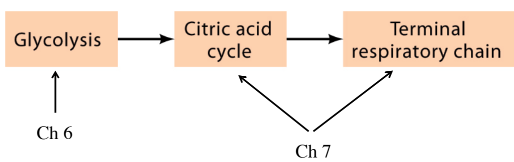
Section 7.6

Biological Oxidations: VERY succinct overview

I. Degradation of glucose



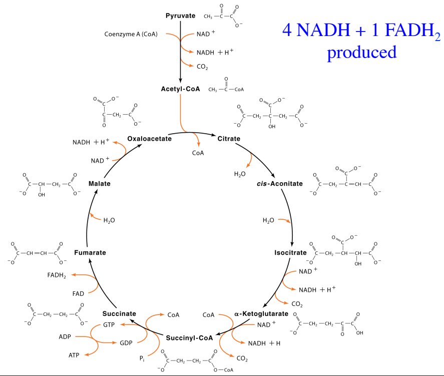
Most of you (not all) have seen this in great detail in Biochemistry. Here we will just give an overview, focusing on the physical chemistry aspects.

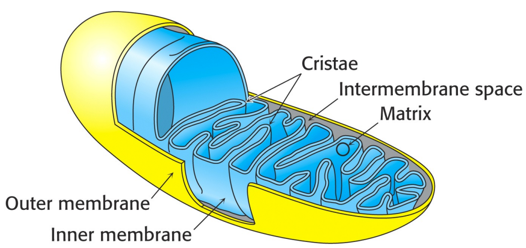
An overview

- Oxidative phosphorylation transforms the NADH and $FADH_2$ produced in the citric acid cycle, glycolysis, or fatty acid oxidation into energy
- The NADH and $FADH_2$ is used to reduce oxygen to water
- During the reduction process protons are transferred from one side of a mitochondrial membrane to the other creating a proton gradiant
- The H^+ gradient is then used to produce ATP

Citric Acid Cycle

4 NADH + 1 $FADH_2$ produced





Oxidative phosphorylation takes place on the inside of the inner membrane of the mitochondria (N side of inner membrane). The inner membrane is impermeable but has specific transporters. The outer membrane is permeable to most small molecules and ions

Electron carriers function in multienzyme complexes

- The electron carriers of the respiratory chain are organized into four membrane-embedded supramolecular complexes: complex I, II, III, & IV.
- These complexes can be physically separated.
- Complexes I and II catalyze electron transfer to ubiquinone from two different electron donors: NADH (complex I) and succinate (complex II);
- Complex III carries electrons from ubiquinone to cytochrome c;
- Complex IV completes the sequence by transferring electrons from cytochrome c to O_2.

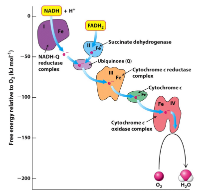
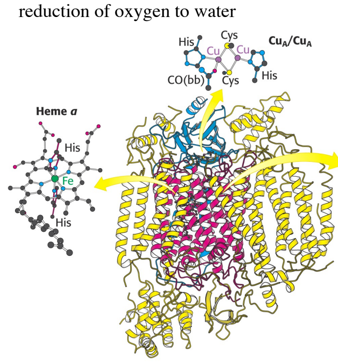


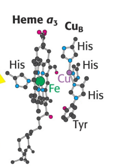
Table 18.2 Components of the mitochondrial electron-transport chain

				Oxidant or reductant		
Enzyme complex	Mass (kd)	Subunits	Prosthetic group	Matrix side	Membrane core	Cytoplasmic side
NADH-Q oxidoreductase	>900	46	FMN Fe-S	NADH	Q	
Succinate-Q reductase	140	4	FAD Fe-S	Succinate	Q	
Q-cytochrome *c* oxidoreductase	250	11	Heme b_H Heme b_L Heme c_1 Fe-S		Q	Cytochrome *c*
Cytochrome *c* oxidase	160	13	Heme *a* Heme a_3 Cu_A and Cu_B			Cytochrome *c*

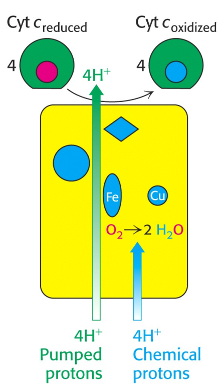
Sources: J. W. DePierre and L. Ernster. *Annu. Rev. Biochem.* 46(1977):215; Y. Hatefi. *Annu Rev. Biochem.* 54(1985);1015; and J. E. Walker. *Q. Rev. Biophys.* 25(1992):253.

