Computational Systems Biology
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Lecture - 35
Introduction to Dynamic Modelling

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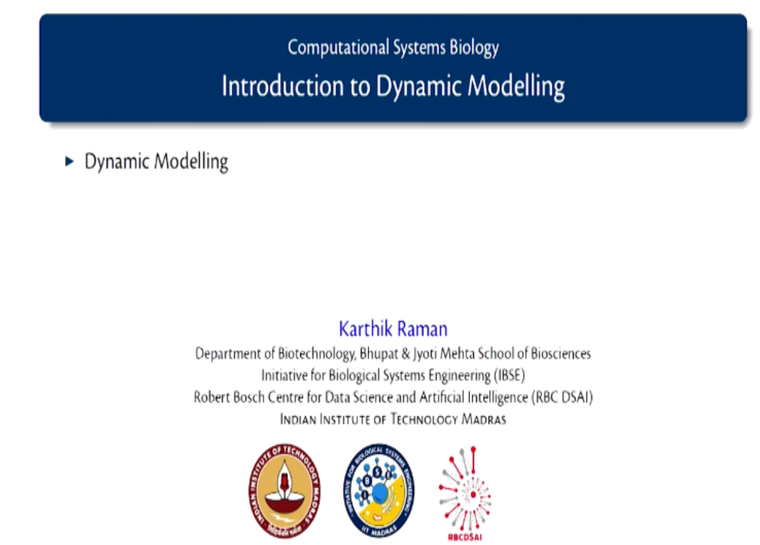

So welcome to this new module wherein we are going to now move on from biological networks to-- mostly static networks to dynamic models and predominantly we will be looking at building OD based models Ordinary Differential equation based models, and you know how one estimates parameters for these model. How one solves ODs and so on. But today we will have a brief introduction to dynamic modeling.

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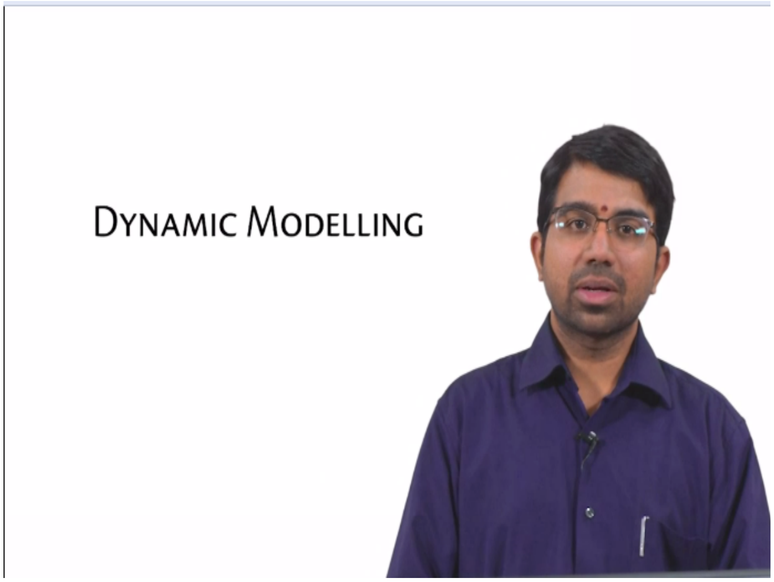

Welcome back. Today we will look at dynamic modeling. Dynamic modeling is actually a very vast ocean of topics. We will pay specific attention to a few topics. Basic dynamic modeling and focus a lot on parameter estimation particularly focusing on direct search algorithms. So what is dynamic modeling?

