



Isn't self-assembly a misnomer? Multi-disciplinary arguments in favor of co-assembly

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ABSTRACT

Self-assembly is a ubiquitous physicochemical phenomenon. It is inherent to molecular recognition effects in the biological domain, and thus presents a basis for understanding the constitution and dynamic organization of living beings. However, it is argued in this paper that the very notion of self-assembly presents an incorrect and misleading one for the physical effects that it stands for. Self-assembly presents a misnomer as each self-assembly process not only depends on, but also includes a certain degree of ordering in the immediate surrounding of the 'self-assembling' entities. Claims are provided to support the idea that every self-assembly process is, in fact, a co-assembly event, as it implies mutual changes and structuring of both the 'self-assembled' system and its nearest surrounding. This point of view is related to the systemic observation that there could be no physical qualities independent on the context of their existence. In order to illustrate that the concept of co-assembly presents only an instance of a more profound and systemic philosophy of life, the examples of the interplay between internal and external factors of development are provided from the fields of quantum and classical physics, biology, evolutionary theory and psychology.

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1. Introduction: defining self-assembly

In order to draw a limit to thinking, we
have to think both sides to this limit.
Ludwig Wittgenstein

Self-assembly is a ubiquitous physicochemical phenomenon. It is inherent to molecular recognition effects in the biological domain, and

thus presents a basis for understanding the constitution and dynamic organization of living beings.

Self-assembly is as a notion increasingly used within the scientific community. Exponentially rising number of papers and citations that mention self-assembly speaks in favor of its large prosperity in the frame of the advanced chemical design (Fig. 1). Yet, the exact definition of this phenomenon does not seem to be very clear and straightforward. The reason is, as we shall see, that the very notion of self-assembly presents an incorrect and misleading one for the physical effects that it stands for.

Obviously, there are a large number of physical phenomena that could be in a colloquial manner denoted as self-assembling. If I drop a pencil from a certain height and it falls on the table, isn't that also a sort of self-assembling phenomenon involving the species of pencil

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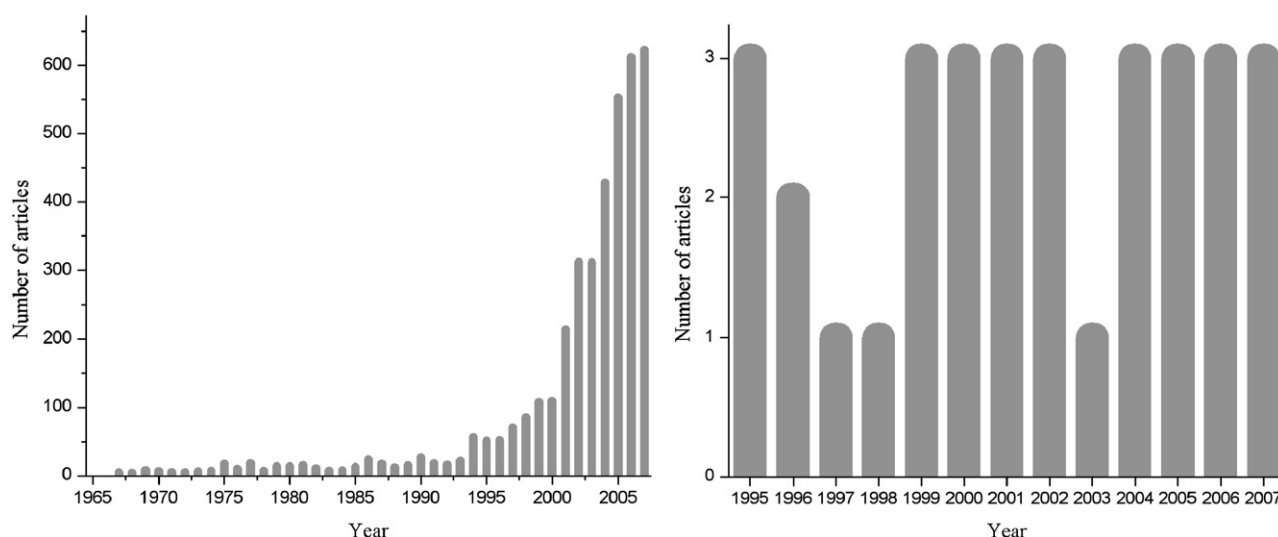


Fig. 1. Exponential increase in the number of scientific articles that contain the word 'self-assembly' in their title (left), and an almost constant number of scientific articles that contain the word 'co-assembly' in their title per year (right). Source: Scirus 2008 database.

and table? In fact, each situation in which a physical entity seeks and reaches an energetically most favorable conformation or position in relation to its environment could be characterized as self-assembling.

However, the actual set of self-assembling phenomena is limited to molecular species stabilized by the so-called weak forces. The latter include hydrogen bonds, hydrophobic interactions, van der Waals forces, salt bridges, coordination complexes, interactions between π -electrons of aromatic rings, etc.

On the other hand, the term 'self-assembly' is normally employed whenever an interaction via the aforementioned forces gives rise to an unpredictable structural or superstructural ordering. It is doubtful whether these same effects would have been denoted as self-assembling had there been a way to theoretically predict and experimentally design them. This 'mystical' aspect of self-assembling physical events is neatly illustrated by the way Donald E. Ingber of Harvard University supplied the definition of self-assembly, absolutely identical to the one of holistic effects: 'The phenomenon in which components join together to form larger, stable structures having new properties that could not have been predicted from the characteristics of their individual parts' [1].

From this point on, however, in using the term 'self-assembly' its strict physicochemical meaning will be implied, and at the end of this discourse we would be left with the aforementioned, mystical meaning of 'self-assembly' as the only reasonable one from the perspective of the current knowledge of phenomena grasped by this notion.

2. Each self-assembly is a co-assembly

Self-assembly obviously presents a misnomer as each self-assembly process not only depends on, but also includes a certain degree of ordering in the immediate surrounding of the 'self-assembling' entities. In the best case, self-assembly could be an approximated limiting condition when the ordering of the medium is regarded as insufficiently significant for the observed process. However, it is always an approximation, as there could be neither quality without context nor a process evolving towards a more ordered state without the reference to its surrounding.

Self-assembly of each molecular or supramolecular structure usually takes place only within a specific surrounding. In fact, a typical trial-and-error search for the conditions that will trigger the desired or only expected, but unforeseen assembly event can be regarded as nothing but a set of variations of the environmental contexts in which the studied entity is set to evolve.

Depending on the nature of the assembled structure, a choice of the convenient parameters that define the nature of the medium could be made. For example, if a highly hydrophobic compound is in question, the use of less polar media than water is normally demonstrated as favorable. The reason is that whenever hydrogen bonding is potentially involved in the self-assembly, there is a chance that the presence of water would disable the formation of the desired structure. The application of a non-polar solvent reduces the competition for hydrogen bonding sites and facilitates the formation of molecular recognition effects via hydrogen bonding. On the other hand, water as a polar solvent presents the most favorable solvent for inducing the association effects between hydrophobic species [2]. But then again, the more water is present, the lesser would be the potential for establishing complexation based on hydrogen bonding. To illustrate the contextual dependence of the strength of hydrogen bond, we can notice that breaking of a hydrogen bond in vacuum requires a significant amount of energy – ca. 25 kJ mol⁻¹ for a peptide hydrogen bond – but in water, as a result of the competition for hydrogen bonds in which the surrounding water molecules are involved, strength of the hydrogen bond between the identical pair of species might be close to zero [3]. Defining the strength of this particular bond is thus inherently related to the nature and composition of the applied medium.

