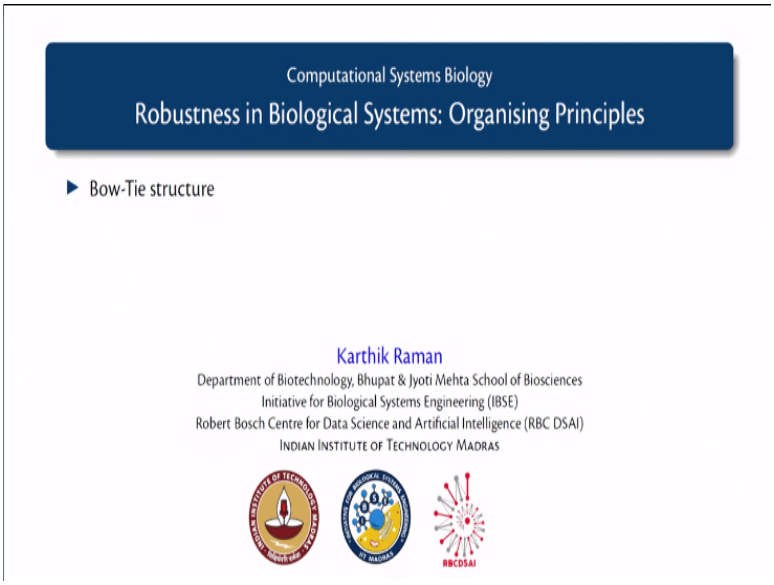
Computational Systems Biology
Karthik Raman
Department of Biotechnology
Indian Institute of Technology – Madras

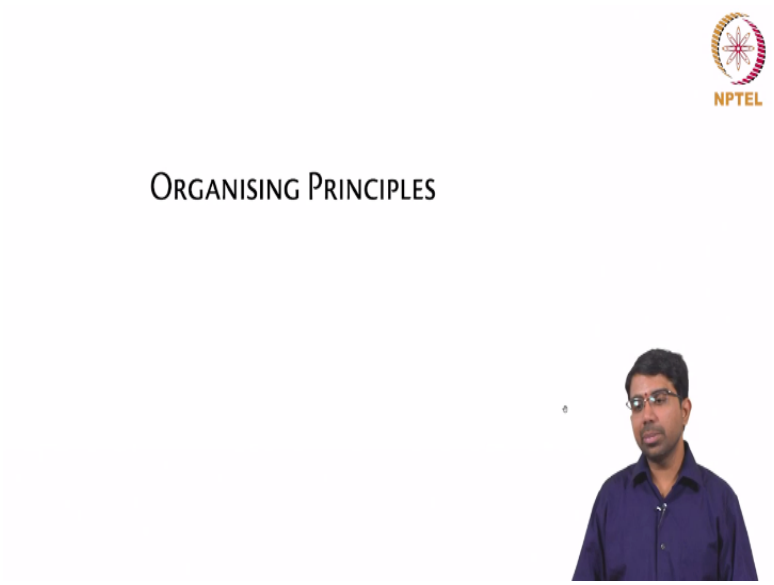
Lecture - 95
Robustness in Biological Systems: Organising Principles

(Refer Slide Time: 00:11)



In today's video, we will continue with our study Robustness in biological systems and we will look at the key organising principles underlying robustness. The most important of which is what is known as Bow-Tie structure.

