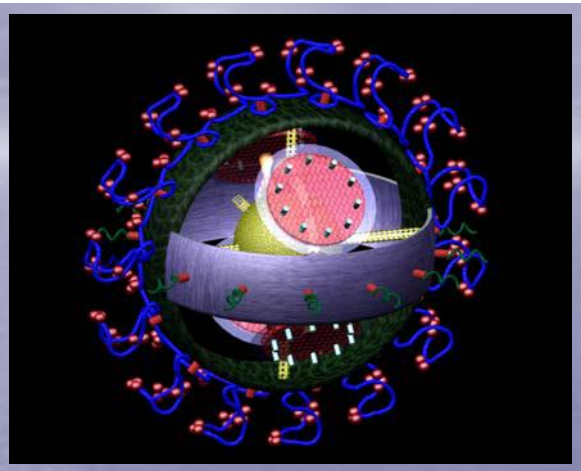
Northeastern
UNIVERSITY



Nano-Robotics in Medical Applications: From Science Fiction to Reality

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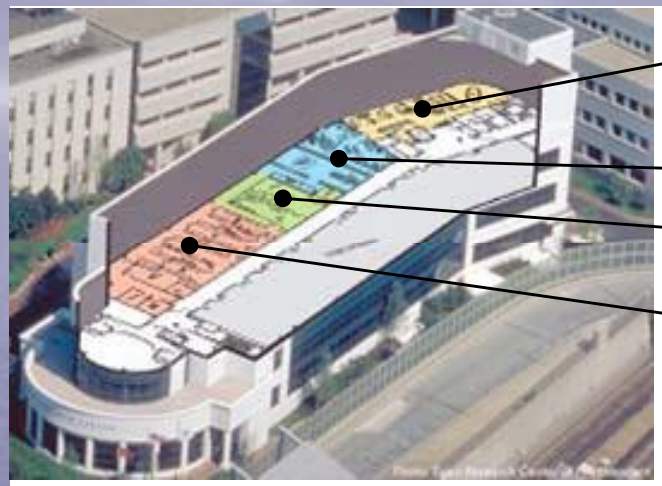
Bio Nanorobotics Laboratory
Department of Mechanical and Industrial Engineering
Northeastern University, Boston, Massachusetts
http://www.bionano.neu.edu

Northeastern University

- Located in Boston MA
- Created in 1898
- 14,000 Undergraduates
- 3,500 Graduate Students
- 90 PhD Programs
- Experiential Learning / Cooperative Education
- Leader in Nanomanufacturing
- Strong PhD Program in Nanomedicine



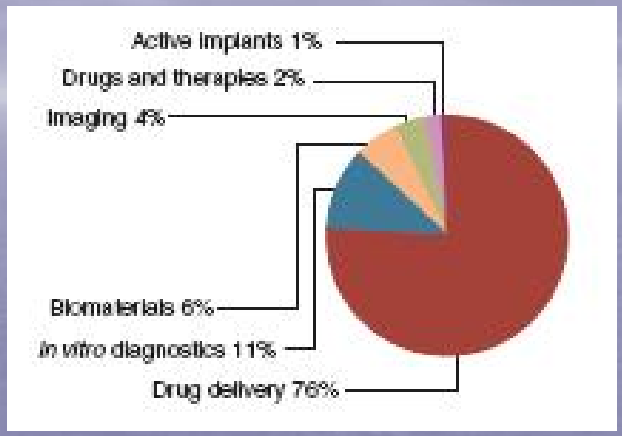
1. Entrepreneur, Corporate Outreach and Staff Area
2. Soft Lithography and Wet Chemistry Lab
3. Lithography and Characterization
4. Cleanroom Facility

George J. Kostas Nanomanufacturing Center at Northeastern University

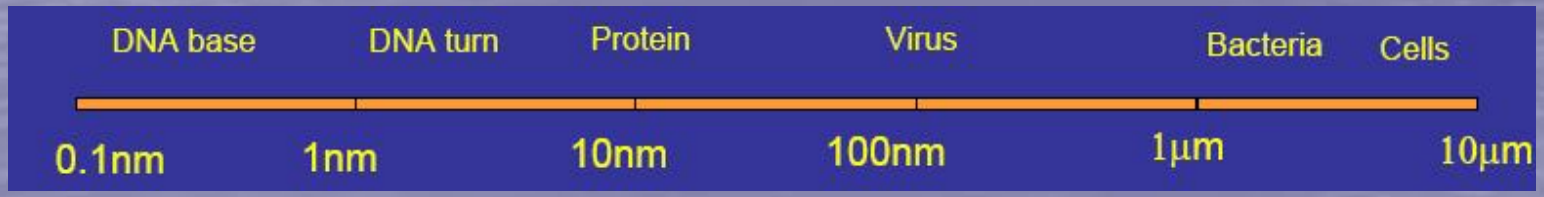
Facilities at the Kostas Nanomanufacturing Center

Nanomedicine

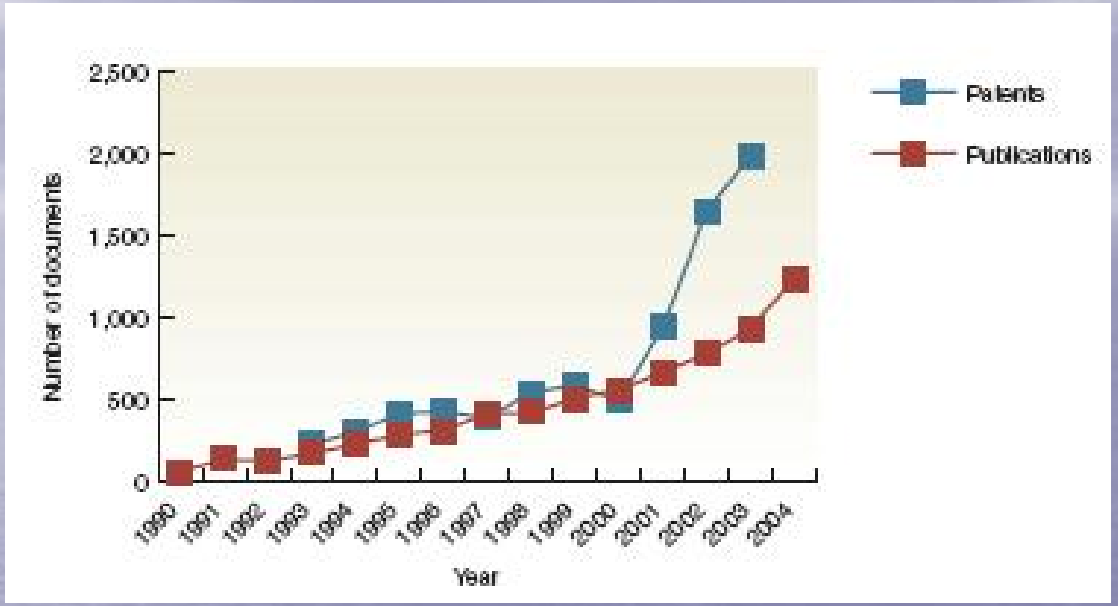
- "Nanomedicine is the process of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body." (Freitas, 2006)
- Nanomedicine: Application of nanotechnology in medicine.
- Nanotechnology refers to the science and engineering activities at the level of atoms and molecules. A nanometer is a billionth of a meter, that is, about 1/80,000 of the diameter of a human hair, or 10 times the diameter of a hydrogen atom.



