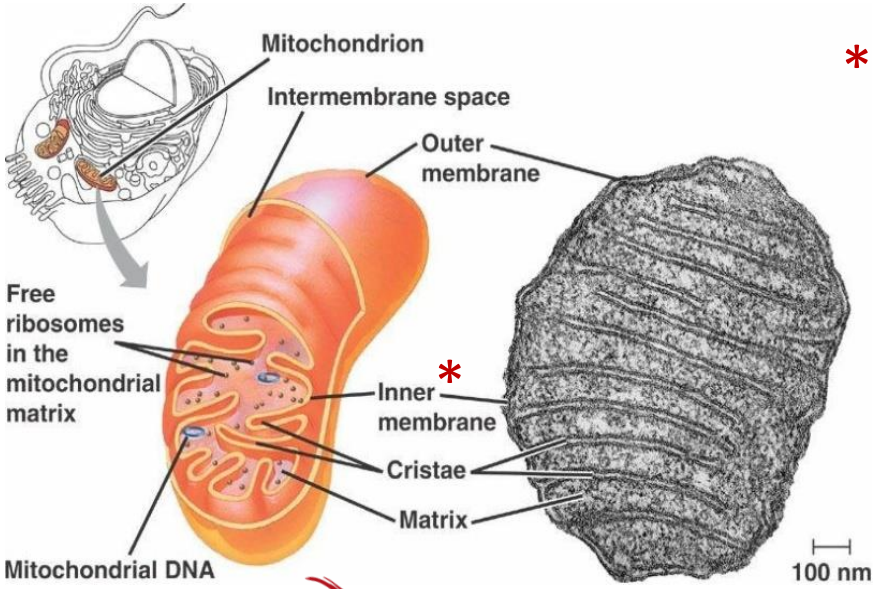
Mitochondria and Diseases

Molecular bases of pathologies - Prof. Francesco Bernardi

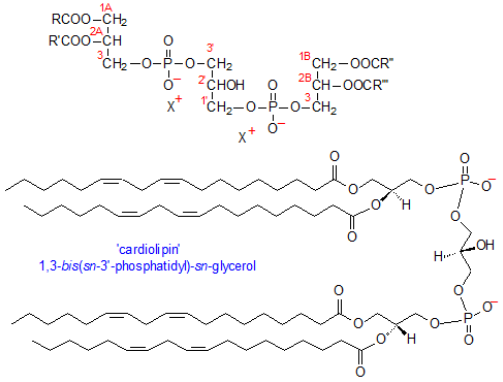
Natascia Caroccia, PhD student

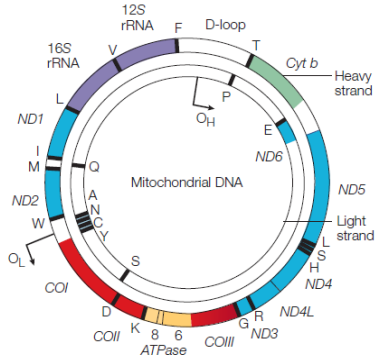
30th November 2017

Mitochondria and energy production



* Cardiolipin

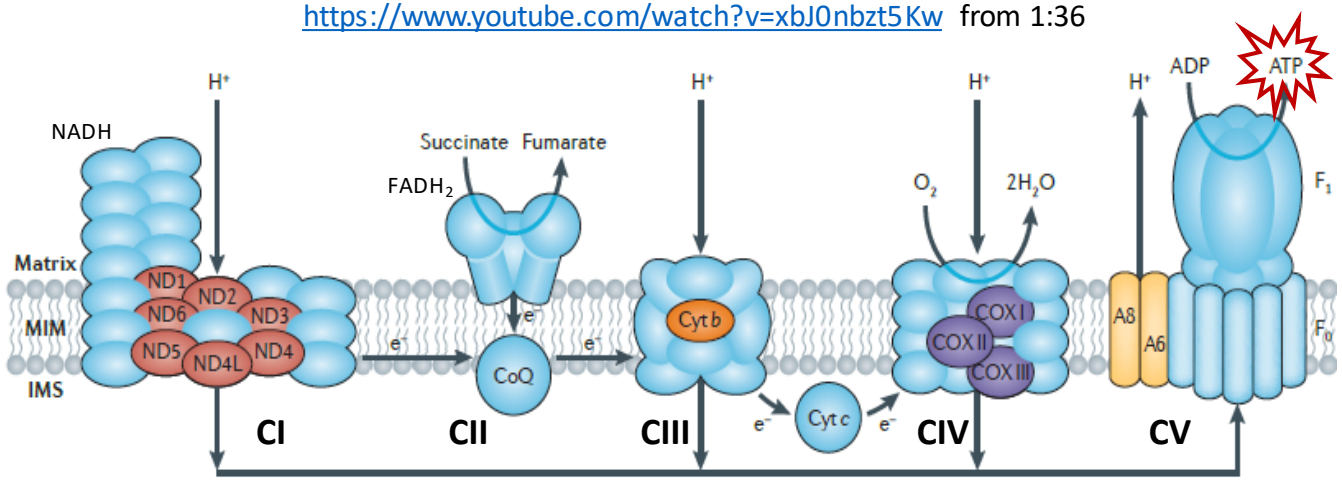




Human mtDNA. Taylor, R.W. and Turnbull, D.M. (2005), *Nature Reviews.*

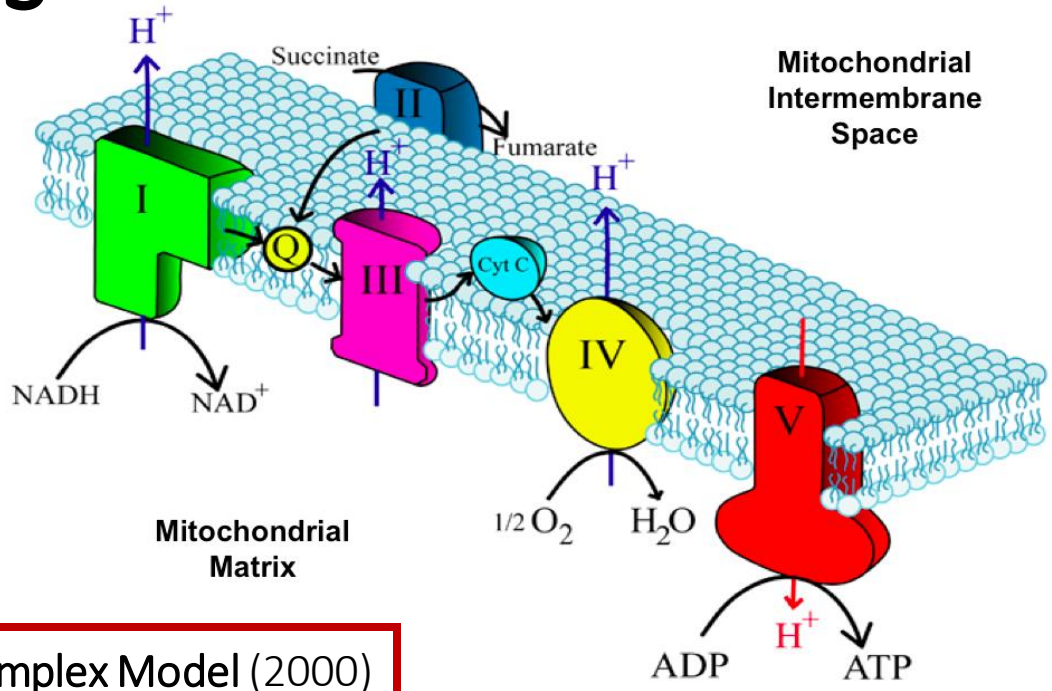
Oxidative phosphorylation (OXPHOS)

