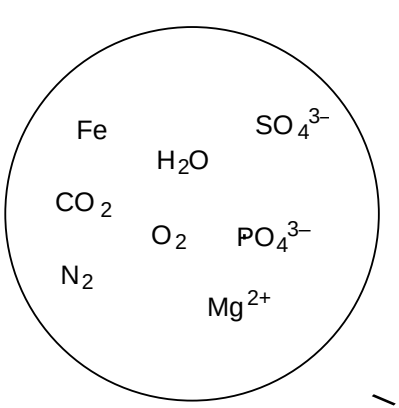
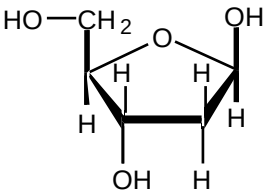
METABOLISM FOR SYSTEMS BIOLOGY

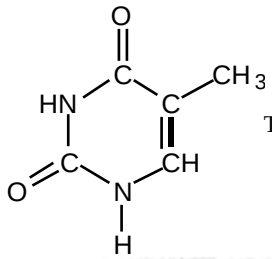
I. INTRODUCTION

Sophisticated Biological Molecules Derive from Simple Environmental Chemicals

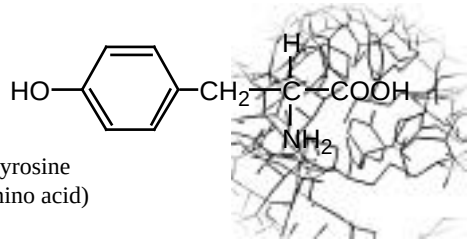




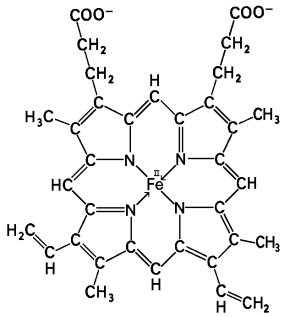
2-Deoxyribose
(sugar)



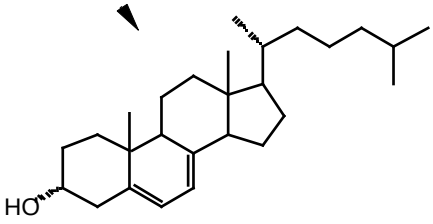
Thymine
(base)



Tyrosine
(amino acid)



Haem
(component of haemoglobin)



Cholesterol
(membrane component and steroid)

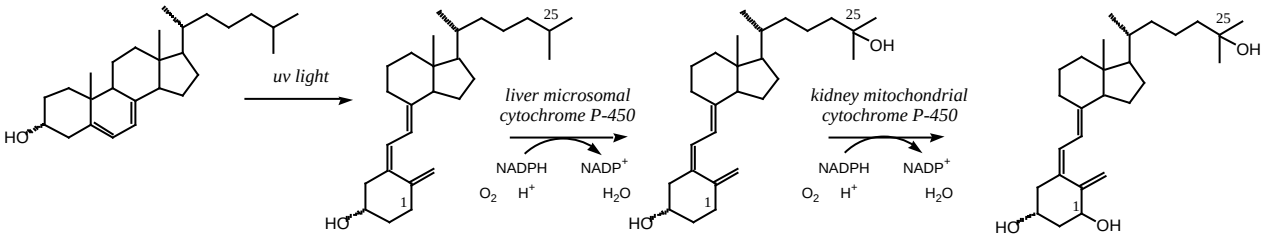
Biological molecules introduced
in Basic Bioinformatics Module

Some other representative
biological molecules

They are synthesized in a sequence of linked steps: a Metabolic Pathway

A ⟶ B ⟶ C ⟶ D ⟶ E ⟶ F ⟶ G ⟶ H ⟶ I ⟶ J

e.g.



7-dehydrocholesterol

Vitamin D_3
(Cholecalciferol)

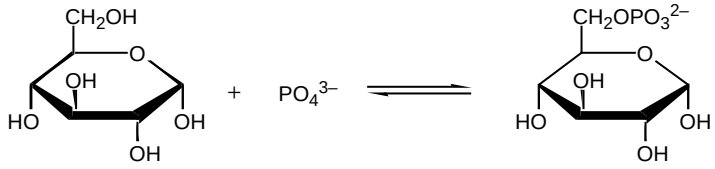
25-hydroxyvitamin D_3

α1,25-dihydroxyvitamin D_3

II. CHARACTERISTICS OF INDIVIDUAL BIOLOGICAL REACTIONS

1. Thermodynamics: Equilibrium, Free Energy Change and Directionality

(i) Description



Glucose Phosphate Glucose 6-phosphate

$$A + B \underset{}{\overset{K_{eq}}{\rightleftharpoons}} C$$

$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]} = \frac{[C]}{[A][B]}$$

$$\Delta G_0 = RT \log_e \frac{[\text{products}]}{[\text{reactants}]} = RT \log_e K_{eq}$$

where ΔG_0 = standard free energy of hydrolysis

R = gas constant

T = absolute temperature

$$\Delta G = \Delta G_0 - RT \log_e \frac{[\text{products}]}{[\text{reactants}]}$$

In order to proceed an overall reaction must have a negative ΔG

(ii) Implications

(a) Influence of concentration of reactants and products

(b) Linkage of unfavourable reactions to favourable ones

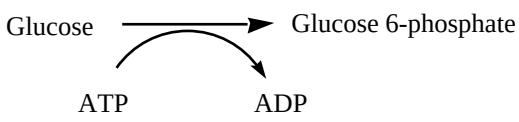
In consecutive reactions

A + B ⟶ C	ΔG = +14 kJ/mole
C ⟶ D	ΔG = –30 kJ/mole
A + B ⟶ D	ΔG = –16 kJ/mole

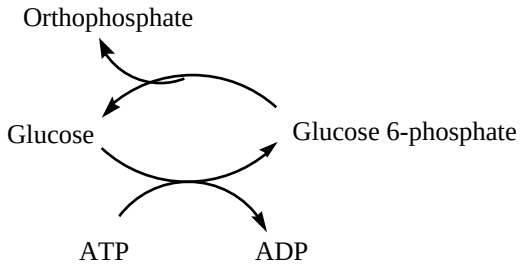
In coupled reactions

A + B ⟶ C	ΔG = +14 kJ/mole
X ⟶ Y	ΔG = –30 kJ/mole
A + B + X ⟶ D + Y	ΔG = –16 kJ/mole

e.g.

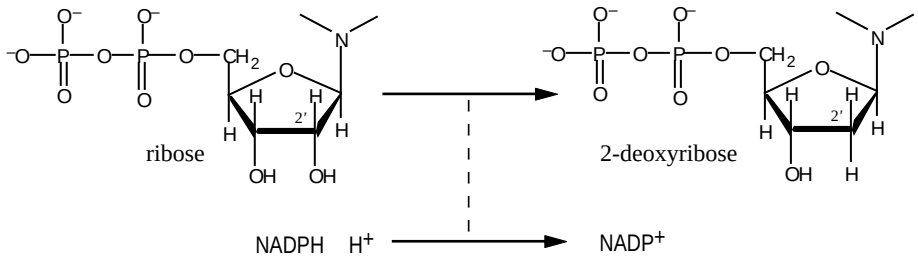


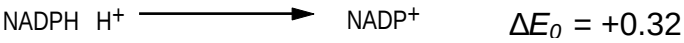
(c) Cases of distinct forward and reverse reactions



(d) Co-factors driving metabolic reductions

e.g.





