Nanotechnology

Sergei Vyboishchikov

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Classes in classroom PB-24

4 hours of lectures per week (attendance is not obligatory):

Monday, Tuesday, Wednesday 19:00–20:07

EVALUATION

Description	Content	Percentage of the total grade	Date
Midterm exam	1st part of the course	50%	~Feb 28, 19:05 PB-24
Final exam	All the course, with emphasis on the 2nd part	50%	Mar 18, 12:00
Recuperation exam	All the course	100%	Apr 1

Exams: Theoretical questions.

Recuperation: The midterm and the final exams are *recuperable in a single* exam that involves the content of the entire course.

Lecture language: English

Exam task problems: English

Language of exam solution: whatever

Tutoring:

- **In-class:** Monday, Tuesday, Wednesday after the class;

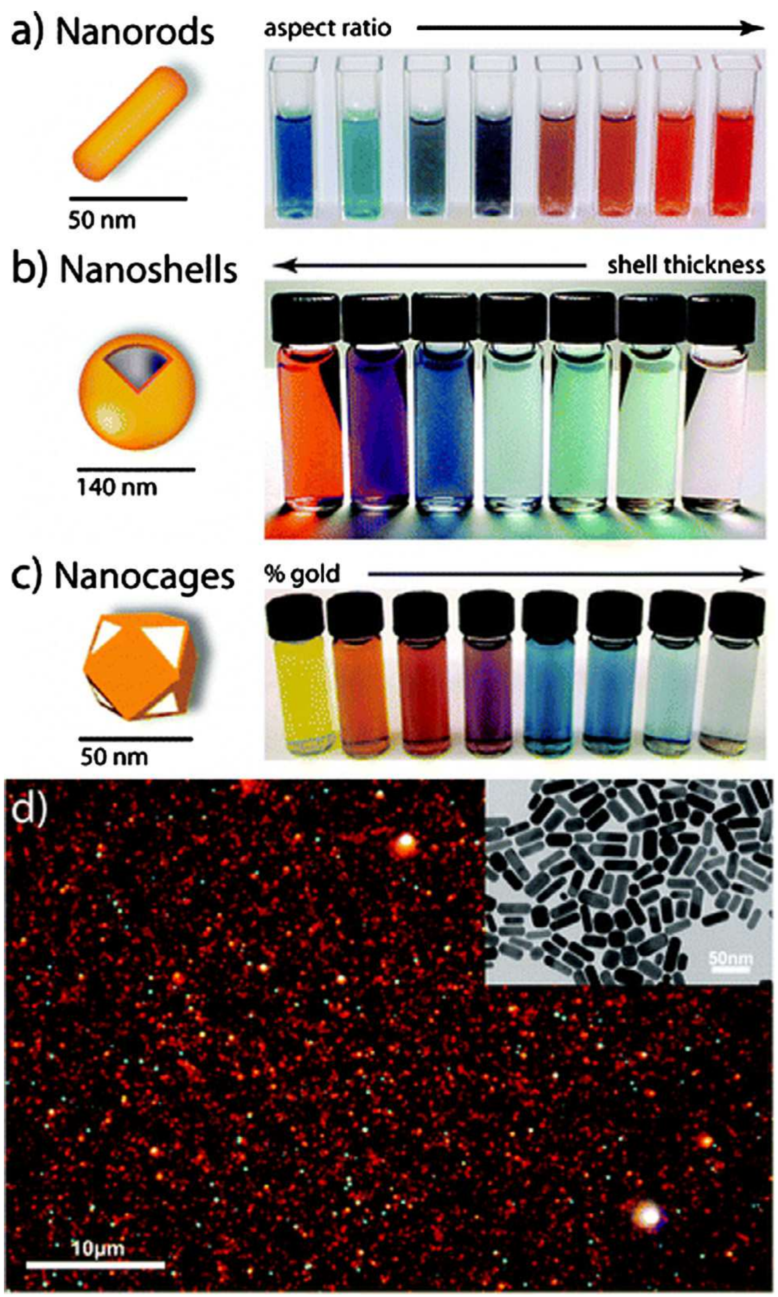
  In-office or **online:** ask for an appointment at sergey.vyboyshchikov@udg.edu

INTRODUCTION TO NANOSCIENCE AND NANOTECHNOLOGIES

νάνος (Greek) = 'dwarf' (*cat.* nan)

- **What are the nanoscience and nanotechnologies?**
  - "*Nanoscience* is the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale".
    - More typically, this means phenomena and properties that are not reducible to those of individual molecules or of the bulk substance.

  - "*Nanotechnologies* are the design, characterization, production, and application of structures, devices, and systems by controlling shape and size at the nanometer scale". Term *Nanotechnology* was coined by Tanigichi in 1974 as "production technology to get the extra high accuracy and ultra fine dimensions, i.e. the preciseness and fineness on the order of 1 nm in length".



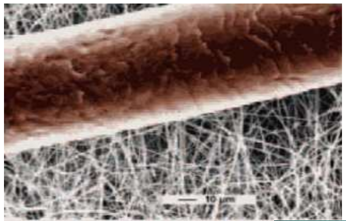
Color dependence of gold nanoparticles on size, shape, and composition

Course chapters:

- General introduction to nanoscience and nanotechnology
- Overview of nanomaterials.
- Nanomaterials – fabrication 1 (nanoparticles and nanomaterials fabrication)
- Nanomedicine / Nanopharmacology
- Methods of studying nanomaterials
- Sensors
- Nanomaterials – fabrication 2 (semiconductors)

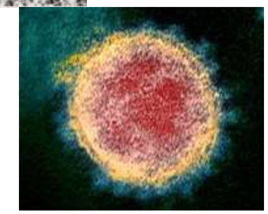
NANOMETER SCALE

A nanometer is about the size of ten atoms in a row

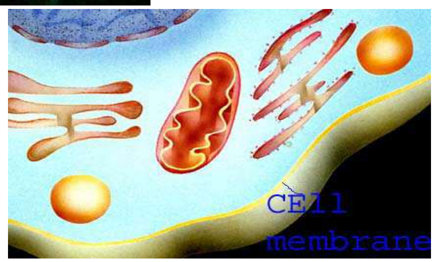


Human hair: 70000 – 100000 nm width

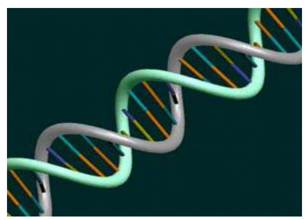
1 nm = 10^{-9} m = 10^{-6} mm = = 10^{-3} µm = 10 ångström



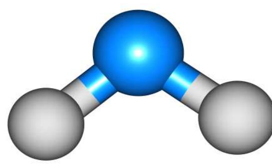
Viruses: 20–500 nm (SARS-CoV-2: 120 nm) diameter



Cell membrane: 6–10 nm thick



DNA: 3 nm diameter



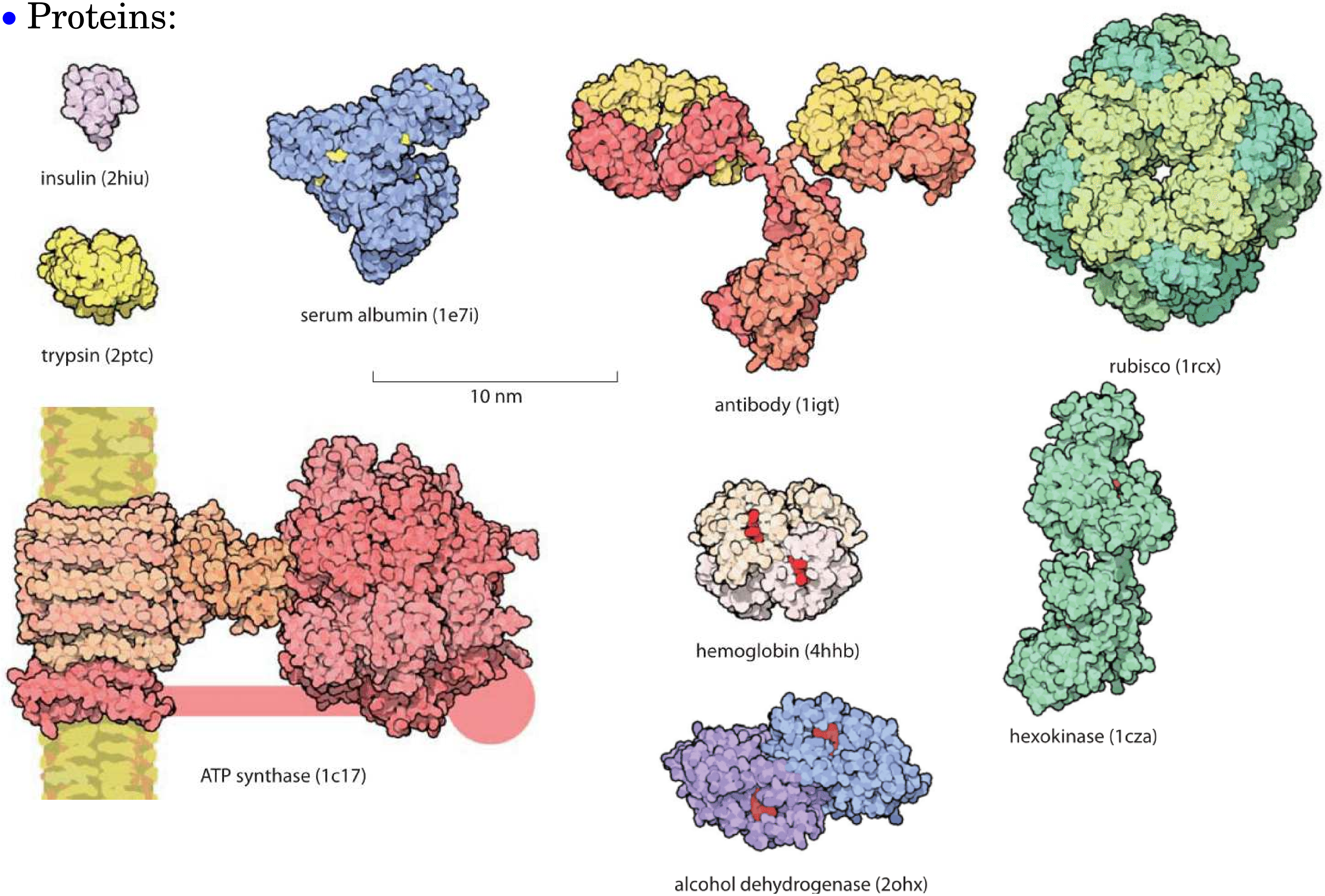
Water molecule – 0.3 nm width

Nanosize: 1 – 100 nm in diameter (typically), but can be larger

7 Huge molecules examples with nice pictures:
https://www.laborpraxis.vogel.de/7-aussergewoehnliche-riesenmolekuele-gal-9198

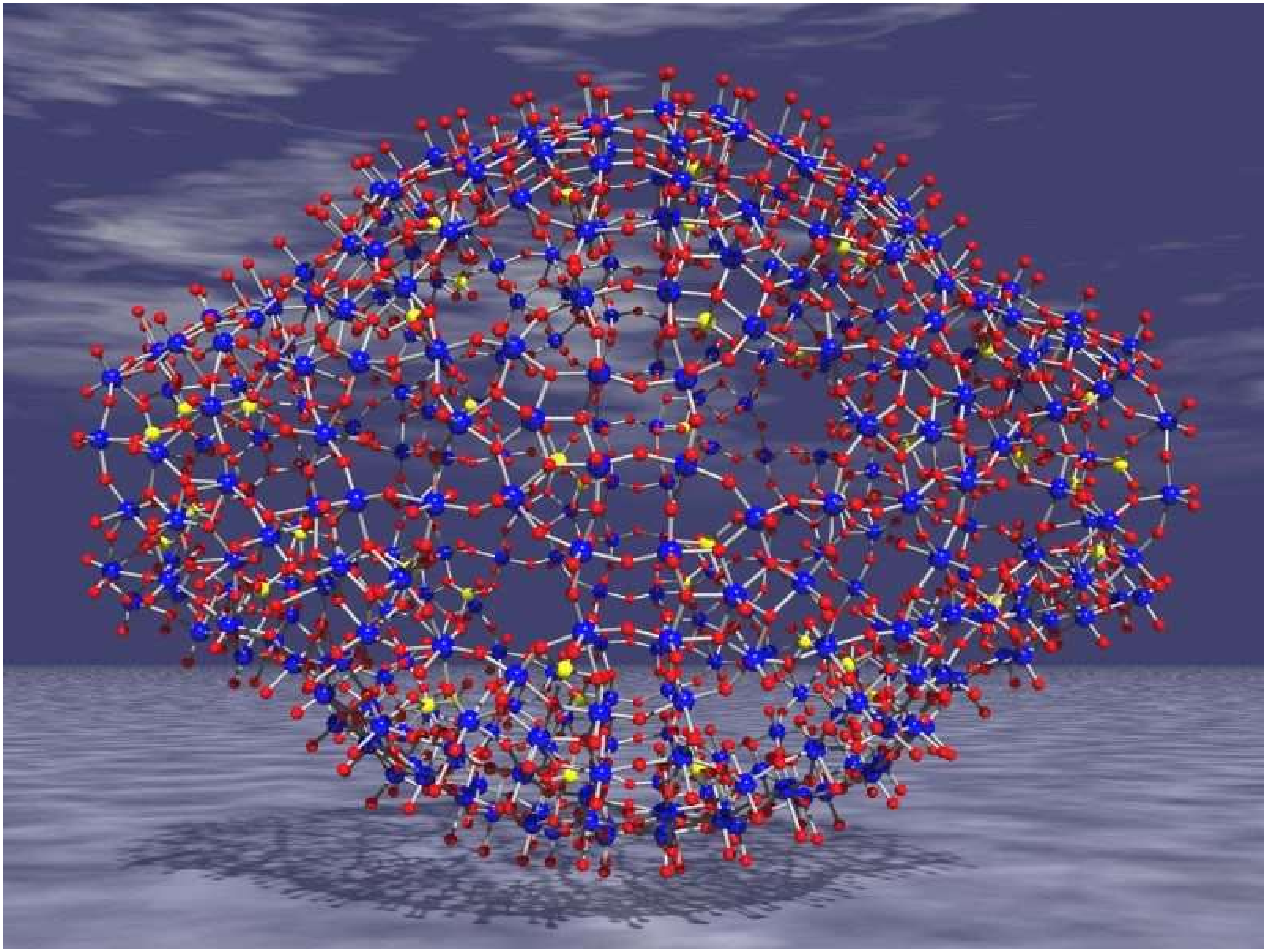
NANOMATERIAL SIZES

- Proteins:



Titin (connectin) (in muscular cells): up to 1000 nm, ~3000 amino acid residues

NANOMATERIAL SIZES

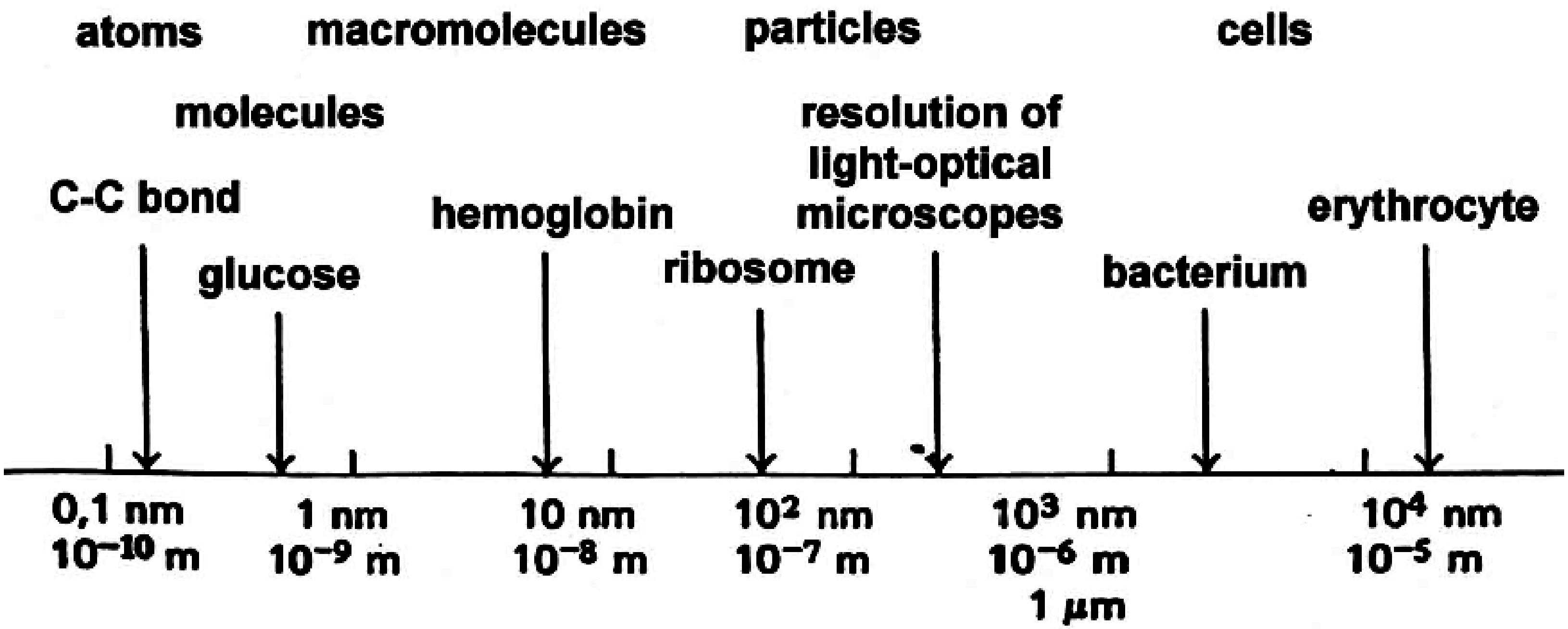


“Nano-hedgehog” ($Mo_{368}O_{1464}H_{480}S_{48}$) – the largest inorganic molecule: ~6 nm

NANOMATERIAL SIZES

- **Visible light wave length = 380** to **750** nm

► Nanoparticles are smaller in size than the wave length of the visible light
$\Rightarrow$ light microscopy is of no use for studying nanoparticles



- Methods available:
Ultramicroscopy; Transmission Electron Microscopy (TEM); Scanning Electron Microscopy (SEM); Atomic Force Microscopy (AFM); Scanning Tunneling Microscopy (STM); Stimulated Emission Depletion Microscopy (STED), etc.

NANOMATERIAL DIMENSIONS

- Classification of nanomaterials according to their dimensions:

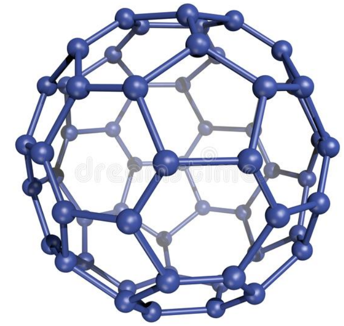
Nanodimensions	**Examples**
3D nano	Nanoparticles, quantum dots, microcapsules, nanoshells, fullerenes, proteins, polysaccharides...
2D nano, (1D macroscopic)	Nanotubes, nanowires, nanofibres
1D nano, (2D macroscopic)	Thin films, layers, and coatings; nanorings; graphene; MXenes

- *Intentionally* and *non-intentionally* produced nanomaterials:
  - ► *Non-intentionally* produced nanomaterials:
    - – Natural: biomacromolecules (proteins, DNA, starch…), viruses, nanoparticles from volcanic eruptions, smokes, milk(?), dust(?)
    - – Human-made: soot nanoparticle, smoke...
  - ► *Intentionally* produced nanomaterials:
    - – Human-fabricated, usually industrially.

ORIGINS OF NANOSCIENCE

- **Mesoscopic physics**:
  A sub-discipline of condensed matter physics which deals with materials and phenomena that have a length scale of between the size of molecules and materials measuring microns, typically 100–1000 nm.
- **Colloid chemistry**:
  A colloidal system = **dispersed phase + continuous phase**
  Particle size: typically 10–200 nm
  Example: milk:
  - casein micelles (~200 nm);
  - fat droplets in milk ~200nm–15 μm
- **Minituarization in technology**:
  Integrated circuits etc.
  Transistor size: ~5 cm (1948); 600 nm (1990); 45 nm (2010); 14 nm (2014); 10 nm (2016); 7 nm (2018) ... in reality bigger (~100×100 nm).
- **Polymer science**
- **Biology/Biochemistry**
  DNA, proteins, viruses, cell membranes…
- **Truly new developments:** Fullerenes, nanotubes,...

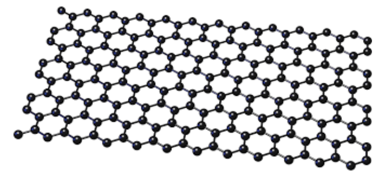
OVERVIEW OF NANOMATERIALS

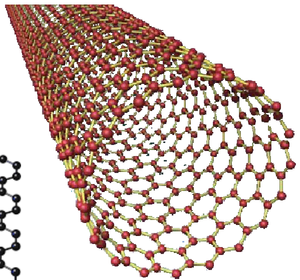


- **Key types of nanomaterials:**

► Fullerenes – allotropes of carbon; hollow clusters of carbon atoms
  – Example: buckminsterfullerene C_{60}

► Carbon nanotubes – allotropes of carbon; hollow tubes of carbon atoms
  – can be single-walled or multi-walled;





► Graphene – a single graphite layer (one-atom thick)
  – unique electronic and mechanical properties;

► Quantum dots – nanosized semiconductor particles:
  – unique electronic properties; used in LED (fluorescence), in nanoelectronics, laser technology, and in nanopharmacology.

► Nanowires – similar to nanotubes (usually *not* carbon), but not hollow.
  – potentially useful in nanoelectronics (lasers, transistors…) and in sensors.

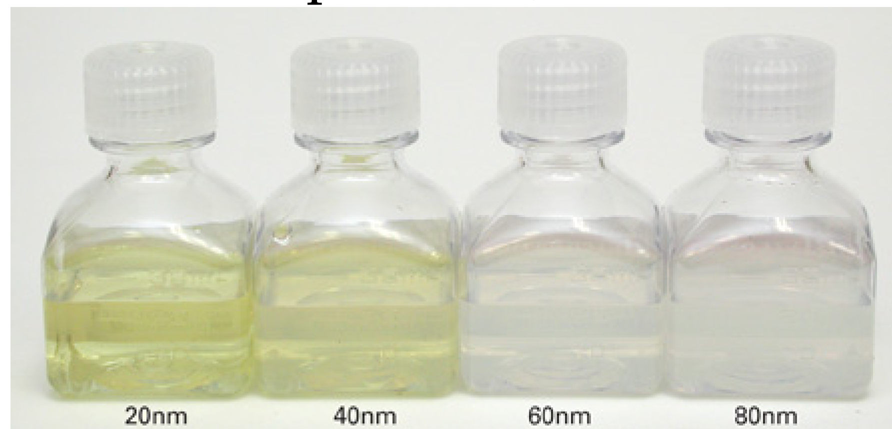
► Zeolites – nanoporous crystalline alumosilicates
  – widely used industrially since a long time as catalysts and adsorbents.

► Metal-organic frameworks (MOF) and Covalent organic frameworks (COF)
  – nanoporous structures – used industrially as catalysts and adsorbents.

► MXenes – 2D metal carbides – used for batteries, supercapacitors, antennas, sensors.

- **Key types of nanomaterials** (*continued*)**:**
  - Colloidal particles:
    - *Metal nanoparticles* (e.g. gold and silver nanoparticles):

gold sols (see page 3)



Silver sols

Particles are *stabilized* and carry overall negative charge.

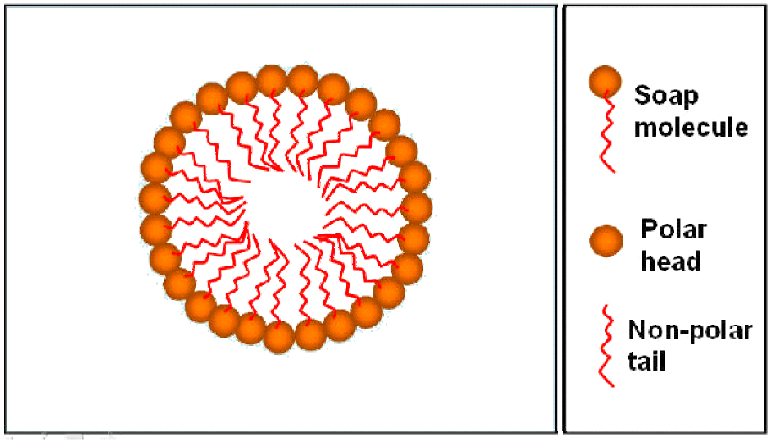
Applications of gold and silver nanoparticles:

sensors (change in optical properties through adsorption on the surface); can be attached to proteins, thiols, and DNA.

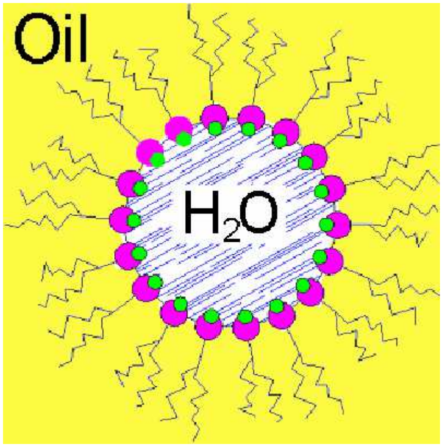
Silver sols have a strong antibacterial activity.

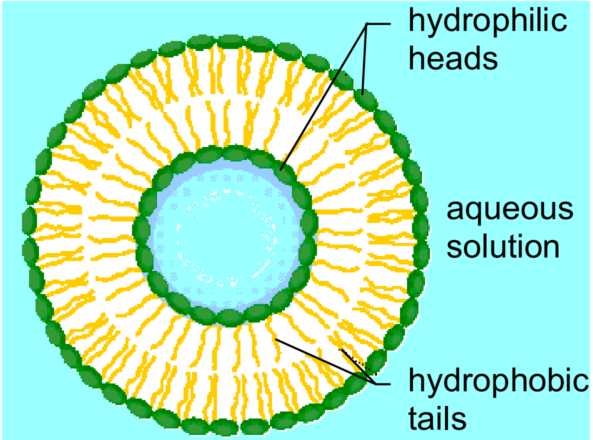
- *Micelles:*

Hydrophobic tail (e.g.. C_nH_{2n+1}) inside, hydrophilic head (e.g. COO^-) outside

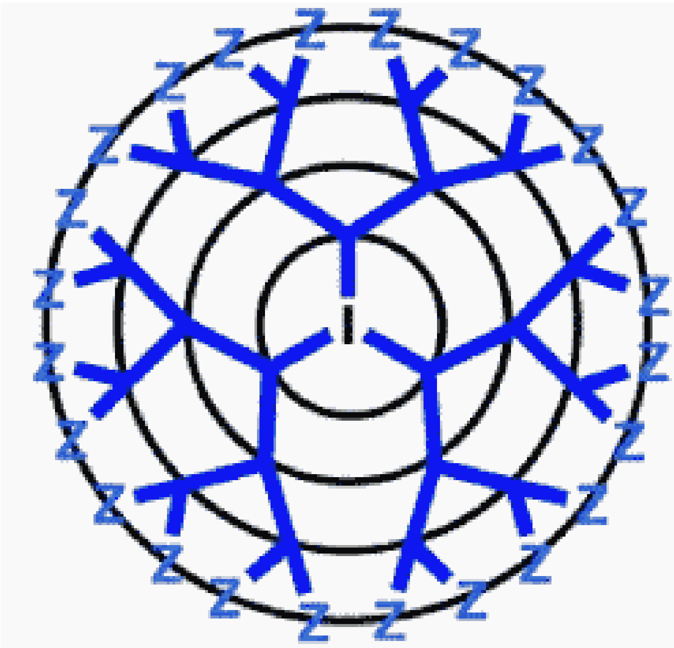


- **Key types of nanomaterials** (*continued*):
  - ▶ Colloidal particles (*continued*):
    - – *Inverse (reverse) micelles* →
    - – *Liposomes:* → →
      similar to micelles, but contain an electrolyte inside
      - widely used in pharmacology.

