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Systems Biology meets Medical Virology

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13 December 2018

The background features a complex network diagram with various nodes and connecting lines. The nodes are represented by circles of different colors (blue, green, pink, yellow) and sizes, some with smaller circles radiating from them, suggesting a hierarchical or interconnected structure. The lines are thin and light-colored, connecting the nodes across the slide.

Outline

- Introduction
 - What is systems biology
- Systems biology
 - Methods for systems biology study
- Systems virology
 - Viral pathogenesis and drug targeting
 - Examples in systems virology study

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Introduction

What is systems biology?

The NIH definition:

Systems biology is an approach in biomedical research to understanding the larger picture – be it at the level of the organism, tissue, or cell – by putting its pieces together.

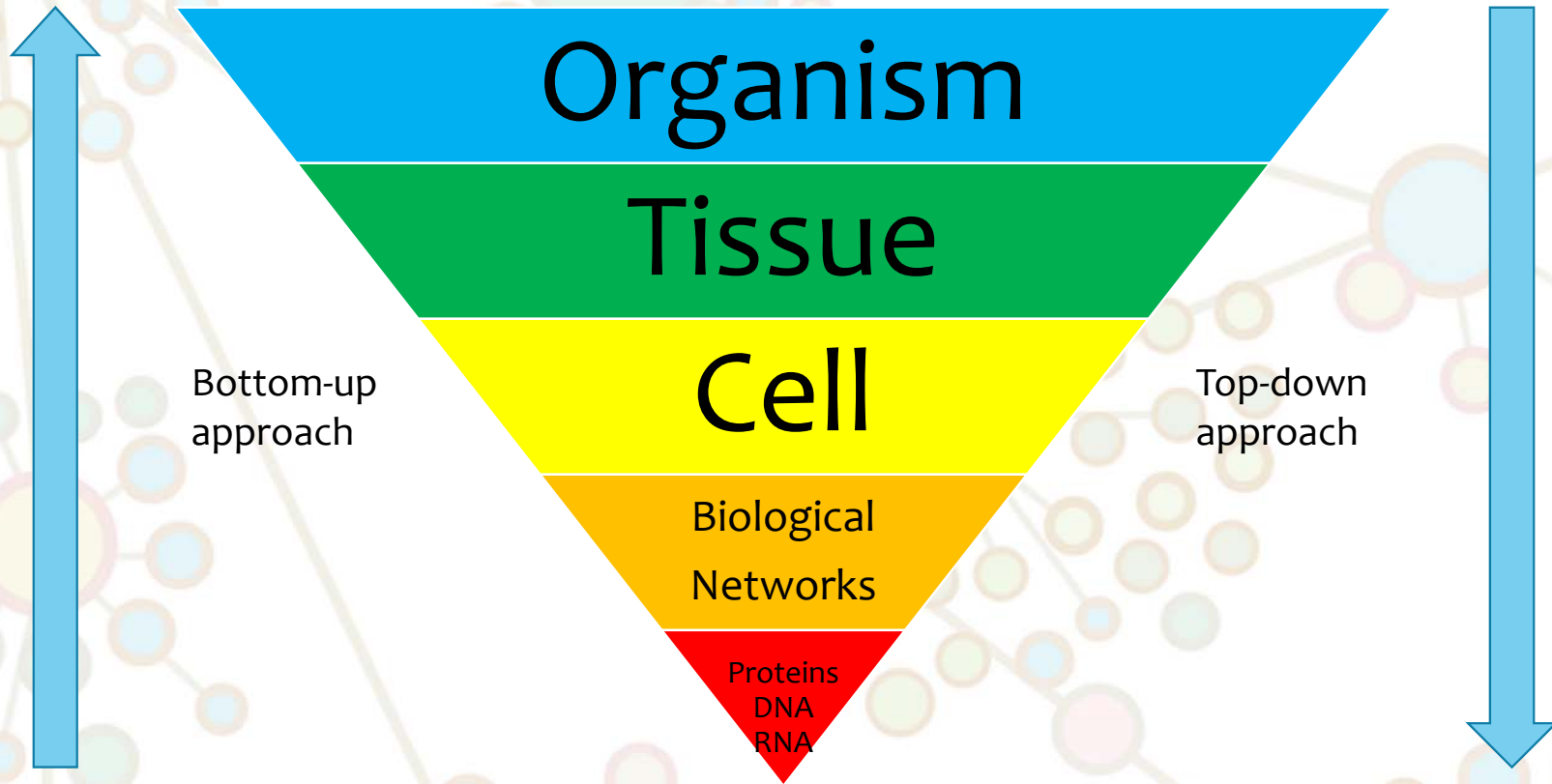
The NIH Catalyst Volume 19 issue 6, 2011

Introduction

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- Take a biological problem at the system's level
- An inter-disciplinary field for investigating the biological systems with a top-down, discovery and model driven approach.
- High-throughput experimental data are used to formulate a predictive model which is further improved by iterative rounds of perturbations in model, testing, and experiment.

