Computational Systems Biology
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Lecture - 74
Elementary Modes

In today's video, we will continue with elementary modes and we will try to understand or fixate these concepts with the help of a slightly more involved example, again a simple one, but having a few more reactions than what we saw yesterday.

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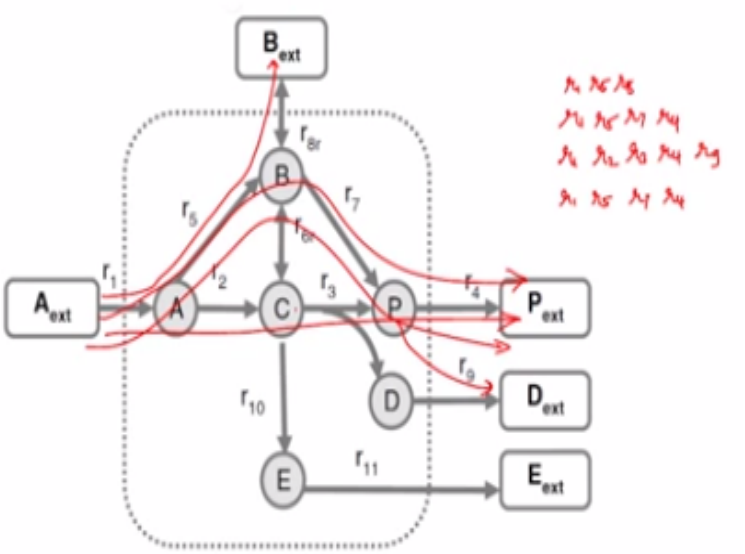

Okay, can we identify the extreme elementary flux modes in this example. **"Professor – student conversation starts"** Where do we use these elementary flux modes in extreme pathway. This is only useful. It is nothing like that. The thing is extreme pathways are easy to understand in terms of basis vectors of the flux ways and extreme pathways are easier to compute. **"Professor – student conversation ends"**

Elementary flux modes are little harder to compute, but both of them are relevant. We will see some used cases in the next slide. For now, can we just try and evaluate, identify the EFMs and EPs in this diagram. Now, you can actually write down the elementary flux modes in extreme pathways based on the reactions. Let us even try to trace them out first. This will be an elementary flux mode as well. This will also be an elementary flux mode.

“Professor – student conversation starts” B to P will be an extreme pathway. **“Professor – student conversation ends”** This is an interesting pathway okay. This is the first extreme pathway. This is R1, R5, R8. Then, you have R1, R5, R7, R4. Then here you would have even this, let us start with this R1, R2, R3, R4. Is that going to operate in steady state? D will accumulate, means to have R9 as well.

“Professor – student conversation starts” Then there is a possibility for E also get included. No, this is a single reaction. But, oh, it is like that okay, okay, okay. Oh. That is the catch. **“Professor – student conversation ends”** Of course, you have this reaction as well. So this will be R1, R5, R7, R4. Only when you have R3, you will need R4 and R9.

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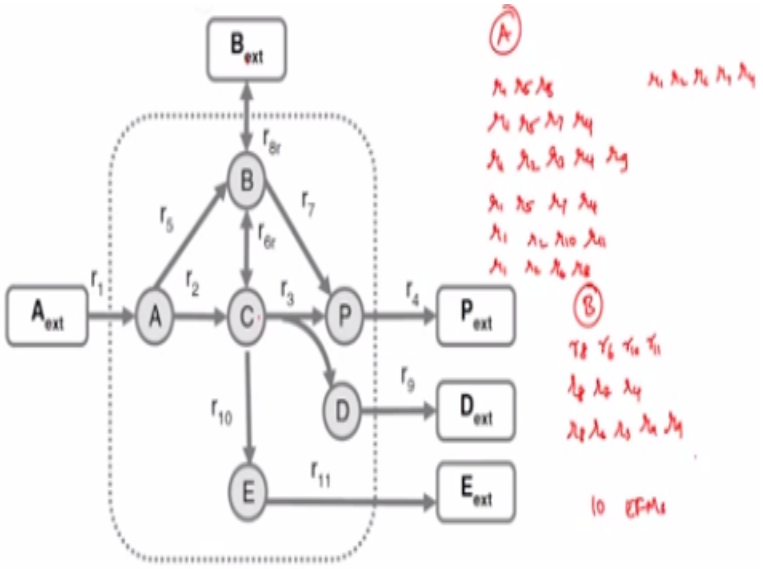

Next you can have, let us try to clean up the pathways, so the next pathways we will have is, let us start with B. **“Professor – student conversation starts”** A, C, E, X. Right. So, R1, R2, R10, R11. **“Professor – student conversation ends”** These are all starting at A. Now, let us look at B. You will have R8, R6, R10, R11 or you can have R8, R7, R4, R8, R6, R3, R4, R9. We have R1, R11 is there. R1 to R11 you can go like this that is taken care of.

