**Computational Systems Biology**
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**Lecture – 55**
**Guest Lecture: Quantitative Systems Pharmacology**

So that is the kind of the cracks of the entire story.

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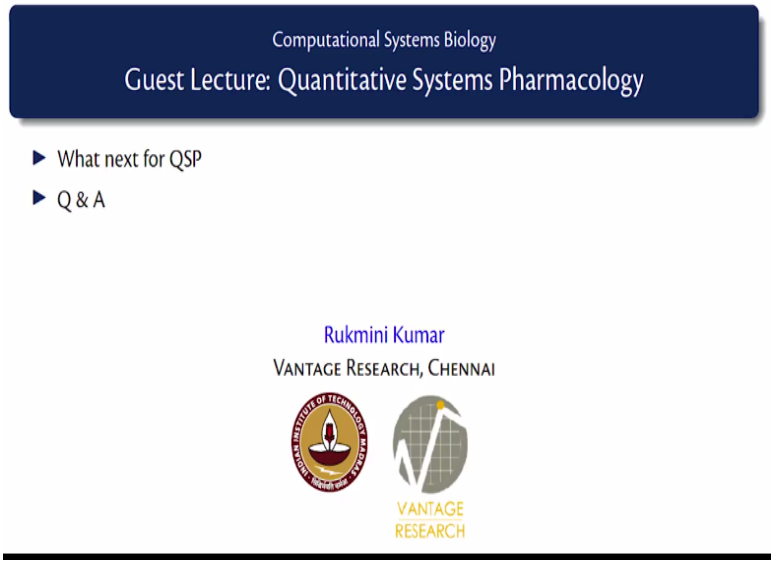


The conclusion and next steps I have for you are what are the trends?

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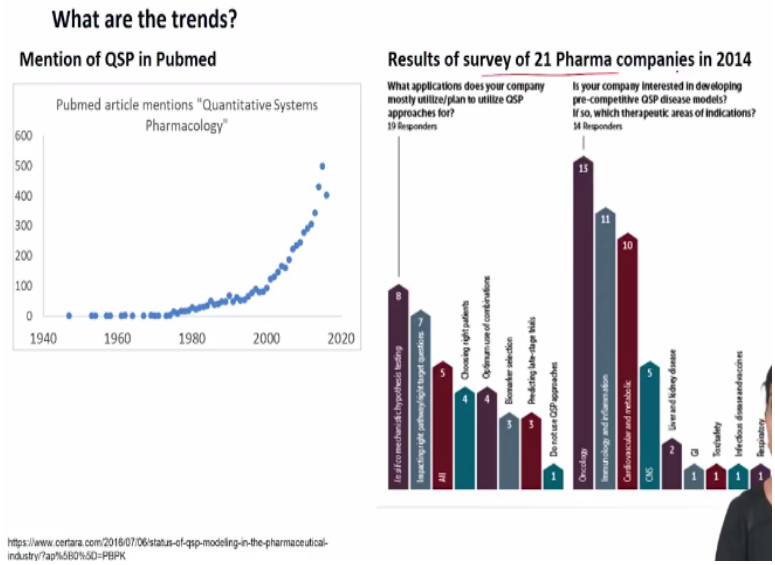

So this is not a very entrenched field in Pharma, this is something which is probably kind of gaining momentum I would say. So here if you look at PubMed mentions of QSP, there is a lot more coming up over the past few years. When you do service a Pharma companies more and more companies are interested in developing these mechanistic physiological moments. What can we do with them?

