Computational Systems Biology
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Lecture - 73
Elementary Modes

In today's video, I will introduce you to this interesting concept known as elementary modes which exist in metabolic networks. We will look at the definitions and then we will also look at a couple of simple examples to understand the concept of elementary modes as well as extreme pathways. We will now look at another concept which is that of elementary modes which are fundamental properties of metabolic networks and let us see how they are useful in making different conclusions about metabolic networks.

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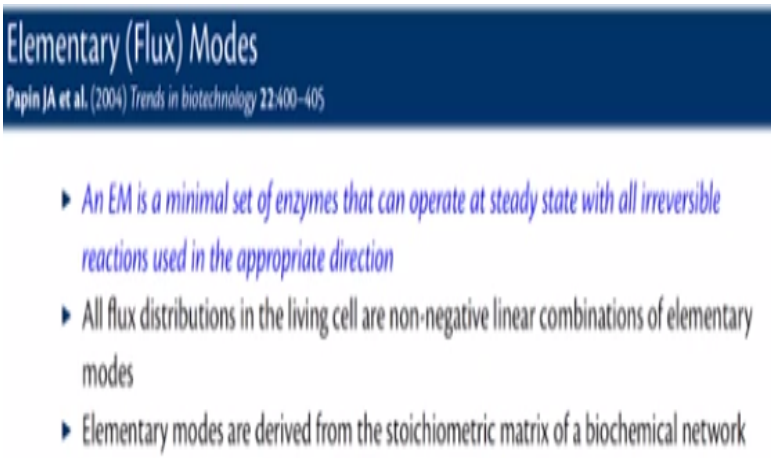

What is an elementary mode? An elementary mode is a minimal set of enzymes that can operate in steady state with all irreversible reactions proceeding in the appropriate direction. Reversible directions can obviously go either way, but irreversible reactions all of them should be proceeding in the correct direction. This is a minimal set of enzymes. All flux distributions in the living cell are some non-negative linear combinations of the fundamental elementary modes.

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$S(v) = 0$

$\alpha_j \leq v_j \leq \beta_j$

...

This also tries to go back together with another concept that we will see shortly, to back to this concept. You have some flux cone; you can think of characterizing every point in the cone based on some fundamental fluxes. Any vector in a space can be written in terms of its basis vectors. So, if you have the basis vector for this entire cone, any valid flux distribution can be written in terms of those basis vectors and so on.

This is a related concept; this is what we will see in the immediate next slide. In fact, it is on the left hand space of the stoichiometric matrix. You are saying Sv = 0, these are all the Vs that satisfy Sv = 0, of course all the other conditions as well. It is a part of the space of all possible flux solutions. Elementary modes are basically derived from the stoichiometric matrix directly, but they are computationally very expensive to compute.

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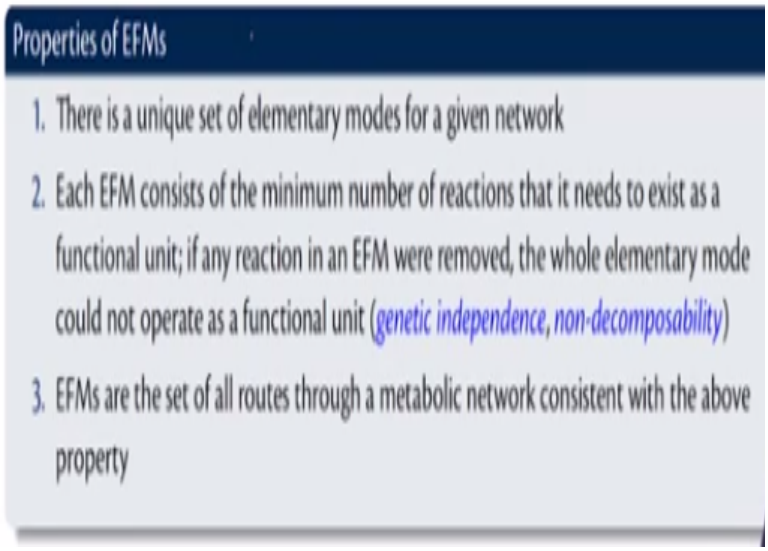

What are the properties of the EFMs? First is there is a unique set of elementary modes for a given network and each EFM consists of the minimum number of reactions it needs to exist in steady state as a functional unit. By definition therefore, if you remove any reaction from an EFM, the elementary mode cannot operate. So, it is a sort of chain of reactions, you can think of any cell to be some combination of EFMs.

