Computational Systems Biology
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Lecture - 05
Fundamentals of Mathematical Modelling

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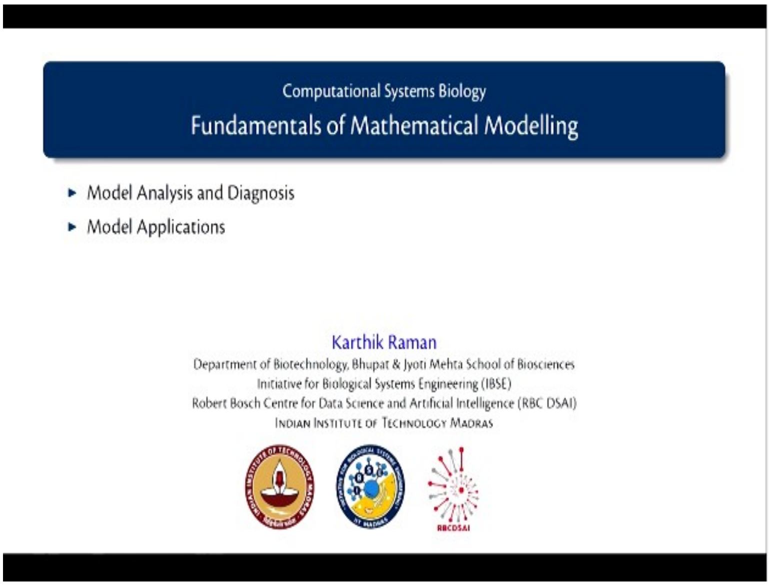

In this video, let us continue with the fundamentals of mathematical modelling and focus on model analysis and diagnosis like overfitting and very important aspects such as those as well as what are the applications once you have a model in hand.

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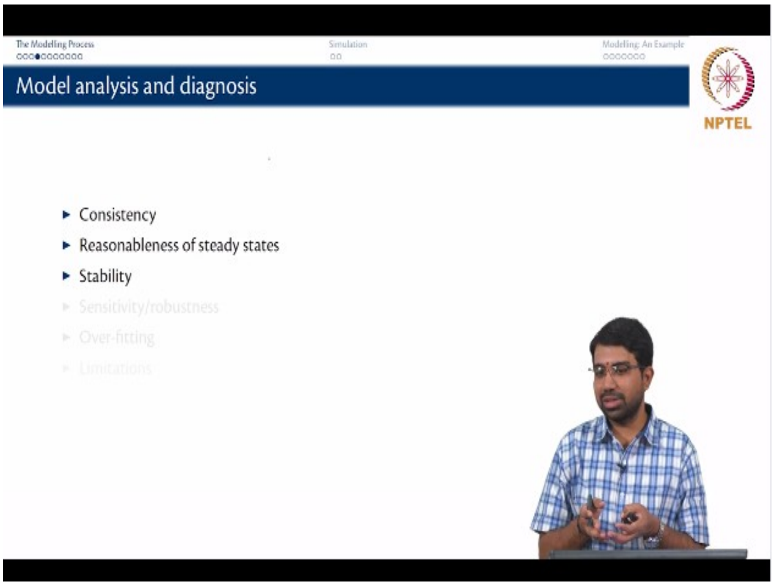

Once you have a model, that is where all the hard work begins. In fact, constructing a model is often very painstaking, you need to go through literature, try to identify what are all the possible interactions you want to account for and so on and put together a bunch of equations.

Once you have a bunch of equations, you have to test them. You have to stress test them to see, are they consistent? Are you getting sensible steady states? Are you getting some unbounded response which never happens in biology? You just can't have an enzyme synthesis, concentration curve that goes like this. There is always some saturation kinetics that occurs. Is the system stable?

What do you mean by stability? **"Student conversation"** So, you give it a small delta change, it will settle to a new state which is close to the original state or it might even return to that state. I think this is a classic example, right?