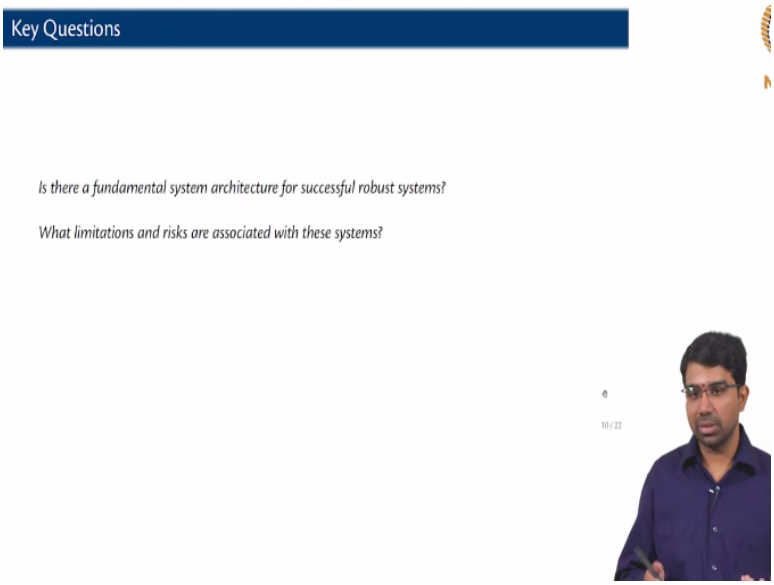
(Refer Slide Time: 00:24)



What are the fundamental organising principles of biological systems in general or robustness? "**Professor – student conversation starts"** Do you know of any design principle any organising principle so far what we have seen? So power was a very commonly observed in biology, why? we will see that exactly, right. "**Professor – student conversation ends"** Exactly, right so power was again connected quite intimately with robustness, right. Because the more number of you know hubs you have and so on, right.

So the – there are you know the hubs can manage the network much more efficiently in some sense, and there are several low degree nodes that will get attach to the hubs and so on and random failure does not affect the network has a whole so on and so forth. And we will see why this works out in reality.

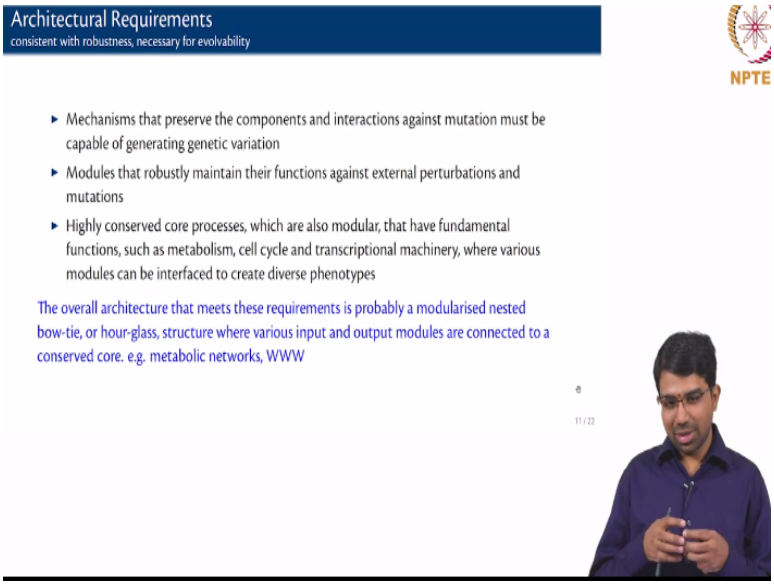
(Refer Slide Time: 01:11)



So the key question, is there a system of fundamental system architecture for designing robust systems? Okay. And if so, what are the limitations and risks associated with such systems? So we could probably answer a power law for this or scale free and what are the limitations and risks associated with the system? Targeted attack, right so that is the challenge. So if you see there is no blanket robustness or uniform robustness across a table, right.

There is robustness subject to something. So there is always you know a boundary for how robust something can be. The more robust you want you may be the more expensive it is to build such a system or you know maintain such a system-- biologically speaking it might demand more ATP more energy.

(Refer Slide Time: 02:00)



So what are the—let us put our wish list down. So within mechanisms that preserves the components and interactions against mutation to also be able to generate variations, right. This becomes a requirement when looking at biological systems. So you need components and interactions you need components you need mechanisms that preserves the components and interactions against mutations but they should also be able to generate some variations.

And that is what you have find right? So you have the same DNA whereas basically this is achieved in terms of a degeneracy you have, right. So DNA mutations generate variations they are also robust, one mutation may not change much, one mutation can change a lot as we have seen example say (()) (02:47) or something but in general the robustness is maintained. Modules that robustly maintain a functions against external perturbations and mutations as important.