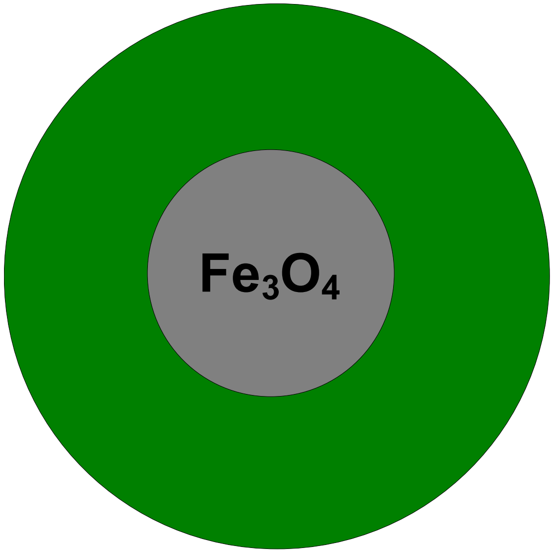




  - ▶ Dendrimers:



  - – Magnetic nanoparticles:

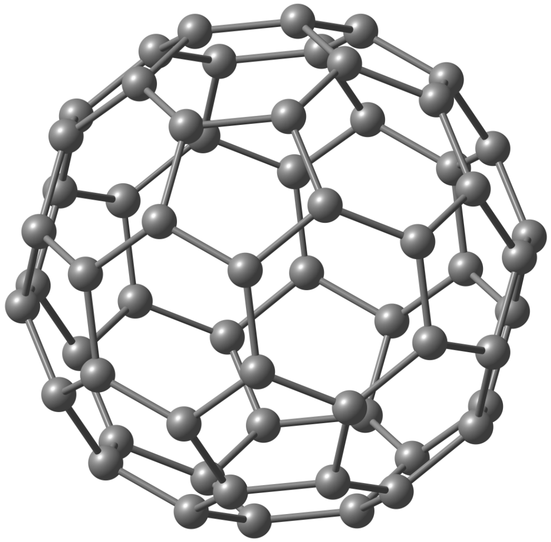


- used for preparing *ferrofluids* (magnetic liquids);
- Therapeutical use (NanoTherm™)

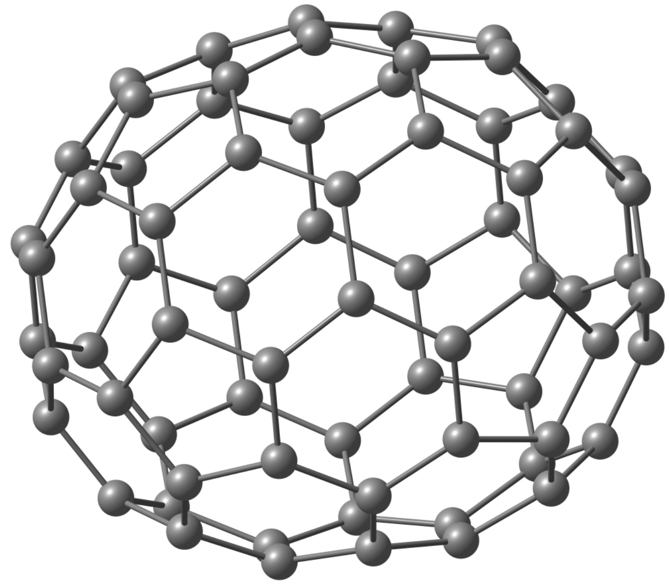
OVERVIEW OF NANOMATERIALS – fullerenes

- **Fullerenes:** (Curl, Kroto, Smalley 1984 – Nobel prize 1996)
    - ► Examples:

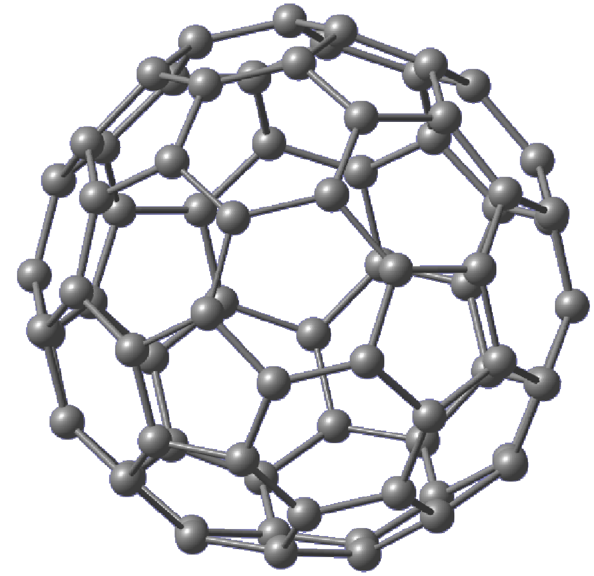
C_{60} buckminsterfullerene



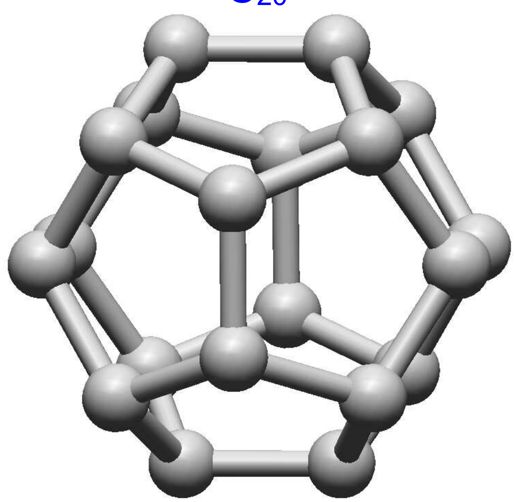
C_{70}



C_{76}

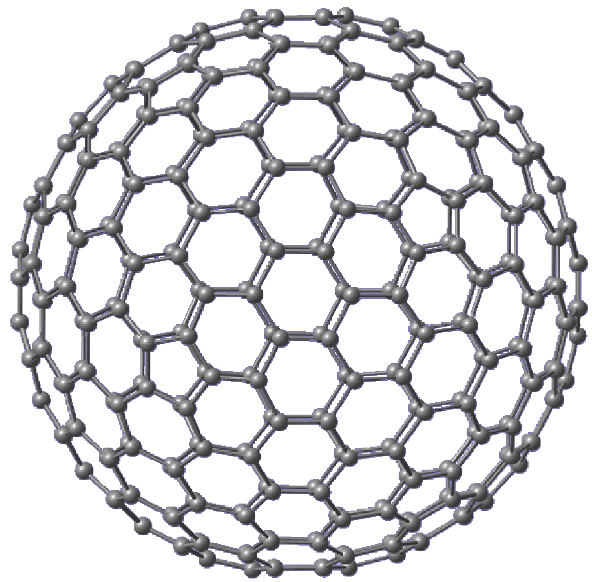


C_{20}

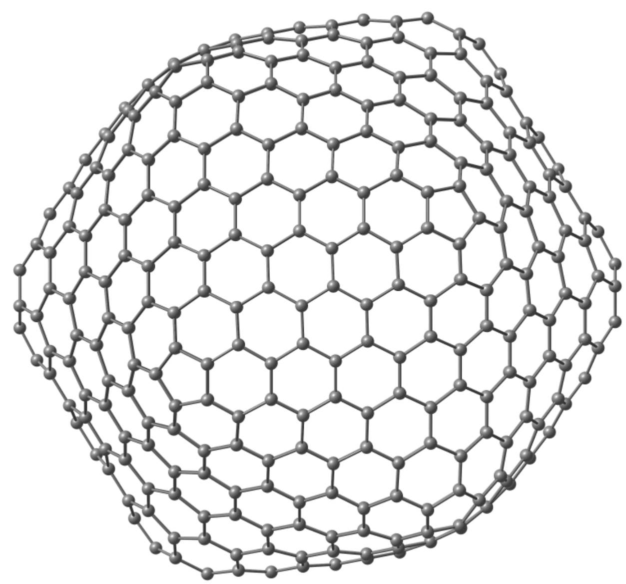


structure under debate

C_{320}

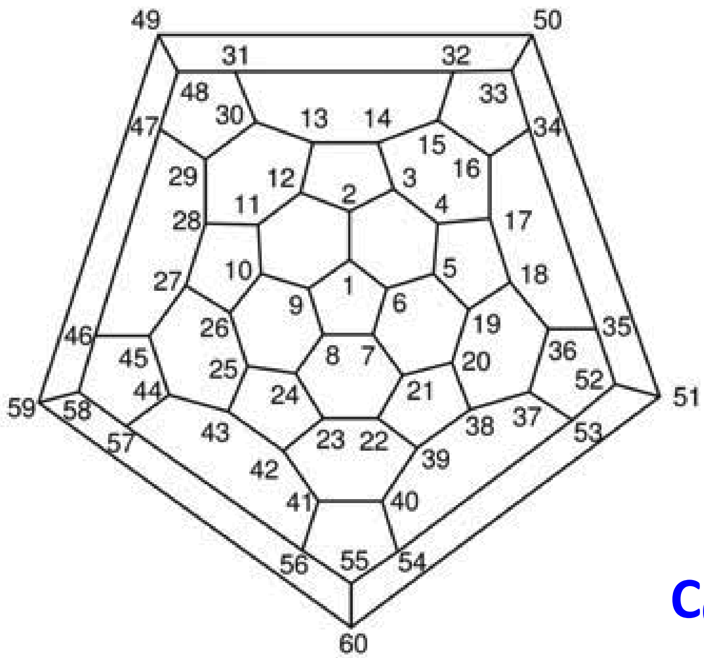


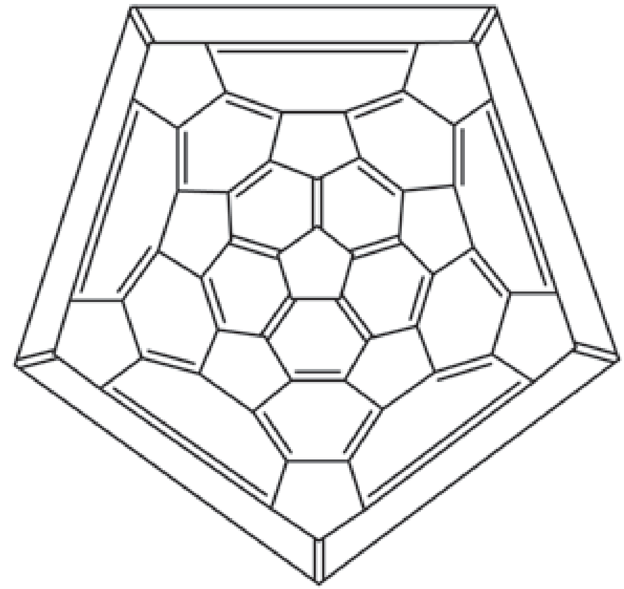
C_{540}



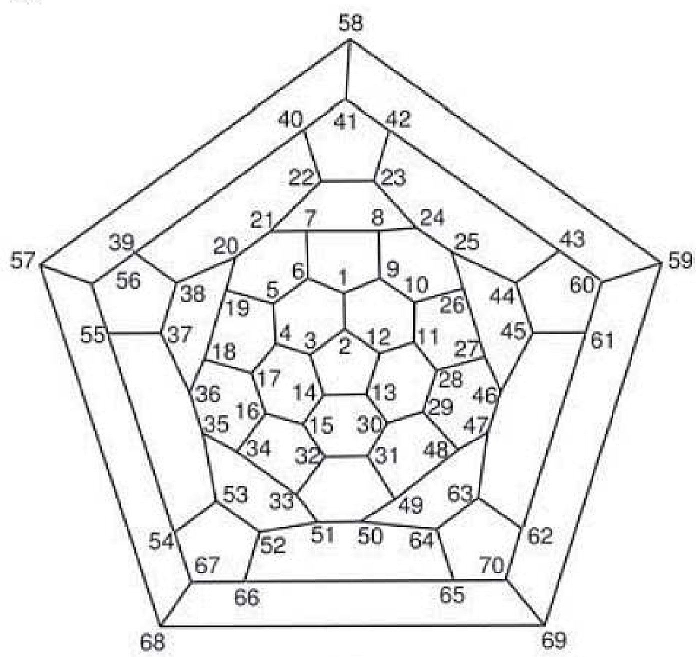
Vyboishchikov (15)

- **Fullerenes: Schlegel diagram**





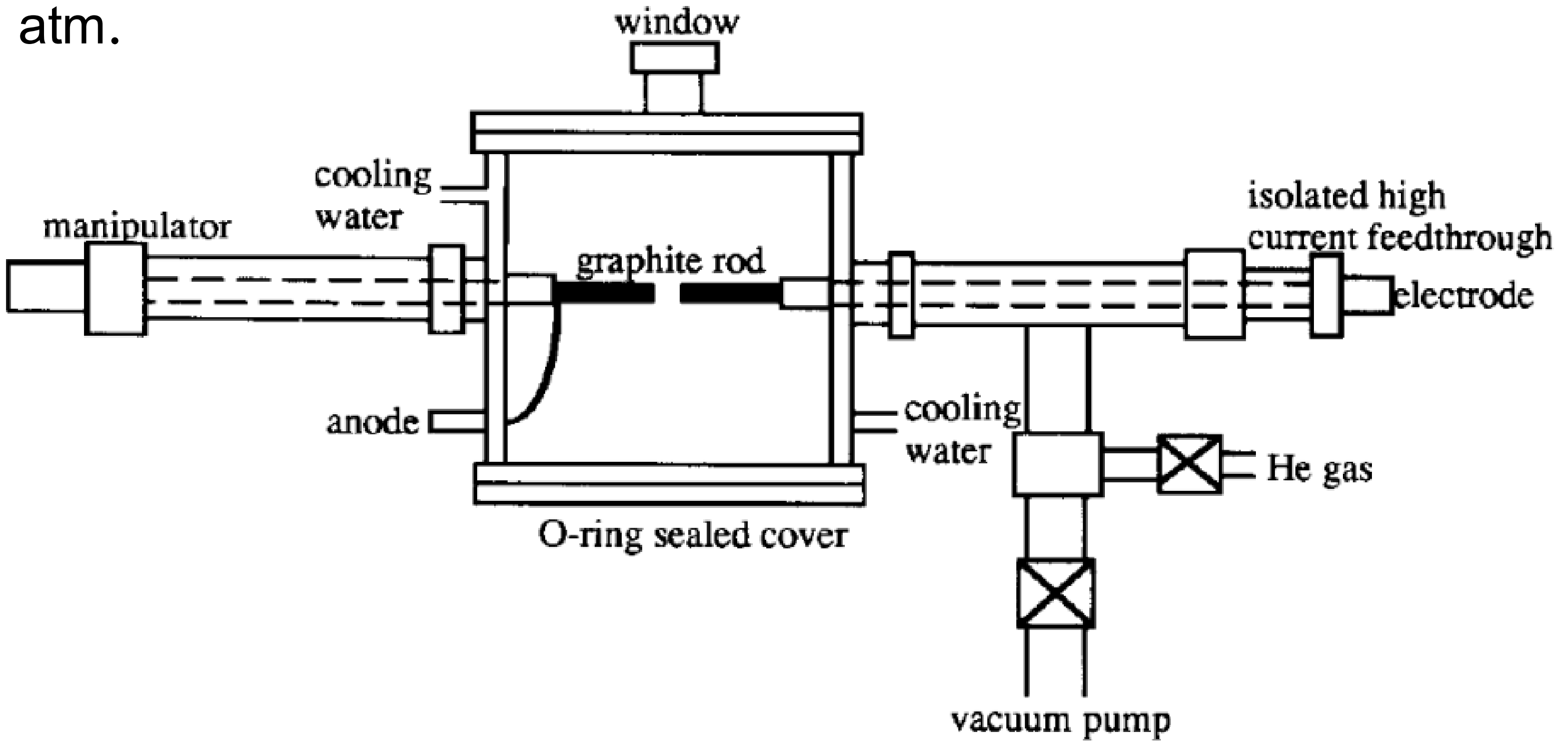
C_{60}



C_{70}

Vyboishchikov (16)

- **Pristine fullerenes:**
  - ▶ Preparation:
    - – Krätschmer–Huffman method: arc vaporization of graphite produces fullerene-containing soot (cat. *sutge*). The chamber is filled with He at 0.2–0.3 atm.



    - – Hydrocarbon combustion (Howard 1991): benzene + O_2 + Ar (10%) in a laminar flame produces C_{60} + C_{70};
    - – Laser ablation of graphite in He atmosphere at ~1200°C;
    - – Other methods: electron-beam evaporation…
    - – Total synthesis: building fullerene cages using methods of organic synthesis (difficult and seldom used).

- **Fullerenes:**
  - All the above methods (page 17) produce (in addition to soot) a crude mixture of fullerenes (mainly C_{60} and C_{70}) $\Rightarrow$ separation is necessary:
    - Extraction of soluble fullerenes from soot (by benzene or toluene) with subsequent chromatography (Al_2O_3 or charcoal/toluene-hexane mixture)
  - Characterization:
    - ^{13}C NMR spectroscopy;
    - Mass spectroscopy;
    - UV-VIS spectroscopy in organic solvent: C_{60} (deep purple), C_{70} (wine red), C_{76-94} (yellow-greenish); note that solid fullerenes are *black*.
    - Infrared spectroscopy;
    - Chromatography (mainly HPLC: http://en.wikipedia.org/wiki/High-performance_liquid_chromatography).

- **Fullerenes:**
  - ► Chemical reactivity: fullerenes are excellent electron acceptors (see also page 23):
    - – Electron affinity between 2.5 and 3 eV, or sometimes higher (similar to that of iodine).
    - – Alkali-metal doped fullerenes (fullerides):

      $K_3C_{60} = (K^+)_3C_{60}^{3-}$

      Cs_3C_{60}

      K_4C_{60}

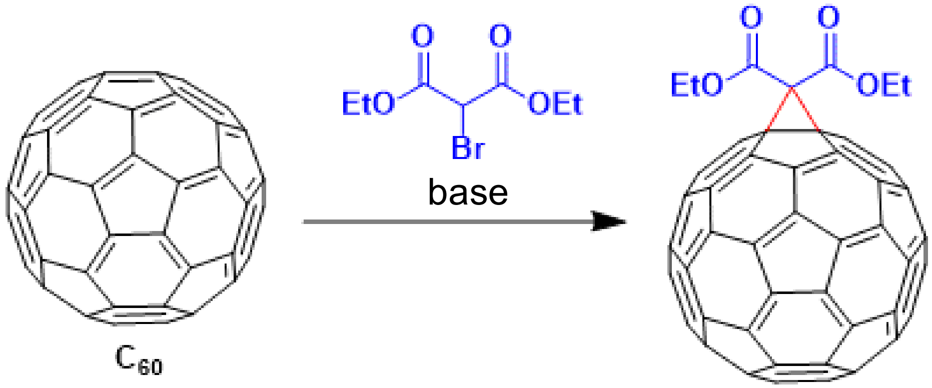
      Na_2C_{60}

      Cs_6C_{60}

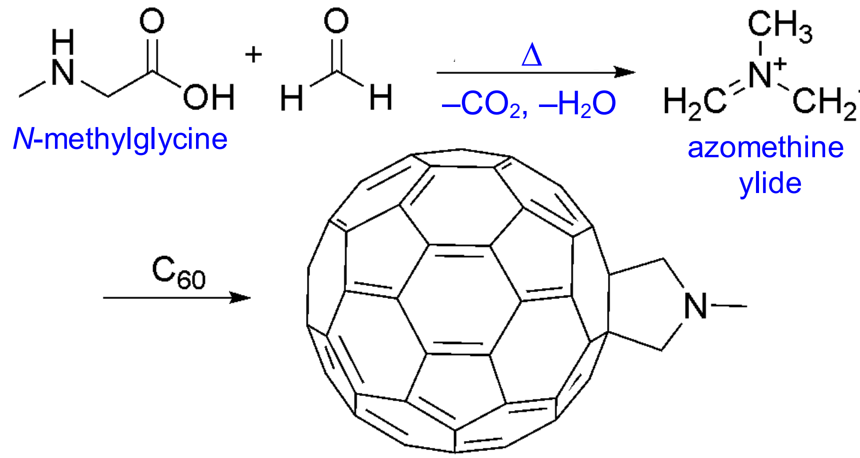
      Ba_4C_{60}

    - Fullerides are ionic substances, but often have metal conductivity or (at low temperatures) *super*conductivity.

- **Pristine fullerenes:**
  - ► Chemical reactivity (functionalization):
    - – Bingel(–Hirsch) reaction:



    - – Prato's reaction

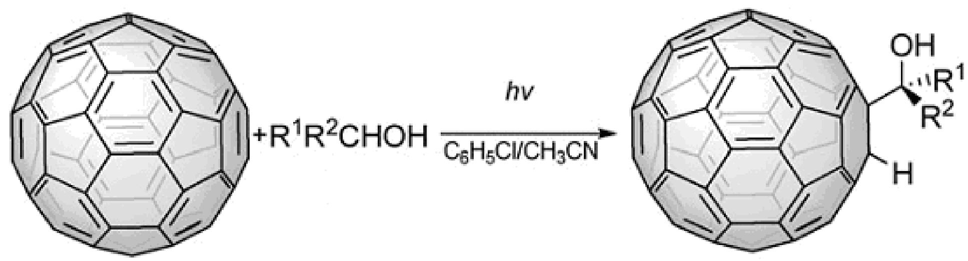


    - – Oxidation:

C_{60} + $R_3N–O$ → $C_{60}O_{1–2}$

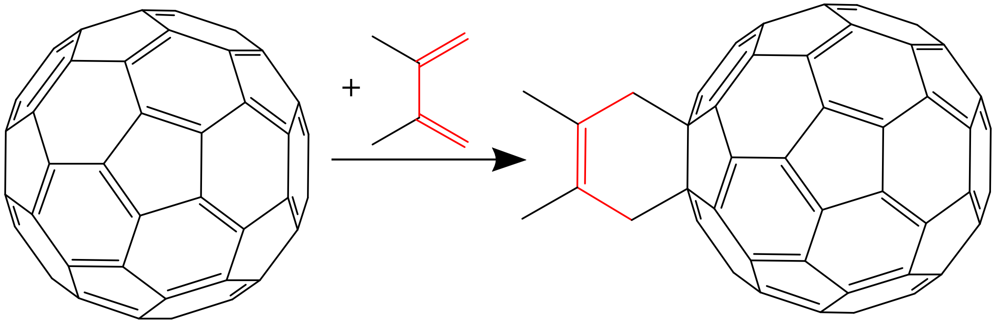
C_{60} + H_2SO_4/HNO_3 → $C_{60}(OH)_{14–16}$

    - – Radical (photochemical) alcohol addition →

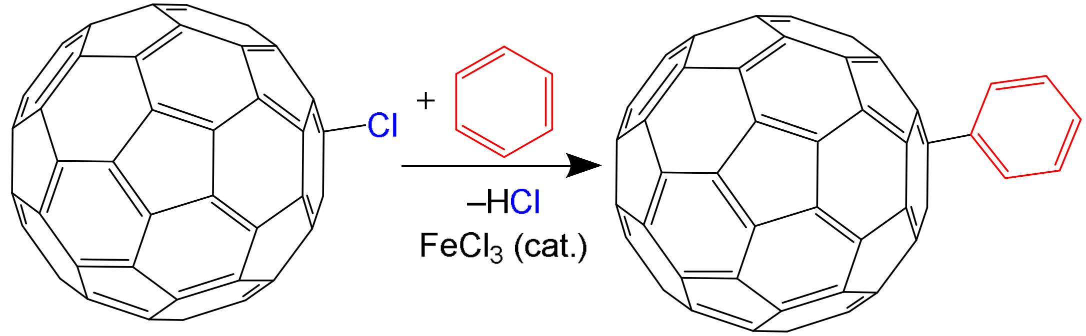


    - – Many others: hydrogenation (→ e.g. $C_{60}H_{18}$, $C_{60}H_{36}$), halogenation (→ e.g. $C_{60}Cl_6$, $C_{60}F_{36}$), Diels–Alder reactions; rich organometallic chemistry (π-complex formation); rich supramolecular chemistry; aromatic electrophilic substitution (e.g., for $C_{60}Cl_6$ – see next page 21).