It is worth noting that nature relies on the presence of water in probably all biochemical processes, but water present in biological media is usually constrained to fine or ultrafine domains, in which its physical properties turn out to be significantly modified [4]. Nuclear magnetic resonance studies have, for example, indicated that as a result of a high immobilization of water molecules, the amount of hydrogen bonding within the aqueous interior of a reverse micelle significantly differs from the one observed in bulk water [5]. Hydrogen bond is due to its versatility in strength and directionality usually considered as the most important of all self-assembly atomic interactions. Its contextual character clearly speaks in favor of the mutual reconstitution of the assembled system and its surrounding in each 'self-assembly' process. The same argument could be employed in the description of hydrophobic interactions, which are merely a manifestation of the peculiar hydrogen bonding properties of water.

However, not only self-assembly reactions in solution, like protein folding (illustrated in Fig. 2) or host-guest molecular recognition interactions imply a co-assembly of the respective medium. The same statement would be valid for another class of self-assembly effects, known as epitaxial self-assembly. In these experiments, the 'self-

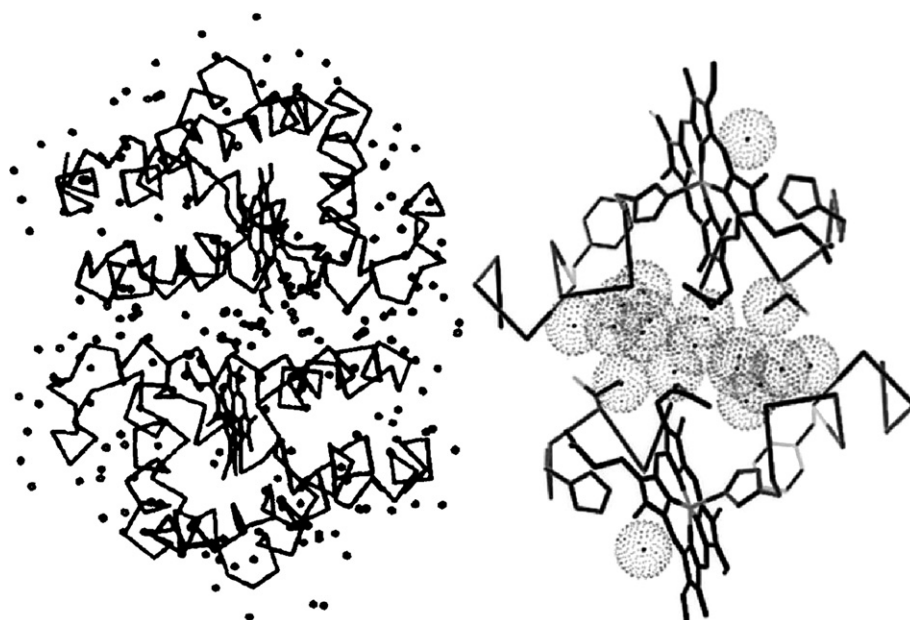


Fig. 2. Stereo diagram of 214 ordered water molecules around deoxy Hbl of dimeric hemoglobin from the arcid clam, *Scapharca inaequivalis* (left), and the central portion of the interface between the two subunits, showing a number of ordered water molecules forming a hydrogen bond network as a route for communication between the two heme groups (right). Because the formation of water molecules changes as the result of oxygen binding to the dimer, it is assumed that these water molecules play a significant role in modulating the intricate balance between alternate allosteric conformations, and act as key mediators for information transfer between hemes. It is apparent that in this case the assemblage of the polypeptide gives rise to an ordered structure of the neighboring water molecules, whereas the ordered water structure stabilizes the particular geometric form of the polypeptide. Reprinted from Refs. [6] and [7].

assembled' compound is deposited on a given substrate and typically at low deposition fluxes and high diffusion rates an organization of the deposited entities within specifically shaped aggregates or periodic networks occurs. However, such assembly effects are highly dependent on the nature of the substrate. Variations in chemical identity and spatial arrangement of the species that constitute the substrate are usually carried out as part of the search for the optimal self-assembly conditions. Therefore, there is again no sense in speaking about self-assembly when, in fact, this process is crucially influenced by an interaction with the substrate and other parameters that define the deposition process, as depicted in Fig. 3.

Often, one of these 'other' parameters is solvent evaporation rate. Namely, as the dispersion of assembling entities is deposited on a substrate, conditions that determine the evaporation of the solvent may turn out to be critical for the 'self-assembly' process. Although the final drying steps are frequently erased from the preparation protocols, they can sometimes be essential for achieving an aesthetic or even highly functional assembly of atomic or molecular species. But in case of such an assembly, the organization of the 'self-assembled' entities is inevitably followed by an ordered pattern of receding of the solvent. Again, it only depends from which side of this co-assembly phenomenon we would observe the spontaneous process of ordering. The latter exists on both sides, and despite the fact that the solvent evaporates and may turn out to be unimportant for the 'self-assembly' procedure, its crucial effect on this process should be at least implicitly acknowledged. Thus, it is the system as a whole, composed of the deposited species, the substrate and the solvent that 'self-assembles' under specific conditions.

3. The example of reverse micelles in light of general colloidal effects

Reverse micelles present nanoscopic aqueous droplets capped with surfactant molecules and dispersed in a non-polar phase [9]. They have frequently been used as media for running chemical reactions in which reactants and products are confined for different purposes, but usually either for the isolation of sensitive compounds, catalysis or equaliza-

tion of the precipitated particle sizes. Despite the prevailing idea that these multi-molecular entities act as templates for the particle growth effects, it has been evidenced that a feedback interaction exists between the processes of crystallization on one side and the reconfiguration of micellar morphologies and modification of their dynamic interaction on the other [10].

Self-assembly phenomena in this case are not in any way analogous to the ones of casting, as is mistakenly frequently observed in the literature. In accordance with the latter perspective, reverse micelles are imagined as inert nano-reactors that confine the growing particles and impose their sizes and shapes upon them. However, mutually disproportional levels of transcription and synergism can vary depending on the method in question, but both levels of evolution, intrinsic and interactional, are inevitably present in all cases.

For example, despite the fact that only spherical or elliptical micelles have been observed and theoretically predicted so far, beside spherically shaped particles, various other morphologies, including rods, filaments, acicular particles, platelets, disks, cubes, pyramids, cylinders and star-shaped patterns were prepared using this method [11] (Fig. 4). Size of the micelles also not necessarily corresponds to the one of the particles precipitated therein. Variations in particle size and shape were often brought about by changes in synthetic factors that were not affecting shapes and sizes of the micelles [12]. Different mechanisms of the chemical reactions carried out within and without the reverse micelles were detected, indicating an obvious influence that these self-assembled aggregates have on the encapsulating reactions, and thus denying the role of passive template agents [13]. Therefore, the concept of reverse micelles as templates in the production of fine particles has to be changed to a dynamic and co-modifying interaction between the crystallizing system and the surfactant assemblies.

