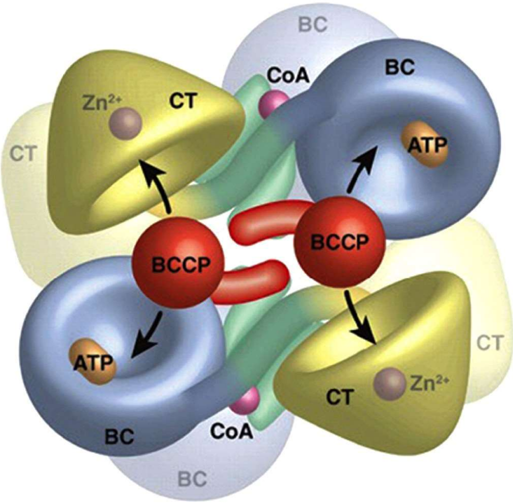
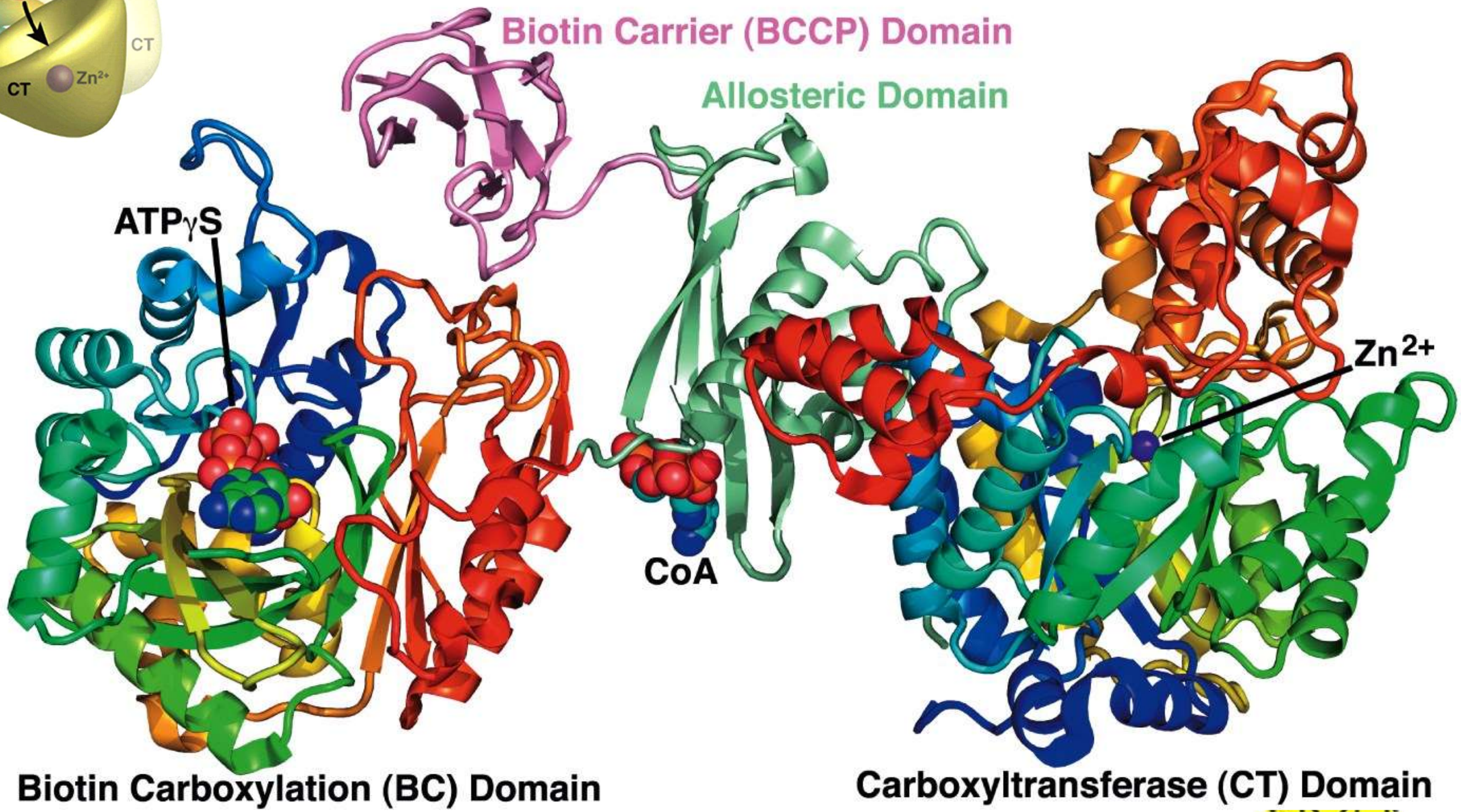
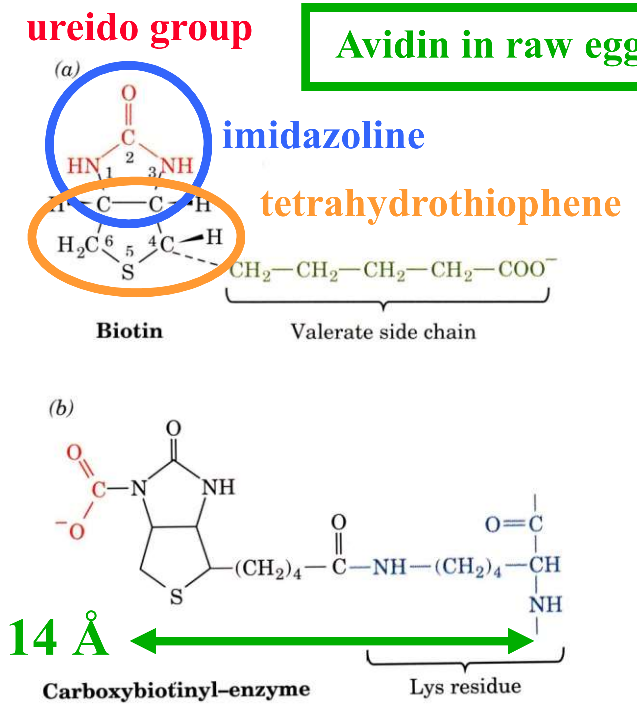
Pyruvate Carboxylase: Yet Another Multi-Enzyme Complex

