# Mathematical Homeostasis Motivated by
## by
## Reed, Nijhout, and Best

Marty Golubitsky
Department of Mathematics
The Ohio State University

## Thanks

| | |
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# Mathematical Formulation
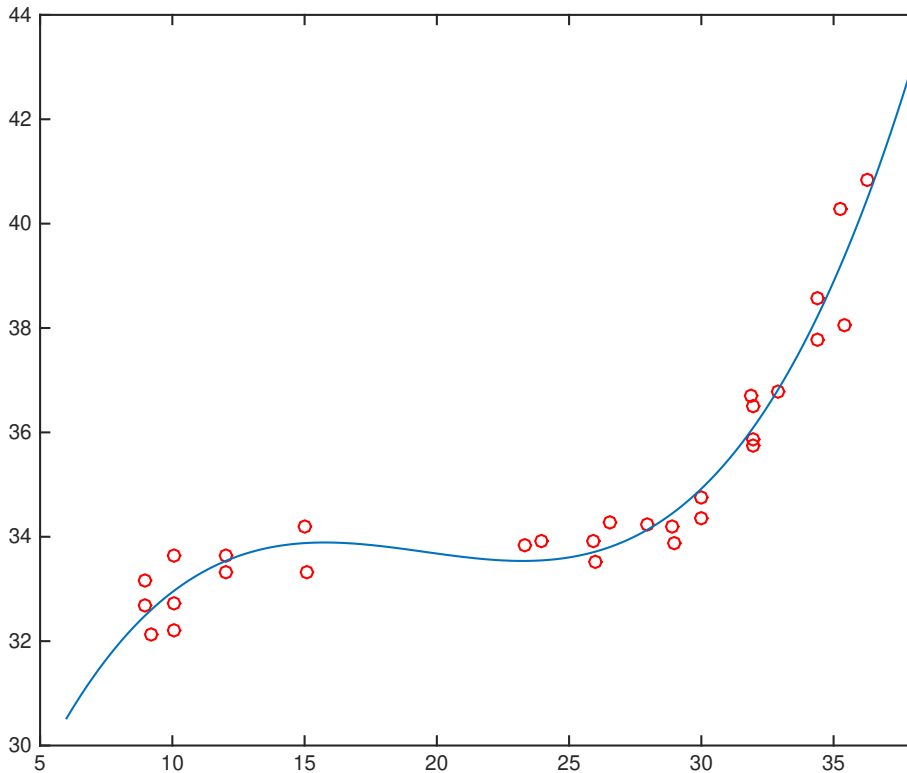# and
# Infinitesimal Homeostasis

- Horizontal: Environmental Temperature

- Vertical: Body Temperature

**P.R. Morrison. Temperature regulation in three Central American mammals, *J. Cell. Compar. Physiol.* 27 (1946)**
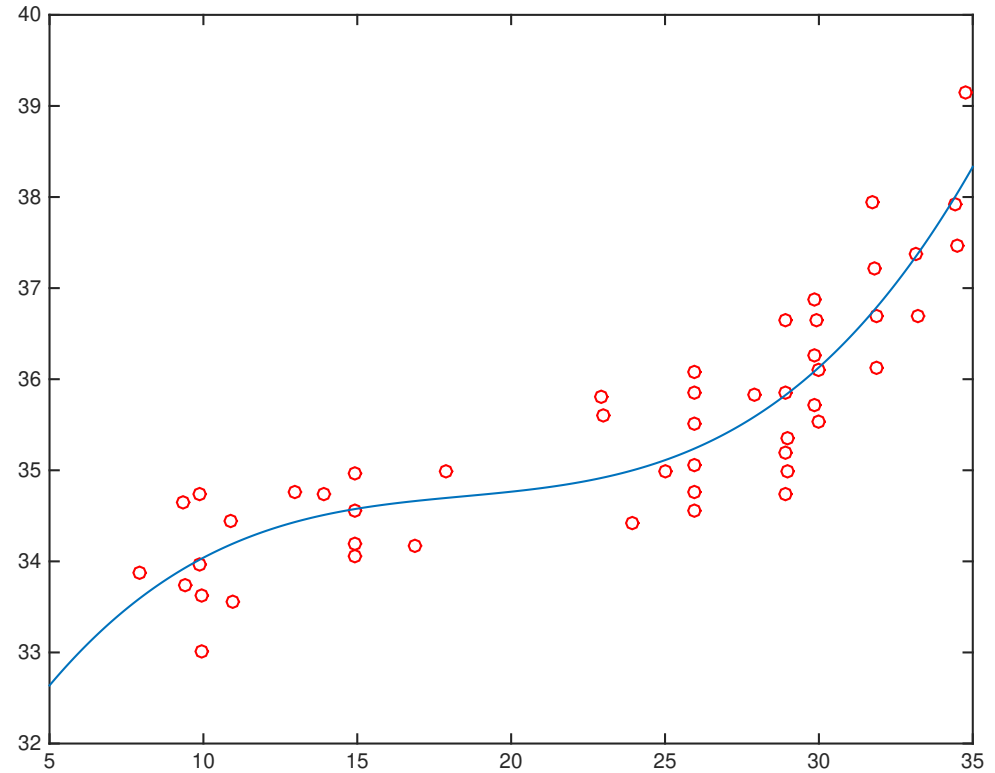
- **Nijhout and Reed** (*Integrative and Comparative Biology* **54**, 2014)