"Professor – student conversation starts" this is for biomass. This is for anything. We will actually look at an example. **"Professor – student conversation ends"** There is some notion of genetic independence and non-decomposability. You cannot breakdown an EFM into anything smaller and they are also genetically independent, meaning like there are different genes in different EFMs and so on.

EFMs are the set of all roots through a metabolic network which are consistent with the above property.

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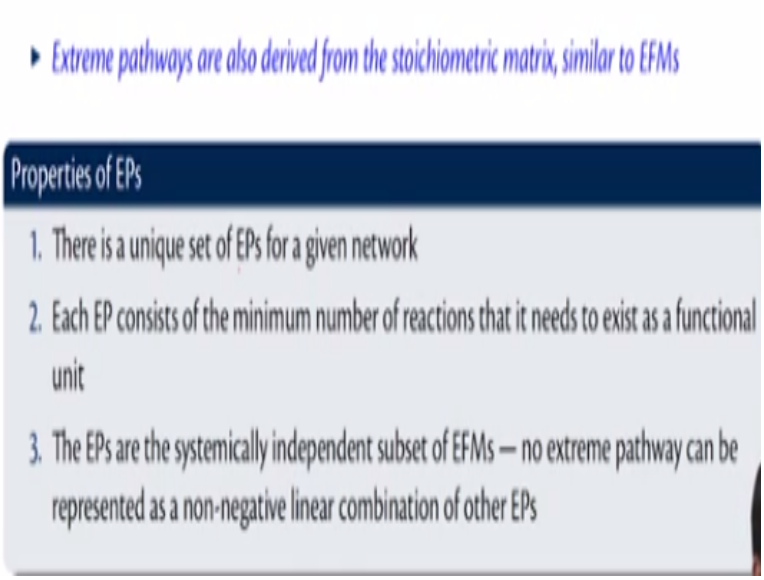

There is also this other concept of extreme pathway. This is mathematically easier to understand in some sense. They are derived from the stoichiometric matrix similar to EFMs. There are unique set of EPs for a given network. Extreme pathway again consists of the minimum number of reactions at least to exist as a functional unit and they are the systemically independent subset of EFMs. No extreme pathway can be represented as a non-negative linear combination of the EFMs. These are basically basis vectors of the flux phase.

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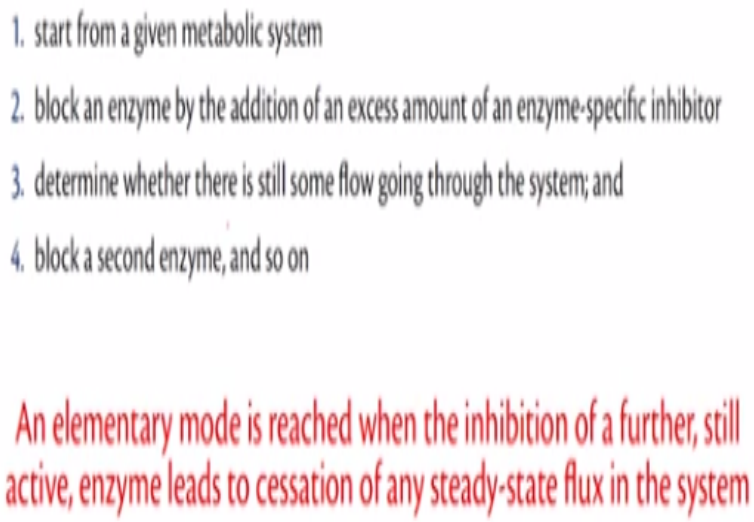

A third way to look at it is there is an operational definition. Start from a given metabolic system, you keep blocking an enzyme with you keep turning of an enzyme one by one and it there is still some flux going through the system, you keep blocking an enzyme and so on. An elementary

mode is reached when the inhibition of any other enzyme will lead to complete cessation of steady-state flux in the system.

