Department of Biomedical Systems

Physicist

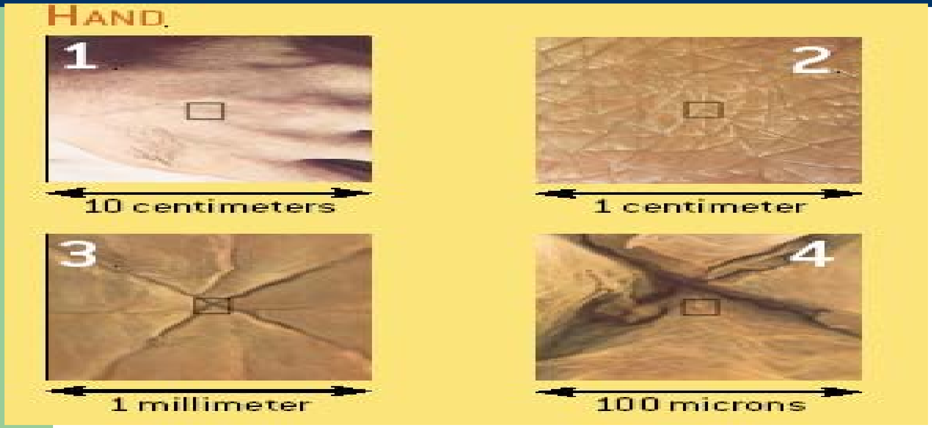
Physician

Integration of macro-, micro- and nanotechnologies for biomedical engineering

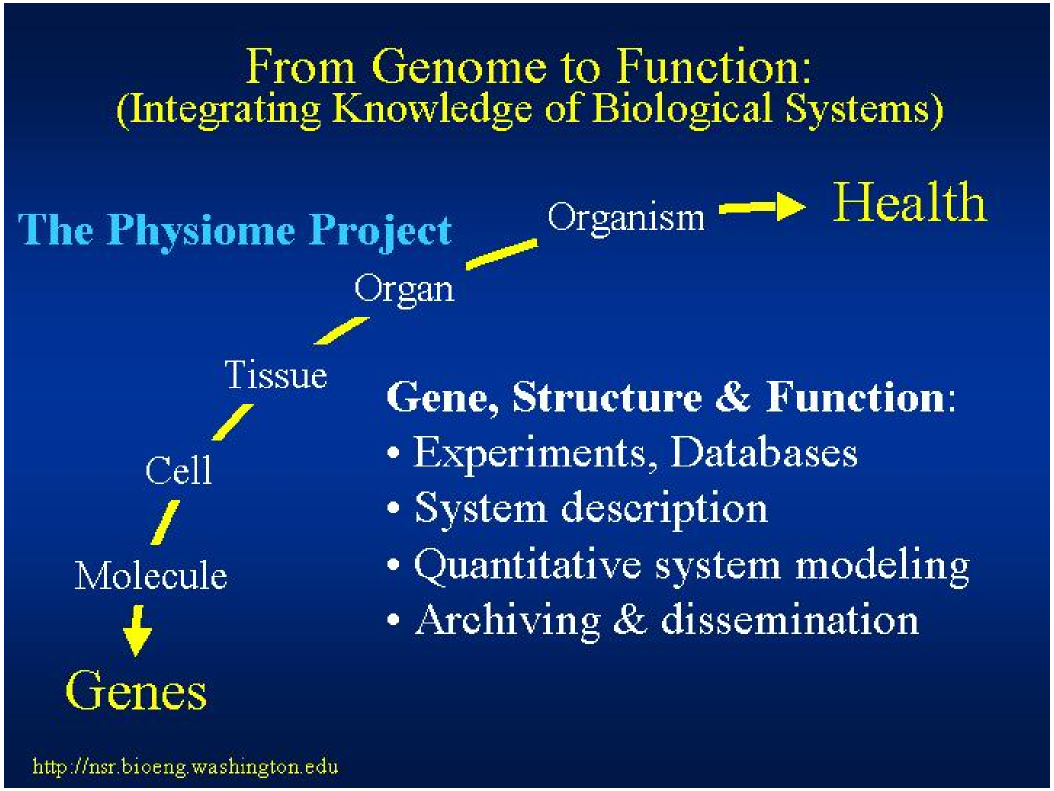
Sergey Selishchev

Macro – micro – nano.
“bottom-up” “top-down”

Macro-micro-nano scales



Physiome project



Integration of macro-,micro and nanotechnologies for diagnostics and treatment of cardiovascular diseases

What challenge

for physicists

from physicians?

Challenges

- Fibrillation – Defibrillation
- Atherosclerosis
- Artificial heart

Macro scale of the heart

Heart of the adult	~ 100 mm	Length: 120 -130 mm Width: 70 – 80 mm
DNA	~ 10 mm	Length in unwrapped conditions
aorta	10 – 30 mm	Internal diameter
arteries	0,5 – 5 mm	Internal diameters

Micro scale of the heart (1)

arterioles	25 – 100 µm	Internal diameter
capillaries	3 – 10 µm	Internal diameter
bacteria	1 – 10 µm	
chromosome	9 µm	Human chromosome

Micro scale of the heart (2)

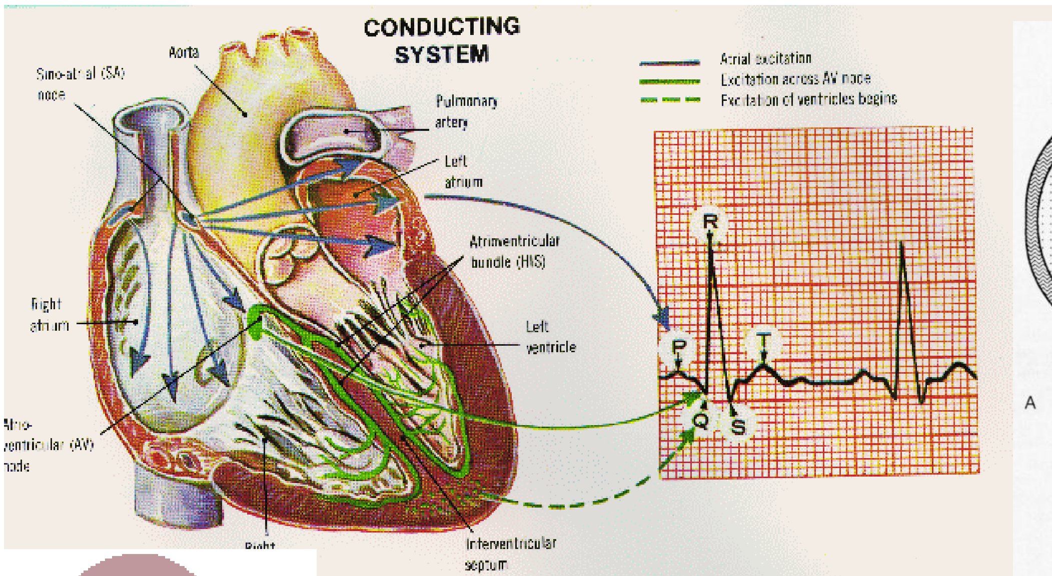
Myocyte	Cylindrical form	Length – 100 µm Diameter – 10 µm
White blood cell	Spherical form	8-15 µm
Red blood cell	Disk form	Diameter – 8 µm Thickness – 1,5 µm
Platelet	Spherical form	3 µm

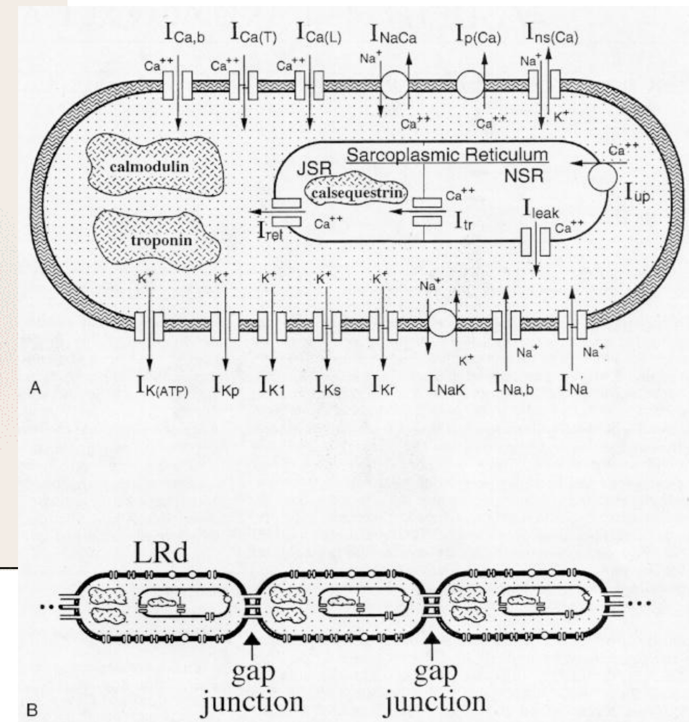
Nano scale of the heart

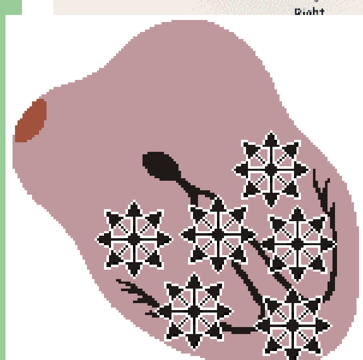
Virus	20 – 200 nm
Protein	7 – 50 nm
Membrane thickness	7 nm
DNA (The cross-section size)	2 nm
Molecular of water	0,3 nm
Atom of hydrogen	0,1 nm

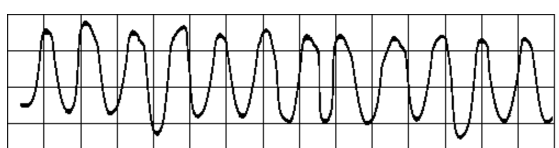
$$U(t,\vec{r}) = \phi_i(t,\vec{r}) - \phi_e(t,\vec{r})$$

