Computational Systems Biology
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Lecture - 59
Flux Balance Analysis

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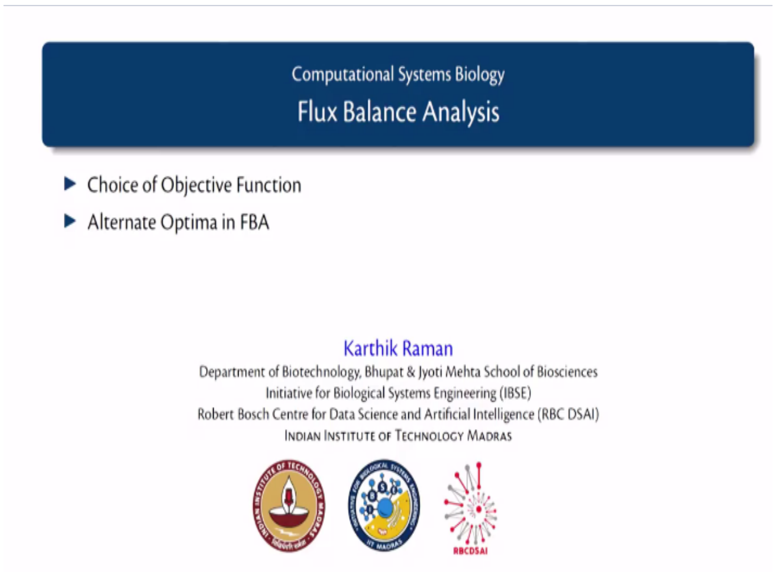

In this video, we will continue with flux balance analysis and we will discuss the choice of objective function in detail, and also understand a very interesting concepts of how they are Alternate Optima that are possible in flux balance analysis or in any you know optimization problem of this sort.

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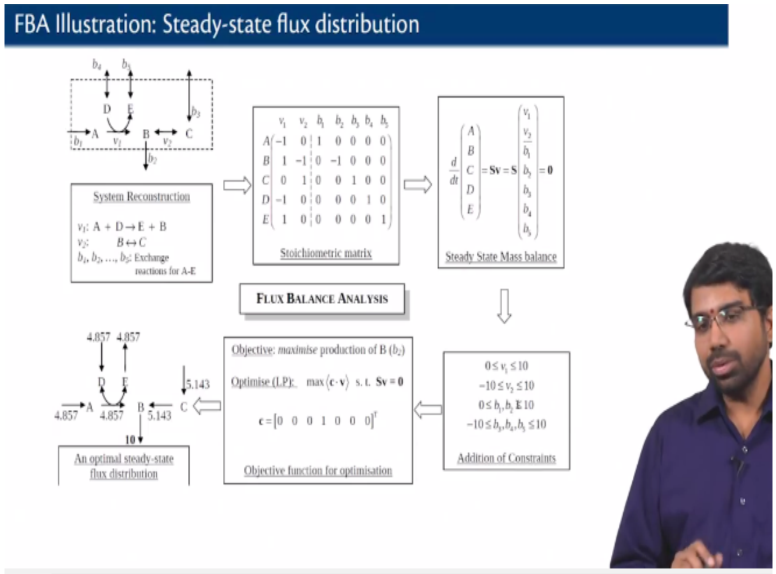

So now I want to draw your attention back to the fact that the solution is unique or the objective function value is unique whereas the possible flux distributions are many. So let us go back to the math of it where did we start in the previous module. Let us say this is v1, this is v2, this is v3; we put in on some linear constraints here and these constraints will basically give you what is known as a flux cone, right these are all your linear constraints, right.

And these are possible solutions and if you have more constraints maybe one of these is the optimal point and so on, right. But for each of these optima you can-- all of these may be equally good-- all of these maybe equally good optima, right. We can obviously say they have different values of v1, v2, v3 but they might end up having the same objective function. In fact, in linear programming they will end up having the same objective function.

If you have one best value that is what you will always get. So what does this mean if we go back here? So here you clearly got it. I will repeat it one last time. You can have 0000 10 55 10 10 10 as one possible solution. Or you could even have 10 10 10 10 10 00 as one another possible solution, these are two extreme solutions and a bunch of solutions in between, right. But beyond that what is it mean when we look at the objective function.

