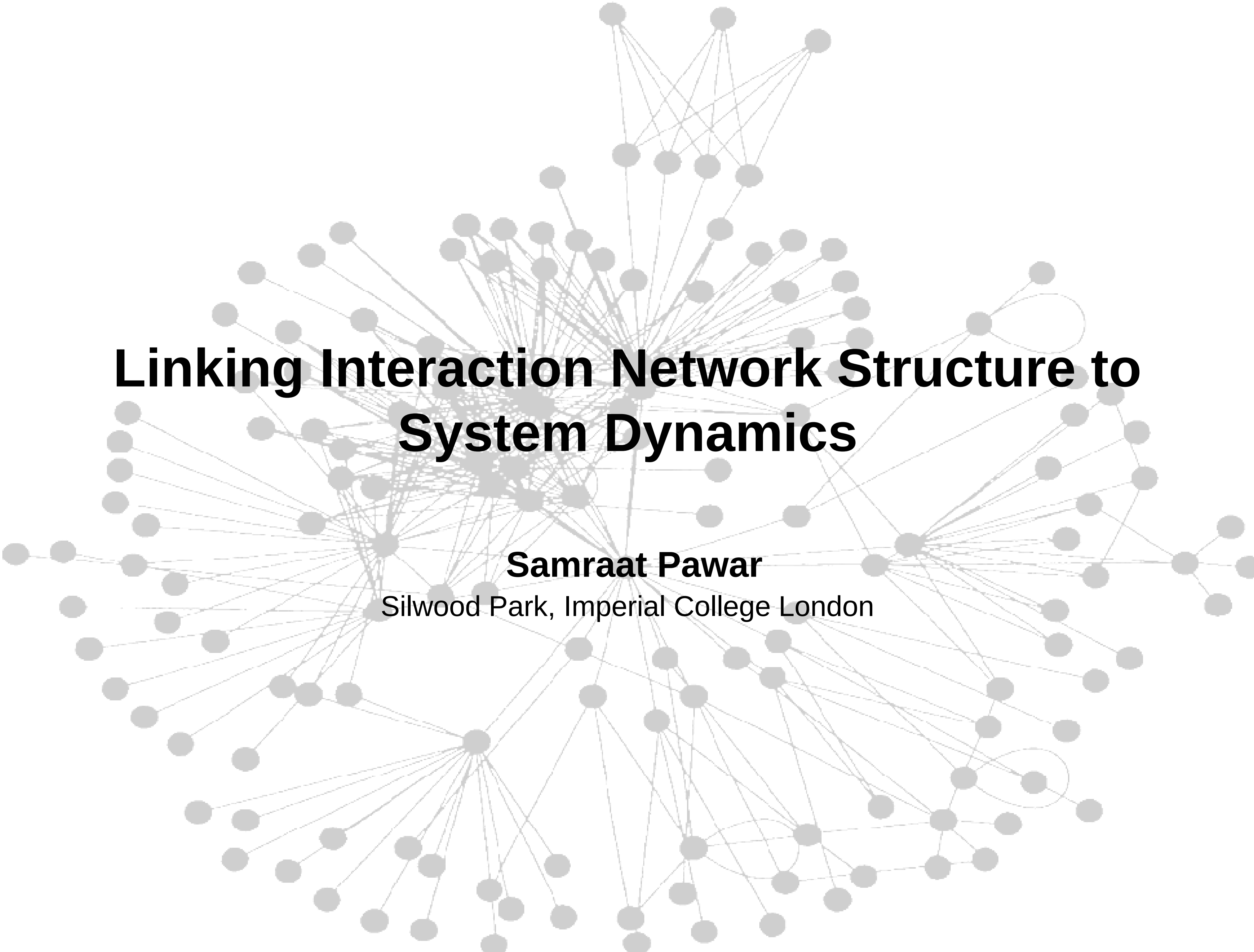

Linking Interaction Network Structure to System Dynamics

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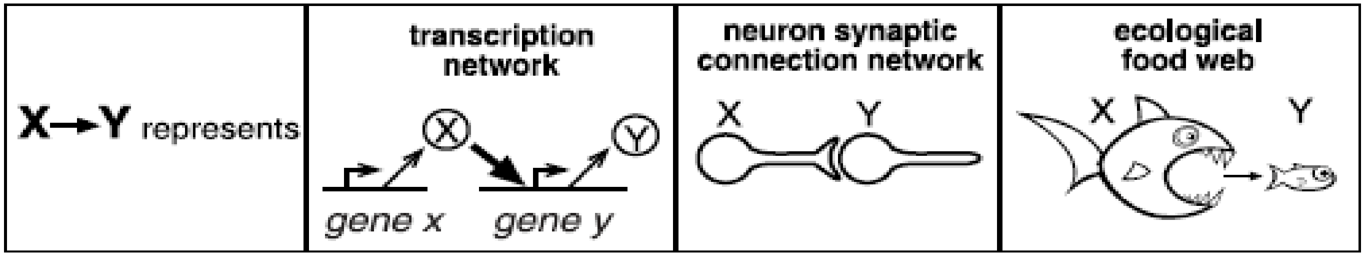
Structure in biological networks

- A general problem in contemporary biology:

  <u>What forces shape network structure</u>, and <u>how does network structure in turn determine the function of its parts</u> (genes, individuals, populations, etc.)?

