The University of Sydney

Old Geology Lecture Theatre, Old Geology Building

23rd February 2009

# Genes in organelles

## Mitochondria, ageing, and sex – energy versus fidelity

John F. Allen* and Carol A. Allen

*Australian Academy of Science Rudi Lemberg Travelling Fellow

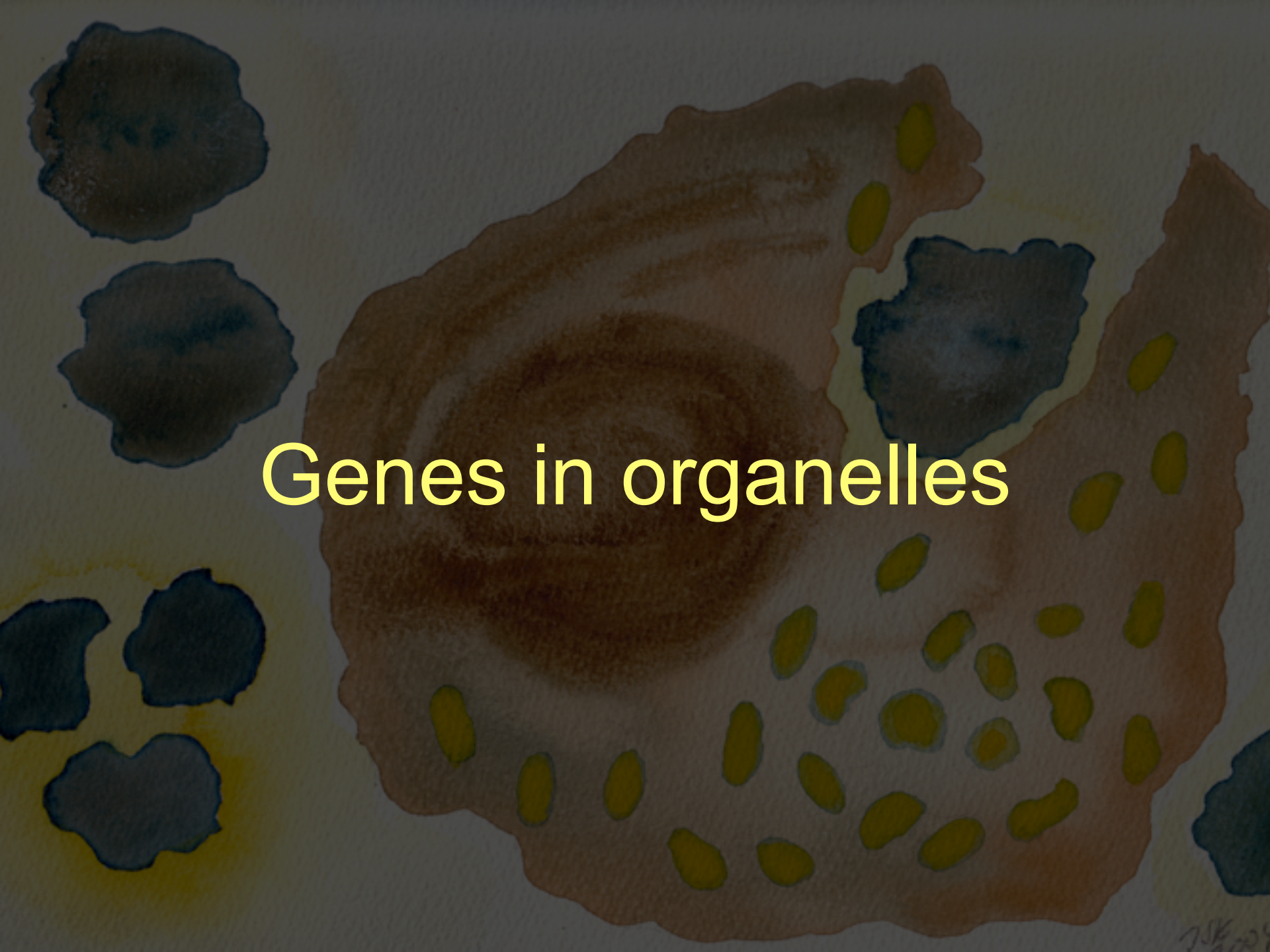
School of Biological and Chemical Sciences, Queen Mary, University of London

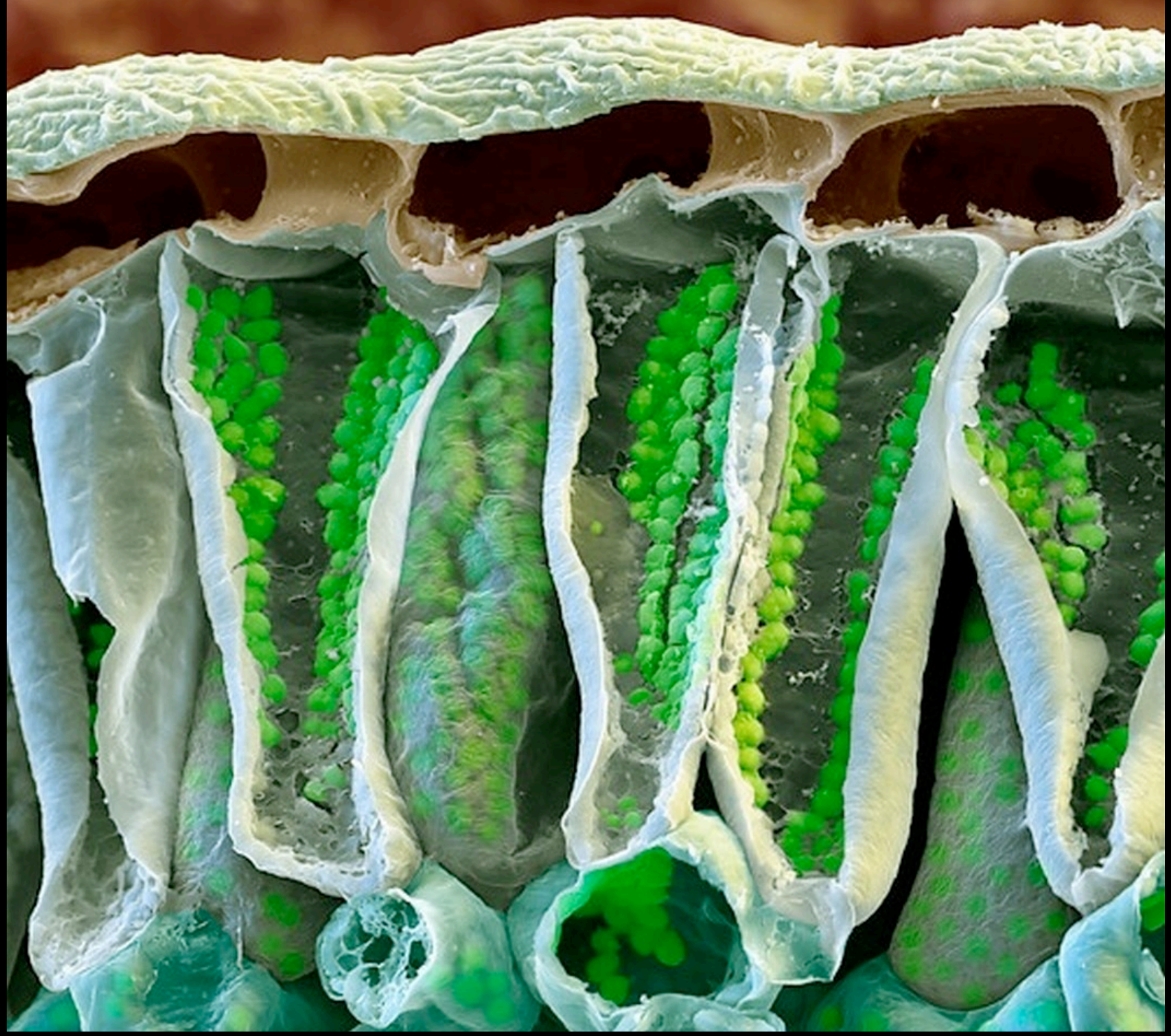
*jfallen.org

Queen Mary
University of London

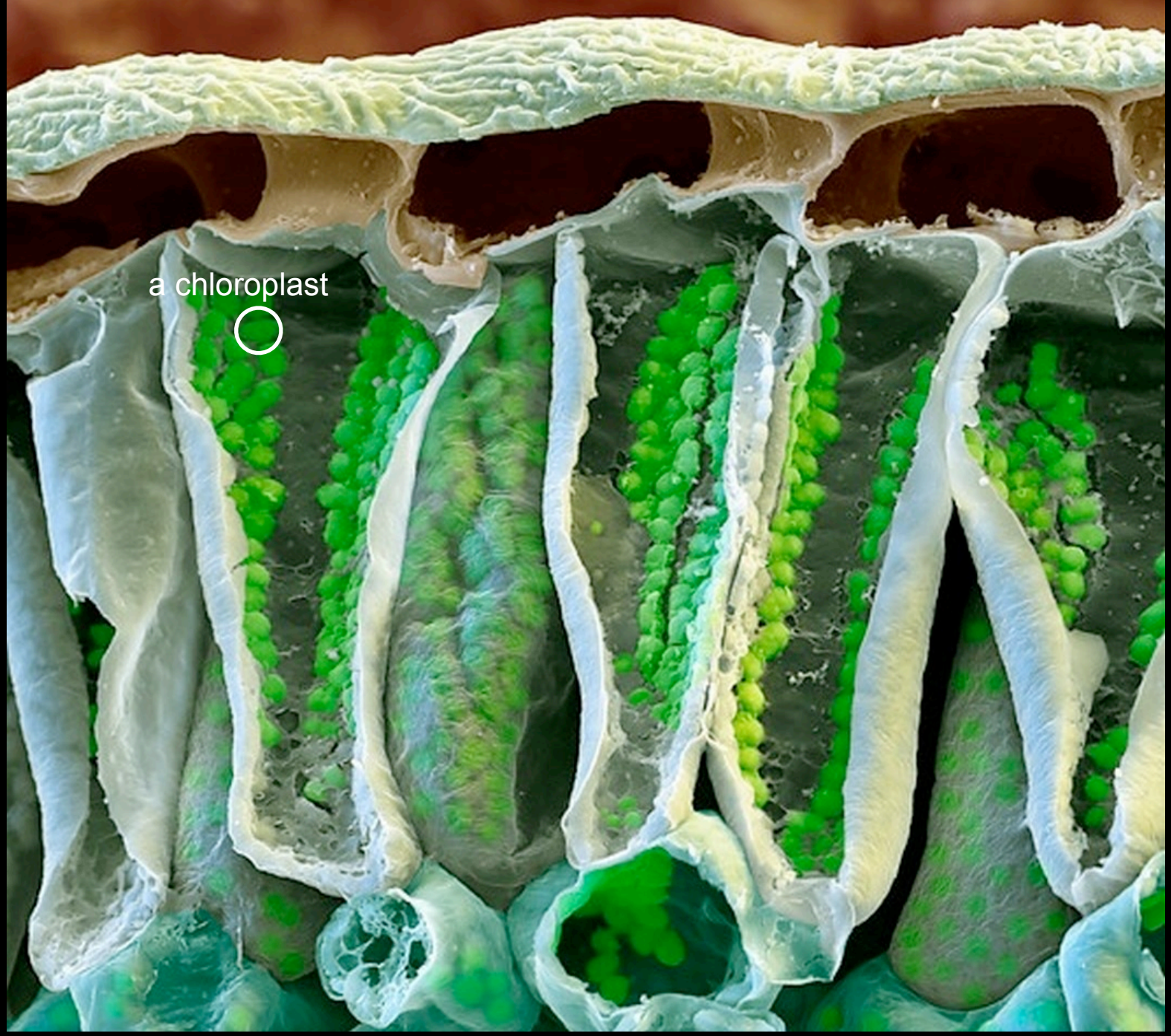
Max Rudolph Lemberg

1896-1975


Genes in organelles



‘Christmas-Rose’ leaf SEM cross-section; Science Photo Library (SPL)

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A mitochondrion—one of many tiny power-houses within cells that control our lives in surprising ways

Mitochondria (singular; mitochondrion).

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**Why?**

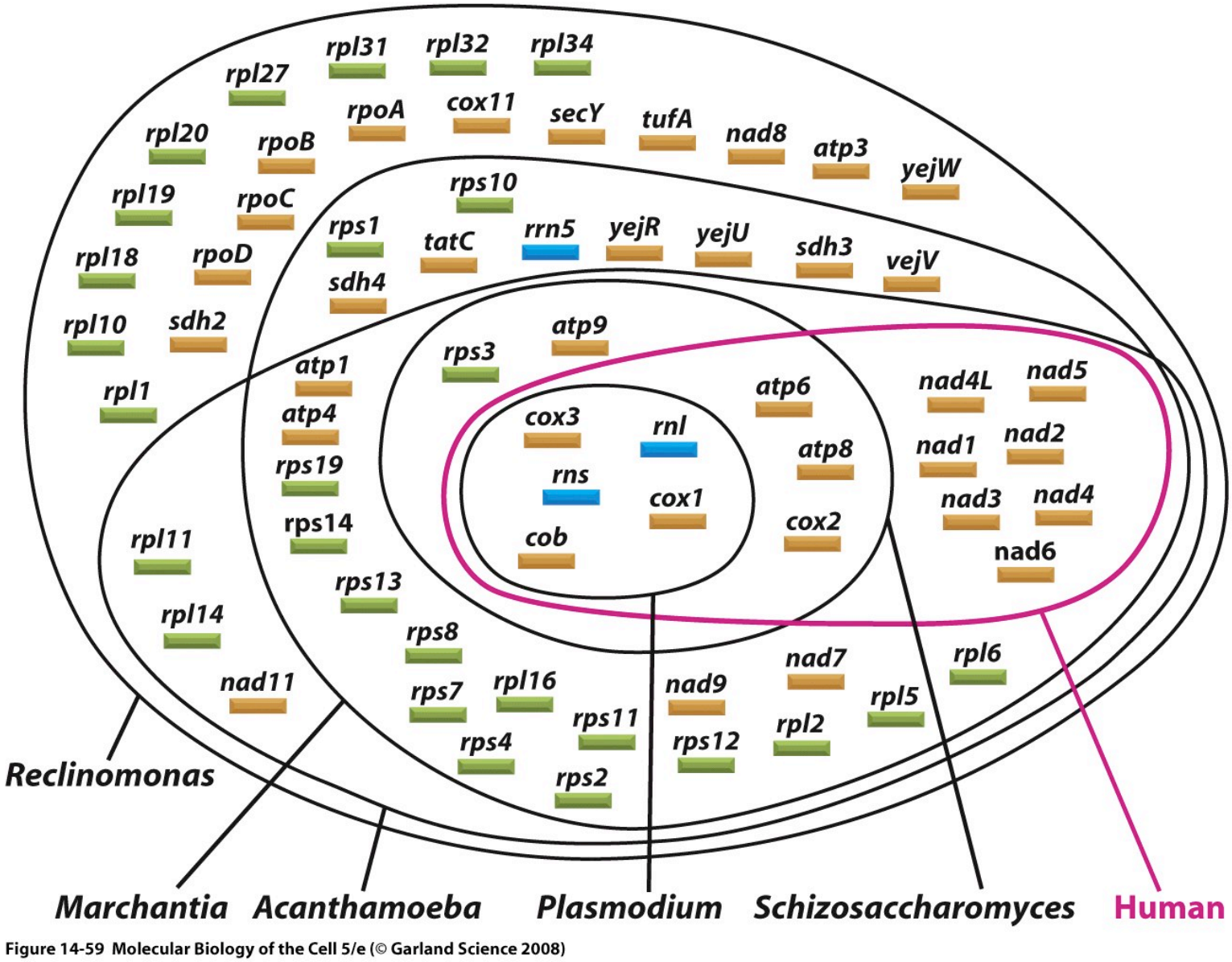
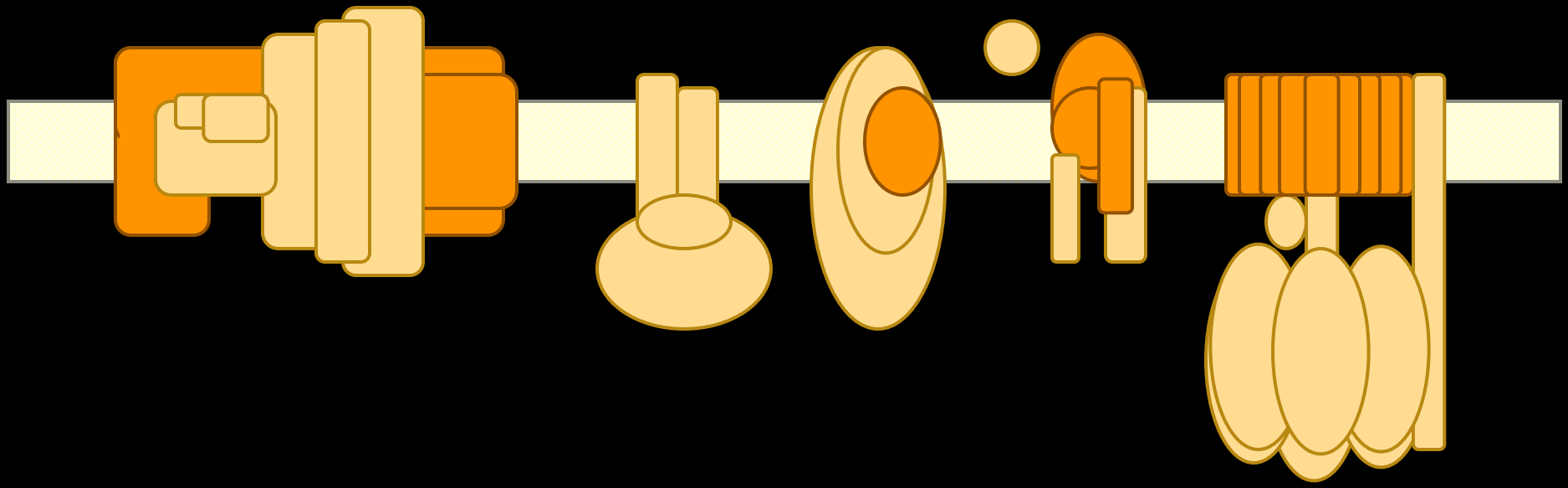
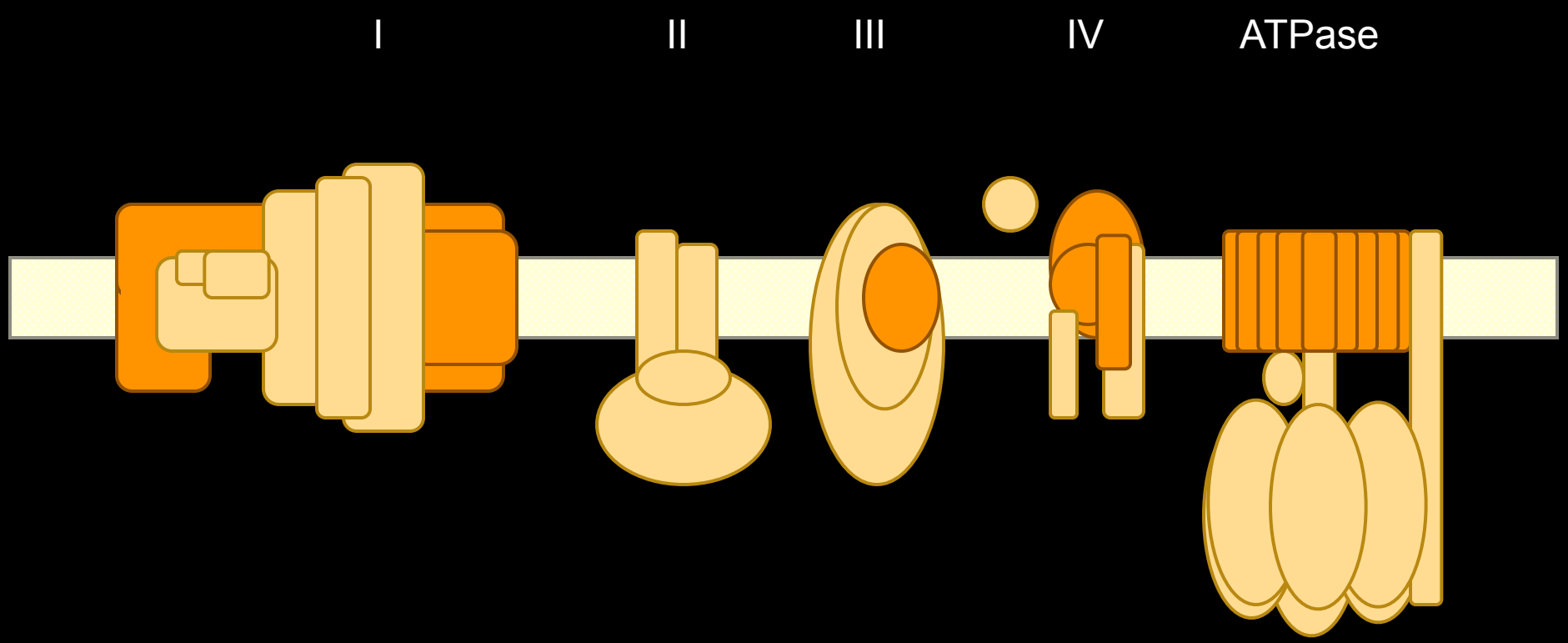


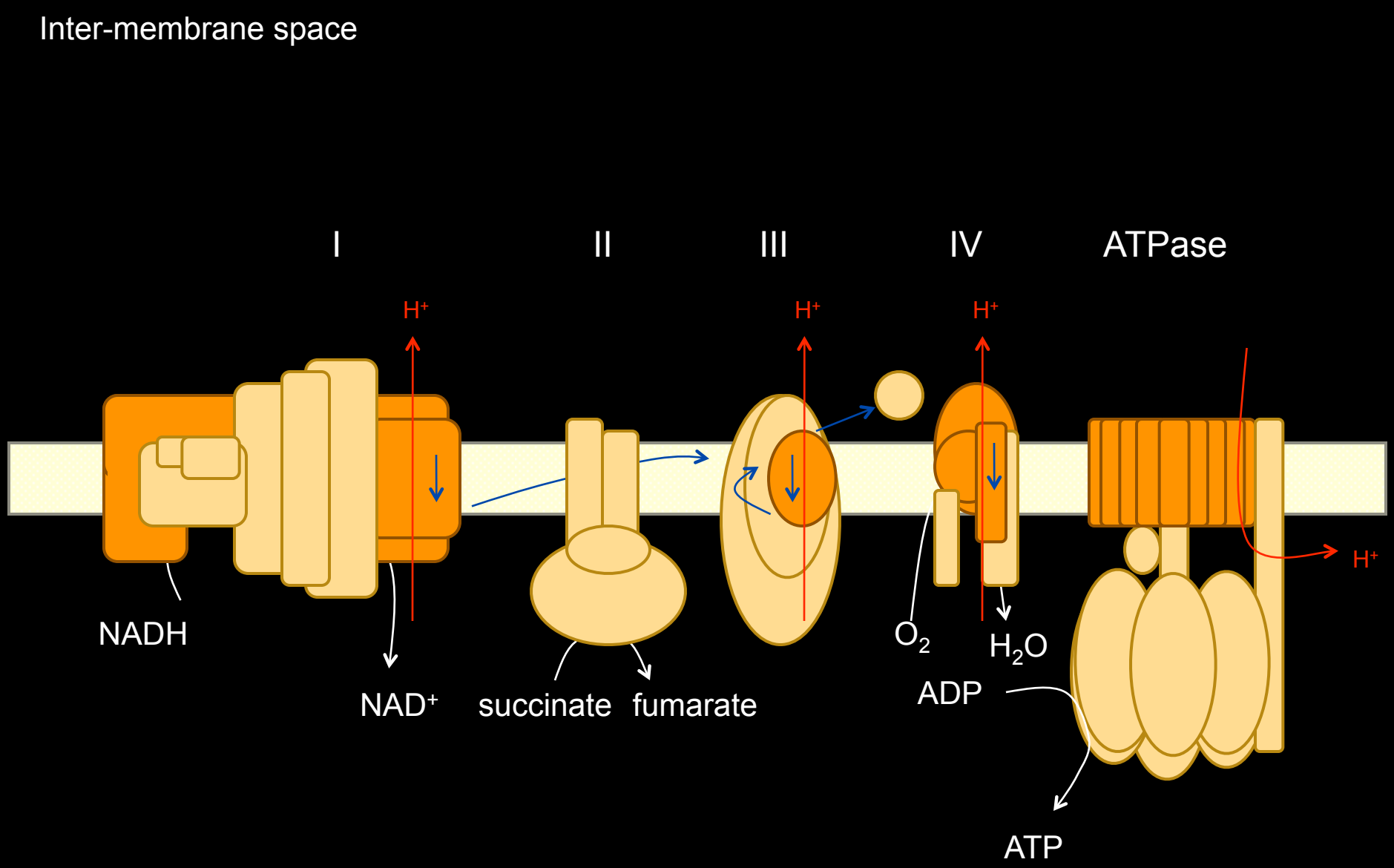

Figure 14-59 Molecular Biology of the Cell 5/e (© Garland Science 2008)

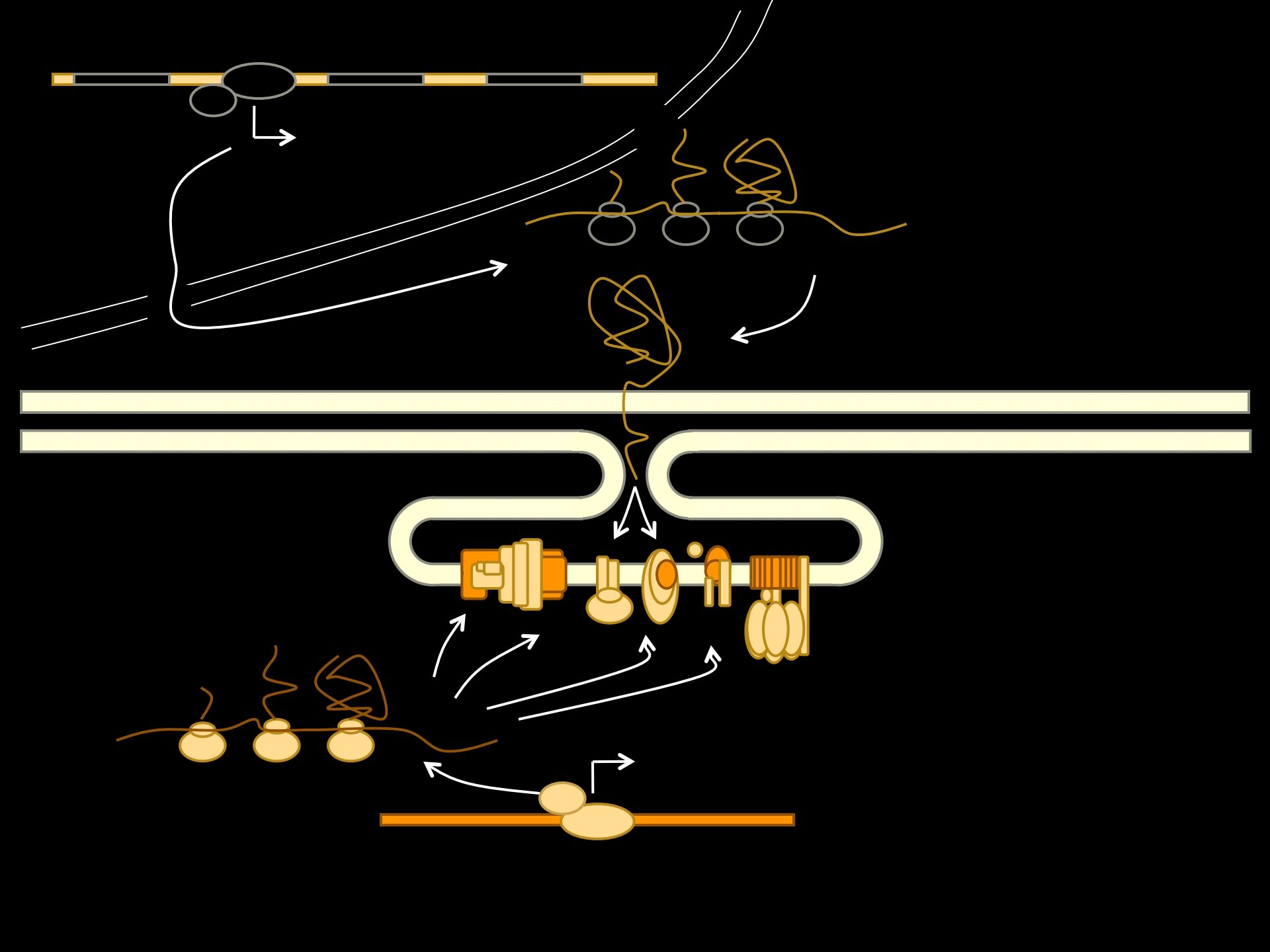
**Comparison of mitochondrial genomes**

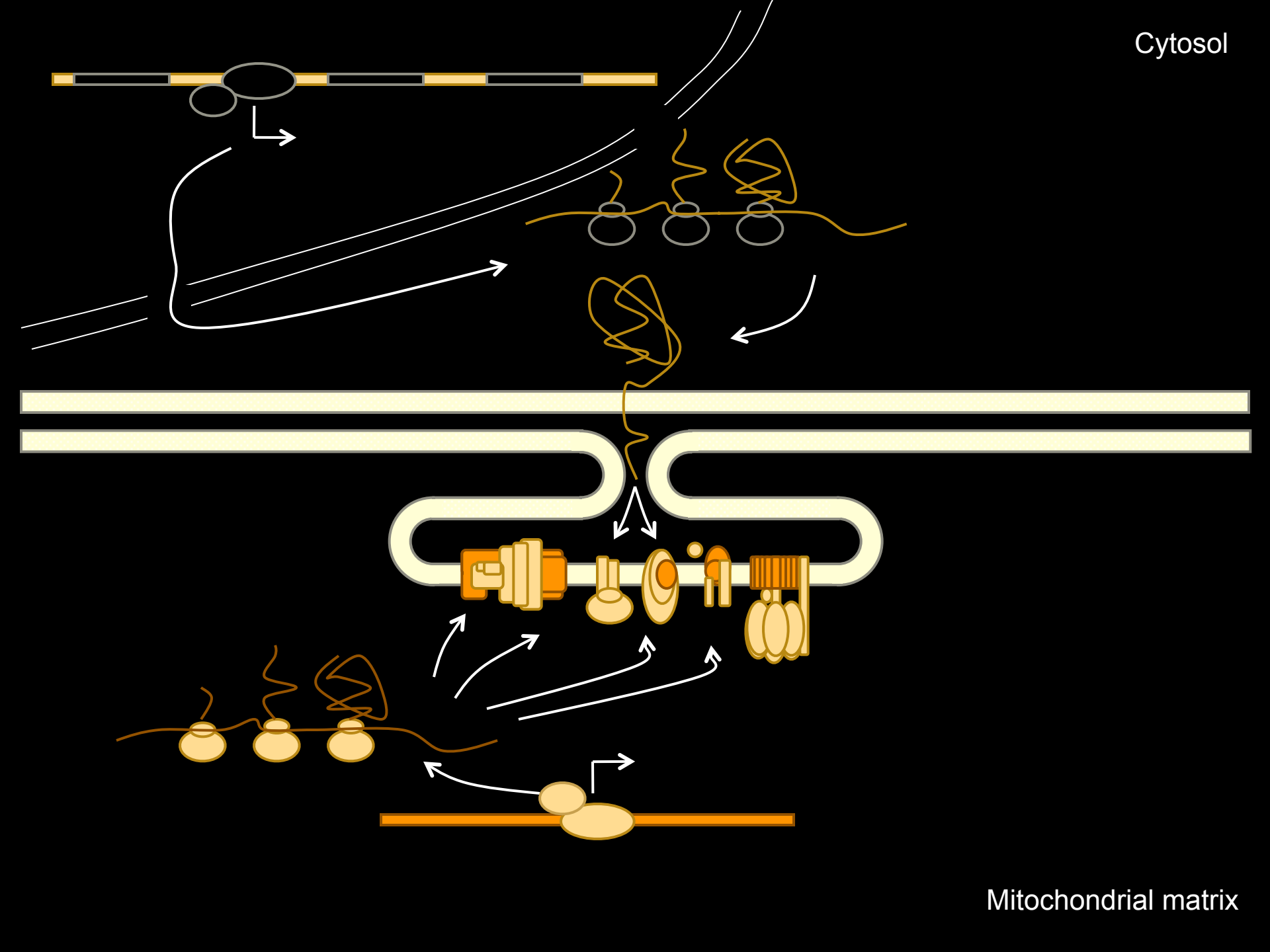
Less complex mitochondrial genomes encode subsets of the proteins and ribosomal RNAs that are encoded by larger mitochondrial genomes. There are only four genes present in all known mitochondrial genomes; these encode ribosomal RNAs *(rns* and *rnl),* cytochrome *b (cob),* and a cytochrome oxidase subunit *(cox1).* Adapted from M.W. Gray et al., *Science* 283:1476-1481, 1999. With permission from AAAS.




