Normal & Impaired Charge Transport in Biological Systems

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Outline

Introduction

- Biological charge transport
- Genetic code; Mutations
- Mitochondrial metabolic machines

Hole migration & mutations in DNA

- Hole on base → Tautomerization → Mutation
- Guanine mutations enhanced

Mitochondrial charge transport → ATP

- Water channels; ATP synthase
- Mutations → Impaired transport → Diseases
- Complex I physics (known & unknown)

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Biological Charge Transport

Ion channels

- > 300 types
- Often gated
- Ions: Cl^-, K^+, Na^+, Ca^{2+}, H^+, etc.
- Drive action potentials (brain, heart, muscles, etc.)

Hole migration in DNA

- Role in mutations

Mitochondrial electron transport chain

- Electron tunneling
- Proton transport
- Effects of mutations

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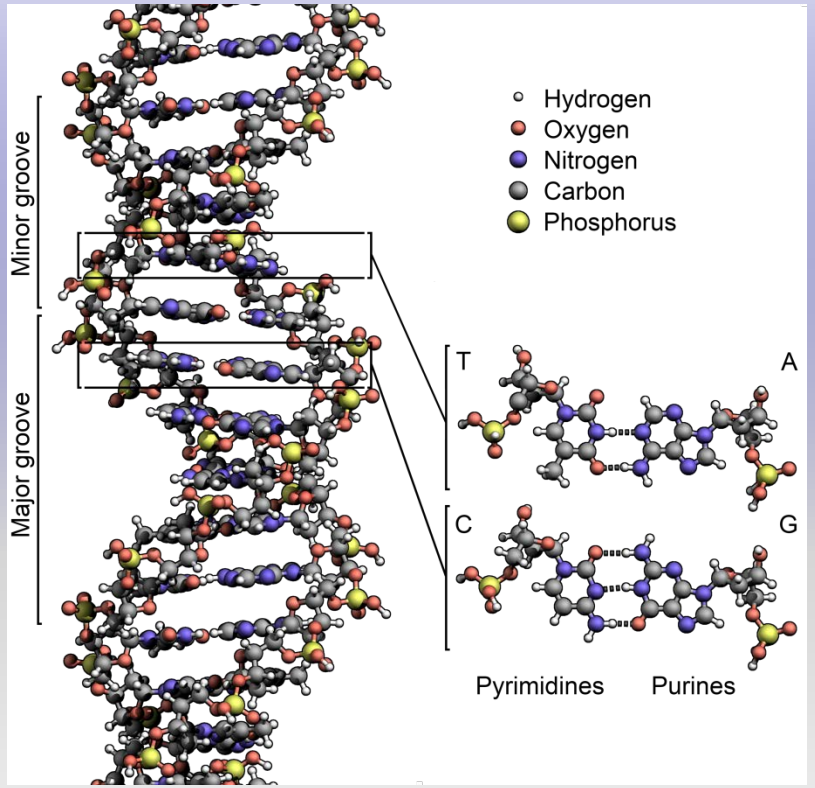
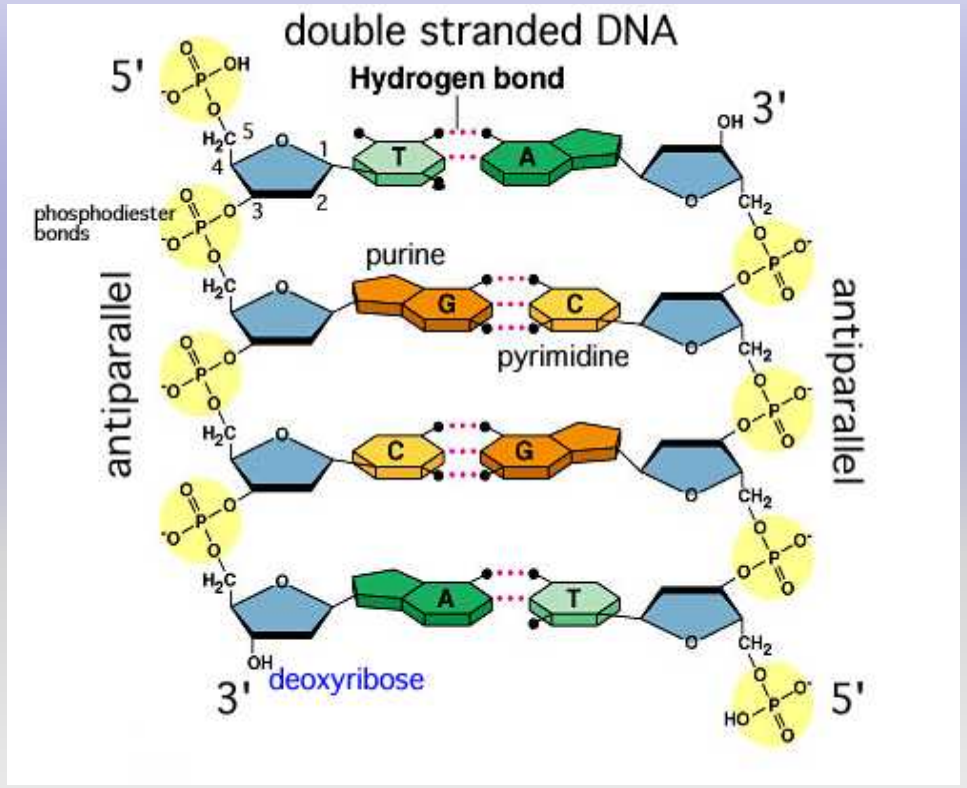
DNA base pair sequence encodes information





Purines: **G**uanine & **A**denine

Pyrimidines: **C**ytosine & **T**hymine

Under normal circumstances: **G** pairs with **C**; **A** pairs with **T**.

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DNA replication

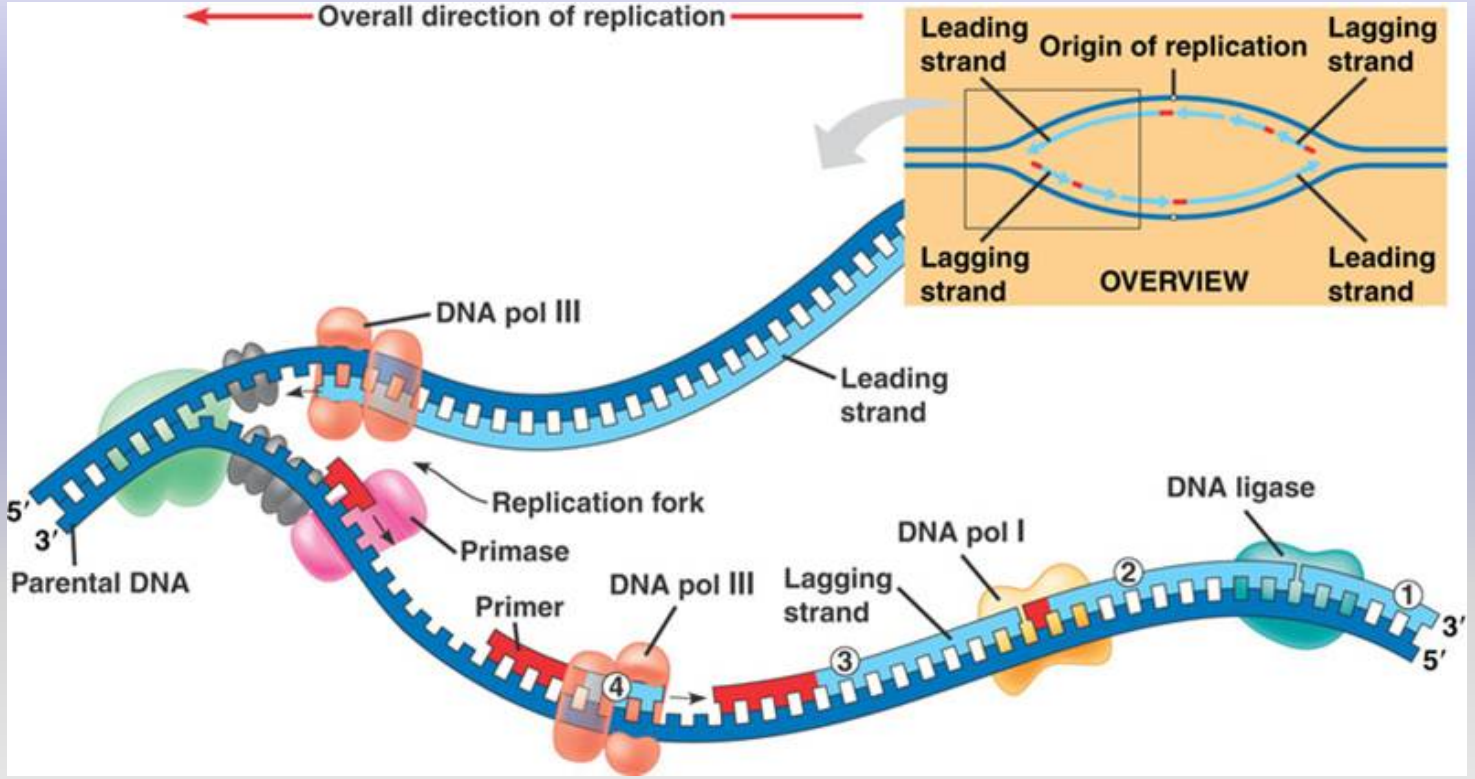


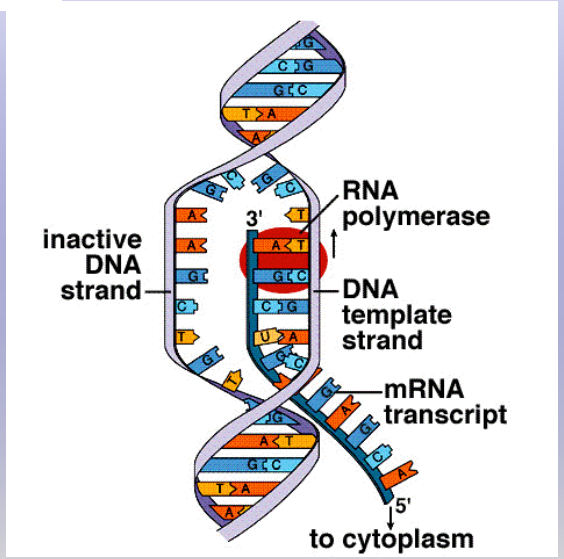
Image from: http://genmed.yolasite.com/fundamentals-of-genetics.php

Replication & repair enzymes →:

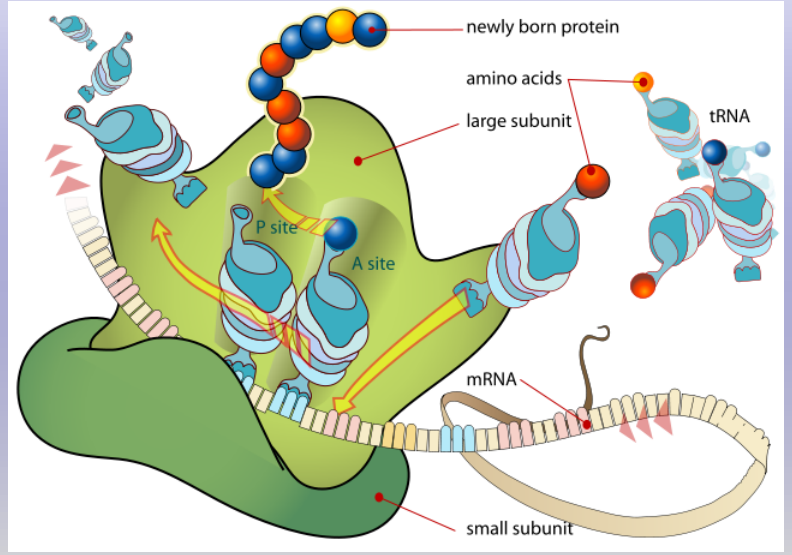
Part of double helix splits → 2 strands;

Complementary bases pair w/ parent strand bases.

Transcription and Translation



http://www.expertsmind.com/topic/microbiology/transcription-92396.aspx



http://www.newworldencyclopedia.org/entry/Translation_(biology)

Transcription: DNA sequence portion (gene) → mRNA.

Translation: mRNA → amino acid sequence = protein.
Proteins fold. What dictates higher level assembly?

Transcription factors + regulatory RNA's + interactions + ???.

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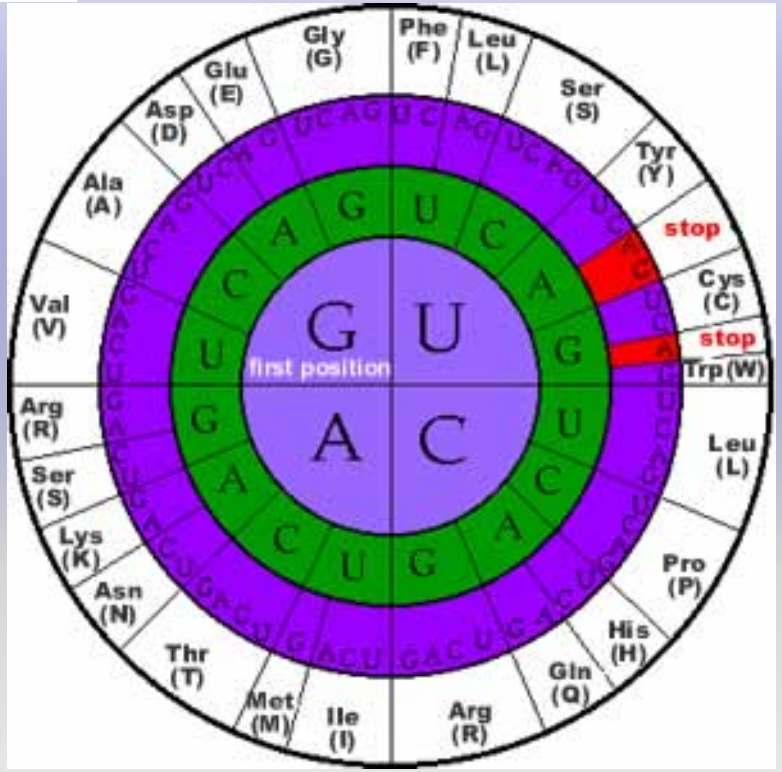
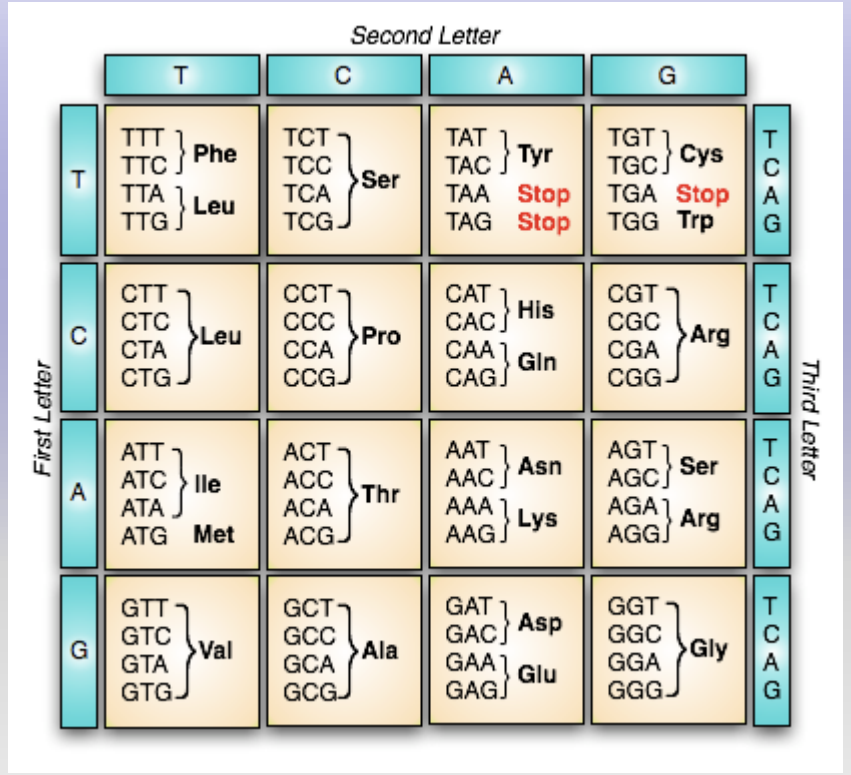
Genetic Code



