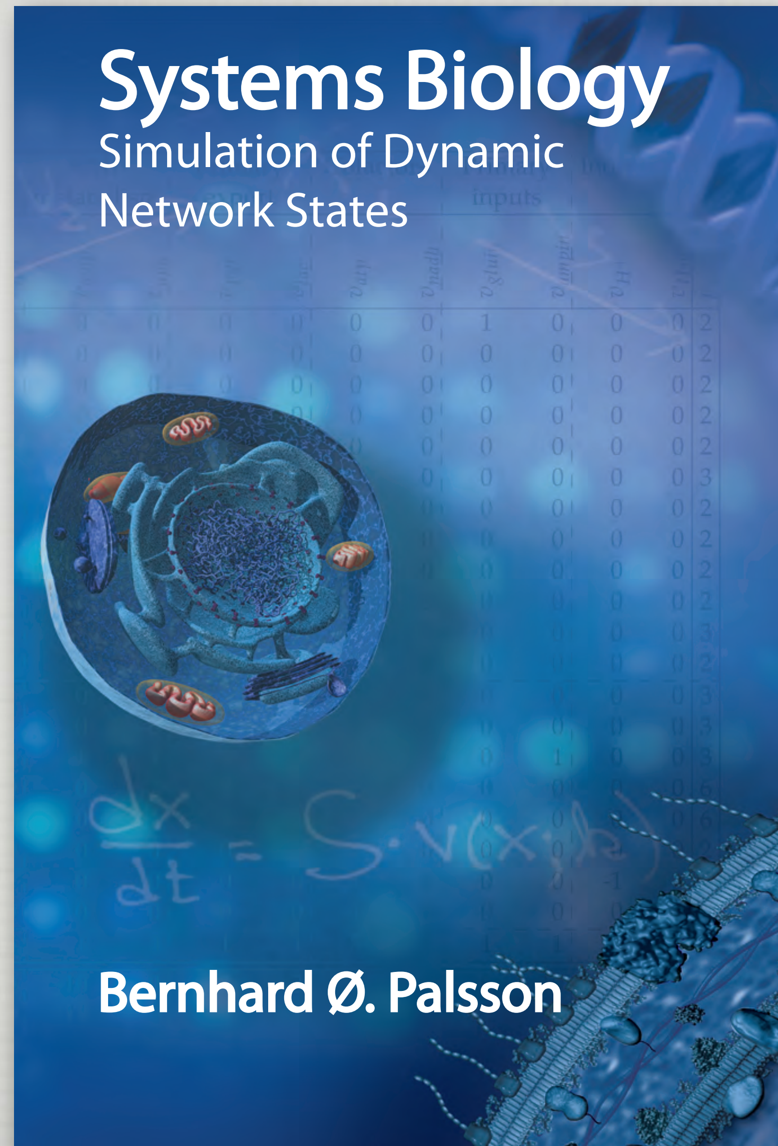

Lecture #8

Stoichiometric Texture

Outline

Outline

- Prosthetic groups, cofactors and carriers

Outline

- Prosthetic groups, cofactors and carriers
- Bi-linear nature of reactions

Outline

- Prosthetic groups, cofactors and carriers
- Bi-linear nature of reactions
- Pathways versus cofactors

Outline

- Prosthetic groups, cofactors and carriers
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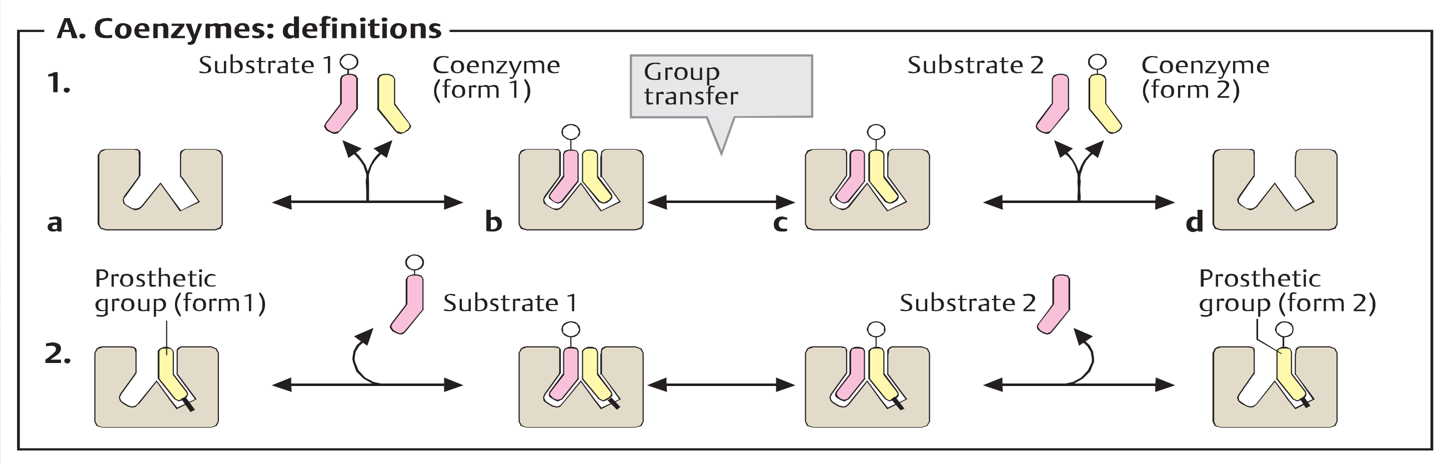
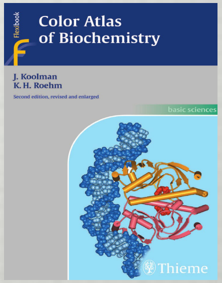
- Pathways versus cofactors
- Basics of high energy bond exchange

Outline

- Prosthetic groups, cofactors and carriers
- Bi-linear nature of reactions
- Pathways versus cofactors
- Basics of high energy bond exchange
- Prototypic pathway models

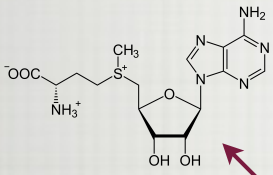
Cofactors, Coenzymes, Prosthetic Groups and Carriers





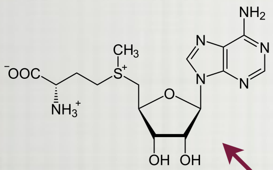
Koolman, J. and Roehm, K.H., Color Atlas of Biochemistry, 2nd Ed., Thieme, New York, 2004.

Basic Cofactor/Carrier Molecules in Metabolism



Coenzyme/carrier	Examples of chemical groups transferred	Dietary precursor in mammals
Carbon		
Biocytin	CO_2	Biotin
Tetrahydrofolate	One-carbon groups	Folate (B9)
Coenzyme A (CoA)	Acyl groups	Pantothenic acid (B5) and other compounds
Thiamine pyrophosphate (TPP)	Aldehydes	Thiamine (B1)
S-Adenosyl methionine	Methyl groups	
Cyano/5′-deoxyadenosyl cobalamin	Rearrangement of vicinal −H and −R groups	Coenzyme B12
Energy		
ATP (NTPs)	P_i or PP_i	
Redox		
Flavin adenin dinucleotide	Electrons	Riboflavin (B2)
Lipoate	Electrons and acyl groups	
Nicotinamide adenine dinucleotide (NAD or NADP)	Hydride ion	
Coenzyme Q	Electrons and protons	Vitamin Q
Cytochromes/heme	Electrons	Iron
Nitrogen		
Pyridoxal phosphate	Amino groups	Pyridoxine (B6)
Glutamate (N_2-fixing plants)	Amino groups	

Basic Cofactor/Carrier Molecules in Metabolism



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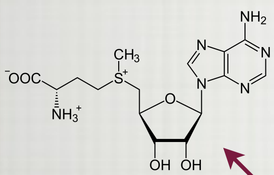

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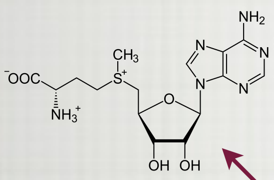

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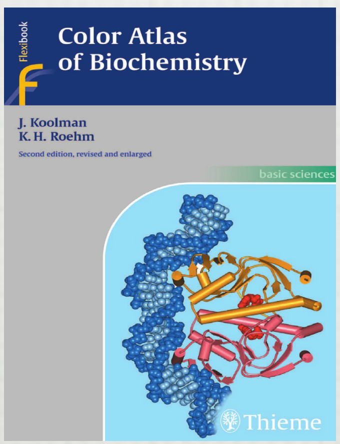
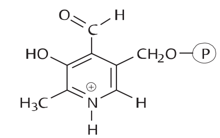
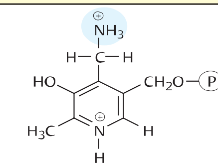
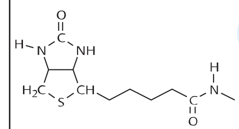
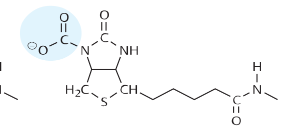
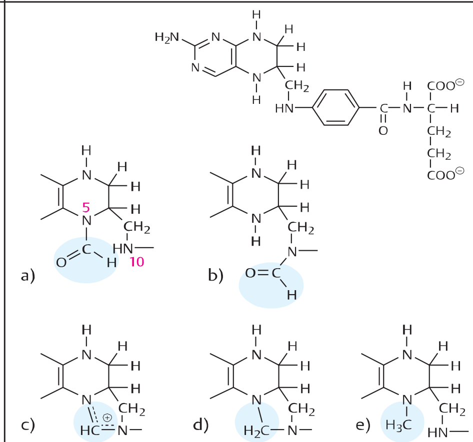
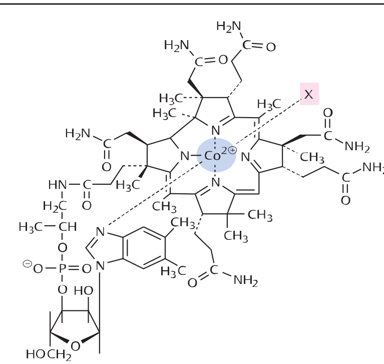
Some examples



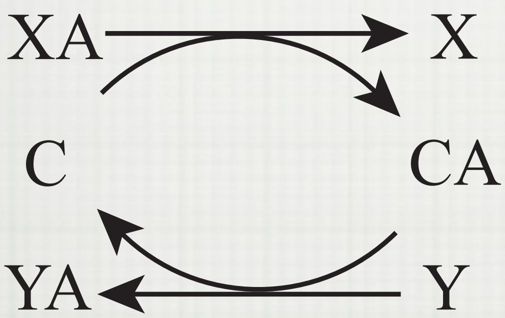
A. Group-transferring coenzymes 2

Coenzyme	Free form	Charged form	Group(s) transferred	Important enzymes
4. Pyridoxal phosphate PLP			Amino group Amino acid residues	Transaminases (2.6.1.n) Many lyases (4.n.n.n)
5. Biotin B			$[CO_2]$	Carboxylases (6.4.1.n)
4. Pyridoxal phosphate THF			C_1 groups a) N^5-Formyl b) N^{10}-Formyl c) N^5N^{10}-Methenyl d) N^5N^{10}-Methylene e) N^5N^{10}-Methyl	C_1 transferases (2.1.n.n)
7. Cobalamin coenzymes			X = Adenosyl- X = Methyl-	Mutases *(5.4.n.n)* Methyl-transferases *(2.1.1.n.)*

The Bi-linear Nature of Biochemical Reactions:

transfer/exchange of properties

Motif:



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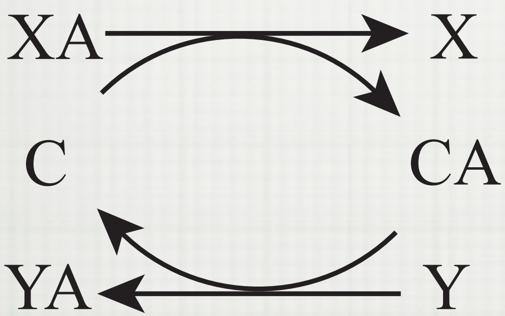

Donor (X)

The Bi-linear Nature of Biochemical Reactions:

transfer/exchange of properties

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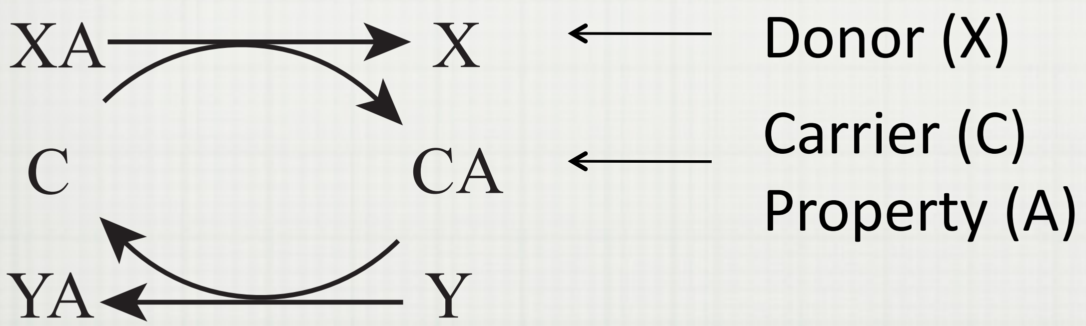

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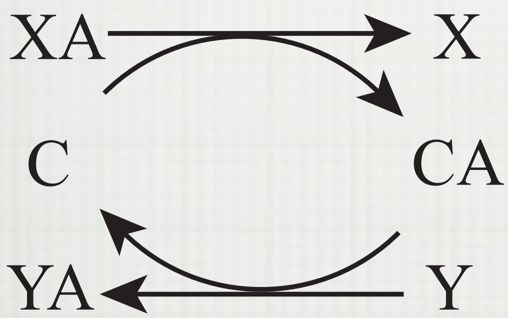

Donor (X)

Carrier (C)

Property (A)

Acceptor (Y)

The Bi-linear Nature of Biochemical Reactions:

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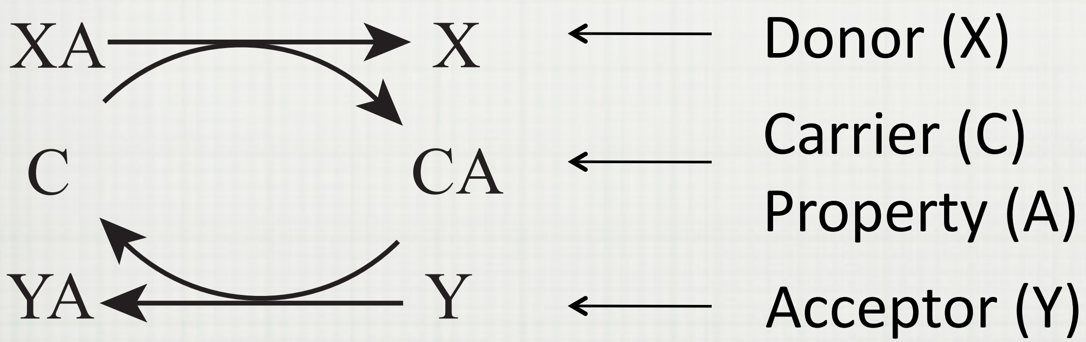
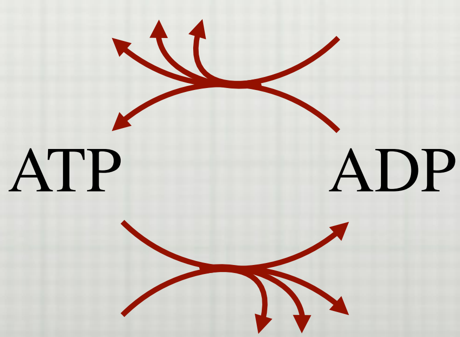


Highly connected carriers:



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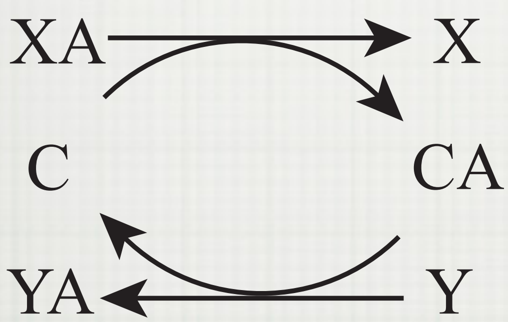


Donor (X)

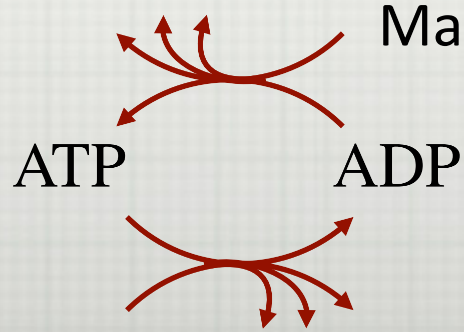
Carrier (C)

Property (A)

Acceptor (Y)

Highly connected carriers:

