The Hypernetwork Model of Complex Systems

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**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.
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.
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?
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.

Reanalysis of Davenport et al.'s (PLoS ONE, 2015) data
Consider $n$ objects (e.g., cells, individuals)
- Measure $p$ (i.e., 5) different attributes (elements) of each object
- Form an $(n \times p)$ 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.
For an evolving system, this game will occur repeatedly, expressed as

Left Cat: CCCCCCCCCCDCCCCCCCCCD
Right Cat: CCCCCCCCCCDCCCCCCCCCR

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

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.

\[
\begin{align*}
\frac{dP_1}{dt} &= Q_1(P_1) + Q_{1\leftarrow 2}(P_2) \\
\frac{dP_2}{dt} &= Q_2(P_2) + Q_{2\leftarrow 1}(P_1)
\end{align*}
\]

**Independent**    **Dependent**

<p>| | | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Mutualism</td>
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<tr>
<td>Antagonism</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Aggression</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Altruism</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>

Bidirectional, signed, and weighted interactions, outperforming traditional models

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

Dynamic Measurements

Dynamic Modeling

Graph Theory
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
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:

$$
\frac{dg_j(t)}{dt} = Q_j(g_j(t): \Theta_j) \\
+ \sum_{j'=1}^{m} Q_{j\leftarrow j'}(g_{j'}(t): \Theta_{jj'}) \\
+ \sum_{j_1=1}^{m} \sum_{j_2=1}^{m} Q_{j\leftarrow j_1j_2}(z_{j_1j_2}(t): \Theta_{jj_1j_2}) \\
+ \sum_{j_1=1}^{m} \sum_{j_2=1}^{m} \sum_{j_3=1}^{m} Q_{j\leftarrow j_1j_2j_3}(z_{j_1j_2j_3}(t): \Theta_{jj_1j_2j_3}) \\
+ \ldots \ j' \neq j = 1, \ldots, m; \ j_1 < j_2 < j_3 = 1, \ldots, m
$$

- 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 $z_{j_1j_2}$?

\[
\frac{dg_j(t)}{dt} = Q_j(g_j(t): \Theta_j)
+ \sum_{j'}^m Q_{j\leftarrow j'}(g_{j'}(t): \Theta_{jj'})
+ \sum_{j_1=1}^m \sum_{j_2=1}^m Q_{j\leftarrow j_1j_2}(z_{j_1j_2}(t): \Theta_{jj_1j_2})

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

- Independent
- First-order
- Second-order

Mutualism $1 \leftrightarrow 2$
Antagonism $1 \leftrightarrow 2$
Aggression $1 \rightarrow 2$
Altruism $1 \rightarrow 2$
How to define and quantify player-player interactions?

*We introduce behavioral ecology theory*

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goose flying and fish schooling
<table>
<thead>
<tr>
<th>Player X</th>
<th>Coop</th>
<th>Player Y</th>
<th>Coop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutualism</td>
<td>Mutualism-based hypernetworks, $z_{mu}$</td>
<td>$z_{mu} = xy/(x-y)$</td>
<td>$z_{al} = (x-y)/x$</td>
</tr>
<tr>
<td>Altruism</td>
<td>Altruism-based hypernetworks, $z_{al}$</td>
<td>$z_{ag} = x/y$</td>
<td>$z_{an} = 1/[xy(x-y)]$</td>
</tr>
<tr>
<td>Aggression</td>
<td>Aggression-based hypernetworks, $z_{ag}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antagonism</td>
<td>Antagonism-based hypernetworks, $z_{an}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

\[
\frac{dg_j(t)}{dt} = Q_j \left( g_j(t): \Theta_j \right) \\
+ \sum_{j'=1}^{m} Q_{j \leftarrow j'} \left( g_{j'}(t): \Theta_{jj'} \right) \\
+ \sum_{j_1=1}^{m} \sum_{j_2=1}^{m} Q_{j \leftarrow j_1j_2} \left( z_{j_1j_2}(t): \Theta_{jj_1j_2} \right) \\
j' \neq j = 1, \ldots, m; j_1 < j_2 = 1, \ldots, m
\]

- The independent component occurs when this player \textbf{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*)
  \[
  \frac{dP_1}{dt} = Q_1(P_1) + Q_{1\rightarrow2}(P_2)
  \]
  \[
  \frac{dP_2}{dt} = Q_2(P_2) + Q_{2\rightarrow1}(P_1)
  \]

- Altrusim/Aggression (*利他/侵害*)

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
Unavailability of high-density time-series measurements
- Impossible to collect
- Ethically impermissible

Limitations to curve fitting
- Time stable
- Resilient to perturbations

Cohesive coordination of multiple tissues → Human health

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

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

Static Allometry (across individuals) (Shingleton 2010)

