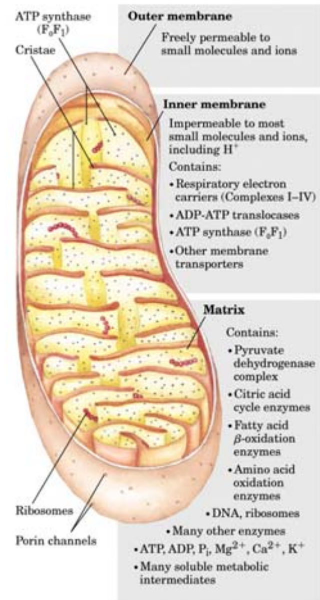
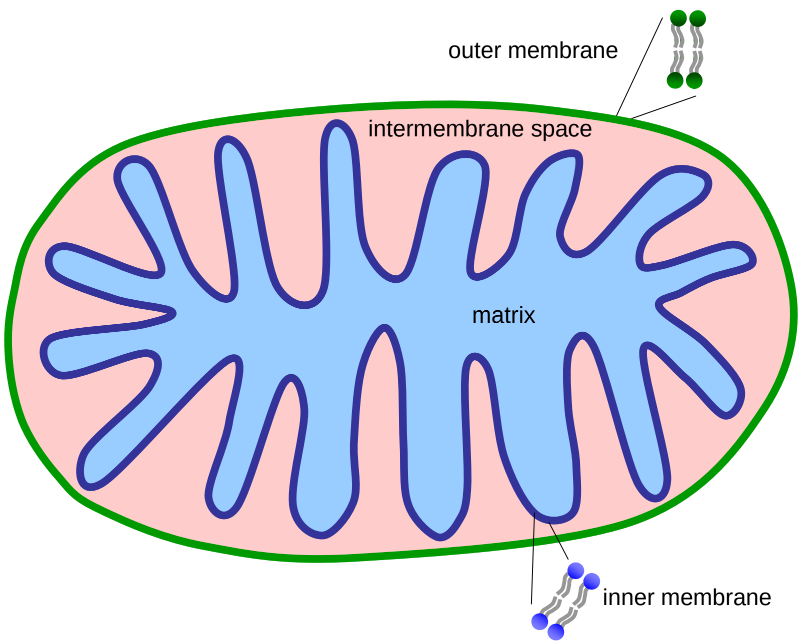
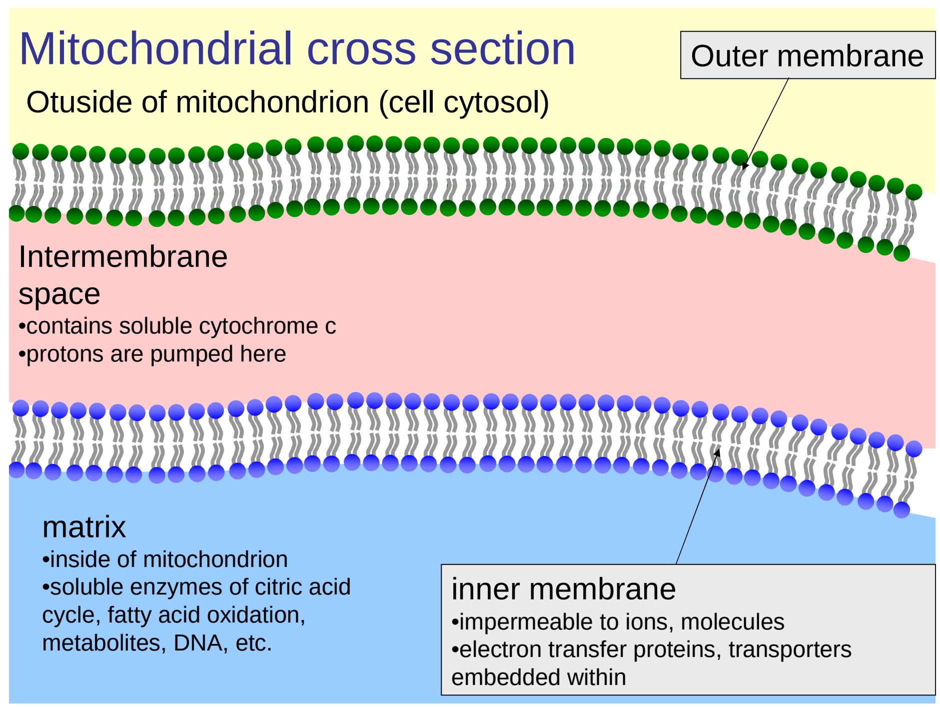
Mitochondrial electron transfer and oxidative phosphorylation







O_2 is a strong oxidizing agent (it likes to be reduced)

NADH is a strong reducing agent (it likes to be oxidized)

table 14–7

Standard Reduction Potentials of Some Biologically Important Half-Reactions, at 25 °C and pH 7

Half-reaction	E'° (V)
$\frac{1}{2}O_2 + 2H^+ + 2e^- \longrightarrow H_2O$	0.816
$Fe^{3+} + e^- \longrightarrow Fe^{2+}$	0.771
$NO_3^- + 2H^+ + 2e^- \longrightarrow NO_2^- + H_2O$	0.421
Cytochrome *f* (Fe^{3+}) + e^- $\longrightarrow$ cytochrome *f* (Fe^{2+})	0.365
$Fe(CN)_6^{3-}$ (ferricyanide) + e^- $\longrightarrow$ $Fe(CN)_6^{4-}$	0.36
Cytochrome a_3 (Fe^{3+}) + e^- $\longrightarrow$ cytochrome a_3(Fe^{2+})	0.35
$O_2 + 2H^+ + 2e^- \longrightarrow H_2O_2$	0.295
Cytochrome *a* (Fe^{3+}) + e^- $\longrightarrow$ cytochrome *a* (Fe^{2+})	0.29
Cytochrome *c* (Fe^{3+}) + e^- $\longrightarrow$ cytochrome *c* (Fe^{2+})	0.254
Cytochrome c_1 (Fe^{3+}) + e^- $\longrightarrow$ cytochrome c_1 (Fe^{2+})	0.22
Cytochrome *b* (Fe^{3+}) + e^- $\longrightarrow$ cytochrome *b* (Fe^{2+})	0.077
Ubiquinone + $2H^+ + 2e^-$ $\longrightarrow$ ubiquinol + H_2	0.045
Fumarate^{2-} + $2H^+ + 2e^-$ $\longrightarrow$ succinate^{2-}	0.031
$2H^+ + 2e^- \longrightarrow H_2$ (at standard conditions, pH 0)	0.000
Crotonyl-CoA + $2H^+ + 2e^-$ $\longrightarrow$ butyryl-CoA	−0.015
Oxaloacetate^{2-} + $2H^+ + 2e^-$ $\longrightarrow$ malate^{2-}	−0.166
Pyruvate$^-$ + $2H^+ + 2e^-$ $\longrightarrow$ lactate$^-$	−0.185
Acetaldehyde + $2H^+ + 2e^-$ $\longrightarrow$ ethanol	−0.197
FAD + $2H^+ + 2e^-$ $\longrightarrow$ $FADH_2$	−0.219*
Glutathione + $2H^+ + 2e^-$ $\longrightarrow$ 2 reduced glutathione	−0.23
$S + 2H^+ + 2e^- \longrightarrow H_2S$	−0.243
Lipoic acid + $2H^+ + 2e^-$ $\longrightarrow$ dihydrolipoic acid	−0.29
$NAD^+ + H^+ + 2e^- \longrightarrow NADH$	−0.320
$NADP^+ + H^+ + 2e^- \longrightarrow NADPH$	−0.324
Acetoacetate + $2H^+ + 2e^-$ $\longrightarrow$ β-hydroxybutyrate	−0.346
α-Ketoglutarate + CO_2 + $2H^+ + 2e^-$ $\longrightarrow$ isocitrate	−0.38
$2H^+ + 2e^- \longrightarrow H_2$ (at pH 7)	−0.414
Ferredoxin (Fe^{3+}) + e^- $\longrightarrow$ ferredoxin (Fe^{2+})	−0.432

Data mostly from Loach, P.A. (1976) In *Handbook of Biochemistry and Molecular Biology*, 3rd edn (Fasman, G.D., ed.), *Physical and Chemical Data*, Vol. I, pp. 122–130, CRC Press, Boca Raton, FL.

*This is the value for free FAD; FAD bound to a specific flavoprotein (for example succinate dehydrogenase) has a different E'°.

- For a redox reaction to be spontaneous, E°' for the overall reaction must have a positive value
- When writing a half reaction in the oxidative direction, the sign of E°' is switched
- The oxidized form of a given redox pair will react spontaneously with the reduced form of any redox pair that is below it in a table of standard reduction potentials

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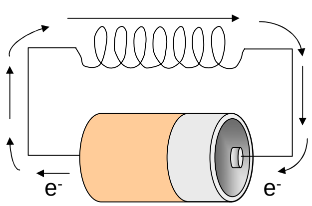
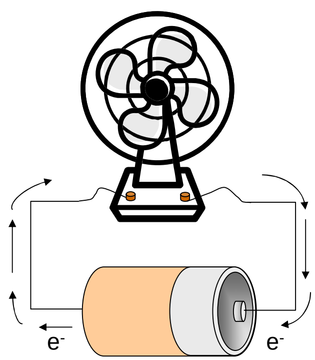
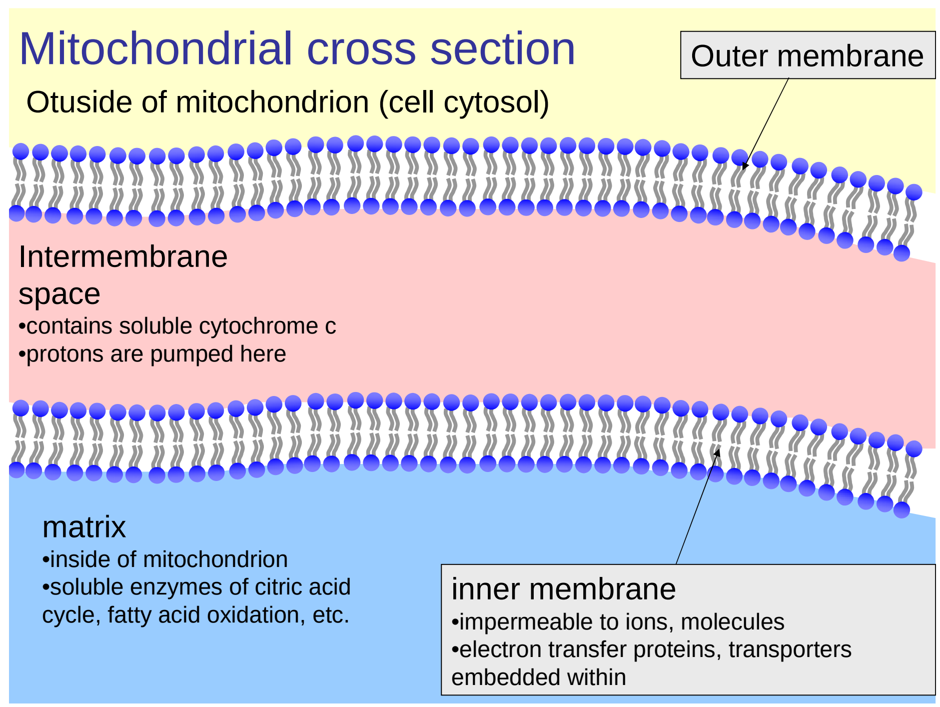
O_2 will be spontaneously reduced by NADH







Ways to transfer electrons

- Direct electron transfer

$$\dot{}Fe^{2+} \quad Cu^{2+}$$

- H atom transfer

$$\cdot H = 1e^- + H^+$$

- Hydride ion transfer

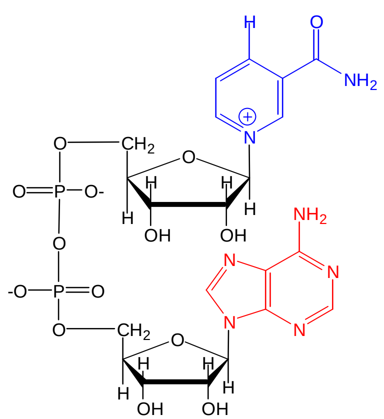
$$:H^- = 2e^- + H^+$$

Redox cofactors mediate biological oxidation/reduction reactions

- “Free” coenzymes
- Protein-bound organic coenzymes
  – Covalent: prosthetic group
  – Noncovalent: “weak” interactions
- Protein-bound organometallic coenzymes
- Protein-bound inorganic cofactors (M^{n+}, sometimes with inorganic S, O, Se)

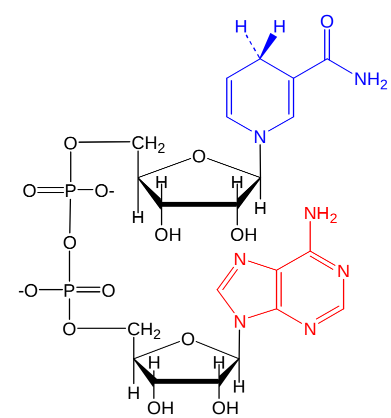
NAD+

Nicotinamide Adenine Dinucleotide



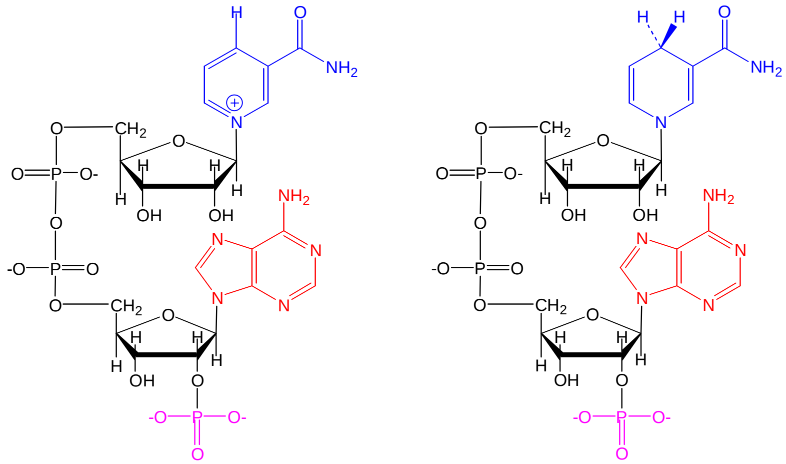
NADH

Reduced Nicotinamide Adenine Dinucleotide



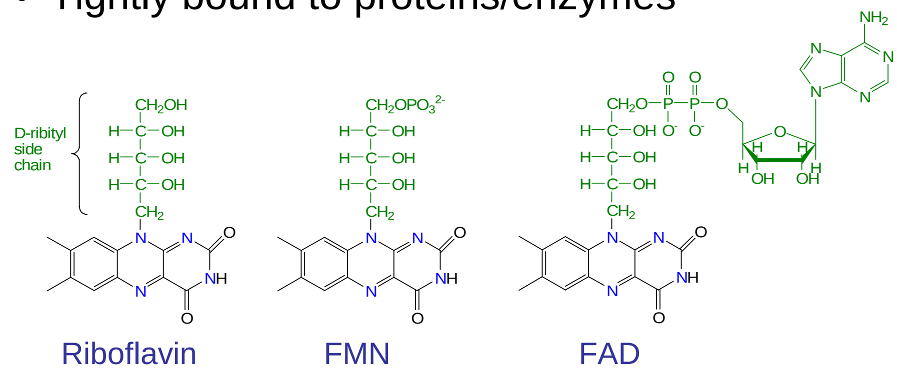
NADP+ and NADPH

Nicotinamide Adenine Dinucleotide Phosphate

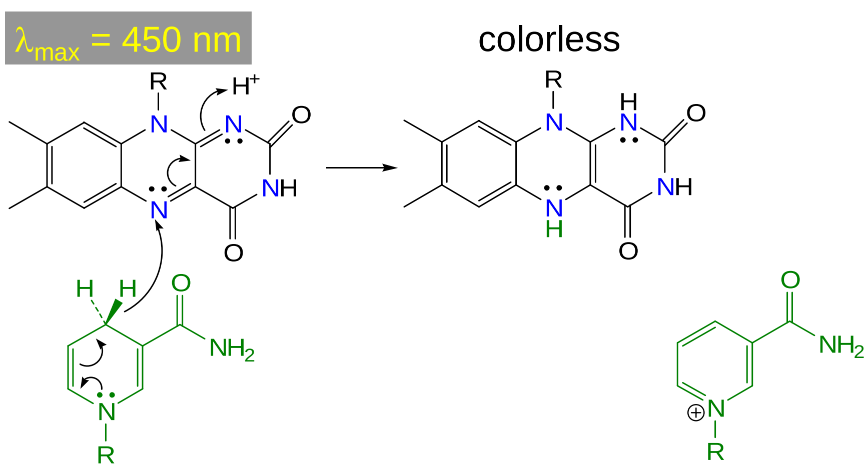


Flavin coenzymes

- Enzymatically modified forms of riboflavin (B_2)
- Tightly bound to proteins/enzymes



Two electron reduction of flavin by hydride transfer from NADH



Sequential one electron reduction of flavin through semiquinone intermediate(s)

