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The Role of Self-Maintaining Resilient Reaction Networks in the Origin and Evolution of Life

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Abstract: We characterize living systems as self-maintaining, resilient “chemical organizations”, i.e. autopoietic networks of reactions that are able to resist a wide range of perturbations. Dissipative structures, such as flames or convection cells, are also self-maintaining, but much less resilient. We try to understand how life could have originated from such self-organized structures, and evolved further, by acquiring various mechanisms to increase resilience. General mechanisms include negative feedback, buffering of resources, and degeneracy (producing the same resources via different pathways). Specific mechanisms use catalysts, such as enzymes, to enable reactions that deal with specific perturbations. This activity can be regulated by “memory” molecules, such as DNA, which selectively produce catalysts when needed. We suggest that major evolutionary transitions take place when living cells of different types or species form a higher-order organization by dividing labor and thus minimizing interference between their reactions.

Keywords: resilience, chemical organization theory, autopoiesis, origin of life, reaction networks, cybernetics, self-organization, autocatalytic sets.

Introduction

The present paper is part of a special issue on evolutionary transformations in biological systems. The focus is on the processes that give rise to the emergence of complex organizations with qualitatively new characteristics. This includes what are known as “major transitions” (Maynard Smith and Szathmary, 1997; West et al., 2015), such as the origin of multicellular organisms, of social systems, and most importantly of life itself. What characterizes such transitions is that initially independent units, such as molecules, cells or individuals, become integrated into a larger, self-maintaining organization. This encompassing system behaves like a

distinct individual with its own goals. This emergent system both constrains and enables certain interactions between its components.

Understanding such a transition within the standard Darwinian theory of evolution is a challenge. Natural selection with its “survival of the fittest” logic seems to predispose individual units to selfishness, i.e. maximizing their own fitness, at the expense of the fitness of others that compete for the same resources (Dawkins, 2006). Even when it is beneficial for a group of units to cooperate, because together they can achieve results they cannot obtain on their own, the biggest benefits tend to accrue to the “free riders”, which profit from the products of the cooperation but without contributing resources themselves. Therefore, it seems as if natural selection prefers selfish exploiters to earnest cooperators, while cooperative organizations, such as those between the cells of a multicellular organism, always appear on the verge of being eroded from within by selfish renegades, such as cancer cells.

To tackle this difficulty, research on evolutionary transitions has been focusing on various mechanisms to overcome the free rider problem. These include kin selection, group selection, reciprocal altruism, as well as the emergence of collective control mechanisms, such as the immune system, that can suppress free riders. This focus on safeguarding the cooperation, however, has tended to obscure the processes that created that cooperation in the first place: how did these initially independent units manage to coordinate their activities in a complex organization, such as a living cell or an organism, that is beneficial to all?

The issue becomes clearer by noting that competition for resources is merely one side of the evolutionary coin. A largely overlooked evolutionary dynamic is selection for *synergy* (Corning, 2021, 2003). Synergy means that activities are complementary so that together they produce more resources than if they would be working on their own. This is what we find in mutualist symbiosis, where the products of one symbiotic organism benefit the other, and vice versa. In such a situation, natural selection will strengthen rather than endanger the cooperation between these two organisms, potentially making them merge into a single organism—a process known as *symbiogenesis* (Agafonov et al., 2021; Corning, 2021) that may explain the major transition from prokaryotes to eukaryotes. However, a priori it does not seem very likely to find two organisms whose needs and offers would be precisely complementary, in the sense that the one would produce what the other consumes. Moreover, this mechanism does not seem to explain the emergence of complex systems consisting of several independent units. This is important in particular when investigating the origin of life, given that the simplest possible living system clearly requires the coordinated activity of a variety of molecules and processes.

Yet, as we will argue in the remainder of this paper, when the different units that interact become more numerous and diverse, it actually becomes easier to discover an overall synergetic arrangement, in which all units benefit from their couplings with other units (Heylighen, 2017). While this may seem counterintuitive if you reason in terms of independent, competing “objects”, passively subjected to the

external “force” of natural selection, the emergence of synergetic arrangements becomes much clearer when seeing these units as processes that feed each other. Therefore, we will start from an ontology based on processes, which we have recently called “relational agency” (Heylighen, 2022a). The idea is that the components that make up a living system should be conceived not as independent objects, but as interconnected processes and agencies. These can be formally modeled by means of *reaction networks* (Veloz and Razeto-Barry, 2017), and in particular by the recent approach of *Chemical Organization Theory* (COT) (Dittrich and Fenizio, 2007; Heylighen et al., 2015). The present paper intends to show how the perspective of relational agency with its formalism of reaction networks can help us to elucidate the origin of life and its evolution, with a focus on the qualitative transformations that make living systems increasingly autonomous, adaptive, and resilient.

What is life?

While there is no consensus on a definition of life, there are a number of characteristics that most thinkers would agree upon. One is that living organisms are far-from-equilibrium systems. That means that they are thermodynamically open, requiring a continuous input of low entropy resources, which they use to maintain their metabolism, while dissipating entropy in the form of waste materials and heat. In that sense, they are *dissipative structures*, i.e. (self-)organized flows of matter and energy (Nicolis and Prigogine, 1977). Next to living organisms, dissipative structures include flames, ocean currents, convection cells, hurricanes and rivers.

What all dissipative structures have in common is that their structure is constituted out of processes, not matter. The matter merely flows in and out of the dynamical structure. These processes have some degree of stability, so that the structure maintains or “survives”, even while all matter in it is replaced. This can be exemplified by the constantly changing composition of a flame or a river: even as the water molecules flowing through the river change, the river itself remains the same. Still, a flame or a river can only persist for as long as there is a constant input of resources, such as fuel for a flame, or rainwater for a river. They vanish or “die” as soon as that resource inflow stops. Living systems have a much greater autonomy: they can generally survive interruptions in their inflow by relying on reserves, switching to different resources if a particular resource is no longer available, or even actively seeking new resources.

This property can be called *self-maintenance*: a living system will act so as to ensure that the structure of processes that constitute it is maintained, even when external conditions change (Mossio and Bich, 2017). The related notion of *autopoiesis* (self-production) has therefore been proposed as a defining characteristic of life by Maturana and Varela (Maturana and Varela, 1980; Razeto-Barry, 2012; Varela, 1979; Varela et al., 1974). Autopoiesis means that the system’s processes are organized in such a way that all the components and processes that make up the

system are continually reconstituted. That implies that whatever is lost or dissipated during some process must be rebuilt by some other process. This also characterizes a living system's *metabolism*: the whole of the reactions inside the organism that break down certain molecules while building up others, so as to ensure a sufficient level of energy and materials to sustain the organism's processes.

Thus, living systems have at their base a *circular* organization: whatever is consumed by some process is produced again by some other process, so that the metabolic cycle can continue without interruption. Such circularity, re-entry or feedback moreover provides the system with a form of *autonomy*: since the inputs of the process are largely constituted by its own outputs, it is to an important degree independent from external conditions for its functioning (Heylighen, 2022b).

Nevertheless, self-maintenance or circularity of process does not yet clearly distinguish a living system from a dissipative structure. For example, as we will discuss further, a convection cell consists of a cyclical flow, where liquid is heated at the bottom of a container, moves up to the surface where it cools, after which it sinks back to the bottom, where it is heated again, ready to start a new heat-move-cool cycle. Rivers are actually part of the hydrological cycle, in which the water carried by the river to the sea evaporates, forming clouds whose rain again flows into the river, thus sustaining it (Mossio and Bich, 2017).

The theory of autopoiesis tries to avoid this problem by demanding that the self-producing system should produce its own structural components, and in particular its physical boundary—such as the membrane of a living cell. Indeed, a flame or a convection cell does not have a stable boundary. Still, it could be argued that a river erodes the channel in which the water flows, while depositing mud on the sides, thus producing its own boundary. Matteo Mossio and colleagues (Montévil and Mossio, 2015; Mossio and Bich, 2017; Mossio and Moreno, 2010) have generalized this requirement by demanding that living systems should produce their own *constraints*, where constraints are stable structures that canalize or guide the processes taking place in the system. Examples of constraints are boundaries, morphological structures, such as blood vessels or skeletons, and enzymes that catalyze particular reactions. For example, most biochemical reactions in a cell are regulated by enzymes, whose production is in turn regulated by DNA, both of which are fundamental constraints of the organism, in turn regulated by other constraints. But again, the river eroding the channel in which it flows can be said to create its own constraint, which canalizes the river and thus its own further development.

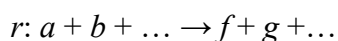
The point we are trying to make is that there does not need to be a strict division between living and non-living systems. If we wish to understand the origin of life, we should be able to conceive *intermediate cases* of self-maintaining systems that are more organized or constrained than dissipative structures, yet simpler than the simplest organisms we know. Such a conception of quasi-living systems is also essential if we wish to investigate the possibilities for life-like organizations outside of DNA-based organisms. Examples include super-organisms (Heylighen, 2007), such as ant colonies, social organizations conceived as “living systems” (Miller,

1995), Earth conceived as a “Gaian” organism (Rubin et al., 2021), life in outer space or on other planets (Centler et al., 2003), and artificial life based in software, hardware or wetware. Instead of assuming a sharp distinction between life and non-life, the way autopoiesis theory does, we therefore propose to study a *continuum of self-maintenance effectiveness*. A system is more effective in maintaining its organization if it can survive in a wider range of conditions. That means that when circumstances arise that push the system away from its standard regime of self-maintenance, it will be able to “bounce back” and recover its autopoiesis. This ability to survive shocks or disturbances is called *resilience* (Beigi, 2019; Folke et al., 2004; Holling, 1973).

