Mathematical and computational methods for understanding the dynamics of biochemical networks

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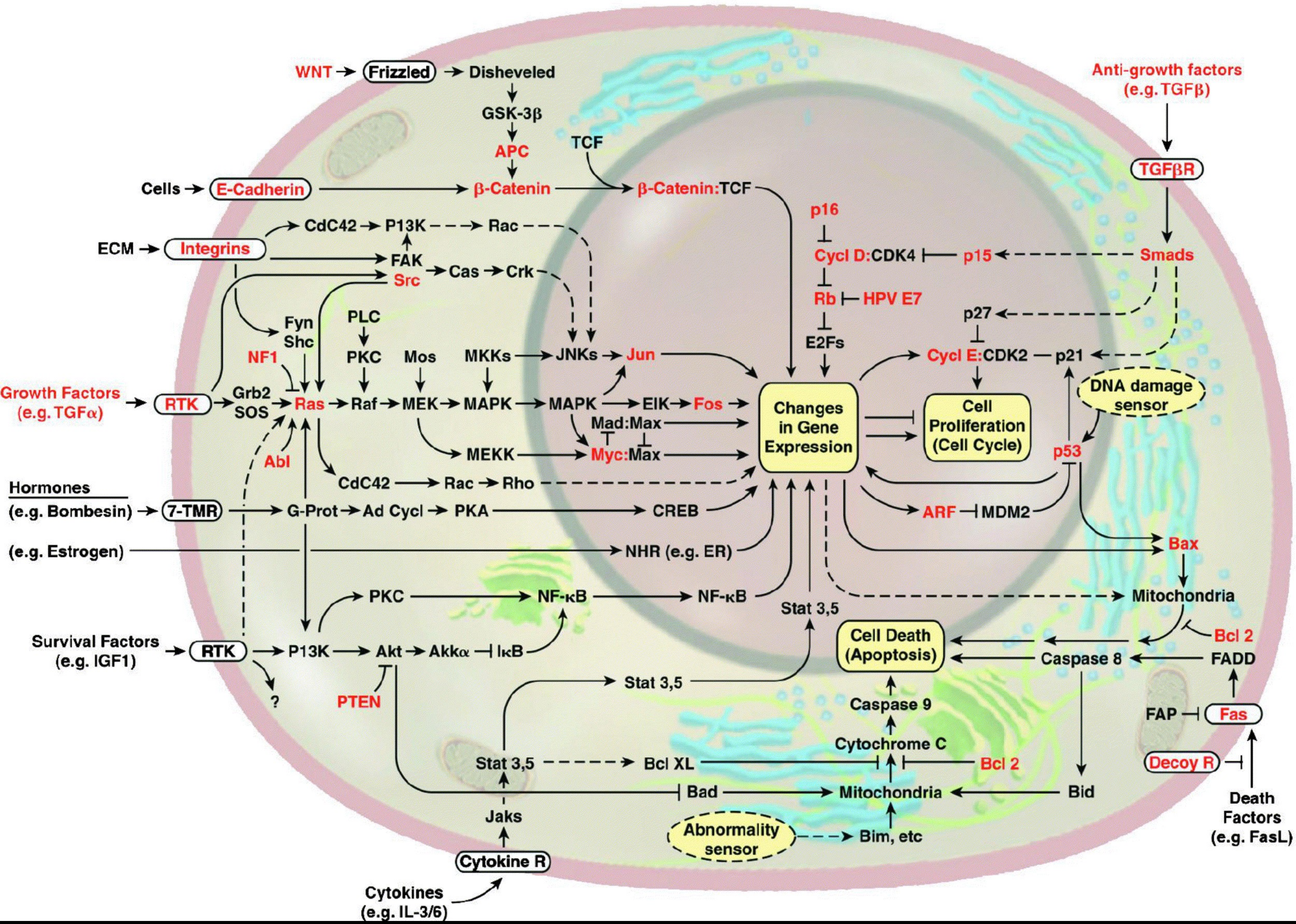
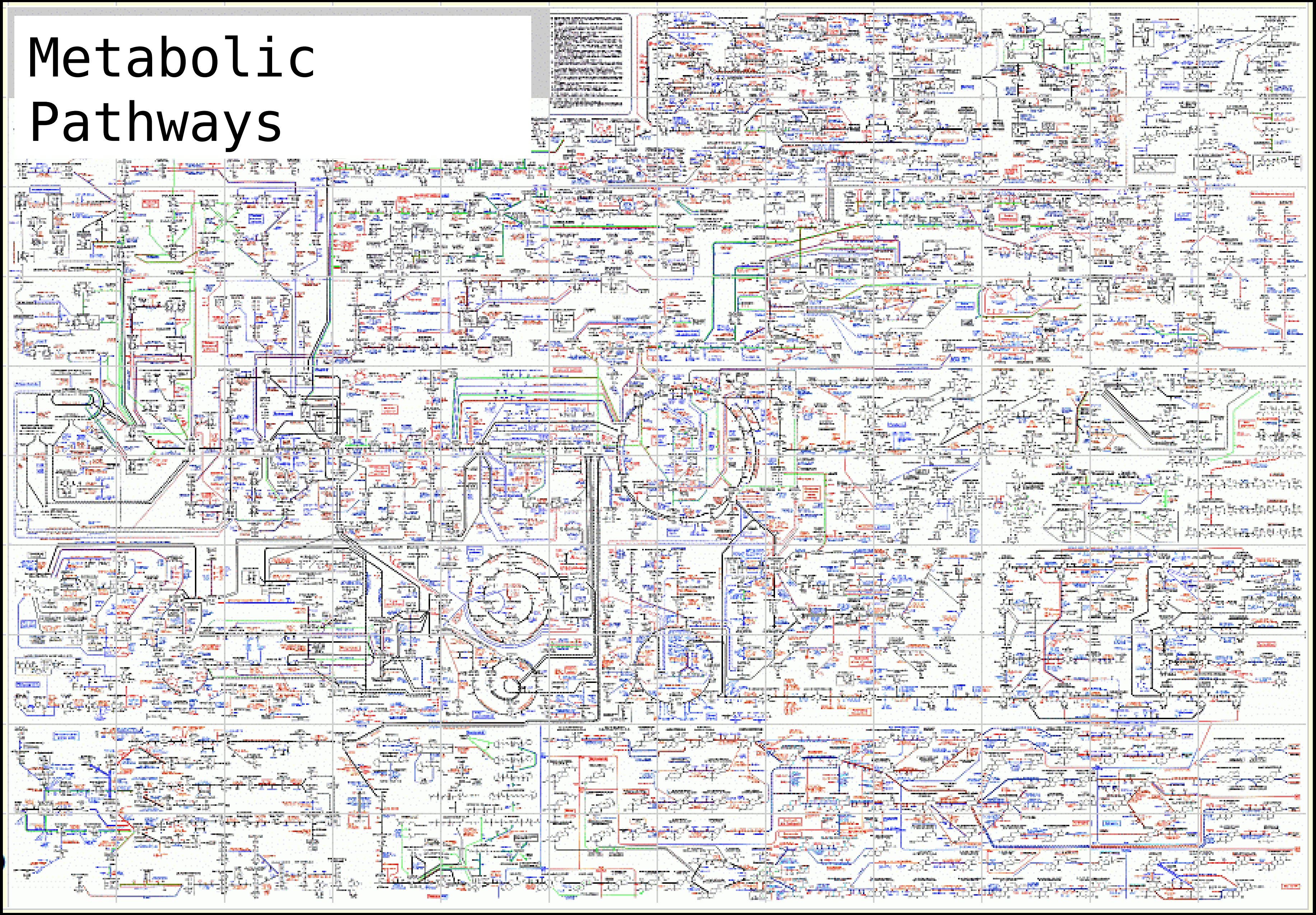
Outline

- *Examples*
- *Bistable biochemical networks*
- *The global attractor conjecture*



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

Metabolic Pathways



Roche Applied Science

Outline

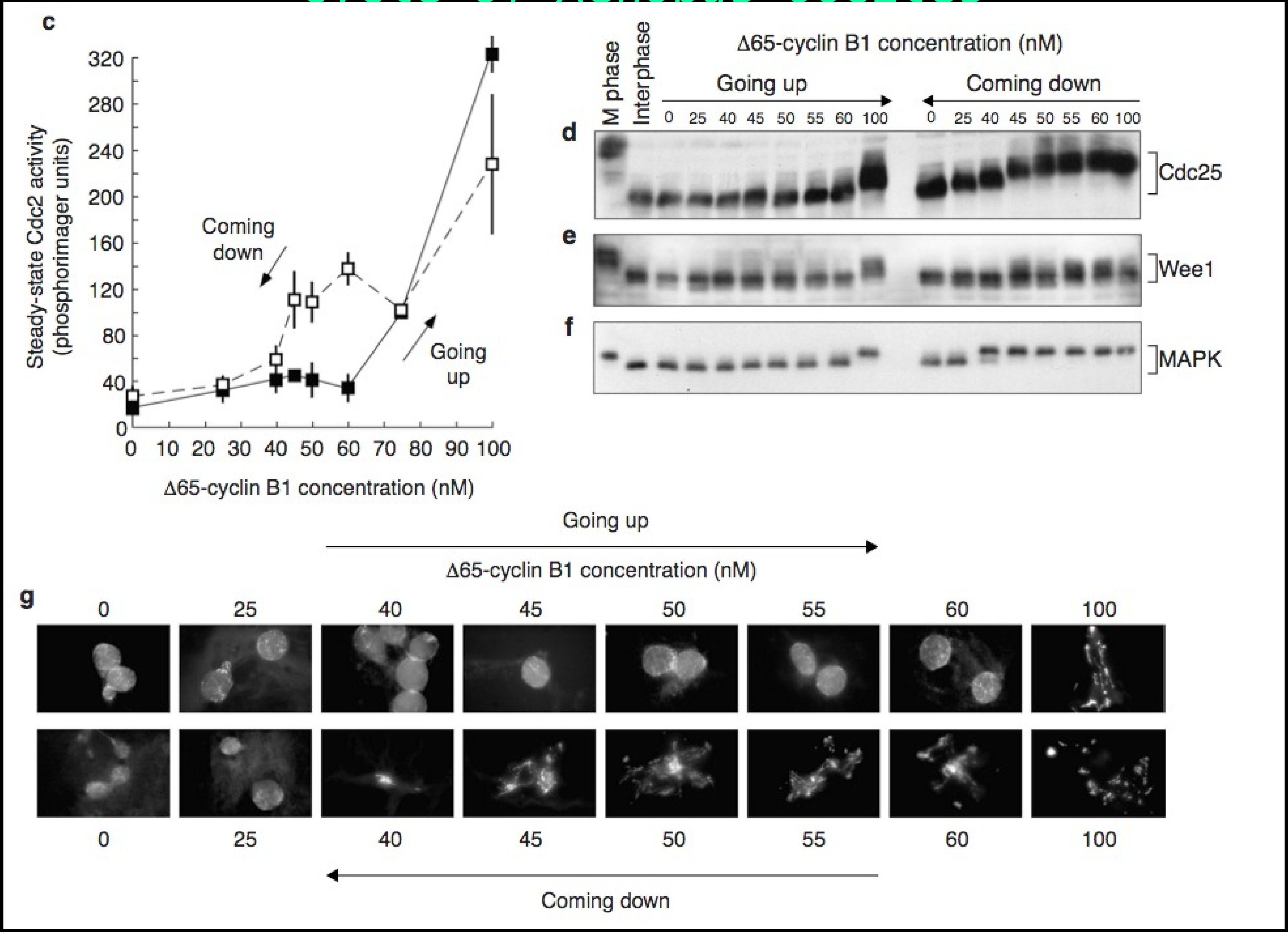
- *Examples*
- *Bistable biochemical networks*
- *The global attractor conjecture*

Bistability and Biochemical Switching

- J. Bailey, **Complex biology with no parameters,** *Nature*, 2001:

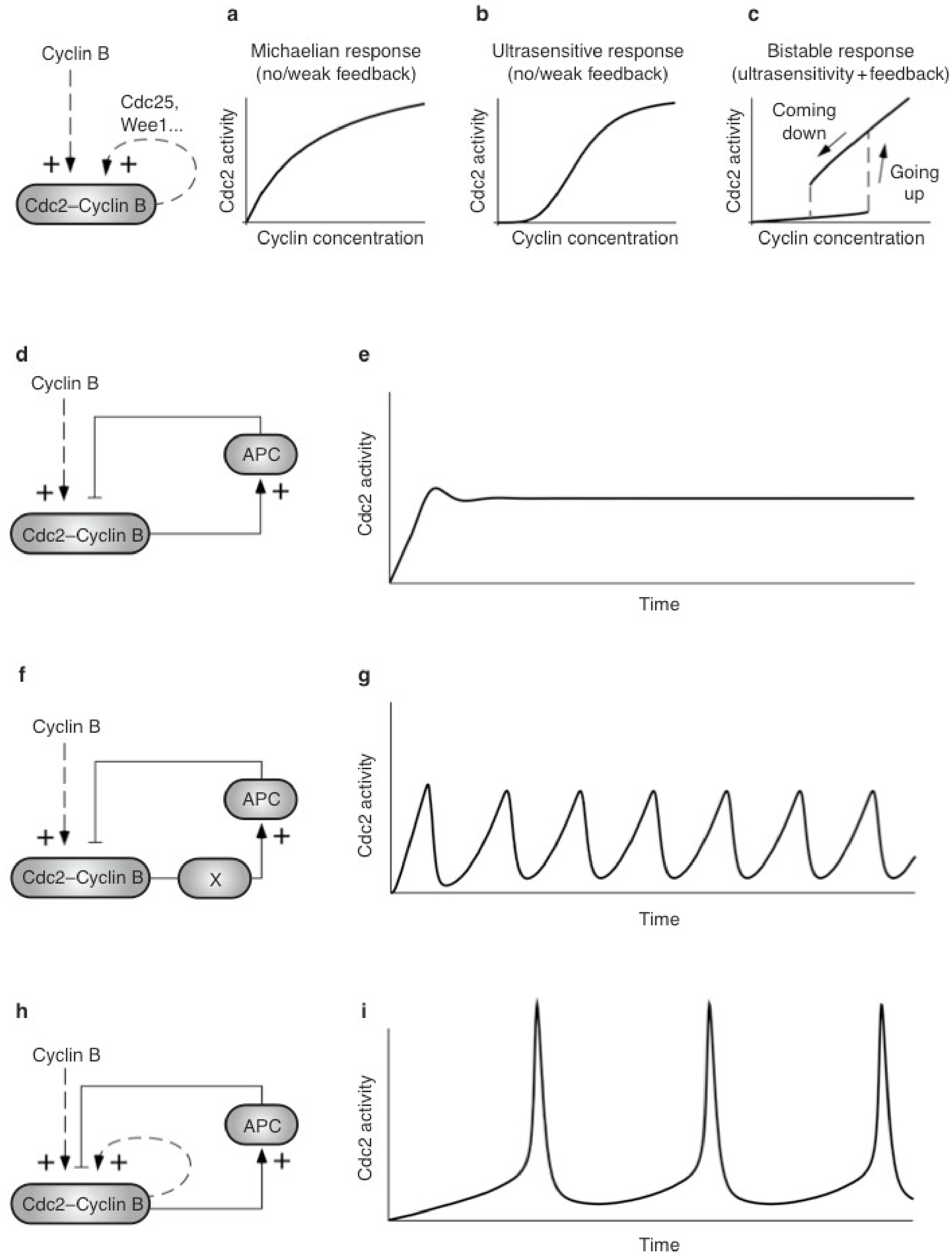
  …does a cell generally operate at one steady state, or can a cell switch under certain circumstances from one steady state to another?

Bistability and hysteresis in the embrionic cell cycle of Xenopus oocites



J. Pomerening, E. Sontag, J. Ferrell, ***Building a cell cycle oscillator: hysteresis and bistability in the activation of Cdc2***, Nature, 2003

Bistability and Biochemical Oscillations



J. Pomerening, E. Sontag, J. Ferrell,
Building a cell cycle oscillator: hysteresis and bistability in the activation of Cdc2,

Given a reaction network, how can we decide if it has the capacity for bistability ?

Some Simple Enzyme Networks and their Capacity for Bistability

	Network	Remark	Capacity for Bistability
1.	$E + S \rightleftarrows ES \rightarrow E + P$	Elementary enzyme catalysis underlying Michaelis-Menten kinetics. $S \rightarrow P$	NO
2.	$E + S \rightleftarrows ES \rightarrow E + P$ $E + I \rightleftarrows EI$	Elementary enzyme catalysis with competitive inhibition $S \rightarrow P$	NO
3.	$E + S \rightleftarrows ES \rightarrow E + P$ $ES + I \rightleftarrows ESI$	Elementary enzyme catalysis with uncompetitive inhibition $S \rightarrow P$	NO
4.	$E + S \rightleftarrows ES \rightarrow E + P$ $E + I \rightleftarrows EI$ $ES + I \rightleftarrows ESI \rightleftarrows EI + S$	Elementary enzyme catalysis with mixed inhibition $S \rightarrow P$	**YES**

	Network	*Remark*	*Capacity for Bistability*
5.	$E + S1 \rightleftarrows ES1$ $S2 + ES1 \rightleftarrows ES1S2 \rightarrow E + P$	Two-substrate enzyme catalysis with ordered substrate-binding $S1 + S2 \rightarrow P$	NO
6.	$E + S1 \rightleftarrows ES1$ $E + S2 \rightleftarrows ES2$ $S2 + ES1 \rightleftarrows ES1S2 \rightleftarrows S1 + ES2$ $\downarrow$ $E + P$	Two-substrate enzyme catalysis with unordered substrate-binding $S1 + S2 \rightarrow P$	**YES**

$$S1 + S2 \xrightarrow{E} P$$

$$S1 + E \underset{2}{\overset{1}{\rightleftarrows}} ES1 \qquad S2 + E \underset{4}{\overset{3}{\rightleftarrows}} ES2$$

$$ES1 + S2 \underset{6}{\overset{5}{\rightleftarrows}} ES1S2 \underset{8}{\overset{7}{\leftrightarrows}} ES2 + S1$$

$$ES1S2 \xrightarrow{9} P + E$$

$$\dot{c}_E = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_3 c_E c_{S2} + k_4 c_{ES2} + k_9 c_{ES1S2}$$

$$\dot{c}_{S1} = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_7 c_{S1} c_{ES2} + k_8 c_{ES1S2} - \xi_{S1} c_{S1} + F_{S1}$$

$$\dot{c}_{S2} = -k_3 c_E c_{S2} + k_4 c_{ES2} - k_5 c_{S2} c_{ES1} + k_6 c_{ES1S2} - \xi_{S2} c_{S2} + F_{S2}$$

$$\dot{c}_{ES1} = k_1 c_E c_{S1} - k_2 c_{ES1} - k_5 c_{ES1} c_{S2} + k_6 c_{ES1S2}$$

$$\dot{c}_{ES2} = k_3 c_E c_{S2} - k_4 c_{ES2} - k_7 c_{ES2} c_{S1} + k_8 c_{ES1S2}$$

$$\dot{c}_{ES1S2} = k_5 c_{S2} c_{ES1} + k_7 c_{S1} c_{ES2} - (k_6 + k_8 + k_9) c_{ES1S2}$$

$$\dot{c}_P = k_9 c_{ES1S2} - \xi_P c_P$$

$$S1 + S2 \xrightarrow{E} P$$

$$S1 + E \underset{2}{\overset{1}{\rightleftarrows}} ES1 \qquad S2 + E \underset{4}{\overset{3}{\rightleftarrows}} ES2$$

$$ES1 + S2 \underset{6}{\overset{5}{\rightleftarrows}} ES1S2 \underset{8}{\overset{7}{\leftrightarrows}} ES2 + S1$$

$$ES1S2 \xrightarrow{9} P + E$$

$$\dot{c}_E = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_3 c_E c_{S2} + k_4 c_{ES2} + k_9 c_{ES1S2}$$

$$\dot{c}_{S1} = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_7 c_{S1} c_{ES2} + k_8 c_{ES1S2} - \xi_{S1} c_{S1} + F_{S1}$$

$$\dot{c}_{S2} = -k_3 c_E c_{S2} + k_4 c_{ES2} - k_5 c_{S2} c_{ES1} + k_6 c_{ES1S2} - \xi_{S2} c_{S2} + F_{S2}$$

$$\dot{c}_{ES1} = k_1 c_E c_{S1} - k_2 c_{ES1} - k_5 c_{ES1} c_{S2} + k_6 c_{ES1S2}$$

$$\dot{c}_{ES2} = k_3 c_E c_{S2} - k_4 c_{ES2} - k_7 c_{ES2} c_{S1} + k_8 c_{ES1S2}$$

$$\dot{c}_{ES1S2} = k_5 c_{S2} c_{ES1} + k_7 c_{S1} c_{ES2} - (k_6 + k_8 + k_9) c_{ES1S2}$$

$$\dot{c}_P = k_9 c_{ES1S2} - \xi_P c_P$$

$$S1 + S2 \xrightarrow{E} P$$

$$S1 + E \underset{2}{\overset{1}{\rightleftarrows}} ES1 \qquad S2 + E \underset{4}{\overset{3}{\rightleftarrows}} ES2$$

$$ES1 + S2 \underset{6}{\overset{5}{\rightleftarrows}} ES1S2 \underset{8}{\overset{7}{\leftrightarrows}} ES2 + S1$$

$$ES1S2 \xrightarrow{9} P + E$$

$$\dot{c}_E = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_3 c_E c_{S2} + k_4 c_{ES2} + k_9 c_{ES1S2}$$

$$\dot{c}_{S1} = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_7 c_{S1} c_{ES2} + k_8 c_{ES1S2} - \xi_{S1} c_{S1} + F_{S1}$$

$$\dot{c}_{S2} = -k_3 c_E c_{S2} + k_4 c_{ES2} - k_5 c_{S2} c_{ES1} + k_6 c_{ES1S2} - \xi_{S2} c_{S2} + F_{S2}$$

$$\dot{c}_{ES1} = k_1 c_E c_{S1} - k_2 c_{ES1} - k_5 c_{ES1} c_{S2} + k_6 c_{ES1S2}$$

$$\dot{c}_{ES2} = k_3 c_E c_{S2} - k_4 c_{ES2} - k_7 c_{ES2} c_{S1} + k_8 c_{ES1S2}$$

$$\dot{c}_{ES1S2} = k_5 c_{S2} c_{ES1} + k_7 c_{S1} c_{ES2} - (k_6 + k_8 + k_9) c_{ES1S2}$$

$$\dot{c}_P = k_9 c_{ES1S2} - \xi_P c_P$$

$$S1 + S2 \xrightarrow{E} P$$

$$S1 + E \underset{2}{\overset{1}{\rightleftarrows}} ES1 \qquad S2 + E \underset{4}{\overset{3}{\rightleftarrows}} ES2$$

$$ES1 + S2 \underset{6}{\overset{5}{\rightleftarrows}} ES1S2 \underset{8}{\overset{7}{\leftrightarrows}} ES2 + S1$$

$$\downarrow 9$$

$$P + E$$

$$\dot{c}_E = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_3 c_E c_{S2} + k_4 c_{ES2} + k_9 c_{ES1S2}$$

$$\dot{c}_{S1} = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_7 c_{S1} c_{ES2} + k_8 c_{ES1S2} - \xi_{S1} c_{S1} + F_{S1}$$

$$\dot{c}_{S2} = -k_3 c_E c_{S2} + k_4 c_{ES2} - k_5 c_{S2} c_{ES1} + k_6 c_{ES1S2} - \xi_{S2} c_{S2} + F_{S2}$$

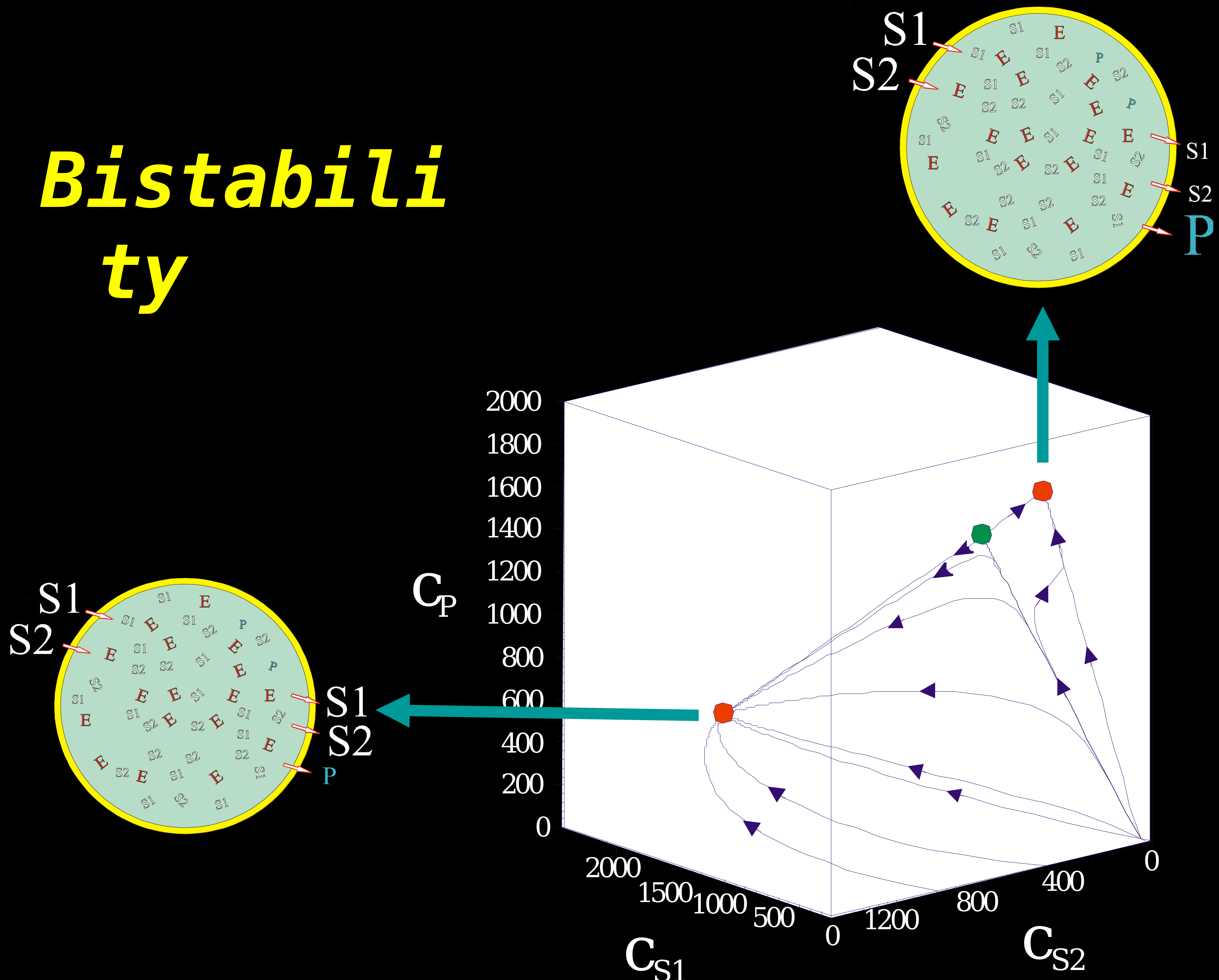
$$\dot{c}_{ES1} = k_1 c_E c_{S1} - k_2 c_{ES1} - k_5 c_{ES1} c_{S2} + k_6 c_{ES1S2}$$

$$\dot{c}_{ES2} = k_3 c_E c_{S2} - k_4 c_{ES2} - k_7 c_{ES2} c_{S1} + k_8 c_{ES1S2}$$

$$\dot{c}_{ES1S2} = k_5 c_{S2} c_{ES1} + k_7 c_{S1} c_{ES2} - (k_6 + k_8 + k_9) c_{ES1S2}$$

$$\dot{c}_P = k_9 c_{ES1S2} - \xi_P c_P$$

Bistability



Vocabulary:

$$A + B \rightleftarrows C$$

$$A + D \rightarrow E \rightleftarrows 2F$$

Vocabulary:

$$A + B \rightleftarrows C$$

$$A + D \rightarrow E \rightleftarrows 2F$$

Species: A, B, C, D, E, F

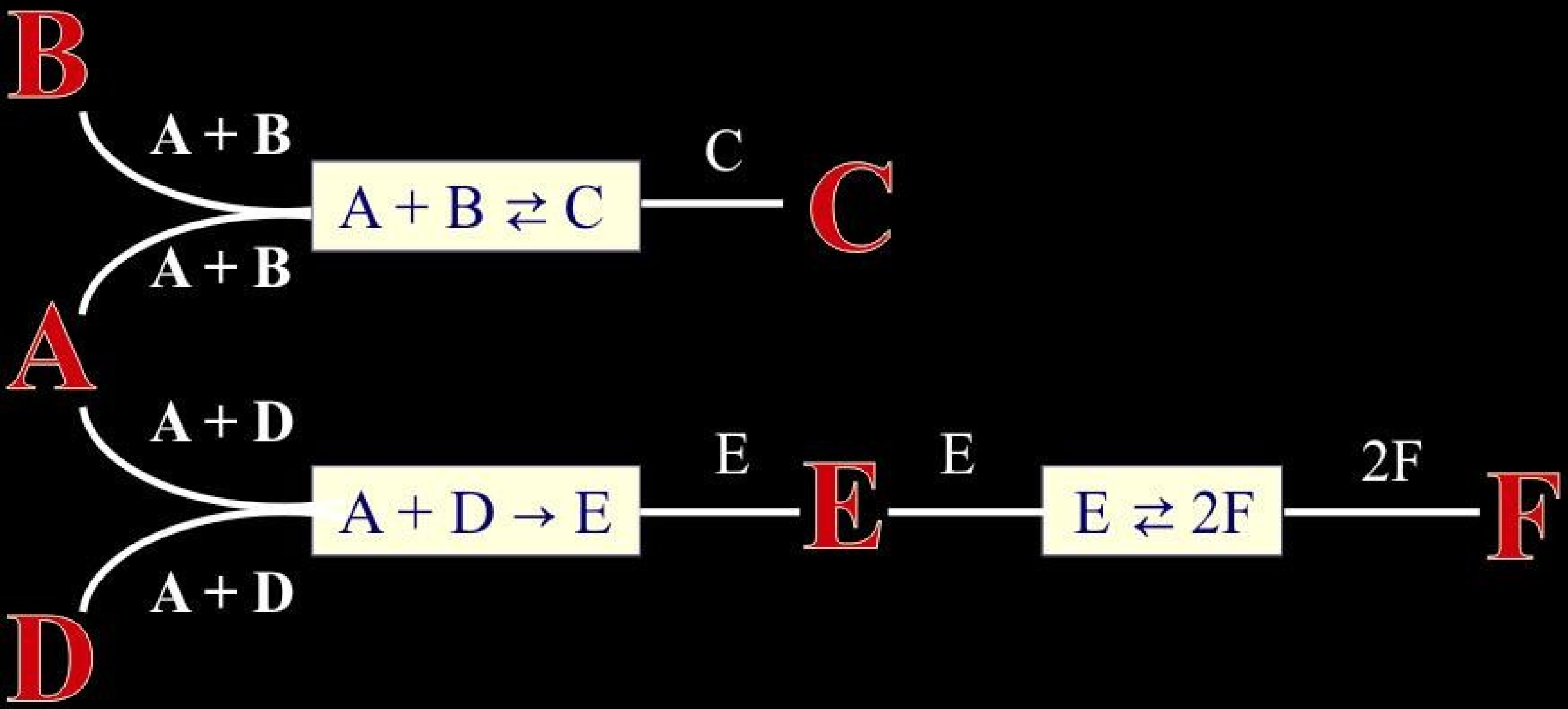
Reactions: $A + B \rightleftarrows C$, $A + D \rightarrow E$, $E \rightleftarrows 2F$

