Systems Biology meets Medical Virology

PhD student: Felix Wong

Supervisor: Prof. Paul KS Chan

Department of Microbiology

Faculty of Medicine

Chinese University of Hong Kong

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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

Introduction

What is systems biology?

The NIH definition:

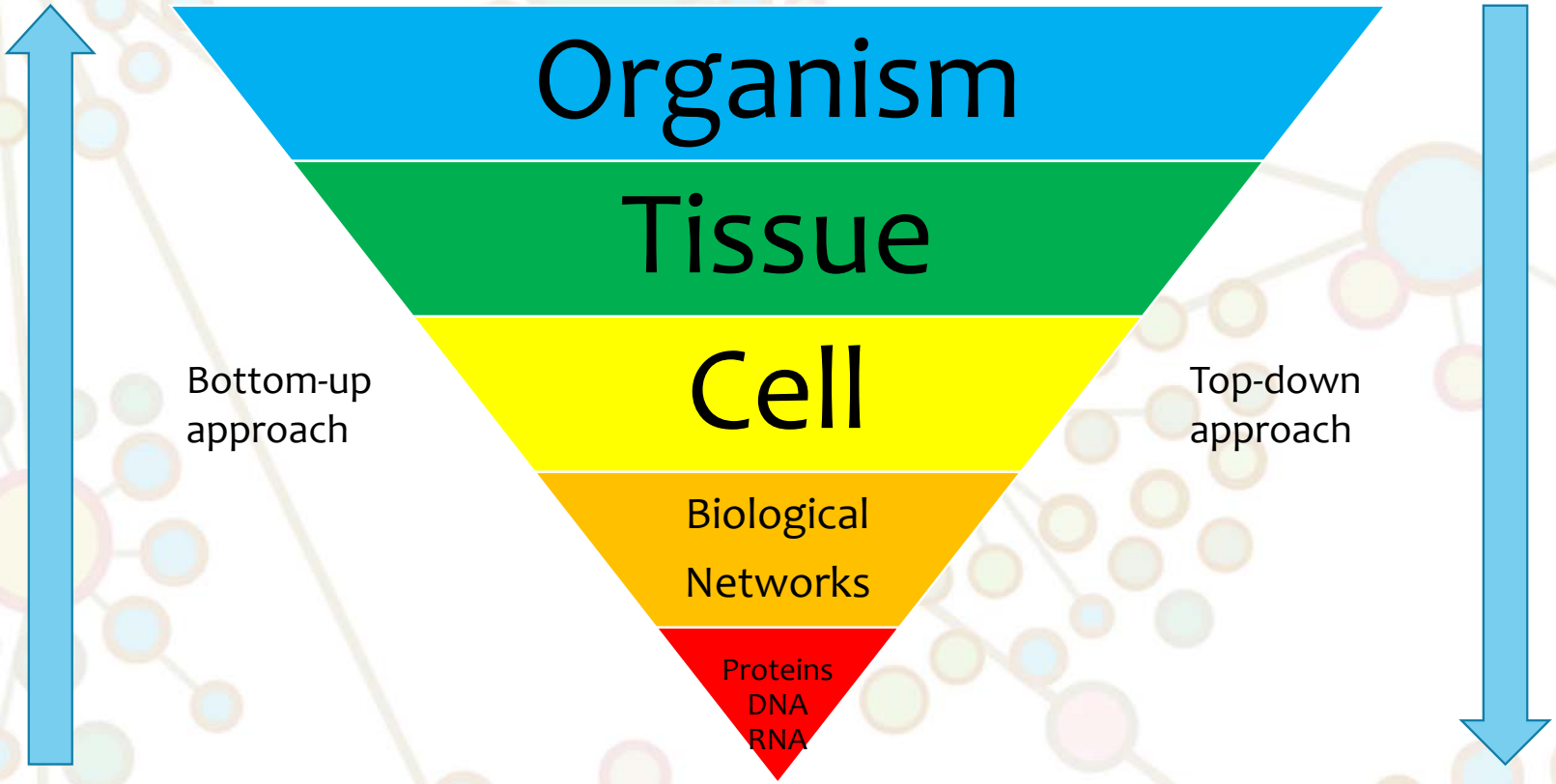
Systems biology is an approach in biomedical research to understanding the larger picture – be it at the level of the organism, tissue, or cell – by putting its pieces together.

