Living Systems are Not Like Machines

Philip Ball in Conversation with Francis Crick Institute Director, Paul Nurse, Part Two

Introduction

Marginalia Review of Books' *Institute for the Meanings of Science is honored to host a conversation between Sir Paul Nurse, Nobel Laureate and Director of the Francis Crick Institute in London, and Dr. Philip Ball, longtime editor at* Nature, *author of over 25 books, most recently*, How Life Works: A User's Guide to the New Biology *(Chicago University Press).*

This conversation is the first in a series of interviews for The Meanings of Life Project: The New Biology, led by Institute Director, Samuel Loncar, and Lead Researcher, Philip Ball. The project brings together a working group of leading scientists, scholars, and industry leaders to advance the new scientific vision of life revealed by modern biology, and synthesized in Ball's book. The project convenes around this major synthesis, and aims to identify a new narrative for this field through a multi-disciplinary integrative approach that seeks to unite fundamental research at the level of genes, molecules and cells to notions of agency, purpose, and meaning in living entities.

In Part Two, Philip Ball and Sir Paul Nurse discuss the intricate complexity of life at the cellular level and the challenges of understanding biological systems. Nurse emphasizes that life is not a simple, algorithmic unfolding of genetic instructions but a highly dynamic process requiring feedback, responsiveness, and adaptability to context. Nurse highlights that cells tolerate and even benefit from a degree of imprecision and variability, which prevents them from becoming stuck in rigid states. This concept of biological "sloppiness" contrasts sharply with engineered machines, which rely on rigid mechanisms and backup systems, underscoring the unique nature of living systems. He also stresses the importance of moving beyond mere data collection toward the develop of theoretical frameworks and ideas that explain how complex life organizes itself in time and space. Ball and Nurse's conversation shifts the perspective away from a reductionist, gene-centric view of biology to a more integrated picture of life as an intelligent and flexible adaptive system.

How Life Manages Complex Information

Philip Ball

It seems to me that a lot of the complexity that's coming in here, and again, particularly for multi-tissue organisms like us, has to do with the fact that there need to be feedbacks and responsiveness in the system. It mustn't actually be simply an unfolding of a program in a kind of algorithmic way. There has to be a sensitivity to the context.

Paul Nurse

I am in the same place as you. The important thing is the management of information. Cells work their way through series of events that lead to outcomes, and there are checks and balances going on during that chain of events so cells don't proceed with one set of reactions unless necessary previous sets of reactions are in place. All this is integrated together, which is the basis of the extraordinary phenomenon of life. Investigating this is complex and difficult.

Let's have a conversation about understanding these networks. Some people think they can be modelled bottom-up. They model every enzyme and its kinetics going on in the cell. Except you don't really. The kinetics are determined mostly in a test tube, which is different compared to a cell. A cell is not a free solution, it has quite different properties. I'm not criticising doing *in vitro* biochemistry, we learn a lot from it, but we should recognise things are different in a cell. We have to try and understand how these thousands of reactions are carried out simultaneously and are coordinated within a cell.

Another problem with modelling is when you've got five hundred reactions or more, you can create anything you like, and as soon as another experiment is done, you create another different variant of the model. It's not very satisfactory.

I think we should try and divide the cell into regulatory modes, black boxes with important inputs and outputs. We don't need to care too much what's going on in the box itself. There might be hundreds components in there, but if we just focus on it as a single regulatory unit, then we need only to describe the major inputs and the major outputs. We still may have to put together hundreds of those, but maybe not thousands of them. Maybe then we've got a chance of sorting out what really is important.

Philip Ball

I would imagine, if we are talking about a black box that might have a hundred, or several hundred components, that there has to be some flexibility with how those systems are working. Because if you're relying on having every one of those components there in the right place, at the right concentration, at the right time, it's not going to happen. There must be something about those systems that is able to accommodate the kind of variability we get in cells.

Paul Nurse

This is correct in my view. I had a research project in my lab carried out by my graduate student, Clovis Basier which emphasized the need for fluidity in the networks. If everything is tightly connected and regulated, the cell runs the risk of getting ‘constipated’, all ‘gooed’ up. It might then end up in some part of control space from where it can never escape.

