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BioSystems 71 (2003) 297–303
BioSystems
www.elsevier.com/locate/biosystems

Physical law *not natural selection* as the major determinant of biological complexity in the subcellular realm: new support for the pre-Darwinian conception of evolution by natural law

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Received 26 February 2003; received in revised form 16 May 2003; accepted 22 May 2003

Abstract

Before Darwin many biologists considered organic forms to be immutable natural forms or types which like inorganic forms such as atoms or crystals are part of a changeless world order and determined by physical law. Adaptations were viewed as secondary modifications of these 'crystal like' abstract afunctional 'givens of physics.' We argue here that much of the emerging picture of biological order in the subcellular realm resembles closely the pre-Darwinian conception of nature. We point out that in the subcellular realm, between nano and micrometers, physical law necessarily plays a far more significant role in organizing matter than in the familiar 'Darwinian world' between millimeters and meters (where matter can be arranged into almost any contingent artifactual arrangement we choose, as witness Lego toys, watches or jumbo jets). Consequently, when deploying matter into complex structures in the subcellular realm the cell must necessarily make extensive use of natural forms—such as the protein and RNA folds, microtubular forms and tensegrity structures—which like atoms or crystals self-organize under the direction of physical law into what are essentially 'pre-Darwinian' afunctional abstract molecular architectures in which adaptations are trivial secondary modifications of what are evidently primary givens of physics.

Keywords: Pre-Darwinian; Protein folds; RNA folds; Microtubular forms; Nanotechnology

1. Introduction

Before Darwin many biologists adhered to a Platonic conception of nature and believed that underlying the diversity of life is a finite set of lawful natural forms or 'types,' which like crystals or atoms are immutable aspects of the eternal world order (Mayr, 1963; Gould, 2002). Conceiving of organic forms as lawful features of the world, one of the major goals of pre-Darwinian biology was to provide a rational and lawful account of how the diversity of organic forms arose via what are termed the 'laws of form' (Gould, 2002). These laws of form would account rationally for the full range of organic forms in the same way as we today explain the diversity of inorganic forms such as crystals or chemical compounds, by various sets of laws—laws of crystallography, laws of chemistry and so forth. Pre-Darwinian biologists did not deny adaptation but saw adaptations as secondary functional modifications of inherent natural forms what Richard

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doi:10.1016/S0303-2647(03)00100-X

Owen, in his *On The Nature of Limbs* (Owen, 1849) calls "primal patterns." Consequently, pre-Darwinian biologists adhered to a 'form' or 'type' first, function second conception of organic form. Goethe took the Form first position to extremes when he asked (Russell, 1916): "we must not suppose that a bull has horns in order to gore, but we must investigate the process by which it comes to have horns in the first place."

After Darwin the whole lawful scheme was overthrown and organic forms came to be seen as contingent mutable assemblages of matter—'clever artifact like contrivances'—put together gradually during the course of evolution primarily by natural selection for biological function, what Richard Dawkins termed cumulative selection (Dawkins, 1986). Thus, organic forms on earth are now considered to represent a tiny finite contingent set (like a set of Lego constructs) drawn by cumulative selection from what is essentially a potentially infinite number of forms. Moreover, just as physics plays only a minimal role in determining the way the parts of a watch or a jumbo jet or a Lego toy are put together, similarly physics is considered to play only a minimal role in the determination of organic form.

Of course no biologist doubts that some biological forms may be given by natural law, the spherical form of the cell, and the flat shape of the cell membrane might be two examples. But on the whole, physical law is considered to have played a very trivial role in evolution and particularly in the generation of biological form. And despite some notable attempts throughout the past century (Thompson, 1917; Kauffman, 1993; Goodwin, 1994) to invoke a role for physical law in the generation of organic form including Thompson's classic *On Growth and Form* (Thompson, 1917), most biologists have remained unconvinced and still see selection, in Kauffman's (1993) words: "as the overwhelming, even the sole source of order in organisms." However, we argue here that in at least one important area of biology—the subcellular realm—there is now increasing evidence which suggests that a substantial amount of order is given by physics and not selection, providing what we believe is the first convincing challenge to the Darwinian claim that cumulative selection for biological function is the major or sole generator of *all* organic form.