- Healthcare Applications of Nanomedicine
(Wagner et al., Nature Biotechnology, 2006)



Market and Activity Evolution



- Nanomedicine Patents and Publications (Wagner et al., Nature Biotechnology, 2006)

Table 1 Commercial efforts in nanomedicine[a]

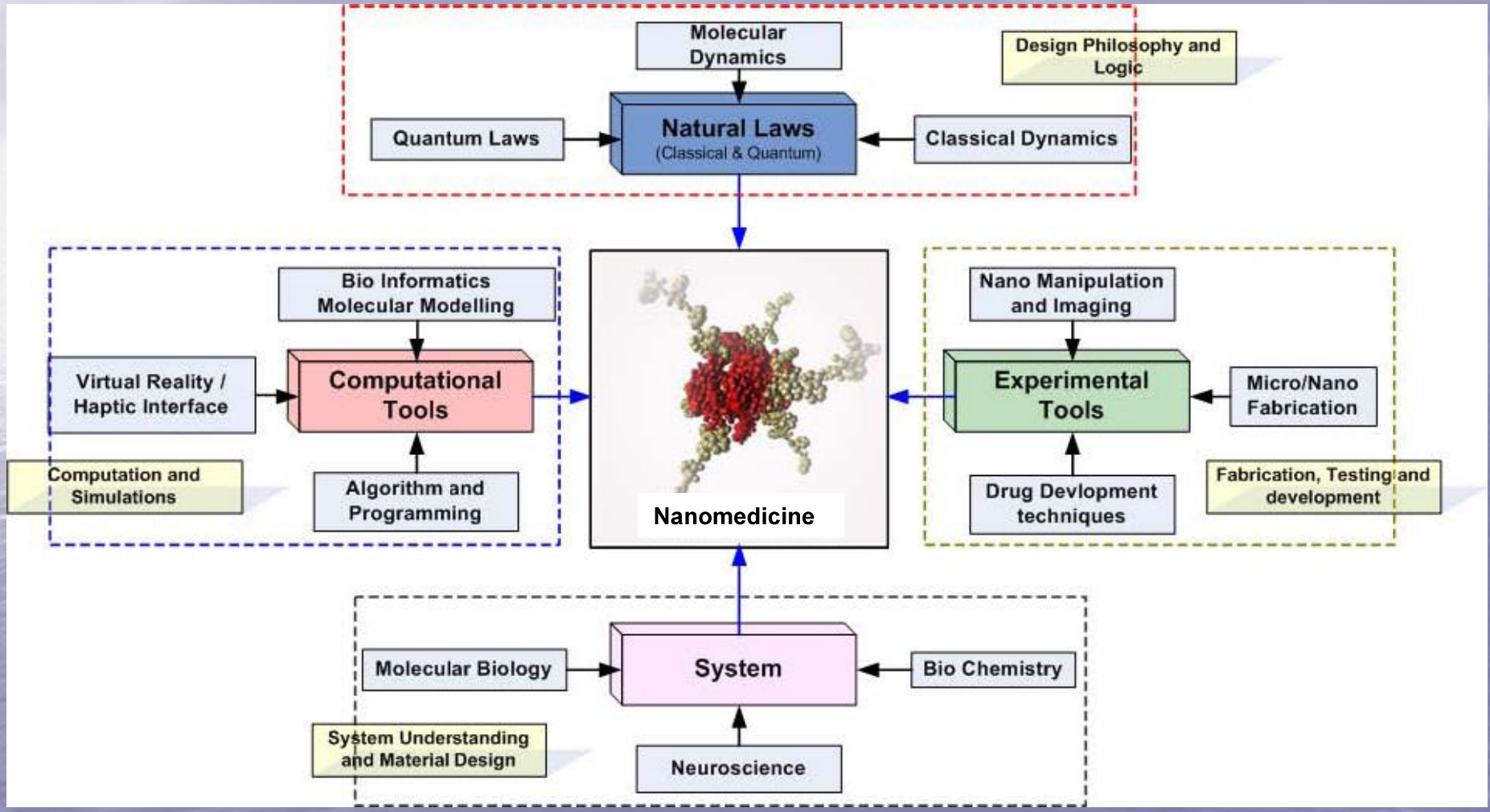
			Product pipeline		
Healthcare sector	Number of products	Sales ($ billions)	Total	Advanced stages[b]	Companies
Drug delivery	23	5.4	98	9	113
Biomaterials	9	0.07	9	6	32
In vivo imaging	3	0.02	8	2	13
In vitro diagnostics	2	0.78	30	4	35
Active implants	1	0.65	5	1	7
Drugs & therapy	0	0	7	1	7
Total	38	6.8	157	23	207

- Nanomedicine Market:$6.8B in 2004; $12B in 2012

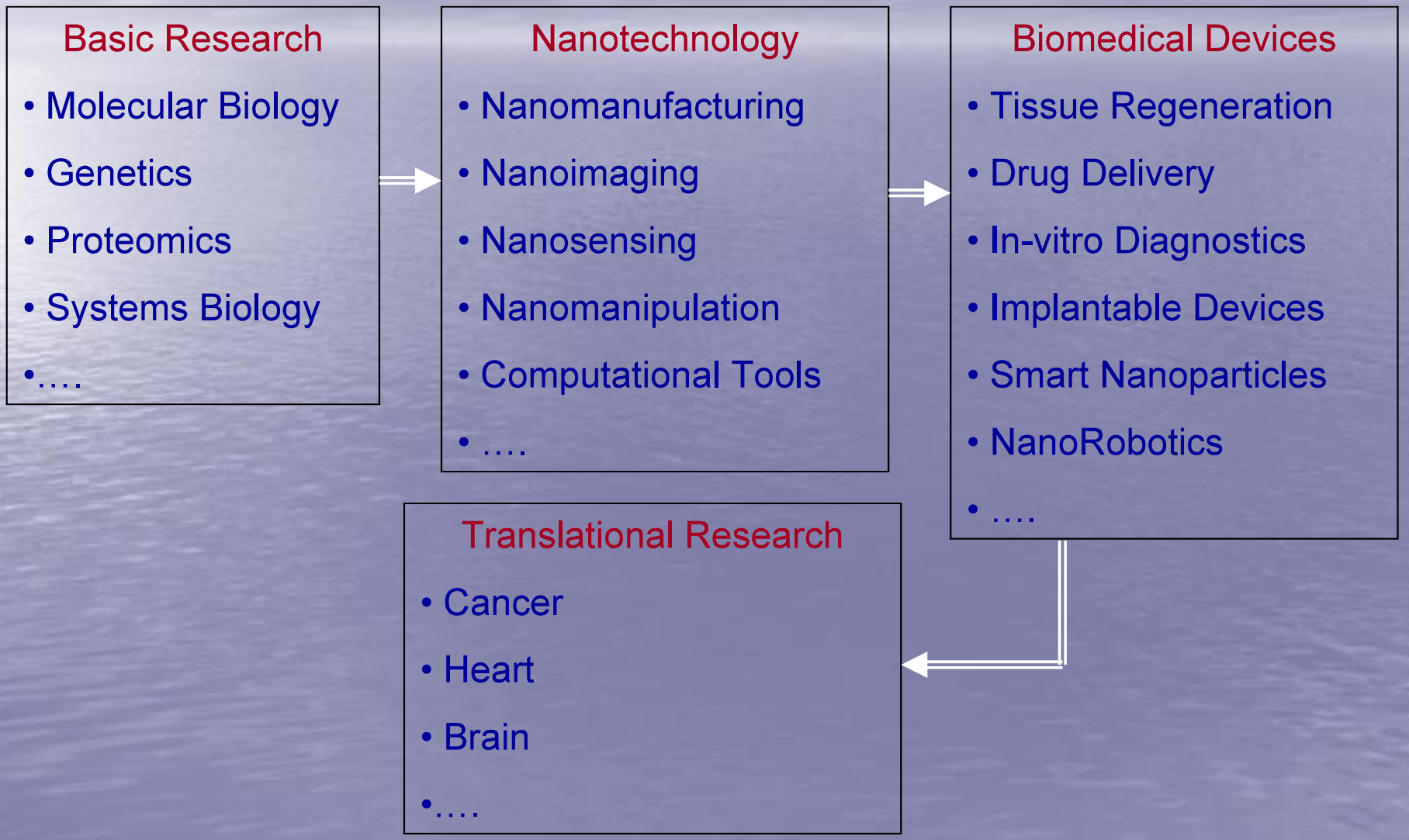
(Wagner et al., Nature Biotechnology, 2006)

