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MATHEMATICAL SCIENCES AND APPLICATIONS

The Hypernetwork Model of Complex Systems

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Nobel Prizes 2021

Physics: Awarded “for groundbreaking contributions to our understanding of complex systems.”

Economics: Awarded “for methodological contributions to the analysis of causal relationships."

- **A complex system is composed of many components that interact with each other in a nonlinear manner.**
- **Interactions may be directional (casual), signed, and weighted.**
- **How to infer causal relationships of complex systems: Physics marries economics.**


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EDITORIAL

Complex systems in the spotlight: next steps after the 2021 Nobel Prize in Physics

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COMPLEX SYSTEMS | BLOG

Celebrating the complexity Nobel prize with perspectives on the future of the field

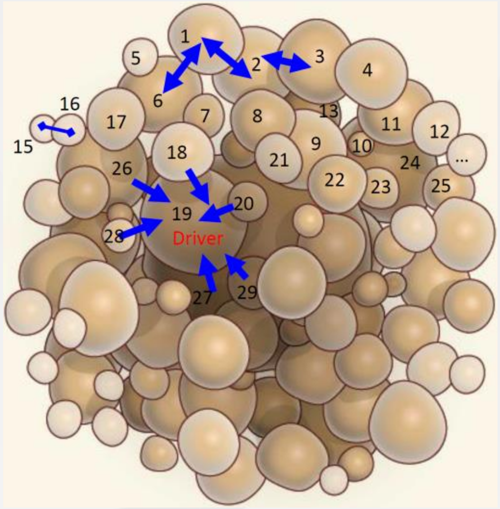
20 Jan 2023 Hamish Johnston

Inferring causal relationships of complex systems has become one of the hottest and most promising topics of research in biology, medicine, engineering, economics, and physics.

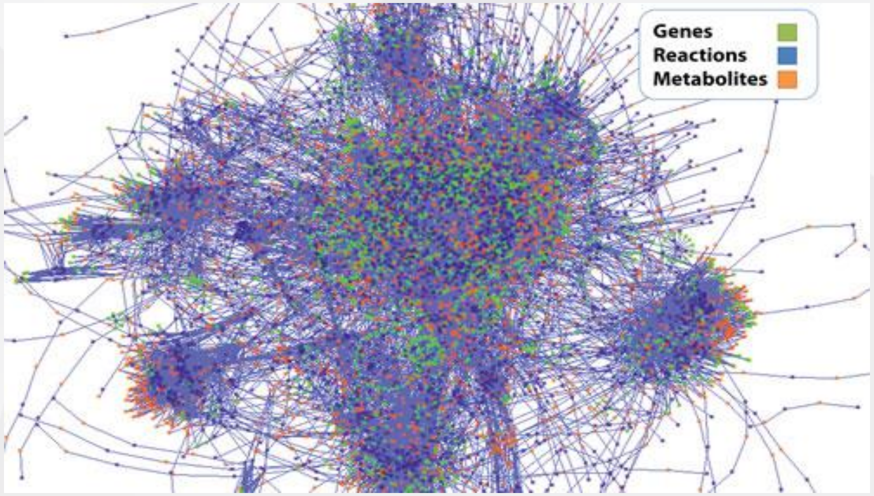
Study Complex Systems: Challenges and Opportunities

- Complex systems are "complex" in terms of the number of components and interactions
- Automatic high-throughput measurement techniques make it possible to monitor any systems.
- How can we extract causal relationships underlying complex systems using these big data sets?

Tumor



Cell

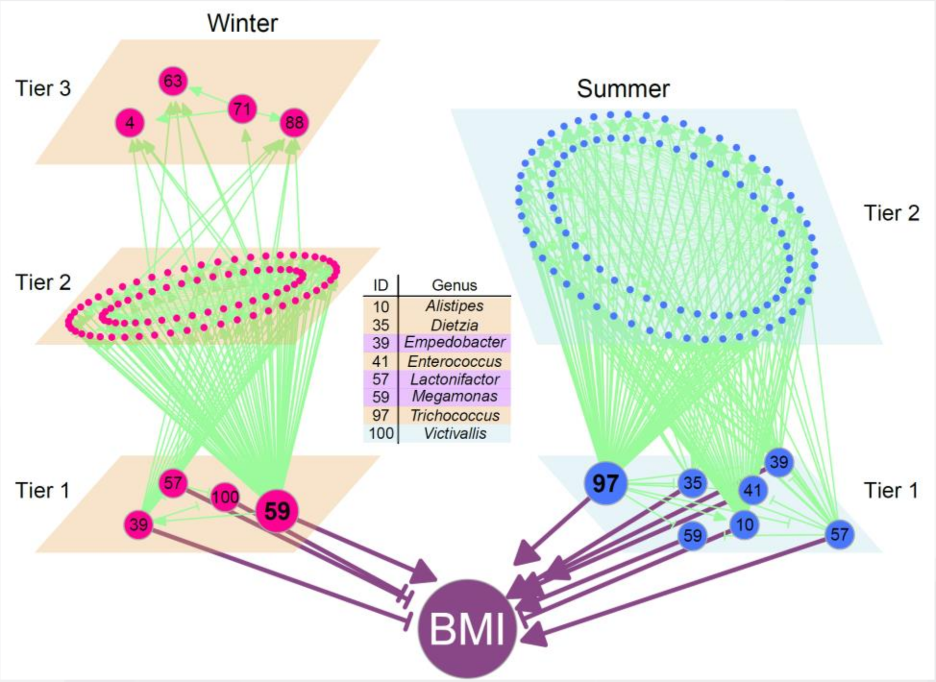


Single-cell analysis (Komarova 2016: Nature)

Network Modeling of Complex Systems

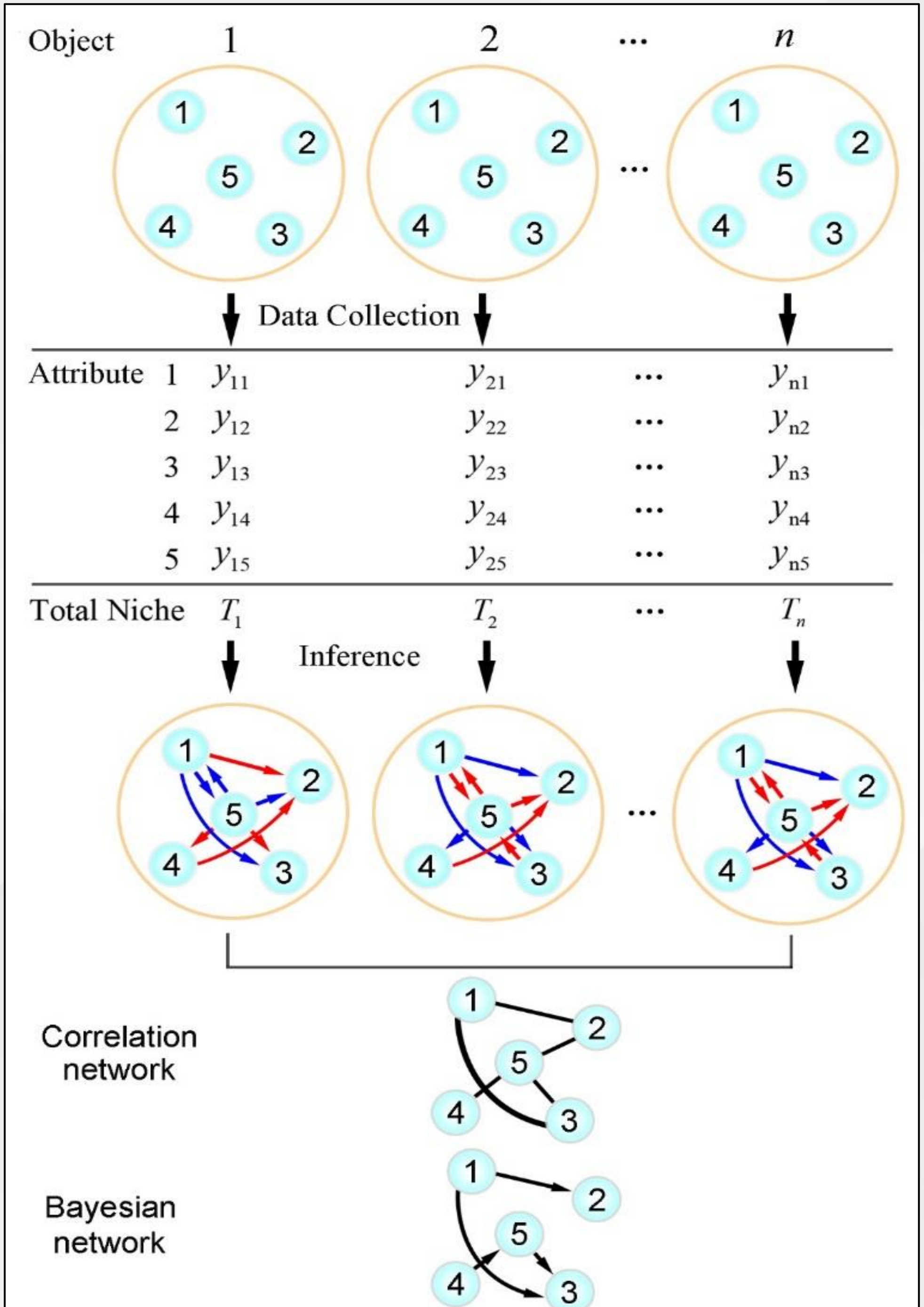
- All components affect system behavior through direct and/or indirect pathways.
- Network models of complex systems capture direct and indirect effects.
- Networks chart a roadmap of how each element flows its signal of influence within the whole system.

The Gut Microbiota



Reanalysis of Davenport et al.'s (PLoS ONE, 2015) data

Experimental Design for Network Inference



- Consider *n* objects (e.g., cells, individuals)
- Measure *p* (i.e., 5) different attributes (elements) of each object
- Form an (*n* x *p*) data matrix

Current approaches can only infer an overall, less informative network.

