Computational Systems Biology
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Lecture - 93
Robustness in Biological Systems

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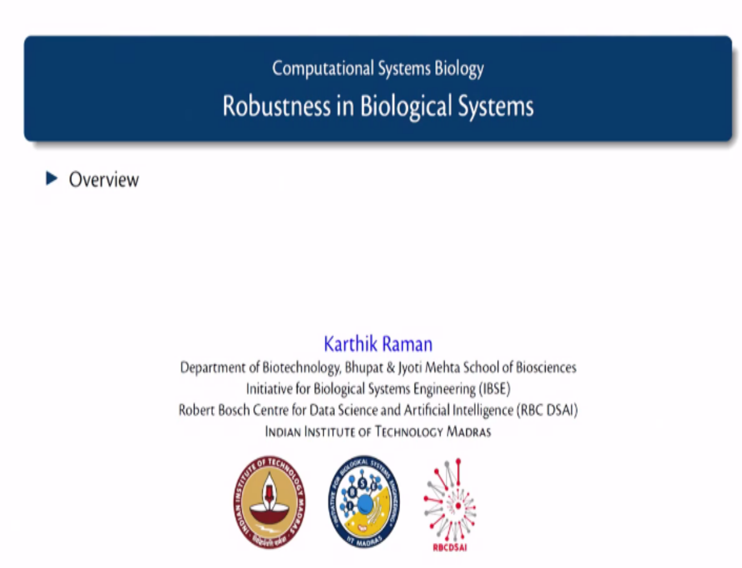

So in this last series of lectures in this course we will start looking at Robustness in biological systems, Robustness versus Evolvability and a bunch of advanced topics including a brief introduction to Synthetic biology. So in today's video I will give you a brief overview of-- the concept of Robustness in biological systems and how it is a very unique property of biological systems.

So welcome back. Let us look at Robustness in biological system. It is a very important and-- essentially an unusual property if you look at, you know engineering systems. In engineering systems are not generally very robust but you can obviously we design them to be robust I mean otherwise you would not have aircrafts flying us from one place to another.

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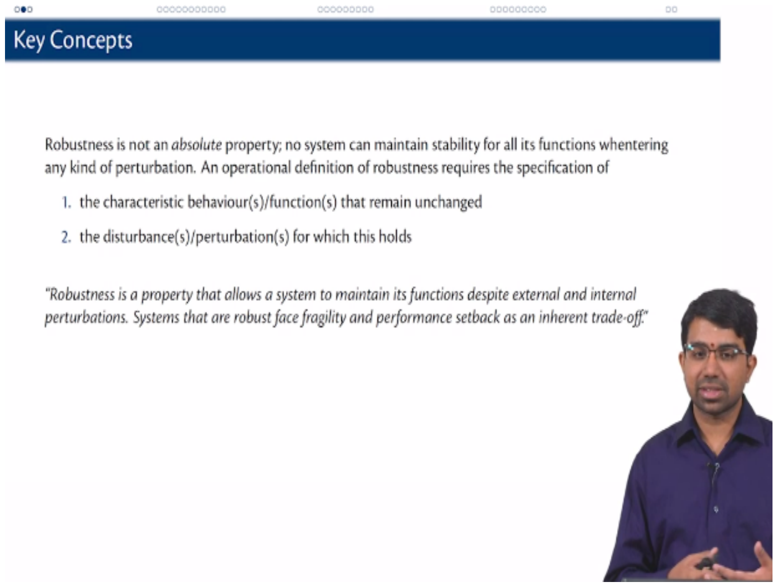

So what is the key concept, so robustness-- one must remember is not an absolute property, right. So you would say for example that human body is robust to several things. So one of the things you can really talk about are body temperature is robust but robustness means there is a range, right. It is not to say that your body temperature is going to be like 37.000 degree Celsius, right.

Your body temperature is going to be slightly up slightly down, it is never going to go to like 60 degrees it is never going to go to 20 degrees as long as you are alive, right. So there is a particular zone in which there is this variation. And if you do not ware enough protective clothing or you know out in the Antarctic in now minus, you body temperature is not going to hold, right. So there is a particular--

So if you want to have an operational definition of Robustness you need to specify what is the characteristic or function that is robust. Let us say in this case body temperature or in essence what is the zone in which it remains robust and what is the level of perturbation, if outside temperature say changes by 15 degrees your body temperature is not going to change. I have enough you know, metabolic machinery to counter act that.