Cytochrome c oxidase (also called complex IV) catalyzes the reduction of oxygen to water





It has two non-covalently attached heme groups and three copper ions.

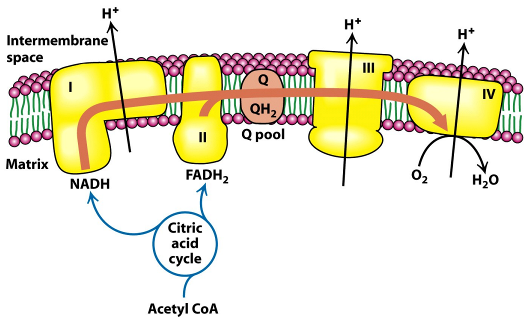


Big picture

Cytochrome c oxidase also manages to pump 4 more protons across the membrane in the process for a total of **8 protons** removed from matrix

4Cyt c_{red} + $8H^+_{matrix}$ + O_2 goes to 4Cyt c_{ox} + $2H_2O$ + $4H^+_{cytosol}$

Summary



Respiratory chain

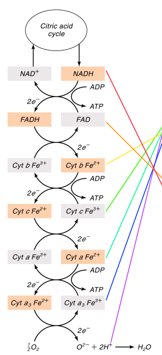
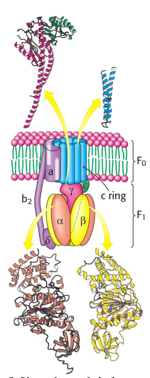


Table 20.1

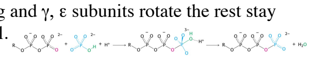
Standard Reduction Potentials for Several Biological Reduction Half-Reactions

