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The enduring value of Gánti's chemoton model and life criteria: Heuristic pursuit of exact theoretical biology

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HIGHLIGHTS

- Gánti's chemoton concept and life criteria are heuristics rather than definitions.
- Chemotons are autocatalytic chemical super-systems that satisfy Gánti's life criteria.
- Gánti's model can effectively guide theoretical and empirical research even if false.

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ABSTRACT

Gánti's chemoton model of the minimal chemical organization of living systems and life criteria for the living state and a living world are characterized. It is argued that these are better interpreted as part of a heuristic pursuit of an exact theoretical biology than as a "definition of life." Several problems with efforts to define life are discussed. Clarifying the proper use of Gánti's ideas to serve constructive engineering idealizations helps to show their enduring value.

1. Introduction

This essay characterizes Tibor Gánti's chemoton model of the minimal chemical organization of living systems and his life criteria for the living state and a living world (e.g., Gánti 2003a, 2003b). It argues that Gánti deployed these concepts in a *heuristic* scientific practice to pursue an *exact* theoretical biology (Griesemer, 2003, 2008, 2013; Griesemer and Szathmáry, 2009). It argues, further, that to characterize Gánti as offering a *definition* of life and an empirically *accurate* or representative model of living systems would be to misunderstand the heuristic role of his ideas in the *joint* pursuit of empirical investigation and theory construction. Clarifying the proper use of Gánti's ideas to serve constructive engineering idealizations helps to show their enduring value. Gánti was a gifted theoretical biologist and a trained and accomplished chemical engineer (see Szathmáry, 2003, and this issue). I seek to characterize how the approach of an engineer with the spirit of a philosopher can be used to pursue an exact theoretical basis for a chemistry of living systems.

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2. On definitions

Conceptual analysis is routinely characterized as supplying necessary and sufficient conditions for a concept. Definitions of terms are likewise characterized in terms of sets of necessary and sufficient conditions: conditions that are individually necessary and jointly sufficient. A bachelor is an unmarried man. It is necessary to be unmarried to be a bachelor. It is necessary to be a man to be a bachelor. To be a bachelor it is sufficient to be both unmarried and a man.

It is also routine among many scientists to offer or ask for a definition of key terms at the beginning of a scientific study to avoid confusion and miscommunication about phenomena, procedures, experiments, models, theories, instruments, and success criteria for hypothesis testing and parameter estimation, and in general to promote scientific understanding.[1] This is often described as "operationalizing" a term or concept: specifying how

[1] "One might think that among the many people working in fields of prebiotic life, artificial life, cell models and the like, one finds many references to a definition of life in the literature. These researchers should know what they are researching or what they are trying to reproduce in their laboratories." (Luisi, 1998, p. 613).

things of a kind are to be understood, detected, measured, or used so as to be in compliance with a definition. Differently put, the role of definitions in science is the investigation of nature's kinds, not concepts (Cleland, 2012). Failure to provide clear, consensus definitions of key terms might be taken as indicative of an "immature" science. Such a view assumes that the purpose of a definition is to stipulate the meanings of terms that figure in scientific theories. Immature sciences either lack theories or have them but lack specificity in what they are talking about.

Not every scientific practice that deals with necessary or sufficient conditions, however, aims at the analysis of concepts, definition of terms, or the constitution of natural kinds. Necessity and/or sufficiency figure in characterizations of causal processes, events, and relations as well. One widely discussed view takes causes to be conditions sufficient for an effect and causal "factors" to be insufficient (by themselves) but non-redundant parts of an unnecessary yet sufficient condition (Mackie, 1974). Causal factors are "INUS" conditions. Striking a match is an INUS condition for lighting. Striking is *insufficient* (you need a rough surface to strike against, dry conditions, oxygen, and so on), but in those conditions the striking is *non-redundant* (necessary in that context and distinct from the other factors it combines with), yet the complex of conditions all together is *unnecessary* (because there are other combinations of factors that can get matches to light), while on the other hand when the striking *does* come together with these particular factors, they are collectively *sufficient* and matches *do* light.