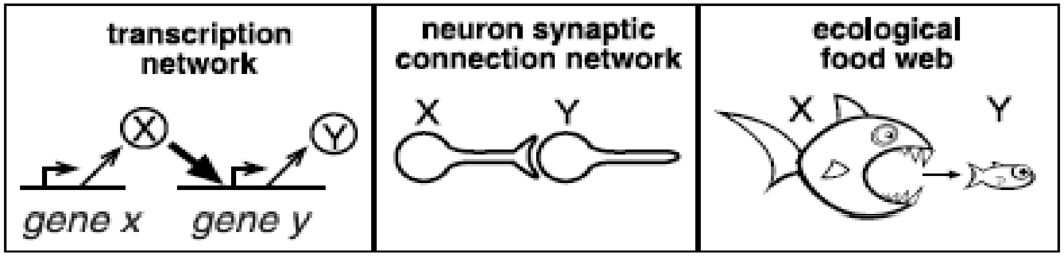
- e.g., Milo et al., Itzkovitz & Alon, etc:



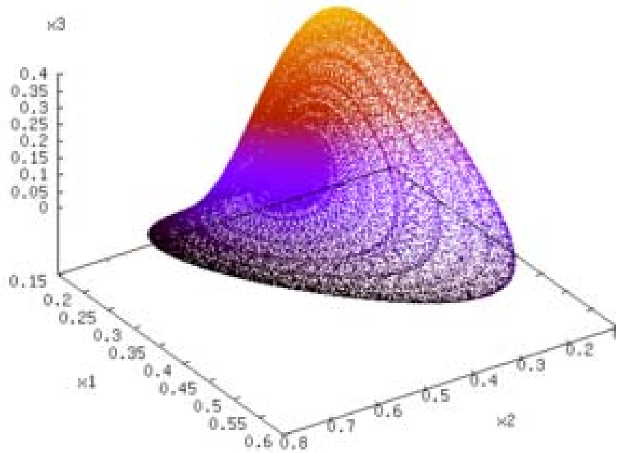
- They essentially ask whether biological networks share structural motifs, and whether similarities and differences can be explained by non-random constraints

What are "system dynamics"?

- The pattern of energy or information flow through the network.



- The effect of these flows on system stability (behavior in its "state-space")



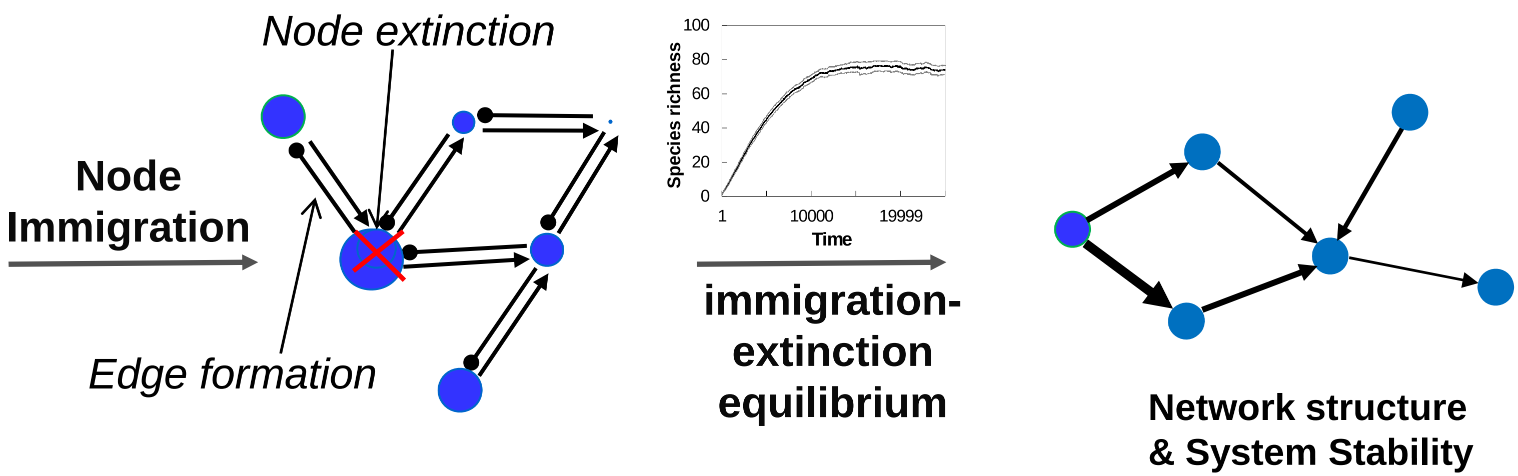
The origins of network structure

How do network individual motifs affect system dynamics?

Examples

- Do certain gene regulatory motifs determine the life or death of an individual organism?
- Do certain interaction network motifs determine community stability (multi-species coexistence)?
- How do food-web motifs determine community assembly and turnover?
- How does connectance determine disease spread in a spatial network?

Networks can be open or closed…



How would this work in the case of genetic and metabolic networks?

- network level, instead of node level extinction and selection

Linking network structure to dynamics

History

- **Recall Mileyko et al. (what about Milo et al.; Itzkovitz & Alon?)**
- Levins, R. (1974). "The qualitative analysis of partially specified systems." Annals of the New York Academy of Sciences 231(1): 123-138.

