Computational Systems Biology
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Lecture - 04
Fundamentals of Mathematical Modelling

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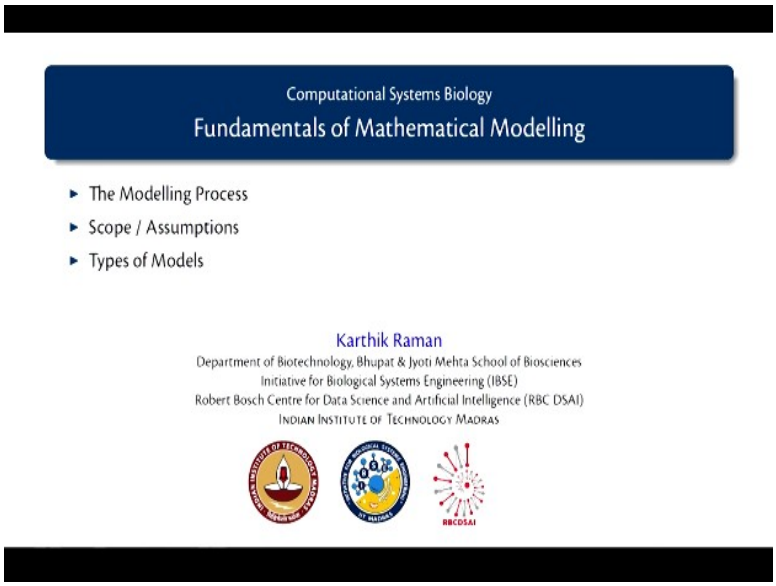

In today's video, we will look at the fundamentals of mathematical modelling and focus on the modelling process itself, particularly things like the scope and assumption that go into a model. And the different types of models like whether they are explanatory, correlative, mechanistic, dynamic and so on right. So, what are the different components of the modelling process itself?

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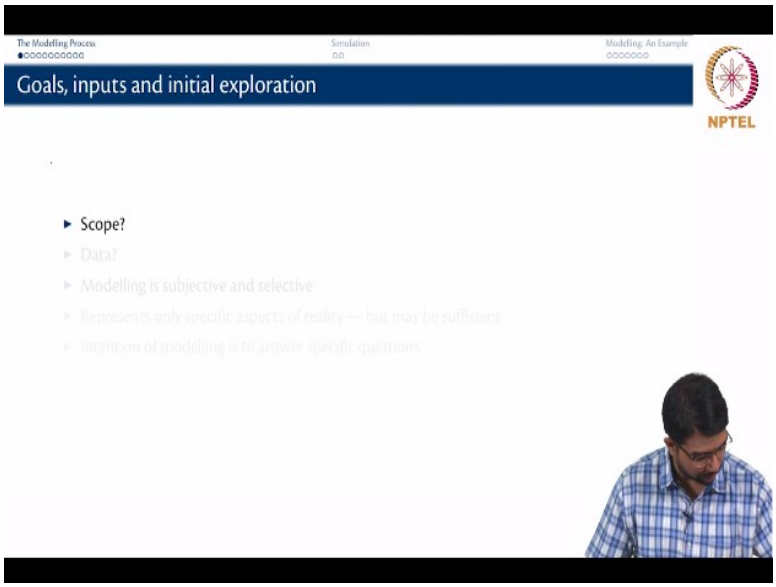

Beginning with what is the scope of a model? This often happens to be one of the most important aspects of modeling. What is the scope of a model? What is the model meant for? What can it describe? What are the conditions it can try and account for? And so on. So, what is the scope of a model? Given any model, I think you need to worry about what is going to be the scope of the model.

Is it going to explain a static system? Is it going to talk about some dynamics? Does it only consider a few states? Like it is an on off system like Boolean systems that we will look on a little later and so on. For any model that you pick and maybe we should again go back to let's keep two models for the class. So, we will have one from biology which would be the Michaelis-Menten model, I presume some of you are familiar with it.

We will anyway look at it during dynamic modelling and the other could be our Duckworth-Lewis model. In either of these, what would be the scope? So, the Michaelis-Menten model is a model of enzyme kinetics. So, what would be the scope of the model? **"Student conversation"** Predict enzyme concentration or rather predict substrate concentration with time.

How does the concentration of a substrate vary with time? Or in fact, typically you use the Michaelis-Menten model to predict for what is the initial rate of a reaction for a given substrate concentration and there are some underlying assumptions. We assume that there are certain type of interactions between the enzyme and the substrate, there are certain specificity between the enzyme and substrate and so on.

