BioChips

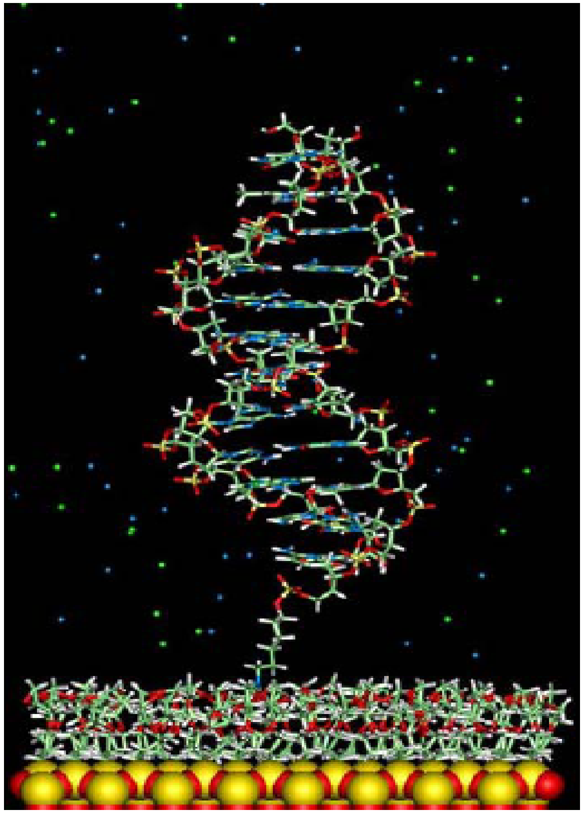
Theory
and
Simulations

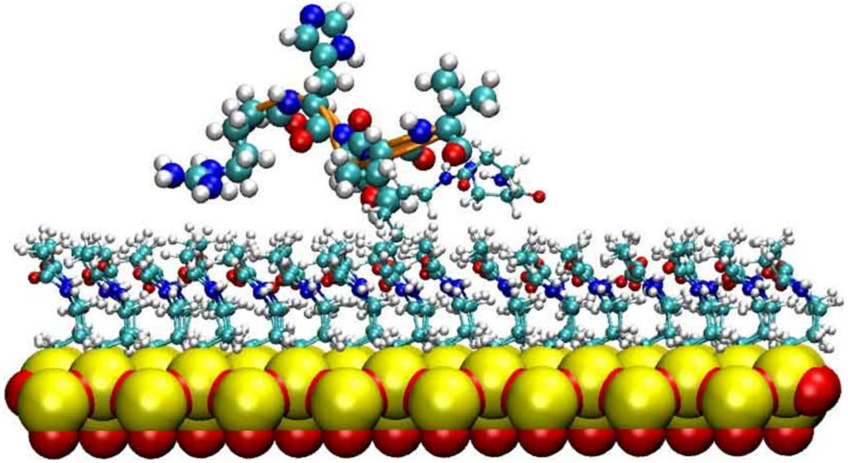
Combination of hard and soft condensed matter

- Hard surface for localization and/or electronics
- Soft biomolecule for tunable molecular recognition

Two examples

DNA Chips and Peptide Chips





DNA Chips

are useful for a variety of tasks

- Disease detection
- Genetic analysis
- Computing

What are the design specific criteria for each usage?
Sequence? Detection limits?

DNA Chips are an Industry

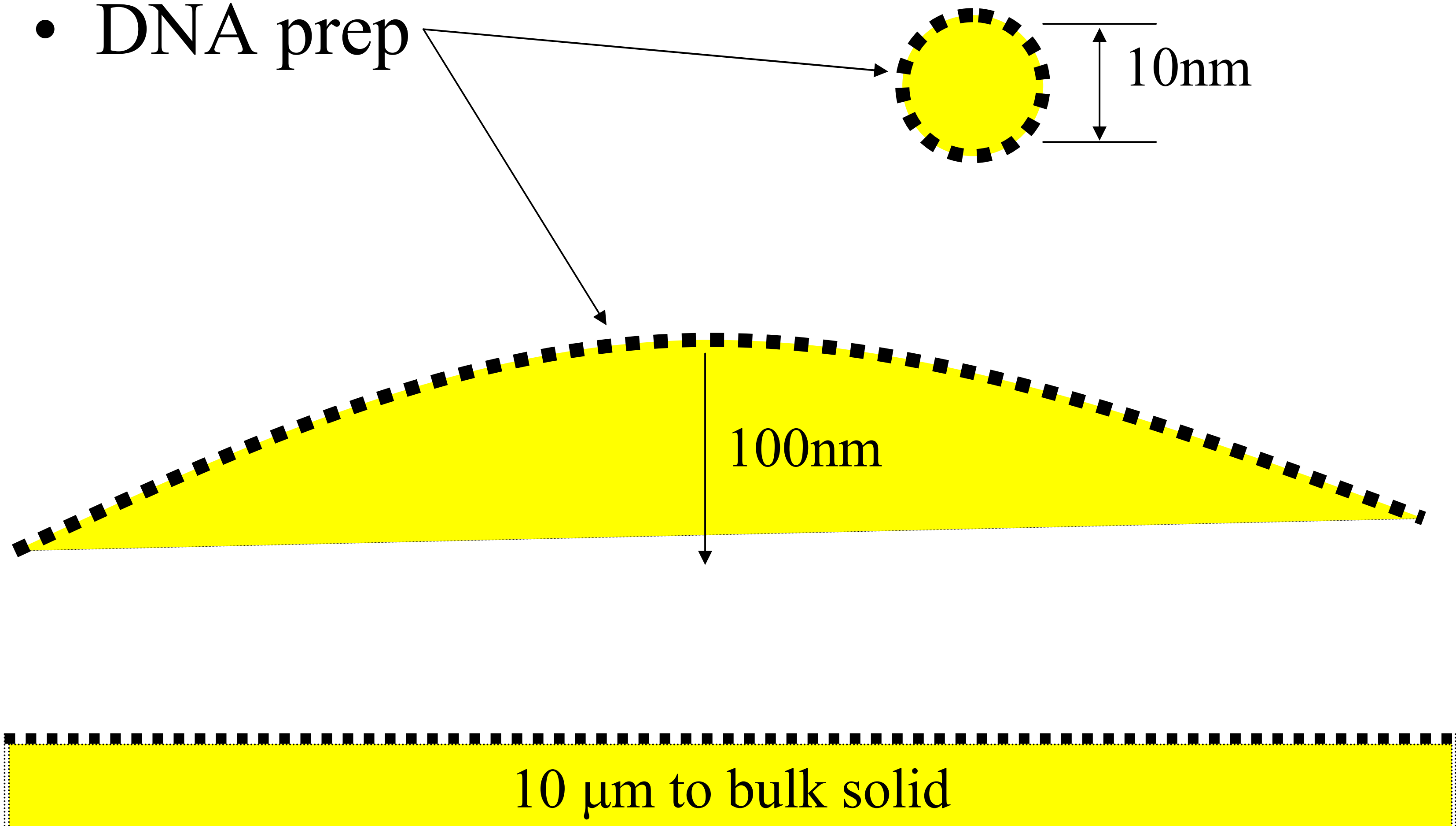
- Currently *O*($1+G/yr)
- Potential to be *O*($100G/yr)

QA/QC problems are

Surface Science problems

Materials and Size Matter

- DNA prep



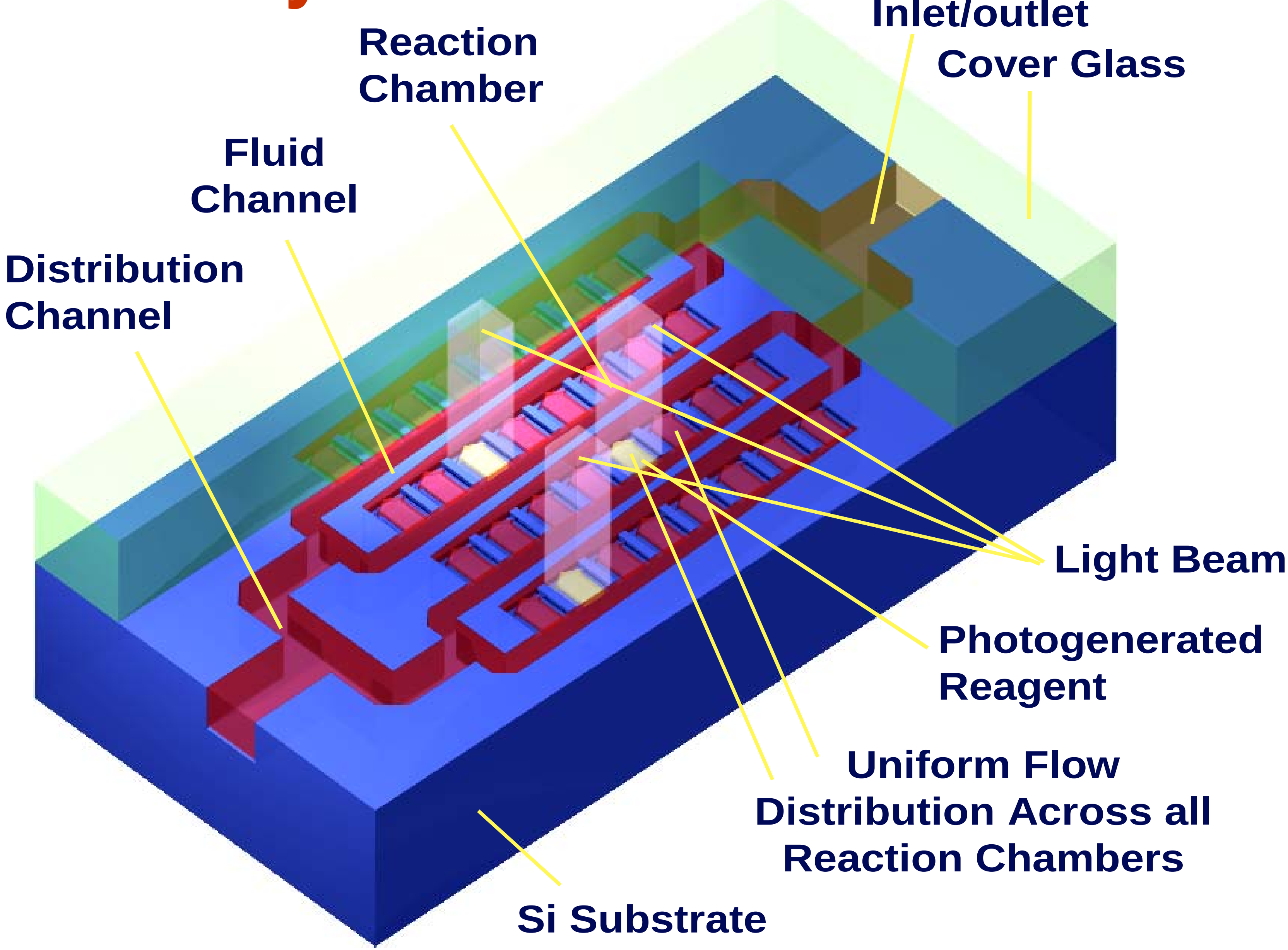
The Experiment

- ***Pick the sequences***
  - ***genetic disease***
  - ***cancer***
  - ***retroviral genes***
  - ***random to detect species***
- ***Smart synthesis with lithography***
- ***Control of purity during each step***
- ***Results & Analysis are not “yes or no”***

