Biology – A Systemic Redefinition?

The terms systems biology and synthetic biology are currently experiencing a boom – something that has already occurred several times in the history of biology. But what do they actually signify in scientific terms? Are they an expression of a far-reaching change within the discipline, or mere promotional buzzwords that simply "fill old wine into new bottles" in order to present it in a more palatable form? An analysis.

TEXT **HANS-JÖRG RHEINBERGER**

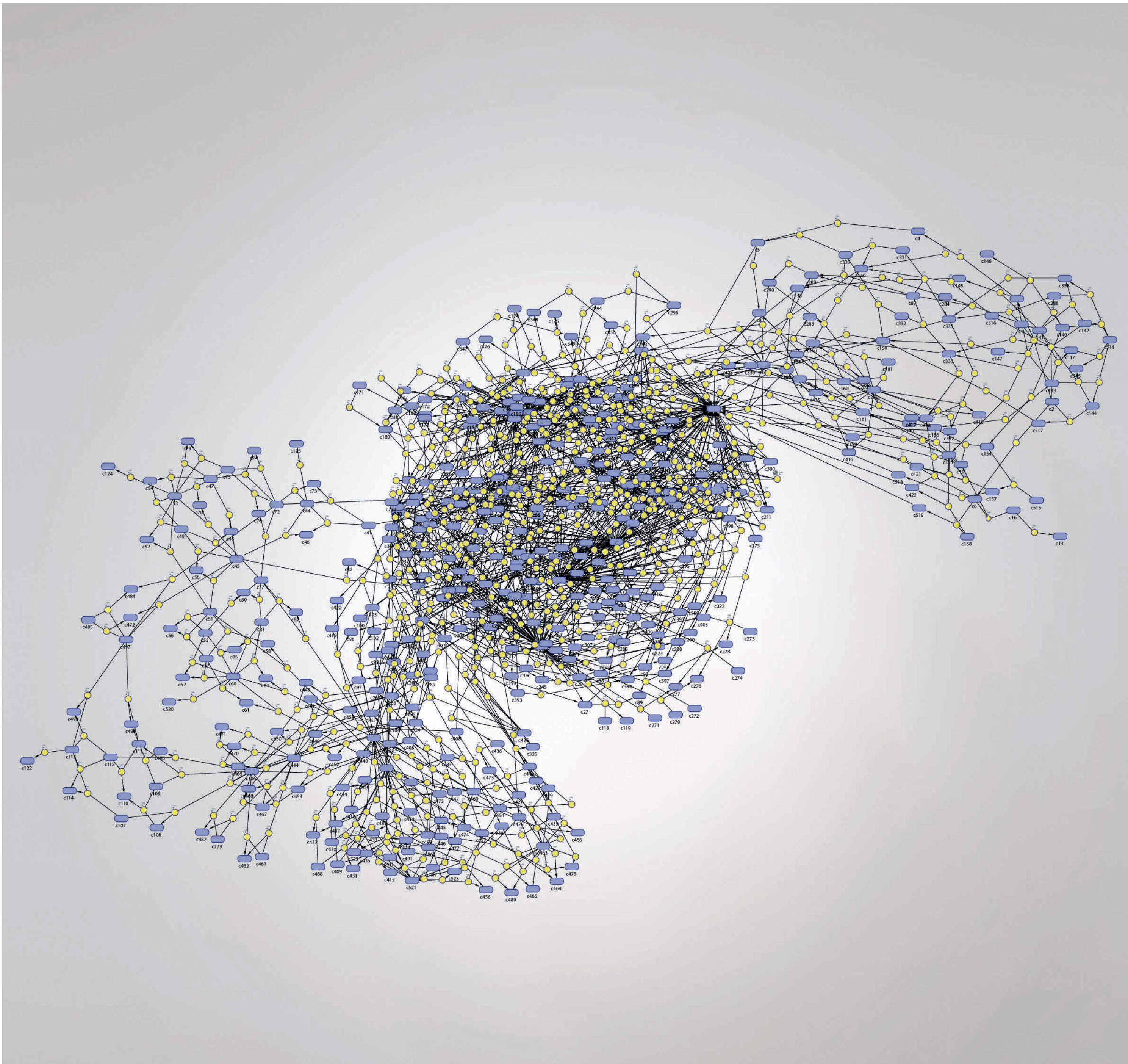
The terms systems biology and synthetic biology are experiencing an inflationary boom in the context of the life sciences. Not only are they being appropriated by research programs, databases, institutes and companies, but increasing numbers of scientists are also using them to describe their work. However, as a look back at the history of biology shows, there is nothing at all new about this phenomenon.