Inter-membrane space
I
II
III
IV
ATPase
Mitochondrial matrix


Inter-membrane space
I
II
III
IV
ATPase
H+
H+
H+
H+
NADH
NAD+
succinate
fumarate
O2
H2O
ADP
ATP
Mitochondrial matrix




Cytosol
Mitochondrial matrix

# Why mitochondria have genomes

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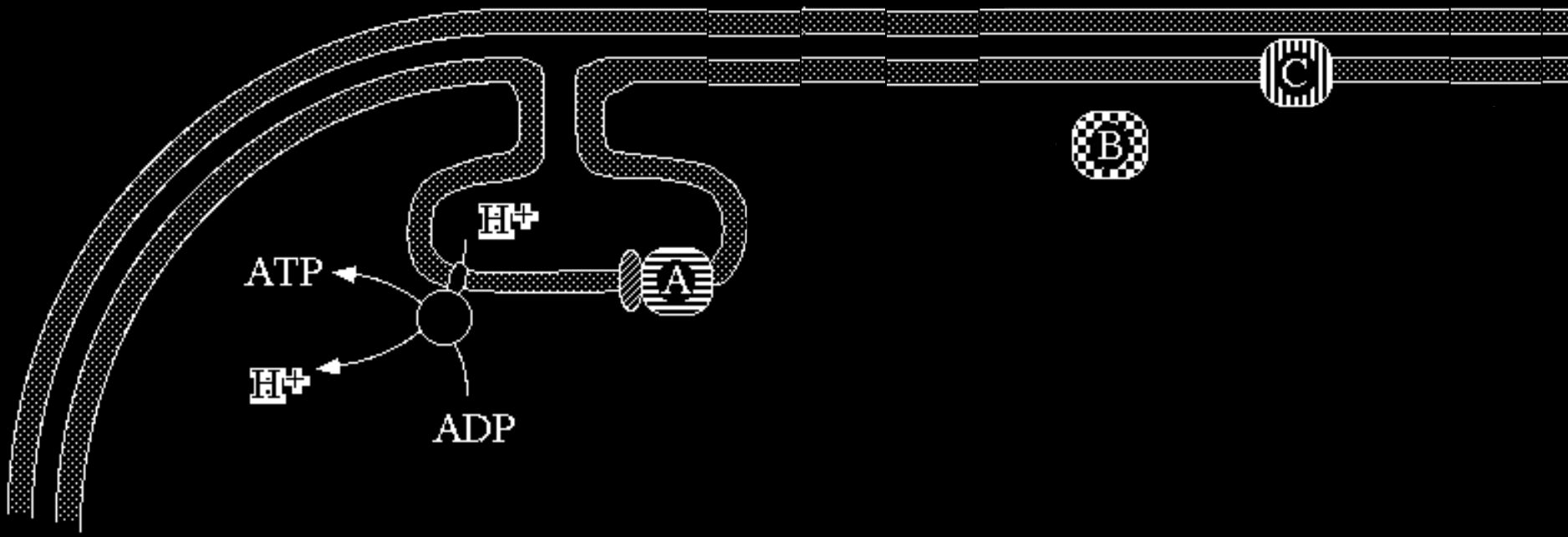
*Redox reactions are chemical reaction in which an electron is transferred from one molecule to another - the basis of biological energy conversion.


C
B
H+
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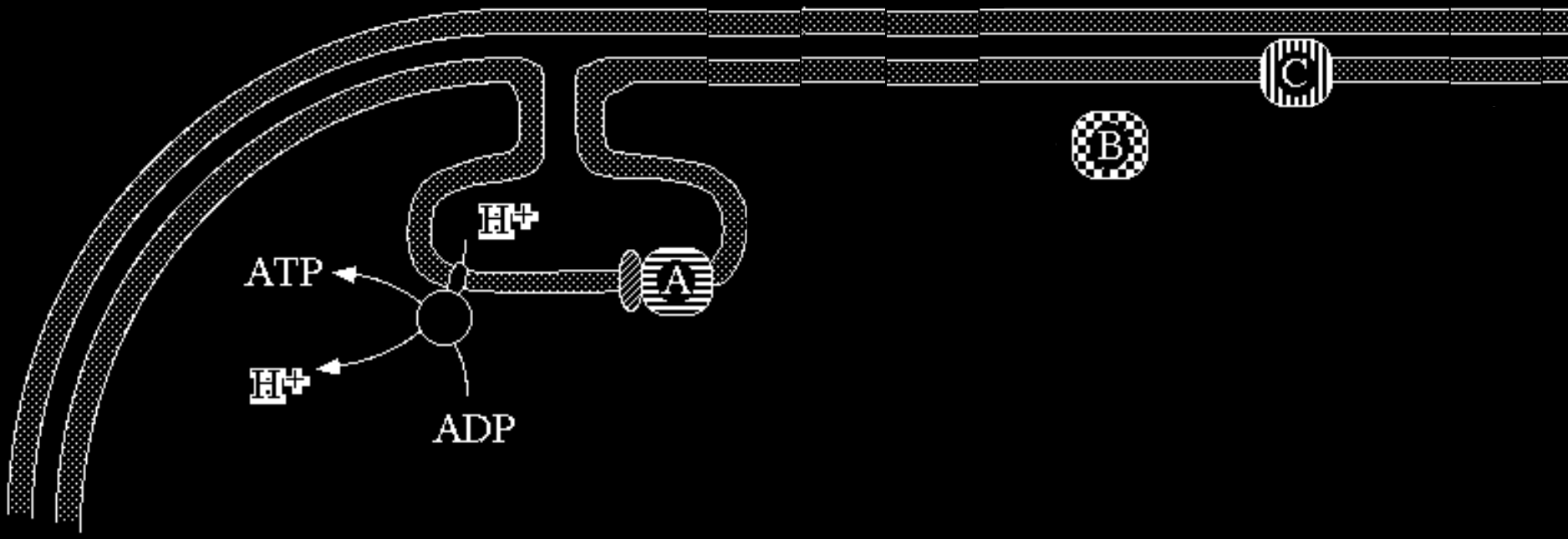
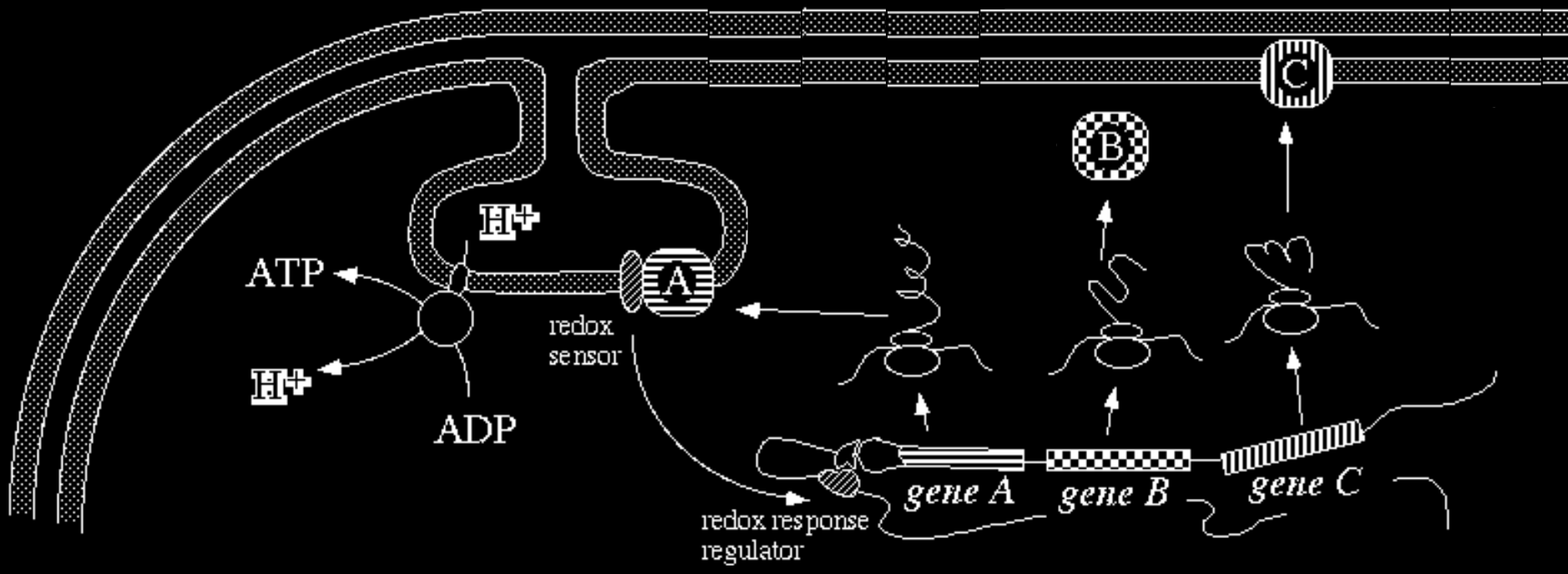
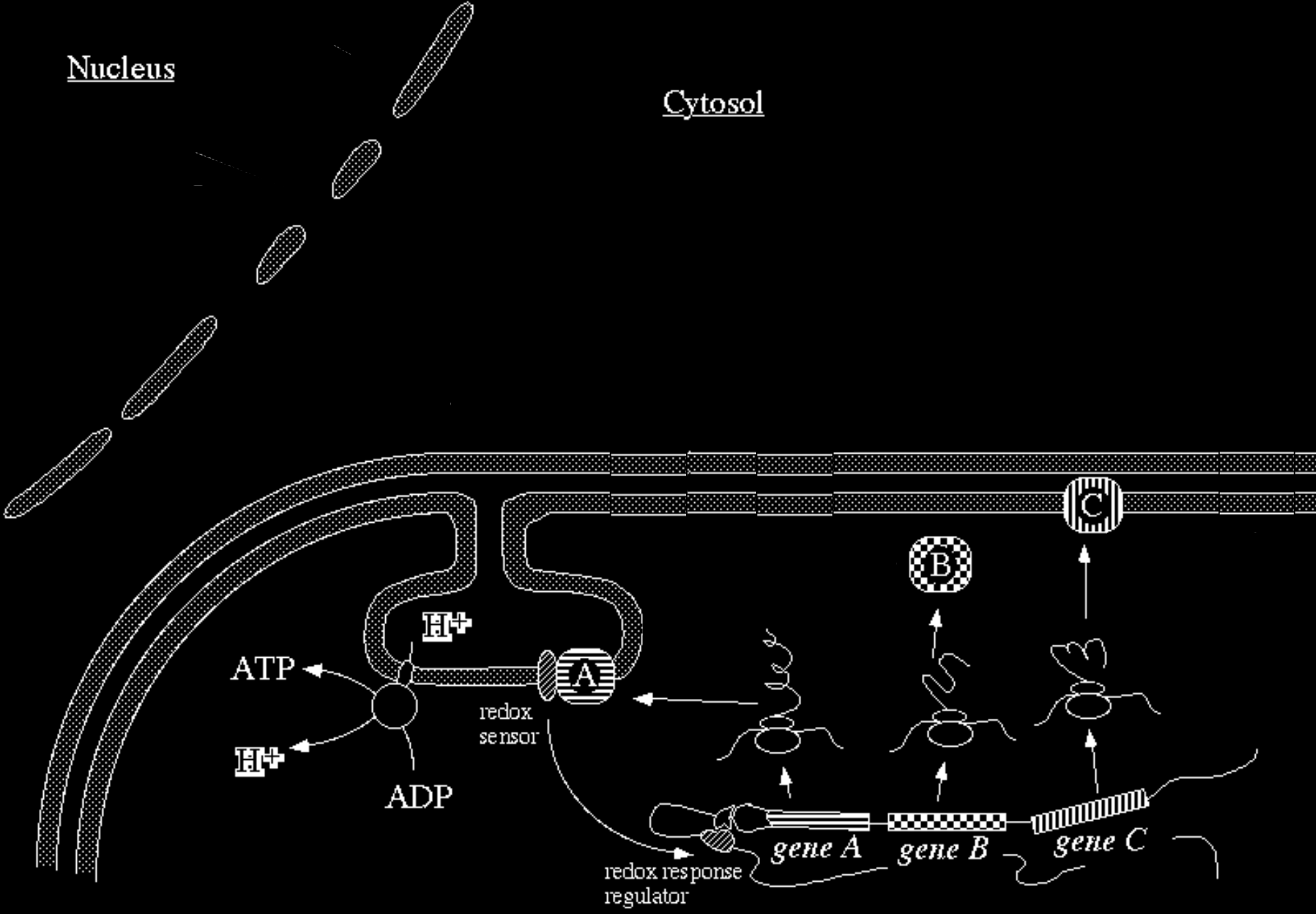


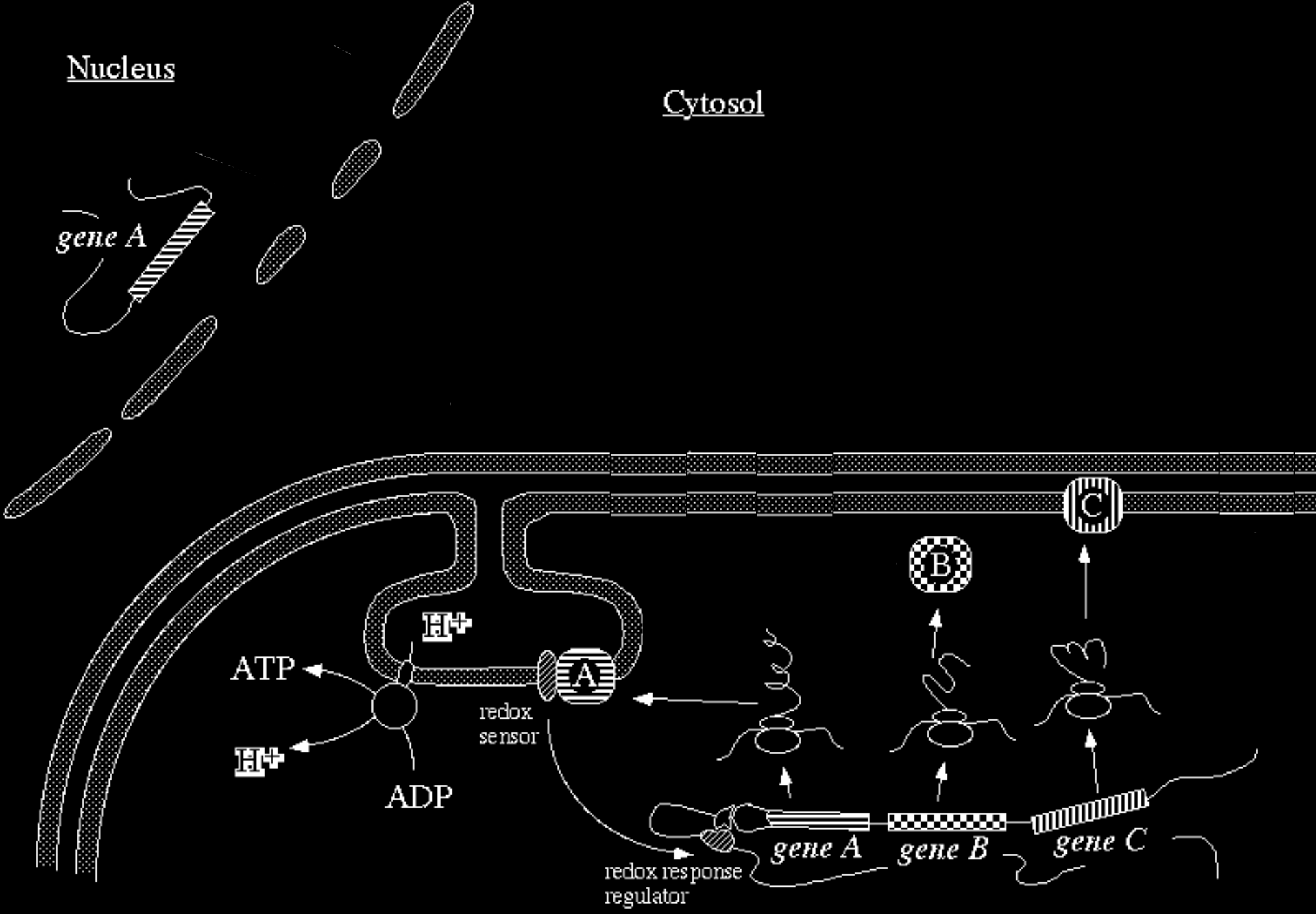

Bacterium


C
B
A
H+
ATP
H+
ADP
redox
sensor
gene A
gene B
gene C
redox response
regulator

Bacterium




Endosymbiont

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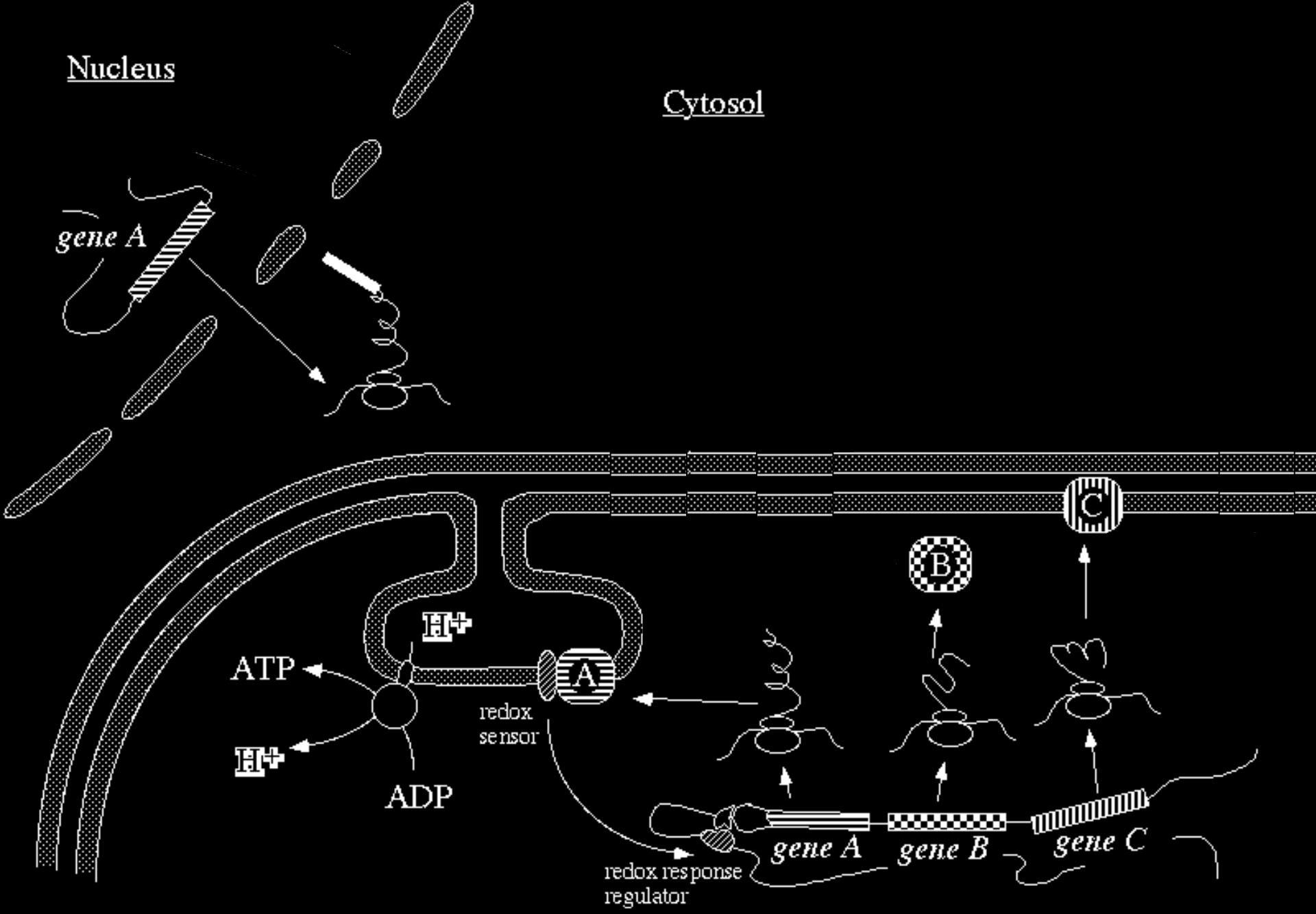


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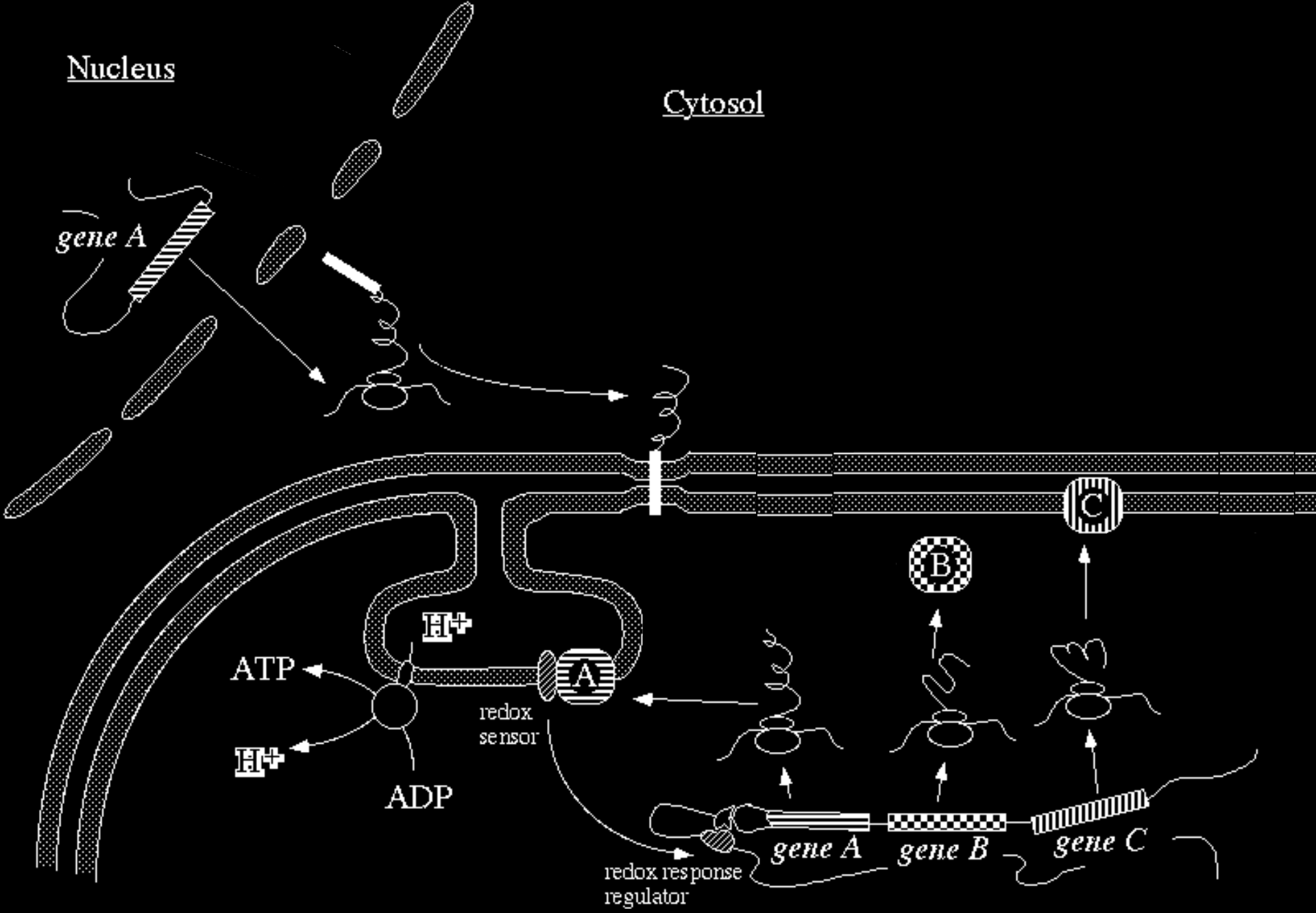


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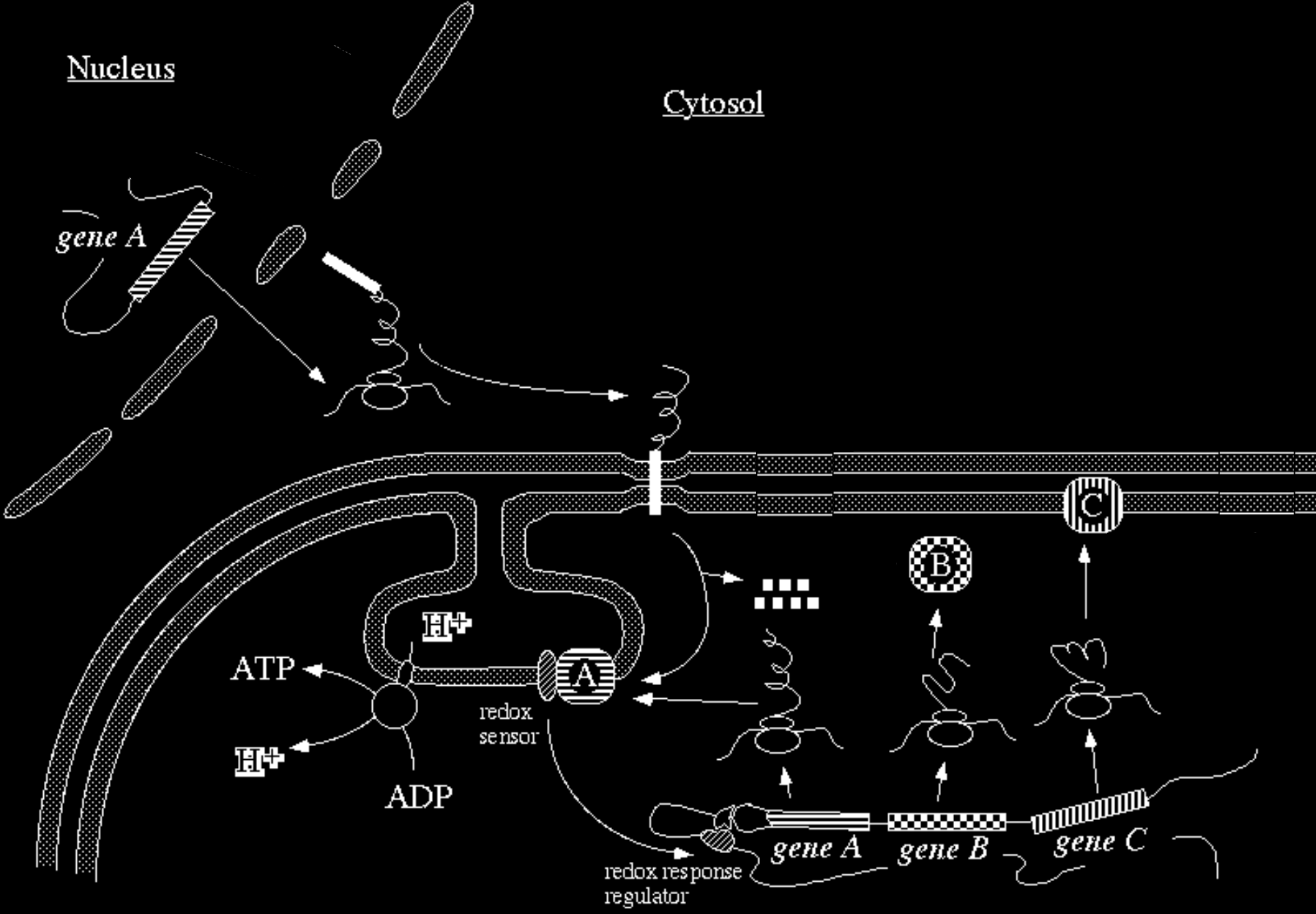


