LECTURE 17: NANOMECHANICS AND BIOCOMPATIBILITY : PROTEIN-BIOMATERIAL INTERACTIONS

Outline :

Objectives: To establish a fundamental qualitative and quantitative scientific foundation in understanding the biocompatibility of biomaterials implanted *in vivo*

Readings: Course Reader Documents 29, 30

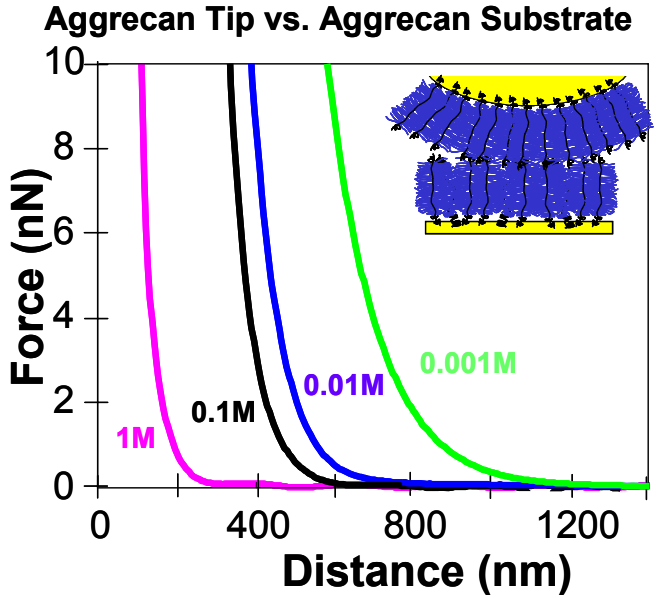
Multimedia : Polymer Brush Demos

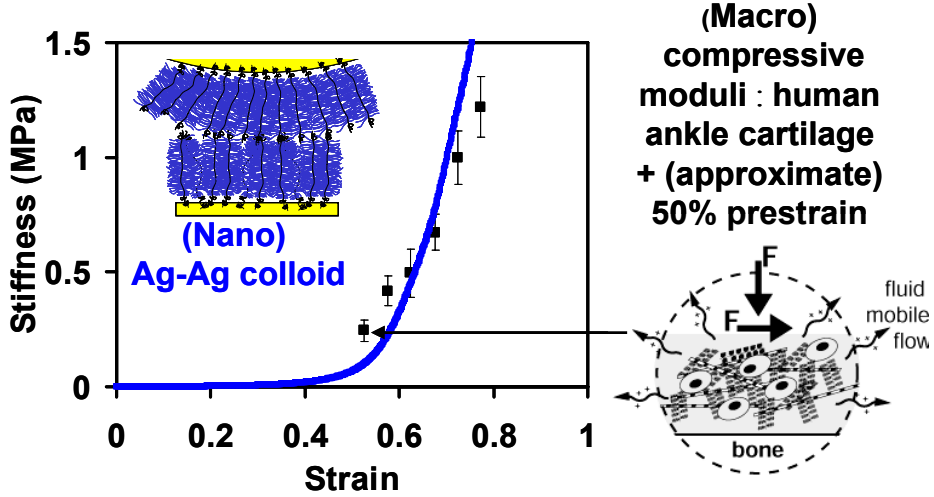
REVIEW : LECTURE 16 NANOMECHANICS OF CARTILAGE

-**Definitions**; articular cartilage function and structure, proteoglycan, aggrecan, hyaluronan, link protein, collagen, chondrocyte, glycosaminoglycan (GAG), chondroitin sulfate

- **Loading Conditions** : withstands ~3 MPa compressive stress and 50% compressive strain (static conditions), equilibrium compressive moduli ~0.1-1MPa

- **Composition** : 80% HOH, collagen (50-60% solid content, mostly type II), aggrecan (30-35% solid content), hyaluronan, ~3-5% cartilage cells (chondrocytes)





● stiffens nonlinearly with increasing strain at the molecular level→ mechanism to prevent large strains that could result in permanent deformation, fracture, or tearing.

