Persistence, permanence, and global stability in reaction network models: some results inspired by thermodynamic principles

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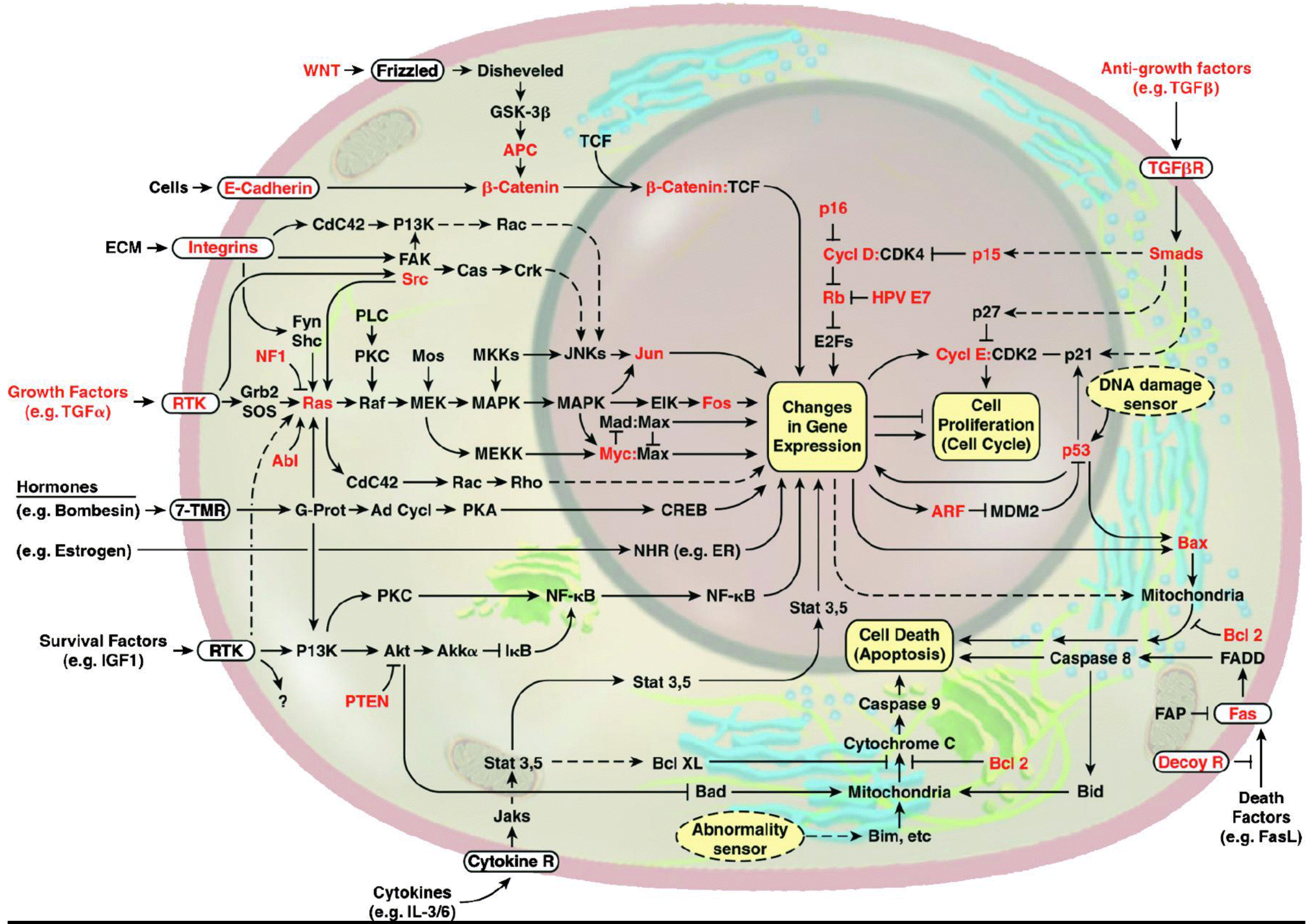
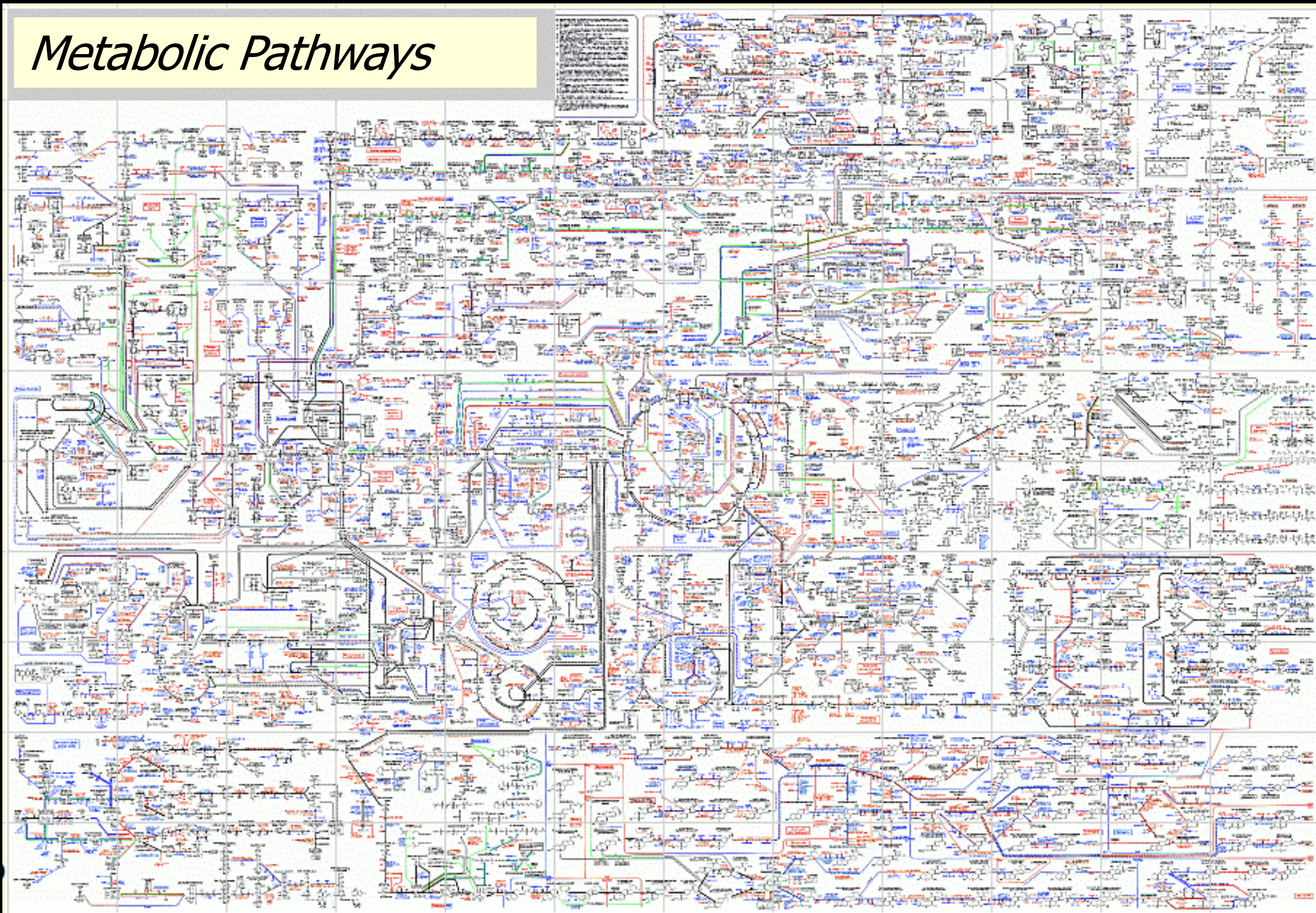


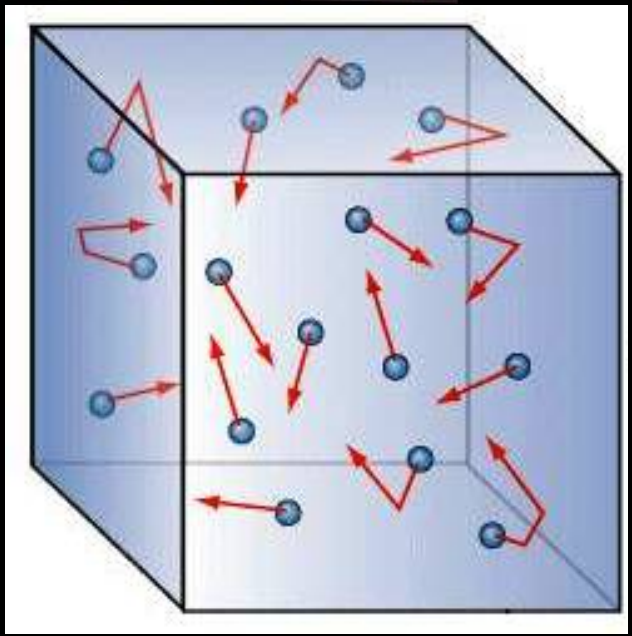
Hanahan and Weinberg, The Hallmarks of Cancer, Cell, 2000.

Metabolic Pathways



Roche Applied Science

Boltzmann's H-theorem: the distribution of velocities of the atoms of a gas converges to the Maxwell distribution



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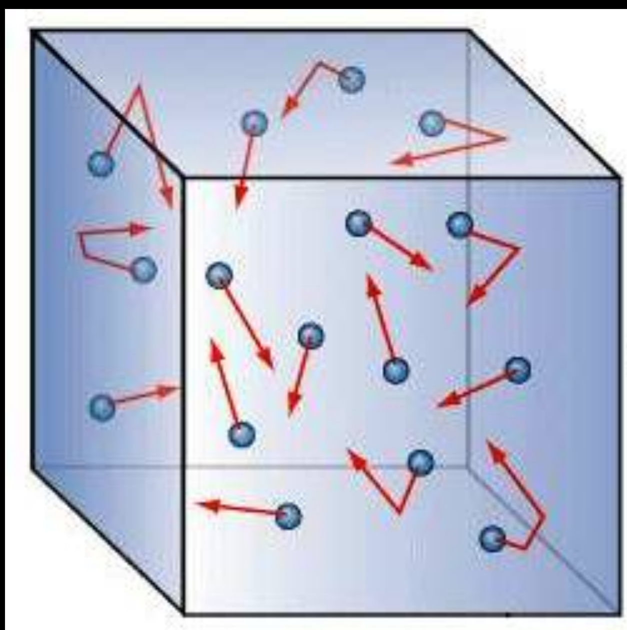

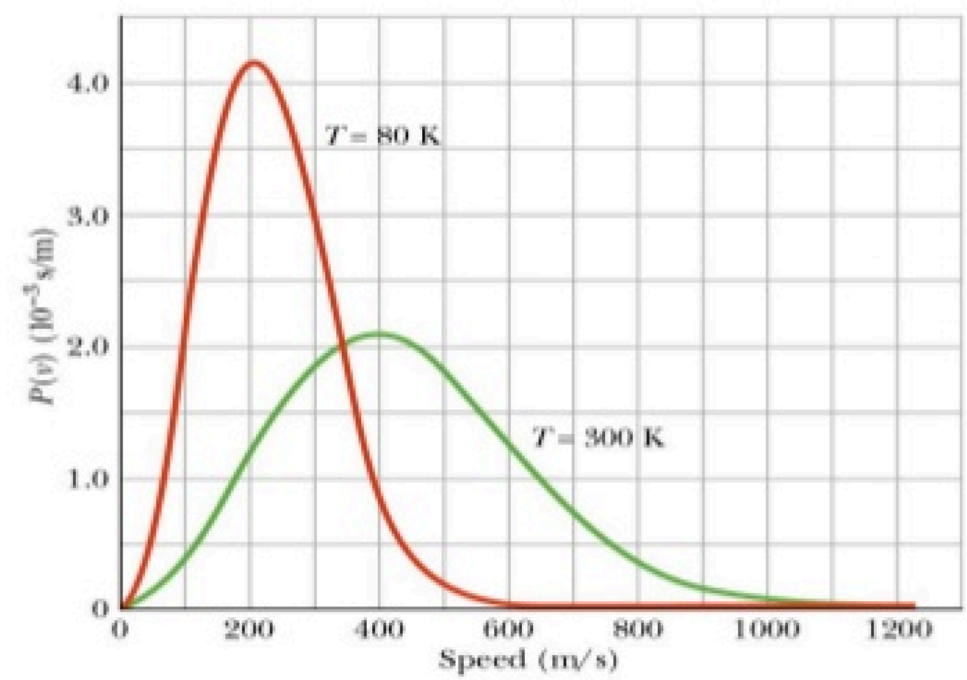

$$f(v) = 4\pi \left(\frac{m}{2\pi kT} \right)^{3/2} v^2 e^{-mv^2/(2kT)}$$

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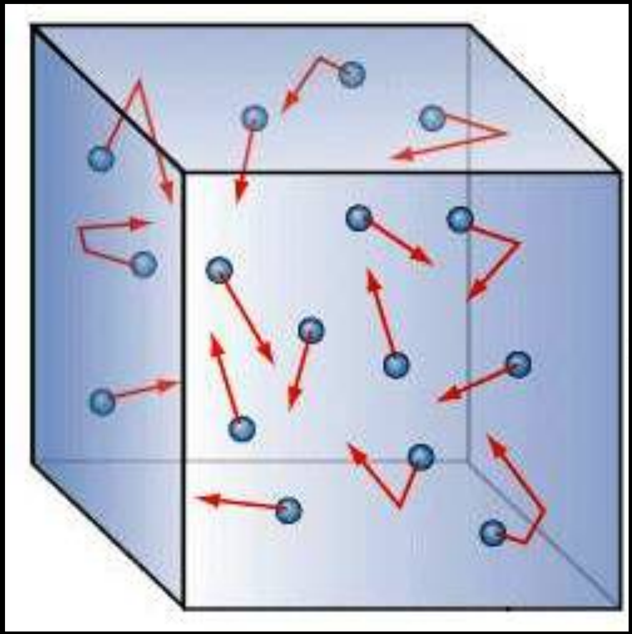
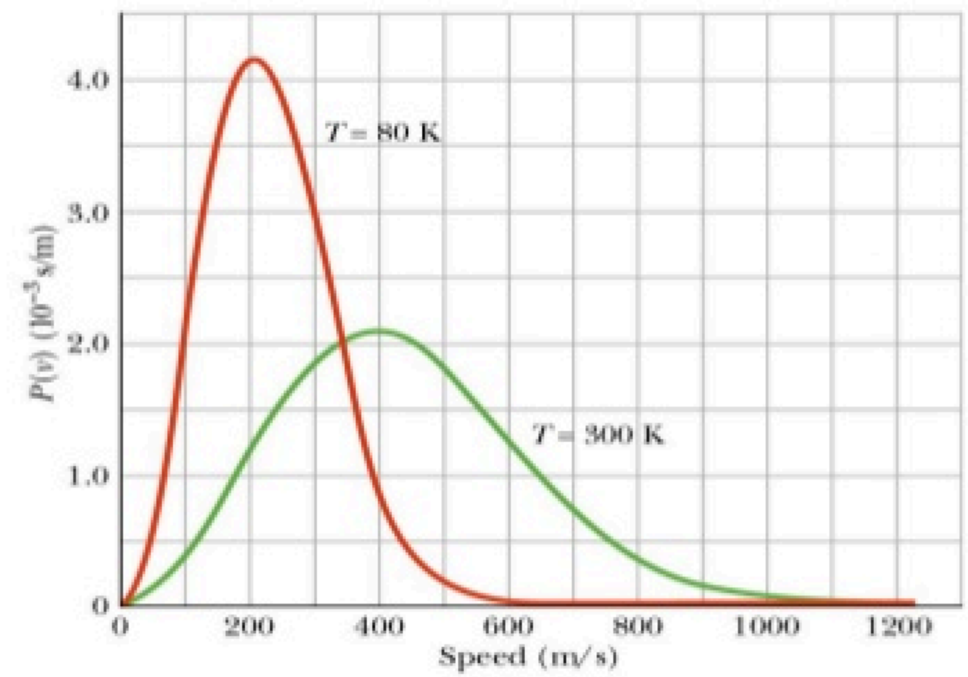
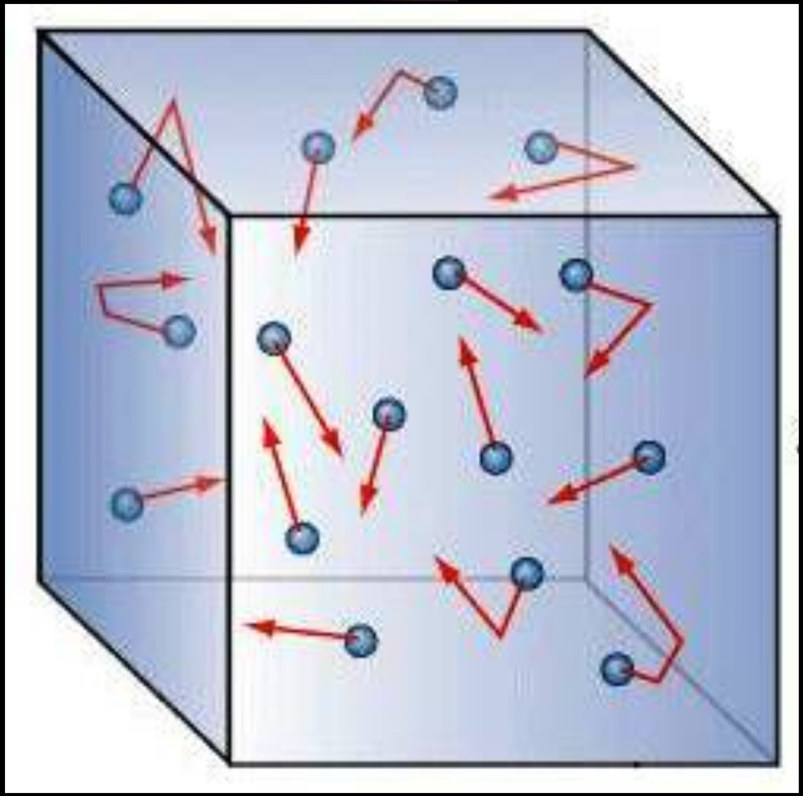




$$f(v) = 4\pi\left(\frac{m}{2\pi kT}\right)^{3/2} v^2 e^{-mv^2/(2kT)}$$

In other words: the Maxwell distribution is a global attractor.