Introduce **chair**
**escape from homeostasis**
**input-output map**
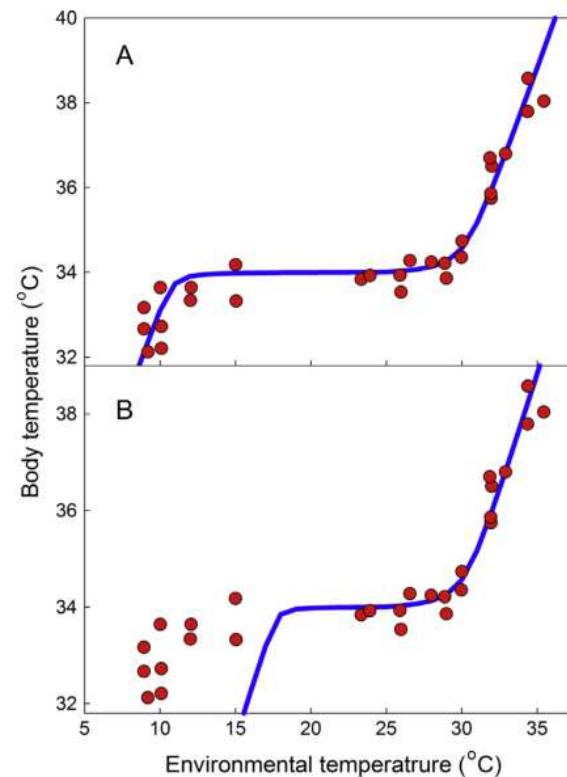
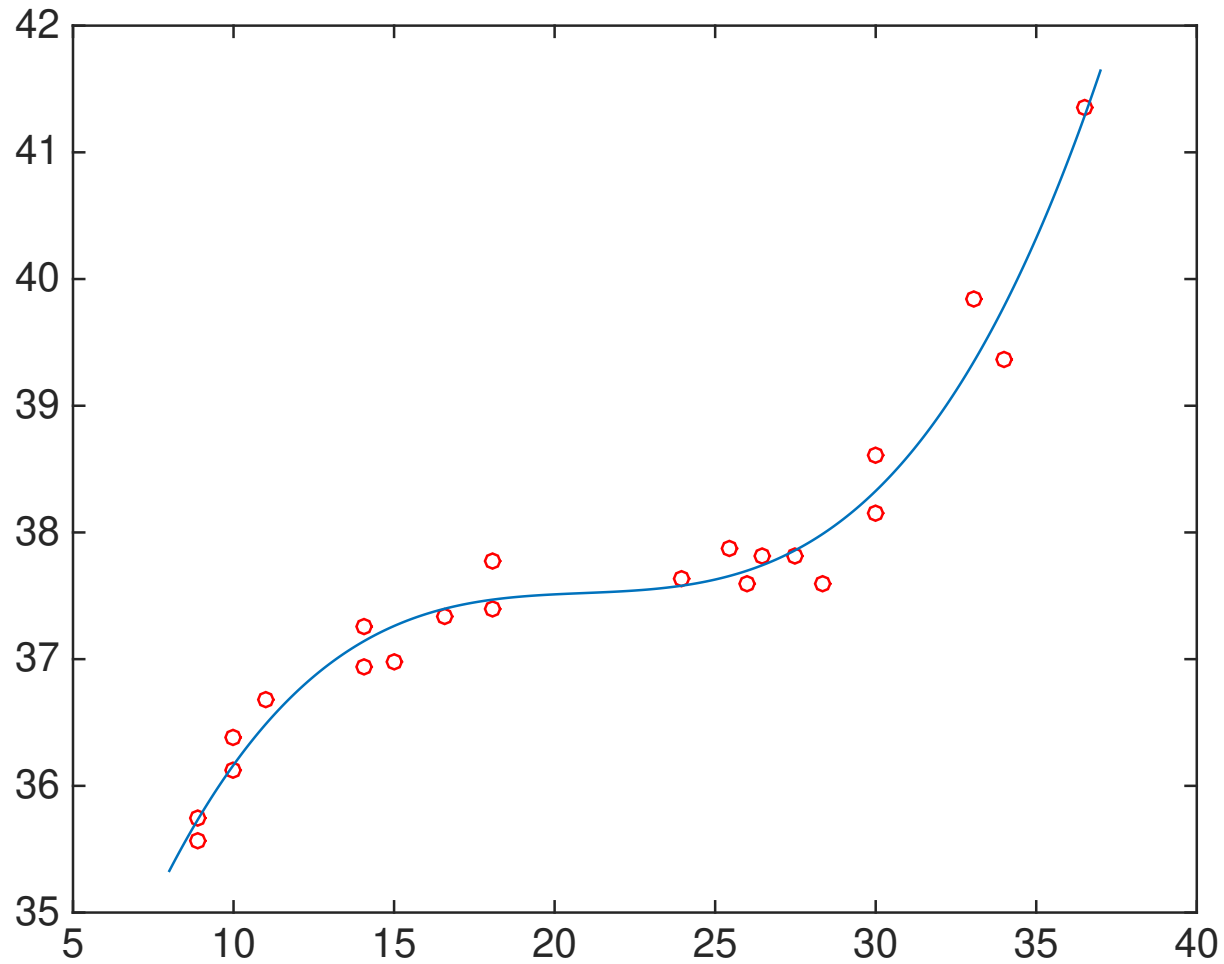# Experimental Evidence for Chairs: Brown and Eten Opossum