- Force vs. Distance converted into Stress, $\sigma = \frac{F}{A_s}$, where A_s= surface interaction area vs. Strain $\varepsilon = \frac{L_f}{L_o} - 1 = \frac{D}{h_o(\text{aggrecan})} - 1$

where h_o(aggrecan)= initial uncompressed height of aggrecan (zero force), Stiffness $= \left(\frac{d\sigma}{d\varepsilon}\right)_{\varepsilon \to 0}$

BIOCOMPATIBILITY OF MATERIALS IMPLANTED *IN VIVO*: DEFINITIONS

Biocompatibility : the ability of a material to perform with an appropriate host response in a specific application, a material that does not producing a toxic, injurious, or immunological response in living tissue; no irritation, inflammation, thrombosis, allergic reactions, coagulation, cancer

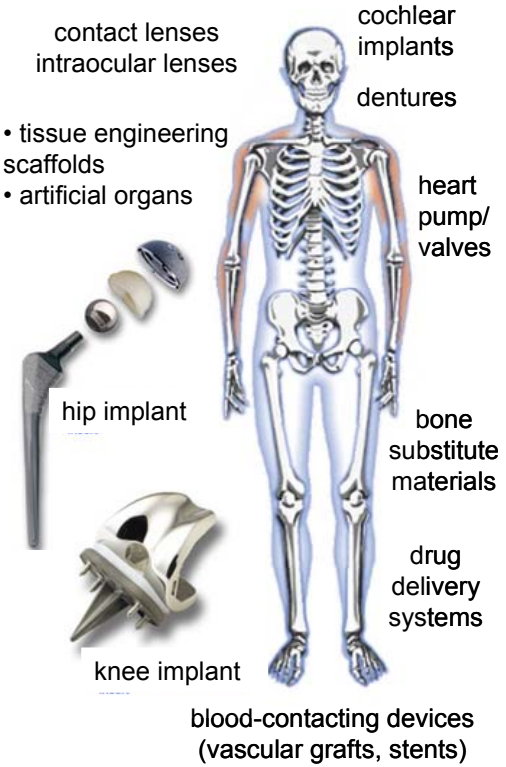
Bioinert - Biomaterials that elicit little or no host response, in terms of nanomechanics a net zero (or close to zero) surface potential with physiological environment, sometimes called "non-fouling"

Interactive or Bioactive- Biomaterials designed to elicit specific, beneficial responses, e.g. ingrowth, bioadhesion.

> **Bioadhesion** : may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. The biological substrate may be cells, bone, dentine, or the mucus coating the surface of a tissue. If adhesive attachment is to a mucus coating, the phenomenon is sometimes referred to as **mucoadhesion**. e.g. cell-to-cell adhesion within a living tissue, wound dressing, and bacteria binding to tooth enamel.

Viable - incorporating live cells at implantation, treated by the host as normal tissue matrices and actively resorbed and/or remodeled

Biofilm : When a biomaterial is exposed a physiological environment the resulting a complex aggregation that may contain biomacromolecules, cells, bacteria, microorganisms



Biomaterial, Biomedical Materials : nonliving (artificial) material intended to interact with a living (biological) system, replacement for “broken” anatomical parts or physiological systems

Examples of Biomaterials; medical implants, heart valves, vascular grafts, contact lenses**,** drug delivery systems**,** scaffolding for tissue regeneration, breast implant, hip joint

TEMPORAL BIOLOGICAL RESPONSES TO IMPLANTED BIOMATERIALS

• living materials respond rapidly to foreign materials (<1 s)

• new layer of protein coats (isolates) biomaterial surface (minutes)