Complexes: $A + B$, C, $A+D$, E, $2F$

The Species-Reaction Graph

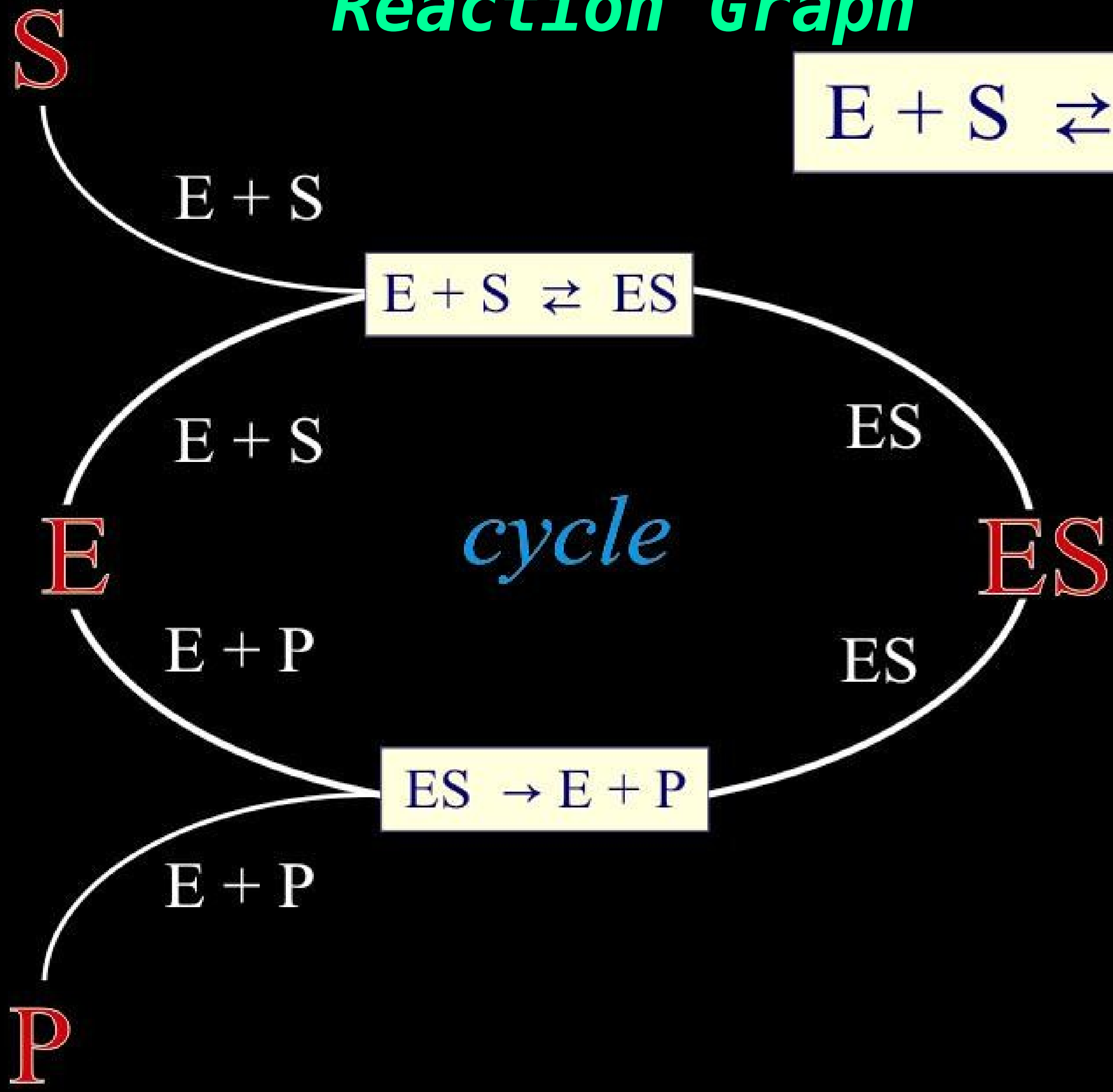
$$A + B \rightleftarrows C$$

$$A + D \rightarrow E \rightleftarrows 2F$$



Another Species-Reaction Graph

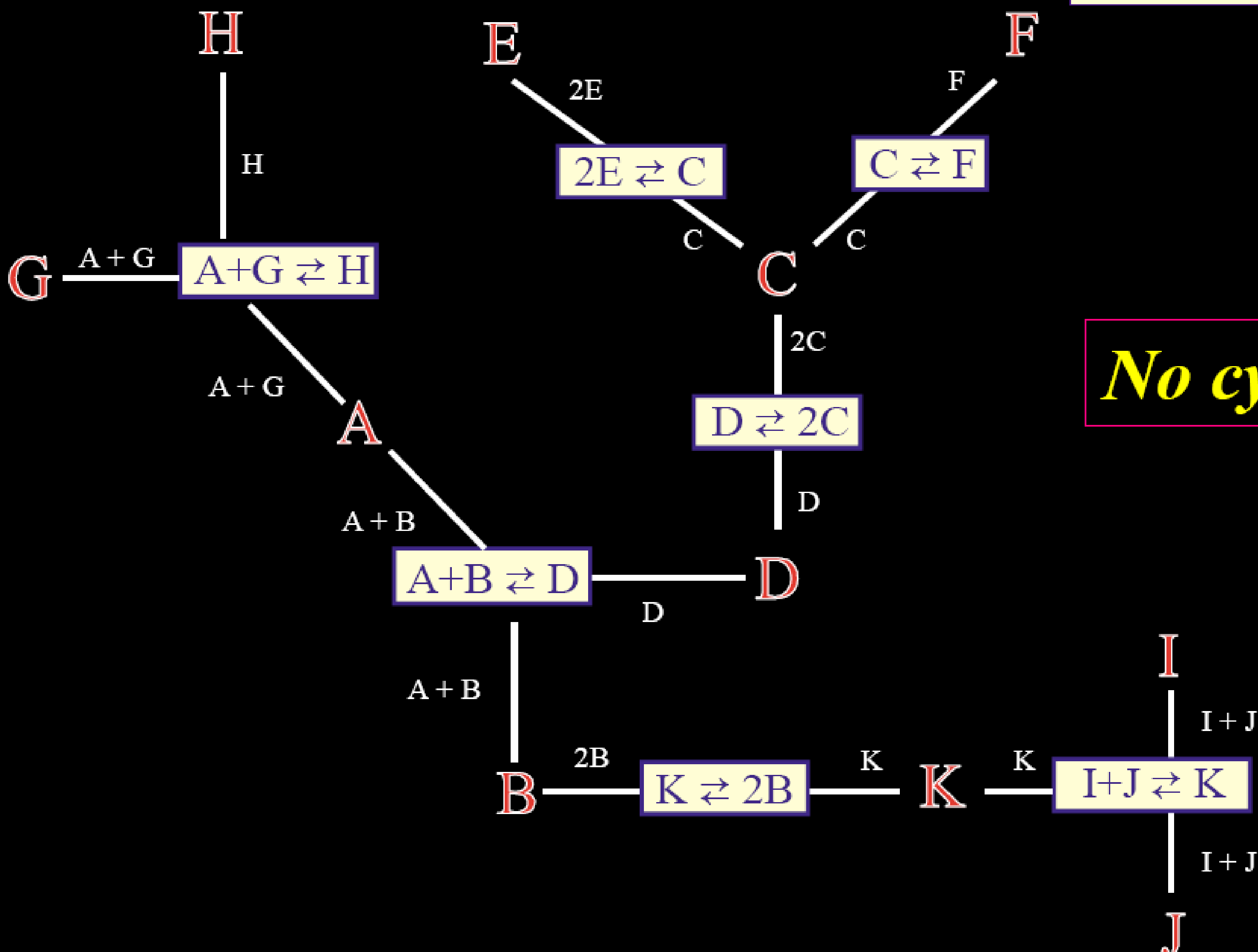
$$E + S \rightleftarrows ES \rightarrow E + P$$



Theorem: *Consider a reaction network for which the species-reaction graph has **no cycles**. Then, **regardless of parameter values**, the corresponding system of mass-action differential equations does not have the capacity for bistability.*

$$A+B \underset{2}{\overset{1}{\rightleftarrows}} D \underset{4}{\overset{3}{\rightleftarrows}} 2C \qquad 2E \underset{6}{\overset{5}{\rightleftarrows}} C \underset{8}{\overset{7}{\rightleftarrows}} F$$

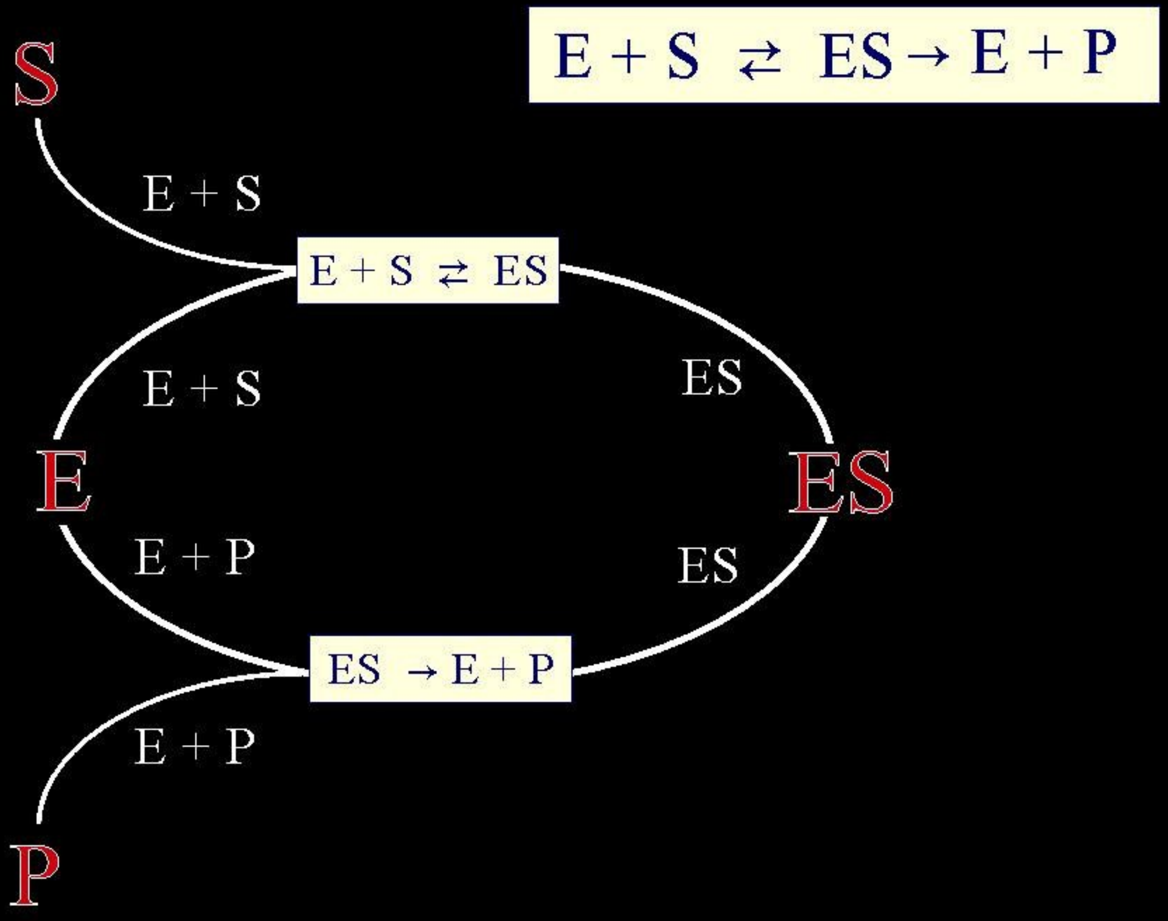
$$A+G \underset{10}{\overset{9}{\rightleftarrows}} H \qquad I+J \underset{11}{\overset{12}{\rightleftarrows}} K \underset{13}{\overset{14}{\rightleftarrows}} 2B$$



No cycles!

Important remark:

Enzyme catalysis generates cycles in the species-reaction graph.

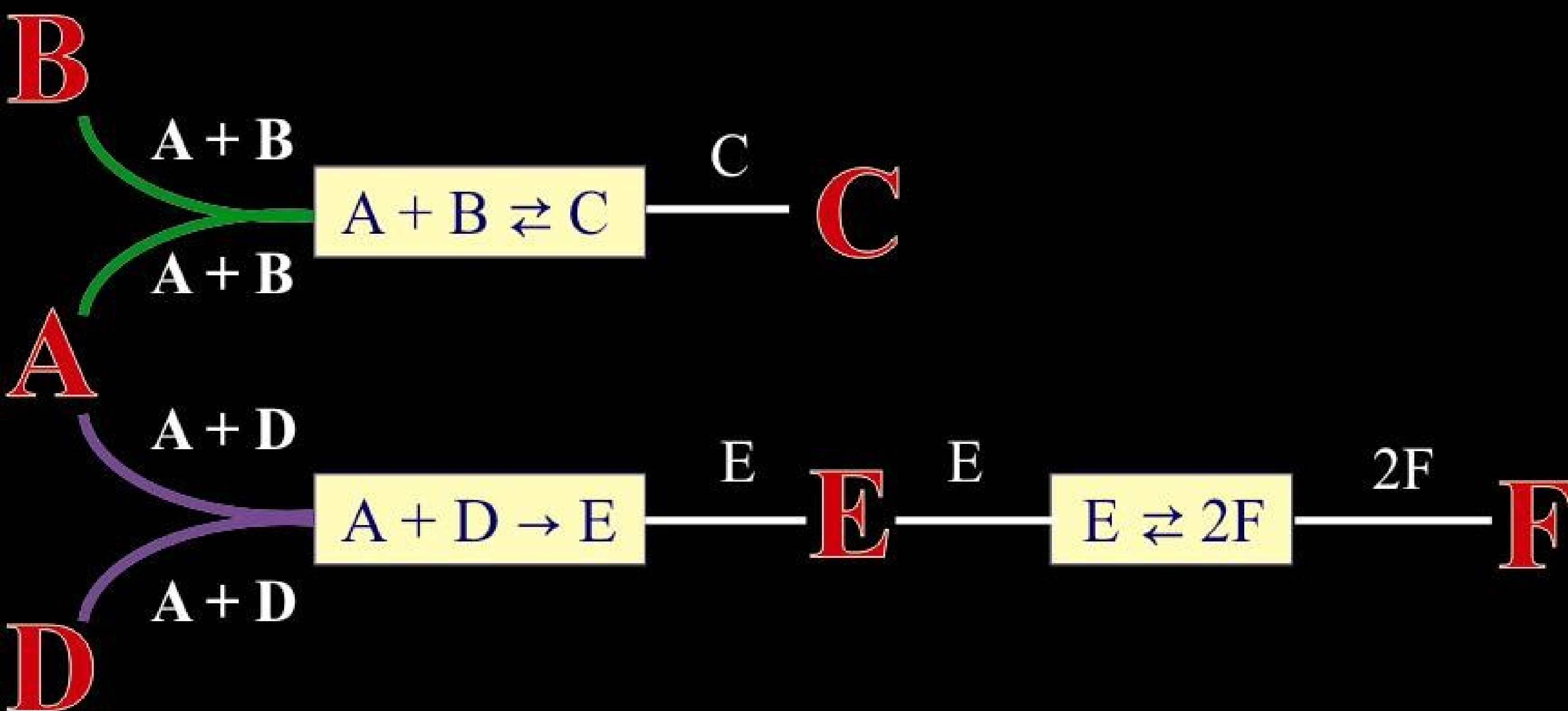


More vocabulary: classifying cycle

o-cycles, ***e-cycles***, and ***s-cycles***

c-Pairs *in the Species-Reaction Graph*

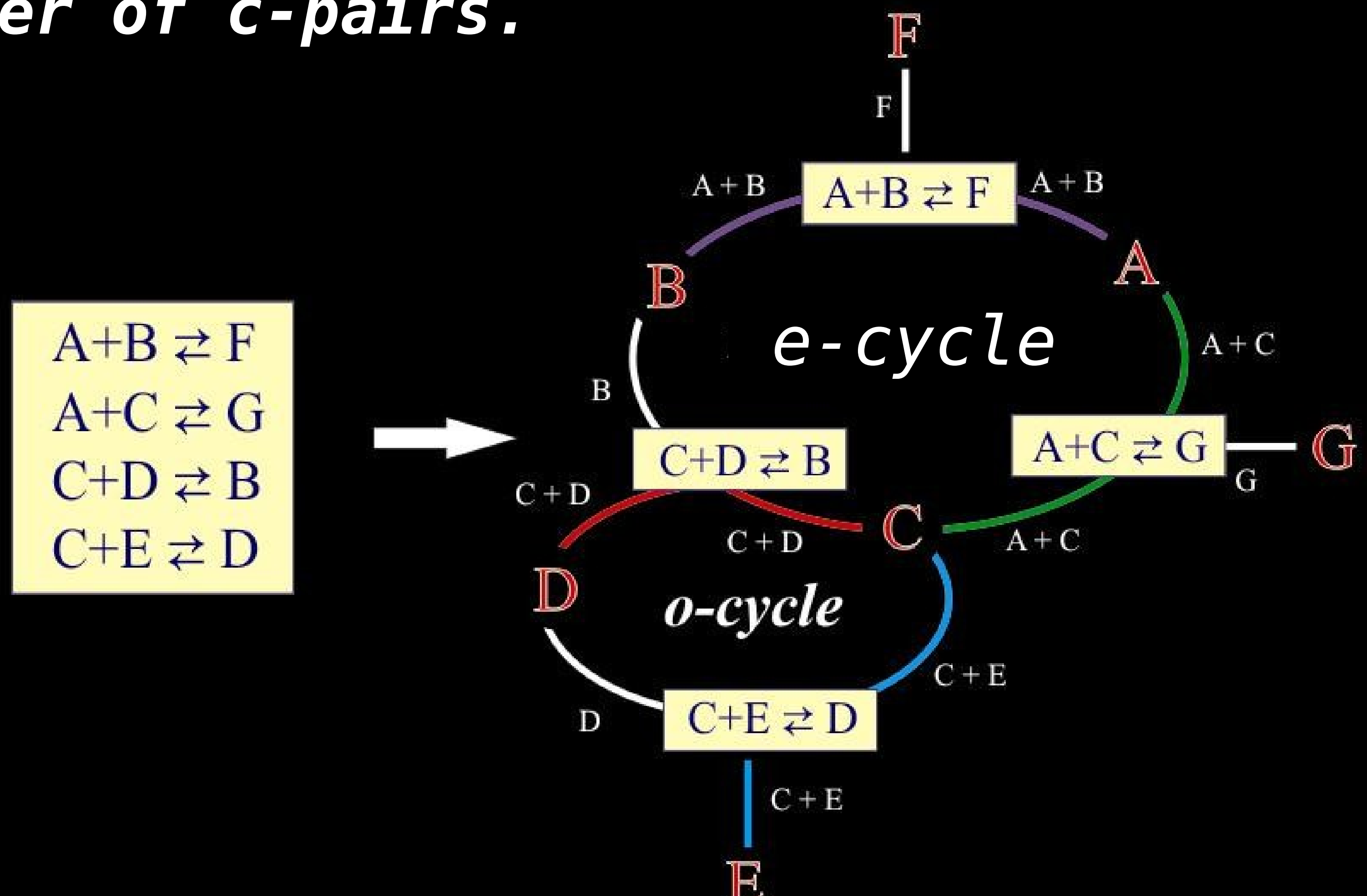
$$A + B \rightleftarrows C$$
$$A + D \rightarrow E \rightleftarrows 2F$$



o-Cycles and e-Cycles

An ***o-cycle*** *is a cycle containing an* ***odd*** *number of c-pairs.*

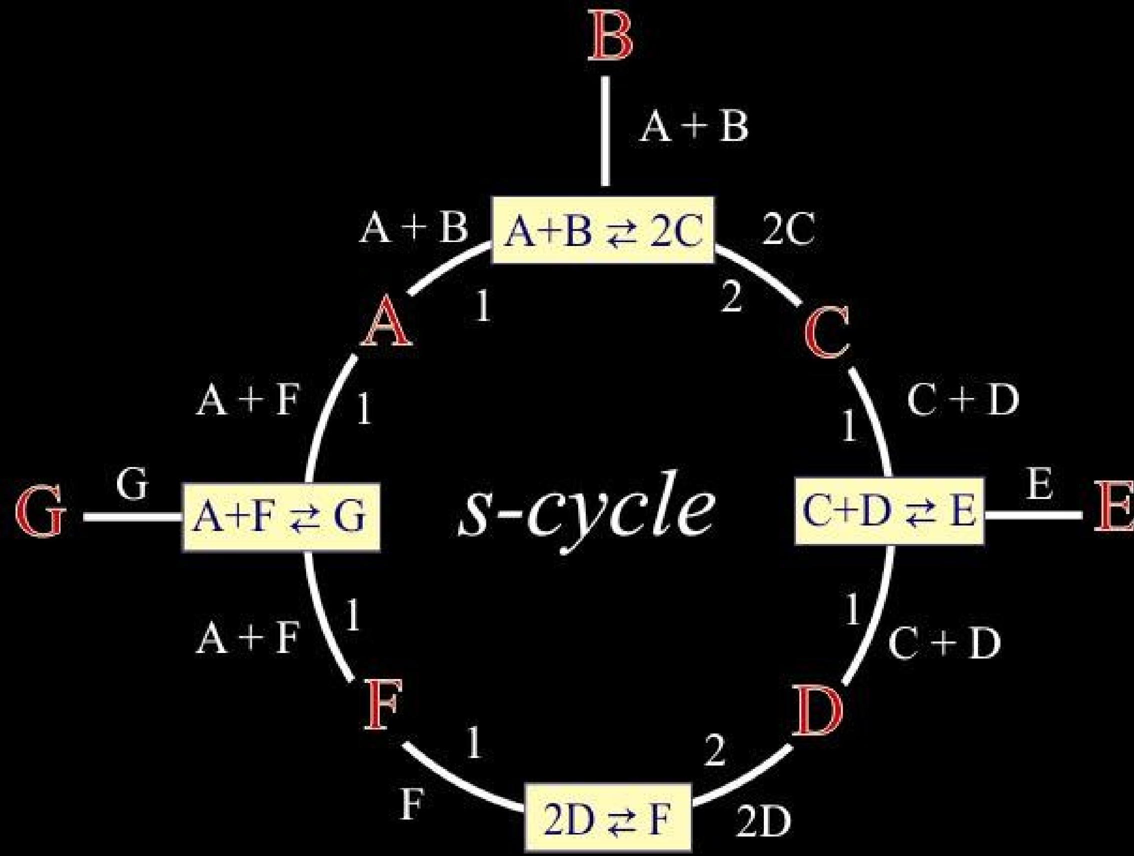
An ***e-cycle*** *is a cycle containing an* ***even*** *number of c-pairs.*



Theorem: *Consider a reaction network for which each cycle in the species-reaction graph is an o-cycle.*
Then, regardless of parameter values, the corresponding system of mass-action differential equations does not have the capacity for bistability.