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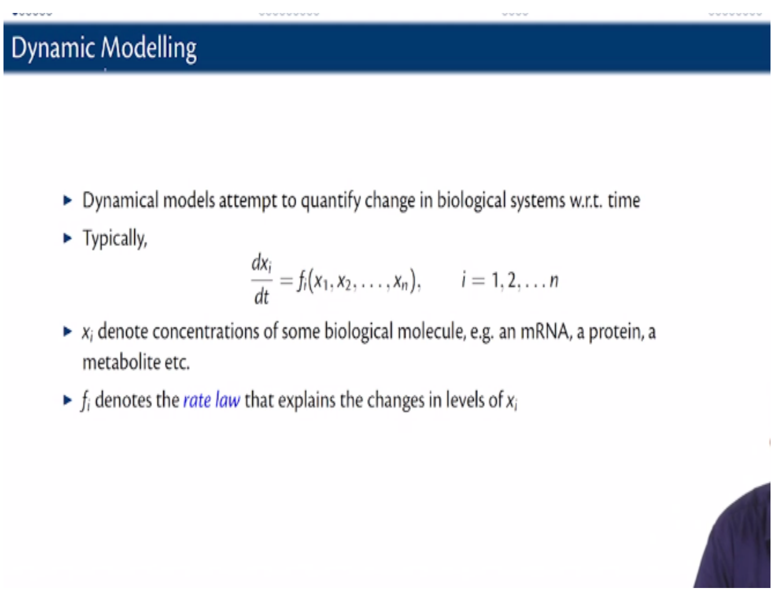

So dynamic modeling basically involves quantifying how biological systems change with respect to time. So there is invariably some dx/dt in these models and since usually written as some function of various concentrations or species or various parameters in the system. So for example xi denotes the concentrations of some biological molecule like an mRNA, a protein or a metabolite and so on.

And fi here essentially denotes some rate law that explains how xi changes with respect to time and whether in response to all the other x's. So you are actually familiar with any of these models if you stop to look at it. We will look at some examples as well, right.

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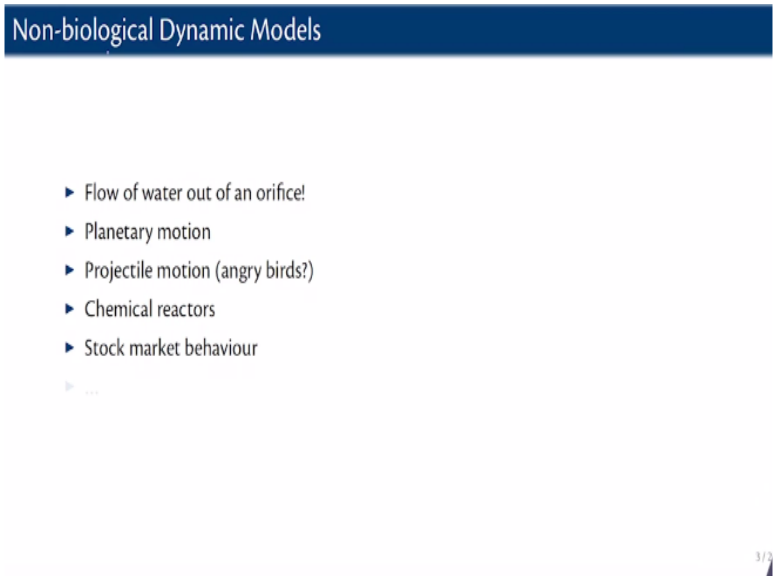

So can you think of non-biological dynamical models? There are many non-biological dynamical models that one normally encounters. Electrical circuits, right there is a lot of variation with respect to time there, okay. What else? **"Professor – student conversation starts"** Time spirit of diseases. Sprit of diseases you can think of modeling it with respect to time, yes. Flow of water. Yeah, flow of water out of a tank and so on. That is the first classic example that you will hear in most mathematical in modeling courses. **"Professor – student conversation ends"**

Planetary motion for sure and Projectile motion or like angry birds and so on and chemical reactors, and very importantly in today's context stock market behavior, right. This is what is very popular in the job market these days. So how does the stock market behavior change with respect to time? How does the price of a particular stock vary with respect to time? Okay, so these are non-biological dynamical models.