So, there is an advantage in being sloppy, because if you're sloppy, most of the time it sort of works. Maybe it doesn't work quite as precisely as we would engineer it to be, but it means that it doesn’t end up somewhere in phase space where it can't do anything more, because its stuck. We came to this conclusion by measuring the rates of overall protein synthesis in a cell. What was interesting about this was that it was very variable cell to cell. So that, if you investigated a population of cells growing under similar conditions, the means of different populations would be identical, but if you looked at cells within each population, the cells were very different.

I'd always thought that there'll be some variability, but it would be small, because there's hundreds of reactions involved in protein synthesis and they'd all average out. But it wasn’t like that. There was a lot of variability. Not only that, if we followed an individual cell over time, say 20-30 minutes, the rate would change moving towards the mean. The cell was correcting itself.

We screened fifty different gene deletions and measured the rates. The level of variability changed with different genes, particularly genes in a pathway called TOR. What this means if it is true, is that the system is much sloppier than we tend to think and also it is genetically controlled.

Human beings like things to be ordered. That's how we are. But maybe cells and living things are more sloppy. Perhaps the cell has to be sloppy to avoid, as I said, getting stuck in phase space.

The Advantages of Sloppiness, Why Life is Not Like a Machine

Philip Ball

Well, that is just the perfect point to launch into what I wanted to speak about in terms of the broader picture of how we talk about these things. Sloppiness is a great way to think about it. I think people can relate to that because we have to have that in our lives. Companies have to have that. When an employee is sick, you can't stop the whole company because they are unwell. We have to manage variability and fluctuations all the time.

But the narrative, I think, that certainly has come out into the public arena—even if it's not the one that geneticists like yourself actually recognize now—is that life is machine-like and that it is a computation that is basically a sort of readout of what's in the genome.

In this story, the information that matters is in the genome, and cells just read that out. That's one of the things that has really changed, ironically, since the end of the Human Genome Project—and perhaps partly because of the fact that that project showed we've only got twenty thousand protein-coding genes to work with. There must be something else to that story.

Do you think that's the case? Do you think that, first of all, we are still stuck in this old paradigm that says life is just a readout of a pre-existing program? And if we are stuck in that story, how do we change the narrative?

Paul Nurse

The changed narrative that you're describing was a way of thinking about life which was more predominant when I was a student, in the 1960s and 1970s. It was talked about by theoreticians a lot. They didn't get that far, but did reflect upon the organization of structures and functions and the forms of life's complexity. For example, Conrad Hal Waddington edited a book, *Towards a Theoretical Biology*, which aimed to develop general principles and frameworks for understanding living systems.

Philip Ball

Yes, and Waddington was, as I understand it, explicitly pushing back on the genetic narrative that was starting to develop.

Paul Nurse

I knew him when he was a Professor in Edinburgh and we used to occasionally go drinking together. He was a geneticist, but had no problems combining that with different ways of thinking.

After that time there was a period, which you're probably referring to, when people talked a lot about genes. From my perspective genes provide a very powerful paradigm, but in trying to understand the complexity of life, while genes are an extremely important element, they are only part of the story. In *What is Life*, I emphasised information and that is what we need to think about as well.

We've also been distracted I think, because of the word "systems biology." I am basically a systems biologist. But we now think too much that systems biology is just collecting lots and lots of data without trying enough to work out what the data means.

People say they are taking a systems approach when they identify and describe the behavior of every protein, every RNA molecule, or whatever. I do that type of work too, but I don't pretend that it explains enough because it doesn't.

Philip Ball

Well, that's one of the many reasons why we're very keen to speak to you about this, because you have said that and you've written about it.

This tendency to collect what can be immensely useful data can, it seems you are suggesting, overwhelm any readiness to step back and actually think, "Well, what does this all this data mean? What are we going to do with it all?"

It is as though we think the understanding is somehow going to fall out of the bottom once we reach a critical mass of data, but that isn't the case.

As you said, "Actually, we need ideas as well. We need theories and we need thinking." So, I wonder whether you feel able to say what you think those ideas might look like?

Paul Nurse

I don't really know but, I do think it is a step forward to say that's what we need to do.

There is a poem, a First World War poem, called “Naming of the Parts.” It was naming the parts of a machine gun I think. We have got too enthralled by the naming of parts, without thinking of how the parts work together to do something.

We have to think more about the ideas that are underpinning life. I think it has a lot to do with understanding complexity, understanding how you can get organization in time and space. I had such a conversation with Sydney Brenner about how to do this, he was a great molecular biologist who also thought about whole organisms. I wondered whether we might need to develop different ‘languages’ to put this together but he disagreed. He said, “No, Paul, we don't. We don't need to do that.” He was probably right but we should think of how we can better describe what is happening and how to link different perspectives together.

