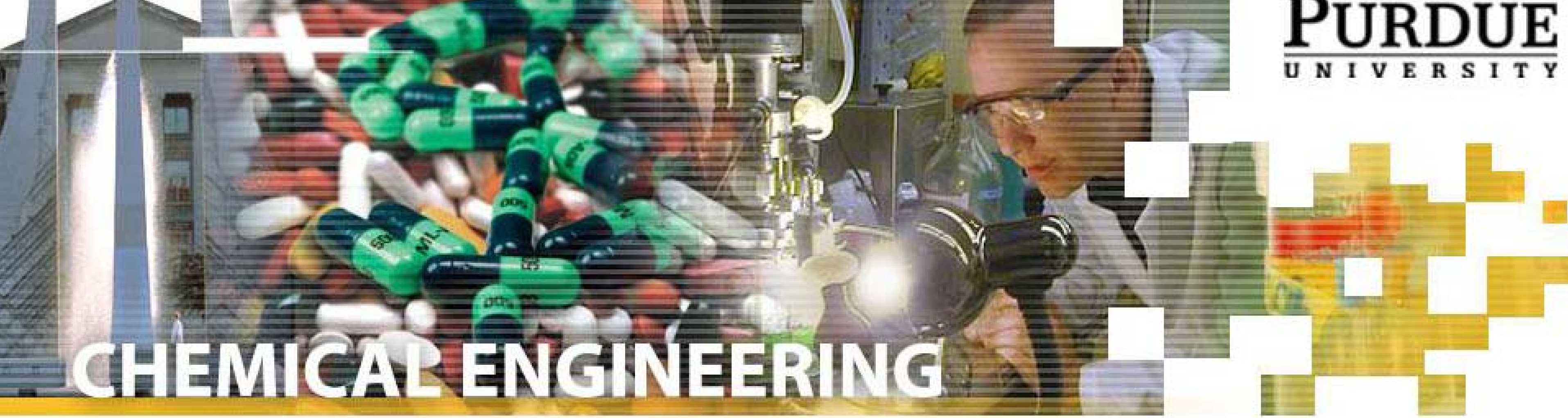

Pharmaceutical Particle Adhesion to Surfaces

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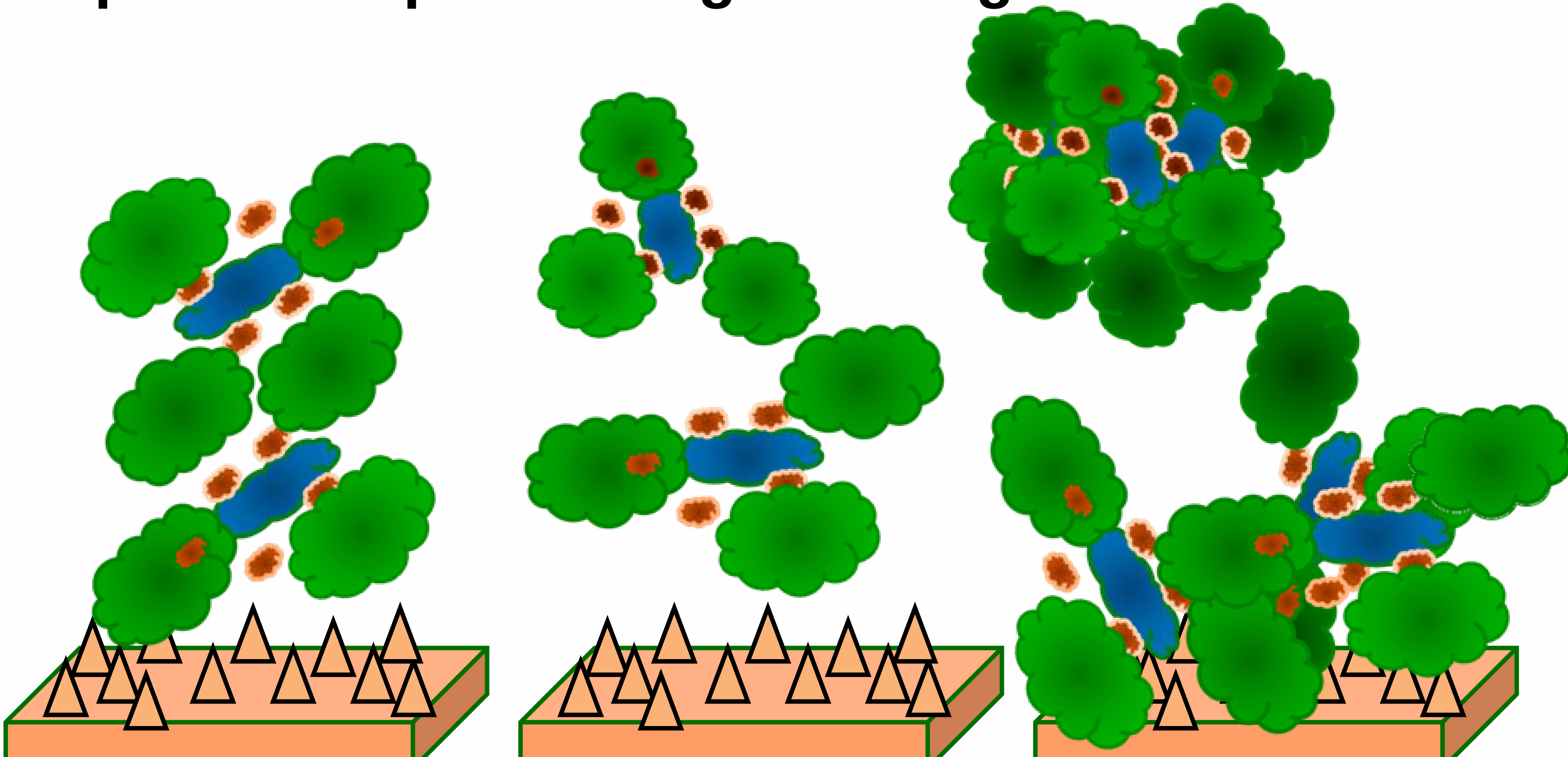
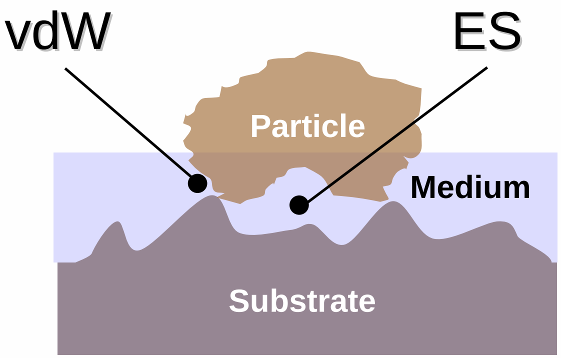
Kyung Min Lee and Stephen Beaudoin
School of Chemical Engineering
Purdue University
W. Lafayette, IN 47906