Resilience makes a system less dependent on external conditions for its self-maintenance, and therefore more autonomous (and thus life-like). It also makes the system more likely to survive in the long term. For example, the flame of a Bunsen burner will not survive a brief interruption in its supply of fuel, while a living organism will generally survive a not overly long interruption in its supply of food. Therefore, evolution through variation and selection of the fittest can be expected to produce increasingly resilient systems. That means that if we wish to understand the origin of life and its further evolutionary transformations, we will need to get a better grasp of the features that make self-maintaining cycles of processes more resilient. To do that, we will now introduce the formalism of reaction networks and chemical organization theory.

Reaction networks

A reaction network is a type of mathematical model inspired by chemical reactions, but where the reactions can represent a variety of physical, chemical, computational, social and/or biological processes (Veloz and Razeto-Barry, 2017). A reaction here represents an elementary process in which some combination of initial conditions (input) is transformed into some different combination of subsequent conditions (output). Such a reaction r is conventionally written as:



More precisely, the model consists of a set of “molecules” or “(molecular) species”: $M = \{a, b, c, d, \dots\}$ and a set of reactions $R = \{r_1, r_2, r_3, \dots\}$. A reaction maps a (multi)set of species onto another (multi)set of species:

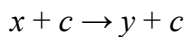
$$r_i \in R: \text{Input}(r_i) \rightarrow \text{Output}(r_i),$$

Here $\text{Input}(r_i)$ and $\text{Output}(r_i)$ are both subsets of M . Note that the network defined by these reactions interconnecting molecules is not a traditional network, i.e. a directed graph (one-to-one connections), but a directed *hypergraph* (many-to-many

connections) (Flamm et al., 2015). That allows the formalism to provide a more realistic description of the complex interactions necessary to understand the origin of life—in contrast with standard network models (e.g. Jain and Krishna, 2001). Using the conventional notation for chemical or physical reactions, we write the elements of the input and output sets as a list of items separated by the “+” operator:

$$r_i: a + b + \dots \rightarrow f + g + \dots, \text{ with } \{a, b, \dots\} = \text{Input}(r_i) \text{ and } \{f, g, \dots\} = \text{Output}(r_i).$$

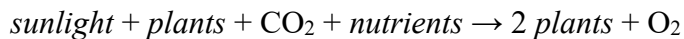
The molecules of the input set are called the “reactants” of the reaction; the molecules of the output set are its “products”. The interpretation is that a reaction represents an elementary process during which the reactants are converted into the products. In other words, the reaction “consumes” the molecules in its input, and “produces” the molecules in its output. Note that a molecule c that is present in both input and output is neither consumed nor produced. It plays the role of what is called a *catalyst* in chemistry: it is necessary for the reaction to take place, but remains invariant during the process:



Such a catalyst can be interpreted as the agency that performs the reaction, given that its presence determines whether or not the reaction takes place (Heylighen, 2022a). Note also that input or output sets can be empty. This can be interpreted as inputs originating or outputs delivered *outside* of the system in consideration. For example, when modeling the growth of plants, one of the reactions is likely to be:



This simply means that the source of sunlight (the Sun) is outside the system being modeled, and therefore we can interpret it as an external input, originating in the environment. Molecules can represent any resources, components or conditions that react with each other in order to produce further molecules. For example, another reaction modeling the growth of plants could be:



Chemical Organization Theory is a simple and elegant model that uses reaction networks to formally express a notion of self-maintenance or primitive autopoiesis (Dittrich and Fenizio, 2007; Heylighen et al., 2015). Consider a subset O of the set of molecules M , together with the subset $R(O)$ of all those reactions that can take place between the molecules of this subset O :

$$r_i \in R(O) \text{ if and only if } r_i \in R \text{ and } \text{Input}(r_i) \subseteq O.$$

$\{O, R(O)\}$ is defined to be a *chemical organization* if it is closed and self-maintaining. *Closed* means that all molecules produced by the reactions in $R(O)$ also belong to O : no new molecules are added to the set by the reactions. *Self-maintaining* means that all molecules consumed by one of the reactions in $R(O)$ are produced again in sufficient amount by some other reaction in $R(O)$: no molecules are removed from the set by the reactions. The two conditions of closure and self-maintenance together mean that the organization $\{O, R(O)\}$ is invariant: everything consumed is produced again. Thus, an active chemical organization provides a simple model of metabolism or autopoiesis (not including the requirement of boundary production).

Fig. 1 depicts a simple example of an organization, with the following components:

Molecules: $O = \{a, b, c, d, e, f, g\}$

Reactions $R(O)$:

External input: $\rightarrow a$

$r_1: g \rightarrow c + b$

$r_2: c \rightarrow f + g + e$

$r_3: d + f \rightarrow b + c$

$r_4: a + b \rightarrow d$

External output: $e \rightarrow$

It is clear that this reaction network is closed, since the output side of the reactions only contains elements of the initial set O . Moreover, it is self-maintaining, because for every element of O that is consumed by one of the reactions, there is another reaction that produces it. For example, g is consumed by r_1 , but produced by r_2 . However, r_2 can only run if c is available, which requires r_3 to run, which in turn requires the availability of d and f . f is already produced from c , which we assumed to be available, while d requires a and b according to r_4 , a is an external input, so it does not need anything further, while b is produced from g , which we also assumed from the start. Thus, there is an overall cycle producing g from g via several branching, intermediate pathways of reactions involving other molecules.

More generally, note that there exists a simple, deterministic algorithm to determine whether a given reaction network is a chemical organization (Dittrich and Fenizio, 2007). Note also that a chemical organization is similar to another kind of self-sustaining reaction network formalism, known as an *autocatalytic set*, which has been developed as a model for the origin of life (Hordijk et al., 2010). The difference is that the autocatalytic model requires that *every* reaction in the network should be catalyzed by some molecule produced by other reactions in the network. This restriction does not hold for chemical organizations, where reactions may or may not be catalyzed. That makes a chemical organization more general than a closed autocatalytic set (Hordijk et al., 2018), and therefore more flexible in modelling self-maintaining systems in between life and non-life.

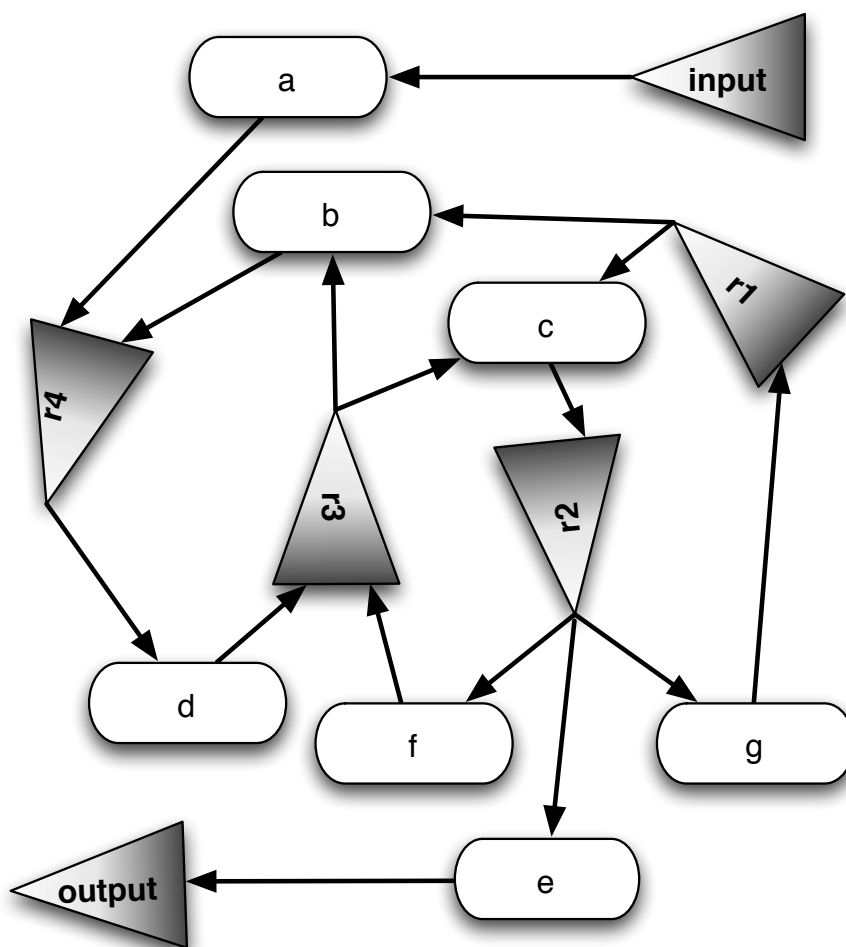


Figure 1: an example of a chemical organization, with rounded rectangles depicting the molecules $\{a, b, \dots\}$ being consumed and produced by the reactions $\{r_1, r_2, \dots\}$, which are depicted by triangles. Note that all molecules consumed by some reaction are produced again by some other reaction—a property called self-maintenance.