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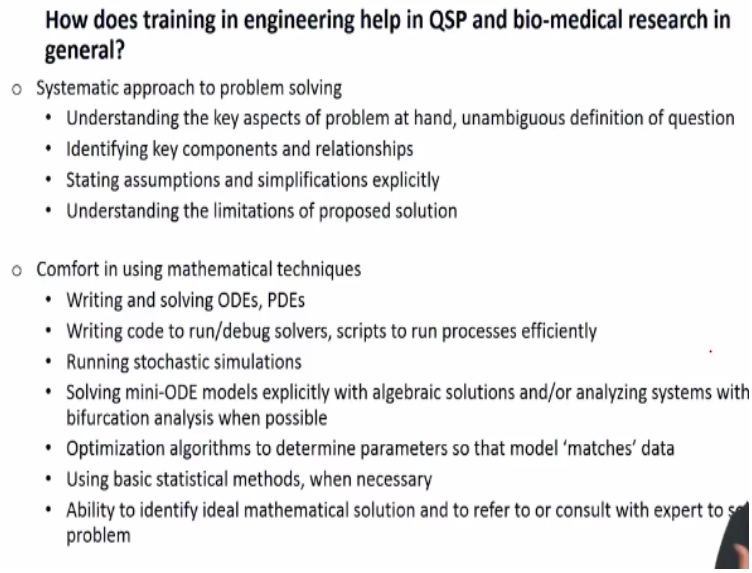


So it is that way it is a very exiting feel. As lot of you have quantitative backgrounds as engineers how is it interested because you why are engineers useful. You want to have a systematic approach to problem solving. You want to understand key aspects of the problem make clear definitions and then you know kind of transfer it to mathematics and be comfortable with running morals, writing code, optimizing, using statistical methods is just to kind of live act intersection of where quantitative stuff and biology needs.

So that is where we are most useful for drug development.

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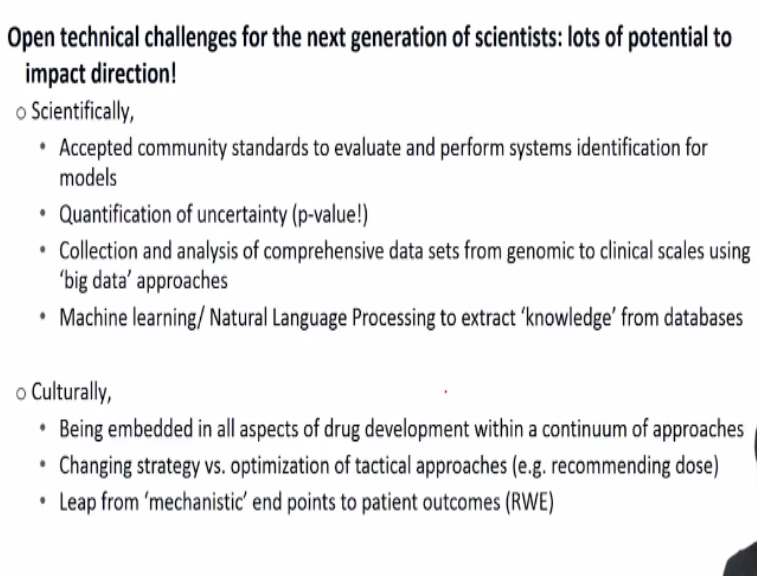


Scientifically it does a lot of like excitement in the field. I think because the field is young there are lot of standards that we need to develop for the field and thus potential impact of people joining the field. We want to make sure there are ways to quantify the uncertainty from these models like standard ways to develop the models etc. Even more interesting we talked about multiple scales.

I did not talk a lot about genomic data, integrating genomic data to mechanism there is a big problem and you know it is a challenging and not solved and using quantitative techniques to kind of bridge that gap is another big thing. When you think of what we spoke about, which is trying to synthesize data from 100s and 1000s of papers, to get the state of the art into a model. So far it is a very time consuming process and lot of us have to read these papers to get this together.

There is a lot of potential to have machine learning, natural language process and techniques to come up with these crystallize ideas so that, that can become a lot faster. So there are lot of interesting problems in this field. Culturally, one of the things that you guys are still in college, but as you have to learn is in the real world a lot of interesting things happen only when people from different backgrounds sit together and try to solve problems.

So culturally pharmaceutical industry as well as biomedical research has obviously been dominated by people who understand the biology, who understand lab work etc and integrating quantitative methods is relatively new and there is a lot of opportunity to kind of be part of that culture and that requires sometime from the engineers as well. We need to make sure we understand the biology and understand enough of the detail to make useful models.

