A Gene Regulatory Network with Autoactivation and Cyclic Repression

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Assumptions and Abstractions in the Model

- Transcription of genes requires binding of the activating proteins
- Repression of transcription is modelled by competitive binding of the repressing proteins
- The binding reactions are assumed to be much faster than transcription and translation and are modelled to be in equilibrium
- Transcription and translation speeds are assumed to be constant
- mRNA and protein degradation are assumed to be constant also

Definitions and Differential Equations

$G = \{G_i \vert i = 1, \ldots, n\}$	...	Genes
$P = \{P_i \vert i = 1, \ldots, n\}$	...	Proteins: transcription factors
$R = \{R_i \vert i = 1, \ldots, n\}$	...	mRNAs
$G_i P_j$	...	complex of G_i with P_j
g_0	...	concentration of G_i
p_i	...	concentration of P_i
r_i	...	concentration of R_i
k^{TL}	...	rate const. for translation
k^{TS}	...	rate const. for transcription of $G_i P_i$
$\bar{k}^P$	...	rate const. for protein degradation
$\bar{k}^R$	...	rate const. for mRNA degradation
K_D	...	diss. const. for $P_i + G_i \rightleftarrows P_i G_i$
K_{DI}	...	diss. const. for $P_{i-1} + G_i \rightleftarrows P_{i-1} G_i$

$$\dot{p}_i = +k^{TL} r_i - \bar{k}^P p_i$$

$$\dot{r}_i = +k^{TS} g_0 \frac{p_i}{K_D + p_i + \frac{K_D}{K_{DI}} p_{i-1}} - \bar{k}^R r_i$$

Definitions and Differential Equations

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K_{DI}	...	diss. const. for $P_{i-1} + G_i \rightleftarrows P_{i-1} G_i$

$$\begin{aligned} \dot{p}_i &= +k^{TL}\, r_i - \bar{k}^P\, p_i \\ \dot{r}_i &= +k^{TS}\, g_0\, \frac{p_i}{K_D + p_i + \frac{K_D}{K_{DI}} p_{i-1}} - \bar{k}^R\, r_i \end{aligned}$$

Rescaling

$$\tau = \frac{t}{1/\bar{k}^R} = t\,\bar{k}^R \qquad x_i = \frac{p_i}{K_D}$$

$$\epsilon = \frac{k^{TL}}{\bar{k}^R} \qquad y_i = \frac{r_i}{K_D}\frac{\epsilon}{\beta} = \frac{r_i}{K}\frac{k^{TL}}{\bar{k}^P}$$

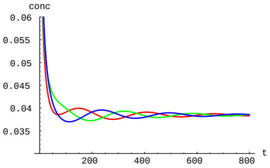
$$\beta = \frac{\bar{k}^P}{\bar{k}^R} \qquad \alpha = \frac{k^{TL}k^{TS}}{\bar{k}^P\bar{k}^R}\frac{g_0}{K_D}$$

$$\rho = \frac{K_D}{K_{DI}}$$

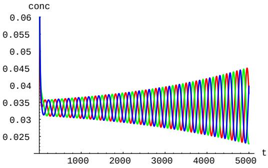
$$x_i' = \beta\,(y_i - x_i)$$

$$y_i' = \alpha\,\frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

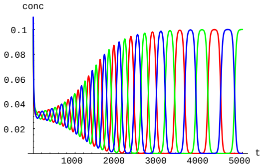
Hopf Bifurcation at central fixed point



(a) $\rho = 1.6$



(b) $\rho = 2.0$



(c) $\rho = 2.25$

Figure: Time course for 3 gene system with $\beta = 1, \alpha = 1.1,$
x_1 : red, x_2 : green, x_3 : red
starting values $x_3 = y_3 = 0.11$, all other $x_i = y_i = 0.1$

Fixed points

$$0 = \beta(y_i - x_i), \qquad 0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

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"Origin" fixed point X^0:

$$x_i^0 = y_i^0 = 0 \quad \forall i : 1 \leq i \leq n$$

Fixed points

$$0 = \beta(y_i - x_i), \qquad 0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

for $\alpha \geq 1$: “Central” fi xed point X^c:

$$x_i^c = y_i^c = \frac{\alpha - 1}{1 + \rho} \quad \forall i : 1 \leq i \leq n$$