$\Delta E_0 = +0.32$

$$\Delta G_0 = -nF\Delta E_0$$

i.e. NADPH can drive reduction reactions with unfavourable ΔG

The most common reducing agent cofactors

Ferredoxin	(strongest reducing agent)
NADPH	(provides reducing power for biosyntheses)
NADH	(similar to NADPH, but used to generate ATP)
$FADH_2$	(not as strong as) NADH, but also used to generate ATP)

(e) Other Co-factors allow energetically favourable donation of small chemical groups

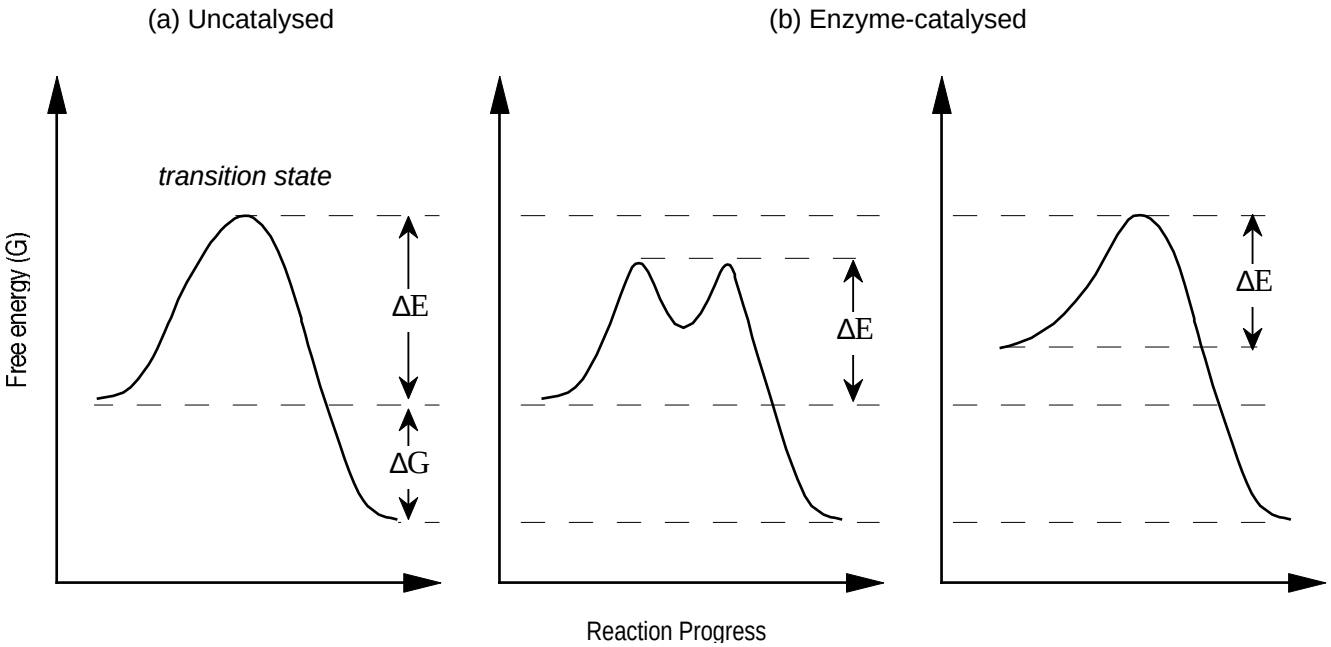
CoenzymeA:	Acyl groups
Biotin:	CO_2
Tetrahydrofolate:	One-carbon groups
S-adenosyl methionine:	Methyl groups

(iv) Text Reference

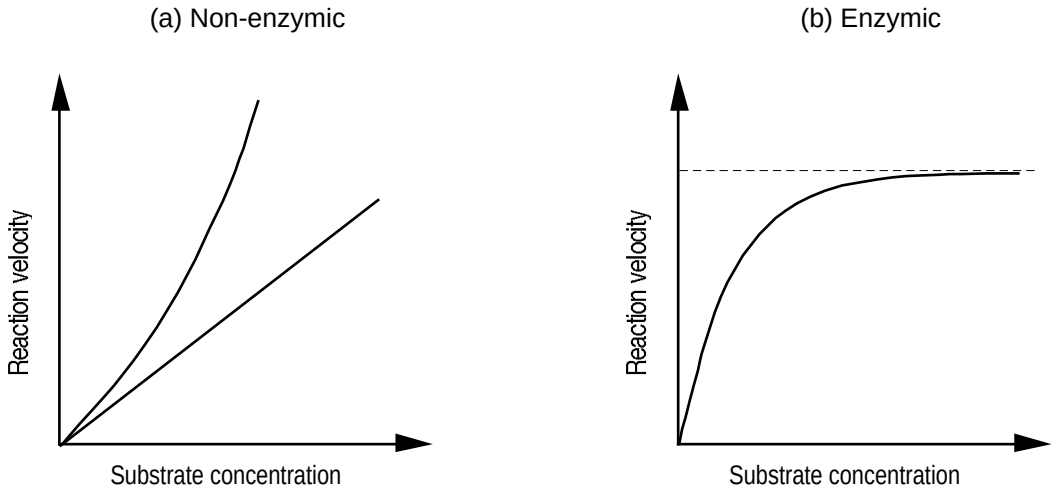
Berg, J. *et al.* Biochemistry (Freeman, 5th ed.), Chapter 14: Metabolism, Basic Concepts and Design

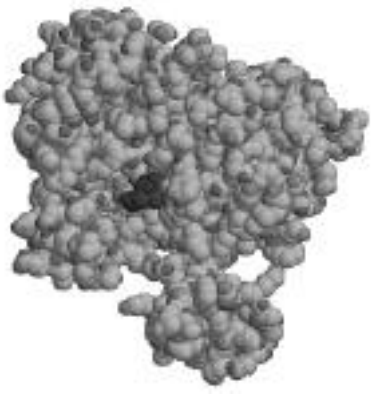
2. Kinetics: Enzymes and Reaction Rate

(i) Thermodynamically feasible reactions and Activation Energy



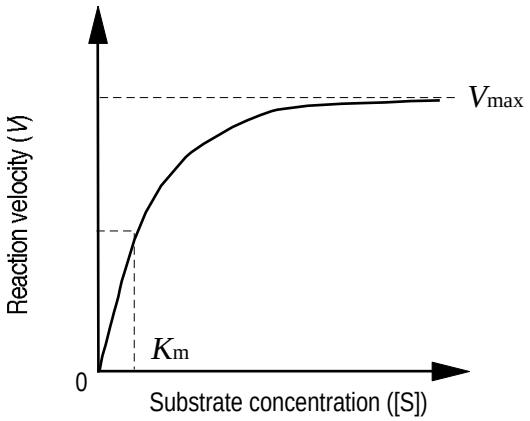
(ii) Enzyme-catalysed reactions and Reaction Rate





$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} P + E$$

(iii) Mathematical Treatment



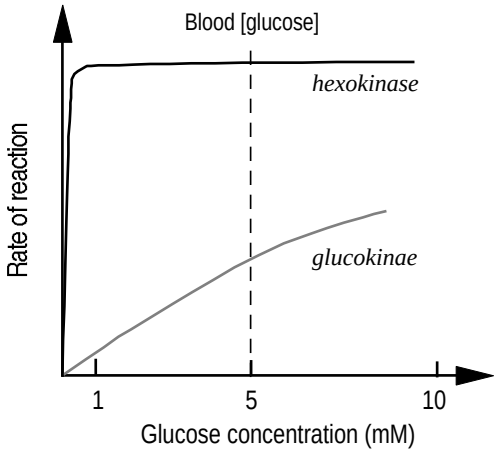
$$V = V_{max} \frac{[S]}{[S] + K_m}$$

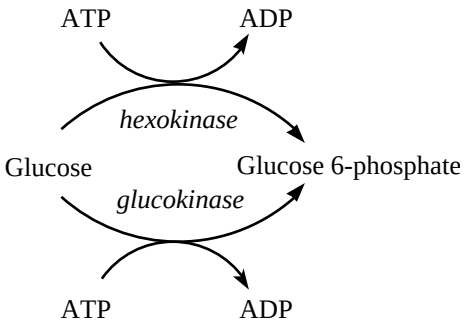
(Michaelis–Menten Equation)