There are also scientific practices that deal with necessary and sufficient conditions which *look like* definitions or conceptual analyses, but do not function like them in practice. Gánti's *heuristic* use of "life criteria" is an example. Purely descriptive or classificatory projects aim to answer questions such as: is desert varnish alive? Is a metabolic cycle contained in a bounding membrane alive? Explanatory projects aim to explain, e.g., why genes are made of nucleic acids rather than, say, amino acids. Gánti's project is *constructive*—framed, in addition, in terms of the problems of guiding the synthesis of artificial living systems in laboratories and guiding the conduct of computer simulations that display emergent dynamical properties characteristic of living systems, one the one hand, and guiding the construction of an exact theory of living systems, on the other hand.[2] This is not to say that Gánti was uninterested in descriptive or explanatory projects. To think of his research program and development of the chemoton model and life criteria only in descriptive or explanatory terms, however, is to miss salient features of the program, to potentially misinterpret his life criteria as a flawed definition of life (even though he used the term 'definition' to characterize this heuristic practice in his publications), and to reject the chemoton model as empirically falsified.

In what follows, it is important to recognize that scientific investigation can involve the joint articulation or "co-production" of theory and empirical results and that this interaction between theory construction and empirical investigation undermines attempts at tidy schemes which seek to place the "definitional project" in any single conceptual role as theoretical or as empirical or even to take definition to have any single logical or conceptual form.

3. Life criteria

The lack of a consensus definition of life across origins of life, synthetic chemistry, and artificial life studies, the many counter-examples to particular definitions, and the debates over whether it is worthwhile even to attempt definitions seem to suggest that these fields are either immature or misguided in their pursuit of definitions. Gánti's body of work on principles of life and chemoton theory seem susceptible to such judgments on grounds that he devoted considerable attention to developing a set of "life criteria" to be used in developing abstract chemical models of minimal living systems.

Gánti distinguished "absolute" life criteria from "potential" life criteria. The former characterize the living state, i.e., the state of anything that qualifies as being alive at a moment of time. Entities must meet the following criteria to be alive at a moment: (1) be an inherent unity, i.e., exhibit emergent properties that are not mere additive compositions of properties of their parts, (2) "perform" metabolism transforming exogenous matter and energy into its own substance, (3) exhibit dynamic or inherent stability of organization, despite any turnover of matter, (4) have component subsystems that carry "surplus information" of potential use by the system as a whole, and (5) have regulated and controlled processes that ensure the maintenance and recurrent functioning of the system as well as directional changes manifest in development and evolution (Gánti, 2003a, pp. 77–78; cf. Griesemer and Szathmáry, 2009, p. 496).

While an entity exhibits the absolute life criteria, it is alive. Thus, the absolute criteria are necessary conditions for being alive. Dead entities fulfilled the set of criteria in the past, but no longer. Entities which temporarily do not fulfill the criteria, e.g., while frozen and thus not performing metabolism, are nonliving. Entities such as bacterial cells cease to exist rather than die when they divide because *they* do not persist as dead entities, even for a moment, past the fission event.

Gánti's potential life criteria are designed to characterize what is necessary for there to be a persistent living world. These criteria include capacities for (1) growth, (2) multiplication, (3) hereditary change, (4) evolution, and (5) mortality (Gánti, 2003a, pp. 78–79; cf. Griesemer, 2003 for a discussion and partial disagreement about how to formulate the potential criteria). Because entities can be alive while lacking a growth or reproductive capacity, there are clearly life criteria which are not absolute, i.e., required to count as alive at a moment. Nevertheless, if no entities in the living state ever reproduced, the prospects for a living world, i.e., a world in which there are entities in the living state, would be dim.

