Valdur Saks

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SYSTEMS BIOLOGY: MOLECULAR SYSTEM BIOENERGETICS

SYSTEMS BIOLOGY -

DEFINITIONS AND HISTORY

Systems Biology is the science that aims to understand how biological function absent from macromolecules in isolation, arises when they are components of their system.

Hans V. Westerhoff

Systems biology towards life in silico: mathematics of the control of living cells.
J Math Biol. 2008 Feb 16

System level properties

The meaning of "systems" itself varies from two macromolecules that interact, to the whole organism and even population, and the aim of Systems Biology is to understand the system level properties of these complex multicomponent processes.

System level *properties mean that they are not predictable from the properties of the isolated components of the cell, not even predictable from gene expression, but depend upon the sum of interactions within the whole system*

CHANGE OF PARADIGMS OF BIOLOGICAL SCIENCES

FROM REDUCTIONISM

Reductionism used to be the philosophical basis of biochemistry and molecular biology when everything, from genes to proteins and organelles - were studied in their isolated state.

TO SYSTEMS BIOLOGY

Systems Biology is a study of integrated systems at all levels: cellular, organ, organism and population and accepts that the physiological whole is greater than the sum of its parts.

Using knowledge from molecular biology, the systems biologist can propose a hypothesis that can be used to mathematically model the system. This model is used to predict how different changes affect the phenotype of a cell, and can be iteratively tested to prove or disprove the model.

Denis Noble
Exp Physiol 2008;93;16-26

Systems Biology: A Brief Overview
Hiroaki Kitano

The reductionist causal chain

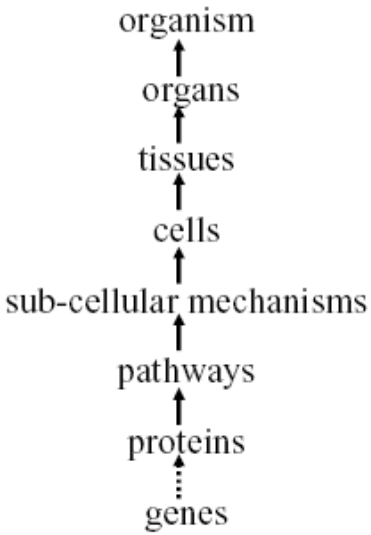


Figure 1. The reductionist 'bottom-up' causal chain (reproduced with permission from Noble, 2006)
This begins with the central dogma that information flows from DNA to proteins (bottom dotted arrow), never the other way, and extends the same concept through all the higher levels.

Identifying all the genes and proteins in an organism is like listing all the parts of an airplane. While such a list provides a catalog of the individual components, by itself it is not sufficient to understand the complexity underlying the engineered object.
We need to know how these parts are assembled to form the structure of the airplane.

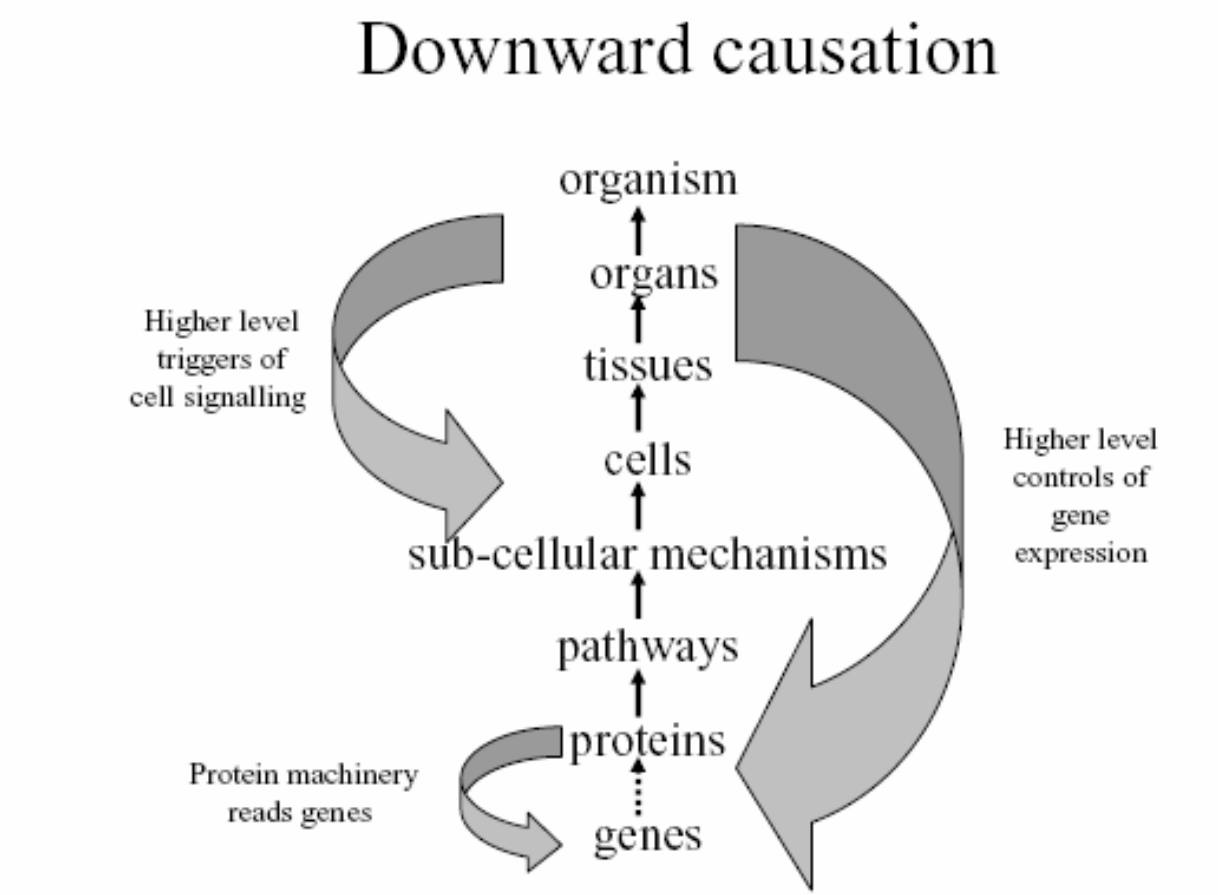
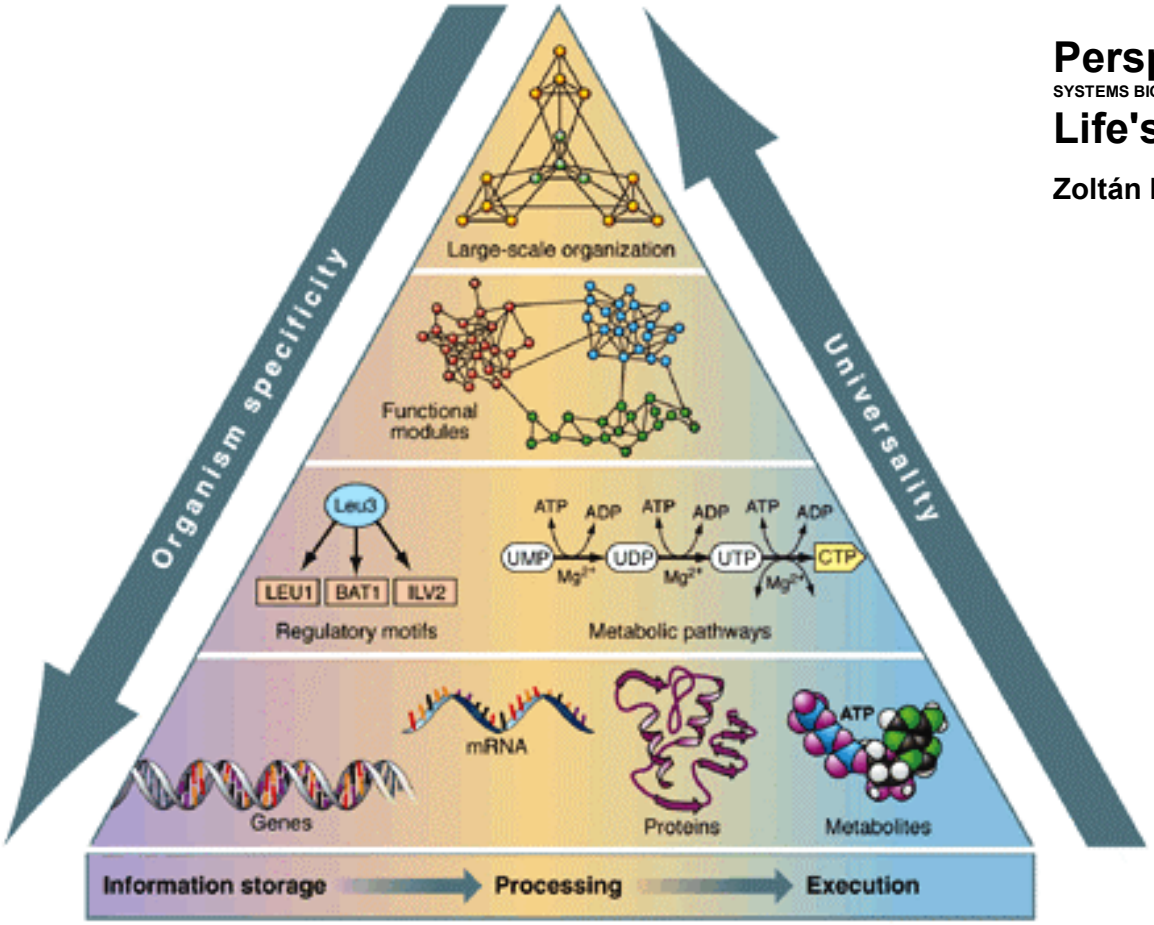


Figure 2. Figure 1 has been completed by adding the downward forms of causation, such as higher levels triggering cell signalling and gene expression

Note the downward-pointing arrow connecting from proteins to genes to indicate that it is protein machinery that reads and interprets gene coding. Loops of interacting downward and upward causation can be built between all levels of biological organization. Reproduced with permission from Noble (2006).



Perspectives

SYSTEMS BIOLOGY:

Life's Complexity Pyramid

Zoltán N. Oltvai and Albert-László Barabási*

Science 25 October2002: Vol. 298. no. 5594, pp. 763 - 764

From the particular to the universal. The bottom of the pyramid shows the traditional representation of the cell's functional organization: genome, transcriptome, proteome, and metabolome (level 1). There is remarkable integration of the various layers both at the regulatory and the structural level. Insights into the logic of cellular organization can be achieved when we view the cell as a complex network in which the components are connected by functional links. At the lowest level, these components form genetic-regulatory motifs or metabolic pathways (level 2), which in turn are the building blocks of functional modules (level 3). These modules are nested, generating a scale-free hierarchical architecture (level 4). Although the individual components are unique to a given organism, the topologic properties of cellular networks share surprising similarities with those of natural and social networks. This suggests that universal organizing principles apply to all networks, from the cell to the World Wide Web.

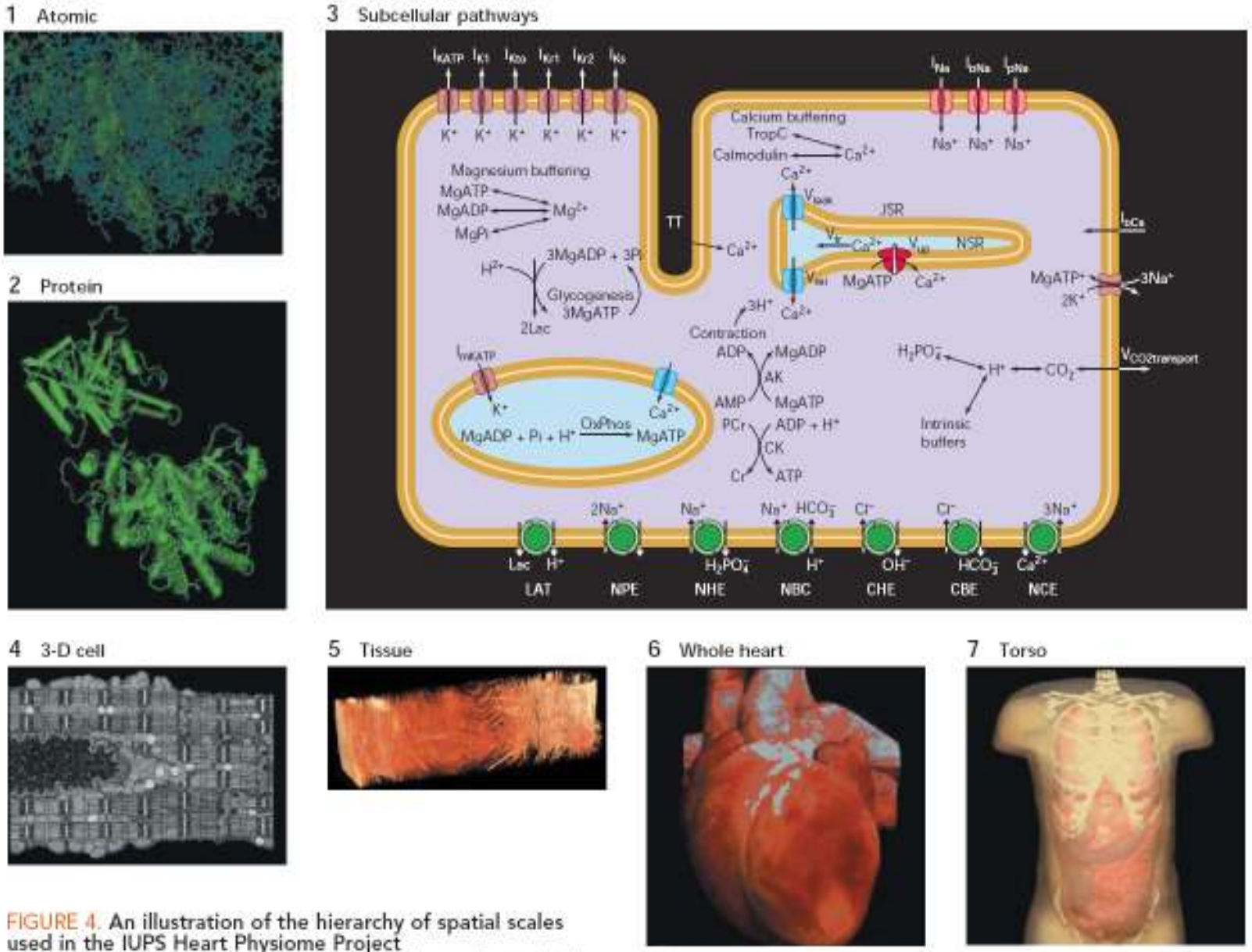
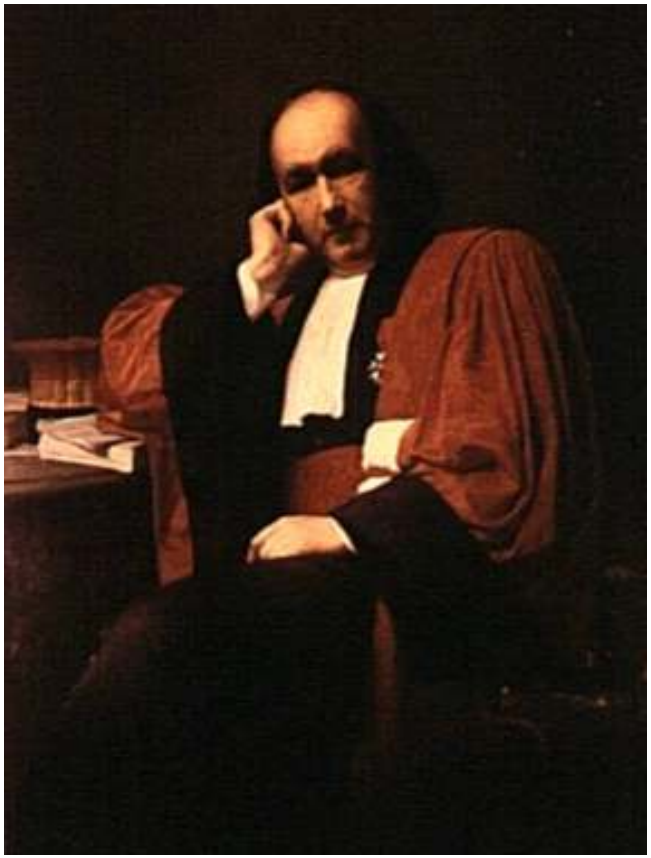


FIGURE 4. **An illustration of the hierarchy of spatial scales used in the IUPS Heart Physiome Project**

The levels are *1*) atomic, shown here by the atomic coordinates for the sarco(endo)plasmic reticulum calcium ATPase (SERCA) from the PDB database (note the 2 bound calcium atoms in white); *2*) protein A, demonstrating a coarser-grained model of structure for the same protein; *3*) subcellular pathways, which include the cell electrophysiology, calcium transport, proton transport, myofilament mechanics, metabolic pathways, and some cell-signaling pathways; *4*) 3-D cell, in this case cardiac muscle cell from electron micrograph; *5*) tissue organization, shown here with collagen fibers in a transmural tissue block from a rat heart; *6*) whole heart (The Auckland Textured Virtual Heart); and *7*) torso (the Auckland Human Torso Model).

HISTORY AND PHILOSOPHICAL BASIS

THERE WAS SYSTEMS BIOLOGY
BEFORE SYSTEMS BIOLOGY!



Claude Bernard (1813-1878)

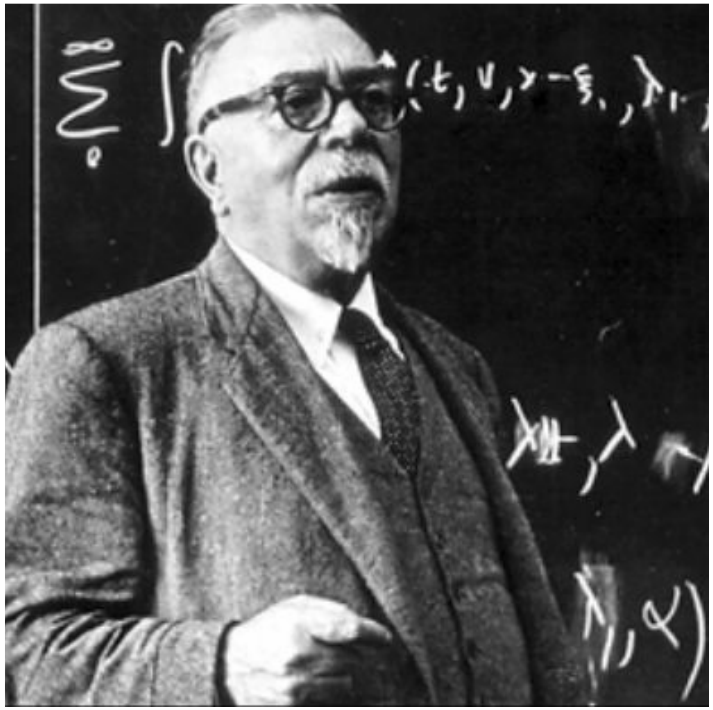
"Introduction a l'étude de la médecine expérimentale". Flammarion, Paris, 1865, 1984

An Introduction to the Study of Experimental Medicine

THEORY OF HOMEOSTASIS – permanence of *milieu intérieur* due to integrated regulatory mechanisms

'The application of mathematics to natural phenomena is the aim of all science, because the expression of the laws of phenomena should always be mathematical.'

(Noble D. Claude Bernard, the first system biologist, and the future of physiology. Exp. Physiol. 93.1, 16-26, 2008)



Norbert Wiener (1894 – 1964)

Norbert Wiener
"**Cybernetics**.
Control and Communication in the
Animal and the Machine"
John Wiley & sons, Inc., New York,
1947

Cybernetics is the interdisciplinary study of the structure of complex systems, especially communication processes, control mechanisms and feedback principles. Cybernetics is closely related to control theory and systems theory.

BIOENERGETICS AND METABOLISM- WHY?

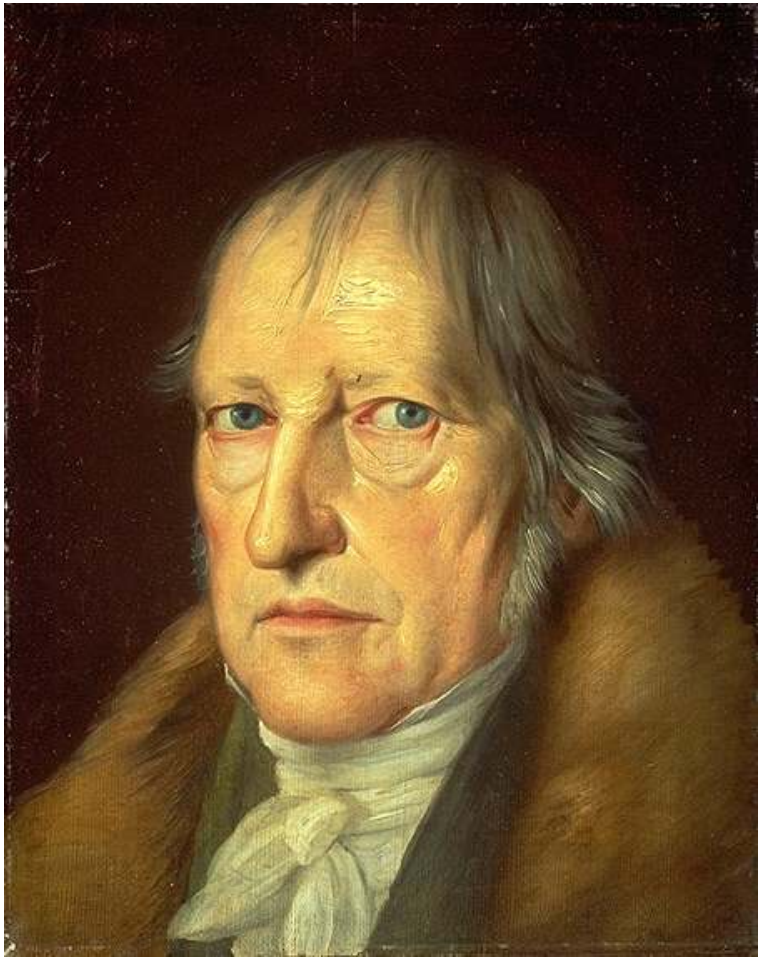
ERWIN SCHROEDINGER,

WHAT IS LIFE? 1944

« A living organism avoids the rapid decay into the inert state of equilibrium and keeps alive by continually drawing from its environment

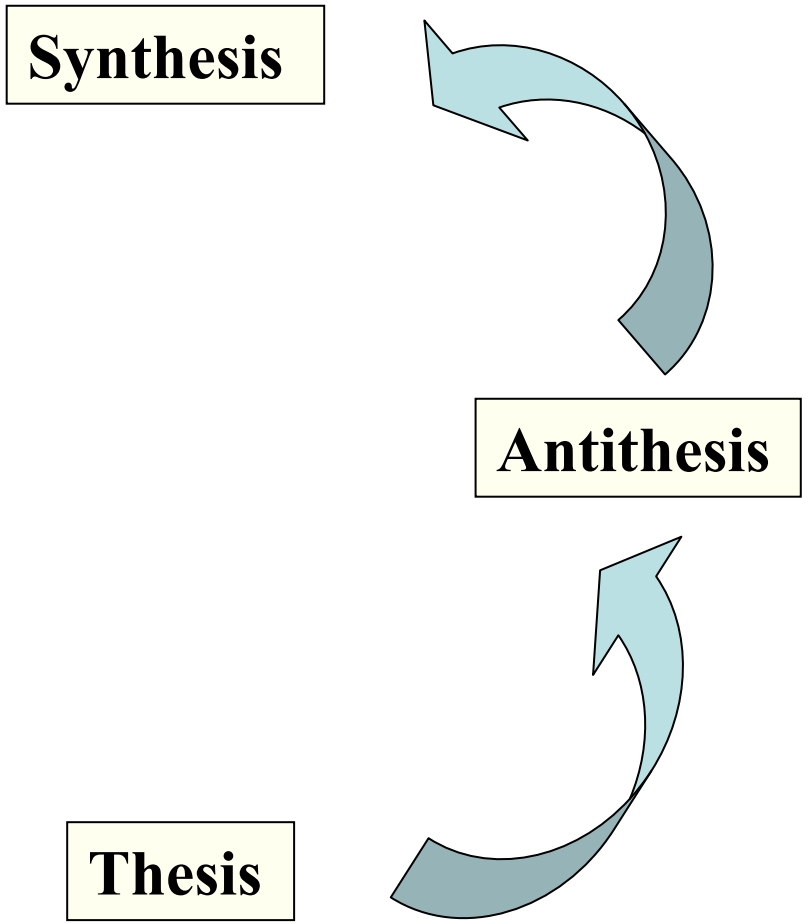
negative entropy.

