SFI-CSSS Week 3 Introduction

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June 26, 2023

Introductory remarks

Experimental week with themes that bridge complexity, mathematics, and empirical work (lab and field work)

Lectures in morning with panels and workshops primarily in afternoon

Meant to teach material but also to question assumptions and relate to cutting-edge research questions and formulation all along the way

Please ask questions

Amazing lineup for speakers!

How to model

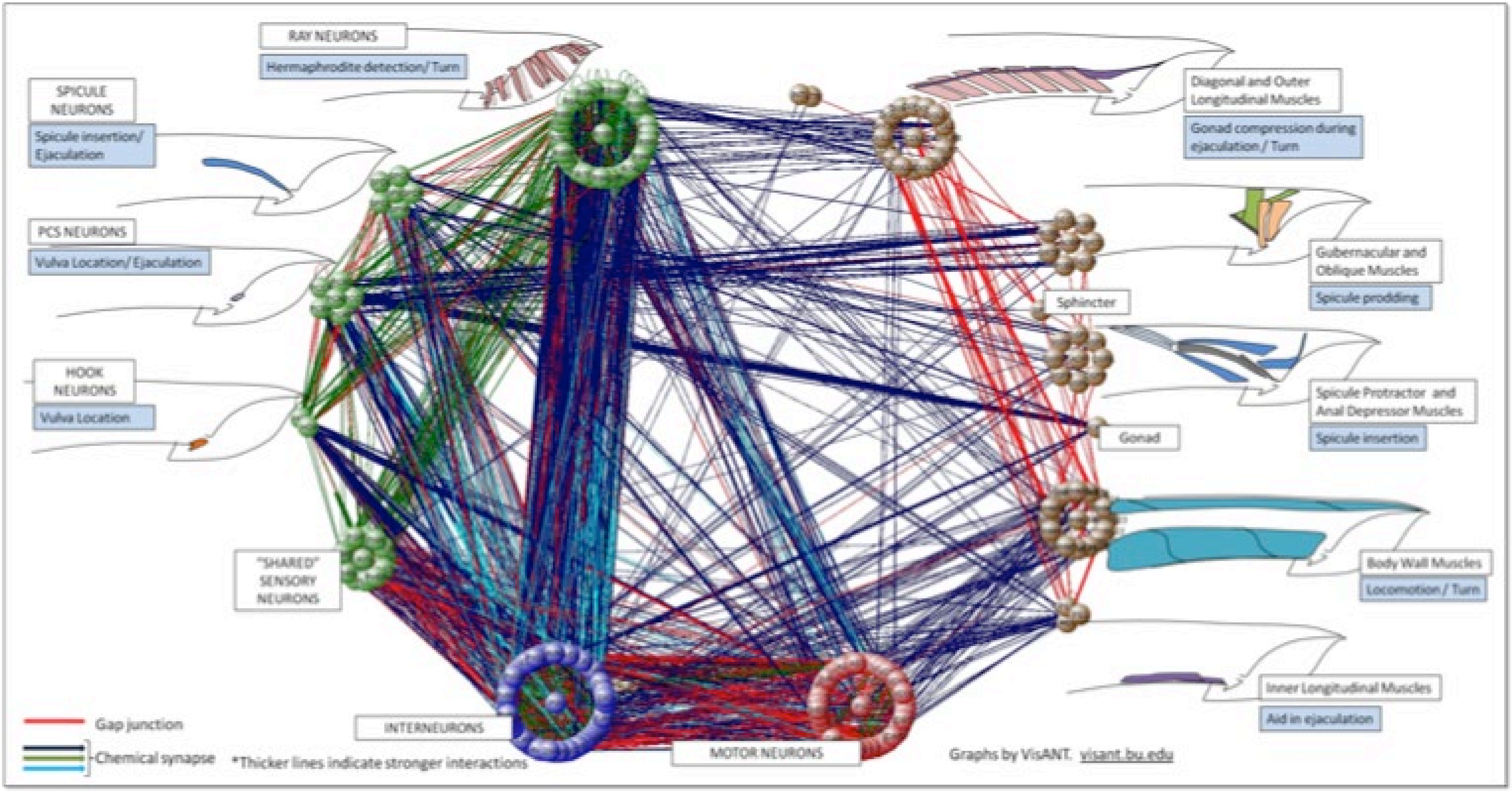
- Draw picture and create notation in intuitive space
- Often trying to describe change with time or space or some other dimension/variable and make some prediction
- Translate picture into mathematical or computational description
- Translating between two teaches a lot about implicit assumptions, potential numerical algorithms and computational approaches, and more
- Mathematics allows us to change spaces, often to one where problem is much easier to solve than in original intuitive space. **Main magic of mathematics** is not just calculation but to **translate to space that is natural for problem** whether or not natural for our brain. Makes analytical, numerical, iterative, analysis, etc, much simpler
- Check intuition and consistency of equations from start to finish and iterate

Complex systems

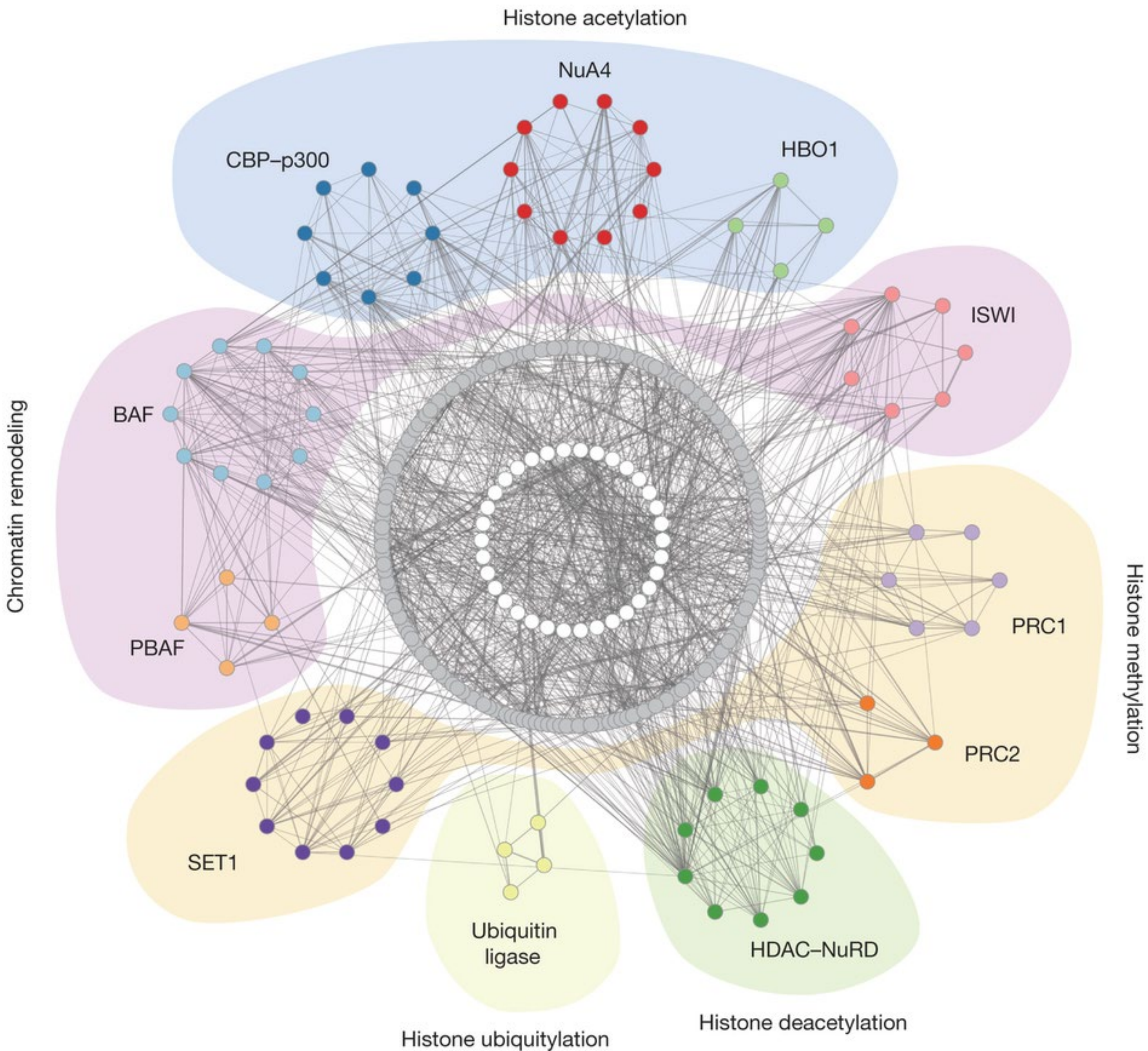
Large, interactive systems represented as networks with pairwise interactions

Contact interactions

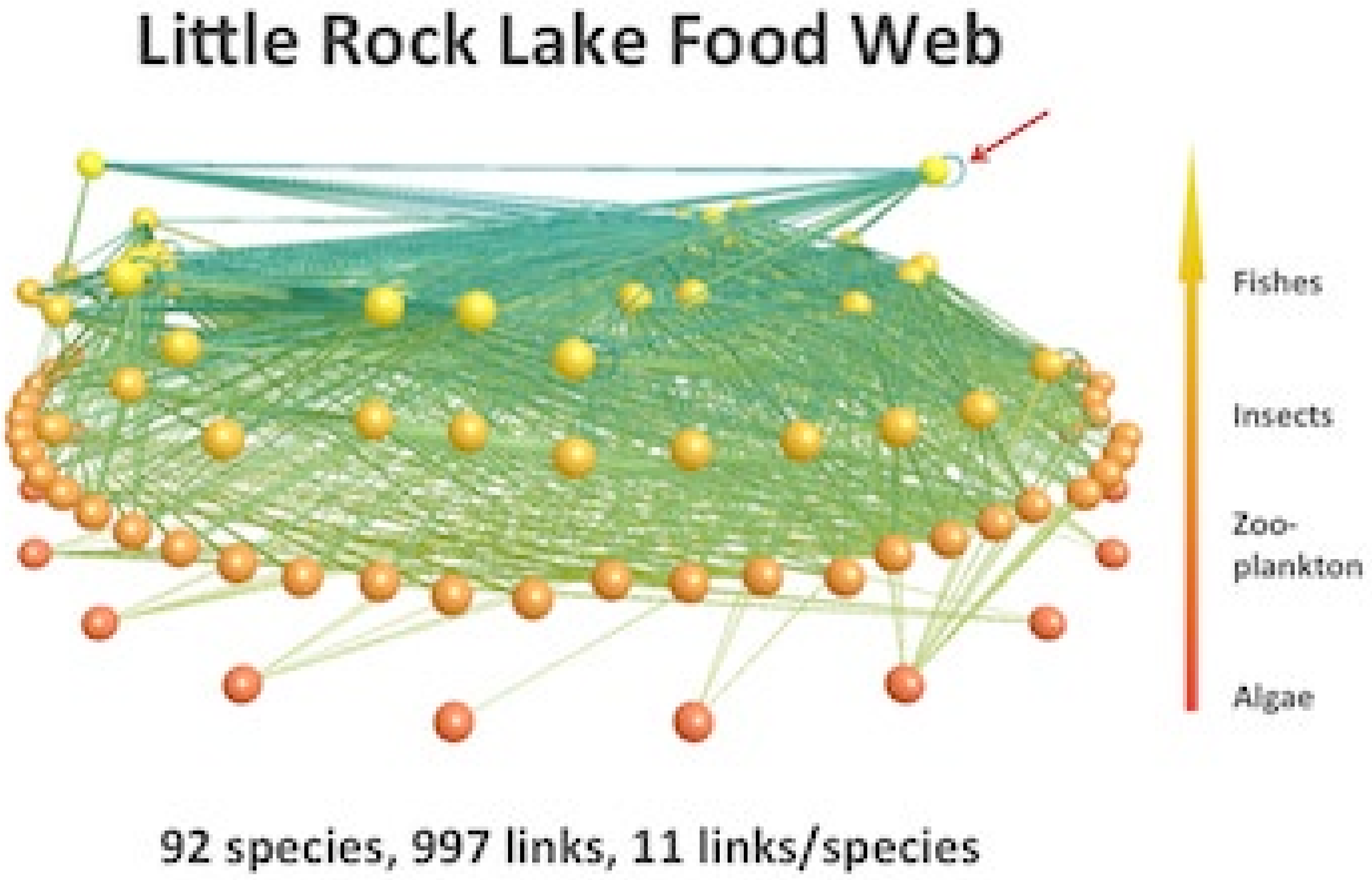
C elegans neurons–Complexity and Stability



