Computational Systems Biology
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Lecture – 52
Guest Lecture: Modelling in Drug Development

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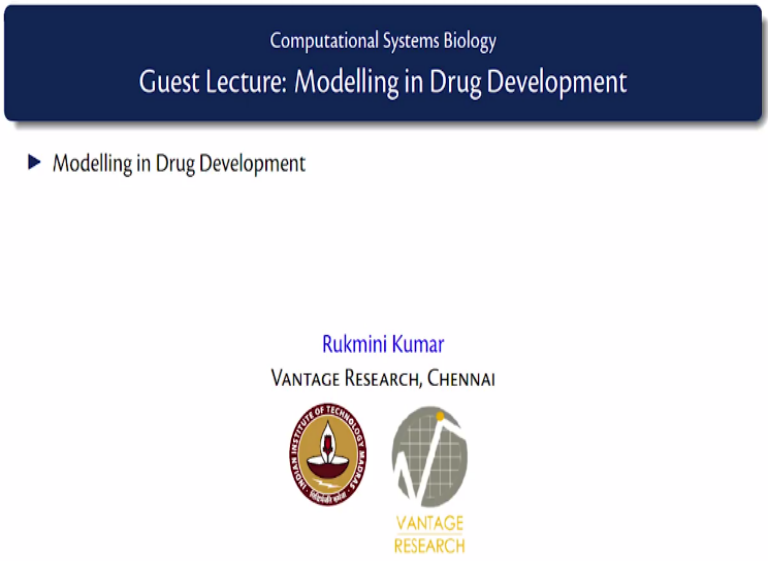

So there are 2 concepts I would like you to get familiar with.

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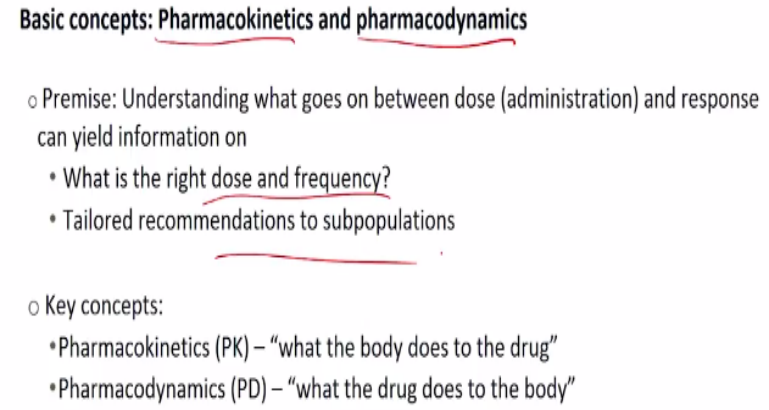

These are called pharmacokinetics and pharmacodynamics. So these are words that you may see being used to lot in the context of development, drug development and definitely in the context of modelling in pharma. So a simple way to think about it is pharmacokinetics is what does the body do to the drug? So you pop a pain pill or you inject or somebody in your family injects insulin into themselves what really happens? What so for instance let us brainstorm a little.

So when, you must have all had a Brufen or Anacin at some point. **"Professor - student conversation starts"** You pop it in what do you think happens to the pill. It dissolves in the blood stream that you are popping in your mouth so the first thing is it goes through your digestive system, but you are absolutely correct. You wanted to reach usually the nervous system at the end, but what does it do is the first thing you need to make sure is you have enough drug to withstand the horrors of the digestive system.

The digestive system can be a very challenging place. **"Professor - student conversation ends"** The stomach is very acidic and then there are all kinds of enzymes which come to digest anything that goes into the stomach and then stuff is absorbed from the intestines into the blood stream. **"Professor - student conversation starts"** What about if you inject insulin? What do you think happens? It goes directly into the blood stream.

So that is the difference between those 2 kinds of administration. There are all other manners of interesting administration. **"Professor - student conversation ends"** You may have seen some drugs which are patches. So people who are who want to quit cigarette they usually have something called a nicotine patch so that is intra dermally you know you are slowly injecting and that goes into the blood stream. Injections themselves can be of different types.

