LECTURE 18: NANOMECHANICS AND BIOCOMPATIBILITY : PROTEIN-BIOMATERIAL INTERACTIONS 2

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 17 NANOMECHANICS AND BIOCOMPATIBILITY : PROTEIN-BIOMATERIAL INTERACTIONS

Definitions : biocompatibility, bioinert, bioactive, bioadhesion, biofilm→ example of biomaterials
Temporal biological response to materials implanted in vivo; Host effects vs. Biomaterial Effects
• 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)

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**

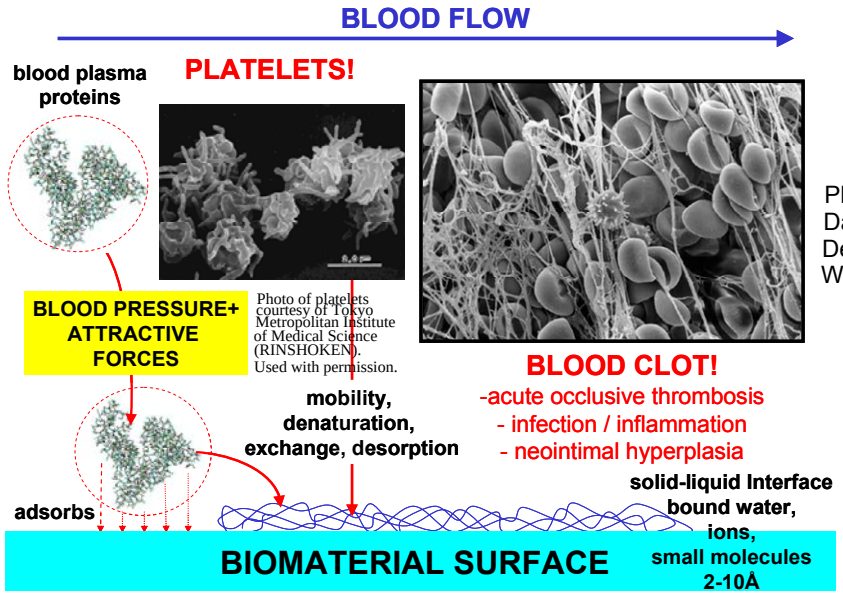

Photo courtesy of David Gregory & Debbie Marshall, Wellcome Images.

EXAMPLE OF A BIOMATERIAL : VASCULAR GRAFTS

Vascular graft : prosthetic tube that acts either a permanent or resorbable artificial replacement for a segment of a damaged blood vessel (e.g. from atherssclerosis, aneurysms, organ transplant, cancer, arteriovenous fistula, diabetes) : $200 million market worldwide

Zhang, et al. J. Biomed. Mtls. Res.60(3), 2002, 502.

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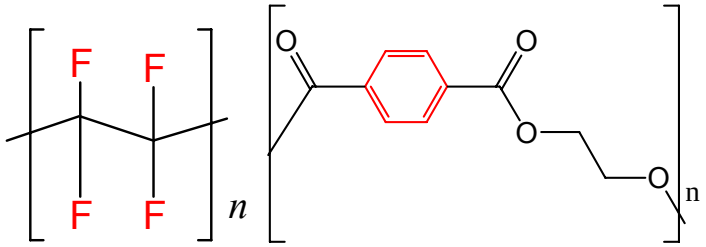
• **expanded polytetrafluoroethylene (Gore-Tex, ePTFE)**
-fibrillated, open cell, microporous (pore size 0.5-30 mm), 70% air, nonbiodegradable, chemically stable, used for 26 yrs, hydrophobic/ nonpolar, flexible

