Distorted Biologic Mechanisms in Evolution and Model Extrapolation

Juan G. Diaz Ochoa
PMQD GmBH
Pelargusstr. 2
70180 Stuttgart
Germany

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Abstract

Explanations based on low level interacting elements are valuable and powerful since they contribute to the identification of mechanisms controlling essential biological functions and responses, if nature is complete and decidable. But this assumption often generates frustration since organisms are still far to be controllable and predictable, implying that the knowledge about mechanisms are often not enough to explain many biological processes. We argue that the accommodation and assimilation of organisms to their environment continuously challenge biological mechanisms, and consequently that systems are fundamentally incomplete and undecidable, in the same way as the halting problem in mathematics is unsolvable. This condition allows a constant creativity that drives evolution, continuously distorting these mechanisms. We introduce a measure of this distortion, which should be useful to determine if the identification of simple mechanisms for modelling in Biology is feasible or not. We test this concept in a population of predators and predated cells with uncertain chemotactic mechanisms and demonstrate how the selection of a given mechanism depends on the whole population. We finally explore this concept in different frameworks and postulate that the identification of predictive mechanisms that can be extrapolated to other organisms is only successful with low distorted mechanisms.

Key Words: Systems Biology; Mechanisms; Distortion; Evolution

Introduction

The combination of both data science and network theory has become a prominent method to understand many complex systems, from biology and medicine to society. Data produces the knowledge necessary to deduce mechanisms responsible of interactions between different elements, if these interactions represent a physical or at least a causal relation between them. With the knowledge of these mechanisms is in principle possible to understand from basic principles biological functions, making real the Cartesian conception of Biology: "I should like you to consider that these (biological) functions follow from the mere arrangement of the machine's organs every bit as naturally as the movements of a clock or other automaton follow from the arrangement of its counter-weights and wheels" (Descartes, Treatise on Man, p.108). Notwithstanding there is still no unified mathematical formalism providing an essential description of complex biological systems, network theory has become a good candidate to be the fundamental basis of this theory, in part because it allows the mathematical implementation of mechanistic explanations.

The obvious relevance of this methodology is the possibility to write predictive models, allowing the extrapolation from one to other system (translation) as well as the extrapolation in the future (prediction). For instance, molecular biology is essentially reductionist, since it assumes that "explanations that come from lower levels are better than explanations that come from higher levels" (see (Tabery et al., 2005)). Thus, biological theories need to be grounded on molecular biology and ultimately physical sciences, for it is only by doing so that they can be improved, corrected, strengthened, and made more accurate and more adequate and completed (Rosenberg, 1997)". Biological theories are then represented by models, which are usually constructed on the base of network theory. Ideally these networks can be experimentally validated, such that these models can be used for different kinds of extrapolation (in time or between

different target systems).

But it is impossible not to feel some discomfort in this development. An extrapolation based on a model requires a perfect and complete mathematical description. This goal can be more or less reached in physical sciences, when perturbation sources are controlled or well characterized, allowing the discovery of fundamental interaction mechanisms. But in complex systems we continuously experience the limits of this methodology, since we are continuously exposed to open and evolving systems.

While it is usually granted that the context of an organism and its evolution takes place after long periods of time, in practice it is difficult to know how fast this evolution is. For instance, in medicine: "disease cannot always be predicted with certainty, and health professionals must identify and modify risk factors. The common unidimensional "one-risk factor to one-disease" approach used in medical epidemiology, however, has certain limitations "(Ahn et al., 2006). This concept is for example the origin of epidemic paradoxes, i.e. spread of apparent diseases in healthy populations simply by adjusting the threshold values of characteristic physiological measurements -like levels of biomarkers- (Ahn et al., 2006). But not only in risk assessment, but also in the identification of evolution this concept is blind. For example, in pharmacology we observe an intermittent adaptation of organisms to substances after long administration times, which are much shorter than time spans for biological evolution (see (Peper, 2009) for a mathematical model considering interactions with the environment)[1].

These facts challenge the construction of models. In effect the myriad of possible interactions motivate a continuous update in the information registered in data bases. Thus, while some canonical pathways are well known, many other interactions, and possible variations, are still unknown and must be constantly updated when these mechanisms are reconstructed.