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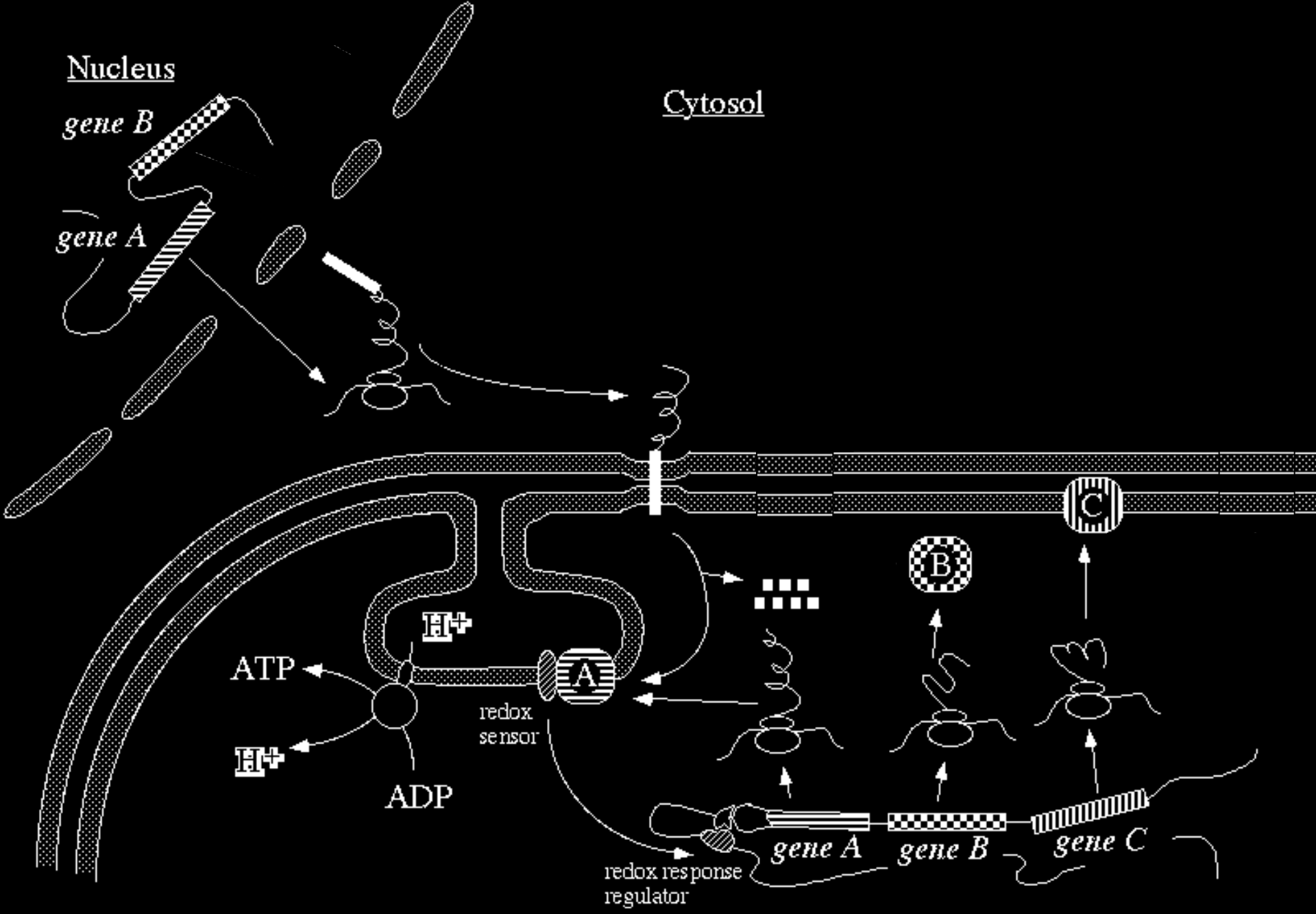


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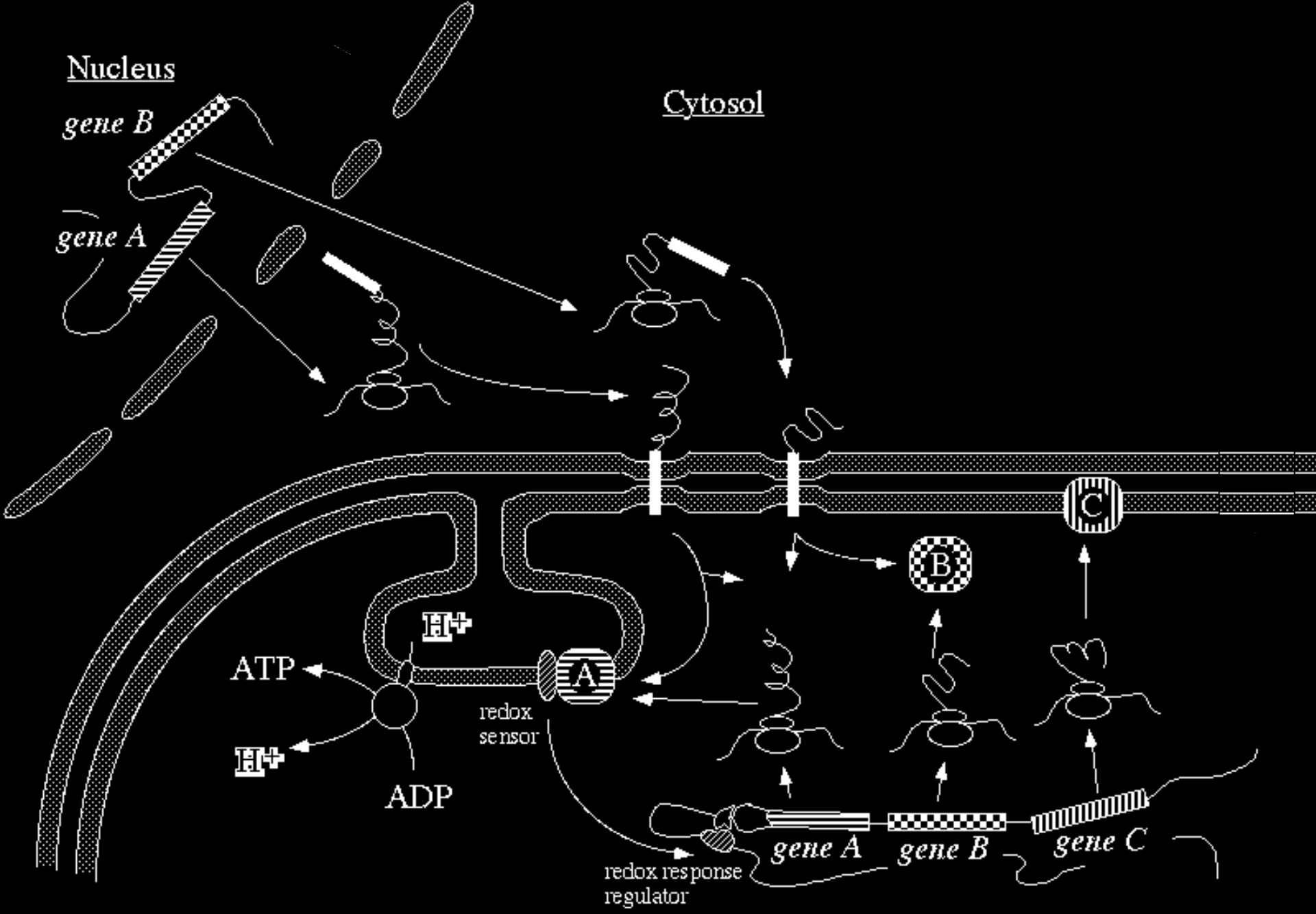


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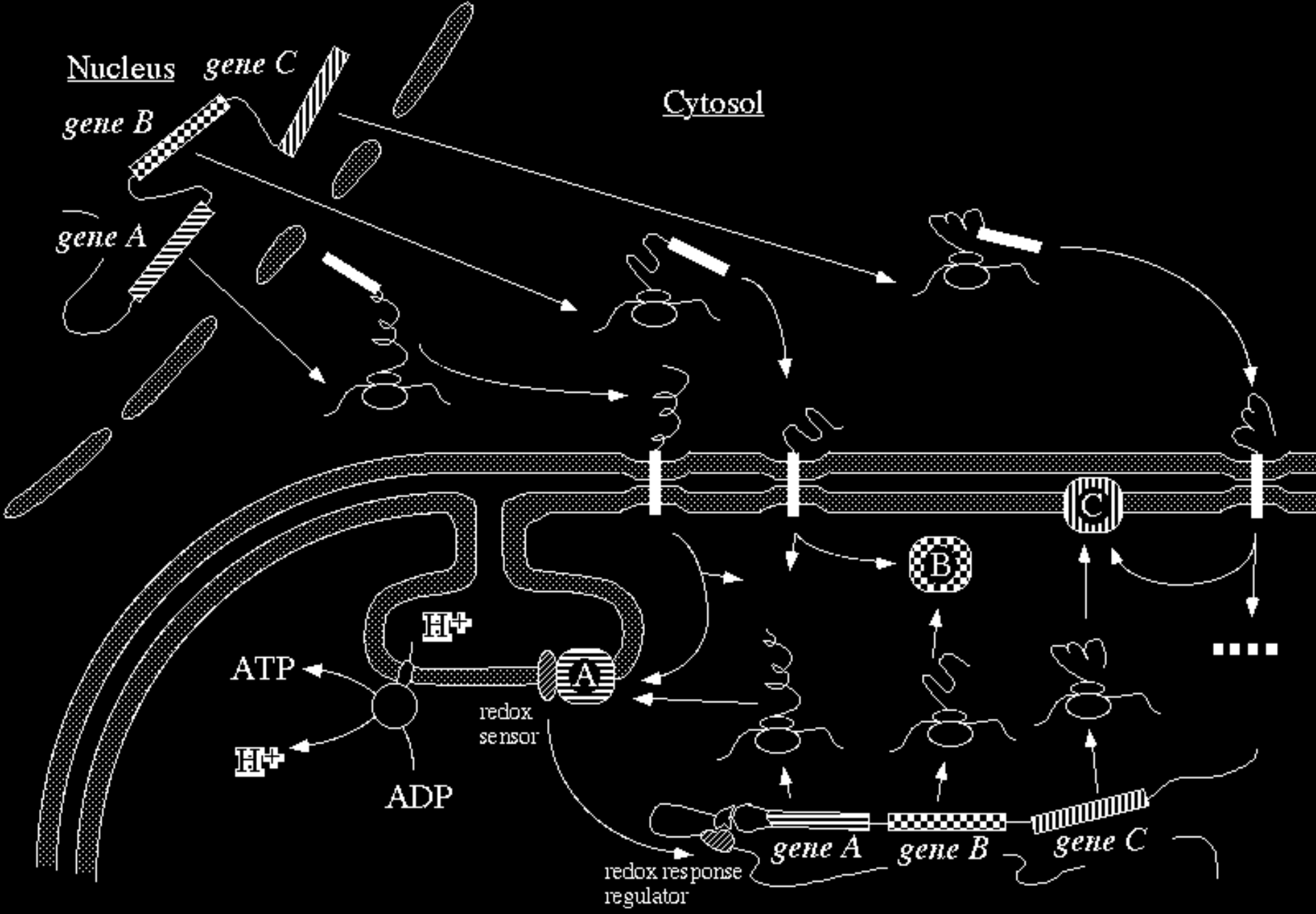


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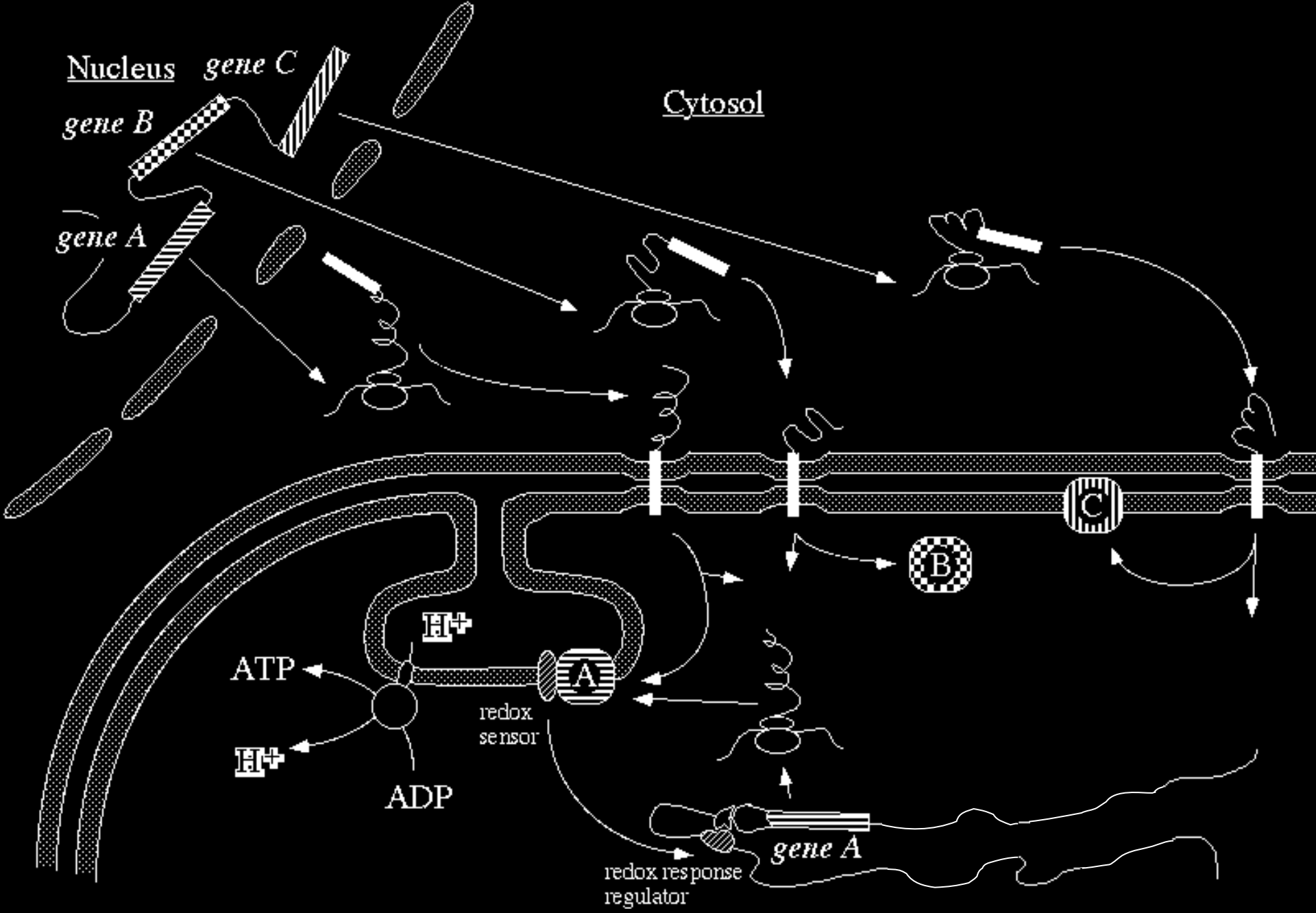


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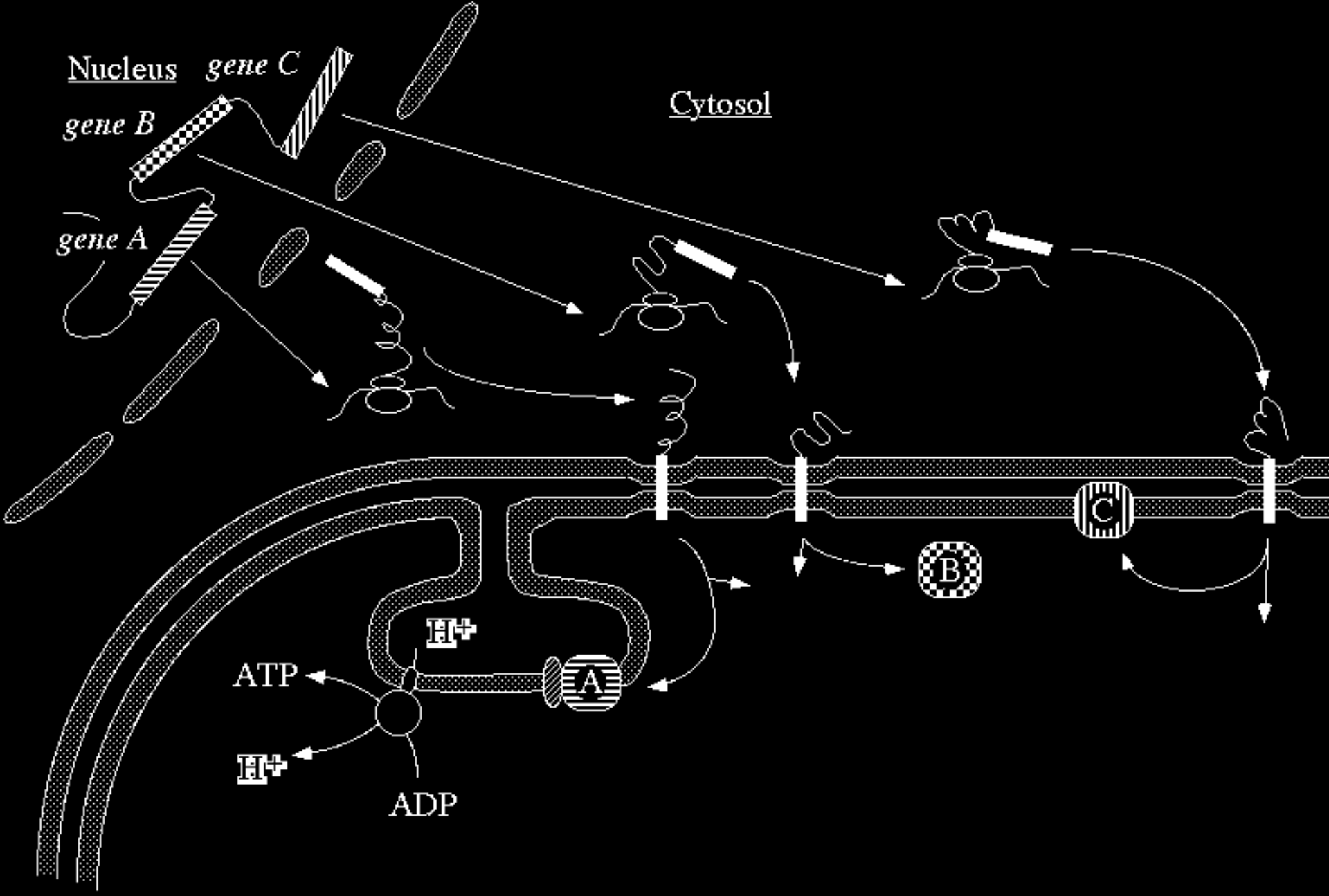


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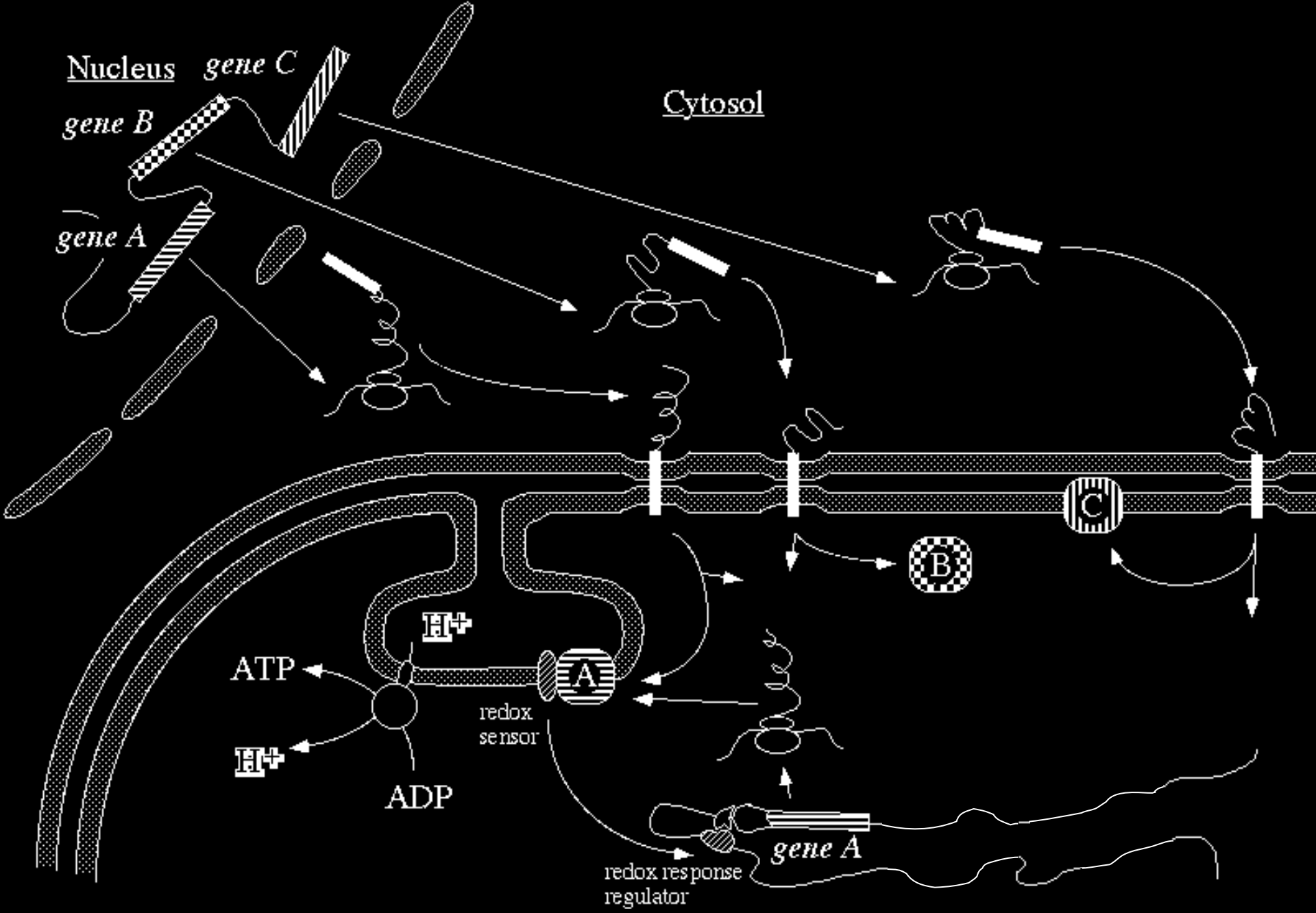


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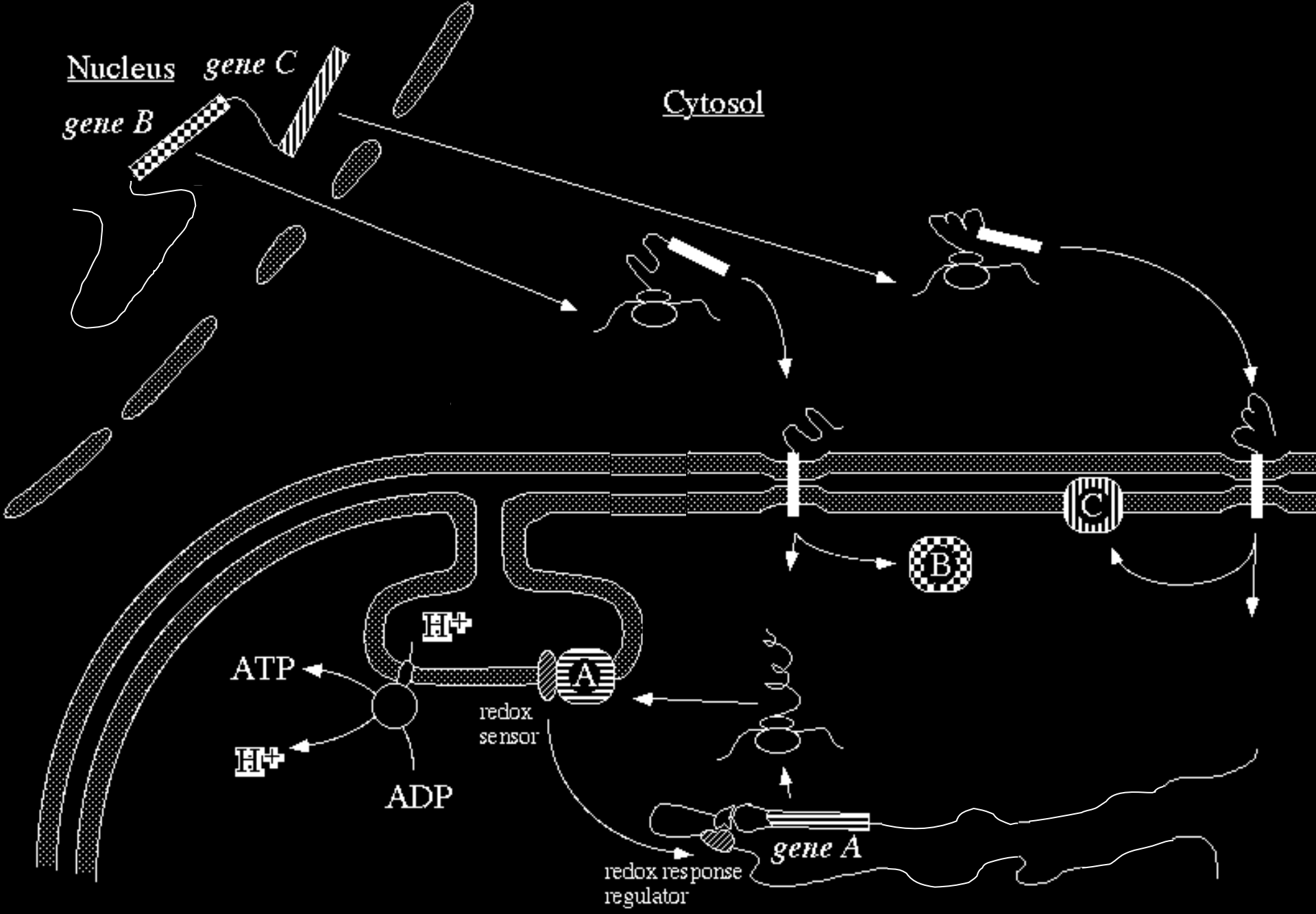
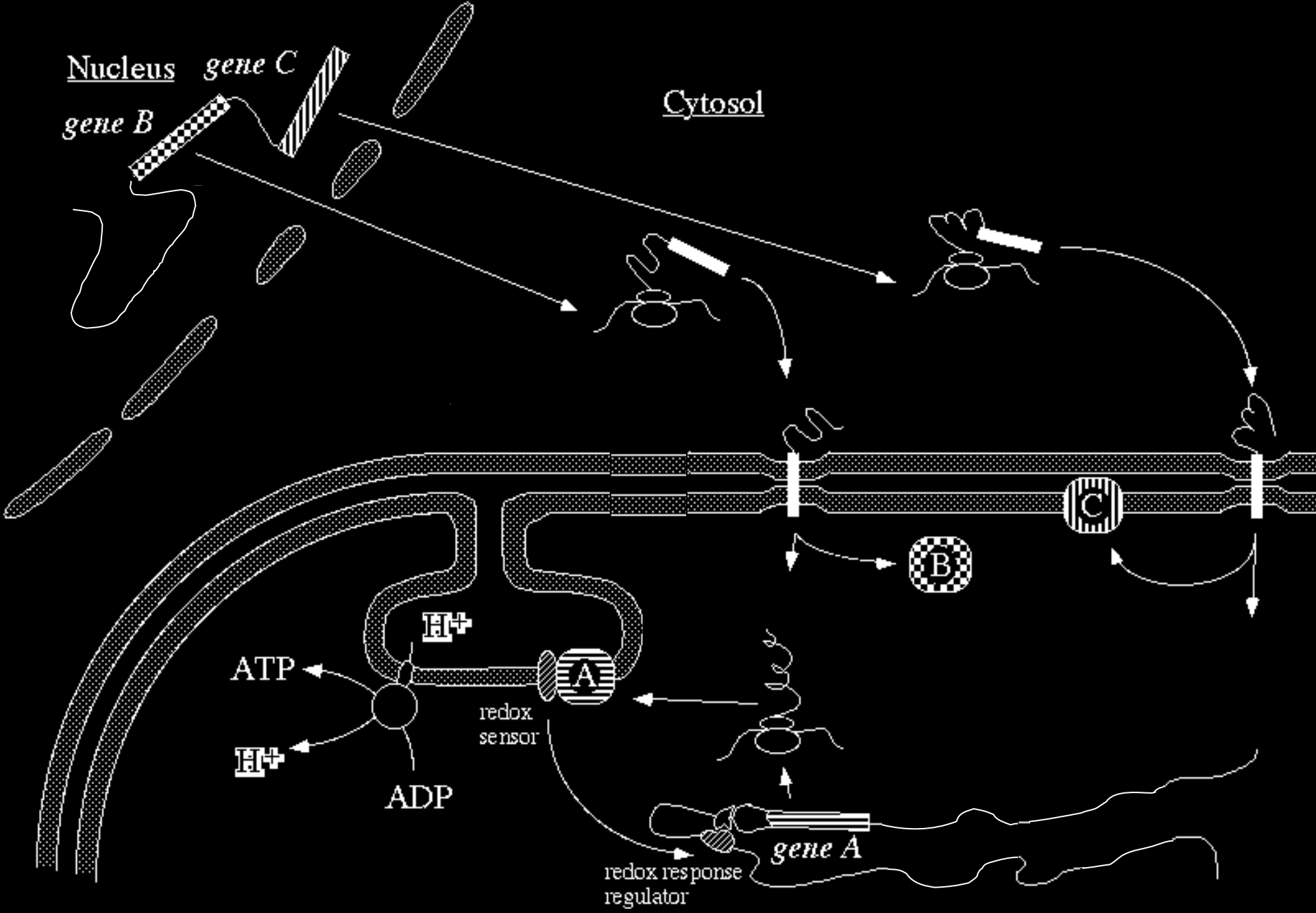
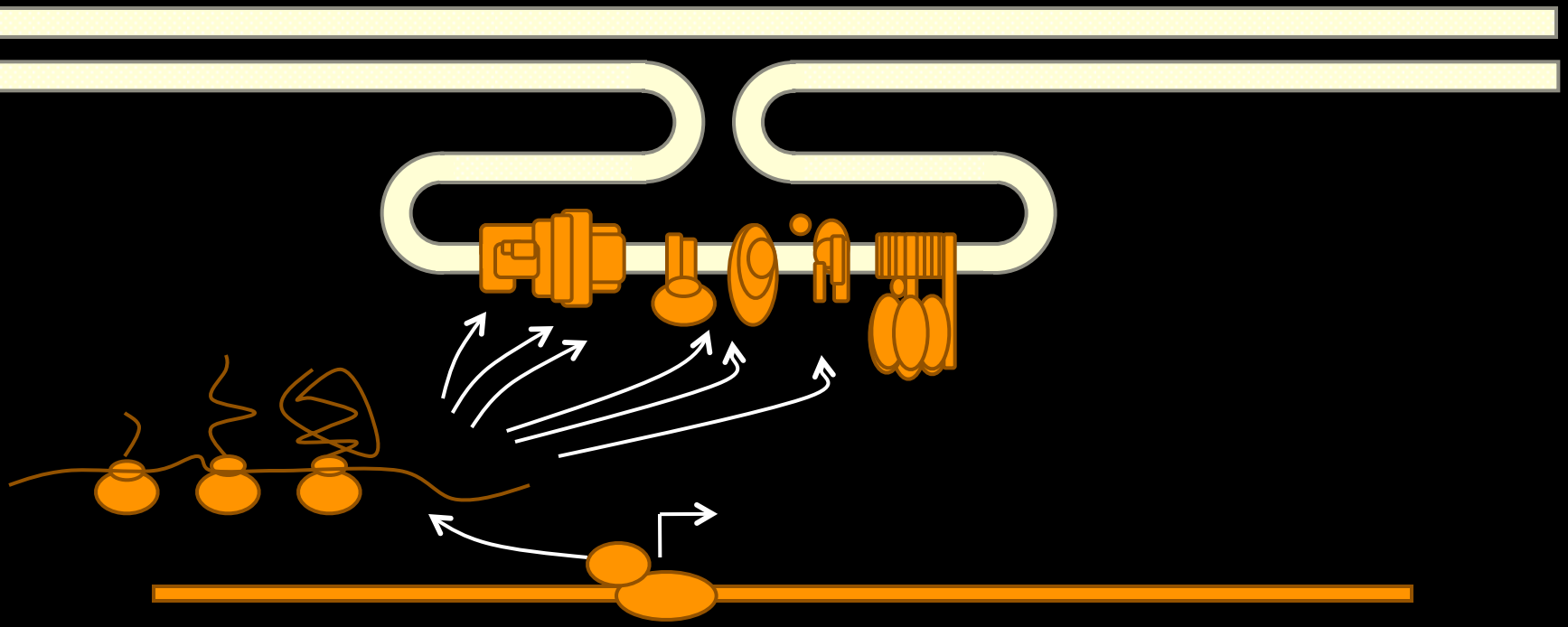


