Principles and Applications of Nanobiotechnology

Prof. Je-Kyun Park

http://nanobio.kaist.ac.kr

Department of BioSystems
Korea Advanced Institute of Science and Technology

Contents

• Introduction

• What is Nanobiotechnology?

• Nanofabrications
  - MEMS/ NEMS, AFM, SAM, Soft lithography, ...

• Nanobiotechnology Applications
  - Nanomedicine, Nanobiosensor (biochip), Nano Fluidics (LOC, Biofluidic devices)
  - Molecular Self-Assembly, Intelligent Drug Delivery Systems (DDS), Nanomachine, Other Nano-Bio Devices & Systems

• Summary

Focus on Nanobiotechnology

This issue looks at some of the emerging life science applications of nanotechnology and nanoscience, a field that has been loosely termed nanobiotechnology. Nanobiotechnology integrates the design of new materials and devices with the exquisite specificity of biological molecules, enzymes and cells. Applications include new types of biomaterials, sensors relying on conformational changes in biomolecules, molecules for use in imaging and tagging macromolecules and cells, and devices, materials and particles for use in drug delivery or directly as therapeutics.

Definition and Scope of Nanotechnology

• Science for exploring the materials and phenomena in the nanometer (atomic, molecular) scale

• Technology for manipulating and controlling the structure and components in the nanometer scale, thus inventing new materials, devices and systems

What is Nanobiotechnology?
Nanobiotechnology

- Nanobiotechnology is the application of nanotechnology to the life sciences. This research field includes two approaches. One is the application of nano-sized tools to biological systems and the other is the use of biological systems as templates in the development of novel nano-sized products.

- Nanobiotechnology is the intersection of inorganic and organic engineering to solve critical problems in biology. These problems can be the creation of new drugs, drug delivery vehicles, diagnostics, sensors, assays, tools such as fluidics, and manufacturing processes for all of the above.

(Source) Ian J. Mehr, “Nanobiotechnology, Commercial Opportunities from Innovative Concepts,” D&M Reports #9072 (2002, 4)


Why Nanobiotechnology?

- Mother Nature did it first. Nature has built nanomachines for millennia.
  - Nature applies nanotechnology daily to grow the multifunctional cells and tissues of plants and animals from a single biological cell
  - A cell is a warehouse of nanoscale machines.

- Biology can teach the physical world of electronics, computing, materials science and manufacturing
  - There exist biomolecular analogues of conventional functional devices

An Animal’s Senses Guide Its Movements

- Nostrils on each side of the head of the salmon allow water to flow into one and out the other
  - Sensory cells in the nostrils detect specific chemicals in the water
  - These cells aid the salmon in its homing ability

- Salmon have a lateral line system, seen here as a blue line along the sides of the fish
  - This enables the salmon to sense the direction and velocity of water currents and thus distinguish which direction is upstream

Capillary-force Actuators

- Surface tension and capillary forces can be controlled actively or passively using different effects: electrocapillary, thermocapillary, and passive capillary.

  Electrocapillary Effect (known as Electrowetting)

  Changes the surface tension between two immiscible, conductive liquids or between a solid surface and a liquid by varying their potential difference.

Machines & Molecular Machines

<table>
<thead>
<tr>
<th>Machines</th>
<th>Molecular machines</th>
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<tbody>
<tr>
<td>Vehicles</td>
<td>Hemoglobin</td>
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<tr>
<td>Assembly lines</td>
<td>Ribosomes</td>
</tr>
<tr>
<td>Motors, generators</td>
<td>ATP synthases</td>
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<tr>
<td>Train tracks</td>
<td>Actin filament network</td>
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<tr>
<td>Train controlling center</td>
<td>Centrosome</td>
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<tr>
<td>Digital databases</td>
<td>Nucleosomes</td>
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<tr>
<td>Copy machines</td>
<td>Polymerases</td>
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<tr>
<td>Chain couplers</td>
<td>Lignosomes</td>
</tr>
<tr>
<td>Bulldozer, destroyer</td>
<td>Proteases, proteosomases</td>
</tr>
<tr>
<td>Mail-sorting machines</td>
<td>Protein sorting mechanisms</td>
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<tr>
<td>Electric fences</td>
<td>Membranes</td>
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<tr>
<td>Gates, keys, passes</td>
<td>Ion channels</td>
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<tr>
<td>Internet nodes</td>
<td>Neuron synapses</td>
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Nanotechnology Impacts on Biology