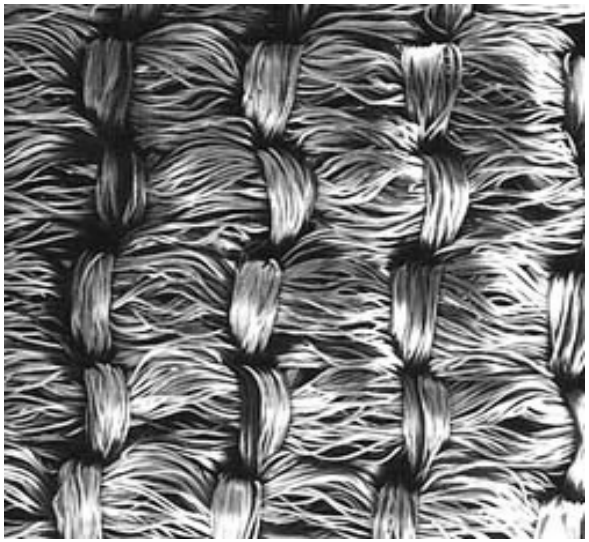


• **polyethylene terephthalate (Dacron, PET)**
-multifilamentous yarn fabricated by weaving/knitting, amphiphilic, smaller pores than ePTFE

• **polyurethane derivatives**

• **bovine collagen** -fibrous, hydrophilic

- **Other design considerations** : proper mechanical properties (modulus, strength), to avoid bursting, kinking, leaking, avoid fraying easy manipulation during surgery



www.vascutek.com

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2nd EXAMPLE OF A BIOMATERIAL : ENDOTRACHEAL TUBE (ETT)

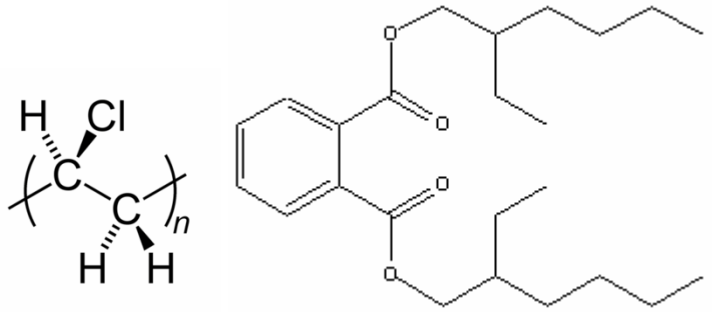
-ETT is a polymeric conduit between the lungs and a ventilator and is used to form a closed system of pulmonary ventilation necessary to maintain optimal respiration, as well as protect the lungs from any foreign material that may be aspirated into the trachea. Most often used in critical intensive care situations to allow the delivery of air to the patient. Insertion of the tube is called **Intubation**, most often used in critical intensive care situations.

-Intubation usually requires general anesthesia and muscle relaxation but can be achieved in the awake patient with local anaesthesia or in an emergency without any anaesthesia, although this is extremely uncomfortable and generally avoided in other circumstances.

-In 2002, there were 30 million intubations.

Diagram of endotracheal tube in use removed due to copyright restrictions.
http://www.nellcor.com/

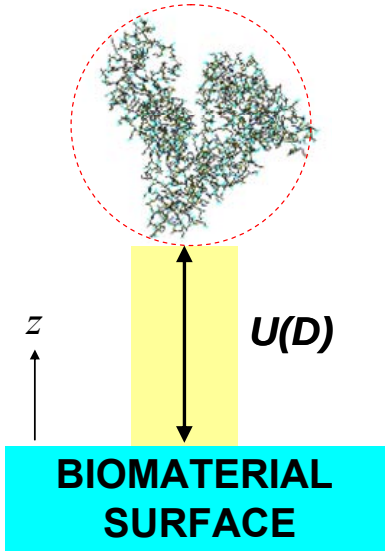
ETTs are made of Poly(vinyl chloride) + 30-40 wt. % of low molecular weight plasticizers, di-ethylhexyl phthalate (DEHP), also referred to as di-octylphthalate (DOP).