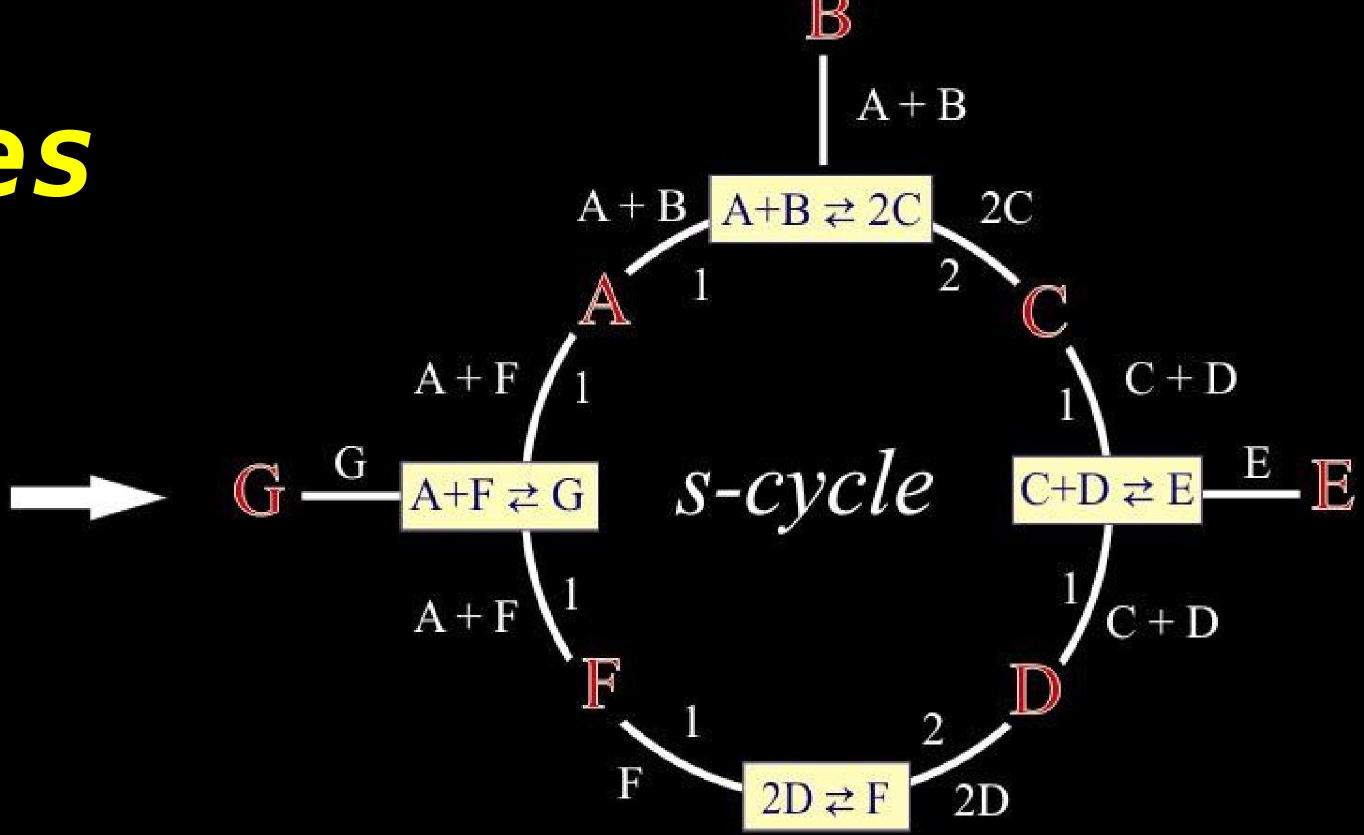
S-Cycles

A+B ⇄ 2C
C+D ⇄ E
2D ⇄ F
A+F ⇄ G



S-Cycles

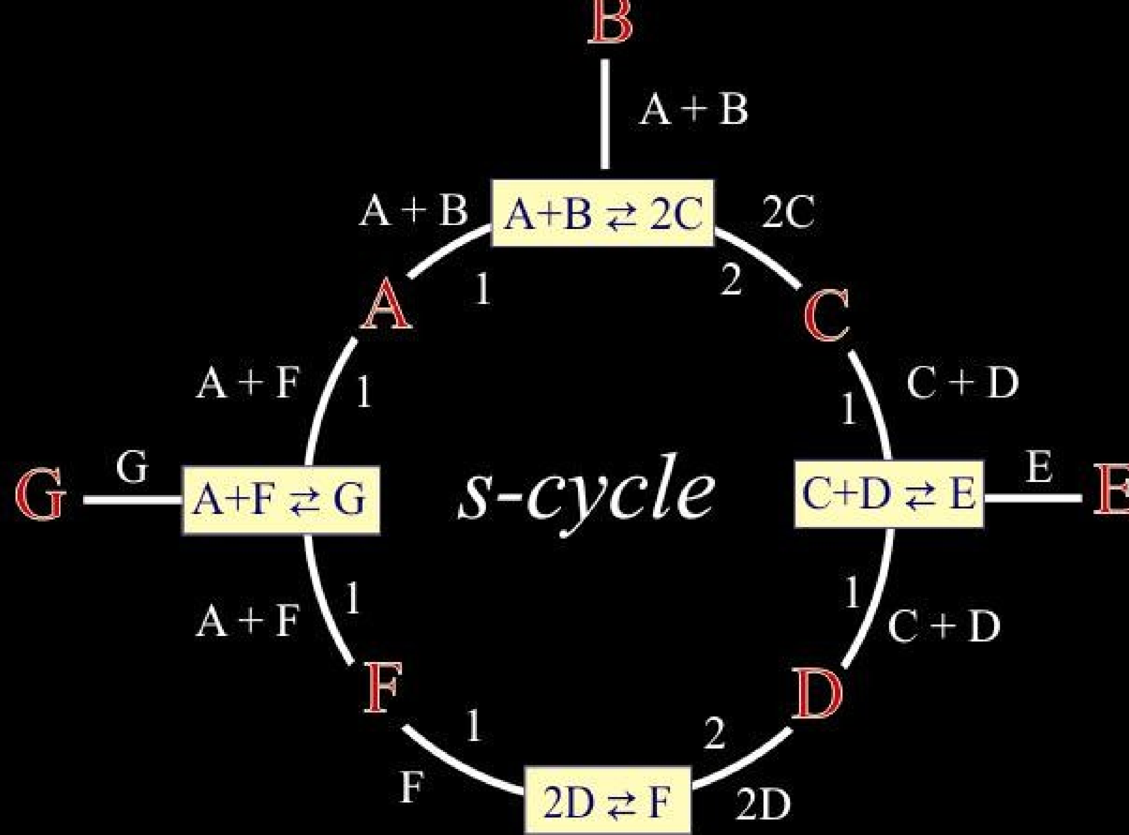
$A+B \rightleftarrows 2C$
$C+D \rightleftarrows E$
$2D \rightleftarrows F$
$A+F \rightleftarrows G$



$$1\times (1/2)\ \times 1\times (1/1) \times 2 \times (1/1) \times 1 \times (1/1)\ = 1$$

s-Cycles

$A+B \rightleftarrows 2C$
$C+D \rightleftarrows E$
$2D \rightleftarrows F$
$A+F \rightleftarrows G$

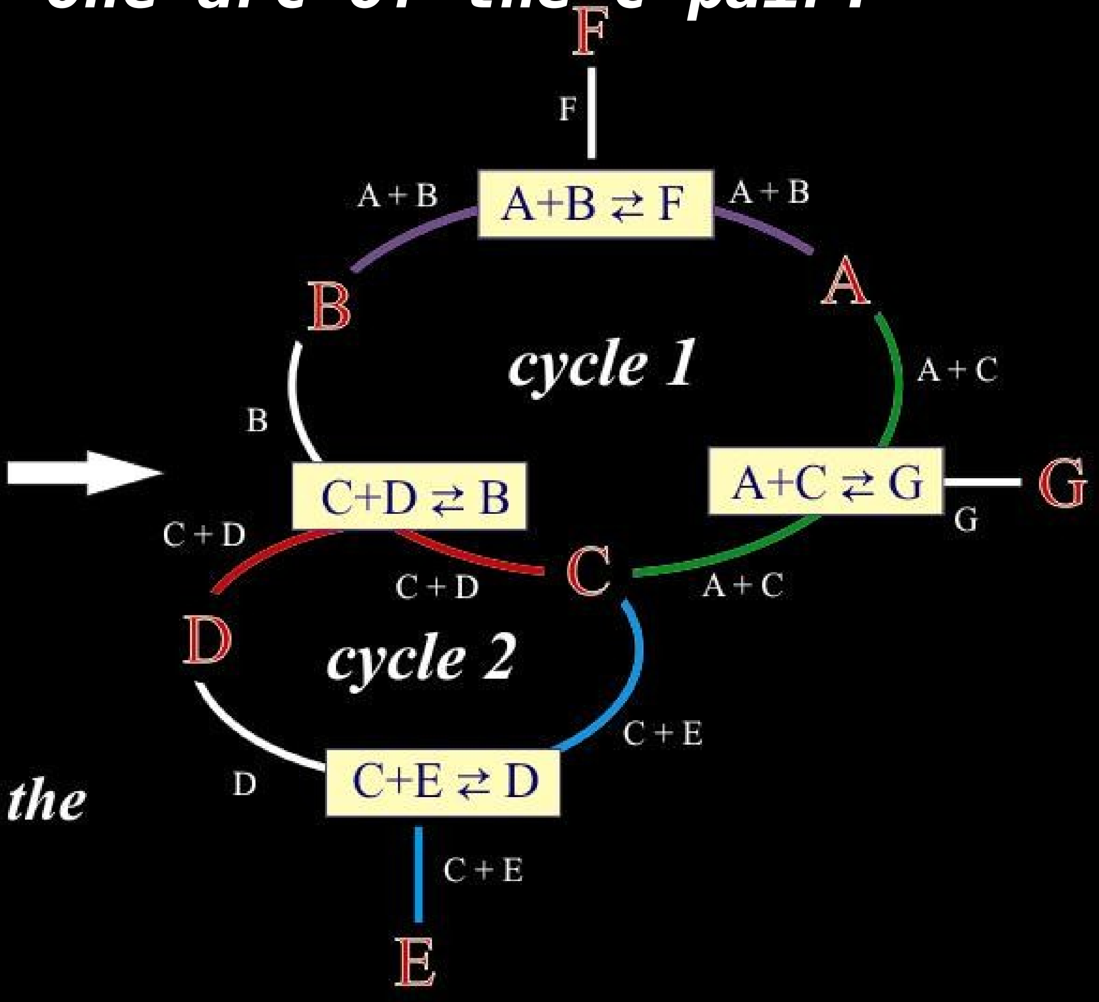


$$1\times(1/2)\ \times 1\times(1/1)\times 2\times(1/1)\times 1\times(1/1)\ = 1$$

Remark: ***If every stoichiometric coefficient in a network is "1", then every cycle in the corresponding Species-Reaction Graph is an s-cycle.***

Two cycles split a c-pair if their combined arcs contain the c-pair and if at least one of the cycles contains only one arc of the c-pair.

A+B ⇄ F
A+C ⇄ G
C+D ⇄ B
C+E ⇄ D



Cycles 1 and 2 split the red c-pair

Theorem: ***Consider a reaction network for which the species-reaction graph has the following properties:***

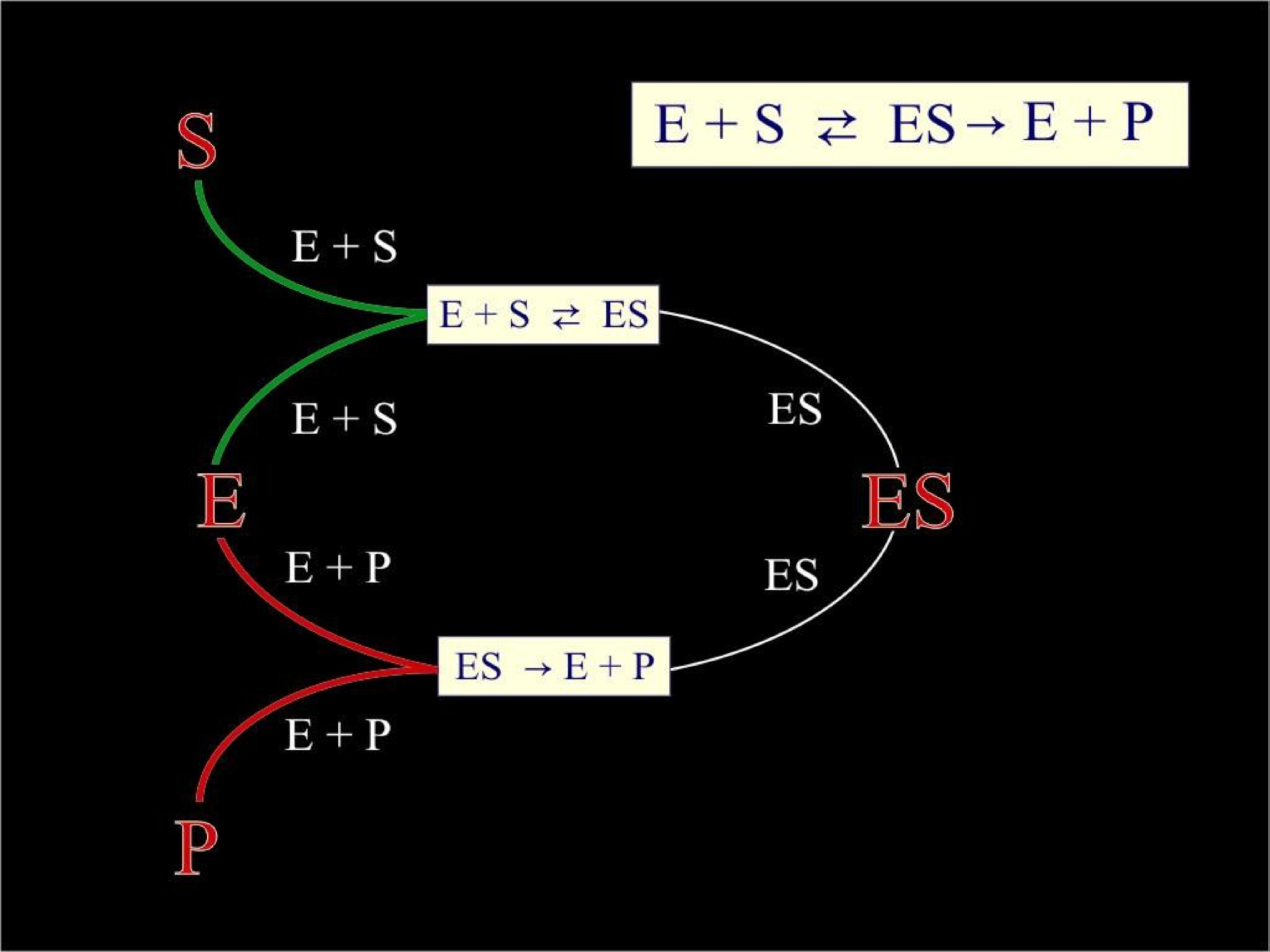
(i) Each cycle is an o-cycle or an s-cycle (or both).

(ii) No c-pair is split by two e-cycles.

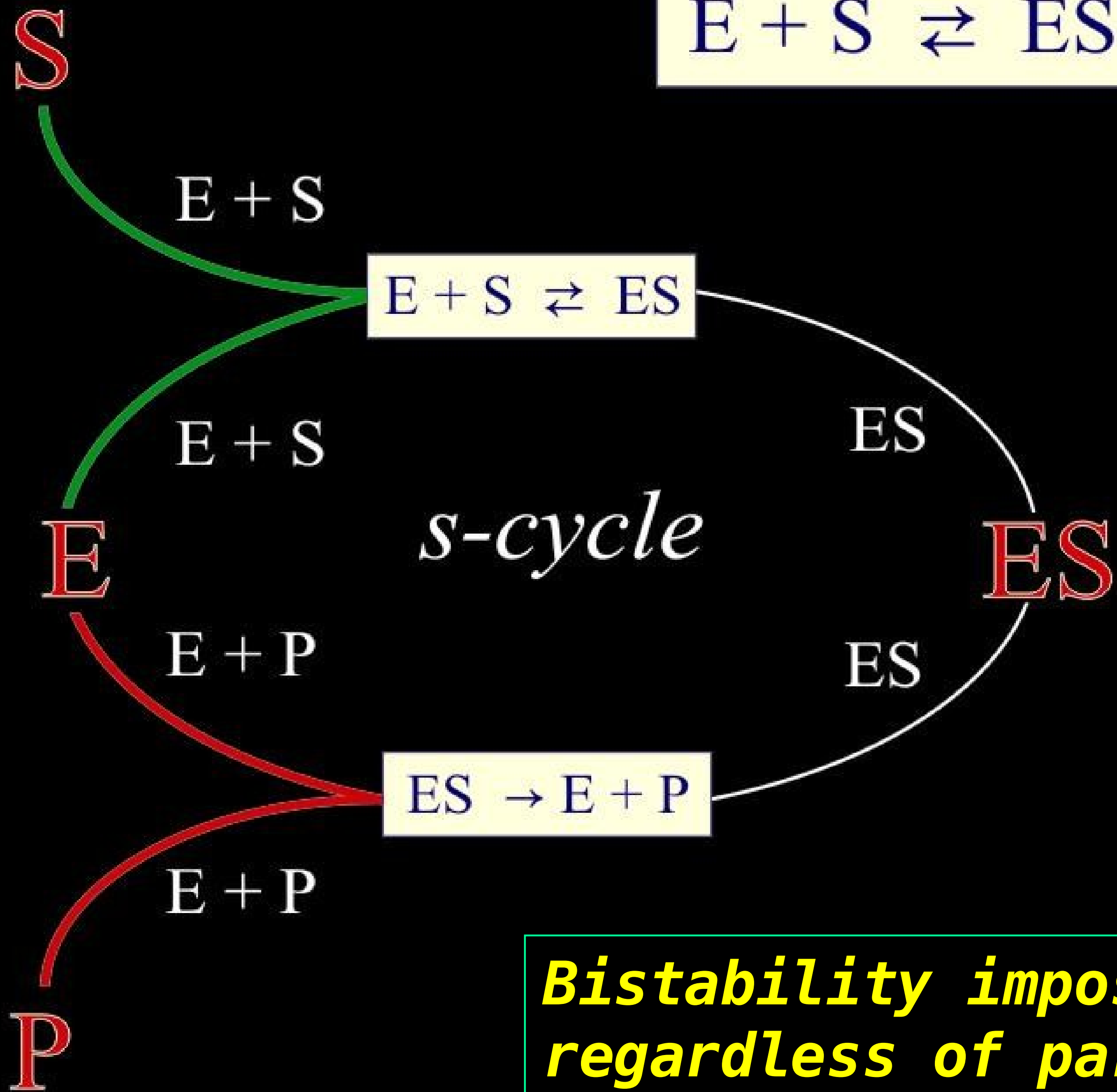
Then, regardless of parameter values, the corresponding system of mass-action differential equations does not have the capacity for bistability.

Some Simple Enzyme Networks and their Capacity for Bistability

	Network	Remark	Capacity for Bistability
1.	$E + S \rightleftarrows ES \rightarrow E + P$	Elementary enzyme catalysis underlying Michaelis-Menten kinetics. $S \rightarrow P$	NO
2.	$E + S \rightleftarrows ES \rightarrow E + P$ $E + I \rightleftarrows EI$	Elementary enzyme catalysis with competitive inhibition $S \rightarrow P$	NO
3.	$E + S \rightleftarrows ES \rightarrow E + P$ $ES + I \rightleftarrows ESI$	Elementary enzyme catalysis with uncompetitive inhibition $S \rightarrow P$	NO
4.	$E + S \rightleftarrows ES \rightarrow E + P$ $E + I \rightleftarrows EI$ $ES + I \rightleftarrows ESI \rightleftarrows EI + S$	Elementary enzyme catalysis with mixed inhibition $S \rightarrow P$	YES


E + S ⇄ ES → E + P
S
E + S
E + S ⇄ ES
E + S
ES
E
ES
E + P
ES
ES → E + P
E + P
P

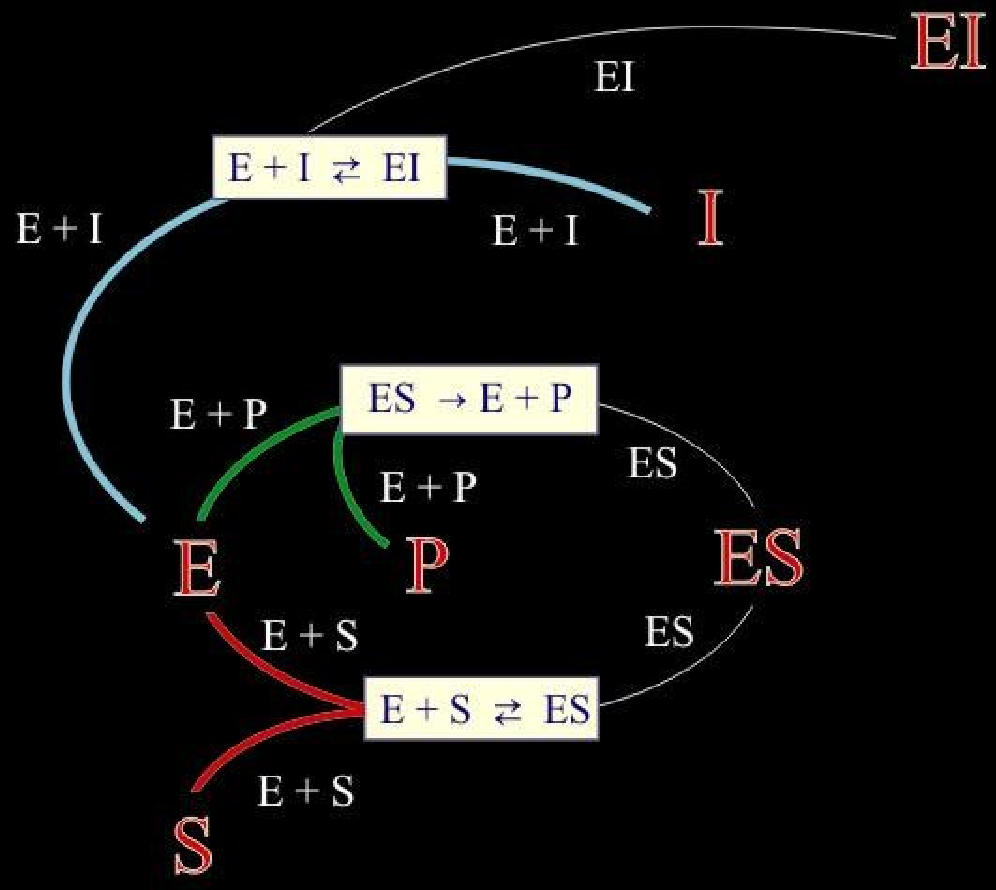
$$E + S \rightleftarrows ES \rightarrow E + P$$



Bistability impossible, regardless of parameter value

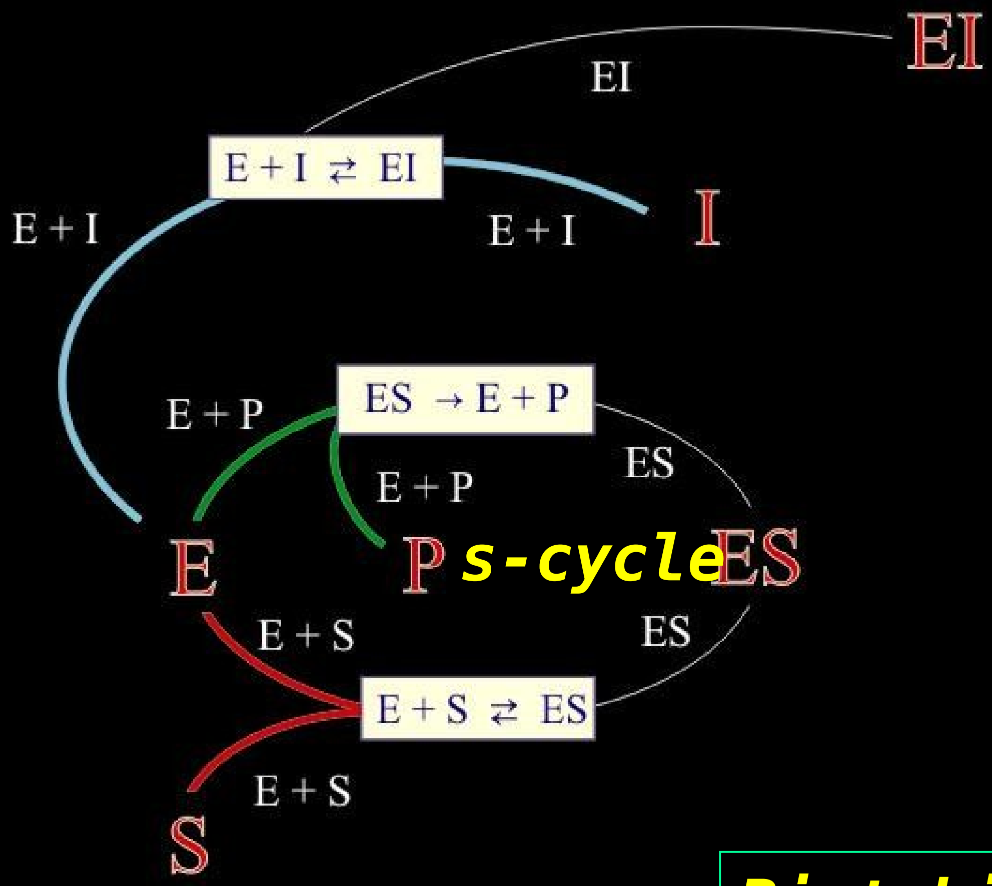
Elementary Enzyme Catalysis with Competitive Inhibition

$E + S \rightleftarrows ES \rightarrow E + P$
$E + I \rightleftarrows EI$



Elementary Enzyme Catalysis with Competitive Inhibition

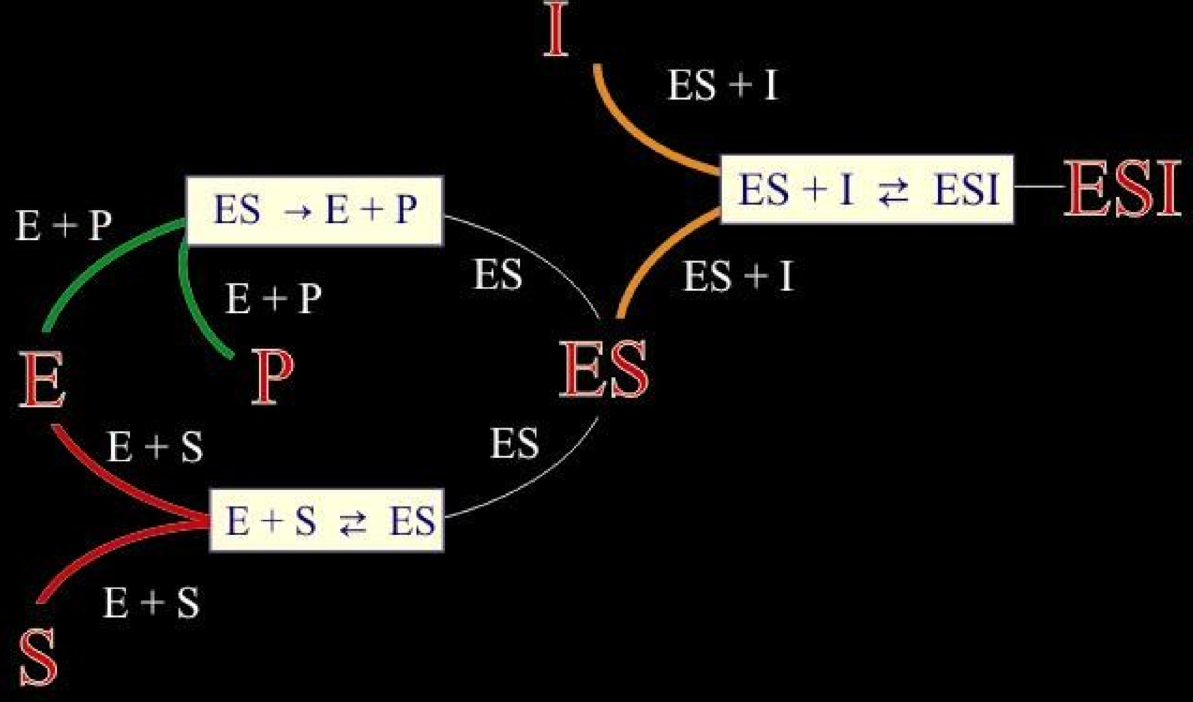
E + S ⇄ ES → E + P
E + I ⇄ EI



Bistability impossible, regardless of parameter value

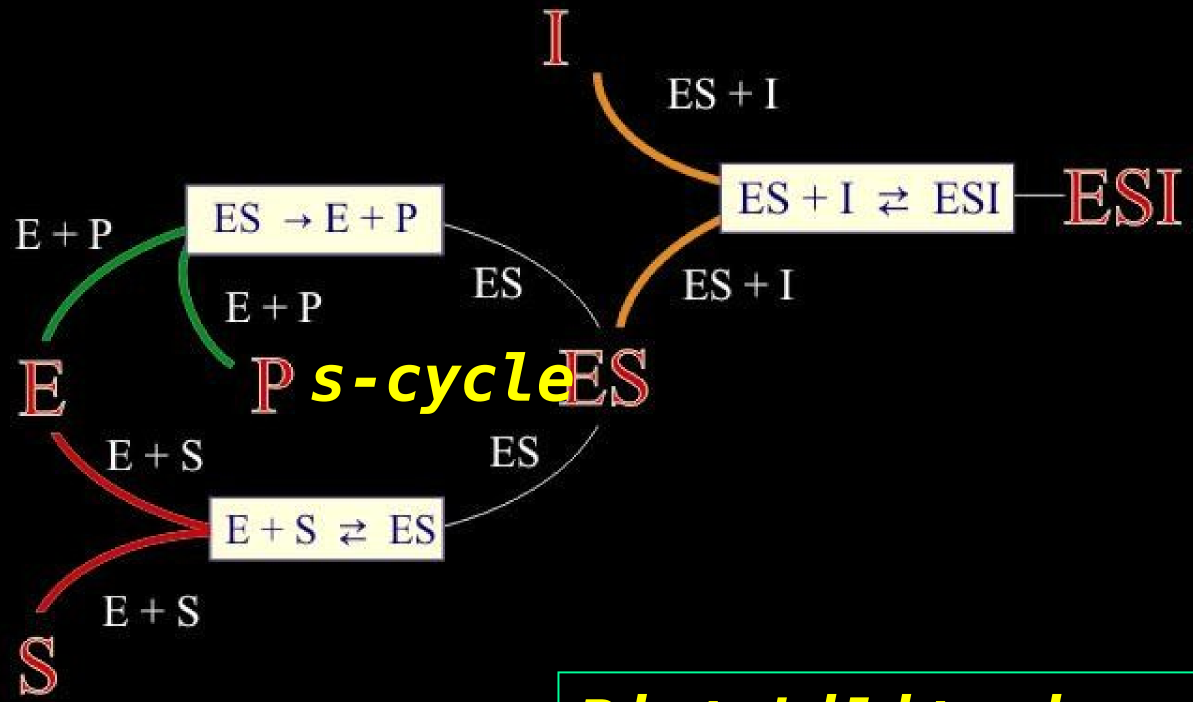
Elementary Enzyme Catalysis with Uncompetitive Inhibition

