Computational Systems Biology
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Lecture - 01
Introduction

Welcome to this course on systems biology, I am Karthik Raman from Biotech. I work in the area of systems biology. So, this is my area of research. And over the next few classes we will try to cover various aspects of systems biology. I will talk you through it as we go on with the slides.

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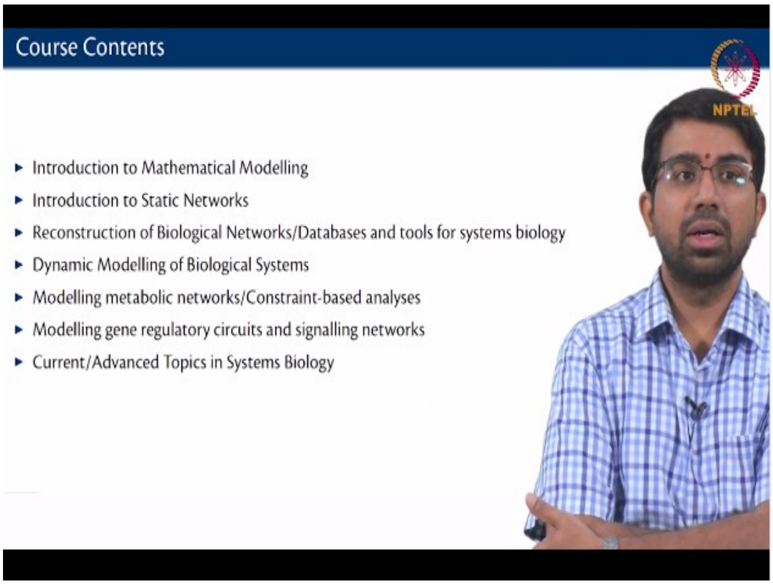

So, the first module will be introduction to mathematical modelling. We will just have an intro of what models are, how do we model systems in general and so on. Followed by this, we will look at static networks. This is more or less graph theory but graph theory is used in biology in different ways. So, we will be looking at graph theory, how graph theory is being used in biology and so on.

And then we will talk about reconstruction of biological networks and databases and tools for systems biology. This is a bunch of methods and tools and databases that are very important for doing any of the other things in the course. If you want to resort to static where do you get the static networks if you want to analyze them or is there a place where you can find dynamic models of biological systems or where do you get all the metabolic networks that we want to analyze later on in the course.

We will then move to dynamic modelling of biological systems followed by metabolic network analysis and constraint-based analysis. Finally, we will touch upon gene regulatory circuits and signaling networks and then a bunch of very interesting advanced topics in systems biology. We will try to touch upon whole cell modelling, we will try to study a few other interesting things like how do you estimate the robustness of biological systems or how evolvable are biological systems and so on.

So,these are some of the things that we will be trying to look at.

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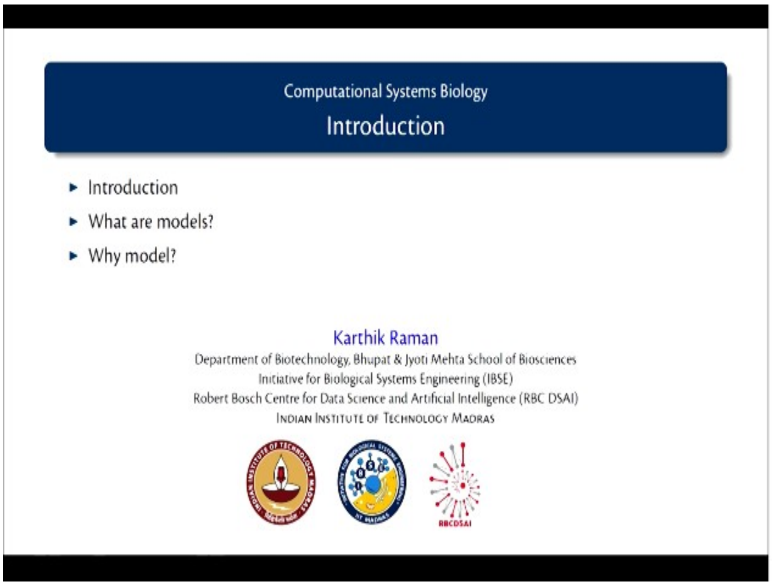

Let us get on with the first set of topics in the course. Today, I will introduce you to the field of computational systems biology and modelling in particular. We will look at what is a model? Why do we model? We will have an interesting discussion about what are all the things we need to model? What are all the reasons why we model? And the need to make predictions and so on and so forth.