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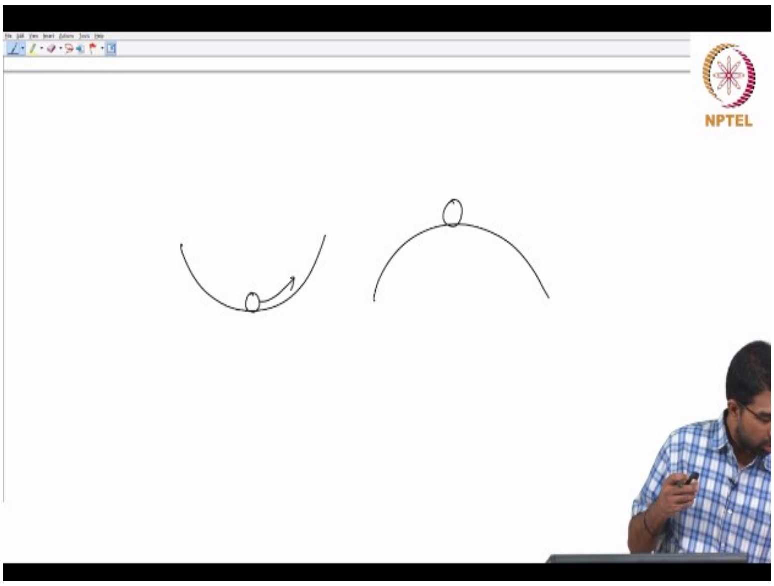

So, these are two bowls. You have a ball here and a ball here. The one on the left is stable, the one on the right is not stable because you move this ball up, it will slide back here, here, here, here and finally settle down. You just give this a small touch, it will basically roll away. So, this could be an initial steady state but it is not at all stable right.

But in biology you typically have stable states. Very unlikely that you have something so delicately balanced. One small change, it just blows up. Because biology is extremely very often characterized by strong robustness and we will worry about definitions of robustness a little later on but robustness usually means the insensitivity to a particular kind of perturbation.

But in biology you will see that a large number of perturbations are actually okay. The system stays stable in the phase of many perturbations. Obviously, you know there is a magnitude that you have to worry about, the kind and nature of perturbation you have to worry about and so on but in comparison to engineering systems you will see that biological systems demonstrate lots more stability and robustness which brings us to sensitivity and robustness.

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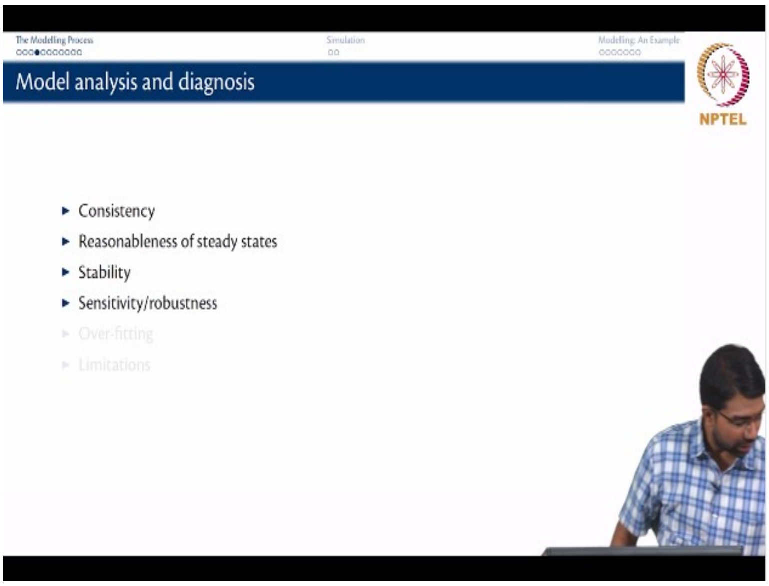

What is the difference between stability and sensitivity? Stability is clear, right? So, you started an initial stage, you give a perturbation, it comes back right. Sensitivity is what is my response for a push. If I give a small push to the ball, does it just fly out of the bowl? Or does it just move a little and so on. And typically, we will worry about sensitivity the classic way to mathematically define sensitivity will be. This is sensitivity.

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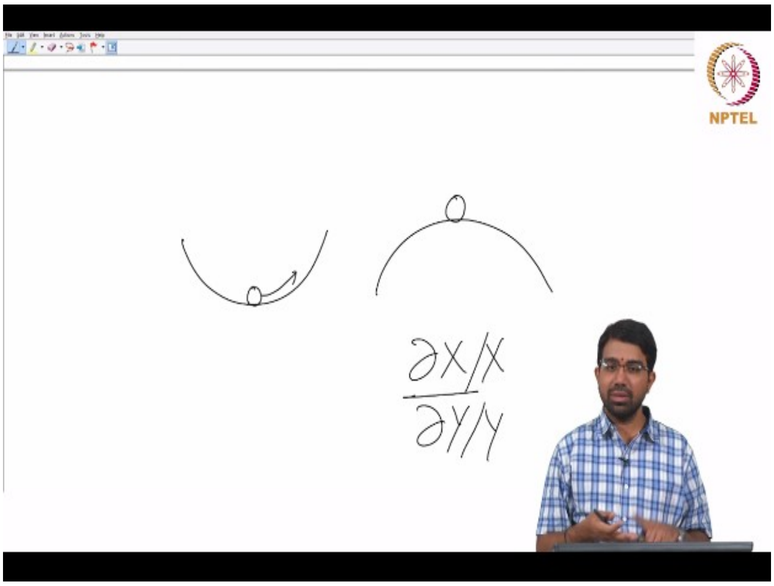