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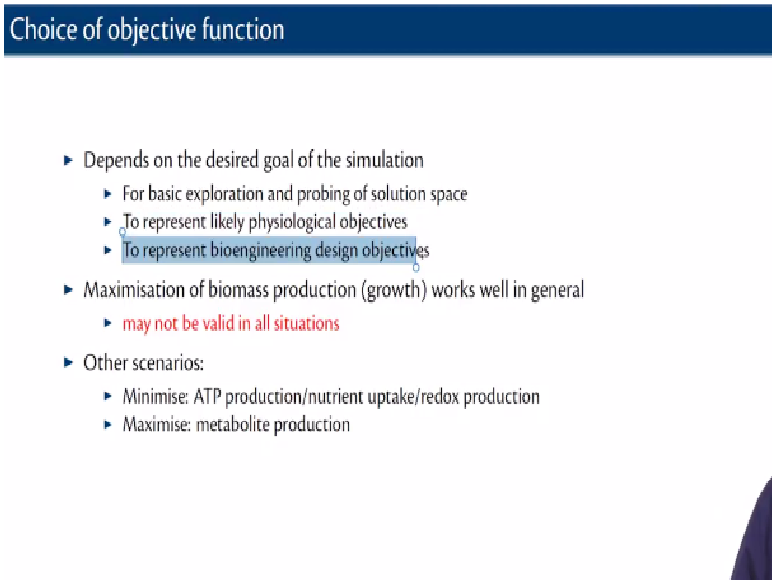

Let us say you are representing a are likely physiological objective or you are representing a bioengineering design objective.

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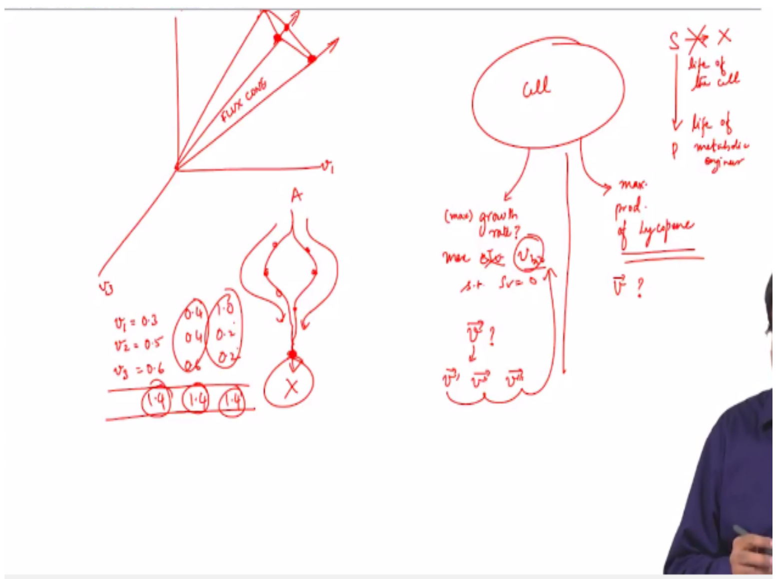

These are two classic cases where you will use FBA. Why would you use FBA? You have a cell and you want to predict what is its growth rate in a particular medium, you can use FBA, right. You compute max C transpose v that is basically some v Biomass such that you get the max possible growth rate, and under ample nutrient conditions usually the cells grow at their maximum growth rate, so this you find that this usually agrees very well and practice.

The other would be max production of let us say Lycopene which is some secondary metabolite and important nutraceutical and so on. You will invariably see that, so somebody once told S to x is the life of the cell, okay Substrate to Biomass, S to p is life of metabolic engineering, right. The cell wants to do S to x but you want to somehow pull it and do S to p. You do not want to totally kill this off to-- the cell is dead what are-- you cannot have any product.

So you want an strike an optimum somewhere here, right. But now if you say maximize production of Lycopene what is the use of the flux distribution that you get here versus the use of the flux distribution that you get here. First thing, this flux distribution if you multiply it with your objective function you will get the growth rate the correct growth rate, but you already have been convinced that you can have—Or let us use, you can have many equivalent flux distributions, they are all equivalent they are not equal but they are all equivalent.