Introduction



Bottom-up
approach

Top-down
approach

Biological
Networks

Proteins
DNA
RNA

Introduction

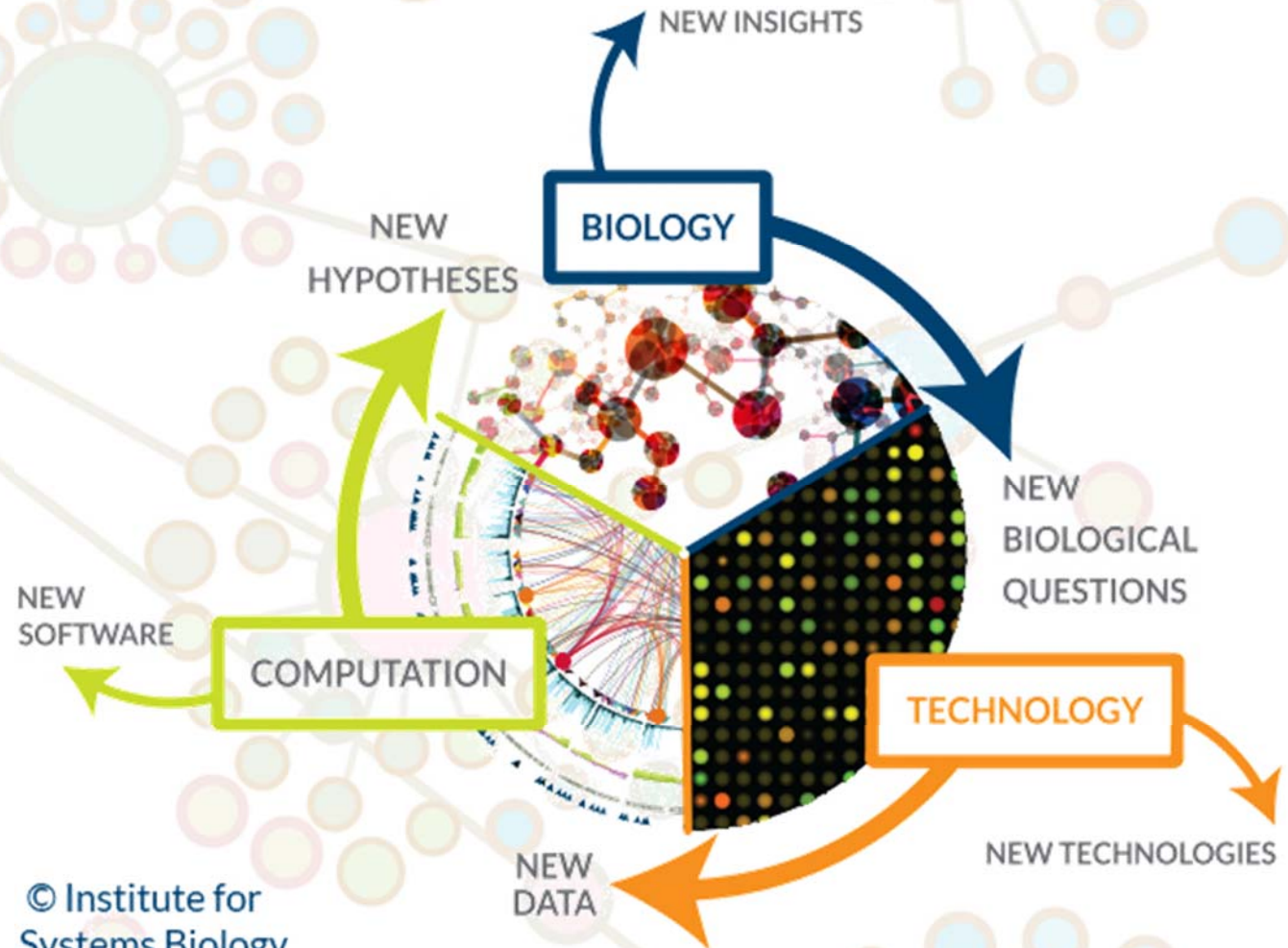
The background features a complex network diagram with various nodes and connections. The nodes are represented by circles in shades of blue, green, yellow, and pink, connected by thin lines. The overall structure is a dense web of interconnected points, suggesting a complex system or network.

- The reductionist approach
 - Dividing the biological systems into different parts, e.g., DNA, RNA, proteins, genes, exome.
 - Studying these parts in isolation and try to infer the properties of the systems by the collections of different parts.
- The systems biology approach
 - Biological systems are complex.
 - The non-linear nature of interactions between each components rendered it impossible to infer the systems' properties by merely the sum of the parts.

Introduction

The systems biology paradigm

- Iterative cycle of refinement
- Predictive model



Introduction

- Why predictive modelling?

Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection

**David D. Ho, Avidan U. Neumann^{††}, Alan S. Perelson[†], Wen Chen,
John M. Leonard[‡] & Martin Markowitz**

Nature, 1995

$$\frac{dV}{dt} = P - cV$$

$$\frac{dV}{dt} = -cV \Rightarrow V(t) = V_0 e^{-ct}$$

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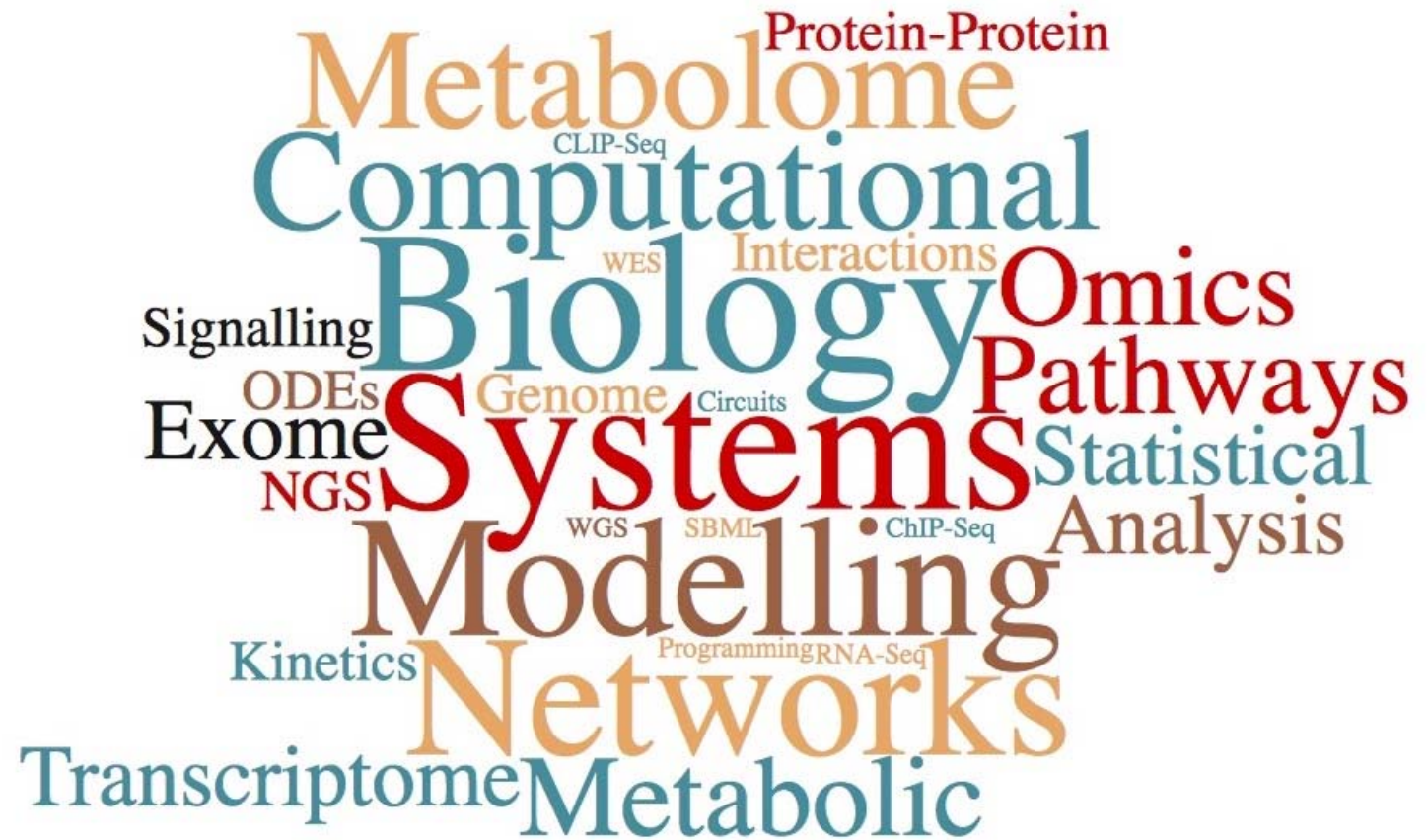
Introduction

Systems Biology

- Systems immunology
- Systems vaccinology
- Cancer systems biology
- Systems virology

Systems Biology

- Mathematical Modelling
- Biological Networks



Mathematical Modelling

- Linear and non-linear dynamics

$$\frac{dx}{dt} = k$$

$$x(t) = x_0 + kt$$

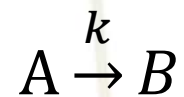
$$\frac{dx}{dt} = kx$$

$$x(t) = x_0 e^{kt}$$

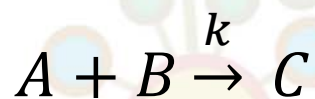
$$\frac{dx}{dt} = kx^2$$

Mathematical Modelling

Mass-action law



$$\frac{d[A]}{dt} = -k[A]$$



$$\frac{d[A]}{dt} = -k[A][B]$$

Michaelis-Menten equation



$$\frac{d[P]}{dt} = \frac{k_2[S]E_0}{\frac{k_{-1} + k_2}{k_1} + [S]}$$

Mathematical Modelling

- *lac* operon in *E. coli*

TABLE 2 A mathematical model for the *lac* operon in *E. coli*

$$\dot{M} = k_M[D]p_{pc}([Ge])\mathcal{P}_R([A]) - (\gamma_M + \mu)M.$$

$$\dot{E} = k_E[M] - (\gamma_E + \mu)[E].$$

$$\dot{L} = k_L\beta_L([Le])\beta_G([Ge])[Q] - 2\phi_M\mathcal{M}([L])[B] - \mu[L].$$