Protein interaction network—Complexity and Stability

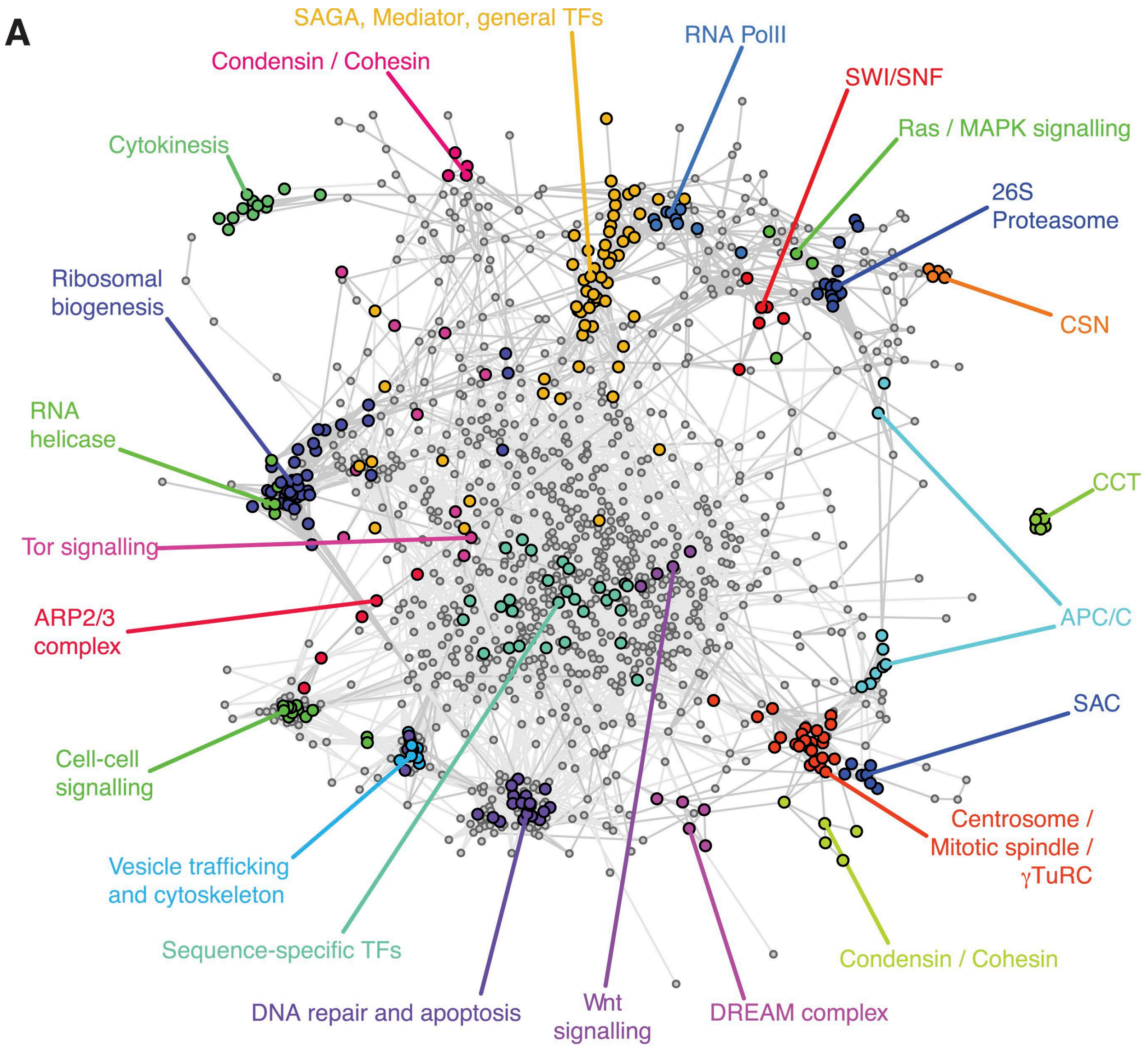


Predator-prey food web—Complexity and Stability

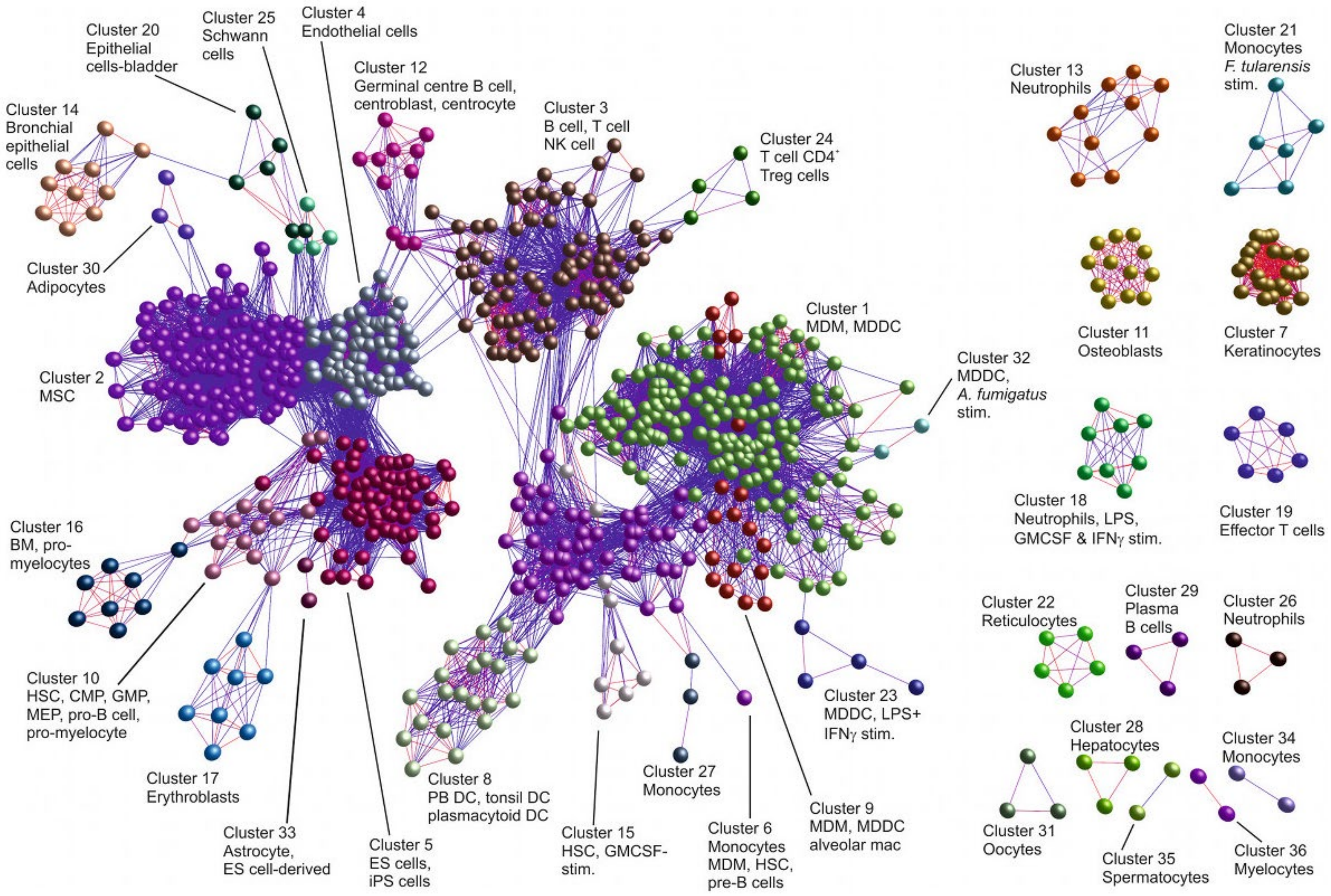


Other ways to construct networks: Non-contact interactions

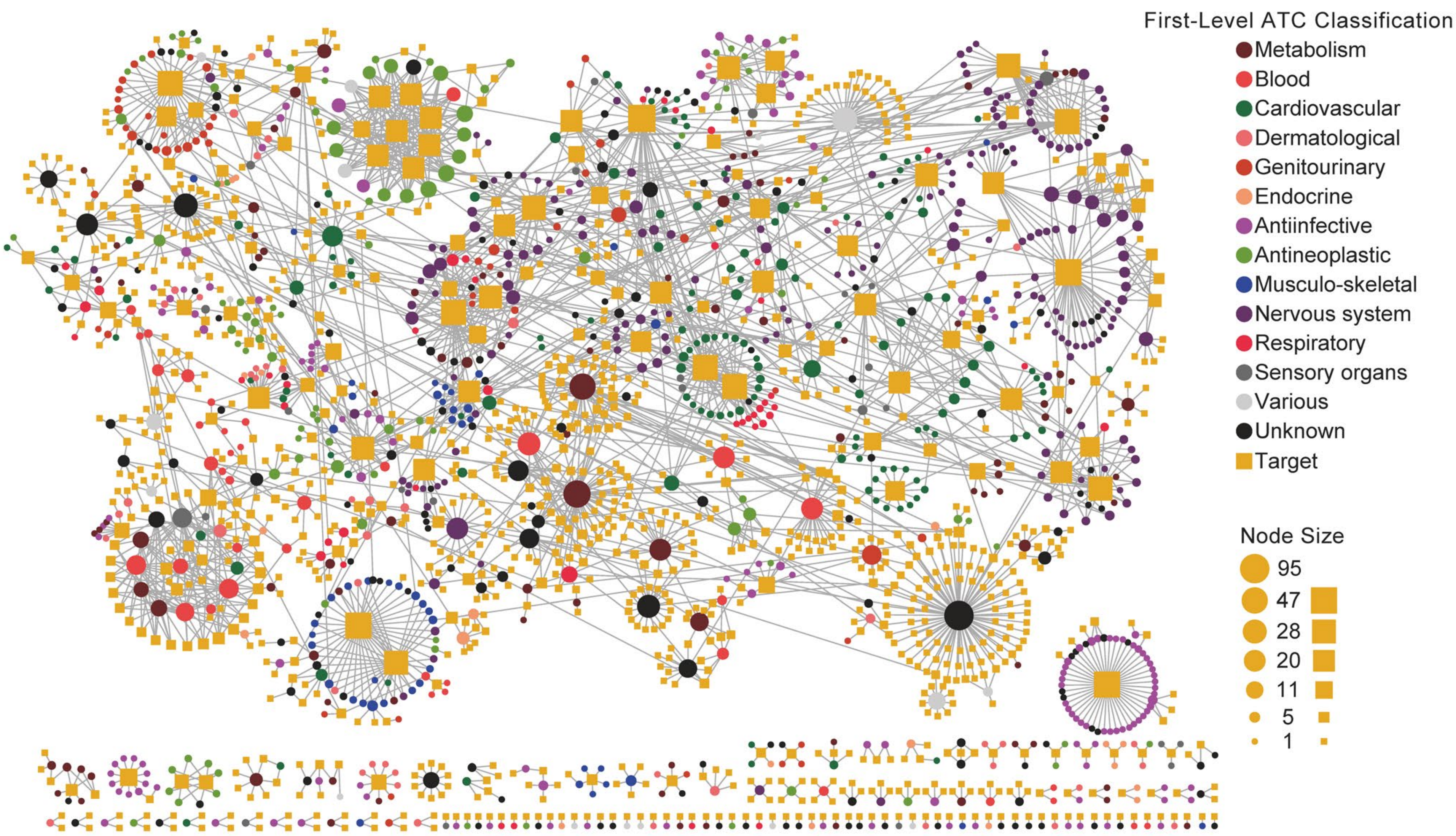
Epistasis and gene interactions—Complexity and Stability



