Computational Systems Biology
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Lecture - 53
Guest Lecture: Quantitative Systems Pharmacology

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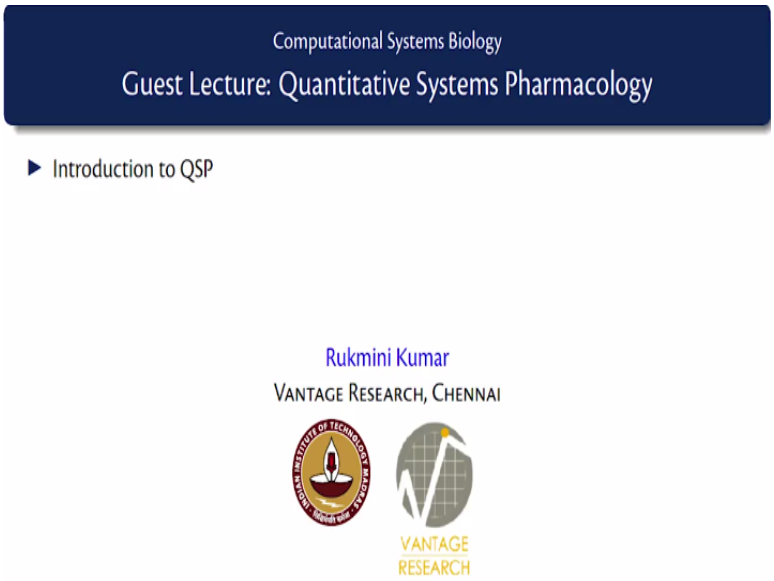

So now what we let us talk about physiological models.

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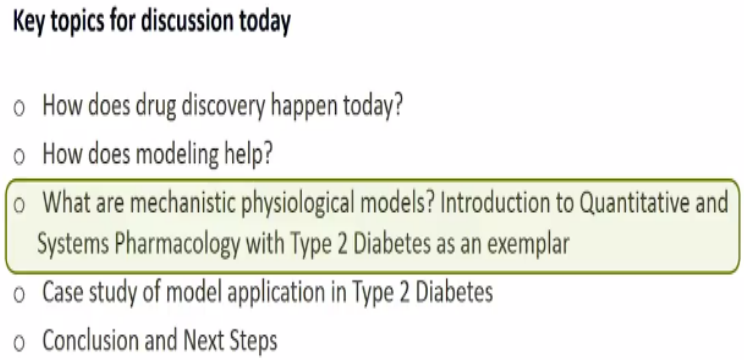

We talked about pharmacokinetics what does the body do the drug? What are the interesting things that can happen to the drug and how we can start thinking about models to capture that? Now let us vague into physiology which can get a lot more complicated a lot more intricate and this is an introduction to quantitative and systems pharmacology how do you develop model of diabetes.

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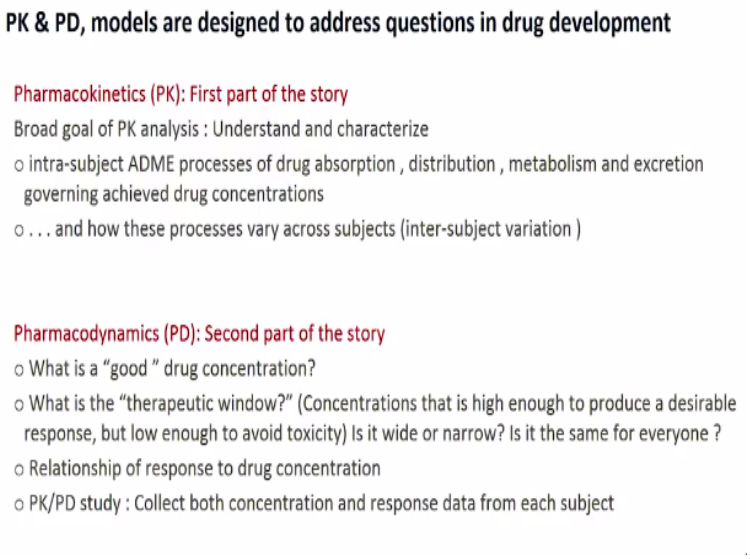

In the second part of the story when it comes to pharmacokinetics like we said some of the things that we care about are what is the good drug concentration does that hit the patient in the therapeutic window because pharmacokinetics is the concentration of the drug. The pharmacodynamics is what does it do to the clinical read out that the patient cares about? Plasma glucose, number of asthma attacks, pain in the joints.

Those are all clinical read-outs the patient cares about how does the drug concentration manipulate that clinical read-out that is what we care about and what are the relationship to drug concentration. So how high should it go? Does it keep going linearly high with the drug or does it saturate at a point and then does not matter how much more drug you give. Does it matter that some patients will respond better to other patients and that depends on the patient's biology so those are all questions that we want to ask.

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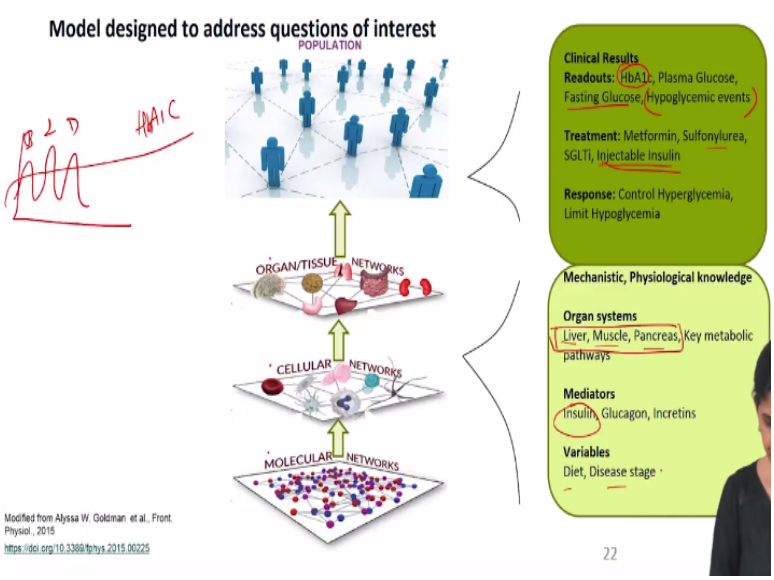

Now in the beginning we looked at this figure and we said drug development is really complex. There are multiple scales. There is the scale of the population that we all see, but we know that when it was underlying scales when it comes to all of the other networks. So let us talk a second about diabetes.