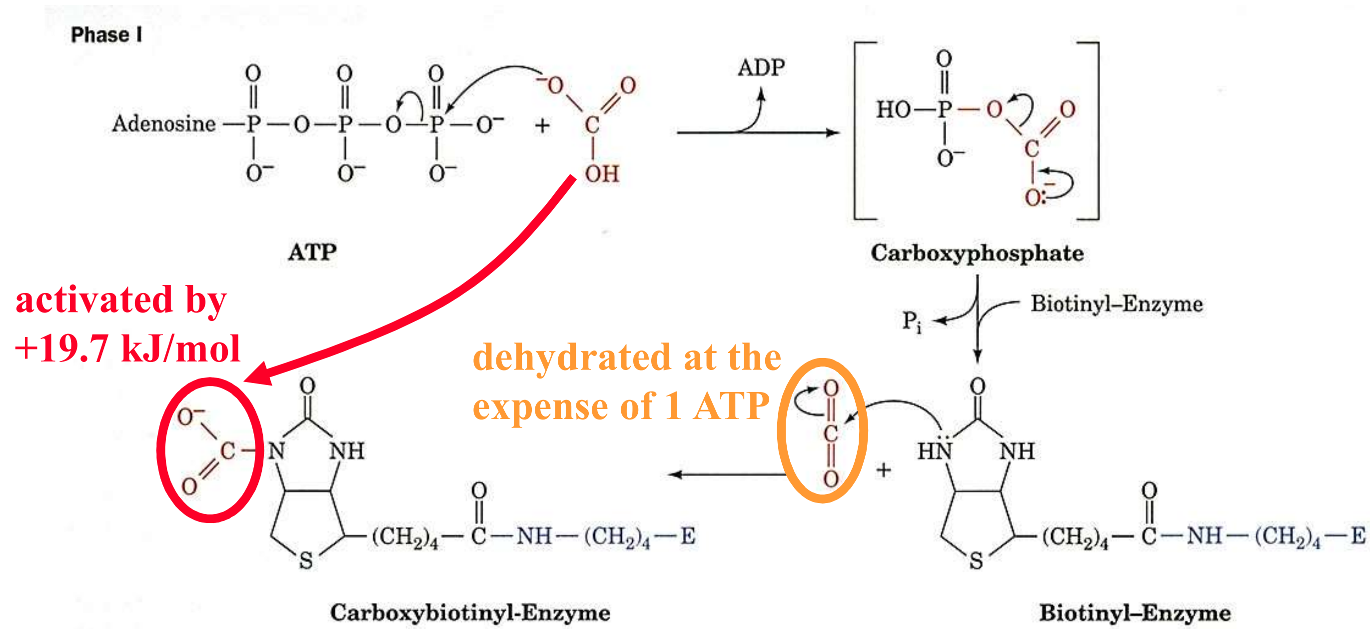




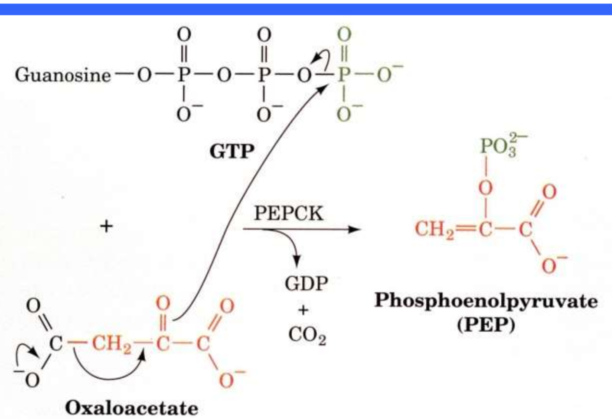
Pyruvate Carboxylase Has a Biotin Arm

Avidin in raw egg white causes biotin (vitamin H) deficiency (and is cytostatic)

