北京雁栖湖应用数学研究院
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Applications of GLMY theory in metabolomic networks of complex diseases

应用拓扑与图神经网络研讨会

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BIMSA

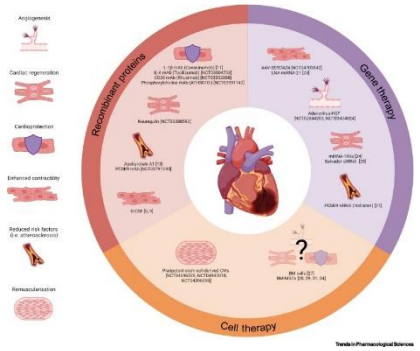
Joint work with Xiang Liu, Ang Dong, Jie Wu, Shing-Tung Yau, and Rongling Wu

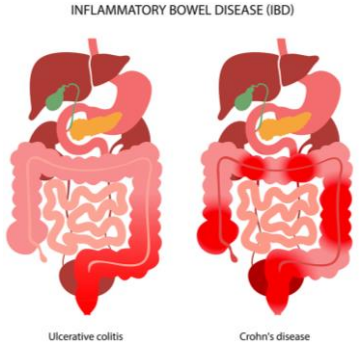
Aug. 2, 2024

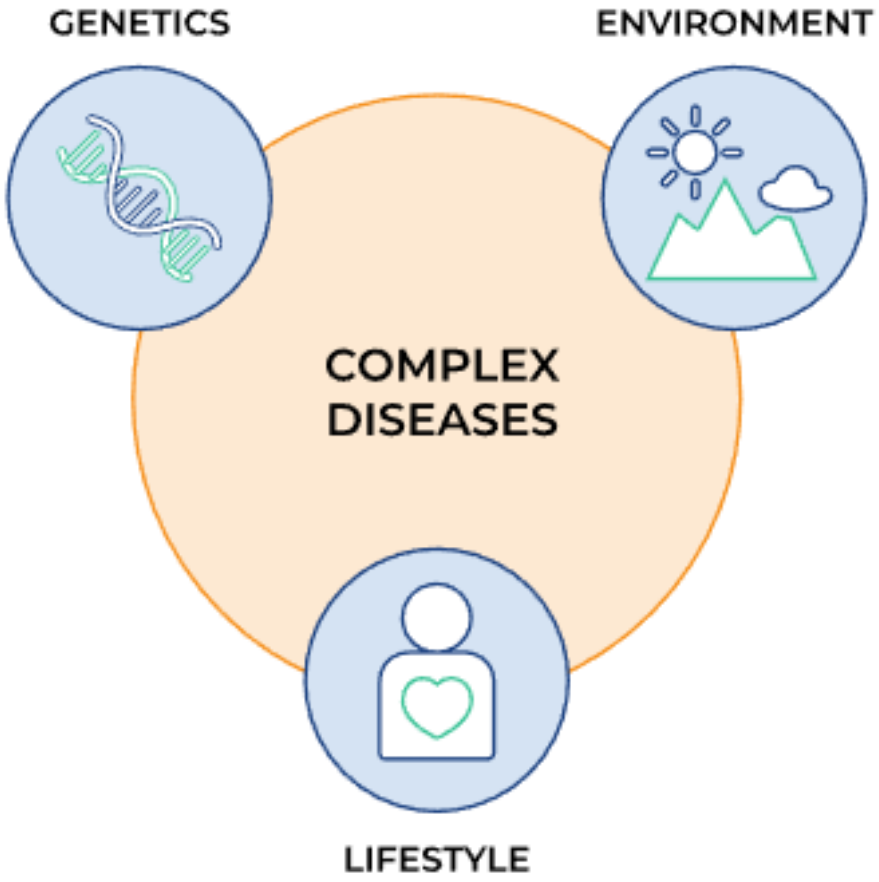
复杂疾病是一组由多基因控制的且不完全符合孟德尔遗传规律的疾病。

- 心血管疾病（Cardiovascular disease）
- 2型糖尿病（Type 2 diabetes）
- 炎症性肠病（ Inflammatory bowel disease ）

复杂疾病的发病机理涉及多种因素，包括遗传、环境和生活方式等。对复杂疾病机理的探索给近代生物学和医学研究带来了巨大挑战。





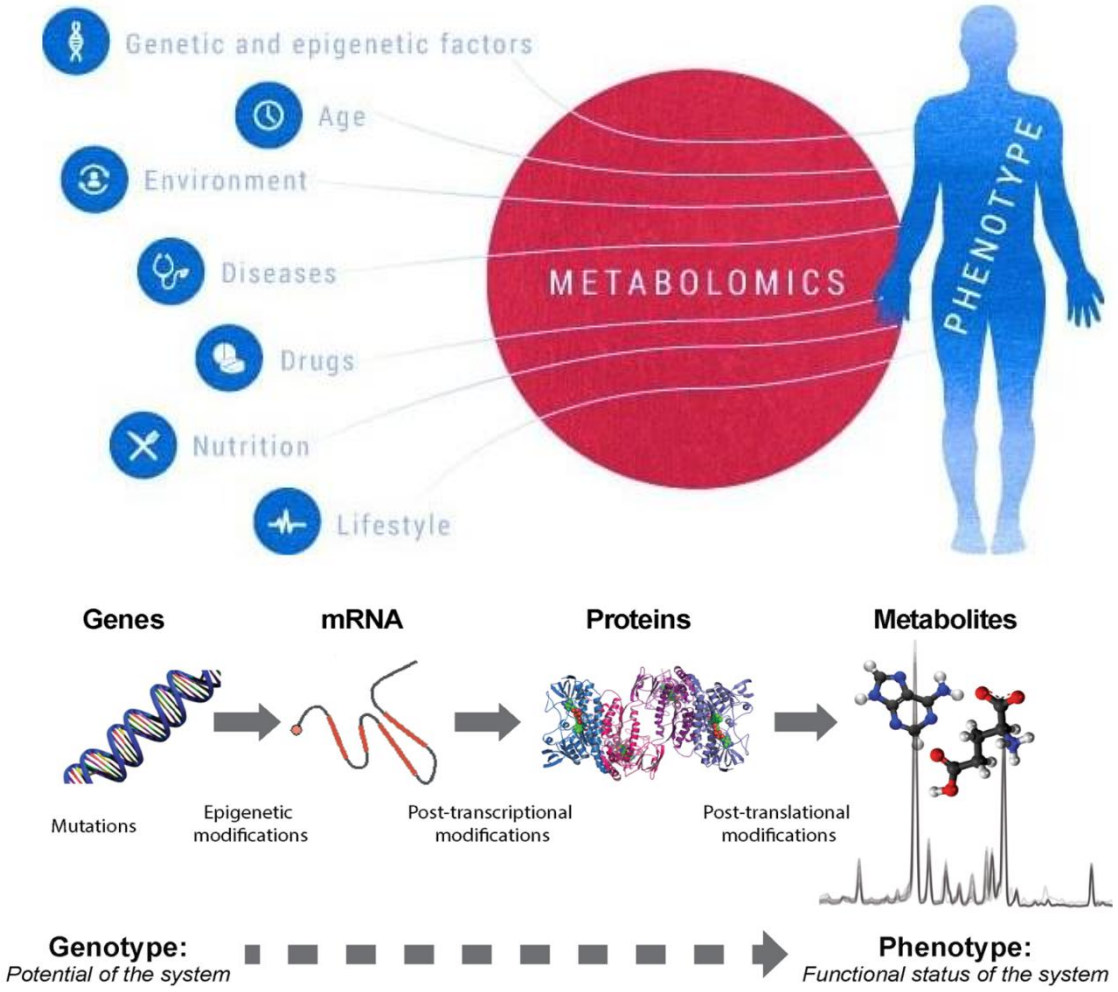


Ahadi, S. et al. Personal aging markers and ageotypes revealed by deep longitudinal profiling. *Nat. Med*,(2020)

新一代测序技术的快速发展产生了从基因组到蛋白质组再到代谢组的大量组学数据。与复杂疾病研究相关的多组学数据层出不穷，产生了人类微生物组计划（Human Microbiome Project, HMP）等与人类疾病相关的数据库。

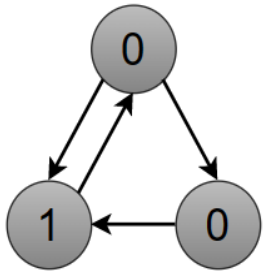
传统的组学数据分析方法通常采用还原论的研究手段，对单一生物分子进行分析，但这种方法无法解析生物分子之间的关系。系统论考虑了组成系统的生物分子之间的相互联系和相互依存性，可以从整体层面把握复杂疾病的形成机制和发展过程。

大量研究表明，生物分子在细胞中共存并共同作用，导致人类健康和疾病的生理和生化变化。网络模型可以从系统层面表征生物分子间的互作关系，目前已被证明是描述复杂系统内部运作规律的强大工具。



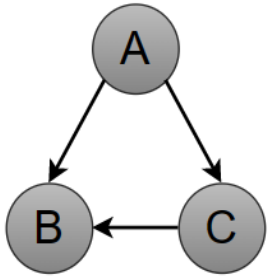
Integrative H M P. The Integrative Human Microbiome Project: dynamic analysis of microbiome-host omics profiles during periods of human health and disease[J]. *Cell host & microbe*, 2014, 16(3): 276-289.
Schüssler-Fiorenza Rose S M, Contrepois K, Moneghetti K J, *et al*. A longitudinal big data approach for precision health[J]. *Nature medicine*, 2019, 25(5): 792-804.