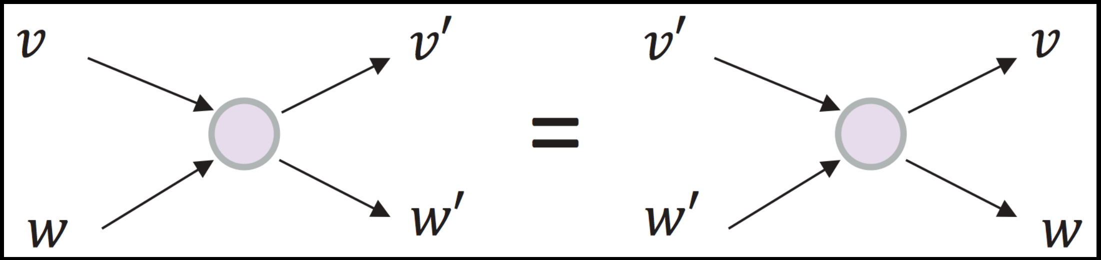
Boltzmann's H-theorem: the distribution of velocities of the atoms of a gas converges to the Maxwell distribution



Boltzmann used a key hypothesis:

"detailed balance"

i.e. the forward and backward transition rates (at equilibrium) balance each other out:



Chemical reaction networks and polynomial dynamical systems: mass action kinetics

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$$X_1 \to X_2$$

Chemical reaction networks and polynomial dynamical systems: mass action kinetics

$$X_1 \to X_2$$

$$\frac{dx_1}{dt} = -kx_1$$

$$\frac{dx_1}{dt} = kx_1$$

Chemical reaction networks and polynomial dynamical systems: mass action kinetics

$$X_1 + X_2 \rightarrow X_3$$

Chemical reaction networks and polynomial dynamical systems: mass action kinetics

$$X_1 + X_2 \to X_3$$

$$\begin{aligned}
\frac{dx_1}{dt} &= -kx_1x_2 \\
\frac{dx_2}{dt} &= -kx_1x_2 \\
\frac{dx_3}{dt} &= kx_1x_2
\end{aligned}$$

Chemical reaction networks and polynomial dynamical systems: mass action kinetics

$$X_1 + X_2 \to X_3 + X_4$$

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\frac{dx_3}{dt} &= kx_1x_2 \\
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Chemical reaction networks and polynomial dynamical systems: mass action kinetics

$$X_1 + X_2 \rightleftharpoons X_3 + X_4$$

Chemical reaction networks and polynomial dynamical systems: mass action kinetics

$$X_1 + X_2 \rightleftharpoons X_3 + X_4$$

$$\begin{aligned}
\frac{dx_1}{dt} &= -k_1 x_1 x_2 + k_2 x_3 x_4 \\
\frac{dx_2}{dt} &= -k_1 x_1 x_2 + k_2 x_3 x_4 \\
\frac{dx_3}{dt} &= k_1 x_1 x_2 - k_2 x_3 x_4 \\
\frac{dx_4}{dt} &= k_1 x_1 x_2 - k_2 x_3 x_4
\end{aligned}$$

Chemical reaction networks and polynomial dynamical systems: mass action kinetics

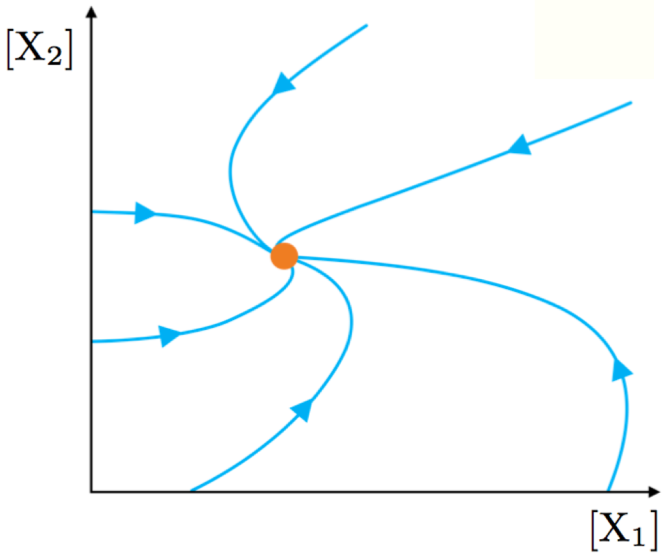
$$\varnothing \xrightarrow{k_1} X_1 \xrightarrow{k_2} X_1 + X_2 \xrightarrow{k_3} \varnothing$$

Chemical reaction networks and polynomial dynamical systems: mass action kinetics

$$\varnothing \xrightarrow{k_1} X_1 \xrightarrow{k_2} X_1 + X_2 \xrightarrow{k_3} \varnothing$$

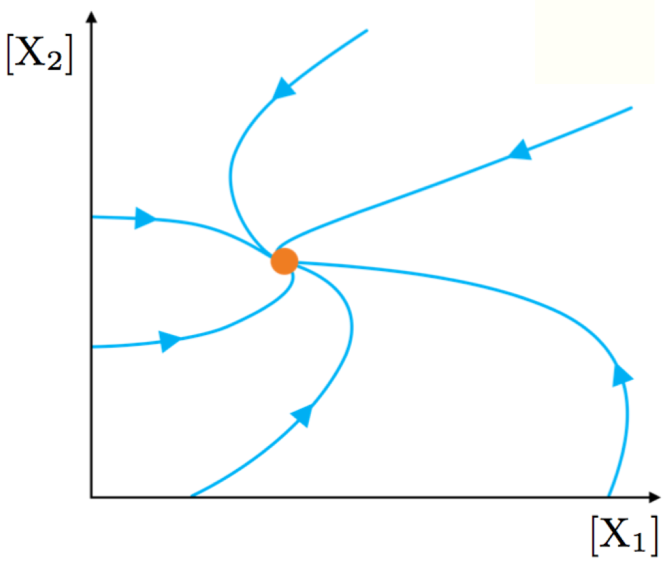
$$\begin{aligned} \frac{dx_1}{dt} &= k_1 - k_3 x_1 x_2 \\ \frac{dx_2}{dt} &= k_2 x_1 - k_3 x_1 x_2 \end{aligned}$$

Chemical reaction networks and polynomial dynamical systems



$$\varnothing \xrightarrow{0.7} X_1 \xrightarrow{1} X_1 + X_2 \xrightarrow{1} \varnothing$$

Chemical reaction networks and polynomial dynamical systems



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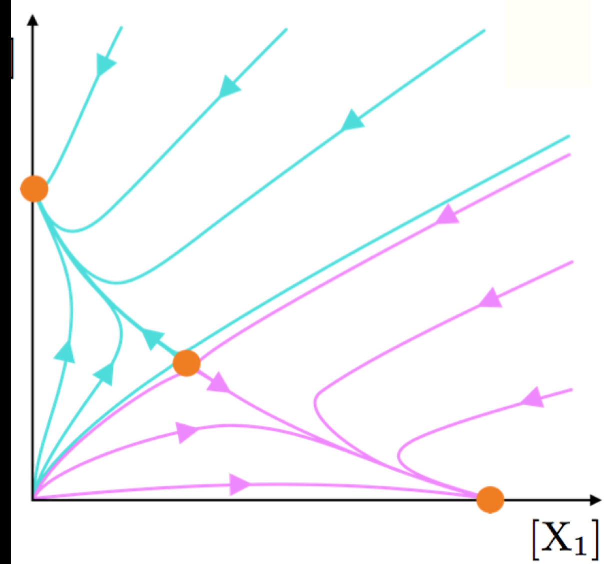
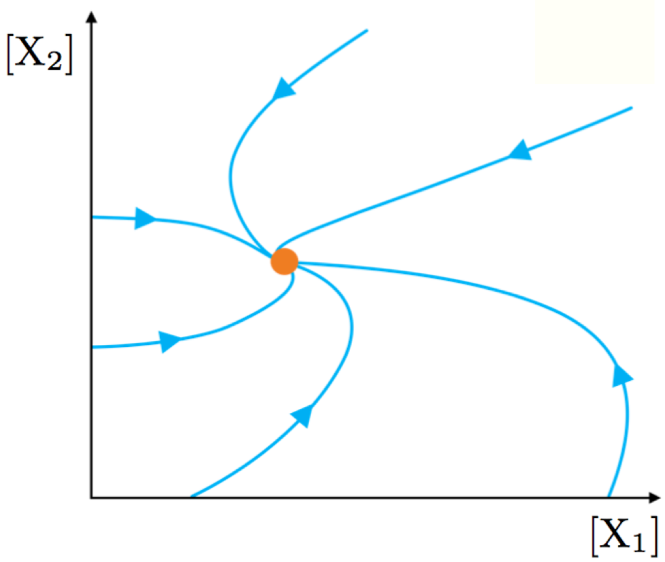


$$X_1 + X_2 \xrightarrow{1} X_1 \underset{1}{\overset{3}{\rightleftharpoons}} 2X_1$$

$$X_1 + X_2 \xrightarrow{2} X_2 \underset{1}{\overset{2}{\rightleftharpoons}} 2X_2$$

Chemical reaction networks and polynomial dynamical systems



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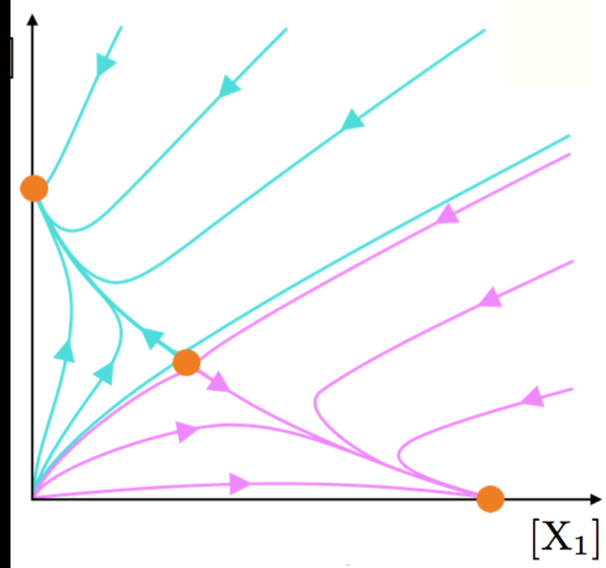

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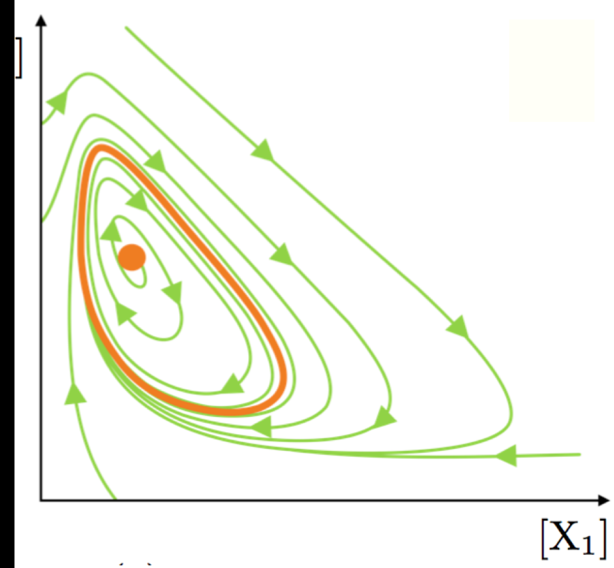
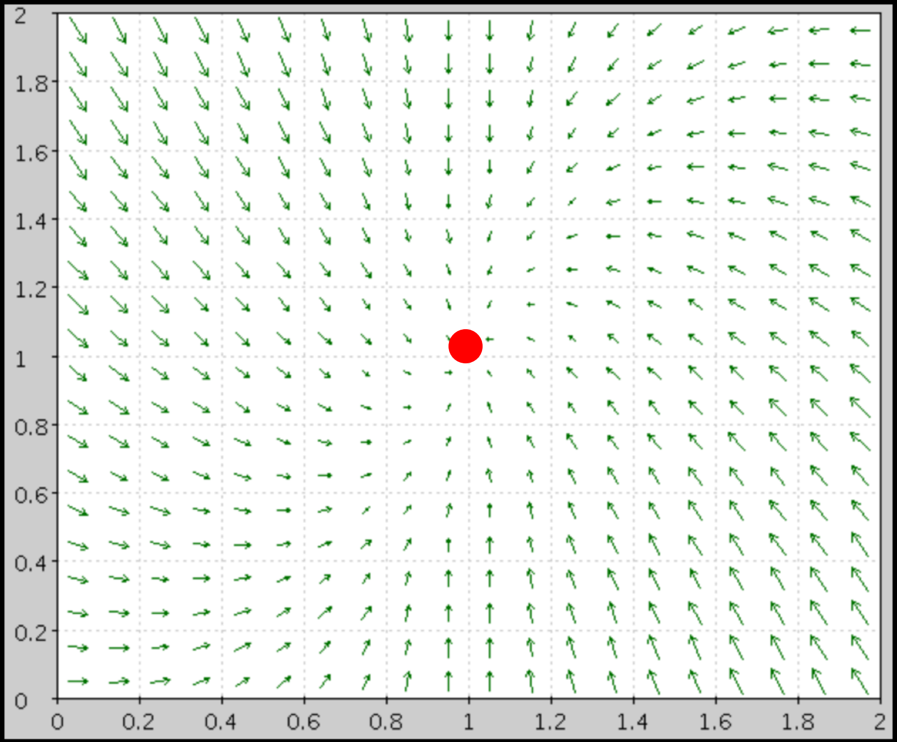


$$\varnothing \rightleftharpoons X_1 \rightleftharpoons X_2 \rightleftharpoons \varnothing$$

$$2X_1 + X_2 \rightleftharpoons 3X_1$$

But, many polynomial systems have very stable dynamics:

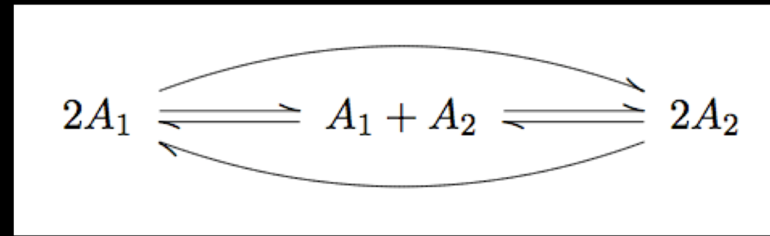
***Global Attractor Conjecture:** complex balanced systems are globally stable (Horn, 1974).*



Why? By analogy to Boltzmann's H-theorem.

Mass-action kinetics

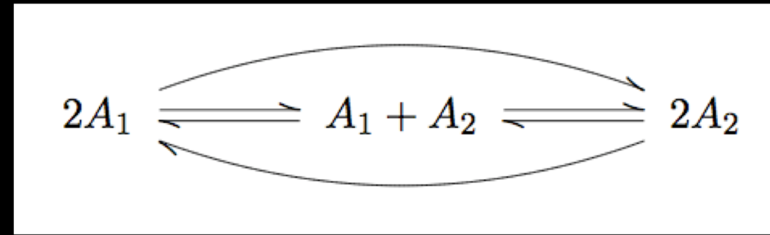
Mass-action kinetics



$$\frac{dx_1}{dt} = -k_1 x_1^2 + k_2 x_1 x_2 - k_3 x_1 x_2 + k_4 x_2^2 - 2k_5 x_1^2 + 2k_6 x_2^2$$

$$\frac{dx_2}{dt} = k_1 x_1^2 - k_2 x_1 x_2 + k_3 x_1 x_2 - k_4 x_2^2 + 2k_5 x_1^2 - 2k_6 x_2^2$$

Mass-action kinetics



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$$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = k_1x_1^2\begin{bmatrix} -1 \\ 1 \end{bmatrix} + k_2x_1x_2\begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_3x_1x_2\begin{bmatrix} -1 \\ 1 \end{bmatrix}$$
$$+k_4x_2^2\begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_5x_1^2\begin{bmatrix} -2 \\ 2 \end{bmatrix} + k_6x_2^2\begin{bmatrix} 2 \\ -2 \end{bmatrix}$$

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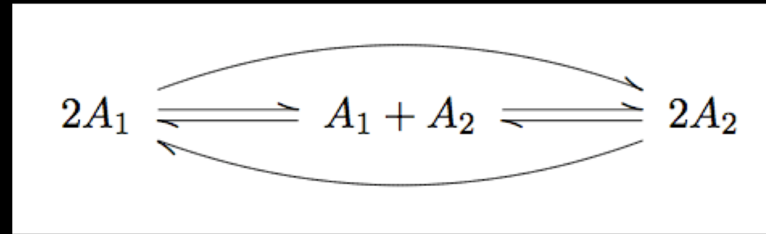

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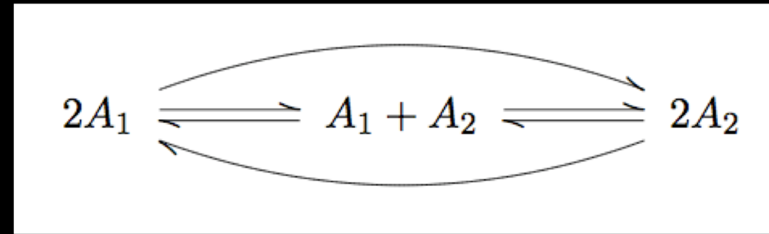

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$$\frac{dx}{dt} = \sum_{i=1}^{n} k_i x^{y_i} (y_i' - y_i)$$

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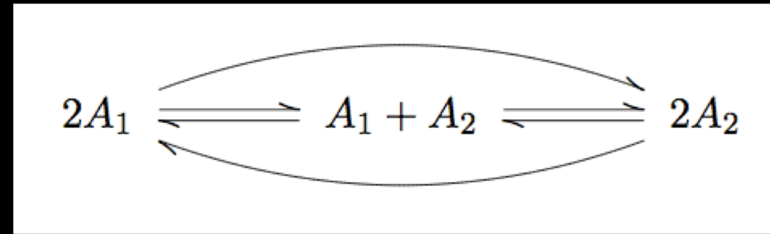

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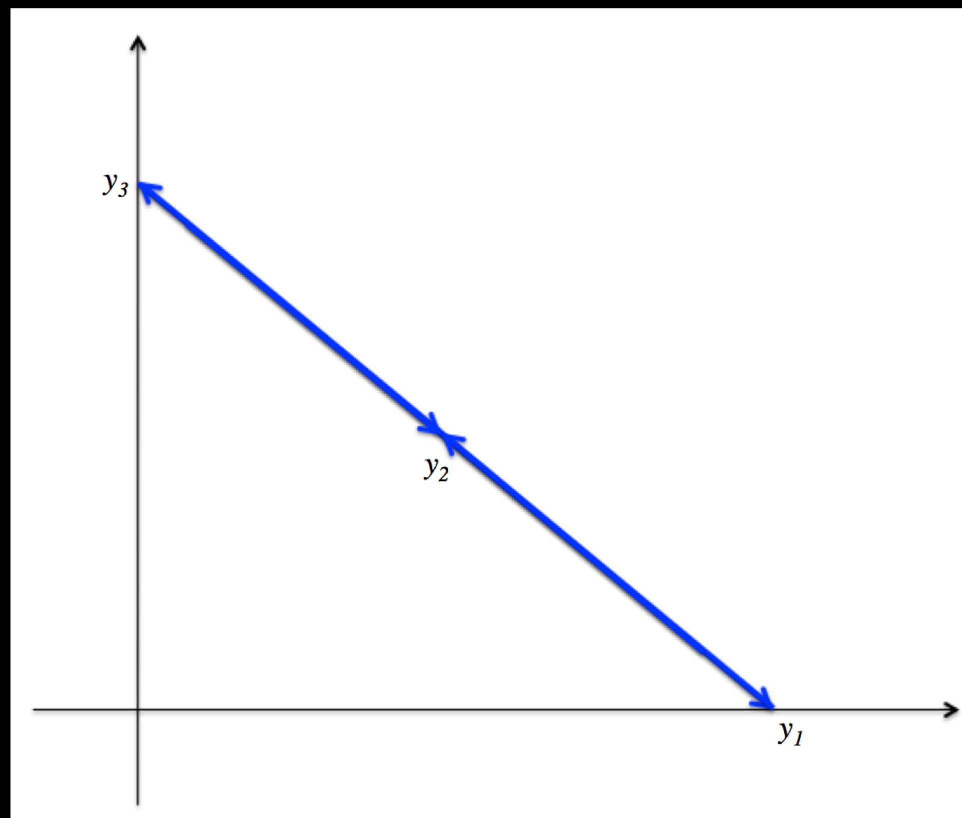