And you typically notice that there are highly conserved core processes, modular processes that have fundamental function such as metabolism, cell cycle and transcriptional and so on where various modules can be interfaced to create diverse phenotypes. So there is this very famous quotation from Jacques Monod, somewhere in ‘40s or ‘50s where he said something like “Whatever is true for E. coli is true for the elephant,” right.

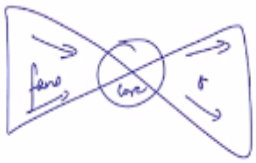
“Professor - student conversation starts” And-- do you agree with him or do you disagree with him? **“Professor - student conversation ends”**

So obviously there are many where one would agree with and there are obviously many points where one would disagree with. But if you look at spirit of statement I think Monod clearly understands that E. coli is different from the elephant, but there are so many things that surprisingly hold for E. coli and the elephant. You will find the TCA as the same Tricarboxylic Acid cycle and glycolysis is not very different from E. coli compare to the elephant.

But elephant will have like several more layouts of regulations there will be several more Glycogene Phosphor releases-- E. Coli does not even like Glycogene, right. But if you look at glycloysis, right it is going to be remarkably similar, right and this is—the core process that we are talking about here. So these are perfected modules, right. And these modules can play well very nicely with one and other.

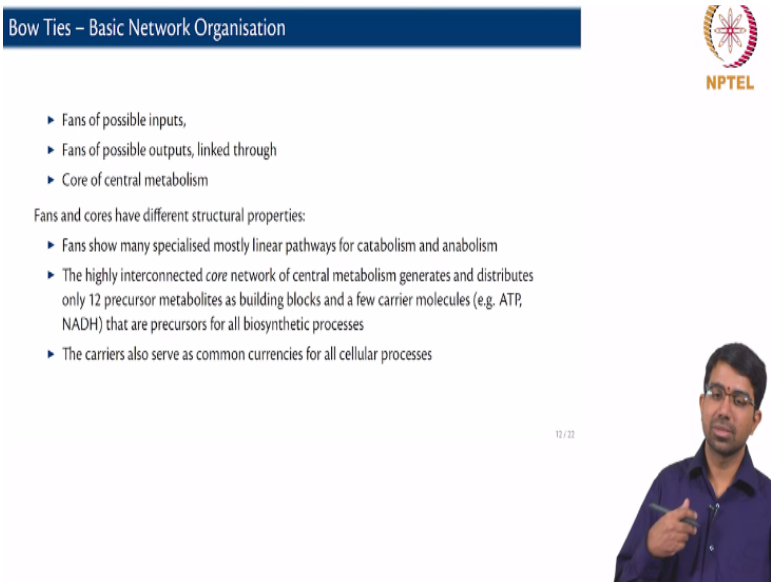
So it turns out that the overall architecture that meets these requirements is a modularised nested bow-tie, or an hour-glass which you know will where you know various input and output modules are connected via conserved core. So what is the bow-tie going to look like?

(Refer Slide Time: 04:36)



Right, this is the bow-tie, right. So this is your core and you can think of this as fans of input and output. Why does this work? Let us just see. So this happens in metabolic networks the World Wide Web and so on, okay.

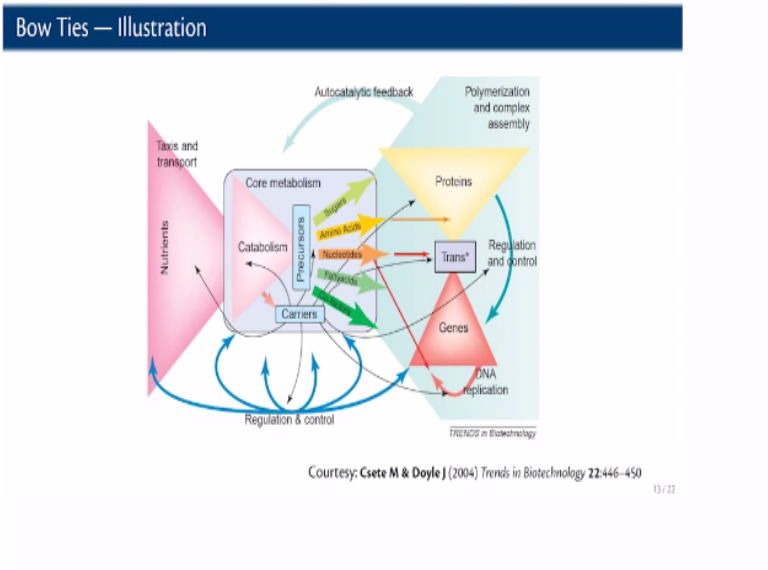
(Refer Slide Time: 05:00)