现有的网络构建方法：



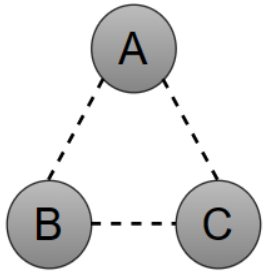
布尔网络

- 仅有0和1两种状态；
- 不能量化作用关系的大小和正负；
- 无法捕捉弱表达基因的调控关系



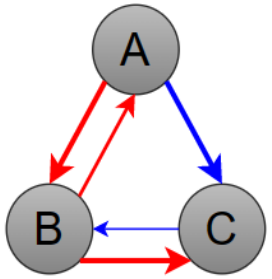
贝叶斯网络

- 不能量化作用关系的大小和正负；
- 没有考虑自我反馈
- 系统复杂且计算量庞大难以估计



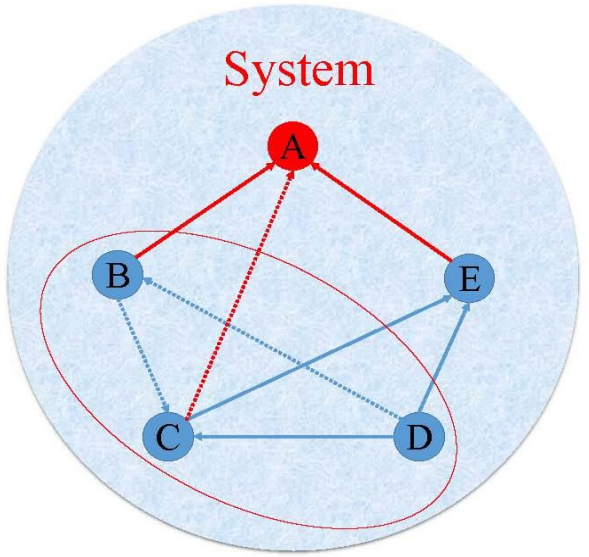
相关性网络

- 假阳性率高；
- 相关并不等于存在作用关系；
- 不能量化作用关系的大小、方向和正负；



微分方程网络

- 不能整体考虑系统内的作用关系；
- 对于超高维的复杂系统不适用。
- 不适用于全基因理论下的网络重构建



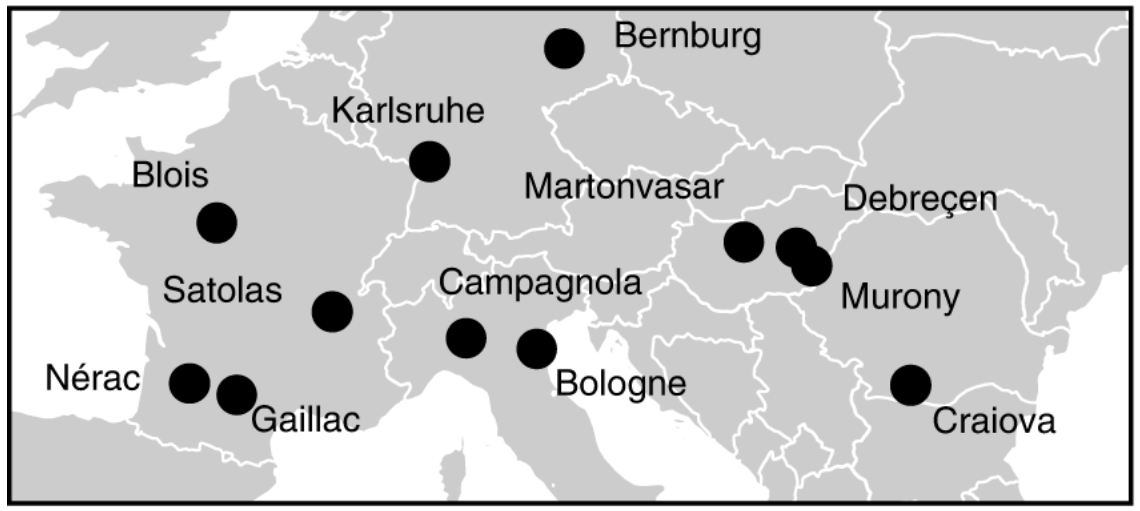
bDSW network

- 双向的（Bidirectional）
- 有符号的（Signed）
- 加权的（ Weighted ）

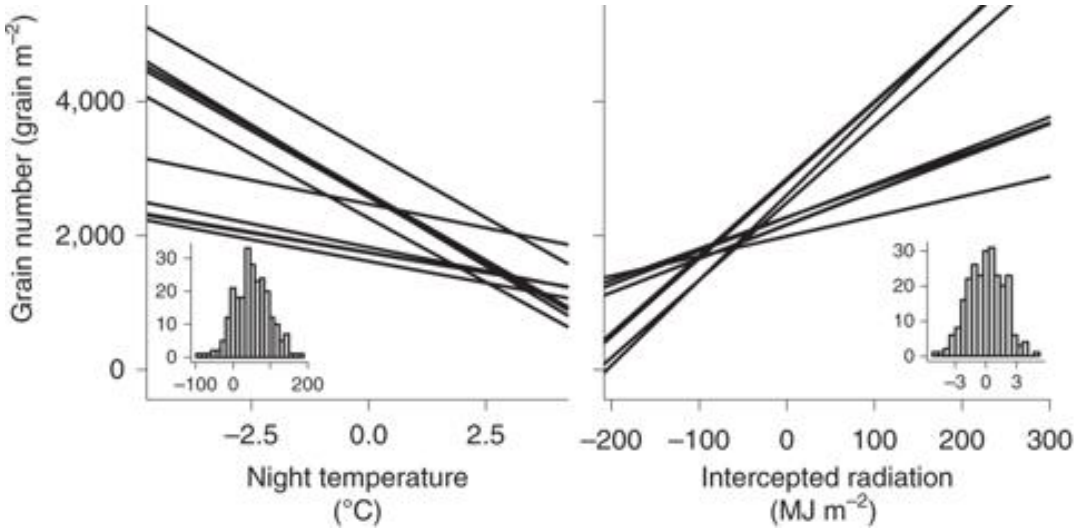
Wu R, Jiang L. Recovering dynamic networks in big static datasets[J]. *Physics Reports*, 2021, 912: 1-57.

Environmental Index: An example (Millet et al. 2019, Nature Genetics)

Predicting maize yield across European environmental conditions

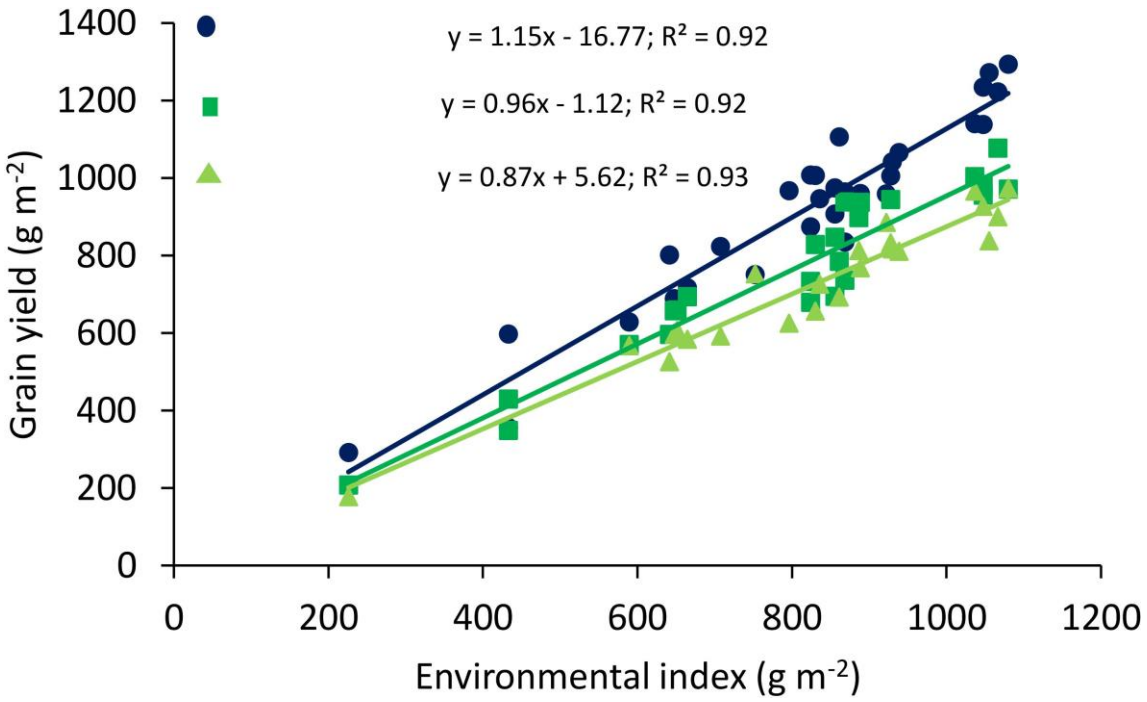


Maize Multi-Site Trial Map



- Maize yield can be well predicted in response to **predictable** environmental factors.
- It is difficult to predict how maize yield responds to **unpredictable** environment.
- Agronomists proposed **environmental index** to evaluate the quality of unpredictable environments (Finlay and Wilkinson 1963)
- Environmental index is the total yield of all maize varieties in a given site.

The yield of individual varieties is a function of environmental index



My hypothesis

Each subject ⟶ a site
Each metabolite ⟶ a variety
Total expression ⟶ Total yield
Expression index ⟶ Environmental index

- The expression level of individual metabolites can be fitted as a function of expression index
- Thus, we can convert static data into its “dynamic” space

The concept of expression index provides a key step for reconstructing idopNetworks

Niche Theory and Allometric Growth Model

Niche theory

- Let y_{ji} denote the value of metabolite j in sample i from a given group of subjects.We calculate and define $E_i = \sum_{j=1}^{m} y_{ji}$ as the ecological niche of sample i. The abundance level of each metabolite can be expressed as a function of ecosystem niche.

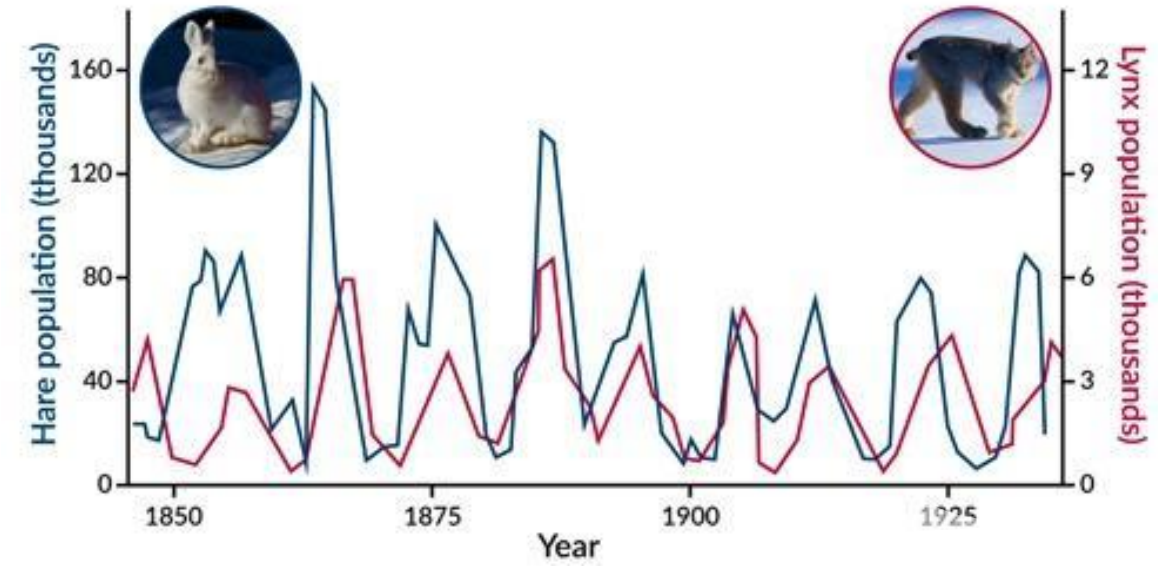
$$E_i = \sum_{j=1}^{m} y_{ji}$$

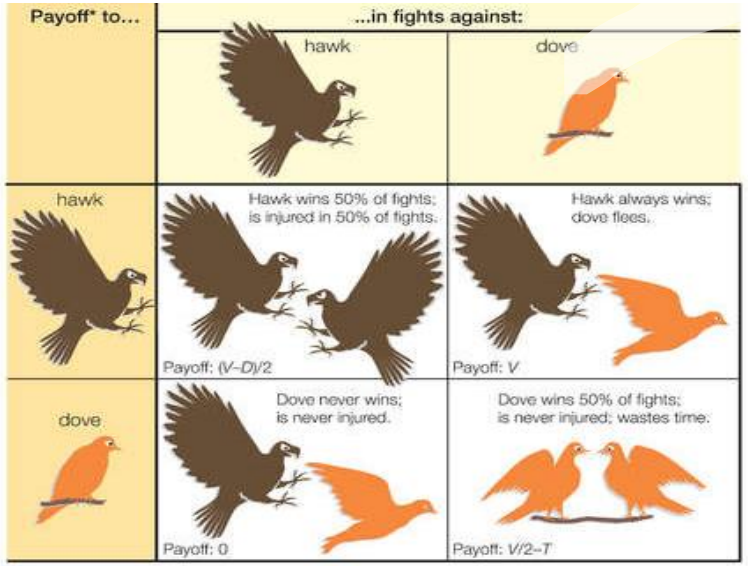
Allometric scaling law

- Mathematically, y_{ji} establishes a part-whole relationship with E_i across samples, which obeys an allometric scaling law described by the power equation:

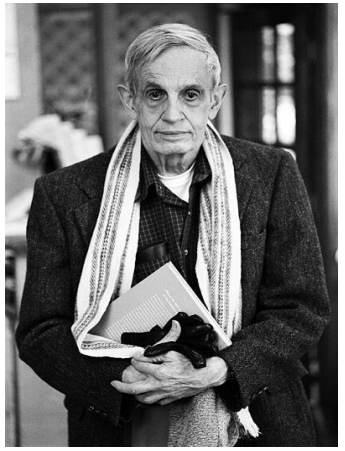
$$y_{ji} = \alpha_j E_i^{\beta_j}$$

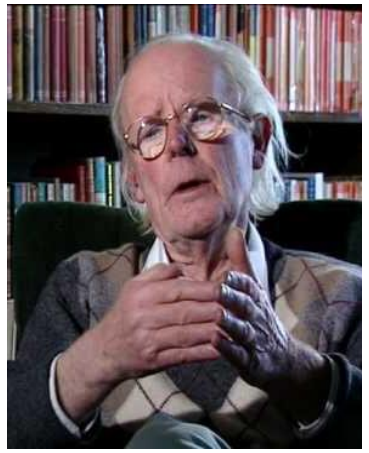
Evolutionary Game Theory and Lotka-Volterra





$$\begin{cases} \dfrac{dx}{dt} = \alpha x - \beta xy \\ \dfrac{dy}{dt} = \delta xy - \gamma y \end{cases}$$





The Nash equilibrium
(Nash 1950, PNAS)

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

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

Payoff of one metabolite (player) is determined by **its own strategy**
And
the strategy of the other metabolites

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

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

Mutualism, antagonism: symmetrical
Aggression, altruism: asymmetrical

- Integrate the Lotka-Volterra equation of evolutionary game theory (Smith and Price 1973):

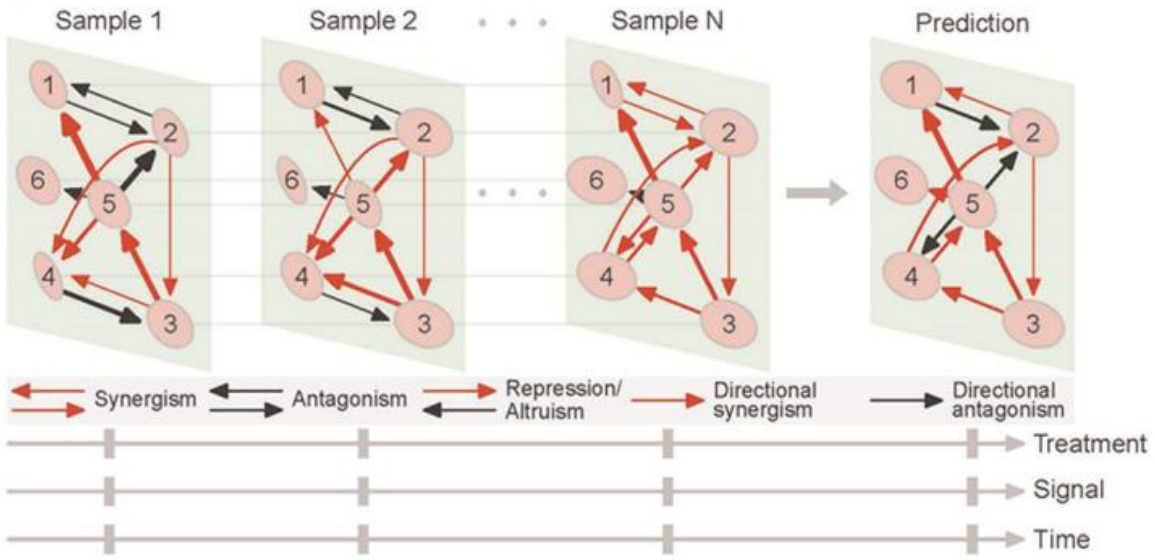
$$\frac{dy_j(E)}{dE} = Q_j\left(y_j(E):\Theta_j\right) + \sum_{j'=1, j'\neq j}^{m} Q_{j\leftarrow j'}\left(y_{j'}(E):\Theta_{jj'}\right)$$