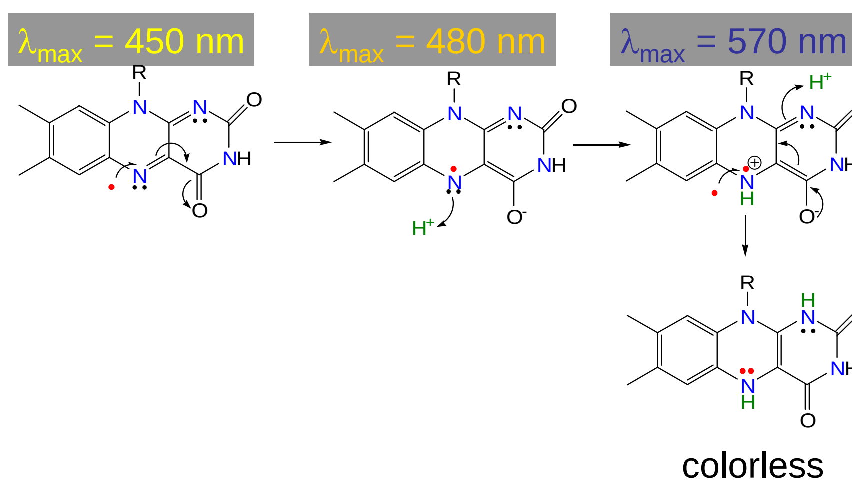
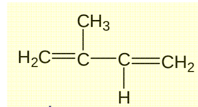


table 14–9

Some Enzymes (Flavoproteins) That Employ Flavin Nucleotide Coenzymes

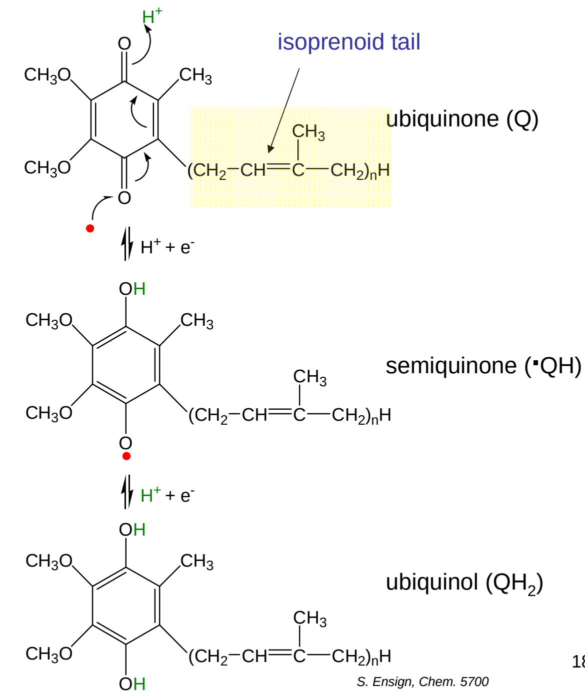
Enzyme	Flavin nucleotide
Fatty acyl–CoA dehydrogenase	FAD
Dihydrolipoyl dehydrogenase	FAD
Succinate dehydrogenase	FAD
Glycerol 3-phosphate dehydrogenase	FAD
Thioredoxin reductase	FAD
NADH dehydrogenase (Complex I)	FMN
Glycolate dehydrogenase	FMN

Reduction of ubiquinone (Coenzyme Q) to the one-electron reduced radical and two-electron reduced forms



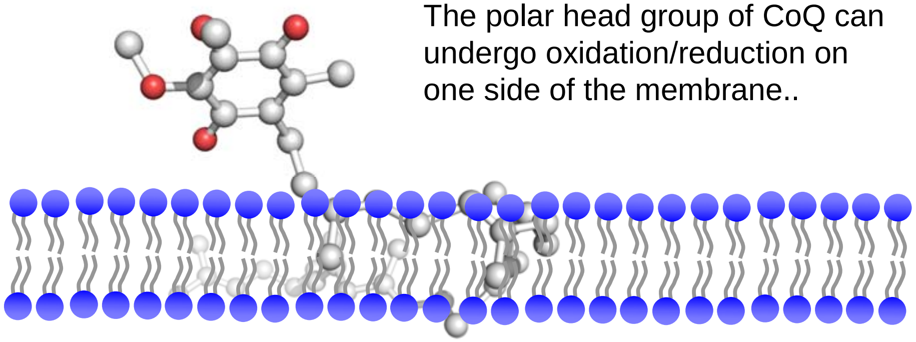
isoprene

n = 10, Coenzyme Q_{10}



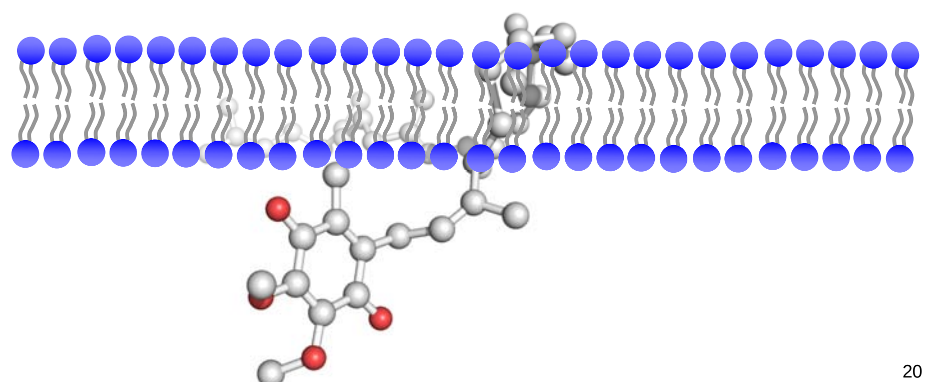
Coenzyme Q is a membrane-bound, amphipathic cofactor

The polar head group of CoQ can undergo oxidation/reduction on one side of the membrane..

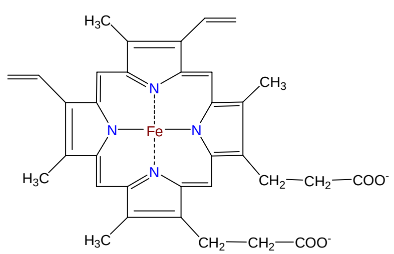


Coenzyme Q is a membrane-bound, amphipathic cofactor

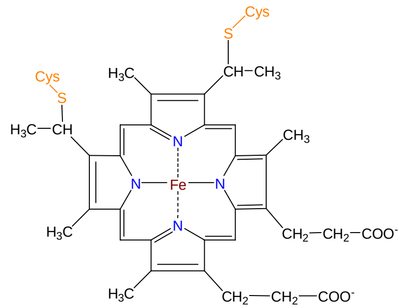
Then flip to the other side of the membrane to complete a redox reaction



Types of hemes in cytochromes

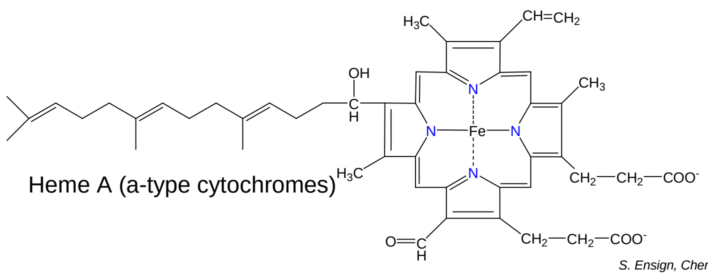


Iron protopophyrin IX
(b-type cytochromes)

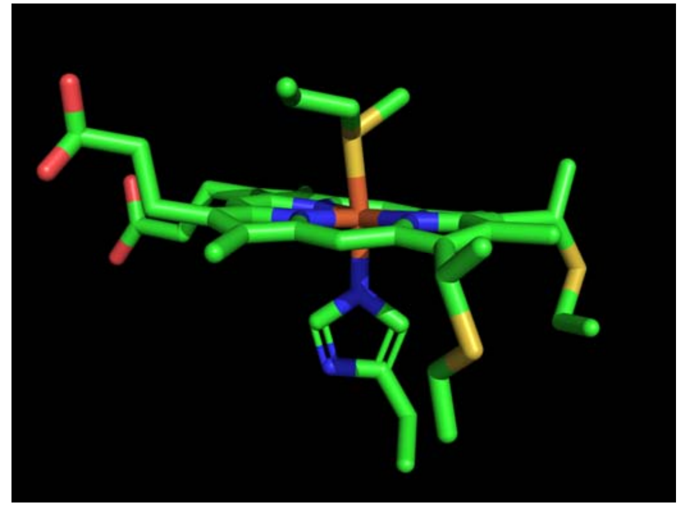


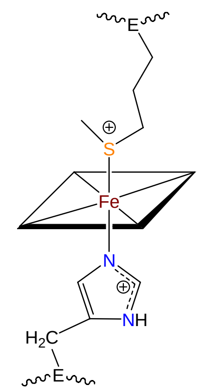
Heme C (c-type cytochromes)

Heme A (a-type cytochromes)

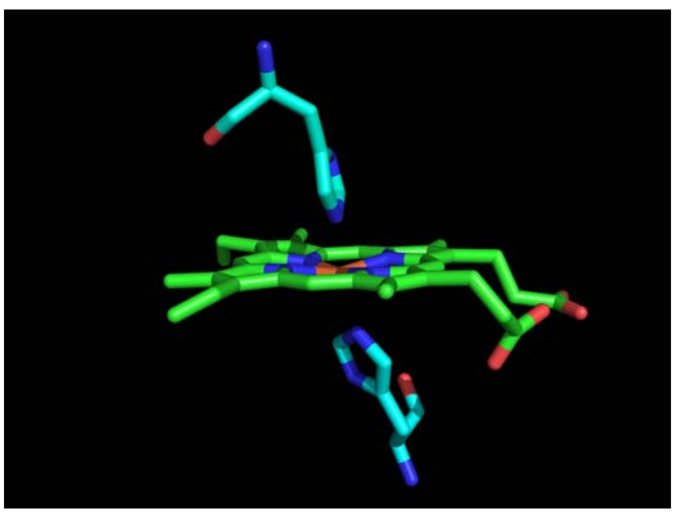


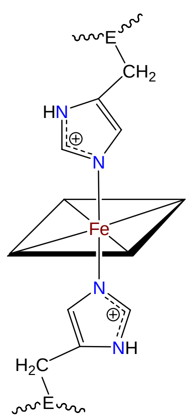
Axial ligands to heme C in cytochrome C



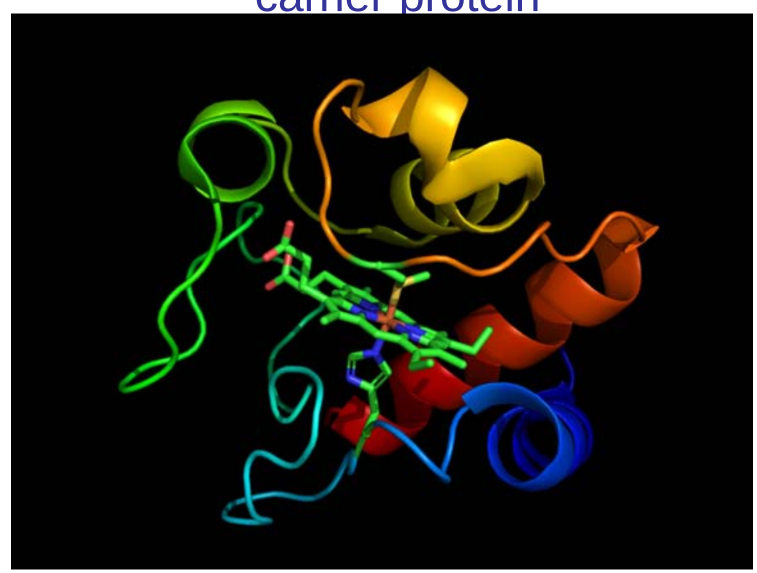


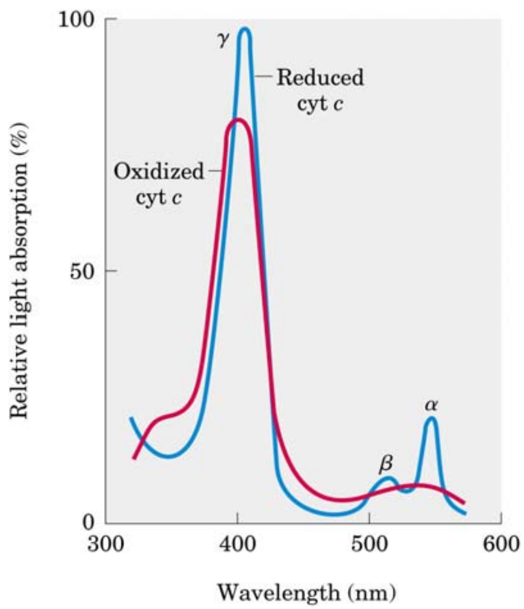
Axial ligands to heme in Cytochrome b_H and b_L





Cytochrome c; a water soluble electron carrier protein

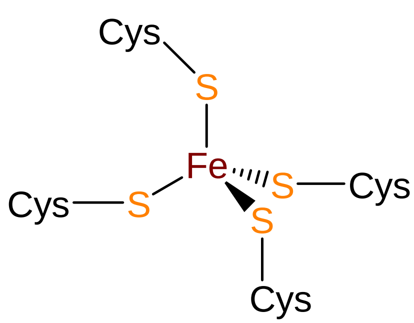


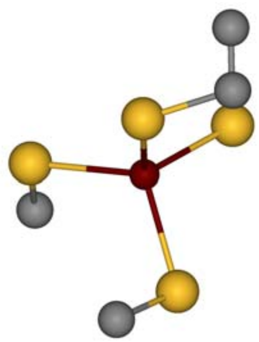


Iron-sulfur clusters

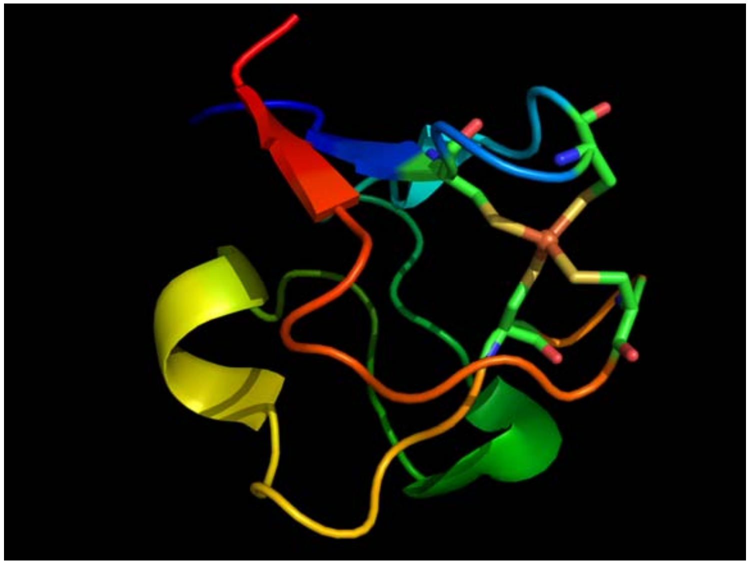
- inorganic cofactors
- Fe only
- Fe + inorganic sulfur
- Covalent ligation to proteins, usually through cysteine residues

Iron-sulfur clusters: "rubredoxin" type

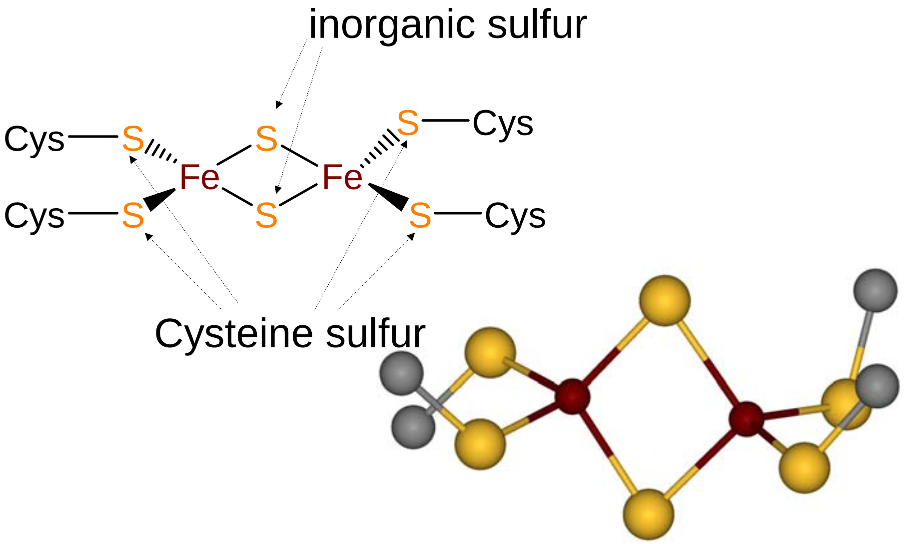




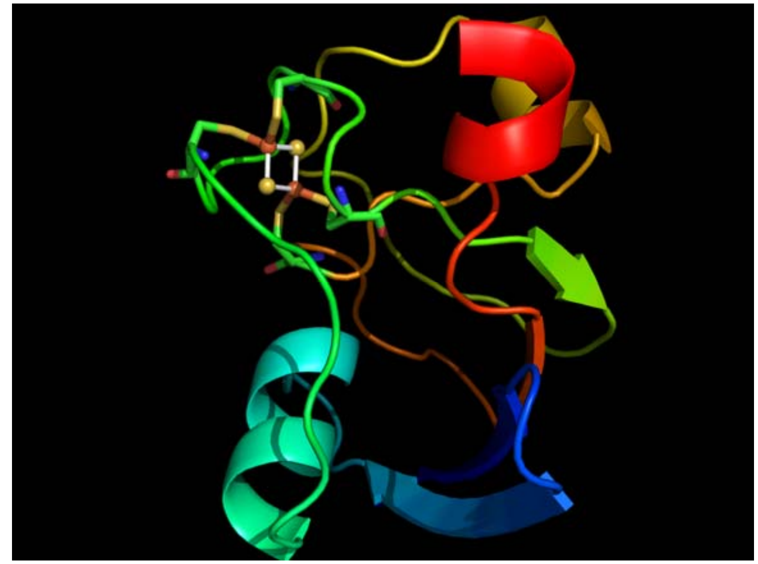
Rubredoxin: inorganic Fe



Iron-sulfur clusters: “ferredoxin” type



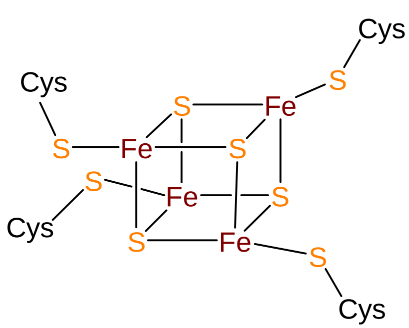
Plant-type ferredoxin: inorganic Fe_2S_2