So you have fans of possible inputs, fans of possible outputs and a core link through a core, right. And what do you observe here? You find that the fans are cores are different structural properties. Fans are mostly linear pathways, right. So one place you will be breaking down catabolism; the other side you will be building up anabolism. But you have a highly connected core or central metabolism which is connected with a few molecules which repeat again and again and again and there it is highly interconnected.

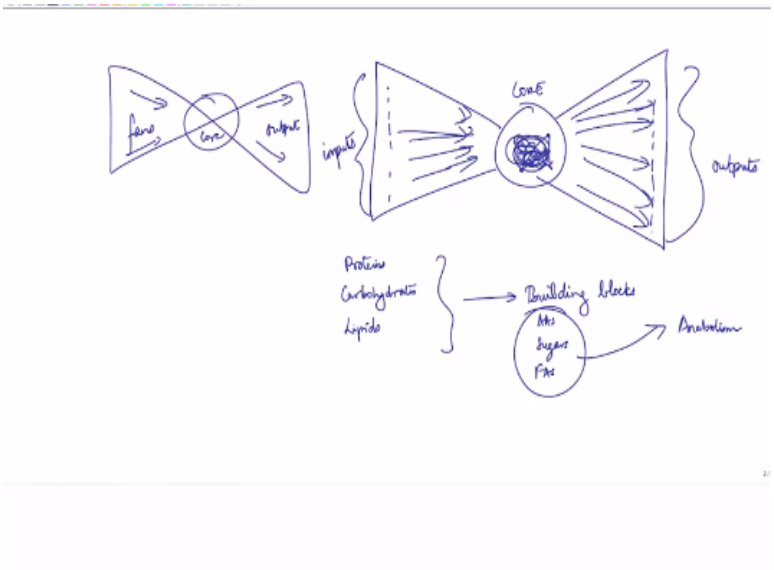
And these there are certain currencies the carriers that establish a protocols here, literally, you know so phosphate is the protocol for energy transfer, right ATP and so on.

(Refer Slide Time: 05:47)



So let us look at this picture it will be clearer. So you have several nutrients which are broken down and then you have a conserved core which breaks down these and builds and makes all these building blocks which then you know go towards much more specialized results. So let us just consider it again. Let us look at this picture; I will draw it little one nicer.

(Refer Slide Time: 06:13)



This look more like a bow-tie and this is a core, right. So one alternative for this is, you have some inputs here, you have some outputs, inputs connected across directly, right. From many of these inputs you can try to make one or more outputs of this. Is there a good architecture? But immediately seem no is the answer but why. Yeah, so if you have too many pathways like this, so if you remove one of these links so maybe you know you do not get this output or so on, right.