- Overall expression level of any metabolic *j* is decomposed into its **independent** component $Q_j(\cdot)$ and **dependent** components $\sum Q_{j|j'}(\cdot)$
- Θ_j and $\Theta_{j|j'}$: independent and dependent ODE parameters
- Quasi-dynamic ODEs (qdODEs) with the time derivative replaced by the EI derivative

IdopNetwork

IdopNetworks we developed favorably combine all features

- **I**nformative (bidirectional, signed, and weighted interactions)
- **D**ynamic (real-time snapshots of a biological process)
- **O**mnidirectional (encapsulating a complete set of interactions into a graph)
- **P**ersonalized (individual-specific, each patient has a network)



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An omnidirectional visualization model of personalized gene regulatory networks

Chixiang Chen[1,2], Libo Jiang[3], Guifang Fu[4], Ming Wang[1,2], Yaqun Wang[5], Biyi Shen[2], Zhenqiu Liu[2], Zuoheng Wang[6], Wei Hou[7], Scott A. Berceli[8,9,10] and Rongling Wu[1,2*]

基于异速生长定律的基因表达指数

生态位理论

本研究将单个受试者的单组学数据总表达量视为一个生态系统，其整体表达水平可以通过所有基因的表达量值的总和来评估，称为表达指数，类似于生态位指数的概念。

假定试验中共收集到来自n个受试者基因组内的m个基因,令y_{ij} 表示给定受试者i (i =1, ..., n)中基因j (j =1, ..., m)的表达量值，计算并定义受试者i的表达指数E_i如下所示：

$$E_i = \sum_{j=1}^{m} y_{ij}$$

异速生长定律

异速生长模型是生物学中为数不多的定律之一，在自然选择下，生物倾向于最大化其代谢能力，以寻求维持和繁殖生命所需的能量和物质。在生命系统中，部分响应于整体的变化在数学上被认为服从异速生长定律，可以简单地用幂方程来描述（West et al., 1997; 1999; Shingleton, 2010）,表示为：

$$y = \alpha x^{\beta}$$

y_{ij}和E_i的比例关系可以用该方程来描述，每个基因的表达水平可以表示为表达指数的函数。其中α表示直线在x轴上的截距，也称为异速生长指数系数，β为比例系数。该方程可以用来拟合部分作为整体的函数是如何变化的。

进化博弈论下的拟动态基因互作网络

Lotka-Volterra模型

Lotka-Volterra（LV）模型也叫作捕食者-猎物模型，描述了捕食者和猎物之间的数量变化关系。通常用以下形式表示：

$$\begin{cases} \frac{dx}{dt} = \alpha x - \beta xy \\ \frac{dy}{dt} = \delta xy - \gamma y \end{cases}$$

其中，x代表猎物的数量，y代表捕食者的数量，t代表时间。参数α表示猎物的出生率、β表示捕食者的出生率、γ表示捕食者对猎物的捕食率、δ表示捕食者的死亡率。当对系统内单一变量研究时可对该模型进行简化推广为广义LV模型：

$$\frac{dx(t)}{dt} = x(t)(r + ax(t))$$

拟动态常微分方程

本模型将一个基因的真实表达量分解为独立部分和依赖部分。这种思想可以用一个拟动态常微分方程组（qdODEs）表示。根据广义LV模型，可以得到：

$$\frac{dy_j(E_i)}{dE_i} = \underbrace{Q_j\left(y_j(E_i):\Theta_j\right)}_{\text{独立部分}} + \underbrace{\sum_{j=1,j'\neq j}^{m} Q_{jj'}\left(y_{j'}(E_i):\Theta_{jj'}\right)}_{\text{依赖部分}}, j = 1,\dots,m$$

其中$Q_j\left(y_j(E_i):\Theta_j\right)$表示基因$j$的独立表达量，$\Sigma Q_{jj'}\left(y_{j'}(E_i):\Theta_{jj'}\right)$表示其他基因对基因$j$的依赖表达量，$j$受到所有可能的其他基因$j'$ $(j' = 1,\dots,j-1,j+1,\dots,m)$的影响。

进化博弈论下的拟动态基因互作网络

拟动态常微分方程求解

拟动态常微分方程组（qdODEs）中独立表达量和依赖表达量随基因表达指数的变化通常没有明确的形式，可以通过勒让德正交多项式（Legendre polynomials, LOP）等非参数方法进行平滑。勒让德多项式的一般形式如下所示：

$$Q_r(v) = \sum_{m=0}^{M} (-1)^m \frac{(2r-2m)!}{2^r m!\,(r-m)!\,(r-2m)!} v^{r-2m}$$

由勒让德多项式平滑后的公式较为复杂，本研究通过四阶龙格库塔法（Four-order Runge-Kutta, RK4）进行拟动态常微分方程组求解。四阶龙格库塔的迭代公式：

$$k_1 = h \cdot f(E_n, y_n)$$
$$k_2 = h \cdot f(E_n + \frac{h}{2}, y_n + \frac{k_1}{2})$$
$$k_3 = h \cdot f(E_n + \frac{h}{2}, y_n + \frac{k_2}{2})$$
$$k_4 = h \cdot f(E_n + h, y_n + k_3)$$
$$y_{n+1} = y_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

利用RK4计算得到拟动态常微分方程组的解后，在最小二乘法（Least Squares Method, LSM）或极大似然估计（Maximum Likelihood Estimate, MLE）框架下，利用BFGS算法优化函数，得到参数的估计值。

最小二乘法表示为：

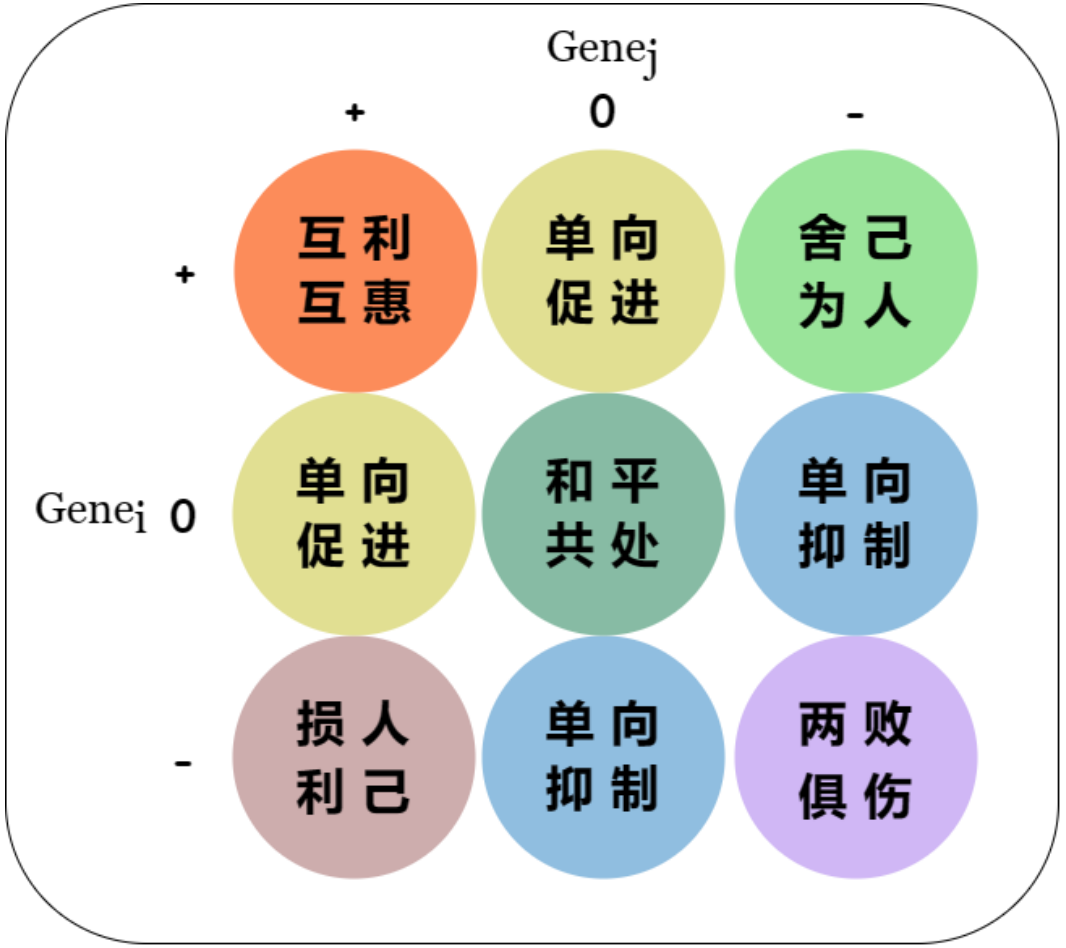
$$\min_{\theta} \sum_{i=1}^{n} [y_i - f(x_i; \theta)]^2$$

极大似然估计表示为：

$$L(\mathbf{y}) = \prod_{i=1}^{n} f_i(\mathbf{y}_1; \ldots; \mathbf{y}_m; \mu_1; \ldots; \mu_m, \boldsymbol{\Sigma})$$

进化博弈论下的拟动态基因互作网络

互作模式分类



通过捕获双向、有符号和加权的基因相互作用的完整信息，得到互作关系的具体效应值。

“+”表示正值，“–”表示负值，“0”表示两基因间没有关联。通过定量描述基因的独立表达和依赖表达，全部的相互作用模式可被划分为9类。

网络稀疏性

变量选择

在实际生物体内，不可能存在全部的基因都相互作用的现象，所以对基因间互作关系进行变量选择降维。LASSO（Least Absolute Shrinkage and Selection Operator）是常用的统计学方法，用于模型稀疏化和特征选择，通过在损失函数中添加 L1 正则项来惩罚模型的系数（Santosa *et al.*, 1986）。LASSO 通过使用系数向量的 L1 范数来约束模型参数范围，使部分系数变为零，从而简化模型。可表示为：

$$min\beta\left\{\frac{1}{2N}\sum_{i=1}^{N}(y_i-\mathbf{x}_i^T\beta)^2+\lambda\parallel\beta\parallel_1\right\}$$

功能聚类

在网络系统中，来自底层成分密集的相互作用构成了复杂系统的复杂性。发育模块理论表明网络可以自然地划分为社区或模块（Newman, 2006; Cantini *et al.*,2015）。表达模式相近的基因可能存在相似的功能，在网络中应该归属于同一模块。本研究采用基于混合模型的功能聚类方法对单组学数据中所有基因进行聚类。

将 m 个基因根据它们随总基因表达指数 $(E_1,\ldots,E_n)$的表达模式分组到L个模块中，功能聚类的似然函数表示为：

$$L(\mathbf{y})=\prod_{j=1}^{m}\left[\pi_1 f_1(\mathbf{y}_j)+\cdots+\pi_j f_1(\mathbf{y}_j)\right]$$

网络稀疏性

功能聚类

使用幂函数对平均向量建模，可以表示为：

$$\mu_l = \left(\mu_l(E_1), \ldots, \mu_l(E_n)\right) = \left(\alpha_l E_1^{\beta_l}, \ldots, \alpha_l E_n^{\beta_l}\right)$$

随后，通过EM算法进行极大似然估计，可以估计平均向量和协方差矩阵的模块比例和参数。

在E步中，通过公式计算属于特定模块l的每个变量j的后验概率：

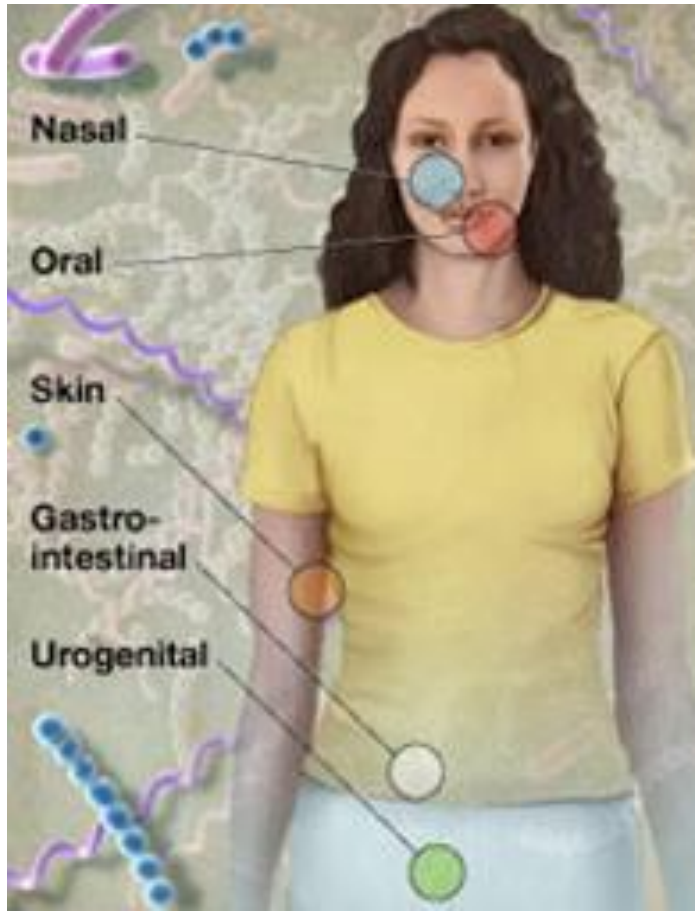
$$\Pi_{ij} = \frac{\pi_l f_l(\mathbf{y}_j)}{\pi_1 f_1(\mathbf{y}_j) + \cdots + \pi_L f_L(\mathbf{y}_j)}$$