Fibrillation

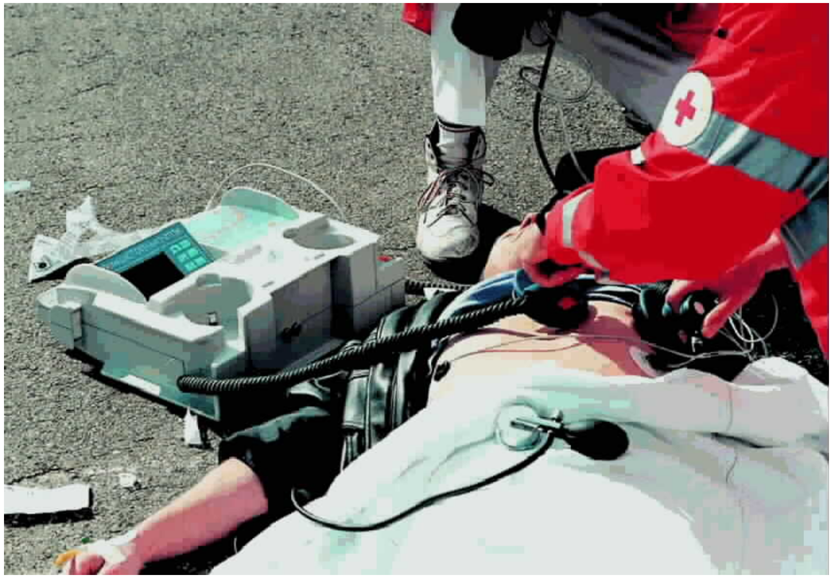








External Defibrillators (20 A, 10 ms) up to 200 – 500 J



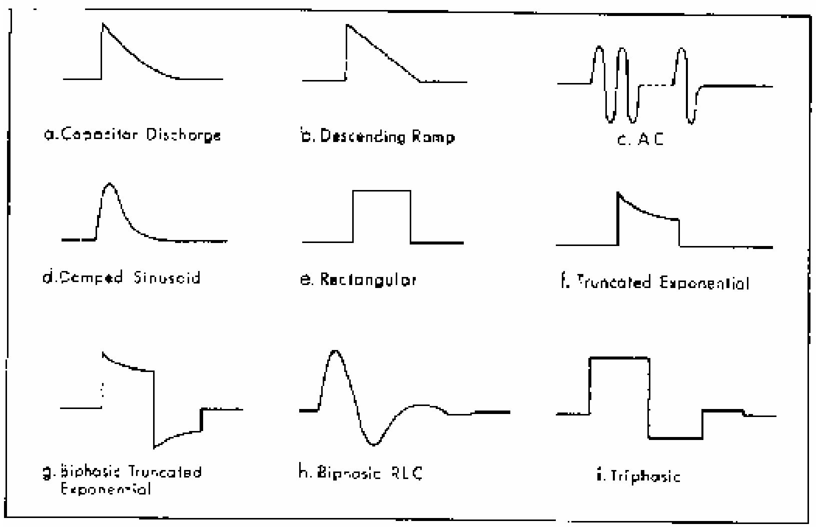
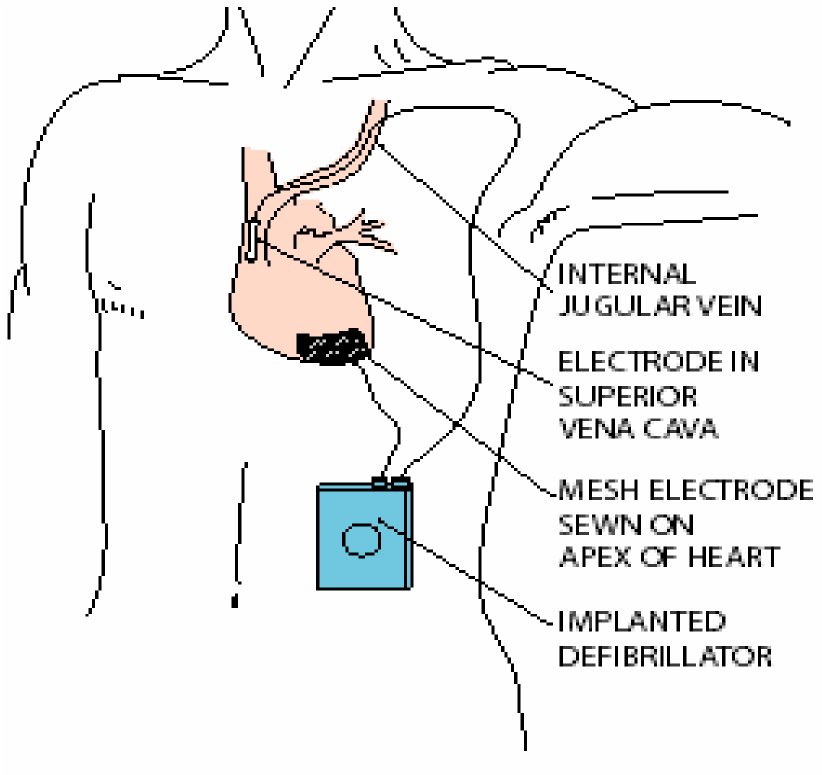
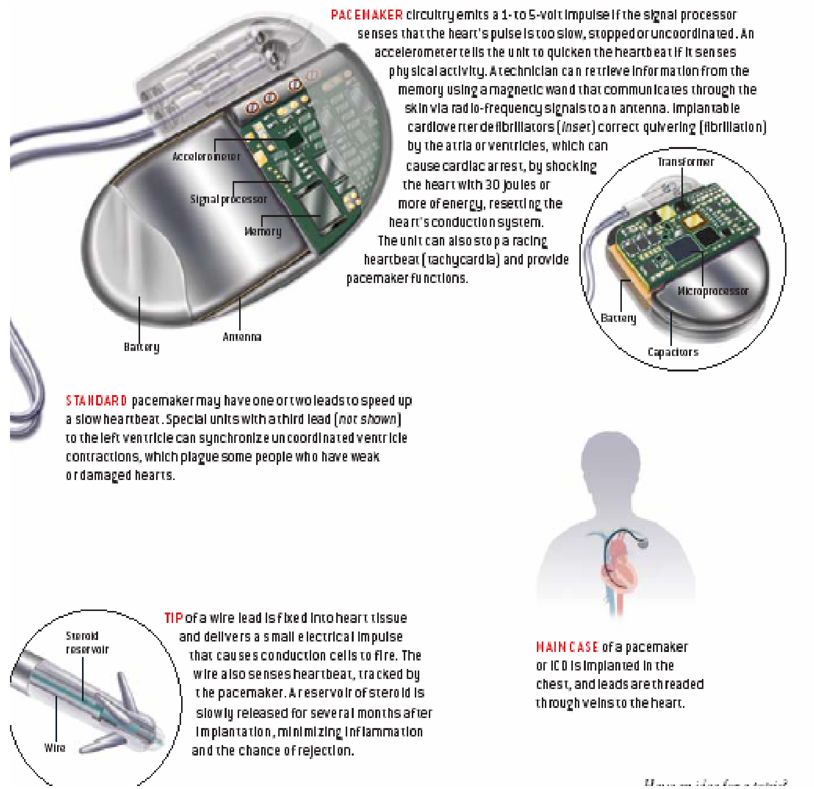


Figure 1. Waveforms that have been used for defibrillation research include decaying exponential (a); descending ramps (b); sinusoids (c); damped sinusoids (d); rectangular (e); truncated exponentials (f); biphasic truncated exponentials (g); biphasic from RLC networks (h); and triphasic (i).