- *10,000 to 100,000 experiments or "reads"*

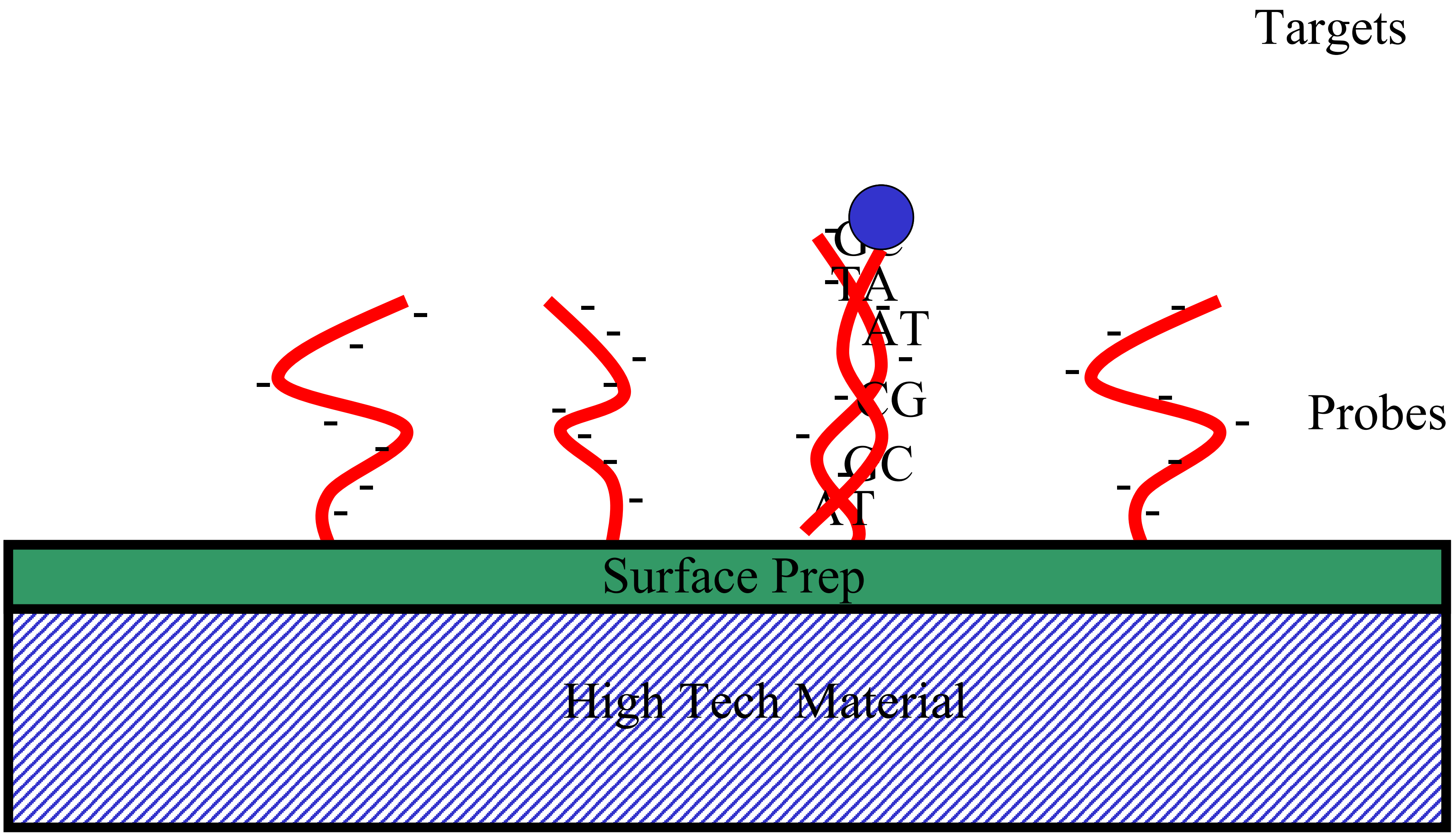
How to detect the signal?

- *Use CCD's*
  - *Color sensitive*
  - *Intensity $\propto$ Concentration*

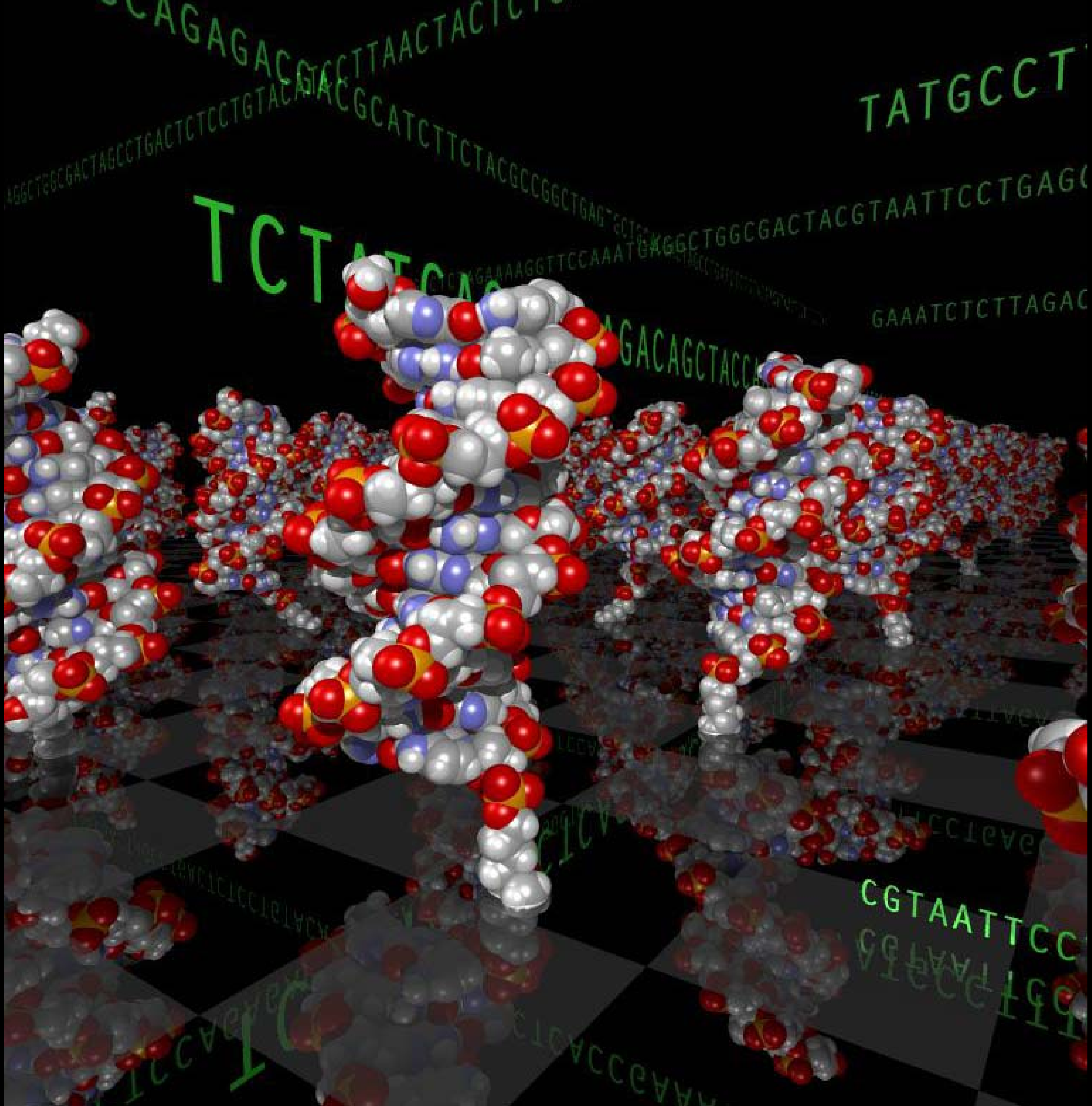

Inlet/outlet
Cover Glass
Reaction Chamber
Fluid Channel
Distribution Channel
Light Beam
Photogenerated Reagent
Uniform Flow Distribution Across all Reaction Chambers
Si Substrate

XL Gao

Salt Water



Targets
GC
TA
AT
CG
GC
AT
Probes
Surface Prep
High Tech Material



TATGCCT
GGCTGGCGACTACGTAATTCCTGAG
GAAATCTCTTAGAC
CGTAATTCC

Parallel Analysis

The *equilibrium* during Hybridization Analysis results in *binary* mistakes in detection.

Qualitative vs. Quantitative analysis

- Presence or Absence complicated by multiple misleading equilibria
- Poor sensitivity (broad melting curves)

Problems in Microarrays Effect Apparent Binding

- Optimal surface preparation; shifts melting T
  - Dielectric, Metal, Hydrophobic moments …
- Signal Strengths
  - 8+ orders of magnitude of intensity
- Spot size/shape distribution
  - Large deviations
  - Missing spots
- Purity of Probes on Surface
  - Chemistry
- Sample preparation
  - Biological prep, synchronization, pcr

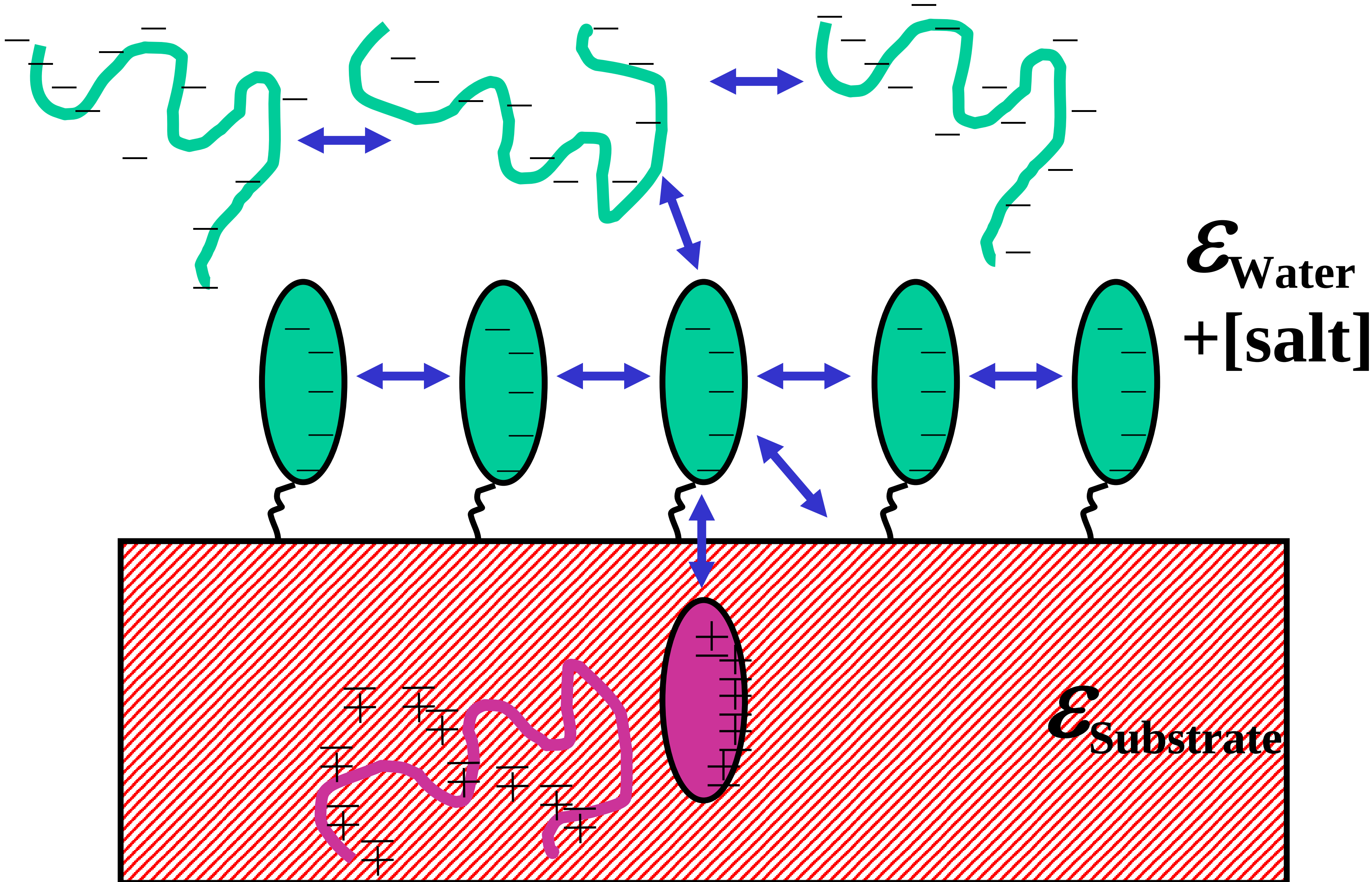
Basic Problem

DNA binding is different in the presence of a surface than in homogeneous solution.