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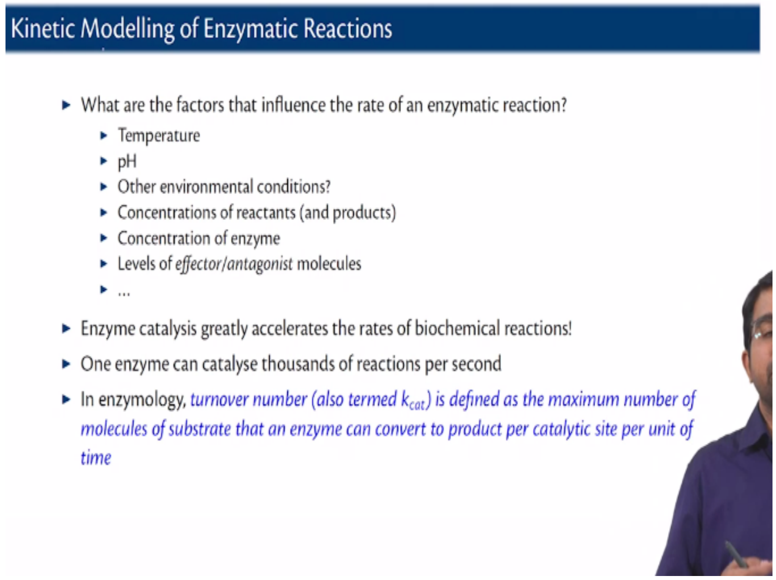

So if you wanted to consider an enzymatic reaction, what are the factors that you would want to consider? You would want to model the effect of-- so you want to model an enzyme catalyzed reaction, what are the factors you would like to consider? So in any modeling exercise we need to establish what is it that is very important central to our model the problem that we are investigating.

What is peripheral, so we may choose to leave it and what are the things that we do not worry about at all, right? So what are these things with respect to an enzyme catalyzed reaction. We obviously want to start off with the concentration of enzyme; concentration of substrate but beyond that what are the other important factors that you may want to consider. Fine, but those are those are part of the model right.

I am talking more about the factors that you want to consider. Temperature would be the first thing that you might want to worry about. Hopefully, you have a constant temperature system and so on but temperature is a very important thing. pH, obviously. What else concentration of what, concentration of substrates as well as many other effectors.

Enzyme and substrate concentration is a given, right that is the first thing that you want to write down when you want to model an enzyme catalyzed reaction, but beyond that you also want to worry about the conservation of various effectors, antagonist molecules and so on. So temperature pH various of the environmental conditions, concentrations of reactants and products obviously, conservation of enzyme again obviously then also levels of effectors and antagonist molecules. You can have an allosteric inhibitor, allosteric activator and so on.

So enzyme catalysis greatly accelerates the rates of biochemical reactions. I am not getting into basic enzyme catalysis here. I'm sure you would have studied it in many other courses. The purpose of this lecture is to introduce you to the concepts of enzyme catalysis or I mean modeling enzyme catalysis catalyzed reactions. You know that one enzyme can catalyze 1000s of reactions per second.

And you may be familiar with this term called k cat which essentially defines the maximum number of substrate molecules that an enzyme can turn over, right per unit of time. What is the law of mass action? What does the law of mass action state? It invariably turns out that many people have the law wrong in their minds. We have the translated version of the simplified version of the law but not the original version of the law.

“Professor – student conversation starts” What is the law of mass action originally state? Yeah, hazard I guess. Rate of the reaction is directly go to the activities of the— product as the mass. Okay. Those are all correct those are all practically useful definitions but that is not the real definition. What is the real definition? What you are saying is correct under certain conditions. If you were to step back what would it have been what should it have been?

So the law of mass action states that the rate of reaction is directly proportional to the probability of collisions between the participating molecules. **“Professor – student conversation end”** In practice that boils down to reactants, concentrations of reactants and so on and so forth activity all that stuff, right. But in essence it is the product of the probability is proportional to the probabilities of collisions between the molecules.

Because with this definition you can apply the model in several cases; even in a stochastic case you may be able to figure out how to apply the model, right. But if we said product of concentrations that is not going to work out in a stochastic case where you do not have concentrations you have molecule numbers out there, right.