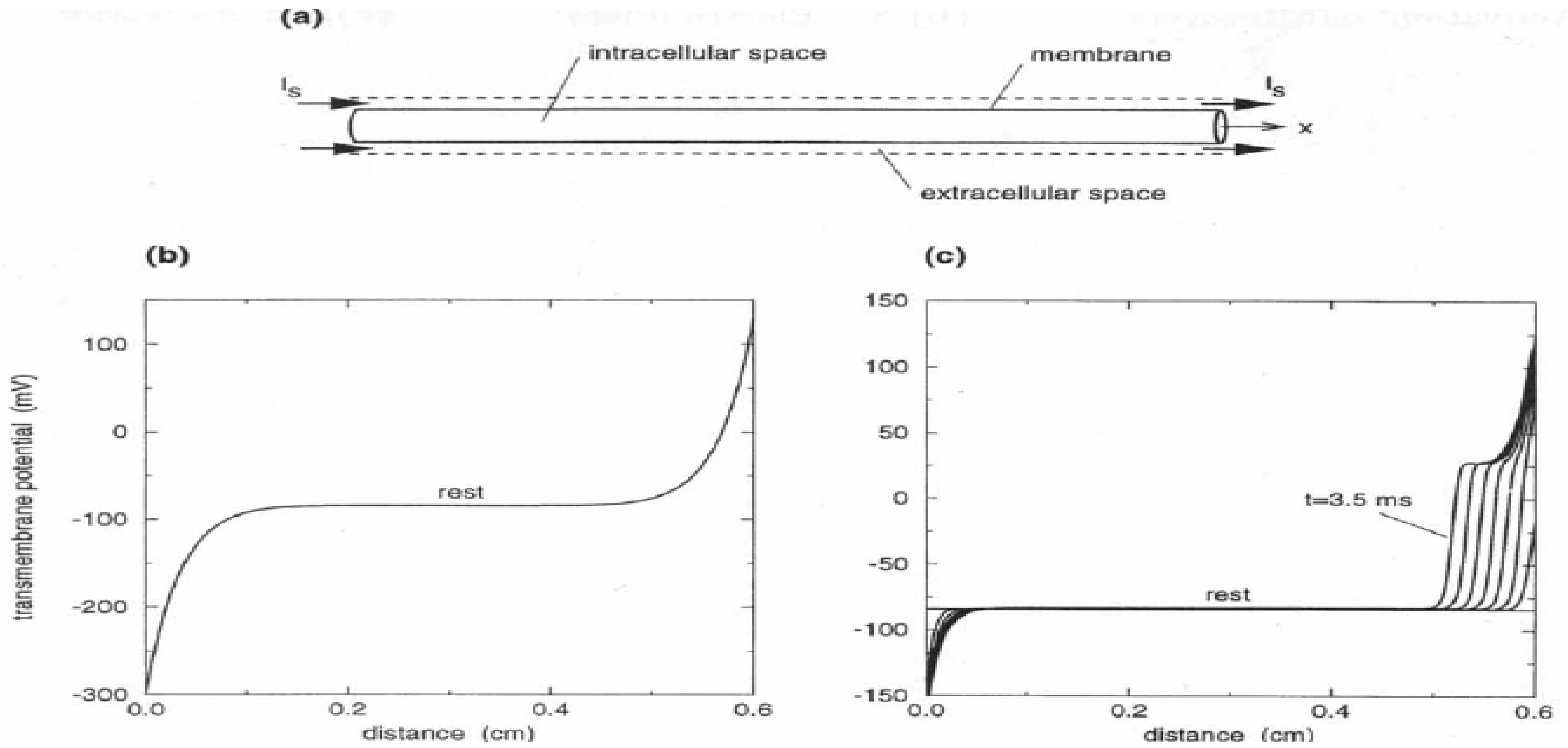
Wearable cardioverter/defibrillator

Implantable cardiostimulator-defibrillator

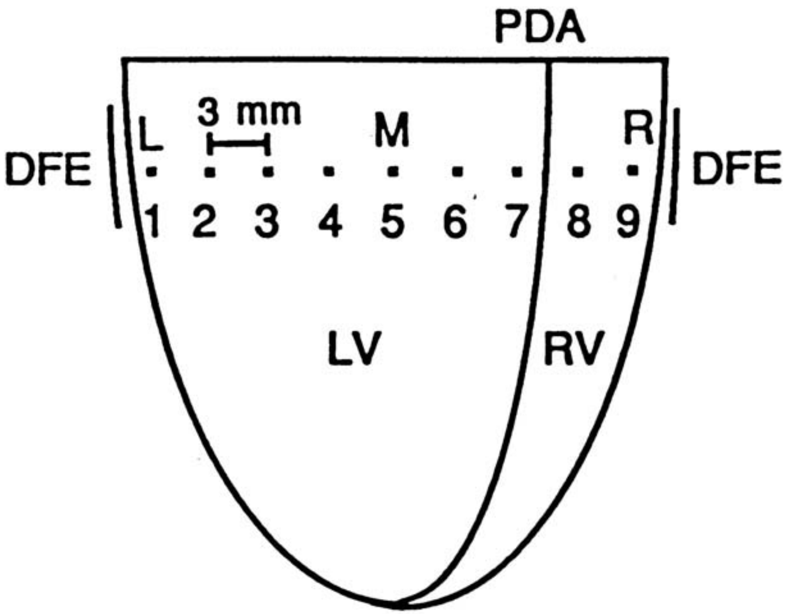


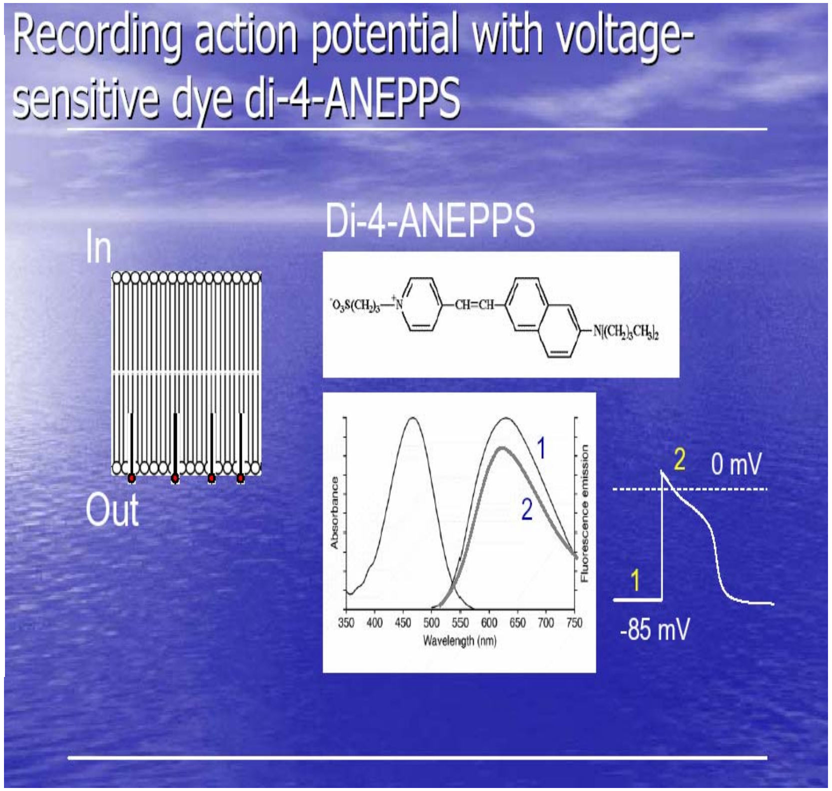


TMP problem

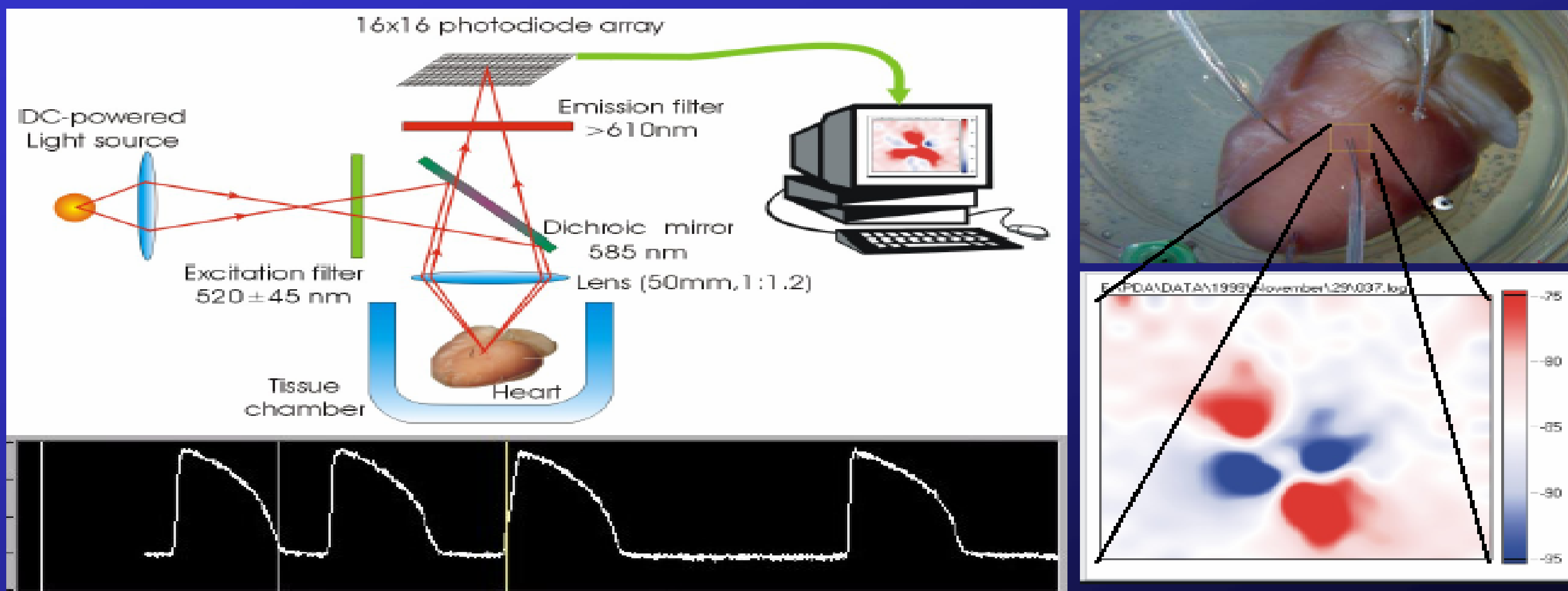

(a)
intracellular space
membrane
I_s
I_s
x
extracellular space
(b)
transmembrane potential (mV)
100
0
-100
-200
-300
0.0
0.2
0.4
0.6
distance (cm)
rest
(c)
150
100
50
0
-50
-100
-150
0.0
0.2
0.4
0.6
distance (cm)
t=3.5 ms
rest

TMP measurement

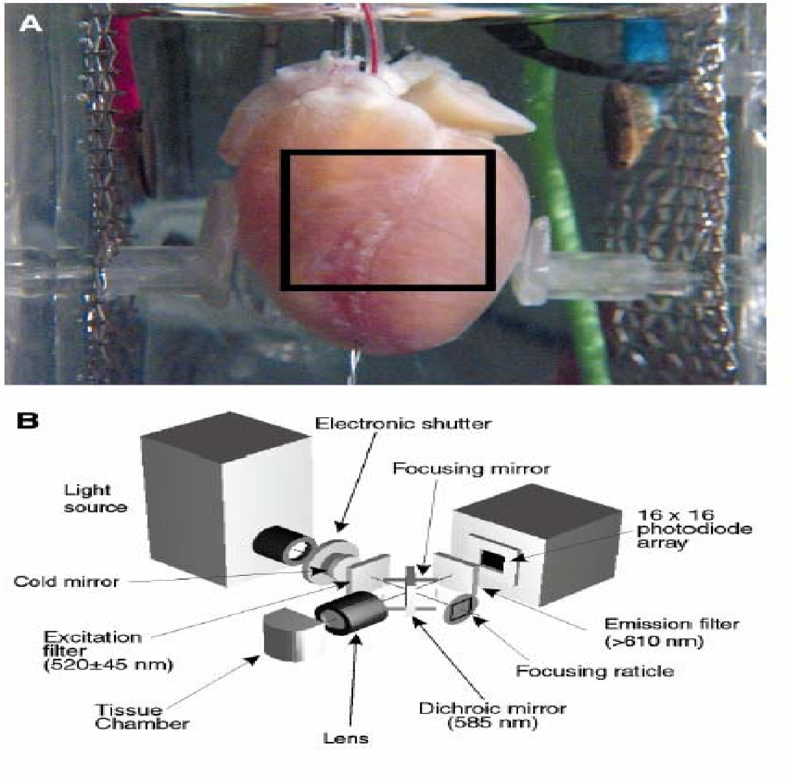




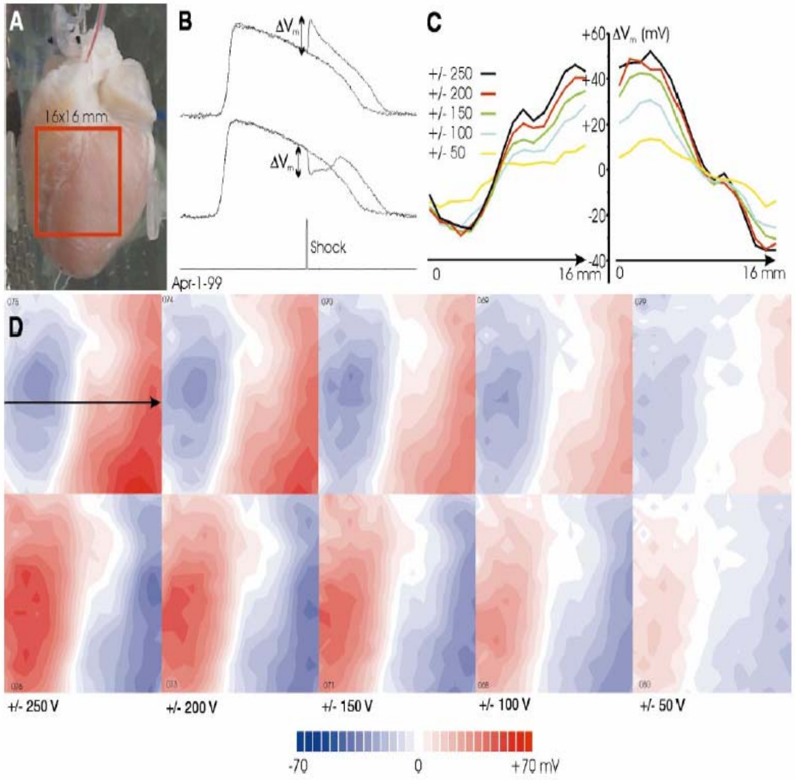
Optical fluorescent imaging of transmembrane potential