What are the causes?

How do we use the changes?

Forces: Surface and Solution



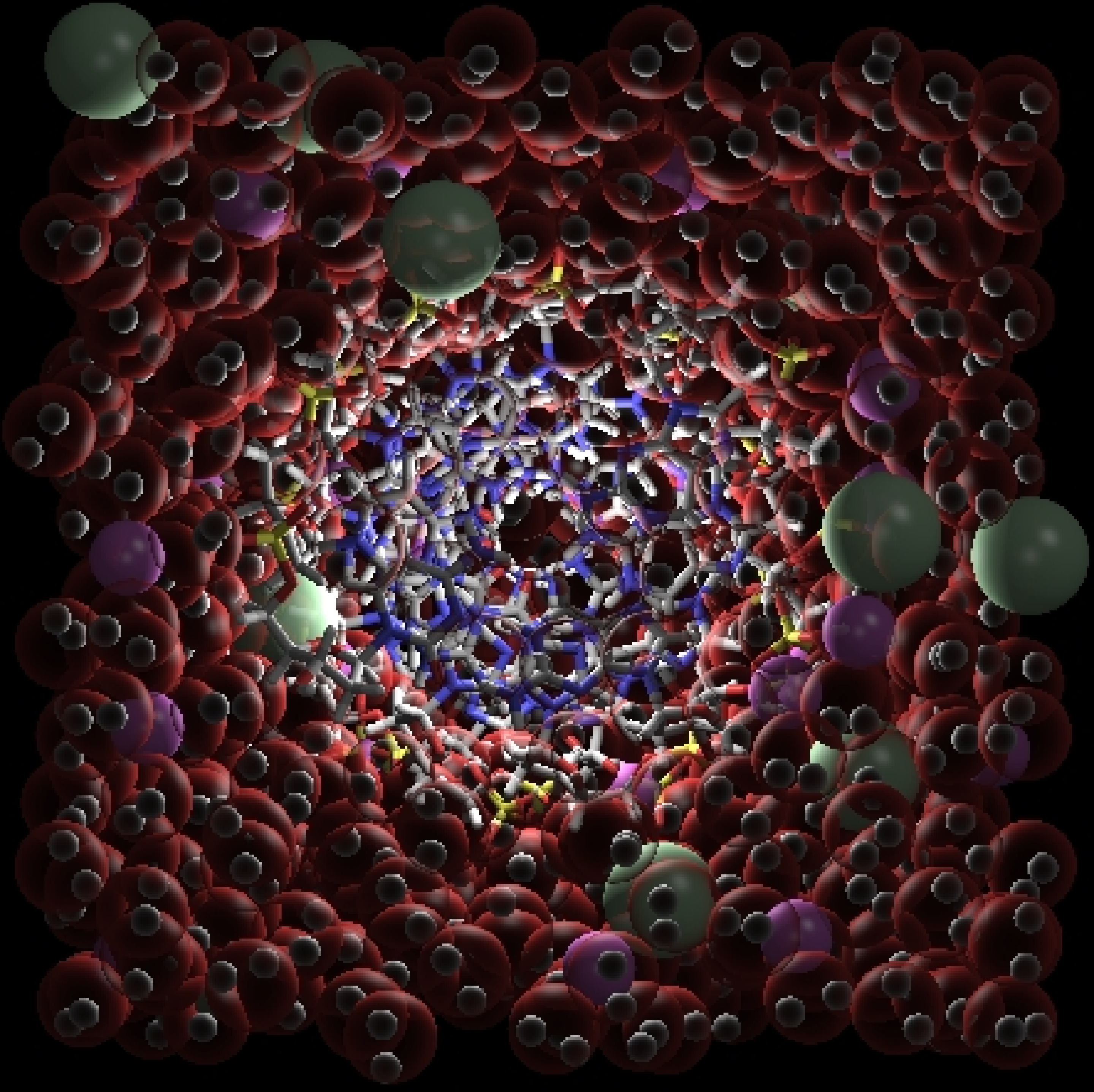
Two Design Areas

- Target and Surface Probe interact with Liquid-Solid Interface *(repulsive or attractive)*

Decreases with distance from Surface (linker length)

- Multiple targets are Repelled by Probe array

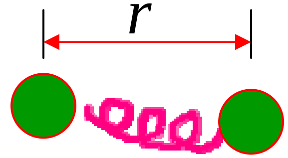
Increases with Probe surface concentration



Computer Simulations start with a force law: Classical in this case

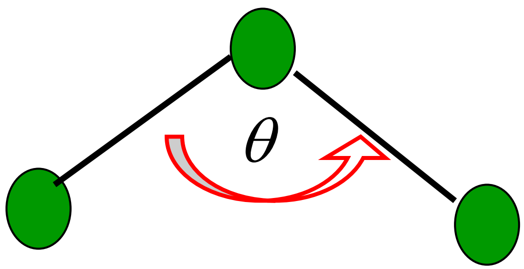
Bonds - 2 body term

- harmonic, Hook's Law spring



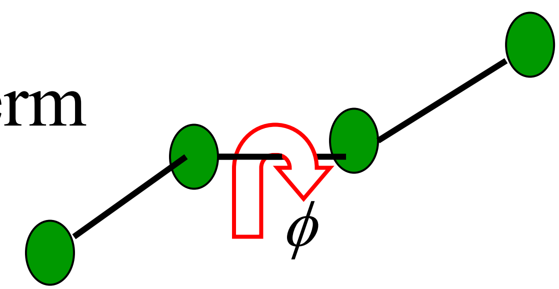
$$\sum_{bonds} K_b (r - r_e)^2$$

Angles - 3 body term



$$\sum_{angles} K_\theta (\theta - \theta_e)^2$$

Dihedrals - 4 body term



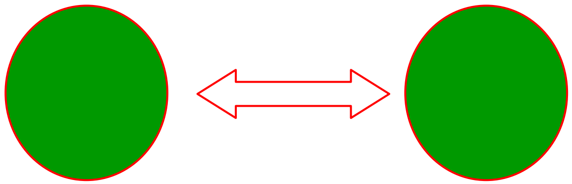
$$\sum_{torsions} K_\phi \left(1 + \cos(n\phi + \delta)\right)$$

n = *multiplicity*

δ =phase

Parameters come from experiments & quantum mechanical studies of small molecules that are chemically similar to segments of the molecule of interest.