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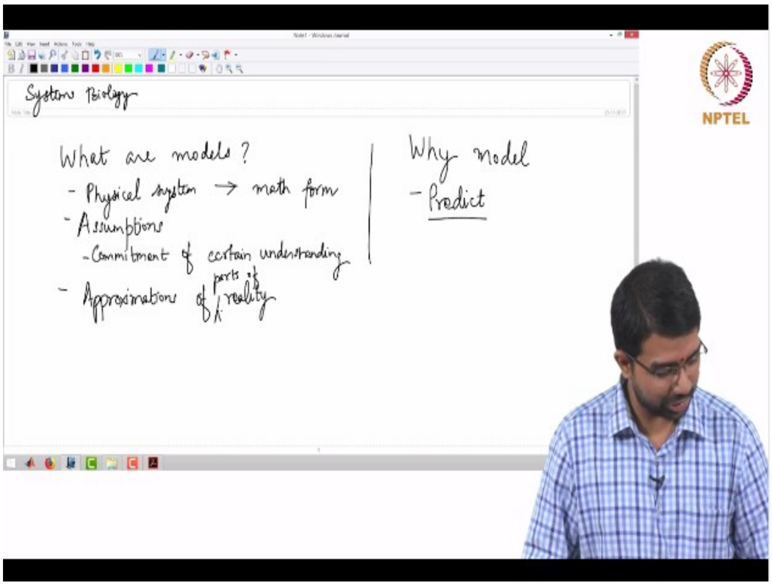

What are models? Physical system to some math form. Ok. So, that comes to the question of why model? This is always the first thing that everybody worries about, right? You always build model so you can predict something. What other aspects do you see of model? what are the important characteristics of a model? Maybe I should write what Priyan said.. are several assumptions that characterize every model.

Or in other words, I would say, it is an important commitment of what you understand about the system. The model is essentially your commitment to certain things, right?. I know I understand x about the system, I understand y about the system, I will take all of them up and mash them into a bunch of equations which will try to describe my system. An important thing to remember is models are approximations of reality.

In fact, we would often go and say that it is not reality but parts of reality, right? You basically choose to model something, you choose to leave out several things, right? One normally says the correct way to model a system is to basically build a model of the universe, right? Because your system does interact with the universe so if you have to go on modelling, you will stop at the universe. But that is not a practical way to model systems.

So, you basically narrow down your field of vision to what is really important about a system, right? Because that then comes back to the question of why do you want to model a system? That is in fact the more important question, right? How do you model a system is going to be completely dictated by why do you want to model a system? We want to make predictions about something, you want to have those things in the model in the first place.

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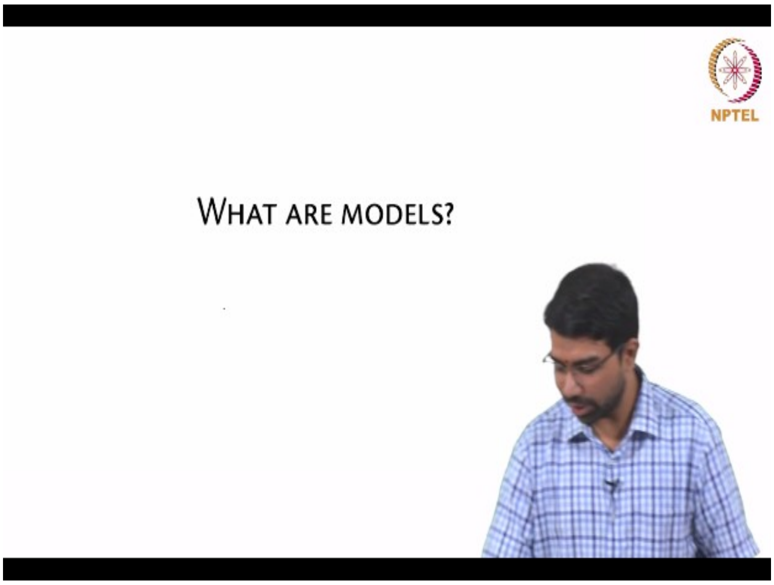

So, there are going to be those kinds of interesting questions that one asks. What are models?

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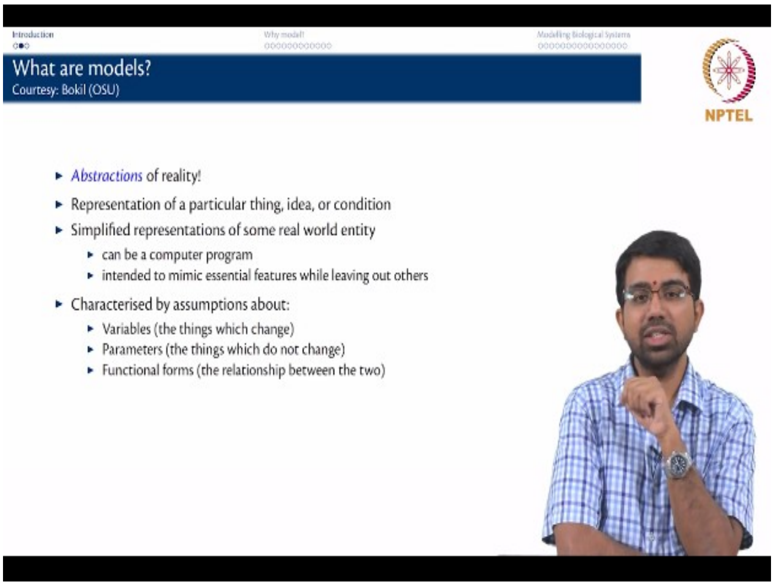

They are abstractions. They are abstractions of some part of reality. They are representations of a particular thing, idea or condition. And we usually talk about mathematical equations. There are other kinds of models that are possible that you can have like correlational models and so on which don’t truly have a solid mathematical foundation to it. And they are simplified representations of some real world entity.

It can also be a program which is what we will often see And most important thing, it intends to mimic essential features of the model while not looking at several other features. I am going to focus on x, y, z which is very important for my prediction for my system for these scenarios. And there are many important assumptions. What do we have? There are variables, the things which change. The parameters, which are like essentially constants. We will worry about it a little later. And functional forms that connect the two.