Brown Opossum

Eten Opossum

**Blue curves** are best least squares fit by a cubic to the data

**P.R. Morrison. Temperature regulation in three Central American mammals**
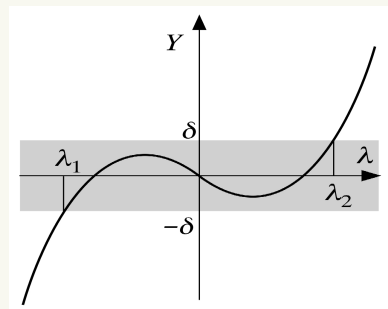
*J Cell Compar Physiol* 27 (1946) 125–137

Homogeneous Cubic in Possum Space

Spiny rat data

# A Singularity Theory for Input-Output Maps

- Let $x_o(\mathcal{I})$ be an input-output map

- Infinitesimal homeostasis if $x_o' = 0$

- infinitesimal chair if $x_o' = x_o'' = 0$ and $x_o''' \neq 0$

- elementary catastrophe theory
  Universal unfolding of chair is $x_o(\mathcal{I}; a) = \mathcal{I}^3 + a\mathcal{I}$

- Structural stability of universal unfolding
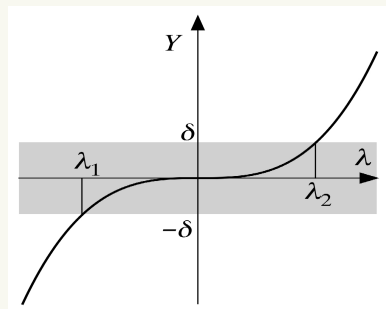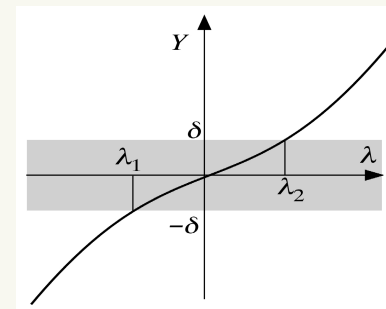


$$a < 0 \qquad\qquad a = 0 \qquad\qquad 0 < a$$

- **Plateau**: interval where $|x_o(\mathcal{I}; a)| < \delta$

  Size of $\delta$-plateau: $2\delta^{1/3} - \dfrac{2}{3\delta^{1/3}}a + O(a^2)$

# Homeostasis
# and
# Biochemical Networks

# Input-Output Map in Networks

Assume $(n+2)$-node network of ODE with input node $\iota$ and output node $o$

$$\dot{X} = \left\{ \begin{array}{rcl} \dot{x}_\iota & = & f_\iota(x_\iota, x_\rho, x_o, \mathcal{I}) \\ \dot{x}_\rho & = & f_\rho(x_\iota, x_\rho, x_o) \\ \dot{x}_o & = & f_\iota(x_\iota, x_\rho, x_o) \end{array} \right\} = F(X, \mathcal{I})$$

where $\rho = $ *regulatory nodes* and $X = (x_\iota, x_\rho, x_o) \in \mathbf{R}^{n+2}$ denotes state variables. The precise dependence (or coupling) of the equations $f_\iota, f_\rho, f_o$ on node state variables is defined by network arrows.