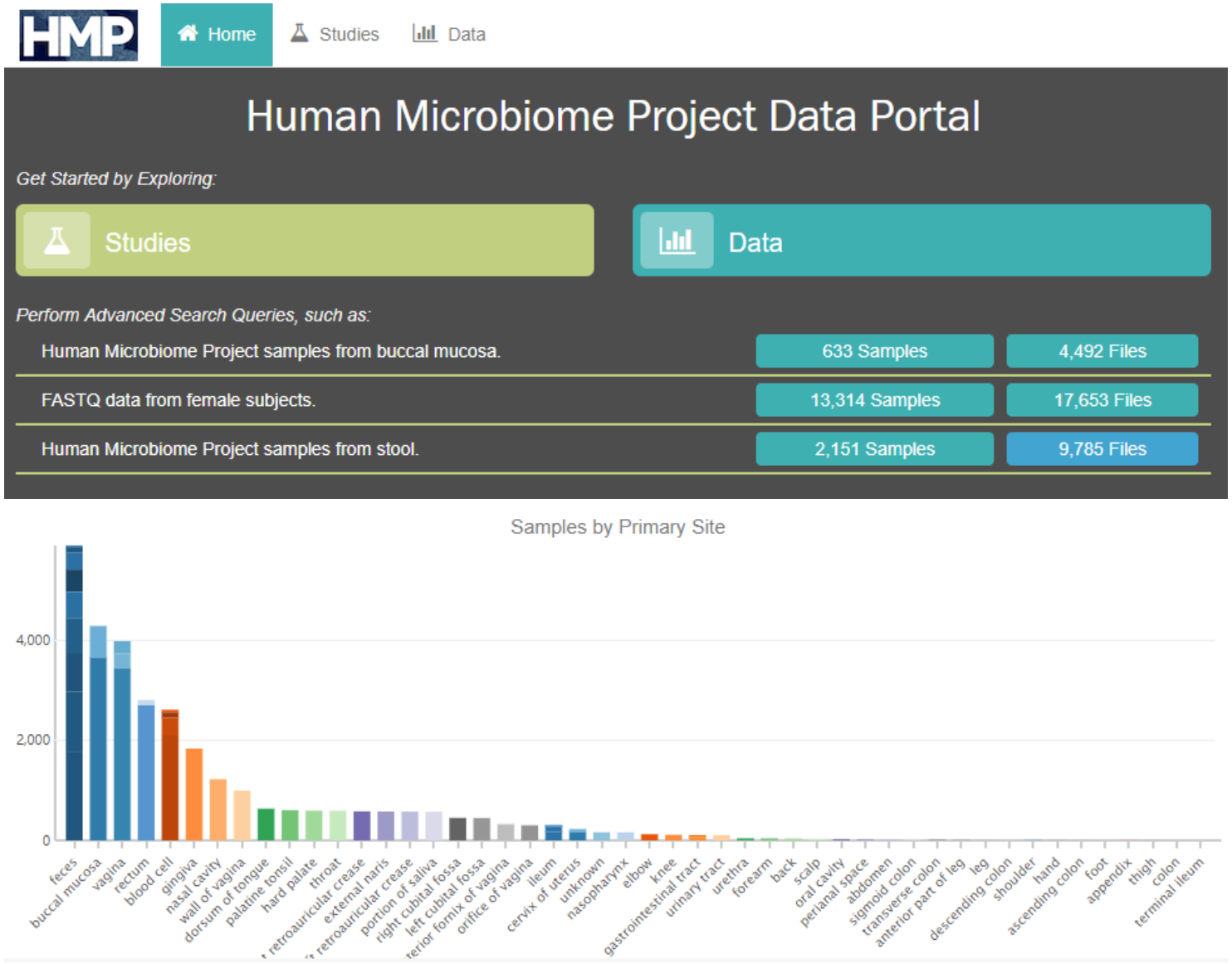
在M步中，估计模块l中的基因占所有基因的比例：

$$\pi_l = \frac{1}{m}\sum_{j=1}^{m} \Pi_{bj}$$

在M步中，使用单纯形算法估计均值向量和协方差矩阵中的参数。重复E步和M步直到获得稳定的估计值。估计每个基因的后验概率，将该基因分配到L个不同的模块中概率最大的模块。通过AIC或BIC确定最佳聚类数。

Data Collection

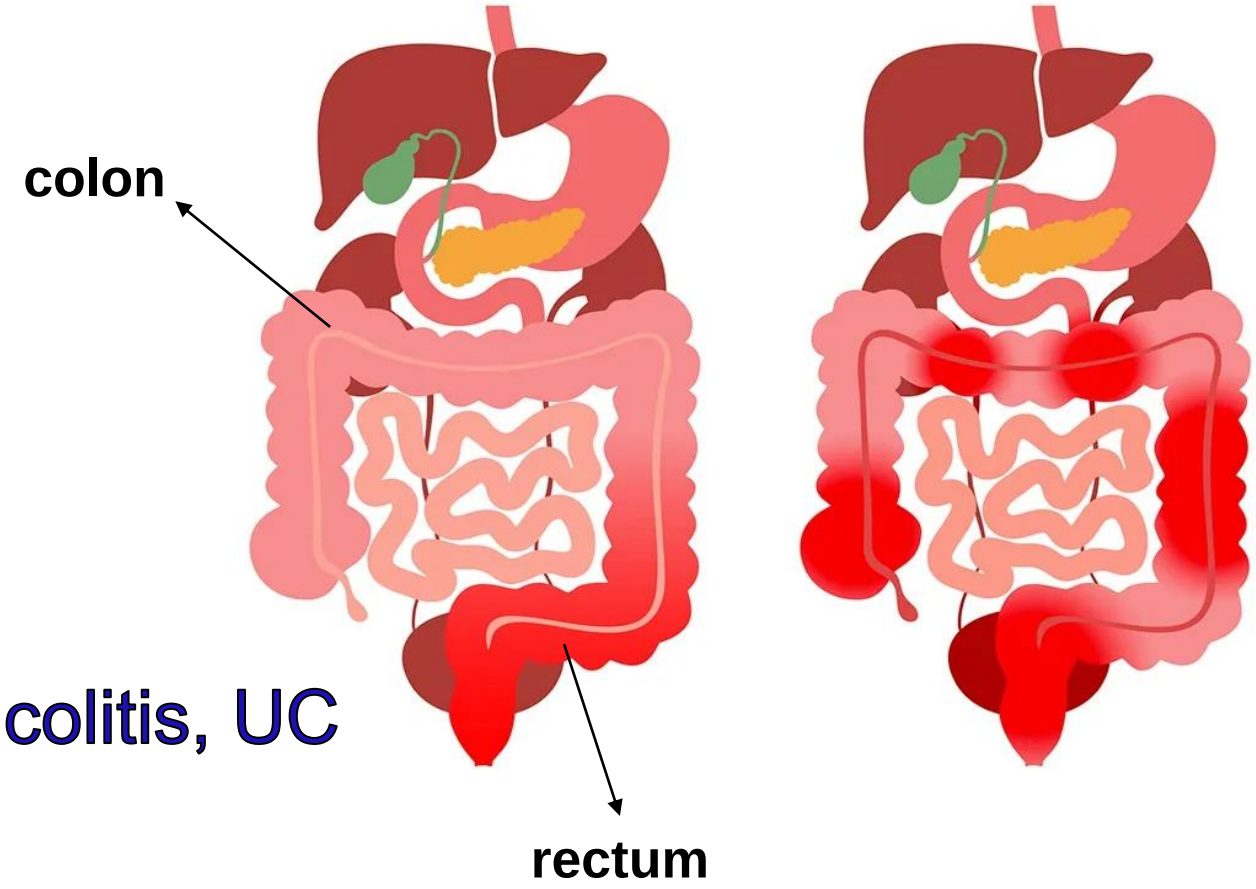




The mission of the HMP was to understanding how the microbiome impacts human health and disease.

The Integrative HMP (iHMP) Research Network Consortium. The Integrative Human Microbiome Project. *Nature*. 569, (2019)