http://virtuallaboratory.colorado.edu/Biofundamentals

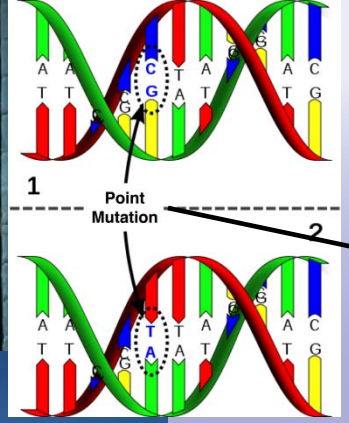


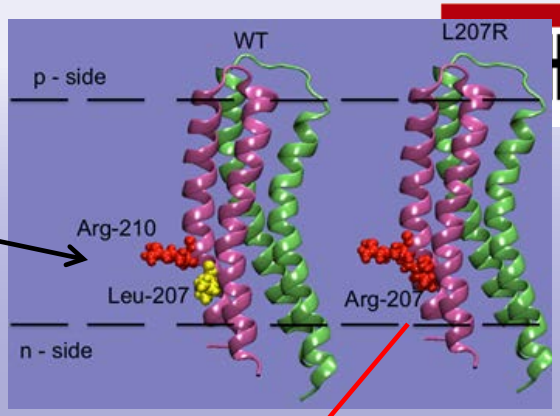
http://plato.stanford.edu/entries/information-biological/

mRNA 3-letter code → amino acid, start, or stop.

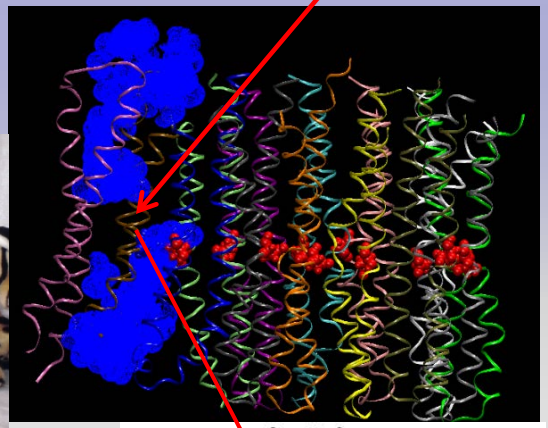
64 combinations, 21 amino acids;

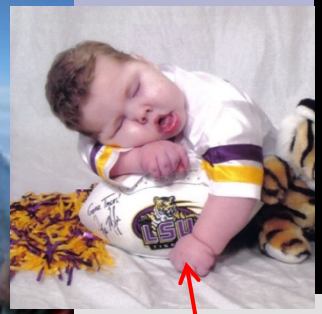
Encoded by original DNA bases. **Copying error → Mutation!**


1
Point
Mutation
2

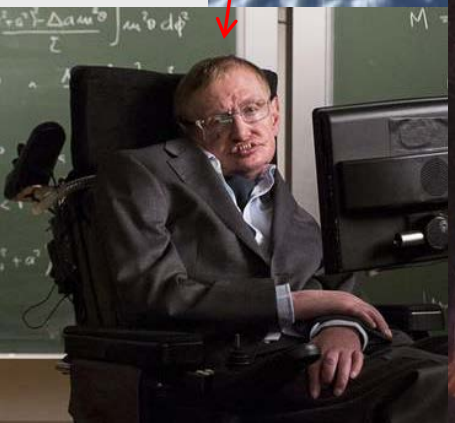

WT
L207R
p - side
Arg-210
Leu-207
Arg-207
n - side

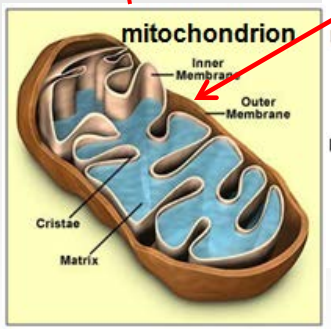

SuperSherpas

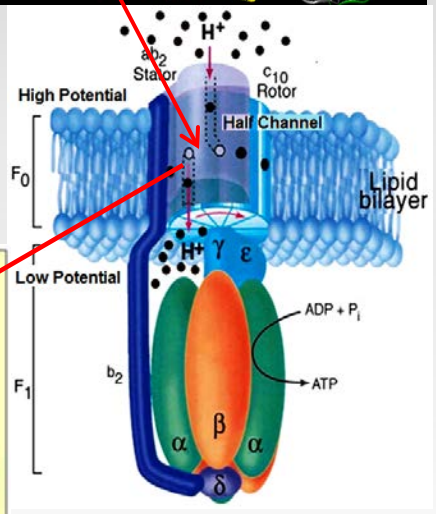




Nqo1
FMN
Nqo3
Nqo2
Nqo5
Nqo16
N2
Nqo4
Nqo9
Nqo6
8(AH1)
Nqo8
Cytoplasm
30 Å
Periplasm
Nqo11
7(TM1)
8(TM1)
Nqo12
Nqo13
Nqo14
Nqo10
Nqo7
180 Å



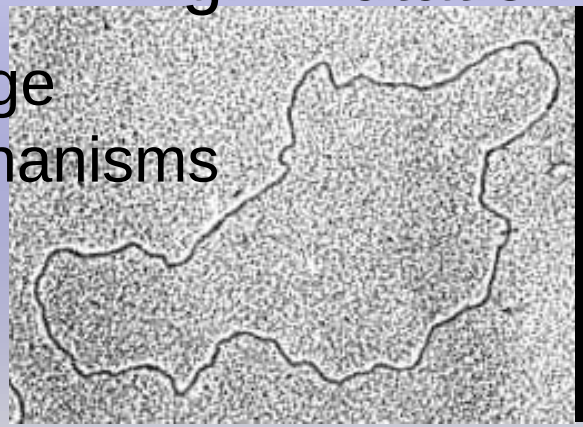

mitochondrion
Inner
Membrane
Outer
Membrane
Cristae
Matrix


H+
a b2
Stator
c10
Rotor
High Potential
Half Channel
F0
Lipid
bilayer
H+
γ
ε
Low Potential
ADP + Pi
F1
b2
ATP
α
β
α
δ

Mitochondria have their own DNA molecules

Mitochondrial DNA ⇔high mutation rate.

- Oxidative damage
- Few repair mechanisms
- Many copies



mtDNA point mutations are implicated in:

- Neurodegenerative disorders
  - LHOP, NARP, Leigh syndrome, ALS, MELAS, AD/PD, etc.
- Age-related illnesses (somatic mutations)
  - Cancer
  - Type 2 diabetes
  - Heart disease

Physical mechanisms are largely unknown.

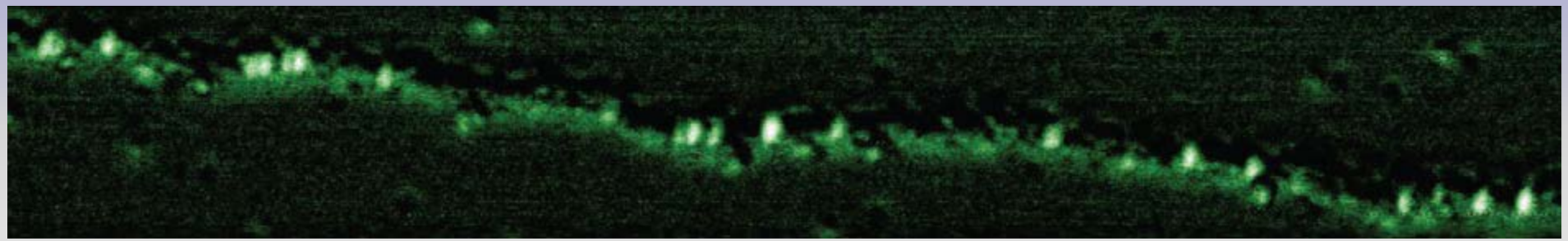
Hole Migration & Mutations in DNA

Guanine base substitutions most common in cancer.

Larman, *PNAS* **109**, 14087 (2012): **G → A (60%)** in mtDNA, cancer.

Guanine sites act as potential wells for holes.

Tanaka, *Nature Nanotechnology* **4**, 518 (2009).



at ggacagact ct t t t act cggt ggcct cact gat t at aaaaacact t ct caagat t ct ggcgt accgt t cct gt ct aaaat ccct t t aat cggcct cct gt t t agct cccgct ct gat t ccaacgaggaaagcacgt t a

Above effects appear causally related

Bacolla, "Guanine holes are prominent targets for mutation …." *PLoS Genetics* **9**, e1003816 (2013).

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Tautomerization Mechanism

Possible mechanism ⇔ Tautomerization → mispair

Cerón-Carrasco, *J. Phys. Chem. B* **114**, 13439 (2010).

Hole on guanine → Shift in hydrogen ion: **G → G***.

G* "incorrectly" pairs w/ **T** → **G*:T**.

G*:T replicates to "correct" but mutated pairing, **A:T**.

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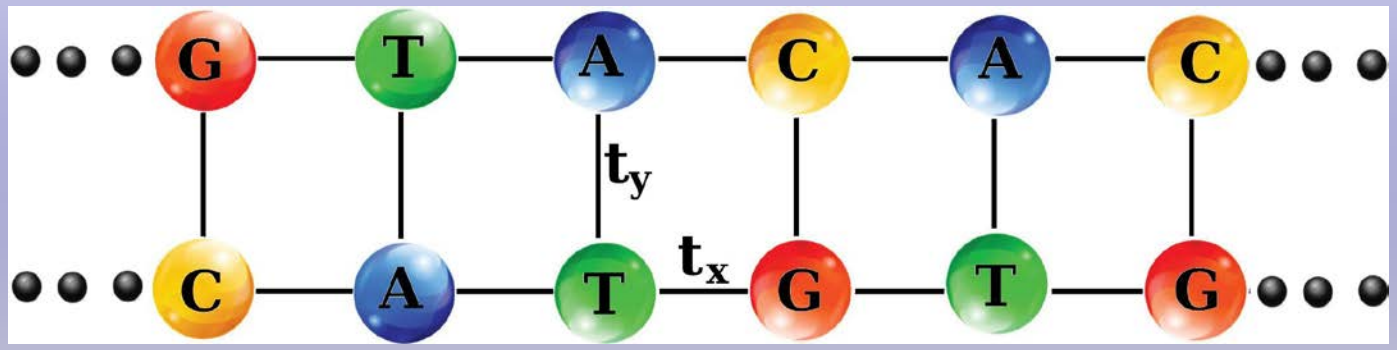
Simplified Model of DNA Chain



Martha Suárez Villagrán

$$\hat{H} = -\sum_{(\ell,m)\sigma}^{N} \left(t_{\ell m} c^{\dagger}_{\ell\sigma} c_{m\sigma} + t_{m\ell} c^{\dagger}_{m\sigma} c_{\ell\sigma} \right) + \sum_{\ell\sigma} \epsilon_{\ell} n_{\ell\sigma}$$

$c_{m\sigma}$ ⇔ hole destruction operator; N-N hopping: t_x = 1.0 eV, t_y = 0.5 eV.

$$E_{\mathrm{G}} = 7.75\,\mathrm{eV},\ E_{\mathrm{C}} = 8.87\,\mathrm{eV},\ E_{\mathrm{T}} = 9.14\,\mathrm{eV}\ \&\ E_{\mathrm{A}} = 8.24\,\mathrm{eV}$$

Diagonalize Hamitonian using actual mtDNA sequence
→ Eigenenergies & eigenfunctions.