K_m

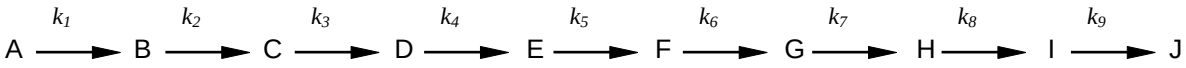
V_{max}

Example of Significance of K_m

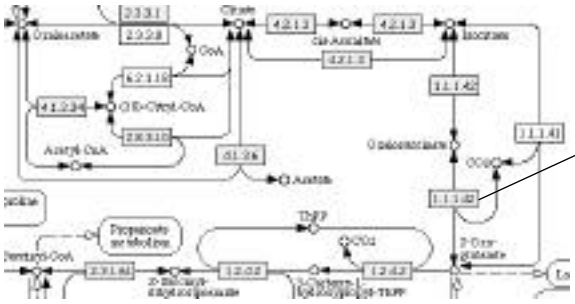




(iv) Idea of Rate-limiting step in a pathway



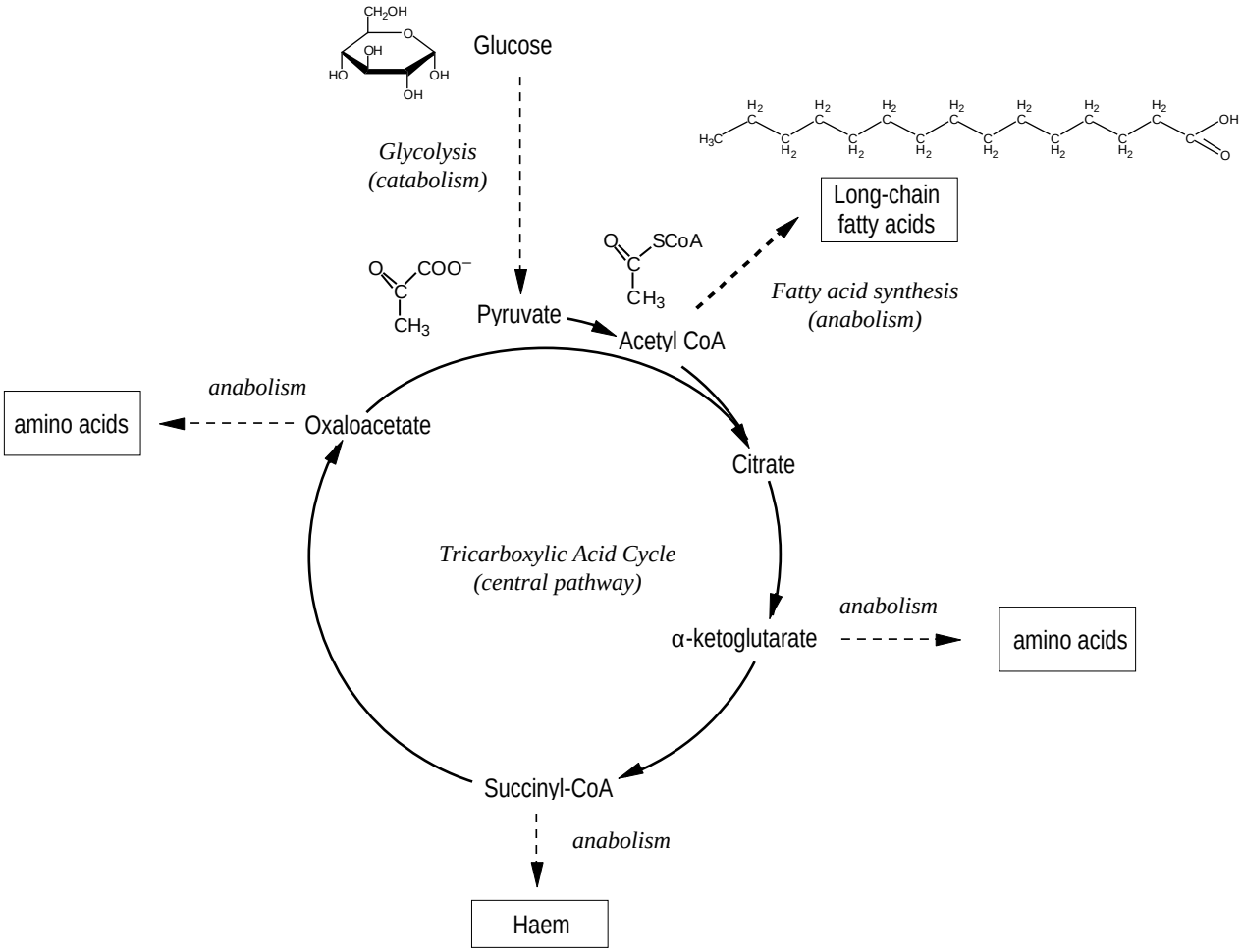
(v) EC (Enzyme Classification) numbers



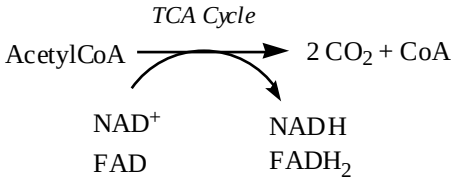
e.g. EC 1.1.1.42 for ICDH

II. GENERAL CHARACTERISTICS OF METABOLIC PATHWAYS

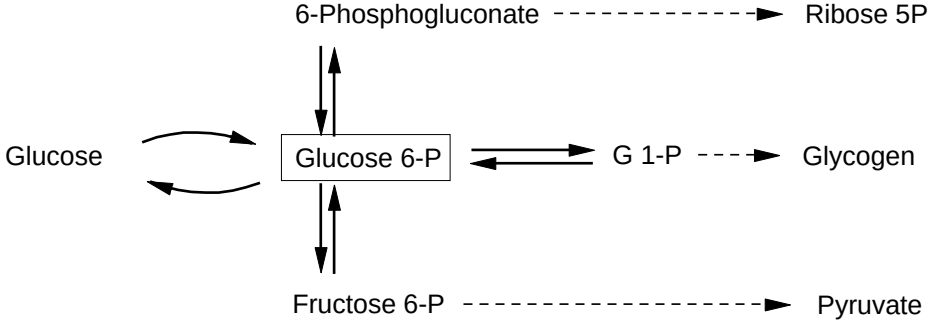
1. Anabolism, Catabolism & Central Pathways



2. Cyclic Pathways

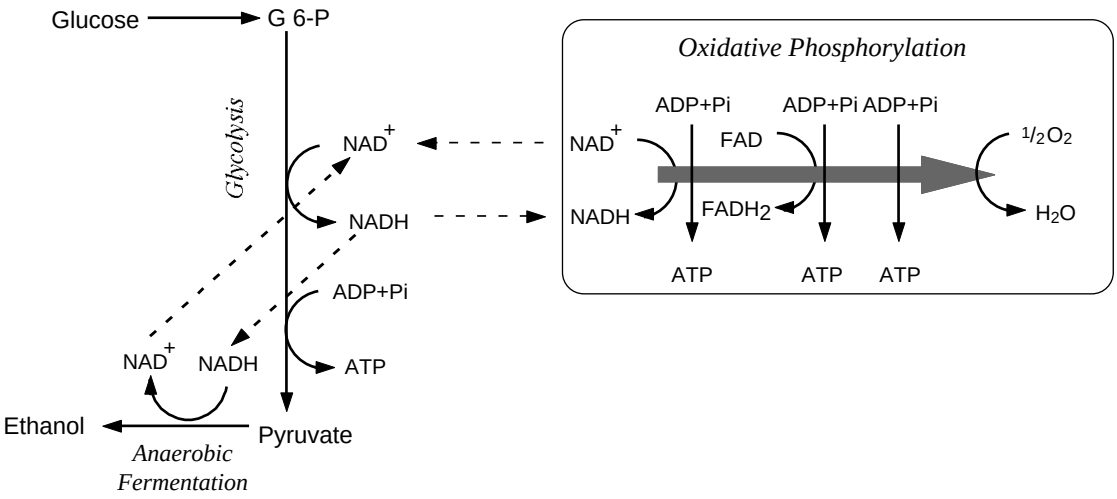


3. Alternative Pathways for Key Intermediates



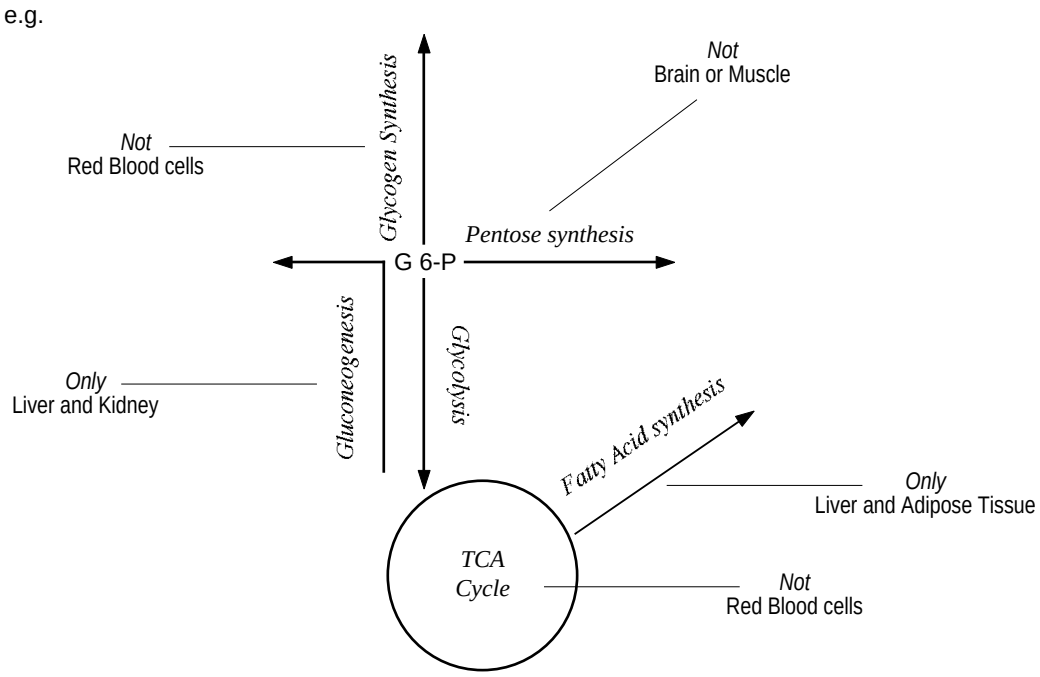
4. Variation in Metabolic Pathways found in cells

(i) The case of aerobic or anaerobic organisms (or tissues)



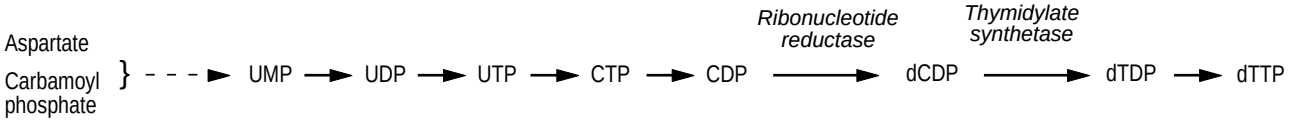
(ii) Tissue differences

e.g.