Self-organization of reaction networks

A reaction network defines a dynamical system (Peter and Dittrich, 2011). The system's states are defined by the amounts or concentrations of the different molecules. Its dynamics is determined by the reactions that change those concentrations by consuming certain molecules while producing others.

Self-organization is commonly defined as the emergence of a global order out of local interactions. Self-organization can be described in a dynamical system as the reaching of an attractor in the system's state space (Heylighen, 2001). Once it has settled in the attractor, the system is by definition constrained: it can no longer reach any states outside of the attractor. This constraint imposes a certain order on the system: it limits the freedom of the components or variables of the system to vary independently.

This understanding of self-organization dates back to the cyberneticist Ashby (Ashby, 1962) (although he spoke about “equilibrium states” rather than using the more modern terminology of “attractor states”). Ashby further noted that if you would conceptually divide the self-organized system into subsystems, then these subsystems could be seen as mutually adapted. Indeed, lack of adaptation would mean that the maladapted subsystems would not be able to survive within the larger system. Their elimination would fundamentally change the system, in contradiction with our assumption that its dynamics has stabilized in an attractor regime.

We can elaborate that insight for reaction networks in the following way. As proven by (Peter and Dittrich, 2011), an attractor with active reactions and a fixed set of molecular species is necessarily an organization, i.e. a subnetwork that is closed and self-maintaining. That is logical, because networks that are not closed or not self-maintaining will by definition gain or lose some of their molecular species, thus turning into different configurations—in contradiction with the assumption that they belong to a stable attractor regime with a fixed set of species. In a reaction network, the most elementary subsystems correspond to reactions, which process an input of molecules into an output of different molecules. Subsystems being mutually adapted then means that these processes “feed” each other with the molecules they need to keep on going. They form as it were an ecosystem of mutually dependent systems (Heylighen, 2022a). Thus, they exhibit a global order, organization or synergy: thanks to their local couplings, the reactions working together produce all the resources necessary to sustain their collective activity

To visualize such an arrangement, we could imagine these processes as arrows, pointing from input to output (see Fig. 1). Mutual adaptation can then be conceived as the different arrows aligning or coupling in such a way that the outputs of some arrows become the inputs of other arrows. For the whole to become self-maintaining, these different couplings must eventually close in on themselves, forming a cyclical flow. However, because reactions typically have several inputs and outputs, the resulting circular organization is in general difficult to represent graphically.

A simpler visual example of such a self-maintaining system is a single convection cell in a liquid heated from below (Bodenschatz et al., 2000; Heylighen, 2021). As depicted in Fig. 2, hot liquid here rises to the surface, flows sideways (e.g. to the left) while cooling down at the surface, then sinks down to the hot bottom of the container, and finally flows sideways in the opposite direction while heating up, after which it rejoins the initial upwards flow of hot liquid. This forms a simple circular process with one external input (heat entering at the bottom) and one external output (heat dissipating at the surface):

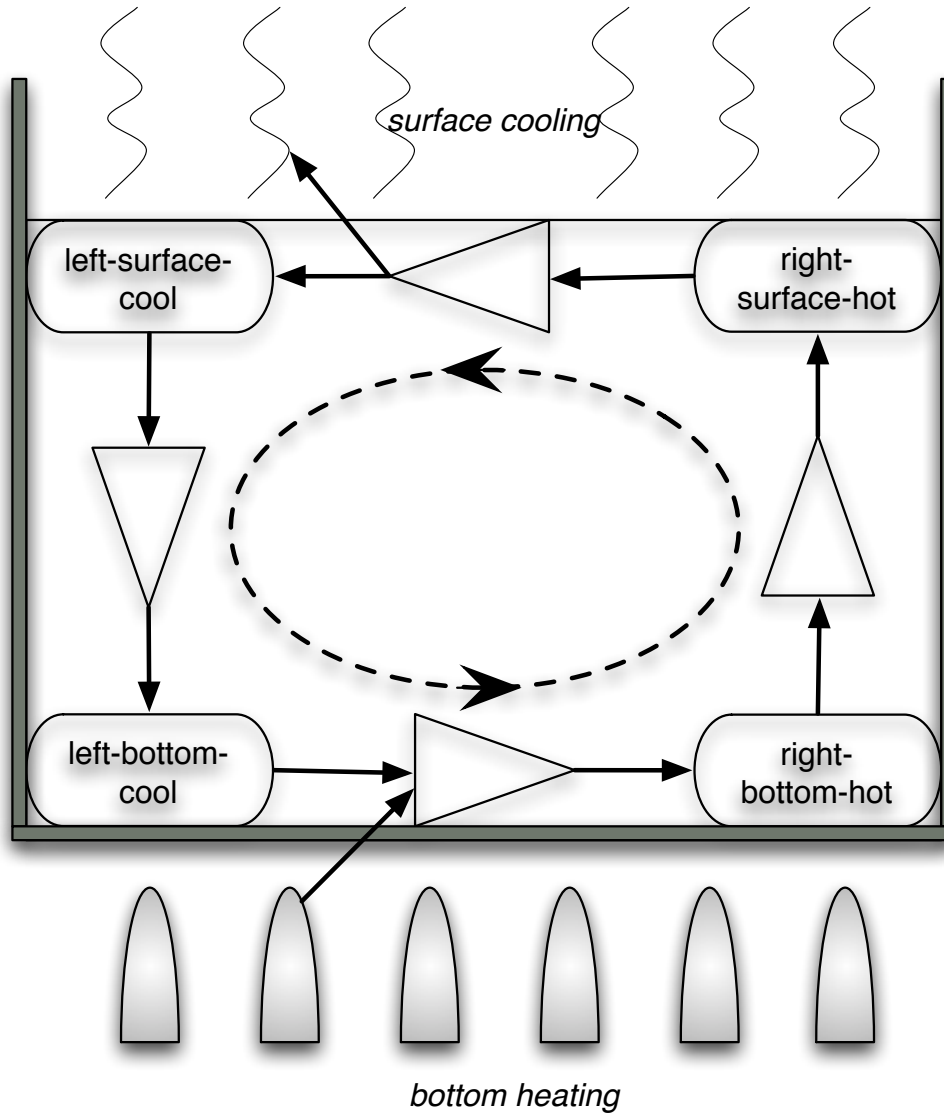


Figure 2: depiction of a convection cell using the notation for a chemical organization (Fig. 1). The liquid in the container is heated from below while cooling at its surface. This engenders a circular—here counterclockwise—flow in which hot liquid at the bottom-right moves up to the surface and then to the left while cooling down, then sinking to the bottom where it now heats up while returning to the bottom-right.

right-bottom-hot → right-surface-hot
 right-surface-hot → left-surface-cool + surface-heat
 left-surface-cool → left-bottom-cool
 left-bottom-cool + bottom-heat → right-bottom-hot
 → surface-heat
 bottom-heat →

Note that this convection cell—a very simple dissipative structure—is the outcome of a process of self-organization with two attractors, one in which the liquid flows in counterclockwise direction (like in the example above), another one in which the direction is clockwise:

left-bottom-hot → left-surface-hot
left-surface-hot → right-surface-cool + surface-heat
right-surface-cool → right-bottom-cool
right-bottom-cool + bottom-heat → left-bottom-hot

Other conceivable configurations are not self-maintaining, because the corresponding flows are not aligned or mutually adapted, i.e. in conflict. For example, consider the following combination of elementary flow processes:

left-bottom-hot → left-surface-hot
left-bottom-cool + bottom-heat → right-bottom-hot
right-surface-hot → left-surface-cool + surface-heat
right-surface-cool → right-bottom-cool

This configuration cannot maintain itself because the input side of some reactions does not match the output side of any other reaction: liquid only flows away from right-surface and left-bottom, but no liquid flows into these spots. Thus, there is insufficient input to keep these reactions going. But if these reactions stop, then the remaining two reactions also no longer get any input, so they must stop as well.

More generally, the self-organization of a reaction network so as to produce a chemical organization is a straightforward process that can be modeled with a simple algorithm (Dittrich and Fenizio, 2007). The process starts with a particular selection of molecular species present at the beginning. These molecules start to react with each other according to the given reactions. These reactions produce additional species. These may react further with the other species available, potentially generating even more additional species. However, at some point this process must come to a halt, because no further species can be generated by the reactions. The resulting reaction network is now by definition closed.

Still, the reactions continue consuming and producing the species that are present. Some of these are consumed but not produced, or consumed more than they can be produced. That means that they are removed from the system eventually. All the remaining species are now by definition being produced at least as much as they are being consumed. That means that the system has become self-maintaining in addition to being closed. In other words, it has become a chemical organization. Such an organization can be understood as an elementary model of a dissipative structure, and potentially a self-producing, living organism.