These variations are rooted in many possible ways to respond to the environment. The interconnection between different scales is a central concept that, despite its growing relevance in sciences, is usually ignored, and which is deeply related to the autopoietic character of biological systems. While a hierarchic construct seems to be a first good approach, if small structures are involved in collective interactions that drive self-organization producing larger structures, this organizational characteristic is not enough to understand how "assimilation" and "accommodation" works for systems included in larger organisms (Bitbol and Luisi, 2004).

We argue that, like condensed matter (Castelvecchi, 2015), processes in biological organisms are fundamentally incomplete and undecidable. Only when these processes are included in the organism a completeness is achieved, making possible the evaluation of predictions using a mathematical formalism. This is basically the background for systems biology. To get this decidability, biological processes require different scales as reference. This implies that systems not simply emerge and are autopoietic, but model themselves, in the spirit of basic cognitive notions as "assimilation", "integration", and "accommodation" to an environment (Bitbol and Luisi, 2004). To this end, we introduce a "distortion" factor to measure how strong these cross-scale interactions are. We use this coefficient as a measure, but also as a criterion for the modeling of complex interacting systems, and deduce a simple toy model for chemostasis, complementing current methods based on network theory. Finally, we discuss this theory in the framework of network theory and explore potential applications.

Vesicles and completeness

Consider for instance the formation of vesicles, starting from a relatively static aqueous system (vesicle) formed by a surfactant *S*. Here a highly lipophilic precursor of *S*, indicated as S–*S*, binds to the boundary of the vesicle and is hydrolysed there. The vesicle grows, and eventually divides into two or more thermodynamic more stable smaller vesicles. The more vesicles that are formed, the more *S*-*S* is bounds and the more vesicles are formed, i.e. the process is auto-catalytic. Since the whole process of hydrolysis and growth takes place because of and within the boundary, the vesicle can be seen as a simple self-reproducing, autopoietic system" (Bitbol and Luisi, 2004).

[1]This adaptation explains why the rolling stones have survived so many time despite drug and general health abuse.

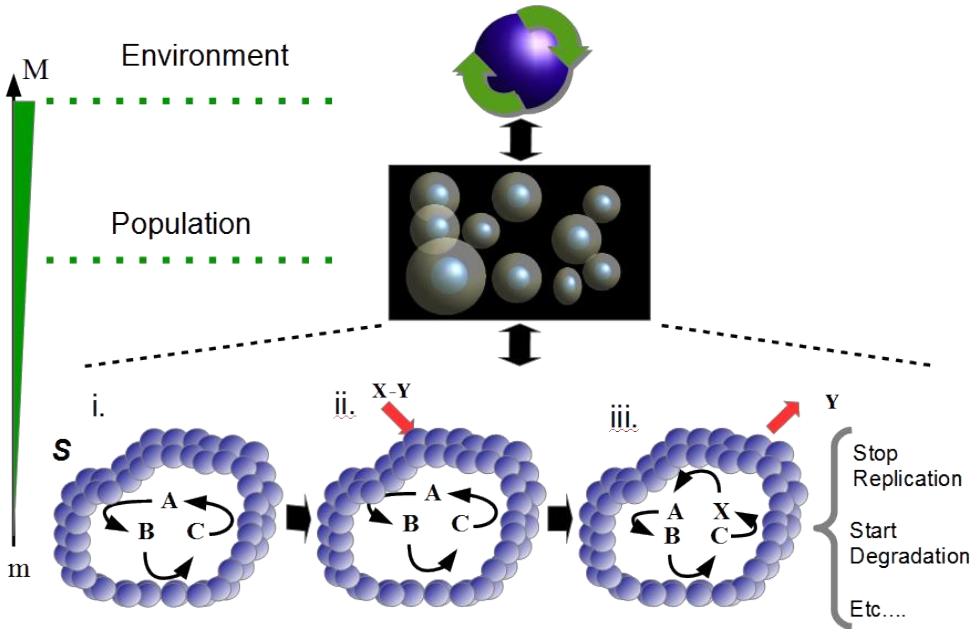


Fig. 1: Example of a vesicle with a membrane formed by a cycle generated with the molecules A, B and C (i) that allows the vesicle replication. After interaction with the nearest population and environment a pair of molecules X-Y is absorbed(ii); thereafter the molecule X is linked into the cycle (iii). This interaction can trigger important "decisions" in the vesicle concerning its maintenance or degradation, or the inhibition of the internal cycle. The cell states are symbolized as a transition from a square (initial vesicle) to a triangle (vesicle with transformed internal cycle and final "decision").