You can have R1 to R3, R4 that is taken care of. It also includes R9 or you can have this R1, R2, R6, R8. You can have R1, R2, R6, R7, R4. You will find it is easier to enumerate the elementary

flux modes, not the extreme pathways. Extreme pathways you will have to like see if they are decomposable and so on. You will find that some of these can be decomposed and so on.

"Professor – student conversation starts" I think whatever we wrote now is elementary flux mode right. All these are elementary flux modes. Some of them are also extreme pathways. For example, this is very well an extreme pathway, this is very well an extreme pathway and so on. But, there are some non-extreme pathways as well. Sir, I am not clear what is extreme pathway. Extreme pathway will be it is non-decomposable. **"Professor – student conversation ends"**

For example, this will be an extreme pathway and in an elementary flux mode and an extreme pathway, this will be an extreme pathway and an elementary flux mode. But, this will be only an elementary flux mode, not an extreme pathway because you can write it out in terms of this extreme pathway and this extreme pathway. Linear combination, in fact 1 + 1, simplest linear combination. Let us see have we missed out anything else.

Let us take a careful look. This is done, this is done, this is done, R1, R2, R6, R8 is done. R1, R2, R6. We have 3, 6, 7. We have 10 EFMs identified. Let us see if that is correct.

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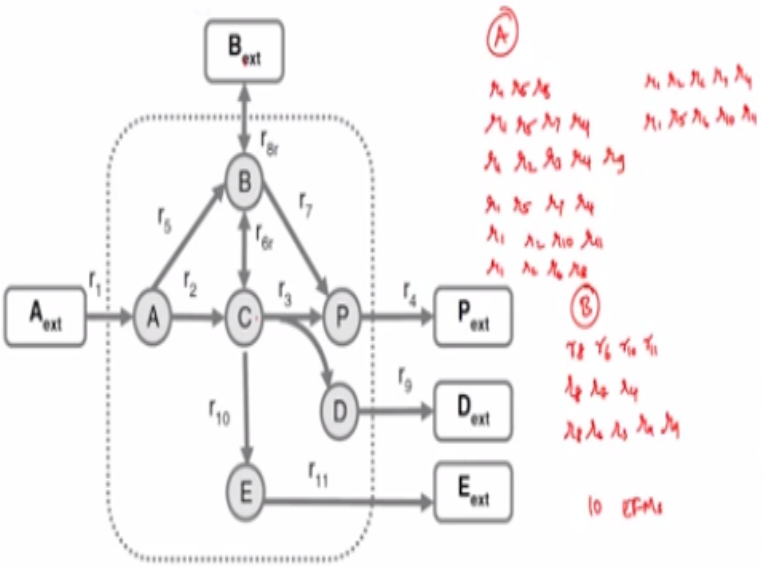

There are 11 EFMs. You just seemed to have missed out one. What is it that we missed out? Is this there R1, R5, R6, R10, R11. That is one we missed.

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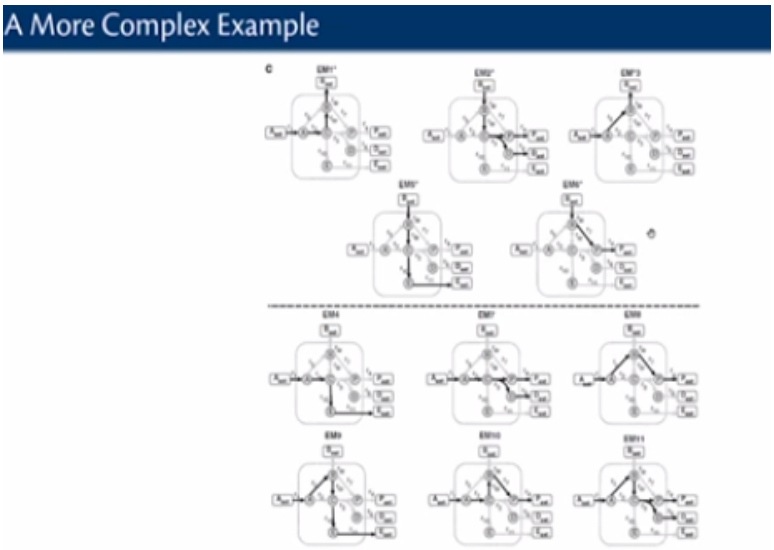

Now if you see, which of these elementary modes and which of these are extreme pathways? All of these are elementary modes, which of these elementary pathways as well? **"Professor – student conversation starts"** First one. The ones at the top. Because if you add them up you can get those in the bottom. **"Professor – student conversation ends"**

Let us see, EM8 is EM3 + EM6. You add these two you get this. Like that you can setup all of these. **"Professor – student conversation starts"** Sir, are all EMFs just path between. Paths between, they are not paths. They have to (()) (08:35) stoichiometry and things like that. They are not just graphical paths. **"Professor – student conversation ends"** Because from C you have to produce P and D.