In thinking about complex systems and life, it might be useful to consider machines that human beings have made. A good metaphor is a laptop computer. When something goes wrong with the computer then it crashes. We recover it simply by turning the computer off and on again, but life obviously cannot work like that! So to avoid having to deal with a cellular control system ‘crashing’ the cell may have evolved a ‘sloppy’ way of working to avoid getting stuck in a control phase space from which it cannot escape. And we always need to remember that cells are far more complex than our laptops.

So sloppiness would be one of the concepts I would explore further. Stochastic behavior is another one. We tend to be over-influenced by enzyme kinetics which works at a population level, and can be described with kinetic equations. But when thinking about the enzyme-substrate relationship, it is more stochastic, and so we have to introduce more thinking about stochastic behavior.

There's another practical reason for thinking more about ideas. There's a range of biology textbooks, some that have been around for years. With each new edition they grow in size because they have added more and more *particulars*. Particulars are important, especially for medicine because you need to be aware of details to treat people. But do you think we're going to excite and stimulate students with more and more particulars, when all they need to do is look them up in Google? Why do they have to remember all these facts? We should be focusing more on ideas in our teaching.

Let me give you an example. There are molecules called GTPases. We can list all these different GTPase proteins and all the things they do. They're called Ras and other names, and they do all sorts of important things. But you can reduce them to a more abstract description such as acting as timers or switches. And if we move

away from just describing the chemistry and the particulars, and deconstruct what we know into switches or toggles or other informational devices, then we might have a better chance of understanding biological processes. We can then put together control modules to build up understanding. That's the sort of thing that we should be thinking about, and maybe that's a route to getting more ideas and more interesting teaching.

Philip Ball

You mentioned that there are practical reasons to want to grapple with these ideas. I thought perhaps you were going to say one of them is we want to make sick people better. We want to find cures. You say a really important and interesting thing in *What is Life?* about that issue.

You say that, actually, if we want to do that, experience leads us to think that the most useful intervention, the most effective intervention, is one that is going to be at the level at which the phenomenon is really occurring. Which doesn't necessarily mean going right down to genes or to molecules. It can be higher up, and that's often what we see medicine doing.

So, in that regard, you also make it clear here that we definitely do need to recognize life as a multi-level phenomenon, with each of the levels not necessarily depending in any fine-grained way on what is going on down below. It's a fairly coarse-grained thing that's coming through to the next level, which has its own set of rules. So if we're wanting to make an intervention, we need to know which of those levels we need to intervene. Is that a fair way of describing what you say?

Life as a Multi-Level Phenomenon

Paul Nurse

Yes, it's a fair way of describing that there are different levels, and explanations should be provided at the level which is most appropriate.

How people normally think about levels is in terms of how these components lead to the level above. What isn't so often talked about is how the levels up constrain the levels down. A higher level of organization can restrict the freedom at the lower level. I think this is important—the reductionism is important, we need to understand that, and it is needed as a starting point. But then we need to know how those components are restricted by higher levels of organisation. We are not thinking about that enough, because biochemists and molecular biologists like me tend to look at the *individual* components at the same level in isolation. We can

increasingly investigate living cells, which will have constraints from higher levels, and I suspect that will open up new ways of thinking.

I first came across such constraints when I was reading a paper from a theological journal. By the way I think it's important to read and think about ideas beyond what you actually study yourself.

Philip Ball

I'm thinking about the issue of top-down control of what's going on at lower levels. One of the things that made me appreciate that that was going on, as I was writing this book, is the issue of splicing: the alternative splicing of proteins.

A single gene can be converted to RNA, and can then be put together in various ways to encode a protein. So, you get different proteins from the same gene. We've known this since the 1970s. And that seems to happen sometimes for some proteins in a tissue-specific way, which kind of really challenges the idea that, "Oh, well, at least we know that the protein is encoded in the gene." Actually, no: part of that decision is made at the higher level of what type of cell it is, what type of tissue it is, and that difference can be crucial. And it was that kind of thing that made me think, "Oh, crikey—there are some new narratives here." And then I came up with this book.