As is schematically presented in Fig. 5, the process of crystallization within reverse micelles inevitably modifies the symmetry of the surrounding mesostructure, resulting in a form of co-adaptation: reverse micelles will template the growing crystals, while the growing crystals will template the micelles. For example, the tendency of the encapsulated crystallites to grow in an anisotropic fashion may impose a

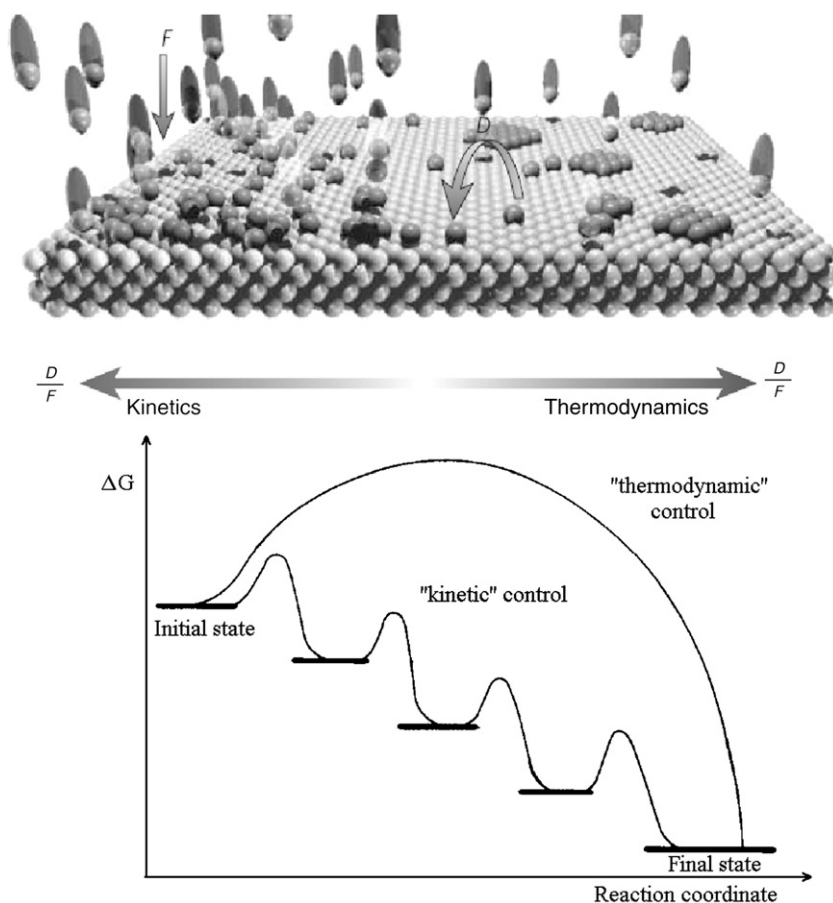


Fig. 3. Scheme representing the process of spontaneous assembly of the deposited species on top of a substrate. The depicted sphere-to-sphere interaction signifies the major role of the substrate in what is misleadingly named as self-assembly process. This process depends on thermal diffusion parameters, solvent identity and evaporation rate, external fields and kinetic effects, and both the nature of the assembling molecules and physicochemical nature of the substrate, including its chemical identity, topography, lattice parameter, surface charge, nature of the adsorbed molecules and ions. It is, therefore, the whole system composed of the deposited species, the substrate and the solvent that 'self-assembles' under certain conditions. The deposition flux (F) and thermal diffusion (D) are inversely proportional, and their ratio determines whether the assembly process would be limited by kinetics or thermodynamics. Reprinted from Ref. [8]. The graph below explains what is usually meant by kinetic and thermodynamic control: the former actually provides catalytic or inhibiting sequence of metastable energy states relative to the latter. However, both transformation pathways rely on the concept of free energy, and are as such inherently thermodynamical. The dichotomy between kinetic and thermodynamic control apparently presents another misnomer, the space for an elaboration of which is lacking in this paper.

decrease in the curvature of encapsulating micelles and lead to a cooperative and mutually favorable balance with an elongation of both the inorganic lattice and the surfactant phase.

One of the requirements for such a cooperative assembly is the formation of comparatively strong binding interactions between the two phases. This could be illustrated by an example in which modifications of surface charges are used to vary the intensity of the electrostatic attraction between the surfactant and the crystal, and thus control the effectiveness of the assembly process. In case of ionic micelles, the addition of electrolyte leads to a reduced repulsion between the charged surfactant head-groups through the screening effect, so that critical micelle concentration, for example, gets shifted to lower values with the increase in the ionic strength of the solvent. Variations of the degree of hydration of both the inorganic surface and surfactant assemblies can be similarly used to control the degree of co-assembling interaction. Namely, with increasing water-to-surfactant molar ratio (known as parameter w), the aqueous core of reverse micelles expands leading to the conditions in which the interface between surfactant head-groups and the growing crystal surface is no longer that intimate so as to promote a favorable co-assembly. Another way to affect the co-assembly interaction would be to manipulate with the dynamics of micelle-micelle interaction. For example, at the corresponding points in the phase diagram of the applied microemulsion one could achieve significant percolation phenomena that imply a higher rate of exchange of reactants and products, and as such predispose the spontaneous organization effects to be less controlled by thermody-

namics and more by kinetics [15]. The system would be thus placed within the set of reaction-limited or aggregation-limited conditions instead of the mesostructuring-limited ones.

When the sole 'self-assembly' of micelles is considered, mutual structuring of surfactant membranes and the supporting polar and non-polar phases takes place. Reverse micelles form only in the particular ranges (L_2) of the phase diagrams that include usually three, but occasionally four major components of the parent microemulsion. Furthermore, changes in temperature or the addition of other ingredients, like salts or co-surfactants, normally modify the area in the phase diagram in which micelles form [16]. Favorable structuring of both the dispersion medium and the confined domains – that is, inner, aqueous phase and the outer, so-called oil phase – is thus required for the process of assembly of micelles. For example, molecules of co-surfactant and the oil phase get tightly incorporated in the zones between individual surfactant molecules, modifying the curvature and stability of the surfactant membrane. Therefore, using the notion of self-assembly does not carry much sense in this case as well.

To further illustrate this, we may refer to infrared spectroscopic measurements which have led to the conclusion that the interfacial layer of water consists of molecules that are tightly bound to surfactant head-groups [17]. Depending on the size of reverse micelles, the encapsulated water may have significantly different solvent properties, ranging from highly structured interiors to free water cores that approximate bulk water solvent characteristics [18].