Collaboration

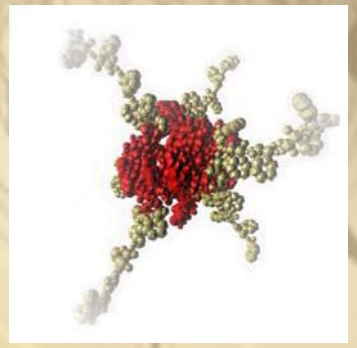
A truly multidisciplinary field



Role of Nanotechnology in Medical Research



The NanoRobotic Concept

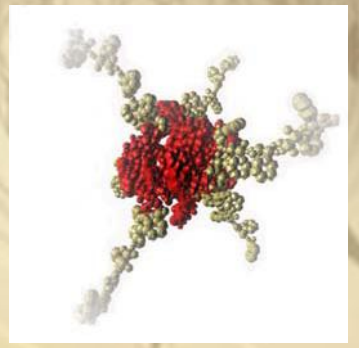


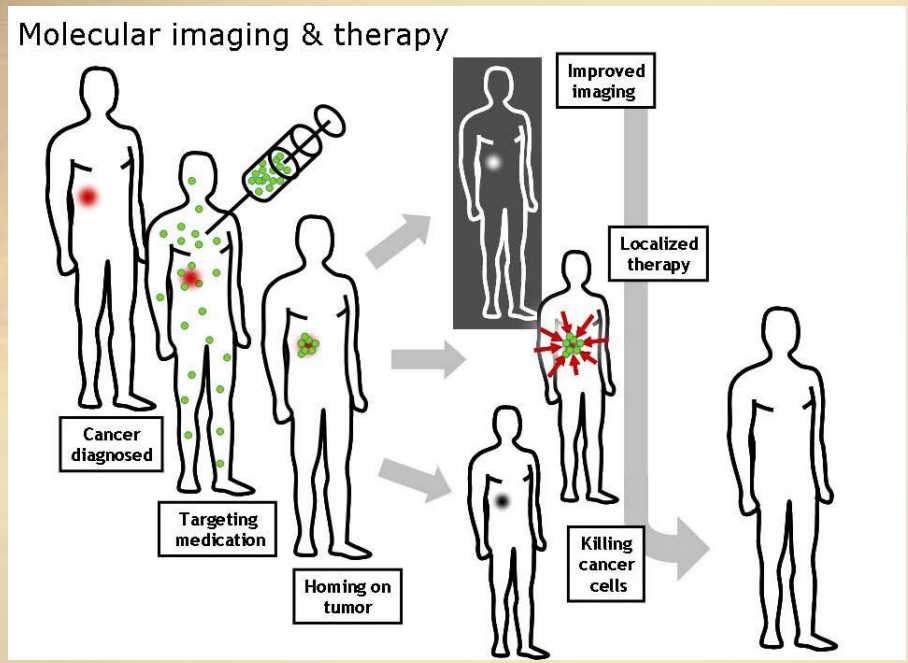
- **Nanorobots** would constitute any **"*smart*"** structure capable of *actuation, sensing, signaling, information processing, intelligence, manipulation and swarm behavior* at nano scale (10^{-9}m).

- ***Bio* nanorobots** – Nanorobots designed (and inspired) by harnessing properties of biological materials (peptides, DNAs), their designs and functionalities. These are inspired not only by nature but machines too.

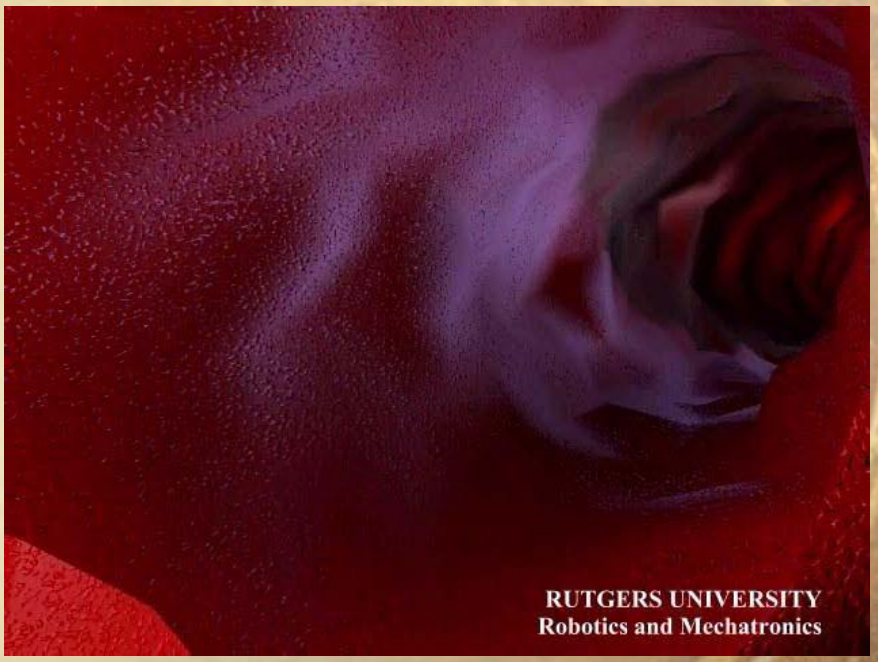
- Nanorobots could propose solutions at most of the nanomedicine problems

NanoRobotics – An Example:
Ultra-Local Drug Delivery





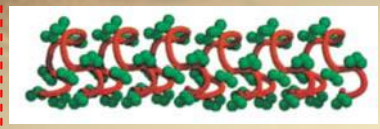
(Opensource Handbook of Nanoscience and Nanotechnology)