The essential thing in integrated metabolism is that the organism succeeds in freeing itself from all entropy it cannot help producing while alive »



Georg Wilhelm Friedrich Hegel
(1770 – 1831)

DIALECTICAL PRINCIPLES OF HISTORICAL DEVELOPMENT:



Synthesis: Systems Biology

Quantitative description of integrated mechanisms of regulation, interaction studies, system level properties

Cybernetics, applied mathematics, computer sciences

Antithesis (reductionism):

systems are dissociated into components - molecular biology and genetics, protein structure, enzymology, kinetics, membrane bioenergetics

Thesis :

System parameters studied: classical physiology, cell physiology, homeostasis discovered

MEDICINE

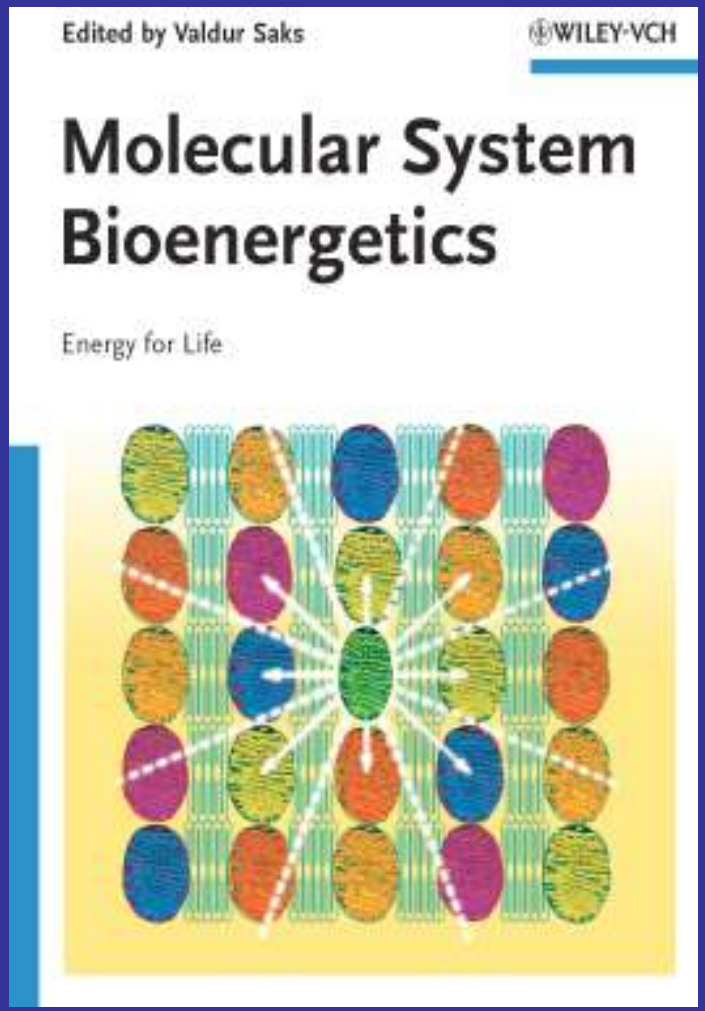
Denis Noble

Claude Bernard, the first systems biologist, and the future of physiology

Exp Physiol 2008;93;16-26

Higher-level control cannot be reduced to lower-level databases like the genome. A major part of the future of physiology surely lies in returning to our roots. Higher level **systems biology is, I suggest, classical physiology** by another name.

MOLECULAR SYSTEM BIOENERGETICS



Description

In this first integrated view, practically each of the world's leading experts has contributed to this one and only authoritative resource on the topic. Bringing systems biology to cellular energetics, they address in detail such novel concepts as metabolite channeling and medical aspects of metabolic syndrome and cancer.

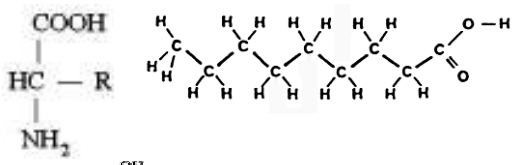
$$dE = E_f - E_0 = dq + dw$$

$$dG_{T,P} = dH_{T,P} - TdS_{T,P} = dE + PdV - TdS \leq 0$$

Le nombre de façons différentes de répartir une même quantité d'énergie dans un état donné du système est appelé la dégénérescence, ω. Boltzmann a démontré que l'entropie est reliée à la dégénérescence par l'équation :

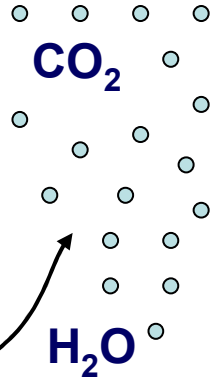
$$S = k_B \log \omega$$

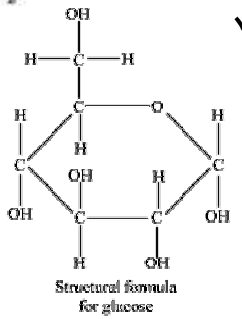
$$\lim_{T \to 0K} S = 0$$



$\Delta S_{ex} > 0$

$\Delta G_{ex} < 0$





O_2

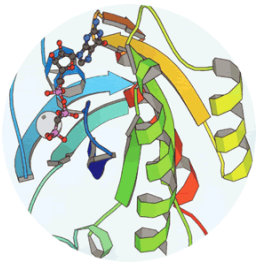
CATABOLISM

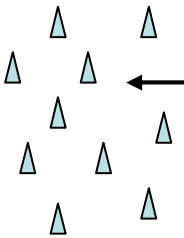
ADP

+Pi

ATP

Wc





ANABOLISM

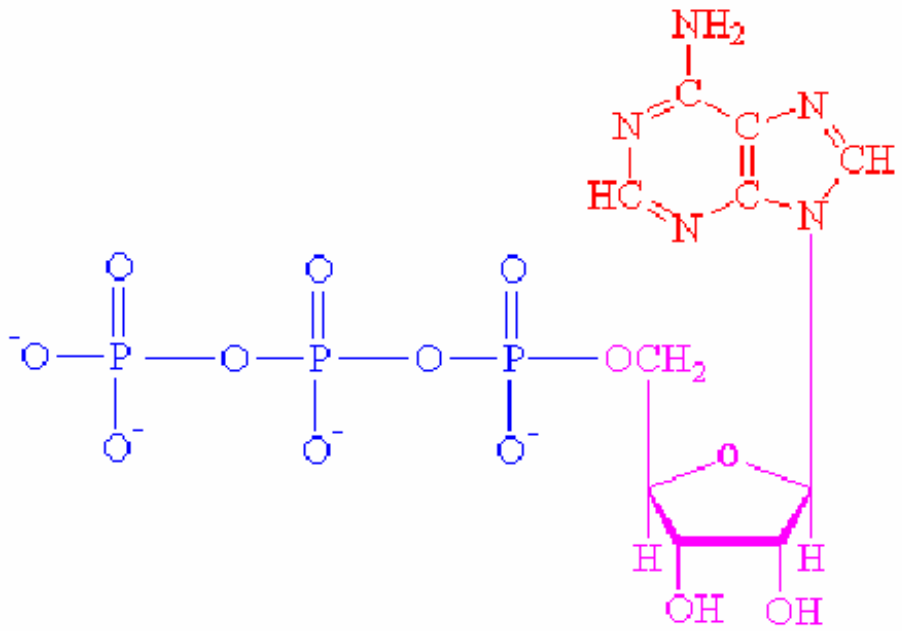
$\Delta S_{in} < 0$

$\Delta S_t = \Delta S_{ex} + \Delta S_i$

If: $|\Delta S_{ex}| > |\Delta Sex|$

$\Delta S_t > 0$!

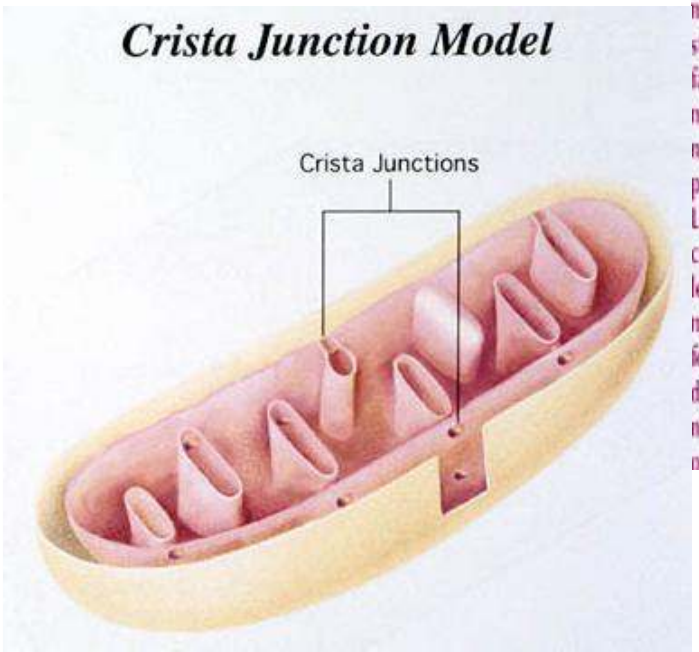
Adenosine Triphosphate



ATP consists of a base, in this case adenine (red), a ribose (magenta) and a phosphate chain (blue).

$$\Delta G_{ATP} = \Delta G^{0}_{ATP} + RT \ln \frac{[ATP]}{[ADP][P_i]}$$

Albert Lehninger et al. discovered in 1949 that oxidative phosphorylation occurs in **Mitochondrion**



NUTRA NEWS
Science, Nutrition, Prévention et Santé

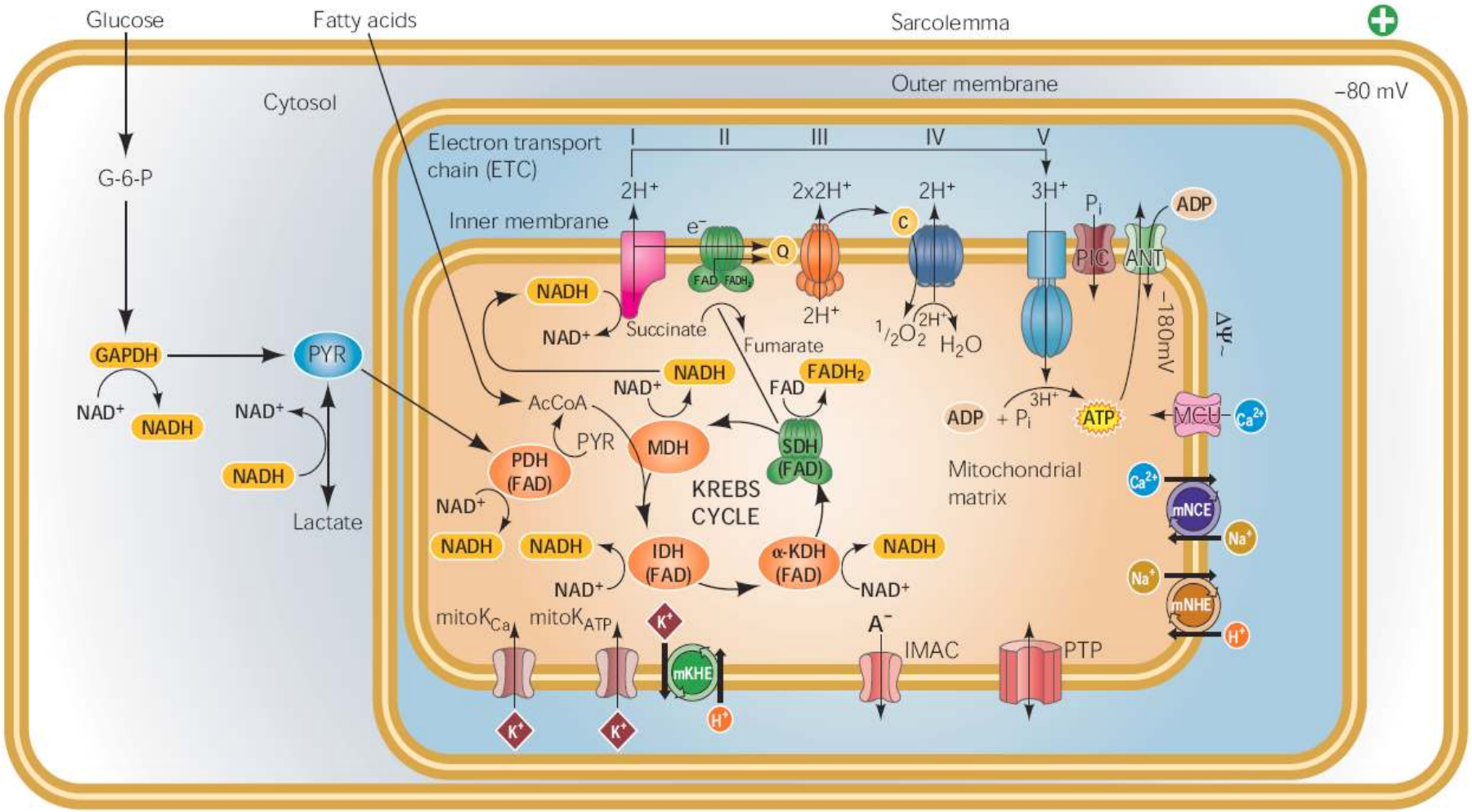
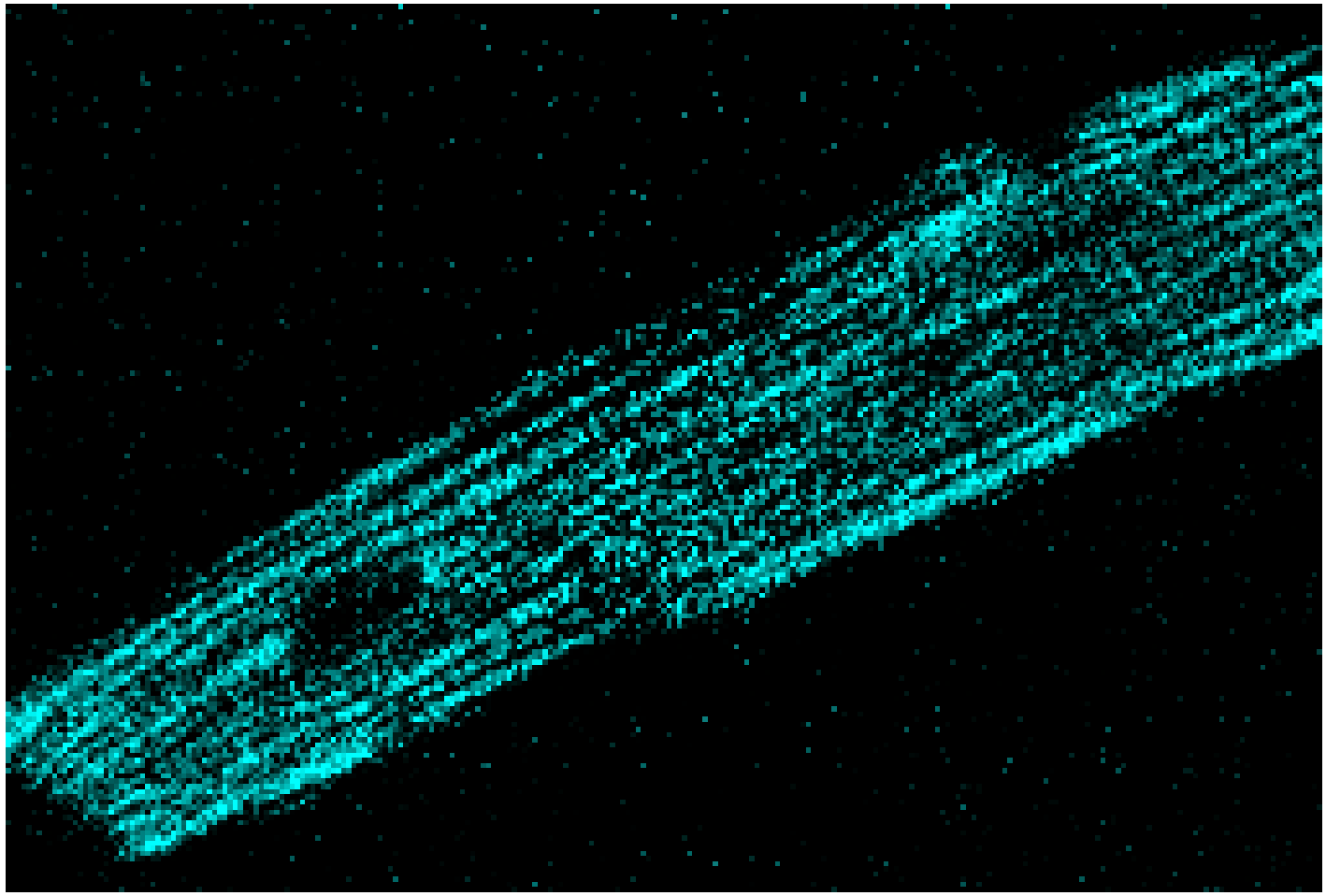
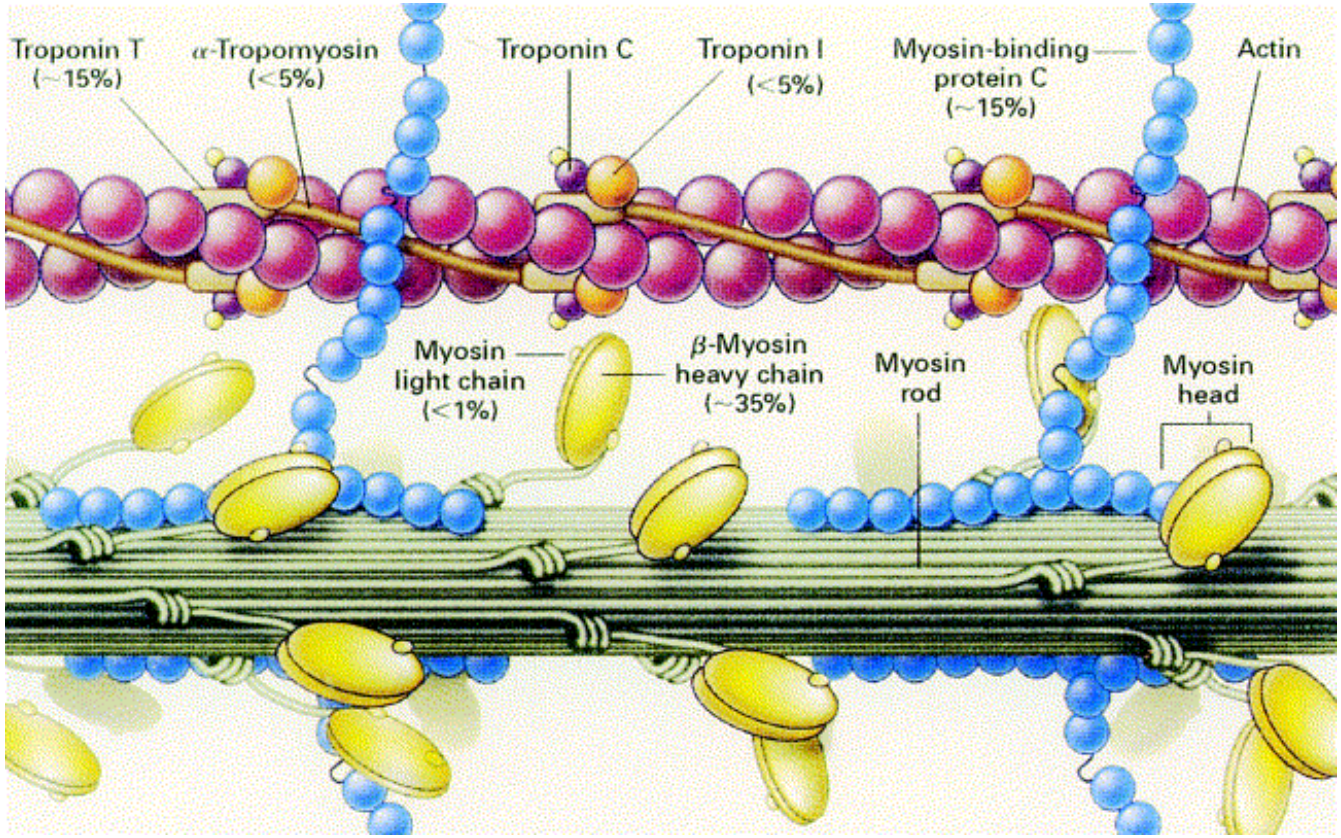


FIGURE 1. **Overview of oxidative phosphorylation in the cardiac cell**

The sequential oxidation of fuels (e.g., fatty acids and glucose) leads to the common substrate for the Krebs cycle, acetyl-CoA, which drives the production of the reducing equivalents NADH and $FADH_2$. Electrons are passed to the electron-transport chain, where coupled redox reactions mediate proton translocation across the inner membrane to establish an electrical potential and pH gradient (proton-motive force) that drives ATP synthesis by the mitochondrial ATP synthase. Ion-selective or nonselective mitochondrial ion channels dissipate energy and alter the ionic balance and volume of the mitochondrial matrix, which is partly compensated by antiporters coupled to H^+ movement. See text for further details. ANT, adenine nucleotide translocase; G-6-P, glucose-6-phosphate; IMAC, inner-membrane anion channel; MCU, mitochondrial Ca^{2+} uniporter; $mitoK_{Ca}$, mitochondrial Ca^{2+}-activated K^+ channel; $mitoK_{ATP}$, mitochondrial ATP-sensitive K^+ channel; PIC, phosphate carrier; PTP, permeability transition pore; PYR, pyruvate; KHE, K^+/H^+ exchanger; NHE, Na^+/H^+ exchanger; NCE, Na^+/Ca^{2+} exchanger; IDH, isocitrate dehydrogenase; KDH, α-ketoglutarate dehydrogenase; MDH, malate dehydrogenase; PDH, pyruvate dehydrogenase; SDH, succinate dehydrogenase.