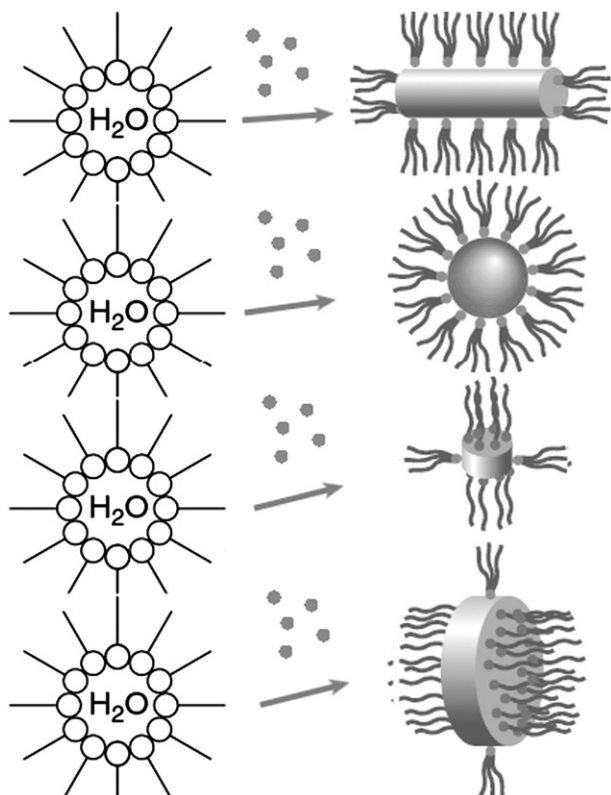


Fig. 4. Despite the tendency to adopt spherical morphologies in the parent microemulsion, once a crystallization process is initiated within their water cores the micelles can undergo drastic modifications in geometry and size. Partially reprinted from Ref. [14].

Dielectric permittivity, polarity, viscosity, diffusion coefficients, acidification gradients have all been evidenced as significantly modified in these confined, nanosized aqueous droplets compared to bulk water [19]. Most important of all, water confined to nanospaces seems to favor molecular recognition, catalytic selectivity and phenomena of spontaneous assembly, as demonstrated by sharp differences in the properties of structurally similar proteases upon their encapsulation within reverse micelles [20].

Water in biological environments actually exists in such ultrafine forms and due to the highly directional character of hydrogen bonds acts as an important information carrier in intracellular processes. For example, nanosized droplets of water with various degrees of ellipticity, ranging from spheres to needles, are considered as crucial for determining and maintaining the tertiary structure and, therefore, the right function of proteins [21]. 'Self-assembly' effects that are inherent to biological processes on the small scale normally imply a simultaneous 'self-assembly' of these fine water regions. The latter process is, however, typically neglected with the usage of the term 'self-assembly' and focusing on only one assembled side in this inevitably reciprocal assembling interaction.

In general, the process of dispersing colloidal particles within a given medium requires a coordination of charged clouds around each one of them so as to preserve the stability of the dispersion. Without the ordered layers of charges around the suspended particles, the particles would normally aggregate and the dispersion would segregate into different phases. By varying pH, the type of electrolyte and its concentration, dielectric constant of the medium (which affect surface charge density), or viscosity of the medium (thus affecting the thermal diffusion), for example, one can modify the properties of the dispersion medium and thus induce or disable specific self-assembly mechanisms. This is all to say that changes in the medium structure are typically applied to initiate what is paradoxically afterwards named as 'self-assembly' process.

The structure of nucleic acids can offer another illustration of this idea. Namely, the charged phosphate groups of nucleic acids generate a cloud of negative potential around these molecules, and are considerably involved in defining the structure, flexibility and biological function thereof [22]. Strong intra-molecular repulsions are reduced by the screening effect of attracted water molecules, inorganic cations, polypeptides (e.g. histones) or small biomolecules (e.g. spermine). Ordered water structure around nucleic acids is the result of extensive hydration effects, and is known to play a significant role in stabilizing these molecules [23]. Ever since its discovery by Watson and Crick in 1953, it has been well documented that a quasi-crystalline structure of water results from the dissolution of DNA in water, and that extensive hydration shells extend up to one-quarter of the length of the dissolved molecules [24]. These layers of water are so well structured that it has been, in fact, proposed that they could be used as a sort of 'hydration fingerprint' for recognizing specific DNA sequences [25]. It has also been suggested that they might play a crucial role in protein–DNA recognition mechanisms [26]. As a result, all serious structural models of nucleic acids that tend to explain their dynamic and biological properties need to necessarily consider the ionic and polar surrounding atmosphere. Depicting the structure of DNA double helix without the reference to the supporting physicochemical surrounding provides an incomplete picture.

In accordance to this, it has become suggested that treating dispersion media as continuous ones is one of the major reasons why the current theories fail to explain many anomalous colloidal effects, including a relatively strong attractive interaction between identically charged species in the presence of multivalent ions [27]. In the standard interpretations of DLVO theory, solvent is presumed to have uniform density and orientation profile, and figures merely through its dielectric constant. In spite of this assumption, there has been a considerable amount of evidence established that instead of having bulk properties all the way down to the contact with another surface, water undergoes modifications in its structure, molecular mobility, hydrogen bonding, relaxation processes and the overall solvent characteristics as it approaches foreign surfaces [28]. For example, as the effect of an unavoidable interaction between solvent molecules and the vessel walls, the confined pure liquid compound shows dumping oscillations in its density with the distance from the vessel wall to its center. When additional surfaces are introduced, the effect becomes even more pronounced, indicating subtle ordering phenomena of the dispersion medium, which is usually by default attributed with uniform properties. Disregard of the effects of hydration, uneven density and molecular orientation of the solvent, coupled with the 'mean field' approximation according to which fluctuations in the simple-ion distributions and surface charges and asymmetries are neglected, presents an approximation that seriously limits the practical scope of the current theories of colloidal phenomena [29]. The effects arising out from the perturbations in solvent structure have thus been many times proposed as keys to explaining colloidal phenomena that appear puzzling from the perspective of DLVO theory [30].

In the end, what is frequently forgotten is that self-assembled systems in solution after formation exist in dynamic equilibrium with their immediate surrounding. In case of fine particles produced by precipitation, this means that the rates of their dissolution and re-crystallization are balanced. This effect explains why relatively lyophilic suspensions are especially prone to Ostwald ripening and the consequent broadening of

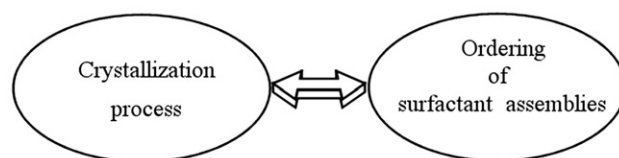


Fig. 5. Interaction between the process of crystallization and the structure of the parent mesophase, represented as the one permeated with feedback loops as a consequence of their mutual templating and adaptation.

the particle dispersity during aging. Thus, the integrity of the self-assembled systems in certain cases largely depends on the continuing interaction with a medium from which it has been formed.

As we see, the neat correlation between the two co-assembling sides presents, in fact, an essential factor that conditions each 'self-assembly' process. However, it is worth recalling that these interactions are based on weak molecular links, and as a result of their inherent sensitivity, even when typified as strong they leave enough room for flexible re-arrangements. As such, they neatly reflect the balance between rigidity and flexibility, apparently typical for all healthy developing natural systems.