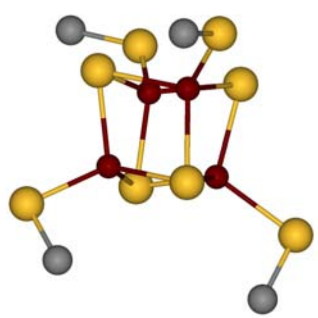


Iron-sulfur clusters: “ferredoxin” type

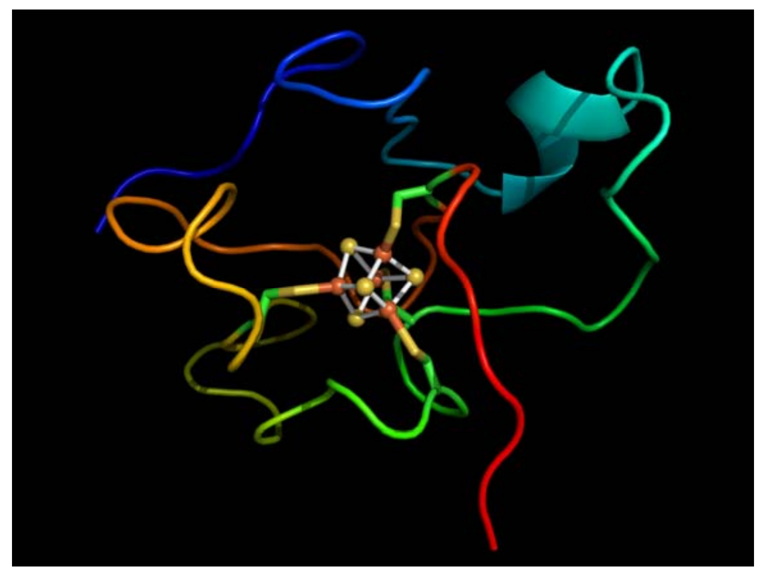
Ligands to Fe:

- Cysteine sulfur
- Inorganic sulfur





Bacterial-type ferredoxin: inorganic Fe_4S_4



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rotenone

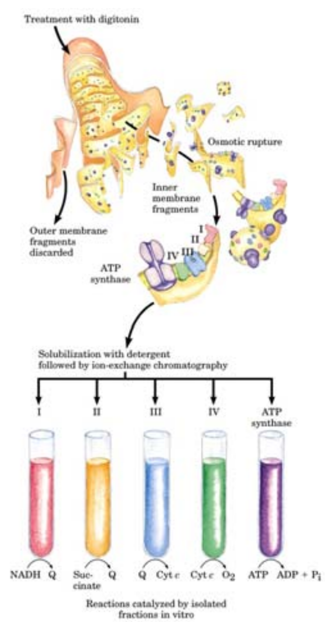
NADH ⟶ Q ⟶ Cyt *b* ⟶ Cyt c_1 ⟶ Cyt *c* ⟶ Cyt $(a + a_3)$ ⟶ O_2

antimycin A

NADH ⟶ Q ⟶ Cyt *b* ⟶ Cyt c_1 ⟶ Cyt *c* ⟶ Cyt $(a + a_3)$ ⟶ O_2

CN^- or CO

NADH ⟶ Q ⟶ Cyt *b* ⟶ Cyt c_1 ⟶ Cyt *c* ⟶ Cyt $(a + a_3)$ ⟶ O_2



Components of the mitochondrial electron transfer chain

Com-plex	Common name	Reaction catalyzed	Proper name	Number of sub-units	cofactors
I	NADH dehydrogenase	NADH + Q + H^+ → NAD^+ + QH_2	NADH:CoQ oxidoreductase	42	FMN, 9 FeS clusters
II	Succinate dehydrogenase	Succinate + Q → fumarate + QH_2	Succinate:CoQ oxidoreductase	5	FAD, $Cytb_{560}$, 3 FeS clusters
III	Cytochrome bc_1	QH_2 + $2CytC_{ox}$ → Q + $2CytC_{red}$ + $2H^+$	CoQ:cytochrome c oxidoreductase	11	cyt b_H, cyt b_L, cyt c_1, Fe-S cluster
IV	Cytochrome oxidase	$4CytC_{red}$ + O_2 + $4H^+$ → $4CytC_{ox}$ + $2H_2O$	Cytochrome c: O_2 oxidoreductase	13	cyt a, cyt a_3, Cu_A, Cu_B

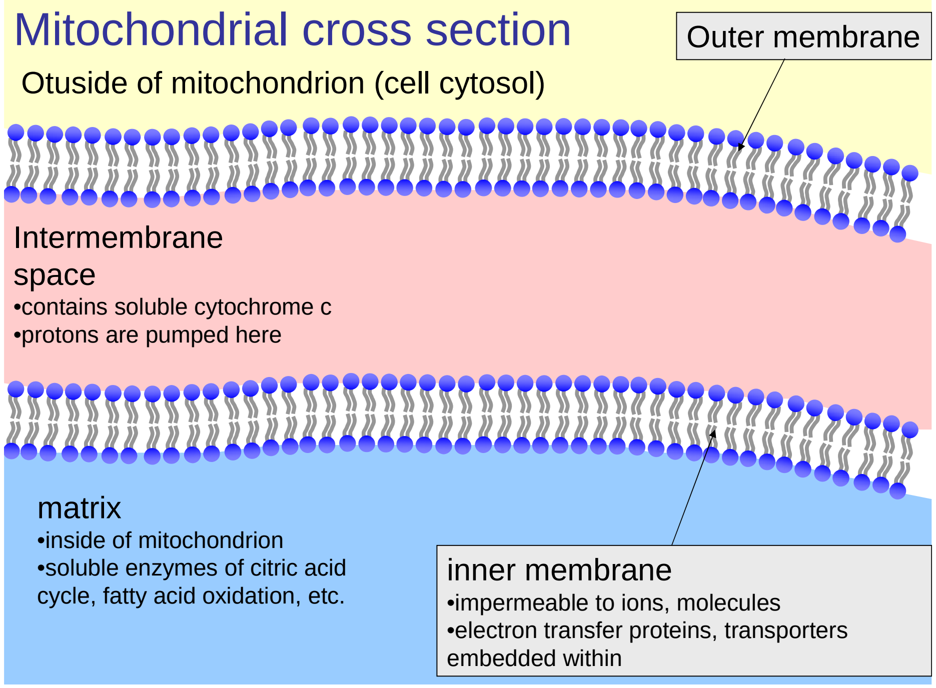
Mitochondrial electron transfer

- focus first on details of electron transfer
- focus second on proton pumping by complexes I, III, and IV

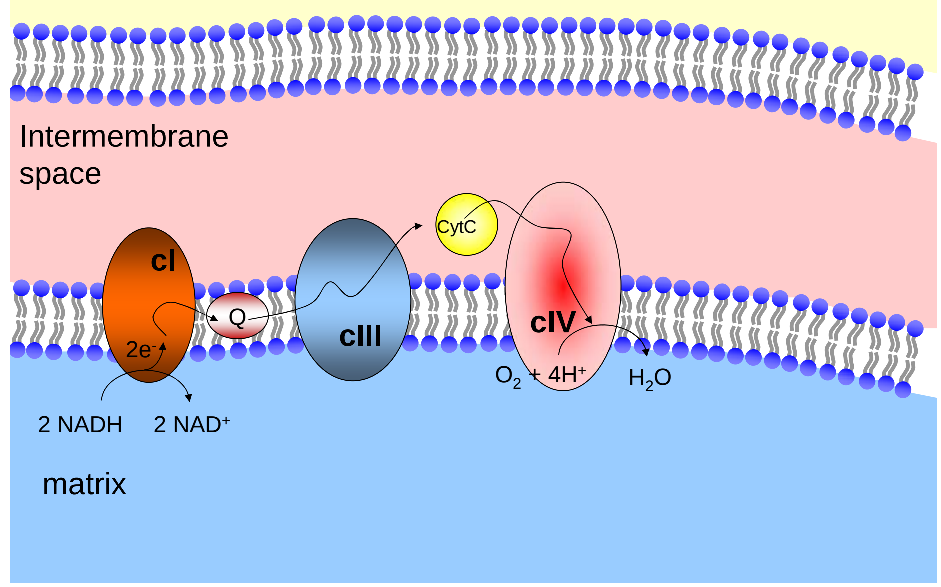
Cofactors transferring electrons from NADH to O_2 in mitochondrial electron transfer

Half reaction	E'° (V)
½ O_2 + $2H^+$ + $2e^-$ → H_2O	0.8166
cIV Cu_B^{2+} + e^- → cIV Cu_B^{1+}	
cIV cytochrome a_3 (Fe^{3+}) + e^- → cIV cytochrome a_3 (Fe^{2+})	0.35
cIV cytochrome a (Fe^{3+}) + e^- → cIV cytochrome a (Fe^{2+})	0.29
cIV Cu_A^{2+} + e^- → cIV Cu_A^{1+}	
cytochrome c (Fe^{3+}) + e^- → cytochrome c (Fe^{2+})	0.254
cIII cytochrome c_1 (Fe^{3+}) + e^- → cIII cytochrome c_1 (Fe^{2+})	0.22
cIII cytochrome b (Fe^{3+}) + e^- →cIII cytochrome b (Fe^{2+})	0.077
cIII cytochrome b_H (Fe^{3+}) + e^- →cIII cytochrome b_H (Fe^{2+})	
cIII cytochrome b_L (Fe^{3+}) + e^- →cIII cytochrome b_L (Fe^{2+})	
cIII Rieske Fe-S $cluster_{ox}$ + e^- → cIII Rieske FeS $cluster_{red}$	
ubiquinone + $2H^+$ + $2e^-$ → ubiquinol	0.045
cI Fe-S $clusters_{ox}$ + e^- → cI FeS $clusters_{red}$	
cI FMN + $2H^+$ + $2e^-$ → cI $FMNH_2$	-0.30
NAD^+ + H^+ + $2e^-$ → NADH	-0.32

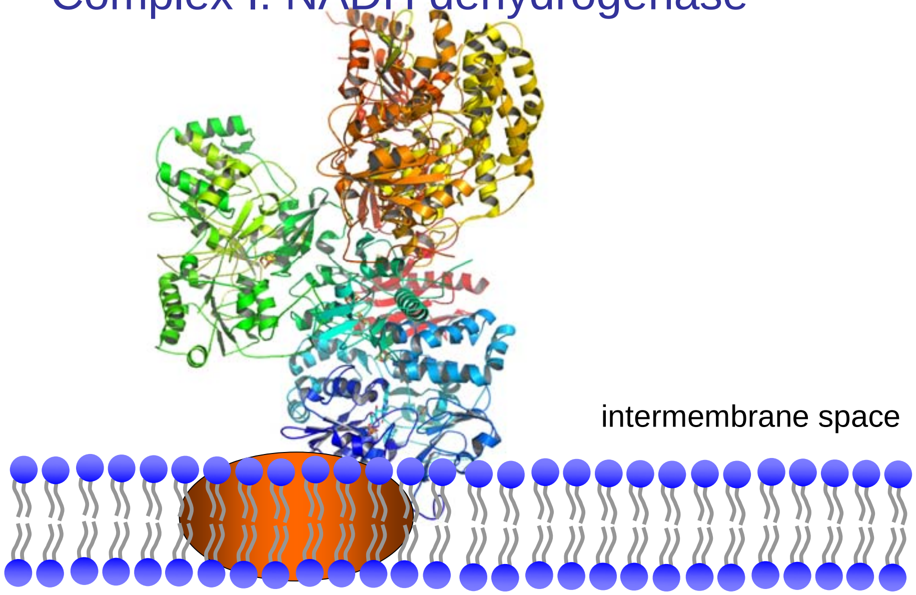
Mitochondrial cross section



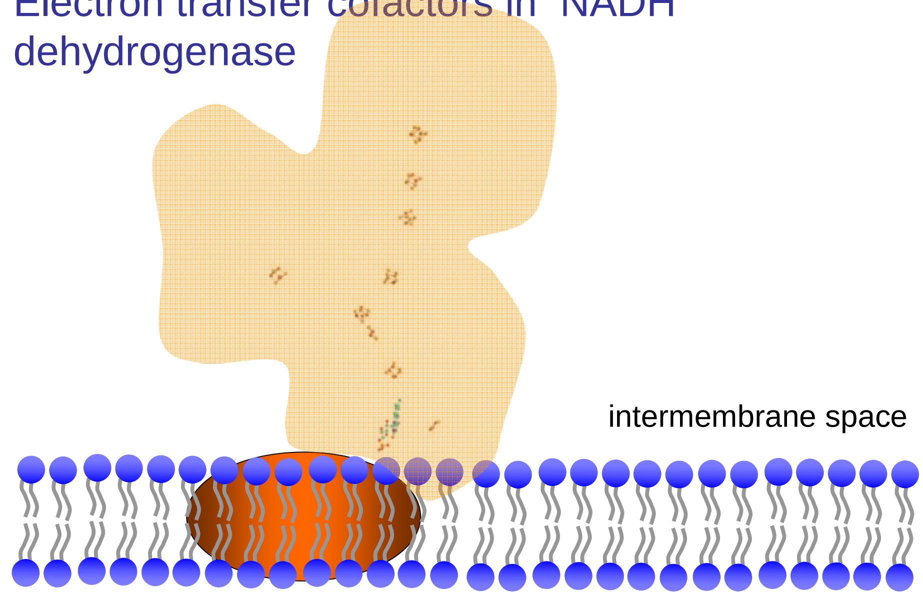
Transfer of electrons from NADH to O_2



Complex I: NADH dehydrogenase

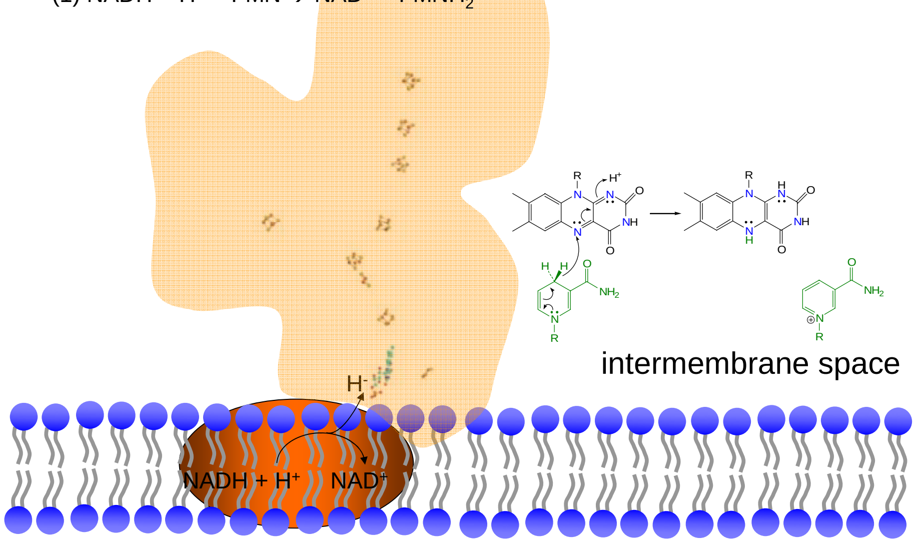


Electron transfer cofactors in NADH dehydrogenase



Electron transfer in NADH dehydrogenase

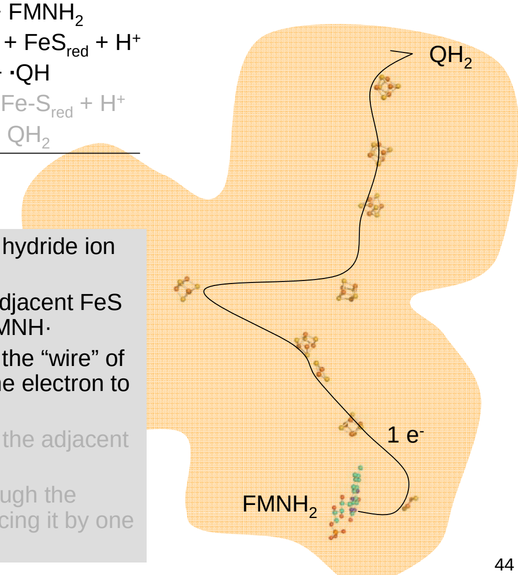
(1) NADH + H^+ + FMN → NAD^+ + $FMNH_2$



Electron transfer in NADH dehydrogenase

(1) NADH + H^+ + FMN → NAD^+ + $FMNH_2$
(2) $FMNH_2$ + FeS_{ox} → FMNH· + FeS_{red} + H^+
(3) FeS_{red} + Q + H+ → FeS_{ox} + ·QH
(4) FMNH· + FeS_{ox} → FMN + $Fe\text{-}S_{red}$ + H^+
(5) FeS_{red} + ·QH + H+ → FeS_{ox} + QH_2