- Bio-Nano-Robot Repairing a Damaged Blood Cell

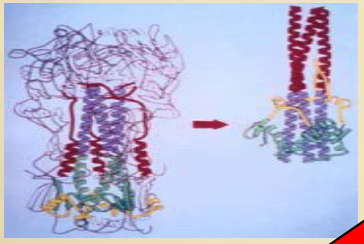
The Roadmap Towards NanoRobotics

Increasing Capability of Bio Nano Systems



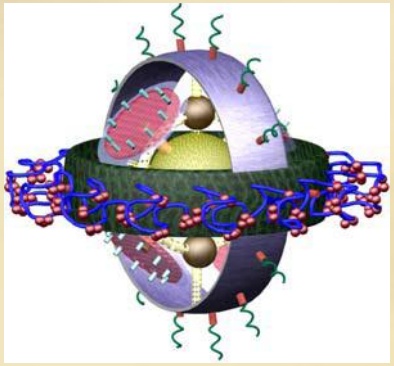
Bio Sensors

DNA Joints



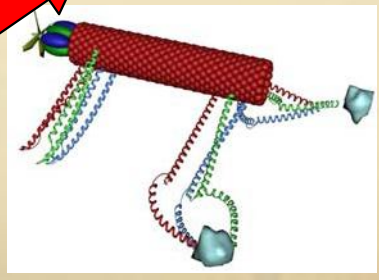
HA a-helix

Bio nano components

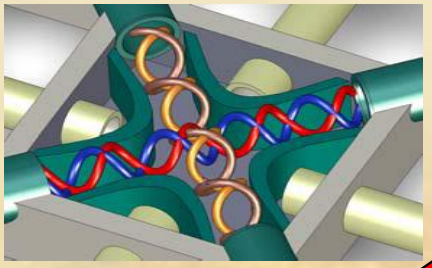


A bio nano robot
Representative Assembly of bio components

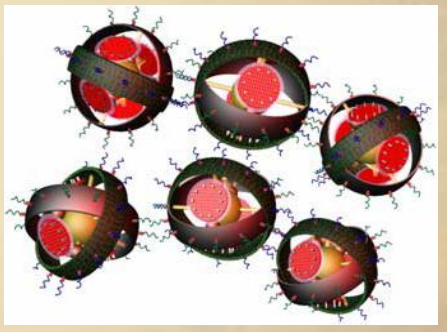
Assembled bio nanorobots



Distributive intelligence programming & control

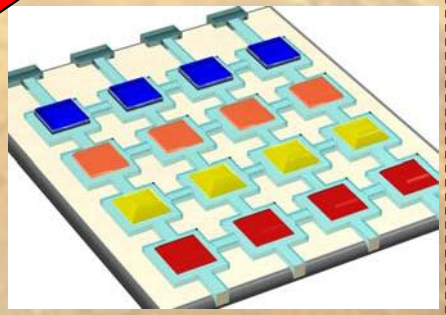


A bio nano computational cell

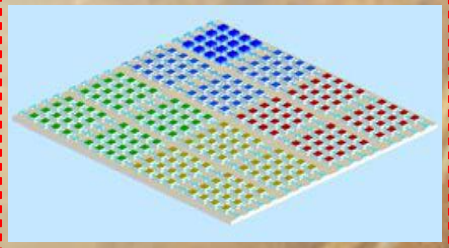


Bio nano swarms

Automatic fabrication and information processing



A Bio nano information processing component

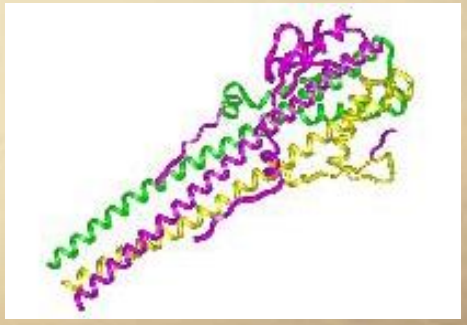


Conceptual automatic fabrication floor

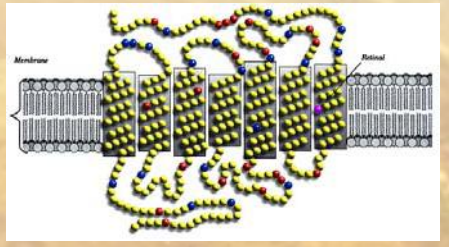
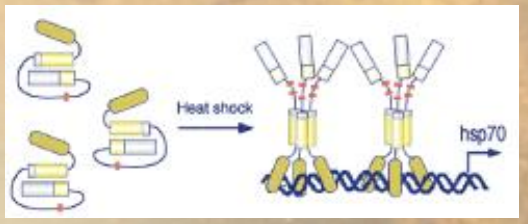
STEP 1 — STEP 2 — STEP 3 — STEP 4

Research Progression

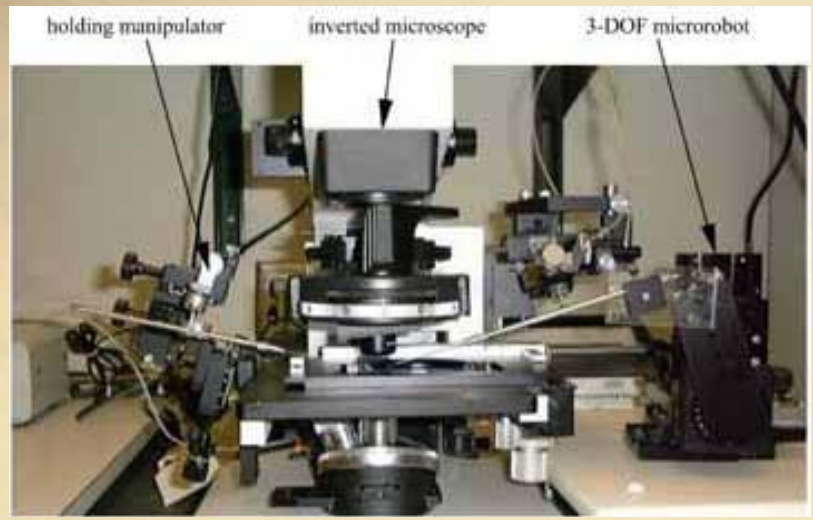
Bottom Up Approach Based on Macro-Nano Equivalence

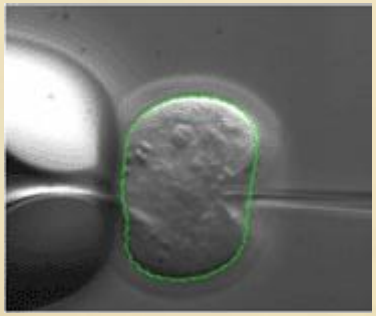
Structural Elements	
Metal, Plastic Polymer	DNA, Nanotubes  
Actuators	
Electric Motors, Pneumatic Actuators, Smart Materials, Batteries, etc.	ATPase, VPL Motor, DNA, CNT  

Bottom Up Approach Based on Macro-Nano Equivalence

Sensors	
Light sensors, force sensors, position sensors, temperature sensors	Rhodopsin, Heat Shock Factor,  CNT based Nanosensors 
Joints	
Revolute, Prismatic, Spherical Joints etc.	DNA Nanodevices, Nanojoints 

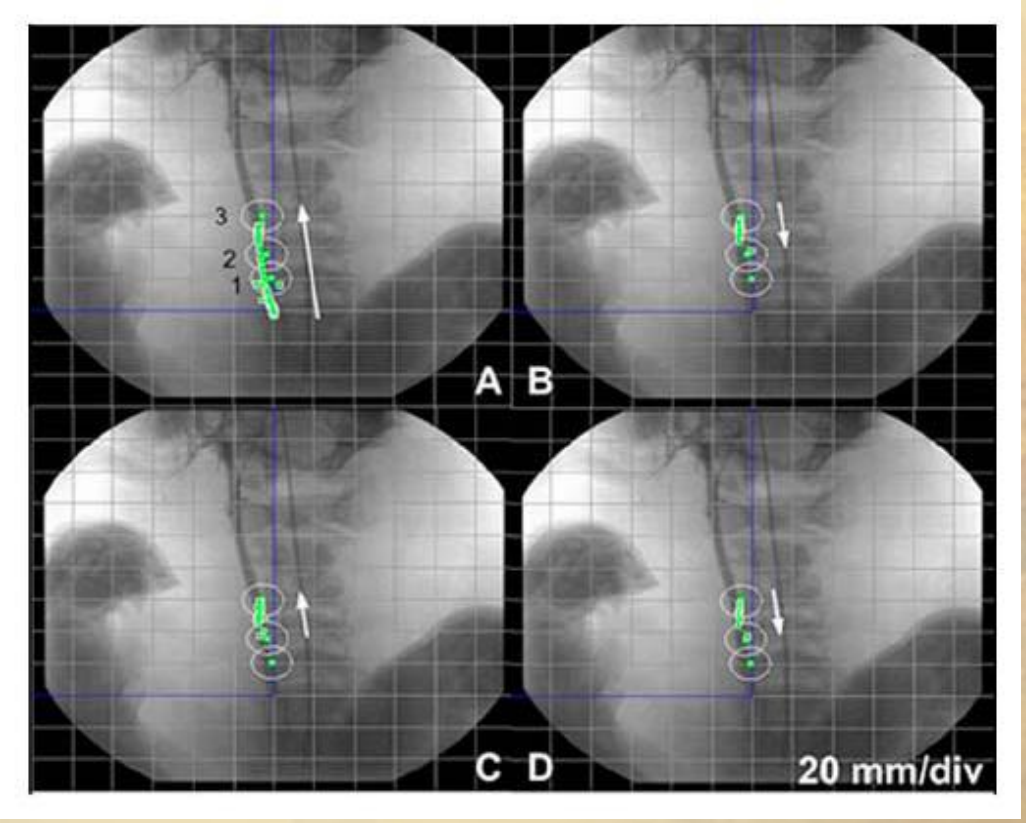
State of the Art on NanoRobotics: *Nanomanipulators*