Many donors



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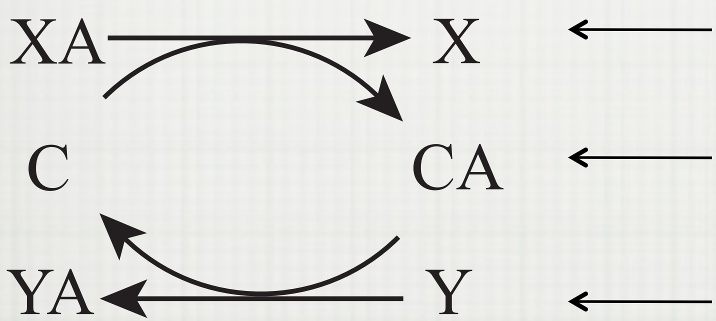

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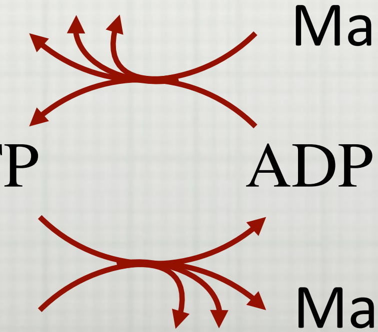


$t \cong 1\text{min}$

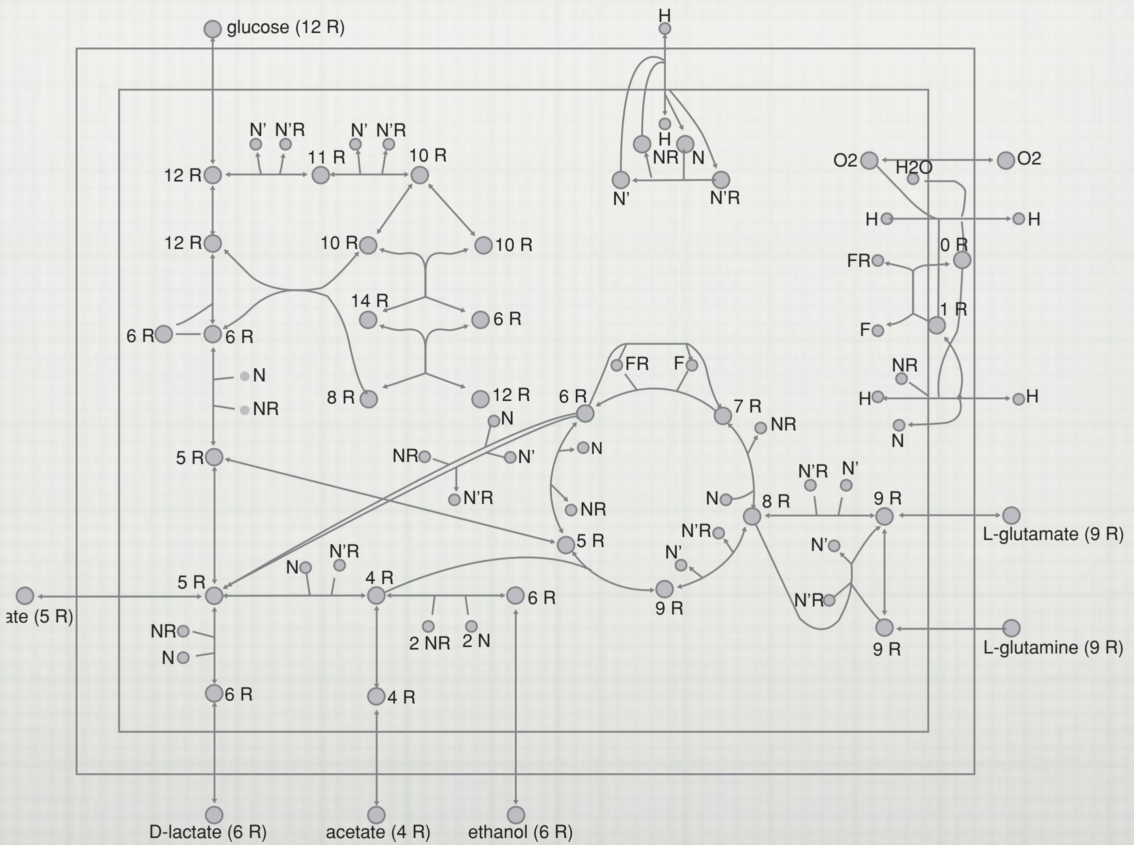
Many, many acceptors

Duality in points of view

PATHWAY VS. KEY COFACTOR VIEW

Redox Trafficking in the Core Metabolic Pathways:

pathway view



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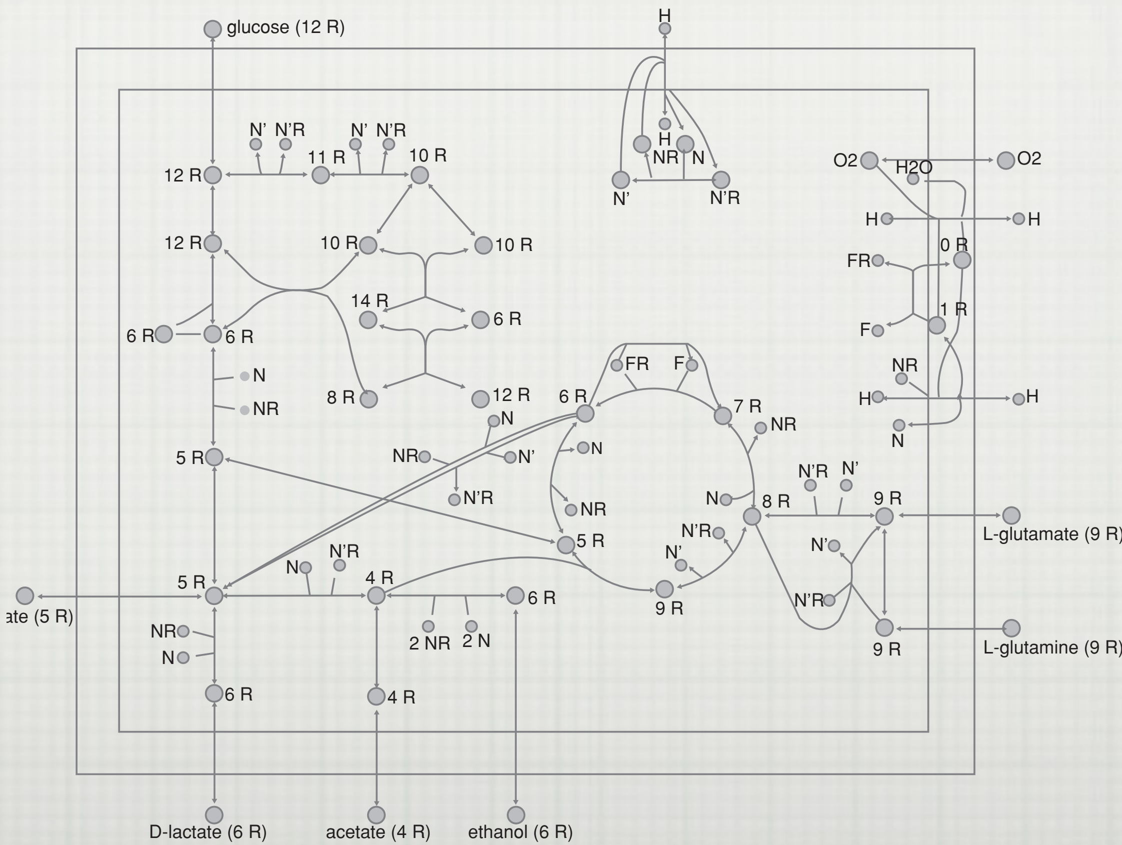
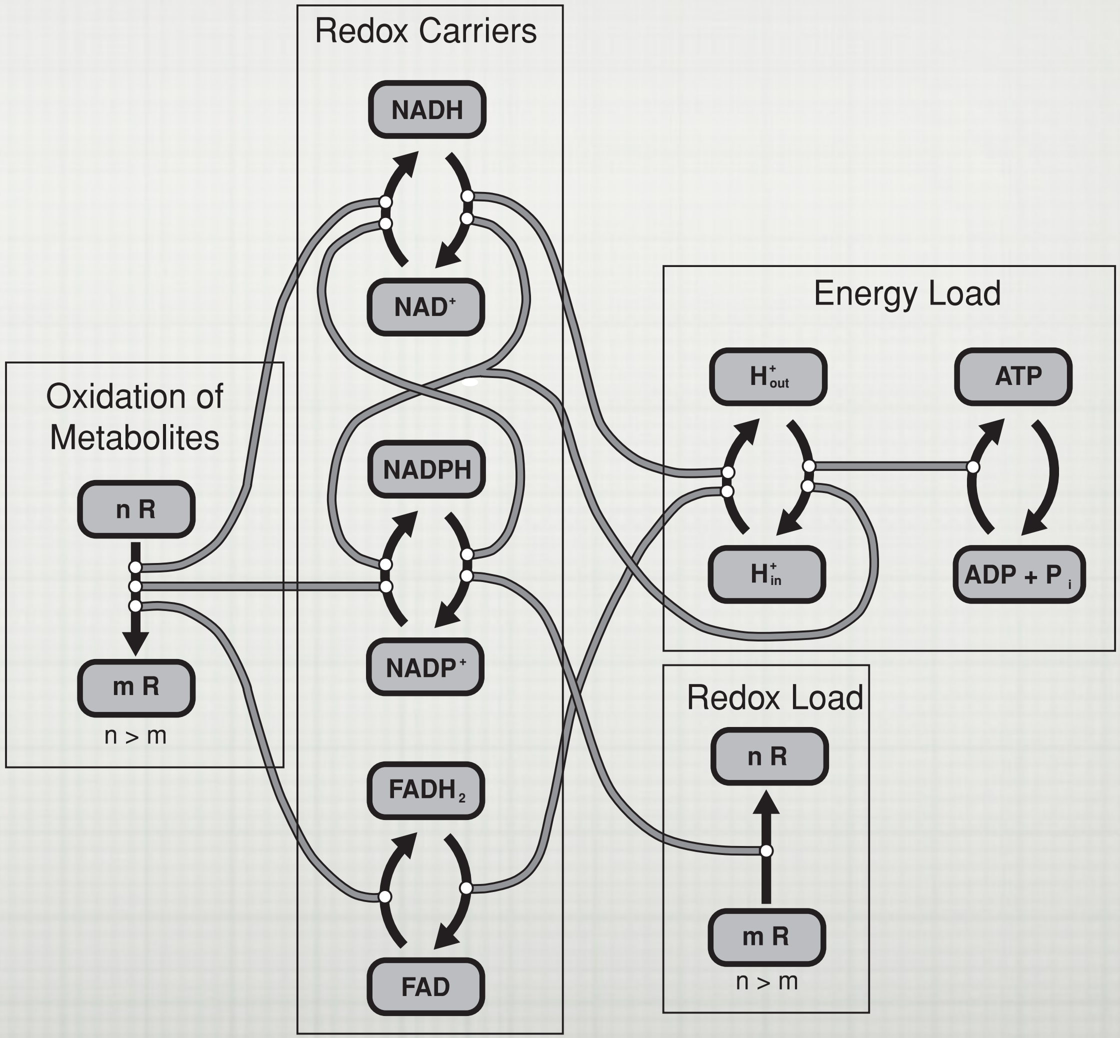


classical viewpoint

Redox Trafficking in the Core Metabolic Pathways:

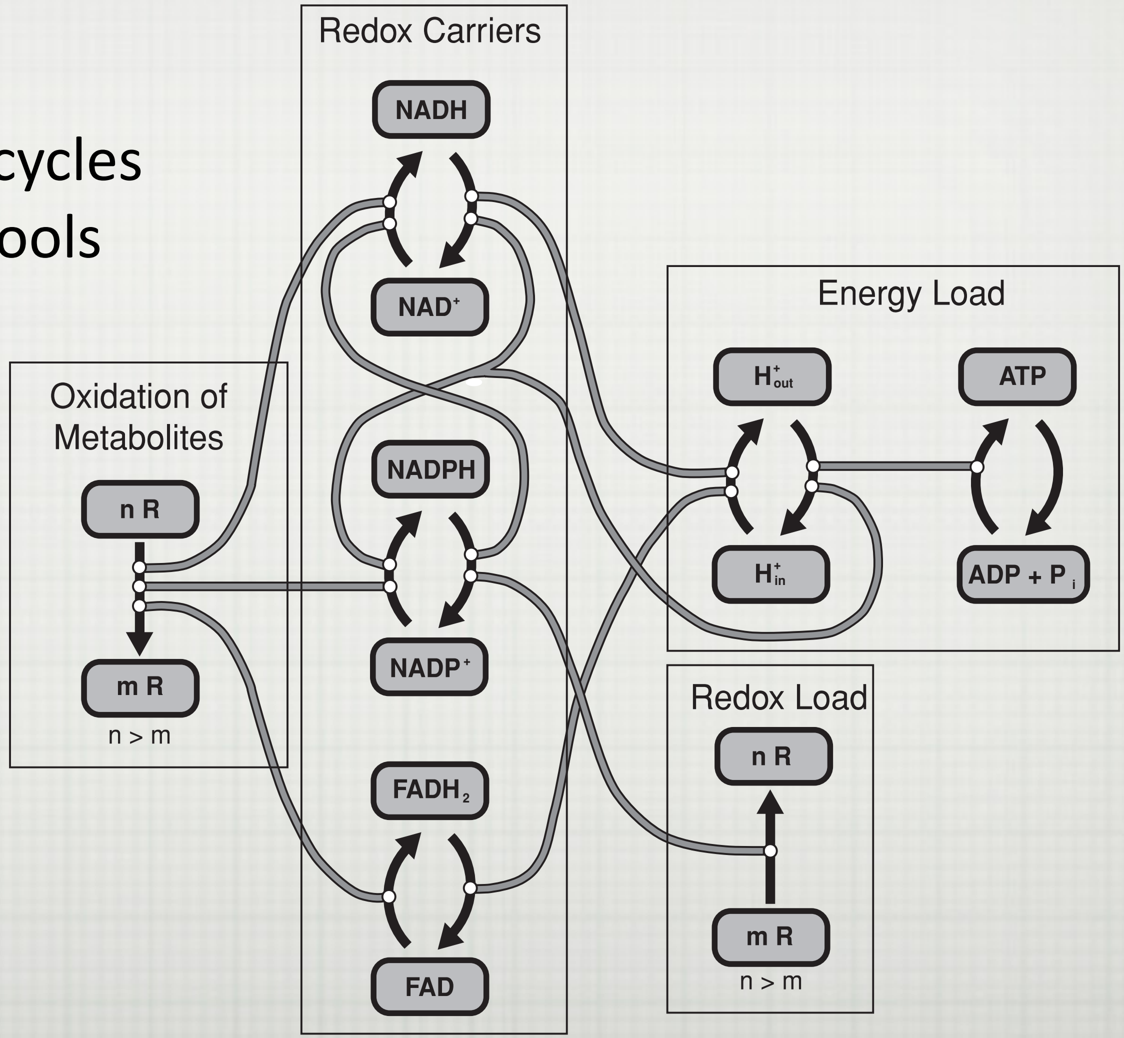
cofactor view



Redox Trafficking in the Core Metabolic Pathways:

cofactor view

A tangle of cycles through pools



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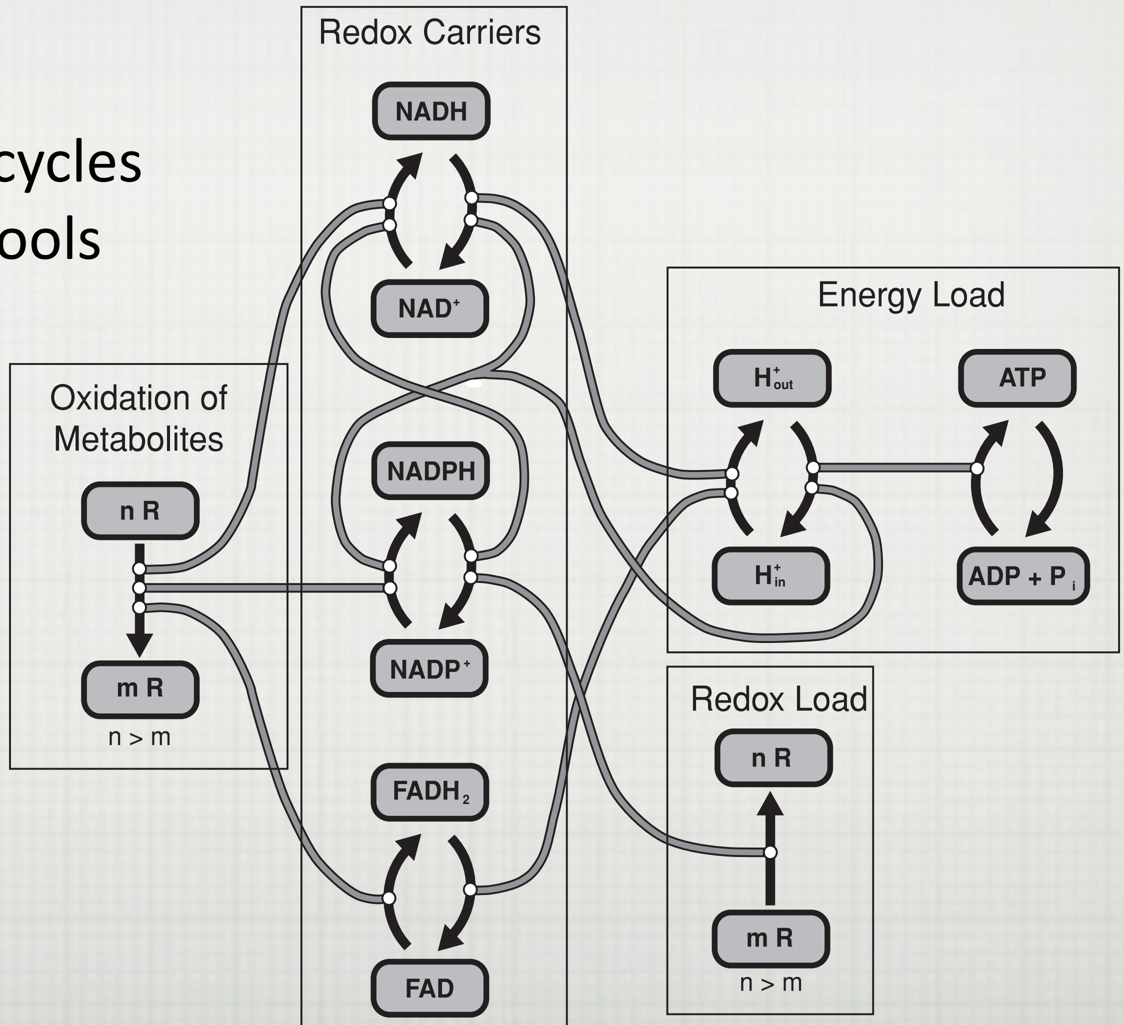