Fixed points

$$0 = \beta (y_i - x_i), \qquad 0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

for $\alpha \geq 1$ and $\rho < 1$: Boundary fi xed points $X^{(B)}$:

$$x_i^{(b)} = y_i^{(b)} = \begin{cases} \alpha - 1 \text{ or } 0 & \text{if } x_{i-1} \text{ and } y_{i-1} = 0 \\ 0 \, or \, (\alpha - 1)(1 - \rho) & \text{otherwise} \end{cases}$$

Fixed points

$$0 = \beta(y_i - x_i), \qquad 0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

for $\alpha \geq 1$ and $\rho > 1$: Boundary fi xed points $X^{(B)}$:

$$x_i^{(b)} = y_i^{(b)} = \begin{cases} \alpha - 1 \text{ or } 0 & \text{if } x_{i-1} \text{ and } y_{i-1} = 0 \\ 0 & \text{otherwise} \end{cases}$$

Jacobian matrix

$$J = \begin{pmatrix}
-\beta & & & & \vdots & \beta & & & \\
& -\beta & & & \vdots & & \beta & & \\
& & \ddots & & \vdots & & & \ddots & \\
& & & -\beta & \vdots & & & & \beta \\
\cdots & \cdots & \cdots & \cdots & & \cdots & \cdots & \cdots & \cdots \\
\frac{\partial \dot{y}_1}{\partial x_1} & & & \frac{\partial \dot{y}_1}{\partial x_n} & \vdots & -1 & & & \\
\frac{\partial \dot{y}_2}{\partial x_1} & \ddots & & & \vdots & & -1 & & \\
& \ddots & \ddots & & \vdots & & & \ddots & \\
& & \frac{\partial \dot{y}_n}{\partial x_{n-1}} & \frac{\partial \dot{y}_n}{\partial x_n} & \vdots & & & & -1
\end{pmatrix}$$

Eigenvalues

$$|J - \lambda 1| = \left| \begin{array}{cccc:cccc} -\beta-\lambda & & & & \beta & & & \\ & -\beta-\lambda & & & & \beta & & \\ & & \ddots & & & & \ddots & \\ & & & -\beta-\lambda & & & & \beta \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \frac{\partial \dot{y}_1}{\partial x_1} & & & \frac{\partial \dot{y}_1}{\partial x_n} & -1-\lambda & & & \\ \frac{\partial \dot{y}_2}{\partial x_1} & \ddots & & & & -1-\lambda & & \\ & \ddots & \ddots & & & & \ddots & \\ & & \frac{\partial \dot{y}_n}{\partial x_{n-1}} & \frac{\partial \dot{y}_n}{\partial x_n} & & & & -1-\lambda \end{array} \right|$$

$$= \beta^{\,n} \left[\prod_{i=1}^{n} \left(\frac{(\lambda+1)(\lambda+\beta)}{\beta} - \frac{\partial \dot{y}_i}{\partial x_i} \right) + (-1)^n \prod_{i=1}^{n} \frac{\partial \dot{y}_i}{\partial x_{i-1}} \right] = 0$$

with:

$$\frac{\partial \dot{y}_i}{\partial x_i} = \alpha \frac{1 + \rho\, x_{i-1}}{(1 + x_i + \rho\, x_{i-1})^2} \qquad \frac{\partial \dot{y}_i}{\partial x_{i-1}} = \alpha \frac{-\rho\, x_i}{(1 + x_i + \rho\, x_{i-1})^2}$$

for origin fixpoint, X^0, and $\beta > 0$:

$$
\begin{aligned}
0 &= \beta^n \left(\frac{(\lambda+1)(\lambda+\beta)}{\beta} - \frac{\partial \dot{y}_i}{\partial x_i} \right)^n \\
0 &= \beta^n \left(\frac{(\lambda+1)(\lambda+\beta)}{\beta} - \alpha \right)^n \\
\lambda &= -\frac{1}{2} \left(\beta + 1 \pm \sqrt[2]{(\beta+1)^2 + 4\beta(\alpha - 1)} \right)
\end{aligned}
$$

