Material and Energy Balances
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Module No # 07
Lecture No # 31
Constraint-based Modeling

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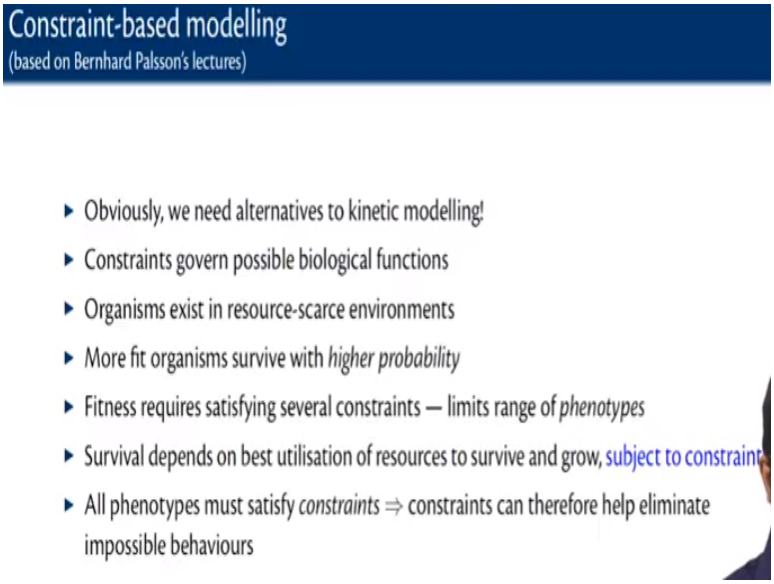

So I think one thing that you may be convinced with already is that we need alternative to kinetics modeling. So why would we need alternatives to kinetic modeling essentially with the key think I want you to hit at right away is that kinetic models involve very large number of parameters. If you want to build (()) (0:33) based kinetic model people have by the way it is very tricky very different simply because you have to estimate something like 2000 parameters.

Unless you have very respectable tight estimate for each of the parameters in priory you are not going to be able to estimate or build such models very effectively. But people are you are bravely attempting this and with good reason but clearly you need to simpler method and you already discussed a beginning that all depends on the questions you want to ask if all I want to know is whether post this genie deletions is my equally I am going to grow or not I do not need to build a dynamic model most likely I do not need a dynamic model.

And we will see how constraint based model actually give you answers to questions like that so in constraint based modeling was were at literally you now know founded by Palsson and colleagues. Palsson was UCST then and I think he is one of the you now major propanance of constraint based modeling and their lab has brought out lot of network and there are many other scientist persons contributed notably (()) (01:38) and few other many others and other people like Nielson and so on.

Who made a lot of contributions to constraint based modeling in terms of building model and using them to make predictions and so on. So what is constant based modeling what do we mean by constraints? I am just asking you generic questions I am not trying to motivate what I am you know (( )) (02:05) what I am going to cover today? But what do we mean by a constraint in general.

Maybe some limitation some I think limitation as a good look right and it also makes a lot of since in the context of biological system it was always talk about a growth limit substrate right. Something of that is how so there is always a constraint that every system as so function with right. So constraints govern all possible biological functions and organisms exist in resource scarce environments.

And fitter organisms survive with higher probability and fitter itself require satisfying several constraints which limits their range of observable Phenotypes. So this point you know I wanted to think about what kind of constraints do we need to satisfy to live or what organisms need to satisfy to survive what constraints must they satisfy. Can you think of simple constraints also nutrients but you know something more macroscopic.

So essentially lot of nutrients and network and so on but other than that there are fundamental constraint of how being an organism can be.