$$[A] = [L].$$

$$[Q] = [E].$$

$$[B] = [E]/4.$$

$$\mu = \varepsilon(J_G([Ge]) + J_L([L])).$$

$$p_{pc}([Ge]) = \frac{p_p(1 + p_c([Ge])(k_{pc} - 1))}{1 + p_p p_c([Ge])(k_{pc} - 1)}.$$

$$p_{cp}([Ge]) = \frac{p_c(1 + p_p([Ge])(k_{pc} - 1))}{1 + p_p p_c([Ge])(k_{pc} - 1)}.$$

$$p_c([Ge]) = \frac{K_G^{n_h}}{K_G^{n_h} + [Ge]^{n_h}}.$$

$$\mathcal{P}_R([A]) = \frac{(1 + \xi_2\rho_1([A]))(1 + \xi_3\rho_1([A])) + \xi_{23}\rho_2([A])}{\prod_{i=1,2,3} (1 + \xi_i\rho_1([A])) + \sum_{\substack{\sigma \in P(1,2,3) \\ \sigma_2 < \sigma_3}} (1 + (p_{cp} - 1)\delta_{2\sigma_1})(1 + \xi_{\sigma_1}\rho_1([A]))\xi_{\sigma_2\sigma_3}\rho_2([A])}.$$

$$\rho_1([A]) = \left(\frac{K_A}{K_A + [A]} \right)^2.$$

$$\rho_2([A]) = \left(\frac{K_A}{K_A + [A]} \right)^4.$$

$$\beta_L([Le]) = \frac{[Le]}{\kappa_L + [Le]}.$$

$$\beta_G([Ge]) = 1 - \phi_G \frac{[Ge]}{\kappa_G + [Ge]}.$$

$$\mathcal{M}([L]) = \frac{[L]}{\kappa_M + [L]}.$$

$$J_G([Ge]) = J_G^{\max} \frac{[Ge]}{[Ge] + \Phi_G}.$$

$$J_L([L]) = 4\phi_M\mathcal{M}([L])[B].$$

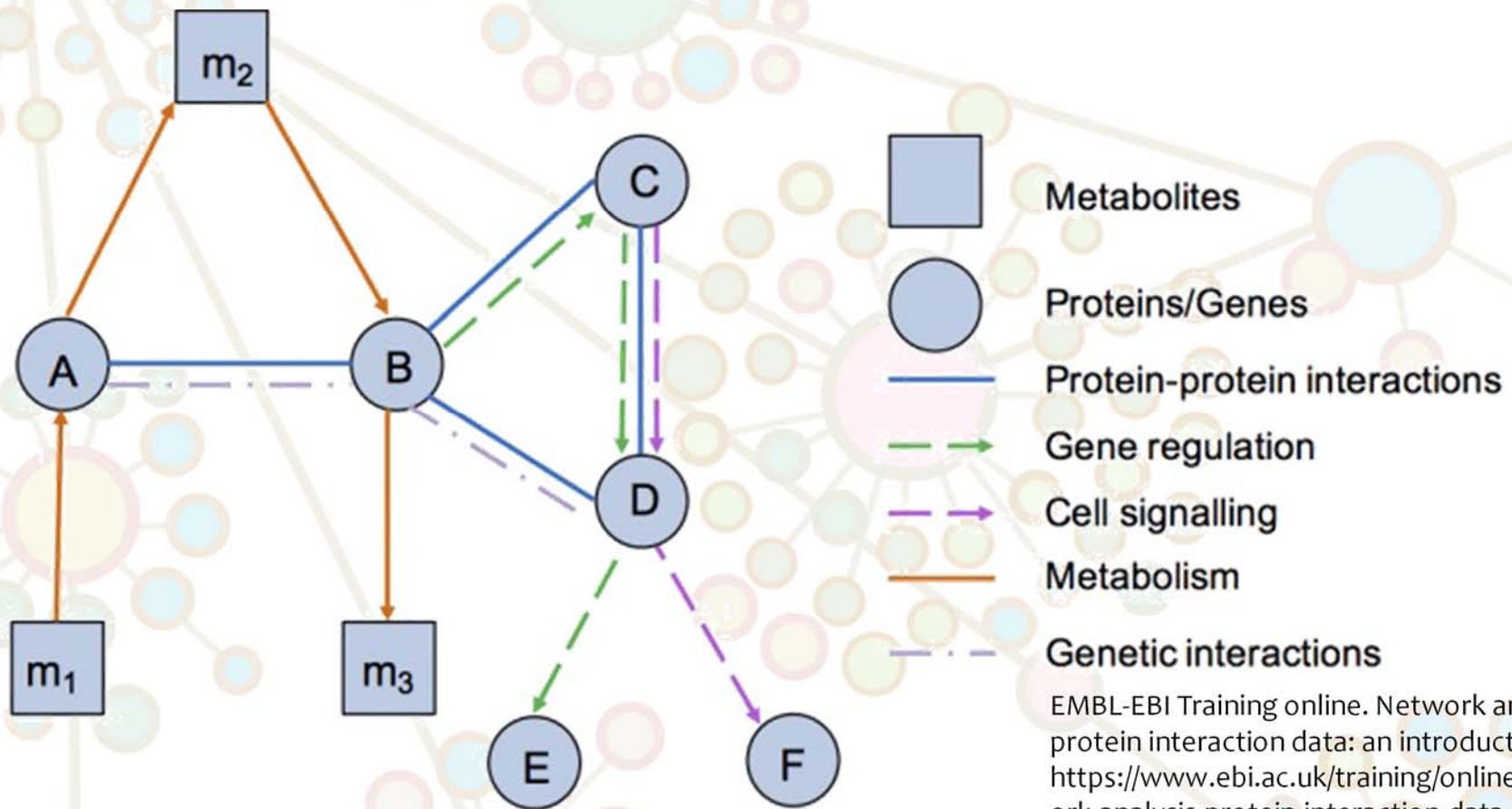
Santillán M. (2011) Biophysical Journal, Vol. 94 p.2065-2081

