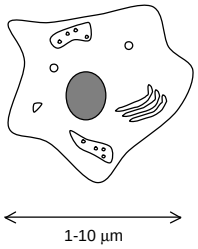
## What is Nano-Bio?

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!



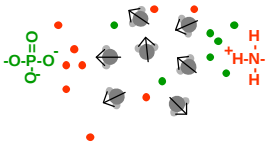

**Cells** …build functional structures
…store / process information
…transduce energy
…replicate
…recognition

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

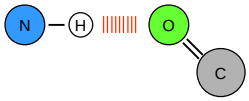
Opportunist: -an infinite source of funding!

## Non-Covalent Interactions

Electrostatic
100 meV
Long range

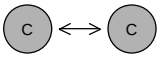



Hydrogen Bond
40 meV




Directional - strongest in a straight line

van der Waals
4 meV

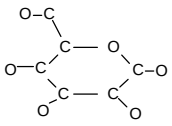



Between any two atoms
Very weak

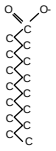
Hydrophobic
100 meV

## Biology: 4 families of small organic molecules

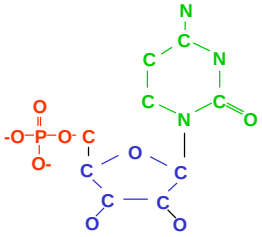
Sugars



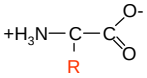
Lipids



Nucleotides

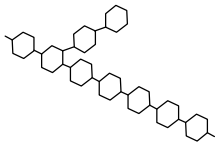


Peptides

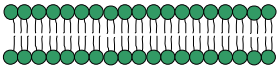


## Larger structures from these building blocks

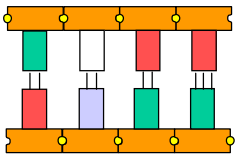
Polysaccharides



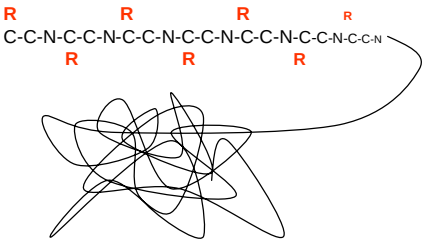
Biomembranes



RNA / DNA



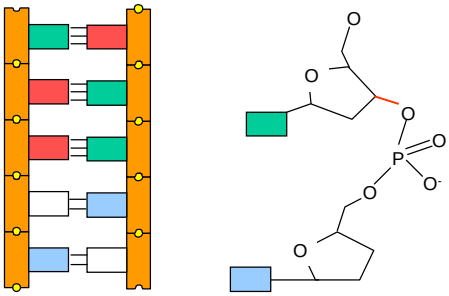
Proteins



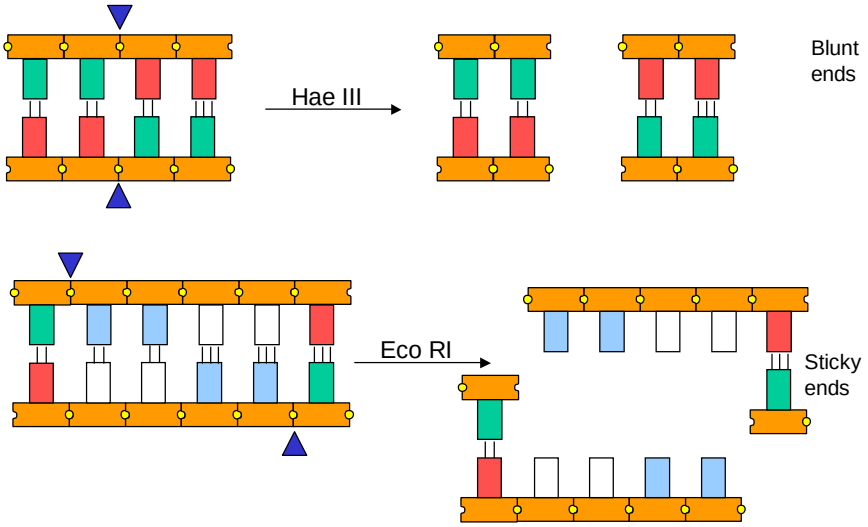
Pre 1970's: DNA was extremely difficult to analyze – long and featureless.

Significant advance: discovery of **<u>restriction nucleases</u>** which cut DNA.