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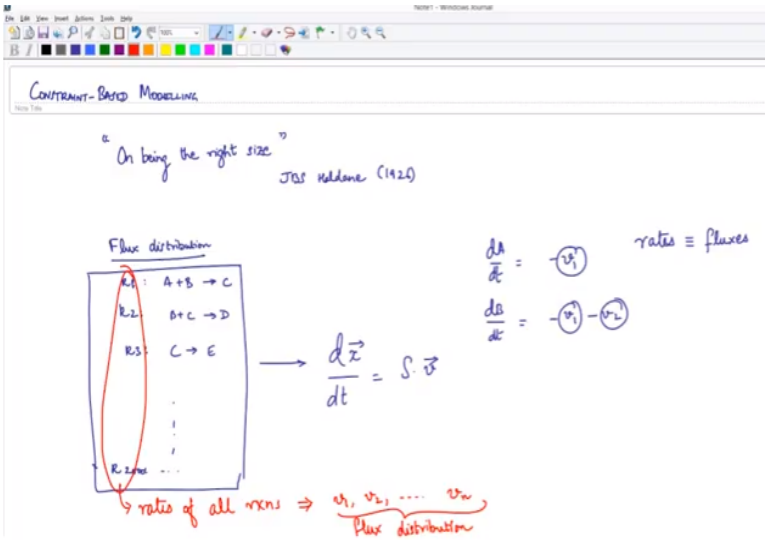

So this is very classic I say which I like to point at point towards that point I really decorated biologist JBS Haldane who essentially wrote this essay in a 1926 I think on being the write size where I essentially argues that a human being can only sobic and elephant can only be sobic whereas an insect does not need to have oxygen in its blood stream because it got a such a small body to power it can take air by diffusion take oxygen by diffusion right.

So there are constraints so if you want to have the bigger animal it has to have better machinery so why do not we have a you know 20 feet tall human could we have ? Well we cool but what would be the challenge in fact that is actually but harden argues right the argue is that the you cannot you know there is some dependency between the weigh and organism can be and the cross section of its bones right there is support that kind of weight right.

But even simpler than that I would think of something before even I go to once yeah can we have a hard that soft enough to pump black 20 feet human being it does it in giraffe's but can do it human right so those might be the constraints so these are some sort of implicit constraints you do not really stop it and think about these constraints but clearly that are some constraints which you have to follow.

If you step to the microscopic level that are clearly other constraints that when has to follow for example thermo dynamics no reaction in your body can violate thermodynamics. No reaction in your body can violate stoichiometric so there are some such obvious constraints that exist in

nature. So fitness requires satisfying several constraints such limits the rate of range of observable (()) (06:22).

And survival depends on the best utilization of resources to survive and grow but always subjective constraints you can never violate constraints. So the next idea is that since phenotypes must satisfy constraints. Constraints can help eliminate impossible behaviors and this is why you know I borrow the classic slide from a Palsson who asks you know.

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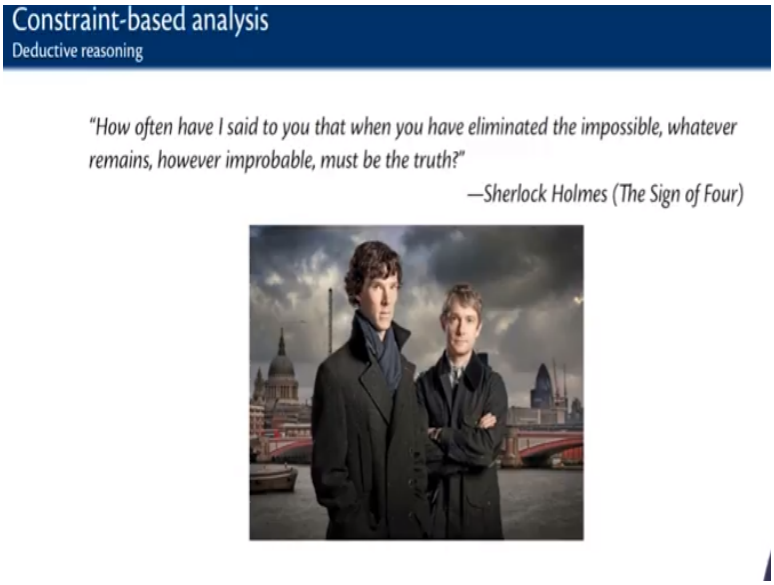

How often I set to you that you eliminated the impossible whatever remains however in probable must be the truth (()) (06:54) character right you must be familiar with Sherlock homes right. So the very classic example on you know you basically start with the pool of specs and then you go about eliminating one by one to arrive at your smaller pool of suspects who are to be tested in the different way.