Surviving perturbations

This simple model of the emergence of self-maintenance might be sufficient in a static environment, i.e. an environment where the external inputs and outputs of molecular species are constant. For example, the flame of a Bunsen burner is a self-maintaining dissipative structure, dependent on a steady input of fuel and oxygen and output (removal) of carbon dioxide and water vapor, while internally producing the heat that is needed to maintain the burning reaction. A convection cell is self-maintaining under the condition of a stable temperature difference between surface and bottom of the liquid, i.e. a steady input of heat at the bottom, and removal of heat at the surface.

In a more typical environment, however, inflows and conditions vary, and different species of molecules may be present or absent at different moments. Such fluctuations in the availability of resources act as perturbations for the self-maintaining system, because they may interrupt reactions crucial for the system's autopoiesis or "metabolism". We can categorize such perturbations on the basis of how deeply they affect the self-maintaining dynamics (Veloz et al., 2022):

- 1) *state perturbations* are changes in the concentration of the molecular species present;
- 2) *process perturbations* are changes in the rate of the reactions taking place (e.g. increasing or decreasing inflows and outflows)
- 3) *structural perturbations* are additions or removals of molecular species or reactions, thus changing the qualitative composition of the system and the reactions that can take place.

For the organization to survive in its present form, it must be able to neutralize the effect of these perturbations so that it can return to its self-maintaining regime after a perturbation made it deviate from that regime. Such ability to "bounce back" from shocks is known as *resilience* (Beigi, 2019; Holling, 1973). In cybernetic terms (Heylighen and Joslyn, 2003), the system is "in control" if it can counteract or compensate any perturbation that makes it deviate from its preferred configuration (goal). Organizations unable to cope with perturbations are eliminated by natural selection. Therefore, we may assume that evolution by variation and selection will produce increasingly resilient organizations, whose implicit goal is self-maintenance (Mossio and Bich, 2017).

Thus, living systems can be seen as acting towards their goal of continuing to be alive. That makes them intrinsically purposive or *goal-directed* (Heylighen, 2022b; Trestman, 2012): instead of passively undergoing the effects of external forces—the way a stone or a particle would—they actively counteract these pulls and pushes so as to retain or regain their preferred state of self-maintenance. Thus, a living system exhibits *agency* (Heylighen, 2022a; Walsh, 2018). It also has implicit preferences or *values*, distinguishing between "good" conditions or resources (which contribute to its

self-maintenance, such as food) and “bad” ones (which perturb or endanger its self-maintenance, such as toxins). This distinction is shown by the system’s reaction to external conditions: exploiting or consuming good resources, while evading or neutralizing bad ones. However, note that the value of a resource is not objectively given, but dependent on the system’s ability to process it: the neutralization of a potentially lethal toxin may actually convert it into food...

In the dynamic systems framework, goal-directedness or resilience can be modeled in terms of the basin of attraction that surrounds the attractor that stands for the self-maintaining configuration (Heylighen, 2022b). That is because perturbations that push the system out of its attractor are automatically compensated by the dynamics, at least as long as the system remains within the basin. Indeed, the basin of an attractor by definition consists of all those states whose further (unperturbed) dynamical evolution leads (back) into the attractor.

The theory of resilience in ecological systems (Holling, 1973; Meyer, 2016; Walker et al., 2004) distinguishes the following relevant features of the basin (Fig. 3):

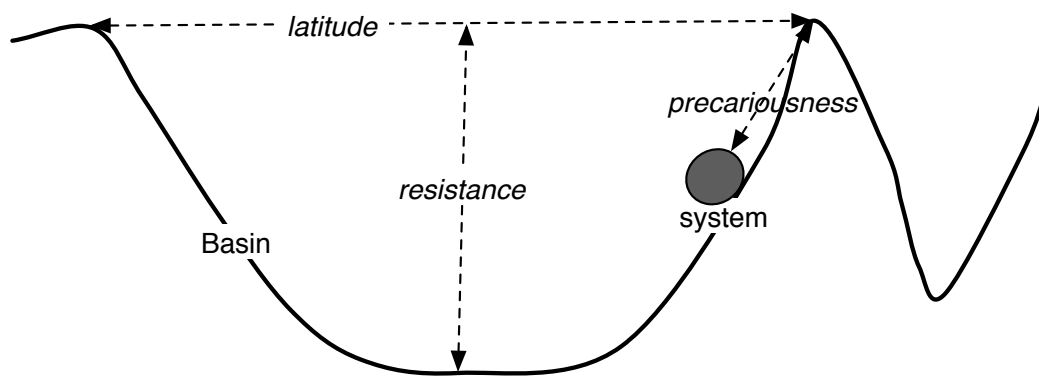


Figure 3: the basin of an attractor exhibiting three aspects of resilience: latitude (width of the basin), resistance (depth of the basin) and precariousness (nearness of the system’s state to the border of the basin)

- *Latitude* corresponds to the size or “width” of the basin. The larger the basin, the more “room” there is for a variety of perturbations to push the system away from the attractor without making it leave the basin—and thus without endangering survival.
- *Resistance* corresponds to the “depth” of the basin. This can be seen as the strength or intensity needed by a perturbation to push the system out of the basin.
- *Precariousness* measures how near the system (or the attractor) is to the border of the basin. That basin may be very large, but if the system is poised just on its border, then a single perturbation may be sufficient to push it out, and thus destroy its self-maintaining regime.

This means that the ideally resilient organization would be situated in the middle of a large and deep basin, so that only a sustained sequence of intense and diverse perturbations could permanently dislodge it from its position. However, we have no reason to assume that a typical organization would have these desirable features. Still, we know that living organisms, in contrast to dissipative structures such as flames or convection cells, are remarkably resilient, and able to adapt to a wide range of conditions. This suggests the following fundamental question for investigating the origin and evolution of life: how can a self-maintaining organization become more resilient?

The general principle of such evolution towards resilience seems clear: variation and selection. We have argued that self-maintaining systems self-organize naturally and easily in a sufficiently rich network of reactions. However, these organizations are likely to undergo perturbations that disrupt their self-maintaining regime. Yet, such a disruption merely brings them to a different state, outside of the initial basin of attraction. Starting from this new initial state they can again self-organize, eventually reaching a new attractor. We may assume that the different attractors of a reaction network have different types of basins, some of which will offer a larger resilience than others. Thus, a perturbation that is not neutralized will merely produce a new variation of a self-maintaining system, which can be either more or less resilient than the previous one. The more resilient, the more likely it is to survive the next perturbations. After many such variations, natural selection is likely to settle on the most resilient organizations encountered, while the less resilient ones are eliminated. Thus, the evolution of an organization can be seen as a continuation of its self-organization, with resilience as the major selection criterion. The question now is which features of a reaction network can contribute to this resilience.

Controlling different types of perturbations

State perturbations are changes in the quantities of certain molecules. Such fluctuations up or down can be regulated through negative feedback. Self-maintaining organizations seem to be characterized by an implicit negative feedback dependent on the rate of the reactions. By definition of self-maintenance, for every reaction that consumes a molecule, there must be one or more reactions that produce that same molecule, and this with an overall rate at least as high as the rate of its consumption. When the concentration of that molecule diminishes, normally the reaction consuming it will slow down. According to the mass-action kinetics typical of chemical reactions, the rate decreases proportionally to the concentration (Dittrich and Fenizio, 2007; Peter et al., 2011). More generally, we can assume that a scarcer resource is more difficult to react with and thus to consume. For example, food, such as fruit, that becomes more difficult to find will not be consumed as quickly. However, the reaction producing that same molecule will not be directly affected by that reduced concentration, because it requires different inputs. For example, the process producing

food, such as growth of fruit on trees, is not directly affected by the amount of food being eaten. The combination of reduced consumption with stable production means that the concentration of the molecule will increase, thus compensating to some degree for the initial decrease. A similar reasoning can be made for increased concentration leading to increased consumption, but stable production.

Note that this is a very general reasoning that may not be applicable in all cases, because the rate of the production reaction may depend on molecules that themselves depend on the molecule that is reduced in concentration. Clarifying the precise conditions for this mechanism to occur will require a deeper computational or mathematical analysis of self-maintaining reaction networks (Busseniers et al., 2021). Yet, at first sight, it does not seem difficult for chemical organizations to develop negative feedbacks that can deal with state perturbations.

Process perturbations are changes in the rate of reactions. Some of these reactions are controlled by the organization, in the sense that the reactants that determine the reaction's rate are all produced within the organization. Assuming that the concentrations of these reactants are subjected to the negative feedback proposed above, we may infer that the rate of these internal reactions will be relatively stable. Moreover, there seems to be a similar negative feedback between a reaction and its reactants: if the reaction would speed up for some reason independent of molecule concentrations (e.g. higher temperature), it would consume its reactants more quickly, thus reducing their concentration. But a reduced availability of reactants, as we argued, would slow down the reaction. Vice versa, a slowdown of the reaction would increase the availability of its reactants, and thus accelerate the same reaction. Thus, it seems easy for the organization to regulate the rate of its internal reactions.

External reactions, which bring resources into the system or export waste products, on the other hand, can vary independently. An example is the rate with which gas is injected into the flame of a Bunsen burner. A reduction of that rate will slow down the production of all internal molecules that are produced from these external resources. For example, a reduced gas supply will result in a smaller, cooler flame that consumes less oxygen. In an organism, reduced supply of food, water or other resources will slow down metabolism. However, a too strong reduction may disrupt self-maintenance, like when a flame becomes too cool to sustain itself, or a person dies of starvation or lack of oxygen. We can distinguish two broad strategies to combat such perturbations: one *quantitative*: increasing production of certain internal resources in order to compensate for the scarcity (e.g. recovering glucose from stored glycogen when glucose is scarce), and one *qualitative*: switching to a different external resource (e.g. consuming a different type of food).