- Stable equilibrium implies family of equilibria

  - Assume <span style="color:red">stable steady-state</span> at $X_0$ when $\mathcal{I} = \mathcal{I}_0$

  - There exists $X(\mathcal{I})$ with $F(X(\mathcal{I}), \mathcal{I}) \equiv 0$ and $X(\mathcal{I}_0) = X_0$

  - <span style="color:red">$x_o(\mathcal{I})$ **is input-output map**</span>

G. and Stewart. Homeostasis, singularities, and networks (2016)

## Jacobian Matrix and Stable Equilibria

$$J = \begin{bmatrix} f_{\iota,x_\iota} & f_{\iota,x_\rho} & f_{\iota,x_o} \\ f_{\rho,x_\iota} & f_{\rho,x_\rho} & f_{\rho,x_o} \\ f_{o,x_\iota} & f_{o,x_\rho} & f_{o,x_o} \end{bmatrix}$$

- Suppose arrow $p \to q$. Then $f_{q,x_p}(X_0)$ is *coupling strength* of arrow

- Coupling is *excitatory* if $f_{q,x_p}(X_0) > 0$, *inhibitory* if $f_{q,x_p}(X_0) < 0$, and *neutral* if $f_{q,x_p}(X_0) = 0$

- NOTE: neutral coupling is NOT absence of coupling

- Standing assumptions

  - $f_{\ell,x_\ell} < 0$: in absence of other coupling substrate degrades

  - $f_{\iota,\mathcal{I}} \neq 0$

# Feedforward Excitation Motif
## Substrate X Activates Enzyme Y that Catabolizes Z
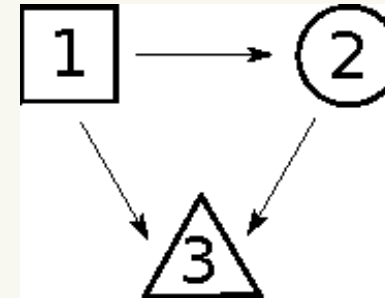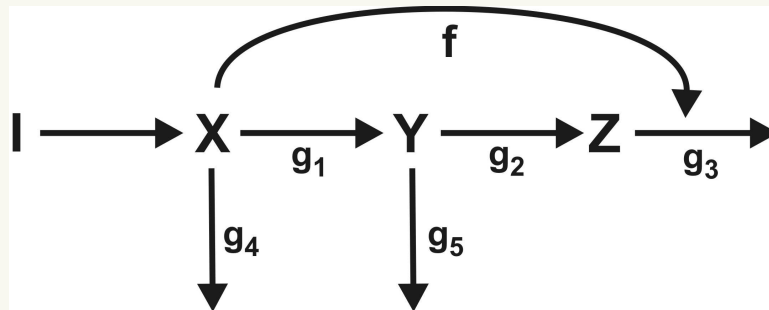
Biochemical system associated with network is:

$$
\begin{aligned}
\dot{x} &= \mathcal{I} - g_1(x) - g_4(x) \\
\dot{y} &= g_1(x) - g_2(y) - g_5(y) \\
\dot{z} &= g_2(y) - h(x,z)
\end{aligned}
\qquad
\begin{aligned}
\dot{x}_\iota &= f_\iota(x_\iota, \mathcal{I}) \\
\dot{x}_\rho &= f_\rho(x_\iota, x_\rho) \\
\dot{x}_o &= f_o(x_\iota, x_\rho, x_o)
\end{aligned}
$$

- $g_i$ are kinetic functions

- Infinitesimal homeostasis    if and only if    $h_x = \dfrac{1}{g_3} \dfrac{g_1' g_2'}{g_2' + g_5'}$

**Reed, Best, G., Stewart , and Nijhout (2017)**

# Substrate Inhibition



$$\dot{x} = \mathcal{I} - g_1(x) - g_4(x)$$
$$\dot{y} = g_1(x) - g_5(y) - g_2(y)$$
$$\dot{z} = g_2(y) - g_3(z)$$

$$\dot{x}_\iota = f_\iota(x_\iota, \mathcal{I})$$
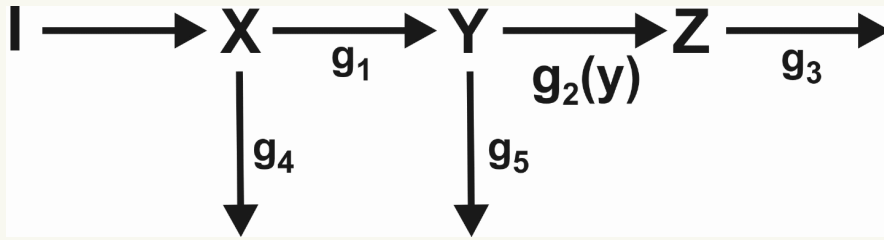$$\dot{x}_\rho = f_\rho(x_\iota, x_\rho)$$
$$\dot{x}_o = f_o(x_\rho, x_o)$$

$$
\begin{aligned}
f_\iota(x_\iota, x_\rho, x_o, \mathcal{I}) &= 0 \\
f_\rho(x_\iota, x_\rho, x_o) &= 0 \\
f_o(x_\iota, x_\rho, x_o) &= 0
\end{aligned}
$$

