

## Question 7: The First Units of Life Were Not Simple Cells

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**Abstract** Five common assumptions about the first cells are challenged by the pre-biotic ecology model and are replaced by the following propositions: firstly, early cells were more complex, more varied and had a greater diversity of constituents than modern cells; secondly, the complexity of a cell is not related to the number of genes it contains, indeed, modern bacteria are as complex as eukaryotes; thirdly, the unit of early life was an ‘ecosystem’ rather than a ‘cell’; fourthly, the early cell needed no genes at all; fifthly, early life depended on non-covalent associations and on catalysts that were not confined to specific reactions. We present here the outlines of a theory that connects findings about modern bacteria with speculations about their origins.

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The criteria needed to help us choose between origins-of-life models are, as for other models, elegance in explaining the data and facility in generating testable predictions. Good models, however, should do more than this: they should help explain other problems. In the case of the early cell, the model might be expected, for example, to tell us something about modern cells, about how the cell cycle is regulated, about how they negotiate phenotype space and in particular about the nature of the bacterial cell (Norris et al. 2004).

Answering the question ‘what is a bacterium?’ entails answering questions that include: ‘what does a cell contain?’, ‘how is it structured?’ and ‘what is it doing?’ Much thinking about the constituents of cells is devoted to nucleic acids and proteins; however, other constituents of major importance include water, ions, poly- $\beta$ -hydroxybutyrate, polyphosphate, polyamines, lipids, polysaccharides and metabolites. To take an example that may be unfamiliar, poly- $\beta$ -hydroxybutyrate and polyphosphate are simple compounds that together form an ion channel in membranes with a selectivity that can be determined by association with peptides (for references, see Norris 2005). Modern cells cannot be understood if their major constituents are ignored and neither, we contend, can early cells.

What of the structures to be found in a bacterium? Advances in microscopy over the last decade or so have led to the proposal that a level of organisation exists mid-way between genes/proteins and whole cells. This is the level of hyperstructures (Norris et al. 1999). In this hypothesis, hyperstructures are spatially extended assemblies of molecules and macromolecules, that are essentially of either a non-equilibrium or an equilibrium nature, that command signalling molecules and macromolecules, that interact with one another, and that determine the phenotype of the cell. The list of candidate hyperstructures includes ribosomal or ‘nucleolar’ hyperstructures, transertion hyperstructures, putative phosphotransferase system and glycolytic hyperstructures, chemosignalling and flagellar hyperstructures, DNA repair hyperstructures, cytoskeletal hyperstructures based on EF-Tu, FtsZ and MreB, and cell cycle hyperstructures responsible for DNA replication, sequestration of newly replicated origins, segregation, compaction and division (Norris et al. 2007). Certain of these hyperstructures depend on the dissipation of energy; these non-equilibrium hyperstructures include those dependent on the coupling of transcription and translation. Others, that might be usefully classed as equilibrium hyperstructures, do not depend on such dissipation and these include the RecA-DNA co-crystal in which DNA is physically protected without the need for energy consumption (Minsky et al. 2002). Non-equilibrium hyperstructures are needed for growth but in an unpredictable and fickle environment, are fragile – and may make the cell fragile – whilst equilibrium hyperstructures are insufficient for growth but are robust – and may contribute to the robustness of the cell.

What is a bacterium doing? We have argued that many species of bacteria must negotiate the vast space of phenotypes available to them so as to generate a coherent diversity of structures and behaviours ready for either life in heaven or survival in hell. This entails the bacterium (which might be characterised as a *hypercomplex* system, see Norris et al. 2005) managing both the diversity of hyperstructures and, in particular, the ratio of non-equilibrium to equilibrium hyperstructures. One way of achieving this is via the cell cycle itself since this permits coherent differentiation (Norris and Madsen 1995; Norris et al. 2002; Segre et al. 2000). Such a strategy becomes valid only at the level of the population where generation of bacteria with a wide range of phenotypes means that some are always ready to exploit a new opportunity or to resist a new danger. In the latter case, for example, a population of *Escherichia coli*, in conditions where all cells can grow, nevertheless

contains non-mutant cells that are not growing and that can therefore survive exposure to antibiotic and later regenerate the population (Balaban et al. 2004).

Here, we join others in arguing that the definition of a bacterial population should be broadened to include bacteriophage. Hypotheses about the evolution of bacteriophage include those in which bacteriophage genomes are considered as collections of functional modules that evolved independently in host genomes and were acquired over time by the bacteriophage as modules; following this, the forerunners of bacteriophage contributed to the evolution of cells by facilitating horizontal exchange of genes (for references, see Hendrix et al. 2000). Our world is estimated to contain over  $10^{30}$  bacteria (Whitman et al. 1998) and over  $10^{31}$  bacteriophage. A significant proportion of the mass of chromosomal DNA is therefore carried by bacteriophage and, in hypotheses in which bacteria exchange their genetic material freely in the form of plasmids and bacteriophage, bacteriophage can become major reservoirs of information. From the perspective of hyperstructures, dynamic assemblies of bacteriophage replicating within bacteria constitute non-equilibrium hyperstructures whilst individual bacteriophage constitute what are effectively equilibrium structures that preserve their precious contents in a range of environments hostile to growing bacteria. It has been proposed that bacteria and bacteriophage form a single super-organism (Mathieu and Sonea 1995). We suggest that it then becomes the entire super-organism that adapts and evolves via exchanges and alterations of hyperstructures.

This vision of modern bacteria has its origins-of-life counterpart in the hypothesis of a pre-biotic ecology in which a rich, diverse and complex world of protocells or composomes exchanged their contents and in which metabolic and replicative functions emerged hand-in-hand in networks of interactions (Hunding et al. 2006; Norris and Raine 1998; Segre et al. 2000). In this community of composomes, non-covalent associations and molecular complementarity played major roles (Root-Bernstein and Dillon 1997). The polymerisation reactions that generated nucleic acids and peptides within collections of composomes were non-specific and occurred, for example, at the interfaces between composomes (Raine and Norris 2007). We have argued previously that a critical aspect of the origin of life was the ability to make the transition between inactive, structurally stable, highly ordered (equilibrium-like) states and active, structurally dynamic (non-equilibrium) states, as do modern viruses and bacteria (Hunding et al. 2006). In our attempt at a unifying hypothesis, individual composomes have their descendants in the equilibrium hyperstructures that constitute bacteriophage and in the sets of equilibrium and non-equilibrium hyperstructures that constitute modern cells, whilst the pre-biotic community of interacting sets of composomes has its echo in the modern community of interacting sets (alias cells) of hyperstructures. Finally, we point out that whilst the construction of minimal cells is valuable for biotechnology, it may prove less valuable for understanding life's origins since, in our scenario, the first cells only had meaning within the context of a population. To investigate this scenario, studies of minimal cells must give way to those of maximal populations.

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