That brings us to the third, and most drastic, challenge for an organization: a structural perturbation, which changes the species of molecules available in the network, and therefore also the reactions triggered by these molecules. (It may also change these reactions directly, but this also implies that certain molecules are added by the new reactions, or removed because they are no longer produced). We can distinguish two common types of structural perturbations:

- a) removal of molecules that play a role in maintaining the metabolic cycle (“resources”, such as food);
- b) addition of molecules that interfere with the metabolic cycle (“toxins”).

A reaction or molecule can be said to *interfere* with an organization if it reacts with one of the organization’s molecules, so that this molecule is consumed by the reaction, reducing its availability for reactions that support self-maintenance. For example, carbon monoxide, CO, binds in the body to hemoglobin. The result is that this hemoglobin molecule can no longer fulfill its function of binding to and thus transporting the critical molecule of oxygen, O₂. Because of that, CO acts as a toxic gas, which has killed many people.

Note that, more broadly, two distinct organizations active in the same volume can interfere with each other, in the sense that molecules of the one may react with molecules of the other, so that these molecules are consumed and neither organization can keep up its self-maintaining cycle. This problem may be avoided by distributing the organizations across space so that there is a limited diffusion of molecules from the one to the other (Peter et al., 2021)

In practice, both removal of food and addition of interfering toxins incapacitate certain reactions necessary for autopoiesis by reducing the inputs they need. To tackle this problem, the organization will need to evolve mechanisms that ensure a steady supply of these inputs, even during perturbations.

Note that a structural perturbation changes the variables that define the state space, and therefore the qualitative dynamics of the system, enabling or disabling certain reactions. In principle, this would require the whole system to undergo a new process of self-organization, in order to settle into a qualitatively different attractor, characterized by a different network of self-maintaining cycles. This is as if a Bunsen burner would suddenly be supplied with a different type of gas, e.g. switching from methane to hydrogen. However, in practice, this does not necessarily interrupt the autopoietic process, provided that most of the other reactions contributing to self-maintenance continue to run. Which or how many reactions must continue to run to consider this as uninterrupted autopoiesis remains an open theoretical issue...

General Resilience strategies

We noted that the main danger threatening an organization is a perturbation that reduces the availability of molecules critical for self-maintenance. A system can evolve different strategies to control this problem. The simplest control mechanism corresponds to what is known as *buffering* (Heylighen, 2014; Heylighen and Joslyn, 2003): accumulating sufficiently large reserves of critical molecules, so that temporary interruptions in their supply can be weathered.

Some molecules are intrinsically abundant, such as the oxygen in the air that animals breathe. Therefore, there will not be much selective pressure for the system to

evolve mechanisms to cope with potential deficiencies—apart from simply breathing in more deeply when internal oxygen levels run low. Other molecules, such as food, can be abundant at certain moments, but not at others, however. Here a good strategy is to convert these molecules into a form that can be stored for the long term. For example, the calories extracted from food in the form of glucose can be stored in the body as glycogen and as fat. The output of the conversion-to-storage reaction must be a molecule that does not participate in common reactions (which otherwise would consume it), but which can be converted back into a reactive form (e.g. glucose) when needed. This may be achieved by a system of reactions that preferentially consume the reactive form, but, lacking this, start converting the non-reactive form to a form that can be consumed for maintenance.

A related storage mechanism operates in Terrence Deacon’s *autogen* model of the origin of life (Deacon, 2011; Deacon et al., 2014; Deacon and Sherman, 2007). Deacon imagines an autocatalytic set of molecules that multiply themselves by consuming abundantly available food molecules. As we noted, an autocatalytic set is a model of self-maintaining reactions that is more restricted than a general chemical organization (Hordijk et al., 2018). Moreover, its default dynamics seems to be one of positive, rather than negative, feedback. Autocatalysis means that a catalytic molecule facilitates its own production. Therefore, increasing concentrations of catalytic molecules lead to increasing rates of the production reactions, which further increase the concentrations of the catalysts. Such an explosive growth must sooner or later come to a halt when the food runs out. This makes an autocatalytic cycle intrinsically less stable than a typical chemical organization—where the feedback is negative by default, because non-catalytic molecules tend to be consumed (rather than produced) more quickly when their concentration increases.

To counter that problem, Deacon imagines a mechanism that converts the autocatalytic molecules to a non-reactive form that can be kept in storage for as long as food is lacking. This happens by the production of “capsid” molecules that stick together. These gradually encapsulate the other molecules in some kind of a rigid cell wall, so that they no longer can react with outside molecules, while being kept closely together. The resulting inert capsule can be seen as a *dormant* form of the autocatalytic network—the equivalent of a dry “spore” or “seed”, ready to break open and start growing when food becomes available again. The only thing needed for that is a reaction between food and capsid molecules that makes the latter lose their grip, so that internal molecules can again start reacting with external food molecules. The *autogen* scenario proposes a simple and elegant mechanism for making autocatalytic networks more resilient. Such encapsulation process may well have played a role in the emergence of the first living cells. However, to understand the origin and evolution of life-like organizations more generally, we need to investigate a wider range of resilience-building mechanisms.

Another strategy to ensure abundant supplies is called *overproduction* in Chemical Organization Theory (Dittrich and Fenizio, 2007; Veloz et al., 2011). This means that under normal conditions of self-maintenance certain molecules are

produced more than they are consumed. Thus, they provide a buffer in case consumption would abnormally increase (e.g. by interference with toxins). The larger the buffer, the larger the *resistance* of the organization to perturbations, i.e. the larger or more intense the perturbation must be in order to push the system out of its basin (see Fig. 2). Note that autocatalysis is a form of overproduction, since the catalysts increase their own production. However, overproduction in an organization does not in general imply a positive feedback, and therefore this strategy does not suffer from the instability noted by Deacon. Overproduction not only helps the system to build up reserves, it allows the system to grow. *Growth* can be seen as another very general resilience strategy: the larger the system, the less likely it is to be destroyed by a perturbation of a limited size.

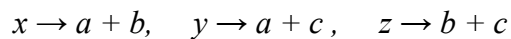
Growth moreover allows *multiplication*, like when a large cell subdivides into two smaller cells. This requires an additional mechanism of boundary formation, similar to the encapsulation in the autogen scenario, or the production of a cell membrane by the production of bilipid molecules that tend to stick together so as to form a two-dimensional, closed sheet. Such autopoietic production and reproduction of a cell-like vesicle is a rather simple process that has already been demonstrated in the laboratory (Luisi, 2003; Walde et al., 1994). Therefore, we will not investigate it further here.

Another reason for not discussing such boundary formation here is that the reaction network formalism a priori does not include topological separations, assuming that all molecules react with each other within the same “reaction vessel”. Still, the formalism allows modeling the distribution of molecules over separate cells by labeling molecules with the cell in which they are supposed to be located (Heylighen et al., 2015; Peter et al., 2011), while assuming that only molecules belonging to the same cell can react with each other. Interactions between cells can then be modeled as reactions of diffusion or exchange of certain molecules between neighboring cells. This simple assumption suggests that subdividing organizations into separate cells increases resilience, because perturbations, such as toxins, that disrupt the metabolism in one cell cannot directly affect other cells. That explains why multiplication (i.e. reproduction) strongly increases the probability of long-term survival of a particular type of organization.

Moreover, the exchange reactions that determine which molecules can enter a cell will in general be selective. A typical cell membrane is “semi-permeable”: it will only let certain molecules diffuse into or out of the cell. This mechanism can obviously be used to keep toxins out and let food in. It moreover makes it more difficult for molecules to diffuse away from the cell, thus ensuring that molecules critical for maintaining the metabolic cycle are always at hand.

Another general resilience strategy common throughout living systems is *degeneracy* (Edelman and Gally, 2001; Whitacre, 2010). Degeneracy means that distinct processes have overlapping functions, or, in other words, that more than one process contributes to a given function. The advantage is that if one of these processes is disrupted (e.g. because of interference or lack of the necessary inputs), there will

still be other processes to fulfill the function. A simple example in the language of reaction networks is the following:



This network produces the molecules $\{a, b, c\}$ from the input or “food” molecules $\{x, y, z\}$. However, note that these same three molecules will still be produced if the supply of either x, y or z is interrupted. That is because these three reactions overlap in the products they produce: the absence of x stops the first reaction from producing a and b , but these two molecules are still being produced by the second and third reactions. The same reasoning applies to the absence of y or z . The larger the degeneracy, i.e. the larger the number of functions that is performed by more than one process, the larger the *latitude* of the system’s basin (see Fig. 3), i.e. the larger the variety of perturbations that the system can survive.