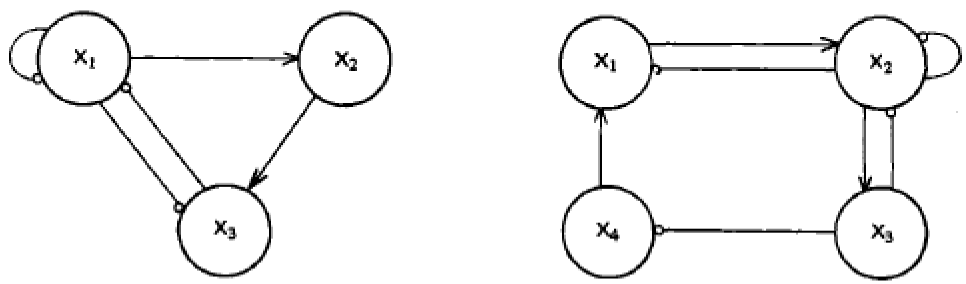


FIGURE 2. Unstable systems with nonnegative feedback. *Left:* the feedback at level 2, F_2, is positive, since it comes entirely from the X_1, X_3 loop. *Right:* $F_3 = 0$. If X_4 were self-damped, instead of X_2, then we would have $F_3 < 0$, since F_3 is a product of disjunct loops of lengths 1 and 2.

- May, R. M. (1971). "Stability in multispecies community models." Mathematical Biosciences 12: 59–79.

  May, R. M. (1972). "Will a large complex system be stable?" Nature 238(5364): 413-414.

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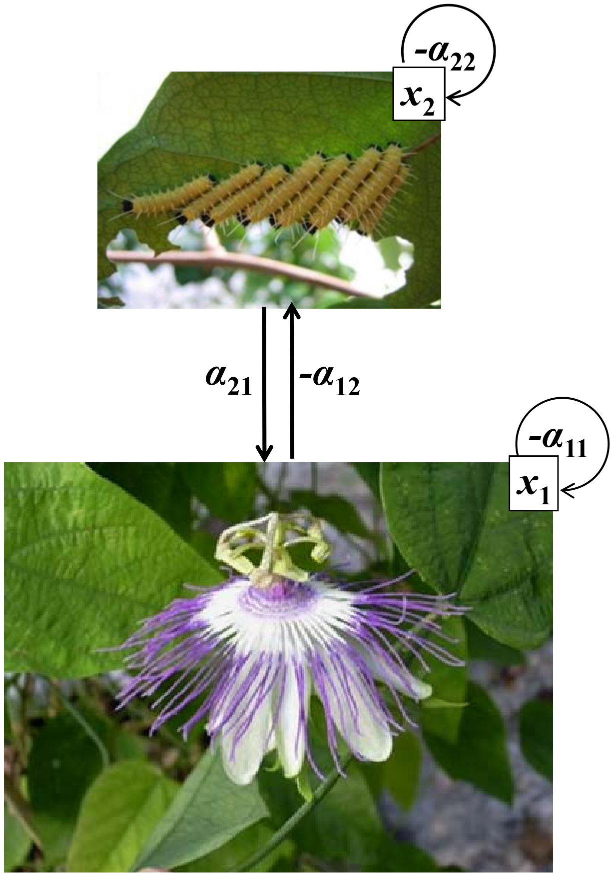
- Neutel et al. (2002) Science; Pawar (2009) J Theor Biol; Stouffer & Bascompte (2010) Ecol Lett; Allesina & Tang, Nature, 2012, etc.

Network structure and dynamics: 2 nodes



b_i = Intrinsic birth rate

d_i = Intrinsic death rate

α_{ii} = Intraspecific search rate

α_{ij} = Interspecific search rate

$\alpha_{ji} = e\alpha_{ij}$

Lotka-Volterra type system of non-linear equations:

$$\frac{dx_1}{dt} = x_1\left(b_1 - d_1 - \alpha_{11}x_1 - \alpha_{12}x_2\right)$$

$$\frac{dx_2}{dt} = x_2\left(-d_2 + \alpha_{21}x_1 - \alpha_{22}x_2\right)$$

Network structure and dynamics: 2 species

A natural way to analyze this system is in terms of matrices and vectors…

$$\frac{dx_1}{dt} = x_1\left(b_1 - d_1 - \alpha_{11}x_1 - \alpha_{12}x_2\right)$$

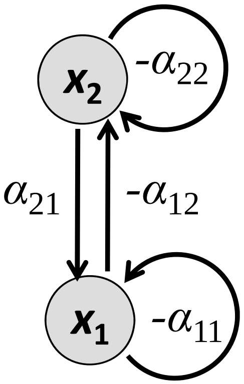
$$\frac{dx_2}{dt} = x_2\left(-d_2 + \alpha_{21}x_1 - \alpha_{22}x_2\right)$$