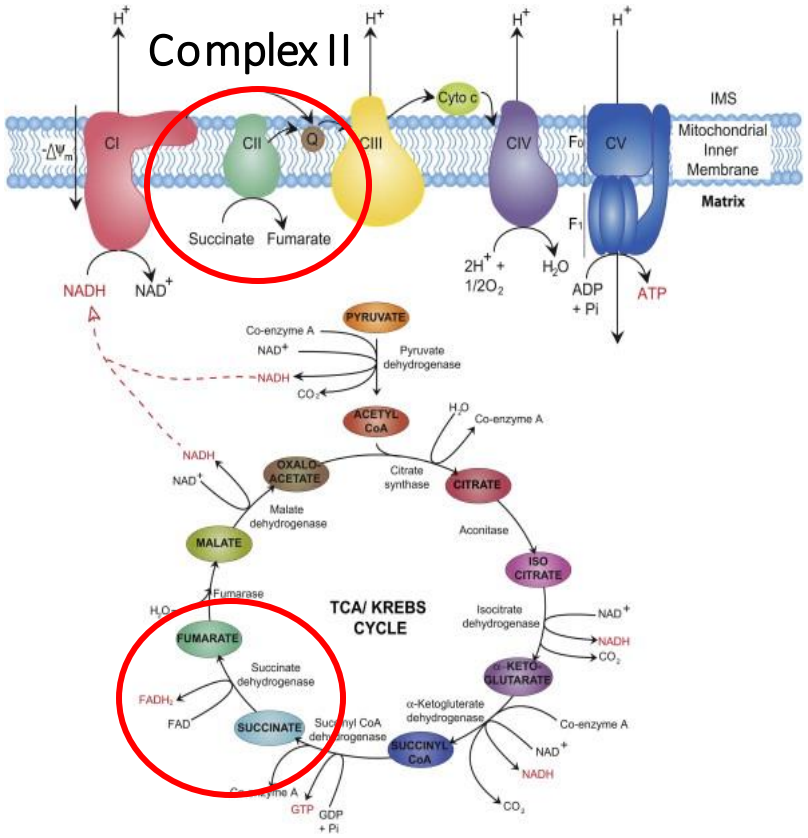
https://www.youtube.com/watch?v=xbJ0nbzt5Kw from 1:36



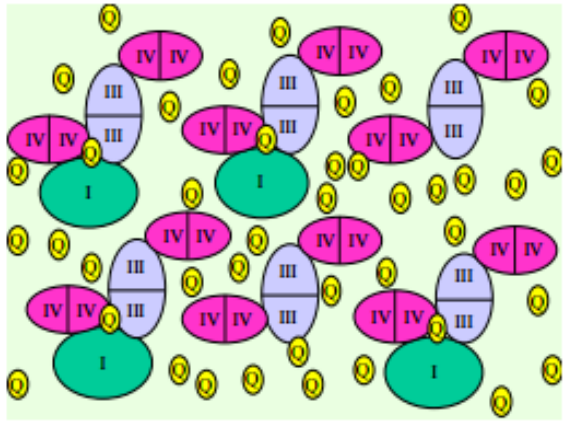
Oxidative phosphorylation. Image modified from Schon et al. (2012), *Nature Reviews*.

Models



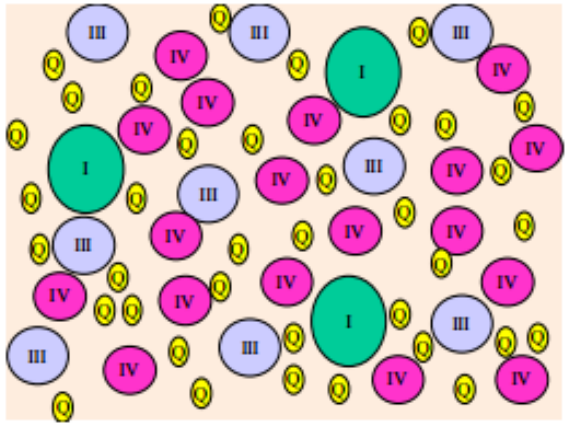


Schagger's **Supercomplex Model** (2000)

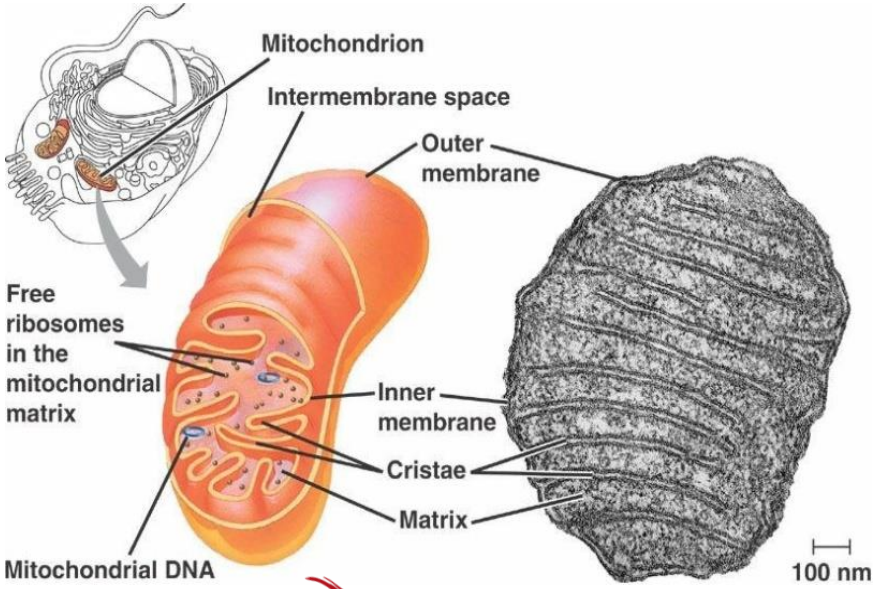


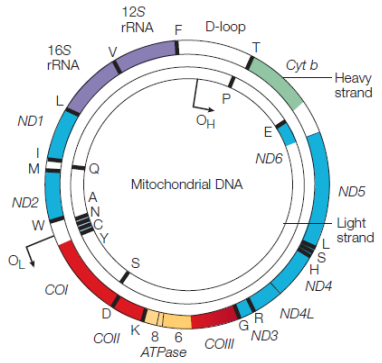
Solid state *vs* Fluid state

Hackenbrock's **Random Collision Model** (1986)