That's it. This is what sensitivity is. We will look at it more closely later on. Typically, you may want to define it like this to keep it dimensionless but basically it is the change in a particular read out to a particular perturbation. I push something, I do something to the system, I raise the temperature by 1 degree Celsius, how does the rate of my reaction change? How does everything else change? Or add a little more of enzyme, how does everything change?

So, this is sensitivity and typically you want your system to show good sensitivity to your parameters. Otherwise you know those parameters are meaningless. You change a parameter, the system remains the same and parameter rather should not have been there in the first place. You will look at all these in greater detail as we go on but the purpose of this lecture is to introduce you to what kinds of things one worries about while building models.

And it is good to be aware of this whole thing when you start the modelling exercise itself. Am I going to be able to test for stability? Is my model sensitive enough? Do I have good data? All these kinds of things one has to start worrying about.

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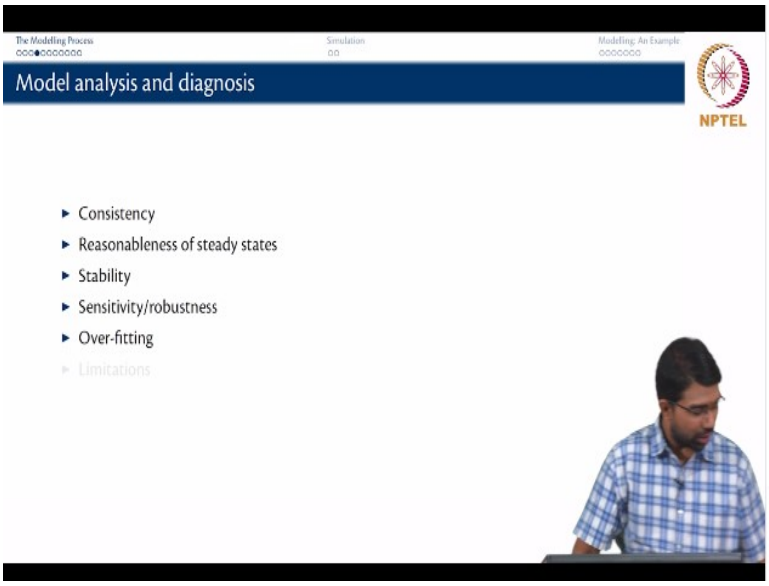

Over-fitting. Another major challenge. What is over-fitting in a general scenario? **“Student conversation”**

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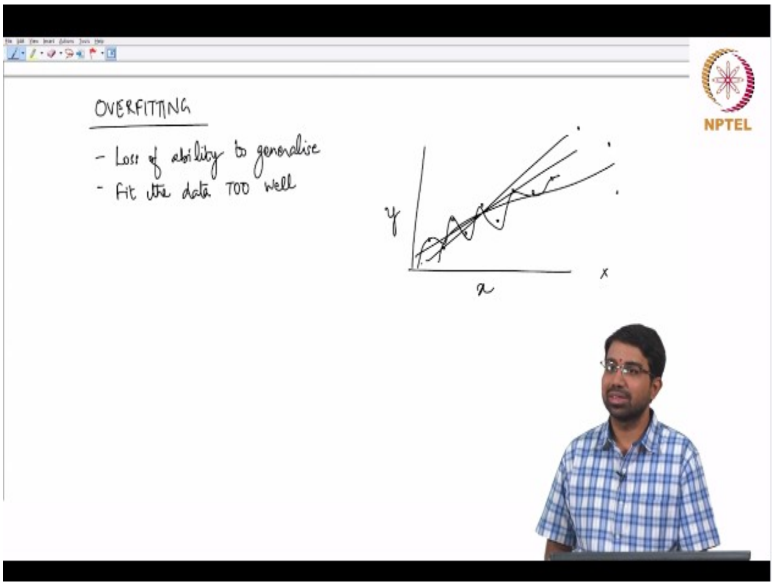

So, one very good way to describe over-fitting is you lose the ability to generalize. You basically fit the data too well. It is somewhat the equivalent as one colleague mentioned, it is equivalent of memorizing the assignment numbers rather than just the assignment concepts. So, you want to only learn the concepts from class, learn the problems that are discussed in class.