4. Protein/mineral co-assembly

A similar example in which the concept of scaffolding is about to cede its place to the concept of co-assembly has been witnessed in the investigation of the process of amelogenesis, that is, the natural growth of dental enamel tissue. The reigning model has for a long time been the one associated with the prior formation of self-assembled protein network which provides the space for the growth of the mineral phase. It is presumed that the transition of the enamel protein assemblies from spherical nanoparticles to ribbons is related to the formation of extremely long hydroxyapatite crystals with the aspect ratio of up to $3 \cdot 10^4$. The major research groups in this field are still in dispute over whether the pre-assembled protein templates the crystal growth or the assembly of the protein phase and the crystal growth occur simultaneously, mutually affecting each other [31]. It is worth pointing out that, although the latter concept, schematized in Fig. 6, seems considerably more realistic [32], even if the protein network assembles first, it does not mean that this process takes place without the corresponding assemblage of the atomic and molecular species that comprise the actual surrounding, related to the depiction of this process presented under the previous subtitle.

Another case of a fascinating co-assembly effect between polypeptide molecules and the growing crystalline phase relates to the application of phage display library for the synthesis of ceramic materials by their precipitation at room temperature. The general concept of the method is the following. In the first stage, a large number of comparatively short polypeptide chains are introduced into a dispersion of the oxide material that is to be subsequently obtained by a precipitation reaction. Only amino acid chains that become adsorbed on the surface of the crystalline particles are chosen for the further study. In the next stage, these well-adsorbing polypeptides are added into the solution of precursor cations, and the precipitation of the latter is initiated. Under specific conditions, a co-assembly reaction between the protein and the ceramic would be triggered, resulting in the formation of the desired material. Some of the compounds that have otherwise

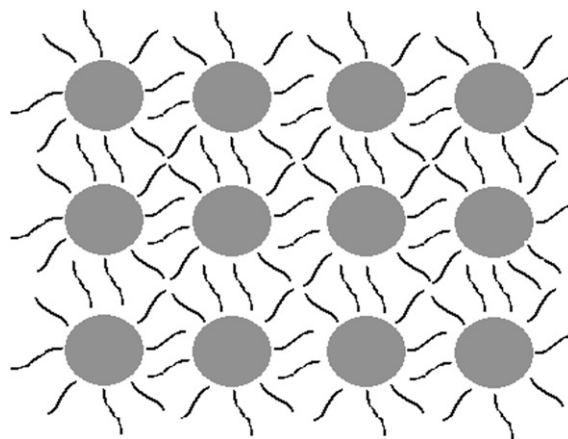


Fig. 7. Drawing of assembled two-dimensional arrays of particles by means of a specific interaction between surfactant molecules adsorbed on the particle surfaces. Note that both spherical particles and surfactant molecules follow an ordered pattern in this co-assembled spatial arrangement.

required processing at ultrahigh temperatures, including calcium molybdate [34] and germania [35], were obtained using this simple method. Many other types of materials with attractive morphologies have been synthesized by promoting a similar co-assembly interaction between a protein phase and an inorganic material [36].

Macromolecules, such as block copolymers, polysaccharides or proteins, are frequently applied as steric agents that by selective adhesion to the particle surfaces promote either repulsion or flocculation of the dispersed entities. Their ordered positioning is in both cases equally required. In particular, when these surface-anchored macromolecules induce the conditions for a 'self-assembly' of the given entities in form of arrays or some other architecture, periodic organization of both the crystalline and macromolecular phase is implied, as depicted in Fig. 7. Once again, it is clear that it always takes a mutual assembly of at least two sides for each 'self-assembly' event to occur. It also explains why interfacial phenomena and self-assembly effects are so closely related.

5. Turning the entropic argument from con to pro

A thermodynamic point of view could be naturally invoked as an antithesis to the concept of co-assembly exposed herein. Namely, according to the laws of thermodynamics, an increasing order within a system is necessarily followed by an increasing disorder in its surrounding. This would mean that an assembly of a more ordered structure from a less ordered one – take protein folding, for example – would be

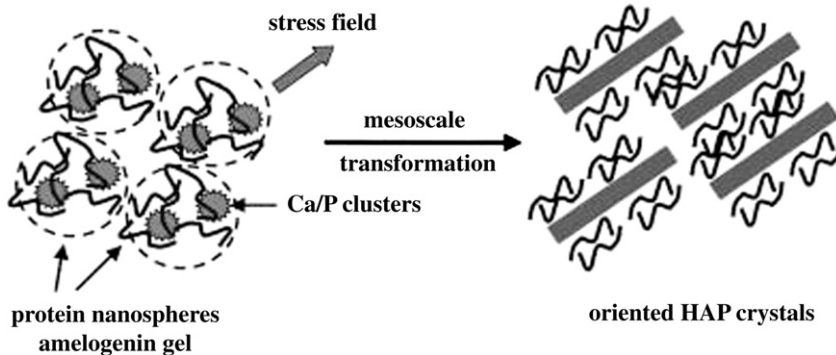


Fig. 6. Model of a reciprocal assembly of the growing crystals of hydroxyapatite and the amelogenin proteins in developing enamel. The aggregation of spherical primary particles of hydroxyapatite in form of rod-shaped crystals is followed by the transformation of the protein nanospheres into filaments anchored on the surface of the growing crystals. What is significant in this model is that it makes no sense asking who is older in this process, that is, which species are guiding and which ones are being guided, as mutual templation and adaptation are expected to take place. Reprinted from Ref. [33].

followed by the transition in the opposite direction in the surrounding of the assembled phase. This is, of course, not necessarily true, as we have seen that an increasing order within a given structure is entailed with a correspondent structuring of its nearby surrounding. The laws of thermodynamics continue to be valid once the system is analyzed in large enough context, but when the surrounding of the assembled system comparable to its size is considered, reciprocal structuring in form of a co-assembly can be normally notified.

If we observe life in general, we would come to the same conclusion. And it is that the complexity of an inner organization of living creatures increases in parallel with the complexity of the planetary surrounding. If we recall how one of the most impressive intellectuals of the 20th century, Gregory Bateson, defined information as a difference that makes a difference [37], and that the amount of readable boundaries both within the world and within our abstract concepts diversify in parallel, we can conclude that order 'within' and order 'without' are directly proportional.