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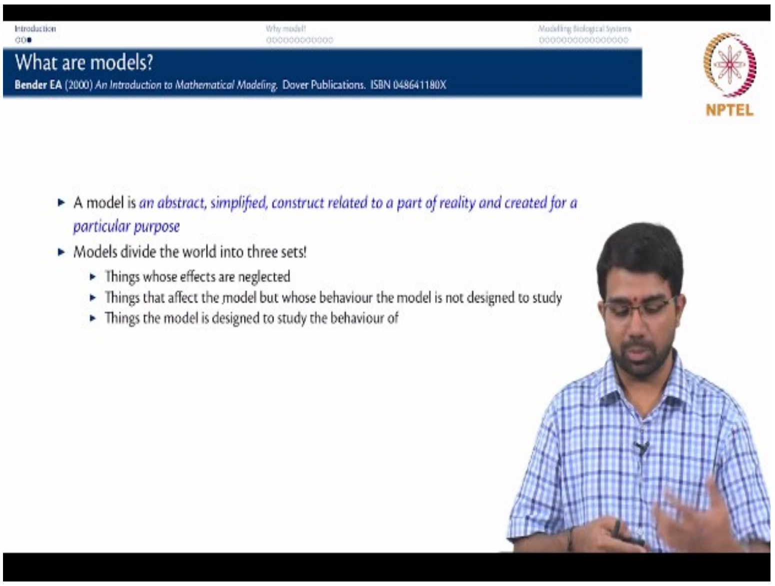

So, a nice definition is...A model is an abstract, simplified, construct related to a part of reality and very importantly created for a particular purpose. A common error that one often encounters when you see papers being published about models or when you enter a modelling exercise is that you do not really..you know are not careful about what purpose the model should be used for.

There are often models that are valid in certain conditions but you tend to apply them in other conditions, right? So, you may have a model that works for predicting the initial rate of a reaction but you use it to predict the rate of a reaction even at steady state and so on. These are classic errors that one does while doing modelling and this might sound really obvious and jump at you but in reality there are very fine errors that people make and usually because one has, after a period of time lost sight of the assumptions.

There are certain assumptions that have gone into your model building. If you lose sight of them at some point of time, you are very likely to make errors. And i like this way of looking at it. The model divides the world into 3 different sets. What are these sets? 1. Things whose effects are neglected. 2. Things which affect the model but I am not equipped to study them or my modelling is not going to cover it, is a design choice by the modeler. I am not going to worry about this because it is too difficult. 3. And things that I am actually worried about, I actually want to really study, right? This is a nice way to look at any model, maybe this is something that you should consider when you prepare an assignment for the assignment about how do you know the different features of your model and so on.

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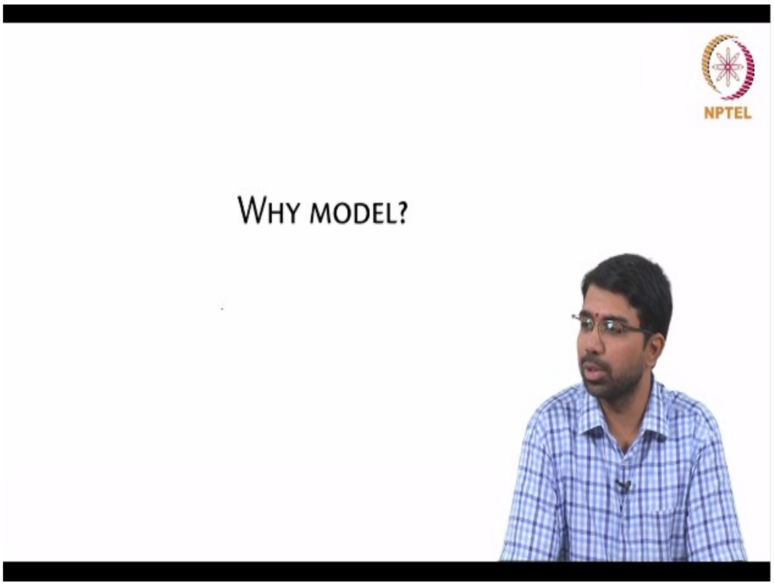

Next important question is, why model? The obvious reason why we model is we want to predict something. Are there other things that you can think of? Why would you model a system?

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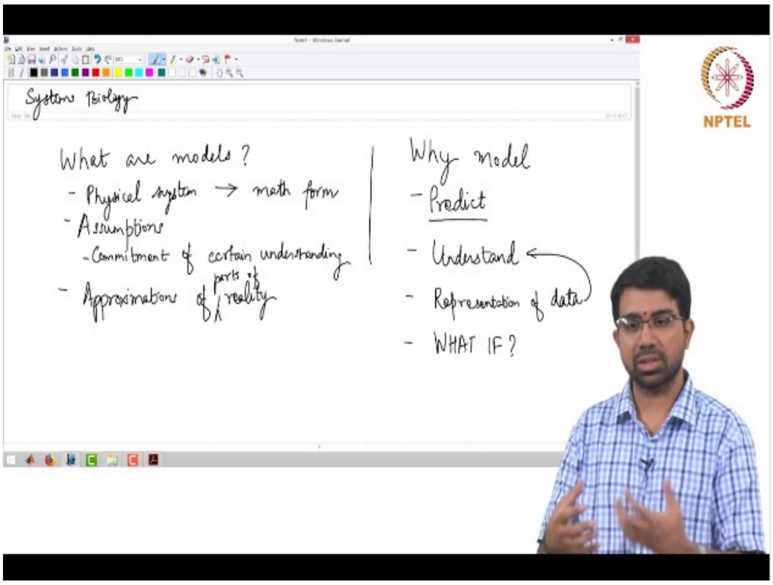

