Bio-Functionalized Surfaces

Hard / Soft Interfaces

Electronic structure, absorption and reactivity properties are tunable

- Change due to interface correlations
- Ionic multilayers screen fields
- Interactions with Applied Electric Fields
- Multiple Dielectric Interfaces

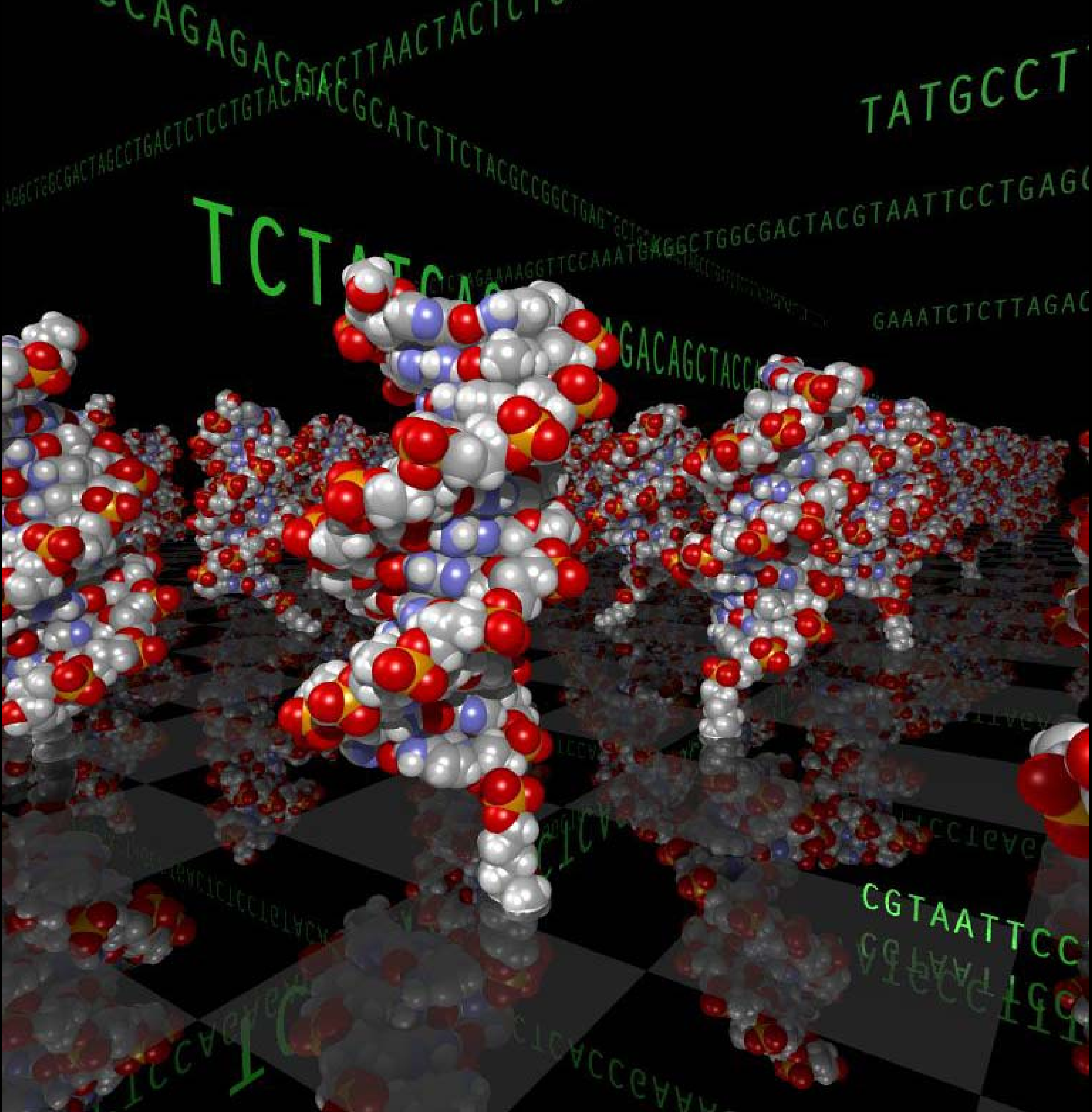
Change the behavior of polymers in the vicinity of the hard, wet surface

Interfaces:
Nano Heterogeneity

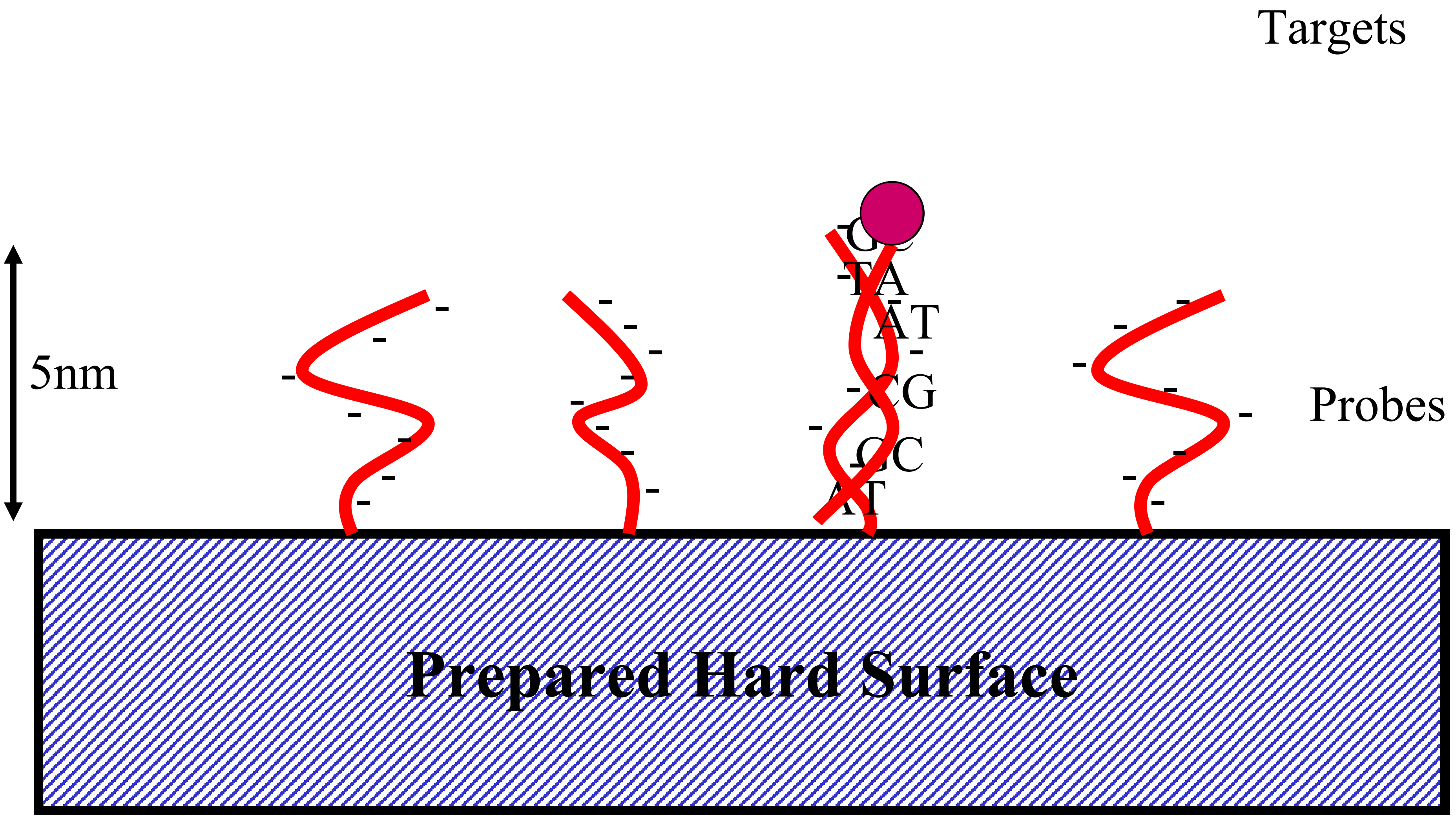
Surfaces, Beads, Shells…

- Changes in Species
- Large Changes in Electric Fields
- Changes in Density

Natural Place for Chemical Work


TATGCCT
GGCTGGCGACTACGTAATTCCTGAG
GAAATCTCTTAGAC
CGTAATTCC

Salt Water



DNA & Protein Microarrays

are useful for a variety of tasks

- Genetic analysis
- Disease detection
- Synthetic Biology
- Computing

Problems in Microarrays

Cross platform comparisons

- Controls
- Validation
- Data bases for comparisons

Nearly impossible due changes in physics and chemistry at the surface

Central Theoretical Issue:

Binding (recognition) is different in the presence of a surface than in homogeneous solution.

