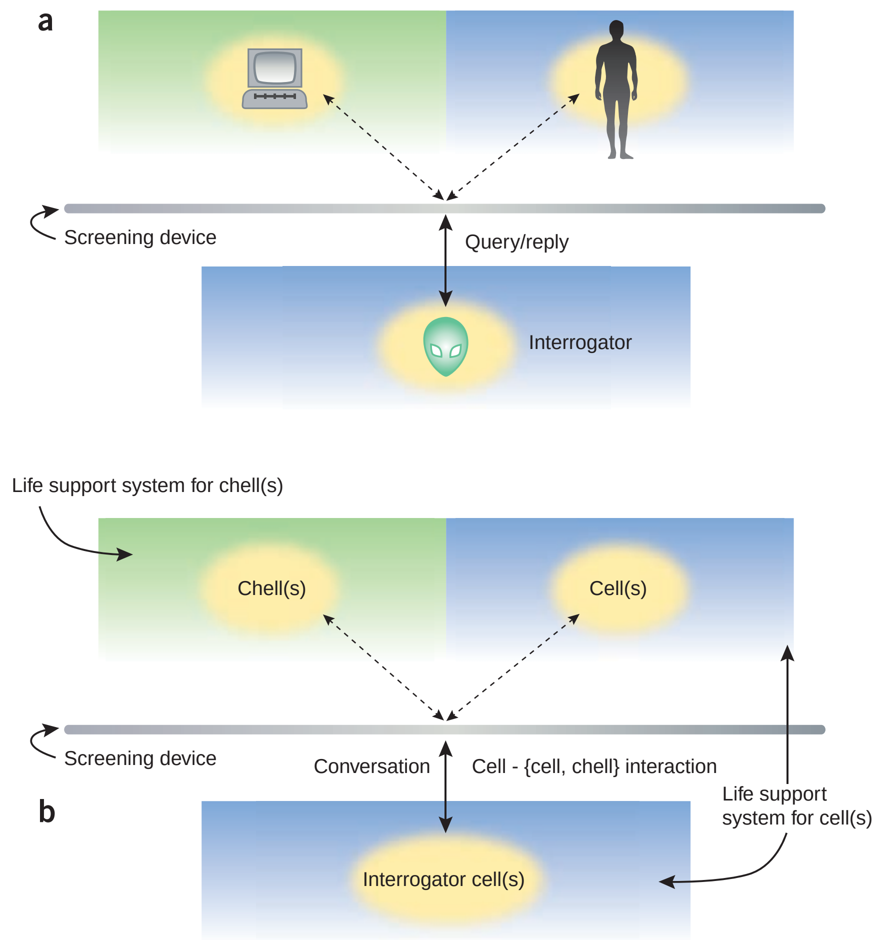

Figure 1 Different takes on Turing. (**a**) Representation of the classic Turing test with an intelligent interrogator (that is, a person, interacting with two compartments, each containing either a computer or a person, the location of which is unknown to the interrogator). (**b**) The extension of this interrogator or interaction between cells and chells (see text) is depicted. It is suggested that cell signaling could be used as the medium for conveying the interactions but other, perhaps simpler, mechanisms could be used.

Parallels

A similar fundamental problem was encountered in the area of artificial intelligence (AI)[12], wherein researchers wrestled with the question of whether machines can think in the absence of a universally accepted, let alone operational, definition of thought (something that remains elusive even to this day). Alan Turing effectively circumvented the problem by proposing the so-called 'imitation game'[13] which later became known as the Turing test. The question 'Can machines think?' was redefined by an operational scenario for AI: can machines imitate the act of thinking such that an interrogator cannot distinguish between a machine and a person?

This is an elegant operational way of assessing whether a machine can think, regardless of what we mean by thought. The power of the imitation game lies first with the fact that it distinguishes between the physical embodiment of a man and his putative thinking abilities and second it provides a mechanism of 'probing' thought by means of questions and answers formulated in a given language. For convenience and to facilitate progress, Turing artificially restricted his broad definition of machines to digital computers comprising storage, executive units and control components, and argued that the restriction was unimportant precisely because of the universality of such contrivances. In this way, the question 'Can machines think?' was replaced by 'Are there imaginable digital computers that would do well in the imitation game?'

The Turing test has proven a remarkably effective concept that has continued since 1950 to provoke discussion in the fields of computer science, philosophy of the mind and cognitive science[13]. The Turing test did not give a definition of 'thought' but it instigated a prolific amount of research, ranging from those trying to build computational devices capable of passing the Turing test, to those who have argued that the Turing test is irrelevant for a theory of thought. Regardless, the concept of the Turing test has helped advance our understanding of AI and represents a paradigm shift in this area. Interestingly, Harel[14] has recently proposed that a kind of Turing test could be used to assess the quality of computer models for systems biology. We believe that just such a touchstone is needed also in the field of artificial cellularity in particular and the recognition of life in general. We therefore propose to use a similar approach here, that of an 'imitation game' that could help answer the analogous question 'Are there artificial chemical systems that would do well in the cellular imitation game' (**Table 1**)?

Conceptualization

To develop a *Gedankenexperiment* version of an idealized cellular imitation game, we propose that the separation of physical embodiment and ability, as in the original Turing test for AI, must be preserved. That is, in this paper, we are not concerned whether the synthetic cell (which we will refer to herein as a 'chell', from chemical cell, to abstract it from any prejudicial notions of physical form) is built as a chemoton[15], the size of a family car or whether it is a microscopic lipid membrane[16].

