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New perspectives on morphogenesis

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Introduction

P. S. O'Shea

Department of Biology, The Open University, Milton Keynes MK7 6AA (England)

The Oxford English Dictionary defines Morphogenesis (Biol) as "that branch of biology which is concerned with the form of animals and plants, and of the structures, homologies and metamorphoses which govern or influences that form". Before modern methods of biological analysis became available, mathematical studies seemed to provide the most accessible route to understanding biological form. D'Arcy Thompson's celebrated essay *On Growth and Form* (1917) is an eloquent example of just how valuable mathematical (geometrical) considerations may be for describing biological structure and also asking the question "why is it like that"? And how he might have looked with admiration at the beautiful 'living' crystals described by Bob Williams and his team.

Mathematical treatments of form have met with mixed success, which may account for the fact that the very attempt has been a topic of lively debate for some time. Watson, for instance in his Silliman Lectures, *Paleontology and the Modern Biology* (New Haven 1951), takes the completely antithetical view to D'Arcy Thompson that "Morphology is a form of logical thought remarkable in that it is not mathematical; indeed its essential elements are not susceptible of mathematical expression" (p. 3). Although, I think the latter merely reflects a different view (or definition) of mathematics otherwise Watson would find himself at odds with virtually all contemporary thought in morphology. Whilst it must be conceded that mathematical descriptions of static biological forms leave a lot to be desired, quantitative treatments of metamorphosis are much more tractable, some of the more fruitful attempts are mentioned by Brian Goodwin in his generalised introductory essay.

With the advent of modern biological and biochemical analysis, the 'spirit was made flesh' and the nature of the living system became more transparent. Huge advances in cell biology, physiology and biochemistry etc. were accompanied by a growing awareness of the nature of morphogenesis. It still remains, however, a rather diffuse research area (it is not even as specific a topic as, say, biochemistry). For even cytodifferentiation, a subject close to the hearts of developmental biologists, may or may not be considered morphogenesis. It may be considered to encompass a variety of disciplines such as comparative anatomy, as well as studies of microscopic 'forms' such as cell surfaces or multi-enzyme complexes. Whilst morphogenetic studies of the former traditionally belong in the domain of evolution, the latter is considered to be molecular biophysics or enzymology. Although fundamental laws (thermodynamics) must be obeyed throughout morphogenesis, some states are preferred despite being equivalent. Certain forms may be expedient and predominate because of historic considerations. Similarly, the principles dictating macroscopic form are not necessarily the same as those dictating molecular form, all this, of course, depends upon how one defines one's terms and one's perspective, for molecular geometry is no less important than anatomy in its relationship to a specified biological function. It is not surprising, therefore, that morphogenesis may be 'all things to all Men'. Consequently and perhaps unfortunately, it is very unusual for an individual to become sufficiently aware of the many aspects of natural sciences, which are necessary to address the many fundamental questions of morphogenesis. An appropriate corruption of Carroll (1865) springs to mind *"you have to run as fast as you can to stay where you are"*.

This latter problem is compounded because the whole conceptual basis of cellular organisation is in a state of flux. The cell has ceased to be the reductionists 'water-filled bag of enzymes and compartments (containing enzymes)'. Eucaryotic cells are now perceived to be very elaborate and to possess many of the properties of long-range organisation. In my opinion this has not ended with the relatively recent discoveries of the cytoskeleton and the extra-cellular matrix; some properties remain to be discovered or have yet to receive widespread recognition. For even at the time of writing these reviews (Summer 1987), in a lecture to the International Botanical Congress held in Berlin, Jeff Schatz stated "... that some of the most important structures of the eucaryotic cytoplasm are still unknown". Thus, how can the developmental biologist understand cellular morphogenesis if the structure (initial, intermediate or final) is unrecognisable?