We want to infer sophisticated networks from this data:

- Networks are object-specific (individualized networks)
- Networks are context-specific (e.g., diseased vs. control)
- Bidirectional, signed, and weighted interactions (fully informative)

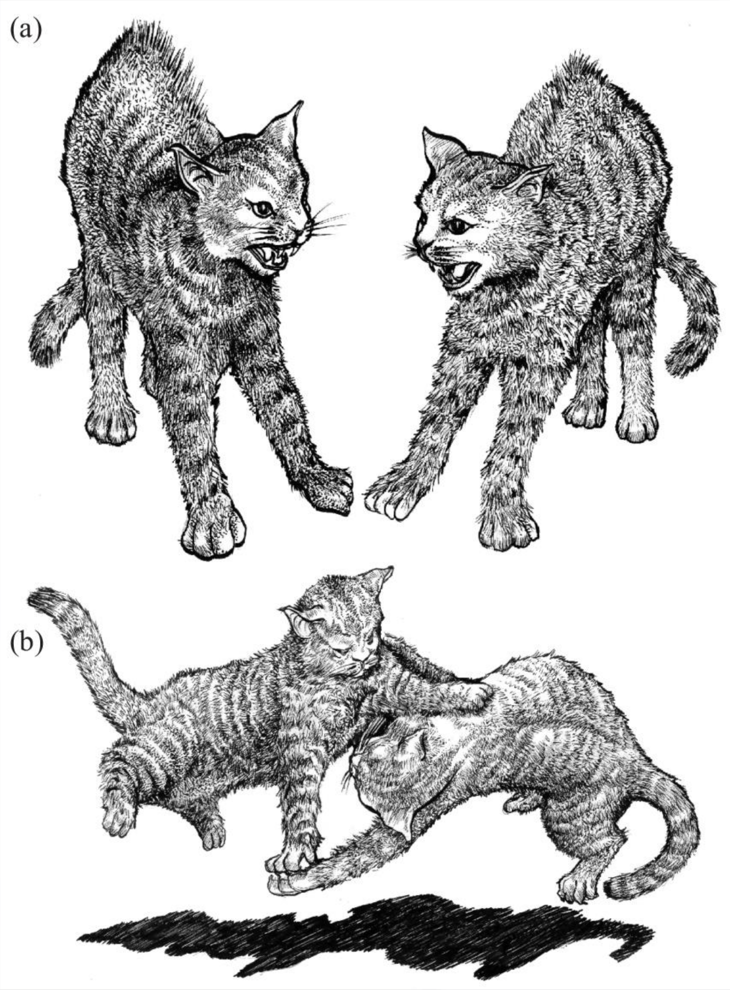
How to infer such sophisticated networks?

We introduce evolutionary game theory

by viewing inter-element interactions as a game

Game Theory

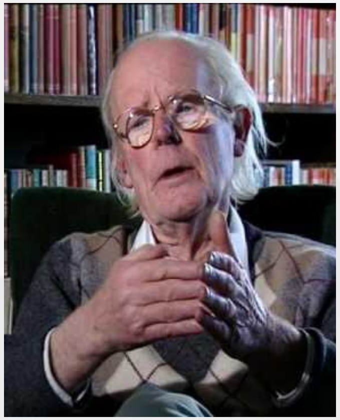
The Nash equilibrium and a tit-for-tat strategy



For an evolving system, this game will occur repeatedly, expressed as

Left Cat CCCCCCCCDCCCCCCCCD
Right Cat CCCCCCCCDCCCCCCCCR

Cooperative strategy (C)
Dangerous strategy (D)
Retreats (R)



The Nash equilibrium (Nash 1950, PNAS)

↓

Evolutionarily stable strategy (ESS) (Smith and Price 1973, Nature)

Quantitative decision theory (Wu et al. 2021)

(1) The bigger cat chooses to cooperate with the smaller cat, when their strength ratio is beyond 0.61 (golden dissection ratio)

(2) The smaller cat would cheat the bigger cat, when their strength ratio is 0.38 to 0.61 (Fibonacci Retracement)

Lotka-Volterra (LV) predator-prey representation of ESS

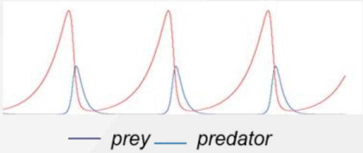
Payoff of one cat (player) is determined by **its own strategy** and **the strategy of the other cat**

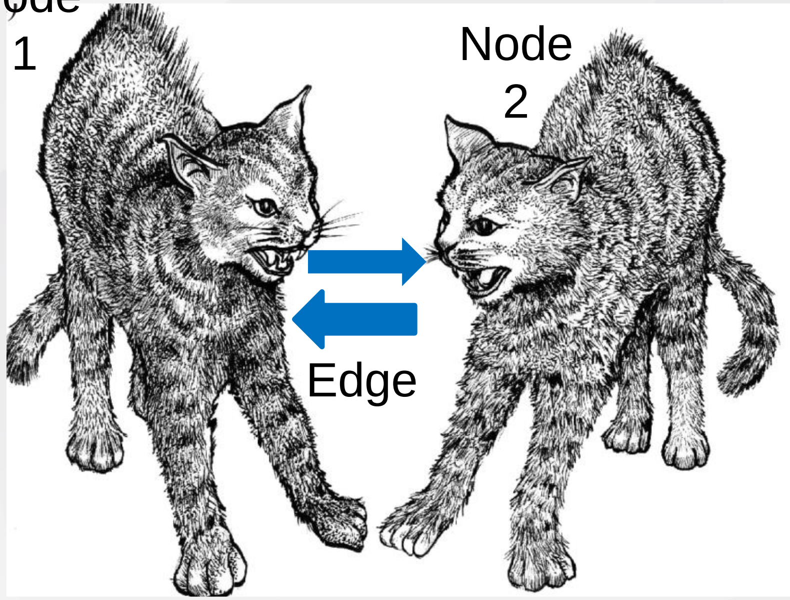
$$dP_1/dt = Q_1(P_1) + Q_{1\leftarrow 2}(P_2)$$
$$dP_2/dt = Q_2(P_2) + Q_{2\leftarrow 1}(P_1)$$

Independent   Dependent


Alfred J. Lotka (1880-1949)


Vito Volterra (1860-1940)





	$Q_{1\leftarrow 2}(P_2)$	$Q_{2\leftarrow 1}(P_1)$
Mutualism	+	+
Antagonism	-	-
Aggression	+	-
Altruism	-	+

Bidirectional, signed, and weighted interactions, outperforming traditional models

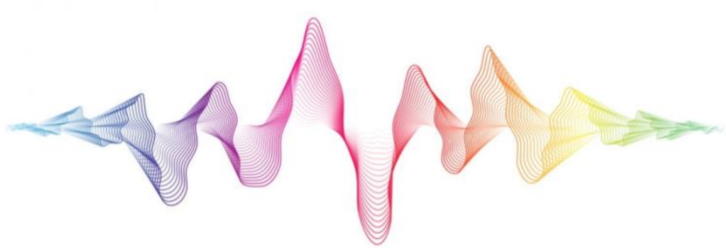
Johnson, C.A., Smith, G.P., Yule, K. *et al.* Coevolutionary transitions from antagonism to mutualism explained by the Co-Opted Antagonist Hypothesis. *Nat Commun* **12**, 2867 (2021).

Dynamic Systems and Dynamic Models

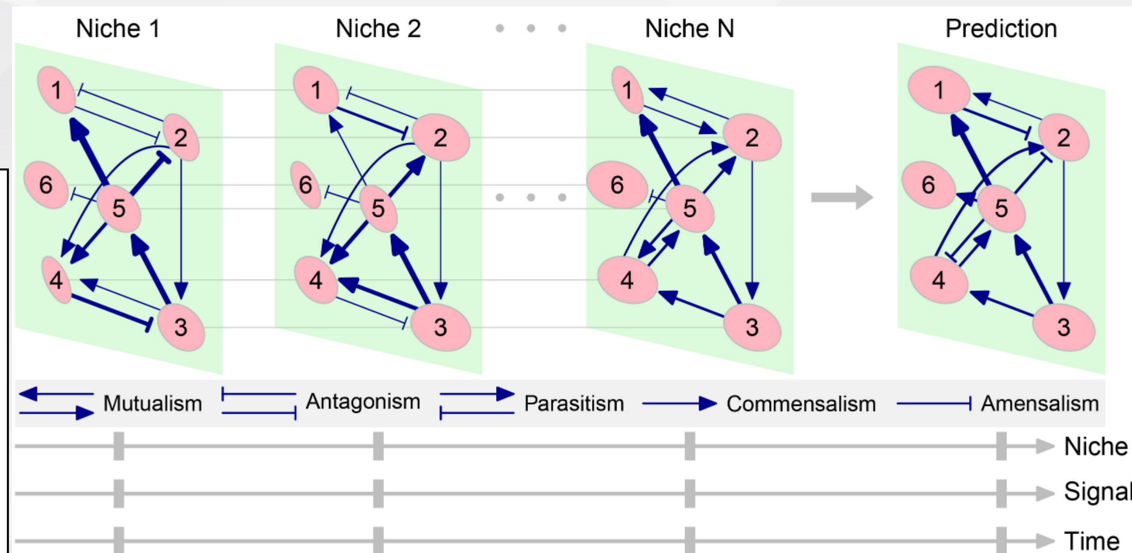
- Differential equations:
  - ➢ Ordinary differential equations (ODE)–simplest
  - ➢ Delay differential equations (DDE)
  - ➢ Hybrid differential equations (HDE)
  - ➢ Partial differential equations (PDE)
  - ➢ Stochastic differential equations (SDE)
- Difference equations and state-space models
- Stochastic processes models: branching process etc.
- Agent-based models and cellular automata

Graph Theory

Dynamic Modeling



Dynamic Measurements



Networks beyond Dyadic Interactions

- **Graph theory: pairwise interactions**
- **Hypergraph theory: high-order interactions**

Taking high-order interactions into account

- Enhance our modeling capacities
- Help to more precisely characterize complex systems

REVIEW

doi:10.1038/nature22898

Beyond pairwise mechanisms of species coexistence in complex communities

Jonathan M. Levine[1], Jordi Bascompte[2], Peter B. Adler[3] & Stefano Allesina[4]

The tremendous diversity of species in ecological communities has motivated a century of research into the mechanisms that maintain biodiversity. However, much of this work examines the coexistence of just pairs of competitors. This approach ignores those mechanisms of coexistence that emerge only in diverse competitive networks. Despite the potential for these mechanisms to create conditions under which the loss of one competitor triggers the loss of others, we lack the knowledge needed to judge their importance for coexistence in nature. Progress requires borrowing insight from the study of multitrophic interaction networks, and coupling empirical data to models of competition.