The surface determines:

Polarization fields

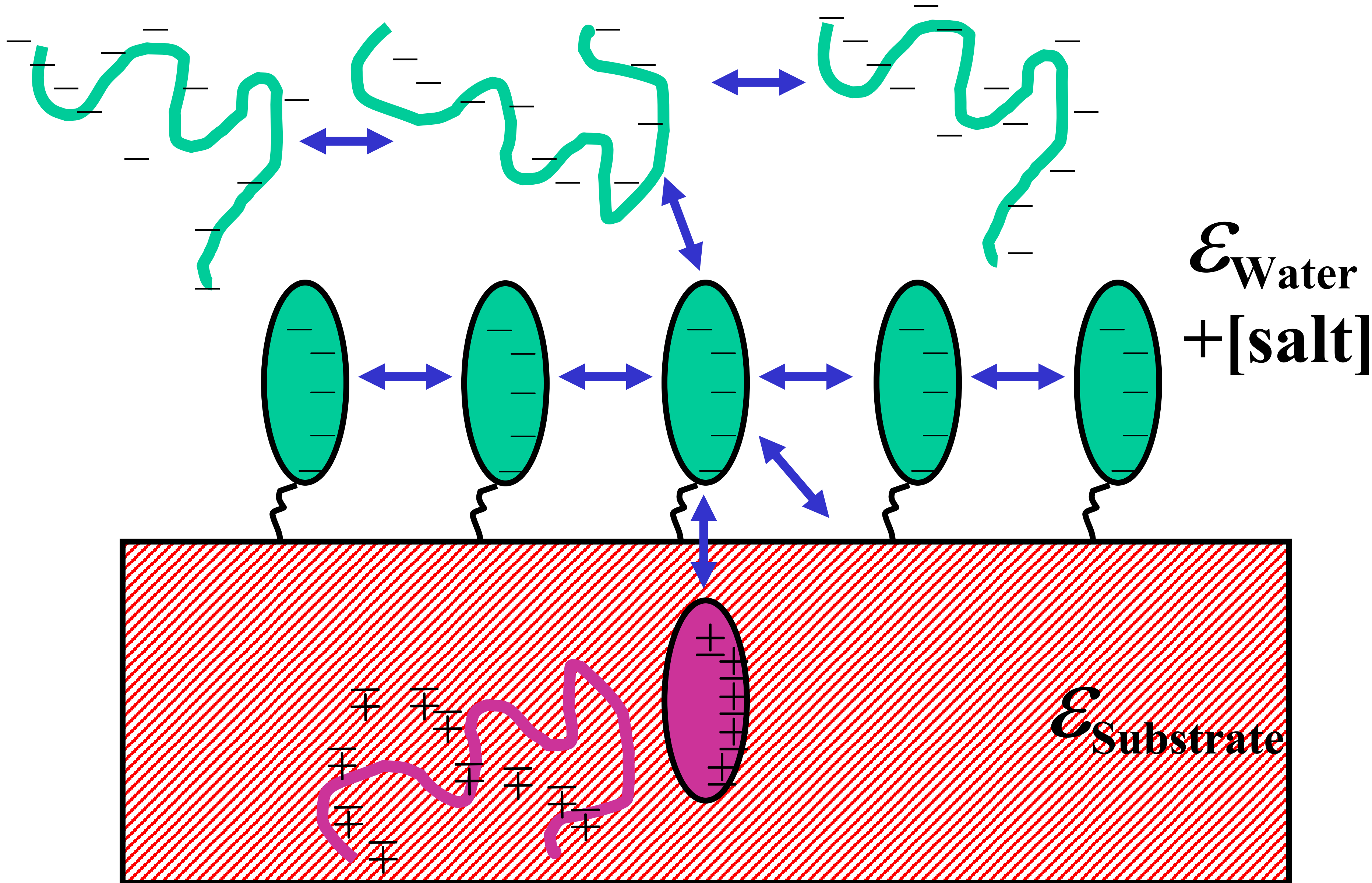
Ionic screening layers

Ultimately: Device response

Simulations, Theory and Data Processing

- ***Simulations at the Atomic Level***
  - ***Detailed, Accurate***
  - ***Expensive Time consuming***
- ***Theory***
  - ***Approximate Rules of Thumb***
- ***Processing the Image Data***
  - ***Must be Fast and Accurate***

Forces: Surface and Solution

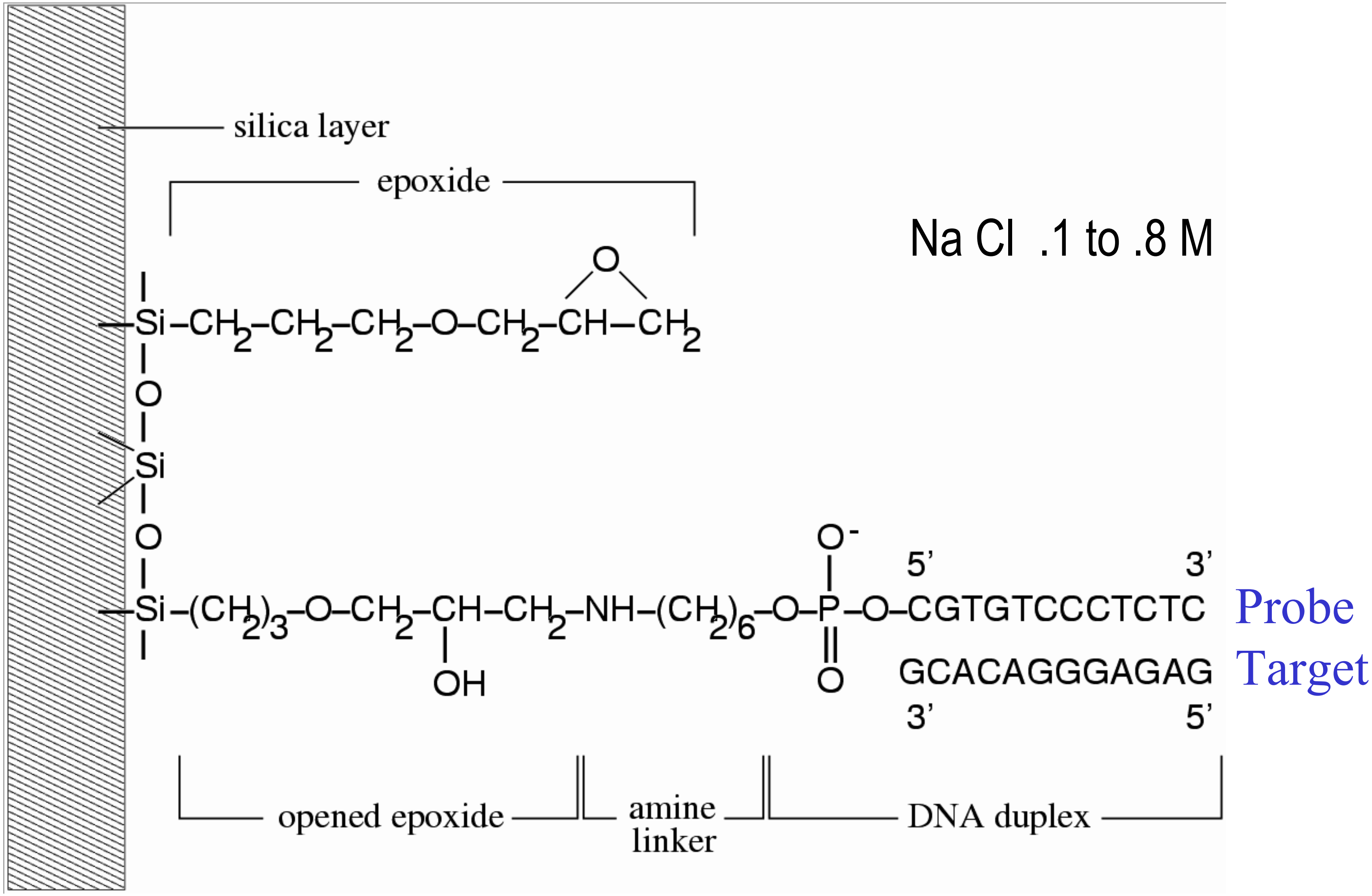


Simulations or Theories of Bio Chips

Set up must include

- Substrate (Au, Si, SiO_2 …)
- Electrostatic fields
- Surface modifications
- Spacers (organic)
- Probe and Target Bio (DNA or protein) strands
- Salt and lots of Water