Cell types and physiology—Complexity and Stability

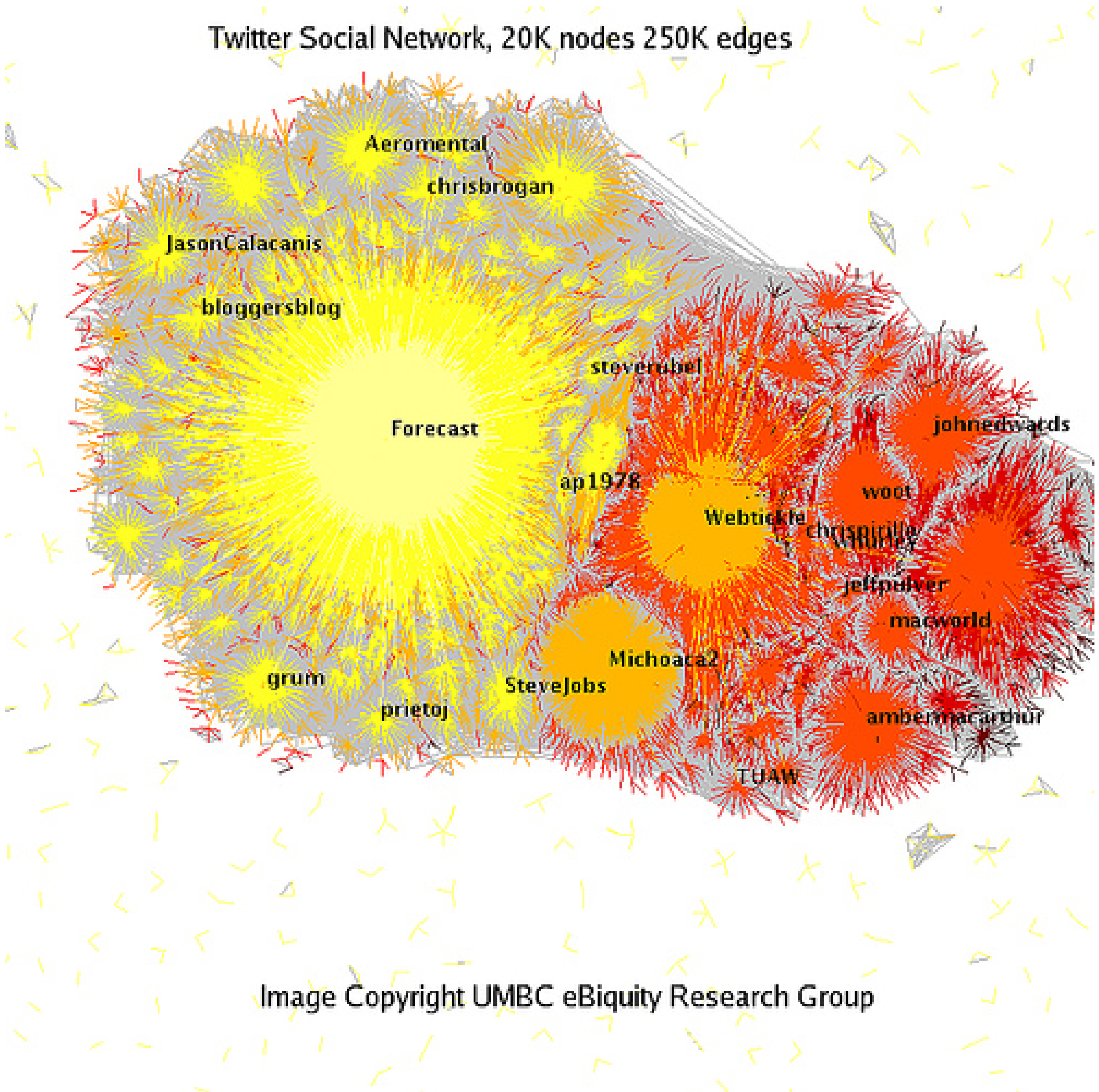


General drug interactions—Complexity and Stability

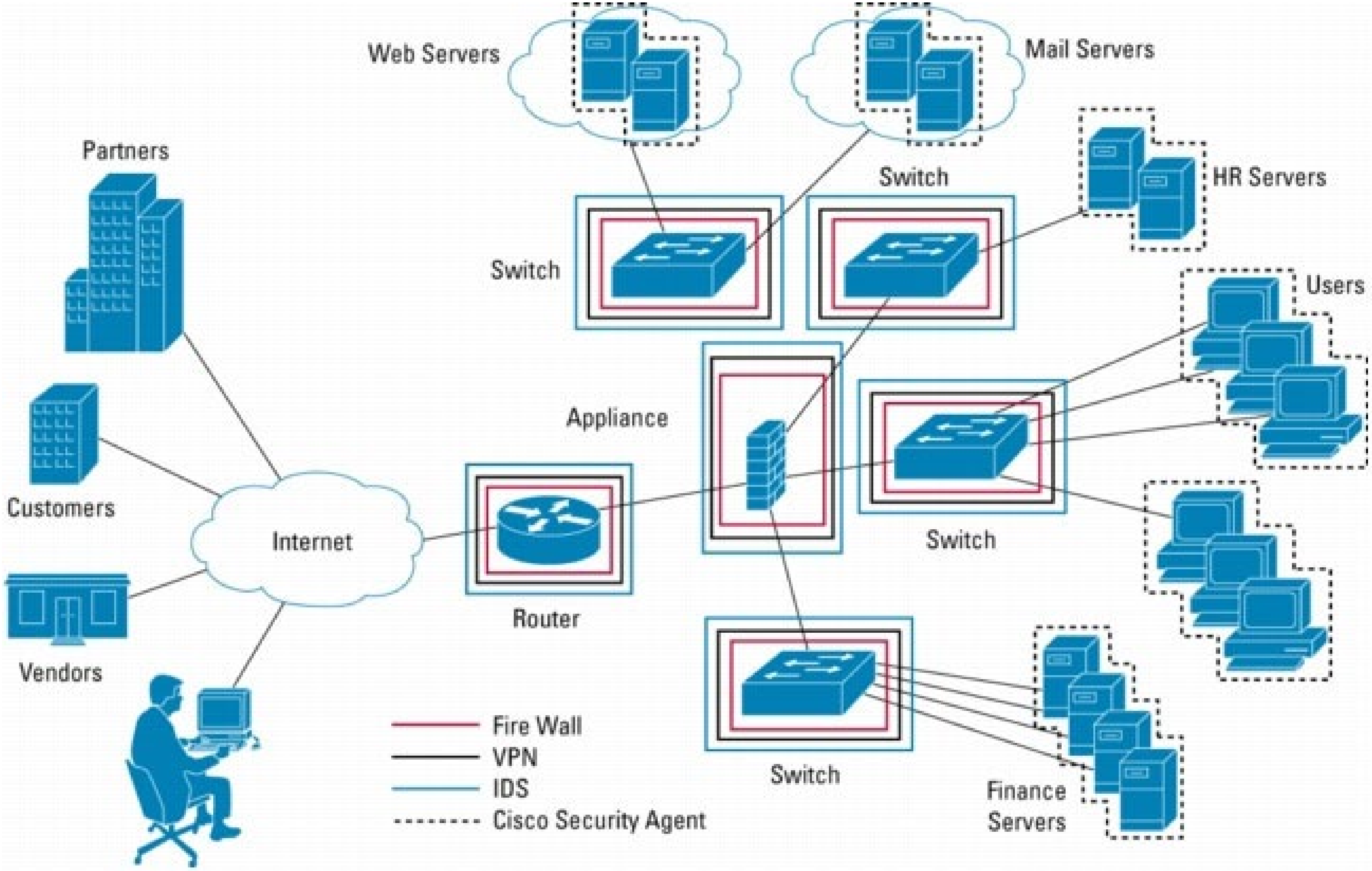


All humans are caught in an inescapable network of mutuality.-Martin Luther King, Jr.

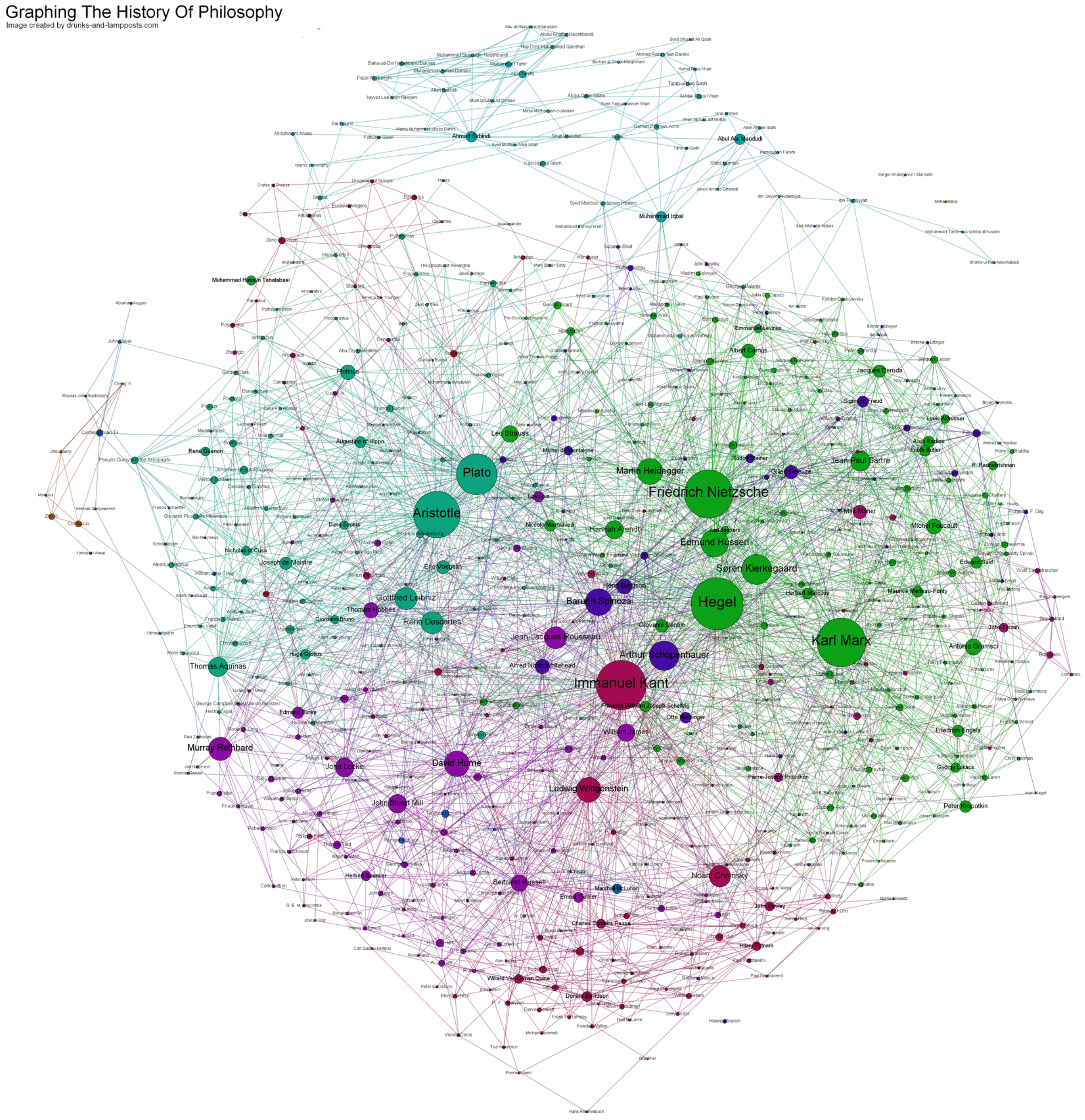
Can display same network in different ways