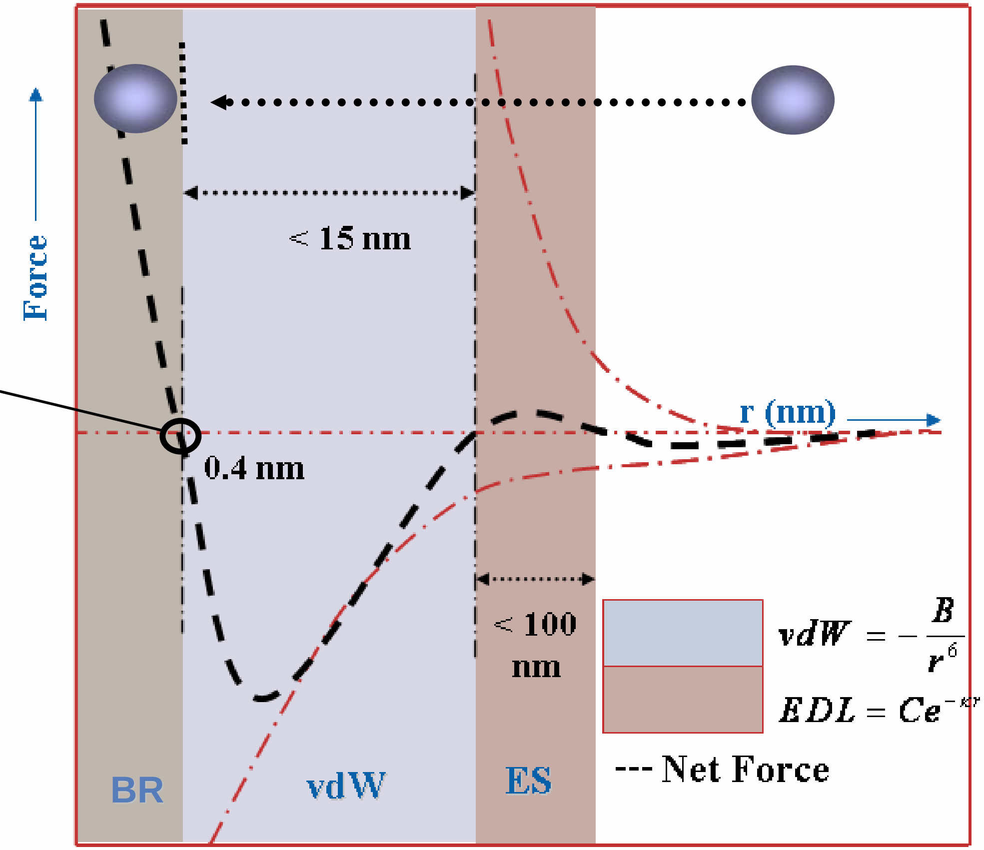
Motivation

- **Adhesion of pharmaceutical particles critically important to processing of dosage forms**



Fundamental Forces in Particle Adhesion



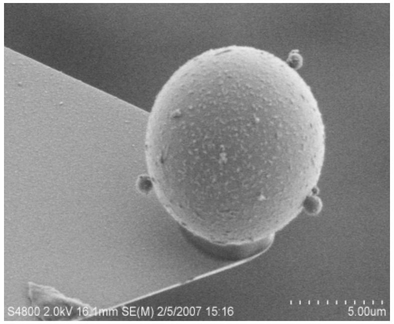


- **van der Waals (vdW)**
  - Interactions between dipoles (and/or induced dipoles)
- **Electrostatic (ES)**
  - Columbic or double layer
- Steric force
- Hydrophobic force
- Chemical bonds

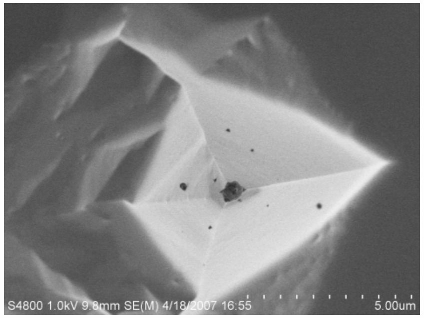
✓ vdW and ES forces are the major contributors in adhesion

Adhesion Force Measurements

Sample Preparation

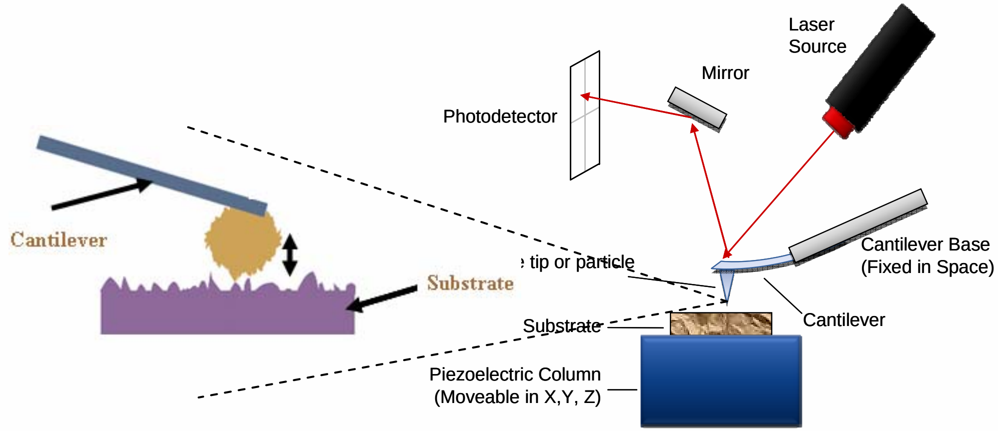


SiO_2 Particle
(~9µm)

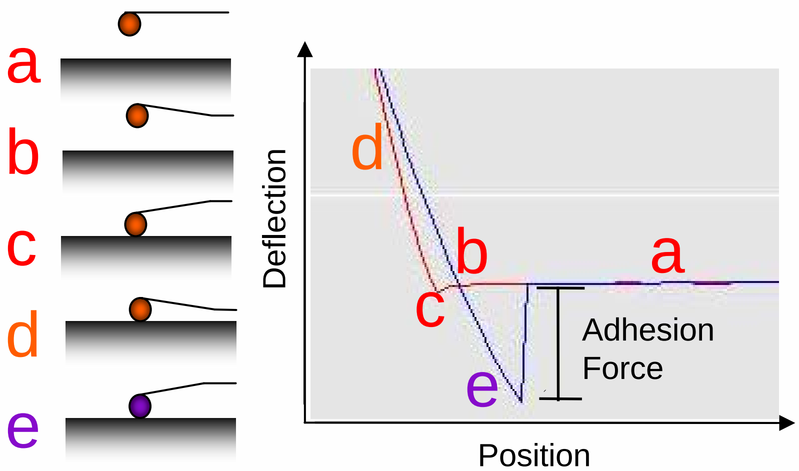


SiO_2 AFM probe (top view)
(ROC ~50 nm)