If the outside temperature increases by 15 degrees there is no problem, I will sweat enough to keep the body temperature as constant as possible, right. So robustness is the property that allow the system to maintain its functions despite external and also internal perturbations, right. And systems that face that are robust they also face some fragility in performance setback as an inherent trade off. So no system is ever absolutely robust to all kinds of perturbations and so on.

Because one thing you wanted to be robust to the kind of perturbation it will experience. So if you are designing a rocket shuttle you wanted to be resistant to certain kinds of—if you are designing a train it is going to be robust you a very different set of temperatures and so on, right. So any system is going to be designed for certain kinds of perturbations and so on. And in biology nothing is really designed but is literally shaped through evolution, right.

And there again it is going to depend on the kind of stresses that it has been exposed to and so on and there are some really fascinating studies which tells you robustness or modularity can emerge as a result of alternating stresses so on and so forth.

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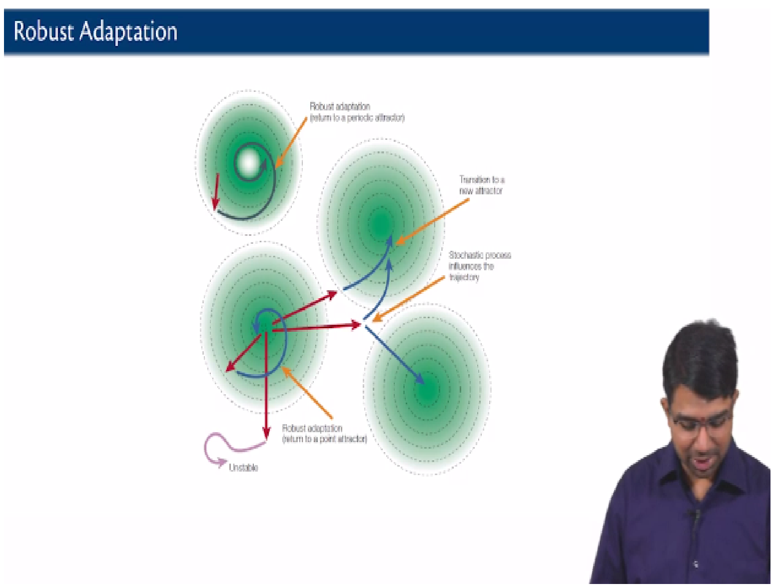

"Professor - student conversation starts" There are many examples of robustness in biological systems. Can we have a few examples? **"Professor - student conversation ends"** Talk about body temperature or something but something little more microscopic. Also you know adaptation is sort of a result of you know robustness is a consequence of adaptation. So you see that organisms invariably adapt, that you take an organism from one situation put it into another situation is going to very well adapt it is going to reach a new state which is-- and it is quite stable, right it responds.

So you suddenly take an organism from one concentration of nutrient and put it to another concentration of nutrient it will slowly adapt to that concentration. Now you suddenly put a lot of salt, give a salt stress it will react with but it will readapt, recalibrate, right. So there is always this very interesting process of adjustment that happens in you know, there is obviously a lot of orchestration of different kinds of networks that go on behind this, goes on behind this.

But you know, the end effect is robustness, right. So there are some properties some clear cut stability that the system demonstrates in the face of certain major perturbations. And what are the underlying features for this robustness to happen? So for example in this picture it shows you how there is a return to attractor, okay. You can pull the system out in this direction but invariably get set back into this system. This is again a mark of robustness.

So this pulling out is the perturbation your engineering and this coming back is the systems inherent nature you know based on whatever network it is indoored with and show on to return to a particular thing. Or in certain cases it might return another gravitational field, another attractor, right. So you can think of these as multiple stable points, steady states, right. And the system can get sucked into this or it can go into completely something else, sometimes it can go unstable, right.

So this is when you do not protect yourself when you stay out in the cold for too long, right it can what happens after a period of time, right. If you are out for like 12 hours in - 15 degrees Celsius you are going to get a frostbite and whatever and so on; it is going to be an unstable response, your homeostasis is just ceases exists thereafter.