Complex-balanced polynomial dynamical systems

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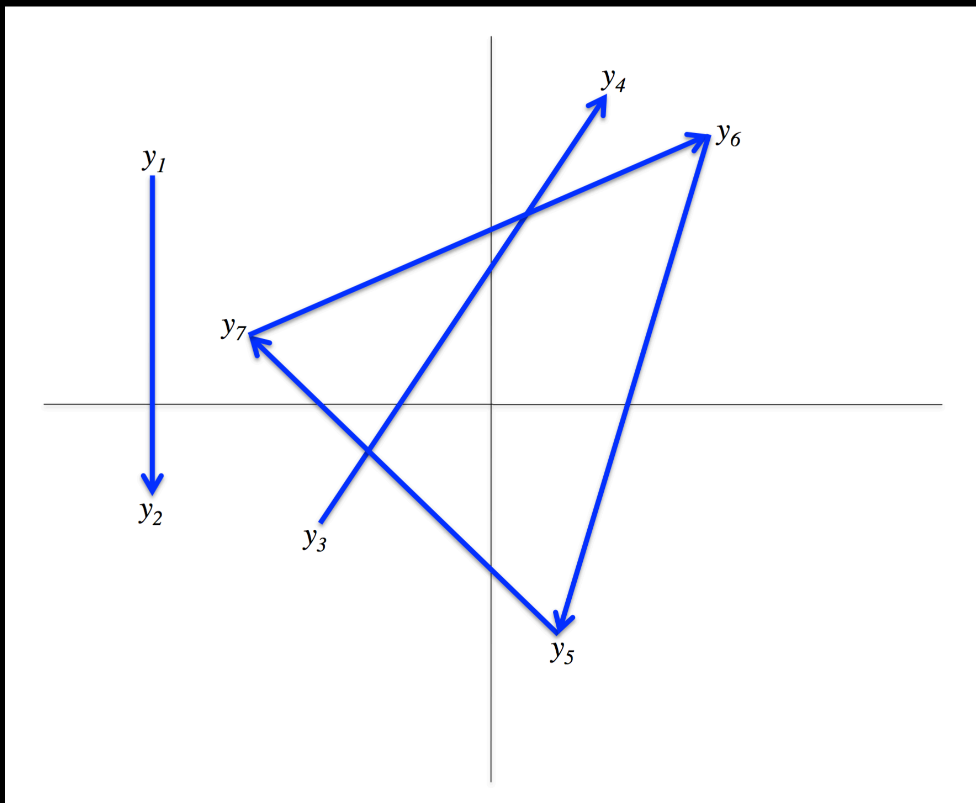
Any polynomial dynamical system can be represented by an "Euclidean embedded graph"



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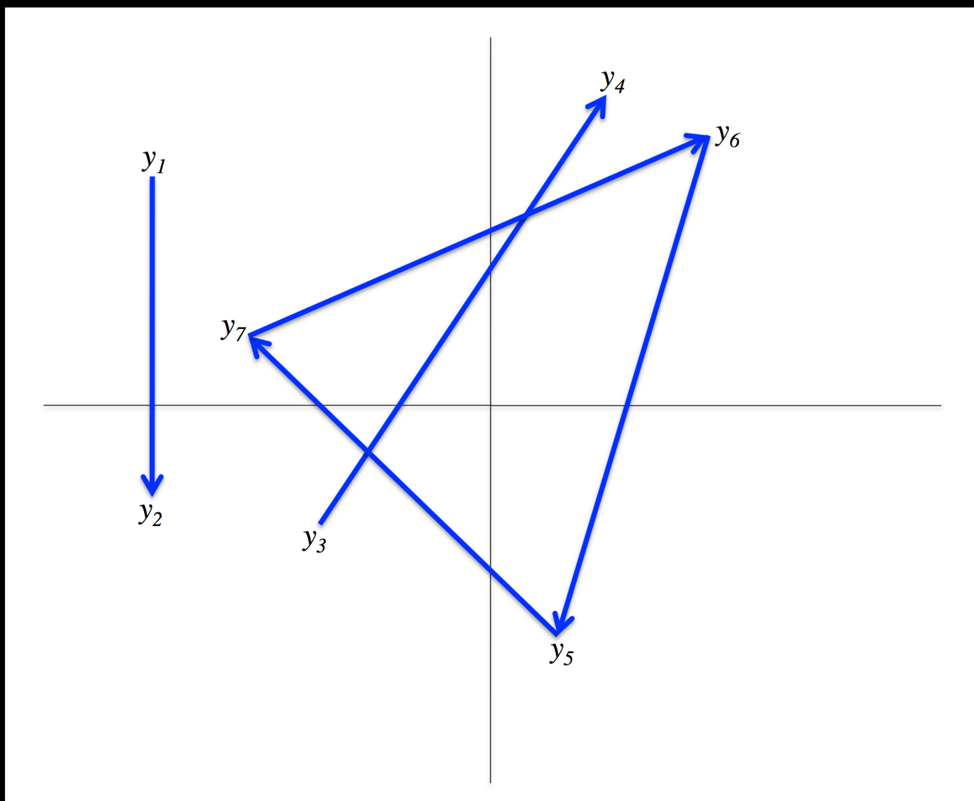

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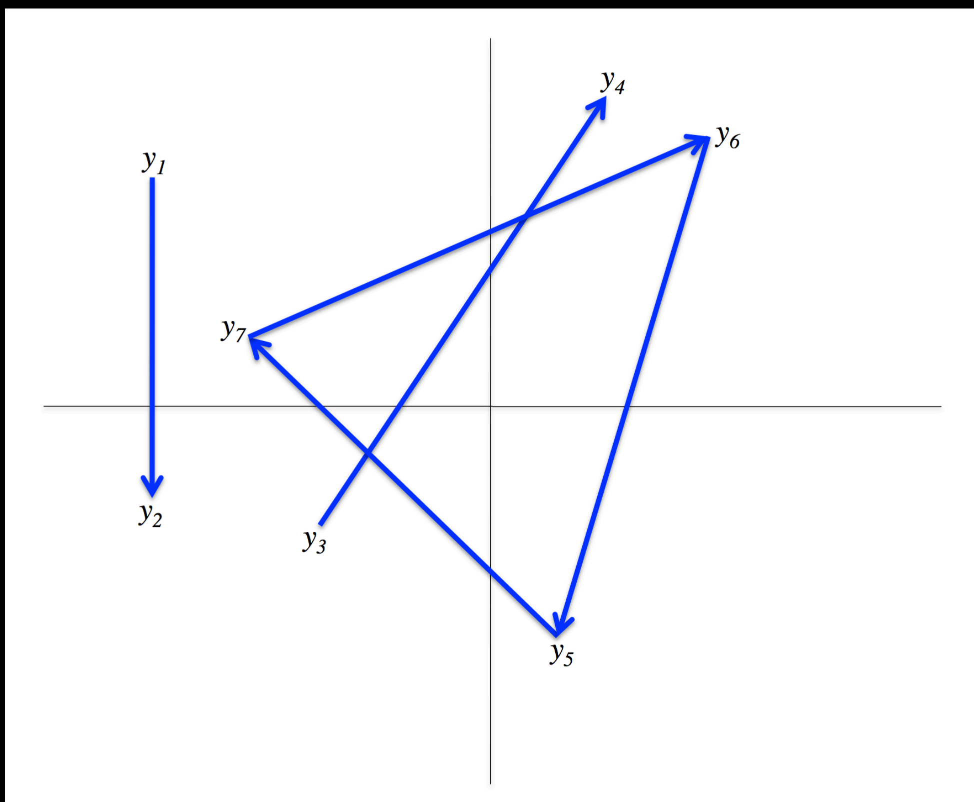

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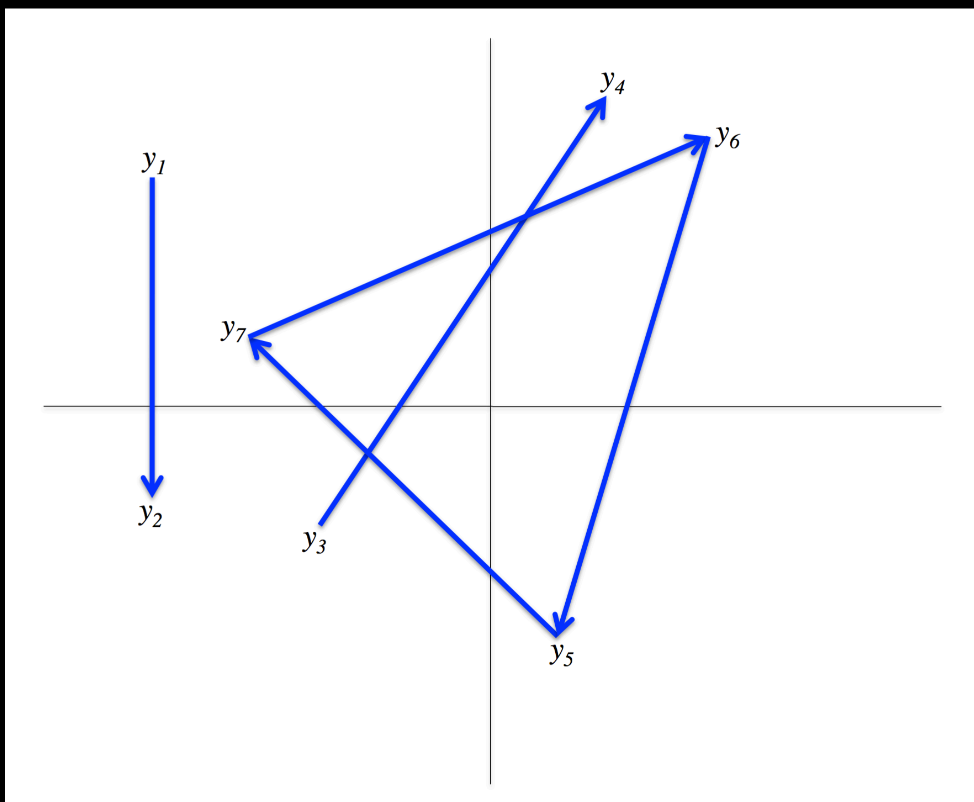

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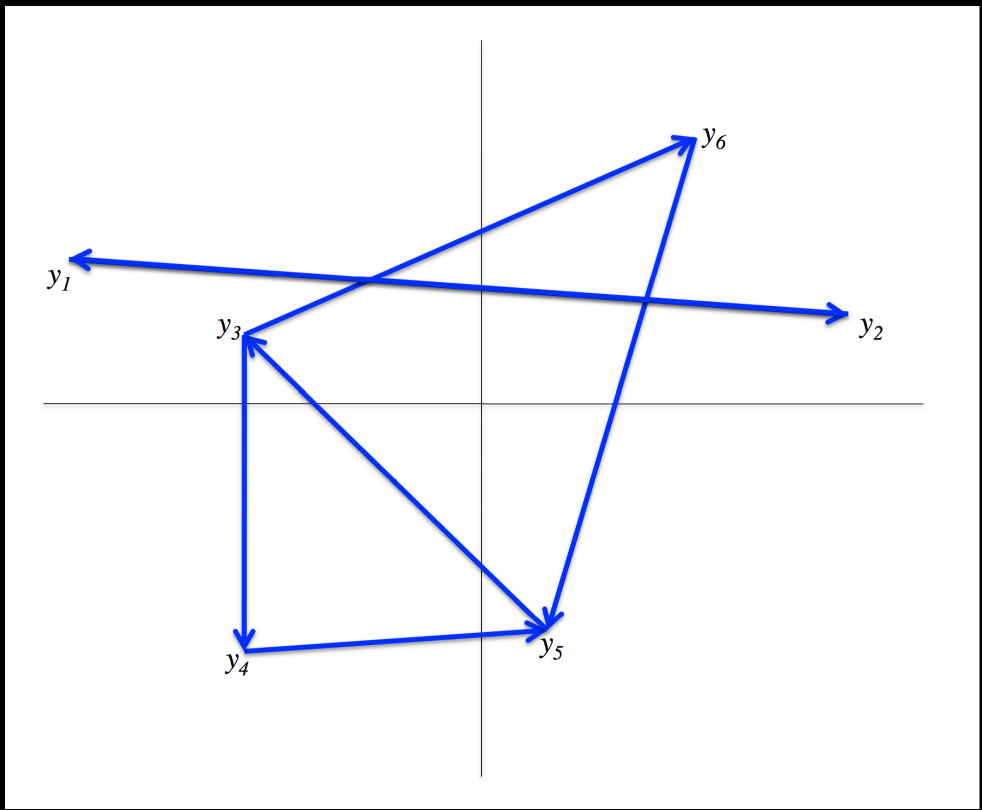

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Theorem. *If a reaction system is complex balanced then there exists a strict Lyapunov function within each linear invariant subspace.*

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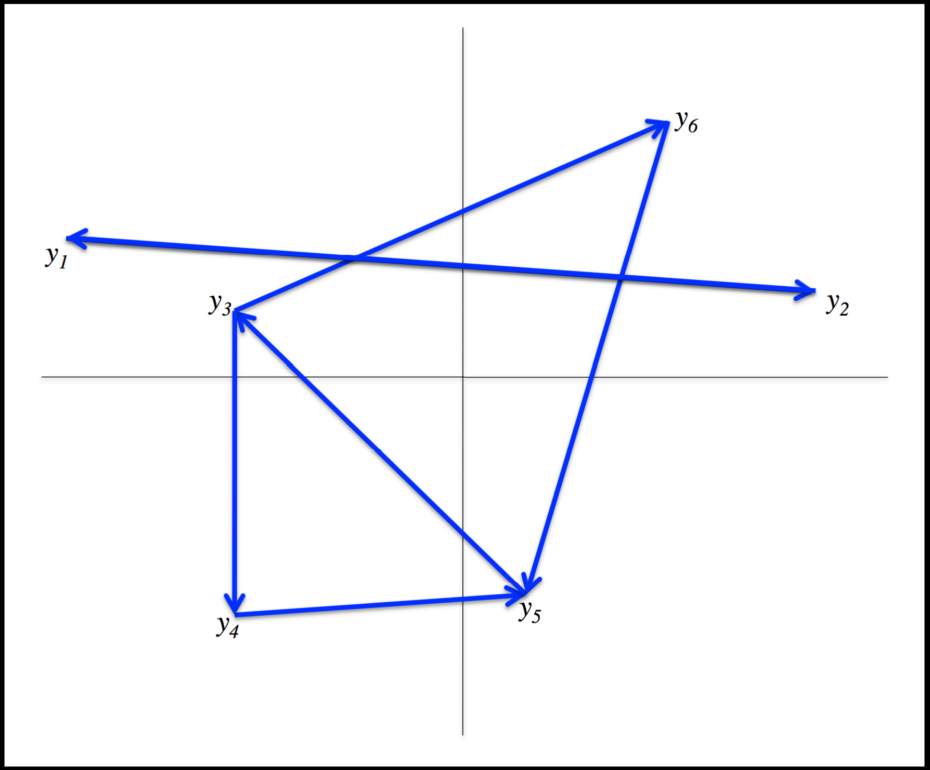

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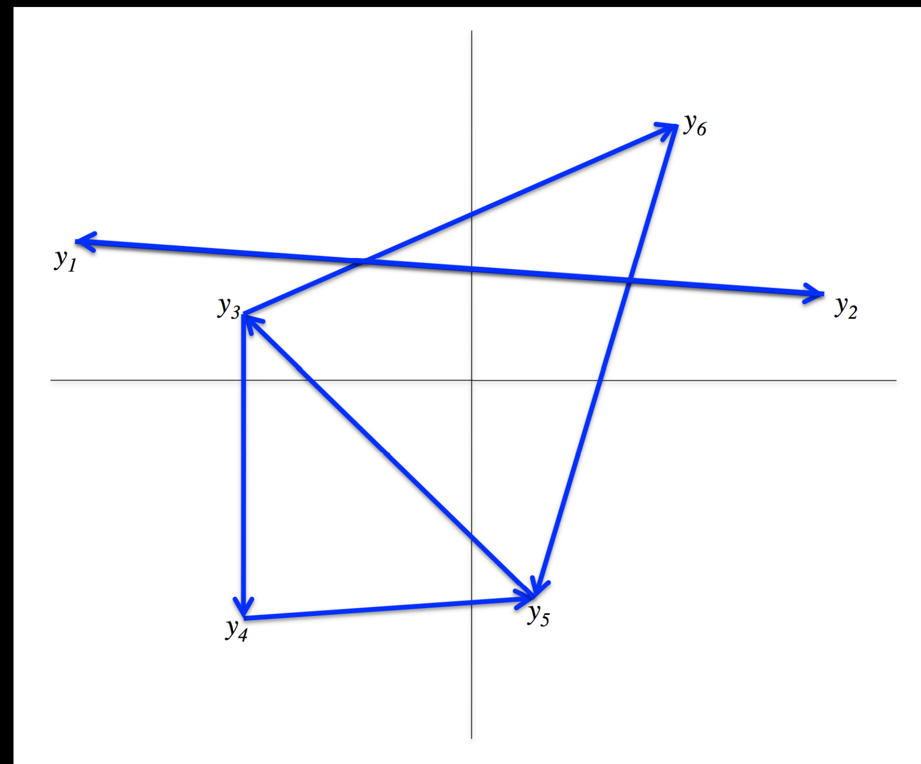