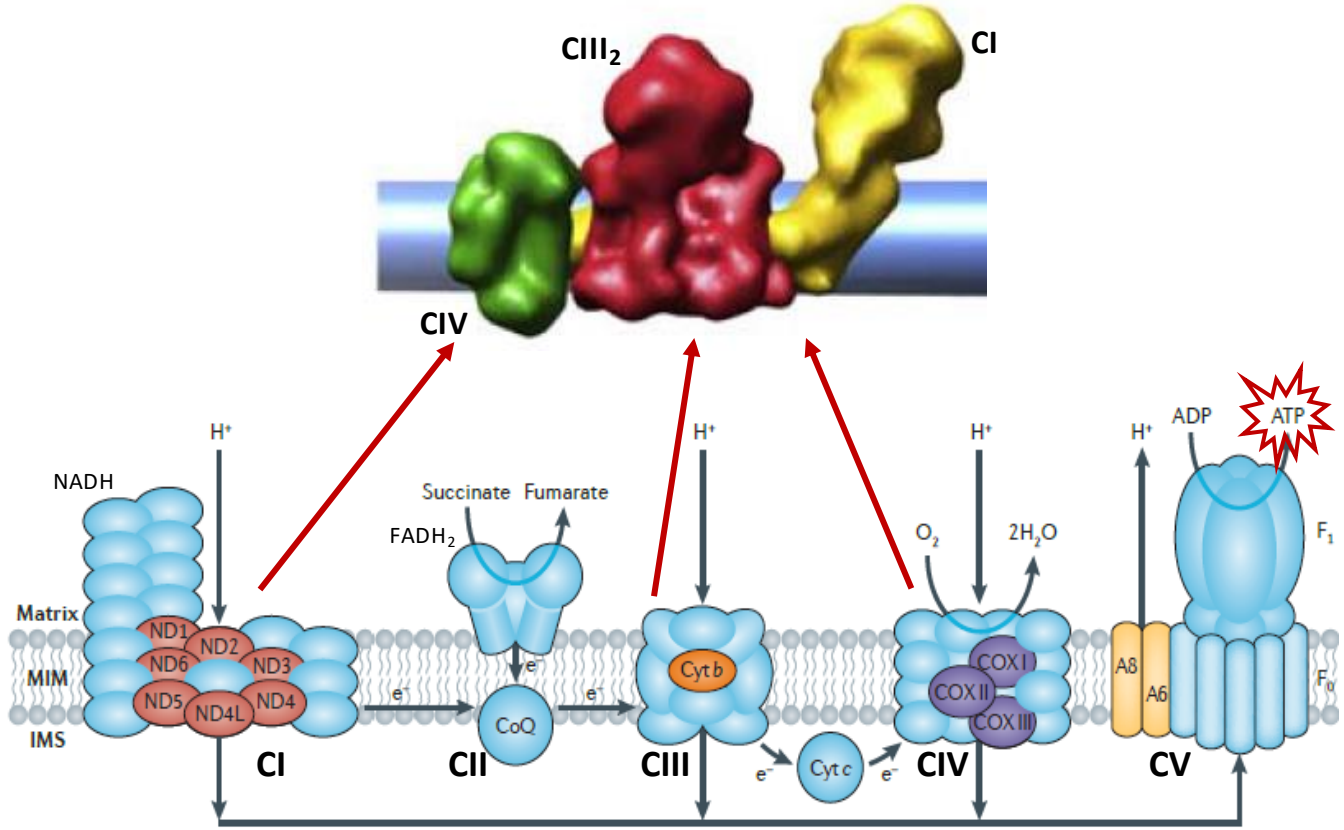
Mitochondria and energy production





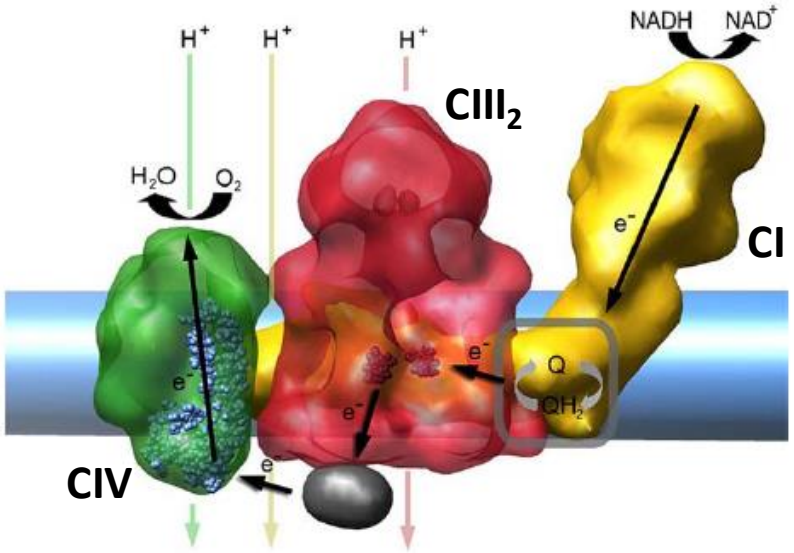
Human mtDNA. Taylor, R.W. and Turnbull, D.M. (2005), *Nature Reviews.*

Supercomplex or Respirasome

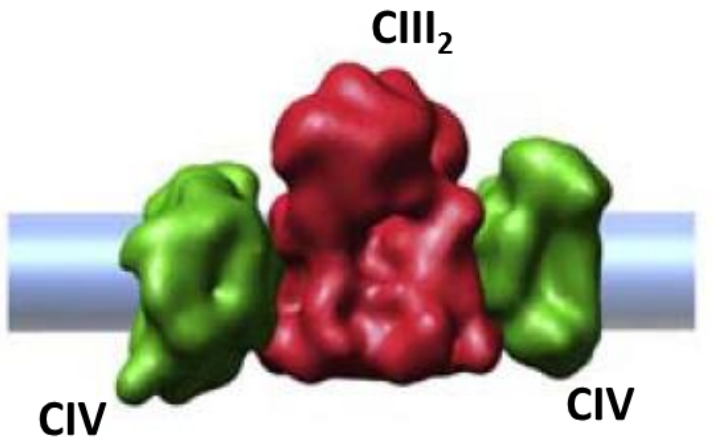


Oxidative phosphorylation. Image modified from Schon et al. (2012), *Nature Reviews*.