The Chemistry



Simulate a simple classical force field

Model the interactions between atoms

- Bonds - 2 body term
  - harmonic, Hooke's law spring

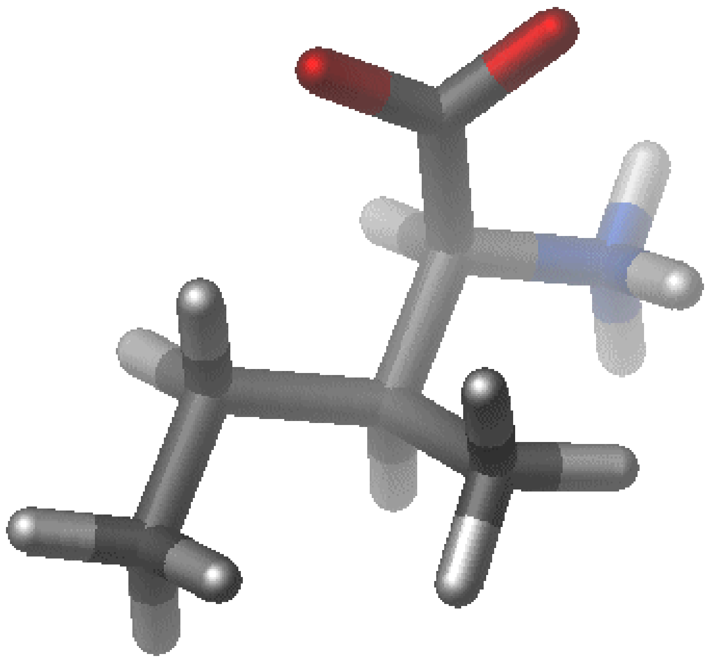
$$\sum_{bonds} K_b (r - r_e)^2$$

- Angles - 3 body term

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

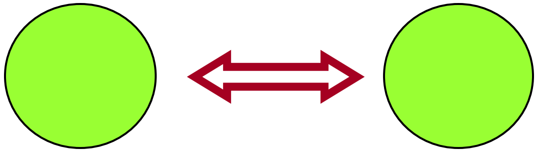
- Dihedrals - 4 body term

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



Source: http://www.ch.embnet.org/MD_tutorial/

Nonbonded Terms



- 2 body terms
- van der Waals (short range) & Coulomb (long range)

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

- Coulomb interaction consumes > 90% computing time

Ewald Sum electrostatics to mimic condensed phase screening

- Periodic Boundary Conditions

Electrostatic Forces Dominate Behavior

$$\mathrm{F = ma} \quad or$$

$$-\nabla V(r) = m\ddot{r}$$

With a classical Molecular Mechanics potential, *V(r)*

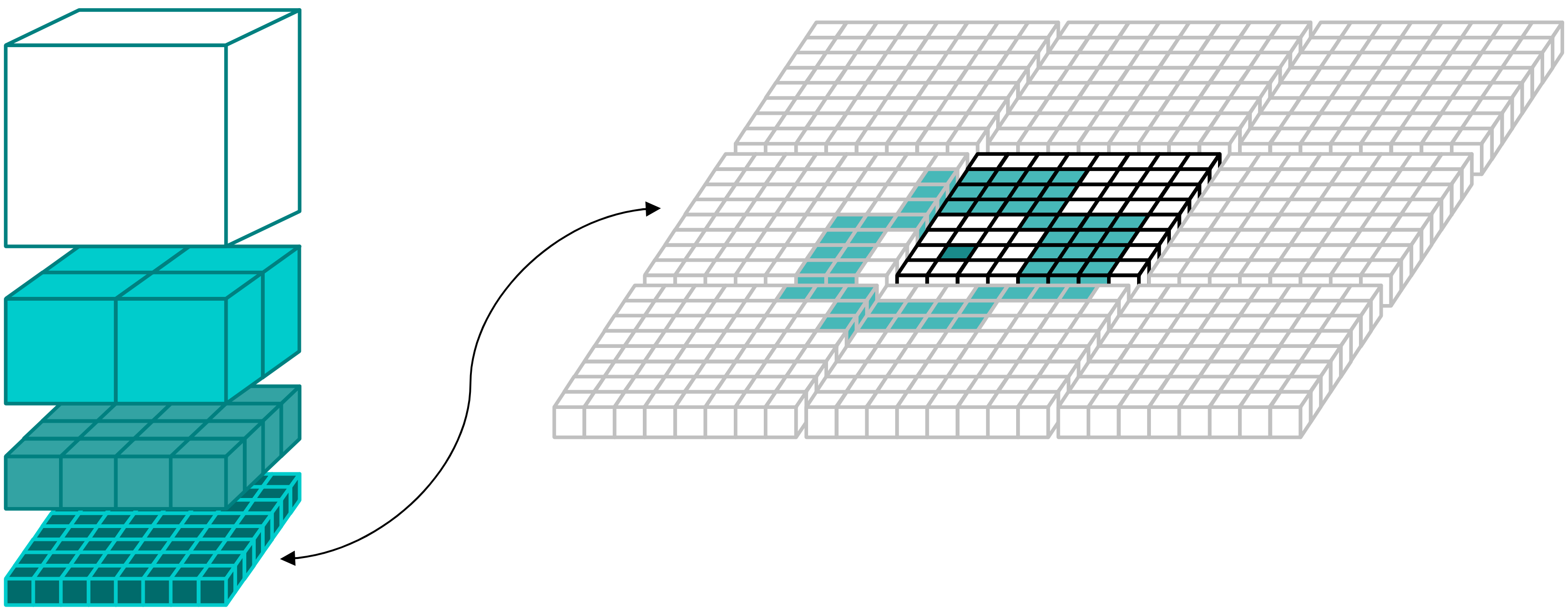
These potentials have only *numerical* solutions.

$$r(t+\Delta t) = r(t) + \dot{r}(t)\Delta t + \tfrac{1}{2!}\ddot{r}(t)\Delta t^2 + 0(\Delta t^3)$$

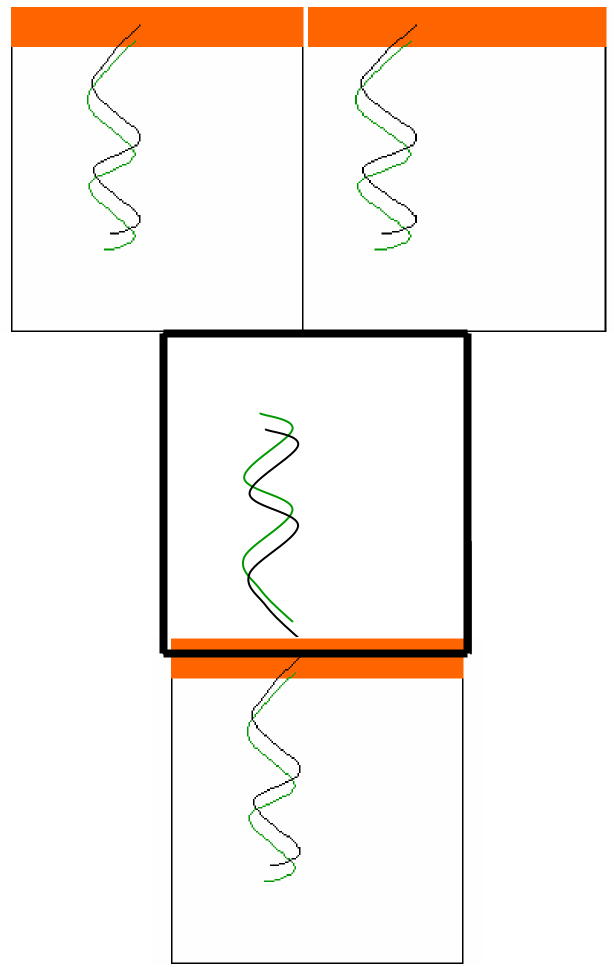
Δt must be small, 10^{-15}s

Ewald Fast Multipole

- Insist on deterministic trajectories
- Relative precision $\Delta F_{ij}<10^{-6}$ wrt Ewald
- Very fine grain communications overlapping and inverse message pulling
- 40x over optimized Ewald for 100K atoms



Periodic Boundaries for Surfaces: Change symmetry



Skew BCs

0 ns

Implications

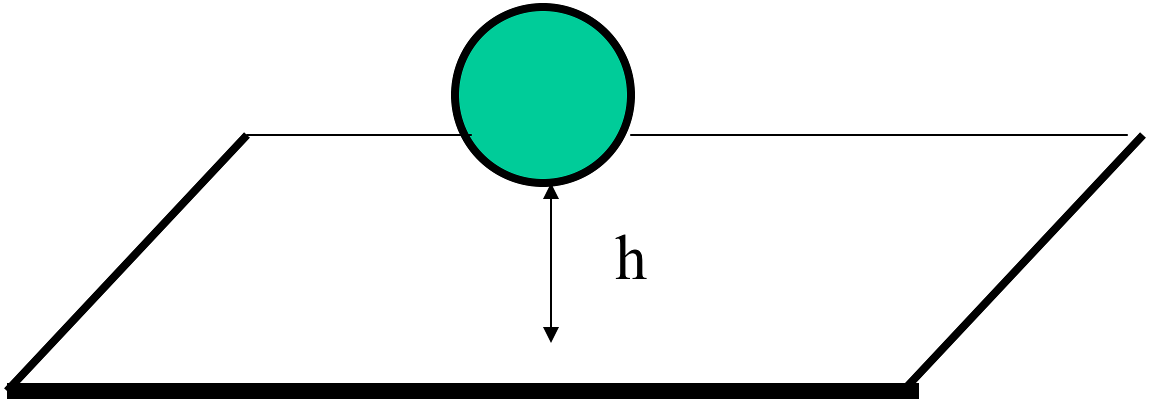
- Colloidal behavior affects
  - synthesis / fabrication
  - and binding
- Tilt restricts possible geometries of pairing
- Low fraying consistent with high affinity and good specificity at low target concentration