The main consumer of ATP is CONTRACTION





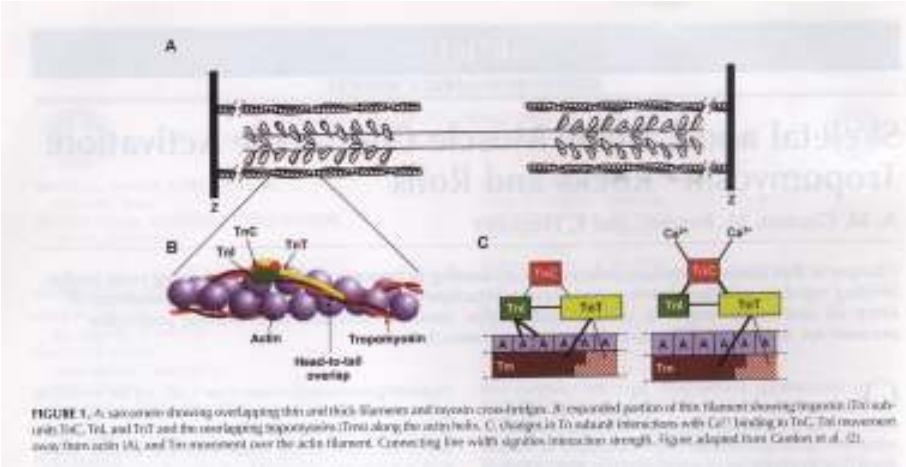


FIGURE 1. A, sarcomere showing overlapping thin and thick filaments and myosin cross-bridges. B, expanded portion of thin filament showing troponin (Tn) subunits TnC, TnI, and TnT and the overlapping tropomyosins (Tms) along the actin helix. C, changes in Tn subunit interactions with Ca^{2+} binding to TnC. TnI movement away from actin (A), and Tm movement over the actin filament. Connecting line width signifies interaction strength. Figure adapted from Gordon et al. (2).

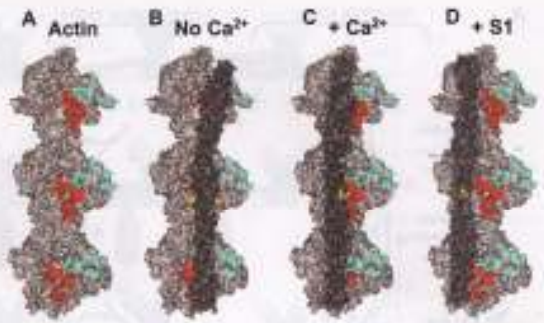


FIGURE 2. Tm movement over the surface of the actin filament at various degrees of activation. In each panel, three sequential actin monomers of one strand of the thin filament are shown (actin structures from Lorenz and Holmes (46). Actin residues are light gray, except for residues 1–4, 24–25, 95–100, shown in light blue) making weak electrostatic interactions with myosin and residues 144–148, 340–346, 332–334, shown in red forming stronger attachments with myosin. In B–D, a surface rendering of a cardiac Tm segment (residues 61–152 of each Tm strand) in dark gray (coordinates from Whitby and Phillips (14); positioned according to Lehman and coworkers (15)) is shown. Arg^{90} of Tm in each strand is shown in yellow to illustrate the putative rolling motion of Tm.

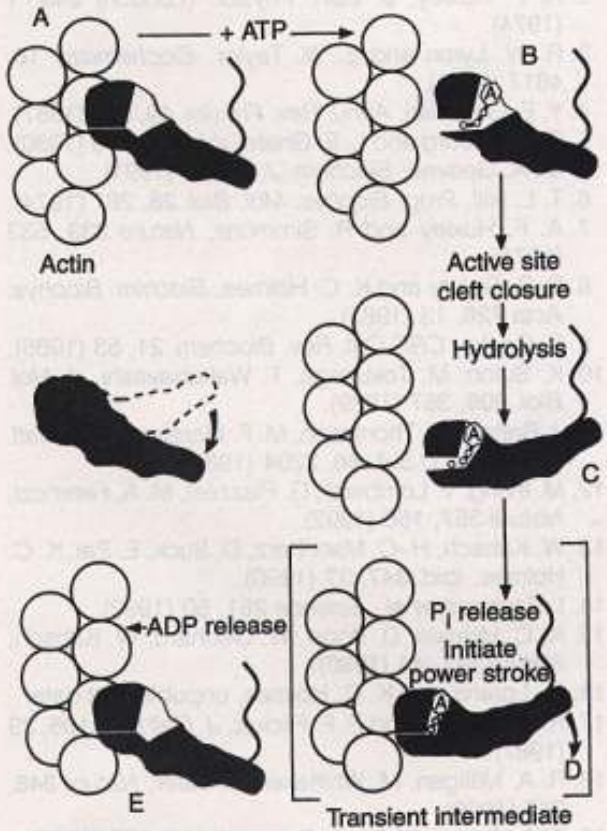
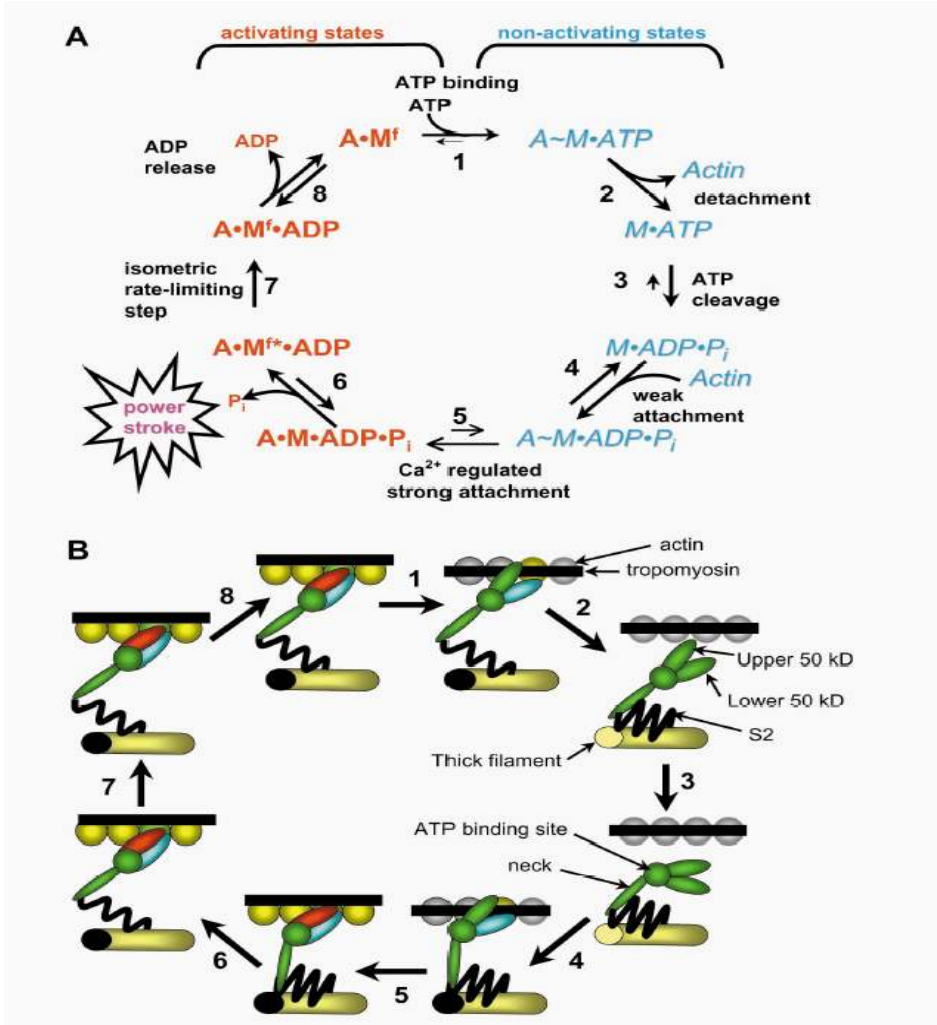
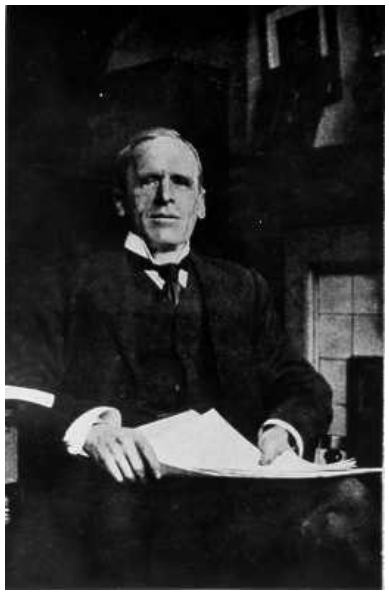


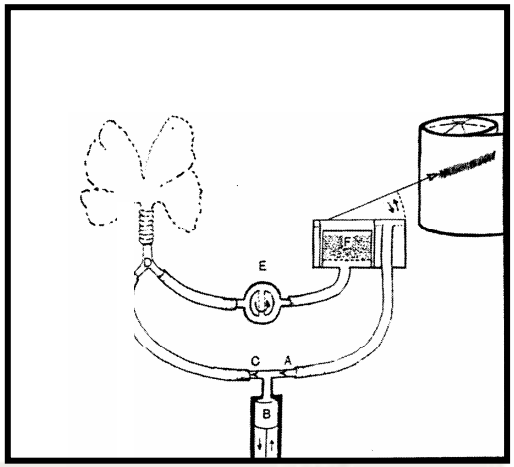
Fig. 5. The contractile cycle incorporating structural features of the myosin head and their proposed involvement in the cycle. Actin is represented as a sphere. In the near axial third of the myosin head, the narrow cleft that splits the 50-kD segment of the myosin heavy chain sequence into two domains is for simplicity represented as a horizontal gap perpendicular to the filament axis. In the model, this cleft lies at an angle of ~30° to the filament axis and the opening and closing of the cleft would not be evident from this view. The representation of the nucleotide-bound state and its associated conformational change relative to the x-ray structure of myosin is conceptual in nature.



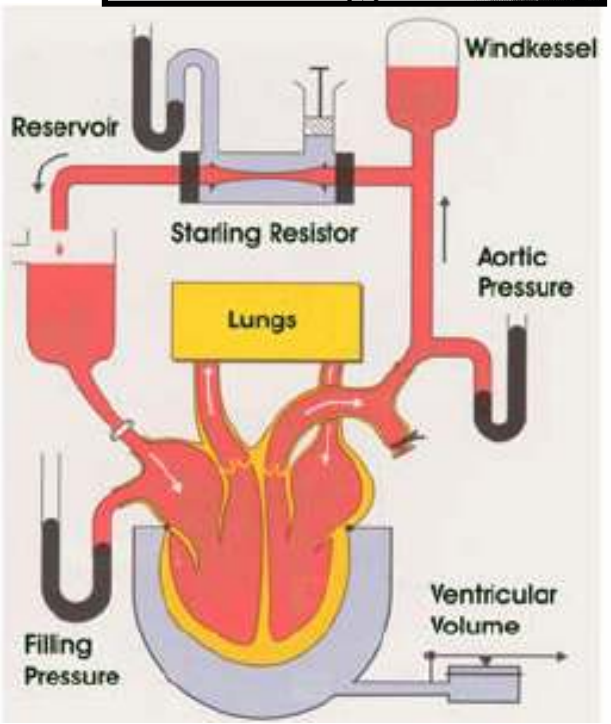
THE ORIGIN OF THE PROBLEM OF RESPIRATION REGULATION



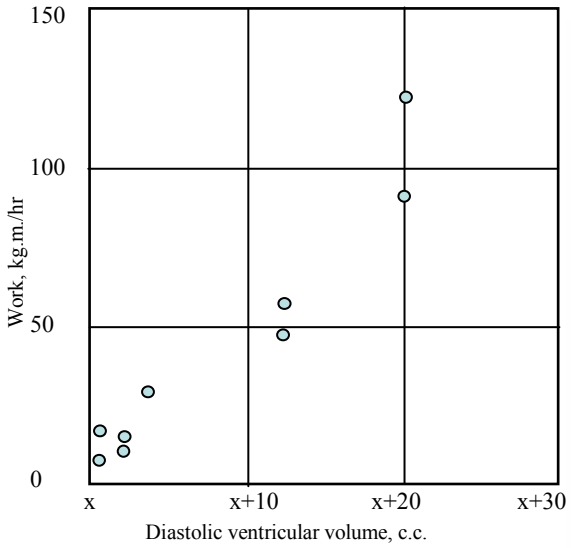
Ernest Starling
1866-1927



Ernest Starling's Set-up:



« ***Rate of oxygen consumption is taken as a measure of the total energy set free in the heart during its activity*** "***(Starling & Visscher, The regulation of energy output of the heart, J.Physiol 62, 243,1926)***



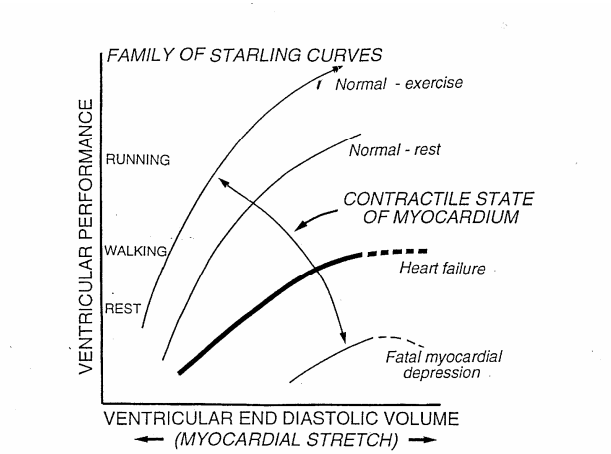
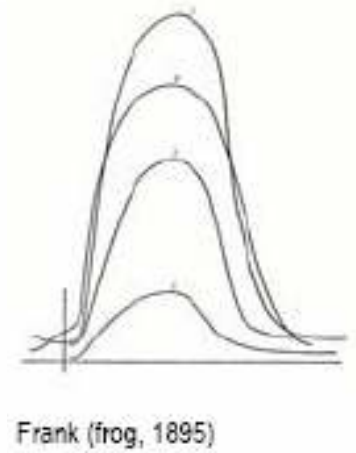
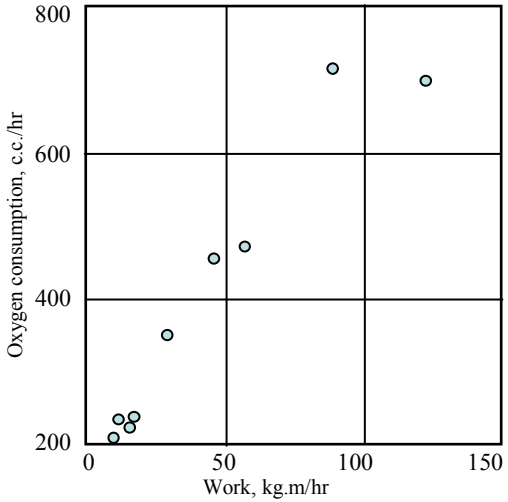


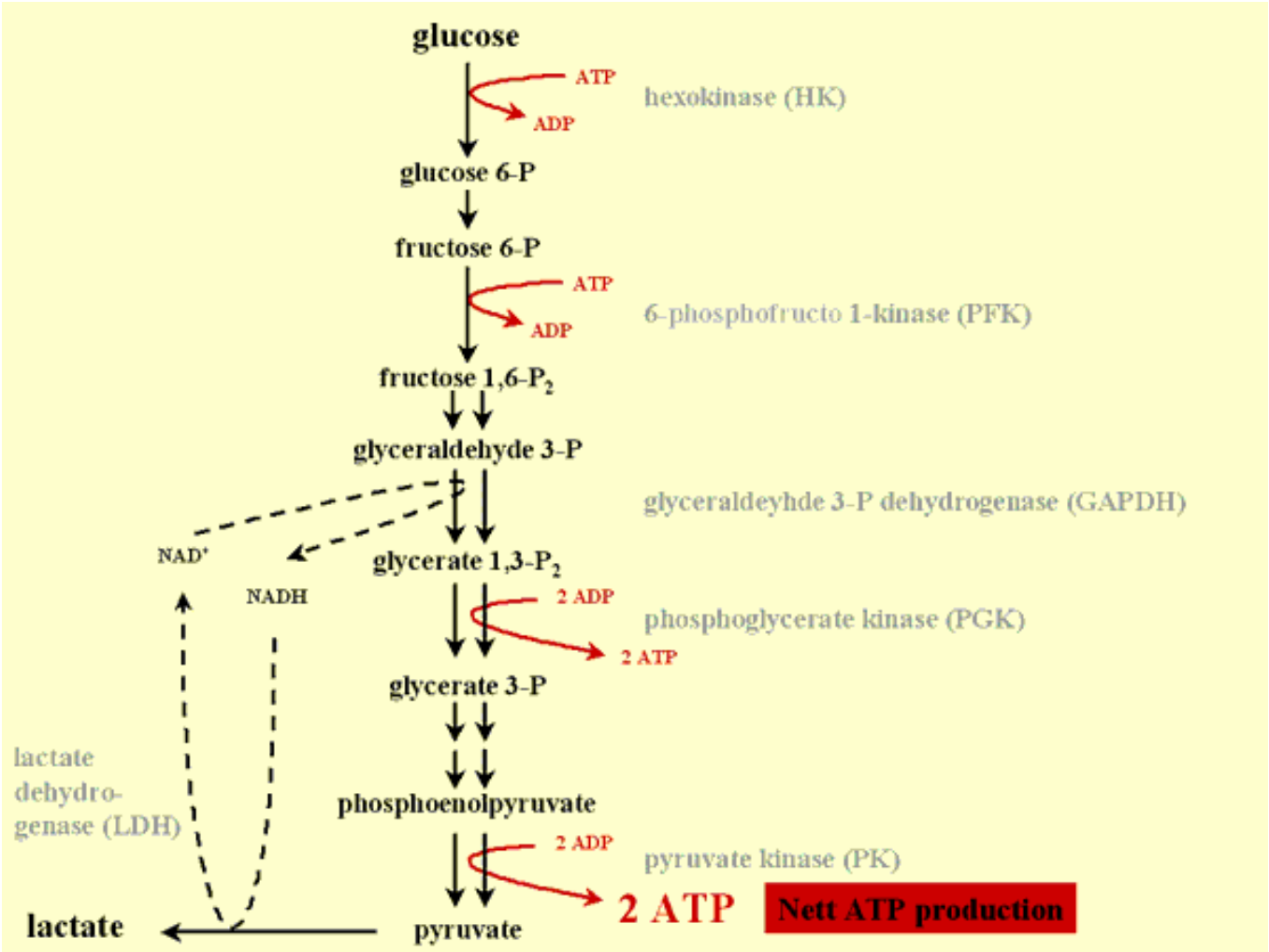
FIG. 12-5. Family of Starling curves. According to Starling's law, increased stretch of myocardial fibers, which increases the ventricular end-diastolic volume, results in greater ventricular performance. Modified with permission from Braunwald et al. (1968). The line for heart failure is based on that shown in Figs. 1 and 2 of Holubarsch et al. (1996).