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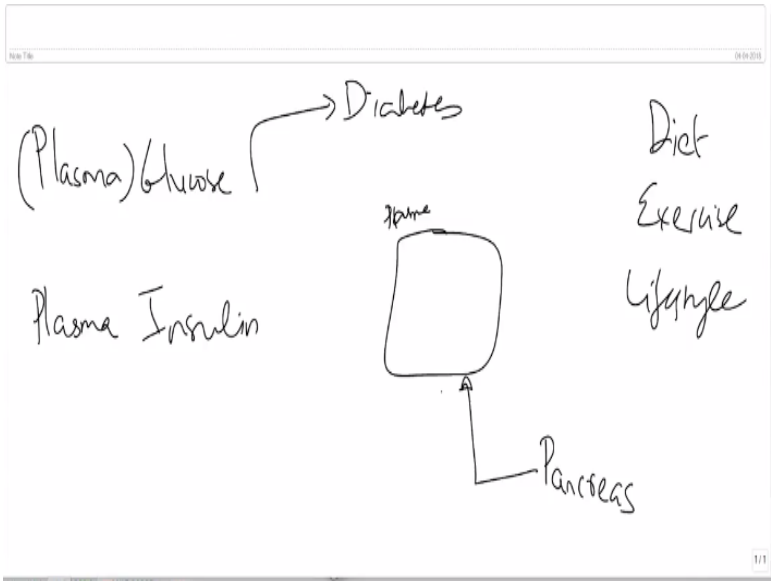

So based on what you know, you know from your family members, from anything that you have read when you think about diabetes what are the things that you think about. What are the clinical thinks? What organs? What are the things that you know about diabetes so far? (()) (02:26) exercise. You can edit it out if it does not work. **"Professor - student conversation starts"** So what ideas on diabetes do you have?

Patients have deficiency of glucose, excess deficiency of glucose correct. So we were talking about glucose in the plasma is important and too much of it is symptomatic and leads to diabetes and too little you want to avoid (()) (02:52). **"Professor - student conversation ends"** What else do you know? Have you seen your relatives prick their finger and test? So really they are testing glucose there. We know insulin plays an important role.

We know diet, exercise, it is a lifestyle disease in many cases, in many cases it is not. So those are some important factors. When it comes to organs, we said okay there is a big compartment that we will call plasma, but we also know that there is organ called the pancreas. We saw that in the dogs when you cut off their pancreas these exhibits symptoms of diabetes. So the pancreas and the insulin it secrets is important to control diabetes.

So the one other thing that you should know because we are going into the disease a little bit is why does it matter that your blood has too much glucose. What little happens is it becomes many, many things happen, but it becomes a disease of a poor circulation so if you know diabetics you know they always worry about keeping their legs safe because at the end of the day the blood becomes too sticky for it to go down the very fine arteries and really profuse the extremes.

So the kidneys can be affected because again they are not profuse as well. There is a lot of sugar in the urine potentially. Their extremities can get pretty sick. They may find it harder to find fight infections because again their blood their systems are not functioning as well because there is a lot of sugar in the blood. So that is a kind of how diabetes and it has other implications for heart disease and hypertension as well and often times.

All 3 happen in the same patient together. So that is a kind of how the disease can start and affect what happens to a person. So 1 other thing that diabetics worry about is HbA1c. So plasma glucose is something that changes every day with a meal so we saw if you plot glucose over a day it can changes up and down with breakfast, lunch, and dinner. So that is how plasma glucose varies. At the end of the day how much glucose is attached to molecule called hemoglobin.

That averages out all of these variations and that is a measure called HbA1c. So that is not something people can measure with the pin prick that is something we have to go the lab, but that is indicative of the seriousness of the disease. The other things they have to measure are fasting glucose as soon as they get up in the morning what is the glucose that gives an indication of the disease and other thing that we talked about hypoglycemic events.

We really do not want them to get hypoglycemic. Existing treatments for diabetes there are metformins, sulphonylurea, there are other drugs (()) (05:53) can focus on insulin because it is like a sledge hammer it is the disease that is just goes against insulin and other treatments are initial start a treatments for insulin. What are the things that are relevant and we will see how these are relevant in a second?

Thus the liver, muscle, pancreas, key pathways of these cells inside the liver muscle and pancreas and all of those become important how the disease evolves, but we will talk in the level of the organ systems. Insulin is not the only hormone which is important. There are others, but let us talk about just insulin and glucose today and the other variables that we talked about diet, exercise, lifestyle etc are important, but we will keep it simple today and talk about what is the simplest model of diabetes you can build.

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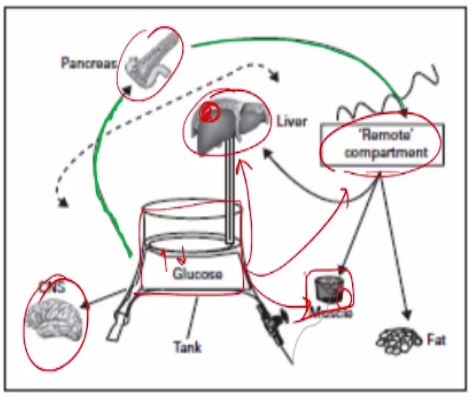
Normal glucose metabolism is regulated by multiple organs and mediators;
Feedback between glucose and insulin is the most critical one



Increased glucose -> Increased insulin -> Increased glucose absorption from central 'tank' -> Decreased glucos

So, in order to do that we will be spending a little bit of time on this picture here today. So we were talking about too much glucose think of the central compartment of the body, the plasma compartment as this tank. It should have an appropriate amount of glucose. If the glucose in this tank is too much that is what you want to avoid chronically, but as glucose increases in this compartment it signals to the pancreas and the pancreas secretes insulin.

And when you have a lot of insulin that increases the glucose absorption from this tank. So this tank you know it goes to the muscle, it can go to the liver, it can go to other tissue that is what happens to the glucose when you have insulin and that eventually decreases the glucose in the central tank. Another important thing to kind of digest you know, keep a mind is glucose is not bad we need glucose as an energy source.

So you may have done intracellular metabolic pathways with Karthik, glucose is a major source of energy you know via ATP for all of these biochemical pathways to occur. So that is why we want to eat glucose. So another you know think that you may be familiar with is the concept of you know marathon runners. So before they want to run a big race the next day they will do what they call carb up.

So the previous night they will eat large amounts of pasta or rice or lot of carbs so that gets stored in a small compartment called glycogen. That is the body's emergency release for glucose. So the next morning when they are running and running and running without a break they have all of this glucose stored up which feeds into their muscle. So that helps their muscle do all the work to run that helps all of the cellular processes that helps them breathe harder etc, etc.

So that is really the physiological role of glucose it just becomes pathological when you look at it a point of diabetes. So glucose is necessary in these remote compartments such as the muscle, the brain which can only function on glucose and other remote compartments. The liver is a critical organ because it is where this little pool of emergency glucose called glycogen sits. So you have glycogen in your liver called liver glycogen. There is also muscle glycogen, but this tends to be important.

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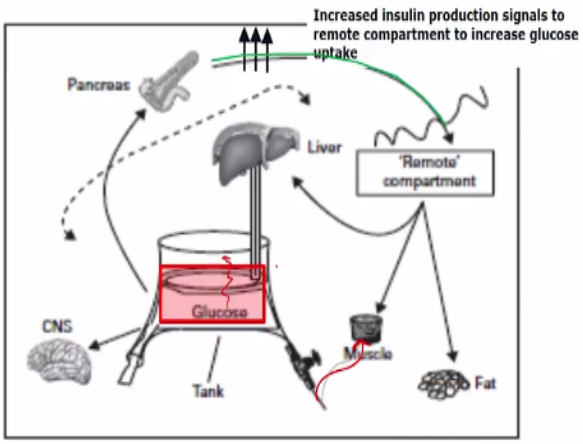
Glucose-insulin (delayed) negative feedback loop is key to maintaining glucose 'homeostasis'



So when the glucose increases in a regular day may be you get up in the morning and you have you know something you have doughnut for breakfast. So as soon as the doughnut goes in the glucose in your plasma increases. When that signal reaches the pancreas hopes there is too much glucose in the blood let us increase insulin so that there is greater absorption into these tissues. So for control systems people etc this is automatically a negative feedback.