$$\Updownarrow$$

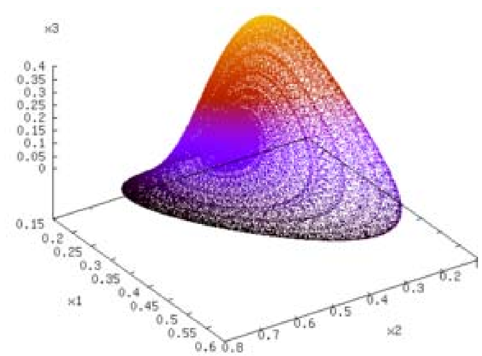
$$\begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{bmatrix} = \begin{bmatrix} x_1 & 0 \\ 0 & x_2 \end{bmatrix}\left(\begin{bmatrix} b_1 - d_1 \\ -d_2 \end{bmatrix} + \left(\begin{bmatrix} -a_{11} & -a_{12} \\ a_{21} & -a_{22} \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix}\right)\right)$$

$$\Updownarrow$$

$$\frac{d\mathbf{x}}{dt} = diag\{x_1, x_2\}\left(\mathbf{b} - \mathbf{d} + \mathbf{A}\mathbf{x}\right)$$



$$\begin{bmatrix} -a_{11} & -a_{12} \\ a_{21} & -a_{22} \end{bmatrix}$$



Network structure and dynamics: 2 species

Analysis of the system $d\mathbf{x}/dt = diag\{x_1, x_2\}(\mathbf{b} - \mathbf{d} + \mathbf{A}\mathbf{x})$

Step 1: Calculate equilibrium population sizes (solve $-\mathbf{A}\hat{\mathbf{x}} = \mathbf{b} - \mathbf{d}$)

$$\hat{x}_1 = -\frac{\begin{vmatrix} b_1 - d_1 & -\alpha_{12} \\ -d_2 & -\alpha_{22} \end{vmatrix}}{\det(\mathbf{A})}, \hat{x}_2 = -\frac{\begin{vmatrix} -\alpha_{11} & b_1 - d_1 \\ \alpha_{21} & -d_2 \end{vmatrix}}{\det(\mathbf{A})}$$

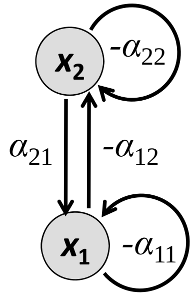
(Cramer's rule)

$$\text{i.e., } \hat{x}_1 = -\frac{\alpha_{22}d_1 - \alpha_{12}d_2 - \alpha_{22}b_1}{\alpha_{11}\alpha_{22} - \alpha_{12}\alpha_{21}}, \hat{x}_2 = -\frac{\alpha_{11}d_2 - \alpha_{21}b_1 + \alpha_{21}d_1}{\alpha_{11}\alpha_{22} - \alpha_{12}\alpha_{21}}$$

What does this tell us in terms of network structure?

det(**A**) > 0 ⇒ $\alpha_{11}\alpha_{22} > \alpha_{12}\alpha_{21}$

⇒ Negative self loop should be stronger than inter-node (species) interaction

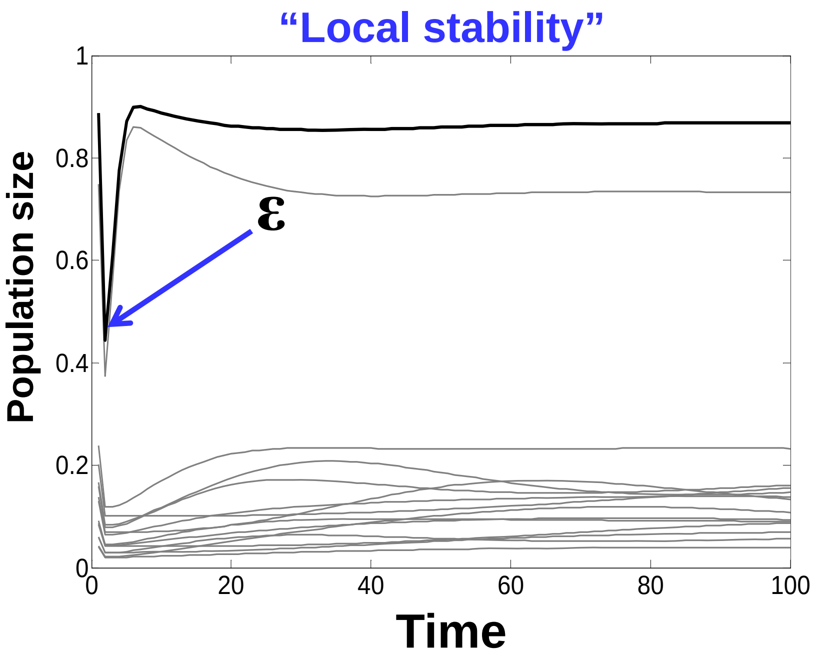


Network structure and dynamics: 2 species

Step 2: Check if equilibrium is at least locally stable – calculate eigenvalues and eigenvectors of the "Jacobian"

$$f(\hat{\mathbf{x}}+\boldsymbol{\varepsilon}) = f(\hat{\mathbf{x}}) + \nabla f(\hat{\mathbf{x}})\boldsymbol{\varepsilon} + O\left(|\boldsymbol{\varepsilon}|^2\right)$$

$$\nabla f(\hat{\mathbf{x}}) = \mathbf{J} = \begin{bmatrix} \dfrac{\partial f(x_1)}{\partial x_1} & \dfrac{\partial f(x_1)}{\partial x_2} \\ \dfrac{\partial f(x_2)}{\partial x_1} & \dfrac{\partial f(x_2)}{\partial x_2} \end{bmatrix}_{x_i = \hat{x}_i}$$