"Any increase in the work demanded of the heart is met by corresponding increase in the oxygen consumption and in the amount of chemical changes taking place" (Starling & Visscher,J.Physiol 62, 243, 1926)

1900 - 1930


glucose
ATP
ADP
hexokinase (HK)
glucose 6-P
fructose 6-P
ATP
ADP
6-phosphofructo 1-kinase (PFK)
fructose 1,6-P2
glyceraldehyde 3-P
glyceraldeyhde 3-P dehydrogenase (GAPDH)
NAD+
NADH
glycerate 1,3-P2
2 ADP
2 ATP
phosphoglycerate kinase (PGK)
glycerate 3-P
lactate dehydro-genase (LDH)
phosphoenolpyruvate
2 ADP
pyruvate kinase (PK)
lactate
pyruvate
2 ATP
Nett ATP production

Otto Meyerhof
The Nobel Prize in Physiology or Medicine 1922
Nobel Lecture

Archibald V. Hill

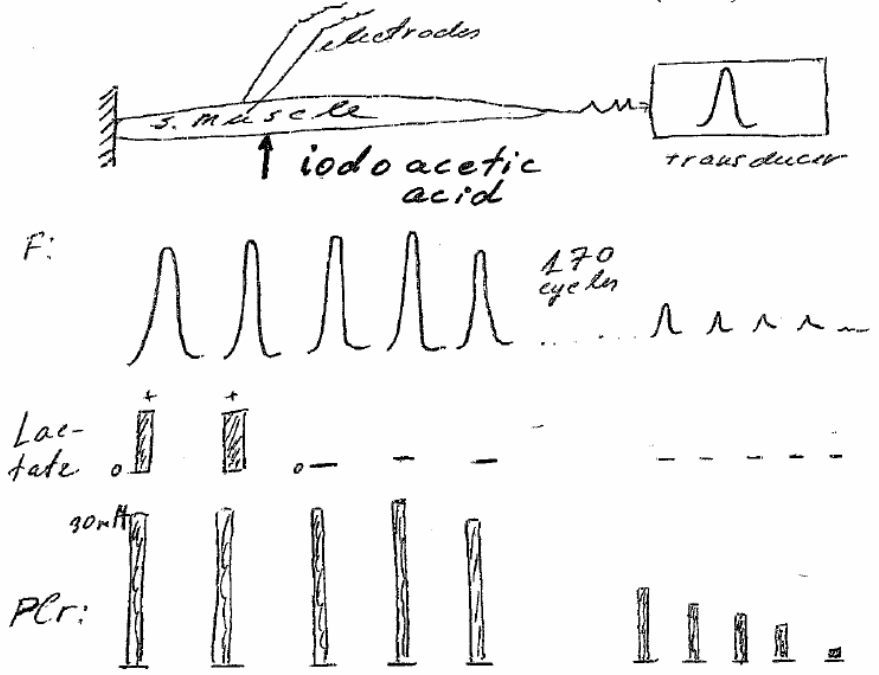
The Mechanism of Muscular Contraction

Nobel Lecture, December 12, 1923
Energy Conversions in Muscle

We can establish that the lactic acid is directly associated with muscle contraction by an exact comparison of the work performed under anaerobic conditions with the formation of lactic acid. As the best expression of the

1930, COPENHAGEN, DENMARK

LUNDSGAARD'S
REVOLUTION IN PHYSIOLOGY (HILL)



CONCLUSION : PCr IS THE IMMEDIATE SOURCE OF CONTRACTION – **FIRST PHOSPHOCREATINE ERA**

HILL AND MEYERHOFF ASK TO TAKE BACK THEIR NOBLE PRICES

"ALACTACID" CONTRACTION

THE REVOLUTION IN MUSCLE PHYSIOLOGY

A.V. Hill

Physiol. Review 12, 56 – 67, 1932

"WE HAVE ALL BEEN RIGHT SOMETIMES

AND

WE HAVE ALL BEEN WRONG OFTEN"

1934 – Karl Lohmann shows that the ATP and PCr are related to each other by thecreatine kinase reaction

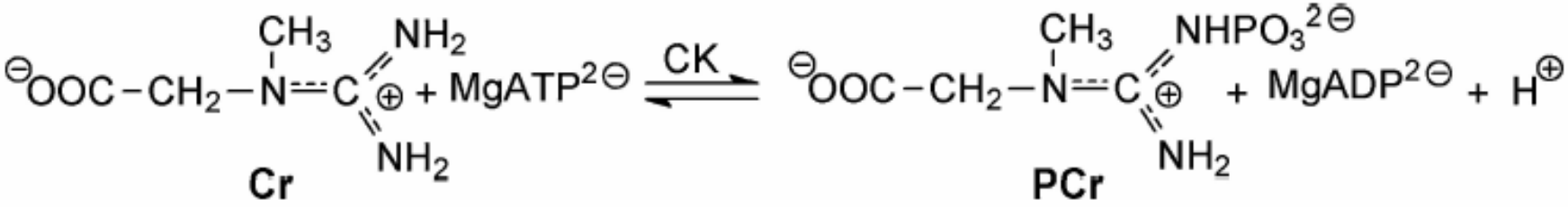
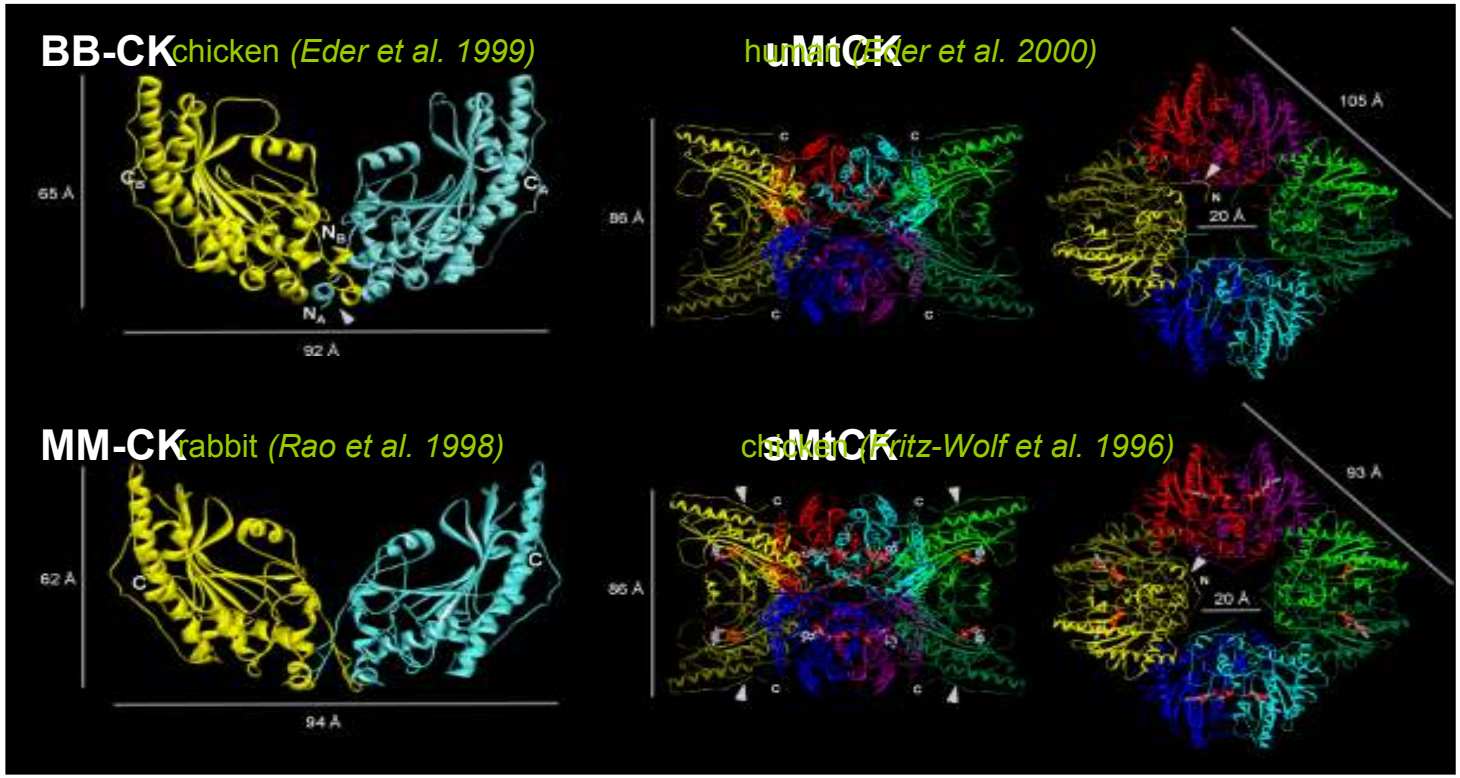
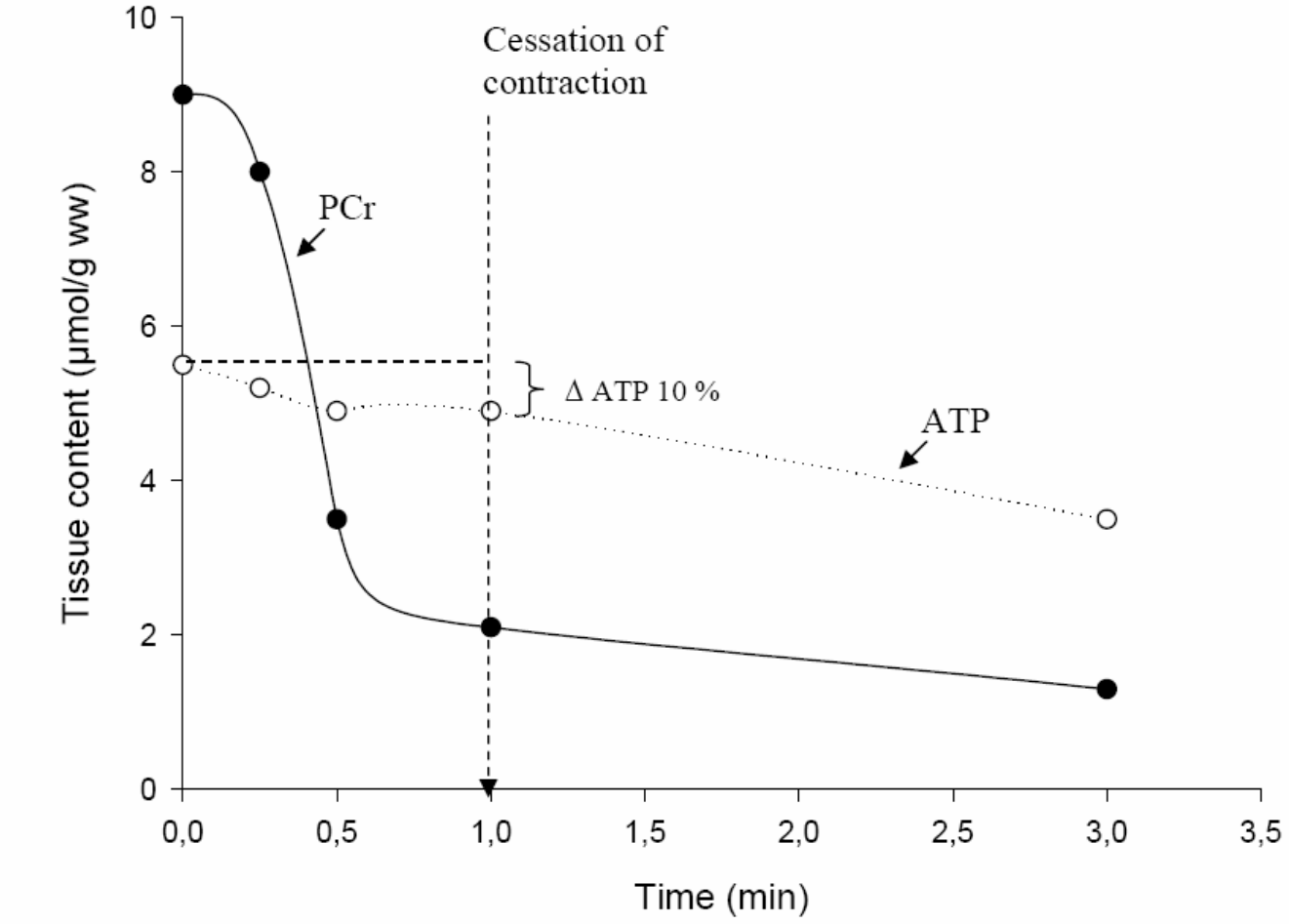


FIGURE 1 Reaction catalyzed by creatine kinase.

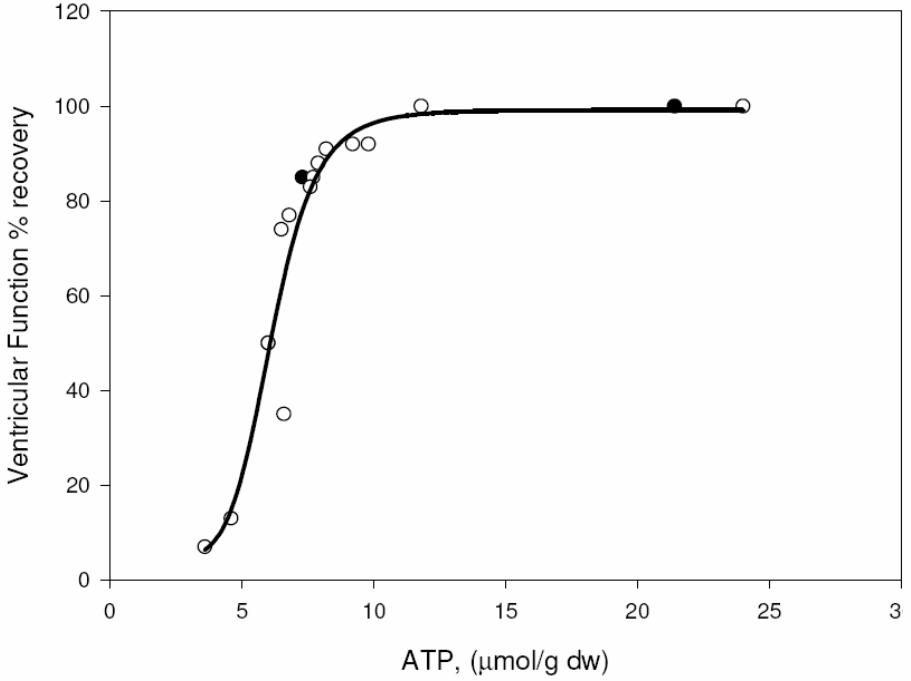


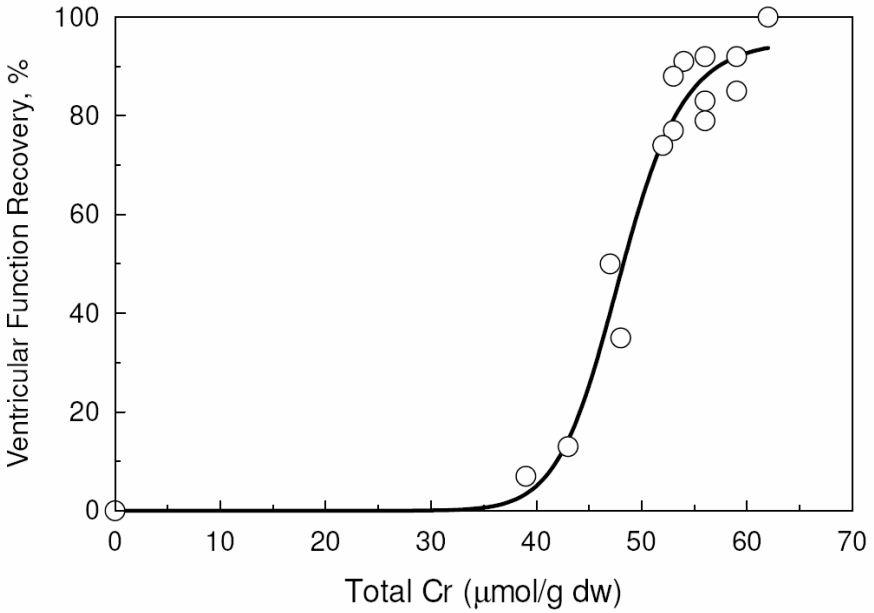
Sigmundur Gudbjarnason, Iceland, Reykjavik, 1971
James Neely, Hershi, USA, 1973

COMPARTMENTATION OF ADENINE NUCLEOTIDES IN HEART CELLS

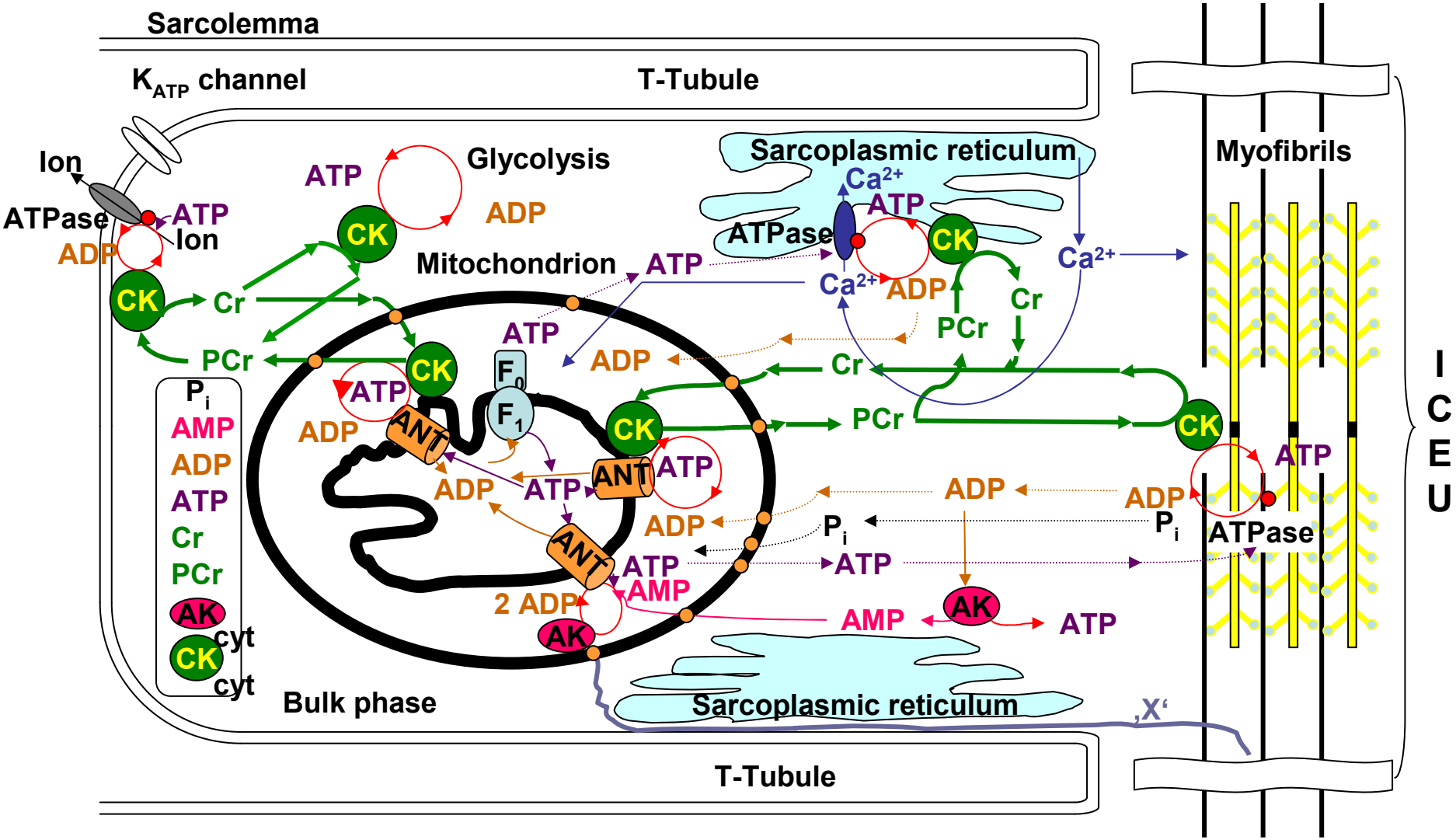


Neely JR, Grotyohann LW. Role of glycolytic products in damage to ischemic myocardium. **Dissociation of adenosine triphosphate levels and recovery of function of reperfused ischemic hearts**. Circ Res. 1984 Dec;55(6):816-24

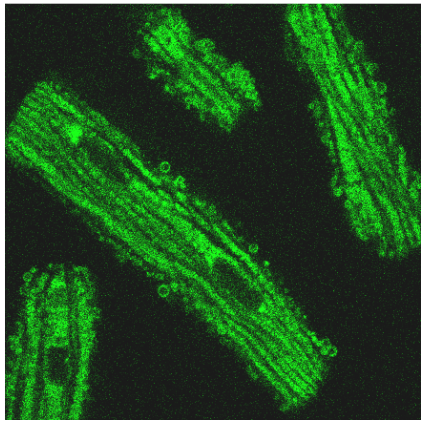


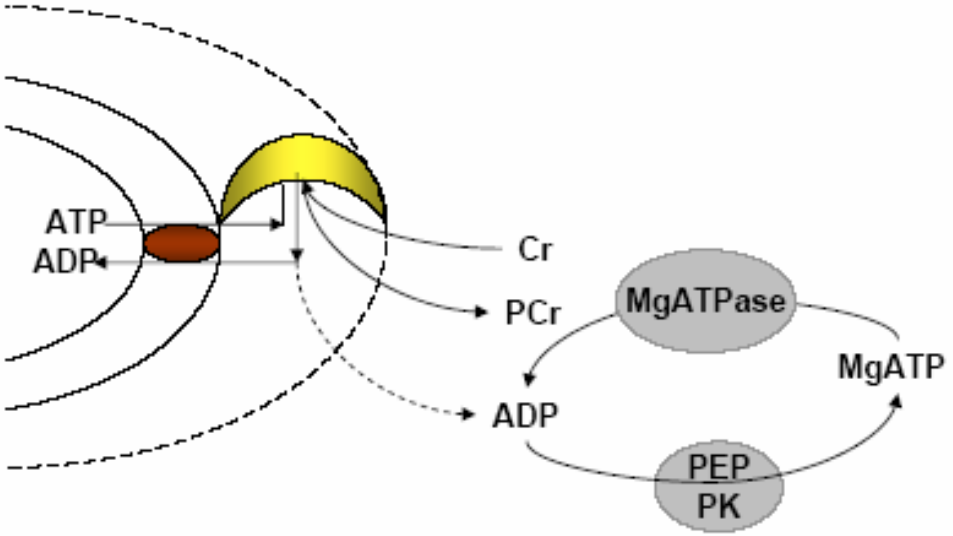


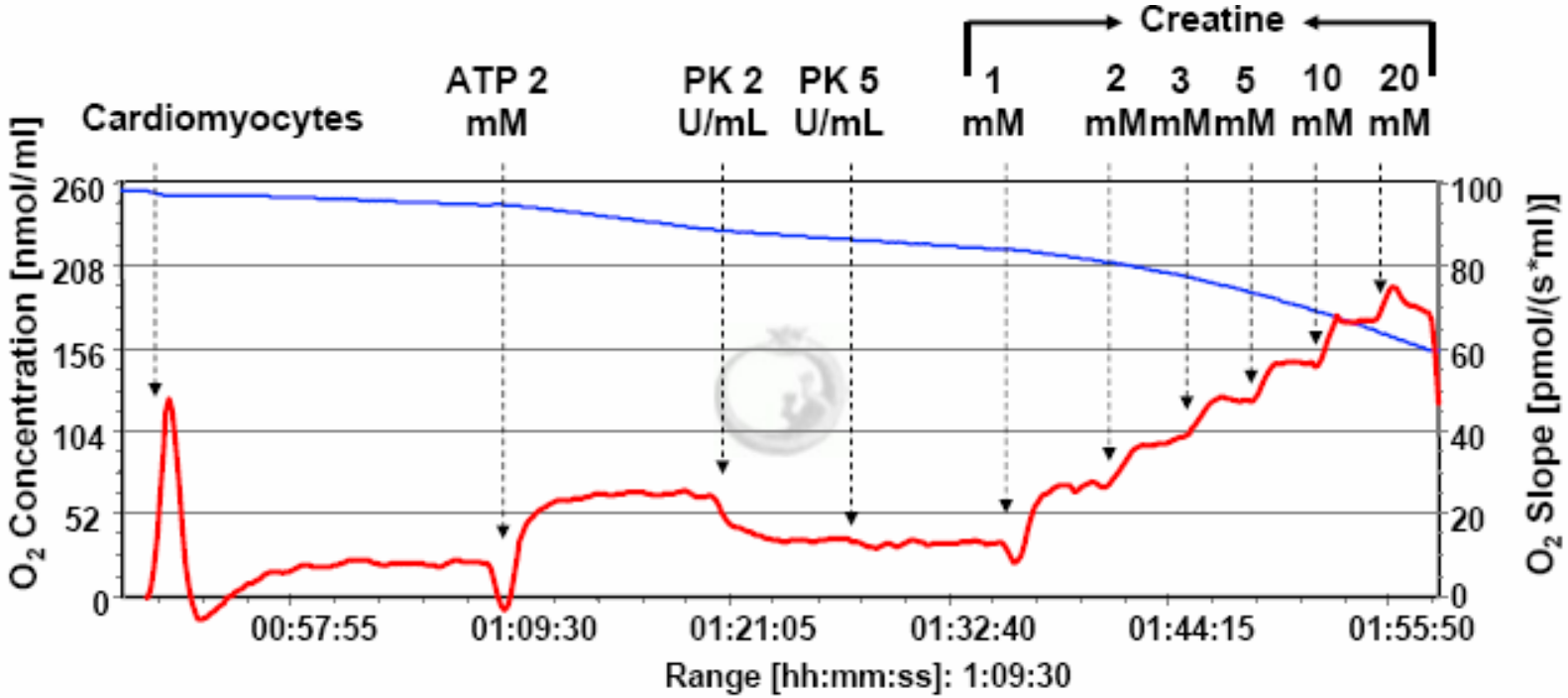
Intracellular Energy Units (ICEU)