So, for all of you that is a simple method of feedback look. Too much of something increases it increases some other thing which causes this to go down. So that is kind of how this is ideally supposed to work.

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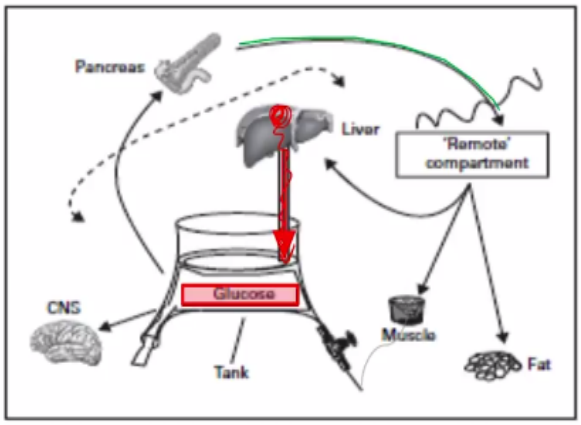
At "fasting", insulin production is low, liver releases glucose



The other aspect like we are talking in Marathons or when you fast. So you have dinner at 8 pm and till the next day morning 8 am you are not eating anything at all. Your body still wants to not go into hypoglycemia so how does that manage that that is where this emergency store of glucose in the liver that kind of trickles out.

And make sure that the glucose is steady through the night as well and that can be kicking when you are fasting, when you are running etc the body still wants to make sure that stays. So in this condition insulin is low and glucose is being shunted out into the plasma insulin is high, glucose is being shunted back up away from the plasma into these remote compartments.

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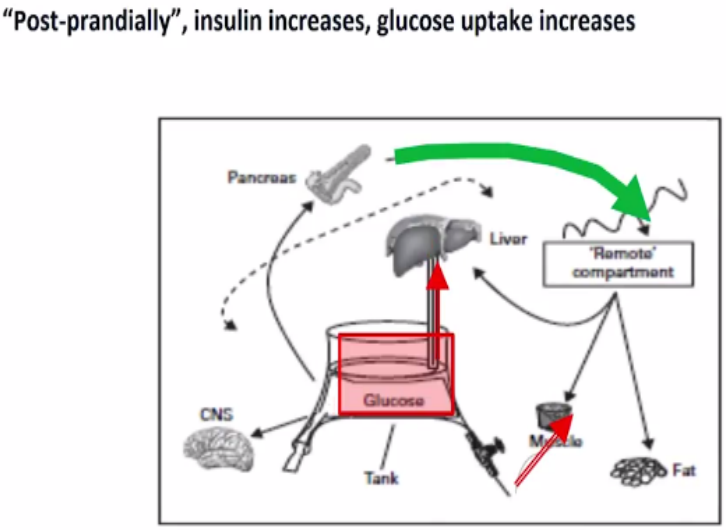

So this is what is happening post prandially.

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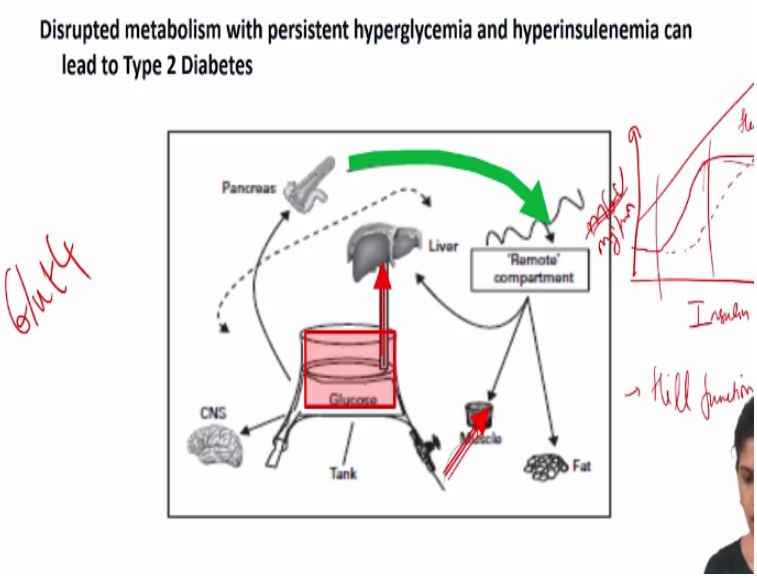

So what really happens if diabetes is that these interactions become you know, disruptive. There are many ways they can get disrupted and I will talk about 1 critical way that they can get disrupted. So here we are talking about glucose can get taken up by a remote compartment. So let us call it muscle and say muscle needs to take up glucose.

So it can take up glucose at a certain rate let us call at rate some milligrams per minute and that is a function of insulin. So what really happens in the biological pathway is insulin signals for the muscles to activate receptors for glucose. So these are called the glut4 receptors and these receptors capture the glucose and take it inside the muscle. So how are we activating these glut4 so when there is not much insulin there is not much glut4 when the insulin increases.

There is a lot of glut4 and when you reach peak insulin there are lot of activity you are shunting everything away. They you reach the max amount of glut4 you have and your body is functioning at max capacity to take up the glucose from the plasma to the muscle compartment. Now if this is the situation in a healthy person what happens in a diabetic? They start to become insulin resistant for many reason so let us go into the pathophysiology for a second.

But what starts to happen is you need more and more insulin to be just as effective. You see what I am saying. So you know what was sufficient for a healthy person to uptake their entire doughnut a person who has diabetes needs to take an injection add all of these extra insulin to

take it up. For engineers the other concept here is these are kind of typical saturating functions you can think off as Hill functions.

And I do not know if you have been working on those in this class, but a lot of functions in biological models tend to be of this kind because there is a range of sensitivity and the saturation. These functions are not usually linear functions like the more insulin you are dump in the more happens these are constraint by biological realities so very often these kind of saturating functions show up a lot in biological models. Excellent.

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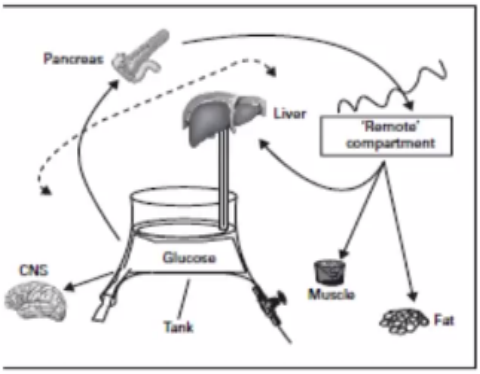
Consolidate understanding of physiology relevant to the goal



So what we want to do when we build a biological model it is already a challenging question to ask you know diabetes is as big complex disease how do you build a model of it. So here we are saying let us get rid of as much detail as we can let us kind of consolidate the basic pieces and let us understand what a physiology we want to capture just to capture glucose and insulin mechanism.