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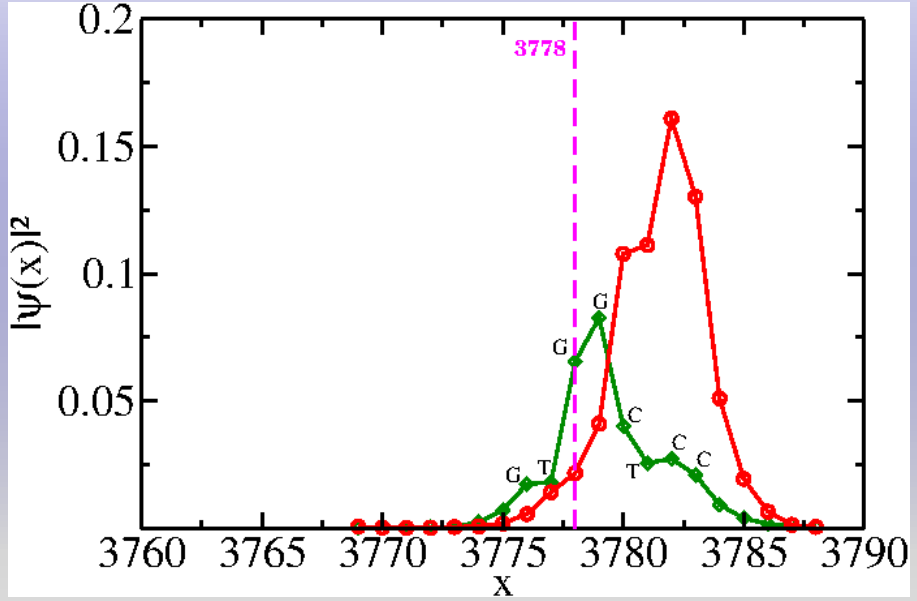
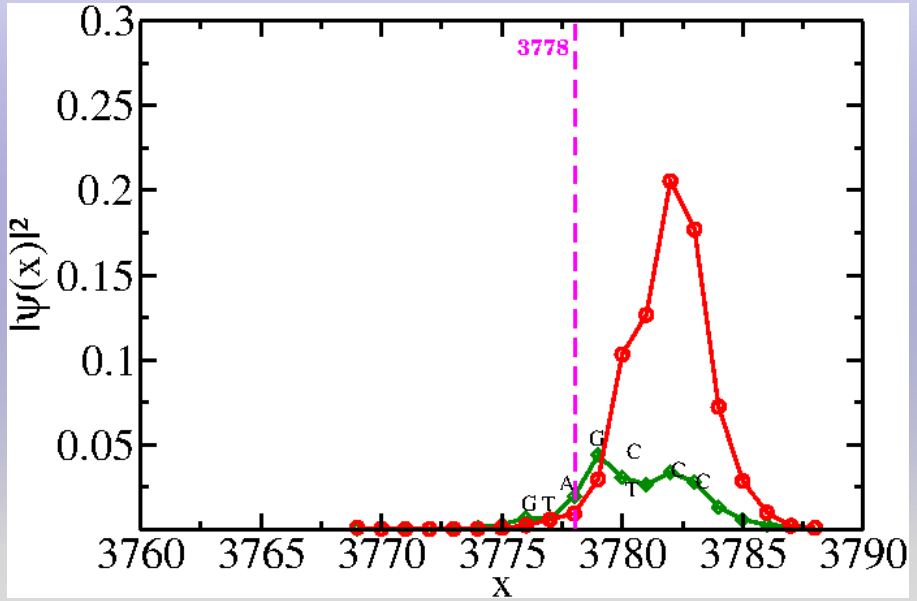
Hole Probabilities Near Mutation Site





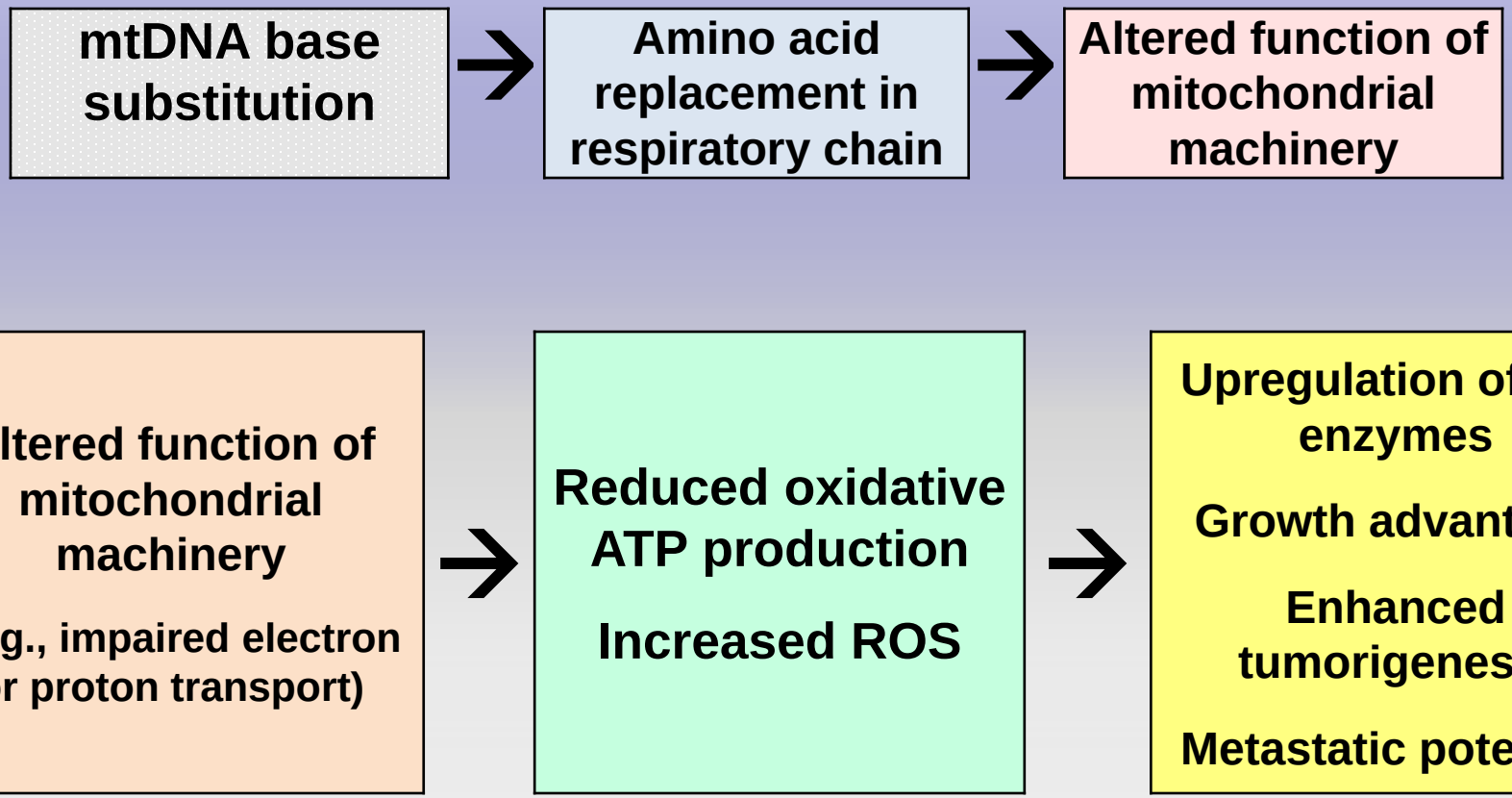
before G → A mutation

after G → A mutation

Hole probabilities ~ mtDNA locus 3378 (cancer-implicated)

Which mutations "survive"?
Perverse Darwinian natural selection ←
Mutation survival in tumor ←
Amino acid replacement effects.

Effects of mtDNA point mutations



In the case of cancer.

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Hypotheses

- Some mtDNA mutations disrupt proton or electron transport by altering water channels.

- mtDNA mutations in cancer "optimally" affect charge transport: ⇑ reactive oxygen species → ⇑ certain enzymes (e.g. HK2).

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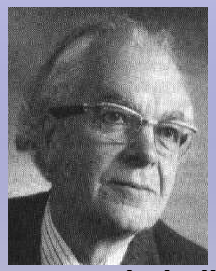
Mitochondrial Electron Transport Chain



Peter Mitchell

NADH NAD+

Complex I

Inside the matrix

Complex III

Complex IV

ADP + P_i

ATP

F_1

F_0

e^-

O_2

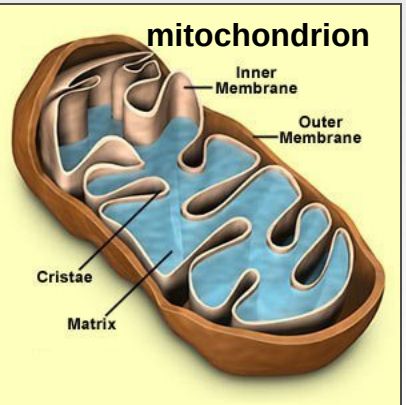
H_2O

Quinone pool

Cytochrome *c*

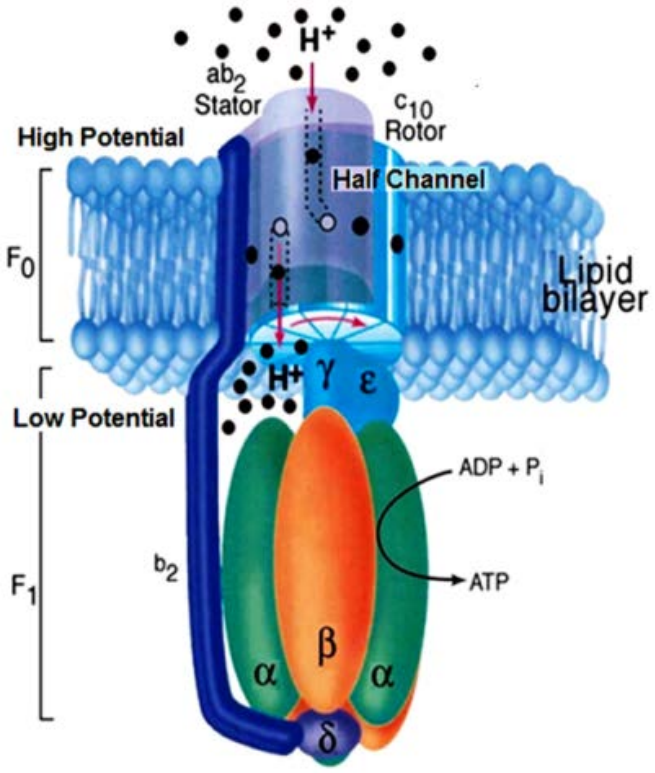
ATP Synthase (F_0F_1)

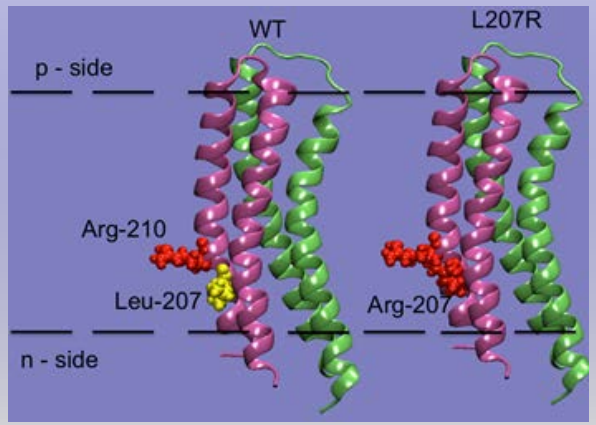
H^+ H^+ H^+ H^+

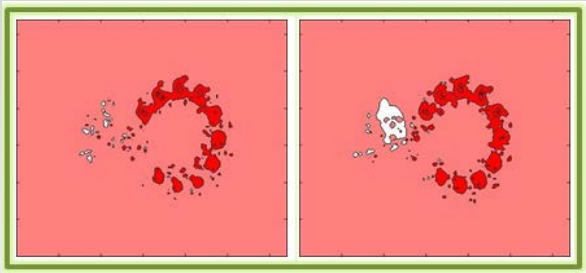


Courtesy of Peter L. Pedersen (Johns Hopkins, 2007)

ATP Synthase







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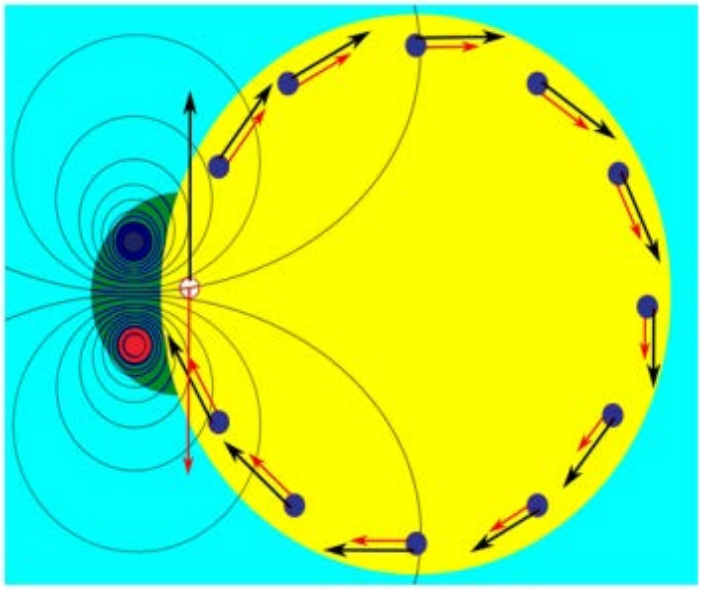
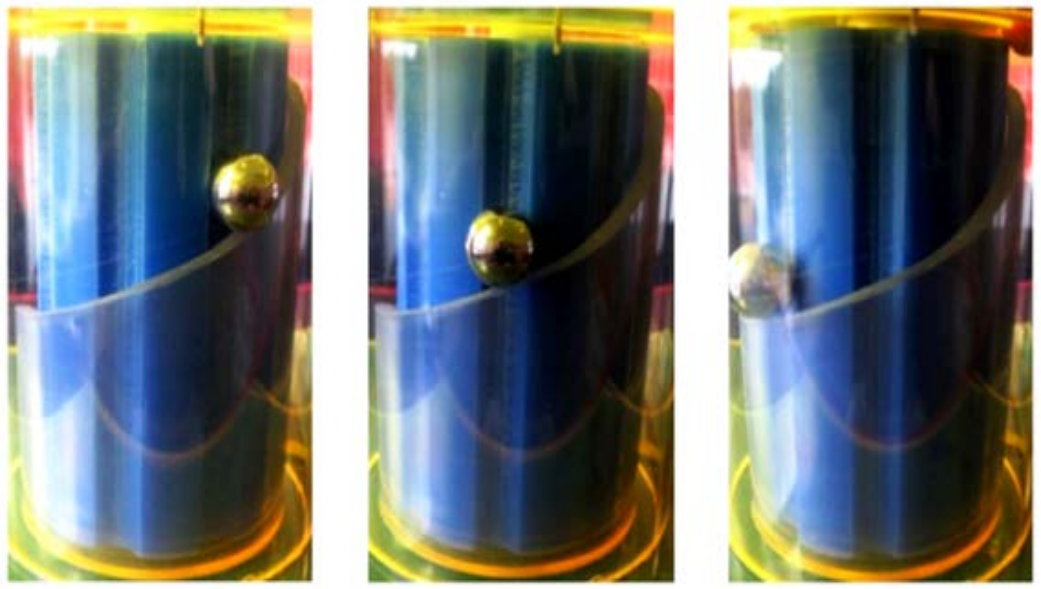
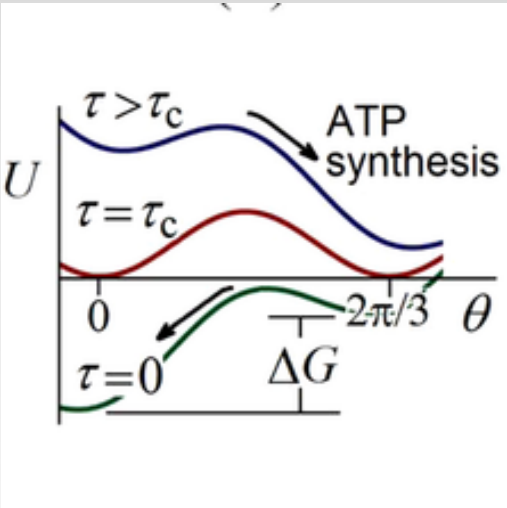
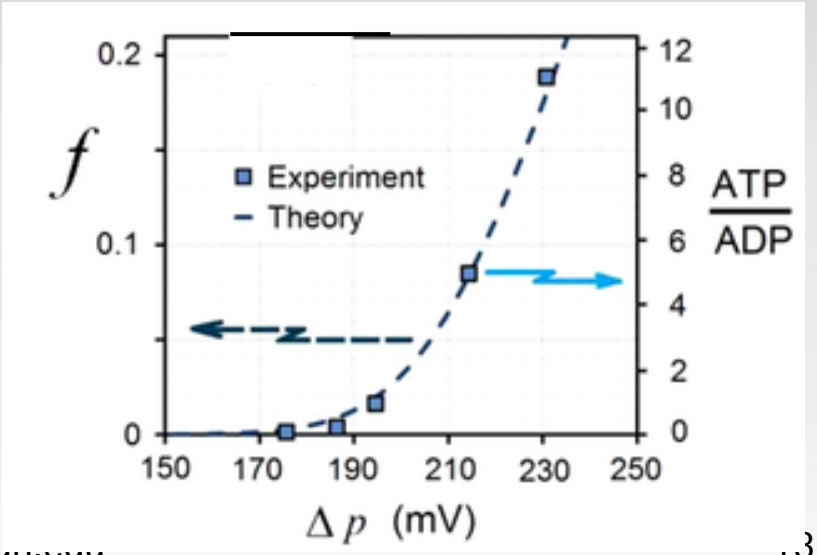
Electric field driven torque in ATP synthase