ΔG & $\Delta\Delta G$

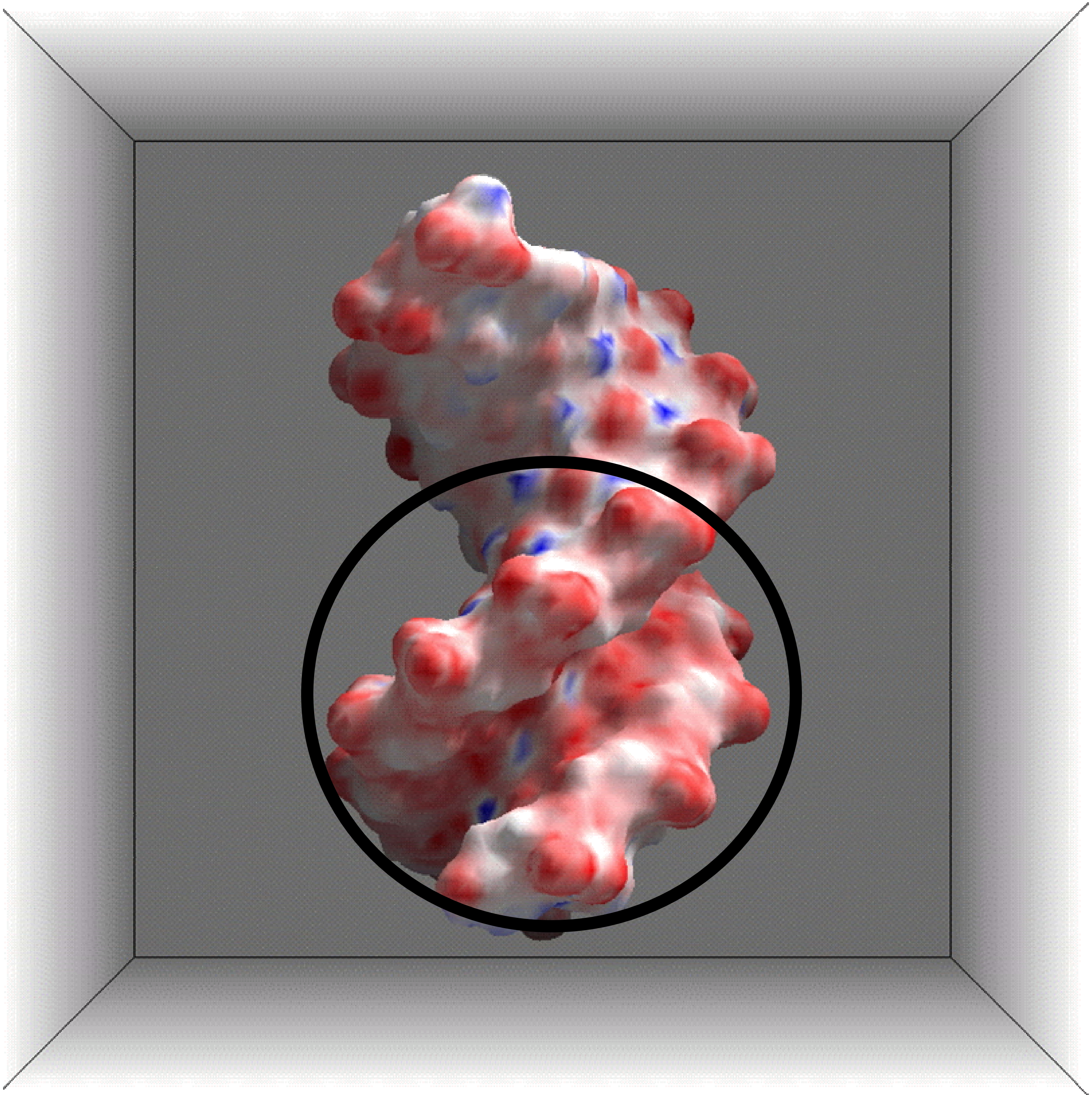
A Simple Model

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

analytic solution

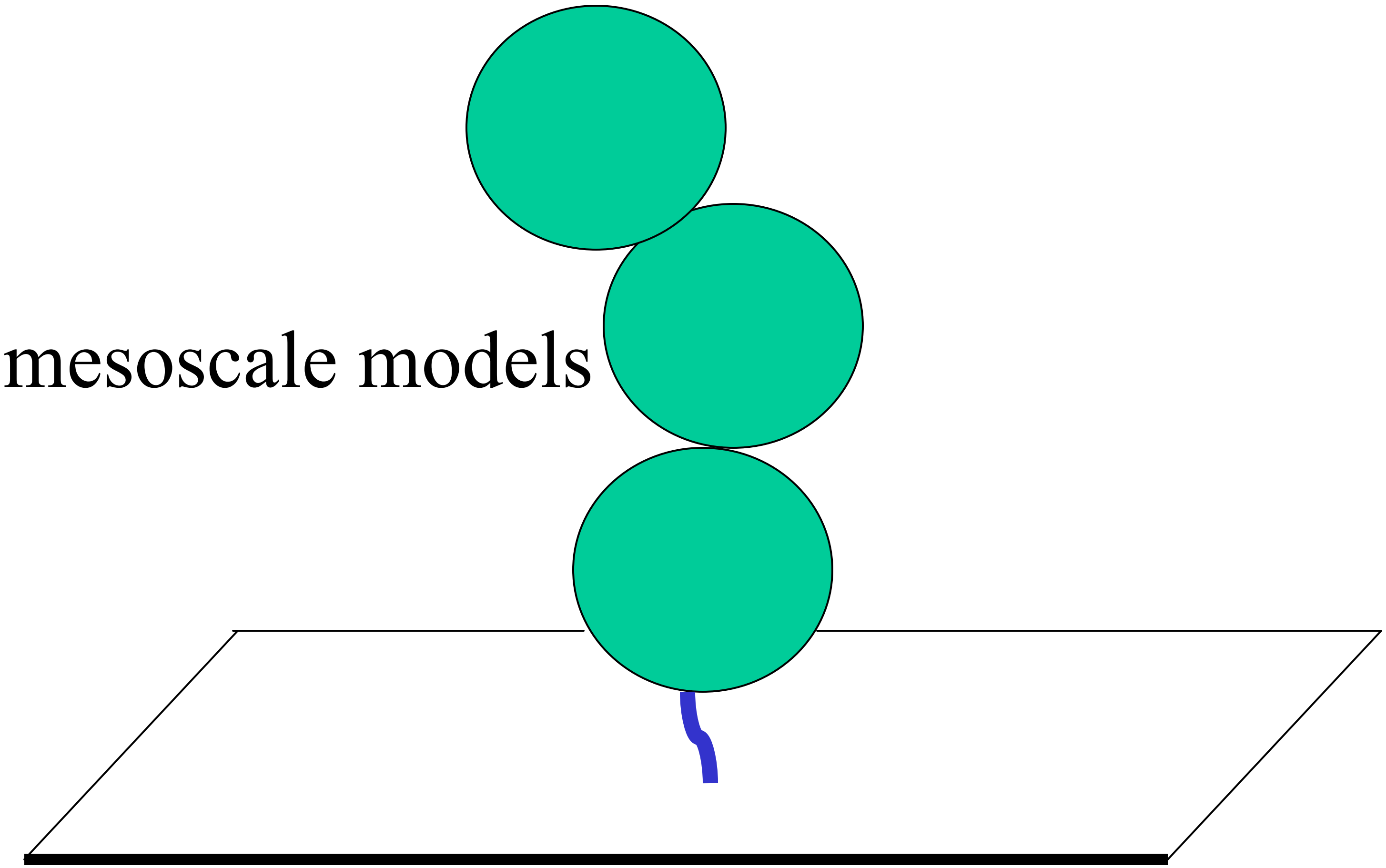


Poly - Ohshima and Kondo, '93
DNA - Vainrub and Pettitt, CPL '00
Ellipse - Garrido and Pettitt, CPC, 07



