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

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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

Facilities at the Kostas Nanomanufacturing Center

George J. Kostas Nanomanufacturing Center at Northeastern University

1. Entrepreneur, Corporate Outreach and Staff Area
2. Soft Lithography and Wet Chemistry Lab
3. Lithography and Characterization
4. Cleanroom Facility
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)
Nanomedicine Patents and Publications  (Wagner et al., Nature Biotechnology, 2006)

(Wagner et al., Nature Biotechnology, 2006)
Collaboration

* A truly multidisciplinary field

Nanomedicine
Role of Nanotechnology in Medical Research

Basic Research
- Molecular Biology
- Genetics
- Proteomics
- Systems Biology
- ...

Nanotechnology
- Nanomanufacturing
- Nanoimaging
- Nanosensing
- Nanomanipulation
- Computational Tools
- ...

Biomedical Devices
- Tissue Regeneration
- Drug Delivery
- In-vitro Diagnostics
- Implantable Devices
- Smart Nanoparticles
- NanoRobotics
- ...

Translational Research
- Cancer
- Heart
- Brain
- ...

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

Molecular imaging & therapy

Cancer diagnosed
Targeting medication
Homing on tumor
Localized therapy
Killing cancer cells
Improved imaging
Localized therapy

(Opensource Handbook of Nanoscience and Nanotechnology)

Bio-Nano-Robot Repairing a Damaged Blood Cell
The Roadmap Towards NanoRobotics

STEP 1

Bio Sensors

DNA Joints

HA a-helix

Bio nano components

STEP 2

A bio nano robot
Representative Assembly of bio components

Assembled bio nanorobots

STEP 3

A bio nano computational cell

Distributive intelligence programming & control

Bio nano swarms

STEP 4

Automatic fabrication and information processing

A Bio nano information processing component

Conceptual automatic fabrication floor

Research Progression
# Bottom Up Approach Based on Macro-Nano Equivalence

<table>
<thead>
<tr>
<th>Structural Elements</th>
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<tbody>
<tr>
<td>Metal, Plastic Polymer</td>
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<table>
<thead>
<tr>
<th>Actuators</th>
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<tbody>
<tr>
<td>Electric Motors,</td>
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<tr>
<td>Pneumatic Actuators,</td>
</tr>
<tr>
<td>Smart Materials, Batteries,</td>
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<tr>
<td>etc.</td>
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</table>
**Bottom Up Approach Based on Macro-Nano Equivalence**

<table>
<thead>
<tr>
<th><strong>Sensors</strong></th>
<th><strong>Joints</strong></th>
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</thead>
<tbody>
<tr>
<td>Light sensors, force sensors, position sensors, temperature sensors</td>
<td>Rhodopsin, Heat Shock Factor, CNT based Nanosensors</td>
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<tr>
<td></td>
<td>DNA Nanodevices, Nanojoints</td>
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<tr>
<td></td>
<td>Revolute, Prismatic, Spherical Joints etc.</td>
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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

[Images of ATP Synthase, ATPase Visualization, Flagella in Bacterial Membrane, Myosin, Kinesin, Dynein Molecule, 1 μm diameter glass bead carried by Kinesins]


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

<table>
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<th>Mutant name</th>
<th>Sequence</th>
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<tbody>
<tr>
<td>WT</td>
<td>$^{243}G_{6}G_{6}G_{6}C_{R} - M_{K}, Q_{L}, E_{D}, K_{K} - V_{E}<em>{E}</em>{L}, L_{S}, K_{K} - N_{Y}<em>{H}</em>{L}<em>{E}</em>{N}<em>{E} - V</em>{A}<em>{R}</em>{L}<em>{K}</em>{K}<em>{L} - V</em>{G}<em>{E}</em>{R}$</td>
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<tr>
<td>M1</td>
<td>$H_{6}H_{6}H_{6}H_{6}H_{6}C_{R} - M_{K}, Q_{L}, E_{D}, K_{K} - V_{E}<em>{E}</em>{L}, L_{S}, K_{K} - N_{Y}<em>{H}</em>{L}<em>{E}</em>{N}<em>{E} - V</em>{A}<em>{R}</em>{L}<em>{K}</em>{K}<em>{L} - V</em>{G}<em>{E}</em>{R}$</td>
</tr>
<tr>
<td>M2</td>
<td>$H_{6}H_{6}H_{6}H_{6}H_{6}C_{R} - M_{K}, Q_{L}, E_{D}, K_{K} - V_{E}<em>{E}</em>{L}, L_{S}, K_{K} - H_{H}<em>{H}</em>{L}<em>{E}</em>{N}<em>{E} - V</em>{A}<em>{R}</em>{L}<em>{K}</em>{K}<em>{L} - V</em>{G}<em>{E}</em>{R}$</td>
</tr>
<tr>
<td>M3</td>
<td>$H_{6}H_{6}H_{6}H_{6}H_{6}C_{R} - M_{K}, Q_{H}, E_{H}, D_{D}, H_{H}, E_{E} - V_{E}<em>{H}</em>{H}<em>{L}, H</em>{S}, K_{K} - N_{N}<em>{H}</em>{L}<em>{E}</em>{N}<em>{E} - V</em>{A}<em>{R}</em>{L}<em>{K}</em>{K}<em>{L} - V</em>{G}<em>{E}</em>{R}$</td>
</tr>
<tr>
<td>M3CT</td>
<td>$G_{6}G_{6}G_{6}G_{6}G_{6}C_{R} - M_{K}, Q_{H}, E_{H}, D_{D}, H_{H}, E_{E} - V_{E}<em>{H}</em>{H}<em>{L}, H</em>{S}, K_{K} - N_{N}<em>{H}</em>{L}<em>{E}</em>{N}<em>{E} - V</em>{A}<em>{R}</em>{L}<em>{K}</em>{K}<em>{L} - V</em>{G}<em>{E}</em>{R}$</td>
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Peptide based Nano-Gripper: Results

Displacement Calculation Using MD Simulations

Force Calculations Using MD Simulations

Experimental Verification Using ESR Spectroscopy
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
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,
Future Challenges for Nanorobotics

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

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