We get,

$$\mathbf{J} = \begin{bmatrix} b_1 - d_1 - 2\alpha_{11}\hat{x}_1 - \alpha_{12}\hat{x}_2 & -\hat{x}_1\alpha_{12} \\ \hat{x}_2\alpha_{21} & -d_2 + \alpha_{21}\hat{x}_1 - 2\alpha_{22}\hat{x}_2 \end{bmatrix} = \begin{bmatrix} -\alpha_{11}\hat{x}_1 & -\hat{x}_1\alpha_{12} \\ \hat{x}_2\alpha_{21} & -\alpha_{22}\hat{x}_2 \end{bmatrix}$$

Eigenvalues of J (solve $\mathbf{J}\mathbf{v} = \lambda\mathbf{v}$) characterize local stability

Network structure and dynamics: 2 species

Eigenvalue (λ) and eigenvector ($\mathbf{v}$): Solve,

$$\mathbf{Jv} = \lambda\mathbf{v} \Rightarrow \mathbf{Jv} - \lambda\mathbf{v} = 0 \Rightarrow (\mathbf{J} - \lambda\mathbf{I})\mathbf{v} = 0 \Rightarrow \mathbf{J} - \lambda\mathbf{I} = 0$$

For our 2 node (species) system,

$$\det(\mathbf{J} - \lambda\mathbf{I}) = \det\left(\begin{bmatrix} -\alpha_{11}\hat{x}_1 & -\alpha_{12}\hat{x}_1 \\ \alpha_{21}\hat{x}_2 & -\alpha_{22}\hat{x}_2 \end{bmatrix} - \begin{bmatrix} \lambda & 0 \\ 0 & \lambda \end{bmatrix}\right)$$

$$= \det\begin{bmatrix} -\alpha_{11}\hat{x}_1 - \lambda & -\alpha_{12}\hat{x}_1 \\ \alpha_{21}\hat{x}_2 & -\alpha_{22}\hat{x}_2 - \lambda \end{bmatrix}$$

Thus we solve the equation

$$\lambda^2 + (\alpha_{22}\hat{x}_2 + \alpha_{11}\hat{x}_1)\lambda + (\alpha_{11}\alpha_{22} + \alpha_{12}\alpha_{21})\hat{x}_1\hat{x}_2 = 0$$

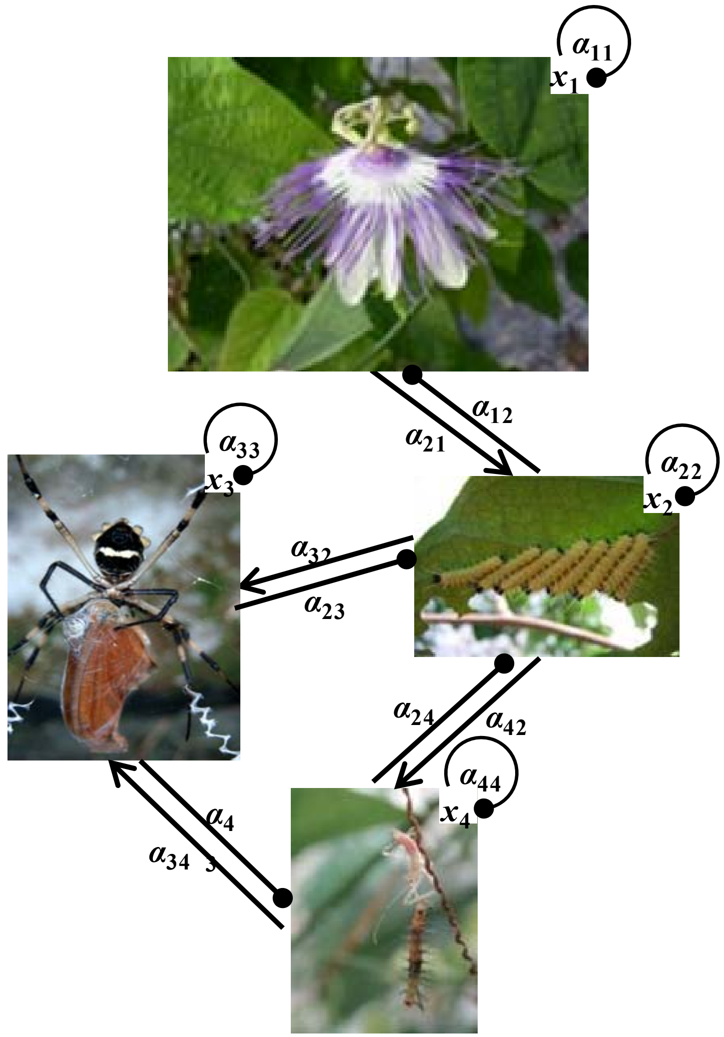
Which gives,

$$\lambda = -\frac{\alpha_{11}\hat{x}_1 + \alpha_{22}\hat{x}_2 + \sqrt{\alpha_{11}^2\hat{x}_1^2 + \alpha_{22}^2\hat{x}_2^2 - 2\hat{x}_1\hat{x}_2(\alpha_{11}\alpha_{22} + 2\alpha_{12}\alpha_{21})}}{2} \; \&$$

$$\lambda = -\frac{\alpha_{11}\hat{x}_1 + \alpha_{22}\hat{x}_2 - \sqrt{\alpha_{11}^2\hat{x}_1^2 + \alpha_{22}^2\hat{x}_2^2 - 2\hat{x}_1\hat{x}_2(\alpha_{11}\alpha_{22} + 2\alpha_{12}\alpha_{21})}}{2}$$

Network structure and dynamics: >2 species

Things get <u>really</u> interesting with > species – then we have real food webs!