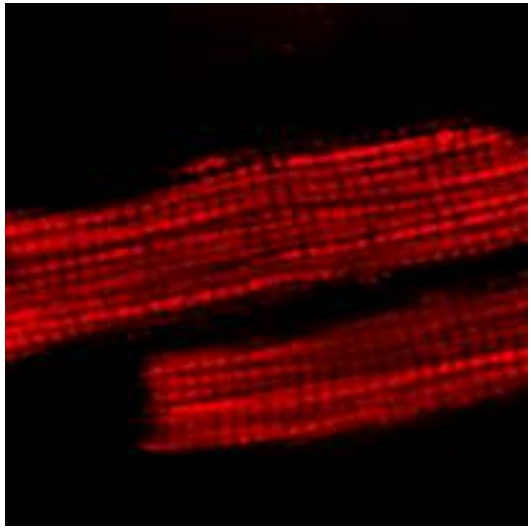


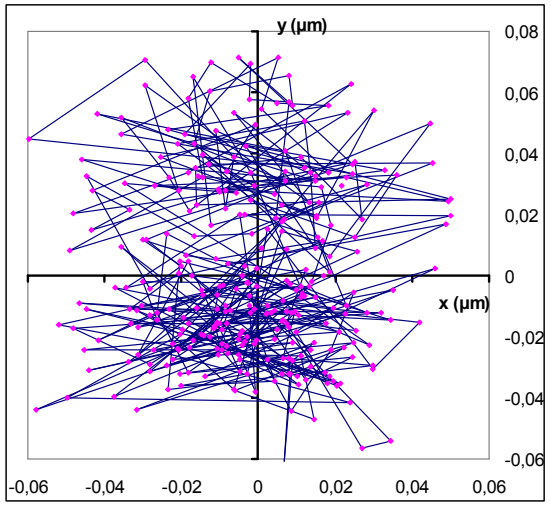
Saks et al. 2007 in « Molecular System Bioenergetics», Wiley-VCH, Weinheim

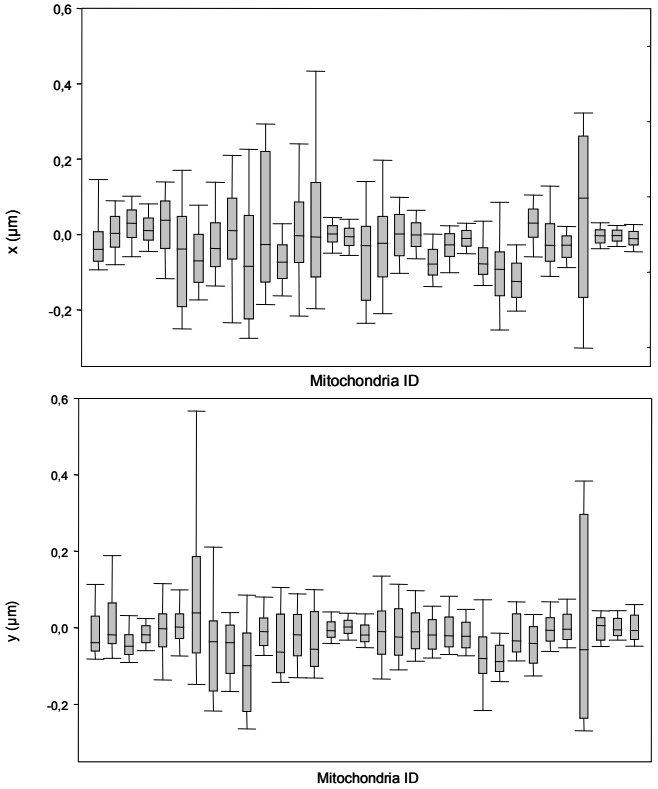


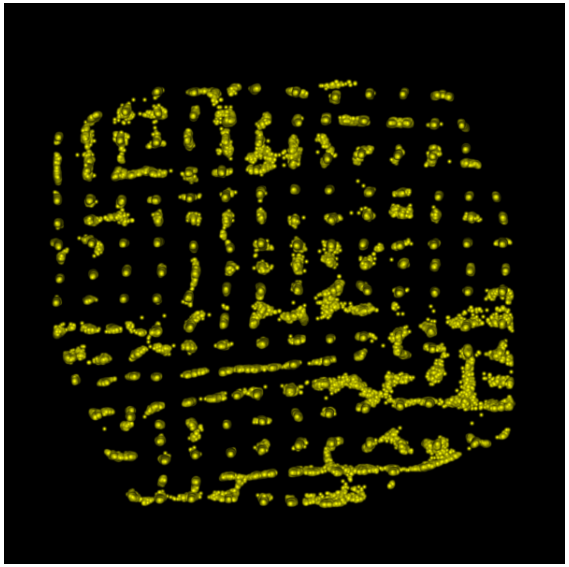

ATP
ADP
Cr
PCr
MgATPase
MgATP
ADP
PEP
PK

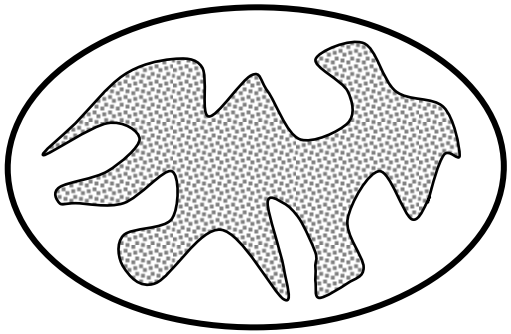

Creatine
Cardiomyocytes
ATP 2 mM
PK 2 U/mL
PK 5 U/mL
1 mM
2 mM
3 mM
5 mM
10 mM
20 mM
O2 Concentration [nmol/ml]
260
208
156
104
52
0
100
80
60
40
20
0
O2 Slope [pmol/(s*ml)]
00:57:55
01:09:30
01:21:05
01:32:40
01:44:15
01:55:50
Range [hh:mm:ss]: 1:09:30

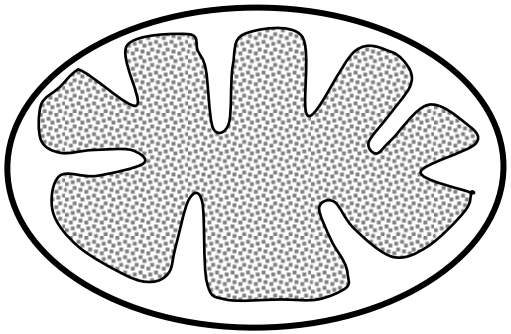




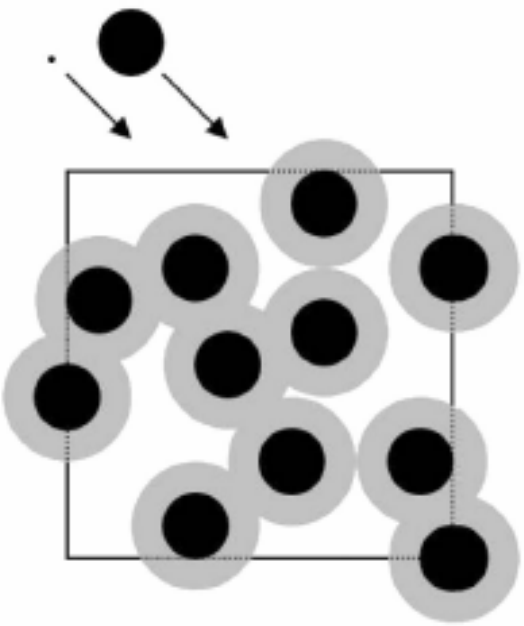








N.Beraud&Y.Usson, Grenoble



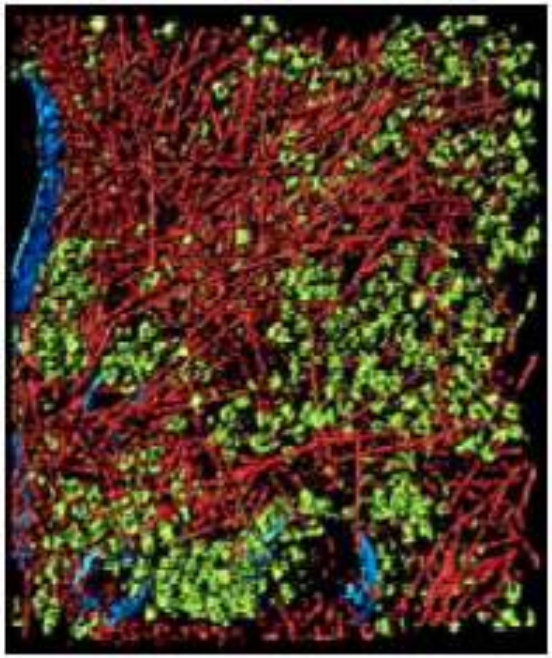
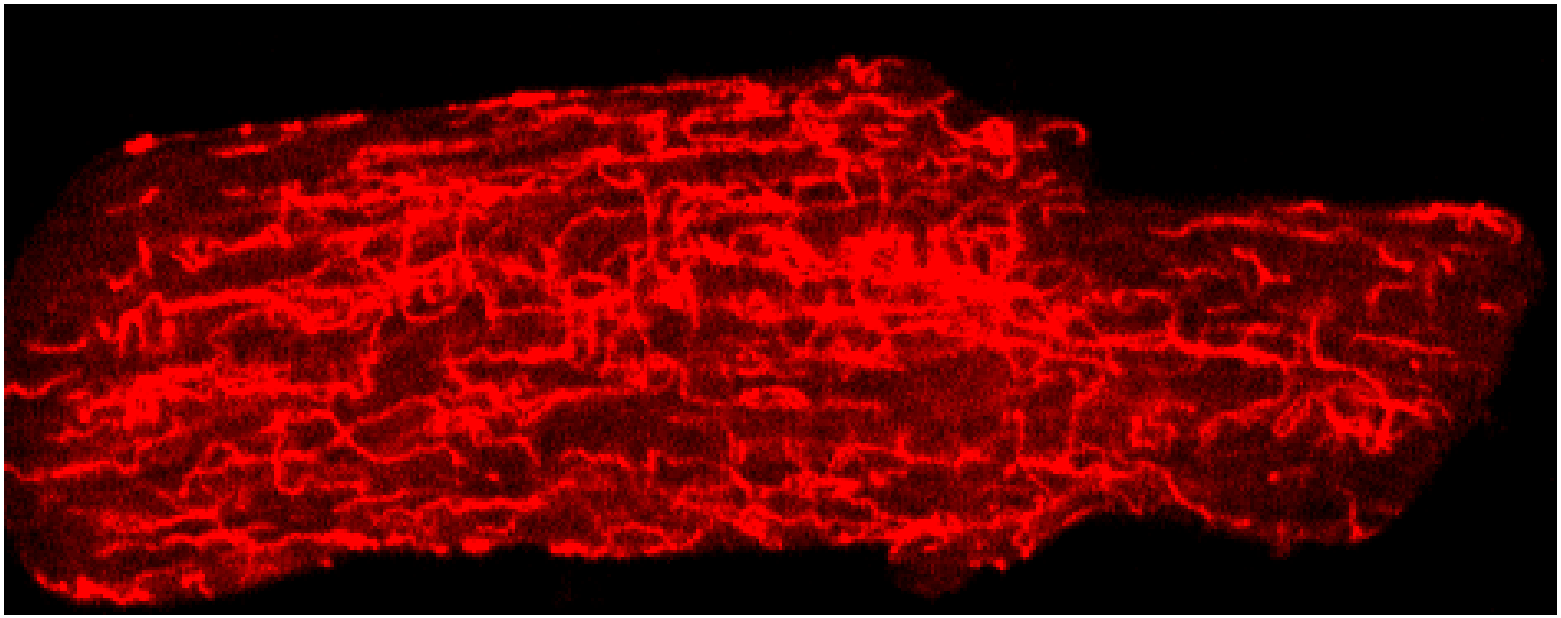


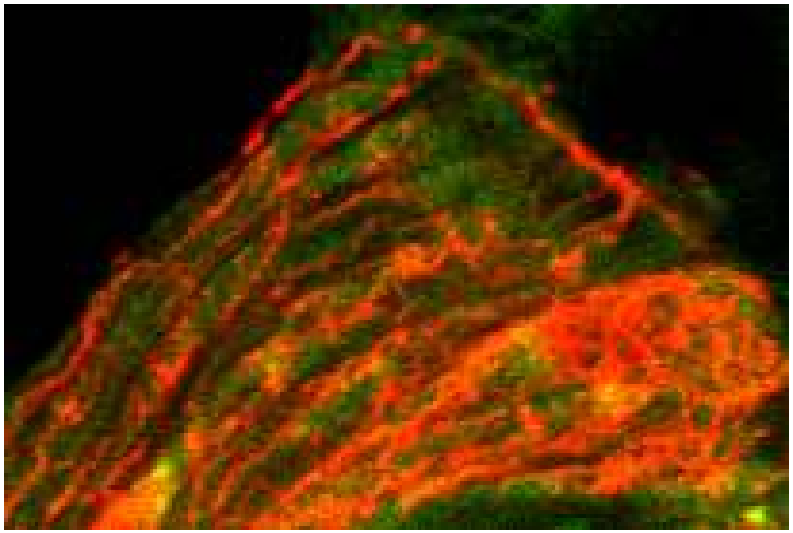
Fig. 1. Computational reconstruction of the cytoplasm of a *Dictyostelium discoideum* cell imaged using cryoelectron tomography. In this visualization the actin filaments (red), membranes (blue), and cytoplasmic complexes, mostly ribosomes (green) can be appreciated. The 2D projection corresponds to a volume of 815 nm × 870 nm × 97 nm. Reprinted with permission from Medalia et al. (2002), Science 298, 1209–1213. Copyright 2002 AAAS.

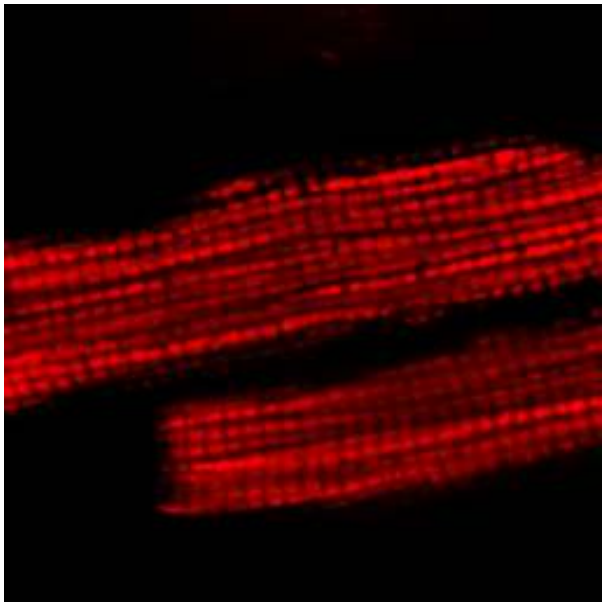
MACROMOLECULAR

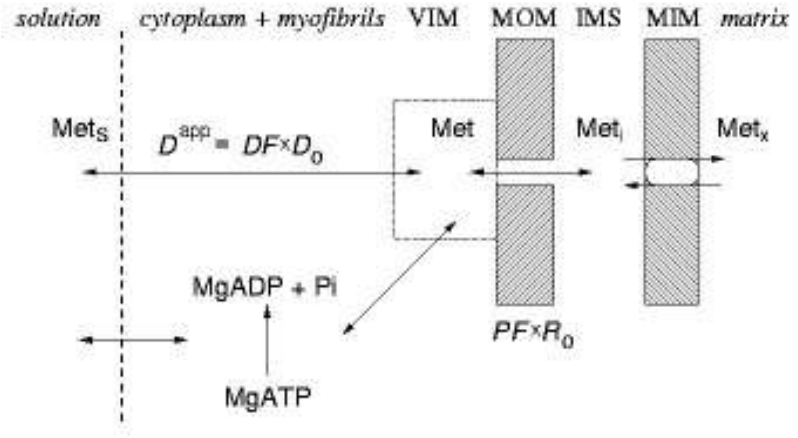
CROWDING

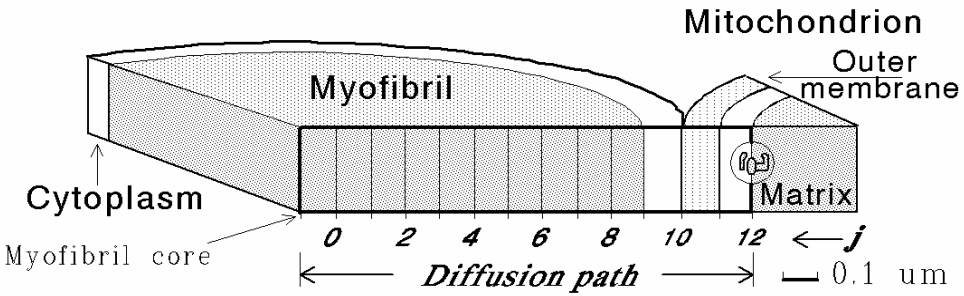
MICROTUBULAR NETWORK AND MITOCHONDRIA IN CARDIOMYOCYTES

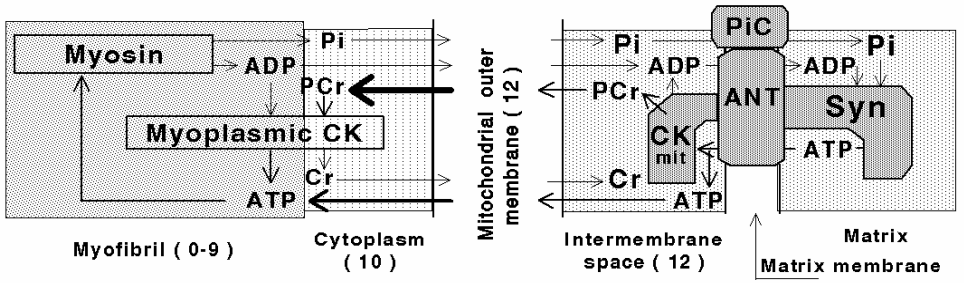


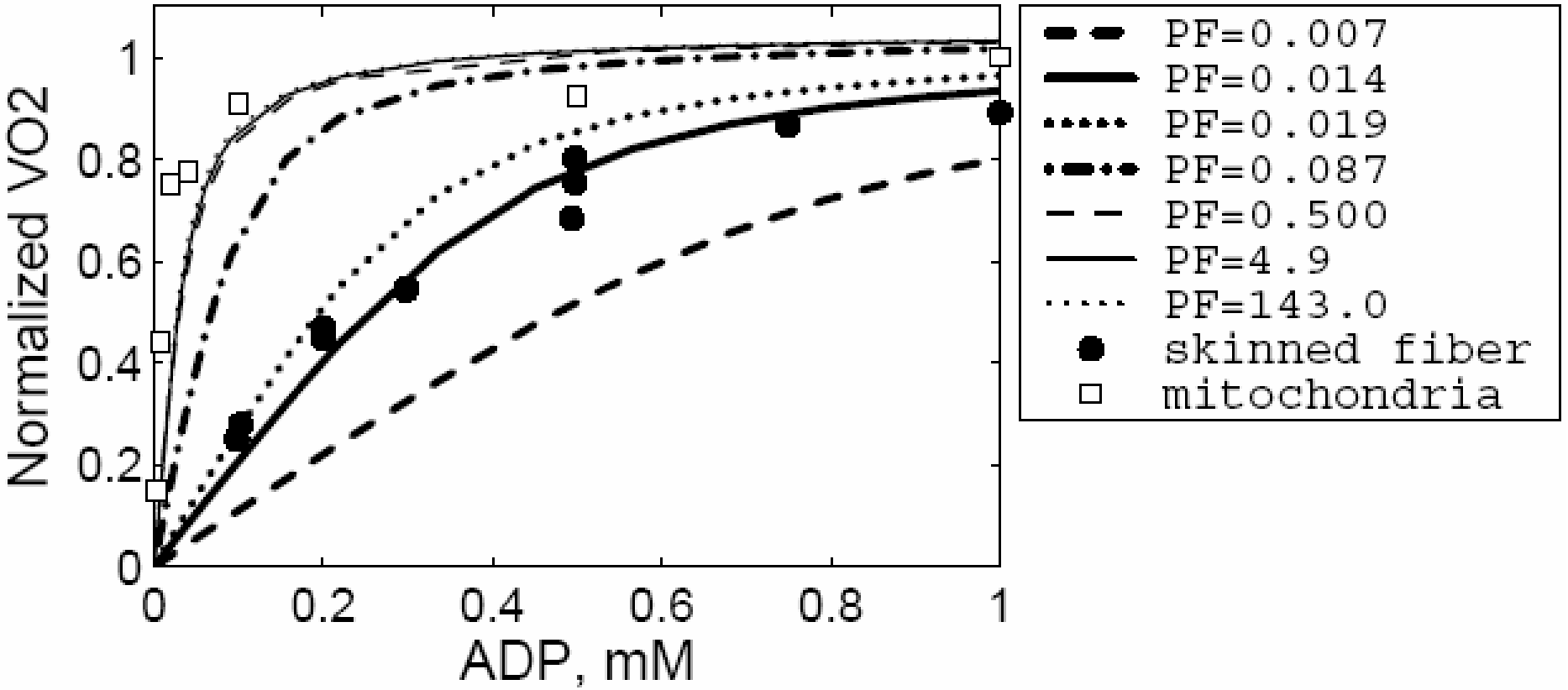





solution
cytoplasm + myofibrils
VIM
MOM
IMS
MIM
matrix
Met_S
D^app = DF×D_0
Met
Met_i
Met_x
MgADP + Pi
MgATP
PF×R_0


Mitochondrion
Outer membrane
Myofibril
Cytoplasm
Matrix
Myofibril core
0 2 4 6 8 10 12 j
Diffusion path
0.1 um