In fact, as a consequence of their macroscopic character, thermodynamic theories inherently analyze each system in reference to its surrounding, but the complexity of the boundary that links and separates the two entities is normally neglected. In order to depict the latter, one would need to deploy the effects that pertain to the size ranges comparable to Brownian motion and quantum fluctuations. They are, however, known for disobeying the second law of thermodynamics, which on the other hand averages their chaotic influence. We should also bear in mind that spontaneous processes need not inevitably lead to a decrease in internal energy, but follow the direction towards a most probable state as determined by the minimal free energy of the system. As a result of the statistical interpretation of the thermodynamic quantities, free energy is represented as the product of exponentially decreasing Boltzmann term and similarly increasing degeneracy factor respective to the total energy of the system. This places the average energy of the system at temperatures different from absolute zero to states higher than the ground one. Therefore, the laws of thermodynamics supply a rather solid framework for explaining spontaneous disorder-to-order phenomena, later named as 'self-assembly'. These laws, of course, do not apply for individual atomic or molecular systems, but they indicate that once a sufficient amount of interfaces is introduced in a physical system, a spontaneous reorganization towards a more complex state may result. On the other hand, the reasons behind the changes in enthalpy and entropy during these transitions frequently appear as counter-intuitive. For example, most transitions of monomeric surfactant solutions to micellar dispersions are exothermic, but this is not always the case. Endothermic micellization is quite common, in which cases the process is thoroughly driven by the increasing entropy. On the other hand, the cause of positive entropy of these transitions is not perfectly clear yet, as it becomes hard to explain how hydrocarbon chains of surfactant molecules possess a higher degree of freedom when assembled into micelles as compared with their dissolved state [38].

Another thermodynamic argument, this time in favor of the proposed thesis, is that every biological creature is thermodynamically open as an incessant exchange of matter and energy is required for the maintenance of its inner biological processes. This means that it is in each circumstance 'structurally coupled' to its surrounding. Ordering of inner levels of organization is thus presupposed to correspond to a similar level of ordering in the outer domain. Simply saying, in order to sustain, biological creatures need to cultivate their environment as much as their own beings. The history of evolution and human race demonstrates how increases in the informational content of biological creatures and their environments have occurred in parallel. This has, of course, not always been the case, as we can recollect the examples of lost civilizations and the dangers of the contemporary trend of increasing human flexibility of choices in spite of its affecting the ability of the natural substrate to support this very same flexibility.

Structural coupling is in the theory of autopoiesis defined as the history of interactions that leads towards a structural congruence

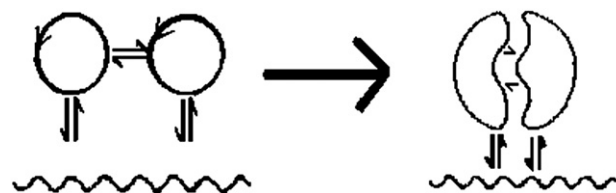


Fig. 8. Scheme from the theory of autopoiesis, depicting the structural coupling and congruence between a pair of semi-autonomous biological entities and their environment. Reprinted from Ref. [41].

between either two or more living creatures or a being and its environment (Fig. 8), as well as the process that leads to coincidence between changes in states of the respective congruent systems [39]. Interaction between a being and its physical surrounding is always mutual, so that any living environment could not be considered as a static, all-absorbing and inert object space, but as a sensitive systemic space that inevitably transforms in parallel with the subject being. Robots were designed so as to either passively adapt to certain environment or insensitively perform the programmed tasks, but the living creatures possess the creative power to co-modify and co-evolve through the interplay between their autonomous aspect and the influence of the environment. Each evolution is thus viewed as co-evolution [40]. Consequently, there is some truth in the natural insight that giraffes grow their necks so as to reach the treetops, whereby the trees grow in height so as to escape the curiosity of browsing giraffes.

6. Orange juggling, behaviorism and other chicken-or-egg paradoxes

As a reflection of the co-assembly phenomenon in the domain of molecular recognition effects, we could be reminded that the world is filled with circular causal relationships in which each cause presents and effect and *vice versa*.

The problem known as 'who came first: chicken or egg' can exist only in frameworks of reasoning pervaded with the neo-Aristotelian idea that if one traces causal relationships back enough in time, one would come to the initial cause. Serious teleological flaws of the latter approach are evidenced anytime one makes an attempt to apply the standard logic in explaining the functions of the simplest feedback loops without generating apparent paradoxes. Even in the case of a thermostat – as simple cybernetic circuit as it can get – an observer can not tell for sure whether it is the thermostat causing the work of the heating/cooling system that maintains the stable temperature in a given environment, or it is the temperature causing the work of the thermostat.

Chuang-tzu once asked: 'Is it the clouds that make the rain or it is the rain that makes clouds?' Today we know that circular causality pervades ecosystems, so that the clouds form rain, but the rain forms clouds as well. Someone can say that this is similar to how humans form their deeds and values that in turn shape humans in a wider existential context. The atomic elements of life are in the constant state of circulation between atmosphere, oceans, biological structures, rocks and sediments of the planetary whole [42], whereas as far as the social aspects of eco-science are considered, John Kenneth Galbraith has written that 'economic life, as always, is a matrix where the result becomes a cause and the cause becomes a result' [43]. Even the laws of classical physics are based on mutual interaction, as Isaac Newton's law of action and reaction neatly demonstrates.

Believe it or not, but the definition of 'controlling' and 'controlled' parts in any control loop presents an arbitrary choice of the observer. For example, if we watch an acrobat in the act of orange juggling (Fig. 9), we may ask whether it is him controlling the oranges or it is the oranges controlling him. Control in terms of imposing constraints over a system's behavior is always dual, so that a necessary precondition of controlling the controlled is to let the controlled control the controlling system in the reciprocal amount [44]. Both the



Fig. 9. For an observer unfamiliar with the concept of human creature and oranges, it would be impossible to determine who is in charge of the control in this act of juggling: the clown or the oranges. If control is defined by the concept of flexibility, then it could be noted that both the clown and the oranges display limited flexibility, and are as such in the state of mutual control.

famous Juvenal's question *Quis custodiet ipsos custodes?* and Bertrand Russel's paradox may therefore exist as insolvable intricacies only in the frameworks of reasoning that rely on employing linear causal relationships as explanatory bases. Autopoietic nature of biological systems, according to which the role of each entity is to produce all the others, presents a nice way to overthrow the idea of the necessity of a linear control in all intelligently behaving systems [45]. In it, genetic constitution of the organism presents only a 'chain' in the complex networks of iterative cellular interactions. Such a shift in the emphasis from the main role of DNA sequence to the major role of epigenetic network seems to be the only way to explain how humans share 98.5% of their DNA with the chimpanzee and have twice genes less than the rice genome. By knowing that DNA codes for the synthesis of proteins, whereby these same proteins are responsible for replicating and maintaining the correct structure and pathways of DNA expression, it becomes obvious that cellular behavior can be explained only in terms of feedback cycles. This explains how the whole field of proteomics was born [46], followed by the transition from understanding molecular biological phenomena as static to dynamic ones (because genome analyses essentially yield static structural data, whereas proteomic analyses ideally provide a dynamic, interactive picture).

As a correlation to the feedback nature of practically all natural events, the Australian philosopher, Ranulph Glanville, proposed a sententious joke about the behavioral psychology: 'The class Skinner was lecturing to decided to smile when he moved to the right and frown when he looked to the left, while lecturing. He ended up standing in the rightmost corner. But the students also had frozen grins on their faces. The control was mutual and interactive, and as unlike Skinner's behavioral model as you can get until you ask the question about why the rats running the maze correctly make the scientists smile' [47]. An observation that an increased level of mastery over natural events leads to both increased disciplining of human beings at all existential aspects and an increased level of slavery in relation to the same controlled natural phenomena (manifested as attachments to those, partly self-imposed environmental constraints), may be naturally inferred from the idea advocated herein. In scientific terms, this implies attachments to implicit assumptions and explanatory paradigms in frame of which the scientists construct hypotheses and experiments, frequently being blind to the fact that all the subsequently derived results and interpretations comprise reflections of these fundamental presuppositions. It is not only the physical world that leaves impressions on our experience, but it is also our implicit aspirations and assumptions that draw impressions on the world as we see it, implying that nature and experience are essentially one and the same.