Here you do not have an example of that sort, but imaging of that reaction were reversible, you need both P and D to form C, which is never taken care of in graph theory, unless you do it very carefully. The substrate graph would not take care of it. In a bipartite graph or hypergraph scenario you might be able to do it. Here you also admit stoichiometry and so one. We have just been looking at a simple example where we are identifying it visually.

But this actually takes the account stoichiometry as well. If you have one A producing 3 B, you have to make sure that the 3 B is taken off into other reactions and so on. One reaction is

possible, but when you have multiple reactions, the 3 B will produce 3 C, say 3 C reacts stoichiometry in a different stoichiometry with something. There is 3 C + D doing something or like C + D doing something, we will need 3 D coming from somewhere else. You have to honor all of that.

The algorithm is quite complex. All of them are very slow and involve literally some sort of exhaustive enumeration and so on. Most of the EFMs algos are relatively slow. It is actually not the question of the algos being slow, the problem is in most large enough networks, you have got an astronomical number of EFMs, talking about like billions of EFMs and millions of EFMs and things like that.

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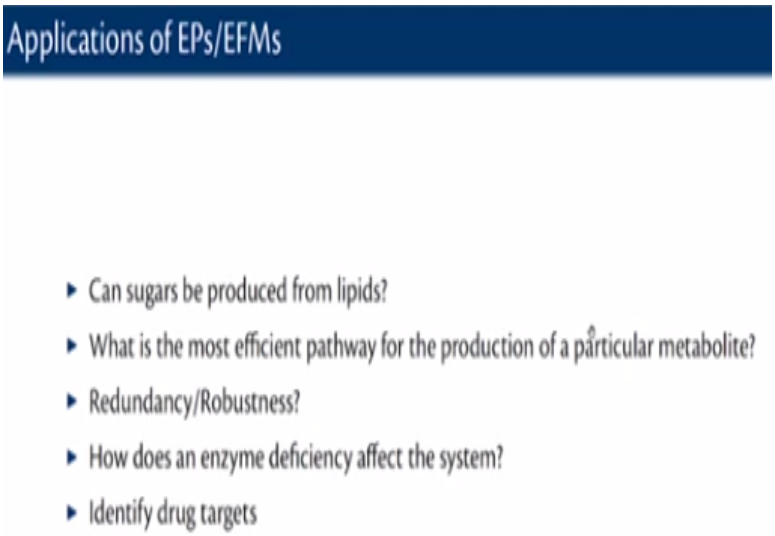

So, there are many interesting applications where EPs and EFMs. So, can sugars be produced from lipids. What is most efficient pathway for the production of a particular metabolite. Like you can look at stoichiometry and things like that. If I use this EFM, I will get X amount of product per Y amount of substrate. If I use this EFM, I will get Z amount of product per X amount of substrate and so on, how redundant.

Do you have multiple EFMs between a pair of compounds? So, that will mean it is pretty robust, because you need to disable both the EFMs to stop the production of the next compound. How does enzyme efficiency affect the system, can you identify drug targets and so on? So if you have

an essential EFM, many of the enzymes in that EFM will be potential drug targets, assuming it is a pathogenic organism.

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This is Steven Schuster, he was one of the pioneers of the elementary flux mode approach and as he says you know it is also useful in determining mineral media and detecting futile cycles and gap filling and so on. The important thing to notice, this is again a very useful technique simply because it does not ask too much information. It only relies on the stoichiometric matrix which you already have.

"Professor – student conversation ends" So you can use this to get minimal genome. You can potentially use this to get minimal genomes. The union of all you know, but finding EFM is already complex. The union of all your essential EFMs will be a minimal genome. No, or extreme pathways. Or the EFM involving biomass. The minimal EFM involving biomass will be a minimal genome. The union of all EFMs involving biomass. No, no, no, that will need not be minimum, if you have one EFM producing biomass your job is done.

The smallest EFM that produces biomass, yes. **"Professor – student conversation ends"** In today's video we covered another example to understand elementary modes. They are slightly more complex example and I hope this has now given you a picture of how and picks elementary modes from a given metabolic network. Of course it gets a lot harder to do it visually the way we

have been doing it on a more complex network and there are many efficient algorithms to do the same.

In the next video we will move on and start looking at applications of constraint base analysis. I will introduce you to some applications, particularly how we go about predicting drug targets in particular metabolic pathway in tuberculosis.