5. Alternative pathways to sythesise a single product

Pathway for dTTP synthesis *de novo*

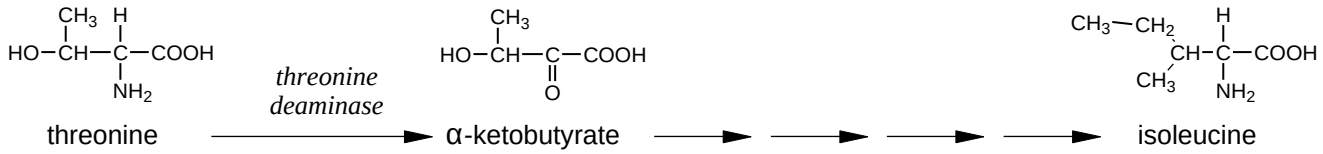


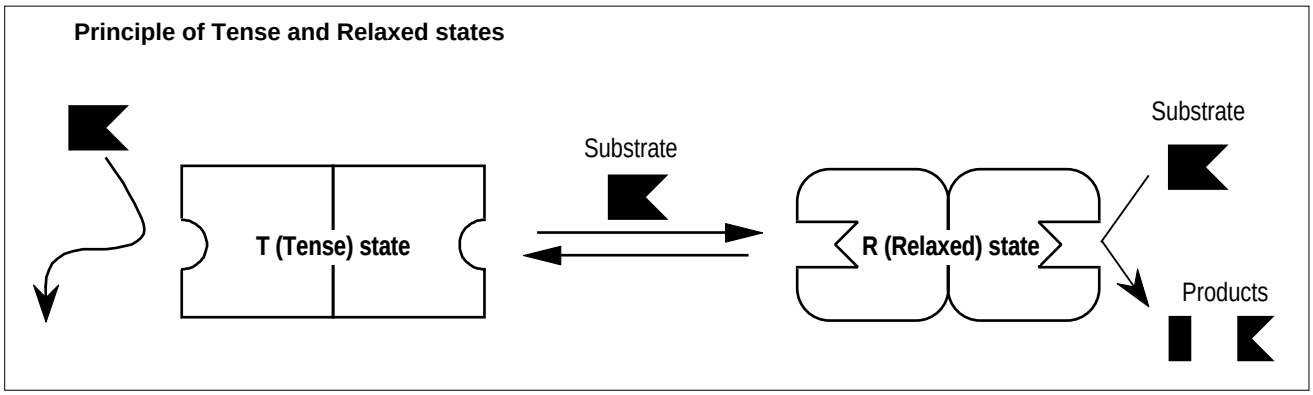
Salvage Pathway for dTTP synthesis

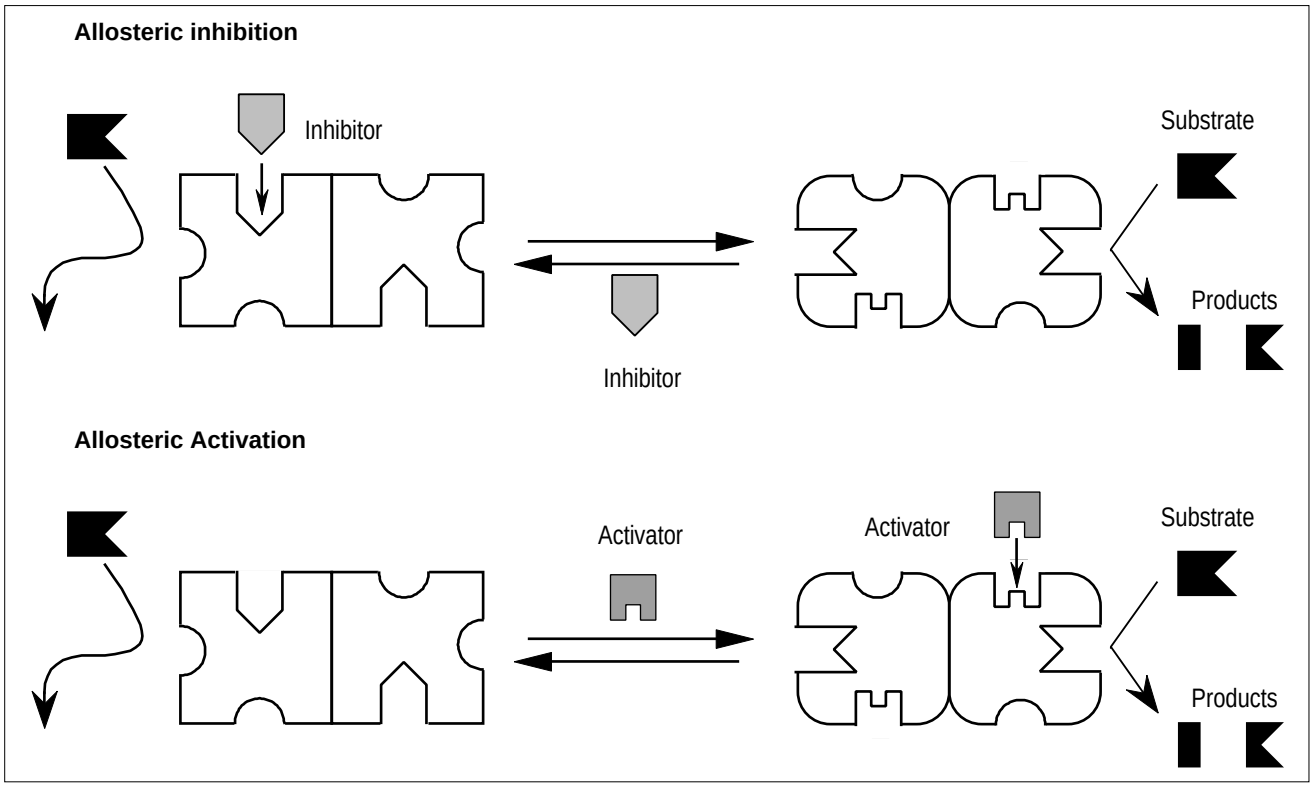
III. REGULATION OF METABOLIC PATHWAYS

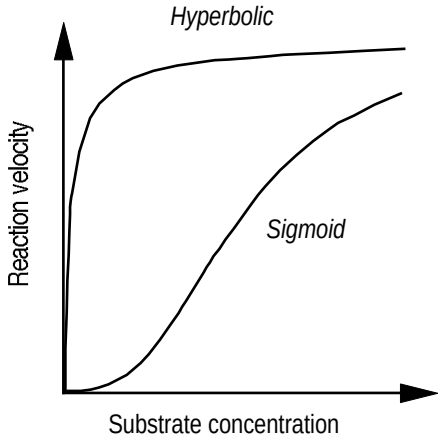
1. Regulation within a Single Cell

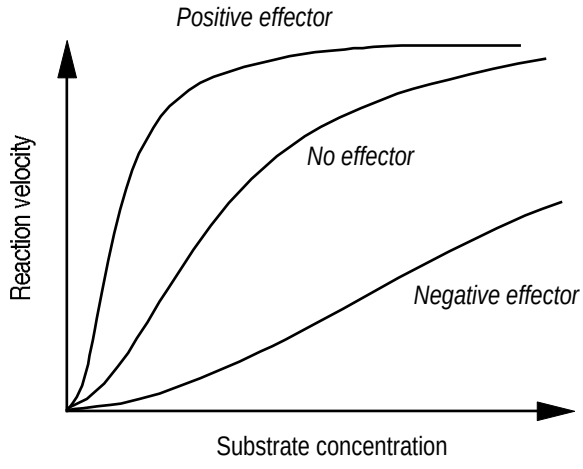