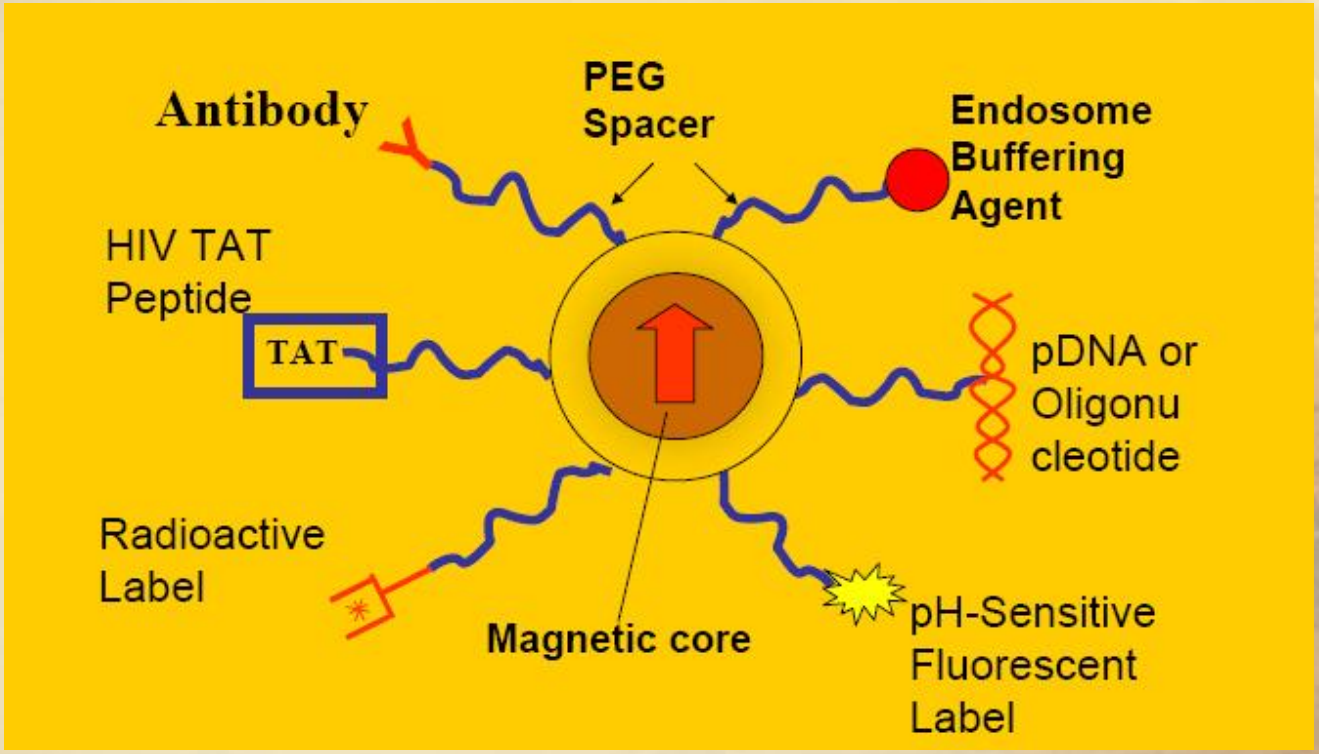
- NanoRobotics for Molecular Biology
- Cell Manipulation Using Nanomanipulators
  (e.g. automated DNA injection - Prof. Brad Nelson's group at ETH)
- Commercial Nanomanipulators (e.g. Zyvex Corp.)

State of the Art on NanoRobotics:
MRI Guided Nanoparticle



- In vivo automatic navigation of a 1.5 mm ferromagnetic bead inside the carotid artery of a living swine (Martel et al., 2007, Applied Physics Letters).

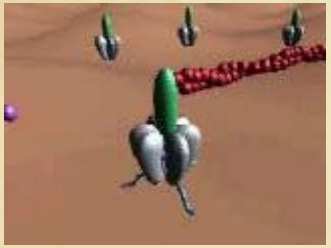
State of the Art on NanoRobotics: *Smart Nanoparticles*



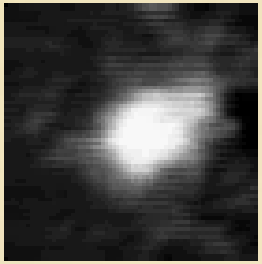
State of the Art on NanoRobotics:
Protein Based Nano Motors and Sensors

Protein Based Molecular Machines

- ATP Synthase Motors, Myosins, Kinesins and Dyneins, Bacterial Flagella Motors
- Advantages: Natural, High Efficiency and Power
- Disadvantages: Bulky, Hard to Interface, Customize and Design, Complex

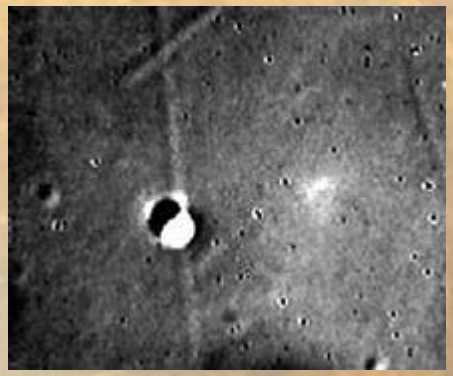


ATP Synthase

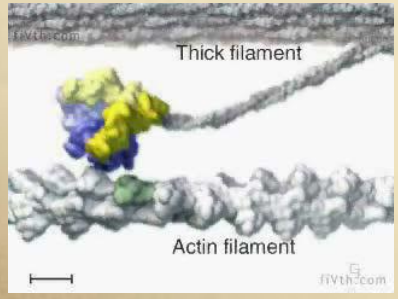


ATPase Visualization[1]

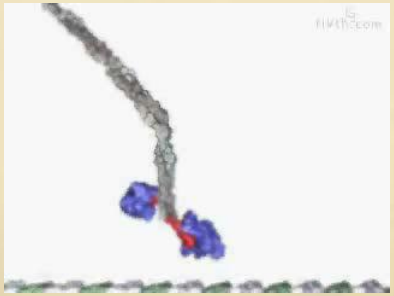
Flagella in Bacterial Membrane



1 µm diameter glass bead carried by Kinesins



Myosin



Kinesin

Dynein Molecule

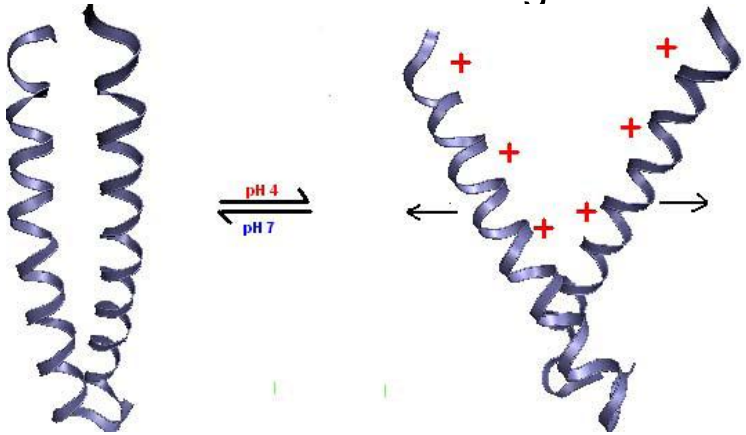
Steffen et al., *Biol. Bulletin.* **193**, 221-222