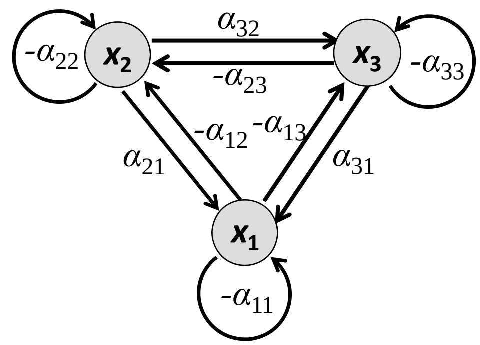


Network structure and dynamics: >2 species

$$\frac{dx_1}{dt} = x_1\left(b_1 - d_1 - \alpha_{11}x_1 - \alpha_{12}x_2 - \alpha_{13}x_3\right)$$

$$\frac{dx_2}{dt} = x_2\left(-d_2 + \alpha_{21}x_1 - \alpha_{22}x_2 - \alpha_{23}x_3\right)$$

$$\frac{dx_3}{dt} = x_3\left(-d_3 + \alpha_{31}x_1 + \alpha_{32}x_2 - \alpha_{33}x_3\right)$$

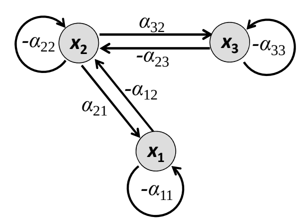


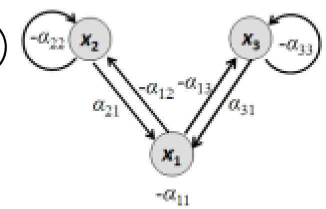
$$\hat{x}_1 = \frac{(b_1 - d_1)(\alpha_{32}\alpha_{23} + \alpha_{22}\alpha_{33}) + d_2(\alpha_{12}\alpha_{33} + \alpha_{32}\alpha_{13}) - d_3(\alpha_{22}\alpha_{13} - \alpha_{23}\alpha_{12})}{\alpha_{31}\alpha_{12}\alpha_{23} - \alpha_{22}\alpha_{11}\alpha_{33} - \alpha_{12}\alpha_{21}\alpha_{33} - \alpha_{11}\alpha_{32}\alpha_{23} - \alpha_{32}\alpha_{21}\alpha_{13} - \alpha_{22}\alpha_{31}\alpha_{13}}$$

$$\hat{x}_2 = \frac{(b_1 - d_1)(\alpha_{21}\alpha_{33} - \alpha_{23}\alpha_{31}) - d_2(\alpha_{11}\alpha_{33} + \alpha_{13}\alpha_{31}) + d_3(\alpha_{21}\alpha_{13} + \alpha_{23}\alpha_{11})}{\alpha_{31}\alpha_{12}\alpha_{23} - \alpha_{22}\alpha_{11}\alpha_{33} - \alpha_{12}\alpha_{21}\alpha_{33} - \alpha_{11}\alpha_{32}\alpha_{23} - \alpha_{32}\alpha_{21}\alpha_{13} - \alpha_{22}\alpha_{31}\alpha_{13}}$$

$$\hat{x}_3 = \frac{(b_1 - d_1)(\alpha_{22}\alpha_{31} + \alpha_{32}\alpha_{21}) - d_2(\alpha_{11}\alpha_{32} - \alpha_{12}\alpha_{31}) - d_3(\alpha_{12}\alpha_{21} + \alpha_{22}\alpha_{11})}{\alpha_{31}\alpha_{12}\alpha_{23} - \alpha_{22}\alpha_{11}\alpha_{33} - \alpha_{12}\alpha_{21}\alpha_{33} - \alpha_{11}\alpha_{32}\alpha_{23} - \alpha_{32}\alpha_{21}\alpha_{13} - \alpha_{22}\alpha_{31}\alpha_{13}}$$

Different sub-systems can be found that differ in dynamical properties and how they are affected by network structure





Network structure and dynamics: >2 species

Simulations (e.g., Stouffer and Bascompte (2010) Ecol Lett)

growth rate maintenance mortality to predation

consumption

$$\frac{\mathrm{d}B_i}{\mathrm{d}t} = r_i G_i B_i - x_i B_i + x_i B_i \sum_{j=\mathrm{prey}} y_i F_{ij} - \sum_{k=\mathrm{pred}} \frac{x_k y_k B_k F_{ki}}{e_{ki}},$$