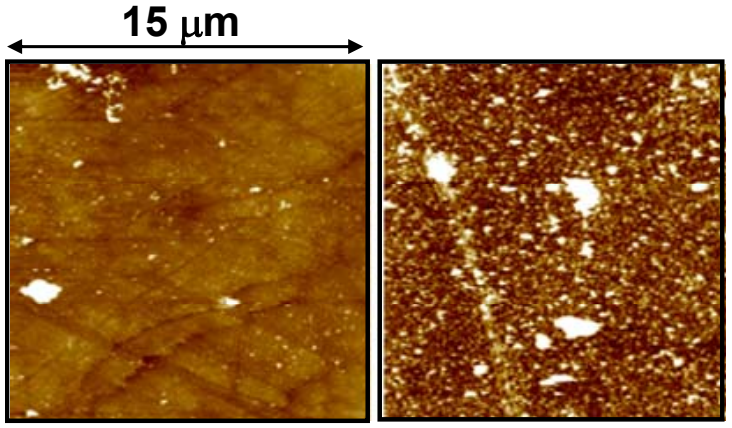
• attachment of platelets, bacteria, yeasts, and additional proteins to surface (minutes-hours)

• alteration in cell and tissue behavior (minutes-years)

Host Effects :
Blood Clots and Thrombosis
Inflammatory Response
Immune Rejection
Fungal Infections and Diseases
Irritation and Inflammation

Biomaterial Degradation
Abrasive Wear
Fatigue
Stress-Corrosion Cracking
Absorption from Biofluids
(*chemical attack)
Mechanical Failure

Fresh out of box after a few minutes



TappingMode AFM images in saline of the convex face of commercial PHEMA soft contact lenses. Fresh "out of the box" contact lens (left) displays scratches on the surface that originate from the mold during the manufacturing process. The scratches are 5 to 10nm in depth and 150 to 850nm in width. Several large isolated features (130 to 250nm in height) are also observed. The RMS roughness on the surface is 14nm. Used contact lens (right) of the same exact type and brand in the left image. The lens surface is coated with particulate adsorbates. A scratch-like feature is visible running top to bottom in the image, and appears decorated with contaminants. The RMS roughness on the surface is 30nm. Scan size for both images is 15μm and z range is 160nm (Veeco, Inc)