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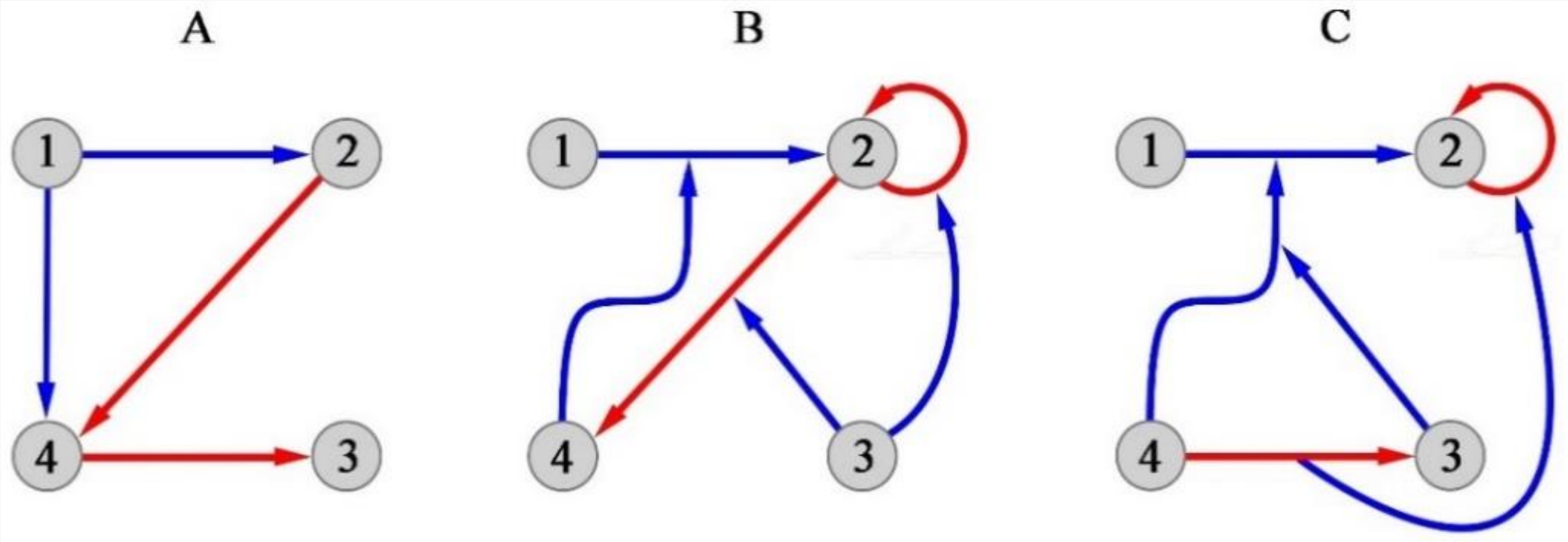
Networks beyond pairwise interactions: Structure and dynamics

Federico Battiston[a,*], Giulia Cencetti[b], Iacopo Iacopini[c,d], Vito Latora[c,e,f,g], Maxime Lucas[h,i,j], Alice Patania[k], Jean-Gabriel Young[l], Giovanni Petri[m,n]

Paradigm Shift:
from Networks to Hypernetworks



- A node affects the interaction between two other nodes
- Interactions between two nodes is affected by a third node

A Hypernetwork Theory: Modeling High-order Interaction Networks

Consider an *m*-dimensional biosystem:

$$\frac{dg_j(t)}{dt} = Q_j\left(g_j(t)\colon\ \Theta_j\right) \qquad \text{Independent}$$
$$+ \sum_{j'=1}^{m} Q_{j\leftarrow j'}\left(g_{j'}(t)\colon\ \Theta_{jj'}\right) \qquad \text{First-order}$$
$$+ \sum_{j_1=1}^{m}\sum_{j_2=1}^{m} Q_{j\leftarrow j_1 j_2}\left(z_{j_1 j_2}(t)\colon\ \Theta_{j j_1 j_2}\right) \qquad \text{Second-order}$$
$$+ \sum_{j_1=1}^{m}\sum_{j_2=1}^{m}\sum_{j_3=1}^{m} Q_{j\leftarrow j_1 j_2 j_3}\left(z_{j_1 j_2 j_3}(t)\colon\ \Theta_{j j_1 j_2 j_3}\right) \qquad \text{Third-order}$$
$$+ \ldots \quad j' \neq j = 1, \ldots, m;\ j_1 < j_2 < j_3 = 1, \ldots, m$$

- **It may include more terms that describe four and higher-way interactions if needed.**
- **Different from pairwise network modeling, it treats predictors as interacting networks at different orders.**

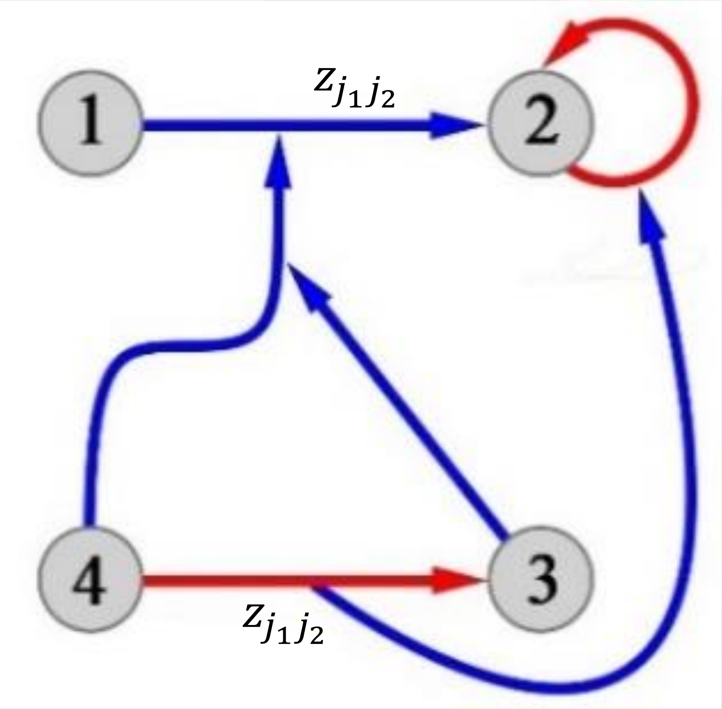
What is the interaction z_{j1j2}?

$$\frac{dg_j(t)}{dt} = Q_j\big(g_j(t): \Theta_j\big) \qquad \text{Independent}$$

$$+ \textstyle\sum_{j'=1}^{m} Q_{j\leftarrow j'}\big(g_{j'}(t): \Theta_{jj'}\big) \qquad \text{First-order}$$

$$+ \textstyle\sum_{j_1=1}^{m}\sum_{j_2=1}^{m} Q_{j\leftarrow j_1 j_2}\big(z_{j_1 j_2}(t): \Theta_{j j_1 j_2}\big) \qquad \text{Second-order}$$

$$j' \neq j = 1, \dots, m;\ j_1 < j_2 = 1, \dots, m$$



Mutualism	1 ↔ 2
Antagonism	1 ↔ 2
Aggression	1 → 2
Altruism	1 → 2

How to define and quantify player-player interactions?

We introduce behavioral ecology theory

goose flying and fish schooling

A quantitative decision theory of animal conflict

(Wu and Jiang et al. 2021, *Heliyon* 7(7): e07621)

Mathemathical descriptors of interactions

Player X \ Player Y	Cooperative	Competitive
Coop	Mutualism	Altruism
Comp	Aggression	Antagonism

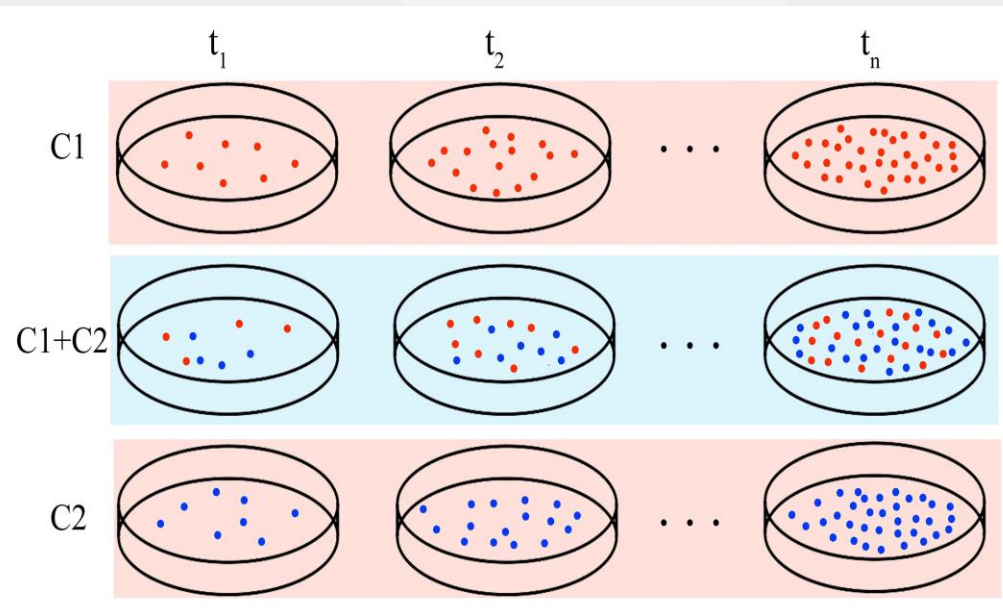
Player X \ Player Y	Cooperative	Competitive
Coop	$z_{mu} = xy/(x-y)$	$z_{al} = (x-y)/x$
Comp	$z_{ag} = x/y$	$z_{an} = 1/[xy(x-y)]$