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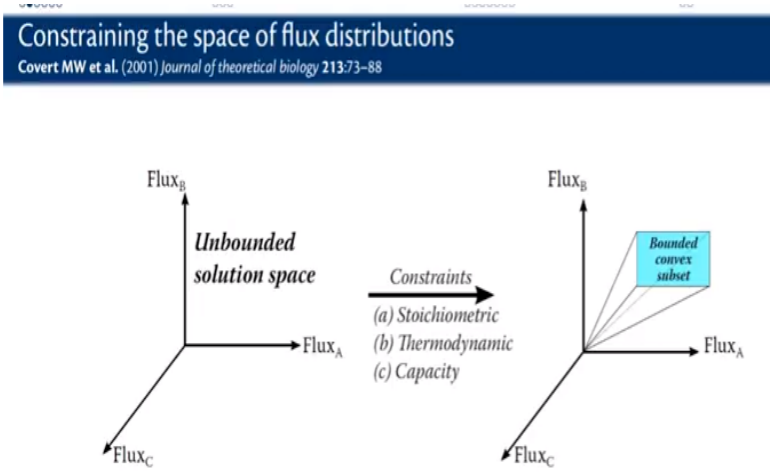

We essentially do the same thing here we start with an unbounded solutions based right. So think as a space of possible solutions what do we mean by a flux distributing in the first place right. I want you do recall what a metabolic network is metabolic network for our purpose is a long set of reactions. As a approximately this is what a metabolic network is if you recall we had an analogy with traffic network and thinks like that and so on.

So this is a metabolic network which can also be written in the form right you remember we did this on how do we write out each fluxes so you will say that DA/DT is going to be –VR1 or –V1 right and DB/DT would be –V1 – V2 right something off flux. So now these are your rates which we also call fluxes what is the flux in general chemical engineering a flow per unit area here we just drop the unit area we just talk about flow or rate of any given chemical reaction.

So given the system we are passed with finding rates of all reactions meaning V1, V2, VN this is what we call a flux distribution. So what are the fluxes of every single every individual reactions in a network? This essential specifies a network for us. So this of this as flux space right is it three dimensional space so you have flux A, flux B, and flux C right. So you just think if three reactions V1, V2, V3 right.

Now you apply constraints to eliminate improbable suspects or impossible infeasible solutions infeasible suspects or solutions. And to come up with the much smaller subset so even know that from one infinite subset we gone to another infinite subset but clearly this is quite restricted.

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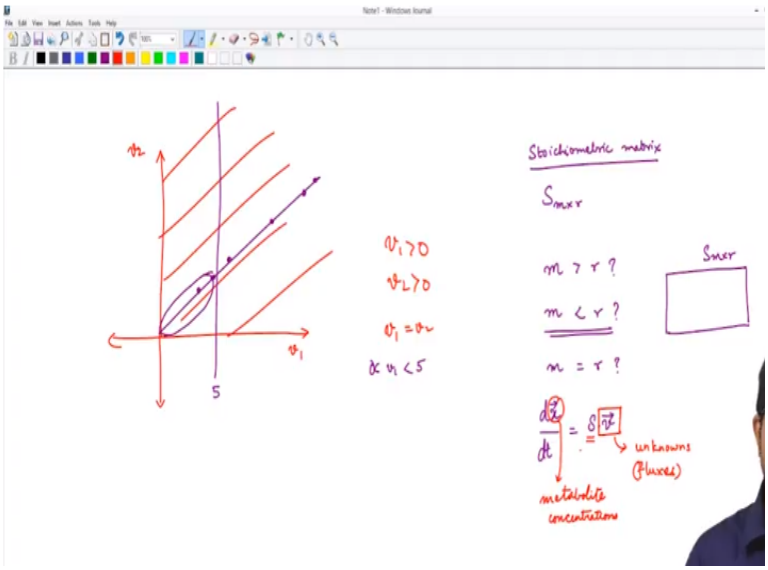

So the ideas is simple what we do is? you may actually be very familiar with something of this sort I will come back to it in a moment in a few slides you start with now any point in this space in fact I should draw it this way any point in this space is a possible solutions right for a system with two reactions. But now if I say V1 greater than 0 V2 greater than 0 it becomes this region now if I say V1 = V2 I becomes this very line right.