- NADH transfers two electrons as a hydride ion to FMN
- FMN transfers one electron to an adjacent FeS center, forming the semiquinone FMNH·
- The electron is transferred through the “wire” of FeS clusters to Q, reducing it by one electron to ·QH
- FMNH· transfers it’s 2nd electron to the adjacent FeS cluster
- ·The 2nd electron is transferred through the “wire” of FeS clusters to ·QH , reducing it by one electron to QH_2



Electron transfer in NADH dehydrogenase

(1) $NADH + H^+ + FMN \rightarrow NAD^+ + FMNH_2$
(2) $FMNH_2 + FeS_{ox} \rightarrow FMNH\cdot + FeS_{red} + H^+$
(3) $FeS_{red} + Q + H^+ \rightarrow FeS_{ox} + \cdot QH$
(4) $FMNH\cdot + FeS_{ox} \rightarrow FMN + Fe\text{-}S_{red} + H^+$
(5) $FeS_{red} + \cdot QH + H^+ \rightarrow FeS_{ox} + QH_2$

- NADH transfers two electrons as a hydride ion to FMN
- FMN transfers one electron to an adjacent FeS center, forming the semiquinone FMNH·
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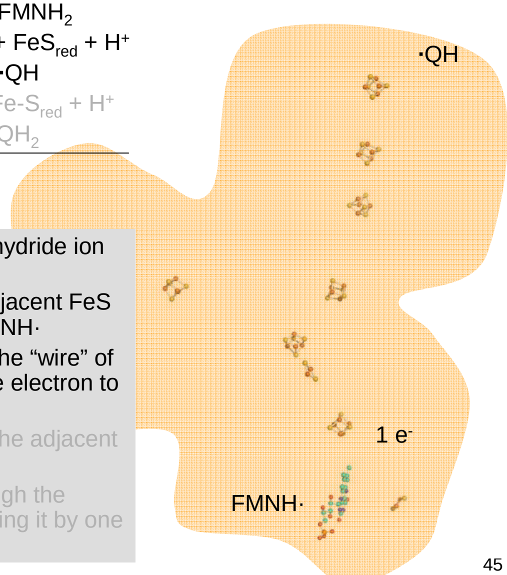

Electron transfer in NADH dehydrogenase

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(5) $FeS_{red} + \cdot QH + H^+ \rightarrow FeS_{ox} + QH_2$

- NADH transfers two electrons as a hydride ion to FMN
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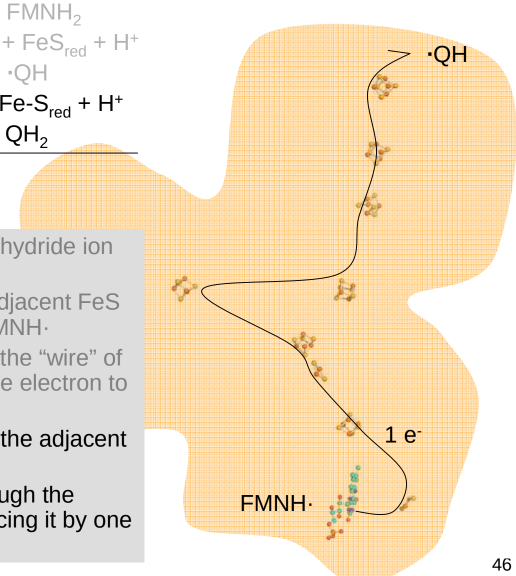

Electron transfer in NADH dehydrogenase

(1) $NADH + H^+ + FMN \rightarrow NAD^+ + FMNH_2$
(2) $FMNH_2 + FeS_{ox} \rightarrow FMNH\cdot + FeS_{red} + H^+$
(3) $FeS_{red} + Q + H^+ \rightarrow FeS_{ox} + \cdot QH$
(4) $FMNH\cdot + FeS_{ox} \rightarrow FMN + Fe\text{-}S_{red} + H^+$
(5) $FeS_{red} + \cdot QH + H^+ \rightarrow FeS_{ox} + QH_2$

- NADH transfers two electrons as a hydride ion to FMN
- FMN transfers one electron to an adjacent FeS center, forming the semiquinone FMNH·
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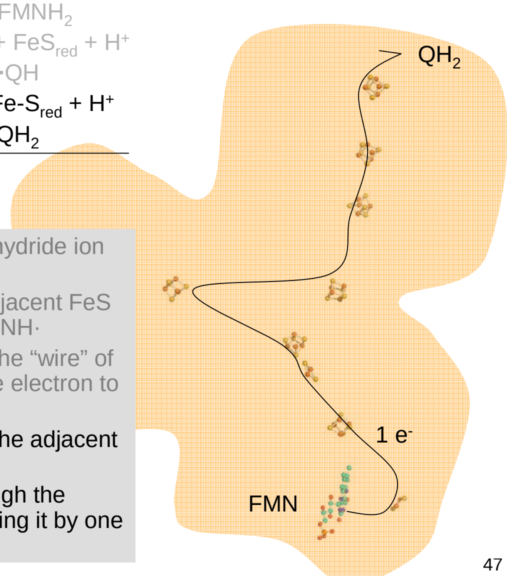
- FMNH· transfers it’s 2nd electron to the adjacent FeS cluster
- ·The 2nd electron is transferred through the “wire” of FeS clusters to ·QH , reducing it by one electron to QH_2

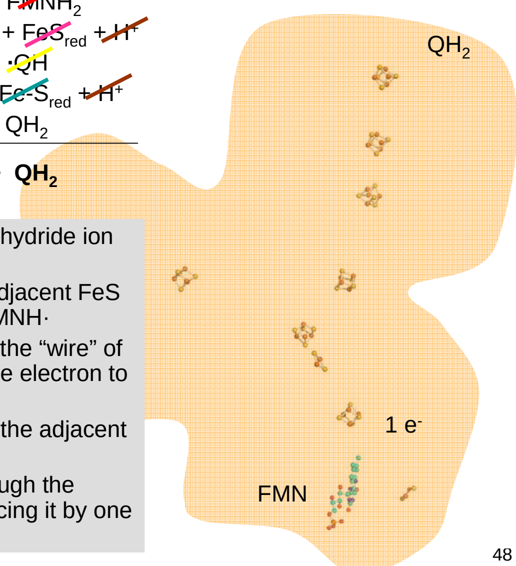


Electron transfer in NADH dehydrogenase

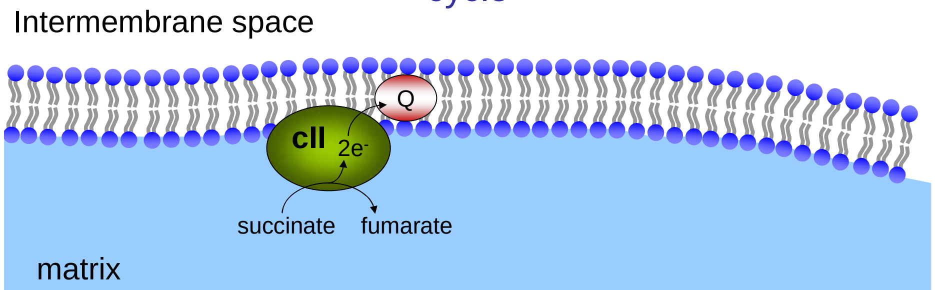
(1) $NADH + H^+ + \cancel{FMN} \rightarrow NAD^+ + \cancel{FMNH_2}$
(2) $\cancel{FMNH_2} + \cancel{FeS_{ox}} \rightarrow \cancel{FMNH\cdot} + \cancel{FeS_{red}} + \cancel{H^+}$
(3) $\cancel{FeS_{red}} + Q + \cancel{H^+} \rightarrow \cancel{FeS_{ox}} + \cancel{\cdot QH}$
(4) $\cancel{FMNH\cdot} + \cancel{FeS_{ox}} \rightarrow \cancel{FMN} + \cancel{Fe\text{-}S_{red}} + \cancel{H^+}$
(5) $\cancel{FeS_{red}} + \cancel{\cdot QH} + \cancel{H^+} \rightarrow \cancel{FeS_{ox}} + QH_2$

Net rxn: $NADH + Q + H^+ \rightarrow NAD^+ + QH_2$

- NADH transfers two electrons as a hydride ion to FMN
- FMN transfers one electron to an adjacent FeS center, forming the semiquinone FMNH·
- The electron is transferred through the “wire” of FeS clusters to Q, reducing it by one electron to ·QH
- FMNH· transfers it’s 2nd electron to the adjacent FeS cluster
- ·The 2nd electron is transferred through the “wire” of FeS clusters to ·QH , reducing it by one electron to QH_2

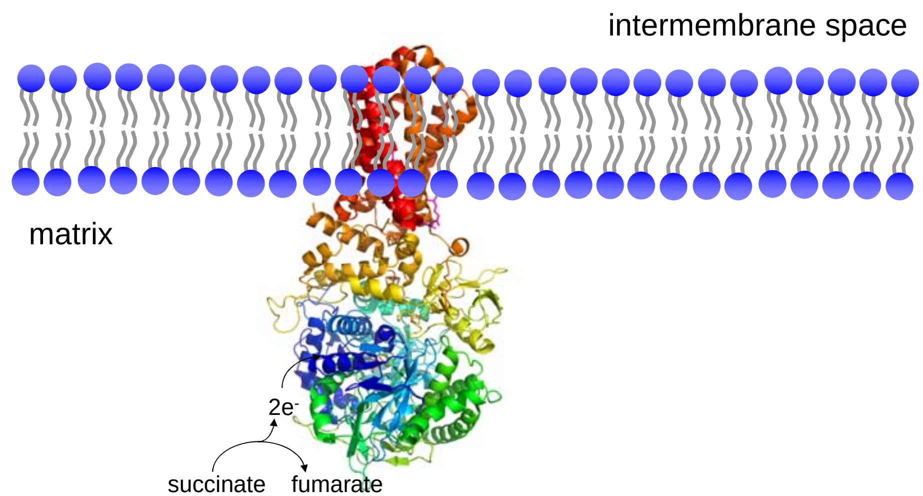


Complex II (succinate dehydrogenase) is the only membrane-bound component of the citric acid cycle

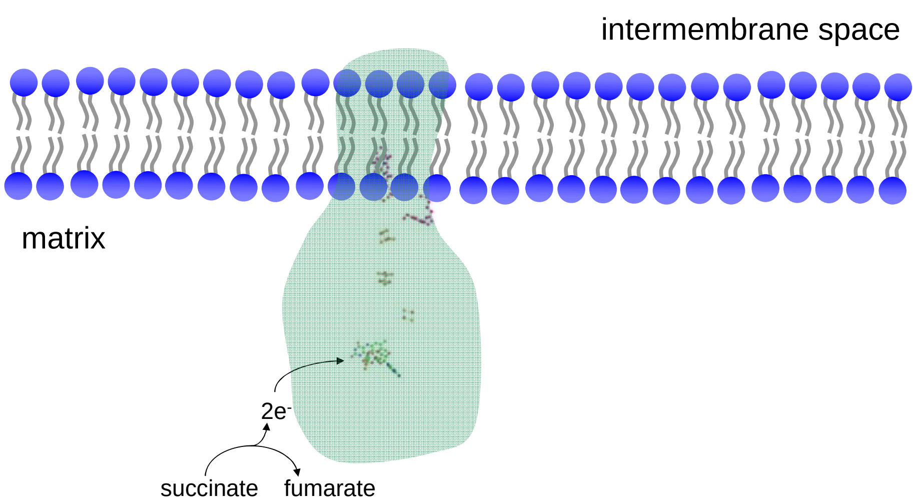


- Asymetrically oriented membrane protein
- FAD is initial electron acceptor
- Electrons are passed through FeS clusters to oxidized coenzyme Q
- Overall reaction: Succinate + Q → fumarate + QH_2

Structure of succinate dehydrogenase

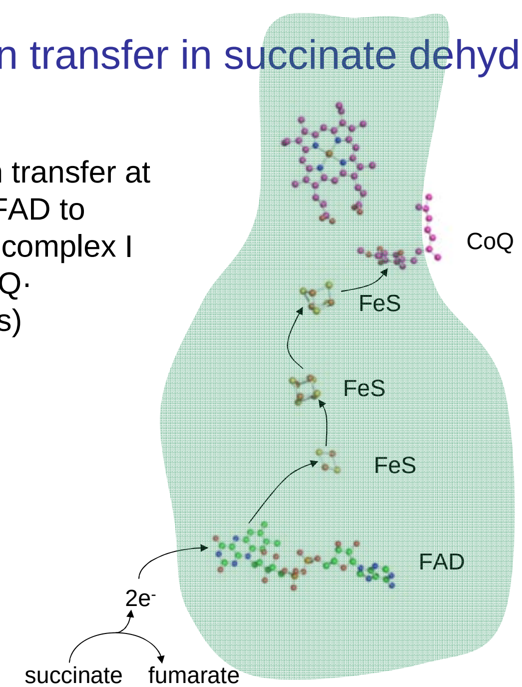


Electron transfer in succinate dehydrogenase

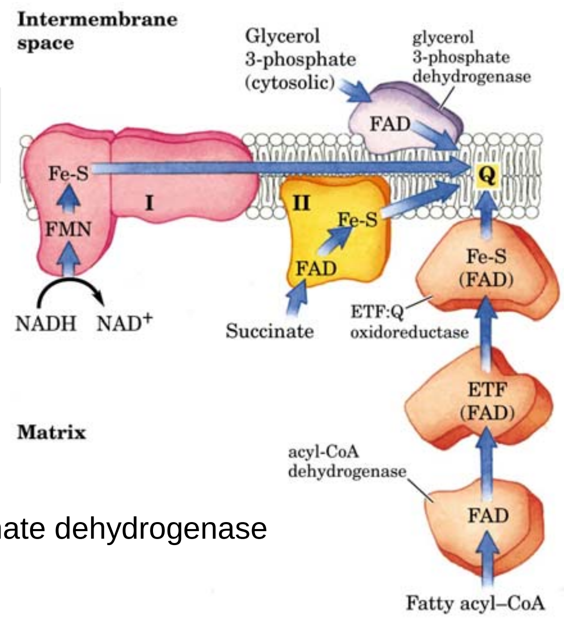


Electron transfer in succinate dehydrogenase

One electron transfer at a time from FAD to CoQ, as per complex I (FADH· and Q· intermediates)

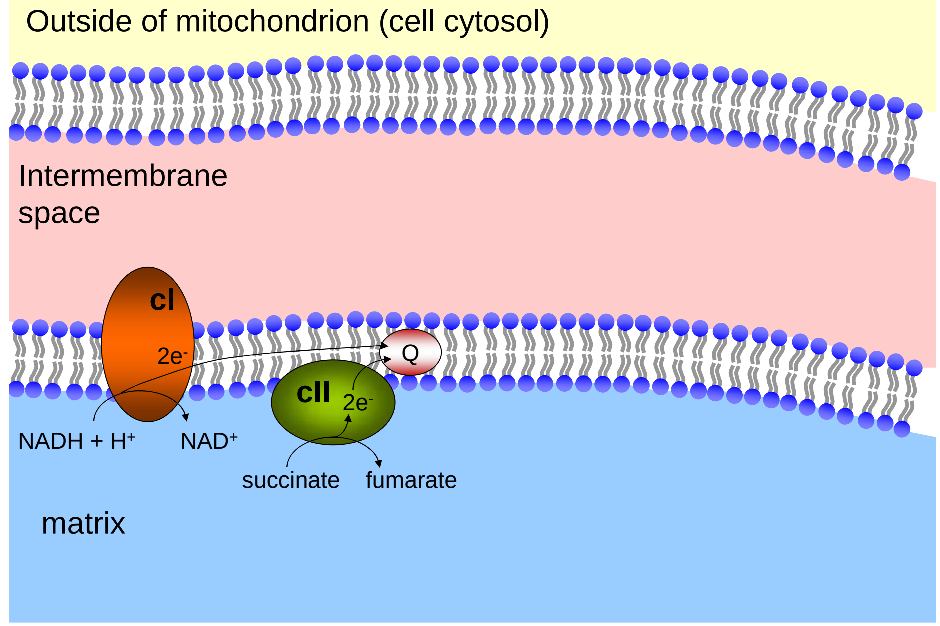


Electron transfer to the CoQ pool

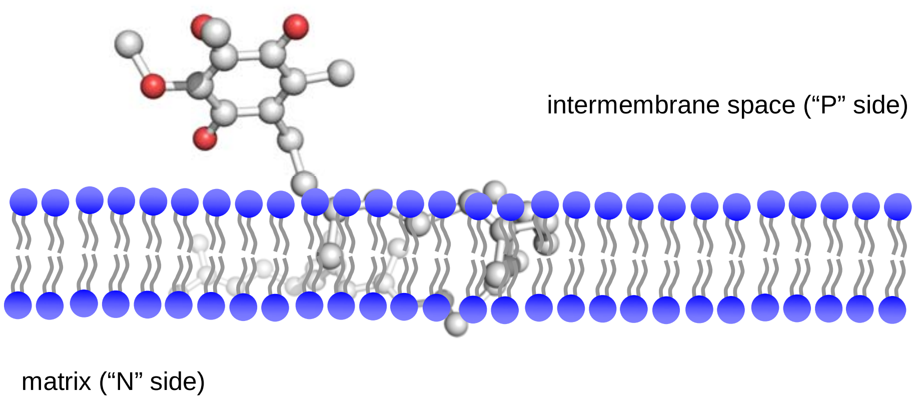


Complex II = succinate dehydrogenase

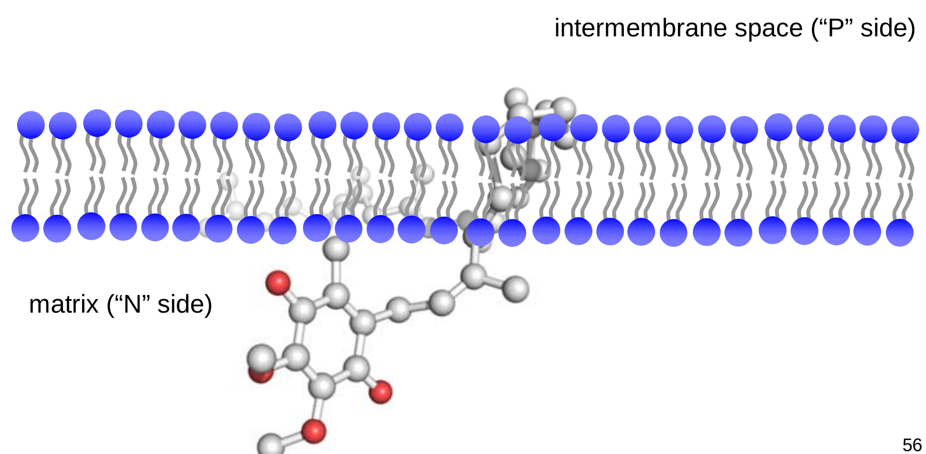
Consolidation of electrons in Coenzyme Q



