Montpellier, September 15, 2009

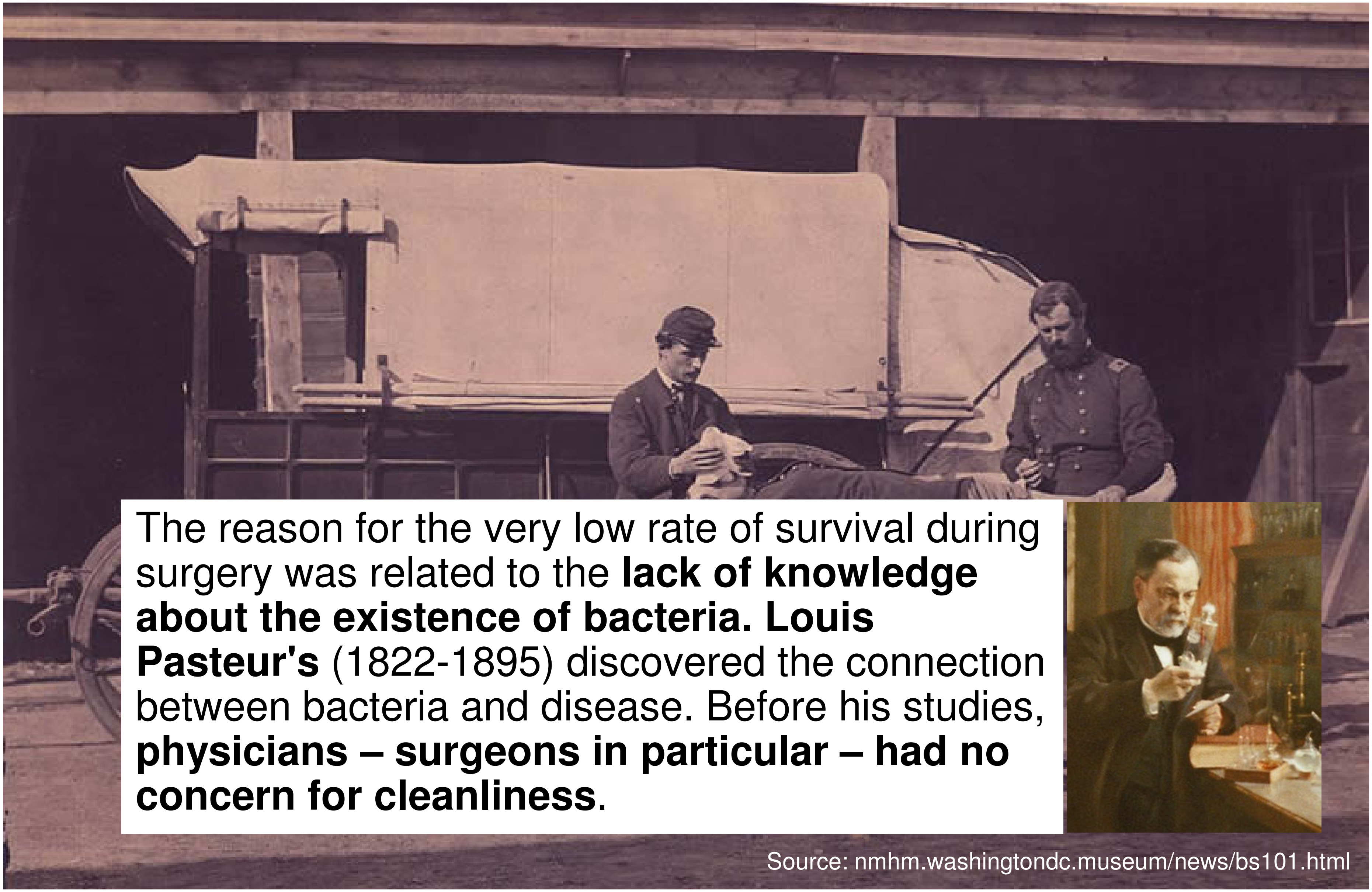
4th Summer School in Surgical Robotics

Future Trends in Surgical Robotics

Cesare Stefanini

Scuola Superiore Sant'Anna, Pisa

Before the birth of modern surgery: The operating room in the 1860-1870



The reason for the very low rate of survival during surgery was related to the **lack of knowledge about the existence of bacteria. Louis Pasteur's** (1822-1895) discovered the connection between bacteria and disease. Before his studies, **physicians – surgeons in particular – had no concern for cleanliness**.

Source: nmhm.washingtondc.museum/news/bs101.html

Convergence to Modern Surgery

- Anesthetics
- Antiseptics
- Anticoagulants
- Antibiotics
- Analgesics

→ Modern surgery

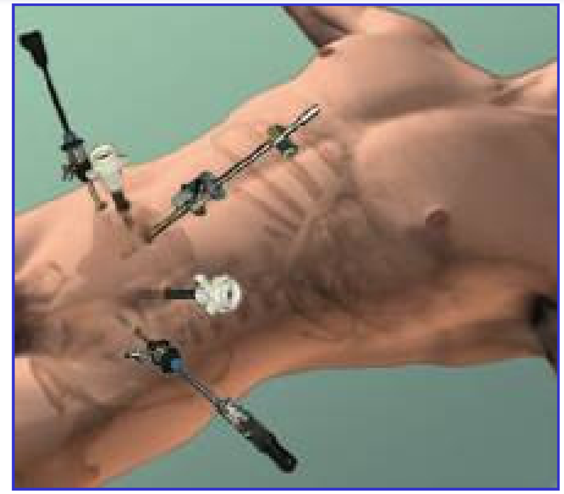
The operating room in the 20th century

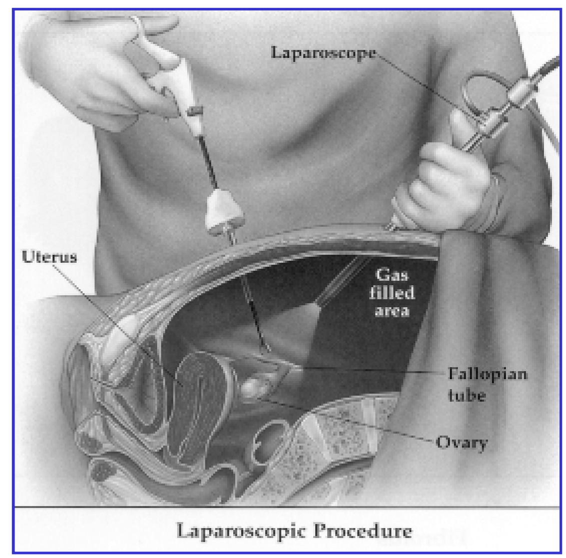
Minimally Invasive Surgery

- Anesthetics
- Antiseptics
- Anticoagulants
- Antibiotics
- Analgesics

→ Modern surgery

Modern surgery + Endoscopic instruments → Minimally invasive Surgery

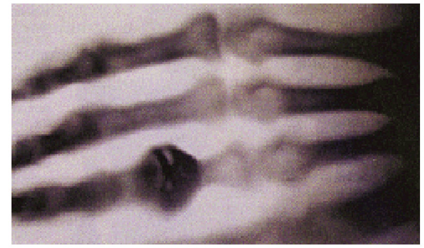


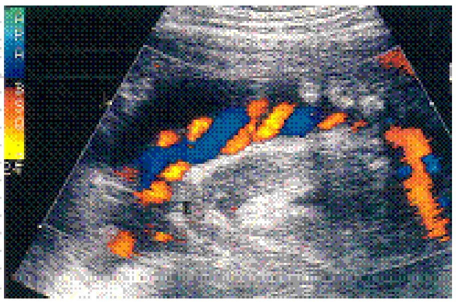


1987: Mouret in Lyon published the first laparoscopic cholecystectomy using video - technique

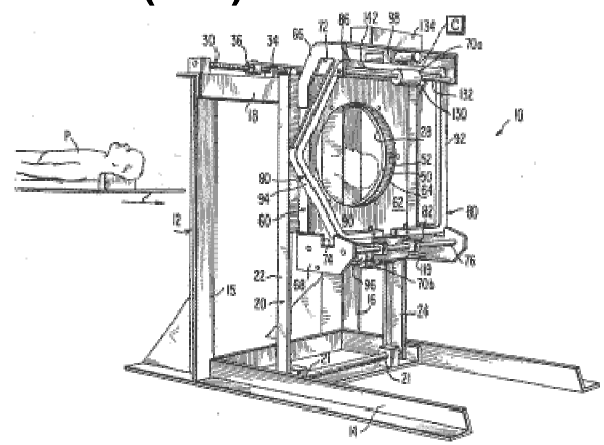
The role of imaging techniques in the evolution of surgery

1895: Röntgen (accidentally) discovered an image cast from his cathode ray generator

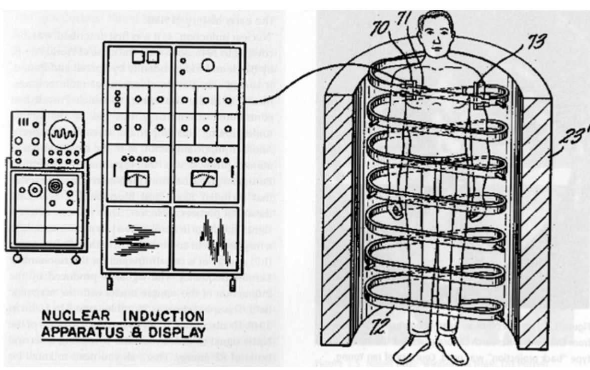




1947-9: Ultrasonic energy was first applied to the human body for medical purposes by George Ludwig at the Naval Medical Research Institute, Bethesda (MD).

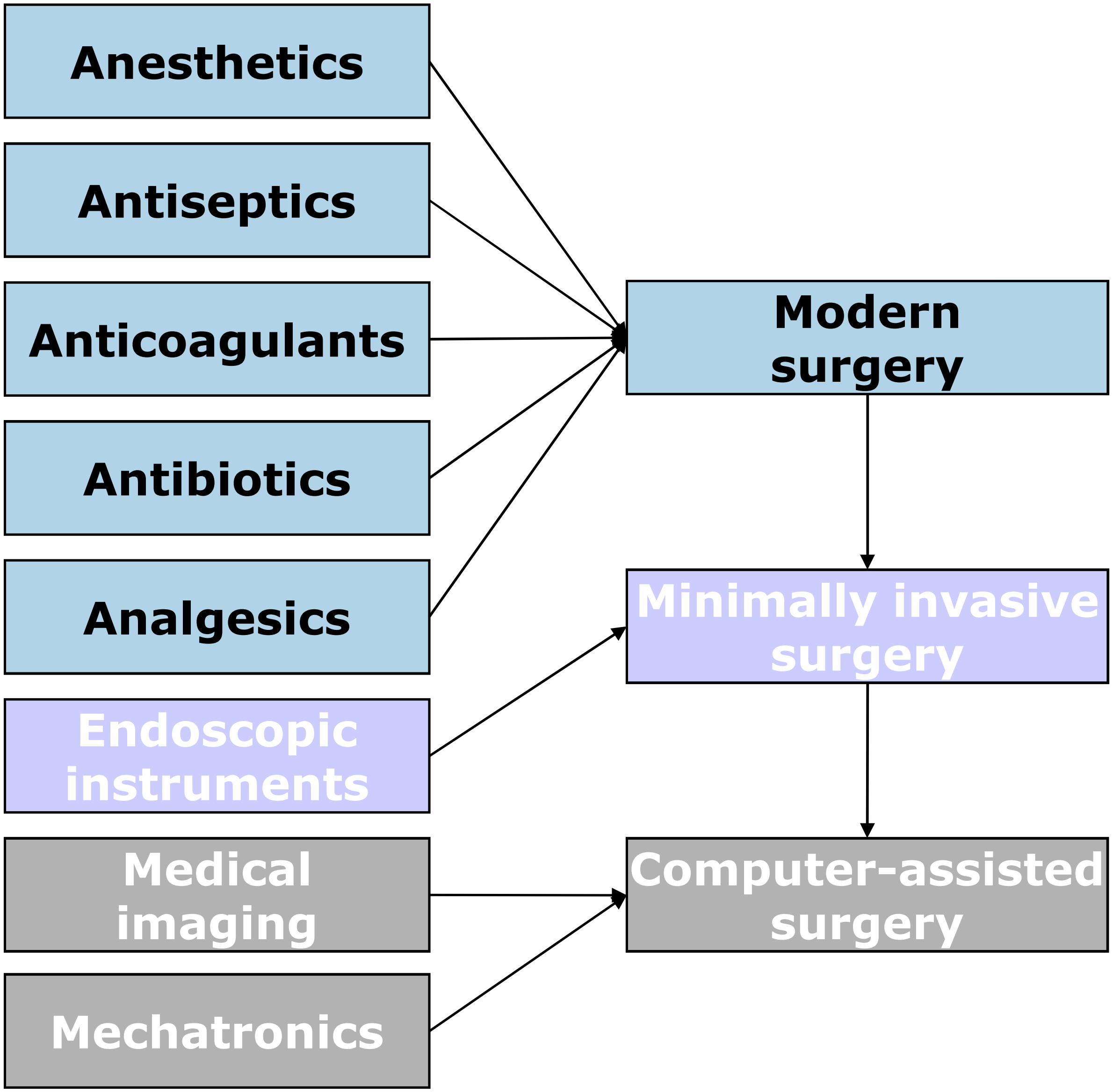


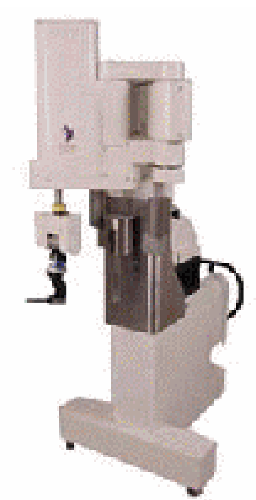
1975: Robert S. Ledley patent #3,922,552 was granted for a "diagnostic X-ray systems" also known as whole body CAT-Scans.

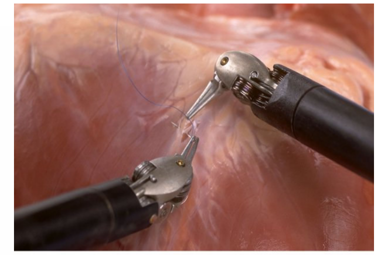


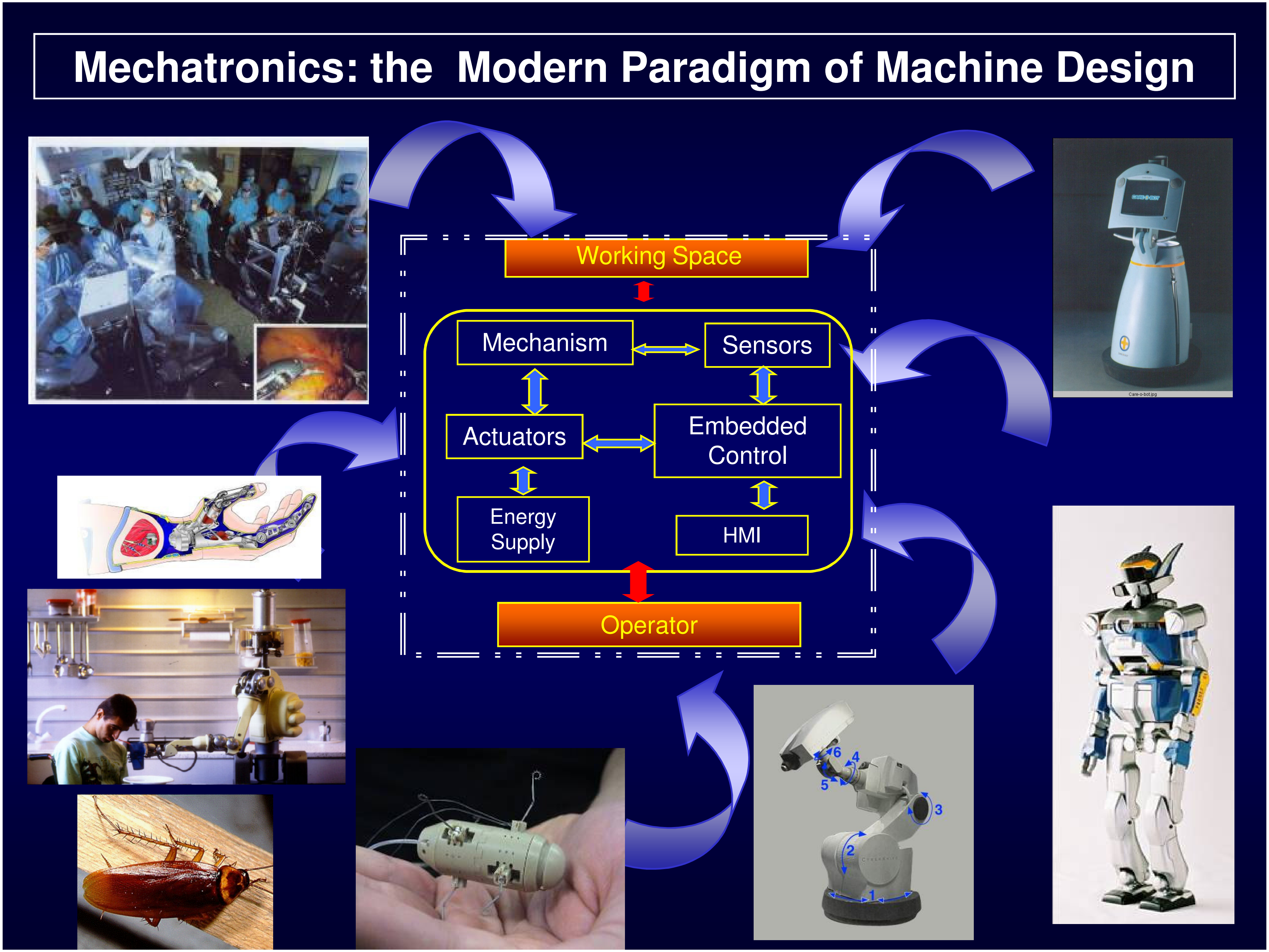
1977: first image of in vivo human anatomy using MRI, a cross section through a finger.

Convergence to Computer Assisted and Robotic Surgery



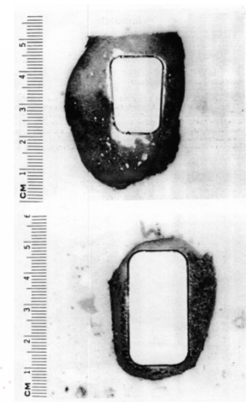





Mechatronics: the Modern Paradigm of Machine Design
Working Space
Mechanism
Sensors
Actuators
Embedded Control
Energy Supply
HMI
Operator
6
4
5
3
2
1

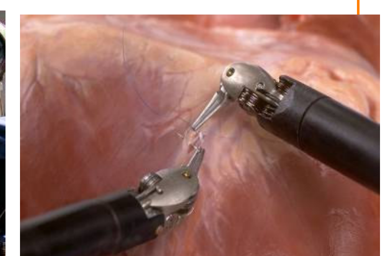
In the '80: mechatronics and robotics as the paradigm of modern machine design for obtaining...

+ Accuracy
+ Predictability
+ Repeatability



= Quality

...also in surgery

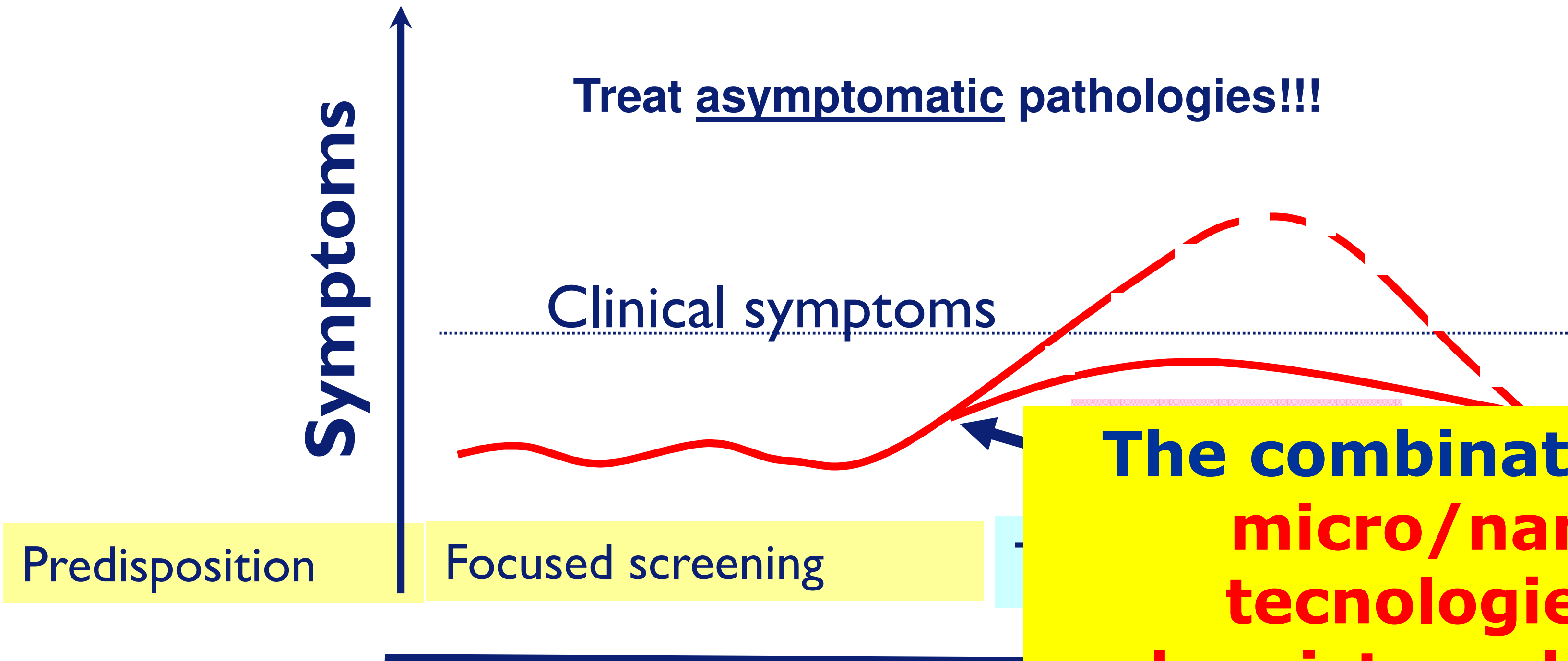


What is next ?

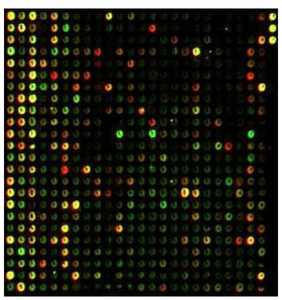
[Future Trends in Surgical Robotics]

Prevention: the role of modern medicine

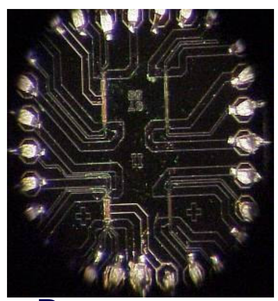
Courtesy by Philips



The combination of micro/nano tecnologies, chemistry, physics and microrobotics will be one of the key technologies enabling future high quality, early and minimal invasive surgery



Gene Chip



Biosensor

Molecular Diagnostics

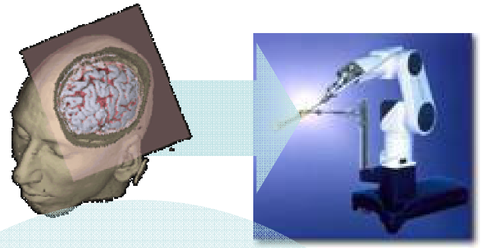
Tomorrow’s technol

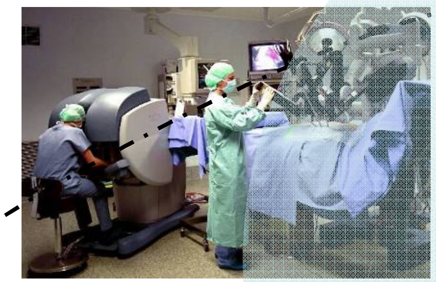
and imaging & molecular therapy

The Evolution of Surgery

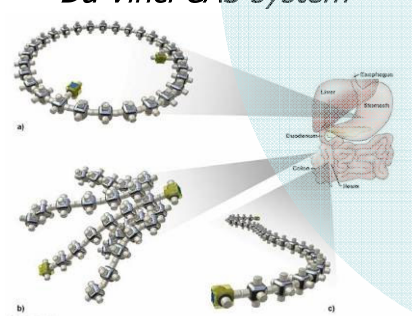
TRADITIONAL SURGERY

MINIMALLY INVASIVE SURGERY

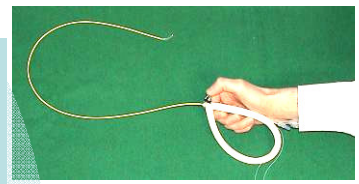




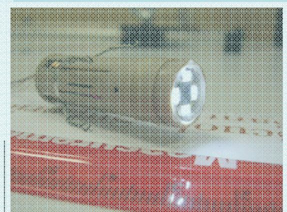
Da Vinci CAS system



ENDOLUMINAL SURGERY



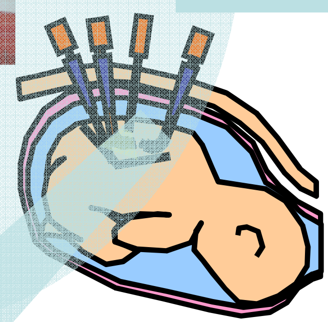
Micro-endoscope for spinal cord

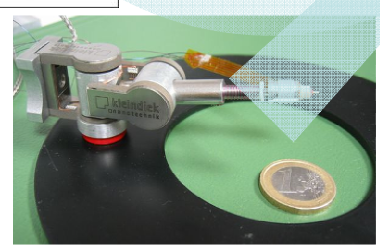


Endoscopic capsules

Reconfigurable surgical systems

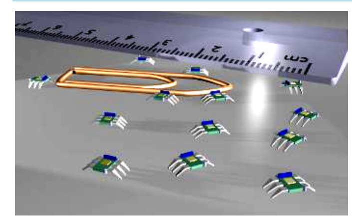
FETAL SURGERY

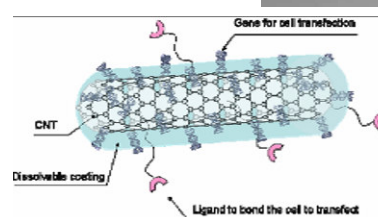




Force-feedback scissor for fetal surgery

CELL SURGERY





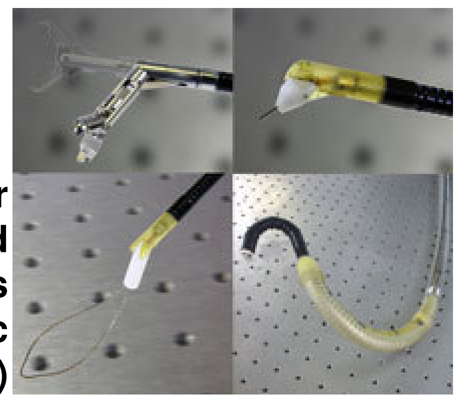
Artificial virus for cell therapy

CRIM

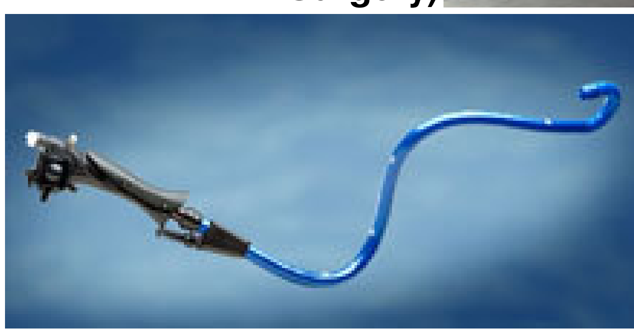
What is Endoluminal Surgery?

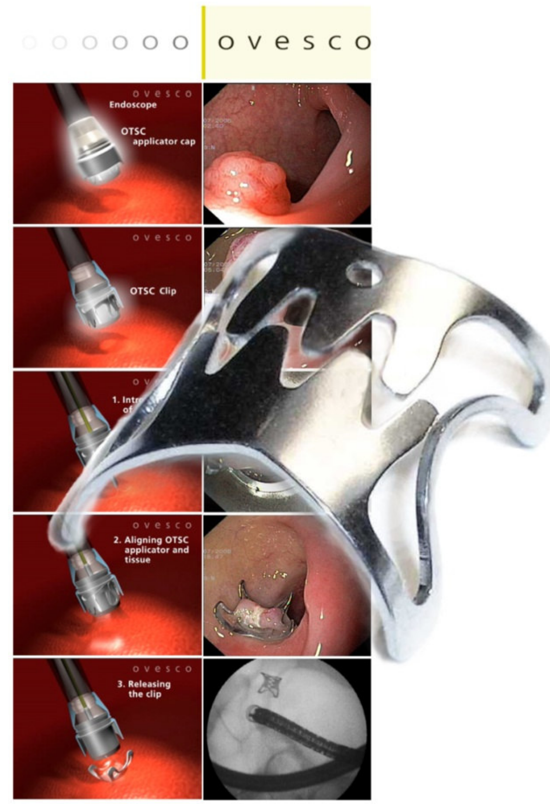
Endoluminal procedures consist of bringing a set of advanced therapeutic and surgical tools to the area of interest by navigating in the *lumina* of the human body, such as the gastrointestinal tract, the urinary apparatus, the circulatory system, etc., with a scarless or minimally invasive access

PillCam for GI tract endoscopy



Instrumentation for endoscopic surgery and NOTES (Natural Orifices Transgastric Endoscopic Surgery)





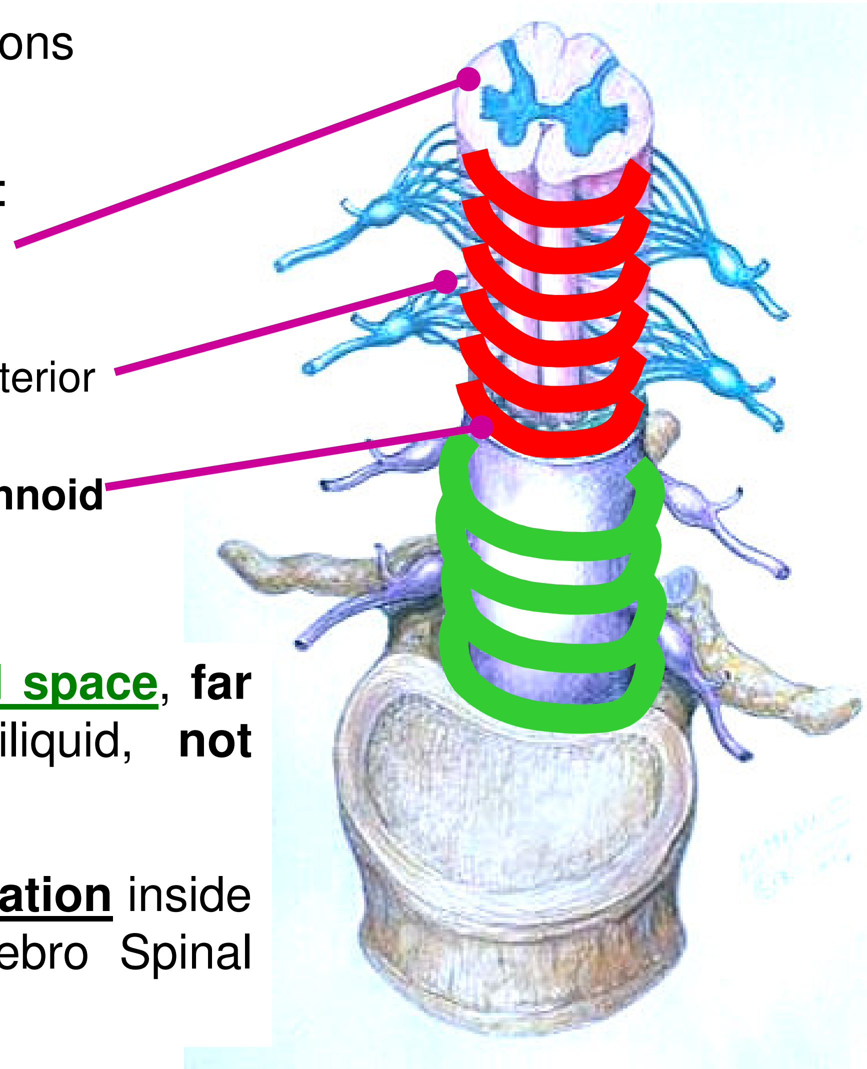
Clip for endoscopic surgery

The Neuroendoscope: an example of new endoluminal ultraminiature tool

NeuroEndoscopy of the spinal cord
the Problem

There is a need for:

- Precise and early diagnosis of spinal cord lesions (300.000 paralyzed persons in Europe)
- Possibility to intervene directly on pathologies:
  - Injection of neurotransmitters and pumping of haematomas in **traumatic lesions**
  - Electro-coagulation of the afferences to the posterior horn in case of **intractable pain**
  - Cleaning of fibrous adherences in case of **arachnoid proliferation**

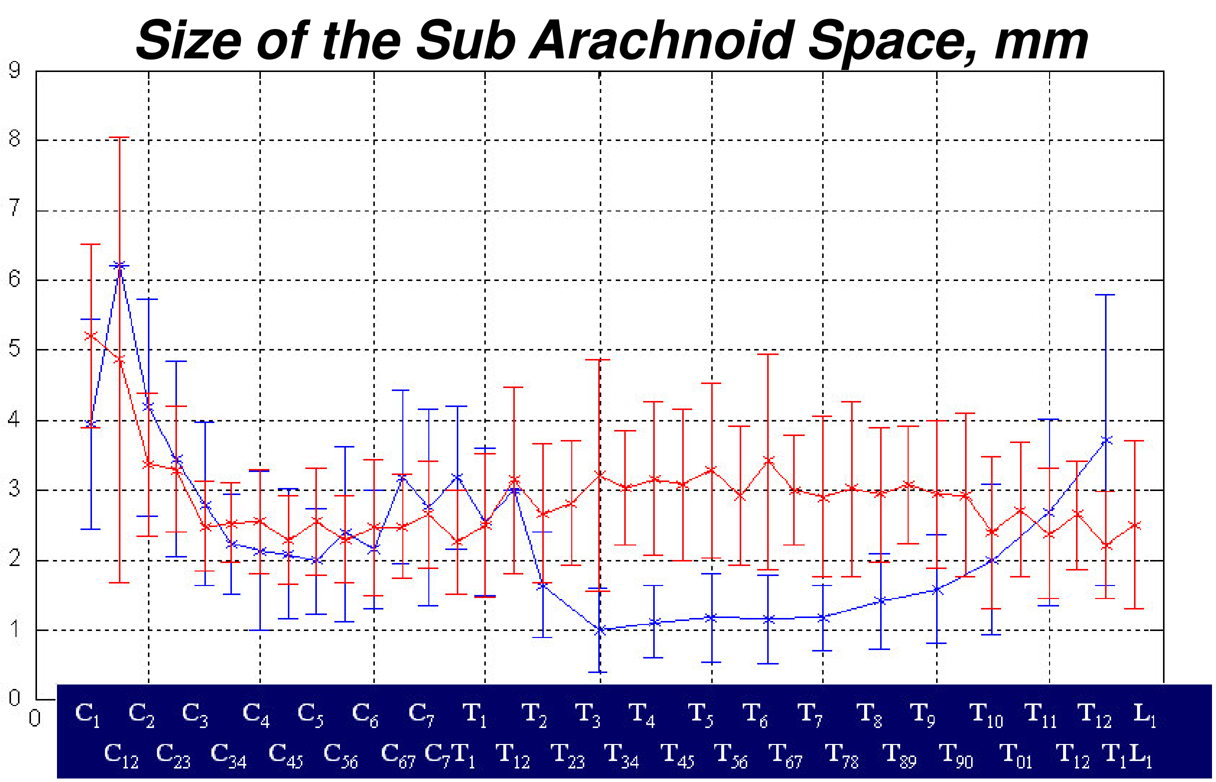


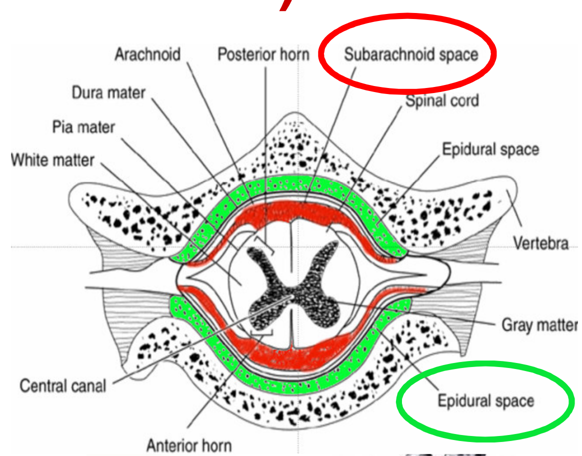
Current procedures are limited to the epidural space, **far** from the spinal cord and filled by semiliquid, **not transparent** fat.

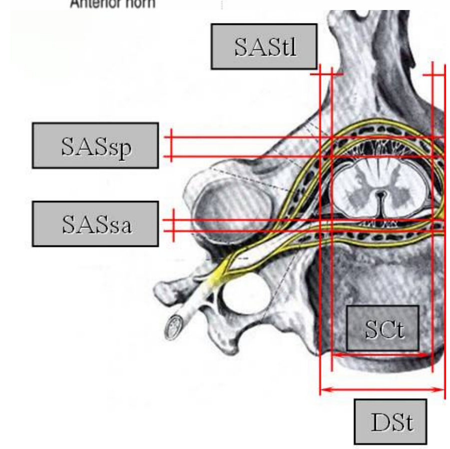
An Endoscopic System is needed for the **navigation** inside the **subarachnoid space** (filled by the Cerebro Spinal Fluid), for diagnosis and intervention.