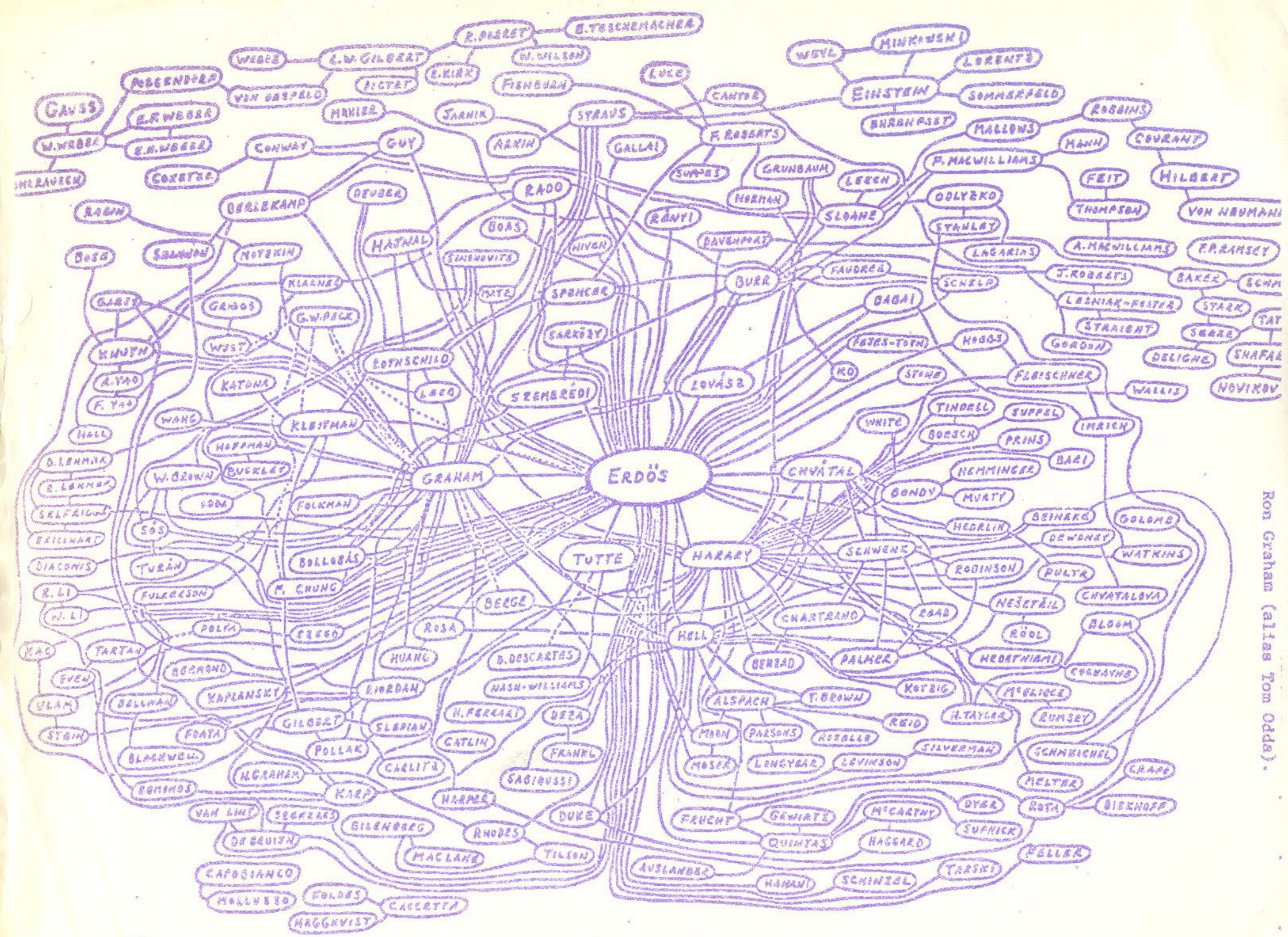
Can look at different network or levels for given system



Can look at different times



Can look at different times



Ron Graham (alias Tom Odda).

Figure 1

To appear in Topics in Graph Theory (F. Harary, ed.) New York Academy of Sciences (1979).

Non-contact interactions (come back to later)

1. How do we measure, quantify, and categorize these non-contact interaction?

2. Are there many interactions?

3. For both contact and non-contact interactions, what about pairwise versus higher-order, emergent interactions? All networks I showed are just pairwise interactions, even ones where interactions are non-contact and inferred.

4. Are there any patterns in types or amounts of interactions that occur at different orders? With increasing orders? Does this suggest ways to deal with combinatorial complexity?

5. Do they matter? Can lead to mix of contact and non-contact networks like primate policing

Stability, Resilience, Robustness, etc.

“True stability results when presumed order and presumed disorder are balanced. A truly stable system expects the unexpected, is prepared to be disrupted, waits to be transformed.”

-Tom Robbins

Read more at: https://www.brainyquote.com/quotes/keywords/stability.html

"A diverse ecosystem will also be resilient, because it contains many species with overlapping ecological functions that can partially replace one another. When a particular species is destroyed by a severe disturbance so that a link in the network is broken, a diverse community will be able to survive and reorganize itself... In other words, the more complex the network is, the more complex its pattern of interconnections, the more resilient it will be."

- Fritjof Capra

"Biological diversity is being lost at a rate unequalled since the appearance of modern ecosystems more than 40 million years ago. A quarter of all mammals are threatened with extinction; and nearly 70% of the world's fish stocks are fully exploited, overexploited or depleted."

- Royal Society

Not just true for ecology, where these ideas were first formulated, but for all the networks we've shown if we want to understand, predict, and manipulate them.

How can we build off last part to get dynamical equations at each node?

For species i with no interactions, we have

$$\frac{dx_i}{dt} = \dot{x}_i(t) = r_i x_i(t)\left(1 - \frac{x_i(t)}{K_i}\right)$$

Convert linear ODEs to matrix form

In matrix form

$$\dot{\mathrm{X}}(t) = \left(I - \mathrm{diag}(\mathrm{X}(t))\mathrm{diag}(K^{-1})\right)\mathrm{diag}(\mathrm{R})\mathrm{X}(t)$$

where

$$\dot{\mathrm{X}}(t) = \begin{vmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \vdots \\ \dot{x}_n(t) \end{vmatrix} \qquad \mathrm{X}(t) = \begin{vmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_n(t) \end{vmatrix}$$

Convert linear ODEs to matrix form

$$\mathrm{diag}(\mathrm{R}) = \begin{vmatrix} r_1 & 0 & 0 \\ 0 & r_2 & 0 \\ 0 & 0 & r_3 \end{vmatrix}$$

$$\mathrm{diag}(\mathrm{R})\mathrm{X}(t) = \begin{vmatrix} r_1 x_1 \\ r_2 x_2 \\ r_3 x_3 \end{vmatrix}$$

Convert linear ODEs to matrix form

In matrix form

$$\dot{\mathrm{X}}(t) = \left(I - \mathrm{diag}(\mathrm{X}(\mathrm{t}))\mathrm{diag}(K^{-1})\right)\mathrm{diag}(\mathrm{R})\mathrm{X}(t)$$

where

For 3 species case

$$\mathrm{I}_3 = \begin{vmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{vmatrix} \qquad \mathrm{diag}(\mathrm{K}^{-1}) = \begin{vmatrix} 1/K_1 & 0 & 0 \\ 0 & 1/K_2 & 0 \\ 0 & 0 & 1/K_3 \end{vmatrix}$$

Add interactions

In matrix form

$$\dot{\mathrm{X}}(t) = \left(\mathrm{diag}(\mathrm{R}) + \mathrm{diag}(\mathrm{X}(t))\mathrm{A}\right)\mathrm{X}(t)$$

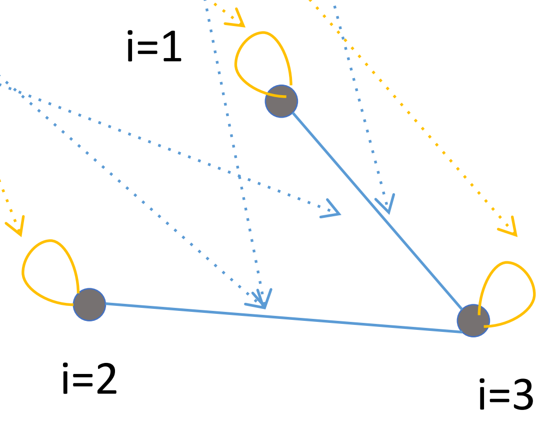
where for 3 species

$$\mathrm{A} = \begin{vmatrix} -r_1/K_1 & \mathrm{A}_{12} & \mathrm{A}_{13} \\ \mathrm{A}_{21} & -r_2/K_2 & \mathrm{A}_{23} \\ \mathrm{A}_{31} & \mathrm{A}_{32} & -r_3/K_3 \end{vmatrix}$$

And no interactions means $\mathrm{A}_{ij} = 0$

Interaction matrix to network

$$A = \begin{vmatrix} -r_1/K_1 & 0 & A_{13} \\ 0 & -r_2/K_2 & A_{23} \\ A_{31} & A_{32} & -r_3/K_3 \end{vmatrix}$$



Entries in interaction are where real specifics of system come in.
That is where lots of insight and knowledge and
choices are made and data is confronted.
Also in forming the terms in the equations to being
with based on interactions. Here assumes standard
random interactions among two things.

Multiply this out into equations

$$\mathrm{diag}(X(t))AX(t) = \begin{vmatrix} -x_1(r_1/K_1)x_1 + x_1 A_{12} x_2 + x_1 A_{13} x_3 \\ x_2 A_{21} x_1 - x_2(r_2/K_2)x_2 + x_2 A_{23} x_3 \\ x_3 A_{31} x_1 + x_3 A_{32} x_2 - x_3(r_3/K_3)x_3 \end{vmatrix}$$

Can see here that the A_{ij} terms couple together species i and j in the differential equations, representing interactions. Sometime called transfer function, but more generally any type of interaction.

Alternative notation

For species *i* with interactions, we have

$$\frac{dx_i}{dt} = \dot{x}_i(t) = r_i x_i(t) + \sum_{j=1}^{n} x_i(t) A_{ij} x_j(t)$$

Add interactions

In matrix form

$$\dot{X}(t) = \Big(\mathrm{diag}(R) + \mathrm{diag}(X(t))A\Big)X(t)$$

No interactions means $A_{ij} = 0$

Positive (increases growth) interactions means $A_{ij} > 0$

Negative (decreases growth) interactions means $A_{ij} < 0$

Why is this form useful?

Because many coupled equations can be written compactly, because linear algebra provides standard methods for changing to different easier space, and for doing stability analysis.

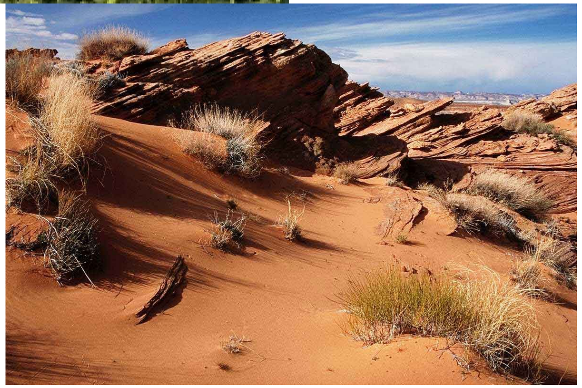
Why ecological networks?