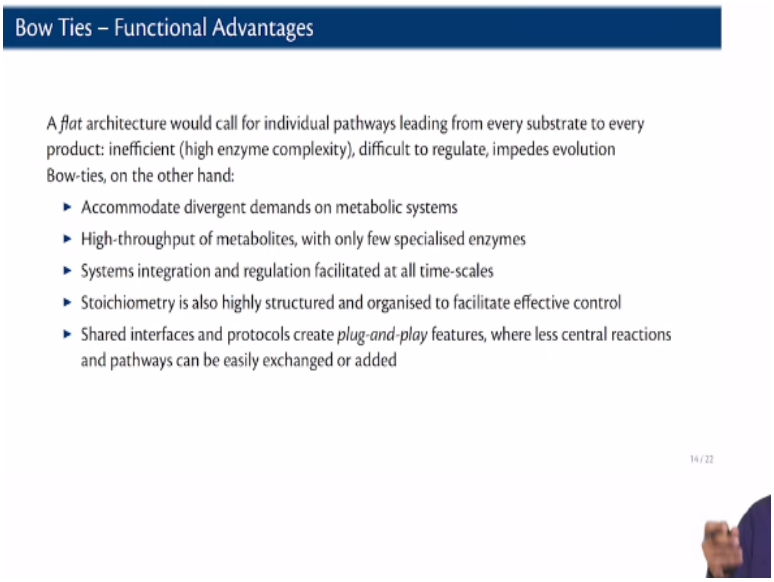
Or you know both of these get affected and so on and so forth. So this basically will not facilitated any regulation or more importantly any adaptation. You cannot, so this is going to be a very fussy pathway, right you remove one thing, you are going to-- or you could have a lot of redundancy which is going to make life even harder, right which is going to be much more expensive. So if you see how things inside the cell operate it is very interesting.

You take all your—let us just talk about metabolism for example. You will take proteins, carbohydrates, lipids and you finally pass them into the various building blocks essentially amino acids, sugars, fatty acids and then you build them again from the ground up. It is not like you take some, some palmitic acid in food and you can just convert it to Oleic acid directly by adding like couple more carbons, never happens, right.

What happens is just all completely broken down into all these fundamental building blocks and then built up. So the advantage you have now is you do not have all of these complicated pathways but instead you have linear pathways here and this is really complicated. The core is highly interconnected, right. So you have this can be converted to this, this can be converted to this, so they are all the core molecules, right.

So all your core molecules are highly, highly interconnected, which is two things. One you cannot afford changes in the core, things go wrong in the core everything goes wrong, much like you hubs, right these are hubs clearly. But, it is very easy to adapt, right. Here you can easily replace some of these pathways by some of other pathways, right. And again here as well. So the only irreplaceable part is at the core, right. So overall you have much more Evolvability and Robustness as a result of this.

(Refer Slide Time: 10:09)

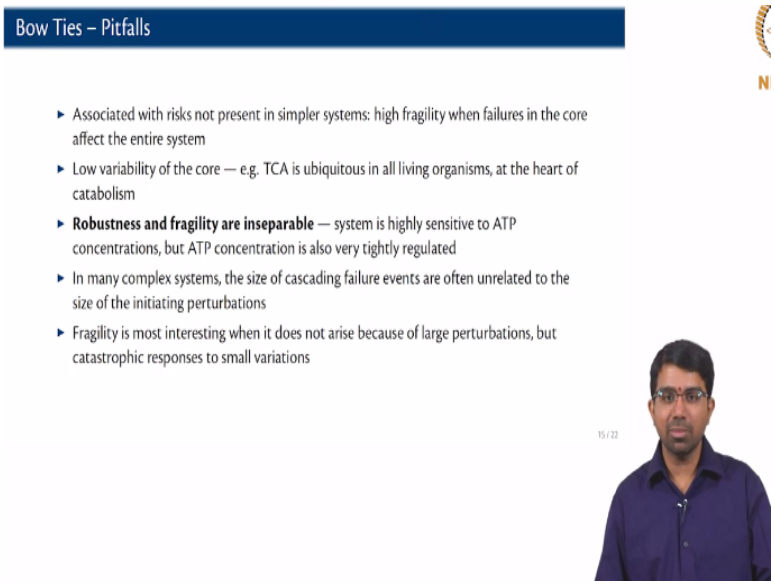


So what are the functional advantages? If you had a flat architecture you will have to have individual pathways from every substrate to every product; is going to be inefficient, very difficult to regulate and utterly unevolvable. On the other hand, Bow-Ties will accommodate divergent demands on metabolic systems. So you can have high metabolite through the systems using just a few functional enzymes.

And you can have integration and regulation facilitated at different timescales, right, so all these can operate across slightly different time scale, right. The core is where you have no latitude. The other things can operate a slightly different time-scales. Stochiometry is also highly structured, right to facilitate control. And these shared interfaces and protocols like say ATP or NADP and so on gives you the plug and play feature which will help you connect you know the less central reactions and the more central reactions.