Genetics became established as a special discipline within the field of biology in the early 20th century. In reality, it was more than that. It went on to develop the claim of representing something akin to an experiment-based general biology, a claim that it succeeded in asserting. Genetics asked the basic questions of life, insofar as this was possible using experimental means. In addition, it introduced to biology the practice of working with model organisms, and established a kind of experimentation that is more or less the distinguishing feature of the field of biology – the crossing experiment as carried out by Gregor Mendel in the mid-19th century.

Genetics asks the basic questions about life

This experimental revolution was accompanied by a conceptual shift. In 1909, the term "gene" was introduced by Wilhelm Johannsen, who also was the first to differentiate between gene and characteristic, that is, between genotype and phenotype. This distinction proved to have far-reaching consequences: it established a hierarchy for organisms based on interior and exterior, center and periphery, essence and appearance. The accompanying trend for gene-centered thinking would leave its mark on the life sciences throughout the 20th century.

The relationship between gene and characteristic enabled the investigation of fundamental questions regarding the manifestations of life. However, the experimental processes available to classical genetics at the time didn't enable scientists to explain what genes consist of and, above all, how they influence the expression of characteristics. >



Network map of a cell: Every biological system consists of a nested network of smaller reaction pathways. Without such complex interconnections, life could not function.

Both of these questions were successfully tackled by molecular genetics, which emerged around the mid-20th century. What occurred at this point was more of a rupture than a seamless transition from classical to molecular genetics. In the course of this molecular biology revolution, a new generation of biophysicists, biochemists and biologists identified nucleic acids as the genetic material, and understood gene expression as a translation of genetic information into biological function.

The subsequent development of molecular genetics into molecular genomics had two further consequences: on the one hand, it pulverized the oversimplified "gene for" concept of classical and early molecular genetics, and, on the other, it led to the emergence of genetic engineering and genome analysis. Genetic engineering and genome analysis, in turn, established a new form of molecular cell biology, which provided a hitherto inconceivable abundance of applications. This new field was developed and refined from the 1970s to the early years of the new millennium without the scientific community deeming it necessary to introduce new names for it.

This situation changed around the turn of the millennium, at the time of the successful completion of the human genome project and the failure of a first wave of gene therapy experiments in medicine. Since then, a profusion of new names for the next stage have been in circulation, many of which are derived from the term genomics: we hear talk of transcriptomics, proteomics, metabolomics, and even organomics.

The supposedly modern terms were in vogue previously

But two terms stand out from all others: systems biology and synthetic biology. Both terms have gained enormous popularity within a very short period and can be found gracing not only daily newspapers, but also scientific journals, including a specialist publication that incorporates both terms in its title: *Systems and Synthetic Biology*.

What the two terms have in common is that, first, the new associated terminology, which would be comparable to that originating in the periods of classical genetics and molecular genetics and could be viewed as the harbinger of a new era, is not clearly identifiable. Second, they are terms that have already been in vogue at various stages in the history of biology.

The term "system" signified different things at various stages in the history of the life sciences. The natural history of the 18th century was shaped and driven by a concept of system as an ordering category for the diversity of life forms. Linné's *Systema naturae* is representative of this trend.

This changed in the late 18th century. Once the term biology was coined and an independent experimental biological science appeared on the scene, the dividing line between physics, chemistry and biology repeatedly ignited the debate as to how organisms could be analyzed without losing sight of life itself. It could even be claimed, perhaps, that the associated new system concept – in the form of a whole that is greater than the sum of its parts – actually launched the idea of biology as a science in the first place. Immanuel Kant referred to living organisms as "organized and self-organizing beings."

In the late 19th century, a debate between development mechanics, on the one hand, and more systemically oriented biologists, on the other, triggered a renewed debate on developmental biology. The theoretical work carried out in the systems biology of the early 20th century focused on concepts like steady state and field. However, its proponents remained outsiders, for the most part; as theorists, they were very much peripheral to experimental biology.

