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Interview with Sydney Brenner[1]

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ABSTRACT

The following text is an edited version of a recent interview with Sydney Brenner who has been at the forefront of many developments in molecular biology since the 1950s. It provides a participant's view on current issues in the history and epistemology of molecular biology. The main issue raised by Brenner regards the relation of molecular biology to the new field of systems biology. Brenner defends the original programme of molecular biology—the molecular explanation of living processes—that in his view has yet to be completed. The programme of systems biology in contrast he views as either trivial or as not achievable since it purports to deal with inverse problems that are impossible to solve in complex living systems. Other issues covered in the conversation concern the impact of the human genome sequencing project, the commercial turn in molecular biology and the contested disciplinary status of the science.

SdC: I would like to start with a very general question. What, in your view, are the main issues for molecular biology today?

SB: I don't think there are any issues. I think people have created a lot of problems, and what still remains I think is the path for explanation. I think this puts molecular biology in contrast with what is called systems biology which is the opposing thing basically, as the two cannot be compared, because systems biology isn't science.

SdC: Systems biology is not science?

SB: We can forget about the claims of systems biology because they cannot be achieved, and I will explain why in a moment. If you say we have to study the system, of course we agree with that. We used to call this physiology. So to me it seems pretty straightforward that the programme of molecular biology just continues to its completion. There's no new path to follow, in my opinion.

SdC: Systems biology was of course one of the topics I hoped to get to.

SB: Of course. Let me try and explain now why I think its programme cannot be achieved, right? So the first thing, it is looking at inverse problems. And these are extremely difficult to deal with but we *know* the conditions under which they can be solved. Let me give you a classic example of an inverse problem. It's the one in crystallography; most people know about the issues there so they can see it pretty quickly. Right, so the question is: can you go from the diffraction pattern to the molecular structure? We know if we have the molecular structure, we can calculate the forward problem. Can you calculate the diffraction pattern? Sure we can because we've got a whole lot of physics and Bragg's law, and all of that stuff. But could we reverse the issue and go backwards? That would be solving crystal structures directly. Now, you can't do it for the simple reason that information is lost. What's the information loss? It's the phase information because all you are measuring is the intensity, and the intensity is the amplitude squared, and if it is '– 4' or '+ 4' you can't tell the difference because both squared are 16. So there is a clear-cut case of a real typical inverse problem.

Alright, how can you solve inverse problems? Well, the first thing you can do is basically to get more information. But you might say, 'Well, why don't we try all the phases and see which one works?' And of course we know that with big molecules you can't do it. You can do it with small molecules. You can do it if

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[1] Sydney Brenner is widely regarded as one of the pioneers of molecular biology. He shared the 2002 Nobel Prize for Physiology and Medicine. For a detailed account of his career see his autobiography (Brenner, 2001).

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you have large computers. You can calculate everything and see the right one that will work. But there's the wonder of molecules—the size of the molecules increases and the number of diffraction spots goes up. It's one of these problems that no computer can solve. We'd be calculating from the beginning of the universe until the end of the universe. Okay. Another thing you could do is inject *a priori* information—which is exactly what Watson and Crick did. What they did is, they made a theory. And of course, the theory was based on other information and so on. And when they put that into the machinery, they got the right answer. So, if you can define the model—in terms of a theory—you can prove that it's correct. But of course, to get to that model, what you have is essentially a statistical distribution of all models, which is enormous. And you cannot treat all possible structures in much the same way. Now, systems biology purports to be able to solve the inverse question. What it intends to do is make enormous numbers of measurements with micro-arrays and everything like that, and then it says that by putting all of this information together, it'll form a model of how the system is working, and that'll be the theory. And this is not achievable. It's not achievable for all the reasons I've given. One, you cannot make the measurements accurately enough, you lose information in making the measurements, just in terms of what you can do. And there is another frightening thing in biology, which is that if you suppose that all those numbers that you measure are fixed numbers—that is they are valid, and you've made accurate measurements of them—you still have to understand that in an evolutionary system, not everything becomes fixed because there are 'don't-care conditions'. So you could have things that fluctuate because by the theorem of natural selection, if it has no effect on the organism or its reproduction, nothing will be selected. If you wish to fix the number in a biological system, whether it is an affinity constant or not, it has to be encoded in some form. And that's the cost in evolution. It all has to be encoded in such a way that it doesn't confuse with anything else. So if you want to do things specifically in biology you have to pay for it in sequence information. But if it doesn't matter, why bother to pay for it? Now that means that many of the numbers that we think we are measuring, which we think will have validity, probably have no validity at all.