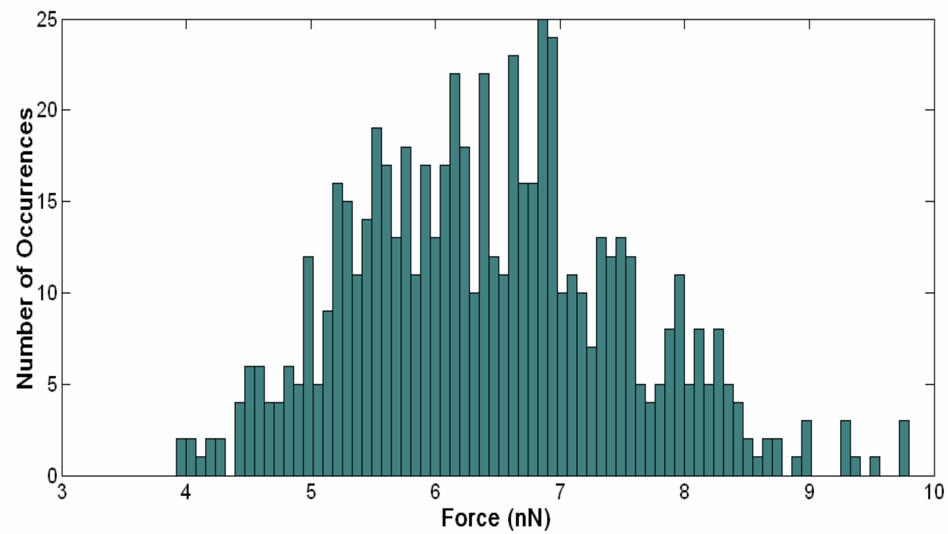
AFM Force Measurement



Typical AFM Force Curve



Measured Force Distribution



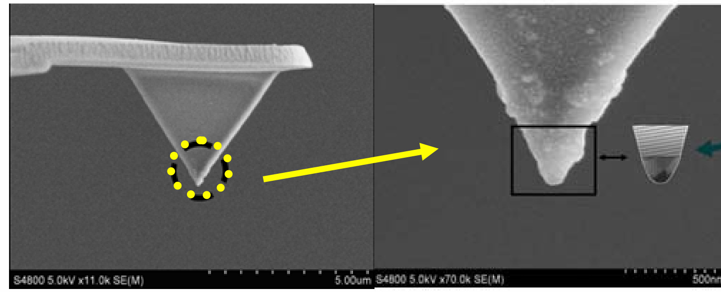
✓ Surface heterogeneity leads to adhesion force distributions

THINK IMPACT

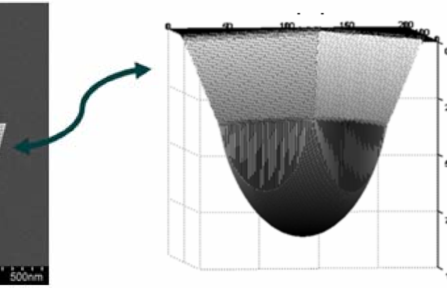
Modeling Adhesion Forces
Surface Characterization

- **Geometry**
  - **- Regular**

FESEM micrograph of SiO_2

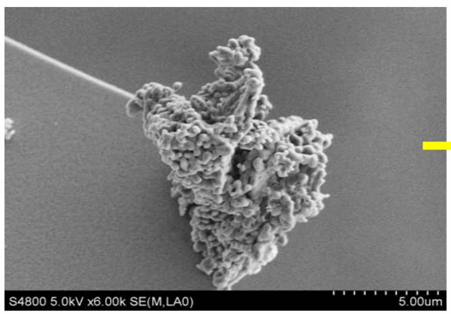


Si_3N_4 Nanosize pyramidal tip **Zoomed-In view: ROC ~ 75nm**

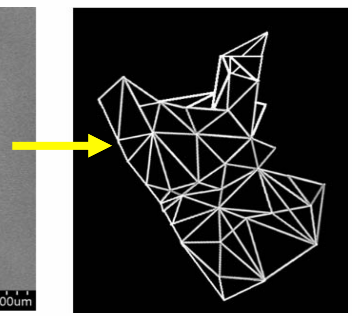


Modeled tip

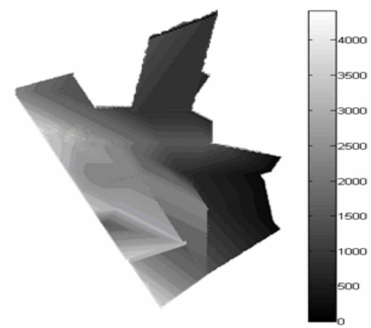
- **Geometry**
  - **- Irregular**



FESEM micrograph of Al_2O_3



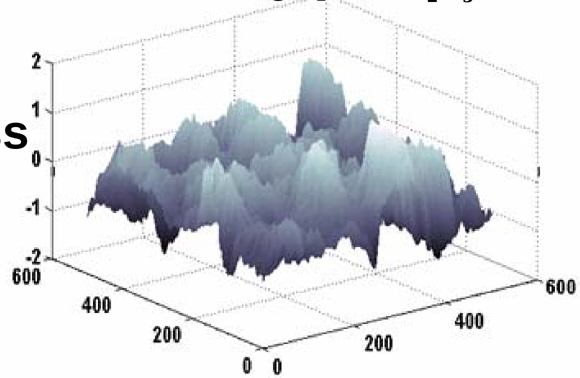
PhotoModeler wire-mesh (Top-view)



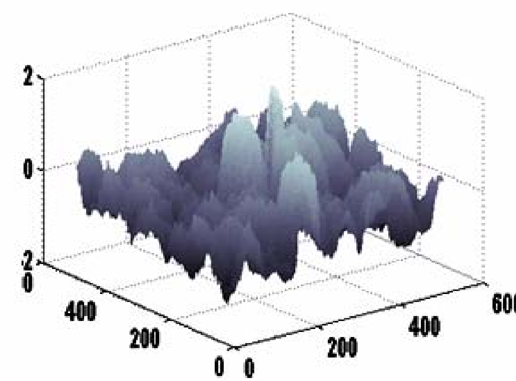
Top-view of the constructed surface

(Height data are in nanometers)

- **Roughness**



AFM scan of Chrome surface

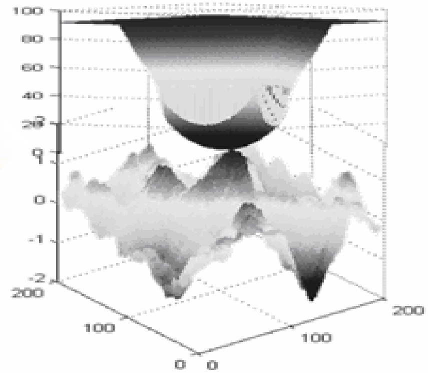


FFT generated Chrome roughness
lom phase shift)

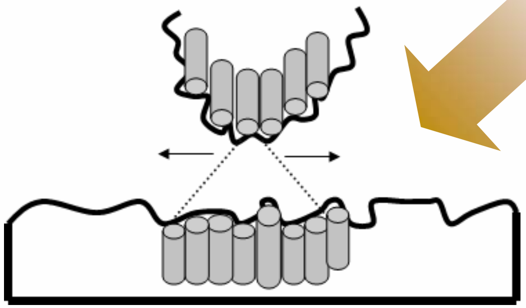
FFT →

$$z_{x,y} = \sum_{k=0}^{M-1} \sum_{l=0}^{N-1} Z_{k,l}\, e^{i2\pi\left[\varphi_{k,l} + \frac{kx}{m} + \frac{ly}{n}\right]}$$

van der Waals (vdW) and Electrostatic (ES) Force Model Description



vdW

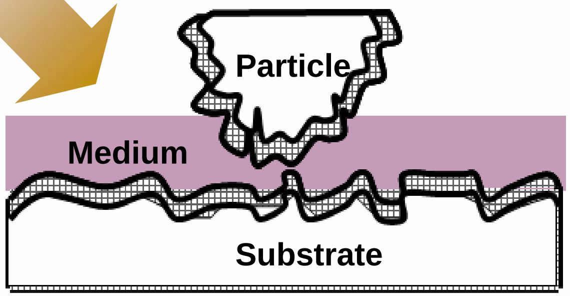


$$F_{1j} = C\frac{\partial}{\partial D}\iiint d\forall_j \iiint \frac{d\forall_1}{r'^6}$$

$$F = \sum_i \sum_j F_{ij}$$

Point-by-point additivity

ES



Double Layer

$\nabla^2\psi = k^2\psi$ Poisson-Boltzmann Eq.