The background features a complex network diagram with various nodes and edges. Nodes are represented by circles in shades of blue, green, yellow, and pink, connected by thin grey lines. The network is dense and interconnected, with some nodes having multiple connections, creating a web-like structure.

Biological Networks

- Biological network is an application of graph theory.
- Graph theory (Wikipedia)
 - The study of graphs, mathematical structures used to model pairwise relations between objects.
 - A graph in this context is made up of vertices, nodes, or points which are connected by edges, arcs, or lines.
- Components of a graph or network
 - Nodes
 - Edges
 - Topology

Biological Networks



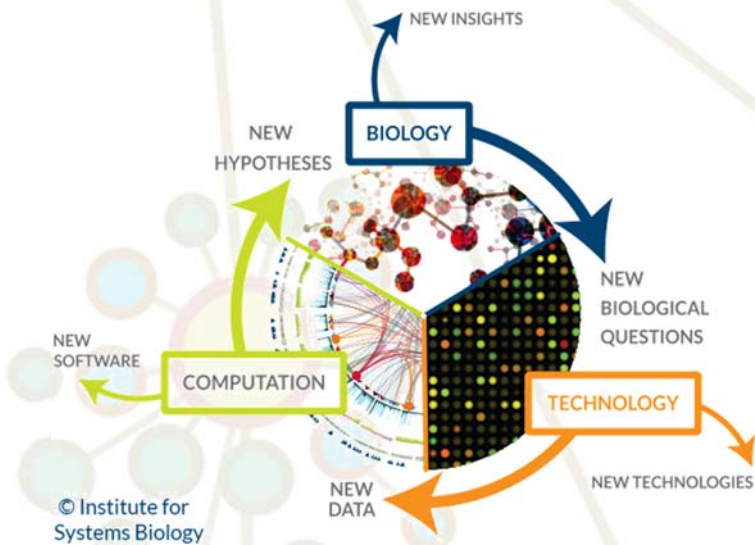
EMBL-EBI Training online. Network analysis of protein interaction data: an introduction
<https://www.ebi.ac.uk/training/online/course/network-analysis-protein-interaction-data-introduction/>