2. Arranging matter in the nanometer world

Because of our familiarity with the assembly of machines, we naturally tend to think that organisms (like engineers) are also free to assemble Darwinian fashion, their 'parts' into any conceivable structure just so long as it may serve some function. This may be true at the organismic or macro level but at the subcellular level, the level between nanometers and micrometers, the behavior of matter is profoundly influenced by a host of physical and chemical forces remote from everyday experience (Lehn, 2002; Whitesides and Grzybowski, 2002). In this alien nano-world even individual atoms can exert remarkable effects as witness the phenomenon of Brownian motion. Here the constraints of physics are ubiquitous and ever present and matter cannot be easily assembled at will into any preferred contingent form (Lehn, 2002; Whitesides and Grzybowski, 2002). This is a world far more like that of chemistry than engineering.

An obvious solution to the problem of deploying matter into complex structures in the nano to micrometer realm is the use of natural forms, like atoms or crystals, which can self-organize under the direction of physical law into complex spatial arrangements. This is now the preferred solution sought by supramolecular chemists and nanotechnologists (Lehn, 2002; Whitesides and Grzybowski, 2002; Sowerby et al., 2001). As Lehn (2002) points out, the goal of supramolecular chemistry and nanotechnology is to gain "increasing control over the complex spatial (structural) and temporal (dynamic) features of matter through self-organization. Self-organization offers to molecular nanotechnology an alternative to both top down miniaturization and bottom up nanofabrication approaches by passing the implementation of tedious fabrication and manipulative procedures." Self-organization is of course how form arises in the inorganic world (Ball, 1999). Galaxies, snow flakes, molecules, drops of water, are all self-organizing natural forms. Each arises as a result of the self-organization of a particular type of matter, in restricted conditions under the direction of natural law. Each represents an abstract ahistoric material 'primal pattern.'

Despite the challenge of assembling contingent arrangements of matter—'Lego like assemblages'—in

the subcellular realm, there is of course no question that a good deal of the spatial order in the cell is 'clever contrivance' and many complex structures, including the bacterial flagellum, phage capsids, cilia, and so forth, are contingent arrangements of matter and their assembly a strikingly mechanical affair. However, it is also increasingly apparent that cells do indeed make very extensive use of self-organization to deploy matter into what are clearly non-contingent—atom or crystal like—complex three-dimensional natural forms.

3. Protein folds

Consider the case of the protein folds. Although entirely counter intuitive, the complex spatial arrangements of the amino acid chains in the 1000 protein folds are as natural and necessary as the arrangements of subatomic particles in atoms or atoms in molecules (Denton and Marshall, 2001). This is now the inescapable conclusion of the past 30 years of research into protein structure and folding which have shown that the protein folds used by life on earth represent a set of about 1000 natural and immutable forms, which like atoms or crystals arise from the natural intrinsic self-organizing properties of their constituents, in this case—amino acid polymers (Ptitsyn and Finkelstein, 1980; Chothia and Finkelstein, 1990; Banavar and Maritan, 2003). Moreover, a number of organization rules, 'laws of form,' which govern the local interactions between the main structural submotifs have been identified, and these restrict the spatial arrangement of amino acid polymers to a tiny set of about 1000 allowable higher-order architectures (Ptitsyn and Finkelstein, 1980; Chothia and Finkelstein, 1990). These rules are analogous to the laws of chemistry or rules of crystallography which determine the form of molecules and crystals or the rules of grammar which determine the form of meaningful letter and word strings in a language. These are nothing more nor less than a set of 'laws of form' like those sought after by pre-Darwinian biology to account lawfully for the diversity of form in the organic world. It is not, as is commonly supposed, the amino acid sequences which specify the three-dimensional form of a protein fold, but rather the abstract laws of protein form. Each of the 1000 allowable folds represents a preferred arrangement of matter which corresponds to an energy minimum (Ptitsyn and Finkelstein, 1980; Banavar and Maritan, 2003). This acts as a pre-existing mold or attractor, drawing the amino acid sequence from its initially disordered structure to its final and predetermined native conformation. So the forms of the folds are given by physics and matter is drawn by a process of free energy minimization into the complex form of the native conformation. In effect, a complex set of three-dimensional atomic architectures is given 'for free' providing life with a wonderful tool box of complex forms on which to build adaptive functions and the whole protein-based biochemistry of life (Denton et al., 2002; Banavar and Maritan, 2003).