Degeneracy appears to be ubiquitous in biology: there is typically more than one metabolic pathway, organ, cell type, neural circuit, ..., that contributes to a given function. The reason is clear: this strongly enhances robustness or resilience. If one of these organs or pathways would break down, the other ones can take over. Note that degeneracy is not the same as redundancy. Having two kidneys is redundant, because they do exactly the same thing, and we can survive with just one of them. As an example of degeneracy, kidneys and liver overlap in the function of excreting toxins, but they do this in different ways, and do not deal with all the same toxins. Degeneracy also contributes to *evolvability*, because it is easier for the organism to experiment with variations in subsystems whose function can be taken over by other subsystems if the variation would change their function (Whitacre, 2010).

On the other hand, degeneracy probably also has a cost, in the sense that the organism needs to maintain a more complex array of subsystems or pathways than strictly needed for its survival. In situations where perturbations threatening to disrupt a particular function are rare, there will not be a selective pressure to develop or maintain a degenerate implementation of that function. For example, most mammals can obtain the essential molecule known as vitamin C both from food and through internal processes. On the other hand, primates (including humans), who evolved eating a fruit-based diet that contained abundant vitamin C, have lost the ability to produce this molecule internally. That makes humans vulnerable to scurvy, a potentially deadly disease caused by a diet lacking in vitamin C.

That suggests that there is a tradeoff between abundance and degeneracy as resilience-building strategies: when a resource is abundant, there is less need to develop degenerate pathways for producing it. This intuition can actually be supported by a mathematical analysis of reaction networks. An organization can be decomposed into overproduced species of molecules, catalyst species that are not consumed or produced, and a “fragile circuit”, which consists of the remaining molecules, which are produced just enough to maintain their concentration (Veloz et al., 2011). It can be proven that the fragile circuit can be decomposed into modules

that are connected only by overproduced species or catalysts. In many cases, such a module can shut down without disrupting the other modules. The larger the number of overproduced species, the larger the number of modules (and thus the smaller the modules). Thus, organizations with many overproduced species seem to be more resistant to perturbations (Veloz et al., 2022), although this will need to be confirmed by a deeper mathematical or computational analysis.

Contingent Resilience Strategies

The resilience mechanisms we discussed until now are not perturbation specific: they merely safeguard the availability of molecules necessary for self-maintenance, whatever the problem that may threaten self-maintenance. Living systems also use more targeted strategies to neutralize specific perturbations. These can be understood with the help of the cybernetic *law of requisite variety* (Ashby, 1958; Aulin-Ahmavaara, 1979; Heylighen and Joslyn, 2003). This principle states that the larger the variety of perturbations the systems may be confronted with, the larger the variety of actions it should be able to execute in order to compensate all these perturbations. The principle is complemented by the *law of requisite knowledge*, which adds that the system moreover should “know” which action to use for which perturbation (Heylighen and Joslyn, 2003). In other words, the system must contain an implicit mapping from the set of potentially perturbing conditions to the set of actions appropriate for each condition (Conant and Ashby, 1970). This knowledge can be expressed very simply in the form of a collection of *condition-action rules*: if condition X is encountered, then perform action Y (Holland et al., 1989). In the present model, the corresponding “if X, then Y” rule can be implemented as a reaction $X \rightarrow Y$ (Heylighen, 2022a). Here, the input plays the role of the condition that is recognized by the system (e.g. presence of a toxin), while the processing of this input into output plays the role of the corresponding action (e.g. conversion of the toxin into a non-toxic molecule).

The law of requisite variety implies that the self-maintaining system should ideally have an extensive *repertoire* of such reactions, so as to be ready to deal with a wide variety of possible perturbing conditions. The larger the repertoire, the greater the latitude of the system’s basin (Fig. 2), i.e. the larger the size of the region in the system’s state space from which it is able to return to its self-maintaining attractor regime. However, the law of requisite knowledge assumes that these reactions would only be active in the right condition, e.g. in the presence of a particular toxin or a particular food to be digested. In the absence of this specific perturbation, the reaction should not take place. That implies that the organization should be able to maintain this repertoire of reactions in a *dormant* state, ready to be activated when the circumstances demand it, but silent otherwise.

However, a reaction without the right input cannot be “maintained”: without molecules to react, there simply is no reaction. What the system needs is a kind of

“toolbox” for its repertoire: a form of storage not so much of resources to be consumed, but of tools available to perform actions when necessary. This can be achieved by means of catalysts: molecules that enable a reaction, but that are not consumed by that reaction, and that therefore remain available after the reaction has taken place. Thus, the organization can increase its resilience by maintaining a store of catalysts that enable various perturbation-neutralizing reactions in the right conditions. In biological systems, this catalytic role is typically performed by enzymes. The larger the store of catalysts/enzymes/tools, the larger the variety of perturbations the systems can survive. Therefore, we can expect that evolution through variation and selection will step-by-step add potentially useful tools to an organization’s toolbox.

There is still the problem that catalysts must be produced by certain reactions, and that they are likely to be consumed by other reactions. These production-consumption reactions may also undergo perturbations, implying that catalyst concentrations may go to zero. This would effectively remove the corresponding condition-action rule from the system’s repertoire, thus making the system vulnerable again to the corresponding perturbing condition. Moreover, catalysts and the reactions they trigger may interfere with other reactions, e.g. by consuming resources, or producing products that consume these resources. Therefore, it is safer not to have all catalysts active at the same time. Both problems—potential loss and interference—can be avoided by converting the catalysts to a non-reactive, dormant form, from which they can be reactivated only when they are needed. This dormant form would function not as a tool ready-to-use (which may get lost or used inappropriately), but as a safely stored *procedure* for making and using the tool (which would guarantee appropriate use at the appropriate time). Thus, what would be stored here is procedural *knowledge* on how to deal with a variety of perturbations.

In biological systems, this procedural knowledge is stored in the genes. A gene, i.e. a coding stretch of DNA, can be seen as a list of instructions for building the enzyme needed to perform a particular reaction. The advantage of DNA is that it is very stable and therefore dependable: it does not get consumed by any reaction, and is produced only during the process of cell division. Therefore, it provides a reliable *memory*, keeping track of all the condition-action rules in the organism’s repertoire. Yet, this memory can be “read off” in order to produce specific enzymes when they are needed.

This storage of control knowledge in the form of DNA is characteristic for biological systems as we presently know them here on Earth. However, if we wish to understand the origin of life from simpler types of self-maintaining systems, here or potentially on other worlds, we cannot assume a specific DNA-like structure as given. Instead, we will assume that primitive self-maintaining systems would more generally be driven by natural selection to incorporate and accumulate molecules or reactions that enhance their resilience. In the scenario we sketched, this is likely to happen in first instance in the form of catalysts (“tools”) that enable reactions that can neutralize common perturbations. In second instance, this may happen in the form of non-

reactive molecules (“procedures”) that in the right conditions can produce the necessary catalysts, thus regulating the latter’s availability. Thus, we propose that life could be characterized by a cybernetic control structure with three levels:

- 1) a self-maintaining network of reactions made resilient by negative feedbacks, buffers, boundaries, and degenerate pathways;
- 2) a store of catalysts that can enable particular reactions in the network in order to deal with particular, temporary perturbations, such as the appearance of toxins or non-standard food types;
- 3) a store of non-reactive molecules that function as a memory and regulator for how to produce the right catalysts at the right moments.

Interestingly, we can immediately think of examples of systems at level (1) (stable dissipative structures, such as rivers) and level (3) (life as we know it), but not at level (2) (except in the formal model of autocatalytic sets). That suggests that the intermediate level (2) organizations would be less stable, so that they lost the competition both with the simpler level (1) and the more sophisticated level (3) organizations. (“tools”)

A possible explanation for the lack of level (2) organizations is provided by the RNA-world hypothesis for the origin of life (Pressman et al., 2015), which is the main competitor of the autocatalytic set hypothesis (Hordijk et al., 2010). In this model, free-floating RNA molecules were initially functioning both as catalysts and as memory molecules. However, later they became specialized in their memory function (eventually to be replaced by the even more stable DNA in that role), leaving the catalyst function to the enzymes. In this scenario, because RNA already had the features required for a memory molecule (such as being able to store an unlimited amount of information in a dependable form that is easy to copy), reaching level (3) was so easy that a sophisticated level (2) organization did not get the time to evolve.

On the other hand, if we make abstraction of the specific biochemical conditions in living cells, we can find level (2) organizations at a different scale: *ecosystems*. An ecosystem is naturally modeled as a chemical organization (Heylighen, 2022a; Veloz, 2019), with reactions representing the consumption and production of both material resources (such as oxygen, compost and minerals) and biological ones (such as different types of plants, animals, fungi, and micro-organisms). Ecosystems are normally self-maintaining: they recycle all their resources, so that everything consumed is produced again in sufficient quantities to keep the system going.

In such an ecological reaction network, biological species typically act as the catalysts or agencies that keep the essential reactions going, and that neutralize perturbations. (Thus, an ecosystem can also be modelled as an autocatalytic set (Gatti et al., 2017).) For example, plants are the catalysts that convert carbon dioxide into oxygen, while decomposers, such as bacteria, convert dead organic matter into minerals consumed by the plants. The concentrations of these catalysts increase and decrease as the resources they thrive on fluctuate, albeit generally subjected to a stabilizing negative feedback of the kind we described earlier (reactions slowing

down when their input becomes less abundant). However, there is no global “memory” that stores the knowledge about how to regulate the ecosystem or how to deal with perturbations. That may explain in part why ecosystems are not always resilient: perturbations such as fertilizer runoff, fires, or invasive species may disrupt the present self-maintaining regime (e.g. a forest) to such a degree that it is transformed into a different one (e.g. a savanna) (Pausas, 2015).