Neuroendoscopy of Spinal Cord
The environment

- The mean is suitable for navigation (Cerebro-Spinal Fluid, water-like liquid)
- The **workspace is extremely small (few millimeters)**

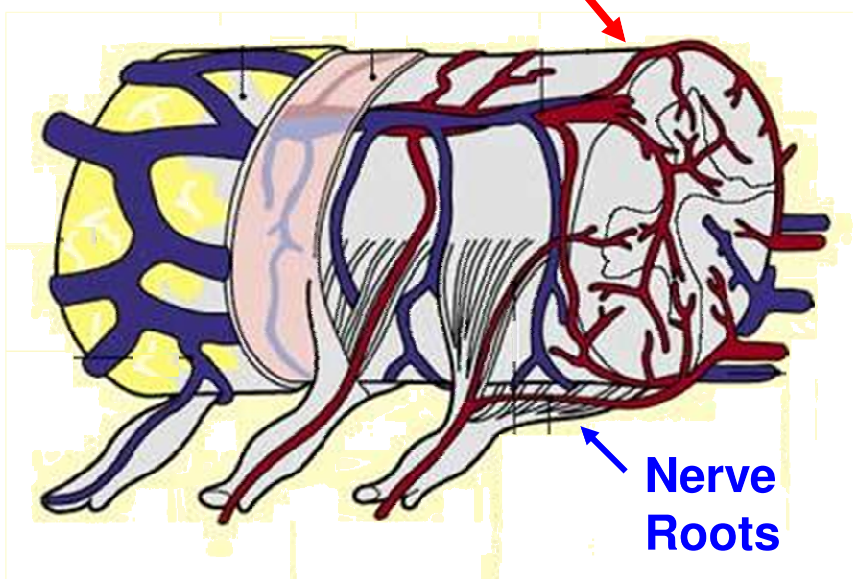




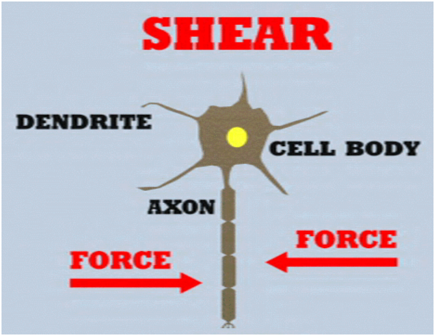


Neuroendoscopy of Spinal Cord
The environment

- The mean is very suiable for navigation (Cerebro-Spinal Fluid, water-like liquid)
- The workspace is extremely small
- Anatomical **structures are very DELICATE** (vessels, nerve roots)

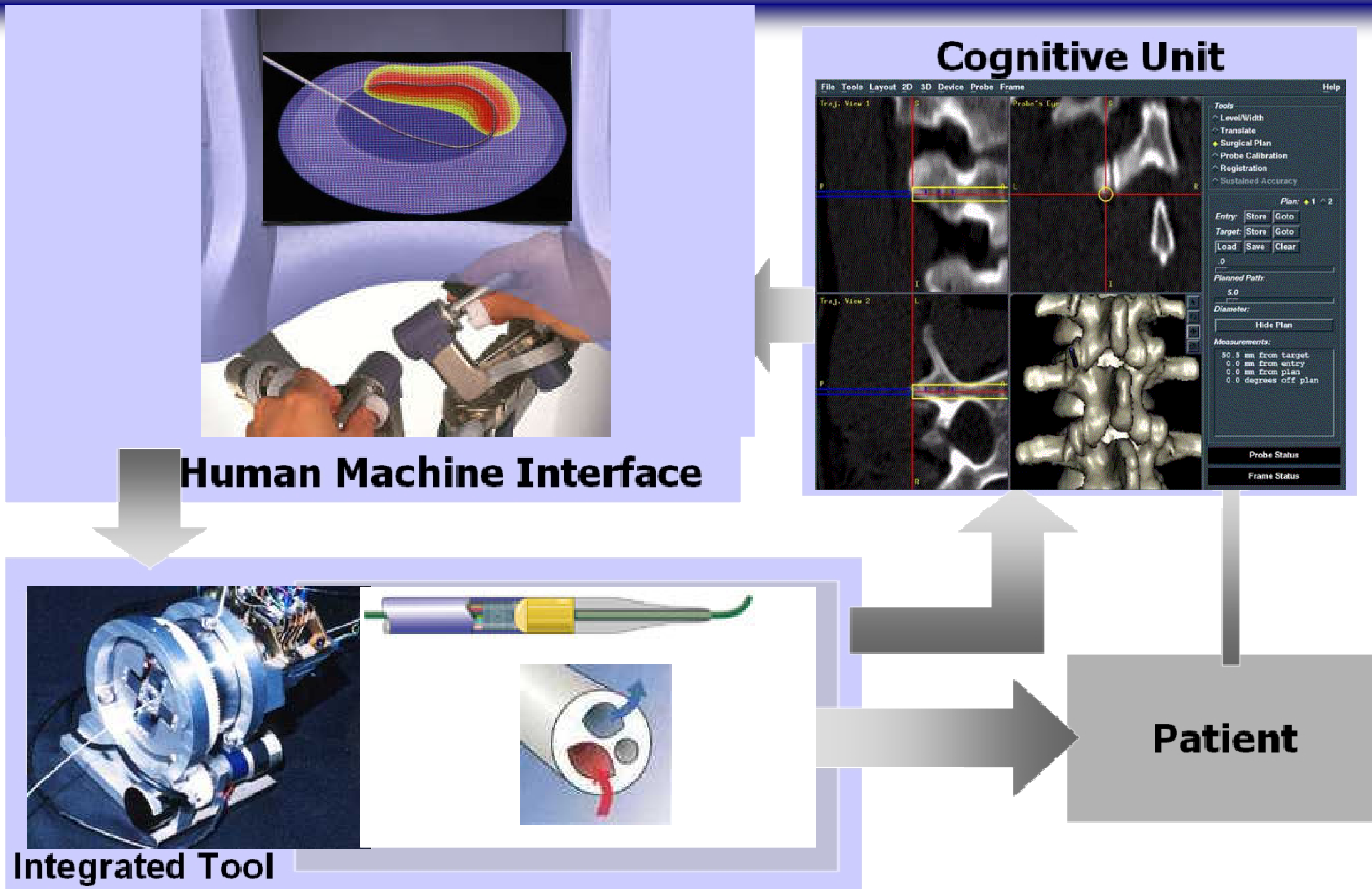


AXONAL DAMAGE



For cord tissue, shear **strains** above 15% represent severe injury.

Need for supervised-control: teleoperated endoluminal system



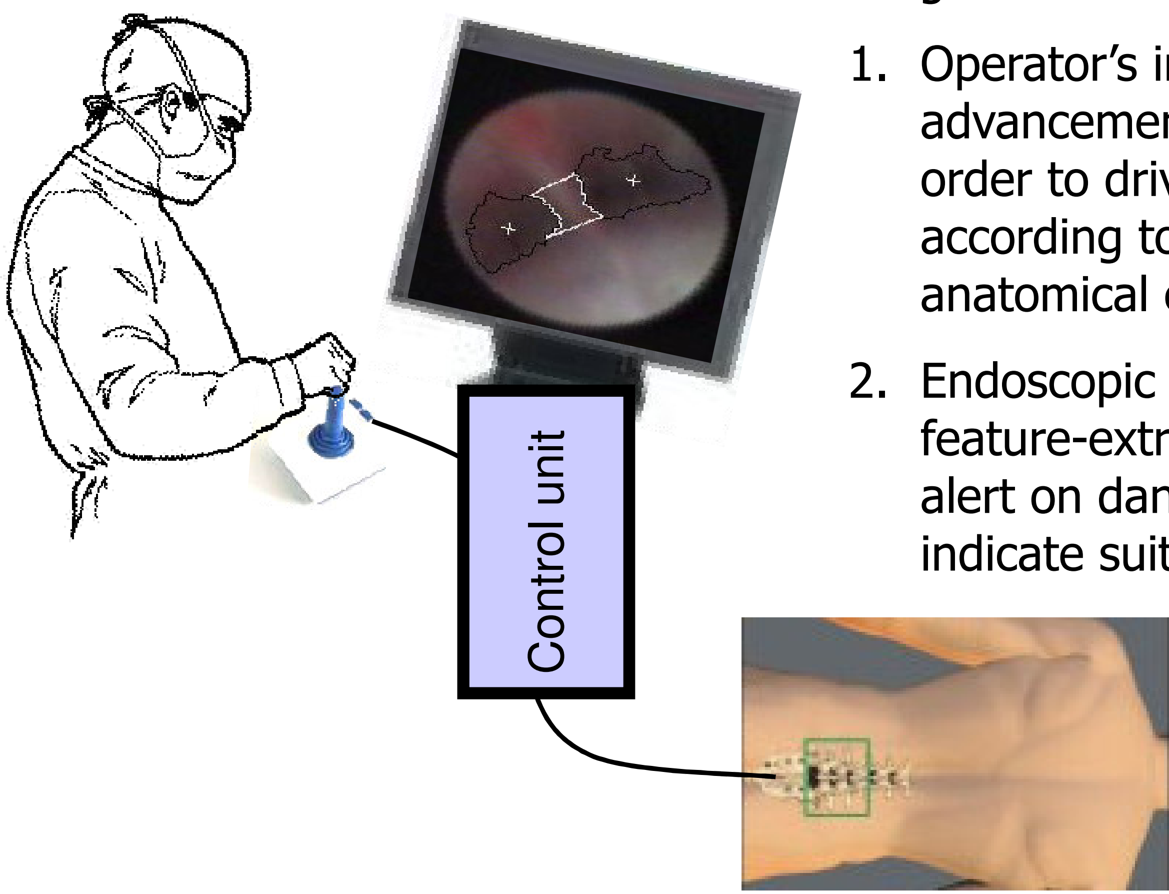
Different levels of supervised-control

Manual	The surgeon has complete control on the tip: the system just signals dangerous situations (imminent collisions,…).
Semi-automatic	***The surgeon has the general control on the steering system, but the navigation module doesn't allow him to navigate too close to delicate structures and it makes easier to find the lumen.***
Automatic	The control of the advancement and of the steering system is left to the navigation module, programmed to reach a "target".

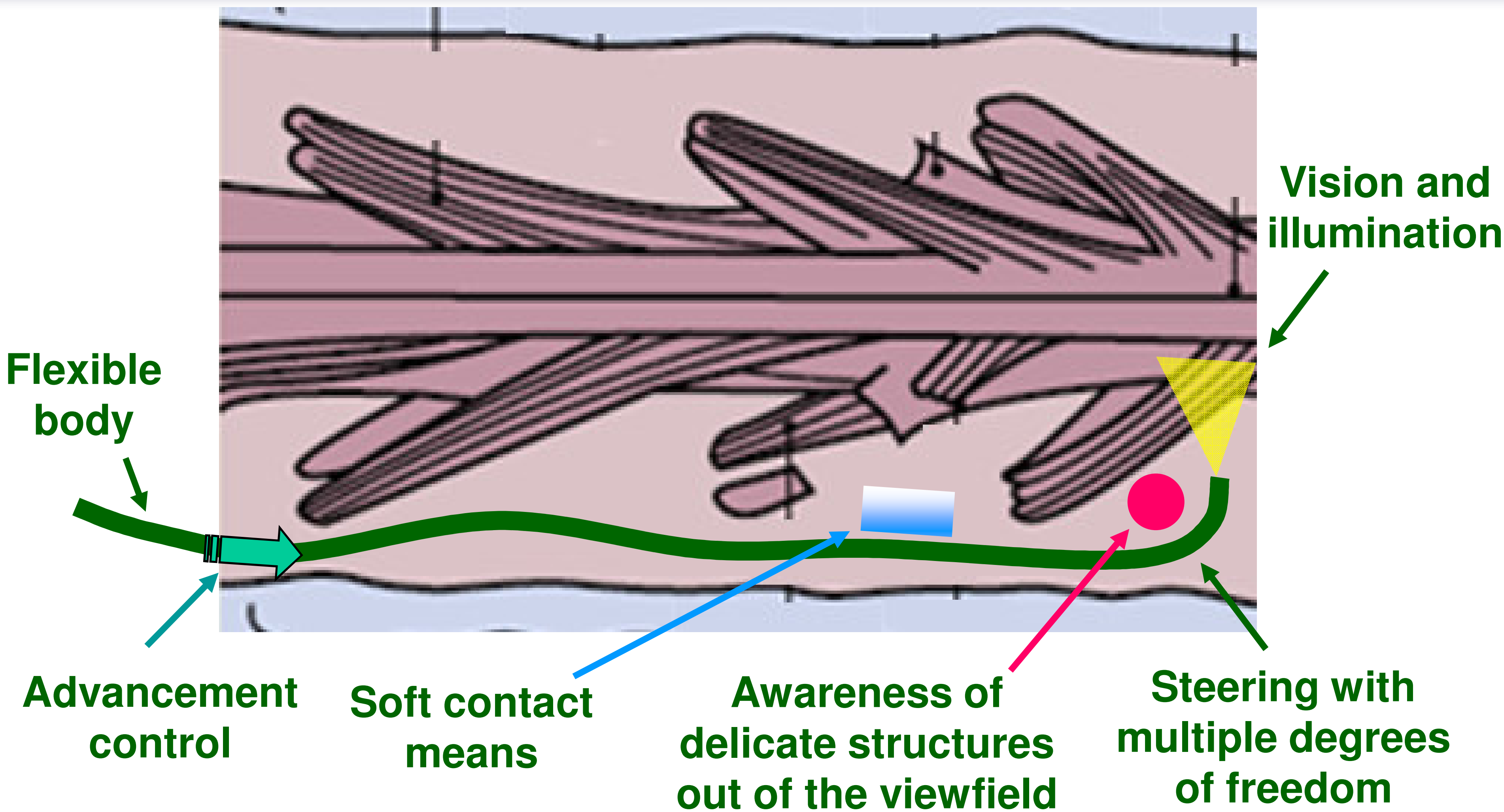
Supervised control

Surgeon's action mediated by the system:

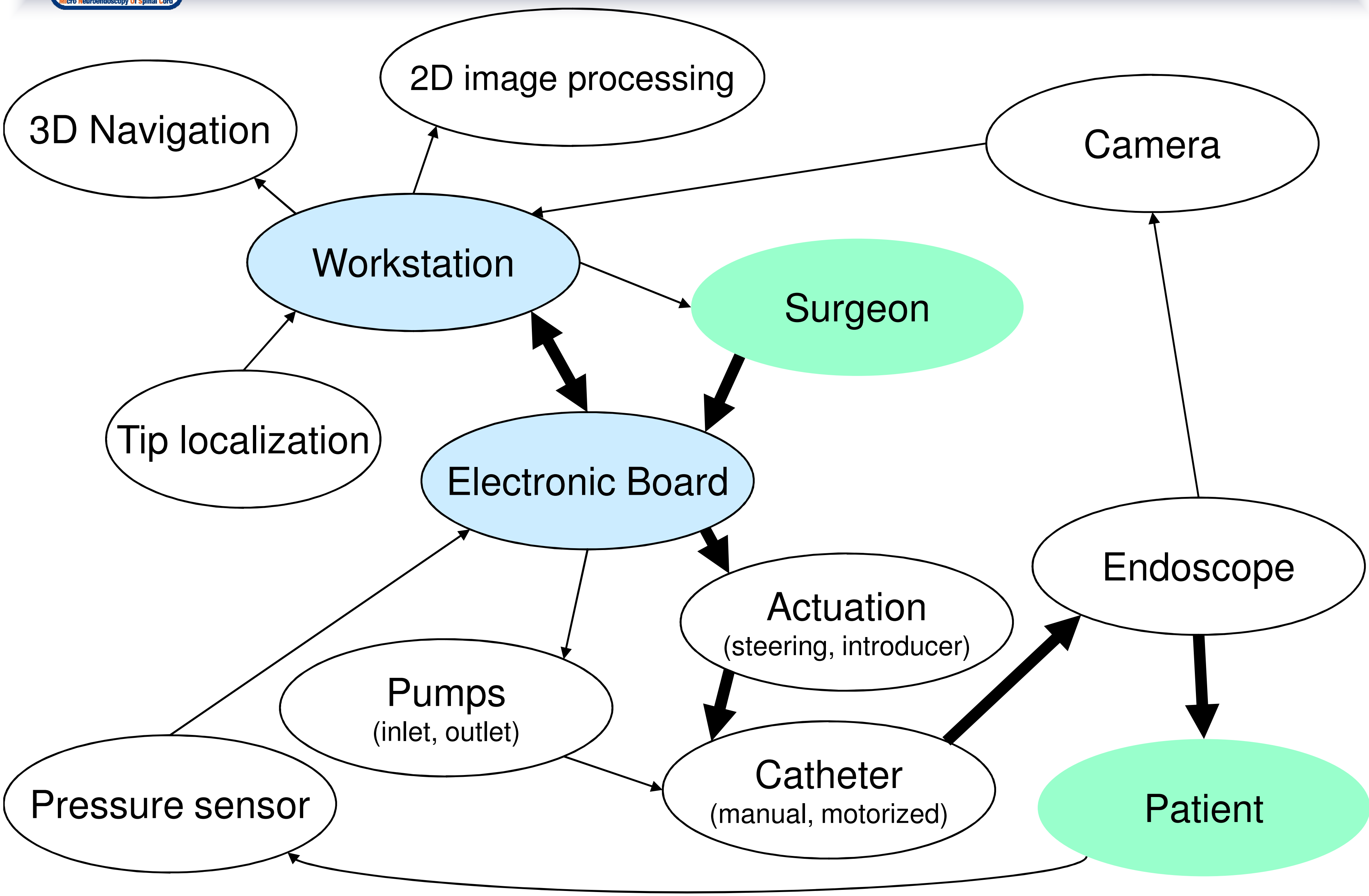
1. Operator's intentions on steering and advancement are used by a control unit in order to drive effectively the navigation according to the commands and to the anatomical constraints.
2. Endoscopic images are added with feature-extraction graphics in order to alert on dangerous structures and to indicate suitable pathways.



Functions required for navigation



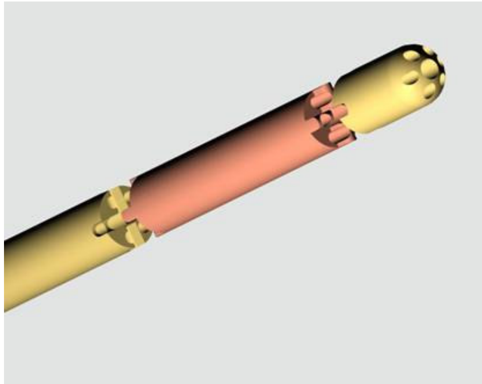
The Minosc solution - architecture

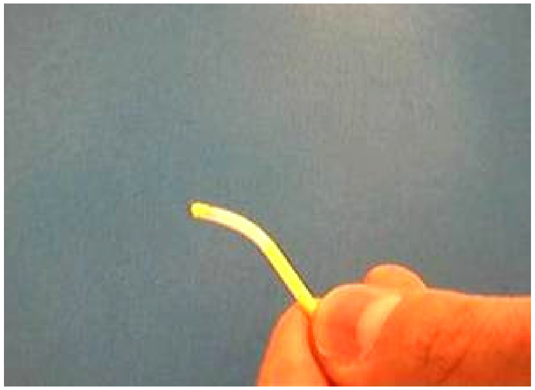


MINOSC – The **Actuated Catheter**

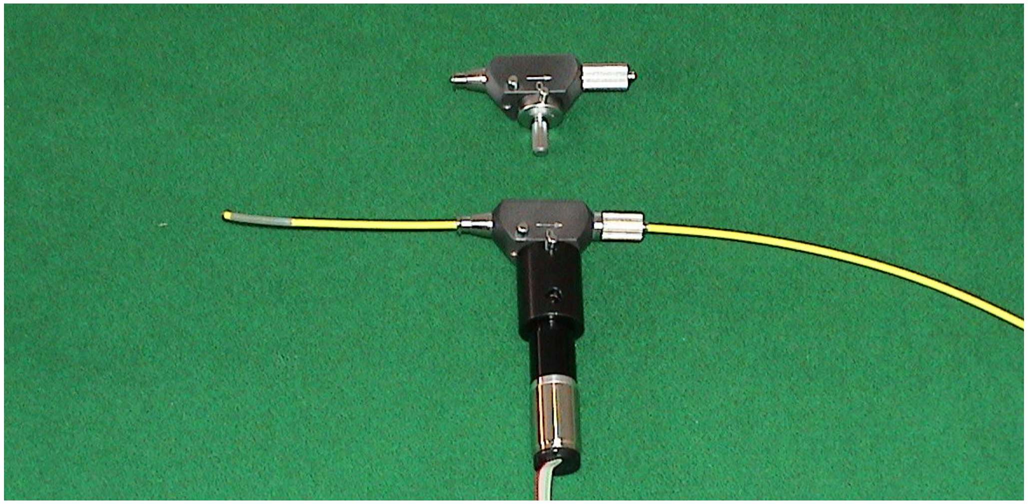
The concept:

- **Mechanical Steering** of the endoscope using *flexure joints* fabricated via Graded Material Technology and Injection Molding.



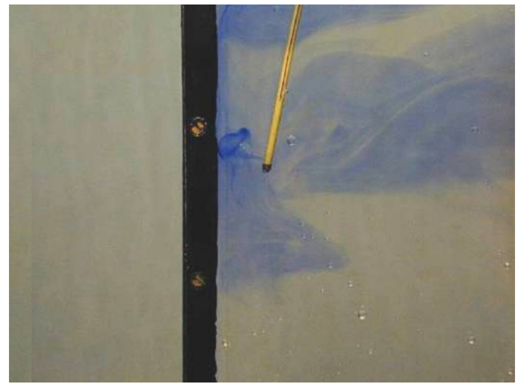


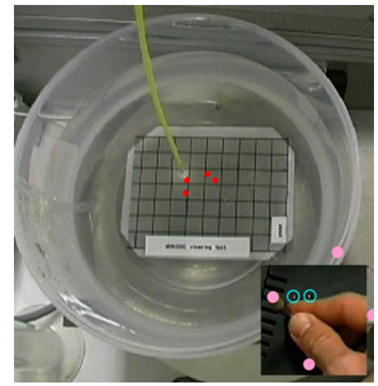
- **Servoassisted introducer** for fine and controlled advancement of the endoscope. Servomotor actuating a STORZ micromanipulator.



MINOSC – The **Fluidic System**

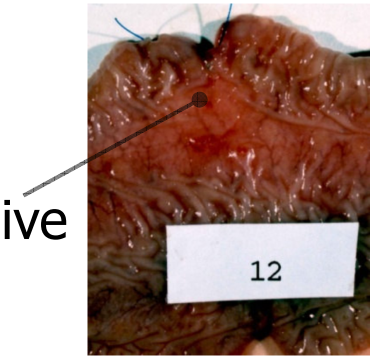
Fluidic navigation system of a microendoscope exploiting *microjets*, in order **not to touch** the tissue

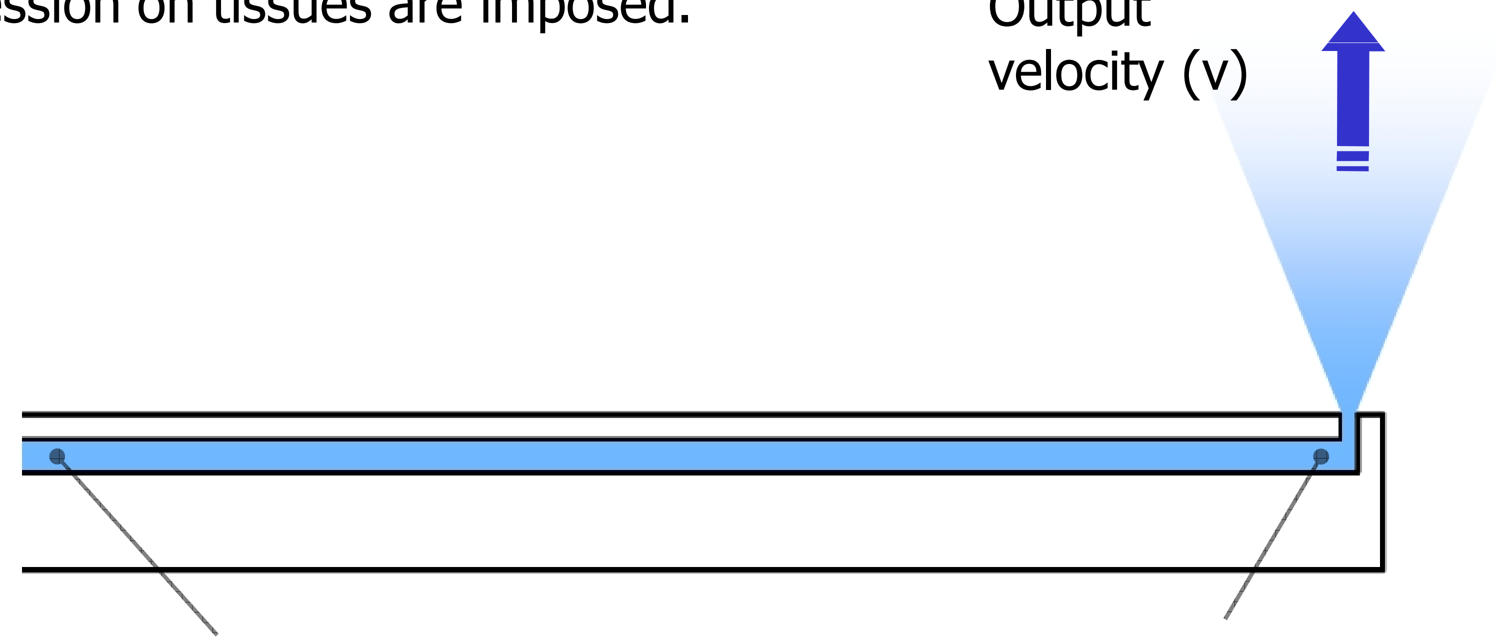




Study of the Jet

- The output velocity is the critical parameter (interaction with tissues).
- Driving pressures have therefore to be chosen once safe values for the compression on tissues are imposed.



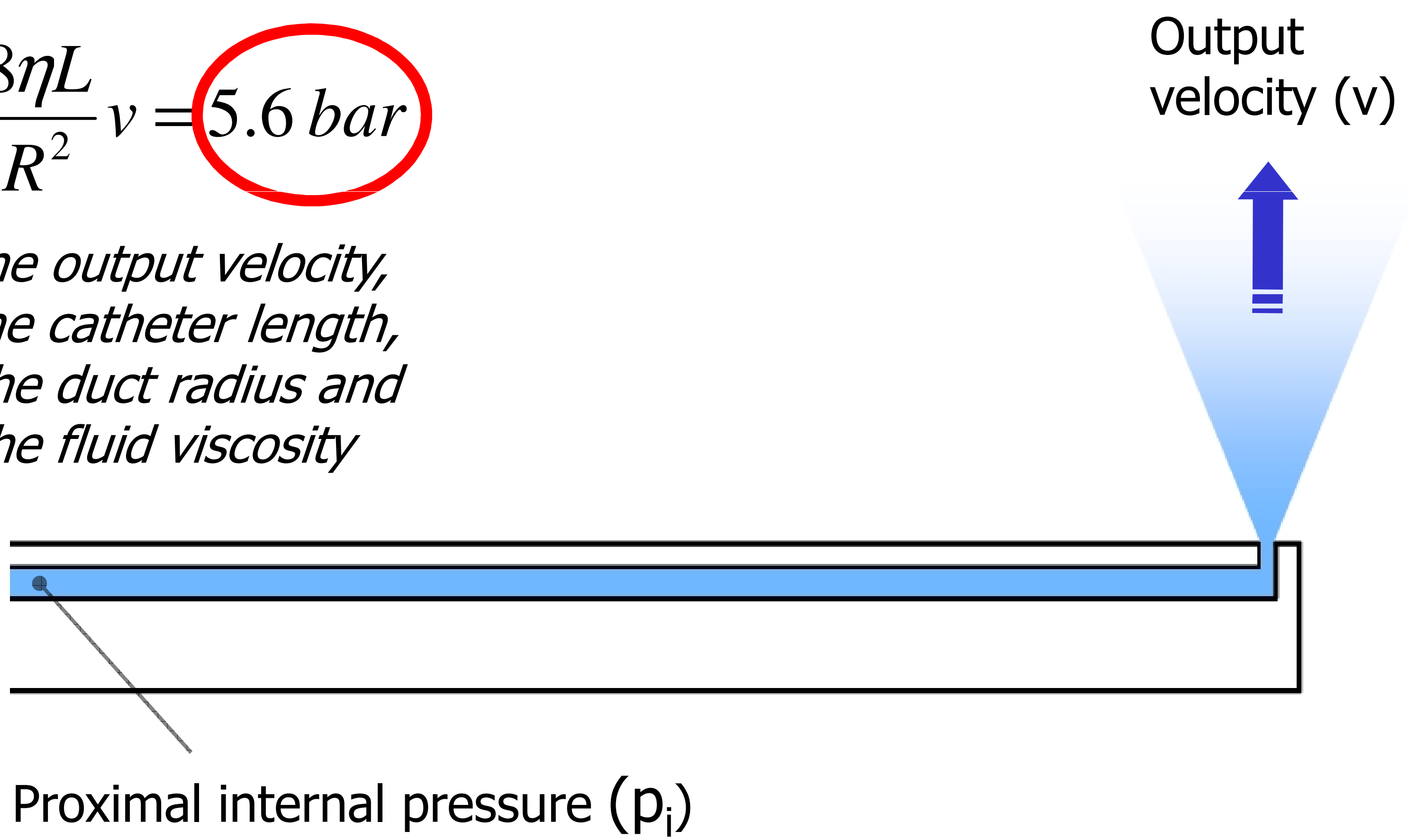


Study of the Jet

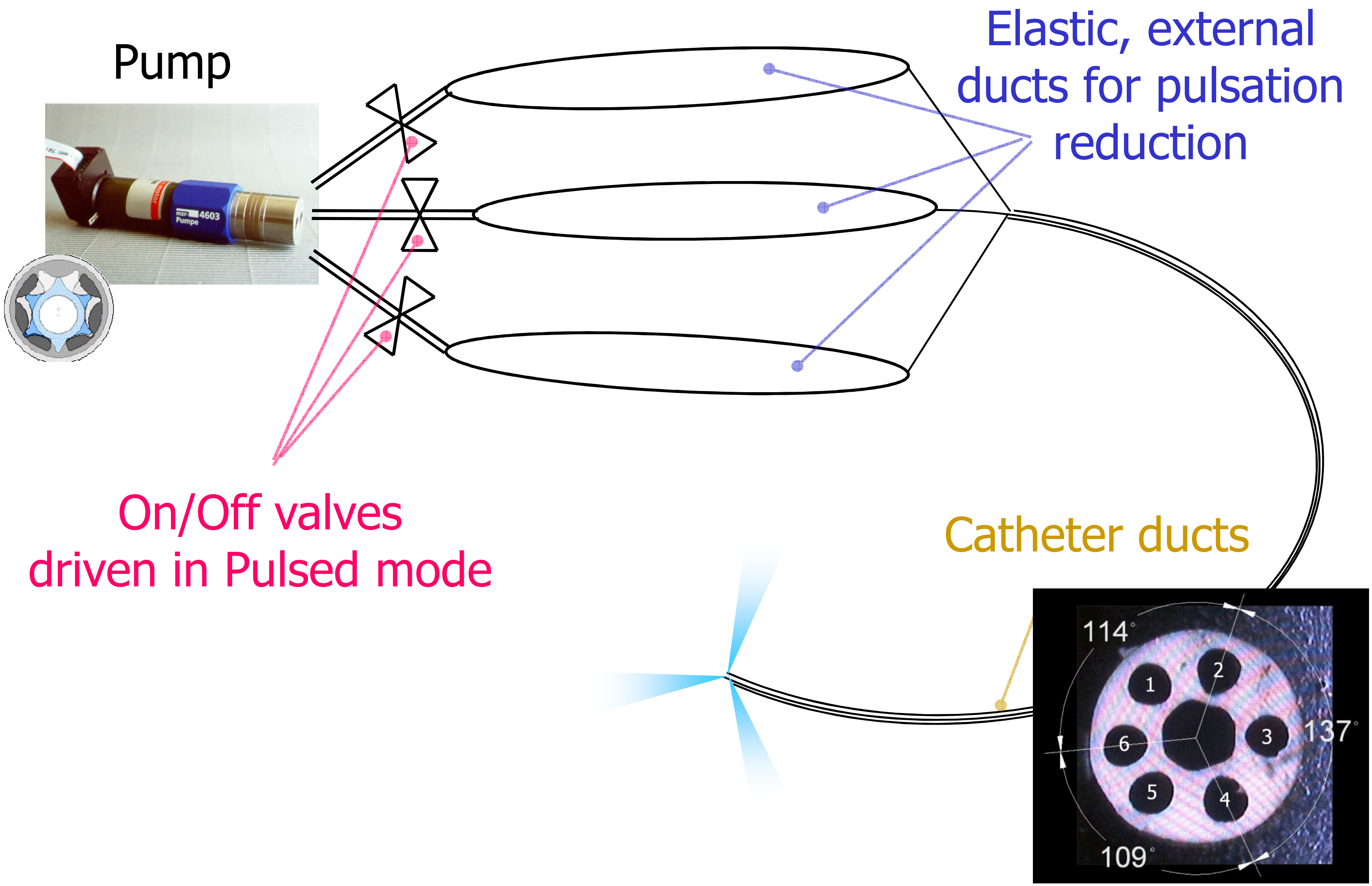
- For an output velocity of 4.4 m/s the proximal pressure to be applied at the catheter is given by the relation (Poiseuille's law):

$$p_i = \frac{8\eta L}{R^2} v = 5.6\, bar$$

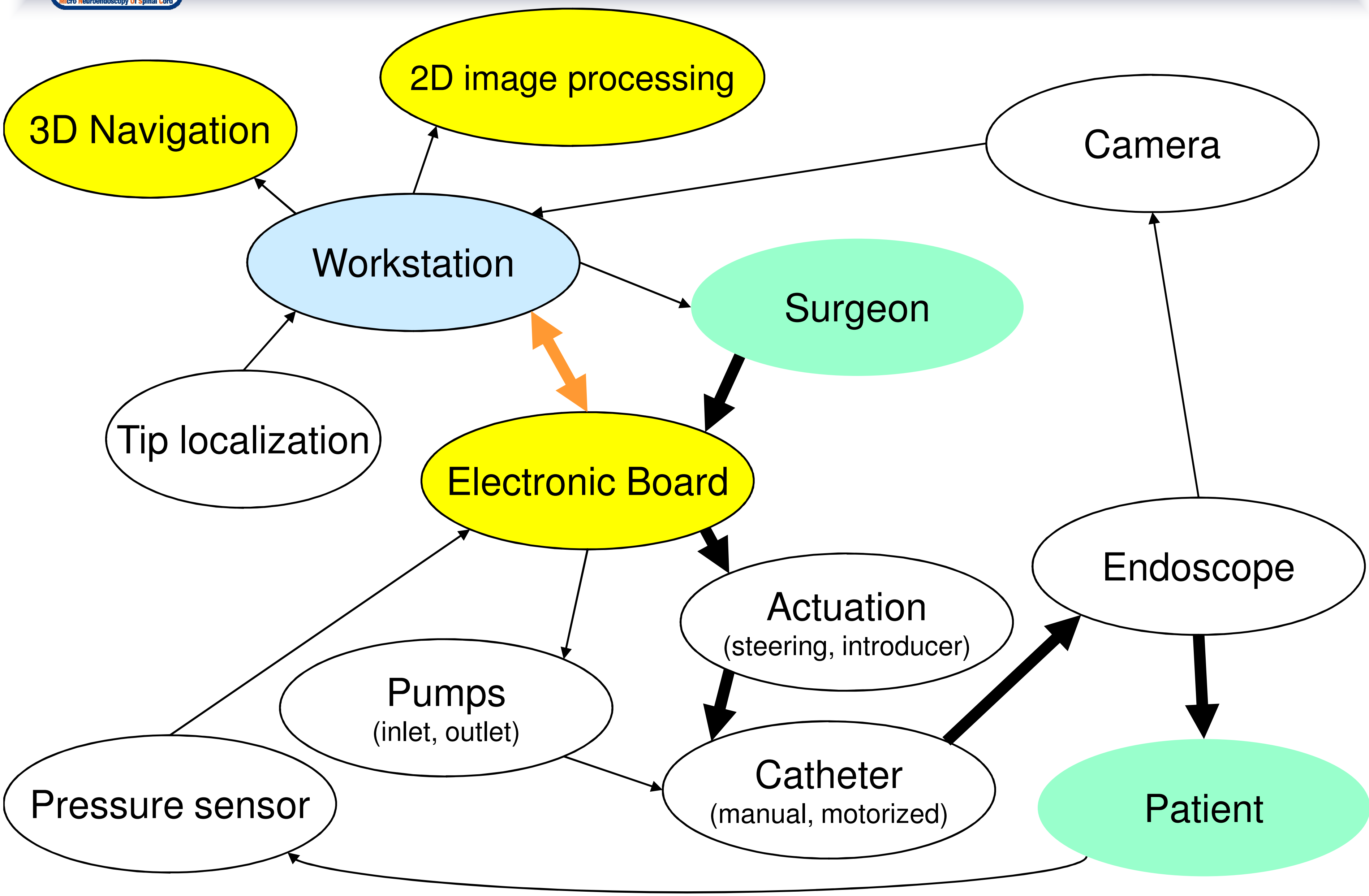
"v" is the output velocity,
"L" is the catheter length,
"R" is the duct radius and
"η" is the fluid viscosity



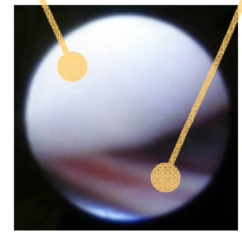
Fluidic Configuration

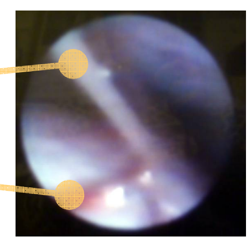


MINOSC – The **Navigation Module**

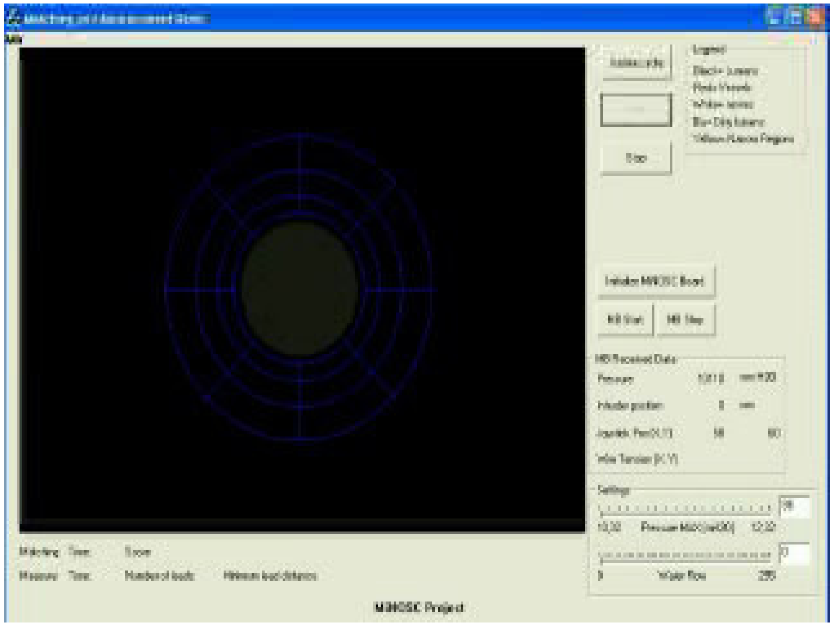


Automatic segmentation of lumen images



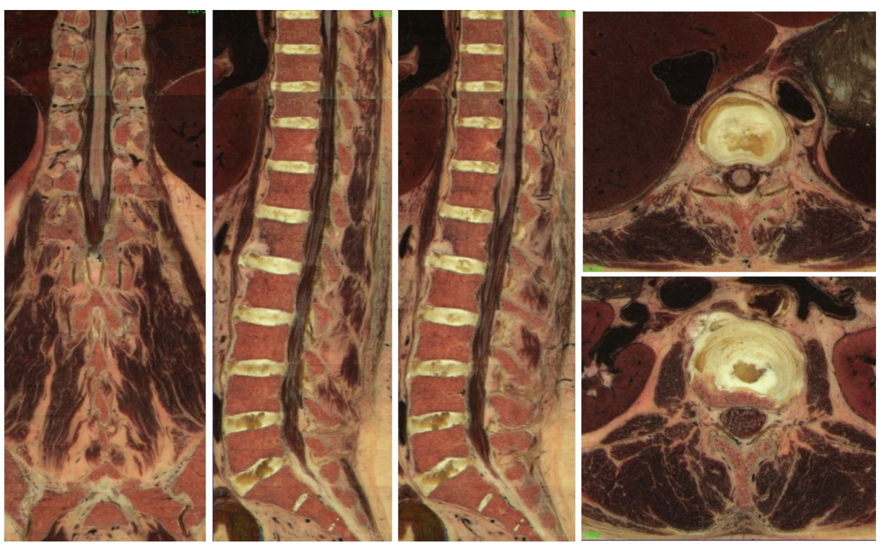


In vivo navigation



The Visible Human Female Dataset

- CT scan: for labeling of bone structures

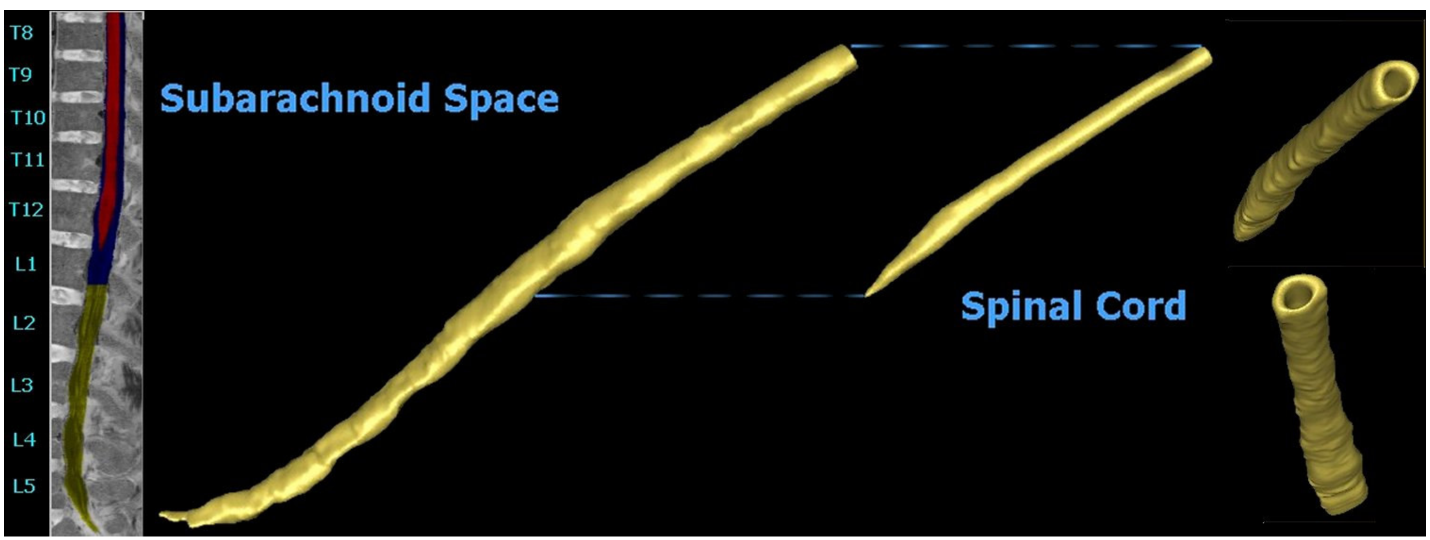


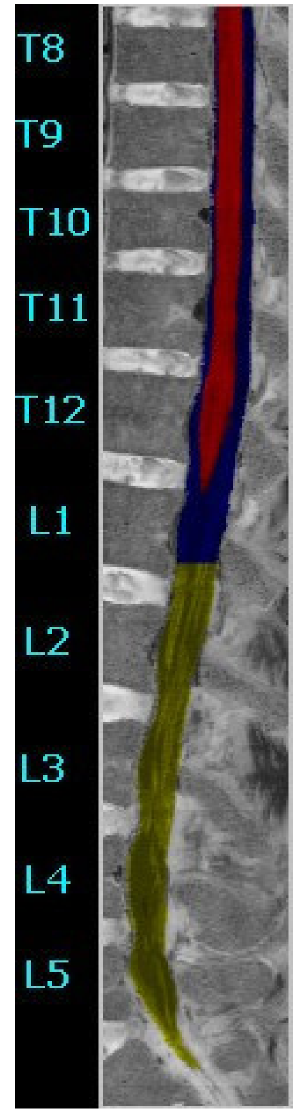
- Color images: for labeling of arachnoid and spinal cord