Inflammatory bowel disease, IBD



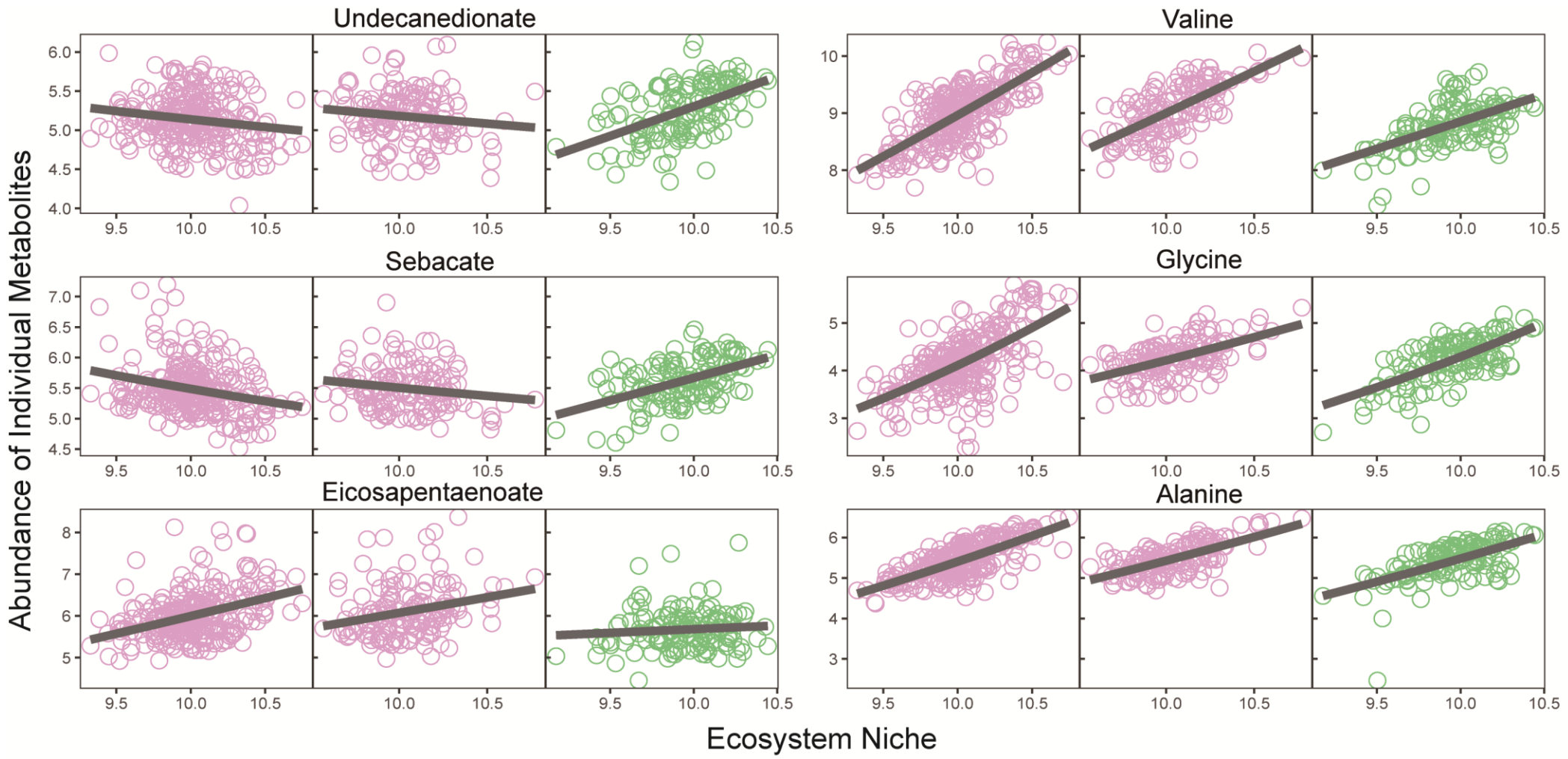
Ulcerative colitis, UC

Crohn’s disease, CD

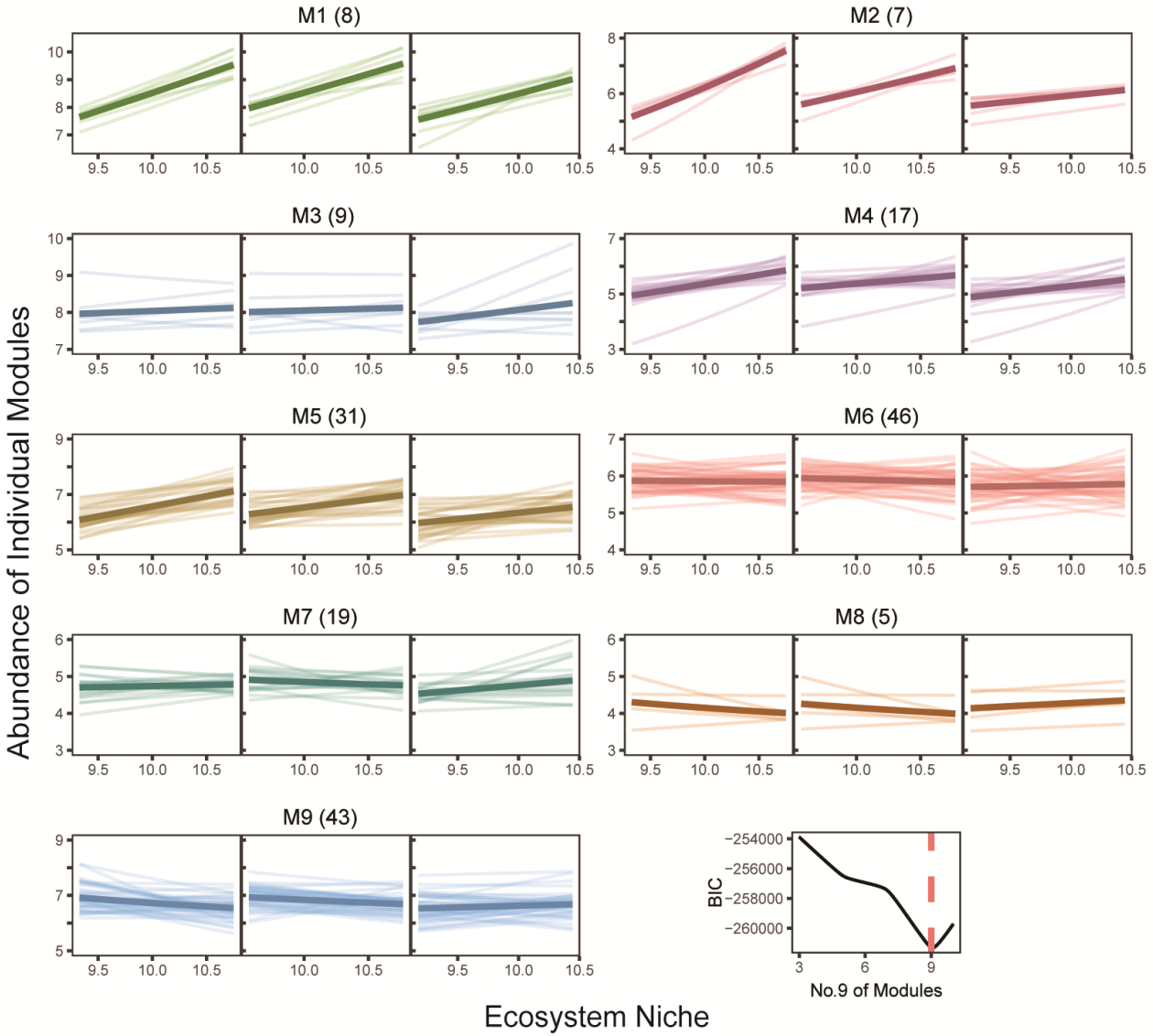
Data Structure

	Healthy					Disease(IBD)									
	HC					CD					UC				
	1	2	3	…	r	1	2	3	…	s	1	2	3	…	t
1	$y_1(1)$	$y_1(2)$	$y_1(3)$	…	$y_1(r)$	$z_1(1)$	$z_1(2)$	$z_1(3)$	…	$z_1(s)$	$x_1(1)$	$x_1(2)$	$x_1(3)$	…	$x_1(t)$
2	$y_2(1)$	$y_2(2)$	$y_2(3)$	…	$y_2(r)$	$z_2(1)$	$z_2(2)$	$z_2(3)$	…	$z_2(s)$	$x_2(1)$	$x_2(2)$	$x_2(3)$	…	$x_2(t)$
…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
m	$y_m(1)$	$y_m(2)$	$y_m(3)$	…	$y_m(r)$	$z_m(1)$	$z_m(2)$	$z_m(3)$	…	$z_m(s)$	$x_m(1)$	$x_m(2)$	$x_m(3)$	…	$x_m(t)$
MI	M_{11}	M_{12}	M_{13}	…	M_{1r}	M_{21}	M_{22}	M_{23}	…	M_{2s}	M_{31}	M_{32}	M_{33}	…	M_{3t}

The goodness-of-fit of the abundance change of metabolites



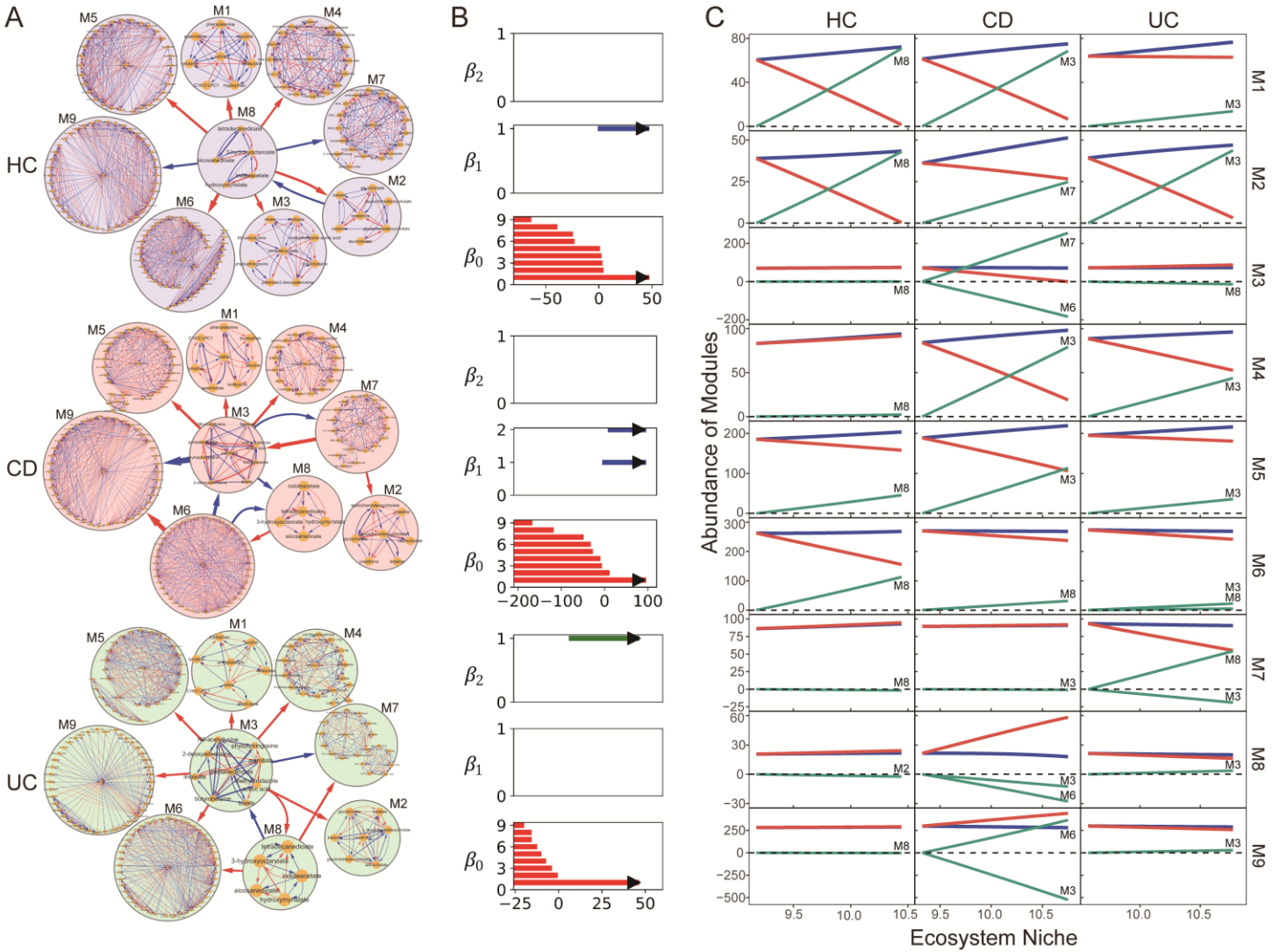
Functional clustering of metabolite expression patterns



This study used a ternary functional clustering algorithm to classify 185 metabolites into 9 different modules (M1-M9) based on the similarity of expression changes in the three populations of HC, CD and UC.

As can be seen from the figure, the expression levels of metabolite expression change with the change of expression index in different patterns.

Two-Layer Metabolic Networks as a Predictor of Disease Risk



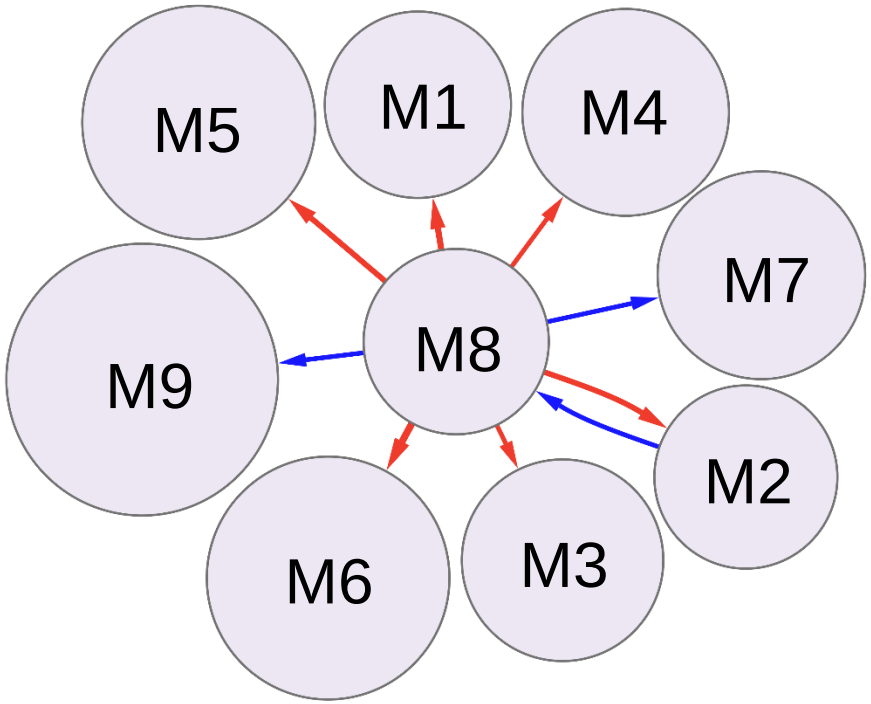
All metabolites are coalesced into two-layer idopNetworks.

Coarse-grained（粗粒度）network at the module level (M1 to M9)

Fine-grained（细粒度）network at the metabolite level

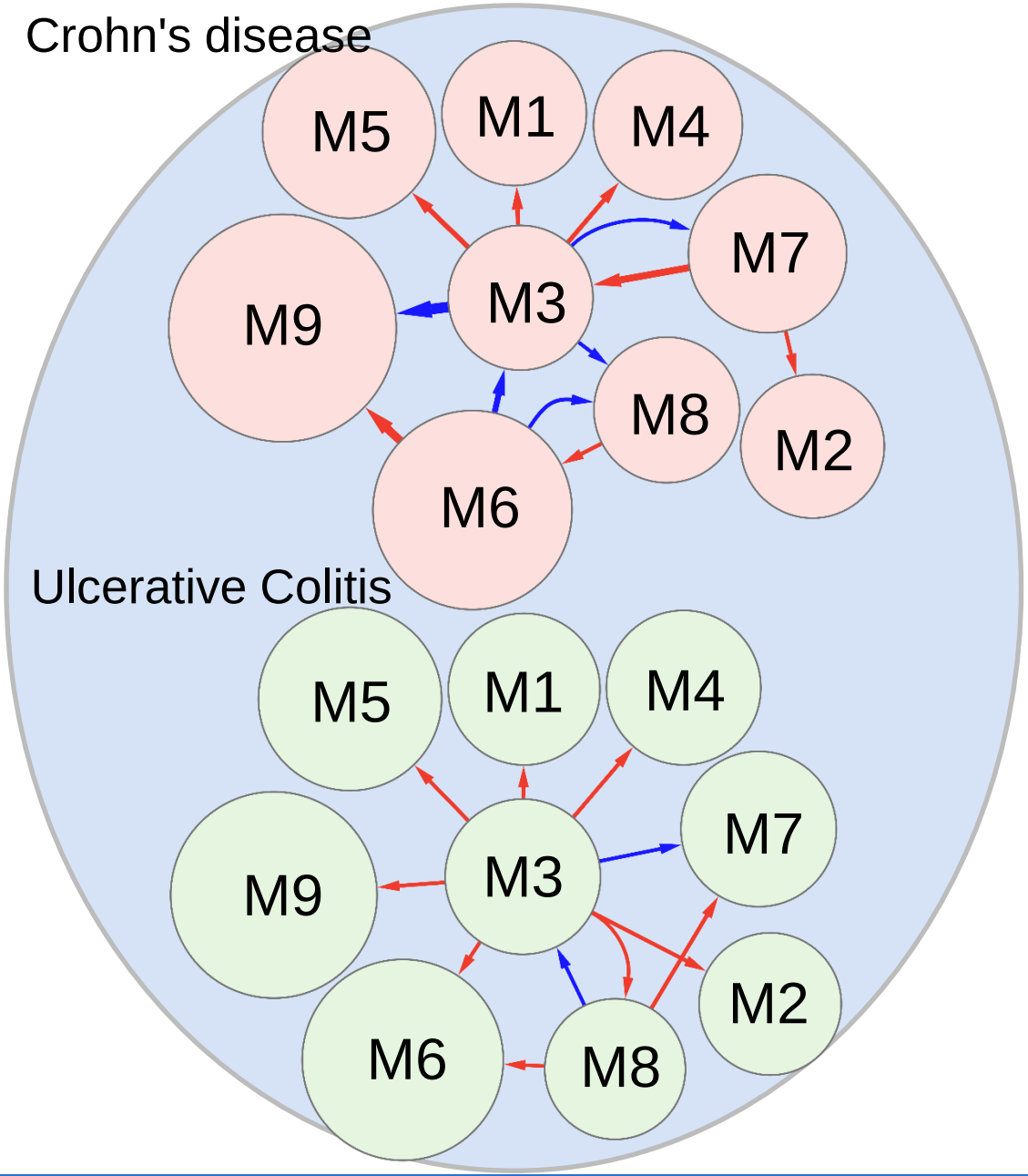
Coarse-grained networks are similar in structure among the three groups.