You could have injections which are intravenous so when you go the hospital because you are dehydrated and they give you drip I think that is where they put it in, but some injections like insulin are intramuscular so it stays in the muscle for a little bit before going to the blood stream. There are some drugs which are inhaled so asthma attacks. If you seen those people have these drugs so those go directly to the lung.

So how you administer a drug and what the body does to the drug that part is called pharmacokinetics and that can get pretty complicated. The next thing is pharmacodynamics. So here what we are doing is once all of these processing is happened to the drug that you have injected what does it do to the body? What part of the body does it go, hit? So when we are talking about you know some of these pain killers.

We know that the target is the nervous system when you are talking about something like an asthma drug then the blood vessels in the lung and the alveoli and those structures in the lung are what that goes after. When you inject insulin the targets are insulin receptors in various organs in the body, in the muscle, in the liver, etc, etc. So what the drug does to the body it is pharmacodynamics.

And we will talk a little bit about what kind of modelling can if and why it is useful to do all of those. At the end of the day the questions you want to answer are still what is the right dose, what is the right frequency can I tailor recommendations all the kinds of questions that we want to ask in the complex process of drug development those are the questions we want to ask using modelling.

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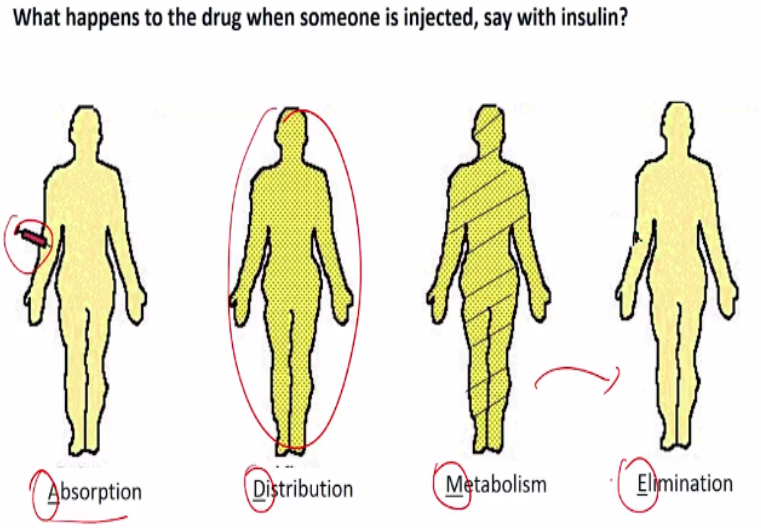

So we were talking about what happens to insulin when it is injected. So this is the site of injection. The first thing that happens is absorption. The second thing is once it is absorbed it is

not sitting in 1 little place in your body it distributes evenly through your body and that is a simplification. We all know we are not like the bags of blood walking around there is all kinds of complicated structure and microstructure inside the body.

But to a simple approximation you think you inject insulin and the entire blood gets suppose you injected 10 units of insulin then that gets dissolved across the volume of blood in your body. Then you come to metabolism. So this a kind of what is the body do to the drug when the body is very good at identifying anything which is a xenobiotic or anything which is far into it. So insulin is a molecule that looks lot like the body.

But anything which comes in any protein will be chopped up, anything new will be cleaned up by these clean up proteins so a lot of or in the case of insulin you know it will go and sit in the receptor and do the job it is supposed to do. Are you guys somewhat familiar with receptor, ligand, and dynamics. You know a lot of work in the cell happens because cells have receptors in their cell walls, something comes, signals to that receptor, downstream.

There is a lot of mechanism and that is how a lot of biochemical process is happened. So insulin is going to signal its receptors and you know that is a way and something you know that may be metabolized and then you have elimination. When you inject insulin or you pop some acetaminophen it is not like it is going to be in your body forever and forever it gets eliminated. The kidney and the liver are the main organs of elimination and the drug gets eliminated.

So at the end of the day, the 1 concept you should be familiar and it is one of those things that you may start seeing if you are interested in this field is ADME: Absorption, distribution, metabolism, and elimination of any drug. So this is a key cornerstone of the concept of pharmacokinetics what happens when a drug is given to a person.