-vinyl monomers and DEHP potential carcinogens, irritant of mucus membranes (DEHP leaches out), damage to trachea begins immediately

KINETICS OF PROTEIN ADSORPTION

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



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

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

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

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

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

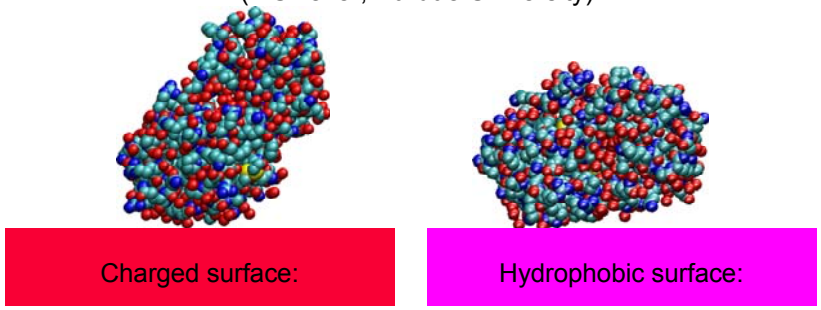
$U_{mf}(z,t)$ - can have many different components, both attractive (e.g. hydrogen, ionic, van der Waals, hydrophobic, electrostatic) and repulsive (e.g. configurational entropy, excluded volume, osmotic, enthalpic, electrostatic, hydration), can lead to complex interaction profiles, will change if conformation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

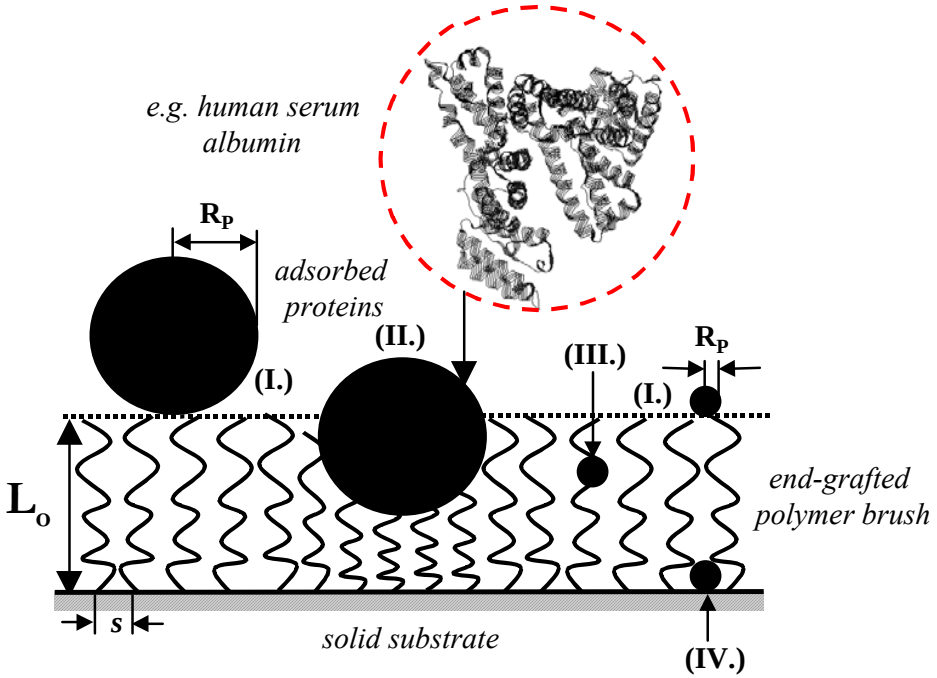
- Secondary stages of protein adsorption depend on shorter range biomolecular adhesive binding processes that take place when the protein is in close contact with the surface (e.g. the conformation, orientation, and mobility of the adsorbed proteins, the time scale of conformational changes, protein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

USE OF STERIC REPULSION TO INHIBIT PROTEIN ADSORPTION

(I. Szleifer, Purdue University)