So, you want to understand the system. Fine. You want to have some representation of data, right? You basically condense a large amount of data into a simplistic model. This again sort of feeds back into understanding the system, right? Understanding is actually one of the more loftier goals of modelling. You want to finally glean some design principle of the system, some fundamental aspect of a system by modelling it.

Prediction is usually why you want to go into modelling. This is again one of the most important aspects of a model-WHAT IF? How does this system behave? What if I change something? And biologists will quite understand this because it is expensive to do experiments, right? Unlike experiments in many other domains or especially in computational experiments, experiments in biology involve time, money, expensive reagents and so on. So can you actually prioritize what experiments to do? That is something that modelling can tell you. I have money to do 10 experiments, can you tell me what are the 10 best experiments to do? That is something a modeler should be able to do. So, WHAT IF is actually a very important aspect of how do you model any system.

It is the key reason for modelling many systems. Anything else? Let us take a detour. There is this very classic paper which tells you how biological systems and biology differs a lot from other fields especially if you are talking about say, electrical engineering. This classic paper is titled, “Can a biologist fix a radio?” I am not sure if many of you have read this paper but it is going to be part of the reading material for today’s class.

And how do you actually fix a radio. Or how do you understand how a radio functions? If you were to take the biologist analogy of it, it would be like pull out this particular capacitor from the radio and see if the radio continues to function. If it does not function, it means that the capacitor is integral to the function of the radio. This is essentially the equivalent of your knockout studies.

We often do knockout studies to understand the function of several genes or a protein in a system because, there is no other simple way to study function, right? Because, essentially biology or understanding biology is one of reverse engineering. You have a really complex system like a laptop or something, you have to figure out how it works. Let’s say you didn’t know anything, how do you start that process?

You are going to like push a few buttons and figure out how it works, right? The same logic extended to biology is one of perturbation. You keep perturbing the system. Throw different conditions at it. Throw different perturbations to it. So, change the wiring of the system and try to understand what is happening. This is a crucial way to study biological systems. And this is also one of the key cornerstones of systems biology.

All through the course we will be seeing how perturbations affect biological systems? Or how do you model perturbations? I remove a gene, what happens? I add a gene, what happens? I overexpress a gene, what happens? I remove a bunch of nodes and edges from a network, what happens? So, these are the questions that we will keep trying to address at different points of the course.

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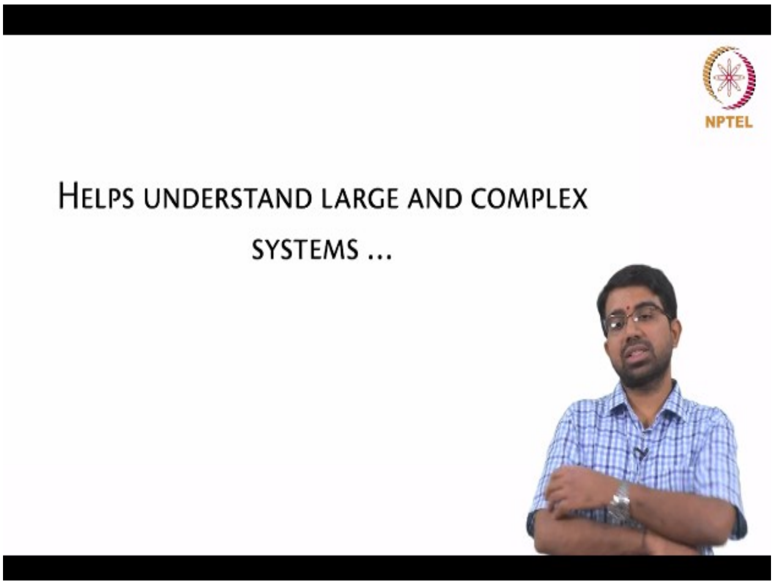

So, why model? It helps us understand large and complex systems. Do large and complex have to go with each other all the time? What do you mean by complex? Complex systems will invariably involve a large number of variables but beyond that yeah so you are slowly coming at something. I am not sure if somebody else is going to latch on to that.

So, I will combine all of that and say that, you have a lot, the number of entities will decide the size of the system. But the number of relationships will decide the complexity of the system, very loosely speaking. If you actually look at a network, the large number of nodes will make it large but a large number of edges will make it complex. But even that is not necessary, right?

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You need some sort of nonlinearity to come in. We will just look at it in a moment.