Nonbonded Terms



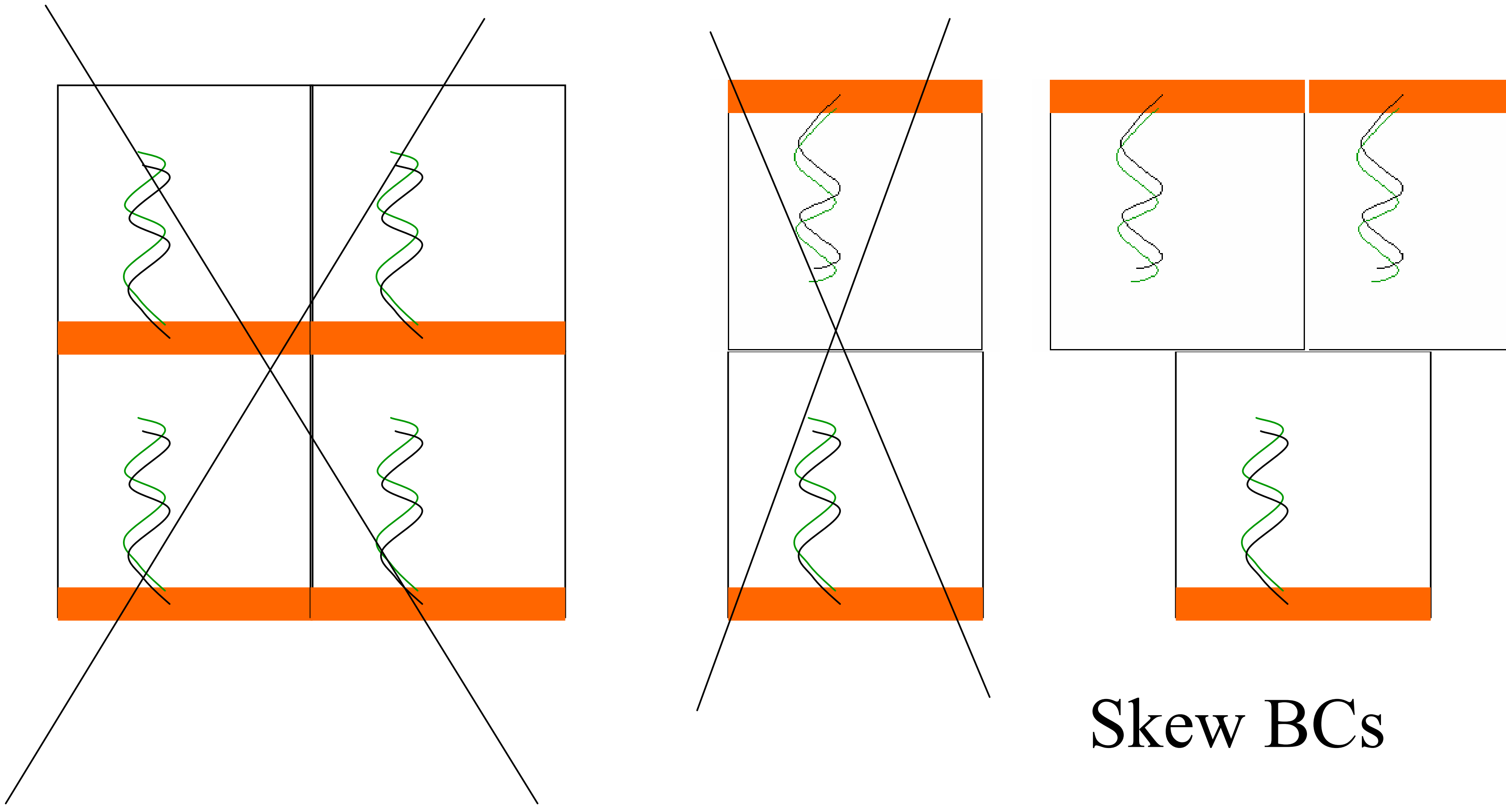
2 body terms

Coulombic & van der Waals

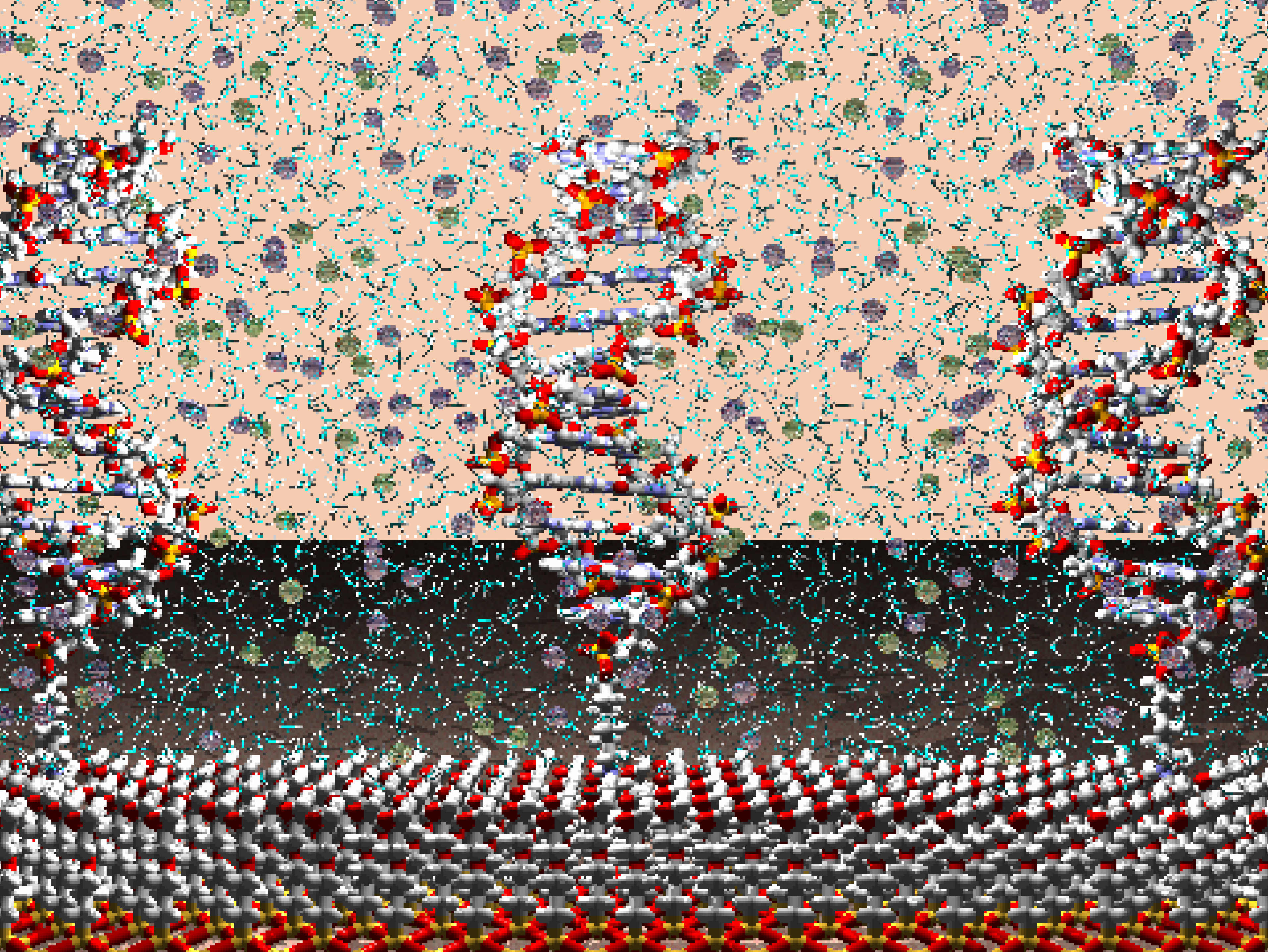
$$\sum_{\substack{Nonbonded \\ pairs\,of\ atoms}} 4\varepsilon_{ij}\left(\left(\frac{\sigma_{ij}}{r}\right)^{12}-\left(\frac{\sigma_{ij}}{r}\right)^{6}\right)+\frac{q_i q_j}{r}$$

Three body and higher nonbonded terms can be incorporated at great expense!

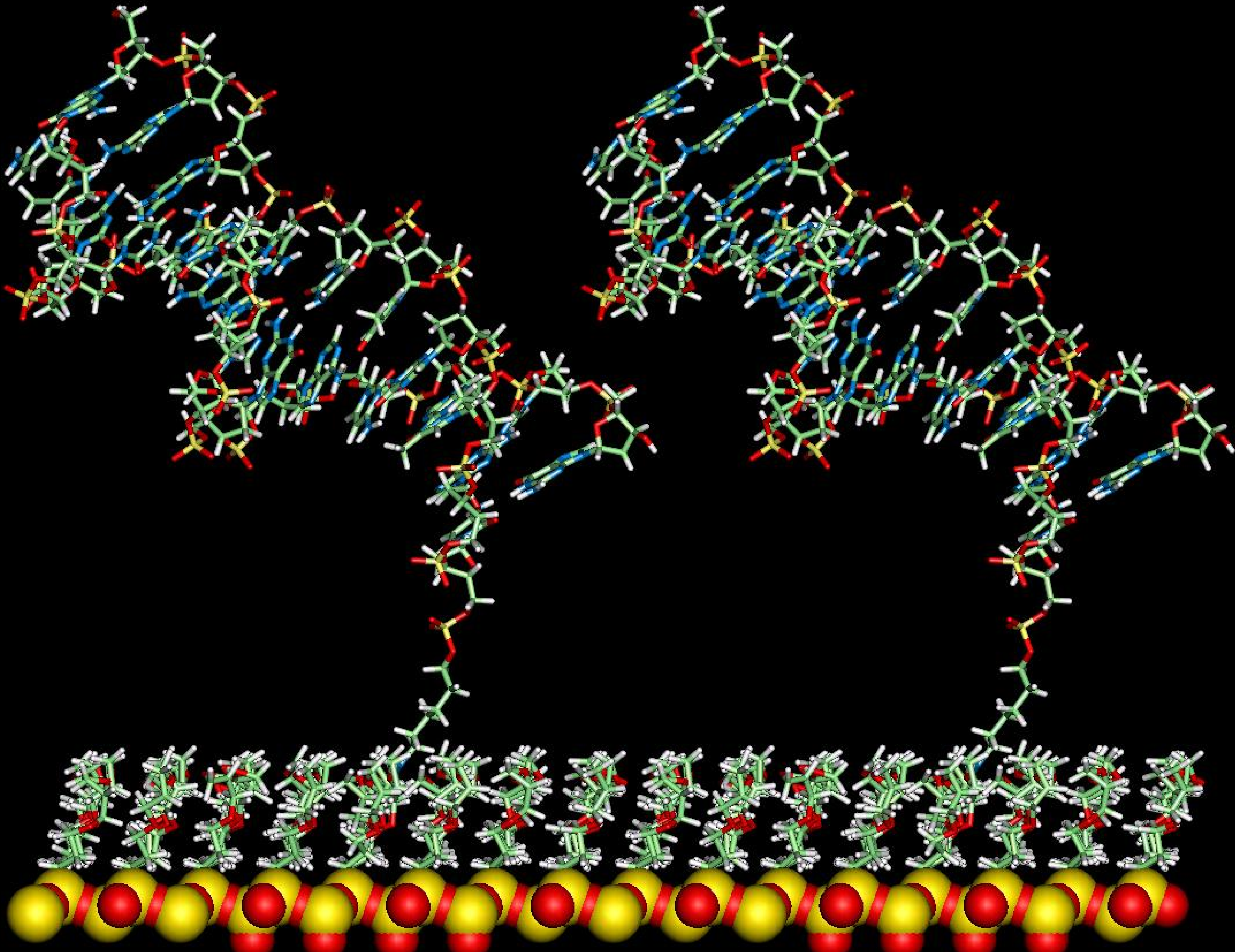
Periodic Boundaries for Surfaces Lamellar mess; Change symmetry



Skew BCs



0 ns



Correlations

- Neither Vertical nor Flat on surface (tilt)
- Low fraying (tight binding)
- Nonuniform Structures
- Linker/spacer effects

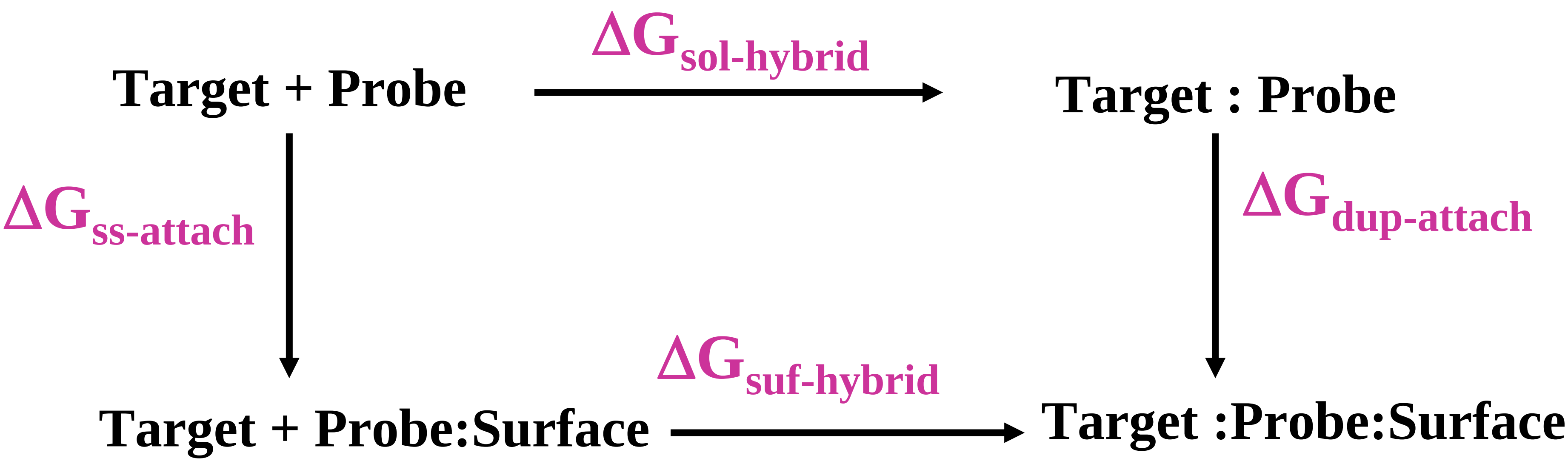
Implications

- Colloidal behavior affects
  - synthesis / fabrication
  - and binding
- Tilt restricts possible geometries of pairing
- Low fraying consistent with high affinity and good specificity at low target concentration