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

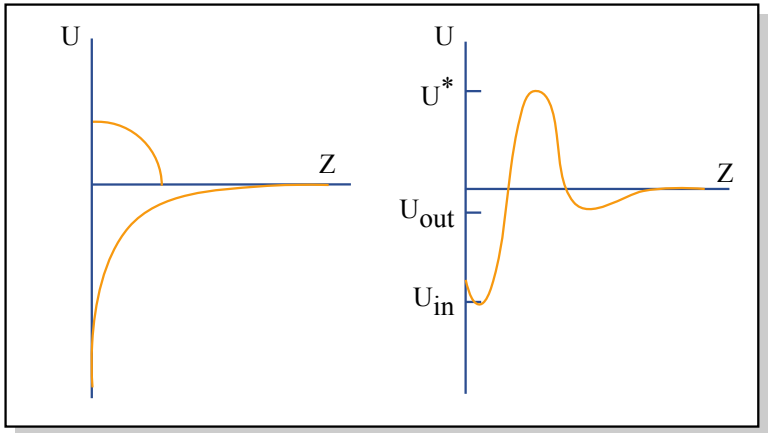


Figure by MIT OCW.
After Halperin, *Langmuir* 1999.

THERMAL MOTION OF POLYMER BRUSHES : MOVIES

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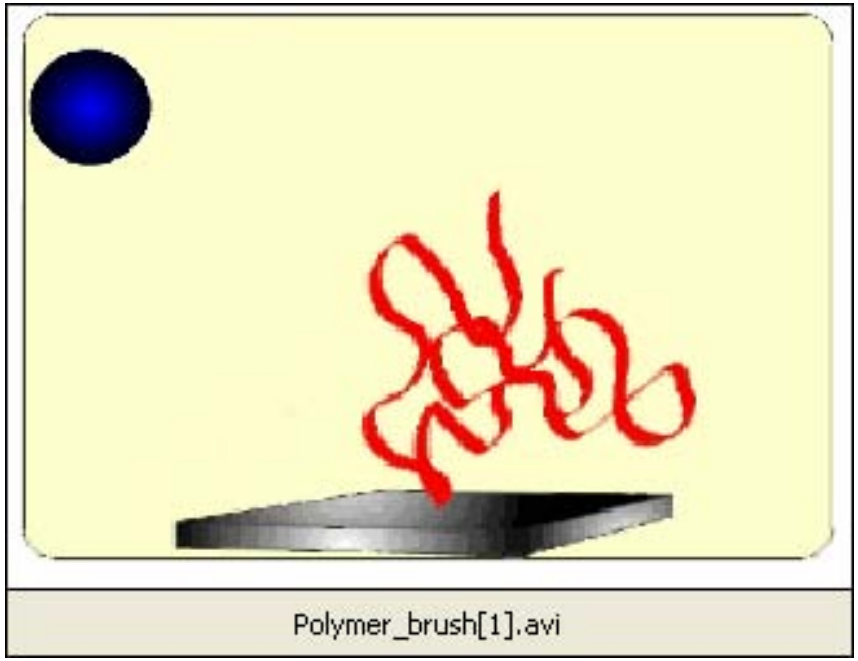
Screenshot from http://www.lassp.cornell.edu/marko/thinlayer.html.



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

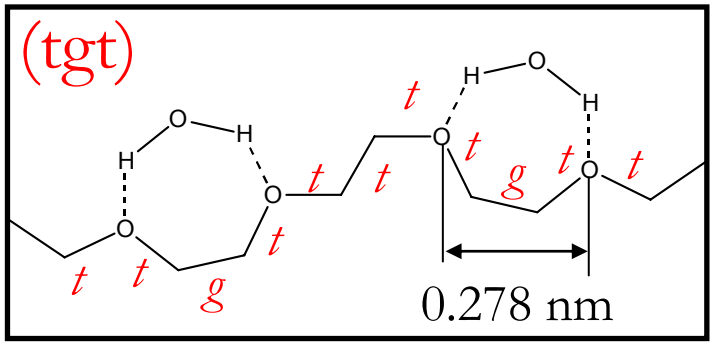
-• locally (7/2) **helical supramolecular structure** (tgt axial repeat = 0.278 nm)