1950's Paradigm:

Complex communities MORE stable than simple communities

1970's Challenge:

Complex communities LESS stable than simple communities



Current & Future Research:

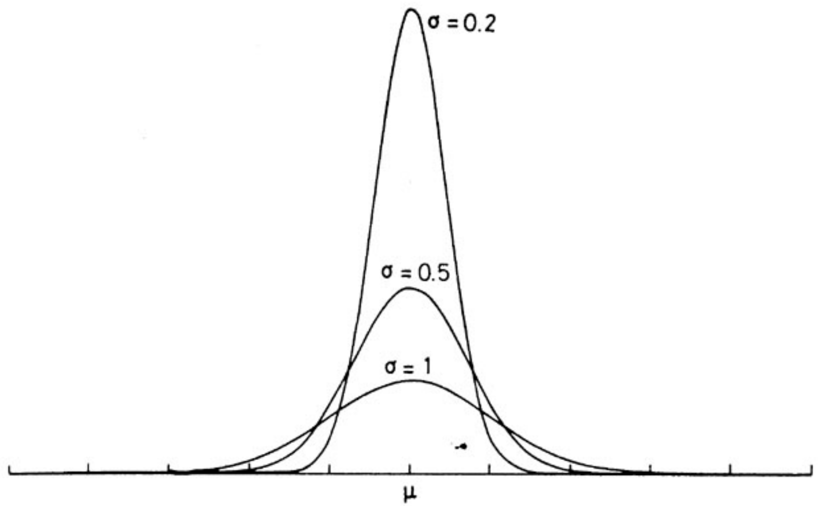
"Devious strategies" that promote stability and species coexistence

Complexity-Stability debate
Lord Bob May model

n—number of proteins or genes or species determines size of nxn matrix

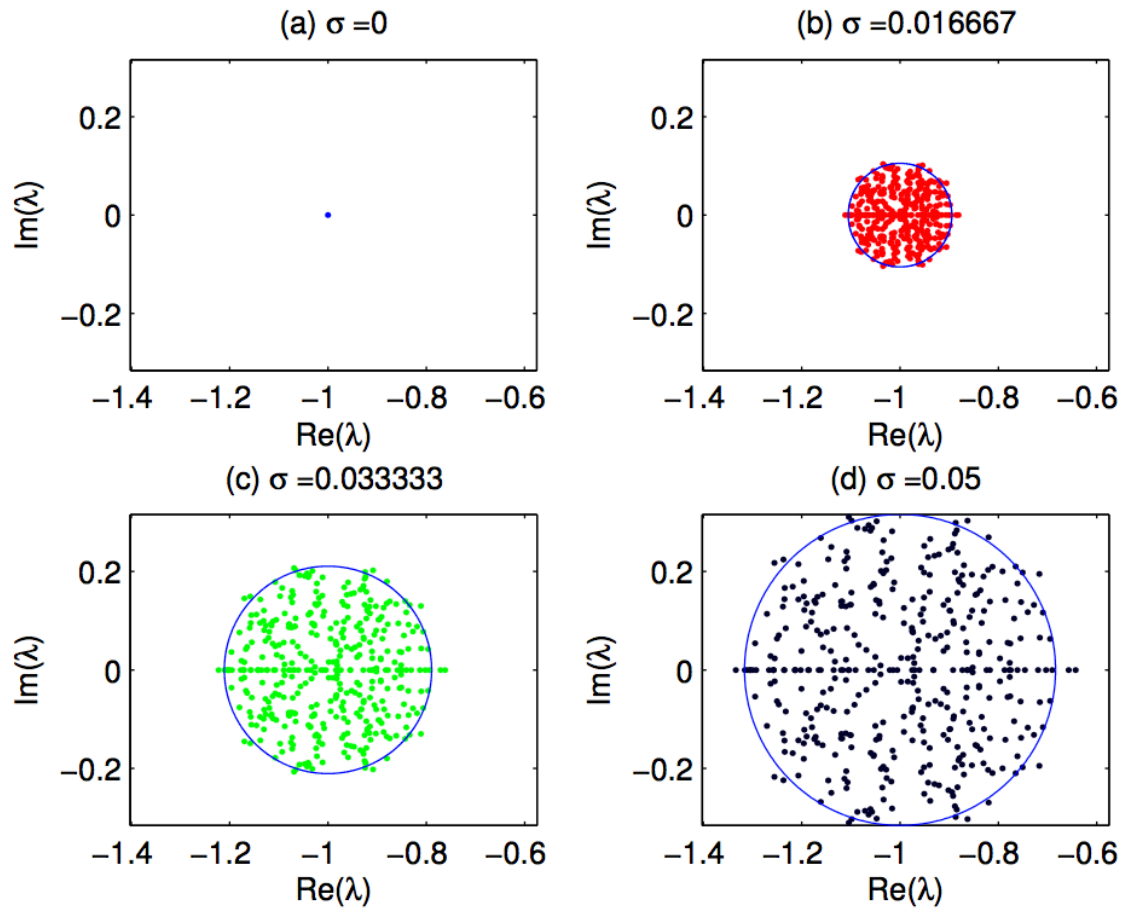
C=(number of links)/(number of pairs)
realized connectance among parts and related to complexity
determines number of non-zero entries in interaction matrix A

σ—standard deviation/width of normal distribution from which interactions are randomly sampled. Related to strength of interaction.



Return to complexity-stability debate

Circle centered at -1 but has diameter that grows as $\sqrt{nC}\sigma$
At some point, right side will cross 0, and then the system will become unstable. So, large complex systems are unstable?



Karl Nyman thesis

Seems counter to what we see in nature. What gives within this framework?

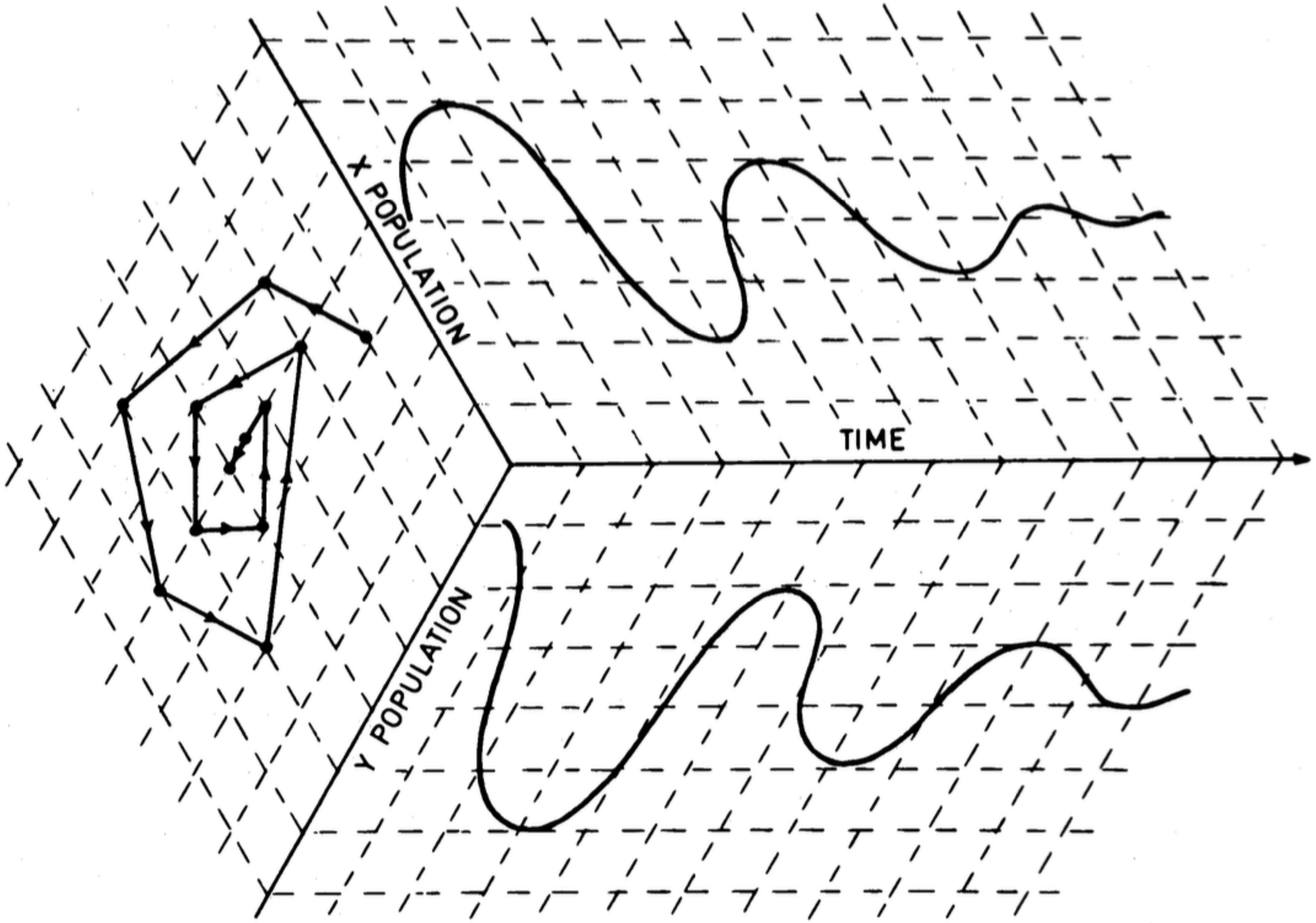
1. Interaction matrices are NOT random. There is structure/hierarchy/modularity through all of these, and this is where a lot of the interesting biological knowledge and reasoning and more math in current research is coming in!—*Dunne*, Allesina, Martinez, O'Dwyer, Venturelli, *Savage, Nilsson Jacobi*

2. Most models assume r and K are constants, but they vary in systematic and important ways.—Venturelli, *Savage, Nilsson Jacobi*

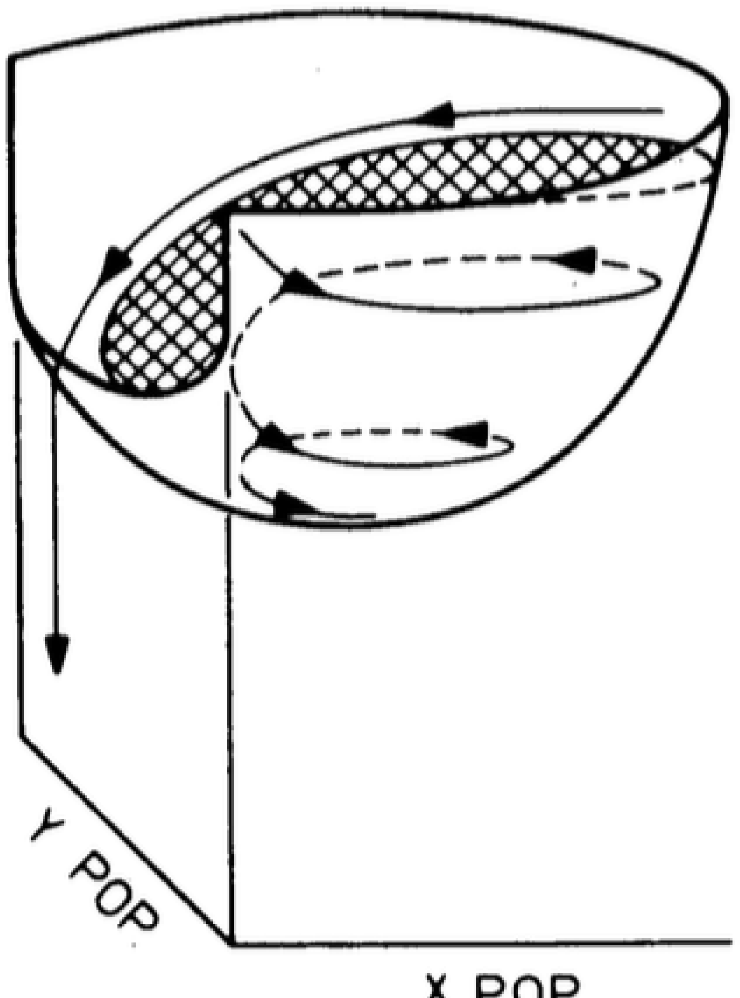
3. Assumes all else is constant, but environment (meaning body, climate, diseases, etc.) can and does change over relevant time scales and that could be very important and essential. Maybe never at equilibrium.—everyone and no one

Holling and Resilience and Persistence
(Not just mathematical stability)

Local Stability Analysis in Phase Space



Domains of Attraction, More Global Analysis, Beyond Infinitesimal Perturbation



Seems counter to what we see in nature. What gives outside this framework?

1. Perturbations are not infinitesimal (think climate change, fires, drought, human land use, other disturbances). Need something more than local stability analysis to deal with this.