They will all give you the same Biomass. This means that the same reaction can vary in flux can occasionally admit more flux or less flux but still have the same Biomass. So they can compensate, very simple example would be, let us say you have A x, this is one pathway, this is one pathway.

So all the flux can go like this; all the flux can go like this or some fraction can go in either way and you can still get the same output, right. So you can have different values for the flux distribution different flux distribution that compute the same growth rate in practice. Does that make sense? So let us say, and let us say your objective function is maximized v1+v2+v3 and this was a solution that you got, right.

So your function value is basically 1.4. There are obviously other solutions that are possibly you can have 0.4 0.6 1.0 0.2 0.2 all these will basically compute the same a optima which is 1.4. So this may mean that you know that more flux is going through this branch less flux is going through this branch whereas this might be in the more-- all the flux is going through this branch and very little is going to this branch and so on, right.

So in different scenarios this is going to be the same in an LP whereas this can vary. So in other words you are very confident of the FBA prediction the growth rate prediction from FBA whereas you are not that sure of the flux distribution that you obtain from FBA. It is only one of the many possible flux distributions, so there are ways to-- so one way you can say is if you want to further constrain make it a unique distribution which is more likely-- you can say can you find min?

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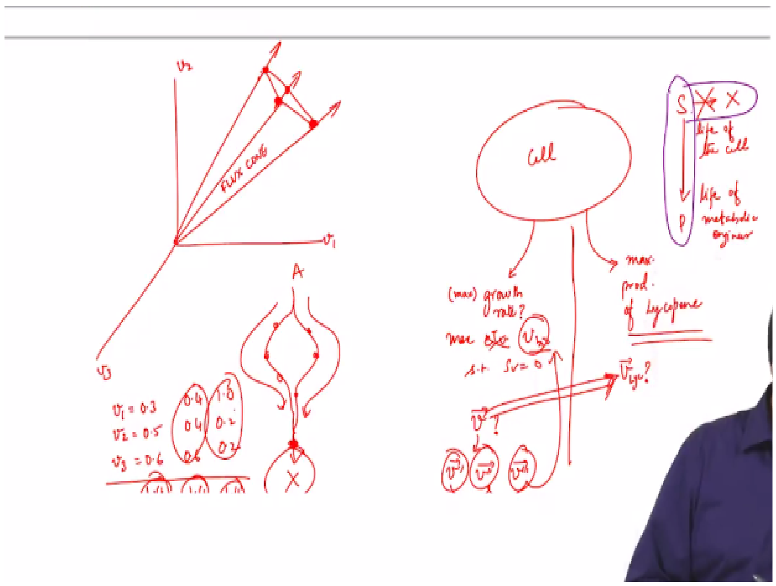

Minimize-- minimize the sum of all fluxes. In fact, if we did this on this problem you would basically get 0000 10-10-10. **“Professor – student conversation starts”** (()) (08:49). No, no, no. So this is an additional constraint. This does not replace, maximize C transpose x; maximize C transpose v. So you say maximize C transpose v and of now when you do this you might get many vs but the same value for C transpose v, same value of objective function, is that clear?

C has only non-zero term. See, that is in example that is not usually the case. So in-- but even in this case-- so that is very good right (()) (09:24) the 0s can multiply anything right. (()) (09:31) so that flux in the vector. Yes, yes okay, fair enough yeah. But-- so but it is very easy to imagine that C*v1 is also equal to some let say some 0.8 is your growth rate; C*v2 is also, this is v1 v2 I need to use slightly different notation, right v1 v2 are element we will consider. So 0.9 and C*v triple prime may also be 0.8. **“Professor – student conversation ends”**

But that is so simple because there are so many, C has so many 0s then I can multiply with many numbers it is still not going to affect your final dot product, right. But anyway that is digging into the nitty-gritties. But the other thing is on top of this—this is like the example I was telling you in the morning; solve x+y=10 such that you also minimize x-y or something.

“Professor – student conversation starts” In this case you take the--**“Professor – student conversation ends”** So then it will immediately give you-- so x+y still target many solutions 10 0; 3 7; 5 5; 7 3; 0 10. Now if you want to minimize x-y it becomes this. So of all the flux distributions that you get, get me the one that has the least absolute some of the fluxes or the least number of non-zero fluxes. We will come back to this at a later stage. It is a very interesting point.