Consolidation of electrons in Coenzyme Q

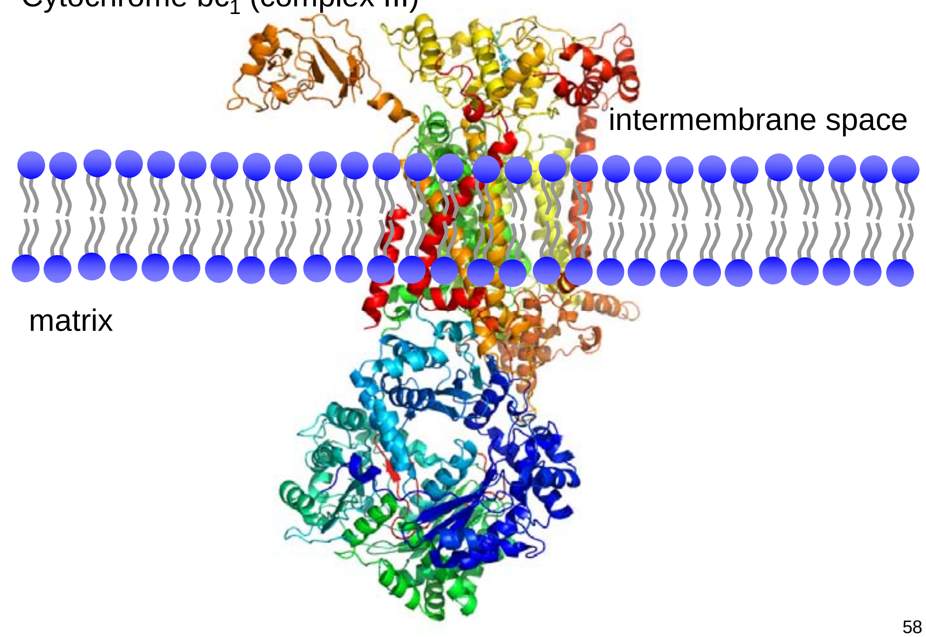


Consolidation of electrons in Coenzyme Q

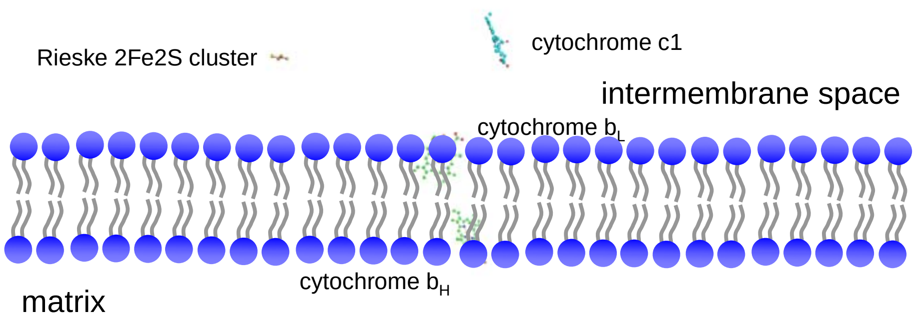


Transfer of electrons from Coenzyme Q to complex III

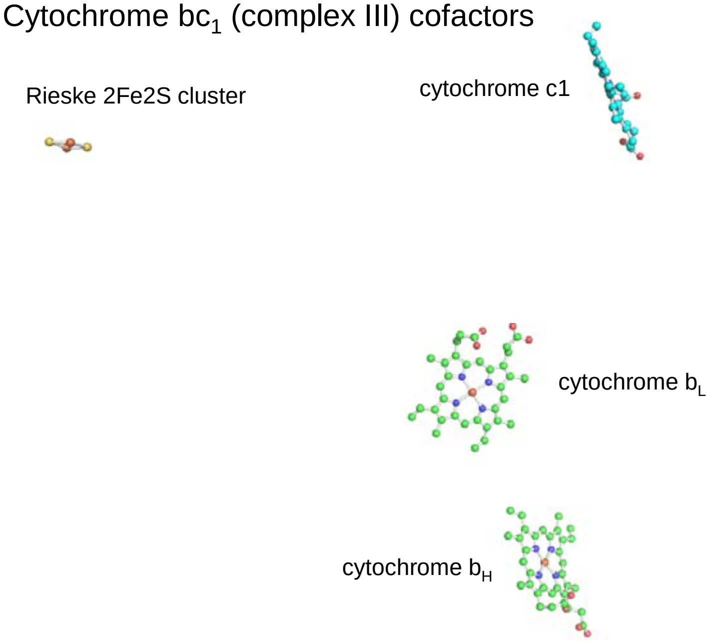
Cytochrome bc_1 (complex III)



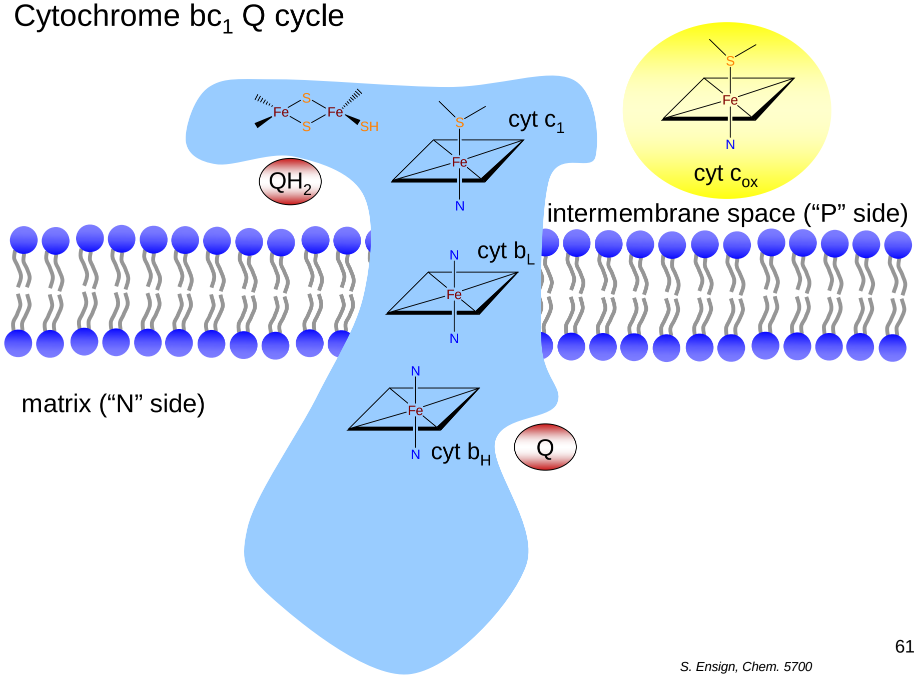
Cytochrome bc_1 (complex III)