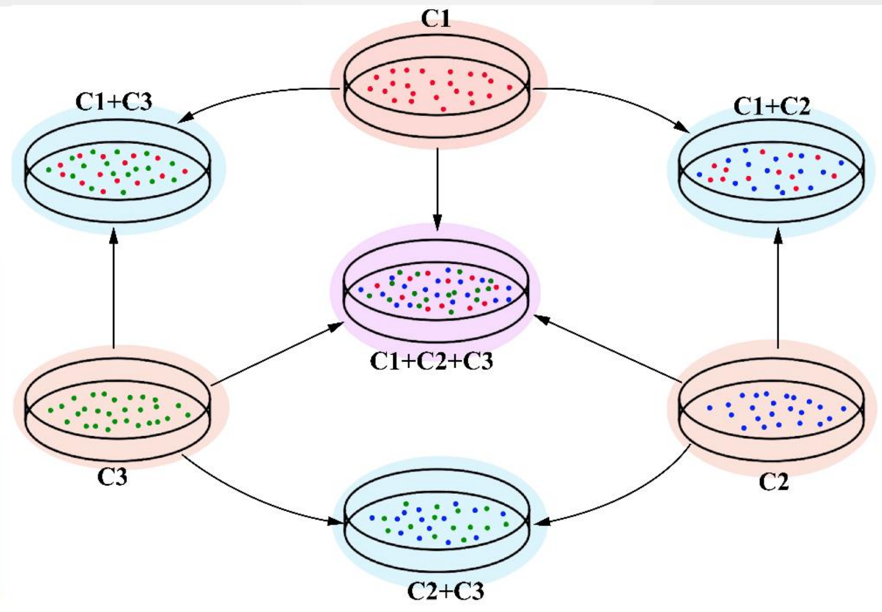
Mutualism-based hypernetworks, z_{mu}
Altruism-based hypernetworks, z_{al}
Aggression-based hypernetworks, z_{ag}
Antagonism-based hypernetworks, z_{an}

Experiemntal validation by Jiang et al. 2019, 2020; Wang et al. 2019, He et al. 2021

Experimental Validation of the Hypernetwork Theory

Randomly choose different lung cancer cell types and cultivate them in monoculture, co-culture, and tri-culture





By Shawn Rice, Penn State College of Medicine

Fundamental Core of the Hypernetwork Theory: Evolutionary Game Dissection

In a socialized environment, the payoff of any player is decomposed in a way like this

$$\frac{dg_j(t)}{dt} = Q_j\left(g_j(t)\colon\, \Theta_j\right) \quad \text{Independent}$$

$$+ \sum_{j'=1}^{m} Q_{j\leftarrow j'}\left(g_{j'}(t)\colon\, \Theta_{jj'}\right) \quad \text{First-order}$$

$$+ \sum_{j_1=1}^{m} \sum_{j_2=1}^{m} Q_{j\leftarrow j_1 j_2}\left(z_{j_1 j_2}(t)\colon\, \Theta_{j j_1 j_2}\right) \quad \text{Second-order}$$

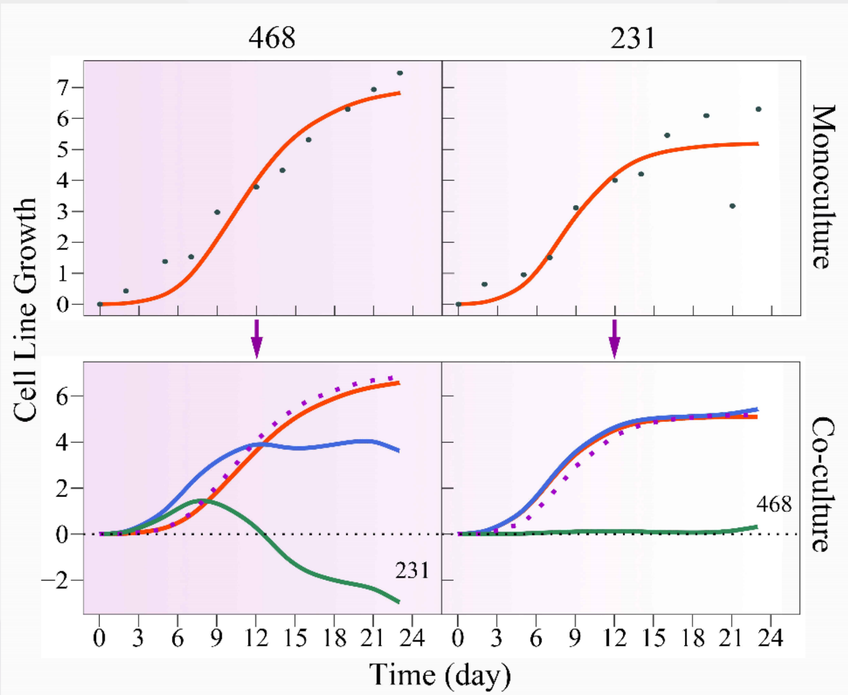
$$j' \neq j = 1, \ldots, m;\ j_1 < j_2 = 1, \ldots, m$$

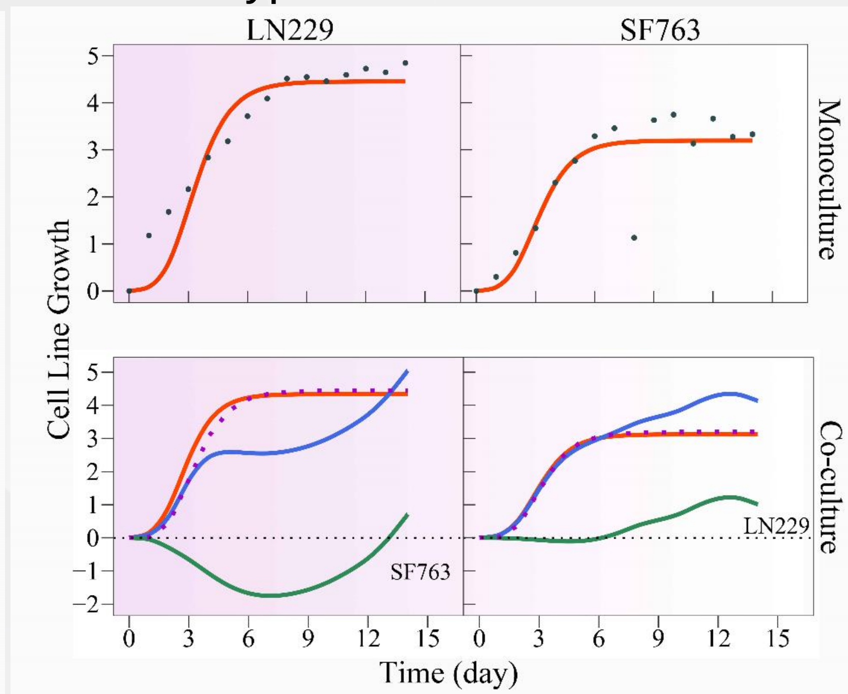
- The independent component occurs when this player **is assumed** to be in isolation.

- If the estimated independent component value is consistent with that value obtained from its monoculture, then this suggests that the dissection theory works.

Experimental Validation from *in vitro* Cultural Experiment

Four lung cancer cell types





Amensalism (偏害)

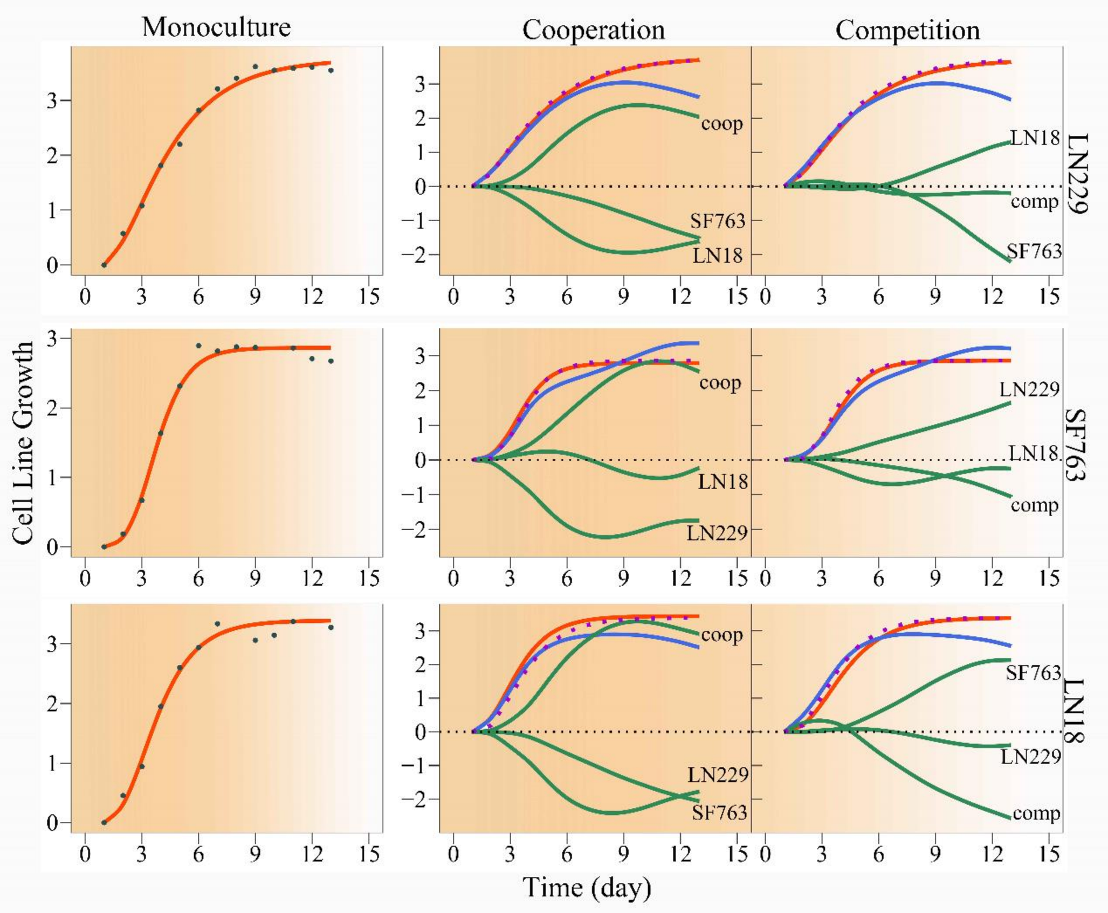
Altrusim/Aggression (利他/侵害)

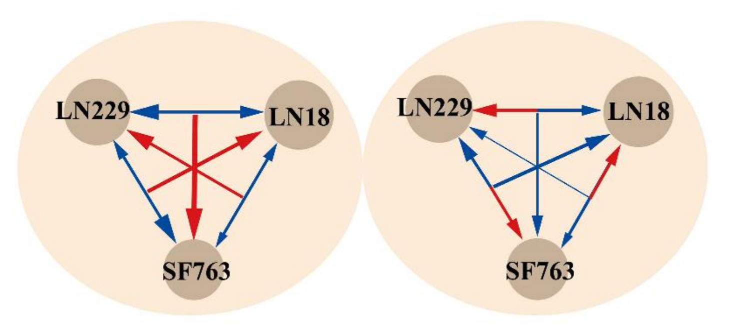
$$dP_1/dt = Q_1(P_1) + Q_{1\leftarrow 2}(P_2)$$
$$dP_2/dt = Q_2(P_2) + Q_{2\leftarrow 1}(P_1)$$

The model works!