Implicit differentiation yields

$$
\begin{bmatrix}
f_{\iota,x_\iota} & f_{\iota,x_\rho} & f_{\iota,x_o} \\
f_{\rho,x_\iota} & f_{\rho,x_\rho} & f_{\rho,x_o} \\
f_{o,x_\iota} & f_{o,x_\rho} & f_{o,x_o}
\end{bmatrix}
\begin{bmatrix}
x'_\iota \\
x'_\rho \\
x'_o
\end{bmatrix}
=
\begin{bmatrix}
-f_{\iota,\mathcal{I}} \\
0 \\
0
\end{bmatrix}
$$

Can use Cramer's rule to solve for $x'_o$

## Computation of Infinitesimal Homeostasis

Let $X_0$ be a stable equilibrium in a system with $n$ regulatory nodes. The input-output function $x_o(\mathcal{I})$ satisfies

$$x'_o = \frac{1}{\det(J)} \det \begin{bmatrix} f_{\iota,x_\iota} & f_{\iota,x_\rho} & -f_{\iota,\mathcal{I}} \\ f_{\rho,x_\iota} & f_{\rho,x_\rho} & 0 \\ f_{o,x_\iota} & f_{o,x_\rho} & 0 \end{bmatrix} = \pm \frac{f_{\iota,\mathcal{I}}}{\det(J)} \det(P)$$
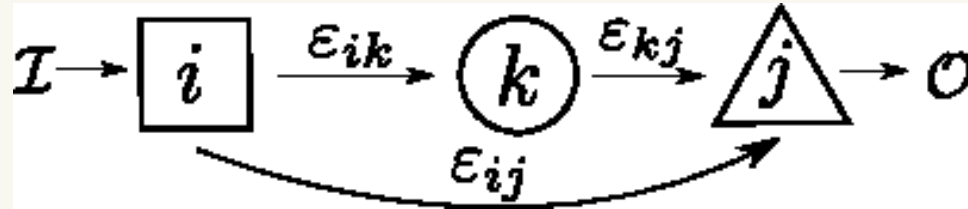
where $P$ is the $(n+1) \times (n+1)$ matrix

$$P = \begin{bmatrix} f_{\rho,x_\iota} & f_{\rho,x_\rho} \\ f_{o,x_\iota} & f_{o,x_\rho} \end{bmatrix}.$$

Hence, $x'_o(\mathcal{I}_0) = 0$ if and only if $\det(P) = 0$ at $(\mathcal{I}_0, X_0)$.

$$P_{FFE} = \begin{bmatrix} f_{\rho,x_\iota} & f_{\rho,x_\rho} \\ f_{o,x_\iota} & f_{o,x_\rho} \end{bmatrix} \qquad P_{SI} = \begin{bmatrix} f_{\rho,x_\iota} & f_{\rho,x_\rho} \\ 0 & f_{o,x_\rho} \end{bmatrix}$$

$$\det(P_{FFE}) = f_{\rho,x_\iota} f_{o,x_\rho} - f_{\rho,x_\rho} f_{o,x_\iota} \qquad \det(P_{SI}) = f_{\rho,x_\iota} f_{o,x_\rho}$$

$$\mathcal{I} \to \boxed{i} \xrightarrow{\varepsilon_{ik}} \left(k\right) \xrightarrow{\varepsilon_{kj}} \triangle j \to \mathcal{O}$$
$$\varepsilon_{ij}$$

- A simple path is *excitatory* if the product of coupling strengths along that path is positive and *inhibitory* if that product is negative

- Infinitesimal homeostasis requires that the two simple paths in feedforward excitation must have opposite signs

## Core Networks

- $q$ is *downstream* from $p$ in $\mathcal{G}$ if there exists a path in $\mathcal{G}$ from $p$ to $q$. Node $p$ is *upstream* from node $q$ if $q$ is downstream from $p$.

- Note: If output node $o$ is not downstream from input node $\iota$, then input-output function $x_o(\mathcal{I})$ is a constant function.

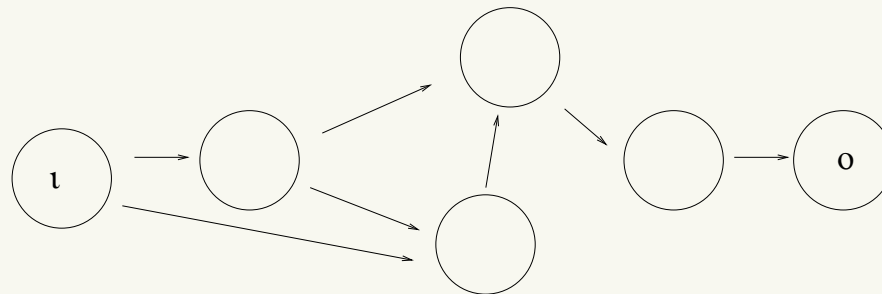  Although technically a form of homeostasis, it is irrelevant.