And the less central reactions can obviously be stopped out more easily without causing damage, right. The core is the constant part, you cannot afford any change in the core, but you can easily disconnect, reconnect put another module take another module in the periphery. This is the advantage that gives you.

(Refer Slide Time: 11:28)



What are the disadvantages, if something goes wrong in the core? Or you have very little leeway in the core as such. So it is associated with risk that are not present in simple systems. These are very complex system, right. So there is high fragility when things in the core go wrong. So there is low variability of the core—one of the obvious disadvantage of this. So when you actually design a drugs it is becomes a pain.

So when you target protein translation I kill all bacteria. I want to kill only a particular diseases causing bacteria but I basically nuke the entire set of bacteria that are there in my beneficial bacteria whatever, right because the core is highly, highly conserved. So in Robustness and Fragility are actually inseparable. So a system is highly sensitive to ATP concentrations, but it is also very tightly regulated. So this is fragility and this is robustness. And it is in the same thing.

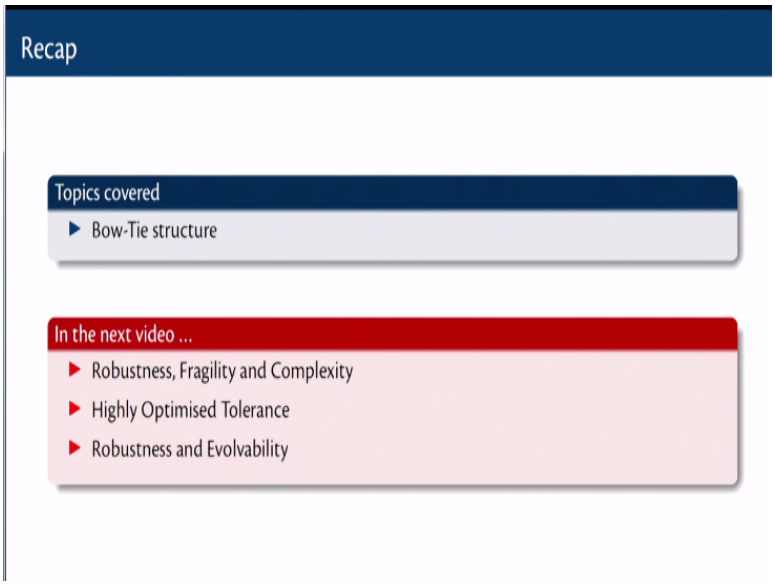
So scale free network is robust because of its hubs and is fragile because of it hubs, very interestingly in many complex systems that size of cascading events are often unrelated to the initial perturbations. You can have like a small change in something which will lead to a completely massive change in the output like almost like a chaotic system, right you have a very-- so these are there are certain axis on which the system is highly, highly sensitive.

Overall the system is very robust but there is certain axis, so the system is extremely sensitive to ATP concentrations, right. Many other things systems will not budge, nothing happens very

robust but if ATP concentrations are like really tweaked around then the system will behave you know very chaotically. And fragility is also therefore interesting because it arises, not because of large perturbation but catastrophic responses to small variations.

Clearly, you see in the scale free network. You might knockout 1 hub and that might really damage the network very badly, right. Any other node you knockout—so knocking 5 nodes, knocking 10 node that is not the problem, it is what you knockout. So the size does not matter but the, you know the relative importance of where you strike and how it cascades through the network is more important.

(Refer Slide Time: 13:55)



So in today's video I hope you understood what is the one very important underlying organisational feature of Robustness in biological systems namely the Bow-Tie architecture. And in the next video, we will start looking at a Tradeoffs, right. So it is not that a system can be completely robust so there is always some fragility as well and there is also a lot of complexity and how all these three quantities are in some sense related.

So there is also this interesting concept called Highly Optimised Tolerance that we will briefly overview. And also introduce you to the concept of Robustness versus Evolvability. Right, so Robustness and Evolvability sound inimical almost right because Robustness is resistance to

change and Evolvability is ability to change, but strangely these 2 coexist in biological systems, we will see how.