A common trigger for such change is the loss of a “keystone species”: a species playing a crucial role in reactions on which many other species depend. A biological species is intrinsically vulnerable to fluctuations in its numbers or specific perturbations (such as extermination by toxins, diseases or predators), because it cannot be produced from other species: once its concentration goes to zero, it cannot be reconstituted, and the ecosystem may drastically change as a result of this loss. The same danger threatens catalysts that cannot be reconstituted from a safely stored memory molecule. In the highly variable environment in which the first self-maintaining organizations were trying to survive, loss of a crucial catalyst may well have been a common occurrence. That would have created a selective pressure to develop some form of stable memory on the basis of which such catalysts could be reconstituted, thus pushing the level (2) organization to level (3). Ecosystems may be less vulnerable to such loss of catalyzing species because their reactions are highly degenerate (species overlap a lot in their ecological functions), and because locally lost species can often be recovered through immigration from another region where the species still survives.

Evolving organizations

We have proposed a broad-stroke scenario for how a living organism could have self-organized and evolved, starting from a self-maintaining organization, and then acquiring increasingly powerful resilience mechanisms that would guarantee its survival in an increasingly wide range of conditions. The further evolution of life is essentially a continuation of that scenario. We will here focus on those evolutionary transformations that change the qualitative organization of a living system. From the point of view of chemical organizations, such changes correspond to the addition or deletion of reactions, or, more generally, pathways of coupled reactions. These reactions either produce resources that help maintain the autopoietic cycle that defines the organism, or they counteract perturbations that may interfere with that cycle. The simplest way to acquire a reaction is via a molecule that catalyzes that reaction.

A simple example of such a transformation is the acquisition of a plasmid by a bacterium. A plasmid is a piece of free-floating DNA, which bacteria can either ingest or extrude. This allows bacteria to exchange genetic information in a manner reminiscent of sexual reproduction. Such a plasmid codes for one or more enzymes. These may be useful for the bacterium under certain conditions. For example, antibiotic resistance is commonly transferred via the exchange of plasmids (Bennett,

2008). For a bacterium, an antibiotic functions as an unusual toxin, i.e. a potentially lethal perturbation that is not part of its natural environment. Therefore, the bacterium's reaction network has not evolved an effective pathway of reactions to neutralize that perturbation. While such a bacterium may be very resilient in normal circumstances, i.e. have a basin characterized by great latitude and resistance, it is still precarious (see Fig. 3), because the presence of one particular species of molecule is sufficient to kill it. The bacterium may reduce its precariousness and thus increase its resilience by incorporating a plasmid that codes for an enzyme that is able to neutralize that antibiotic molecule.

It is interesting to note that the retention of such a plasmid seems to bear a cost to the bacterium (Björkman and Andersson, 2000)—as suggested by the observation that bacteria that are no longer threatened by this antibiotic tend to lose their resistance. This seems to confirm our previous suggestion that degeneracy has a cost in terms of the system having to maintain a more complex organization. Another plausible explanation is our suggestion that the reactions catalyzed by different enzymes may interfere with each other: perhaps the antibiotic-neutralizing enzyme produces some molecules that react with other molecules in the bacterial metabolism, thus reducing their availability for self-maintenance. On the other hand, it has been observed that bacteria eventually seem to get better at retaining their antibiotic-resistance, suggesting that continuing evolution may reduce these costs (Björkman and Andersson, 2000), perhaps by developing further pathways that reduce such interference effects.

More generally, it seems that increasing the complexity of the self-maintaining metabolism by adding pathways would increase the risk of interference between the increasing number of reactions that all take place within the same “reaction vessel”. (We plan to test that hypothesis through a computer simulation of self-organization and evolution of resilience in random reaction networks (Heylighen, 2022b; Veloz et al., 2022).) This problem can be avoided by subdividing this vessel into separate cells, so that different reactions occur in different cells, without interference.

This is the solution implemented by *multicellular organisms*: in such organisms, there are different tissues and organs consisting of different cell types, such as neurons, muscle cells, or liver cells. In each type, only certain genes are “expressed”, i.e. actively participating in the cell's metabolism. These are the genes coding for enzymes required for performing that cell type's specific function—such as enzymes that neutralize specific toxins for liver cells. The other genes are silent. Each cell is a self-maintaining system, which, however, is dependent on input that comes from the rest of the organism, such as oxygen or glucose. That cell in turn produces an output, such as hormones or neurotransmitters, which is taken up by certain other cells. Thus, cells interact by exchanging a number of molecules that is *limited*, i.e. significantly smaller than the number of molecules being produced and consumed within each cell. That limited exchange minimizes the risk of interference, while enabling a division-of-labor type of cooperative arrangement, in which each

cell type produces the resources for which it is specialized, while relying on other cells in the organism for the other resources it needs to perform this function.

In such a multicellular organism, each cell plays the role of an agent or agency (Heylighen, 2022a), which converts certain inputs into certain outputs, and thus contributes to the maintenance of the overall organism. The organism as a whole can then be seen as a *super-organization*, i.e. a self-maintaining, closed network of reactions between resources and agencies, but where the agencies (the cells) are themselves self-maintaining organizations.

Evolving super-organizations

We proposed that multicellular division of labor allows organisms to become more complex and thus acquire a wide variety of enzymes and pathways that can deal with a wide variety of perturbations, while avoiding the problem of interference. However, this does not yet explain how such a coordination and collaboration between different cells could have evolved. In other words, the issue now is to better understand the mechanisms leading up to major evolutionary transitions, in which a number of independent units become integrated into a cooperative whole.

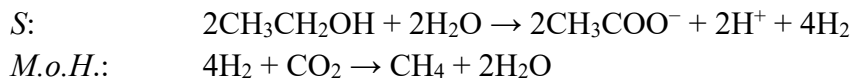
As we suggested in the introduction, the evolution of cooperation appears intrinsically problematic if you start from the assumption that these units are in competition for the same resources. Helping another unit then means helping a competitor to consume more of what you need for yourself. However, if units are complementary, in the sense that the one produces what the other needs, then cooperation is beneficial from start to finish, and there will be no temptation to “defect” from the cooperative arrangement.

Such overall complementarity or synergy is the default relationship between the different reactions in an organization: each produces what others consume and consumes what others produce, so as to collectively maintain the flow of resources. This coordination is achieved through the self-organization of a reaction network as we sketched it, in which reactions initiate and maintain only when they get a sufficient input from some other reaction(s).

We can generalize this complementarity between reactions to one between “agencies”, i.e. to some degree autonomous units that catalyze or perform a number of input-output conversions, i.e. higher-order reactions (Heylighen, 2022a; Heylighen et al., 2015). Such agencies could be genes, cells, organisms, people or firms. The same dynamics of self-organization will apply to the interaction between such agencies, resulting in the emergence of a closed, self-maintaining “ecosystem” of symbiotic agencies (Heylighen, 2022a; Veloz and Flores, 2021).

An example of such a synergetic cooperation between different types of cells is the phenomenon of *syntrophy* (Morris et al., 2013), in which one type of cells produces what another consumes. A classic illustration is formed by a culture of

methanogenic bacteria that actually consist of two strains, conventionally denoted as *S* and *M.o.H.*, which perform the following chemical reactions:



Here, *S* not only “feeds” its companion *M.o.H.* by producing H_2 , but *M.o.H.* helps *S* in this production by consuming the resulting H_2 which otherwise would interfere with the metabolism of *S*. This type of interaction has been called “obligately mutualistic metabolism”, because the one agent cannot perform some of its critical metabolic functions without the contribution of the other (Morris et al., 2013).

We normally do not consider cultures or ecosystems as individuals because they lack clear boundaries: they are distributed across space, and agencies such as organisms can easily enter or leave them. However, in some cases the symbiotic assembly is spatially localized. One example is a bacterial film—although here there is no concrete boundary enclosing the diverse microscopic agents. A clearer case is *endosymbiosis*: organisms living within the boundaries of another organism. For example, our intestines contain an ecosystem of microorganisms, known as the gut microbiome, which includes bacteria, fungi and viruses. These consume some of the non-digestible parts of the food we eat, such as fibers, and in return produce some of the B-vitamins that our body needs. This is a clear case of mutualist symbiosis in which both partners benefit from the interaction, forming a self-maintaining whole. Thus, the human body and its microbiome together form a super-organization consisting of individual cells as collaborating sub-organizations.

However, being part of an organization or ecosystem does not imply that all partners equally profit. The microbiome may also contain parasites that consume resources without producing anything useful in return. This seems to be a general issue for organizations, which has not been investigated yet: while the whole may be self-maintaining, it is quite possible that certain reactions, pathways or cycles consume some of the overproduced molecular species, leaving enough for self-maintenance, however, while not contributing to that self-maintenance through their products. Thus, although the self-organization of reaction networks proposes a simple scenario for the emergence of cooperation, this scenario does not exclude the appearance of something akin to free riders, which in this context may be called “parasitic processes”.

