Computational Systems Biology
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Lecture - 94
Robustness in Biological Systems: Mechanisms

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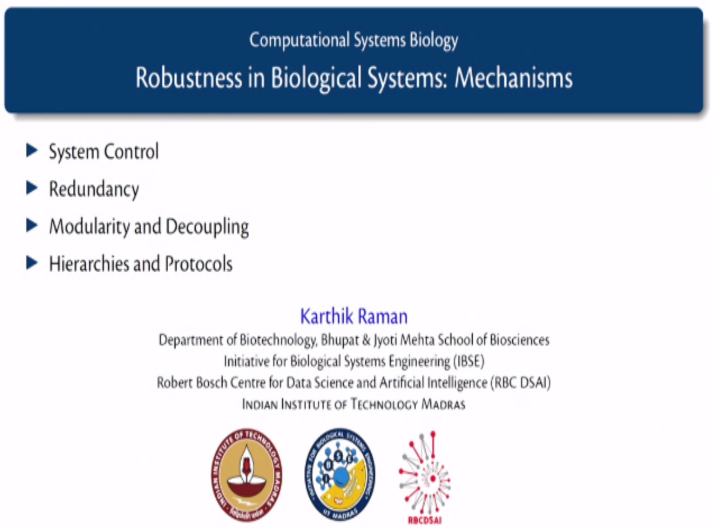

In today's lecture we will continue with our study of Robustness in biological systems and we will study the different mechanisms underlying robustness namely System Control, Redundancy or Diversity that contribute towards Robustness and Modularity and Decoupling as well as Hierarchies and Protocols that are you know, existence in biological systems that enable robustness.

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So let us continue looking at the mechanisms for Robustness in biological systems.

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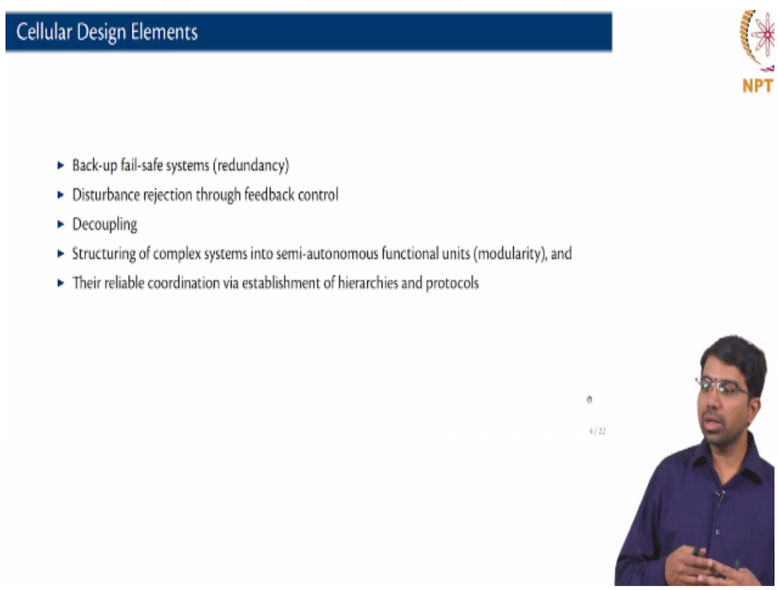

So we did talk about Back-up or fail-safe systems or redundancy then Disturbance rejection through feedback control, Decoupling, Modularity and-- you cannot have decoupled modules but then they need to be coordinated. How do you coordinate these modules and so on? You need to establish certain hierarchies and protocols. So how do these things come within different kinds of systems be it engineering systems or more interestingly for us here biological systems.

How do you coordinate these various systems?

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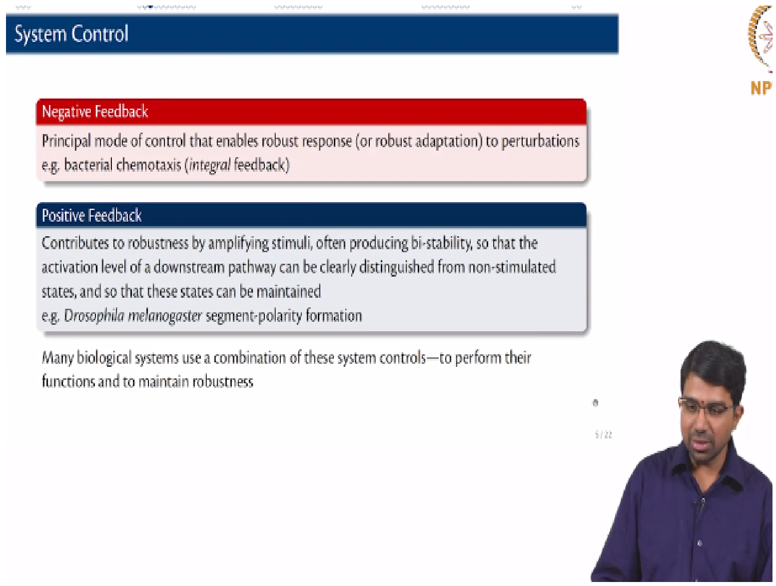

So you need to obviously control these systems and that is typically via some you know negative feedback or positive feedback. So how does negative feedback work? So some disturbance is there and you compensate for that disturbance, right. So for example that happens all the time chemotaxis and so on so you have a system that is you know that there randomly rolling, tumbling in some direction and then there is a-- it senses that there is some other signal coming in from a different place.