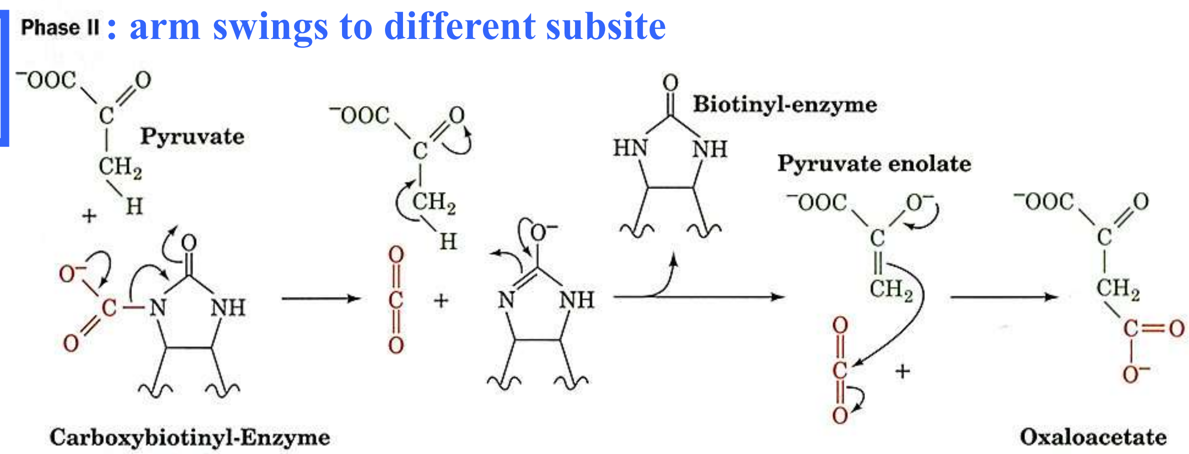




PEP Carboxykinase uses "activated" CO_2 and GTP to make high-energy PEP



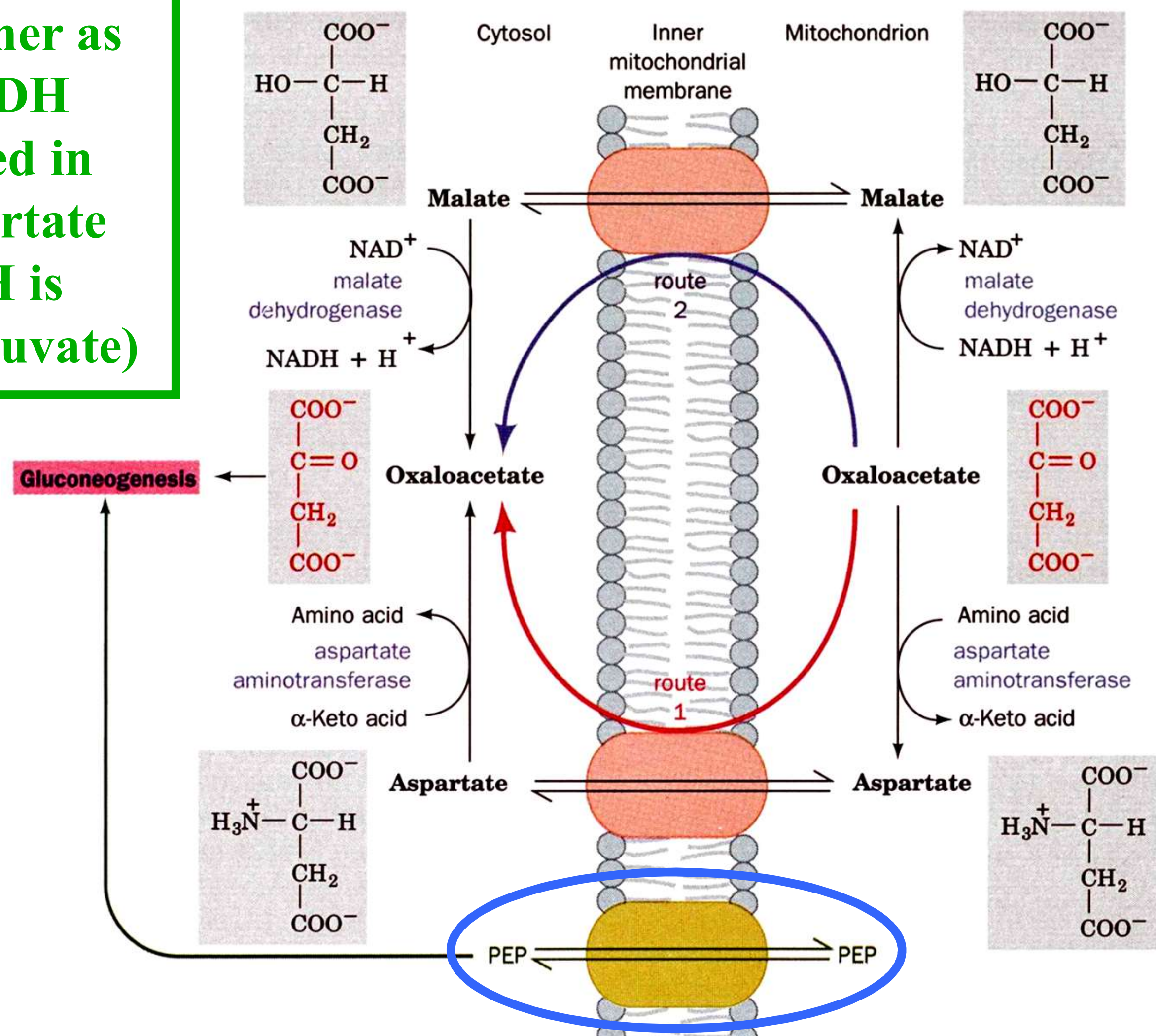
Phase II : arm swings to different subsite



BUT WAIT: Pyruvate Carboxylase is mitochondrial, PEPCK mitochondrial and/or cytosolic, other gluconeogenesis cytosolic

PEP & Oxaloacetate Have to Leave & Enter the Mitochondrial Matrix

Oxaloacetate is shuttled either as malate (carrying also NADH reducing equivalents needed in gluconeogenesis) or as aspartate (without NADH, if NADH is available from lactate → pyruvate)



PEP is transported directly and specifically

Glycolysis and Gluconeogenesis as Two Opposing Pathways Have to be Regulated

Glycolysis:

Glucose + 2NAD$^+$ + 2ADP + 2P$_i$ $\rightarrow$ 2Pyruvate + 2NADH + 4H$^+$ + **2ATP** + 2H$_2$O

Gluconeogenesis:

2Pyruvate + 2NADH + 4H$^+$ + **4ATP** + **2GTP** + 6H$_2$O $\rightarrow$ Glucose + 2NAD$^+$ + 4ADP + 2GDP+ 6P$_i$

As a "futile cycle" :

