Computational Systems Biology
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Lecture - 61
Other Constraint-Based Approaches

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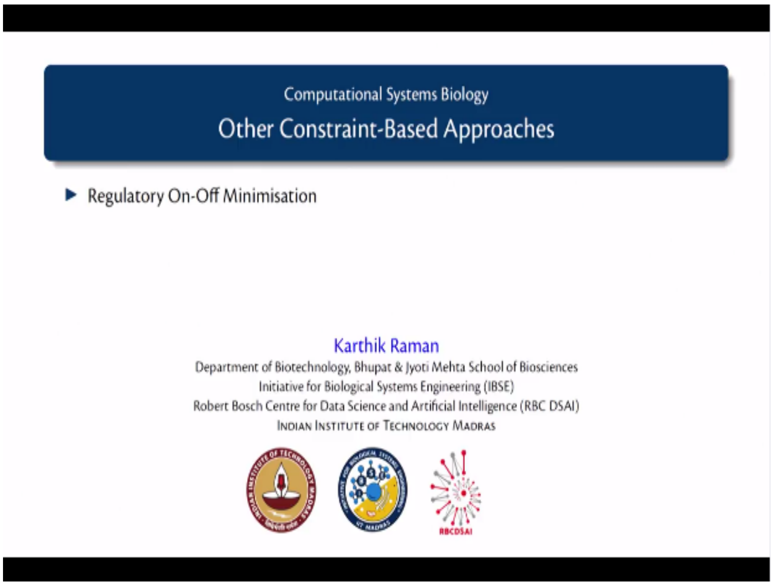

In this lecture, we will discuss another constraint-based approach which is you know similar in spirit to minimization of metabolic adjustment we saw in the previous lecture but this tries to minimize the number of flux changes from a given flux vector.

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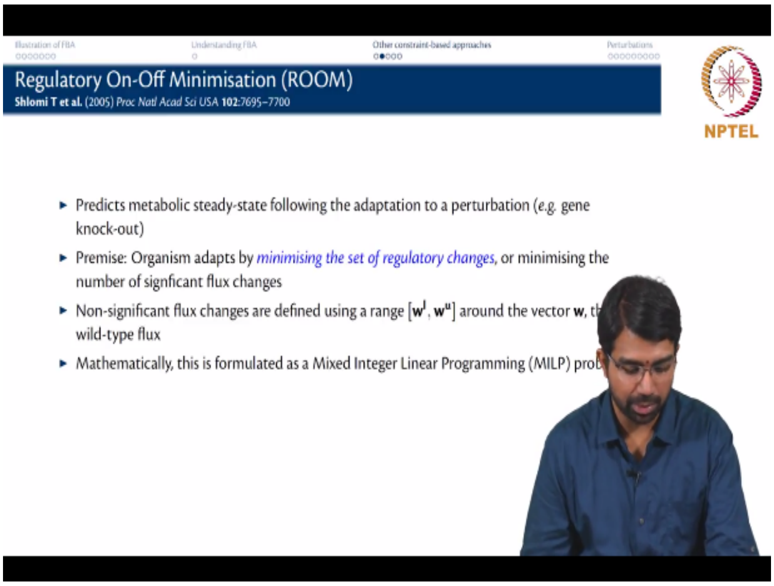

The alternative approach that I just talked about which is closer to you know in spirit to the l0 norm optimization is again tries to predict the metabolic steady state following the adaptation to a perturbation. So the premise is that the organism adapts by minimizing the set of regulatory changes. In the previous case, we talked about minimizing the distance from the wild tape flux.

You know the whole flux vector as such organism does not think vectorially right. So the wild type vector and the deletion vector are as close as possible in space. Why cannot it be the same because you have changed a constraint. If that constraint is useless right, it is possible, it is possible that you deleted a reaction that was not carrying a flux when you will sit right there.

If not you will have to move away from it. So here the premise is the organism adapts by minimizing the set of regulatory changes which makes somewhat more sense right. So the organism only says my budget for reorganization is about 10 enzymes. So I will try to change 10 fluxes and try to keep as close as possible to the original vector. So non-significant flux changes are defined using a range and ignored right.