The NIH Catalyst Volume 19 issue 6, 2011

Introduction

- 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



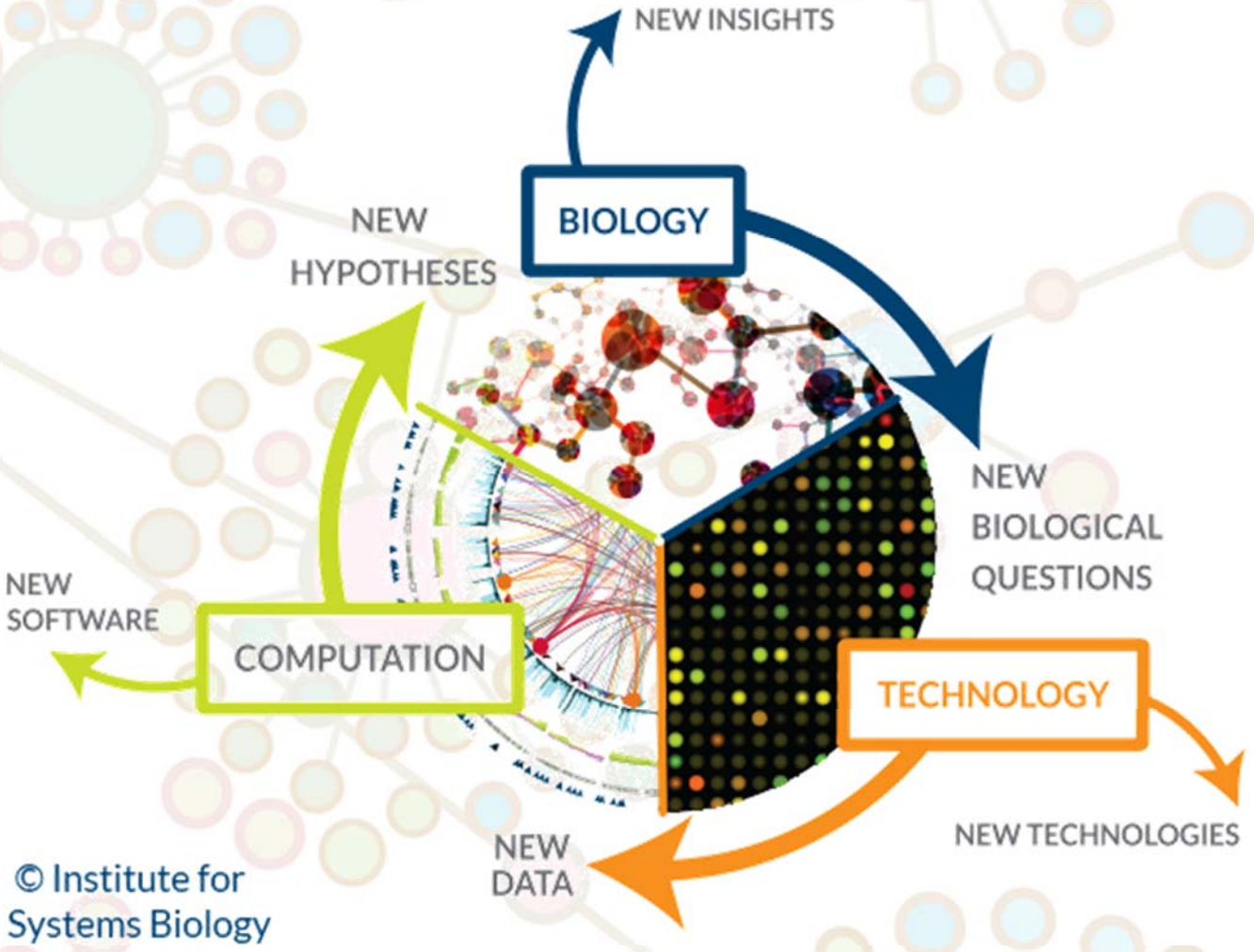
Introduction

- 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

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

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

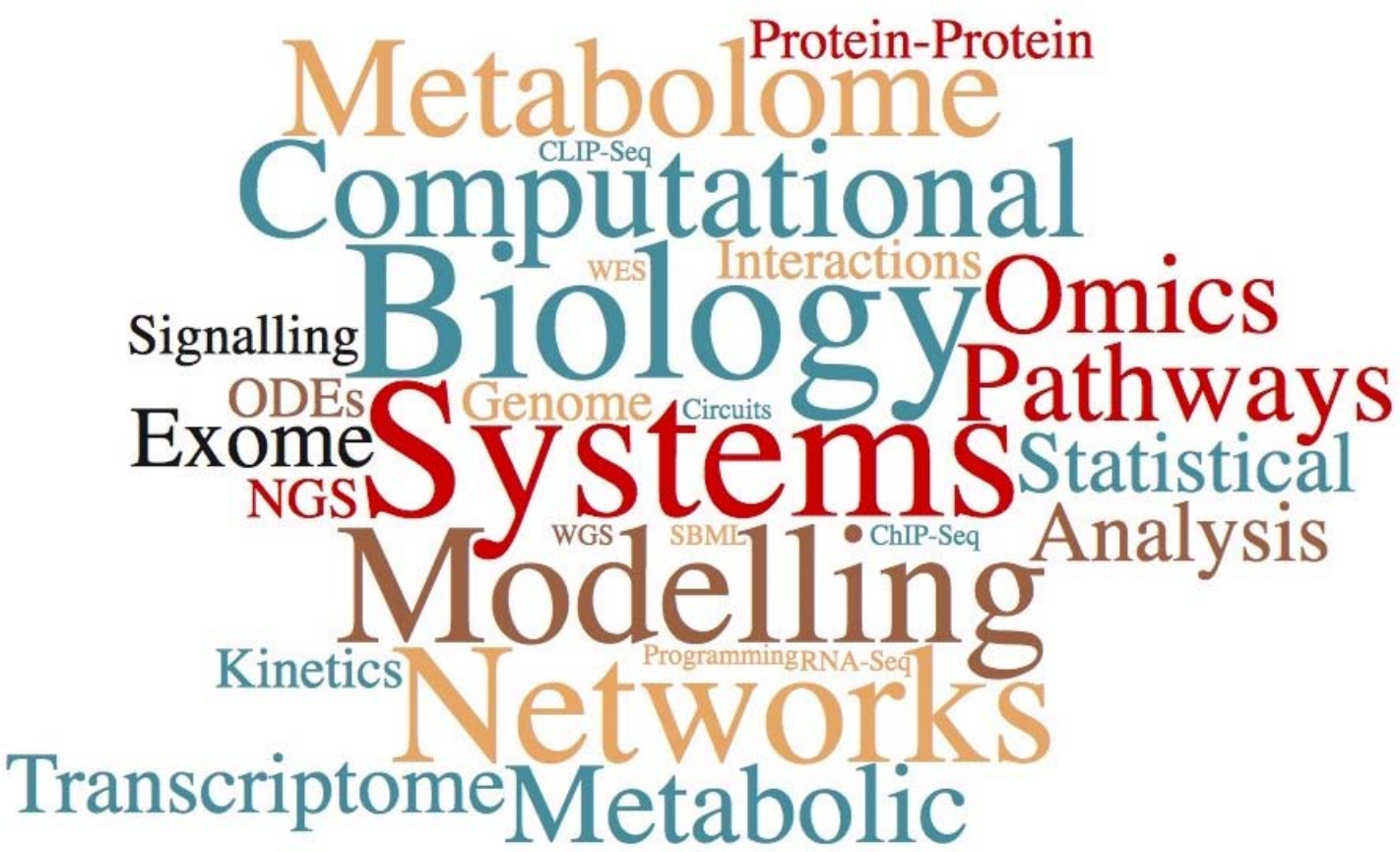
Introduction

Systems Biology

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