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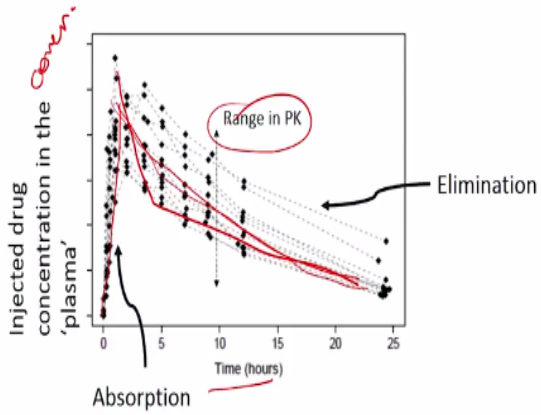
The concentration of the injected drug in the 'plasma' compartment after a single injection to 10 individuals



Now we can start to get even more quantitative and say hey I have injected a person with insulin in fact in this case I have injected 10 people with insulin and then I want to see what happens. I am also measuring what happens to the insulin in a compartment and loosely called plasma, but it can be measured in the blood of the plasma and there are all kinds of more detailed which I am not going to go into.

But you can generally think of you know how much insulin is there in the plasma. So this is in some units of concentration over time. So this is the absorption phase and as you can tell at time 0 when you give the injection there is not much going on boom you see some increase in insulin as the insulin gets absorbed and you see this decrease as it gets metabolized and eliminated. So before we will go any further as people of quantitative backgrounds and engineers you can already start thinking how this looks like an exponential decay.

So that is something that you can model. If you think it is a little more complicated may be it is a biexponential. You know it comes down fast and then goes away a little slow so those we can start getting into some interesting mathematical ways to represent what is happening in the system, but the important points are the basic concepts of absorption, elimination are seen in these curves. The other important thing to remember as people who want to be in health, biology, or life sciences variability.

So it is variability in many control settings often comes from second order, third order variables that the model does not care about so you can usually allocate that as noise, but in biology when you do the same experiment in 10 settings you are not going after 1 curve, because 10 different human beings will behave differently because their parameters are going to be different. So variability is something that we need to acknowledge a way up front when we worry about things like this.

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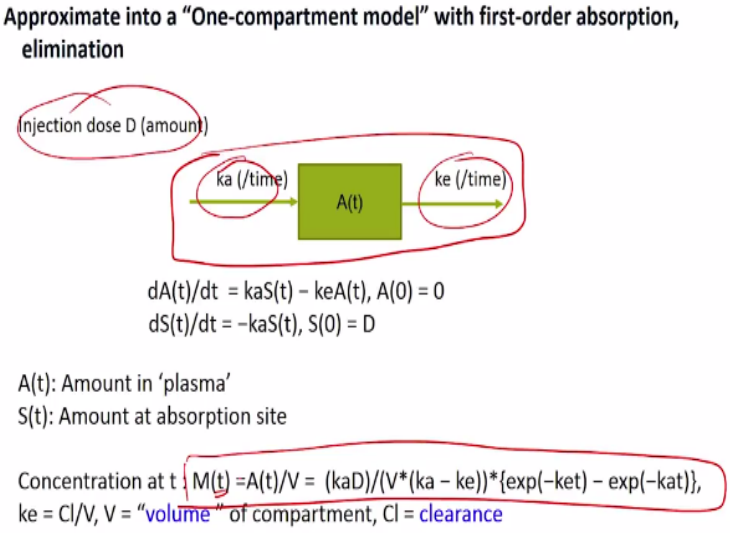

So that is the basics of PK. So now let us get into some more juicer details of the mathematics and say how would I model the system? Anytime you want to make a model you first want to visualize what exactly am I doing and here this is what we are trying to visualize. All the complexity of the human body was saying that is 1 box it is obviously a simplification. It will not work in all conditions.