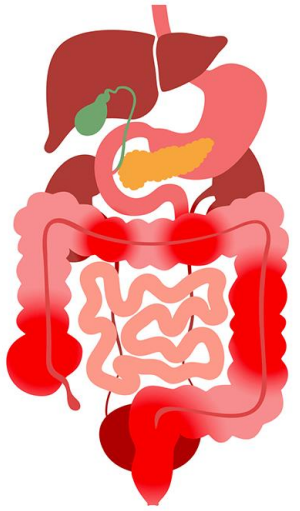
Healthy



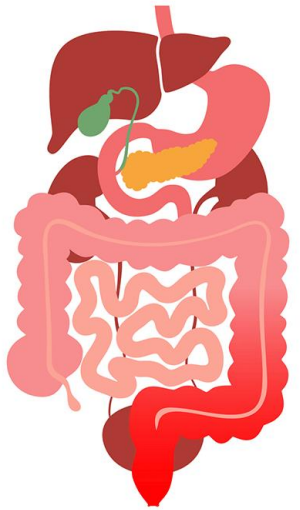
Crohn's disease

Ulcerative Colitis



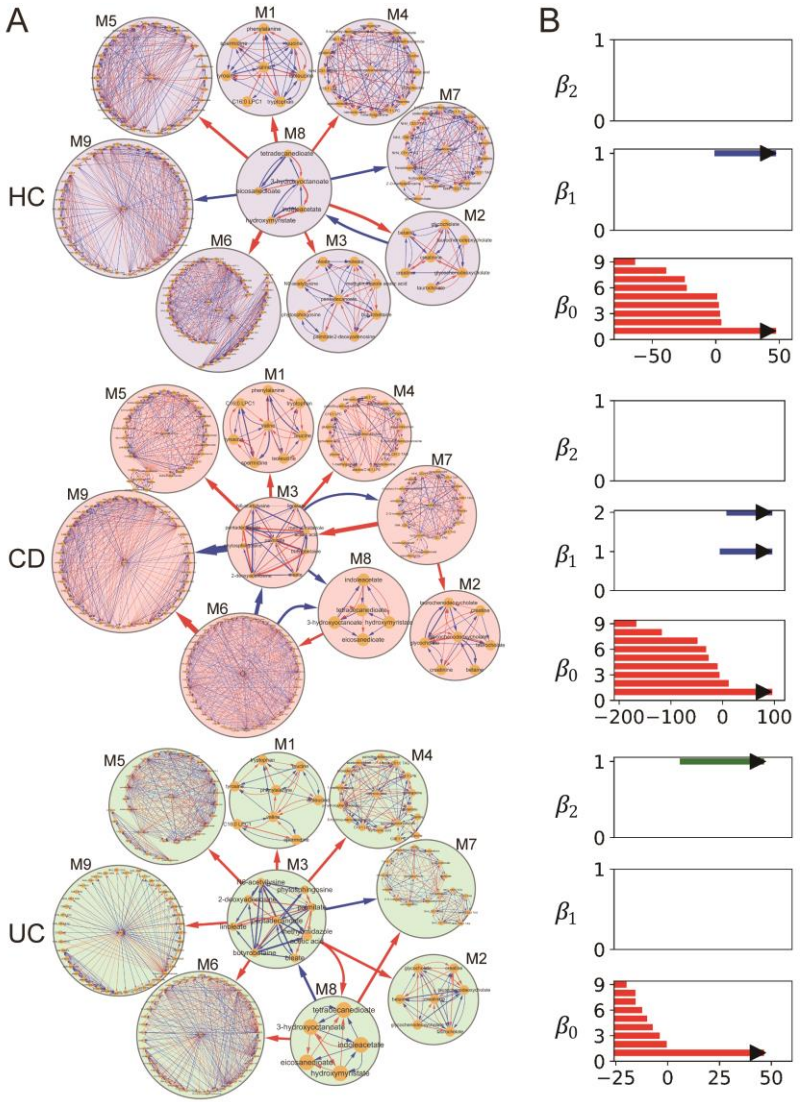


Crohn's disease



Ulcerative colitis

Two-Layer Metabolic Networks as a Predictor of Disease Risk



For the coarse-grained networks:

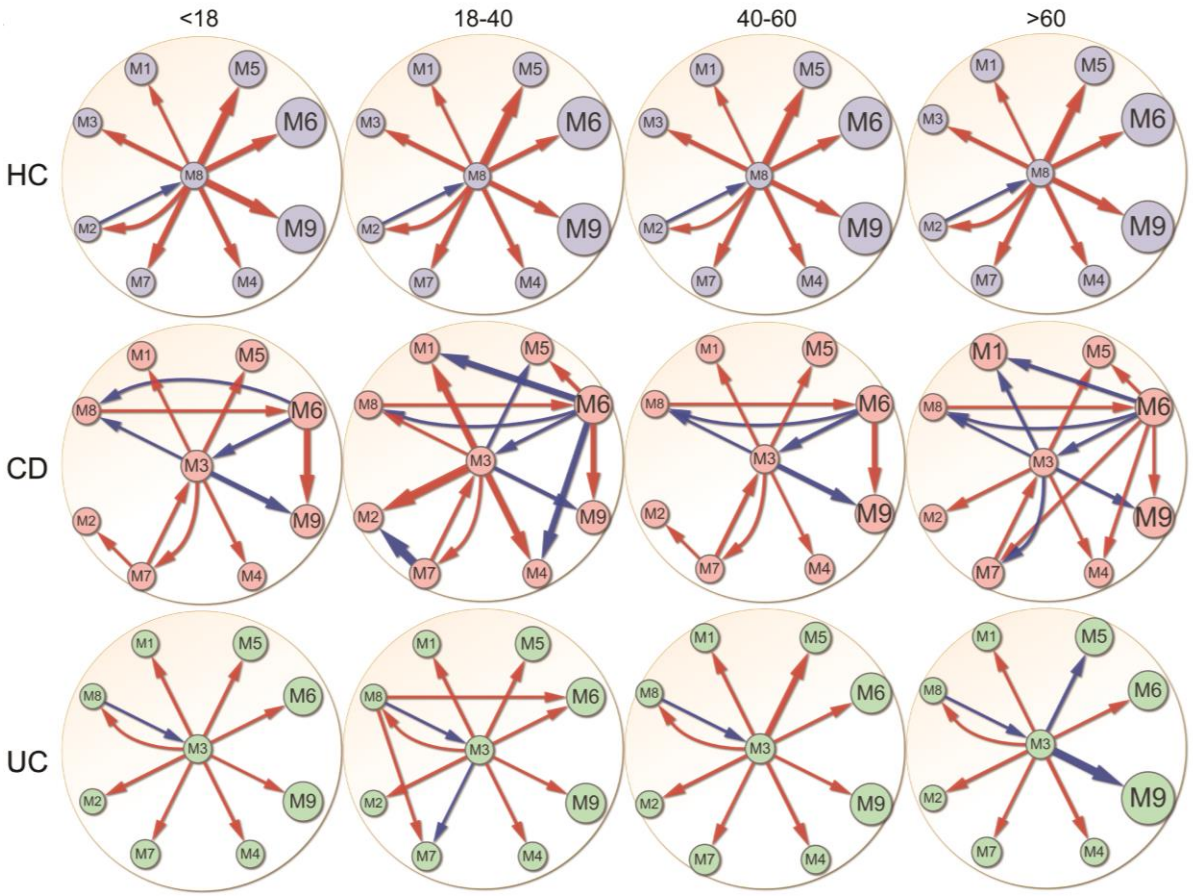
In the healthy group
M2 and M8 contain a loop in dimension one and this topological feature disappears in IBD state.

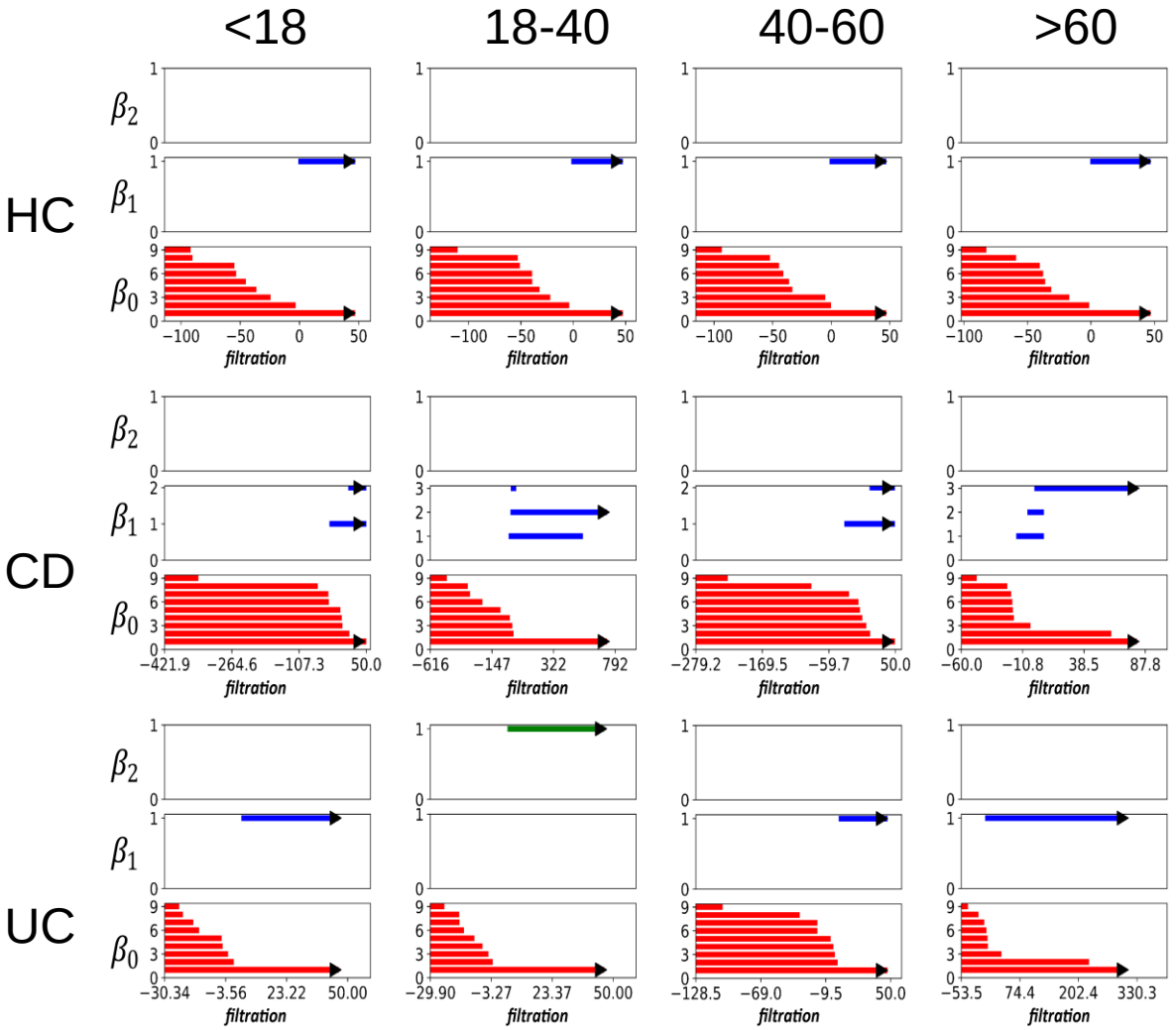
In the CD group
(M3, M7) and (M6, M8) have two one-dimensional loops.

In the UC group
There has no one-dimensional loops but produces a dimension two homology group, leading to nonzero second Betti numbers with M3, M6, M7, and M8.

The topological change of the coarse-grained networks is **numerical** from the healthy to CD state but **structural** from the healthy to UC state.