(i) Modulation of Enzyme Activity





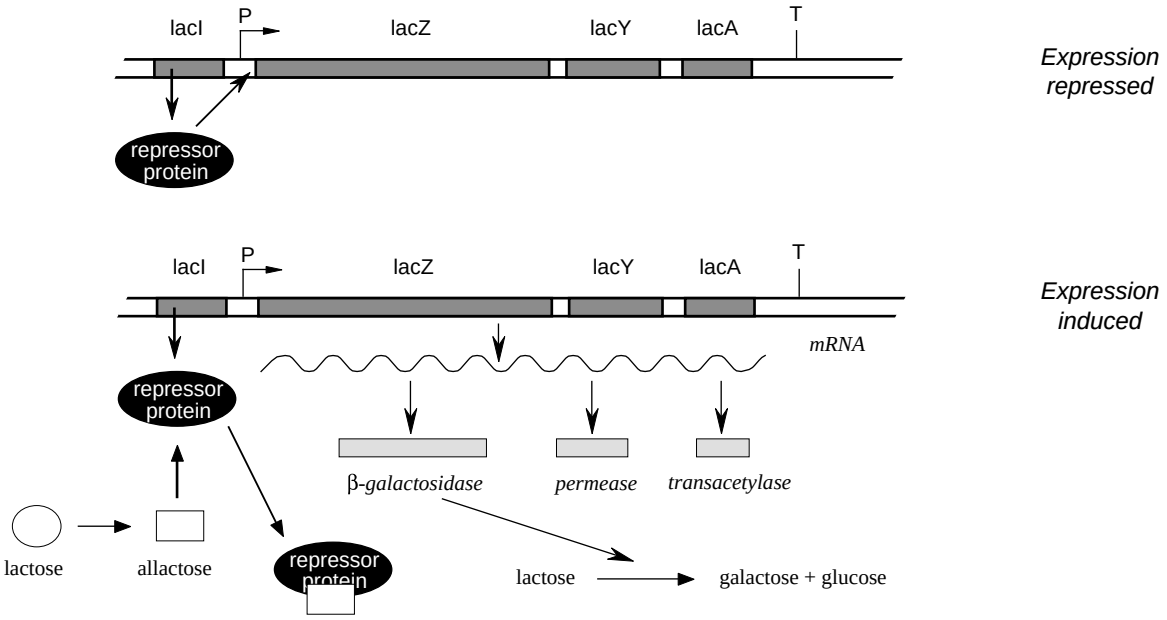






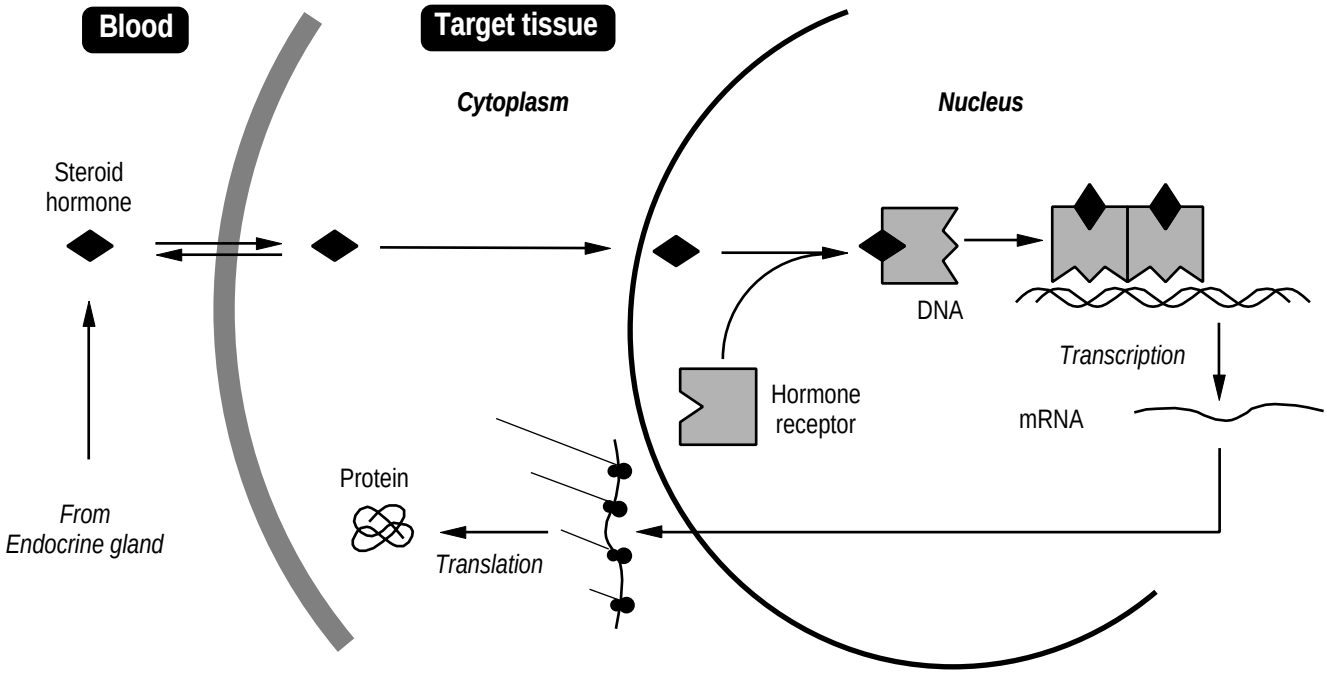
(ii) Modulation of Enzyme Synthesis

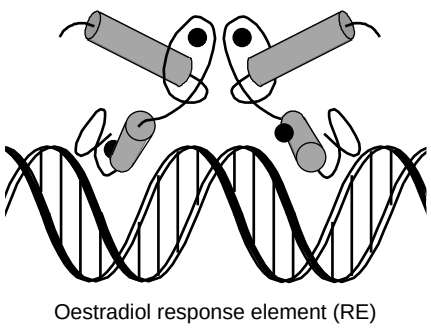
The *lac* operon



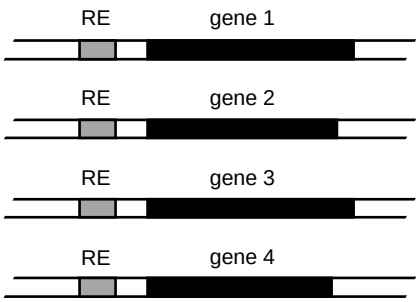
2. Integrated Regulation between differentiated tissues

(i) Regulation of transcription

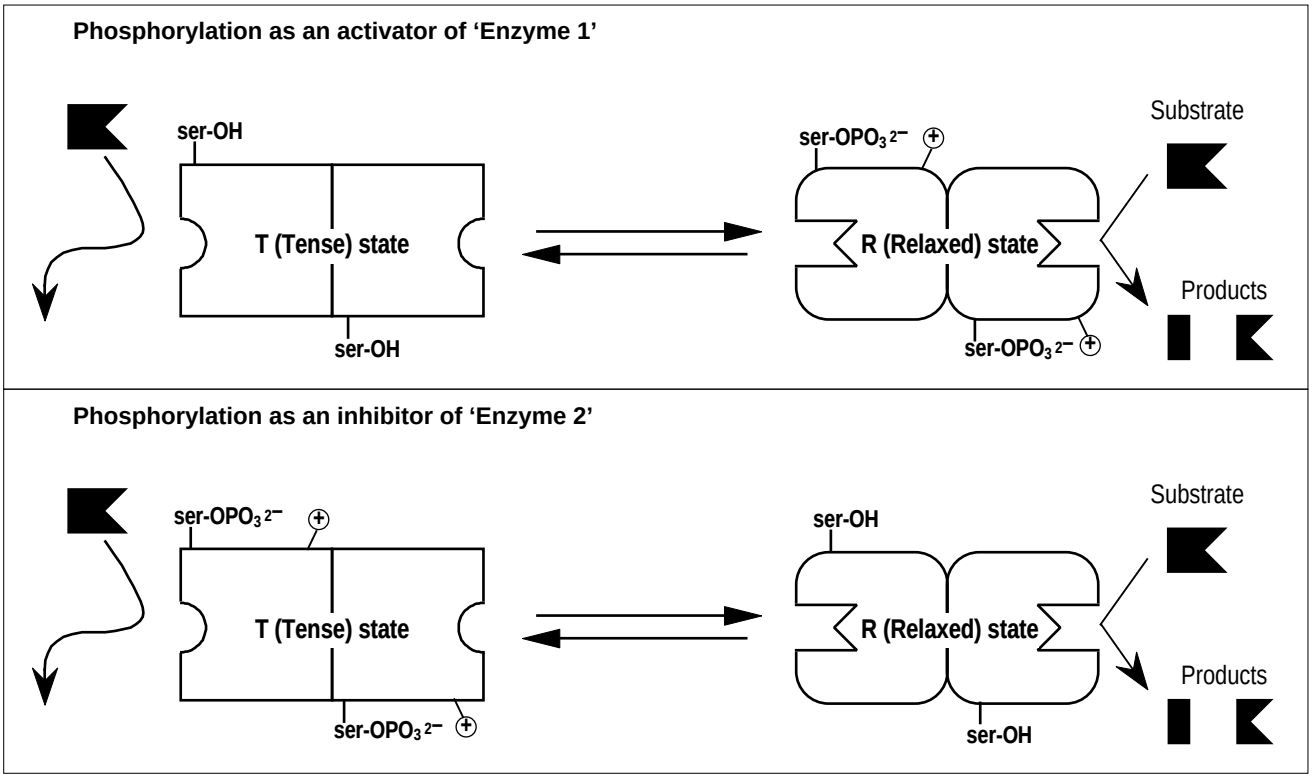




Oestradiol response element (RE)