$E + S \rightleftarrows ES \rightarrow E + P$
$ES + I \rightleftarrows ESI$



Elementary Enzyme Catalysis with Uncompetitive Inhibition

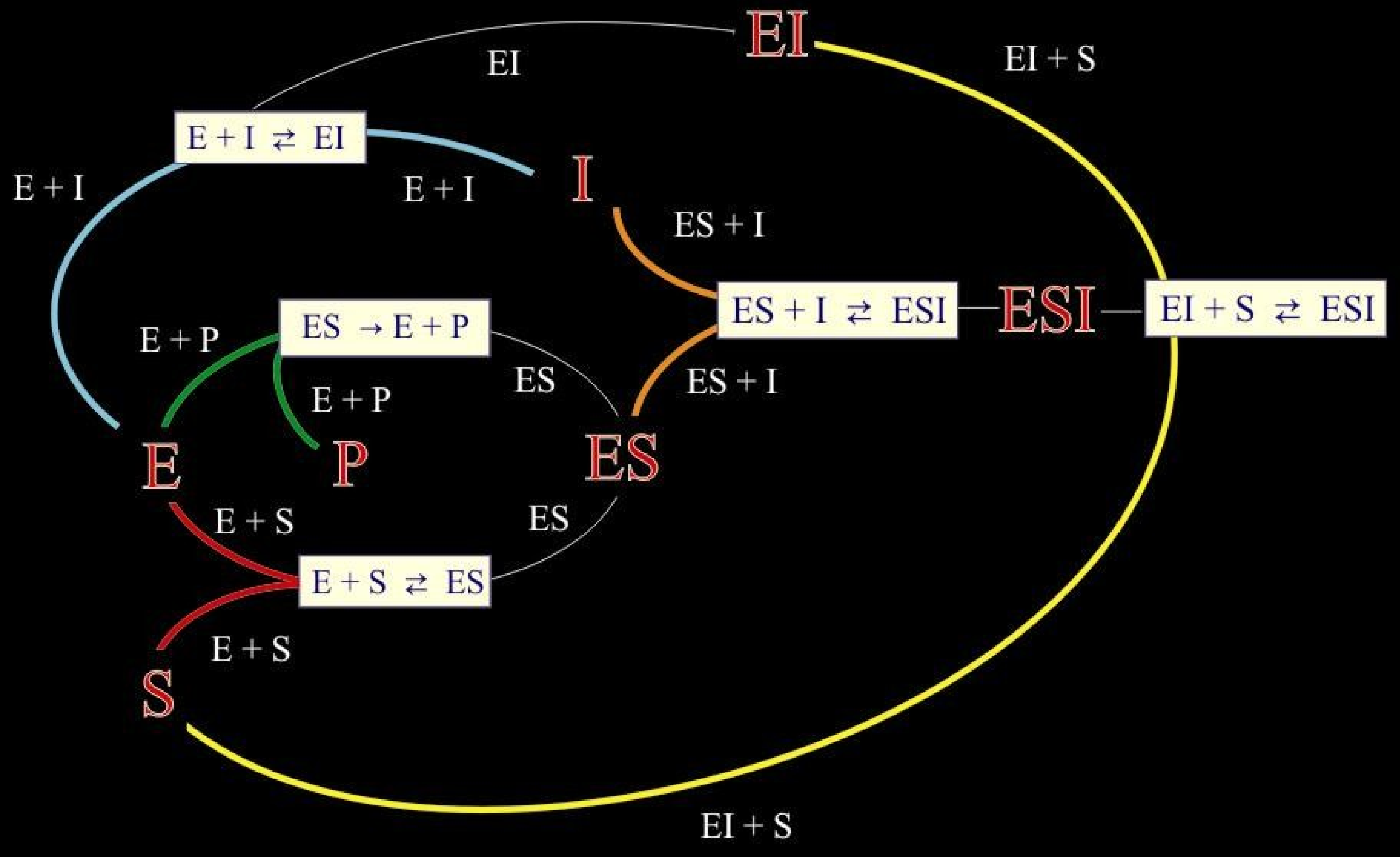
E + S ⇄ ES → E + P
ES + I ⇄ ESI



Bistability impossible, regardless of parameter value

Elementary Enzyme Catalysis with Mixed Inhibition

E + S ⇄ ES → E + P
E + I ⇄ EI
EI + S ⇄ ES ⇄ ES + I



Theorem: ***Consider a reaction network for which the species-reaction graph has the following properties:***

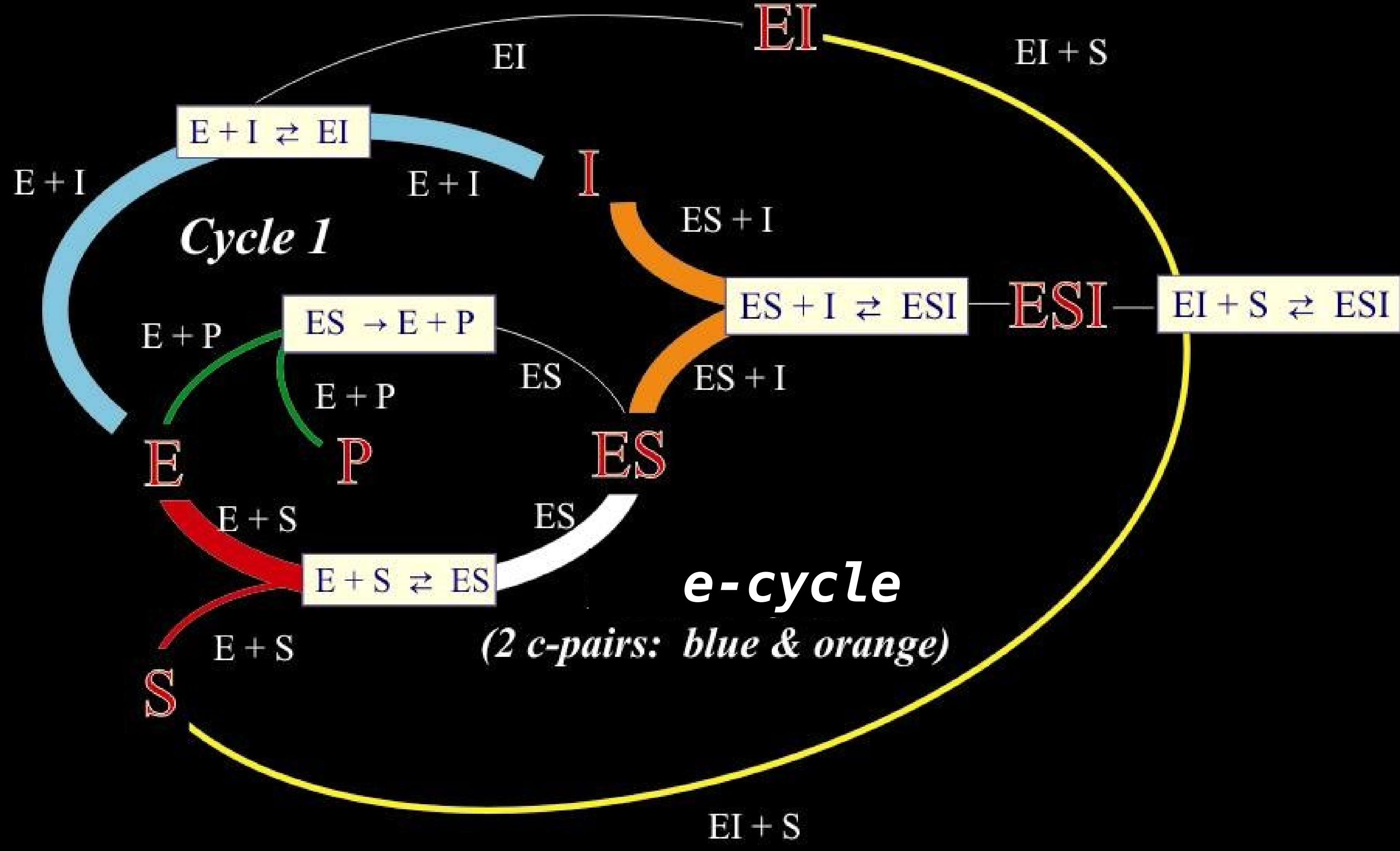
(i) Each cycle is an o-cycle or an s-cycle (or both).

(ii) No c-pair is split by two e-cycles.

Then, regardless of parameter values, the corresponding system of mass-action differential equations does not have the capacity for bistability.

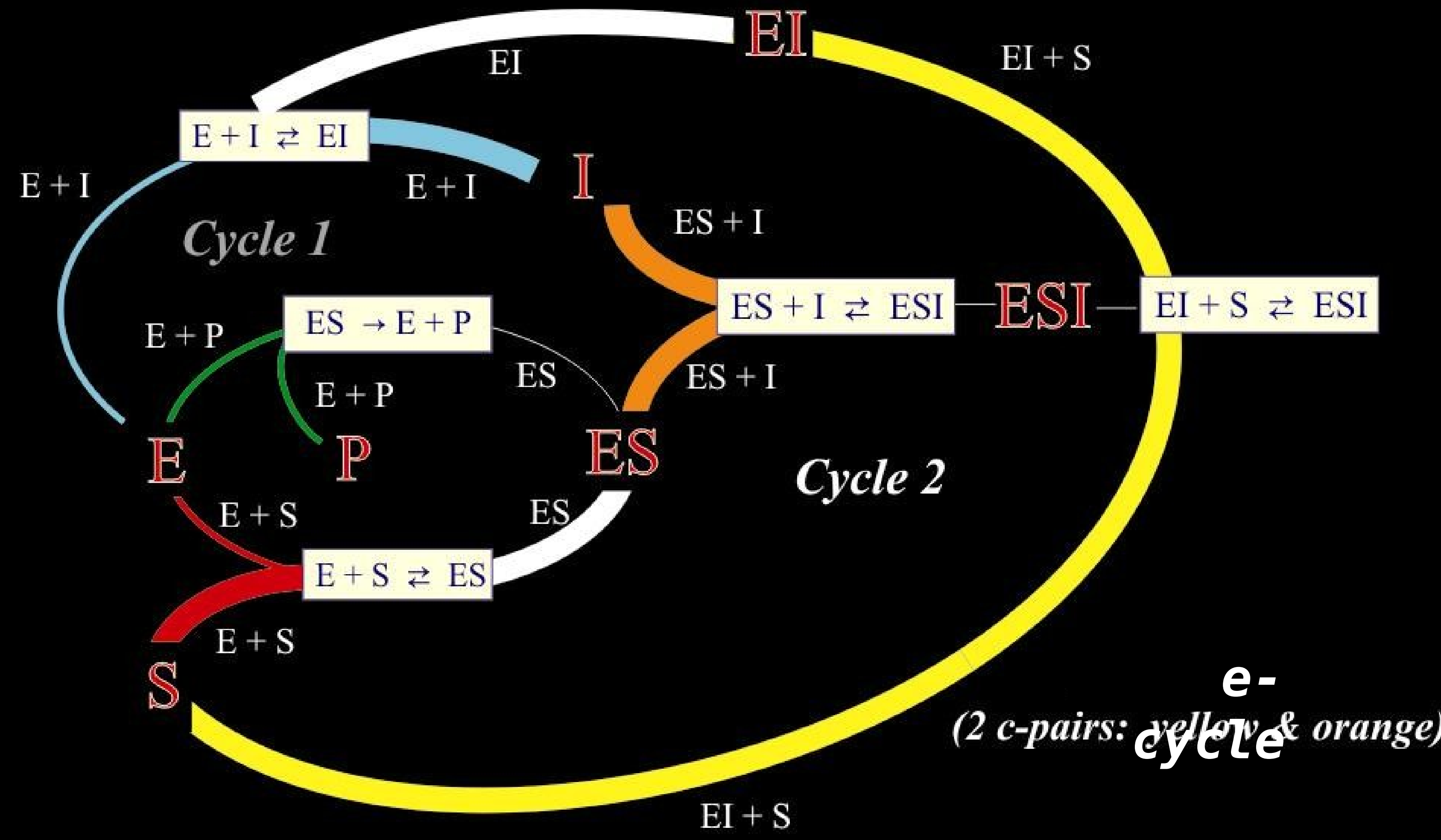
Elementary Enzyme Catalysis with Mixed Inhibition

E + S ⇄ ES → E + P
E + I ⇄ EI
EI + S ⇄ ES ⇄ ES + I



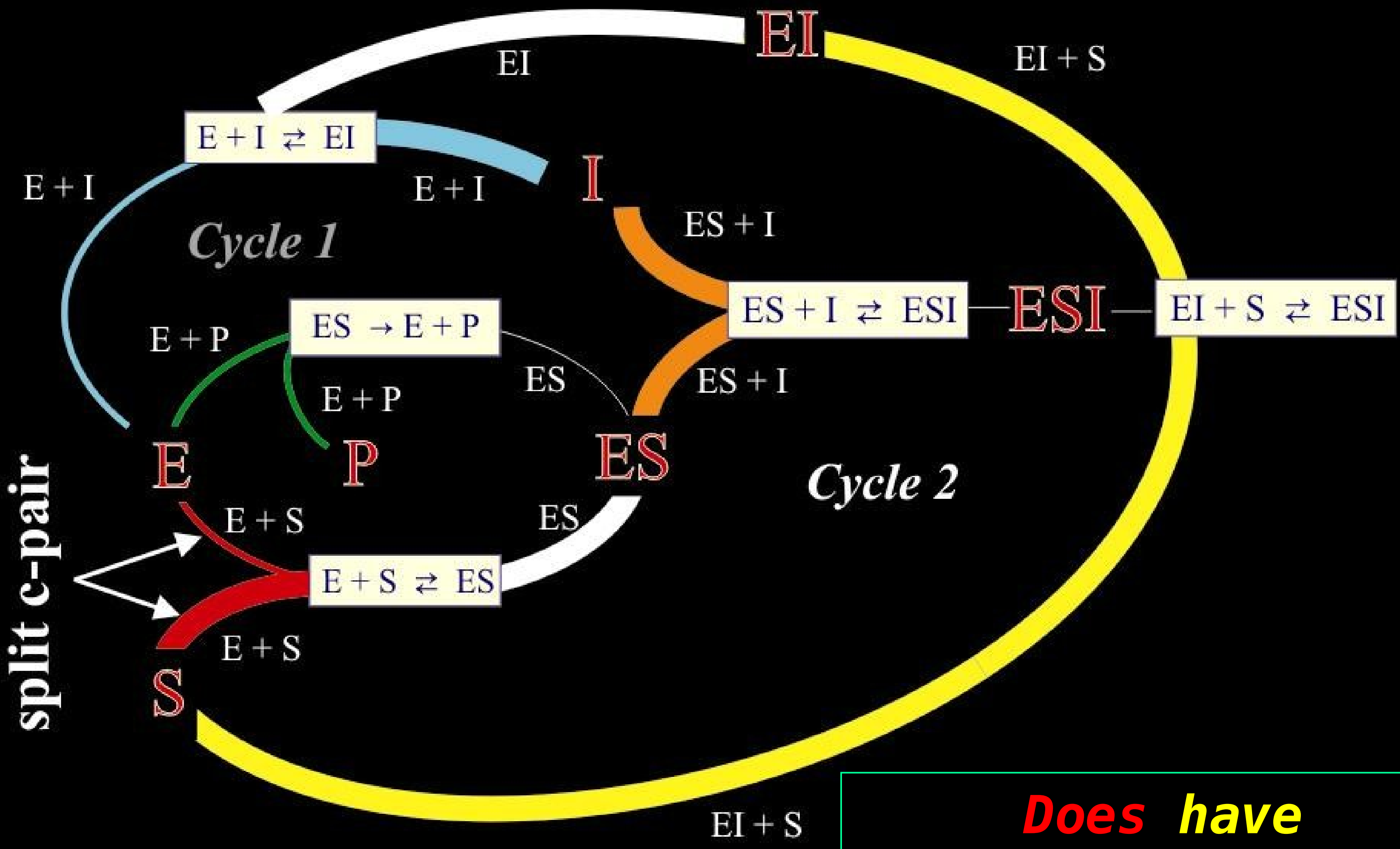
Elementary Enzyme Catalysis with Mixed Inhibition

E + S ⇄ ES → E + P
E + I ⇄ EI
EI + S ⇄ ES ⇄ ES + I



Elementary Enzyme Catalysis with Mixed Inhibition

E + S ⇄ ES → E + P
E + I ⇄ EI
EI + S ⇄ ES ⇄ ES + I



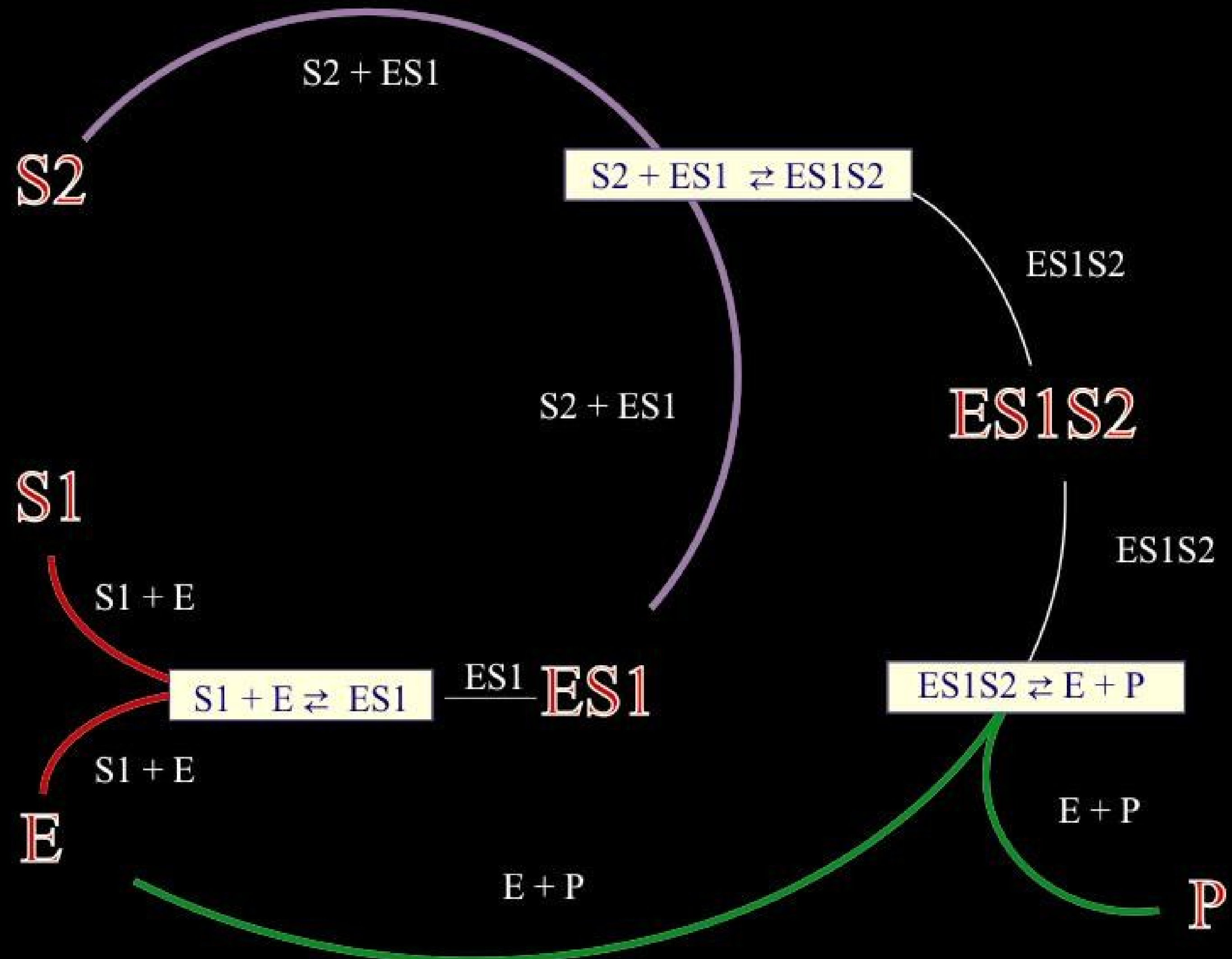
Does have capacity for

	Network	*Remark*	*Capacity for Bistability*
5.	$E + S1 \rightleftarrows ES1$ $S2 + ES1 \rightleftarrows ES1S2 \rightarrow E + P$	Two-substrate enzyme catalysis with ordered substrate-binding $S1 + S2 \rightarrow P$	NO
6.	$E + S1 \rightleftarrows ES1$ $E + S2 \rightleftarrows ES2$ $S2 + ES1 \rightleftarrows ES1S2 \rightleftarrows S1 + ES2$ $\downarrow$ $E + P$	Two-substrate enzyme catalysis with unordered substrate-binding $S1 + S2 \rightarrow P$	**YES**

Two-Substrate Enzyme Catalysis with Ordered Binding

$S1 + E \rightleftarrows ES1$

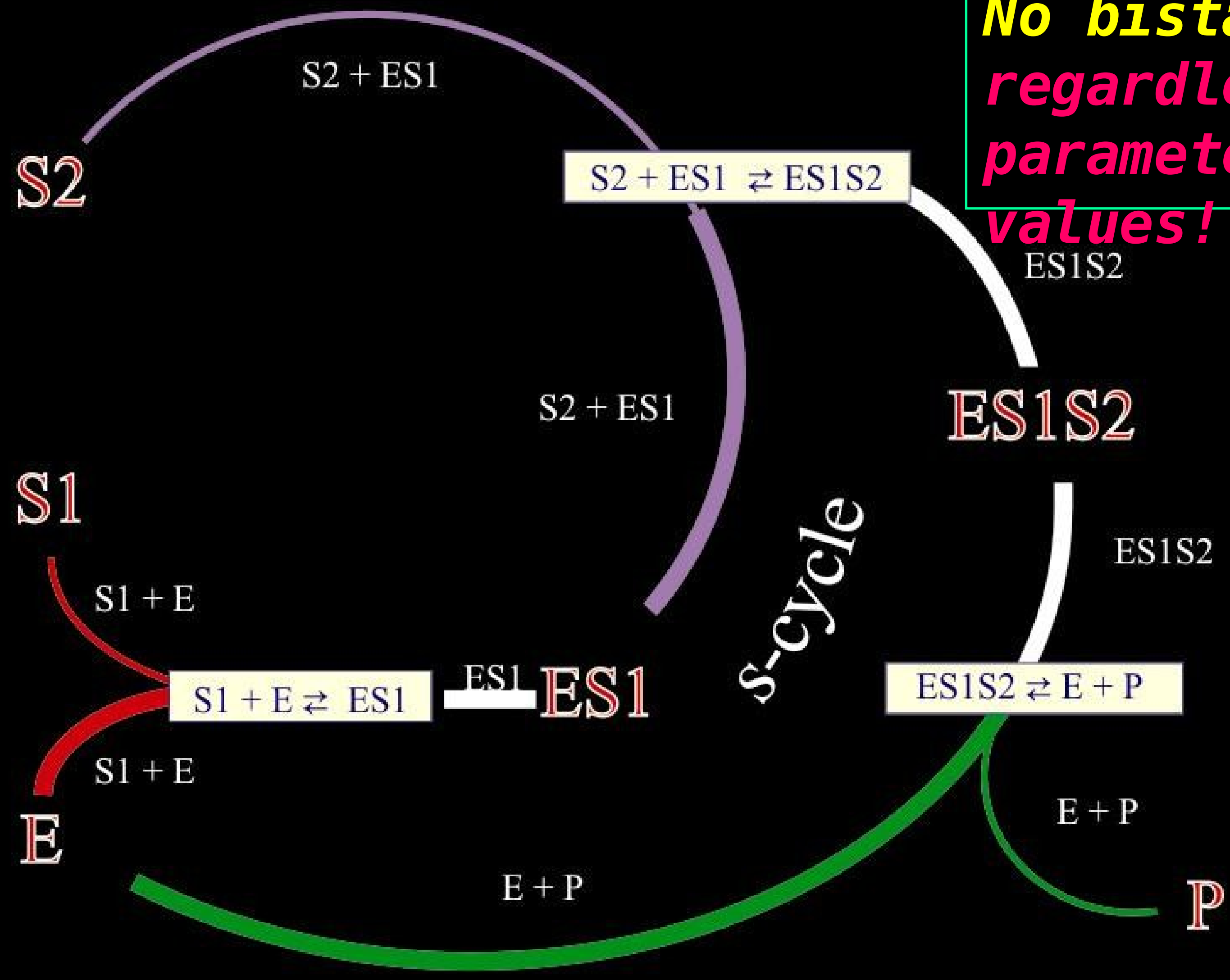
$S2 + ES1 \rightleftarrows ES1S2 \rightarrow E + P$