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



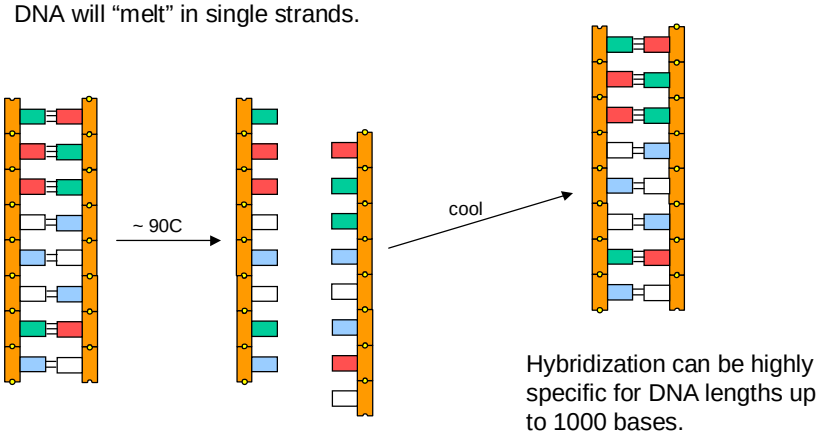

## Restriction Nucleases



## Denaturization / Hybridization

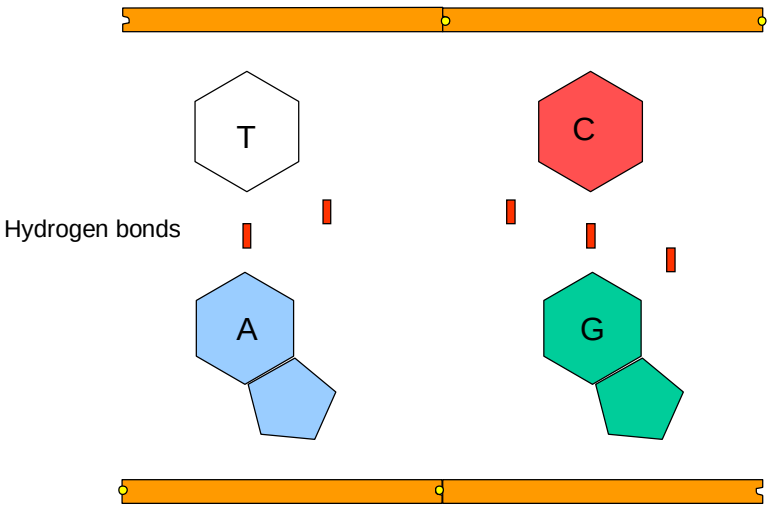
At high temperature or extreme pH, hydrogen bonds will break and DNA will “melt” in single strands.

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




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

## Why So Specific?

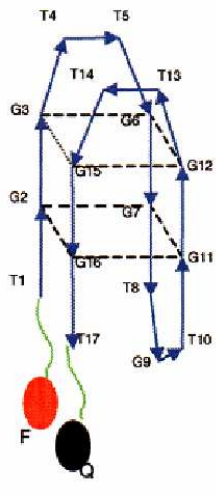


## DNA Nanomotor

single strand, 17 bp DNA:

TGGTTGGTGTGGTTGGT

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

TG GTT GGT GTG GTT GGT :**nanomoter**
**α**: GTA GTC CGC GAC CAA CCA CAC CAA CCA

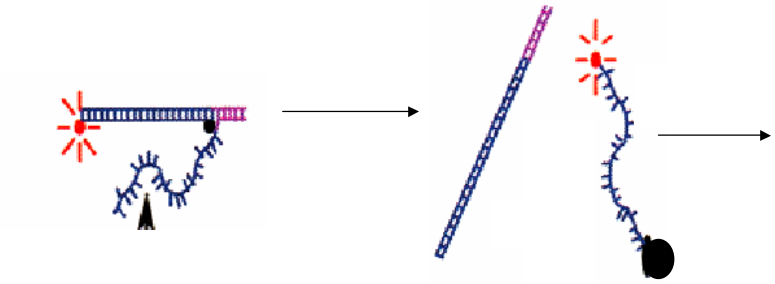
Sticky End

## DNA Nanomotor

Add complementary strand b:

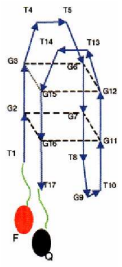
TG GTT GGT GTG GTT GGT :**nanomoter**
**α**: GTA GTC CGC GAC CAA CCA CAC CAA CCA
**β**: CAT CAG GCG TCG GTT GGT GTG GTT GGT

Initiated by sticky end pairing, propagated by branch migration

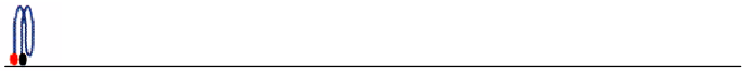


## DNA Nanomotor

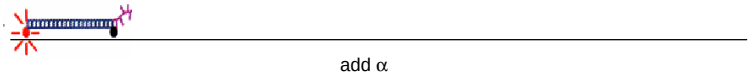
Nanomoter re-folds into its tetraplex state:



## DUTE Nanomotor

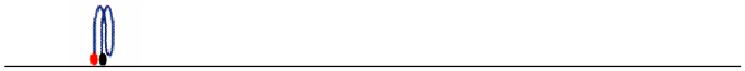


## DUTE Nanomotor



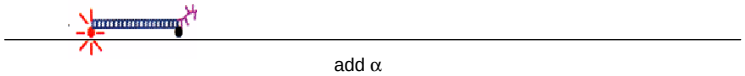
add α

## DUTE Nanomotor



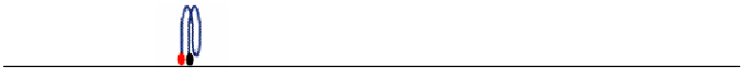
add β

## DUTE Nanomotor



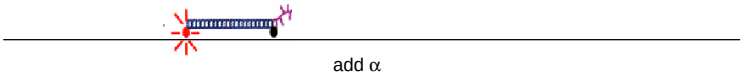
add α

## DUTE Nanomotor



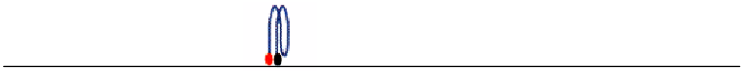
add β

## DUTE Nanomotor



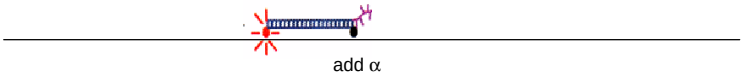
add α

## DUTE Nanomotor



add β

## DUTE Nanomotor

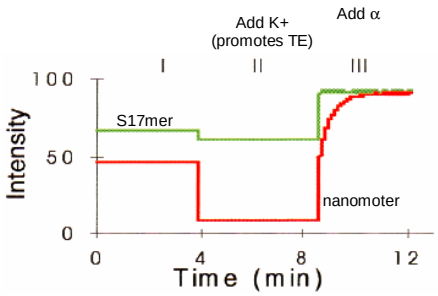


add α

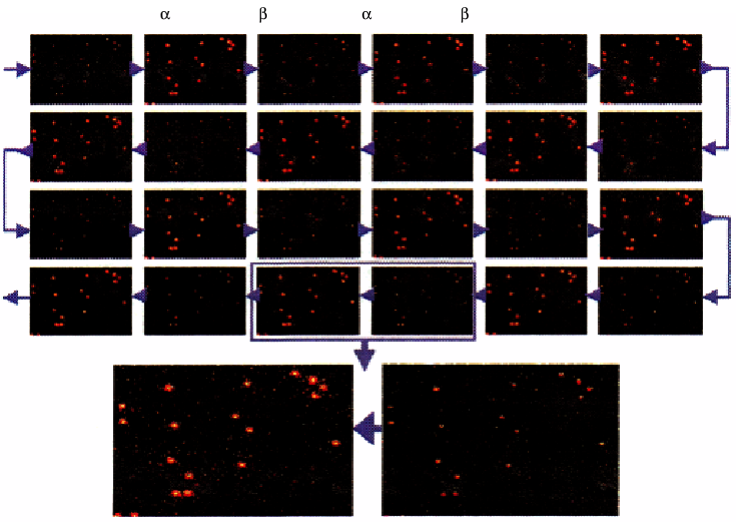
## FRET Signal

fluoresce

quenched

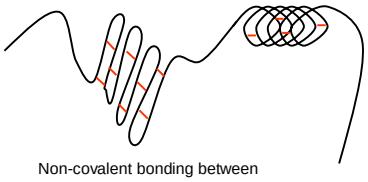



## Nanomotors on Surfaces



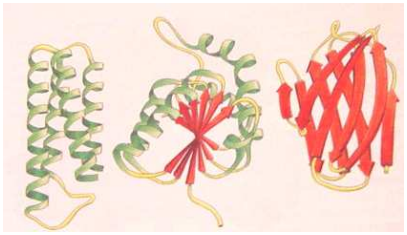
## Protein Structure

Secondary



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

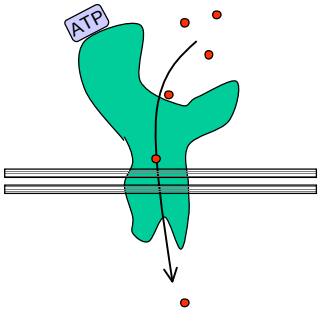
Tertiary



SEQUENCE → STRUCTURE → FUNCTION

## Protein Binding

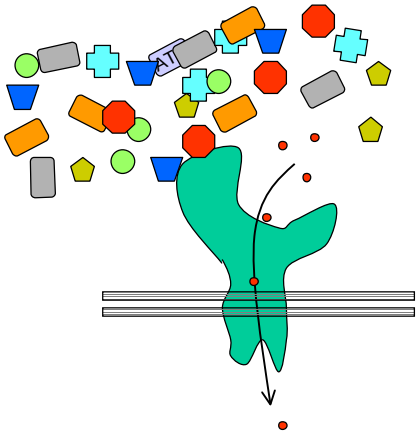
Protein function requires binding other molecules.



## Protein Binding

Protein function requires binding other molecules.

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

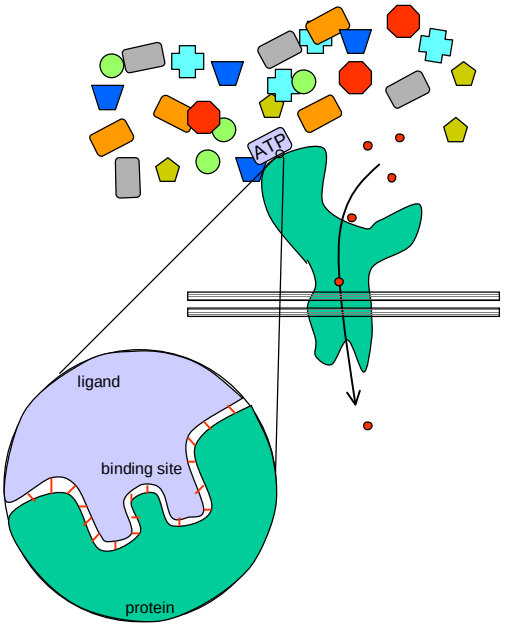



## Protein Binding

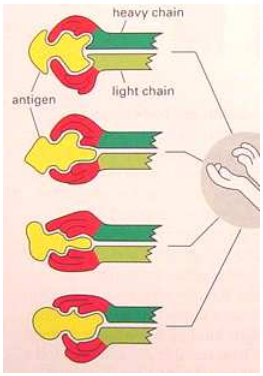
Protein function requires binding other molecules.

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

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

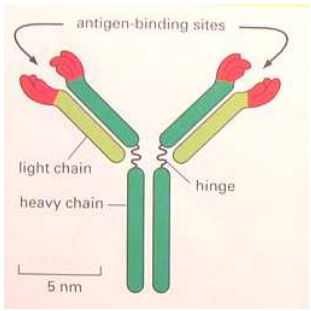


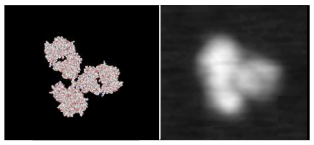
## Antibodies



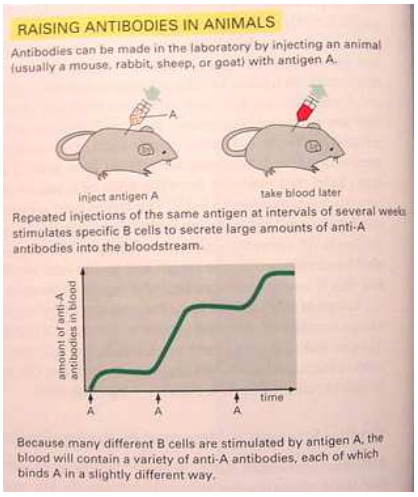

Strong, specific binding molecules.