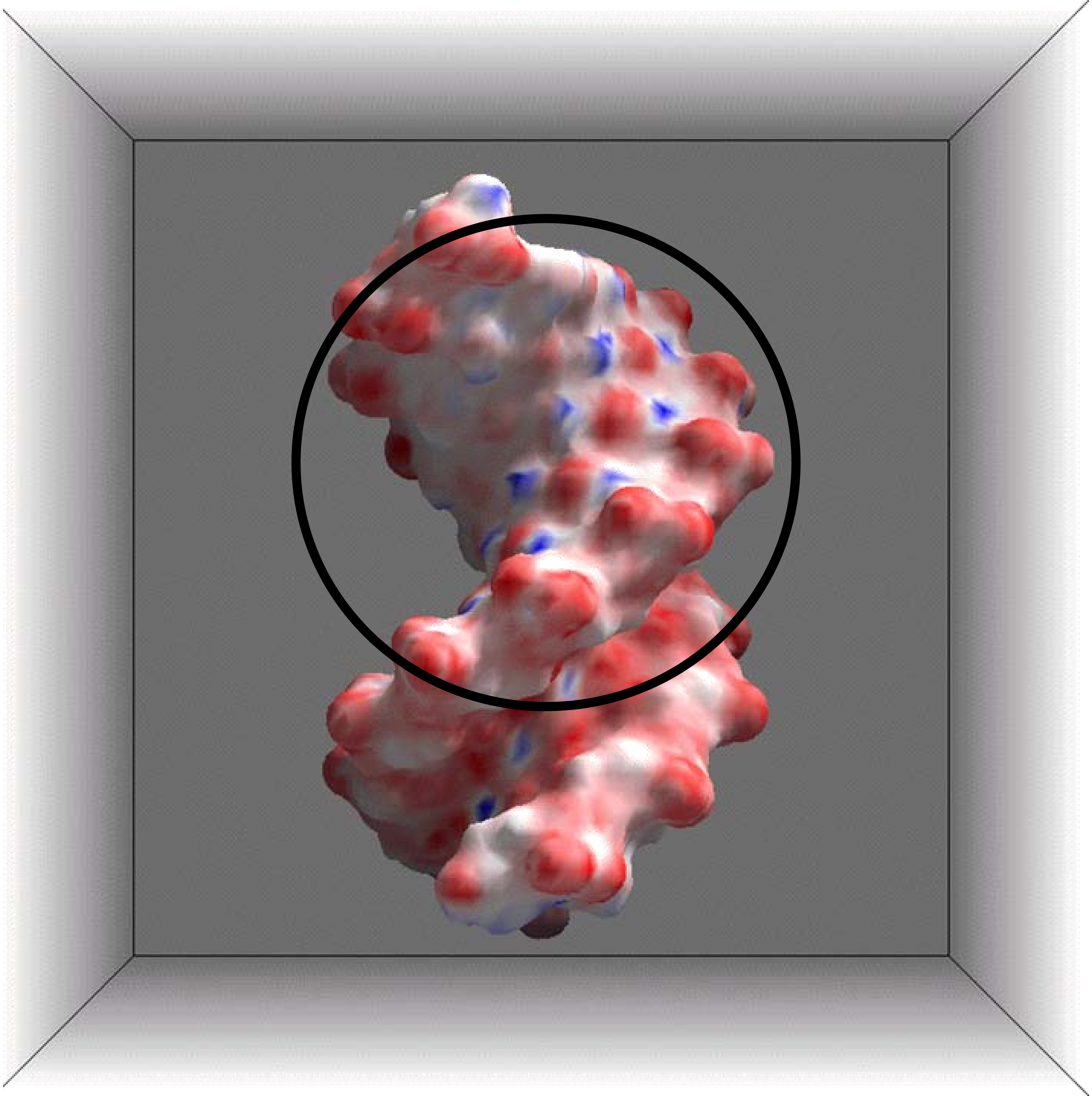
ΔG & $\Delta\Delta G$

Theory

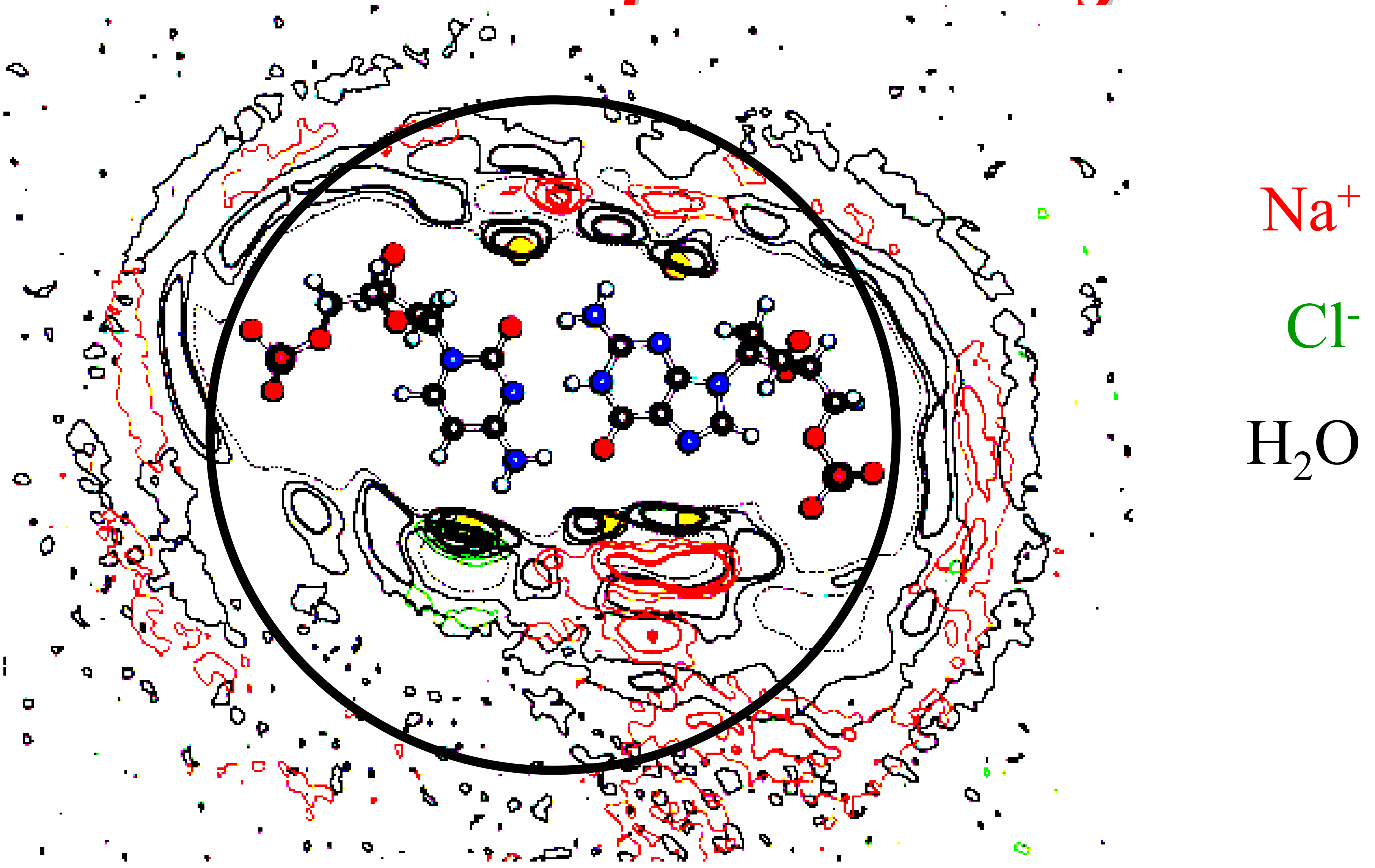
Object: to Analyze the free energy difference of hybridization between that in solution and on a surface



$$\Delta G_{sol\text{-}hybrid} - \Delta G_{suf\text{-}hybrid} = \Delta G_{dup\text{-}att} - \Delta G_{ss\text{-}att}$$



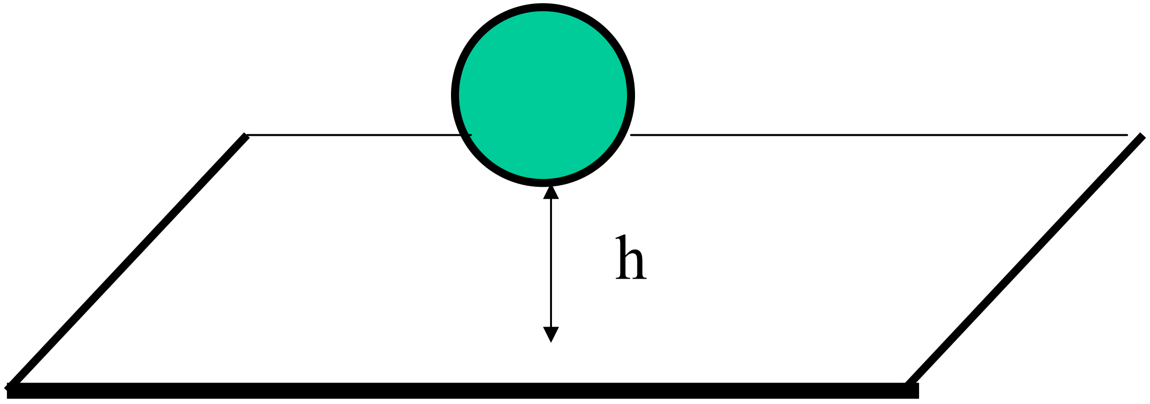
The ions and water penetrate the grooves.



Need a Simple Model

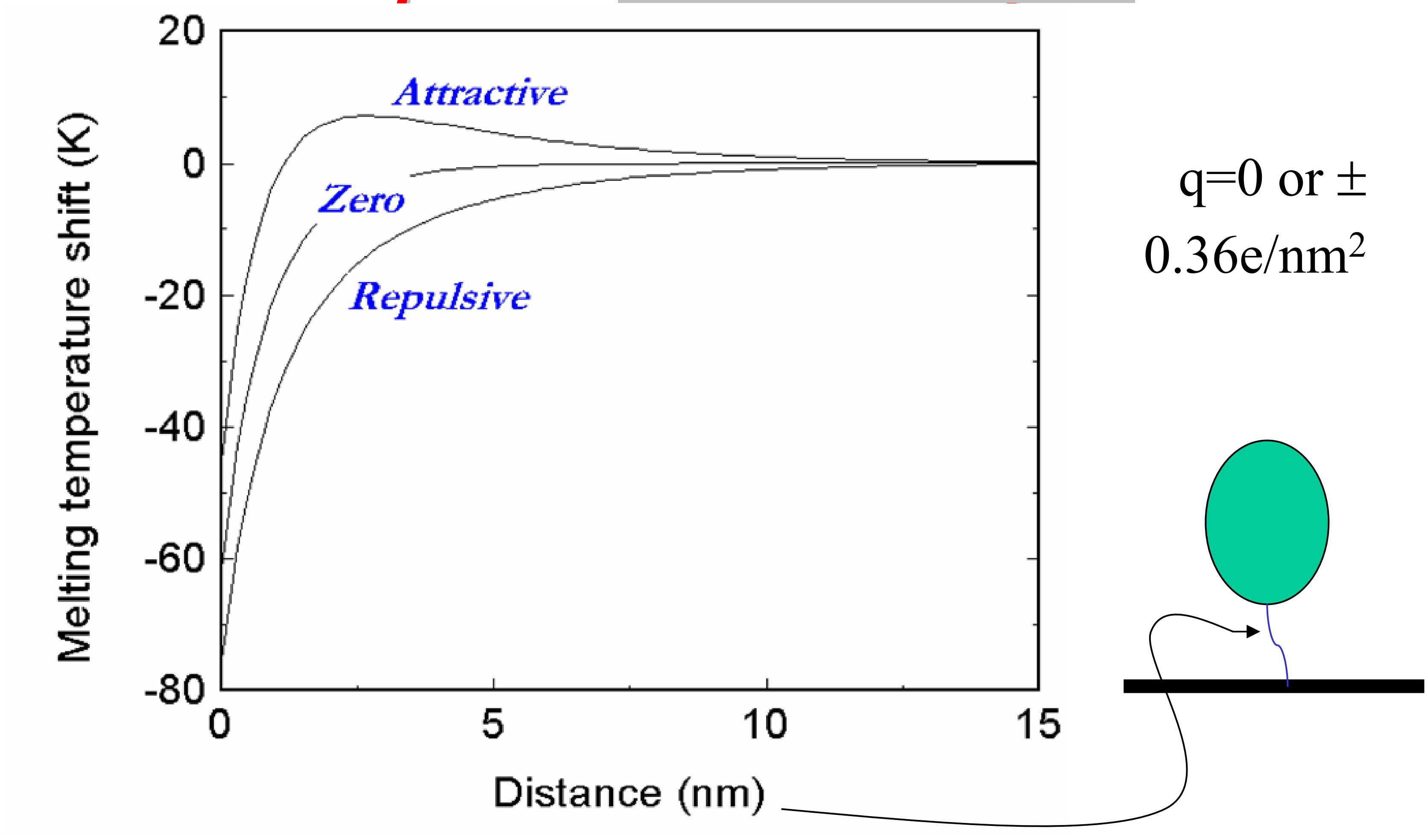
- Ion permeable 20 Å spheroid over a plane/surface
  - 8 bp in aqueous saline solution over a surface
- Linear Poisson-Boltzmann has an