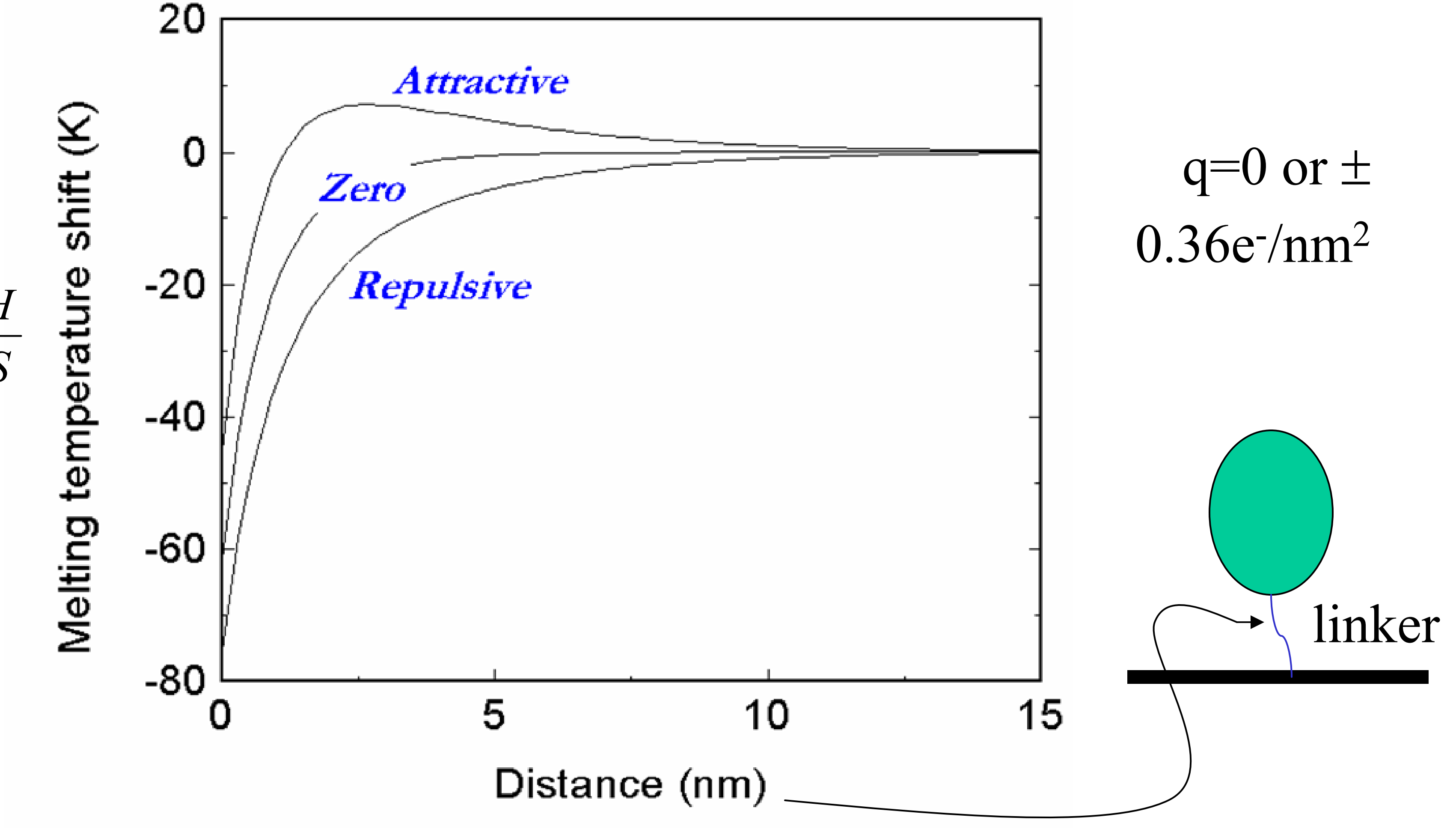
Longer Sequences are possible

True mesoscale models



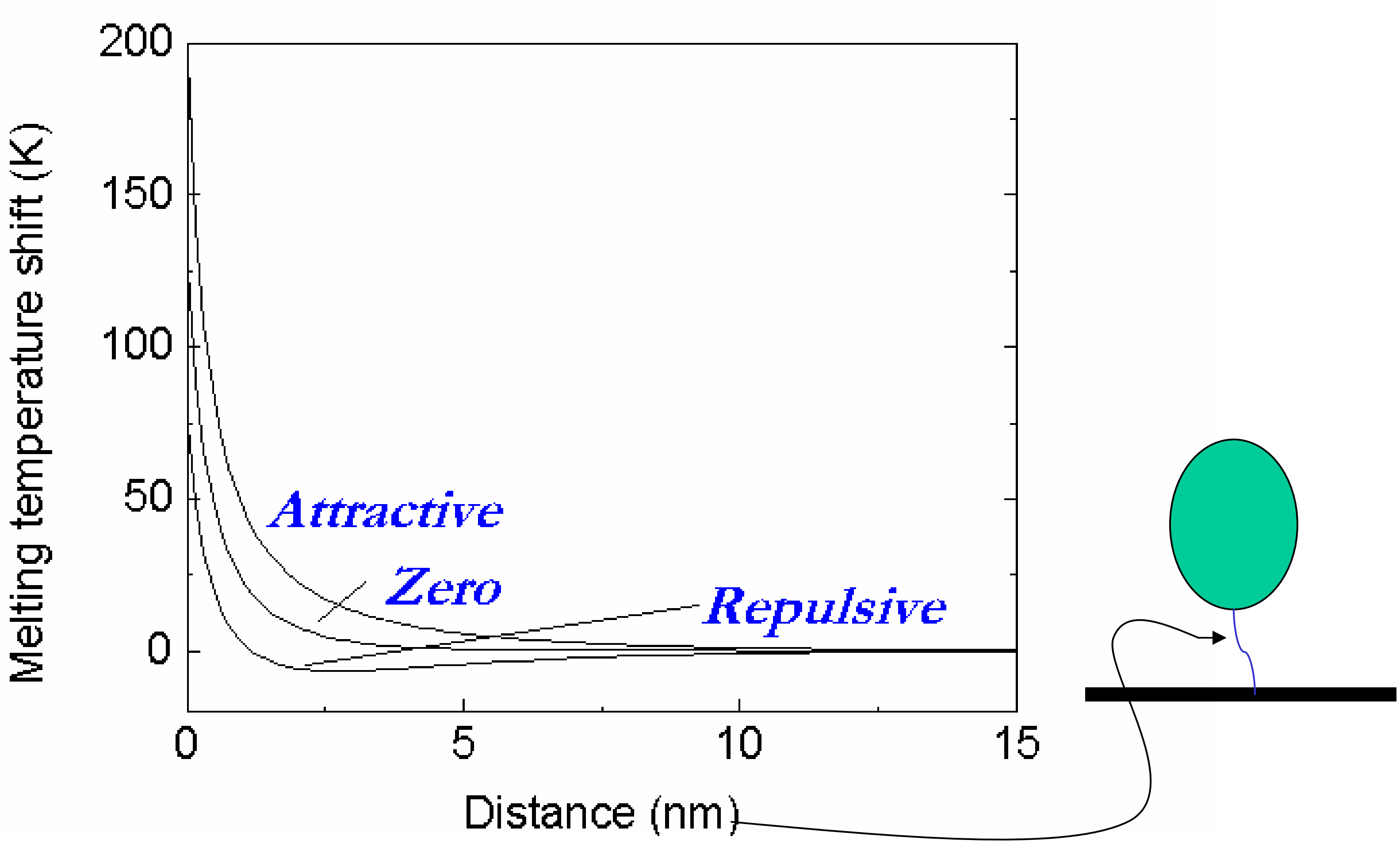
The shift of the dissociation free energy or temperature for an immobilized 8 base pair oligonucleotide duplex at 0.01M NaCl as a function of the distance from a ***charged dielectric surface***