Age Trends of Metabolic Networks

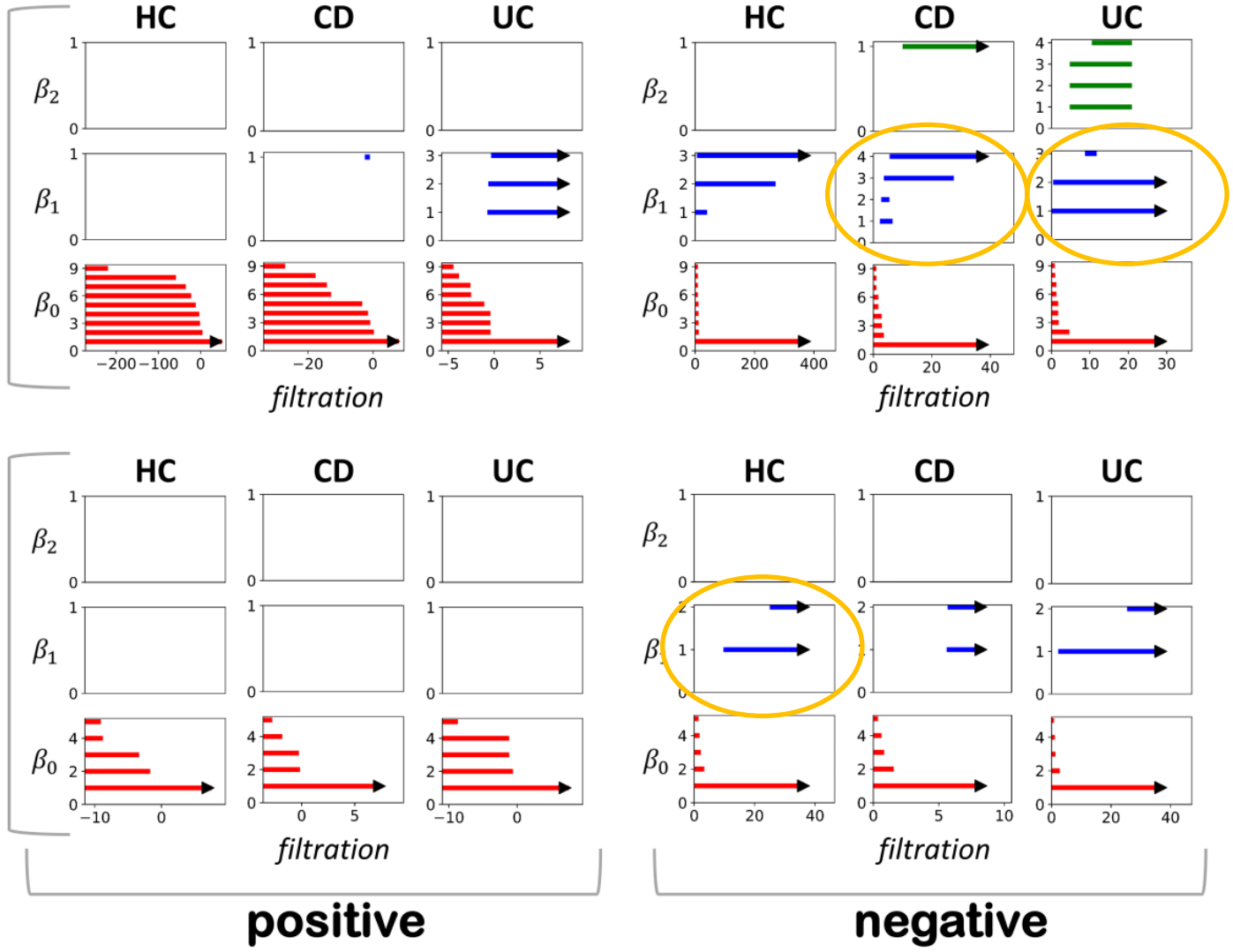




Persistent GLMY homology derived from the positive and negative links

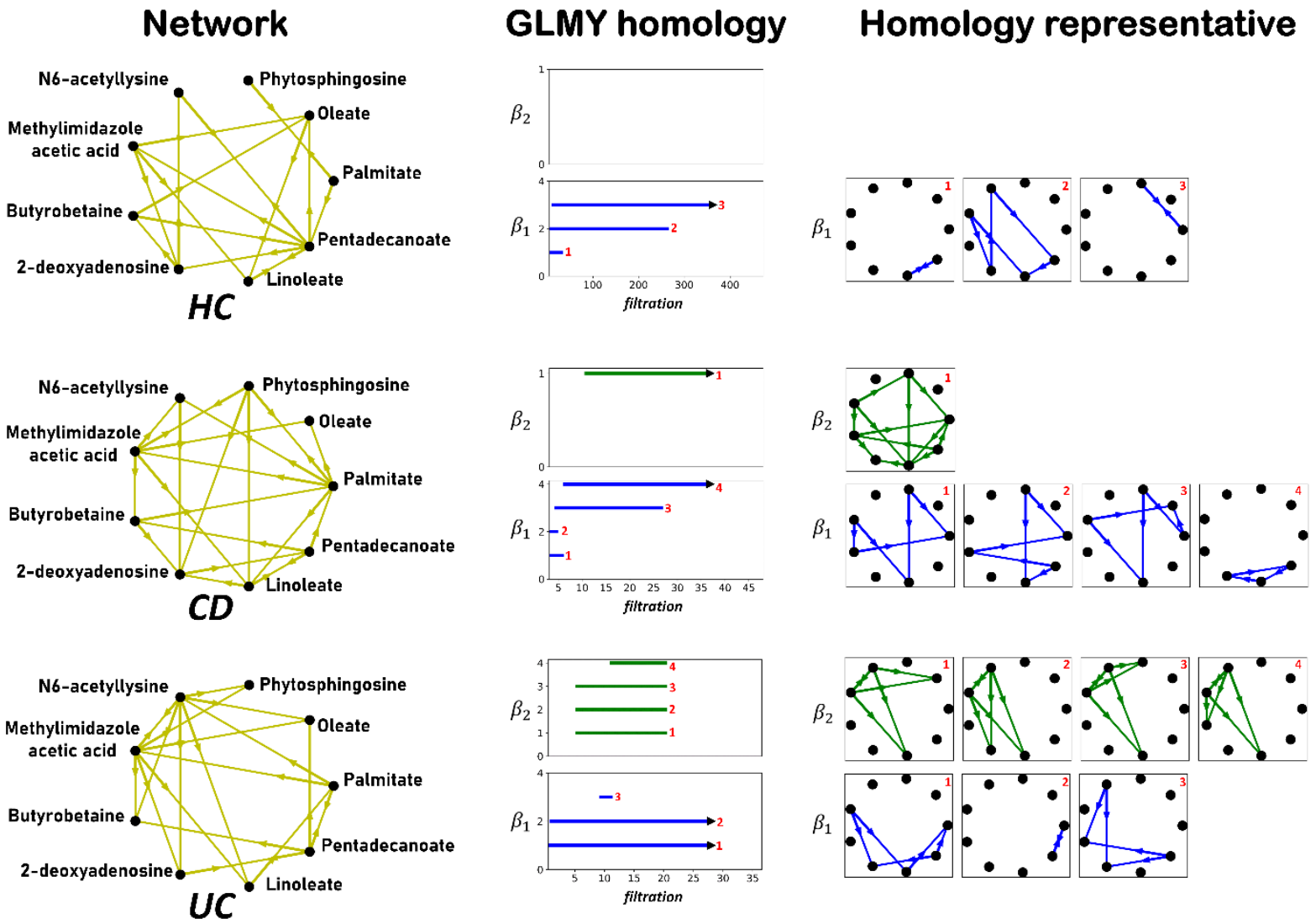
IBD hub

Healthy hub



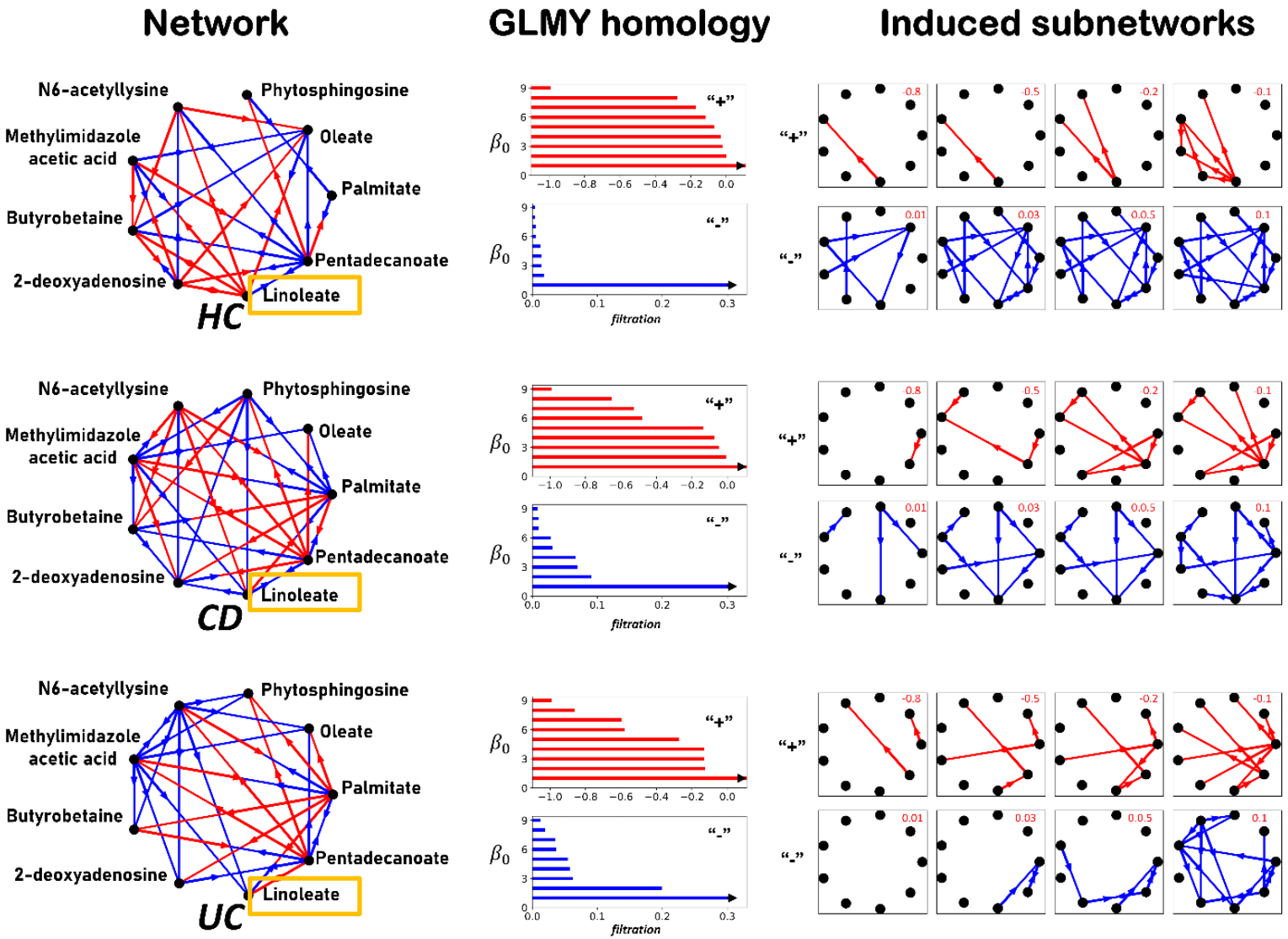
Increasing Betti numbers are associated with increasing network complexity, it can be inferred that the disease networks are more complex than the healthy network.

Detailed topological dissection of metabolic networks for three groups



1.N6-acetyllysine（N6-乙酰赖氨酸） 2.Methylimidazole acetic acid（甲基咪唑乙酸） 3.Butyrobetaine (丁基甜菜碱) 4.2-Deoxyadenosine（2-脱氧腺苷）
5.Linoleate（亚油酸酯） 6.Pentadecanoate（戊基棕榈酸） 7.Palmitate （棕榈酸） 8.Oleate （油酸） 9.Phytosphingosine（植物鞘氨醇）

Detailed topological dissection of metabolic networks at dimension zero



1.N6-acetyllysine（N6-乙酰赖氨酸） 2.Methylimidazole acetic acid（甲基咪唑乙酸） 3.Butyrobetaine (丁基甜菜碱) 4.2-Deoxyadenosine（2-脱氧腺苷）
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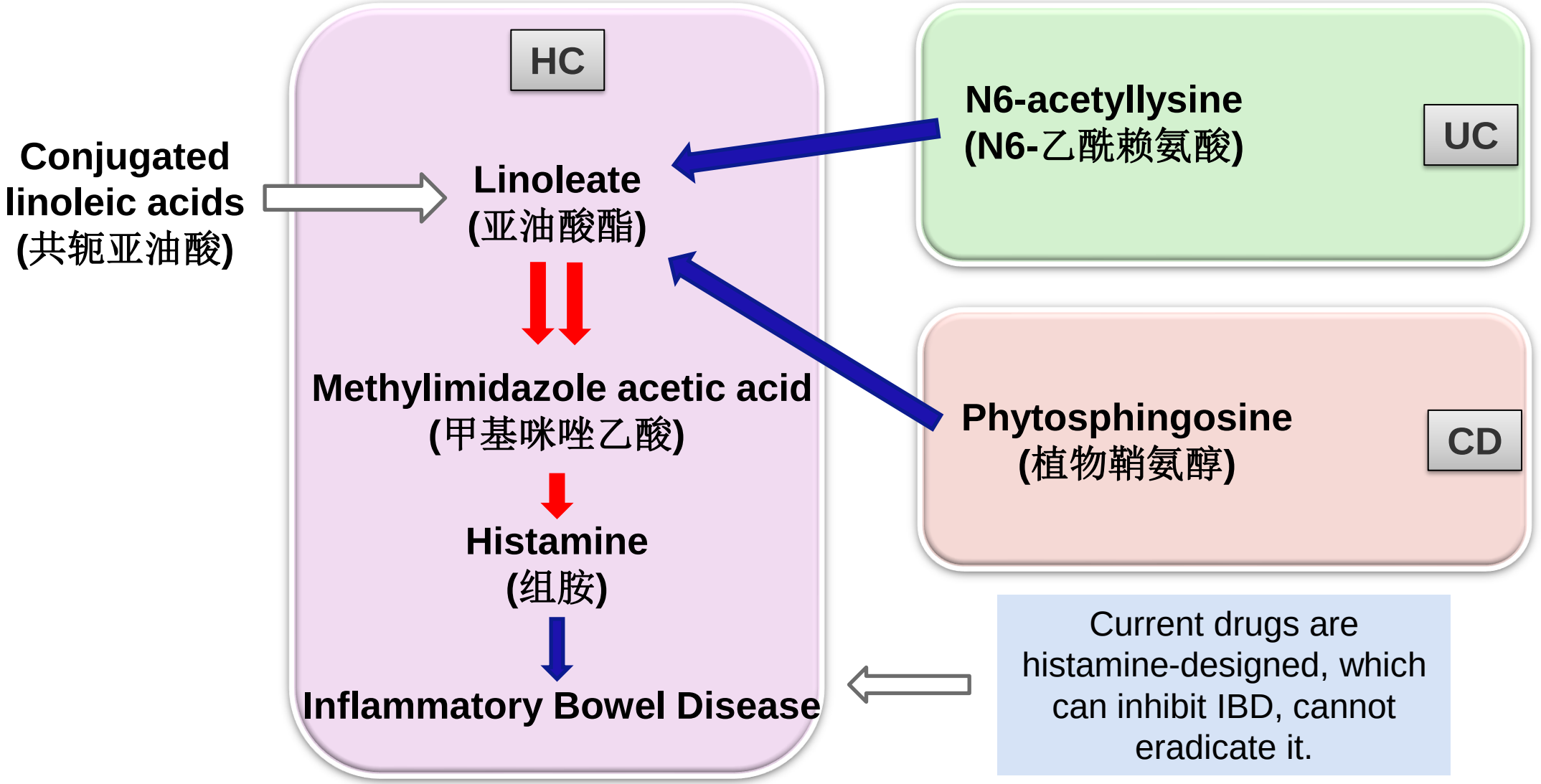
Detecting the topological pathway of inflammatory form



Conclusions

- We develop and apply a statistical physics model to reconstruct and dissect metabolic networks for healthy and IBD subjects and characterize the emergent topological properties.