analytic solution

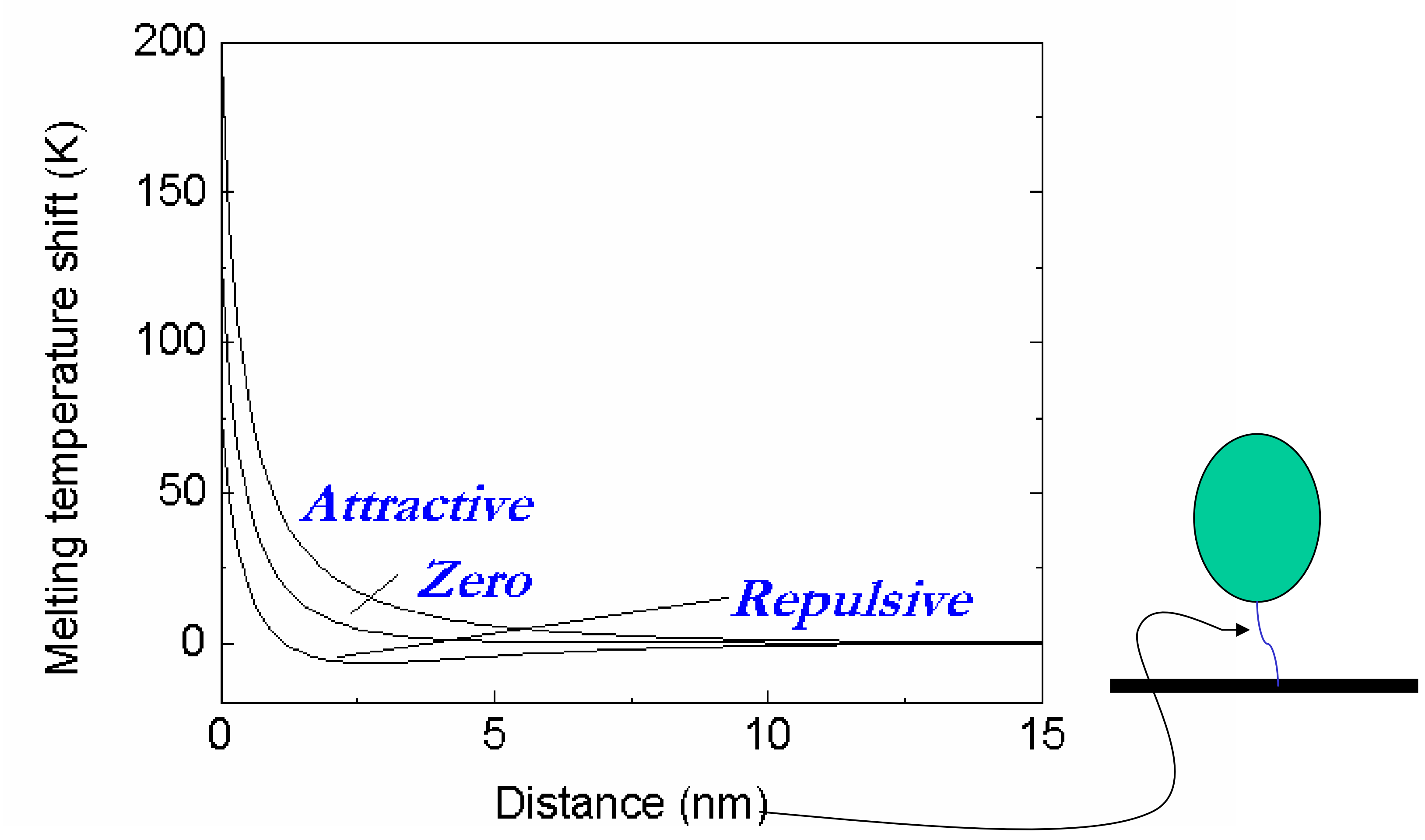


I.D. - Ohshima and Kondo, '93 Finite C - Vainrub and Pettitt, '02
Elipsoidal Geometry- Garrido and Pettitt, '08

The shift of the melting temperature for an immobilized 8 base pair oligonucleotide duplex at 0.01M NaCl as a function of the distance from a dielectric surface



Surface at a constant potential for a __metal__ coated substrate @ .01 M NaCl

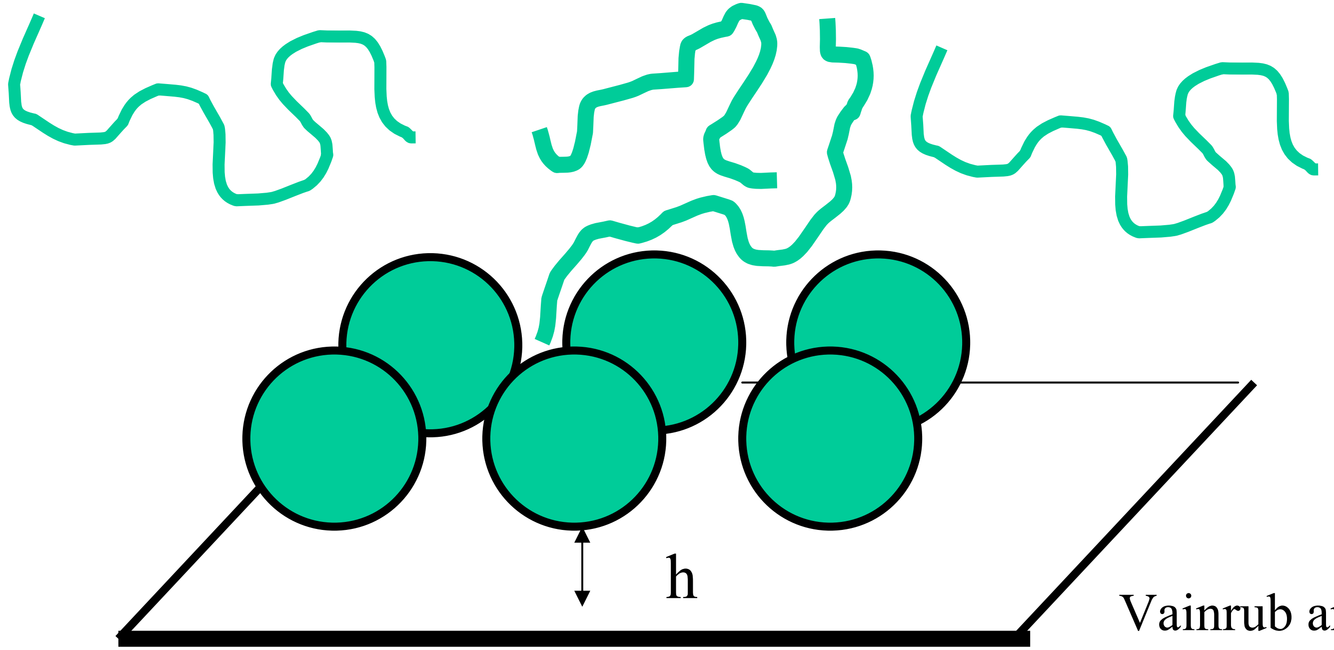


Effects of Crowding with High Coverage

- Target Concentration
- Surface Coverage
- Tether Length
- Solvent Dielectric
- Salt Concentration

Yet Another Simple Model

- Ion permeable 20 Å spheres over a plane/surface
  - in aqueous saline solution at finite density
- Linear Poisson-Boltzmann still has an analytic solution



Vainrub and Pettitt, ‘02

Melting curve temperature and width vs. surface probe density (coverage) is simple

In solution

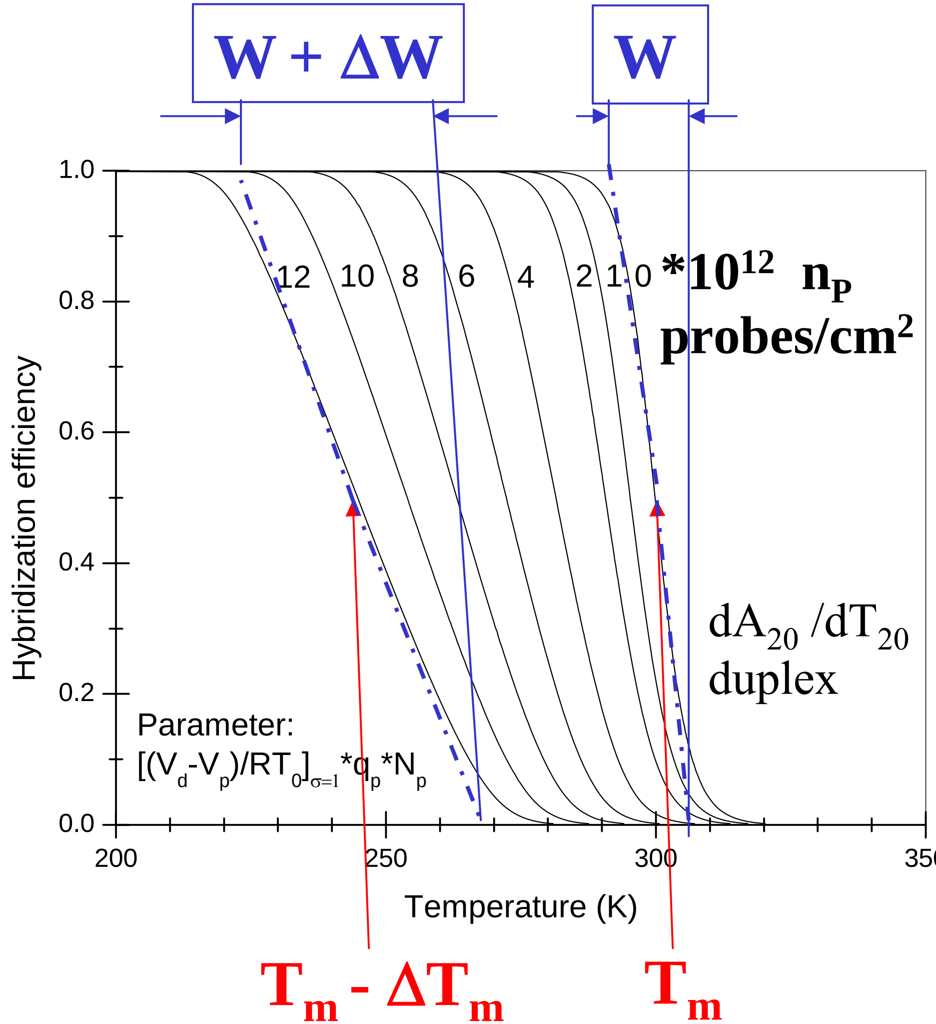
$$T_m = \Delta H_0 / (\Delta S_0 - R \ln C)$$

$$W = 4RT_m^2/\Delta H_0$$

On-array: Isotherms

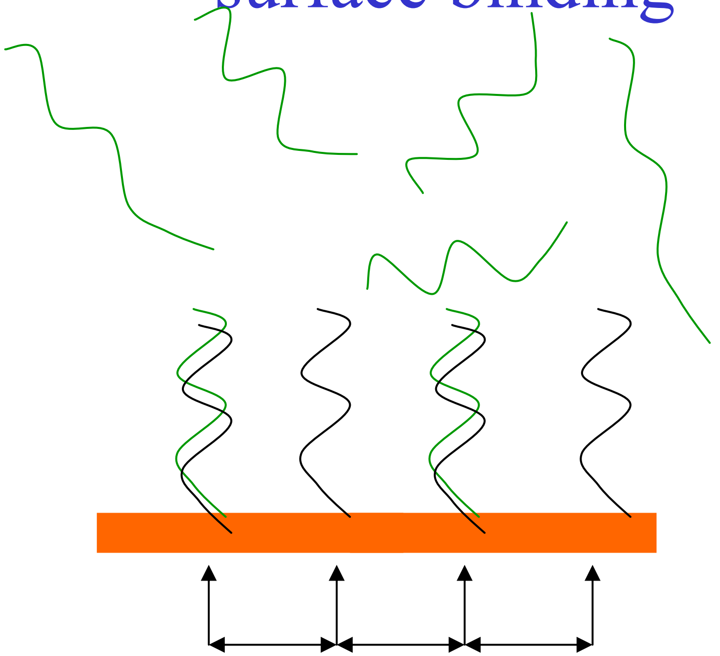
$$\Delta T_m = \frac{3wZ^2 n_p}{2\Delta H_0 + 3wZ^2 n_p}$$