Splitting of labeled volume

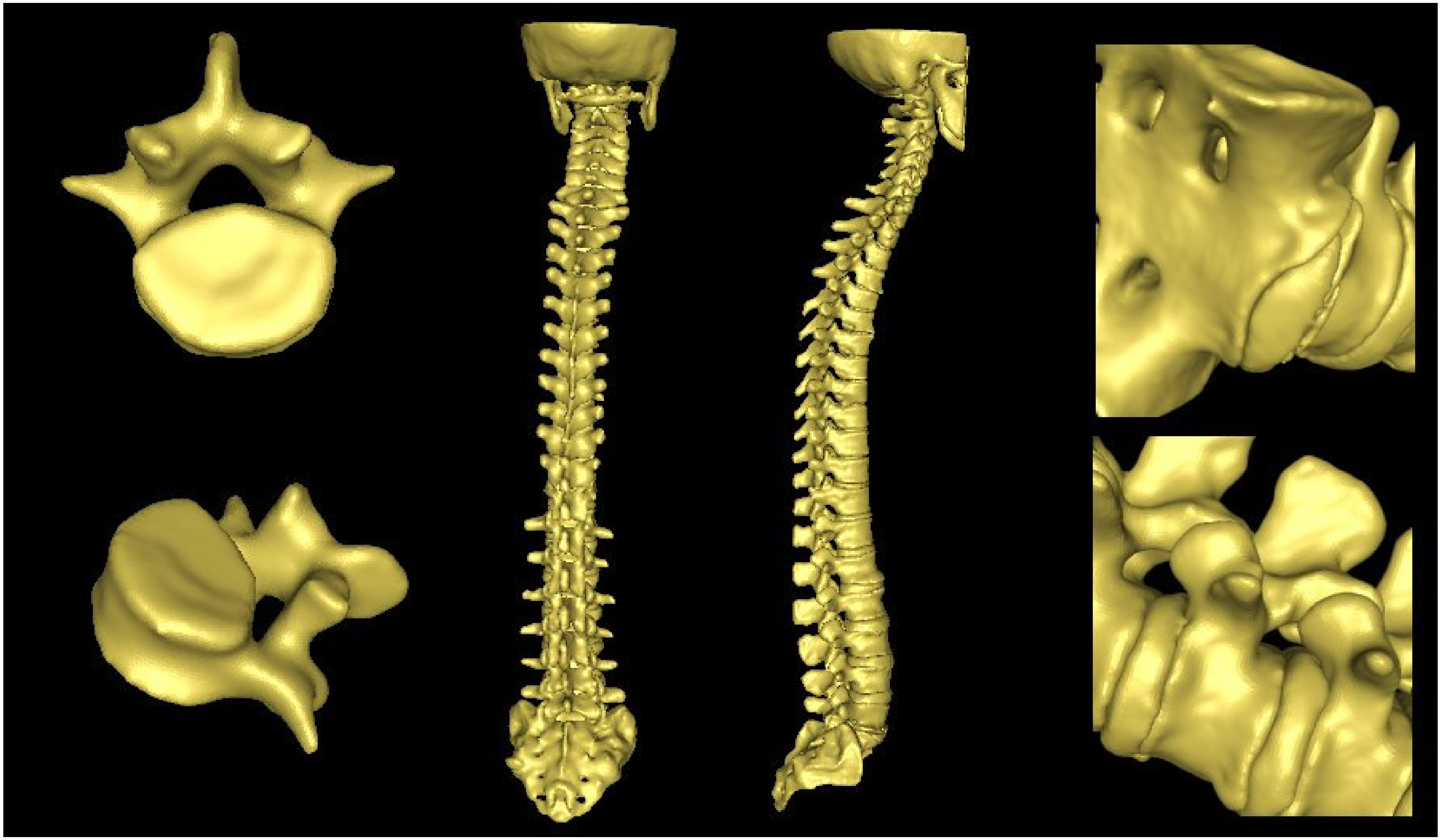
- This is needed for fitting the objects inside the 3D printer workspace

- We did this procedure just for the arachnoid





The 3D Model of the bones



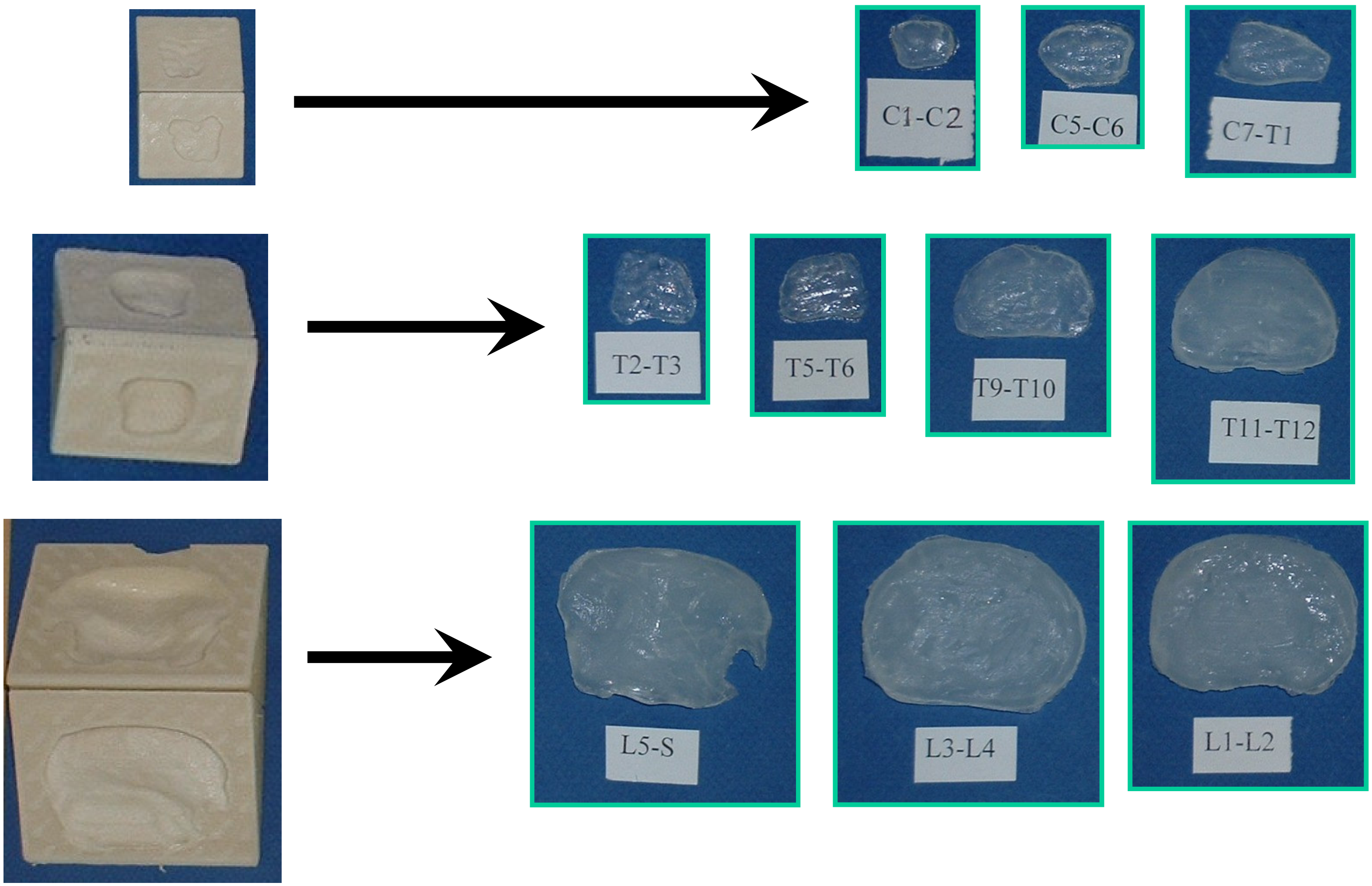
Singol components

Assembled Spine Model

Details of fitting of the components

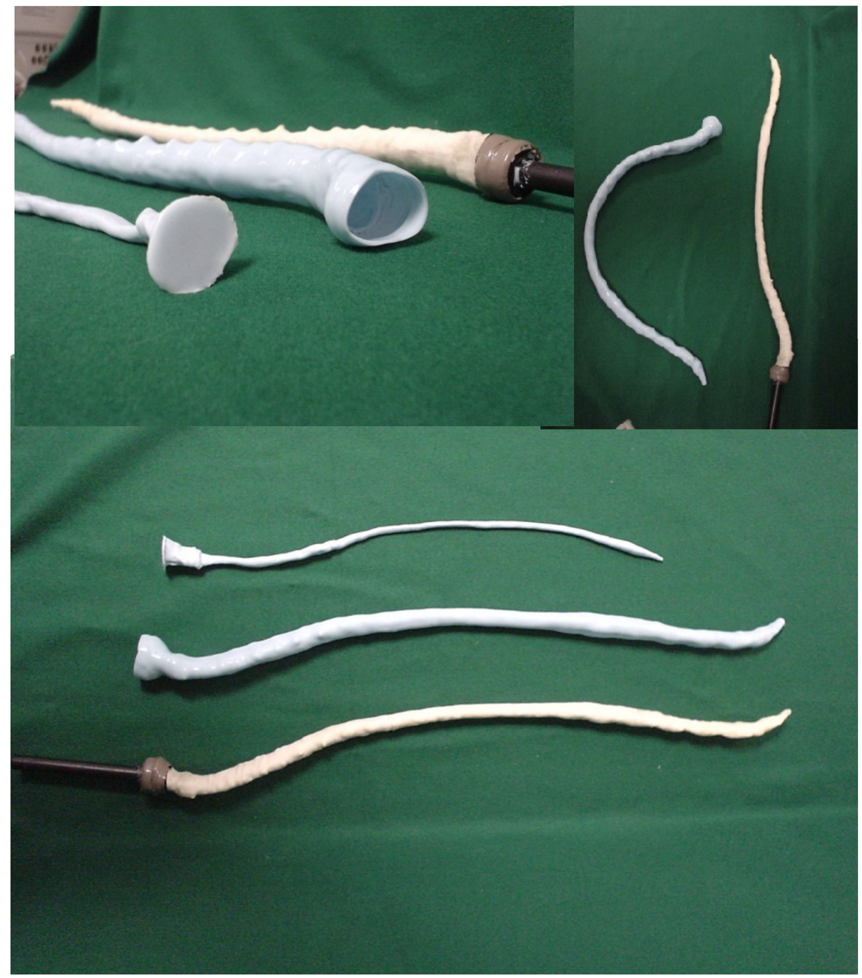
The physical objects

- Disc molds
- Discs

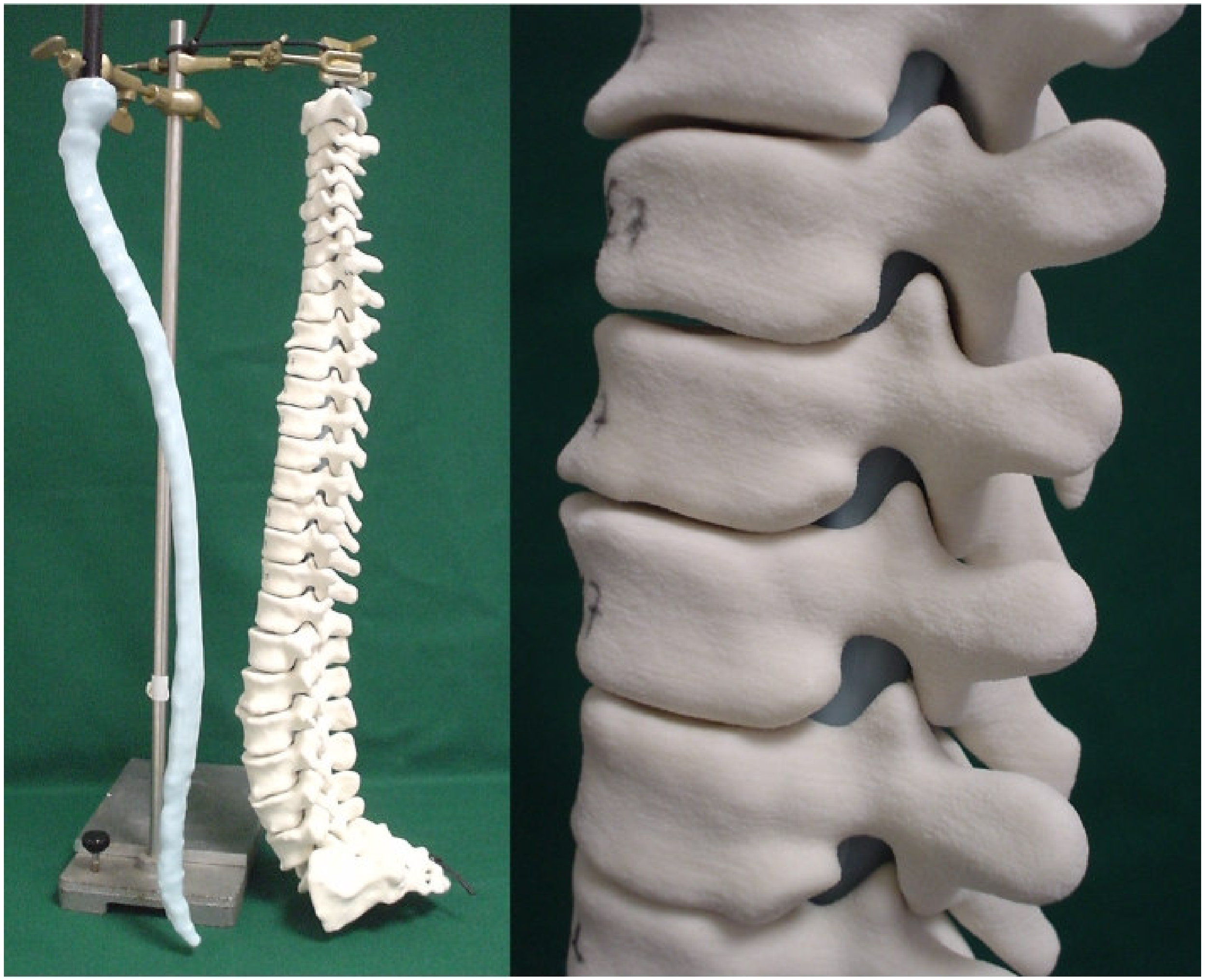


The physical objects

- The arachnoid and the spinal cord (soft material: silicon):



The “real scale” spine model



Partially assembled: vertebra + arachnoid

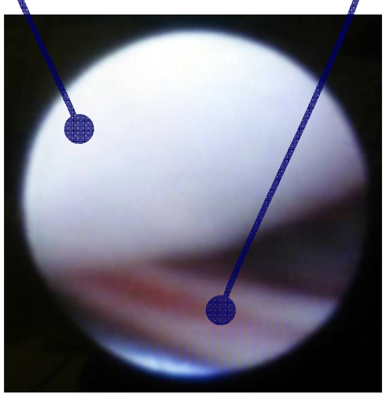
In-vivo validation

In vivo experiments in pigs in Ozzano (Bologna), 2002-2005.

Successful endoscopy (see images below) of the whole spinal cord, from lumbar access up to cervical tract, with **direct nerve stimulation through endoluminal electrode**

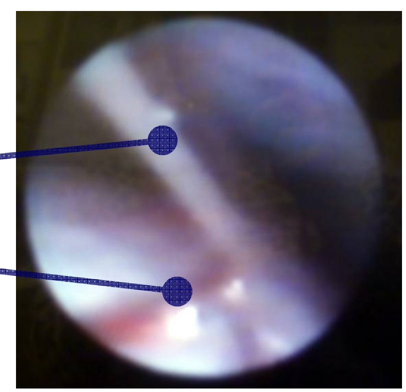
Pia Mater

nerve root with blood vessel



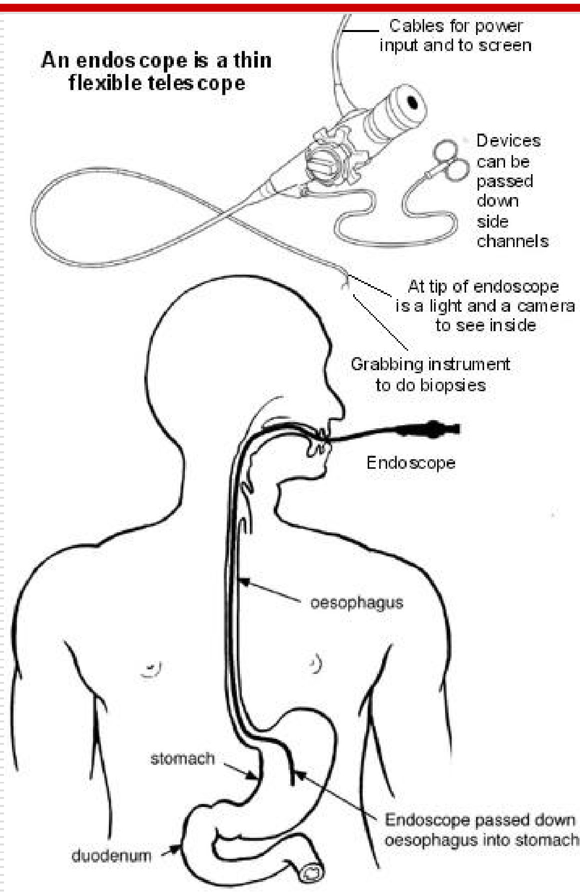
Nerve root

Pia Mater with blood vessel



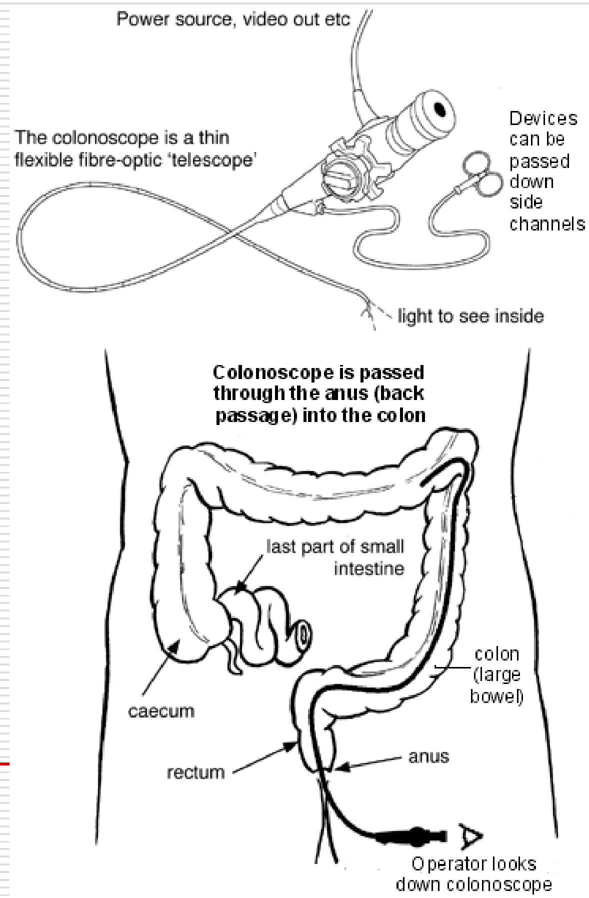
Robotic capsules: intervention from inside the body

Before May 2000: diagnosis of the gut



A Gastroscope for exploring the esophagus and the stomach

A Colonoscope for exploring the colon

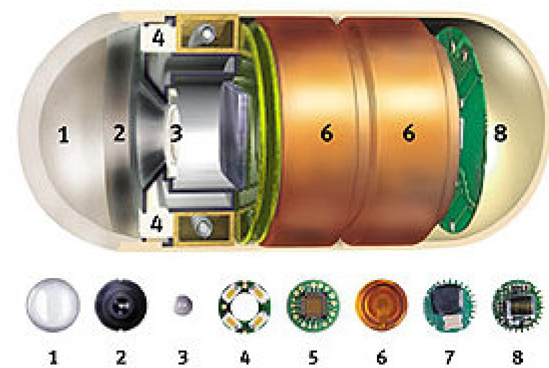


?

And for the small intestine?

After May 2000: Given Imaging (now PillCam) capsule for endoscopy

Graphic provided by Given Imaging, Inc.



Inside the M2A Capsule

1. Optical dome
2. Lens holder
3. Lens
4. Illuminating LEDs (Light Emitting Diode)
5. CMOS (Complementary Metal Oxide Semiconductor) imager
6. Battery
7. ASIC (Application Specific Integrated Circuit) transmitter
8. Antenna

The Advent of Wireless Capsular Endoscopy (WCE)

Capsular Endoscopy: roadmaps by Olympus (presented by Mr. Shymoiama, President – MicroMachine Summit 2005)

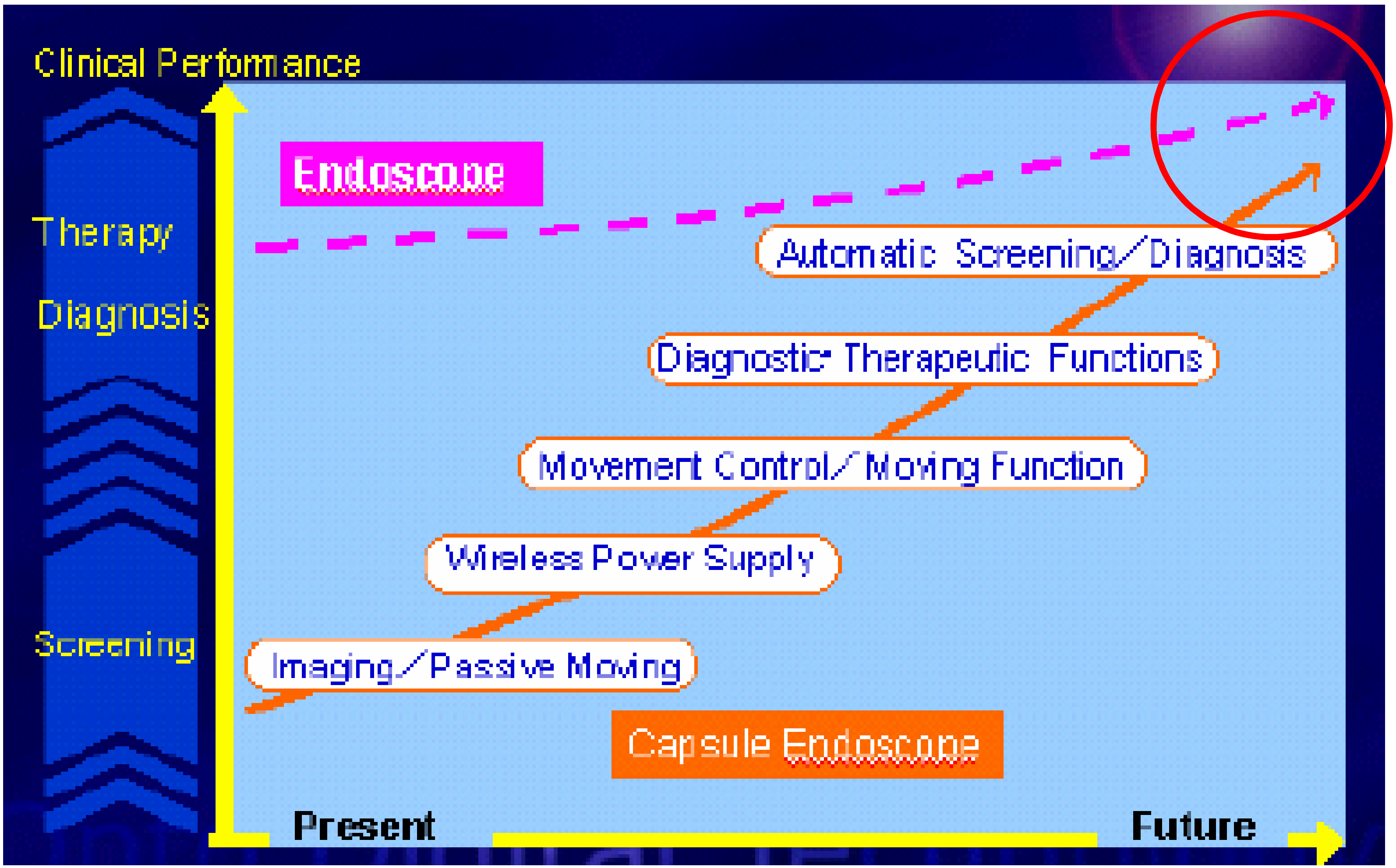


Figure 2. Technological challenge of a future versatile capsule endoscope

Single capsule approach

Diagnosis and simple therapeutic endoluminal tasks

Swallowable capsule (about 2 cm^3) with diagnostic functions (i.e. visualization) and simple robotic mechanisms (e.g. locomotion means, therapeutic suturing, etc.)

- Therapeutic capsule for suturing clip release

- Swimming capsule for stomach diagnosis
- Capsule with legs/flaps for tubular organs exploration, with or without magnetic assistance

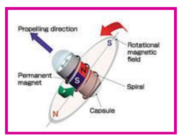
The State of the Art: basically single video capsules for painless diagnosis in the GI tract

Given Imaging

Now: PillCam™ SB, PillCam™ ESO for video acquisition inside small bowel and esophagus. PillCam™ COLON for colon.

Olympus

Now: Endo Capsule for video acquisition inside small bowel and esophagus



Soon: active and battery free pill for diagnosis inside the whole GI tract

Intelligent Microsystem Center

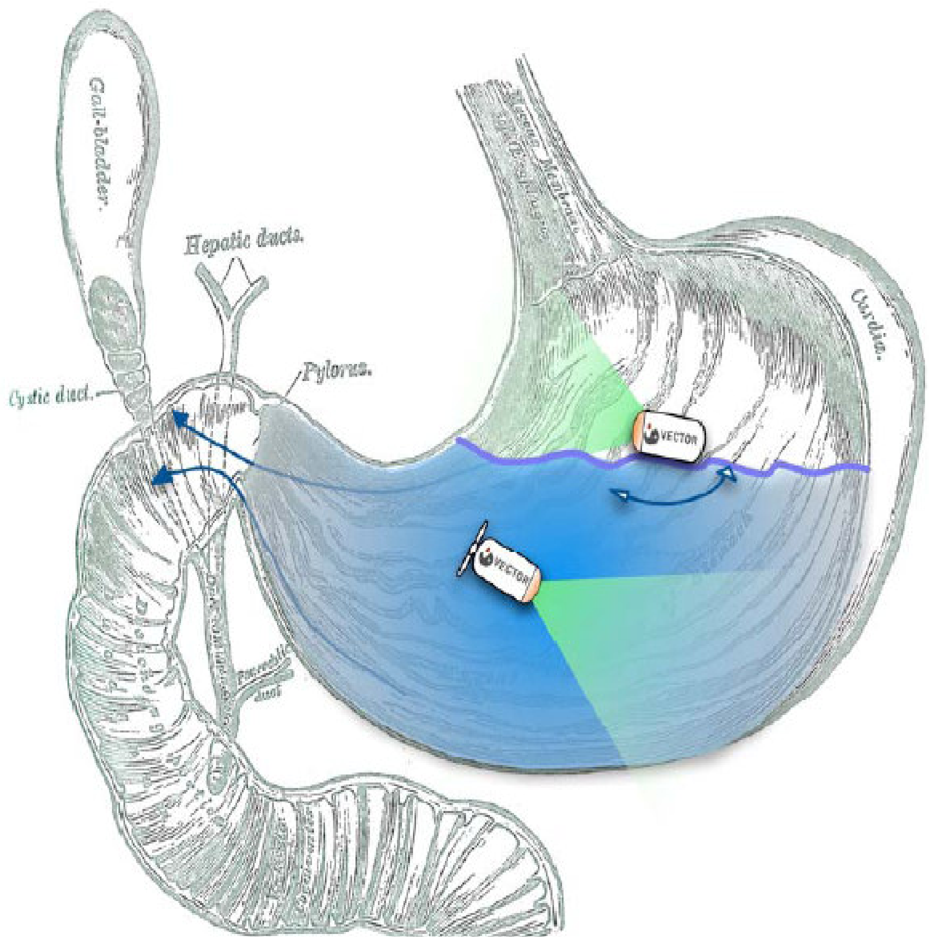
MiRO for video acquisition inside small bowel

Jinshan Science and Technology Group

OMOM Capsule Endoscopy System for video acquisition inside small bowel

Single capsule approach: swimming locomotion

Ingestion of liquid in context with the examination allows to obtain organ distension, thus making possible a low power 3D locomotion in the stomach



Concept: Liquid filling

Mechanism:

- Wireless capsule
- Gastric distension through liquid ingestion
- Capsule diving or floating

Possible challenges:

- Debris in water impairs vision.
- Steering of capsule inside water
- Coordination between endoscopic procedure steps and fluid intake

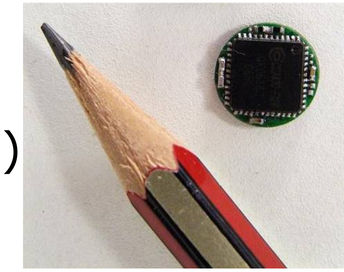
Research conducted:

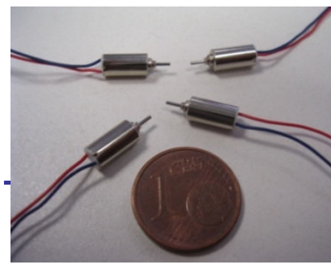
- In vivo animal labs with prototypes
- Human voluteer study with off-the-shelf devices on the clinical fasibility of underwater capsule endoscopy.

Single capsule approach: swimming locomotion

In the capsule:

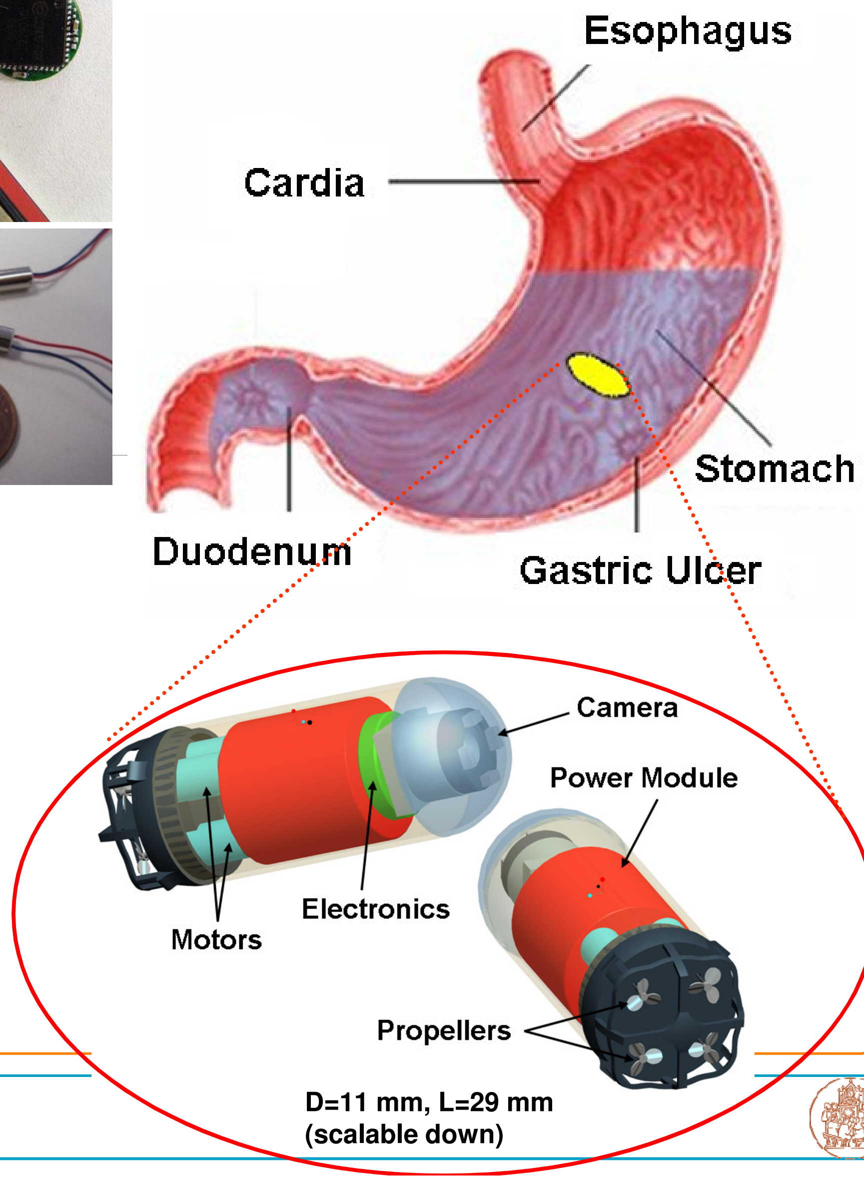
- Control/Telemetry module
  - TI CC2430 (Zigbee + µC)
- 4 DC brushless motors
  - Didel MK04S-24, 2400rps
  - 3.0V, 15mA/V no load
- 4 propellers in the rear side
- 1 battery: LP20, Plantraco Ltd.-Canada, 20mAh,3.7V; or a power module for inductive power supply

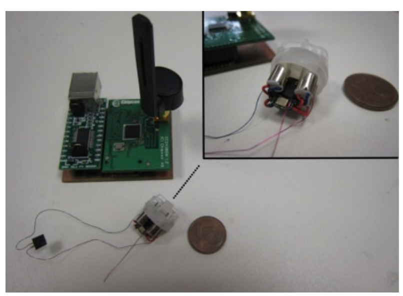




External "dongle":

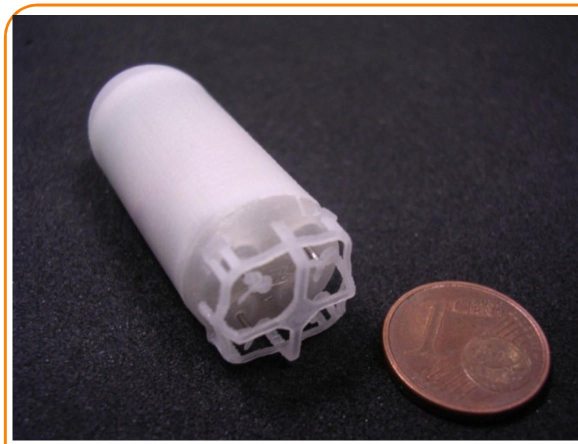
- TI CC2430 (Zigbee + µC)
- USB front-end





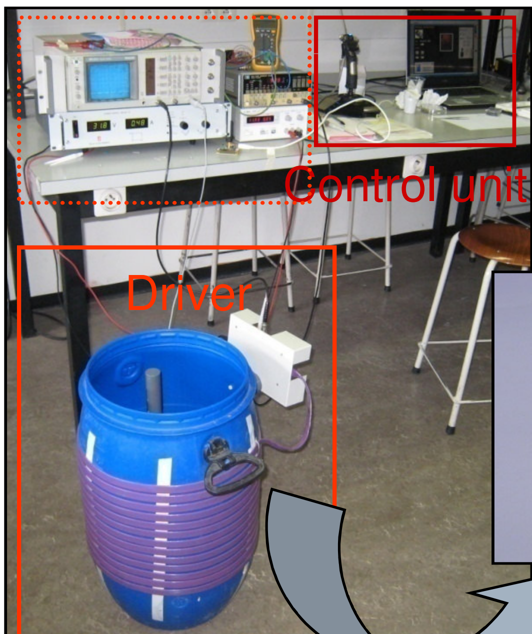
Patent submitted for the 4 propellers operation

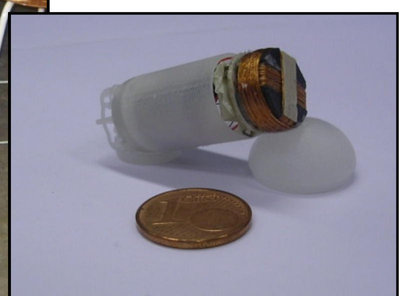
Single capsule approach: swimming locomotion



Fine control of steering and speed in 3D

Ex vivo test in stomach of pig filled with water

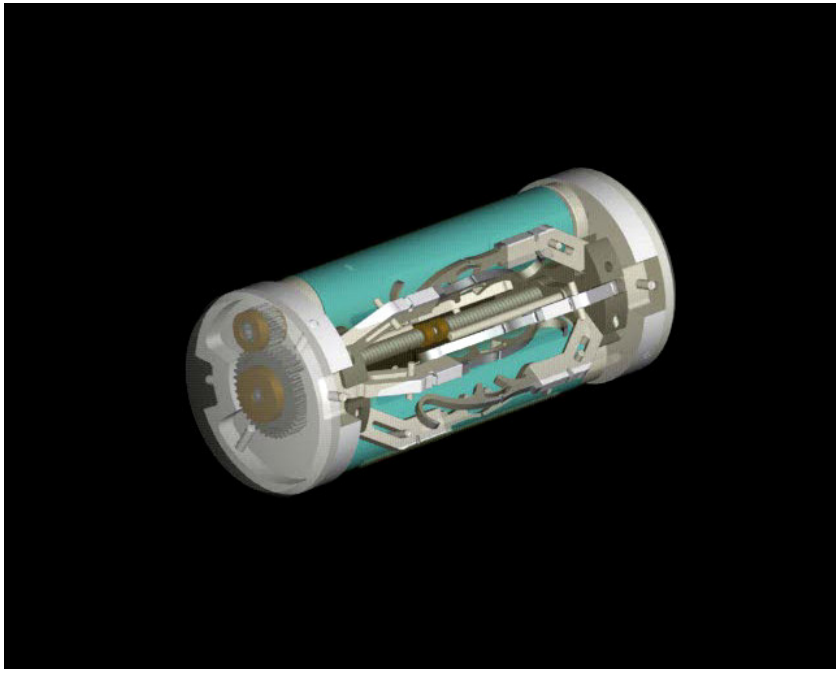




Inductive powering allows to overcome operation time limitations related to limited lifetime of on-board batteries

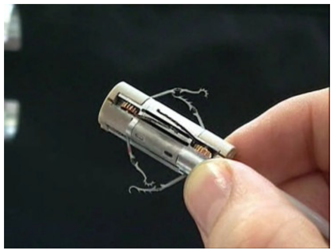
Single capsule approach: legged capsule for tubular organs

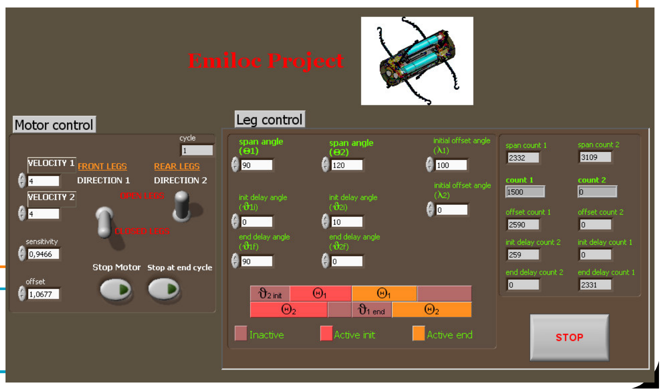
Obtaining an active locomotion in tubular organs of the GI tract, that cannot be inflated or filled with water, means having propulsion mechanisms able to open and distend the tissue around the capsule.