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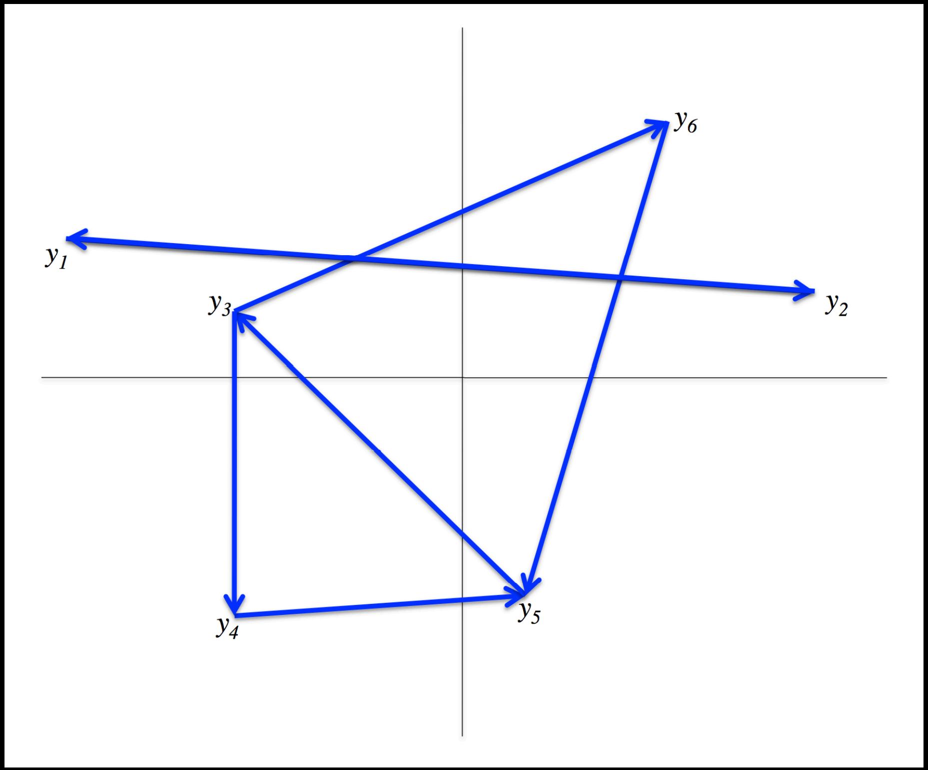

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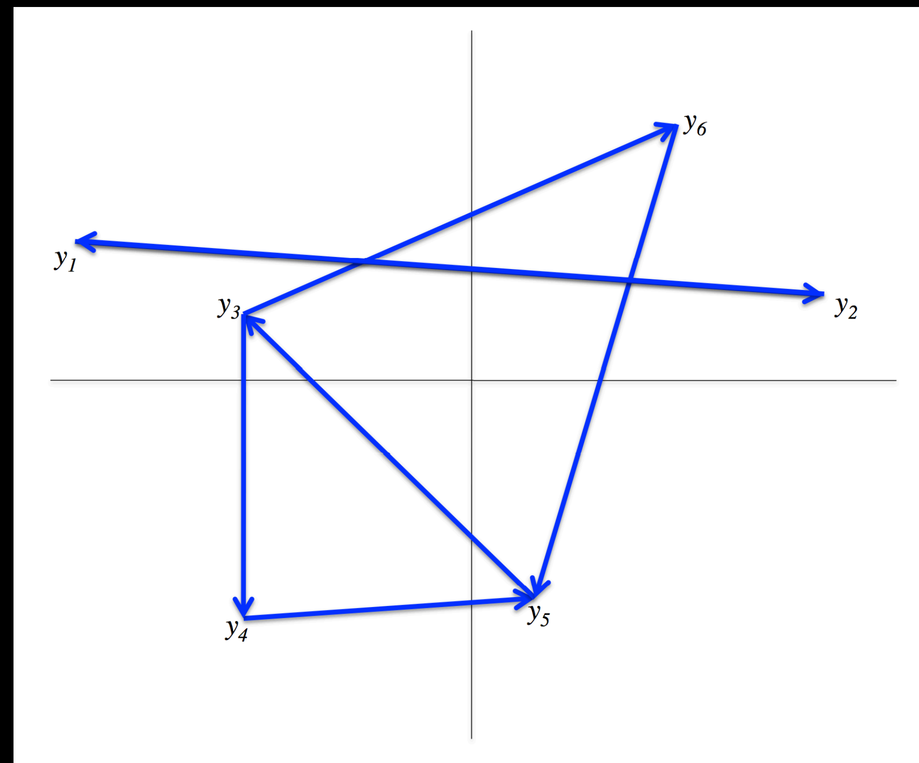

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$$L(\boldsymbol{x}) = \sum_{j=1}^{n} x_i (\ln x_i - \ln x_i^* - 1)$$

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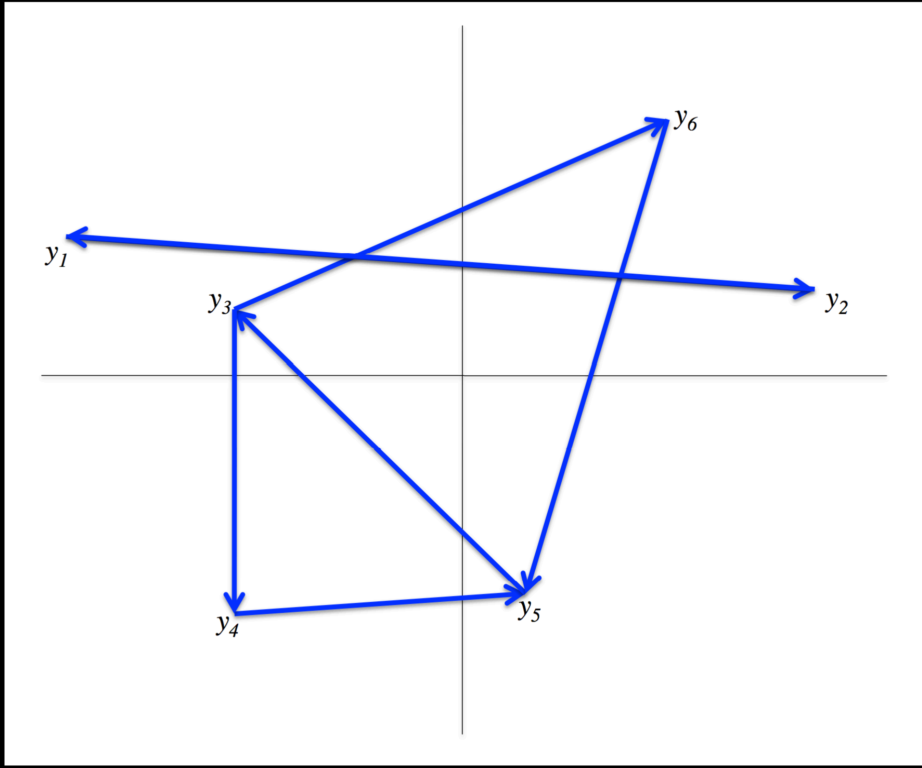

Conjecture (Horn 1974). If a system is complex balanced then it has a globally attracting point within each linear invariant subspace.

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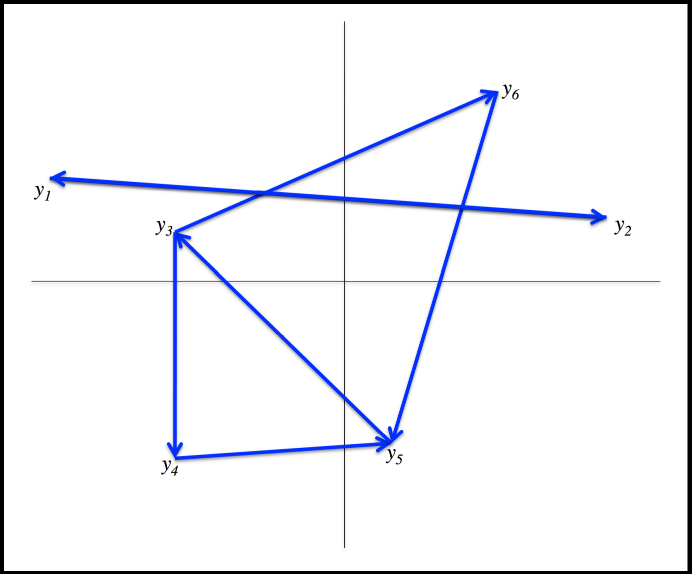

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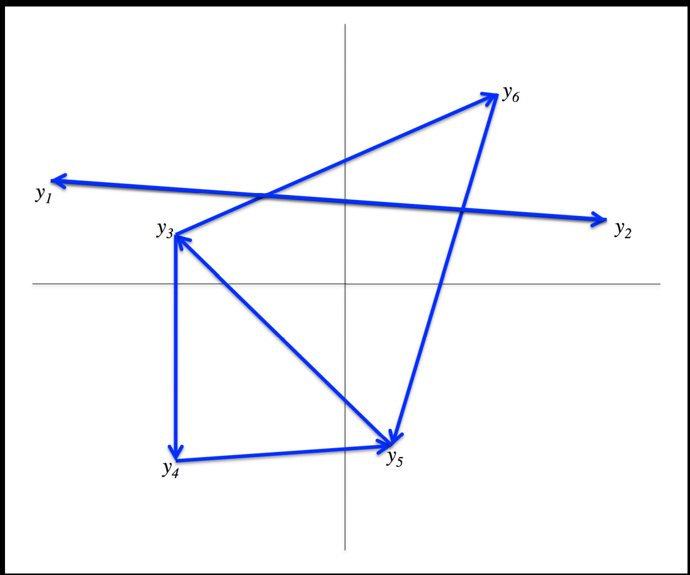

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Remark 1: if the graph G is weakly reversible and embedding is in "general position" then the system is guaranteed to be complex balanced (by the deficiency zero theorem).

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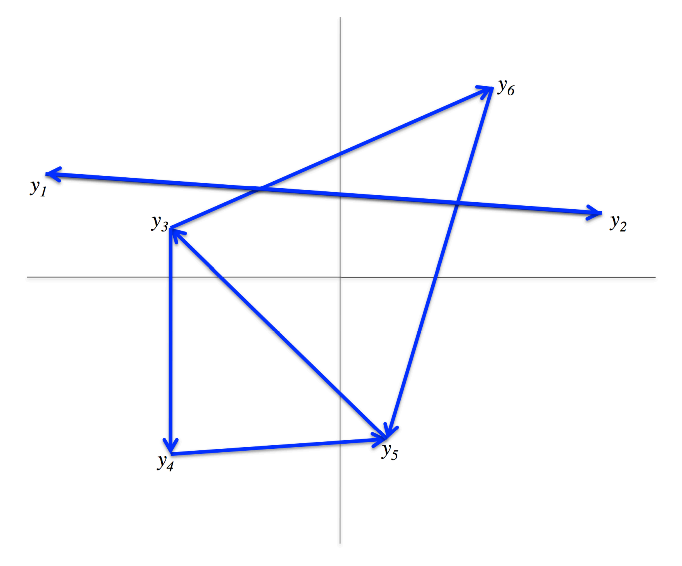

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Remark 1: if the graph G is weakly reversible and embedding is in "general position" then the system is guaranteed to be complex balanced (by the deficiency zero theorem).

Remark 2: The "Extended Permanence Conjecture" says that if the graph G is weakly reversible then the system is variable-k permanent.

Timeline

Timeline

1876: Boltzmann, entropy, the H-theorem

1901: Wegscheider, the Wegscheider paradox

1930: Onsager, the reciprocal relations

1962: Wei and Prater, linear systems, global strict Lyapunov function

1967: Shear, reversible systems with unique steady state, global strict Lyapunov function

1968: Higgins, points out Shear's error

1972: Horn and Jackson, complex balanced systems, global strict Lyapunov function

1972: Horn and Feinberg, deficiency zero theorem

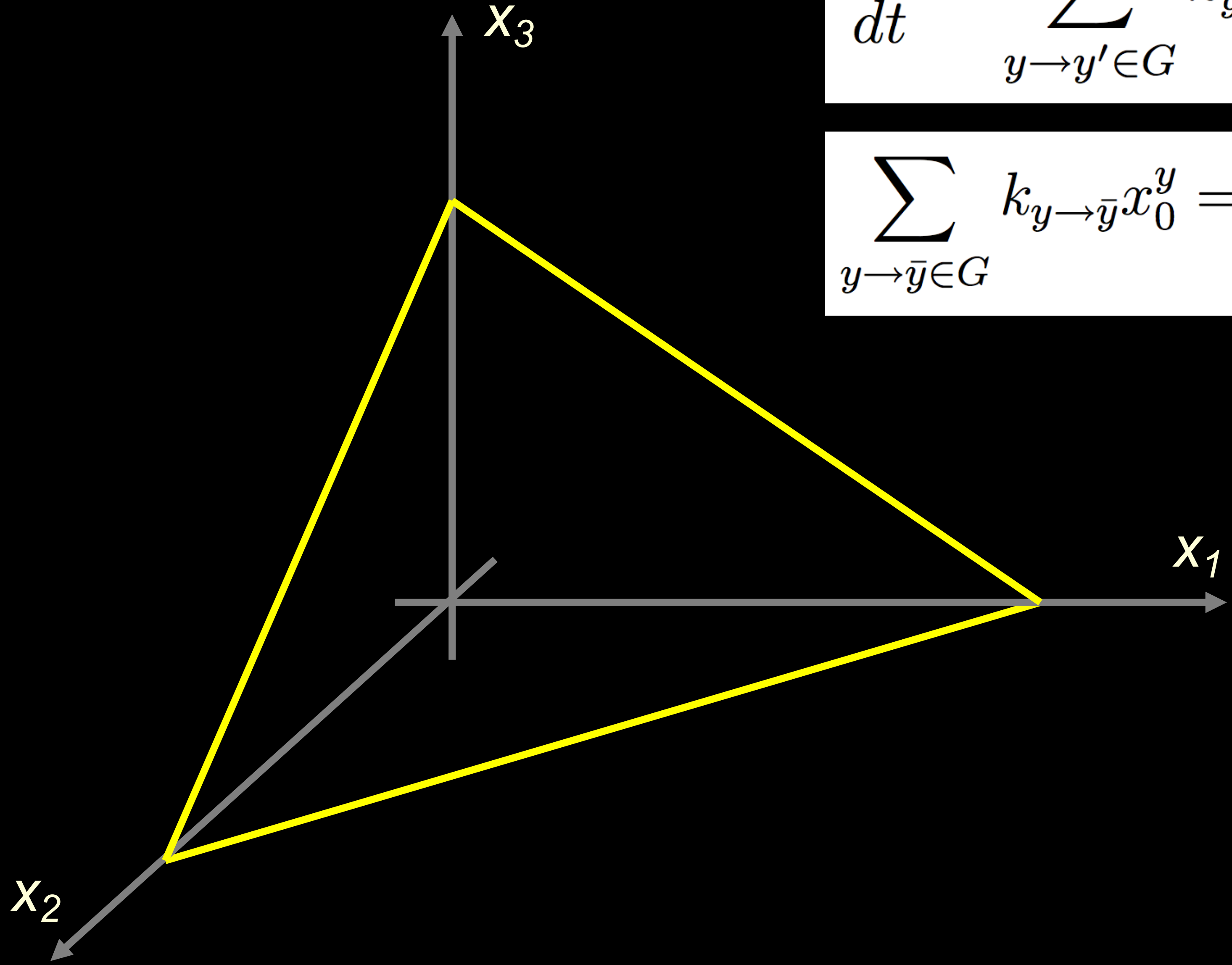
1972: Kurtz, connection between stochastic and deterministic mass-action kinetics

1974: Horn, the Global Attractor Conjecture

The Global Attractor Conjecture

$$\frac{dx}{dt} = \sum_{y \to y' \in G} k_{y \to y'} x^y (y' - y)$$

$$\sum_{y \to \bar{y} \in G} k_{y \to \bar{y}} x_0^y = \sum_{\bar{y} \to y \in G} k_{\bar{y} \to y} x_0^{\bar{y}}$$



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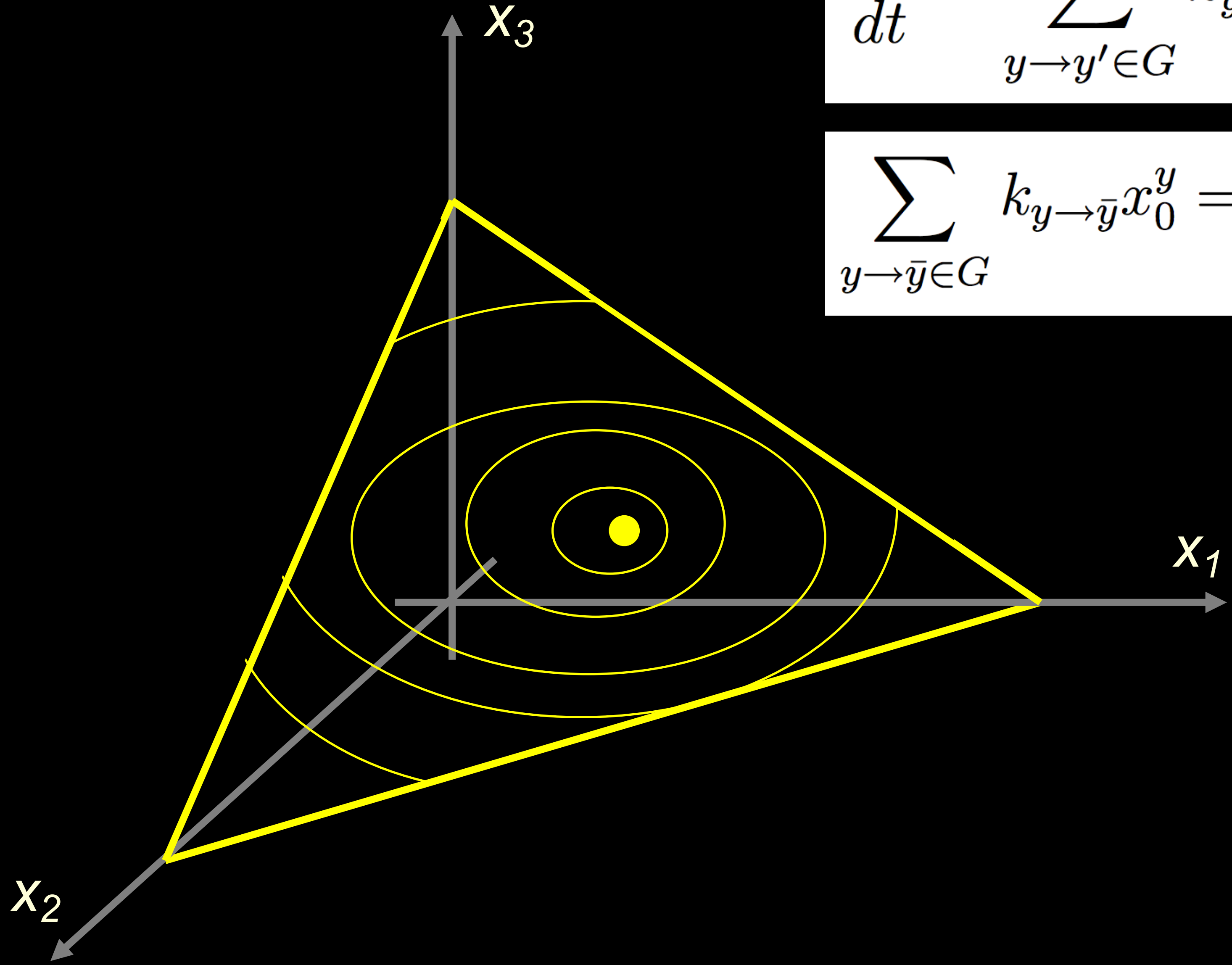