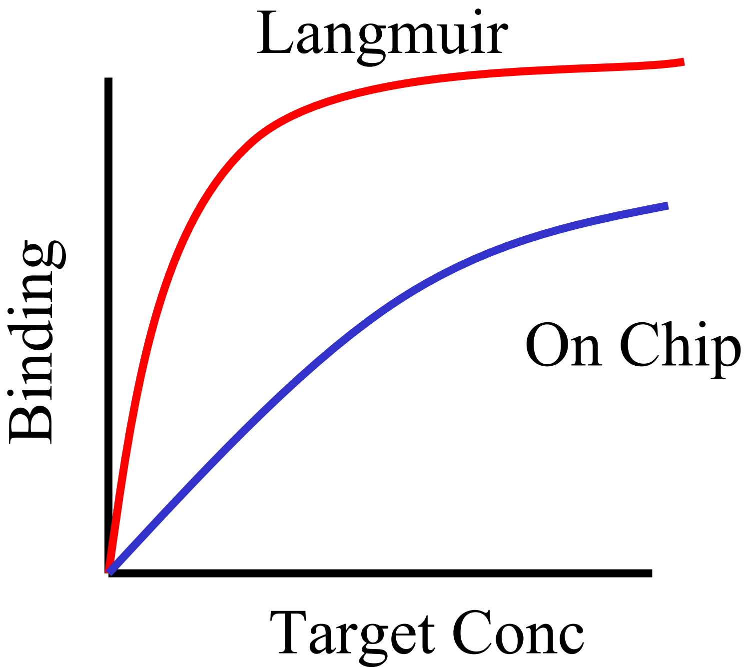
$$\Delta W = \frac{2}{3}\Delta T_m$$



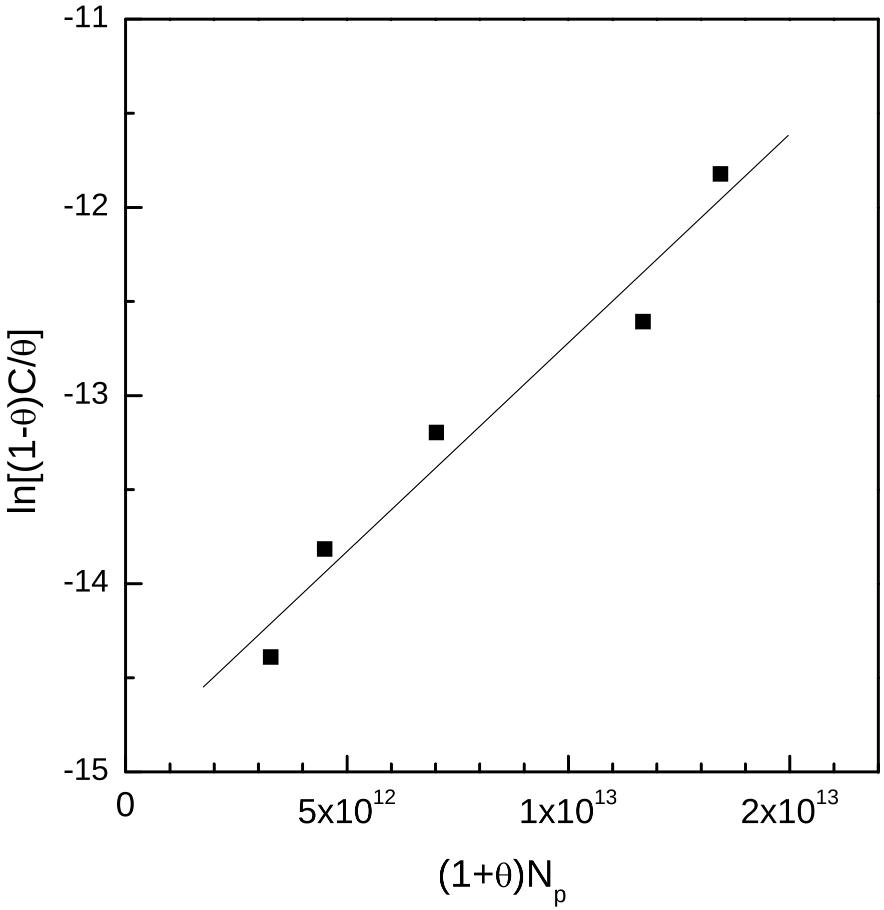
Coulomb Blockage Dominates Optimum spacing

High negative charge density repels target surface binding





Comparison with Experimental Isotherm

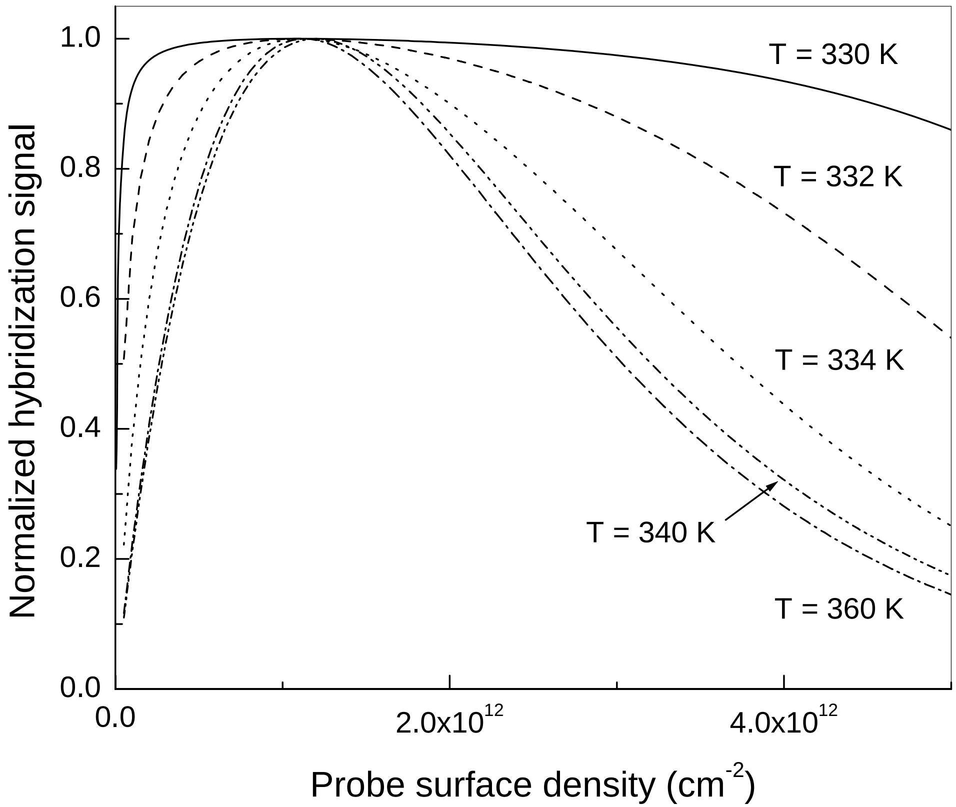


Accord with experiments:

- Low on-array hybridization efficiency (Guo et al 1994, Shchepinov et al 1995)
- Broadening and down-temperature shift of melting curve (Forman et al 1998,
- Lu et al 2002)
- Surface probe density effects (Peterson et al 2001, Steel et al 1998, Watterson 2000)

Mean field predicts the Peak of sensitivity

$$n_p = \frac{RT}{wZ_P^2}$$



Vainrub and Pettitt, JACS (2003)

cDNA arrays have more problems.

What is the structure of DNA on a positively charged Surface?

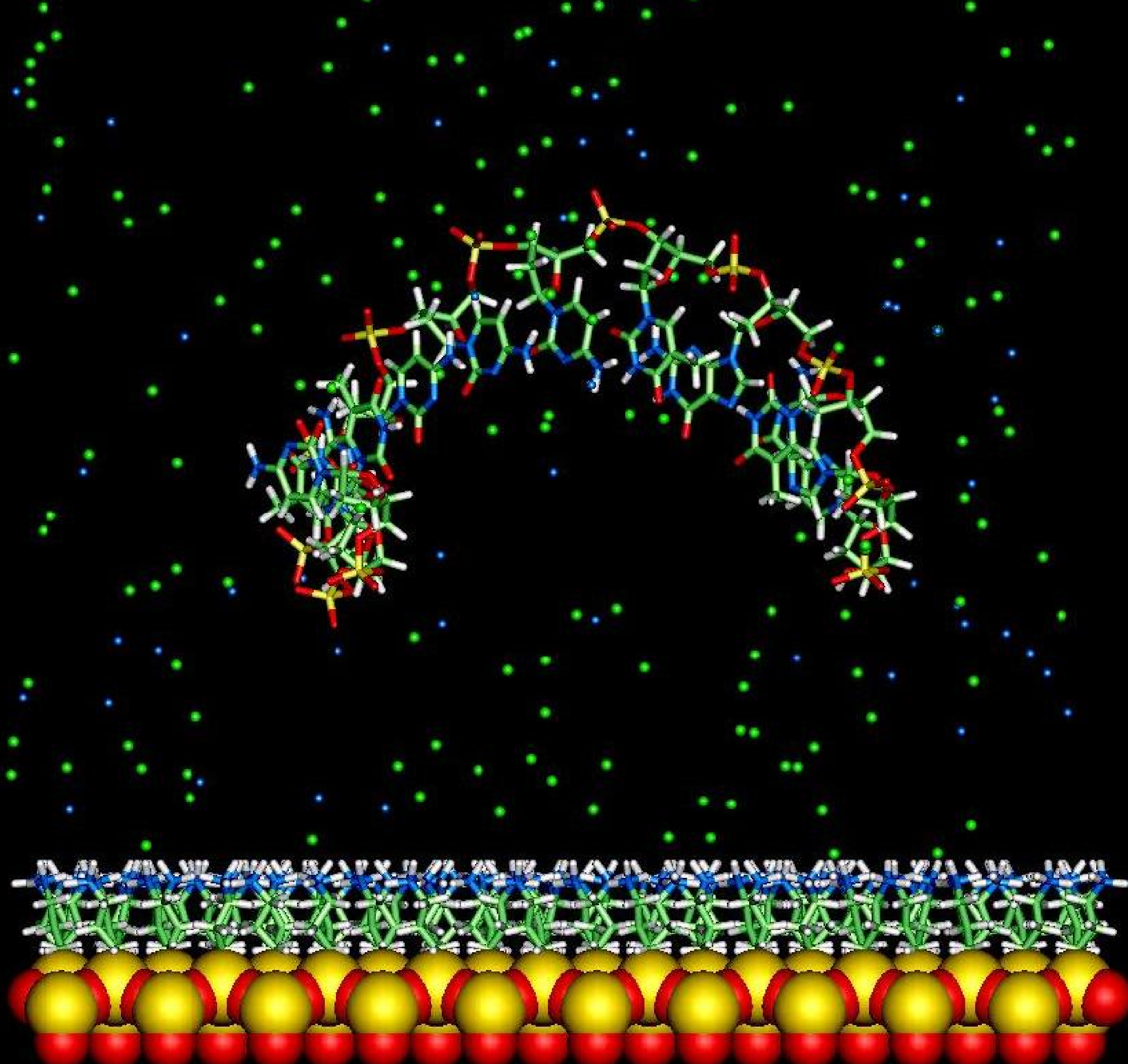
(Poly-lysine or polyamines)