$$k = \sqrt{\frac{e^2\sum_i z_i^2 n_{i0}}{\varepsilon_0 \varepsilon_r K_B T}}$$ Reciprocal Debye length

Constant potential boundary conditions

Columbic

$$F_{el} = \left(\frac{1}{4\pi\varepsilon}\right)\left(\frac{q^2 R(D+R)}{((D^2+2RD)^2)^2}\right)$$

+

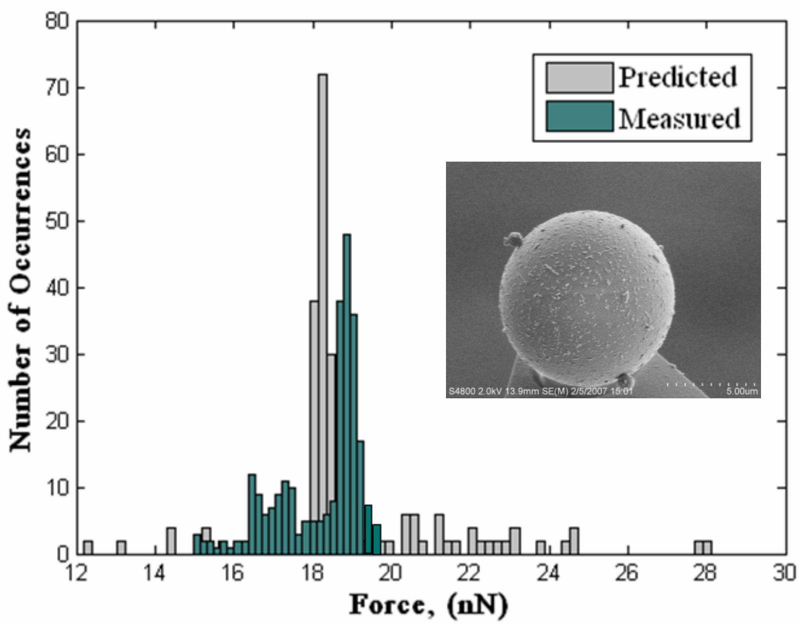
$$F_{Adhesion} = F_{vdW} + F_{ES}$$

Adhesion in Micron-Scale Particle-Substrate System

- **Particle geometry and particle and substrate roughness were measured and modeled**

Regular geometry

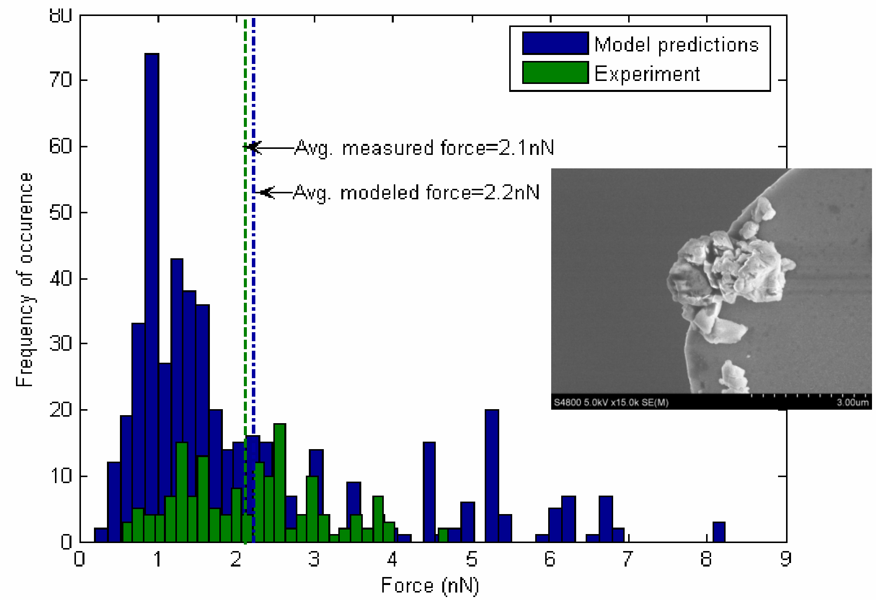
Silica particle (~3u) on TaO_xN_y in air



$F_{,\ av\text{-}Measured}$: 18 nN; $F_{,\ av\text{-}Predicted}$: 19 nN

Irregular geometry

Silicon nitride particle 4.1 μm on TaO_xN_y in DI water

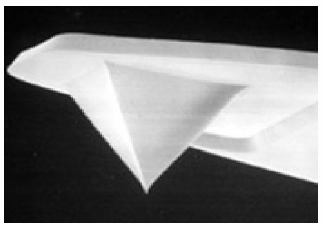


$F_{,\ av\text{-}Measured}$: 2 nN; $F_{,\ av\text{-}Predicted}$: 2 nN

- Range of predicted force is wider than measured
  - ✓ Measured forces are in the range of model predictions

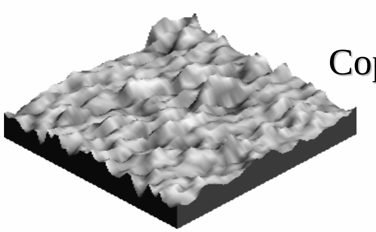
Adhesion of Nanosized Body-Substrate System

- Measured and Predicted Adhesion Forces: Silicon Nitride AFM Probe on Copper Surface in Air
  - Tip-1: ROC ~ 30nm
  - Tip-2: ROC ~ 50nm