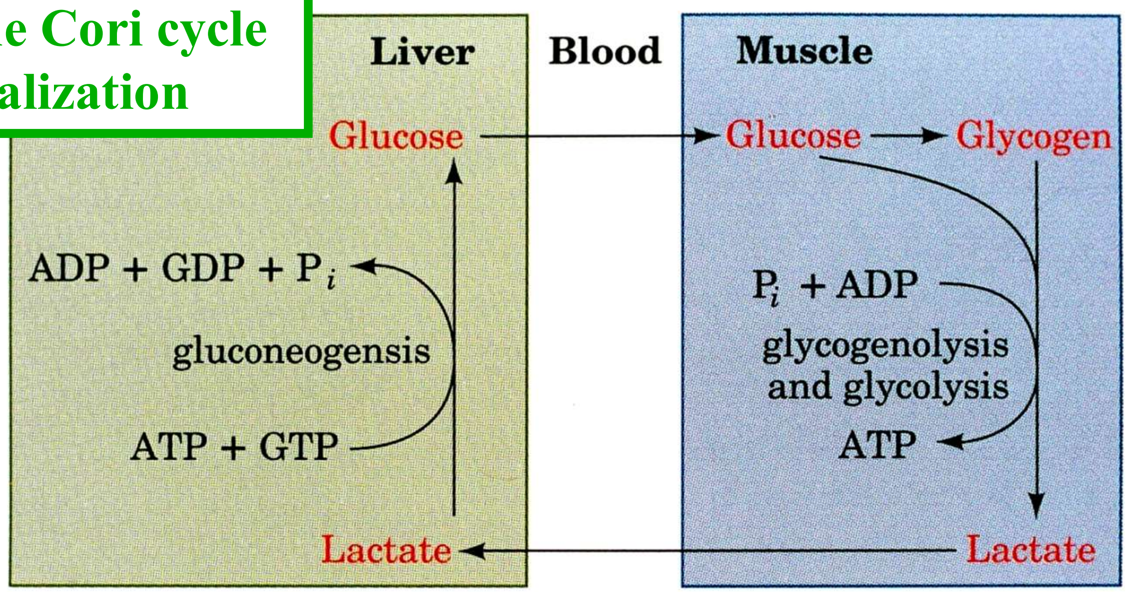
2ATP + **2GTP** + 4H$_2$O $\rightarrow$ 2ADP + 2GDP+ 4P$_i$

$\Rightarrow$ **Must be prevented!** $\Rightarrow$ **Regulation!**

The liver, the altruistic organ: The Cori cycle allows for tissue compartmentalization

TABLE 21-1. REGULATORS OF GLUCONEOGENIC ENZYME ACTIVITY

Enzyme	Allosteric Inhibitors	Allosteric Activators	Enzyme Phosphorylation	Protein Synthesis
PFK	ATP, citrate	AMP, F2,6P		
FBPase	AMP, F2,6P			
PK unique	Alanine	F1,6P	Inactivates	
Pyruvate carboxylase		Acetyl-CoA		
PEPCK				Stimulated by glucagon
PFK-2	Citrate	AMP, F6P, P_i	Inactivates	
FBPase-2	F6P	Glycerol-3-P	Activates	



Chapter 23: What have we learned?

☺ Gluconeogenesis = Glycolysis reversed: The three key steps that have to be bypassed

☺ Oxaloacetate as a key metabolite

☺ The pyruvate carboxylase mechanism

☺ How to shuttle oxaloacetate out of the mitochondrion

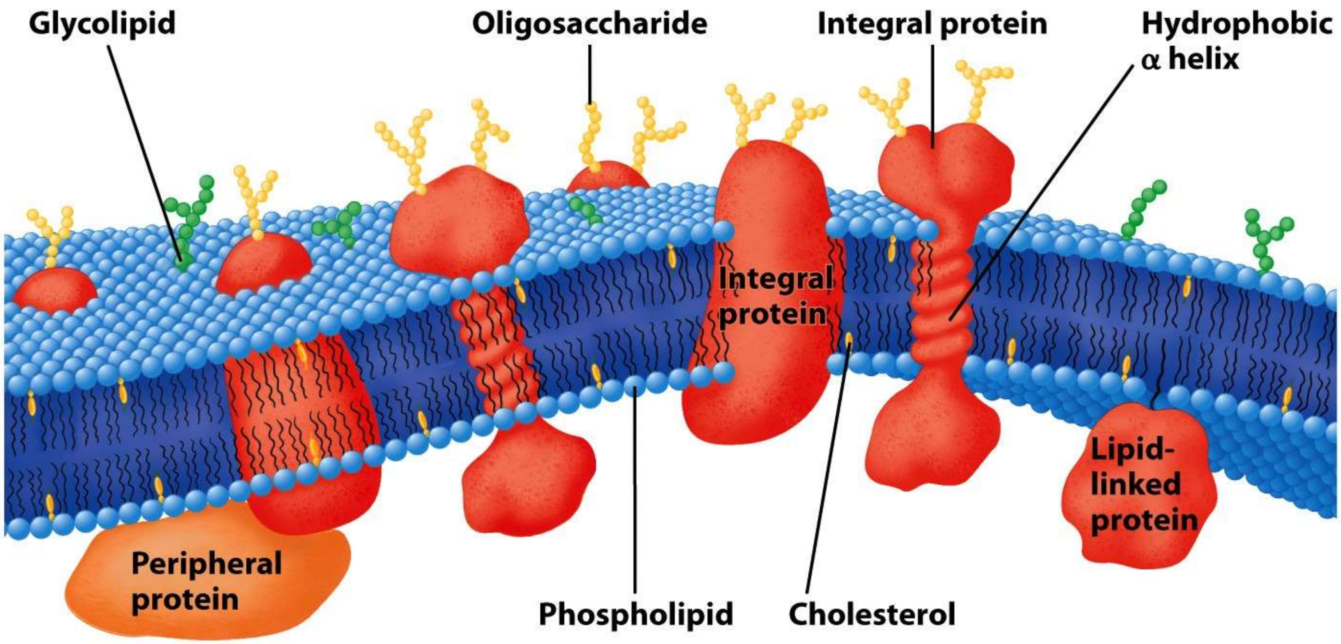
☺ Energetics and Regulation of gluconeogenesis; the Cori cycle; ~~Lance Armstrong's story~~