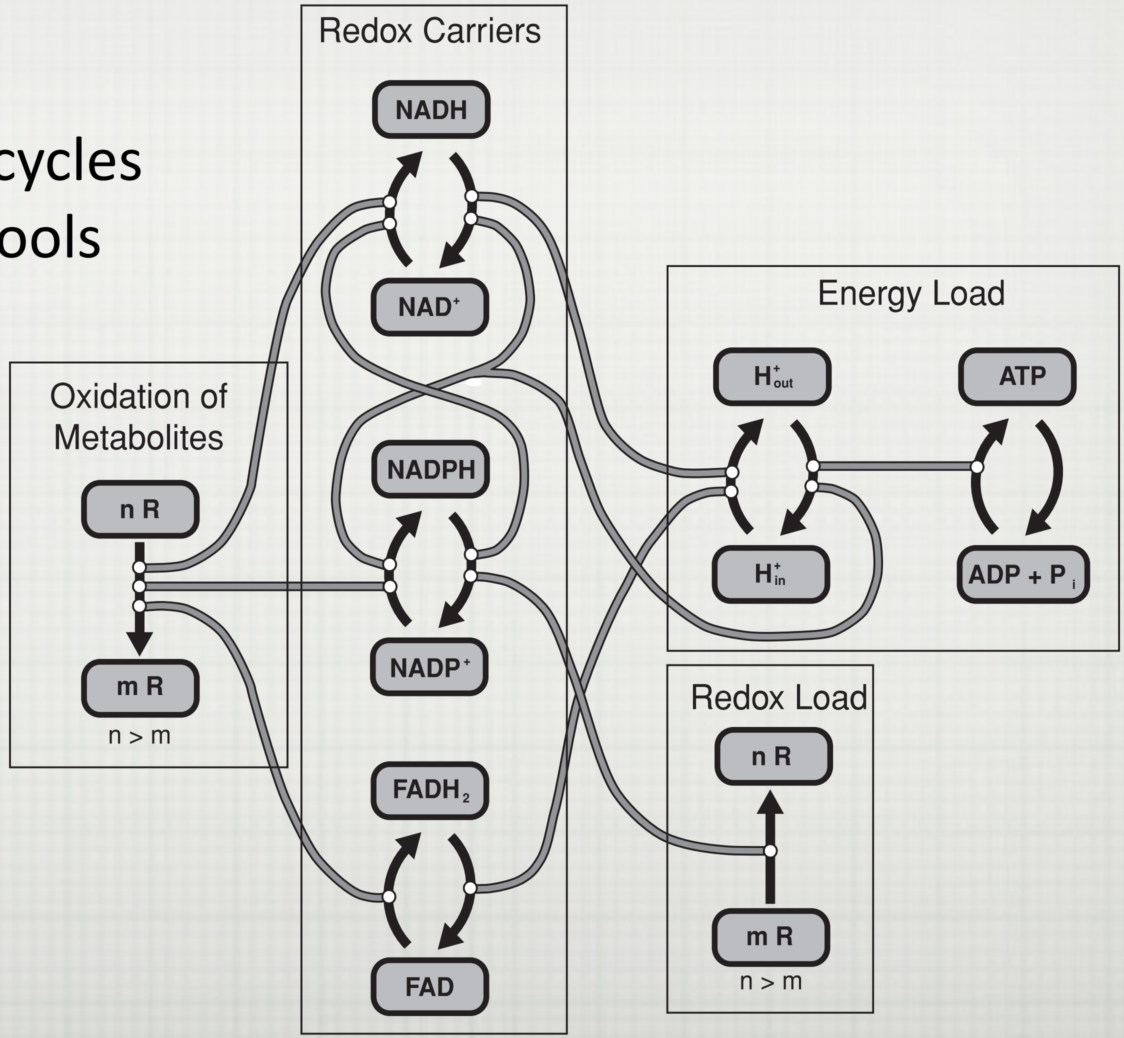
systems viewpoint

Redox Trafficking in the Core Metabolic Pathways:

cofactor view

A tangle of cycles through pools

e⁻ donor →



systems viewpoint

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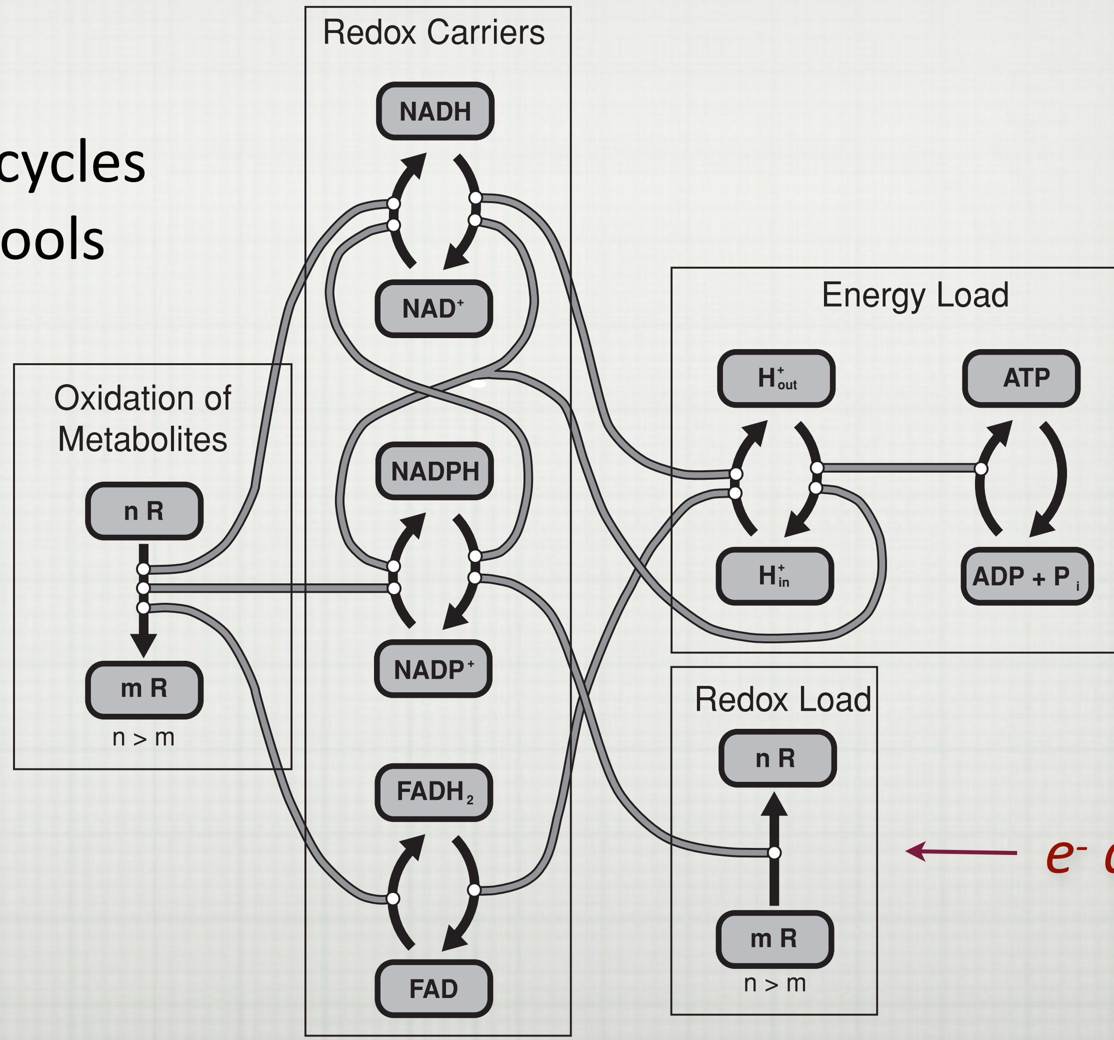


← *e^- acceptor*

systems viewpoint

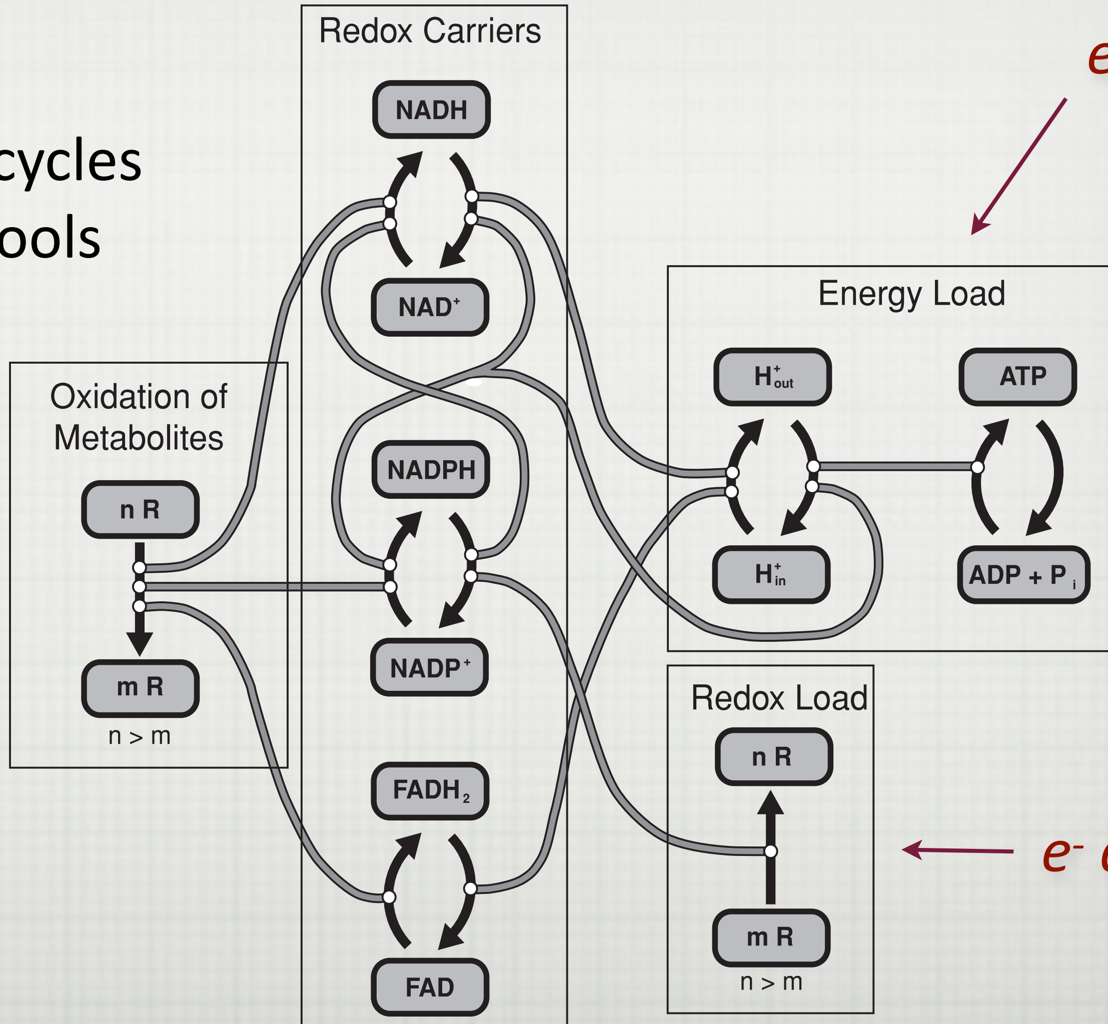
Redox Trafficking in the Core Metabolic Pathways:

cofactor view

A tangle of cycles
through pools

e^- -> ~P

e^- donor →



← *e^- acceptor*

systems viewpoint

Stepwise model construction

HIGH-ENERGY PHOSPHATE GROUP EXCHANGE

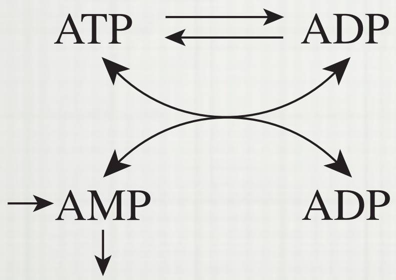
The Basics of High-Energy Phosphate Bond Trafficking

Chemical Representation

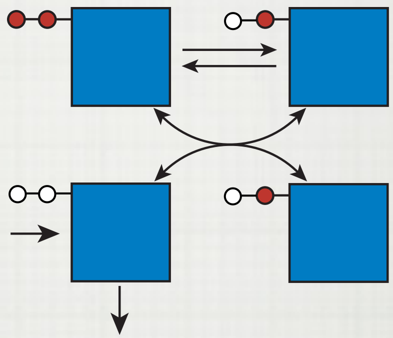
Pictorial Representation

The Basics of High-Energy Phosphate Bond Trafficking

Chemical Representation

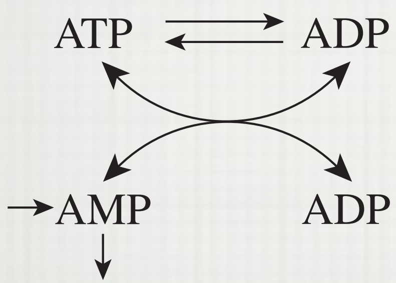


Pictorial Representation

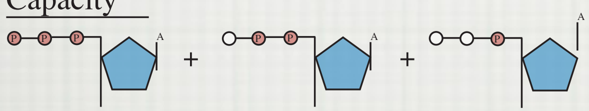


The Basics of High-Energy Phosphate Bond Trafficking

Chemical Representation

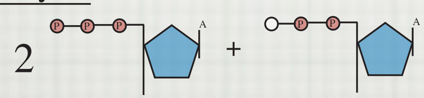


Capacity



ATP + ADP + AMP

Occupancy



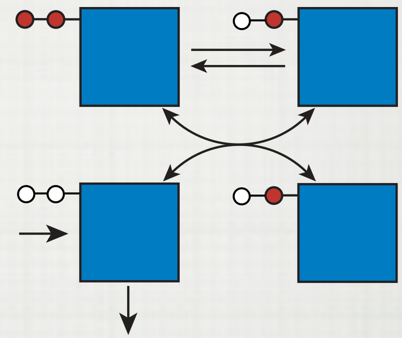
2ATP + ADP

Charge

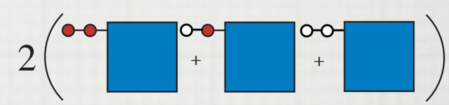
$$\text{E.C.} = \frac{\text{occupancy}}{\text{capacity}}$$

$$= \frac{2\text{ATP} + \text{ADP}}{2(\text{ATP} + \text{ADP} + \text{AMP})}$$

Pictorial Representation



Capacity



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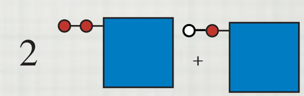

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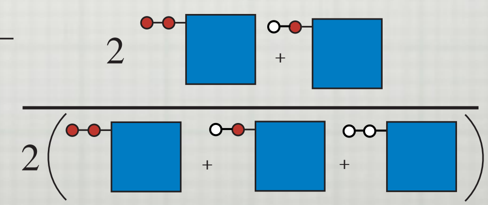

1. Distribution of High Energy Bonds

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<u>*Chemistry*</u>

$$K_{\mathrm{eq}} \simeq 1 \therefore \quad \Delta G^{\circ} = -\mathrm{RT}ln(K_{\mathrm{eq}}) = 0$$

$$\text{ADP} \quad + \quad \text{ADP} \quad \rightleftharpoons \quad \text{AMP} \quad + \quad \text{ATP}$$

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ADP + ADP $\rightleftharpoons$ AMP + ATP

$$[\mathrm{ATP}] = 1.6mM \;\; , \;\; [\mathrm{ADP}] \simeq 0.4mM \;\; , \;\; [\mathrm{AMP}] \simeq 0.1 \;\; , \;\; K_{\text{eq}} = \frac{[\mathrm{AMP}][\mathrm{ATP}]}{[\mathrm{ADP}]^2} \sim 1$$