Mitochondrial supercomplexes in mammals



High molecular weight supercomplexes
CI_1+$CIII_2$+CIV_n (where n= 0-4)

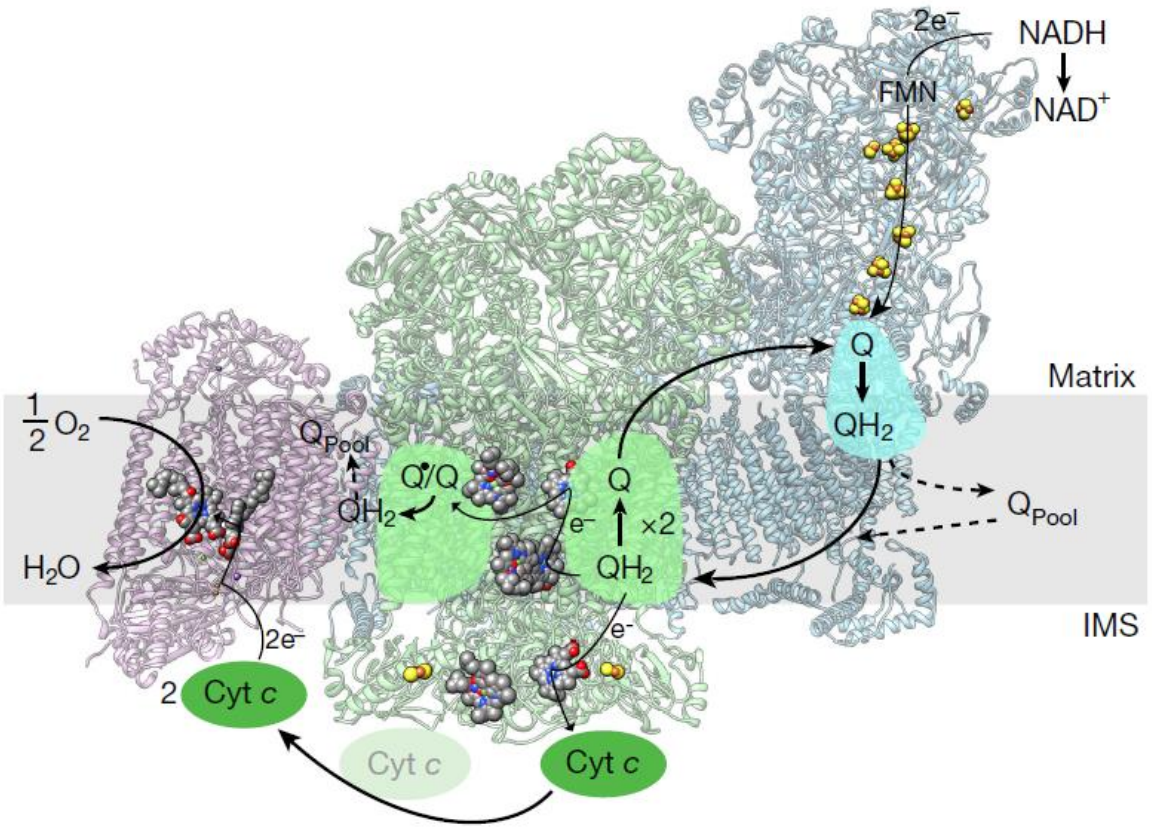


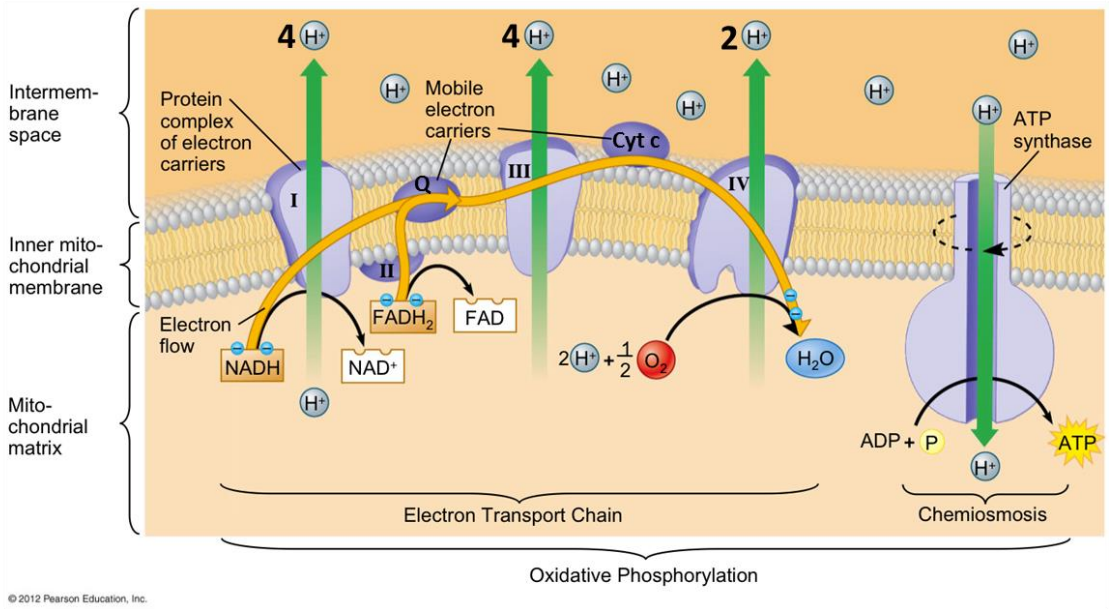
Low molecular weight supercomplexes
$CIII_2$+CIV_n (where n= 1-4)