M. Quirini et al., ICRA 2007

1. **Diameter: 11.1 mm;**
2. **Length: 28 mm (+camera);**
3. **12 legs;**
4. **2 DC brushless motors (NAMIKI);**
5. **Force at the leg's tip of about 1N;**
6. **No frontal latex balloon required;**
7. **On board electronics drivers;**
8. **Power consumption: 0.66 W.**



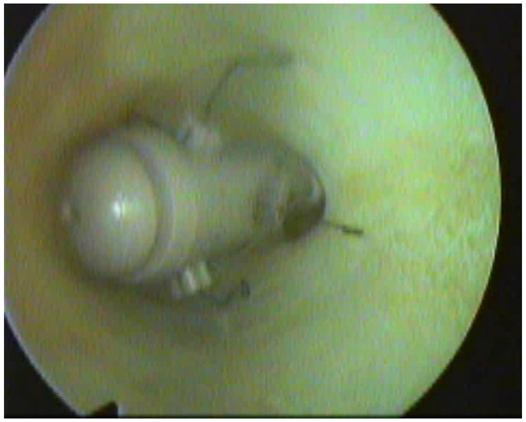


Patent filed

Single capsule approach: legged capsule for tubular organs

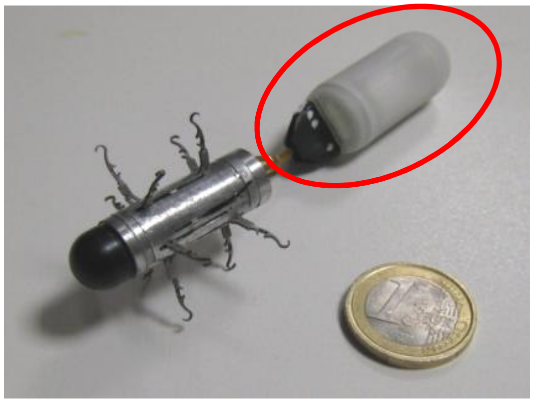
Simulator test

Colon test (5 cm/min)



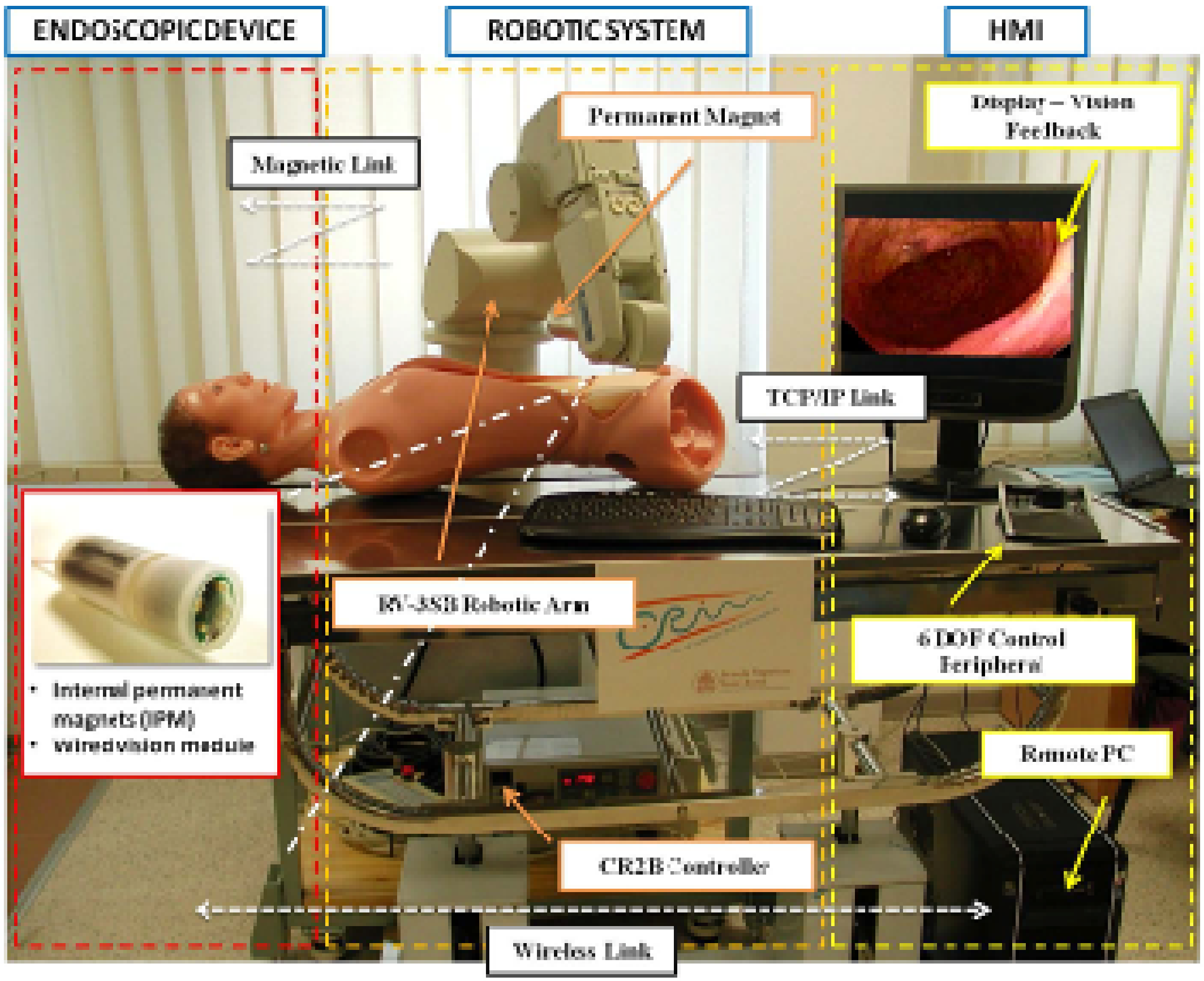
M. Quirini, S. Scapellato, A. Menciassi, P. Dario, F. Rieber, C.-N. Ho, S. Schostek, M.O. Schurr, “Feasibility proof of a legged locomotion capsule for the GI tract”, GASTROINTESTINAL ENDOSCOPY, 67(7), 2008

By considering the power budget for all the capsule functions (vision, locomotion, communication), the single capsule approach shows dramatic limitations: a tender capsule solution would be necessary!



…or we could integrate external locomotion mechanisms – based on interactions of magnetic fields - with simpler internal locomotion mechanisms for fine positioning…

Hybrid locomotion strategy: external magnetic guidance and one internal degree of freedom

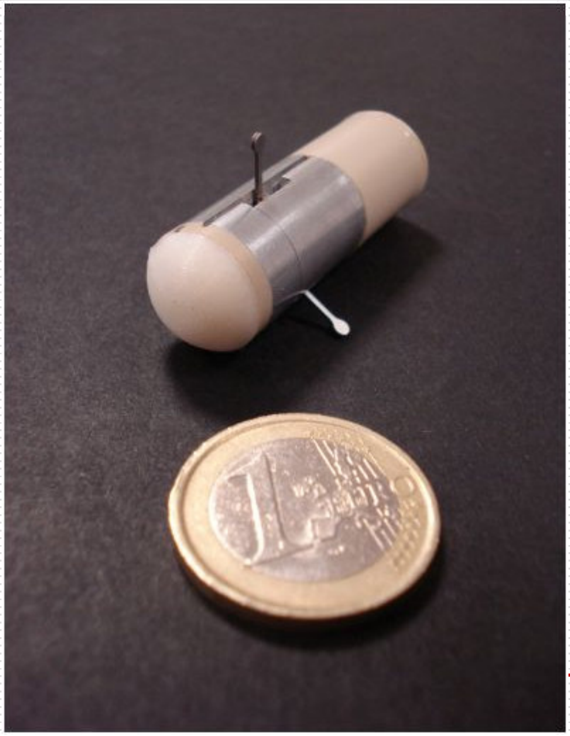


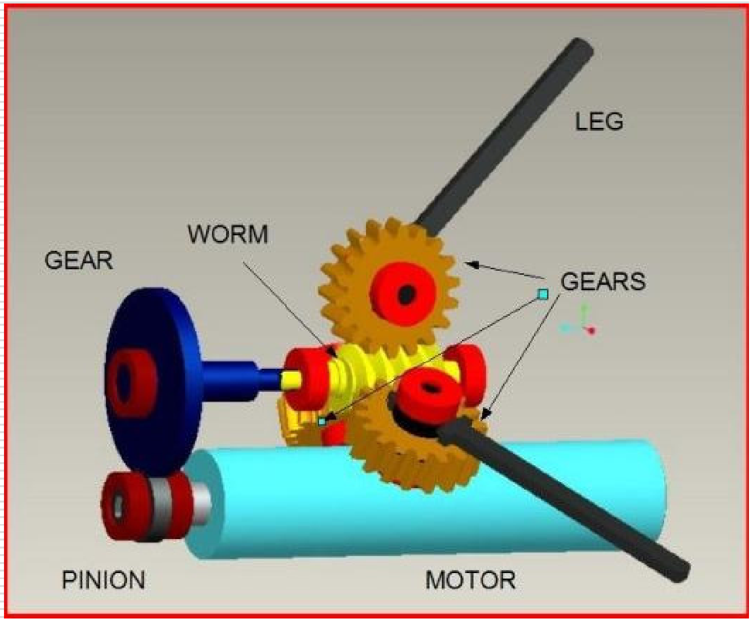
Magnetic capsule in vivo with distended tissue

Magnetic capsule in vivo with collapsed tissue

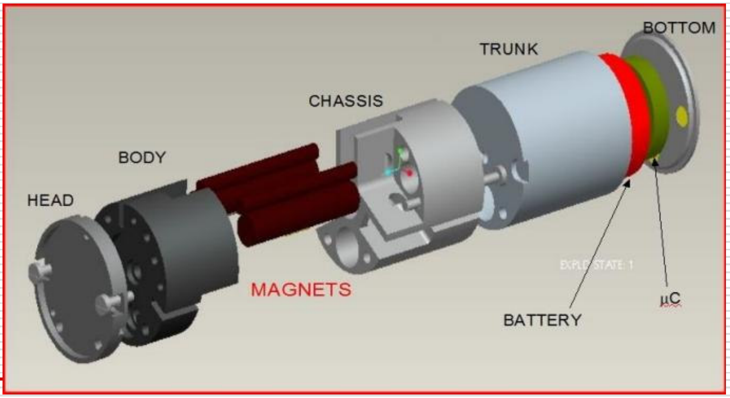
The hybrid approach
– with legs/flaps

- The hybrid capsule is a trade-off solution between external and internal locomotion systems. It should be able to manage collapsed areas of the GI tract exploiting the flaps or legs to modify the external shape of the capsule thus distending the intestine wall.

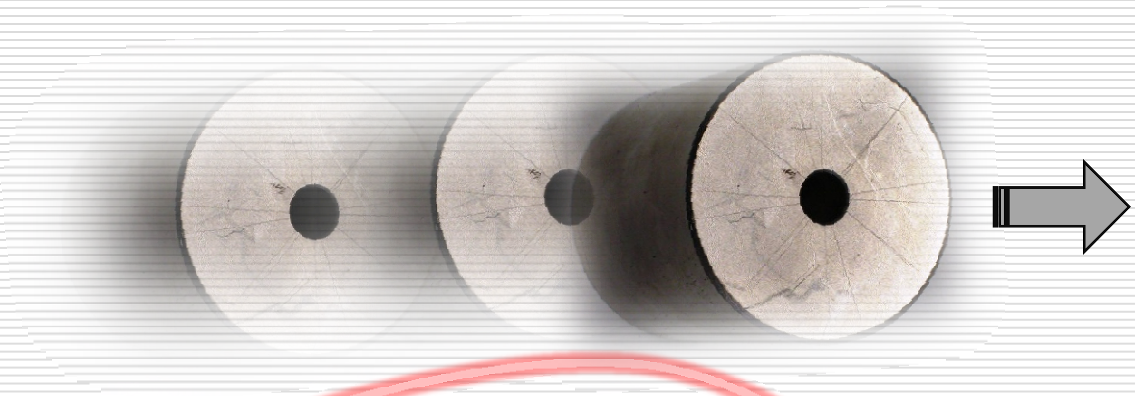




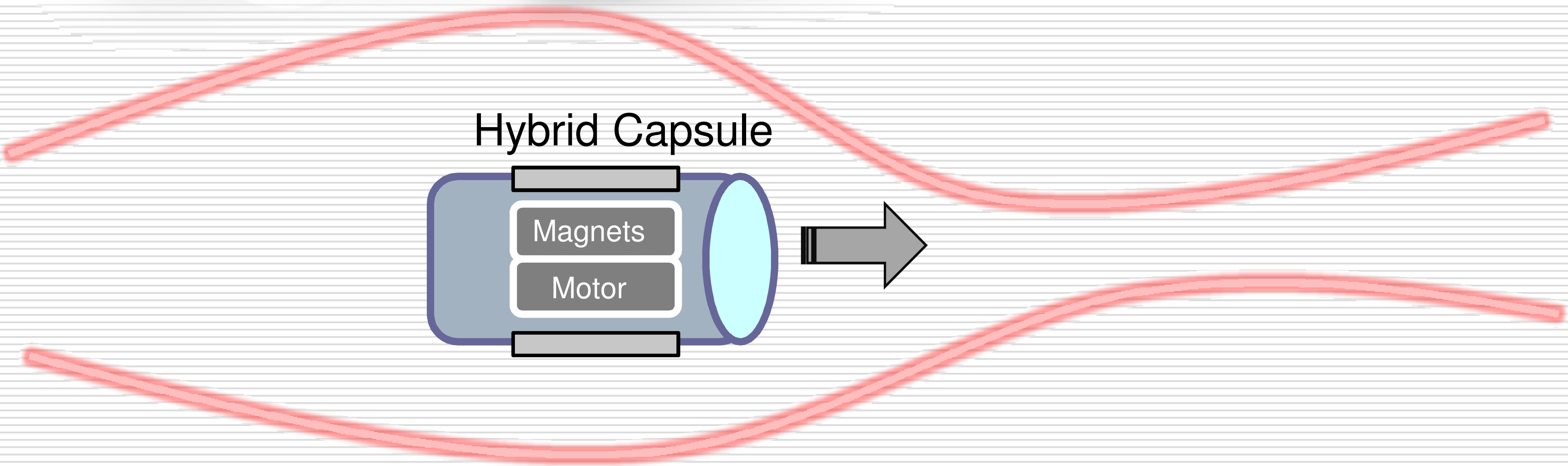
In vivo test
March 5
2009



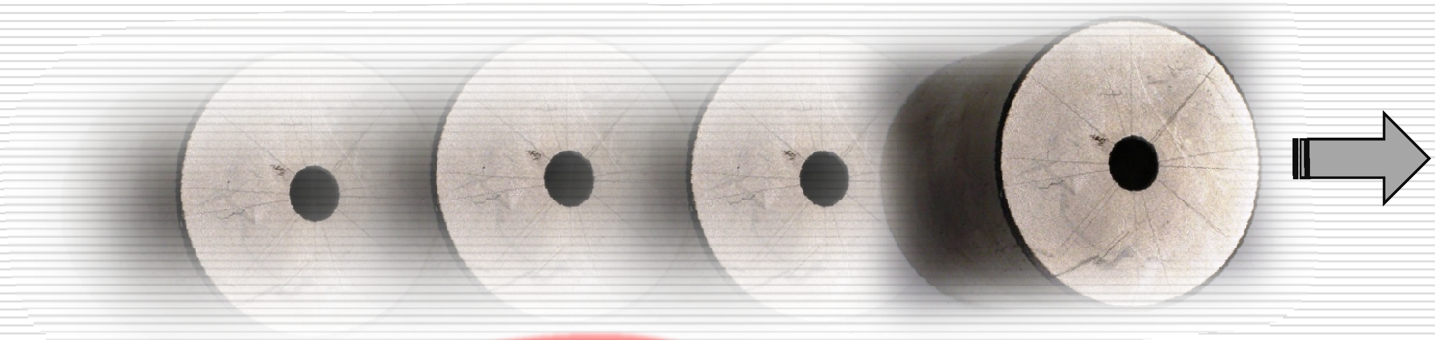
Hybrid Capsule– Lesson Learned



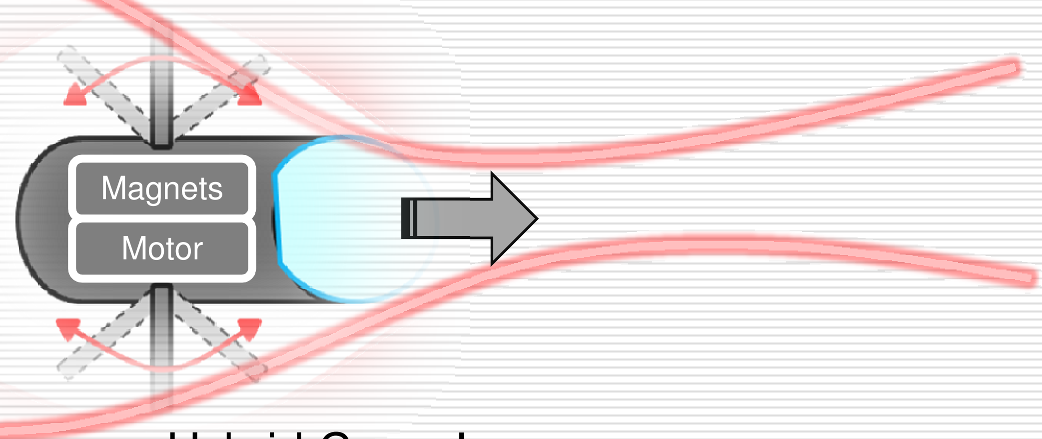
The Hybrid capsule is able to travel distended path of th GI tract by means of the only magnetic module



Hybrid Capsule– Lesson Learned

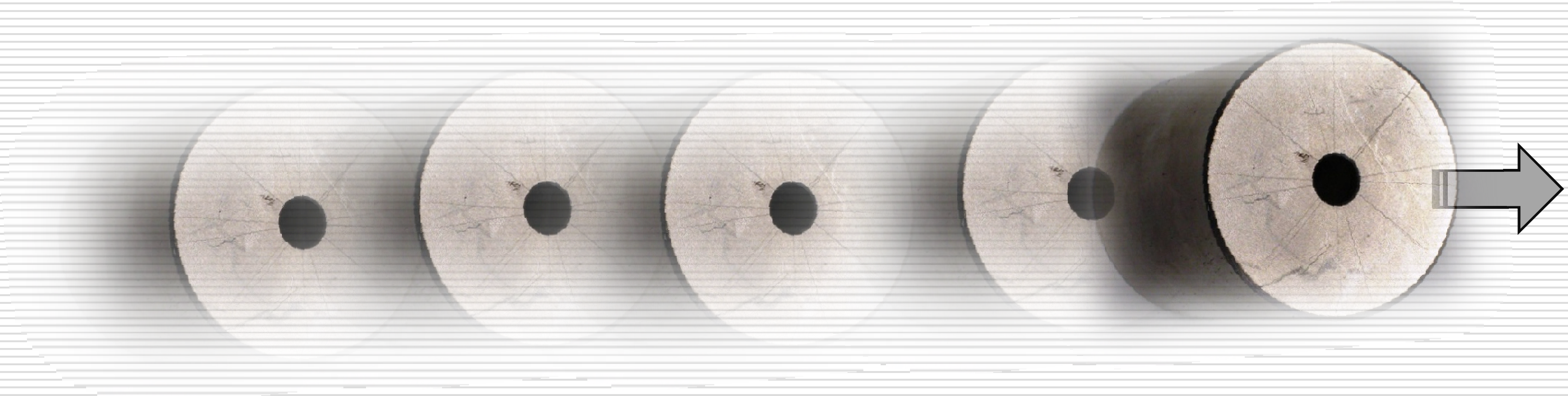


Exploiting the flap system the colon is distended and the frictional forces on the wall are reduced



Hybrid Capsule

Hybrid Capsule– Lesson Learned

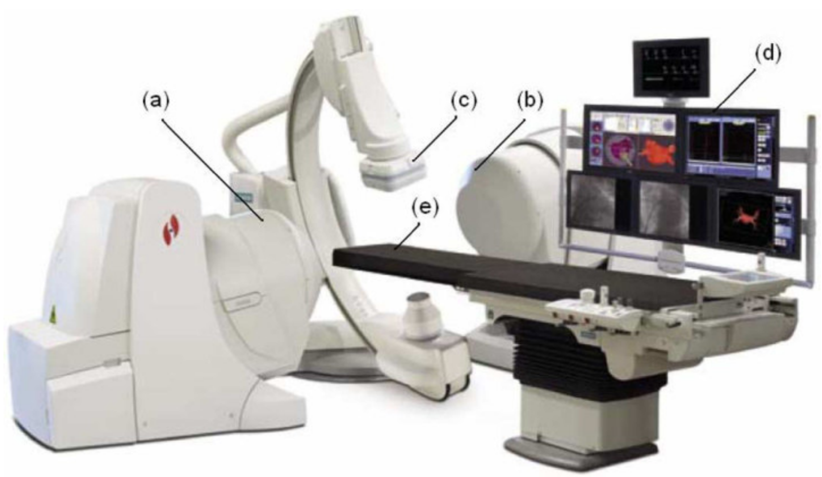


Exploiting the magnetic module the hybrid capsule is now able to travel the entire GI tract

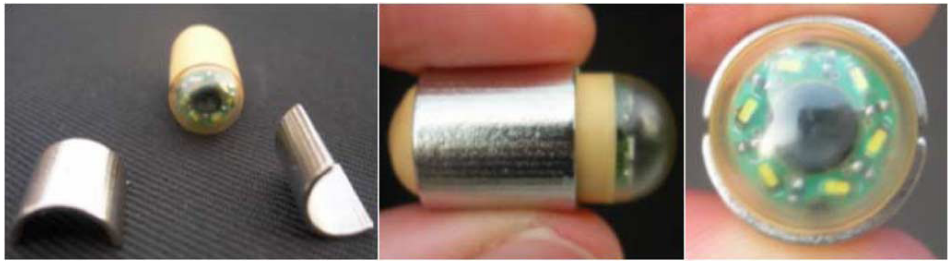
Hybrid Capsule

Magnetic actuation in endoscopy and surgery

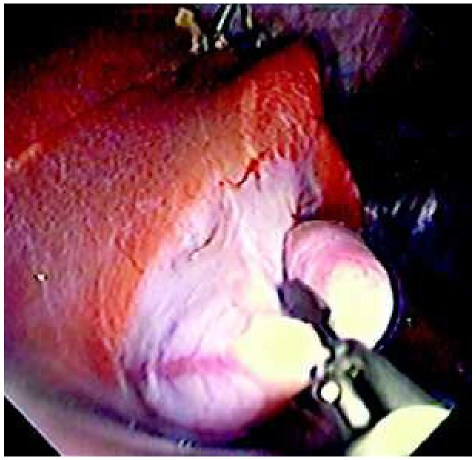
The use of magnetic fields to control and steer assistive and operative devices is increasing in endoluminal and transluminal surgical and diagnostic applications.



Niobe magnetic navigation system developed by Stereotaxis. (a) and (b) Couple of permanent magnets. (c) Fluoroscopic scanner. (d) Visualization displays. (e) Patient's table



Magnetic Maneuvering of Endoscopic Capsules by Means of a Robotic Navigation System [Carpi-Pappone (2009) IEEE Trans. On Biomed. Eng.]



Magnetic retraction in natural–orifice transluminal endoscopic surgery (NOTES): addressing the problem of traction and countert-raction [Ryou and Thompson (2009), Endoscopy vol.41]

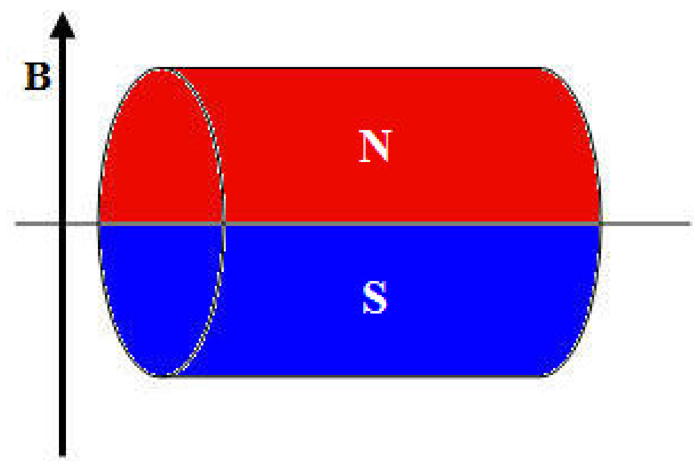
Limitations of current solutions

- **Magnetic forces change abruptly with distance: limited external motions can change dramatically the magnetic link**
- **Moving large external magnets or external coils means to set up a powerful and high precision robotic system (see MRI and NIOBE system)**
- **Manual operation of external magnetic handles linked to internal magnetic grippers or trocars turns out to be unsafe for patients (due to abrupt magnetic field variations)**

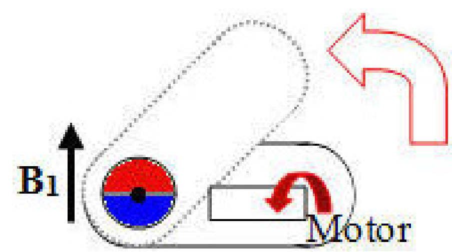
An alternative solution

Exploiting the alignment between external and internal magnetic fields to rotate the device *around* the magnetic vector thanks to an embedded miniaturized actuator

Advantages



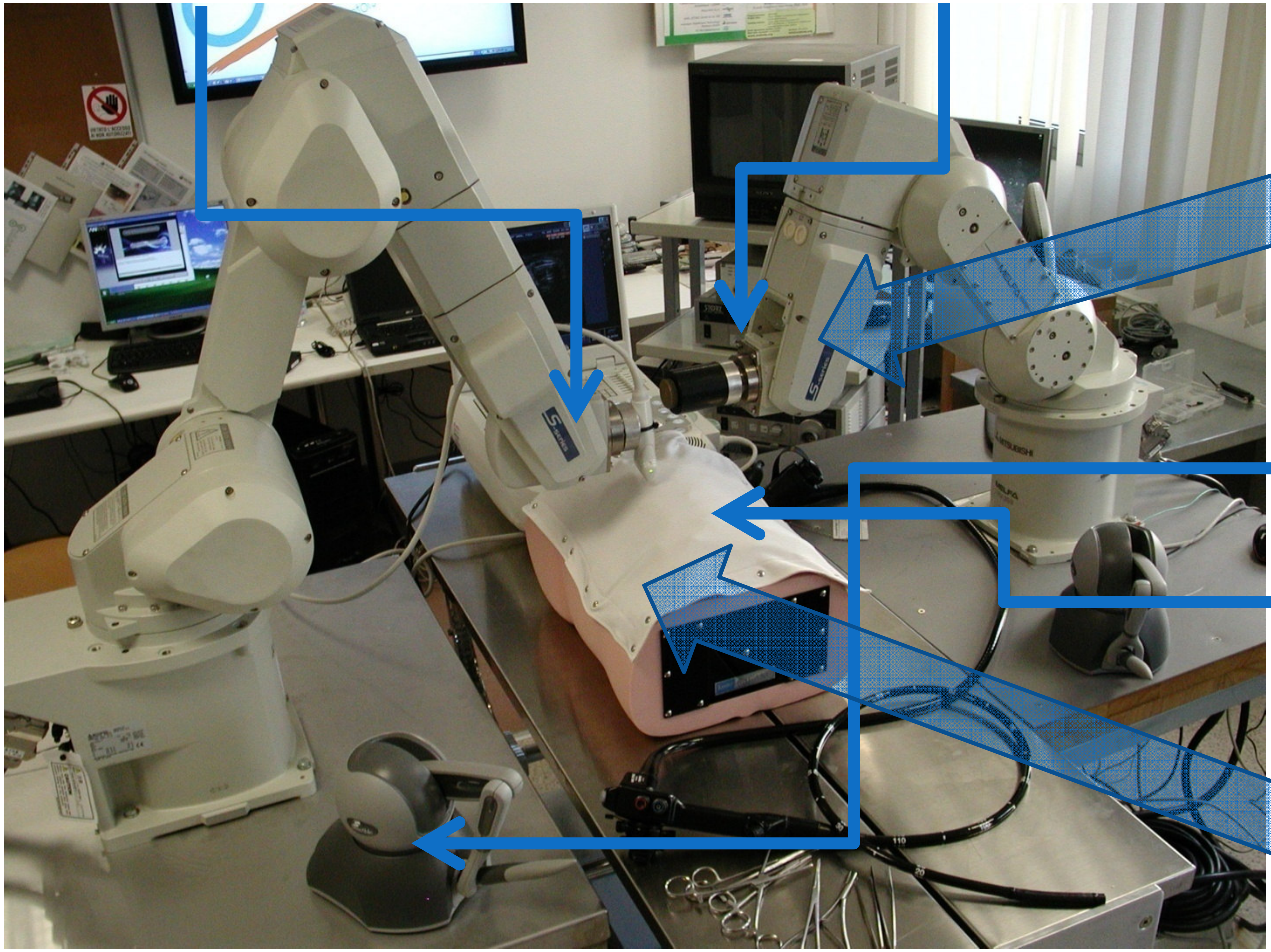
- **High precision, basically related to the resolution of the internal actuator**
- **Simple external set-up just to keep the magnet (or the coils) in position during the fine orientation of the device (e.g. the camera system of an endoscopic capsule)**

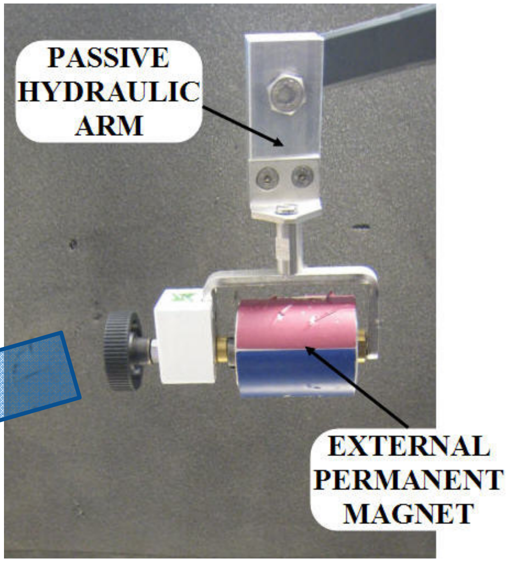


The set up for capsule orientation in endoscopy

Robotic manipulator for US localization

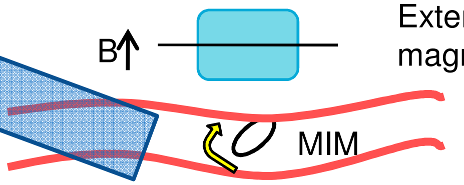
Robotic manipulator for external magnet motion/positioning





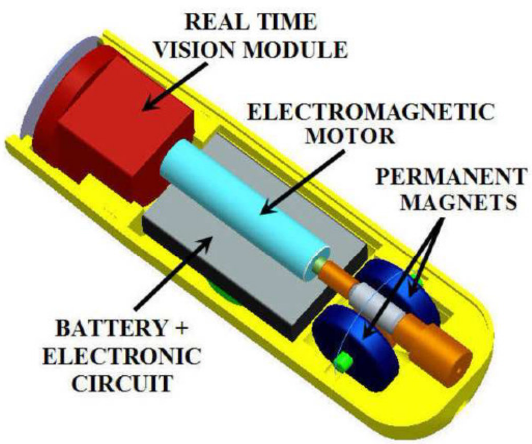
Haptic interface for capsule control

Lower GI tract phatom model

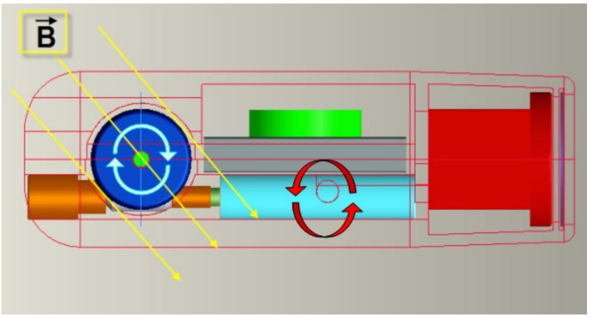


MIM: Magnetic Internal Mechanism

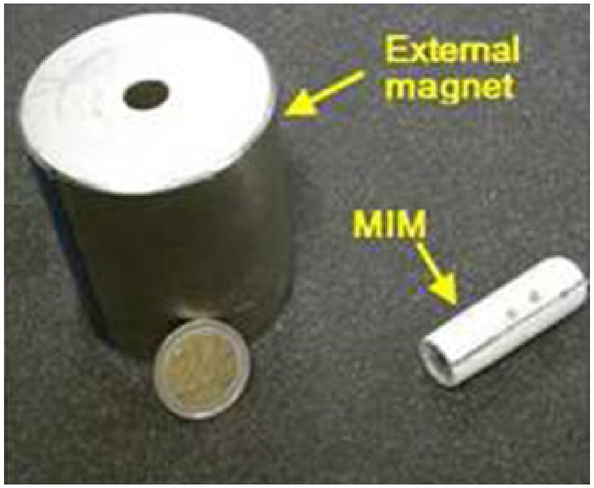
Combination of one internal degree of freedom generated by one motor with the force produced by a magnetic link between external and internal magnets.



Motor
Magnet(s)
Battery
Camera
Electronic circuit

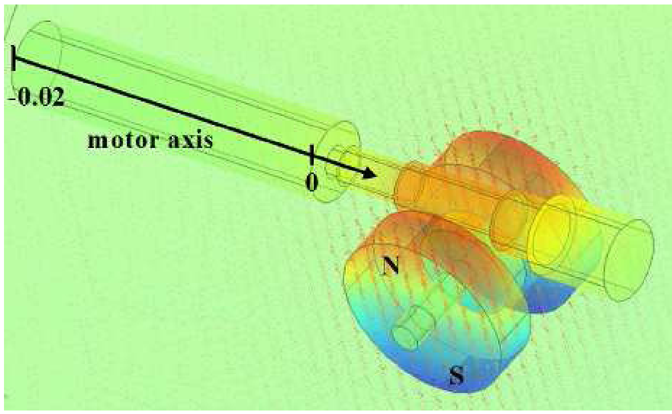


The magnet/s tend to align to an external magnetic field B. When the motor is activated a rotation of the entire capsule is produced.

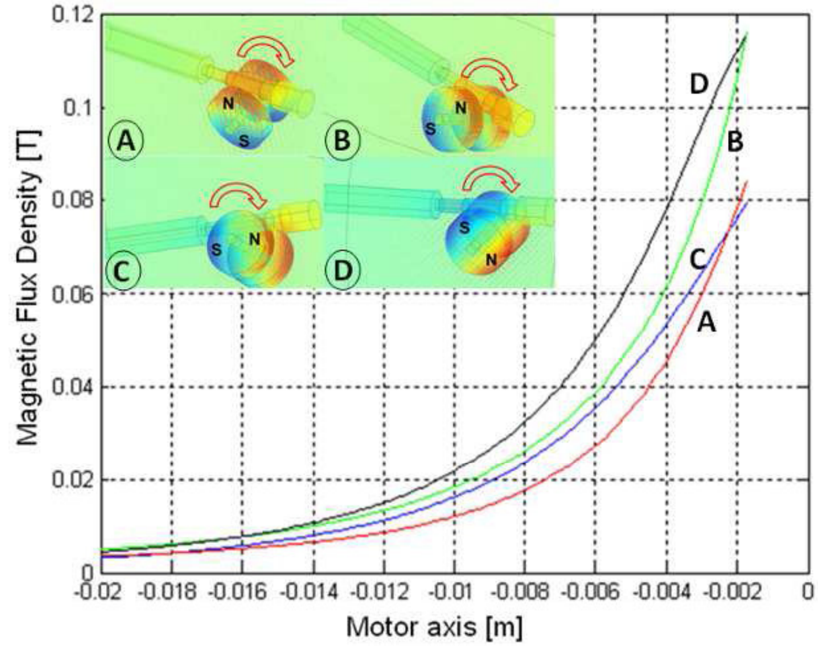


The MIM allows to **finely orienting the capsule**, and to **obtain very precise movements of the camera** once rough positioning has been achieved by external magnetic locomotion

Magnetic link dimensioning



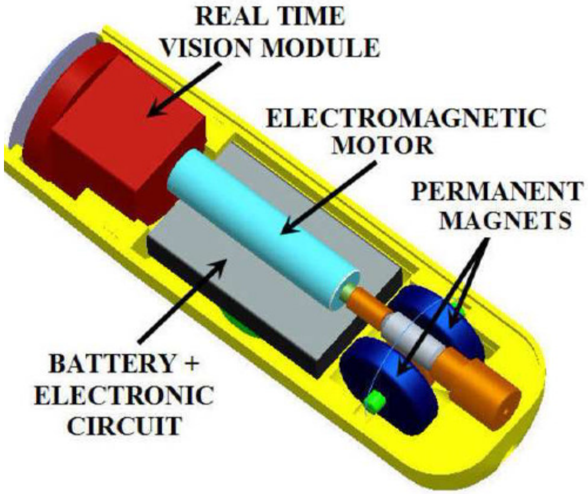
Simulation of the magnetic field generated by the internal magnets on the motor axis

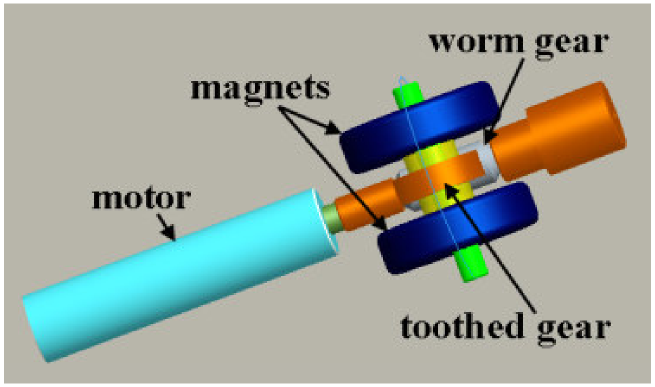


Magnetic flux density generated by the internal magnets onto the motor axis for different configurations.