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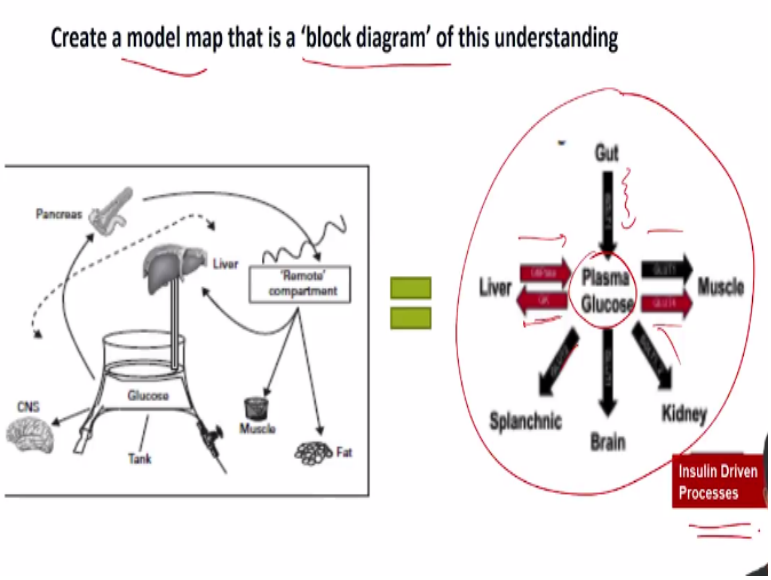

So the first thing that we do in any you know model creation is to have a model map which is a block diagram which summarizes this understanding. So in this case we have plasma glucose at the critical compartment. You get food in once you have food in it can go to the muscle, it can go to the brain, it can go to the kidney.

The liver is a source which can take up glucose also give back glucose so we have this block diagram and some of these process are driven by insulin which is again critical. So this is how glucose and insulin play. So once you have this type of block diagram which is again a vast simplification of a complex disease but nevertheless useful then you can do the next thing.

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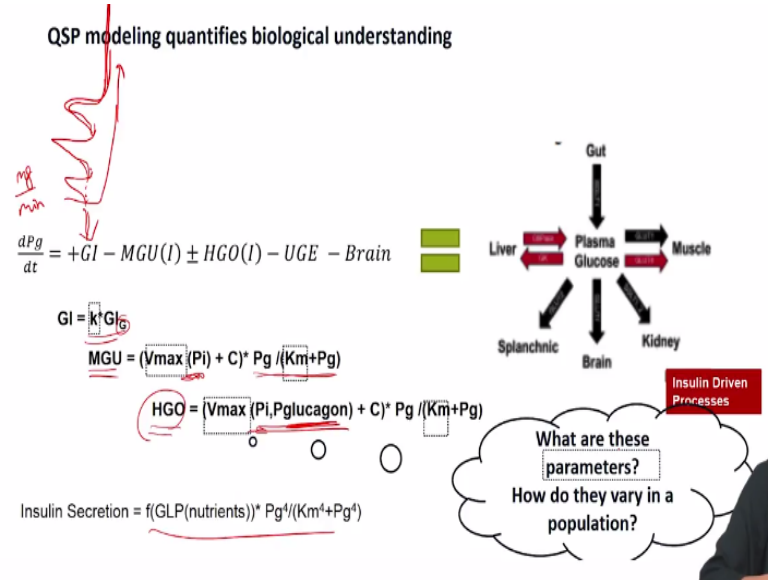

You can write a simple flux balance equation. You can say the rate at which plasma glucose changes with time, depends on how much comes in from the gut or the gastrointestinal tract, how much is taken up by the muscle which is a function of insulin HGO is hepatic glucose output, hepatic is anything concerned with the liver. So what does the liver do? It can either take up glucose or give out glucose. So that is what the liver does.

You may lose some glucose in the urine, your brain and other tissues may take some of this glucose. So there you have it just the day to day mechanism of glucose and insulin you can start capturing n a simple equation. Now you want to this is just the fluxes so let us start putting some Maths behind it. So the what comes in from the gut usually we are saying it is a linear process of absorption this is the gut glucose.

What shows up into the plasma is linearly is a linear function of that. The more you need the faster it goes into the plasma. Muscle glucose output so muscle glucose uptake so that is the function of insulin and we will figure out how complicated a function of insulin it can be and it has a typical Hill function format so that the more glucose is there is you know there is more increase to a point but the muscle cannot take up as fast as you know it cannot increase linear with glucose.

Similarly, what is the liver do, it has insulin and there is other hormone called glucagon. We have not gone into that, but that is the hormone which is important when you are fasting. That is the hormone which prevents hypoglycemia. So this insulin and glucagon affect how much glucose comes into that. So this entire equation you can think of in terms of some milligrams per minute and you know solve for what is happening.

Your big flux in can be what you eat. So if you eat doughnuts then you have some pasta for lunch and then you have some rice for dinner that is the amount of glucose you are going to be eating. Suppose you miss breakfast this is going to look like this and then maybe you eat more than usual for lunch and that is what you have for dinner and then there is 8 hours where you sleep. So that is the flux of glucose the gut sees.

So then we can start thinking of what happens to insulin secretion and I am not going to all these details. But the next important thing to worry about as modelers I am sure you started to worry about this is questions of systems identification. So how what was you know that is all fair and good to come up with the model. It is all fair and good to write what I think is happening, but what are these parameters. How should I start thinking about how to make them what numbers to put there?

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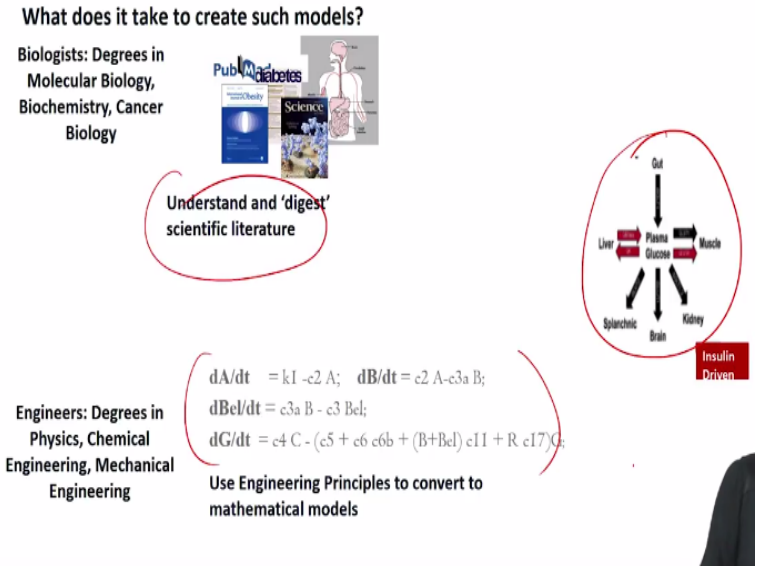

So then I have to talk a little bit about the cultural aspects of how such models are made. So this is not something that you know you can think up overnight and just write up. This often involves a lot of intense effort and activity from interdisciplinary teams even in our company for instance we have biologist. They have degrees in molecular biology, biochemistry, cancer biology whatever is relevant in this case endocrinology metabolism you have engineers many of you like here you know I have a degree in physics.