Systems Biology

- Mathematical Modelling
- Biological Networks



Mathematical Modelling

- Linear and non-linear dynamics

$$\frac{dx}{dt} = k \qquad x(t) = x_0 + kt$$

$$\frac{dx}{dt} = kx \qquad x(t) = x_0 e^{kt}$$

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

Mathematical Modelling

Mass-action law

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

$$A + B \xrightarrow{k} C \qquad \frac{d[A]}{dt} = -k[A][B]$$

Michaelis-Menten equation

$$E + S \rightleftarrows ES \xrightarrow{k2} E + P$$

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

Mathematical Modelling

- *lac* operon in *E. coli*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

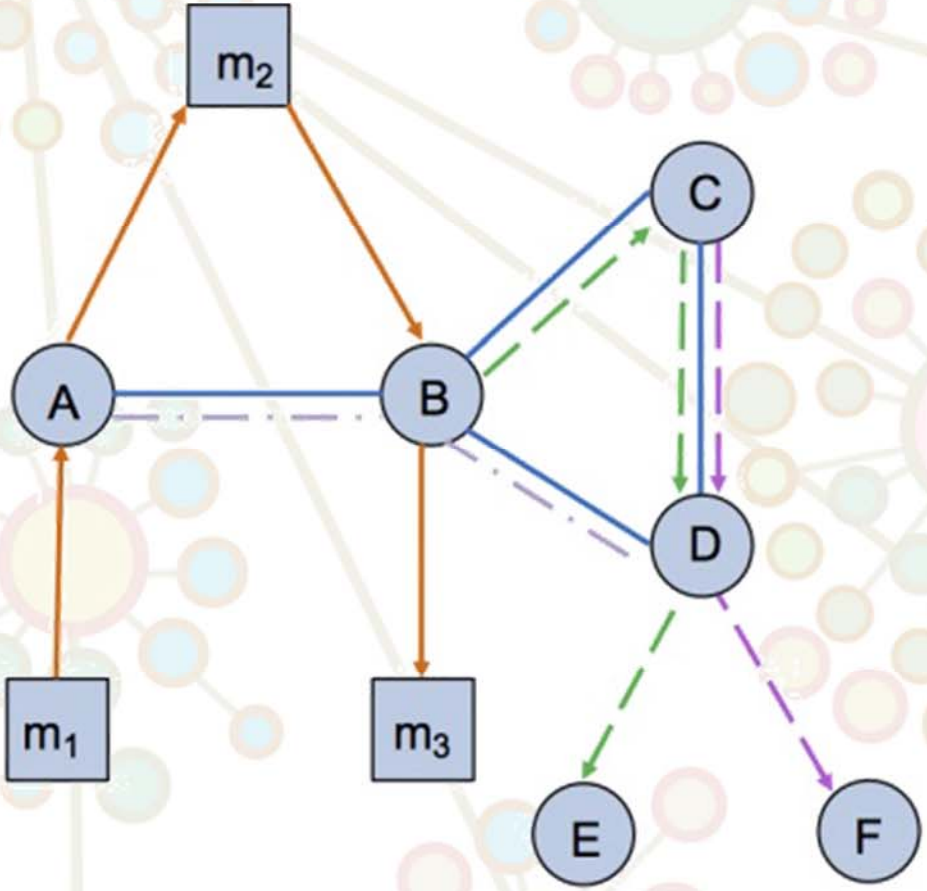
$$J_L([L]) = 4\phi_M\mathcal{M}([L])[B].$$

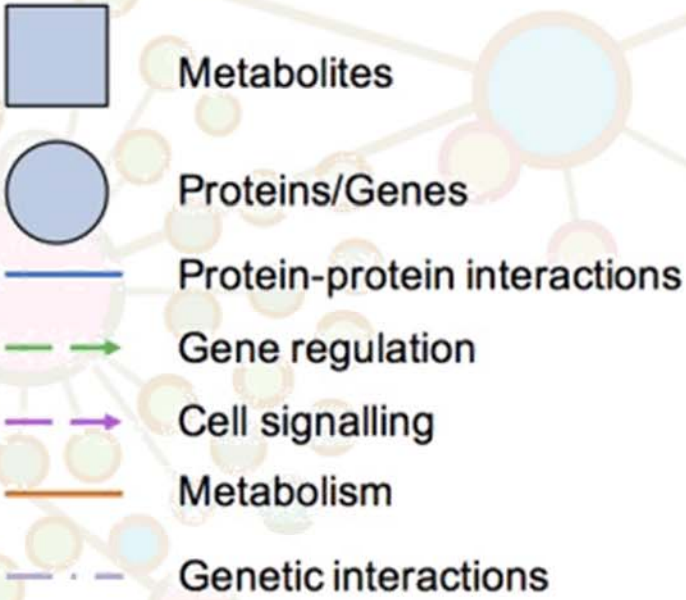
Santillán M. (2011) Biophysical Journal, Vol. 94 p.2065-2081