Additionally, these simple vesicles can contain simple internal reactions mechanisms, as for instance when "the membrane (***S***) is formed from the molecule ***B*** through a process characterized by a generation velocity *v*. Then, ***S*** decays with velocity *v_dec* . Assume additionally that the precursor metabolite **A** enters from the environment, and that ***B*** decays into ***C,*** which is eventually expelled." This process can continue at infinite if it is homeostatic and has access to energy sources able to maintain it. At this point all these processes are mechanistic, and can be described using simple ordinary differential equations (see figure 1a).

Here results useful to consider the work of Maturana and Varela concerning how the interaction between autopoietic unit and environment can change., accounting basic concepts of cognition. Indeed, there is cognition whenever "there is: (a) an environmental cause, for instance in the example of the vesicles an outer molecule ***X-Y*** ; (b) a resulting effect from the unit, here the inception of the molecule ***X*** in the cycle and the release of the metabolite ***Y*** ; and (c) an adaptive virtue of the effect (Bitbol and Luisi, 2004), for instance the inhibition of the vesicle reproduction, triggering of a degradation process, etc..

The fact that molecules ***X-Y*** may trigger or inhibit the internal processes (from the unit) implies an *external decision* about the next state of the vesicle, regarding the population of other vesicles and the environment. The population with the initial set of reactions (square symbol in figure 1) surely fulfills all thermodynamic constraints, and is associated to a high fitness. But these optimal conditions do not help the vesicle to decide about, for example, when to stop or continue the replication process.

In this example, biological processes cannot make decisions "by themselves" based only on mechanistic (and physical) notions. We suspect that this issue is common for many systems in biology and other sciences. For instance, for 2D lattices of atoms "the undecidability 'at infinity' means that even if the spectral gap is known for a certain finite-size lattice, it could change abruptly — from gapless to gapped or vice versa — when the size increases, even by just a single extra atom. And because it is "provably impossible" to predict when — or if — it will do so it will be difficult to draw general conclusions from experiments or simulations "(Castelvecchi, 2015) (Cubitt et al., 2015); this is a remarkable result since it extends a well-known concept from Mathematics/Informatics into physics. We postulate that internal properties in vesicles is like changes in internal states in atoms, such that populations of vesicles behave like a Touring Machine that are unable to halt by themselves. Therefore, in this framework biological processes require assimilation and accommodation.

Thus, our hypothesis is that biological systems are inherently incomplete, and that assimilation and accommodation help them to be complete and decidable. For instance, if the population of vesicles has enough energy then they can eventually continue reproducing (like an immortal cancer cell in a tumor), which is nothing different to an infinite

iteration of a Touring machine. Only when this unit belongs to an organism this process will be decided (i.e. can continue forever or can be stopped) according to the functionality of the population as an organism.

Mathematical theory: Completeness and mechanisms

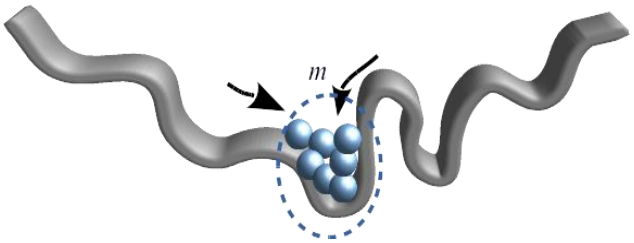
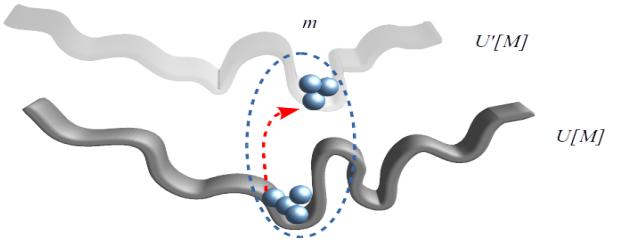
Assume an organism with several interacting molecules. In biology, the availability of resources depends on the feeding of our process, and is therefore a relative quantity that is usually finite, such that a process halts after some period of time. Even if biological systems are like physical systems that are driven by external energy sources and that dissipate energy from the environment (England, 2012, 2015), these processes will not stop if the amount of energy from the external source is infinite. Thus

Axiom 1
A biological process that runs independent to other organisms and has access to relative infinite available resources, will not halt.