Instead, we are interested in the fact that the chell in question should be able to communicate with natural cells (directly or via a relay) in such a way that, as in the spirit of the original imitation game, it can be interrogated by the latter. In such a case, it is not necessary that the language used for interrogating the chell is universal, as was the case for human languages[17] in the original Turing test. On the contrary, the language by which a chell is interrogated by the natural cell should be sufficiently sophisticated so as to appropriately distinguish between alternative outputs from realizable experiments. We envision that as our knowledge of both chells and natural cells increases, better and better experiments will be possible that will distinguish ever more detailed and fine-grained hypothetical properties and features of living matter. In turn, this will give rise to richer and richer communication languages between the artificial and natural entities.

Within this *Gedankenexperiment,* we could think of a cellular imitation game setup (see **Fig. 1**) where the chell must imitate a natural cell and where an instance of the latter plays the role of interrogator through properly configured screening and life-support devices[18]. In this idealized cellular imitation game, interrogation could take place following any of a series of increasingly more complex and sophisticated mechanisms, starting perhaps with a relatively simple quorum-sensing type of language based on, for example, low molecular weight signaling molecules[19], and moving toward mechanical transduction[20], bio-film formation and swarming patterns of behavior[21]. Even as simple a mechanism as quorum sensing offers enough flexibility by virtue of it being 'Turing complete'[22] (that is, it offers the potential of generating any recursively enumerable language).

In any case, the mechanism for interrogation should be immaterial as the critical aspect of the life-imitating game is whether a natural cell as interrogator can or cannot distinguish one of its own kind from the chell. As the human experimenter would be setting up the screening and life-support devices for both the artificial and natural systems, it is the researcher who, as his/her knowledge advances, can implement more refined versions of the cellular imitation game. This mechanism strengthens the imitation game by implementing what Harel[14] has called a "Popperian twist." Thus, even if a chell successfully passed, let's say, a test based on quorum sensing, it might still fail to succeed on a more sophisticated version of the imitation game where the interrogator cell uses, for example, mechanical transduction at the cell membrane or horizontal gene transfer as a probing (that is, communication) language[23].

Implementation

We have discussed above an idealized version of a cellular imitation game in the hope of objectively measuring lifelike features of artificial chemical systems. Current technology would seem to severely limit the chances of implementing such an idealized cellular imitation test in the foreseeable future. It might, however, still be possible to define, with the help of the synthetic biology/artificial life, origins of life and astro/exobiology research communities, a practical realization that, although not following the details of a Turing test, would share its philosophy. We propose that such a practical realization might draw some inspiration from the highly successful critical assessment of protein structure prediction (CASP) program[24].

CASP, which runs every two years, has to date completed six cycles and has used the following guiding principles. In the hope of creating a mechanism for predicting tertiary protein structure from primary structure alone, researchers post primary protein sequences as a 'challenge'. Competing parties who 'take the bait' opt to predict a given three-dimensional (tertiary) protein structure; subsequent comparison with the determined three-dimensional structure provides a ready and effective illumination of successful predictive strategies and models. At a latter stage, the very process of assessment itself also became a field of endeavor—under critical assessment of fully automated structure prediction methods (CAFASP)[25] and EVA (evaluation of protein structure prediction servers)[26]. The net result of the CASP competition has been an enormous advance in the capacity to predict (and compare) predictions of protein structures.

We propose that the same paradigmatic shift in our ability to conceive and judge progress in artificial life and 'cellularity' could be engendered by a similar assessment exercise. We and others have therefore come together to organize a competition that we provisionally entitle the Critical Assessment of Artificial Chemical Cells (CRAACC). Details of this competition will soon be published.

Conclusions

To surmount the notorious difficulties of defining and recognizing life, we should evaluate theories of life not in relation with our current preconceptions, but by how well they explain (by a purposeful engineering effort to imitate) living phenomena and thus how satisfactorily they resolve the puzzles of life[27,28]. The idealized cellular imitation game we propose here does not seek to encompass all existing preconceptions of life but rather, by circumventing them, seeks to stir controversies that could help to advance our chemical, biological, physical and computational understanding of the meaning of life. Even if, as in the case of the original AI Turing test, 50 years from now we would find ourselves to be no closer to a rigorous definition of life, we will nevertheless know better what life is not!

Moreover, advances in our understanding of how cellular chemical structures might imitate a living system, however defined, not only is of theoretical relevance but also, perhaps more importantly, may have a profound practical impact. The chells may be able to do useful work of a conventional chemical nature (e.g., the conversion of CO_2 to more environmentally benign substances), to mimic simple functions of natural cells (e.g., simple metabolic processes to produce useful secondary metabolites) or to carry out novel computation within regimes that are currently beyond our technology (e.g., medical nanonics (nanorobots or any other nanomolecular process/system) or chemically based systems for modeling cellular processes).

Although a purist's version of the imitation game might not be possible at our current stage of technological development, it is our hope that a more down-to-earth version of it, as implemented by CRAACC, will have a similar rallying effect in our community as CASP had in the structural biology community. Turing incorrectly predicted that a computer would successfully pass his test for AI within 50 years. Thus far, this has not happened. Will chells do better?

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