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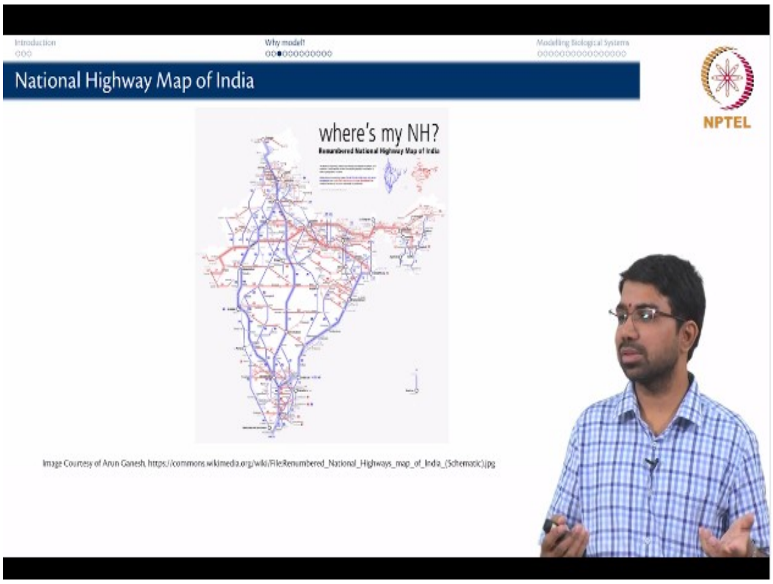

So, one classic example of a very large network which is not too complex is a road network. This is like really large, right? You have 100s of cities connected in very complex ways. You see only a few of them. There are only the highways on this map. But if you really look at all the roads that are there, it is going to be a very, very large network. But I wouldn't say it is too complex.

You easily understand the network. You know how to go from one point to another. You know if one road is shut down, what is the other road to take? Or is there another road to take at all?

So, it is easy to find out some of these things whereas, in a complex system you wouldn’t understand what happens if I shut down say, if no cars are allowed to Delhi tomorrow, what happens?

It is easy to say here but in a complex system, it is just going to be very difficult. If you pull out a node from a network, what happens? It becomes very difficult.

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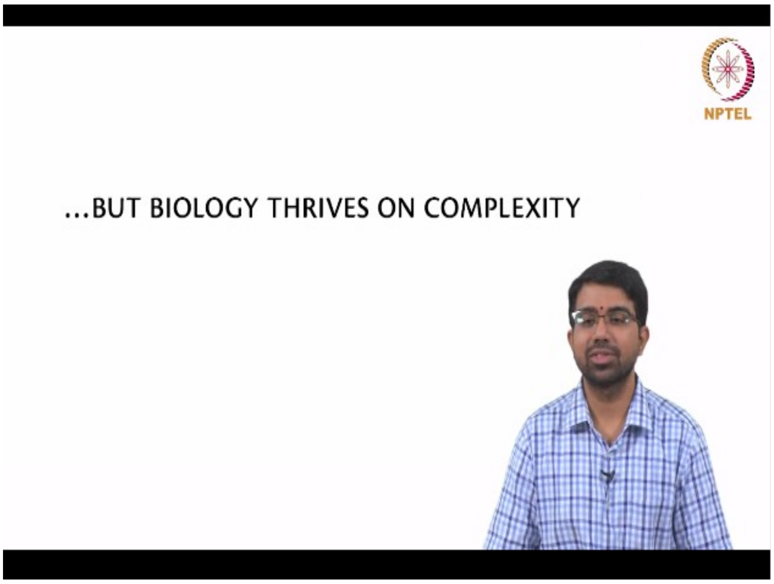

But biology thrives on complexity, right?

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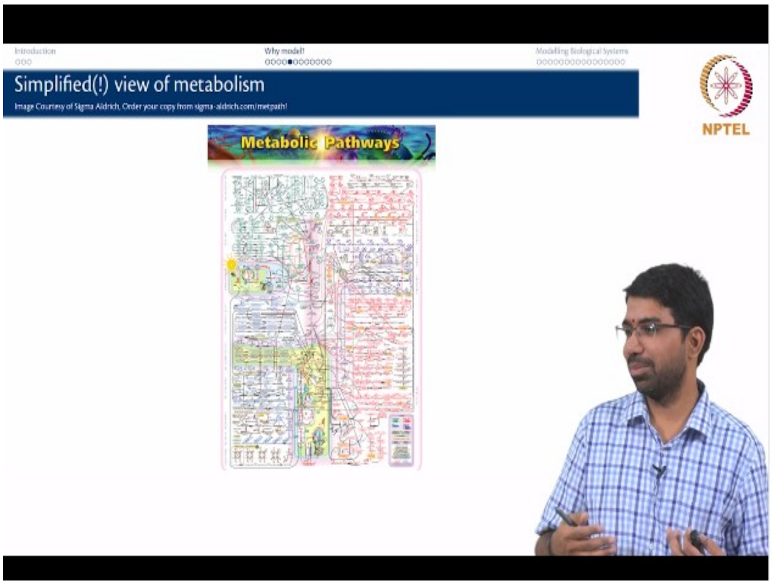

As a peak at this complexity, look at this picture. So, this is what we usually call a simplified view of metabolism. Sort of, to intimidate any person who steps into biological modelling but why is thisa simplified view? For starters, I have one chemical being shown anywhere here, right? All these represent a single chemical but you can imagine there are Avogadro number of these molecules within a single cell.

There will be like nanomolar concentrations and each of them will have different fates. Some of them may take this route, some of them might take this route, some of them might take this route. Some of them might be cycling here and there are several compartments. Not all of them are shown here and I am still talking about a single cell. And then you have cells which are organized into tissues, then into organs, then into organisms, which live in an ecosystem.