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__*Dynamics*__

$$\frac{d}{dt}\begin{pmatrix} \text{ATP} \\ \text{ADP} \\ \text{AMP} \end{pmatrix} = \begin{pmatrix} 1 \\ -2 \\ 1 \end{pmatrix} v_{\text{distr}} \;\; ; \;\; v_{\text{distr}} = k_{\text{distr}} \left([\text{ADP}]^2 - \frac{[\text{AMP}][\text{ATP}]}{K_{\text{eq}}} \right)$$

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Chemistry

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Dynamics

$$\frac{d}{dt}\begin{pmatrix} \text{ATP} \\ \text{ADP} \\ \text{AMP} \end{pmatrix} = \begin{pmatrix} 1 \\ -2 \\ 1 \end{pmatrix} v_{\text{distr}} \;;\; v_{\text{distr}} = k_{\text{distr}}\left([\text{ADP}]^2 - \frac{[\text{AMP}][\text{ATP}]}{K_{\text{eq}}}\right)$$

"fast"; 1000/min

2. ATP Use and Formation

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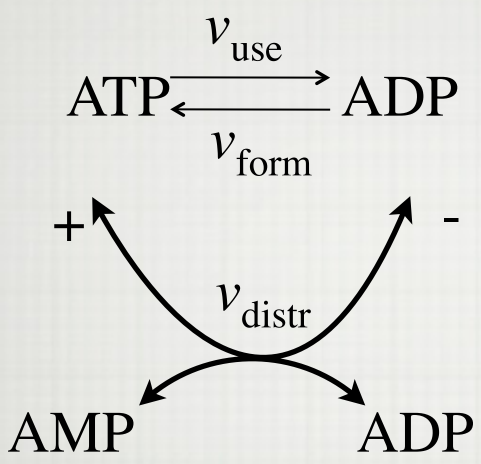
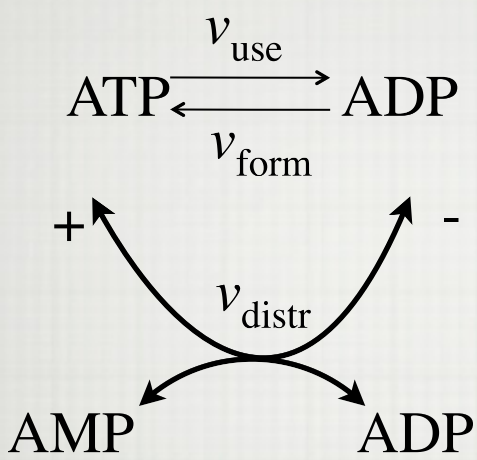
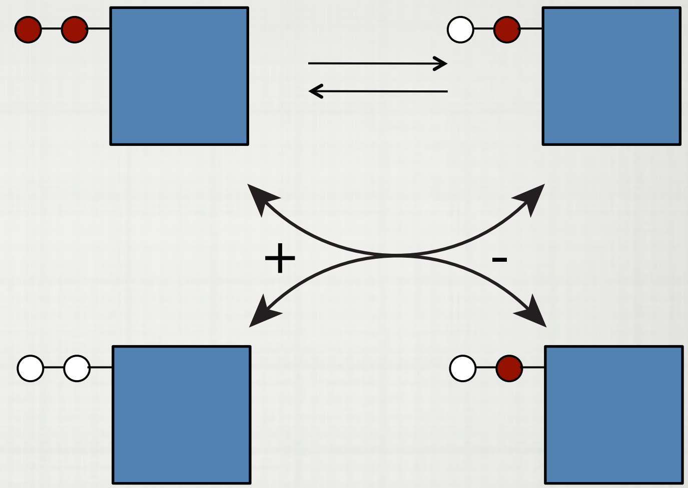
Chemistry



2. ATP Use and Formation

Chemistry





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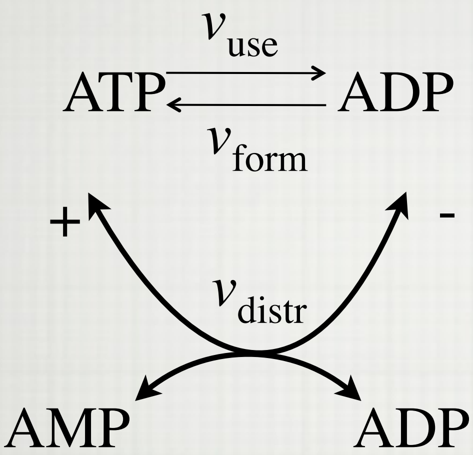
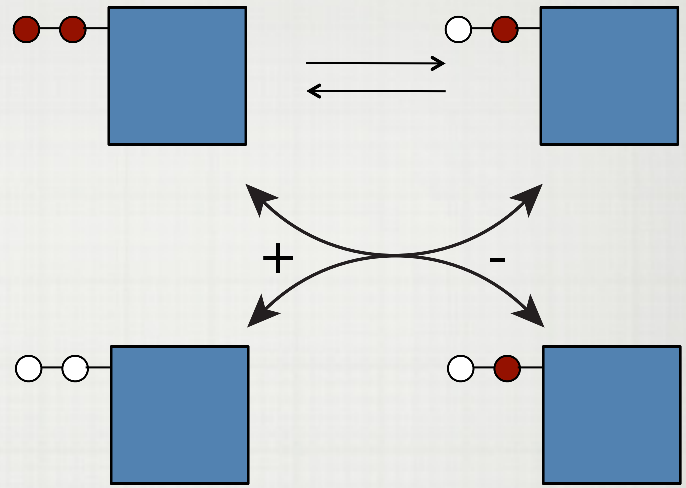
Chemistry





Dynamics

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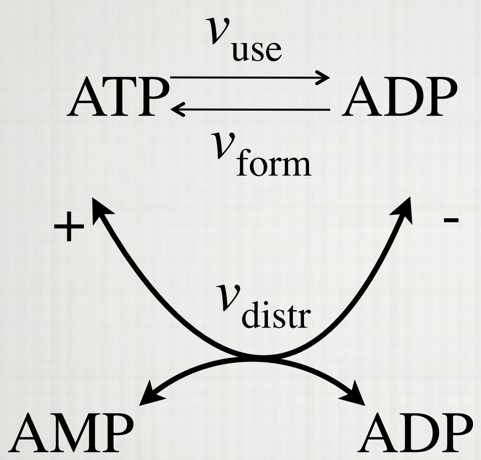
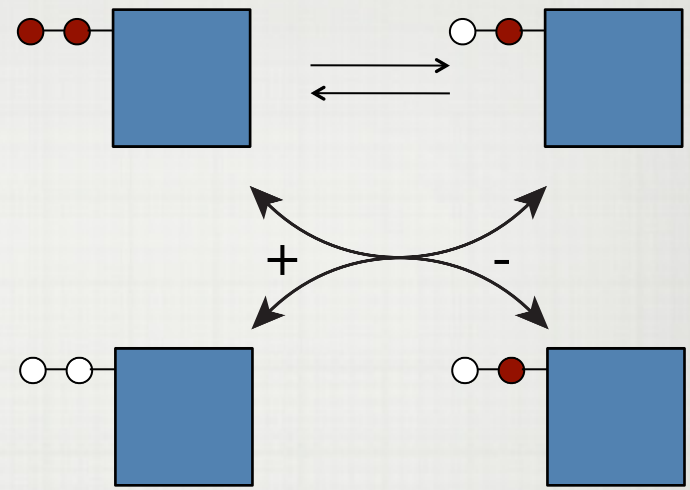
$$

2. ATP Use and Formation

Chemistry





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$$\frac{d\text{ATP}}{dt} = v_{\text{distr}} - v_{\text{use}} + v_{\text{form}}$$

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2. ATP Use and Formation

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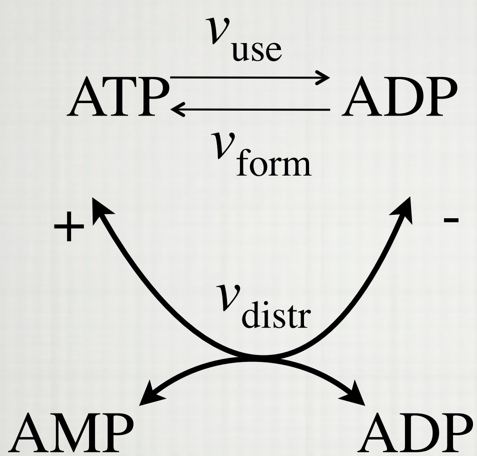

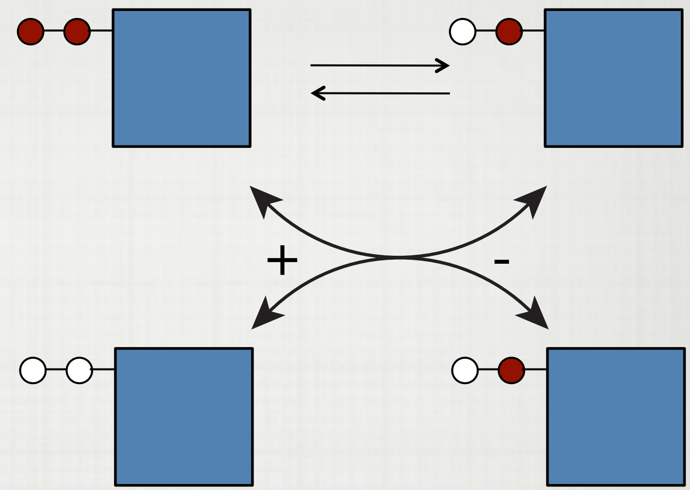

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$$\boxed{v_{\text{use}} \simeq 10mM/min}$$

$$v_{\text{use}} = k_{\text{use}}[\text{ATP}]$$

- $k_{\text{use}} \simeq \dfrac{10mM/min}{1.6mM} = 6.25/min$

$$v_{\text{form}} = k_{\text{form}}[\text{ADP}]$$

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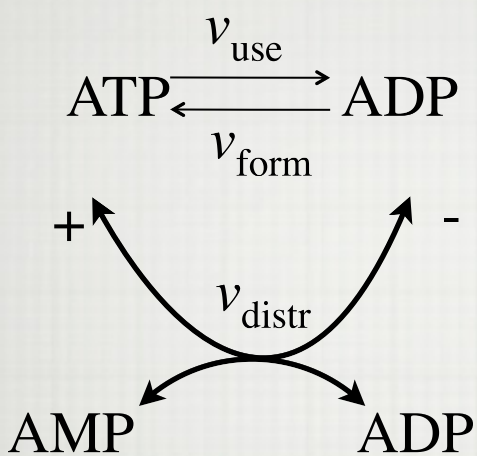
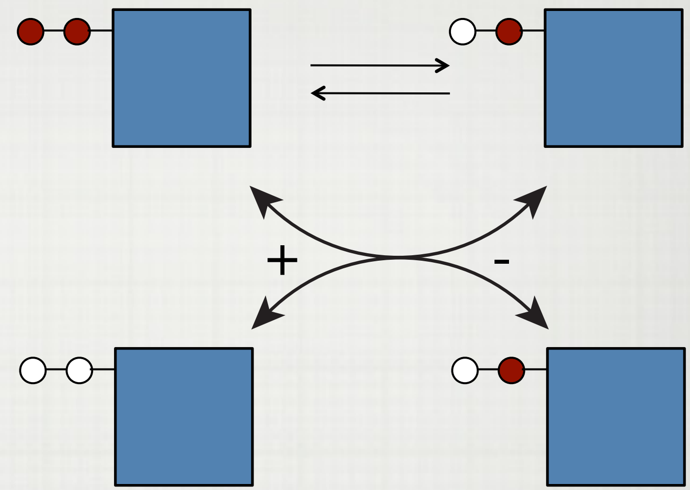
Chemistry





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$$\downarrow$$

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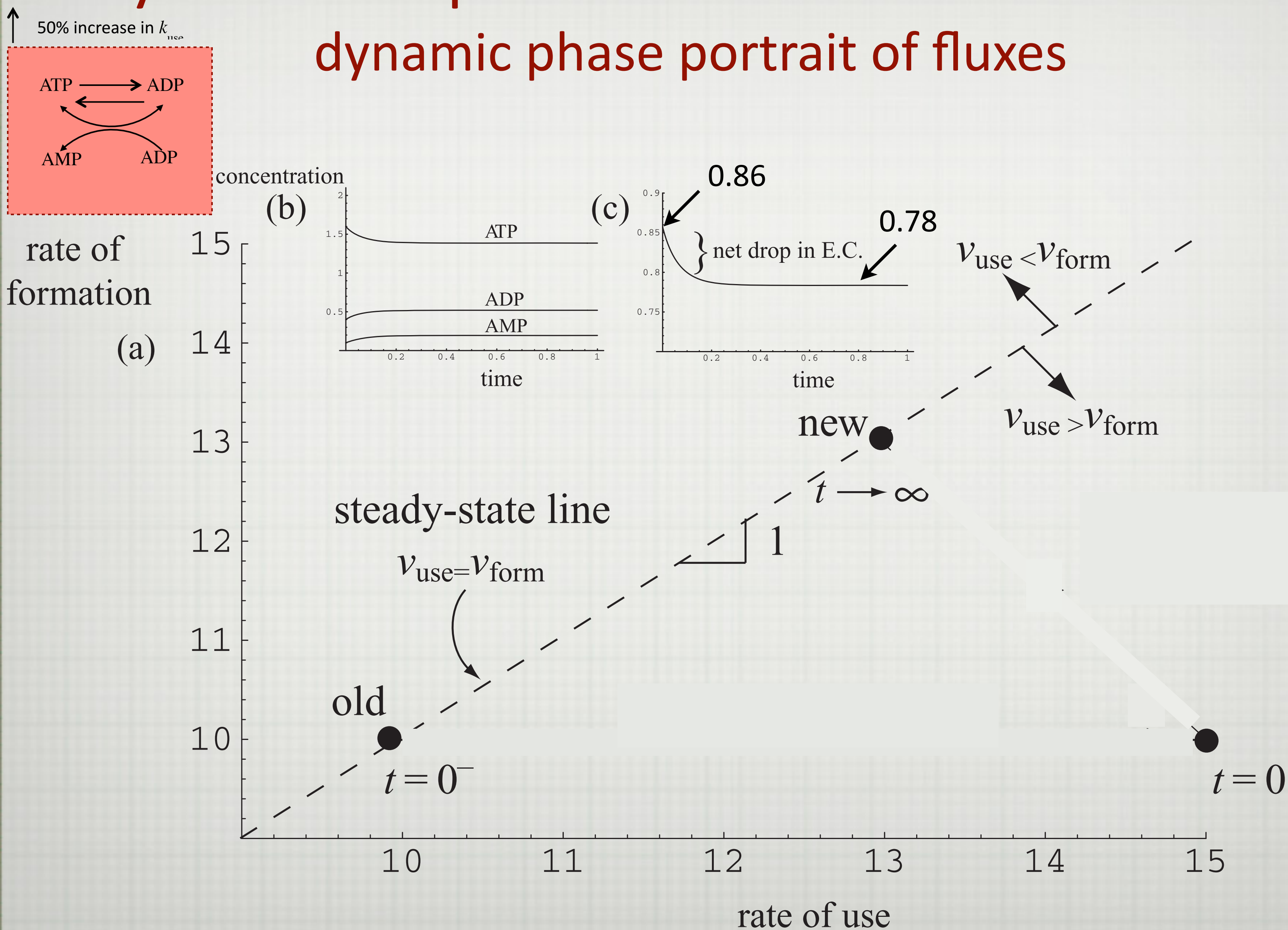
Energy Charge

$$EC = \frac{2(1.6)+0.4}{2(1.6+0.4+0.1)} = \frac{3.6}{4.2} = \frac{6}{7} = 0.86$$

Dynamic Response to a Load Perturbation:

dynamic phase portrait of fluxes



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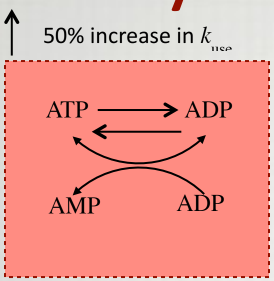