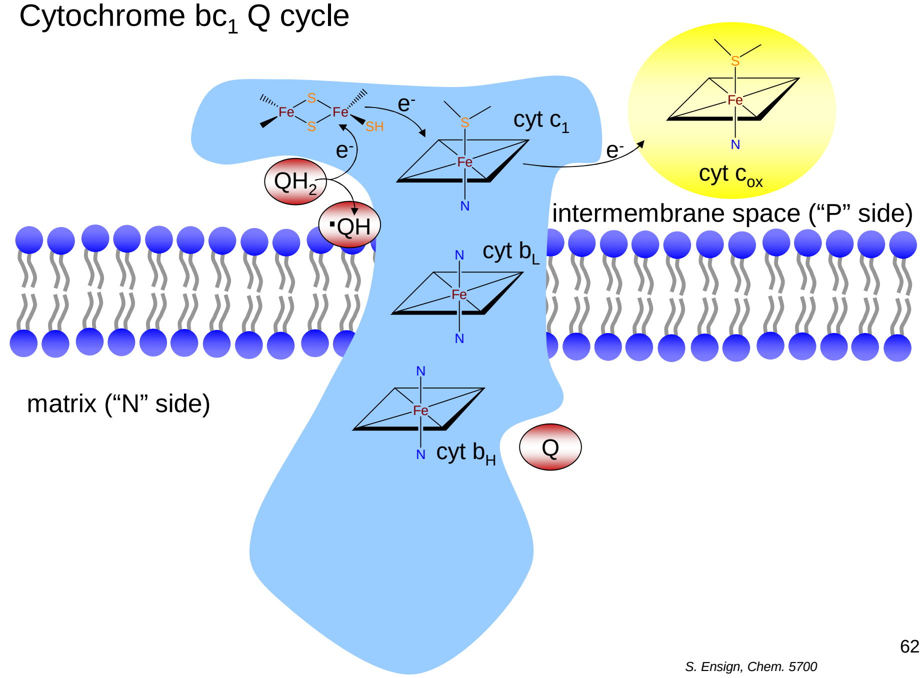
Cytochrome bc_1 (complex III) cofactors



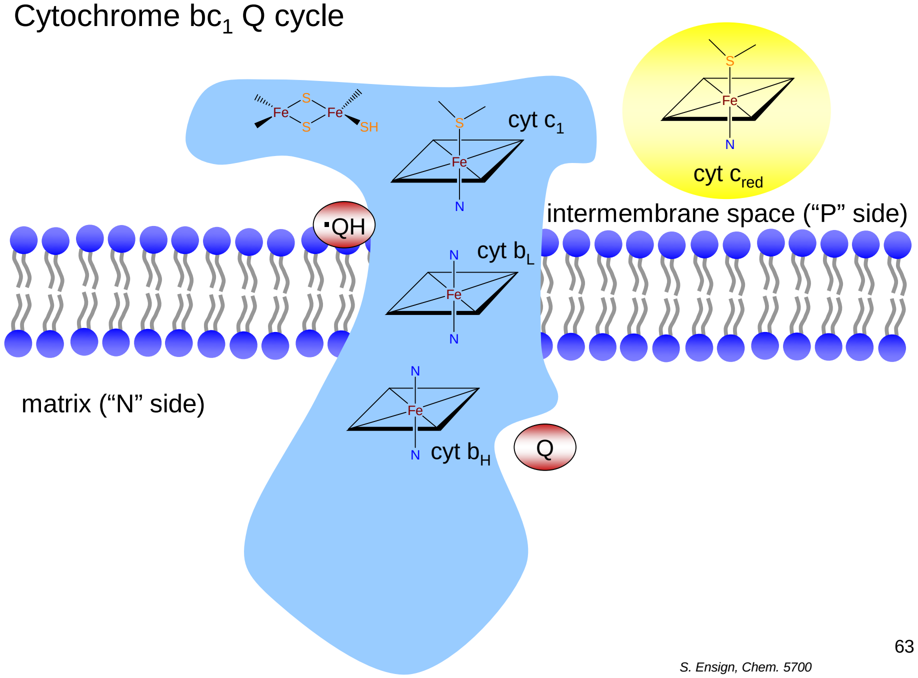
Cytochrome bc_1 Q cycle



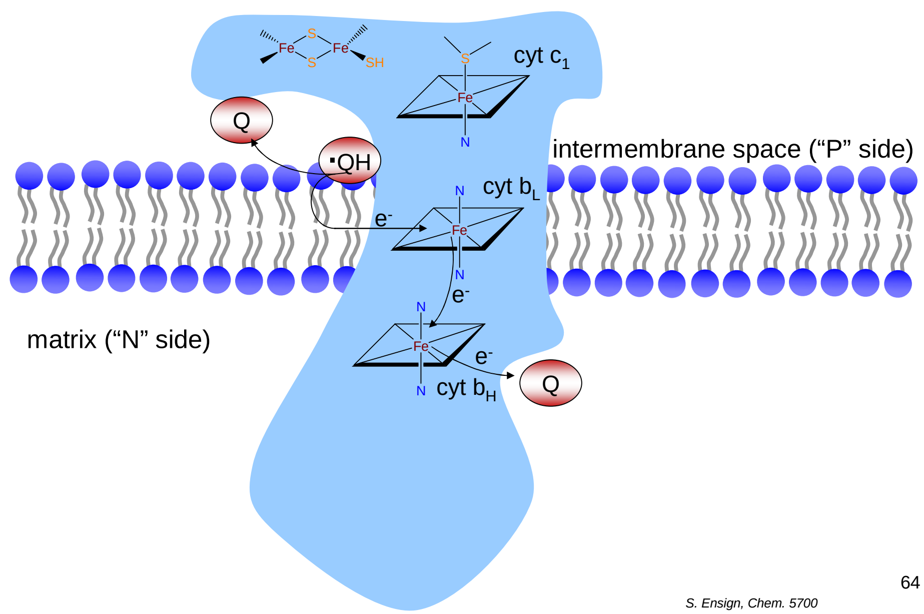
Cytochrome bc_1 Q cycle



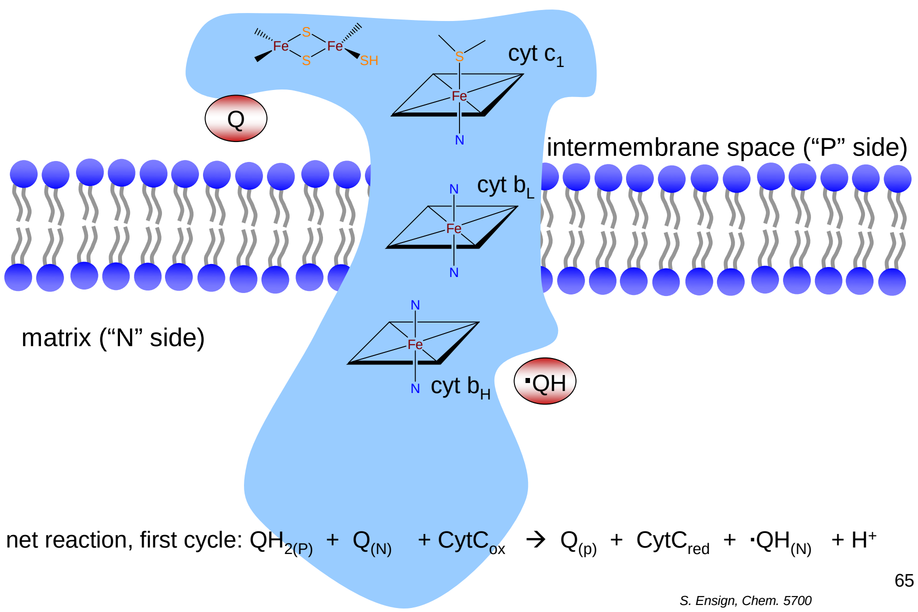
Cytochrome bc_1 Q cycle



Cytochrome bc_1 Q cycle

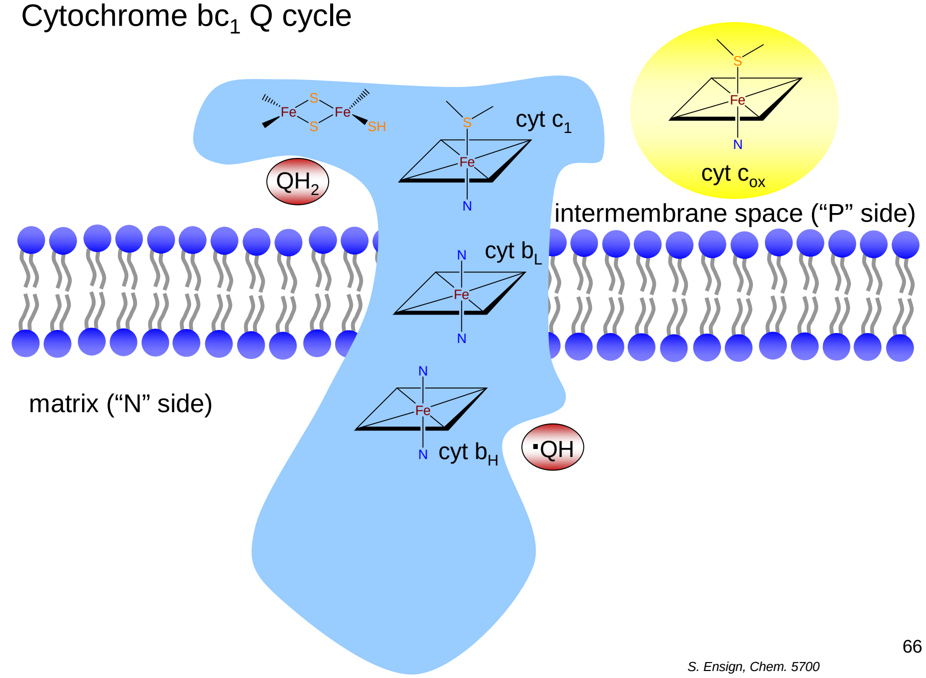


Cytochrome bc_1 Q cycle

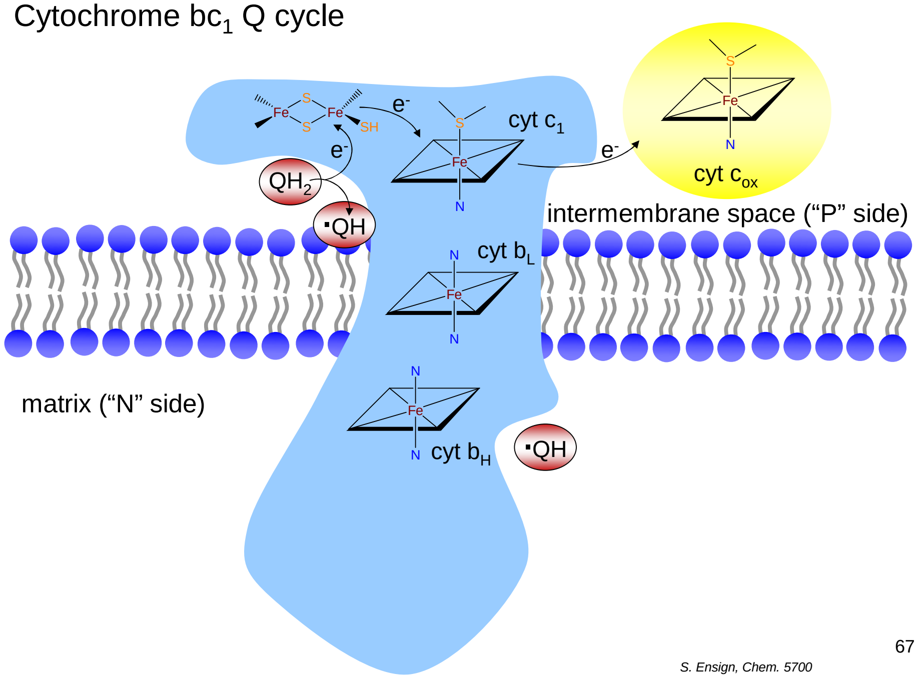


net reaction, first cycle: $QH_{2(P)}$ + $Q_{(N)}$ + $CytC_{ox}$ → $Q_{(p)}$ + $CytC_{red}$ + $\cdot QH_{(N)}$ + H^+

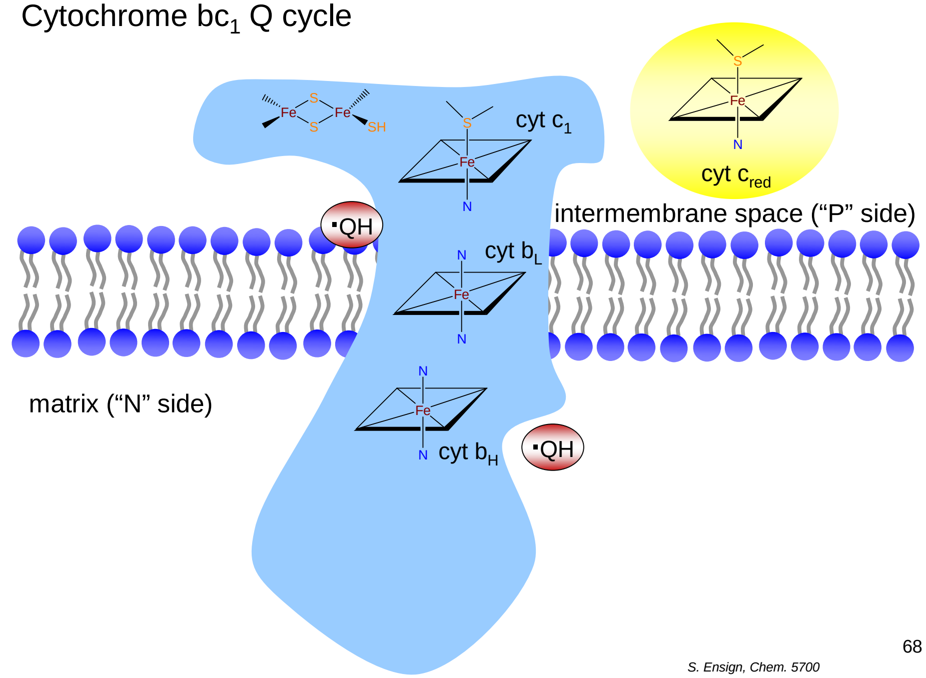
Cytochrome bc_1 Q cycle



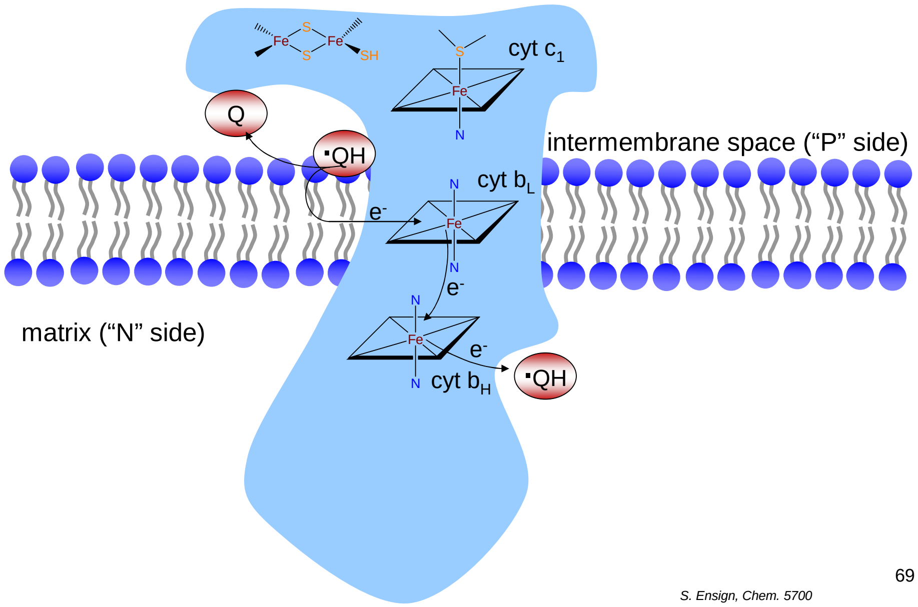
Cytochrome bc_1 Q cycle



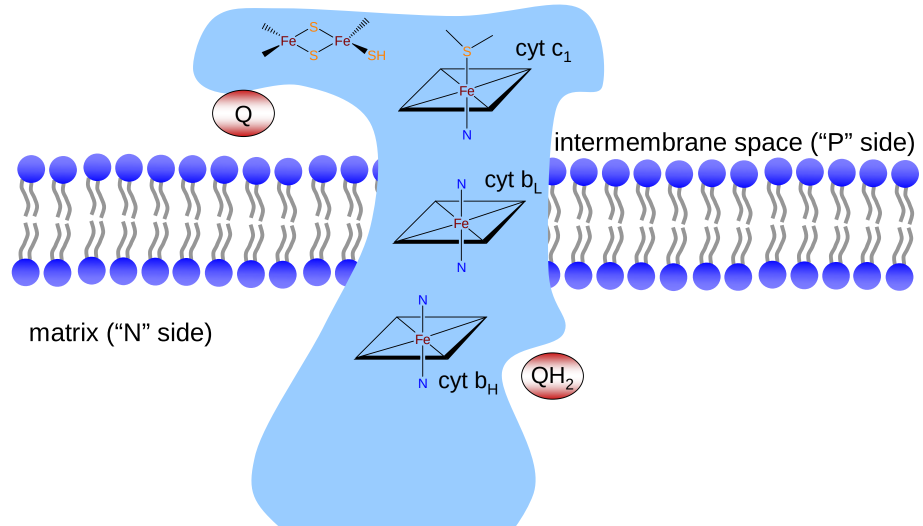
Cytochrome bc_1 Q cycle



Cytochrome bc_1 Q cycle



Cytochrome bc_1 Q cycle



net reaction, 2nd cycle: $QH_{2(P)} + \cdot QH_{(N)} + CytC_{ox} \rightarrow Q_{(p)} + CytC_{red} + QH_{2(N)} + H^+$

Summary of the Q cycle

first cycle: $QH_{2(P)} + Q_{(N)} + CytC_{ox} \rightarrow Q_{(p)} + CytC_{red} + \cdot QH_{(N)} + H^+$

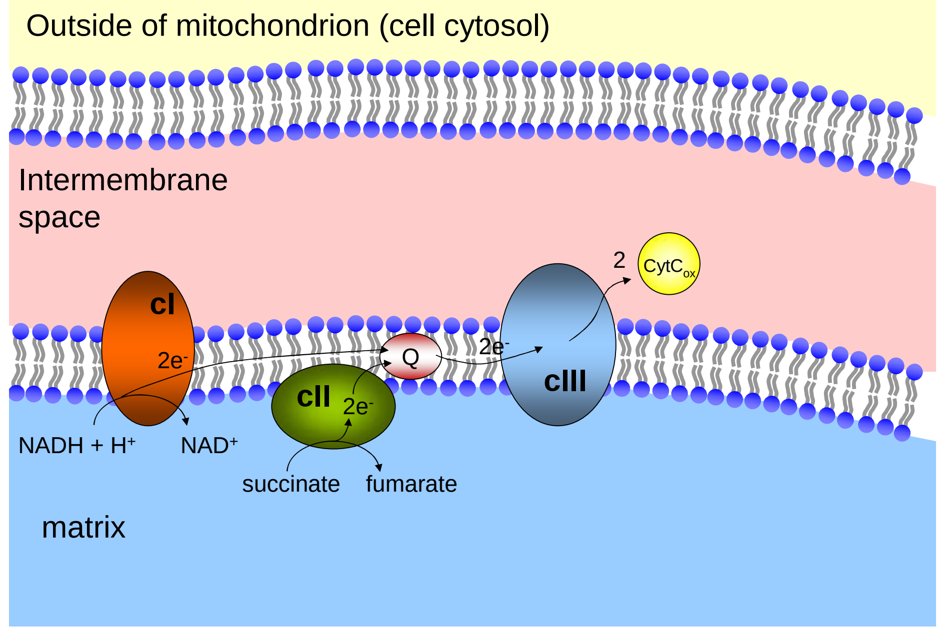
2nd cycle: $QH_{2(P)} + \cdot QH_{(N)} + CytC_{ox} \rightarrow Q_{(p)} + CytC_{red} + QH_{2(N)} + H^+$

---

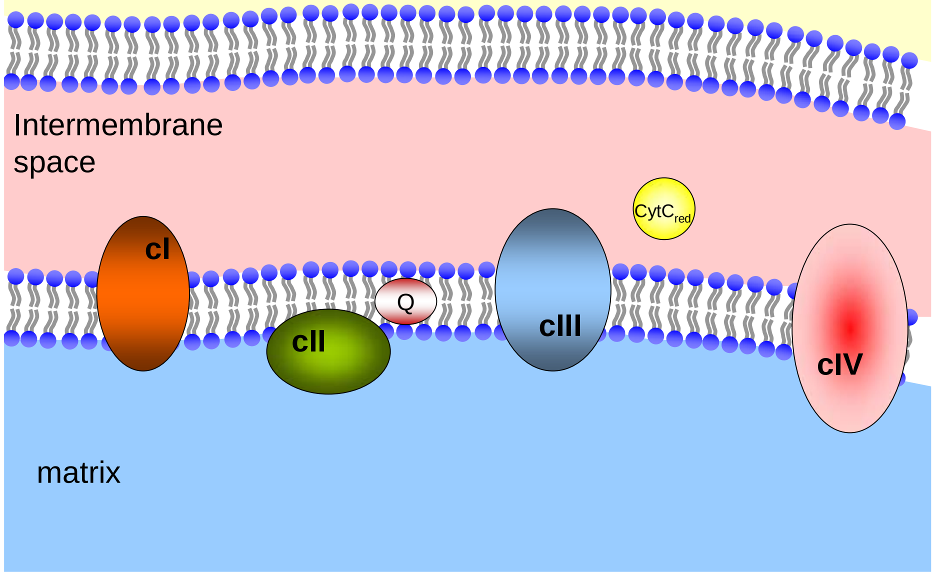
overall reaction: $2\ QH_{2(P)} + Q_{(N)} + 2\ CytC_{ox} \rightarrow 2\ Q_{(p)} + 2\ CytC_{red} + QH_{2(N)} + 2\ H^+$

net reaction: $QH_2 + 2\ CytC_{ox} \rightarrow Q + 2\ CytC_{red} + + 2\ H^+$

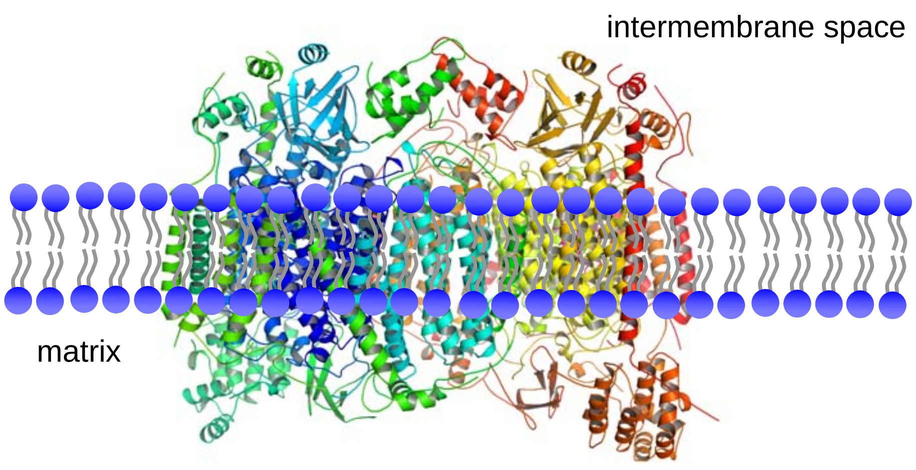
Consolidation of electrons in cytochrome C



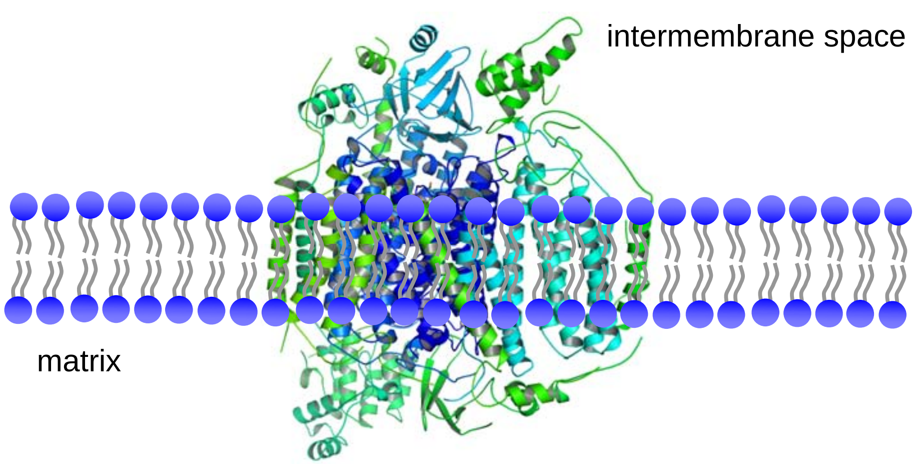
Transfer of electrons from cytochrome C to complex IV