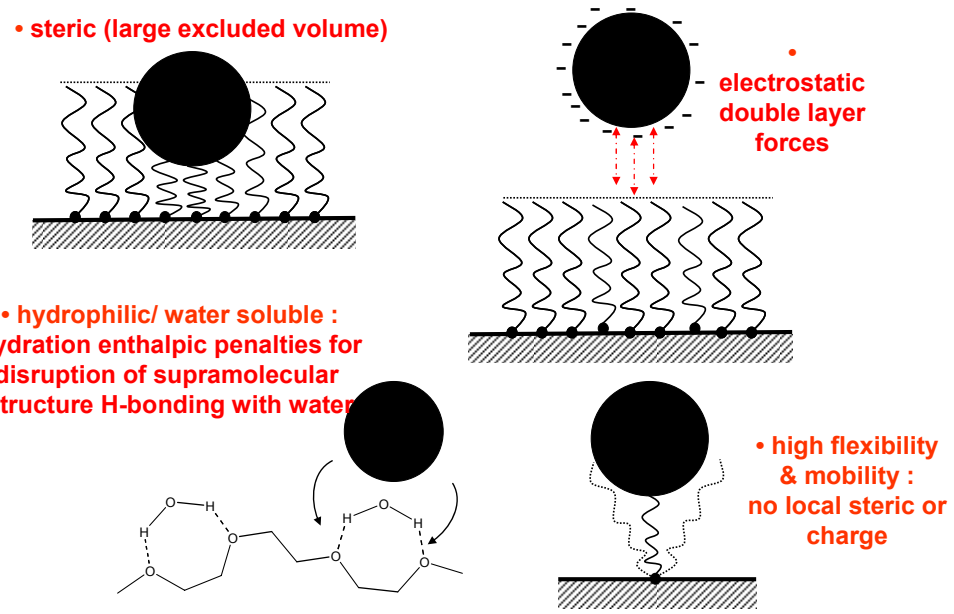
-high **flexibility**, molecular **mobility**