Analyzed by Li Feng

Tri-culture: Experiment 1 – LN229, SF763, LN18

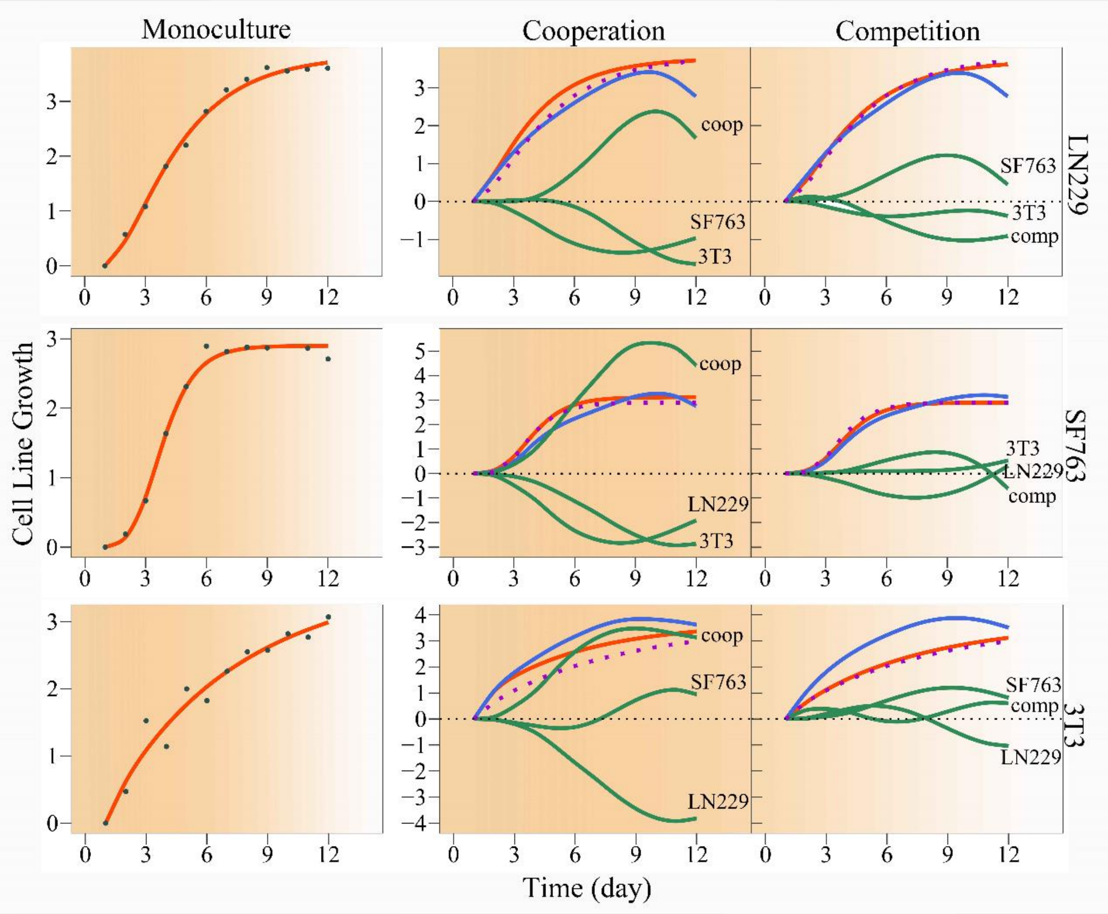


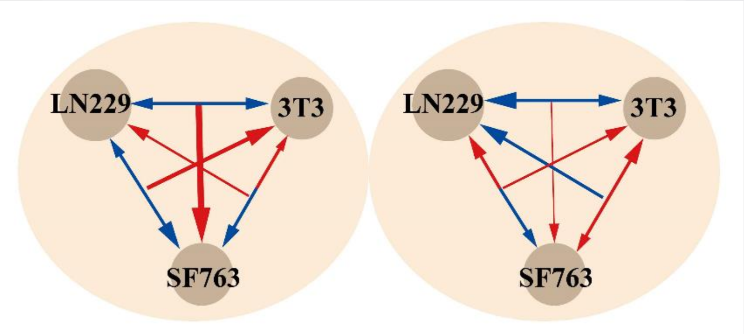


LN229 = Independent
- SF763
- LN18
+ Cooperation

Uncouple their cooperation, making cell growth inhibited

Tri-culture: Experiment 2 – LN229, SF763, 3T3





LN229 = Independent
- SF763
- 3T3
+ Cooperation

Uncouple their cooperation, making cell growth inhibited

Disadvantages of Dynamic Models

Unavailability of high-density time-series measurements

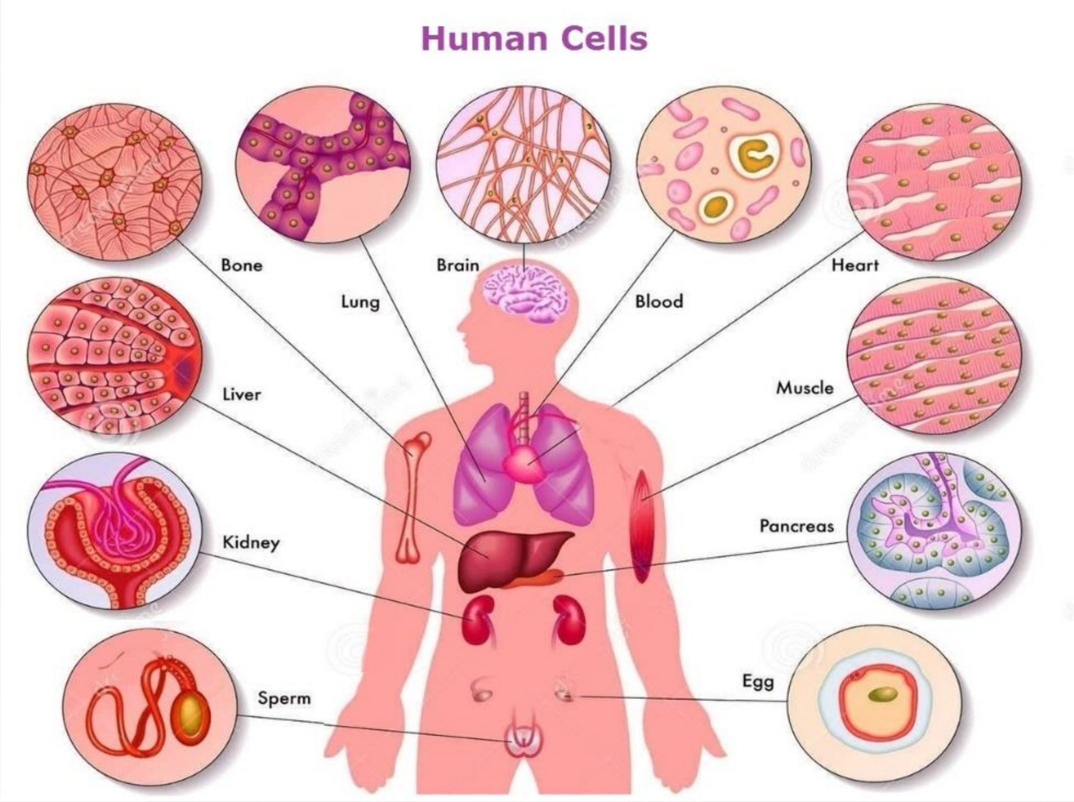
- Impossible to collect
- Ethically impermissible

Limitations to curve fitting

- Time stable
- Resilient to perturbations

The GTEx (Genotype-Tissue Expression) Project: transcriptome measured only once for one donor
https://commonfund.nih.gov/gtex