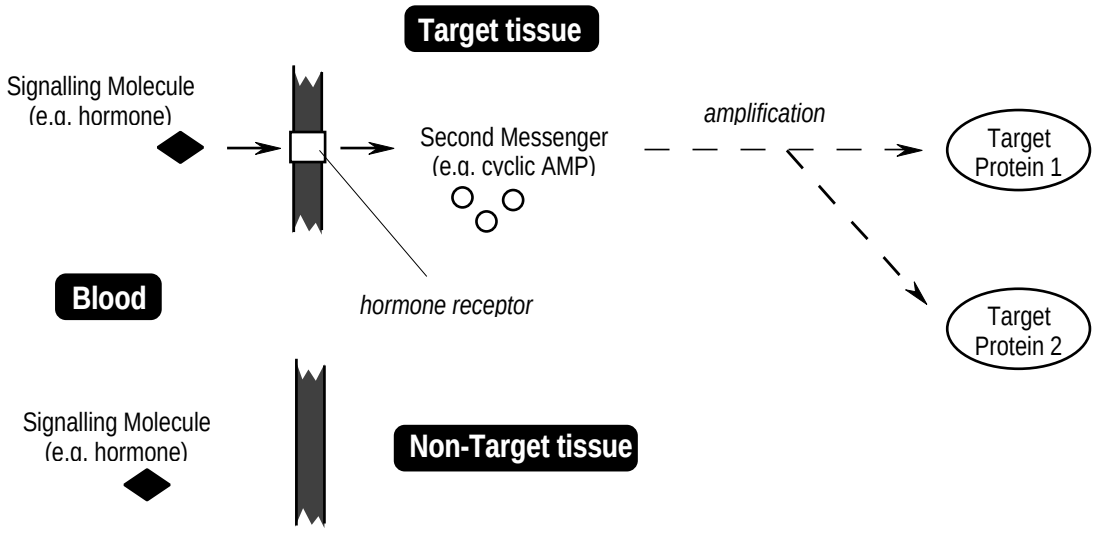


(ii) Regulation of Protein Activity, e.g. by Phosphorylation



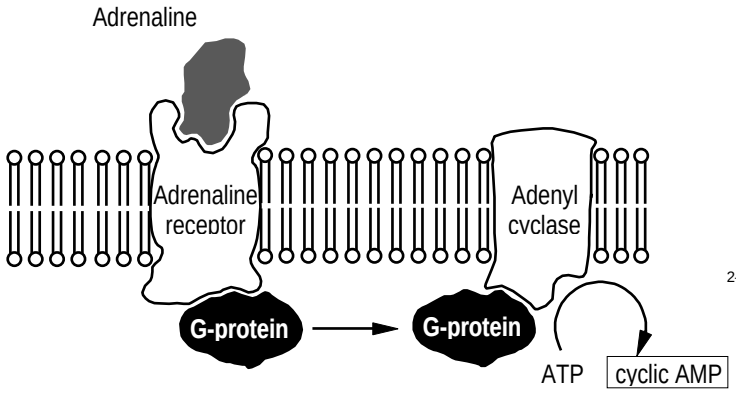
(iii) Signal Transduction

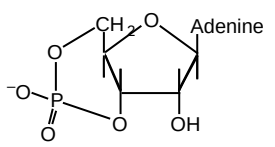
(a) Principles



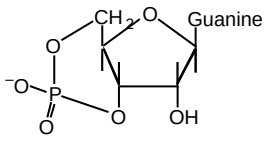
- Receptors determine target tissues of hormones/agonists
- Second messengers transduce effects within cells
- Gene expression patterns determine responses in target tissues
- Molecular systems limit the duration of the effects of agonists