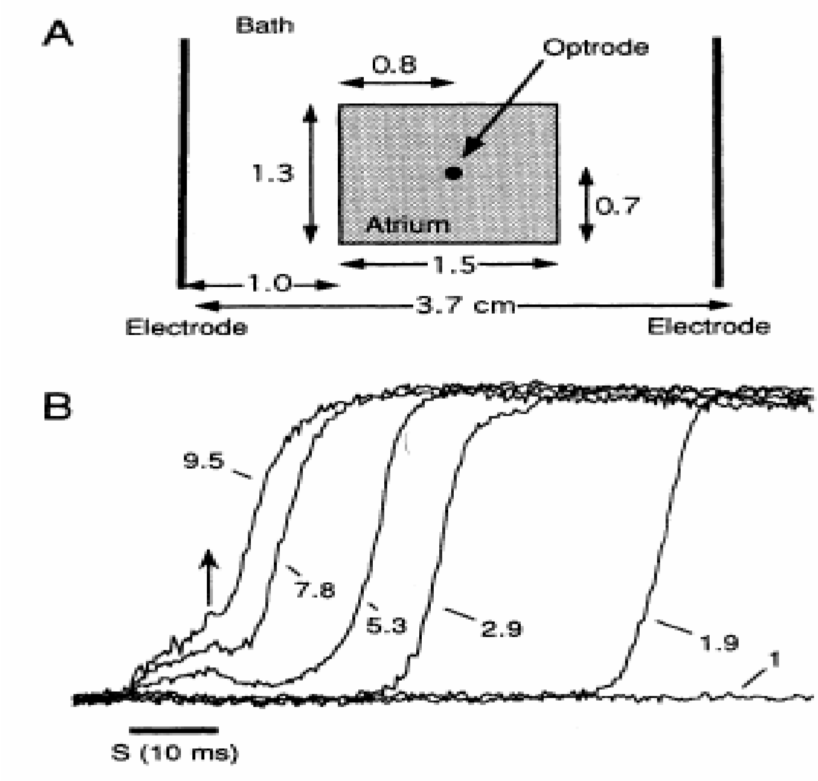
TMP measurement at the electrical stimulation



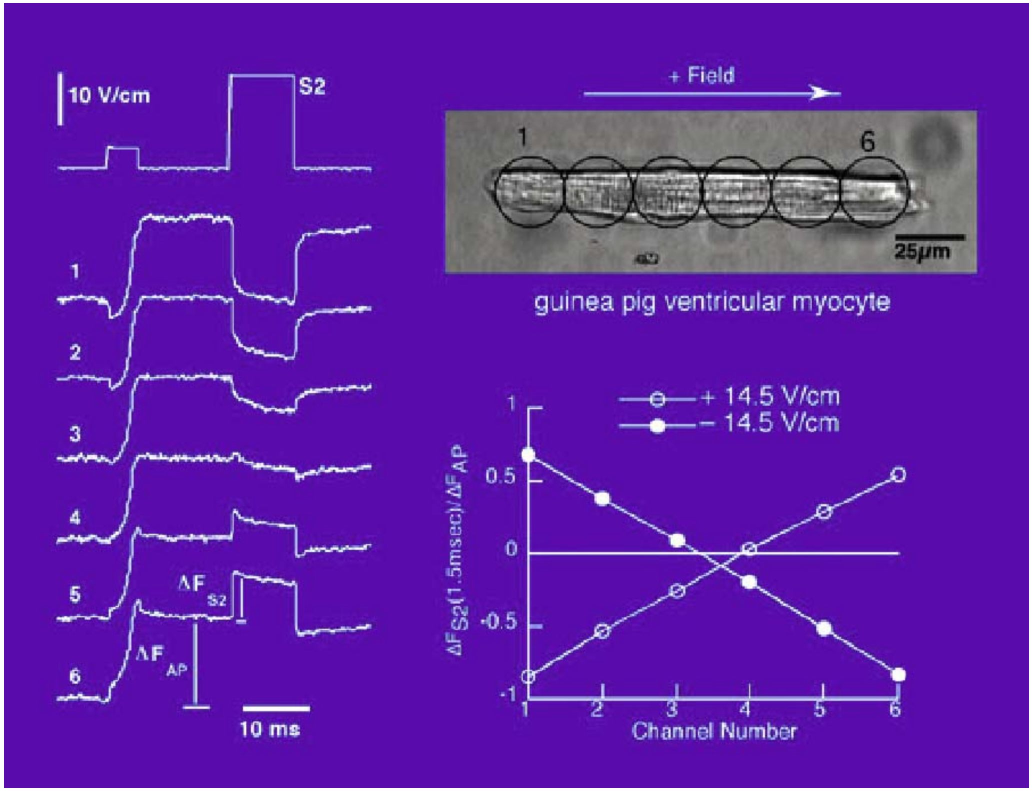
Spatio-temporal distributions of the TMP