So there is lot of scientific and cultural challenges well. So I think that basically it. Any questions? **"Professor - student conversation starts"** So in the complex networks that you mentioned where there were like several nodes and all so were those networks like inclusive of molecular components or cellular components as well.

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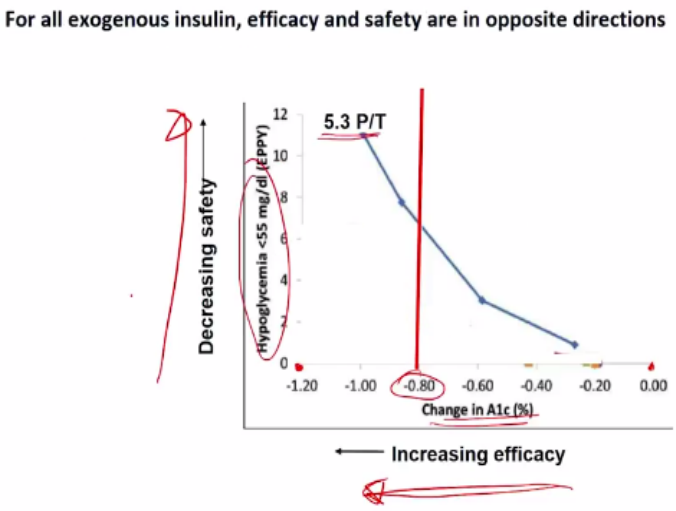


In the diabetes model, I mentioned very often not molecular. So we only go as far as some cellular path so maybe there are some enzymes and proteins but not you know single molecular types of. It is how do proteins interact with you know across cells so that is usually the level, but you can have QSP models which are intracellular signally. So once there is a signal comes in what is the signal transaction within a cell. There are whole class of models like that.

So in the beginning when you are talking about drug development you talked about how to integrate this and how to find out whether how does it percolates to the entire population so can you make the doubt by just looking at a QSP model due. So it depends on the level of detail that

you are asking the question. So for instance the diabetes examples we had you can just say insulin increases flow from the plasma to the muscle.

So that is 1 level of detail that will help you when you are trying to recreate a clinical trial, when you are trying to understand some data, when you are trying to understand how much to do, but suppose the customer or the pharma company has a drug which increases the amount of receptors in that arrow till model is that sufficient. You need to go into 1 level of detail deeper and say now I am going to model the receptors, the ligands, the intracellular signaling.

And search and then develop a model of that degree of detail do that pertubation and see what happens. **"Professor - student conversation ends"** So really what I spoke about today is a kind of a gross large level model of glucose and insulin, but the model you want to develop should answer the question that you are interested in. Do I make sense? In general, I think when you think of a QSP model what you are really thinking of is something that is spans skills.

You know goes from like a cellular level to organ level, organ level to clinical level ideally we want some clinical level, but if not you know definitely span those levels so that you are able to integrate a lot of knowledge. No in fact there are acute and chronic effects. I think chronically it may induce people to actually store more and eat more and things like that. Acutely, I am not really very clear of what happens.

Definitely your point is correct that lipids are another source of energy for the body. So any time glucose is low, you metabolize lipids to be used, but the problem with hypoglycemia is an extreme and your brain cannot use lipids. Your brain still has to use glucose. So the only compromises the lipids can get converted to something called ketones which can be used by the brain, but not for the long term.

So hypoglycemia is to be avoided at all costs. So that is definitely the things. **"Professor - student conversation starts"** You mentioned about the variability right. So some patients might have it and your model has to somewhere go around it. By doing that we consider that what part or portion of the population is the way is particular kind of response is seen more. So you are

right may be this is where you are going and tell me and helping but it is possible that diabetes has many sub-operations.

So some people are diabetic because their pancreas is just not secreting enough insulin it has become very weak. Other people are diabetic because there is too much fat deposited in their muscle so when the signal comes it is not reading it that clearly. So you may need different treatments for those 2 and the same treatment may not work for those 2. So that kind of analysis of subpopulations we definitely do with parameters.

It has to be guided by the data and hypotheses like this. Is there genetic reasons to diabetic like can you name that. There have been lot of what they called these GWAS type studies. So when in the 90s the big problem is was once you figure out what is in your DNA, once you figure out your genome then we will able to tell for sure what disease you are going to get. That works in single you know when there is single nucleotide changes.