4. Chemoton model

Gánti offered a model of a fluid state automaton—a chemical automaton or chemoton—as a contrast to von Neumann's model of a solid-state self-reproducing automaton (von Neumann and Burks, 1966). While it inspired much thought about the possibility that computing and other kinds of physical machinery might emulate or even *be* life, Gánti argued that von Neumann's model could not fulfill his life criteria due to the geometrical constraints of the solid-state (cf. Penrose, 1959). He argued instead that the only kinds of systems which could fulfill all of the life criteria, including reproduction (the multiplication potential life criterion) would be fluid state, chemical automata (Gánti 2003a, 2003b; cf. Griesemer, 2003, pp. 175–178).

A chemoton is any autocatalytic chemical super-system composed of three autocatalytic subsystems (Fig. 1): (1) GEN: a genetic polymeric material (pV) comprised of monomers (V) undergoing (template) replication, (2) MET: a metabolic network of monomers (Ai) that plays an equilibrating role, running on the energetic difference between food input (Xi) and waste output (Yi), and (3) MEM: a membrane (Tm) comprised of components synthesized from products of the metabolic network (T*) and the genetic cycle (R) (reviewed in Griesemer and Szathmáry, 2009).

[2] Luisi is another origins of life researcher who recognizes that "definitions" should serve constructive as well as descriptive purposes: "Once decided upon, the definition should also help to design experiments on the production of minimal life in the laboratory, consistent with the definition" (Luisi, 1998, p. 619).

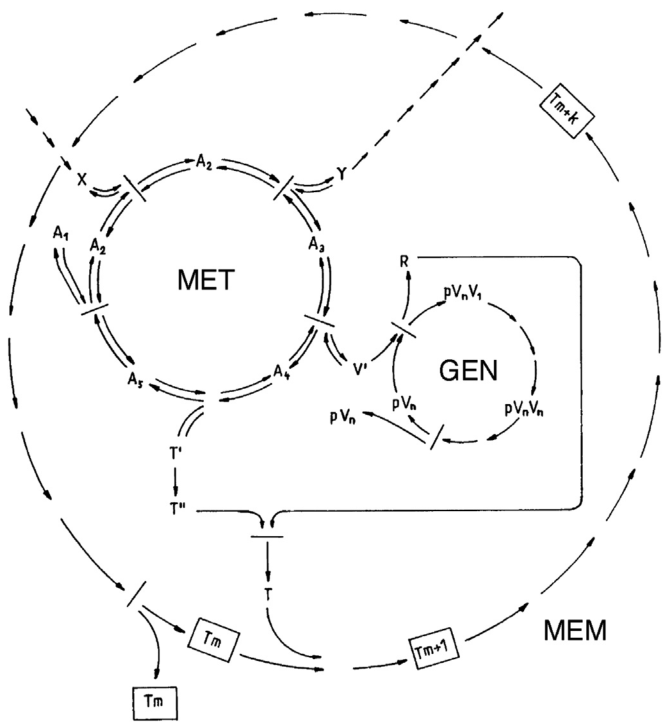

Fig. 1. Gánti's minimal model of a full "AND"-coupled chemoton consisting of a metabolic cycle (MET), a main or genetic cycle (GEN) and a boundary or membrane cycle (MEM). Arrows indicate reaction pathways. See text for descriptions of subsystem components. After Gánti (1997), Fig. 1. cf. Griesemer and Szathmáry (2009), Fig. 22.1, p. 486. The legend in (Gánti 1997, p. 587) reads: "Three self-producing subsystems coupled stoichiometrically: Cycle $A \rightarrow 2A$, template poly-condensation $pVn \rightarrow 2pVn$ and membrane formation $Tm \rightarrow 2Tm$. This coupling results in a proliferating, program-controlled fluid automaton, known as a chemoton."Reprinted from Journal of Theoretical Biology, 187, Tibor Gánti, Biogenesis Itself, 583–593, Copyright 1997, with permission from Elsevier.

