Course Name: I think Biology

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Lecture:9

W2L9_Experimentation vs Theory_Discussion

Hello everyone and welcome back to the NPTEL course, I Think Biology. I am Prachi Gupta and today we have a lecture on experimentation versus theory in biology. So this session is going to be a special interview on this topic. Joining us today is Dr. Shashi Thutupalli, who is a researcher and associate professor at National Centre for Biological Sciences. He has more than 10 years of experience in research and teaching.

His research interest focuses on understanding living world, origin and organization of the living world. And for his research, he combines theoretical and experimental techniques from diverse range of topics such as physics, engineering and biology. Welcome Dr. Shashi, thank you for joining us today.

Can you start with telling us more about your area of research? Right, So as you said, the work that goes on in our lab is at the interface of many disciplines and the traditional disciplines such as engineering and physics and biology. But the source of our questions are from the living world right? So very broadly speaking, we are interested in asking how does the living world operate? For example, how does a cell operate? And to answer that question, we draw from techniques in biology, engineering and physics and mathematics and so on. We draw tools and techniques from these various disciplines but one must understand that the natural world inherently has no disciplines. It's operates free of these disciplinary constraints, it's just operates.

And it's only how we view it in order to classify our knowledge and understanding that we impose these disciplines on something like the living world. And That said, in my lab what we are trying to do and I'll give you one example of the various things, what sort of organization or what sort of organizational principles underlie living systems? Okay, so let me give you a very concrete example. There is this question that one can ask of the living world because organisms out there range from the very small single cells such as bacteria and so on to the very large such as a blue whale for example right?. A question might be because we call all of these things living, what is common among all of these things? This has been a trait that has driven our curiosity for a long time and of course we have identified many features and that is what we call biology or the living world and so on. So And we have discovered many features such as all these various objects that we have talked about such as the bacteria or the blue whale, they exhibit certain features, they grow, they divide, they metabolize, they have a certain chemistry, biochemistry, they all have DNA and so on and so forth.

There are these common principles. One may ask a slightly higher level question, how do they metabolize? Okay Because they all need to convert food into function as well as their own body mass and so on. How do they made, is there anything common in the way they metabolize? And so people have been asking, so let's say if I ask about how much or what the metabolic rate of an organism is as a function of the size of the organism, is there something systematic or relationship between these two quantities? right? And so this has been over the years codified as the so called Kleiber's law in biology and this data is comes in the form of a graph because we plot this. On the y axis of this graph is the metabolic rate of an organism. On the x axis of this graph is the size of the organisms. Okay.

And one might say, hey, there need not be any trend between these two to start with okay. If I look, is there some simple relationship connecting these, there may not be. But it so turns out that there is a very simple and beautiful relationship where if I look at the metabolic rate of an organism as a function of its size, all the data seems to fall on some line Right?, on a log log scale, which means that it has some power log behavior. So then the question becomes, I mean, there's something very systematic here. Why is this the case? Is there something very fundamental and universal about the way organisms metabolize? Right? So that's a question that we are trying to tackle in my lab. right?

So what people have done typically so far has been to collect a lot of data from organisms in the real world, make measurements of this metabolic rate and say, hey, I'm going to make something very systematic and then try and understand what is the underlying cause for such a relationship between the size of organisms and the metabolic rate. So we are devising, for example, an experiment to do this where we are generating in the lab organisms which span many orders of magnitude in size and then trying to measure the y-axis in very controlled ways in the laboratory and then asking, can I generate an understanding from that? What does it mean now to generate an understanding? It means ultimately to describe a theory okay? Okay in order for us to make sense of these observations. Okay. So in that sense, there is a strong interplay between theory and the experiment, the experiment here being making the measurement of the metabolic rate, generating the organisms in the lab and so on. Can you elaborate on what theory really is? As I said, we want to use theory to understand this is what I said. Right? So let's take a step back and ask what theory itself is and maybe to even begin answer that question, we have to take two steps back and say what does doing science really entail? Right? Doing science means that we are making observations of the real world and once we have a set of observations, we ask the question, is there something underlying these observations which helps us organize these observations? okay Just like what we talked about earlier where we said I have all these objects, bacteria, cats, mice and so on and we want to classify them and we have classified them into biology. Right? Yeah

So just like that, you know people in the past used to make observations of the positions of the stars and from the positions, from these observations, they started to notice that there are some patterns which come about and these patterns are both spatial, meaning that some stars and planets occur in some spatial locations but they also occur with some periodicity. So now once we have made these observations of the real world, we start to think about these patterns and apply let's say some statistical measures to explain those patterns in some quantitative way, Right? some let's say periodicity with which these planets and stars appear in the sky Right? and so on. So that becomes data which we want to explain now Right? and out of that data has also come about some statistical relationship but the statistical relationship is simply a pattern that we have observed. It's not an explanation of the pattern. Right? The explanation, the mechanistic explanation of that pattern comes from what we call a theory. Okay ? okay.