SdC: But isn't that a problem that molecular biologists would also run against?

SB: No, no. Molecular biologists actually solve the forward problem. That is, they can find out what each of the components is doing, and then compute the whole from this. Now of course people say, 'No, you can't get that information about a system from the individual components'.

SdC: Because of emergent properties—.

SB: That's another thing that I raise my gun against.

SdC: (Laughs)

SB: So, let me tell you that the correct quotation is that 'the whole is greater than the sum of the parts studied *in isolation*'. The whole cannot be greater than the sum of the parts and their interactions. In fact, it is the interactions of the parts that compute the whole. I just put it in form of 'compute' but what is the nature of this computation? This depends on the way you look at so-called elaborate systems and some other problems. I believe that people hold their hands up in horror over 'we've got twenty thousand genes expressing, and everything is a mishmash, and how are we going to sort this out?' Well, that's a problem biology would have to solve. And I believe that biology never solves many problems because they're all like income tax. Namely, it is criminal to evade, but legal to avoid. So biology has no molecular tricks. Instead of measuring concentration, for example—which of course has to be fixed in all of these models, and people scratch their heads about it—it counts molecules. I can give you all the detailed molecular mechanisms as to how molecules are counted, because they are by the actual structure of the thing itself. So basically, the task of molecular biology is to just get on with finding out what the pieces do, what they interact with, and putting that into the equation. So it is not a system of a lot of things interacting and running around. That's nonsense. Because if it were, we wouldn't be here basically, because those systems are metastable; they either explode or collapse. They cannot maintain such a state. So by the evidence of our existence, and by the existence of other complex structures, we know that cannot be the case. And some solution has had to be found. So I think you've just got to see what there is. Now, why do I still say molecular biology? Actually, the actual unit to look at, in biology, is not the molecule, or the gene, it's the cell.

SdC: So that's where systems biologists and molecular biologists could actually meet, because they would both say that.

SB: Yeah. Of course they both say that. But we say that it has to be done at the level of the cell, as it is the useful intermediate level of all analysis. And then you have something that effectively can cover the whole of living matter because it's all based on cells, whether there's one cell or many cells. And you can consider the cell as a network of molecules (using network in a general sense). And you can consider the body as a network of cells. So it's all now to be explained as a sort of branch of communication. And that's the way I think we've got to look at it. All these units send messages to each other.

SdC: So would you still want to speak about systems? Or do you not need the term system?

SB: No, I don't need the term 'systems biology'. I want to explain the brain. I know that it is a very complicated system. I know that there is behaviour of the entire system. I'm not going to explain it by systems biology. I'm going to say that the brain is a network of neurons. So first I find out about neurons and then—it is what I call middle-out as opposed to top-down and bottom-out. You go from neurons or cells to the organisms and from cells downwards to the molecules. And our task is simply to formulate this in the correct way.

SdC: How would you respond to the argument that the molecular level is too reductive? I have in mind the example of the table and the atoms. If we want to explain the table, and speak about atoms, we don't get very far because what a table is can't be explained on the level of atoms.

SB: That's okay, but biology is different. The whole basis of what we are, and what we do, and how we grow and develop, die, perform, act is encoded at the molecular level. At the end of the day our fundamental problem is to understand exactly what this genetic script really means. That's why we have to stay at the molecular level. Because, we know that if we would go through all of these levels and we would find that this interaction between two proteins was this little strip of this gene, and a little strip of that gene—. And this change can then be amplified throughout all the levels of interpretation. So I see no difficulty. I mean, I wouldn't want to explain everything in terms of molecular motion. So people say, 'Well, how do you account for stochastic things?' You see, we can look at stochastic things, but at the end of the day, there must be some way of ignoring all the problems or using them. That's the other thing, biology learns to use various things. So that's all our task is. And I see all the people say, 'We don't need molecular biology. We make measurements of the output and we will deduce the nature of what's in the box'. I think it's not achievable. Hadamard