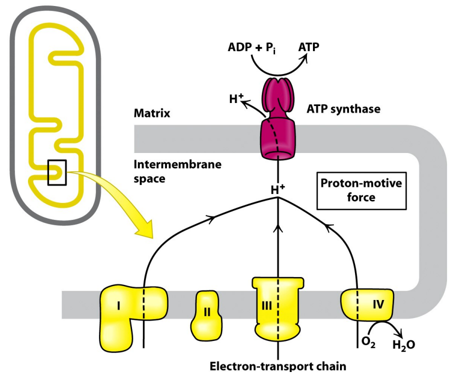
Reduction Half-Reaction	$\mathscr{E}_o'$ (V)
$\frac{1}{2}O_2 + 2 H^+ + 2 e^- \longrightarrow H_2O$	0.816
$Fe^{3+} + e^- \longrightarrow Fe^{2+}$	0.771
Photosystem P700	0.430
$NO_3^- + 2 H^+ + 2 e^- \longrightarrow NO_2^- + H_2O$	0.421
Cytochrome $f(Fe^{3+}) + e^- \longrightarrow$ cytochrome $f(Fe^{2+})$	0.365
Cytochrome $a_3(Fe^{3+}) + e^- \longrightarrow$ cytochrome $a_3(Fe^{2+})$	0.350
Cytochrome $a(Fe^{3+}) + e^- \longrightarrow$ cytochrome $a(Fe^{2+})$	0.290
Rieske Fe-S$(Fe^{3+}) + e^- \longrightarrow$ Rieske Fe-S(Fe^{2+})	0.280
Cytochrome $c\ (Fe^{3+}) + e^- \longrightarrow$ cytochrome $c\ (Fe^{2+})$	0.254
Cytochrome $c_1(Fe^{3+}) + e^- \longrightarrow$ cytochrome $c_1(Fe^{2+})$	0.220
$UQH\cdot + H^+ + e^- \longrightarrow UQH_2$ (UQ = coenzyme Q)	0.190
$UQ + 2 H^+ + 2 e^- \longrightarrow UQH_2$	0.060
Cytochrome $b_H(Fe^{3+}) + e^- \longrightarrow$ cytochrome $b_H(Fe^{2+})$	0.050
Fumarate $+ 2 H^+ + 2 e^- \longrightarrow$ succinate	0.031
$UQ + H^+ + e^- \longrightarrow UQH\cdot$	0.030
Cytochrome $b_5(Fe^{3+}) + e^- \longrightarrow$ cytochrome $b_5\ (Fe^{2+})$	0.020
$[FAD] + 2 H^+ + 2 e^- \longrightarrow [FADH_2]$	0.003–0.091*
Cytochrome $b_L(Fe^{3+}) + e^- \longrightarrow$ cytochrome $b_L(Fe^{2+})$	−0.100
Oxaloacetate $+ 2 H^+ + 2 e^- \longrightarrow$ malate	−0.166
Pyruvate $+ 2 H^+ + 2 e^- \longrightarrow$ lactate	−0.185
Acetaldehyde $+ 2 H^+ + 2 e^- \longrightarrow$ ethanol	−0.197
$FMN + 2 H^+ + 2 e^- \longrightarrow FMNH_2$	−0.219
$FAD + 2 H^+ + 2 e^- \longrightarrow FADH_2$	−0.219
Glutathione (oxidized) $+ 2 H^+ + 2 e^- \longrightarrow$ 2 glutathione (reduced)	−0.230
Lipoic acid $+ 2 H^+ + 2 e^- \longrightarrow$ dihydrolipoic acid	−0.290
1,3-Bisphosphoglycerate $+ 2 H^+ + 2 e^- \longrightarrow$ glyceraldehyde-3-phosphate $+ P_i$	−0.290
$NAD^+ + 2 H^+ + 2 e^- \longrightarrow NADH + H^+$	−0.320
$NADP^+ + 2 H^+ + 2 e^- \longrightarrow NADPH + H^+$	−0.320
Lipoyl dehydrogenase $[FAD] + 2 H^+ + 2 e^- \longrightarrow$ lipoyl dehydrogenase $[FADH_2]$	−0.340
α-Ketoglutarate $+ CO_2 + 2 H^+ + 2 e^- \longrightarrow$ isocitrate	−0.380
$2 H^+ + 2 e^- \longrightarrow H_2$	−0.421
Ferredoxin (spinach) $(Fe^{3+}) + e^- \longrightarrow$ ferredoxin (spinach) (Fe^{2+})	−0.430
Succinate $+ CO_2 + 2 H^+ + 2 e^- \longrightarrow \alpha$-ketoglutarate $+ H_2O$	−0.670



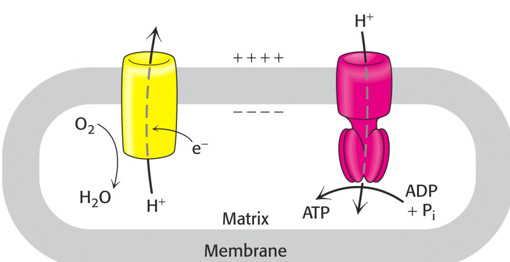
Mitochondrial matrix

Structure of ATP synthase. The F_1 contains 3α, 3β, γ, δ, ε subunits. The α and β subunits alternate in a hexameric ring. The β subunit participates in catalysis.The center consists of γ, ε subunits which breaks the symmetry of the hexameric ring.
F_0 contains a proton channel. The 10-14 **c** subunits are embedded in the membrane as a ring. The **a** subunit is on the outside and both **a** and **c** are important for the channel. The F_0 and F_1 are connected through the γ, ε subunits and the **a**, **b**, δ subunits. The **c** ring and γ, ε subunits rotate the rest stay still.