- The **magnetic flux density** decreases with the distance *d* from the magnets as $1/d^3$, yielding values ranging from 0 T to 0.12 T on the motor.
- Experimental tests demonstrated that **such field does not affect the motor functionality**.
- The effect of the external magnet has been estimated as 10 times smaller than the effect of the internal magnets, because of the large operating distance (10 cm).

Design and manufacturing





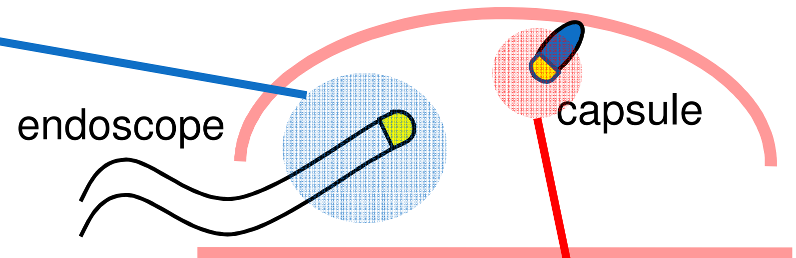
Size of first prototype:
- ➢**15.6 mm in diameter,**
- ➢**48 mm in length,**
- ➢**14.4 g in weight**

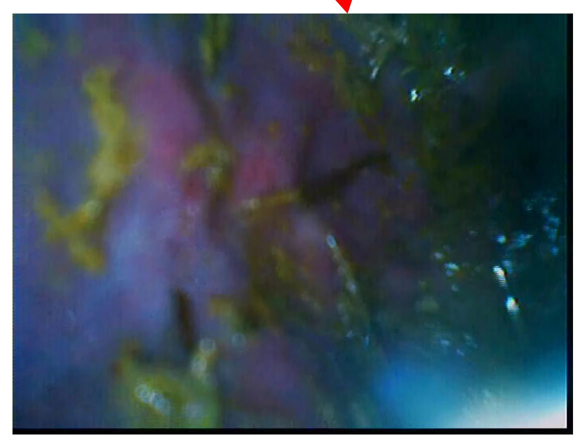
MIM capsule components:

➢one motor (Namiki Precision Jewel Co., Japan), with a stall torque of 5.7 mNm, 4 mm in diameter and 19 mm in length.
➢two permanent magnets diametrically magnetized (N52 NdFeB, Supermagnete, CH)
➢a camera (Misumi Co., Taiwan)
➢a battery (3.7 V, 20Ma/h, Plantraco, Canada)
➢an electronic circuit for control and wireless communication.

In vivo test

The feasibility study was performed with two female 30 kg domestic pigs.



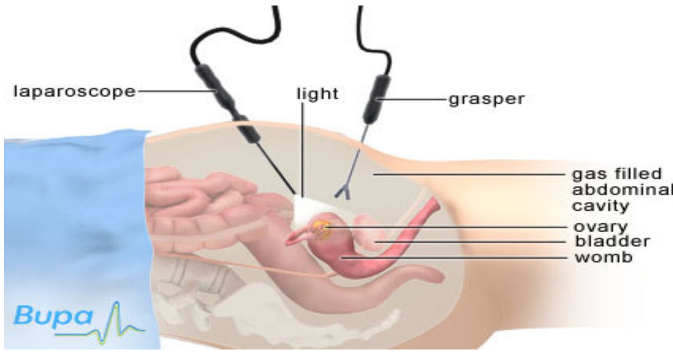


The procedure required approximately 10 min.
At the end of the experiments, the capsule remained fully functional and the mucosa was not damaged.

Additional applications: high resolution camera, wired connection, miniaturization for fitting in trocars

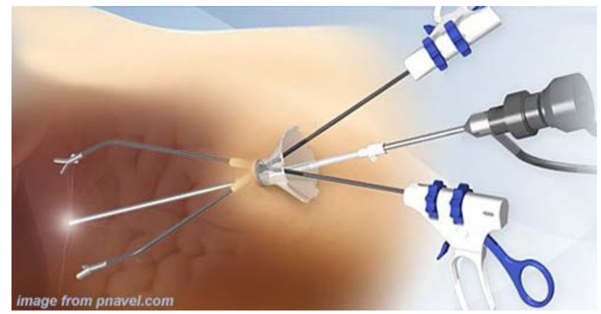
Laparoscopy:

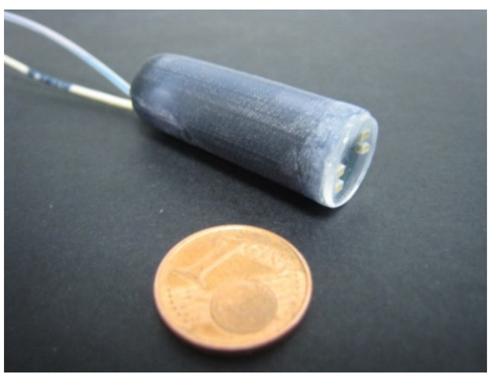
The MIM allows to eliminate one hole for the camera



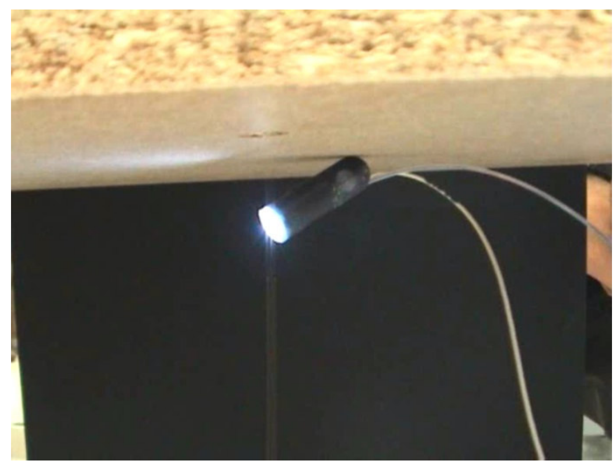
Single port laparoscopy:

The MIM allows to eliminate one rigid instrument





- Wired cylinder
- Diameter = 12.7 mm
- Length = 39 mm
- Weight = 7.7 g
- Storz CCD camera



Single capsule approach

Diagnosis and simple therapeutic endoluminal tasks

Swallowable capsule (about 2 cm^3) with diagnostic functions (i.e. visualization) and simple robotic mechanisms (e.g. locomotion means, therapeutic suturing, etc.)

•Therapeutic capsule for suturing clip release

•Swimming capsule for stomach diagnosis
•Capsule with legs/flaps for tubular organs exploration, with or without magnetic assistance

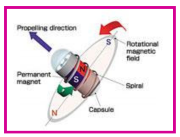
The State of the Art: basically single video capsules for painless diagnosis in the GI tract

Given Imaging

Now: PillCam™ SB, PillCam™ ESO for video acquisition inside small bowel and esophagus. PillCam™ COLON for colon.

Olympus

Now: Endo Capsule for video acquisition inside small bowel and esophagus



Soon: active and battery free pill for diagnosis inside the whole GI tract

Intelligent Microsystem Center

MiRO for video acquisition inside small bowel

Jinshan Science and Technology Group

OMOM Capsule Endoscopy System for video acquisition inside small bowel

Single capsule approach: simple therapeutic tasks

OTSC CLIP

Flexible endoscope based clip relese

Robotic magnetic steering

OTSC in NOTES (gastric closure)

Wireless capsule based clip release

Main Components

- Magnets for external magnetic steering
- Motor and mechanism for clip releasing
- Wireless motor controller
- Battery
- Vision system (not yet integrated)

Valdastri P; Quaglia C; Susilo E; Menciassi A; Dario P; Ho C N; Anhoeck G; Schurr M O "Wireless therapeutic endoscopic capsule: in vivo experiment" - Endoscopy 2008;4 0(12):979-82.

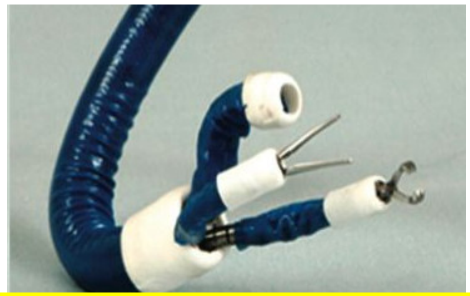
Different robots for different endoluminal tasks

Diagnosis and simple therapeutic endoluminal tasks → Swallowable capsule (about 2 cm^3) with diagnostic functions (i.e. visualization) and simple robotic mechanisms (e.g. locomotion means, therapeutic suturing, etc.)

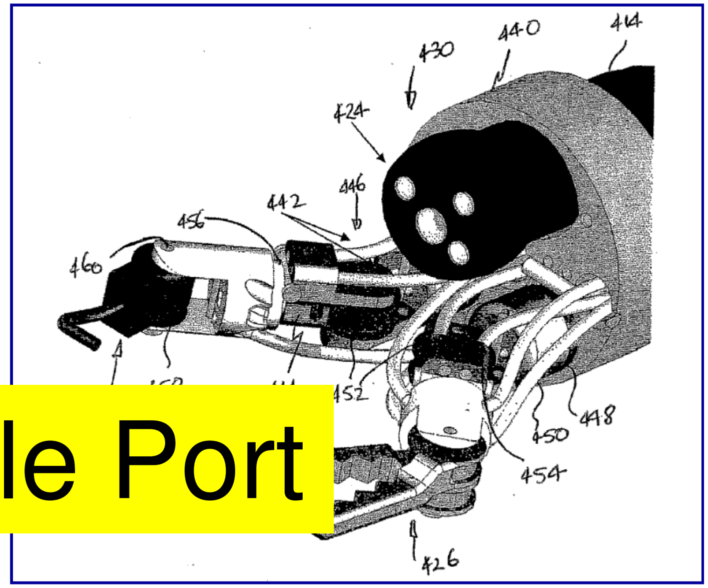
Bimanual scarless endoscopic surgery requiring advanced kinematics → **Multiple capsules/modules for building up an interventional robot with advanced capabilities in terms of therapy and diagnosis**

Examples of devices for improving the kinematics with an endoluminal approach

EndoVia (Hansen Me

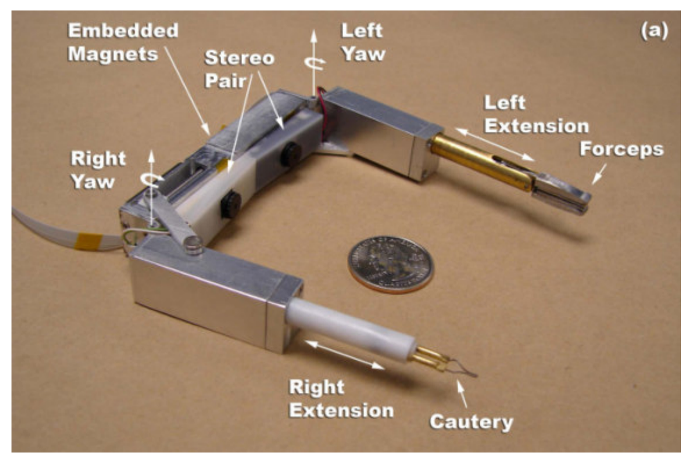


Bimanual – Single Port



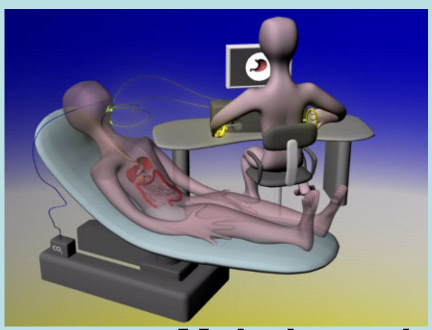
National University of Singapore

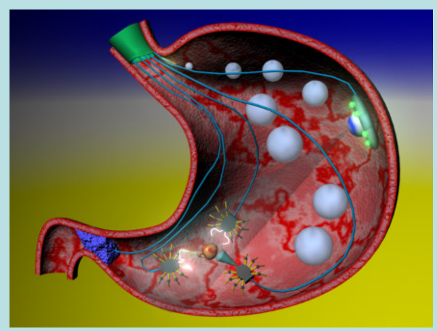
Nebraska Surgical Solutions, Inc., USA



ARAKNES - Array of Robots Augmenting the KiNematics of Endoluminal Surgery

The ultimate goal: to integrate the advantages of traditional open surgery, laparoscopic surgery (MIS), and robotics surgery into a deeply innovative system for <u>bi-manual, ambulatory, tethered, visible scarless surgery, based on an array of smart microrobotic instrumentation</u>





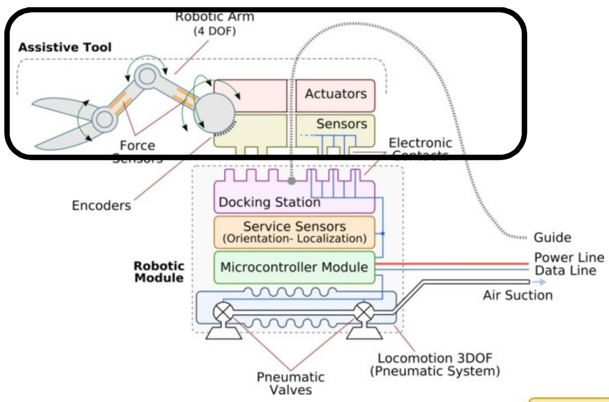
Main intended interventions:

Endoluminal and transluminal surgery (bariatric surgery, local excision, others)

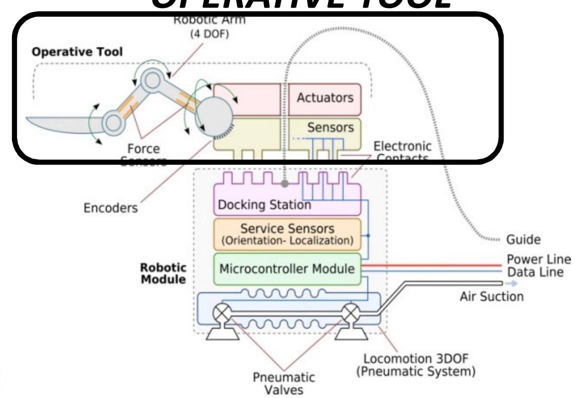
Single-port laparoscopy

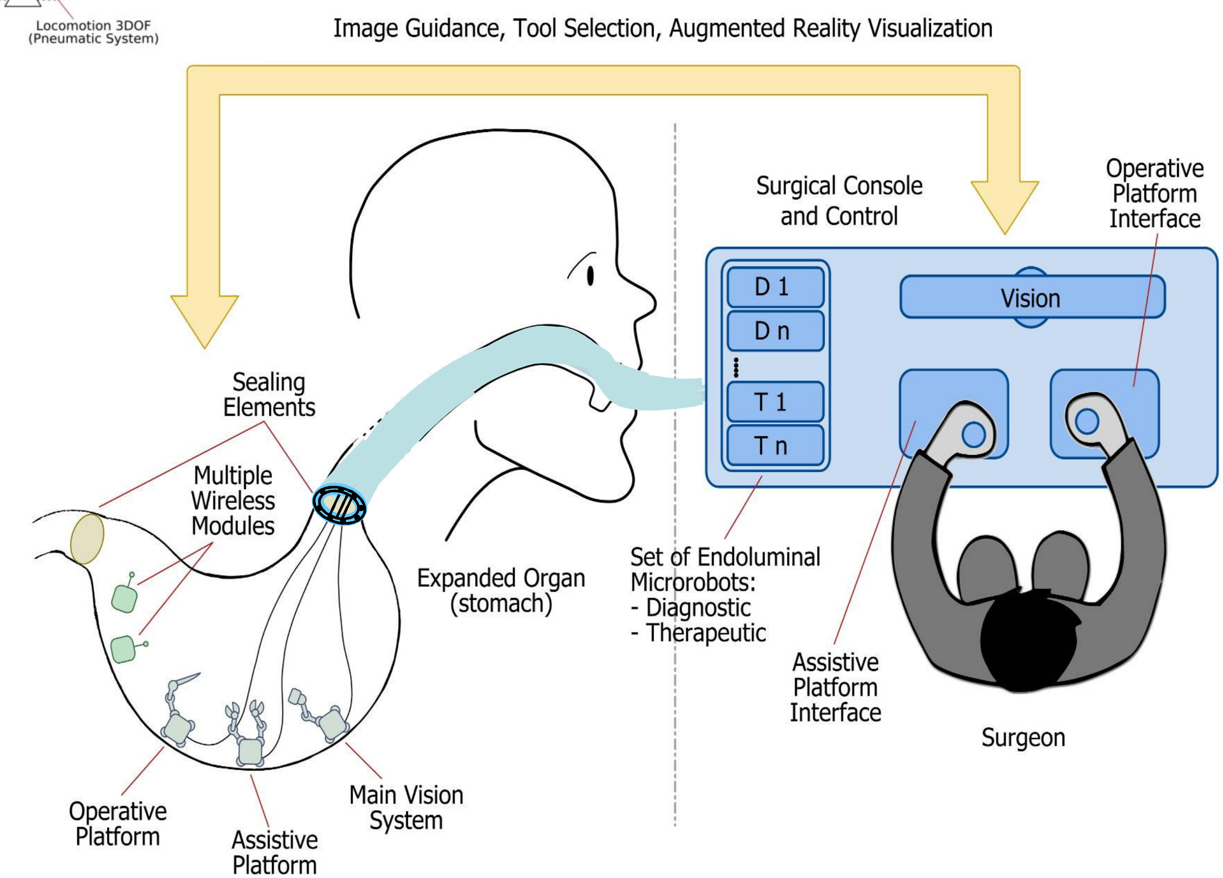
ARAKNES - Array of Robots Augmenting the KiNematics of Endoluminal Surgery

ASSISTIVE TOOL



OPERATIVE TOOL

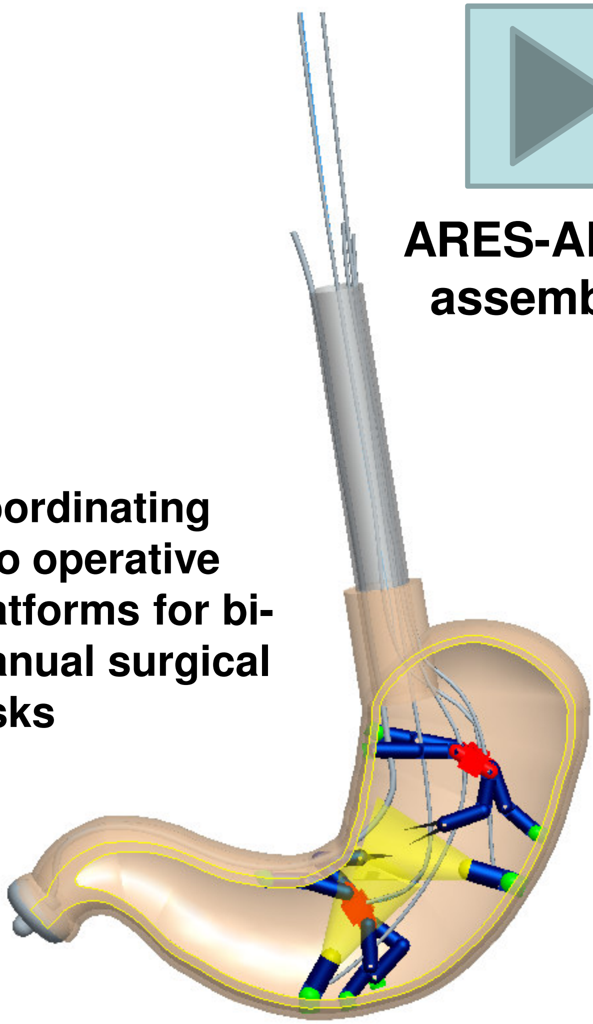




ARAKNES platform concept

A.R.A.K.N.E.S.
Array of Robots Augmenting the KiNematics of Endoluminal Surgery

Coordinating two operative platforms for bi-manual surgical tasks

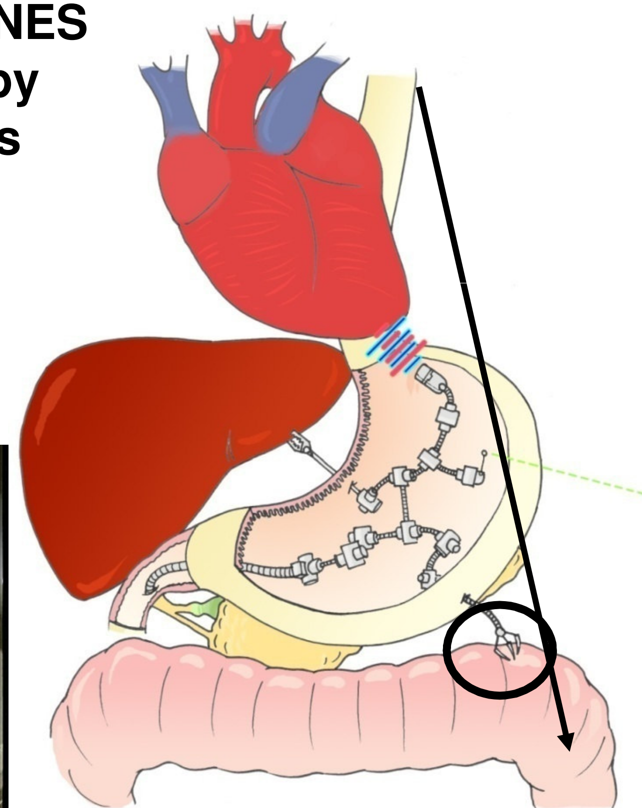


ARES-ARAKNES assembly plan

ARES-ARAKNES assembly by guidewires

Robot finally assembled in the porcine stomach

Towards novel instrumentation for NOTES

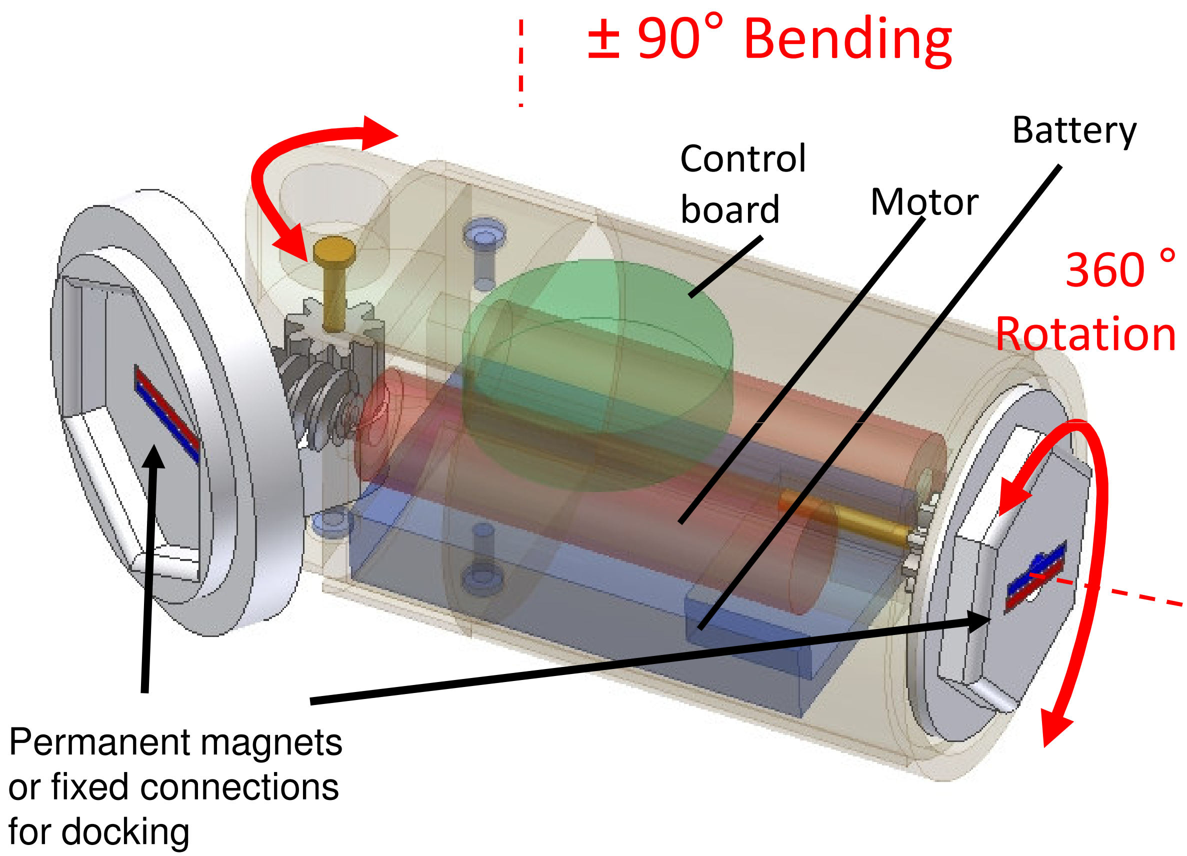


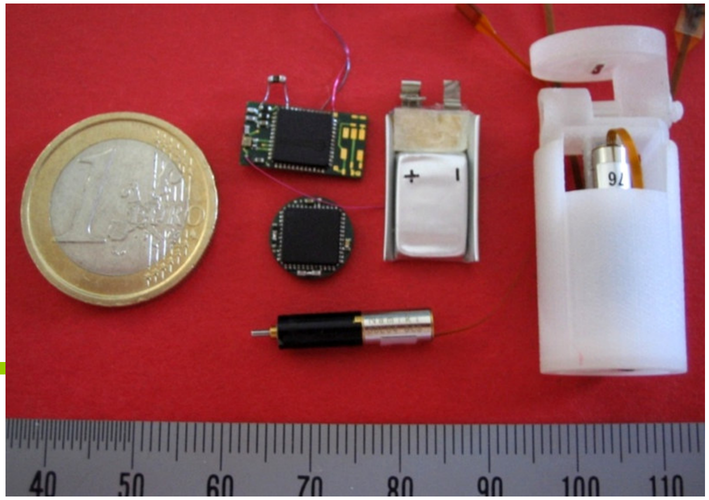
The ARAKNES Project has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement num. 224565.

Patent submitted for the procedure and the single module

The basic module

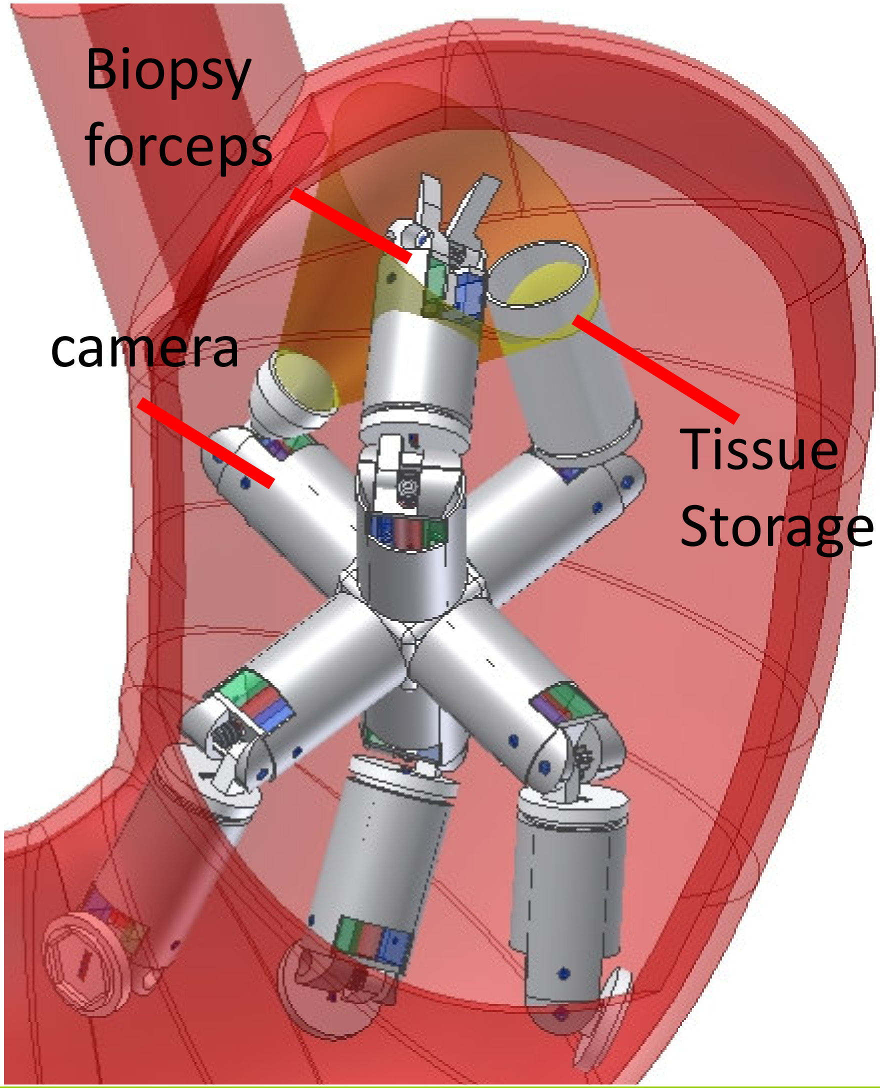
ϕ 15.4mm * L 36.5mm : 4mm motor x2, Li-Po battery, Controller



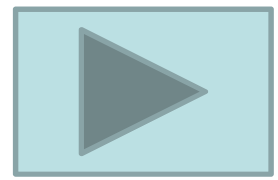


The ARAKNES Project has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement num. 224565.

Example of a multi-module robot integrating a grasping tool



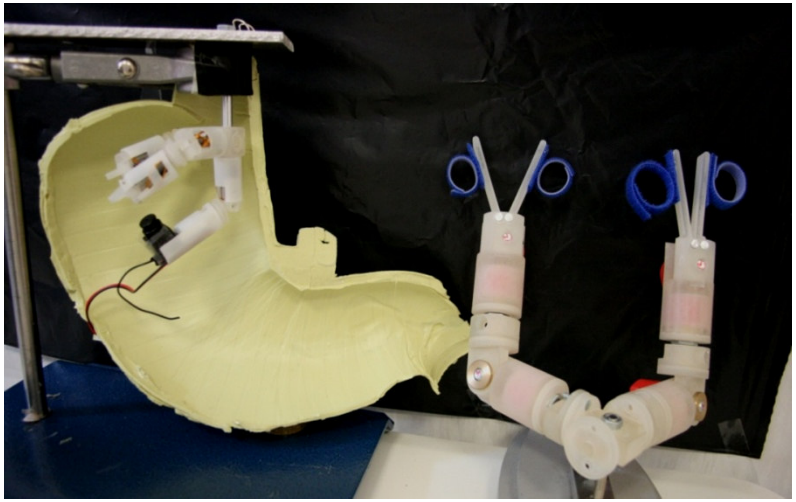
12 Modules
- -Camera X1
- -Forceps X1
- -Storage X1
- -Central X1
- -Structural X8

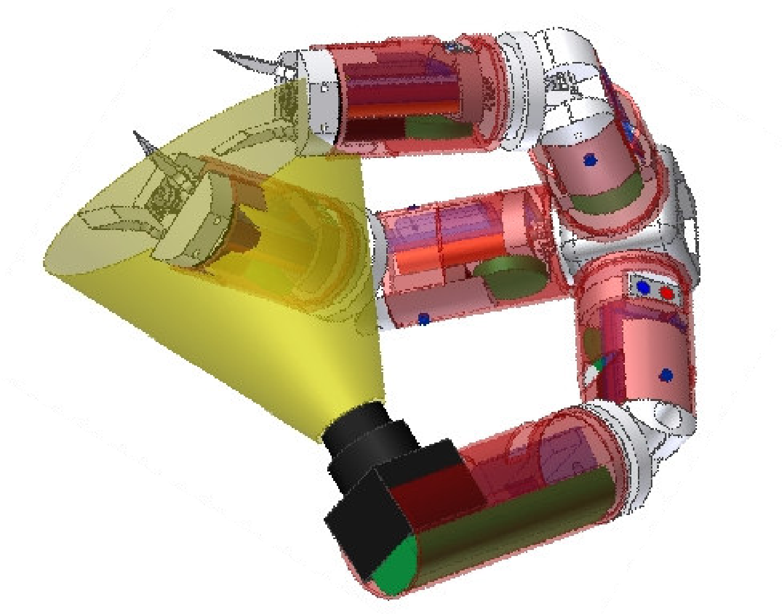


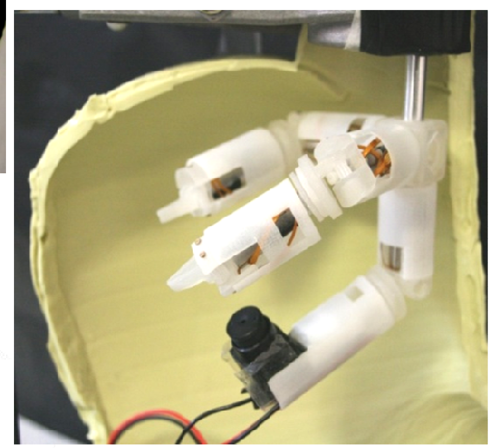
ARES-ARAKNES system performance

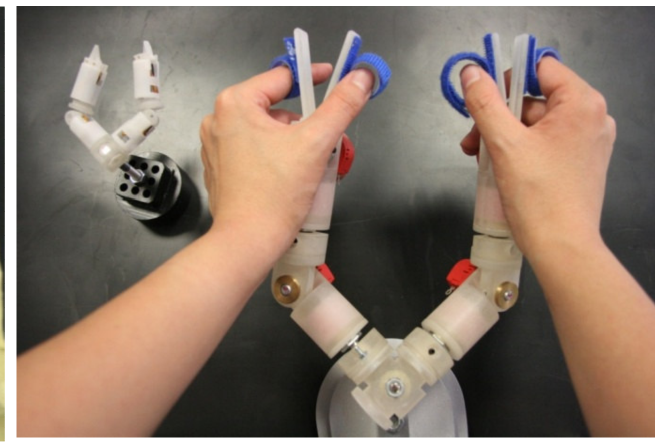
The ARAKNES Project has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement num. 224565.