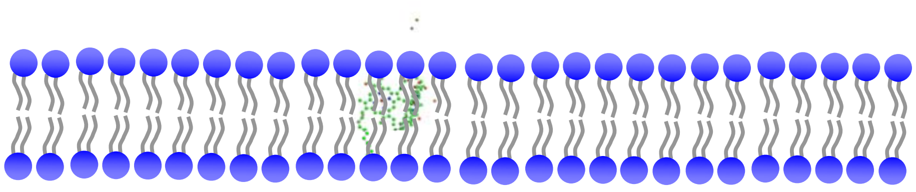
Complex IV: cytochrome oxidase dimer



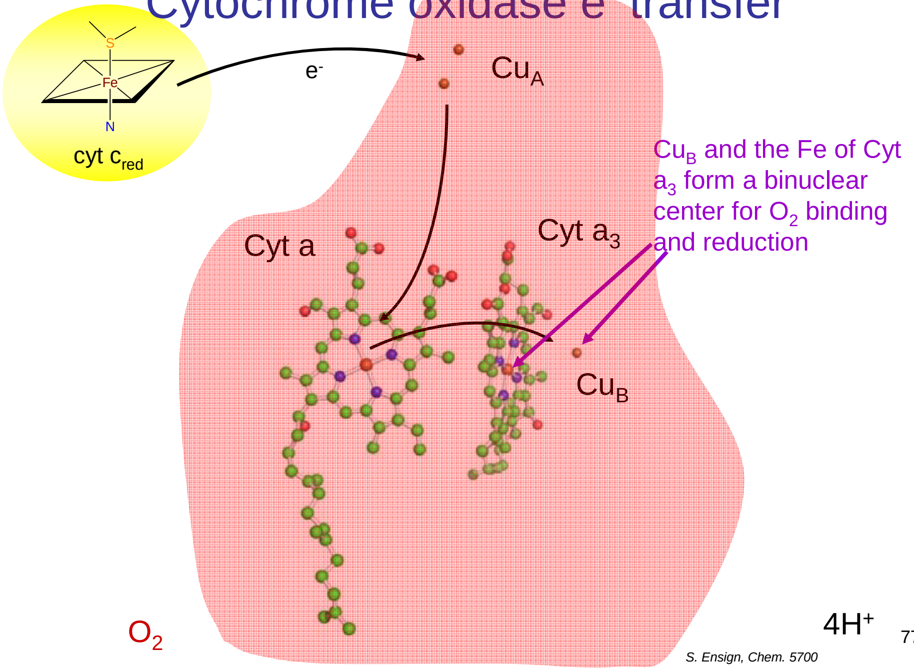
Cytochrome oxidase monomer



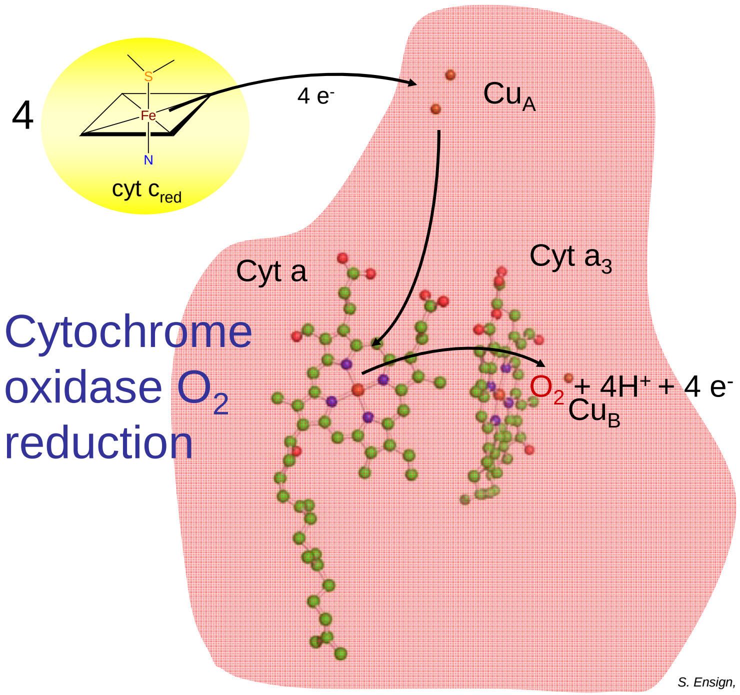
Cytochrome oxidase cofactors



Cytochrome oxidase e⁻ transfer



Cytochrome oxidase O_2 reduction



$O_2 + 4H^+ + 4\ e^- \rightarrow 2\ H_2O$

Mechanism of O_2 reduction by cytochrome oxidase

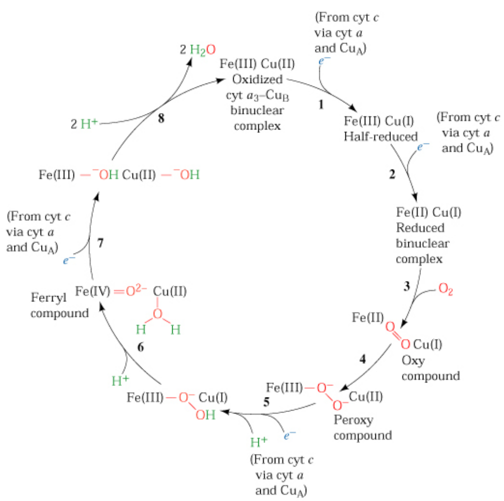


Figure 17-17. The cytochrome *c* oxidase reaction. [Modified from Vartosis, C., Zhang, Y., Appelman, E.H., and Babcock, G.T., *Proc. Natl. Acad. Sci.* 90, 240 (1993).]

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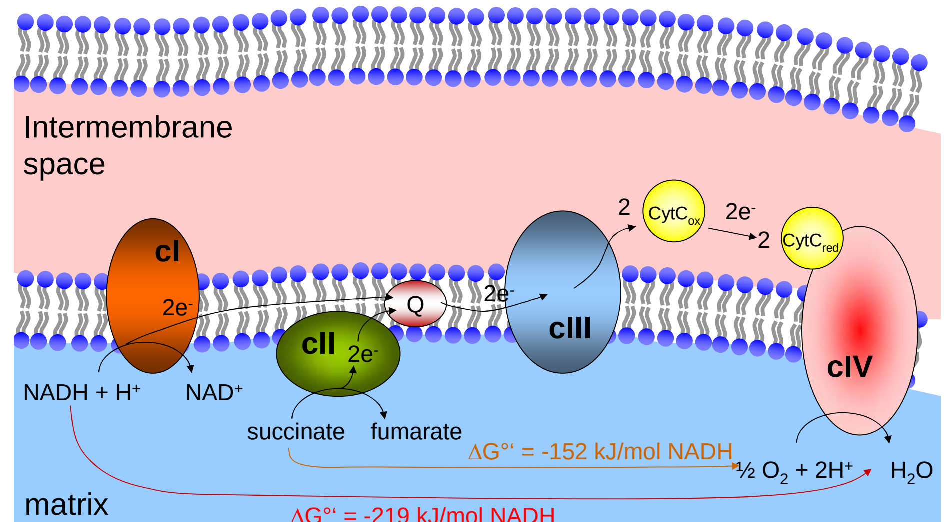
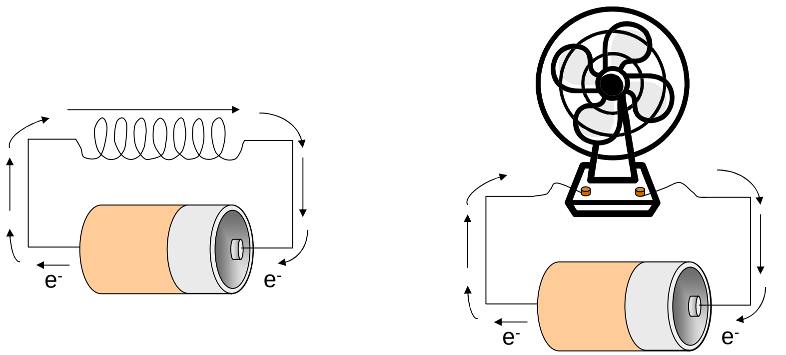
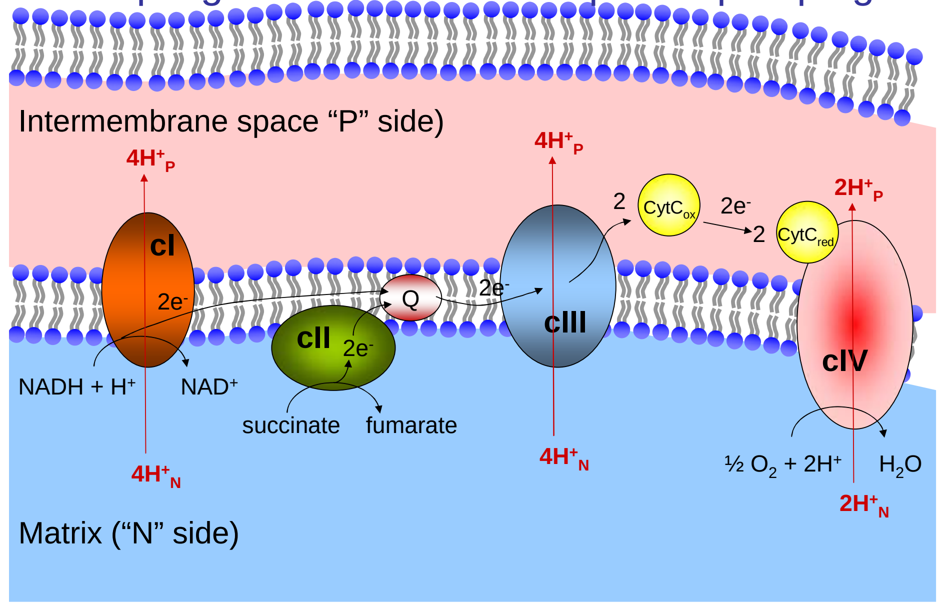
Summary of pathway of electron transfer from NADH or succinate to O_2 (shown per two electrons transferred)



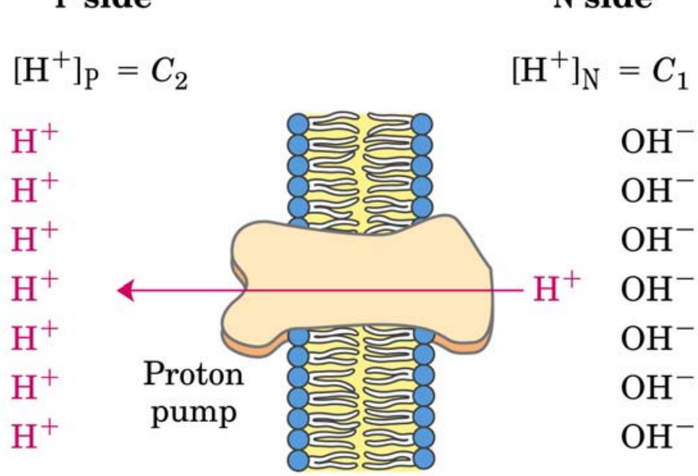
How is the free energy released during electron transfer to O_2 conserved and used to synthesize ATP?



Complexes I, III, and IV are also proton pumps, coupling electron transfer to proton pumping



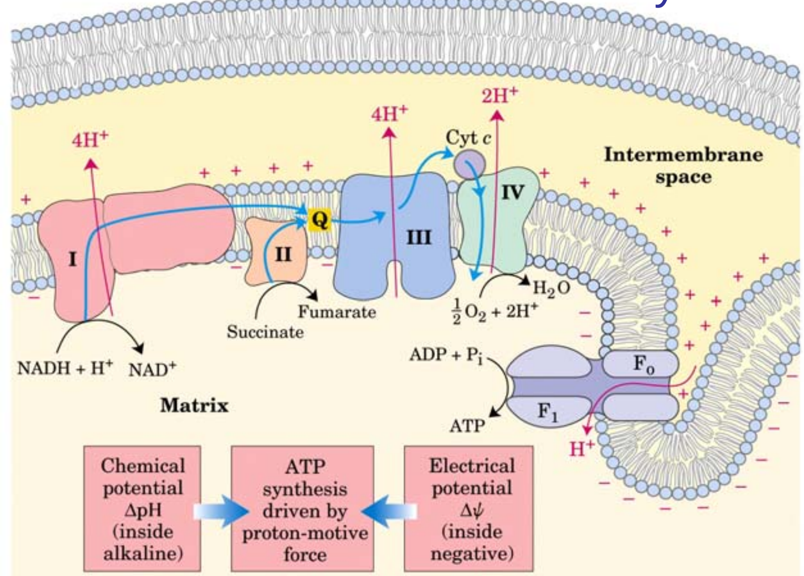
The transmembrane "proton motive force"



$$\Delta G = RT \ln (C_2/C_1) + Z\mathcal{F}\Delta\psi$$

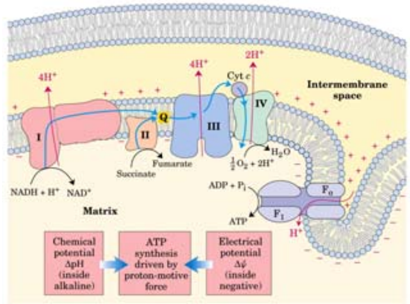
Chemical potential $= 2.3RT\,\boxed{\Delta\mathrm{pH}} + \mathcal{F}\boxed{\Delta\psi}$ electrical potential

The Chemiosmotic Theory

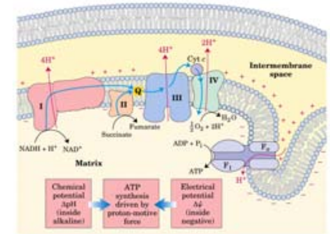


The Chemiosmotic Theory

- How many protons are pumped into the innermembrane space during electron transfer?
  - Complex I → complex IV
  - Complex II → complex IV
- How many protons are moved back into the matrix to make a single ATP?



Keeping track of proton movement



Complex I: (two electron inventory)
Net Reaction: $NADH + Q + H^+ \rightarrow NAD^+ + QH_2$
Proton Inventory reaction: $NADH + Q + 5H^+_N \rightarrow NAD^+ + QH_2 + 4H^+_P$

Complex II: (two electron inventory)
Net Reaction: Succinate $+ Q \rightarrow$ fumarate $+ QH_2$
Proton Inventory reaction: $C_4H_2H_2O_4^{2-} + Q \rightarrow C_4H_2O_4^{2-} + QH_2$

Complex III: (two electron inventory)
Net Reaction: $QH_2 + 2CytC_{ox} \rightarrow Q + 2CytC_{red} + 2H^+$
Proton Inventory reaction: $QH_2 + 2CytC_{ox} + 2H^+_N \rightarrow Q + 2CytC_{red} + 4H^+_P$

Complex IV: (two electron inventory)
Net Reaction: $2CytC_{red} + ½ O_2 + 2H^+ \rightarrow 2CytC_{ox} + H_2O$
Proton Inventory reaction: $2CytC_{red} + ½ O_2 + 4H^+_N \rightarrow 2CytC_{ox} + H_2O + 2H^+_P$

Complex I: (two electron inventory)
Net Reaction: $NADH + Q + H^+ \rightarrow NAD^+ + QH_2$
Proton Inventory reaction: $NADH + Q + 5H^+_N \rightarrow NAD^+ + QH_2 + 4H^+_P$

Complex II: (two electron inventory)
Net Reaction: Succinate $+ Q \rightarrow$ fumarate $+ QH_2$
Proton Inventory reaction: $C_4H_2H_2O_4^{2-} + Q \rightarrow C_4H_2O_4^{2-} + QH_2$
Complex III: (two electron inventory)
Net Reaction: $QH_2 + 2CytC_{ox} \rightarrow Q + 2CytC_{red} + 2H^+$
Proton Inventory reaction: $QH_2 + 2CytC_{ox} + 2H^+_N \rightarrow Q + 2CytC_{red} + 4H^+_P$

Complex IV: (two electron inventory)
Net Reaction: $2CytC_{red} + ½ O_2 + 2H^+ \rightarrow 2CytC_{ox} + H_2O$
Proton Inventory reaction: $2CytC_{red} + ½ O_2 + 4H^+_N \rightarrow 2CytC_{ox} + H_2O + 2H^+_P$

Overall reaction with NADH:
Net: $NADH + ½ O_2 + H^+ \rightarrow NAD^+ + H_2O$
Proton Inventory rxn: $NADH + ½ O_2 + H^+ + 10H^+_N \rightarrow NAD^+ + H_2O + 10H^+_P$

Overall reaction with succinate:
Net: $C_4H_4O_4^{2-} + ½ O_2 \rightarrow C_4H_2O_4^{2-} + H_2O$
Proton Inventory rxn: $C_4H_2H_2O_4^{2-} + ½ O_2 + 6\ H^+_N \rightarrow C_4H_2O_4^{2-} + H_2O + 6H^+_P$

Keeping track of proton movement

Overall reaction with NADH:
Net: $NADH + ½ O_2 + H^+ \rightarrow NAD^+ + H_2O$
Proton Inventory rxn: $NADH + ½ O_2 + H^+ + 10H^+_N \rightarrow NAD^+ + H_2O + 10H^+_P$

Overall reaction with succinate:
Net: $C_4H_4O_4^{2-} + ½ O_2 \rightarrow C_4H_2O_4^{2-} + H_2O$
Proton Inventory rxn: $C_4H_2H_2O_4^{2-} + ½ O_2 + 6\ H^+_N \rightarrow C_4H_2O_4^{2-} + H_2O + 6H^+_P$

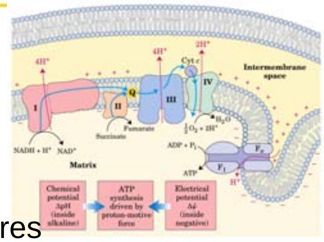
- Electron transfer from NADH results in removal of 12 hydrogen atoms from the mitochondrial matrix, with 10 of the hydrogens being pumped as H^+ into the intermembrane space
- Electron transfer from succinate results in removal of 8 hydrogen atoms from the mitochondrial matrix, with 6 of the hydrogens being pumped as H^+ into the intermembrane space

table 19–4

Some Agents That Interfere with Oxidative Phosphorylation or Photophosphorylation

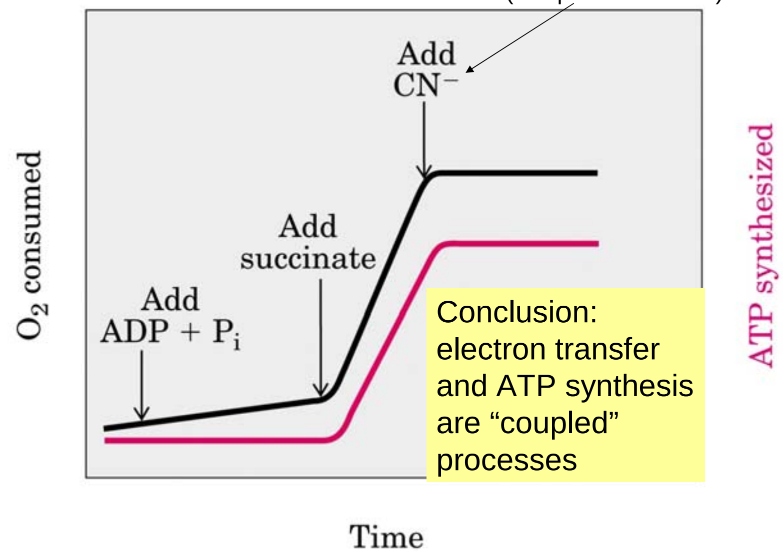
Type of interference	Compound*	Target/mode of action
Inhibition of electron transfer	Cyanide Carbon monoxide	Inhibit cytochrome oxidase
	Antimycin A	Blocks electron transfer from cytochrome *b* to cytochrome c_1
	Myxothiazol Rotenone Amytal Piericidin A	Prevent electron transfer from Fe-S center to ubiquinone
	DCMU	Competes with Q_B for binding site in PSII
Inhibition of ATP synthase	Aurovertin	Inhibits F_1
	Oligomycin Venturicidin	Inhibit F_o and CF_o
	DCCD	Blocks proton flow through F_o and CF_o
Uncoupling of phosphorylation from electron transfer	FCCP DNP	Hydrophobic proton carriers
	Valinomycin	K^+ ionophore
	Thermogenin	Forms proton-conducting pores in inner membrane of brown fat mitochondria
Inhibition of ATP-ADP exchange	Atractyloside	Inhibits adenine nucleotide translocase

*DCMU is 3-(3,4-dichlorophenyl)-1,1-dimethylurea; DCCD, dicyclohexylcarbodiimide; FCCP, cyanide-*p*-trifluoromethoxyphenylhydrazone; DNP, 2,4-dinitrophenol.

