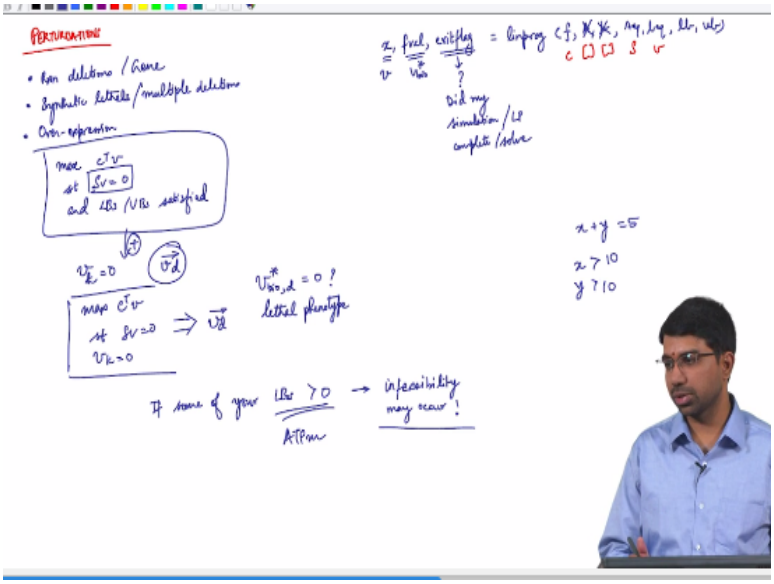
Computational Systems Biology
Karthik Raman
Department of Biotechnology
Indian Institute of Technology – Madras

Lecture – 80
Constraint-based Modelling of Metabolic Networks: Recap

In today's recap video, we will have an overview of the different types of perturbations one can make the metabolic networks and how we can set them up as optimisation problems and now how do we go about perturbations right that is the immediate next thing to start worrying about.

(Refer Slide Time: 00:31)



So, how do you perturb the models, so what kind of perturbations did we look at; reaction, deletions, synthetic lethals or multiple, so you can also delete genes and lastly overexpression. Now let us say stop for a moment and think back what happens how do you stimulate each of these, right you basically start with the original flux balance solution formulation right, which is this and plus, what do you add to this?

For a deletion, how do you simulated deletion? So, add an additional constraints saying vd = 0 right, or let us just say vk = 0, for some reactions that we want to delete, for a single reaction or multiple reactions right and let us say the solution here is going to be vd, right, so it is going to be the same thing, max C transpose v such that Sv = 0, additionally vk = 0 right and this will give you a solution vd, right.

What happens if; it is the essential reaction or it is a lethal phenotype, so one thing we did not think about so far is; should you always be able to solve this, what is the system look like; so it is a linear system of equations, with potentially infinitely many solutions and you are adding some additional constraints and you are maximising a linear objective function, right. So, are you supposed to be able to solve this always, are there scenarios where you may not be able to solve it.

So, think back for a moment to the, cobra toolbox or to linprog, right, was there something of importance there, how did we call linprog, you would have call linprog something like x, is that right something of this sort right, so this is nothing but your v, this is nothing but your; this is your exec flag, did my simulation or LP complete or solve; right, this of course does not exist for us, basically we use blanks, this is S, this is v, this is LB, UB and this is c.

So, everything fine so far, any doubts, okay, so will this solve or not, will this always solve? What kind of constraints we are imposing; are we imposing constraints that may break the system or it is not a big problem. So, one thing you need to immediately see here is that v =0 is a perfectly valid solution, it is not an interesting solution but it is a trivial and practically always existent solution except if you have certain lower bounce.

So, if you have if some of your LB's are >0 infeasibility may occur, classic example for this; ATPm, so very well this becomes a tricky scenario now, you may have to find out that you have a infeasible solution and therefore conclude that it is actually a lethal phenotype, see normally, we conclude that there is a lethal phenotype only if you get a 0 solution, a 0 optimal solution. So, like my maximum growth rate possible is actually 0, right.

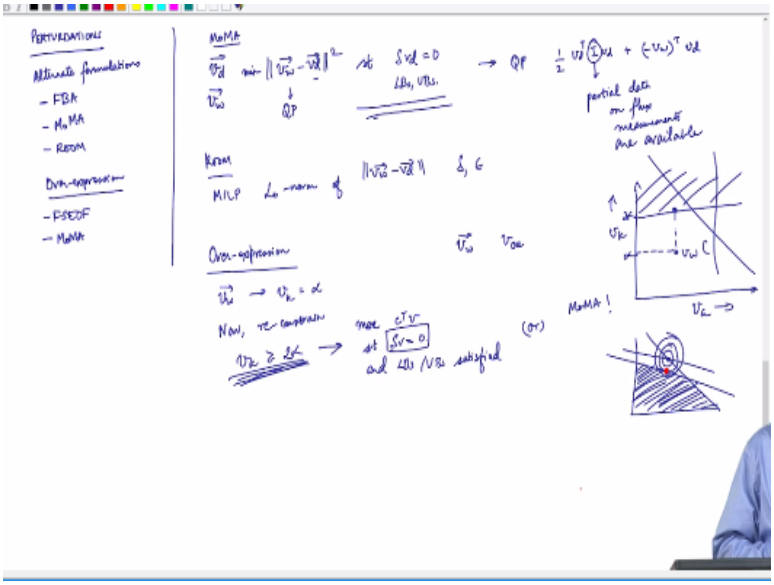
Whereas, in this case alone, you may have infeasibility which will lead you to conclude that clearly I could not make my ATP, I could not make enough ATP, whereas required to survival, so I have an infeasibility hence lethal phenotype, so this is something to remember, okay. **"Professor – student conversation starts"** biomass will be 0 but there are cases where you

would not be able to; so you are saying that LB is 8.3 right, maybe I am not able to get LB of 8.3.