(b) Some Second Messengers

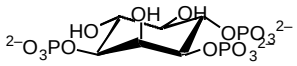




cyclic AMP



cyclic GMP



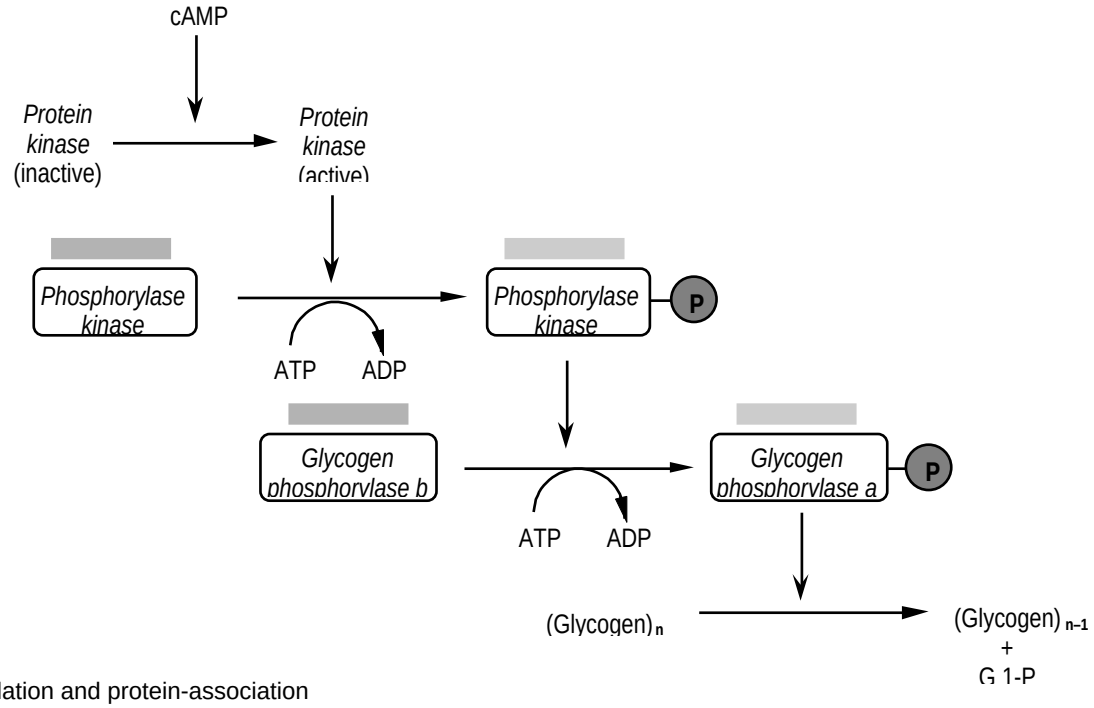
inositol 1,4,5,trisphosphate

Ca^{2-}

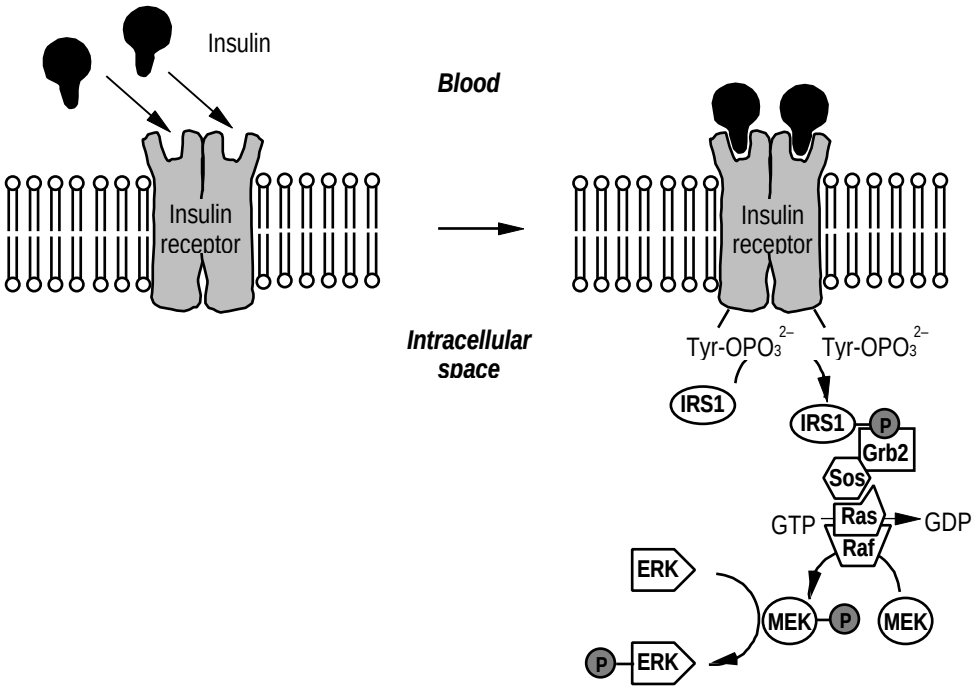
calcium ions

(c) Different types of amplification cascades

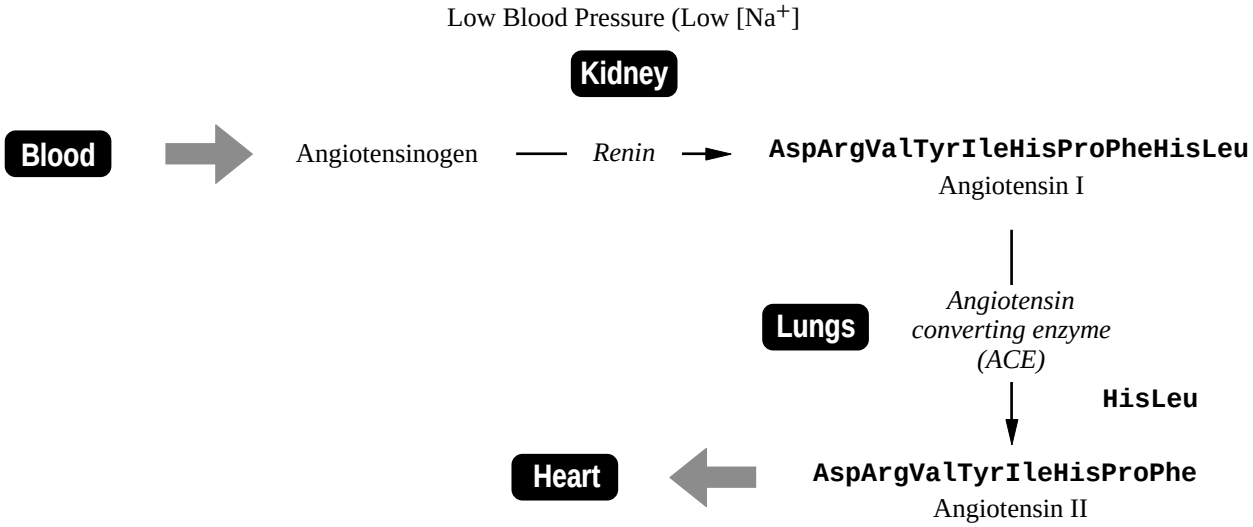
Intermolecular Phosphorylation cascade



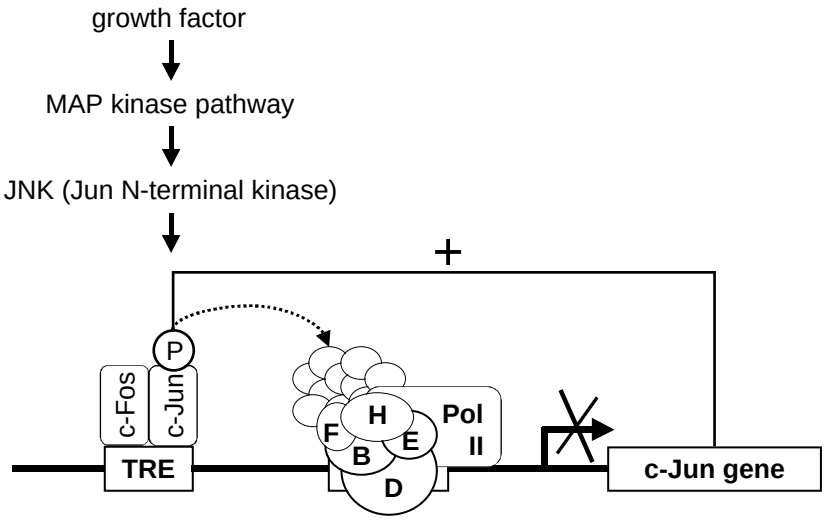
Phophorylation and protein-association



Proteolysis

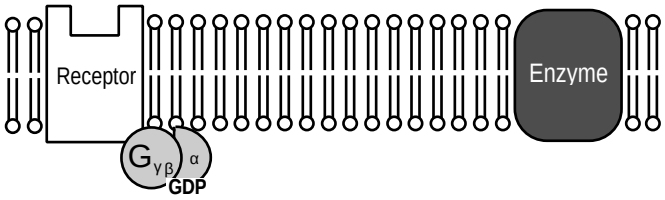


(d) Complexity of effects on Transcription



(e) G proteins and signal dissipation

∂



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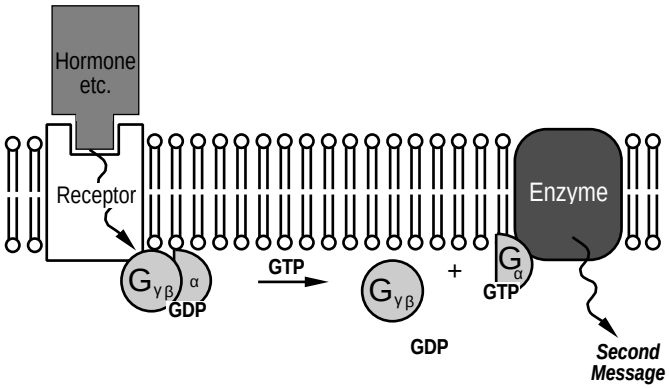

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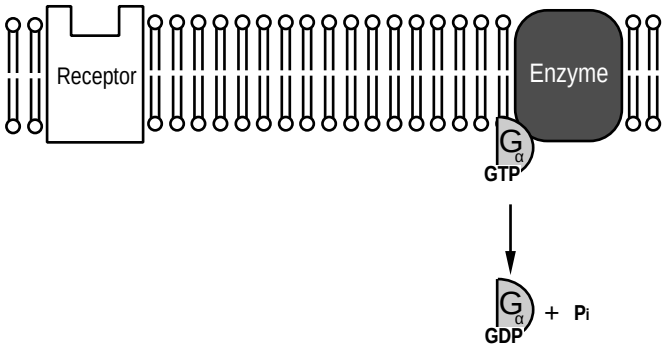

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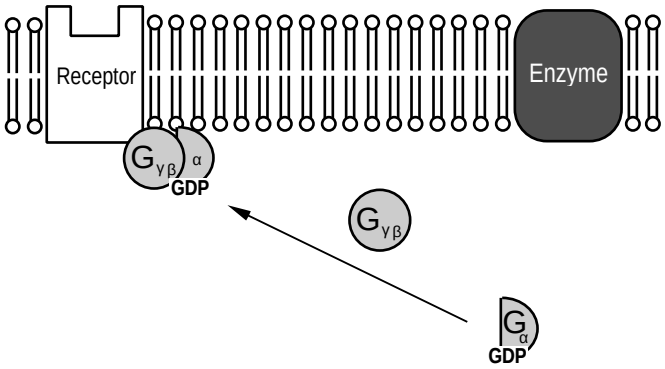
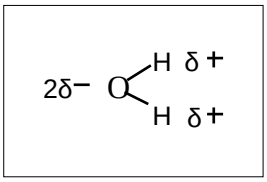
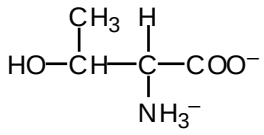
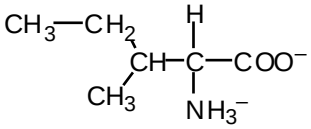


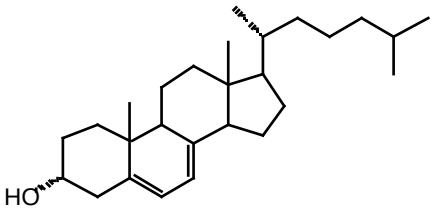
IV. COMPARTMENTATION & MEMBRANES IN LIVING SYSTEMS

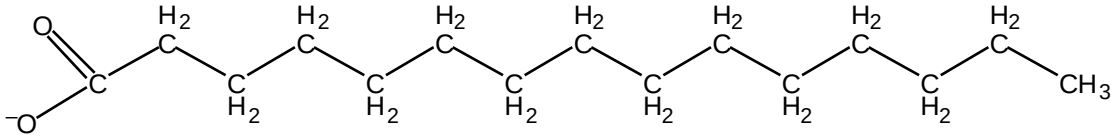
The aqueous milieu of life: hydrophobic and hydrophilic molecules







