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By Melissa Lee Phillips

NEWS

## How oxygen changed metabolism

Organisms used one of four basic types of metabolic networks after oxygen appeared on Earth

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Metabolic networks come in just four basic types, according to a [bioinformatics study](#) in this week's *Science*, which also shows that oxygen is required for the largest and most complex networks. The enzymatic reactions that take place in oxygen-dependent networks evolved after molecular [oxygen](#) appeared on Earth around 2.2 billion years ago, and some of these adaptations may have been important in a [subsequent explosion](#) of multicellular life, according to the authors.

"It is an intriguingly fresh approach to the whole problem of [biochemical complexity](#)," said [Joseph Kirschvink](#) of the California Institute of Technology in Pasadena, who was not involved in the study.

[Previous work](#) by first author [Jason Raymond](#) of Lawrence Livermore National Laboratory in California revealed that, in aerobic organisms, many anoxic enzymatic reactions

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were replaced with new reactions and enzymes. To see if this finding held true for entire metabolic pathways, Raymond and co-author [Daniel Segrè](#) of Boston University used a method called [metabolic network expansion](#) to simulate metabolic networks that could develop under different conditions.

Each simulation started with a set of randomly chosen metabolites, which were allowed to interact with each other according to rules of enzymatic reactions detailed in the [Kyoto Encyclopedia of Genes and Genomes](#). At the time the simulations were performed, this database contained information on more than 6,000 different enzymatic reactions derived from 70 genomes.

After running 100,000 simulations -- each with a different set of 10 to 100 starting metabolites -- Raymond and Segrè found that every generated metabolic network could be placed in one of four major groups, with each group showing more than 95% identical reactions and metabolites. "You might expect to see 100,000 completely different networks," Raymond told *The Scientist*, but "we only saw really four different types of networks."

The four groups were different sizes and showed different levels of connectivity, and the smaller groups mainly contained reactions and metabolites also present in the larger groups. "The way that these networks get larger is essentially by growing new domains that are still attached to parts of a core network," Raymond said.

The largest and most interconnected of the four groups was only reached in simulations that included molecular oxygen. Networks from this group contained as many as 1,000 more reactions than the networks generated without oxygen. About half of these oxygen-

dependent reactions do not explicitly use oxygen but belong to pathways that rely on it, Raymond said. These types of oxygen-dependent reactions would not have been found in studies of individual reactions, but rather require a “whole-metabolome approach to this problem,” he said.

Finding that all metabolic networks fall into just four groups is “really intriguing,” said [Andreas Wagner](#) of the University of New Mexico in Albuquerque, “and it also adds a lot of potential for future work... It’s a highly original approach.”

The researchers also grouped different organisms together based on which anoxic enzymes they possessed, and they found that the organisms clustered in the same way as in traditional genome-based phylogenies. However, when they grouped organisms by enzymes needed for oxic metabolism, the clusters did not mirror patterns of speciation but instead depended on whether an organism prefers an aerobic or anaerobic lifestyle. This finding suggests that adaptation to molecular oxygen occurred either independently in different lineages or through horizontal gene transfer after all three domains of life had appeared, Raymond said.

Some genetic studies have suggested that organisms were using oxygen well before 2.2 billion years ago, but “their analysis really supports the hypothesis that oxygen arose late,” Kirschvink said, “and that’s actually what we see in the rock record.”

Still, Raymond and Segrè’s approach “has one serious shortcoming,” according to Wagner -- in many of the sampled genomes, enzymatic reactions are inferred based on sequence similarity to known enzymes in another organism. It’s possible that similar sequences may not code for the same enzymes or that different enzymes may

catalyze the same reaction, Wagner said.

Because the authors used statistical analyses to draw most of their conclusions, however, uncertainties in the genomics approach may not matter too much, according to **Christian Forst** of Los Alamos National Laboratory in New Mexico. But when they look at “which particular enzyme, which particular part of the pathway, is used in an organism... then the error would be more serious,” Forst said.

“That also raises the point that there are a lot of reactions that we still don’t know about,” Raymond added. “Our knowledge of metabolic networks is continually growing as we discover and sequence and characterize new organisms.”

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