$$T_m = \frac{\Delta H}{\Delta S}$$



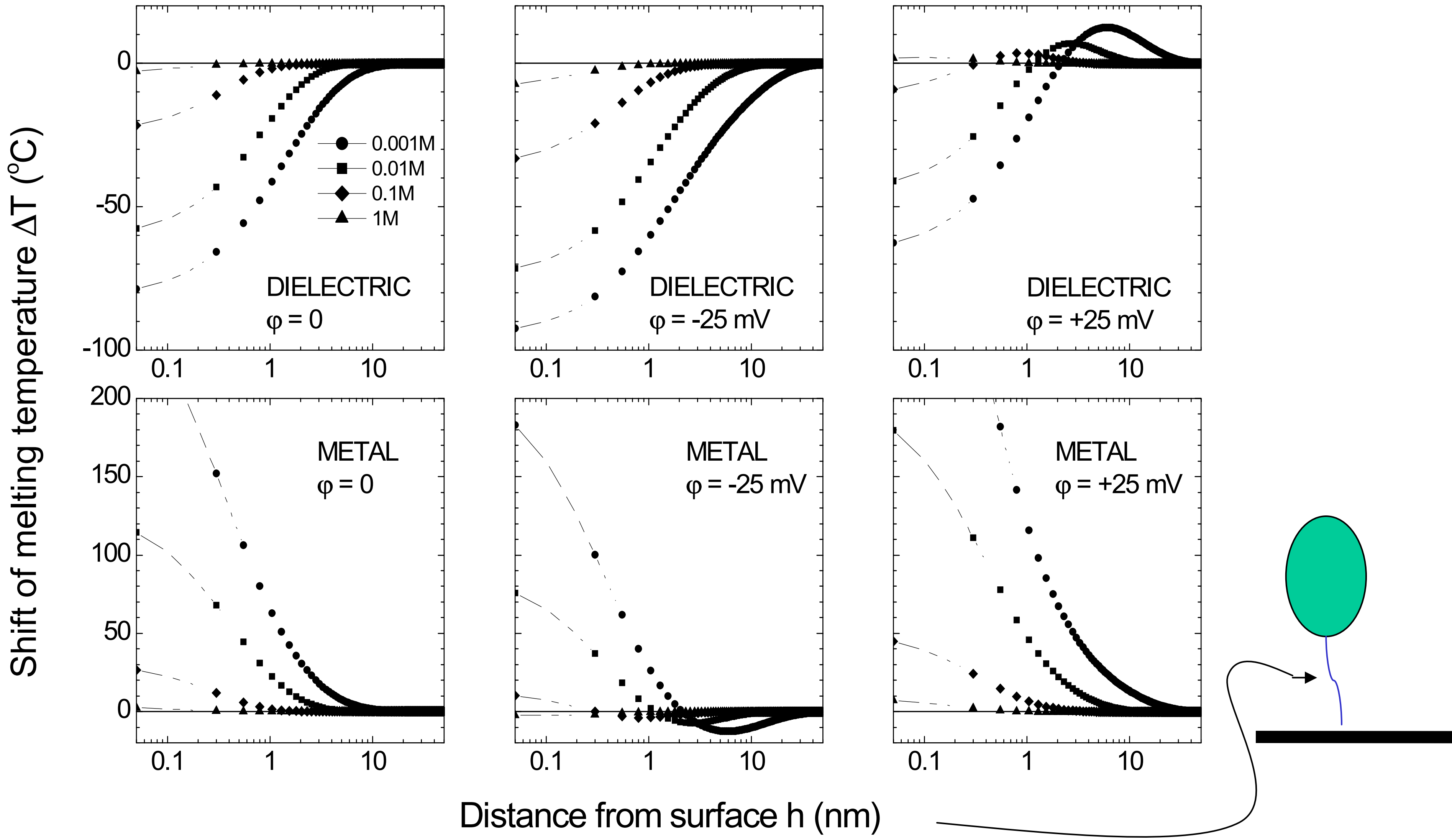
q=0 or ± 0.36e⁻/nm²

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



Response to E-fields

Salt and Substrate Material Effects on 8-bp DNA



Finite Concentration and Coverage

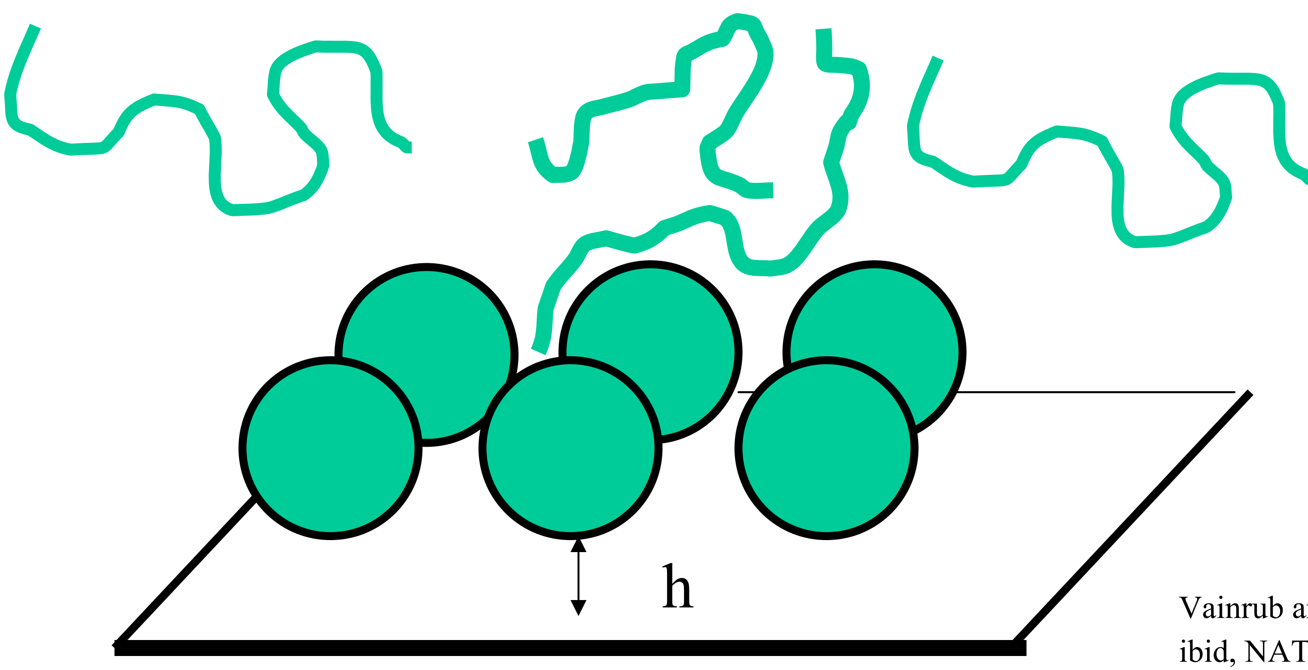
$\nabla^2\phi = \kappa^2\phi$ outside the sphere and plane,

$\nabla^2\phi = \kappa^2\phi - (\rho/\varepsilon\varepsilon_0)$ inside the sphere,

$\phi|_{r=a+} = \phi|_{r=a-}\,,\ {}_r\,\phi|_{r=a+} = {}_r\,\phi|_{r=a-}$ on the sphere,

$\phi|_{z=0+} = \phi|_{r=0-}\,,\ {}_z\,\phi|_{z=0+} - {}_r\,\phi|_{z=0-} = -\sigma/\varepsilon\varepsilon_0$ on the plane.

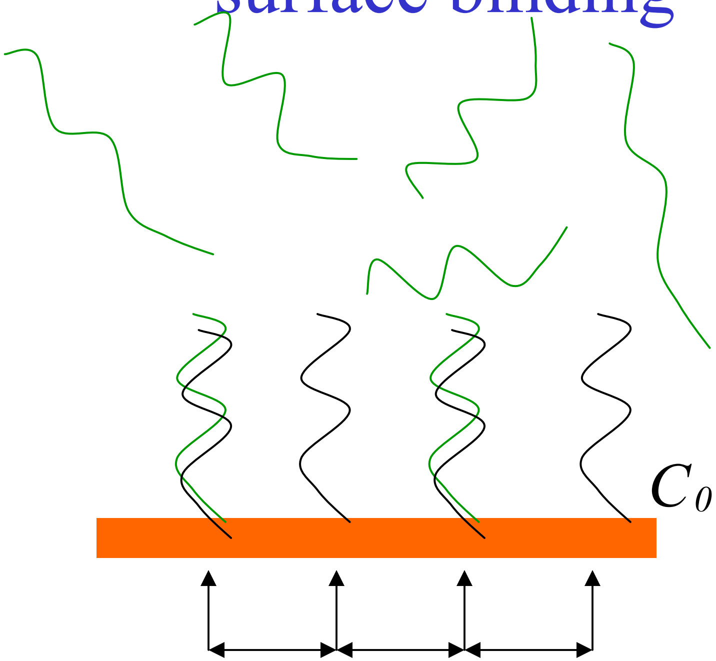
Different from O & K



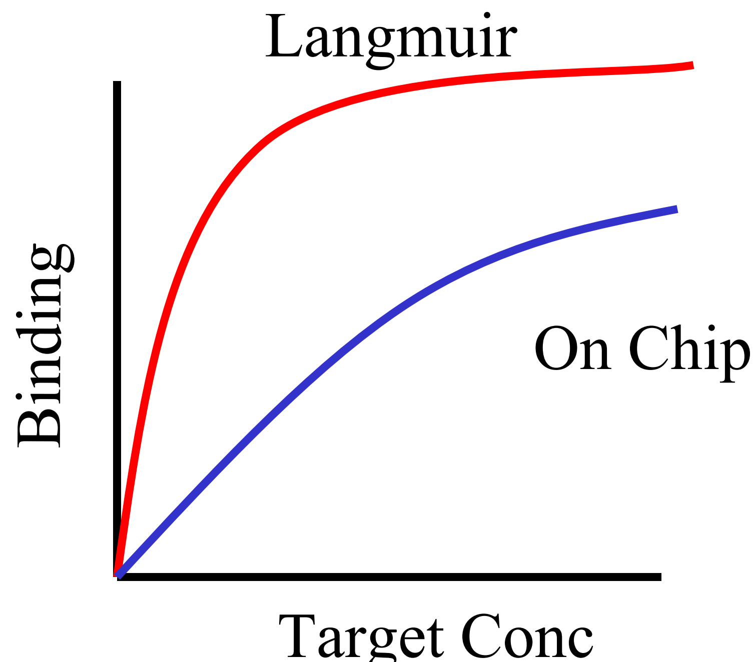
Vainrub and Pettitt, Biopolymers '02
ibid, NATO Sci , '05

