EMBO
reports

editorial

Too complex to comprehend?

The English mathematician and philosopher Alfred North Whitehead (1861–1947) said, “seek simplicity and distrust it”—a quote I first encountered as an essay title in my final biochemistry exams at university. The fact that it has stuck in my mind might be related to the traumatic circumstances of this experience, but is probably also due to its inherent wisdom. The words resonate with the development of science; practicing scientists seek out simplistic, utilitarian descriptions of reality and distrust them for their simplicity. But, because we know that our descriptions are only approximations, we are able to continue to refine our understanding. Yet, the process is rarely straightforward or predictable, and without a regular critical assessment of our knowledge and without asking new questions, we would remain in an erroneous comfort zone.

All research is based on the belief that eventually any puzzle can be solved and any phenomenon comprehended, if only we do the right experiments in a rigorous manner. Time and again, however, we arrive at an impasse where the available techniques are insufficient to discover the next piece of information needed to understand the bigger picture. Sometimes we are simply ignorant of different interpretations or other elements that could help to explain our subject of study; sometimes a total readjustment of the context of the experiments is required. One recent example of this is the role of RNA in controlling gene expression and other processes. We need to reinterpret the diverse functions of RNA to include the observations that RNA molecules play roles that were previously attributed only to proteins. Similarly, we can easily get locked into common images and metaphors of how systems work; thousands of colourful figures showing how bubbles of transcription factors bind to a straight line of DNA have undoubtedly influenced our interpretation of gene expression experiments. In reality, the process is highly dynamic and many important events occur at a distance from the promoter, but it will take time before we are able to fully integrate these results into our thinking or even create suitable methods to illustrate these interactions.

Yet even if we have all the components and know their contexts, and integrate all of these into our analyses and experiments, the presumption that we will finally understand ‘everything’ might still be wrong. Research in the life sciences has been through various phases that have been influenced by different philosophies. Classically, scientists described the nature, appearance and behaviour of whole organisms, and understanding was gained from descriptive prose. In time, biochemists moved in the opposite direction and began to deconstruct organisms into their manifold components, believing that this would give them greater insight into how they worked. Molecular biologists then further developed the reductionist approach, providing mechanistic insights that explained the biochemistry, in addition to describing even more components of the cell. Today, systems biology aims to integrate all these data while adding the elements of time and space to describe these processes as mathematical models. Accordingly, the practitioners have been changing as well. The early botanists and zoologists were first joined by chemists, then by physicists, and today, biology attracts many mathematicians, computing experts and engineers.

Scientists have therefore tried many approaches, but it seems that the more we attempt to dissect and understand nature, the more complicated things become. Often in the past it has appeared that cause and effect can be linked by a linear line drawing, such as the early descriptions of signal transduction cascades. But now there are many such interconnected lines and, without doubt, there are many more awaiting discovery. Ever since the breakthrough moment when Watson and Crick described DNA as a double helix, we thought that we had a clear understanding of how this molecule stores and transmits genetic information. Now we are beginning to realise that the surrounding chromatin, in conjunction with related and unrelated proteins modified dynamically, generates new possibilities and combinations.

Today, other aspects are even closer to being ’black boxes’. Membranes are no longer nicely defined borders between compartments, but are actually something much more complex that we are finding increasingly difficult to understand. Add to this the study of lipids and sugar residues and their biological functions—which is still at the ‘simplicity’ stage—and then try to combine all of these elements and others, together with the dimension of time, and the sheer number of possible permutations is beyond our ability to compute or understand; and this is just a single cell. If we expand this to organs, organisms, their interaction with the environment and whole ecosystems, it becomes clear that we should be very humble whenever we think that we are close to understanding life, even at its molecular level.

In the early twentieth century, the theory of relativity and quantum physics enabled physicists to understand a range of phenomena that could not be explained by using the tools and methods of classic Newtonian physics. But these concepts presume nonlinear interactions and they are so complex that the human mind finds it difficult to understand them intuitively; biology might be heading in a similar direction. Although we are perhaps not ready for nonlinear complex models of living entities, and are still looking at life as a series of domino events with linear consequences, this will change over time. Whitehead’s quote might well become increasingly relevant soon and the concept might even be extrapolated to the point where the complexity is beyond our comprehension.

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doi:10.1038/sj.embor.7401041

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