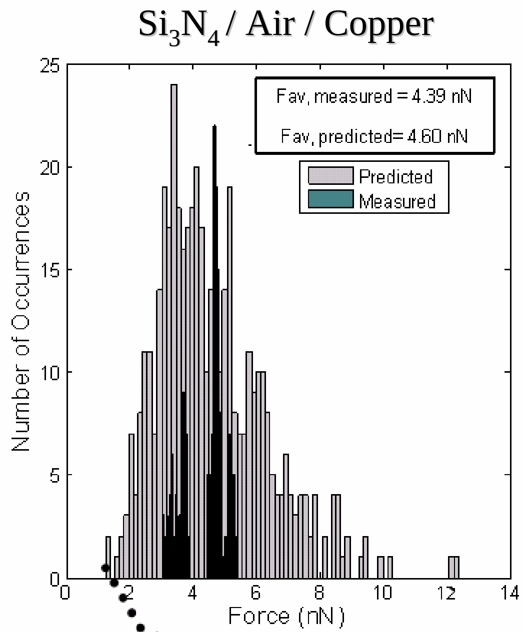


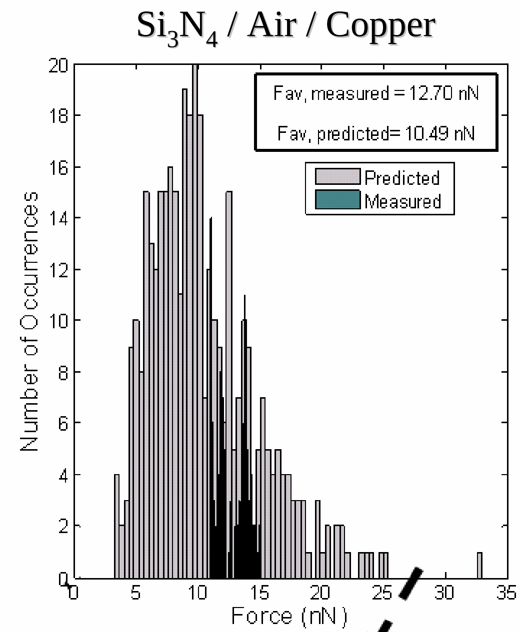
Si_3N_4

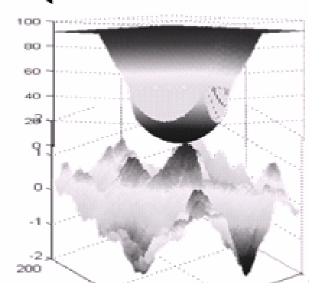
+

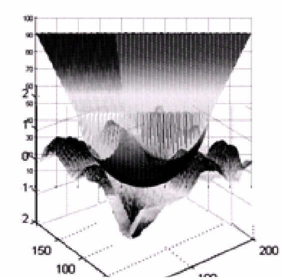


Copper



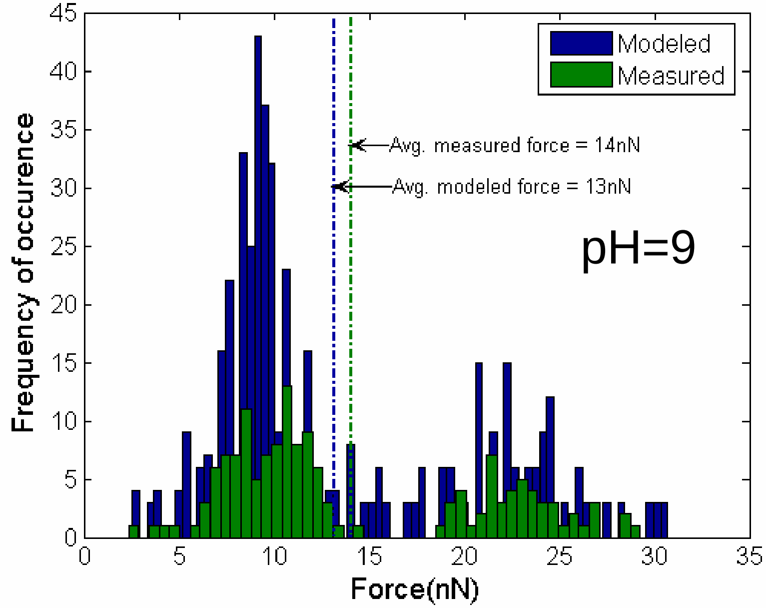




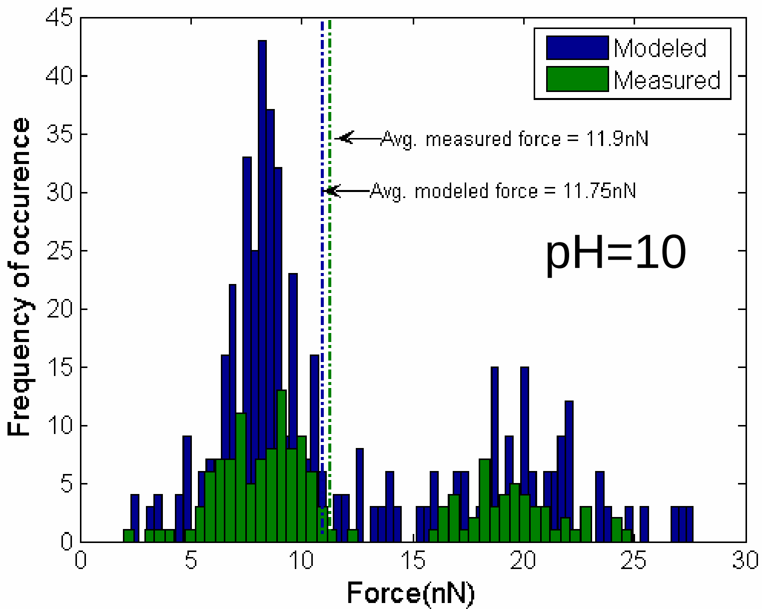


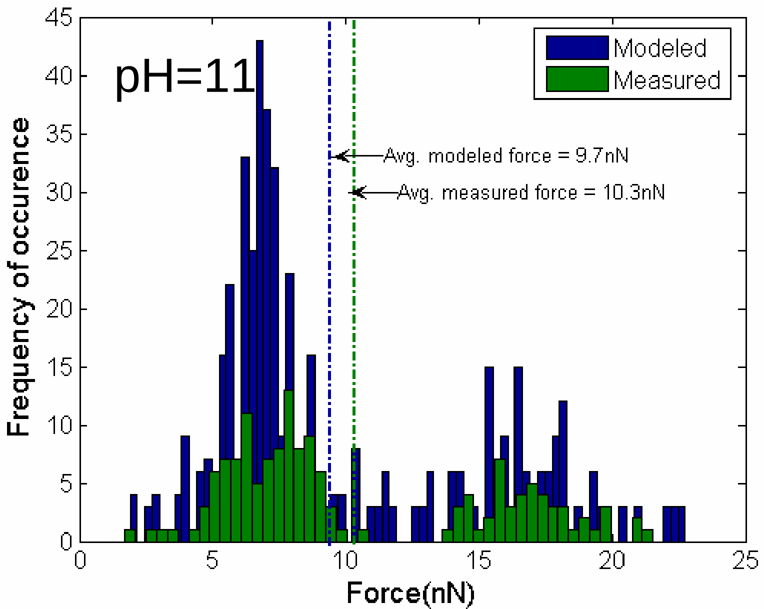
- **Substrates: CrO_xN_y, Ru, TaO_xN_y, MoSi, quartz, SiO_2**
- **Environments: air, DI water**
  - ✓ Measured forces are in the range of model predictions