So to sort of give, to make this even more concrete, there were these observations of the positions of stars and planets and so on and which was done by many people in the past Yeah and someone like Kepler came and formulated simple relationships between the periodicity of an orbit and the position of a planet and so on and then came Newton Right? Yeah and he said Aah, based on this data and these statistical observations, I propose a quote unquote theory Right? which proposes a mechanistic reason for why we observe that statistical pattern. Okay? Yeah What does this mechanistic reason mean in this case? He invoked the concept of a force on a body, the fact that a force can emanate from something called a potential, that can be a certain form of a potential and then going, and then here comes in this particular example the use of mathematics. Right? So he formulated this theory or ideas in a set of mathematical equations okay which then allows him insight not only to explain these observed data but also potentially make predictions Yeah into the future or not just into the future but also into other systems. Right? For example, famously the apple falling down from a tree. He was somehow in a stroke of genius able to connect the apple falling from a tree to these planetary motions Right? Yeah and that in some sense is an understanding that we get of this phenomenon of gravitation Yeah right? which is the theory which we have used to organize our knowledge about these planetary motions or motions in the real world and so on and so forth.

Can you give us some examples on where theory is used in biology? Yeah, that's a very interesting thing because we started from biology, we have gone now into an observation of the physical world but there are equally old and interesting applications of theory in biology as well. A very famous one that we many of us would have heard about is the so-called theory of evolution that Darwin has Darwin has proposed and at first glance a difference between let's say

Newton's theory of gravity and Darwin's theory of evolution might be that one seems mathematical the other not. Yeah That could be one difference that we can note. And the other of course is obvious which is that this is a theory of the biological world right? But the way both these theories have come about is very similar in their origin in the sense that there was a set of data and observations. Right? In the case of gravitation there was a set of observations related to planetary motions so on and so forth and in the case of the theory of evolution there is a set of observations that people have been making about the real world Yeah trying to classify organisms into different taxa and so on and so forth and what Darwin did was to use all of that data and sort of bring them together within a framework which is to say that I can now explain or I can propose an explanation for where all of this diversity in the living world might have come from yeah right? And which is to say that he has combined this idea of heredity and diversity and a process of selection and so on Yeah which ultimately gives rise to the diversity that we see in the natural world. Yeah

So that's one example of a theory in biology and I must also say over here that in this way of thinking a theory is an organization of facts and data into a framework that we can use to explain the world right? But a theory is not just a way to organize things but it also provides us an opportunity to make predictions Yeah of other situations that may not have been captured by this data okay okay? And so here is an interesting example of such a scenario. Again a very well known example in biology not at the scale of ecologies and evolution but at the other end of the spectrum the very small that of the structure of the DNA Yeah right? So famously Watson and Crick figured out the helical structure of the DNA but they also proposed from their model building and generation of theories that there was a certain way in which the basis of this DNA paired with each other and here comes the predictive power of their theory which is that once they had figured out that this molecule had such a structure and such an organization they said this could mean that this is a way in which the DNA molecule can make a copy of itself Yeah right? And not just that so that is a prediction that you know there is a mechanism which exists for the copying based on this theory that I have developed but they also suggested there could be a code that this molecule is having Yeah right?

So this is a very simple example of a predictive power of theory which we will verify later. Really interesting examples also you have talked about physical world and biological world but how do these physical principles they shape our living world? Right yeah absolutely so the principles of physics, chemistry Yeah they operate without care for whether they are operating on an object which is purely physical in nature okay or biological in nature etc. Right? So in this sense biology is constrained by the laws of physics and chemistry. Biology is not outside of what is possible within the realm of physics and biology and therefore principles that emanate from these physical forces etc. do indeed govern how biological organisms themselves are organized or function. Okay For example the shapes of organisms okay these cannot you cannot form a shape which is unallowed by the laws of physics and chemistry. Right? Okay You cannot for example our muscles cannot generate forces which are disallowed by the laws of physics and chemistry. Right? So that is one way to think about it.