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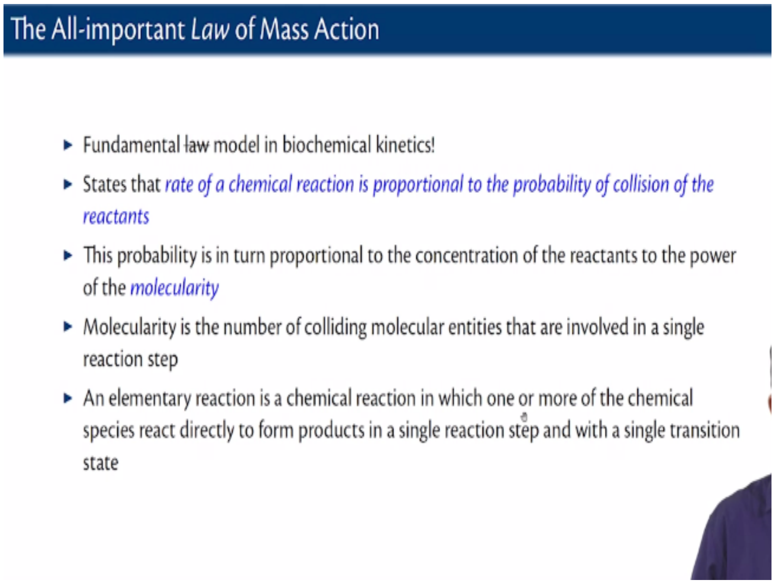

So it states the rate of a chemical reaction is proportional to the probability of collision of the various reactants. This probability is in turn proportional to concentrations to the power of molecularity given an elementary reaction, okay. What is an elementary reaction? **"Professor – student conversation starts"** One step. What do you mean by one step? There are no intermediates. Does the single step reaction not have an intermediate?

Yeah so one transition state, right. So single step reaction with a single transition state, fair enough. **"Professor – student conversation ends"** So molecularity is the number of more colliding molecular entities in a single reaction step, elementary reaction is a chemical reaction in which one or more of the chemical species react directly to form products in a single reaction step with a single transition state, no other intermediates right. So these are all things that you must have studied in roughly 8th class but mostly forgotten, right the fundamental concepts.

because we only use the derived concepts later on, right everybody remembers, if I gave you aa+bb giving cc+dd you will immediately say Ka to the ab to the b will be the rates of the forward reaction and things like that. So consider this simple reaction.

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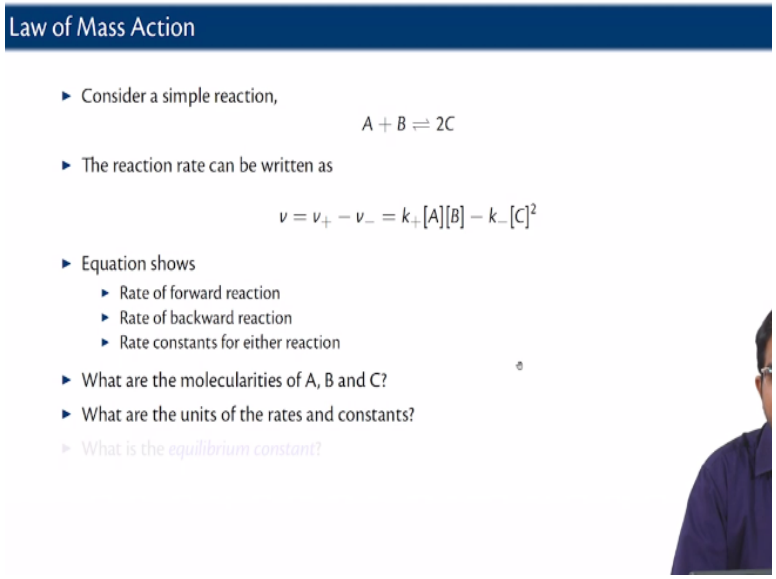

What is the rate of this reaction? What is the rate of the forward reaction? Kab, right. And the reverse reaction Kc squared, yeah, k+ and k- fair enough, so the equation shows the rate of the forward reaction the rate of the backward reaction and rate constants for either reaction. What are the molecularity of A, B and C? 1, 1 and 2.