Of course no protein fold used in the cell is a purely 'abstract afunctional structure' like a crystal or an atom. On the contrary, every fold is adapted for some biological function. But these are invariably secondary adaptations of what are clearly 'abstract atomic patterns'—natural forms. In the case of some of the so-called superfolds such as the triosephosphate isomerase (TIM) barrel, an eight stranded alpha/beta bundle the same fold is secondarily modified for many completely unrelated enzymic functions (Brandon and Tooze, 1999). The globin fold has also been secondarily modified as evidenced by the various functional adaptations to oxygen uptake and carriage exhibited by myoglobin and the various vertebrate haemoglobins.

The biological fitness of the folds is greatly enhanced by their accessibility in sequence space. It is now clear that many different amino acid sequences can fold into the same three-dimensional form (Brandon and Tooze, 1999) and sometimes the same sequence can fold into two different folds (Cordes et al., 2000). Evidently, the rules of fold form are highly restrictive at the level of three-dimensional structure, permitting only 1000 atomic patterns, but highly permissive in terms of sequence—a high proportion of sequences can fold into one or another fold. By analogy with language, we might think of the rules of syntax (fold architecture) as being very strict but the rules of spelling (fold sequence) very lax. Consequently, although the folds are immutable and discontinuosly distributed in fold space they can still be easily found (spelt) in sequence space and utilized by the cell.

4. RNA folds

Another set of 'pre-Darwinian' lawful self-organizing forms utilized by the cell to deploy matter into complex three-dimensional conformations are the RNA folds. Although less in known about the determinants of RNA structure, the various secondary structural motifs—hairpin loops, the A-form double helix, pseudoknots, etc., (Moore, 1999; Burkard et al., 1999) are also like the alpha helix and beta sheet in proteins, natural forms which spontaneously arise out of the intrinsic properties of RNA polymers. These motifs self-organize into complex three-dimensional structures which represent the native conformations of RNA molecules (Moore, 1999; Burkard et al., 1999). The process of folding of the RNA molecule is also driven like the folding of a protein by free energy minimization which draws the RNA polymer like the amino acid polymer into a defined energy minimum (Burkard et al., 1999; Russell et al., 2002). Consequently, like proteins, RNAs exhibit self-organizing robustness. They fold into their native structures via multiple paths (Russell et al., 2002) and are tolerant of changes in primary structure (Fontana and Schuster, 1998). Many very dissimilar sequences can sometimes fold into the same form such as the hammerhead ribozyme (Salehi-Ashtiano and Szostak, 2001). Again, like some proteins, RNA sequences are known which can fold into two completely different structures (Schultes and Bartel, 2000). So, although RNA folds are discontinuously distributed in sequence space (Salehi-Ashtiano and Szostak, 2001; Fontana and Schuster, 1998), they are relatively common and easy to find—spelling is lax, syntax strict. Consequently, the RNA folds are, in the words of Schultes and Bartel (2000), "attractive biopolymers for the birth of new functional folds in early evolution." Again, like the protein folds each RNA fold utilized in the cell is adapted for some biological function. The hammer head ribozyme for cleaving RNA, the tRNA and ribosomal RNA folds for protein synthesis.

Whether there is a very limited set of a few thousand RNA folds as in the case of the proteins is not known. Nevertheless, it is clear that the number of folds is bound to be, as in the case of the proteins, vastly less than the number of possible sequences. And it is also clear that in the case of both proteins and RNAs, three-dimensional forms are determined by constructional rules—'laws of protein form' and 'laws of RNA form' reminiscent of the pre-Darwinian laws of form. Ultimately, at least in principle, it should be possible to predict all protein folds and all RNA folds from knowledge of their respective 'laws of form.' In short, both protein and RNA folds are natural self-organizing forms.

We note further that physical law determines not just the intricate spatial arrangements of atoms in each fold (RNA and protein) and their accessibility in sequence space, but intriguingly provides an abundance throughout the cosmos of the proteogenic amino acids and nucleotide bases out of which the folds are constructed (Miller, 1987). The fact that cells use protein and RNA folds is evidently a matter of law, not contingency. In this context Salehi-Ashtiani and Szostak comment on the in vitro evolution of the hammerhead ribozyme (2001): "Our results suggest that the evolutionary process may have been channeled, in nature as in the laboratory, towards repeated selection of the simplest solution to a biochemical problem." This channeling is surely not only towards the hammerhead ribozyme, but also towards the whole basic set of protein and RNA forms utilized by the cell. We speculate that these two sets of forms may be the most accessible types of self-organizing macromolecular forms and that carbon-based life throughout the cosmos may utilize the same basic tool kit of protein and RNA folds.

