Life

In search of the simplest cell

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Top-down, bottom-up; RNA-based, lipid-based; theory, experiment — there are many different ways of investigating what constitutes a 'minimal cell'. Progress requires finding common themes between them.

In investigating the origin of life and the simplest possible life forms, one needs to enquire about the composition and working of a minimal cell that has some form of metabolism, genetic replication from a template, and boundary (membrane) production. Approaches to this intriguing problem are discussed in Tibor Gánti's *The Principles of Life* (Oxford Univ. Press, 2003), and were also debated at a meeting last December*.

Identifying the necessary and sufficient features of life has a long tradition in theoretical biology. But living systems are products of evolution, and an answer in very general terms, even if possible, is likely to remain purely phenomenological: going deeper into mechanisms means having to account for the organization of various processes, and such organization has been realized in several different ways by evolution. Eukaryotic cells (such as those from which we are made) are much more complicated than prokaryotes (such as bacteria), and eukaryotes harbour organelles that were once free-living bacteria. A further complication is that multicellular organisms consist of building blocks — cells — that are also alive. So aiming for a general model of all kinds of living beings would be fruitless; instead, such models have to be tied to particular levels of biological organization.

Basically, there are two approaches to the 'minimal cell': the top-down and the bottom-up. The top-down approach aims at simplifying existing small organisms, possibly arriving at a minimal genome. Some research to this end takes *Buchnera*, a symbiotic bacterium that lives inside aphids, as a rewarding example (A. Moya, Univ. Valencia). This analysis is complemented by an investigation of the duplication and divergence of genes (A. Lazcano, Univ. Mexico). Remarkably, these approaches converged on the conclusion that genes dealing with RNA biosynthesis are absolutely indispensable in this framework. This may be linked to the idea of life's origins in an 'RNA world', although such an inference is far from immediate.

Top-down approaches seem to point to a minimum genome size of slightly more than 200 genes. Care should be taken, however, in blindly accepting such a figure. For example, although some gene set A and gene set B may not be common to all bacteria, that does not mean that (A and B) are dispensable. It may well mean that (A or B) is essential, because the cell has to solve a problem by using either A or B. Only experiments can have the final word on these issues.

There was general agreement that a top-down approach will not take us quite to the bottom, to the minimal possible cells in chemical terms. All putative cells, however small, will have a genetic code and a means of transcribing and translating that code. Given the complexity of this system, it is difficult to believe, either logically or historically, that the simplest living chemical system could have had these components.

The bottom-up approach aims at constructing artificial chemical supersystems that could be considered alive. No such experimental system exists yet; at least one component is always missing. Metabolism seems to be the stepchild in the family: what most researchers in the field used to call metabolism is usually a trivial outcome of the fact that both template replication and membrane growth need some material input. This input is usually simplified to a conversion reaction from precursors to products.

Even systems missing one or the other component can, of course, advance our understanding. Such systems could be called 'infrabiological', because they are not quite biological but are similar to living systems in some crucial respects: elementary combinatorics suggests that out of metabolism (M), boundary (B) and template (T) three dual systems can be built — MT, MB, TB. In particular, coupling of compartment formation with some form of template replication (TB) is the subject of many experiments.

Following earlier work on liposomes (P. Walde, Univ. Zurich), protein expression in these entities has become a viable prospect: liposomes are tiny bags with walls made of layers of phospholipids, like the phospholipids that make up cell membranes. Even composite systems incorporating gene transcription and translation are now possible in liposomes. For example, an artificial stretch of DNA can harbour the gene for T7 RNA polymerase, an enzyme that catalyses the production of RNA from DNA, which in turn induces the expression of green fluorescent protein as an indicator of translation (T. Yomo, Univ. Osaka;

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100 YEARS AGO

The Preparation of the Child for Science. **A great change in the character of the books concerned with the teaching of science has taken place during the last twenty years or so. A quarter of a century ago the claims of science to a place in the school curriculum were being advocated vigorously, and men of science had still to convince reigning schoolmasters that no education was complete which ignored the growth of natural knowledge and failed to recognise that an acquaintance with the phenomena of nature is necessary to intelligent living. Speaking broadly, it may be said that most classicists even admit now that there are faculties of the human mind which are best developed by practice in observation and experiment. One consequence of the success which has followed the persistent efforts of Huxley and his followers – to secure in the school an adequate recognition of the educative power of science – has been that modern books on science teaching are concerned almost entirely with inquiries into the best methods of instructing young people, by means of practical exercises, how to observe accurately and to reason intelligently.**
From *Nature* 2 February 1905.

50 YEARS AGO

Principles of Geomorphology. **Geomorphology as a science has grown up in the railway age. A hint of what was coming might be espied in those eighteenth-century travellers who, like Gilpin, began very haltingly to display an interest in the form of landscape rather than its formalized versions. A hundred years later and the trains have reached Lucerne; soon we are well into the age of physiography, that pleasant ill-defined compost which made an agreeable part of the later Victorian education. A further hundred years, and this lively branch of science has given birth to a remarkable variety of new and odd words such as pediplains, steptoes and fluviraption… Progress has been rapid; yet the discussion of the characteristics, origin and development of land-forms will long continue to provide an attractive and challenging mental discipline and a valuable education. Geomorphology not only gives scope for the exploratory and cartographical type of mind but also allows abundant opportunity to increase with time the precision of measurement, examination and analysis. Probing, indeed, may gradually replace mapping in this as in other fields.**
From *Nature* 5 February 1955.