This because the mechanism (or program) is not able to contradict itself deciding when to halt. For example, in the case of the vesicles if they have enough energy, and preserve high fitness (for instance under the absence of any predator consuming these vesicles, optimal *in vivo* conditions, etc.), they will continue self-reproducing. In our example of the vesicles, the constant reproduction and replication allows the optimal dissipation of energy from the environment.

This is also like immortal cancer cells, for instance HeLa cell lines. This can also be valid for reproducing organisms with apoptosis but uncontrolled reproduction. Clearly, being part of a larger organism or environment implies that processes must be decidable[2].

Table 1. Illustration of homeostasis and evolutionary pressure on landscapes

	Example 1: Homeostasis is related to the optimization of landscape in a control function (for instance fitness). Each element (small spheres), as well as the whole organism (sphere population enclosed in a dotted circle) search this optimal function. Biological functions emerge from the search of an optimal in this landscape.
	Example 2: The control function *U[M]* is locally optimized, but the whole population is eventually constrained to a different landscape *U'[M]*. The gap *ΔU[M]* depends on the accommodation and assimilation of the organism (population) to the environment, or equivalently to the use in the organism of compensating mechanisms, such that biological functions are decided.

Consider that processes can emerge in a natural way. Physics and chemistry do not prohibit infinite cycles if systems are open and processes behave as algorithms or deterministic mechanisms. If the mechanisms are embedded in an organism, then "the response to the stimulus is attenuated to reduce the effect of the stimulus" (Peper et. al.) such that processes or cycles can be maintained for very long periods of time. "Adaptation, on the other hand, is an additive process where the disturbance is counteracted by compensating mechanisms". This adaptation is responsible for the development of tolerance against environmental offenses in the organism, like drug tolerance (Peper et al. 1988).

We argue that this adaptation, and development of tolerance, is only possible when different scales are anchored to different preferred control functions. Either the elements automatically look for the optimal value in a control function or decide which is the preferred control function to be optimized regarding a different scale in the whole organism, which is equivalent to the definition of compensating mechanisms. This mechanism is not blind, and set compensating mechanisms respect to different scales (for instance the whole population); this simultaneously helps the system to be decidable. This implies a gap in the control function (energy landscape, dissipation forces, fitness landscape, etc.), as is illustrated in the table 1. We argue that this can work considering internal reservoirs.

[2]Note that we restrict here our attention to simple biological processes. For a relation between the Kolmogorov complexity and Biology through genetic code see works about meta-mathematics (Chaitin, 2012)

In resume, different scales induce a gap in the control function $\Delta U[M]$, which is proportional to compensating mechanisms or to internal reservoirs, and which is able to induce mechanisms that help to decide about the function depending on $U[M]$. The decision to jump in this gap is not autopoietic (self-organized or co-evolutive), as has been shown by Bitbol et al. (Bitbol and Luisi, 2004).

Thus, *the mechanisms of an organism accept several surrogate structures in different scales that induce a gap in a control function allowing accommodation and assimilation to the environment,*

Structures are for example represented by a network of molecular interactions, food networks, etc. Thus, s*urrogate networks are essentially inconsistent, i.e. it is impossible to define consistent networks related to well defined and complete control functions.*

This sentence is close to the Rice Theorem, which states that for any non-trivial property of partial functions (in this case networks), no general and effective method can decide whether an algorithm computes a partial function with that property[3] . Therefore, this implies that the single elements in the system must be also considered as independent observers.

For example, single vesicles are nodes that belong to the scale *m*, whereas large populations of vesicles are grouped in nodes that belong to a larger scale *M*. Since we handle with two populations of vesicles, one with a simple homeostatic mechanism, and other with a modified mechanism that incorporates the molecule X regulating the membrane formation, we define two clusters. Thus, we essentially handle two groups with different connectivity g_{ij}. In our example, there is a transition from one population with connectivity g_{ij} to other population with different connectivity g'_{ij}. In this context, a decision implies a change in the internal structure of the vesicle.