5. Supramolecular forms

Proteins and RNAs are examples of static self-organizing forms, systems at global or local minima which may require energy to form but once formed do not require an input of energy. Another type of self-organizing forms used by the cell are dynamic and energy dissipating—where the interactions responsible for the formation of structures or patterns between components only occur if the system is dissipating energy (Whitesides and Grzybowski, 2002).

The classic biological example of a dynamic self-organizing system that arises spontaneously from its basic constituents is the bipolar aster. At each cell division the spindle apparatus organizes itself out of microtubules and molecular motors. A striking fact about the self-organization of the bipolar aster is that

each time it self-organizes into its final form, it follows (like a protein folding) a different path to its final form. In addition, like a protein fold, the spindle is robust and able to recover its 'correct form' after all manner of perturbations. The process was described by Kirschner and Mitchison (1986): "Dynamic instability produces a rapid turnover of microtubule configurations and intermediate structures produced during prometaphase in genetically identical cells are highly variable. This variability goes far beyond thermal fluctuations, so that in each cell division a different sequence of structures is produced in the pathway of spindle morphogenesis. The most stable configuration at metaphase is reached *not by following a map* (or blueprint) *but by following a gradient of increasingly more stable structures*" (our emphasis). In other words, the final form represents some sort of natural free energy minimum which draws the components of the aster into what is a preferred or lawful conformation.

The aster is not the only microtubular form, which arises by the self-organization of microtubules and molecular motors. Merely by altering the relative concentration of the motor protein kinesin and tubulin it is possible to generate a variety of microtubular forms in vitro (Nedelec et al., 1997). These diverse forms are the 'lawful' outcome of local dynamic interactions between a few basic molecular components. These studies imply that microtubular forms represent another set of afunctional, ahistoric forms—pre-Darwinian types, which arise spontaneously, like the protein and RNA folds, out of the intrinsic properties of their basic material constituents governed by a unique set of constructional rules.

Another means by which the cell appears to deploy matter into complex ahistoric three-dimensional forms is by the exploitation of tensegrity (Stamenovic and Wang, 2000; Boal, 2002). Tensegrity structures in the cell consist of microtubules (compression elements) and microfilaments (elastic tension bearing elements). When stress is applied to these tensegrity structures they undergo discrete types of transformations which reverse when the pressure is released. One classic set of tensegrity structures are the various geodesic forms seen in the coated pits and in various cell membranes such as that of the red blood cell (Jandl, 1996). Although the study of cellular tensegrity structures is only just beginning, it seems likely that they will represent another set of abstract material patterns governed by a set of rules—laws of form—which predict a finite set of ahistoric stable architectures constructed out of a few basic elements (microtubules and microfilaments).

We note here in passing that studies of cellular automata like those of Wolfram (2002), show not only how easily complex global forms (analogous to a protein fold or the aster) can be generated by simple rules defining a set of local interactions between participating components (analogous to interactions between alpha helices, molecular motors, microtubules, etc.) but also illustrate that such global forms are bound to be fundamentally non-adaptive and afunctional patterns. In other words 'rule generated order' always gives Owen's ahistoric 'primal patterns.' And this implies that if self-organization plays a significant role in the generation of cellular and organismic form then there may be more non-adaptive order in biology than most biologist currently accept.

6. Form first 'primal patterns'

It is clear that an impressive and growing inventory of organic forms utilized by the cell are evidently natural forms and givens of physics—abstract afunctional architectures which are genuine universals, which like atoms or crystals will occur throughout the cosmos wherever there is carbon-based life. Of course all the self-organizing forms utilized by the cell are also secondarily adapted to serve various biological functions.