Although these subsystem descriptions bring to mind nucleic acid polymer genes, the carbohydrates of intermediary metabolism, and lipid bilayer membranes, the chemoton model is really a quite general representation of the functional organization of any structure that satisfies chemical conditions for catalysis, autocatalysis, and chemical mass-balance, organized in such a way that the super-system satisfies the absolute life criteria. In particular, each autocatalytic subsystem must be stoichiometric. The super-system may also be stoichiometrically determined, as in the model represented in the figure showing a strict stoichiometric "AND" coupling between the subsystems, where V′ and A4 are shown as joint products of A3. Alternatively, if this reaction coupling were "OR" (either V′ or A4 would be produced), then the super-system is stoichiometrically indeterminate, since the genetic cycle could then "turn" an indeterminate multiple of times relative to the others (for more detailed description, see Griesemer and Szathmáry (2009, p. 485); for Gánti's cycle stoichiometry representing the operation of chemical cycles in terms of a turning number, see Gánti (2003b, vol. 1)).

Because diverse kinds of chemical systems may have chemoton organization and because Gánti argued that all of the diverse living systems inhabiting Earth do, there can be no single description or model of chemoton *mechanisms* (Griesemer and Szathmáry, 2009). In particular, there can be no single, general representation of the kinds of *couplings* among autocatalytic subsystems comprising chemotons. Couplings can be disjunctive or conjunctive, for example. This implies that there can be no single interpretation or model of *how* chemoton organizations fulfill the "jointly sufficient" part of "necessary and sufficient conditions" of the absolute criteria for the living state.

Although joint sufficiency of the life criteria may mean logical conjunction (logical-AND), the causal mechanisms which link the properties named, e.g., inherent unity or stability (absolute criteria 1 and 3) and information-carrying (absolute criterion 4), may be linked disjunctively (causal-OR). That is, the simple logical structure of the criteria may not map straightforwardly to the "interactionally complex" (Wimsatt, 1974) functional organization of causal mechanisms.

5. The problem with definitions

The argument that the chemoton is the minimum chemical organization for life appears to treat the life criteria as a *definition* to *stipulate* what constitutes the living state and then to apply the definition to show that the chemoton model satisfies it. Pedagogically, this is indeed what Gánti does to demonstrate that the chemoton can function as an exact model fulfilling the absolute life criteria Gánti, 2003b. The demonstration shows that anything operating with chemoton organization would count as alive according to the criteria. The conditions in the definition are treated as necessary for life. The organization of the model is sufficient to satisfy the definition. So, the features of the model can be used as probes to search and test for satisfaction of the definition. We must not, however, confuse pedagogy with the research agenda.

Two kinds of problems for Gánti's view would seem apparent from this argument. First, Gánti's life criteria as discussed above may not describe everything scientists intuitively wish to treat as alive or they may describe as alive things that some would not wish to treat as such, so the criteria may be neither necessary nor sufficient. Cleland and Chyba (2002, 2007) and Cleland (2012) point out that definitions formulated in terms of known, familiar life (and instruments and probes designed to detect it) would not be able to recognize "shadow" life forms organized differently or built from different materials than known forms, e.g. life that originated elsewhere in the universe than on Earth. The problem is that "our scientific ideas about life are based upon a single example [Earth life] that may not be very representative of life" (Cleland, 2012, p. 130). Cleland concludes that "from a scientific perspective, explicating the nature of life by means of either a traditional or nontraditional definition of life is fundamentally misguided." (Cleland, 2012, p. 131)

For example, since the absolute life criteria include metabolism, no "replicator first" process of the origin of life can declare life to have arisen among self-catalytic replicating molecules on the assumption that these cannot perform metabolism. The life criteria seem, therefore, to rule out "by definition" some conceptions of the origins of life that would claim sufficiency of self-replication, or replicator dynamics, or evolutionary capacity (that something is alive if it can be a unit of evolution exhibiting multiplication, variation, and heredity, where the basis of all three of these properties is replication).