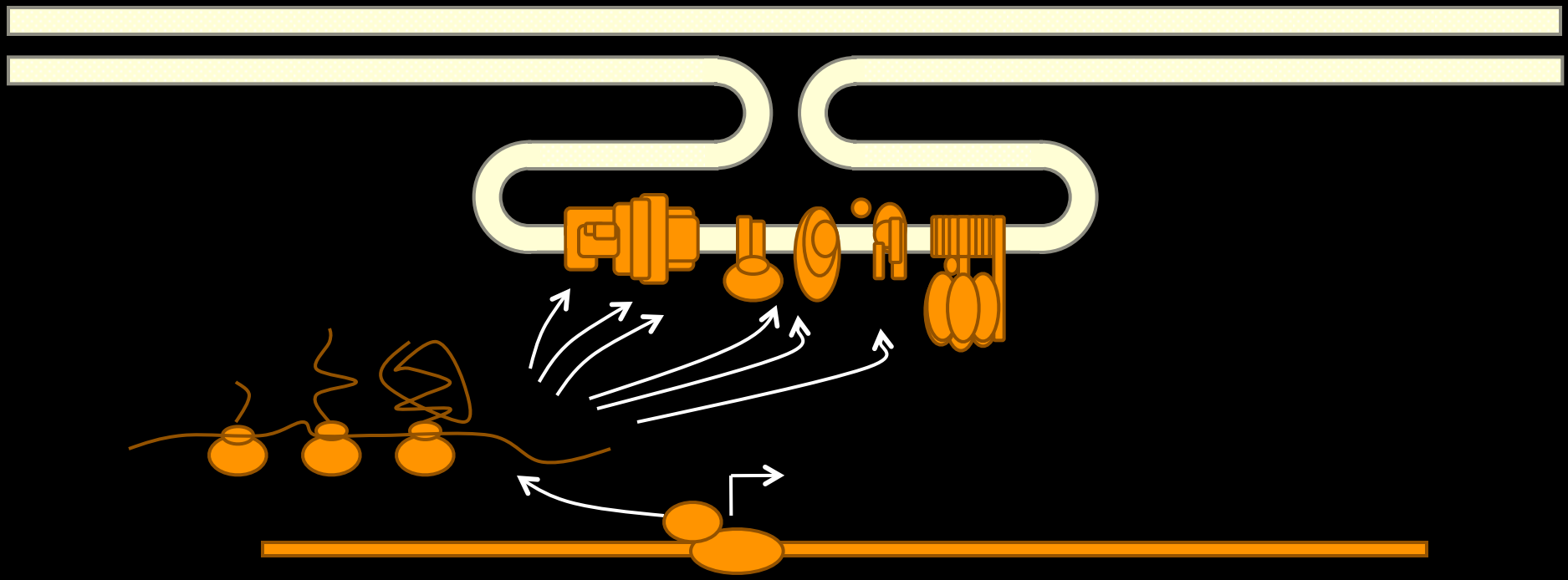

Bioenergetic organelle




Bioenergetic organelle

Allen JF (1993) Control of Gene Expression by Redox Potential and the Requirement for Chloroplast and Mitochondrial Genomes. *Journal of Theoretical Biology* 165: 609-631





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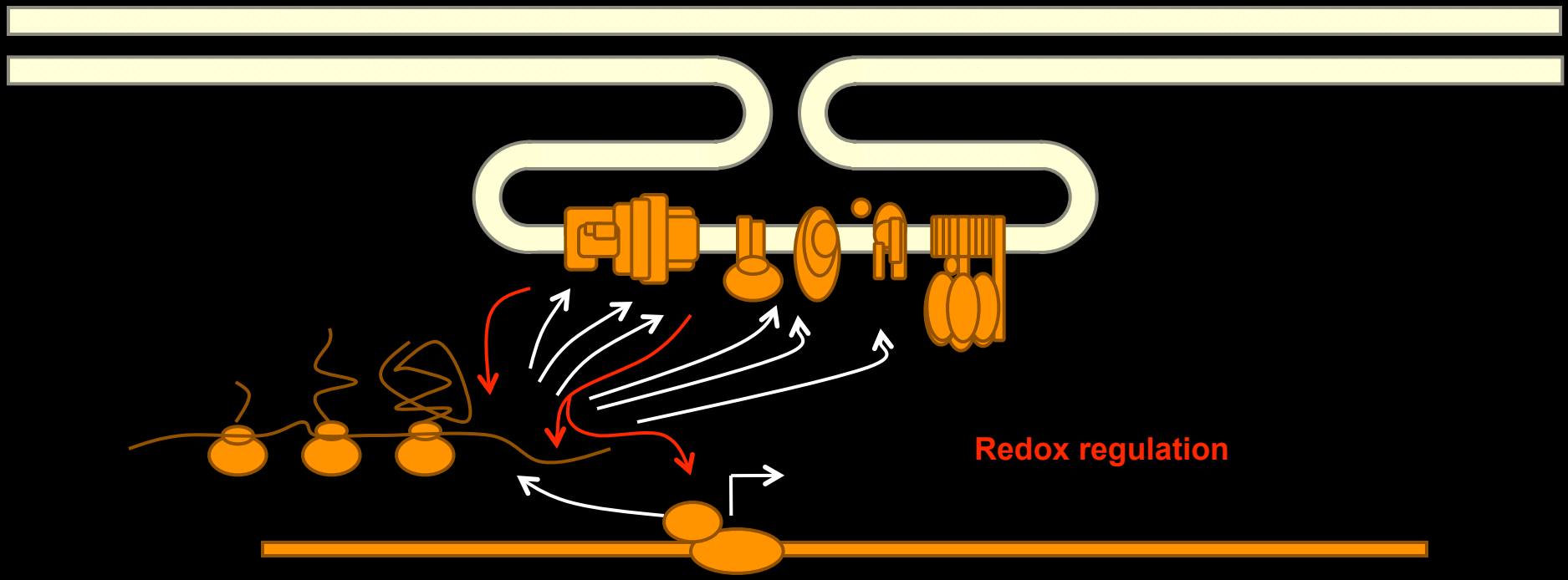


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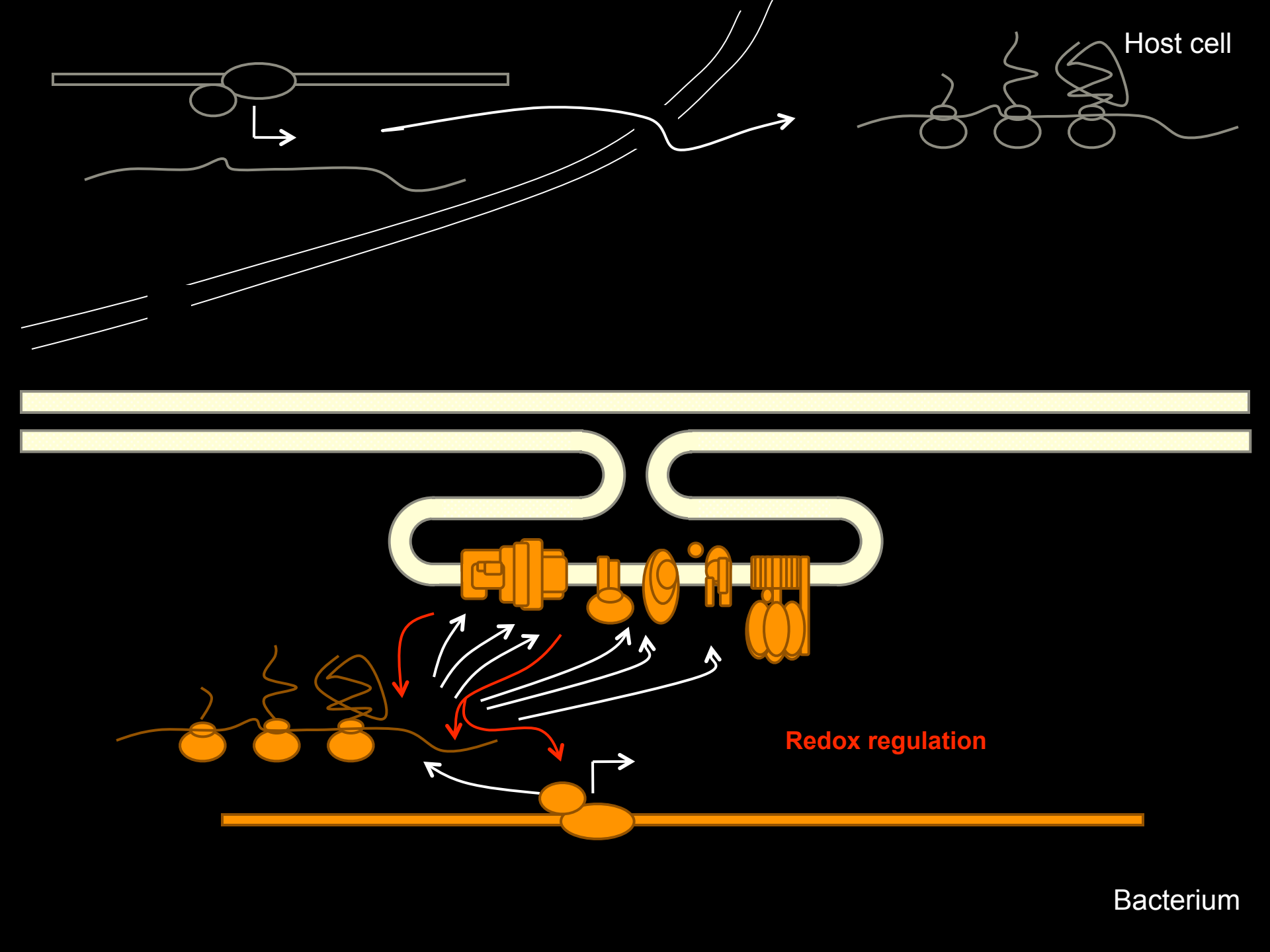
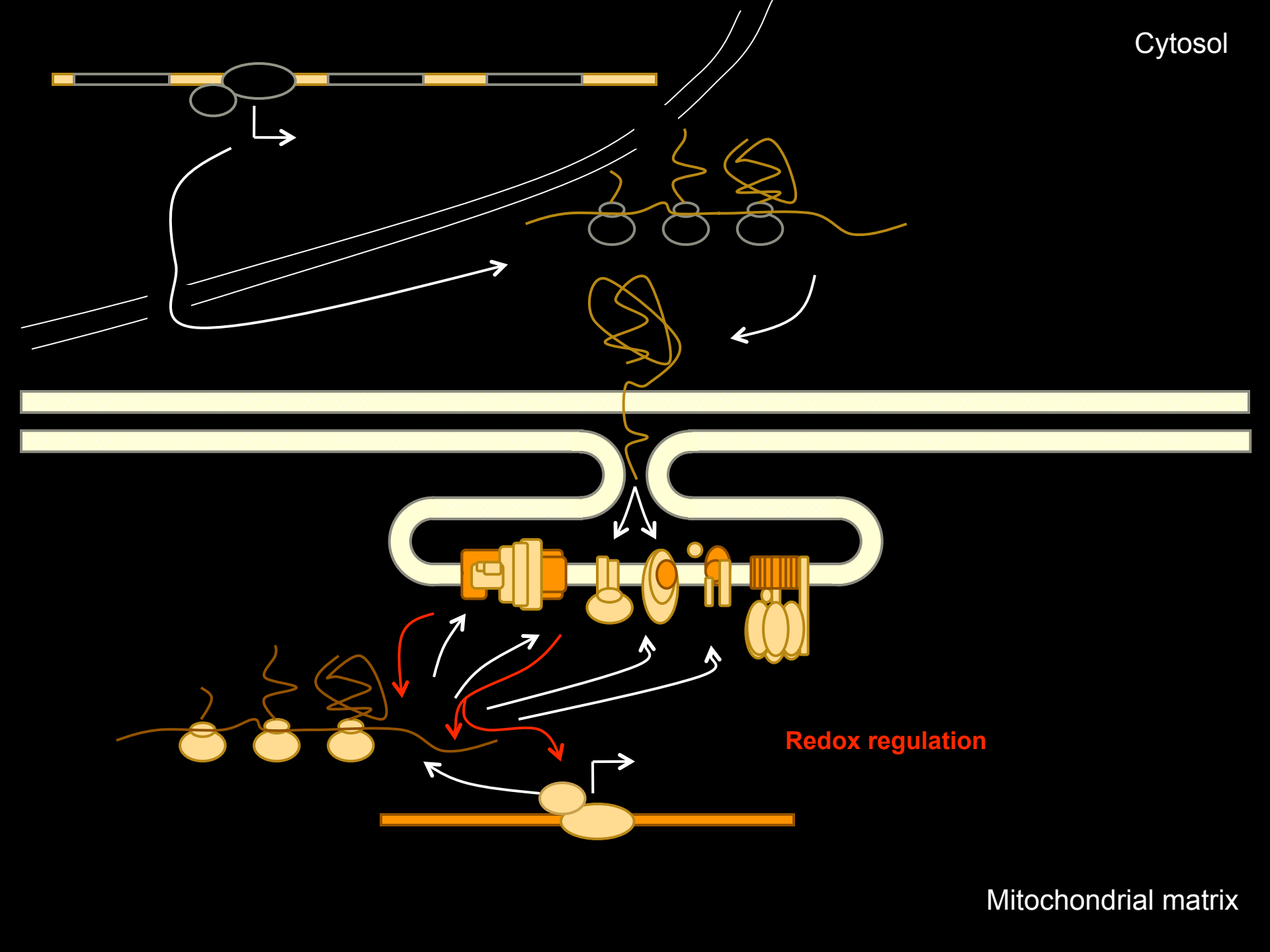

Host cell
Redox regulation
Bacterium


Cytosol
Redox regulation
Mitochondrial matrix

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**Co**-Location (of gene and gene product)
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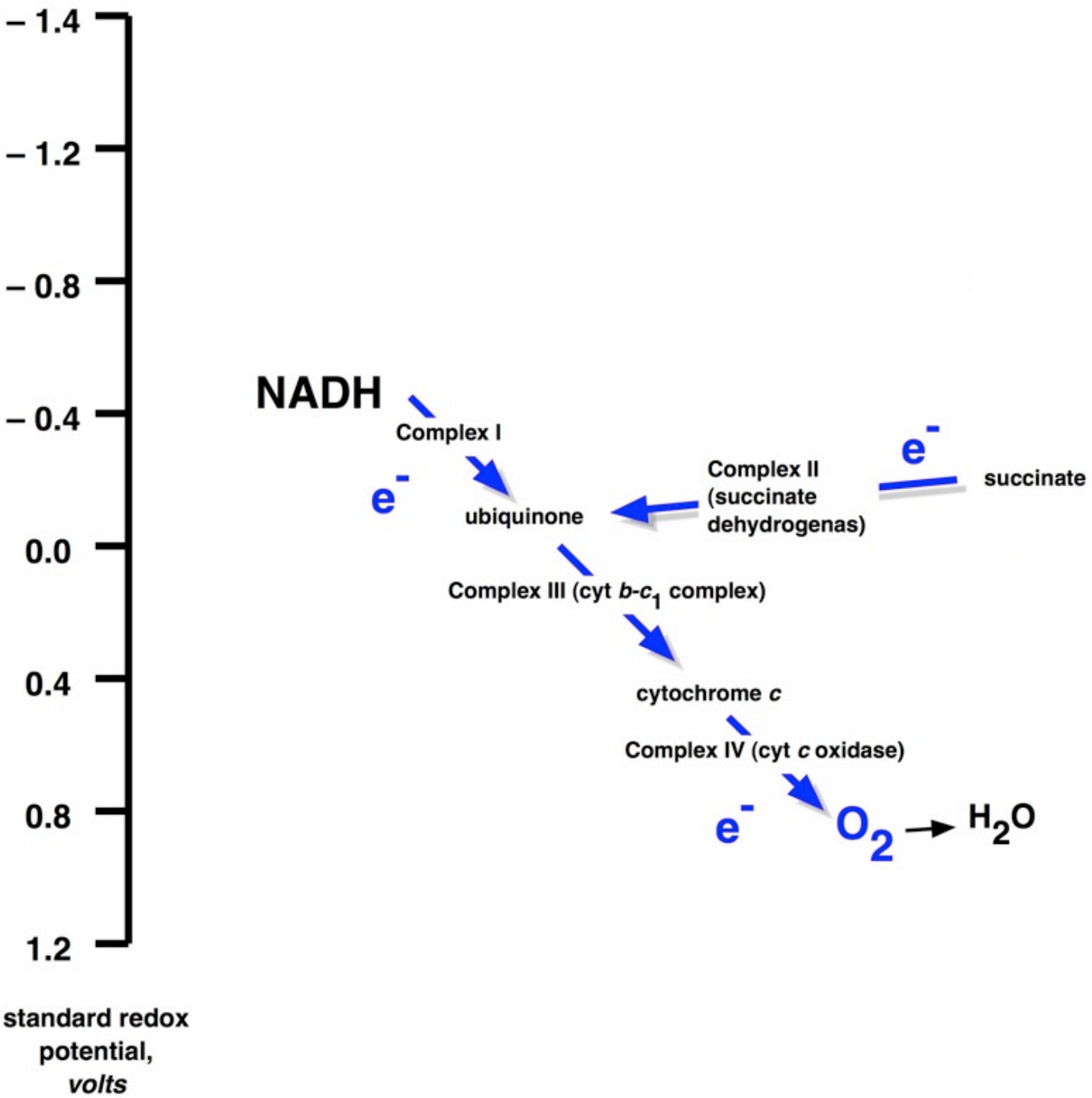
5.....