So every solution on this is a possibility right and if I know something more if I know you know 0 less than V1 less than 5 right that might say that all the solutions are on this part. Let us say this is 5 so you can this constrains basically help eliminate impossible behaviors impossible flux solutions what kind of constraints put how do we impose these constraints let us look at it.

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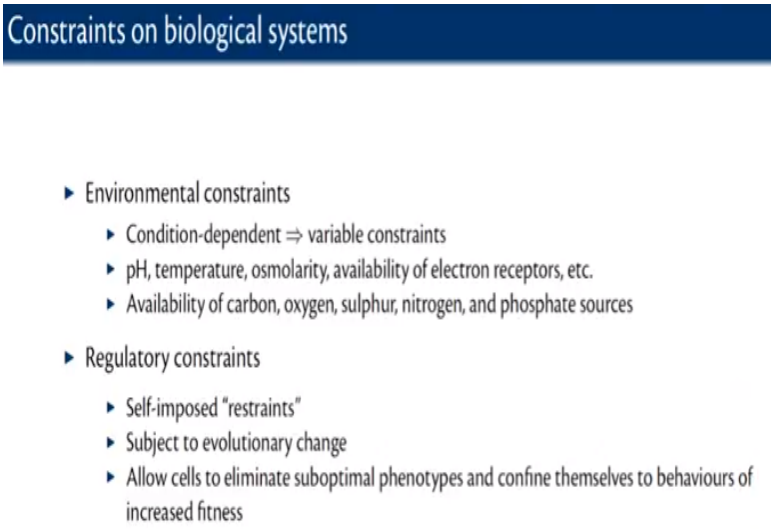

So you can think of different types of constraints some classic examples would be environmental constraints (())(12:49) something everybody thinks about first of what are the nutrients available what is the availability of carbon, Oxygen and sulfur nitrogen and phosphate sources of course PH temperature, osmolality and availability of NADH, NDPH and so on and you know many of this are condition dependent constraints so they are actually variable they cannot fix.

This is 1 set of constraints the other really interesting set of constraints are there are some self-imposed restraints by the cell which was almost counter intuitive right. So you expect the cell will do something the conditions are actually feasible for cell to do something but it actually does not why can you think of an example. Well so that could be one yeah right because it is it is not something so it you think site potentially survive with larger volume something or it has to breakdown into two yes what else.

But that is that is not a cells impose restraints actually right what to do if self-imposed restraint actually right. What do a self-imposed restraint the cell can go but it may choose not to for example. I think very familiar with two examples of distrait where does the cell choose not to use as the constraint caterpillar depression right there will be a classic example (()) (14:49) for the cell the cell should be growing.

But it will just use of should be growing at a higher rate using glucose and lactose but it is just use should be growing at a higher rate using both glucose and lactose but it will choose to you

only glucose because it will calculate the pressure on utilization of lactose. Once glucose is exhausted we have carbon dioxide and you know the lactose enzymes are then expressed the genes are expressed and then the lactose metabolism kicks in.

So the shell is the shell essentially chooses not to use lactose right so another very similar example as in chooses not to grow right so the condition seen to be reasonable if I growth but this cell is trying to eliminate a suboptimal phenotype which could be reasonable growth and a some harsh patients and confined some cell to a behavior of increase fitness it really depends upon the design fitness but if you talk about fitness as the ability to cell drive and you know live one for more generation may be the cell is leaving that by correlating right.

So the sword is more stable and when the condition become more favorable the cell can no again start growing and so on right.

