

Computational Systems Biology
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Lecture - 96
Robustness in Biological Systems: Trade-offs

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Computational Systems Biology
Robustness in Biological Systems: Trade-offs

- ▶ Robustness, Fragility and Complexity
- ▶ Highly Optimised Tolerance
- ▶ Robustness and Evolvability


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The slide features a dark blue header with the title 'Computational Systems Biology' and 'Robustness in Biological Systems: Trade-offs'. Below the header, there are three bullet points: '▶ Robustness, Fragility and Complexity', '▶ Highly Optimised Tolerance', and '▶ Robustness and Evolvability'. At the bottom, the presenter's name 'Karthik Raman' is listed along with his affiliations: 'Department of Biotechnology, Bhupat & Jyoti Mehta School of Biosciences', 'Initiative for Biological Systems Engineering (IBSE)', and 'Robert Bosch Centre for Data Science and Artificial Intelligence (RBC DSAI)'. The IIT Madras logo is also present. Three logos are shown at the bottom: the IIT Madras logo, the IBSE logo, and the RBC DSAI logo.


In today's lecture, we will continue with robustness in biological systems and particularly study what are all the trade-offs involved in robustness. So there is robustness on one hand, fragility on the other hand and you know these systems are all parts of a complex biological system. So how do robustness, fragility and complexity go hand in hand, we will also look at this concept called highly optimized tolerance.

And I will also try to introduce you to the concepts of evolvability and how it strangely coexists with robustness.

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ROBUSTNESS TRADE-OFFS: ROBUSTNESS, FRAGILITY AND COMPLEXITY




So what are the trade-offs that we need to consider while looking at robustness?
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Introduction 00:00	Mechanisms 00:00:00:00:00:00	Engineering Principles 00:00:00:00:00	Robustness Trade-offs 00:00:00:00:00	Conclusions 00
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Robustness, Fragility and Complexity



- ▶ Despite the variety of mechanisms for robustness, cells are sensitive to quantitatively minor but extremely powerful perturbations such as oncogenic mutations that enable profound changes at a genomic scale
- ▶ There appear to be principal limitations regarding how robust systems can be...
- ▶ Co-existence of extremes in robustness and fragility (*robust yet fragile*) is possibly the most salient feature of highly evolved complexity



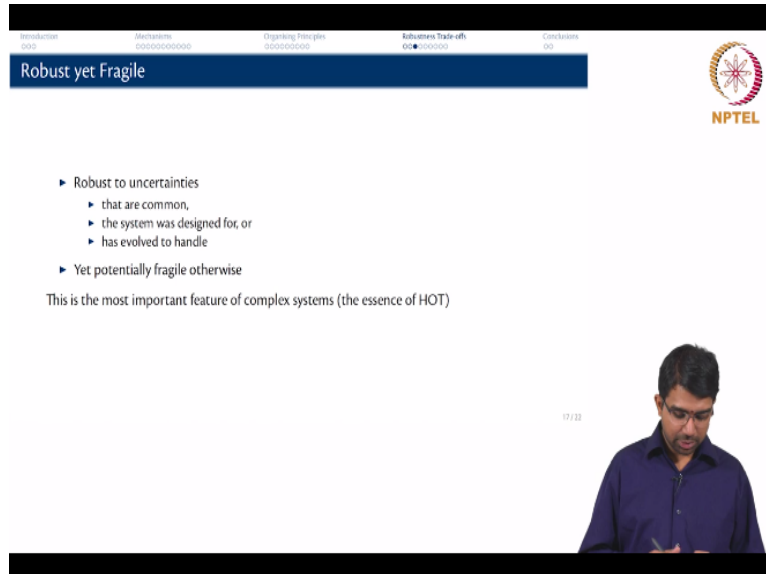
So despite the various mechanisms that we talked about for robustness, cells are sensitive to quantitatively minor but extremely powerful changes such as you know some mutations and so on like oncogenic mutations still a mutation right. We have mutations going on all the time in the body but certain so where an oncogene gets mutated cancer sets in and so on right and it seems that there are principle limitations on how robust a system can be.

There is some quality that needs to be concerned in some sense right and this is kind of pointed towards by the co-existence of extremes in robustness and fragility right and this happens in highly evolved complex systems right. So it is very robust yet fragile. Classic

examples, scale free network, it is very robust but potentially fragile. I can knock out 5 nodes and destroy the network.


I would not be able to do that in the random network. You can argue the random network is not very connected to begin with but you know a scale free network can just collapse spectacularly right.