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

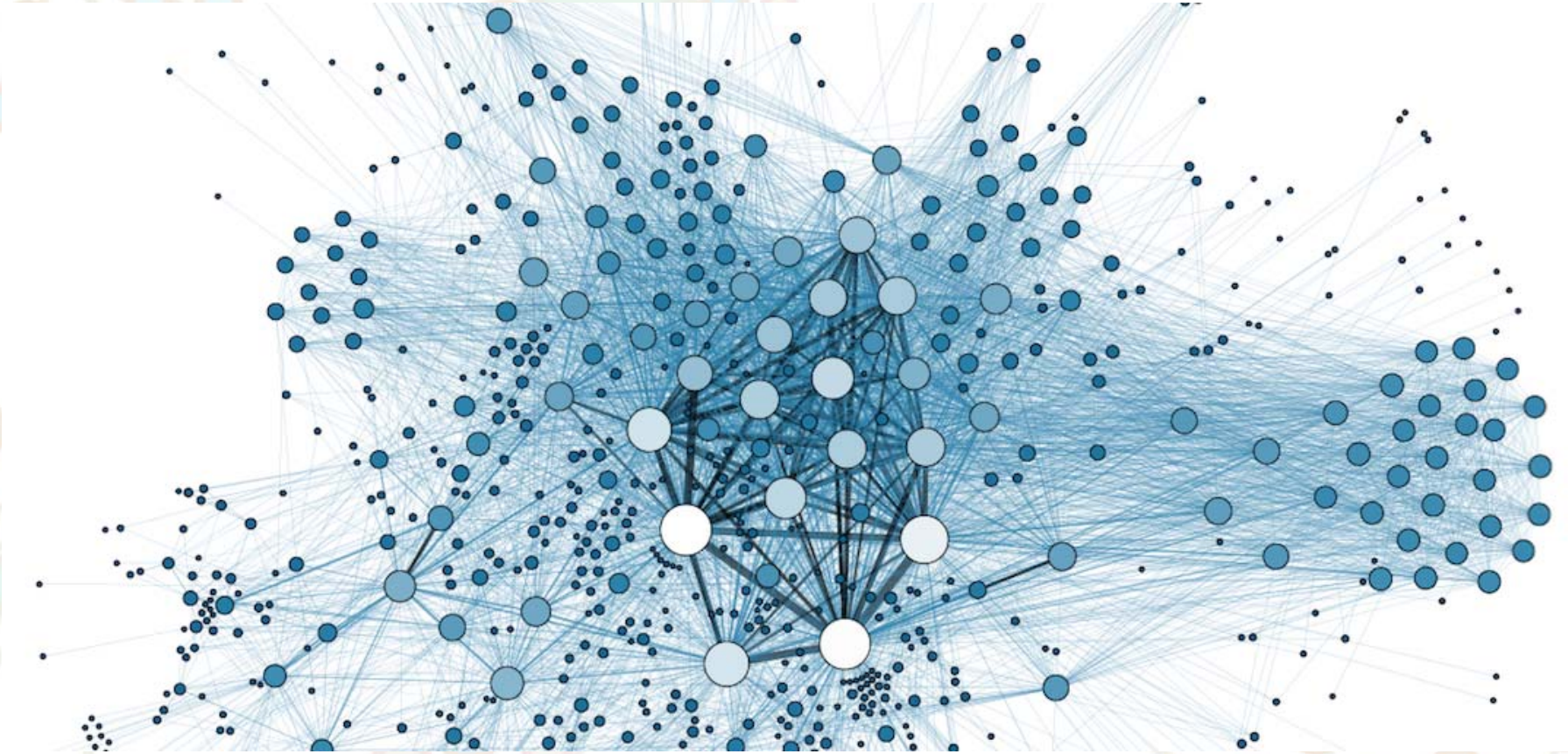
Biological Networks





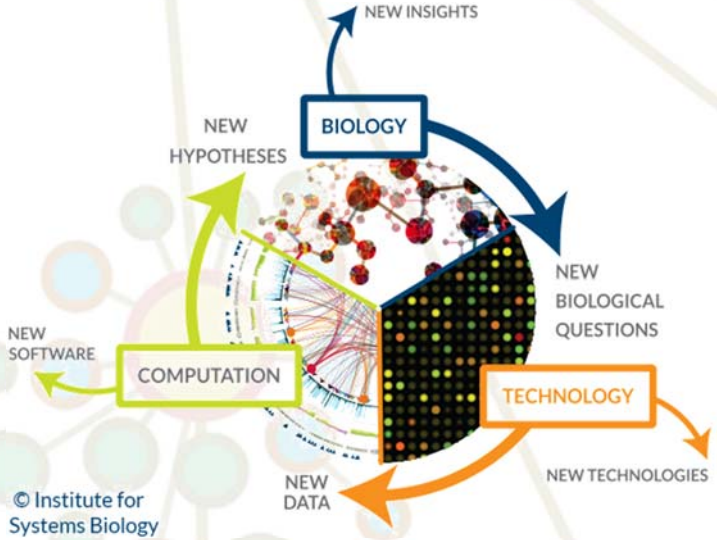
EMBL-EBI Training online. Network analysis of protein interaction data: an introduction https://www.ebi.ac.uk/training/online/course/network-analysis-protein-interaction-data-introduction/