So you basically say that flux can change by 2, 3% it is not a big deal but any change more than 5% I want to minimize it. The number of 5%, 10% changes will be minimized. Mathematically, this becomes an MILP problem, a mixed integer linear programming problem.

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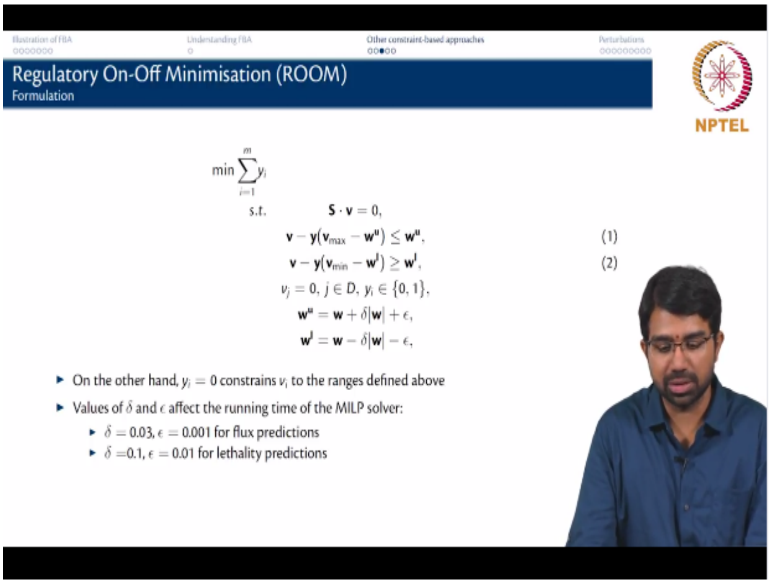

What is the formulation? The formulation looks like this. So in this formulation we are trying to minimize the number of significant flux changes and you proxy it that by another variable yi and you are minimizing that and if you carefully look at equations 1 and 2, it essentially points in that direction. So if you basically ignore these, let just say that delta is 0, epsilon is 0 that will be a very strict kind of condition right saying I am not tolerating any flux change right.

So if you said delta is 0, epsilon is 0 then w and wl are both w right so then your equation basically becomes what happens to the equation. When yi=1 it will be v-v max v<=v max and v>=v min right. They basically simplify to the trivial constraint right. So even if you have you know delta epsilon so you are saying yi=1 for a significant flux change in vi and yi=0 otherwise.

For yi=1, the inequalities do not impose any new constraint. When we have yi=0, it constraints vi to the ranges defined here. So within some epsilon, so this is some percentage, delta is some percentage change and epsilon is something above that. So these are essentially two parameters that you can tune to assess your predictions right. So they basically said that delta=0.1 and epsilon=0.01 was good for lethality predictions whereas for predicting growth rates these delta's were more reasonable.

The main idea here is that you can come up with different formulations based on what makes more sense with respect to the biology you are interested in right. Is it more important to minimize the overall flux changes or is it more important to minimize the number of flux changes and so on.

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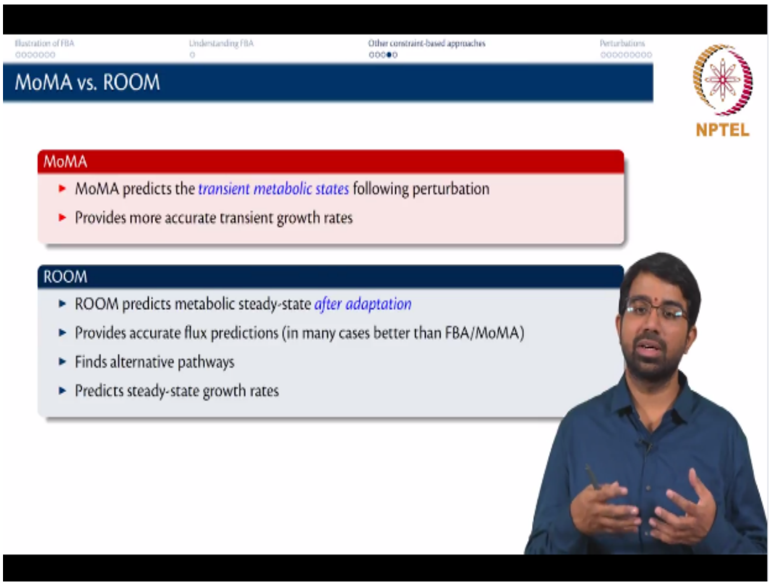

So to come back to the previous question on you know where is the steady-state it turns out that MoMA predicts the transient metabolic states following perturbation whereas ROOM predicts the steady-state after adaptation which does seem very reasonable right. So the cell initially tries to minimize the overall change but it settles down to a state where there are only few changes from original.