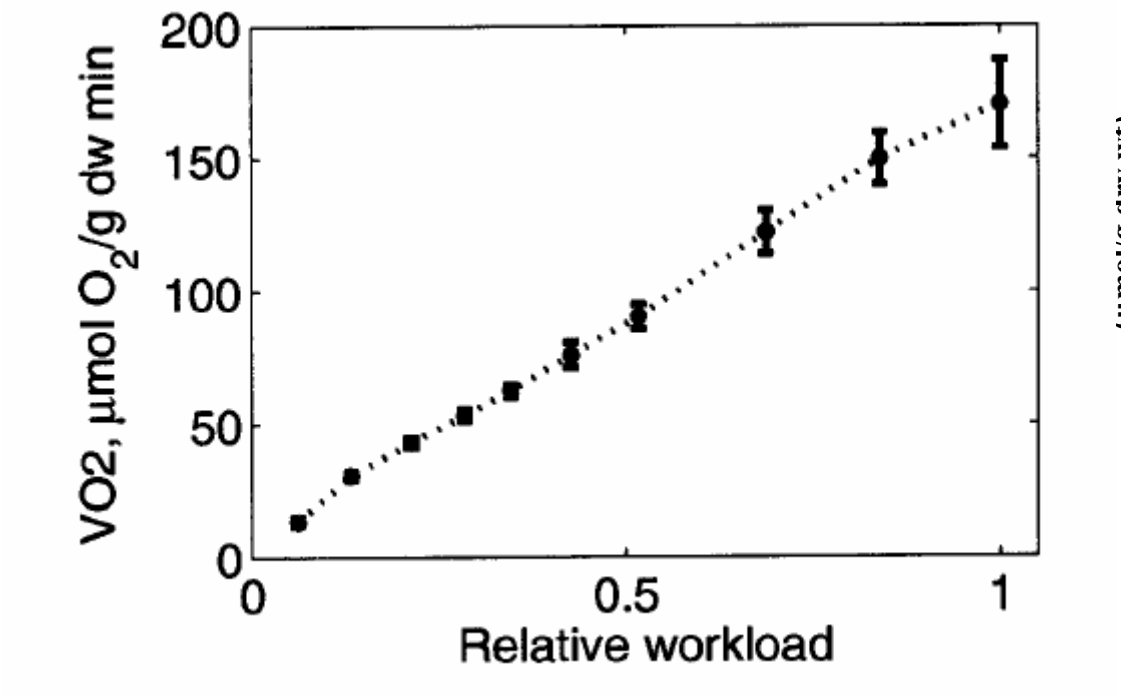

Myosin
ADP
Pi
PCr
Myoplasmic CK
Cr
ATP
Myofibril (0-9)
Cytoplasm (10)
Mitochondrial outer membrane (12)
PiC
Pi
ADP
PCr
ANT
Syn
CK mit
ATP
Cr
Intermembrane space (12)
Matrix
Matrix membrane


Normalized VO2
ADP, mM
0
0.2
0.4
0.6
0.8
1
PF=0.007
PF=0.014
PF=0.019
PF=0.087
PF=0.500
PF=4.9
PF=143.0
skinned fiber
mitochondria

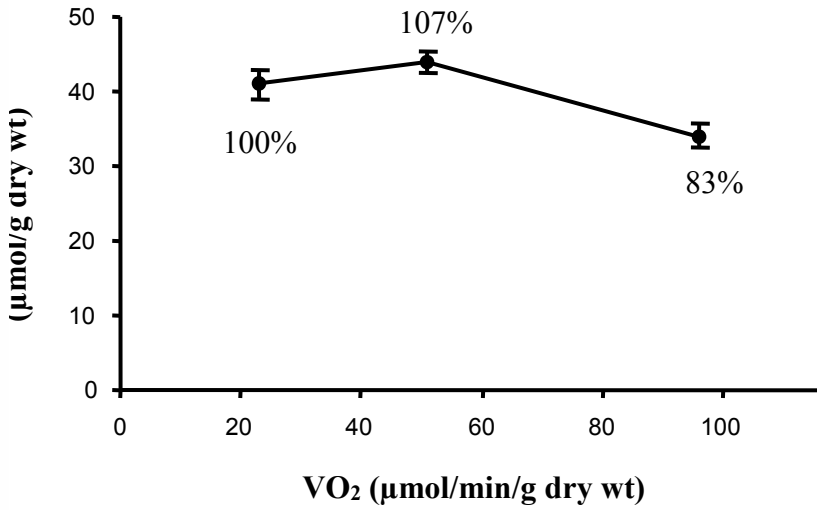
FRANK-STARLING LAW AND RESPIRATION

Suga et al.:

$$VO_2 = A \times PVA + B$$



Williamson et al. Circ.Res. 38, I39-I51,1976



Neely et al. Biochem.J. 128,147-159, 1972

WHICH MECHANISM OF REGULATION OF RESPIRATION *in vivo* EXPLAINS THE METABOLIC ASPECTS OF FRANK-STARLING LAW?

Hypotheses proposed:

1. Cytoplasmic ADP in equilibrium CK reaction (Meyer et al. 1984 and many others)?

2. Parallel regulation of contraction and respiration by calcium?

3. METABOLIC FEEDBACK REGULATION VIA PHOSPHOTRANSFER NETWORKS

LIMITATIONS OF THE EQUILIBRIUM CREATINE KINASE THEORY

MgADP + Phosphocreatine + H^+ ➢ MgATP + Creatine

$[ADP] = [ATP][CREATINE]/[PCR]K'eq$

$[ADP]_{cyt} = 50 – 100\ \mu M$

Since the apparent Km for ADP in isolated mitochondria ≅ 20 μM, under physiological conditions respiration should be always activated by 80%

THIS CONTRADICTS TO EXPERIMENTAL OBSERVATIONS,

INCLUDING THE METABOLIC STABILITY

CONCLUSION:

CALCIUM HYPOTHESIS

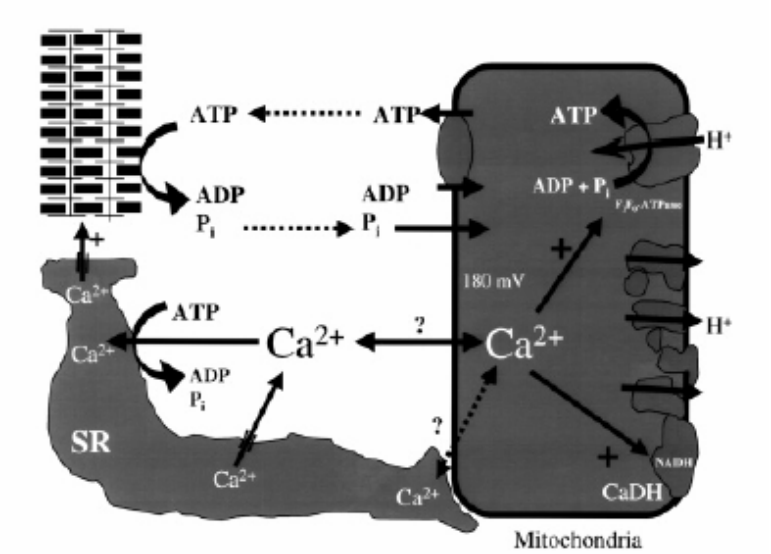
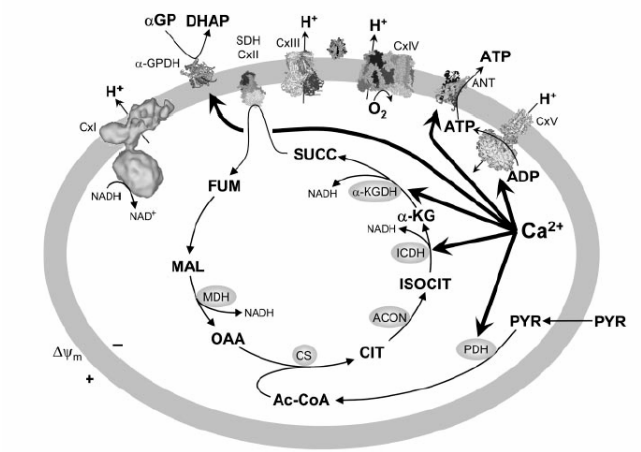
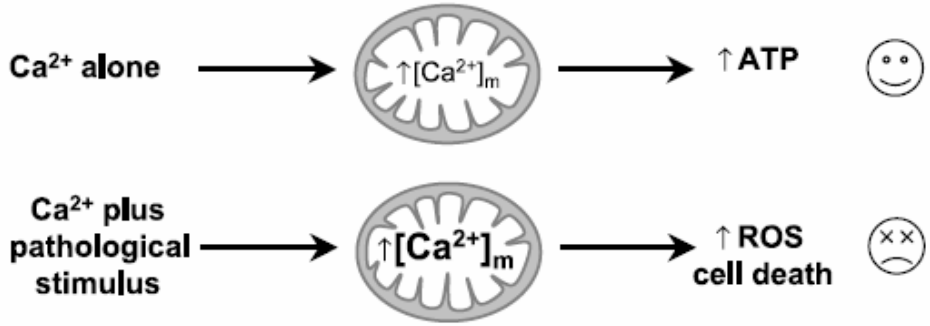


Figure 7 Summary of the Ca^{2+} parallel activation scheme. Both classical ADP and Pi feedback and Ca^{2+} parallel activation is proposed to play a significant role. The transport of Ca^{2+} from the cytosol or the SR to and from the mitochondria is poorly defined.

(Balaban, J.mol.Cell.Cardiol. 34,1259-1271,2002)





Am J Physiol Cell Physiol 287: C817–C833, 2004;
10.1152/ajpcell.00139.2004.

Calcium, ATP, and ROS: a mitochondrial love-hate triangle

Paul S. Brookes, Yisang Yoon, James L. Robotham, M. W. Anders, and Shey-Shing Sheu
Departments of Anesthesiology, Pharmacology, and Physiology and Mitochondrial Research Interest Group, University of Rochester Medical Center, Rochester New York 14642

THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 276, No. 4, Issue of January 26, pp. 2586–2599, 2001 Printed in U.S.A.

Calcium Activation of Heart Mitochondrial Oxidative Phosphorylation

RAPID KINETICS OF $n\dot{V}_{O_2}$, NADH, AND LIGHT SCATTERING*

Received for publication, April 6, 2000, and in revised form, October 5, 2000
Published, JBC Papers in Press, October 11, 2000, DOI 10.1074/jbc.M002923200

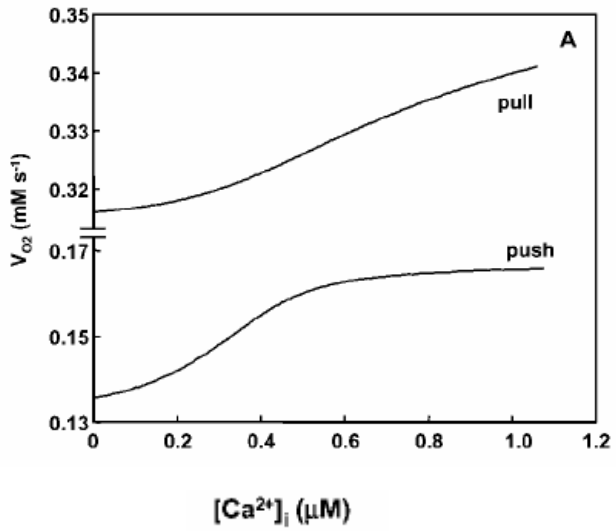
Paul R. Territo‡, Stephanie A. French, Mary C. Dunleavy, Frank J. Evans, and Robert S. Balaban

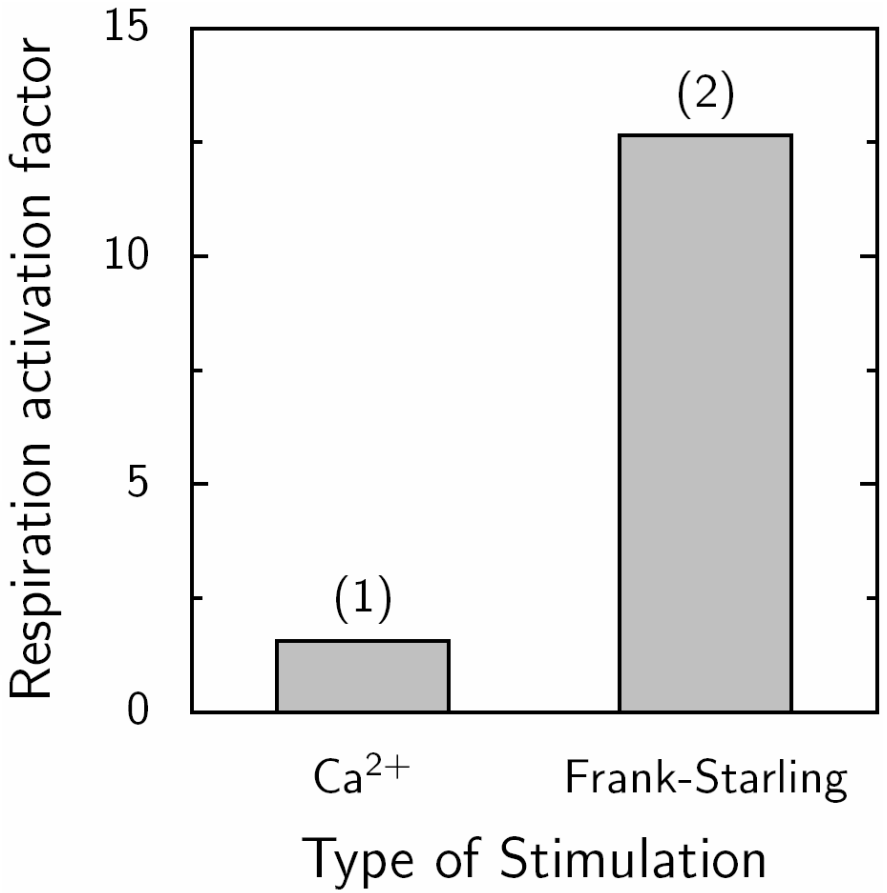
$[Ca^{2+}]$	O_2 consumption	r^2	n
nM	*nmol O_2, nmol Cyt_a^{-1}, min^{-1}*		
0	196.6 ± 25.5	0.773 ± 0.082	78
25	232.9 ± 11.7	0.922 ± 0.065	7
62	260.3 ± 29.7[a]	0.970 ± 0.018	8
172	288.3 ± 27.2[a]	0.988 ± 0.004	8
535	307.2 ± 16.0[a]	0.991 ± 0.002	43
1090	295.4 ± 16.8[a]	0.985 ± 0.006	6
1835	249.0 ± 28.4	0.990 ± 0.002	7

2734 Biophysical Journal Volume 84 April 2003 2734–2755

An Integrated Model of Cardiac Mitochondrial Energy Metabolism and Calcium Dynamics

Sonia Cortassa,* Miguel A. Aon,* Eduardo Marbán,*† Raimond L. Winslow,†* and Brian O'Rourke*





"WE HAVE ALL BEEN RIGHT SOMETIMES AND

WE HAVE ALL BEEN WRONG OFTEN"

"*WE HAVE ALL BEEN RIGHT SOMETIMES AND*

WE HAVE ALL BEEN WRONG OFTEN"

Am J Physiol Heart Circ Physiol 282: H1081–H1091, 2002;
10.1152/ajpheart.00498.2001.

Load dependence of ventricular performance explained by model of calcium-myofilament interactions

JUICHIRO SHIMIZU, KOJI TODAKA, AND DANIEL BURKHOFF
Division of Circulatory Physiology, College of Physicians and Surgeons, Columbia University, New York, New York 10032

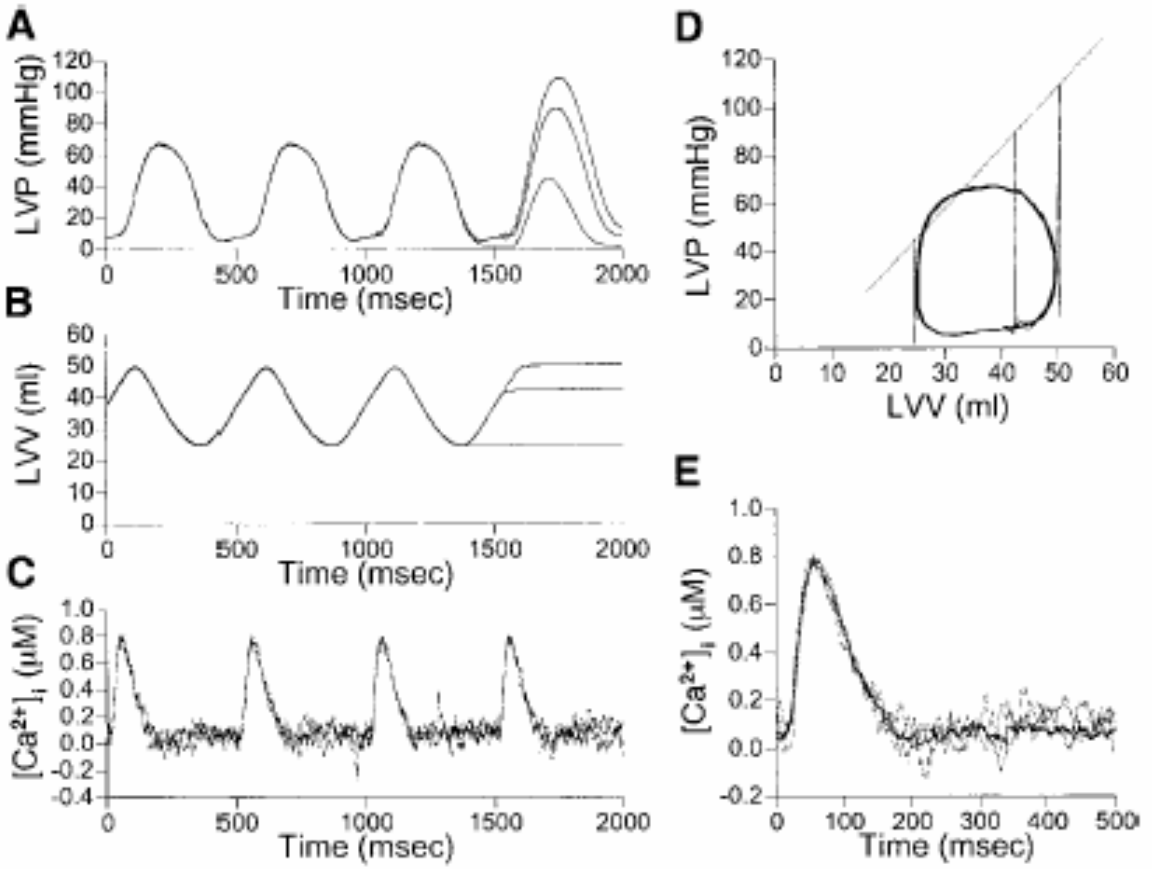
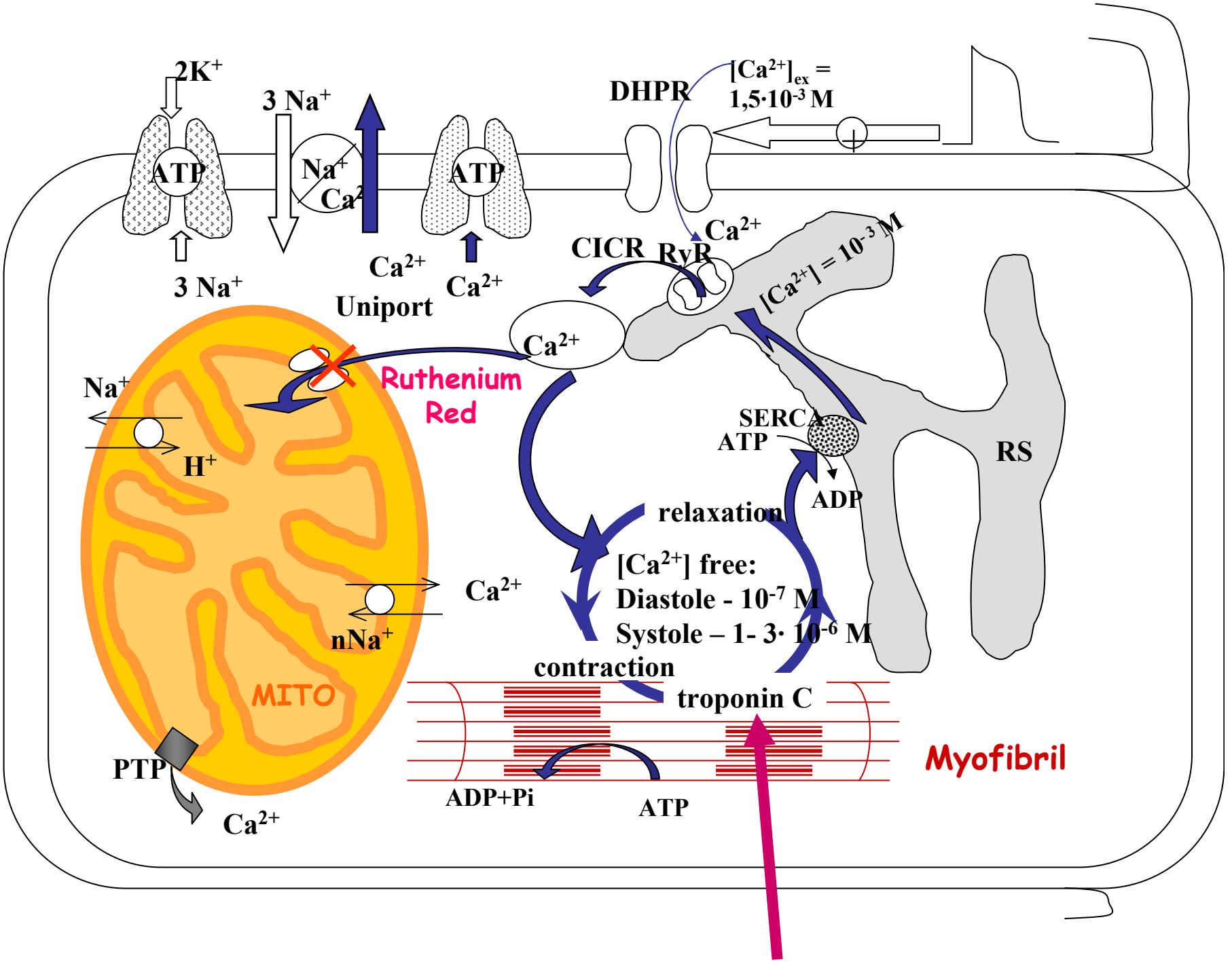


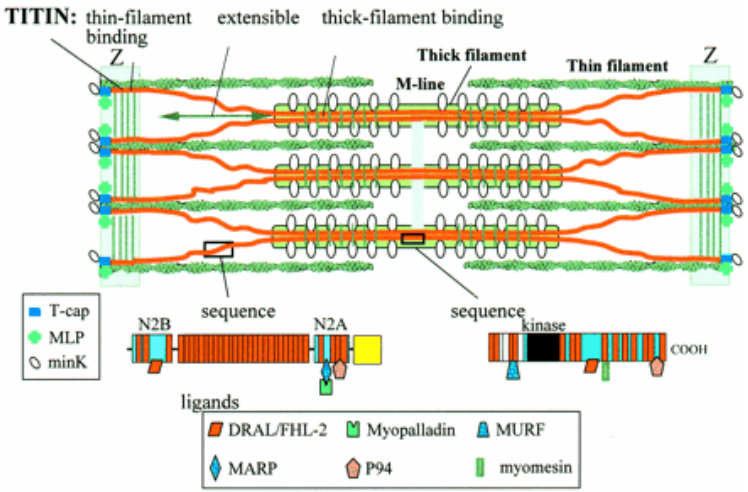
Fig. 2. Representative left ventricular (LV) pressure (LVP; *A*), volume (LVV; *B*), and calcium transients ($[Ca^{2+}]_i$; *C*) measured during steady-state ejecting contractions and on the first isovolumic beat of variously timed volume clamps. *D*: LVP-LVV loops corresponding to *A* and *B*. There is an approximately linear relationship between peak pressure and volume on the isovolumic contractions, and the pressure-volume loop of the ejecting beat "breaks through" this line. *E*: superimposed averaged $[Ca^{2+}]_i$ during steady-state ejecting contractions (dotted line) and during isovolumic contractions at the 3 different volumes; there is no detectable difference between these tracings.