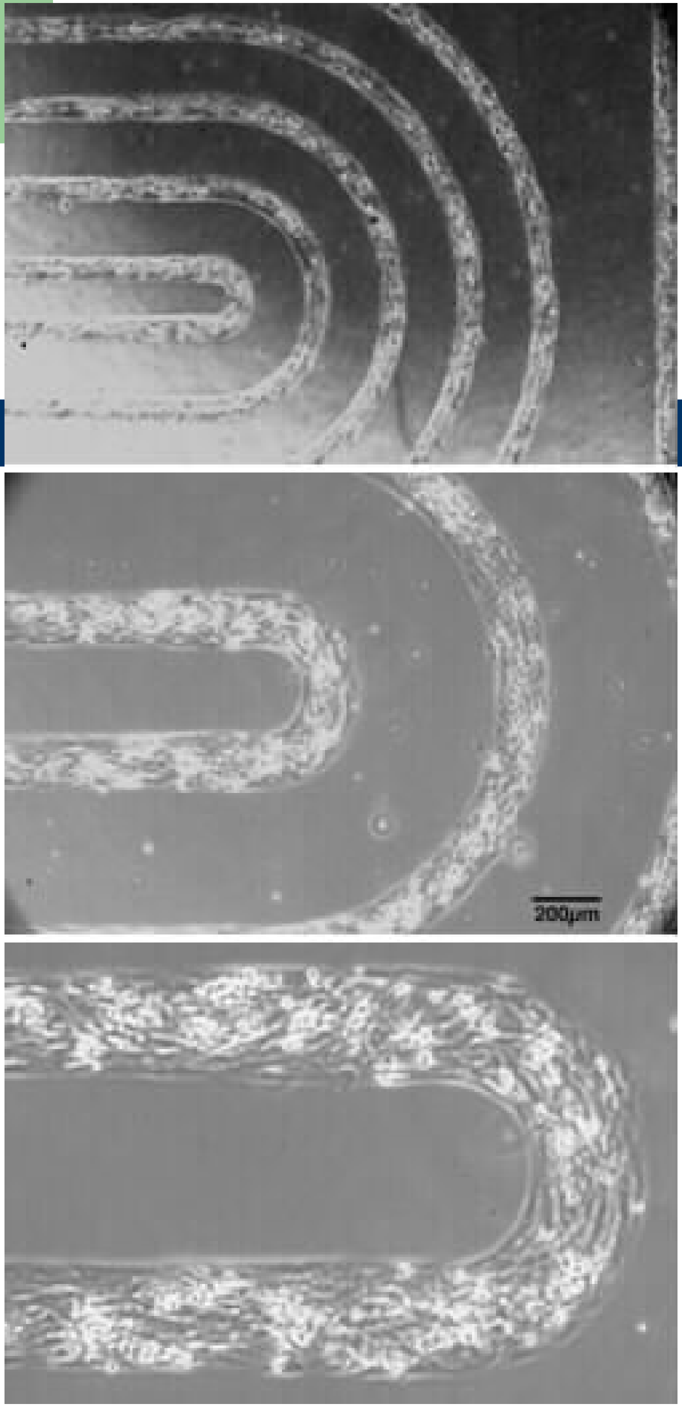


TMP measurement in atrium

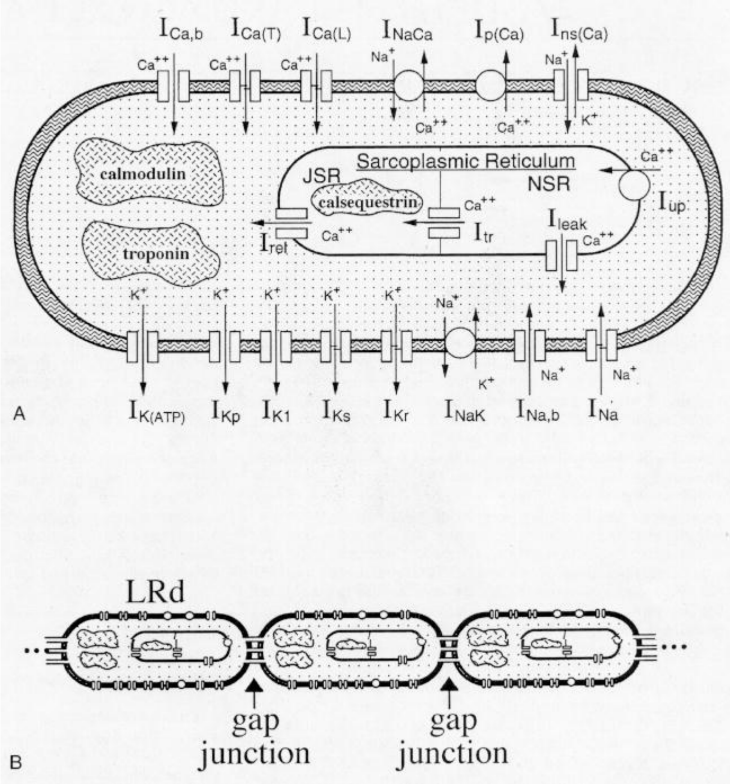


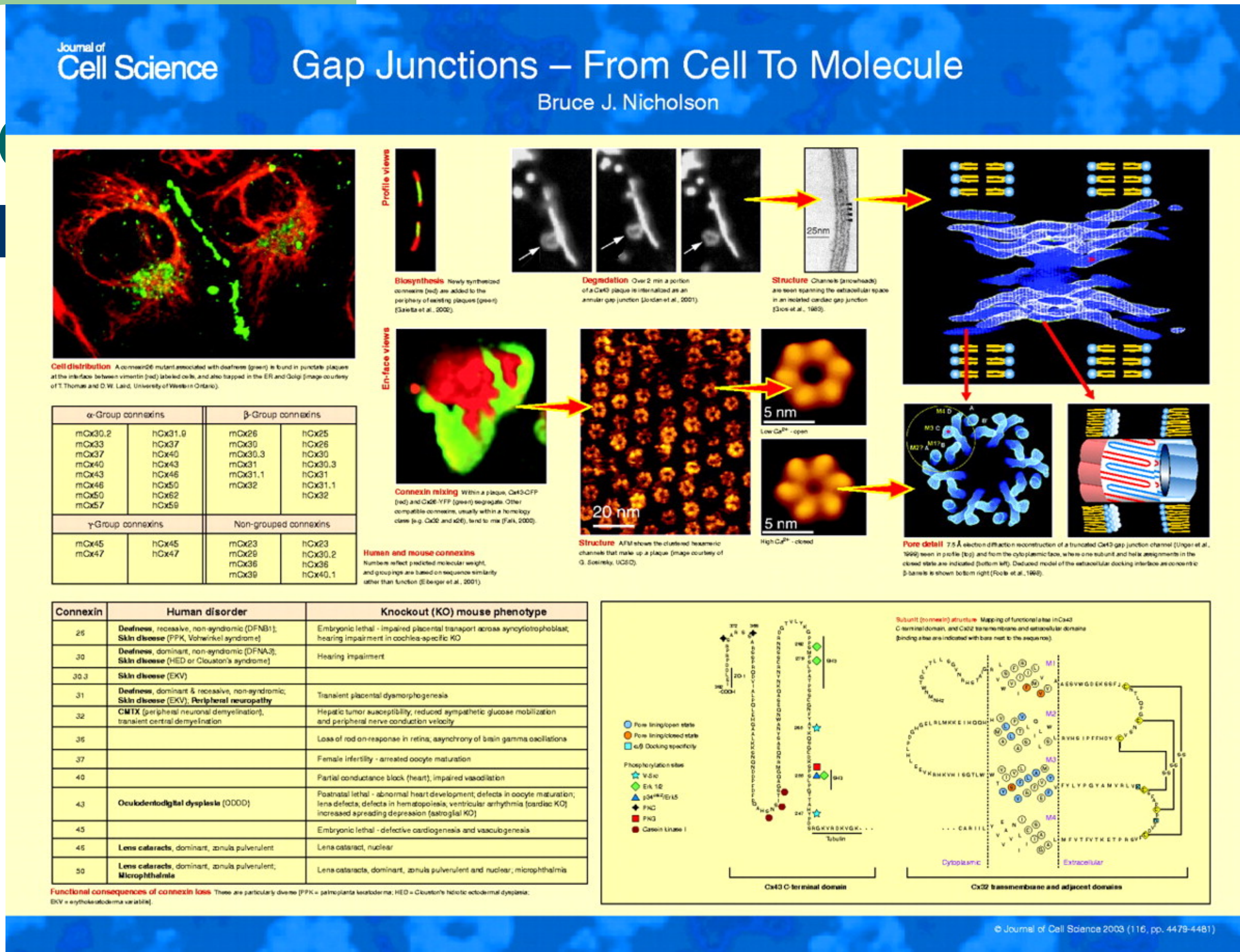
TMP measurement in cells




200μm

Cell of heart





Journal of Cell Science
Gap Junctions – From Cell To Molecule
Bruce J. Nicholson
Profile views
En-face views
Biosynthesis
Degradation
Structure
25nm
Connexin mixing
20 nm
5 nm
5 nm
Pore detail
Cell distribution A connexin26 mutant associated with deafness (green) is found in punctate plaques at the interface between vimentin (red) labeled cells, and also trapped in the ER and Golgi (image courtesy of T. Thomas and D.W. Laird, University of Western Ontario).

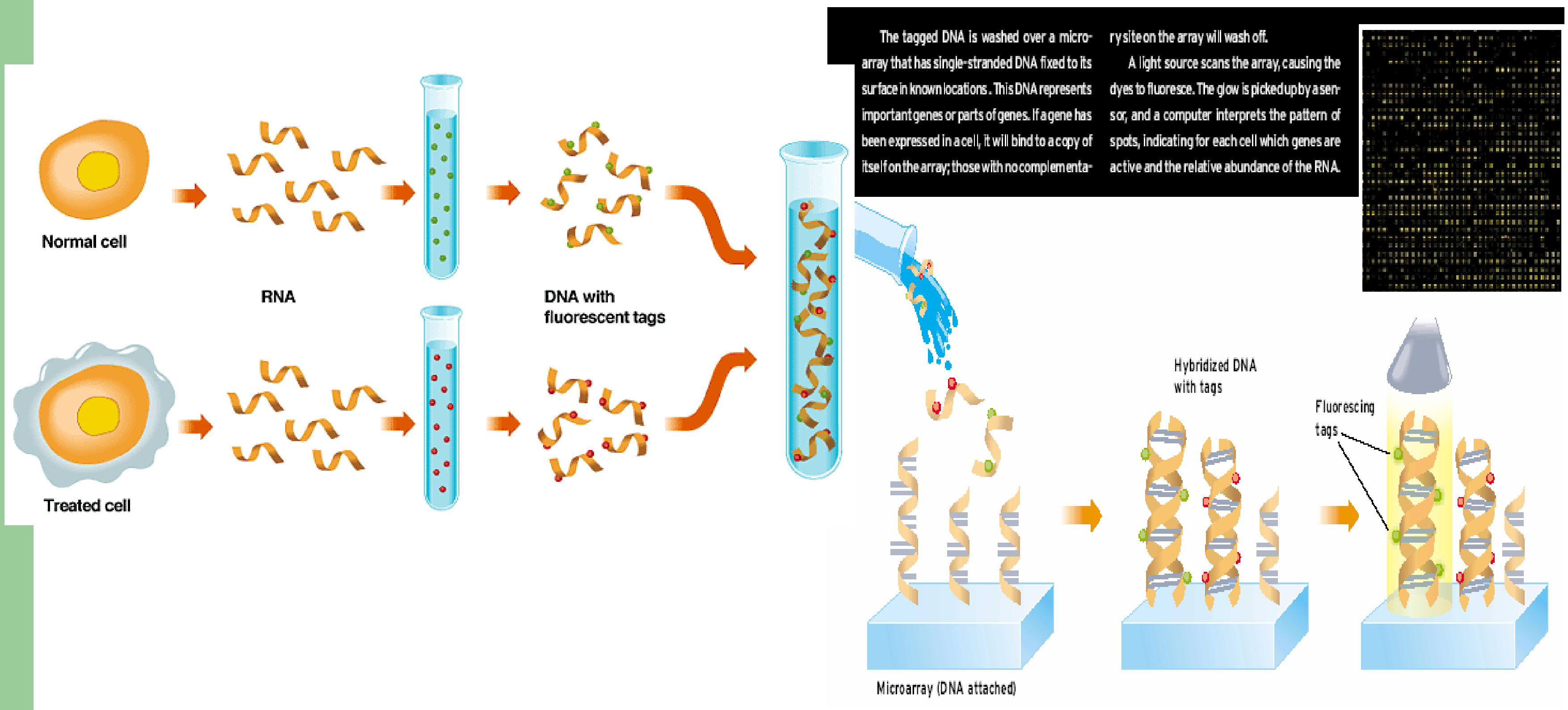
α-Group connexins		β-Group connexins	
mCx30.2 mCx33 mCx37 mCx40 mCx43 mCx46 mCx50 mCx57	hCx31.9 hCx37 hCx40 hCx43 hCx46 hCx50 hCx62 hCx59	mCx26 mCx30 mCx30.3 mCx31 mCx31.1 mCx32	hCx25 hCx26 hCx30 hCx30.3 hCx31 hCx31.1 hCx32
γ-Group connexins		Non-grouped connexins	
mCx45 mCx47	hCx45 hCx47	mCx23 mCx29 mCx36 mCx39	hCx23 hCx30.2 hCx36 hCx40.1

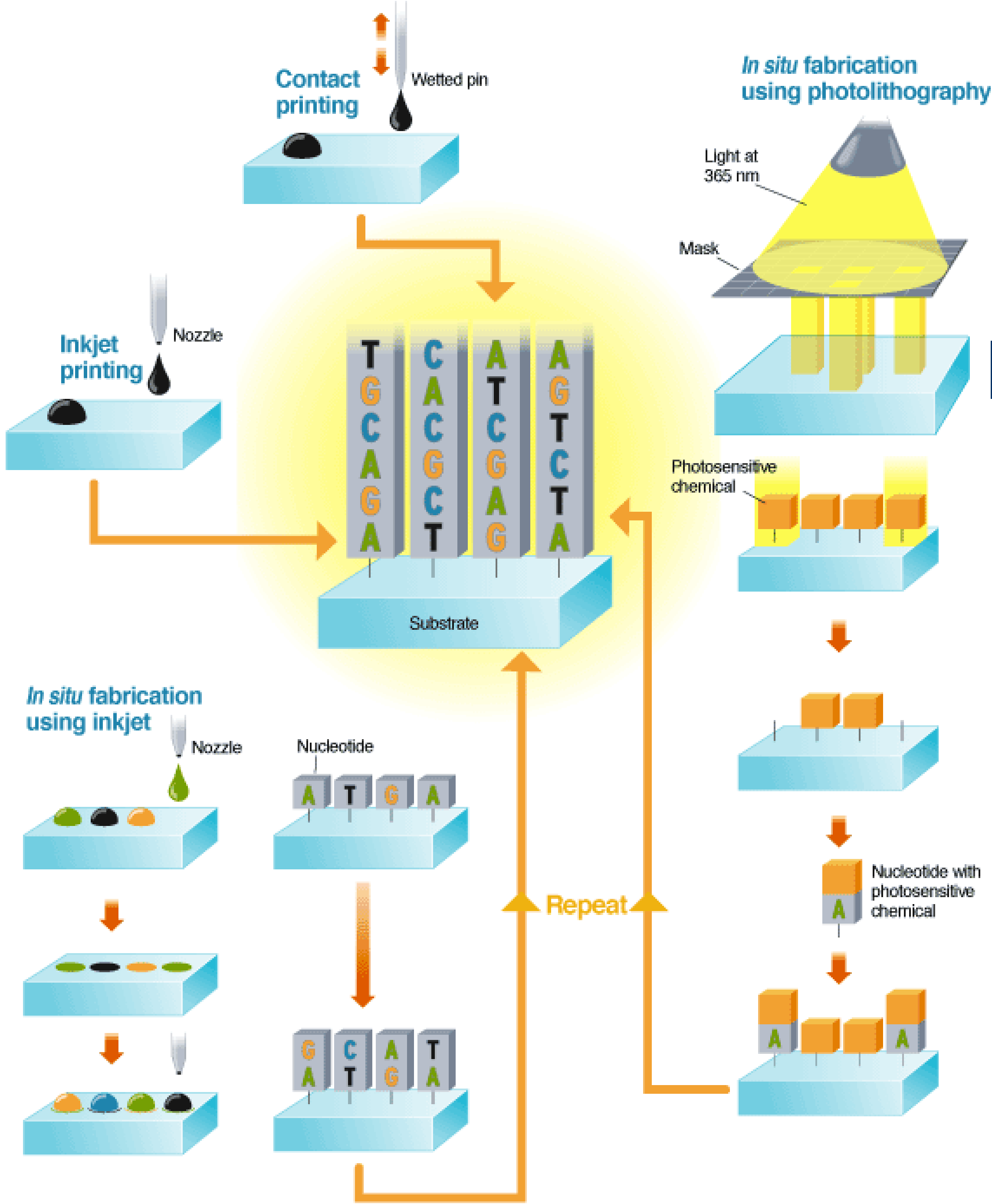
Human and mouse connexins Numbers reflect predicted molecular weight, and groupings are based on sequence similarity rather than function (Eiberger et al., 2001).