7. A tiny molecule on its way to the sea

An illustration of the contextual character of natural qualities can be given with an example of a molecule of water immersed in a river stream. As we stand on the bridge and enjoy the river's flow, we may wonder how many different descriptive contexts need to be applied to understand and model the movement of a tiny molecule of water in this stream and predict its pattern of movement.

First of all, in order to outline the behavior of water molecules in an aqueous medium, instead of solely focusing on intrinsic structure of a single water molecule, one would need to take into account the effects of their interaction with the surrounding species. Electron clouds of atomic and molecular bonds are non-locally distributed in relation to the bound nucleons and are sensitive to the slightest changes in their immediate surrounding. This explains why in order for a chemical reaction to be effectively carried out, it is not enough only to bring the reactants into a close contact as the classical chemical descriptions might have suggested. Instead, an adjustment of the whole physical context that surrounds the interacting entities needs to be performed [48]. Whereas such a contextual reaction sphere may be reasonably approximated to span only up to a nanometer in diameter in case of simple chemical reactions, it can be significantly more extended in examples of reactions that take place in biological environments. This is why the Nobel Laureate, Richard E. Smalley, charmingly observed the following: 'Much like you can't make a boy and a girl fall in love with each other simply by pushing them together, you cannot make precise chemistry occur as desired between two molecular objects with simple mechanical motion along a few degrees of freedom in the assembler-fixed frame of reference. Chemistry, like love, is more subtle than that. You need to guide the reactants down a particular reaction coordinate, and this coordinate treads through a many-dimensional hyperspace' [49]. This viewpoint is obviously in disparity with the modern mechanistic ideals which state that any structure conceivable could be made by a non-contextual manipulation of individual atoms and molecules [50].

Nevertheless, behavior of water molecules could not be perfectly predicted even in some of the simplest physical settings by invoking only intrinsic quantum configurations and bonding effects with the nearest neighbors. This is due to enormous complexity of calculations that need to precede the corresponding predictions. Any realistic solution would comprise an inaccuracy at the atomic level as the consequence of expansion of indeterministic and probabilistic effects that follow any extrapolation of quantum size effects to macroscopic levels of observation. Application of the body of knowledge related to the less intricate domain (comparing to quantum physical chemistry) of classical chemistry is thus frequently more practical in describing complex surroundings of particular reactions. In addition to invoking physicochemical concepts related to pH value, ionic strength, viscosity, capillarity, osmotic effects, surface tension, cohesion and adhesion, reference to the laws of thermodynamics should be drawn to explain the effects of heat on the averaged molecular behavior. Hydraulic, hydrostatic and hydrodynamic principles, related to the concepts of water density, buoyancy, viscosity, vorticity, Reynolds number and various complex streamline effects, would be normally employed in attempts to describe and predict the movement of water in relation to solid bodies (as in the context of naval navigation or calculation of flux of water through pipelines or along river beds) immersed in water [51]. Newton's law of gravity may become relevant in the context of explaining tidal effects, whereby to describe the movement of water molecules in a river stream it is also necessary to consult geography, hydrogeology, hydrometeorology, oceanography and climatology. An overall scheme of atmospheric and planetary movements of water molecules in biogeochemical cycles would require reliance on the studies of general Earth science, geophysics and ecology.

8. Contextual definition of energy

We have seen that the movement of individual water molecules in a river stream is not determined by their intrinsic structural patterns only, but by the relations between the latter and the overall context of planetary ecological patterns. Similarly, physical qualities could not be defined non-contextually, that is, without taking into account the complete environment of the entities attributed with specific qualities.

At this point, we can be reminded of the concept of energy. This notion, being one of the basic physical qualities within the empirical tradition of science, could not be defined or employed reasonably with paying one's attention only to relations that constitute the system attributed with the quality of energy. How could we define energy of a passing electron without any reference to the medium through which it passes? As the theory of relativity teaches us, there are only relative movements and relative physical qualities, so that each definition of change has to refer to a fixed frame of reference. Each natural quality is inherently outlined by the qualities of its physical surrounding, as shown in Fig. 10.

The qualitative concept of energy has to be used in reference to the total set of potential effects that arise from interactions between the given system and its environment during their co-evolution in space and time. For practical reasons, this endless range of effects and the corresponding infinitely spreading character of qualities of the system under investigation normally become subdued to finite sets of relations by means of convenient approximations.

Energy could be, therefore, defined as the potential of specific quantitative contributions of a given system to alterations of the order of its environment. Correspondingly, the classical biochemical truism which states that 'structure defines function' might be modified to a conceptual representation according to which the function of a system is a harmony of relations through which a natural whole interacts with its surrounding and, as such, 'spreads' its inherent qualities outward. This way of representing physical qualities is inherent to the quantum field theory, in which physical entities are represented as limitlessly spreading 'rays' of intrinsic qualities. The principle of observing the same qualities of identical species but in different atomic environments is also inherently related to numerous physicochemical characterization techniques. Spectroscopies that employ the effects of nuclear magnetic resonance, Raman scattering, optical, ultraviolet and Mössbauer absorption are some of the techniques in which a sophisticated structural characterization of the system is based on the observation of changes in qualities of specific species that follow modifications of their atomic and molecular surroundings.

Qualities of any natural system thus cannot be said to end with its physical boundaries. Instead, they are determined by the interaction of the system with the physical context of its existence. Our focus should

not be confined to the internal outlines of the investigated system, but opened towards its overall existential context. Such an enlightening shift in awareness from a tight focus on the very physical objects to their contextual interaction corresponds to a paradigmatic shift in our thinking. Just like the meaning of a line, a letter, a word or a sentence could not be evaluated until we get to grasp the larger textual wholes that they constitute, any quality that we endow the physical objects with has to be formed through our reference to the interactive frames larger than the very objects in question. However, the question of where the system ends and where the environment begins will turn out to be increasingly crucial and harder to define as human interference with physical systems becomes more complex and sensitive. For example, even though molecular biologists have traditionally drawn their models against uniformly colored backgrounds, the active volumes of macromolecules are nowadays increasingly drawn so as to extend beyond their formal boundaries, although at the cost of limiting the timescales and conformational spaces that can be assessed in molecular dynamics simulations.

Another point, which if elaborated would trespass the limits of this article, would be that of a co-transformational observational interference between the qualities of the observing system and the properties of the observed system that inevitably takes place during each cognitive and experimental activity. In this context, we could be reminded of Heisenberg's uncertainty principle, which tells us that there are no physical qualities independent of the qualities of the observer. Aside from referring to both intrinsic and contextual physical qualities, each definition of any natural quality, thus, has to refer to the properties of the observer. Simply saying, there are no natural qualities that are not simultaneously experiential, and *vice versa*.