K. Tsumoto, Mie Univ., Tsu). The snag is, of course, that these systems contain components taken from contemporary cells, and are far from being self-sufficient.

Replication can also happen in liposomes. RNA from the phage Qβ (a virus infecting bacteria) can be incorporated in liposomes (T. Yomo) and be replicated by a replicase enzyme provided by the experimenter. A common by-product of RNA replication is the advent of smaller, faster-replicating mutant RNA molecules, which take over the population. This apparently failed to happen in these experiments, but the reason is debatable. Maybe self-association of template and copy strands reduced competition to such an extent that coexistence is guaranteed (G. von Kiedrowksi, Univ. Bochum). Or perhaps the efficient mutants simply failed to arise owing to the small number of replication cycles (E. Szathmáry).

Experimental work is increasingly being complemented by computational investigations. For example, it is possible to account for the growth and fission of compartments in simulations of molecular-assembly dynamics (T. Igekami, Univ. Tokyo). On the genetic side, the origin of heredity was demonstrated in a simulated system of cross-catalytic autocatalytic networks (K. Kaneko, Univ. Tokyo). Kaneko argued that 'minority control' is a possible origin of heredity in a bag of genes that constitutes a primordial genome, in that genes with a lower copy number have a more decisive influence on the protocell's simulated behaviour. It is difficult to assess the importance of this finding, as there is no example of the particular network modelled. But the idea may prove helpful in attempts to produce more realistic constructions.

According to the 'composome' model, in which micelles or vesicles are formed from amphiphilic compounds — those having one end that is hydrophilic and the other hydrophobic — there is the prospect of constructing a 'lipid world'. Here, a hereditary component arises from alternative autocatalytic sets of lipids (D. Segré, Harvard Med. School).

Clearly, there is a divide between the top-down and bottom-up approaches, and between theoretical and experimental investigations. In the future, for example, one would like to see more realistic models of the primordial genome and, conversely, an experimental approach to the lipid world. An aim in the coming years will be to bridge those gaps — hence the great value of meetings such as this. ■

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Surface chemistry

Approximate challenges

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There is growing evidence that the usual approach to modelling chemical events at surfaces is incomplete — an important concern in studies of the many catalytic processes that involve surface reactions.

To describe all the transformations through which a molecule must go during a chemical reaction is a daunting task. The intermediate transition states of a reaction are hard to examine directly, and theory is needed to obtain a full understanding of all the relevant interactions. In 1927, Born and Oppenheimer formulated an 'approximation', which greatly simplified such calculations. Their theory has been crucial to advances in theoretical and chemical physics. It is therefore of great interest when the Born–Oppenheimer approximation breaks down, which may be the case particularly for reactions that take place at surfaces. On page 503 of this issue[1], Jason White and colleagues provide the clearest example to date of such a case.

The break-up of a chemical bond involves a large bond vibration — in other words, a large relative motion of the two atoms that make up the bond. Rather than taking into account all the interactions involved, the Born–Oppenheimer approximation treats the motion of atomic nuclei separately from electronic excitation. This is justified by the fact that nuclei are much heavier than electrons and move more slowly. Therefore — it is assumed — when nuclei move, as they do during the formation or breaking of a bond, electrons will simply readjust quickly.

Many theoretical methods use this approximation, and solve the Schrödinger equation (the fundamental equation that describes all such interactions) in terms of electrons moving in slowly changing, stationary frameworks of nuclear arrangements. The result can be visualized as a 'potential-energy surface', which plots the solutions of the Schrödinger equation as a function of a molecule's changing structure during a reaction — a popular method for describing chemical reactions. However, although the Born–Oppenheimer approximation has been widely tested for gas-phase reactions and its limitations are known, the situation for reactions at surfaces is much less clear.

In their experiments, White and colleagues[1] prepared nitric oxide molecules in highly excited vibrational states, so that the atoms were subjected to large motion, close to the limit at which the molecules will break up. The excited molecules were scattered from a specially prepared metal surface from which electrons could escape easily. A detector above the surface picked up any electron emission. The experiment's main observation was that when the vibrational energy of the incident nitric oxide molecule exceeded the binding energy of electrons in the surface, electrons were directly emitted from the surface. This finding points to a coupling between nuclear motion and electronic excitation, and therefore indicates that the Born–Oppenheimer approximation is invalid in this case.

The research by White *et al.* extends work in which electronic excitation was produced at metal surfaces by bombardment with various gas-phase species (mostly atoms such as oxygen, hydrogen and nitrogen, high-kinetic-energy rare gases and some molecules)[2,3]. In one of these experiments[3], electrons in the metal tunnelled through a potential-energy barrier to a semiconductor substrate as a result of the bombardment. The charge flow induced in the semiconductor as a result of the tunnelling electrons was termed a 'chemicurrent', to reflect the chemical cause of the electronic excitation.

Although these previous results also point to a breakdown of the Born–Oppenheimer approximation, the situation is somewhat harder to interpret because the electronic excitation is most probably mediated by 'phonons' — vibrational excitations in the substrate itself. White and colleagues' experiment bypasses this poorly defined intermediate step.

Experiments of the type presented by White *et al.* (and the closely related chemicurrent work[3]) serve as a warning over the widespread use of potential-energy surface models, and should act as an impetus for modifying the conceptual framework used in surface chemistry. There have been attempts to include electronic excitation in theoretical models, but the task is a daunting one and has been limited by a lack of clear experimental findings. The new experiments provide well-characterized results to guide further theoretical development. ■

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