"Professor – student conversation start" So entire (()) (04:58). It will become 0. This is not with the specific objective function if you see. If you go back to the example of pipes that we were talking about, this is just one series of pipes that can independently carry water. It is not dependent on any other pipe, the genetic independence criterion that we were talking about. Minimal genome has a goal. Here there is no goal as such. Here the goal is just that they are able to produce the last reaction.

What is the last reaction? Some steady state subset of enzymes which carries flux it will just become clearer when you look at the example. Okay. **"Professor – student conversation ends"**

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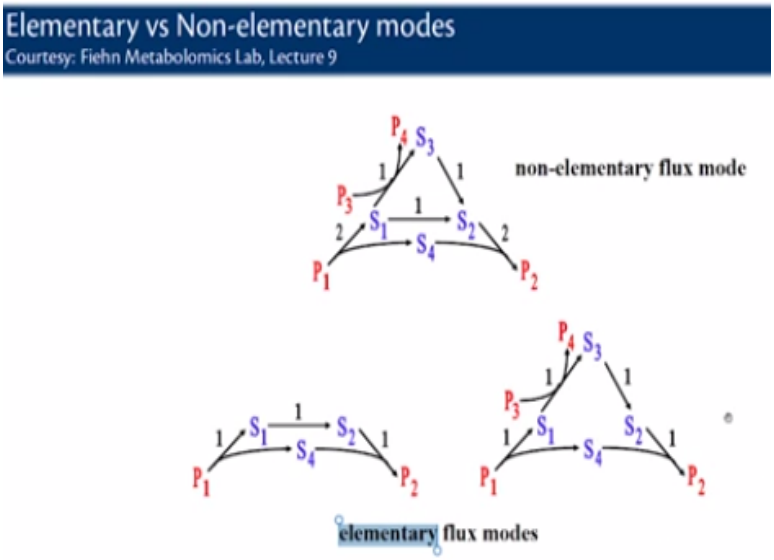

Let us look at this example. What is an elementary flux mode? You have P1, S4, P2, but this is not an elementary mode because P1 produces S1 and S4. So, there is a reaction where S2 produces P2, which comes from S1. This together becomes the elementary mode. This reaction produces something and these two metabolites are used up in this reaction to finally form this product.

You have three reactions in this elementary mode. You have P1 giving S1 + S4, S1 giving S2 and S2 + S4 giving P2. This is also an elementary mode where P1 gives S1 + S4, S1 + P3 gives S3 + P4, S3 gives S2, S2 gives P2. This is not an elementary mode because there are two subsets of enzymes that can carry steady-state flux, the two indicated at the bottom. You can decompose this flux mode in terms of these two elementary flux modes.

"Professor – student conversation starts" P1 to P2 same S4 parts present in both the elementary flux. P1 gives S4, S4 gives P2, again P1 gives S4. S4 does not give P2, it is S4 + S2 giving P2. This is how the reactions get written in a biochemistry textbook, it can be a little confusing, but you have to immediately catch that. P1 is S1 + S4, S2 + S4 gives P2 that is the next reaction. **"Professor – student conversation ends"**

It is basically some sort of one into another, which means like from one input to one output. Basically a biomass is never a single output. Your biomass is like several outputs, but you can think of a particular input to a particular output as an EFM.