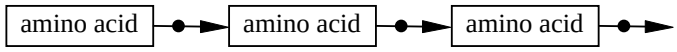




Proteins and the hydrophobic effect

Digital Representation: A C D E F G H I K L M N P Q R S T V W Y

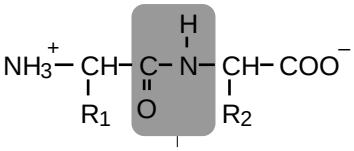
Chemical cartoon:



amino acid = ala, cys etc.
→● = peptide bond

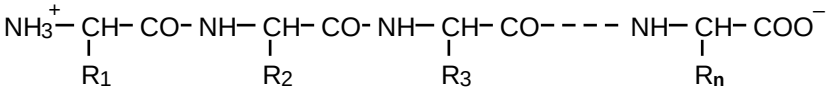
Amino acids

Dipeptide

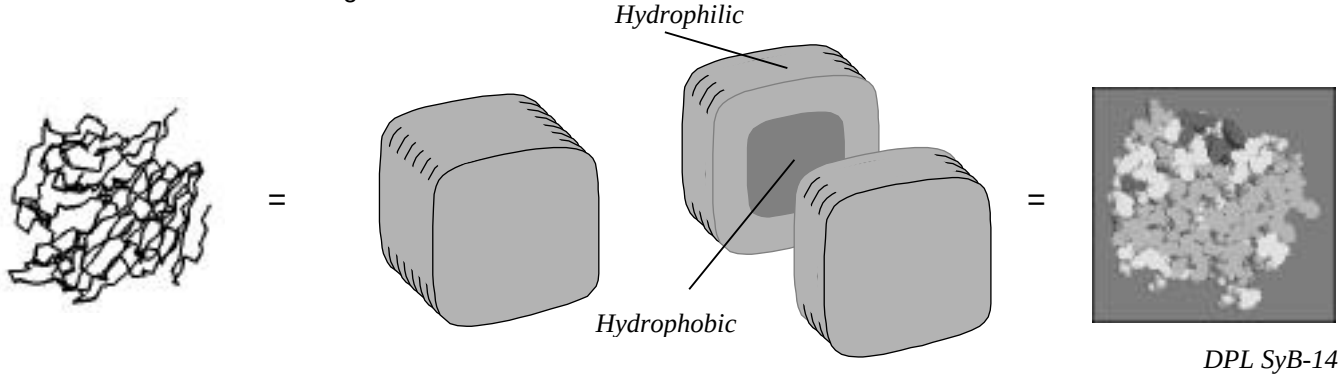


Peptide bond

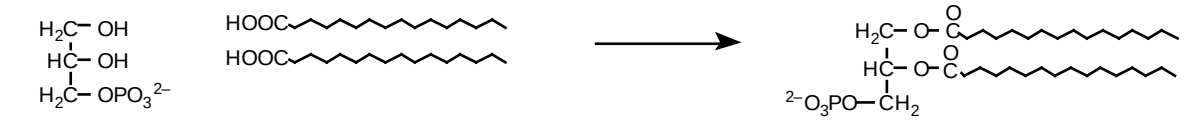
Protein (polypeptide)

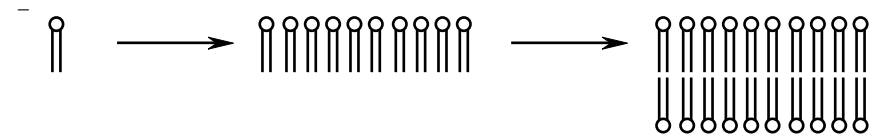


Three-dimensional folding

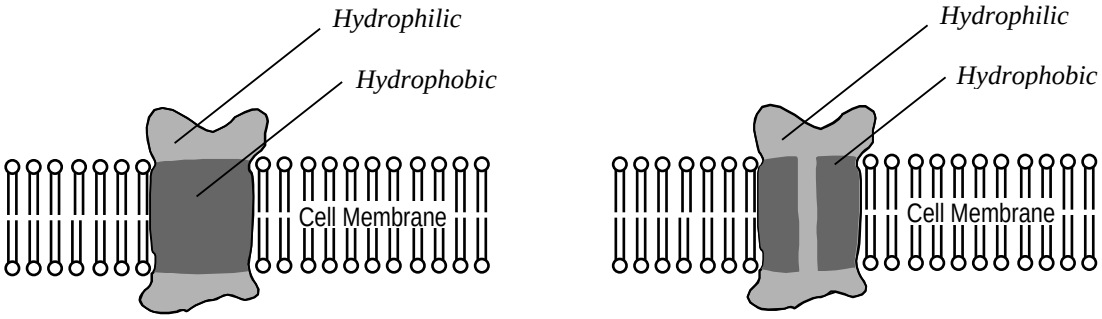


General structure of cell membranes

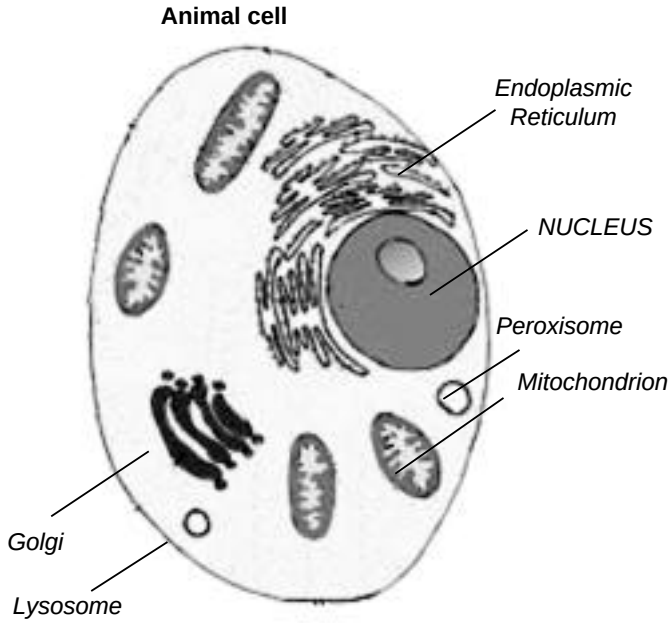




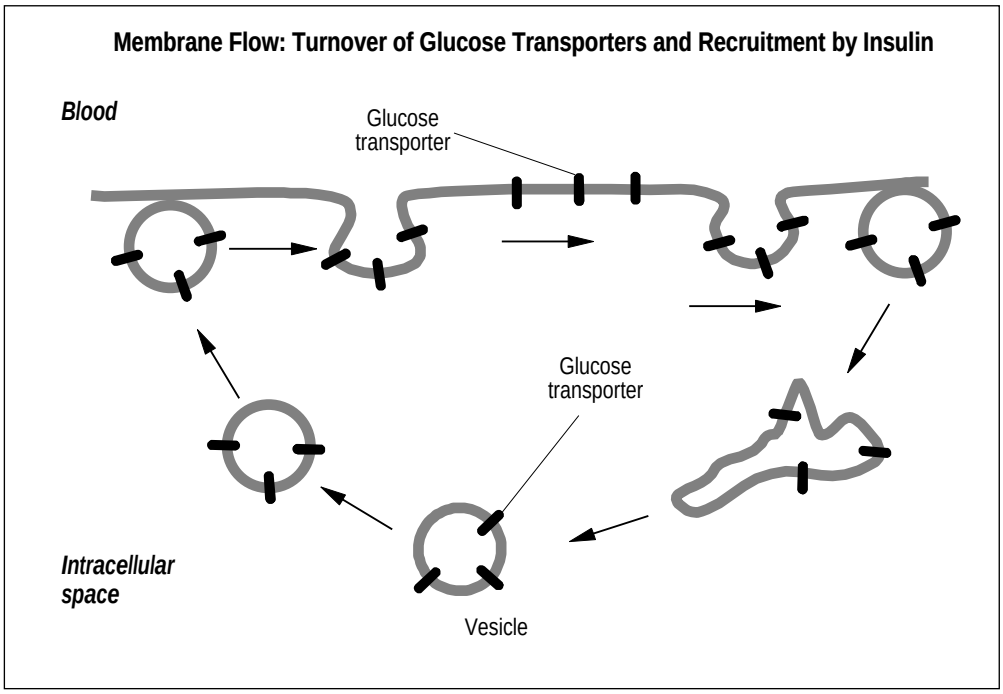
Proteins in membranes



The different types of membranes in an animal cell



(a) Cell (plasma) membrane



(b) Nuclear membrane

(c) Mitochondrial membrane