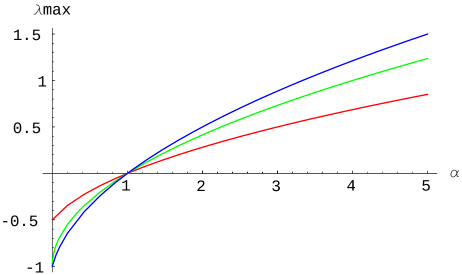


Figure: λ_{max} of X^0, for $\beta = 0.5$: red, 1 : green, 1.5 : blue

Stability of “central” fixed-point X^c

$$x_i^c = y_i^c = \frac{\alpha - 1}{1 + \rho} \quad \forall i : 1 \leq i \leq n$$

$$\lambda_{max} = -\frac{(\beta + 1)}{2} - \sqrt[2]{\left(\frac{\beta - 1}{2}\right)^2 + \beta (D + z_n N)}$$

where

$$z_n = \begin{cases} e^{\frac{i\pi}{n}} & \text{if } n = odd \\ 1 & \text{if } n = even \end{cases}$$

and

$$D = \frac{1 + \alpha\rho}{\alpha (1 + \rho)}$$

$$N = \frac{(\alpha - 1)\rho}{\alpha (1 + \rho)}$$

Stability of “central” fixed-point X^c

$$x_i^c = y_i^c = \frac{\alpha - 1}{1 + \rho} \quad \forall i : 1 \leq i \leq n$$

$$\lambda_{max} = -\frac{(\beta + 1)}{2} - \sqrt[2]{\left(\frac{\beta - 1}{2}\right)^2 + \beta \left(D + z_n N\right)}$$

λ_{max} depends on β in following way:

$$\lambda_{max}\left(\frac{1}{\beta}\right) = \frac{1}{\beta}\lambda_{max}\left(\beta\right)$$

so that the sign of λ_{max} is symmetrical around the plane $\beta = 1$ if β is scaled logarithmically

System with even n, "central" fixed-point X^c

$$x_i^c = y_i^c = \frac{\alpha - 1}{1+\rho} \quad \forall i : 1 \le i \le n$$

$$\lambda_{max} = -\frac{1}{2}\left(\beta + 1 - \sqrt[2]{(\beta-1)^2 + 4\beta\frac{1+\rho(2\alpha-1)}{\alpha(\rho+1)}}\right)$$

$$\Re(\lambda_{max}) = 0 \Leftrightarrow \rho = 1$$

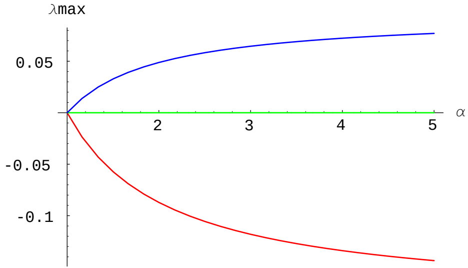


Figure: λ_{max} of X^c with $n = even$ for
$\beta = 1$ and $\rho = 0.5$: red, 1 : green, 1.5 : blue

2 fixed-points at $\tilde{X}$

$$\tilde{x}_{i+2k} = \tilde{y}_{i+2k} = \alpha - 1 \quad \tilde{x}_{i+2k+1} = \tilde{y}_{i+2k+1} = 0 \qquad \forall k : 0 \leq k \leq \frac{n}{2}$$

$$\lambda_{max} = -\frac{1}{2}\left(\beta + 1 - \sqrt[2]{(\beta-1)^2 + 4\beta \sqrt[2]{\frac{\alpha}{\rho(\alpha-1)}}}\right)$$

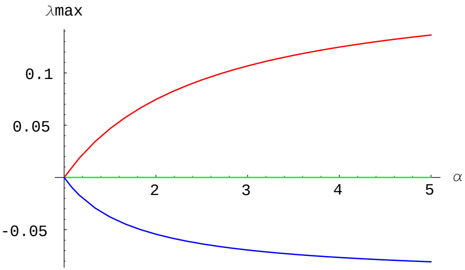
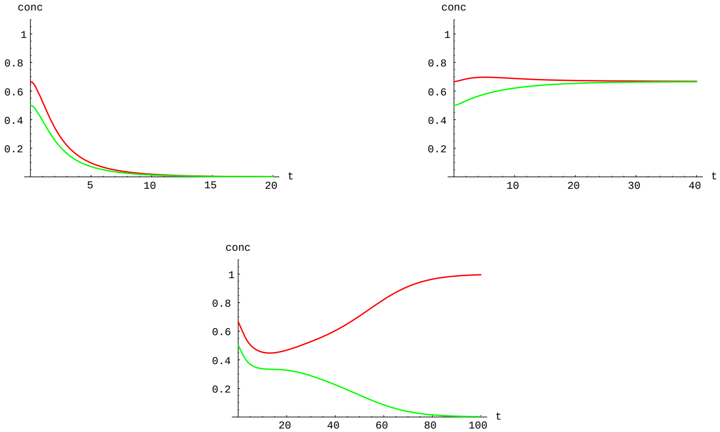