# **Co**-location for **R**edox **R**egulation - **CoRR**

Prediction

Experimental results

Redox regulatory control of mitochondrial and chloroplast gene expression


– 1.4
– 1.2
– 0.8
– 0.4
0.0
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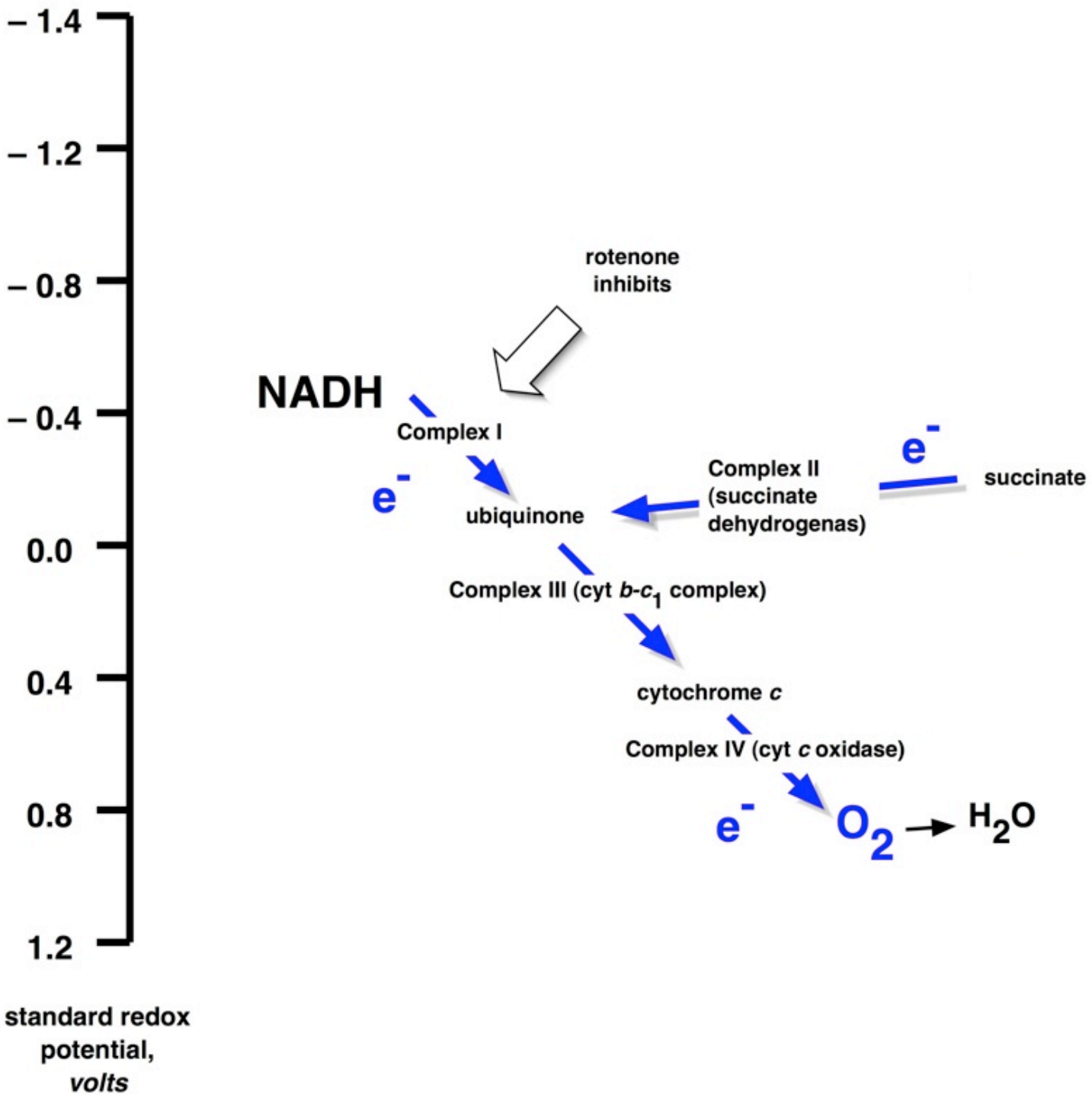
1.2
standard redox potential, volts
NADH
Complex I
e-
ubiquinone
Complex II (succinate dehydrogenas)
e-
succinate
Complex III (cyt b-c1 complex)
cytochrome c
Complex IV (cyt c oxidase)
e-
O2
H2O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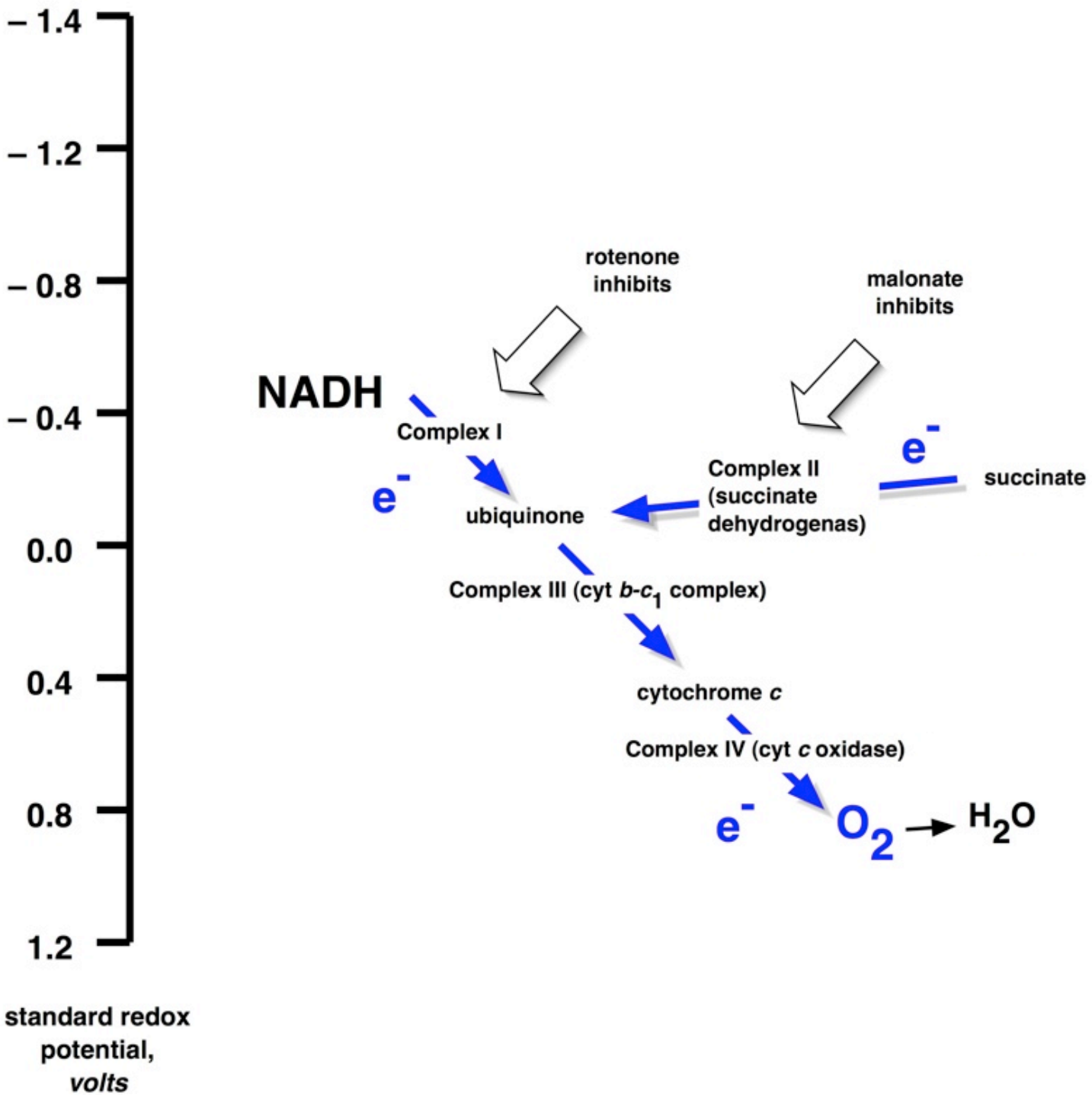
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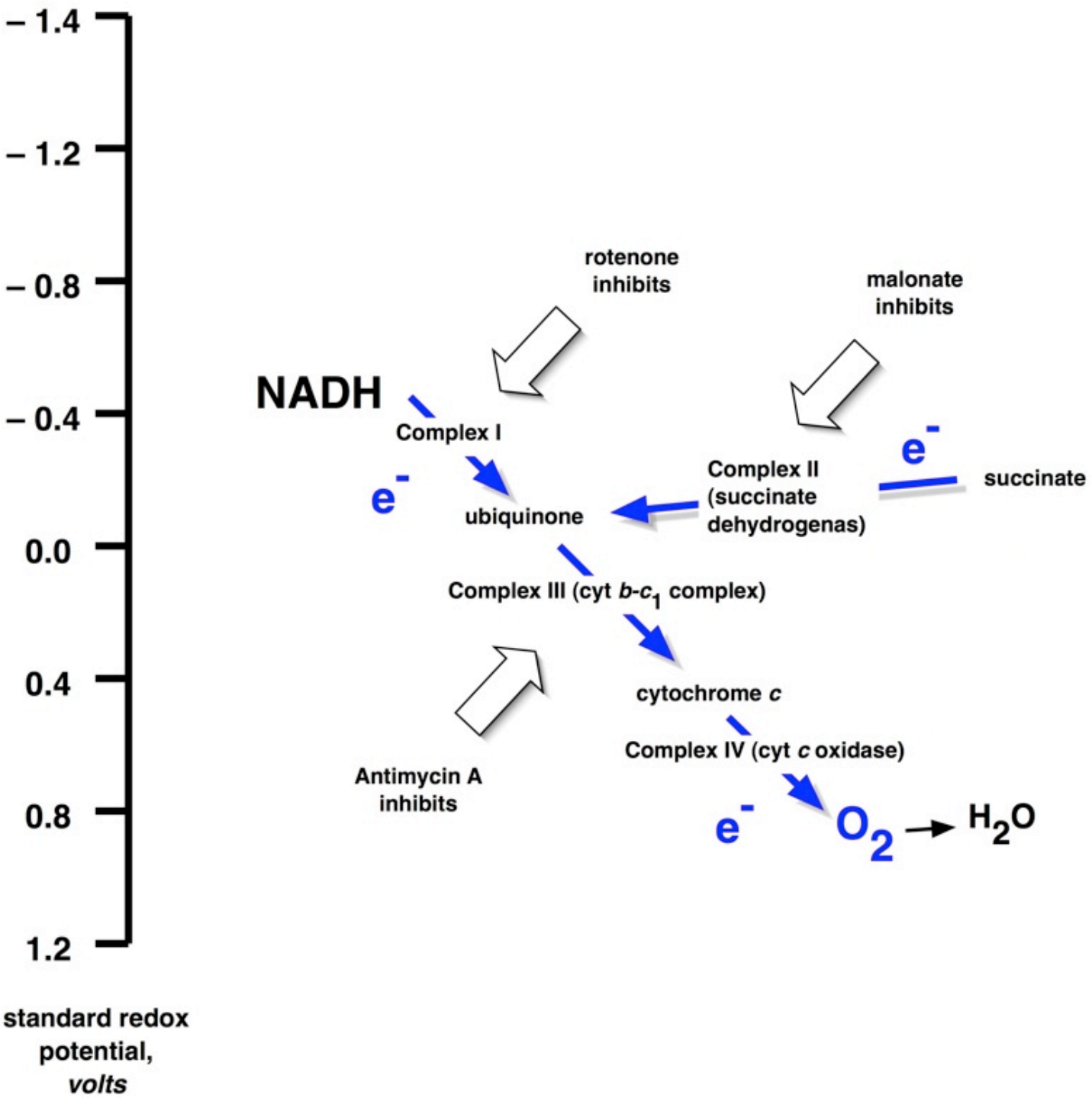
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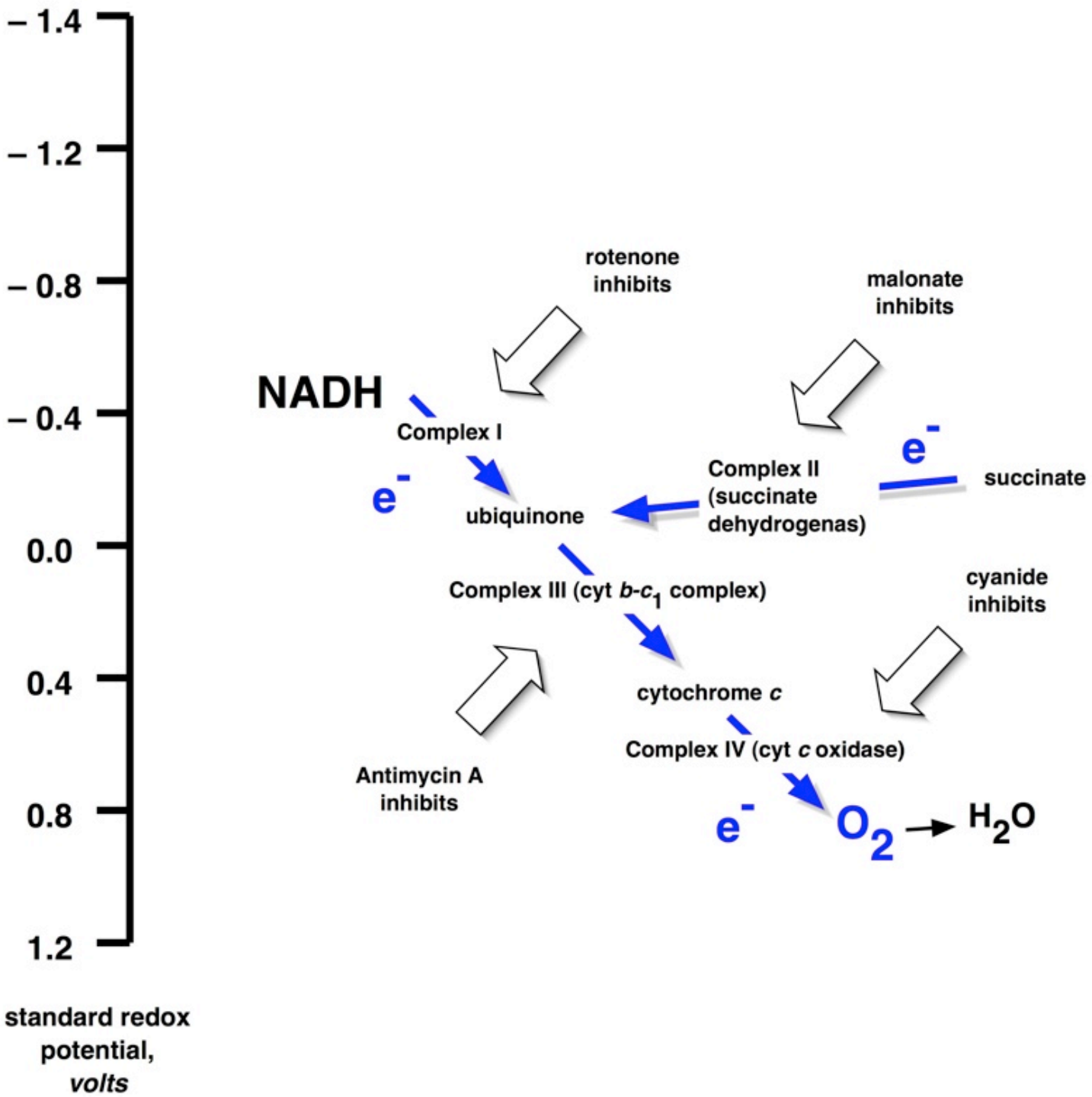
cytochrome c
Complex IV (cyt c oxidase)
Antimycin A inhibits
e-
O2
H2O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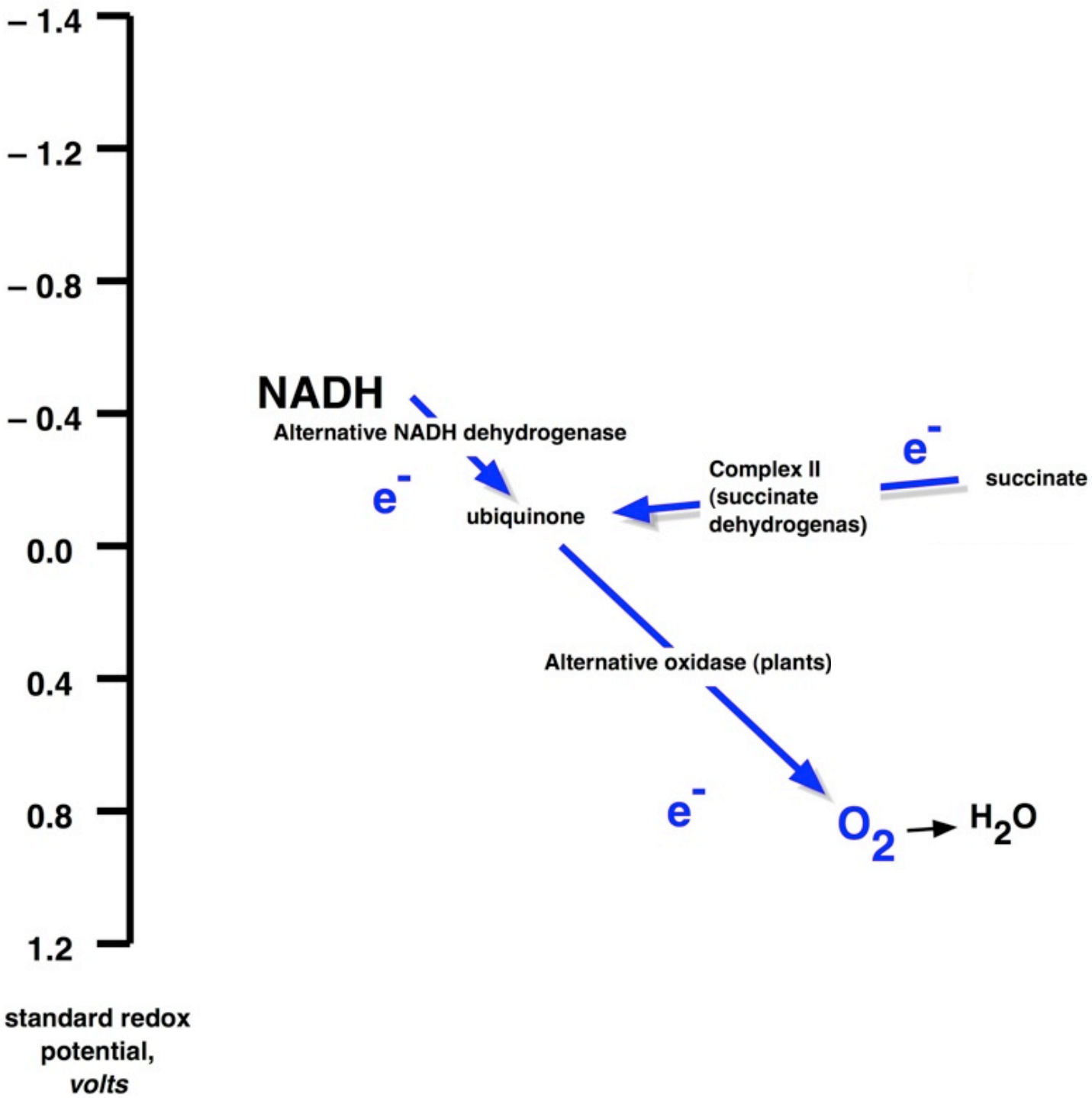
cyanide inhibits
cytochrome c
Antimycin A inhibits
Complex IV (cyt c oxidase)
e-
O2
H2O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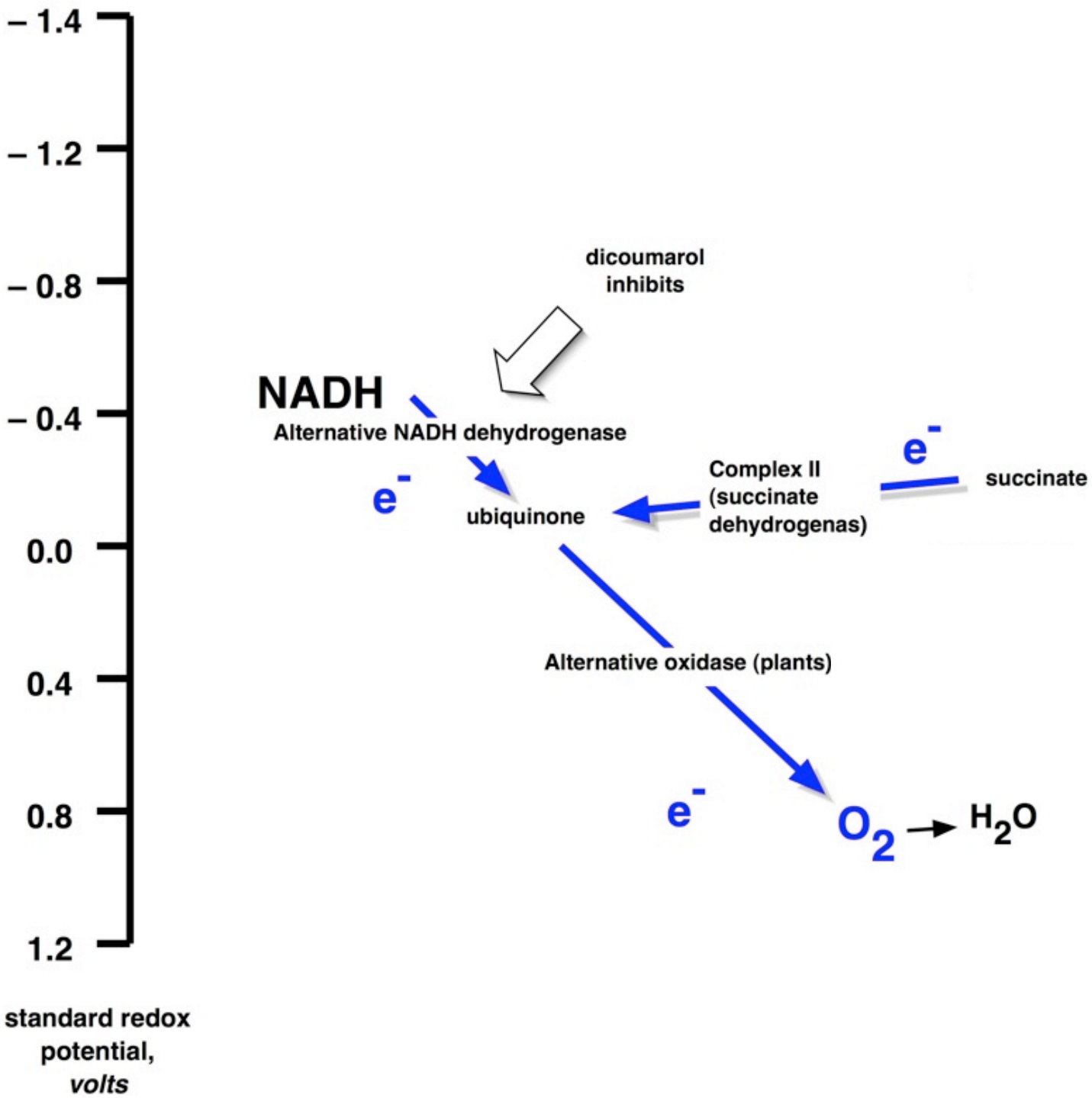
succinate
Alternative oxidase (plants)
e-
O2
H2O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dicoumarol inhibits
NADH
Alternative NADH dehydrogenase
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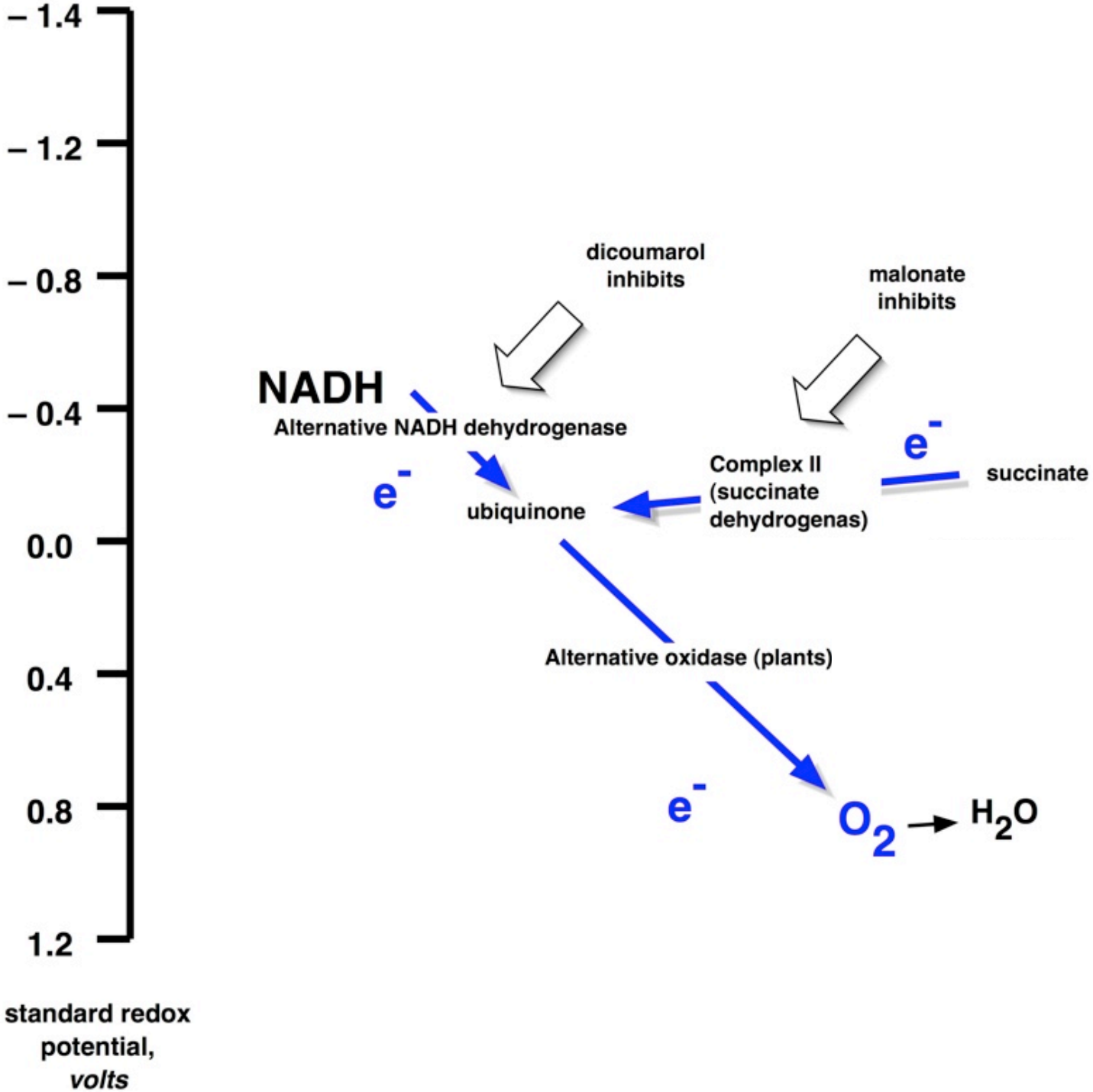
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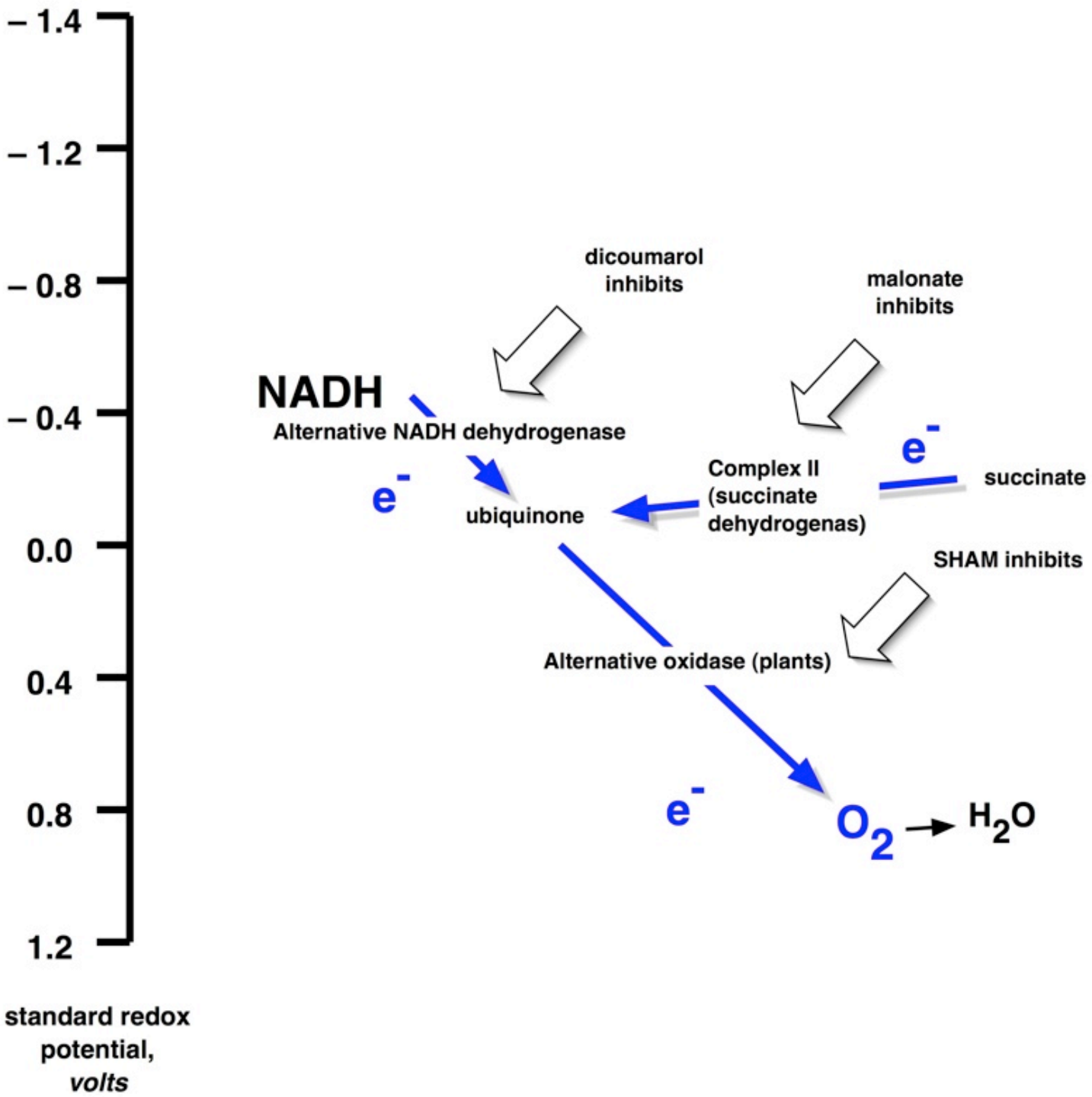
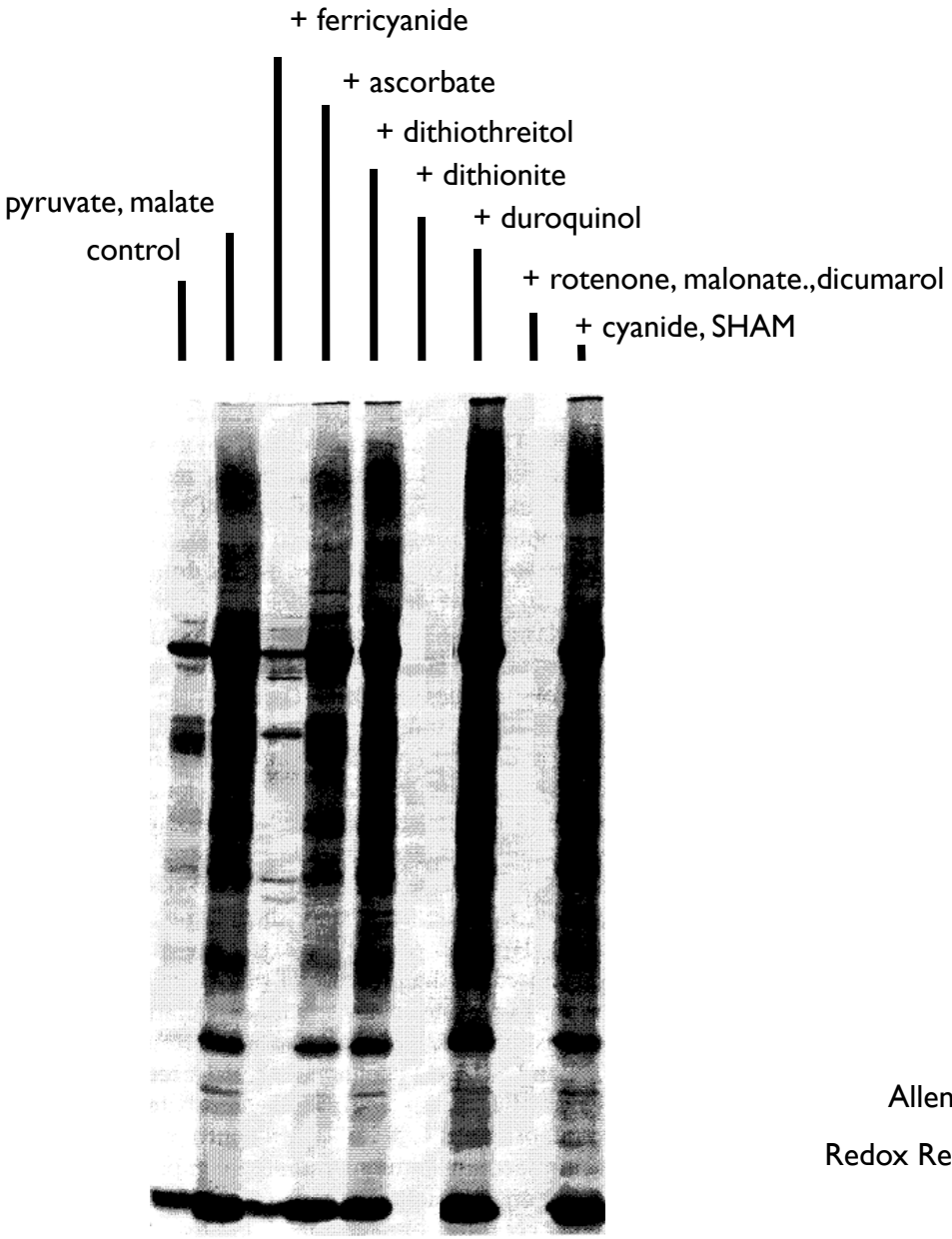
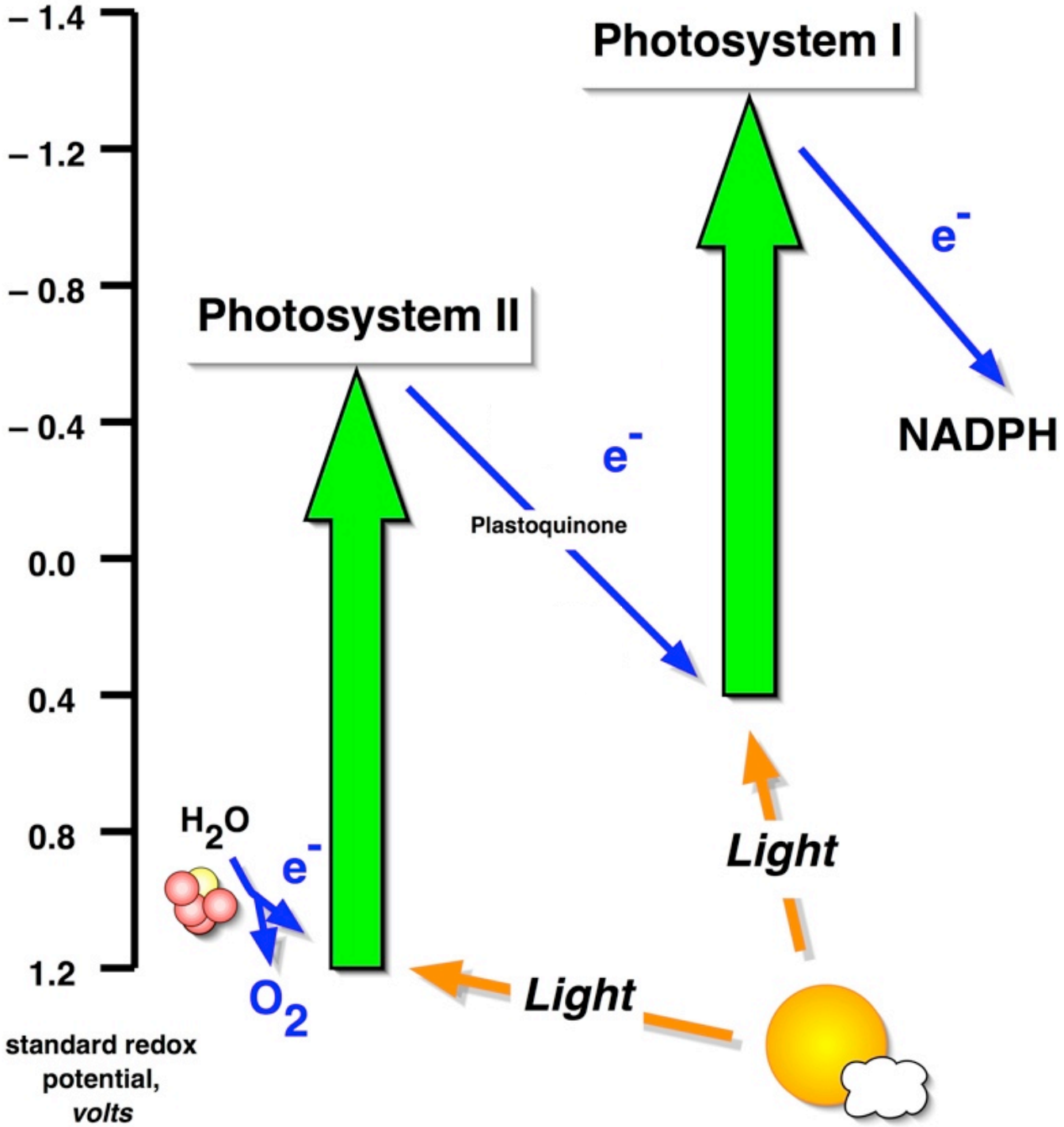

– 1.4
– 1.2
– 0.8
– 0.4
0.0
0.4
0.8
1.2
standard redox potential, volts
dicoumarol inhibits
malonate inhibits
NADH
Alternative NADH dehydrogenase
e-
ubiquinone
Complex II (succinate dehydrogenas)
e-
succinate
SHAM inhibits
Alternative oxidase (plants)
e-
O2
H2O