Connexin	Human disorder	Knockout (KO) mouse phenotype
26	**Deafness**, recessive, non-syndromic (DFNB1); **Skin disease** (PPK, Vohwinkel syndrome)	Embryonic lethal - impaired placental transport across syncytiotrophoblast; hearing impairment in cochlea-specific KO
30	**Deafness**, dominant, non-syndromic (DFNA3); **Skin disease** (HED or Clouston's syndrome)	Hearing impairment
30.3	**Skin disease** (EKV)	
31	**Deafness**, dominant & recessive, non-syndromic; **Skin disease** (EKV); **Peripheral neuropathy**	Transient placental dysmorphogenesis
32	**CMTX** (peripheral neuronal demyelination), transient central demyelination	Hepatic tumor susceptibility; reduced sympathetic glucose mobilization and peripheral nerve conduction velocity
36		Loss of rod on-response in retina; asynchrony of brain gamma oscillations
37		Female infertility - arrested oocyte maturation
40		Partial conductance block (heart); impaired vasodilation
43	**Oculodentodigital dysplasia** (ODDD)	Postnatal lethal - abnormal heart development; defects in oocyte maturation; lens defects; defects in hematopoiesis; ventricular arrhythmia (cardiac KO) increased spreading depression (astroglial KO)
45		Embryonic lethal - defective cardiogenesis and vasculogenesis
46	**Lens cataracts**, dominant, zonula pulverulent	Lens cataract, nuclear
50	**Lens cataracts**, dominant, zonula pulverulent; **Microphthalmia**	Lens cataracts, dominant, zonula pulverulent and nuclear; microphthalmia

Functional consequences of connexin loss These are particularly diverse [PPK = palmoplanta keratoderma; HED = Clouston's hidiotic ectodermal dysplasia; EKV = erythokeratoderma variabilis].
Cx43 C-terminal domain
Cx32 transmembrane and adjacent domains
Cytoplasmic
Extracellular
M1
M2
M3
M4
Tubulin
© Journal of Cell Science 2003 (116, pp. 4479-4481)

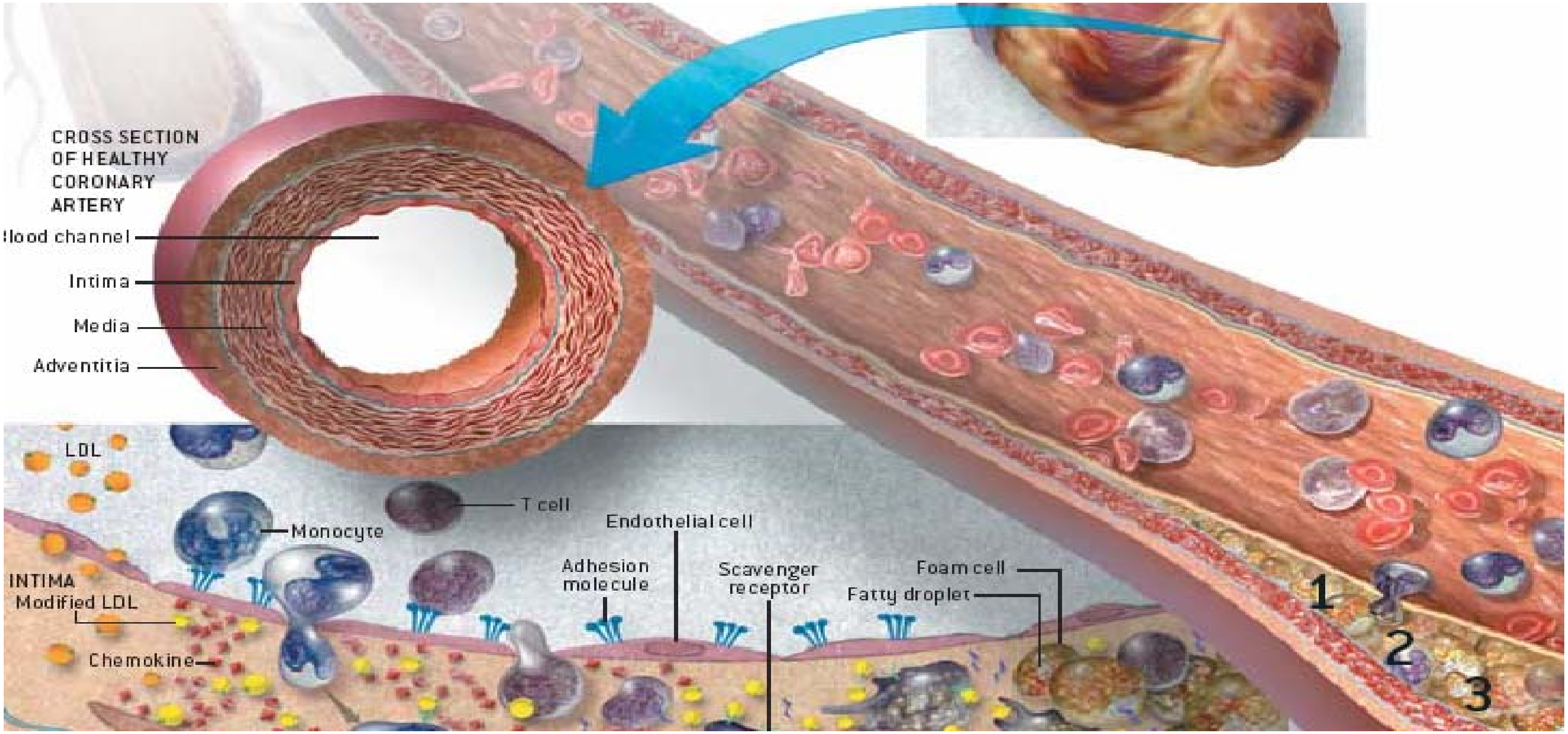
Biochip


Normal cell
RNA
DNA with fluorescent tags
Treated cell
The tagged DNA is washed over a micro-array that has single-stranded DNA fixed to its surface in known locations. This DNA represents important genes or parts of genes. If a gene has been expressed in a cell, it will bind to a copy of itself on the array; those with no complementa-ry site on the array will wash off.
A light source scans the array, causing the dyes to fluoresce. The glow is picked up by a sensor, and a computer interprets the pattern of spots, indicating for each cell which genes are active and the relative abundance of the RNA.
Hybridized DNA with tags
Fluorescing tags
Microarray (DNA attached)

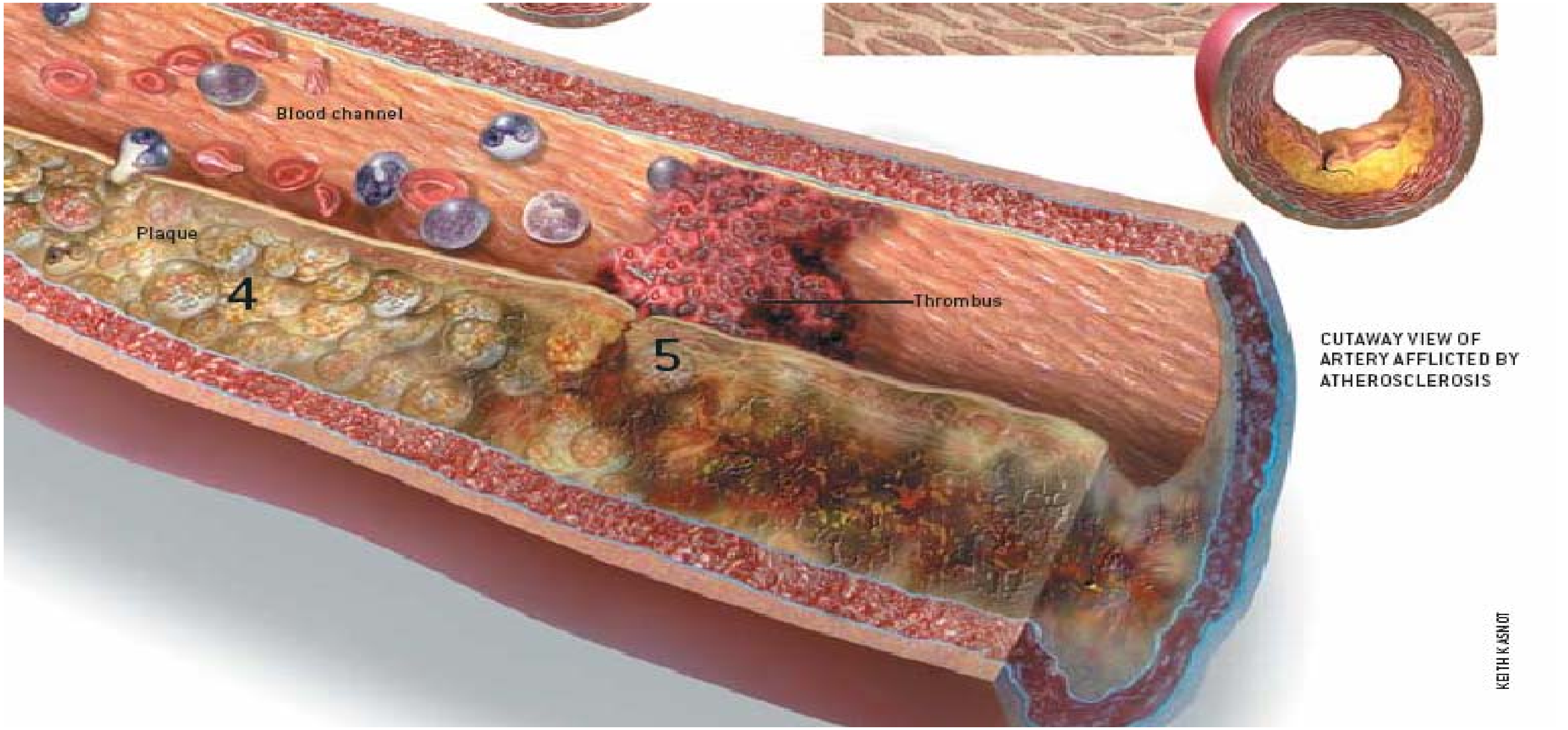


Contact printing
Wetted pin
In situ fabrication using photolithography
Light at 365 nm
Mask
Inkjet printing
Nozzle
Substrate
Photosensitive chemical
In situ fabrication using inkjet
Nozzle
Nucleotide
Repeat
Nucleotide with photosensitive chemical