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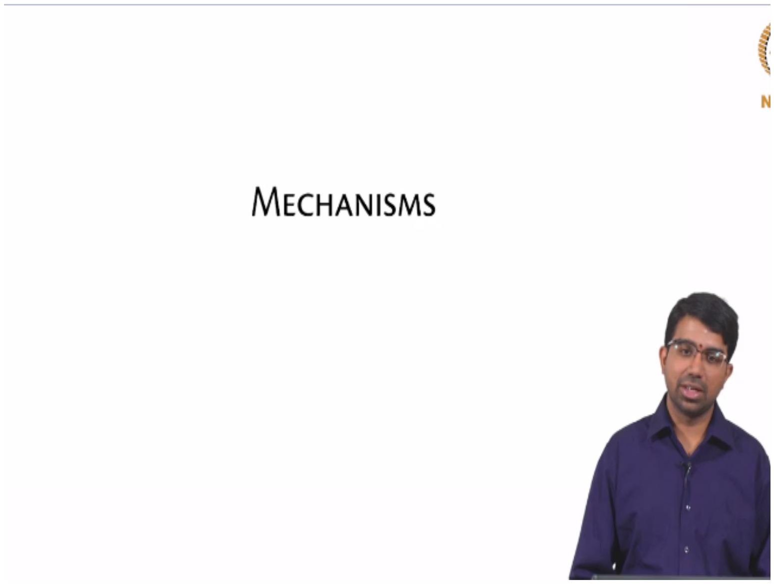

So what are mechanisms underlying robustness and you might be able to think of a few, right from your understanding of engineering system and so on. So can you think of certain concepts that are underlying robustness, let us see how many of them work out in biology.

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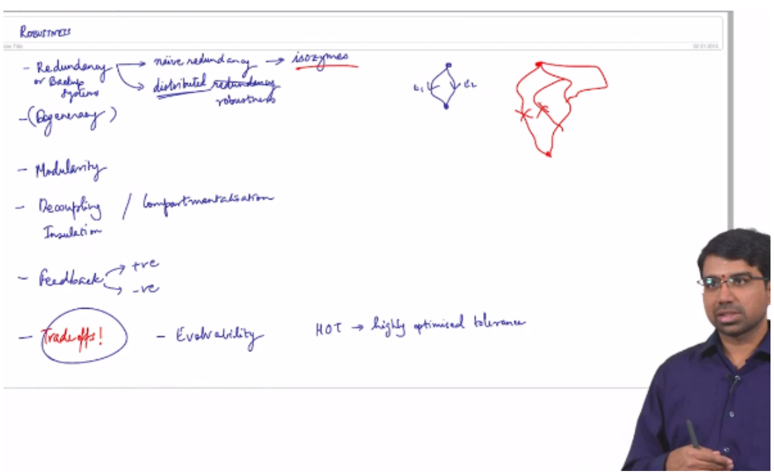

What are the underlying principles for robustness? Fair enough. So robustness in sensitivity are sort of (()) (06:10), I agree. But what are the mechanisms that afford robustness? So fair enough that would be redundancy, right. So in fact there is a very nice review by Hiroki Kitano which have set off based this lecture on and I will share that paper on the class website as well. So it always gives the example of aeroplanes, aeroplanes are really robust, right.

They got to be because they survive very testing conditions. And you have redundancy in aeroplanes. You have multiple—you know that all aeroplanes have multiple engines, right. So you know central first aspect of redundancy, not just engines you have different onboard computers also have you know there is some redundancy built-in. And you need redundancy in different levels, right and that is where biological becomes very interesting.

So redundancy I would like to classify it as maybe naïve redundancy which is basically having one more copy, right. You have instead of one person you have two people to do the same job, so if one person does not turn up the second person takes care of the job. So if one engine fails the second engine kicks in. So this is like what you would in biology this would be something like isozymes. You have two enzymes that can do the same reaction essentially.

You also have distributed redundancy where you find that there are two—this is—I do not think this is ever observed in engineering systems because engineering systems are designed you know in a very bottom of fashion right, so you know what to put together and you usually do not have emergent properties in engineering systems. You actually do not want emergent properties, right. You do not want something unpredictable coming out when you—

When you put A and B together you just want them to work as you know you would expect not something completely new happening, right whereas in biological systems you have this sort of distributed redundancy wherein you have to completely different pathways which can end up compensating for one another. So it is not, you cannot narrow it down to A compensates for B. And there is something even say when we studied synthetically lethals and so on.

I really like the idea of synthetic lethals because it gives you a good peak into how redundancy has emerged in biological system, right. So you could have-- so this could be a synthetic lethal, right. So let us say this is some A and this is some B and these are two enzymes. But invariably you do not see something as simple as this but you see something and so on, right. So there is a layers of redundancy that are built in.

And finally you know you will there is still the same compensation but it is just far more robust, right. And you cannot easily break the system down. You cannot just say you know delete this, and delete this, the system will die there are some more you know complexity to it so there are like more layers; it is a lot more complex than just having plain isozymes and so on. So this kind of very interesting behaviours are observed in biological systems. So very good, redundancy is one important concept, what else?