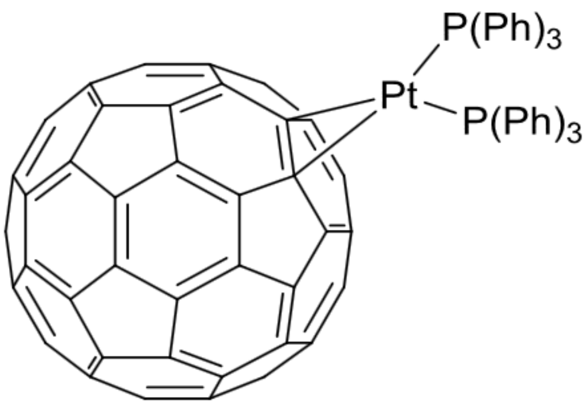
Diels–Alder reaction:

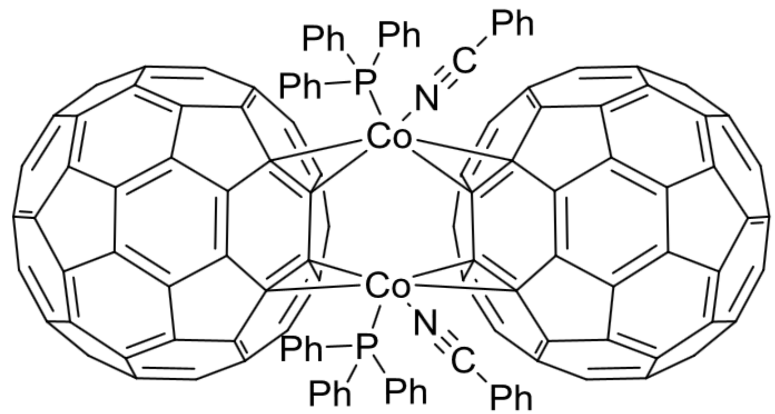


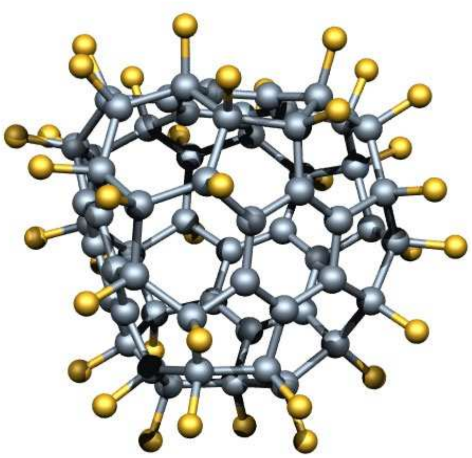
aromatic electrophilic substitution



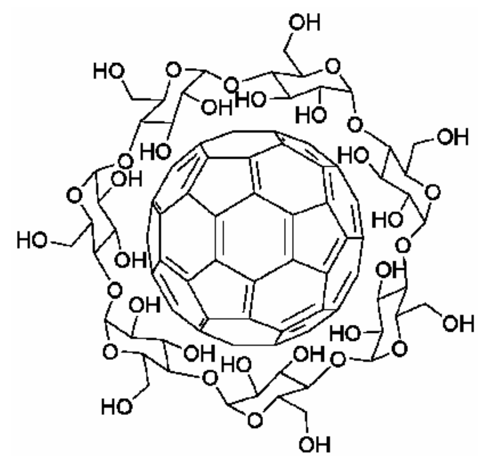
fullerene π-complexes (examples):







$C_{60}H_{36}$

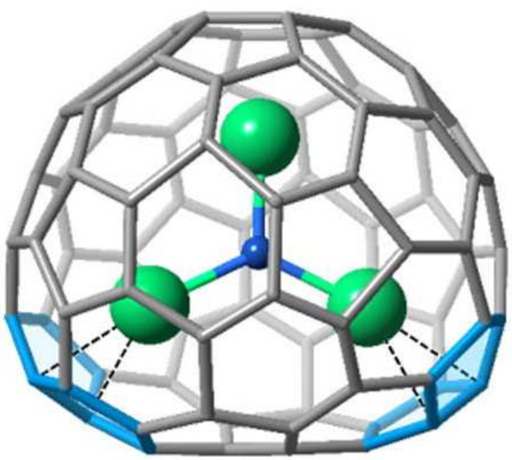


supramolecular complex with cyclodextrin

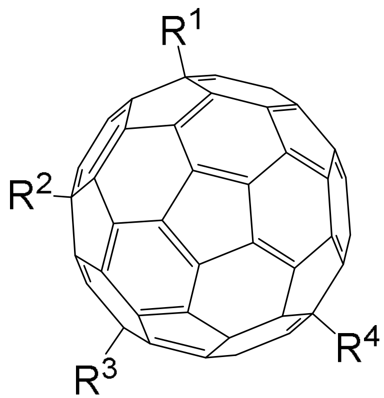
- **Endohedral (metal-encapsulated) fullerenes**:
  - Preparation by the Krätschmer–Huffman method or laser ablation from graphite containing a *metal oxide*:
    - Examples: $La@C_{60}$, $Sc@C_{80}$, $Y@C_{80}$, $La_2@C_{80}$, $Y_2@C_{82}$, $Sc_2@C_{82}$, $Gd_2@C_{92}$
  - Preparation by sophisticated chemical synthesis:
    - $He@C_{60}$, $H_2@C_{60}$, $H_2O@C_{60}$, $HF@C_{60}$, $CH_4@C_{60}$, $Ar@C_{60}$.

  Also fullerides such as $K_3ArC_{60} = (K^+)_3[Ar@C_{60}^{3-}]$

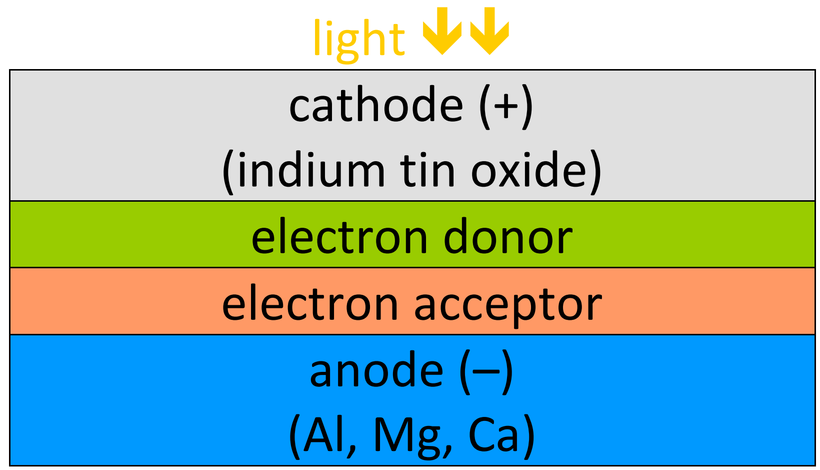
- **Trimetallic nitride endohedral fullerenes**:
  - Preparation by the Krätschmer–Huffman method at ~1100 °C from graphite containing M_2O_3 (M = Sc or lanthanoid) + Fe_3N_4 in N_2 atmosphere.
  - Examples: $Gd_3N@C_{78}$.



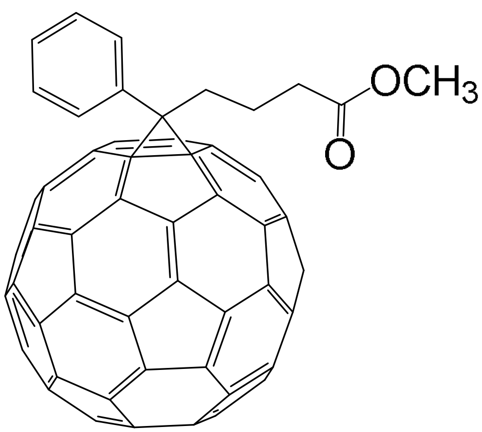
- **Fullerenes:**
  - ► Possible applications:
    - – In *cosmetics* (usage discontinued):
      - antioxidant (“radical sponge”); reacts with free radicals (up to 20 radicals per fullerene molecule);
    - – In *diagnostics*: $Gd_2@C_{92}$ is a potential paramagnetic contrast agent in medical NMR imaging.
    - – As dry lubricants.



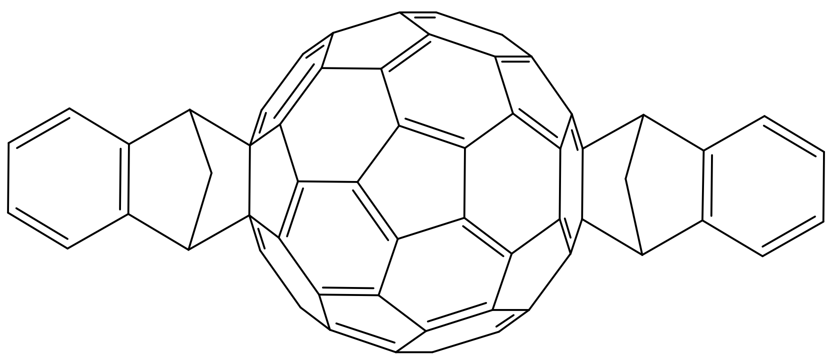
- **Fullerenes:**
  - ▶ Possible applications (*continued*):
    - – In *photovoltaics* for organic solar cells – as *electron acceptors* in polymer-fullerene solar cells (other types of solar cells (without fullerenes: semiconductor; perovskite)



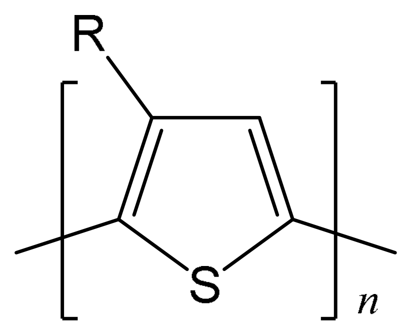
bilayer organic photovoltaic cell



PCBM
(electron acceptor)

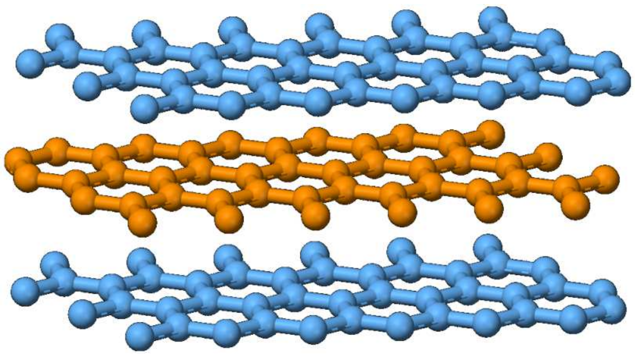


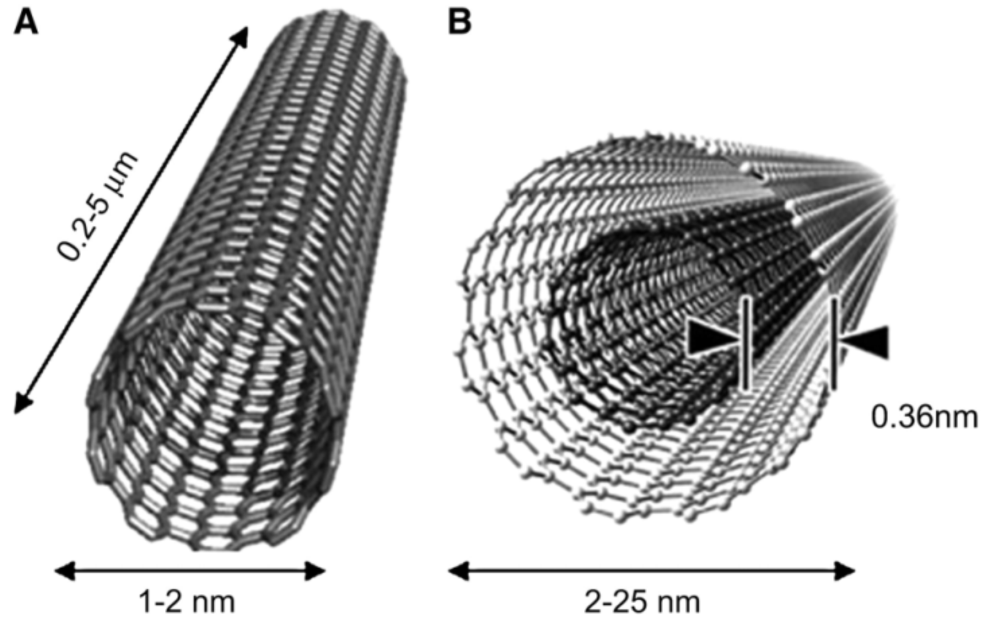
ICBA
(electron acceptor)



substituted polythiophene
(electron donor)

- **Carbon nanotubes:**
  - ► single-wall(ed) *vs*. multi-wall(ed):
  - ► can be formally deduced from a single graphite layer (*graphene*):

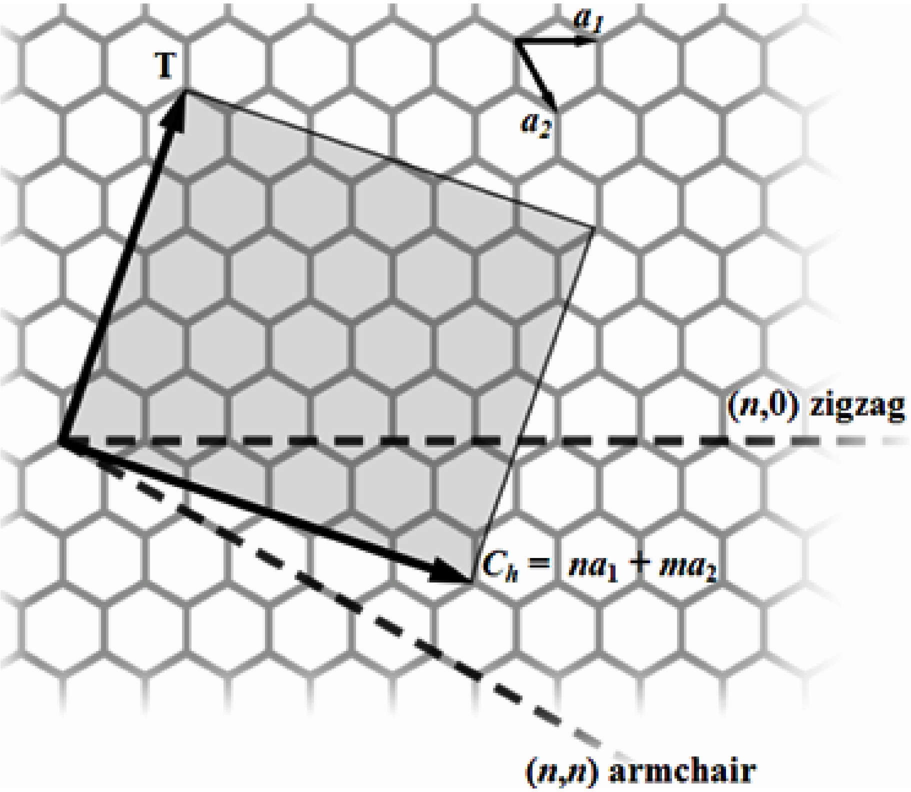




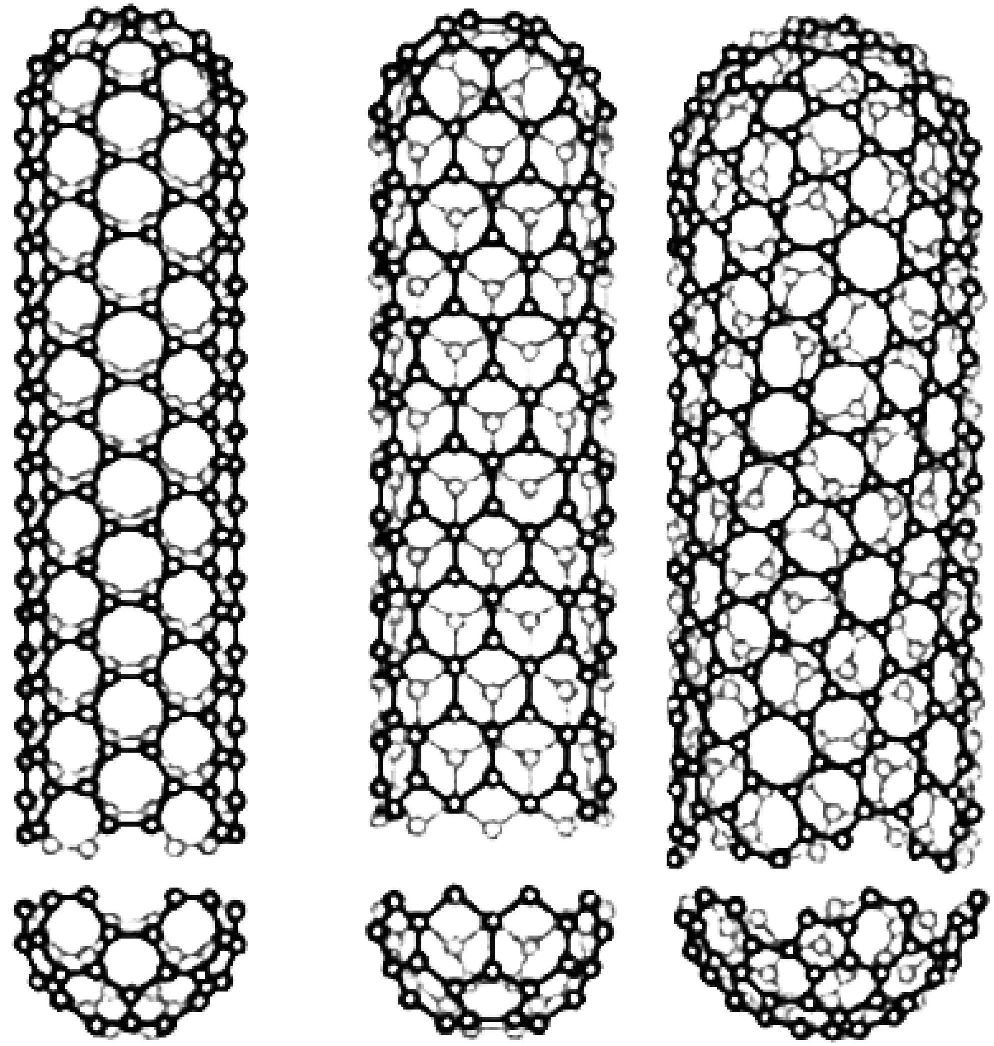
by appropriately wrapping (see next page).

- ► Single-walled nanotubes: are usually *capped* (see next page).
  – Uncapping nanotubes (example): refluxing with conc. $H_2SO_4 + HNO_3$ at 120–180 °C.
- ► The most frequent diameter for single-walled nanotubes: ~1.4 nm.
- ► Tube length: µm or mm are typical; up to 50 cm obtained.
- ► Types of multi-walled nanotubes:
  – *Russian-doll* type: concentric graphite sheets;
    — distance between the sheet is close to that in graphite (~0.34 nm)
  – *Parchment* type: a single sheet of graphite is rolled in around itself.

- **Carbon nanotubes:** (Iijima 1991)
  - ► Nomenclature of single-wall nanotubes (*opt*:



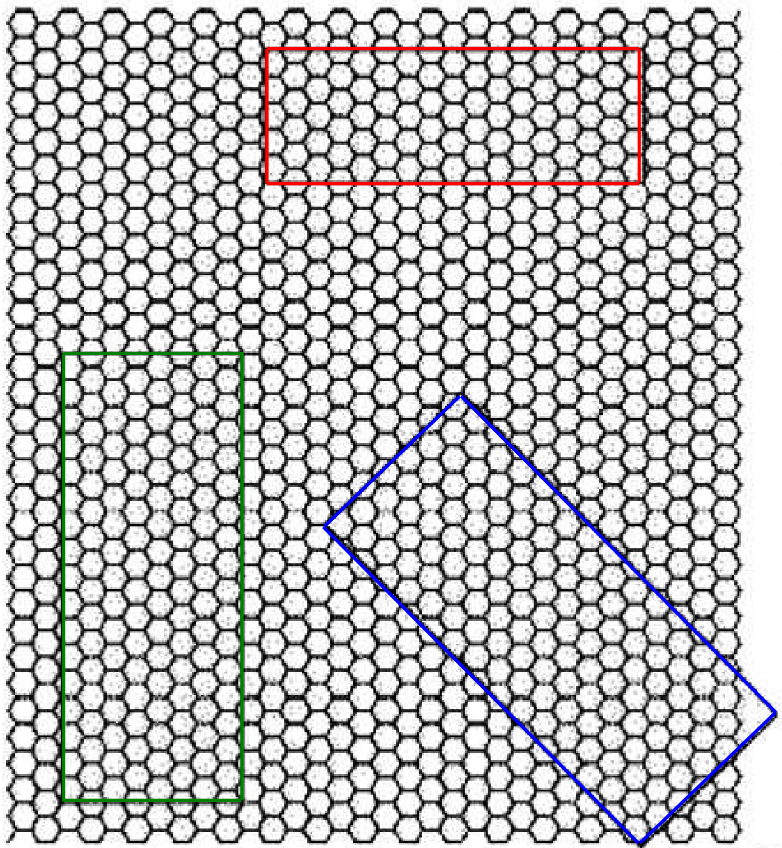
can be *capped* or *uncapped* →

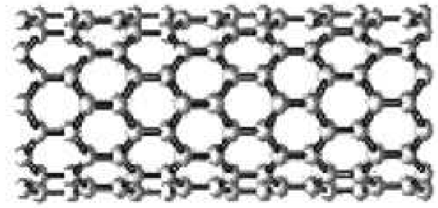


armchair zigzag helical (chiral)

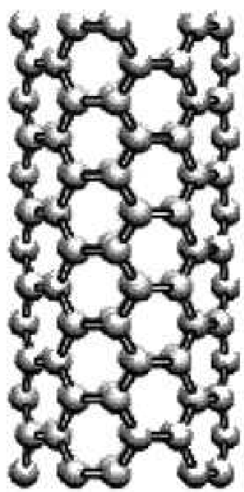
The direction of wrapping (n, m) is given by the vector $C_h = n\boldsymbol{a}_1 + m\boldsymbol{a}_2$, which serves as a base of a cylinder. The T vector is always perpendicular to C_h.

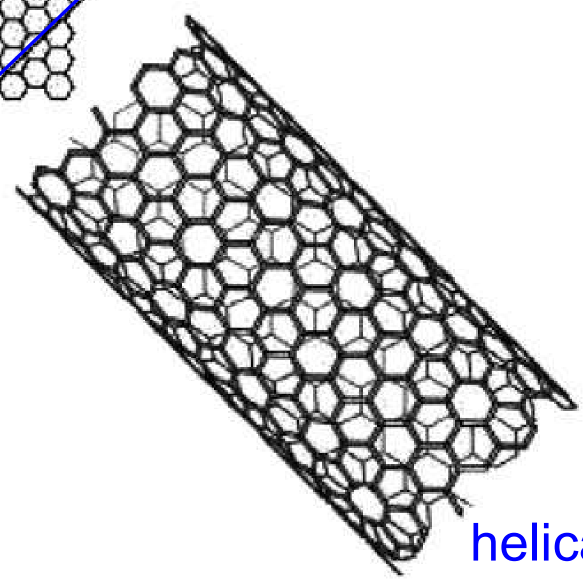
OVERVIEW OF NANOMATERIALS – carbon nanotubes



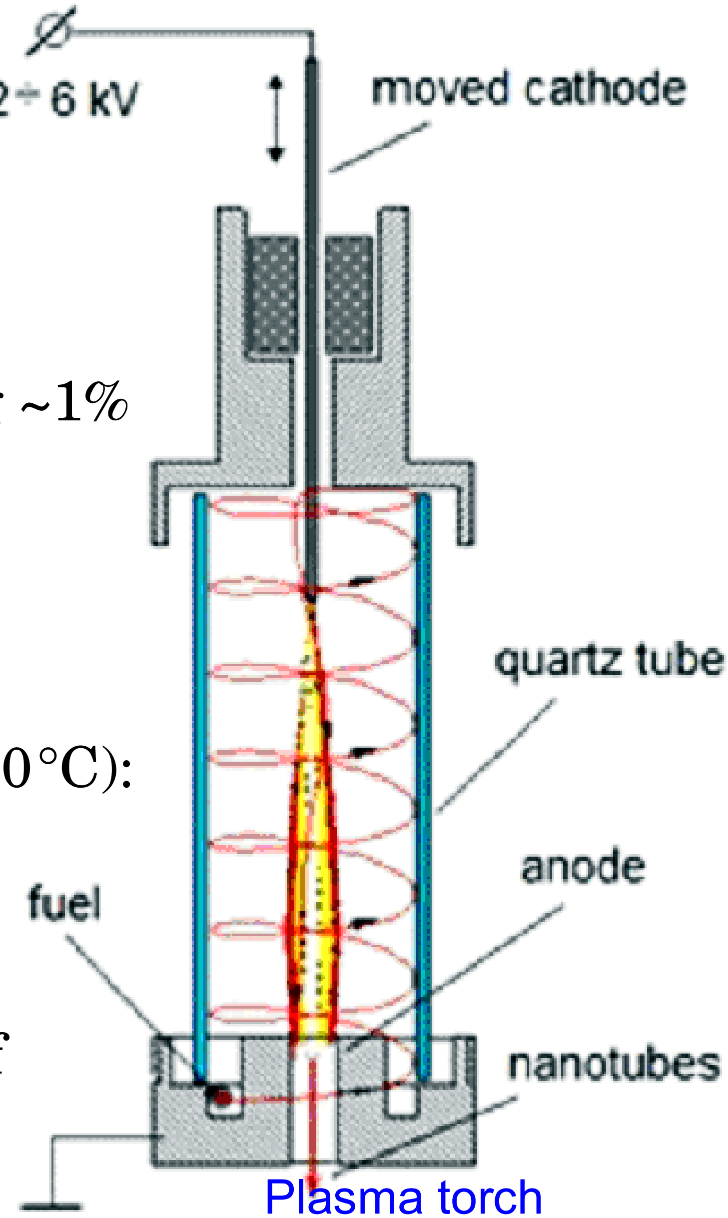


The smaller side of the rectangle in the base of the cylinder

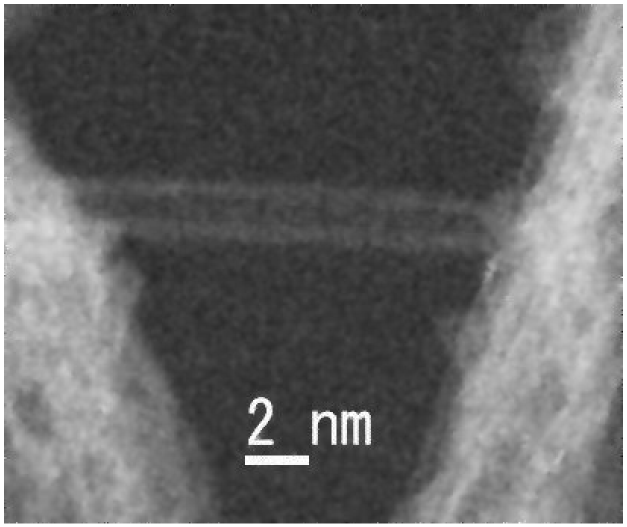


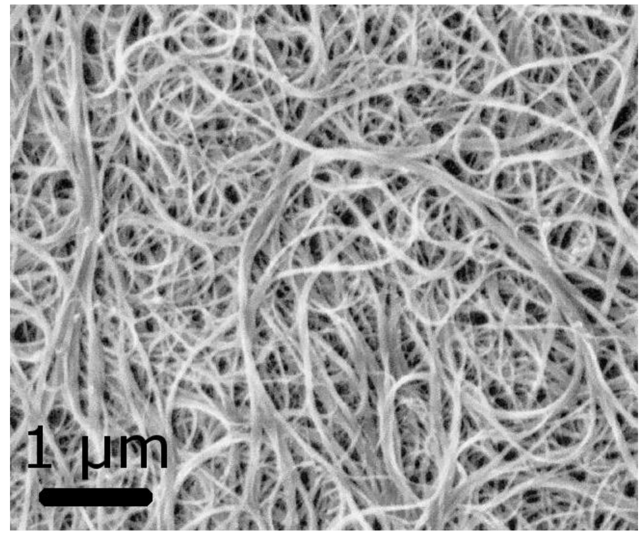


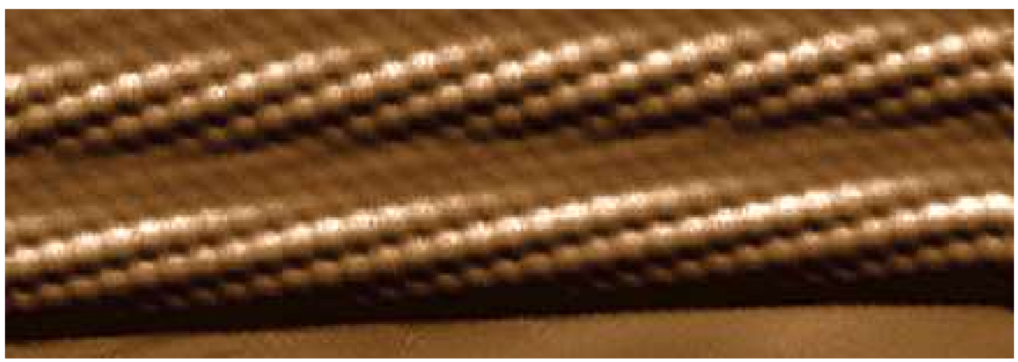
- **Carbon nanotubes:**
  - ► Preparation: common feature – use of a metal catalyst (Fe, Co, Ni etc.)
    - — Electric arc;
    - — Laser ablation (graphite targets containing ~1% of Co or Ni);
    - — Plasma torch →: high-voltage discharge at atmospheric pressure and ~500°C: $C_2H_4 + Fe(C_5H_5)_2$ in Ar atmosphere.
    - — Chemical vapor deposition (CVD) (500–1000°C): On catalyst substrate (Fe, Co, Ni, etc.) with CH_4/air mixtures or on hot W wires;
    - — Super-growth CVD: water is added; allows to obtain "forests" of mm-long nanotubes.