$$\tau = \frac{ne}{2\pi}\Delta p$$





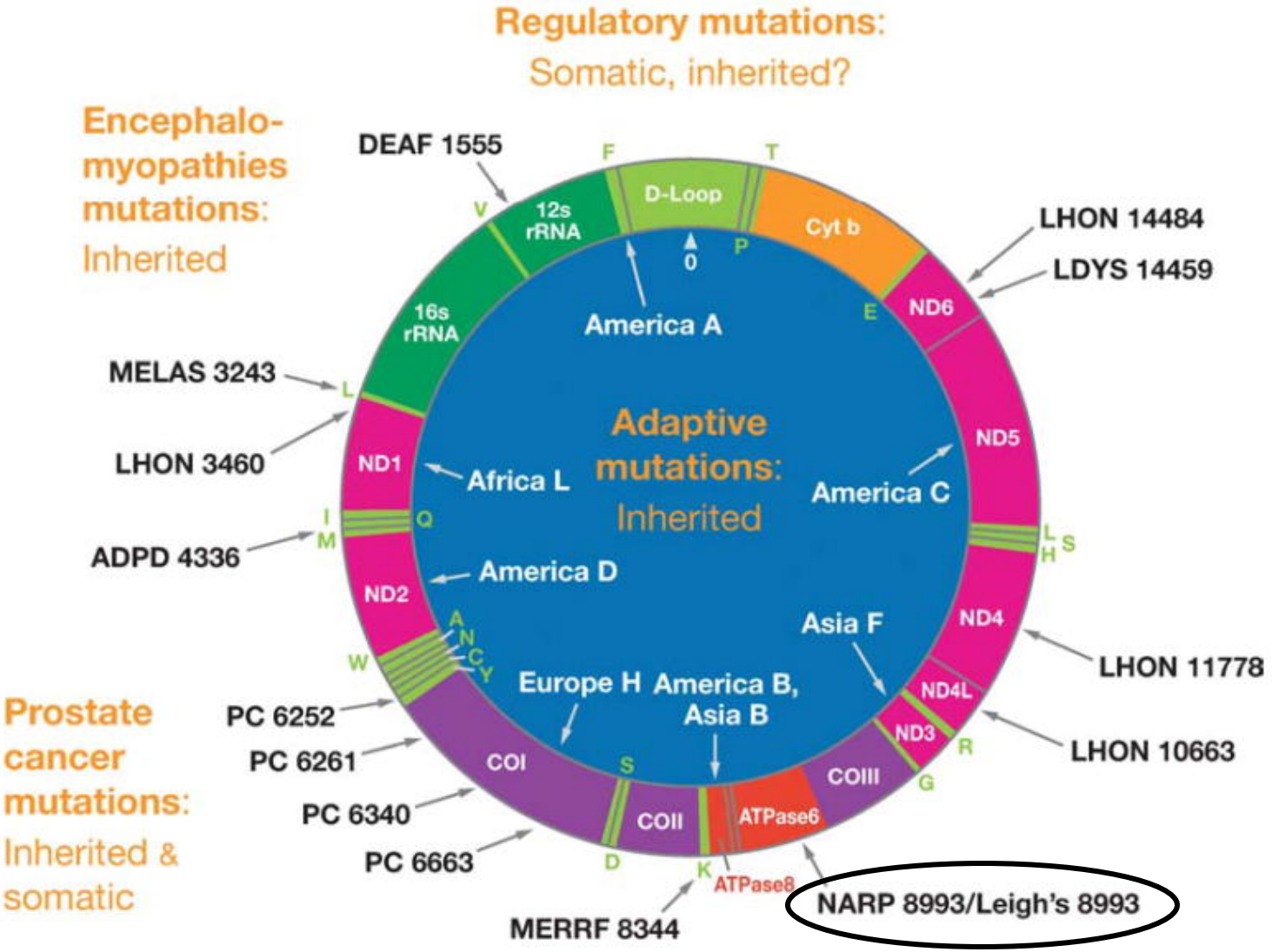
Miller et al., *PLoS ONE* **8**, e74978 (2013).

The Mitochondrial Genome:

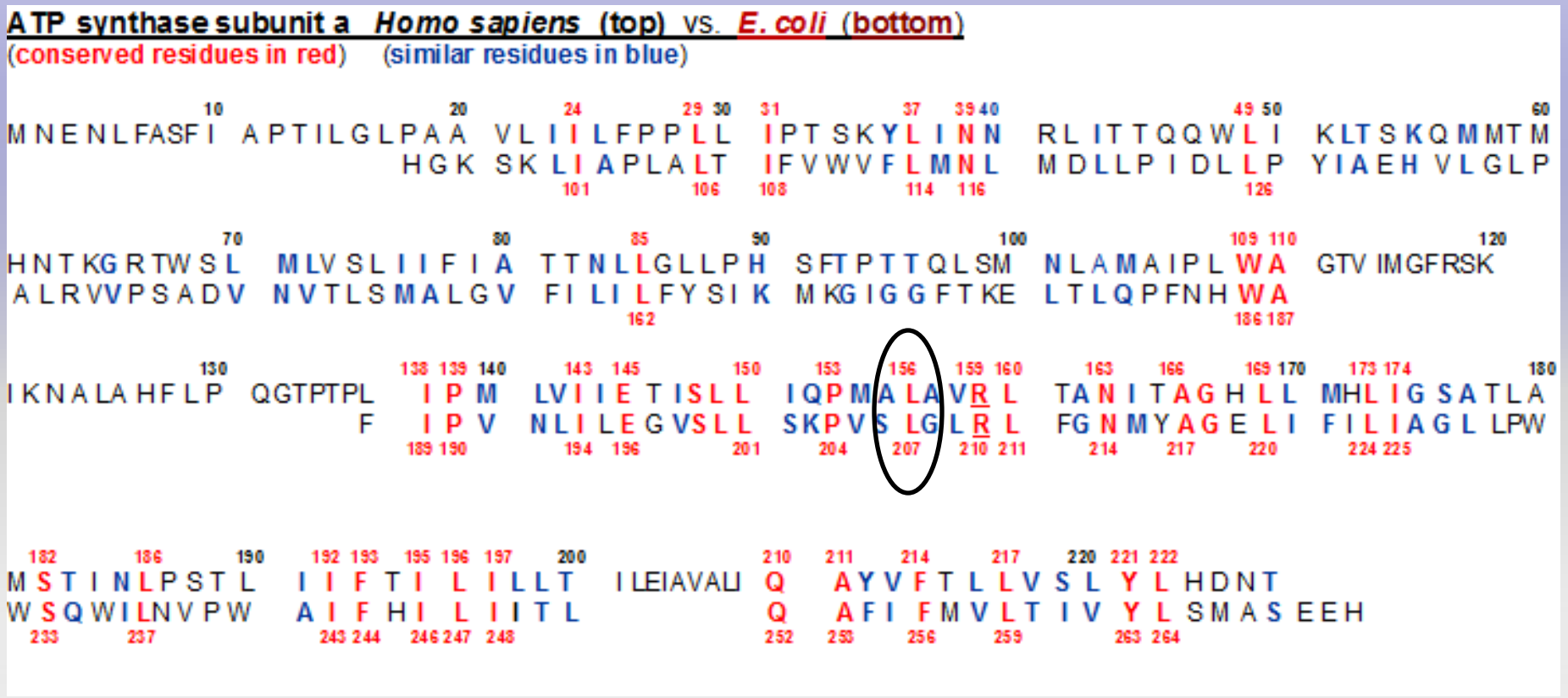
mtDNA = 37 genes

Extra-cellular plasmids (chromosomes) ~ 1500 genes

(Wallace, DC. Annu. Rev. Genet. 2005. **39**:359–407)



ATP Synthase *a*-subunit sequence homology: *H. sapiens* vs. *E. coli*



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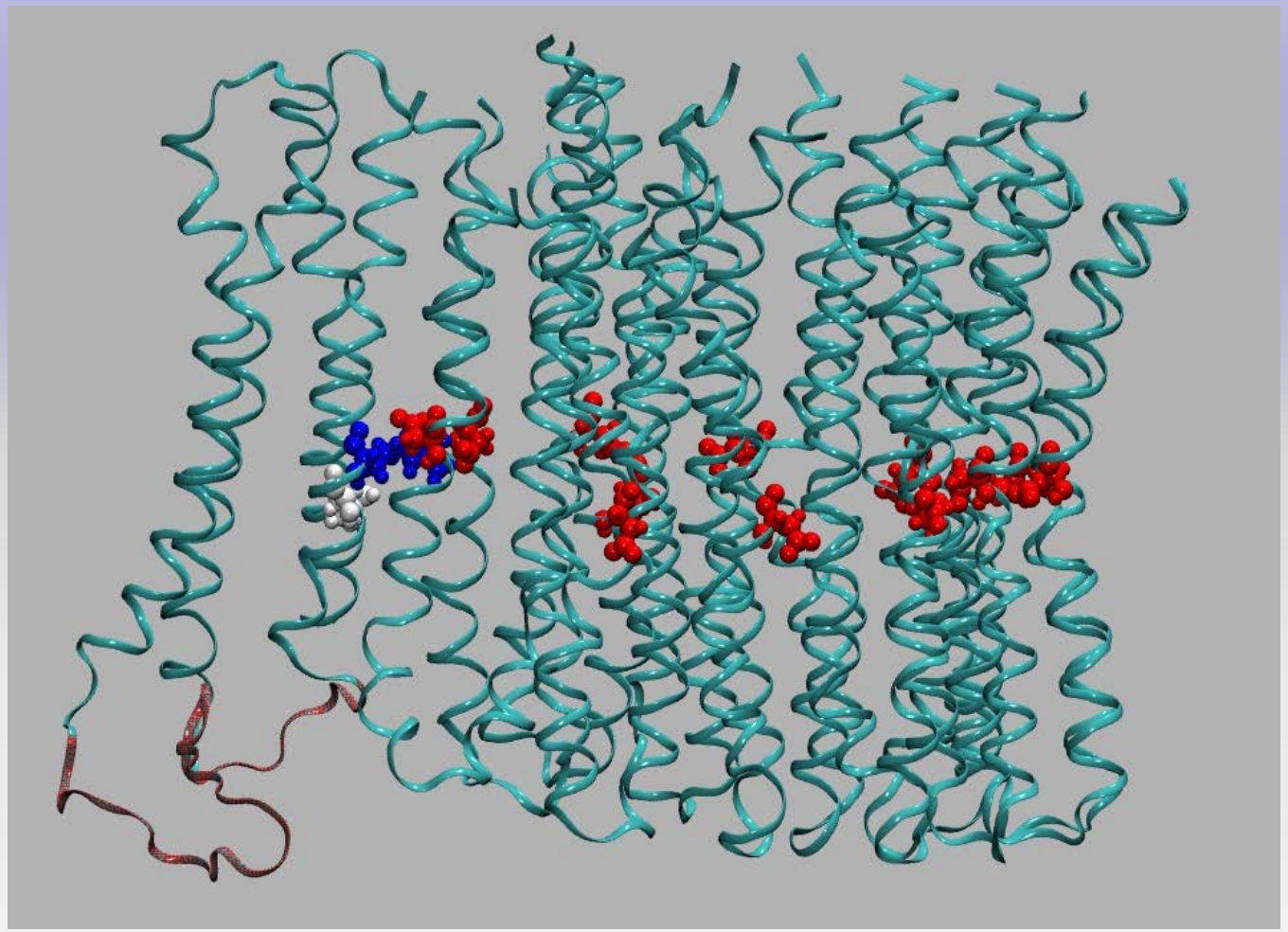
Fo-ATP Synthase *ac* complex