Remove antigens from an organism.

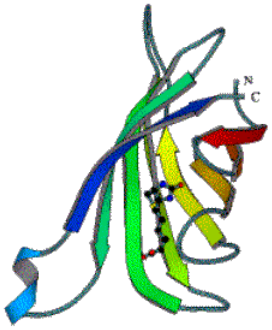


Antibodies are technologically useful because they can be “raised” against any small molecule *or nanostructure*.

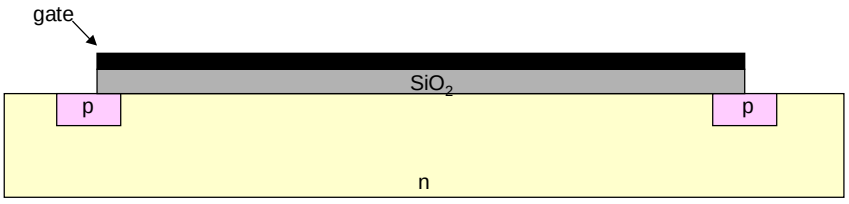


## Biotin/Streptavidin

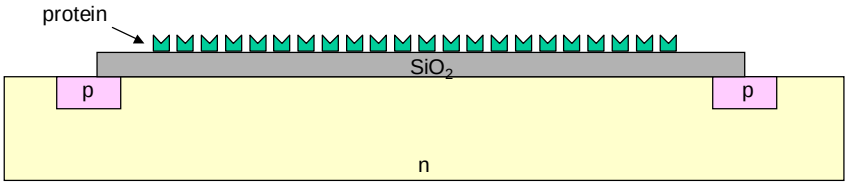



Strong, permanent bond.
Stable over wide range of T and pH.

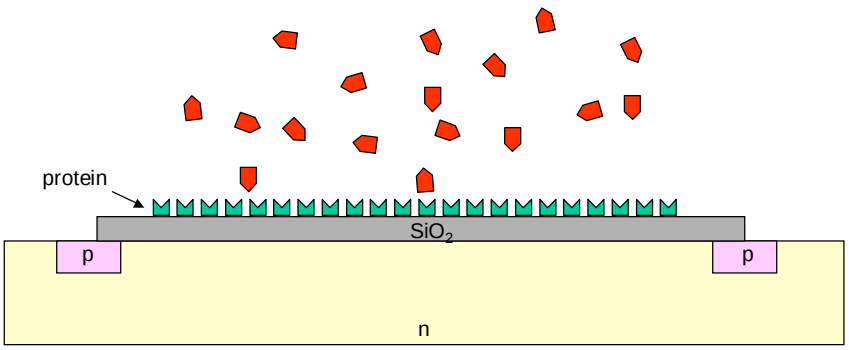
## MOSFET



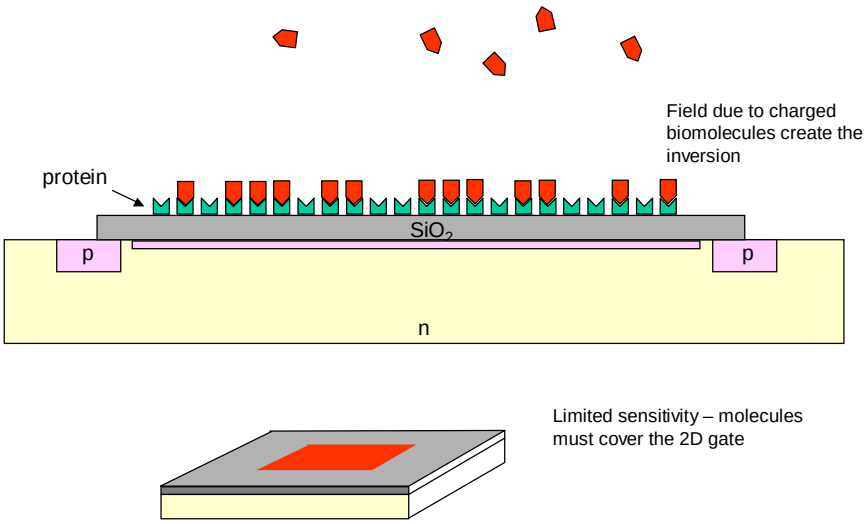
BioMOSFET




BioMOSFET



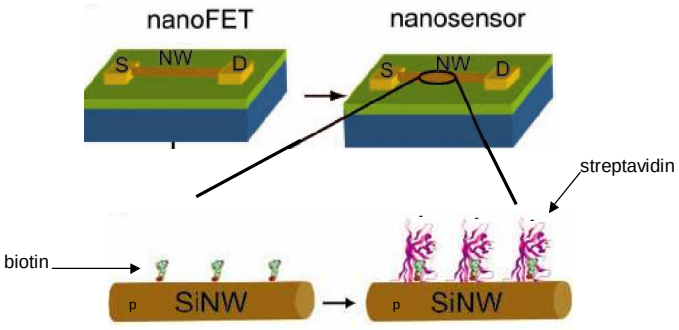
## BioMOSFET






Limited sensitivity – molecules must cover the 2D gate

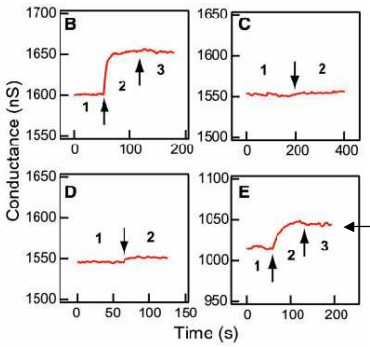
## Nanowire Nanosensors




Science 293, p1289

## Nanowire Nanosensors

Biotin/Streptavidin

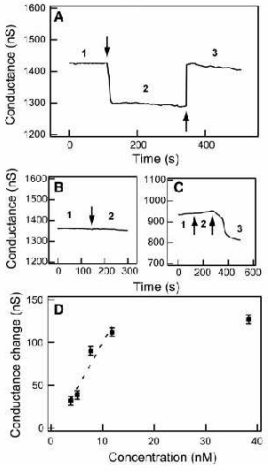



25 pM streptavidin

1D systems are more sensitive to surface effects.