From the point of view of physics the dissipation mechanisms and internal energy reservoirs are relative quantities, such that there is a gap of energy depending on the halting condition imposed by an organism. This gap is proportional to the distortion of the interaction structure g_{ij} associated to the corresponding mechanism, as is illustrated in the table 1

The distortion factor is defined as

D = 0; no distortion iff. system is complete and isolated. Thus, a change in the structure of interactions is improbable.

Mechanisms, identified at a scale *m*, do not detects changes in the environment or the whole population (in a characteristic scale *M*), such that a model can be described in a single scale or hierarchical scales. Simultaneously this implies that $\Delta U = 0$ (see table 1). Physical systems are characterized by $D = 0$.

On the other hand:

D >> 0 iff system is incomplete (undecidable), but is decided respect to different scales in an organism.

Since $\Delta U > 0$, structures g_{ij} change in response to environmental changes (accommodation and assimilation). Similar to the definition of distortion in mathematics, it can be defined here as

$$D = \frac{\Delta g_{ij}}{\Delta O(M)}$$

where $O(M)$ is the distance between two different states of the system in the scale M (for instance measured as a Hamming distance). Thus, living systems are characterized by $D \gg 0$.

Our additional postulate is that *D* increases for large incompleteness, but organisms try to keep their incompleteness low (which is equivalent to have a low distortion). Respect this point we see that autopoiesis can be maintained iff the system is complete. Low incompleteness is in this context like have design principles (A. Kremmling (Sehr et al., 2015)).

[3] https://en.wikipedia.org/wiki/Rice%27s_theorem ; http://www.jstor.org/stable/1990888?seq=1#page_scan_tab_contents

Example: a modified predator-prey system with chemostatic response

Due that intrinsic networks are not consistent, there are several possible responses that can be assigned to different networks. To illustrate this, we employ an example for chemotaxis where we are unable to decide between two candidate networks associated to two different responses to stimuli.

Here, "perfect adaptation of a signaling response turns out to be quite restrictive in terms of the number of possible ways it can be achieved. A recent analysis suggested that the 'architecture' or topology, of the underlying signaling networks would be expected to fall into two classes: those containing a negative (integral) feedback (NFB) and those that contain two parallel initially diverging and ultimately converging pathways, affecting the output in opposite ways. The latter network type has been termed an 'incoherent feed-forward' loop (iFFL)" (Chang and Levchenko, 2013)(Chang and Levchenko, 2013). The, "adaptation to temporally changing inputs can be a key in this response". In figure 4 the results for each response are presented assuming stimuli that linearly increases with the time.

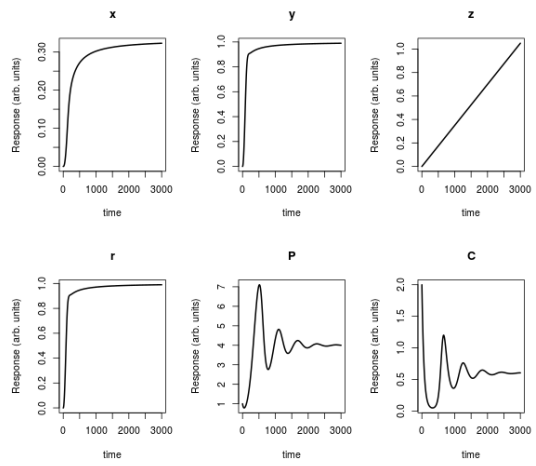


Fig. 2A Non-adaptive response, with a population with low propagation velocity

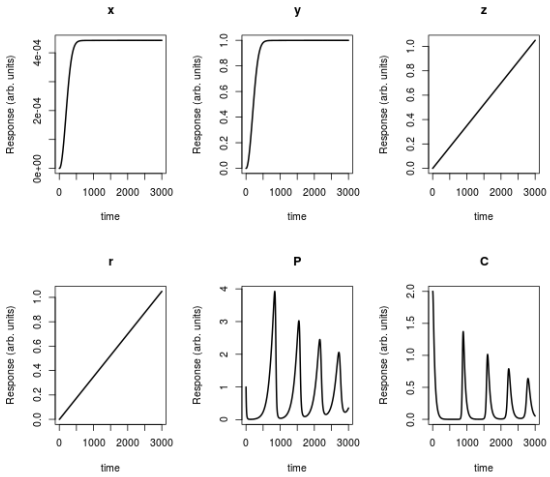


Fig. 2B Adaptive response, with a population with high propagation velocity

The notion of distortion is in this model useful to track the completeness of the system. Additionally, to seek the reduction of the distortion helps us to define a co-evolution of internal chemo-static states in the population.