Biological Networks

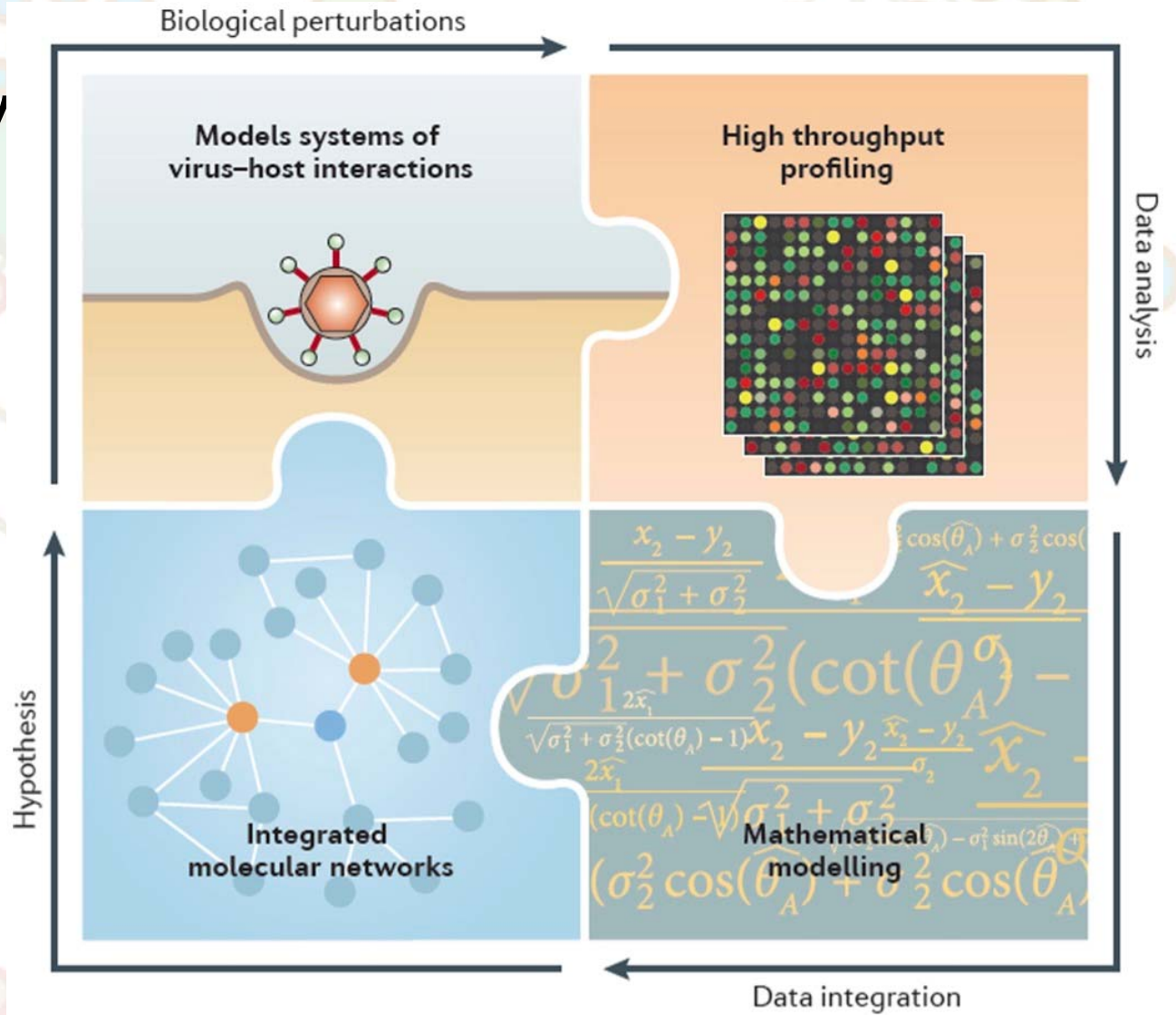


Systems Virology

The systems virology paradigm



Law G. et al. 2013 Nat Rev Microbiol
p. 455-466



Systems Virology

The background features a complex network diagram with various nodes and connections. The nodes are represented by circles of different colors (blue, green, pink, yellow) and sizes, connected by thin lines. The overall structure is a dense web of interactions, with some larger central nodes and many smaller peripheral nodes.

- Application of systems biology approach to the study in virology
 - Host-virus interactions during viral infection
 - Cellular response networks
 - Virus pathogenesis
 - Drug targeting
- Examples of systems virology
 - Gene expression signatures
 - Disruption of cellular metabolism
 - Virus-host interactomes
 - Therapeutic targets

Systems Virology

Gene expression signatures in respiratory viral infection

- Host gene expression during lethal and non-lethal viral infection
- “Cytokine storm”
- Genes which expression changed during infection had been identified
- Identity of genes expressed differently are similar between lethal and non-lethal infection
- The magnitude and timing of host response is also crucial

Systems Virology

The background features a complex network diagram with various nodes and connections. The nodes are represented by circles of different colors (blue, green, yellow, pink) and sizes, connected by thin lines. The overall structure is a dense web of interconnected points, suggesting a systems-level view of biological or metabolic processes.

Disruption of host cellular metabolism

- A lot of metabolites increase significantly during CMV infection
- Types of metabolites change are specific to different viral infection
- New hypothesis of the virus hijacking of host metabolism generated from these findings

Systems Virology

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Virus-host interactomes

- Protein-protein interaction
- Yeast two-hybrid system
- Common and virus-specific human protein targets identified
- Many common protein targets are multifunctional hub
- Viral proteins interact with multiple host proteins
- Viral proteins rewiring of host cellular signaling and pathways that might be related to tumourigenesis



Systems Virology

Example 1

Frequent Release of Low Amounts of Herpes Simplex Virus from Neurons: Results of a Mathematical Model