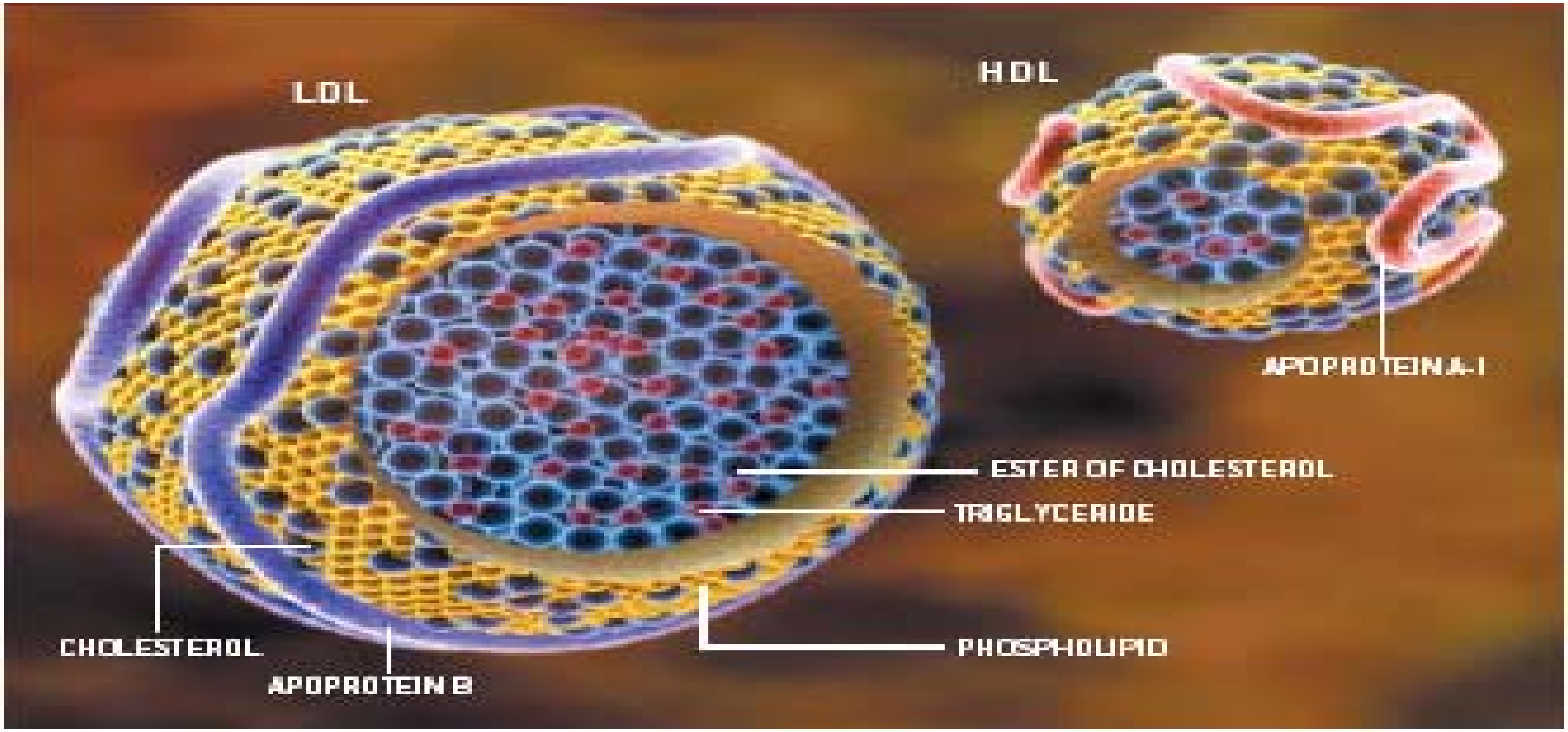
Atherosclerosis (1-3 stages)



Atherosclerosis (4-5 stages)



LDL, HDL



LDL
HDL
APOPROTEIN A-I
ESTER OF CHOLESTEROL
TRIGLYCERIDE
CHOLESTEROL
APOPROTEIN B
PHOSPHOLIPID

Detection of Biomolecules Using In_2O_3 Nanowires

Chao Li, Daihua Zhang, Bo Lei, and Chongwu Zhou
Dept. of Electrical Engineering - Electrophysics
University of Southern California

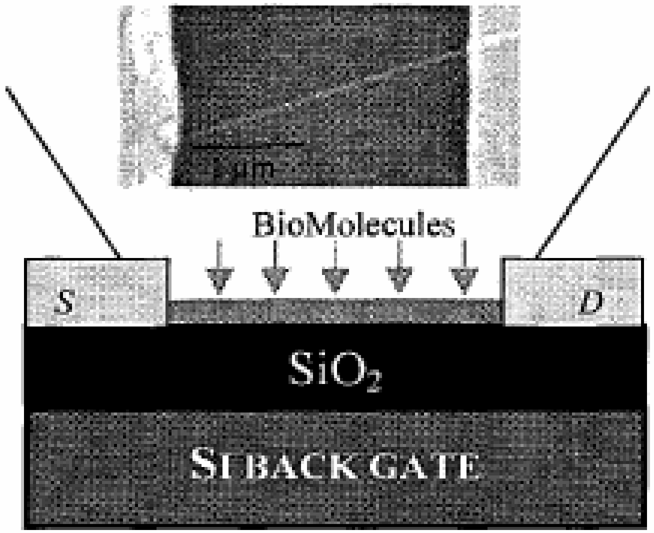


Figure 1. Scheme for molecular absorption on an In_2O_3 nanowire device and a SEM image of the device, which clearly showed a nanowire bridging drain and source electrode.

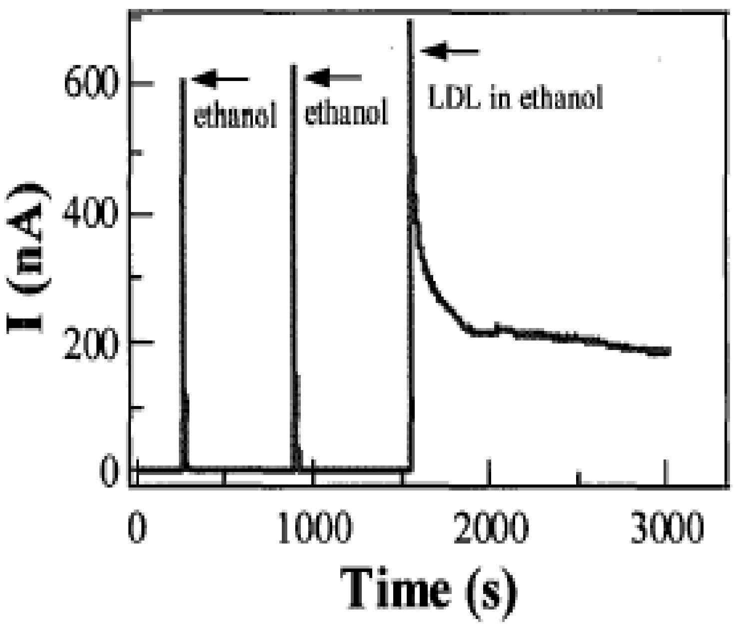
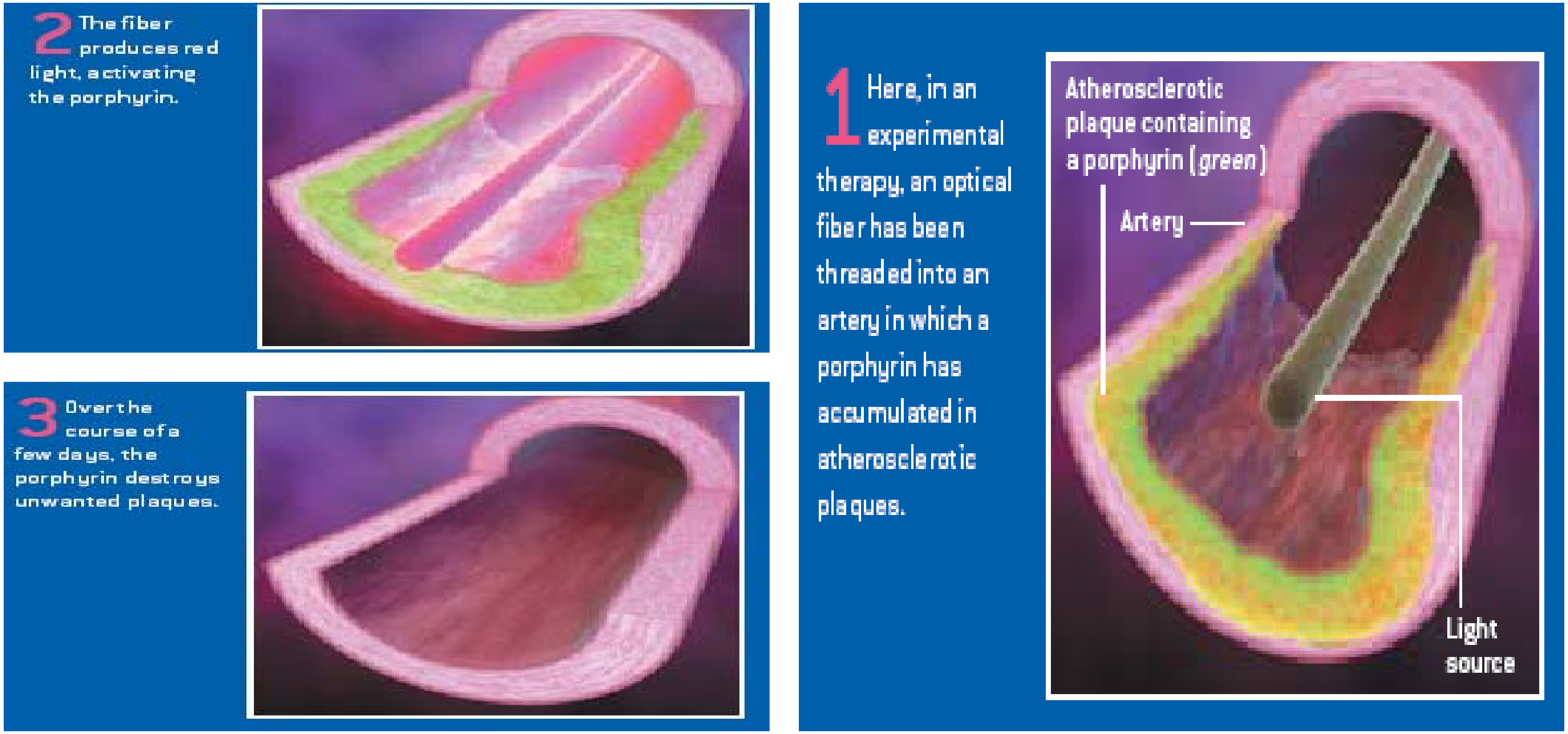


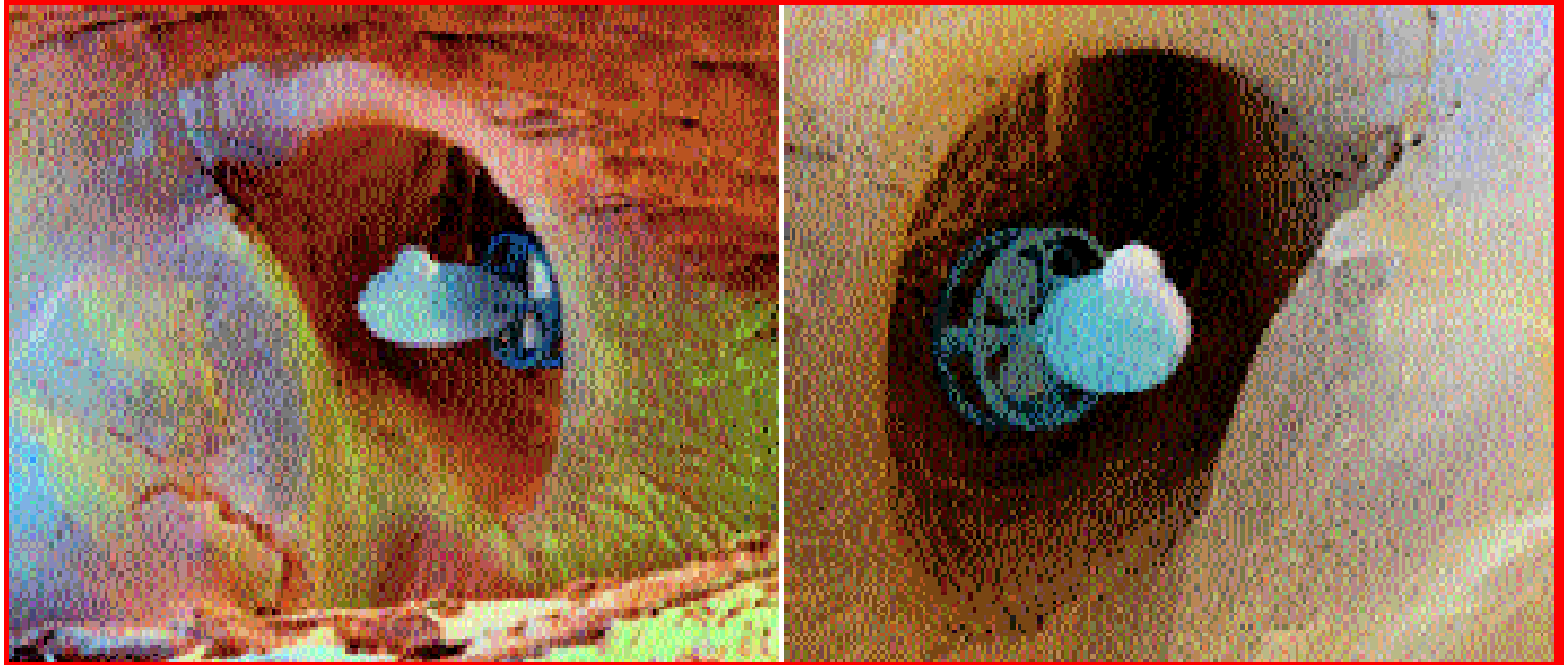
Figure 3. Time domain measurement for the device after exposure to pure ethanol twice and then LDL in ethanol.