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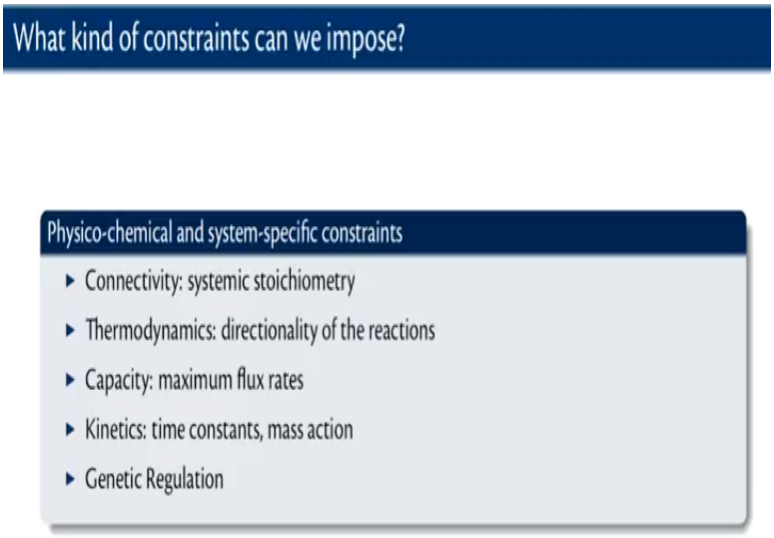

So there are some such self-imposed restraints as such we will focus on similar constraints essentially coming from system stoichiometric first up what is stoichiometry? Invert ratios right so there are clear dependencies so one more glucose produced exactly one mole of lactose not a molecule more not a molecule less.

One mole of glucose will produce exactly to moles of pyruvate where glycolysis so this becomes nice constraints and of course there is thermo dynamics there are some reactions that can only go

in a particular direction some reaction could be reversible they can go and either direction but you know there are such constraints then there are maximum flux rates right so every enzyme as a particular turn over number right it may not be able to turn over more than X number of molecules per second.

And you know there are genetic regulation thus you need to worry about time constraints mass action there are many other constraints that you may be able to think up of but most important I would say connectivity thermodynamics and capacity. So what would this translate into practice we will see shortly.

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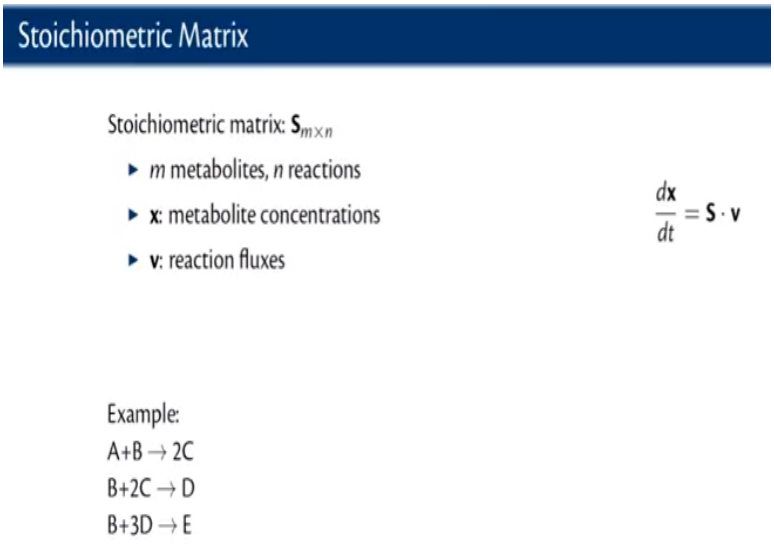

So let us take a very simple example what is the size of the stoichiometry systems? 5 cross 3 metabolites and 3 reactions and you have a 5 cross 3 system so let us just go back to the concept of stoichiometry matrix what do you think do you usually have more metabolites and reactions or more reactions that metabolites are roughly the same number of metabolites and reactions.

So are you going to have a square stoichiometric or fag stoichiometric or a tall metric tall that would be in this why right but the same metabolite can also participate in more than original reaction right. So you will see that ATP participates in 100 reactions and may be glucose participate in like 30, 40 reactions and there are other metabolites in participate only in one or two reactions you might see a sort of you know power there as a nominee right.

So you would normally observe that the metabolites mix and match same reactions obviously some metabolites let us keep changing so invariably you have M less than R which means you have fewer rows than column and have a fag stoichiometry matrixes we will see what implications this as so for now remember that set up the equations like DX / DT this S into DT right.

So what the (()) (20:14) fluxes what is X yeah concentrations metabolite concentration rate of change of metabolite concentrations linked via they stoichiometric matrix.