Figure: λ_{max} of $\tilde{X}$ with $n = even$ for
$\beta = 1$ and $\rho = 0.5$: red, 1 : green, 1.5 : blue

A simple system of four genes:

$$\begin{aligned}
\dot{x}_1 &= \beta(y_1 - x_1) & \dot{y}_1 &= \alpha\frac{x_1}{1 + x_1 + \rho x_4} - y_1 \\
\dot{x}_2 &= \beta(y_2 - x_2) & \dot{y}_2 &= \alpha\frac{x_2}{1 + x_2 + \rho x_1} - y_2 \\
\dot{x}_3 &= \beta(y_3 - x_3) & \dot{y}_3 &= \alpha\frac{x_3}{1 + x_3 + \rho x_2} - y_3 \\
\dot{x}_4 &= \beta(y_4 - x_4) & \dot{y}_4 &= \alpha\frac{x_4}{1 + x_4 + \rho x_3} - y_4
\end{aligned}$$

Bifurcations for a simple system of four genes



Time course for 4 gene system with $\beta = 1, x_1$: red, x_2 : green starting values $x_1 = y_1 = 0.6$, all other $x_i = y_i = 0.5$ a: $\alpha = 0.5, \rho = 1.5$, b: $\alpha = 2, \rho = 0.5$, c: $\alpha = 2, \rho = 1.5$

Central fixed-point X^c for system with odd n

$$x_i^c = y_i^c = \frac{\alpha - 1}{1 + \rho} \quad \forall i : 1 \leq i \leq n$$

$$\lambda_{max} = -\frac{(\beta + 1)}{2} - \sqrt[2]{\left(\frac{\beta - 1}{2}\right)^2 + \beta\left(D + e^{\frac{i\pi}{n}} N\right)}$$

with

$$D = \frac{1 + \alpha\rho}{\alpha(1 + \rho)}$$

$$N = \frac{(\alpha - 1)\rho}{\alpha(1 + \rho)}$$

Central fixed-point X^c for system with odd n

$$
\begin{aligned}
x_i^c = y_i^c &= \frac{\alpha - 1}{1 + \rho} \quad \forall i : 1 \leq i \leq n \\
\lambda_{max} &= -\frac{(\beta + 1)}{2} - \sqrt[2]{\left(\frac{\beta - 1}{2}\right)^2 + \beta\left(D + e^{\frac{i\pi}{n}} N\right)}
\end{aligned}
$$

$$
\Re\left(\lambda_{max}\right) = -\frac{(\beta + 1)}{2} - \sqrt[2]{P + \sqrt[2]{P^2 + Q^2}}
$$

where:

$$
\begin{aligned}
P &= \frac{1}{2}\left[\left(\frac{\beta - 1}{2}\right)^2 + cos\left(\frac{\pi}{n}\right)\beta N + \beta D\right] \\
Q &= \frac{1}{2} sin\left(\frac{\pi}{n}\right)\beta N
\end{aligned}
$$

Central fixed-point X^c for system with odd n

$$x_i^c = y_i^c = \frac{\alpha - 1}{1+\rho} \quad \forall i : 1 \leq i \leq n$$

$$\lambda_{max} = -\frac{(\beta+1)}{2} - \sqrt[2]{\left(\frac{\beta-1}{2}\right)^2 + \beta\left(D + e^{\frac{i\pi}{n}} N\right)}$$

leads to:

$$\Re\left(\lambda_{max}\right)|_{\beta=0} = 0 \quad ; \quad \Re\left(\lambda_{max}\right)|_{\beta=\infty} = \left(cos\left(\frac{\pi}{n}\right) - \frac{1}{\rho}\right) N$$

$$\Re\left(\lambda_{max}\right)|_{\beta=1} = 0 \quad \Leftrightarrow \quad cos\left(\frac{\pi}{n}\right) + \frac{1}{4} sin^2\left(\frac{\pi}{n}\right) N - \frac{1}{\rho} = 0$$

with:

$$N = \frac{(\alpha-1)\,\rho}{\alpha\,(1+\rho)}$$

Central fixed-point X^c for system with odd n

So for systems of size n stability boundaries exist between:

$$\frac{1}{\cos\left(\frac{\pi}{n}\right)} > \rho > \rho_{stab}$$

with:

$$\rho_{stab}^2\left(\cos\left(\frac{\pi}{n}\right)+\frac{1}{4}\sin^2\left(\frac{\pi}{n}\right)\right)+\rho_{stab}\left(\cos\left(\frac{\pi}{n}\right)-1\right)-1=0$$