So this is in fact called L1 norm minimization. We will come back to this in much greater detail at a later point. So now to come back to this a very interesting consequence of this is, what does it mean, when I say to represent a bioengineering design objective. It is the same as saying maximum production of Lycopene, right. So once again let us repeat this. What does this mean?

These are possible states of the cell. This means that reaction 1 in the cell is going to go at the rate of v prime element 1. Reaction to in the cell is going to go at the rate of v prime element 2 and so on, right. So this means that the final growth rate is going to be v bio but it can be any of these possible configurations the cell can take. What does this mean on the other? I say maximize production of Lycopene.

It tells you what is the theoretical maximum Lycopene that is producible by the cell. What about the flux distribution? Can you attach any significant to it? **“Professor – student conversation starts”** No, you have to change yourself. Potentially, right. **“Professor – student conversation ends”** So you have, so currently what FBA will give you is it will give you one configuration of the cell which can give you the maximum Lycopene production.

We can now see how far that is from your current configuration. So you can say this is your current configuration and this is the you know alternate configuration and how far are these two distributions, right. So potentially you want to read reroute you want to induce provide suitable inducements to the cell in terms of our expressions or knockouts to pull it closer to this—you know desired reality.

So this is the desired reality, right. More of the substrates going towards your product of interest then towards the sales product of interest, so is that clear? So it is very important to understand that there are alternate optima, okay. So in any modelling exercise this is important to understand that to interpret your to be able to interpret your results. So with confidence you can say that my FBA solution is my expected growth rate of the cell under whatever nutrient conditions we have specified, right.

Whereas the flux distribution is one of many possibilities, we do not know which one of them the cell might actually be inhabiting so to speak. But when you do the same thing for say like Lycopene or some secondary metabolite it turns out that the solution that you get maybe one possibility that will give you maximal Lycopene and the one usual part is whatever max Lycopene you get is the theoretical maximum.

If you know that your cell your current biotechnological process is already producing 90% of that or 95% of that you may not want to worry about it, right. Because there might be some non-ideality and this is anyway no model is perfect, okay. But on the other hand if your current biochemical—bioprocess is producing at say 60% of the theoretical maximum, the very fertile ground for further investigation to see what kind of manipulations you can employee to get the cell to produce more of Lycopene or whatever product of—

You should be able to quantify that, maybe a putting in a gene deletion couple of over expressions I can simulate that. We will see how to do that in like in immediate next class.

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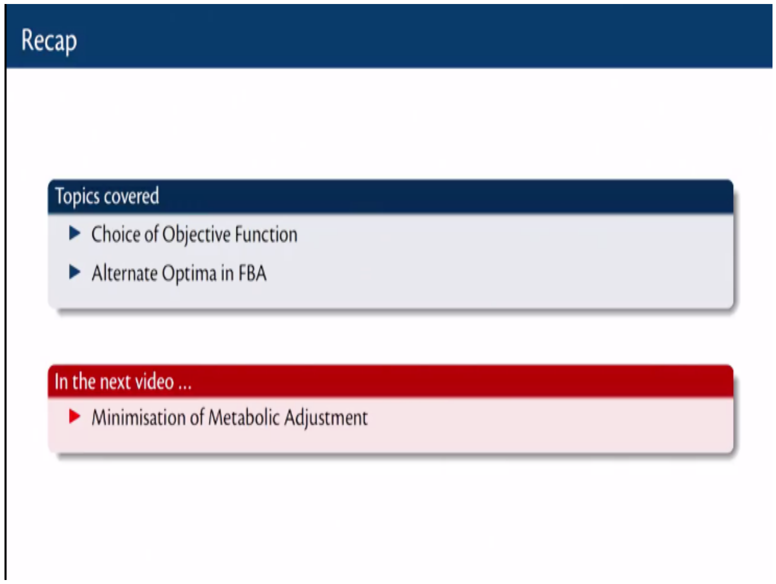

In this video we had an overview of how we go about picking the correct objective function be it for over producing a metabolite or maximizing the growth and so on. And we looked at the concept of Alternate Optima in Flux Balance Analysis. In the video, we will see how we can sort of circumvent and the need for maximization of growth rate and use a slightly different objective function which turns out to be quadratic.

So this technique which we will discuss about next class is known as Minimization of Metabolic Adjustment.