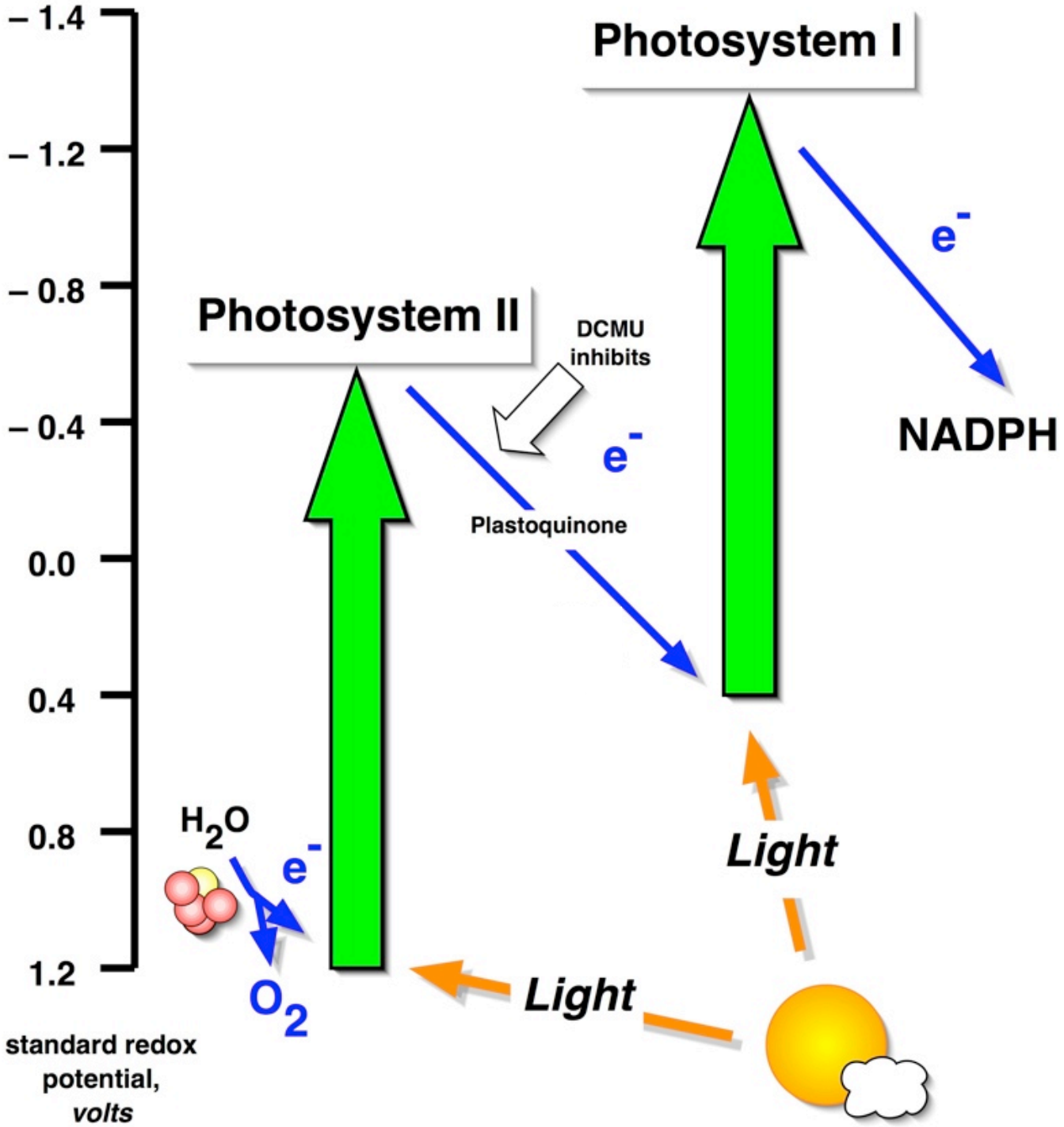


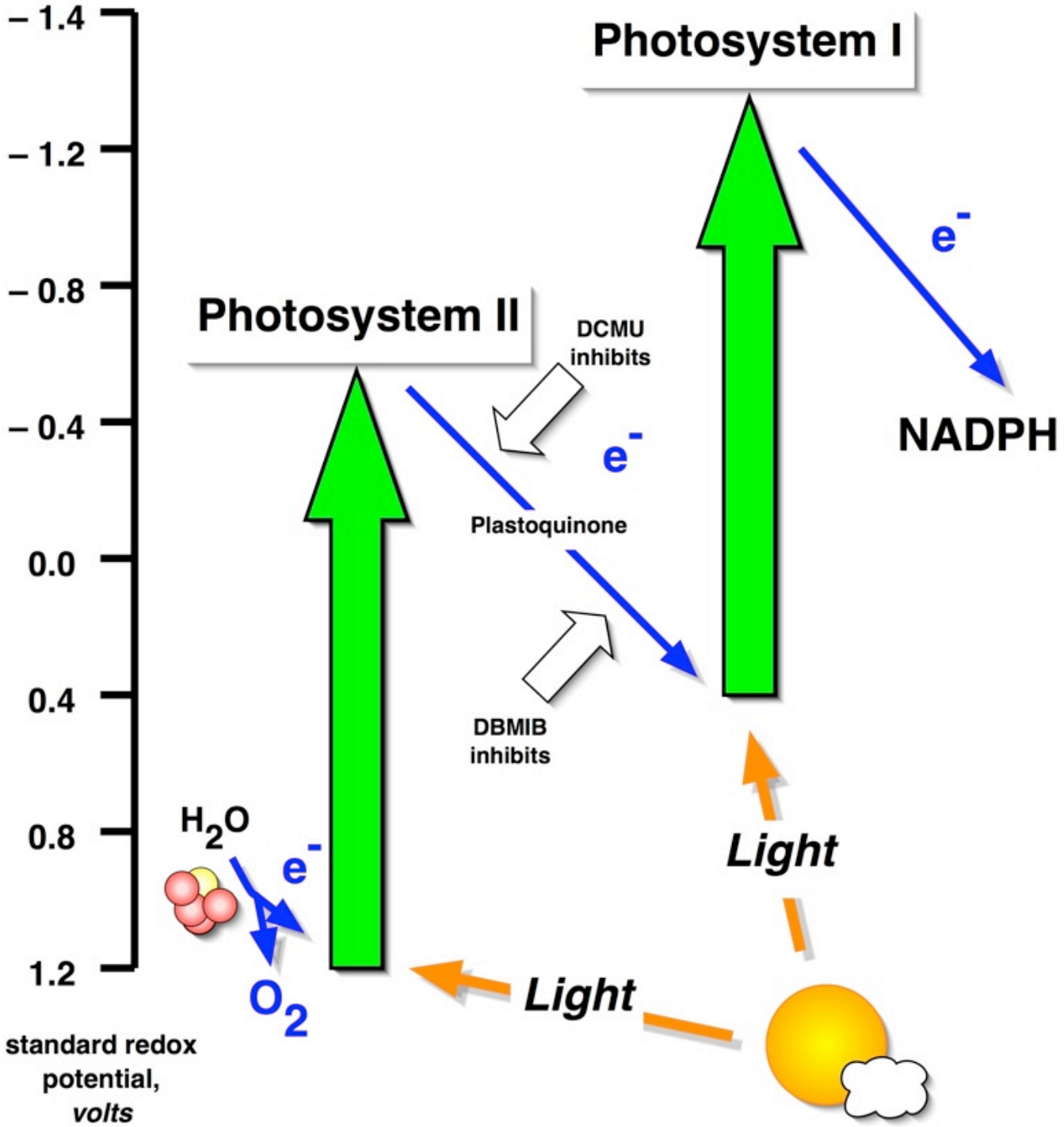

Allen, C.A. et al

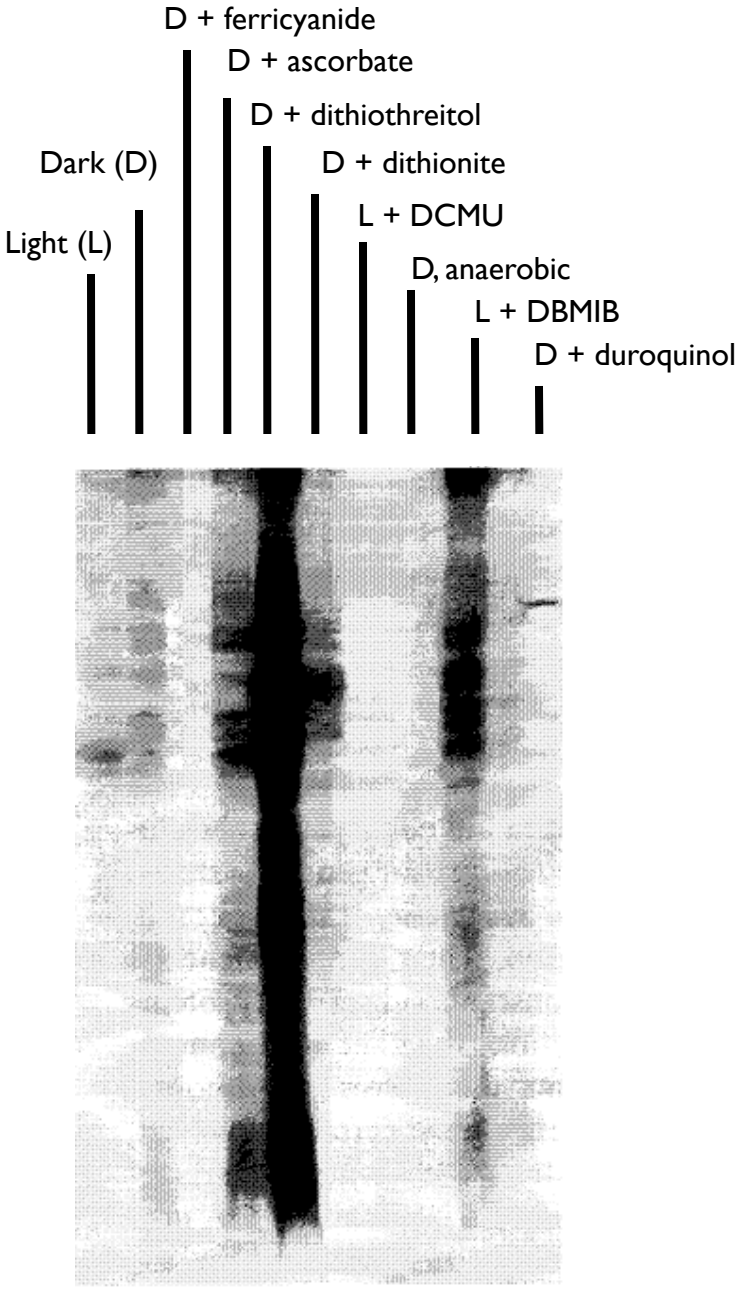
Redox Report 1, 119-123

$^{35}$S-methionine labelling of newly synthesised proteins in pea leaf mitochondria


– 1.4
– 1.2
– 0.8
– 0.4
0.0
0.4
0.8
1.2
standard redox potential, volts
Photosystem I
Photosystem II
e-
NADPH
e-
Plastoquinone
H2O
e-
O2
Light
Light


– 1.4
– 1.2
– 0.8
– 0.4
0.0
0.4
0.8
1.2
standard redox potential, volts
Photosystem I
Photosystem II
DCMU inhibits
e-
e-
NADPH
Plastoquinone
H2O
e-
O2
Light
Light

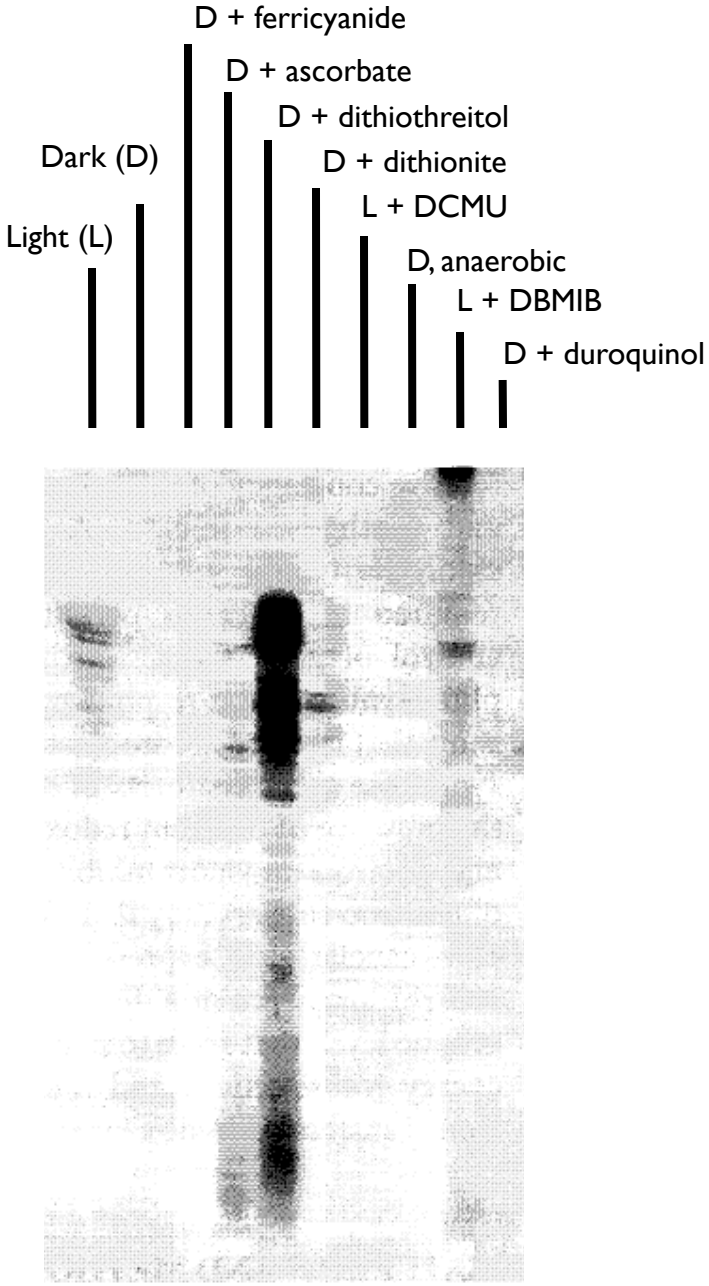

– 1.4
– 1.2
– 0.8
– 0.4
0.0
0.4
0.8
1.2
standard redox potential, volts
Photosystem I
Photosystem II
DCMU inhibits
e-
Plastoquinone
DBMIB inhibits
NADPH
H2O
e-
O2
Light
Light




Allen, C.A. et al

Redox Report 1, 119-123

$^{35}$S-methionine labelling of newly synthesised proteins in pea leaf thylakoids




Allen, C.A. et al

Redox Report 1, 119-123

$^{35}$S-methionine labelling of newly synthesised proteins in pea leaf chloroplast stroma

# **Co**-location for **R**edox **R**egulation - **CoRR**

Prediction

Experimental results

Redox regulatory control of chloroplast and mitochondrial transcription


31. 7. 2001


31. 7. 2001


31. 7. 2001


Light I
31. 7. 2001

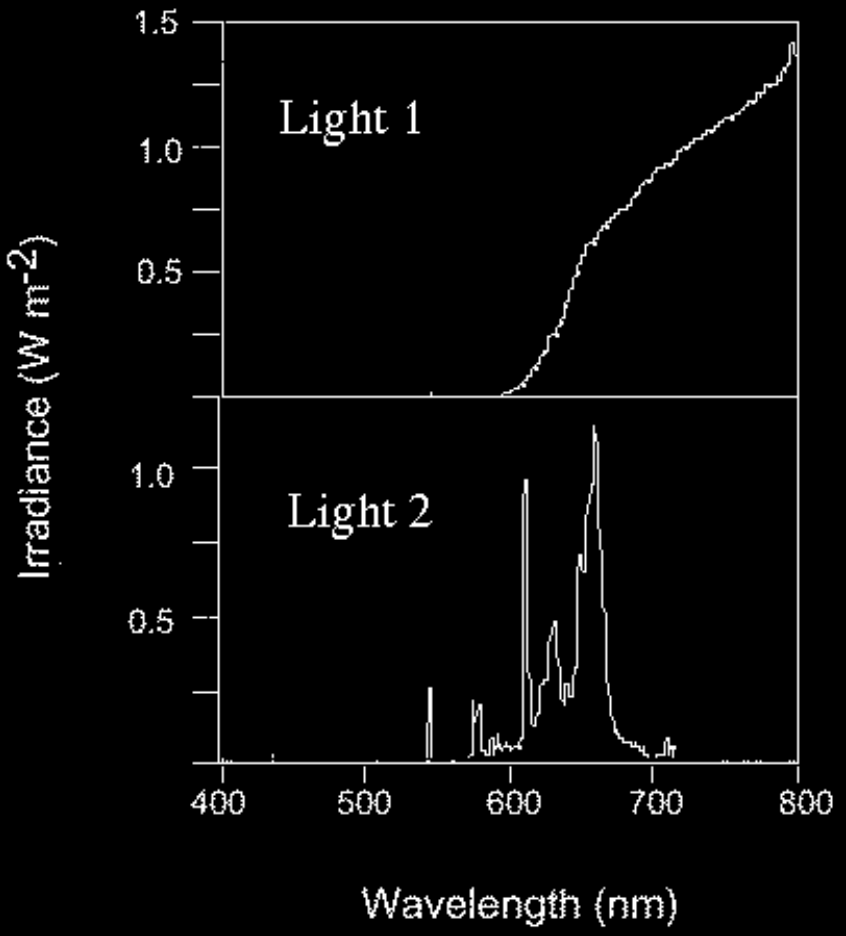

31. 7. 2001

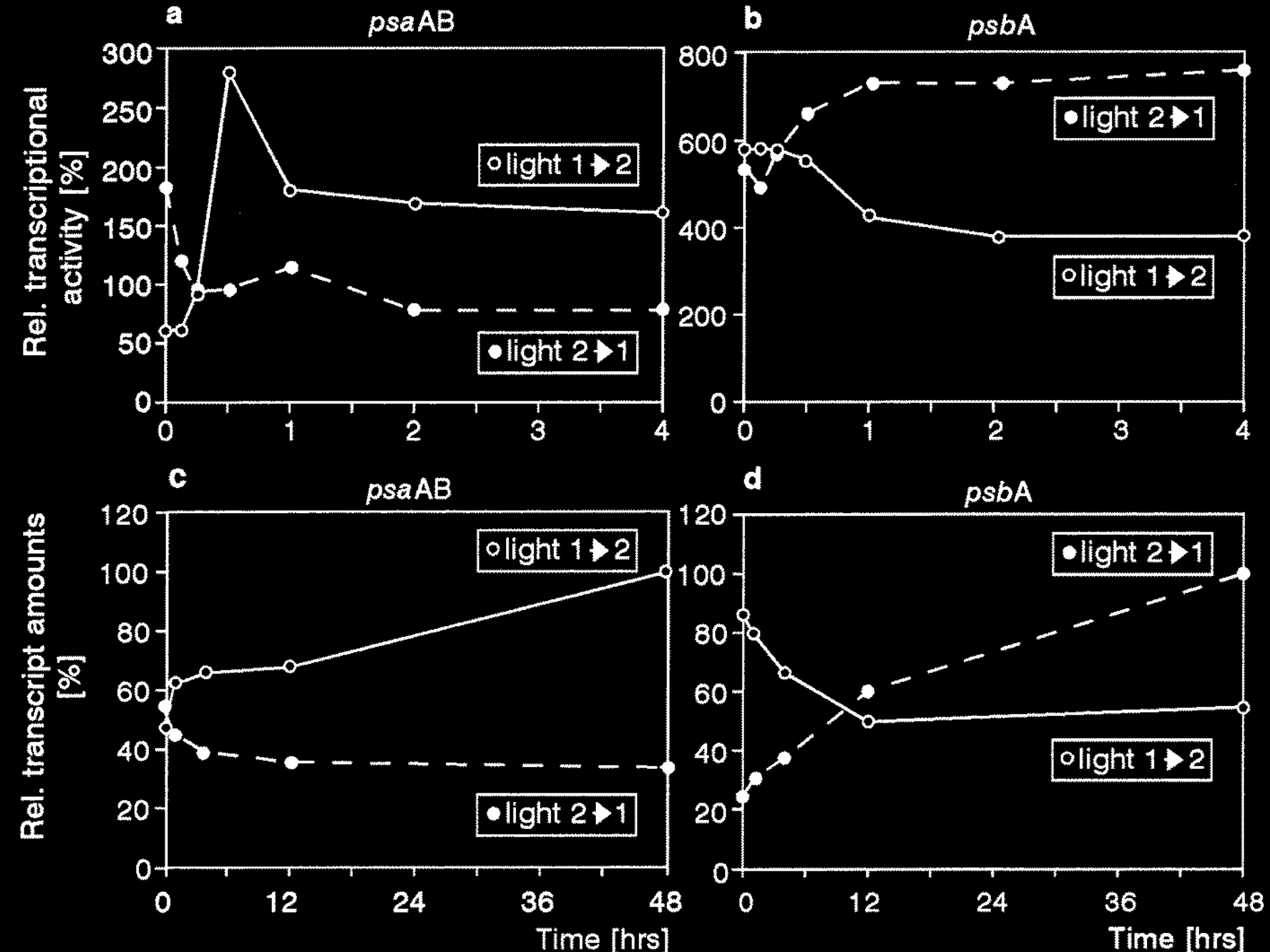

Light 1
31. 7. 2001


Light 2
31. 7. 2001


Light 1
31. 7. 2001


Light 2
31. 7. 2001


Light 1
Light 2
Irradiance (W m-2)
Wavelength (nm)
1.5
1.0
0.5
1.0
0.5
400
500
600
700
800


a
psaAB
b
psbA
c
psaAB
d
psbA
Rel. transcriptional activity [%]
Rel. transcript amounts [%]
light 1 ▶ 2
light 2 ▶ 1
Time [hrs]
0
50
100
150
200
250
300
400
600
800
20
40
60
80
120
1
2
3
4
12
24
36
48

# **Co**-location for **R**edox **R**egulation - **CoRR**

Prediction

Experimental results

Persistence of "bacterial" redox signalling components in chloroplasts and mitochondria

# The ancestral symbiont sensor kinase CSK links photosynthesis with gene expression in chloroplasts

Sujith Puthiyaveetil*, T. Anthony Kavanagh†, Peter Cain‡, James A. Sullivan*, Christine A. Newell§, John C. Gray§, Colin Robinson‡, Mark van der Giezen¶, Matthew B. Rogers¶, and John F. Allen*‖

*School of Biological and Chemical Sciences, Queen Mary, University of London, Mile End Road, London E1 4NS, United Kingdom; †Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, Ireland; ‡Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, United Kingdom; §Department of Plant Sciences, University of Cambridge, Downing Street, Cambridge CB2 3EA, United Kingdom; and ¶Centre for Eukaryotic Evolutionary Microbiology, School of Biosciences, University of Exeter, Exeter EX4 4QD, United Kingdom

Communicated by Elisabeth Gantt, University of Maryland, College Park, MD, April 25, 2008 (received for review February 15, 2008)

**We describe a novel, typically prokaryotic, sensor kinase in chloroplasts of green plants. The gene for this chloroplast sensor kinase (CSK) is found in cyanobacteria, prokaryotes from which chloroplasts evolved. The CSK gene has moved, during evolution, from the ancestral chloroplast to the nuclear genomes of eukaryotic algae and green plants. The CSK protein is now synthesised in the cytosol of photosynthetic eukaryotes and imported into their chloroplasts as a protein precursor. In the model higher plant *Arabidopsis thaliana*, CSK is autophosphorylated and required for control of transcription of chloroplast genes by the redox state of an electron carrier connecting photosystems I and II. CSK therefore provides a redox regulatory mechanism that couples photosynthesis to gene expression. This mechanism is inherited directly from the cyanobacterial ancestor of chloroplasts, is intrinsic to chloroplasts, and is targeted to chloroplast genes.**

limited to a few examples in certain nongreen algal groups, where there are just one or two two-component genes of uncertain function in the chloroplast genome itself (8).

Author contributions: S.P. and J.F.A. designed research; S.P., T.A.K., P.C., C.A.N., and J.F.A. performed research; S.P., T.A.K., J.A.S., and M.v.d.G. contributed new reagents/analytic tools; S.P., T.A.K., P.C., J.C.G., C.R., M.v.d.G., M.B.R., and J.F.A. analyzed data; and S.P. and J.F.A. wrote the paper.

The authors declare no conflict of interest.

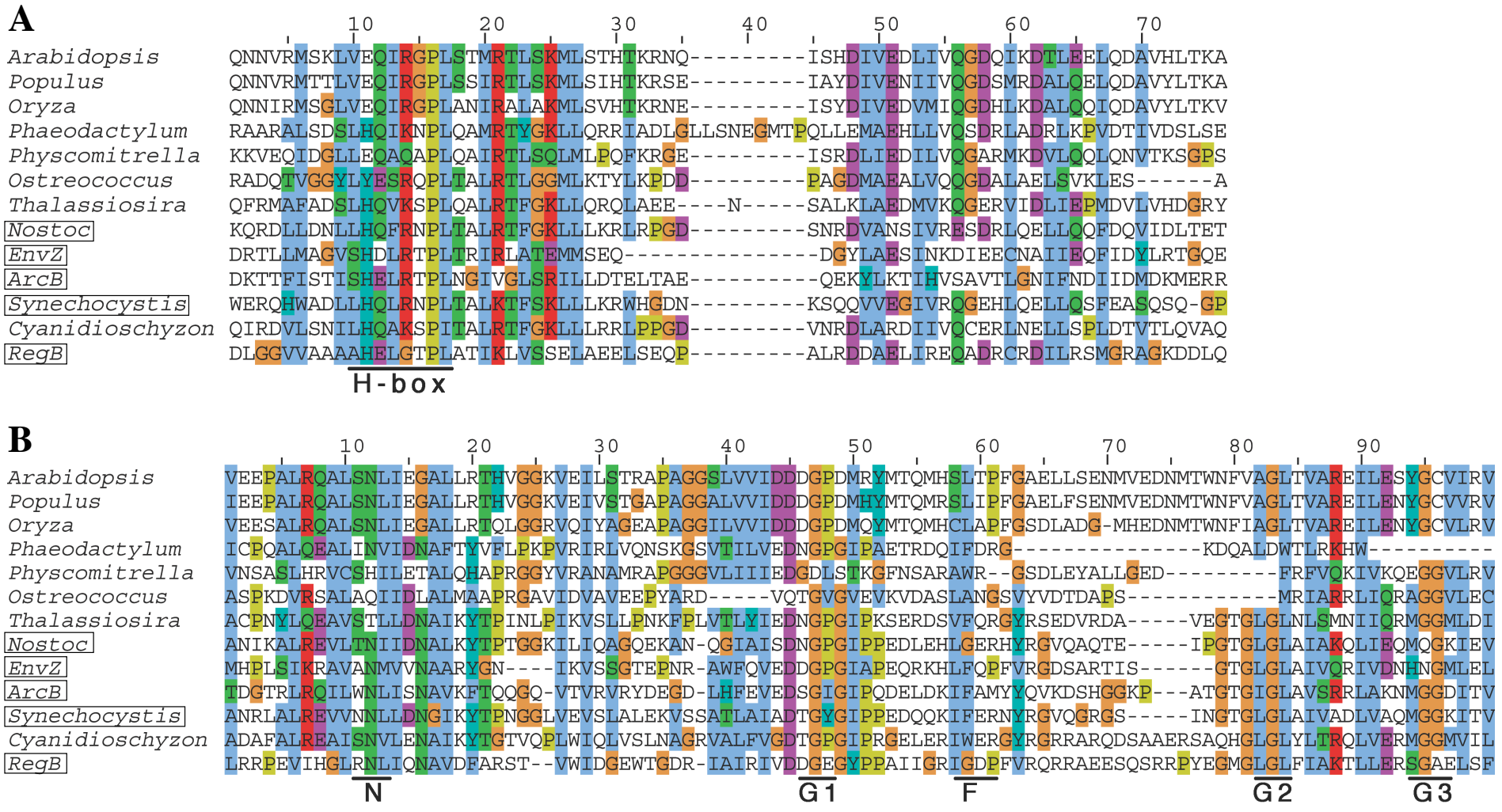
Freely available online through the PNAS open access option.

‖To whom correspondence should be addressed. E-mail: j.f.allen@qmul.ac.uk.

This article contains supporting information online at www.pnas.org/cgi/content/full/0803928105/DCSupplemental.

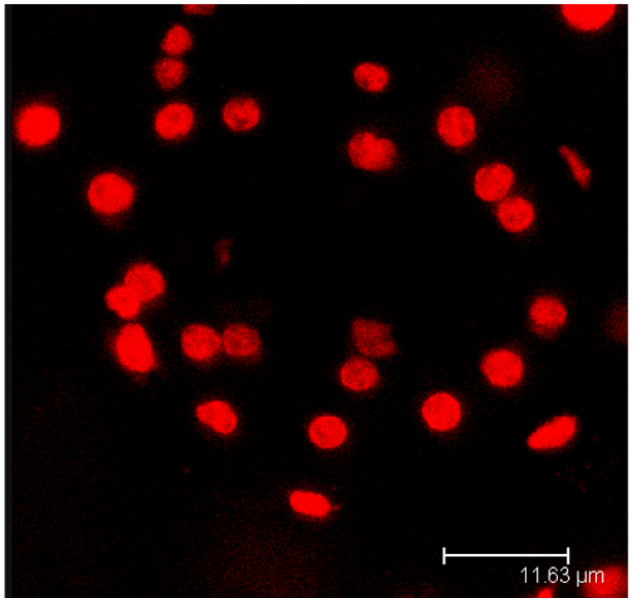
# CSK

- **C**hloroplast **S**ensor **K**inase
- A Histidine sensor kinase homologous with Hik2 of cyanobacteria
- A *Redox Sensor*
- Sujith Puthiyaveetil




Puthiyaveetil S, Kavanagh TA, Cain P, Sullivan JA, Newell CA, Gray JC, Robinson C, van der Giezen M, Rogers MB, Allen JF (2008) The ancestral symbiont sensor kinase CSK links photosynthesis with gene expression in chloroplasts. *Proceedings of the National Academy of Sciences of the United States of America* 105: 10061-10066.

**A**

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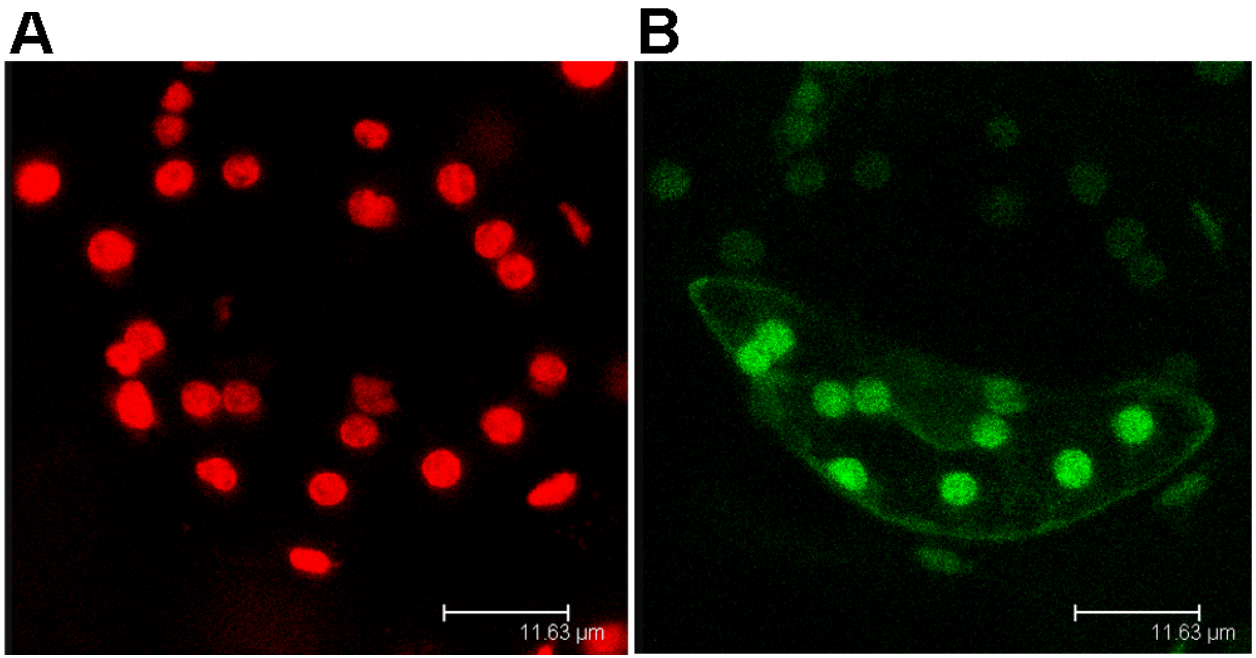


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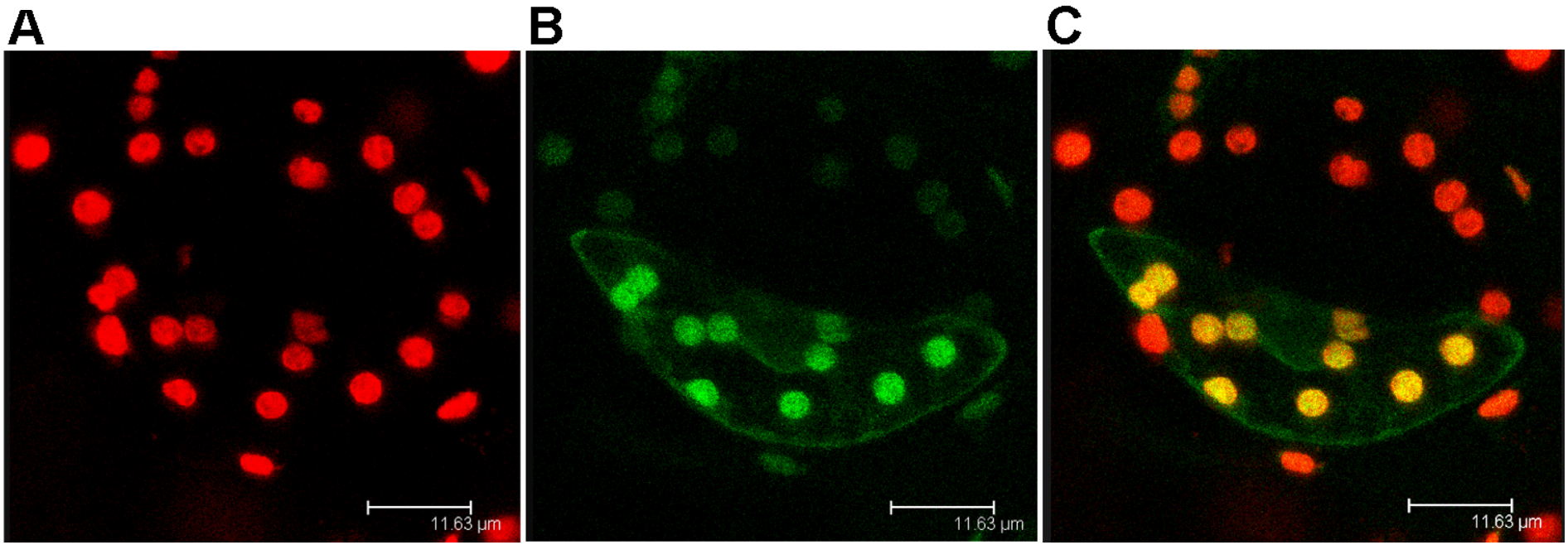