Because they reduce the amount of resources available for combating perturbations, such parasitic pathways also reduce the resilience of the overall organizations. Therefore, long-term evolution is likely to develop mechanisms that suppress such free-riding processes. This positive development is enhanced by the long-term tendency of parasites evolving to become mutualists (Dawkins, 2006). The reason is that it is to the benefit of the parasite that its host would be fit, i.e. ready to produce plenty of the resources that the parasite needs. Therefore, there is a selective pressure for the parasite to adapt so as not to weaken, but rather strengthen its host.

Moreover, even before such evolution has taken place, a parasitic process will not on its own kill an organization, because we started by assuming that it is part of a self-maintaining organization.

Let us then assume that the symbiosis between different agencies is synergetic and that they are localized within the same boundary. In that case, mutual dependency will tend to become stronger through an increasing division of labor, in which each of the organisms specializes in the function it performs most efficiently, while “outsourcing” potentially interfering or competing functions to its symbiotic partners—until it no longer can perform those functions independently. This is the origin of symbiogenesis, in which the symbiotic organisms merge into a single superorganism (Agafonov et al., 2021; Corning, 2021). The classic example is the eukaryotic cell, which appears to have evolved as a merger of simpler, prokaryotic cells (López-García and Moreira, 2020), which are now still recognizable as organelles within the larger cell. A potential other example is the emergence of chromosomes (Maynard Smith and Szathmáry, 1997), as cooperative assemblies of “selfish genes” that initially may have acted as individual agencies, but which got integrated into a single structure because the reactions their products control are complementary (Heylighen, 2022a).

Following this logic, the emergence of multicellular organisms is trickier to explain, because cells belonging to the same species normally have the same inputs and outputs, thus being a priori in a situation of competition rather than synergy. However, if these cells would already have evolved the level (3) capability to selectively switch on or switch off genes together with their resulting enzyme products, then they could avoid competition by activating different pathways that consume and produce different resources. They would thus become more complementary, e.g. by specializing in digesting different types of food, or combating different perturbations. The initial differentiation may have been triggered by spatial localization: the cells on the outside border of a ball of cells would naturally come into contact with different perturbations and resources than those on the inside, therefore expressing different sets of genes. Such topological differentiation is as yet difficult to model with reaction networks—although (Peter et al., 2021) have made a start. Therefore, we will not investigate the issue in this paper, but leave it open for further research.

Conclusion

We have conceived a living system as a *self-maintaining, resilient* network of processes or reactions. This conception generalizes and clarifies the notion of *autopoiesis* that has been proposed as a definition of life (Maturana and Varela, 1980; Razeto-Barry, 2012; Varela et al., 1974).

The generalization consists in the fact that dissipative structures, such as flames or convection cells, can also be seen as self-maintaining flows, albeit with a very poor resilience, unlike living systems. This led us to conceive a continuum of

resilience, with dissipative structures and living organisms at the opposite ends of that continuum. The zone in between, where resilience is limited, then defines a space for systems intermediate between life and non-life. This is the space in which life is likely to have originated, through a self-organizing evolution that gradually increased resilience.

The clarification consists in the fact that self-maintenance (unlike the rather complex notion of autopoiesis) can be modeled simply and precisely by means of the reaction network formalism. The equivalent of an autopoietic system here is defined as a *chemical organization*. This is a network of “molecules” and reactions, such that all molecules consumed by reactions are also produced by these same reactions, in an amount at least as much as what is consumed. This network is also closed, in the sense that the reactions do not produce any molecules that are not already part of the network. Thus, an organization can be seen as properly *autonomous*, *organizationally closed*, or *autopoietic* (except that there is no requirement for an organization to produce a topological boundary).

While the notion of self-maintenance is formally defined (Dittrich and Fenizio, 2007), the notion of resilience as yet remains more vague. The literature on resilience in ecosystems proposes to model the concept in terms of the basin of attraction of a dynamical system (Meyer, 2016). A reaction network defines such a dynamical system, with the concentrations of the molecules as the variables, and the reactions as defining the dynamics. The attractors of this dynamics are self-maintaining organizations. That means that such organizations tend to self-organize: an arbitrary combination of molecules will react, producing new molecules and consuming existing ones, until the remaining set of molecules no longer changes, i.e. has become closed and self-maintaining. While this mechanism of self-organization is clearly specified, it is not clear how resilient the resulting attractor will be when confronted with external perturbations, i.e. how wide and deep its surrounding basin of attraction is.

To start investigating this issue, we distinguished three types of perturbations: state perturbations, in which the concentration of a molecule changes, process perturbations, in which the rate of a reaction changes, and structural perturbations, in which a reaction or species of molecules is added or removed, thus initiating or disabling reactions with existing molecules. We argued that organizations tend to have implicit negative feedbacks that can to some degree compensate for the first two types of perturbations, by slowing down reactions when the concentration of the molecules they consume diminishes.

Perturbations of the third type are more dangerous, though, because they may remove a critical resource, or add a “toxin” that interferes with the reactions necessary for self-maintenance. We sketched two general strategies that an organization can evolve to cope with such perturbations. One is to produce or store an abundance of resources, so as to be able to compensate for a temporary interruption in their supply. Another is to make the network more degenerate, in the sense of evolving distinct pathways for producing the same resources. Then, if one pathway is interrupted, the

resource can still be produced via another one. We suggested that there is a trade-off between both strategies, in the sense that they both have a cost, but the presence of the one tends to reduce the need to develop or maintain the other.

The cybernetic law of requisite variety entails that such broad strategies must be complemented by more specific counteractions, in order to deal with a wide variety of specific perturbations that occur occasionally. This requires a repertoire of condition-action rules. These can be implemented by catalysts that remain inactive most of the time, but that trigger the right reactions when needed, e.g. so as to neutralize a specific toxin or digest an unusual type of food. The problem with a reserve of freely available catalysts, however, is that they may get consumed through reactions with other molecules, or that they may trigger reactions under inappropriate conditions, thus interfering with other reactions taking place. A possible solution is to develop a store of non-reactive “memory” molecules, from which the catalysts can be generated (only) when needed, but which are otherwise silent, while being dependably retained.

Life as we know it has evolved DNA to play the role of this memory molecule, and enzymes to play the role of the catalysts. Thus, life could be characterized as a self-maintaining system that has increased its resilience by developing three subsequent levels of control mechanisms: 1) negative feedback, buffering and degeneracy to absorb general perturbations; 2) catalysts or “agencies” to counteract specific perturbations; 3) a memory store, to ensure that the right catalysts are made available at the right moment.

This analysis suggests that we may better understand the origin of life by developing a scenario showing how these different mechanisms could have evolved through the variation and selection of a self-maintaining reaction network. We plan to model such evolution by means of a computer simulation in which randomly generated reaction networks are first allowed to self-organize into an organization, and then subjected to random perturbations (Heylighen, 2022b). These perturbations are likely to push the system out of any attractors with a small, unstable basin, hopefully allowing it to settle into a highly resilient attractor—i.e. one with a basin characterized by high latitude and resistance and low precariousness. If our preliminary scenario is realistic, the resulting resilient organization should exhibit several of the control mechanisms proposed in this paper. However, it may well have discovered additional, as yet unconceived strategies to increase resilience. An analysis of the resilient organizations evolved in this way may teach us about such novel strategies, thus potentially clarifying the steps needed by a complex self-maintaining system to acquire the autonomy we associate with life.

Another issue for future research is how mechanisms of self-maintenance and resilience may be strengthened by distributing them over separate agencies, such as cells or symbiotic organisms. We have suggested that dividing functions across spatially separated systems would reduce the problem of interference between reactions, while promoting cooperation between these divisions through the exchange of a limited number of reaction products (Peter et al., 2021). Such a synergetic

division of labor can be found in ecosystems and symbiotic assemblies, while explaining the symbiogenic origin of more complex organisms such as eukaryotes. Major evolutionary transitions, such as the emergence of multicellularity, are likely to follow a similar dynamics, in which cells differentiate by activating different sets of genes and then “align” or coordinate their inputs and outputs so as to form a self-maintaining super-organization.

While there are still many questions and complex issues to be investigated, we hope to have shown that reaction networks and self-maintaining organizations provide a very promising approach to tackle one of the most fundamental problems of all: the definition, origin and evolutionary transformation of life. Although this approach may appear rather abstract and formal, ignoring concrete questions about the physical structure of biological molecules and organisms, the advantage of this abstraction is generalizability. The functional mechanisms, structures and strategies for building self-maintenance and resilience we have sketched can in principle be investigated in systems very different from DNA-based cells and organisms. These include dissipative structures, ecosystems, social systems, software, robotic systems, and physico-chemical systems, such as planetary atmospheres (Centler and Dittrich, 2007), or even the network of nuclear reactions that maintain the “metabolism” of a star. Each of these systems could in principle evolve “life-like” autopoietic organizations. Recognizing such organizations is a central issue in domains of study such as artificial life, the Gaia hypothesis (Rubin et al., 2021) and astrobiology (Centler et al., 2003). The present paper has proposed several plausible mechanisms and characteristics to look out for when searching for such self-organizing quasi-life forms.

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Declarations of interest:

none

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