Szathmáry et al. (2005) and Griesemer and Szathmáry (2009) explore various sub-chemoton organizations as possible evolutionary pathways to full chemoton organization, e.g., "infra-biological" systems combining any two of the three subsystems of the full chemoton organization: metabolism plus membrane (boundary), metabolism plus genetic system (template), or membrane plus template. Griesemer and Szathmáry (2009) also consider "proto-biological" chemotons which have simpler versions of each of the three subsystems but which lack some of the chemical properties of Gánti's model (e.g. super-system autocatalysis or stoichiometric coupling of subsystems). Are any of these infra- or proto-biological systems alive? Gánti's argument implies the answer is "no" on the grounds that none of them fulfill all of the absolute life criteria. But why is that the right conclusion rather than that his life criteria require "too much"?

A related problem is that there are marginal entities which seem salient to consider from the point of view of a theoretical biology, but which are either ruled out or ruled in as alive by a definition of life. On Gánti's criteria, viruses are not alive because they do not perform metabolism in the sense that virus particles lack a metabolic cycle. On the NASA definition that 'Life is a self-sustained chemical system capable of undergoing Darwinian evolution' (see Joyce, 1994), it would appear that viruses are alive, at least in the sense that populations of them may satisfy Darwinian conditions of heritable variation in fitness and be self-sustaining in so far as they are capable of infecting cells to get the materials and machinery they need for replication. On the other hand, if self-sustainment can be achieved by co-opting the metabolic cycle of a host, why should we not consider that viruses "perform metabolism" but in the unusual sense that they control the metabolism of a different "inherent unity" rather than themselves?

So, are viruses alive on Gánti's criteria? A "definitionalist" may say "no" and be glad of the clear line drawn between life and non-life by the interpretation of Gánti's life criteria as supplying *definitive* necessary and sufficient conditions. A definition-skeptic may conclude that whether a definition rules viruses in or out of the category 'alive,' it is a mistake to do so because it either rules in that which is not alive or closes investigation to this "shadow" form of life. The uncertainty may lead some to conclude that it is a "matter of taste" whether a marginal or shadow case should be ruled in or out. I suggest a different interpretation that depends on the view described in the next section: The heuristic use of life criteria together with a theoretical model (such as Gánti's chemoton model) can treat viruses, shadow life, and other cases at various transition points between non-life and life as *both* in and out of the category 'alive.' An exact theory must make sharp domain distinctions and the formalization of an exact theoretical biology will impose one. But a "fossilized" theory which is inflexible about its domain is a dead *scientific* theory, just as "rational mechanics" is now a branch of mathematics rather than physics. Productive scientific theories must also guide empirical inquiry into the margins and boundaries of their domains. And the heuristic use of life criteria allows for the breakdown of the criteria in the face of marginal, vague, and borderline cases. An *empirical* model might well treat a certain virus as alive by representing, for example, its chemoton organization as a *hybridized* structure in which *the virus* forms an inherent unity by coupling host metabolism and host membrane temporarily with virus genetic cycle by shedding its own protein-coat boundary and co-opting host metabolism by means of viral enzymes. Griesemer (2014) works out this kind of scenario for HIV-1, although without explicit stoichiometry.

Second, just in virtue of something's having the chemoton model's organization, it could not *live* because the model does not address or solve a long list of chemical problems any real chemoton implementation would face. For example, membrane (semi-)permeability is not represented in the model (Ruiz-Mirazo and Mavelli, 2008). Without that property a chemoton could not take up food (X) or excrete waste (Y) without also possibly losing its core metabolic molecules (Ai), genetic monomer precursors (V') and polymers (pVn), and membrane precursors (R, T$*$) to diffusion and thus its inherent unity, dynamic or inherent stability, regulation, and control (Griesemer and Szathmáry, 2009, Szathmáry et al., 2005). Moreover, for any real chemistry (as opposed to the idealization presented in the model), there would likely be potentially poisoning side reactions in addition to the preferred reactions, so the model is incomplete in ways that may undermine the operation of any empirical system it might be used to represent (Griesemer and Szathmáry (2009) review these and other problems). So, it appears that the chemoton model is too incomplete to determine whether it (or any system with chemoton organization) actually satisfies the life criteria.