BLOOD-BIOMATERIAL INTERACTIONS

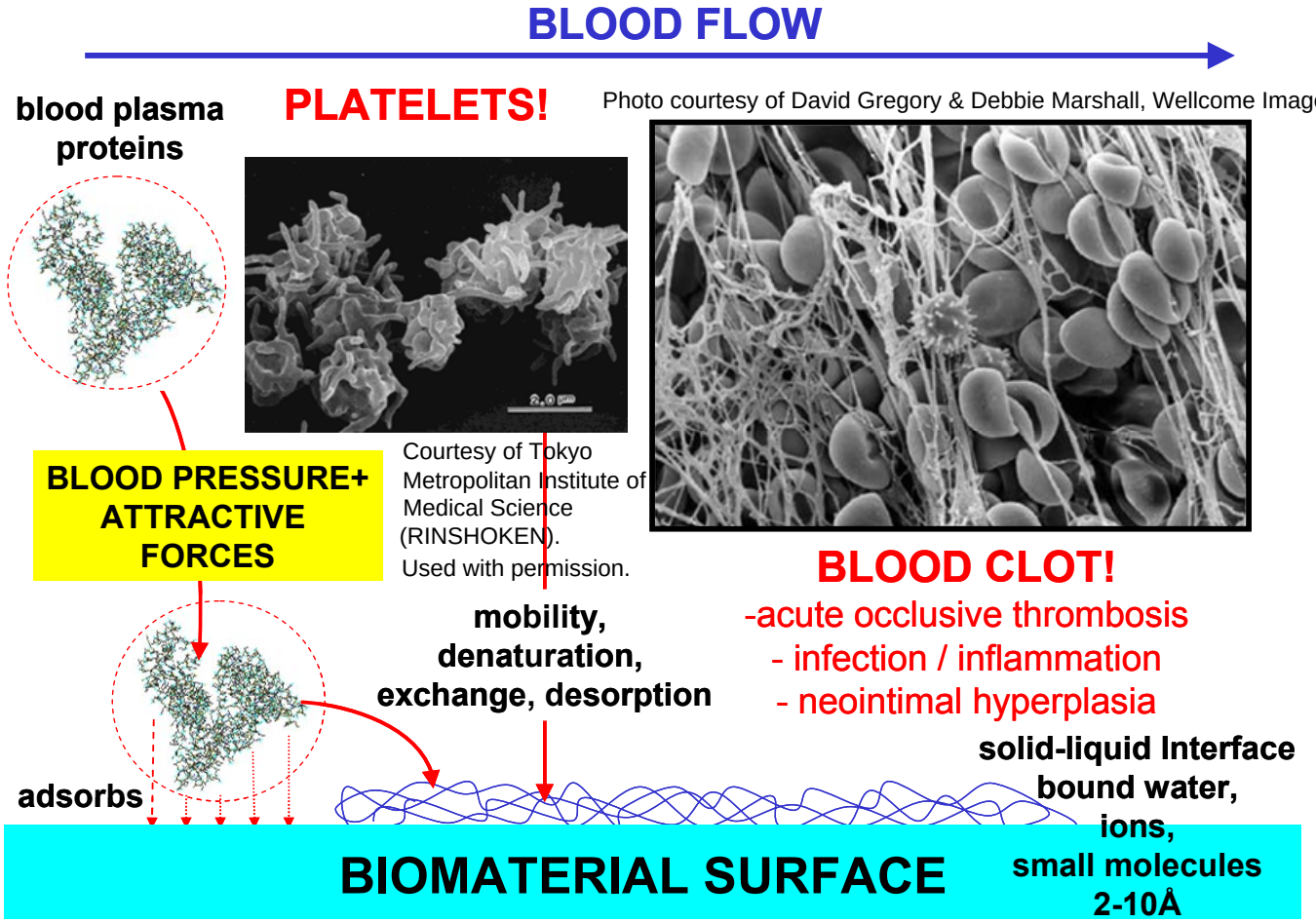
Blood Compositions and Solution Conditions :

pH7.15 - 7.35
IS=0.15 M
Temperature ~37°C

-cells and platelets (~45 wt.%)

The liquid portion of the blood, the plasma or serum (55 wt. %), is a complex solution containing more than 90% wate

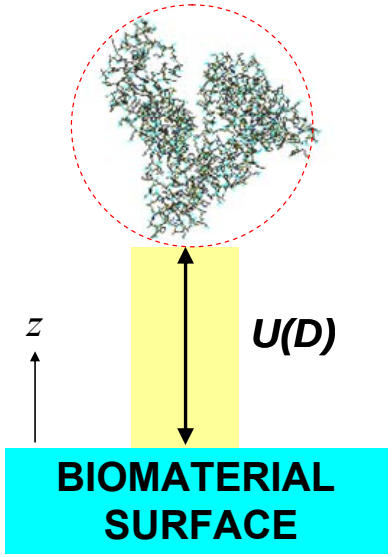
- 6-8 wt.% proteins in plasma (over 3,000 different types), including :
-58% albumins
-38% globulins
-4% fibrinogens



-The majority of blood plasma proteins are net negatively charged. Each has its' own heterogeneous surface chemistry and unique intermolecular potential with biomaterial surface that changes and evolves with time *in vivo*.
→ **want bioinert surface**

KINETICS OF PROTEIN ADSORPTION

Molecules can be brought to the surface by diffusion; (I. Szleifer, Purdue University)