"As the rate of the change increases, the cells would tend to maximize their response, recognizing that they move in the direction leading them more precisely towards the source of the chemoattractant." However, some organisms will require an adaptation to the external response, i.e. when they approached to the source they minimize their response, requiring the iFFL but not the NFB architecture. Relevant in this case is the difficulty to exactly define or identify the underlying network. We see here a system that is incomplete, i.e. two different competing models, eventually based on common molecular interactions; both can perfectly explain the behavior of the system.

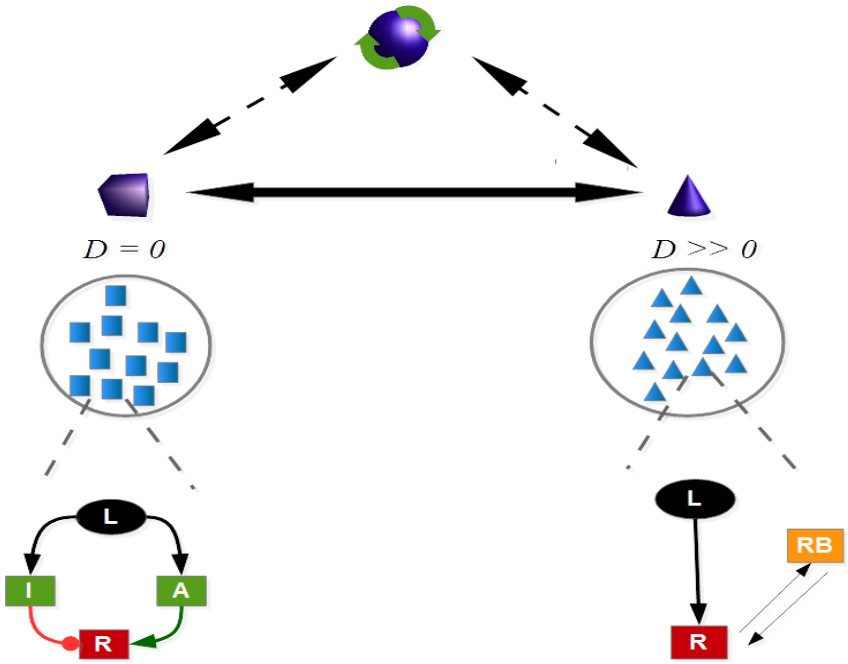


Fig. 3: Example in chemotaxis where a population must decide between two different kind of responses: one for negative feedback (left - squares) and incoherent feed-forward loop (right - triangles), depending on the interaction of the whole population with the environment (predator's population).

We argue that both responses can belong to a cell able to adapt its response to an external source. To this end, one of both responses must be selected depending on whether the whole system (the population as organism) is incomplete or not. We do that if the cell prefers an adaptive response, only if this response lies below a threshold value. Thus, the cells as an organism "decide" ("accommodation") which response is better depending on how the population of consumers (predators) behaves. In this way, we establish a direct interaction between the single organisms and the whole population.

We construct a toy model using the following steps:

- Assume that consumers (C, population of predators) are close to a chemical stimulus that is frequented by a population of bacteria that is predated (P). In our example the stimuli growths proportional to the time.
- The bacteria have a variable response: switch from adaptive to non-adaptive – response. The bacteria alone cannot "decide" which is the better response; this decision is made as an organism, but accounting the whole population and its environment in the scale *M*. The response will depend on the population of predators.
- If *C* (population of predators) is relatively low, then preferred response remains constant; otherwise, if the population of predators increase above a critical number, then the preferred response changes from a non-adaptive into an adaptive response, which is equivalent to $D = \Delta r / \Delta C > 0$
- This change in the response influences the velocity towards the stimuli: a non-adaptive response is related to high propagation velocity towards the stimuli. Otherwise, an adaptive response is related to a slow propagation velocity (see experiments about changes of velocities for aggregation of bacteria in chemotaxis)

This "trick" should affect the number of predators, and should influence the cycles of the population.