2. Maybe not stable with respect to system but with respect to biodiversity, ecosystem functioning, traits, life stages–all of which can involve species extinctions and replacements—*Moeller, Klausmeier, Litchman, Nilsson Jacobi, de Roos, Marquet, MacGregor-Fors,*

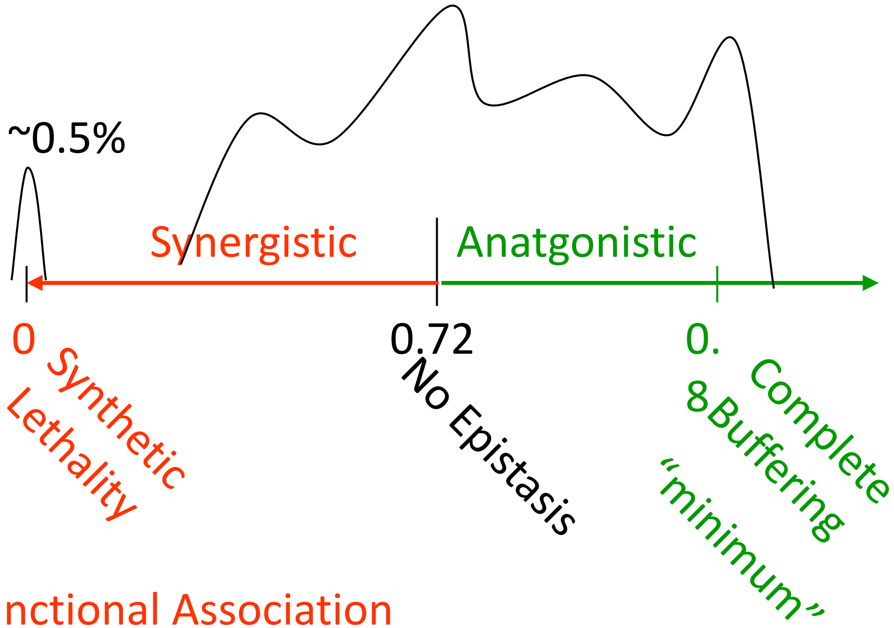
3. How does evolution really fit and allow parameters/traits/etc to respond and change in time?—*Derryberry, Alarcon, Yeh, Marquet, Moeller, Litchman*

Non-contact interaction networks

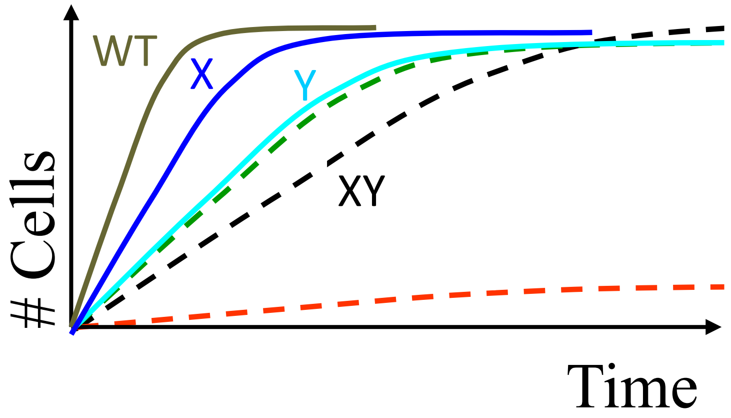
Pair Test—Quantitative genetic interactions

Proliferation Rates

		Gene X	
		+	-
Gene Y	+	1	0.9
	-	0.8	? 0 / 0.72 / 0.8



Functional Association



Pair Test—Measures of epistasis (interactions)

In symbols, no interaction means

$$w_{xy} = w_x w_y$$

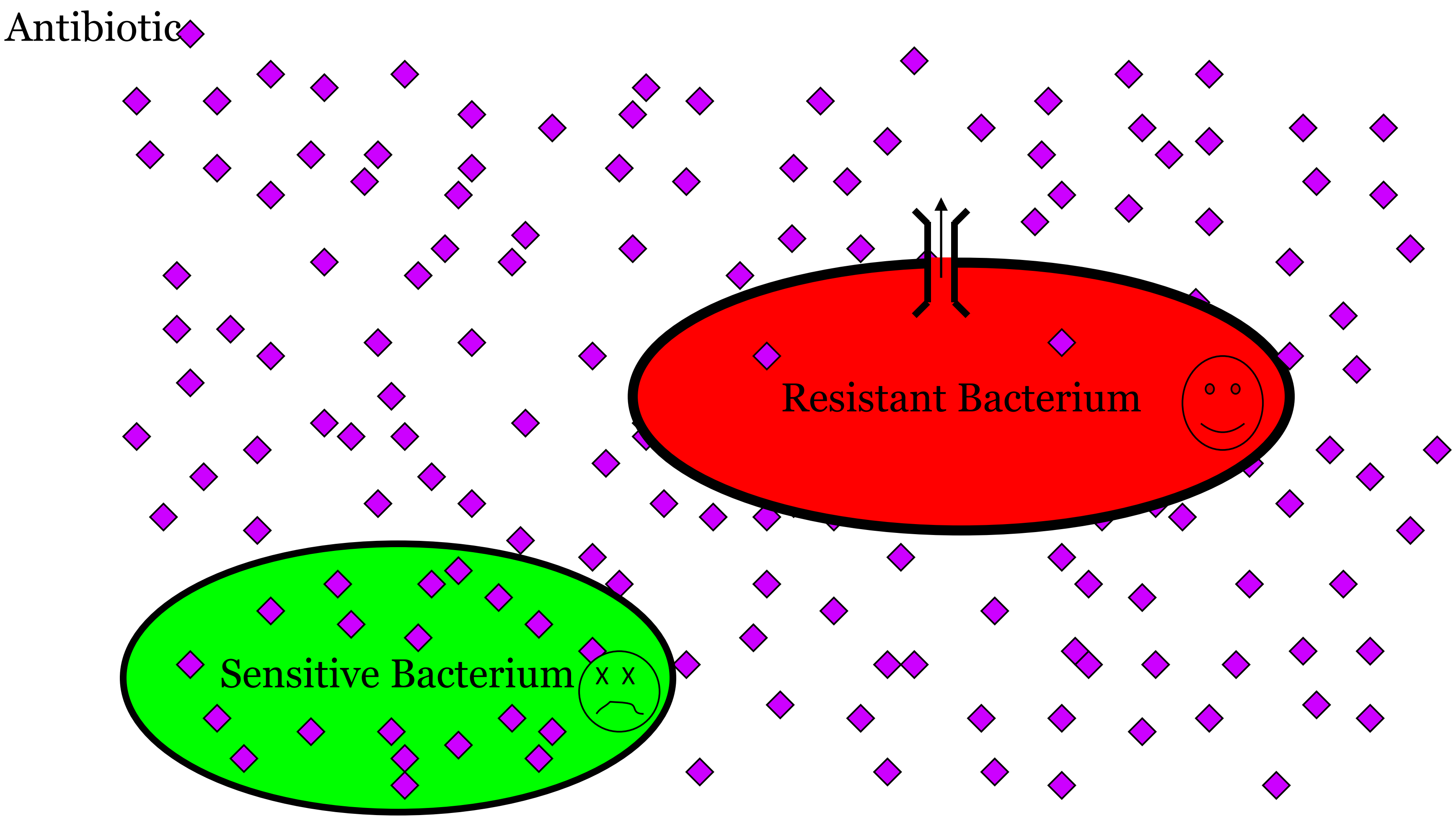
So if the difference does not equal zero, this means there is an interaction. Measure of Deviation from Additivity

$$DA = \varepsilon = w_{xy} - w_x w_y$$

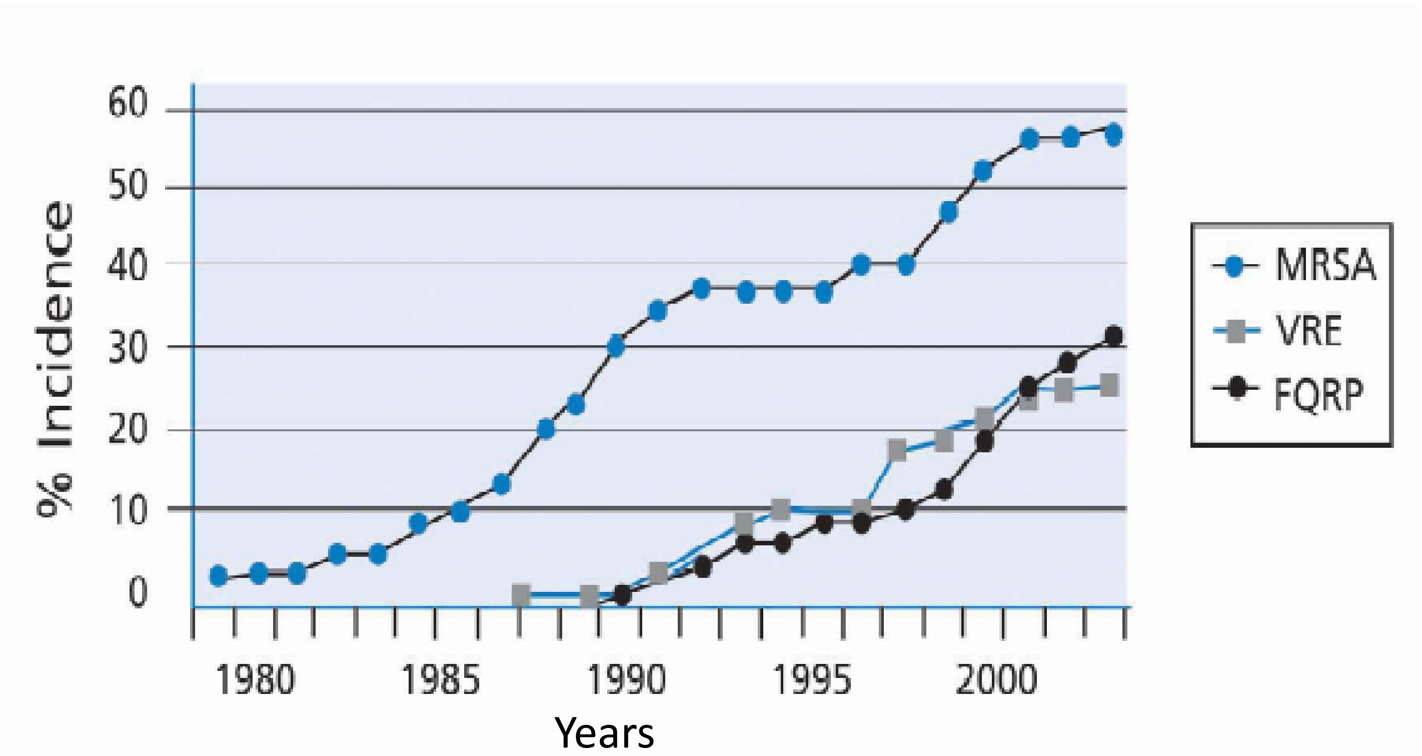
Some pathogens grow very quickly

They can be killed by antibiotics…

…but some bacteria can become resistant to the drug



Antibiotic resistance a growing public health threat



1987 1992 1997 2002 2007

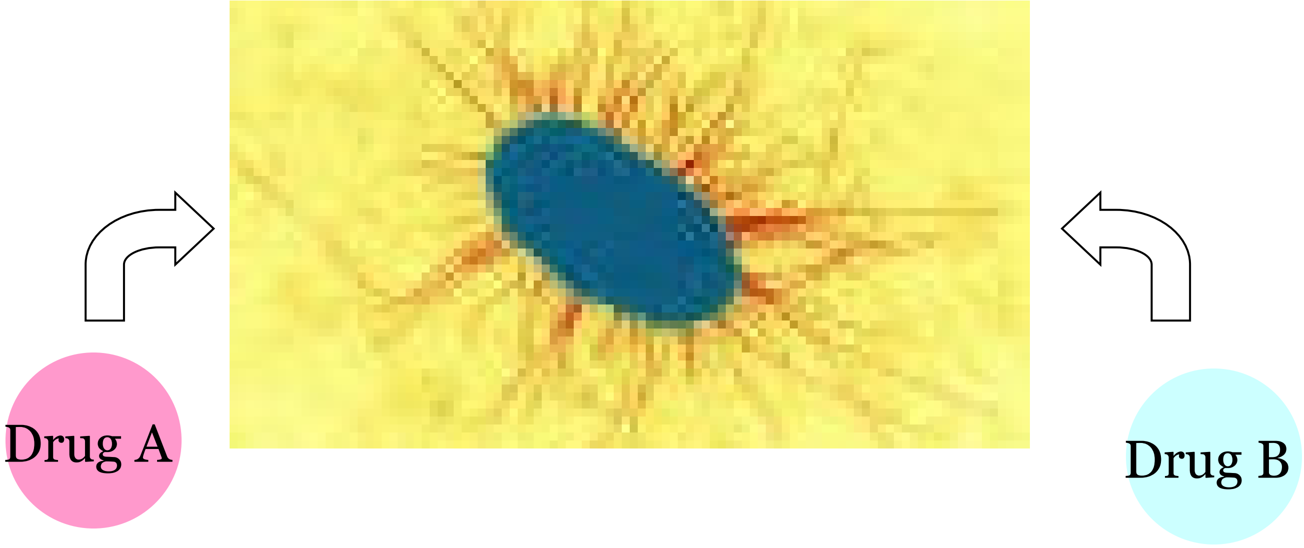
Spellberg, et. al., *CID* May 1 2004, Modified