And there are like, the enzyme might have more than one site for the substrate to bind, there are all these things that one can incorporate into the model. So, the scope is, it cannot talk about may be a simple model will not talk about the presence of multiple substrates, inhibitors and so on. The basic model will only talk about a single enzyme, single substrate, single step reaction with a single transition state and so on.

So these are the kinds of limitations that you need to be aware of when you start looking at any model. What is the scope of the model? Here the scope is trying to describe enzyme substrate kinetics right and how is it going to affect? So, you can make some predictions.

What is going to be the rate if I increase a substrate beyond a particular limit? What is going to be the rate of the reaction?

Or if the substrate is in very low concentrations, is it a zero order reaction or a first order reaction? You can ask these kinds of questions of the model. And typically to construct most models you will also require some data about the system. So, given some data, given some information, knowledge about the system, you will start building a model. What kind of data are available?

So, let's again look at the Michaelis-Menten model. I will quickly describe the model so it will be helpful.

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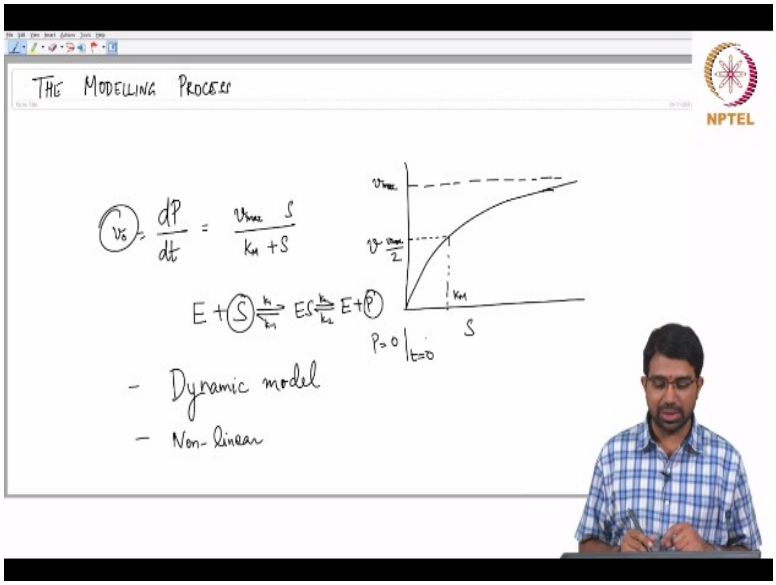

The Michaelis-Menten model basically says something like okay or rather I would say

$$v_0 = \frac{dP}{dT} = \frac{v_m . S}{k_m + S}$$

Where, Vo is the initial rate of the reaction, S is substrate concentration, Vm is the maximum rate, Km is the substrate concentration at which the reaction rate is half of Vm , P is the product concentration. So, typically your question is what is the rate of product formation which is actually,

$$\frac{dP}{dT} = -\frac{dS\,dP}{dT\,dT} = -\frac{dS}{dT}$$

What is the rate at which the product gets formed? We will look at this in greater detail as we go on. For now, let us just focus on the fact that what kind of a model is this? This is a non-linear model. And what can it predict? The initial rate of the reaction nothing else, only the initial rate of the reaction. Why is it initial rate? There are other things that we need to worry about so maybe we will look at it a little later on.

Because we assume that,

$$P = 0|_{t=0} P = 0|_{t=0}$$

So, there are certain assumptions that go back but I took this example because this is a common model that everybody is familiar with and in fact the important thing to know it is that it is actually a model. People think it is a Michaelis-Menten law or something like that just like mass action kinetics itself is not a law. It's an approximate model to tell you how chemical species interact with one another. So, you need to be aware of these things and the limitations.