So everything responds but finally the cell settles down to a state which is similar to the original state but has a few more changes right. So in many cases in different cases MoMA and ROOM have you know shown better performance and so on. So ROOM is also able to predict steady-state growth rates and find alternative pathways but you will see that in current literature most of these techniques are not very heavily used.

People still use mostly FBA but these techniques have some very interesting (()) (05:20) as I will try to tell you in a later class because we have some reason to work wherein we find this MoMA, ROOM based formulation is very nice to understand how an organism reroutes its fluxes under a perturbation. So what is the minimal rerouting an organism needs to achieve and so on.

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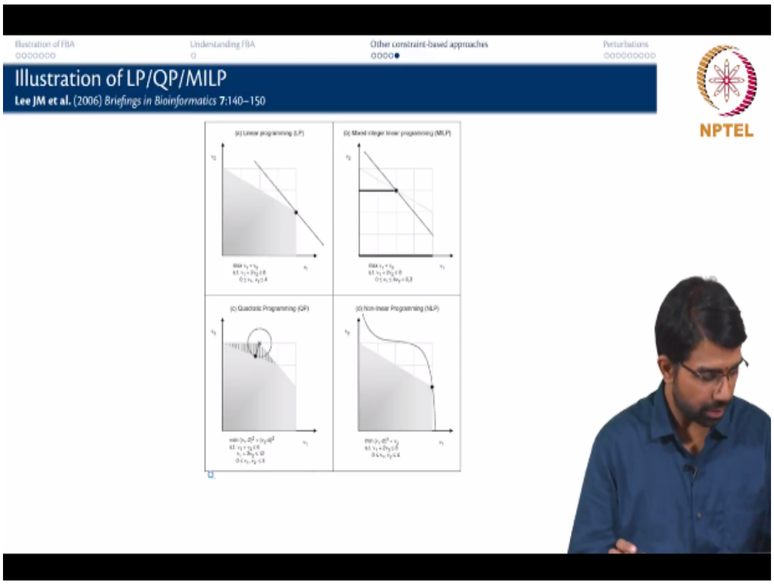

So this is the pictorial representation. So this is plain old linear programming right. We have been talking about this for the last few classes. So I have some linear constraints and this dotted line is your linear objective function, it says maximize v1+v2 that is this line. In the next, let us look at panel c where basically you have a quadratic function, what is the function here?

If the distance which is shown as a circle right so you can think of concentric circles as expanding distance around the original wild type point and you have move to a new point based on the deletion. A new constraint has brought you this right and this is a mixed integer linear programming. Why is it integer? You want some of the solutions to be integers, may be x's can be you know some of the solutions can be integers.

And then you have nonlinear programming, you have you know some optimization function like minimize v1-2 the whole cube+v2. So this is how the objective function looks and may be this is your optimum. **"Professor - student conversation starts."** Yeah, in all cases the constraints are linear. The objective function for optimization is nonlinear, mixed integer or whatever is the wild type flux, original flux.

This was the previous optima and this is the new, so where the circle intersects with the constraint like what we had here. **"Professor - student conversation ends."**