You can actually model at any of these levels. In this course, we will more or less restrict to a cell. We will look at how there are different networks within a cell. How there are metabolic networks, there are gene regulatory networks, signal transaction networks and so on within a cell And, how do we model all of them and the interactions between these kinds of networks.

So, this is actually a very interesting view of what happens within the cell. This is a metabolic chart that usually adorns lots of walls in biochemistry labs and so on.

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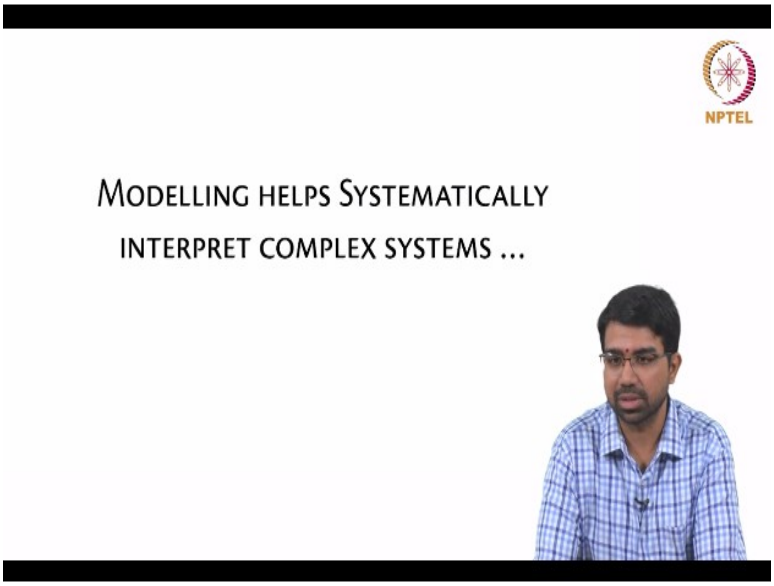

Modelling helps us systematically interpret various complex systems.

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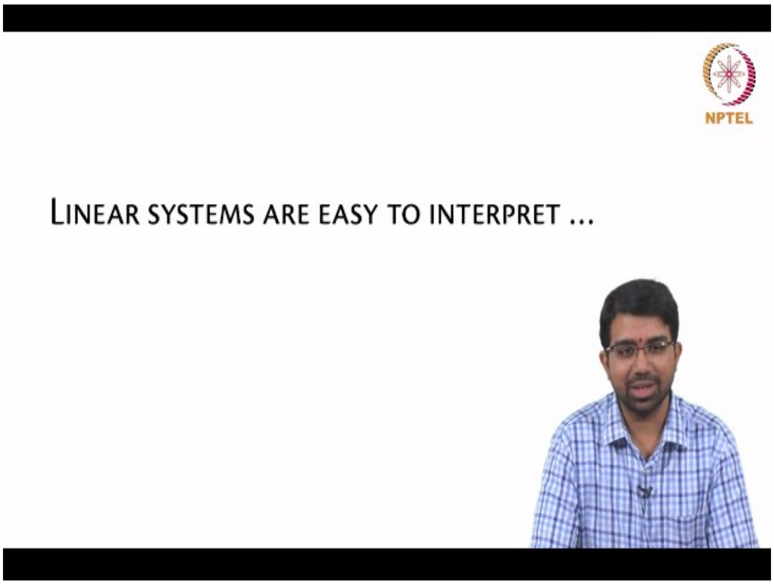

Because our minds are very nicely tuned to understand linear systems, right? You know exactly what'll happen when you perturb a linear system and you will be able to see that the behaviour of a linear system does not change drastically if you give it a push.

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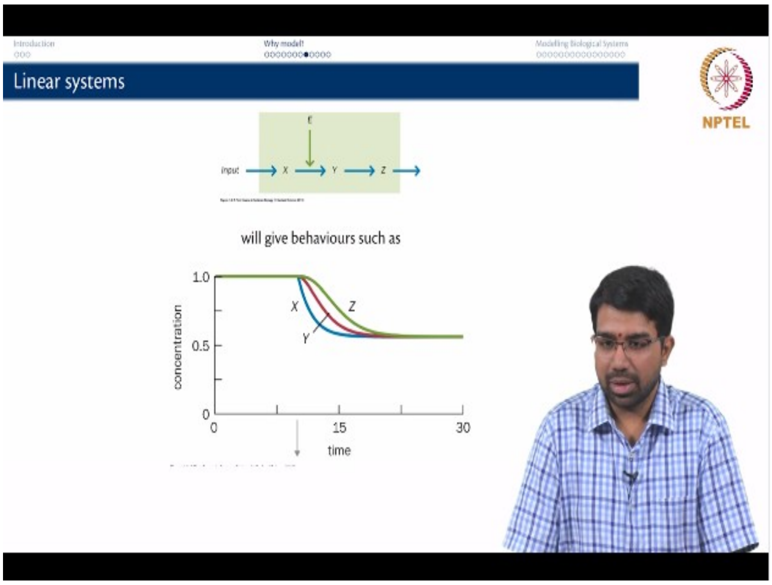

For example, you might have seen a system like this where there is one metabolite being converted to another to another and so on. A chain of reactions. And there is an enzyme which is catalyzing. No big deal! So, this will give behaviours like this. Very nice, right?