FQRP = Floroquinolone-resistant *Pseudomonas aeruginosa*

Main Question

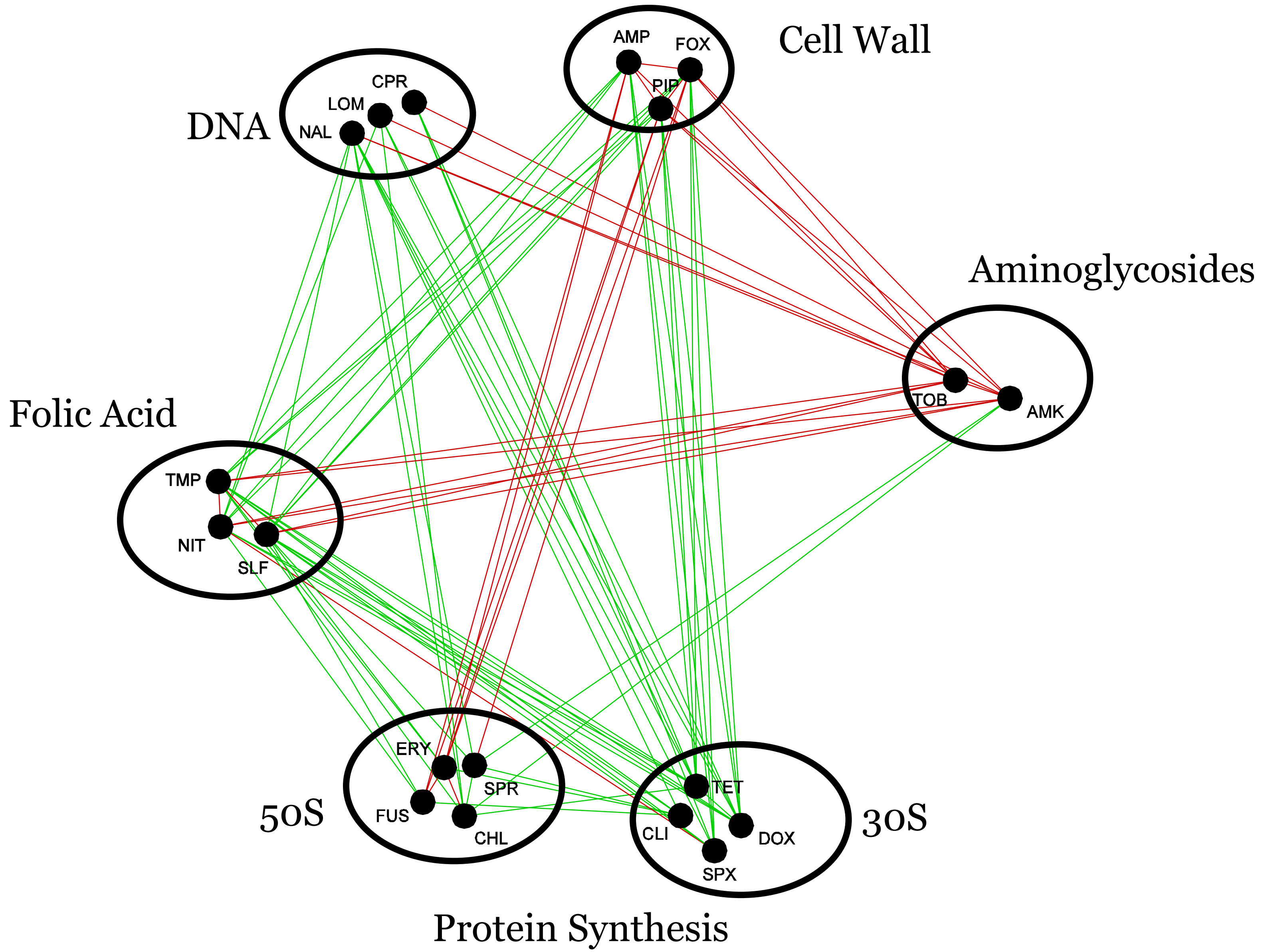
How do drugs interact with each other, and how can we use their interactions to determine their mechanisms of action?

Multiple drugs combine to fight bacteria



Two drugs can interact with each other to produce varying effects

Drug-Drug Network Functional Classification



Yeh, et al. – Nature Genetics 2006

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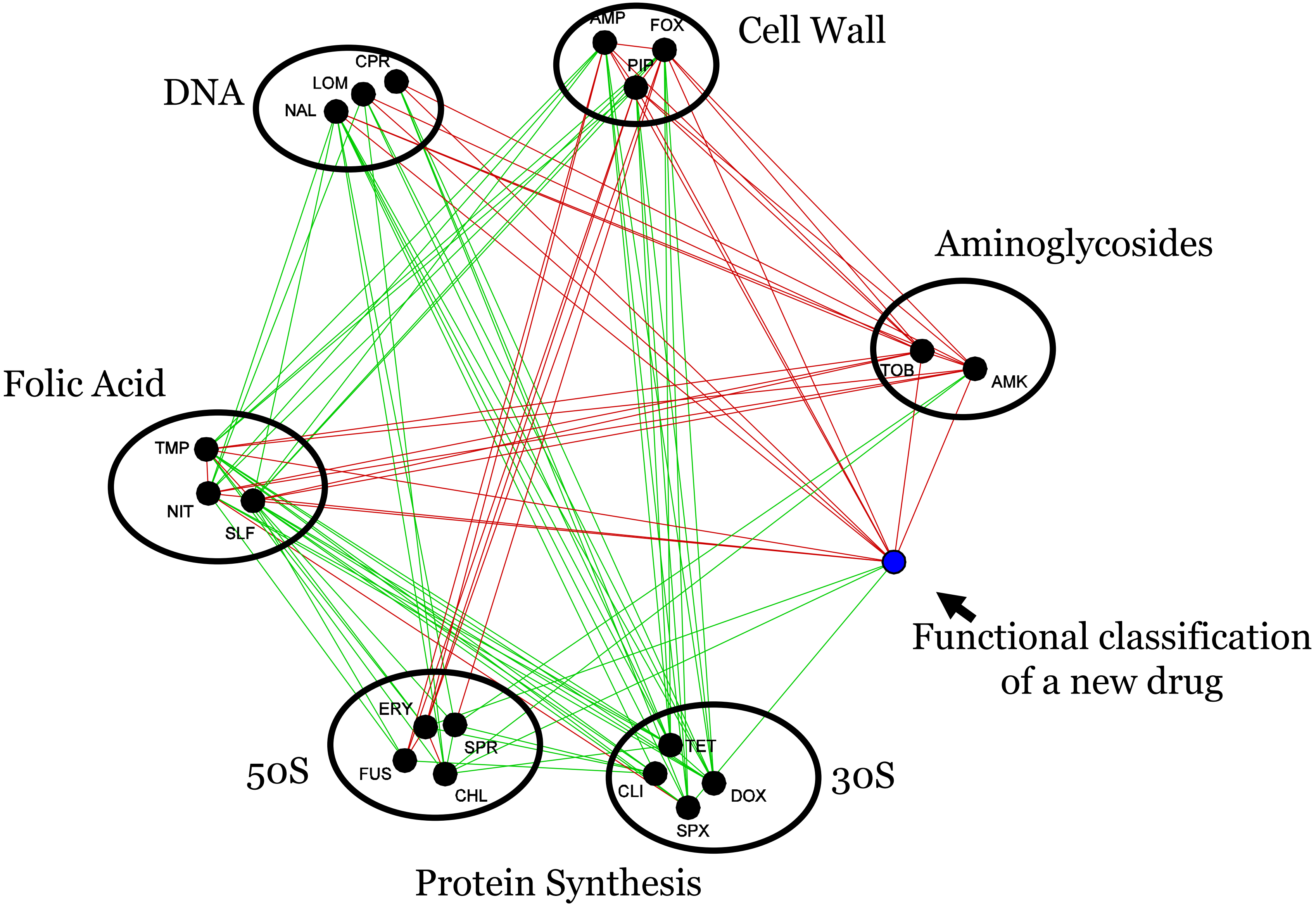

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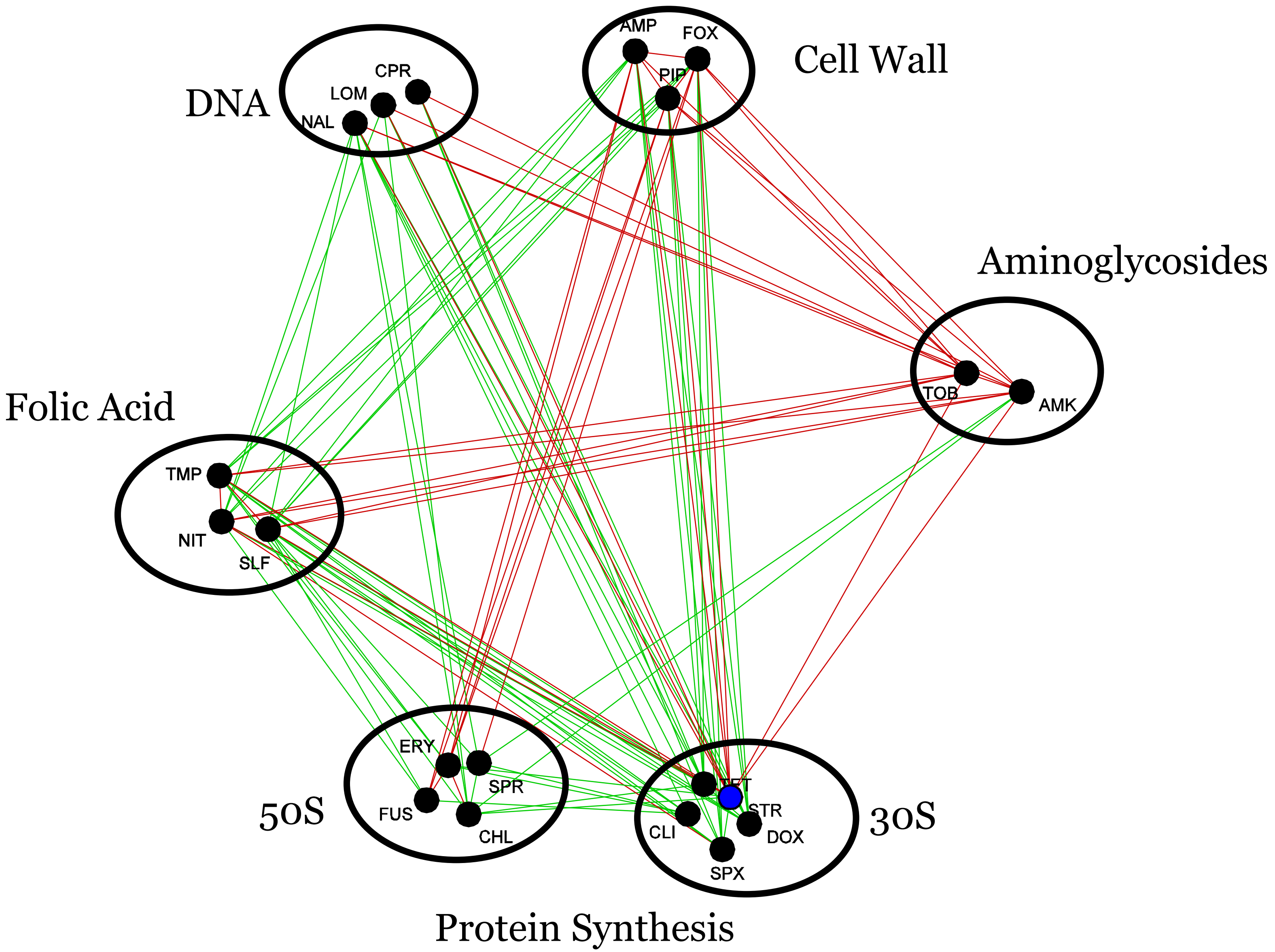