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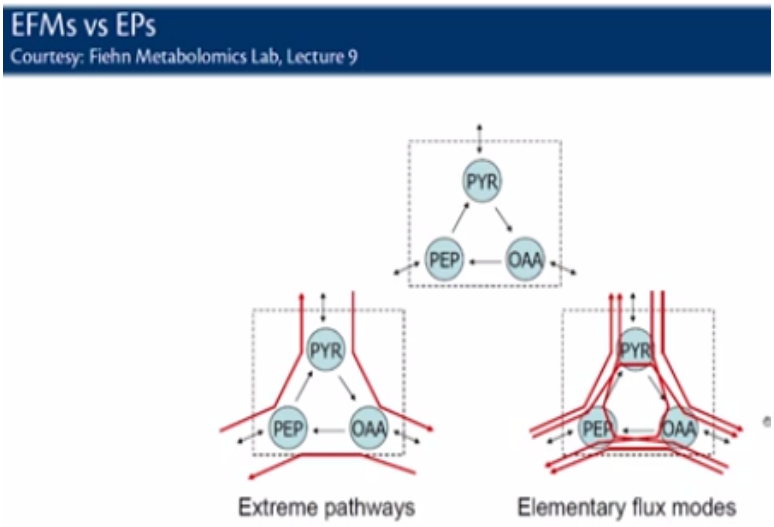

Let us look at one more example. Let us consider this example wherein we have PYR, PEP and OAA.

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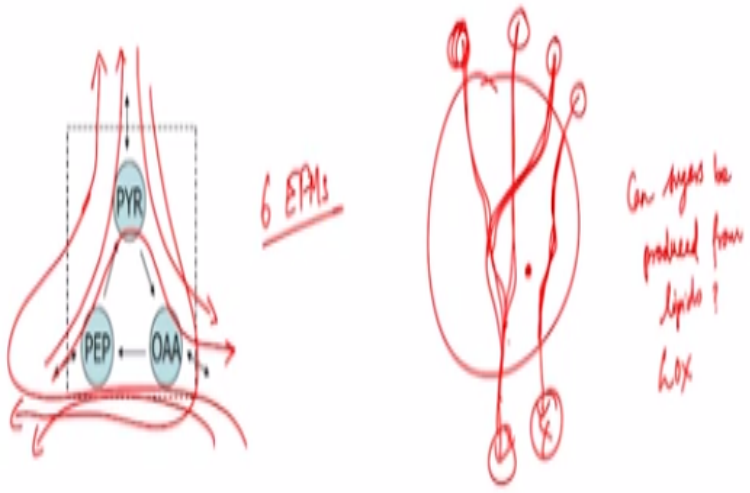

Let us consider this simple set of reactions. What are all the elementary flux modes? What is an elementary flux mode again? It can carry steady-state flux with all irreversible reactions going in the correct direction. Here there are three irreversible reactions and three reversible reactions. Now, how would you compute the elementary flux modes? How would you identify the elementary flux modes?

Let us start at PEP. It can start at PEP and go in this direction, that will become an elementary mode or it can start at PEP, go to pyruvate and then go here. Both the irreversible reactions are in the correct way. You can have similar for the other two. You can have something that goes like this, something that goes like this, and something that goes like this and something that goes like this. There are 6 EFMs. Every start and every end.

You can identify if there is an EFM beginning at any particular reaction and going all the way up to any other reaction. **"Professor – student conversation starts"** In the E. coli network you showed us yesterday, in fact those two pathways that were on. They would not be part of the same EFM. Synthetic lethal would never be part of the same EFM. Because an EFM is minimal in the sense you turn off anything in an EFM there will be no more flux through the system to the EFM, assuming that the EFM itself is essential. **"Professor – student conversation ends"**

Let us say this is biomass and there is some other non-essential pathway that is going on. This is still lightly an EFM, but it would not be even lethal. If this is not produced, may be nothing happens to the cell, but these may be essential EFMs. If you remove anything in these EFMs, it will be lethal.

"Professor – student conversation starts" So, in the case of a cell like this an EFM should be defined as any (()) (10:49) starts from outside. Yeah, so there is some source to some sink. So it cannot just be a network. No, no, because it has to be functional in a steady state. It cannot just like stop somewhere here. It has to go all the way. Because no steady state can stop within the cell. It all starts at your carbon source or something like that. **"Professor – student conversation ends"**

You can look at smaller EFMs, they do make sense, but in general this is how one likes to look at EFMs. You can look at smaller EFMs, for example one very interesting application of EFMs is that can sugars be produced from lipids. Opposite of this is the diabetics nightmare. So, all excess sugar in the body goes to lipids and so on and causes lots of issues. We know very well that lipids can be produced from sugars, can sugars be produced from lipids.