With this latter point in mind, many universities (whether they are aware of it or not) teach their students that cytoplasm behaves like a sort of nutrient broth serving up the cell with whatever is required. Any 3-D structure exhibited by the whole cell (e.g. the doughnut shape of erythrocytes) is merely a consequence of the architectural attributes of the cytoskeleton. The cytoplasm may seem, therefore, to be a completely homogeneous soup with its elements (soluble proteins, metabolic substrates, ions, water, etc.) exhibiting chaotic behaviour as a result of Brownian motion. Consequently, it is almost counter-intuitive to expect the cell to 'spontaneously' generate and consolidate spatial pattern. On this basis, biologists have looked to the genome as the causal or directive agent of morphogenesis. Yet, it may be argued that such a response does not even address the question. Nevertheless, not even the most zealous neo-Lamarckist would argue that the gene does not have its role to play (although I have probably come across one or two who would try). Before continuing, however, perhaps I ought to mention that some opinions presented by individuals throughout this review synthesis do not necessarily represent those of the other contributors.

Thus far I have suggested that there are three major limitations to understanding the fundamental principles or mechanisms underlying morphogenesis: i) The problem has only recently been identified. ii) Multi-disciplinary analyses (both experimental and theoretical) are necessary. iii) Important structures within the eucaryotic cell remain to be recognised.

This review series is then, amongst other things, an attempt to focus attention on all three of these basic problems. Replying in order to: i) Professor Goodwin has related some of the valiant attempts to devise unifying theories of morphogenesis of which there have been many failures, mainly related to the problem of definition I mentioned above. What is required is a causal mechanism which explains how characteristic biological forms arise from an apparently homogeneous origin within a specified time domain. Goodwin does indeed describe some solutions to this problem. Despite this I am sure he would also concede that morphogenesis still remains a phenomenon in need of rigorous characterisation. It is necessary to ascertain which 'forces' coupled with certain genetic and biochemical mechanisms within a specified spatial domain elicit a given morphological response. But, at least the problem has now been identified and restated such that it may be addressed. Hence, this review series begins with a brief history of developmental biology and by stating and then reformulating the problem of morphogenesis. With some of these notions in mind Stern and Canning then take up the story by considering gastrulation, a much-studied process that has occupied a place fairly central to what most people's idea of morphogenesis really is.

ii) Of vital importance is the emergence of several non-invasive techniques to study developing systems. Three of the most promising are represented in this review series and are described by Lohman and Ratcliffe (NMR imaging), Swithenby (SQUID magnetometry) and Nuccitelli (vibrating electrode). Perhaps the most valuable attribute of these techniques, however, is that they provide spatio-temporal information about the nature and disposition of structures within and around single cells or tissues. Similarly, David Deranleau has developed an ingeneous light-scattering method to look at changes of cell shape with a time window not covered by the other techniques. Together with techniques such as FRAP (*F*luorescence *R*ecovery *A*fter *P*hotobleaching) to monitor membrane development and spectroscopic studies of ions as reported by indicator dyes (such as Fura-II) and the X-ray microprobe, it means that at last, a solitary living cell may be examined at the molecular level. And by coupling these new technical advances with the more established electrophysiological, biochemical and molecular genetic studies, we now have a most powerful repertoire of techniques with which to study morphogenesis and cell biology.

iii) Finally, the question posed by Jeff Schatz is addressed in terms of well-established physicochemical concepts: Professor Williams and co-workers, Professor Nuccitelli and myself discuss the principles of bio-molecular assembly and physical fields in order to show that the cell is a complex ordered dynamic system. Similarly Deranleau considers stochastic mechanisms responsible for cell metamorphosis. In my contribution which ends the review series, I have attempted to catalogue those physical fields which may be significant in cell biology and morphogenesis.

This review series was originally conceived to consider biophysical aspects of cell biology but it evolved to address the exciting problems of morphogenesis. One should not really attempt to address such a problem without some recourse to molecular biology (i.e. genes) but space would not permit such a luxury. We hope, however, that we have provided more than enough food for thought, for the most striking element of this review synthesis is that it illustrates a technical and intellectual revolution is taking place from which morphogenesis will surely yield its secrets.

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