

Understanding Life—now for the hard part!

It's a beautiful Sunday and you convince your family to climb the nearby hill that shimmers in the sunshine. But as you walk through the forests on your way, you find that the hill is not quite as close as you thought, and that there is some marshy land between you and your goal. And as your children grow tired and start asking 'Are we there yet?', you reply 'almost' with a confidence that hides reality.

We scientists have been on similar journeys for some time. Our goal, grandiosely presented, is to understand life in its multiple forms and variations, and in the process to provide benefits for humankind and society. And we frequently announce that we are 'almost there'... but are we? Or are we merely providing the typical answer that parents give to tired children on a trip that turns out to be longer than expected? How many grant applications carry the message that 'support for this work will make a significant difference to the curing of some disease'? Whereas, in reality, we know that this is but a small foothill on the much longer road to the summit.

I recently did a PubMed search for 'estrogen receptor', the understanding of which is the challenge for my research group. The number of papers I found with 'estrogen receptor' in the title or abstract was the equivalent of publishing one paper per day over a period of 70 years, or the scientific output of an institute with about 500 researchers working solely on that topic for a period of almost 100 years, if you assume that each paper involves 2 years of laboratory work. Clearly, an enormous amount of information has been accumulated. Many small hills have been successfully climbed, but we are still some distance from understanding this simple molecule that plays a crucial role in major diseases such as breast cancer and osteoporosis. What is true for this steroid hormone receptor is equally true for many other molecules as well. One reason for this apparent gap between productivity and understanding may be

that many of the papers are just excellent answers to the questions 'What will happen if I do this?' or 'Is there a connection between molecule A and molecule B?', but seldom does a researcher set out to answer the question 'What does it all mean?'.

Laboratories all over the world constantly generate new pieces of the jigsaw puzzle that is life, but the effort to put them into an integrated picture is still postponed. Furthermore, the pieces of the puzzle that we present in our publications are just cartoons of how the data we generated fit with our understanding of reality. Most scientists have worked, until recently, in the context of 'hypothesis-based research'. But strangely, we have not bothered too much with defining the larger context for our experiments. Perhaps we were not able to do so because we had only an inadequate number of jigsaw pieces to allow us to sketch an outline of the whole picture, the overall hypothesis. I should distinguish the concept of a 'question' from that of a 'hypothesis'. We all drive our research forward by asking questions, but perhaps we should check if we have a hypothesis.

But the fact that the journey to the summit is not, in my opinion, even near the last few kilometres, is also because the terrain that we are crossing is becoming more difficult. Explaining the action of a transcription factor such as the estrogen receptor in a two-dimensional diagram, where a series of nice artwork ovals sit on a line that represents DNA, is to avoid, for practical reasons, the fact that real life is in multiple dimensions, is not static and is more complicated than any diagram could ever be. The cell is not a bubble of nicely ordered molecules: it is a cauldron of colliding super-concentrated proteins and other components. And time brings another dimension to it that gets lost in the arrows that we draw to show that protein A activates protein B. The concept of Heisenberg's uncertainty principle applies to biology as well as to quantum physics: the entity that we are studying is

constantly altering such that we will never be able to get an accurate description of it. Furthermore, there will be no 'one size fits all' solution to biological problems, as each cell must be looked at in a different context. But we study our molecules in a few model systems and then extrapolate the results. And our '*Escherichia coli*' system is presumably atypical simply because of the fact that we have chosen it in the first place. We have to be honest enough and accept the fact that we ultimately aim to understand cells and tissues that are significantly more limiting and demanding than our model system. In fact, the topic that we present as a justification for funding may be beyond the scope of available techniques.

A final pessimistic consequence of this reflection is that we are about to land on a new and hostile alien planet deprived of oxygen. We have been capable of achieving much in an environment where intuition and a single human brain have been sufficient to integrate available information in the life sciences. But now, the sheer amount of information is threatening to overwhelm us. Perhaps we are facing the same crisis of understanding that physics had 80 years ago before the advent of relativity and quantum physics. Linear thinking and presentation of life as we understand it may not be enough any more and simply accumulating more pieces of information may ultimately confuse rather than clarify. We may be close to putting together the outer pieces where one part guides us to the neighbouring part of the puzzle. But that may be only another small hill before we reach the summit that has increasingly become shrouded in a cloud of uncertainty. Perhaps we should think about the distance to our goal first, before we tell our companions and funding agencies that 'we are almost there'.

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