We have people who are chemical engineers, mechanical engineers and such and we need to understand and digest to scientific literature. So how many of you here are familiar with PubMed, so lot of you are. So basically that is one data base which kind of collapses a lot of scientific work done over decades and a lot of the work is in searchable format and you can pull up the information. Engineers were good at writing equations. So we can use engineering

principles once we all arrive at a map we like. We can use these engineering principles to convert the biology into mathematics. So it takes a lot of joint work.

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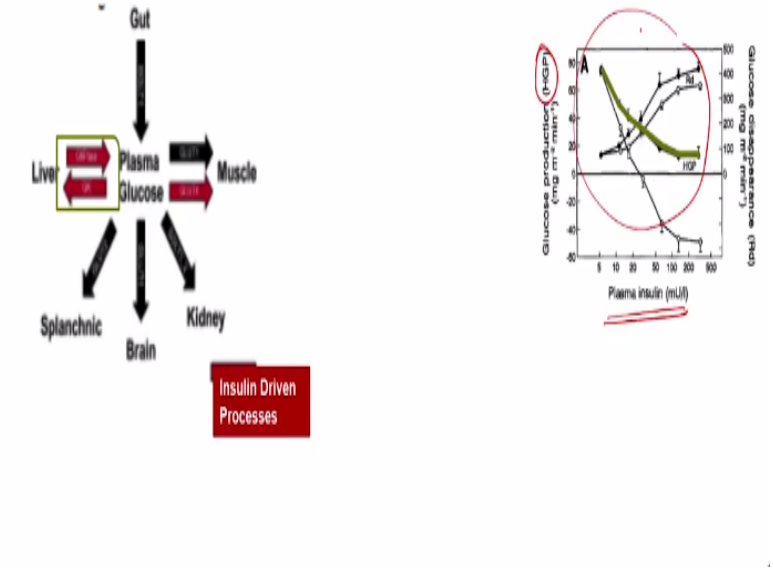

So in this case for example, there are papers which where people have measured how much glucose is produced by the liver under various conditions of insulin. So these can be very complex experiments where you have people who have signed up to do this. You inject them with insulin and you monitor them careful and you make sure you understand based on flux balances how much glucose is being secreted by the liver. So these dose response curves we can get from the basics science data.

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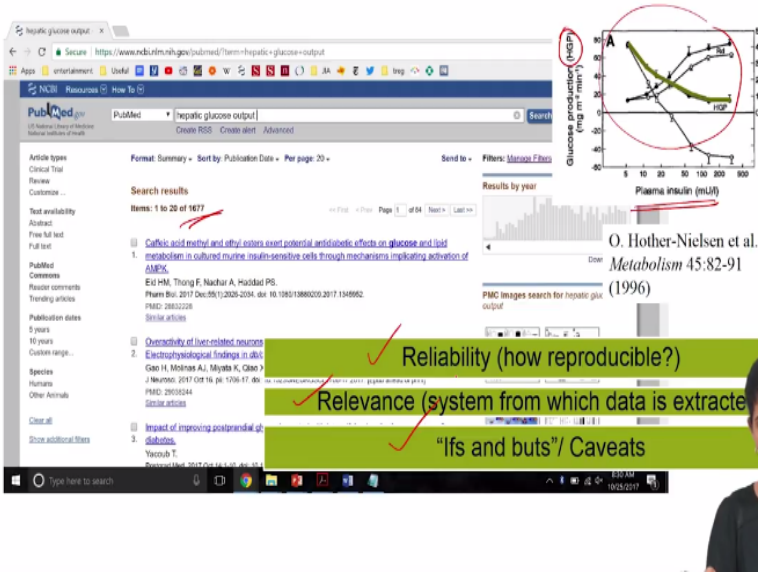

Maybe as an exercise we can also come up with some of these searches that you can do on PubMed. Another point of caution here is as you may know once you search for something in PubMed you may get a 1000 hits. So here we got like more than 1500 hits so then you want to ask the questions of these papers that I see how many do I think are reliable you know I had the results been reproduced have been cited a lot and used a lot how do I judge that relevance.

If this data comes from some if the same data comes from a rat or a human, I want to build a model as a human so I will choose the human data. On the other hand, there may be situations where you have no human data. So lot of cancer models come from mouse model data because that is the best that you have. So how reliable, how relevant, there are always Caveats as you read these papers they can be pretty dense understanding the methods and making sure you have the right data to put in your model is very important.

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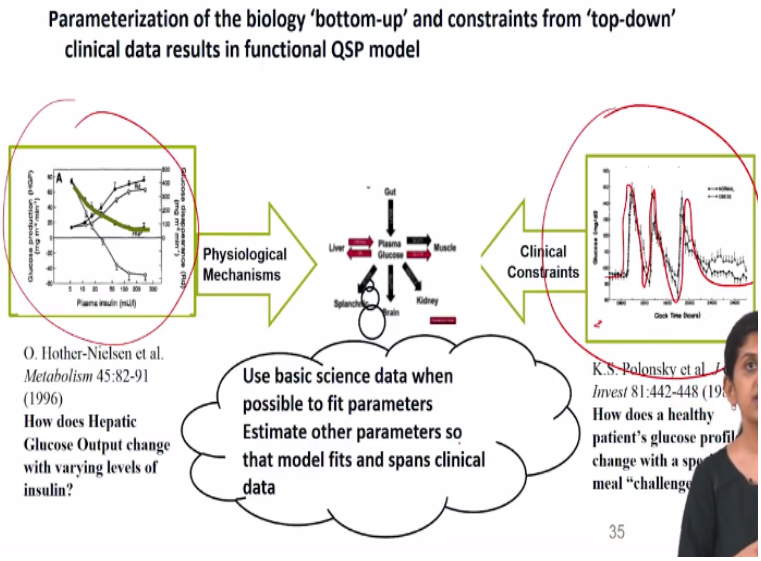

Then you have clinical constraints once you put this entire model together what are the things you want to see. So here for instance is data from a 3 meal challenge. So this was somebody who carefully measured how much glucose they gave to this healthy people carefully measured the glucose and said this is how the glucose changes over the course from 7 am to 6 am in the next morning. So over 24 hours given these meals this is how I expect glucose to change.

So given this kind of bottom up data of what is happening in each of these arrows and these fluxes and going from 1 box to the other to top down data which tells me when I put all of this together how should my system function. Those are the kinds of data that will be used to constraint and come up with parameterizations for models. Have any of you worked on model development exercises or recreate existing models.

We have any familiarity with that at this point, not so much yet. So, no model development yet. So may be again for this bit we can kind of come up with something small so you guys can play with something like this. So basics science data when possible to fit parameters, estimate other parameters so that the model fits and spans the clinical data.