What are the units of the rates and constants? **"Professor – student conversation starts"** (()) (08:58). Fine, rate is always concentration per unit time. What about the rate constant? Depends upon the order of the rate constant, right. **"Professor – student conversation ends"** If it is a first order rate constant will be per second; if it is a second order rate constant it will be concentration to the inverse of concentration; inverse of time, right. It is basically concentration to the 1-n per unit time.

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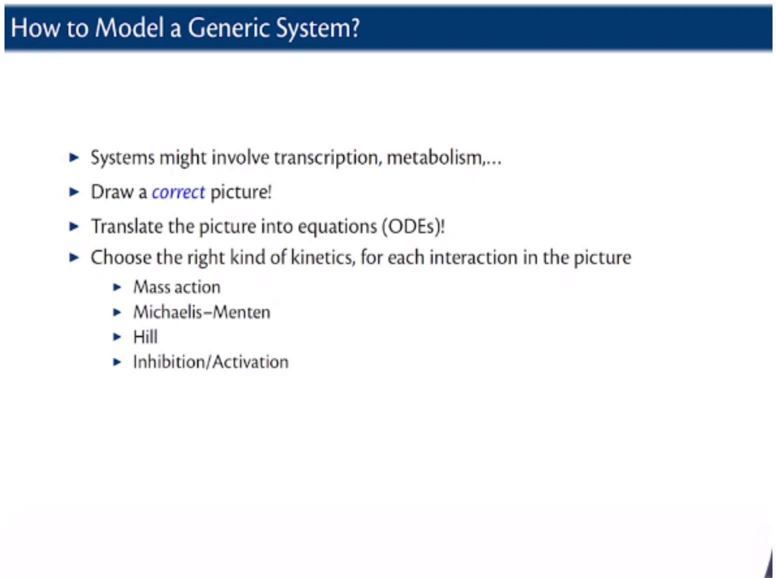

So how do you model a generic system? Because we are talking about in general modeling biological systems, so they may involve multiple things like transcription, translation, signaling, metabolism and so on. So how would you in model such systems. You need to first start with potentially a correct picture or rather the whole set of interactions that are involved and then translate these pictures into differential equations, mostly ordinary differential equation.

Choose the right kind of kinetics for each interaction that you would you might have it for a signaling kind of reaction what is the kinetics; for our transcriptional reaction what is the kinetics; for a for a metabolic enzyme catalyzed reaction what is the kinetics. You may use a combination of Mass action, Michaelis-Menten, Hill and so on. And you may have slightly modified models if you are looking at Inhibition and Activation and so on.

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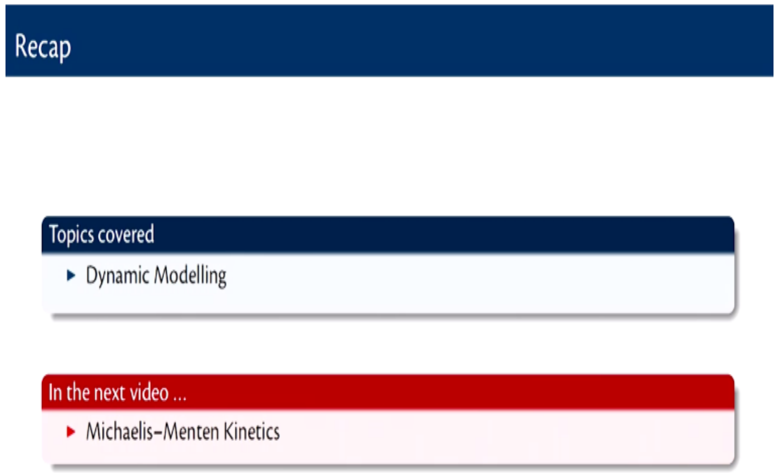

So today we saw a brief introduction to dynamic modeling and in the next video we will fix some of these concepts by looking at the ever evergreen classic example of Michaelis-Menten Kinetics.