Two temptations arise from considering these kinds of problems, one about the criteria and one about the model. One is to conclude, because counterexamples seem always at hand and there is little consensus among the many definitions of life available, that defining life is either impossible or pointless (e.g. Machery, 2012), so the project should be given up. The other temptation is to conclude that because the chemoton model is unrealistic, i.e., entities merely having chemoton organization could not live, then the model is falsified and should be given up.

These two problems arise, however, from treating the life criteria as individually necessary and jointly sufficient conditions *in a logical sense* for a system to be alive. Joint sufficiency is usually assumed to mean that *logical conjunction* of the necessary conditions generates the sufficient condition. In other words, the problems stem from treating the life criteria as a stipulative definition (see Machery, 2012, p. 157) of life with the structure of sufficient conditions specified logically rather than in theoretical scientific terms. Bedau (2012), for example, argues that the life/non-life divide is a matter of degree rather than kind, which requires a different logic than disjunction or conjunction can provide.

Moreover, the chemoton model is treated in this "definitional framework" as a model of *empirical* systems that, while simpler than contemporary living cells, would count as alive according to the life criteria (taken as a definition). So, if the chemoton model fails to be accurate in relevant respects, the temptation is to conclude it should be abandoned in favor of a more accurate representation. In contrast, as alluded in the alternative interpretation above of viruses as creating chemoton organization by hybridization, I suggest that Gánti's chemoton model and life criteria be taken as components of a single, joint theoretical construct used for *both* theoretical and empirical purposes (Griesemer, 2003).

6. A heuristic engineering perspective on Gánti's life criteria and chemoton model

Definitions are sometimes treated as components of a theory (along with laws or other general claims), i.e., as "theoretical definitions." In contrast to stipulative definitions that are designed to fix the meanings of terms, theoretical definitions are "tentative and revisable in light of empirical evidence" (Cleland, 2012, p. 128).

However, theoretical definitions tend to structure empirical research in terms of a fixed structure of hypothesis testing: if an empirical phenomenon exhibits the set of properties specified in all of the individually necessary conditions expressed in a definition, then it is confirmed that the phenomenon falls under the theoretical definition, theory or natural kind. Failure to exhibit the relevant properties is either taken as a disconfirmation or an anomaly.

The question then is: what is to be done with the discovered anomalies? This depends on the nature of the scientific enterprise at hand. The theoretical definition could be held fixed—as part of a finished theory—and the search for phenomena that fit the theory continued. This is to treat the definition as a *formalized* theory (see below). Just ignore the phenomena that do not fit and move on until the domain is covered or else work to *make* anomalous phenomena fit through reinterpretation or analysis of data, revision of measurement techniques, or improvement of instrumentation. Those are options under Kuhn's concept of "normal science" in which empirical practice using a mature scientific theory delimits what counts as anomalous, i.e., as a violation of an accepted paradigm (Kuhn, 1970). Or, the definition itself could be revised in light of the anomaly. That also can be understood either as Kuhnian normal science tinkering to resolve anomaly or it could lead to crisis and scientific revolution.

Cleland (2012, p. 141) characterizes an alternative approach based on the use of "tentative criteria" rather than theoretical definitions of life to intentionally *search for* anomalies rather than for new instances of familiar forms of life. She suggests incorporating the most disparate features of familiar life into tentative criteria, not to expect that any of the criteria need be universal (since Earth life is only "one example" of life), and not to assume that what is common (or rare) to familiar life is thereby essential or common (or rare) elsewhere, e.g., on other planets or as the result of laboratory synthesis.