System is much more complex

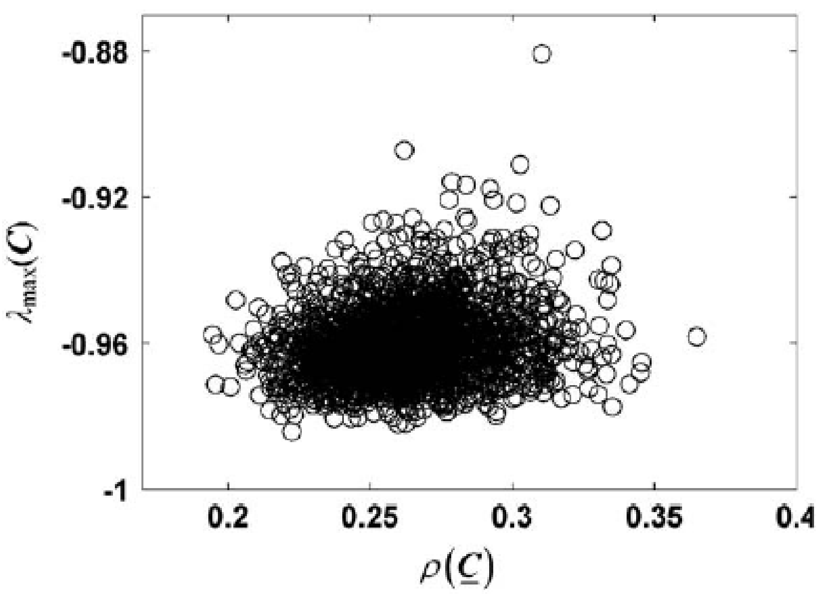
Type 2 functional response

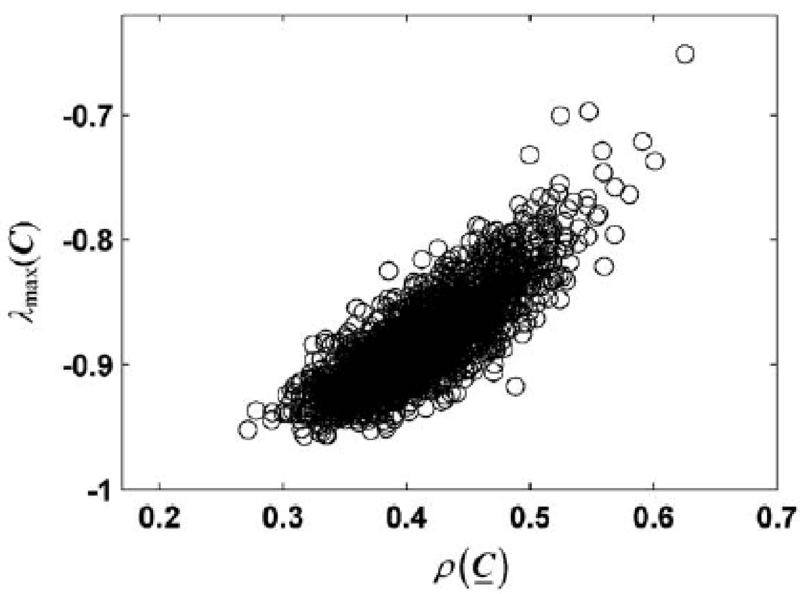
$$F_{ij} = \frac{w_{ij} B_j}{B_0 + \sum_{k=\mathrm{prey}} w_{ik} B_k}$$

Network structure and dynamics

Link structure of **J** to the network's dynamics by using properties of the spectral radius ($\rho(.)$)

$$\mathbf{C} = \begin{bmatrix} -\alpha_{11}\hat{x}_1 & -\hat{x}_1\alpha_{12} \\ \hat{x}_2\alpha_{21} & -\alpha_{22}\hat{x}_2 \end{bmatrix} \longrightarrow \mathbf{C} = \begin{bmatrix} \alpha_{11}\hat{x}_1 & \hat{x}_1\alpha_{12} \\ \hat{x}_2\alpha_{21} & \alpha_{22}\hat{x}_2 \end{bmatrix}$$

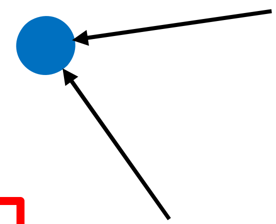




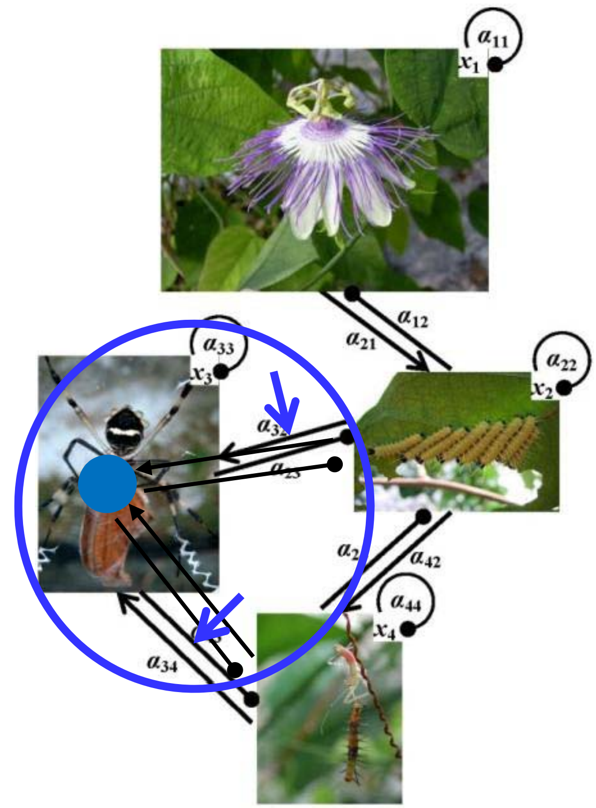
Interlinking network topology and dynamics

Now link stability (eigenvalues) to network structure

Stability (probability of stable coexistence) is limited by a key toplogical measure: *Number of resource species of consumer species (node's in-degree).*

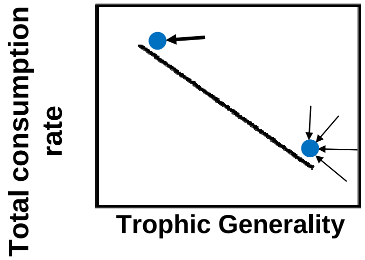


This motif (across all species) limits community stability.

