Computational Systems Biology
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Lecture - 60
Other Constraint-Based Approaches

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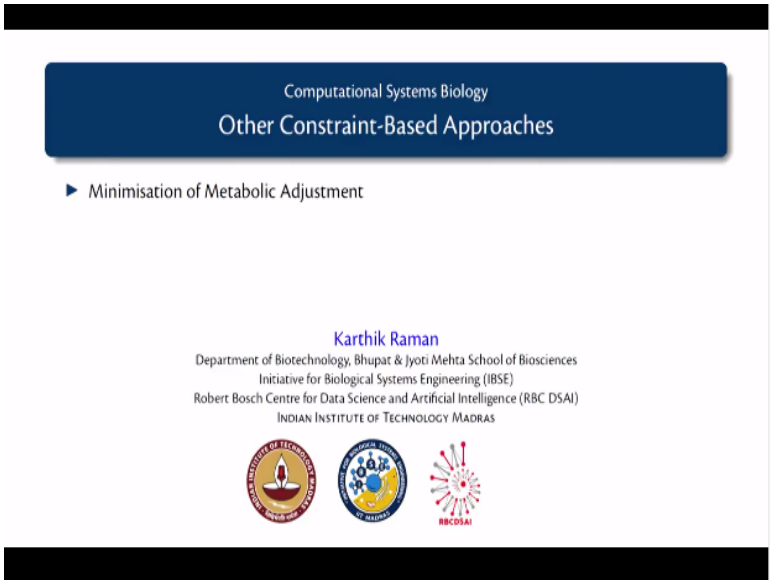

In the next couple of videos, we will look at other constraint-based approaches which are sort of based on flux balance analysis but they have different kinds of objective functions. So they use the same mass balance constraints and so on but instead have a different objective function that is more useful in appropriate scenarios. So the first of them is what is known as minimisation of metabolic adjustment.

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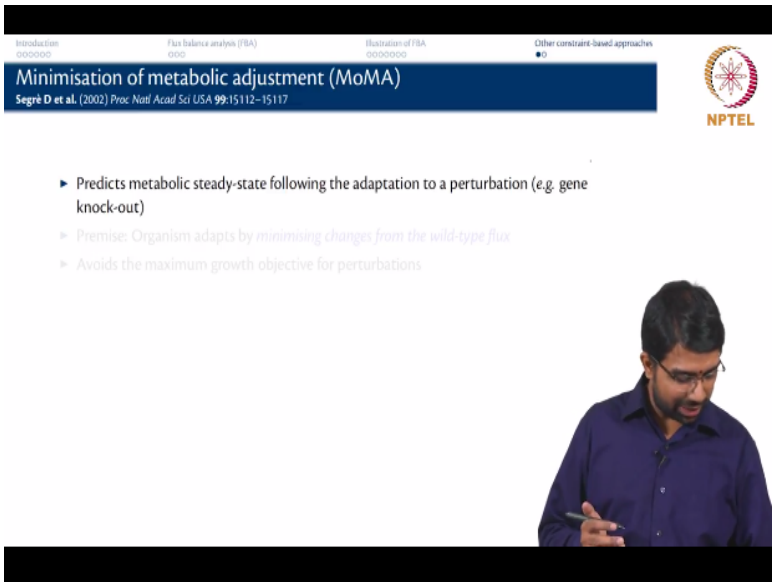

So Segre and coworkers basically came up with another strategy which said it may not be valid as I had on my previous slide.