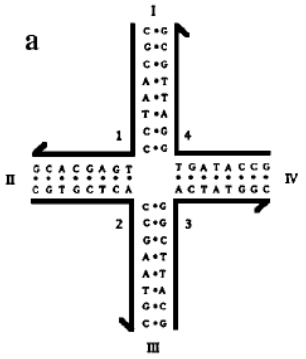
## Nanowire Nanosensors

Biotin/Antibiotin - reversible

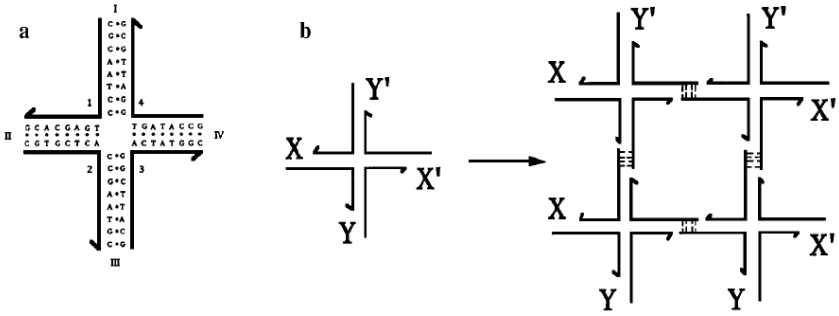


## Synthetic Immobile DNA Junctions

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

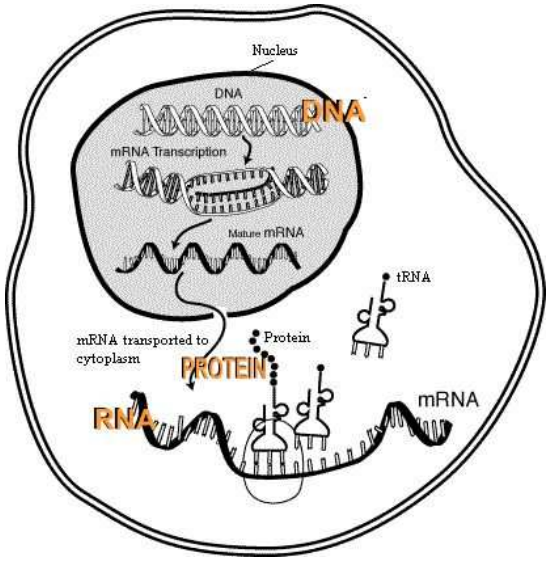



NC Seeman, Ann. Rev. Biophys. Biomol. Struct. **27**, p225 (1998).



# Central Dogma

of Molecular Biology




DNA

↓ (transcription)

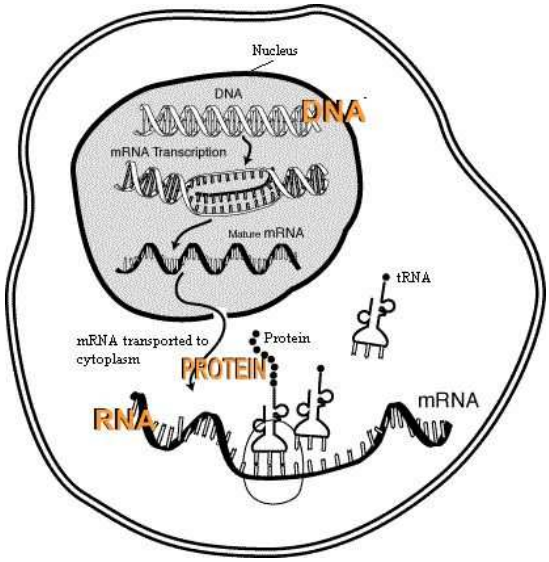
RNA

↓ (translation)

Protein

# Central Dogma

of Molecular Biology




DNA

↓ (transcription)

RNA

↓ (translation)

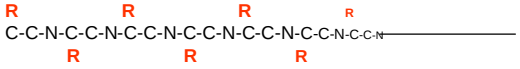
Protein

Three DNA bases code for one protein residue.

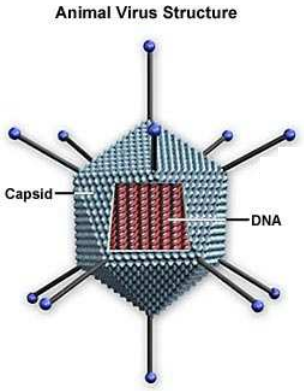
SECOND POSITION

| FIRST POSITION | U | C | A | G | THIRD POSITION |
|---|---|---|---|---|---|
| U | phenyl-alanine | serine | tyrosine | cysteine | U |
| | | | | | C |
| | leucine | | stop | stop | A |
| | | | stop | tryptophan | G |
| C | leucine | proline | histidine | arginine | U |
| | | | | | C |
| | | | glutamine | | A |
| | | | | | G |
| A | isoleucine | threonine | asparagine | serine | U |
| | | | | | C |
| | * methionine | | lysine | arginine | A |
| | | | | | G |
| G | valine | alanine | aspartic acid | glycine | U |
| | | | | | C |
| | | | glutamic acid | | A |
| | | | | | G |