[1]Noji et al., *Nature*, **386**:(6622), 299-302

Peptide based Nano-Gripper

- **Transcription Factor in Yeast**, **GCN4, Leucine Zipper**

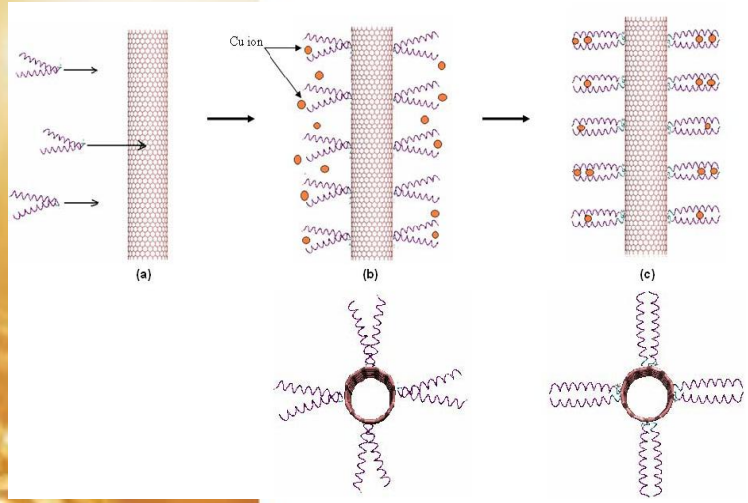
- The tweezer mechanism should be **reversible**
- Introduce amino acids with different degree of ionization at **varying pH**
- Specifically **histidines** can be incorporated at ‘e’ and ‘g’ positions
- Ionized amino acids will generate **repulsive electrostatic charges** and make the helices move away
- The **hydrophobic interactions** should bring the helices back once the pH is increased



Collaborator: Prof. Martin Yarmush, Center of Engineering in Medicine, MGH - Harvard

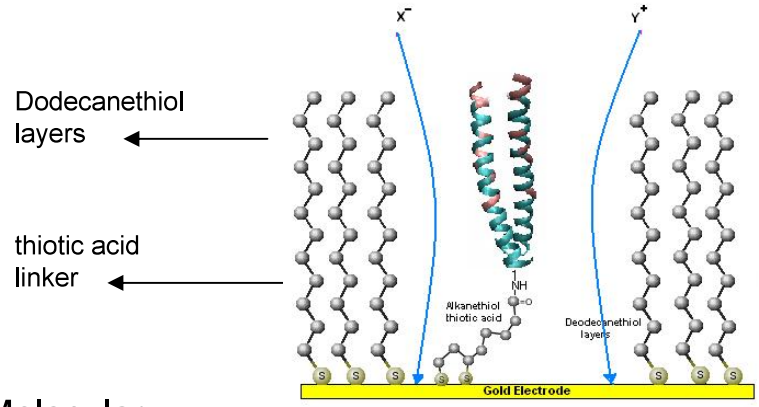
Peptide based Nano-Gripper:
Potential Applications

Metal-ion Sensor

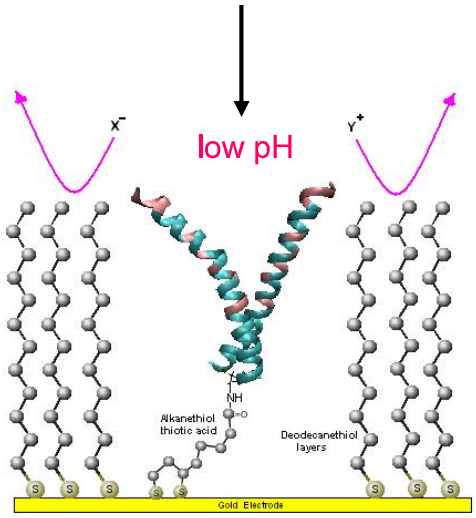


Schematic of a Molecular Tweezer based bio-sensor for metallic ions. The nanoTweezer binds the metallic ions at neutral pH and can release them at low pH.

Molecular Switch

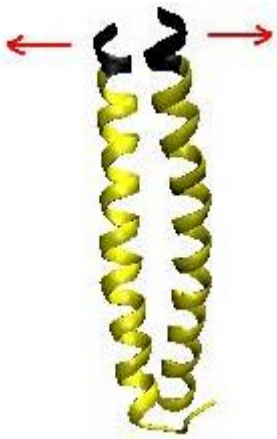


Schematic of a Molecular Tweezer based molecular switch or a pH sensor which relies on the change in conformation at low pH. (a) At pH 7 the peptide is in compact configuration and the ions have access to the gold substrate; (b) At low pH the peptide is in 'open' configuration and the access of the ions is blocked by the passivating dodecanethiol layers resulting in reduced conductivity.

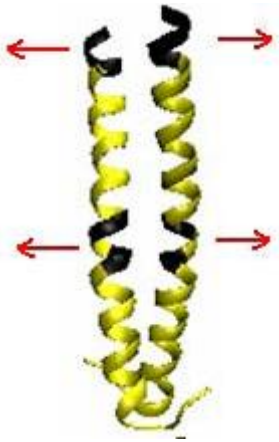


Peptide based Nano-Gripper: *Architectures*

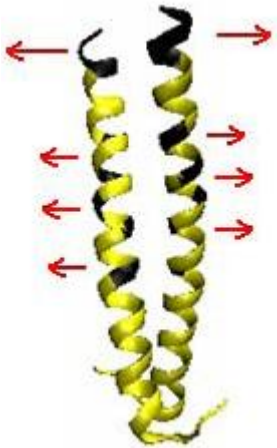
Wild-type



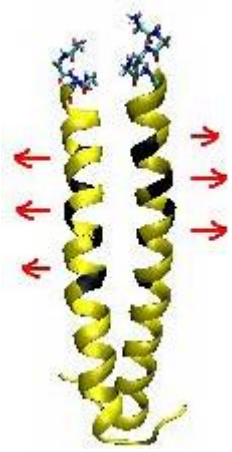
Mutant M1



Mutant M2



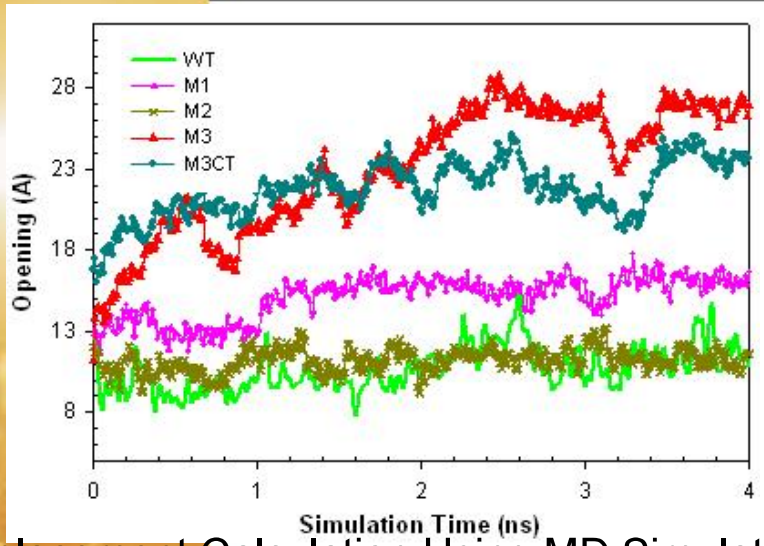
Mutant M3



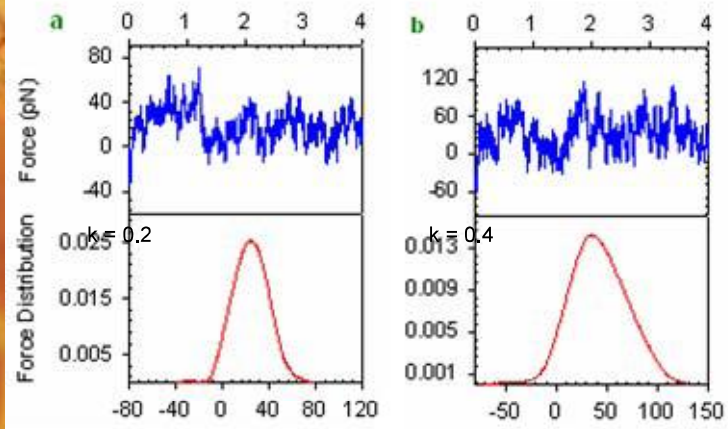
Control M3CT

Mutant name	Sequence
	a b c d e f g a b c d e f g a b c d e f g a b c d e f g
WT	^{243}GGGGGCR - MKQLEDK - VEELLSK - NYHLENE - VARLKKL - VGER^{281}
M1	HHHHHCR - MKQLEDK - VEELLSK - NYHLENE - VARLKKL - VGER
M2	HHHHHCR - MKQLEDK - VEELHHK - HHHLENE - VARLKKL - VGER
M3	HHHHHCR - MKQHEDH - VEHLHSK - NHHLENE - VARLKKL -VGER
M3CT	GGGGGCR - MKQHEDH - VEHLHSK - NHHLENE - VARLKKL - VGER