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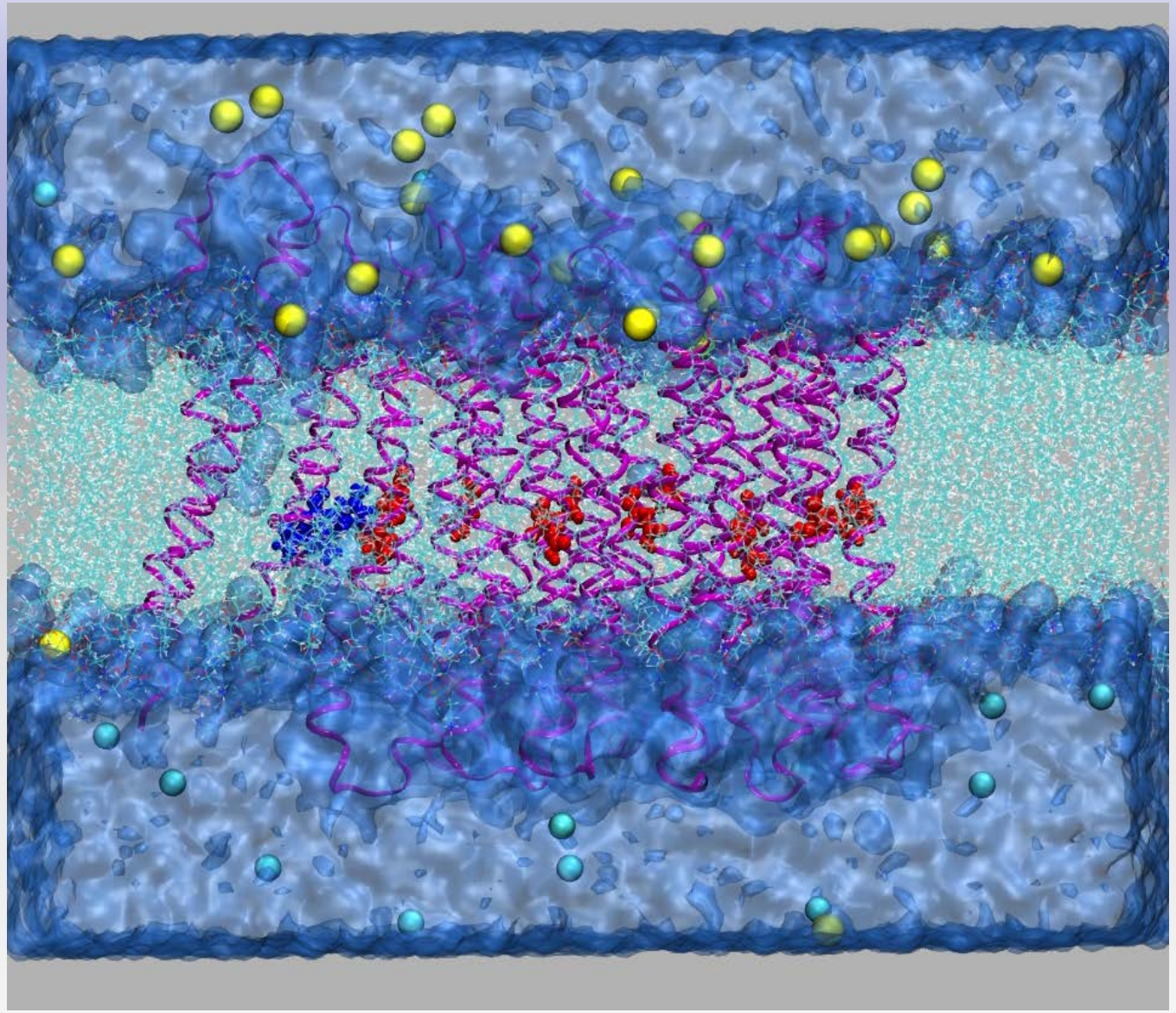
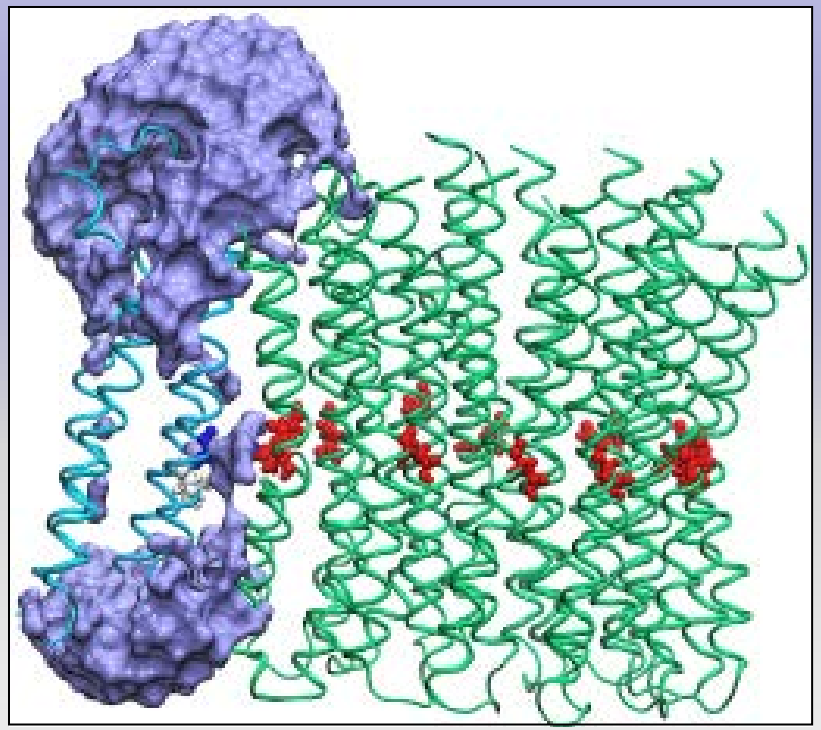
MD simulations via NAMD

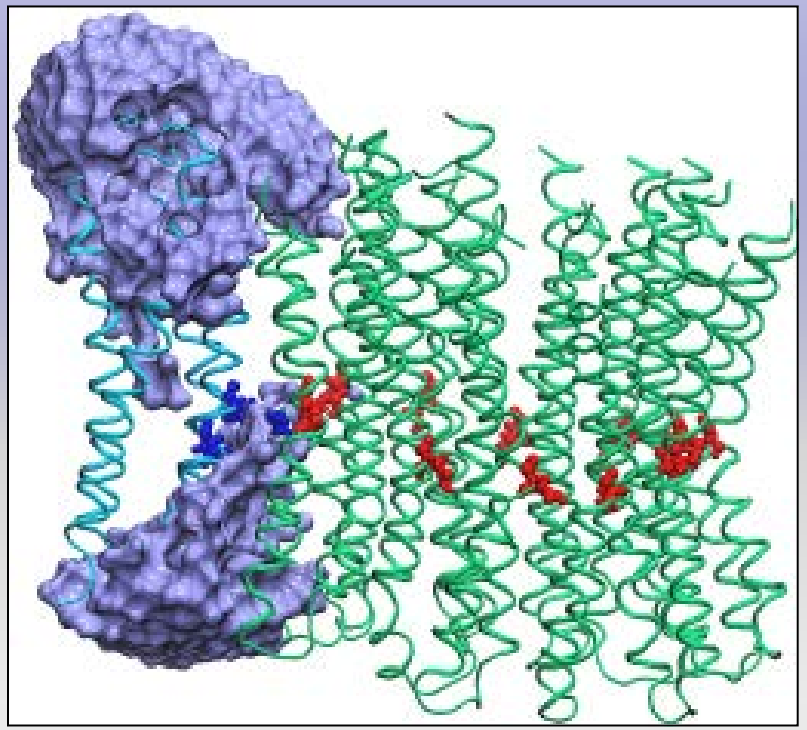


Sladja Maric

Proton conducting water channels

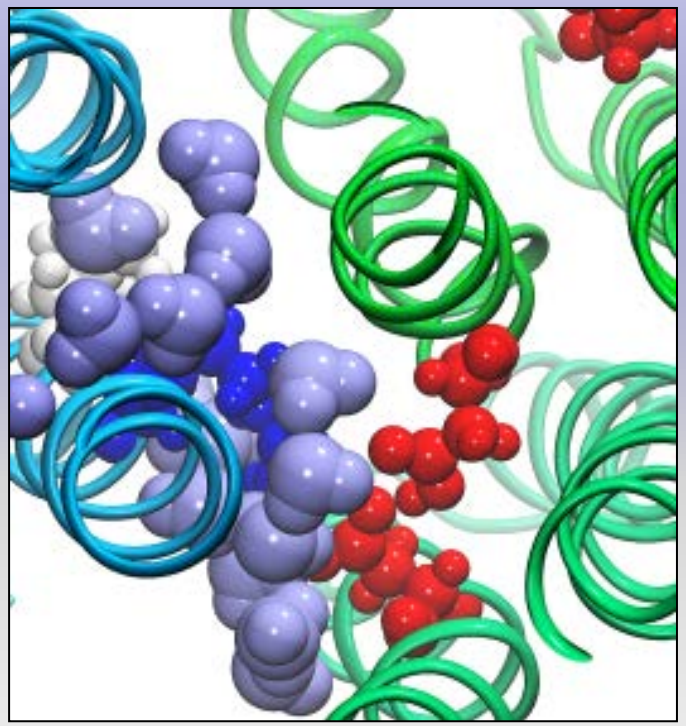


Normal (wild-type)

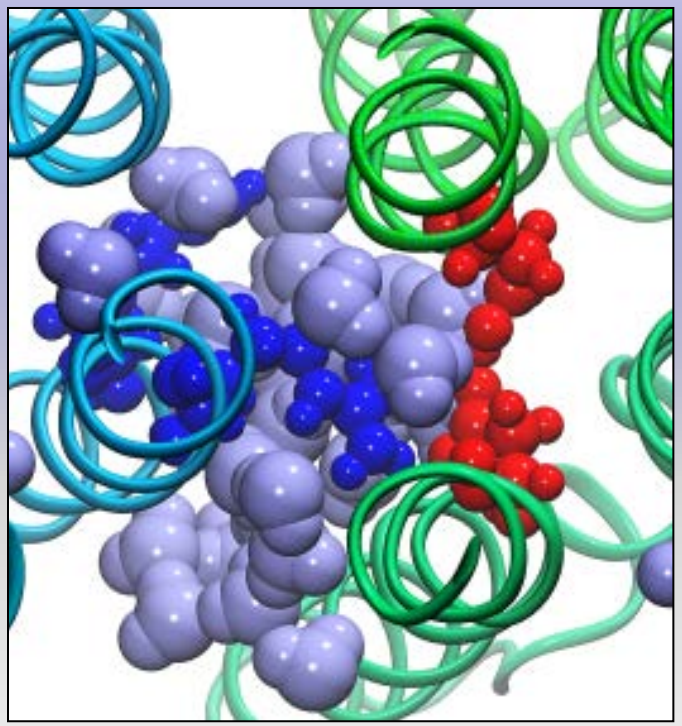


Mutated (8993 T → G)
Leucine → Arginine @ 207

Coupling of water to proton-binding sites

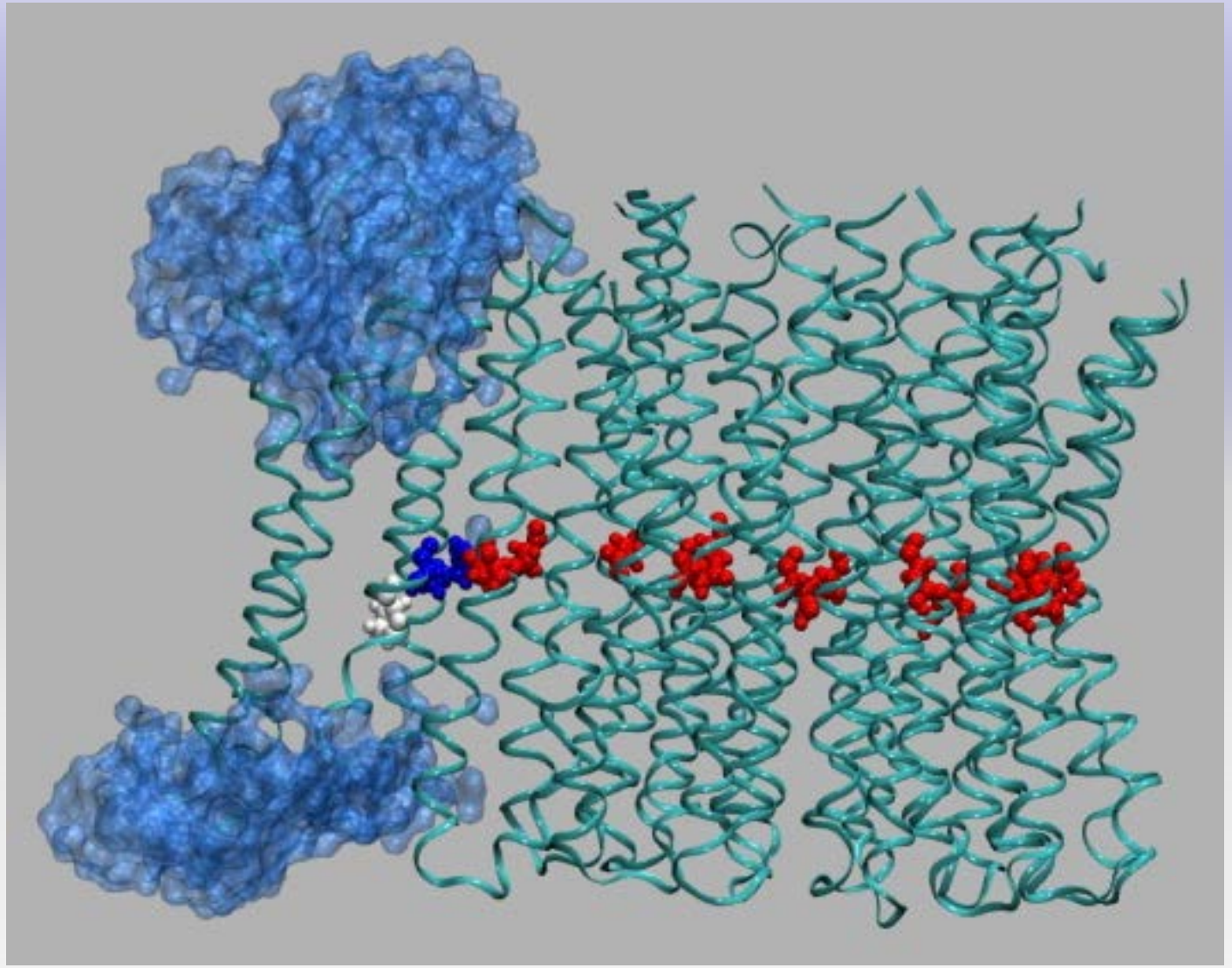


Normal (wild-type)



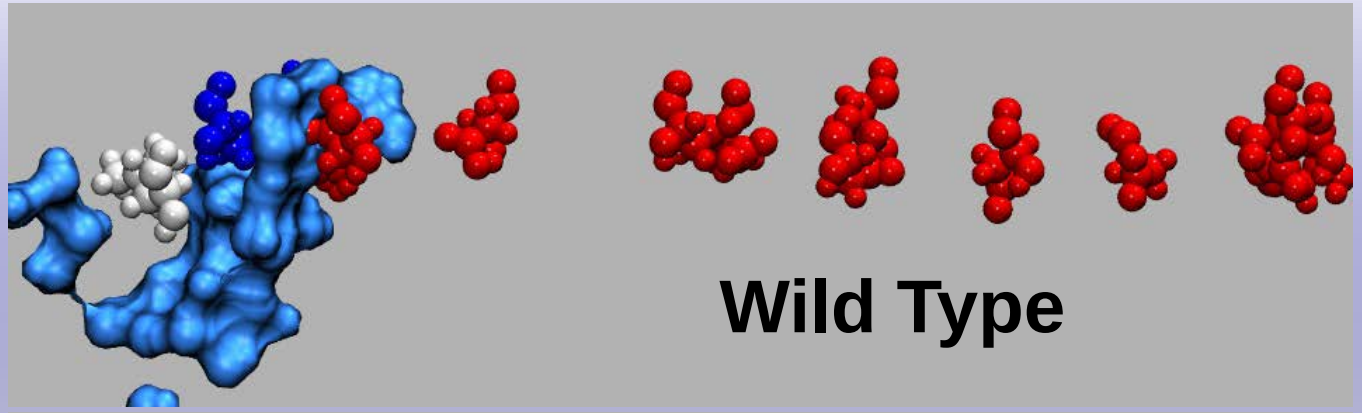
Mutated (8993 T → G)
Leucine → Arginine @ 207