Biological Networks

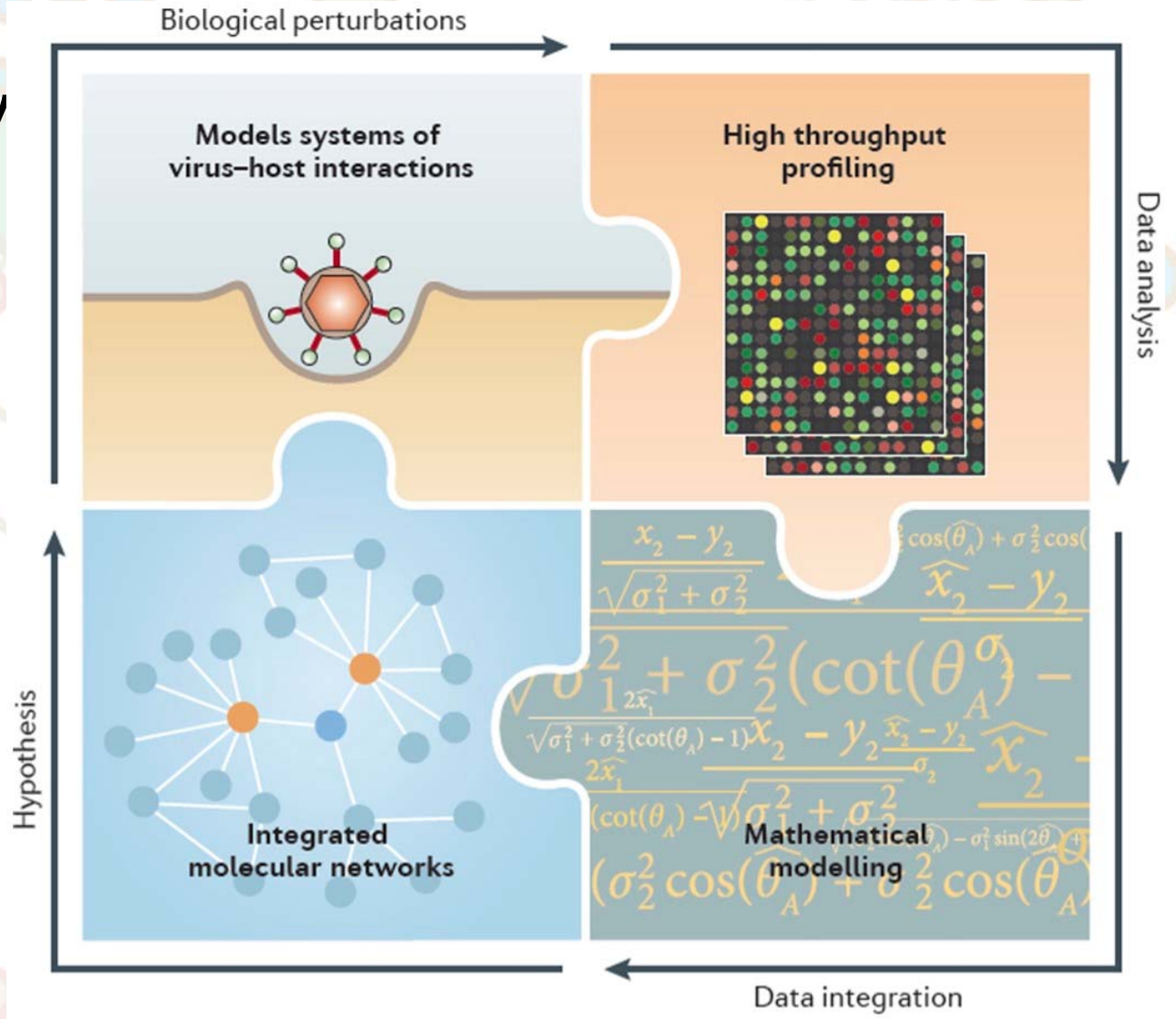


Systems Virology

The systems virology paradigm



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



Systems Virology

- 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

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

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

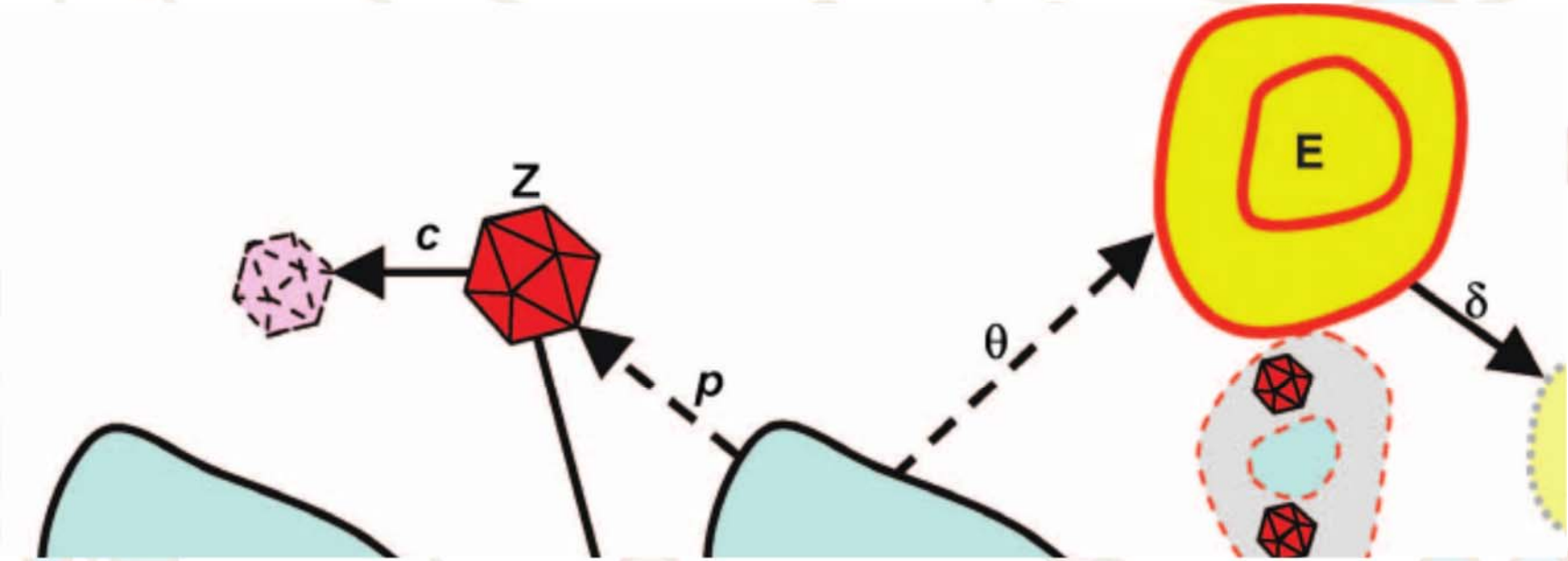
Joshua T. Schiffer,[1,2]* Laith Abu-Raddad,[2,3,4] Karen E. Mark,[1,2] Jia Zhu,[2,5] Stacy Selke,[5] Amalia Magaret,[6] Anna Wald,[1,2,6,7] Lawrence Corey[1,2,6]