But we are saying it is a box and then at some rate stuff is coming into the box. At some rate stuff is leaving the box. So we can say Ka and Ke the rates of absorption and the rates of elimination and you can say initially you gave a single dose and the amount is D. So you say you give D units of insulin. It gets absorbed at a rate of Ka per minute. It gets eliminated at a rate of ka per minute and we have the machinery of differential equations to write that up.

These differential equations are simple enough that if you want to do something which is a concentration which is what we saw in the previous chart you can solve that exactly in terms of all of the parameters that you have and the volume of the system that you estimate and say at the end of the day the at time t this is what I expect the concentration of insulin to be. We are on to something, something which was a very may be mysterious thing about somebody injecting themselves with insulin potentially can be simplified in normal simplification.

But a useful simplification, in terms of a 1 compartment pharmacokinetic model. Ok we are on to something. **"Professor - student conversation starts"** Where are we getting D and n here, you are only considering a and e. So in this model I kept it simple but you can think of if you want to have some more time for the distribution to happen may be it happens over 2 compartments I did not go into that so you are correct. If you really and so that is 1 thing.

The metabolism is another thing to think about in a sense that often you give 1 drug it gets metabolized and chopped up into some daughter chemicals which are then used. **"Professor - student conversation ends"** So distribution and metabolism can get complicated to model and understand. In this case, I chose to keep it simple and say something comes in something goes out which is an injection like that, but you can have more complicated models that starts worrying about those things.

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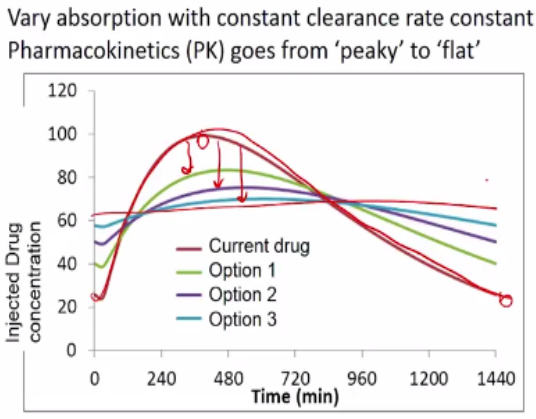
Some fun with simple PK models, changing model parameters



And this potentially we can have as an exercise for you guys to do. Is everybody familiar with MATLAB or what is the software Karthik asks you to do a home working, MATLAB. So we can start getting interesting with things like this. We can make more complicated models. You can have 1 compartment models, 2 compartment models and such, but what I want to show you here is even with these simple PK models you can start playing with the properties of drugs.

So these may be drugs that you are designing, some drugs which are already in the market, so we can pick up some papers and try to reproduce the trajectories that you see of those drugs, but here in a slightly more complicated model what you can do is you can start playing with the drug. The current drug is this red curve here. As you can see it has got a pretty peaky profile. The peaky profile you can try to quantify it by saying what is a peak over the trough.

Over a 24-hour period how much higher is the peak over the trough. Now for what are the reasons if you are not comfortable with that and if you want to make this less peaky you can start varying the Ka or the Ke and we can have an exercise to figure out which will work to make the drug flatter and flatter. At the end of the day another important concept in this is area under the curve.

So you know you guys area under the curve so we may still want to keep the area under the curve the same, but we may want to have a flatter profile. So these models help us understand how do we want to change these so that the profile is a little more to our liking. Now does this have a real world application, indeed.

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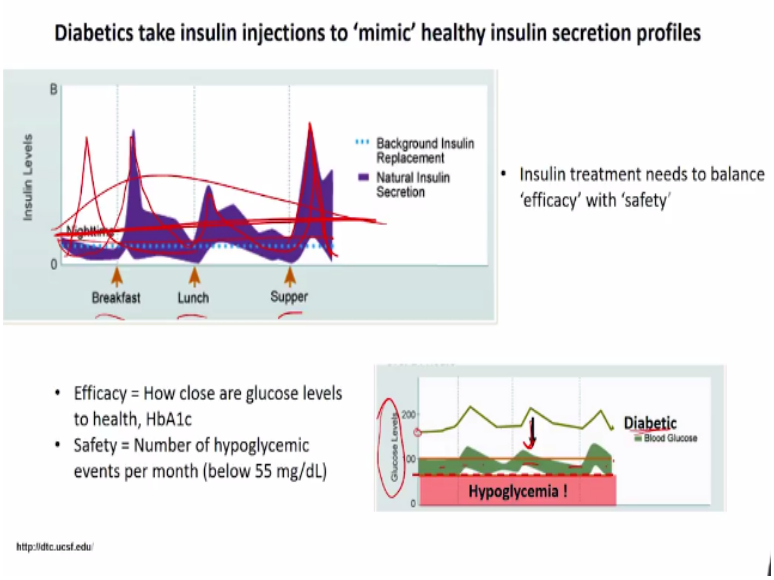

