# METABOLIC NETWORKS

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# UNBRANCHED METABOLIC NETWORKS

- The simplest metabolic network is an unbranched pathway.
- All reaction rates equal at steady-state, so the pathway flux is the steady-state of every reaction.
- If there is an irreversible action in the chain, the first reaction has a fixed rate and so dictates the pathway flux.

# UNBRANCHED METABOLIC NETWORKS

- For reversible reactions (and assuming first-order enzyme reactions), the pathway flux is:

$$J = \{[S_0]q_1q_2..q_n - [P]\}/\{q_1q_2..q_n/[e_1]k_1 + q_2..q_n/[e_2]k_2 ..+ q_n/[e_n]k_n\}$$

where [S] is substrate concentration, [P] is product concentration, [e] is enzyme concentration, q is ratio of forward and reverse reactions and k is forward product reaction constant.

# UNBRANCHED METABOLIC NETWORKS

- Pathways are responsive (high sensitivity with respect to appropriate input signals) and flux is robust (insensitive) to perturbations.
- Product is generated when called for; else, production rate is kept low.
- End-product inhibition most common (allosteric)

# UNBRANCHED METABOLIC NETWORKS

- Robust to disturbances in demand for product P
- Robust to perturbations in enzyme activity levels
- Responsive to changes in the availability of substrate S.
- Elastic.
- Potential for instability as strong negative feedback coupled with inherent time delay in long pathway can lead to oscillatory behavior.