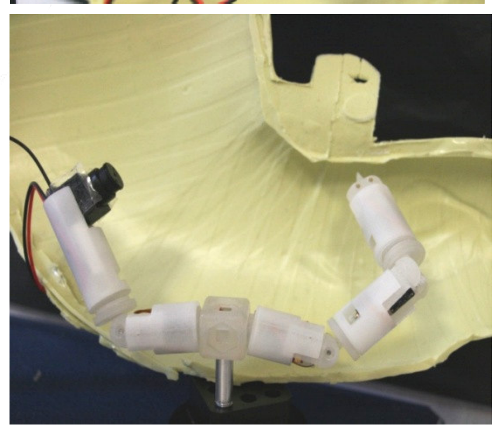
Surgeon – robot interaction

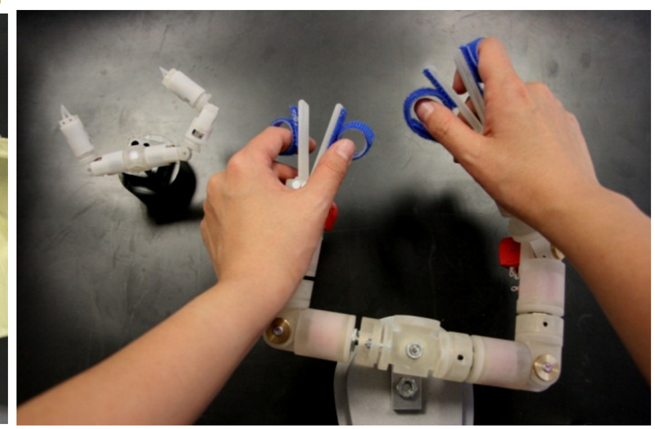






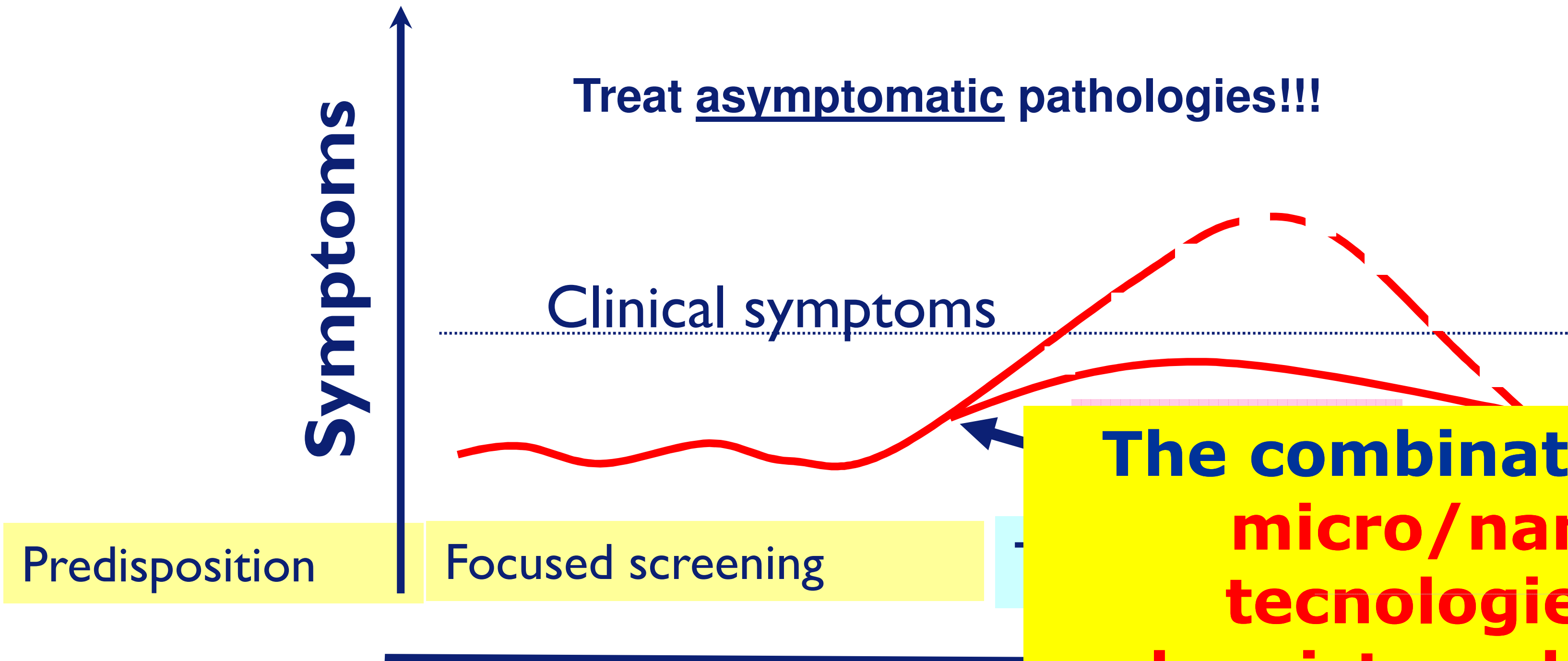




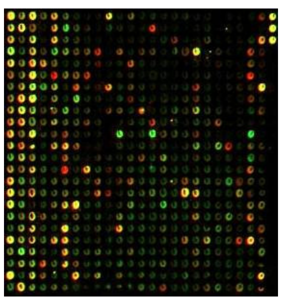


Prevention: the role of modern medicine

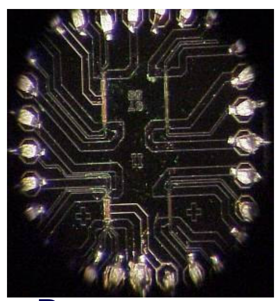
Courtesy by Philips



The combination of micro/nano tecnologies, chemistry, physics and microrobotics will be one of the key technologies enabling future high quality, early and minimal invasive surgery



Gene Chip



Biosensor

Molecular Diagnostics

Tomorrow's technolo

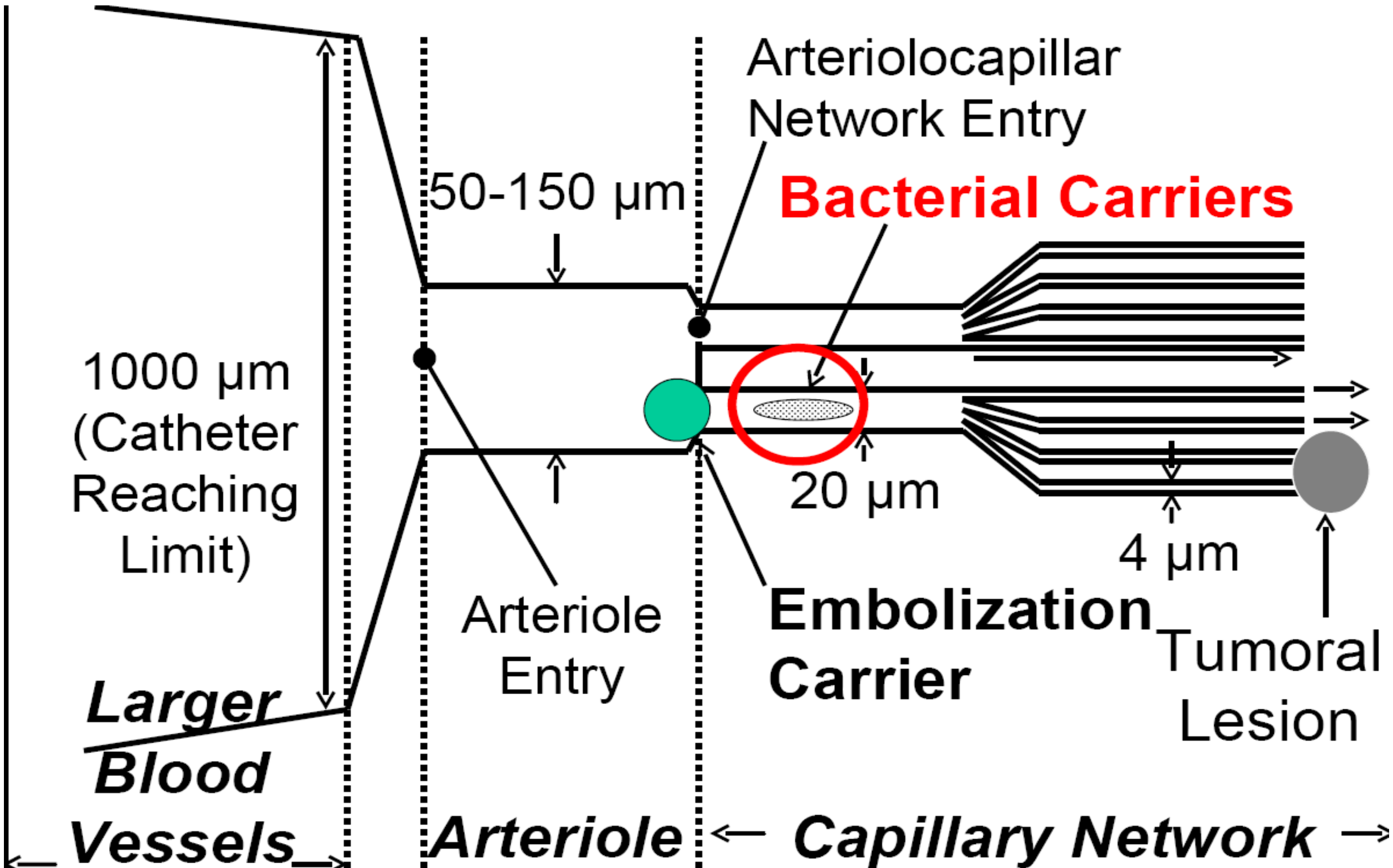
and imaging & molecular therapy

more advanced solutions for MRI guided nano-therapy

FANTASTIC VOYAGE—FROM FICTION TO REALITY

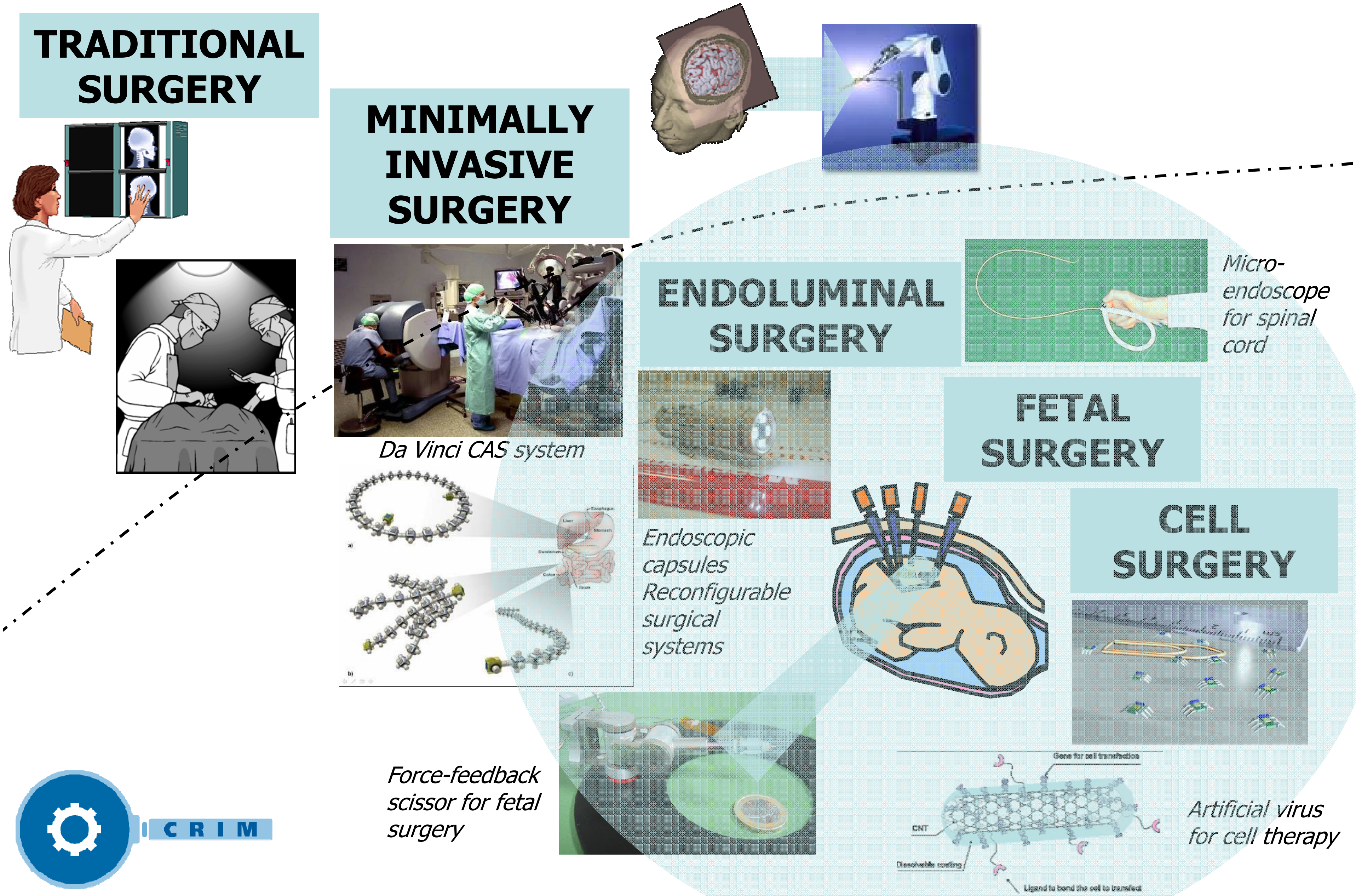
ÉCOLE POLYTECHNIQUE DE MONTRÉAL RESEARCHERS MAKE NEW INROADS FOR CANCER TREATMENT BY USING MRI TO TRACK AND PROPEL DEVICES THROUGH THE BLOODSTREAM.

By Véronique Barker



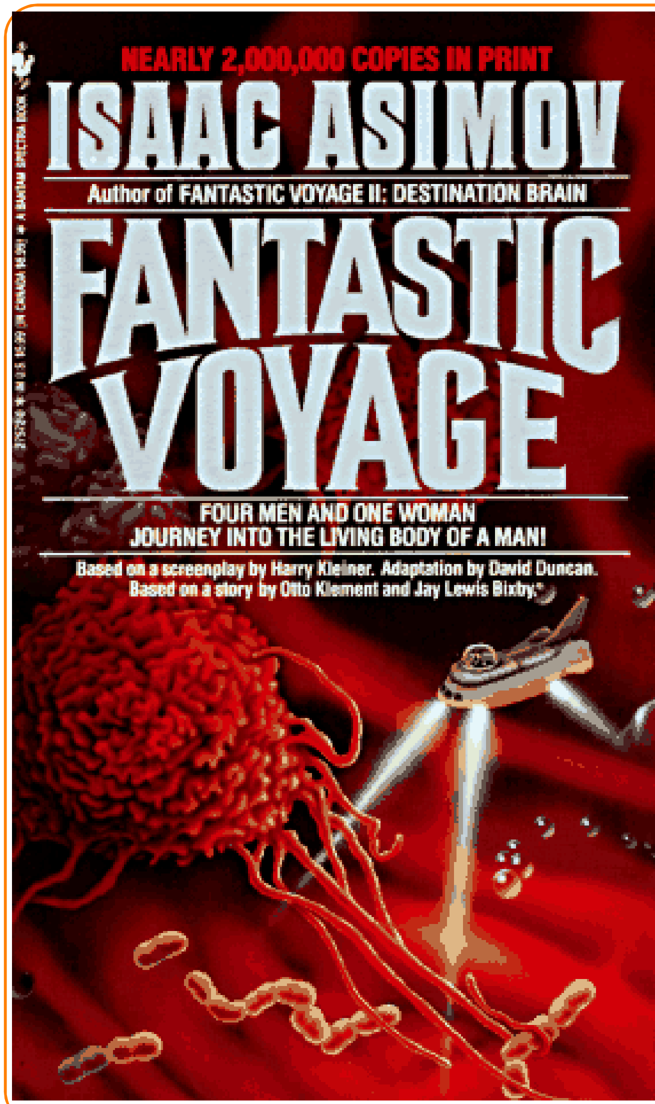
Magnetotactic bacteria for therapeutics delivery under magnetic field and MRI

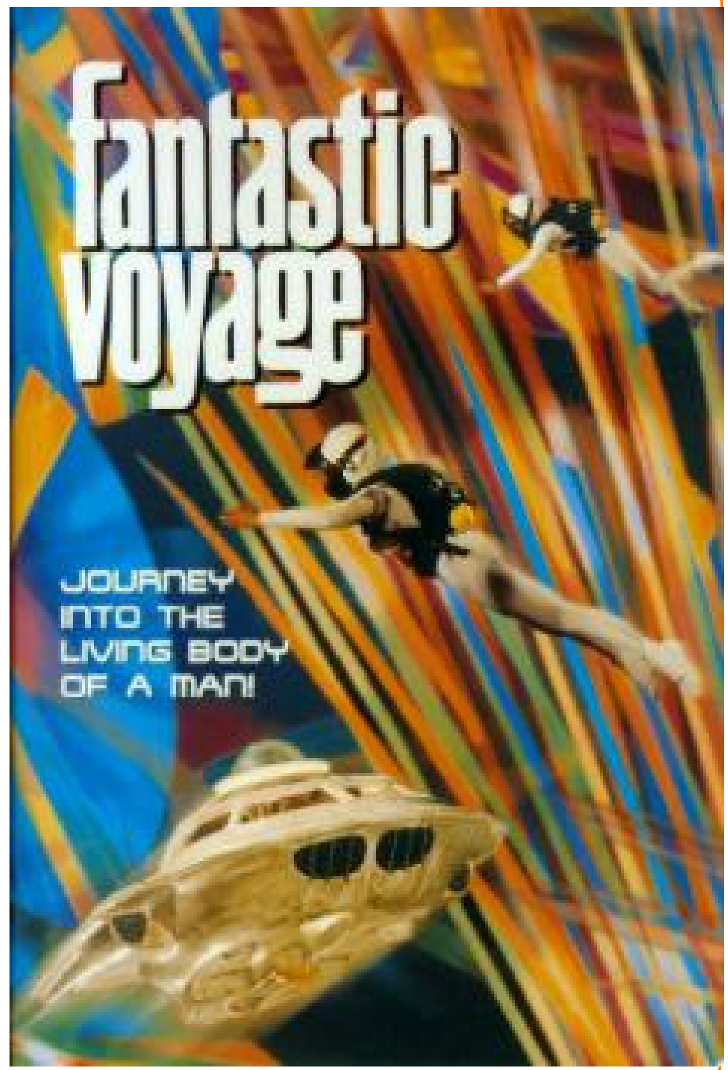
The Evolution of Surgery



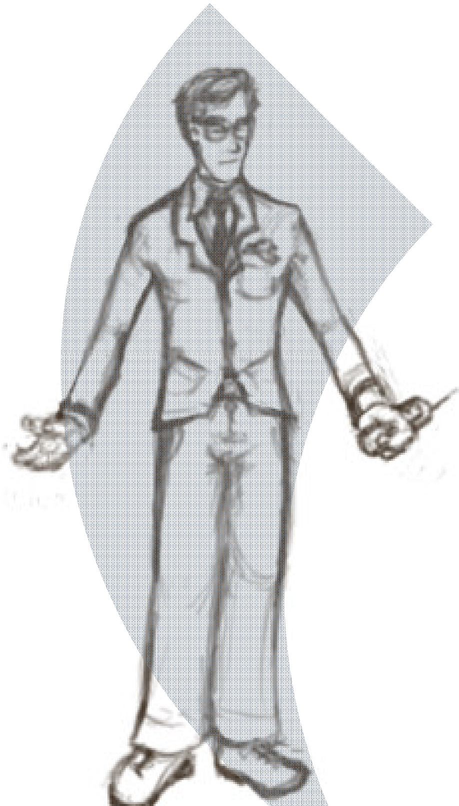
CRIM

Beyond Endoluminal Surgery: microrobots exploring the human body autonomously

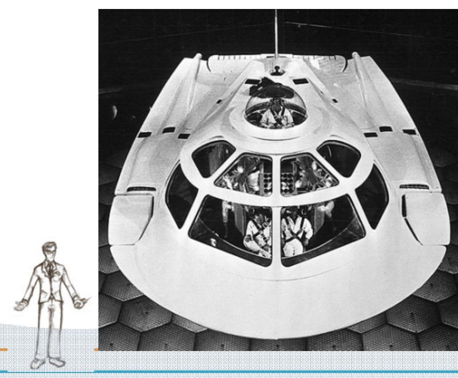


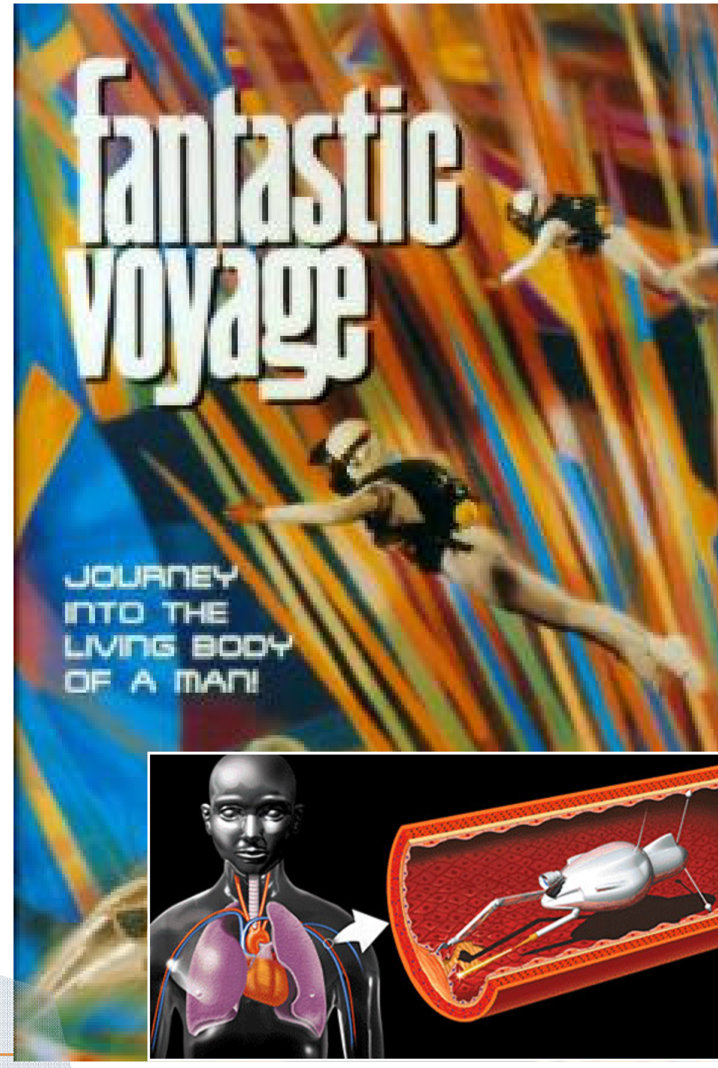


New strategies for locomotion and control are needed

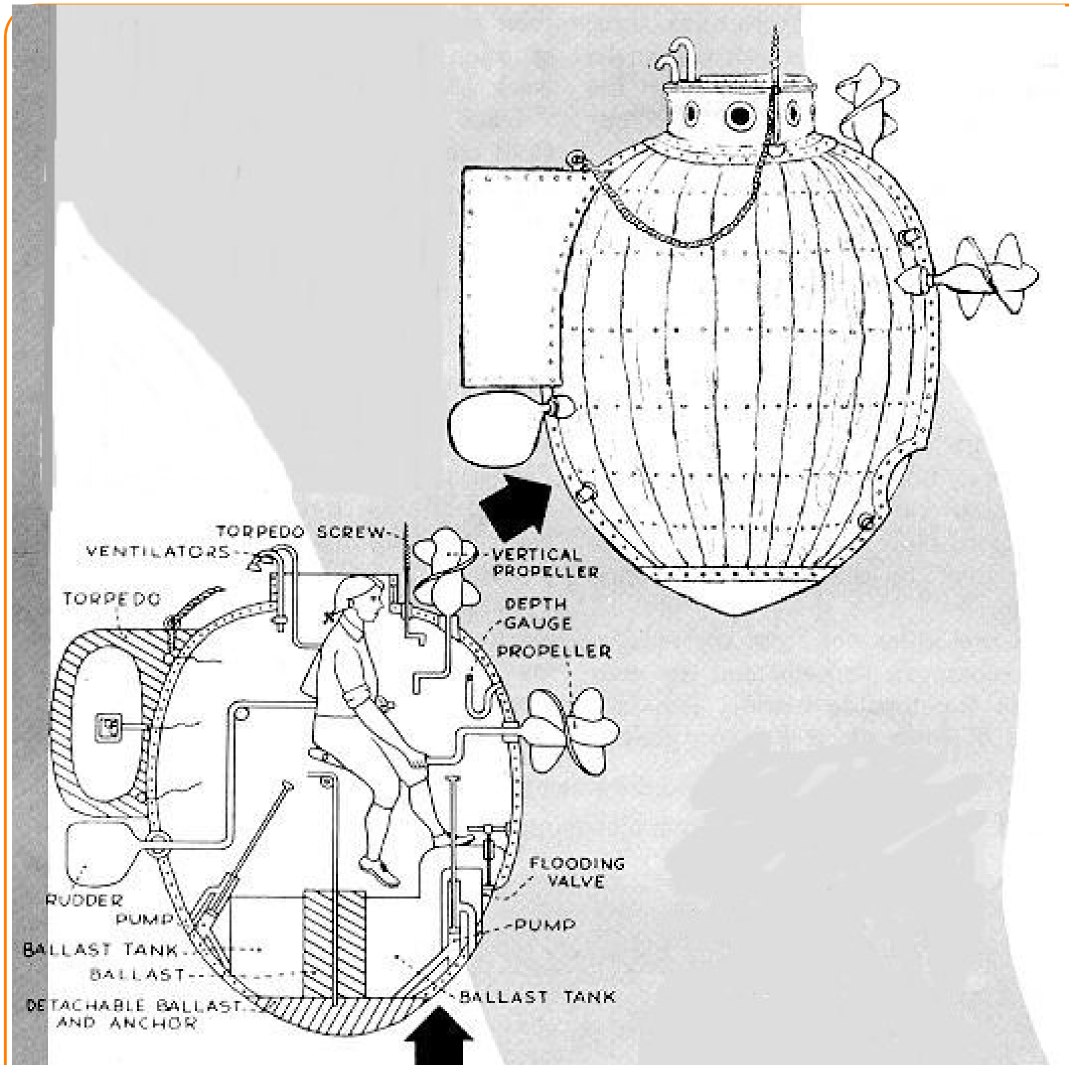


The science fiction dream: “shrinking” the operator and putting him/her inside the machine





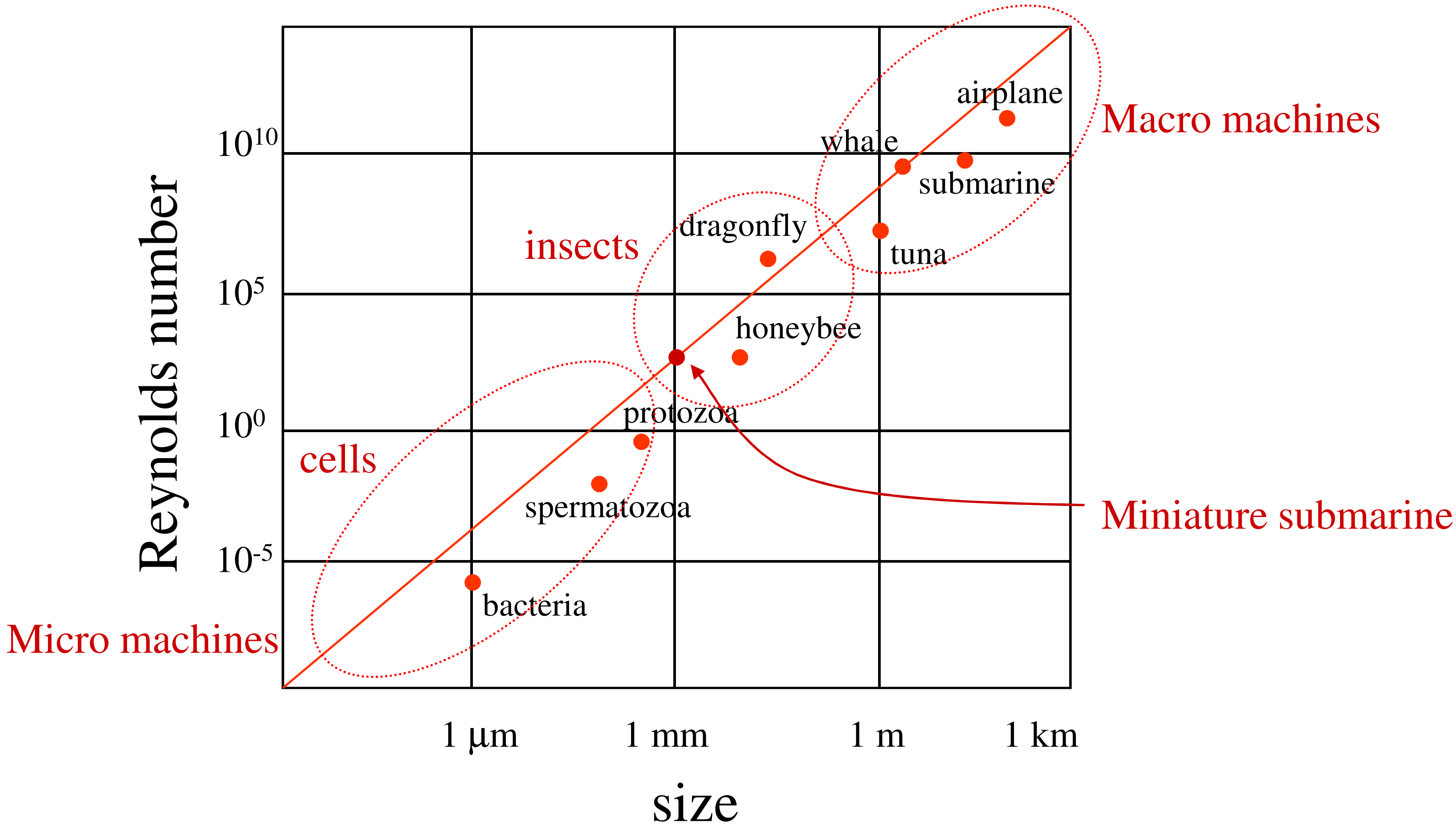
Is it possible to shrink a medical submarine by using the same design rules used in mechanical engineering?



The submarine *Turtle* built by David Bushnell in 1776.

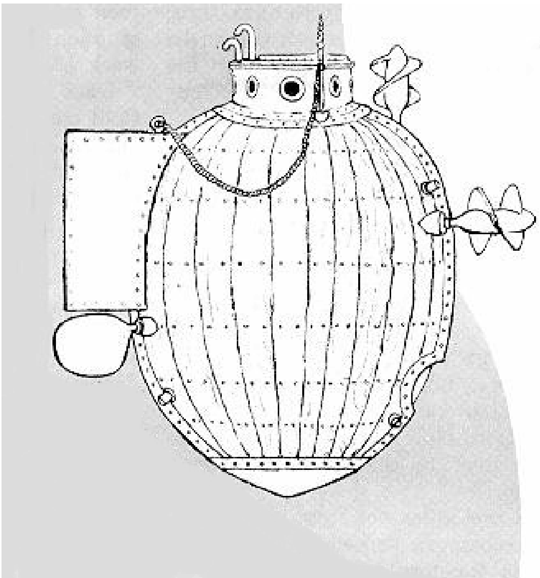
THE PROBLEM:
Scaling a Submarine from a diameter of 2.5 m down to a diameter of 1 mm

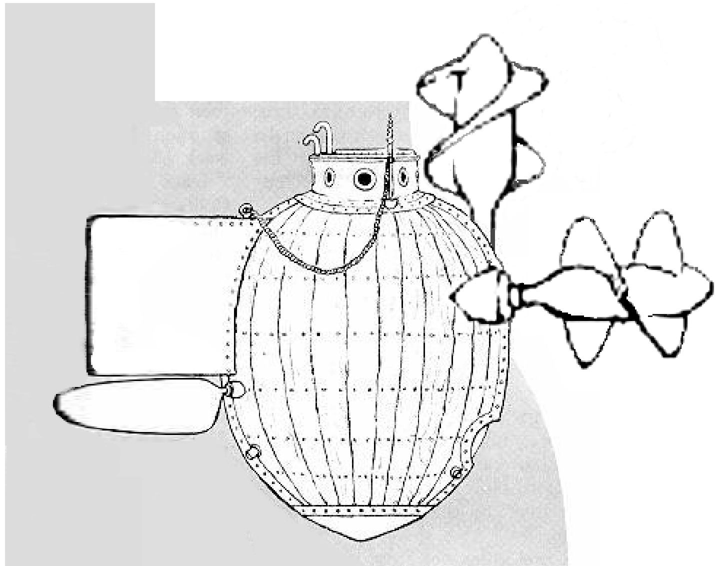
Viscous resistance is dominant in (biological) micro-machines



Reynolds number: $\frac{\text{inertial force}}{\text{viscous resistance}}$

The scaled submarine





2.5 m

0.5 mm

Propulsion type: *Human*

Propeller efficiency: **0.9**

Speed: **0.5 m/s**

Engine Power: **200 W**

Propulsion type: *Electrical*

Propeller efficiency: **3.5 10^{-8}**

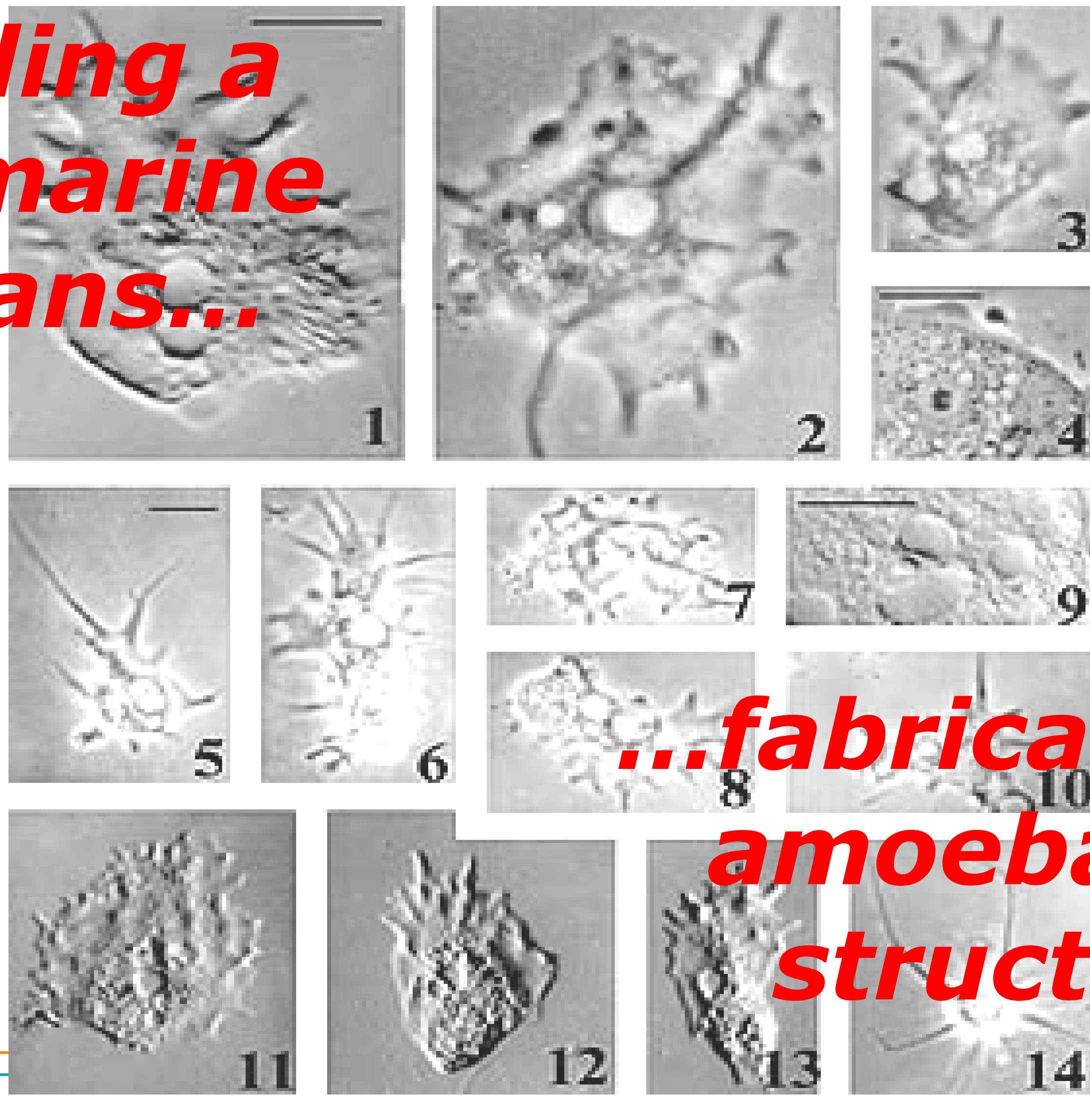
Speed: **0.1 mm/s**

Engine Power: **1.3 µW**

Propellers have been un-proportionally scaled to preserve their efficiency and robustness. Directionality organs have been amplified to balance the submarine.

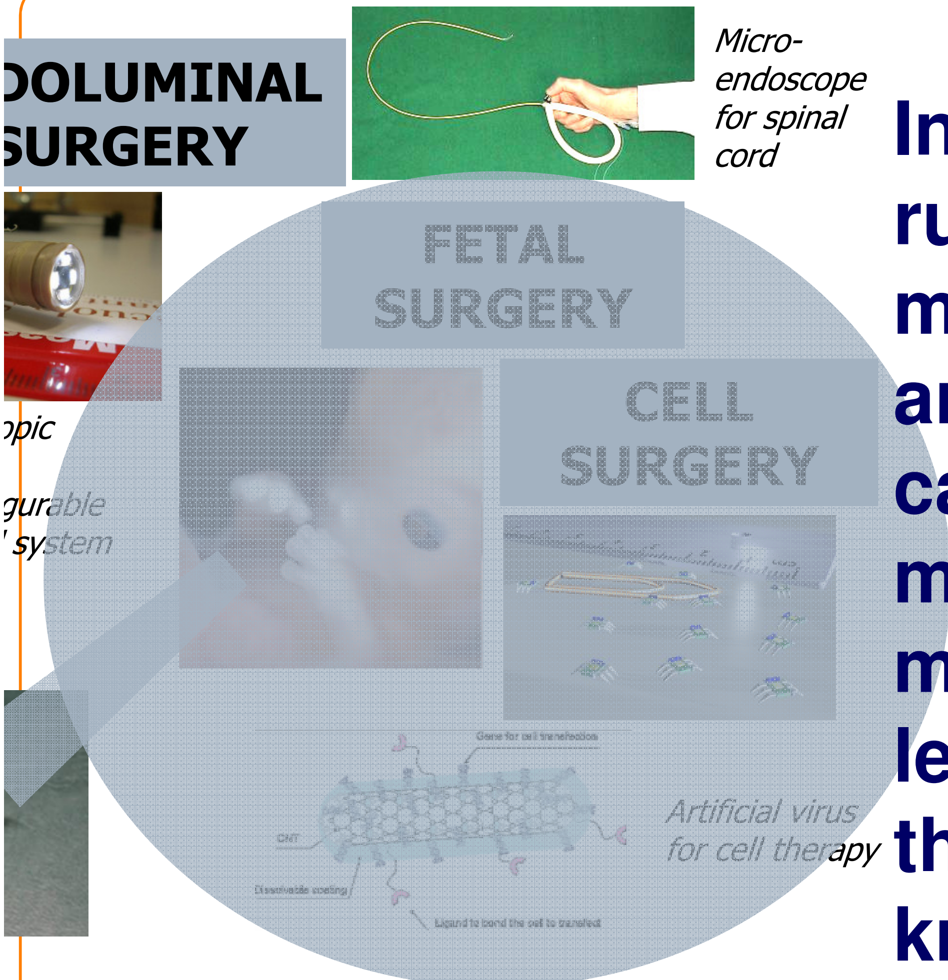
Learning from Nature

Scaling a submarine means...



...fabricating an amoeba-like structure!

What is needed beyond the millimetric scale?