Photodynamic therapy



Self-sufficient micro-robot

Figure 1: Microsubmarine built by Microtec.



Swimming Surgical Micro-Robot

Jon Edd[1†], Sébastien Payen[1†], Boris Rubinsky[1], Marshall L. Stoller[2], and Metin Sitti[3]

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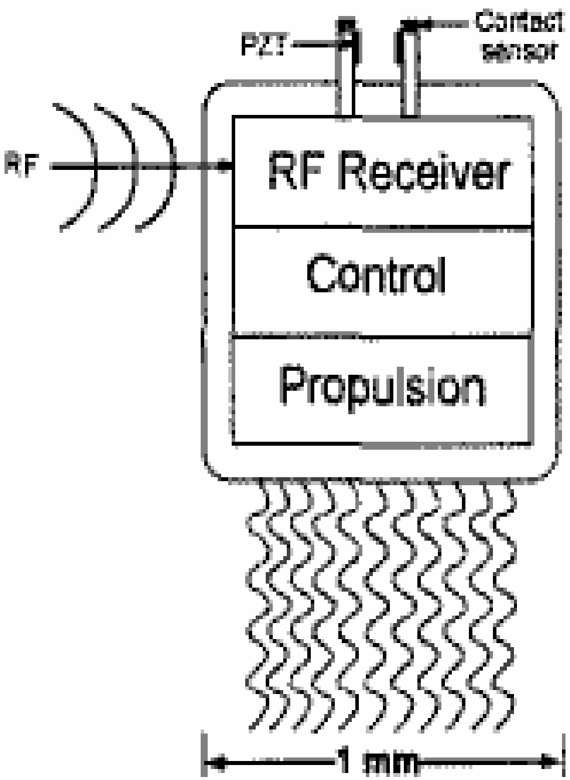
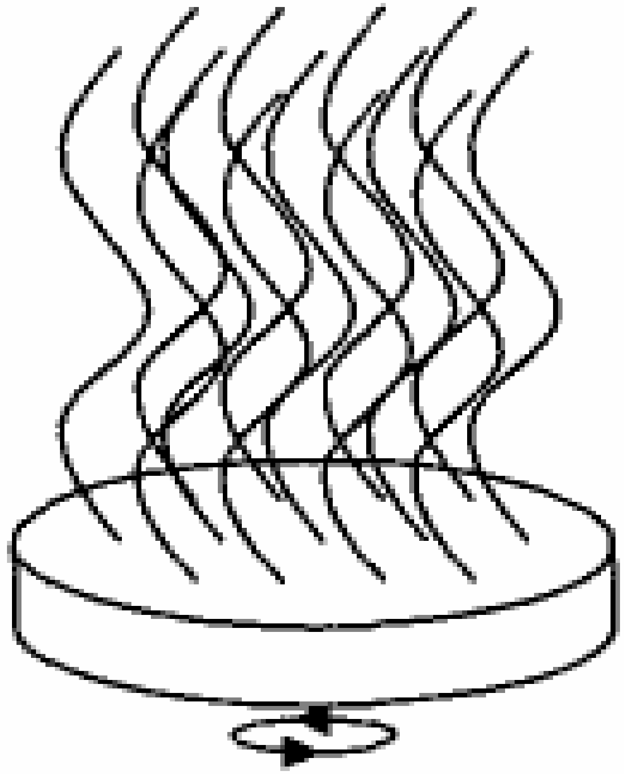
[2]Department of Urology, University of California, San Francisco, CA 94143
[3]Dept. of Mechanical Eng. and Robotics Institute, Carnegie Mellon University, PA 15213
{jonedd, spayen, rubinsky}@me.berkeley.edu, mstoller@urol.ucsf.edu, sitti@cmu.edu





DETC2004
ASME Design Engineering Technical Conferences
28th Biennial Mechanisms and Robotics Conference
Salt Lake City, Utah, USA, September 28 to October 2, 2004

NANOROBOTICS CONTROL DESIGN: A PRACTICAL APPROACH TUTORIAL

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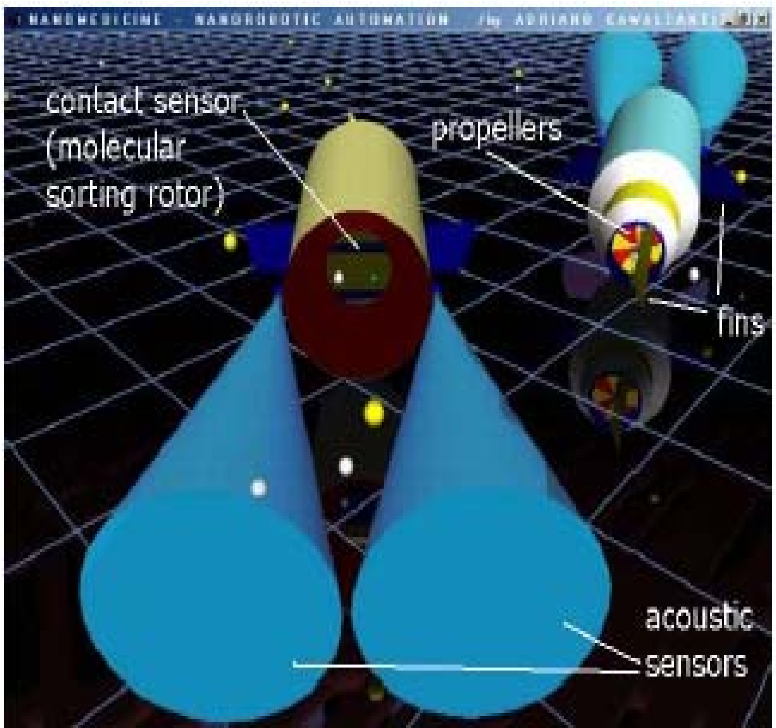


Fig. 2. Molecular identification.

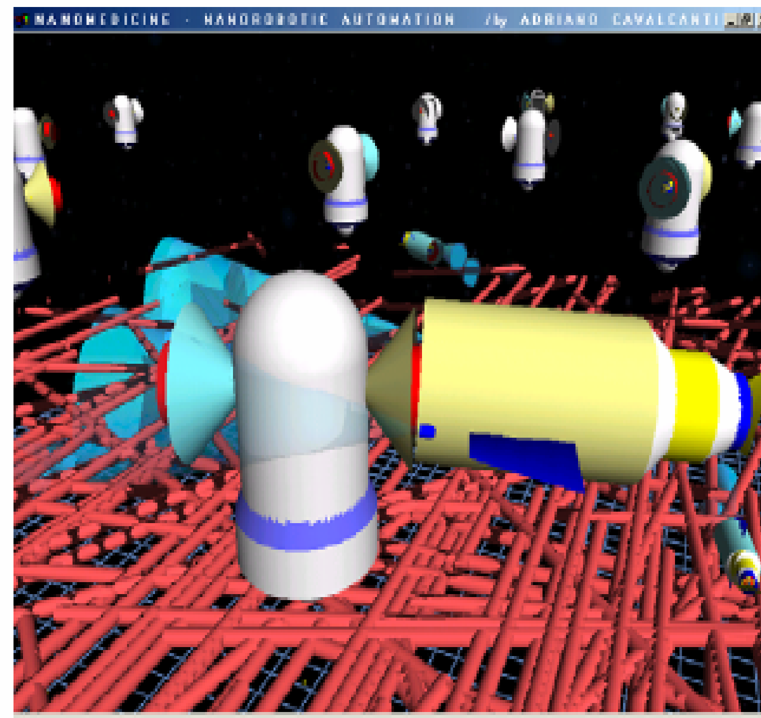
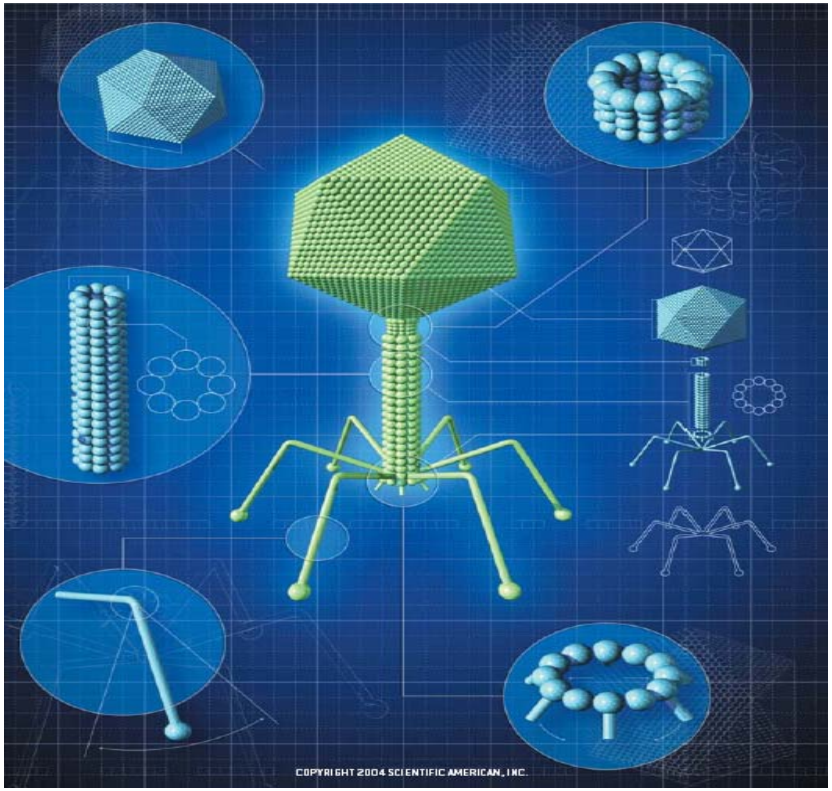


Fig. 3. Nanorobot molecule delivery.

Nanorobots


NCD - NANOROBOT CONTROL DESIGN
by ADRIANO CAVALCANTI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Artificial heart

Future