- More generally, we can remove nodes that are

  - NOT downstream from $\iota$
  - NOT upstream from $o$

- We call remaining nodes and arrows the *core network*

- A *simple path* is a path from $\iota$ to $o$ that visits a given node at most once

# Theorems

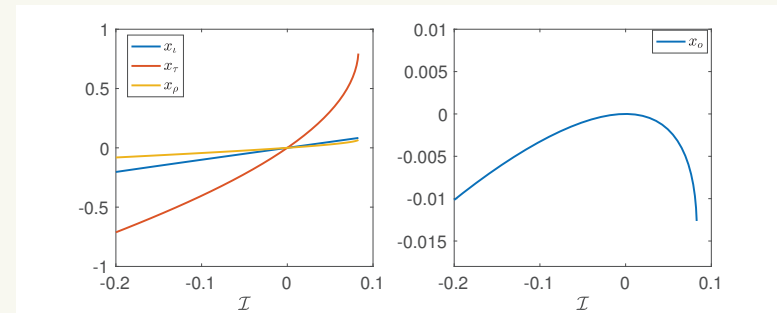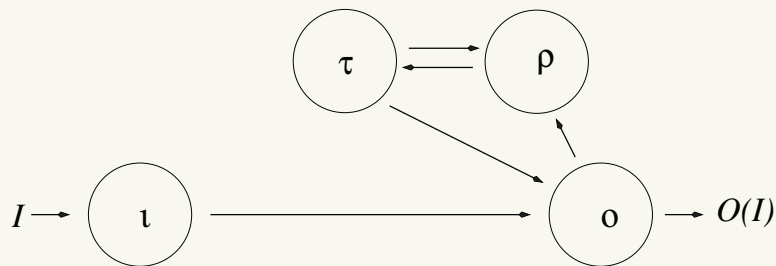- *Haldane homeostasis* is homeostasis that is forced by neutral coupling in a given arrow

  Theorem: An arrow can exhibit Haldane homeostasis if and only if that arrow is on every simple path.

- Structural homeostasis is found by balance coupling strengths on two or more simple paths

- Nodes in core not on simple path are *appendage nodes*

- Theorem (one simple path case): Appendage homeostasis is possible if and only if there is a cycle in the appendage nodes



$$\dot{x}_\iota = f_\iota(x_\iota, \mathcal{I})$$
$$\dot{x}_\rho = f_\rho(x_\rho, x_\tau, x_o)$$
$$\dot{x}_\tau = f_\tau(x_\rho, x_\tau)$$
$$\dot{x}_o = f_o(x_\iota, x_\tau, x_o)$$

$$\det(P) = f_{o,x_\iota}(f_{\rho,x_\rho} f_{\tau,x_\tau} - f_{\rho,x_\tau} f_{\tau,x_\rho}) = 0$$

Infinitesimal homeostasis can occur either by Haldane or by having both arrows between two appendage nodes be either excitatory or inhibitory.

Think of the appendage nodes as controller nodes.