Cohesive coordination of multiple tissues → Human health

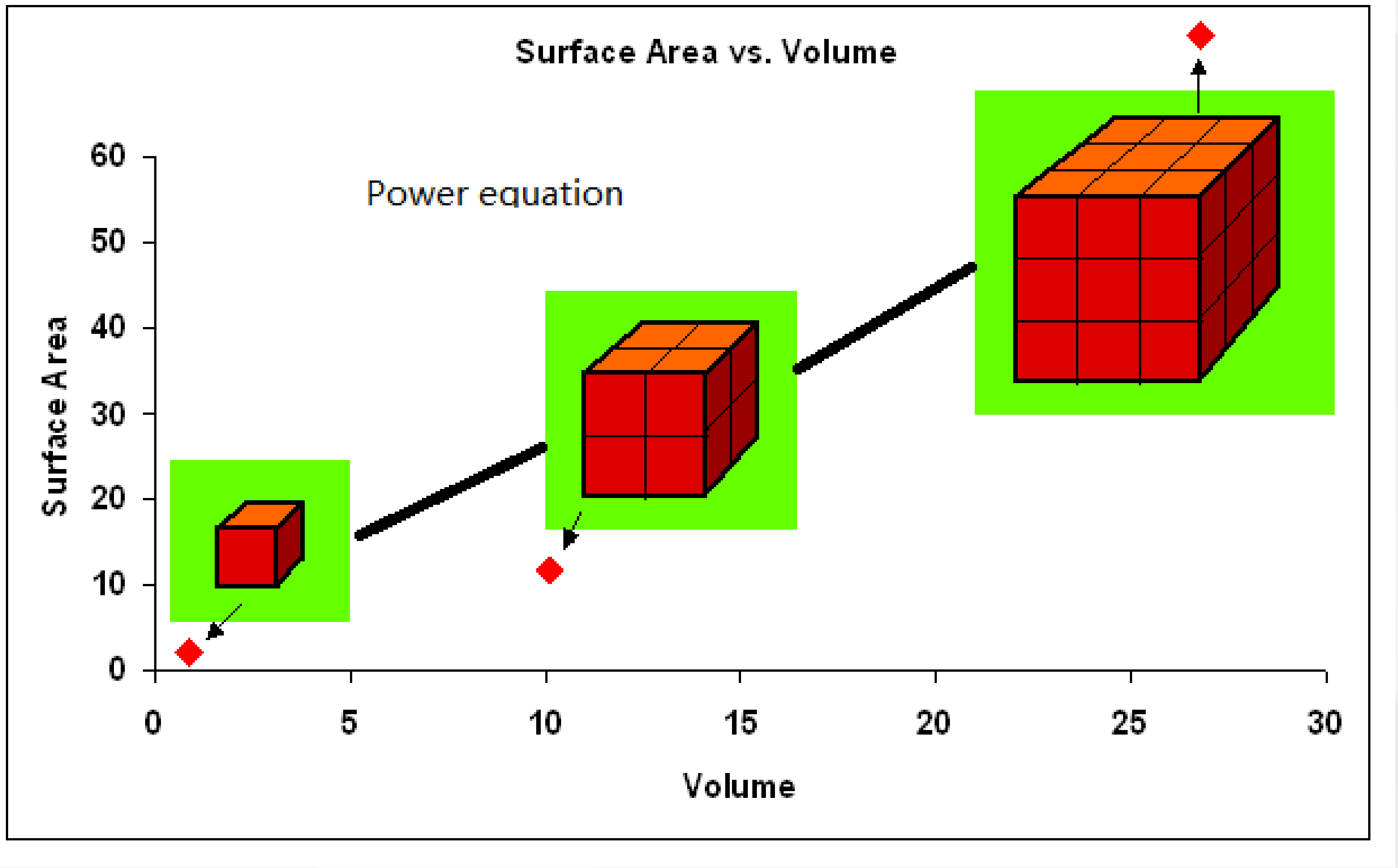


How to convert static data into their quasi-dynamic representation?

We implement allometric scaling law

Allometric scaling law is a Physical Law:

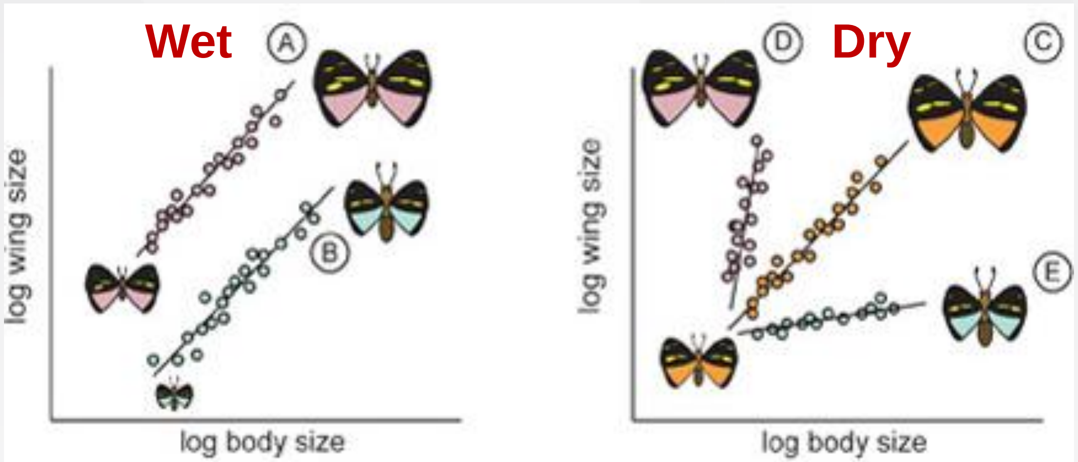
Part-whole relationship



Allometric Scaling Law is a Biological Law

Universal in nature

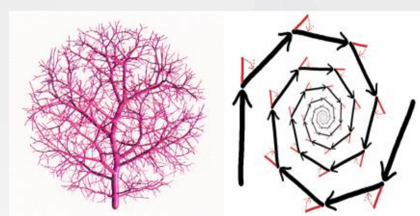
Individual elements vs. their whole system is the part-whole relationship.



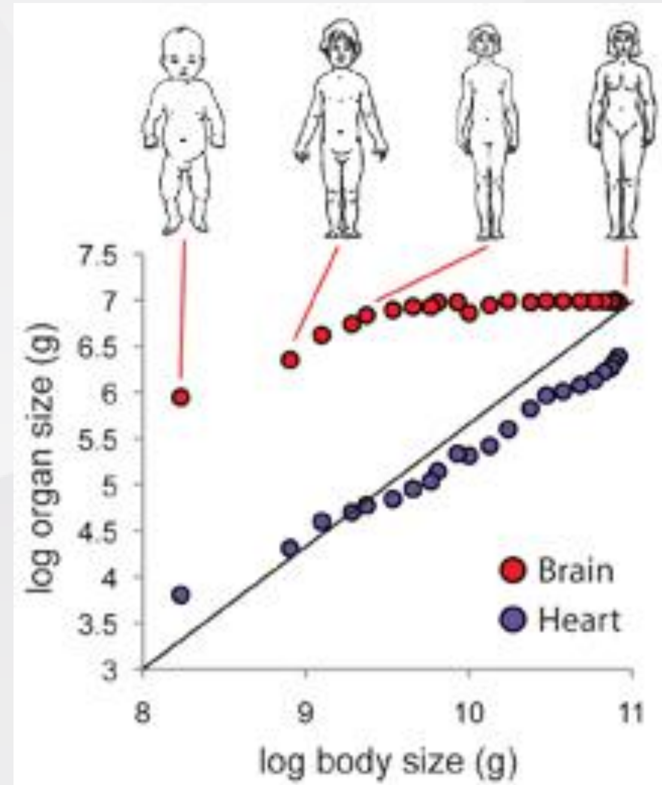
Static Allometry (across individuals) (Shingleton 2010)

Power equation: $Y = \alpha X^{\beta}$, where α is the intercept and β is the slope

West et al. (1997, Science) proposed a fractal model to interpret the power law.



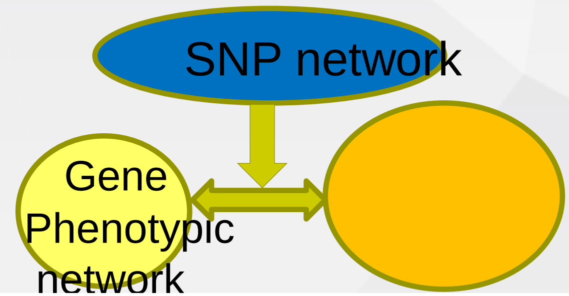
West, Brown, Enquist

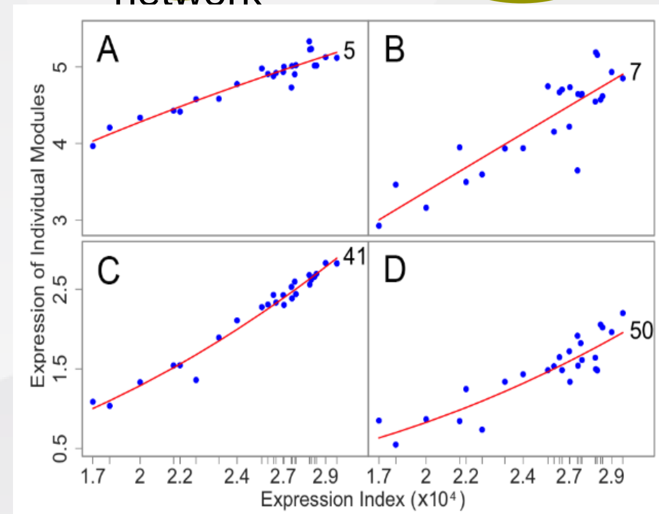


Ontogenetic Allometry (across ages)

GTEx Data Structure

Individual	1				…	n			
Tissue	1	2	…	R_1		1	2	…	R_n
Gene expression									
1	$y_{11}(1)$	$y_{11}(2)$	…	$y_{11}(R_1)$	…	$y_{1n}(1)$	$y_{1n}(2)$	…	$y_{1n}(R_n)$
2	$y_{21}(1)$	$y_{21}(2)$	…	$y_{21}(R_1)$	…	$y_{2n}(1)$	$y_{2n}(2)$	…	$y_{2n}(R_n)$
…									
m	$y_{m1}(1)$	$y_{m1}(2)$	…	$y_{m1}(R_1)$	…	$y_{mn}(1)$	$y_{mn}(2)$	…	$y_{mn}(R_n)$
	T_{11}	T_{12}	…	T_{1R1}	…	T_{n1}	T_{n2}	…	T_{nRn}
Histological and clinical									
1	$z_{11}(1)$	$z_{11}(2)$	…	$z_{11}(R_1)$	…	$z_{1n}(1)$	$z_{1n}(2)$	…	$z_{1n}(R_n)$
2	$z_{21}(1)$	$z_{21}(2)$	…	$z_{21}(R_1)$	…	$z_{2n}(1)$	$z_{2n}(2)$	…	$z_{2n}(R_n)$
…									
p	$z_{m1}(1)$	$z_{m1}(2)$	…	$z_{m1}(R_1)$	…	$z_{mn}(1)$	$z_{mn}(2)$	…	$z_{mn}(R_n)$
SNP									
1		AA			…		aa		
2		AA			…		Aa		
…									
q		aa			…		AA		