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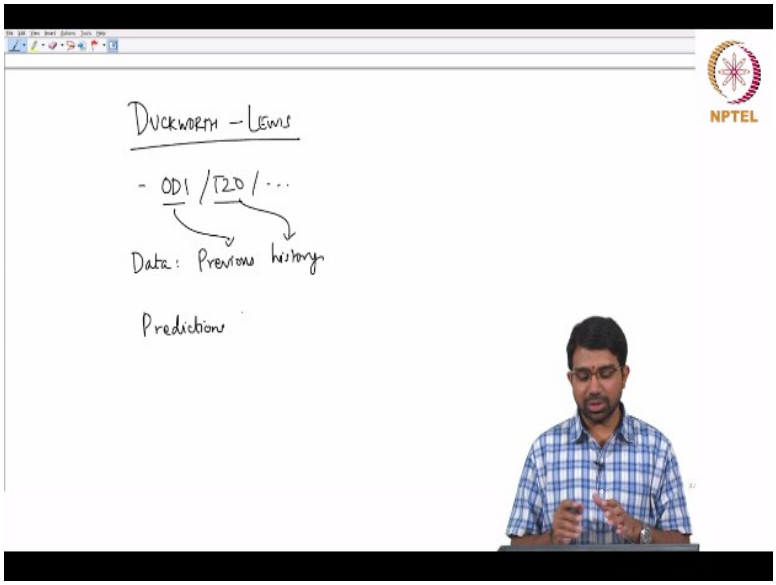

If you now were to look at another model. So, what is the scope of this model? **"Student conversation starts."** The scope basically involves the kind of you will have to say whether it is ODI/T20. So, it is applicable only to cricket matches involving 11 players a side. That kind of thing. And depending upon each of these, there will be certain limitations and so on. But what is the data that it relies on? Some previous history.

And you will have it for different kinds of matches. So, for ODI you will have a different set of data. For T20, you will have a different set of data and so on. And depending upon this, the model will change. You can choose to leave out, since you have dynamically changing rules, you may want to leave out the matches that were played under an older set of rules for example.

If you had like longer power play, shorter power plays, those kinds of things. So, potentially you need to be aware of when is the model applicable and do people actually worry about this is a different question. But when is the model really applicable? Under what scenarios can the model be reliably applied because finally what you want to do is make some predictions, right?

And you can always see if your predictions are making sense or not. You can use it on previous games and so on. So, there are a few things that you want to start worrying about.

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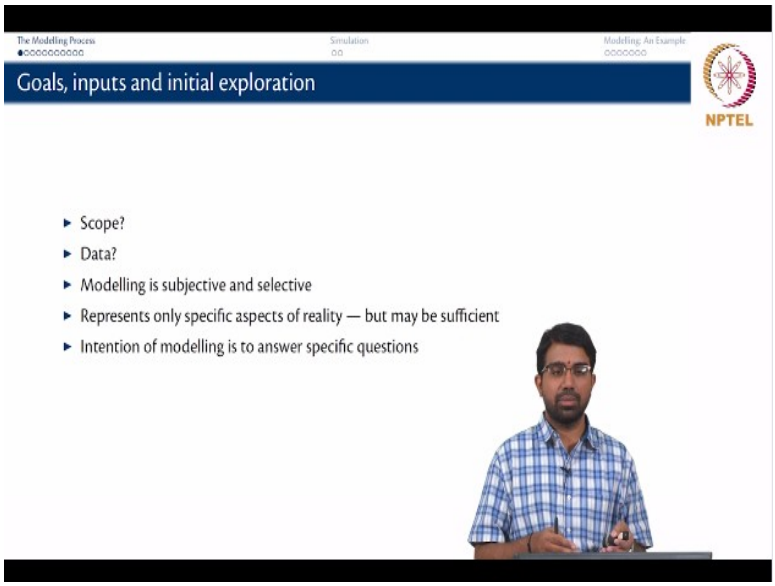

Going back, what is the scope of the model? And what kind of data we have available at our disposal? So in enzyme kinetics experiment, what kind of data you might have? **"Student conversation"** Concentration of enzyme, concentration of substrate, rate of reaction, you may have value such as those which you will need to incorporate into a model and then fit some parameters and guess some equations and so on.

The important thing is that modelling is both subjective and selective. So, it is selective because we choose to model only certain things. We do not model all the components in a

system. Typically, we are not even worrying about other enzymes that are present in the system. It is possible that another enzyme may interact with your substrate to a small extent but we typically will leave it out.

Whereas, you know, we focus on the one substrate that we are currently considering. So, one enzyme, one substrate remains our focus. **"Student conversation."** There are multiple assumptions, right? It is assumed that there is a free diffusion and there are no spatial heterogeneities and things like that. There are a whole lot of assumptions underlying the Michaelis-Menten model which we will look at when we study dynamical systems.

For today, I am just trying to introduce you to the very basic aspects of the model and build from there on. It represents only specific aspects of reality but that is usually sufficient because it always depends on what is that you want to predict. If you want time course predictions and so on you have to use a dynamic model. If you do not want time course predictions, you may get away by using a static model.