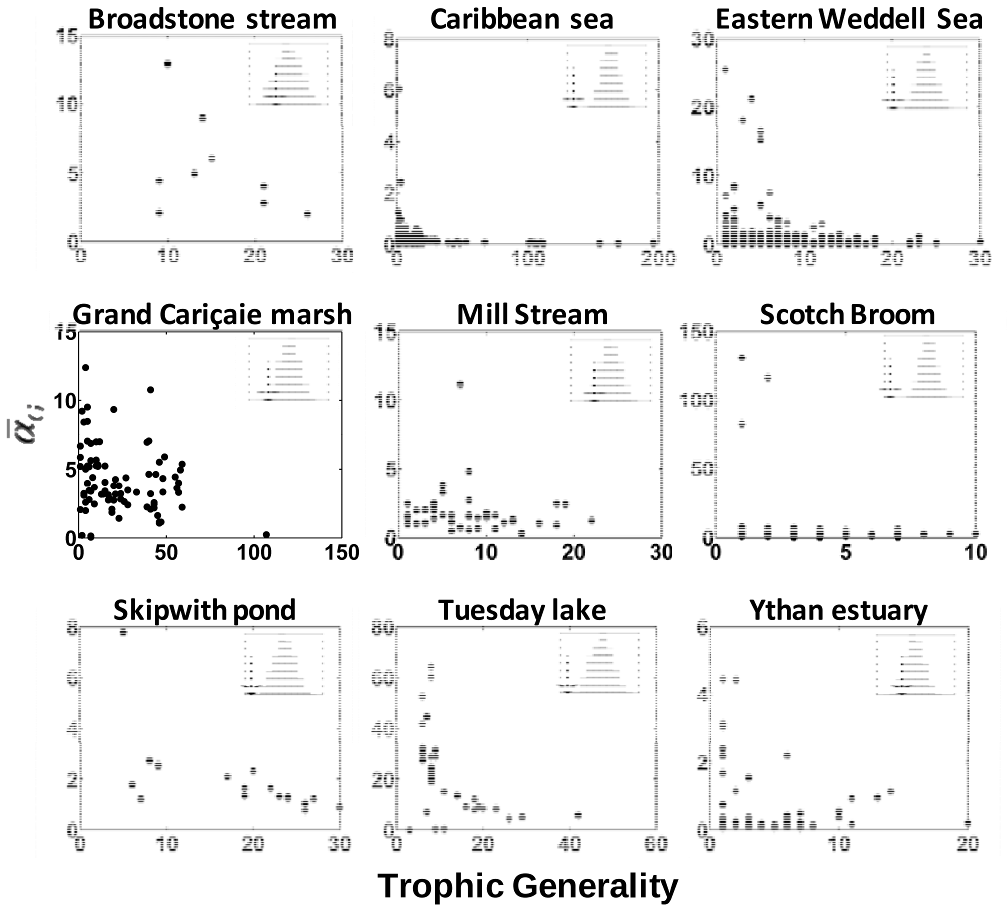


Pawar, 2009, *J. Theor. Biol.*

Structural signatures in real communities



Species' biomass intake should decrease with generality



- 6 strongly ($p < 0.05$), 3 weakly ($p < 0.25$) significant with constrained randomizations

- None show an opposite pattern

Summary

- Interaction network (e.g., food-web, autocatalytic network) dynamics can be mathematically linked to network structure
- Simulations are often necessary, but interesting solutions and approximations can be found (e.g., ISS concept)
- In open systems (e.g., food-webs) stabilizing motifs can increase in proportion through invasion-extinction dynamics – *the origins of motifs and higher-level selection*
- Many open questions remain: Data are a major constraint in certain systems (apart from gene networks!)

Conclusions and questions

Motif persistence is not tied to web persistence

Most common motifs are tied to web persistence

Are there larger motifs where persistence in isolation and persistence of whole web do match? If so, those motifs might be the real building blocks.

Do webs with different patterns of motifs that imply less persistence have greater short term robustness?

How do prey selection and dynamics of motifs and motif representation change in time? What does this mean for our results?

Readings

1. Milo, R., Itzkovitz, S., Kashtan, N., Levitt, R., Shen-Orr, S., Ayzenshtat, I., *et al.* (2004). Superfamilies of evolved and designed networks. *Science*, 303, 1538–1542.
2. Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D. & Alon, U. (2002). Network motifs: simple building blocks of complex networks. *Science*, 298, 824–7.
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7. Pawar, S. (2009). Community assembly, stability and signatures of dynamical constraints on food web structure. *J. Theor. Biol.*, 259, 601–612.