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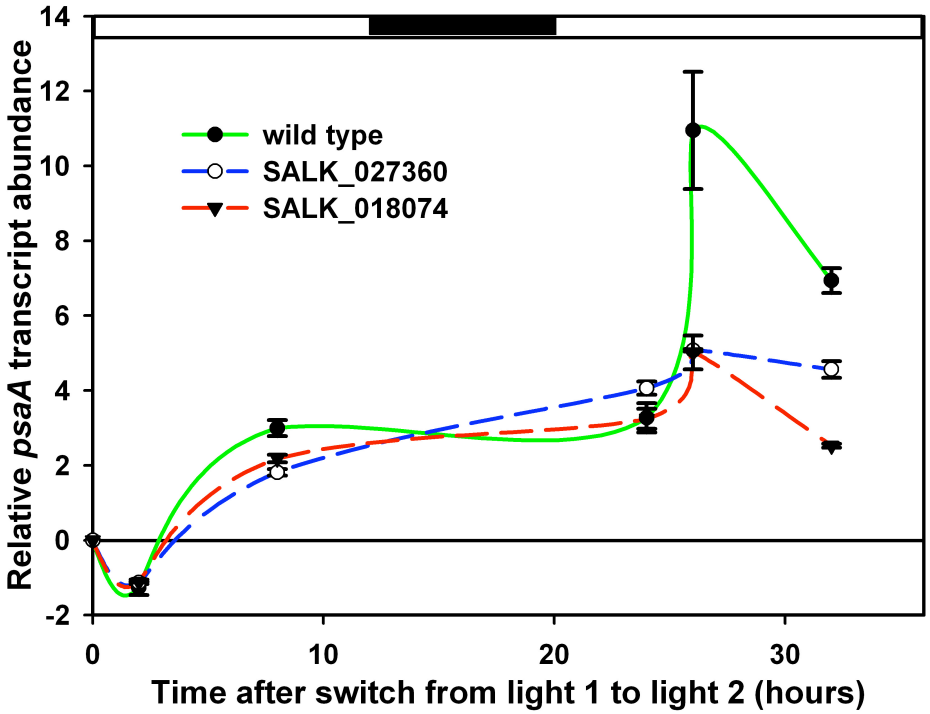


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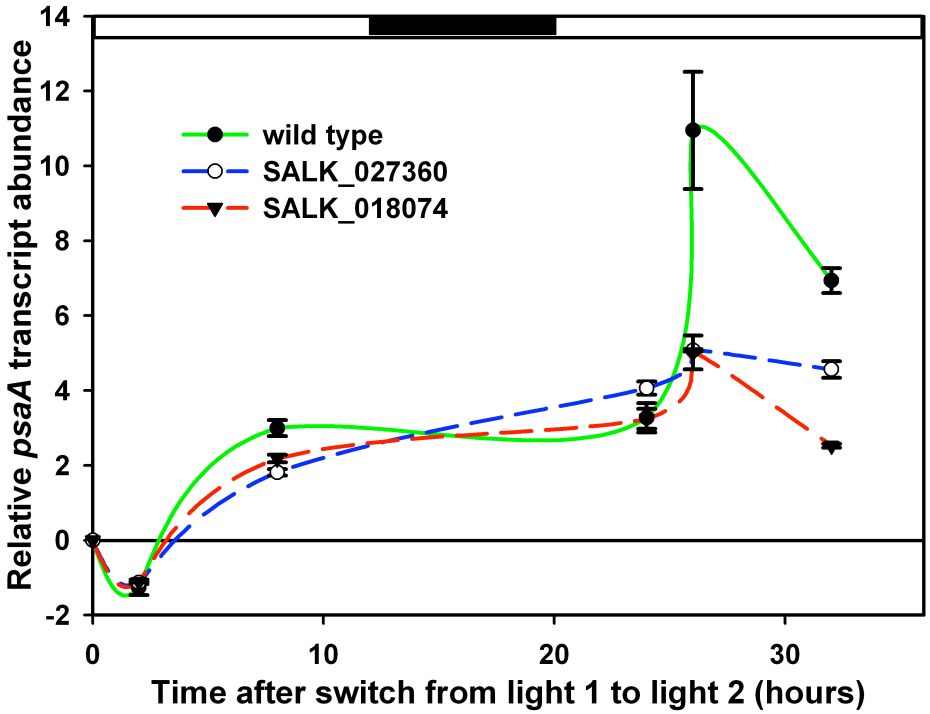


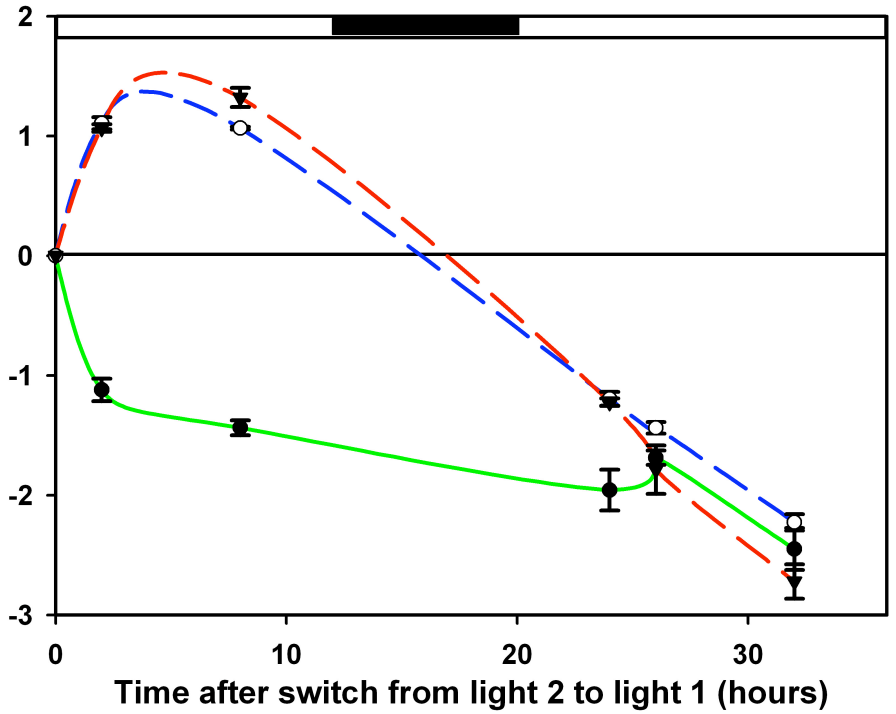


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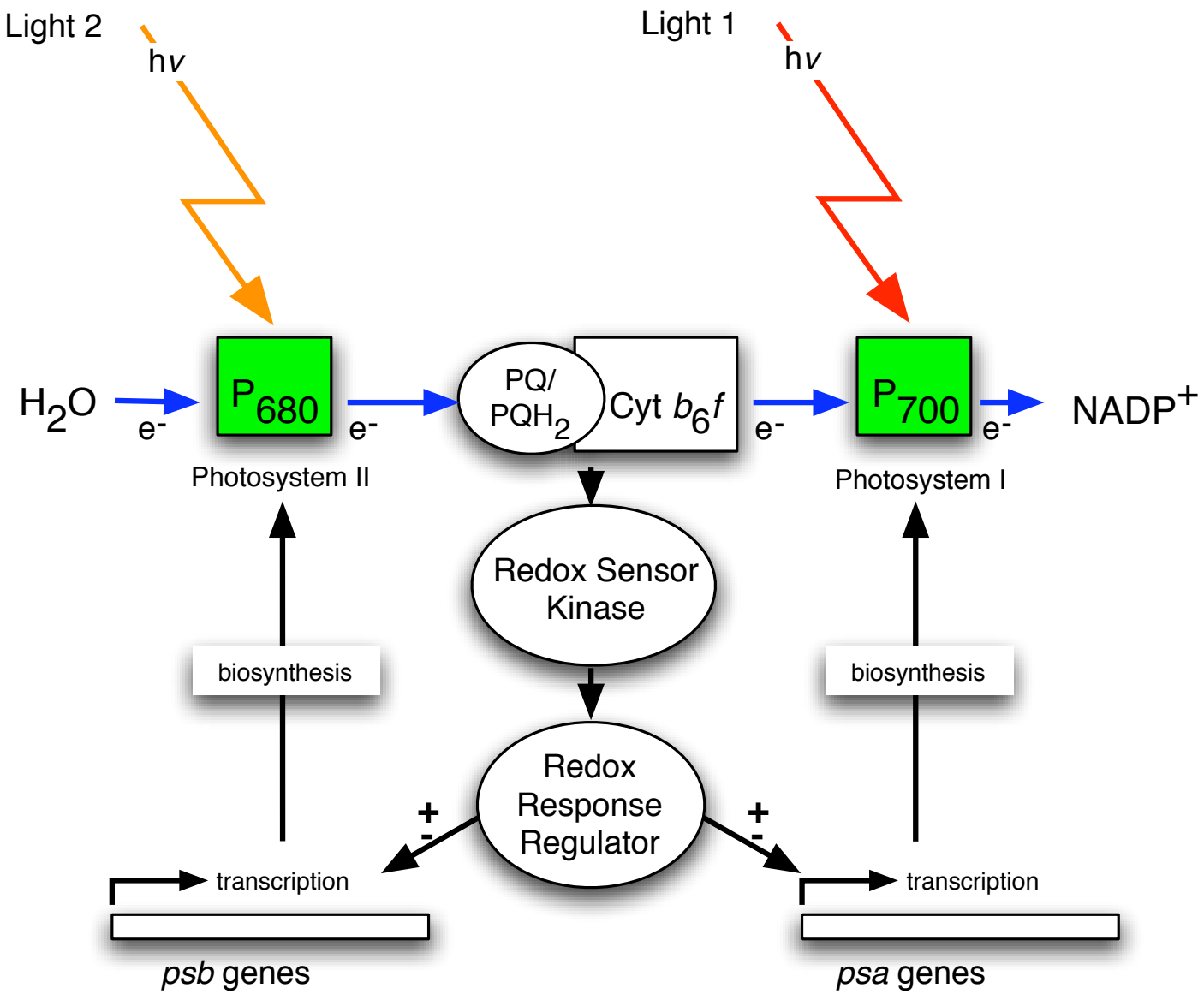
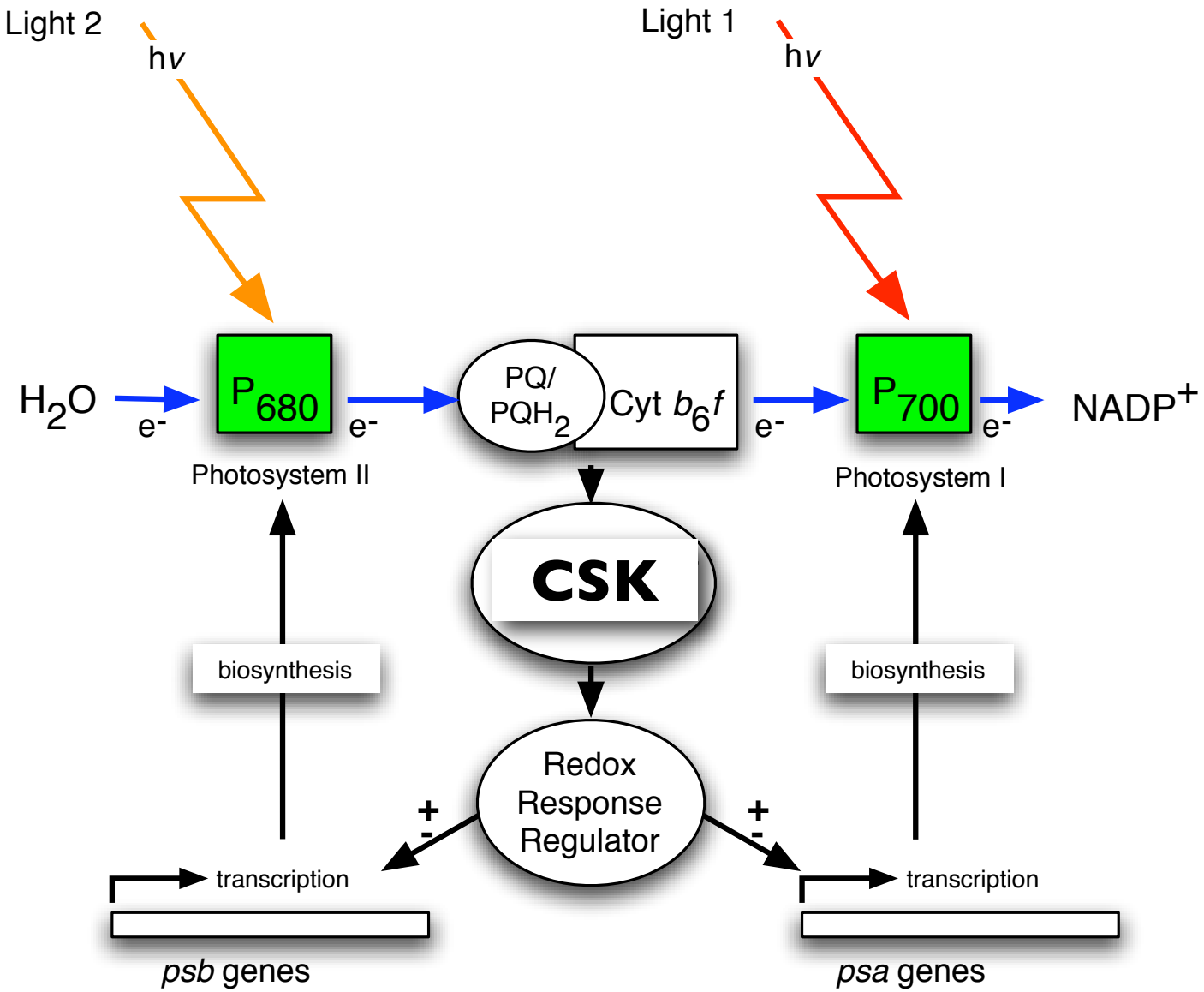



Puthiyaveetil S and Allen JF (2008)
Transients in chloroplast gene transcription
*Biochemical and Biophysical Research Communications*. 368: 871-874

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*Biochemical and Biophysical Research Communications*. 368: 871-874


The costs of DNA in mitochondria

# Why Do We Still Have a Maternally Inherited Mitochondrial DNA? Insights from Evolutionary Medicine

Douglas C. Wallace

Center for Molecular and Mitochondrial Medicine and Genetics, Departments of Biological Chemistry, Ecology and Evolutionary Biology, and Pediatrics, University of California, Irvine, California 92697-3940; email: dwallace@uci.edu

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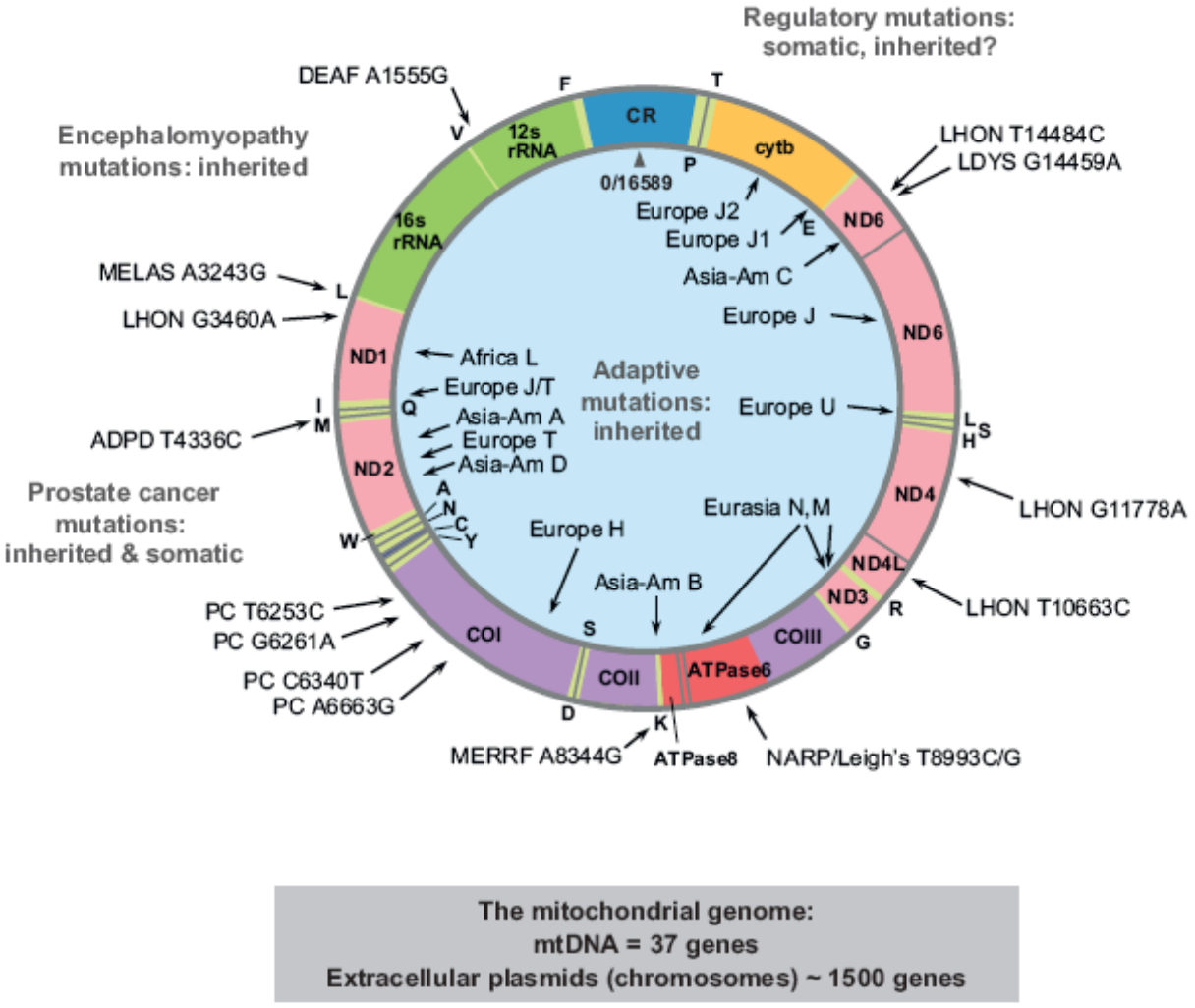
0066-4154/07/0707-0781$20.00

## Key Words

adaptation, genomic evolution, mitochondrial disease, mtDNA, oxidative phosphorylation, proton-translocating OXPHOS complexes

## Abstract

The human cell is a symbiosis of two life forms, the nucleus-cytosol and the mitochondrion. The nucleus-cytosol emphasizes structure and its genes are Mendelian, whereas the mitochondrion specializes in energy and its mitochondrial DNA (mtDNA) genes are maternal. Mitochondria oxidize calories via oxidative phosphorylation (OXPHOS) to generate a mitochondrial inner membrane proton gradient ($\Delta P$). $\Delta P$ then acts as a source of potential energy to produce ATP, generate heat, regulate reactive oxygen species (ROS), and control apoptosis, etc. Interspecific comparisons of mtDNAs have revealed that the mtDNA retains a core set of electron and proton carrier genes for the proton-translocating OXPHOS complexes I, III, IV, and V. Human mtDNA analysis has revealed these genes frequently contain region-specific adaptive polymorphisms. Therefore, the mtDNA with its energy controlling genes may have been retained to permit rapid adaptation to new environments.




**The mitochondrial genome:**
**mtDNA = 37 genes**
**Extracellular plasmids (chromosomes) ~ 1500 genes**

## Figure 2

The human mtDNA map. The human mtDNA encompasses three classes of clinically relevant mutations: recent maternally inherited disease-causing mutations, examples of which are shown on the outside of the circular map; ancient geographically correlated and frequently adaptive polymorphic variants, examples presented inside the circle; and somatic mutations that accumulate with age in postmitotic tissues and provide the aging clock. Letters around the outside perimeter indicate cognate amino acids of the tRNA genes. Letters within the ring represent the proteins encoded by the gene sector, all of which are integral membrane components of the proton-translocating complexes of OXPHOS. The polypeptides, corresponding gene, and complexes are ND1-4, -4L, -5, and -6 (*nad1-4, -4l, -5*, and *-6* gene) of complex I; cytb or cytochrome *b* (*cob* gene) of complex III; COI-III (*cox1–3* genes) of complex IV; and ATP6 and ATP8 (*atp6* and *atp8* genes) of complex V.

# The mitochondrial theory of ageing (“aging” - U.S.)

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“Errors” in electron transfer - transfers to the “wrong” electron acceptor - occur at fixed frequency.

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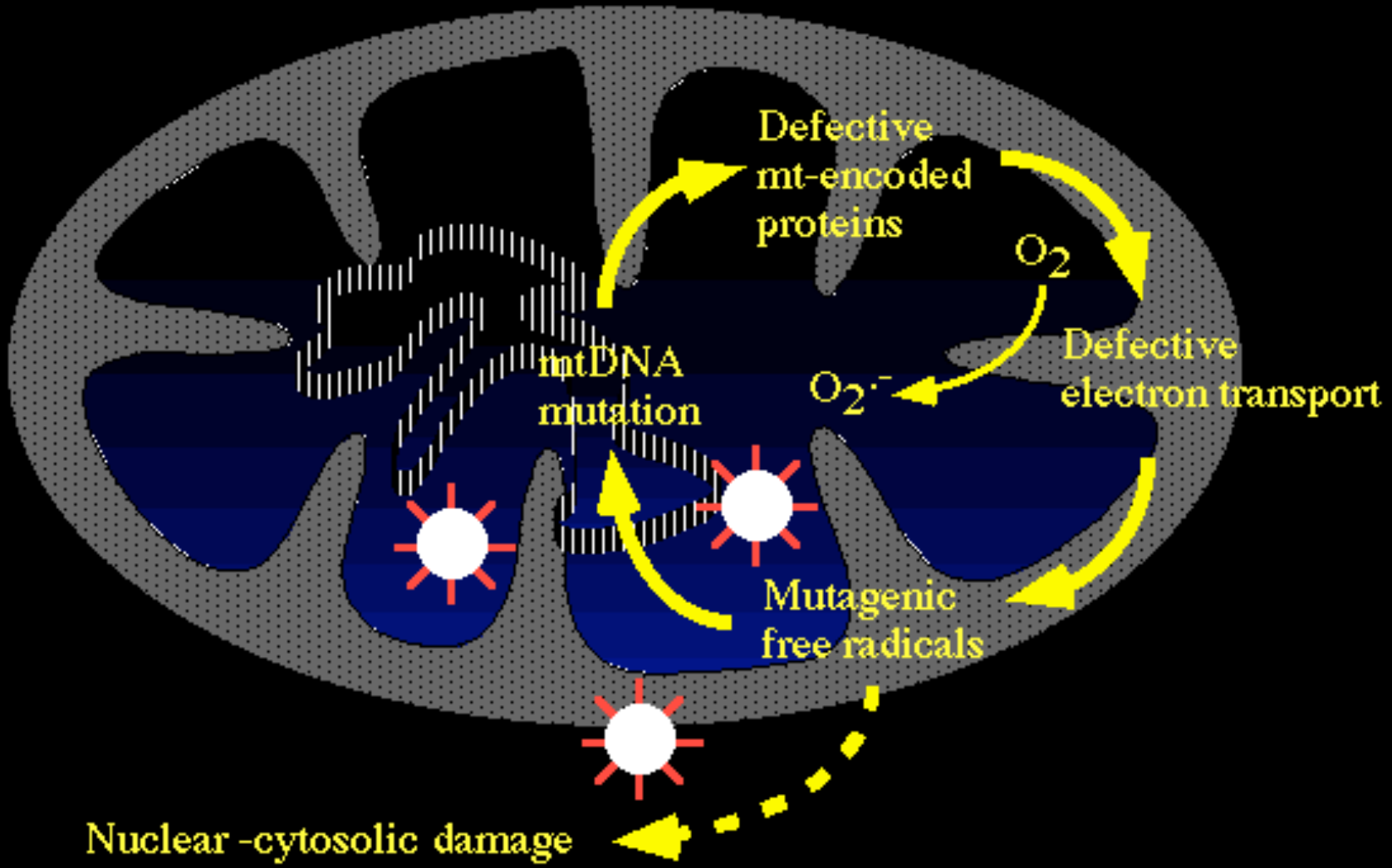
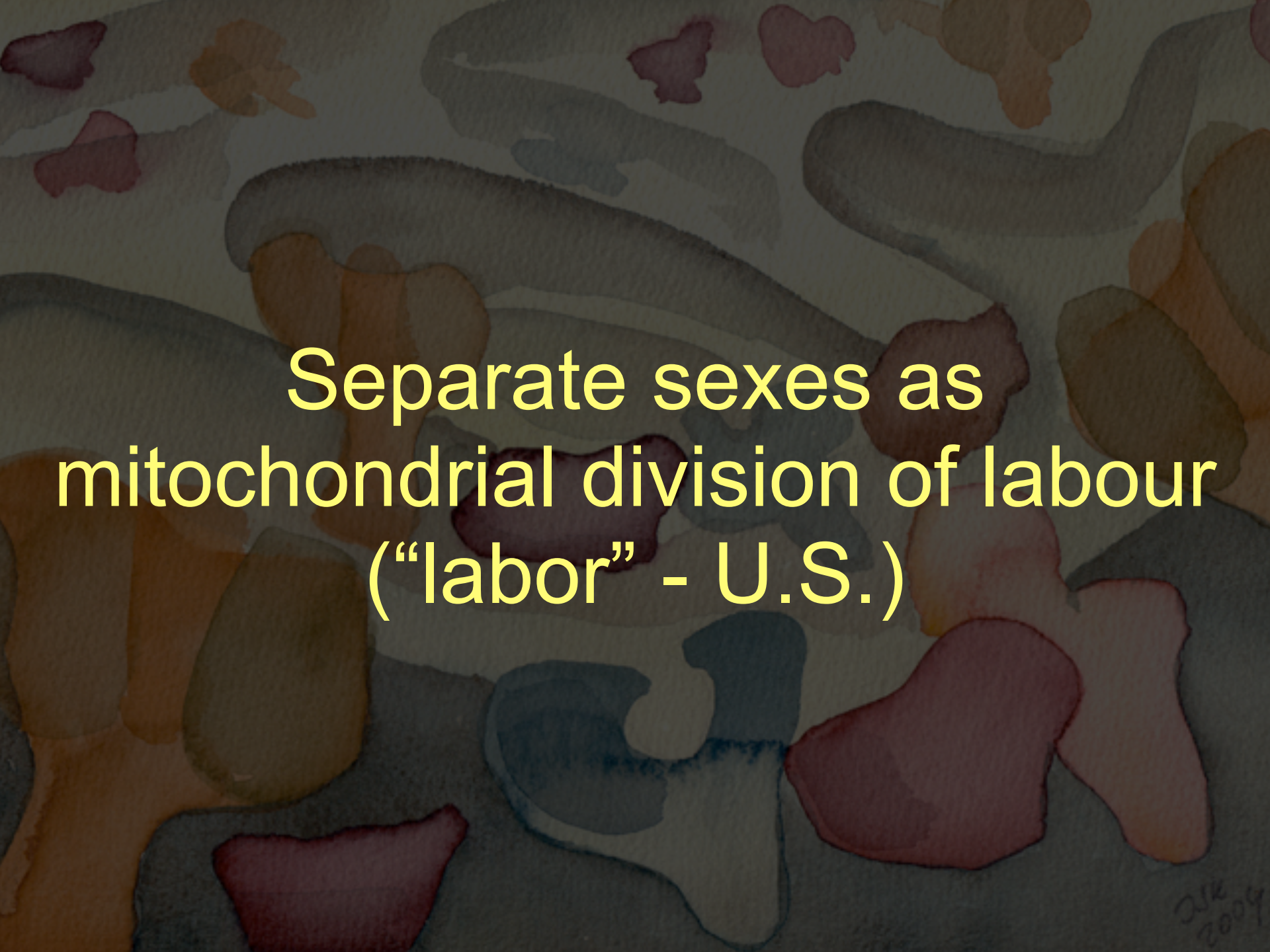
The products of these reactions damage mitochondrial genes, which then produce defective proteins, which then make more "errors" in electron transfer....damaging more genes, making more defective proteins....and so on.


Defective
mt-encoded
proteins
$O_2$
Defective
electron transport
mtDNA
mutation
$O_2^{\cdot -}$
Mutagenic
free radicals
Nuclear -cytosolic damage


Separate sexes as
mitochondrial division of labour
(“labor” - U.S.)

# Why there are two sexes

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**Problem:** Mitochondrial Ageing predicts that offspring should inherit their mothers' acquired state of accumulated damage, but they evidently do not. Babies are not born at the physical age of their mothers.