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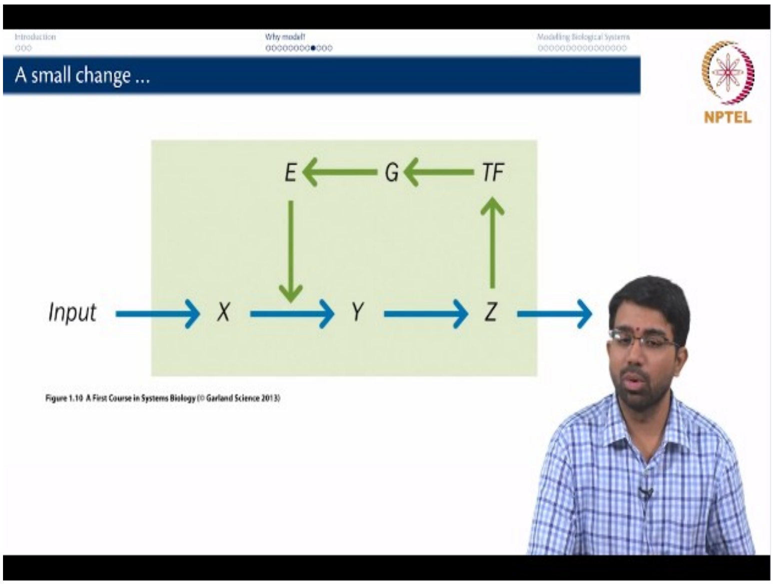

But what happens, when you just introduce some more complexity into the system? You just have a very simple feedback loop that is inserted in the system. The moment you do something like this, you get a whole different spectrum of behaviours.

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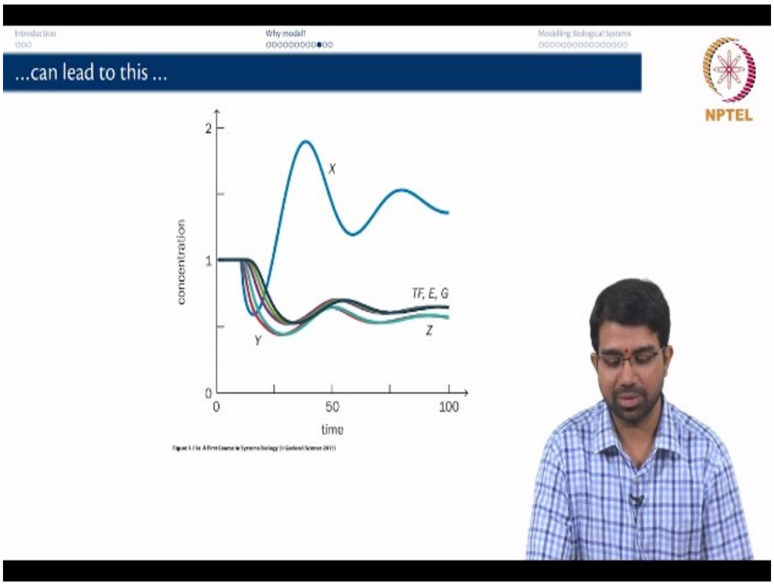

You can have something like this, doesn't seem too bad.

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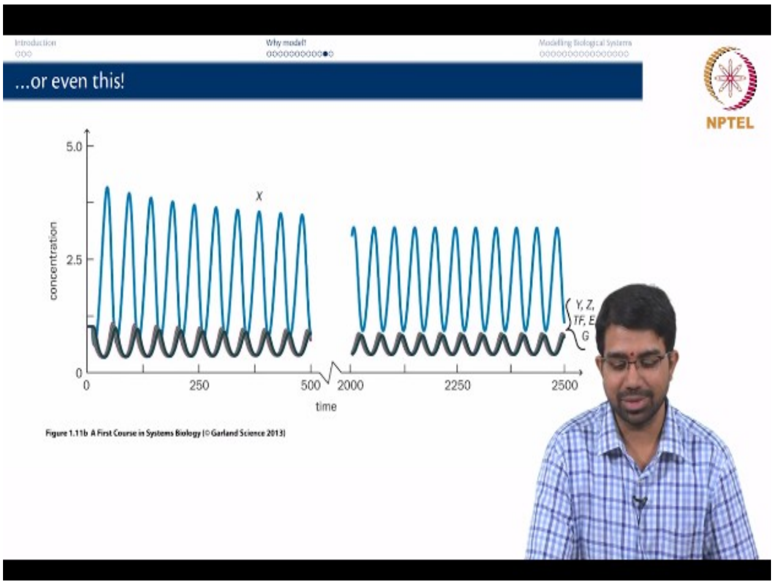

You can have something like this and so on. You get even oscillations and all kinds of complexities when you start working with nonlinear systems. And all of you might know by this time that all biological systems are really complex, really nonlinear.