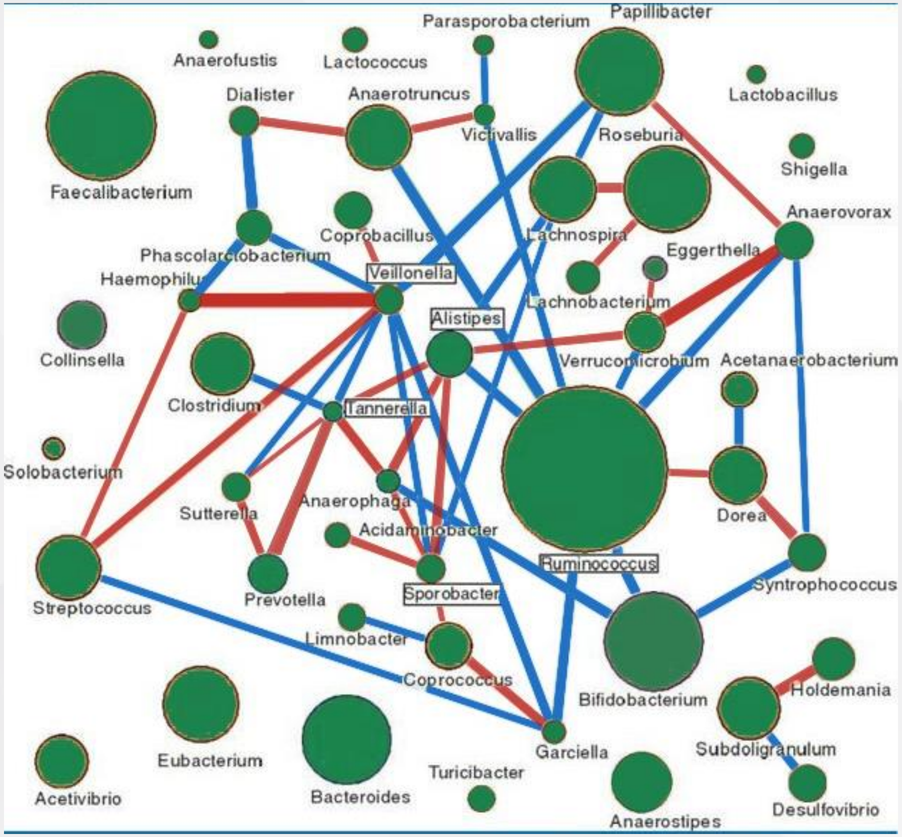




- Expression index (EI) is defined as the sum of expression of all genes
- Scaling individual genes vs. EI

Data Modeling of Hypernetworks: A Preliminary Result

The Gut Microbiota



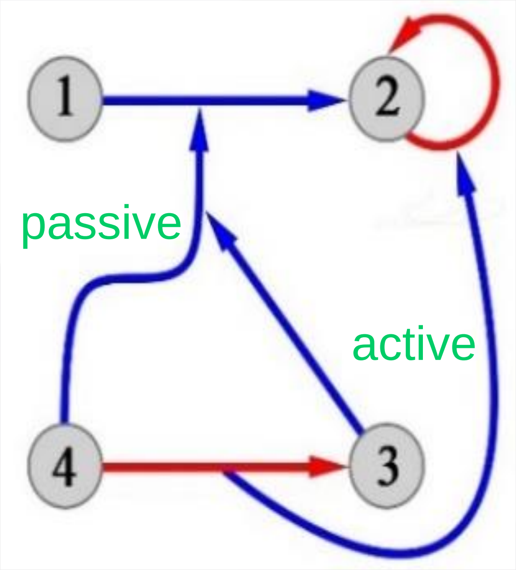
Davenport et al.'s (2015) data

- Include 184 Amish samples from a founder, the Hutterites
- Measured at phylum, class, order, family, genus, and species levels in the winter and the coming summer.

Eight phyla: Hypergraph-based qdODEs

$$\dot{y}_j(T_i) = Q_j\left(y_j(T_i){:}\,\Theta_j\right) + \sum_{j'=1}^{8} Q_{jj'}\left(y_{j'}(T_i){:}\,\Theta_{jj'}\right) + \sum_{j_1=1}^{8}\sum_{j_2=1}^{8} Q_{j\leftarrow j_1 j_2}\left(z_{j_1 j_2}(T_i){:}\,\Theta_{j\leftarrow j_1 j_2}\right)$$

$$\dot{z}_{j_1 j_2}(T_i) = Q_{j_1 j_2}\left(z_{j_1 j_2}(T_i){:}\,\Theta_{j_1 j_2}\right) + \sum_{j=1}^{8} Q_{j_1 j_2\leftarrow j}\left(y_j(T_i){:}\,\Theta_{j_1 j_2\leftarrow j}\right)$$



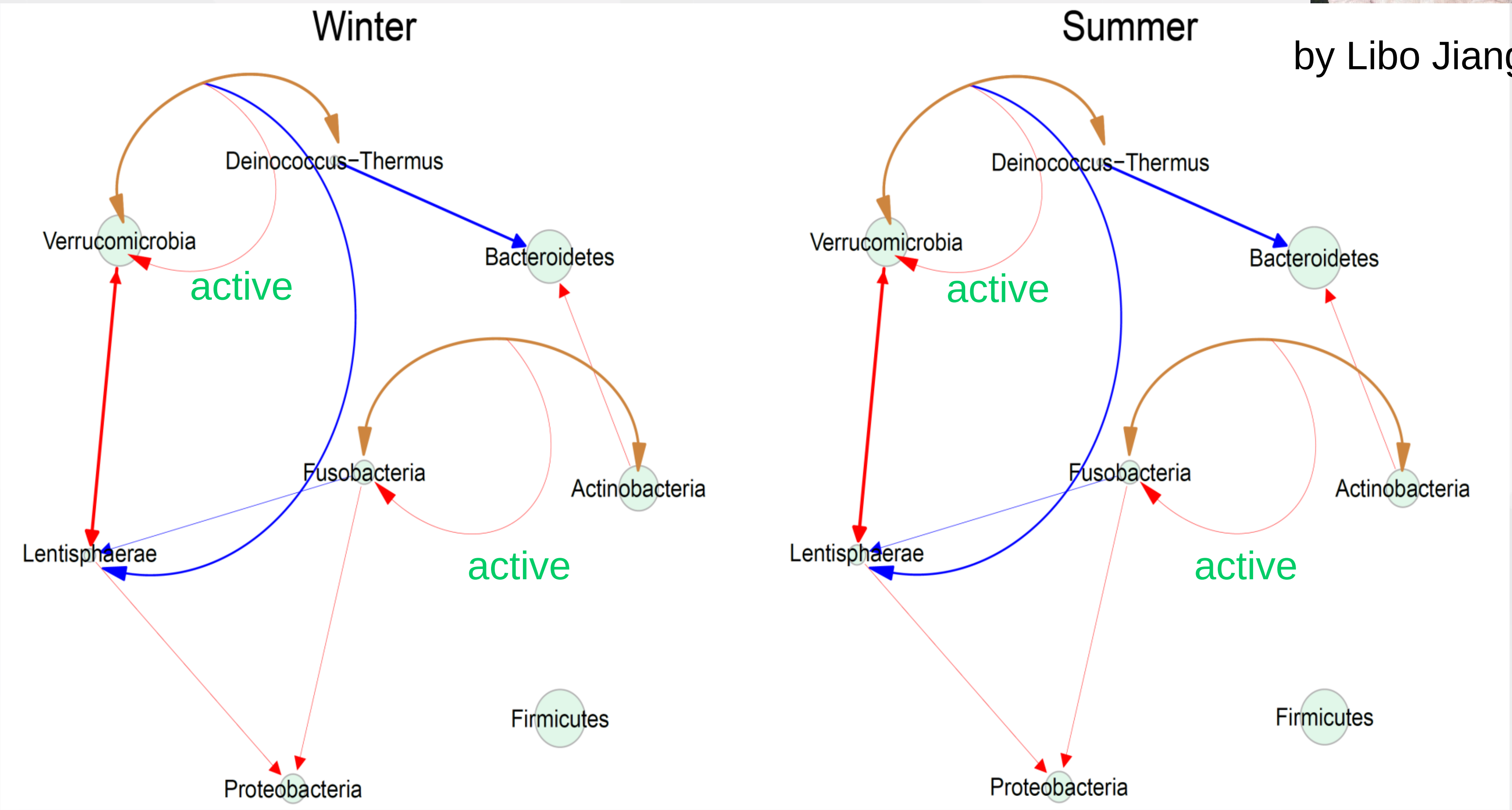
High-order networks include

(1) how a pairwise interaction actively affects a node (phylum)

(2) how a dyadic interaction is passively affected by a node

Pairwise interaction is defined by z_{j1j2}

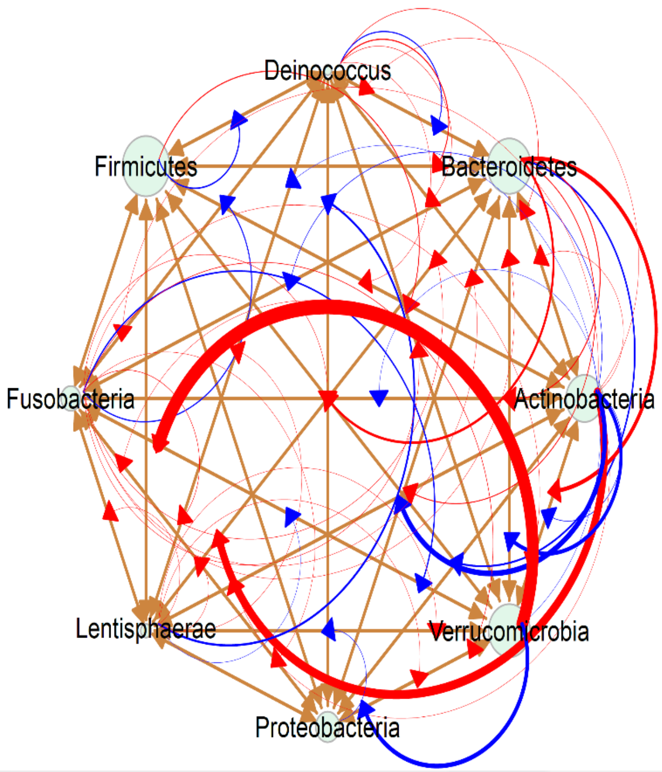
Active Hypernetworks (mutualism)



by Libo Jiang

Passive Hypernetworks (mutualism)

