thetic catalysts for the commercial production of O_2 and H_2 (*17*, *19*). However, at present, this remains a dream. Two points emphasize the difficulty of catalyzing this reaction. First, the lack of diversity in the composition and structure of the inorganic core in all photosystem II complexes examined to date attests to a unique functionality that has remained essentially unchanged in 3 billion years of evolution. Second, the lack of manmade catalysts, of any kind, for the commercial scale production of oxygen attests to the synthetic challenge. Chemistry is, however, catching up with nature. Recently, two examples of manganese complexes that produce O_2 have appeared (*19*, *20*). Synthetic complexes containing the cuboidal Mn_4O_4 core, a close structural and electronic relative of the photosynthetic core, have been found to exhibit unique reactivity in water oxidation/O_2 evolution (*21*, *22*).

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PERSPECTIVES: ECOLOGY

The Advantages of Togetherness

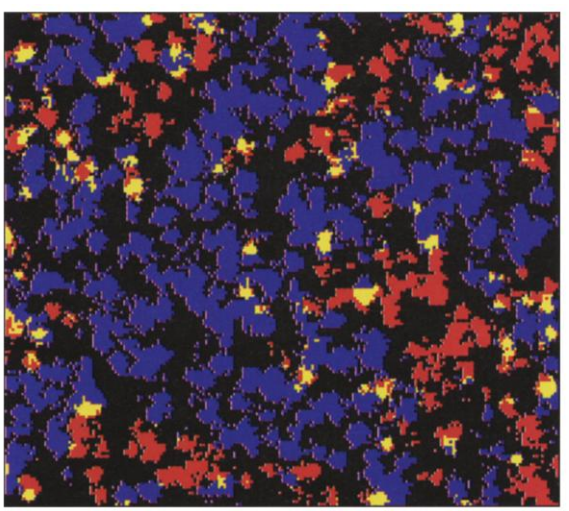
Edward Cox and John Bonner

There is general agreement that unicellular organisms became multicellular early in the course of evolution because the increase in size produced a selective advantage that encouraged their togetherness. Multicellularity arose independently many times, and no doubt the advantages were not always the same each time. On page 504 of this week's issue, Pfeiffer *et al.* (*1*) suggest one advantage that multicellularity conferred on heterotrophs—eukaryotic organisms that take up organic food, such as amino acids and sugars, directly from the environment.

Heterotrophs obtain energy from a food source either in the absence (fermentation) or presence (aerobic respiration) of oxygen. Both pathways yield the energy-rich molecule adenosine triphosphate (ATP), but each pathway makes a different thermodynamic trade-off between the yield and rate of ATP production. Although ATP can be rapidly synthesized by fermentation, the yield is very low. Respiration, on the other hand, yields 10 times as much ATP, but at a much slower rate. The interplay between yield of ATP and its rate of production is an essential feature of evolution, and this is the reasoning that Pfeiffer *et al.* follow.

Through mathematical modeling, the authors play out the consequences of this argument in a model environment in which two types of heterotroph—one a respirator (high ATP yield, low production rate) and the other a fermenter (low ATP yield, high production rate)—compete for a food source (such as sugar) (see the figure). If they compete for the food in a well-mixed environment, that is, one in which the food and the two types of heterotroph are uniformly distributed, then the fermenter may well win the competition. Although the fermenter is less efficient at producing ATP, it has the advantage because it can quickly use up the food—it trades efficiency for rate. Such a fermenting beast will have fewer offspring than the respirator, but will quickly exhaust the food on which the aerobic competitor depends (although in the model the two can come to equilibrium under the right set of conditions).

Now look what happens when the fermenter, respirator and food are allowed to diffuse within the environment in two dimensions. As the mixed population of heterotrophs competes for the food, islands of fermenters and respirators spring up and coexist for a while. In the simplest case—a respirator and a fermenter making their living from a single food source through two different metabolic pathways—the rate at which the food is used up heavily depends on the rate at which both heterotrophs and the food diffuse through the environment. The authors found that when the food has a low influx rate, that is, when it reaches the organisms slowly, respirators are favored, whereas when the food is immediately available and diffuses rapidly, fermenters are favored. When both the food and heterotrophs diffuse slowly, respirators have the advantage because they can use up the food slowly and maximally in their patch, outcompeting fermenters that depend on an inefficient use of the food to produce relatively few offspring. In contrast, when both the food and heterotrophs diffuse rapidly, the fermenters have the advantage because they quickly use up the food, exploiting rate over yield.



The hare and the tortoise. The distribution of heterotrophic organisms—respirators (blue) and fermenters (red)—in an environment containing a food source for which they compete. Yellow denotes areas where both fermenters and respirators are present, black denotes areas where neither organism is present. If the diffusion rate of the food is high, it tends to be more uniformly distributed and the fermenters are favored because they quickly but inefficiently convert the food source into the energy-rich molecule ATP. If the diffusion rate of the food is low and its distribution patchy, the respirators are favored because they can cluster around local concentrations of the food and efficiently but slowly convert it into ATP.