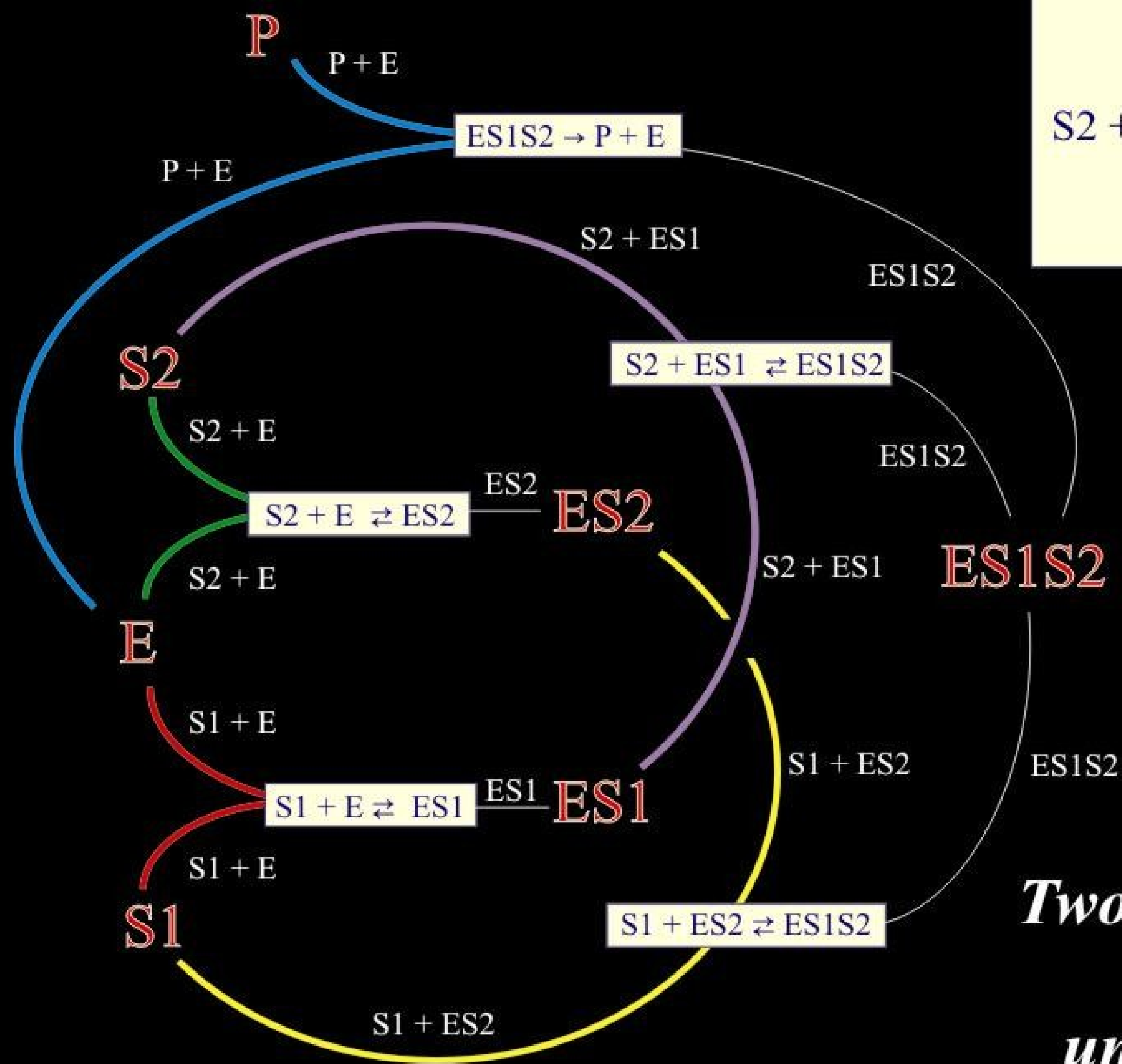


Two-Substrate Enzyme Catalysis with Ordered Binding

$$S1 + E \rightleftarrows ES1$$
$$S2 + ES1 \rightleftarrows ES1S2 \rightarrow E + P$$

No bistability, regardless of parameter values!





$$S1 + E \rightleftarrows ES1$$
$$S2 + E \rightleftarrows ES2$$
$$S2 + ES1 \rightleftarrows ES1S2 \rightleftarrows S1 + ES2$$
$$\downarrow$$
$$P + E$$

Two-substrate enzyme catalysis with unordered binding

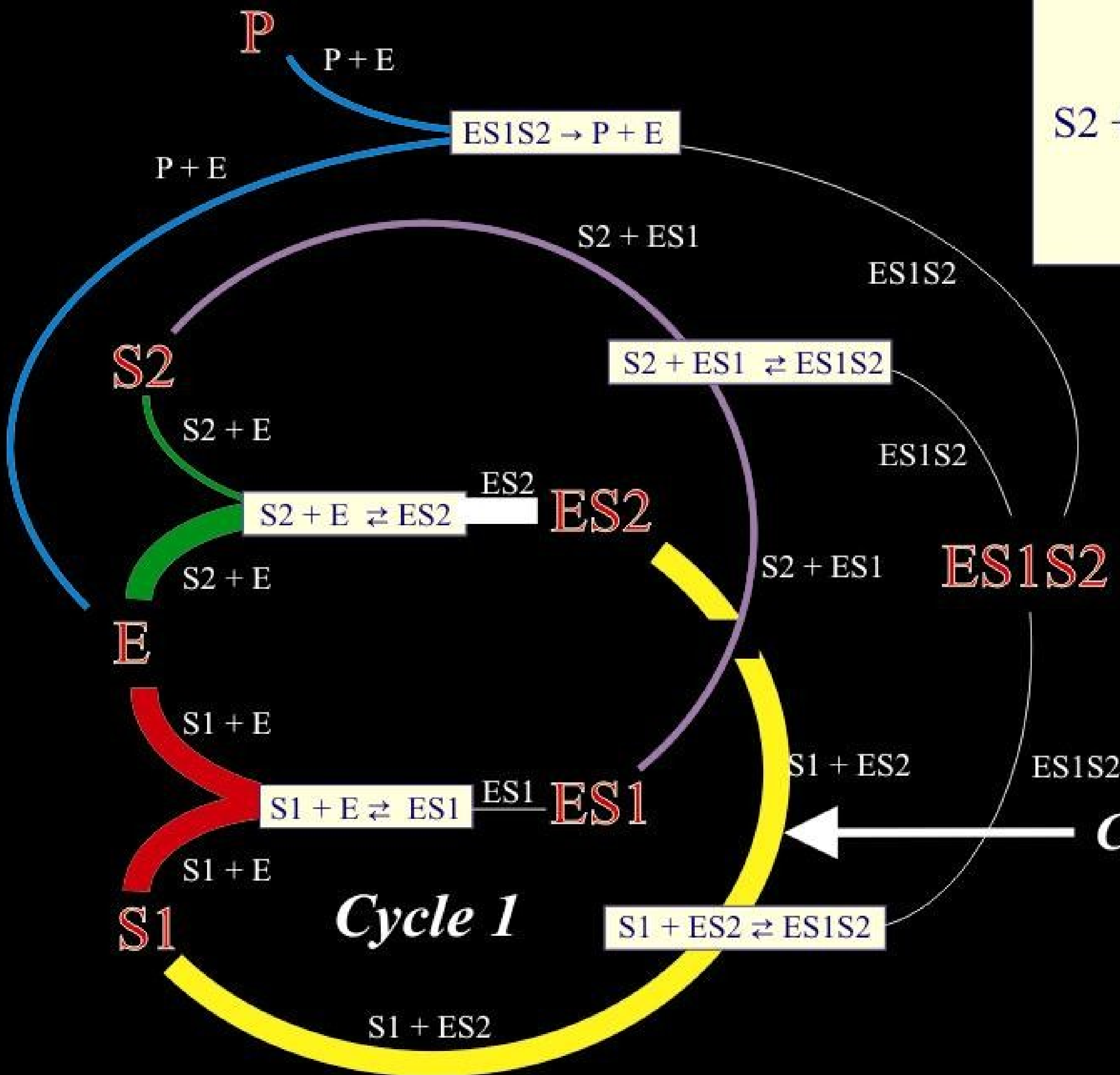
Theorem: ***Consider a reaction network for which the species-reaction graph has the following properties:***

(i) Each cycle is an o-cycle or an s-cycle (or both).

(ii) No c-pair is split by two e-cycles.

Then, regardless of parameter values, the corresponding system of mass-action differential equations does not have the capacity for bistability.

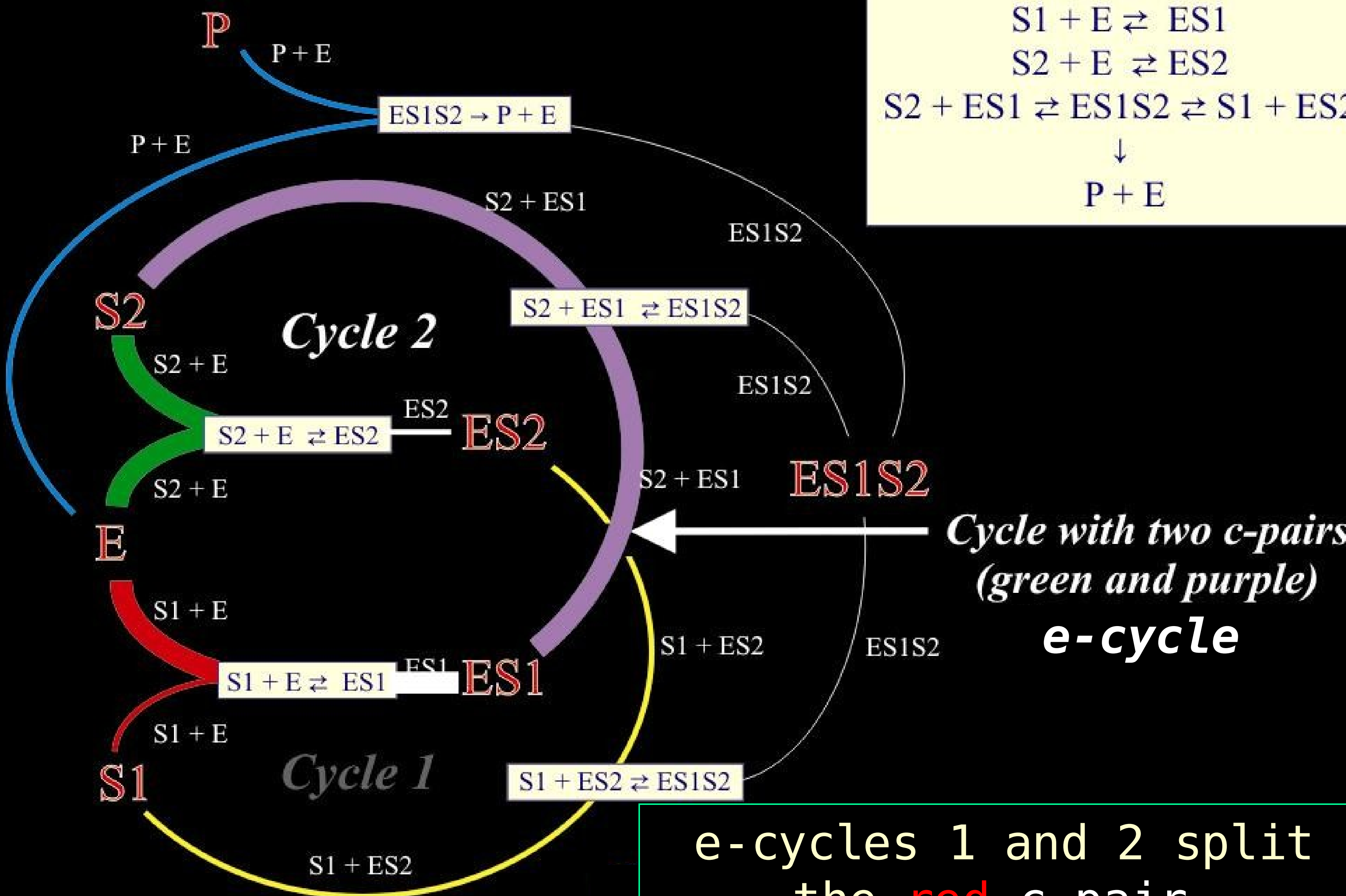
$$
\begin{gathered}
S1 + E \rightleftarrows ES1 \\
S2 + E \rightleftarrows ES2 \\
S2 + ES1 \rightleftarrows ES1S2 \rightleftarrows S1 + ES2 \\
\downarrow \\
P + E
\end{gathered}
$$



Cycle with two c-pairs
(red and yellow)

e-cycle

$$S1 + E \rightleftarrows ES1$$
$$S2 + E \rightleftarrows ES2$$
$$S2 + ES1 \rightleftarrows ES1S2 \rightleftarrows S1 + ES2$$
$$\downarrow$$
$$P + E$$



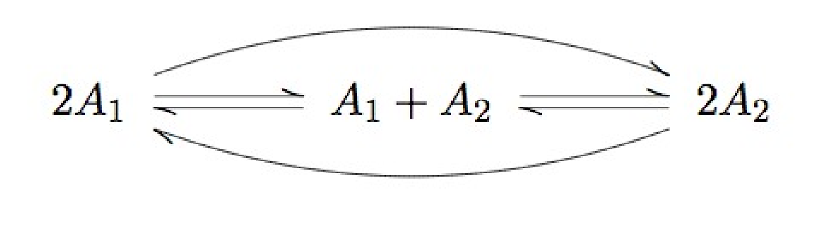
e-cycles 1 and 2 split the red c-pair.

Does have capacity for

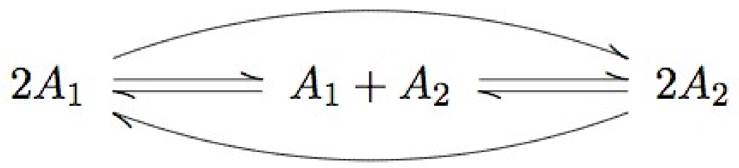
Outline

- *Examples*
- *Bistable biochemical networks*
- *The global attractor conjecture*

Mass-action kinetics



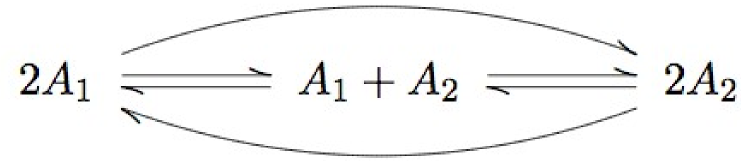
Mass-action kinetics



$$\dot{c}_{A_1} = -k_{2A_1\to A_1+A_2}c_{A_1}^2 + k_{A_1+A_2\to 2A_1}c_{A_1}c_{A_2} - k_{A_1+A_2\to 2A_2}c_{A_1}c_{A_2}$$
$$+ k_{2A_2\to A_1+A_2}c_{A_2}^2 - 2k_{2A_1\to 2A_2}c_{A_1}^2 + 2k_{2A_2\to 2A_1}c_{A_2}^2$$

$$\dot{c}_{A_2} = k_{2A_1\to A_1+A_2}c_{A_1}^2 - k_{A_1+A_2\to 2A_1}c_{A_1}c_{A_2} + k_{A_1+A_2\to 2A_2}c_{A_1}c_{A_2}$$
$$- k_{2A_2\to A_1+A_2}c_{A_2}^2 + 2k_{2A_1\to 2A_2}c_{A_1}^2 - 2k_{2A_2\to 2A_1}c_{A_2}^2$$

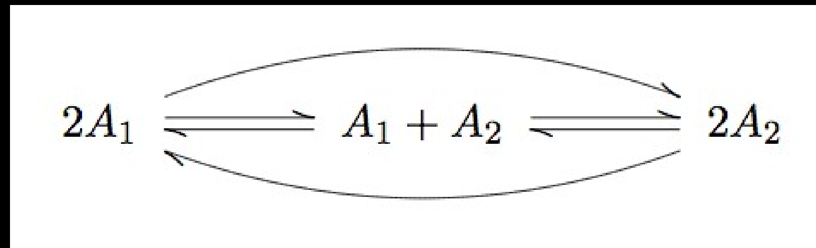
Mass-action kinetics



$$
\begin{aligned}
\dot{c}_{A_1} = \; & -k_{2A_1\to A_1+A_2} c_{A_1}^2 + k_{A_1+A_2\to 2A_1} c_{A_1} c_{A_2} - k_{A_1+A_2\to 2A_2} c_{A_1} c_{A_2} \\
& + k_{2A_2\to A_1+A_2} c_{A_2}^2 - 2k_{2A_1\to 2A_2} c_{A_1}^2 + 2k_{2A_2\to 2A_1} c_{A_2}^2 \\
\dot{c}_{A_2} = \; & k_{2A_1\to A_1+A_2} c_{A_1}^2 - k_{A_1+A_2\to 2A_1} c_{A_1} c_{A_2} + k_{A_1+A_2\to 2A_2} c_{A_1} c_{A_2} \\
& - k_{2A_2\to A_1+A_2} c_{A_2}^2 + 2k_{2A_1\to 2A_2} c_{A_1}^2 - 2k_{2A_2\to 2A_1} c_{A_2}^2
\end{aligned}
$$

$$
\begin{aligned}
\begin{bmatrix} \dot{c}_1 \\ \dot{c}_2 \end{bmatrix} = \; & k_{2A_1\to A_1+A_2} c^{2A_1} \begin{bmatrix} -1 \\ 1 \end{bmatrix} + k_{A_1+A_2\to 2A_1} c^{A_1+A_2} \begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_{A_1+A_2\to 2A_2} c^{A_1+A_2} \begin{bmatrix} -1 \\ 1 \end{bmatrix} \\
& + k_{2A_2\to A_1+A_2} c^{2A_2} \begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_{2A_1\to 2A_2} c^{2A_1} \begin{bmatrix} -2 \\ 2 \end{bmatrix} + k_{2A_2\to 2A_1} c^{2A_2} \begin{bmatrix} 2 \\ -2 \end{bmatrix}.
\end{aligned}
$$

Mass-action kinetics



$$\begin{bmatrix} \dot{c}_1 \\ \dot{c}_2 \end{bmatrix} = k_{2A_1 \to A_1+A_2} c^{2A_1} \begin{bmatrix} -1 \\ 1 \end{bmatrix} + k_{A_1+A_2 \to 2A_1} c^{A_1+A_2} \begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_{A_1+A_2 \to 2A_2} c^{A_1+A_2} \begin{bmatrix} -1 \\ 1 \end{bmatrix}$$

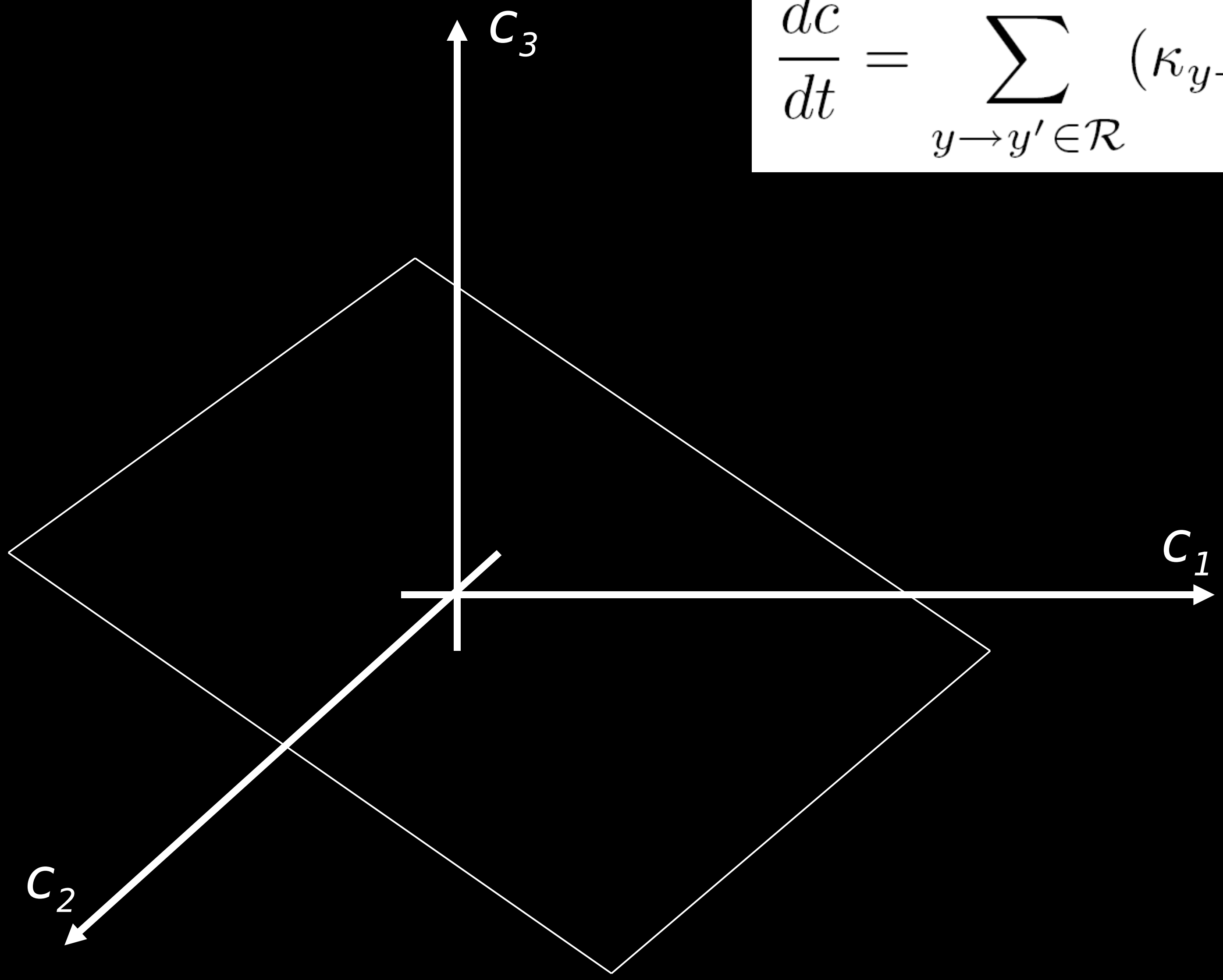
$$+ k_{2A_2 \to A_1+A_2} c^{2A_2} \begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_{2A_1 \to 2A_2} c^{2A_1} \begin{bmatrix} -2 \\ 2 \end{bmatrix} + k_{2A_2 \to 2A_1} c^{2A_2} \begin{bmatrix} 2 \\ -2 \end{bmatrix} .$$

$$\dot{c} = \sum_{y \to y' \in \mathscr{R}} k_{y \to y'} c^y (y' - y)$$

$$c^y = \prod_{s \in \mathcal{S}} (c_s)^{y_s}$$

Invariant subspaces

$$\frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y)$$



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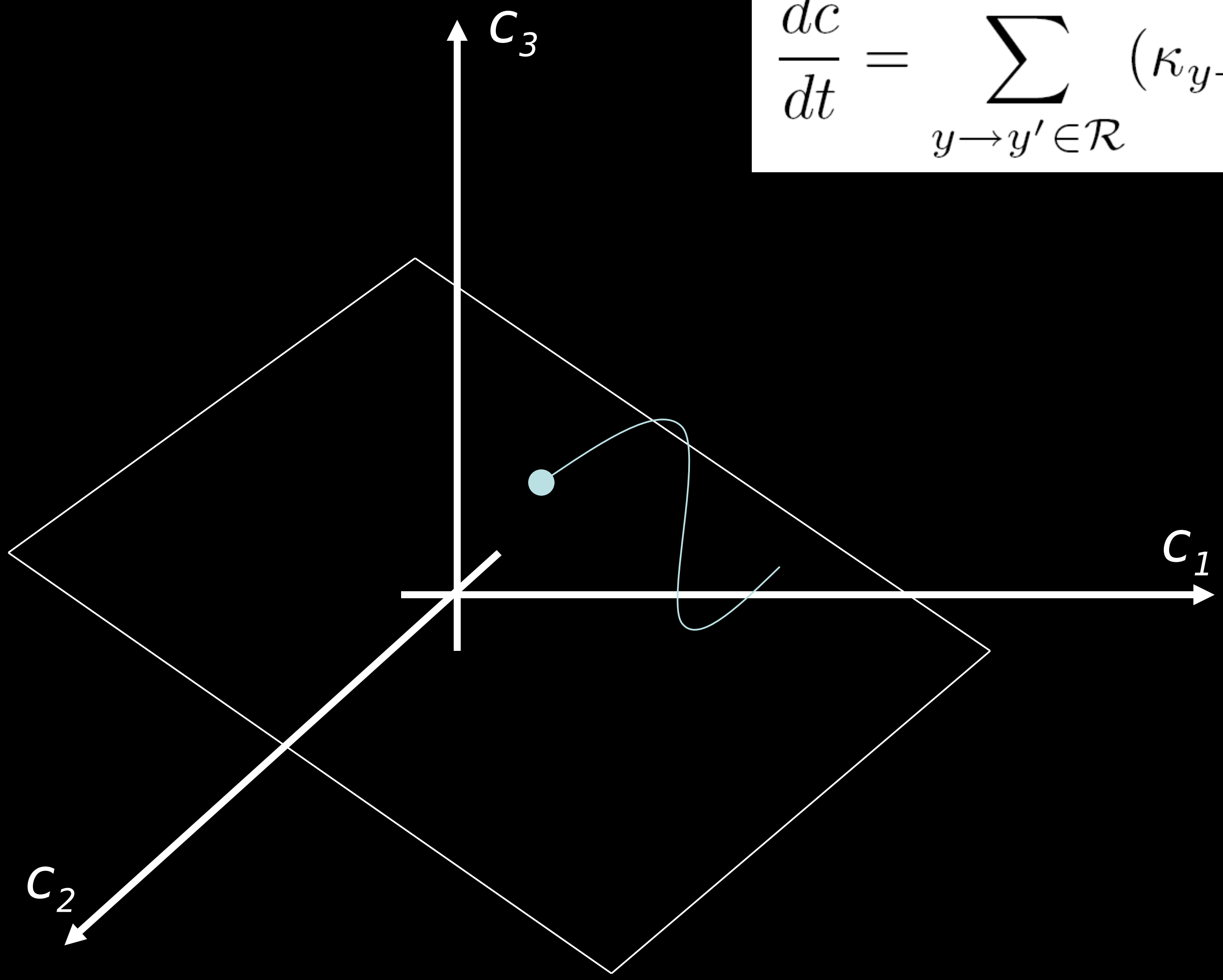