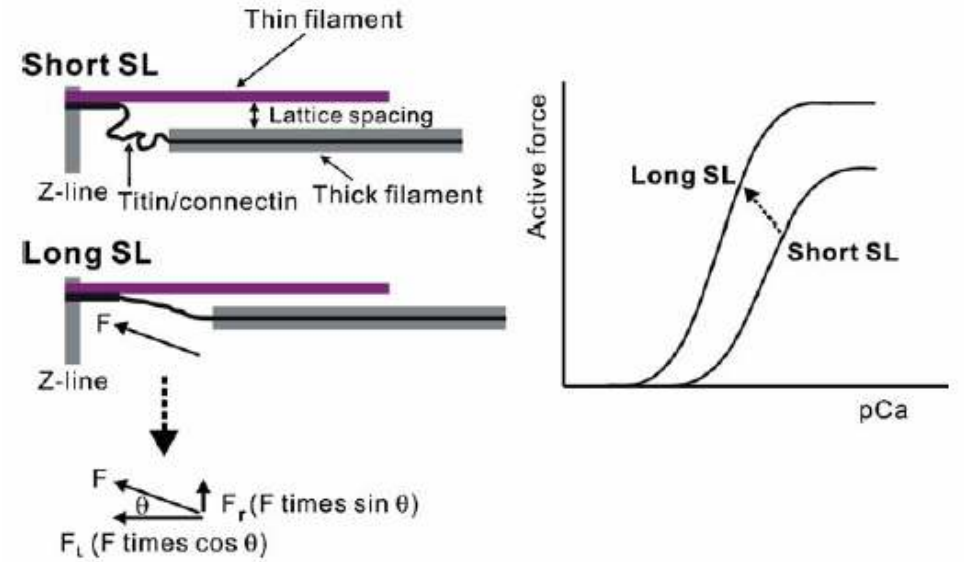

2K+
3 Na+
ATP
Na+
Ca2+
ATP
DHPR
[Ca2+]ex =
1,5·10-3 M
3 Na+
Ca2+
Uniport
Ca2+
CICR
RyR
Ca2+
[Ca2+] = 10-3 M
Ca2+
Na+
Ruthenium
Red
H+
SERCA
ATP
RS
ADP
relaxation
[Ca2+] free:
Diastole - 10-7 M
Systole – 1- 3· 10-6 M
Ca2+
nNa+
MITO
contraction
troponin C
Myofibril
PTP
Ca2+
ADP+Pi
ATP

Length-dependent activation of sarcomeres

Hibberd MG and Jewell BR. Calcium and length-dependent production in rat ventricular muscle. J. Physiol. 329:527,1982

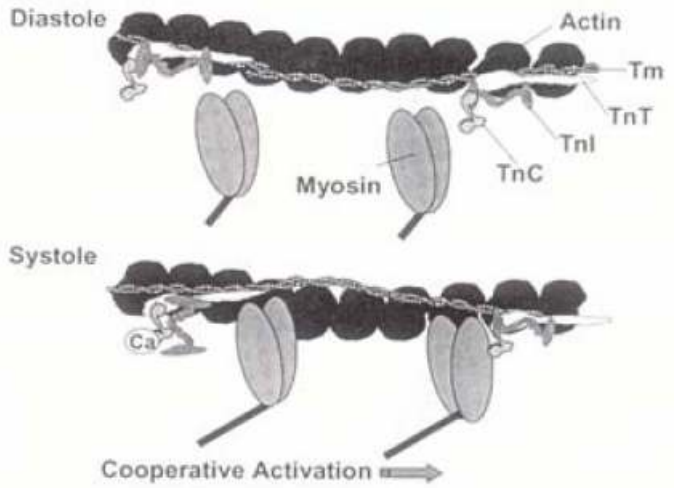
1. ***Changes in muofilament lattice spacing***
(*Granzier et al. Circulation Research 94:284, 2004)*





Crossbridge Cooperativity:

Formation of crossbridge → shift of tropomyosin → increases probability of downstream crossbridge formation

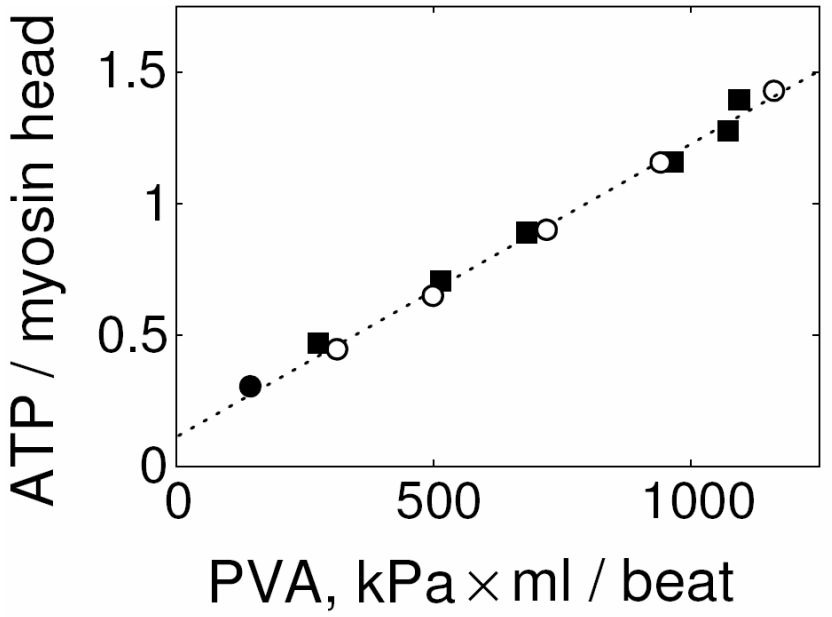


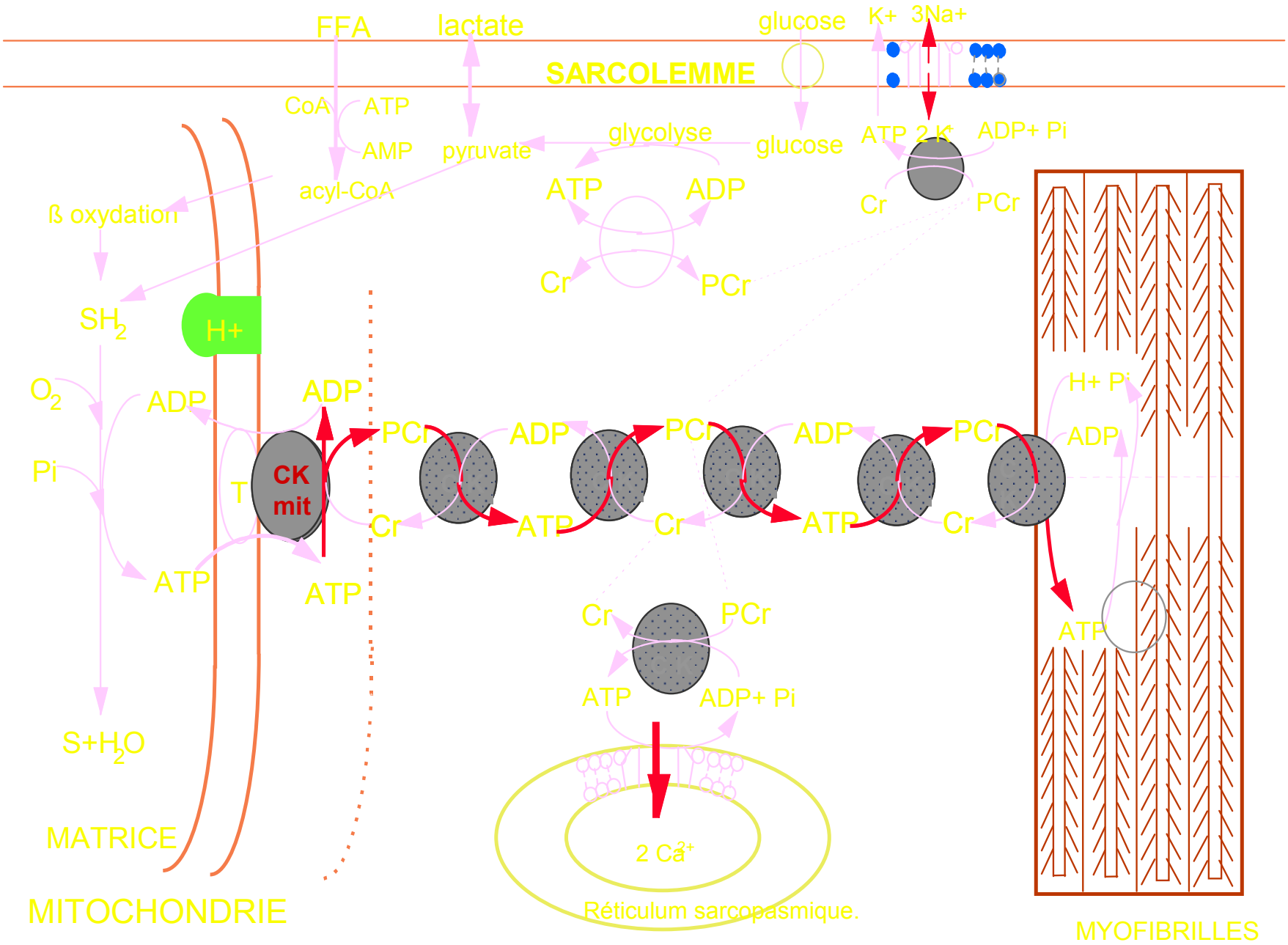
Bers DM. Excitation–contraction coupling and cardiac force. Kluwer Academic Publishers 2002: p.25.

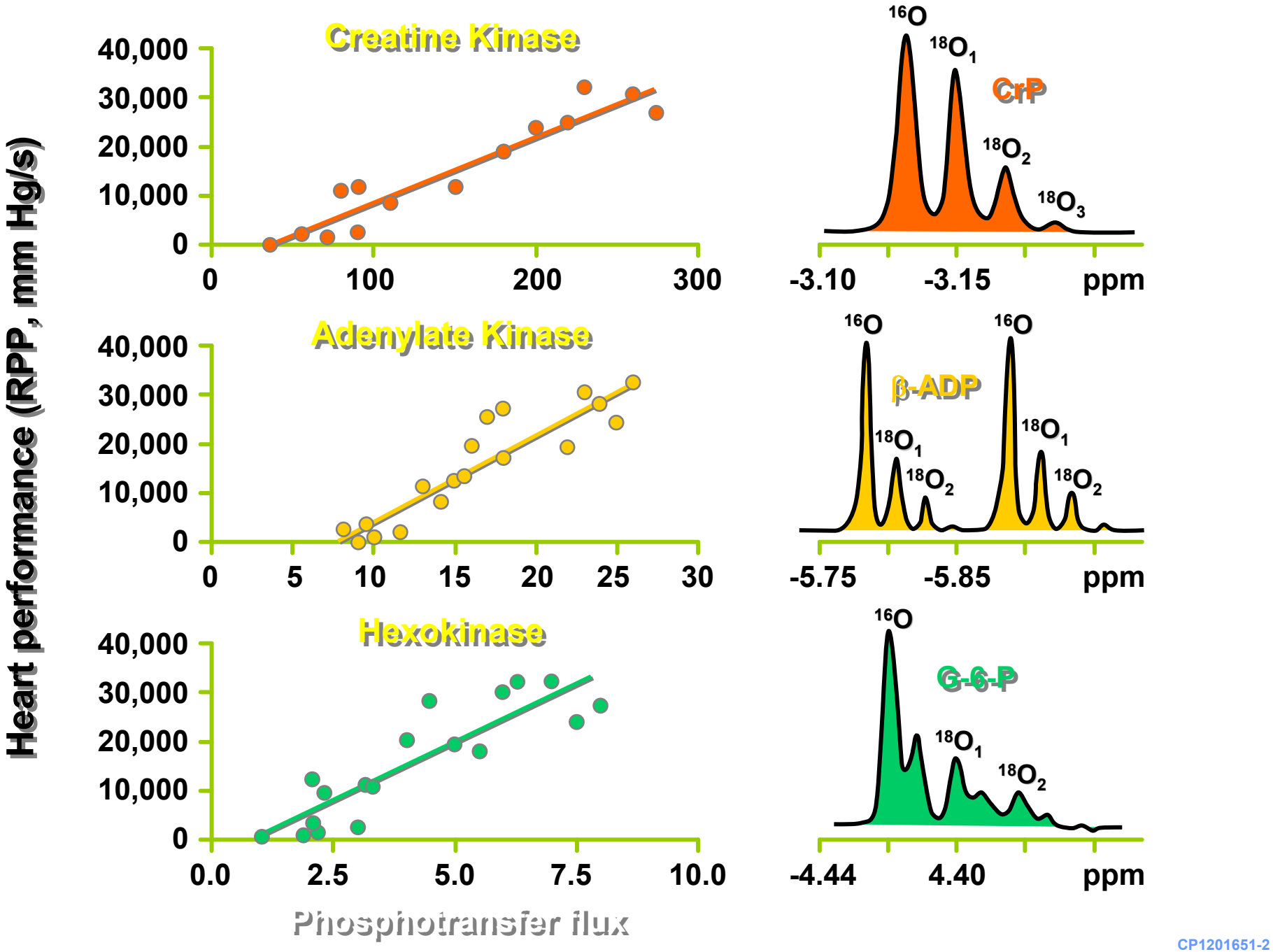
2. Positive cooperativity of croosbridge binding to actin *(Robinson et al. J.Mol.Biol. 322,1065,2002)*

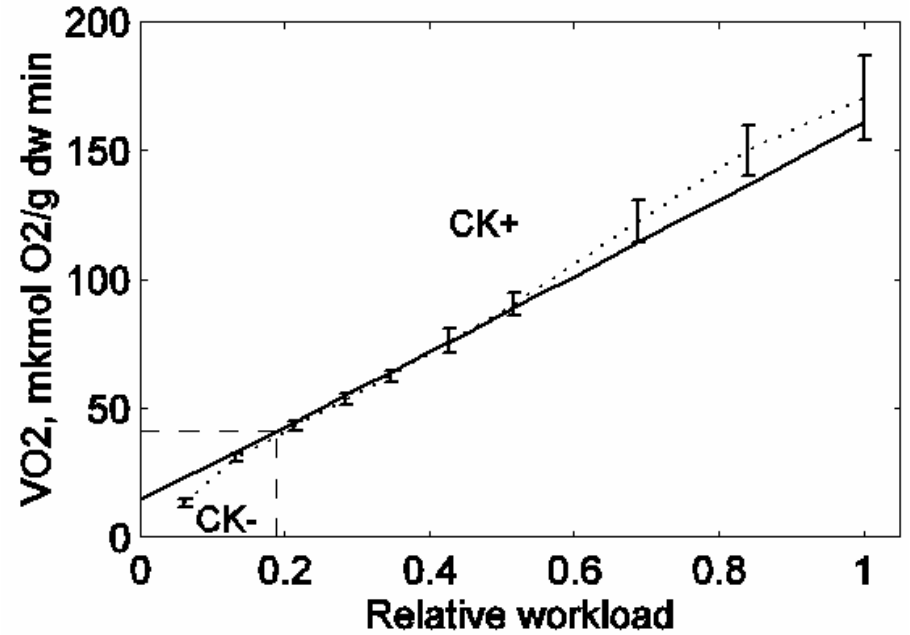
3. Increase of affinity of troponin complex for calcium induced by strong binding of crossbridges *(Landesberg&Sideman, Am.J.Physiol.276,H998,1999)*

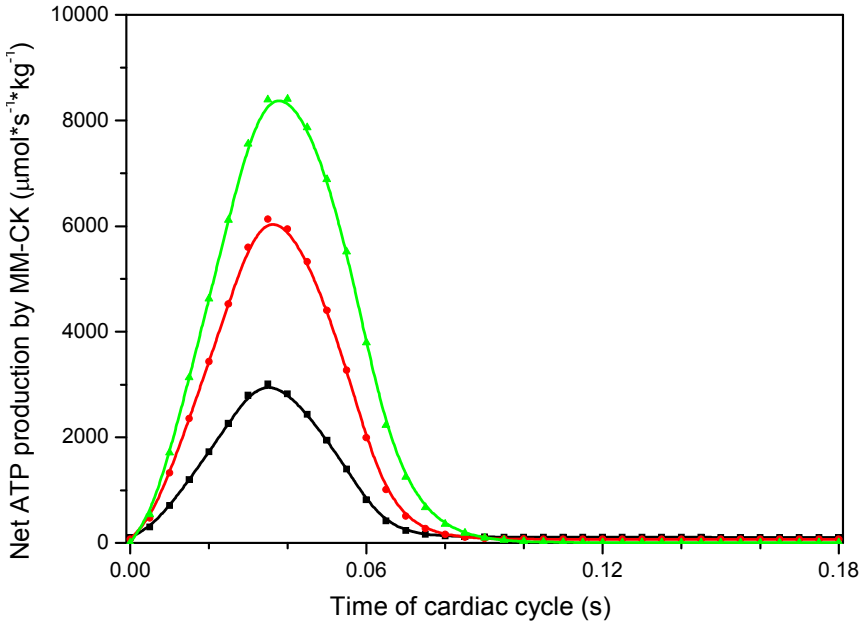
THE RESULT:

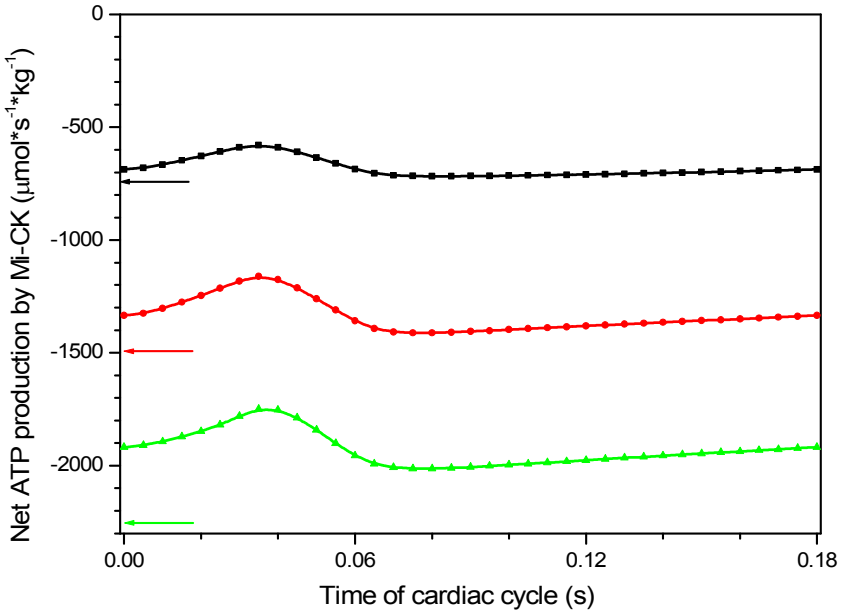


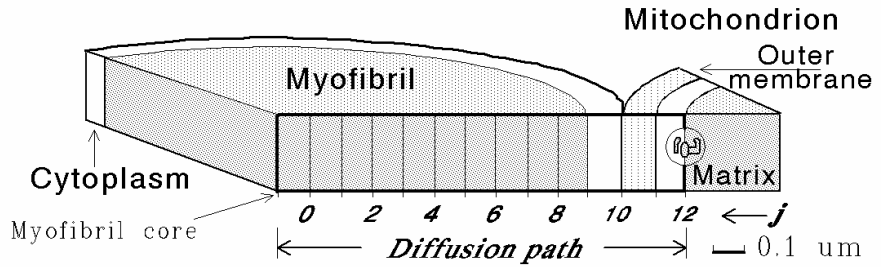

FFA
lactate
glucose
K+ 3Na+
SARCOLEMME
CoA
ATP
AMP
pyruvate
glycolyse
glucose
ATP 2 K+
ADP+ Pi
acyl-CoA
ß oxydation
ATP
ADP
Cr
PCr
SH2
H+
O2
ADP
ADP
PCr
ADP
PCr
ADP
PCr
H+ Pi
ADP
Pi
T
CK mit
Cr
ATP
ATP
Cr
ATP
Cr
ATP
ATP
Cr
PCr
ATP
ADP+ Pi
S+H2O
MATRICE
2 Ca2+
Réticulum sarcoplasmique.
MITOCHONDRIE
MYOFIBRILLES

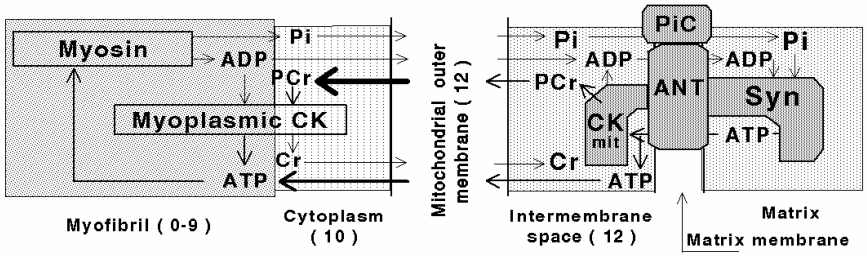

Heart performance (RPP, mm Hg/s)
Creatine Kinase
40,000
30,000
20,000
10,000
0
0
100
200
300
16O
18O1
CrP
18O2
18O3
-3.10
-3.15
ppm
Adenylate Kinase
40,000
30,000
20,000
10,000
0
0
5
10
15
20
25
30
16O
β-ADP
18O1
18O2
16O
18O1
18O2
-5.75
-5.85
ppm
Hexokinase
40,000
30,000
20,000
10,000
0
0.0
2.5
5.0
7.5
10.0
16O
G-6-P
18O1
18O2
-4.44
4.40
ppm
Phosphotransfer flux
CP1201651-2