* and start

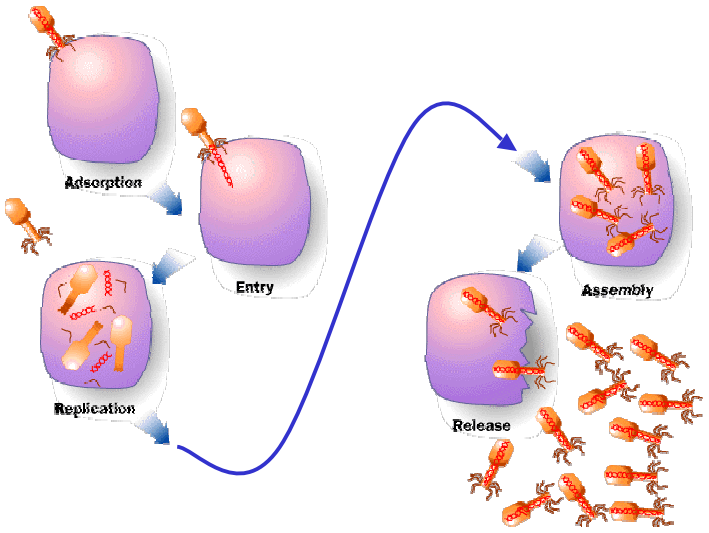



# Virus




Small (30 - 300 nm)
Simple
Parasitic
Not technically living

# Virus “Life” Cycle




## Selection of peptides with semiconducting binding specificity for directed nanocrystal assembly

Whaley, et al. Nature 405, p665 (2000).

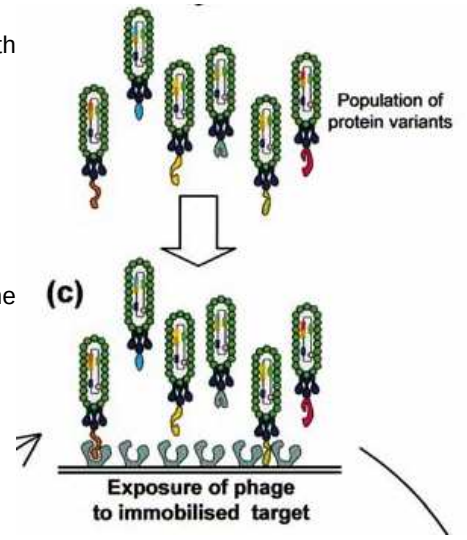
Biomolecules can …. fabricate inorganic nanomaterials
…. assemble them into structures
…. be easily synthesized and manipulated

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

GaAs(100) GaAs(111)A GaAs(111)B InP(100) Si(100)

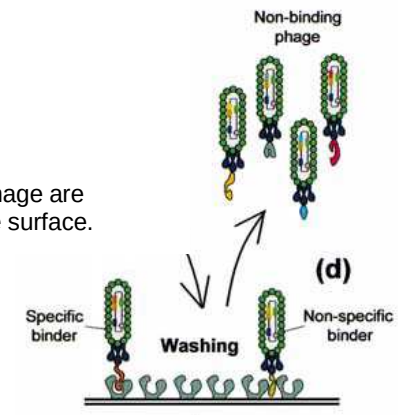
# Phage Display

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

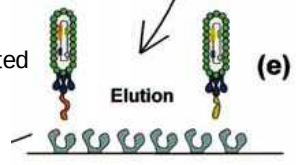


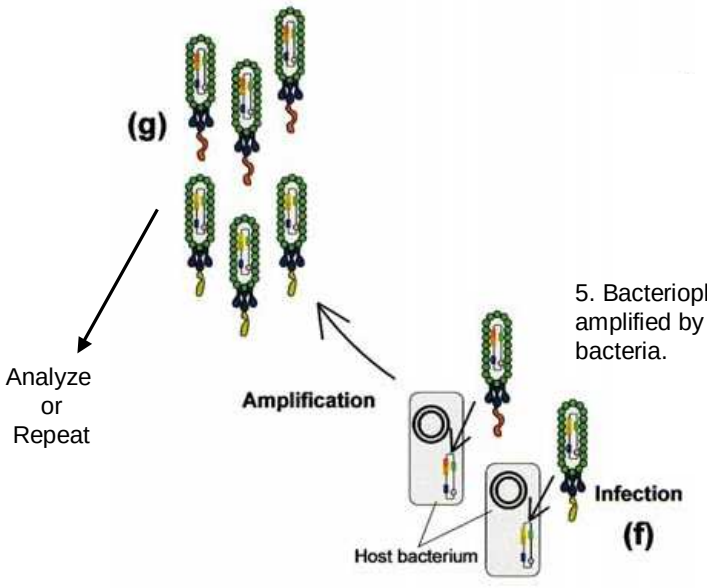

2. Phage exposed to the target of interest….

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




4. Bound phage are eluted from the surface.

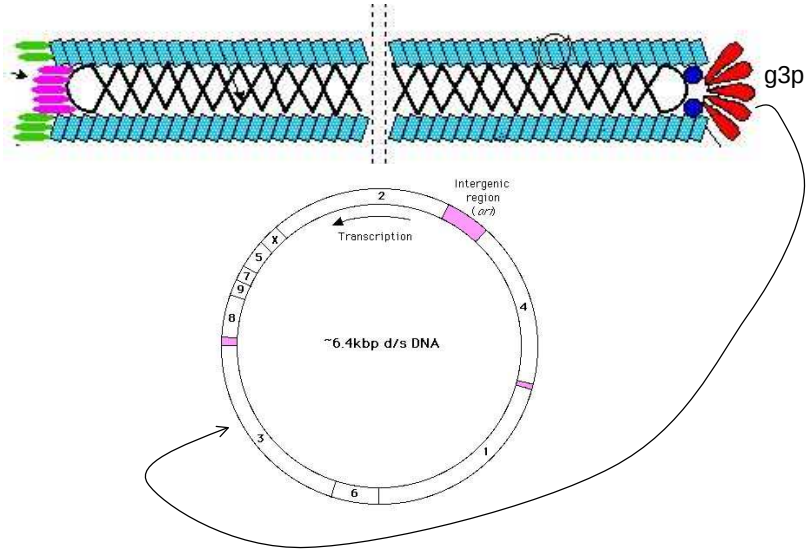





5. Bacteriophage are amplified by infecting bacteria.

## Bacteriophage M13

900 nm x 9 nm, 5 proteins, 9 genes



## Phage Display with Electronic Materials

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

Expose to clean semiconductor surfaces.