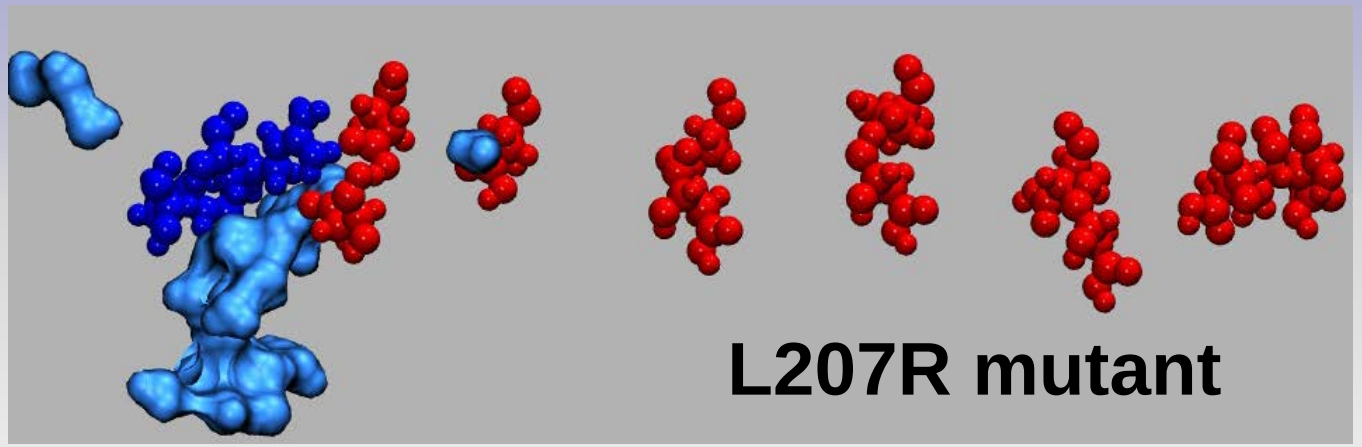
Proton conducting water channels (L207P)

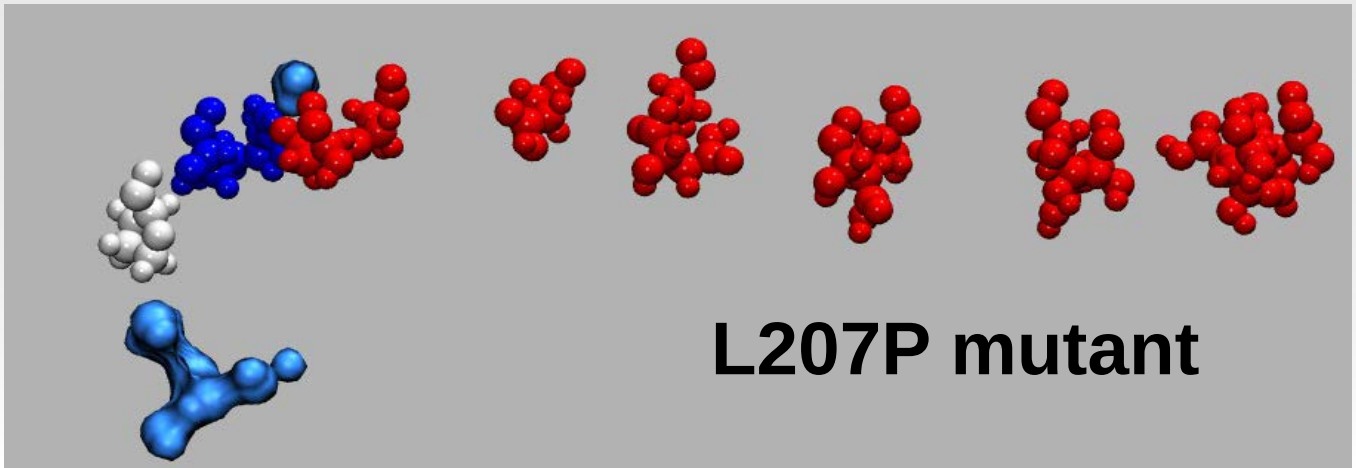


8993 T→C mutation: NARP, Leigh syndrome

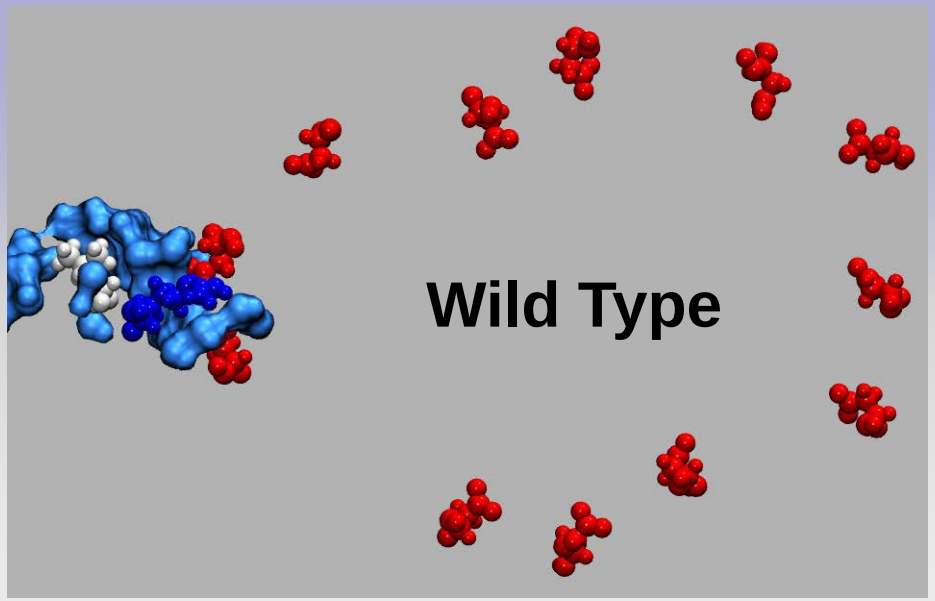
Side views: 207, R210, Asp61 (c-ring)

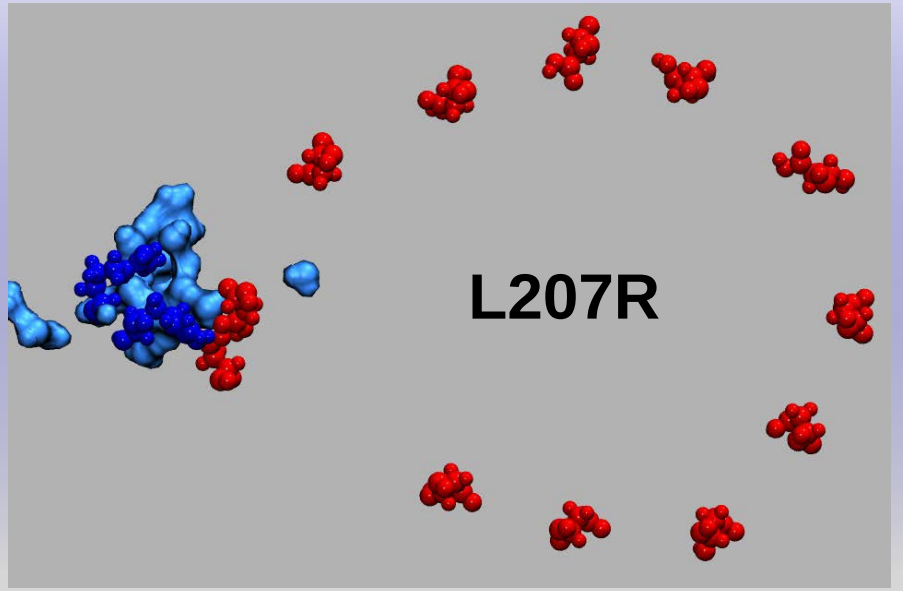


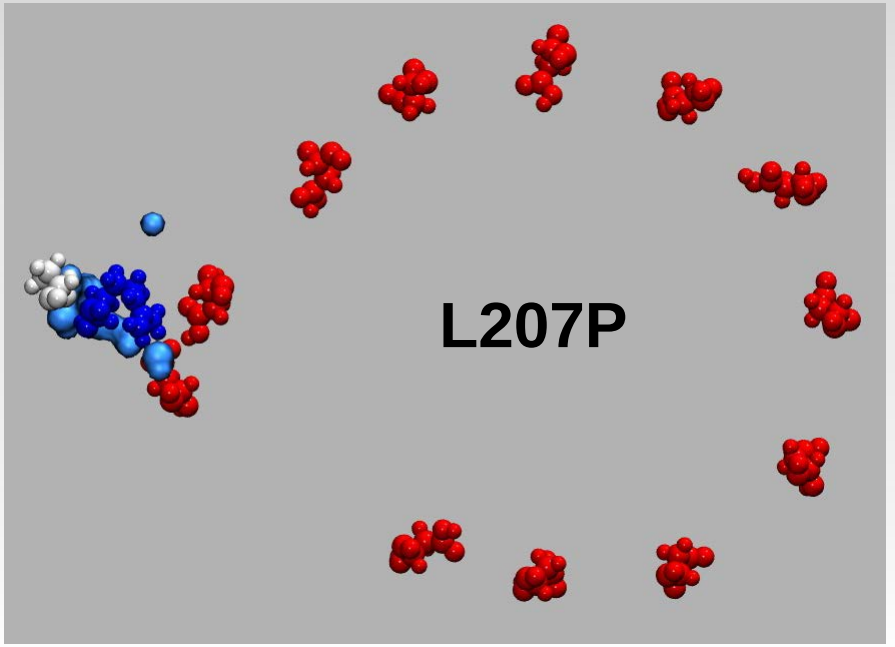




Top views: 207, R210, Asp61 (c-ring)







Complex I; Respirasome Supercomplex

Electron transport in respirasome

Speculative model of complex I function

Water channel formation in complex I

Quantum “Goldilocks” effect for electron transport?

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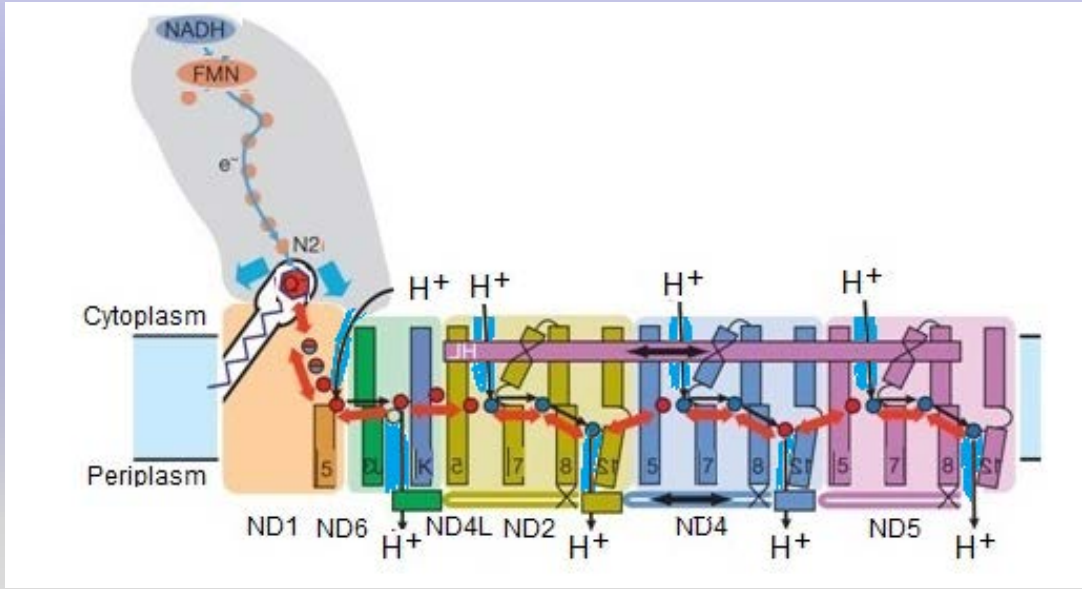
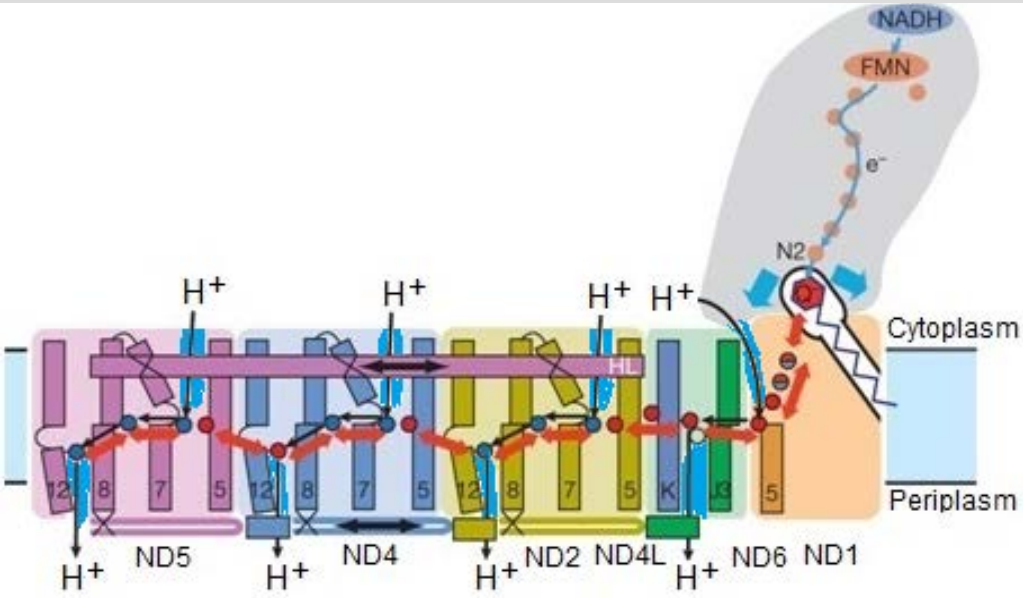
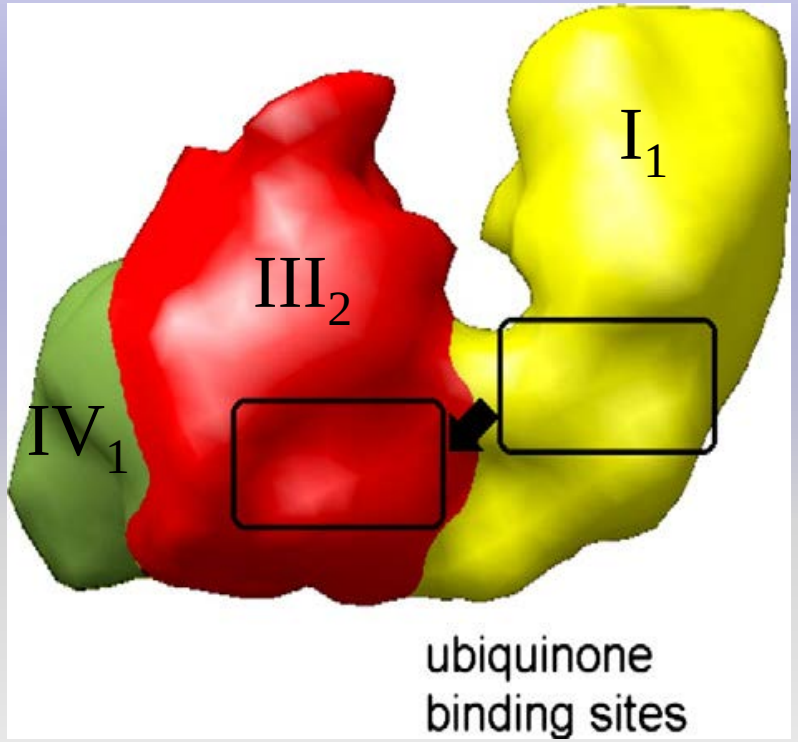
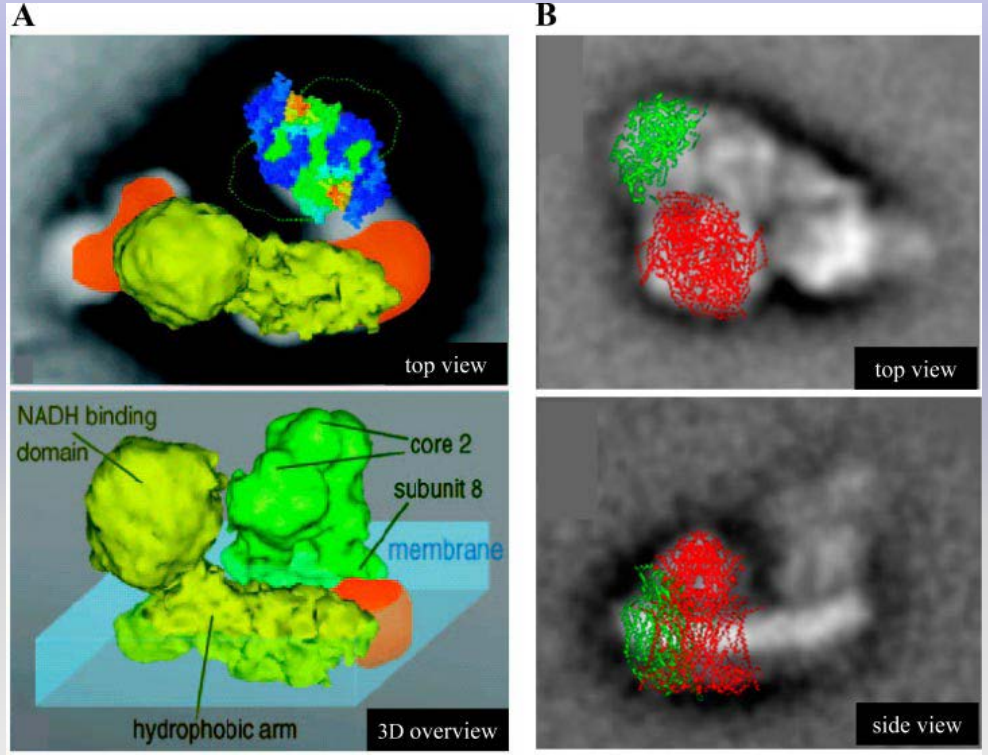
Mitochondrial Complex I