You want to just rank certain components and terms of their importance to affect a particular system, we could look at a static network as we will shortly see right. We should also remember that the intention of modelling is always to answer specific questions. You never want to answer every possible question using the same model. A model is therefore, crafted very carefully to answer a specific bunch of questions alone.

For example, does an increase in substrate beyond this concentration have a major effect on the rate of the reaction? This would be a very specific question that the Michaelis-Menten model can answer. It may not be able to answer something like what happens if there are 10 other substrates that can interact with my enzyme. You have to adapt the model to that scenario. The model as such cannot answer this.

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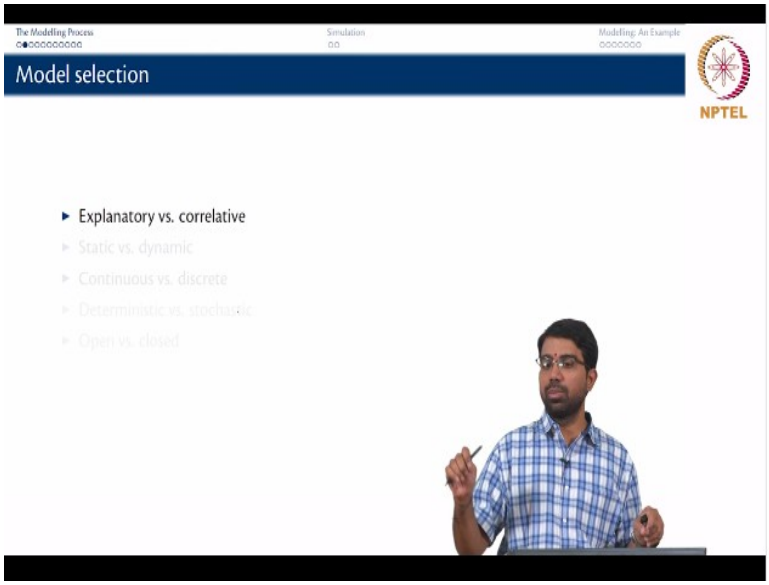

You can have different types of models. You can have an explanatory model versus a correlative model. So, an explanatory model has some sort of insights into the model. I know A interacts with B, B interacts with C, the importance of the AB interaction is this much So, if that increases, something happens and so on whereas, in a correlative model you know if this is the input, this is the output.

You don't understand what's the process. You have no insights into the process. Typically if you built a machine learning model, in many cases that might be a correlative model. I know that if these are the parameters, this would be my output.

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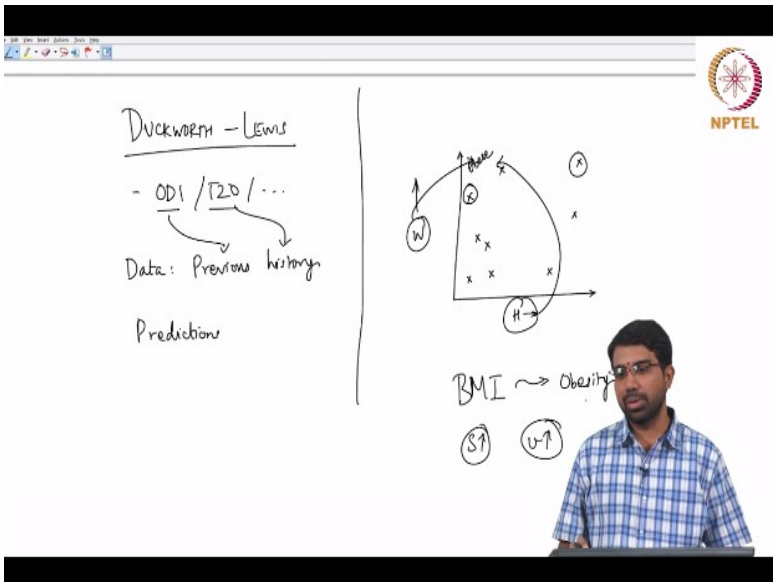

A simple example would be so let's say this is height and this is weight. And you have people who and you may be able to say that somebody who has very low height and very high height

is obese or may have some other propensity to get a particular disease. In fact here you may be able to make some sort of inference saying okay I can but in fact see here you will see that there are correlations.

So you will see that higher the weight, there is a higher chance of obesity but if the height increases then that goes away So, you can't just correlate plain weight to obesity or plain height to obesity maybe if you compute a better thing like body mass index, you may have a better correlation with obesity. So, in many cases you may just have correlations without an understanding of any of the mechanisms.