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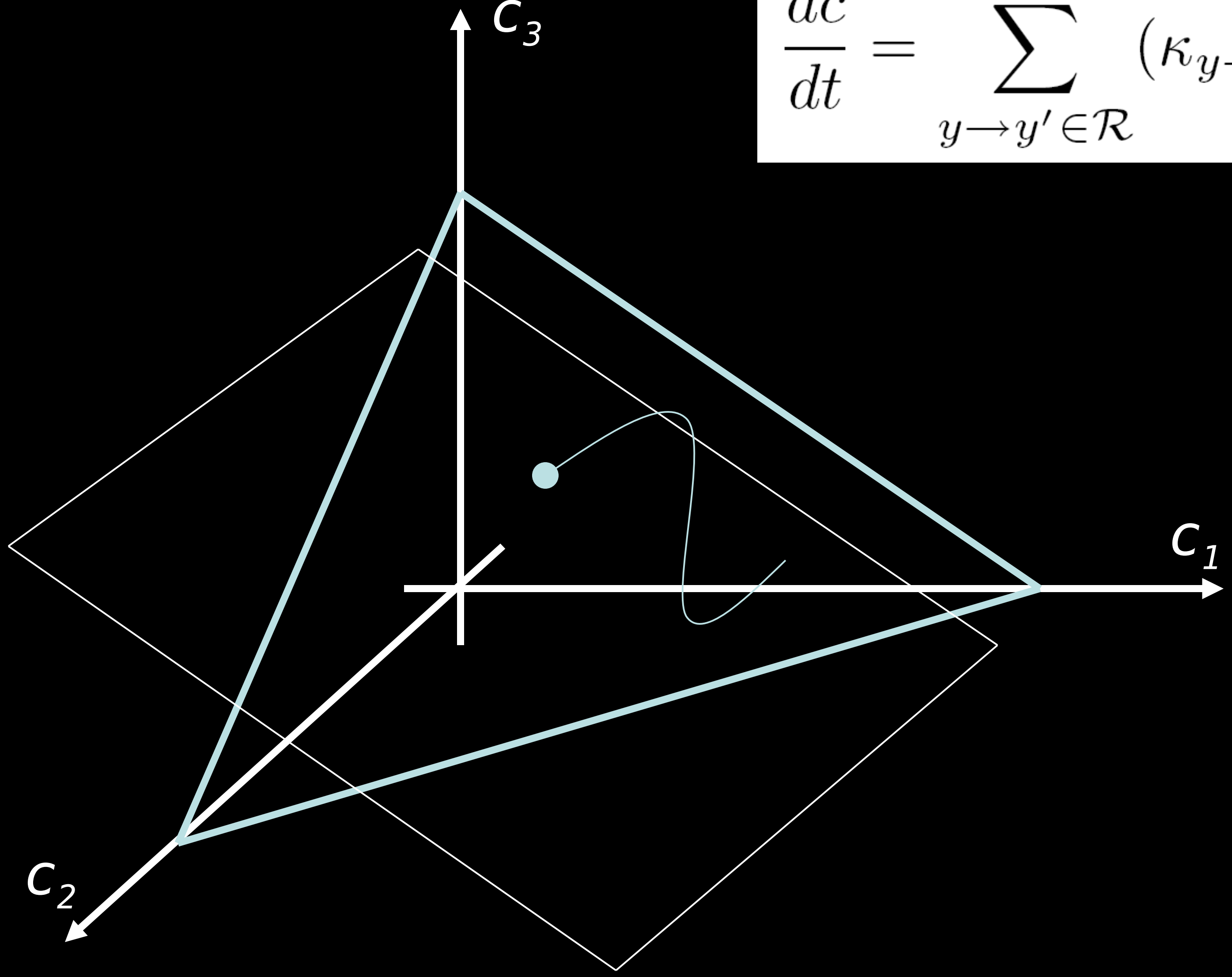

Invariant subspaces

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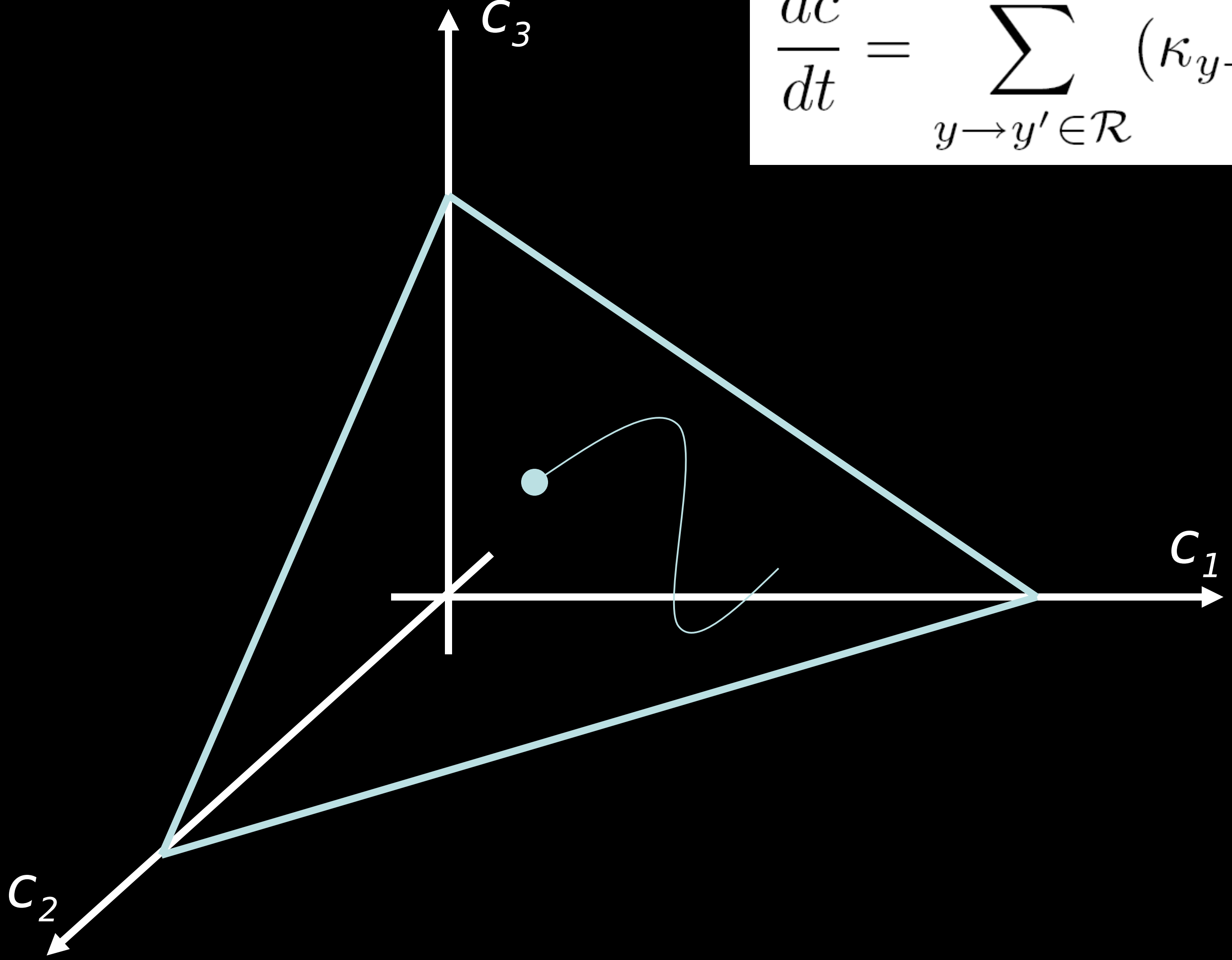
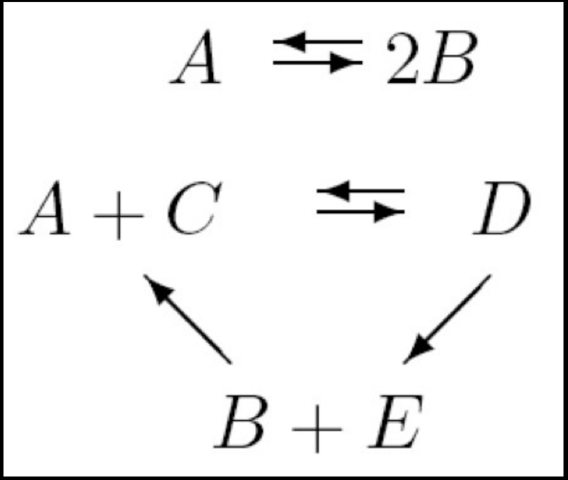


Deficiency theory (Feinberg, Horn, and Jackson)



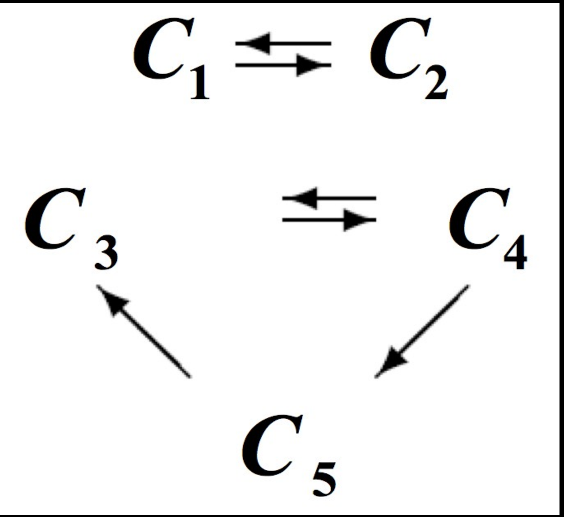
Definition. *The deficiency of a reaction network is*

n - l - s, where

n = the number of complexes

l = the number of linkage classes

s = the dimension of the stoichiometric subspace



$$
\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E\ .
\end{aligned}
$$

Example: $S = \text{span}\{2B - A, A + C - D, B + E - D, B + E - A - C\}$.

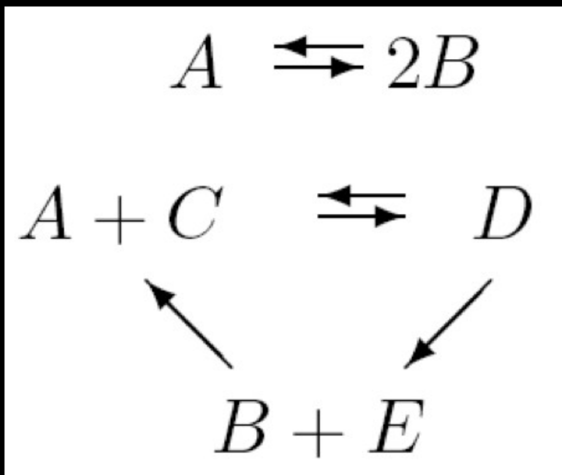
Since $B + E - A - C = (B + E - D) - (A + C - D)$, this simplifies further to give

$$S = \text{span}\{2B - A, A + C - D, B + E - D\}$$

Deficiency zero theory (Feinberg, Horn, and Jackson)

Theorem. *If a reaction network has deficiency zero, then there exists a unique positive equilibrium in each stoichiometric subspace, and this equilibrium is complex balanced.*

Deficiency theory (Feinberg, Horn, and Jackson)



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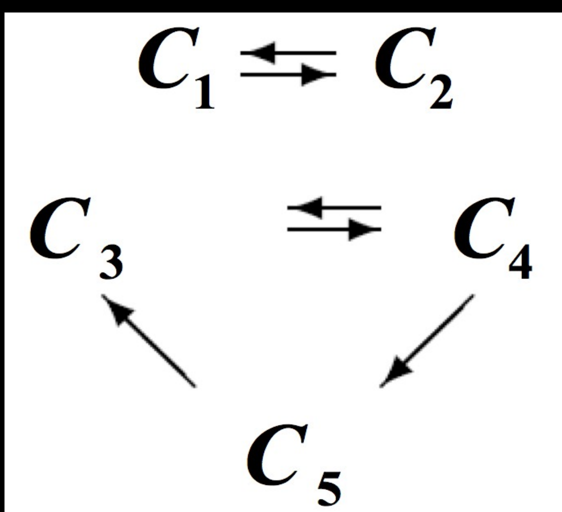

$$
\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \,.
\end{aligned}
$$

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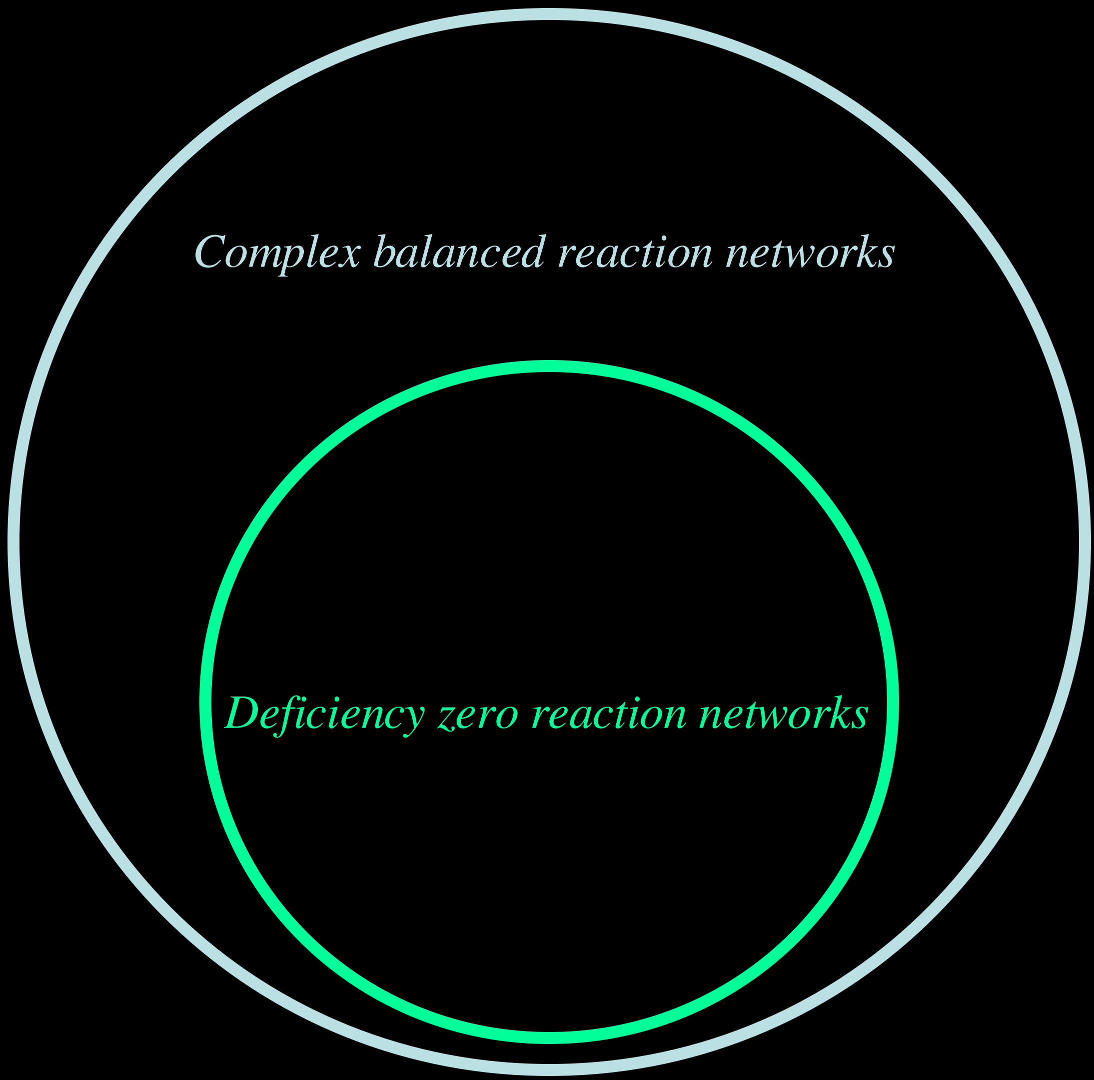
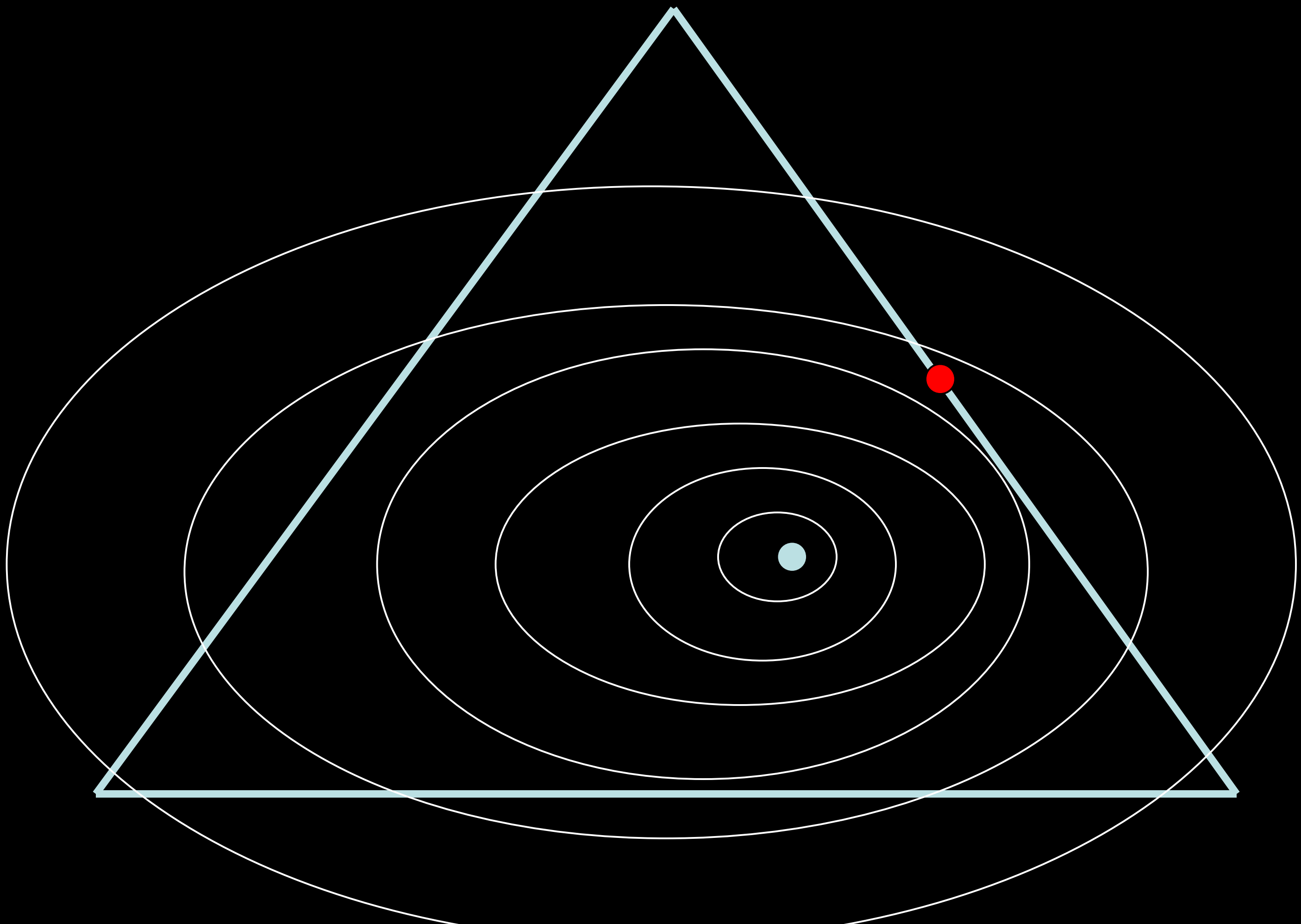
Deficiency zero theory (Feinberg, Horn, and Jackson)

Theorem. *If a reaction network has deficiency zero, then there exists a unique positive equilibrium in each stoichiometric subspace, and this equilibrium is complex balanced.*

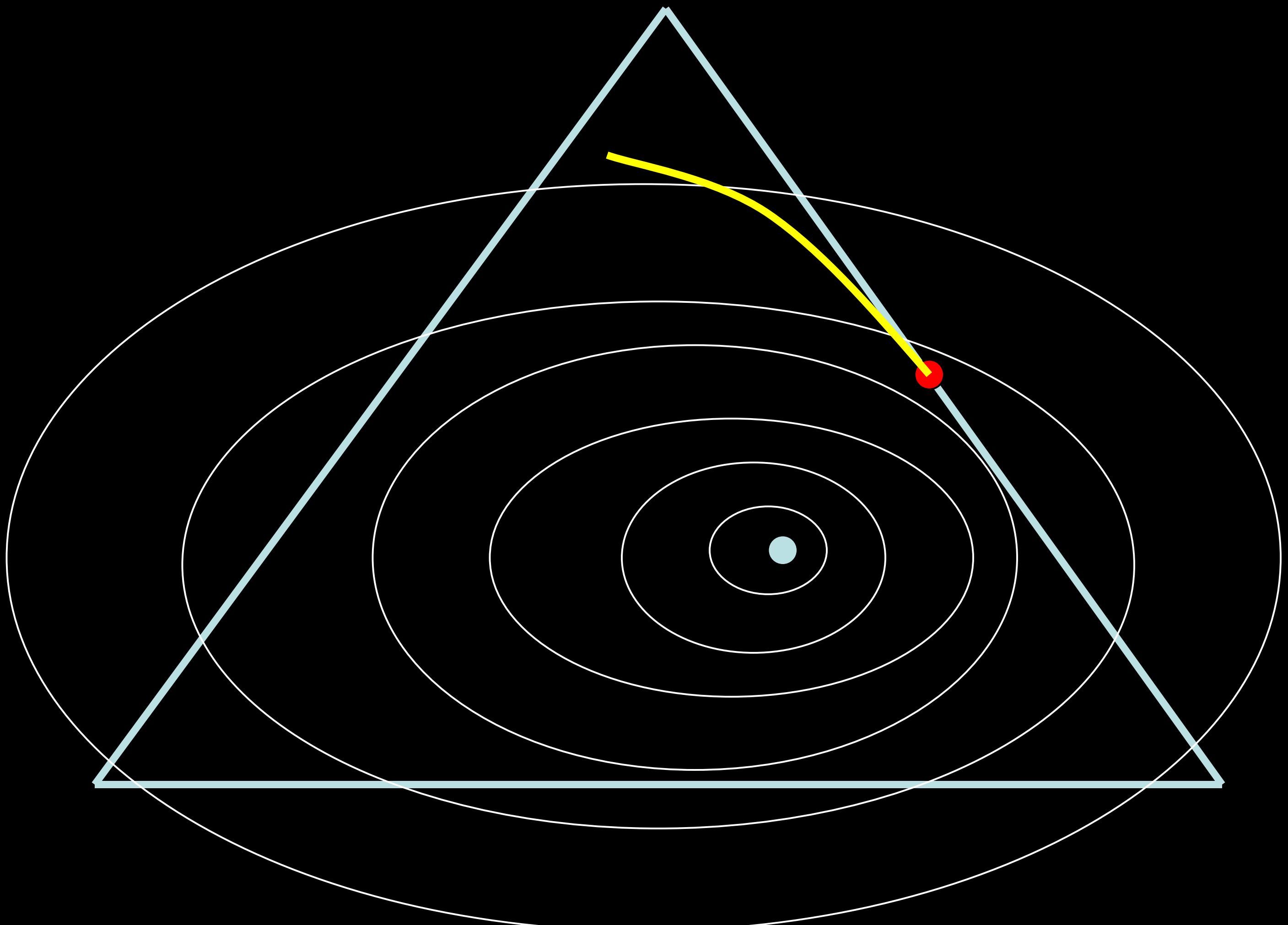
Theorem. *If a reaction network has complex balanced equilibrium, then, for each stoichiometric subspace, there exists a strict Lyapunov function with a minimum at that equilibrium.*


Complex balanced reaction networks
Deficiency zero reaction networks

Lyapunov function and boundary equilibria

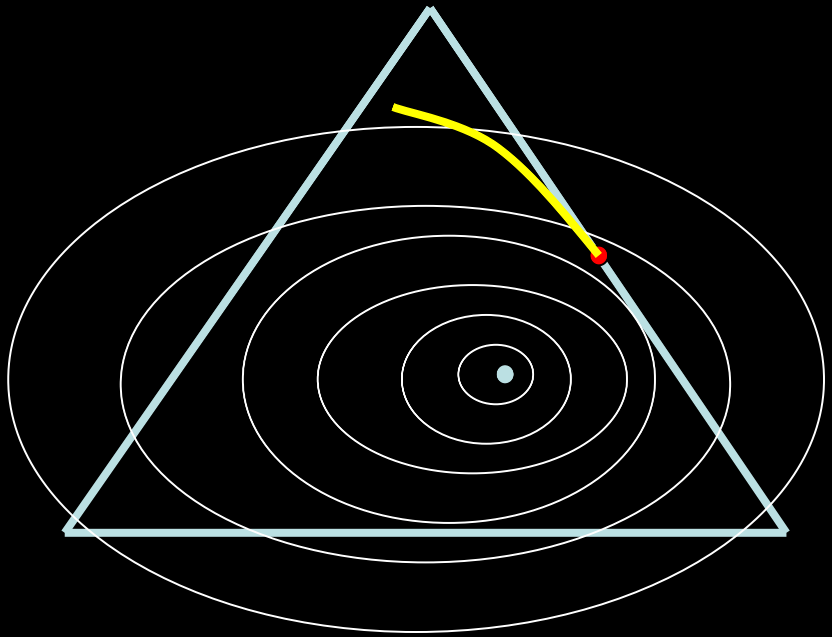


Lyapunov function and boundary equilibria



Global Attractor Conjecture

Conjecture. *If a reaction network has a complex balanced equilibrium, then any trajectory with positive initial condition converges to that equilibrium.*



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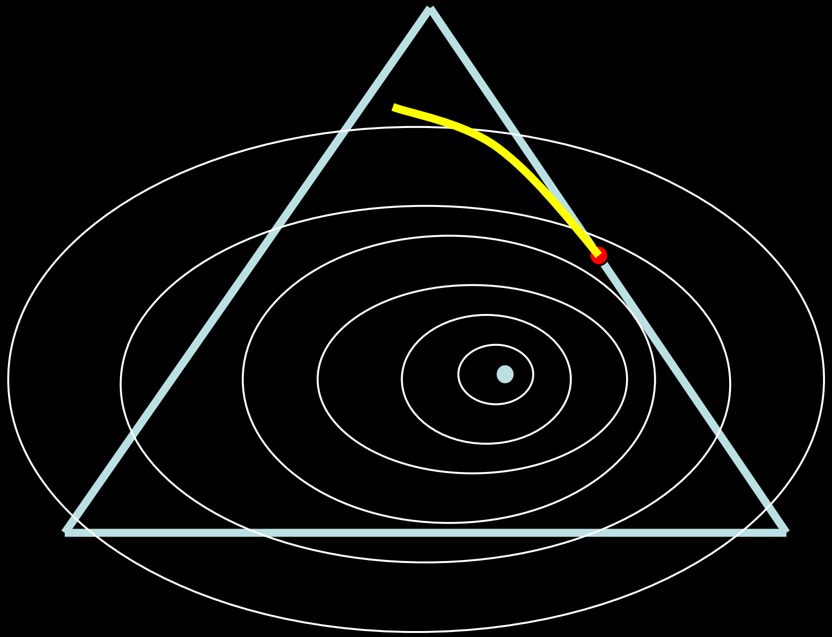

How do we prove this?

No boundary equilibria.
(Angeli, De Leenheer, Sontag)

Even if there exist boundary equilibria, they are "repelling".