Respirasome Supercomplex



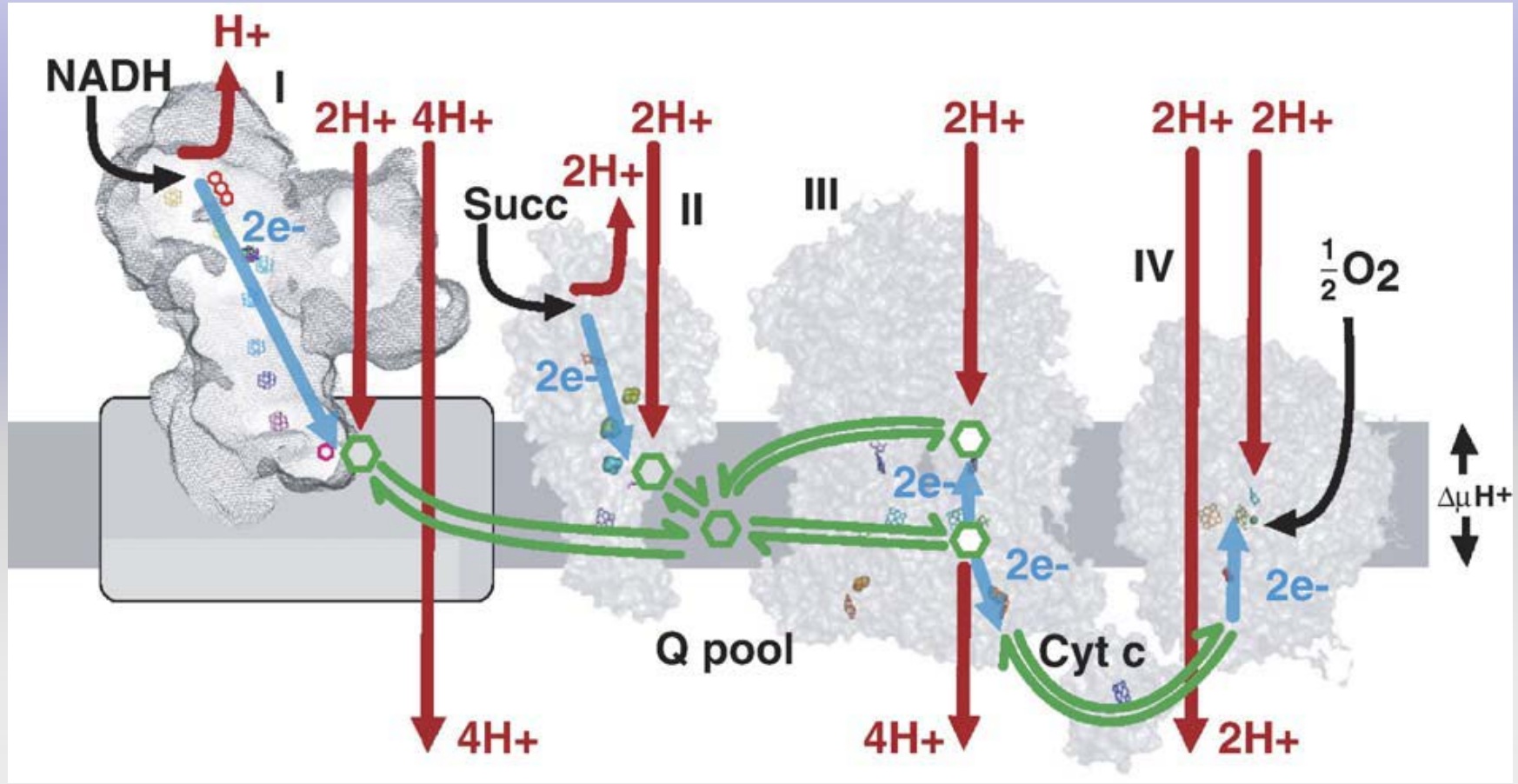


Genova et al., *BBA* **1777**, 740 ('08)

Lenaz et al., *AJP-Cell Physiol*. **292**, C1221 ('07)

EM database EMD-1318
http://www.ebi.ac.uk/msd/index.html

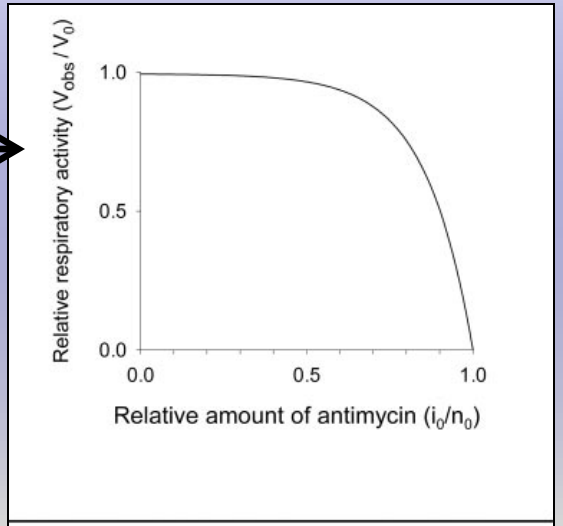
Electron Pathways in Respiratory Chain



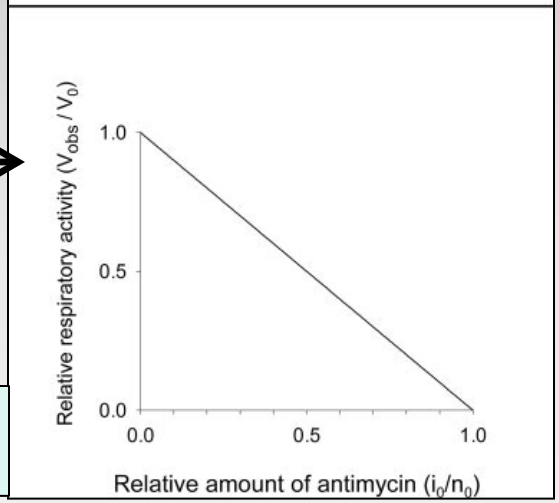
Moser et al., *BBA* **1757**, 1096 ('06)

Kinetics of Electron Transfer

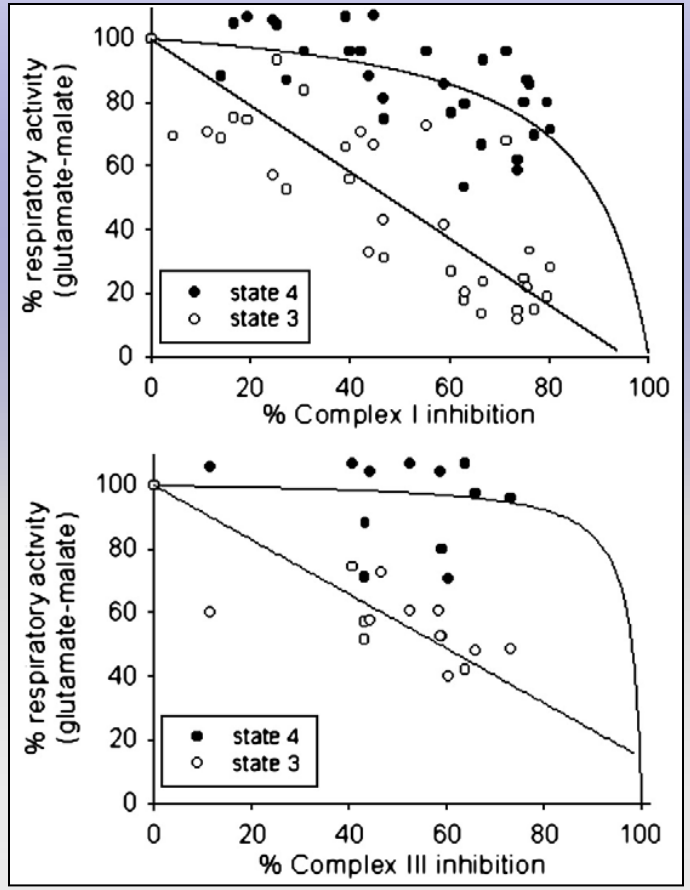
Theory (state 3): Diffusion of CoQ e^- carriers.



Theory (state 3): Channeling of e^-'s: I → III via CoQ.



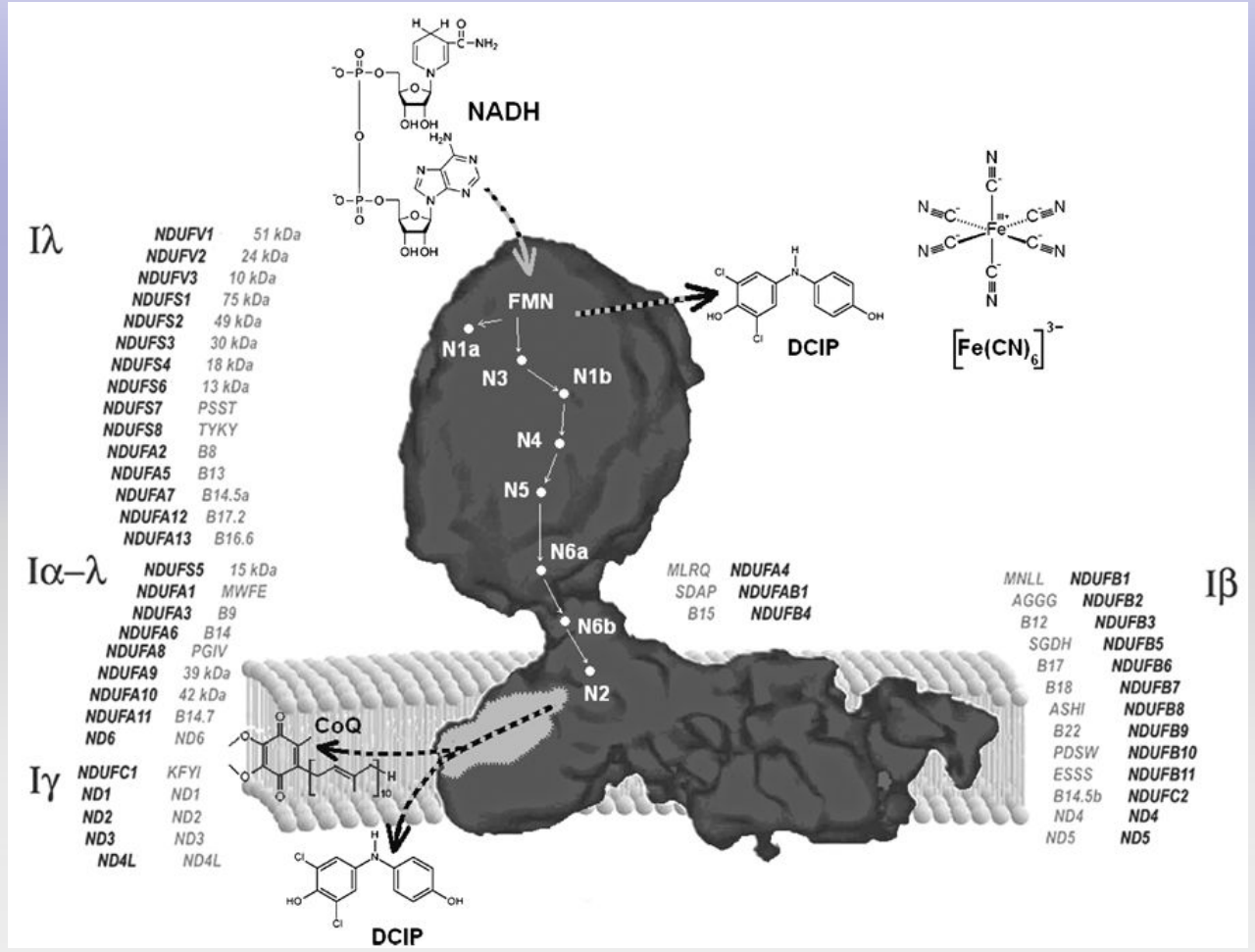
Lenaz et al., *AJP-Cell Physiol*. **292**, C1221 ('07)