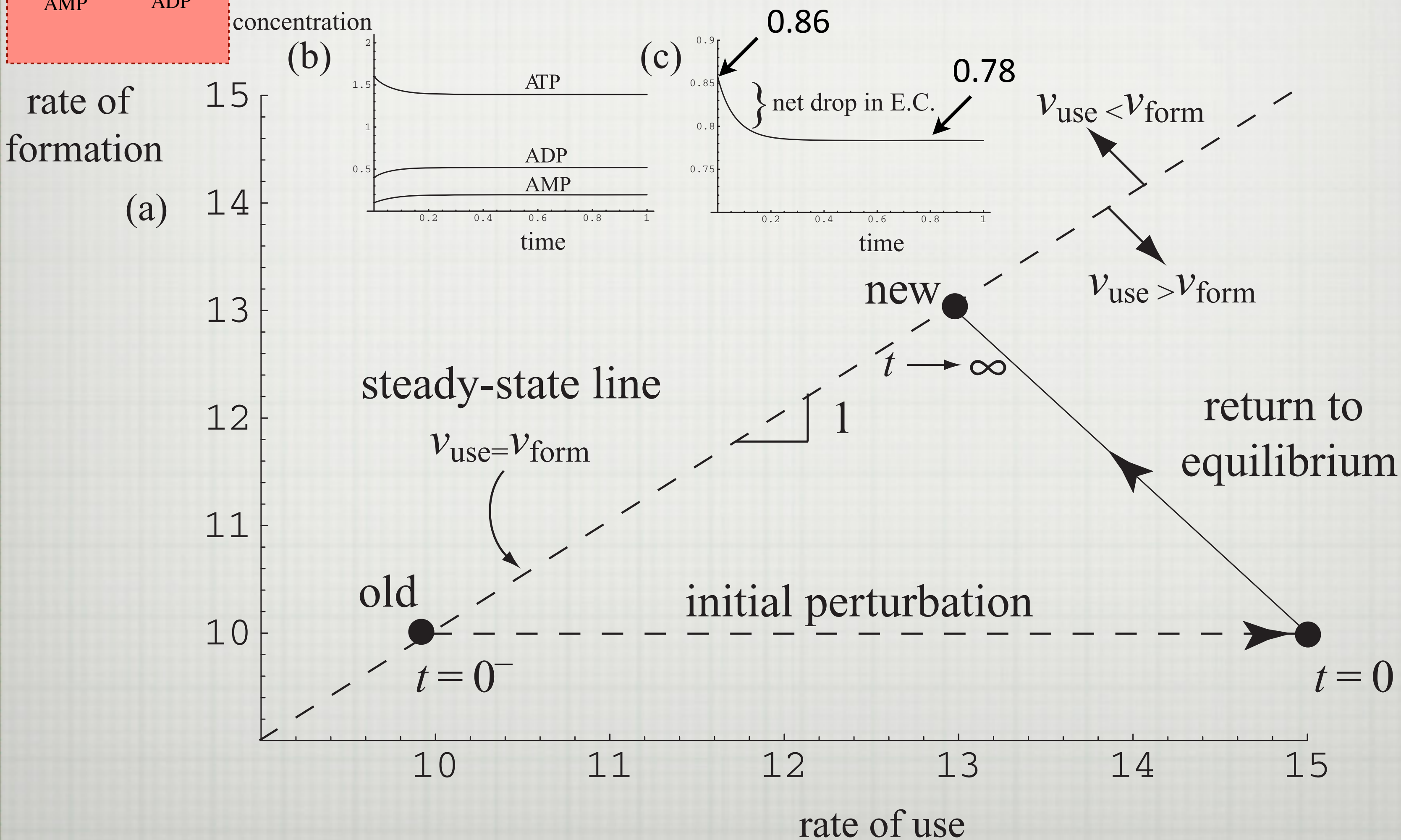

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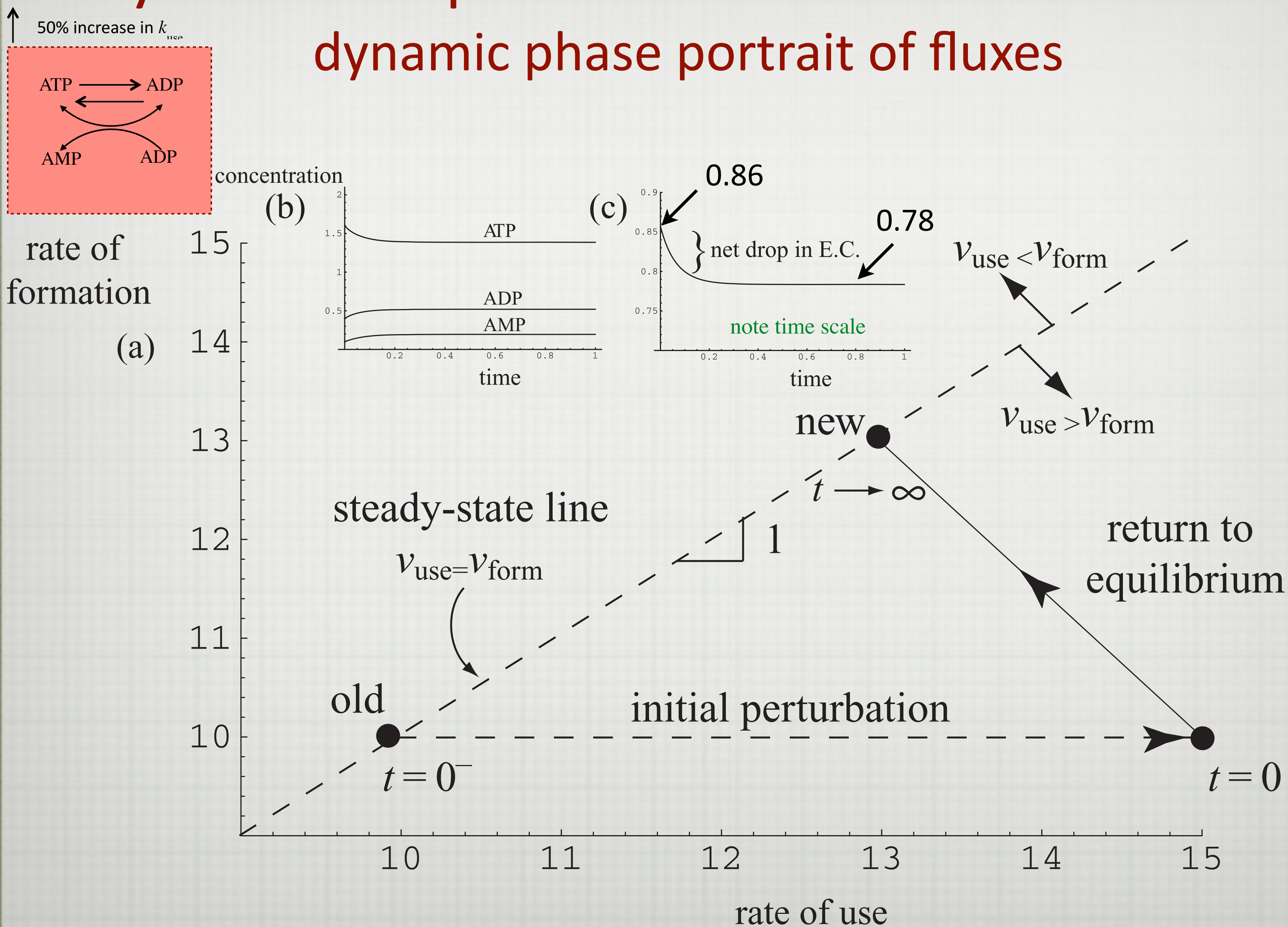
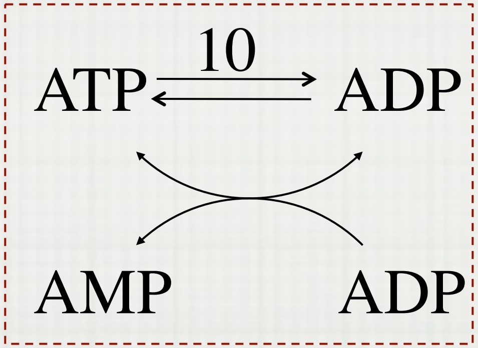


3. Open System:

AMP made and degraded

Chemistry



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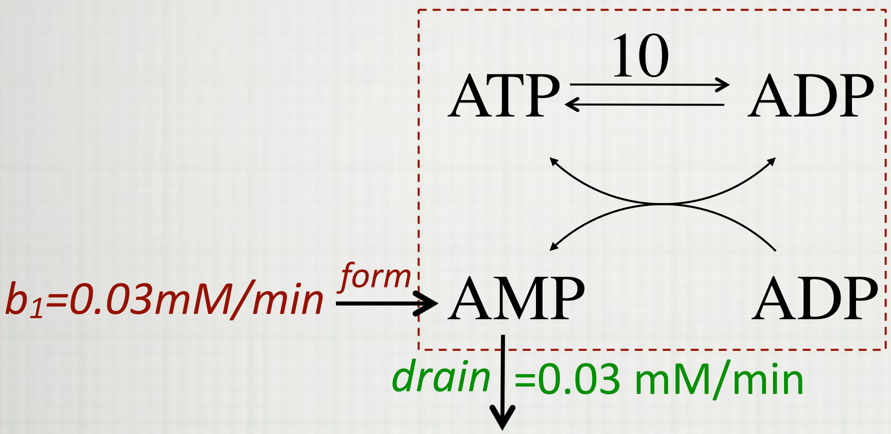

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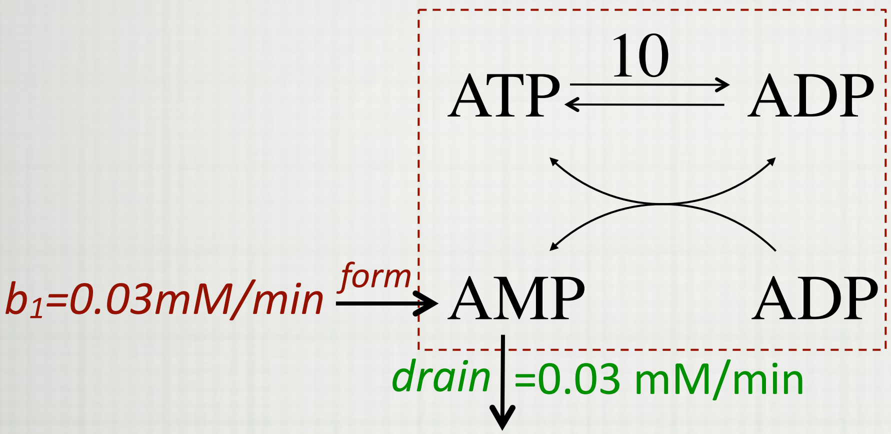

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$$= 0.3/min$$

$\therefore$ very slow

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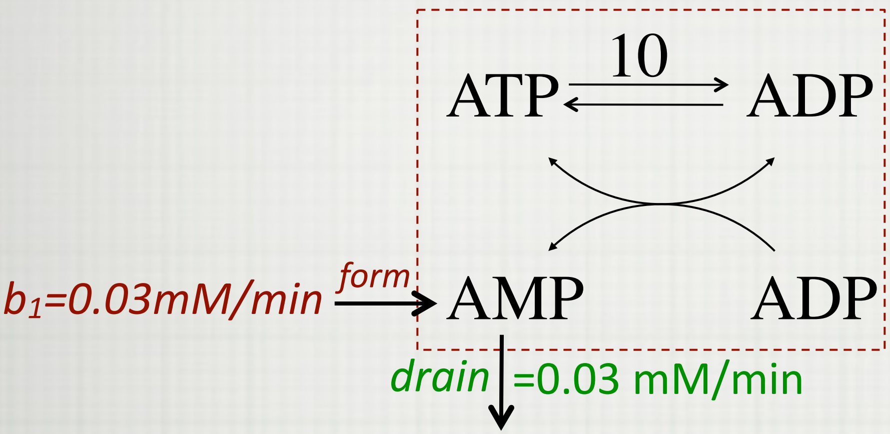

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$$\begin{pmatrix} 1 & -1 & 1 & 0 & 0 \\ -2 & 1 & -1 & 0 & 0 \\ 1 & 0 & 0 & -1 & 1 \end{pmatrix} \begin{pmatrix} v_{\text{distr}} \\ v_{\text{use}} \\ v_{\text{form}} \\ v_{\text{drain}} \\ b_1 \end{pmatrix}$$

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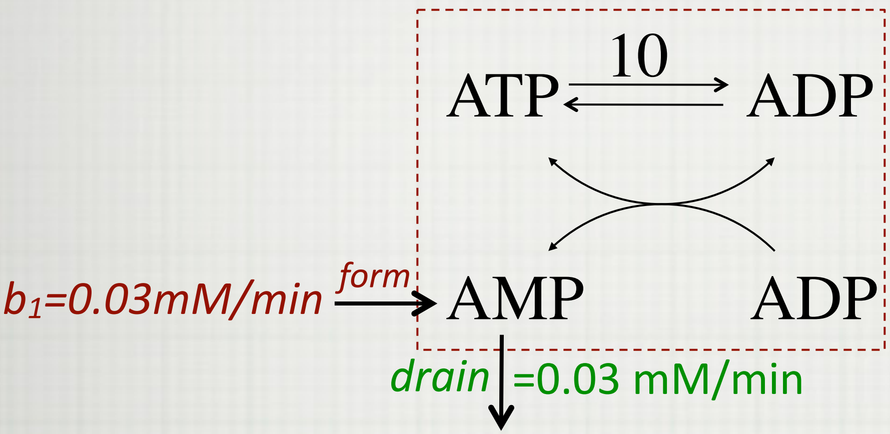

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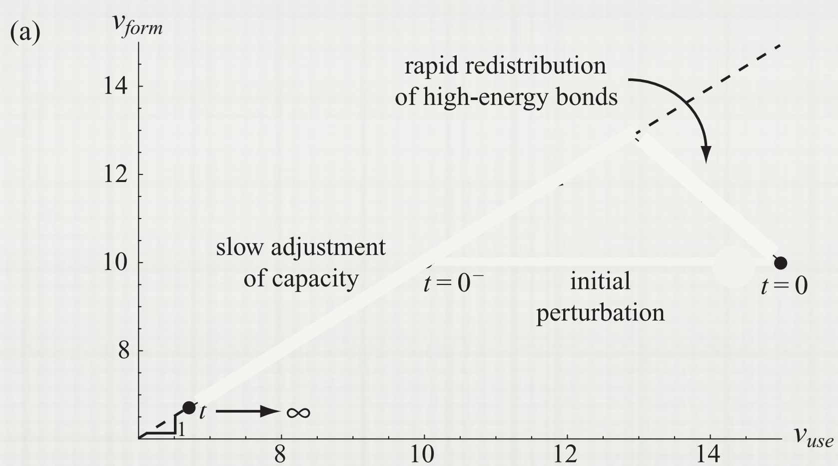
3 different time scales:

rate constants	1000/min;	6 to 25/min;	0.3/min
time response	0.001 min;	0.04-0.167 min;	3.3 min

Dynamic Response to a Load Perturbation

($k_{use,ATP}$ ↑50%) (flux phase portraits)



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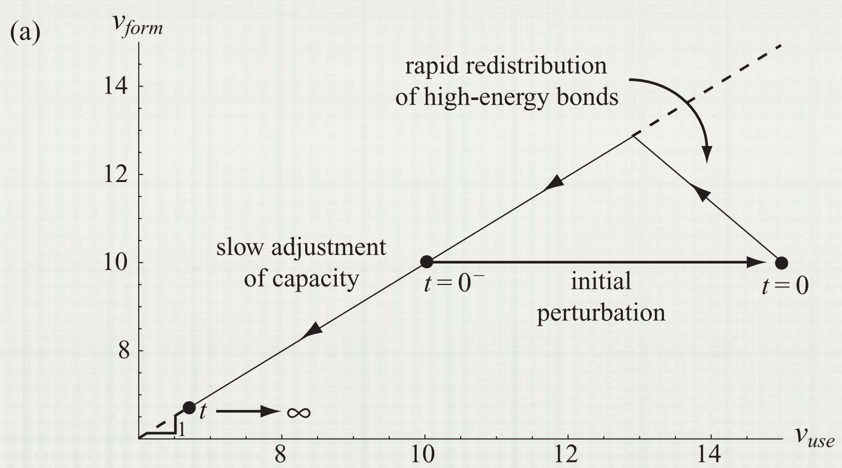