- **functional advantages**
- **structural advantages**

Images modified from Vonck, J. and Schäfer, E. (2009) *Biochim. Biophys. Acta*

Electron flow through the respirasome

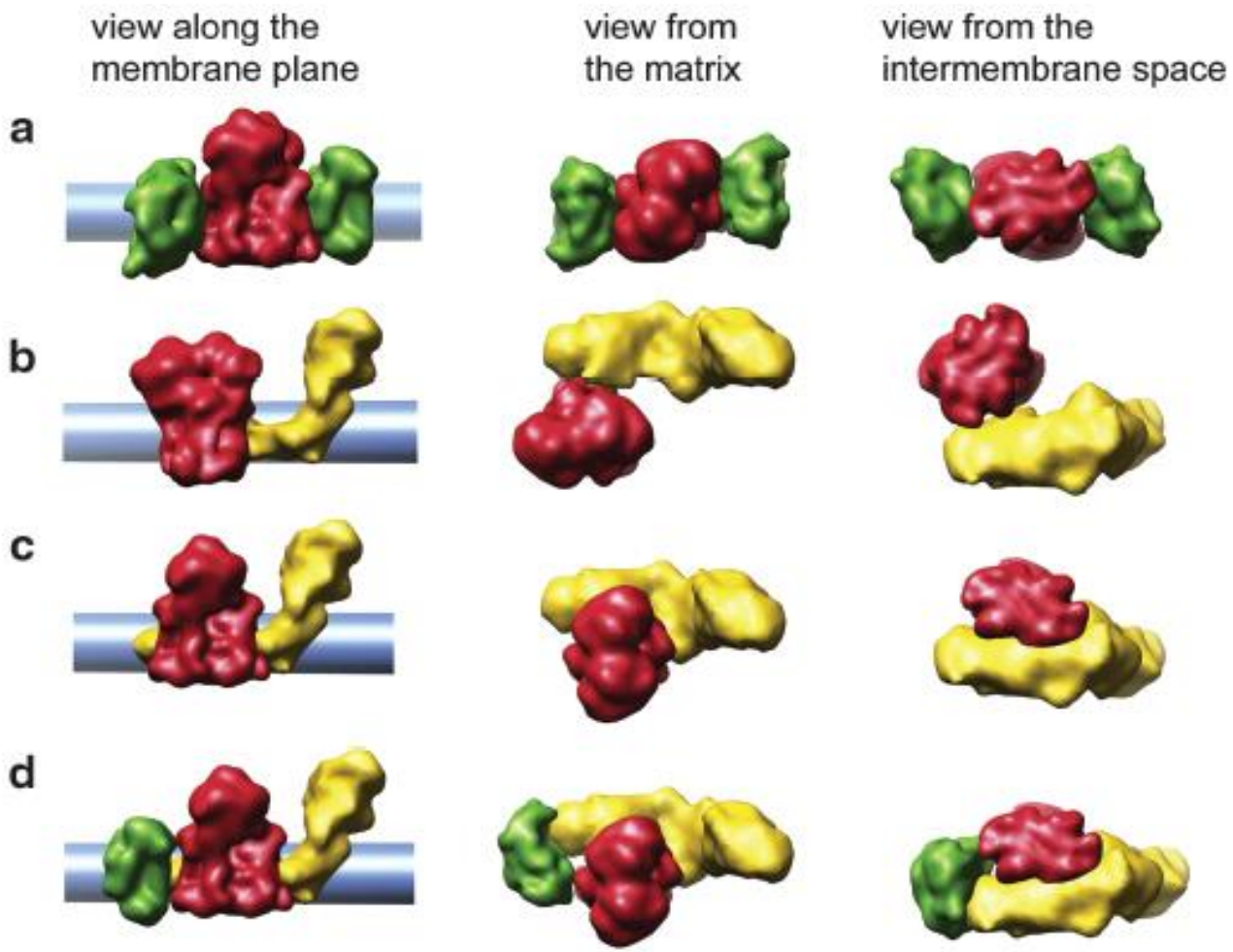




- Substrate channelling
- ROS production

Schematic of electron flow through the tight respirasome. Image from Letts et al. (2016), *Nature*.

Supercomplex models



$CIII_2$+CIV_2 from *Saccharomyces cerevisiae*

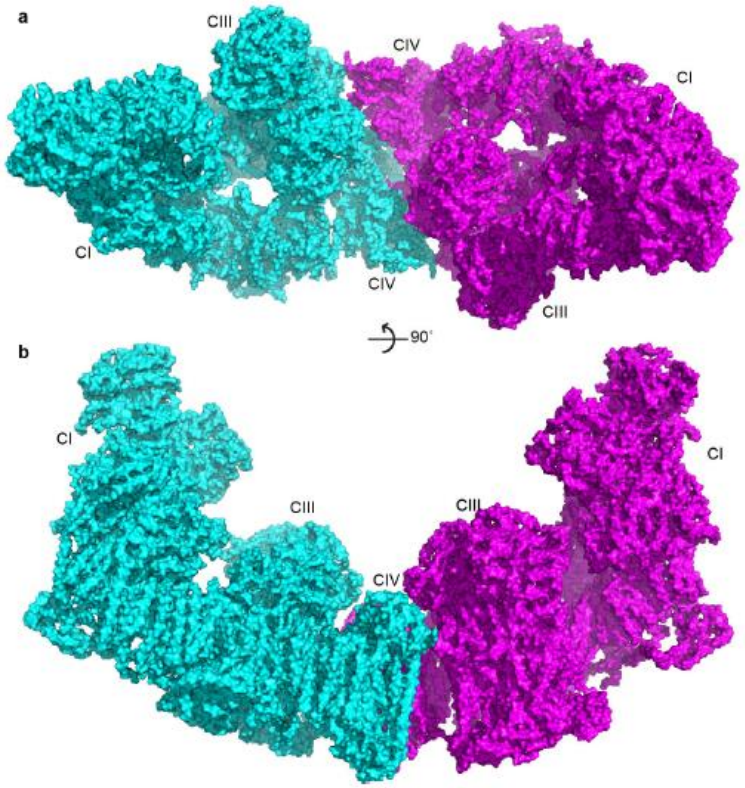
CI_1+$CIII_2$ from *Arabidopsis thaliana*