So, I wanted to ask you, finally, if there are developments that happened over the past, say, twenty or thirty years in biology and cell biology and molecular biology that have prompted a change in your thinking about how things happen, how life all works.

Paul Nurse

I've been lucky that I was trained, in my early research life, in a more loose and open way of thinking about mechanisms. Only later could we exploit the power of the ability to manipulate genes. That is why I worked with yeast because we could do gene editing in 1980, which was very powerful. But the experiments were also embedded into an ideal way of thinking which was helpful.

There is a lot of variety in detailed mechanisms, but the basic principles can bring clarity. I tend to hang on to basic principles, so I don't get bewildered with all the complexity. Some might criticise that as being too simple though.

The way we worked out the details of cell cycle regulation was to strip the system down to the simplest control system that worked. Human cells have many cyclin-dependent kinases and many different cyclins, and there's a great variety of different

things that probably reflect the need of a multicellular organism to work. When we started with working on this in fission yeast—we discovered six different CDK/Cyclin complexes. Six for meiosis, four for mitosis. Then we found we could engineer a cell which could work perfectly well with just one CDK/Cyclin complex. Now, what we were doing was to simplify the system so that we have the capability of understanding it, and then with that understanding we can better understand complexity. If you try and understand complexity first, then you might just get confused. When Mendel did his experiments, he worked with around six different species of flower and could not make sense of most of them. The traits in them were polygenic, polygenic in determining characters. So he chose the pea and he chose characteristics, which gave simpler answers because they were more monogenic. He chose them because he got ratios like three to one, nine to three to three to one, and could interpret them in terms of particles which led to the concept of the gene.

Mendel was choosing a biological system which was simpler to understand, which could then be used to understand complex ones. And what we've done with our yeast cell cycle studies is to make the control system simpler so we could work out principles, before trying to interpret the complexities.

Samuel Loncar

Paul, your spoke so much about management of information, the incredible power to measure size and fundamentally, therefore, the capacity to organize space and time.

So, what you're talking about in the cell is a *system* that can organize space and time dynamically for its own interest. Would you object if a person said all of the traits you describe in the cell are traits of executive intelligence?

Paul Nurse

Ah, yes, ‘intelligence.’ When we're thinking of cells and what they do, purposeful behaviors, you can reasonably ask, “is this an example of intelligence?”

If we only imagine intelligence in terms of human behavior then it isn’t helpful. It doesn't make any sense, because we're thinking about the way a brain works, which doesn’t apply to a cell. But if we have a wider view of intelligence, then it's not unreasonable to say that the cell is behaving intelligently to produce purpose and agency.

These terms are related one with another, and if it's helpful to include intelligence, then I think we should do it. If it encourages people to think about these ideas and

about how the cell works, as against endless descriptions of lots and lots of molecules, that's got to be a good thing.

Philip Ball

So, you're happy to think of cells, in some sense, as intelligent entities?

Paul Nurse

Yes, as long as we define intelligence in a more open way.

Philip Ball

Paul, you have put context around so many of the things that I was hoping to cover and that I hope this project generally will cover, so that's going to be fantastically helpful.

Samuel Loncar

Yes, thank you both.

Paul Nurse

That was very good. Thank you.

This interview has been edited for clarity.

Paul Nurse *is a geneticist and cell biologist whose discoveries have helped to explain how the cell controls its cycle of growth and division. Working in fission yeast, he showed that the cdc2 gene encodes a protein kinase, which ensures the cell is ready to copy its DNA and divide. His contributions to cell biology and cancer research were recognized with a knighthood in 1999, and his endeavours relating to the discovery of cell cycle regulatory molecules saw him jointly awarded the Nobel Prize for Physiology or Medicine in 2001. Over the last thirty years, he has held many senior research leadership roles. In 2010, he was elected as President of the Royal Society for a five-year term and since 2011, he has been the Director and Chief Executive of the Francis Crick Institute. He is currently President-Elect of the Royal Society for a second term.*

Philip Ball *is a scientist, writer, and a former editor at the journal* Nature. *He has won numerous awards and has published more than twenty-five books, most recently* How Life Works: A User's Guide to the New Biology; The Book of Minds: How to Understand Ourselves and Other Beings, From Animals to Aliens; *and* The Modern Myths: Adventures in the Machinery of the Popular Imagination*. He writes on science for many magazines and journals internationally and is the* Marginalia Review of Books' *Editor for Science. Follow* @philipcball.bsky.social

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