But if you were to memorize the numbers then you are able to only solve the problem if it has the same numbers. So, a classic example you may all see in for over-fitting is in case of regression. You have a simple system like this and you want to build some sort of correlation.

There is y and there is x. So, you may think that this is a good correlative model to explain y versus x.

Maybe this is another good model but this could also be a model but a really weird model would be this. So, the problem with this model is that it perfectly reproduces the original data but it might really, so when I get a new point, so for this x, I might have to predict this y but this might predict something here or something here depending upon how it has been fluctuating right.

So, you have memorized the noise in the dataset as well instead of just the trend in the dataset. This becomes an important thing to worry about and this has very fundamental implications. How big should your model be? How many parameters should you have? The more parameters you have, you run a greater risk of over-fitting. But then there are so many processes to describe. So, then I might need more parameters.

So, you have an interesting trade-off that needs to be arrived at. So, you need to worry about all of these things.

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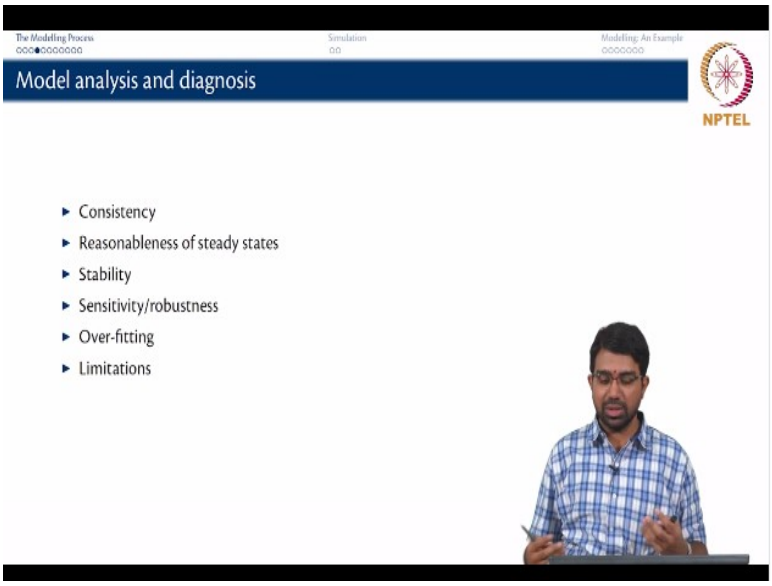

And always, always, always be aware of the limitations of any model that you use. So, Michaelis-Menten will work only in certain scenarios. The system has to have Freidrich diffusion, the temperature of the system should not change. There are no other interfering factors and so on and things like that. So, there are a number of assumptions that underlie every single model and usually people gloss over them and ignore them and make mistakes.

A classic model that was used to study how a drug is distributed basically had this problem. So, people just started using that model in all scenarios whereas it was only acceptable for low concentrations of drug and so on. When you extrapolate something, you need to understand how far you can extrapolate. If you have data from t=1 to t=200 minutes may be you can extrapolate it to t=240 minutes.

But you may not be able to extrapolate it to 10 days because you do not know how the curve is going to change, how the other parameters are going to change as the simulation proceeds.

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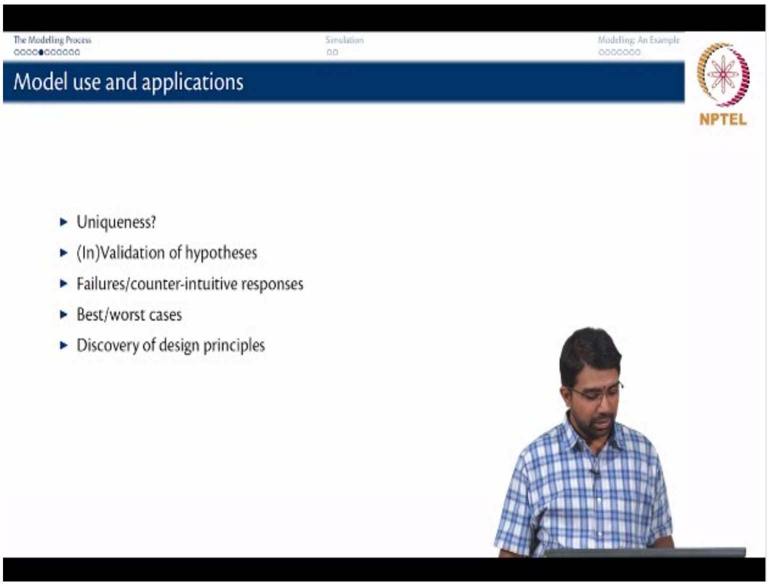