$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial z^2}; C = concentration, D = diffusion\ coefficient, z = distance, t = time$$

$$\frac{\partial \rho_{protein}(z,t)}{\partial t} = D\left[\underbrace{\frac{\partial^2 \rho_{protein}(z,t)}{\partial z^2}}_{\text{Ideal diffusion-controlled regime controlled only by density gradient}} + \underbrace{\frac{\partial}{\partial z}\left(\rho_{protein}(z,t)\frac{\partial U_{mf}(z,t)}{\partial z}\right)}_{\text{Kinetically activated regime, "driven" diffusion, motion that arises from surface-protein interactions}}\right]$$

$\rho_{protein}(z,t) = local\ density\ of\ protein\ molecules$

$U_{mf}(z,t) = net\ "potential\ of\ mean\ force"\ including\ protein\text{-}surface\ potential$

$\rightarrow more\ complex\ theories\ take\ into\ account\ protein\text{-}protein\ interactions\ and\ protein\ conformational\ changes$

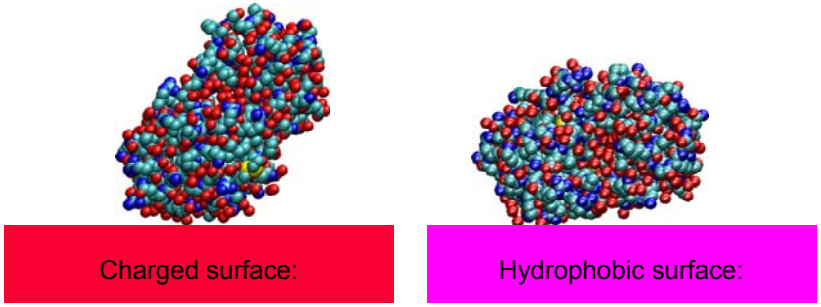
$U_{mf}(z,t)$ - can have many different components, both attractive (e.g. hydrogen, ionic, van der Waals, hydrophobic, electrostatic) and repulsive (e.g. configurational entropy, excluded volume, osmotic, enthalpic, electrostatic, hydration), can lead to complex interaction profiles, will change if conformation of protein changes

- Initial protein adsorption will be determined by longer range, larger spatial length scale of averaged surface properties (e.g. average surface charge per unit area→EDL)

- Secondary stages of protein adsorption depend on shorter range biomolecular adhesive binding processes that take place when the protein is in close contact with the surface (e.g. the conformation, orientation, and mobility of the adsorbed proteins, the time scale of conformational changes, protein exchange and desorption, and interactions of adsorbed proteins with each other).