Interactions between Si_3N_4 and SiO_2 in Aqueous NH_4OH

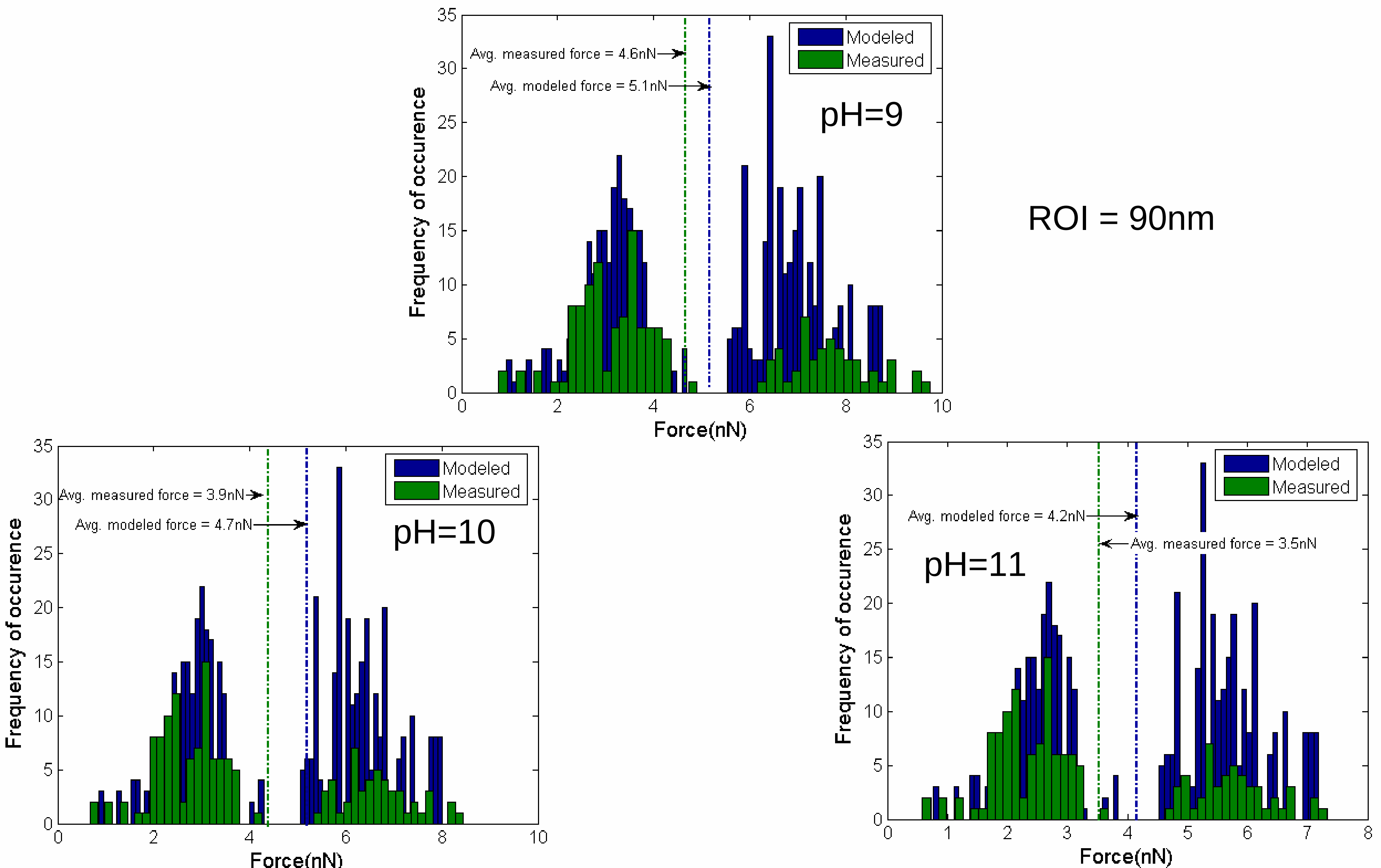


Particle size= 3.2μm





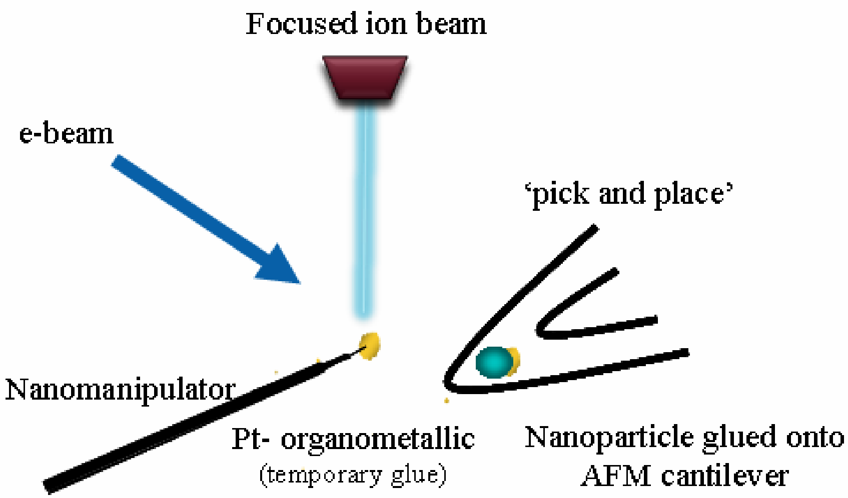
Interactions between Si_3N_4 and SiO_2 in Aqueous NH_4OH



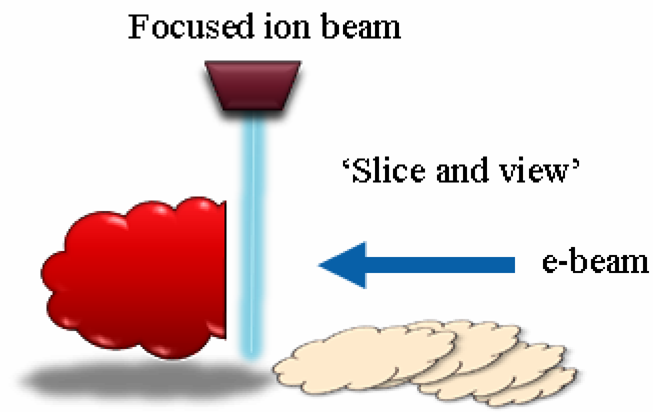
ROI = 90nm

Next Generation Experimental Approach

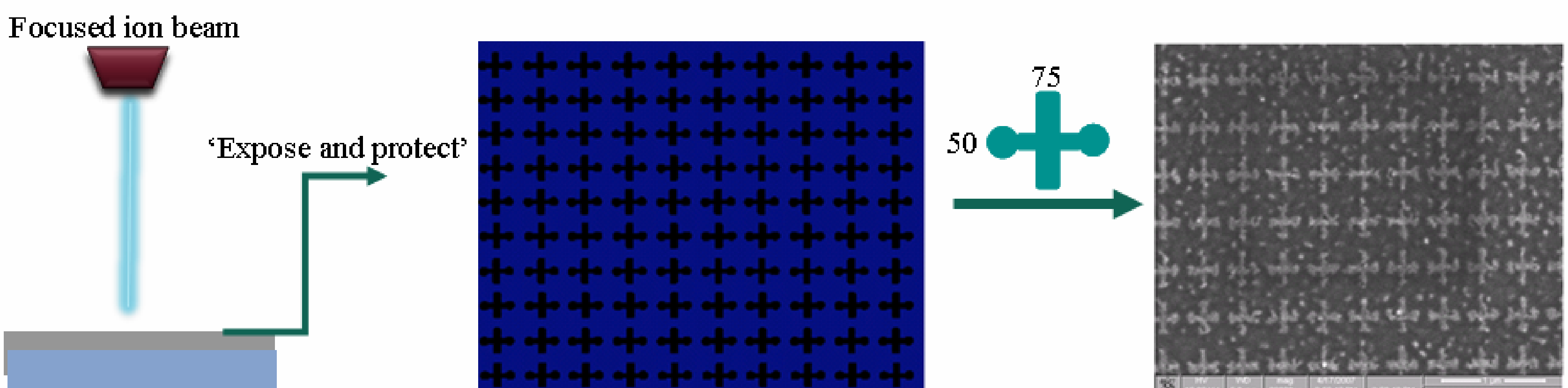
Nanoparticle mounting technique: “nano-welding”



Geometry characterization: rigorous approach

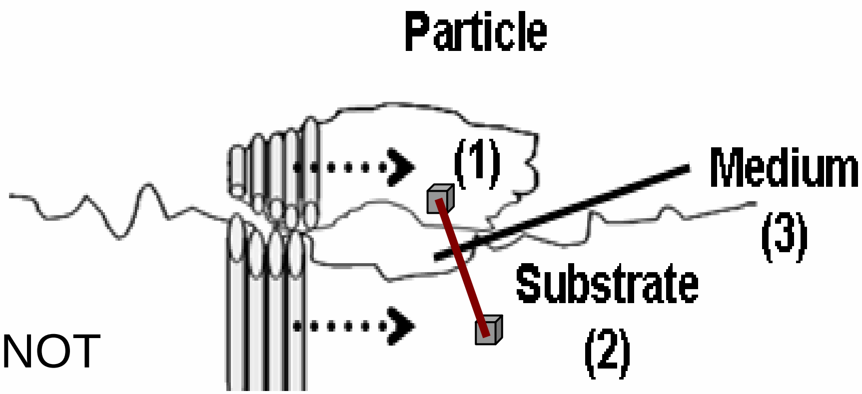


Patterned substrate preparation



Conventional vdW Force Modeling Approach

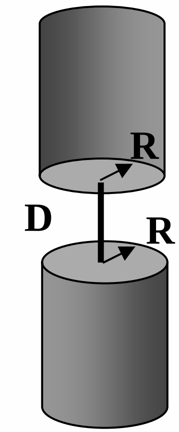
- Rigorous approach



$$F_{12} = -C\frac{\partial}{\partial D}\iiint d\forall_2 \iiint \frac{d\forall_1}{r'^6}$$

