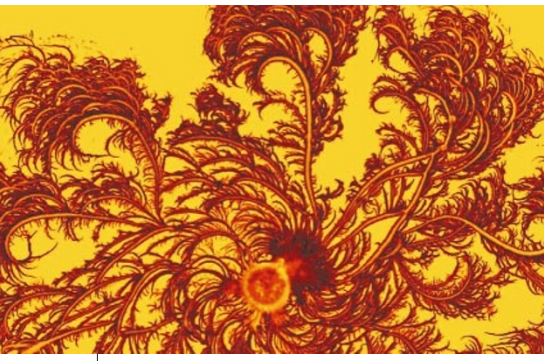

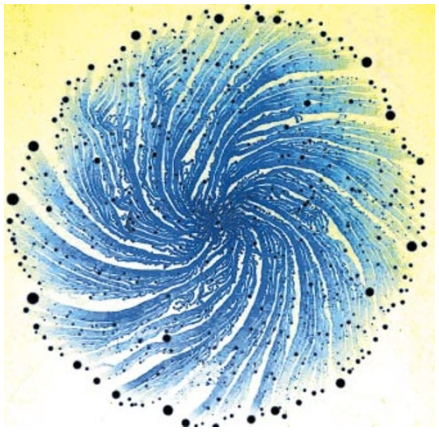

Complex patterns exhibited during colonial cooperative self-organization of *Paenibacillus dendritiformis* (top) and *Paenibacillus vortex* (bottom) show chiral asymmetry (all the branches have a twist with the same handedness). This observed chirality on the macroscopic (colonial) level results (via singular interplay) from the chirality of the flagella of the bacteria (the micro level). *P. vortex* shows organization of vortices (dots) composed of thousands of bacteria, which all circulate around a common centre. The delicate balance between order and chaos persists over many length scales, lending an unmistakable aesthetic quality to these images.

ent balance between the various competing tendencies leading to the formation of the pattern. Lending support to this notion is the well-studied example of diffusion-controlled growth. The same morphologies appear repeatedly in different systems exhibiting this underlying pattern-forming competition, with length scales ranging from micrometres to metres. This perspective brings to mind the idea of a morphology diagram, by analogy with a phase diagram for systems in equilibrium. In equilibrium, for given conditions, the phase that minimizes the free energy is selected and observed. The existence of an equivalent principle for dynamic non-equilibrium (open) systems is the most profound unsolved question in the study of pattern formation.

The power of cooperation

Among non-equilibrium systems, living organisms are the most challenging ones scientists can study. Although pattern formation exists throughout the biological world, cooperative microbial behaviour seems a natural choice of a starting point to apply the lessons learned from azoic systems to living ones. Bacteria are the simplest organisms, yet a wealth of beautiful patterns are formed during colonial development of various bacterial strains. Some of the observed spatio-temporal patterns are reminiscent of those observed in non-living systems. Others exhibit an even richer behaviour, reflecting the additional layers of complexity involved in colonial development.

As in non-living systems, patterns emerge from the singular interplay between the micro level (the individual cell) and the macro level (the colony). That is, there must be an internal consistency between the microscopic interactions brought about by single-cell behaviour and the overall macroscopic organization of the colony as a whole. The building blocks of the colonies are themselves living systems, each having its own autonomous self-interest and internal degrees of freedom. At the same time, efficient adaptation of the colony to adverse growth conditions requires self-organization on higher levels — function follows form — and this can be achieved only via cooperative behaviour by the individual cells.

Thus, bacteria have developed sophisticated cooperative behaviour and intricate communication capabilities, including: direct cell-to-cell physical interactions via membrane-bound polymers, the collective production of extracellular 'wetting' fluid for movement on hard surfaces; long-range chemical signalling, such as quorum sensing; and chemotactic signalling, the collective activation and deactivation of genes, and even the exchange of genetic material.

The communication capabilities enable each bacterial cell to be both an actor and a spectator (using Niels Bohr's expression) during the complex patterning. The single-cell dynamics determine the macroscopic pattern even as it itself is shaped by that self-same pattern. For researchers in the pattern-formation field, the communication, regulation and control mechanisms that ultimately control the observable morphologies offer a modelling challenge that far surpasses that considered to date within the context of non-living processes. It should be evident to microbiologists that colonies have sophisticated capabilities for coping with hostile environmental conditions, capabilities that cannot be studied by focusing exclusively on the behaviour of the single bacterium.

Clues about complexity

Understanding pattern formation is intimately related to understanding the notion of complexity in open systems. Complexity is an oft-used word that still lacks any precise definition. Structural complexity might refer to patterns with repeating yet variable units; in this sense, completely disordered structures are as simple as perfectly repeating ones. Functional complexity might be related to systems whose dynamic properties are not simply explained by detailed understanding of the constituent parts, perhaps because of feedback from the macro level. Unfortunately, neither of these intuitive notions has led to an objective operational measure.

An essential question in complex systems is the extent to which one can formulate theories that permit sensible predictions of the macroscopic behaviour of open systems without having to simulate in mind-numbing detail all the microscopic degrees of freedom. In physical systems in equilibrium, we are typically confronted with this question in the context of a two-level micro–macro interplay. We deal with this via the introduction of the entropy as an additional variable on the macro level. The entropy is a measure of (the logarithm of) the number of possible microscopic states for a given macro state of the system. Hence, it can be viewed as either our lack of information about the micro-level (looking from the macro level) or as the freedom in the microdynamics for given imposed macroscopic conditions (looking from the micro level).