Is your model unique? These are all very difficult sometimes almost bordering on philosophy questions. Is there one model that can describe my system well enough? But better still, can you invalidate hypothesis? This is in fact one of the most useful aspects of any modelling exercise. You start with a hypothesis. you can't prove it. Can you show that if you make these assumptions the model breaks down?

The model cannot explain your reality then you may have in fact succeeded in invalidating your hypothesis. Validating your hypothesis is a harder problem, maybe there is a case that you have not examined where your model could break down so you may never be 100% convinced about validating a hypothesis but you may be able to invalidate hypothesis more easily. And this is just like whenever you write a computer program you want to make sure it works in all scenarios.

So, you may have to stress test it. Does it give some weird response if you give some weird inputs? So, you have to stress test your model particularly at some at what you may perceive as the boundaries of your model right, for very low concentrations does it work or you know maybe it just falsifies some assumptions so you should not be even considering it right.

So how does that work right and what are the best or worst cases and the biggest loftiest goal of them all can you actually identify design principles underlying your system right. Using model as a way to interrogate your system to finally understand the design of the system itself right because as we discussed already the moment you commit to a model, you already have certain hypothesis that you have committed to.

You have a certain mathematical understanding of the system, given this mathematical understanding can you extend it, can you you know understand oh this is how the system works, I need for a system to show this behaviour it needs to have these kinds of connections, these kinds of you know wiring between the different components that exist and so on or I can say if I find 2, 3 feedback loops in a system it is always going to be stable know something like that.

Or if I do not find 2 feedback loops in a system, it is never going to be stable. You may be able to come up with certain design principles of this sort right. These are basically principles that you glean out of your modelling and why do we need to resort a modeling for this because a model can be operated under several conditions, you can make several perturbations, you can make a very large number of what if questions with the model, answer them with the model.

And then use it to identify okay is this making sense, oh this seems to be the overall overarching principle underlying the system and so on.

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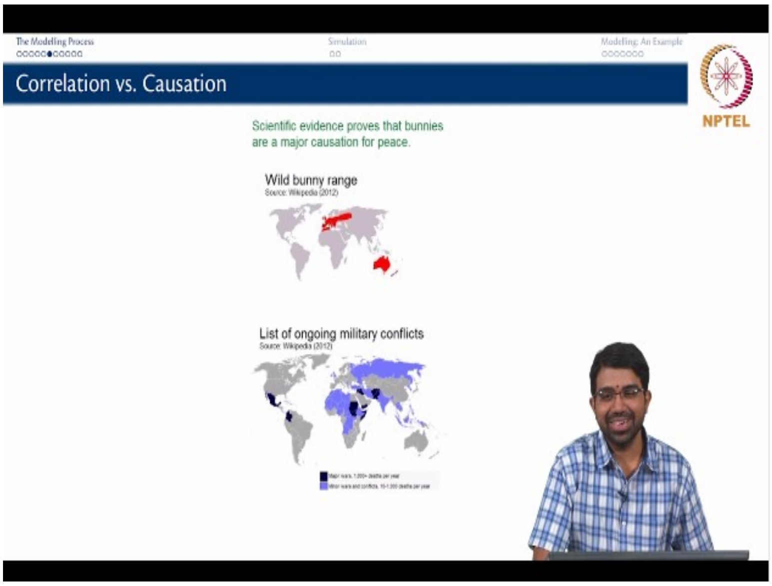

And a lot of times you may end up with dangerous mistakes such as these right. So correlation does not always imply causation. There are cases where it can but it is a very tenuous thing and you have to be careful. So this is a kind of funny thing which says that bunnies are major causation for world peace right. So wherever you have bunnies you do not find any conflicts or worse right which obviously does not make sense.

I think you had some very interesting correlations like that right so you know that number of noble prizes is well correlated with per capita chocolate consumption right and so on right.