✓ Numerical approach
✓ Extremely computationally expensive- NOT practical

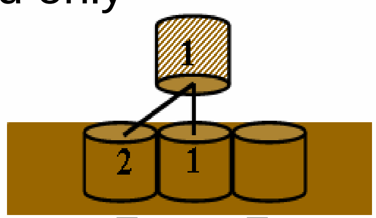
- Traditional approach *(1-1 interaction)*



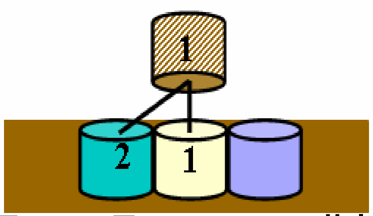
$$F_{12} = \sum_{\forall i} F_{i-i}$$ Hamaker's vdW expression for parallel flat plate

$$\ldots\text{Where } F_{i-i} = \frac{A(\pi R^2)}{6\pi D^3}$$

✓ Hamaker's flat plate approximation is valid only for large cylinders (R>>D)
  - Limited to large mesh size
✓ Off-axis interactions not considered
  - Limited to homogeneous surfaces



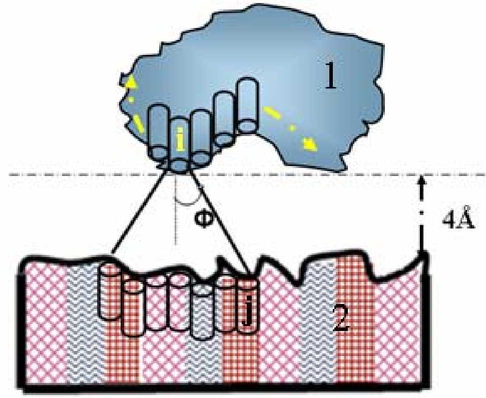
$F_{1\text{-}1} >> F_{1\text{-}2}$



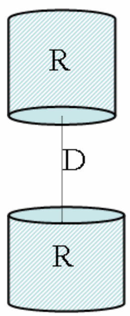
$F_{1\text{-}2} > F_{1\text{-}1}$ …possible!!

Adhesion Force Modeling between Nanosized Inhomogeneous Surfaces

- vdW Force *(1-many interactions)*
  - Mathematical surfaces are discretized into fine mesh of small cylindrical elements

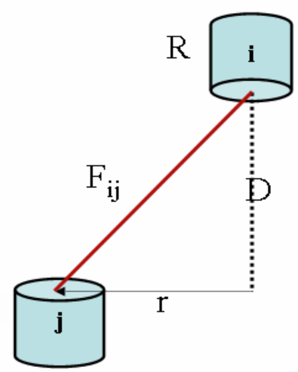


$$F_{12} = -C \frac{\partial}{\partial D} \iiint d\forall_2 \iiint \frac{d\forall_1}{r'^6} = \sum_i \sum_{\forall j} F_{ij}$$



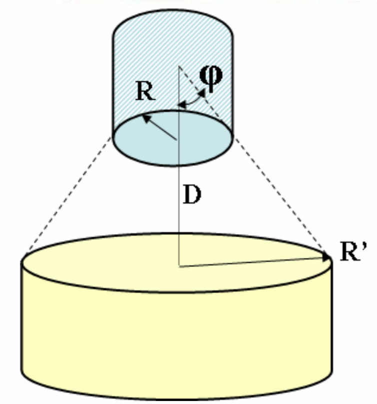
vdW force co-axial cylinders

- Analytical expression available only for large cylinders



vdW force non-axial cylinders

- No analytical expression available



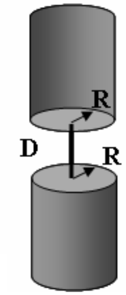
View angle (φ) of cylindrical element:

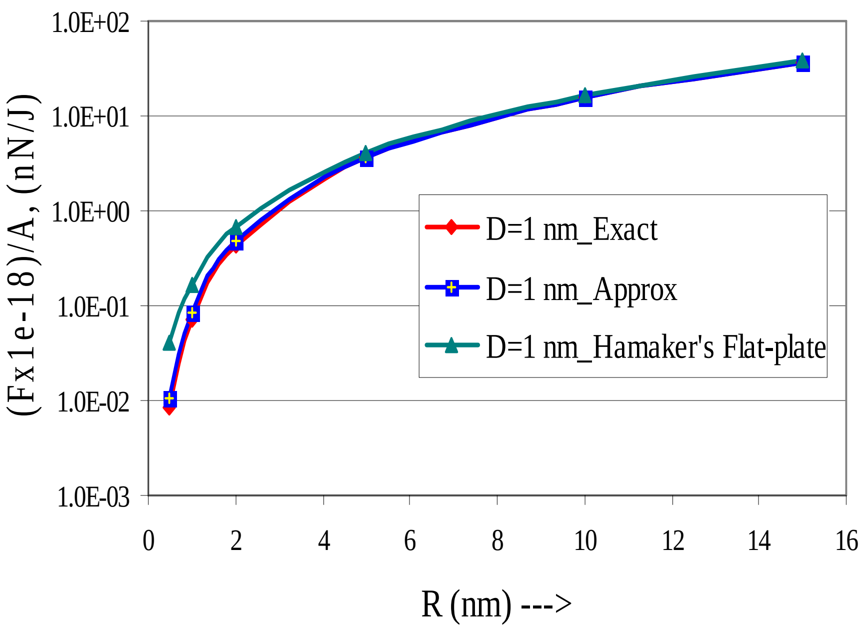
- Provide vdW-dominated region
- No analytical expression available

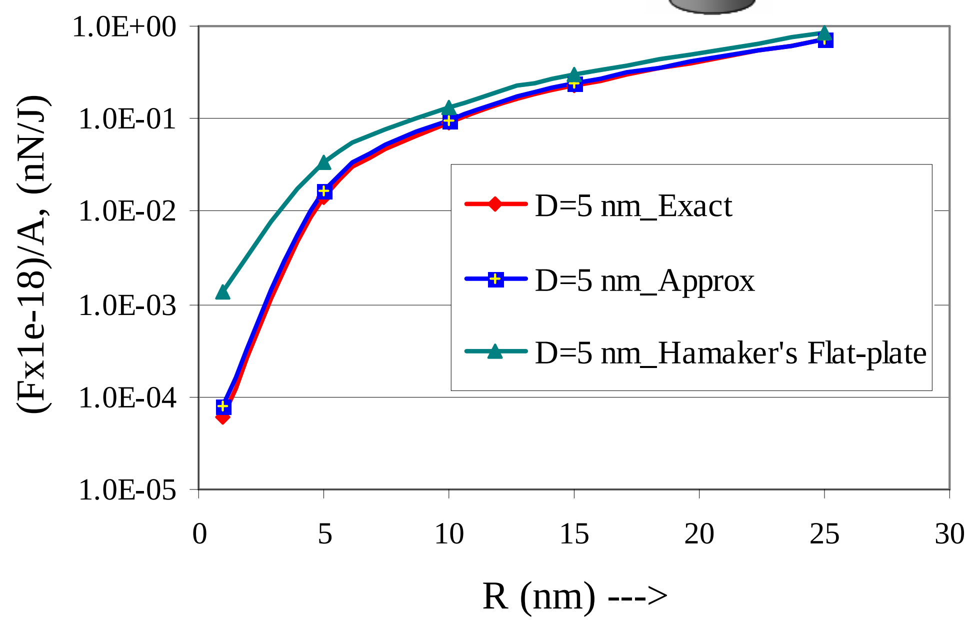
✓Analytical expressions for these interactions are required to reduce computation time