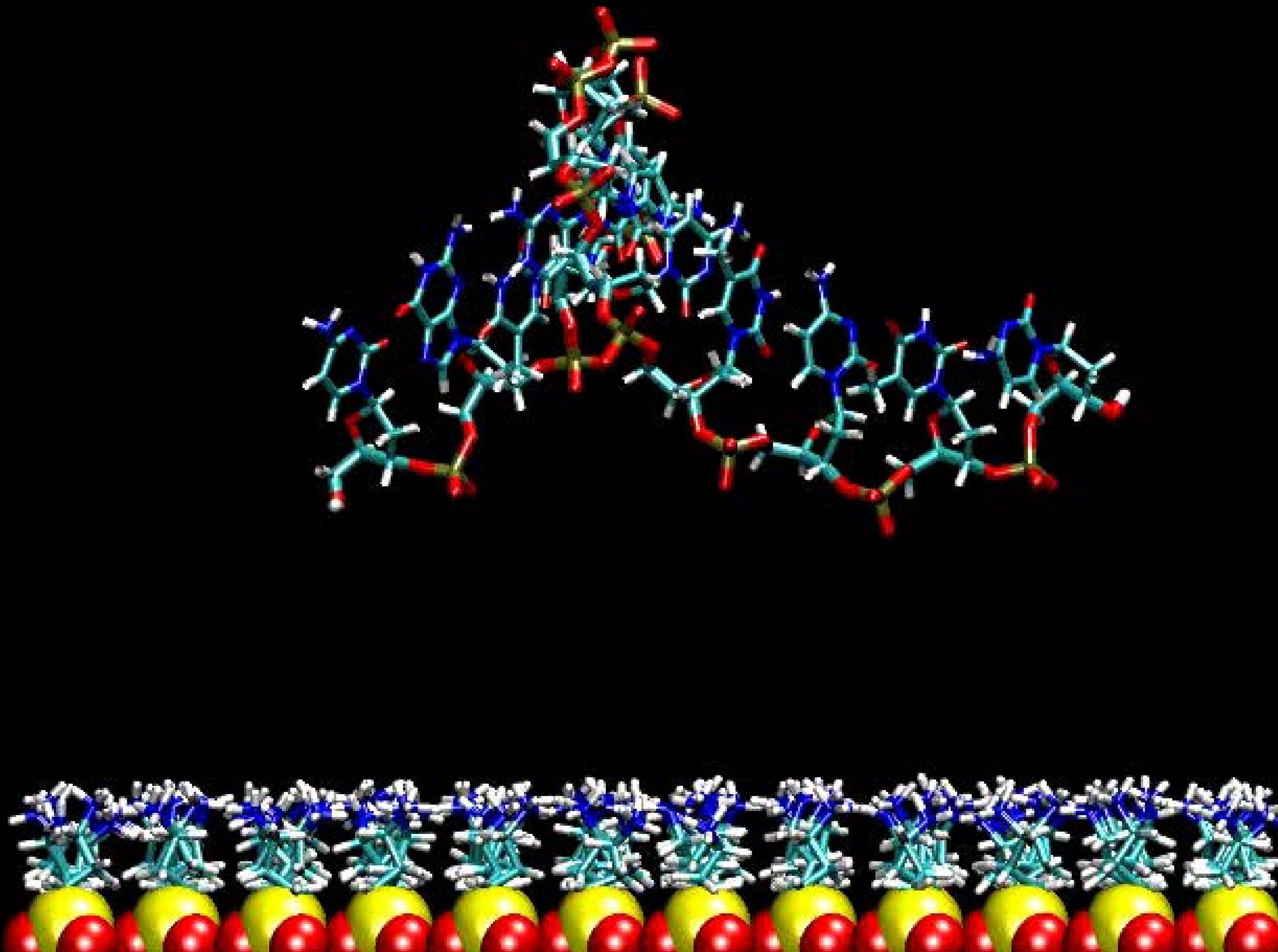
Surface experiments for structure are tough.

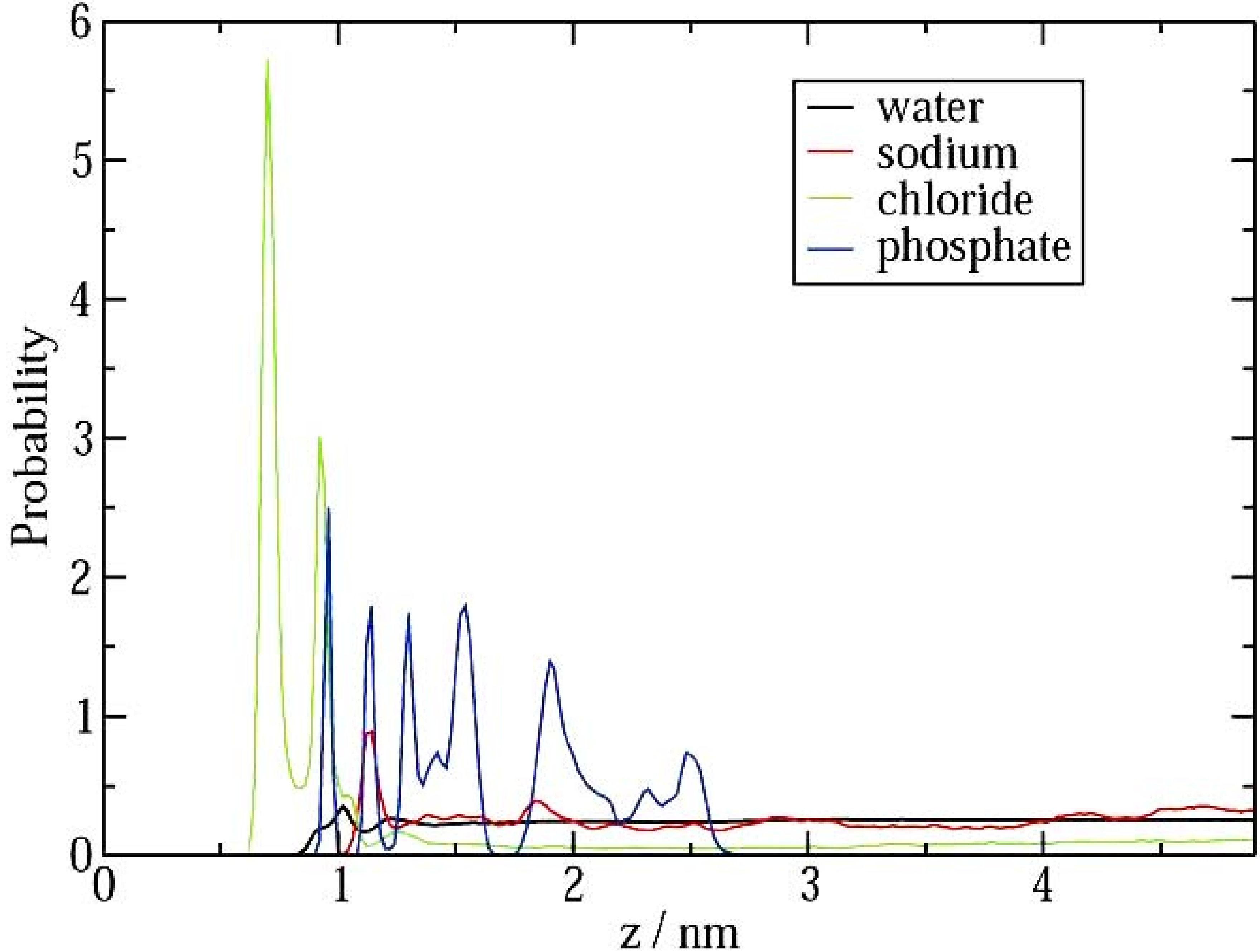
So simulate.

Near a charged surface

- Different local ion conc.
- Reports of enhanced binding
- Reports of enhanced kinetics
- Same geometry?







water
sodium
chloride
phosphate
Probability
z / nm
0
1
2
3
4
5
6
0
1
2
3
4

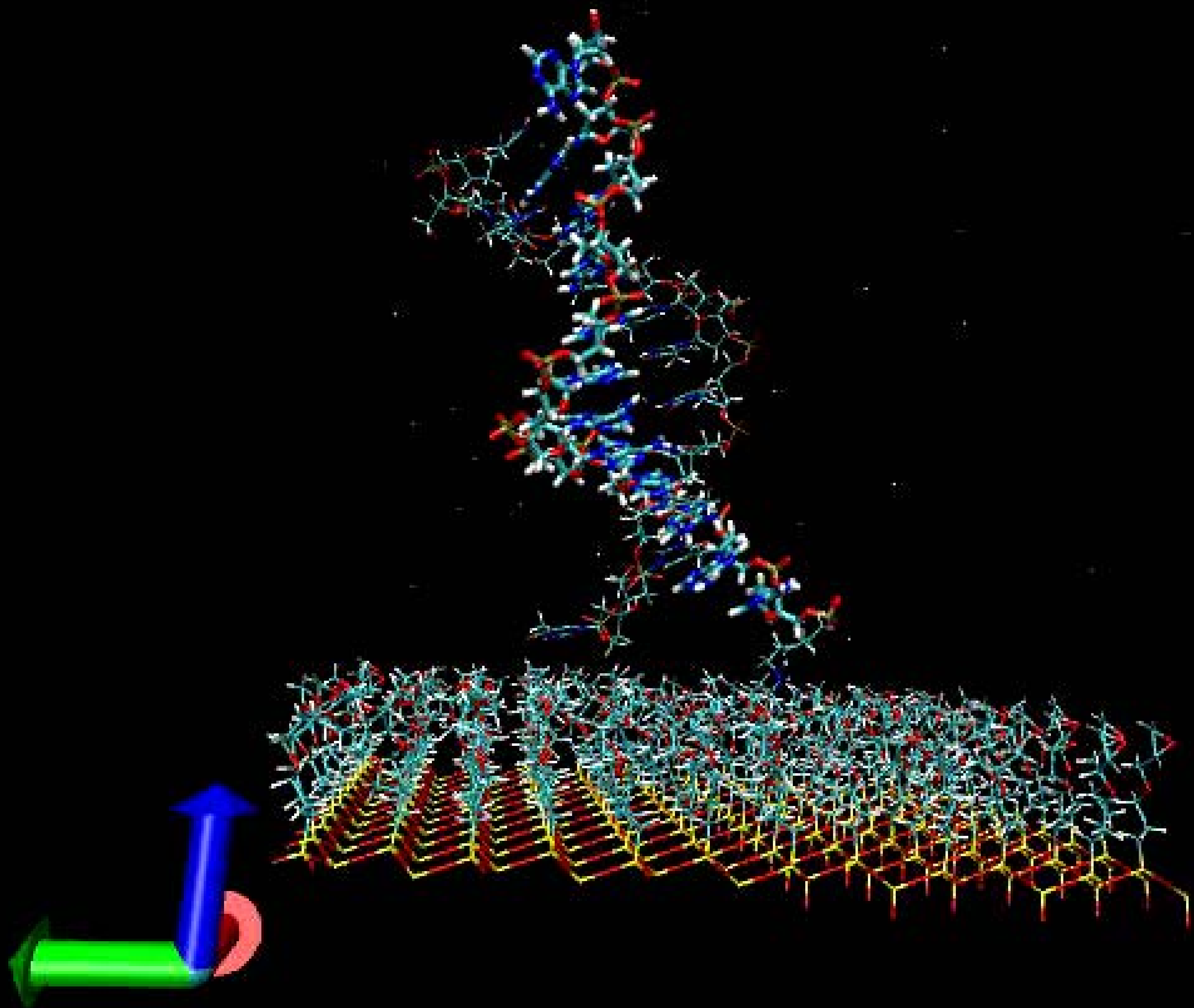
Lessons for Designs

Sequence length determines criteria

- Potential Sequence-Information Content
- Melting Temperature Range
- Melting Temperature Width (SNPs)

Surface design affects detectability

Surface fidelity has large effects



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UNIVERSITY OF HOUSTON

IN TIME

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