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

Science Translational Medicine, 2009

Systems Virology

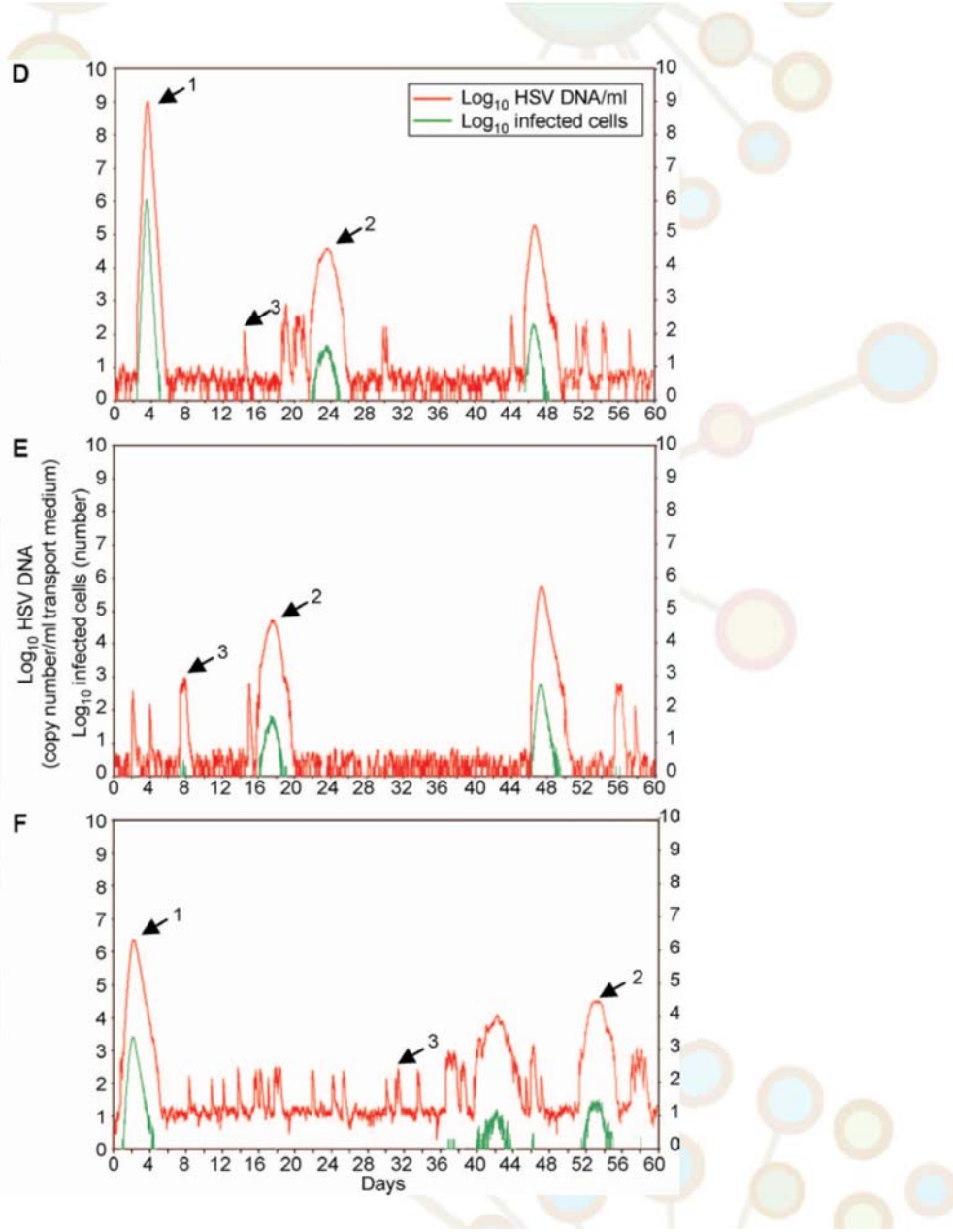
Mathematical models



Systems Virology

Simulations

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



Systems Virology

- Example 2

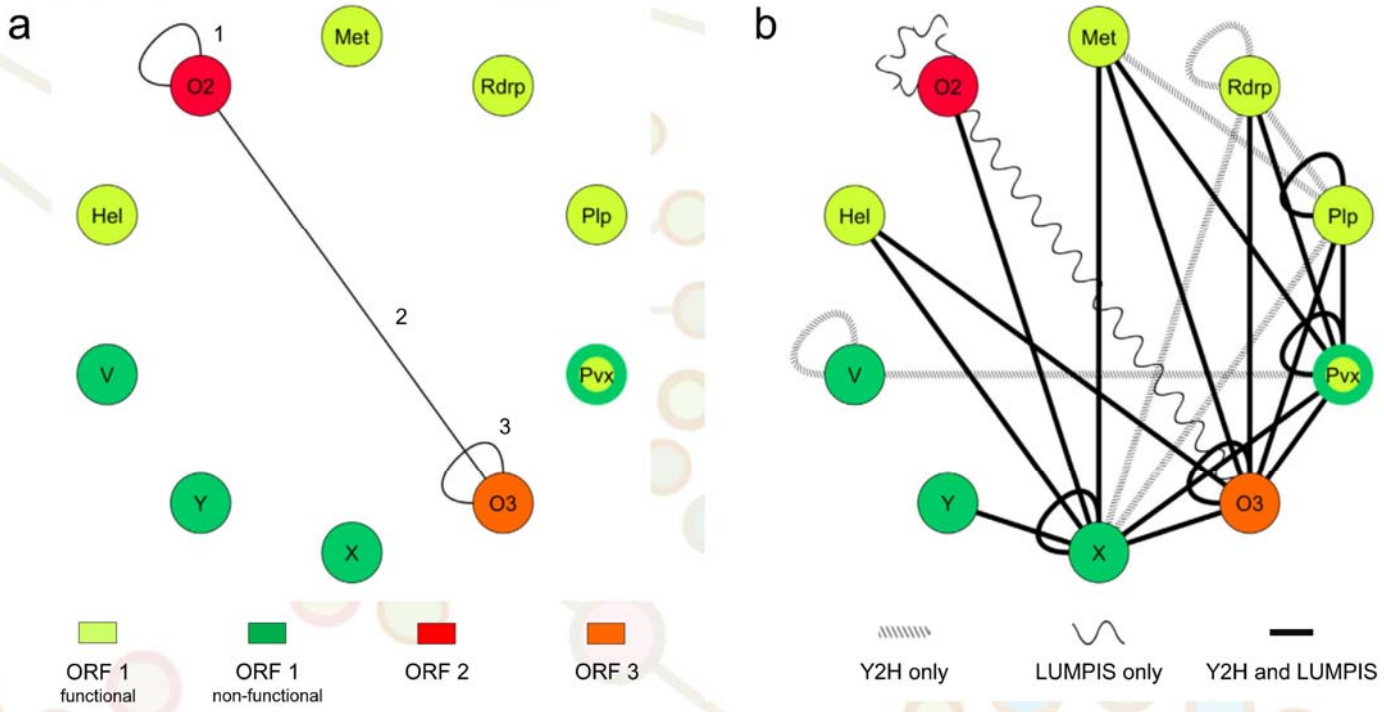
The Hepatitis E virus intraviral interactome

Andreas Osterman[1,*], Thorsten Stellberger[2,3,*], Anna Gebhardt[1,†], Marisa Kurz[1], Caroline C. Friedel[4], Peter Uetz[2,5], Hans Nitschko[1], Armin Baiker[3] & Maria G. Vizoso-Pinto[1,6]

Scientific Reports, 2015

Systems Virology

- Interactome network
- Possible drug targets



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.
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