Coulomb Blockage Dominates Optimum DNA spacing

High negative charge density repels target surface binding



Probe surface density



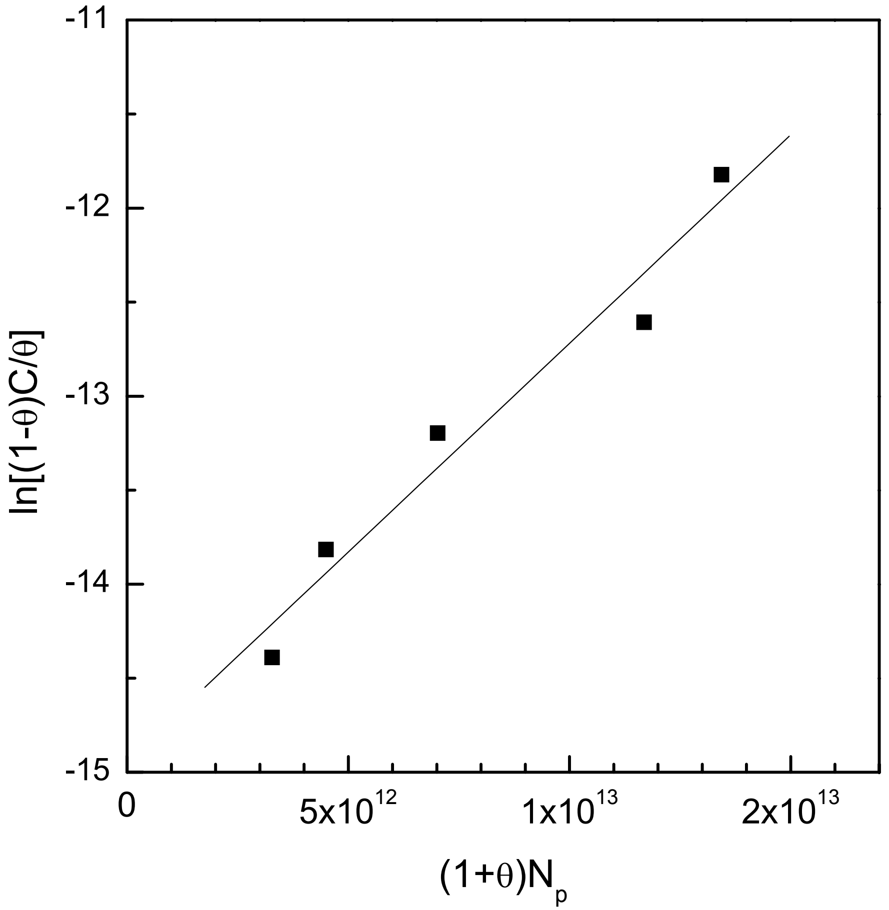
$$C_0 = \frac{\theta}{1-\theta}\,\boldsymbol{exp}\left(\frac{\Delta H_0 - T\Delta S_0}{RT}\right)\exp\left[\frac{wn_P Z_P (Z_P + Z_T\theta)}{RT}\right]$$

hybridization efficiency θ ($0 \le \theta \le 1$)

target concentration C_0

Vainrub&Pettitt PRE (2004)

Fit 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)

Melting curve temperature and width

Analytic wrt surface probe density (coverage)

In solution

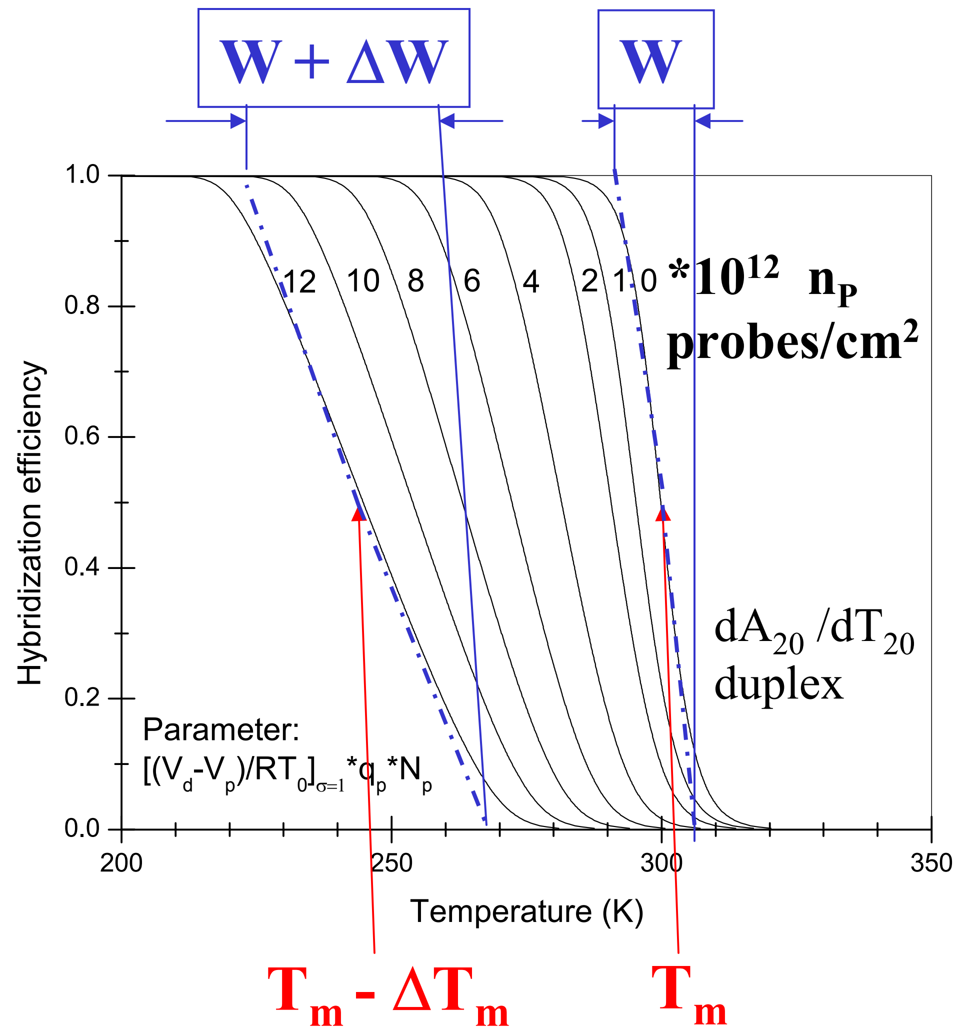
$T_m = \Delta H_0 / (\Delta S_0 - R \ln C)$