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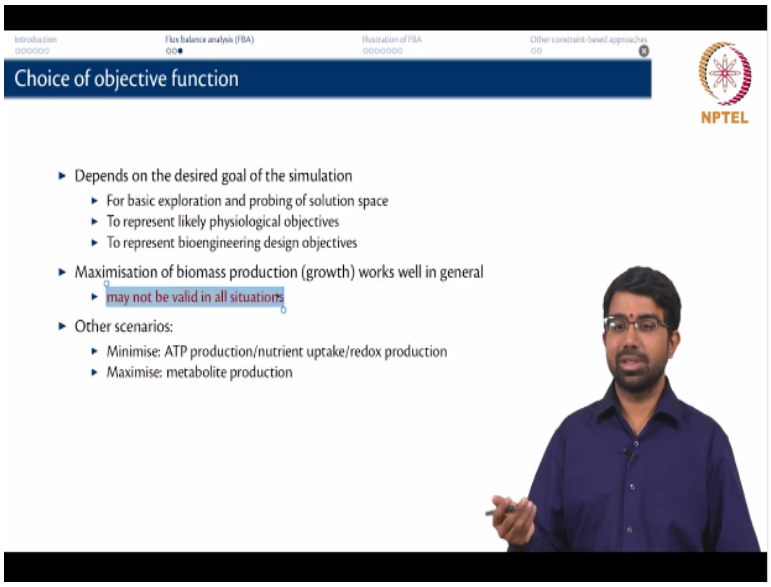

This may not be valid in all situations just keep saying maximize growth rate, maximize growth rate when you are essentially harassing a cell by knocking out a couple of genes you do not expect the cell to maximize its growth rate, it might only be trying to survive right. So the hypothesis here is that the cell survives by minimizing its metabolic adjustment right.

So to speak at a particular metabolic state it moves to the nearest metabolic state that has complaint with your new constraints. So which brings us to the first question how do you delete a gene? How do you delete a gene from a metabolic model from a model? **"Professor - student conversation starts."** What metabolite I am asking you about removing a gene. No, the gene is basically an enzyme which catalyzes the reaction.

So you need to remove a particular reaction from the model. So how do you remove a reaction from a model? So you can basically remove the entire column from the stoichiometric matrix that would be an ideal way, the easier way is to basically add additional constraints in v5=0. You want to remove a reaction 5 you say v5=0, once you do that you have a new optimization to solve right **"Professor - student conversation ends."**

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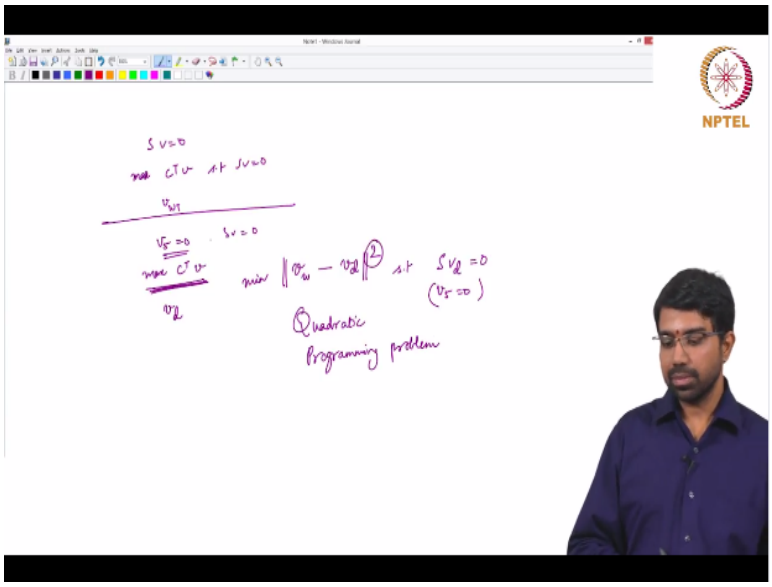

Sv=0 always right, let us not even worry about it. So now let us say you did maximize c transpose v such that sv=0 and you came with some v wild type. Now I say go and delete reaction 5 so I say v5=0 in addition to Sv=0 and I again maximize c transpose v to find some other v dash which is v deleted, some other v which is v deleted but it may not be fair to ask the cell to maximize its growth, it is under some stress.

So what Segre and coworker suggested was why not we minimize the distance between vw and vd. Mathematically what would this be right so minimize such that svd=0. Of course, you know v5=0 as well whatever deletion you inflicted on the organism. So this becomes a quadratic programming problem because you see the square.