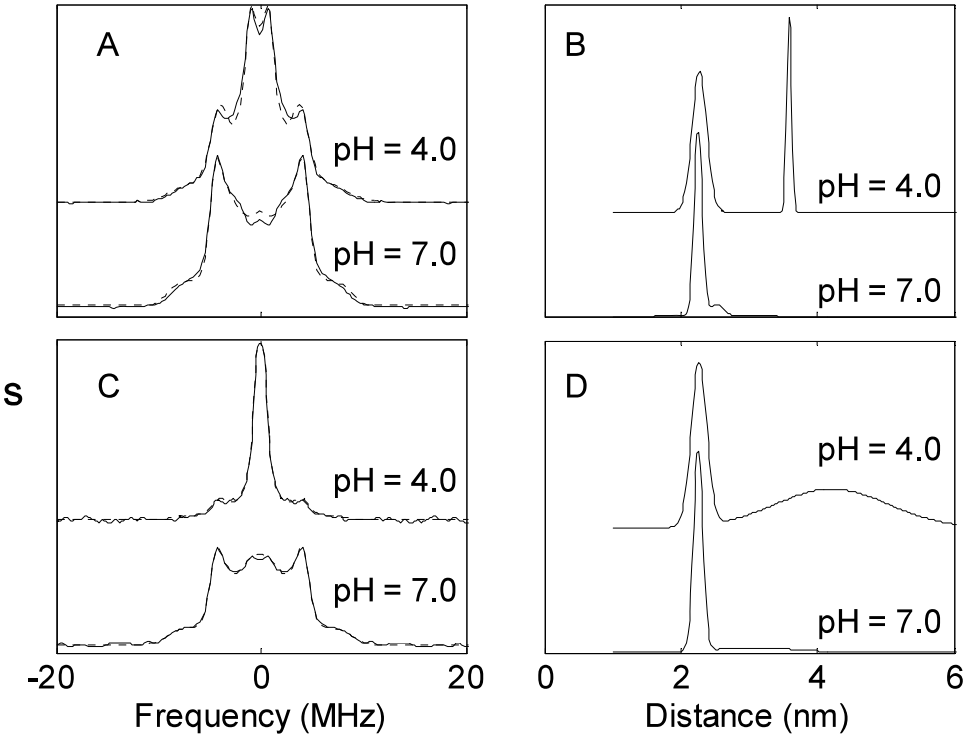
Peptide based Nano-Gripper: *Results*



Displacement Calculation Using MD Simulations

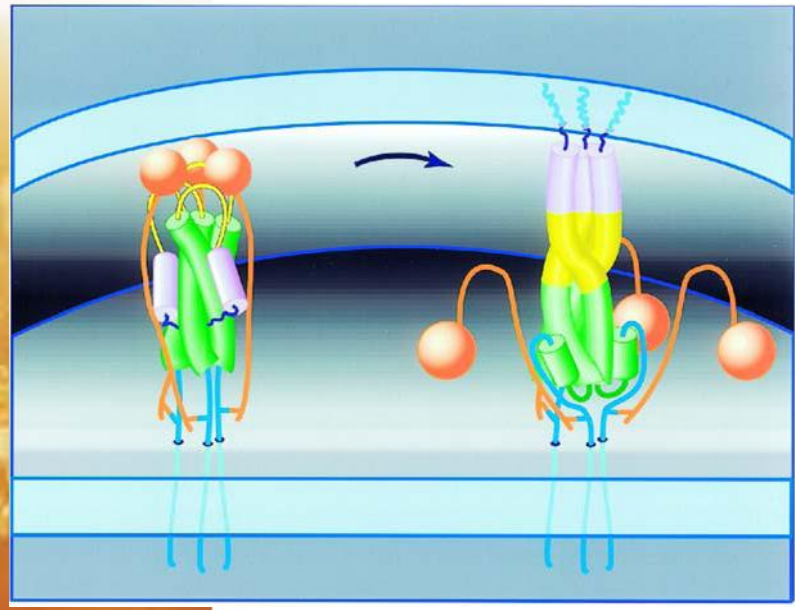


Force Calculations Using MD Simulations



Experimental Verification Using ESR Spectrocopy

Viral Protein Nano Motor



- Influenza hemagglutinin (HA) is a viral surface protein.
- Upon interaction with a cell surface receptor, it is endocytosed.
- In the endosome, the pH drops to 5.0 and the HA protein undergoes a dramatic conformational change to promote fusion.
- The lower pH of 5.0 allows the protein to cross an energy barrier and refold into a more stable conformation.
- Computational and experimental study showed the validity of the concepts and its dependence on temperature and salt concentration.

Collaborator: Prof. Martin Yarmush, Center of Engineering in Medicine, MGH - Harvard

NanoActuators and NanoSensors for Medical Applications - NANOMA

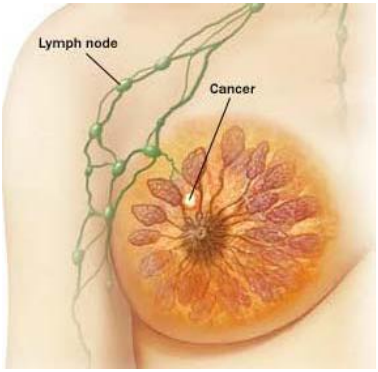
NANOMA aims at developing drug delivery microrobotic systems (composed of nanoActuators and nanoSensors) for the propulsion and navigation of ferromagnetic microcapsules in the cardiovascular system through the induction on magnetic gradients.

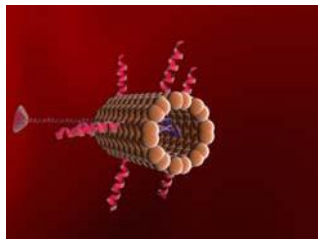
New approach for diagnosing and treating breast cancer :

1. **Enhanced diagnostics using MRI,**
2. ***In-Vivo* propulsion and navigation,**
3. **Targeted drug delivery using functionalized nanovectors.**