# Homeostasis

# and

# Gene Regulatory Networks
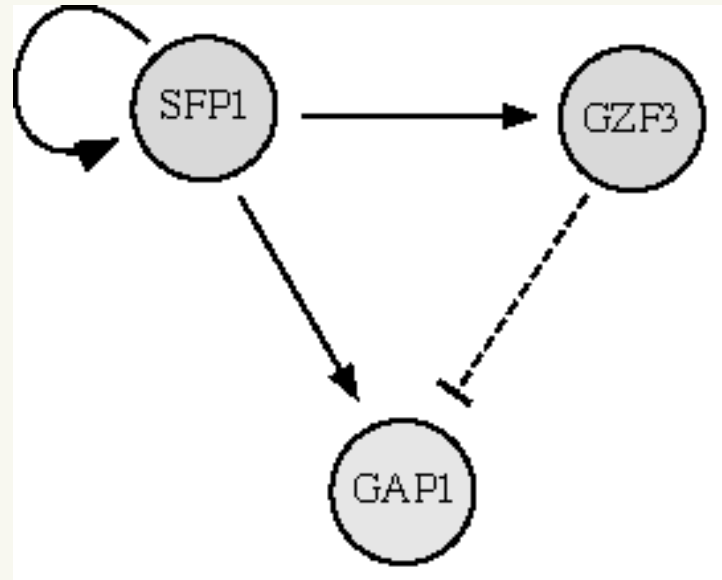
# **Housekeeping Genes**

Figure 1: A GRN motif of yeast *Saccharomyces cerevisiae*. Feed-forward loop involving genes SFP1, GZF3 regulating the housekeeping gene GAP1. Note that gene SFP1 is a self-regulated GRN motif. Adapted from: GDB (`http://www.yeastgenome.org`)
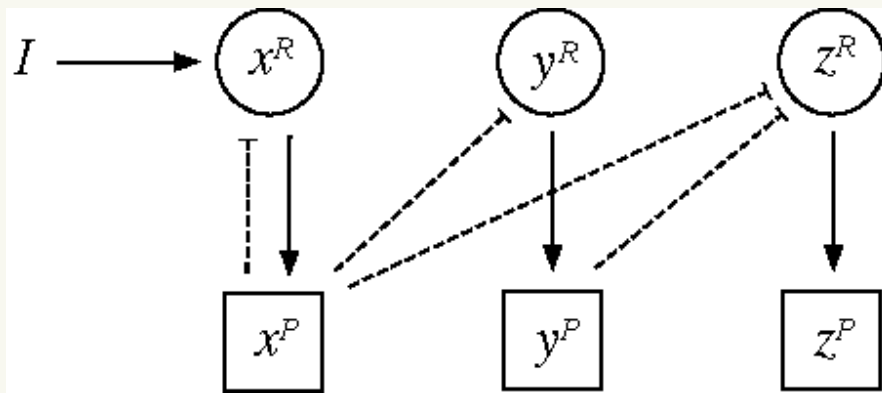
Figure 2: A 3-gene 6-node feed-forward loop. Circles = mRNA; squares = proteins; solid lines = excitatory coupling; dashed lines = inhibitory coupling.

Equations corresponding to GRN motif are

$$\dot{x^R} = f^R(x^R, x^P) + I$$

$$\dot{x^P} = f^P(x^R, x^P)$$

$$\dot{y^R} = g^R(x^P, y^R)$$
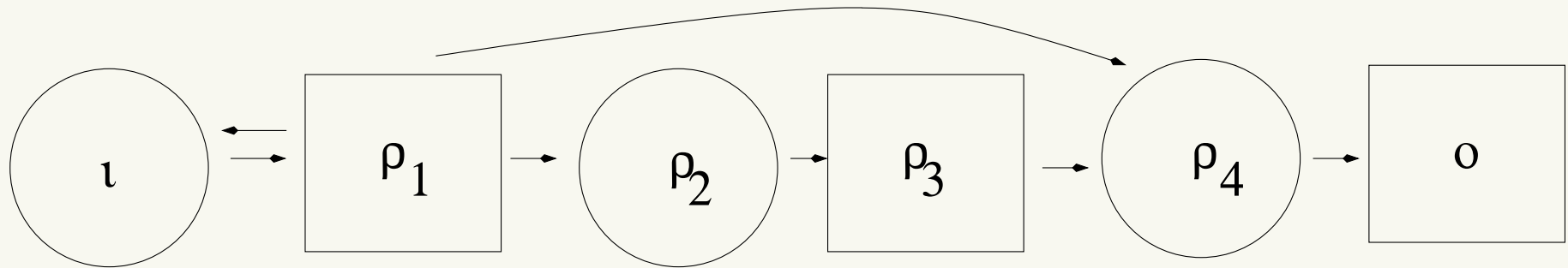
$$\dot{y^P} = g^P(y^R, y^P)$$

$$\dot{z^R} = h^R(x^P, y^P, z^R)$$

$$\dot{z^P} = h^P(z^R, z^P)$$

Input parameter $I$ represents action of upstream transcription factors that affect the $x$-gene and do not come from $y$ or $z$ genes.

**Goal**: Find regions of homeostasis in the steady-state protein concentration $z^P$ as a function of the input parameter $I$

# Homeostasis Analysis on Feed-Forward Loop



$$\det(P) = f_{\rho_1, x_\iota} f_{o, x_{\rho_4}} (f_{\rho_2, x_{\rho_1}} f_{\rho_3, x_{\rho_2}} f_{\rho_4, x_{\rho_3}} + f_{\rho_2, x_{\rho_2}} f_{\rho_3, x_{\rho_3}} f_{\rho_4, x_{\rho_1}})$$

- Haldane homeostasis is possible for $\iota \to \rho_1$ or $\rho_4 \to o$

- Structural homeostasis balances $\rho_1 \to \rho_2 \to \rho_3 \to \rho_4$ with $\rho_1 \to \rho_4$