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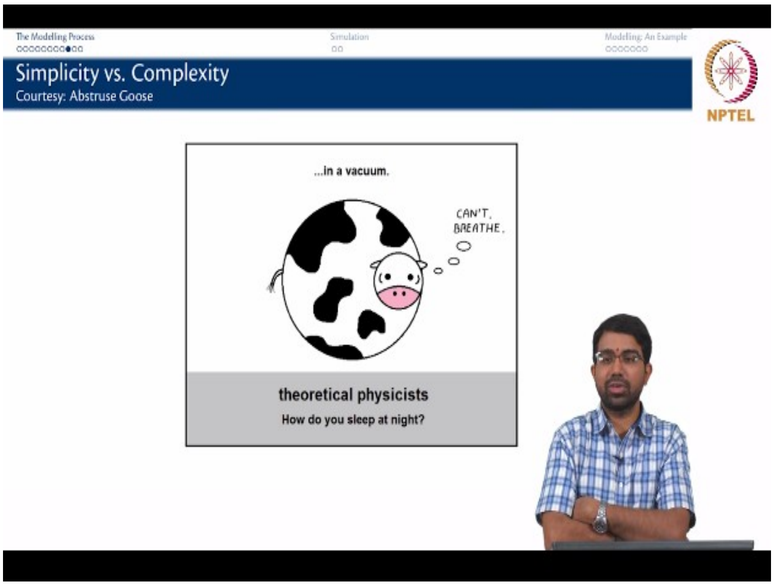

So you have to be careful about those things and I think this is the cartoon that many of you may be familiar with so this is exactly what we do not want to do today right, we can build more and more accurate models you do not have to worry about building a you know spherical curve of uniform density ignoring the effects of gravity in a vacuum right. So we want to go beyond these simplistic models.

And actually build realistic models that can see the final proof of the model is if it can predict your reality, you throw it into a new situation it should be able to predict what happens right. If it is unable to do that the model is not very useful right.

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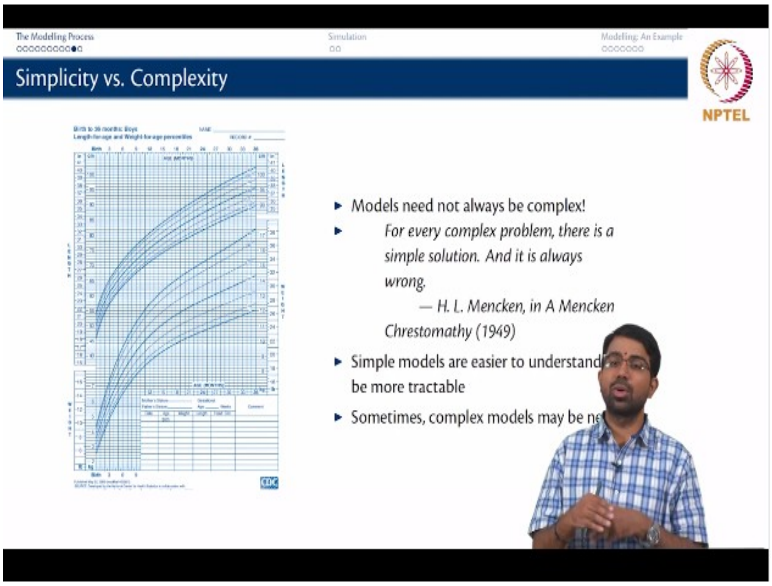

And models need not always be complex, so this is the very, very simple model which says how height and weight are correlated right or height and age or weight and age are correlated. So if you see there are many curves that you see here, so this curve basically says so this says that so only 5 percentile of the people are below this curve and only 5 percentile of the people are above this curve.

So basically this is the curve where 90% of the population falls in right. So if this is the birth weight, this is how the child is expected to evolve. If this is the birth height, this is how the child is expected to evolve right reasonable I mean growth is such a complex thing right. You know how much food the child takes, how much activity he or she has, what is the genetic makeup, what is the nutrition of the parent.

In fact, there are projects that are carefully looking at these as well but beyond all of these you can build a simplistic model but well the model may not be very useful right. It could just be wrong as some people say and simple models are easier to understand and maybe more tractable but they may not always be helpful, you may compulsorily need to build more complex models right.

What will decide whether you need a simple model or a complex model? **"Professor - student conversation starts."** Exactly, right it is always what drives modelling is the question you want to finally answer that is always the prime thing, you should always keep that in mind right **"Professor - student conversation ends."** Other things are also so you may want to have you know lofty goal but you may never have the data that helps you answer those questions given that case you cannot even build the model right.