The other way to think about it is to say hey look given a set of physical and chemical constraints how can that shape or how can that constrain the functional organization of biological systems. Okay This theory in biology that we are using is theory in biology different from theory in other disciplines? Right so again maybe we take a step back over here and remind ourselves Yeah what we said about what theory was. Theory is a way of organizing the knowledge or data that we have collected about the world right. So in that sense there is no difference from a theory that is applicable to biology or physics. It is a framework which we have used to understand data.

In one case the data has come from observations of the physical world. In the other case it has come from observations of the living world right. And that said the other thing about theory is that it also has this predictive power namely that based on a set of observations I have come up with a framework and the power of this framework is that not only does it explain what we have seen but it also has the potential to say look now if I look over there which you haven't looked at before you might find this answer right. So that is another application for a theory and all of this is common to both physics as well as biology and even chemistry right. This way of developing theories and using theories.

Where a difference comes is in the very complexity of the biological world that we deal with okay right? Biology is much much more complex yeah in its origin, in its functions and all of that compared to the objects of study in the physical world right? And therefore therefore it is not obvious at all that the kind of theories that we develop and the way the kind of tools for example the mathematical tools okay that we use to describe the physical world may not necessarily be adequate for the descriptions of the biological world right?. Okay So that is more a limitation of the language or the mathematics that we may use to describe biological systems but once that is developed theory or framework its use in organization and its use in making predictions is the same across disciplines. Okay As you mentioned that mathematical principles are a little bit different in physical and biological system. Am I understanding it correctly?

Right. Maybe I should elaborate and clarify. So it is not that we use a different mathematics okay so to speak when we describe the physical world or the biological world currently. It is It is the same language of mathematics okay that we use. What I was trying to allude to is that the kind of mathematics that we have or the kind of reasoning that we have from that framework okay may not be adequate okay currently in its form to the application to the biological world. Okay

But that said I must clarify that there have already been spectacular examples and spectacularly successful examples of using mathematics in explaining biological phenomena. Okay Darwin's theory, the theory of evolution being one such right. Even though Darwin himself did not develop the mathematics people later such as Fisher, Wright, Haldane and so on developed a variety of mathematical tools which are used in understanding this process. Okay How does mathematics help us to understand these biological processes? Can you give more examples for us? Right. So a concrete example that I can give you also comes from thinking about evolution Okay and this is the particular example of asking if mutations in biology yeah and by mutations we mean when organisms grow and replicate they not necessarily replicate perfectly they make copies which are slightly different from the parent and so on and that ultimately gives rise to selection and so on as as you all may know.

So the question that is being that is being answered is the following one which is do these mutations occur spontaneously at random or do they occur in response to some selection pressure Okay that is imposed on them? So this was famously asked and answered by a pair of scientists called Luria and Delbruck. Okay Luria was a biologist and Delbruck was a physicist who entered this field. So in this experiment what Luria and Delbruck did was to ask if bacteria Okay have the resistance to survive the attack from a virus, Okay right, if they have If they have resistance to a virus and whether that resistance is pre-existing, in other words those those mutations appeared in the bacteria beforehand Okay or did they appear when they were presented exposure to the virus. Okay So that that was how they devised the experiment. Let us remind ourselves the question here is are mutations in these bacteria or more broadly in living systems occurring spontaneously or are they occurring when they are faced with any particular situation Okay in which that mutation may be useful. Right? Okay.

So what they did was to have many different conditions where they exposed these bacteria to viruses okay? Okay and based on a mathematical framework that they had developed they said that if I look at the number of bacteria that have survived in these various replicates of the experiment yeah it should follow a certain distribution. If it follows a certain distribution it means that the mutations were pre-existing. If it doesn't follow a certain distribution it means that they are occurring in response to exposure to the viruses. Yeah okay And what they found was that the mutations in the bacteria which gave the bacteria resistance to survive exposure to the viruses were existing already beforehand, even before they were exposed to the viruses and they were able to come to this conclusion because of the mathematical framework okay that they had developed. And in some it is not a very sophisticated mathematical technique in the sense that it relies simply on counting statistics.

And therefore such a mathematics although very rigorous and although fairly sophisticated is not inaccessible in general. Okay yeah That's a very interesting example. So how do theory and experiment feed into each other? Ha This that I just talked about is a fantastic example of how theory and experiment fed into each other. In this particular case they started with a question yeah and they had a they had a certain theory or an math in this case the theory had already resulted in a mathematical framework yeah that they had in mind and then they devised an experiment and based on the measurement that they made in that experiment they were able to compare the outcomes of the experiment with the theory that they had developed or they had in mind. Yeah right? And so this is a very nice example of how theory and experiment went hand in hand. Right?