CI_1+$CIII_2$ from *Bos taurus*

CI_1+$CIII_2$+CIV_1 from *Bos taurus*

Vonck, J. e Schäfer, E. (2009) *Biochim. Biophys. Acta*

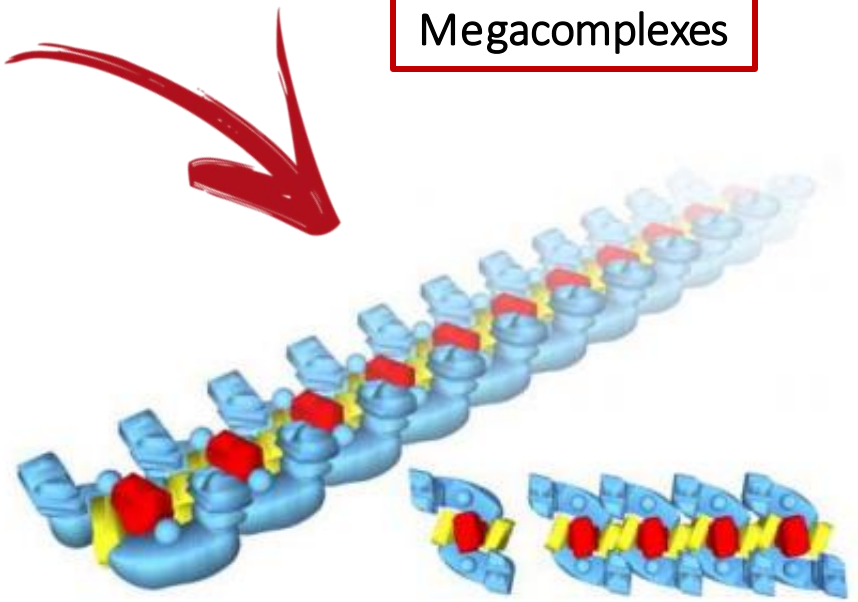
Respiratory strings model



View from the mitochondrial matrix

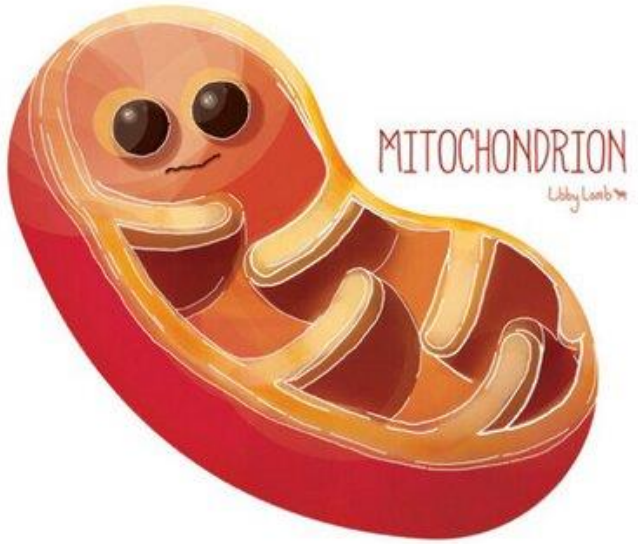
Side view in the membrane plane

Megacomplexes



Modelling of putative higher-order organization of respiratory chain. Image from Letts et al. (2016), *Nature*.

Mitochondrial disorders



Mitochondrial genetic disorders refer to a group of conditions that affect the mitochondria.

People with these conditions can present at any age with almost any affected body system.

Brain, **muscles**, **heart**, liver, nerves, eyes, ears and kidneys are the organs and tissues most commonly affected. Symptom severity can also vary widely.

Mitochondrial genetic disorders can be caused by **mutations** in either the mitochondrial DNA or nuclear DNA that lead to dysfunction of the mitochondria and inadequate production of energy.

Those caused by mutations in mitochondrial DNA are transmitted by maternal inheritance, while those caused by mutations in nuclear DNA may follow an autosomal dominant, autosomal recessive, or X-linked pattern of inheritance.

Leigh syndrome

- Onset in the first years of life
- Progressive loss of mental and movement abilities (**psychomotor regression**)
- Death within two to three years (usually due to respiratory failure)

A small number of individuals do not develop symptoms until adulthood or have symptoms that worsen more slowly.

The **first signs** of Leigh syndrome:

- Vomiting
- Diarrhea
- Difficulty swallowing (dysphagia)

These problems often result in an inability to grow and gain weight at the expected rate.

Leigh syndrome affects at least **1 in 40,000 newborns**.
The condition is more common in certain populations.
(For example, the condition occurs in approximately 1 in 2,000 newborns in the Saguenay Lac-Saint-Jean region of Quebec in Canada)

Leigh syndrome

- weak muscle tone (**hypotonia**)
- involuntary muscle contractions (**dystonia**)
- problems with movement and balance (**ataxia**).

} Severe muscle and movement problems

Loss of sensation and weakness in the limbs (**peripheral neuropathy**), common in people with Leigh syndrome, may also make movement difficult.

- Weakness or paralysis of the muscles that move the eyes (**ophthalmoparesis**)
- Rapid, involuntary eye movements (nystagmus)
- Degeneration of the optic nerves (**optic atrophy**)

Severe **breathing problems** are common, and these problems can worsen until they cause acute respiratory failure. Some affected individuals develop **hypertrophic cardiomyopathy.** In addition, **excessive lactate amounts** are often found in the blood, urine, or cerebrospinal fluid.

The signs and symptoms of Leigh syndrome are caused in part by **brain lesions**. These regions include the basal ganglia, the cerebellum and the brainstem. The brain lesions are often accompanied by loss of the myelin coating around nerves (**demyelination**).

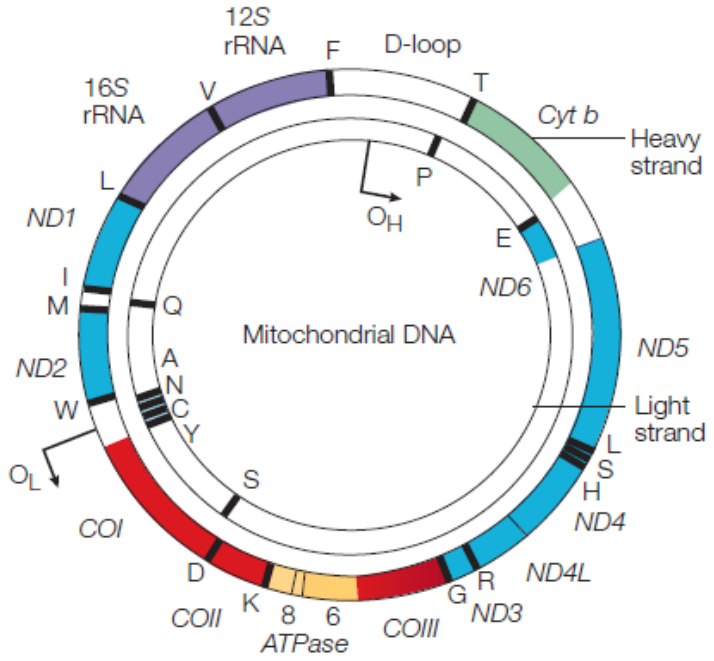
https://www.youtube.com/watch?v=LPyYyKYrlKs

Leigh syndrome

Leigh syndrome can be caused by mutations in one of more than **75 different genes** in:

- nuclear DNA
- mitochondrial DNA (mtDNA) **20%**

Most genes associated with Leigh syndrome are involved in the **process of energy production** in mitochondria. Indeed, these gene mutations affect proteins in OXPHOS complexes or disrupt their assembly. These mutations reduce or eliminate the activity of one or more of these complexes.



