What is Nano-Bio?

Physicist: study of molecular interactions
- application of "nano-tools" to study biological systems.

Biotech: application of nano-tools to detect, treat, and prevent disease

Biologists: we've been studying Nano-Bio for several hundred years!

Chemist / Mat Sci: exploit molecular biology to make new materials

Opportunist: an infinite source of funding!

Non-Covalent Interactions

**Electrostatic**
100 meV
Long range

**Hydrogen Bond**
40 meV
Directional - strongest in a straight line

**van der Waals**
4 meV
Between any two atoms
Very weak

**Hydrophobic**
100 meV
minimize contact with water

Cells...build functional structures
...store / process information
...transduce energy
...replicate
...recognition
Biology: 4 families of small organic molecules

- Sugars
- Lipids
- Nucleotides
- Peptides

Larger structures from these building blocks

- Polysaccharides
- Biomembranes
- RNA / DNA
- Proteins
Pre 1970's: DNA was extremely difficult to analyze – long and featureless.

Significant advance: discovery of **restriction nuclease**s which cut DNA.

Target – phosphodiester bonds at a specific 4-8 base sequence.
**Denaturization / Hybridization**

At high temperature or extreme pH, hydrogen bonds will break and DNA will “melt” in single strands.

Slow cooling (or normalizing pH) allows hydrogen bonds to reform:

Hybridization can be highly specific for DNA lengths up to 1000 bases.

**Why So Specific?**

Hydrogen bonds

- T
- A
- C
- G
DNA Nanomotor

single strand, 17 bp DNA:
TGGTTGGTGTTGGT

Exists as a tetraplex structure in isolation:

Li and Tan, Nano Lett 2, 315 (2002)

DNA Nanomotor

Forms duplex double strand in presence of α

\[\alpha: \text{GTA GTC CGC GAC CAA CCA CAC CAA CCA}\]

Sticky End

Li and Tan, Nano Lett 2, 315 (2002)
DNA Nanomotor

Add complementary strand b:

\[ \text{TG GTT GGT GTT GGT} \]
\[ \text{nanomoter} \]
\[ \alpha: \text{GTA GTC CGC GAC CAA CCA CAC CAA CCA} \]
\[ \beta: \text{CAT CAG GCG TCG GTT GGT GTT GGT} \]

Initiated by sticky end pairing, propagated by branch migration

DNA Nanomotor

Nanomoter re-folds into its tetraplex state:
DUTE Nanomotor

DUTE Nanomotor

add $\alpha$
DUTE Nanomotor

add \( \beta \)

DUTE Nanomotor

add \( \alpha \)
FRET Signal

- fluoresce
- quenched

Nanomotors on Surfaces

Add $\alpha$

Add $K^+$ (promotes TE)
Protein Structure

Secondary

Non-covalent bonding between residues within the protein creates structural motifs.

Tertiary

SEQUENCE ➔ STRUCTURE ➔ FUNCTION

Protein Binding

Protein function requires binding other molecules.
Protein function requires binding other molecules.

Yet this binding must be highly SPECIFIC to avoid binding other molecules.

Specificity is achieved through a set of weak non-covalent bonds and matching contour between the protein and ligand.
Antibodies

Strong, specific binding molecules.
Remove antigens from an organism.

Antibodies are technologically useful because they can be “raised” against any small molecule or nanostructure.
Biotin/Streptavidin

Strong, permanent bond.
Stable over wide range of T and pH.

MOSFET

n
p

SiO₂

gate

p

n
BioMOSFET

Field due to charged biomolecules create the inversion

Limited sensitivity – molecules must cover the 2D gate

Nanowire Nanosensors

NanofET

Biotin

streptavidin

Nanosensor

Science 293, p1289
Nanowire Nanosensors

Biotin/Streptavidin

1D systems are more sensitive to surface effects.

25 pM streptavidin

Nanowire Nanosensors

Biotin/Antibiotin - reversible
Synthetic Immobile DNA Junctions

Genomic DNA strictly linear, but branch junctions exist transiently in nature and can be stabilized.

Central Dogma of Molecular Biology

DNA (transcription) → RNA (translation) → Protein
Three DNA bases code for one protein residue.

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<tr>
<th>FIRST POSITION</th>
<th>SECOND POSITION</th>
<th>THIRD POSITION</th>
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<td>U</td>
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* not used

R R R R
C-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C
R R R

Virus

Small (30 - 300 nm)
Simple
Parasitic
Not technically living
Selection of peptides with semiconducting binding specificity for directed nanocrystal assembly

Biomolecules can .... fabricate inorganic nanomaterials .... assemble them into structures .... be easily synthesized and manipulated

Can we extend this to inorganic materials with interesting electronic properties?

- GaAs(100)
- GaAs(111)A
- GaAs(111)B
- InP(100)
- Si(100)
Phage Display

1. Combinatorial phage libraries synthesized with millions of peptide sequences on coat...

2. Phage exposed to the target of interest....

3. Non-bound phage are washed from the surface.

4. Bound phage are eluted from the surface.
5. Bacteriophage are amplified by infecting bacteria.

**Bacteriophage M13**

900 nm x 9 nm, 5 proteins, 9 genes
Phage Display with Electronic Materials

Insert $\sim 10^9$ different 12 residue peptides into g3p.

Expose to clean semiconductor surfaces.

Wash and elute to isolate binding peptides.

Amplified by $10^6$ in bacteria.

Repeat 3 to 5 times.

Analyze genome of binding M13s

Sequences which bind GaAs (100)
**Phage display selects for an increased proportion of residues that can donate an electron pair to the GaAs surface.**

**The 12-mer peptide sequences should be extended, and may be longer than necessary (working on 7-mers).**
Demonstrating Specificity

Peptide/Semiconductor interaction
- structural?
- chemical?
- electronic?

Lipids

DOPC
Biomembrane

Supported Membrane

Substrate
Detection of Molecular Interactions at Membrane Surfaces through Colloid Phase Transitions
Michael M. Baksh et al., *Nature* 427, 139 - 141

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**Supported Membrane Dynamics**

**A**

**B**

**C**

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**Detection of Molecular Interactions at Membrane Surfaces through Colloid Phase Transitions**

Michael M. Baksh et al., *Nature* 427, 139 - 141
Colloids are near a phase transition, determined by the colloid pair interaction.

Add receptor protein

Presence of the receptor protein alters the spacing, thus altering the van der Waals contribution to the pair interaction.
Ligand: Trisialoganglioside (G\textsubscript{TIB})
Receptor: Tetanus toxin (TT)

Quantify with the pair distribution function:
\[ g(r) = e^{-w(r)/K_BT} \]

Phase transition provides signal amplification to observe molecular event.

Control

Gm1 only alters the pair potential with the Cholera Toxin B