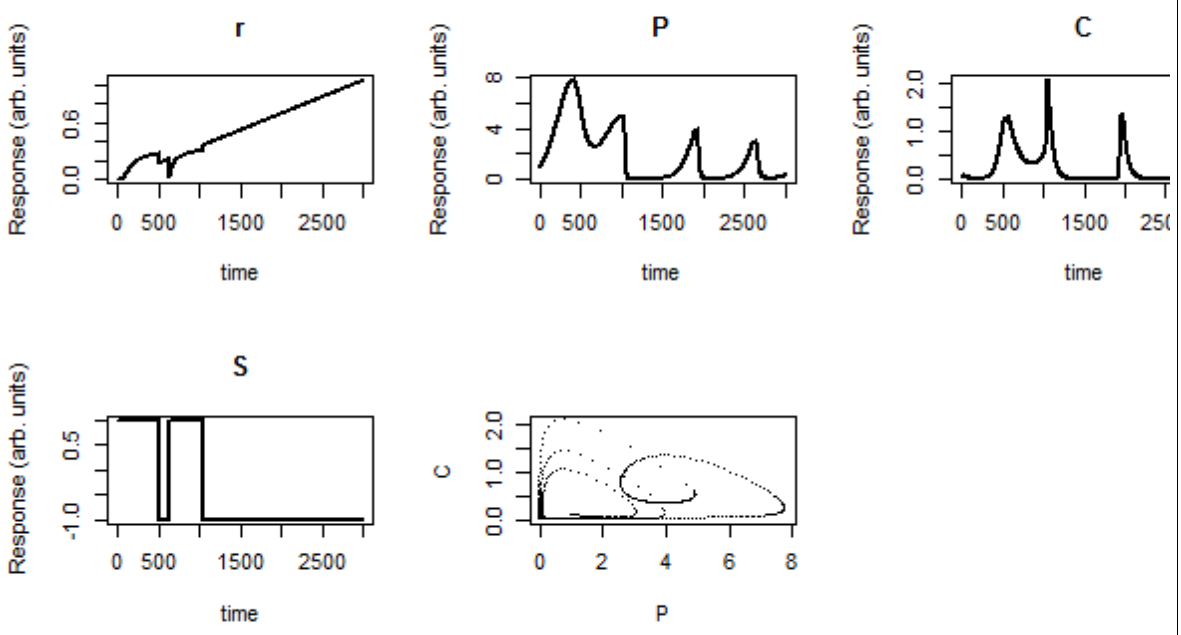


Fig. 5 In figure above, P are the predated population (in our example bacteria) and C are consumers. S detects which response has been selected: S = 1 is for a non-adaptive response; S = -1 for adaptive response.

In this example, there is apparently a co-evolution. However, observe that the underlying network is incomplete since it has two potential background models that mutually compete; the apparent co-evolution is the decision to adopt one or other response depending on the pressure over the whole population. In this process, there is a constant distortion, until the organism meets a "decision" and select only one kind of response.

Observe that the selected parameters generate a critical behavior, in which the cells alternatively select two of the responses. The change of response depending to the predator's population imply a high distortion (which is known in this model). The additional oscillation of this distortion implies self-organization in the population dynamics and the adaptation of the response.

Above a critical value of the stimuli the cell finally selects one response, implying that $D = 0$. This transition is visualized in the phase diagram in figure 5.

Discussion

The construction of theories requires completeness to make them predictive. However, we continuously experience a challenge to this completeness in different levels. For example, writing a text like this article is an example about how difficult is to retain completeness in the transmitted message and decide when to stop. The goal is to write a code that works like a mechanism in the minds of other people; but so many ideas and concepts compete, making difficult to find a complete sentence, or decide when to stop writing. In the extreme case the text derives into magical realism. This also applies to our daily life and business, as well as biology in writing end expressing the genetic code.

In nature, there is thus very often incompleteness and undecidability. Several mechanisms can run to infinity, as we have shown in our example for the vesicles (section 2). However, the interaction with the environment, as well as the selection of functionality induces a primitive cognition that helps to decide these processes, considering accommodation and assimilation (Bitbol and Luisi, 2004). Constant changes in the environment imply a change of the

initial completeness. And living organisms continuously try to maintain a decidability or relative completeness.

This sets a limit in our ability to identify models in systems biology: while a mechanism can be valid under certain circumstances, continuous assimilation and accommodation of organisms challenge the completeness of these mechanisms. This implies a distortion of interaction mechanisms. A measure of this distortion is thus helpful to decide when a model is predictive or can be extrapolated.