In the 1950s and 1960s, biological cybernetics shifted the focus in biology from the molecular level to behavior, to systems-based thinking. In its wake, molecular biologist and Nobel laureate Fran-

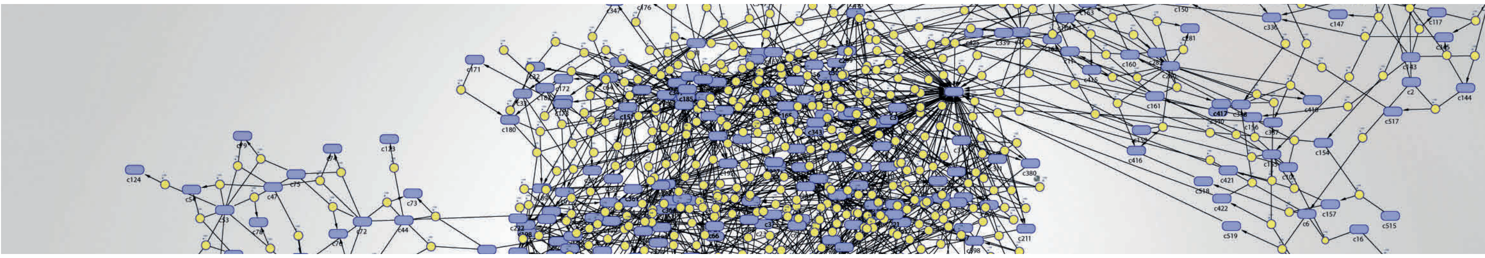


Photo: Birgit Schoeberl, Merrimack Pharmaceuticals

çois Jacob proposed the general concept of the integron for the hierarchy of the feedback loops to which organisms are subjected. Interestingly, simultaneous to the emergence of genetic engineering in the 1970s and the sequencing boom of the 1980s and 1990s, the term cybernetics slowly but surely disappeared from the biological literature, and concepts like the integron were hardly adopted at all.

So what characterizes the current increasingly forceful call for a systems biology? Sydney Brenner, who was awarded the 2002 Nobel Prize for his research on the genetic regulation of organ development in the roundworm *Caenorhabditis elegans*, views it as nothing more than an empty buzzword. "Systems biology is not a science," he stated categorically in a recent interview. He expressed the view that the important new insights in the life sciences will continue to be gained through the tried and tested analytical modus of molecular biology.

A new generation of life scientists clearly takes a different view. However, clarification is urgently required as to precisely what constitutes the systemic character of contemporary systems biology. Has the focus on the genetic level of organisms come to an end? Are there new concepts that extend or even replace the repertoire of molecular biology – genetic program, structural gene and regulator gene? It appears that concepts like that of the network, which is widely disseminated in the sciences today, are far too general to assume such a role.

Or is the use of the term systems biology justified by new laboratory and computer technologies? Today, high-throughput technologies like DNA and protein chips and the new generation of sequencing processes produce vast volumes of data on cellular processes. In this context, however, the term "system" is more an expression that refers to the immense volumes of data that are generated in the laboratories with the help of chips and robots and that can no longer be evaluated without the help of computer programs.

What would be referred to here is thus primarily a technical system – namely one involving the organization of the biologists' work and, therefore, a parallel world of data production and processing – and less so the characteristics of the organism, the actual object of this work. If this were to be the case, the question would arise, of course, as to how the two worlds relate to each other. Unfortunately, those involved are making little or no effort to establish clarity on such issues.