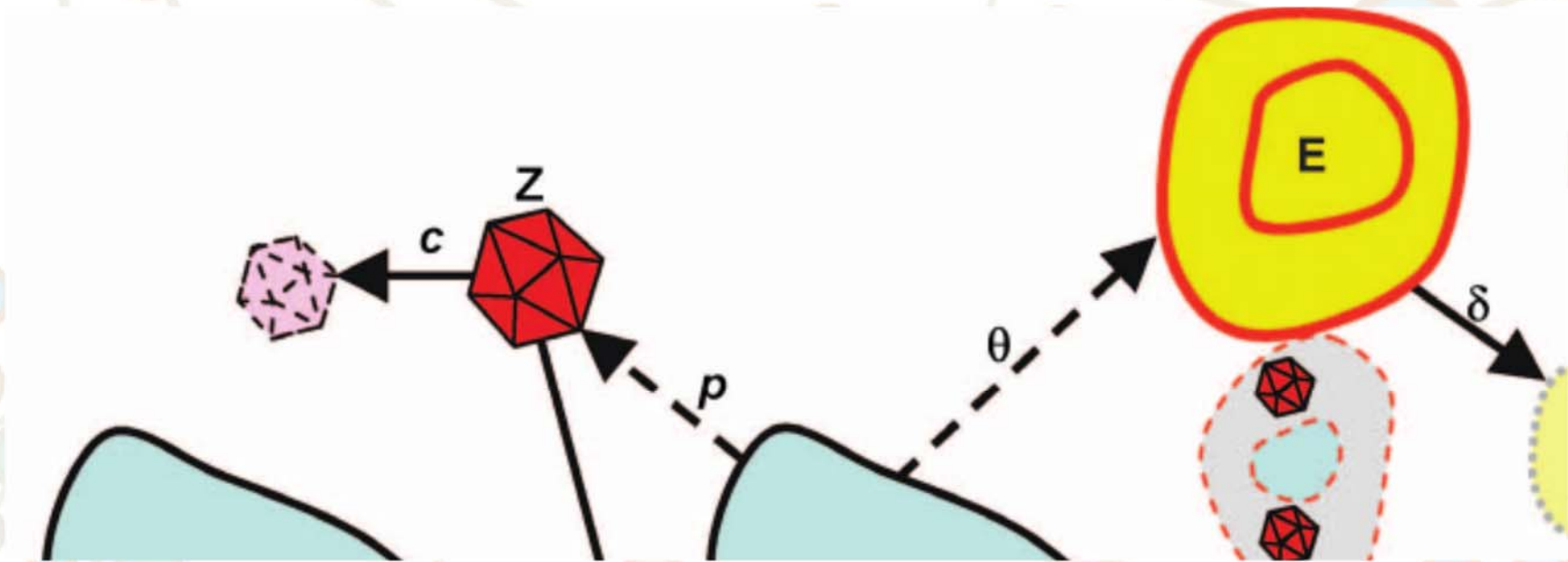
**Joshua T. Schiffer,^{1,2*} Laith Abu-Raddad,^{2,3,4} Karen E. Mark,^{1,2} Jia Zhu,^{2,5} Stacy Selke,⁵
Amalia Magaret,⁶ Anna Wald,^{1,2,6,7} Lawrence Corey^{1,2,6}**

(Published 18 November 2009; Volume 1 Issue 7 7ra16)

Science Translational
Medicine, 2009

Systems Virology

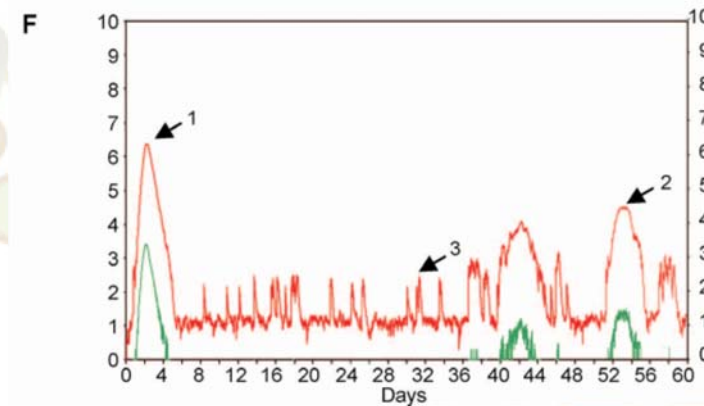
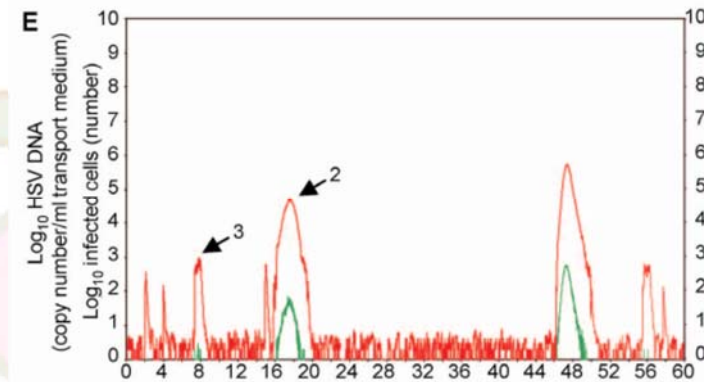
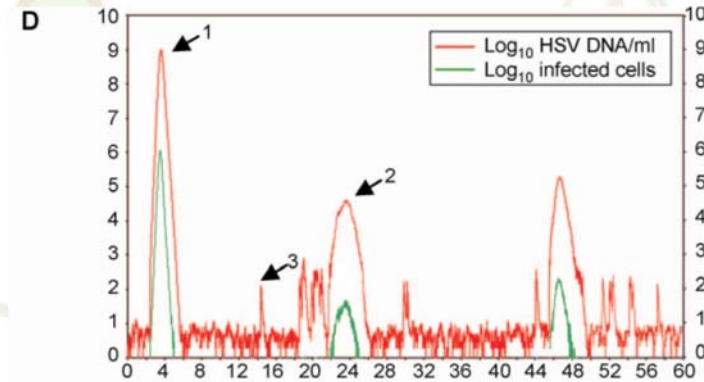
Mathematical models