- Nanotechnology also offers researchers the chance to detect rare events or molecules that are present only at low concentrations.
- As nanotechnology brings more tools to the biologist’s bench, the divisions between the fields of science will begin to break down.
- “The combination of microfluidics and nanotechnology will transform how biologists do everything.”
**Nanofabrications**

MEMS/ NEMS  
Self-Assembly  
Dip-Pen Nanolithography  
Soft-Lithography  
PDMS Molding  
Nanoparticles, Nanowires, Nanotubes

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**What is MEMS/ NEMS?**

- Integrated micro devices or systems combining electrical and mechanical components fabricated using integrated circuit (IC) compatible batch-processing techniques and range in size from micrometers to millimeters
  
  In US: MEMS, Micromachining  
  In Europe: Micro Systems Technology (MST)  
  In Japan: Micromachines, Microrobots

- Miniaturization of non-electrical (optical, thermofluidic, biochemical) components

**MEMS: Micro Electro Mechanical Systems**  
**NEMS: Nano Electro Mechanical Systems**

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**What is BioMEMS/NEMS?**

- A Paradigm Shift in the Making  
  "MEMS become BioMEMS" (BioPhotonics 2000.6)

- Implementation of MEMS/NEMS to Bio-related areas (Bio Micro/Nano Electro Mechanical Systems)

- Needs
  
  - Lower chip cost (Glass or plastic chips)
  - Reduction of expensive reagents & test compound used
  - Integration of multiple functions onto a single chip (Micro total analysis system (µ-TAS), Lab-on-a-chip)
  - Point-of-care (POC) diagnostics (Easy sample preparation)
  - High throughput (Microfluidic HTS disposables)

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**Biotechnological & Biomedical Microsystems**

- Tools for Chemistry, Molecular Biology and Biochemistry
  - Sample preparation, Molecular separation  
  - Small-scale organic synthesis  
  - Amplification of nucleic acids/ Sequences

- Tools for Cell Biology
  - Cell mechanics & dynamics, Cell culture devices  
  - Dielectrophoresis, Flow cytometry, Cell sorting

- Tools for Medicine, Biomedical Devices
  - Minimally invasive surgery  
  - Neural prostheses  
  - Implantable devices, DDS

- Miniaturized analytical systems
  - Genomics and proteomics  
  - Clinical analysis, Environmental testing, and Warfare defense  
  - High throughput screening

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**Self-Assembly**

1. Surface group (terminal functionality)  
2. Alkyl, or derivatized alkyl group  
3. Surface-active head group

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Dip-Pen Nanolithography

Soft lithography
- Self-Assembled Monolayers (SAMs)
- Contact Printing, Replica Molding, and Embossing
- Elastomeric Stamps and Molds
- Masters and Rapid Prototyping

Nanobarcodes™ Particles
- Cylindrically-shaped, striped metal particles, readout based on differential reflectivity using an optical microscope
- Multiplexed DNA assays
- Multiplexed Oligo Titrations
- Multiplexed Sandwich immunoassays
- Proximity-based Bioassays

Synthetic Methods for 1-Dimensional Nanostructures
Thermal chemical vapor deposition (CVD)

Nanobiotechnology Applications
Nanomedicine
- Nanobiosensor (biochip)
- Nano Fluidics (LOC, Biofluidic devices)
- Molecular Self-Assembly
- Intelligent Drug Delivery Systems (DDS)
- Nanomachine
- Other Nano-Bio Devices & Systems

A Grand Plan for Medicine
Quantum Dot Nanocrystals

Size- and material-dependent optical properties

Nanobiotechnology Applications

Nanomedicine

Nanobiosensor (biochip)

Nano Fluidics (LOC, Biofluidic devices)

Molecular Self-Assembly

Intelligent Drug Delivery Systems (DDS)

Nanomachine

Other Nano-Bio Devices & Systems

Translating Biomolecular Recognition into Nanomechanics

Biological samples can be screened for the presence of particular genetic sequences using small beams (cantilevers) of the type employed in atomic force microscopes.