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So we will follow this up in the next class. Let us look at some other constrain-based approaches, FBA is the vanilla basic constraint-based approaches. There are many constraint-based approaches that have been built more or less related to FBA but they use different ideas for objective function, different optimization formulations and so on. So the first what is the major in some sense a weakness of FBA.

It necessitates this objective function no matter what. So yesterday we were looking at how do we optimize in terms whenever there is a gene deletion right.

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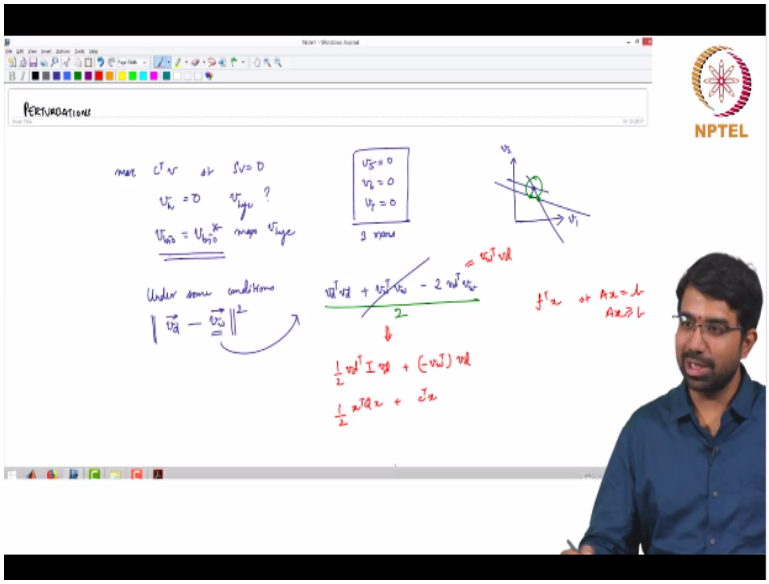

So I said we will stick to the same formulation right, so which basically looks like maximize c transpose v such that sv=0 but additionally some vk=0. This means this reaction is additionally pinned to 0. You can even pin it to some value right. So for example if you wanted to find out what is the max, we were talking about this yesterday right v of lycopene you might say that v bio=v bio star and now maximize v lycopene right.

So this is basically another constraint wherein we are pinning fluxes, so note this idea of pinning fluxes so you pin a flux to a particular value or pin a flux to a 0 value and so on right but the issue comes when you say you want to maximize growth again. Let us say you are saying v5=0, v6=0, v7=0. You have knocked out 3 reactions, would the organism still be trying to maximize its growth?

See what is your FB objective function? You are literally trying to second guess what the organism is doing. Under abundant nutrient conditions, the organism is trying to maximize its

growth probably so when you assume that we get a nice way to the experimental predictions and so on but what happens when you are deleting too many genes and so on. The organism may not be able to grow as freely as before.

So maybe one hypothesis that people came up with was under some conditions the organism finds a new distribution that is minimally different from the wild type distribution. Mathematically, how would we put this and you can square it as well. What is this translate into? Let us look, so this is vd transpose vd+vw transpose vw-2vd transpose vw. You can leave this out, it is a constant right.

What is vw? The initial flux distribution which you might have experimentally measured or obtained via FBA again, both are possibilities. You obtained it through some other means right, you know what was the initial state of the cell, so if you want to look at it pictorially of course we can look at only two dimensions. So pictorially let us say this was the initial optimum and now you have an additional constraint which might be making one of these 0.

But let us say the constraint changes like this or it is too close. Let us look at something like this. You have to find the new optimum, if you were to use FBA you might say this is the new optimum but now you might find what is closest to the original point in terms of this and what does this translate to I will just write it a little differently. Let just divide by 2 and this will give us 1/2 vd transpose I vd.

I am just putting the identity matrix in between-+-vw transpose*vd. We could have written this anyway right. This is the same as writing so why I am writing it in this form, I am trying to bring it to the canonical QP form quadratic programming formulation right. So what is your LP to remind you is f transpose x such that Ax=B, you can also have Ax>=B whatever. The QP formulation is similar, it is 1/2 x transpose Ax+B transpose x or more correct terminology would be 1/2 x transpose Qx+your good old c transpose x.