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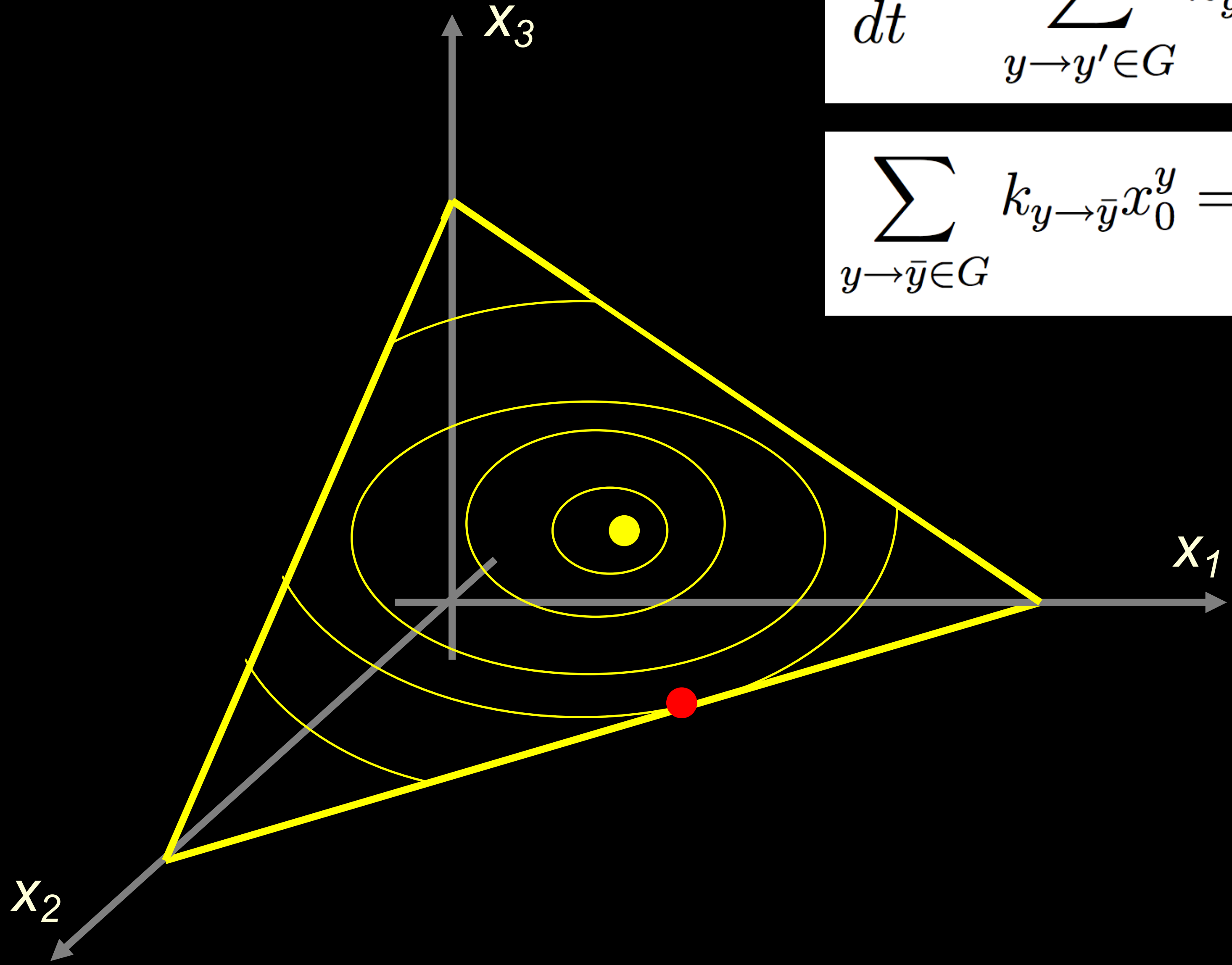

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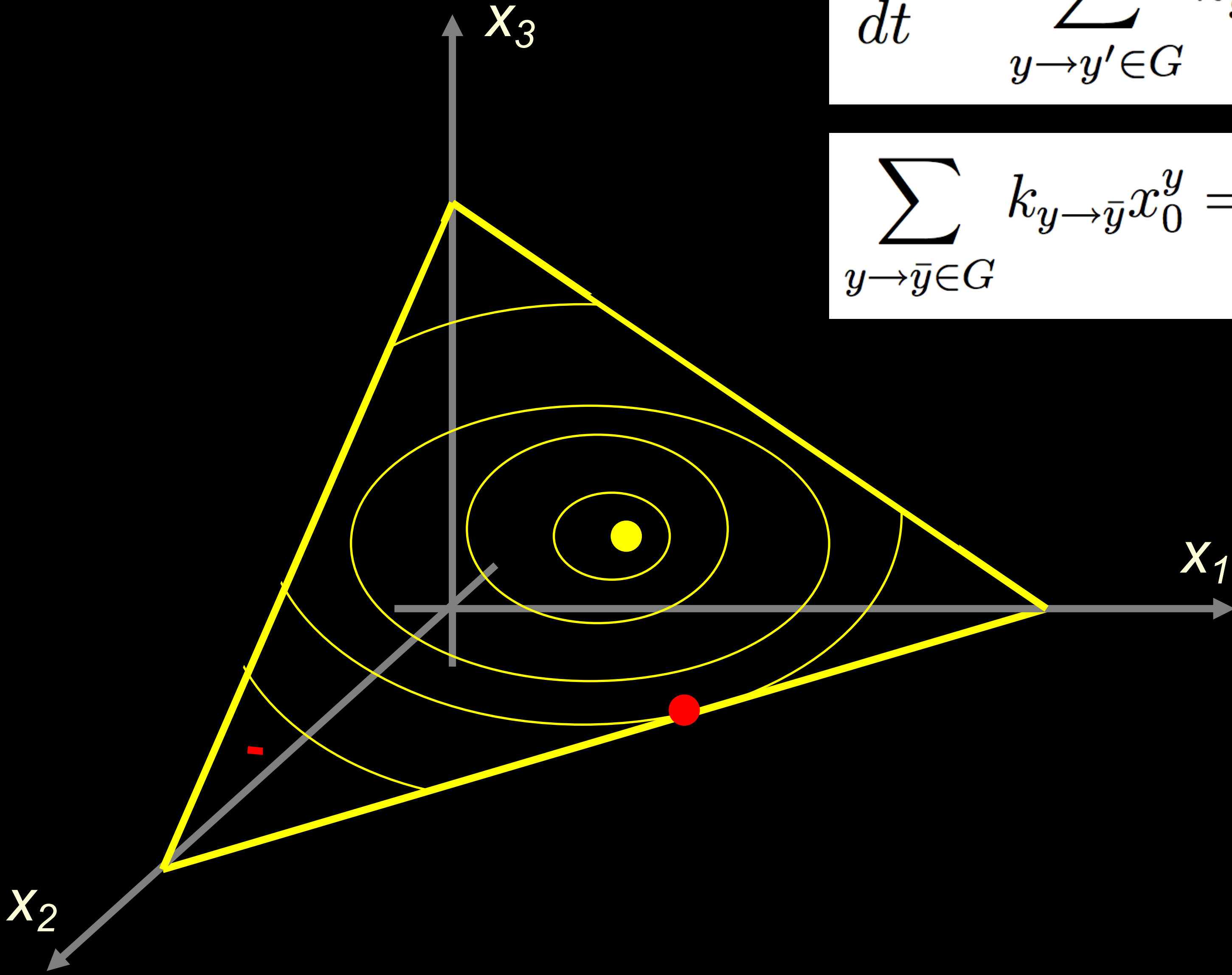

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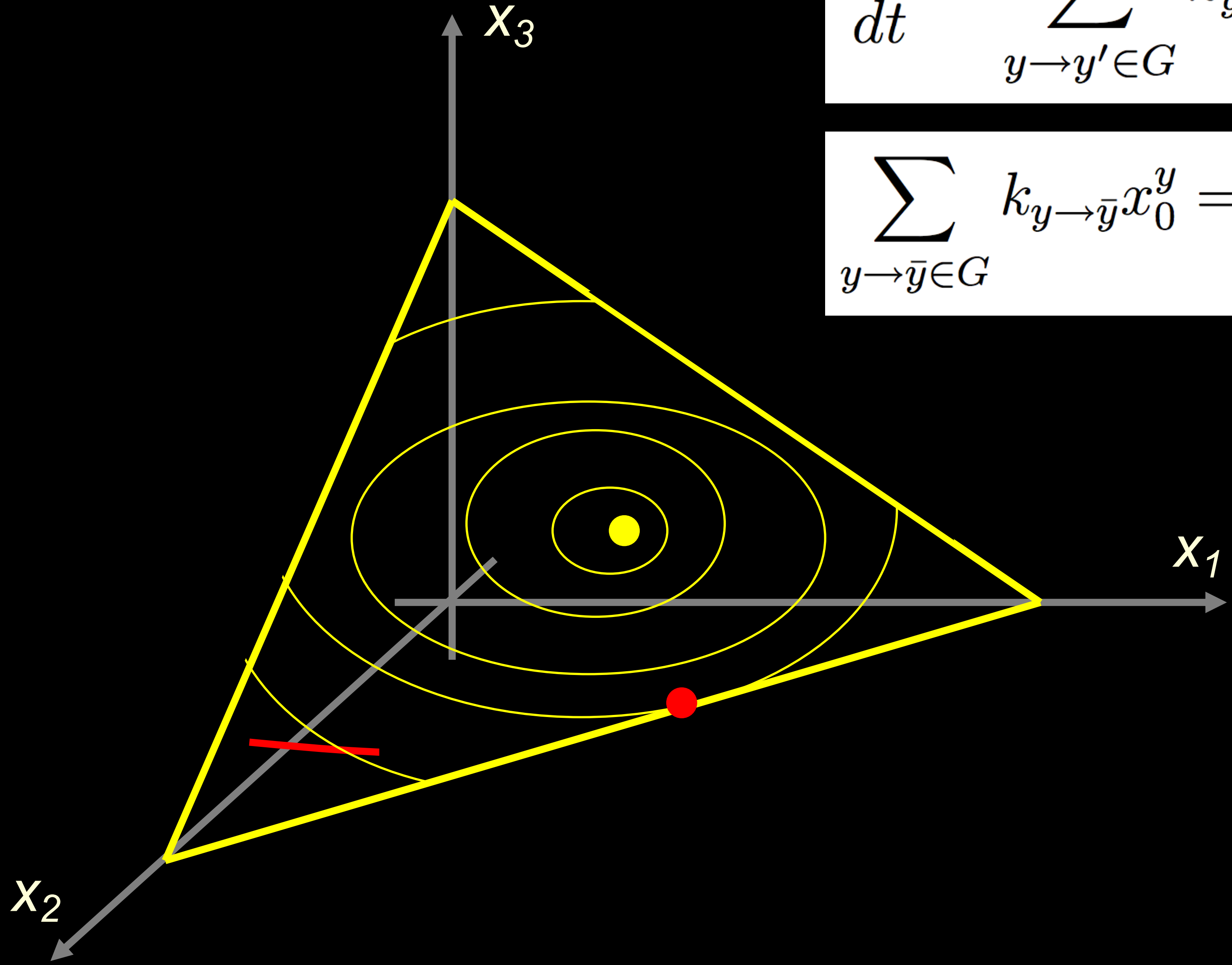

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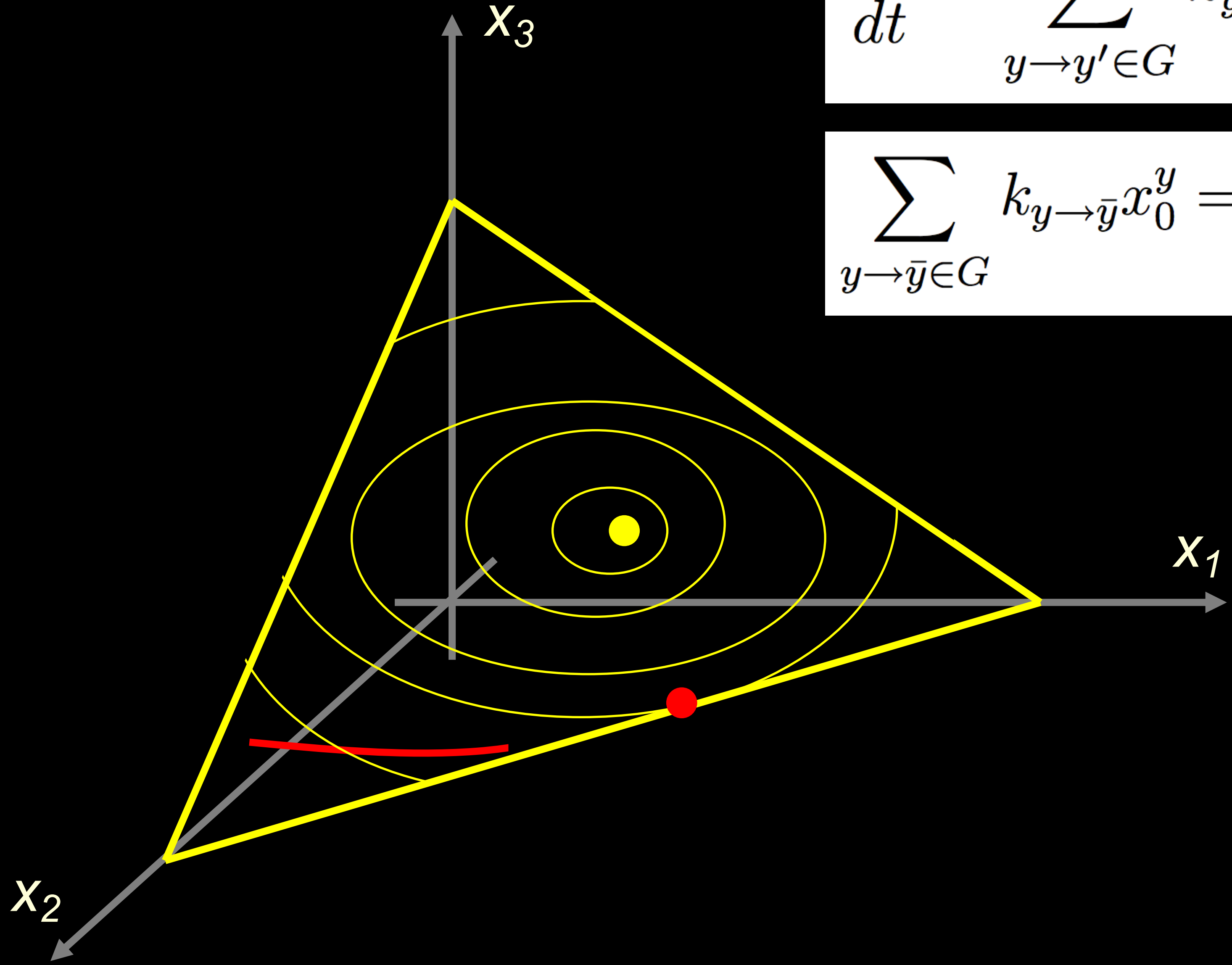

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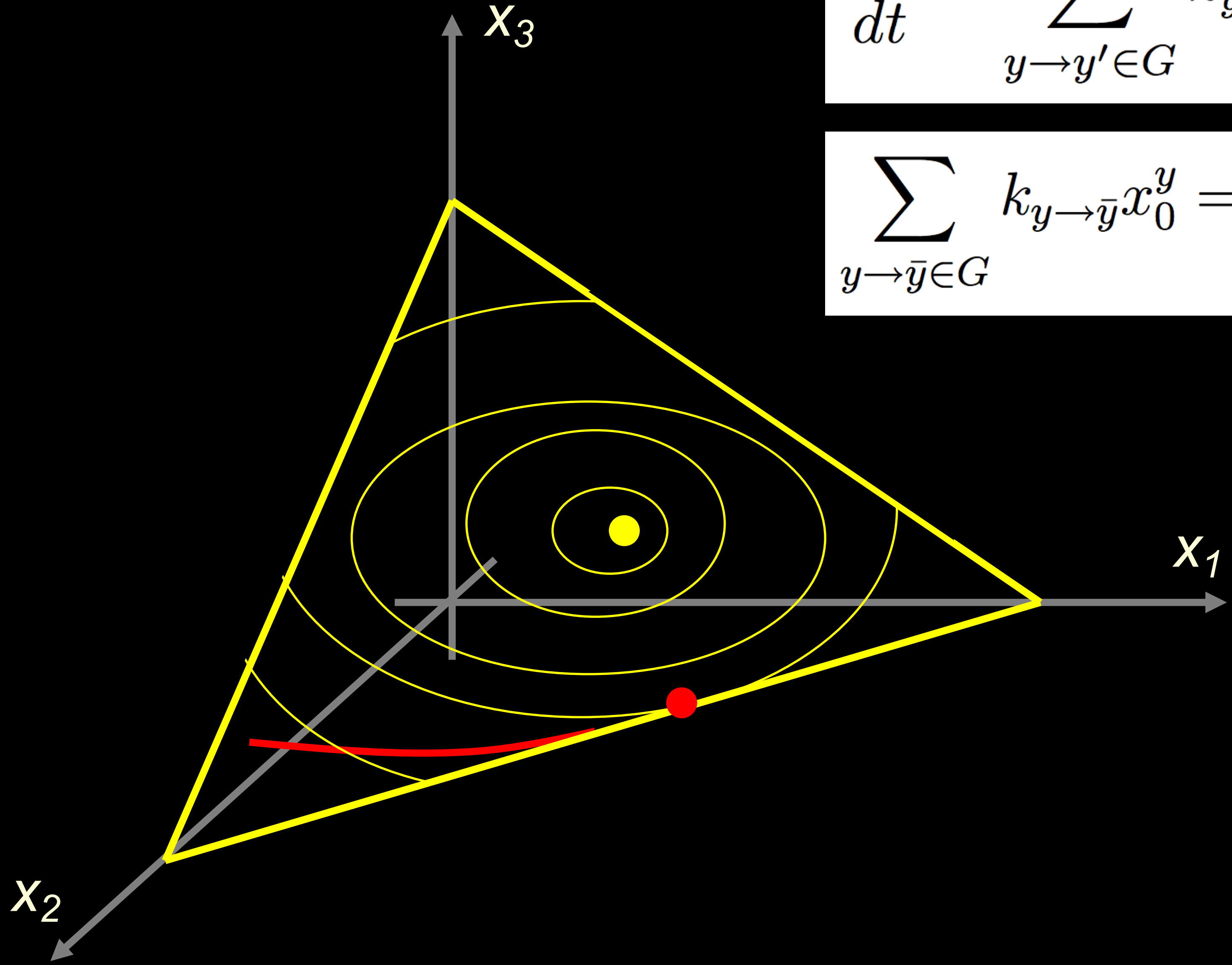