- Analyze the topology of complex networks through GLMY homology theory. We find that network homologies can well characterize differences between healthy networks and diseased networks.

- Network differences can be detected in many topological aspects, but we find a general trend in health state–specific differences due to linoleate and its topological features at different dimensions.

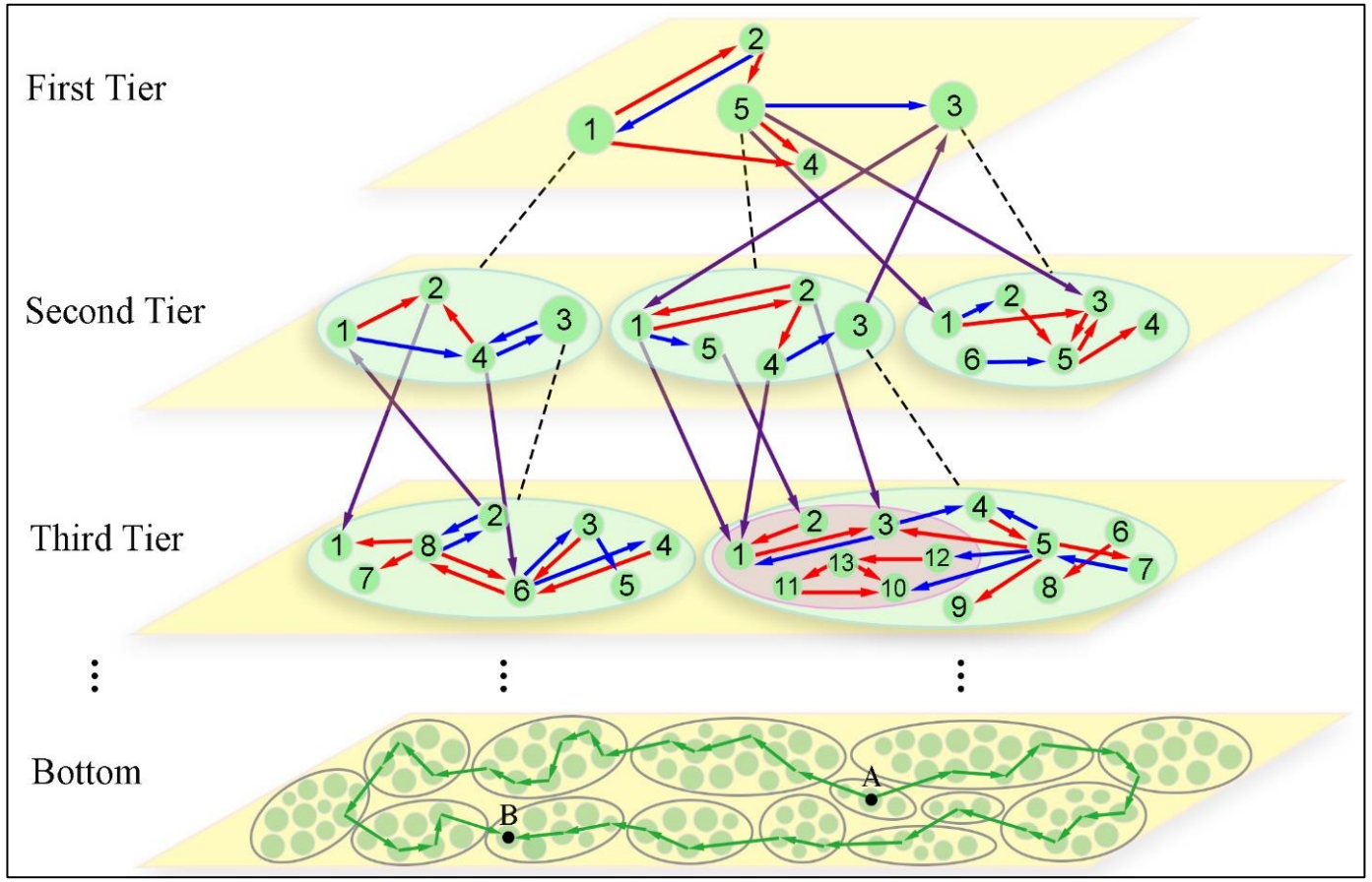
Conclusions

- Conjugated linoleic acids (CLA) is composed of linoleate, which considered to be beneficial for health. Provision of CLA in the intestinal lumen could be considered to prevent inflammatory diseases.

- To shift the metabolite network of a UC individual to be topologically equivalent to the healthy individual, one can design a therapeutic intervention to minimize the inhibitive effect on linoleate.

- Further investigation is needed to explore the strength of the relationships between GLMY homologies and disease phenotypes in order to alter metabolic function and interdependence by discovering optimal therapeutic interventions for IBD disease.

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



idopNetwork has proved its power to dissect the internal workings of complex systems, such as the gut microbiota (Cao et al. 2021), the vaginal microbiota (Wang et al. 2022), cancer genomics (Sun et al. 2021), tumor-microenvironment interactions (Sang et al. 2023), and combinational therapies (Sang et al. 2022).

idopNetwork 0.1.2 Reference Articles Search for

idopNetwork_vignette

Ang Dong

06/07/2023

Source: vignettes/idopNetwork_vignette.Rmd

```
library(idopNetwork)
backup_options <- options()
#load pre-computered results
test_result = idopNetwork:::test_result
```

About

idopNetwork is packed as a cartographic tool that performs power curve fitting, classification, variable selection, microbial abundance decomposition, and network visualization based on microbial 16S rRNA gene sequencing metadata.

For complete details on the use and execution of this protocol, please refer to Chen et al and Cao et al.

1. Input data

idopNetwork: A Network Tool to Dissect Spatial Community Ecology

Most existing approaches for network reconstruction can only infer an overall network and, also, fail to capture a complete set of network properties. To address these issues, a new model has been developed, which converts static data into their 'dynamic' form. 'idopNetwork' is an 'R' interface to this model, it can inferring informative, dynamic, omnidirectional and personalized networks. For more information on functional clustering part, see Kim et al. (2008) <doi:10.1534/genetics.108.093690>, Wang et al. (2011) <doi:10.1093/bib/bbr032>. For more information on our model, see Chen et al. (2019) <doi:10.1038/s41540-019-0116-1>, and Cao et al. (2022) <doi:10.1080/19490976.2022.2106103>.

Version:	0.1.2
Depends:	R (≥ 3.50)
Imports:	grDevices, stats, mvtnorm, orthopolynom, parallel, deSolve, ggplot2, reshape2, glmnet, igraph, scales, patchwork
Suggests:	covr, knitr, rmarkdown
Published:	2023-04-18
DOI:	10.32614/CRAN.package.idopNetwork
Author:	Ang Dong
Maintainer:	Ang Dong <fantasys05227 at gmail.com>
BugReports:	https://github.com/cxzdsa2332/idopNetwork/issues
License:	GPL (≥ 3)
URL:	https://github.com/cxzdsa2332/idopNetwork
NeedsCompilation:	no
Materials:	README
CRAN checks:	idopNetwork results

On this page

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Methods in Ecology and Evolution

APPLICATION

idopNetwork: A network tool to dissect spatial community ecology

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[2]Beijing Yanqi Lake Institute of Mathematical Sciences and Applications, Beijing, China

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Funding information
Beijing Forestry University

Handling Editor: Timothée Poisot

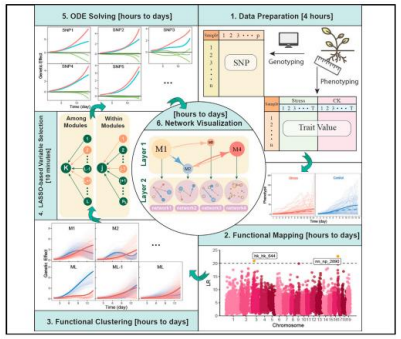
Abstract

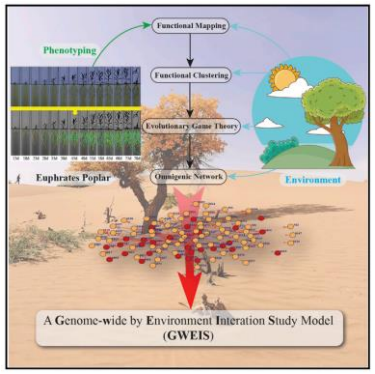
1. Network models have been used as a tool to characterize internal workings of complex systems. The amount of topological and functional information extracted from a network depend on the method of network inference and the type of network data.
2. An interdisciplinary computational model has been proposed to reconstruct informative, dynamic, omnidirectional and personalized networks (idopNetwork) from any data domains including static data.
3. We implement idopNetwork as an R-based cartographic tool to characterize spatially varying interspecies interaction networks using the abundance data of multiple species from different geographical locations. This tool provides a unified framework for integrating power curve fitting based on allometrical scaling law, functional clustering, LASSO-based variable selection, quasi-dynamic ordinary differential equation solving, species abundance decomposition and network visualization. It coalesces all species from different spaces into location-specific networks.
4. We demonstrate the utility of this tool by analysing different organs that are spatially interconnected via microbiomes within the host using two datasets from the gut microbiota and plant microbiota. Given that biodiversity and organization vary biogeographically at different scales, idopNetwork will find its widespread application to modelling and estimating interspecific interactions with differing functions across space.

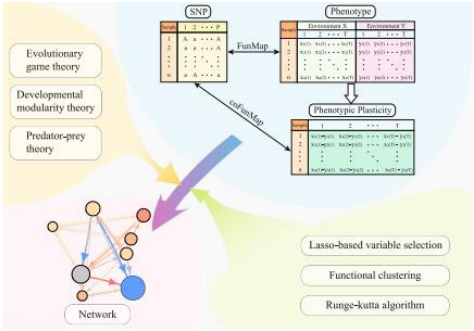
Functional mapping – Fungraph – idopNetwork

模型开发

- 个性化基因调控网络的全方位可视化模型（npj systems biology and applications, 2019）
- 为自然异源四倍体群体建立连锁不平衡网络模型的框架（MIEE, 2021）
- 在大型静态数据集中恢复动态网络（Physics Report, 2021）
- FunGraph：一种用于重建复杂性状的全基因多层相互作用网络的统计协议（STAR Protocol, 2021 ）
- 肿瘤微环境串扰的基因组物理学（ Physics Report, 2023）
- idopNetwork：一种剖析空间社区生态的网络工具（MIEE, 2023）

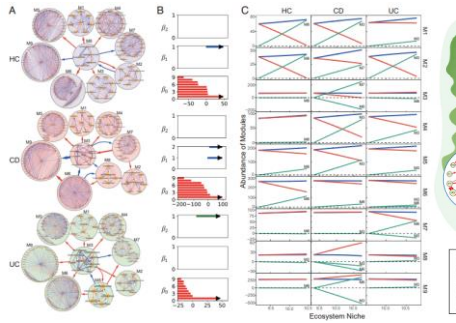


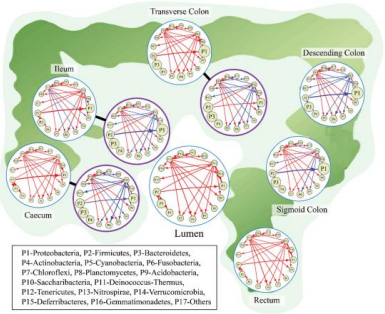


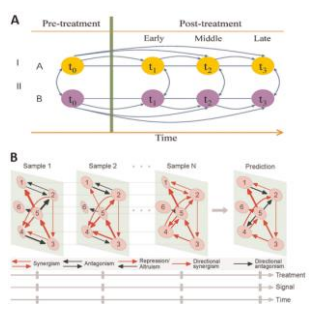


模型应用

- 通过全基因相互作用组网络对全基因组与环境相互作用进行建模（Cell report, 2021）
- 推断塑造表型可塑性和进化的多层相互作用组网络（Nature communication, 2021）
- 肠道微生物群空间相互作用网络建模（Gut Microbes, 2022）
- 复杂疾病的代谢组学物理学（PNAS, 2023）
- 药物反应的多效上位性缠绕模型（Drug Discovery Today, 2023）
- 嵌套互惠实验设计来绘制跨代表型可塑性的遗传结构（Horticulture Research, 2024 ）







Thanks for your attention!

Do you have any question?

Emali: shuangwu@bimsa.cn