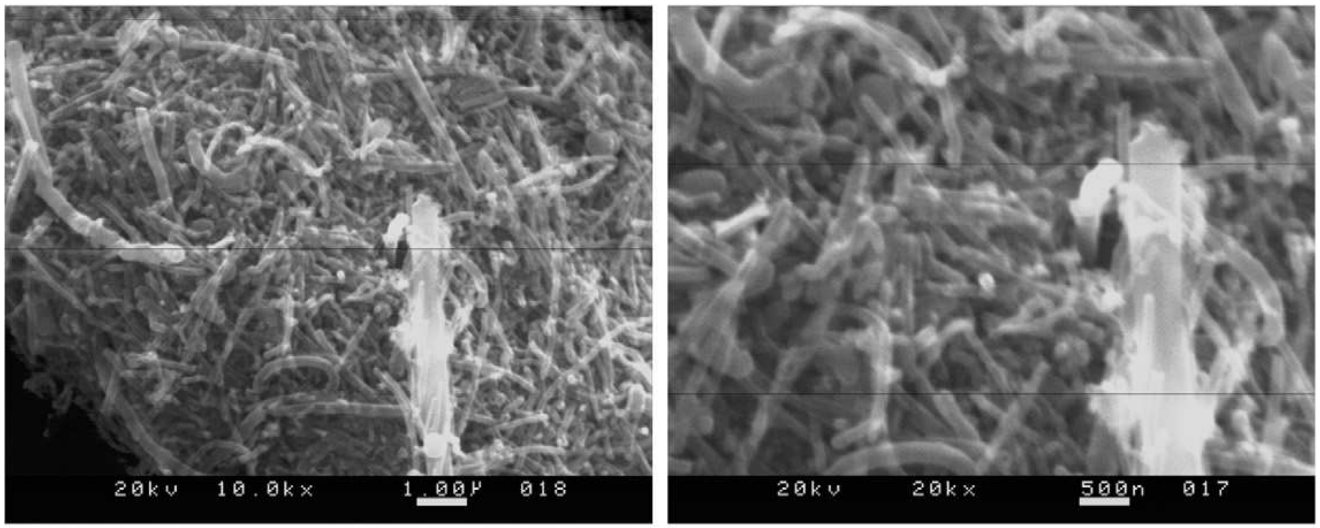
- **Carbon nanotubes:**
  - Characterization:
    - Transmission electron microscopy;
    - Scanning electron microscopy;
    - Scanning tunneling microscopy;



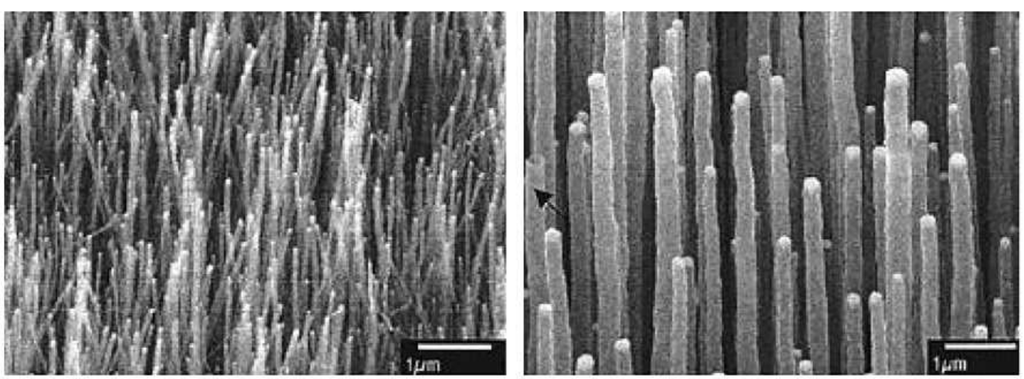




(a)



(b)

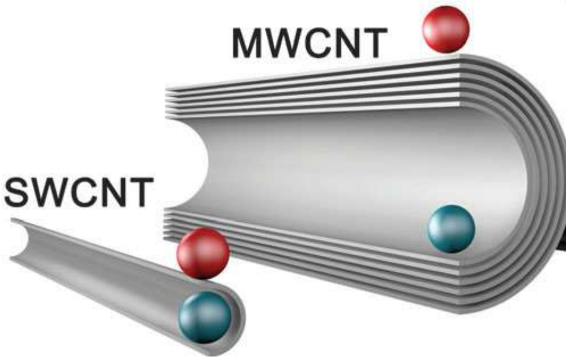


(c)

Vyboishchikov (30)

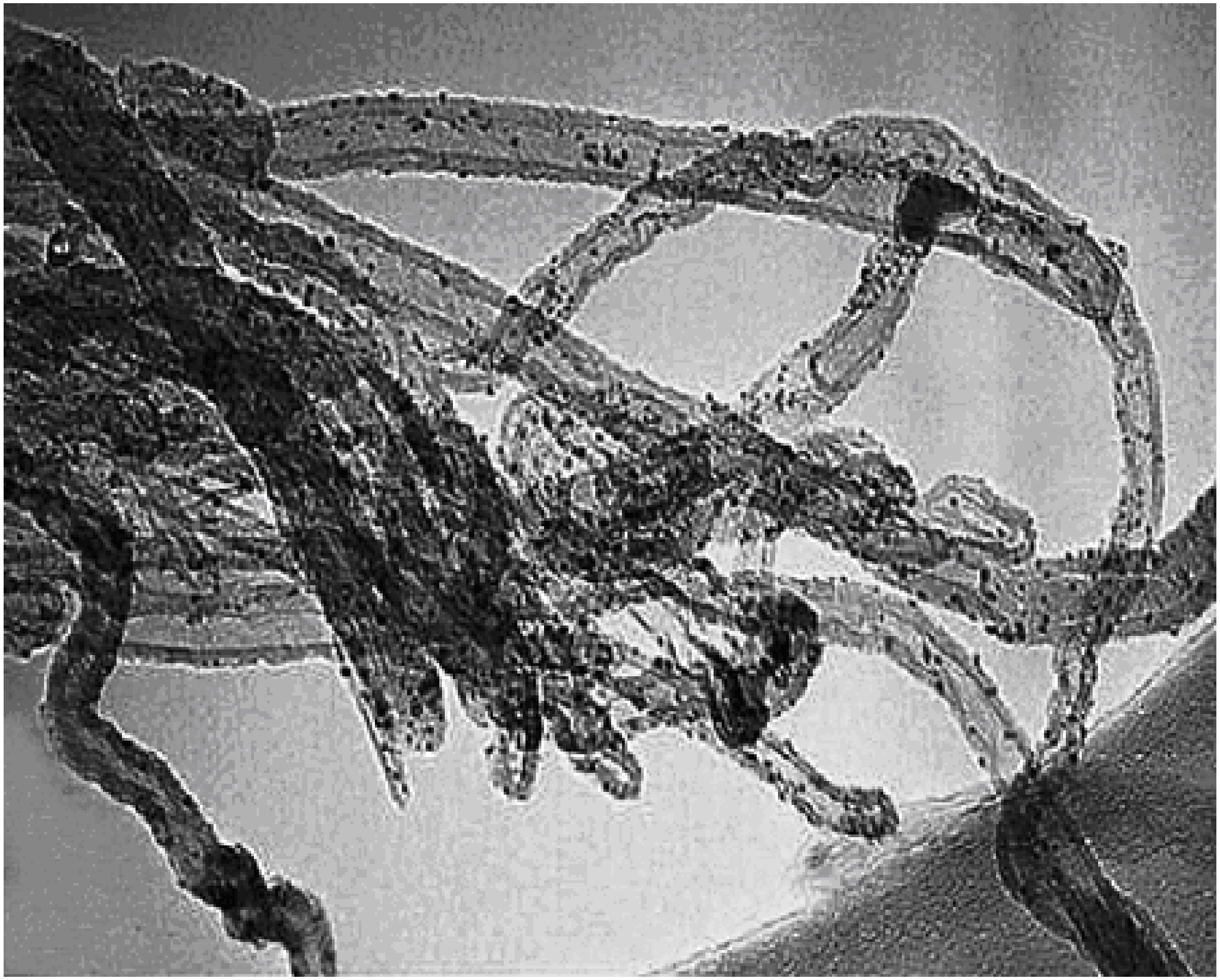
- **Carbon nanotubes:**
  - ► *Chemical properties*:
    - – stable in inert atmosphere up to ~1500–1800 °C
    - – very good adsorbents:
      - surface area up to 1000 m^2/g (*cf*. up to 1500 m^2/g for charcoal).
  - ► *Chemical reactivity*: vary widely;
    - – usually more reactive than graphite, but less reactive than fullerenes.
    - – Caps (if present) are more reactive than walls;
    - – On walls, defect sites are usually active.

- **Carbon nanotubes as catalytic support:**
  - ► *Chemical reactivity confined within carbon nanotubes* (Chem. Soc. Rev., 2016, 45, 4727)



For *narrow* nanotubes the encapsulalation energy is much higher that the external adsorption energy

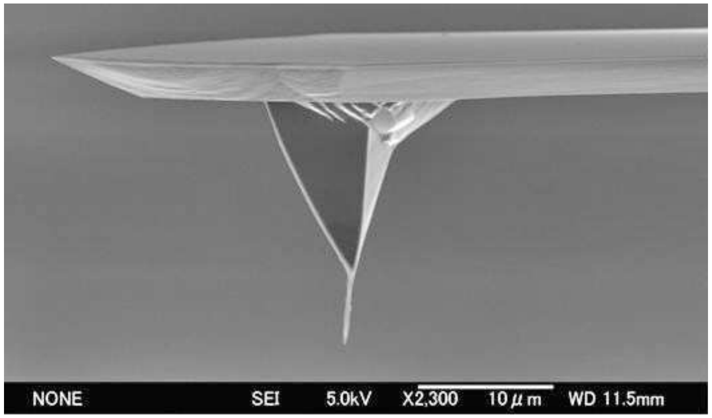
  - ► *Potential effects of confinement in a nanotube*:
    - – Increased local concentration ⇒ reaction rate increases;
    - – The catalyst (metal nanoparticles) is usually inside the nanotube;
    - – Often improved catalytic activity and higher catalyst stability.
    - – Reactions:
      - Hydrogenation (Ni, Pd, Pt, Ru, Au, Cu catalysts)
      - Oxidation (Co, TiO_2, Pt, Au catalysts)
      - NH_3 synthesis (Ru catalysts)
      - Alkyne hydrosilylation (Ru catalysts)
      - many others



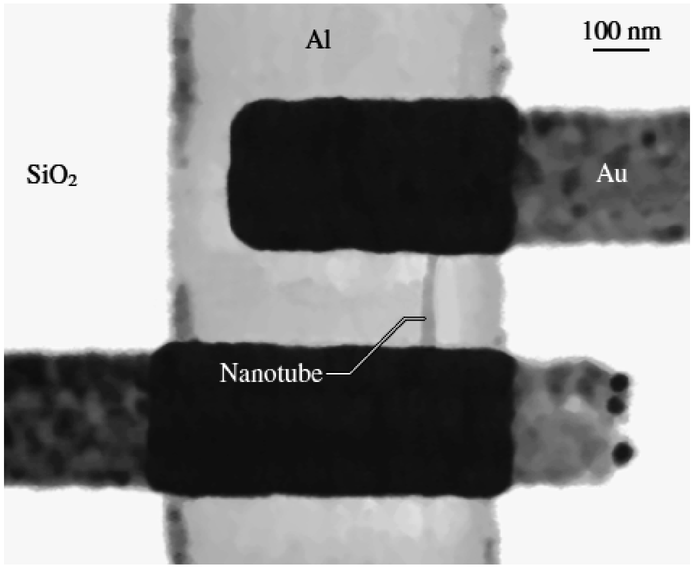
Rh nanoparticles supported on the surface of a multi-wall nanotube
(Transmission electron microscopy image)

- **Carbon nanotubes:**
  - *Physical properties*:
    - Mechanically strong (with respect to both bending and stretching), but also elastic:
    - Nanotubes are excellent *thermal conductors* (along the tube).
    - Some nanotubes are *metallic conductors* (1-D conductors along the tube axis); others are *semiconductors*:
      - Armchair nanotubes are *metallic*, while some zigzag and helical are *semiconductors*, some other are *metallic*.

- **Carbon nanotubes applications:** thousands tons/year world production.
  - ► Use of *mechanical* properties of nanotubes:
    - – 0.1% nanotubes added to *aluminum* increases strength twice;
    - – Nanotubes are allegedly found in (17th-century!) Damascus steel;
    - – 0.001% nanotubes added to *concrete* increases strength by 50%
  - ► Use of *electric* properties of nanotubes:
    - – 0.01% nanotubes added to *plastics* makes them conducting (antistatic properties);
    - – provide conductivity to colored and transparent *coatings*.
  - ► Others:
    - – nanotubes in *coating* reduce biofouling of ships by algae;
    - – for hydrogen storage (H_2 up to 10% weight – not enough for an industrial use);
  - ► *Use in electronics*:
    - – in photovoltaics for polymer *solar cells* (in the polymer layer to improve the conductivity or as electrodes);
    - – as *tips* for Atomic Force Microscopy;



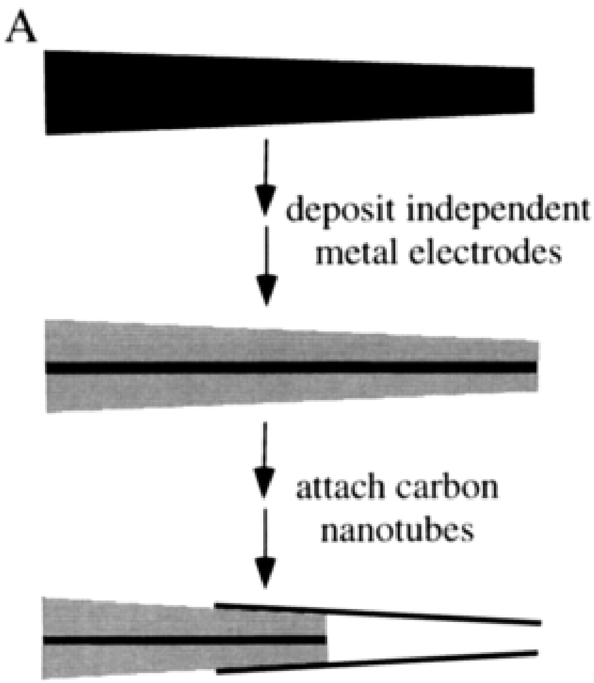
- **Carbon nanotubes applications** (*continued*):
  - ► A nanotube field-effect transistor (FET): a carbon nanotube serves as the FET channel – used as *chemical sensor* (e.g. for gas detection):

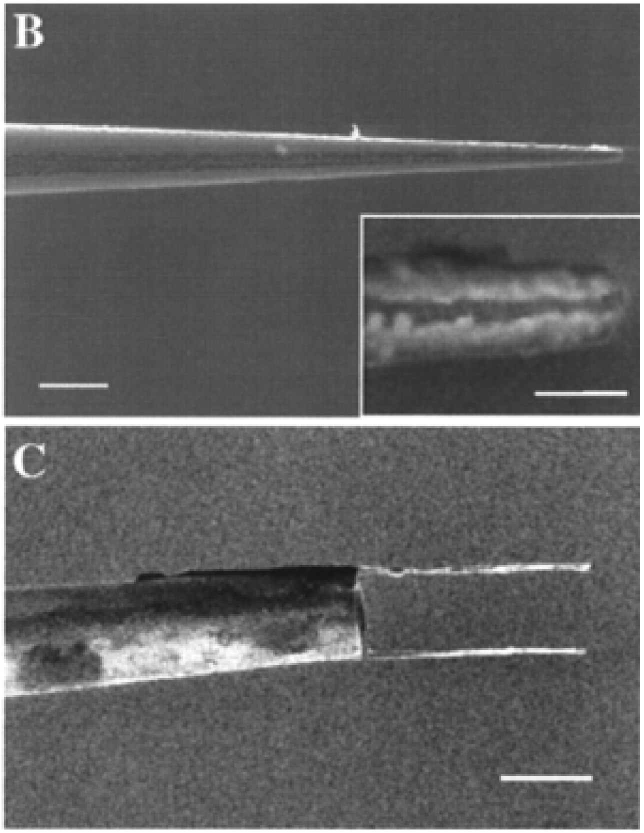


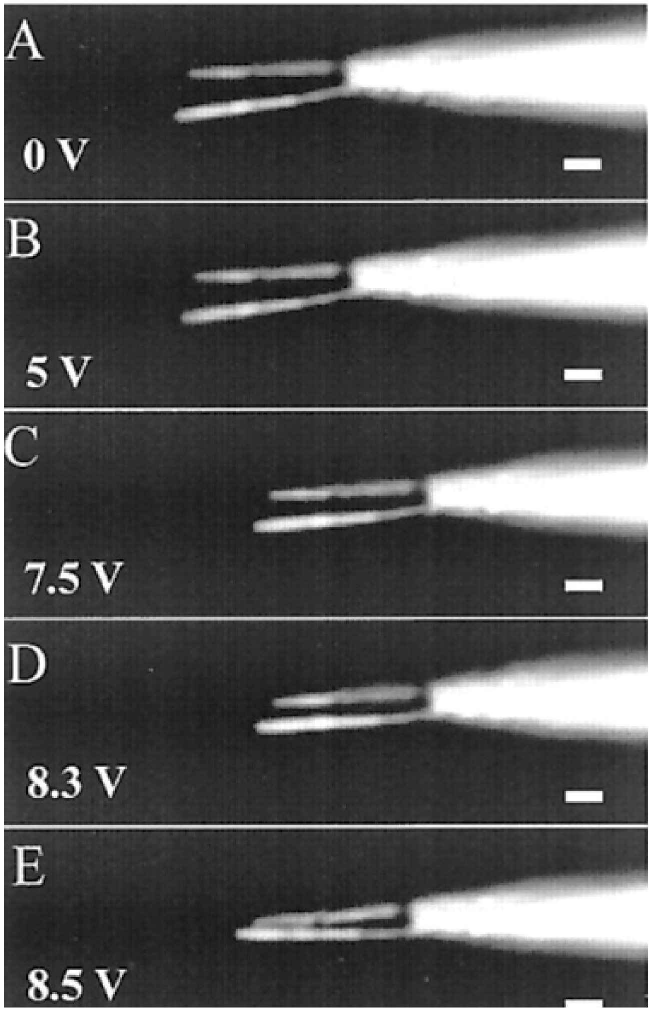
– also for *biosensors*:

The nanotubes are functionalized with *antibodies* or *aptamers* that selectively bind to the target molecule. Nanotube conductance changes.

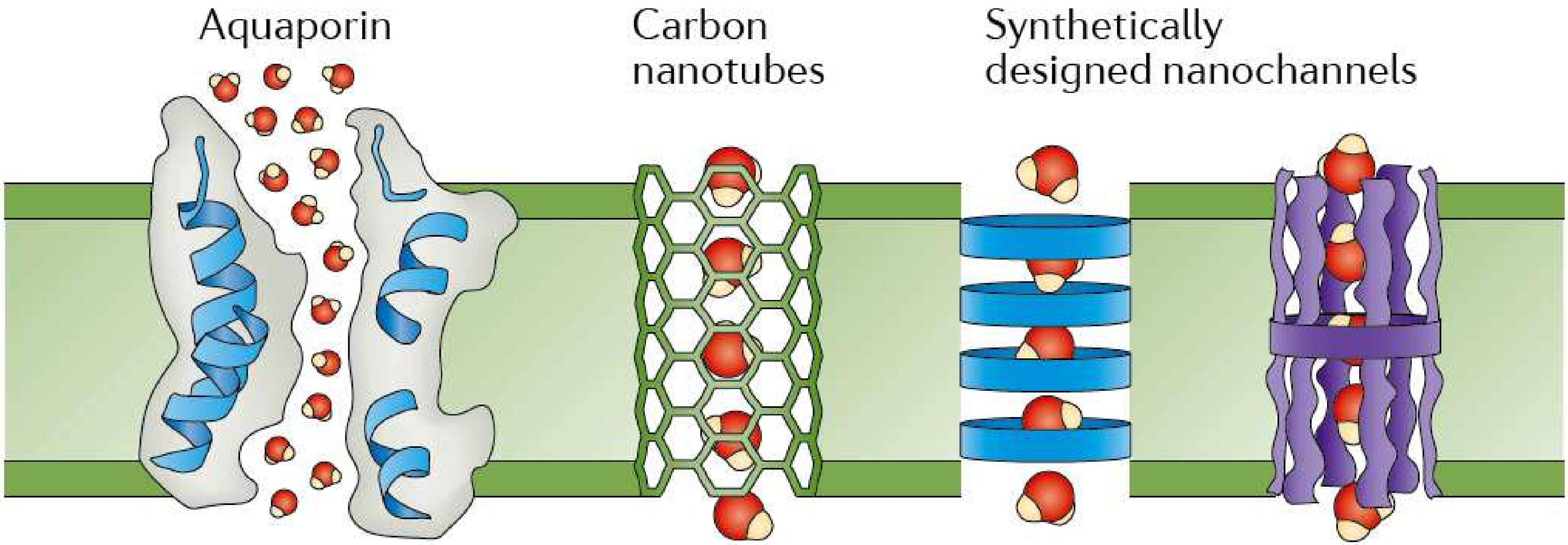
- **Carbon nanotubes applications** (*continued*):
  - ► In carbon nanotubes *actuators* (e.g. nanotweezers (cat. *pinça*))



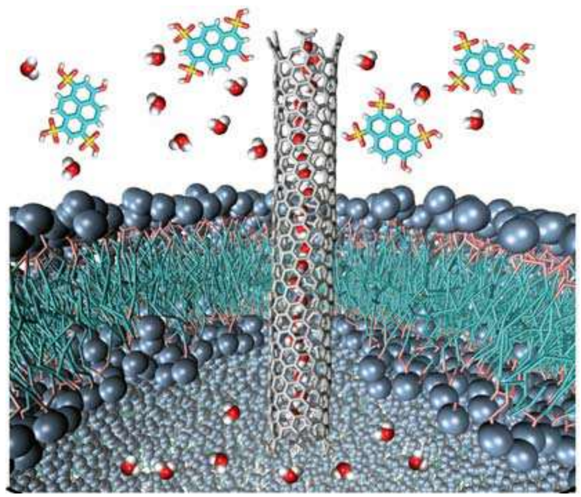




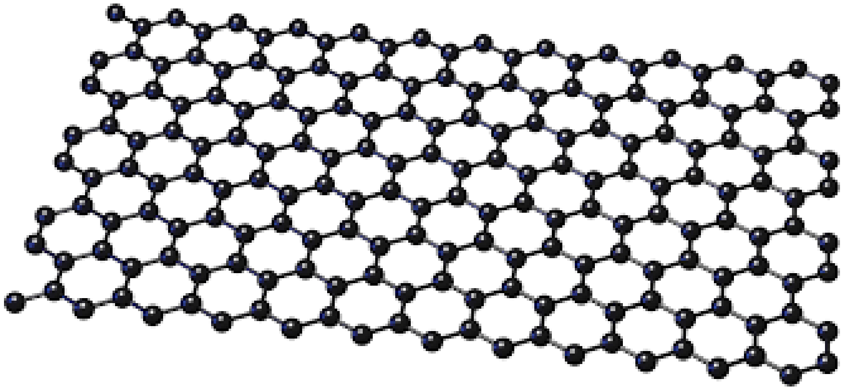
- **Water desalination:**
  - ► "Classical": distillation, ion exhange, freezing…
  - ► Modern: nanofiltration, reverse osmosis, electrodialysis reversal…



  - ► Carbon nanotube usage for water desalination: credits to Aleksandr Noy



OVERVIEW OF NANOMATERIALS – graphene

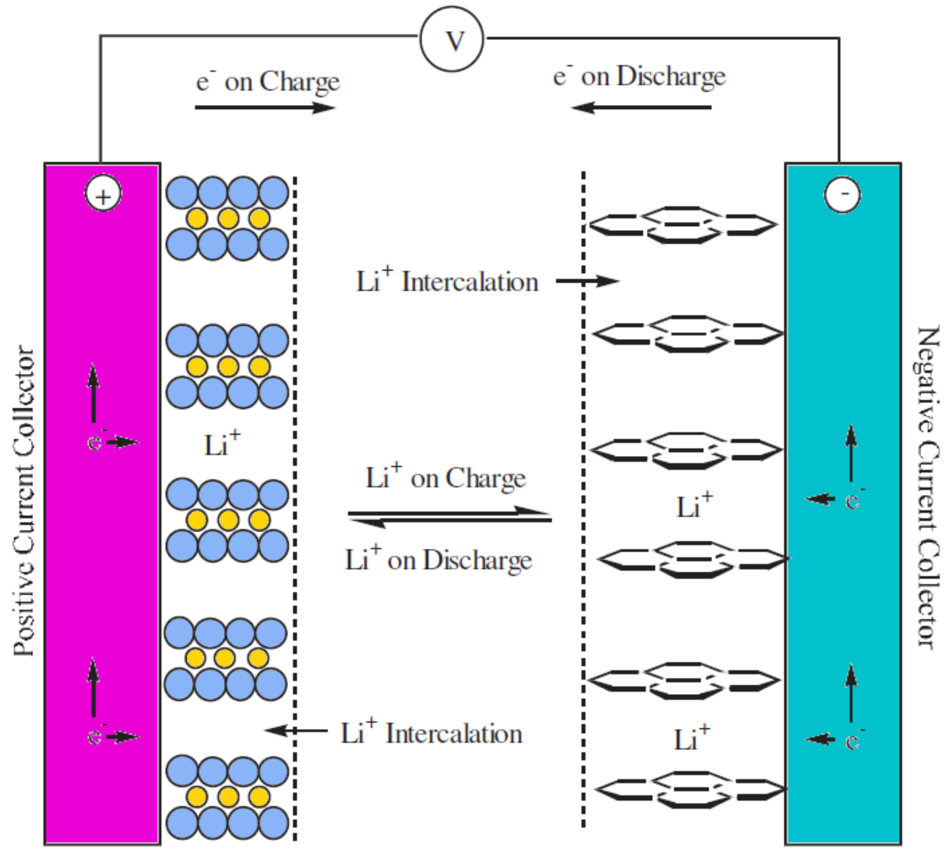


- **Graphene** = graphite monolayer:
  usually on a substrate
  Nobel prize 2010 in physics to Geim and Novoselov
- **Isolation from graphite:**
  - Mechanical exfoliation:
    “Scotch-tape” technique from graphite.
  - Sonication:
    Ultrasound in the presence of surfactants or ionic liquids.
- **Synthesis:**
  - Spraying fullerenes on a substrate at ultrasonic speeds:
  - Chemical vapor deposition (CVD).
- **Unique electrodynamic properties:**
  - Zero-gap semiconductor:
    electric conductor, but not really metallic; different both from conventional semiconductors, from metals, and from bulk graphite;
  - High thermal conductivity;
- **Mechanical properties:**
  - extremely strong, but brittle (*think what it means!*)

- Graphene usage:
  - ▶ as a transparent electrode (instead of indium tin oxide) for *solar cells*.
  - ▶ in *cooling systems* of Huawei smartphones within (due to high thermal conductivity)
  - ▶ in lithium-ion batteries (on the negative electrode);
- A lithium-ion battery:

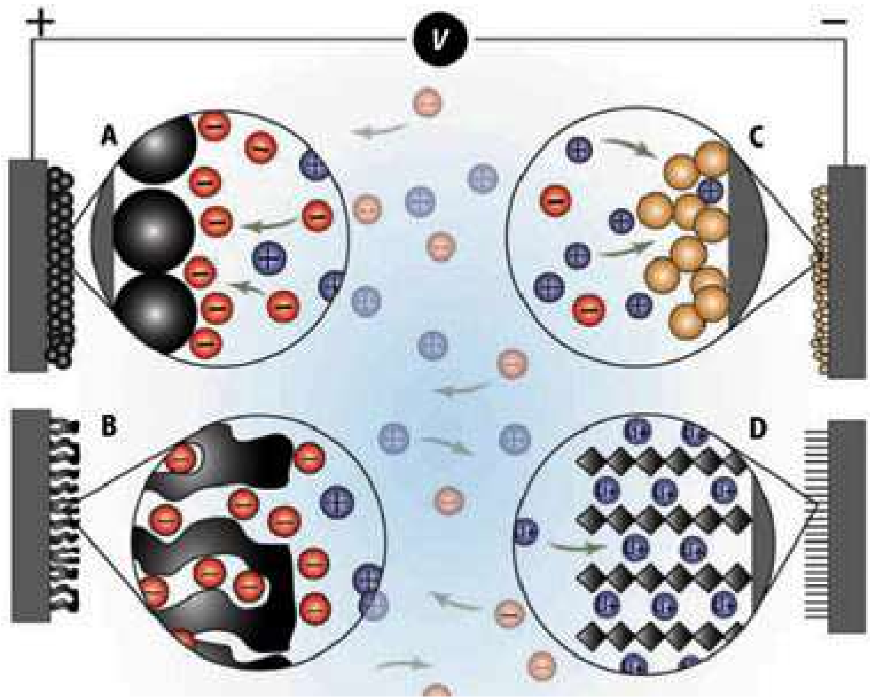
  (+) electrode: $LiCoO_2 - e^- \rightarrow Li^+ + CoO_2$

  (–) electrode: $xC + Li^+ + e^- \rightarrow C_xLi$ (intercalation of Li into charcoal or graphene)



Vyboishchikov (40)

► in supercapacitors (= electrochemical capacitors) – devices using the electric capacity of the electrical double layer. Graphene works better than the traditional material (activated coal).