Global Attractor Conjecture

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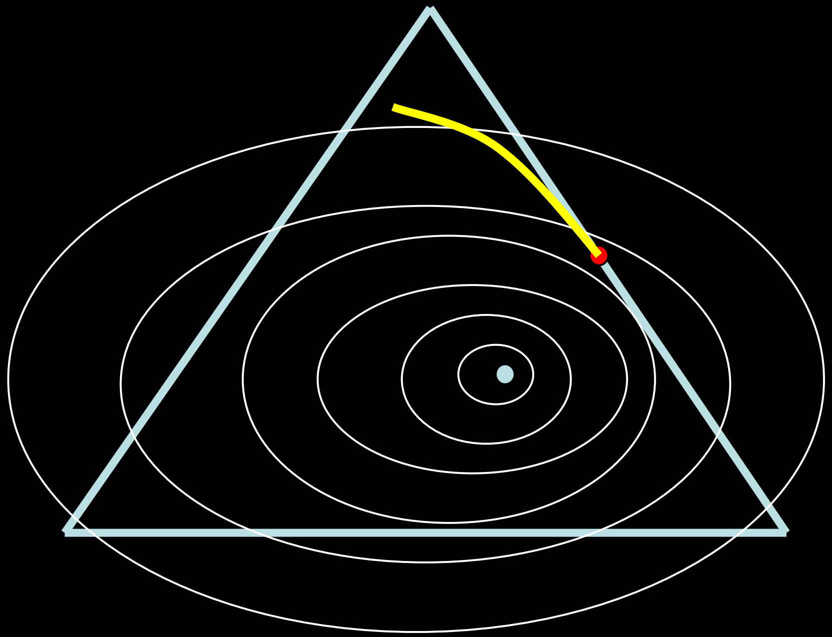
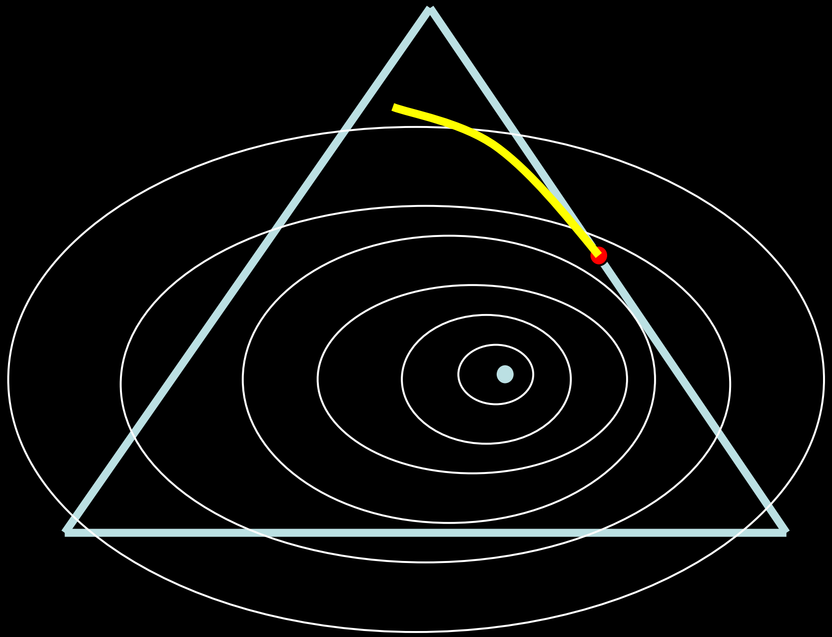


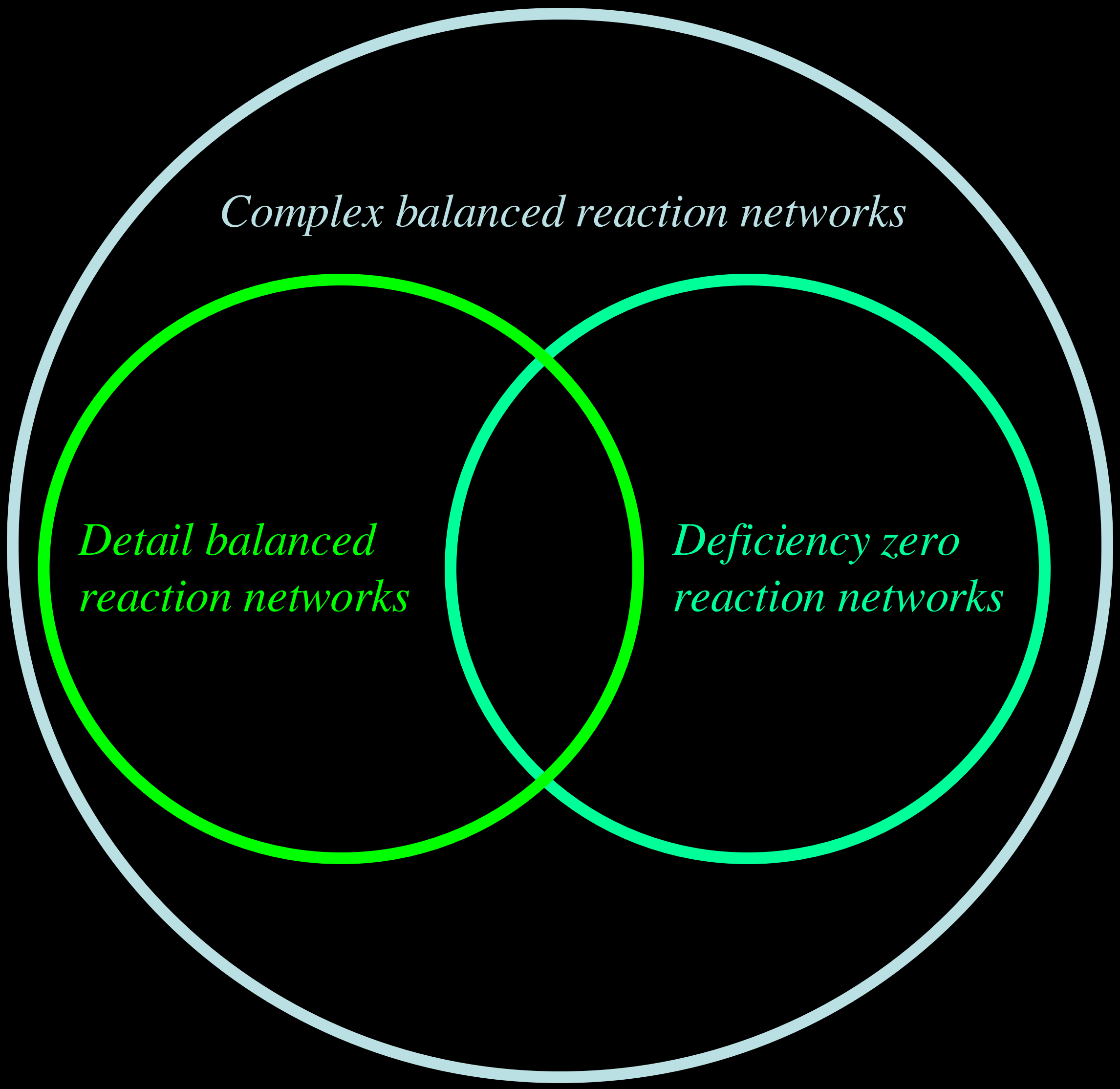
Theorem 1. *If a reaction network has a complex balanced equilibrium, then no trajectory with positive initial condition can converge to a vertex of its stoichiometric compatibility class.*

Global Attractor Conjecture

Conjecture. *If a reaction network has a complex balanced equilibrium, then any trajectory with positive initial condition converges to that equilibrium.*

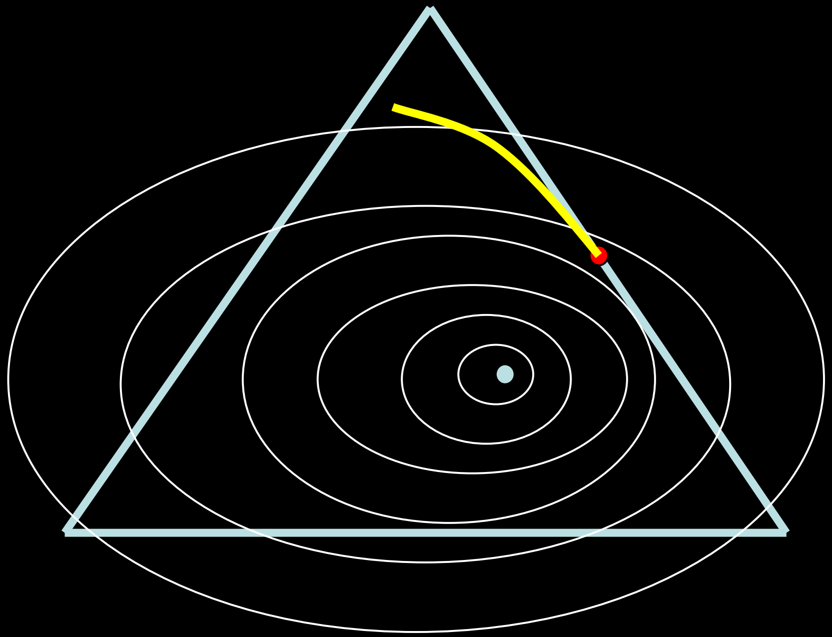


Theorem 2. *If a reaction network has a detailed balanced equilibrium, then no trajectory with positive initial condition can converge to a bounded facet of its stoichiometric compatibility class.*


Complex balanced reaction networks
Detail balanced reaction networks
Deficiency zero reaction networks

Global Attractor Conjecture

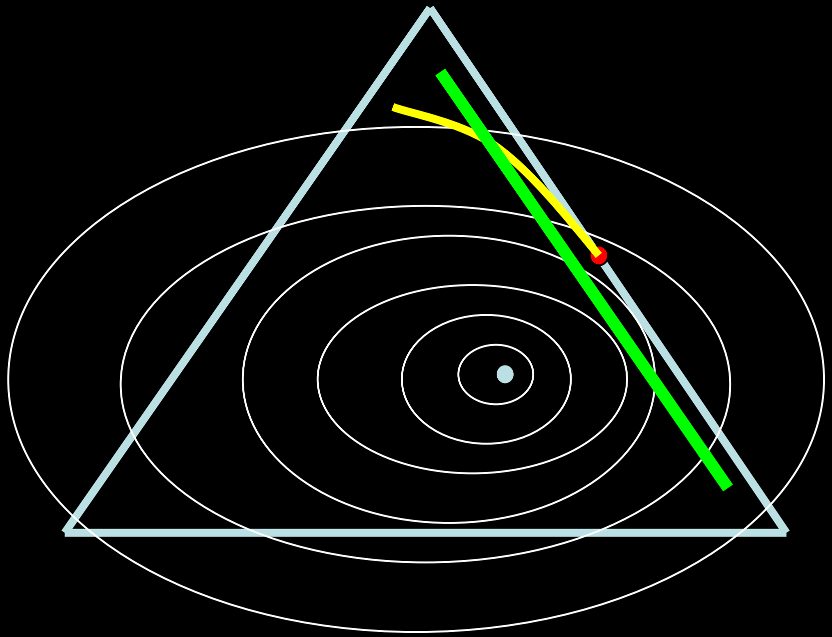
Conjecture. *If a reaction network has a complex balanced equilibrium, then any trajectory with positive initial condition converges to that equilibrium.*



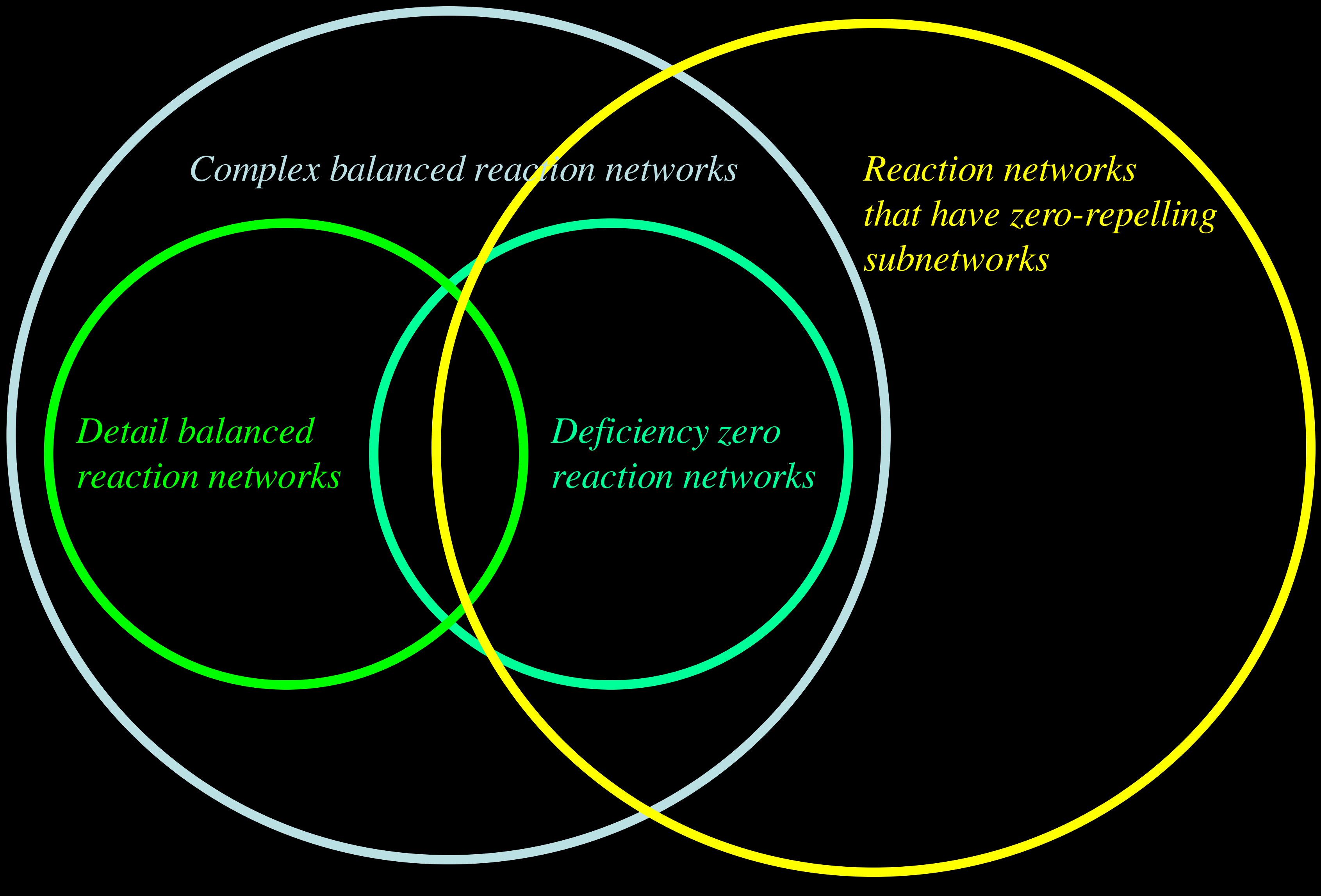
Theorem 3. *If a reaction network has stoichiometric subspace of dimension two, then any trajectory with positive initial condition converges to that equilibrium.*

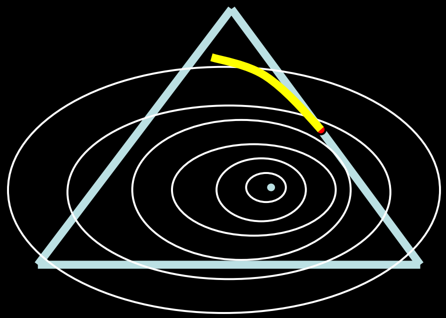
Global Attractor Conjecture

Conjecture. *If a reaction network has a complex balanced equilibrium, then any trajectory with positive initial condition converges to that equilibrium.*



Theorem 4. *If a reaction network has zero-repelling subnetworks, then no trajectory with positive initial condition can converge to a boundary point.*


Complex balanced reaction networks
Reaction networks
that have zero-repelling
subnetworks
Detail balanced
reaction networks
Deficiency zero
reaction networks



Summary

- Conjecture: the complex balancing equilibrium is global attractor.
- The complex balancing equilibrium always exists if the deficiency is zero.
- Proof, under additional assumptions: either the rate constants satisfy additional conditions, or the reaction network has special structure.

Collaborators

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Bernd Sturmfels, Department of Mathematics, UC Berkeley.

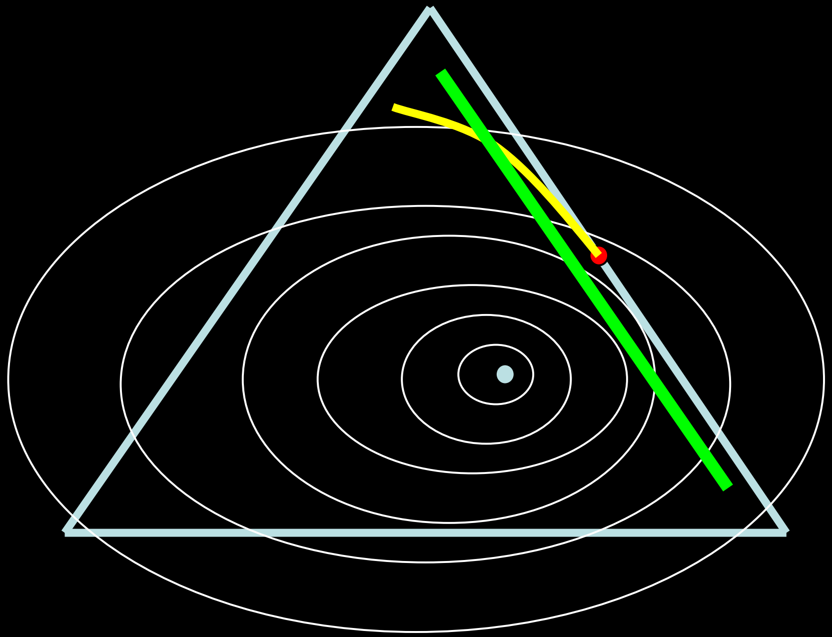
Anne Shiu, Department of Mathematics, Department of Mathematics, UC Berkeley.

Alicia Dickenstein, Department of Mathematics, University of Buenos Aires.

Support: NSF and DOE BACTER Institute.

Global Attractor Conjecture

Conjecture. *If a reaction network has a complex balanced equilibrium, then any trajectory with positive initial condition converges to that equilibrium.*



General Reference

Craciun, G., Tang, Y. and Feinberg, M., Understanding bistability in complex enzyme-driven reaction networks, *Proc. Nat. Acad. Sci. USA,* **103**, 8697-8702, 2006.

References for Proofs

Craciun, G. and Feinberg, M., Multiple equilibria in complex chemical reaction networks: I. The injectivity property, *S.I.A.M. J. Appl. Math*., **65**, 1526-1546, 2005.

Craciun, G. and Feinberg, M., Multiple equilibria in complex chemical reaction networks: II. The species-reaction graph, *S.I.A.M. J. of Appl. Math.,* **66,** 1321-1338, 2006.

Craciun, G. and Feinberg, M., Multiple equilibria in complex chemical reaction networks: Extensions to entrapped species models, *I.E.E. Proc. Systems Biology*, **153,** 179-186, 2006

Given a reaction network, does it have multiple equilibria ?

$$S1 + S2 \xrightarrow{E} P$$

$$S1 + E \underset{2}{\overset{1}{\rightleftarrows}} ES1 \qquad S2 + E \underset{4}{\overset{3}{\rightleftarrows}} ES2$$

$$ES1 + S2 \underset{6}{\overset{5}{\rightleftarrows}} ES1S2 \underset{8}{\overset{7}{\leftrightarrows}} ES2 + S1$$

$$\downarrow 9$$

$$P + E$$

$$
\begin{aligned}
\dot{c}_E &= -k_1 c_E c_{S1} + k_2 c_{ES1} - k_3 c_E c_{S2} + k_4 c_{ES2} + k_9 c_{ES1S2} \\
\dot{c}_{S1} &= -k_1 c_E c_{S1} + k_2 c_{ES1} - k_7 c_{S1} c_{ES2} + k_8 c_{ES1S2} - \xi_{S1} c_{S1} + F_{S1} \\
\dot{c}_{S2} &= -k_3 c_E c_{S2} + k_4 c_{ES2} - k_5 c_{S2} c_{ES1} + k_6 c_{ES1S2} - \xi_{S2} c_{S2} + F_{S2} \\
\dot{c}_{ES1} &= k_1 c_E c_{S1} - k_2 c_{ES1} - k_5 c_{ES1} c_{S2} + k_6 c_{ES1S2} \\
\dot{c}_{ES2} &= k_3 c_E c_{S2} - k_4 c_{ES2} - k_7 c_{ES2} c_{S1} + k_8 c_{ES1S2} \\
\dot{c}_{ES1S2} &= k_5 c_{S2} c_{ES1} + k_7 c_{S1} c_{ES2} - (k_6 + k_8 + k_9) c_{ES1S2} \\
\dot{c}_P &= k_9 c_{ES1S2} - \xi_P c_P
\end{aligned}
$$

$$S1 + S2 \xrightarrow{E} P$$

$$S1 + E \underset{2}{\overset{1}{\rightleftarrows}} ES1 \qquad S2 + E \underset{4}{\overset{3}{\rightleftarrows}} ES2$$

$$ES1 + S2 \underset{6}{\overset{5}{\rightleftarrows}} ES1S2 \underset{8}{\overset{7}{\leftrightarrows}} ES2 + S1$$

$$\downarrow 9$$

$$P + E$$

$$\begin{aligned}
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\dot{c}_{S1} &= -k_1 c_E c_{S1} + k_2 c_{ES1} - k_7 c_{S1} c_{ES2} + k_8 c_{ES1S2} - \xi_{S1} c_{S1} + F_{S1} \\
\dot{c}_{S2} &= -k_3 c_E c_{S2} + k_4 c_{ES2} - k_5 c_{S2} c_{ES1} + k_6 c_{ES1S2} - \xi_{S2} c_{S2} + F_{S2} \\
\dot{c}_{ES1} &= k_1 c_E c_{S1} - k_2 c_{ES1} - k_5 c_{ES1} c_{S2} + k_6 c_{ES1S2} \\
\dot{c}_{ES2} &= k_3 c_E c_{S2} - k_4 c_{ES2} - k_7 c_{ES2} c_{S1} + k_8 c_{ES1S2} \\
\dot{c}_{ES1S2} &= k_5 c_{S2} c_{ES1} + k_7 c_{S1} c_{ES2} - (k_6 + k_8 + k_9) c_{ES1S2} \\
\dot{c}_P &= k_9 c_{ES1S2} - \xi_P c_P
\end{aligned}$$

$p(c,k)$

The Jacobian Criterion

Theorem. *For a fully diffusive reaction network, the associated polynomial function p(c,k) is* ***injective for all k*** *if and only if the determinant of the Jacobian*

$$\det\left(\frac{\partial p}{\partial c}(c,k)\right)$$

does not vanish for any k*.*

Example

$$
\begin{aligned}
c_A^f &= c_A + k_{A+B\to C}c_Ac_B - k_{C\to A+B}c_C + 2k_{2A+D\to X}c_A^2c_D \\
&\quad -2k_{X\to 2A+D}c_X + 2k_{2A+D\to Y}c_A^2c_D - 2k_{Y\to 2A+D}c_Y \\
c_B^f &= c_B + k_{A+B\to C}c_Ac_B - k_{C\to A+B}c_C - k_{Z\to B+D}c_Z \\
&\quad +k_{B+D\to Z}c_Bc_D \\
c_C^f &= c_C - k_{A+B\to C}c_Ac_B + k_{C\to A+B}c_C - k_{D\to C+W}c_D \\
&\quad +k_{C+W\to D}c_Cc_W \\
c_D^f &= c_D - k_{X\to 2A+D}c_X + k_{2A+D\to X}c_A^2c_D - k_{Y\to 2A+D}c_Y \\
&\quad +k_{2A+D\to Y}c_A^2c_D + k_{D\to C+W}c_D - k_{C+W\to D}c_Cc_W \\
&\quad +k_{B+D\to Z}c_Bc_D - k_{Z\to B+D}c_Z \\
c_W^f &= c_W - k_{D\to C+W}c_D + k_{C+W\to D}c_Cc_W \\
c_X^f &= c_X + k_{X\to 2A+D}c_X - k_{2A+D\to X}c_A^2c_D \\
c_Y^f &= c_Y - k_{2A+D\to Y}c_A^2c_D + k_{Y\to 2A+D}c_Y \\
c_Z^f &= c_Z - k_{B+D\to Z}c_Bc_D + k_{Z\to B+D}c_Z
\end{aligned}
$$

← **$p(c,k)$**

Coefficients of monomials in the determinant of the Jacobian of $p(c,k)$:

10	4	4	1	4	6	9	9	4	4	4	1	4	1	4	4	4	4	9	4	4
1	4	4	1	1	4	4	1	1	1	4	4	4	4	4	4	6	4	4	4	4
1	1	4	1	1	4	1	1	1	4	4	1	1	15	4	1	4	4	4	1	1
9	1	4	9	4	4	4	1	1	4	15	4	1	9	1	1	1	1	1	1	1
3	3	3	4	1	4	4	4	1	1	4	4	9	1	1	4	4	4	4	15	1
1	4	4	1	1	4	1	6	4	4	4	4	1	1	4	4	4	4	10	1	4
4	4	4	4	6	1	1	4	4	4	6	4	2	1	2	1	1	1	4	10	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	3	1	3	1	3	1	1	4
4	4	1	1	1	1	1	4	4	1	1	6	4	4	1	4	1	1	9	1	1
1	4	1	1	1	1	4	1	4	4	4	2	1	10	4	4	4	4	1	4	1
1	1	4	1	1	1	1	4	1	4	2	1	1	6	4	4	4	15	1	1	6
2	4	1	1	4	4	1	4	1	4	4	1	4	4	4	4	1	4	1	1	2
4	4	4	4	4	4	4	1	4	4	1	1	1	1	4	4	1	4	1	1	1
1	4	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	3	1	1	1	1	3	1	1	1	1	4	4	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	4	1	1	1	1	1	1	1	1	1	1	1	4	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1	1																			

The determinant of the Jacobian does not vanish !

Which polynomial dynamical systems can arise from mass-action kinetics?

Which polynomial dynamical systems can arise from mass-action kinetics?

Theorem. *An n-dimensional polynomial dynamical system can arise from mass-action kinetics if and only if it can be written as*

$$dc_1/dt = P_1(c_1, \ldots, c_n) - c_1 Q_1(c_1, \ldots, c_n)$$

$$dc_2/dt = P_2(c_1, \ldots, c_n) - c_2 Q_2(c_1, \ldots, c_n)$$

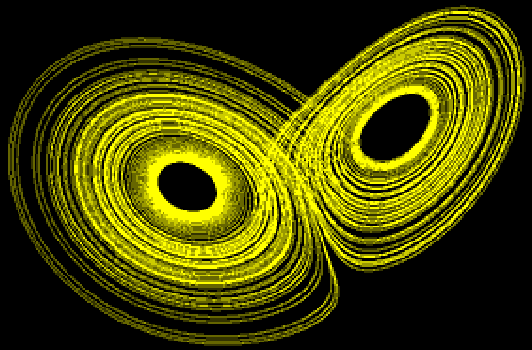
$$\ldots$$

$$dc_n/dt = P_n(c_1, \ldots, c_n) - c_n Q_n(c_1, \ldots, c_n)$$

for some polynomials P_i and Q_i with non-negative coefficients.