-**low van der Waals attraction**

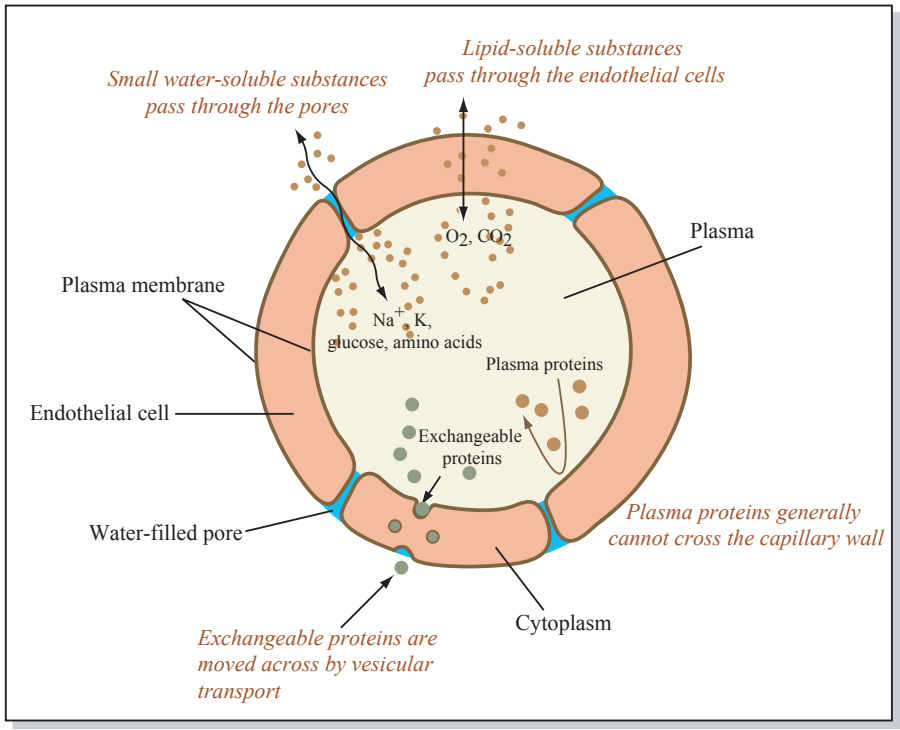
• **neutral**

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





BLOOD VESSELS The outer component of a cell surface; usually contains strongly acidic sugars, hence it carries a negative electric charge. A thick endothelial glycocalyx provides the endothelial surface with a nonadherent shield, during inflammation, it reduces in size to allow adhesion of leukocytes.



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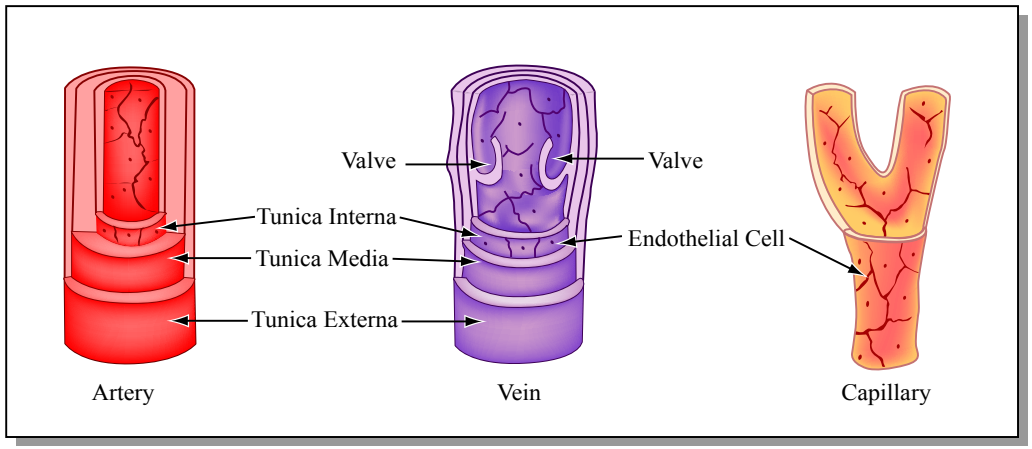

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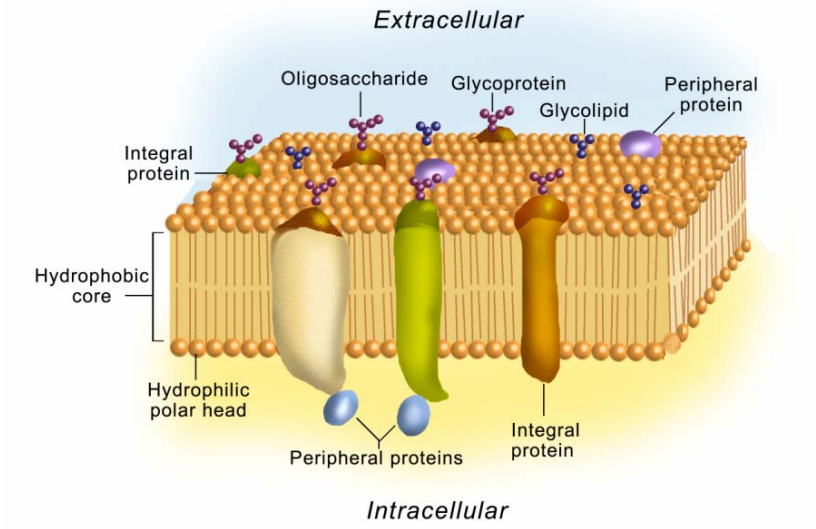
Fig. 10-44 in Alberts, *Molecular Biology of the Cell*, 4th ed.
Photo showing structure of glycolcalyx, cytosol, nucleus and plasma membrane.



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