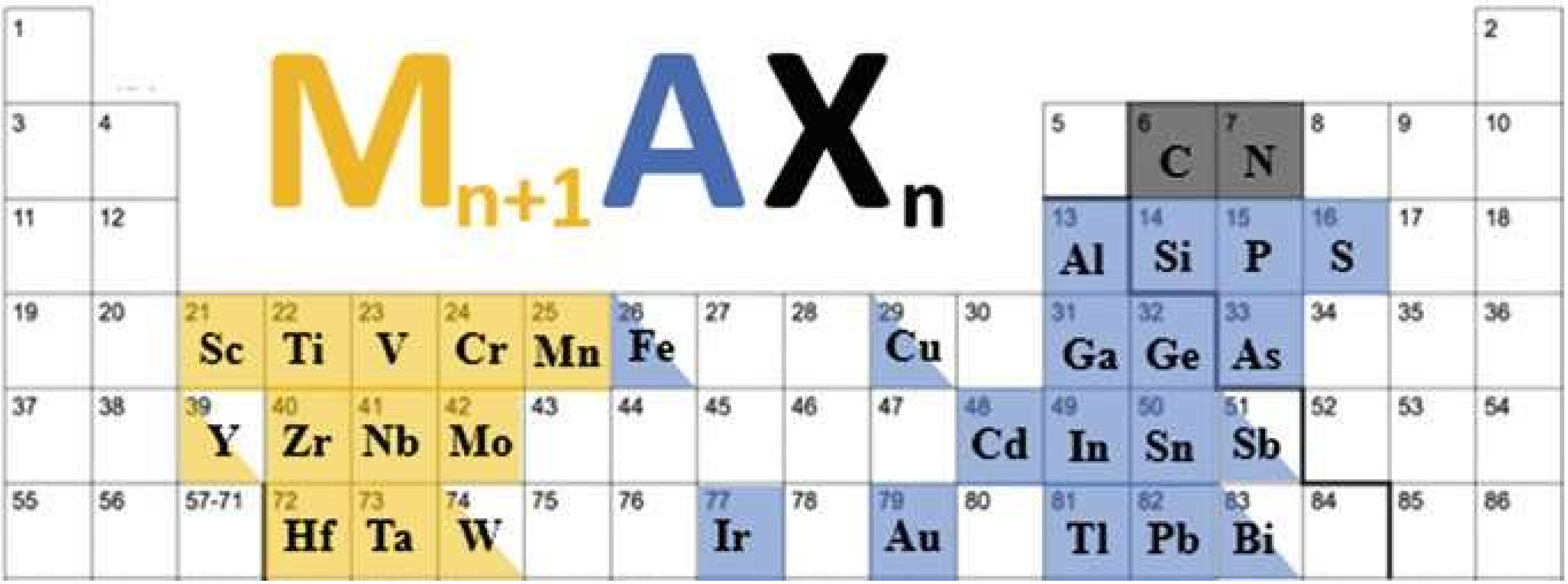


► in sensors;

► for water filtration and desalination.

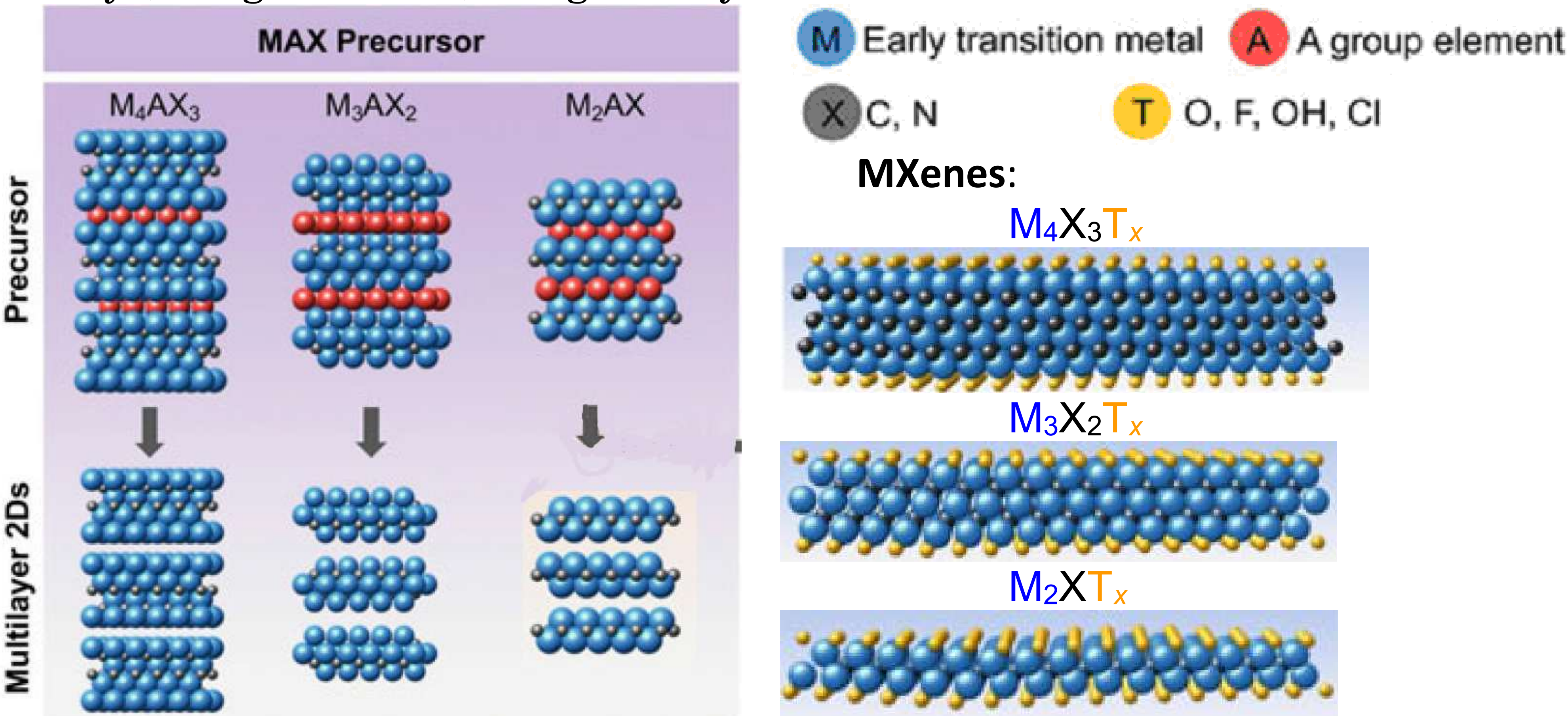
OVERVIEW OF NANOMATERIALS – MXenes

- **MXenes:** 2D transition-metal *carbides* and *nitrides*. (Yuri Gogotsi 2011)
  - Formula: $M_{n+1}X_nT_x = M_{n+1}C_nT_x$ or $M_{n+1}N_nT_x$
    M is a group 3–6 transition metal
    T = –O, –F, –OH, or –Cl is the *surface termination*
    n = 1 to 3.



  - Name: from *MAX phase* (layered carbides and nitrides in which $M_{n+1}X_n$ layers are bound together with layers of an element A (typically Al). Examples: Ti_3AlC_2, Mo_2TiAlC_2, $Mo_2Ti_2AlC_3$ (see next page 43).
  - ~30 various MXenes synthesized.
  - Electrical conductors or semiconductors.

- **MXenes:** synthesis: by selective etching of the A layers from MAX phases: MAX phases: mixed layered inorganic carbides or nitrides with intercalating "metallic" and "ceramic" layers. MAX phases are not nanomaterials, just ordinary (though unusual) inorganic crystalline materials known since 1950s.



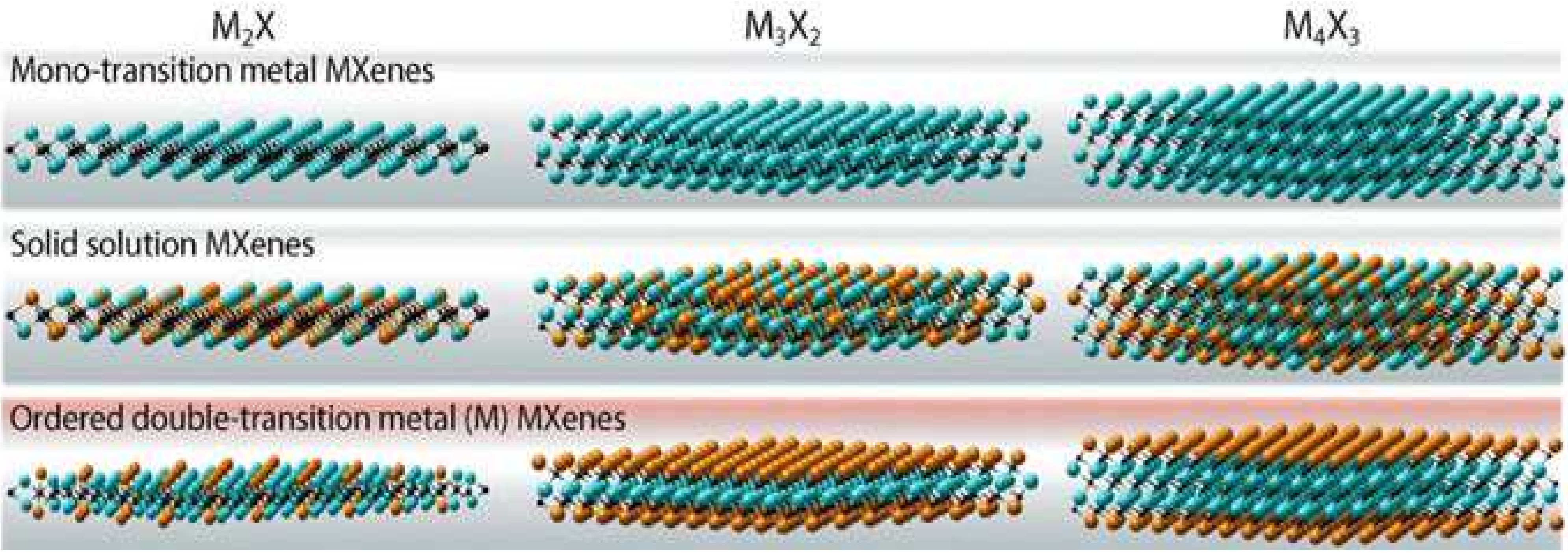
Synthesis of M_2XT_x, $M_3X_2T_x$, and $M_4X_3T_x$ MXenes as multilayer powders from MAX phases by ***etching***. Surface termination (O, F, or OH) is always present.

► Etching agents: HF, $[NMe_4]OH$

► Individual layers can be obtained by spraying.

- **MXenes** examples:
  - Sc_2CT_x, Ti_2CT_x, Nb_2CT_x
  - $Mo_4C_3T_x$, Ti_2CT_x, Nb_2CT_x
  - $Ti_3C_2T_x$
  - $(Ti,V)_3C_2T_x$, $(Ti,Nb)_3C_2T_x$ – solid-solution MXenes
  - $(Cr_2V)C_2T_x$, $(Mo_2Zr)C_2T_x$ – ordered double transition-metal MXenes

- **MXenes** structure:

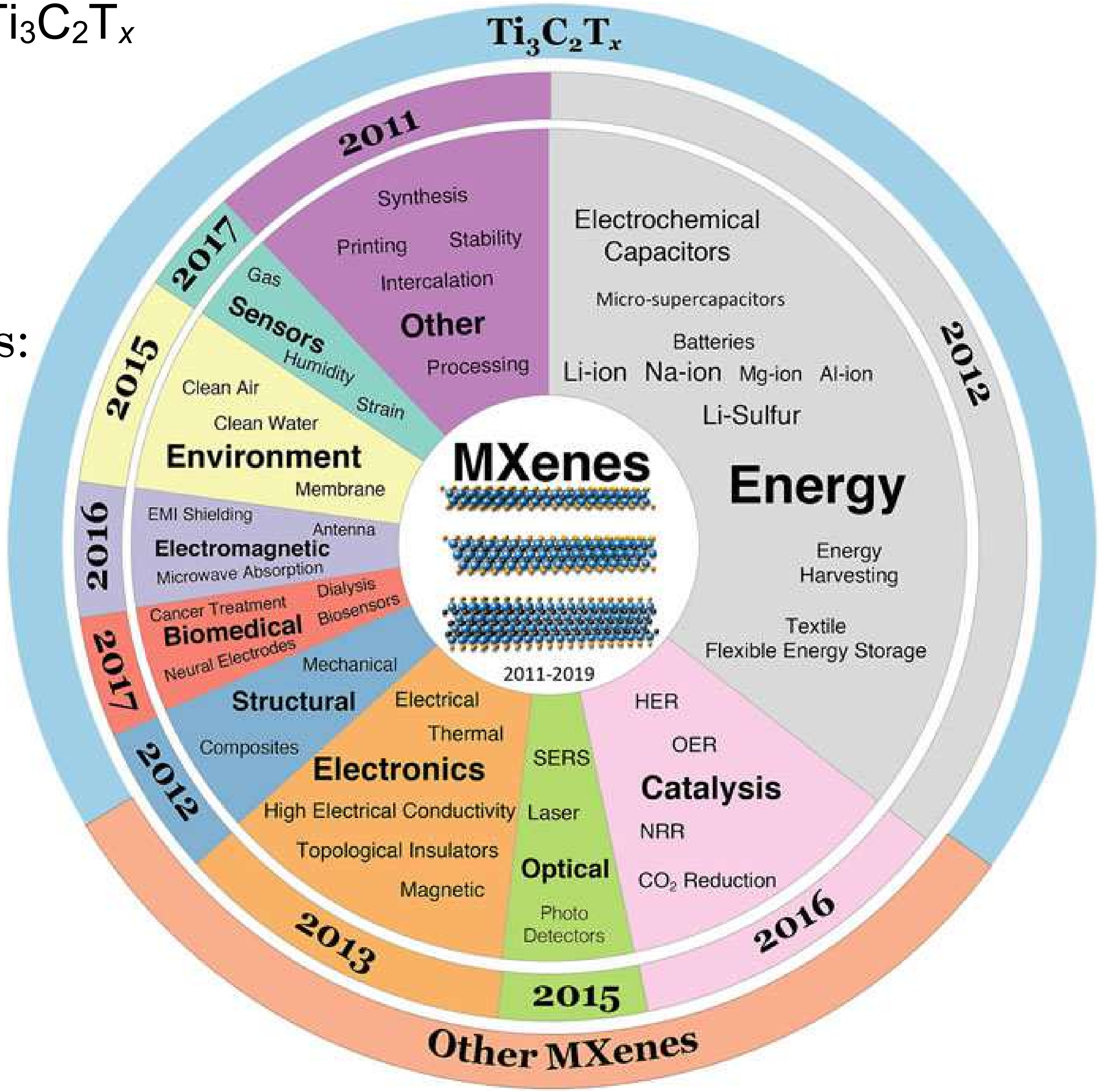


- **MXenes** usage: Mostly $Ti_3C_2T_x$

► For supercapacitors: $Ti_3C_2(OH)_x$ as negative-electrode material.

► For lithium-ion (and lithium-sulfur) batteries: $Ti_3C_2F_x$ as negative electrode.

► For electromagnetic shielding and as microwave-absorbing materials.

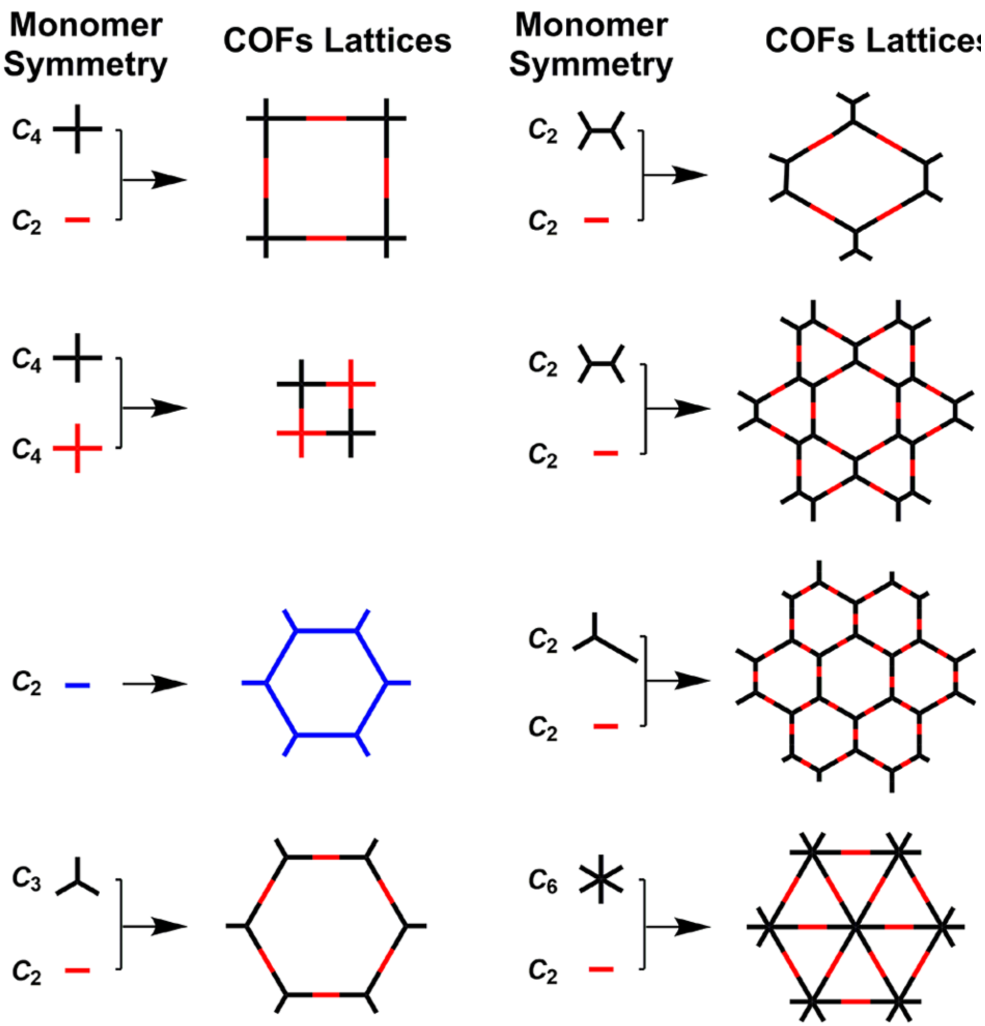


- **MXenes** usage (*continued*):
  - For *water treatment* – specially prepared $Ti_3C_2T_x$ as membranes
  - For *catalysis*
  - For *gas censors*: electric conductivity changes upon adsorption of ammonia or acetone
  - For *transparent conductive electrodes*
  - Biomedical applications:
    - *sensors*;
    - *photothermal treatment* (MXene heated by near infrared radiation inside tumor cells)
    - *Antimicrobal treatment*.

OVERVIEW OF NANOMATERIALS – COF

- **COFs**: covalent-organic frameworks are crystalline porous organic polymers with permanent porosity and highly ordered structures.

► typically co-polymers of two rigid symmetric monomers (building blocks):



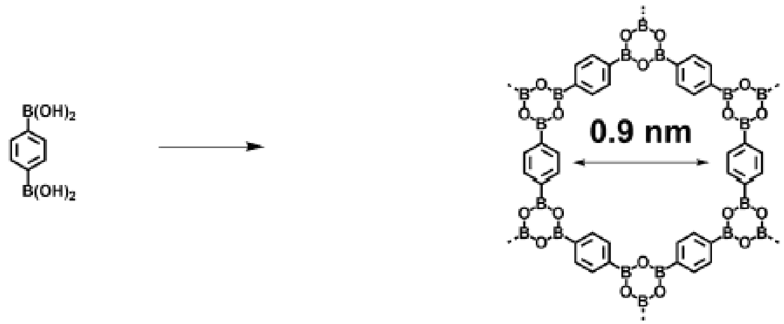
Linkages:

–CHO + H_2N– → –CH=N–

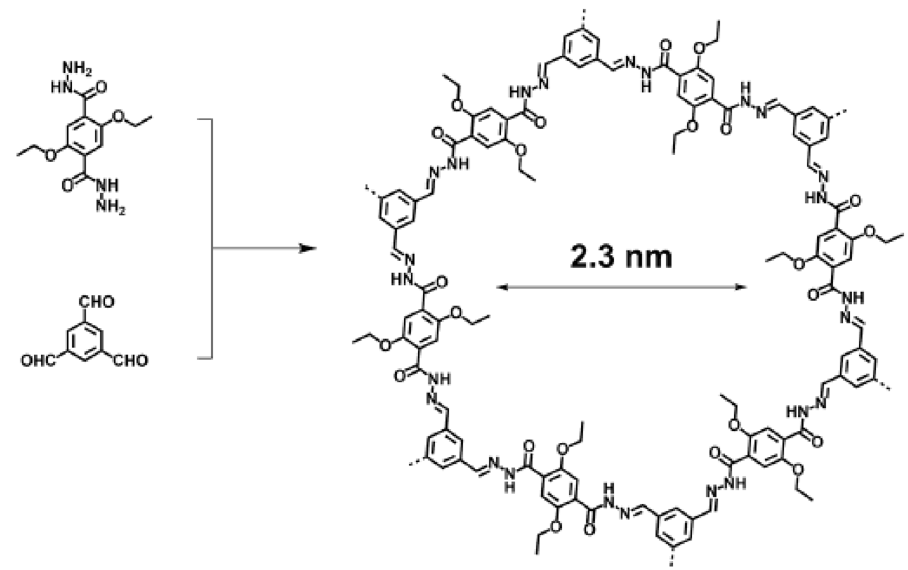
–CHO + H_2N–NH–C(O)– → –CH=N–NH–C(O)–

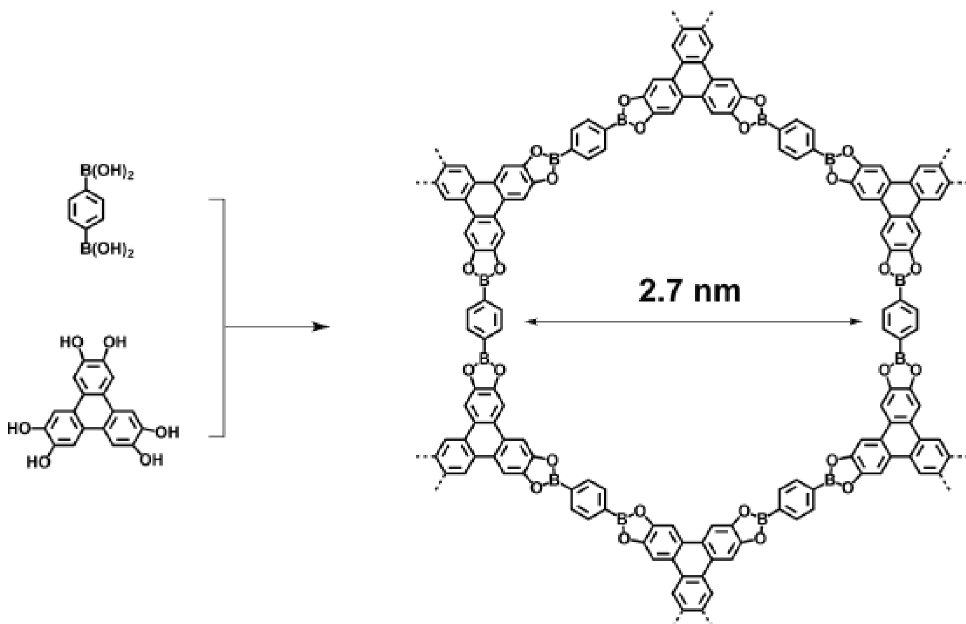
–OH + HO–B– → –O–B–

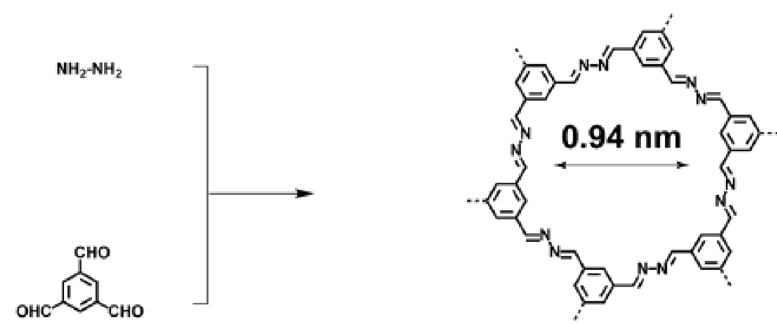
► COFs: examples:



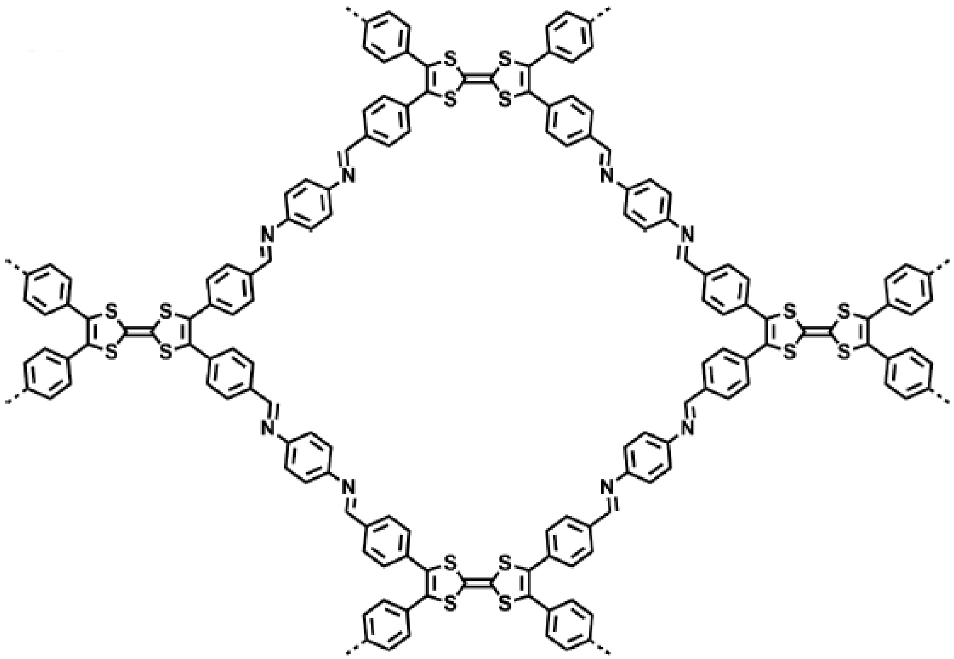
COF-1

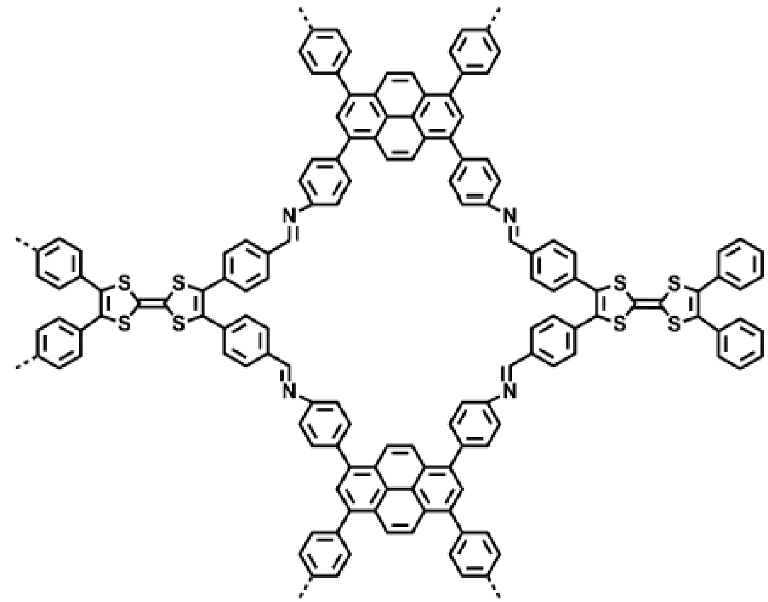




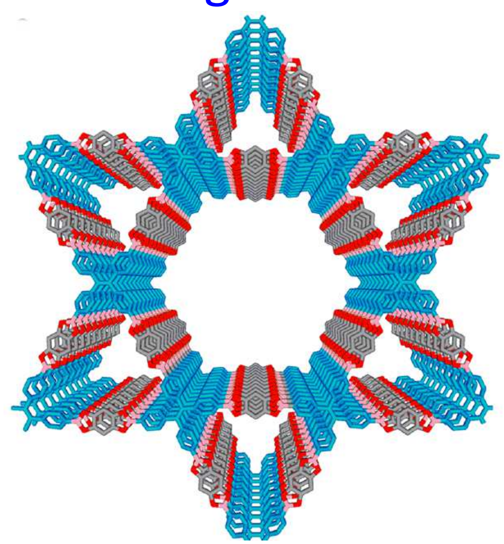


► COFs: more examples:



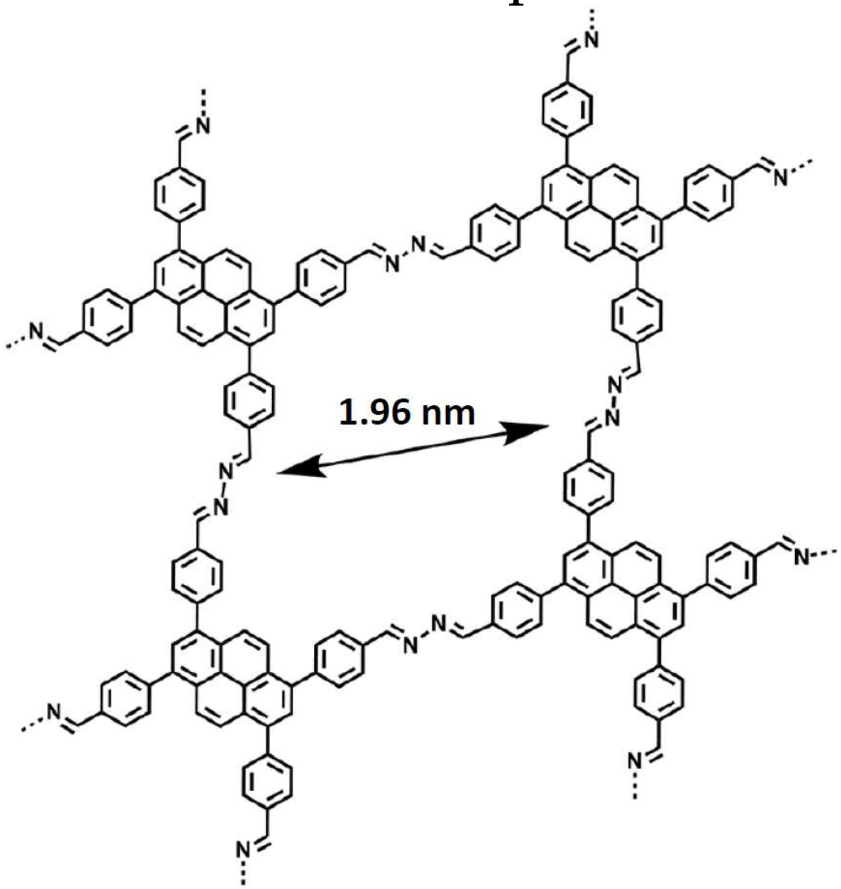


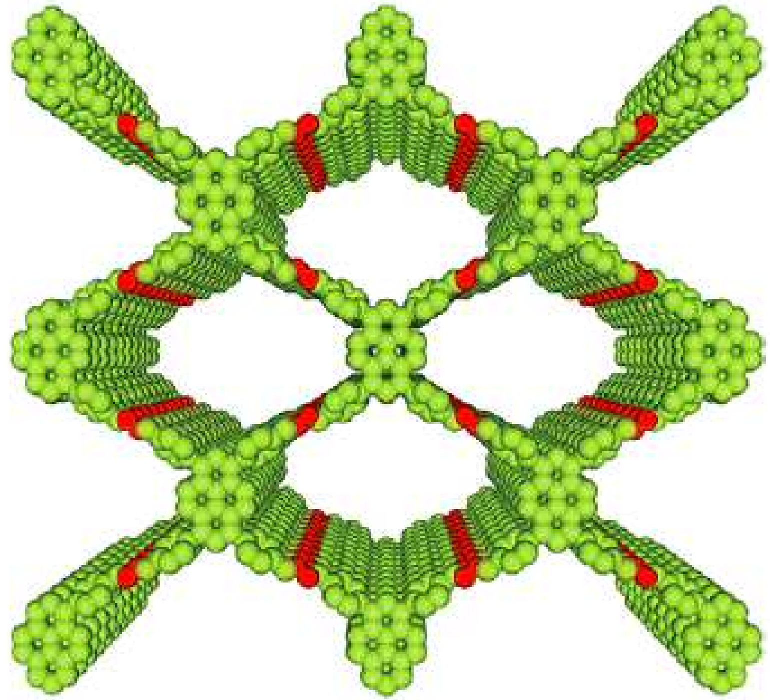
conducting COFs



luminiscent COF

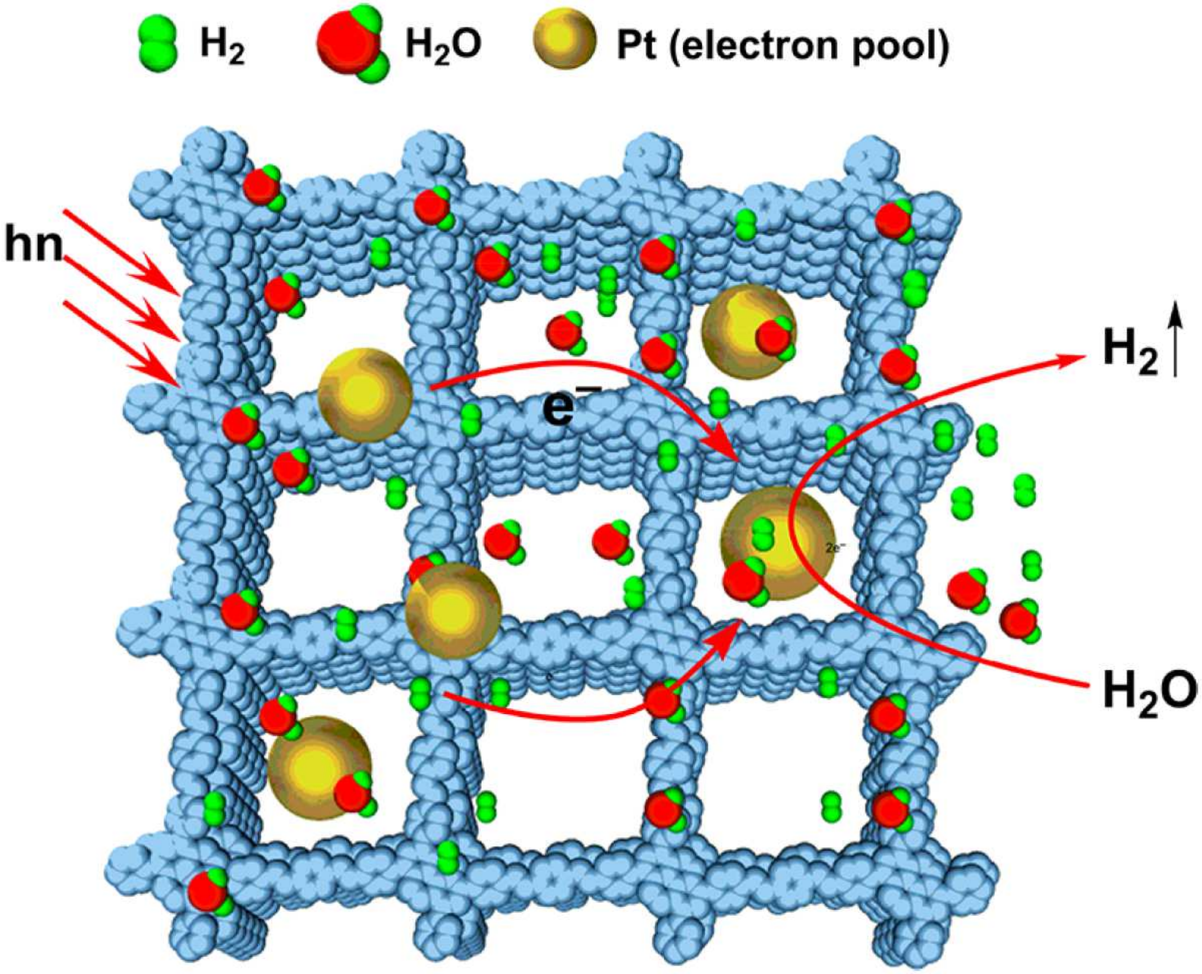
► COFs: more examples:





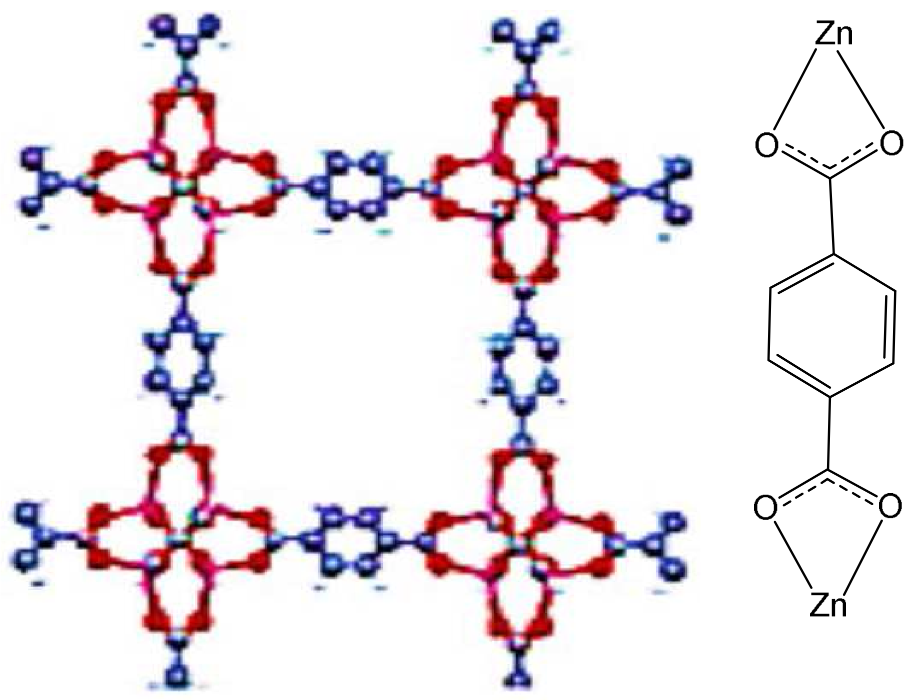
COF for sensing explosive (a luminiscent material; the sensor is based on luminiscence quenching in the presence of nitroaromatic compounds)

- COFs: catalysis
  - Photochemical water splitting (sophisticated H_2 evolution from water on certain COFs in conjunction with Pt nanoprticles):

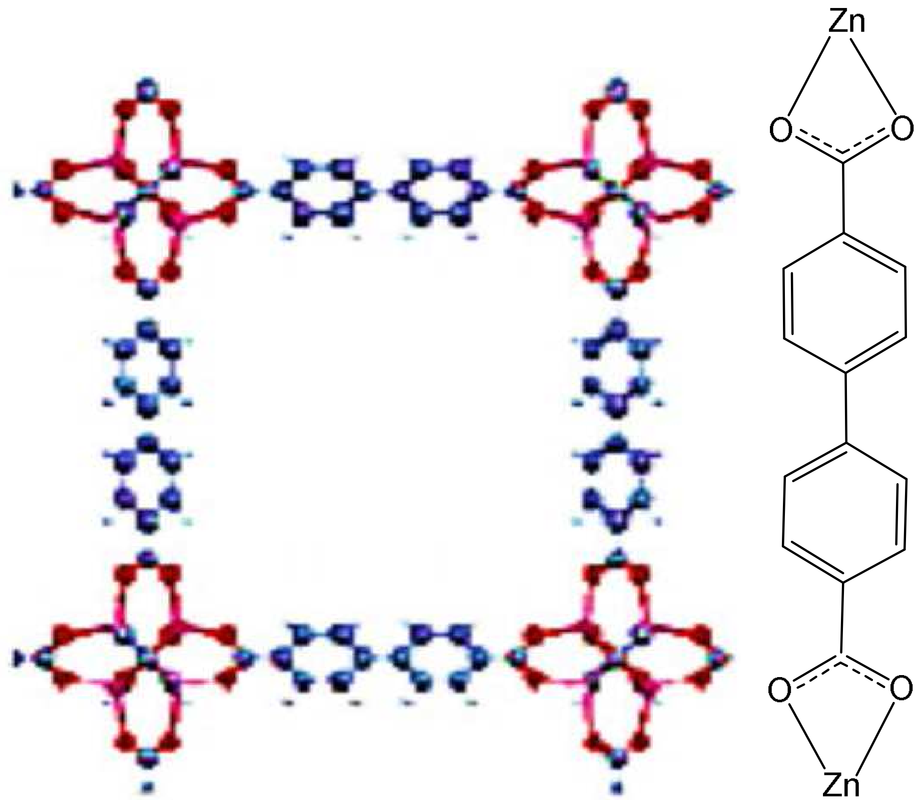


OVERVIEW OF NANOMATERIALS – MOF

- **MOFs**: metal-organic frameworks are porous coordination polymers



IRMOF-1 ($Zn_4O(BDC)_3$)
pore size: 1.12 nm



IRMOF-10 ($Zn_4O(BPDC)_3$)
pore size: 1.54 nm

► Structure:

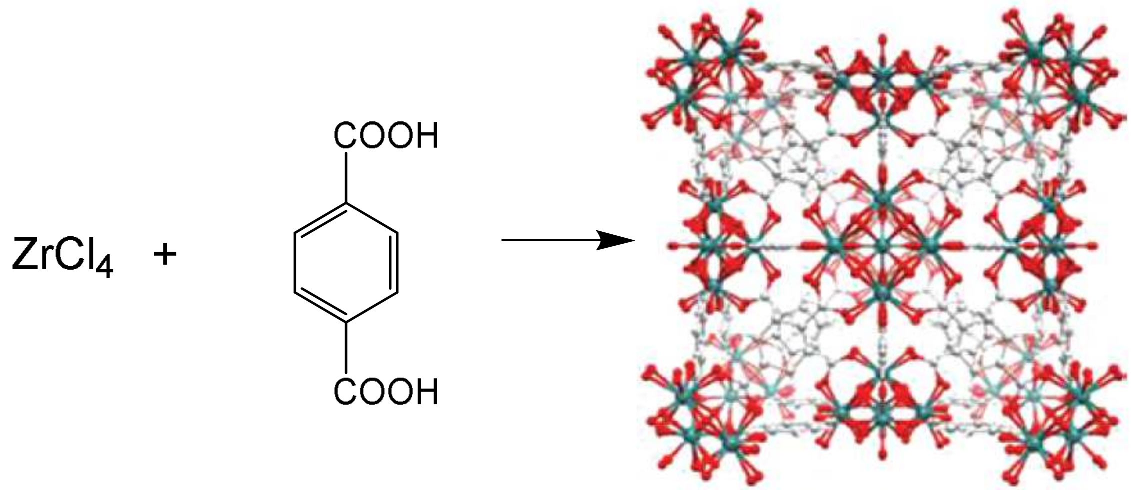
– Metal ions: Zn^{2+}, Cu^{2+}, Mn^{2+}, Fe^{3+}, V^{3+}, Al^{3+}, Cr^{3+}, Zr^{4+} ...

– Bridging ligands: must be rigid; often di- or tricarboxylates or diamines

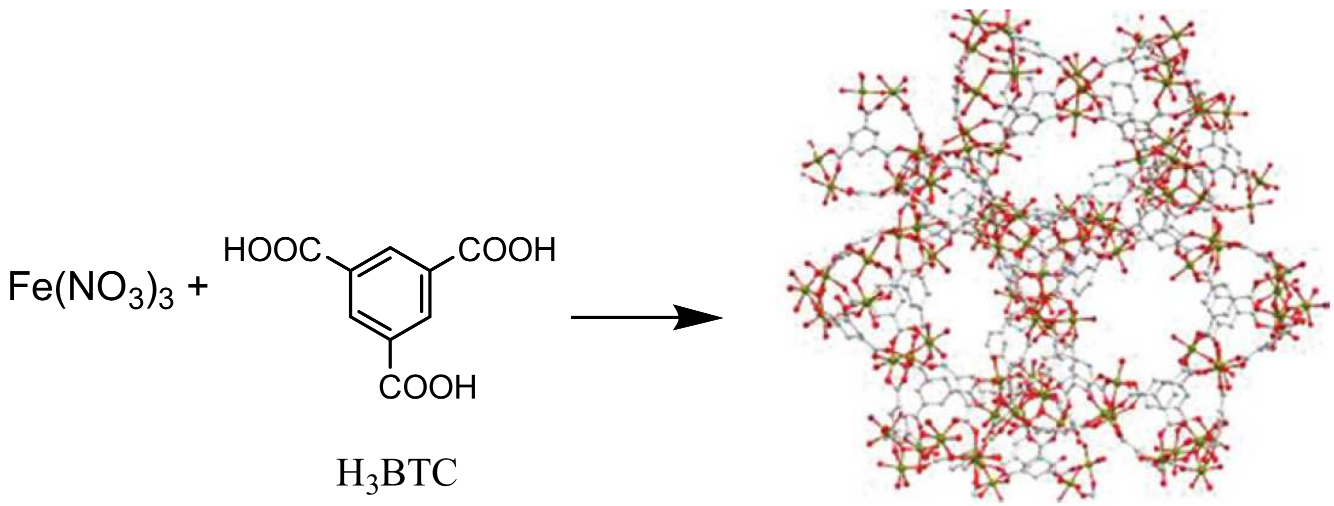
– may contain small counterions (Na^+, NO_3^-...)

– Pores: 0.8 – 2.5 nm, but can be larger.

- **MOFs**: synthesis:
  - ► Hydrothermal – in autoclave from a hot aqueous solution (≥100 °C) under pressure followed by washing with an organic solvent and drying.

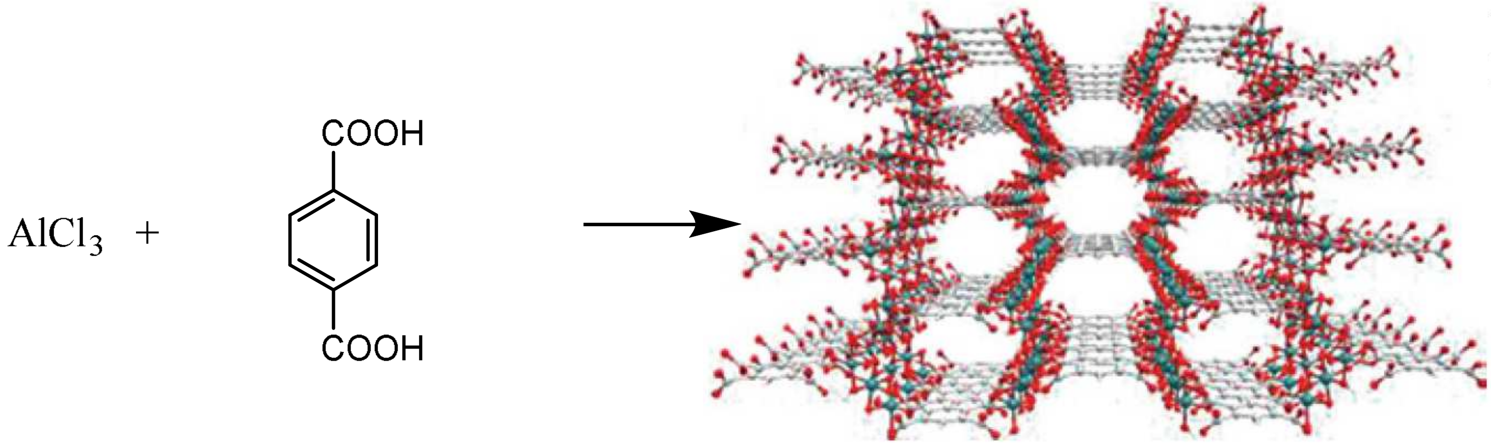


$[Zr_6O_4(BDC)_2]$ **UiO-66**

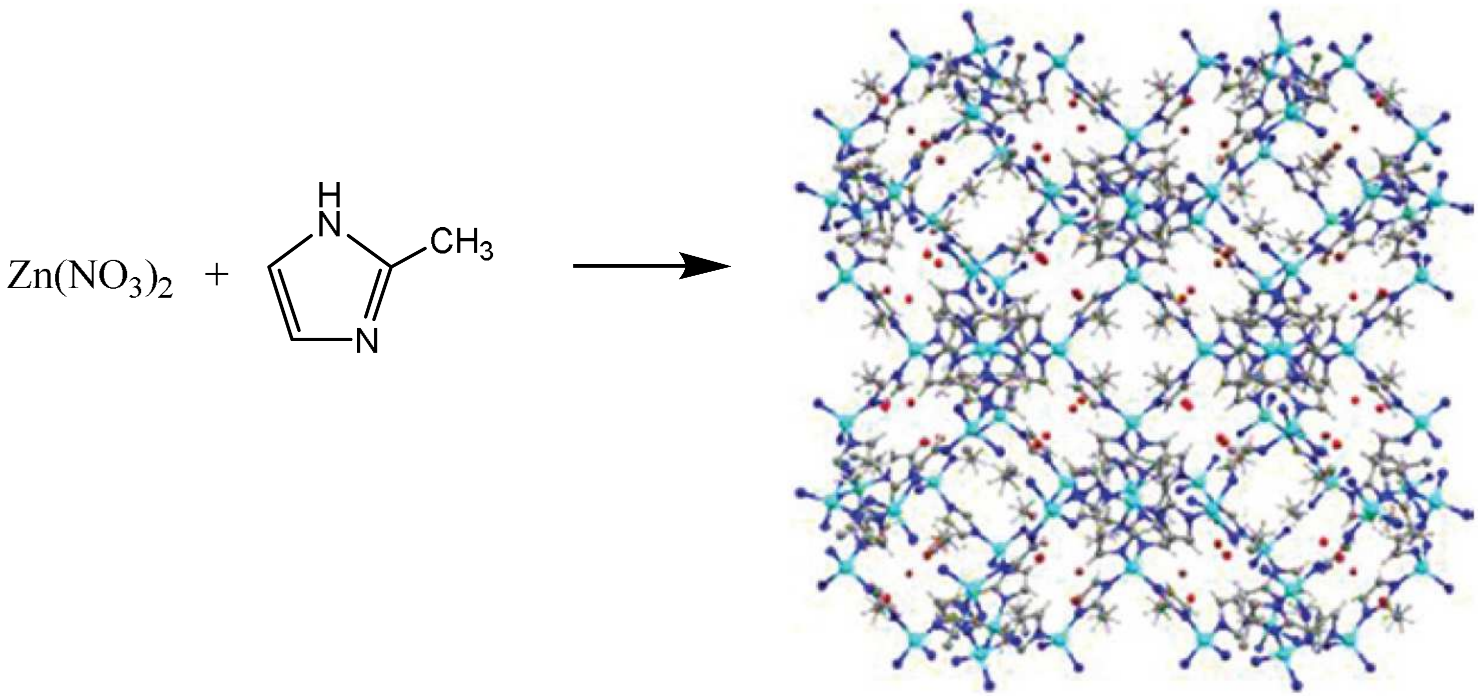


$[Fe_3O(H_2O)_2OH(BTC)_3]_2 \cdot nH_2O$
Basolite F300

► Hydrothermal synthesis of MOFs (continued)

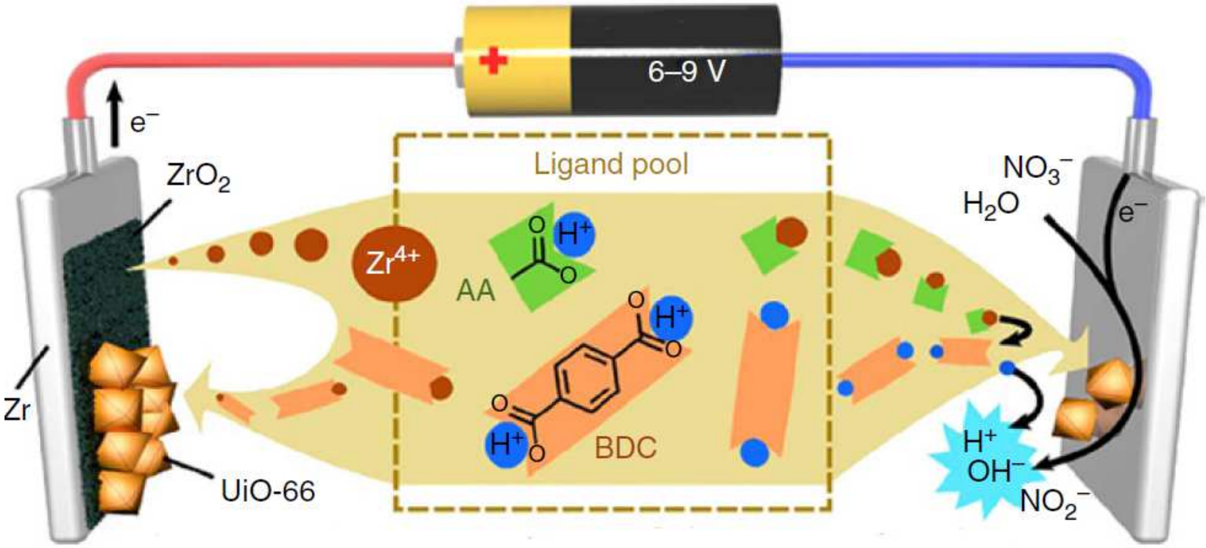


$[Al_4(BDC)(H_2O)_4]\cdot 5H_2O$ **MIL-53**

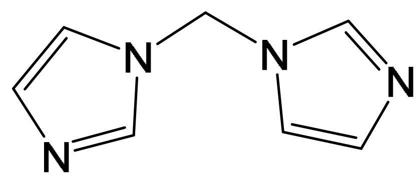


$Zn(MeIM)_2 \cdot nH_2O$ **ZIF-8**

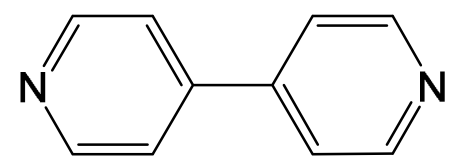
- **MOFs**: synthesis (*continued*):
  - ► Electrochemical synthesis: sacrificial metal anode as a metal source



- **MOFs**: applications
  - ► Separation (like classical "molecular sieves" – alumosilicates):
    - – Gas separation and purification, e.g. Cu(BDC) MOF for eliminating CO_2 from methane: preferential adsorption of CO_2 on the MOF; $Zn_2(BIM)_4$ MOF with small pores for separing CO_2 and H_2.
  - ► Gas storage:
    - – $Co_2(4,4'\text{-bipy})_3(NO_3)_4$ MOF; other Zr-, Zn, Al-based MOFs for methane storage.