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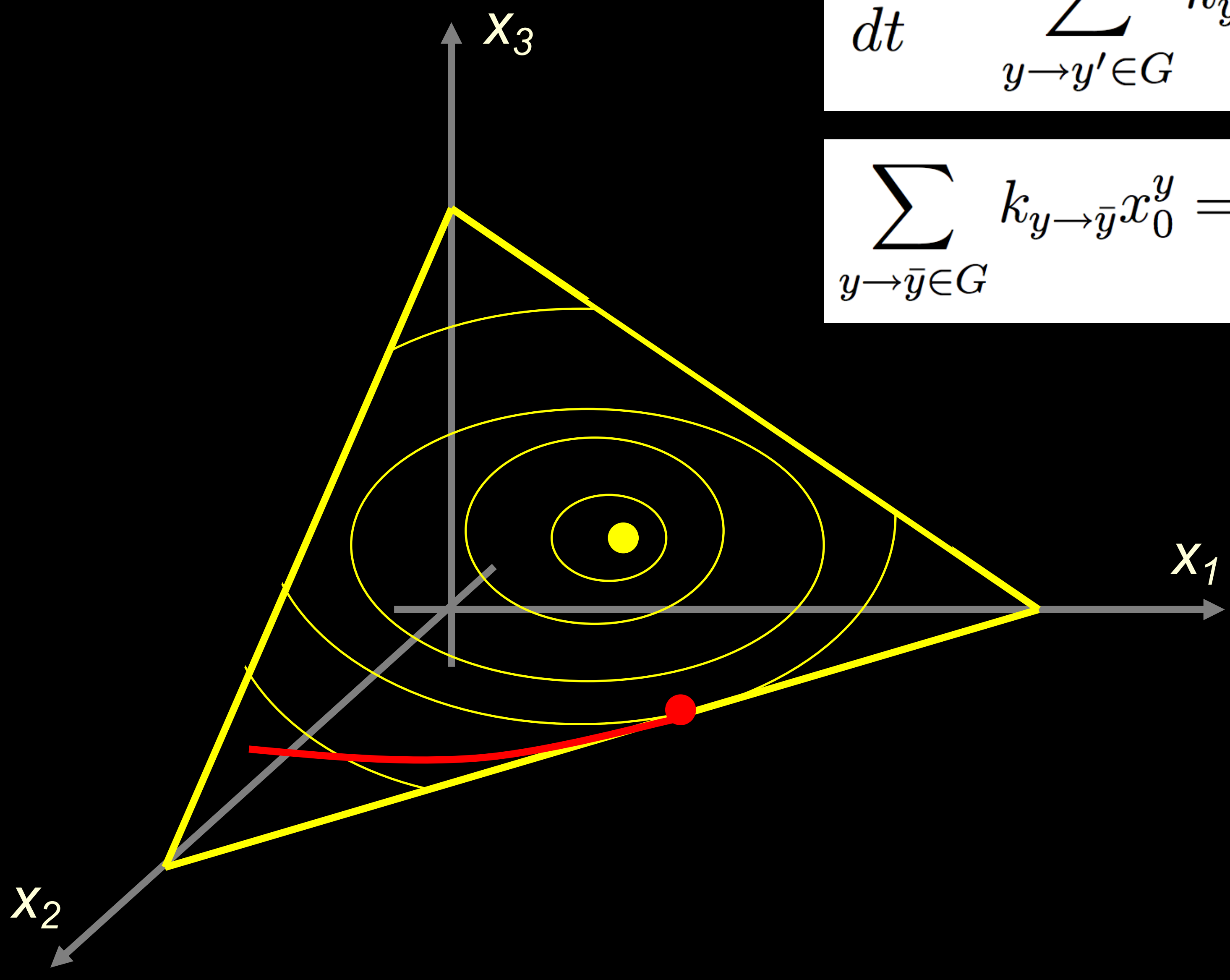

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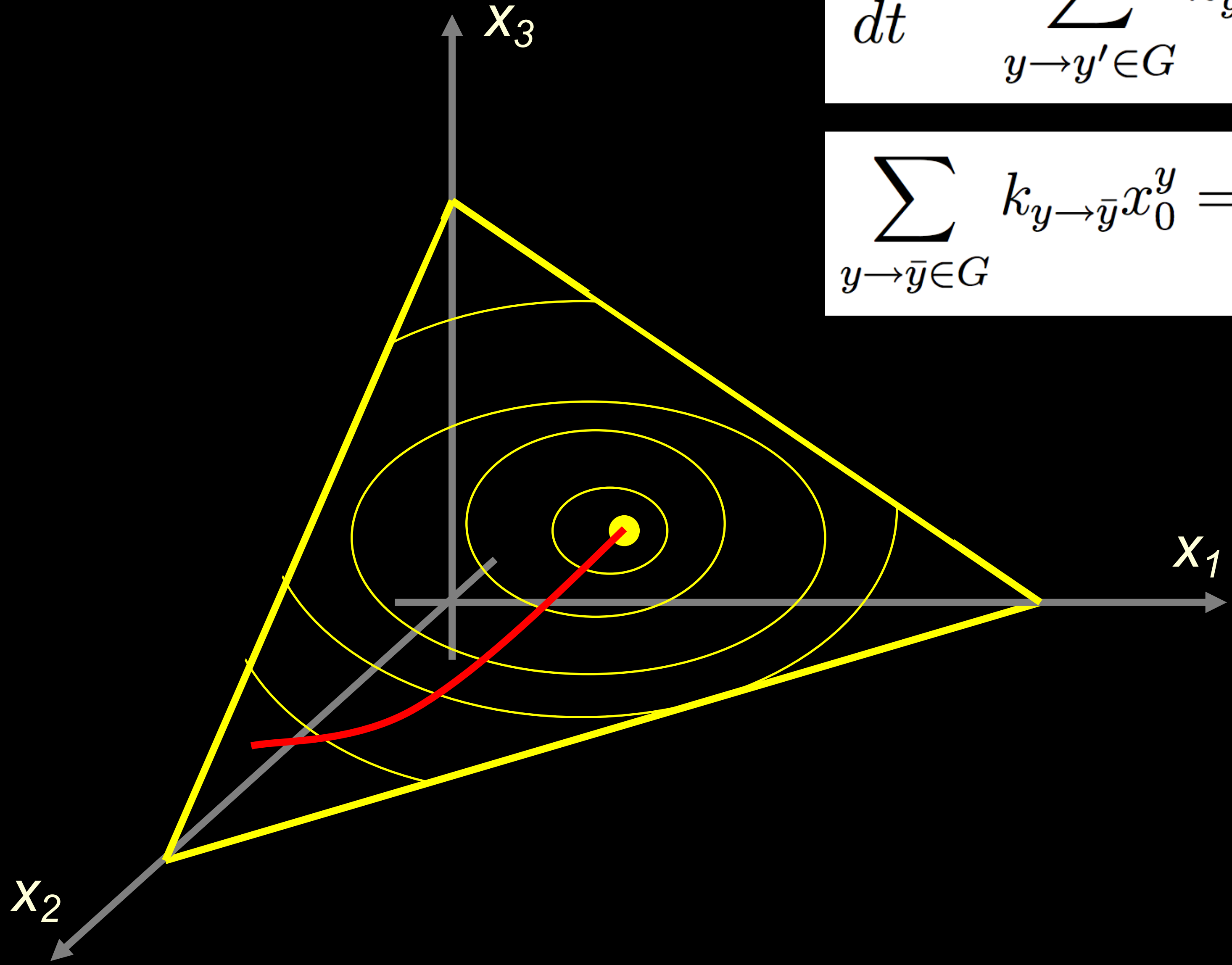


Global Attractor Conjecture: towards an "algebraic thermodynamics"

1972: Horn and Jackson, complex balanced systems, global strict Lyapunov function

1972: Horn and Feinberg, deficiency zero theorem

1990s, early 2000s: Siegel, Sontag, boundary equilibria, global stability

2007: Craciun, Dickenstein, Shiu, Sturmfels, proof of special case of 2D global attractor conjecture

2009: Anderson and Shiu, proof of 2D global attractor conjecture

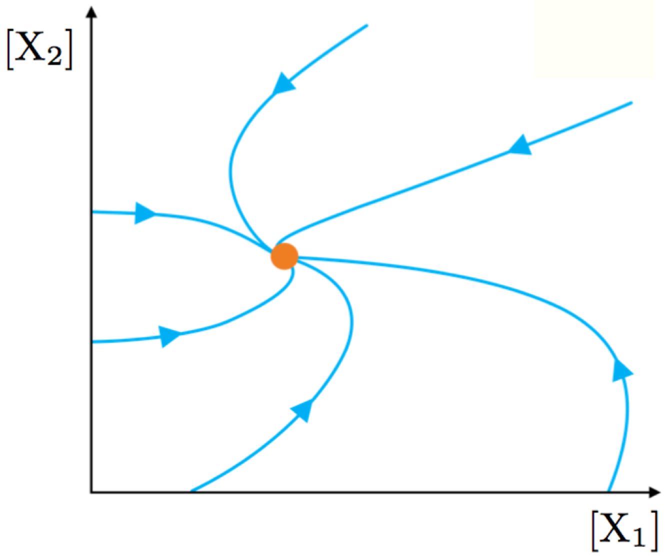
2010: Craciun, Nazarov, Pantea, introduce permanence conjecture, proof of 3D global attractor conjecture

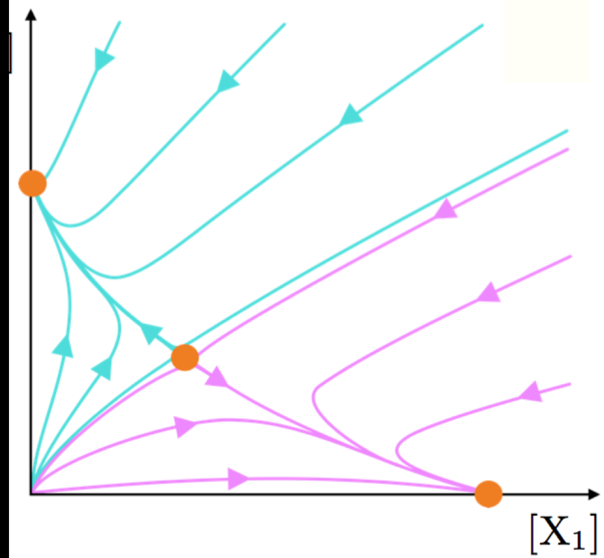
2011: Anderson, proof of global attractor conjecture for single linkage class

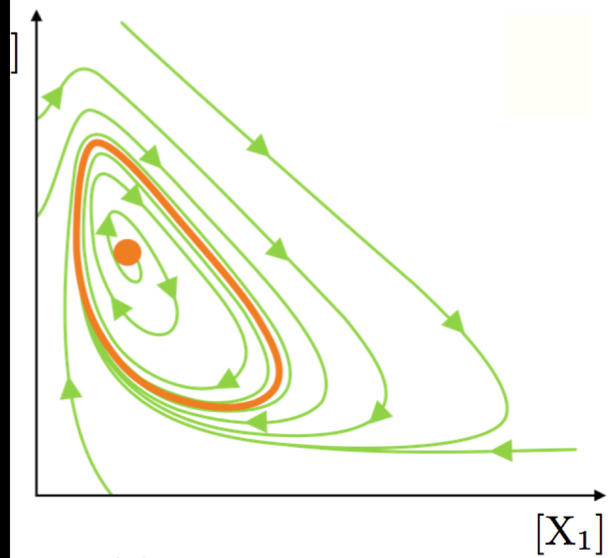
2013: Gopalkrishnan, Miller, Shiu, proof of global attractor conjecture for strongly endotactic networks

The big picture

The big picture







$$\varnothing \xrightarrow{0.7} X_1 \xrightarrow{1} X_1 + X_2 \xrightarrow{1} \varnothing$$

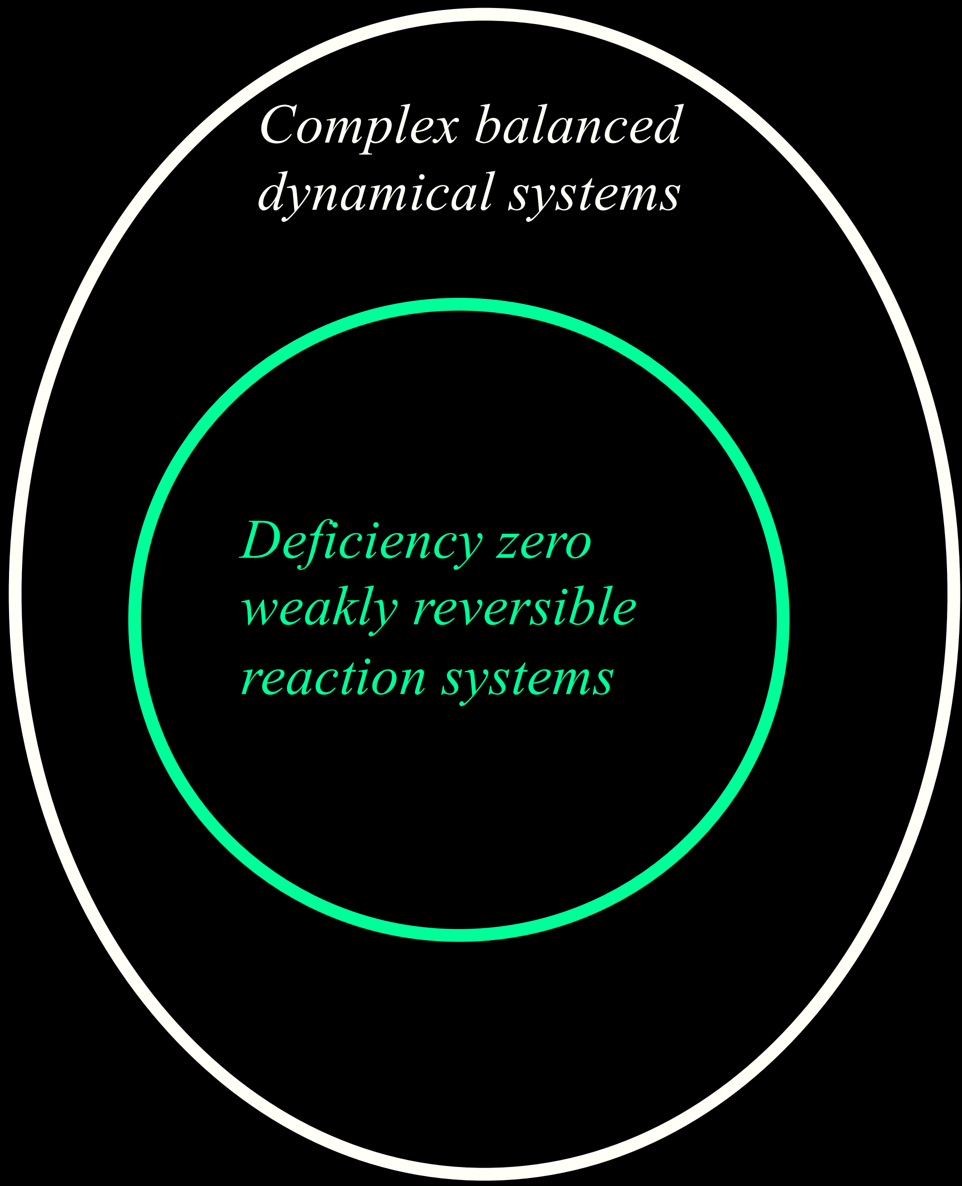
$$X_1 + X_2 \xrightarrow{1} X_1 \underset{1}{\overset{3}{\rightleftharpoons}} 2X_1$$

$$X_1 + X_2 \xrightarrow{2} X_2 \underset{1}{\overset{2}{\rightleftharpoons}} 2X_2$$

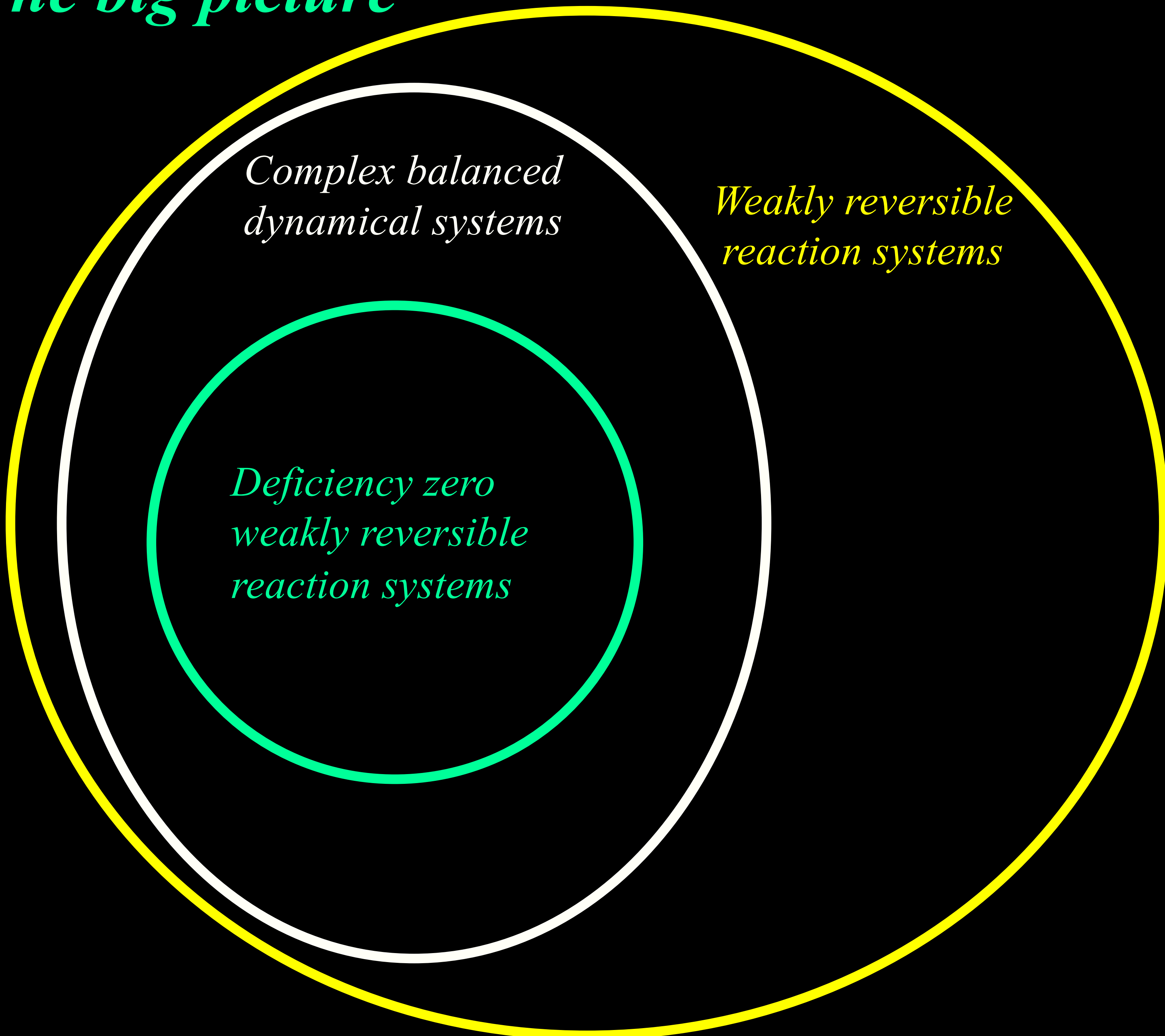
$$\varnothing \rightleftharpoons X_1 \rightleftharpoons X_2 \rightleftharpoons \varnothing$$