So you need to adjust your current direction of current vector of movement towards the gradient and move towards that, right. So that is a response, it is a feedback to based on the new signal that has come in, right. You can also have positive feedback which contribute robustness by amplifying stimuli, right. And typically positive feedback will give rise to a step a sigmoidal kind of function or more ideally a step function where you a bi-stable system wherein you are either in off state or at another on state wherein in you are stable, okay.

So this contributes the robustness. The amplify stimuli often having bi-stability so that the activation level of a downstream pathway can be clearly distinguished from non-stimulated states, right so that you can either maintain it as off or at on. And this happens in for example Drosophia, segment-polarity and so on. You can read a little more about this, I will share the paper with you as I was talking about.

But basically, you have two types of feedback both negative feedback and positive feedback which help you, you know maintain robustness, right. And there is a combination of all these that happens in given biological system.

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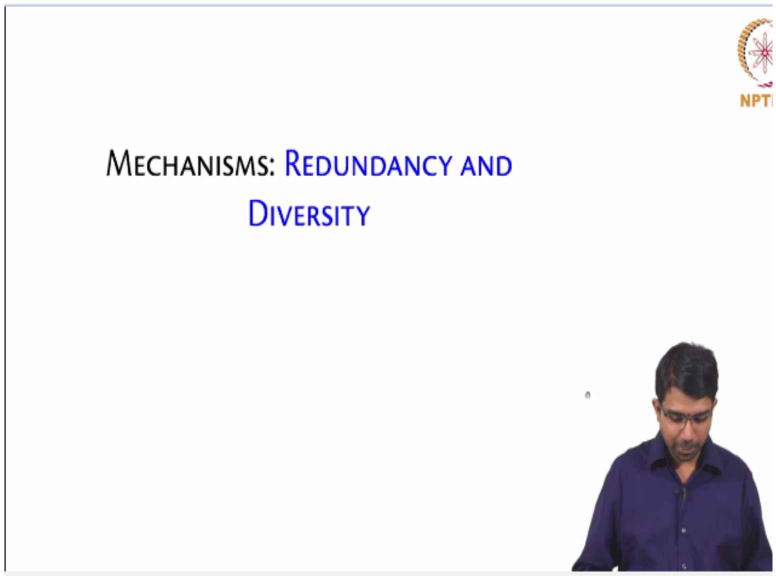

So then you need both redundancy and diversity. So what do you mean by—you understand what is redundancy right. What is diversity? In biological term one would call it heterogeneity, right. So you do not have to homogenous things doing the same thing, the two reasonably different ways of doing same thing because if I have to identical things there is a good chance that having common mode failure.

It is something that if there is a perturbation that A is susceptible to B might also susceptible to the same perturbation. So we have two very similar proteins catalysing the same thing the same reaction. Suppose there is a temperature heat soak both proteins may get denatured, right. So you have not availed of any of the advantages of the redundancy. By diversity you have a different way of doing the same thing which is very likely different from the original way.

For example, the equivalent on this is what you have in an aircraft so you have the same you know entity that is been computed by two different algorithms. So if the algorithm 1 fails or computer 1 fails computer 2 is you know need not fail, right. But if you have two computers that are identical both might actually fail. This is something that one often worries about while setting up hard drive arrays, you might have all heard of RAID arrays right.

Redundant Array of Independent Disk. So the thing is you usually put same types of drives in those arrays and you know you may redundant the copy there are many RAID levels and so on. Let us now get into those details but maybe there is a same manufacturing defect in both of them. So you are much better of like putting two different branded drives of the same size rather than two identical drives from the same batch maybe there is a same buck right.

Both of them fail after you know, certain months of operation, right. So that is not diverse, right. It is redundant but diverse. By diversity you would want completely different type of drive, maybe slightly larger drive from a different manufacturer, and manufacturer in a different batch which is very likely not going to have the same average failure rate as the original one. Okay.