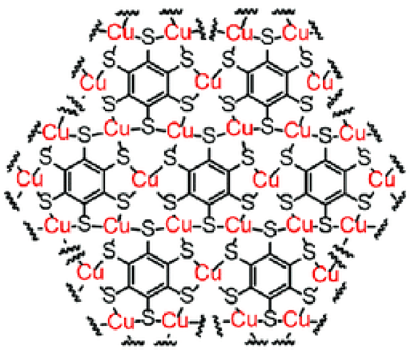
BIM = bis(1-imidazolyl)-methane



4,4′-bipyridine

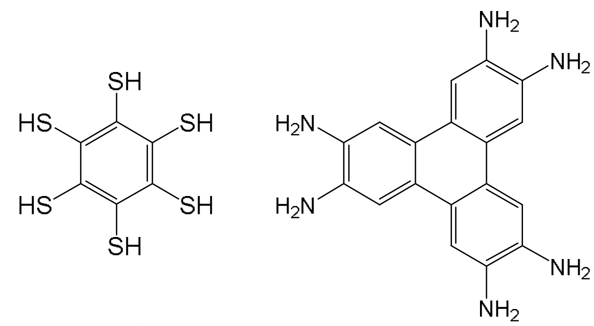
OVERVIEW OF NANOMATERIALS – MOF

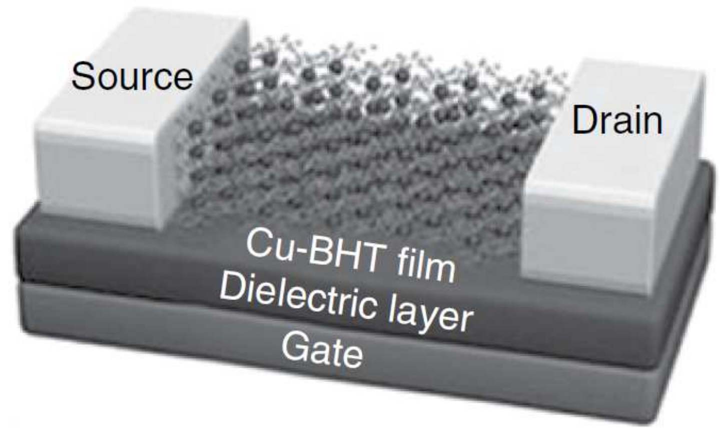
- **MOFs**: applications (*continued*):
  - ► In electronics: Cu_3(BenzeneHexaThiolate) and Ni_3(HexaIminoTriPhenylene)$_2$ MOF for field-effect transistors



Cu_3(BHT)

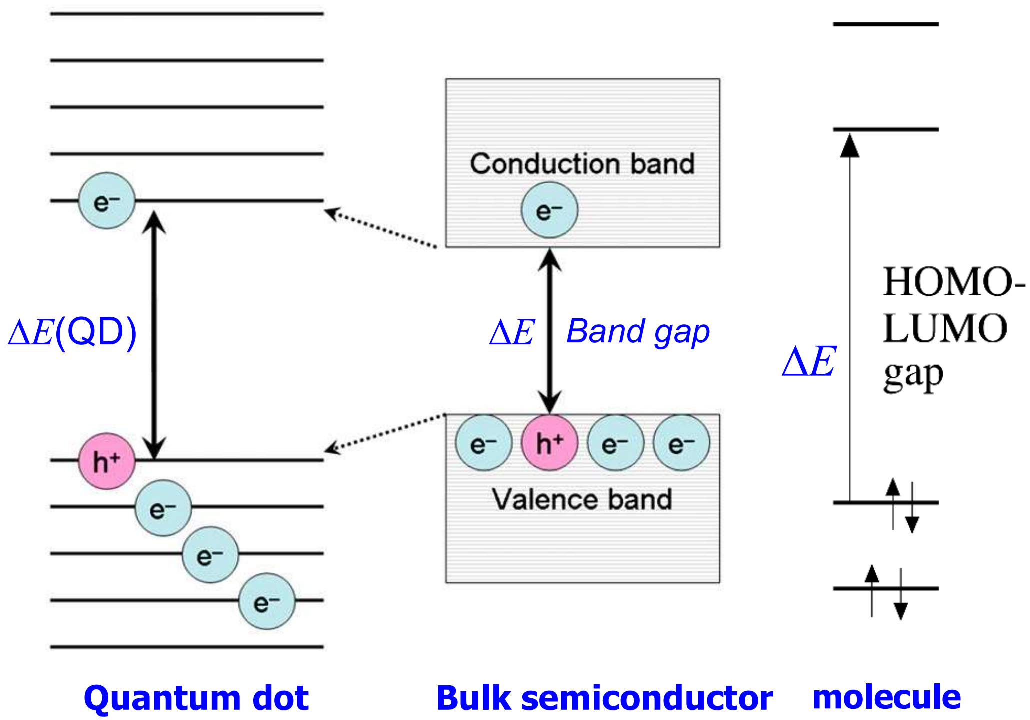
Ni_3(HITP)$_2$





  - ► For catalysis:
    - Both as support (e.g. for Pd or Pt) and on their own (confinement of reactants inside the MOF nanopores; catalysis directly on a metal center):
      – various chemical reactions: hydrogenation, cross-couplings, esterification...

- **Quantum dots:** 2023 Nobel prize in chemistry to Bawendi, Brus, and Ekimov:
  - ▶ A quantum dot is a nanosize piece of a crystalline semiconductor material.
  - ▶ Originally discovered by Ekimov in CuCl-containing molten glasses; unconsciously used by medieval glassmakers for stained glasses.
  - ▶ Quantum behavior is observed when the quantum dot is sufficiently small.
    - – Discrete energy levels of a free particle in a spherical box
  - ▶ The band gap is size-dependent:

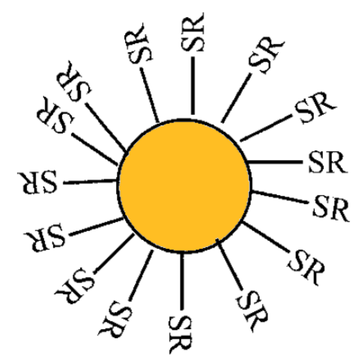


- **Quantum dots:**
  - *Examples*:
    - CdSe, ZnSe, ZnS, CdS, PbS, HgS, InAs, InP, but also Si, Ge;
    - Size: 100–100 000 atoms ≈ 10–50 atoms in diameter ≈ 2–10 nm
  - *Preparation* of CdS/ZnS quantum dots:
    - Colloidal synthesis (most common):

      1) A colloid must be stabilized ⇒ Cd^{2+} (aq.) + a water-soluble polymer; then S^{2-} is added ⇒ The polymer competes with S^{2-} for Cd^{2+} ⇒ aggregation is prevented.
         - Temperature, pH, reagent concentration influence the particle size;

      or

      2) Adding thiols to terminate the particle growth. Thiolate-capped quantum dots are formed →



    - Biosynthesis:
      Yeast, certain bacteria and tomatoes (and likely other organisms) produce CdS quantum dots from $CdCl_2$ and sulfur-containing sources (S^{2-}, SO_4^{2-}, Cys, Met...); the CdS is coated with peptides.
      - *as a detoxication response to an overload of Cd.*

- **Quantum dots:**
  - *Preparation* (continued):
    - Preparation of Si quantum dots (Ge is similar):
      - Gas-phase pyrolysis of SiH_4 or Si_2H_6;
      - Reduction of $SiCl_4$ or $SiHCl_3$ in an organic solvent:

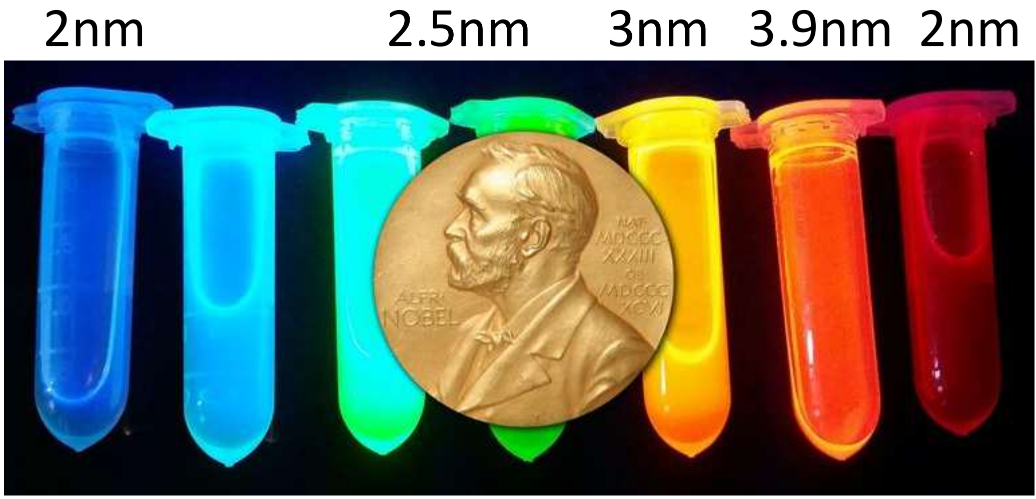
        Na(naphthalene) + $SiCl_4$

        $LiAlH_4$ + $SiCl_4$
      - Reaction of $SiCl_4$ with a *silicide* (Zintl phase) in an organic solvent (e.g. dimethoxyethane):

        NaSi + $SiCl_4$

        Mg_2Si + $SiCl_4$

- **Quantum dots:**
  - ► *Physical properties*:
    - – *Photoluminiscence* – electrons are excited by photons (often UV) from the valence band to the conductance band; then a photon is emitted;
      - High quantum yields (up to 0.5);
      - Narrow emission bands;
      - High stability (compared to organic dyes)
    - – *Electroluminiscence* – electrons are excited by electric current.



CdSe quantum dots

  - ► Applications – *photoluminiscence*:
    - – Photoluminiscent dyes;
    - – Sensors: quantum yield of a quantum dot on adsorbates on coating;
    - – Medical applications (to be discussed later).

- Ekimov's original CuCl quantum dots are *not* luminiscent, just colored.

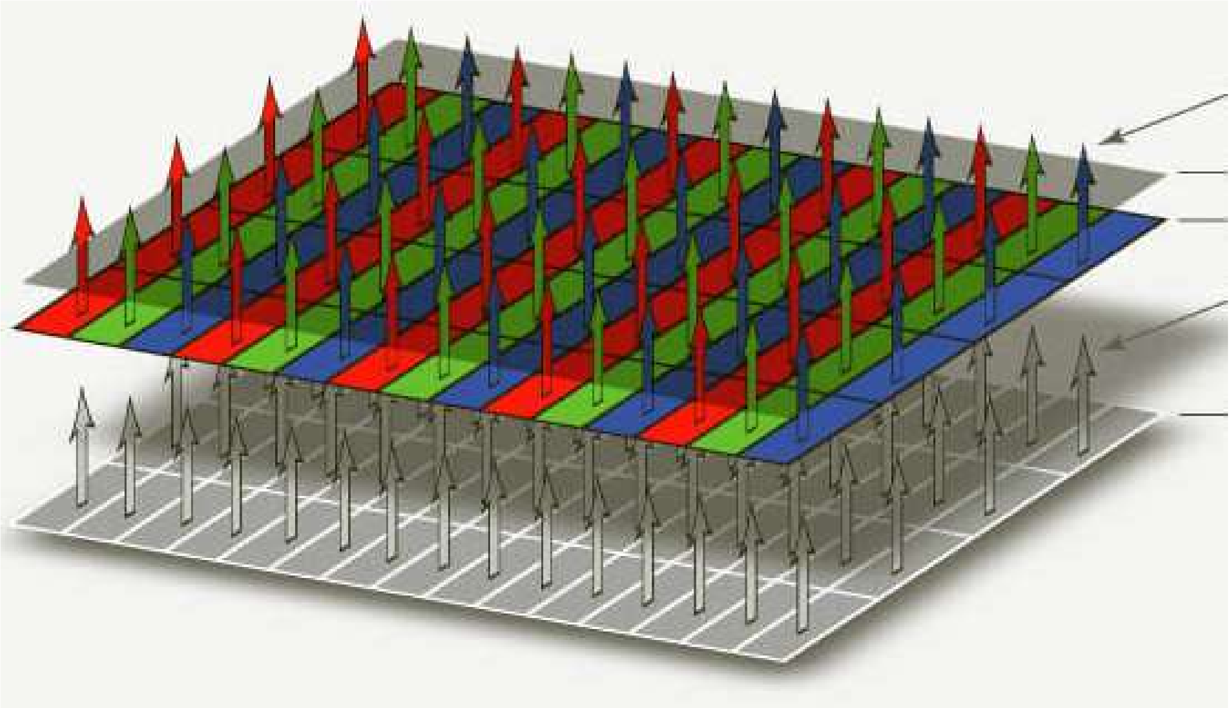
OVERVIEW OF NANOMATERIALS – quantum dots

► Applications – *electroluminiscence*:

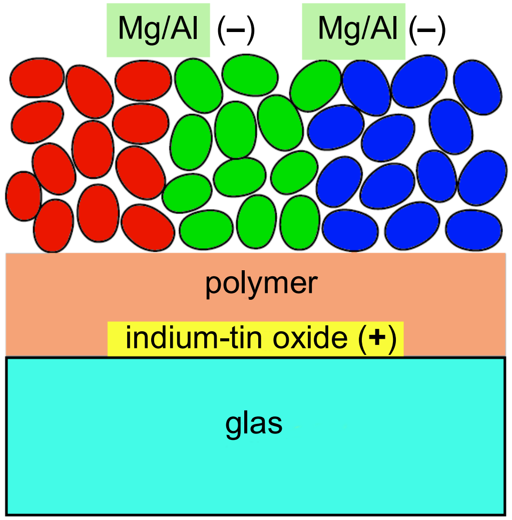
– Light-emission devices (LED) – based on electroluminiscence; color pixels made directly from quantum dots – marketed by LG, Samsung (2–10 nm quantum dots); see e.g. https://www.amazon.es/dp/B0BQNCBL8L

– Laser (stimulated emission similar to luminiscence);

How a quantum-dot based device works:



Positive electrode: transparent, conducting indium-tin oxide; negative electrode: magnesium–silver. The electrical current passes through the quantum dots, resulting in the emission of photons. The size of the quantum dot determines the wavelength of the *electroluminescence*.

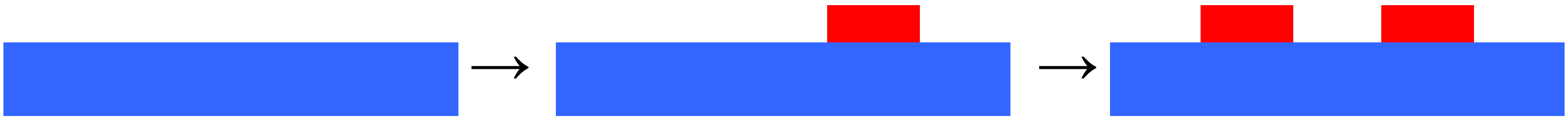


- ***Cancer diagnostics*** with ***quantum dots***:
  - ► Examples:
    - – Quantum dots coated with polyacrylate and covalently linked ("conjugated") to antibodies;
    - – Immunofluorescent labeling of breast cancer marker HER2 and prostata cancer marker PSMA; both *in vitro* and *in vivo*.
  - · The fluorescence is *specific* for the target and *brighter* and more *photostable* than comparable organic dyes.

NANOMATERIALS – FABRICATION 1

- **“Bottom-Up” and “Top-Down” approaches:**

► The “*bottom-up*” approach: nanomaterial is obtained by assembling atomic or molecular precursors to form the desired structure:



– Physical Vapour Deposition (PVD);

– Chemical Vapour Deposition (CVD);

– Molecular Beam Epitaxy;

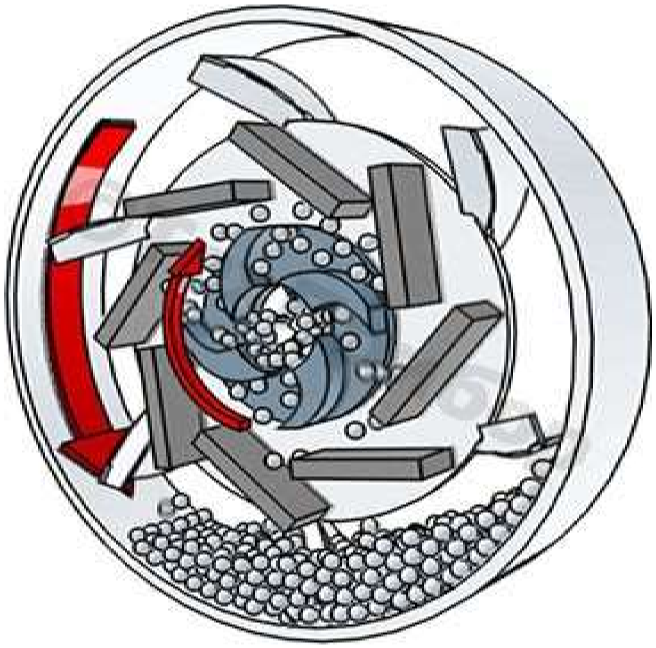
– Writing atom by atom;

– Sol-Gel Process;

► The “*top-down*” approach: nanomaterial is obtained from a bulk by progressive removal of material:

– Photolithography;
– Etching;
– Electrospray (see page 65);
– Electrospinning (see page 66);

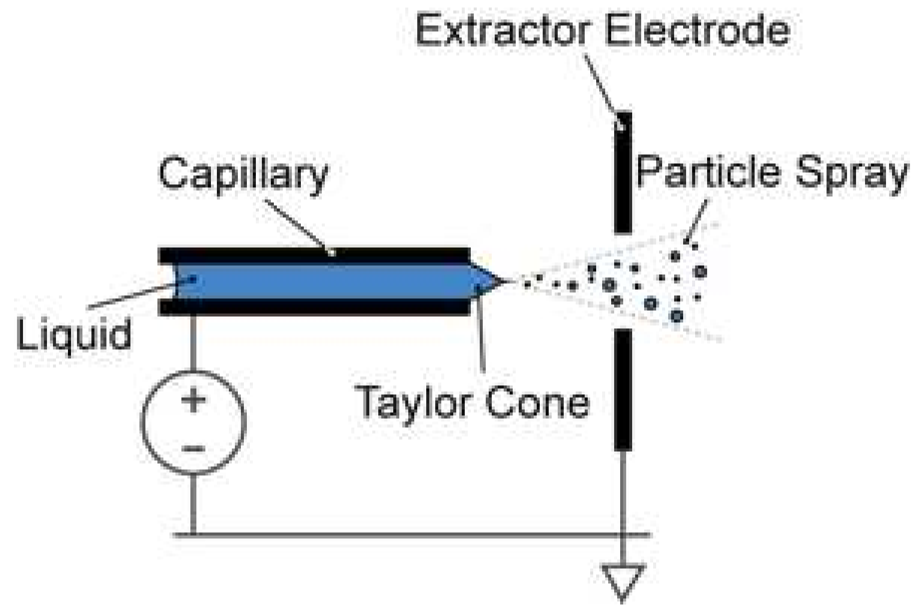
- **Mechanical methods:**
  - ► Ball mills – often used for preparing metal-oxide nanoparticles:



  - ► Dispersion of liquids or melts by a liquid or gas stream:
    - – Metal powders: Fe, Al, Cu, Pb, Zn, Ti, W...
    - – Cooling rates: $10^3 - 10^8$ °C per second

- **Electrospray**

  ▶ Liquid surface is polarized by a strong electric field ⇒ surface charges ⇒ repulsion ⇒ liquid meniscus changes its shape (“Taylor cone”).

  ▶ Small charged droplets leave the surface and continue splitting.

  – Very small particle sizes (up to atomic) are possible.

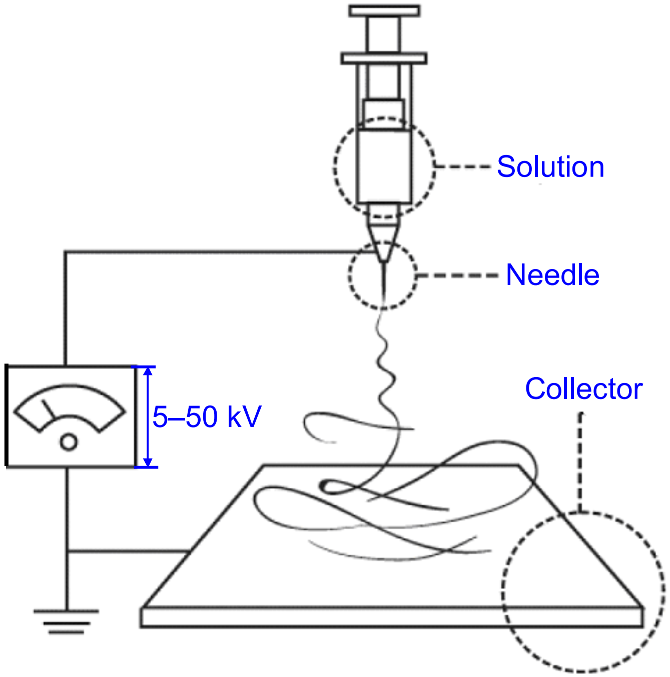
- **Electrospray applications:**

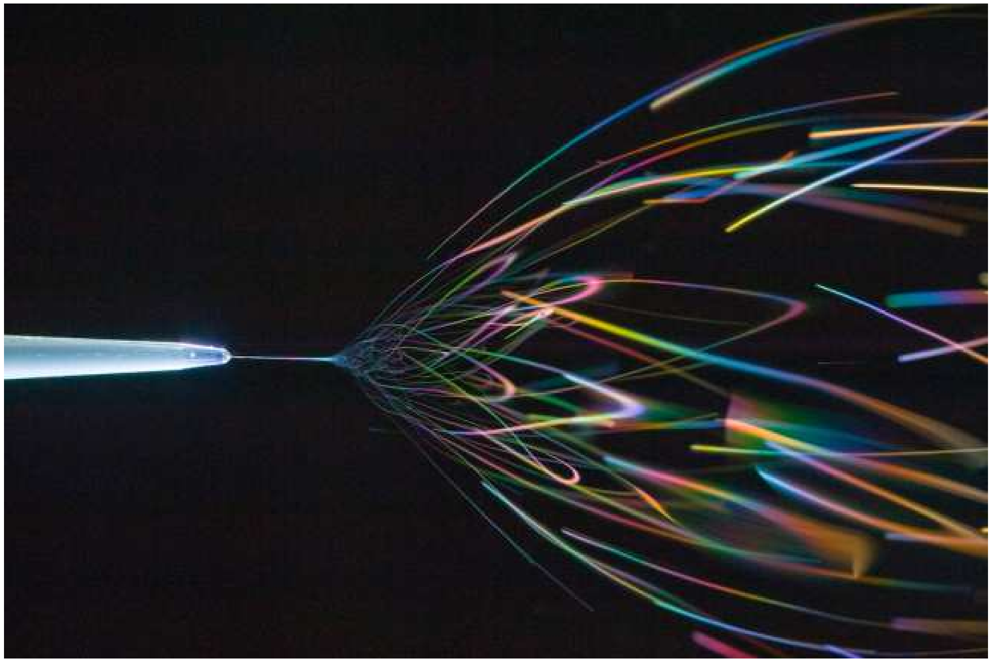
  ▶ Electrospray ionization in mass spectrometry (including analysis of large biomolecules);

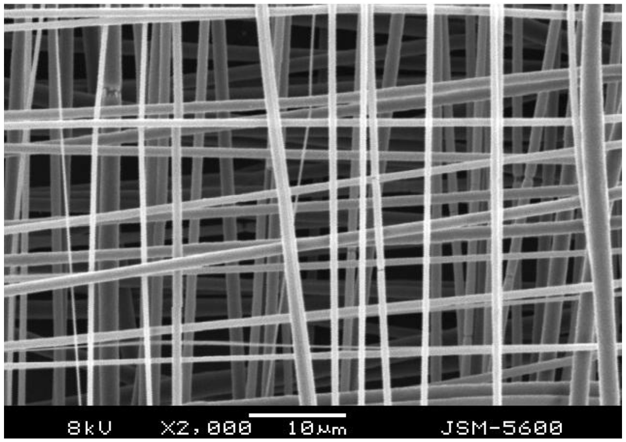
  ▶ Electrospinning (see next page 66);

  ▶ Deposition of particles for nanostructures:
  – spraying colloids (one particle per droplet); solvent evaporates on the fly, leaving a single particle, which is deposited on a target.