Wimsatt (2007) characterizes a similar alternative to traditional "conjecture and refutation" or "normal science" approaches that fit anomalies to theories (and thus to theoretical definitions). Wimsatt calls his approach an "engineering" perspective. The aim of theoretical modeling is not merely to *search for* anomalies and thus to tinker with tentative criteria to resolve them, but to "*metabolize*" anomalies, i.e., to actively seek the *breakdown* of models constructed using the aid of tentative criteria. Systematic study of patterns of breakdown of models is a means to "truer theories" (Wimsatt, 1987). Differently put, better, i.e., more robust, theories can only be engineered by studying *patterns* of failure in models broken by anomalies. On the engineering approach, models are made to be broken and anomalies are used as tools for theory construction. So it is no reason to reject, i.e., stop using, a model that it is broken. Indeed, that is precisely when a model becomes interesting.

Wimsatt's account brings to the fore that theoretical models work *together* with tentative criteria in inexact sciences as surrogates for the mature theories that characterize Kuhnian normal science. Anomalies are detected in terms of the failure of models to *reconcile* tentative criteria with the behavior of the model in applied empirical circumstances. These are typically failures of robustness.

The metabolism of anomaly involves the mutual adjustment of models and criteria, which together serve dual purposes: to construct theories and to guide empirical practice more deeply into anomalous phenomena. Gánti's use of life criteria fits this engineering practice. His 1971 chemoton model included only a metabolism and a "main" (genetic) cycle (Gánti, 1971). The membrane subsystem was added in 1974 and thereafter to specify how inherent unity and stability as well as some of the potential criteria could be satisfied. This responsiveness shows that the model is playing a role in theory construction, as a model satisfying theoretical principles and not only a representational role relating to empirical phenomena.

A further idea is needed to capture the full spirit of Gánti's research enterprise: a distinction between exact and inexact science (Gánti, 2003a, Griesemer, 2013). Gánti points out that "… it is not the real world which the exact sciences are capable of treating with an arbitrary exactness, but their own model systems" (Gánti, 2003a, p. 55). His scientific goal is to construct an exact theory of living systems. This construction process can be characterized as "formalization" (Griesemer, 2013). Formalization allows "… forms, e.g., as represented in theoretical models, to be studied independently of the empirical content of a subject-matter domain" (Griesemer, 2013, p. 298). One such study of form would be of the patterns and ways in which behavior of chemoton models as elicited in computer simulations or chemical calculations conforms *or fails to conform* to a set of proposed tentative life criteria. This empirical practice would be part of an "inexact" science in so far as it is not expected that the model exactly satisfies *tentative* criteria (serving as surrogate for a formalized theory), but rather that tests of satisfaction are a means of articulating and refining the *criteria* in order to construct the principles of a theory.

Exactness depends on the *use* of theories (or their informal surrogates) to control (delimit) subject-matter domains and to align theoretical with empirical models. Inexact biological sciences tolerate a degree of "mismatch" between theoretical and empirical models and concepts (Griesemer, 2013). In Gánti's case, this means that there are two kinds of uses of the chemoton model + life criteria. One use is theoretical, a process of theory construction by working to articulate the model to fit the criteria and tinkering with the criteria to adjust to the model so that general dynamical equations can be developed that describe the operation of the model such that its emergent behavior satisfies all life criteria. The other use is empirical, to compare the organization of the theoretical model to real phenomena or data and to use the theoretical model as a platform for empirical model development. This is the territory explored, for example, by Ruiz-Mirazo and Mavelli (2008) when they add empirically known features of membranes in familiar life forms to a chemoton model in order to model molecular trans-membrane mechanisms that couple internal chemical reactions with transport processes. Ruiz-Mirazo et al. (2014) show how Gánti's theoretical scheme can be fruitfully applied to classify the wide diversity of experimental approaches that have been developed in recent decades within the field of origins of life. Their work further supports the value of Gánti's exact use of the chemoton model and life criteria as a theoretical scheme that can drive empirical research programs, even those whose goals and motivations are not related, in any obvious way, with it.