Not *mass-action kinetics: the Lorenz equa*

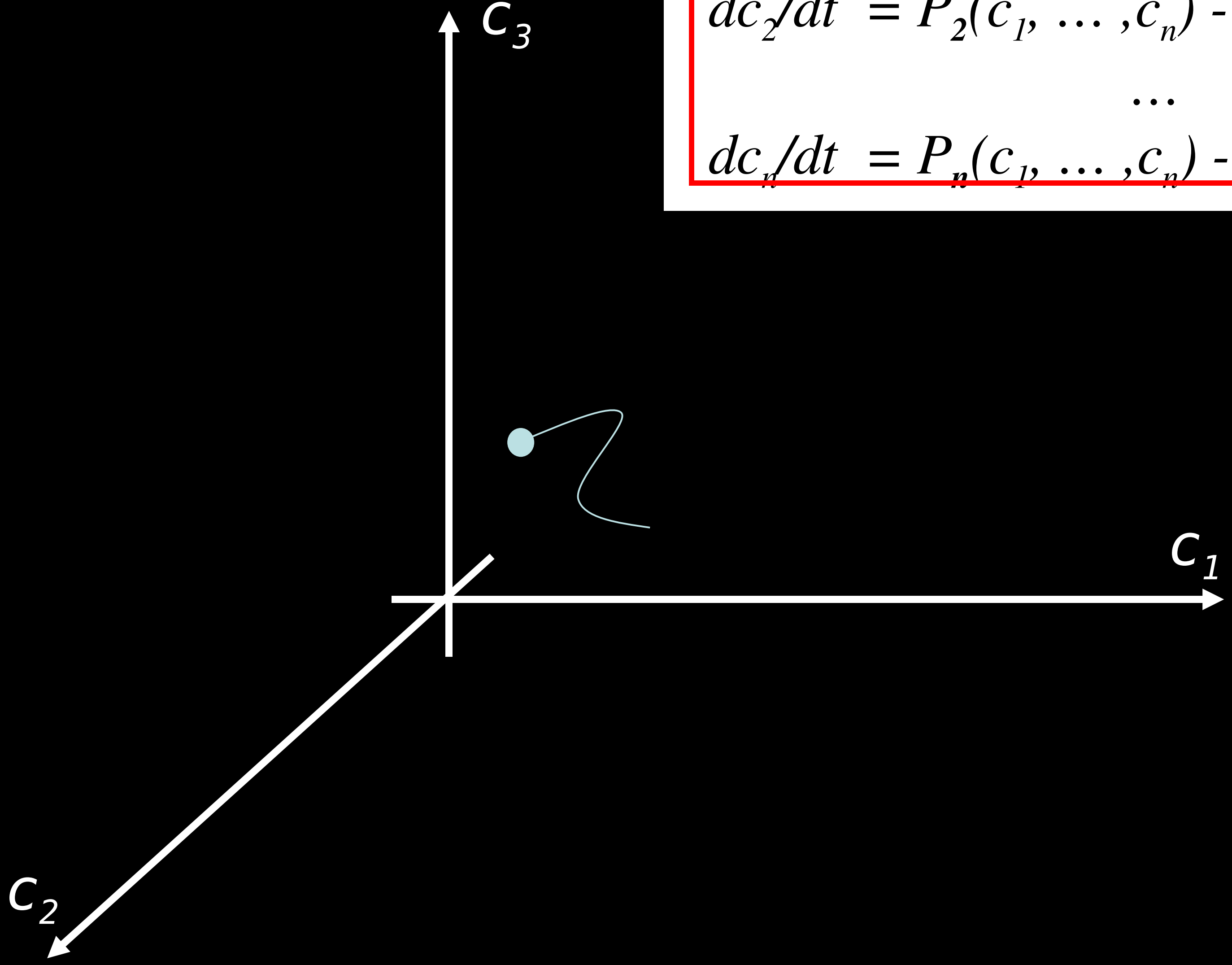
$$
\begin{aligned}
dx/dt &= ay - ax \\
dy/dt &= cx - y - xz \\
dz/dt &= xy - bz
\end{aligned}
$$



$$
\begin{aligned}
dc_1/dt &= P_{\mathbf{1}}(c_1, \ldots, c_n) - c_1 Q_{\mathbf{1}}(c_1, \ldots, c_n) \\
dc_2/dt &= P_{\mathbf{2}}(c_1, \ldots, c_n) - c_2 Q_{\mathbf{2}}(c_1, \ldots, c_n) \\
&\ldots \\
dc_n/dt &= P_{\mathbf{n}}(c_1, \ldots, c_n) - c_n Q_{\mathbf{n}}(c_1, \ldots, c_n)
\end{aligned}
$$

The positive quadrant is an invari

$$dc_1/dt = P_1(c_1, \ldots, c_n) - c_1 Q_1(c_1, \ldots, c_n)$$
$$dc_2/dt = P_2(c_1, \ldots, c_n) - c_2 Q_2(c_1, \ldots, c_n)$$
$$\ldots$$
$$dc_n/dt = P_n(c_1, \ldots, c_n) - c_n Q_n(c_1, \ldots, c_n)$$



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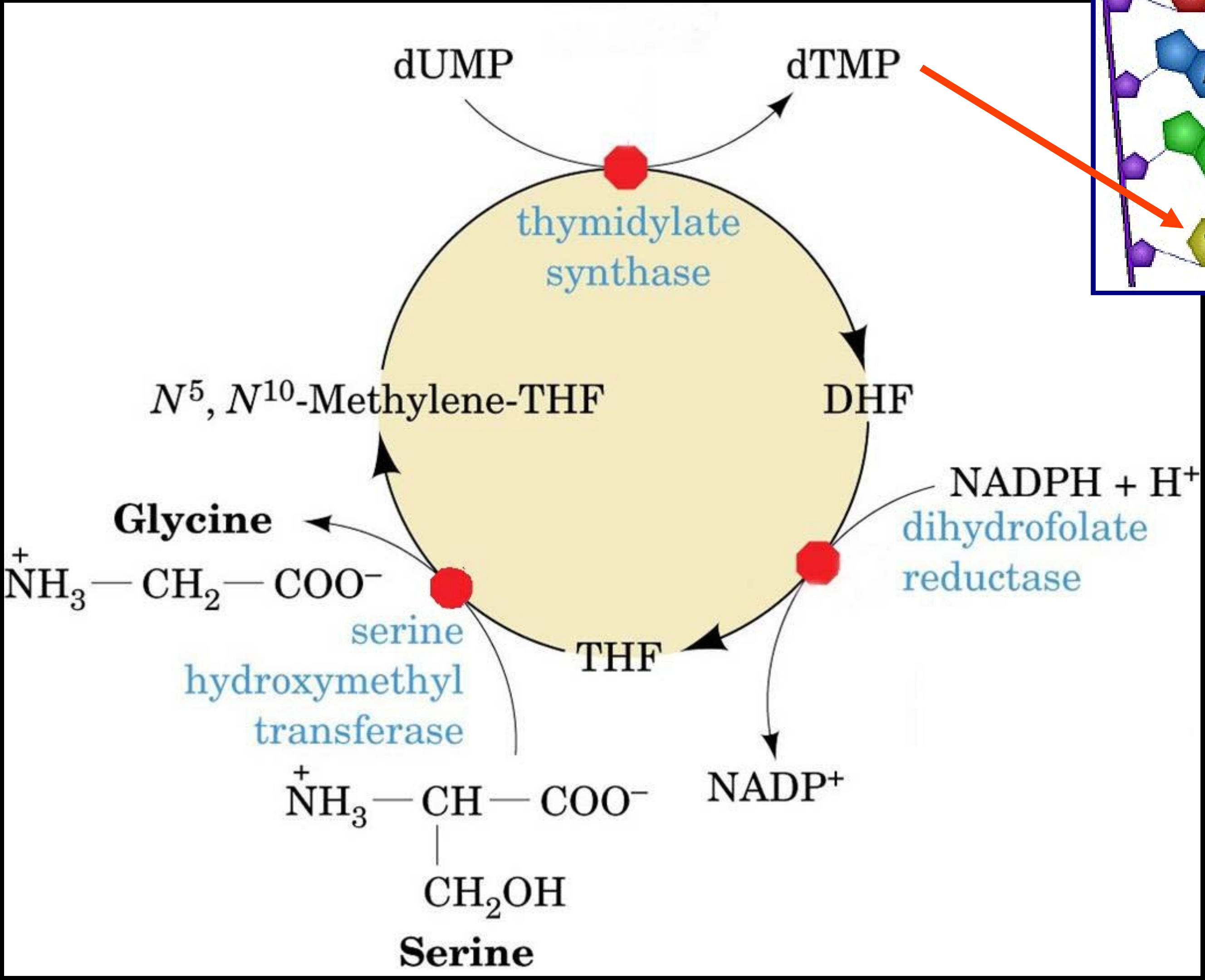
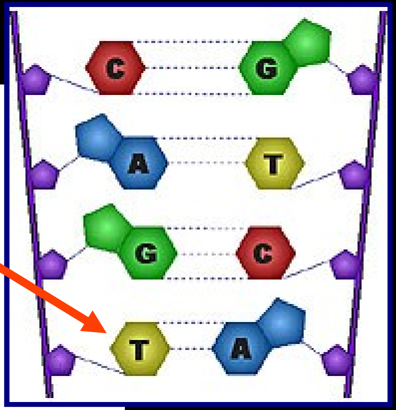
Entrapped species models

Theorem. *Consider some reaction network which contains some entrapped species. If the corresponding fully diffusive network does not admit multiple equilibria, then the reaction network does not admit multiple equilibria.*

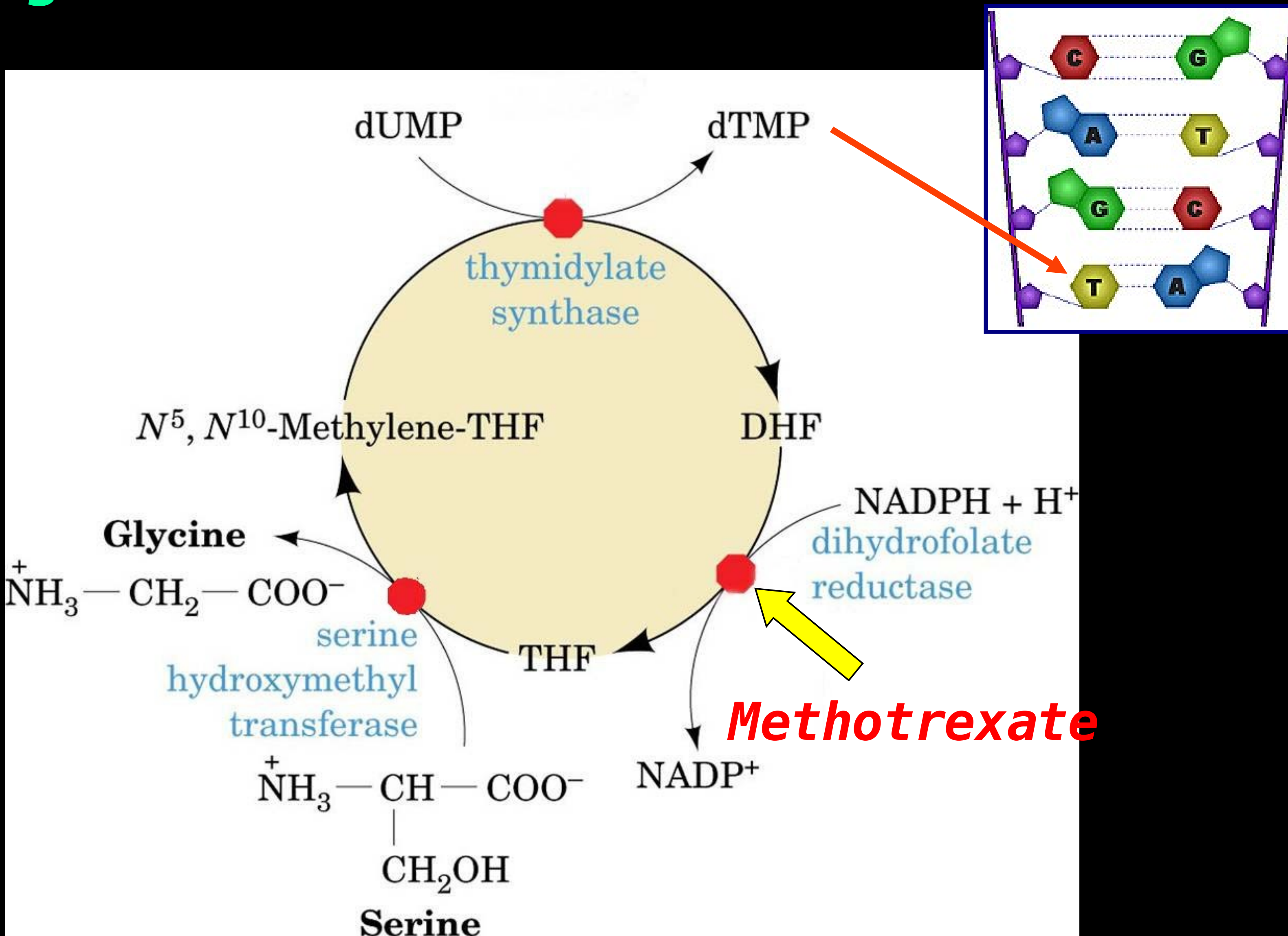
Methotrexate: How a Cancer Drug Works





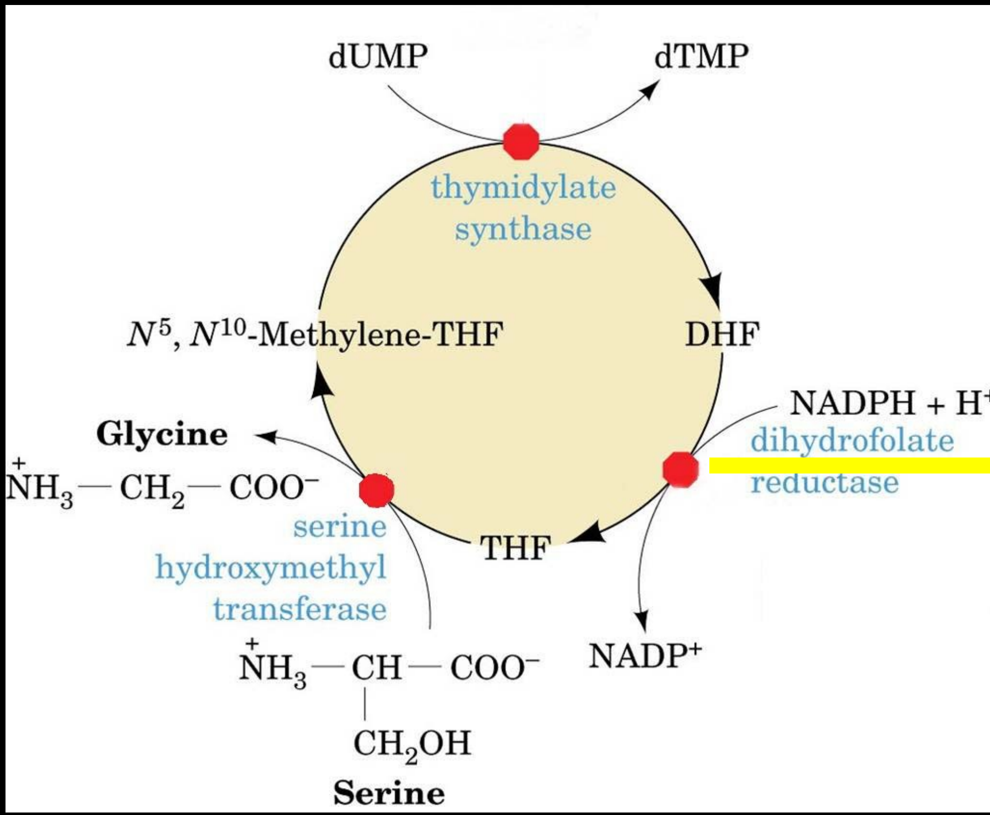
After Voet & Voet,

Methotrexate: How a Cancer Drug Works



After Voet & Voet,

Inside the DHFR Red Dot (No Methotrexate!)



$$E + H2F \underset{14}{\overset{264}{\rightleftharpoons}} EH2F$$

$$EH2F + NH \underset{19}{\overset{24}{\rightleftharpoons}} ENHH2F$$

$$ENHH2F \underset{37}{\overset{1360}{\rightleftharpoons}} ENH4F$$

$$ENH4F \underset{24}{\overset{46}{\rightleftharpoons}} EN + H4F$$

$$E + NH \underset{1.7}{\overset{38}{\rightleftharpoons}} ENH$$

$$ENH + H2F \underset{94}{\overset{98}{\rightleftharpoons}} ENHH2F$$

$$E + N \underset{32}{\overset{17}{\rightleftharpoons}} EN$$

$$EH4F \underset{117}{\overset{5.1}{\rightleftharpoons}} E + H4F$$

$$ENH + H4F \underset{225}{\overset{14}{\rightleftharpoons}} ENHH4F$$

$$ENHH4F \underset{4.4}{\overset{100}{\rightleftharpoons}} EH4F + NH$$

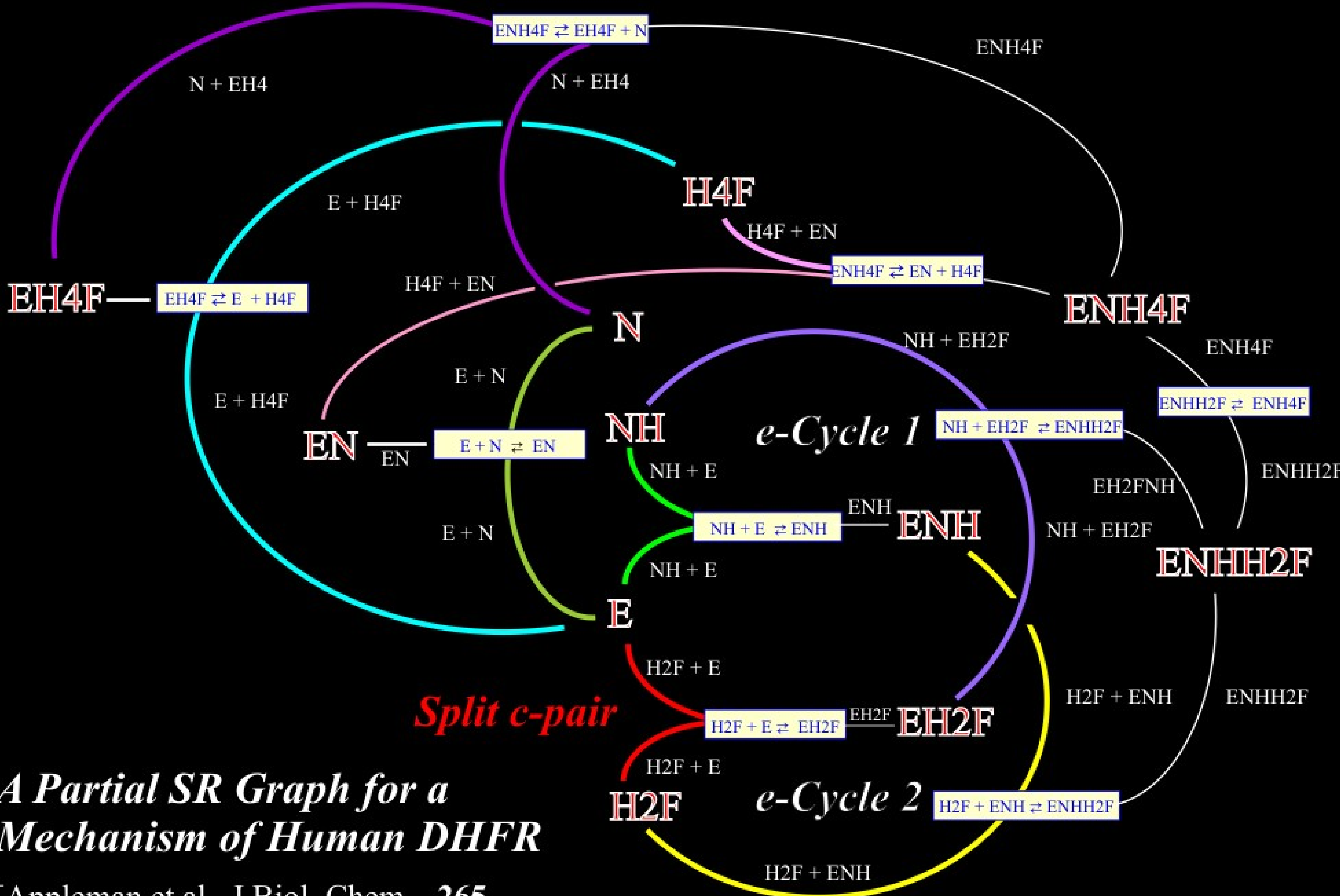
$$EH4F + N \underset{84}{\overset{0.7}{\rightleftharpoons}} ENH4F$$

$$EH2F + N \underset{4.6}{\overset{20}{\rightleftharpoons}} ENH2F$$

$$EN + H2F \underset{1.3}{\overset{110}{\rightleftharpoons}} ENH2F$$

Mechanism and rate constants from Appleman et al.,
J. Biol. Chem., ***265****, 2740-2748, (1990).*

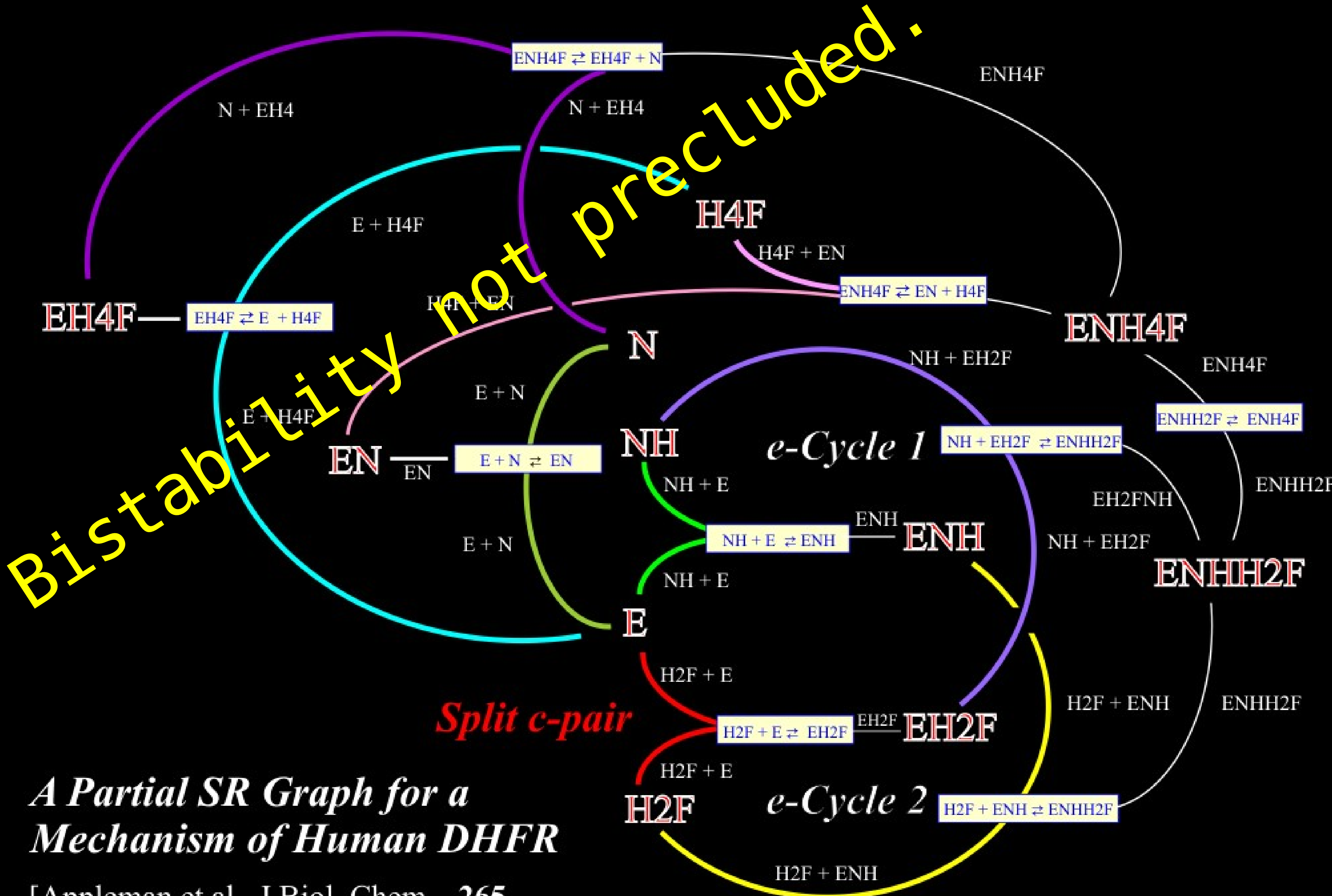
E = Human DHFR NH = NADPH H2F = H2folate N = NADP H4F = H4folate



A Partial SR Graph for a Mechanism of Human DHFR

[Appleman et al, J.Biol. Chem., **265**, 2740-2748 (1990)]

E = Human DHFR NH = NAPDH N = NAPD H2F = H2Folate H4F = H4Folate



A Partial SR Graph for a Mechanism of Human DHFR

[Appleman et al, J.Biol. Chem., **265**, 2740-2748 (1990)]

E = Human DHFR   NH = NAPDH   N = NAPD   H2F = H2Folate   H4F = H4Folate

Bistability Inside the DHFR Red Dot (No Methotrexate)

$$E + H2F \underset{14}{\overset{264}{\rightleftharpoons}} EH2F$$

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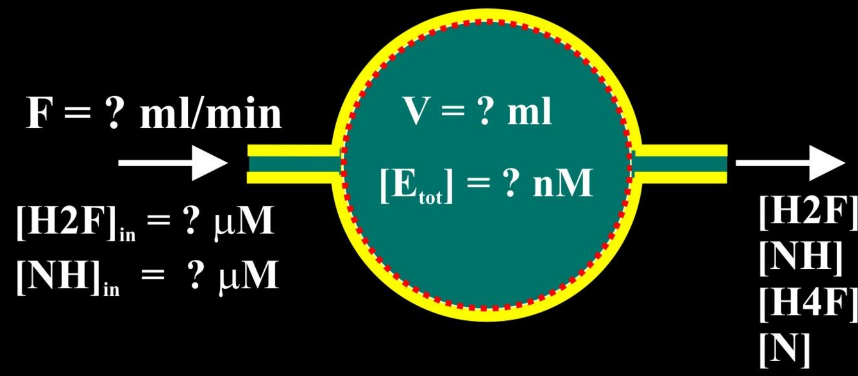

H2F + NH + H › H4F + N

Bistability Inside the DHFR Red Dot (No Methotrexate)

$$E + H2F \underset{14}{\overset{264}{\rightleftharpoons}} EH2F$$

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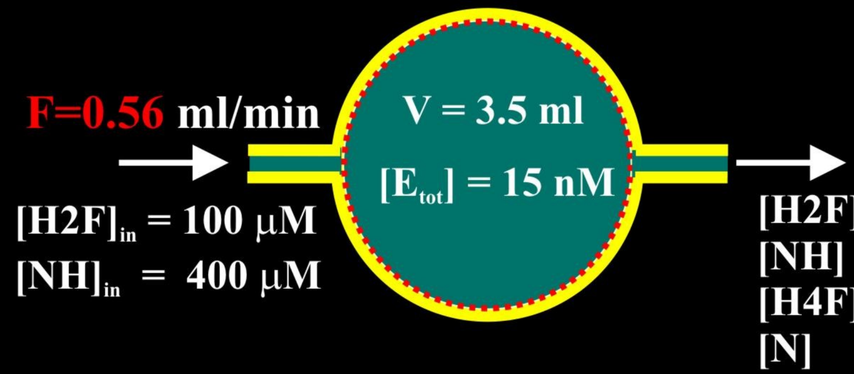

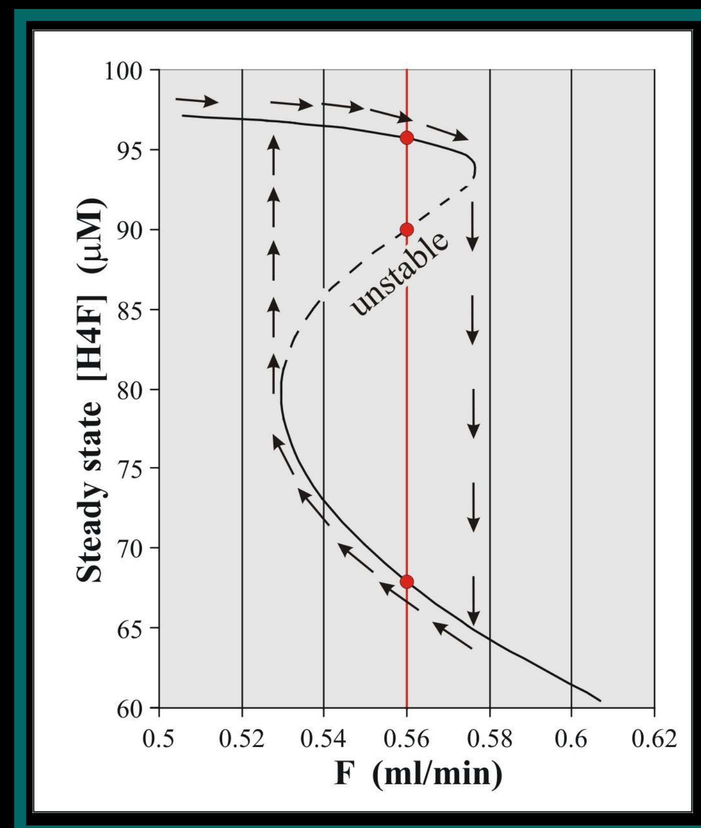

Bistability Inside the DHFR Red Dot (No Methotrexate)

$$E + H2F \underset{14}{\overset{264}{\rightleftharpoons}} EH2F$$

$$EH2F + NH \underset{19}{\overset{24}{\rightleftharpoons}} ENHH2F$$

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$$ENH4F \underset{24}{\overset{46}{\rightleftharpoons}} EN + H4F$$

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