Systems Virology

Simulations

- Predicts the episodes of virus shedding
- Confirmed prediction by experimental data
- Sub-clinical shedding





Systems Virology

- Example 2

The Hepatitis E virus intraviral interactome

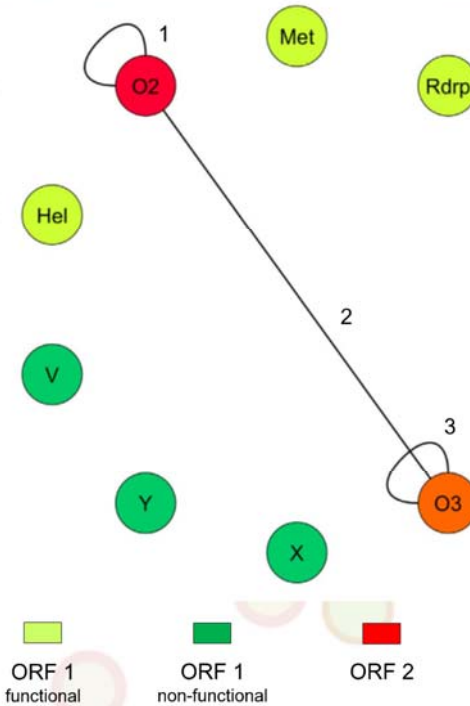
Andreas Osterman^{1,*}, Thorsten Stellberger^{2,3,*}, Anna Gebhardt^{1,†}, Marisa Kurz¹,
Caroline C. Friedel⁴, Peter Uetz^{2,5}, Hans Nitschko¹, Armin Baiker³ & Maria G. Vizoso-Pinto^{1,6}

Scientific Reports,
2015

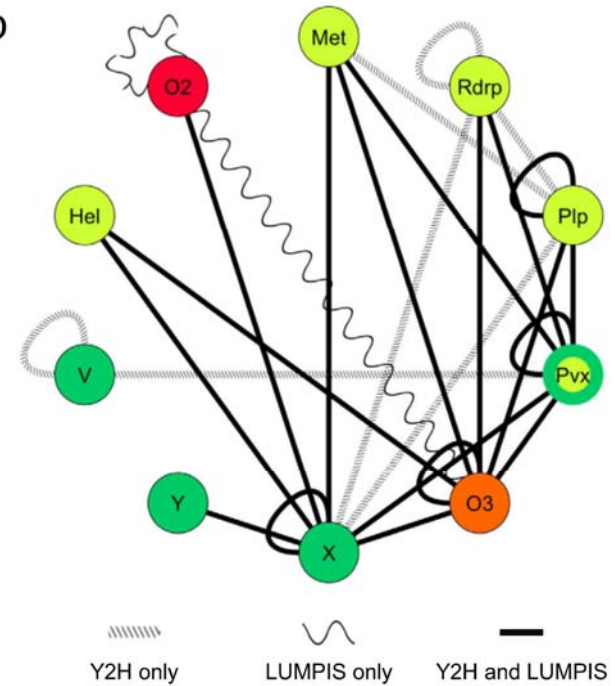
Systems Virology

- Interactome network
- Possible drug targets

a



b



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Criticism of systems virology

- Discovery-based not hypothesis-driven
- Slow and expensive
- Maybe the only way to understand the emergent properties in some dynamic systems
- Hypothesis generator
- Analogy to AlphaGo

Reference

- Aderem, A. et al., 2011. A systems biology approach to infectious disease research: innovating the pathogen-host research paradigm. *mBio*, 2(1), pp.e00325–10.
- Kollmus, H., Wilk, E. & Schughart, K., 2014. Systems biology and systems genetics - novel innovative approaches to study host-pathogen interactions during influenza infection. *Current opinion in virology*, 6, pp.47–54.
- Law, G.L. et al., 2013. Systems virology: host-directed approaches to viral pathogenesis and drug targeting. *Nature Reviews Microbiology*, 11(7), pp.455–466.
- Russell, C.D. & Baillie, J.K., 2017. Treatable traits and therapeutic targets: Goals for systems biology in infectious disease. *Current Opinion in Systems Biology*, 2, pp.140–146.