Why is this form important because that is what every solver will use right? So every solver will expect arguments in this form.

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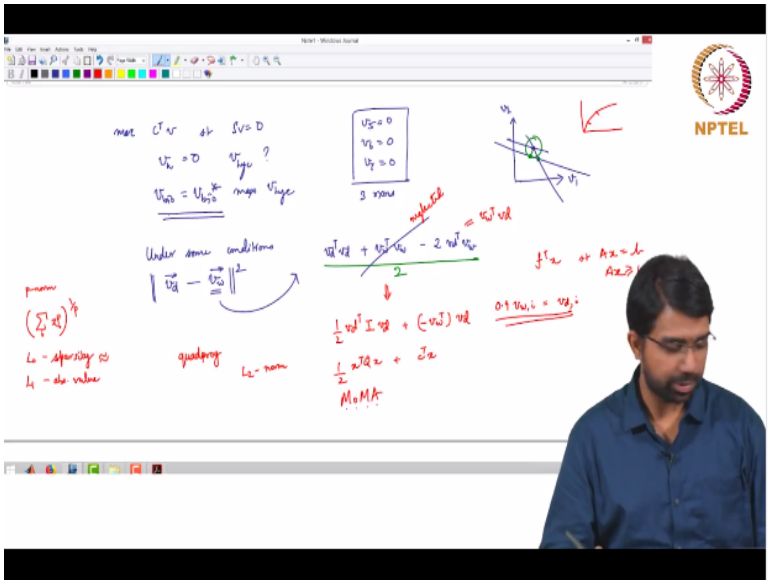

So let us go back to matrix now **"Professor - student conversation starts."** I is the identity matrix which is same as Q. So you will need to give an identity matrix to MATLAB or whatever quadratic programming solver you are using, we give an identity matrix and here you will give the negated version of the wild type flux.

It is not 0, I am just ignoring it. It is just a large positive quantity. I do not have to worry about optimizing it. If I am going to optimize x square+4 I might suggest x optimize x square, it is going to be giving me the same result. Yeah this is not 0, this is neglected. So there is one catch here right. When you say minimize the change, you are essentially trying to do this geometric distance right.

You are seeing this is basically vw-vd norm of vw-vd or what you would call the l2 norm right. What is p norm? This is the p norm, so what is l0? So L0 talks about sparsity, l1 just absolute value, l2 is your normal vector Euclidean distance essentially. So these are the more important norms. Yes, yes so that is the objective, the objective function itself changes and what is l infinity, maximum value. **"Professor - student conversation ends."**

It is biased towards the maximum value in the vector, everything else will be discarded right when you do it to the infiniteth power, so these p norms are interesting important. So what I am building towards is now we are saying that you will potentially be okay with the solution where let us say you know for argument sake let us say this is the distribution that you get right so every flux has changed by some 10% lower as moved in this direction right.

But the problem with that is what does it mean biologically let us come back to biology. It means that biologically every flux has to change by 10%, this is a lot of effort for your cell right. It has to change the levels of so many enzymes and potentially right it could if it is in a particular zone it can be a passive regulation. So if you are on this range of the Michaelis-Menten curve, the regulation is easy.

You just go up, go down, you linearly change right. If the substrate concentration goes down, you can quickly change but anyway that apart if you want to achieve this the cell must do some significant regulatory machinery change say stop this, stop this, stop this, increase that increase that something of that sort which is a lot of work. So another group of scientist suggested that instead of minimizing the l2 norm why do not we minimize the number of significant changes which is approximately this but not exactly.

"Professor - student conversation starts." Number of changes, I am just talking about the number so how sparse is that vector, I remember we also briefly discussed this and we were looking at network reconstruction right. Can you find a sparse reconstruction from your microarray data right? We say you know some xia sigma wixi where gi is sigma alpha I gi and we will find a sparse alpha vector that will map the network right. **"Professor - student conversation ends."**

So this technique that we just saw is called so it is spelled with the small r, capital O, minimization of metabolic adjustment.