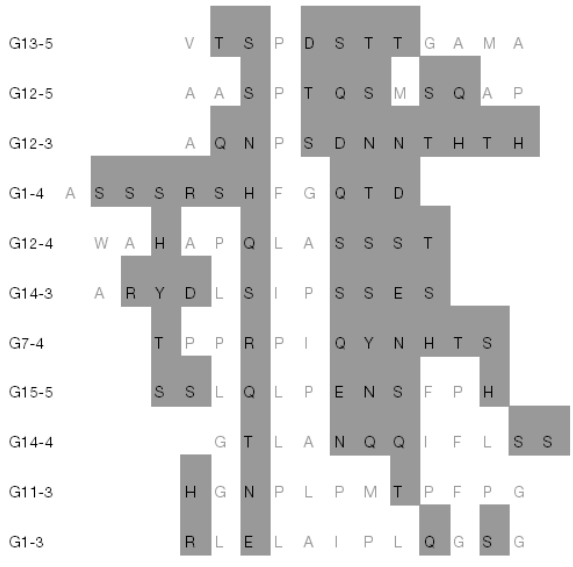
Wash and elute to isolate binding peptides.

Amplified by $10^6$ in bacteria.

Repeat 3 to 5 times.

Analyze genome of binding M13s

## Sequences which bind GaAs (100)



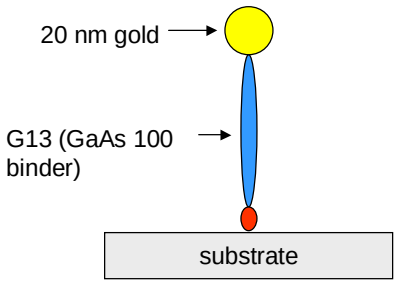
## Sequences which bind GaAs (100)

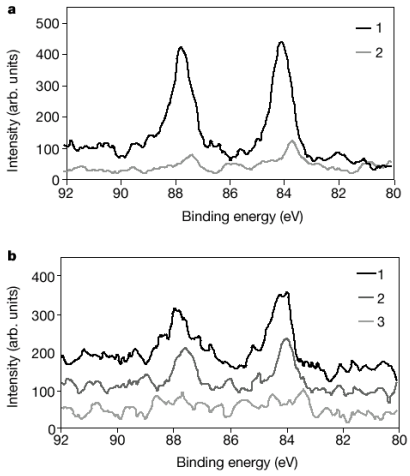
| group type | random occurrence | third round | fourth round | fifth round |
|---|---|---|---|---|
| Lewis Base | 34% | 41% | 48% | 55% |

**phage display selects for an increased proportion of residues that can donate an electron pair to the GaAs surface.

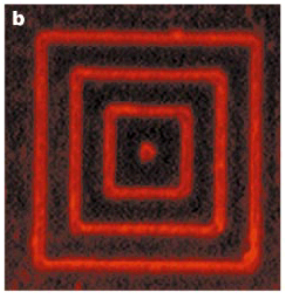
**the 12-mer peptides sequences should be extended, and may be longer than necessary (working on 7-mers)

## Demonstrating Specificity

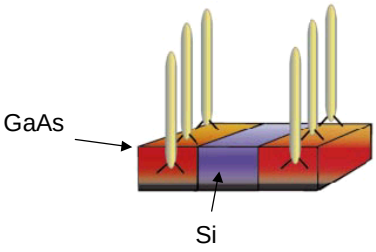


## Demonstrating Specificity

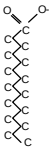



<u>Peptide/Semiconductor interaction</u>
structural?
chemical?
electronic?