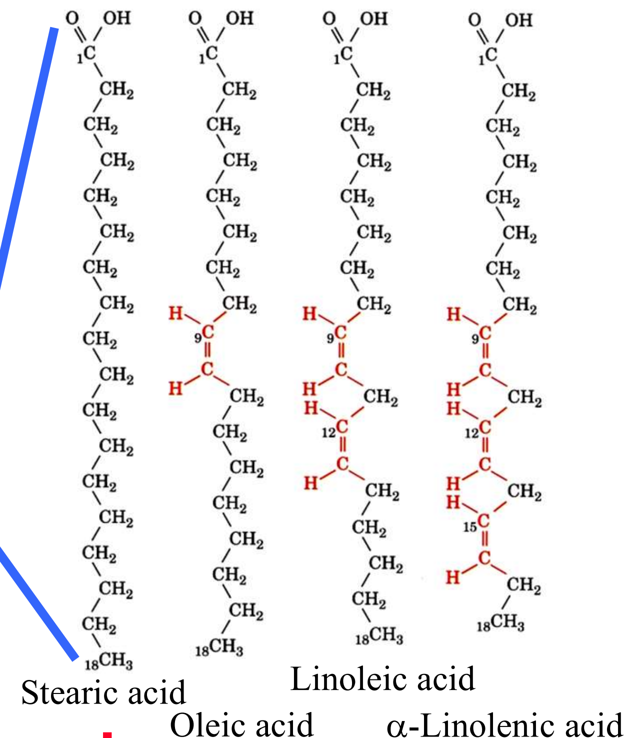
Review: Lipids and Membranes

Greek: lipos = fat

Voet & Voet, Chapter 12

➢ soluble in organic solvents (CH_3OH, $CHCl_3$), not in water ⇒ easy fractionation





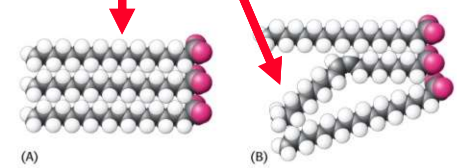


TABLE 11-1. THE COMMON BIOLOGICAL FATTY ACIDS

Symbol[a]	Common Name	Systematic Name	Structure	mp (°C)
Saturated fatty acids				
12:0	Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$	44.2
14:0	Myristic acid	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$	52
16:0	Palmitic acid	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$	63.1
18:0	Stearic acid	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$	69.6
20:0	Arachidic acid	Eicosanoic acid	$CH_3(CH_2)_{18}COOH$	75.4
22:0	Behenic acid	Docosanoic acid	$CH_3(CH_2)_{20}COOH$	81
24:0	Lignoceric acid	Tetracosanoic acid	$CH_3(CH_2)_{22}COOH$	84.2
Unsaturated fatty acids (all double bonds are cis)				
16:1	Palmitoleic acid	9-Hexadecenoic acid	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	−0.5
18:1	Oleic acid	9-Octadecenoic acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	13.4
18:2	Linoleic acid	9,12-Octadecadienoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COOH$	−9
18:3	α-Linolenic acid	9,12,15-Octadecatrienoic acid	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COOH$	−17
18:3	γ-Linolenic acid	6,9,12-Octadecatrienoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_3(CH_2)_3COOH$	
20:4	Arachidonic acid	5,8,11,14-Eicosatetraenoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH$	−49.5
20:5	EPA	5,8,11,14,17-Eicosapentanoic acid	$CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2COOH$	−54
24:1	Nervonic acid	15-Tetracosenoic acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_{13}COOH$	39