So, I will actually be; it will be infeasible, so if constraint is not satisfied then you do not even have a solution, if your constraint is satisfied and you get a 0 solution it is a different story, if your constraint is not even satisfied then you have a different problem, this is what I am trying to emphasise here. It depends, so sometimes if that constraint is satisfied and other constraint are in satisfied then you will get a fair and square, 0 and lethal phenotype.

There are scenarios where you; it is like saying solve x + y = 5, right so x < you know and give it some infeasible constraint and you know you say that x > 10, y > 10, we can never solve this, right, you will get an infeasible solution.

(Refer Slide Time: 08:53)



So, while at perturbations, we studied alternate formulations right, so let us say FBA is already one formulation, we then studied minimisation of metabolic adjustment, room and then for overexpression, we study FSEOF, we can also use MoMA to study overexpression or anything else basically, right, so what is MoMA, right? We now said that it is not very fair to say that the object function must always be growth maximisation.

Because there are cases, where clearly the organism may not be able to sustain maximal growth example under several gene deletions or even a single gene deletion, so in that case we said let us say vd is your new vector flux distribution and vw was an original flux distribution, we said we will minimise this of course, subject to LB's and UB's right, so this became a quadratic programming formulation.

Room; came up with an MILB by trying to reduce the L0 norm of but you know it had some additional variations like it had 2 parameters; delta and Epsilon that could be varied and so on and so forth, right but essentially, these were different takes on you know the same constraint based formulation without using FBA or the maximum growth rate objective function of FBA. **"Professor – student conversation starts."**

So, the new bio star is also as close as possible by definition to the original one, it is; so you are trying to keep the vectors as close as possible, so the biomass can change but you are trying to keep the fluxes as close as possible, true, true but the idea is; this is going to better capture what the cell is doing. **"Professor – student conversation ends."** So, now let us look at how would you use MoMA to fit fluxes, right?

We did discuss that briefly, so it becomes very similar right, so should look at the quadratic programming formulation and it look something like half, this was the canonical quadratic formulation of course, subject is v = 0 and this whole stuff, LB's and UB's, right, we then said that this matrix will change if only partial data on flux measurements are available, right, this is something I want you to verify.

But now let us just do a slightly different problem, how would you simulate overexpression with MoMA, or before that how do you just simulate; how do you even simulate over expression? So, you basically, solve first and you get a wild type flux and now let us say some vk = some alpha, right, now reconstrain right, vk > = 2 alpha and run the same old FBA formulation or you can go in for MoMA.

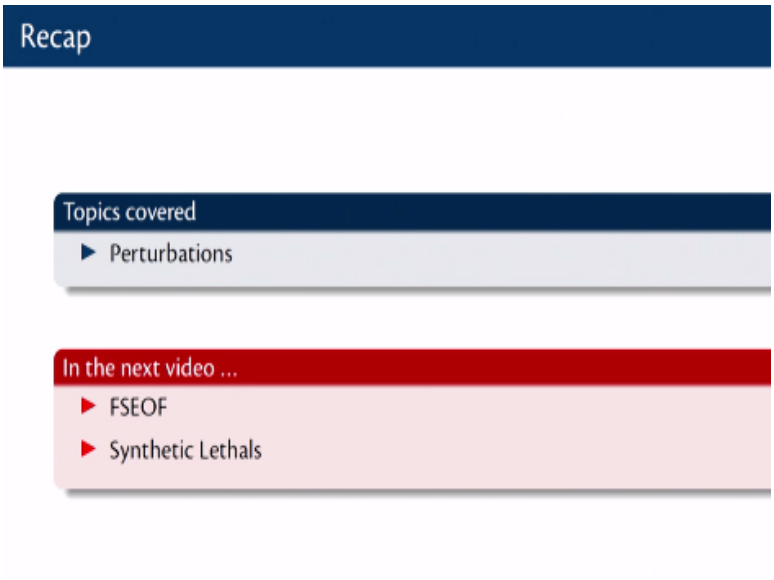
How do you do MoMA in this case? It is just identical to this except you have a different set of constraints, you have instead of these constraints, you have an additional constraint that vk > 2 alpha and of course, you again run the risk of infeasibility, right anytime you leave out 0 from your solution space, you have a possibility that the solution may not be feasible, how will you run MoMA; in the same way, right.

You have a flux vector; initial flux vector, right, you have a new flux vector vd or voe and you now minimise the distance from this flux vector and the original flux vector subject to the new constraints, so subject to all these Sv = 0, usual constraints and additionally, ask for a vk > = 2 alpha. So, of vk is > 2 alpha, what is the nearest space, so let us see if we can capture it geometrically.

Let us say this is vw, right, so now I am saying find something here that right, let us say this is; so vk, let us say va or something. Now, I am saying that, it is quite more correctly, so this is some alpha and this is 2 alpha. Now, I am going to say that vk is > 2 alpha, so find the closest flux that agrees with other constraints may be there are other constraints like this, like this whatever, so find the closest flux using MoMA.

So, if you remember if we actually had constraints like this and so on MoMA essentially, looks in circles around this, right, these are contours where vw – vd is same, out of all of these which of these cuts my new constraint; let us say these are my new constraints, so maybe I would put this as the new optimal; new optimal. So, is this all coming together nicely right, you can see how flux balance analysis and related techniques can be used across a spectrum of situations.

(Refer Slide Time: 17:24)



So, in today's video's title we started of with perturbations and we will continue with perturbations tomorrow as well, now building on what we studied about deletions and so on towards synthetic lethals and FSEOF, which is used to study overexpression.