The surface of each cantilever is coated with DNA able to bind to one particular target sequence.

Bioelectronic Sensor

Electrochemical DNA Sensors

Nanobiotechnology Applications

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Molecular Self-Assembly

Intelligent Drug Delivery Systems (DDS)

Nanomachine

Other Nano-Bio Devices & Systems
In microchannels in which either width or height is less than ~200 µm,

- Aqueous flow is generally laminar, not turbulent
- Diffusion is an efficient process for mixing the dissolved contents of two or more fluids
  - Diffusion-based Separation: H-Filter
- Particles can also be separated by diffusion according to their size

How does one successfully build a lab-on-a-chip?

- What is the optimal channel dimension?
- What is the optimal voltage for injection?
- Is Joule heating critical?
- How to enable Multiplexing?
- How to minimize dispersion?
- How to Enhance signal to noise ratio?
- What is the optimal flow rate?
- Is “sample stacking” necessary?
- What is the optimal Voltage for injection?

Lab-on-a-chip tech goes reconfigurable

- Electrodes make chip programmable
- How does one successfully build a lab-on-a-chip?
- Logic and Microcontroller
- Rotary Mixer
- Mixing, Tempering

Microfluidic Comparator Chip

- Nanoliter-Scale Nucleic Acid Processor
- Other Nano-Bio Devices & Systems
- Intelligent Drug Delivery Systems (DDS)
- Molecular Self-Assembly
- Intelligent Drug Delivery Systems (DDS)
- Nanomachine
- Nanobiosensor (biochip)
- Nanomedicine
- Molecular Self-Assembly

Nano Fluidics (LOC, Biofluidic devices)

Nanobiotechnology Applications

- Other Nano-Bio Devices & Systems
Biomolecular Recognition of Semiconductor Quantum Dots and Magnetic Materials

**Peptide combinatorial approach**
- Select peptides with high affinity for specific semiconductor structures and crystal orientations using molecular recognition
  - Phage display and bacterial display
- Rationally design peptides and polymers to assemble nanoparticles in 2D and 3D structures


Ordering of Quantum Dots Using Genetically Engineered Viruses

**A Controlled-Release Microchip for Drug Delivery**

Nanobiotechnology Applications

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**Other Nano-Bio Devices & Systems**

NanoGate Implant, iMEDD, Inc.

**Nanobiotechnology Applications**

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**Nanomachine**
**Other Nano-Bio Devices & Systems**
Biomechanical Motor

Blood vessel wall
Red blood cell
Plaque attack
The diseased section of the blood vessel is covered with a type of plaque containing cholesterol.

Waste away
The nanobot would either remain inside the blood system, constantly performing its task, or it would be programmed to biodegrade safely, carrying the waste plaque out of the human body.

Getting the needle
A hypodermic syringe, less than 0.02 in (0.5 mm) in diameter, would inject nanobots into the blood vessel.

Dishing it up
A communication dish would send & receive instructions & data from a controller outside of the body.

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Micro-cleaner
A vacuum hose would suck up the waste plaque for safe storage inside the nanobot.

Saw 'n' scrape
An incredibly small rotary saw would scrape the plaque free from the blood vessel wall.

Nanobiotechnology
Applications

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Conventional Patch Clamp vs. Microchip

• Operator
• Micromanipulator
• Microscope
• Pipette puller
• Microforge
• Faraday cage
• Air table
• Perfusion system

Future Visions

• Engineers of the future will have expertise in both biology and technology.
• Biology already has nanomachines.

Take lessons from Mother Nature

- Engineered biomolecular machines
- Nanomedical surgical implements
- Molecular healing and repair of injury and disease
- Smart drugs
- NEMS
- Mobile nanopharmacies, nanomachines, …