$$2X_1 + X_2 \rightleftharpoons 3X_1$$

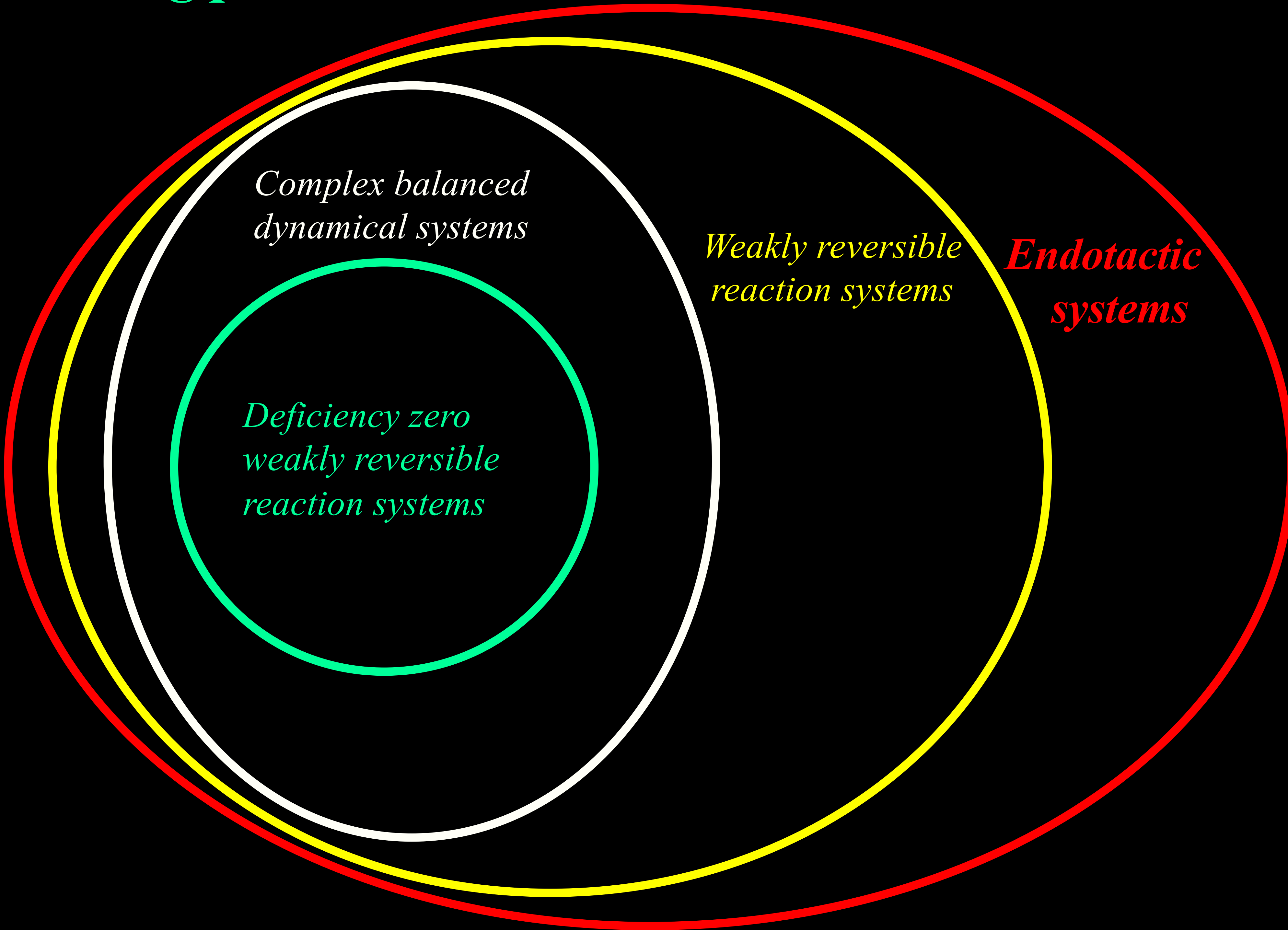
The big picture

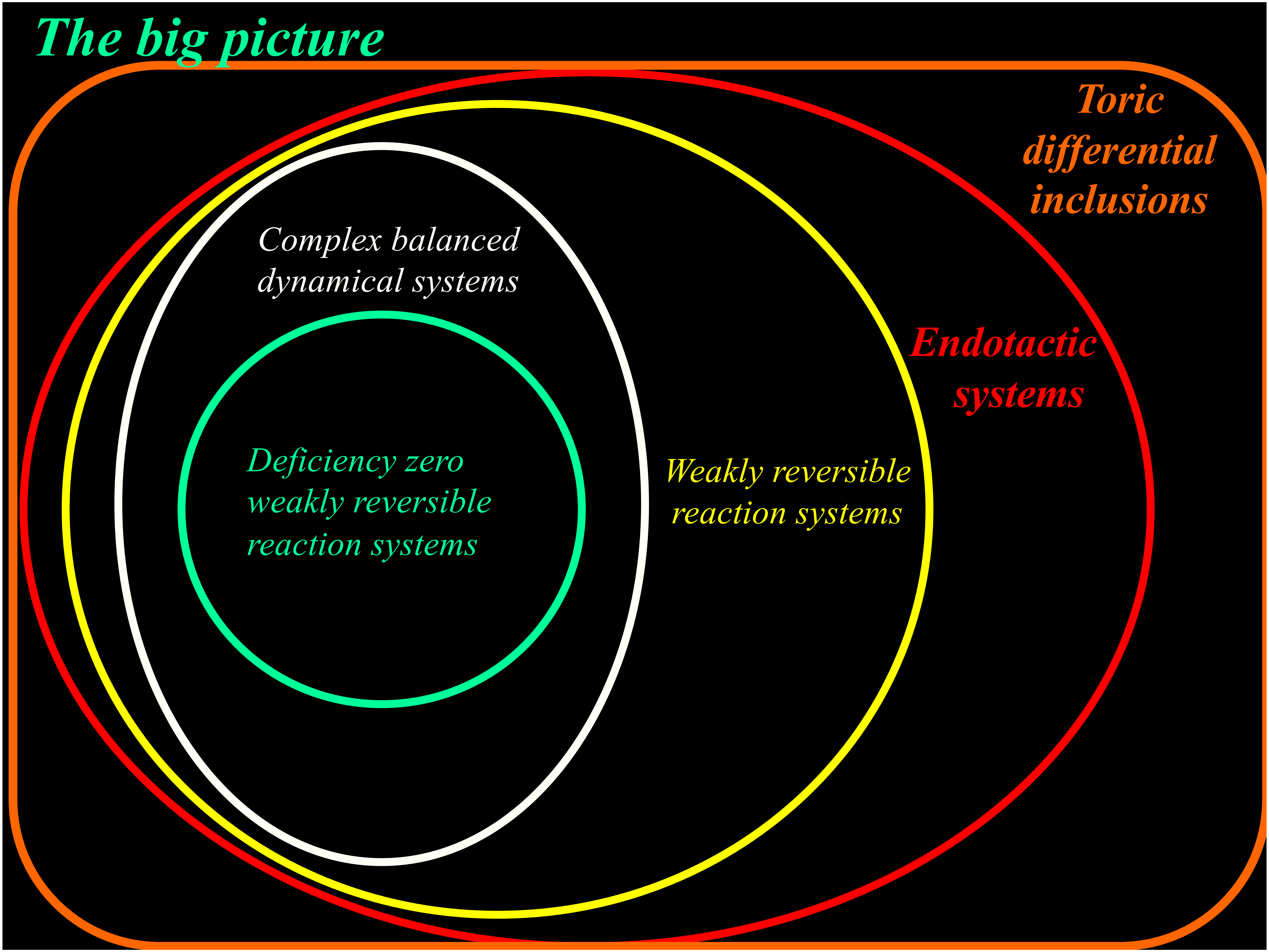


The big picture

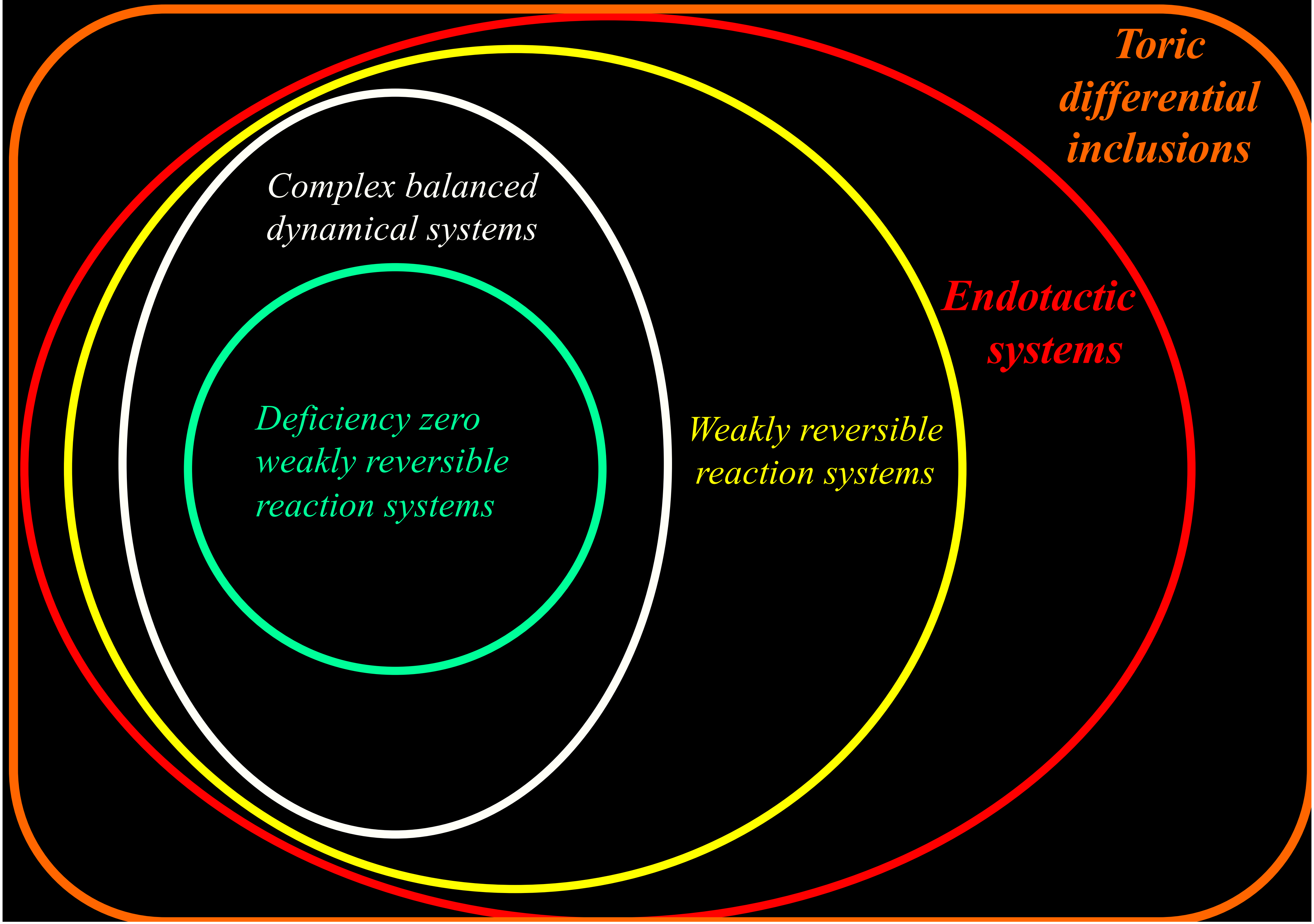


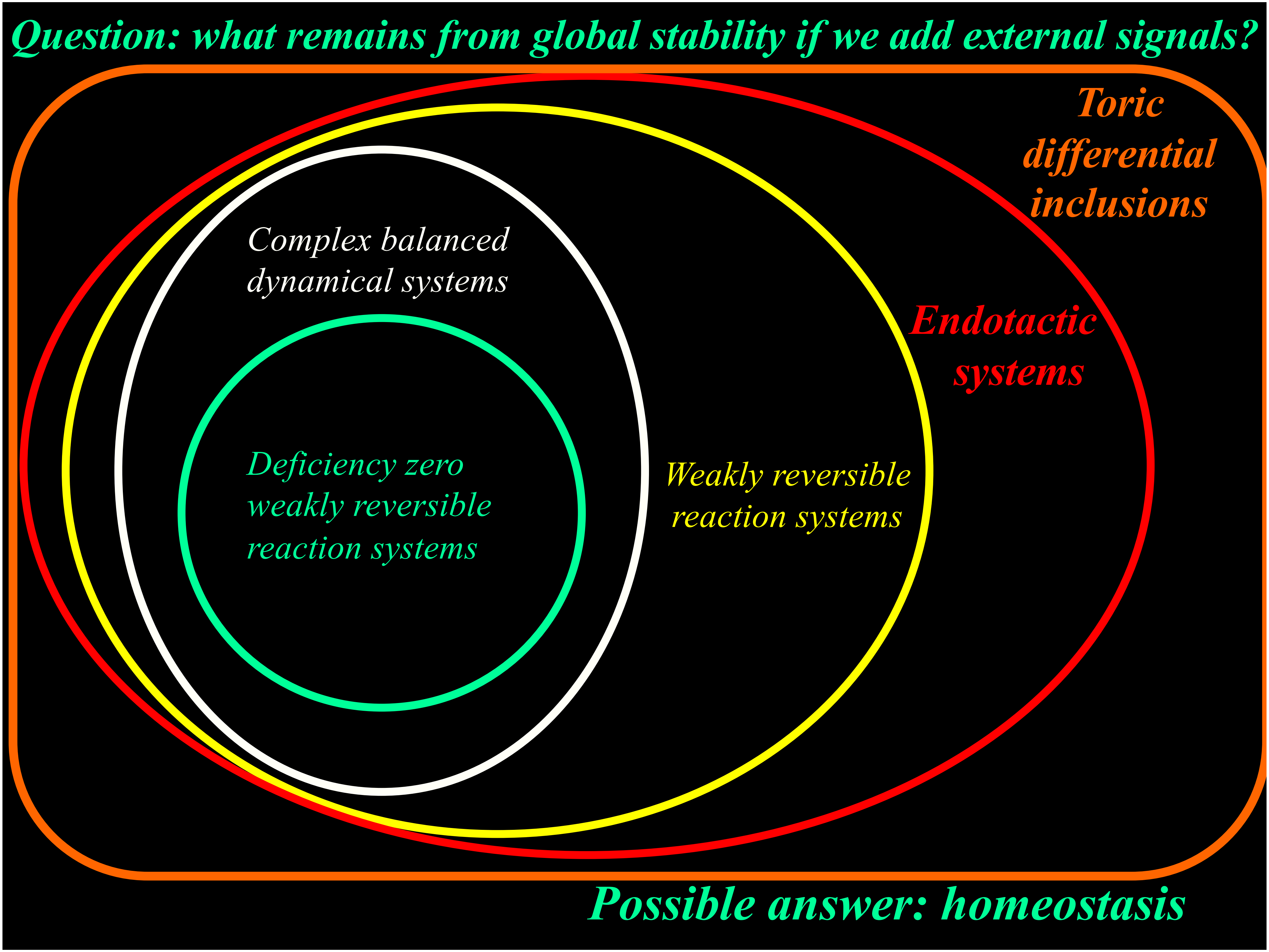
The big picture




The big picture
Toric differential inclusions
Endotactic systems
Weakly reversible reaction systems
Complex balanced dynamical systems
Deficiency zero weakly reversible reaction systems

Question: what remains from global stability if we add external signals?

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Toric differential inclusions
Endotactic systems
Weakly reversible reaction systems
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Possible answer: homeostasis

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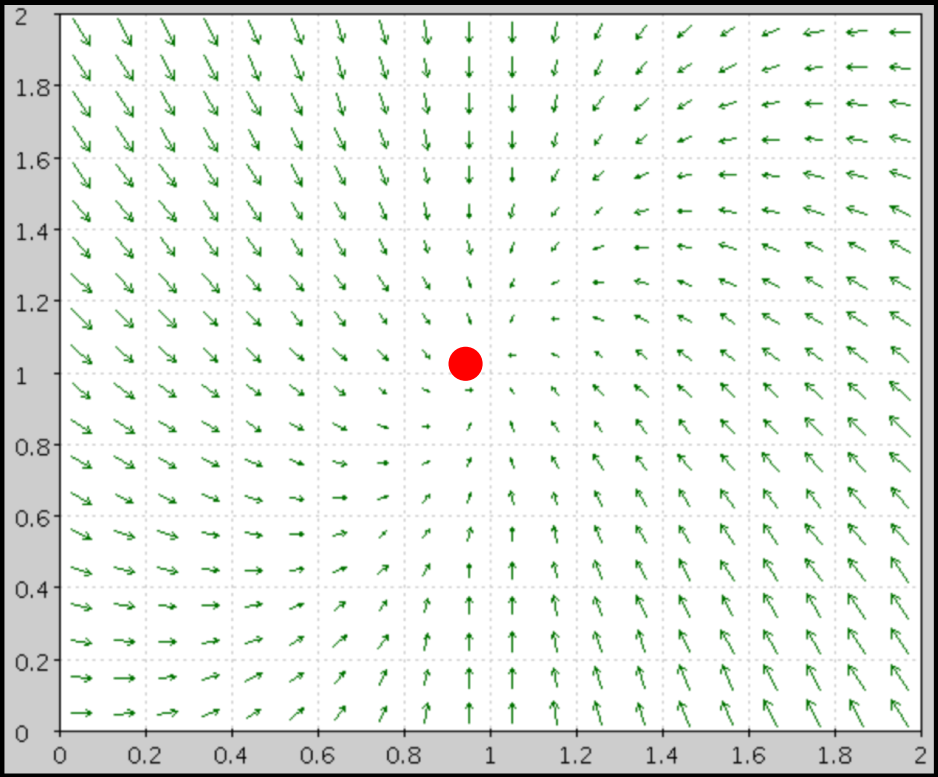
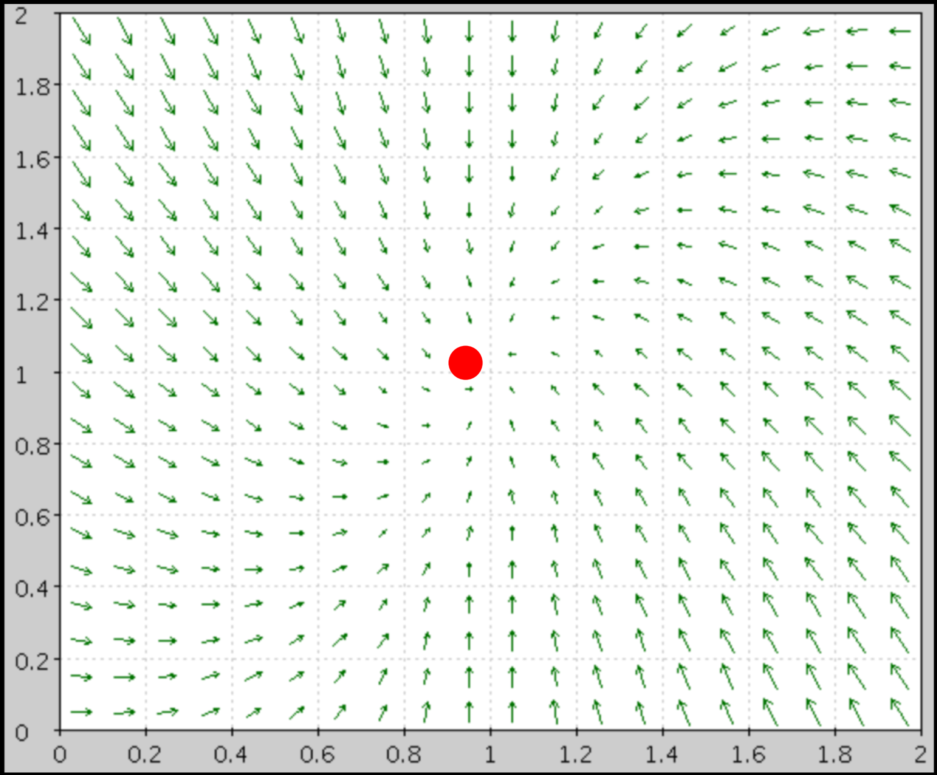