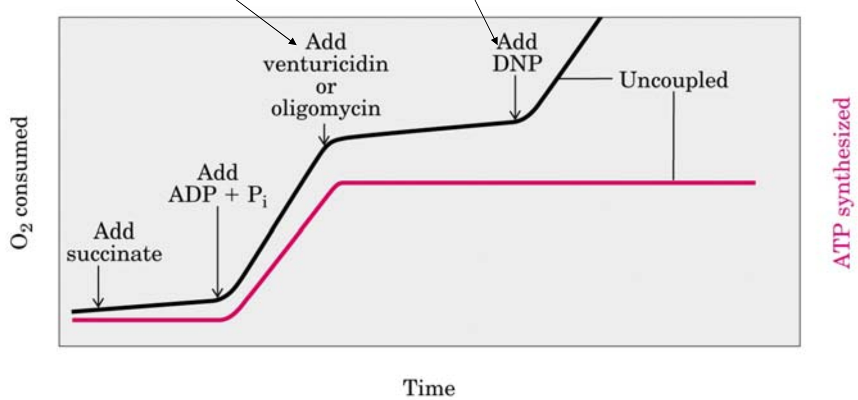


- Electron transfer chain inhibitors
- ATP synthesis inhibitors
- Uncouplers: protonophores and ionophores

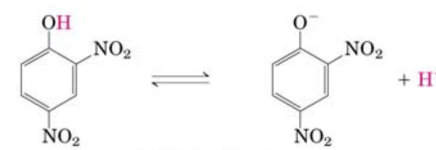
Measurement of O_2 consumption and ATP synthesis in isolated mitochondrial suspensions



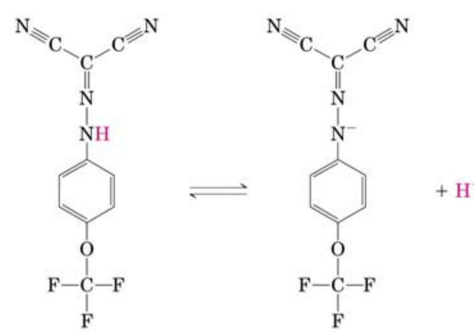
Conclusion: electron transfer and ATP synthesis are “coupled” processes



Conclusion: Electron transfer and ATP synthesis can be “uncoupled” by a protonophore

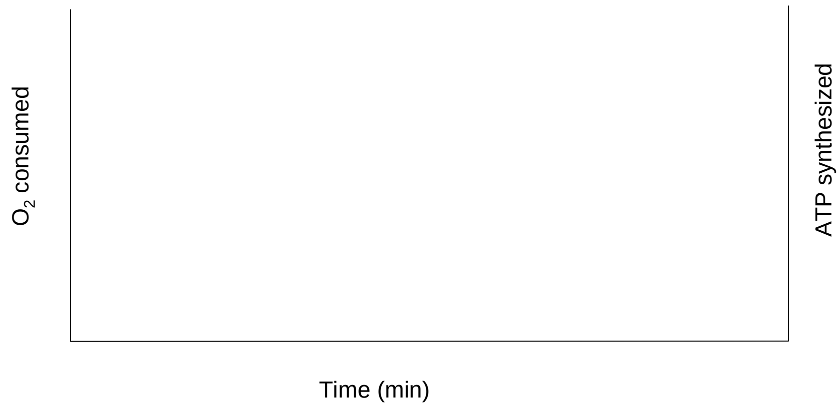


2,4-Dinitrophenol (DNP)

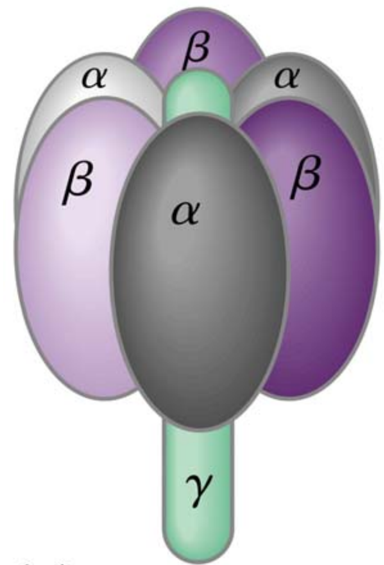


Carbonylcyanide-*p*-trifluoromethoxyphenylhydrazone (FCCP)

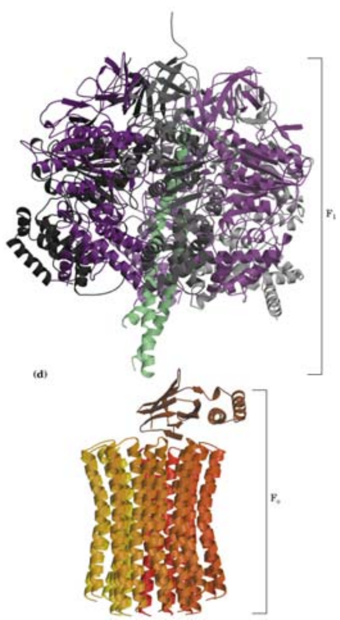
What would happen to succinate-dependent O_2 consumption and ATP synthesis in the presence of a potassium ionophore?



The core subunits of the ATP synthase F1 component



(a)



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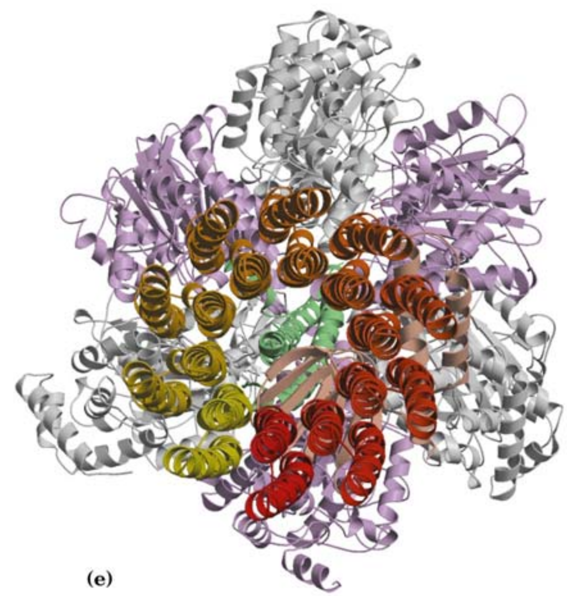

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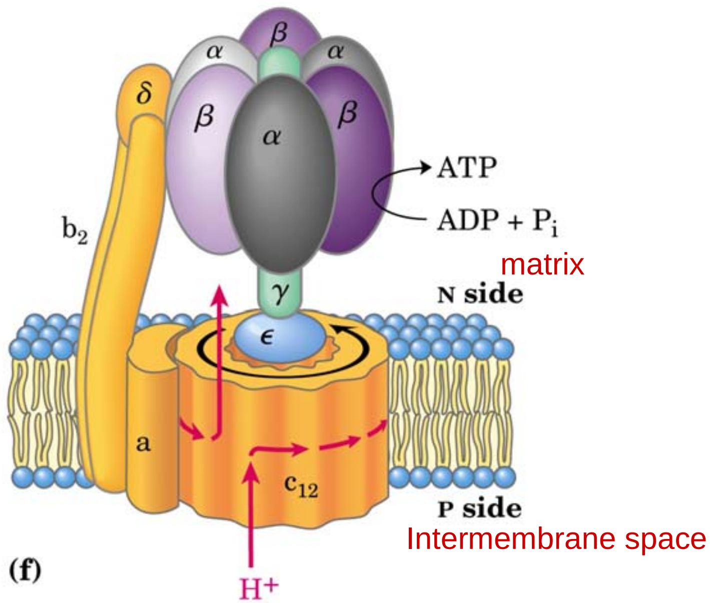
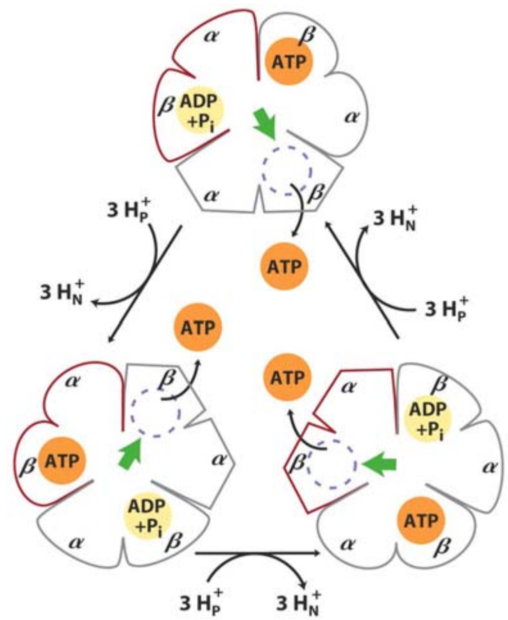
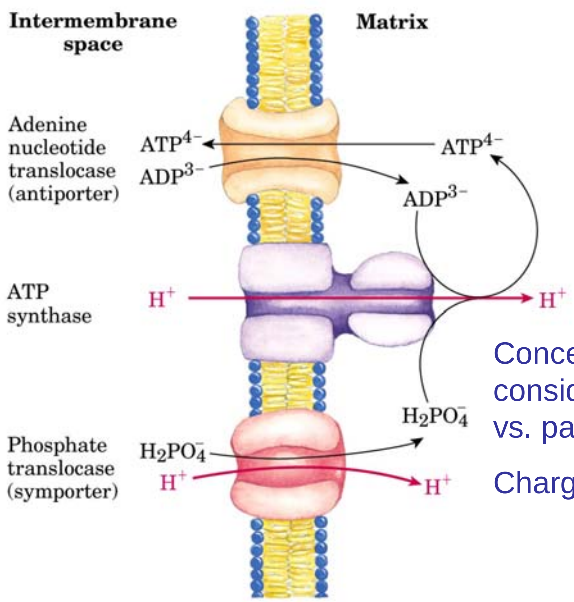




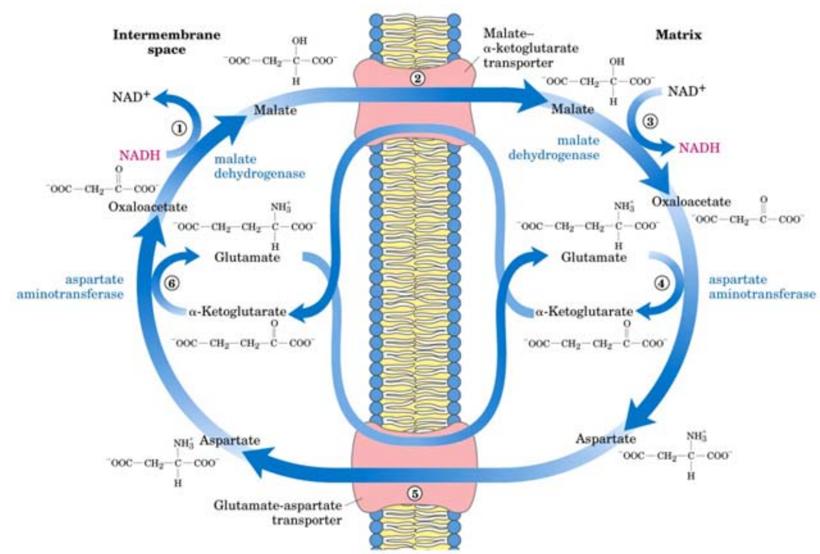
Transport of mitochondrial ATP to the cytosol



Concentration considerations (active vs. passive)?

Charge considerations?

"Transport" of cytosolic NADH to the mitochondrion: The malate-aspartate shuttle



“Transport” of cytosolic NADH to the mitochondrion: The glycerol-3-phosphate shuttle

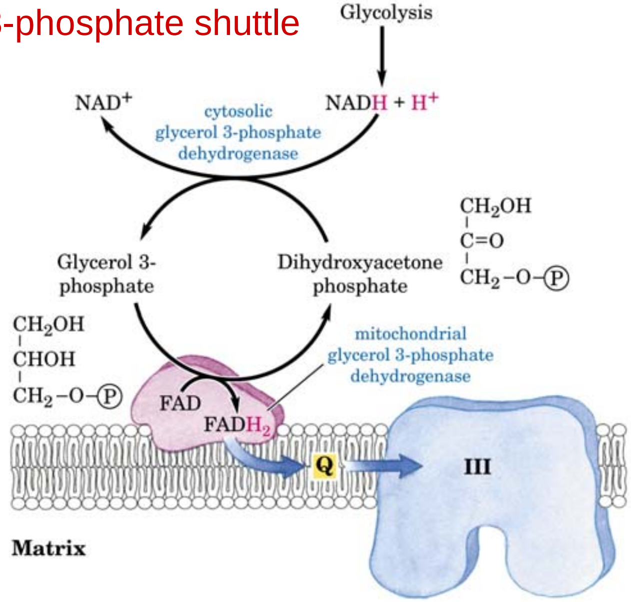
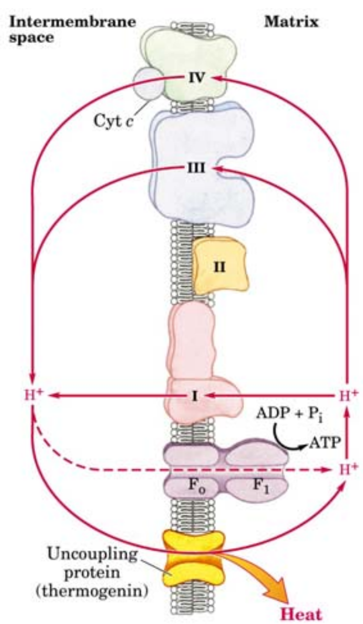


table 19–5

ATP Yield from Complete Oxidation of Glucose

Process	Direct product	Final ATP
Glycolysis	2 NADH (cytosolic)	3 or 5*
	2 ATP	2
Pyruvate oxidation (two per glucose)	2 NADH (mitochondrial matrix)	5
Acetyl-CoA oxidation in citric acid cycle (two per glucose)	6 NADH (mitochondrial matrix)	15
	2 $FADH_2$	3
	2 ATP or 2 GTP	2
Total yield per glucose		30 or 32

*The number depends on which shuttle system transfers reducing equivalents into mitochondria.



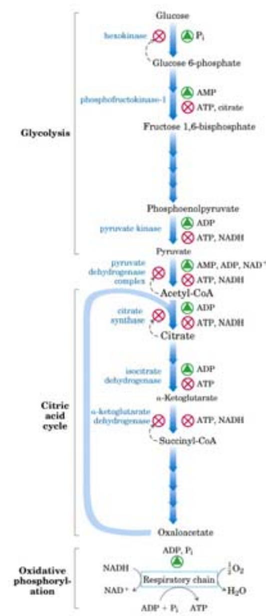


table 19–6

Respiratory Proteins Encoded by the Human Mitochondrial Chromosome

Complex	Total number of subunits	Number of subunits encoded by mitochondrial DNA
I NADH dehydrogenase	>25	7
II Succinate dehydrogenase	4	0
III Ubiquinone:cytochrome *c* oxidoreductase	9	1
IV Cytochrome oxidase	13	3
V ATP synthase	12	2