The origin of cell division

The origin of life is among the deepest unexplained mysteries. How did the first self-replicating entities emerge, providing the material on which the selective mechanism of evolution could then operate? The most primitive known self-replicating forms of life are far too complex to have sprung from the pre-evolutionary environment through chance alone. Consequently, for the last century, scientists have sought mechanisms that would make the originating event more routine, perhaps even likely, given enough time.

Perhaps a single breakthrough idea will one day settle the matter. More likely, the truth may emerge piecemeal as a half dozen or so ideas from different settings fit together with an unforeseen synergy. One such component idea now getting increasing attention is that cell-like geometrical enclosures can exert control over key molecular processes. Modern living cells depend on myriad closed containers — from the cell itself and complex organelles to much simpler vesicles — to constrain the movement and interaction of molecules. Such confinement, as several recent strands of research suggest, may also have encouraged life-like chemistry in the pre-evolutionary past.

One obvious requirement for life is the emergence of physical cells that are able to grow, by taking resources from the environment, and also divide, thereby increasing their numbers. A natural idea — going back to biochemist Alexander Oparin in the 1920s — is that droplets forming under the right conditions in complex liquids might already act this way, and could have played a role as early chemical reaction centres. A recent study by David Zwicker *et al.* demonstrates conceptually one way that basic physics might cause such growth and division (*Nat. Phys.* **13,** 408–413; 2017).

The team studied a simple theoretical model for the behaviour of liquid droplets in systems driven away from thermodynamic equilibrium by an applied energy flow. As a result of a chemical disequilibrium, chemical reactions tend to drive droplets to add key material, making them grow. At the same time, however, droplet growth eventually leads to instabilities — linked to the changing shape of the droplets — that make cells divide into progeny. The study suggests that chemically active droplets could be plausible as prebiotic protocells,

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acting as containers to protect and feed a prebiotic metabolism.

This theoretical work remains to be confirmed in real experiments. But it rests on well-understood principles, and suggests that droplets that grow, divide and proliferate like cells could be natural in the pre-evolutionary environment. This could be part of a pathway to life's emergence. But another feature — the occasional merging of such cells — may also be key to developing self-replication based on inherited genomic information.

One of the leading scenarios for life's emergence rests on RNA molecules, which can both store information in the sequence of their base pairs and also act as enzymes to catalyse reactions. These dual features motivated the hypothesis — the 'RNA world' scenario — that life started when RNA molecules evolved to form sets able to catalyse their own reproduction. In this setting, a key issue is the time required for chance molecular events to bring together a minimal autocatalytic set of RNA molecules. The longer the time, the less plausible the scenario. Earlier this year, mathematical biologist Sam Sinai and colleagues argued that physical compartmentalization, combined with occasional merging, might greatly reduce the time, making the RNA scenario more plausible.

As they reasoned, if N is the minimal number of component RNAs, and p the small probability for any one component to be present, then the baseline probability of formation of the minimal set is $\sim p^N$. Hence, the time needed grows exponentially with N. However, if RNA components don't float around freely in the primordial soup, but reside within protocells, their contents remain together for longer periods, making interaction more likely. Even more crucially, if protocells can merge together, they can also assemble larger sets of components from smaller ones. Sinai and colleagues showed that merging of rudimentary protocells — in the form of droplets or anything else — would make the time for achieving a minimal RNA set grow only algebraically in N, rather than exponentially (preprint at http://arxiv.org/abs/1612.00825; 2016). Merging of physically distinct protocells could aid the discovery of a self-replication machinery.

This raises a further question: are there natural conditions that might lead to such protocell merging? There are basic physical processes leading to droplet merging. But other recent work by mathematicians Ole Peters and Alexander Adamou (preprint at http://arxiv.org/abs/1506.03414; 2015) points to a basic statistical diversification that could also have acted in the pre-evolutionary era to make merging events more common.

Imagine some prebiotic world in which many growing and dividing protocells containing RNA float about while harvesting basic chemicals crucial to their growth. The growth of such cells won't be steady and constant, but stochastic, influenced by noise linked to environmental fluctuations. One would expect different cells to experience different conditions. As larger cells can harvest more material to support growth, one would also expect the mathematical growth process to be multiplicative — cells grow in proportion to their current size. The natural mathematical model for such growth is geometric Brownian motion and, as Peters and Adamou have shown, the time-average growth rate for a population of such growing cells is significantly enhanced by occasional merging events.

In effect, the existence of merging events means that cells experiencing bad outcomes may get temporary help from resources gathered by others that were recently more fortunate. The effect simply reflects a sharing of resources, and diversification of risks, made possible through merging.

Again, merging brings a surprising benefit. If any simple mechanism could support merging in a population of already growing and dividing protocells, then it should be amplified and spread through the population, becoming the norm.

This is an admittedly speculative linking together of several ongoing strands of research. We'll wait to see if some, or all, of these ideas play an important part in our eventual understanding of the true origins of life. ❐

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