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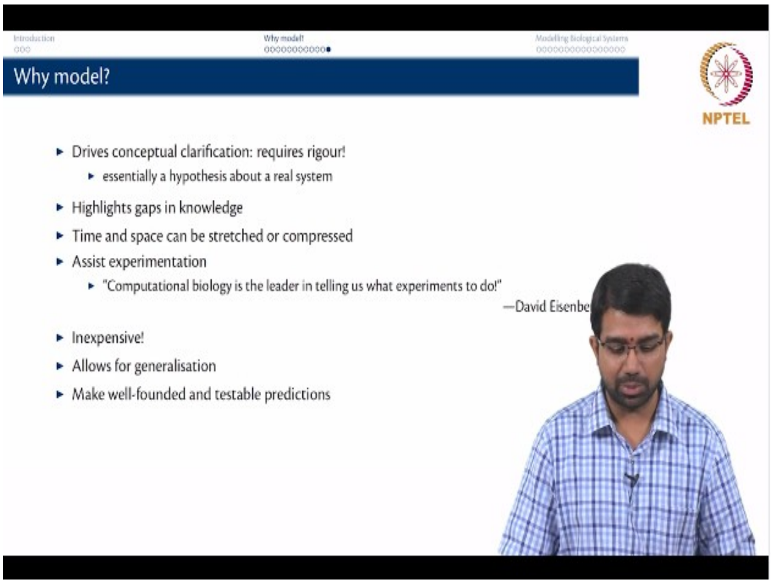

So, why model? Most one very important aspect is, it drives conceptual clarification and it requires some rigour, right? As I said, you basically covet to a hypothesis about a real system. And then, it highlights gaps in knowledge. This is another very important aspect of modelling a system. You build a model of a system, you find that it does not work, you find that it has certain disagreements with what is observed in reality, what is observed through experiments.

You know then there is a particular gap that needs to be fixed. This is usually what we call the systems biology cycle. I will talk to you in little more detail in the next class but basically you start with a bunch of hypotheses. You build a model. You test it against the reality, you find certain gaps. You go back and plug those gaps. It may not directly tell you that yes, this is the gap but a lot of the effort in modelling goes into identifying these gaps and trying to figure out how to bridge these gaps in a model.

The most useful aspect in a lot of cases is that the time or space can be stretched or compressed. Because somethings might take days to happen. Say, *E. coli* will take 15 minutes to double. That is already fast. But you can actually simulate several generations of *E. coli* evolution and so on. And that will probably take you only a few minutes on a computer which means that you can really predict things that are stretched, you can compress things across space.

Most important, models assist experimentation. As David Eisenberg once told, he's one of the most successful and famous structural biologist or you could even call him a structural bioinformatician. So, he said that computational biology is the leader in telling us what experiments to do. That is one of the most important aspects of computational biology and this usually comes off as a bit of a tension between computational people and experimental people.

Experimental people feel that computational people are trying to say that computation is the all important thing and so on. I think, as a computational biologist or a systems biologist, what you need to understand is that without experiments there can be no biology. But without analyzing those experiments using computational tools, there can still be no biology, right?

So, it requires a very tight collaboration between experimental and computational biologists to do any useful science today. Practically! And I'll show you a little more on that a little later. Relatively inexpensive,right? Modelling is not too expensive. It requires a lot of cerebral activity but it is otherwise not too expensive. Because lot of these modelling methods that we'll talk about do not require so much of computation and so on.

And it allows for generalization. You build a model, you can generalize it to several things. You can start building classes. Oh this network appears to have this kind of a behavior. So. I know that these kind of networks behave in this fashion so I can apply all of these to my existing network and so on. And make well-found and testable predictions. You want to make well-founded and testable predictions of biological systems.

A model gives you the ability to do that, right? You have a foundation for making a prediction and then you go and validate it or invalidate it. In fact, invalidation is a very, very important aspect. You might never be able to validate certain things but if you start with the hypothesis and you see that there is a big breakdown when you compare it to real data, you can invalidate your hypothesis and may be try to reframe your hypothesis, build a different model and so on.

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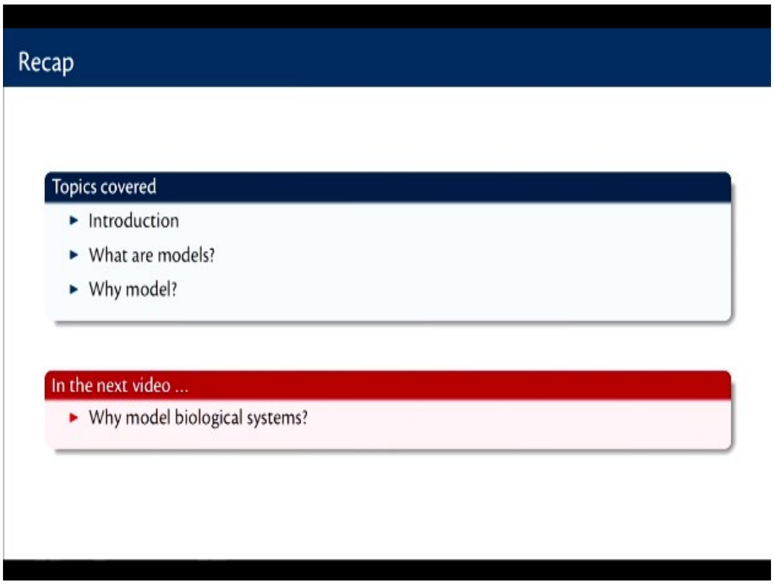

So, today we have had a brief introduction to the field of systems biology. We have seen what are models? And why do we need to model and so on. And in the next video, we will start focusing on why do we need to model biological systems? And what are the advantages of or what is the motivation for modelling biological systems? Or what is the motivation for modelling biological systems today, in terms of the new data that have come in and so on?