Computational Systems Biology
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Lecture – 79
Constraint-based Modelling of Metabolic Networks: Recap

We are nearing the end of this long module on constraint based modelling of metabolic networks, so I will give you a quick recap of all the concepts we have done so far, beginning with stoichiometric matrix, the constraints when imposes on metabolic networks and what are the possible choices for the objective function. So, welcome back let us recap constraint based modelling today.

You studied a whole lot of techniques and a whole lot of applications for constraint based modelling, so let us try to recap it to make sure we have understood everything. So, why did we go in for constraint based modelling in the first place? We essentially said that it was very difficult to model very large systems using kinetic modelling, there is no question of estimating like if you have 1500 reactions in E coli, you cannot estimate vm and km for each of those reactions.

So, not going to be estimating about 3000 parameters, although there are ways to build, you know genome scale kinetic models, it always depends on the ability to accurately estimate parameters or have prior estimates for parameters, the absence of that kind of information, it becomes very difficult to stimulate genome scale kinetic models or even estimate parameters for genome scale kinetic models.

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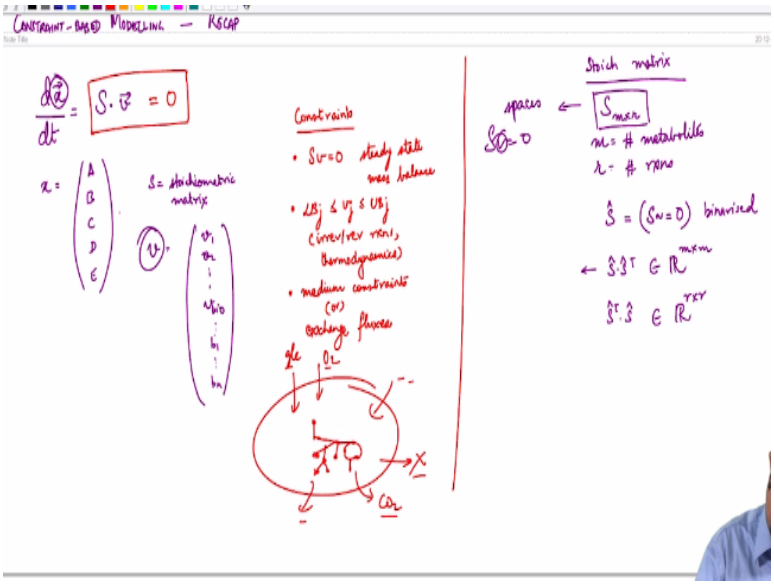

So, given that the first thing that we went ahead and look at was what is; how do we formulate the system, so the classic formulation we started with was; right, were x is nothing but a vector of metabolite concentrations, s is your stoichiometric matrix and v is your flux vector, right, we can have internal, external fluxes everything inside of this vector, okay. So, for each of these, you could actually write kinetic equations, right.

So, dx/ da/dt, you can have a kinetic equation, it will be some k * a – k2 * b and so on and so forth, right. So, let us say this is stoichiometric matrix again, so this is going to be s, m cross r; m is number of metabolites, r is number of reactions. Now let us just think for a moment, what let us consider the matrix s cap, which is you know in Matlab terms, I would just say or essentially a binarized version of the stoichiometric matrix.

What is going to be the size of this matrix and s cap transpose, what do these 2 matrices tell you? More or less, right, it actually tries to tell you, so you are saying that whether he is asking if it is adjacency matrix for a substrate graph and it is more or less that so, what this gives you is; it tells you the incidence of every metabolite in every reaction, right, so it now will connect metabolites that are you know linked to one another, neutrally the substrate graph, right.

And what is the diagonal that is why it is not a substrate graph, what is the diagonal? The number of reactions at metabolites participates in, right, so that is going to be the diagonal. So, you can

think of what happens when you multiply s cap transpose into S cap as well, right these are 2 interesting matrices and in fact, the most interesting matrix is of course this stoichiometric matrix itself and there are several spaces associated with this matrix.

So, you should go and read about it, you know the left null space and so on, so in fact, all are vectors of interest belong in the left null space of s, which means that Sv = 0, what are all the v? v is that satisfy this equation of Sv = 0, right this is the first place are we started. So, now what are your constraints; we say this is constraint based modelling, where did you get your constraints from?

So, we said we will impose different kind of constraint, the first importance set of constraint is what we already have here essentially, at steady state this becomes Sv = 0, what is this constraint; mass balance, steady state mass balance, right, what are the constraints did we impose? Some lower bounce and upper bounce, this also accounted somewhat for thermodynamics.