Human mtDNA. Taylor, R.W. and Turnbull, D.M. (2005), *Nature Reviews.*

Leigh syndrome

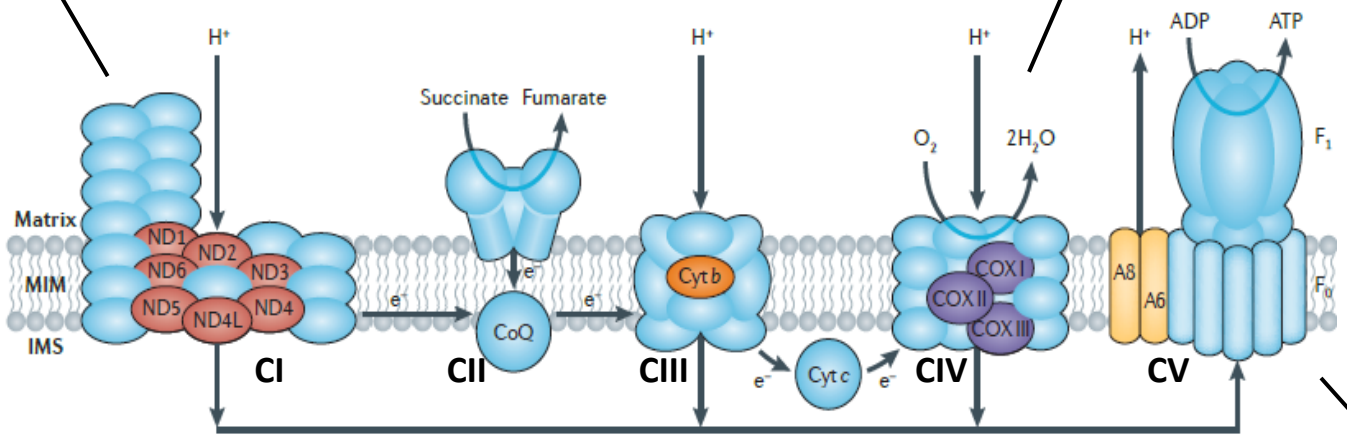
1/3

Disruption of complex I

25 genes involved (either nuclear or mtDNA)

15%

Disruption of complex IV



Oxidative phosphorylation. Image modified from Schon et al. (2012), *Nature Reviews*.

SURF1 gene

- Nuclear gene
- CIV assembly factor

Complex V - ATP synthase

10%

MT-ATP6 gene

- Mitochondrial gene
- ATP synthase membrane subunit 6

Other DNA mutations associated with Leigh syndrome decrease the activity of other OXPHOS complexes or lead to reduced formation of mitochondrial proteins, all of which impair mitochondrial energy production.

Leigh syndrome can be caused by mutations in genes that form the **pyruvate dehydrogenase complex** or **coenzyme Q10**, both of which are involved in mitochondrial energy production. Mutations in genes that direct the **replication of mtDNA** or the production of mitochondrial proteins can also disrupt mitochondrial energy production.

Leigh syndrome

Impaired oxidative phosphorylation can lead to **cell death** because of decreased energy available in the cell.

Certain tissues that require large amounts of energy, such as the **brain**, **muscles**, and **heart**, seem especially sensitive to decreases in cellular energy.

Cell death in the brain likely causes the characteristic **lesions** seen in Leigh syndrome, which contribute to the signs and symptoms of the condition. Cell death in other sensitive tissues may also contribute to the features of Leigh syndrome.

Leigh syndrome

Leigh syndrome can have different **inheritance** patterns:

1. autosomal recessive

This pattern of inheritance applies to most of the Leigh syndrome-associated genes contained in **nuclear DNA**, including *SURF1*.

2. mitochondrial pattern (maternal inheritance) 20%

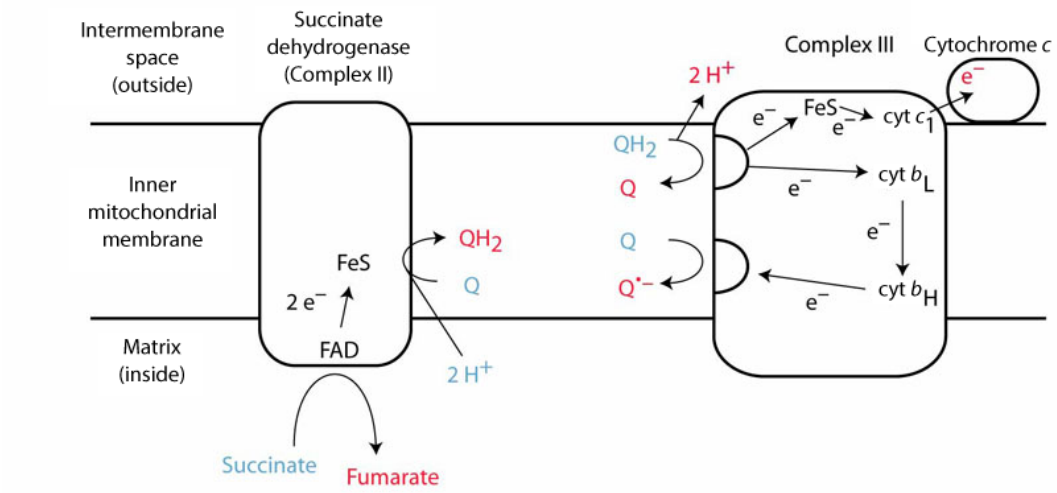
This pattern of inheritance applies to genes contained in **mtDNA**, including *MT-ATP6*.

3. X-linked recessive pattern

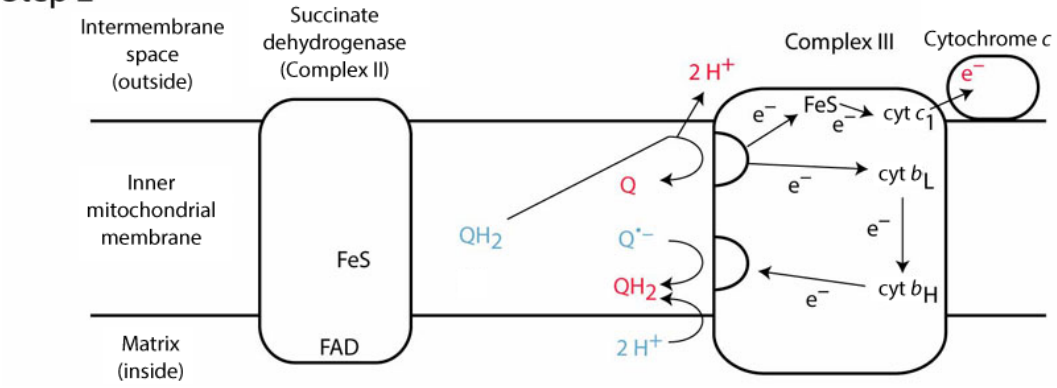
In a small number of affected individuals with mutations in **nuclear DNA**. The condition has this pattern of inheritance when the mutated gene is located on the **X chromosome**.