Genova et al., *BBA* **1777**, 740('08)

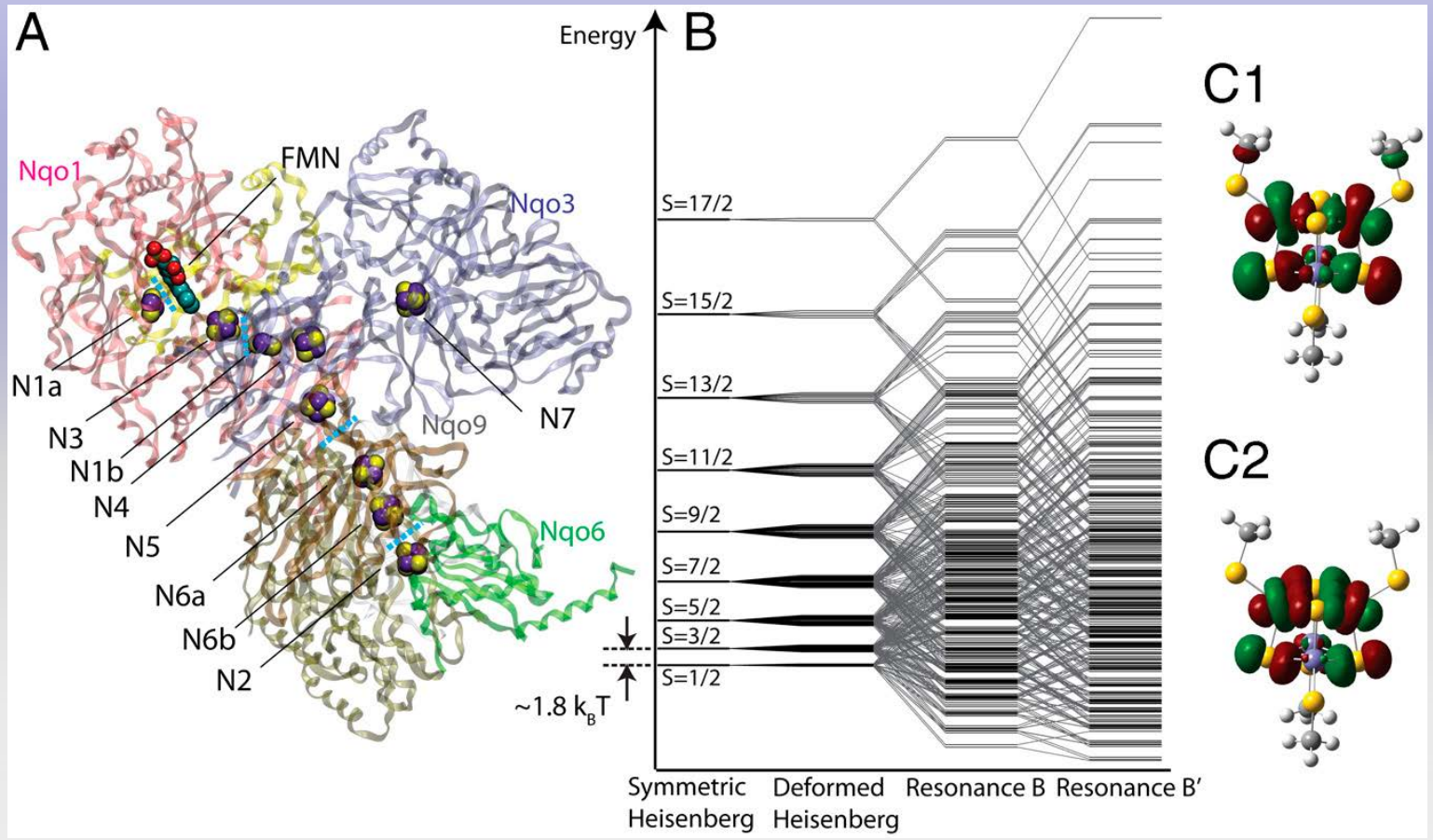
"…Complex I & Complex III behave as a single enzyme …"

Electron Transfer in Mitochondrial Complex I



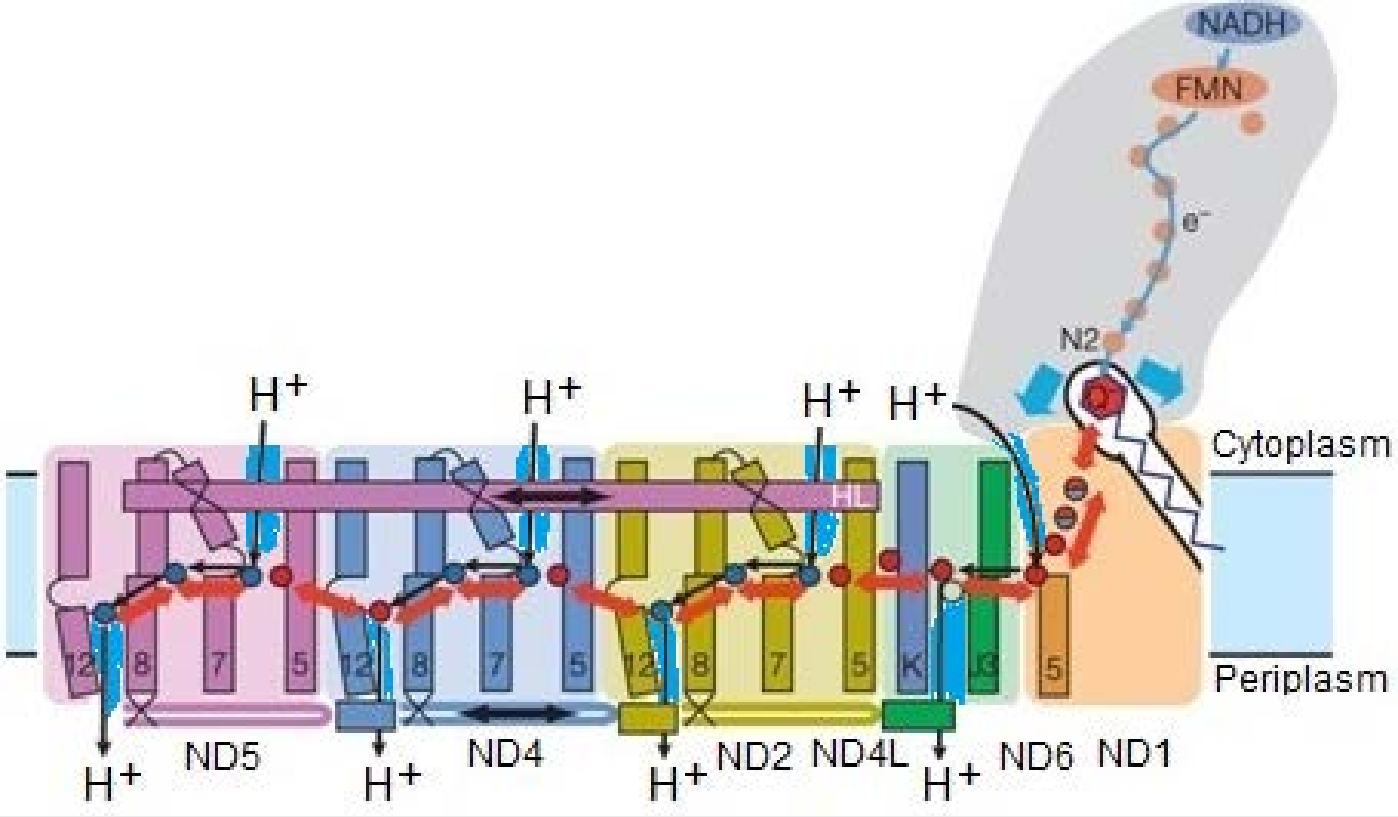
Lenaz & Genova, *Antioxid. Redox Signal.* **12**, 961 ('10)

Electron Tunneling in Mitochondrial Complex I



Hayashi & Stuchebrukhov, *PNAS*, 2010

Schematic of Complex I



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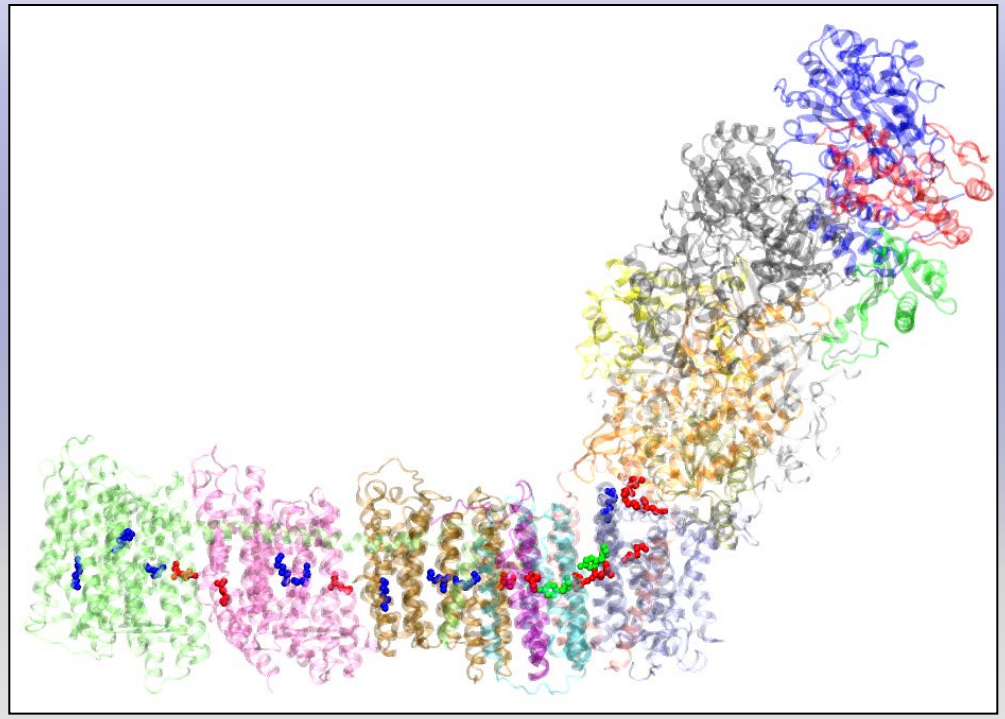
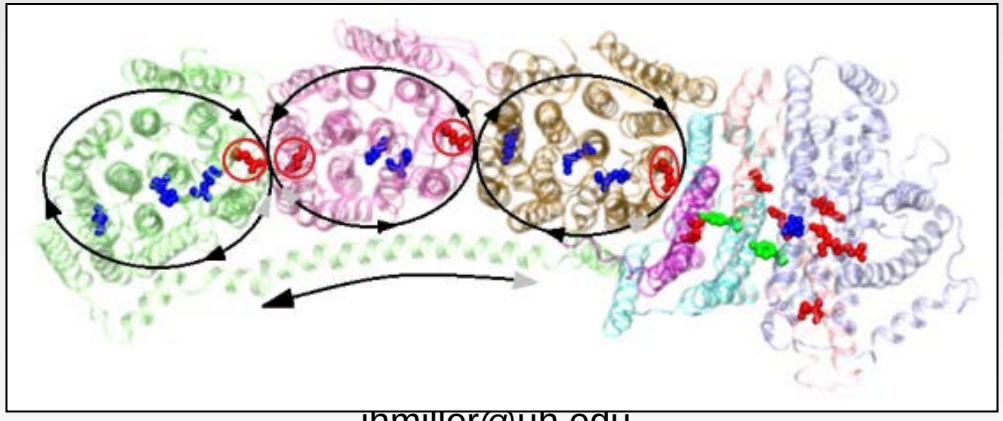
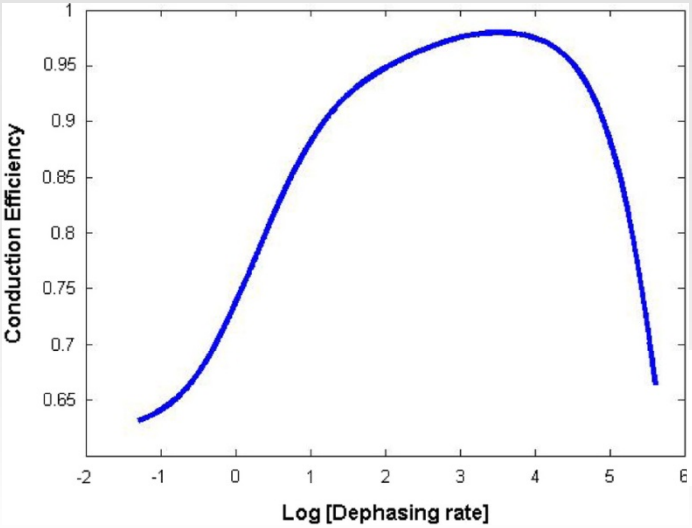
Complex I: Possible proton transport mechanism

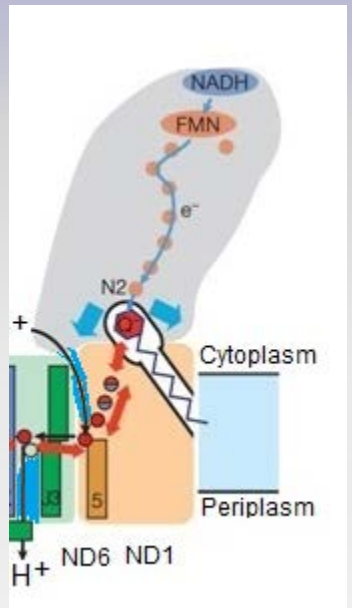




Quantum "Goldilocks" effect for electron transport?

- Why is optimum body temperature in narrow range ~ 37°C?
- Perhaps to optimize electron transport rates: thermal fluctuations overcome localization w/o destroying quantum coherence.
  - Interplay between coherence & decoherence ⇔ "just right." (Seth Lloyd)





Huelga, *Contemporary Physics* **54**, 181 (2013).

Thank you!

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