Winter



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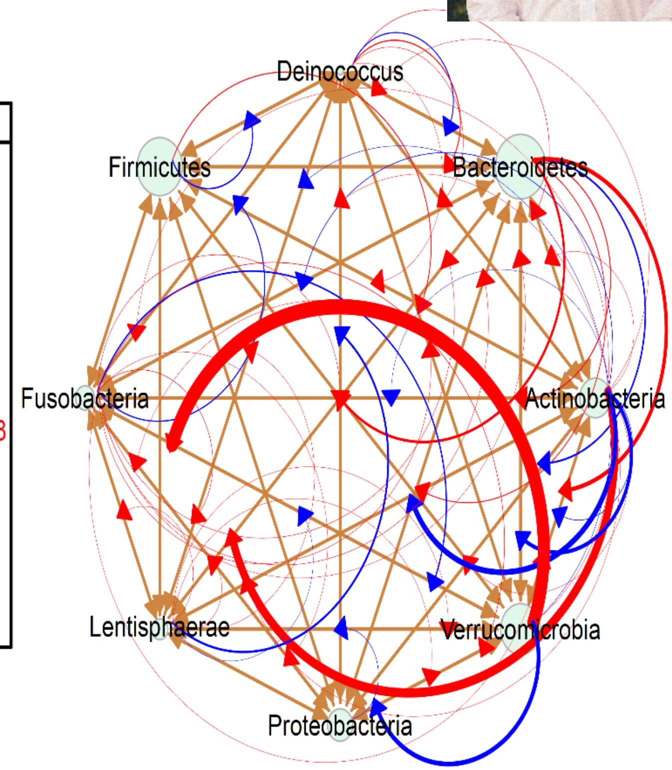
Phylum	Mutualism
1 Actinobacteria	12 15 16 18 23 25 26 27 28 35
2 Bacteroidetes	16 17 18 26 28
3 Deinococcus −Thermus	12 13 14 23 24
4 Firmicutes	14 34
5 Fusobacteria	18 26 27 28 35 36 37 38 57 58 78
6 Lentisphaerae	36 37 56 57 58 68 78
7 Proteobacteria	68
8 Verrucomicrobia	36 57 58 78

Summer



passive

passive

Hypernetwork Implications

Four categories of hypernetworks:

- Mutualism-based hypernetworks
- Antagonism-based hypernetworks
- Altruism-based hypernetworks
- Aggression-based hypernetworks

Cancer control as an example

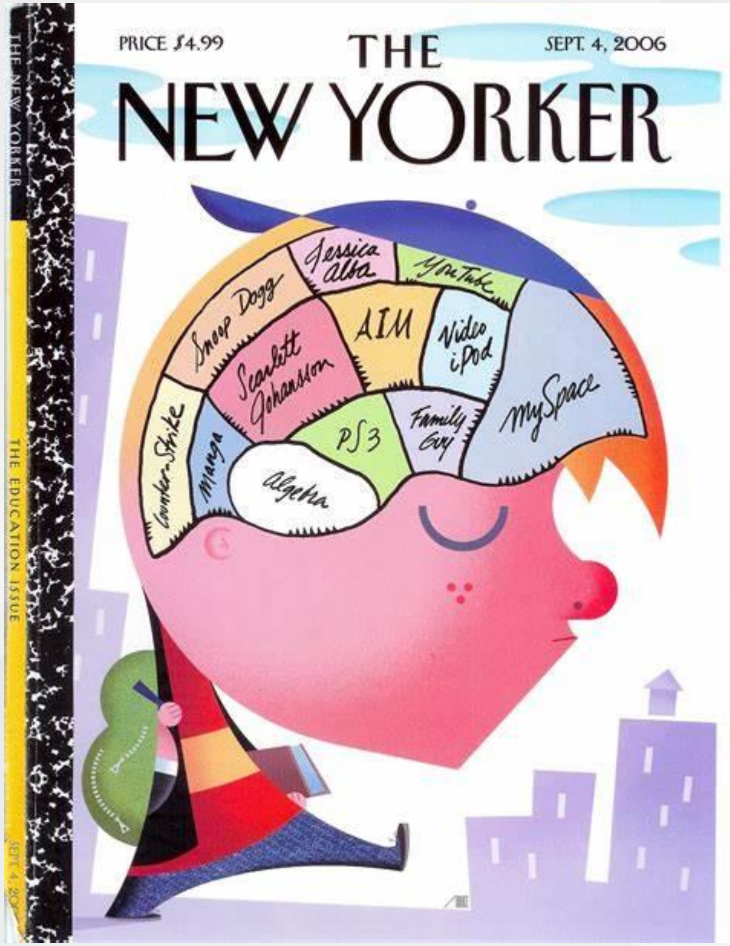
- If a cell promotes the cooperation of two cancer cells, then a drug is developed to dismiss the function of this cell.

- If the cooperation of two cells activates the growth of a cancer cell, then a drug is designed to decouple their cooperation.

How to reconstruct networks from big data?

We integrate developmental modularity theory

Modularity of Mind

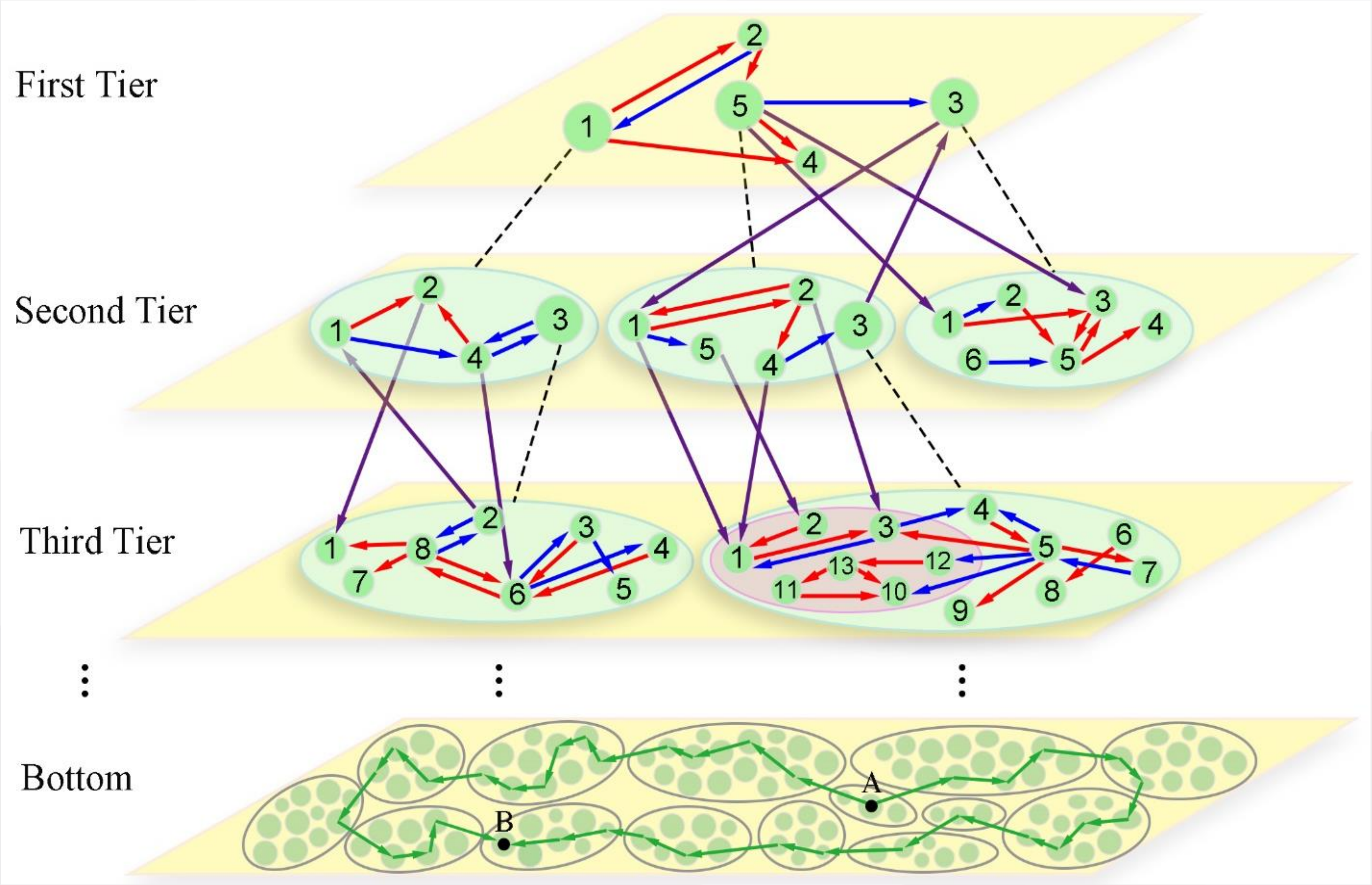


A human brain has distinct regions that think and function differently

- Divide all elements into distinct modules based on their similarity of dynamic change pattern by functional clustering (Kim et al. 2008, Genetics; Wang et al. 2012, Briefings in Bioinformatics).
- Divide each module into submodule
- Divide each submodule into sub-submodule.

- This process stops until the number of elements reaches Dunbar's number.

A multilayer, multiplex, and multifunctional network from any number of elements



Informative
- Causal
- Stable
- Sparse

Dynamic

Omnidirectional

Personalized

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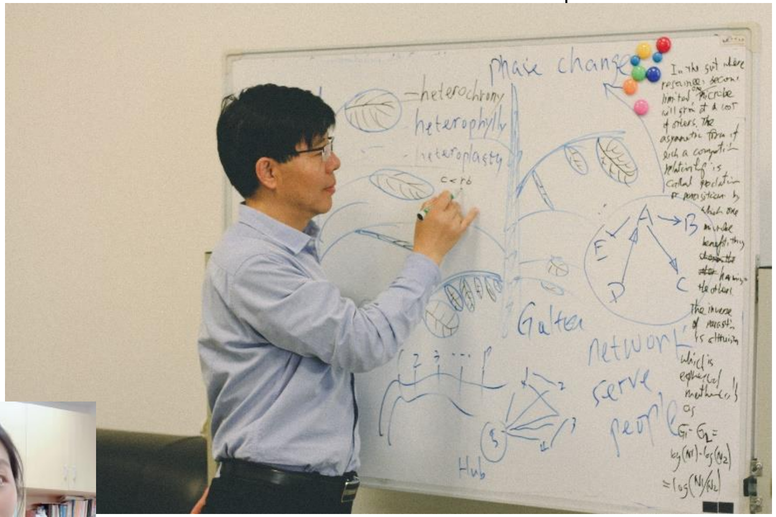

    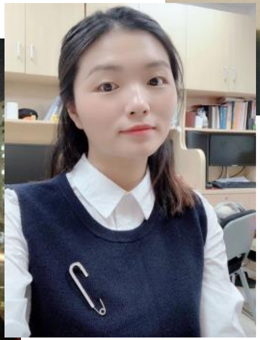

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An interdisciplinary team

Thank You!