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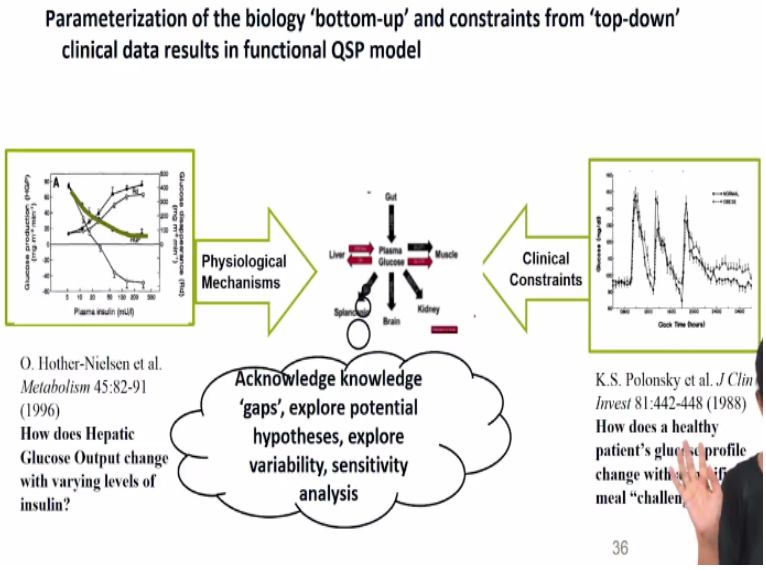

But at the end of the day this is not a perfect process. So that is something deep caution that I have to leave you with as well not all of the arrows are well characterized. There is going to be gaps and understanding. There is going to be variability. Some people believe hypothesis A, some people believe hypothesis B so as a modeler either you can say there is no strong data to believe B.

So I am going to go with hypothesis A or you can say I am going to model hypothesis A and B put it all together in a system and see what the implications are with the modelling. Can the

model help delineate between hypothesis A and B. So those are some questions which come away all the time as well variability.

You know some people see a 2-fold increase in glucose when they eat a meal, but some people see a 3-fold increase. All of that is within normal range, so we will not be able to capture all of that. So classic modelling techniques such as sensitivity analysis are also very important in QSP and we know we can look up some more papers to confirm that to follow that to kind of follow that.

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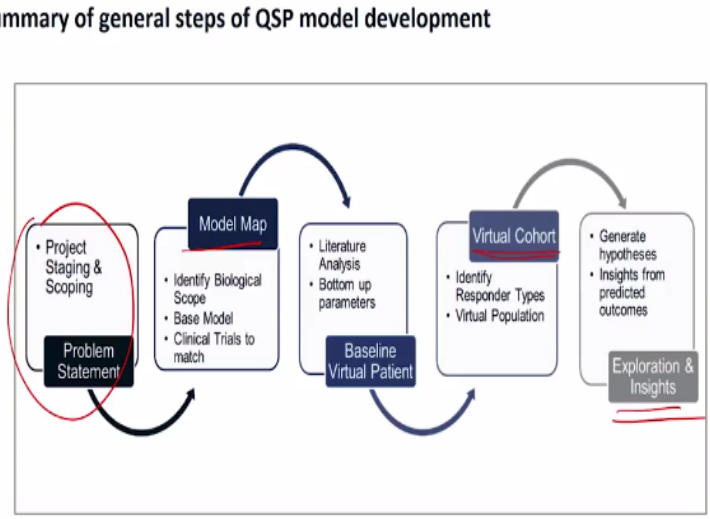

So overall I want to summarize what I have walked through so far developing a model of disease physiology is not a simple project it is a typically a complicated project, but like all scientific endeavors you want to start by making sure you understand what your problem statement is come up with a right kind of model map there does half the battle in designing the project. Once you get that done, you want to make sure you get at least 1 what we think of is virtual patient in the field of QSP.

So here is a model which has physiology and once I run it what happened in that model I call a virtual patient and then I can try new drugs in that patient, I can try variability on the patient, I can do experiment in that patient, because I think of that as 1 virtual patient. Then you can come

up with a virtual cohort which is more of these patient variable parameters and then you can start doing some serious research with just in the modelling.

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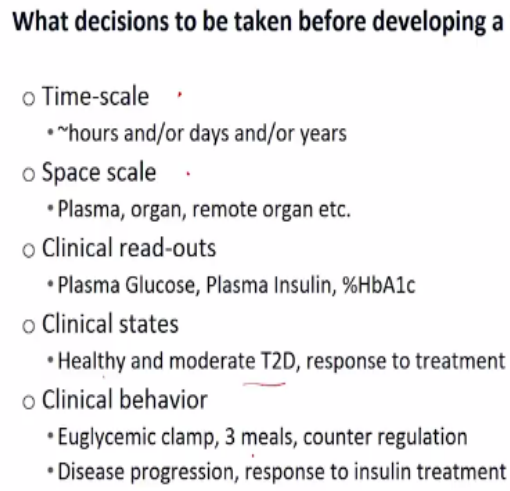

Few of the things to remember in any model development process what is the time scale, what is the space scale like in the design that we were talking about what are the clinical read outs that you want, what are the clinical states that you want, you want healthy, you want moderate diabetic, how do they respond to treatment, what kind of clinical behaviours so these are kind of the design questions that you need to keep in mind.

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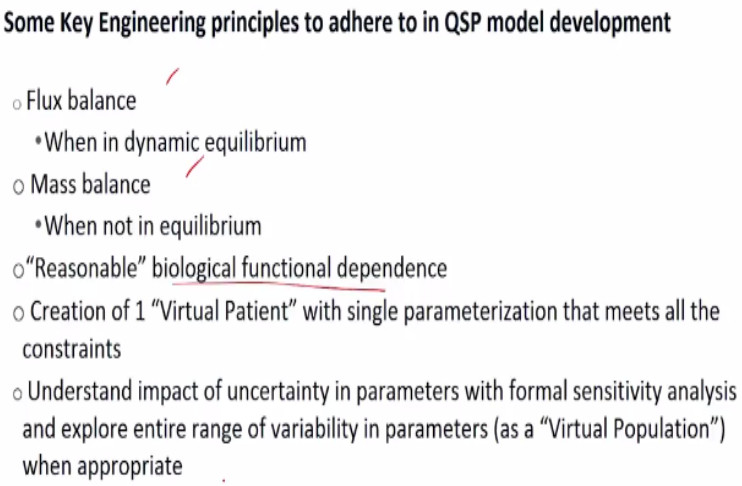

Some key engineering principles in any modelling exercise flux balance, mass balance, reasonable biological function dependence, this starts to go from science to art because this depends on the modeler's experience in judgment and such making sure you come up with versioning of the model so this becomes very important. You cannot boil the ocean at the first time you want to build a modeler diabetes. You want to slowly layer in more and more detail.

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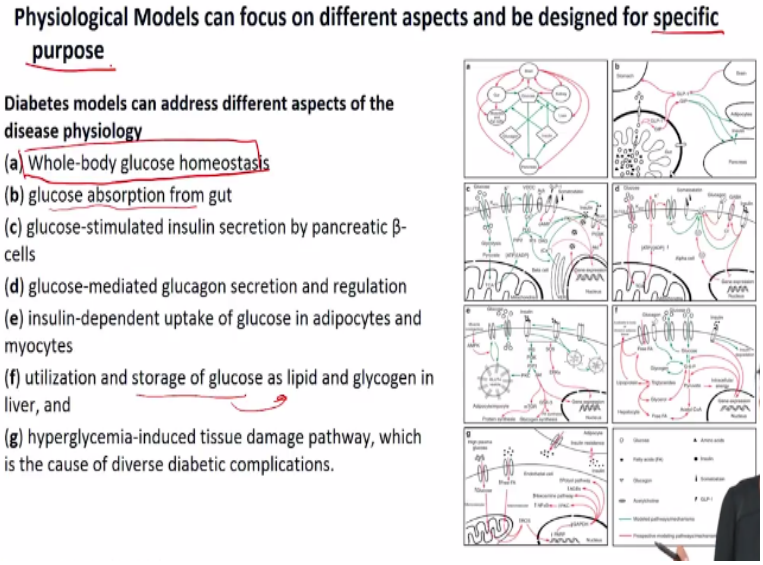

So the one other thing as you go you know and discover more is what I had been talking about you can think of as a whole body model of glucose and insulin, but people have many, many different kinds of model. So you go to PubMed and try to search for mathematical models of diabetes you can have all kinds of variation. What we spoke about like as I said is whole body glucose and insulin, but some people worry just about glucose absorption from the gut just that first part.