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Introduction 0:00
Resilience 00:00:00:00:00
Engineering Principles 00:00:00:00
Robustness Trade-offs 00:00:00:00
Conclusions 00


Robust yet Fragile



- ▶ Robust to uncertainties
 - ▶ that are common,
 - ▶ the system was designed for, or
 - ▶ has evolved to handle
- ▶ Yet potentially fragile otherwise

This is the most important feature of complex systems (the essence of HOT)

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So what is the characteristic of these robust yet fragile systems? They are robust yet fragile systems. They are robust to uncertainties that have been anticipated or you know common or evolved for and so on but very in fragile otherwise like a targeted attack. So this is called highly optimized tolerance right.

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ROBUSTNESS TRADE-OFFS: HIGHLY
OPTIMISED TOLERANCE



So what is highly optimized tolerance?

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The slide is titled "Highly Optimised Tolerance (HOT)" and features the NPTEL logo in the top right corner. A navigation bar at the top includes "Introduction 00:00", "Mechanisms 00:00:00:00", "Organizing Principles 00:00:00:00", "Robustness Trade-offs 00:00:00:00", and "Conclusions 00:00". The main content consists of three bullet points:

- ▶ Robustness trade-offs are mandated by fixed and limited resources: trade-offs result from robustness being a somewhat *conserved* quantity
- ▶ Making one feature robust to a class of perturbations makes the same or other features fragile to that or other perturbations
- ▶ In design (engineering) or evolution (biology), robustness, which is adapted to the intended function of a system and the associated uncertainties, must be carefully distributed

A video inset in the bottom right shows a man in a blue shirt speaking. The slide number "18 / 22" is visible in the bottom right corner of the slide area.

So robustness trade-offs are mandated by fixed and limited resources and trade-offs result from robustness being somewhat conserved right. There is only total so much robustness that a system can have and how it is distributed across definite aspects of the system. So if you make one feature very robust to a class of perturbations, it could make the same feature or some other features very fragile to the same or different class of perturbations right.

Again you can recall the example of scale free networks wherein you know you made the network very robust to node failure but only random node failure. When you have targeted node attack or targeted failure, it does not hold. So in both engineering and evolution robustness adapted to the internet function of a system and the associated uncertainties must be carefully distributed right.

So we talked about how robustness can be distributed right. You have distributed redundancy and so on so you need to make sure that the core of the system is sufficiently guarded, sufficiently controlled, sufficiently there is redundancy in the core as well and so on.

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Highly Optimised Tolerance (HOT)

HOT emphasises a necessary connection between complexity and robustness, e.g. cellular complexity seems to arise mainly from robustness as a design goal: shielding certain functions of a system may require additional control loops, leading to higher complexity and **new potential sources** of fragility!

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So highly optimized tolerance emphasizes a necessary connection between also complexity and robustness and cellular complexity seems to arise mainly from robustness as a design goal right, you could have a very simple system that performs a same function right with maybe half the number of genes but if you look at say E. coli, it is just remarkably robust right.

You can delete 30% of the genes in E. coli or even more without making an effect right but there is a cost, there is always a cost right so there is probably you know more the size is bigger so the organism requires more ATP to survive and so on and so forth. So this is always a trade-off somewhere here. So you know if you want to shield certain functions, you want to insulate something you want more loops, more regulation, more complexity, more sources of fragility right.

So we have more complexity, more additional components, so failure in those components also becomes a potential source of fragility right.

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ROBUSTNESS TRADE-OFFS: CHARACTERISTICS OF HOT SYSTEMS



So these trade-offs are a classic characteristic of these highly optimized tolerance systems.

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Introduction 0:00 Introduction 0:00:00:00:00:00:00 Engineering Principles 0:00:00:00:00 Robustness Trade-offs 0:00:00:00:00 Conclusions 0:00

Characteristics of HOT systems

- ▶ High efficiency, performance and robustness to designed-for uncertainties
- ▶ Hypersensitivity to design flaws and unanticipated perturbations — *robust yet fragile* external behaviour
- ▶ Highly structured, non-generic self-dissimilar internal configurations
- ▶ Power laws

HOT claims these are the most important features of complexity — these are neither accidents in evolution or artifacts of engineering design^{a,b}!

^aCarlson JM & Doyle J (1999) *Physical Review E* 60 1411–1417
^bCarlson JM & Doyle JC (2002) *Proc Natl Acad Sci U S A* 99 Suppl 1 2538–2545

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So they are highly efficient and very high performance and robustness to uncertainties that have been accounted for or evolved for. Yet hypersensitive to what they call design flaws or unanticipated perturbations so you have robust yet fragile behaviour and typically you have highly structured, non-generic, self-dissimilar internal configurations right. So there is a lot of diversity in the internal configuration where all your robustness is distributed and typically ends up with power laws.

So the highly optimized tolerance theory claims that these are the most important features of complexity and neither accidents and evolution or artifacts of engineering design.