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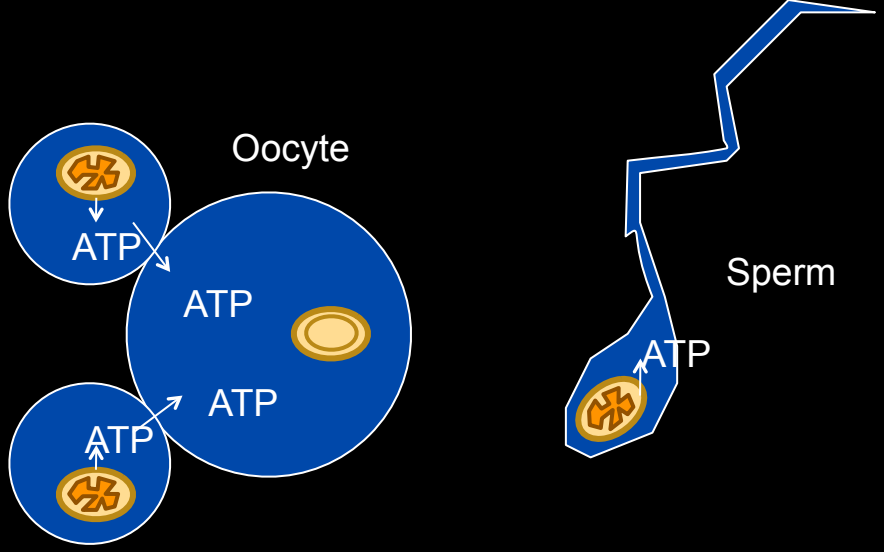
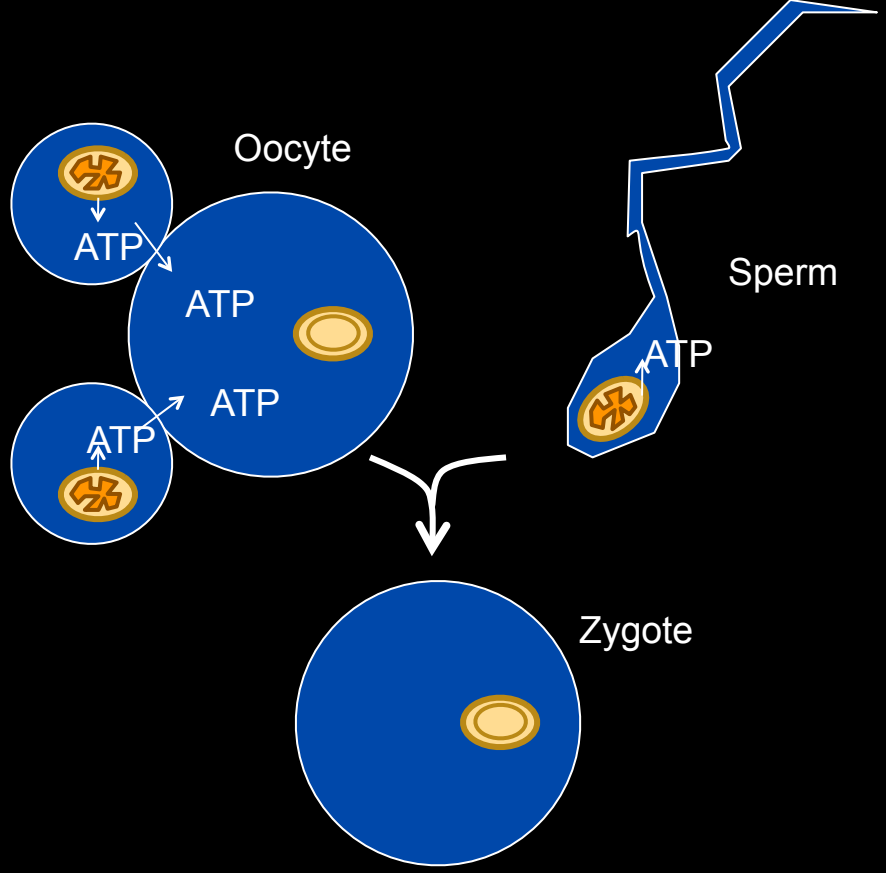
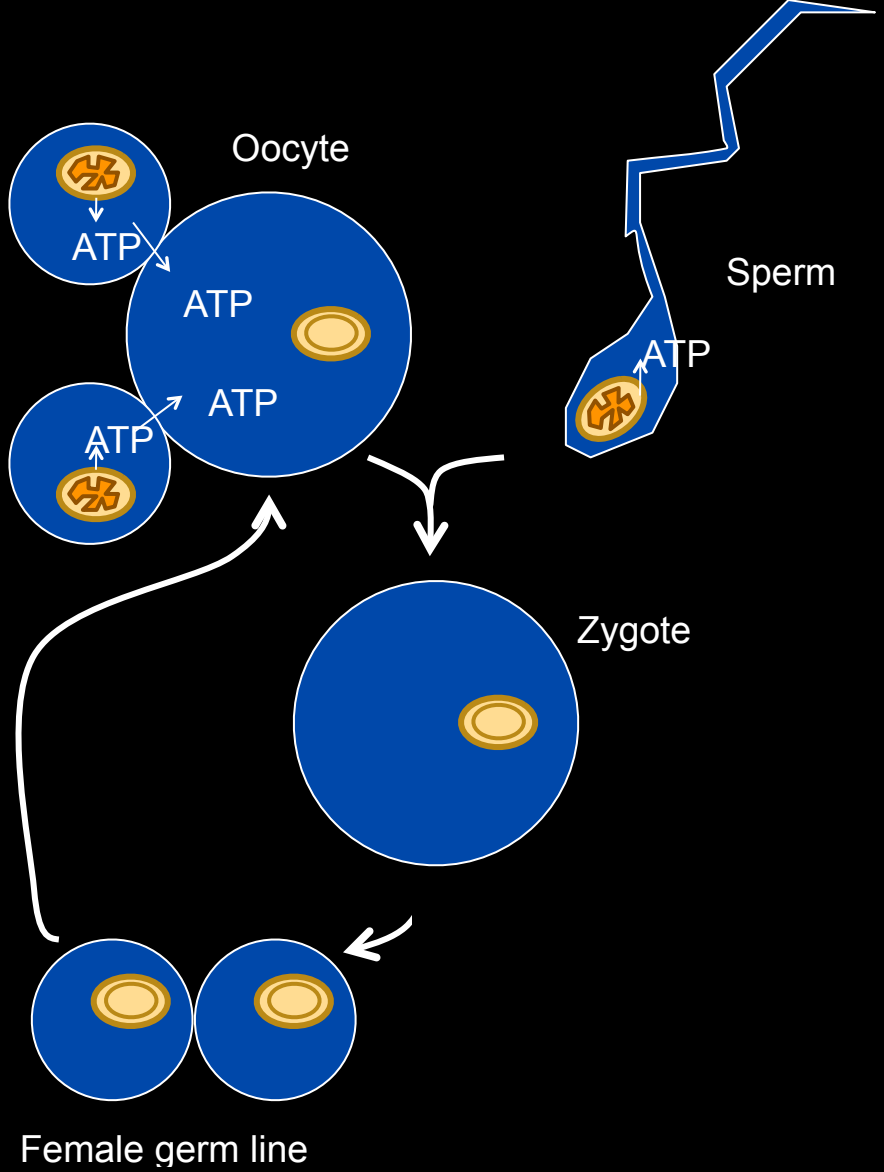
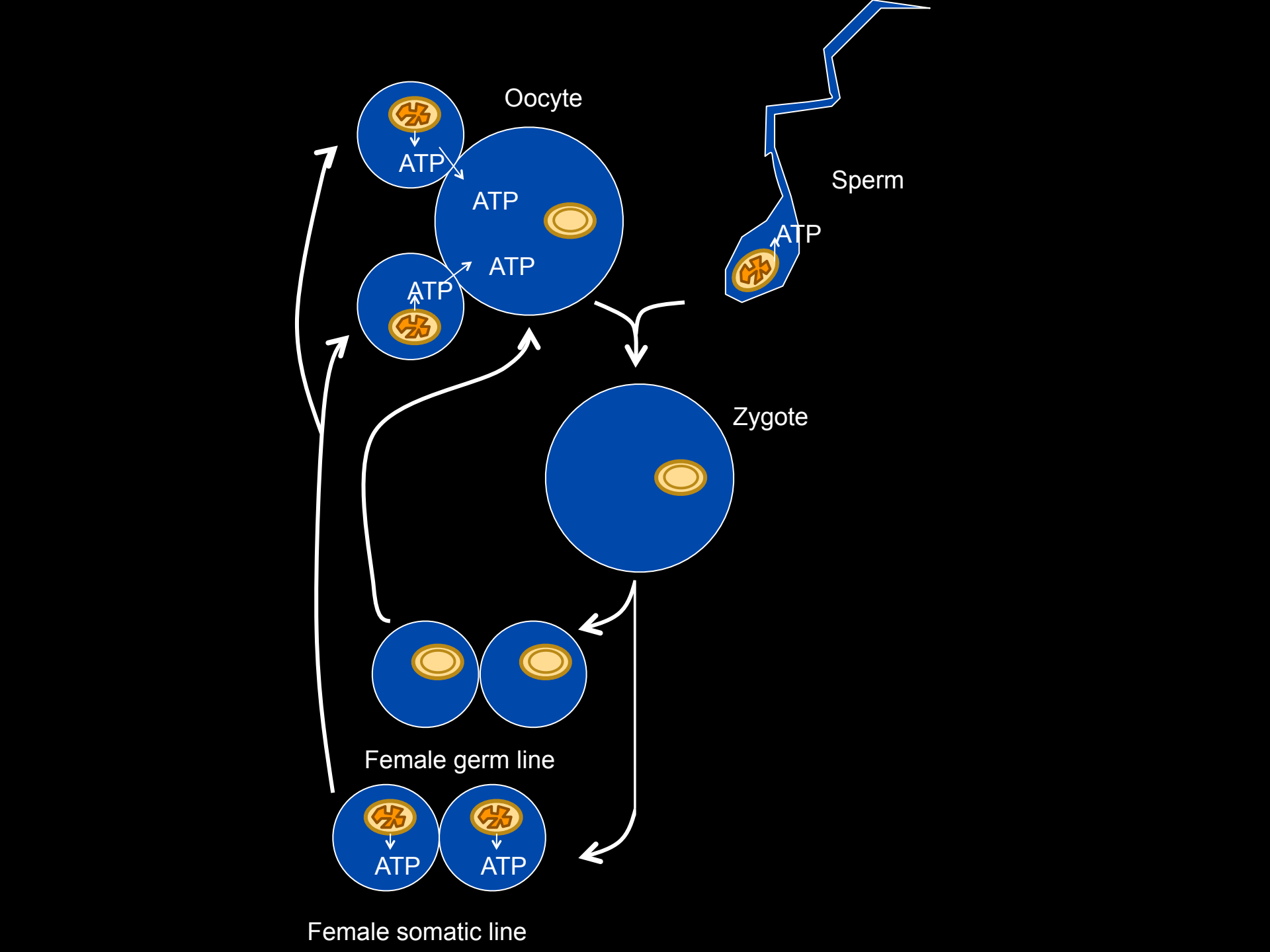
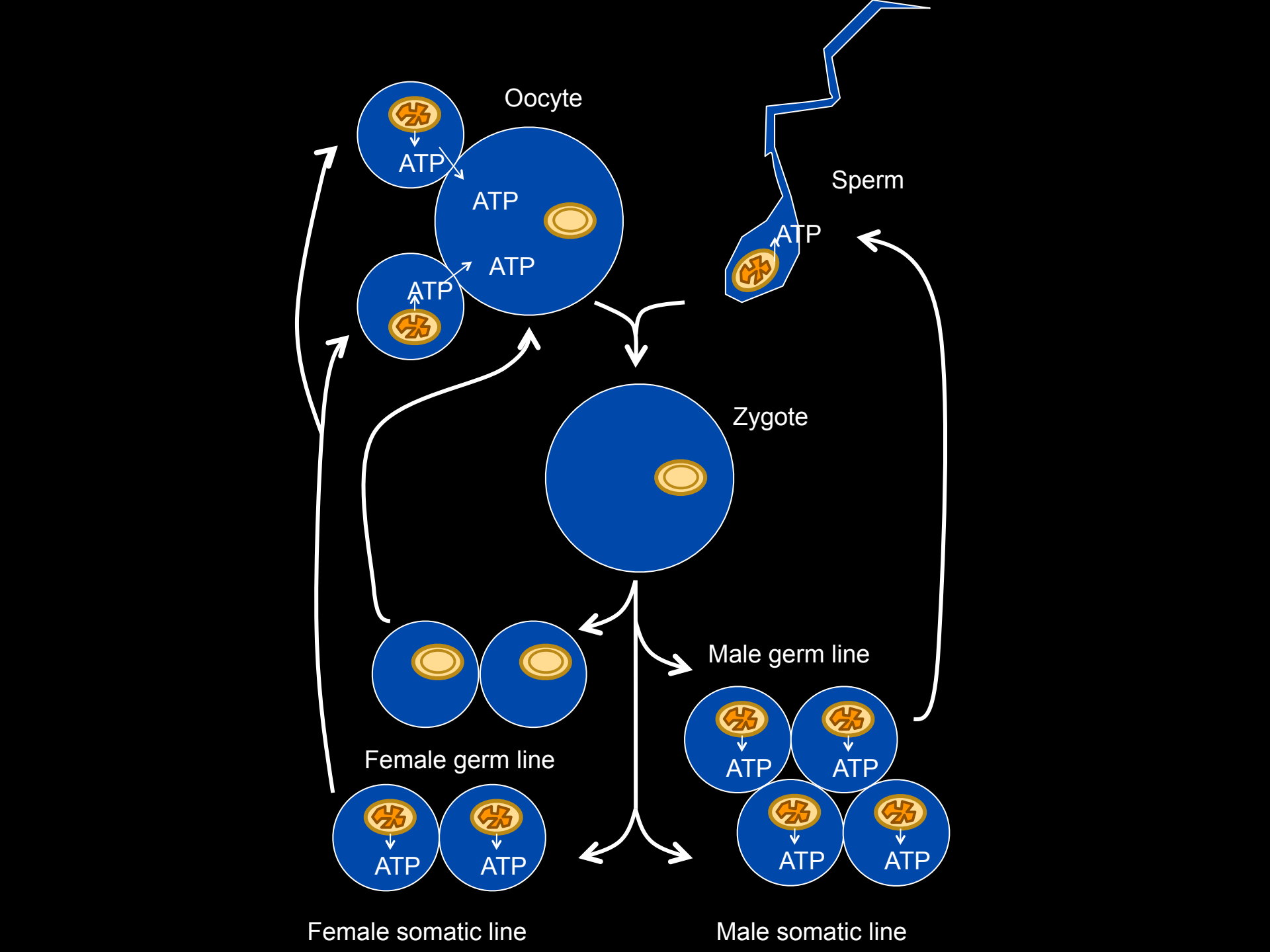
And they can never be both.

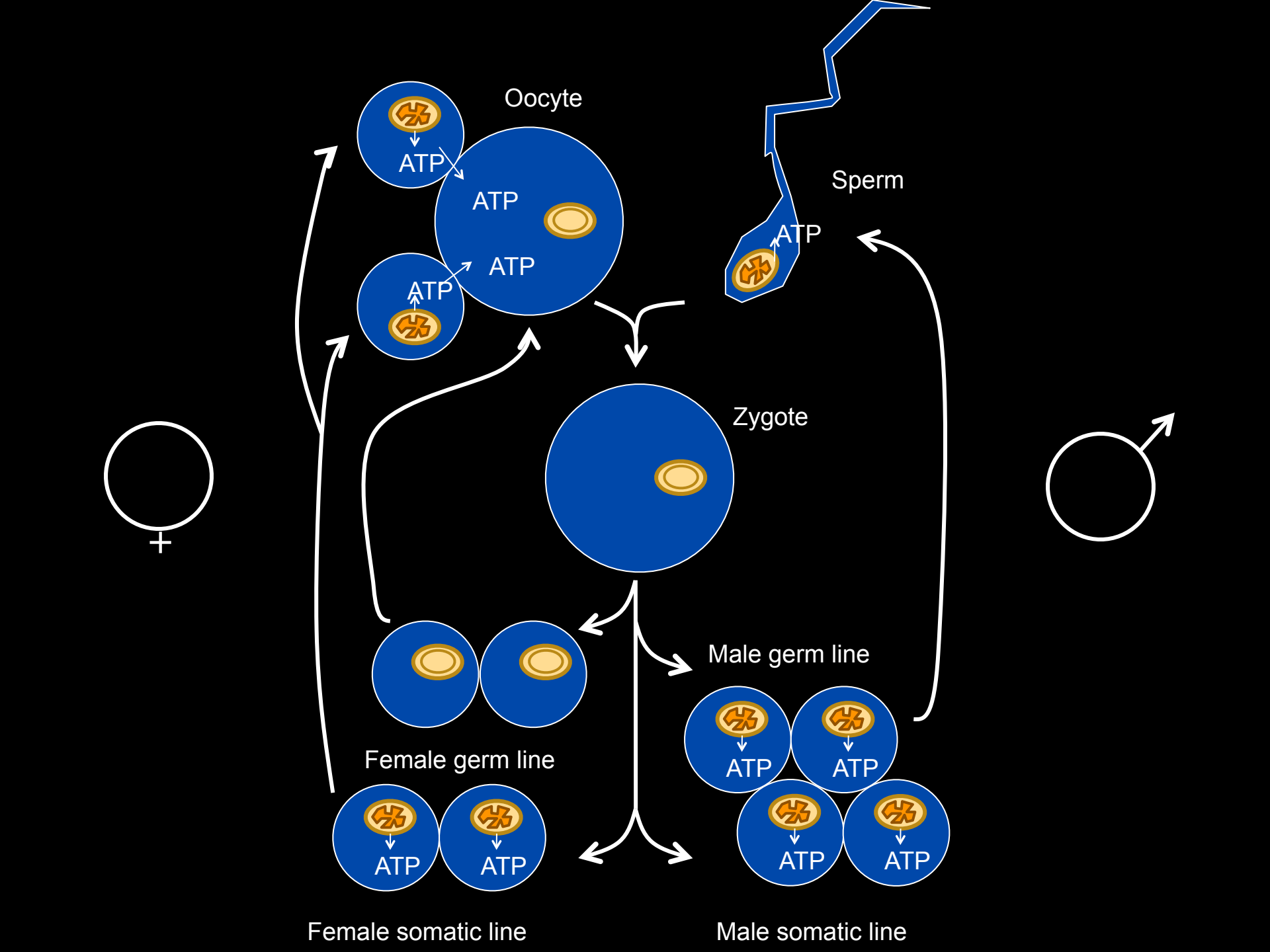

Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP

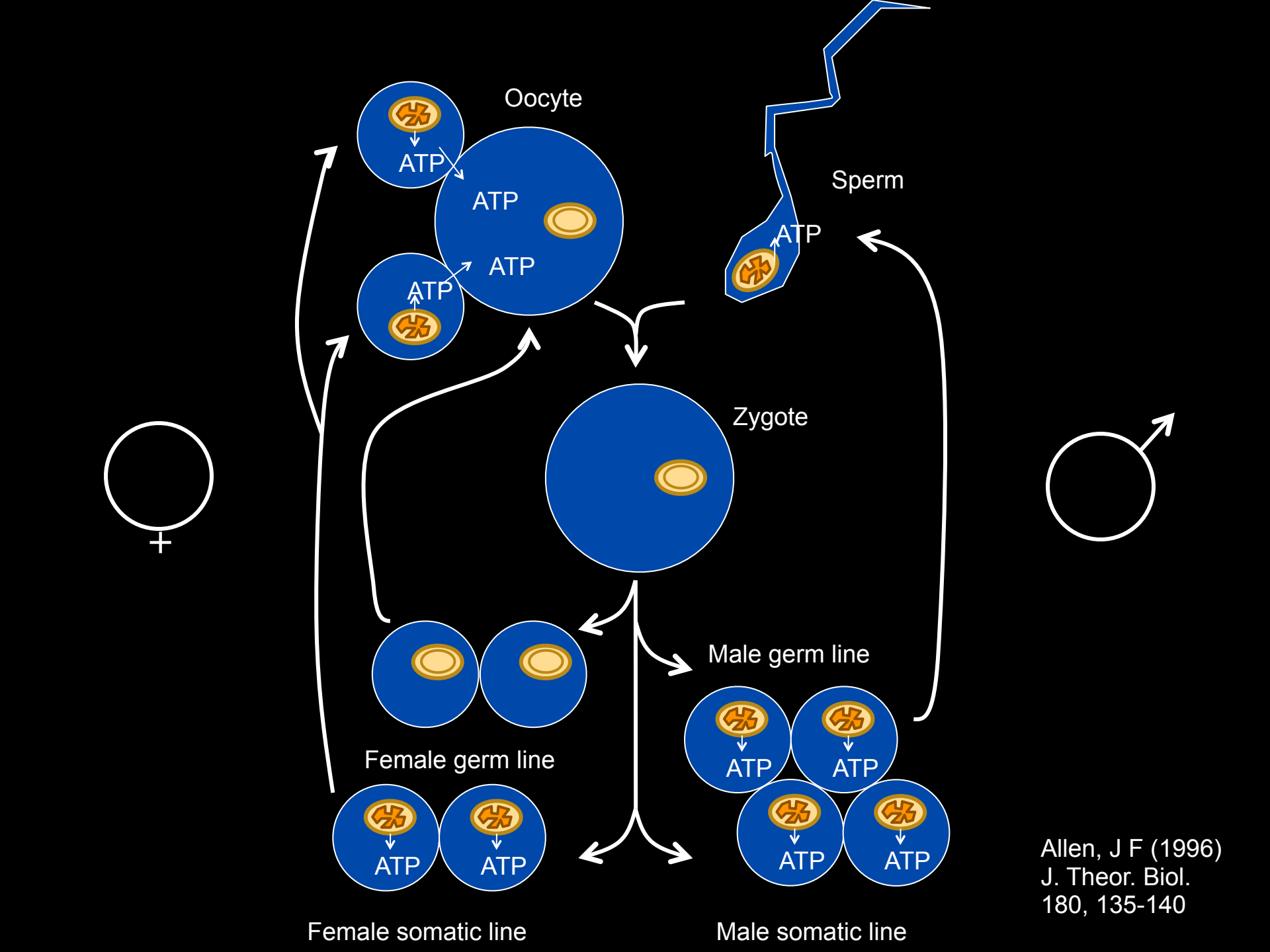

Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote


Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote
Female germ line

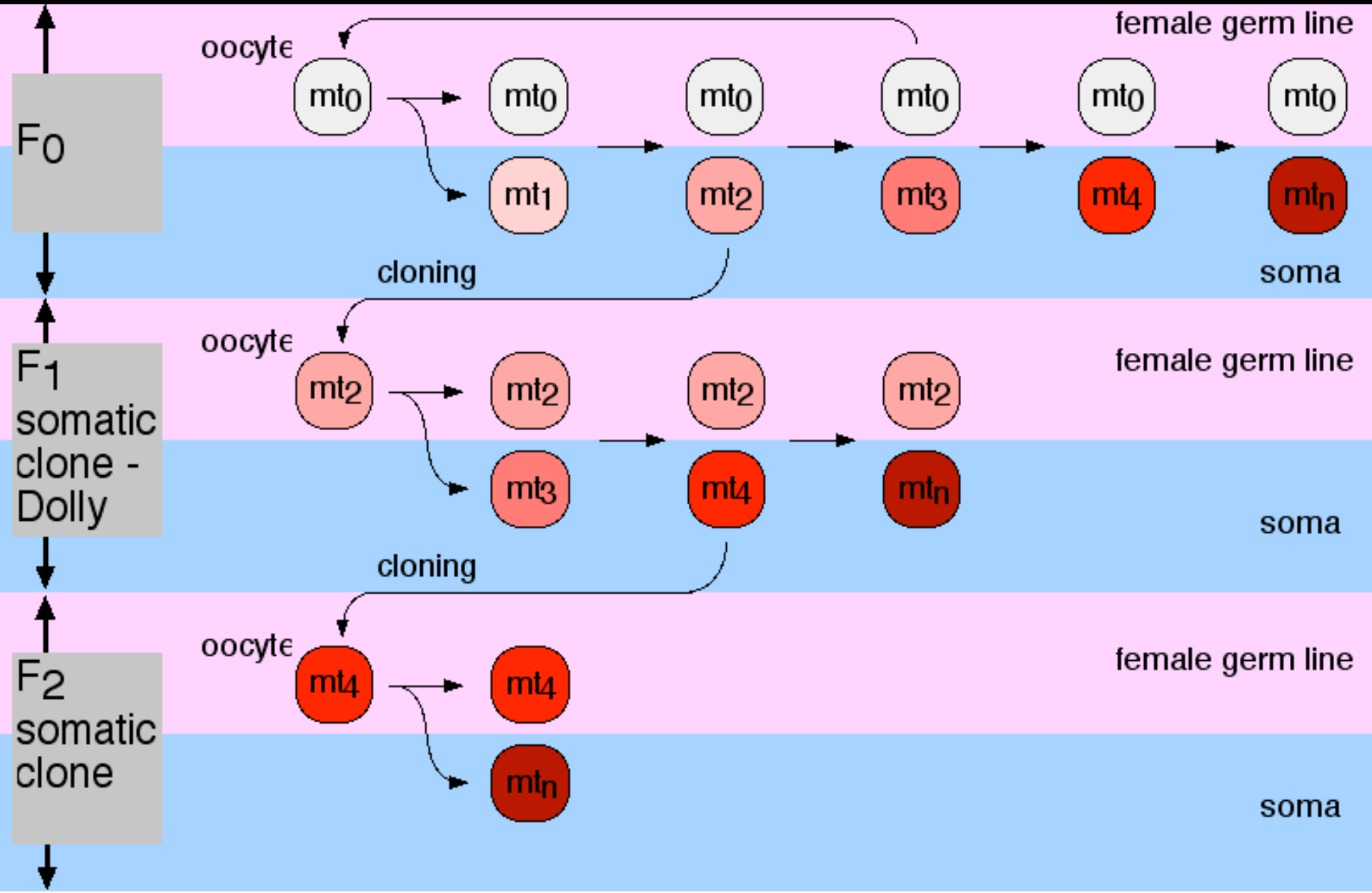

Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote
Female germ line
ATP
ATP
Female somatic line


Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote
Male germ line
ATP
ATP
ATP
ATP
Female germ line
ATP
ATP
Female somatic line
Male somatic line


Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote
Male germ line
ATP
ATP
ATP
ATP
Female germ line
ATP
ATP
Female somatic line
Male somatic line




Allen, J F (1996)
J. Theor. Biol.
180, 135-140




Allen JF, and Allen CA. IUBMB Life 48: 369-372, 1999

Somatic, reproductive cloning will produce “elderly” offspring if somatic mitochondria are introduced into the oocyte.

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Dolly, the Finn Dorset ewe, the first mammal to be cloned from an adult cell. Finn Dorset sheep normally live to 11 or 12 years. Dolly had been suffering from lung cancer and died of a drug overdose on 14th February 2003, aged 5. Dolly is survived by three or four of her six lambs.

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**Obituary: Dolly the Sheep**
http://www.nature.com/nsu/030210/030210-15.html

## Separate sexes as mitochondrial division of labour

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– Oocytes (eggs) carry protected, template mitochondria, and are therefore sequestered at an early stage in female development

– Females have a time-limited reproductive capacity - oocyte mitochondria become useless as genetic templates after a certain threshold of damage is reached

– Somatic, reproductive cloning will produce “elderly” offspring if somatic mitochondria are introduced into the oocyte. Dolly: 6+5=11

– An immortal line of genetic template mitochondria in the female germ line; … from egg back to egg

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– but are predicted to exist also in female germ lines as protected genetic templates, incapable of energy conversion, and from which all other mitochondria and chloroplasts derive

# Coda. Two views of mitochondria
View 1

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John Burn (Newcastle Institute of Clinical Genetics). Quoted in *The Times*, 9th September 2005

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Mitochondria:

– *"…are not part of the genetic material that we consider makes us as human beings."*

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John Burn (Newcastle Institute of Clinical Genetics). Quoted in *The Times*, 9th September 2005

Mitochondria:

– *"…are not part of the genetic material that we consider makes us as human beings."*

*"My belief is that what we are doing is changing a battery that doesn't work for one that does….Changing the mitochondria won't affect the important DNA."*

# Coda. Two views of mitochondria
View 2

# Coda. Two views of mitochondria
# View 2

Nick Lane. *Power, Sex, Suicide. Mitochondria and the Meaning of Life.* Oxford University Press. 2005.

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Mitochondria:

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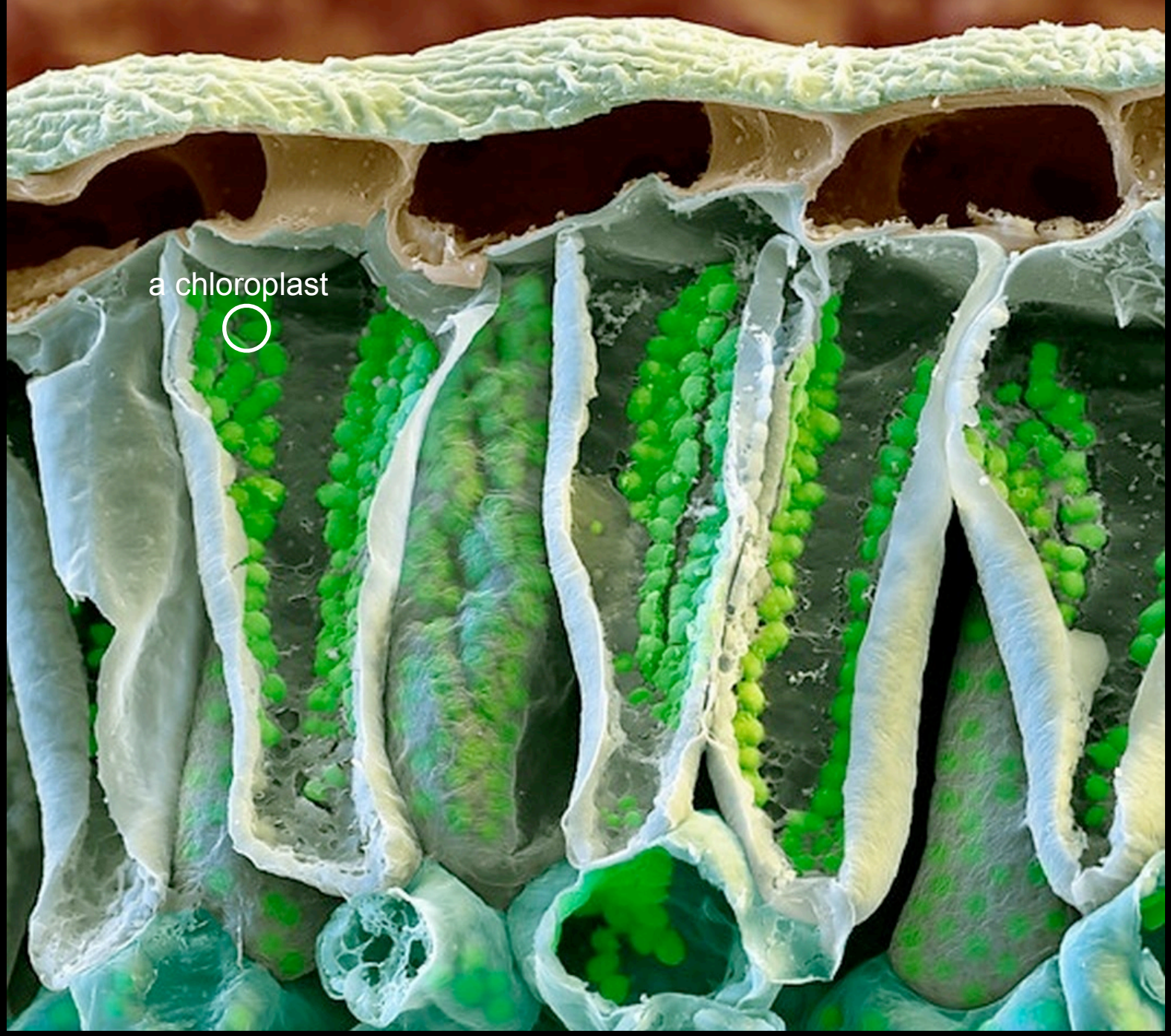
Mitochondria:

– *"…give striking new insights into why we are here at all, whether we are alone in the universe, why we have our sense of individuality, why we should make love, where we trace our ancestral roots, why we must age and die—in short, into the meaning of life."*




‘Christmas-Rose’ leaf SEM cross-section; Science Photo Library (SPL)

A mitochondrion—one of many tiny power-houses within cells that control our lives in surprising ways

Queen Mary
University of London

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Australian Academy of Science

Rudi Lemberg
1896-1975


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Iskander Ibrahim
John F. Allen
Azma Shiyam
Thomas Buckland
Sujith Puthiyaveetil


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The end. Thank you for listening.