But this is not always the case. Okay As we talked about earlier, observations yeah came before some systematic investigation was performed or some statistical patterns were observed in data. Right? So in that sense an observation leads to a pattern which leads to a hypothesis okay which can lead to a theory which then subsequently might give rise to more predictions and therefore more experiments and measurements. So it's sort of a circular loop but more often than not it always starts or not just more often than not the development of theory initially is led by some observations we need an explanation. Yeah But once that is there, for example in current physics you know the correspondence between theory and experiment has been so strong, the inter the cross talk between theory and experiment has been so strong that theory often leads experiment in physics. Okay. And therefore experiments are often looking to confirm some theoretical predictions rather than the other way around. Ah okay interesting.

So in this interplay between theory and experiment where do simulations fit in? Ah That's a very nice question because one often imagines simulations to sort of be a substitute for theory or to be theory itself yeah and and so on. So one must understand what exactly is a simulation. A simulation is often performed on a computer these days but that need not be the case. Right ? okay It could it could have been performed on some physical model itself which a good example of that again is the famous Watson and Crick study right? So they had developed these ball and stick models of the of the DNA. Right?

So in some ways with their playing around with many different combinations they were simulating many different possibilities in their physical model. Okay Often these days this is done on a computer rather than by physical models. Right? And so what we are saying over here is that before simulating something one has a model of something. Okay. One might even view of the model as a starting point for a theory itself. A model in some ways is an abstraction of the world okay saying that I am going to incorporate this feature and this feature and this feature and not try to include everything. Okay. Right?

And then ask based on these features that I have put in and based on some assumptions that I have made yeah can I start generating things which look similar to what is observed in the real world. Okay? So once a model has been developed and let's say it has been translated into the language of mathematics okay or into some algorithmic form that can be implemented on a computer. And that is what we would call a simulation. Okay. And what these simulations allow us often to do is one to check theoretical ideas okay in a fairly fast manner without having to perform in some cases costly experiments. Okay. Or it might also allow us to explore situations in which performing experiments is very difficult. Okay?

It might allow us to change some conditions okay which are not so easily tuned in an experimental setting. Okay. And that is the power of simulation. Okay interesting. Once a simulation has been done, one might then say okay I will perform an experiment in order to see if there is a correspondence between those two as well. Okay. And what that allows us later is to gain confidence in the assumptions that we have made in order to build a model and develop a simulation. You talked about that sometimes we instead of doing experiments we start with simulations, right? So how accurate are these simulations in predicting the results of an experiment? Right.

So what I what I said was before starting with the simulation there is a model that we develop yeah that we want to simulate. And this model by construction is an approximation of the real situation. What do we mean by that? We mean that we are not capturing every single detail of the real world okay into this model. We are abstracting it and including only features which we think are relevant and important.

Okay. Right. And therefore if we have not included all the important ones, a simulation will not be accurate okay in capturing the real situation and also capturing what an experiment will result in. Okay. That is one source where there will be a mismatch. Okay. And another source of mismatch is maybe not every parameter or every number which describes the real world situation or an experimental situation is known to great precision.

Okay. And there could be another source of mismatch between a simulation and experiment. And one must also here understand what we mean by similarity or matching between. And what are we happy with? Ultimately that is what governs the success. Yeah How? when do we call a simulation successful? Yes In some cases it might be a trend in the data that we are looking for to capture.

Okay. In some other cases it might be the actual numerical matching of data that is generated from an experiment with a computer simulation that we have done. Right? So it depends really on what we want to ultimately capture in order to call something accurate or inaccurate and so on. Okay. I just would like to ask you, can you give us any example if you are using any simulation and model in your own experiments or in your own research? Okay.

So a particular example I will give you about this interplay of theory, simulation and experiment from our own work yeah is from the world of understanding how bacteria organize themselves. Interesting. So bacteria as you all know are these unicellular creatures which don't necessarily live by themselves.

They live in groups. Yeah. And therefore group behavior is very relevant in understanding the functioning or organization of these bacterial populations. So there is an interesting phenomenon that certain kind of bacteria display which is that when they run out of food a large group of bacteria spontaneously come together and aggregate and form a collective structure called a fruiting body. Interesting. Okay and so this is useful for the bacteria to survive the starvation but also useful for them to you know look for food which might come later and and so on.