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So Robustness can be enhanced obviously if there are multiple means to achieve a specific function. So a failure of one gene or one enzyme can be rescued by some other substituting enzymes of gene. And alternative or fail-safe mechanism is usually attainted by having multiple heterogeneous components and modules with overlapping functions. So you have, you have module 1 and 2 maybe module 2 and 3 can takeover together for 1 and 2, right.

Or maybe 2, 3 and 4 will do the same job as 1 and 2, right so you can have different—how does it happen in biology? This happens normally by duplication, right. So it is a very common process that happens in most especially in very heavily smaller organisms so (()) (06:06) have several gene your Saccharomyces cerevisiae that you see today as a result of several gene duplication events that happened in the past.

So you had something known as a whole-gene duplication as well as a small scale gene duplication event. So either a bunch of gene scale duplicated or a whole entire genome gets duplicated, because of these there is a lot of redundancy that can happen. So initially if you had an essential gene you had only one copy of it and there was no latitude for that to mutate and so on. If you have two copies they can slowly divergence function.

May this gene can still do the same thing as it was doing all along whereas this gene can take on some allied functions which can be very useful say in different environment and so on and so forth. And alternative mechanisms are obviously coupled with control to ensure robustness. Maybe the cell will not express both genes at the same time. If you have isozymes it will express only one of them and when the first one goes off it will start expressing the next one, right.

So there is a control mechanism that underlies this whole robustness aspect of the cell. And the existence of alternative mechanisms allows regulatory feedback to remain intact even though there are several perturbations. And you need very specific regulatory networks to achieve this because you need to control across several maybe there is metabolic layer there is a regulatory layer, you need to transcend across these levels to control the cell carefully.

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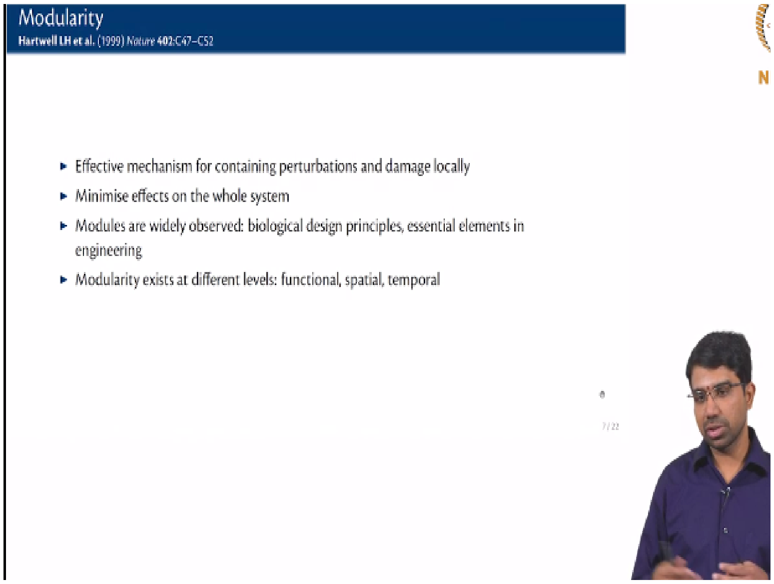

The other very interesting mechanism is one of modularity. So it is an effective mechanism for basically insulating certain perturbations. So you have one module maybe only that starts failing or you know mutation only affects that module. This is intimately connected with decoupling as well. RAID modules are somewhat decoupled, this minimises effects on the whole system. So you find it widely be it biology or in engineering, right.

You always have to play plug-and-play modules, right. And if you know few classes we talked synthetic biology where this is a vision, right you want to have plug-and-play modules. I put an oscillator into the cell it just works, right. I plug it into the rest of the modules that are already existing the cell it starts working as, as we imagined, okay. And you can have different types of modularity functional, spatial, temporal, right.

I think what is spatial modularity? Easiest of them like compartmentalization. Functional modularity is two different functions it could be even redundant but two different modules trying to do different functions or same functions. Temporal is one module is active at one time step the other module only happens at a very different time step. So they do not overlap in time. So modules do not overlap in time, space or maybe function.

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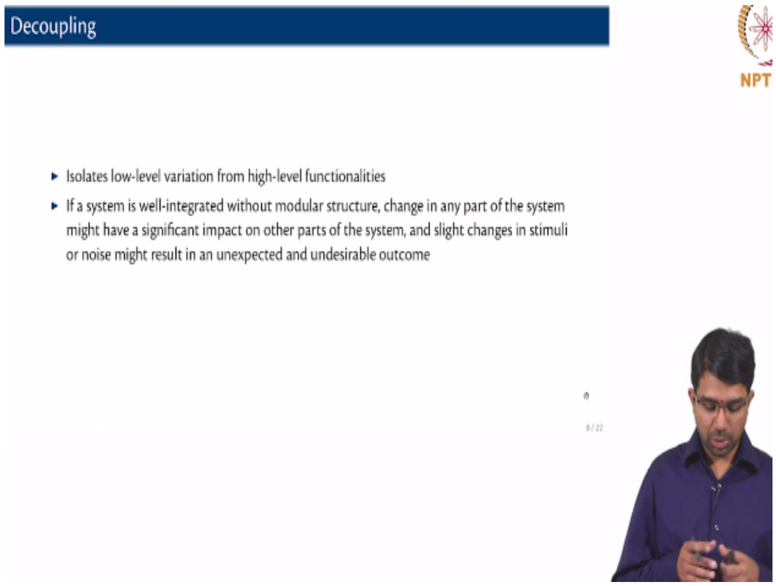