So in some diseases which are driven by small changes yes, that you can tell, you can test a fetus and say this kid is probably going to be sick of this disease, but diseases like diabetes, autoimmune diseases tend to be multi-factorial so you know there may be a lot of genetic variation that predisposes you or makes you more susceptible than some other people, but not everybody with that profile is definitely going to get diabetes and not everybody who does not have that profile is guaranteed not to have diabetes.

So that kind of demarcation based on genetic data is not available for the more complex diseases. It is possible if we have data from 10s of millions of people and we have better quantitative techniques. It is possible that we can come up with the risk number. We based on your genome, you are 90% going to get diabetes. Based on your genome there is only 10% chance. Even at the end of the day, these diseases, there has to be an interaction between lifestyle and a gene.

So, you know the studies actually in obesity where immigrants to first world countries they get obese, they get metabolic disease, but their cousins who stayed back do not get those diseases. So genetically these are very similar people, but they behave very differently because of the

environment where they are in. Most complex diseases there is going to be a part of the environment, but up to your point I do not think you still have a test to say that your risk is x% with any degree of confidence.

**"Professor - student conversation ends"** Again there is a promise that will helps us identify targets. So you can see the chain of thought. So if I find what is wrong in the genome of a diabetic person that means I know what proteins are not doing well. Once I know what proteins are not doing well that can be a drug target I can go after, but I feel like in the last few decades that is not quite played out like that.

I think this targeted drug identification was not worked as well as we thought and part of is it the data is may be too sparse, may be the biology is more complex than we thought it was and so what works for some people does not work for other people so that is the way that a drug cannot be generally successful. So that promise of going from a GWAS to drug I do not think that works for any particular drug in these kind of diseases. To 1 place it has worked is cancer.

So there is you know if you have certain type of breast cancer there is a drug that you can get which is almost in 90% cure for your, but that means that you have to take a biopsy make sure that you have that particular mutation so that Avastin can I forgot that name that works for you. So that kind of stuff exists, but for the more complex lifestyle plus gene diseases we do not have a slam dunk case for to move from one into the other.

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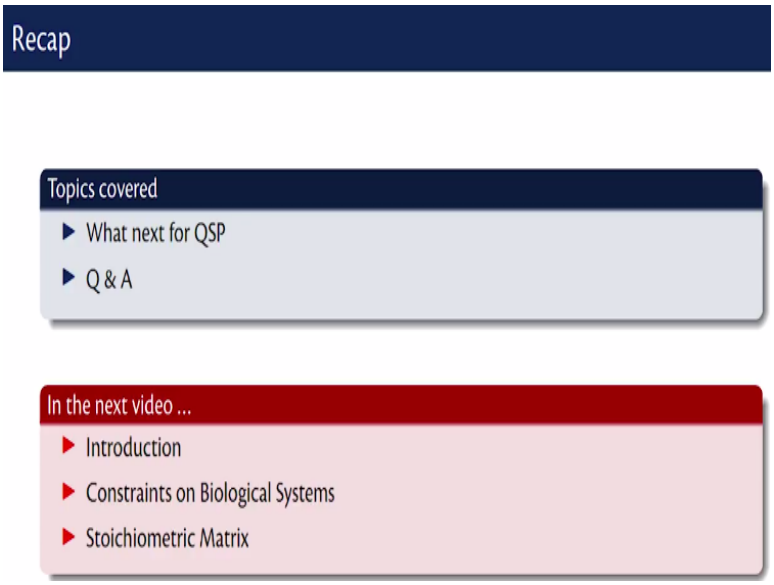


So I hope through the series of videos you have had a good introduction to quantitative system pharmacology and how drug development and modelling are helpful in the pharmaceutical industry and in the next video I will be back where in we talk about constraint-based approaches to model biological systems. I will introduce you to constraints based approaches. We will talk a little bit about what are the constraints that permit biological systems and also the all important concepts of the stoichiometric matrix which is central to all of our next few lectures.