Normal & Impaired Charge Transport in Biological Systems

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Introduction

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

Hole migration & mutations in DNA

• Hole on base $\rightarrow$ Tautomerization $\rightarrow$ Mutation
• Guanine mutations enhanced

Mitochondrial charge transport $\rightarrow$ ATP

• Water channels; ATP synthase
• Mutations $\rightarrow$ Impaired transport $\rightarrow$ Diseases
• Complex I physics (known & unknown)
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
DNA base pair sequence encodes information

Purines: Guanine & Adenine
Pyrimidines: Cytosine & Thymine

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

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DNA replication

Replication & repair enzymes →:

Part of double helix splits → 2 strands;
Complementary bases pair w/ parent strand bases.

Image from: http://genmed.yolasite.com/fundamentals-of-genetics.php
Transcription: DNA sequence portion (gene) $\rightarrow$ mRNA.

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

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

http://www.newworldencyclopedia.org/entry/Translation_(biology)
mRNA 3-letter code $\rightarrow$ amino acid, start, or stop.

64 combinations, 21 amino acids;

Encoded by original DNA bases. **Copying error $\rightarrow$ Mutation!**
Mitochondria have their own DNA molecules

Mitochondrial DNA \(\leftrightarrow\) 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.
Guanine base substitutions most common in cancer.

Guanine sites act as potential wells for holes.

Above effects appear causally related
Possible mechanism ⇔ Tautomerization → mispair


Hole on guanine → Shift in hydrogen ion: $G \rightarrow G^*$.  

$G^*$ “incorrectly” pairs w/ $T \rightarrow G^*:T$.  

$G^*:T$ replicates to “correct” but mutated pairing, $A:T$.  

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

$E_G = 7.75$ eV, $E_C = 8.87$ eV, $E_T = 9.14$ eV & $E_A = 8.24$ eV

Diagonalize Hamiltonian using actual mtDNA sequence $\rightarrow$ Eigenenergies & eigenfunctions.
Hole Probabilities Near Mutation Site

before G $\rightarrow$ A mutation  

after G $\rightarrow$ A mutation  

Hole probabilities $\sim$ mtDNA locus 3378 (cancer-implicated)

Which mutations “survive”?  
Perverse Darwinian natural selection $\leftarrow$  
Mutation survival in tumor $\leftarrow$  
Amino acid replacement effects.
Effects of mtDNA point mutations

mtDNA base substitution $\rightarrow$ Amino acid replacement in respiratory chain $\rightarrow$ Altered function of mitochondrial machinery

Altered function of mitochondrial machinery
(e.g., impaired electron or proton transport) $\rightarrow$ Reduced oxidative ATP production
Increased ROS $\rightarrow$ Upregulation of key enzymes
Growth advantage
Enhanced tumorigenesis
Metastatic potential

In the case of cancer.
Hypotheses

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

• mtDNA mutations in cancer “optimally” affect charge transport: \( \uparrow \) reactive oxygen species \( \rightarrow \) \( \uparrow \) certain enzymes (e.g. HK2).
Mitochondrial Electron Transport Chain

NADH → NAD⁺
Complex I

Inside the matrix

Complex III

Complex IV

Cytochrome c

Quinone pool

e⁻ → e⁻

ADP + Pᵢ → ATP

H⁺

O₂

H₂O

ATP Synthase (F₀F₁)

F₁

F₀

H⁺

Courtesy of Peter L. Pedersen (Johns Hopkins, 2007)
ATP Synthase
Electric field driven torque in ATP synthase

\[ \tau = \frac{ne}{2\pi} \Delta p \]

The Mitochondrial Genome:
mtDNA = 37 genes
Extra-cellular plasmids (chromosomes) ~ 1500 genes

ATP Synthase α-subunit sequence homology: 
*H. sapiens* vs. *E. coli*
Fo-ATP Synthase ac complex
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)

Wild Type

L207R mutant

L207P mutant
Top views: 207, R210, Asp61 (c-ring)

Wild Type

L207R

L207P
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?
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)
Theory (state 3): Diffusion of CoQ $e^-$ carriers.

Theory (state 3): Channeling of $e^-$'s: I $\rightarrow$ 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
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)

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