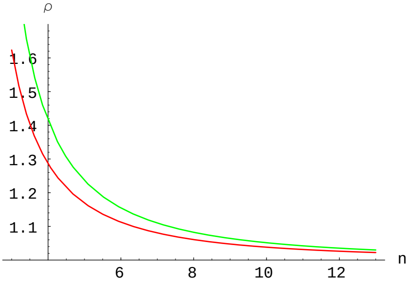


Figure: $\frac{1}{\cos\left(\frac{\pi}{n}\right)}$, green, and ρ_{stab}, red, in dependency of n

Heteroclinic cycles in odd systems

For n odd, $\alpha > 1$ and $\rho > 1$ the system has the following properties:
It is permanent if $\lambda > \frac{n-1}{2}\mu$.
It has an attracting heteroclinic cycle if $\lambda < \frac{n-1}{2}\mu$.
with:

$$\begin{aligned} \lambda &= -\frac{(\beta+1)}{2} + \sqrt[2]{\left(\frac{\beta-1}{2}\right)^2 + \beta\alpha} \\ -\mu &= -\frac{(\beta+1)}{2} + \sqrt[2]{\left(\frac{\beta-1}{2}\right)^2 + \beta\frac{\alpha}{1+\rho(\alpha-1)}} \end{aligned}$$

The heteroclinic cycle connects the following fi xed points:

$$\begin{aligned} n = 3 \quad &: \quad S_1 \to S_2 \to S_3 \to S_1 \\ n = 5 \quad &: \quad S_{13} \to S_{35} \to S_{52} \to S_{24} \to S_{41} \to S_{13} \end{aligned}$$

Heteroclinic cycles in odd systems

$$\left(\lambda - \frac{n-1}{2}\mu\right)|_{\beta=1} = 0 \quad \Leftrightarrow \quad \rho = \frac{1}{\alpha - 1}\left(\frac{\alpha}{\left(\frac{n+1}{n-1} - \frac{2}{n-1}\sqrt[2]{\alpha}\right)^2} - 1\right)$$

$$\alpha \to 1 \Leftrightarrow \rho(\alpha) \to \frac{n+1}{n-1} \qquad \rho(\alpha) \to \infty \Leftrightarrow \alpha \to \left(\frac{n+1}{2}\right)^2$$

$$\left(\lambda - \frac{n-1}{2}\mu\right)|_{\beta=\infty} = 0 \quad \Leftrightarrow \quad \rho = \frac{1}{\alpha - 1}\left(\frac{\alpha}{\left(1 - \frac{2}{n-1}(\alpha - 1)\right)} - 1\right)$$

$$\alpha \to 1 \Leftrightarrow \rho(\alpha) \to \frac{n+1}{n-1} \qquad \rho(\alpha) \to \infty \Leftrightarrow \alpha \to \frac{n+1}{2}$$

Heteroclinic cycles in odd systems

For $\beta = 1$:

$$\alpha \to 1 \Leftrightarrow \rho(\alpha) \to \frac{n+1}{n-1} \qquad \rho(\alpha) \to \infty \Leftrightarrow \alpha \to \left(\frac{n+1}{2}\right)^2$$

For $\beta = \infty$:

$$\alpha \to 1 \Leftrightarrow \rho(\alpha) \to \frac{n+1}{n-1} \qquad \rho(\alpha) \to \infty \Leftrightarrow \alpha \to \frac{n+1}{2}$$

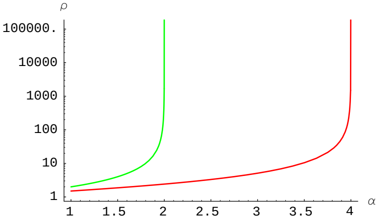


Figure: Stability boundaries for the heteroclinic cycle in the symmetry plane $\beta = 1$,red, and $\beta = \infty$,green, for $n = 3$

A System with 3 genes

Rescaled differential equations:

$$\begin{aligned}
\dot{x}_1 &= \beta\,(y_1 - x_1) & \dot{y}_1 &= \alpha\,\frac{x_1}{1 + x_1 + \rho x_3} - y_1 \\
\dot{x}_2 &= \beta\,(y_2 - x_2) & \dot{y}_2 &= \alpha\,\frac{x_2}{1 + x_2 + \rho x_1} - y_2 \\
\dot{x}_3 &= \beta\,(y_3 - x_3) & \dot{y}_3 &= \alpha\,\frac{x_3}{1 + x_3 + \rho x_2} - y_3
\end{aligned}$$