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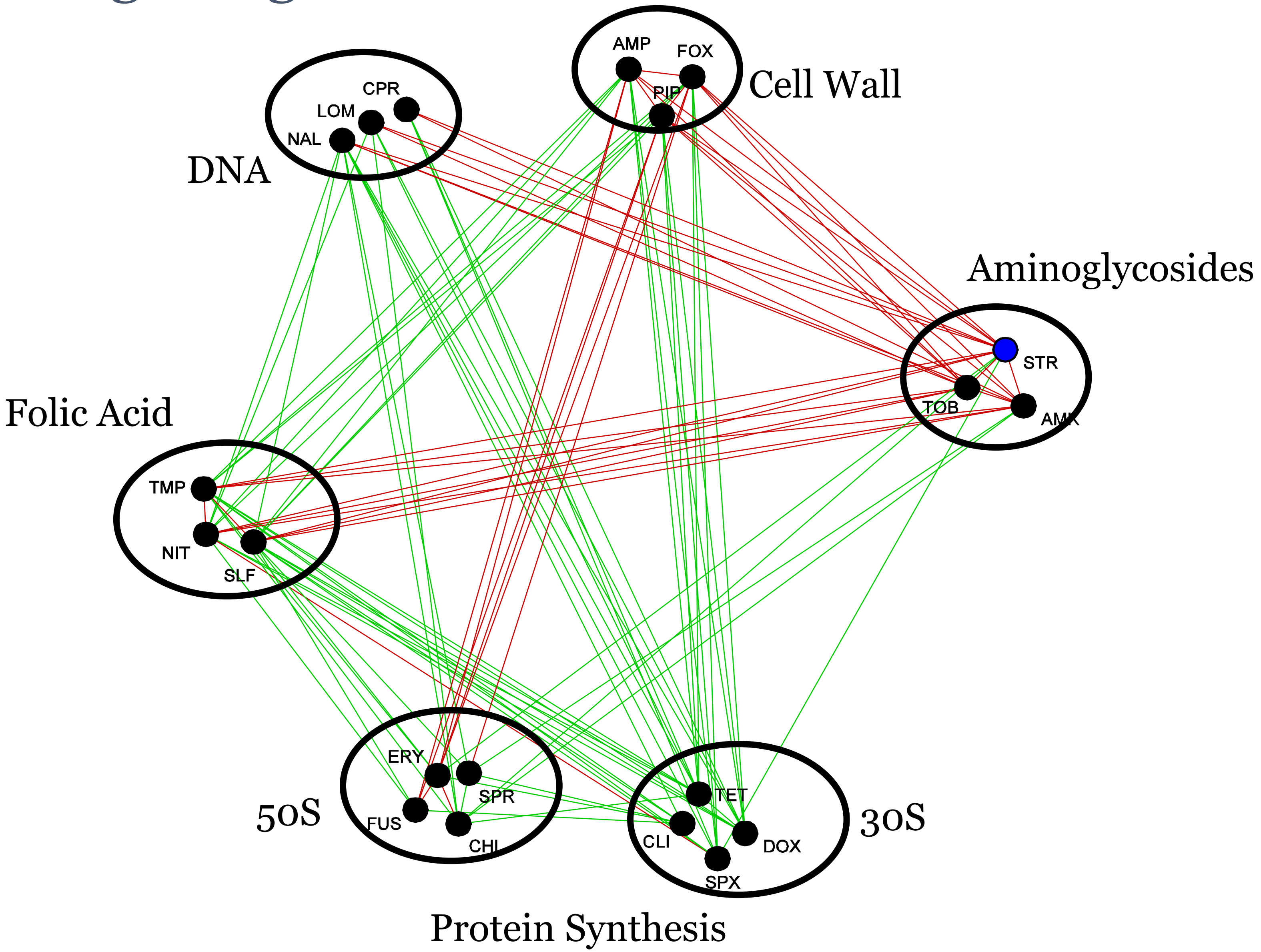

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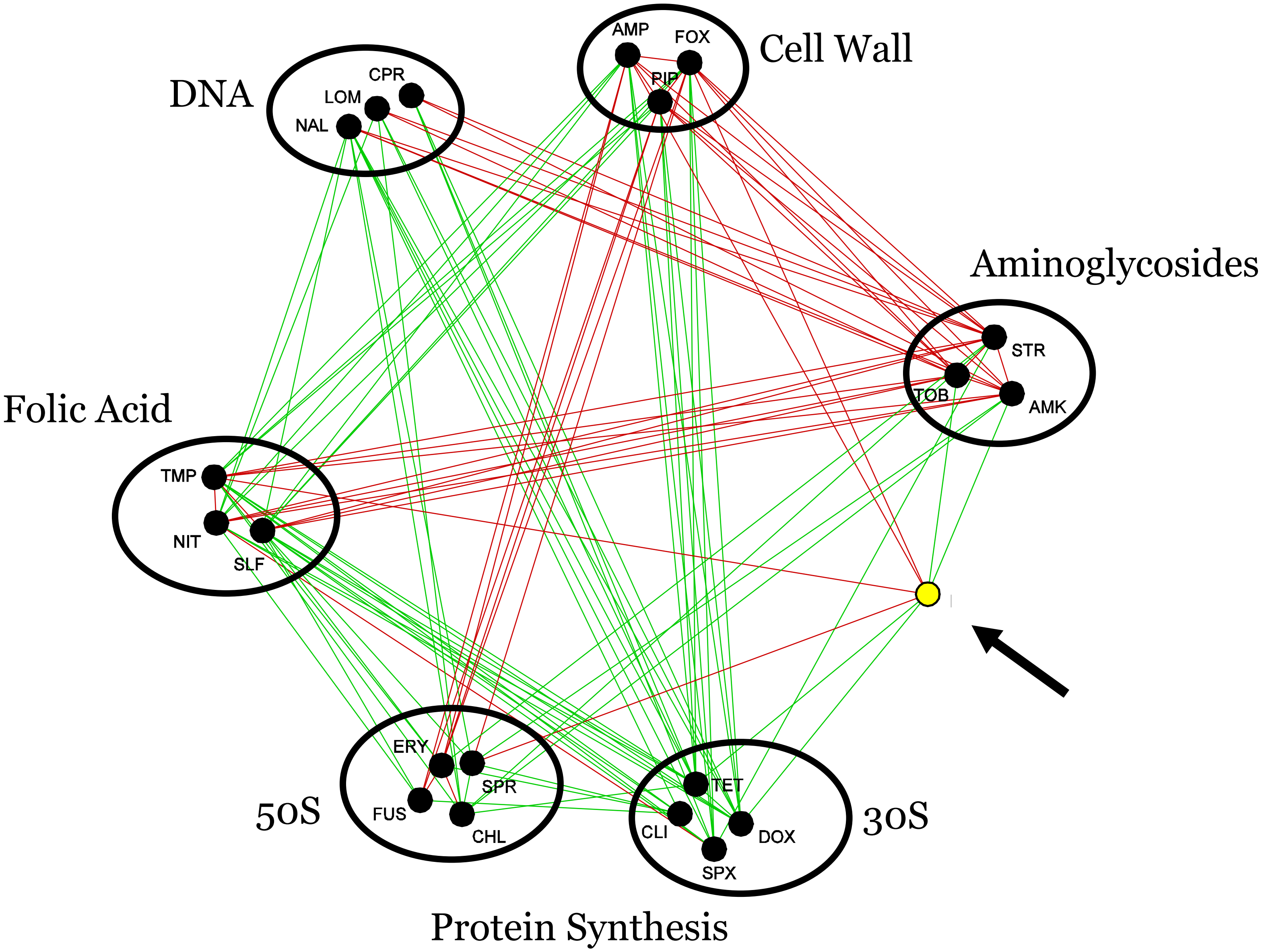

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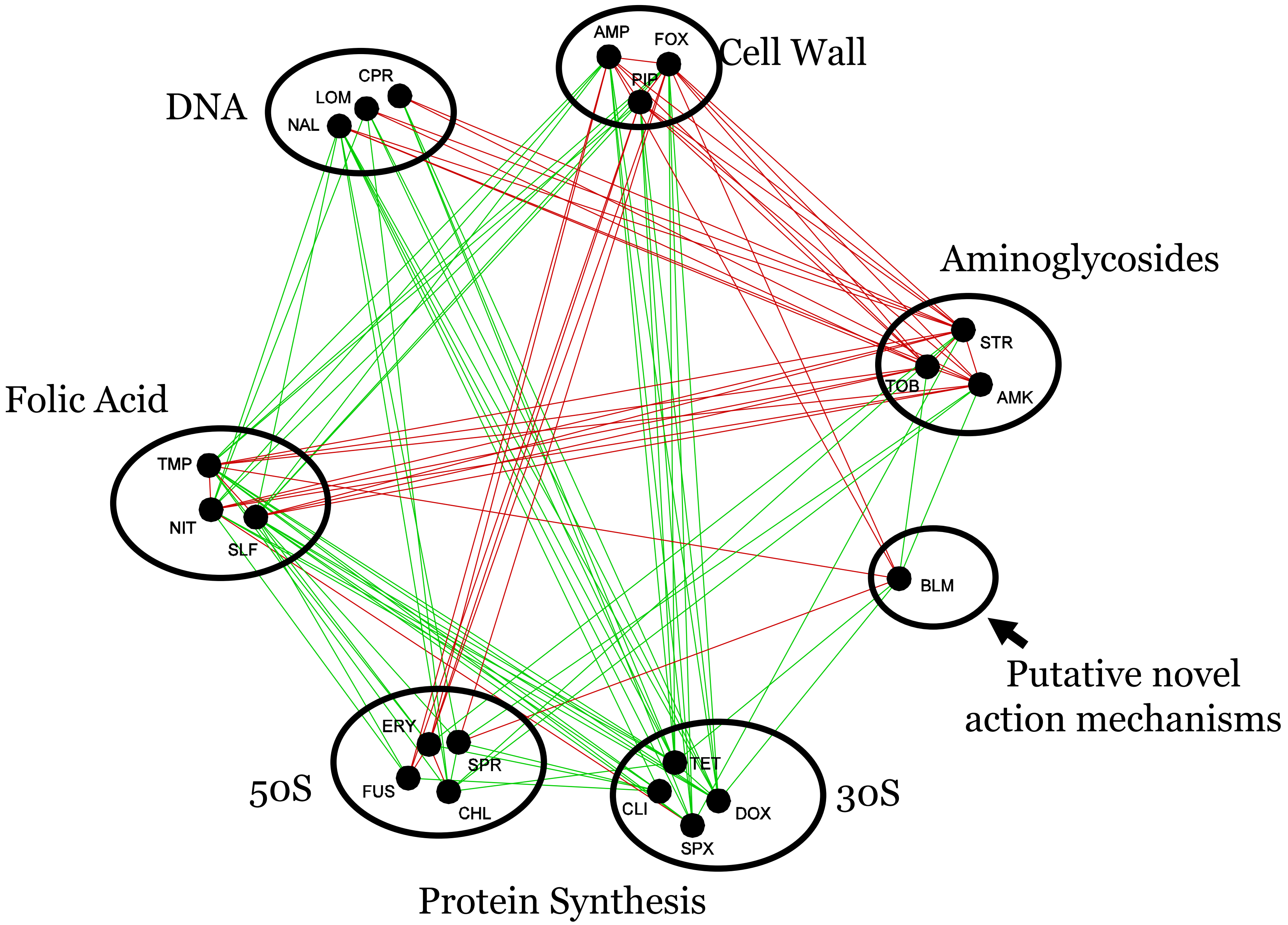

Yeh et al. – Nature Genetics 2006

Conclusions

- Drugs can be classified by their underlying mechanism of action based only on properties of their interaction network.

- Drugs with novel mechanism of action can be identified as drugs that cannot be classified with any existing groups.