Summary



$\Delta G^{o\prime} = -\nu F E^{o\prime}$

Nernst Equation $E = E^o - RT/(\nu F) * \ln K$

$RT/F = 0.0257$ V (at T=298 K)

$$E^{o'} = E^{o'}_{ox} + E^{o'}_{red}$$

$0.5O_2 + 2H^+ + 2e^- \longrightarrow H_2O$ $\quad E_0 = +0.82$ V

$NAD^+ + H^+ + 2e- \longrightarrow NADH$ $\quad E_0 = -0.32$ V

$\Delta G^{o'} = -2 * 96{,}485$ C mol^{-1}$*(+0.82-(-0.32))$ V

$= -220$ kJ/mol $= -52.6$ kcal/mol

How many ATPs??

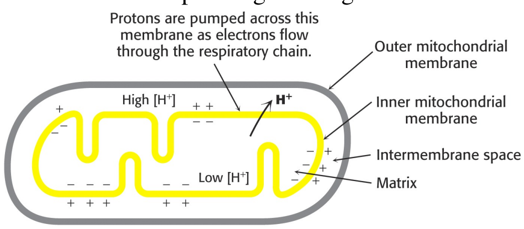
How many protons can you pump accross the membrane with 52.6 cal/mol?

$$\Delta G = RT\ln(c_1/c_2) + ZF\Delta V$$

Where c1 and c2 are the concentrations on the ion on each side of the membrane, Z is the charge on the ion, and ΔV is the potential in volts across the membrane

Under typical conditions the pH inside is 1.4 units lower than outside and the membrane potential is 0.14 V (outside more positive) so ΔG is 5.3 kcal/mol of protons.

How does the proton gradient generate ATP?



$NADH + 0.5O_2 + H^+$ going to $NAD^+ + H_2O$ $\Delta G^{0\prime}$ = -52.6 kcal/mol

10 H^+ transferred H^+_{matrix} going to $H^+_{cytosol}$ ΔG = +5.2 kcal/mol

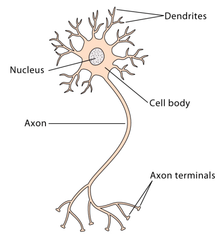
$ADP + P_i + H^+$ going to $ATP + H_2O$ $\Delta G^{0\prime}$ = +7.3 kcal/mol

TABLE 18.4 ATP yield from the complete oxidation of glucose

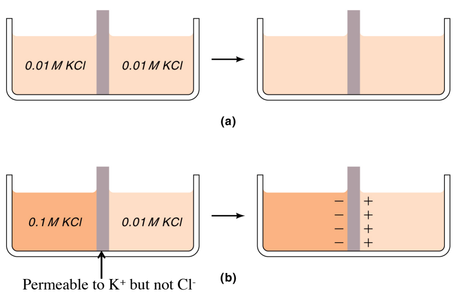
Reaction sequence	ATP yield per glucose molecule
Glycolysis: Conversion of glucose into pyruvate (in the cytosol)	
Phosphorylation of glucose	− 1
Phosphorylation of fructose 6-phosphate	− 1
Dephosphorylation of 2 molecules of 1,3-BPG	+ 2
Dephosphorylation of 2 molecules of phosphoenolpyruvate	+ 2
2 molecules of NADH are formed in the oxidation of 2 molecules of glyceraldehyde 3-phosphate	
Conversion of pyruvate into acetyl CoA (inside mitochondria)	
2 molecules of NADH are formed	
Citric acid cycle (inside mitochondria)	
2 molecules of guanosine triphosphate are formed from 2 molecules of succinyl CoA	+ 2
6 molecules of NADH are formed in the oxidation of 2 molecules each of isocitrate, α-ketoglutarate, and malate	
2 molecules of $FADH_2$ are formed in the oxidation of 2 molecules of succinate	
Oxidative phosphorylation (inside mitochondria)	
2 molecules of NADH formed in glycolysis; each yields 1.5 molecules of ATP (assuming transport of NADH by the glycerol 3-phosphate shuttle)	+ 3
2 molecules of NADH formed in the oxidative decarboxylation of pyruvate; each yields 2.5 molecules of ATP	+ 5
2 molecules of $FADH_2$ formed in the citric acid cycle; each yields 1.5 molecules of ATP	+ 3
6 molecules of NADH formed in the citric acid cycle; each yields 2.5 molecules of ATP	+ 15
NET YIELD PER MOLECULE OF GLUCOSE	+ 30