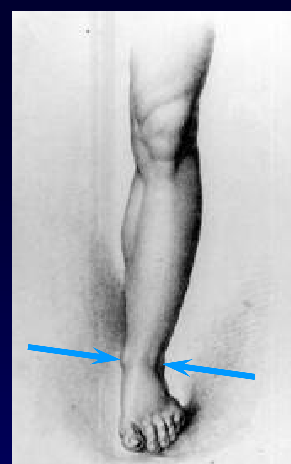
In the millimeter scale, rules derived from microengineering, fluidics and some hints from nature can help to design effective microrobots. In the micro/nano scale (at the level of cellular surgery and therapy machines) new knowledge and disciplines must contribute

Scaling mechanical structures is not a trivial task: surface and volume forces

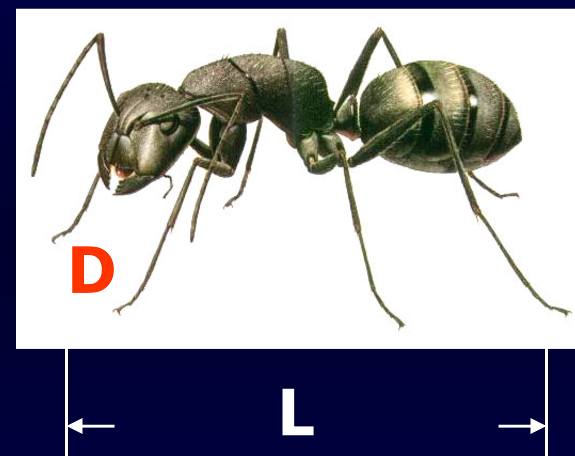
$C_S = 16\%$

$$C_S = \frac{D}{L}$$

$C_S = 10\%$



$C_S = 0{,}8\%$



$$C_S = \sqrt{K \frac{\rho g}{\sigma} \cdot L}$$

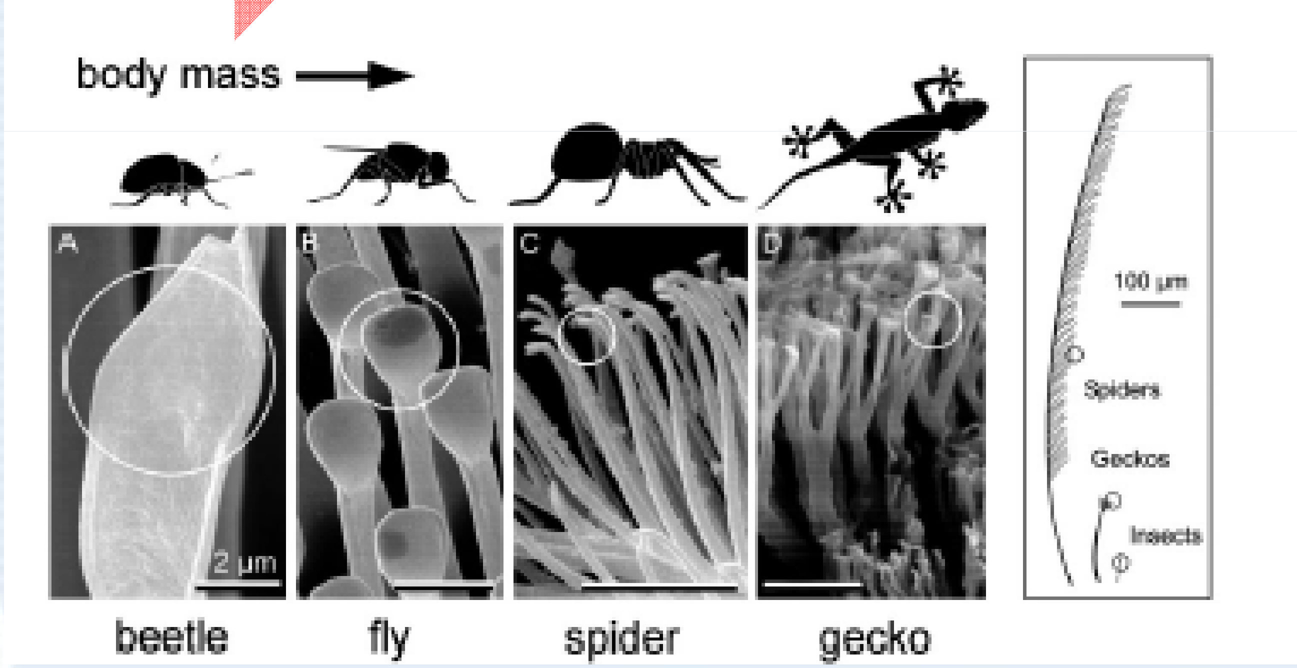
When the size of a structure decreases, thinner sections can better withstand volume forces

Where "nano-knowledge" meets the mini- and micro-domain: Shaping the leg hooks for a safe and flexible attachment…

From micro to nano contacts in biological attachment devices

Eduard Arzt[†‡], Stanislav Gorb[†§], and Ralph Spolenak[†]

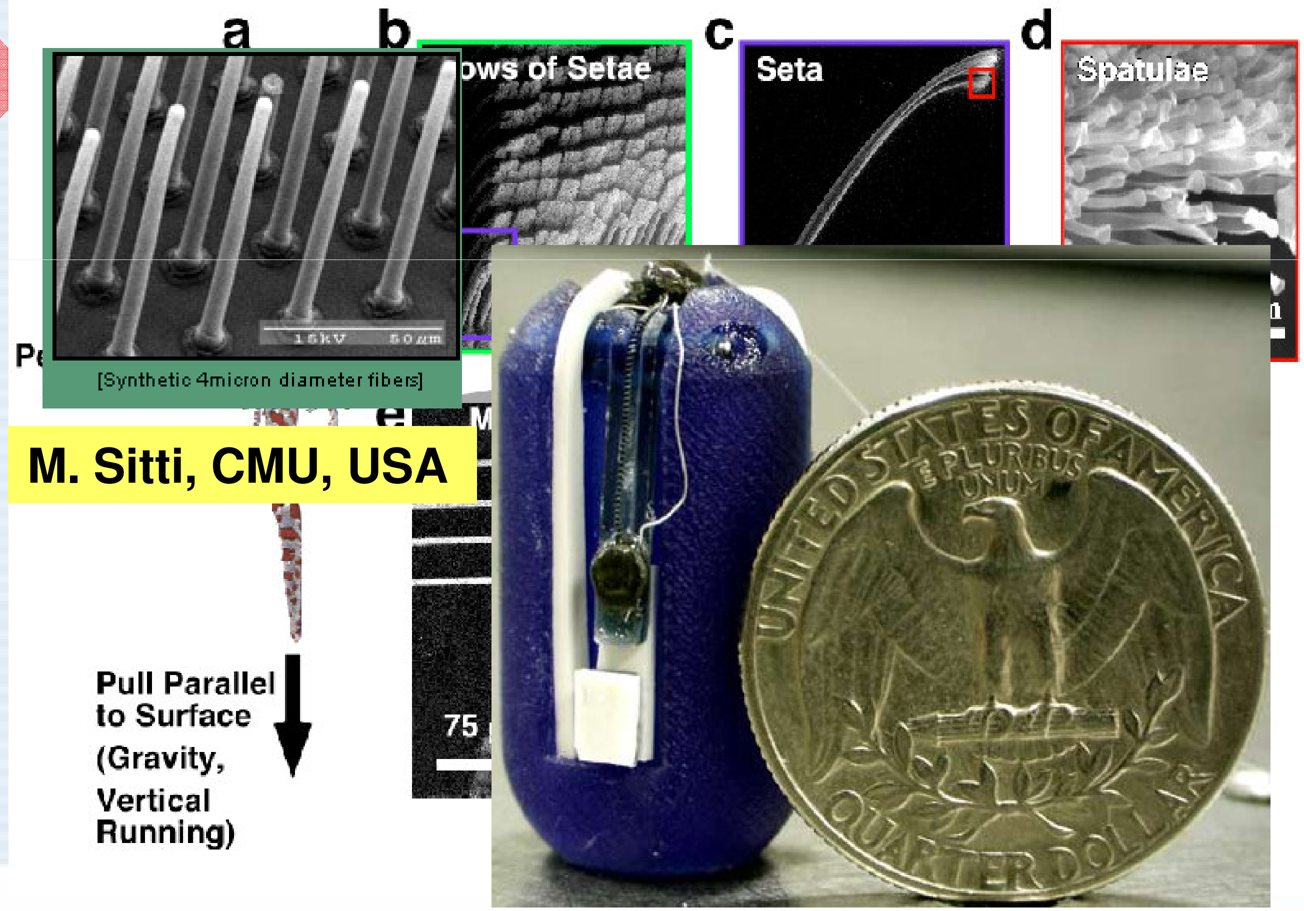
[†]Max Planck Institute for Metals Research, Heisenbergstrasse 3, 70569 Stuttgart, Germany; and [§]Biological Microtribology Group, Max Planck Institute of Developmental Biology, Spemannstrasse 35, 72076 Tübingen, Germany



Terminal elements (circles) in animals with hairy design of attachment pads. Note that heavier animals exhibit finer adhesion structures.

Where “nano-knowledge” meets the mini- and micro-domain: Shaping the leg hooks for a safe and flexible attachment…

Adhesive force of a single gecko foot-hair, K. Autumn, et al., Nature , vol. 405, pp. 681-685, June 8, 2000.



M. Sitti, CMU, USA

SCALING LAWS – (Classical) Mechanics

Let L denote a characteristic length-scale; then (*):

Inertial momentum: $I \sim mL^2$	L^5
Mass (fixed density): m	L^3
Gravitational force	L^3
Adhesion (Van der Waals) forces	L^2
Striction (i.e. adhesion + friction) forces	L^2
Elastic potential energy (linear spring, fixed stiffness)	L^2
Period of oscillation (linear spring, fixed stiffness)	$L^{3/2}$
Capillary forces	L

← molecular rotors are expected to rotate fast: 10-100 GHz!

← gravity becomes negligible!

Note: a constrained down-sizing (e.g. keeping the material stress fixed) lead to different scaling…

(*) **provided that**:

- it is possible/reasonable to consider the relevant entities as (well-defined) constants;

- the geometric scaling is homothetic (not correct for mostly-planar devices).

SCALING LAWS – Electromagnetism

Let L denote a characteristic length-scale; then (idem):

Force between two coils (fixed current density)	L^4
Force coil - permanent magnet (fixed current density)	L^3
Capacitor stored energy (fixed charge density)	L^3
Capacitor stored energy (fixed voltage)	L
Capacitance (parallel plates, fixed dielectic)	L
Ohmic current (fixed voltage)	L
Ohmic resistance (fixed conductivity)	L^{-1}
Power dissipated per unit area	L^{-1}

Very fast decreasing

Slow decreasing

Note:

- constrained down-sizings (e.g. keeping fixed the electrostatic field) lead to different scalings;

- usually the current density is increased when down-sizing (to increase the magnetic field); the resulting heat can be effectively removed;

- quantum mechanical effects more important here than for mechanics (classical continuum models are useless at very small scales)

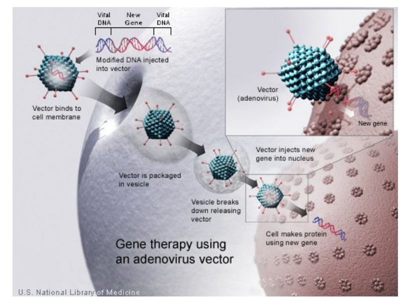
Cell Therapy and Surgery

- Physics
- Life Science
- Chemistry
- Neuroscience
- Genetics

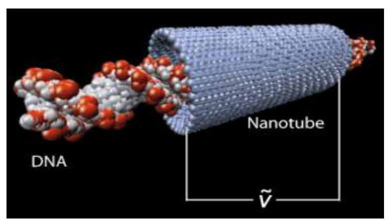
→ **Cell Surgery and Therapy**

Minimally Invasive Surgery → **Endoluminal Surgery** → **Cell Surgery and Therapy**

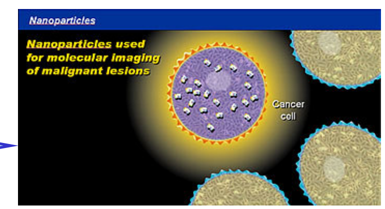
Drug delivery →



Gene/DNA therapy →



Cellular ablation →

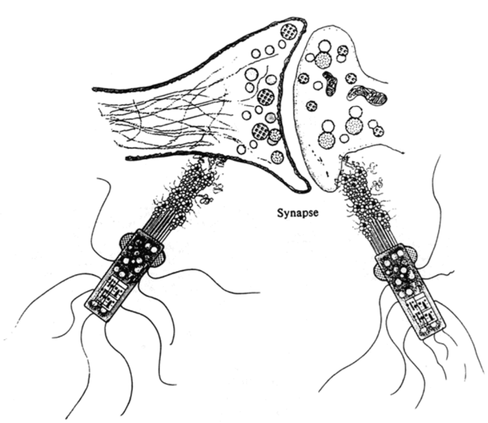


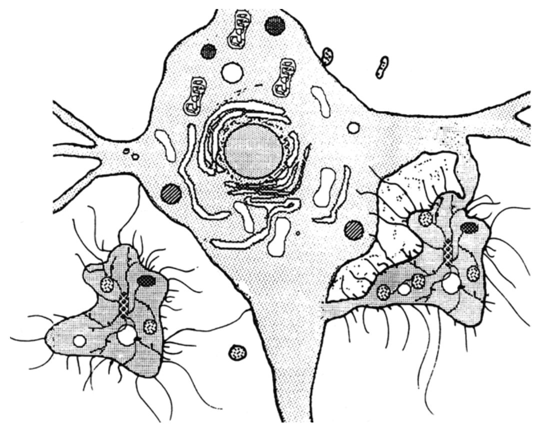
→ Medical Nano-Robotics & NEMS: from 1960 until now

1977: First conceptual design of biological inspired nano-robots

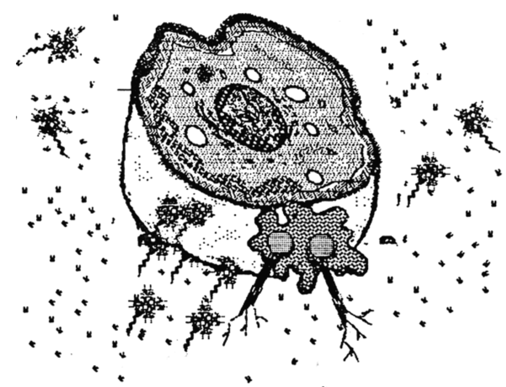
"The Anabolocyte: A Biological Approach to Repairing Cryoinjury," Michael G. Darwin*, **Life Extension Magazine**: A Journal of the Life Extension Sciences 1(July/August 1977):80-83.

*Institute for Advanced Biological Studies (IABS) in Indianapolis (merged with the California-based Alcor Life Extension Foundation in 1982)





Cell Repair Underway With Molecular Repair Devices



1985: Advanced conceptual design of biological inspired nano-robots

"Molecular Technology and Cell Repair Machines," K. Eric Drexler*, paper published in **Claustrophobia Magazine** (August-October 1985) and in Cryonics Magazine (Dec 1985 - January 1986).

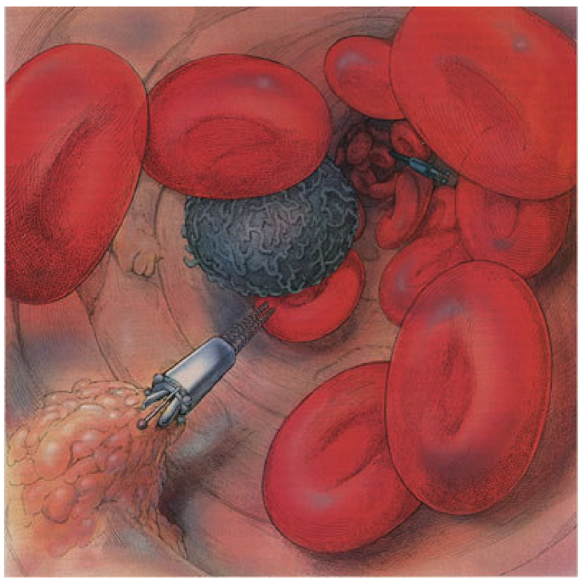
*MIT, USA

→ Medical Nano-Robotics & NEMS: from 1960 until now

1988: Design of swimming nanomachines and immuno machines

"Nanotechnology -- Wherein Molecular Computers Control Tiny Circulatory Submarines," A.K. Dewdney*, **Scientific American** 258 (January 1988):100-103 (101)

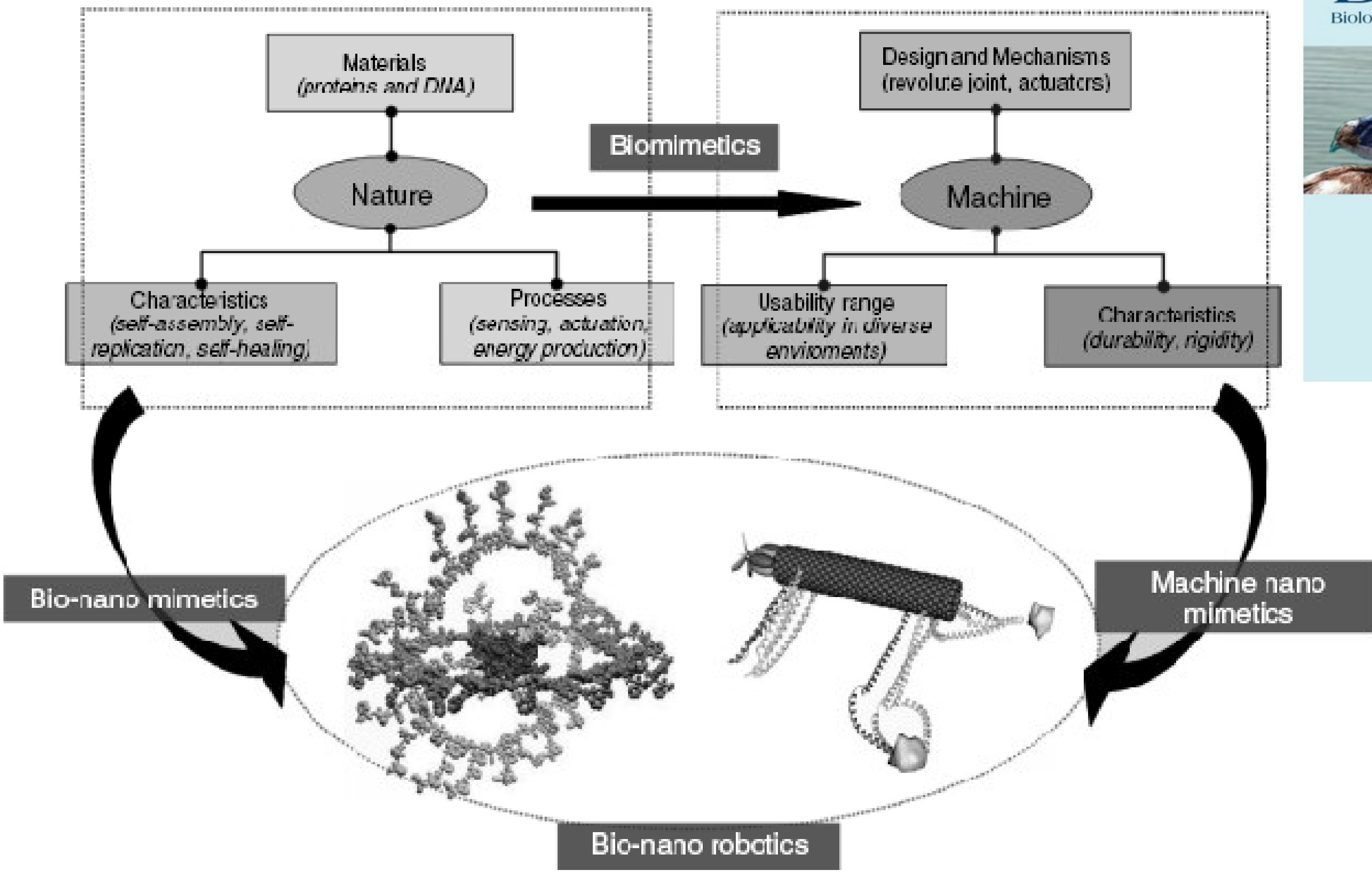
* Professor of computer science at the University of Western Ontario

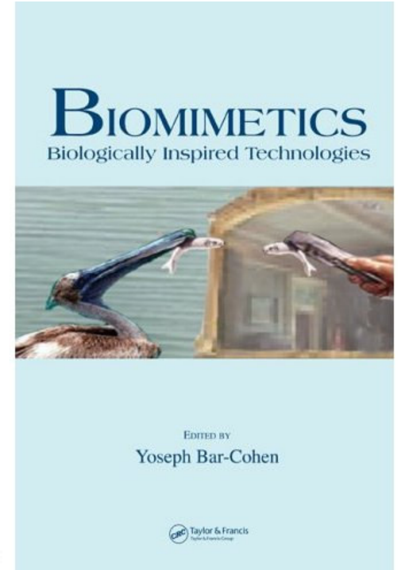


Nanosubmarine. *A nanomachine swimming through a capillary attacks a fat deposit (such as normally may accompany an arteriosclerotic lesion).*

Immune machines. *Medical nanodevices could augment the immune system by finding and disabling unwanted bacteria and viruses*

2005: Bio-nanorobotics as discipline

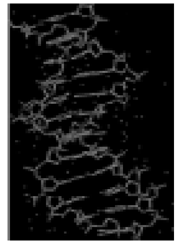
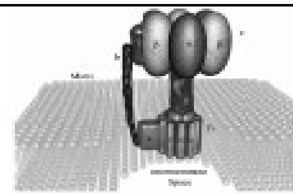
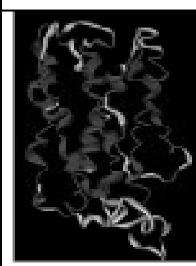
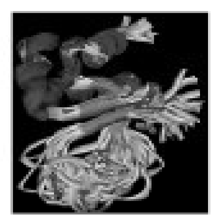


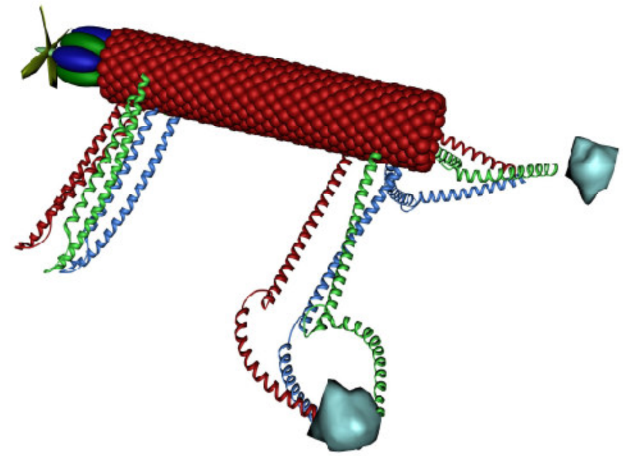


Biomimetics: Biologically Inspired Technologies (by Bar-Cohen)

Bio-Nanorobotics: A Field Inspired by Nature A. Ummat, A. Dubey, and C. Mavroidis

Macro- and bio-nano-equivalence of robot components.

Component	MacroRobots	Bio-Nano Robots
Structural Elements- Links	Metal, Plastic Polymer	 DNA [PDBfile:119D] Nanotubes
Joints	Metal, Plastic Polymer material *Revolute joints* *Prismatic joints* *Spherical joints* *Cylindrical joints*	*DNA* hinge *Molecular* bonds, Synthetic joints
Actuators	Electric motors, Pneumatic motors, Hydraulic motors, Smart material-based actuators	 ATPase protein flagella motors, DNA actuators, Viral protein motors etc.
Transmission Elements	Springs (Metal,Polyvinyl) Bearings Gears	β Sheets Molecular camshaft design Smith ss (2001). United States Patent No. 6,200,782 13 March 2001.
Sensors	Light sensors, force sensors, position sensors, temperature sensors	 Rhodopsin [PDB file-1JFP]  Heat Shock Factor [PDB file–3HSF]



A vision of a nano-organism: CNTs form the main body; peptide limbs are used for locomotion and manipulation. A biomolecular motor at the head propels the device. The "nano-robot" flowing inside a blood vessel, finds an infected cell. It attaches on the cell and projects a drug to repair or destroy the infected cell.

Some examples of nanotechnologies contributing to endoluminal and cell surgery

Specific feature of our approach: stressing the <u>controllability</u> of the surgical and therapy tasks by adding some external control <u>without relying just on natural processes</u>

Exploitation of chemical and physical properties of nanomaterials in endoluminal and cell surgery

Carbon nanotubes (CNTs): blending physical and chemical properties for electroporation, localized hyperthermia, magnetic guided drug delivery, DNA transfection

Boron nitride nanotubes (BNNTs): from nanotubes to nanotransducers! Enhanced physical properties with the same chemical properties of CNTs

Magnetic nanofilms: merging the magnetic control with the therapeutic abilities of nanofilms in endoluminal surgery

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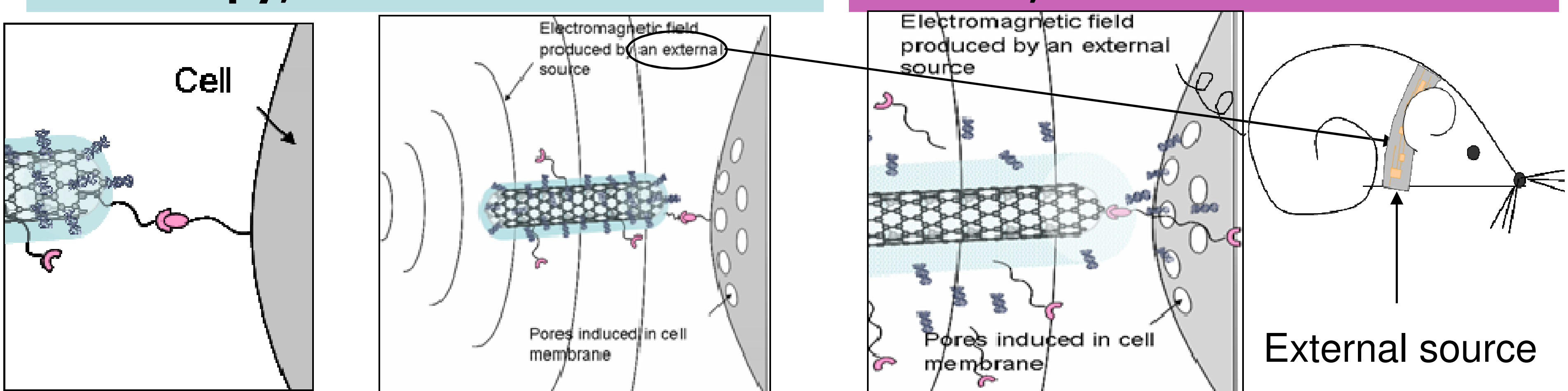
Nano-machines for cell therapy: the NINIVE project (www.niniveproject.org, 6FP NMP 033378)

OBJECTIVE and NOVEL CONVERGING APPROACH:

combining physical and chemical properties of CNTs holds great promise for the development of a new class of CNT-based drugs and therapies extremely controlled (i.e. much more controlled that methodologies based on diffusion, phagocytosis, endocytosis)

Electrical properties (conductive and semi-conductive CNTs); optical properties; strong anisotropy; etc.

Covalent bonding of CNT surface; non-covalent absorption on the CNT surface; etc.



Cellular vector – cell binding

Cell electroporation via the cellular vector

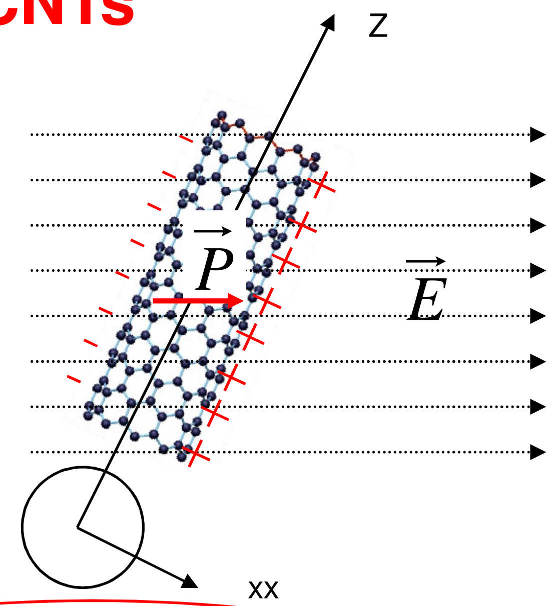
The coating dissolves, genes are released and diffuse across the pores

Our idea: to exploit the highly anisotropic electrical properties of CNTs

carbon nanotubes to a uniform external electric field **E**. The main response of the electrons is the formation of an induced dipole moment **p**. The quantity that relates the two is the polarizability tensor α, defined by $\mathbf{p} = \alpha \mathbf{E}$.

TABLE I. Static polarizabilities per unit length (in Å^2) of various carbon nanotubes of radius R (Å). In cases where $n_1 - n_2$ is a multiple of three, α_{zz} is extremely large and is not given.

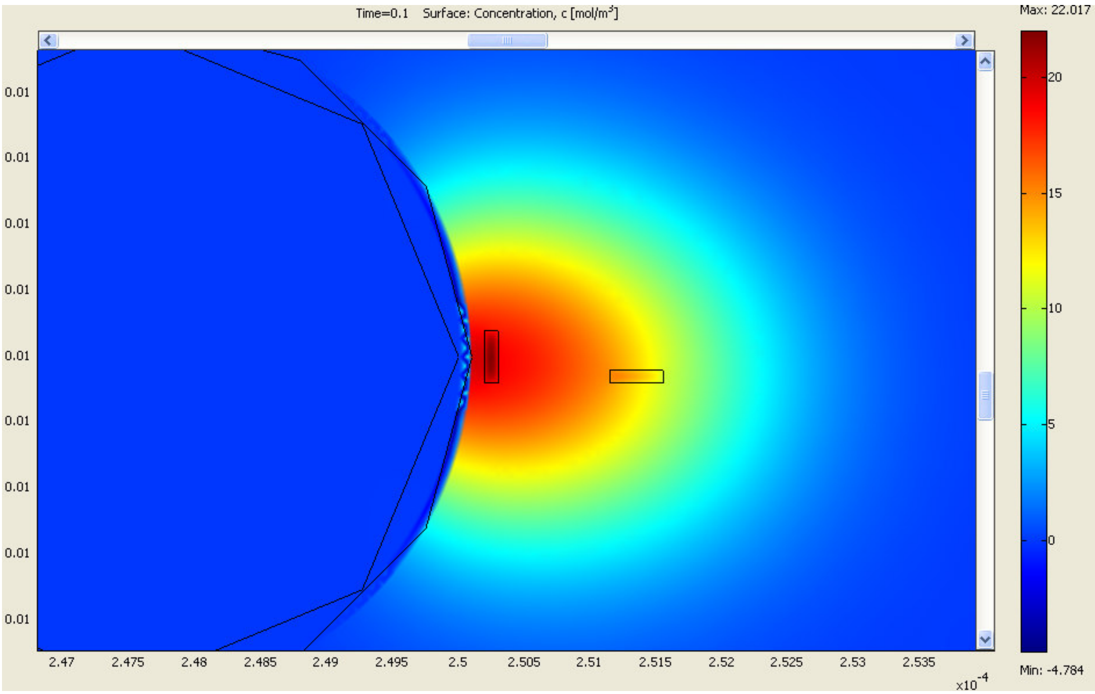
Tube (n_1, n_2)	R	α_{zz}	α_{0xx}	α_{xx}
(9,0)	3.57		40.6	8.9
(10,0)	3.94	174.7	48.5	10.3
(11,0)	4.33	171.6	57.8	12.1
(12,0)	4.73		65.7	13.9
(13,0)	5.12	292.4	76.1	15.8
(14,0)	5.52	268.3	87.4	17.9
(15,0)	5.91		97.4	20.1
(16,0)	6.30	445.5	109.9	22.4
(17,0)	6.70	401.4	123.6	24.9
(18,0)	7.09		136.3	27.4
(19,0)	7.49	651.1	150.6	30.2
(4,4)	2.73		26.6	6.0
(5,5)	3.41		37.4	8.3
(6,6)	4.10		49.8	11.0
(4,2)	2.09	49.1	18.8	4.2
(5,2)	2.46		23.1	5.2



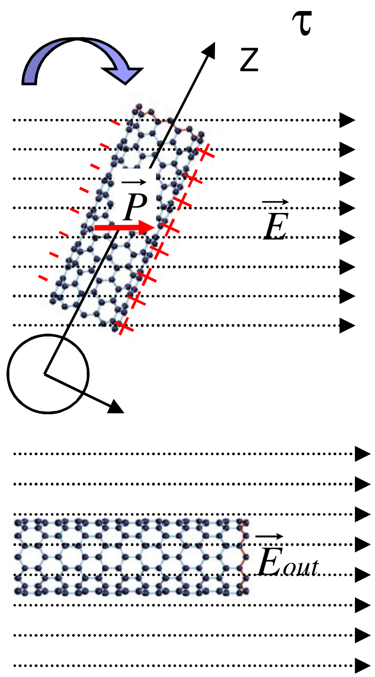
$$\alpha(\omega) = \begin{pmatrix} \dfrac{\alpha_{0xx}(\omega)}{1 + 2\frac{\alpha_{0xx}(\omega)}{R^2}} & 0 \\ 0 & \alpha_{0zz}(\omega) \end{pmatrix}$$

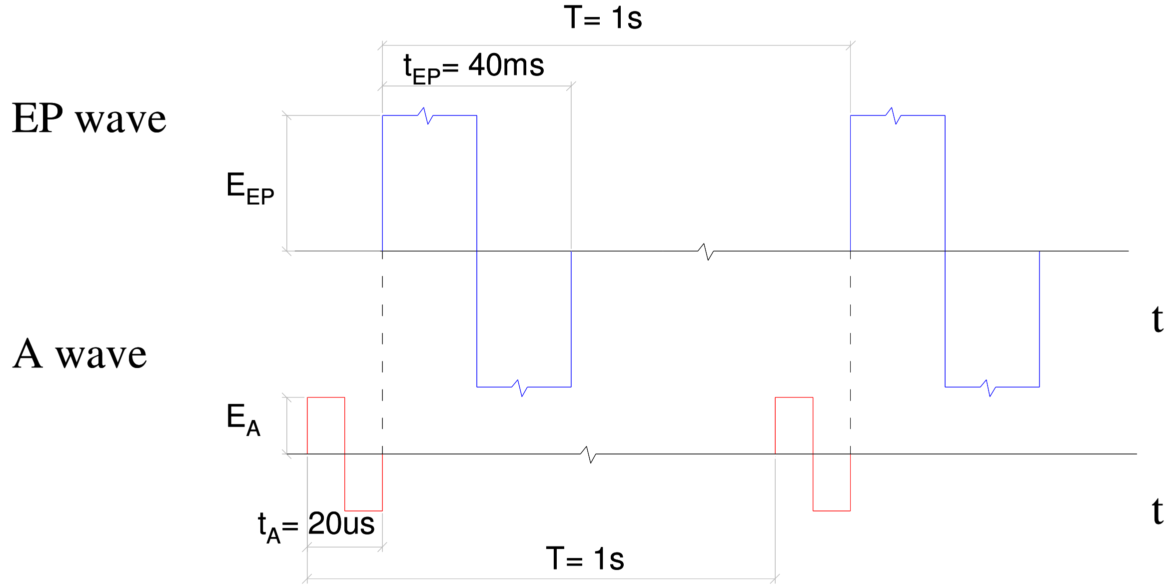
The polarizability tensor is highly anisotropic, as a consequence of the inherent anisotropy of tubes

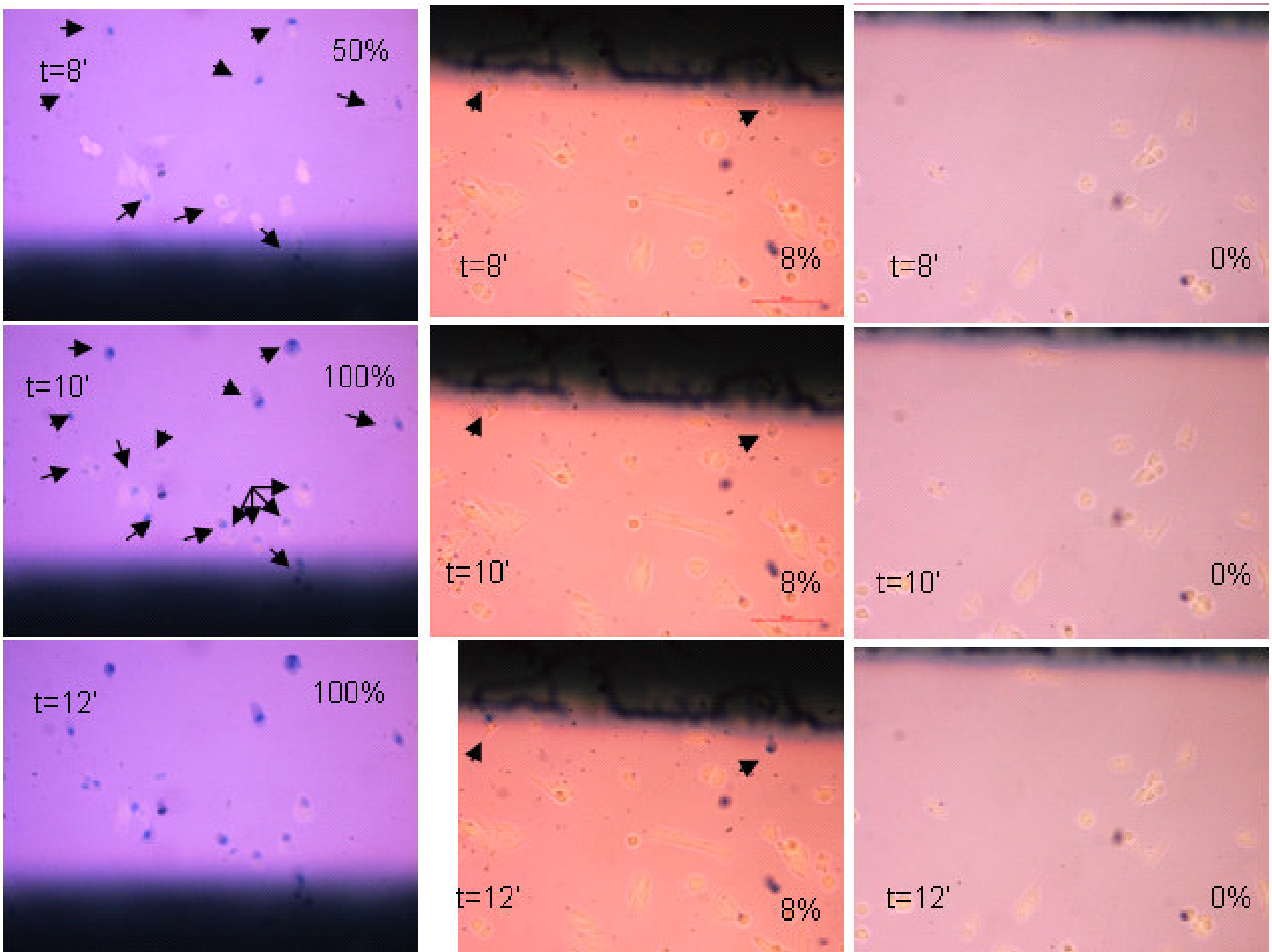
Benedict L-X, Louie S-G, Cohen M-L (1995) *Phys. Rev. B* 52:8541



Modelling the CNT as drug delivery system: field amplification thanks to the CNT vector



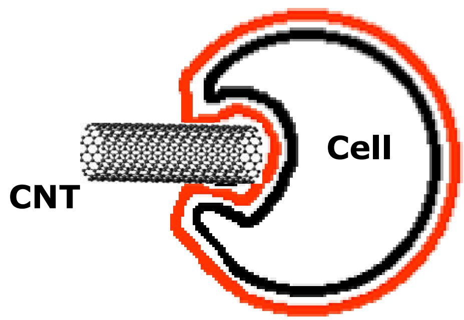


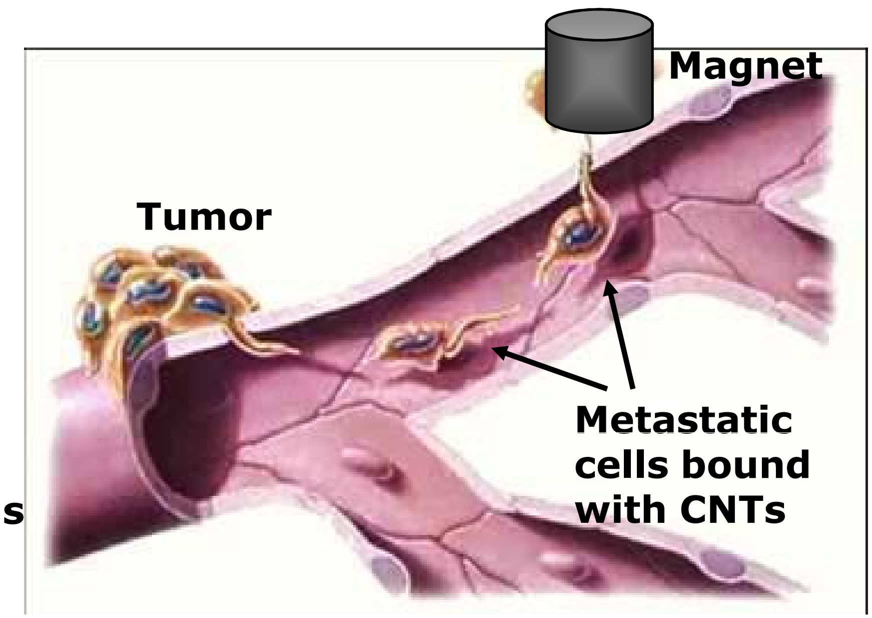


Electropermeabilization assays of fibroblast cells. Left column: EP wave + A wave; pulsing medium: PBS solution containing 2-4 mg/ml of Trypan Blue and 5-10 µg/ml of MWCNT. Middle column: EP wave; pulsing medium: PBS solution containing 2-4 mg/ml of Trypan Blue and 5-10 µg/ml of MWCNT. Right column: EP wave + A wave; pulsing medium: PBS solution containing 2-4 mg/ml of Trypan Blue. Percentage calculated on cells which permeabilize after t=0.