Fixed points

$$0 = \beta(y_i - x_i),$$

$$0 = \alpha\frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

"Origin" fixed point X^0:

$$X = (x_1, x_2, x_3, y_1, y_2, y_3)$$
$$X^0 = (0, 0, 0, 0, 0, 0)$$

Fixed points

$$0 = \beta(y_i - x_i),$$

$$0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

“Origin” fi xed point X^0:

$$\begin{aligned} X &= (x_1, x_2, x_3, y_1, y_2, y_3) \\ X^0 &= (0, 0, 0, 0, 0, 0) \end{aligned}$$

Fixed points

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Fixed points

$$0 = \beta(y_i - x_i), \qquad 0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

for $\alpha \geq 1$, "Central" fixed-point X^c:

$$X^c = \left(\frac{\alpha - 1}{1 + \rho}, \frac{\alpha - 1}{1 + \rho}, \frac{\alpha - 1}{1 + \rho}, \frac{\alpha - 1}{1 + \rho}, \frac{\alpha - 1}{1 + \rho}, \frac{\alpha - 1}{1 + \rho} \right)$$

Fixed points

$$0 = \beta(y_i - x_i), \qquad 0 = \alpha\frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

for $\alpha \geq 1$, "Central" fixed-point X^c:

$$X^c = \left(\frac{\alpha-1}{1+\rho}, \frac{\alpha-1}{1+\rho}, \frac{\alpha-1}{1+\rho}, \frac{\alpha-1}{1+\rho}, \frac{\alpha-1}{1+\rho}, \frac{\alpha-1}{1+\rho}\right)$$

for $\alpha \geq 1$ and $\rho < 1$, Boundary fixed-points $X^{(k)}$:

$$\begin{aligned} X^{(1)} &= (\alpha-1, 0, 0, \alpha-1, 0, 0) \\ X^{(2)} &= (0, \alpha-1, 0, 0, \alpha-1, 0) \\ X^{(3)} &= (0, 0, \alpha-1, 0, 0, 0, \alpha-1) \end{aligned}$$

Fixed points

$$0 = \beta(y_i - x_i), \qquad 0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

Fixed points

$$0 = \beta(y_i - x_i), \qquad 0 = \alpha \frac{x_i}{1 + x_i + \rho x_{i-1}} - y_i$$

For $\alpha \geq 1, \rho \leq 1$,"Plane" fi xed points X^{k*}::

$$\begin{aligned} X^{1*} &= (\alpha - 1, (\alpha - 1)(1 - \rho), 0, \alpha - 1, (\alpha - 1)(1 - \rho), 0) \\ X^{2*} &= (0, \alpha - 1, (\alpha - 1)(1 - \rho), 0, \alpha - 1, (\alpha - 1)(1 - \rho)) \\ X^{3*} &= ((\alpha - 1)(1 - \rho), 0, \alpha - 1, 0, (\alpha - 1)(1 - \rho), 0, \alpha - 1) \end{aligned}$$

Jacobian Matrix and Eigenvalues

From:

$$J = \frac{\partial(\dot{x}_i, \dot{y}_i)}{\partial(x_j, y_j)} = \begin{pmatrix} -\beta & & & \beta & & \\ & -\beta & & & \beta & \\ & & -\beta & & & \beta \\ \frac{\partial \dot{y}_1}{\partial x_1} & & \frac{\partial \dot{y}_1}{\partial x_3} & -1 & & \\ \frac{\partial \dot{y}_2}{\partial x_1} & \frac{\partial \dot{y}_2}{\partial x_2} & & & -1 & \\ & \frac{\partial \dot{y}_3}{\partial x_2} & \frac{\partial \dot{y}_3}{\partial x_3} & & & -1 \end{pmatrix}$$

follows for the Eigenvalues λ:

$$\beta^3 \left[\prod_{i=1}^{3} \left(\frac{(\lambda+1)(\lambda+\beta)}{\beta} - \frac{\partial \dot{y}_i}{\partial x_i} \right) - \prod_{i=1}^{3} \frac{\partial \dot{y}_i}{\partial x_{i-1}} \right] = 0$$

$$\prod_{i=1}^{3} \left(\frac{(\lambda+1)(\lambda+\beta)}{\beta} - \frac{\partial \dot{y}_i}{\partial x_i} \right) = (-1) \prod_{i=1}^{3} \left(-\frac{\partial \dot{y}_i}{\partial x_{i-1}} \right)$$

with:

$$\frac{\partial \dot{y}_i}{\partial x_i} = \alpha \frac{1 + \rho x_{i-1}}{(1 + x_i + \rho x_{i-1})^2} \qquad \frac{\partial \dot{y}_i}{\partial x_{i-1}} = \alpha \frac{-\rho x_i}{(1 + x_i + \rho x_{i-1})^2}$$