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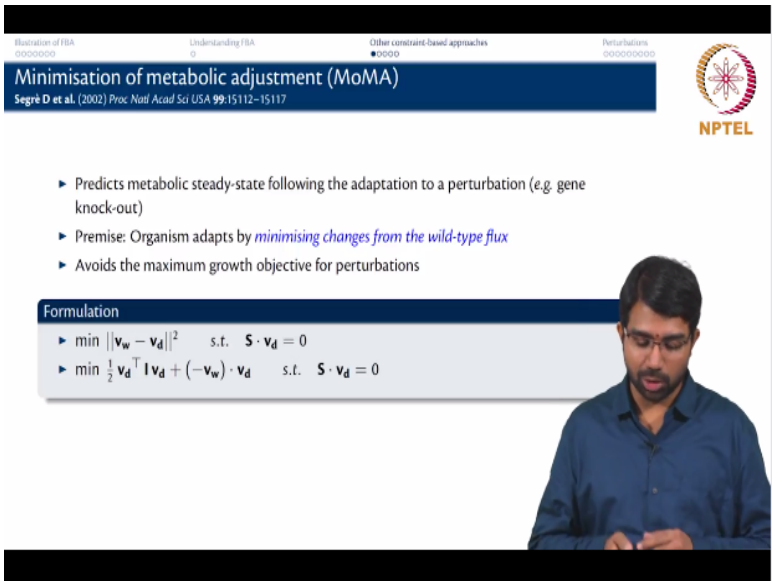

That is l2 norm. So the idea is this method is good at predicting metabolic steady-state following the adaption to a perturbation like a gene knockout. Premise is that an organism adapts to any stress or any perturbation by minimizing the changes from the wild type flux and this avoids the maximum growth objective function which is where we started. We said to delete a few genes and then say it write a maximized growth seems to be a harsh ask of the cell.

The cell may not be doing that, so the formulation is this. You remember of course sv=0 always, inviolable stoichiometry constraints. We are talking about steady states so there is some change you inflicted like a deletion. Do you have a new steady state or are we still in the transient state right? That is a good question, we will come back to that in a moment.

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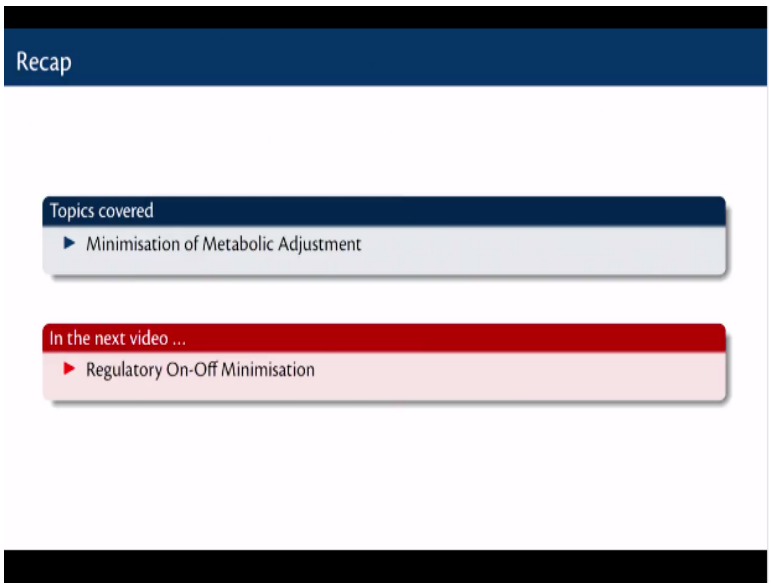

In this video, I hope you got an introduction to this interesting technique known as minimization of metabolic adjustment. It is also very useful when you want to fit experimentally measured fluxes or when you want to see if your model can admit or fit the experimentally measured fluxes. In the next video, we will look at a related technique known as regulatory on-off minimization.

So both of these techniques try to minimize the differences from an original flux vector which may be obtained either through experiments or through FBA and have different premises for going about what they do.