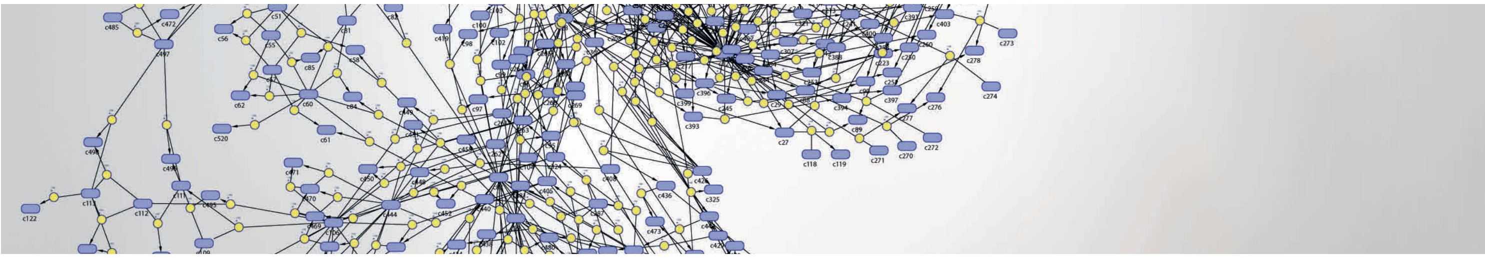
This brings us to synthetic biology. Once Louis Pasteur's view that organisms arise only from existing seeds and do not spontaneously appear on Earth became established during the course of the 19th century, biology focused on the question as to how organic life could arise on Earth throughout the 20th century. To the present day, however, the corresponding syntheses have been merely fragmentary. And the current concept of synthetic biology relates only to the periphery of these approaches.

Is it about the organism – or the organization of scientific research?

Scientists repeatedly referred to synthetic biology over the course of the 20th century, initially in conjunction with synthetic chemistry. The aim of this discipline was not only to recreate organic substances from existing elements in the laboratory, but also to generate substances that don't occur in nature in this form.

The term was also used occasionally in connection with the initial successes of genetic engineering in the 1970s. However, it did not become widely established at the time. Instead, the terms genetic technology and genetic engineering took hold and went on to dominate the public debate for three decades.

The boom in the use of the terms synthetic biology and systems biology began only with the start of the new millennium. Here, too, we must question



whether this is merely a swapping of labels that is not scientifically motivated, and constitutes an attempt to steer public perception in a new direction. Or has there been a qualitative leap in the concepts and techniques for the manipulation of life as compared with the 20th century that would justify the adoption of a new name?

The use of the term is vague. Today, the experiments by American researcher Craig Venter come under the term synthetic biology. Venter tries to recreate entire bacterial genomes artificially and wants to use them to replace a natural genome. The term also covers the experiments carried out to define a minimal bacterial genome that would just suffice to enable a bacterium to reproduce.

Synthetic biology also includes the permanent incorporation of biological-chemical subsystems into organisms that provide the latter with new characteristics. In addition, the use of modified nucleic acids as genetic material and the attempts to change the genetic code are also considered to be synthetic biology.

But don't all of these cases merely involve the application or further development of technologies that, until ten years ago, were referred to as genetic

The new linguistic label responds to the general skepticism

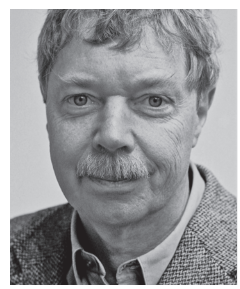
engineering or, more generally, biotechnology? What is the reason for this new self description?

Two scenarios are conceivable. The first and more controversial of the two would be that the soft concept of synthesis is used today to encourage a more positive attitude to the deliberate and permanent modification of living organisms, and involves the adoption of a new linguistic label in response to the widespread skepticism toward genetic engineering with a view to attracting new funding.

The other scenario is that the life sciences actually are undergoing a transition on a scale that is eclipsing molecular biology and the recombinant DNA technologies of the last century, and heralding a new era of biological evolution controlled by people.

If this is the case, Darwin will ultimately be overtaken by his own analogy. As is generally known, he based his theory of natural evolution on the model of artificial selection familiar to him from the breeders of his time. Today, we may well be facing a situation in which the breeders ("designers") of our time are really getting down to business. However, this would require an entirely different debate. ◂

THE AUTHOR



Hans-Jörg Rheinberger, born in 1946, is a Director at the Max Planck Institute for the History of Science in Berlin. His work deals primarily with the changes to which the issues and experimental approaches in biology have been subjected over time. A native of Liechtenstein, he studied biology and philosophy in Tübingen and Berlin, and is a member of the Berlin-Brandenburg Academy of Sciences and the German Academy of Sciences Leopoldina.

Photo: Birgit Schoeberl, Merrimack Pharmaceuticals (top), MPI for the History of Science (small photo)