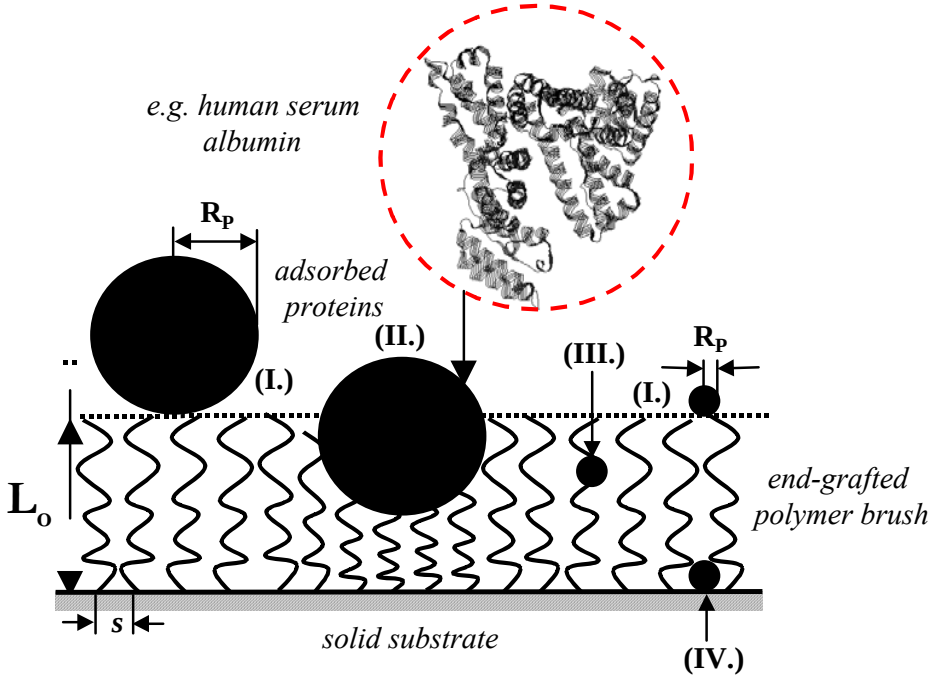
USE OF STERIC REPULSION TO INHIBIT PROTEIN ADSORPTION

(I. Szleifer, Purdue University)



Charged surface:	Hydrophobic surface:
proteins expose charged groups.	proteins expose hydrophobic patches.

Courtesy of Igal Szeilfer. Used with permission.



→ generally can't use charged surface EDL repulsion as a mechanism to inhibit protein adsorption

→ one method: use steric repulsion of surface functionalized (chemisorption, physisorption) with polymers

Modes of protein adsorption:
(I.) adsorption of proteins to the top boundary of the polymer brush
(II.) local compression of the polymer brush by a strongly adsorbed protein
(III.) protein interpenetration into the brush followed by the non-covalent complexation of the protein and polymer chain
(IV.) adsorption of proteins to the underlying biomaterial surface via interpenetration with little disturbance of the polymer brush

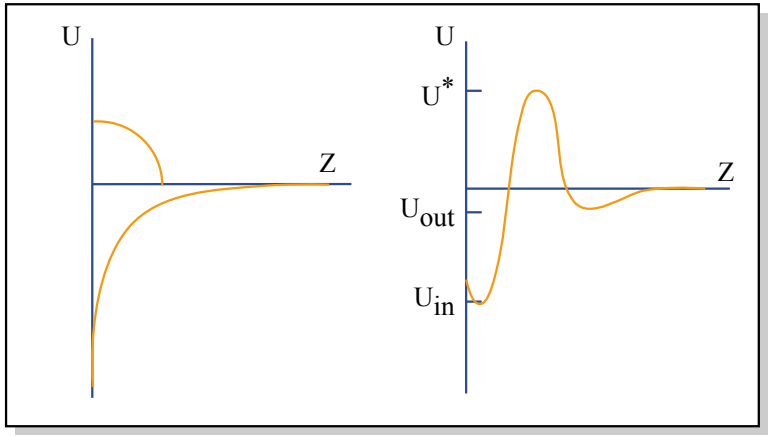


Figure by MIT OCW.
After Halperin, *Langmuir* 1999.

THERMAL MOTION OF POLYMER BRUSHES : MOVIES

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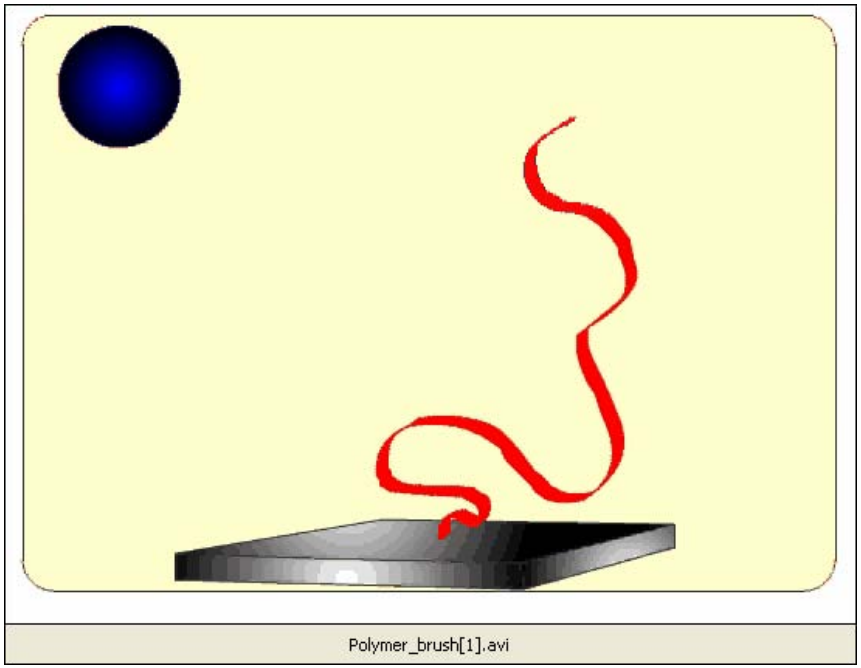
Screenshot from http://www.lassp.cornell.edu/marko/thinlayer.html.