So that comes back to your point right but always what decides how you want to model a system is what you want to answer in the end, you want to answer a simple yes no question, does this enzyme affect this reaction or not, I would build a completely different model versus is a 10% increase in this enzyme going to afford a 15% increase in the rate of the reaction right, that is going to demand an entirely different modelling scheme.

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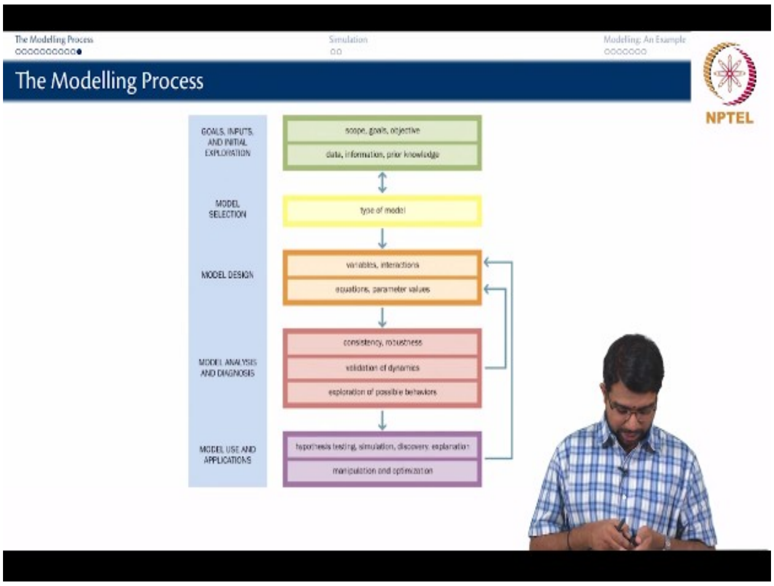

So this is a kind of overview of what we discussed so far. So you need to first look at what are the goals of the modelling exercise, what are your available inputs and do some initial exploration right and then choose a model this is where the distinction between the science and the art are blurred right, so is modeling a science or modelling an art right. It is an open question right.

It is a science in some sense but then there is lot of subjectivity to it which becomes an art in some sense right. So what are the aspects of model design you need to worry about, there are certain variables, what are their interactions, what are the equations that connect these variables and represent the interactions, what are the parameter values and so on and then study the model.

Is it consistent, is it reasonable, does it have sensible steady states, if it is stable, is it able to give you reliable responses compared to what you observe in experiments and so on and the use of the model that is what we all are in for right. Can you test a hypothesis, can you simulate unused scenario, can you predict the future behaviour of the model so on and so forth right?

So this is you know in sense a broad overview of the basic aspects of modelling right and we typically talk about modelling and simulation together right. What is modelling and what is simulation? **"Professor - student conversation starts."** In a sense right so building a model is basically writing down on coding up a large set of mathematical equations that represents certain interactions in a system crudely speaking.

Simulation is basically running the model and asking all your what if questions. The most important aspect of a simulation is that it will compress time and or space right. You can talk about see it does not take 3 hours to simulate a Michaelis-Menten system for 3 hours right. So it basically can compress time and you can ask very interesting questions. **"Professor - student conversation ends."**

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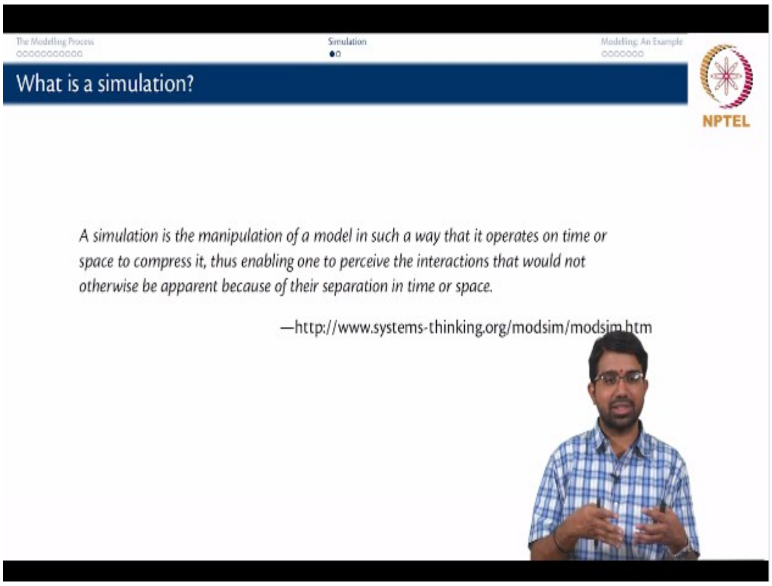

So what is the simulation? It is the manipulation of a model in such a way that it operates on time or space to compress it and most importantly help us perceive interactions that were otherwise not visible right because you have compressed it, you can actually see certain interactions that you were not able to observe otherwise.