What were the constraints on the E coli core model; yes, Sv = 0, yes we put some lower bounce and upper bounce, what else, we did not feed the model something right, so what are the medium constraints or exchange fluxes, right, what are your medium constraint versus exchange fluxes and so on, right so you had a cell, you said you take so much of glucose, so much of O2, some biomass, some CO2 and so on.

And of course, there is a complex metabolic network this going on here, right but what you have are a glucose uptake flux and oxygen uptake flux, any other uptake fluxes and what our secretion fluxes; CO2 mean a net ATP generation consumption whatever, right.

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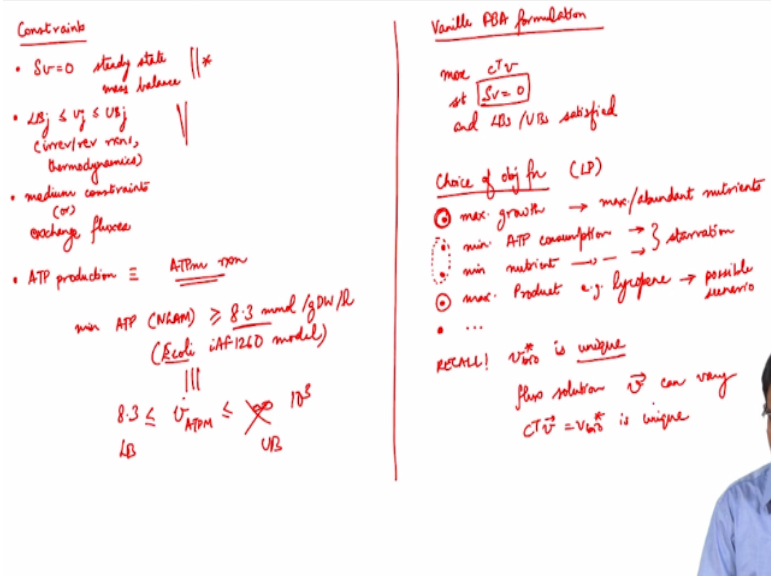

And another important constraint we briefly discussed that of ATP production, or what is usually called the ATP maintenance; mATP or ATPm reaction in many models, most models have this, this is literally calibrated, right, it is made to fit experimental data, right, you say something like my minimum ATP non growth associated maintenance ATP is something of this sort, this is the constraint that is there actually in E coli iAF 1260 model.

What does this mean again, do you recall, so the cell requires some energy, some ATP over and above what it requires in metabolism, whatever is there in metabolism is kind of captured in these constraints, right, is essentially here, but the cell has some ATP requirement that goes over and above this for survival and this is called non growth associated maintenance and this is fold into one flux.

So, this is; how does this translate mathematically? Infinity or let us say a large number, **"Professor – student conversation starts"** yeah, that is what this is, right, so this is LB, this is UB, so this constraint becomes important **"Professor – student conversation ends"** but not there is a potential catch right, as always in this course let us try to emphasise on practice rather than theory, what happens when you actually try and stimulate this?

So, what happens; okay, so let us just recall, so maybe we will come back return in a moment, right. What is the vanilla FBA formulation; this what we just had on the previous screen, it is

maximise c transpose v such that Sv = 0 and why did we go here because we said this is a fat matrix with infinitely many solutions, you need to pick one solution and this we said was identical to the you know simple problem we used to solve in school about you know factory making tables and chairs right.

So, there instead of tables and chairs, we now have several metabolites and instead of profit, we have an arbitrary objective function we pick right but usually, we pick the objective function of; so now the next important thing is choice of objective function, what are the possibilities? Maximise growth or minimise ATP consumption, minimise nutrient consumption, maximise some product like lycopene.

The LP case, these are the objective functions right, so what do each of these translate to; so this tries to capture a cell growing under maximum nutrient conditions, these 2 probably try to capture growth under starvation, what about this; this captures a possible metabolic state, where lycopene is maximised, right so out of these, this is a little different right, maximise growth is good in the sense it is able to capture really what is happening, right.

And maybe to some extent, these also capture what is going on within the cell but this is not necessarily what happens within the cell but it tells you that under a particular condition this can very well happen, right or if you want to maximise lycopene, this is the kind of rerouting a fluxes that must occur and may be you want to figure out how to perturb a system to really get there, so that is what, so this is a possible scenario.

And at this point, recall; recall what that your v bio star is unique right but the flux solution right, the vector itself can vary, c transpose v is unique of important, is that fair enough, important to remember this.

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So, in today's video we started off with a recap of constraint based modelling of metabolic networks, we revisited the concept of stoichiometric matrix, what are all the constraints on a metabolic network as well as how we go about picking a good objective function for our simulation. In the next video, we will look at how metabolic networks can be perturb, what kind of perturbations are done and how one stimulates the effect of these perturbations.