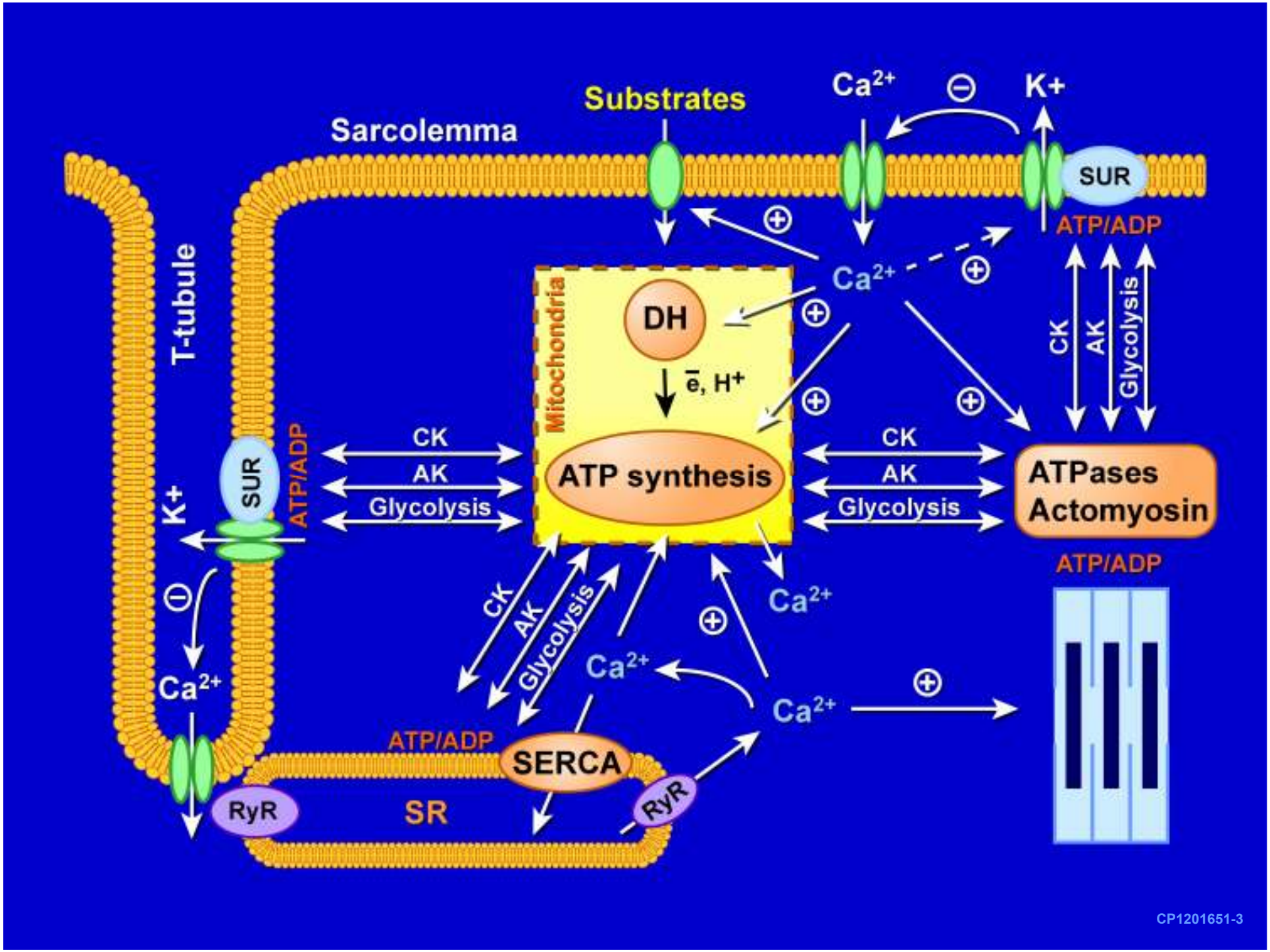


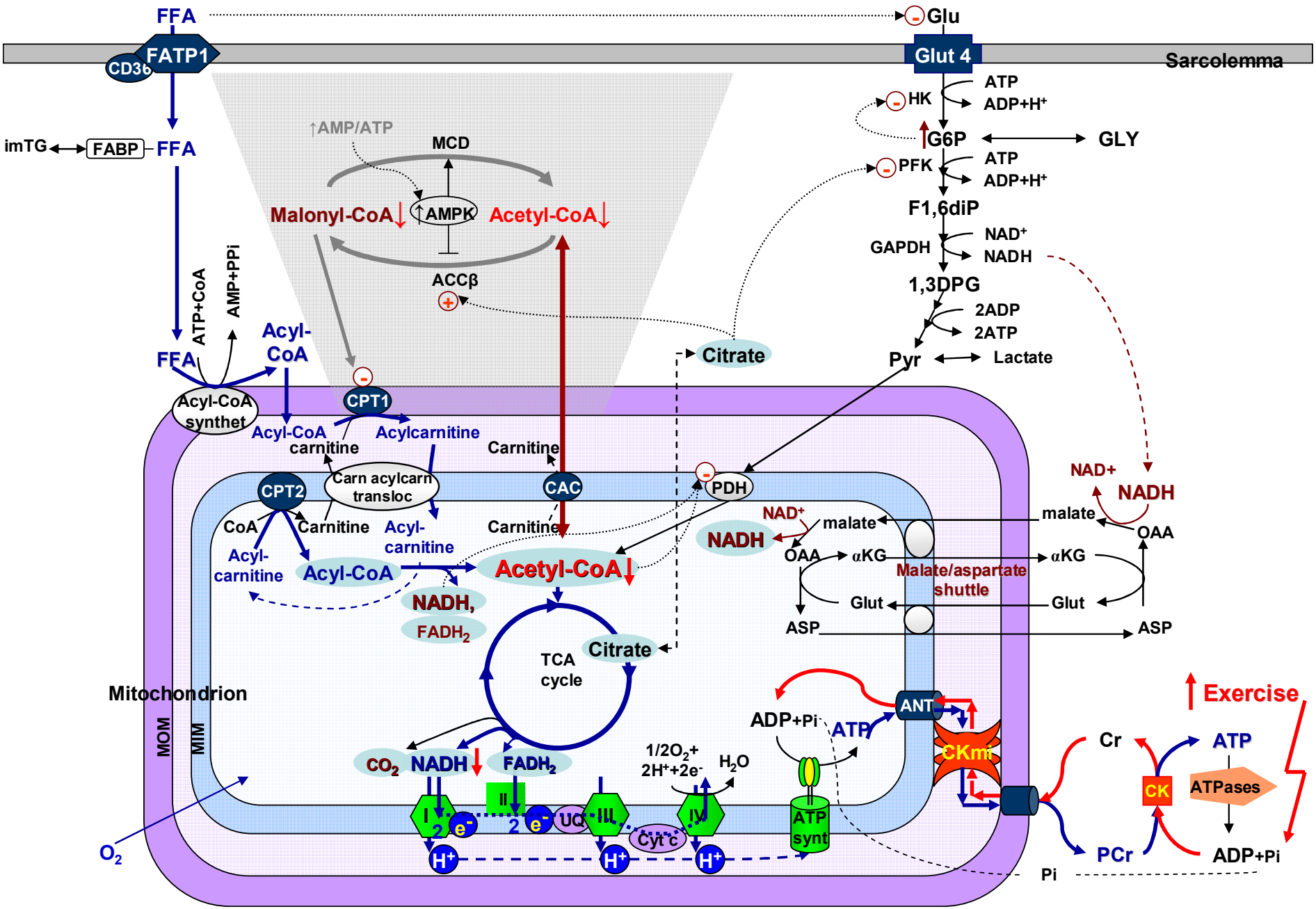


http://cens.ioc.ee/~markov/etransfer/current_model.pdf

THE REGULATION OF HEART ENERGETICS UNDER THE FRANK-STARLING LAW CAN BE QUANTITATIVELY EXPLAINED BY METABOLIC FEEDBACK SIGNALLING WITHIN THE STRUCTURALLY ORGANIZED ENERGTIC UNITS AND ENERGY TRANSFER AND SIGNALLING NETWORKS

THIS TYPE REGULATION RESULTS IN METABOLIC STABILITY (HOMEOSTASIS)


Substrates
Sarcolemma
Ca2+
K+
SUR
ATP/ADP
T-tubule
Mitochondria
DH
ē, H+
CK
AK
Glycolysis
ATP synthesis
ATPases
Actomyosin
SERCA
RyR
SR
CP1201651-3


FFA
FATP1
CD36
Glu
Glut 4
Sarcolemma
imTG
FABP
FFA
↑AMP/ATP
MCD
Malonyl-CoA↓
↑AMPK
Acetyl-CoA↓
ACCβ
HK
ATP
ADP+H+
G6P
GLY
PFK
ATP
ADP+H+
F1,6diP
GAPDH
NAD+
NADH
1,3DPG
2ADP
2ATP
Pyr
Lactate
ATP+CoA
AMP+PPi
Acyl-CoA synthet
FFA
Acyl-CoA
CPT1
Citrate
Acyl-CoA carnitine
Acylcarnitine
Carnitine
CPT2
Carn acylcarn transloc
CAC
PDH
CoA
Carnitine
Acyl-carnitine
Acyl-carnitine
Acyl-CoA
Acetyl-CoA↓
Carnitine
NADH,
FADH2
TCA cycle
Citrate
NAD+
NADH
malate
OAA
αKG
Malate/aspartate shuttle
αKG
Glut
Glut
ASP
ASP
NAD+
NADH
malate
OAA
Mitochondrion
MOM
MIM
ADP+Pi
ATP
ANT
CKmi
Exercise
Cr
ATP
CK
ATPases
ADP+Pi
PCr
Pi
CO2
NADH
FADH2
1/2O2+ 2H++2e-
H2O
I
II
III
IV
UQ
Cyt c
ATP synt
O2
H+
H+
H+

MECHANISMS OF DISEASE

N Engl J Med 2007;356:1140-51.

The Failing Heart — An Engine Out of

Stefan Neubauer, M.D., F.R.C.P.

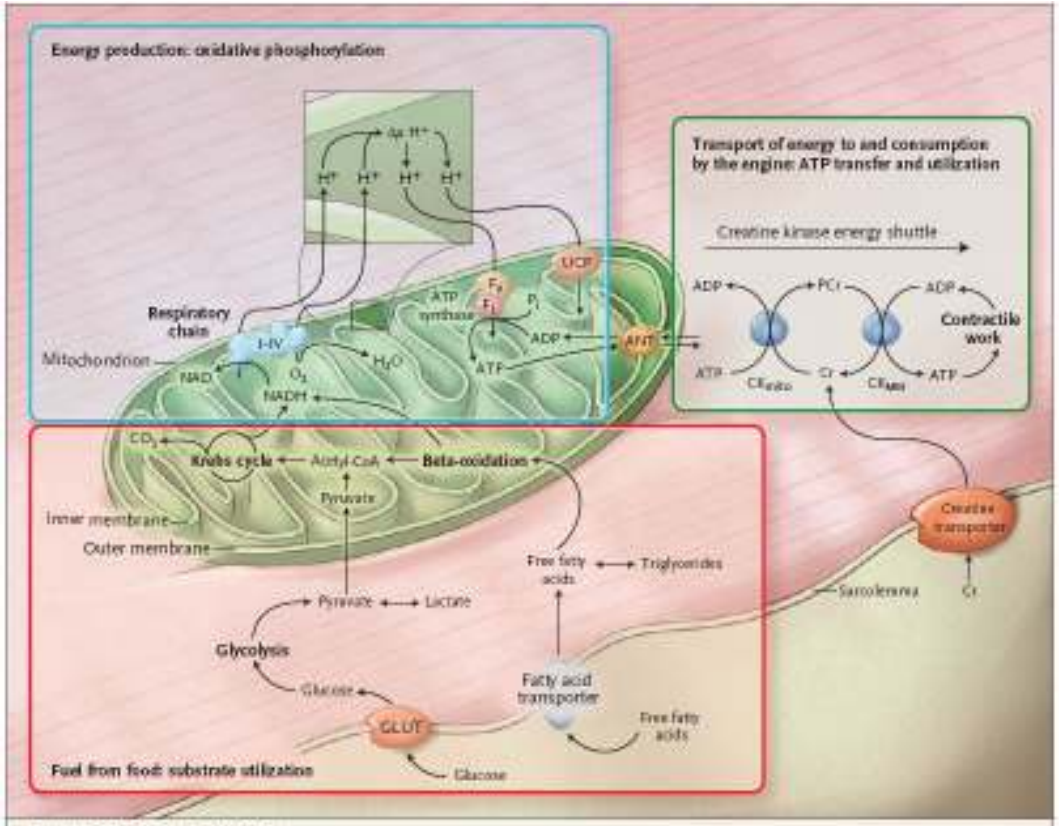


Figure 1. Cardiac Energy Metabolism.

Energy metabolism in the heart has three components. The first is substrate utilization (outlined in red), the cellular uptake of substrates and their breakdown by beta-oxidation and glycolysis; these processes result in the formation of acetyl coenzyme A (CoA), which is fed into the Krebs cycle and produces NADH and carbon dioxide (CO_2). The second component is oxidative phosphorylation (outlined in blue), the production of energy. Respiratory-chain complexes I through IV transfer electrons from NADH to oxygen, thereby creating a proton electrochemical gradient ($\Delta\mu$ H^+) across the inner mitochondrial membrane as well as NAD and water. This gradient drives the F_o, F_1 ATP synthase, which produces ATP by phosphorylating ADP. Uncoupling proteins (UCPs) cause mitochondria to produce heat rather than ATP. The third component is energy transfer and utilization (outlined in green), the transport of energy to and consumption by myofibrillar ATPase and other ATP-consuming reactions, such as sarcolemmal and sarcoplasmic reticulum ion pumps. ATP transfer is achieved by the creatine kinase energy shuttle. Creatine, which is not produced in the heart, is taken up by the creatine transporter. GLUT denotes glucose transporter, P_i inorganic phosphate, ANT adenine nucleotide translocase, PCr phosphocreatine, Cr free creatine, CK_{mito} mitochondrial creatine kinase isoenzyme, and CK_{MM} myofibrillar creatine kinase isoenzyme.

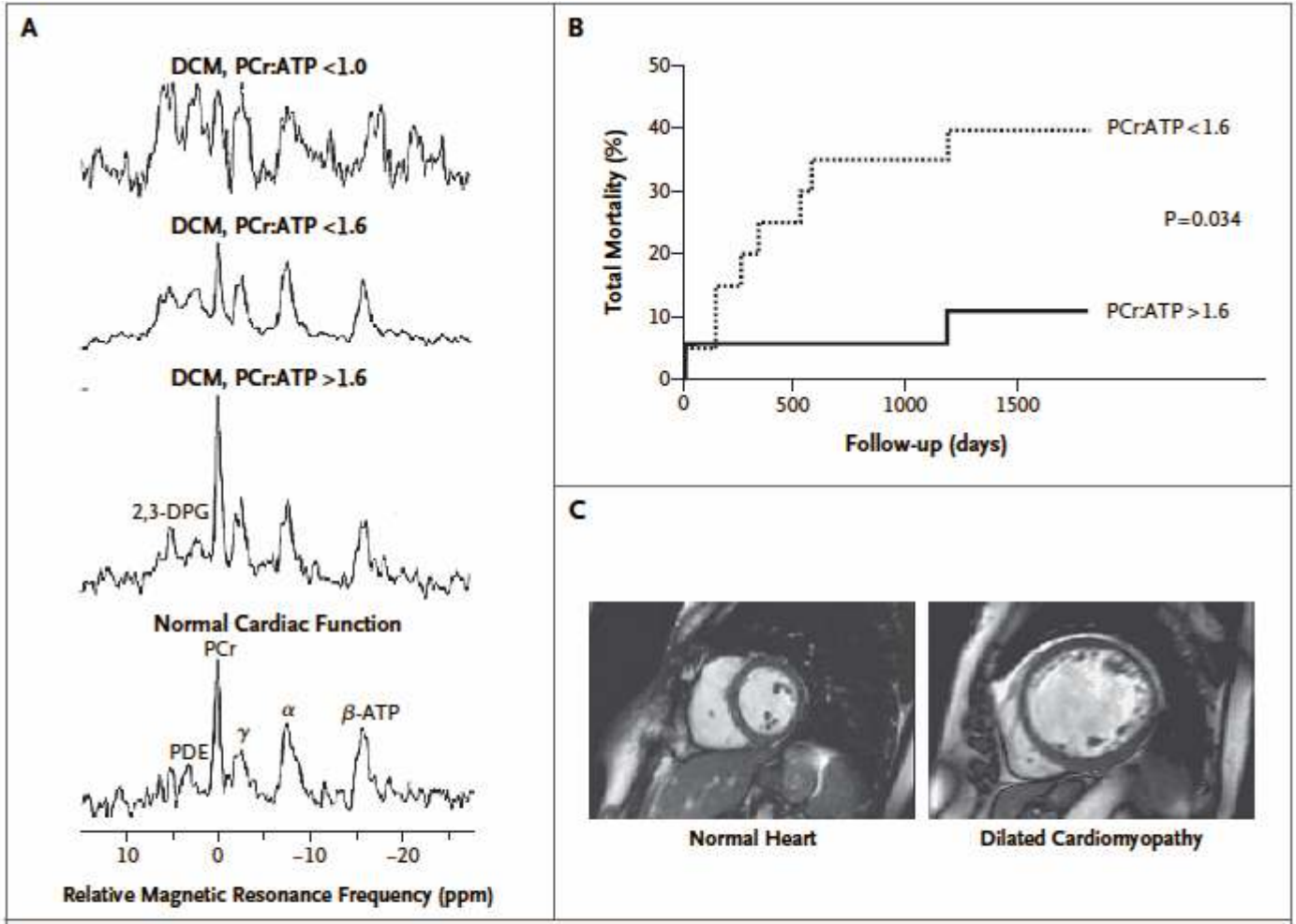
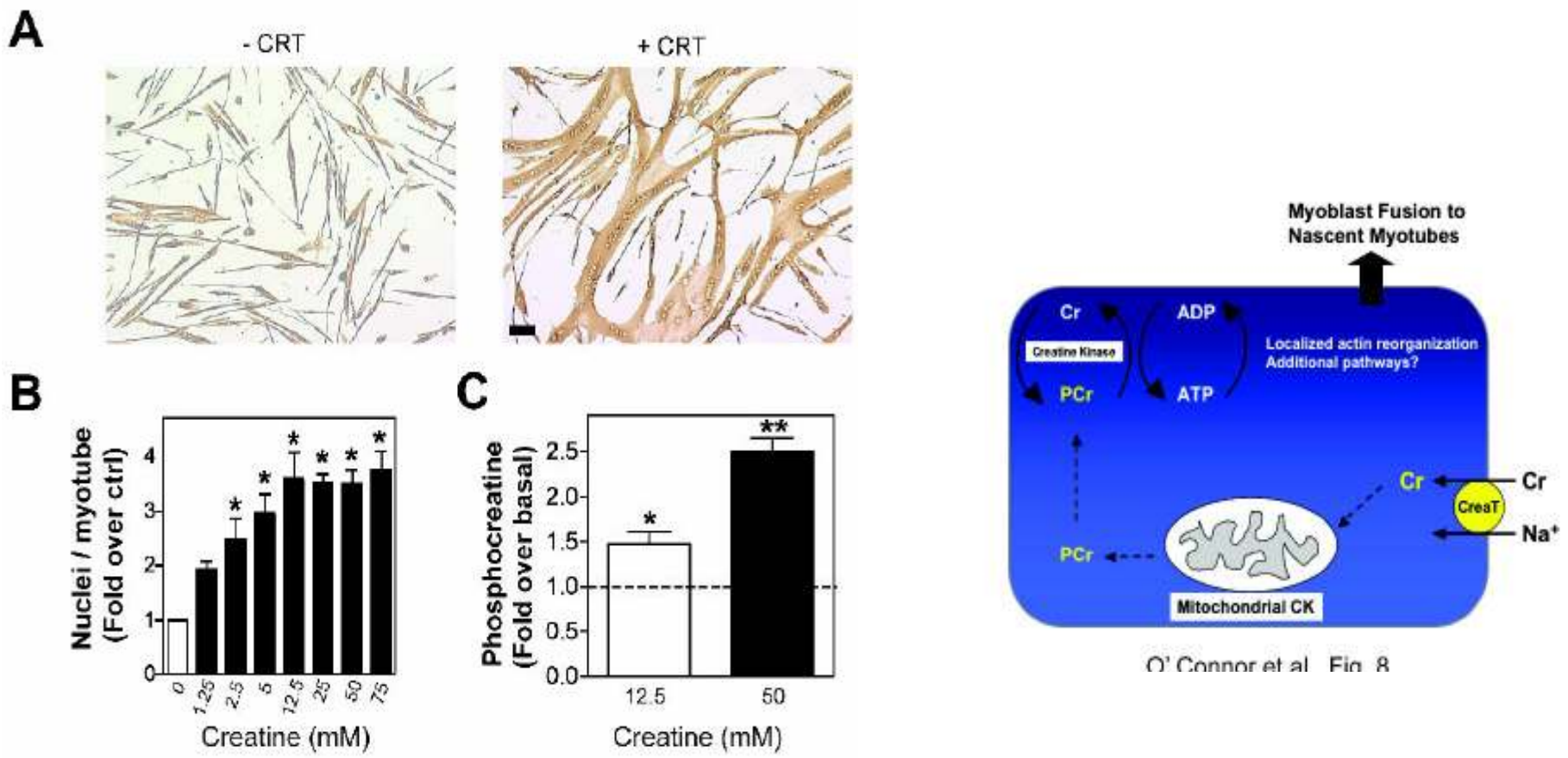


Figure 2. The Phosphocreatine:ATP Ratio in Heart Failure.

Panel A shows cardiac ^{31}P-MR spectra in (from bottom to top) a healthy subject, a patient with dilated cardiomyopathy (DCM) and a normal phosphocreatine (PCr):ATP ratio (>1.6; 1.6 was the median of the ratio), a patient with DCM and a reduced PCr:ATP ratio (<1.6), and a patient with DCM and a severely reduced PCr:ATP ratio (<1.0). The patient with the severely reduced ratio died 7 days after undergoing magnetic resonance examination. 2,3-DPG denotes 2,3-diphosphoglycerate, PDE phosphodiesters, and γ, α, and β phosphorus atoms of ATP. Panel B shows a Kaplan–Meier life-table analysis of mortality in two groups of patients with DCM: one with a higher PCr:ATP ratio and one with a lower ratio. Patients with an initially low ratio had an increased mortality over the study period (average follow-up, 2.5 years). Data are from Neubauer et al.[37] Panel C shows short-axis cine MRI scans of a normal heart and the severely dilated heart of a patient with DCM.



O' Connor et al. Fig. 8

Physiology in Press

Phosphocreatine as an energy source for actin cytoskeletal rearrangements during myoblast fusion

Roddy S. O' Connor, Craig M. Steeds, Robert Wiseman and Grace Pavlath

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The Journal of Physiology
May 2008

PERSPECTIVES

Running title : Phosphocreatine-creatine kinase in muscle cells

THE PHOSPHOCREATINE - CREATINE KINASE SYSTEM HELPS TO SHAPE THE MUSCLE CELLS AND TO KEEP THEM HEALTHY AND ALIVE

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