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

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

Ontogenetic Allometry (across ages)
### GTEx Data Structure

<table>
<thead>
<tr>
<th>Individual</th>
<th>1</th>
<th>...</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>1</td>
<td>...</td>
<td>R₁</td>
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</tbody>
</table>

#### Gene expression

<table>
<thead>
<tr>
<th>Gene expression</th>
<th>1</th>
<th>...</th>
<th>R₁</th>
<th>1</th>
<th>...</th>
<th>Rₙ</th>
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<tbody>
<tr>
<td>1</td>
<td>y₁₁(1)</td>
<td>y₁₁(2)</td>
<td>...</td>
<td>y₁₁(R₁)</td>
<td>...</td>
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<tr>
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<td>y₂₁(1)</td>
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<td>...</td>
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<td>...</td>
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</tr>
<tr>
<td>m</td>
<td>yₘ₁(1)</td>
<td>yₘ₁(2)</td>
<td>...</td>
<td>yₘ₁(R₁)</td>
<td>...</td>
<td>yₘ₁(Rₙ)</td>
</tr>
</tbody>
</table>

| T₁₁ | T₁₂ | ... | T₁R₁ | ... | Tₙ₁ | Tₙ₂ | ... | TₙRₙ |

#### Histological and clinical

<table>
<thead>
<tr>
<th>Histological and clinical</th>
<th>1</th>
<th>...</th>
<th>R₁</th>
<th>1</th>
<th>...</th>
<th>Rₙ</th>
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<tbody>
<tr>
<td>1</td>
<td>z₁₁(1)</td>
<td>z₁₁(2)</td>
<td>...</td>
<td>z₁₁(R₁)</td>
<td>...</td>
<td>z₁₁(Rₙ)</td>
</tr>
<tr>
<td>2</td>
<td>z₂₁(1)</td>
<td>z₂₁(2)</td>
<td>...</td>
<td>z₂₁(R₁)</td>
<td>...</td>
<td>z₂₁(Rₙ)</td>
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</tr>
<tr>
<td>p</td>
<td>zₚ₁(1)</td>
<td>zₚ₁(2)</td>
<td>...</td>
<td>zₚ₁(R₁)</td>
<td>...</td>
<td>zₚ₁(Rₙ)</td>
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</table>

#### SNP

<table>
<thead>
<tr>
<th>SNP</th>
<th>AA</th>
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<th>aa</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
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<td>...</td>
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<tr>
<td>q</td>
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</tbody>
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- **Expression index (EI) is defined as the sum of expression of all genes**
- **Scaling individual genes vs. EI**
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.
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 $z_{j_1j_2}$

Eight phyla: Hypergraph-based qdODEs

\[
\dot{y}_j(T_i) = Q_j(y_j(T_i); \Theta_j) + \sum_{j'=1}^{8} Q_{jj'}(y_{j'}(T_i); \Theta_{jj'}) + \sum_{j_1=1}^{8} \sum_{j_2=1}^{8} Q_{j\leftarrow j_1j_2}(z_{j_1j_2}(T_i); \Theta_{j\leftarrow j_1j_2})
\]

\[
\dot{z}_{j_1j_2}(T_i) = Q_{j_1j_2}(z_{j_1j_2}(T_i); \Theta_{j_1j_2}) + \sum_{j=1}^{8} Q_{j_1j_2\leftarrow j}(y_j(T_i); \Theta_{j_1j_2\leftarrow j})
\]
Active Hypernetworks (mutualism)

by Libo Jiang
Passive Hypernetworks (mutualism)

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Mutualism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Actinobacteria</td>
<td>12 15 16 18 23 25 26 27 28 35</td>
</tr>
<tr>
<td>2 Bacteroidetes</td>
<td>16 17 18 26 28</td>
</tr>
<tr>
<td>3 Deinococcus-Thermus</td>
<td>12 13 14 23 24</td>
</tr>
<tr>
<td>4 Firmicutes</td>
<td>14 34</td>
</tr>
<tr>
<td>5 Fusobacteria</td>
<td>18 26 27 28 35 36 37 38 57 58 78</td>
</tr>
<tr>
<td>6 Lentisphaerae</td>
<td>36 37 56 57 58 68 78</td>
</tr>
<tr>
<td>7 Proteobacteria</td>
<td>68</td>
</tr>
<tr>
<td>8 Verrucomicrobia</td>
<td>36 57 58 78</td>
</tr>
</tbody>
</table>
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
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
Acknowledgements

• Beijing Institute of Mathematical Sciences and Applications
• Tsinghua University Yau Mathematical Sciences Center
• Beijing Forestry University
• Pennsylvania State University

An interdisciplinary team
Thank You!