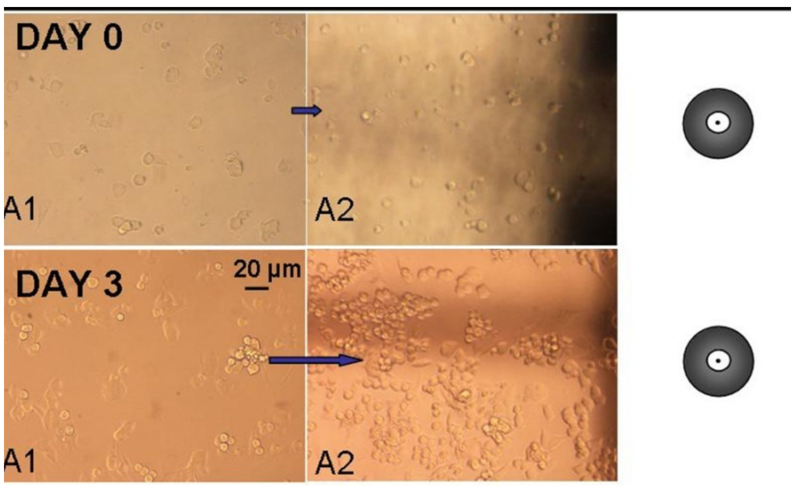
Cell manipulation with magnetic carbon nanotubes

Once the CNTs (naturally magnetic thanks to residuals) are attached or internalized, cells can be concentrated in a desired compartment for subsequent localized therapy.





CNT can be functionalized to bind target cells (such as metastatic cells) or to be internalized by the cells; in this sense cells become magnetotactic and can be drag and collected by a permanent magnet.

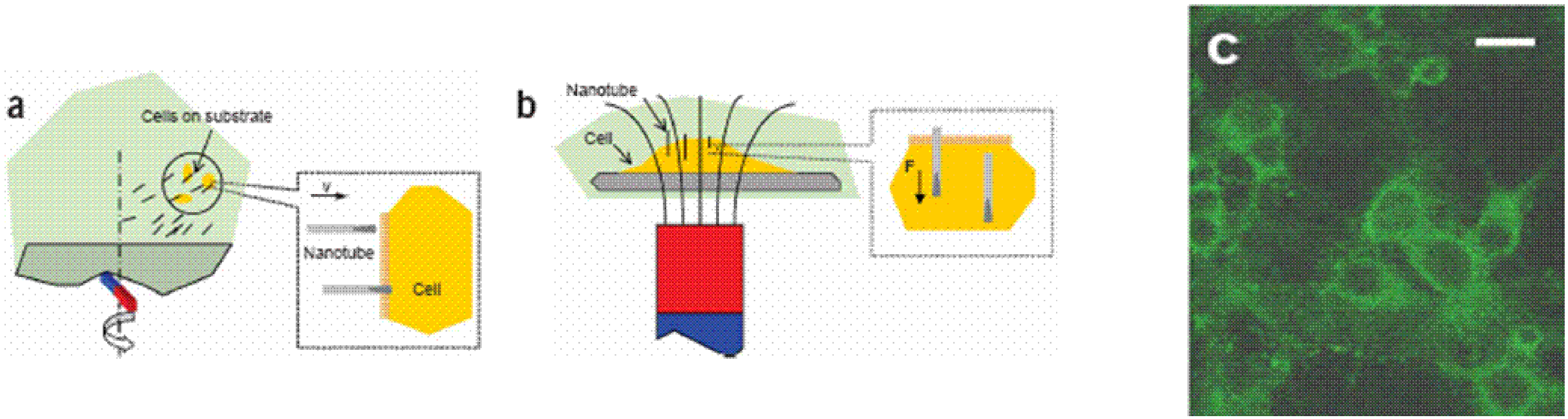


Human Neuroblastoma cells (SH-SY5Y) displacement after 3 days in culture with MWNTs-modified medium. Control sample not showed (with Nikon TE2000U inverted optical microscope, magnifications 20x).

V. Pensabene, O. Vittorio, S. Raffa, A. Menciassi, P. Dario, "Neuroblastoma cells displacement by magnetic carbon nanotubes", IEEE Trans. On NanoBioScience, 2008.

Exploitation of magnetic properties of CNTs entrapping nickel particle catalysts

Highly efficient molecular delivery into mammalian cells using carbon nanotube spearing, Cai et al., 2005



Results. f-CNTs with a DNA strain containing the sequence coding for the enhanced green fluorescent protein (pEGFP-c1). After preliminary spearing by rotating field of nanotubes (a), the cells were transferred to culture dishes containing nanotube free medium for enhancing the spearing by a static field of a permanent magnet (b). The cells were efficiently transfected as confirmed by fluorescent microscopy measurements and it was demonstrated that both spearing steps are necessary for an efficient transduction (c).

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Boron nitride nanotubes (BNNTs) in medicine

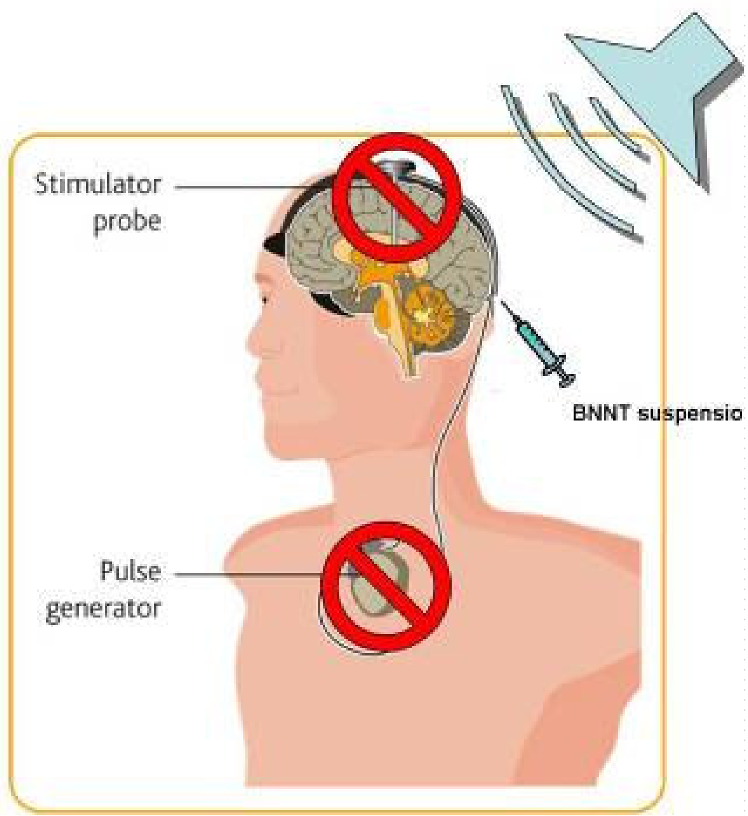
- A BNNT is structurally analogue to a carbon nanotube in nature: alternating B and N atoms entirely substitute for C atoms in a graphitic like sheet with almost no change in atomic spacing
- Excellent chemical and physical properties
- Piezoelectric behaviour (!!!)
- Biomedical applications totally unexplored

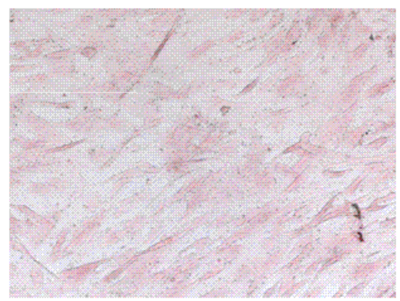
Ciofani G., Raffa V., Menciassi A., Cuschieri A. - Boron nitride nanotubes: an innovative tool for nanomedicine - Nano Today, 4(1): 8-10 (2009)

Perspectives related to PZT properties

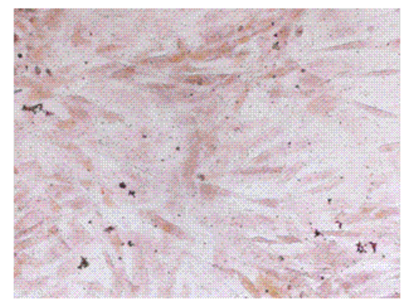
The piezoelectric properties of BNNTs make them attractive candidates as **bionanotransducers**. If stimulated with non-invasive ultrasounds, they should be able to generate electrical field.

We are carrying out experiments on cells sensible to electrical field (neurons, osteoblasts, muscle cells, etc.) and **preliminary results on primary human osteoblasts show a significant increment of osteocalcine and calcium content after incubation with BNNTs and stimulation with US**.



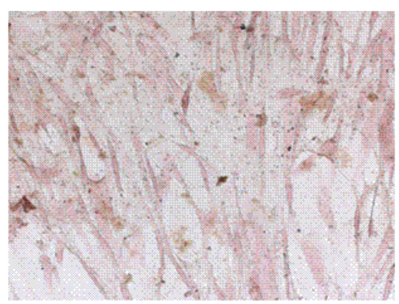


HOBs

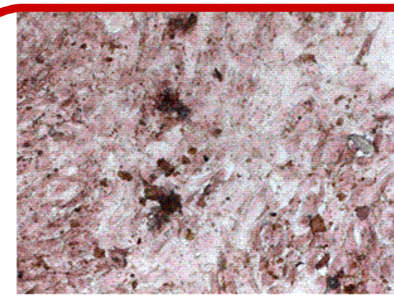


HOBs + US

Von Kossa staining for calcium salts (in black)



HOBs + BNNTs



HOBs + BNNTs + US

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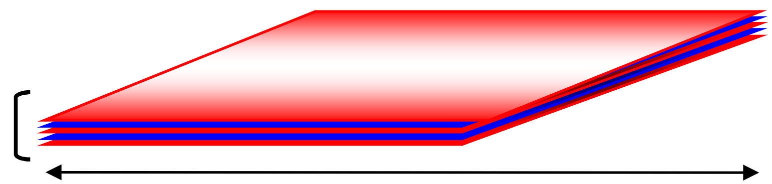
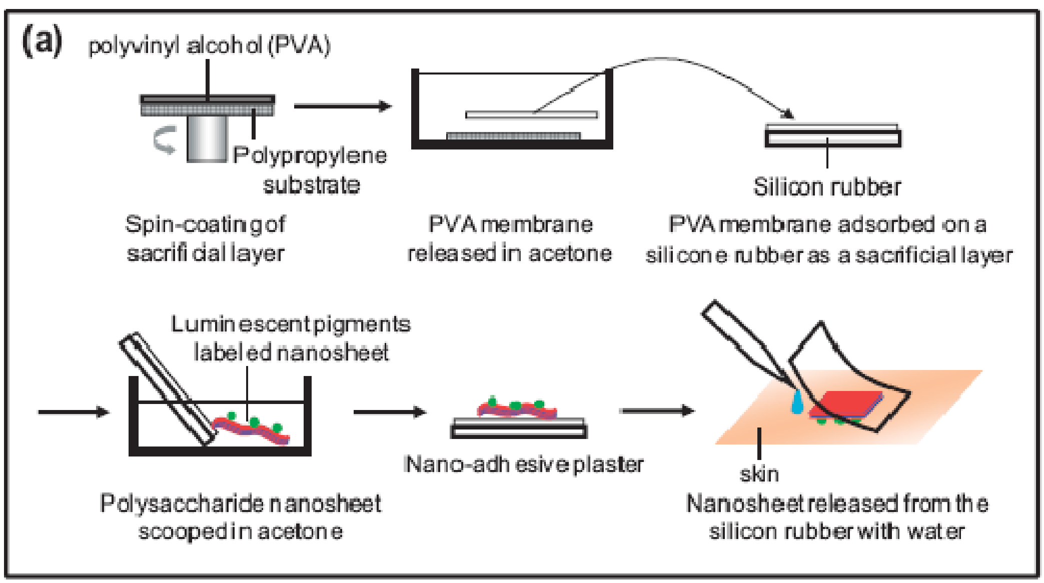
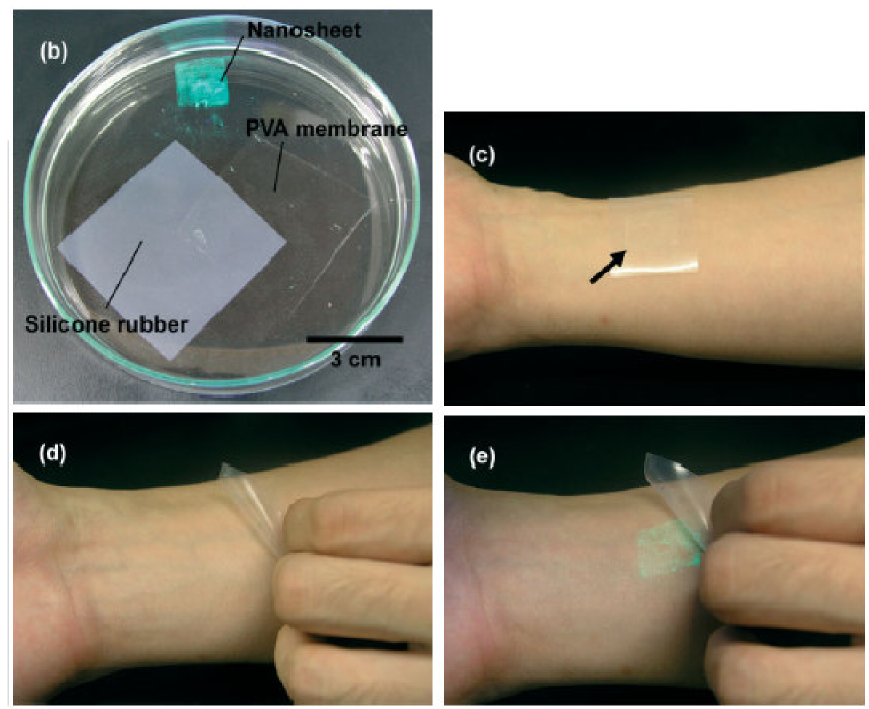
Polymer ultra-thin nanosheet



Huge aspect ratio (>10^6) - **Large contact area** - **Non-covalent adhesion**

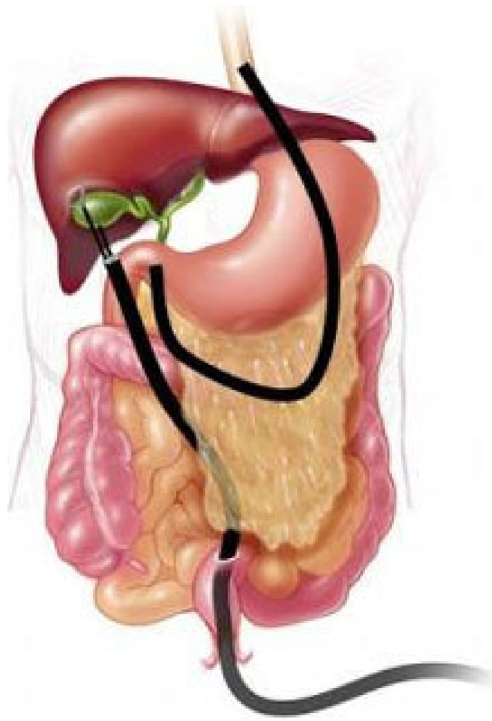
Adv. Mat., 2007, Ubiquitous Transference of a Free-Standing Polysaccharide Nanosheet with the Development of a Nano-Adhesive Plaster, **T. Fujie, Y. Okamura, S. Takeoka.**



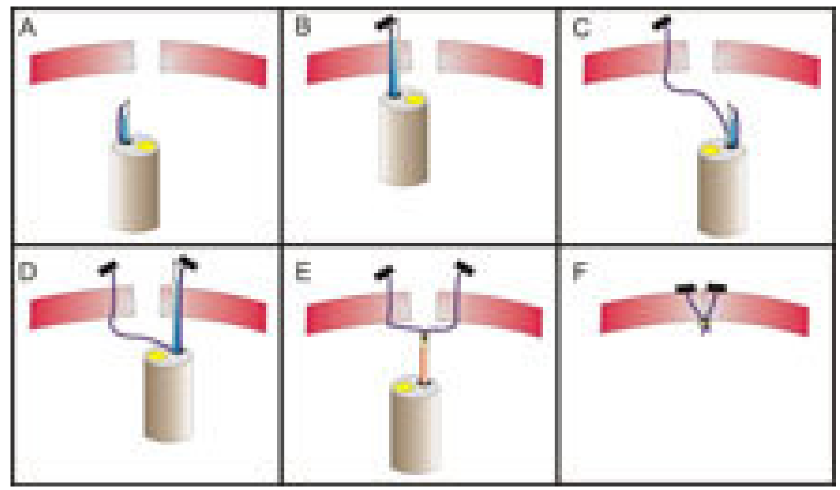


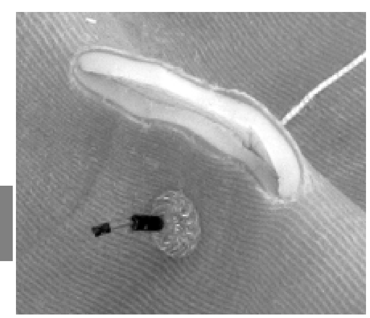
Polymer ultra-thin nanosheet for endoluminal surgery

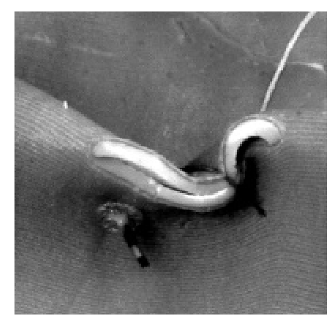
In **NOTES** (Natural Orifice Transluminal Endoscopic Surgery), access to the target organs is obtained through holes made in stomach/female reproductive/lung wall.



Conventional technique to close a hole using endoluminal devices

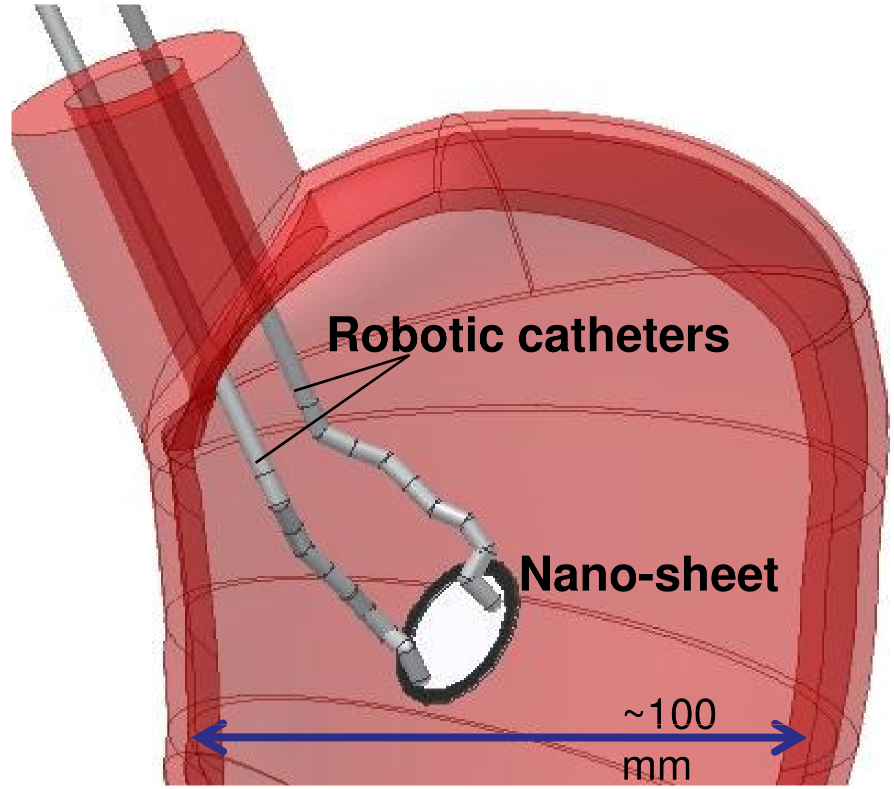




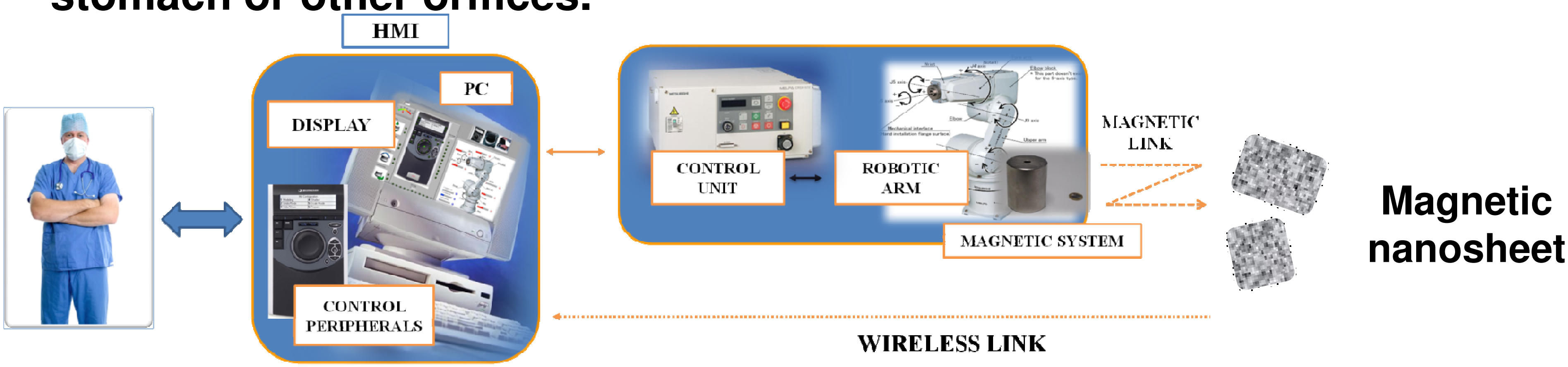


Non invasive, flexible, efficient methods for hole closing are deeply investigated because current techniques show many limitations

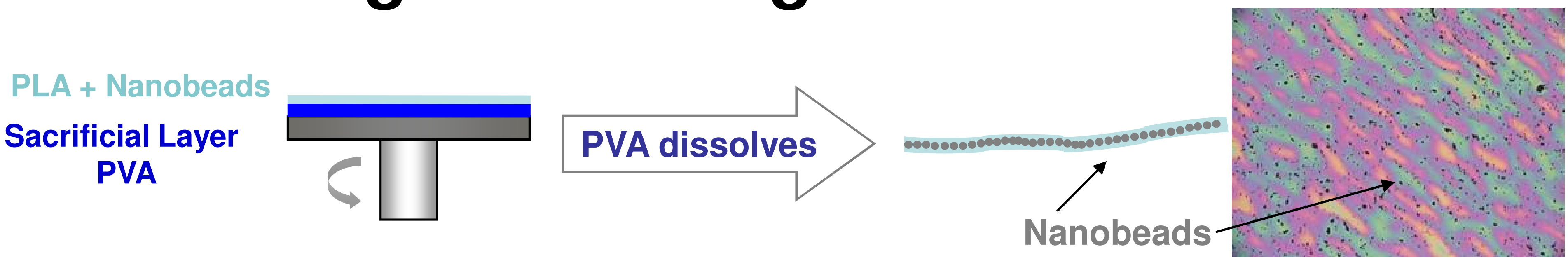
- Thanks to their flexibility, these nanofilms can be proposed as <u>nanoplasters</u> for closing incisions and wounding in endoluminal surgery procedures.
- They can be stored in small channels of endoscope and can be delivered without loosing their flexibility.



Adding magnetic properties to the film, nanosheets can be precisely positioned in situ with catheters or robotic modules inside the stomach or other orifices.



Homogeneous Magnetic Nanosheets

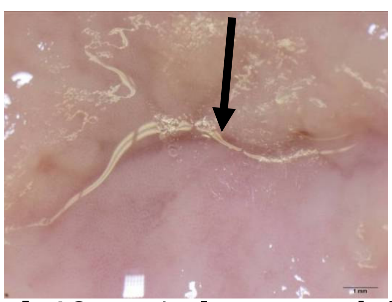


Manipulation test

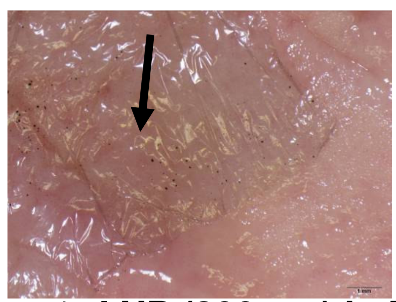
A Neodymium Iron Boron permanent magnet (Br= 350 mT) is used to move the film in saline solution and finally the film is controlled and attached on the tissue.

Video-magnetic manipulation

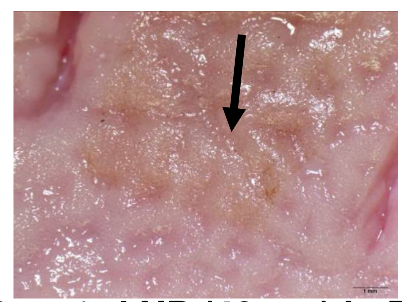
Attachment of nanofilms on stomach tissue



PLA 10 mg/ml, no particles



10 mg/ml NP (200 nm) in PLA 10 mg/ml

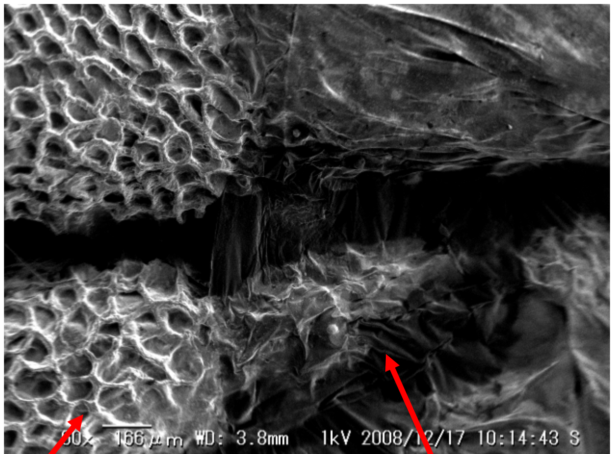


10 mg/ml NP (40 nm) in PLA 10 mg/ml

After the removal of the liquid, the film adhere on the surface and, thanks to the nanometric thickness, it precisely fits the morphology of the tissue.

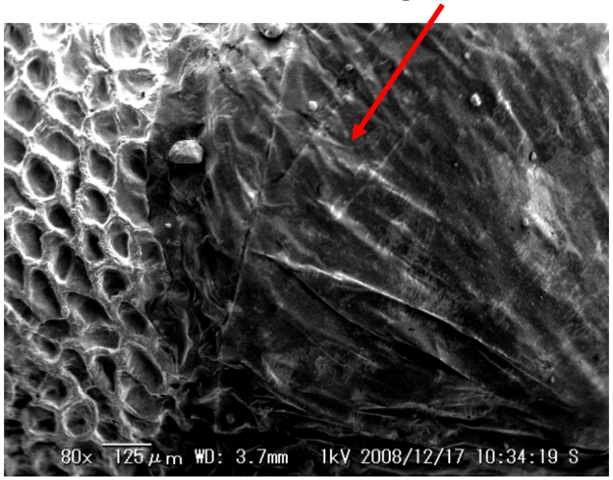
Magnetic nanofilms as nanoplaster for endoluminal surgery

10 mg/ml NP (200 nm) in PLA 20 mg/ml

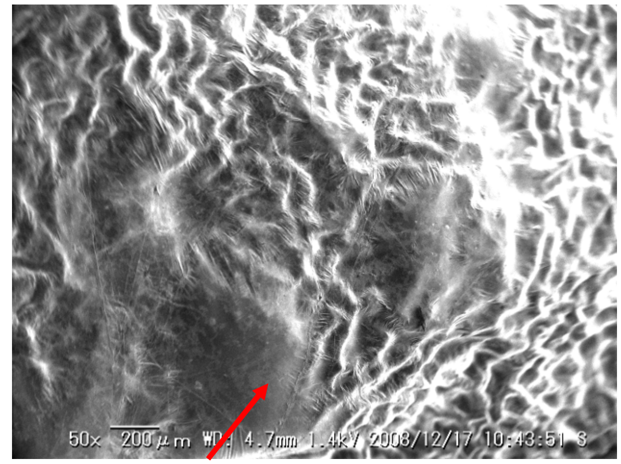


Film covering an incision on the mucosal wall

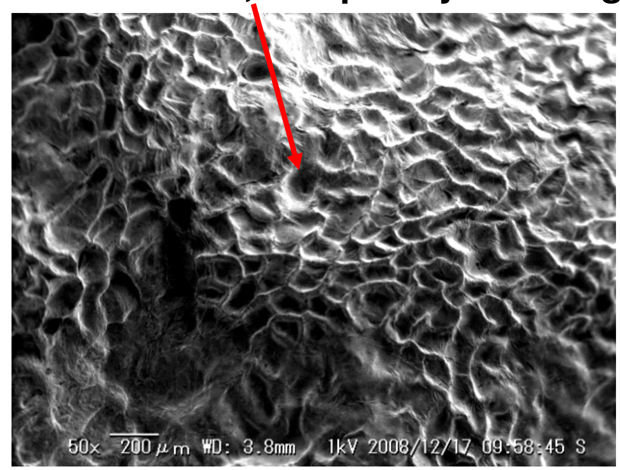
gastric wall **magnetic nanofilm**



10 mg/ml NP (40 nm) in PLA 10 mg/ml

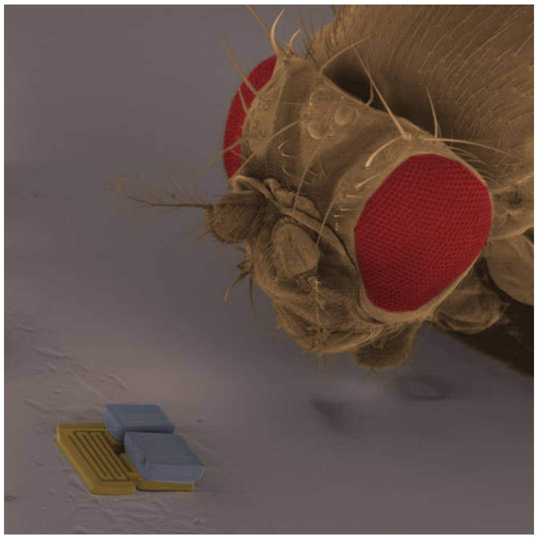


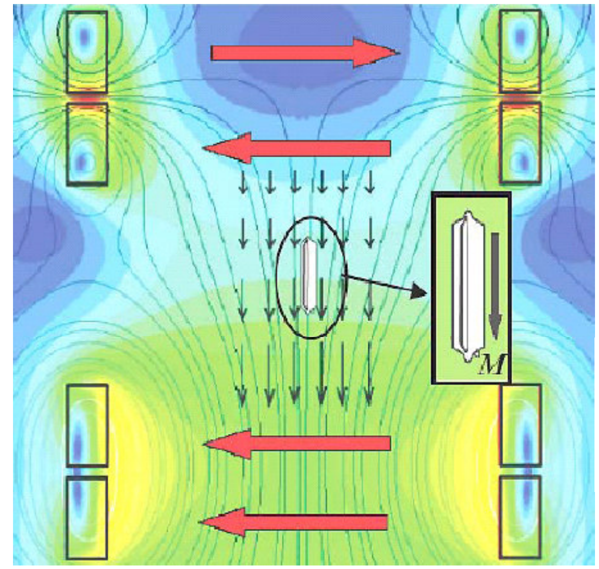
The film follows the folds of the mucosal wall, completely covering it.



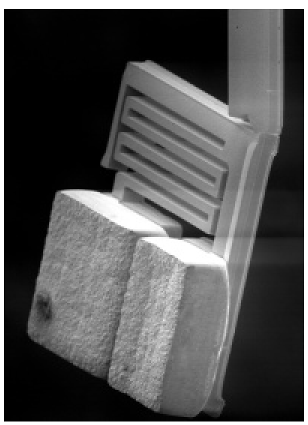
Bio-micro-robotics for untethered mobile machines in the human body

(B. Nelson, IRIS, ETHZ)

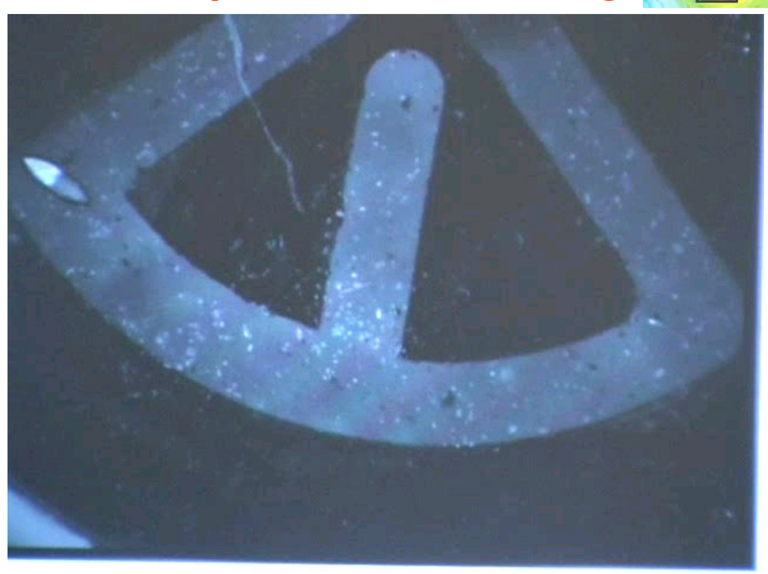


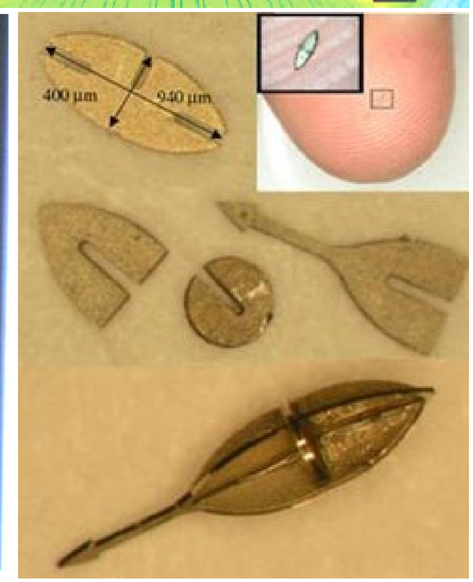


Conceptual drawing of a magnetic microrobot steered with external magnetic fields. The microrobot is magnetized along its major axis. Four solenoid coils are placed coaxially with the large arrows indicating the direction of current flow. Tests already performed for ophthalmologic surgery and eye pressure monitoring



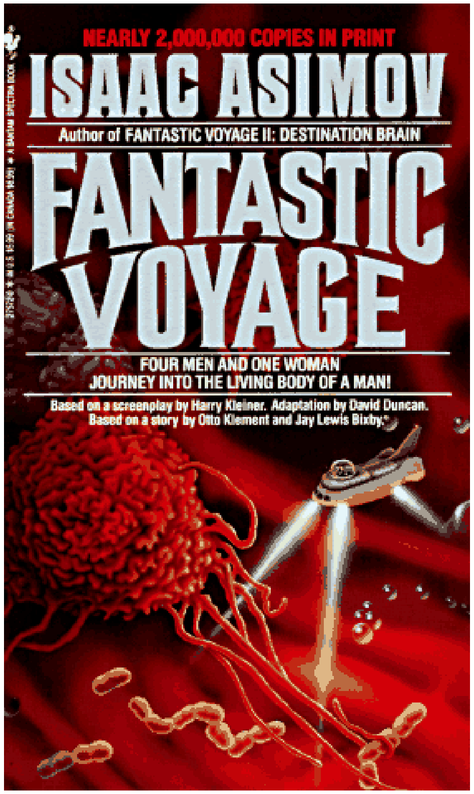
A resonanant magnetic microrobot with a fruit fly





Future scenario

Should we say that every human will soon have a smart mobile robot inside?...

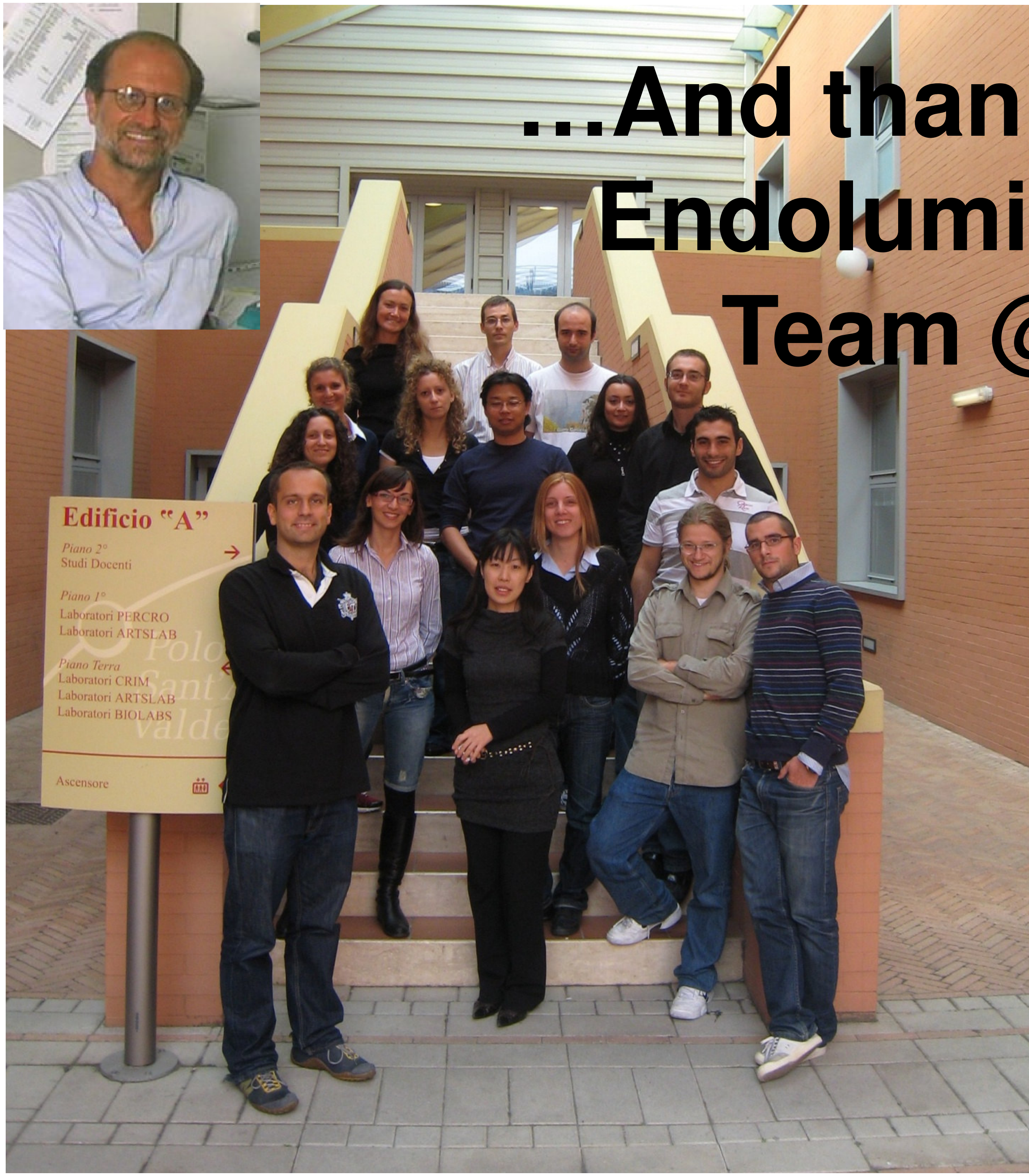


THANK YOU ! ...

Concluding remarks

- Modern Surgery evolved thanks to the convergence of some knowledge and new scientific findings available in the 19th century
- Current trends of robotic surgery are towards minimally invasiveness, miniaturization of tools, extremely early diagnosis (down to the cell level)
- Future surgery will benefit in a dramatic way by the convergence of many disciplines, basically life science, physics, chemistry, neuroscience, nanotechnology, etc.
- Real micro and nanorobots for surgical applications are beginning to appear

...And thanks to all the Endoluminal Robotic Team @ CRIM Lab



Questions?