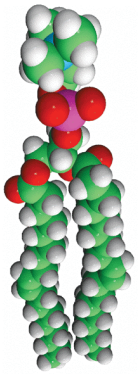



## Lipids

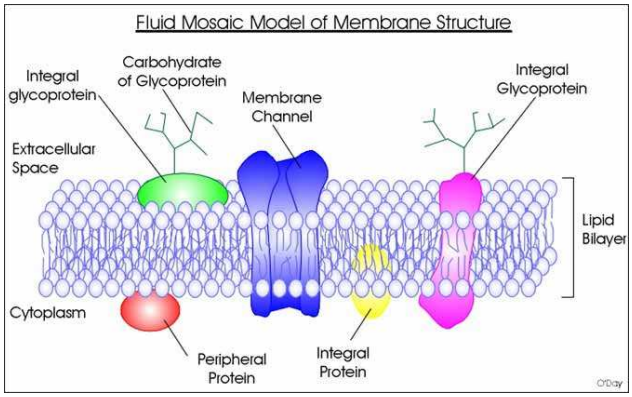
<u>Lipids</u>



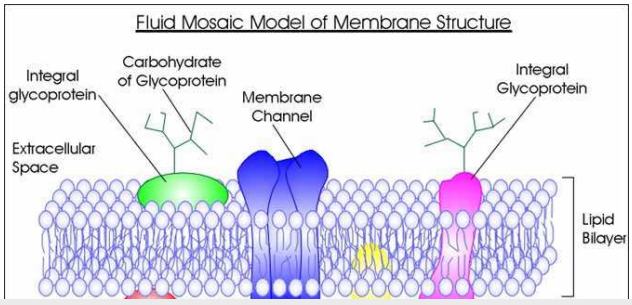
<u>DOPC</u>



# Biomembrane

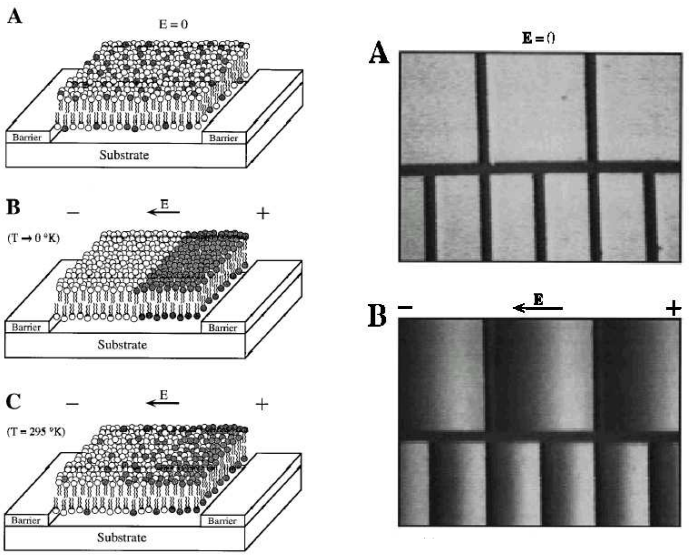



# Supported Membrane



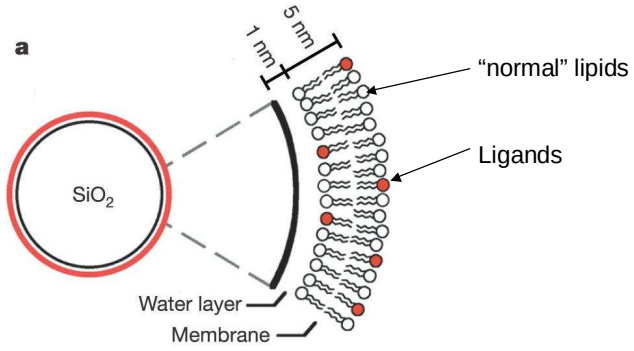

**Substrate**

## Supported Membrane Dynamics

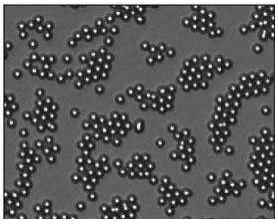



## Detection of Molecular Interactions at Membrane Surfaces through Colloid Phase Transitions

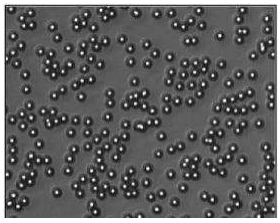
Michael M. Baksh et al ,*Nature* 427, 139 - 141



Condensed phases
(neutral or negative membrane)

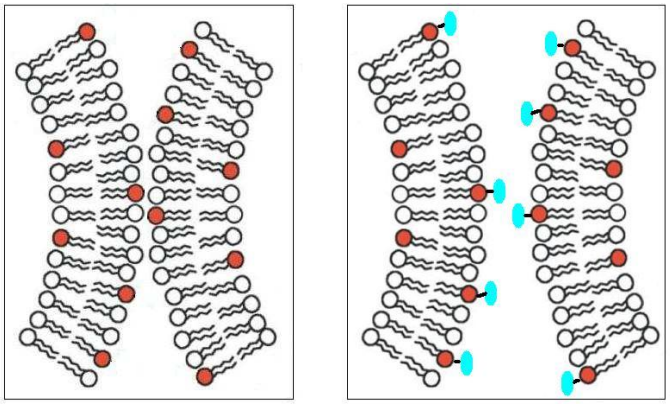


Dispersed phases
(positive membrane)



Colloids are near a phase transition, determined by the colloid pair interaction.

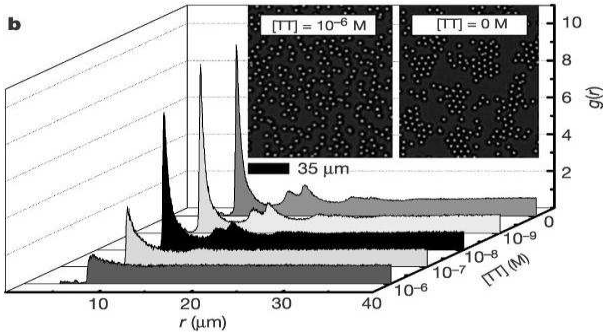
Add receptor protein



Presence of the receptor protein alters the spacing, thus altering the van der Waals contribution to the pair interacion.

Ligand: Trisialoganglioside ($G_{T1B}$)

Receptor: Tetanus toxin (TT)

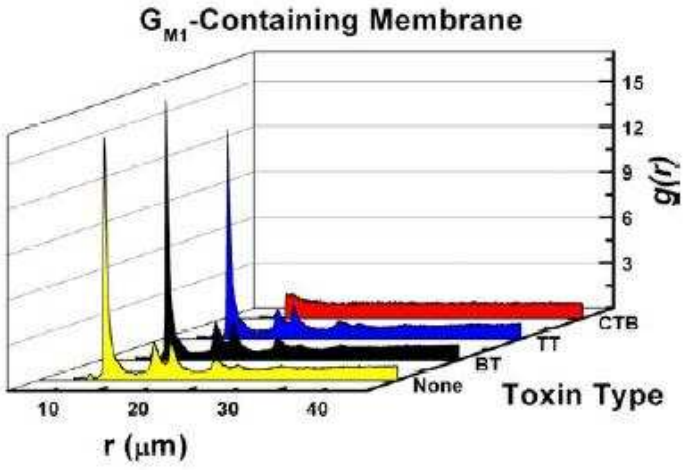



Quantify with the pair distribution function:

$$g(r) = e^{-w(r)/K_B T}$$

Phase transition provides signal amplification to observe molecular event.

Control




Gm1 only alters the pair potential with the Cholera Toxin B