The globin fold, for example, is adapted to transport oxygen. The hammer head ribozyme is adapted to cleave RNA and the bipolar aster to separate chromosomes. In many cases, basic forms are adapted to function together in multimolecular complexes such as the ribosome and transcriptional assemblies. Nor is there any doubt that these secondary adaptations are contingent modifications put together by selection. But the role of selection in shaping this vast and rapidly growing inventory of forms is clearly trivial and secondary. We can think of each protein and RNA fold, each microtubular form and tensegrity structure as being an abstract atomic pattern analogous to one of Owen's (1849) "primal patterns" upon which a variety of adaptive solutions are secondarily imposed. The core order of each form, whether it be the globin fold, the

tetrahymena ribozyme, the bipolar aster or a geodesic tensegrity structure, is not a contingent arrangement of matter put together by selection (analogous to a Lego toy or watch), but a physically determined abstract arrangement of atoms like a crystal or a molecule.

The emerging world of abstract subcellular form corresponds in a remarkable way to the pre-Darwinian conception of nature. The overall picture would certainly have appealed to Goethe and Owen! Interestingly, even the in vitro selection method used to search for new RNA folds (Beaudry and Joyce, 1992) involves two basic steps which echo the pre-Darwinian conception of evolution. This strategy involves firstly a search of fold space for a natural RNA fold (equivalent to one of Owen's primal patterns such as the pentadactyl pattern of the vertebrate limb) and secondly, subjecting the fold to Darwinian evolution to optimize function (equivalent to modifying the basic primal pentadactyl pattern into an adaptive structure—a flipper or a wing).

7. Intrinsic robustness

We have argued here that at the nano to micro level, cells (like nanotechnologists) are obliged to, and indeed do make extensive use of natural self-organizing forms to deploy matter into complex three-dimensional structures, thereby providing 'complexity for free.' Their use may however, be of necessity for another reason. Natural self-organizing forms possess an intrinsic natural robustness—a massive and surely decisive advantage over contingent mutable 'artifact like' forms. The protein folds, for example, recover their native conformations after all manner of deformations caused by the continual buffeting they suffer in the cells interior. This robust ability to find their way to their native form *from various starting points via various paths* is a simple consequence of their being natural forms. 'Nature' as it were is continually drawing a partially unfolded protein back via a multitude of different paths into its free energy minimum, just as a ball in a bowl is continually drawn back to the bottom of the bowl. The folds are also highly tolerant of variations in their amino acid sequences (this follows from the fact that the rules of spelling are lax—see above). Thus they are also robust in the face of mutational insults. Like the protein folds, the RNA folds, the spindle apparatus, and tensegrity structures all exhibit the same robust ability to achieve and maintain their native conformations in the face of multiple challenges. The contrast between the robustness of such natural forms and 'fragility' of contingent assemblages like the bacterial flagellum, various bacteriophage particles, transcriptional assemblies etc., is striking. The assembly of these 'bio-artifacts' occurs generally along highly defined paths and is highly liable to mutational disruption as witness the vast number of individual mutations which disrupt bacteriophage assembly (Lewin, 1977). Moreover, such contingent forms cannot arrive at their proper form from multiple starting points and via multiple routes. The lack of robustness of such 'bio-artifacts' contrasts with the robustness of natural self-organized forms such as the protein folds or spindle apparatus. We suggest that the lack of natural robustness makes it unlikely that even if the cell could create all its three-dimensional complexity by assembling contingent arrangements of matter we doubt if such 'fabricated cells' would possess the necessary robustness to thrive and reproduce.

8. Conclusion

We have proposed here a novel interpretation of the subcellular realm as an emerging 'pre-Darwinian world' in which much of the molecular and supramolecular architecture consists of self-organizing natural forms determined by physical law, in which adaptations are secondary modifications of what are clearly afunctional and ahistoric primary 'givens of physics.' The subcellular world is thus the first important realm of biology in which the early 19th century idea of evolution by natural law discarded as archaic by most biologists since Darwin, is being finally vindicated. We are intrigued by the many similarities between the pre-Darwinian world view and the developing picture of life at the nano level and particularly by the fact that if nanotechnology is ever to achieve its goal of self-replication then it will have to utilize, *not advanced machines*, but *self-organizing natural forms* reminiscent of the natural types of early 19th century biology. We also predict that many of the organic forms used by cells on earth may be genuine universals and occur in carbon-based cellular life throughout the cosmos.

We conclude that the subcellular realm is a *Form* first *Function* second world where physics rules, where order arises from the self-organizing properties of matter and where the pre-Darwinian metaphor of the crystal is fast eclipsing the post-Darwinian metaphor of the watch.

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