So decoupling, so this isolates low-level variation from high-level functionalities. So if a system is well integrated without modular structure any small change in one part of the system might have very, you know far reaching changes in other parts of the system and this is problematic. So you might have a small noise will give you a very bad outcome and so on.

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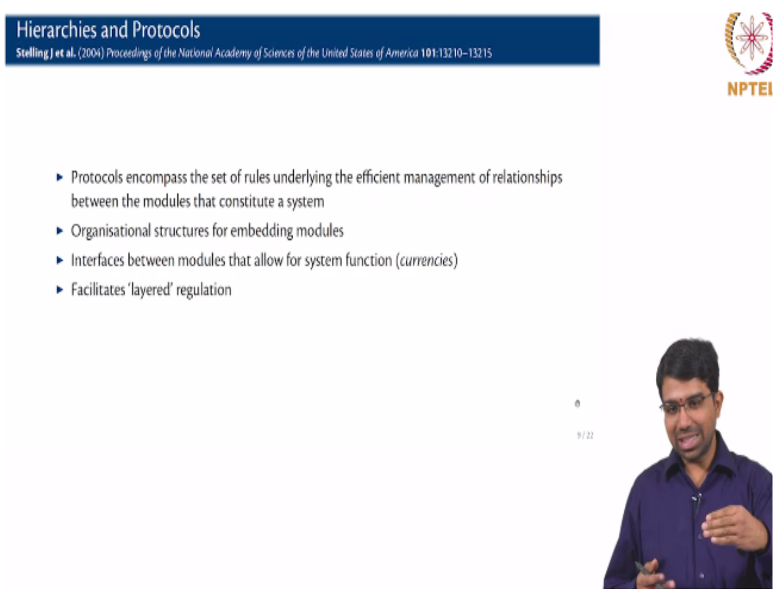

Next interesting part is that of hierarchies and protocols. So how do you orchestrate this within the cell? So Protocols encompass the set of rules underlying all the relationship between the different relationships, right. So what is the language within the cell? Usually some sort of small molecules the transfer signals or you know ATP and so on. And there is an organizational structure in which these modules are embedded. Let us see what it is.

And you also need some currency for system function like ATP or you know NAD, some energy molecules, protons and so on. And this facilitates a sort of layered regulation. So if you see any signalling cascade you will see that there are, you know several layers at which you can affect control and there are molecules that transmit information across these layers.

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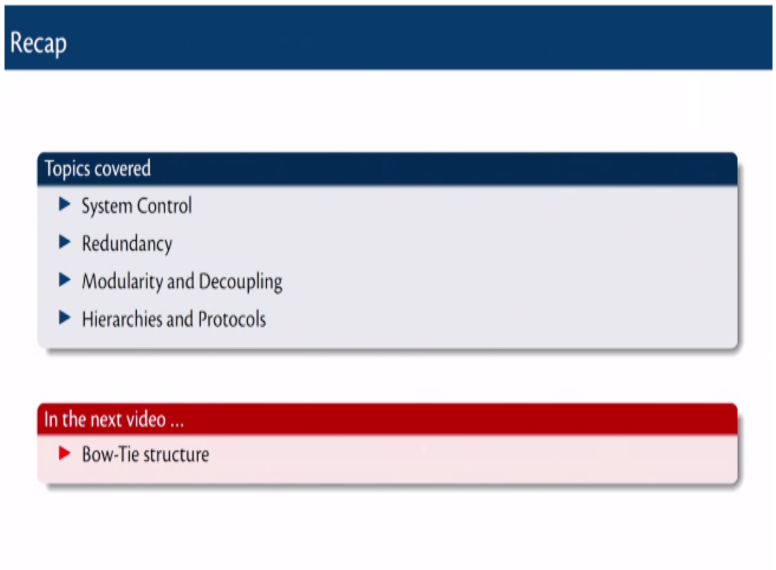

So in today's video we looked at some of the interesting mechanisms that enable robustness in biological systems such as System Control, Redundancy, Modularity and so on. And in the next video we will start looking at the organizational principles or the key structural feature that enable robustness basically a Bow-Tie structure.