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

On-array: Isotherms

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

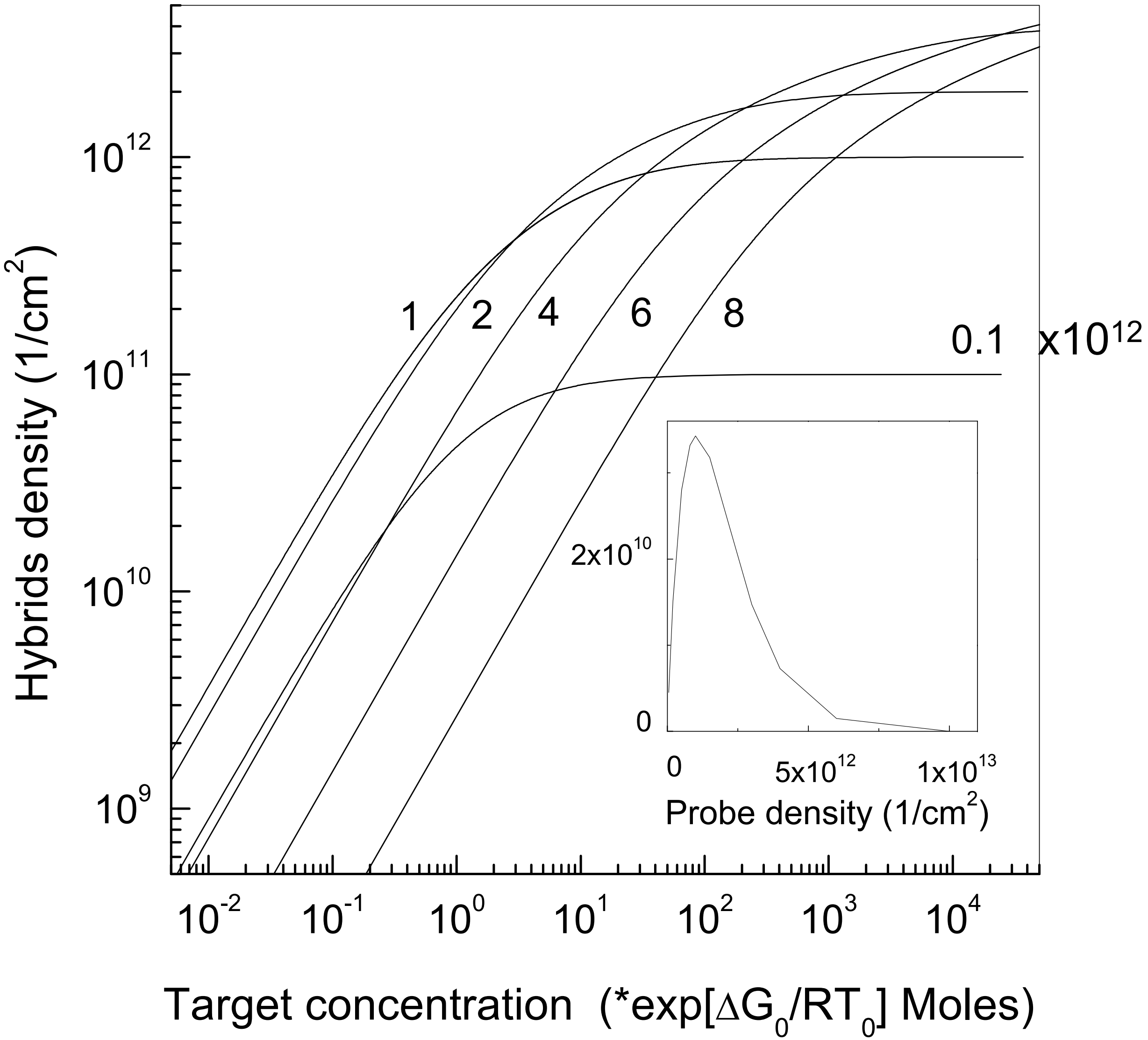
$$\Delta W = \frac{2}{3}\Delta T_m$$



Critical for SNP detection design

Pettitt et al *NATO Sci* 206, 381 (2005)

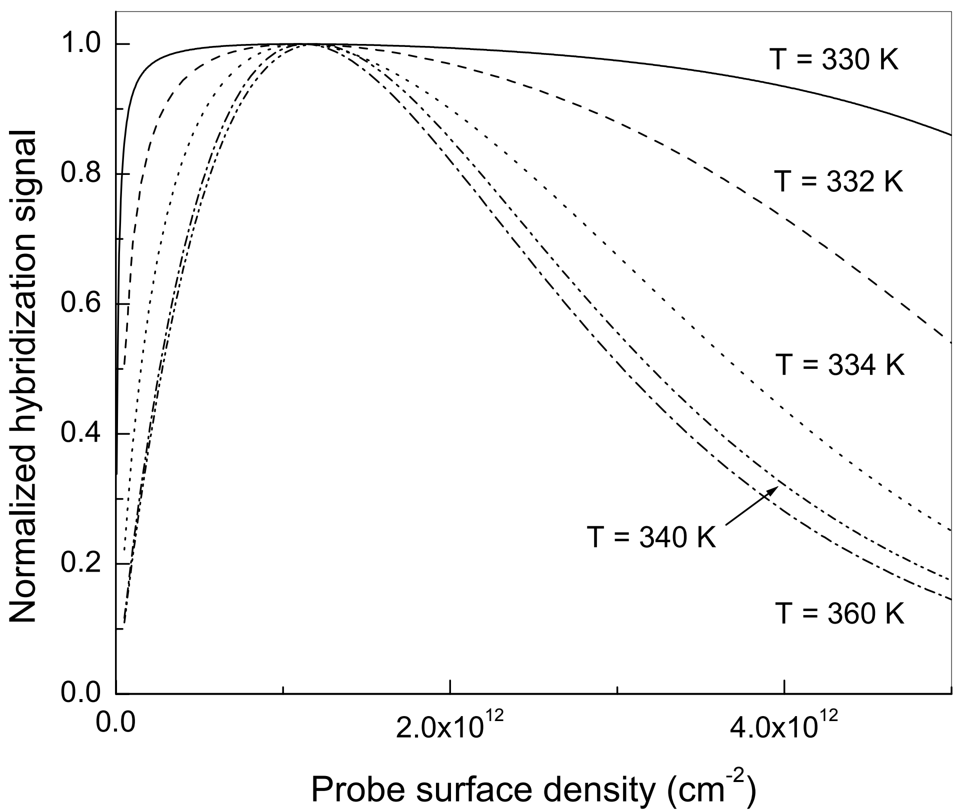
Strength and linearity of hybridization signal



Vainrub and Pettitt JACS (2003); ibid Biopolymers, (2004)

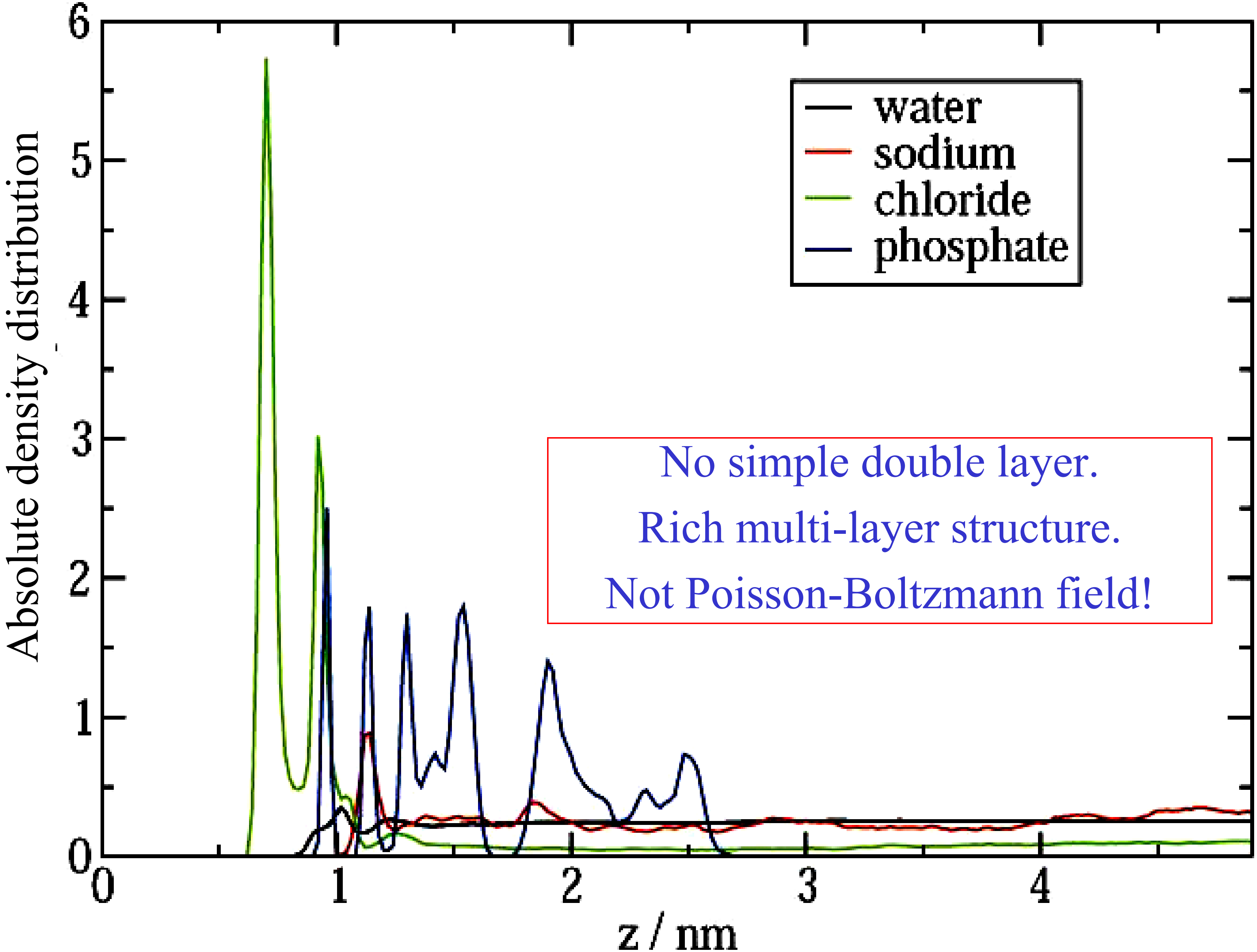
Peak of sensitivity also Analytic

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



Vainrub and Pettitt, JACS (2003)

Density Waves at a +ve charged Surface



We Have Strong Correlations

- Concentration is a poor variable
- Activity is required
- Many non mean field correlations are important
- Multiple length scales competing

To design for Affinity and Specificity

- Use Electric fields
  - Effects of DNA with poly cations
- Use surface effects
  - Layered hard materials
- Use more quantitative theories
  - non m.f.

Conclusion

To control the surfaces we must use cleaner environments:

Micro and nano features for bio chips deserve the same standards as the computer chip industry

Clean rooms with wet and dry facilities

Bio + Nano

Arnold Vainrub

Clem Wong

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Khawla Qamhieh

Alex Micu

Keck Center for Computational Biology

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Rosina Georgiadis,

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