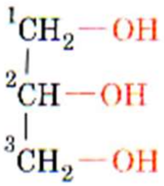
[a] Number of carbon atoms : Number of double bonds.

Source: Dawson, R.M.C., Elliott, D.C., Elliott, W.H., and Jones, K.M., *Data for Biochemical Research* (3rd ed.), Chapter 8, Clarendon Press (1986).

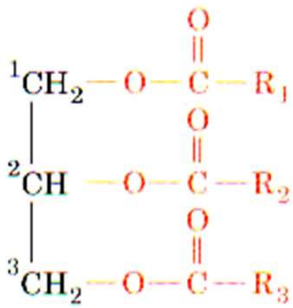
- ➢ fatty acids of $<C_{14}$ or $>C_{20}$ are uncommon
- ➢ most have even # of Cs (biosynthesized from C_2)
- ➢ >50% of natural fatty acids are unsaturated
- ➢ unconjugated cis configuration
- ➢ melting point (mp) decreases with unsaturation

Triacylglycerols, the Fatty Ones

- Triacylglycerols = triglycerides = neutral fats = fats and oils in plants and animal



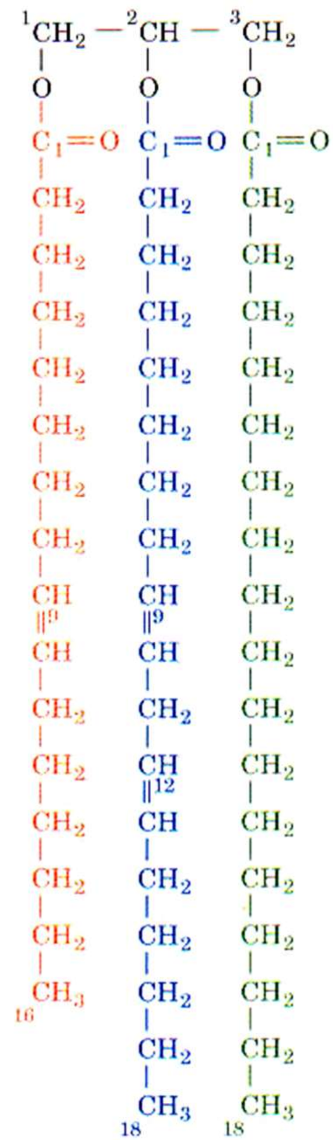
Glycerol



Triacylglycerol

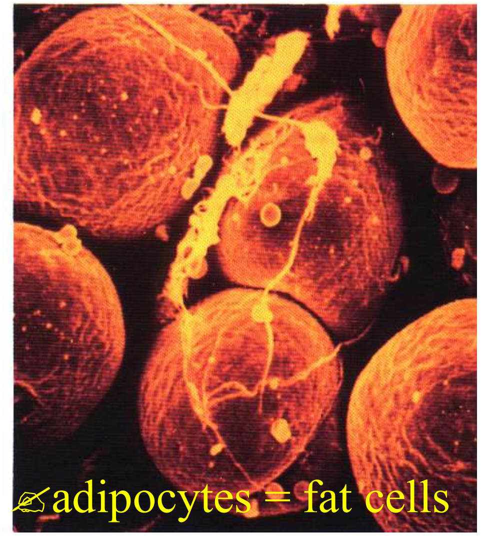
- Simple triacylglycerols contain only 1 type of fatty acids

- Mixed triacylglycerols are more common:



1-Palmitoleoyl-2-linoleoyl-3-stearoyl-glycerol

- Triacylglycerols are a highly efficient form of stored energy (less oxidized than carbohydrates or amino acids, and anhydrous ⇒ 6-fold higher metabolic energy than glycogen which binds 2-fold its weight of water)



- store 2-3 months (!) of energy supply (21%/26% of body weight!)

- insulation (whales, seals, penguins!)