Q cycle inside Complex III

Step 1



Step 2



Inside Complex IV

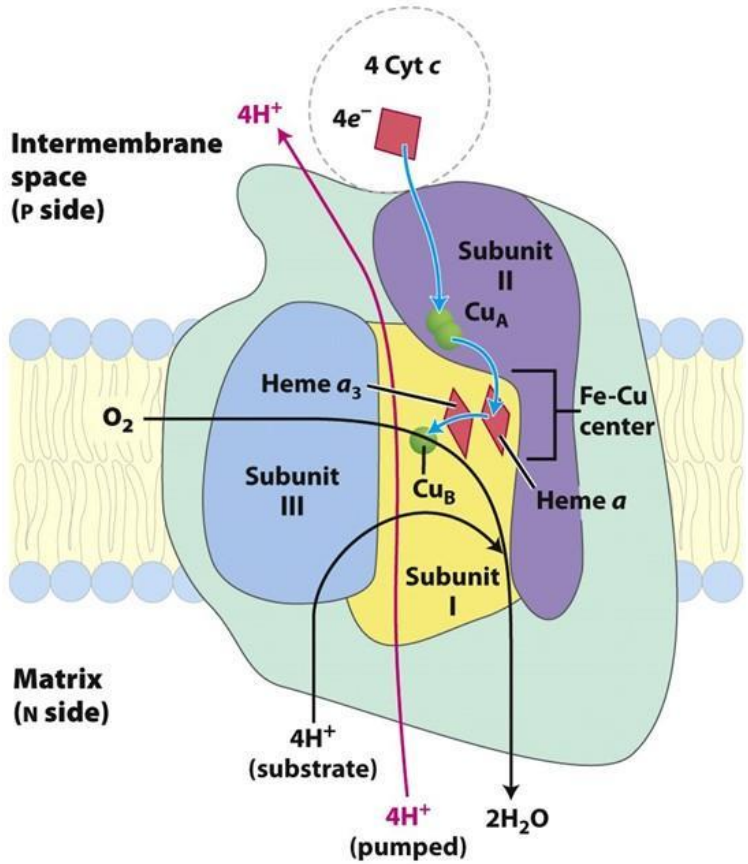
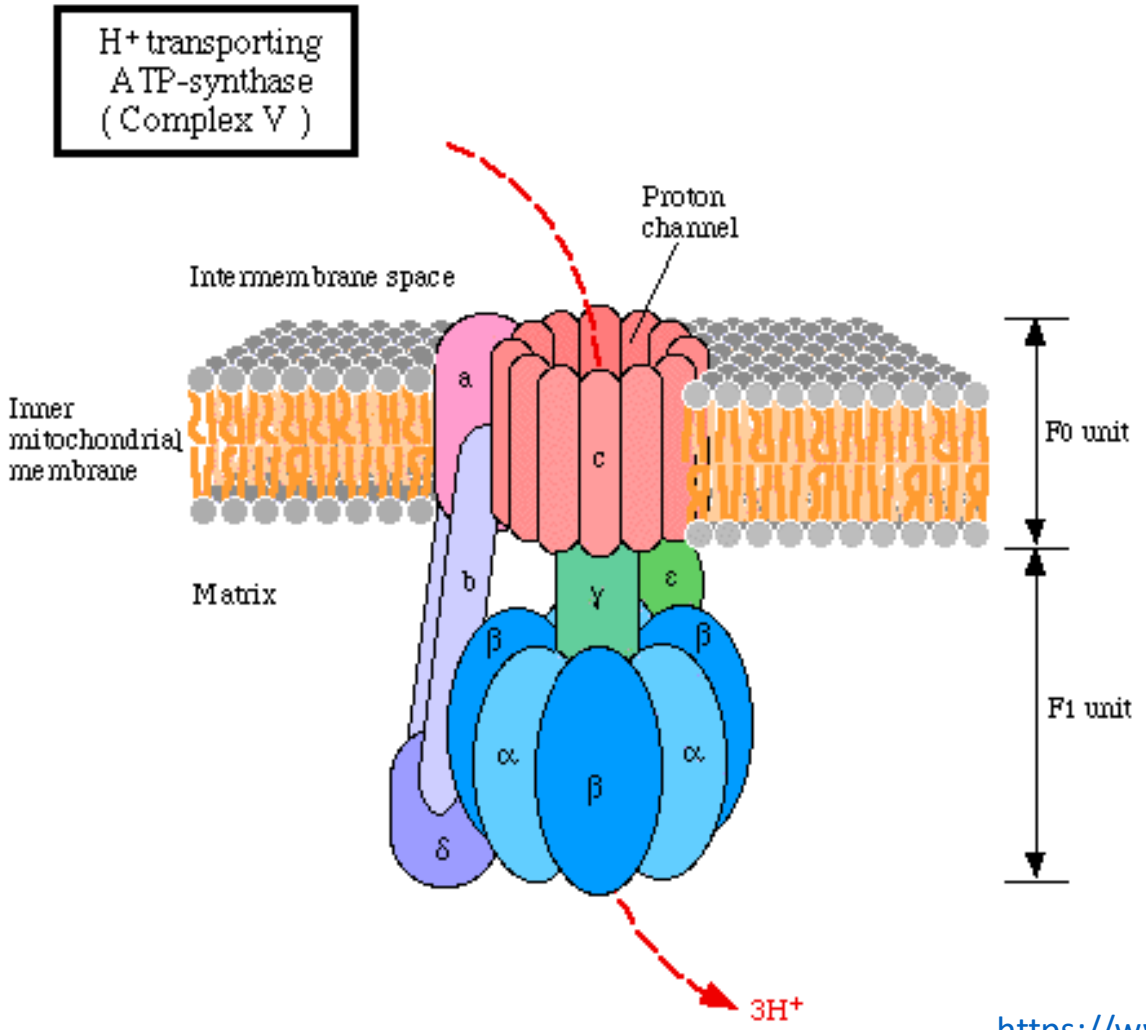


Figure 19-14
Lehninger Principles of Biochemistry, Fifth Edition

ATP synthase - Complex V



https://www.youtube.com/watch?v=3y1dO4nNaKY