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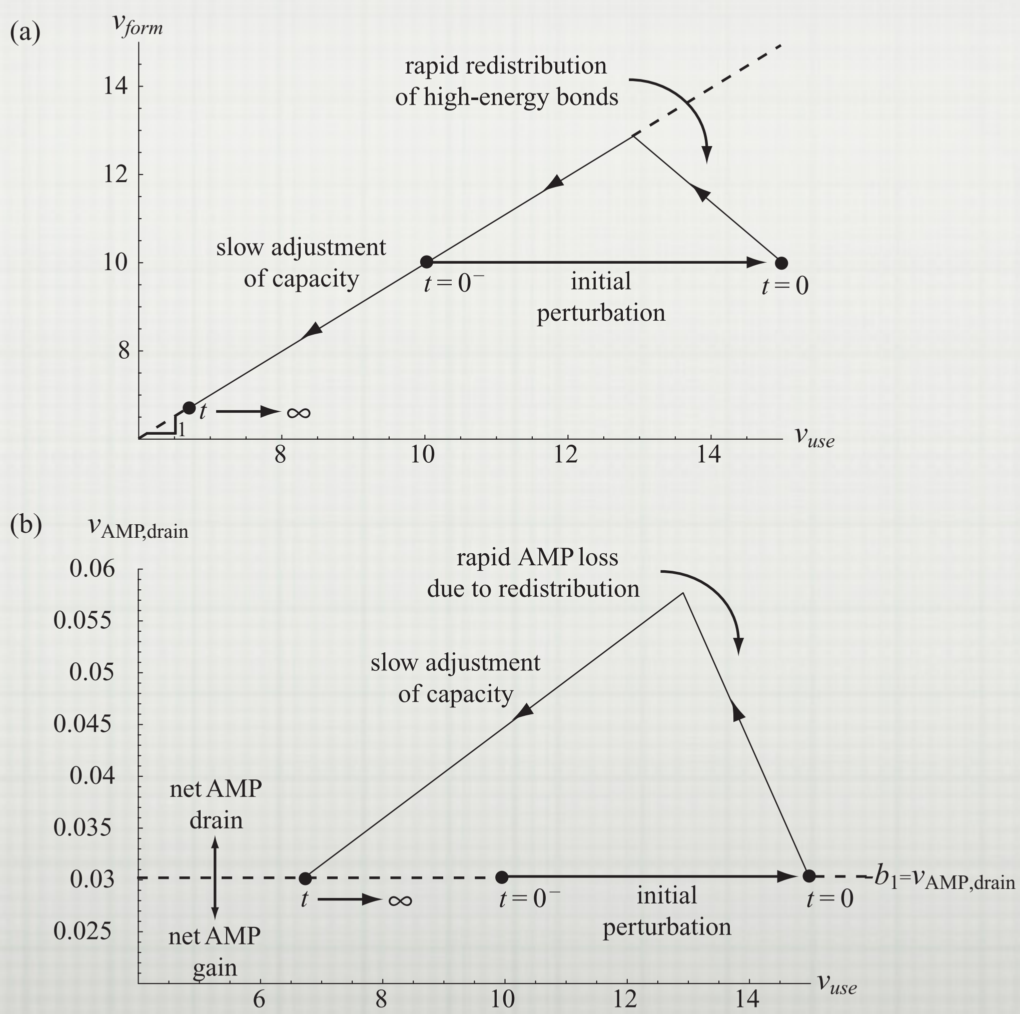
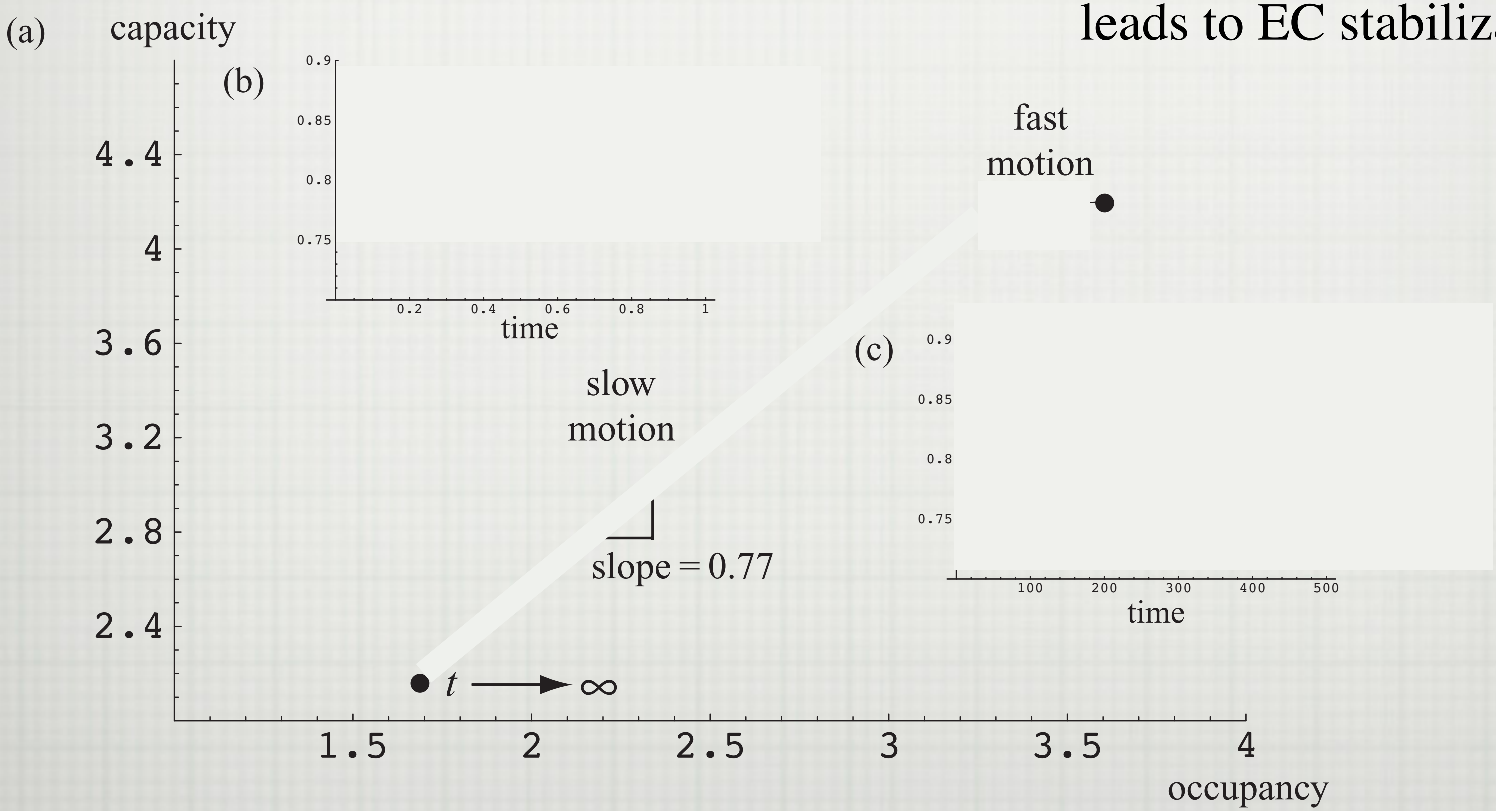


Dynamic Response:

capacity and charge

Principle #1: Network structure leads to EC stabilization



p(t)=Px(t)

Dynamic Response:

capacity and charge

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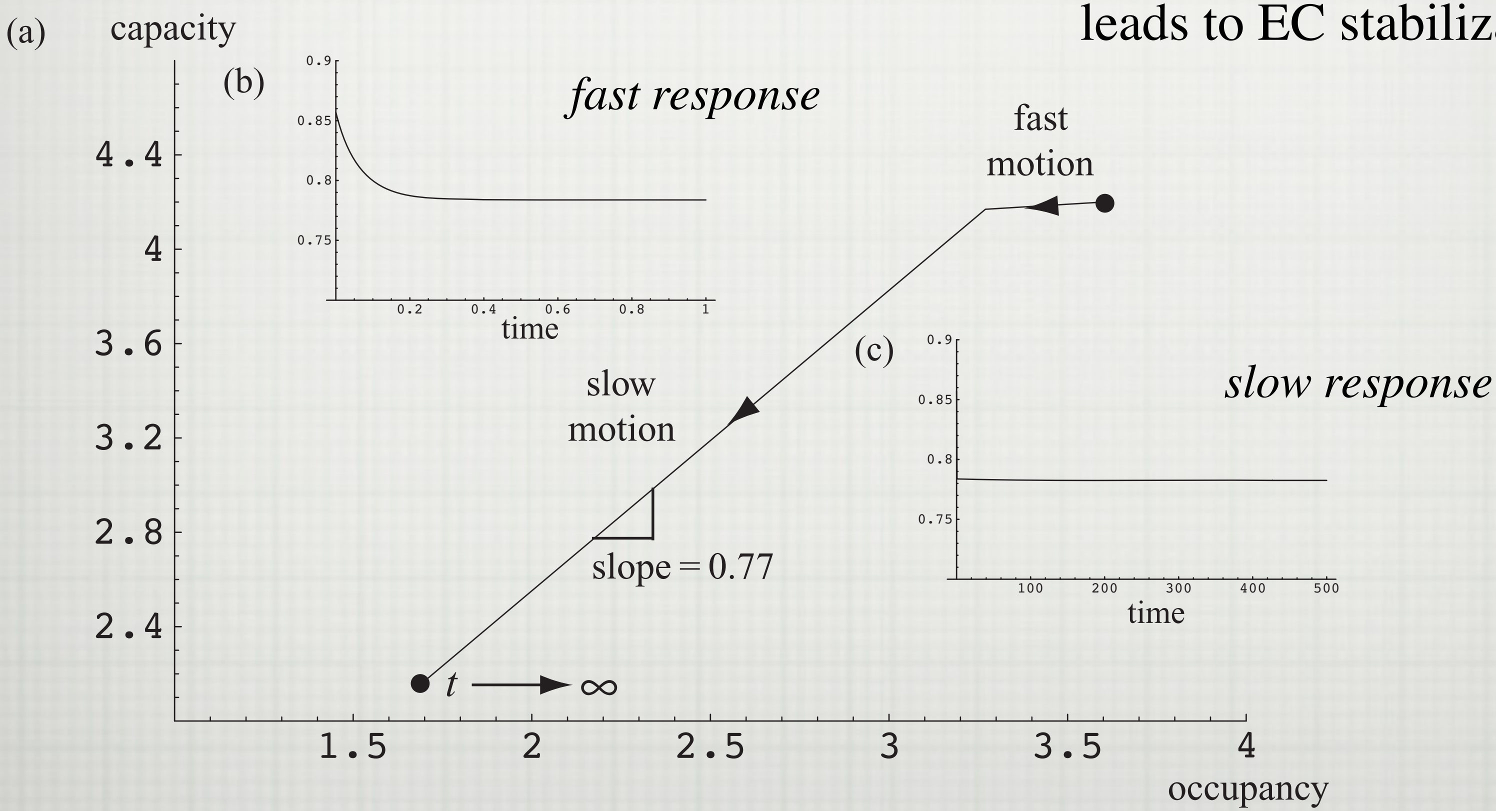

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Dynamic Response:

capacity and charge

Capacity
2(ATP+ADP+AMP)

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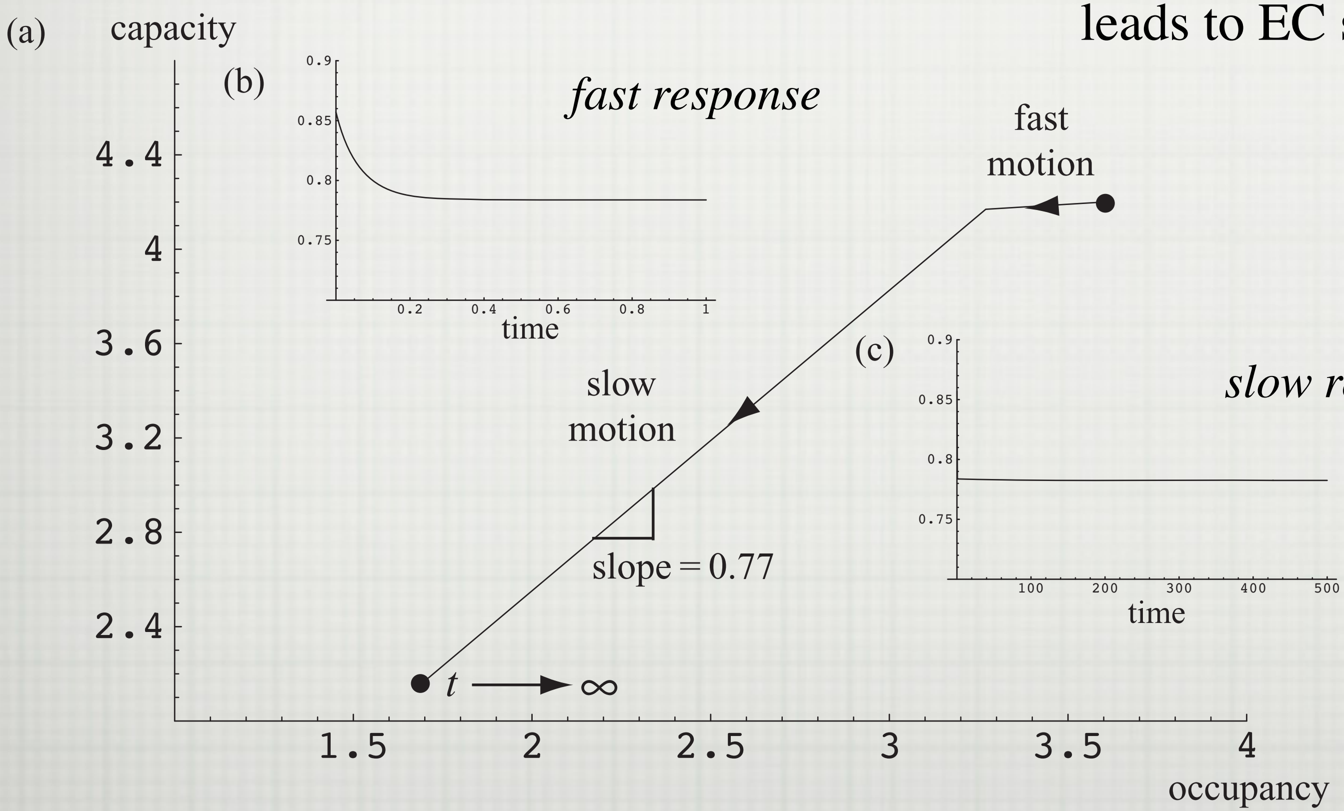


Occupancy
2ATP+ADP

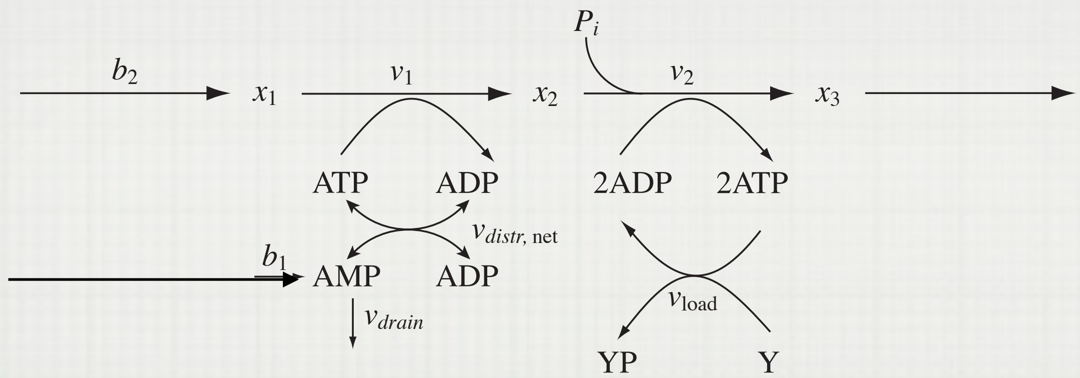
p(t)=Px(t)

Open system with fixed input

PROTOTYPIC METABOLIC PATHWAYS WITH COFACTORS

Open System:

charging and discharging metabolites



Principle # 2:
"it takes P ($) to
make P ($)"

Open System:

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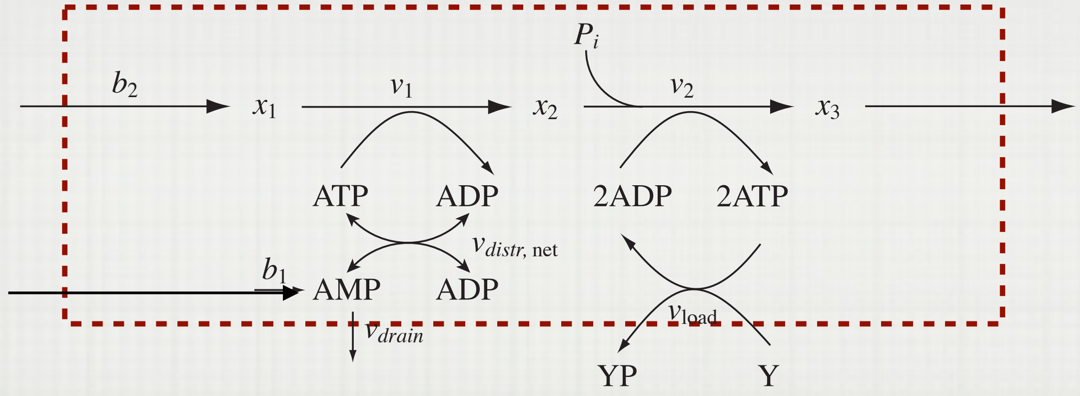

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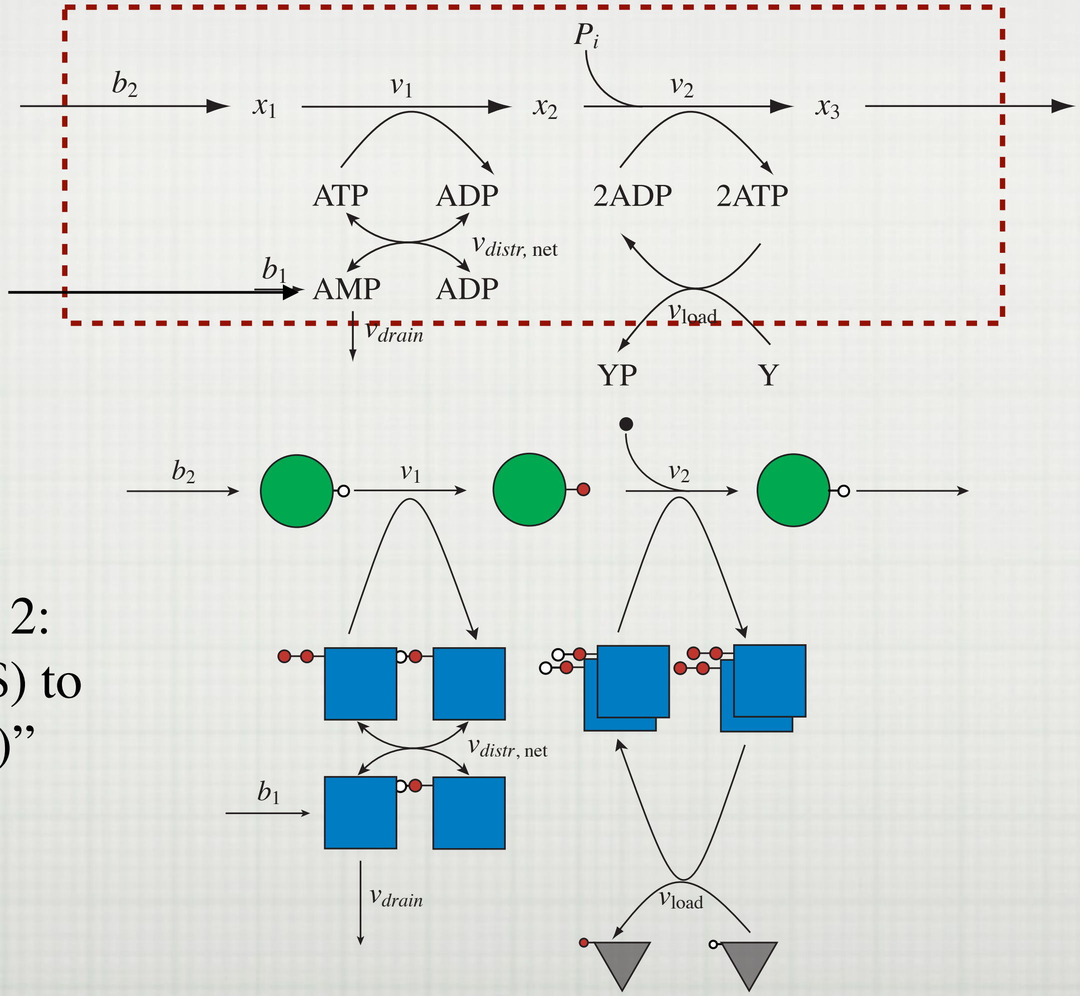