Courtesy of Prof. Jan Hoh. Used with permission.

(right) : (*J. Hoh (John Hopkins U) : *http://www.hohlab.bs.jhmi.edu/index.html)*

POLY(ETHYLENE OXIDE) AS A BIOINERT COATING

The most extensively used polymer for biomaterial surface coatings:

- **hydrophilic** and **water-soluble** at RT

-forms an extensive **H-bonding** network; intramolecular H- bond bridges between -O- groups and HOH→ large excluded volume

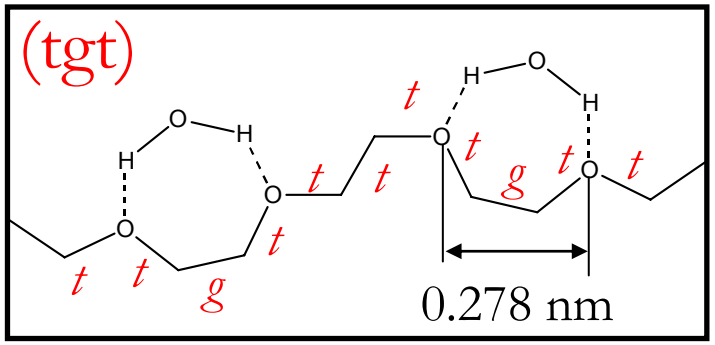
-• locally (7/2) **helical supramolecular structure** (tgt axial repeat = 0.278 nm)

-high **flexibility**, molecular **mobility**

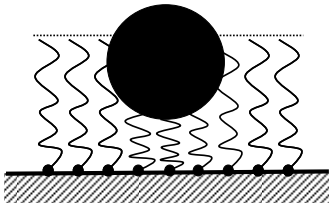
-**low van der Waals attraction**

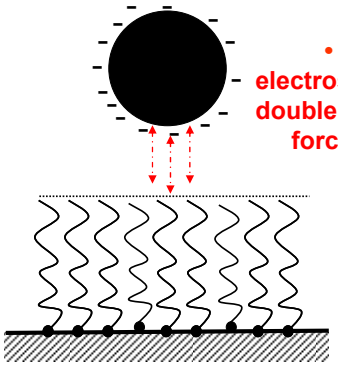
• **neutral**

However:
-poor mechanical stability
-protein adhesion reported under certain conditions (long implant times)
-maintains some hydrophobic character



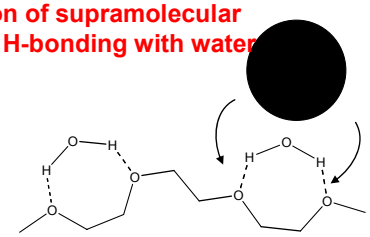
• steric (large excluded volume)





• electrostatic double layer forces

• hydrophilic/ water soluble : hydration enthalpic penalties for disruption of supramolecular structure H-bonding with water



• high flexibility & mobility : no local steric or charge

• neutrality : won't attract oppositely charged species