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Here comes the interesting part. There are some organisms that have both unicellular and multicellular forms: One form is capable of respiration, whereas the other is a fermenter. As Pasteur showed, the bread mold *Mucor* forms a network of threadlike filaments (a multicellular mycelium) that breaks down a food source in the presence of oxygen through aerobic respiration. In the absence of oxygen, however, it produces unicellular, yeastlike forms that are capable of fermenting the food. In other words, fermentation in *Mucor* is associated with the unicellular state, and respiration with the multicellular mycelium. The authors conclude that multicellularity arose precisely because the formation of multicellular organisms allowed cells to benefit from the efficiency of aerobic respiration in the presence of a slowly diffusing food source. The evolution of aerobic respiration allowed a kind of energetic luxury that in turn permitted the development of large genomes and cellular specialization. The Pfeiffer *et al.* work is interesting because it couples thermodynamics, biochemistry, and population biology to suggest a way in which multicellularity could have originated.

There is a different but somewhat parallel example in nature that fits in with this scheme. Two simple, and no doubt ancient organisms—the myxobacteria and the true slime molds or myxomycetes—feed and grow into a large mass before they form spore-bearing fruiting bodies that stick up into the air for effective dispersal of the spores. In the case of the myxobacteria, the individual bacterial cells group into swarms and, as Dworkin (*2*) pointed out some years ago, by doing so they are able to feed more effectively. Their strategy has a feature not found in the Pfeiffer *et al.* model. The myxobacteria obtain their energy from solid food, but to do so they must pump out extracellular enzymes that convert food into small organic molecules that can then be absorbed and converted into ATP by aerobic respiration. Dworkin appropriately called this phenomenon—the grouping of cells into large masses to enhance their ability to degrade food into small molecules—"wolf-pack feeding." So, there is a different but analogous advantage to the myxobacteria becoming multicellular.

This brief summary of the Pfeiffer *et al.* work does not do credit to all of the interesting details that the authors muster or to how their findings relate to the global problem of the evolution of multicellularity. As Pfeiffer *et al.* point out, their argument only applies to heterotrophs, and there are a number of photosynthetic organisms—nonheterotrophs or autotrophs—that independently invented multicellularity (*3*). They also raise the key point that the kind of advantage they propose for multicellularity means that it must have occurred after the atmosphere of Earth was invaded by oxygen and aerobic respiration was "invented." Bacteria were the first to acquire aerobic respiration. Later, eukaryotic cells evolved by the symbiotic incorporation of bacterial respirators, the forerunners of mitochondria. One wonders if Pfeiffer *et al.*'s argument about the advantage that multicellularity confers on eukaryotic respirators might also apply to prokaryotic respirators? We do not know of any existing multicellular prokaryotes that would fit that bill, but they might well have existed millions of years ago and become extinct (or perhaps they do exist and are waiting to be discovered).

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PERSPECTIVES: SIGNAL TRANSDUCTION

How Do Cells Sense Oxygen?

Hao Zhu and H. Franklin Bunn

In the early 20th century, the fledgling disciplines of physiology and biochemistry became interested in how animals and cells respond to changes in the amount of oxygen in their environment (oxygen homeostasis). Since then, much has been learned about how the cardiovascular and respiratory systems adjust to low oxygen tensions in tissues (hypoxia), how changes in tissue oxygen tension affect cellular metabolism and, within the last decade, how hypoxia affects programs of gene expression. But there is still much to learn about the ways in which cells sense reduced oxygen tensions and activate signal transduction pathways that lead to physiologically appropriate changes in gene expression. Papers by Ivan *et al.* on page 464 (*1*) and Jaakkola *et al.* on page 468 (*2*) in this week's issue add considerably to our understanding of this process by unraveling how a transcription complex, hypoxia inducible factor (HIF), controls gene expression in response to changes in oxygen tension.

When mammalian tissues are challenged by hypoxia, the expression of a number of physiologically important proteins is increased. For example, there is increased production of erythropoietin, a cytokine required for the formation of red blood cells; an increase in the number of erythrocytes enhances the delivery of oxygen to tissues. Vascular endothelial growth factor (VEGF) is a key regulator of blood vessel growth (angiogenesis). The induction of VEGF expression in hypoxic tissues results in enhanced blood flow, thereby providing protection against ischemic injury. VEGF is also important for tumor angiogenesis (*3*). Tyrosine hydroxylase is the rate-limiting enzyme in dopamine synthesis. The up-regulation of this enzyme in glomus cells of the carotid body in the neck enables the hypoxic animal to achieve a sustained increase in ventilation. Hypoxia also induces synthesis of certain glycolytic enzymes, enabling intracellular levels of the energy-rich molecule adenosine triphosphate to be maintained.

In hypoxic cells, the up-regulation of these and many other proteins depends on the activation of the HIF family of transcription factors (*3*). Heterodimers composed of HIFα and HIFβ subunits bind to pentanucleotide (5′-RCGTG-3′) response elements in genes encoding the proteins up-regulated in response to hypoxia. The HIF subunits are members of the PAS protein family, which includes not only transcription factors but also other proteins that sense perturbations in a cell's environment. For example, FixL in *Rhizobium* bacteria, a heuristic distant relative of PAS family members, is an oxygen-sensing fusion protein containing a heme binding domain and a protein kinase domain (*4*).

The HIF subunits are widely, perhaps universally, expressed in the cells and tissues of mammals, flies, worms and probably most other creatures. The β subunit, commonly called ARNT (arylhydrocarbon nuclear translocator), is a partner for the arylhydrocarbon receptor and is abundantly expressed independently of oxygen tension. In contrast, HIFα (*5*) cannot be detected unless cells are challenged by hypoxia. Above a critical intracellular oxygen ten-

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