How can I make that slow what kind of meal should I give you know people think about you know a doughnut which has white sugar is a lot slower to is a lot faster to absorb then something which has more complex carbohydrate? So you can go into a lot of detail for each of these processes. So you know how do you store glucose. Glucose can be converted to fat. So people can get fat just from eating a diet of just rice.

Rice is only carbohydrate, but there are processes where that can get converted to lipid. So how does that happen? So you can go into a lot of detail on various parts of the diabetes, but really what you want to remember as a modeler is ask the question what is the purpose, why am I building this model and build a model fit for that purpose.

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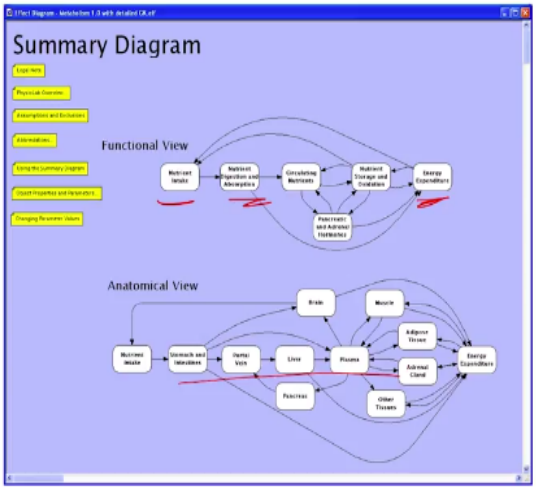
Example of a large-scale physiological model: Entelos Metabolism PhysioLab©



So diabetes models can get very big. Karthik wanted me to share the sense of you know how big can these model get. So this is a model that exists in the field. It was made by a company called Entelos. It is huge and it contains all kinds of pieces. You know the nutrient intake, how does it get absorbed, how does energy expenditure, so you know you can eat a lot, but if you run a lot will you still get say you still get fat, you know those are some questions you can ask and what are the various organs involved.

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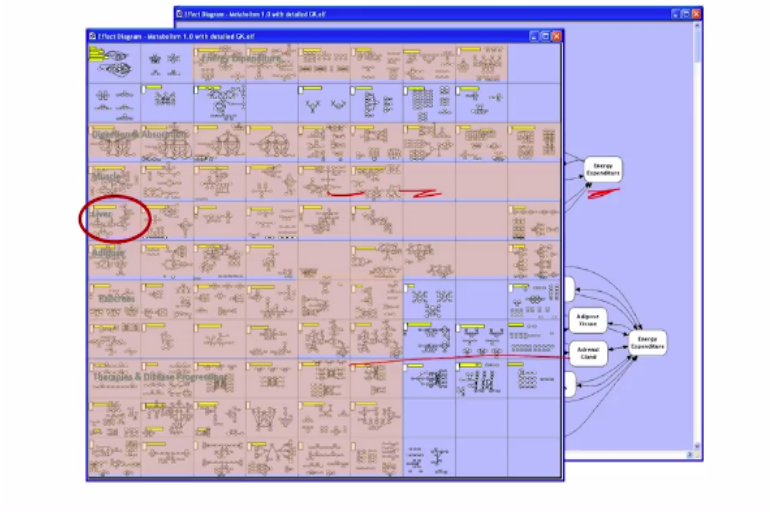
Example of a large-scale physiological model: Entelos Metabolism PhysioLab©



So this was built in special software and then you can say this is the range of things. Each of these is a species which has an OD attached to it and this is the block diagram of it. So for instance, energy expenditure, what is happing in the liver adipose, etc.

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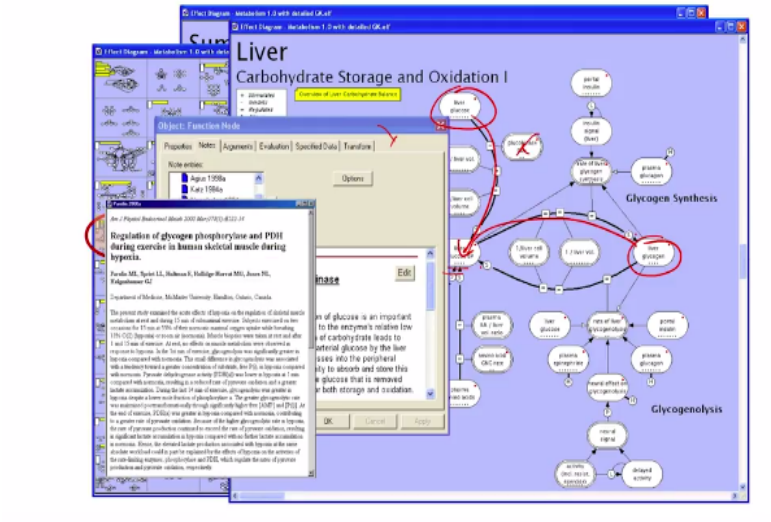
Example of a large-scale physiological model: Entelos Metabolism PhysioLab©



Once you come to the liver we are talking about it can get stored as glycogen. So you have liver glucose that goes into another pathway called into another substrate called glucose (())(27:02) through some pathways and then goes into liver glycogen. So that process which we just represented with 1 arrow can get incredibly complex. I can have multiple things which effect it and you can have a much more complicated model to address that and it make sure that you have the right papers to support it.

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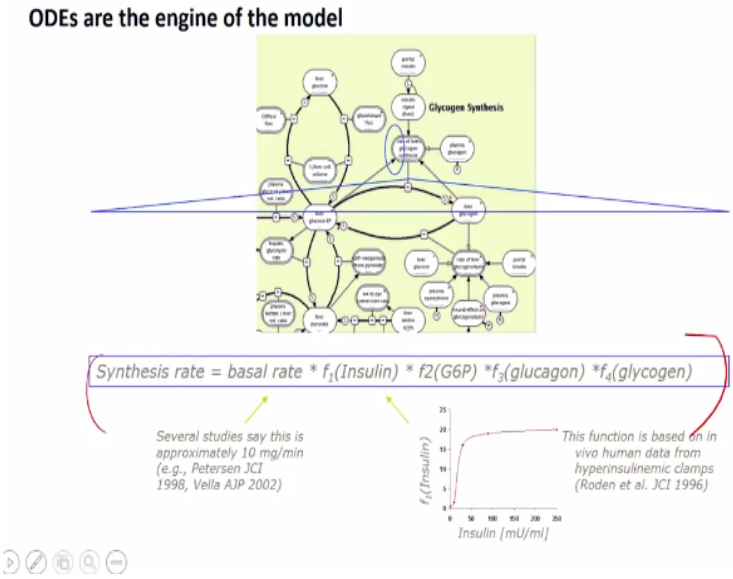

But at the end of the day even all of this is supported mathematically by differential equations.