Validation of the Derived vdW Force Expression

- **A comparison of approximated and exact solution**





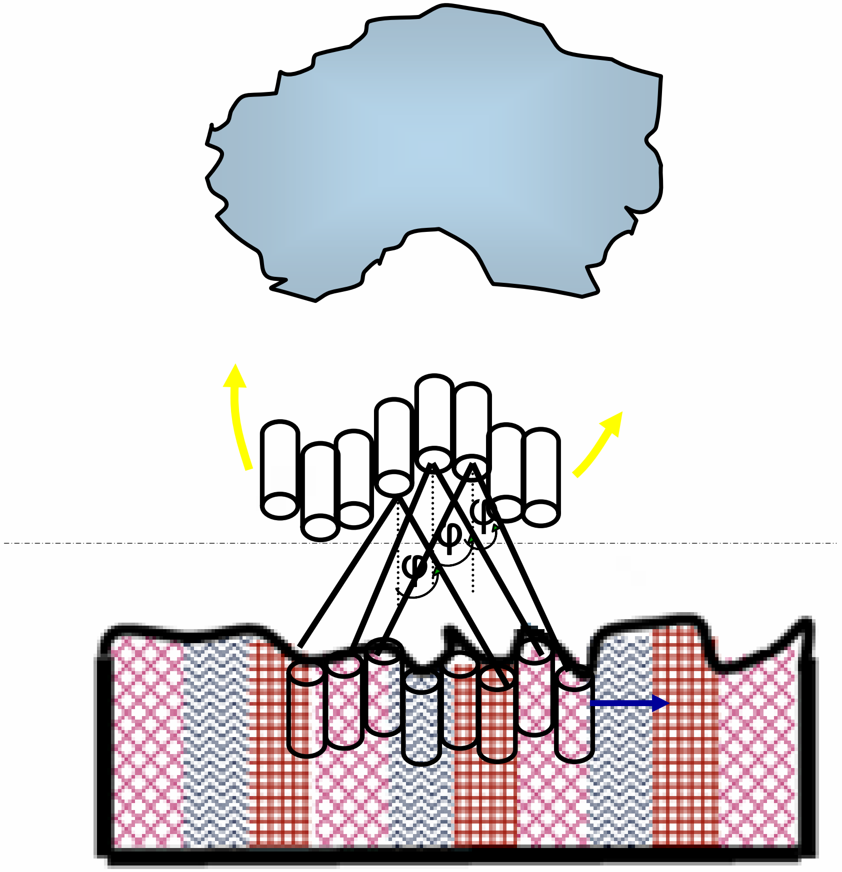


- Derived analytical expression matches well with exact solution obtained numerically
- Hamaker's flat plate approximation can not be used for fine mesh size in vdW force calculation

Proposed Modeling Approach

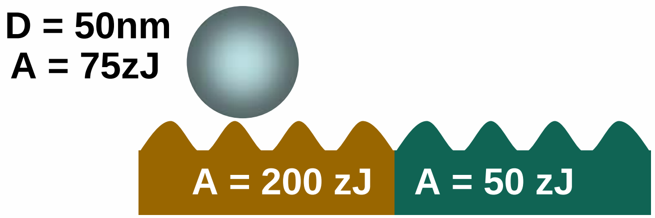
- **vdW Force**

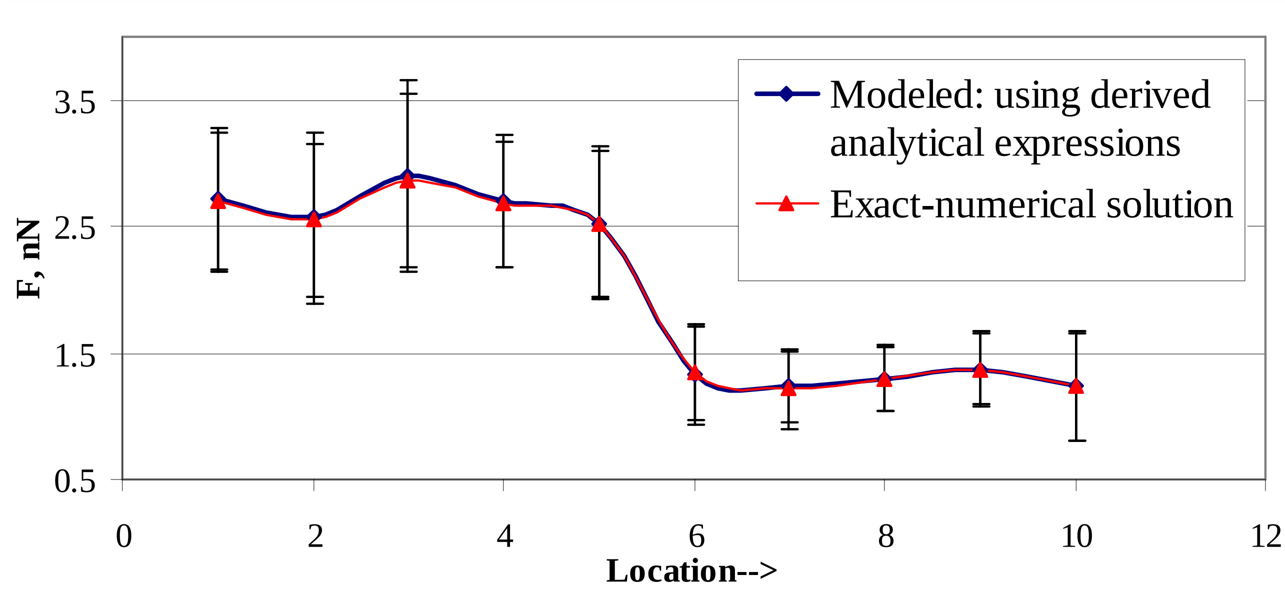
$$F_{12} = -C\frac{\partial}{\partial D}\iiint d\forall_2 \iiint \frac{d\forall_1}{r'^6} = \sum_i \sum_{\forall j(\varphi)} F_{ij}$$



Validation

- **Theoretical validation of modeling approach**
  - Smooth sphere and flat plate with defined roughness





- Derived approximate analytical expressions with proposed modeling approach give similar result as the exact numerical solution
- Force measurement between nanoparticles and patterned surface – In process

Conclusions

- **Continuum vdW force models can be applied from micron- to nano-scale**
- **A finite volume methodology has been identified to describe nanopatterned regions**
  - Validated theoretically
  - Experimental work still underway

Acknowledgments

- **Financial Support Provided By**
  - Purdue Shreve Trust
  - Intel
  - NSF ERC for Structured Organic Particulate Systems (C-SOPS)