For example, if you didn't have the Michaelis-Menten model and you said when S goes up V goes up but you may be able to say that for given S there is a particular V or so on. You may be able to establish some sort of correlations but it will be very difficult to understand what happens in different ranges and so on because a correlative model may not be able to explain the dynamics that underlie a particular system.

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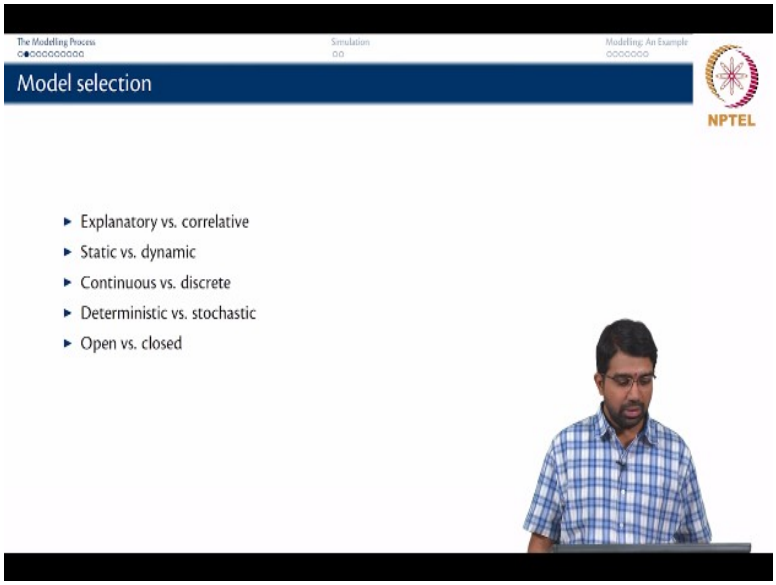

A static versus a dynamic model. So, dynamic model you always have something changing, right? Typically, time. You worry about temporal changes, you could worry about spatial changes, you could worry about different kinds of changes but typically you worry about time, dS/dT.

How does the concentration of my substrate change with time? You could have continuous or discrete models.

In a continuous model, you could have time that is very continuous. So, every instant of time actually counts whereas in a discrete model you will have discrete sets of time. So, there is a particular state today, there is a particular state tomorrow or a particular state at this point of time which depends on you know a particular state in another point of time and so on. So, the variable need not be continuous.

And very important, you can have deterministic models versus stochastic models. So, deterministic model, the outcome is always going to be the same, right? A stochastic model has several things that affect the probability of various outcomes. So, you may observe different outcomes depending upon the initial conditions and so on right. For a deterministic model given a set of initial conditions, you will observe the same final conditions.

For a stochastic model that is not so. There is sufficient variation and various things can happen. You can have an open versus a close system, a system may exchange matter with the environment, may not exchange matter with the environment or it could exchange energy with environment and so on.

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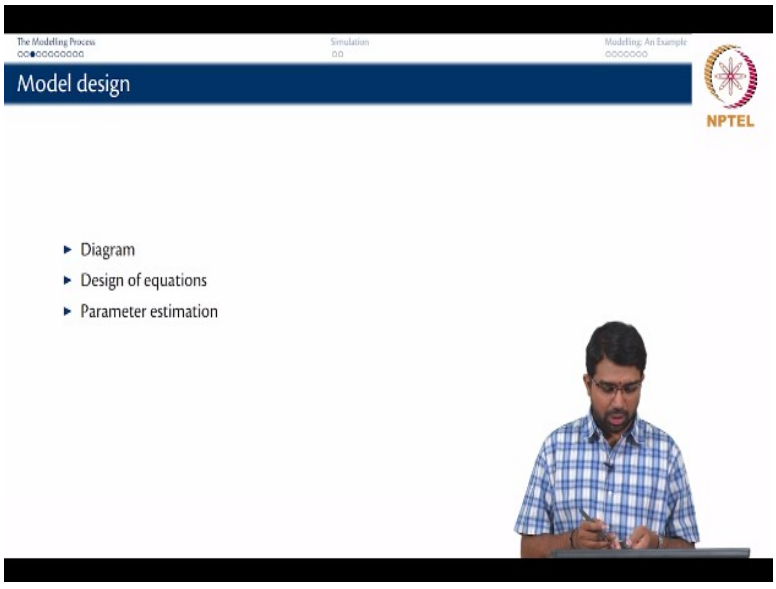

So, what are the different steps of modelling? Typically you start with the diagram. This is typically. It does not really hold when you start looking at very large biological systems, there is no way you can sketch it but if you typically may want to build smaller systems for like smaller modules in your large system and connect them all together. May be you are modelling a signaling pathway, you will start with the typical diagram.