"Origin" Fixed Point X^0

$$X^0 = (0,0,0,0,0,0)$$
$$\lambda = -\frac{1}{2}\left(\beta + 1 \pm \sqrt[2]{(\beta+1)^2 + 4\beta(\alpha - 1)}\right)$$

for $\beta = 1$:

$$\lambda = -1 \pm \sqrt[2]{\alpha}$$

“Central” fixed point X^c

$$x_i^c = y_i^c = \frac{\alpha - 1}{1 + \rho} \qquad \frac{\partial \dot{y}_i}{\partial x_i} = \frac{1 + \rho\,\alpha}{\alpha\,(1 + \rho)} \qquad \frac{\partial \dot{y}_i}{\partial x_{i-1}} = -\frac{\rho\,(\alpha - 1)}{\alpha\,(1 + \rho)}$$

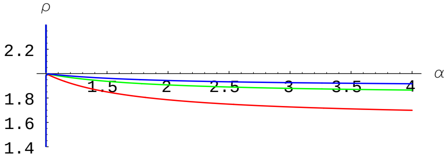
Eigenvalues:

$$\lambda \;=\; -\frac{1}{2}\left[\beta + 1 \pm \sqrt[2]{(\beta - 1)^2 + 4\beta\left(\frac{1 + \rho\,\alpha}{\alpha\,(1 + \rho)} + \sqrt[3]{-1}\frac{\rho\,(\alpha - 1)}{\alpha\,(1 + \rho)}\right)}\right]$$

for $\beta = 1$:

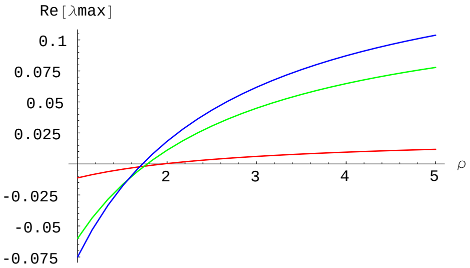
$$\lambda \;=\; -1 \pm \sqrt[2]{\frac{1 + \rho\,\alpha}{\alpha\,(1 + \rho)} + \sqrt[3]{-1}\frac{\rho\,(\alpha - 1)}{\alpha\,(1 + \rho)}}$$

Hopf Bifurcation: $\Re(\lambda_{\max}) = 0$



Realpart of $\lambda_{\max}$ for $\beta = 1$ and $\alpha = 1.1:$ red, $2.1:$ green, $3.1:$ blue

Bifurcation values of α and ρ for $\beta = 1:$ red, $8:$ green, $15:$ blue



“Corner” fixed point $X^{(1)}$

$$X^{(1)} = (\alpha - 1, 0, 0, \alpha - 1, 0, 0)$$

$$\begin{aligned}
\lambda_{1,2} &= -\frac{1+\beta}{2} \pm \sqrt{\left(\frac{1-\beta}{2}\right)^2 + \beta \, \frac{1}{\alpha}} \\
\lambda_{3,4} &= -\frac{1+\beta}{2} \pm \sqrt{\left(\frac{1-\beta}{2}\right)^2 + \beta \, \frac{\alpha}{1+\rho\,(\alpha-1)}} \\
\lambda_{5,6} &= -\frac{1+\beta}{2} \pm \sqrt{\left(\frac{1-\beta}{2}\right)^2 + \beta \, \alpha}
\end{aligned}$$

“Corner” fixed point $X^{(1)}$

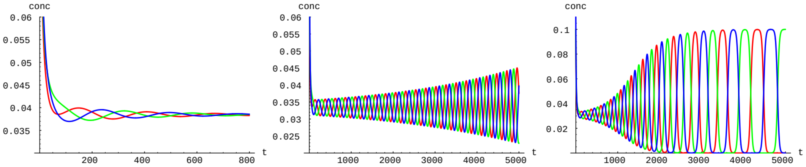
For $\beta = 1$:

$$\begin{aligned}
\lambda_{1,2} &= -1 \pm \sqrt{\frac{1}{\alpha}} \\
\lambda_{3,4} &= -1 \pm \sqrt{\frac{\alpha}{1 + \rho(\alpha - 1)}} \\
\lambda_{5,6} &= -1 \pm \sqrt{\alpha}
\end{aligned}$$