Source: The ATP yield of oxidative phosphorylation is based on values given in P. C. Hinkle, M. A. Kumar, A. Resetar, and D. L. Harris, *Biochemistry* 30(1991):3576.
Note: The current value of 30 molecules of ATP per molecule of glucose supersedes the earlier one of 36 molecules of ATP. The stoichiometries of proton pumping, ATP synthesis, and metabolite transport should be regarded as estimates. About two more molecules of ATP are formed per molecule of glucose oxidized when the malate–aspartate shuttle rather than the glycerol 3-phosphate shuttle is used.

II. Membrane Potentials: Focus on Neurons, Action Potential



Differential membrane permeability and osmotic pressure lead to membrane potential



Distribution of ions and membrane potential for typical nerve cell

Maintained by active transport

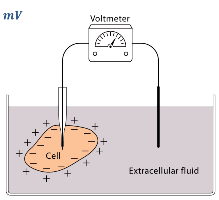
Concentration/mM		
Ion	Intracellular	Extracellular
Na^+	15	150
K^+	150	5
Cl^-	10	110

$$E_{K^+} = E^o_{K^+} - \frac{0.0257\,V}{\nu} ln[K^+]$$

$$\Delta E_{K^+} = E^o_{K^+,in} - E^o_{K^+,ex} = 0.0257\,V \frac{ln[K^+]_{ex}}{ln[K^+]_{in}} = -87\,mV$$

$$\Delta E_{Na^+} = 0.0257\,V \frac{ln[Na^+]_{ex}}{ln[Na^+]_{in}} = 59\,mV$$

Net appears to be only – 28 mV, but differential permeability has been neglected (experiment: -70 mV).



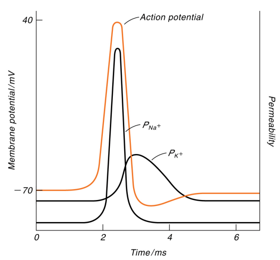
Goldman Equation

Close to measured value of -70 mV

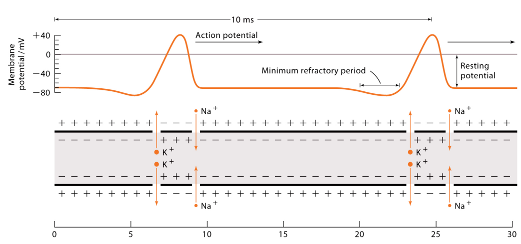
$$E = 0.0257\ V\ ln\frac{[K^+]_{ex}P_{K^+} + [Na^+]_{ex}P_{Na^+} + [Cl^-]_{in}P_{Cl^-}}{[K^+]_{in}P_{K^+} + [Na^+]_{in}P_{Na^+} + [Cl^-]_{ex}P_{Cl^-}} = -81\ mV$$

P_x = membrane permeability of ion

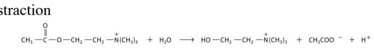
Action potential originates signal



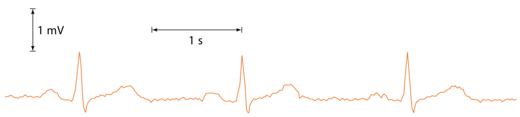
- Depolarization
- Voltage-gated ion channel
- Threshold potential



- Release of neurotrasmitter
- Initial muscle constraction
- …



EKG



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