# Housekeeping Genes in Yeast in Self-Regulated GRN

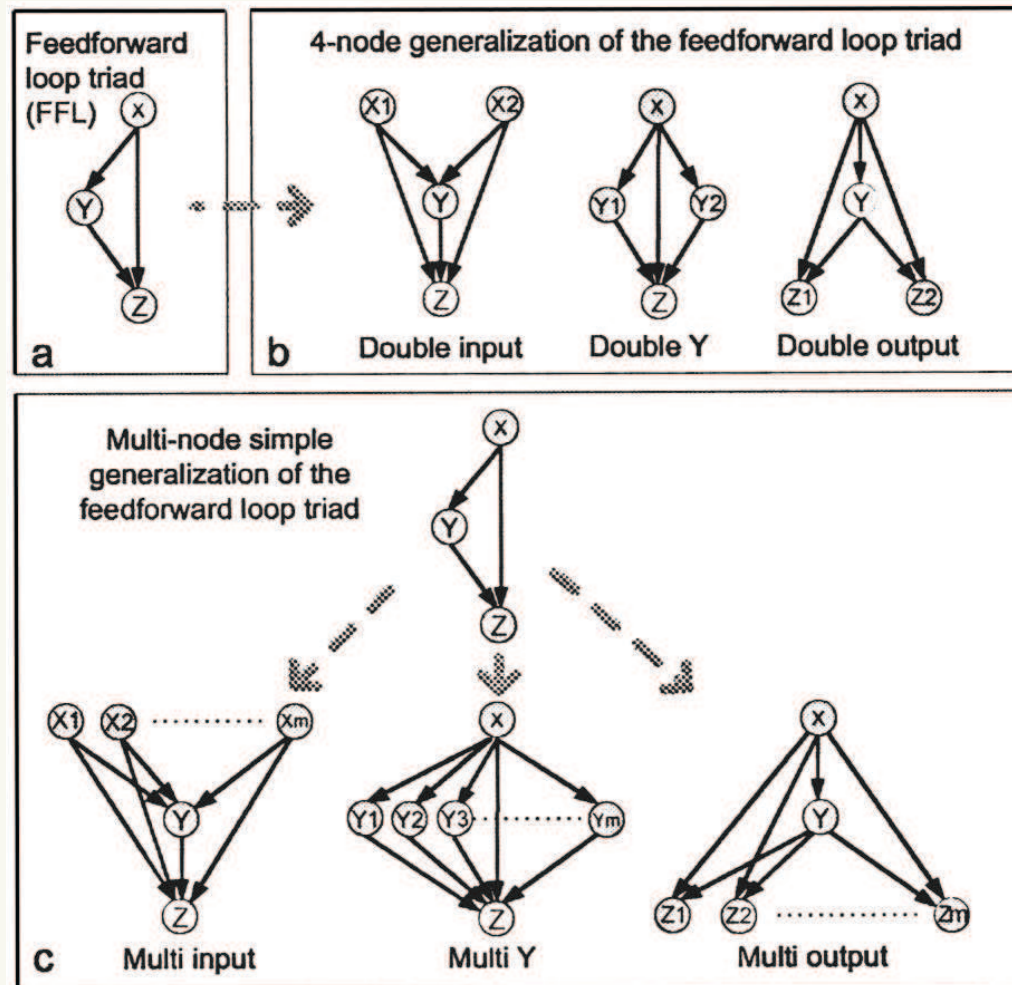| Gene | Ref | Gene | Ref |
|------|-----|------|-----|
| ACT1 | 1, 2 | PGK1 | 1, 2 |
| ARF1 | 1, 2 | GAP1 | 2 |
| CCW12 | 1, 2 | TDH3 | 1, 2 |
| FBA1 | 1, 2 | TPI1 | 1, 2 |
| PDA1 | 3, 2 | UBC6 | 3, 2 |

10 candidate housekeeping genes in YEAST thought to occur in FFL.

| Gene | #FFL | Ref |
|------|------|-----|
| ALG9 | 2 | 3, 2 |
| CDC19 | 7 | 1,2 |
| RPS26A | 5 | 1,2 |

3 candidate housekeeping genes in YEAST thought to occur in Multiple-Input FFL. # of overlapping FFLs also indicated

(a)  FFL has 3 nodes: X (input node), Y (internal), and Z (output node)
(b)  4-node generalizations of FFL: X is duplicated to form double-X

# Bibliography

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- F. Antoneli, M. Golubitsky and I. Stewart. Homeostasis in a feed forward loop gene regulatory network motif. J. Theoretical Biology. 445 (2018) 103-109.

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- M. Golubitsky and I. Stewart. Homeostasis, singularities and networks. J. Mathematical Biology. 74 (2017) 387–407

- M. Reed, J. Best, M. Golubitsky, I. Stewart and H.F. Nijhout. Analysis of homeostatic mechanisms in biochemical networks. Bull. Math. Biol. 79(9) (2017) 1–24.