An *exact* theoretical biology is a science for which there is a formalized theory which is exactly true of its *theoretical* models and which can guide inquiry into an *empirical* domain *specified* (i.e., *defined*) by the theory. Giere (1988) characterizes theories as definitions in this sense, e.g., treating Newton's theory as a definition of the class (domain) of physical systems satisfying Newton's laws (i.e., principles or "criteria"). In formalized sciences the *theory* may fail to describe empirical phenomena in some respect or to some degree of accuracy if those respects or phenomena are not within the domain specified by the theory. Rather than a falsification of formalized chemoton theory (Gánti, 2003b) due to the fact that real membranes are semi-permeable, or that real genetic replication depends on nucleotide base-pair complementarity, such facts pinpoint "mismatches" between the theoretical chemoton model and empirical models. Falsification is of the *relation* between these classes of models which does not undermine the *heuristic* value of the chemoton as a "false model" in the sense of Wimsatt (1987).

Empirical inquiry in an exact theoretical biology is guided by means of *empirical* models. Empirical models represent phenomena by making various idealizations and approximations which depart from the structure of the *theoretical* models to varying degrees and respects. Gánti's full research program involves the construction of a formal chemical theory of living systems which fulfill the life criteria that the theoretical chemoton model has been demonstrated to satisfy. It also involves the simulation of chemoton behavior as a means of generating patterns that can be compared to data from empirical systems. The breakdown of the theoretical model is what an engineering approach to the search for, and metabolism of, anomalies seeks in the service of building a robust theory. A good example of this kind of use of chemoton models is Mavelli and Ruiz-Mirazo (2007). The mismatch between the chemoton model and the empirical behavior of real living systems modeled by Mavelli and Ruiz-Mirazo (2007) shows just where the empirical models get interesting, from the point of view of a robustness analysis.

One way to understand the concern of philosophers like Cleland and Machery about definitions of life is that, if treated *as* formalized theories of natural kinds, they will function to delimit the domain of inquiry. Such use of definitions is likely to exclude some life forms from the domain (e.g., "shadow" life or some laboratory constructions) or to radically mislead researchers about the nature of the domain. This "premature" formalization has the effect of constraining inquiry and, even where anomalies are discovered, provides no guidance for "metabolizing" them. A formalized theory *specifies* its domain, so to study phenomena outside the domain is simply to change the topic and render the theory irrelevant or inapplicable. Newtonian physics is formalized in this sense. To study quantum phenomena is simply to step outside the Newtonian domain and Newtonian practice. But a formalized, exact theory that is also used heuristically in conjunction with models and tentative criteria can be open to modification of the domain in the face of model breakdown and even to modifications of theory. Exact theories need not be rigid or fossilized if this heuristic role in guiding empirical inquiry is recognized as another face of "definitional" projects.

7. Conclusion

It would be quite easy to dismiss Gánti's work as outmoded because we know that the chemoton model fails to represent many features of known living systems, because no chemical system having only chemoton organization without further properties specified could actually live and meet Gánti's life criteria, or because his life criteria, taken as a *definition* of life may restrict the domain of life to systems with a particular functional form, e.g., ruling out viruses as alive by definition rather than by empirical discovery.

I have argued instead that we should view Gánti's work as presenting a *heuristic* structure and engineering strategy: the chemoton model plus life criteria constitute a platform for the development of a formal theory which the chemoton model satisfies exactly and a platform on which the life criteria can serve as a probe for empirical anomalies in real systems that yield systematic patterns of model breakdown. The search for a robust understanding of life should be viewed as a dynamic enterprise, involving continual and mutual adjustments of theory and practice, not an effort to encapsulate "life" in a formula or definition. Gánti's work has enduring value as a heuristic basis from which new models have been, and are being, evolved.

Competing interests

I declare that I do not have any competing interests.

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