If so, then that can be used. In fact, you find that this happens in a lot of plants and all that. This was in glyoxylate shunt and things like that. It turns out that you can identify this very nicely using EFMs. Is there an independent pathway, which goes from sugars, from lipids to sugars? **"Professor – student conversation starts"** So EFM is something like independent pathways. Yeah. They are systemically independent. It does not rely on anything else to function.

So it is like IJK vectors like everything. Something like that. That is the extreme pathways. The one difference between an EFM and extreme pathway is that EFM could be decomposed. **"Professor – student conversation ends"**

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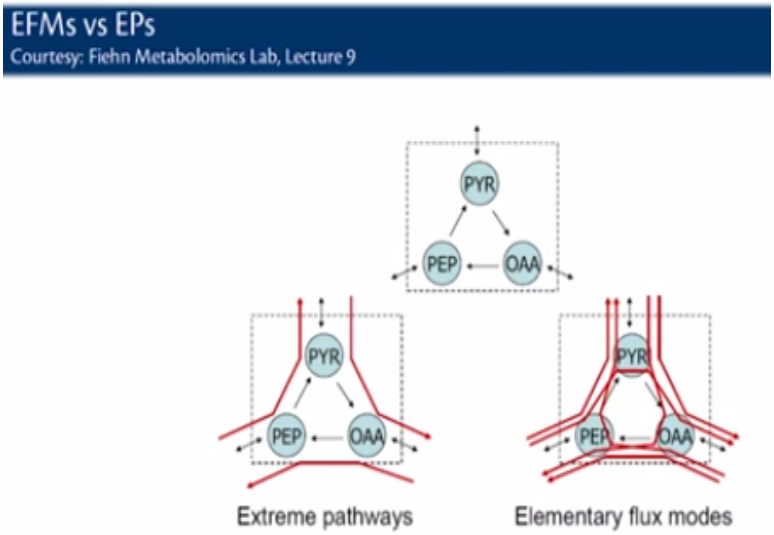

If you see this example there are only three extreme pathways. These are the only extreme pathways, because you add these two you get this EFM. EFMs can be broken down in terms of linear combinations of extreme pathways. An extreme pathway itself can never be broken down further into linear combinations or anything like that. This plus this will actually give you this. Linear combination of extreme pathways will give you EFMs.

Extreme pathways are simpler. EFMs can be a little more complex. Even here if you remove, this reaction is not there, so you will just have pyruvate accumulating. You need three reactions in any EFM. If you add these four reactions in the EFM and you deleted any of these reactions that is going to be an accumulation. It cannot work in steady state.

"Professor – student conversation starts" So same as extreme pathway, but if you take a combination of the extreme pathways, if you remove a combination of. If you remove a reaction from an extreme pathway, the extreme pathway also would not function. Exactly, so if you take an elementary console, which is a combination of extreme pathways, and remove reaction, you still have one proper flux here because that is an extreme pathway.

No, what is your example, you are looking at this plus this right. h. Remove those. This goes out because of that. This pyruvate going out. It is no longer part of the extreme pathway. The extreme pathway is this, this and this, the elementary flux mode. **"Professor – student**

conversation ends" This is one extreme pathway, this is another extreme pathway, the elementary flux mode is going to be this.

You cannot remove anything from that. Because pyruvate will accumulate or oxaloacetate will accumulate. If you remove this, oxaloacetate accumulates, if you remove this pyruvate will accumulate. You need this reaction which goes out, which is no longer there in the extreme pathway. This reaction is not part of the elementary flux mode. When you add these two extreme pathways, this reaction no longer exists.

In general, extreme pathways are simpler. Because linear combinations of them could be an elementary flux mode. In today's video, I hope you got a good introduction to the concept of elementary modes and extreme pathways, these are fundamentally connected with the flux space that is given by the stoichiometric matrix and we look at some definitions and also some examples. In the next video we will look at a slightly more complex example to fixate these concepts of elementary modes and extreme pathways.