We use this concept to model several responses in chemotaxis, if the distortion is larger than zero and that different responses associated to different interaction networks are selected depending on the population of predators. This example allows us not only to model making use of this distortion, but also to exemplify this assimilation and accommodation depending on the evolution of the populations of bacteria and predators.

However, chemotaxis, is not the single field where these concepts can be applied. For instance, the evolution of Cyano bacteria and evolution of first organisms on the earth is an example about how the molecular interactions adapt to the environment, implying incompleteness and distortion [4] Cancer is also a potential candidate: "The oxygen-deprived cells (environment) suffer an excess of DNA methylation, which silences the expression of tumor-suppressing genes, thereby enabling aberrant cellular behavior and enhancing tumor growth. "[5] (Thienpont et al., 2016). This also is related to the way how cancer is treated: while several efforts focus on the identification of biological mechanisms for the targeted treatment of the disease, the practical application has shown that this strategy often not only does not work, but is in some cases harmful to the patient. This problem is not only rooted in the complexity of the cancer mechanisms, but also on the capability of the cancer cells to evolve and develop tolerance and mutate against treatments [6]

Also in physics, there are potential traces of incompleteness. For instance, a toy model for spin-ice can also illustrate this incompleteness and distortion, with a connectivity of microscopic states depend on whole energy landscape (Ochoa, 2014). It also implies that equations of life, for instance relating entropy with replication, are only valid when the energy gap of internal reservoirs respect the environment is zero (England, 2012). And we suspect that in other fields like social or economic systems similar mechanisms are observable, despite the fact of the inability of social systems to develop structures like biological organisms.

These facts speak against the possibility to define laws for complex systems. Perhaps only rules can be identified; but rules are not laws. This is true not only for biology, but also for social and economic sciences. Mathematically this has a profound implication: whereas in physical systems it is possible to recognize laws and fundamental models that in principle work in every part of the universe, for the rest of complex systems there are rules, rather than laws, that are often full of exceptions.

Mathematically this also implies that there is no methodology to produce good universal predictions. This is only valid when $D = 0$. Once we want to predict something we are confronted to the necessity to constantly collect information.

This also implies that when using networks to describe mechanisms certain mathematical laws must be considered more as a rule that can be subjected to exceptions. For example, the concept of scale-free distribution of nodes is perhaps a rule (Barabási, 2009), but not a law, which can be continuously challenged by the incompleteness of molecular networks (Khanin and Wit, 2006).

Concluding remarks

This work is an alternative to the conventional bottom-up or up-bottom approaches to comprehend living systems. In our opinion there is not a hierarchy of scales, but much more an interaction across different scales. Incompleteness is also the impossibility to know how an organism and its mechanisms has specific functions regarding evolutionary pressures. Certainty there are well defined functions, but organisms across scales fulfill so many functions, that it results difficult to make optimal definitions. This is also an example of incompleteness. As we have shown in our toy model, it results hopeless to distinguish one optimal function. Instead, it is more useful to consider different functions and try to solve one solution by accepting that the organisms decide which function will adopt depending on how consistent it is respect their environment.

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[4] http://ed.ted.com/lessons/how-a-single-celled-organism-almost-wiped-out-life-on-earth-anusuya-willis?utm_source=TED-Ed+Subscribers&utm_campaign=073216f33e-2013_09_219_19_2013&utm_medium=email&utm_term=0_1aaccced48-073216f33e-48502045

[5] http://www.genengnews.com/gen-news-highlights/cancers-grow-by-throwing-epigenetic-smother-parties/81253107/

[6] http://www.nature.com/nature/journal/v537/n7619_supp/full/537S63a.html

These ideas follow a fundamental question: can biology be explained using fundamental theories or even physics? Our answer is: some times. Sometimes is possible to define laws, but in general there are only rules. We also recognize that in Biology rules are non-invariant. This position is not a pessimistic statement, but is instead a stimulating chance, that is coupled to our current technological ability to increase measurements and use data and artificial intelligence to better understand and advance in the field of systems biology. This is relevant not only from the point of view of natural principles, but also in applications in medicine and biotechnology, and even in our capacity to adapt ourselves as society and humans to the nature.

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