So we are talking about insulin again and let us get into a little bit more about the physiology and the biology here. So if you look at how healthy people secrete insulin that is this purple kind of area here. So there is a lot of variation, but at the end of the day for every meal people secrete some insulin. So you know your body you try to eat some meal in order to process that insulin is secreted and you have that nice 3 peak pattern.

But you want to have a drug that mimics that pattern. So if you are a diabetic either you do not have enough insulin or you have no insulin at all. So you do not want a drug profile which is flat. You do not want the drug profile which is too peaky. You want to keep varying the drug profiles so that you are able to match the endogenous insulin secretion. So then how many of your family members inject insulin more than once a day. Do you over a meal?

So some people if they are really sick they need a meal time insulin. So before breakfast, before lunch, before dinner, so that insulin will have a peaky pharmacokinetic profile. It will do something like that and people whose insulin is somewhat whose diabetic is somewhat under control or early in the game they often take insulin which have a flat or a gentle profile like that. So that, that takes care of their insulin coverage through the day.

So these are kind of some real world questions that we will have to grapple with when we are thinking about pharmacokinetics. **"Professor - student conversation starts"** (()) (14:07) peaky

to a flat to converge. Why do we want that? That is the thing that I had here. So the reason you have to be careful when you dose people with insulin is that you do not want to overdose them. So here we will talk a little bit more about the physiology, but let me give you a little peak here **"Professor - student conversation ends"**

So this is glucose levels. So if you are sick your glucose levels are high. So this is the diabetic's glucose levels, he starts at may be 150 milligrams per deciliter that is how glucose is measured. You start with that much and that is how your glucose profile looks every day. But your job as the drug developer is to bring that down so you want to bring it down to a healthy level which is that green area here, but you have to be careful.

You do not want to bring it down too much because glucose is an essential fuel. If you have too little glucose your brain will not have enough glucose to process and you may go into something called hypoglycemia. Again those that have relatives that have diabetes this is very important. They usually have some candy or some juice in the fridge because if they have too much medication or if they have medication and they skipped the meal bad things can happen.

They can get dizzy. They can get very tired because you have over shot your therapeutic window. So that is another concept in drug development. You almost always have a therapeutic window. You want to make something go low, but not too low. You want to make something go high but not too high.

So that is the reason you do not want to have too peaky in insulin, because you do not want to overshoot your efficacy. You do not want to have or if it is for a meal you want to make sure it is peaky enough and goes away. So those are some of the reasons what we may want to manipulate the pk. that was a good question.

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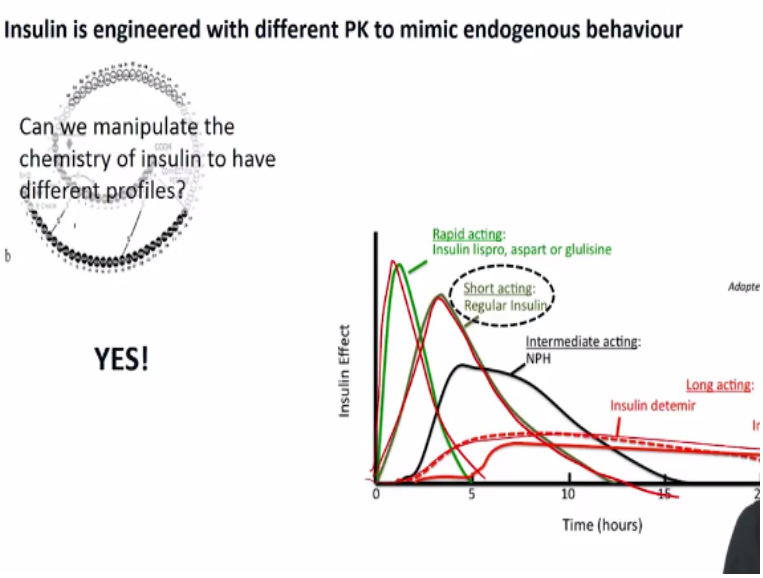