So there will be some sort of degeneracy, right. And I would probably try to pull that under redundancy in some sense, right or you know it is more of an observation it is not a direct principle, right. So this very much happens, right you, you always find the low k1 and high k2 will give similar behaviour to high k1 low k2 perhaps, right. And this is you know this is sort of the distributed redundancy that we are talking about.

This is what we would call distributed redundancy or even distributed robustness, right. So then you always find modules in biological systems, right. So there is modularity, decoupling, we also have compartmentalization, right. You have some very interesting concept such as these we pervade across biological levels, right. So modularity is having or decoupling and you can also say in some sense insulation, right.

You want certain perturbation to be restricted to certain zones. You do not everything to respond to the same thing, right. So you have certain modules which will—so all these are sort of interconnected you cannot, it is literally difficult to decouple all of these right, so you have redundancy, modularity, decoupling and they are all (()) (11:55), right. There are so many such fundamental concepts that underlying robustness, right.

And we will see how each of these come out as important for achieving robustness. Any other concepts you can think of. You can even think of that as redundancy, right. So your lactose utilization system is the backup to your glucose utilization system. Well, it needs to exist in the first place and it needs to be able to switch. And you can think of many other concepts that will come in here as well, right.

So if something has to be-- so the many of these would be bi-stable systems. So they will be stable in one state or they will get kicked into another state where they will again be stable, right. So this arises via positive feedback and so on and so forth, so all these become underlying concepts for robustness. So you need to have feedback, right and it could be either-- and the other thing to really worry about is—this is not exactly robustness principle as such. What are the tradeoffs?

Well, evolvability is very important we will kind of get to that. So it almost sounds like counter right. Robustness is resistance to change. Evolvability is ability to change and they go hand and hand in biological systems. We will see how that happens, right that is going to be the topic for the next couple of classes, right. But the thing to understand is there is a lot of tradeoffs you need to worry about, right.

Even if you are going to design synthetic circuit, right. We are going to talk about synthetic biology as well. If you have to design a synthetic circuit you cannot you have to be careful about how you set it up, right. You-- it has to be somewhat tuneable, somewhat robust but then if you wanted to be like super, super robust then you may have expended a lot of energy, right nothing is going to happen with that ATP.

So you have to, you have a budget for robustness right, and that becomes very interesting, so this is what usually manifest has HOT or Highly Optimised Tolerance. So sort of common aspect found in several engineering systems and so on. The nice concept which talks about how robust systems are also inherently fragile, they are robust on certain axis but they are fragile on other axis.

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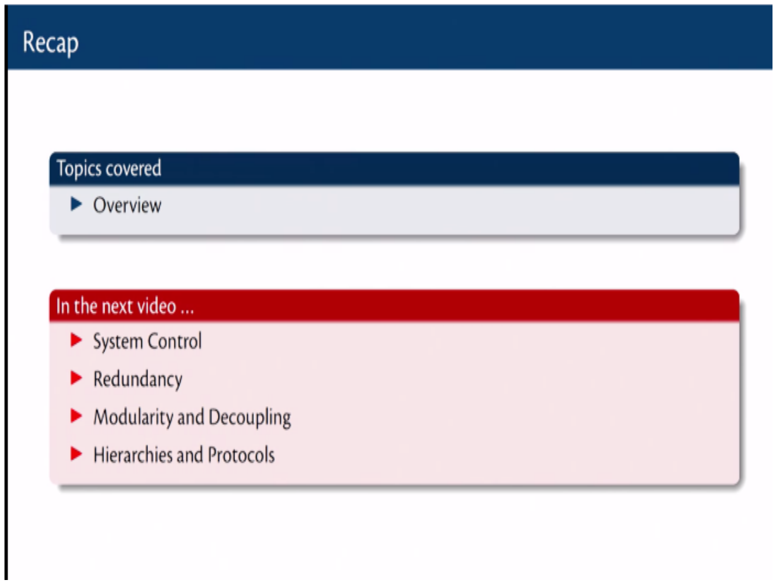

In today's video we had an overview of the concepts of Robustness in biological systems. And in the next few videos we will start looking at the mechanism underlying robustness and so on. In the very next video, we will look at the key mechanisms underlying robustness namely System Control, Redundancy, Modularity and Decoupling and what kind of Hierarchies and Protocols are used in biological systems which all contribute to robustness in different ways.