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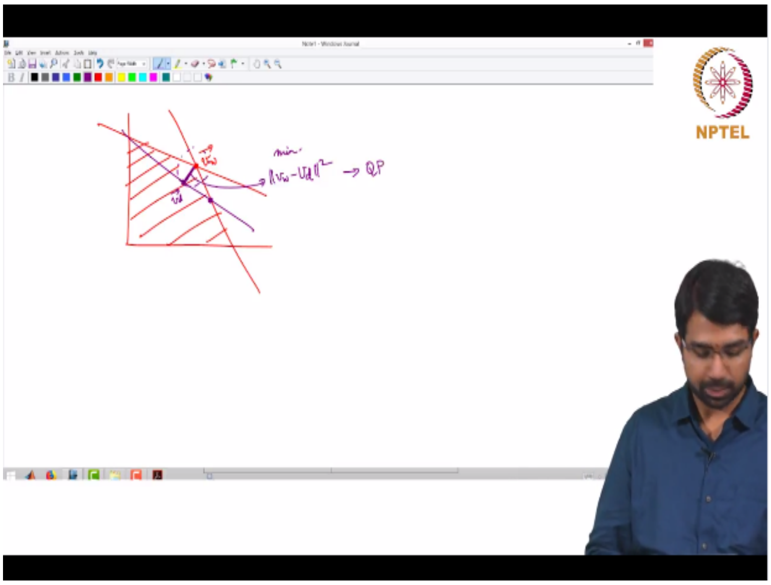

So this is the original feasible space right which means your optima was likely here right or here or here right. Now I have a change right which means my FBA predicted optimum will be here whereas the MoMA predicted optimum will be here closest to the you know you basically draw a perpendicular from there right. So closest to the, so this is vw, this is vd and you get this by minimizing which is nothing but a QP **"Professor - student conversation starts."**

Good question, so v and y you have 2 sets that is why it is a mixed integer linear programming problem, y is an additional variable, v is not integers, so v are real's that is why it is mixed otherwise you would have called it an integer programming problem IP. Yes, see you have introduced new decision variables into the mix; you are initially trying to find only vi's. Now you are trying to jointly estimate vi's and yi's.

Yi's are all integers, vi's are of course real numbers. So it is like all the integer points so maybe you know I could even draw it a little differently. I have to show v1 and y1. It is too difficult to show it in one dimension but it has to pass through the grid points. So in some sense you can just think of it like this. Let us say the x axis is v1 and the y axis is y1, so y values have to be integers.

So it only considered the places where the subjective function intersects the horizontal grid lines. **"Professor - student conversation ends."**

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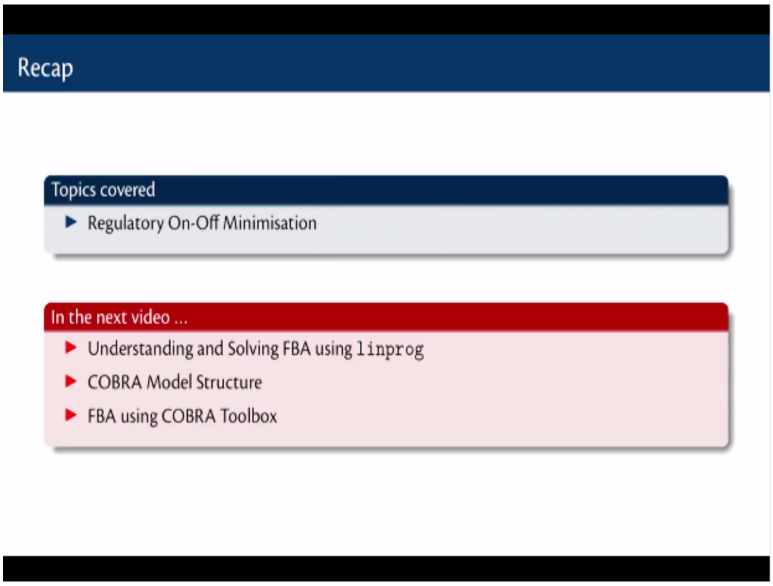

So in this lecture, we covered another interesting constraint-based modelling technique known as ROOM or regulatory on-off minimization which try to minimize the number of flux changes. This has implications for you know other kinds of things as well which we have not discussed today for example how do we find you know the rerouting that happens in metabolic networks on the deletion of a particular reaction.

In the next video, we will go back to MATLAB. We will have a lab session wherein we will understand FBA, the various components of the linear programming problem by using the simple function called linprog which is the standard LP optimizer in MATLAB. We will also understand what is the COBRA tool box from MATLAB which is a very popular tool box for doing constraint-based reconstruction analysis that is what COBRA stands for.

So what is the model structure look like for a COBRA based model and how we can perform FBA using the COBRA tool box.