So you know this is kind of what we were talking about but the other magic and another area for engineers to contribute to is really the protein engineering. So we can do fascinating things with proteins. So if you talk about insulin we said okay 1960 we sequence the protein. So we were able to generate around insulin, but not only are able to generate our own insulin, we can make that insulin less or more absorbent.

So the original insulin which was just our human insulin that had a PK profile which looks like this. So that had the original PK profile which looks like this, but today just from engineering the proteins making adding some fat to them, adding some extra protein to them, adding some nonsense peptide to them. Whatever, not fat the peptide and protein whatever you add to them you can kind of change the way the PK is.

You can make them eliminate faster, so this can be a rapid acting insulin somebody takes right before breakfast or you can make it very slow to absorb and very slow to go away and have a daylong flat coverage. So that is kind of how multiple disciplines come together to make something complex and you know have all of that knowledge behind then.

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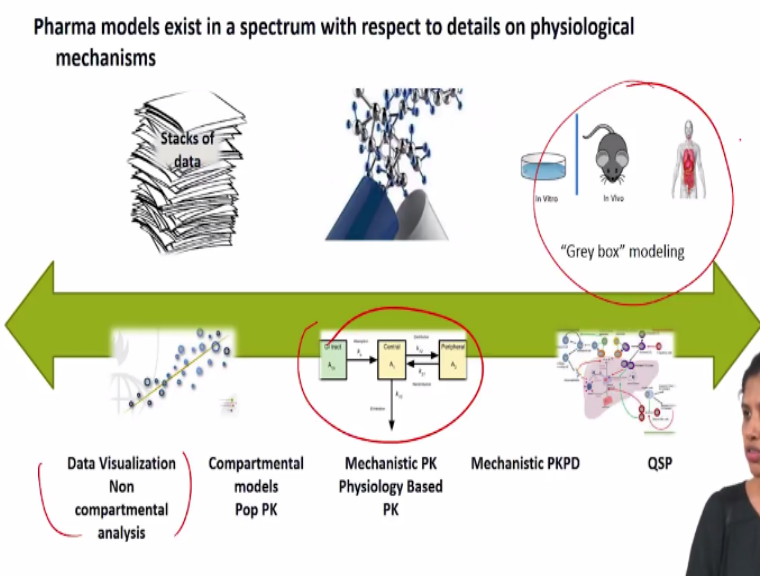

So modelling in pharma exists across the spectrum. So there are statistical model so lot of you may be familiar with them so this is when you have a lot of data, you want to start visualizing it, building regression models, these are in modelling terminology often called black box models because you are saying I do not know how y is dependent on x, but it is some functional form with fits all the data and I am not going into any more detail than that.

So that you can do when you have a lot of data. All the way of the other end is what we call grey box model. So you can say y = f(x), but wait this x is actually x1, x2, x3, x4 and I know that x1 increases y, x2 decreases y, beyond a threshold and what are the more complicated interactions. So that is what we can think of is knowledge based modelling. So we have emotion of what the system looks like in our heads and you want to implement that mathematically.

So that is grey box model. All of these can happen in pharma. Something in between also. So here like the model we just spoke about it is a gross simplification. It is not even close to what happens in reality, but it works and while it is not a complete black box model because we have some understanding of what is happening. So there is a range of such models and I will be talking a little bit more about models all the way on the right hand side here.

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Recap

Topics covered

- Modelling in Drug Development

In the next video ...

- Introduction to QSP