Might complexity, properly defined, replace entropy as a fundamental property of macroscopic open systems? It is certainly intriguing that such systems tend to evolve in the direction of increased complexity as they are driven further from equilibrium. Future work on patterns, especially in living organisms, will no doubt offer some needed clues. ■

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FURTHER READING

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Correction: In the Millennium Essay "A cellular cornucopia" (*Nature* **408,** 773; 2000), the lizard was mistakenly cited in place of the newt in the context of limb regeneration.

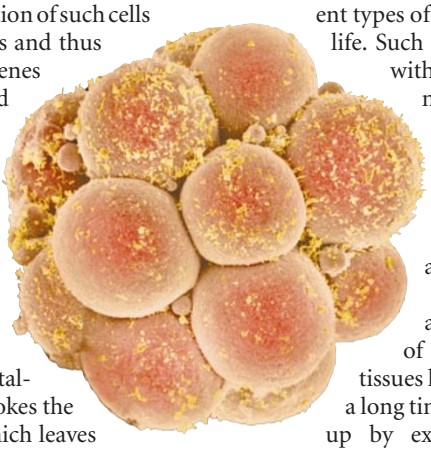
A cellular cornucopia

Stem cells generate new possibilities for research and therapy.

Margaret Buckingham

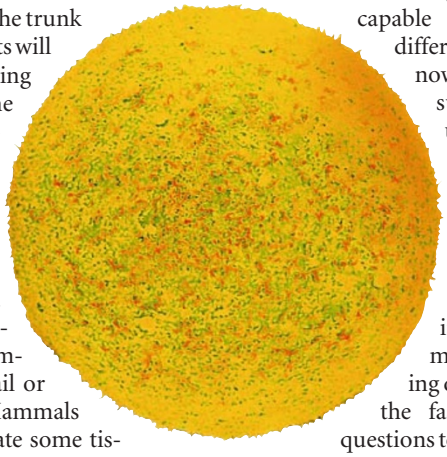
Cells with the capacity to re-make parts of the body, or a whole organism, have always excited the imagination. The magic of the process by which a single fertilized egg develops into an embryo, leading to the birth of a new individual, can now be unmasked at the molecular level. The actions of signalling molecules gradually restrict a cell's possibilities, modifying the repertoire of genetic information that it expresses. The universal nature of this selective strategy, with similar molecules acting at different sites within the same embryo in species as different as insects and humans, has been one of the revelations of modern developmental biology.

A major technological breakthrough was the isolation of early embryonic cells that can be replicated *in vitro* while retaining their capacity to contribute to all tissue types. This phenomenon of totipotency opened the way to genetic manipulation of such cells to create mouse mutants and thus test the function of genes during development and in the adult.



YORGOS NIKAS/SPL

Such totipotent cells, together with multipotent cells that can renew themselves and contribute to some, but not all, cell types, were called stem cells long before they had become an experimentalist's tool. Their name evokes the stem of a plant from which leaves and flowers bud. It is also the root of a word that remains after all suffixes or prefixes have been removed. It is here that the linguistic comparison becomes interesting. The stem, from the Latin for a thread, grows up from the root to generate all the other parts of the plant. In German, *Stammzellen* has similar connotations to the English stem cells, but in French, *les cellules souches* implies something slightly different. The *souche* of a tree is what is left when the tree is cut down — the roots and base of the trunk from which new shoots will grow, eventually leading to new trees. Hence the French word incorporates the idea of regeneration as well as of birth.



Adult animals, even adult vertebrates, can undergo a degree of regeneration. A lizard, for example, can regrow its tail or even an entire limb. Mammals can partially regenerate some tissues, such as liver or muscle, but not others, such as heart. Bone marrow is an adult tissue where replicating precursor cells are present, leading to the repeated generation of different types of blood cell throughout life. Such plasticity is associated with a susceptibility to malignancy, not seen in tissues such as the heart, where the lock that prevents cells re-entering the cycle is virtually unbreakable.

The existence of adult stem cells capable of contributing to many tissues had been suspected for a long time, but was not backed up by experimental evidence; even the regenerative lizard's tail probably depends on the reversion of differentiated cells. Cells are not totally inflexible in the fate that they adopt — a classic experiment in frogs showed that the nucleus of an adult cell introduced into an embryonic cell can contribute to embryo development. The recent production of Dolly the sheep was a further demonstration that it is possible to clone an individual by using the genetic information from one of its cells to make a 'genocopy'; although, despite all the media hype associated with this phantasm of immortality, a genocopy is not necessarily a phenocopy.

In the case of Dolly, it is not exactly clear what the adult cell was. In the past two years, however, thanks to the availability of appropriate molecular markers, it has now been demonstrated that many adult tissues do contain stem cells. This was first shown in bone marrow, which contains cells capable of colonizing many different tissue types. It is now possible to separate such cells, which have unlimited proliferative capacity and are multipotent, from many different adult tissues. The embryonic origin of these cells and why they remain blind to the instructions that normally restrict cell fate during development are among the fascinating fundamental questions to be answered.

The potential applications of stem cells for the repopulation of damaged tissue is of major biomedical interest. The use of human embryonic stem cells raises ethical issues as well as practical problems, not the least of which is controlling the behaviour of an embryonic cell in an adult environment. For adult stem cells, the issue is why they do not play a bigger role in regeneration normally and how to manipulate them so that they can. At the dawn of the new century, we have found the elusive stem cell. Now we have to master its magic so that new tissue can indeed stem from it, as new shoots grow from the *souche* of the tree. ■

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Even adult vertebrates can undergo a degree of regeneration — a lizard, for example, can regrow its tail or a limb.

A wealth of possibilities: the cells in young embryos can differentiate into a multitude of different tissues.