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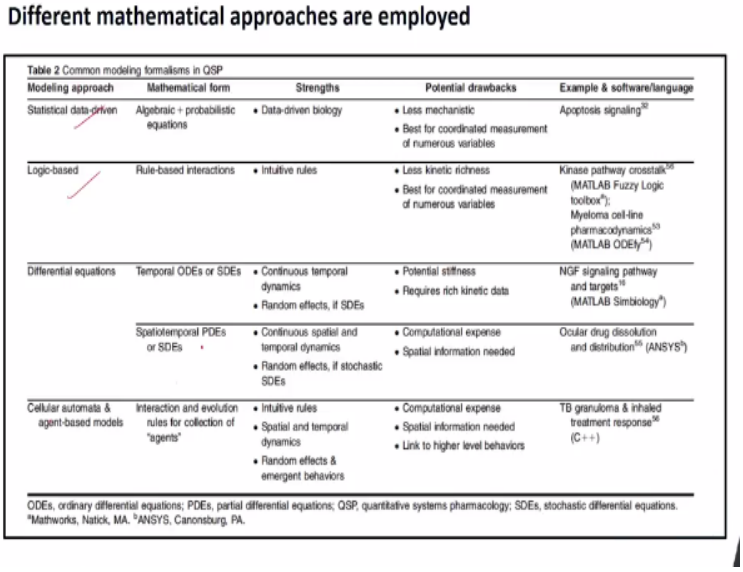

But differential equations are not the only methods employed. People can have many different approaches. We have talked a little bit about statistical. You can have logic based. Differential equation, which are ODEs, PDEs, SDEs, cellular automata I do not know if you guys are familiar with it. These are agent based models where you have simpler rules and a spatial structure to kind of see how your species are interacting.

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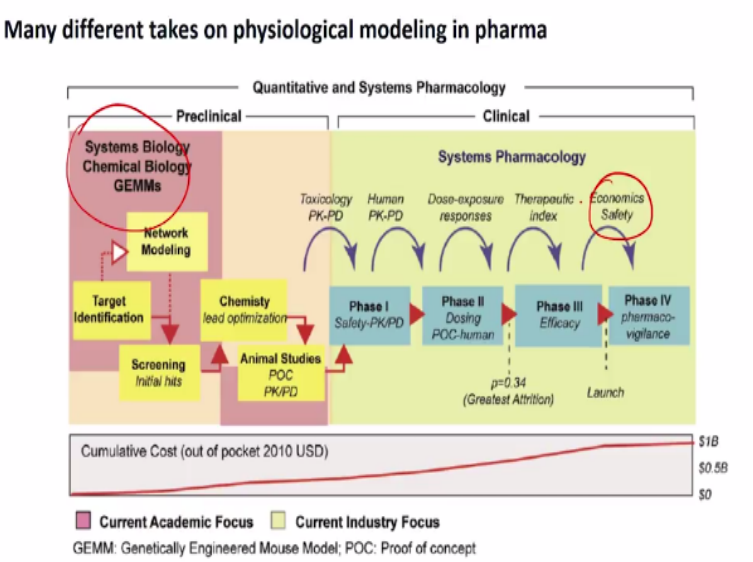

So the field can get pretty complex and you may have seen some models about systems biology, you know intracellular models. So those can be other model those can be some kinds of models which modelers do in pharma in QSP in general all the way to the other end economics. So you can have morals which say if I give this drug to a population of Indian patients how much do I expect to see in return in terms of increased quality of life. So all of those, those are kind of a ranges of approaches which engineers use to understand this process.

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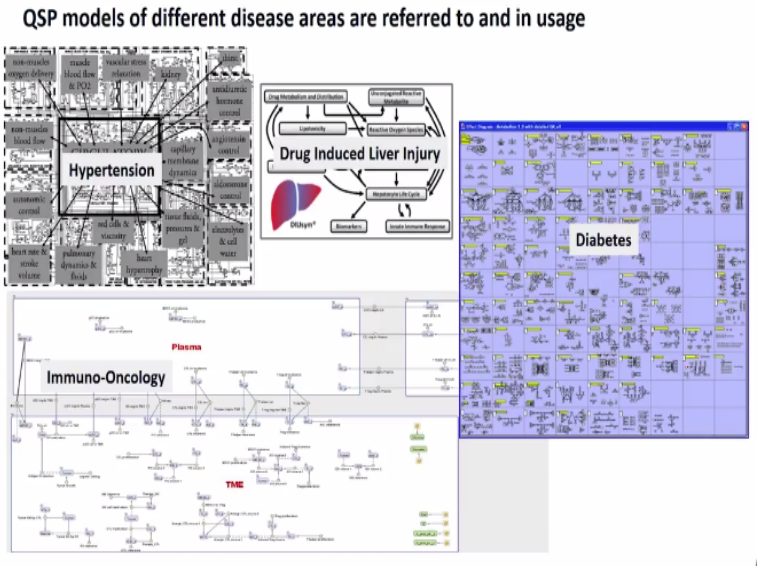

We have talked only about diabetes, but there are many other diseases for which there are models and usage, and these are some of those.

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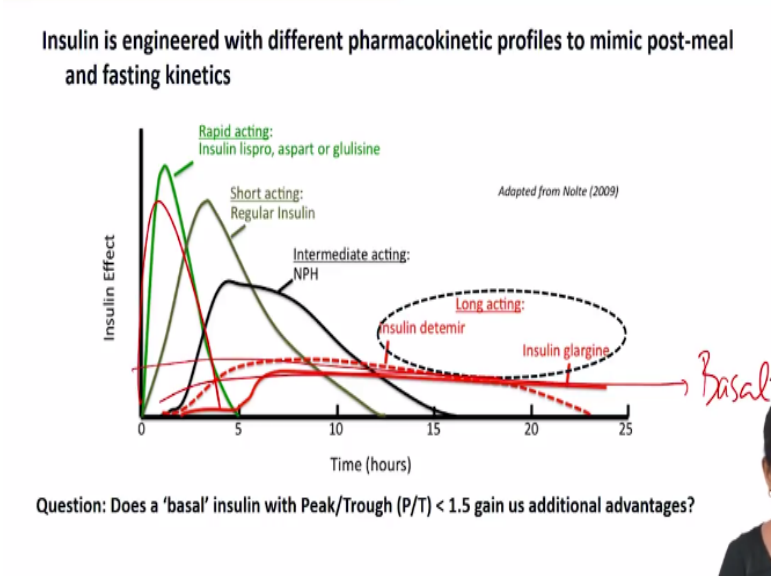

Let me now walking through a small case study of how this kind of modelling can be useful. What results can it come up with? So we were talking a little about how the pharmacokinetics can change. So we have a very rapid acting insulin here and we have a very flat insulin here and this insulin is what people called people call basal insulin in the field of insulin.

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