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Introduction 0:00 Mechanisms 0:00:00:00:00 Organizing Principles 0:00:00:00:00 Robustness Trade-offs 0:00:00:00:00 Conclusions 0:00

Robustness and Evolvability

NPTEL

- ▶ Evolvability is extremely important; the generic mechanisms and structures responsible for robustness facilitate evolution
- ▶ Genetic redundancy allows duplicate genes to acquire new functions without perturbing the cells under most conditions
- ▶ Feedback control supports normal operation even during evolutionary changes
- ▶ Exchange of modules (e.g. biosynthetic pathways) through lateral gene transfer lets organisms easily gain completely new functions
- ▶ Protocols (e.g. ATP) greatly facilitate plug-and-play mechanisms

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How do we now reason with evolvability right, so evolvability is extremely important? What is evolvability? It is the ability to generate change whereas robustness is the ability to resist change or ability to not change right and it turns out that in biological systems as we will also see in the next class, the generic mechanisms and structures responsible for robustness also nicely facilitate evolution right.

Because we had like a conserved core and a very flexible you know fan, it turns out that this exact structure actually obviously we have seen that it facilitates robustness, it also helps evolvability because you have a lot of latitude to vary in these fans. The core is conserved but it is a small part so say 70% of the systems is open to variation which can be beneficially used right.

So for example genetic redundancy or gene duplication allows genes to acquire new functions without sacrificing cellular function. I have a gene, it has now duplicated, I have two genes performing the same function, so there is no selection pressure on in fact the either of the genes. One of the genes is free to evolve as long as it leaves behind the other for performing that critical function right.

And feedback control supports normal operation even during these changes and perturbations and you can also have you can import modules, lot of time you see antibiotic resistance you know these clusters are taken by horizontal gene transfer or lateral gene transfer. These are available to a cell in the environment of wherever it just picks these, integrates them into the existing cellular machinery right.

And you have the same protocol across cells right or across pathways or across systems.

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The slide is titled "Conclusions" and features a navigation bar at the top with the following items: Introduction (00:00), Mechanisms (00:00:00:00), Organizing Principles (00:00:00:00), Robustness Trade-offs (00:00:00:00), and Conclusions (00:00:00:00). The NPTEL logo is in the top right corner. The main content is a list of bullet points:

- ▶ Robustness is a fundamental property of biological systems
- ▶ Robustness facilitates evolvability; evolution selects robust traits
- ▶ Specific architectural features required, e.g. bow-ties
- ▶ Basic mechanisms provide robustness to a system: control, modularity, redundancy, decoupling
- ▶ Evolutions of organisms ↔ Evolution of control systems
- ▶ Systems evolved to be robust against certain perturbations are extremely fragile to unexpected perturbations
- ▶ 'Robust, yet fragile' trade-off — fundamental to complex dynamic systems

A small inset video in the bottom right corner shows a man with glasses and a blue shirt speaking. The slide number "22 / 23" is visible in the bottom right area of the slide content.

So to conclude robustness is the fundamental property of merely all biological systems, it facilitates evolvability and in fact evolution selects for robust traits right. We will see how these nice seemingly contradictory concepts are very well aligned with one another and there are specific architectural features that are required like bow-ties or power laws and so on and the basic mechanisms that we saw are control absolutely important, modularity, redundancy and decoupling.

And you can think of the evolution of organisms is actually evolution of control systems right. So can you better evolve control systems right, so because an organism cannot evolve an isolation, the entire control system as a whole evolves and the one catch with many of these systems like our scale free networks is that if they are robust under certain perturbations, they are extremely fragile to certain other perturbations right.

And this sort of trade-off of robust yet fragile is seemingly fundamental to most complex systems and particularly also to biological systems.

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Recap

Topics covered

- ▶ Robustness, Fragility and Complexity
- ▶ Highly Optimised Tolerance
- ▶ Robustness and Evolvability

In the next video ...

- ▶ Parametric Robustness
- ▶ 'Topological' Robustness
- ▶ Evolvability

In today's lecture, we looked at the concepts of robustness, fragility and complexity and how they are all interrelated and complexity is one key factor underlying biological systems and you know how robust they are and how fragile they are depending upon a lot of interesting factors and we also looked at this concept of highly optimized tolerance and you know how power laws are rampant in biological systems.

And I briefly introduced you to the concept of robustness and evolvability which brings me nicely to the next video wherein we will focus a little more on how do we systematically study the relationships between robustness and evolvability in biological systems. We will start with the study of parametric robustness, so what happens when you change a particular parameter, how robust is the system and topological robustness which is what happens when you start rewiring a system and how robustness and evolvability are intertwined.