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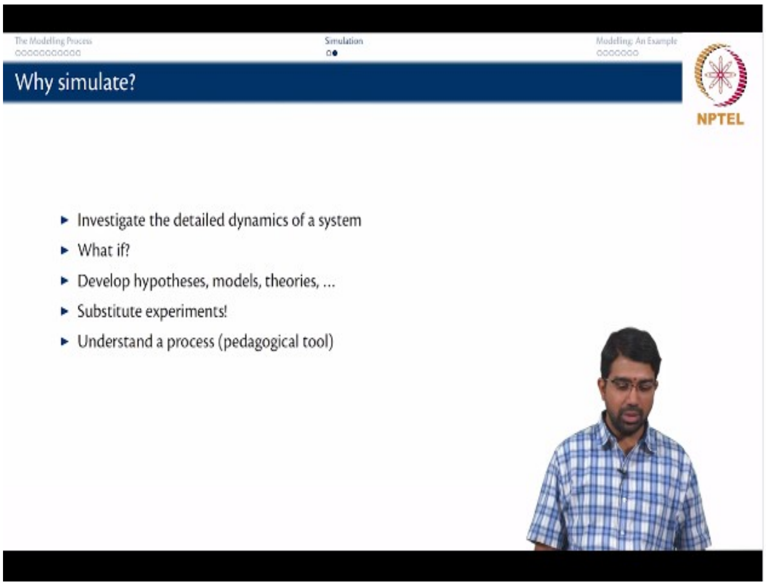

So why simulate, you want to investigate the detailed dynamics of the system, most importantly and practically always you want to ask a lot of what if questions about the system, what if this happens, what if the enzyme concentration is doubled and so on. Again develop hypothesis, models, theories and so on. Actually substitute experiments and a very useful pedagogical tool, very helpful for me to teach a class such as this right.

We will simulate several things, we will simulate interactions between enzymes and substrates, we will simulate interactions between metabolites in a cell, we will simulate how a network changes if you change various properties of a network and so on right, how does the connectivity of a network change as you change certain parameters in a network so on and so forth. So let us discuss all of this in light of a nice example.

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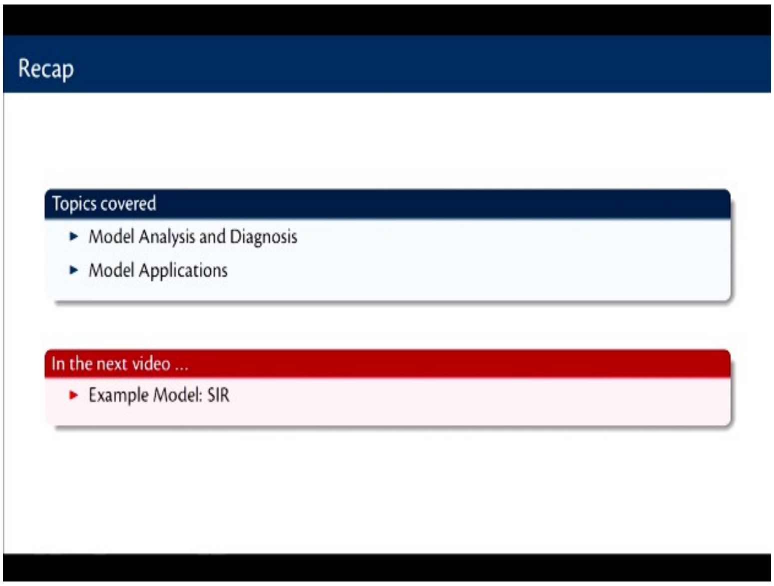

So in today's video, we have looked at model analysis and diagnosis as well as the applications of models and in the next video we will revisit the SIR model and take a closer look in terms of you know diagram and the equations, the parameters involved and so on which will help fix several of these ideas that we have discussed in the last few videos.