Globally stable system

$$\frac{dx}{dt} = \sum_{y \to y' \in G} k_{y \to y'} x^y (y' - y)$$

$$\frac{dx}{dt} = \sum_{y \to y' \in G} k_{y \to y'}(t) x^y (y' - y)$$



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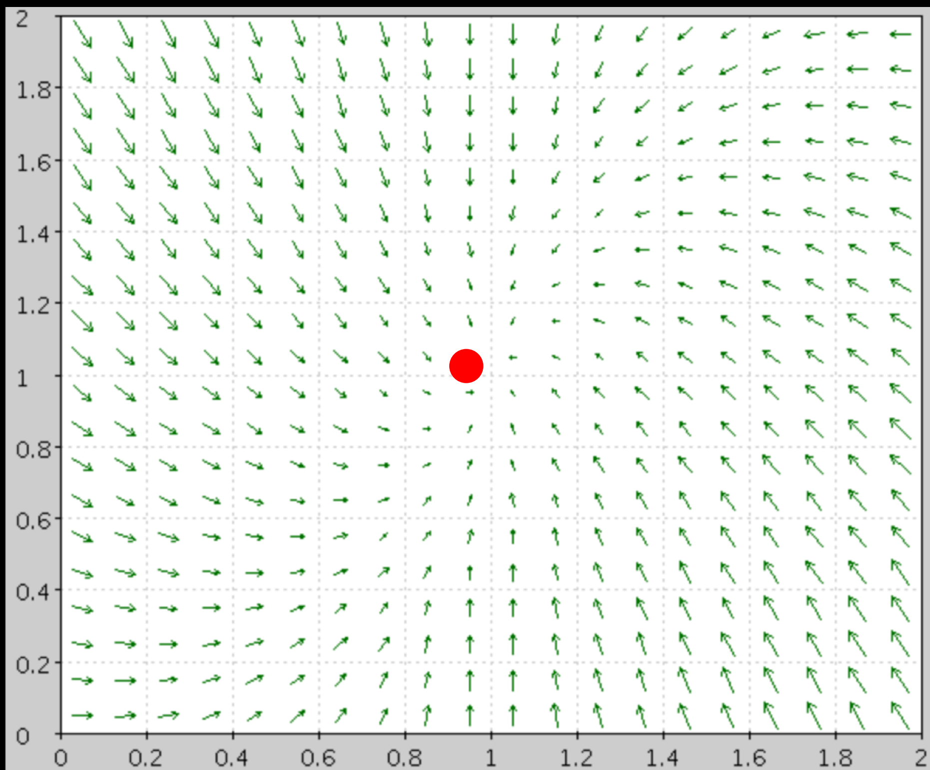

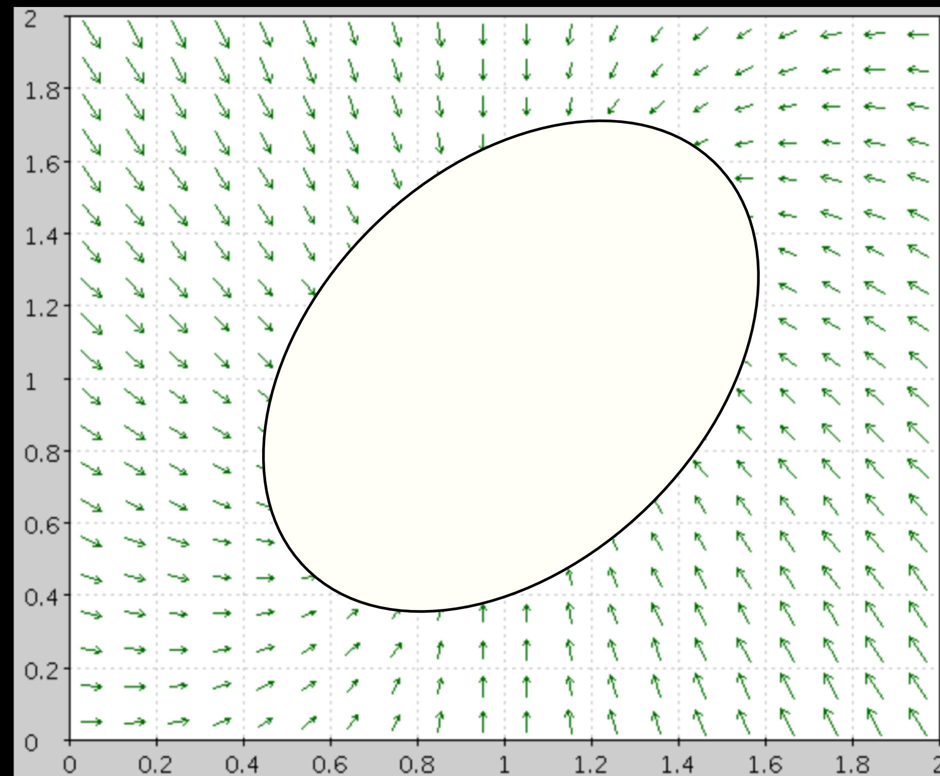

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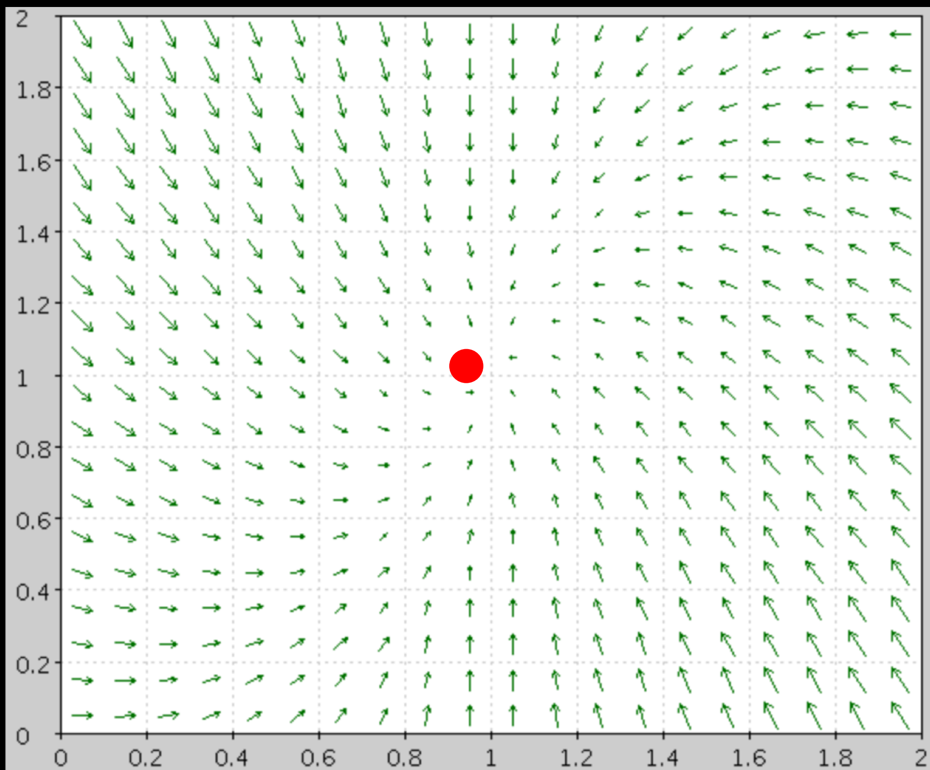
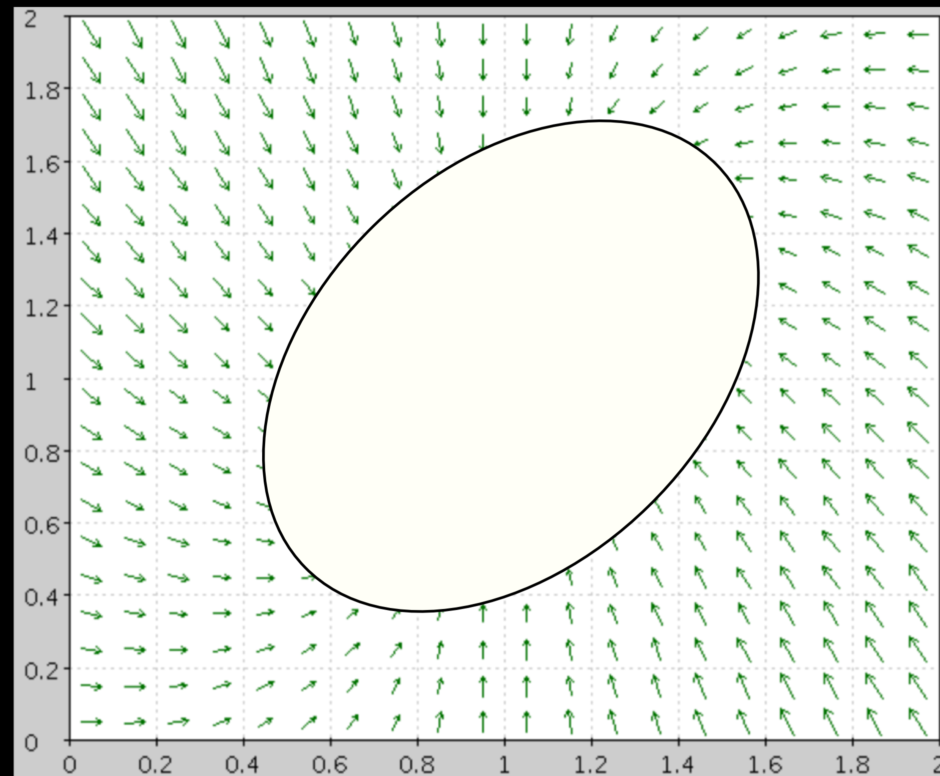
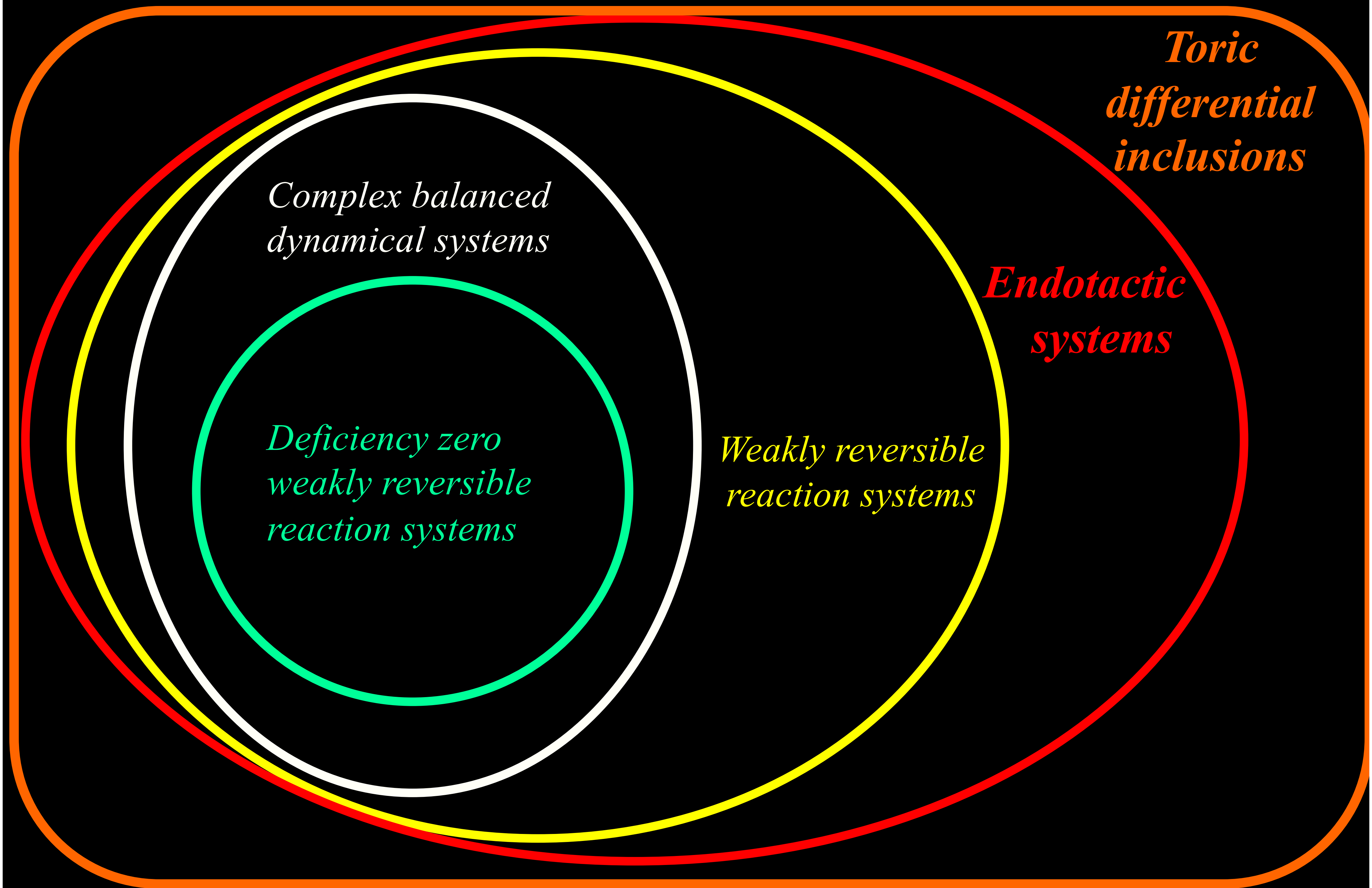


Globally stable system



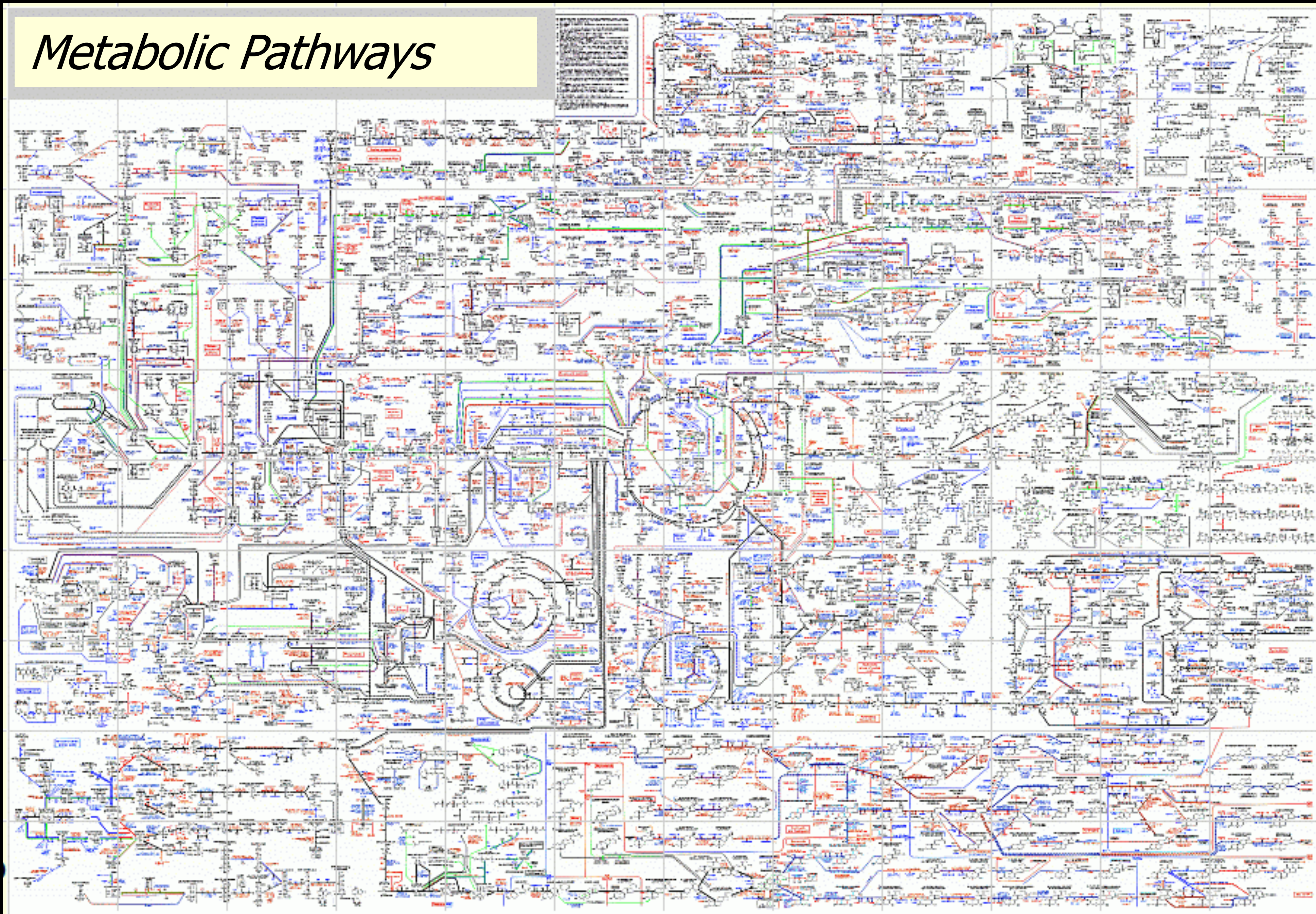
Robustly permanent system

Question: what remains from global stability if we add external signals?



Possible answer: homeostasis

Metabolic Pathways



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