For $\rho > 1$:

$$\begin{aligned}
-1 + \sqrt{\alpha} &> 0 \\
\lambda &< 0 \quad \text{otherwise}
\end{aligned}$$

Hopf Bifurcation at central fixed point



(a) $\rho = 1.6$ (b) $\rho = 2.0$ (c) $\rho = 2.25$

Figure: Time course for 3 gene system with $\beta = 1, \alpha = 1.1$,
x_1 : red, x_2 : green, x_3 : red
starting values $x_3 = y_3 = 0.11$, all other $x_i = y_i = 0.1$

Hopf Bifurcation at Central Fixed Point

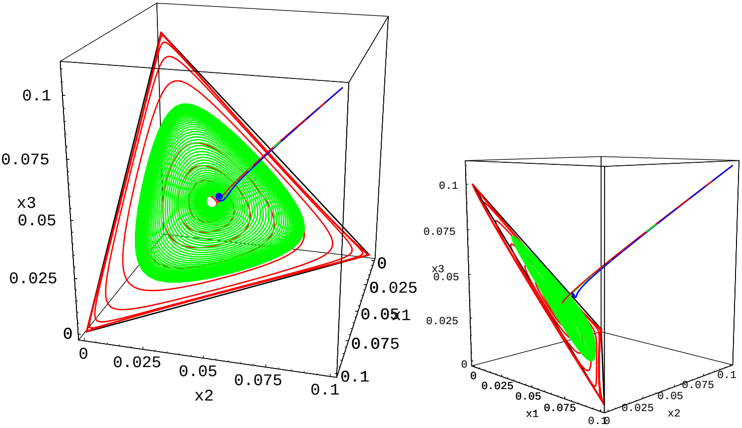
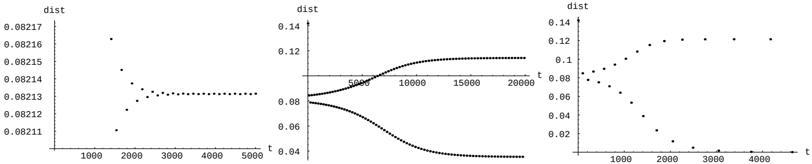


Figure: Trajectories in x_1, x_2, x_3 subspace of phasespace with
$\beta = 1, \alpha = 1.1,\ \rho = 2.25:$ red, $2:$ green, $1.6:$ red
starting values $x_3 = y_3 = 0.11$, all other $x_i = y_i = 0.1$

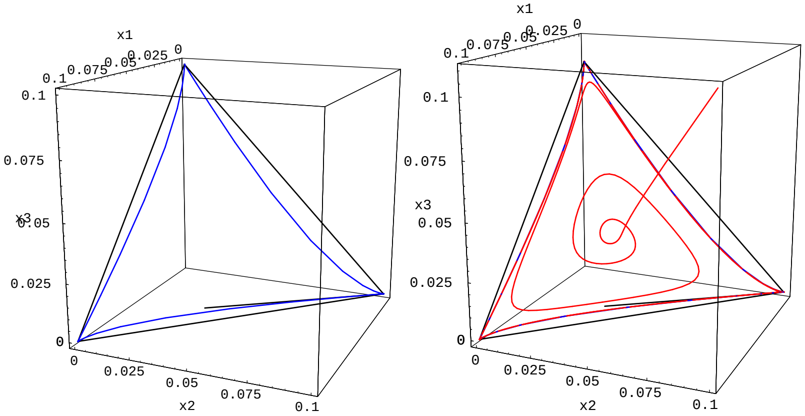
Hopf Bifurcation at Central Fixed Point



(a) $\rho = 1.6$ (b) $\rho = 2.0$ (c) $\rho = 2.25$

Figure: Distances to $(0, 0, \alpha - 1)$ on a poincare section along $x_1 = x_2$ in the x_1, x_2, x_3 subspace of phasespace.
$\beta = 1, \alpha = 1.1$,
starting values $x_3 = y_3 = 0.11$, all other $x_i = y_i = 0.1$

Heteroclinic Orbits



(a) (b)

Figure: Heteroclinic orbits (*blue*) between the corner saddle points in the x_1, x_2, x_3 subspace of phasespace. Trajectory (*red*) for system with: $\beta = 1, \alpha = 1.1, \rho = 3$

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