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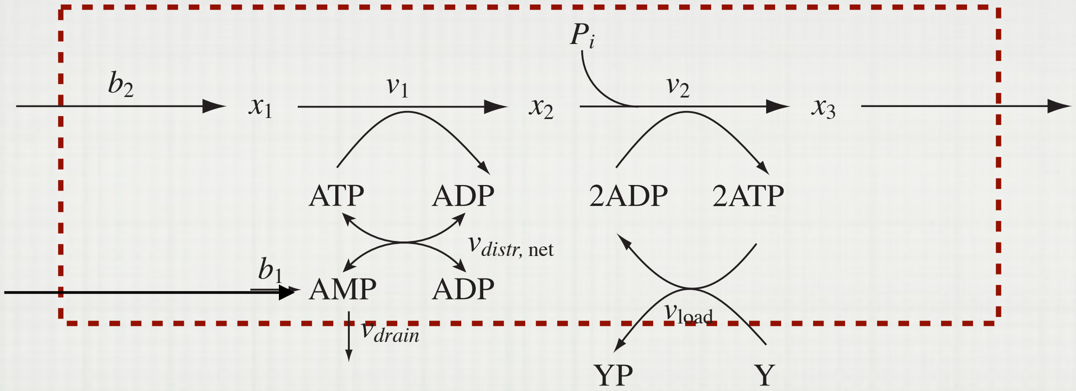

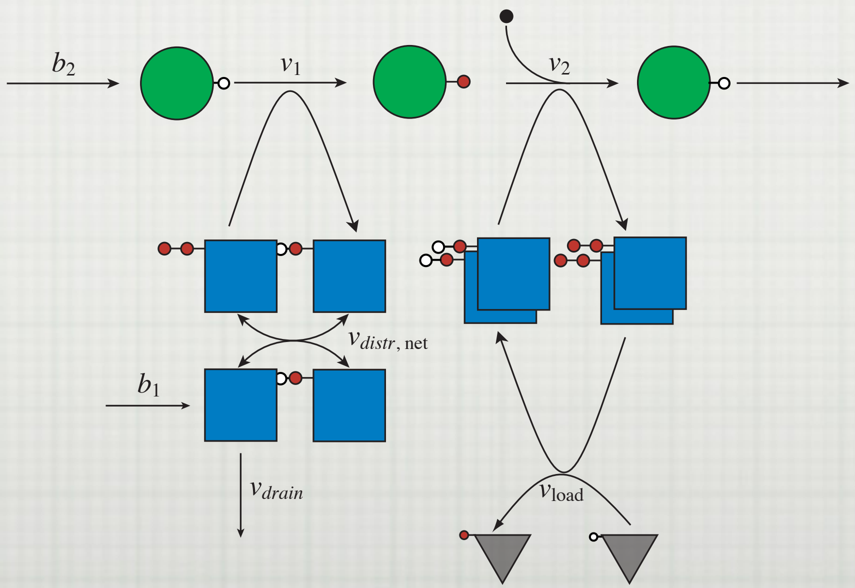

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Energy bonds for 'charging' < 'recovery'

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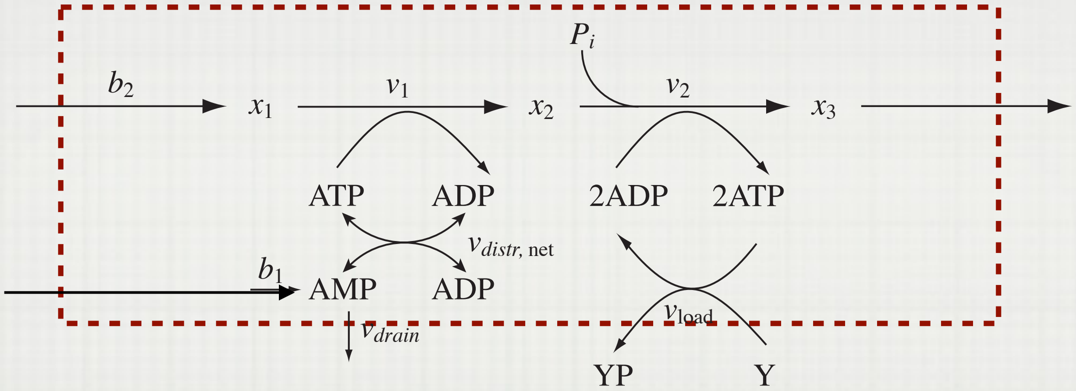

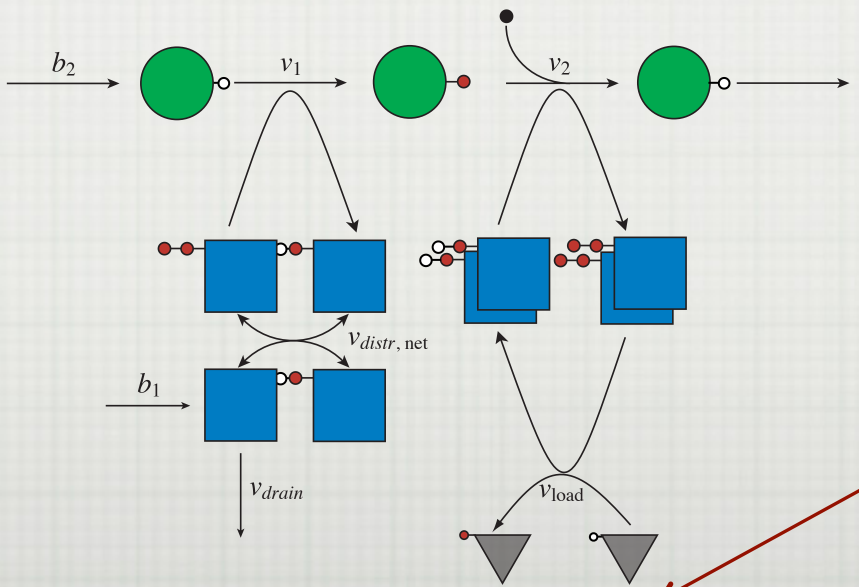

Principle # 2:
"it takes P ($) to make P ($)"

enabling a load to be placed on a system

Energy bonds for 'charging' < 'recovery'

Dynamic Responses to a Load Perturbation

$$
\begin{aligned}
b_1 &= 0.03 \\
b_2 &= 5 \\
k_{a4} &= b_1/.1 \\
k_{load} &= 5/1.6 \\
k_{s1} &= 5/1.6 \\
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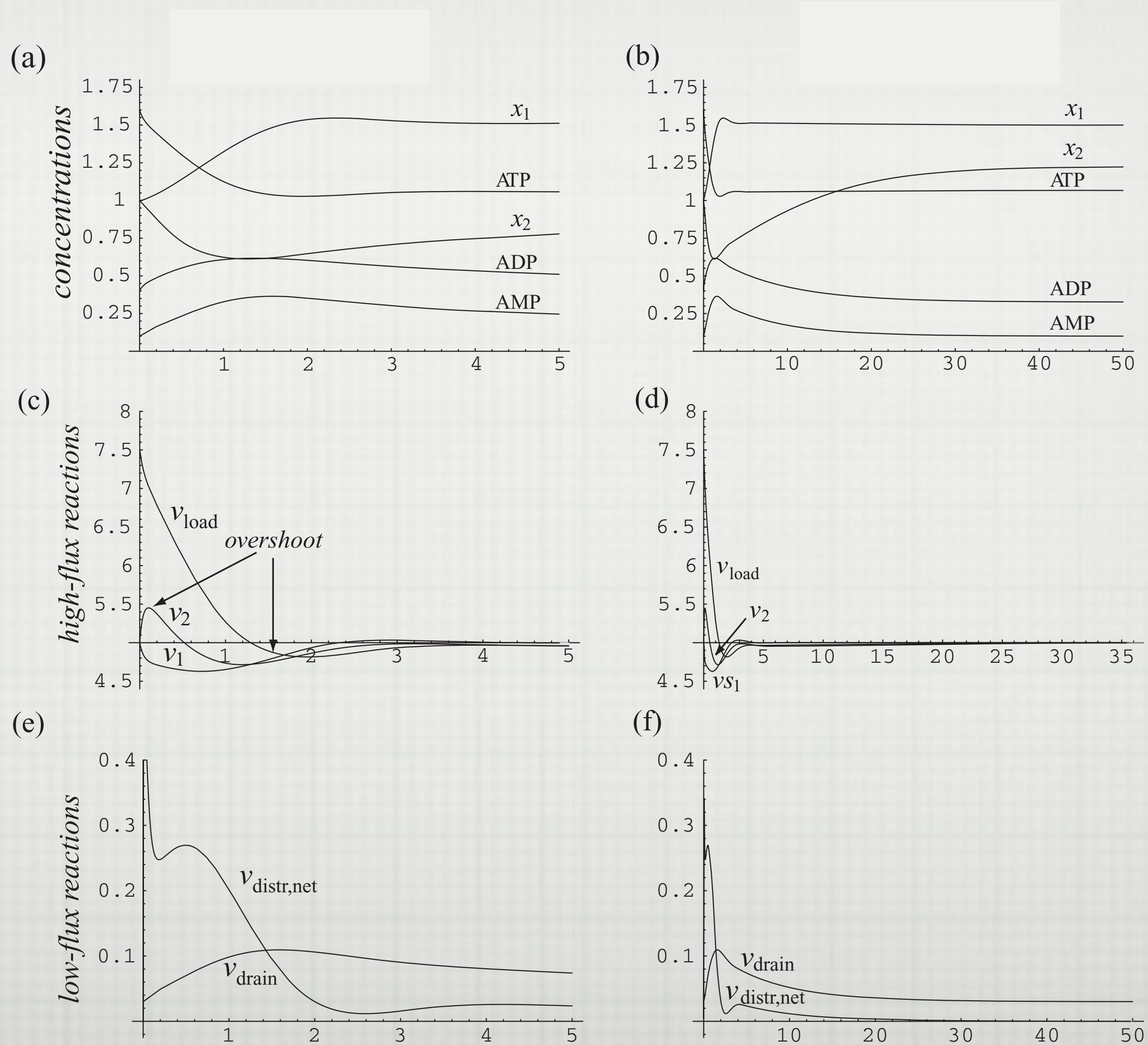
\end{aligned}
$$



Dynamic Responses to a Load Perturbation

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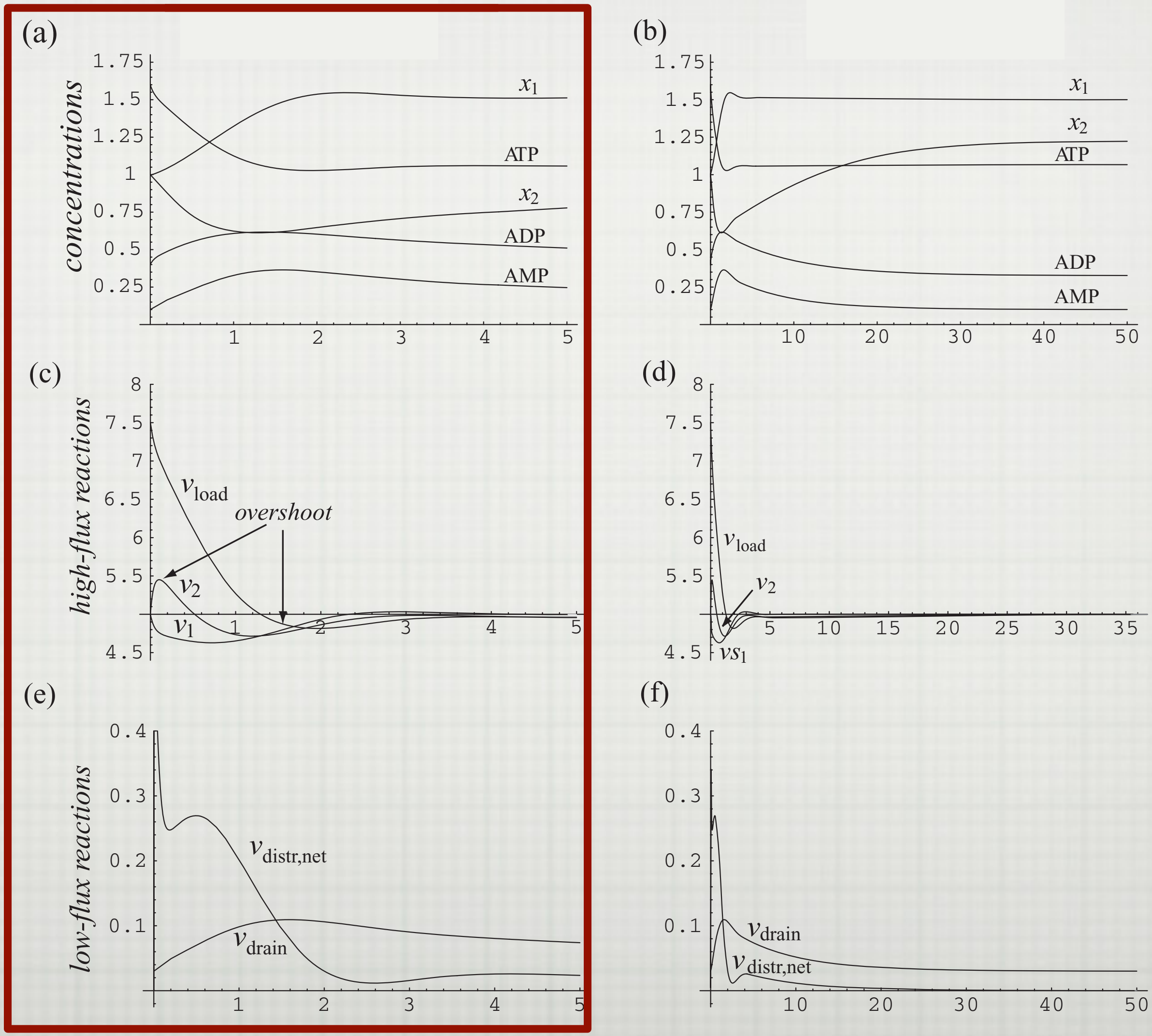