So how do we understand such a process? Okay. okay And as physicists when we looked at how this process is occurring it looked like that the bacteria were behaving like oil which is separating from water. Okay. So to make things more concrete when the bacteria are well fed they were everywhere sort of like well mixed like oil and water well mixed as soon as you put them together. But as soon as they start just like oil separates from water spontaneously these bacteria seem to spontaneously come together and form this blob like the oil droplet into what we are calling a fruiting body.

Okay. So now the theory or the framework that we have invoked in order to understand this is the theory of phase separation. Okay. Right? So now we can say now that we have a theoretical framework in mind is this process that we are observing in the bacteria falling under the theoretical framework?

Right. So then we did some experimental investigations. Okay. So we made measurements of how these bacteria come together and so on. And does that resemble how for example a droplet of oil will phase separate from water? How fast does it form that droplet? How big does it form? And so on. And therefore by making these measurements we were able to quantitatively by putting numbers on these things match these two processes.

Okay. So that's experiment and a theoretical framework. And you might ask now where does simulation fit into this picture? Yeah. Okay. So there is a key difference between oil and bacteria. Right. One is the most obvious difference is that one is living the other is not.

Yeah. here is another key difference which is that bacteria are moving like cars whereas the molecules of oil do a Brownian motion. They're not moving like cars. Okay. So that's a fundamental difference. But what we have done is to invoke a theory which is applicable to this okay setting of oil and water.

Right. So now we can ask the question instead of bacteria if I simulate an object which can move like bacteria. Okay Yeah. And I put many of them like I have many bumper cars which are moving. Will they also spontaneously aggregate and form such a grouping? Right? Yeah.

Right. So now that's a question that I can answer on a computer. Right. Okay. I can build a simulation which has a feature that there are many agents which can all move.

Yeah. And interact. And then we see also in the simulation that they come together to form a group. Oh, interesting. Okay. And what's even nicer is that they quantitatively match the measurements or the experiments that we have made on the bacteria and the predictions from the theory of phase separations.

Yeah. Right? But the model or the simulation that we have done is neither of an oil and water molecule nor of a bacteria in all its detail. Right? Okay. We have only considered an object that can move. So there is an assumption that we have made that only this feature of the bacteria is important for this behavior.

Okay. Right? Yeah. And therefore in sort of referring back to one of your previous questions, we are now happy with the quantitative comparison between this experiment theory and simulation because it captures this one feature. Okay. But this has, if we were to ask about the growth and division of bacteria, this is not a simulation for that.

Right. Right. So this is very specific. The model is very specific. The simulation is very specific to that condition. Okay. It has made certain assumptions and it is testing under those assumptions how do these things match. And in this case, we were lucky to have got a good and reasonable answer.

That's a really interesting experiment and simulation. So I would like to ask you how does even one develop this intuition about bridging the gap between theory and experiment? Like what advice would you give to biology students who want to learn more about theory and experiments? Right. So I hope by now through this discussion yeah we have realized that the process of doing science itself is an interplay between theory, experiment, observation and a cycling back and forth constantly between these endeavors. Okay. And somehow by how things have developed in the way we teach and how we have collect knowledge and organize knowledge, yeah biology and there is an impression that it is non-mathematical in nature. Yes.

But this is not true at all, which hopefully I have also yeah convinced you. For example, I reiterate Darwin's theory is at its core mathematical. Yes. Right? You know, unlike this notion or rather contrary to this notion that people have that there is no use of mathematics in biology, I think there is an immense use of quantitative thinking, quantitative way of operating in studying biology.

Right? And therefore, and this is becoming increasingly so yeah in in current day research that biologists are required to use more and more quantitative methods in not only learning the subject but also in doing research in the subject and so on. And therefore, for undergrads studying biology currently, I think it is of immense value to not be shy and not be afraid of engaging with mathematical, quantitative and physical thinking. And this need not be, you know, and this should probably be at a level that such a person is comfortable with and not to shun it completely but to be open to it. Some biologists may go all the way. I know, for example, of biologists who have been trained at the undergraduate level as biologists but have gone on to do PhDs in pure mathematics.

Oh. So the shift has been that dramatic. So that's not that may not be the case all the time. Yeah. Right. But I think to study or take courses in statistics and probability theory and, you know, ways of analyzing data in a quantitative ways so on and so forth might be very useful for the undergraduate biologist.

Thank you, Dr. Shashi, for joining us today. This was such an insightful conversation about theory and experimentation. I learned a lot about this topic and I hope you all learned about it as well. If you have any questions more on this topic, you can write to us on discussion forum and we will be happy to answer your questions. Thank you. See you next time.