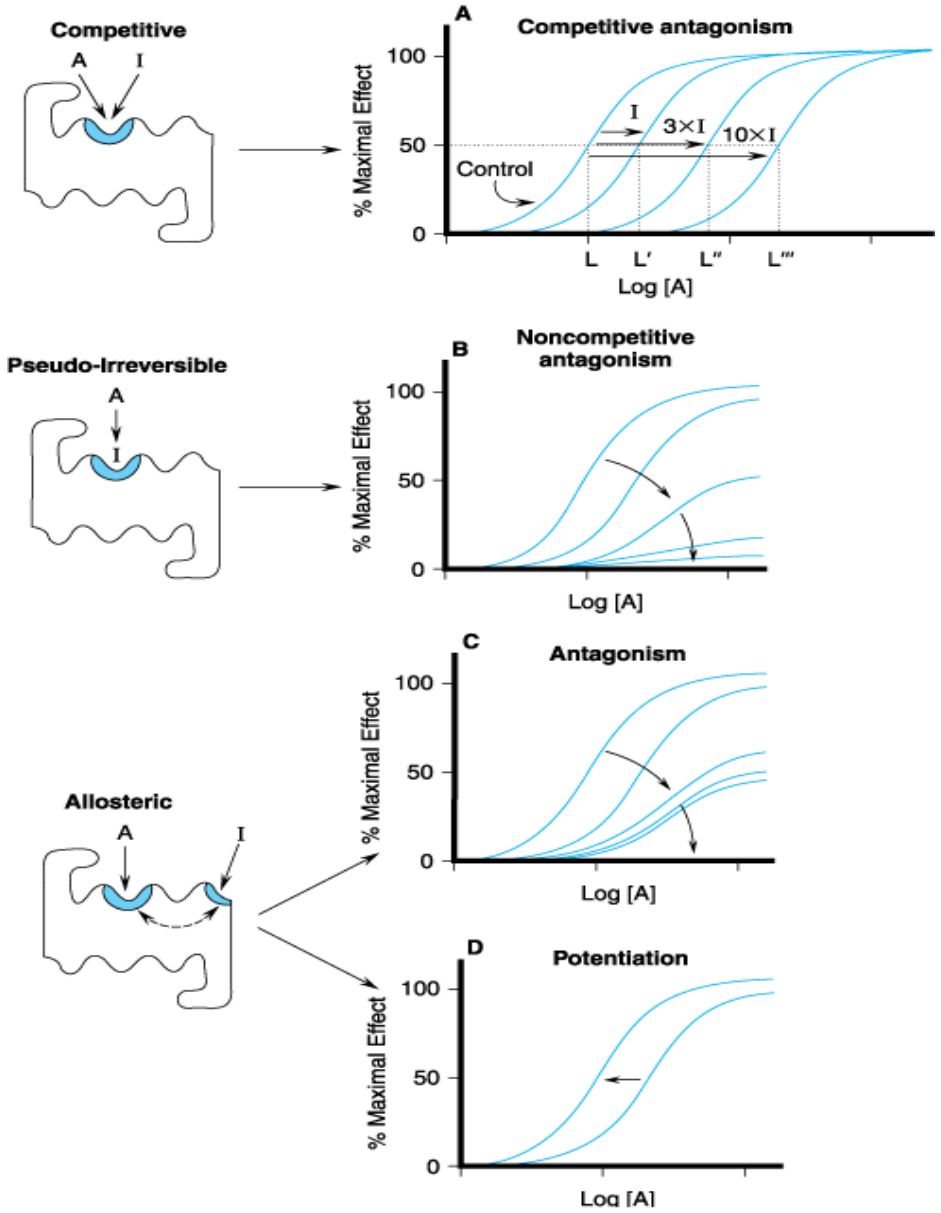




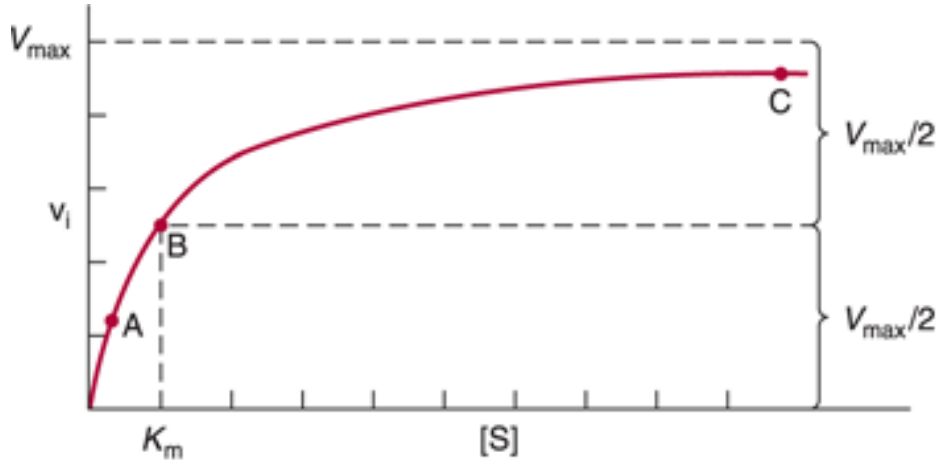

Fig. 1-11 Accessed 08/01/2010

A. Competitive antagonism
B. Irreversible antagonism.
C. Allosteric effects occur when the enzyme binds to a different site on the substrate to inhibit response.
D. Allosteric effects occur when the enzyme binds to a different site on the substrate to potentiate response. The allosteric effect is saturable; inhibition reaches a limiting value when the allosteric site is fully occupied.

# UNBRANCHED METABOLIC NETWORKS

- Experimental observations of enzyme-catalyzed reactions show that they do not obey mass action laws.
- The rate of an enzyme catalyzed reaction approaches a limiting value as the substrate abundance grows (entire enzyme pool is working).
- S + E $\rightleftarrows$ C-S $\rightleftarrows$ C-P $\rightleftarrows$ P + E
- Yields Michaelis-Menten equation
- Rate law is hyperbolic.
- If Inhibitor present, present in greater abundance than enzyme, same equation.

# Enzyme kinetics






Effect of substrate concentration on the initial velocity of an enzyme-catalyzed reaction.

Fig. 8-4 Accessed 08/01/2010

# BRANCHED METABOLIC NETWORKS

- Most networks are highly branched, sharing metabolites among multiple pathways.
- Sequential feedback
- The end-product of each branch inhibits flux through the respective branch
- Consumption of the initial substrate is only inhibited by common intermediates.
- Efficient.

# BRANCHED METABOLIC NETWORKS

- Nested feedback
- End-products inhibit one or more of the shared steps in the pathway.
- Inefficiency can be tempered by enzyme multiplicity, in which multiple enzymes catalyze a single reaction.
- Each end-product has influence over a portion of the shared flux.
- Most common.

# BRANCHED METABOLIC NETWORKS

- Methionine → S-adenosylmethionine is a two enzyme dependent reaction in the liver (MAT I and MAT III)
- S-adenosylmethionine → S-adenosylhomocysteine is dependent upon two methylation reactions.
- S-adenosylhomocysteine → homocysteine interconversion is in rapid equilibrium as enzyme is ten times more abundant than others in pathway.

# BRANCHED METABOLIC NETWORKS

- MAT I is inhibited by S-adenosylmethionine.
- MAT III shows a sigmoidal dependence on methionine (cooperative) and is allosterically activated by by S-adenosylmethionine.

# BRANCHED METABOLIC NETWORKS

- Methylation reactions
- Glycine N-methyltransferase, shows a sigmoidal dependence on methionine (cooperative) and is inhibited by S-adenosylhomocysteine.
- All other methylation reactions are inhibited by S-adenosylmethionine.
- Homocysteine consumption follows a mass action law.

# BRANCHED METABOLIC NETWORKS

- At low methionine concentrations, the S-adenosylmethionine concentration drops immediately and remains steady
- S-adenosylmethionine  concentration relaxes over hours.
- Flux is through MAT I and other methylation reactions.

# BRANCHED METABOLIC NETWORKS

- At the high S-adenosylmethionine state, the system is bistable
- The positive feedback on MAT III increases the flux through MAT III while the negative feedback on MAT I decreases the flux through that reaction.
- MAT III carries the bulk of S-adenosylmethionine production.
- GNMT flux is increased.

# BRANCHED METABOLIC NETWORKS

- Bistability keeps methionine level steady.
- When methionine levels rise, the system switches to the high S-adenosylmethionine state, shuttling extra methionine directly to S-adenosylhomocysteine without affecting the other methylation reactions in the cell
- A safety measure that insulates methylation reactions from alterations in methionine levels.

# BRANCHED METABOLIC NETWORKS