Dynamic Responses to a Load Perturbation

Fast

Slow

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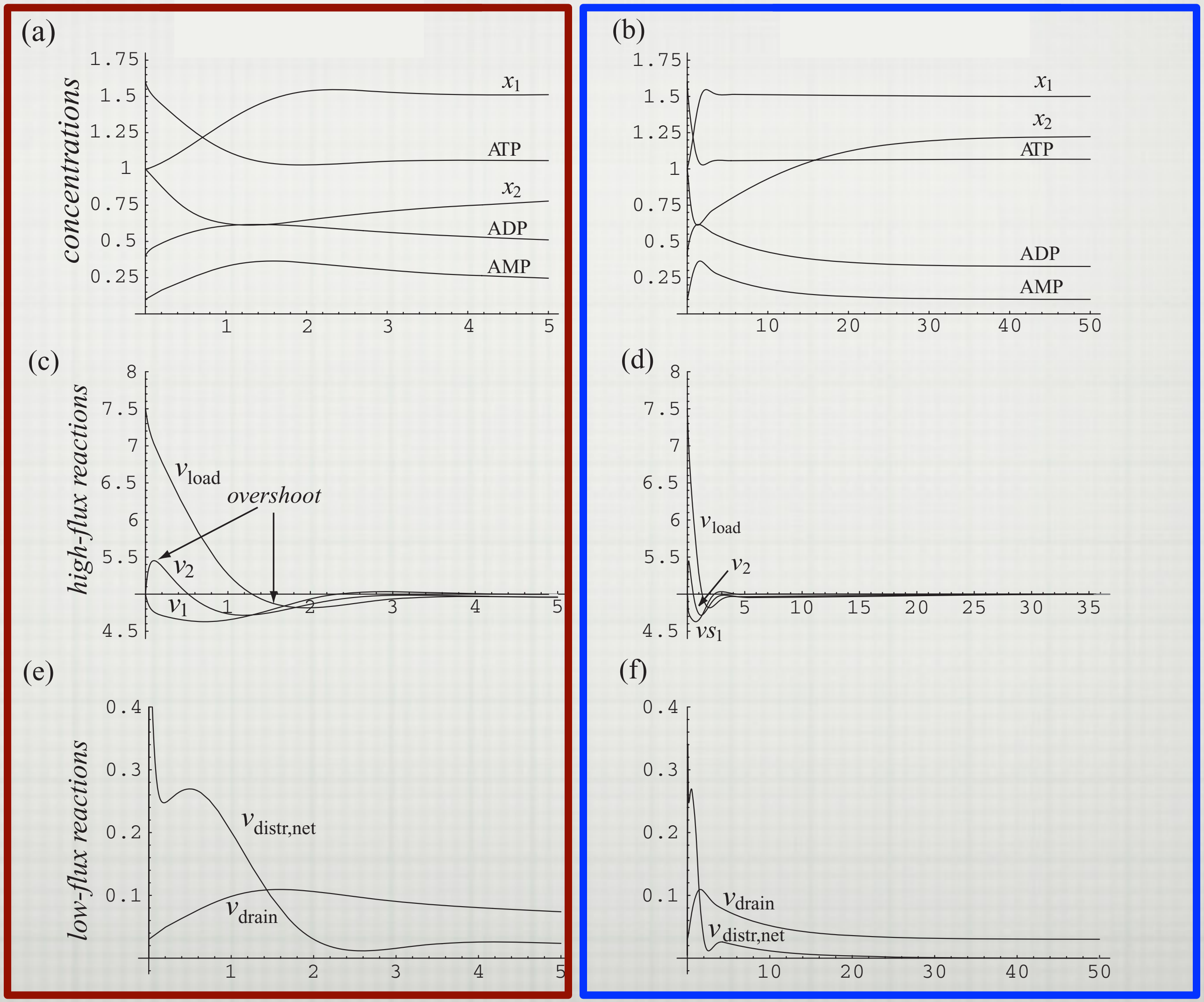
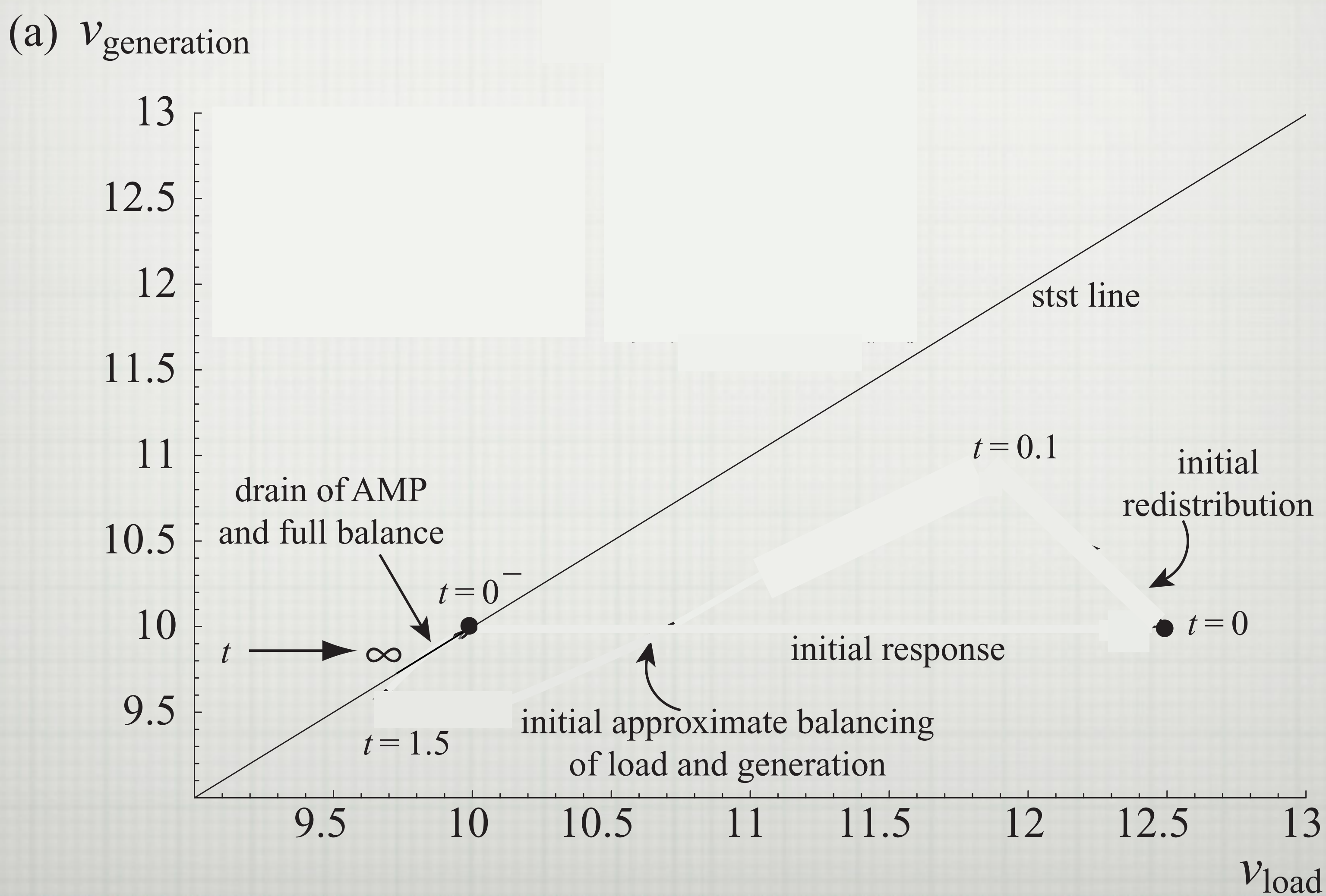


Dynamic Response (con’t)

flux phase portrait



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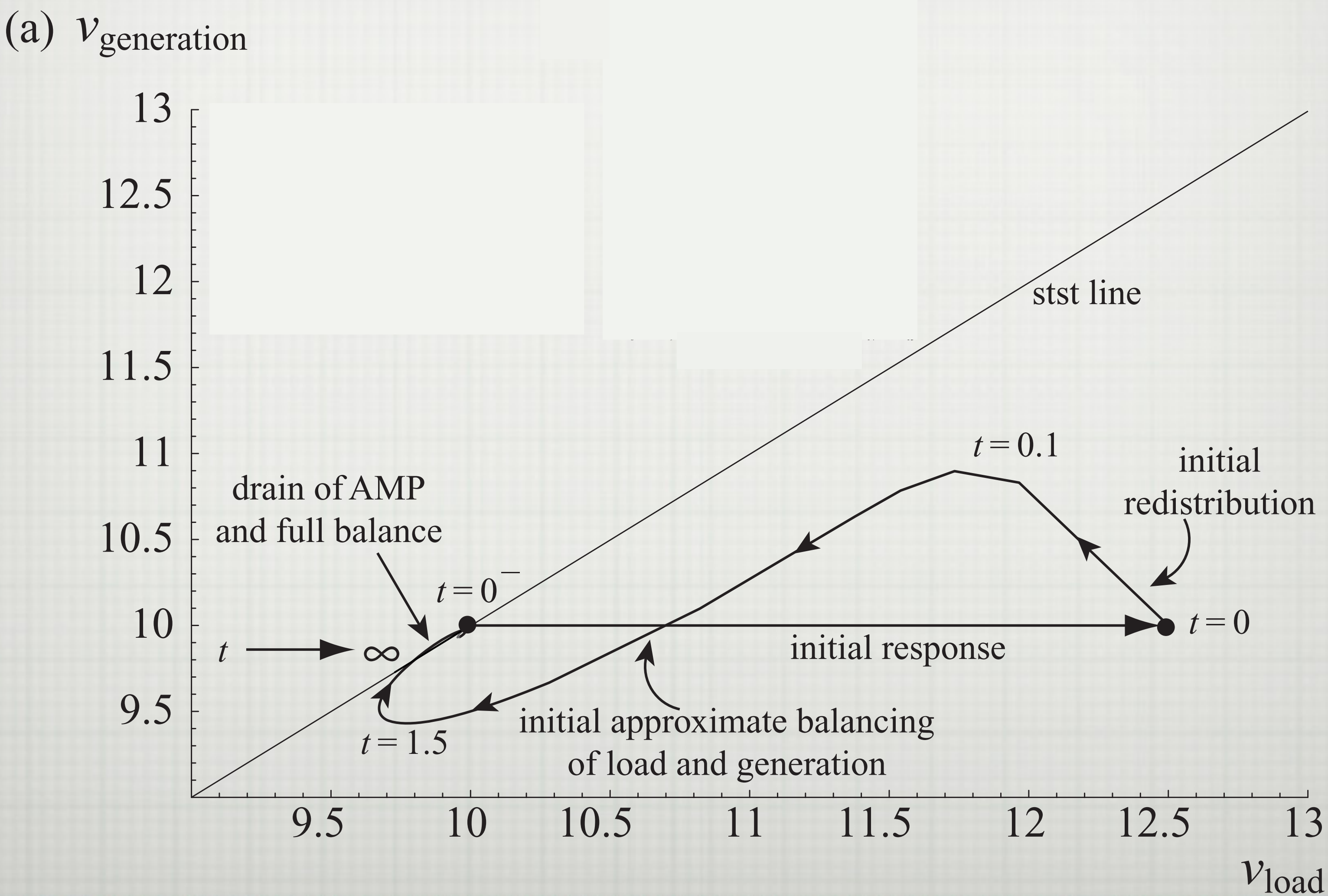

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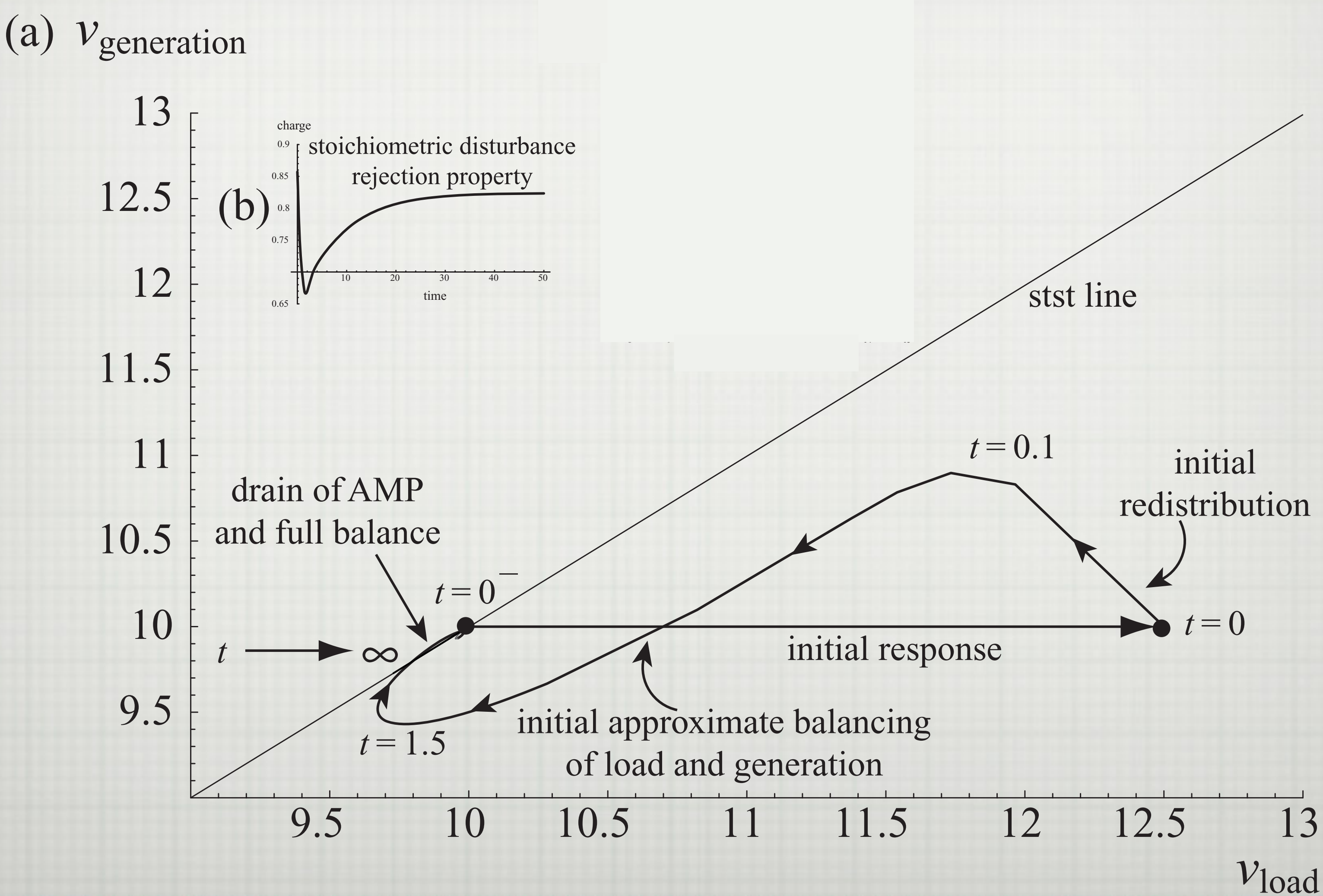

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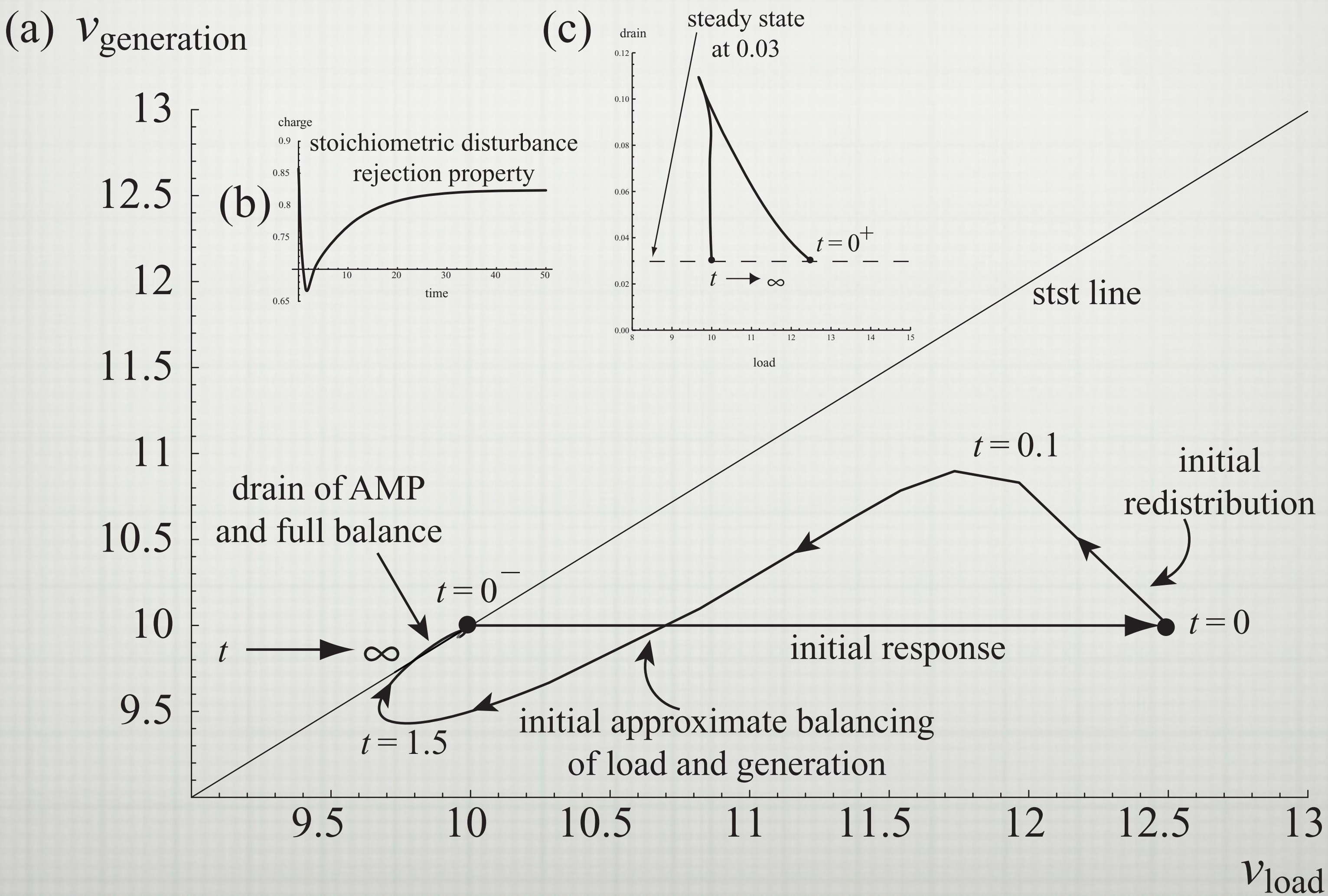

Differences from the un-coupled ATP generation module

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- The 'case studied,' was an increase in ATP rate of use of 50% as before

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- The time scales are typically separated.

The End