Magnetic microcapsule sterring using MRI ystem

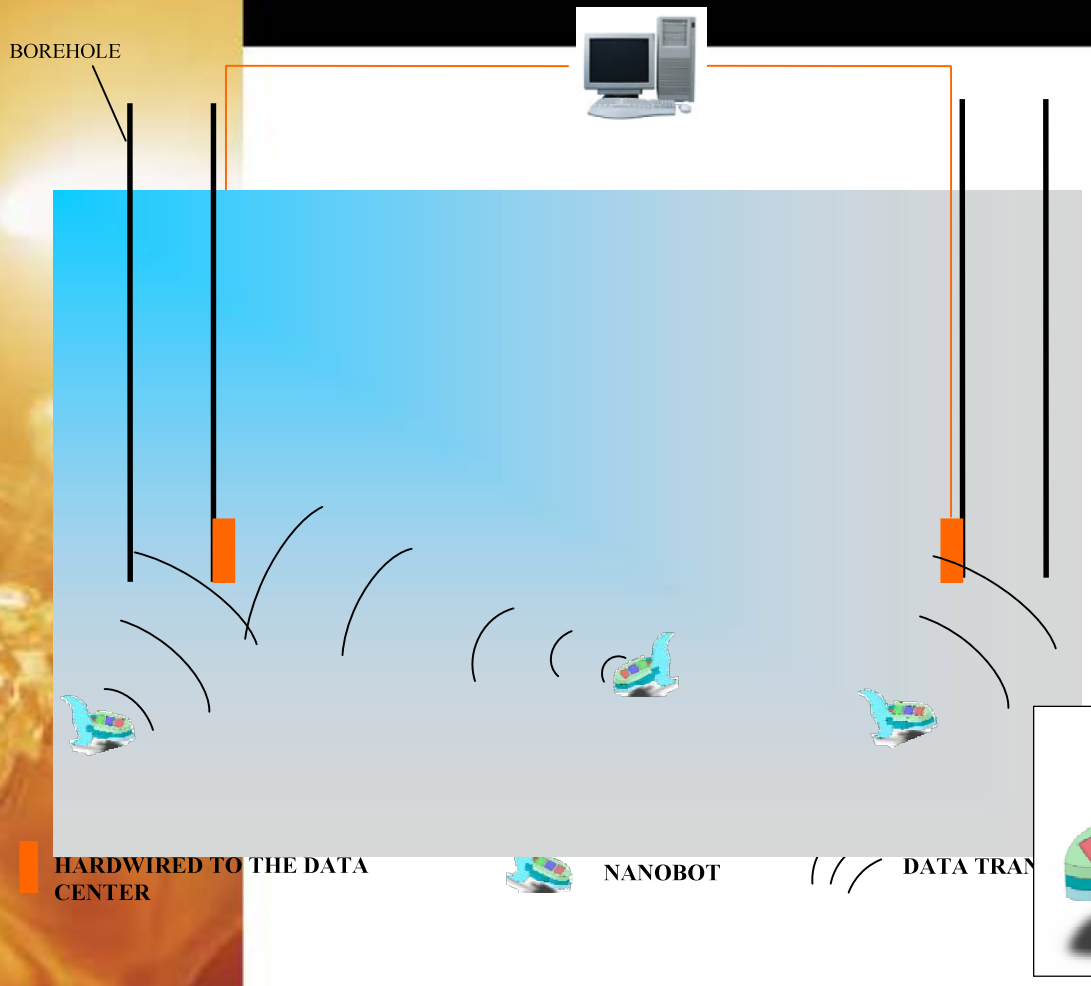
Early cancer stage I

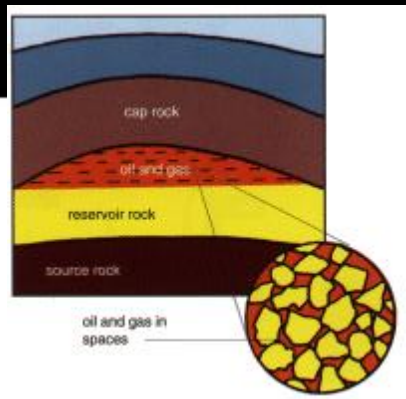


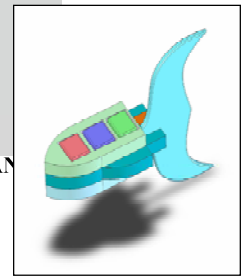


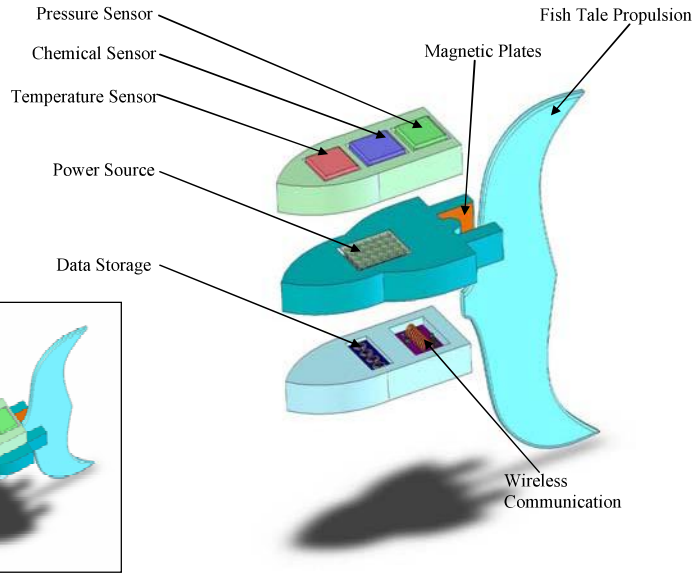
Microcaprule-based drug delivey

Nanorobots for the Oil Industry



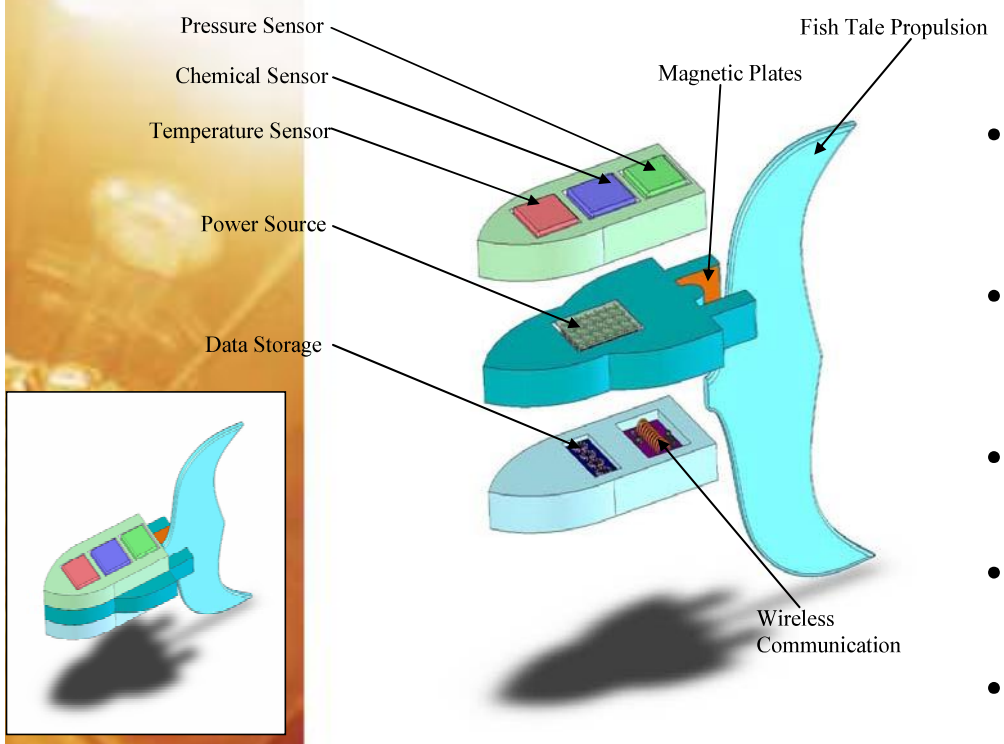






Develop novel nanobots for the monitoring of deep oil reservoirs

Future Challenges for Nanorobotics



- Assembly of a Fully Functional Nanorobot
- Closed Loop Control and Guidance at the Nano-Scale
- Wirelless Communication at the Nano-Scale – Data Transfer
- Power Generation at the Nanoscale
- Accurate Modeling at the Nanoscale
- Going Smaller and Smaller (~100nm total)

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