9. Co-assembly as a reflection of a broader philosophy of life

The idea that each self-assembly process is inherently dependent on the physical conditions that surround the 'self-assembled' entities presents a reflection of a wider philosophical and systemic perspective, according to which not a single physical quality could be defined without the reference to its existential context. The notion of self-assembly can be understood as a misnomer and a remnant of an obsolete tradition of knowledge, epitomized by the concepts of monologue, autocracy, linearity and objectivity. The concept of co-assembly is, on the other hand, a natural reflection of the modern ideals of relationship, dialogue, inter-subjectivity and co-creation [52].

However, in the end it is always the interplay between inner organization of the system and its interaction with the environment that is responsible for all the observed qualities thereof. And this is a systemic assertion, which means that it could be applied in case of all natural systems, irrespective of their size and complexity. For example, atomic wave functions depend both on the intrinsic electronic configuration and the interaction with the surrounding atoms. The protein folding processes depend both on the amino acid sequence and the physicochemical surrounding. The folding mechanisms are not determined by the amino acid sequence solely (as proposed by now classical Anfinsen's model), but by numerous environmental factors that proteins are inherently sensitive to, so that changes in the tertiary structure can sometimes produce a drastic effect on the secondary structure of the individual peptide chains, including the occasional transformations of α -helices to β -sheets [53]. Examining peptide structure (and consequently the function) in one environmental context could not be, therefore, directly conversed to another context. For example, transmembrane surface receptors may not exhibit almost any intricate structure at all in the isolated state, but when returned back to their *in vivo*, lipid membrane surrounding, they may immediately display well-defined helices. As stated earlier, due to the tightly coupled dynamics between a protein and the solvent, they are often conceived as a single entity with a unique energy landscape [54]. Proteins can be, in fact, considered as engaged in a continuous feedback interaction in which they influence their

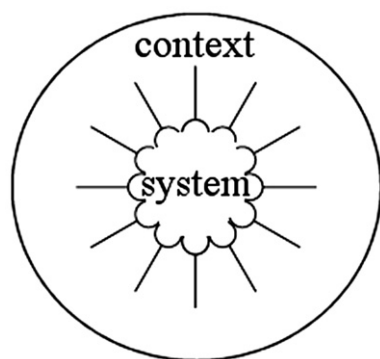


Fig. 10. Qualities ascribed to each natural system are the product of its interaction with a given physical context. Both the physical context and the inner organization of the system are involved in the definition of its qualities. In this drawing, the lines of interaction figuring at the boundary between the system and its environment present the reflections of the system's qualities.

solvation environment, but are in turn “finely tuned” and modified by the latter [55]. As a result of the fact that in spite of the identical primary structure (i.e. amino acid sequence) there is an impossibility of maintaining an unchanging physicochemical surrounding throughout time, no protein molecule ever has exactly the same conformation as any other. Also, due to incessant conformational fluctuations that each macromolecular structure is subject to, no protein molecule has ever existed in the same conformation twice. As we see, sometimes it may not be the intrinsic structural versatility that brings about the qualitative diversity of the system, but incessantly changing existential contexts that are involved in the definition of the qualities of the system are responsible for this effect. Subatomic particles may be, for example, depicted as structurally identical, though their different interrelation with their physical contexts results in their unique qualities. Free electron moving in an electric field and an electron belonging to an atom may have identical intrinsic organization, but differences in physical context endow them with different qualities.

Then, the patterns of expression of a single cell depend both on its genetic structure and the intercellular communication. At more complex levels of biological organization, we may note that neither the paradigms of genetic determinism nor behaviorism could be considered as valid in themselves. The only justifiable explanation of the traits and behavior of biological creatures has to deal as much with the inner factors of development as with the outer, environmental and social ones. Also, the ideas that the evolution of life proceeds only from inside (as envisioned by neo-Darwinian evolutionists) or that it is influenced only from outside (as proclaimed by Lamarck) are nowadays getting merged into co-evolutionary models that explain evolution as a phenomenon in which inner and environmental factors meet. The reason why a stone has adopted a certain shape lies both in its inner atomic composition and thereupon defined crystal structure on one side, and the environmental influences occurring at the stages of its crystallization and aging on the other. In the end, the meaning of each one of these words is partly determined by their intrinsic structure, but partly by the context in which they are found. And so forth.

To sum up, the thesis proposed in this work is not to say that intrinsic molecular factors are not involved in ‘self-assembly’ processes. It is to say that it is the interaction between these inherent properties and predispositions of the studied systems on one side, and the qualities of their physical surrounding on the other, that define when and how the given ‘self-assembly’ phenomena will occur.

In fact, a right balance between the forces responsible for self-organizational perturbations on one side and constructive interactive effects on the other needs to be established for the purpose of reaching superior supramolecular architectures that would be both aesthetically pleasing and pragmatically functional. ‘If the former are predominant, then phase-separated structures will be synthesized, whereas domination of the latter can result in non-equilibrium conjugated architectures’ [33], noticed Stephen Mann of Bristol University. The same harmonious balance between inwardness and interactivity might be acknowledged as essential for a sustainable evolution of the majority, if not all, natural systems.

10. Conclusion

Arguments ranging from the field of physical chemistry to thermodynamics to cybernetics to biological evolution are given in support of the idea that the notion of self-assembly presents a misnomer. Every self-assembly phenomenon is inherently related to restructuring and reorganization of the physical context that enwraps the former. Each self-assembly should be, therefore, strictly saying, considered as a co-assembly. On certain occasions, the corresponding assembly of the physical surrounding seems to be a minor and negligible one, but even then it inevitably conditions the ‘self-assembly’ process. The majority of the provided examples dealt with the use of surfactant mesophases for the formation of fine particles, protein folding processes, DNA structure,

protein–mineral interactions, the role of hydrogen bonds, and the epitaxial assembly effects. In addition, references to the feedback nature of ecological principles, co-evolutionary nature of the interaction between biological entities and their environment, contextual nature of physical measurements and the laws of classical physics were drawn with the purpose of instantiating the physicochemical phenomena of ‘self-assembly’ in a more general, systemic perspective. Thus, there are many reasons why self-assembly should be renamed to co-assembly, or at least redefined so as to represent a unilateral and approximate view of co-assembly processes. The latter perspective could be, however, applied only in situations in which modifications of the physical contexts involved in the assembly are insignificant for the purpose and outlines of the given study.

In the end, the conclusion of this paper falls down to a few simple words proclaimed by Martin Buber: ‘All real living is meeting’ [56]. This is certainly true for the field of modern physical chemistry as well. Today it is involved in a ‘softening’ shift of interest away from the strong bonds and reactions, and towards weak forces and interactions. The need for a more profound understanding of the ‘self-assembly’ phenomena and a more frequent underlying reference to ‘co-assembly’ has been outlined in this work. It would be undoubtedly beneficial for the proper development of both the conceptual models and experimental efforts of the modern physical chemistry.

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