This is A, this regulates B, this activates C and so on. And the next step is design the equations. What kinds of interactions are happening? What kind of math describes the interaction between these different entities that we are talking about? And then the parameters. We looked at it yesterday. There are certain variables which are connected with one another by parameters.

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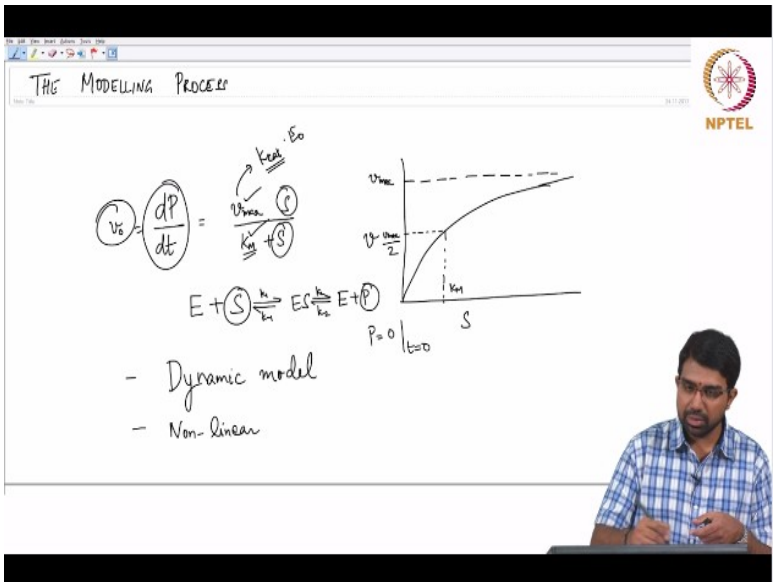

And just like in if you go back to the Michaelis-Menten example,

$$v_0 = \frac{dP}{dT} = \frac{v_m.S}{k_m + S}$$

Vmax is a parameter and Km is a parameter. So, in fact,

$$v_m = k_{cat} * E_0 v_m = k_{cat} * E_0$$

Where, Kcat is the turnover number and E0 is the initial enzyme concentration.

So, Kcat is your parameter and Km is another parameter. These are sort of constants for a given enzyme at a particular temperature and so on and so forth. There will always be certain accompanying assumptions that you need to be aware of. So, these are your variables and these are the functional forms connected via the parameters.

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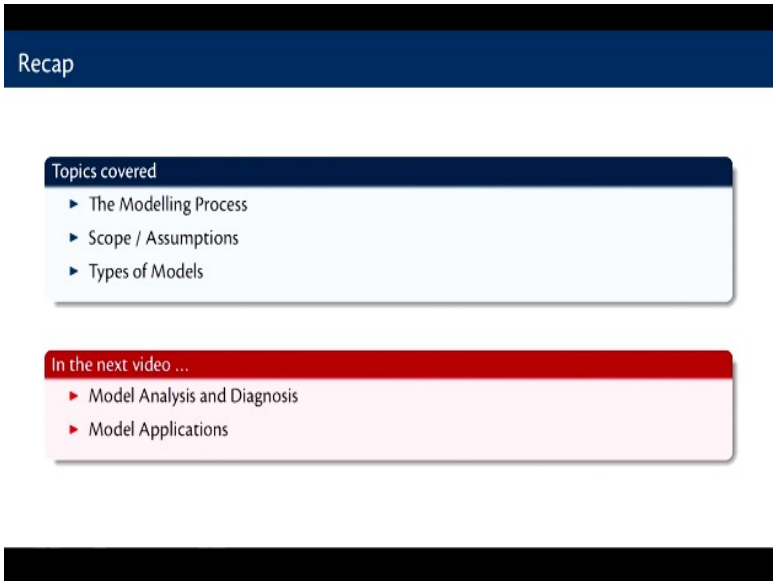

So, in today's video, we had a look at the modelling process itself particularly the scope and assumptions and so on and different types of models. In the next video, we will look at something very important. What is it that you want to do when you have a model in hand? Model analysis and model diagnosis and the applications of any of the models that we build.