- **Electrospinning**
  - Fine polymer fibers (micro/nano) are drawn electrically from a liquid;
  - Polymer solutions or (less common) melts are used.
  - Resulting fiber diameter: hundreds of nanometers.

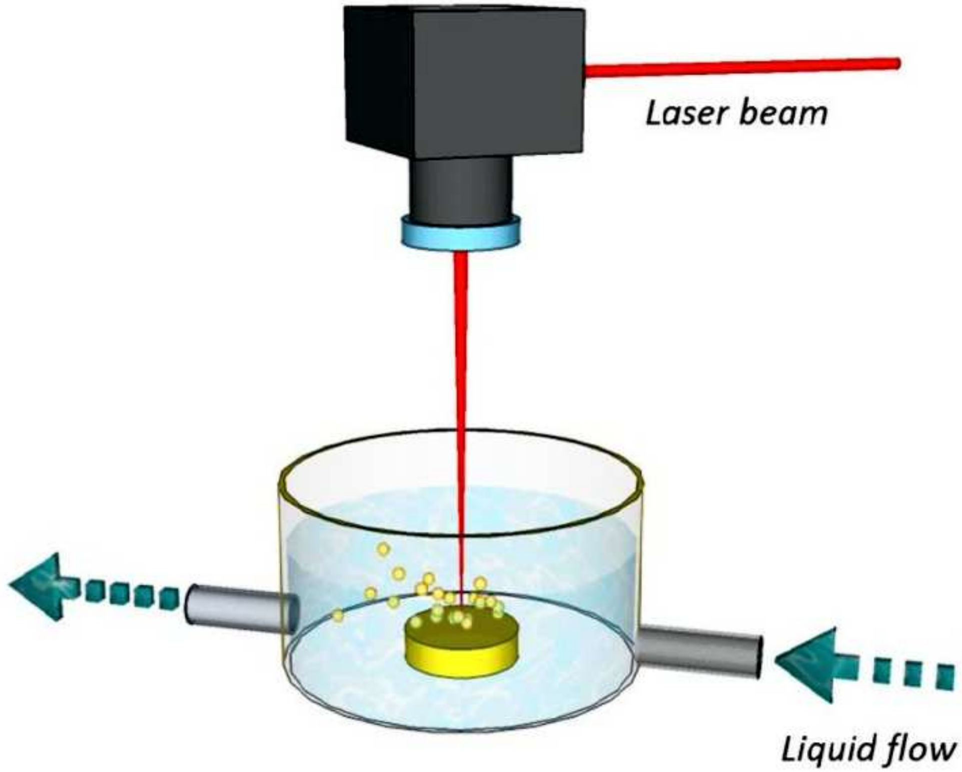






- **Physical vapor deposition (PVD)**
  - ► Widely used in *microelectronics* for deposing conducting metallic films.
  - ► Also used for Si, GeO_2, SnO_2, Ga_2O_3, ZnO, SnO_2 ,... nanoparticles.
  - ► Three steps: evaporation, transport, condensation.
  - ► Evaporation temperatures: ~500–1200 °C
  - ► Low-pressure (~0.01 atm) noble gas (He, Ar) atmosphere (not vacuum);
  - ► The nanoparticles formed are usually removed by a blade (scraper) made of a hard material (not for films).

- **Laser ablation**
  - ► Similar to PVD, but laser puls is employed for heating:



  - ► Typically performed in a liquid (water, alcohols, chlorinated hydrocarbons, DMSO ($(CH_3)_2SO$)...), sometimes gas, but *not* vacuum.
  - ► Suitable for obtaining nanoparticles of:
    - – Metals (Ag, Au, Cu, Pd, Ti, Zn, Co, Ni) and alloys;
    - – Oxides: TiO_2, CuO, ZnO;
    - – Semiconductors: Si, Ge, CdS, ZnSe...
    - – In the gas phase is also suitable for fullerenes and carbon nanotubes.

- **Sol-gel process**

  – *Sol* is a colloid solution of a *solid phase* in a *liquid*.

► Sol-gel process consists of a number of steps (Stöber process – silica gel formation – as an example):

– Precursor → colloid (sol). A *precursor* is typically an organic alkoxide: $(CH_3O)_4Si$ (TMOS), $(C_2H_5O)_4Si$ (TEOS).

– *Hydrolysis* (sometimes with acid or base catalyst):

$(CH_3O)_4Si + H_2O \rightarrow (CH_3O)_3Si(OH) + CH_3OH$

$(CH_3O)_3Si(OH) + H_2O \rightarrow (CH_3O)_2Si(OH)_2 + CH_3OH$

$(CH_3O)_2Si(OH)_2 + H_2O \rightarrow (CH_3O)Si(OH)_3 + CH_3OH$ ...

Condensation / polymerization:

$(CH_3O)_3Si(OH) + (CH_3O)_3Si(OH) \rightarrow (CH_3O)_3Si{-}O{-}Si(OCH_3)_3 + H_2O$

$(CH_3O)_2Si(OH)_2 + (CH_3O)_3Si(OH) \rightarrow (CH_3O)_2(OH)Si{-}O{-}Si(OCH_3)_3 + H_2O$

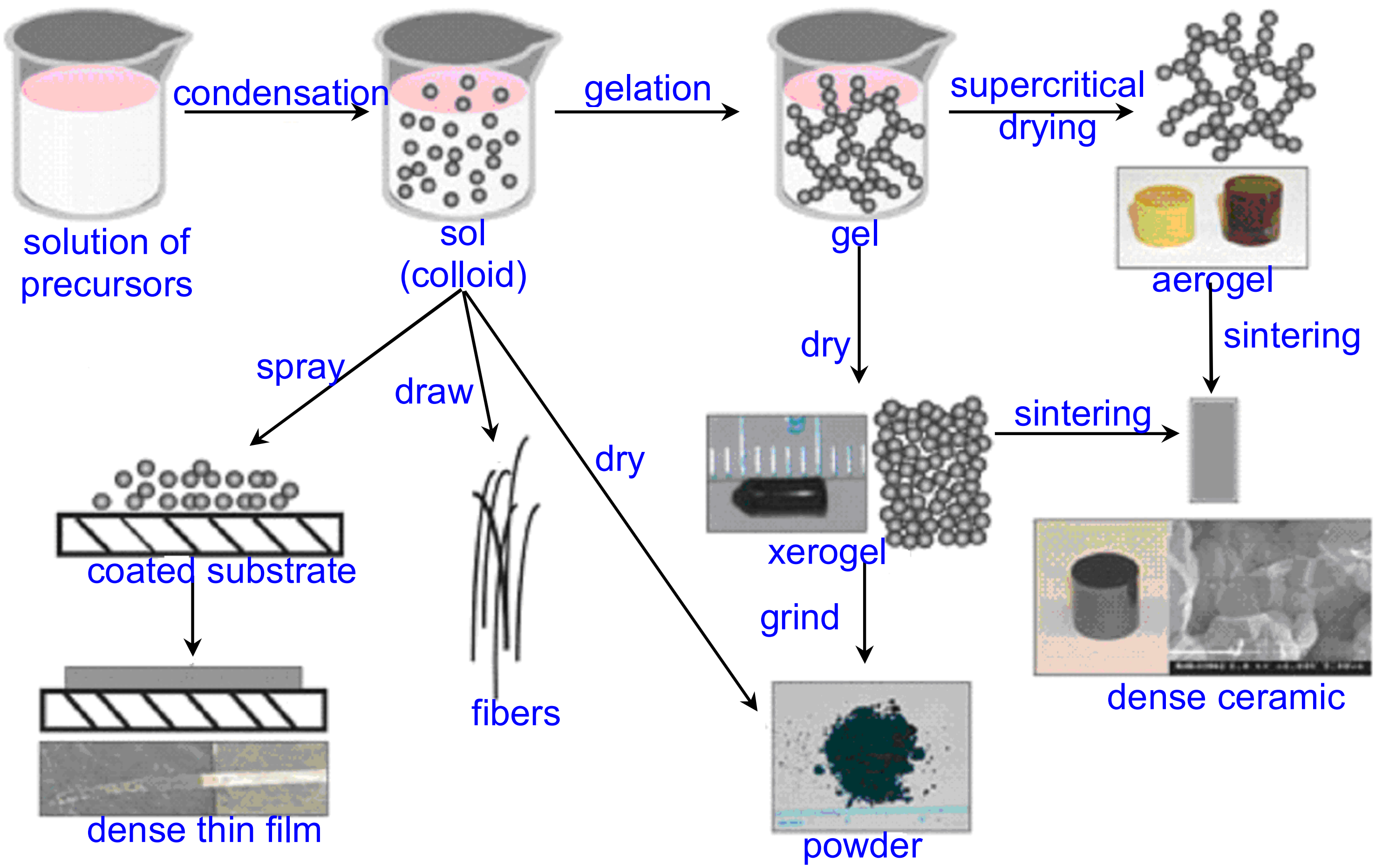
$(CH_3O)_2(OH)Si{-}O{-}Si(OCH_3)_3 + (CH_3O)_2Si(OH)_2 \rightarrow$

$(CH_3O)_2(Si(OH)(CH_3O)_2Si{-}O)Si{-}O{-}Si(OCH_3)_3 + H_2O$ ...

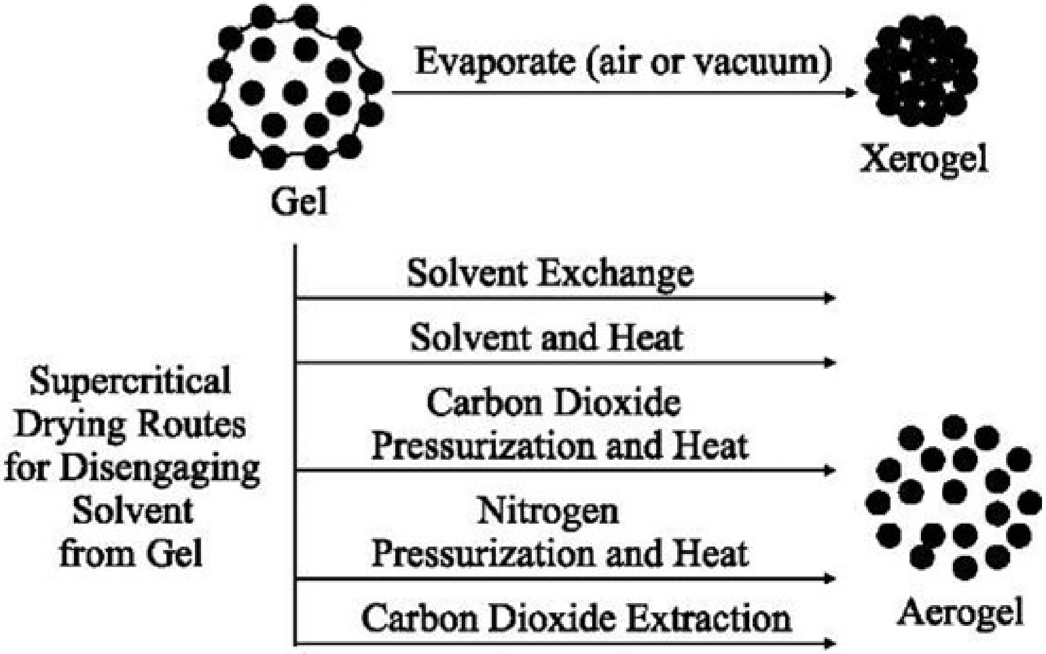
Such condensation results in formation of large "molecules" with Si–O–Si–O network (and possibly some H_2O molecules) inside and OH or OR groups both inside and outside ⇒ a colloid particle ⇒ **sol**.

- **Sol-gel process**
  - *Particle agglomeration (gelation):*
    As the hydrolysis proceeds further, the particles become cross-linked
    ⇒ **gel** – a colloid network system filled by a solvent.
    Gels exhibit no flow (when in steady-state).

► The sol-gel process is used for preparing silica gels and other hydrogels (alumo gels, alumosilicate gels etc.)



- **Sol-gel products** – comments:
  - ► Viscoelasticity: gels are non-fluid when in steady-state, but behave like liquids when agitated (non-Newtonian fluid).
  - ► Drying of a gel under *normal* conditions occurs *with shrinking* to produce a xerogel [zɪərədʒɛl]. Example: dry silica gel – pore diameter from 2.5 nm to micrometers, specific surface area up to 800 m^2/g.



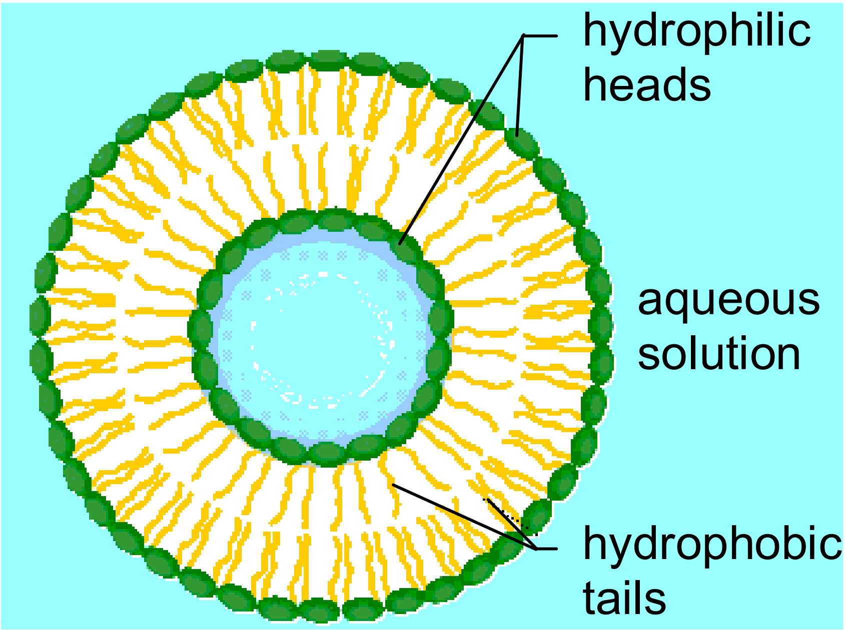
  - ► Drying of a gel under *supercritical* conditions occurs *without shrinking* to produce an aerogel. Example: silica aerogel – very low density (0.003 g/cm^3), very low refraction index (~1), very low sound speed (~100 m/s).
  - ► Sintering both aerogels and xerogels yields glassy substance (ceramics).

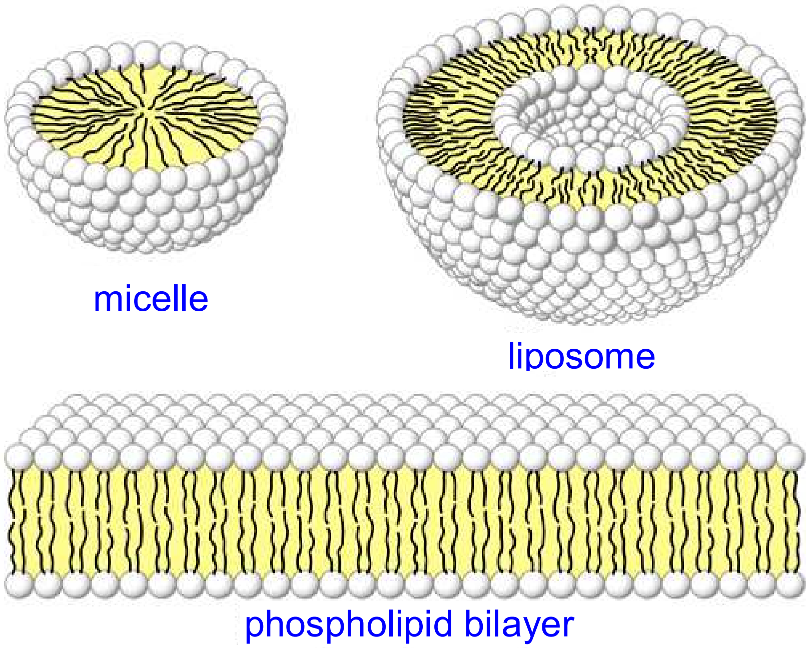
- ***Nanomedicine*** is medical application of nanotechnology.
  - ► Nanomedicine uses nanoparticles or nanostructures for diagnosis, prevention, and treatment of diseases;
  - ► Design of nano-sized therapeutics and of drug delivery systems – nanopharmacology.
  - ► Medical research: using analytical tools and devices to achieve a better understanding of the molecular basis of disease.

- ***Nanoparticle-based drug delivery*** – a central point of nanopharmacology
  - ► *Drug delivery* at macroscopic level: process of administering a drug to achieve a therapeutic effect (intramuscular, intravenous, nasal, ...) – this is *not* what we are going to study.
  - ► *Drug delivery* at microscopic level: (selective) delivery of a drug to a particular tissue.
    - – Mostly *liposomes* and *polymer-drug conjugates* (>80%).
    - – Solid lipid nanoparticle (Covid vaccine)
  - ► Main challenge: optimization (usually increasing) of half-life time of the drug:
    - – To slow down degradation of hydrophilic drugs (to avoid that they decompose too rapidly)
    - – To avoid that hydrophobic drugs release too slowly.

- ***Liposomes*** are spherical lipid vesicles with a bilayered membrane (see page 14)

► *Drug delivery* at microscopic level: the challenge is to deliver the drug to a particular tissue to achieve a selective therapeutic effect.





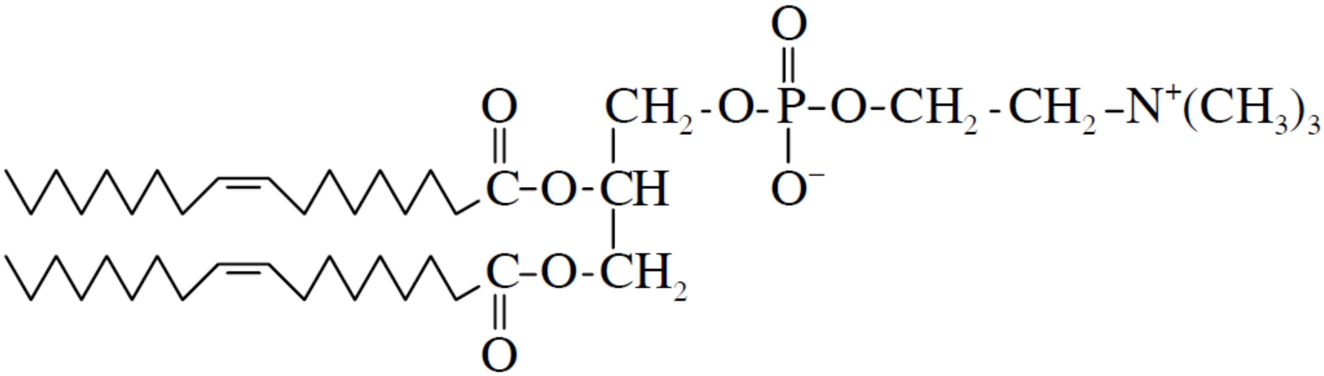
► The membrane consists of a (phospho)lipid bilayer that works as a surfactant, with a hydrophilic head toward an aqueous solution.

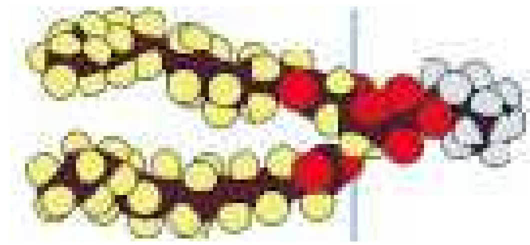
– quite similar to a cell membrane.

► The aqueous solution is both outside and inside the *liposome*.

► On the contrary, there is no aqueous solution inside a *micelle*.

- ***Liposomes*** *(continued)*
  - ► Example of a phospholipid: phosphatidylcholine (e.g. lecithin):

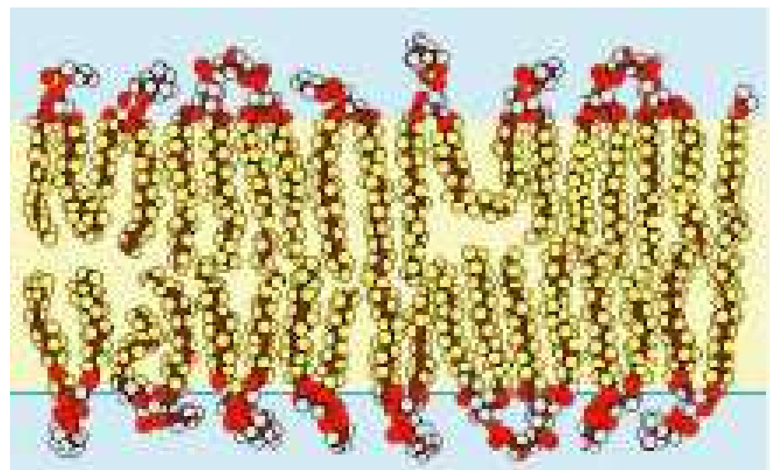




polar head

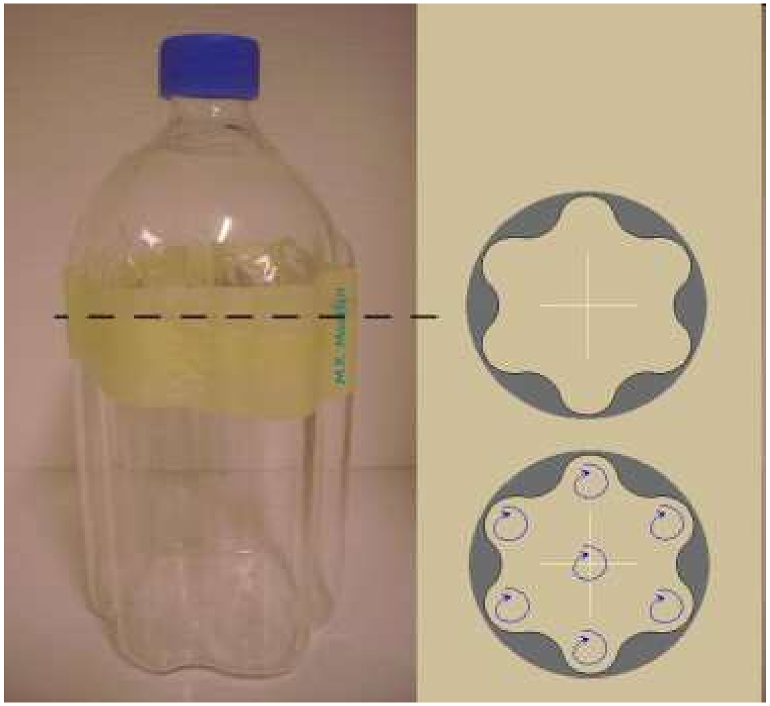
unpolar chains

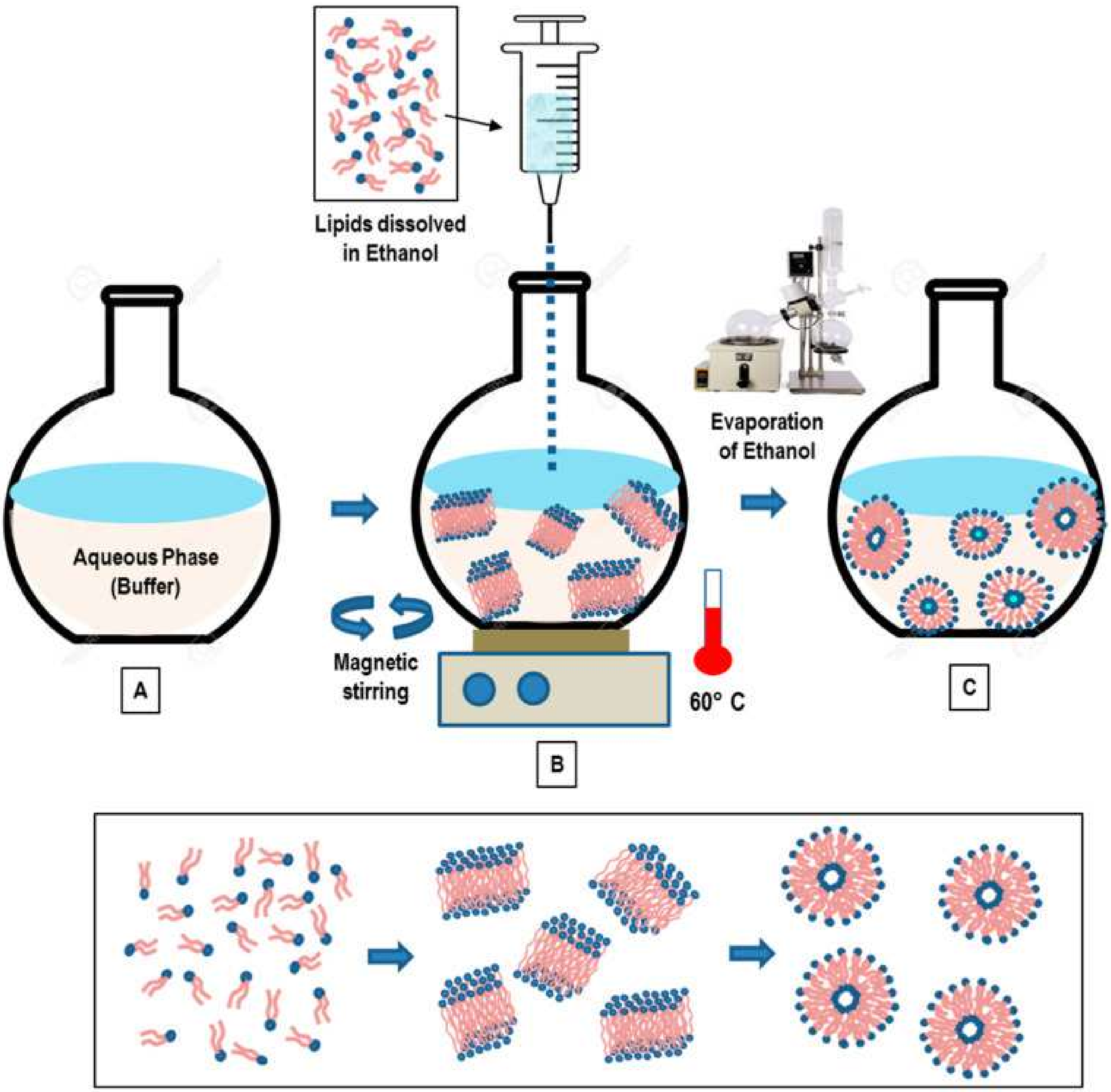
phospholipid bilayer



- ► Unilamellar liposomes : with one membrane and one vesicle of aqueous solution, *see above* (size: 20–100 nm (*small unilamellar liposomes*); 100–1000 nm (*large*); >1000 nm (*giant*).
- ► *Multilamellar liposomes* : with several membranes and layers of aqueous solution, *onion*-like structure (size: 80–5000 nm).

- ***Liposome*** fabrication:
  - ► Some lipid vesicles, but not necessarily liposomes, are formed when a phospholipid (e.g., lecithin) is placed into an aqueous solution, upon some stirring.
  - ► Typically, sonication (ultrasound) is applied. High intensity is needed to obtain unilamellar liposomes.
    - – Sonication is a "gross" method, as it can damage the drug to be incorporated into the liposome.
  - ► Extrusion: pressing a suspension of a lyophilized lipide through a (poly-carbonate) membrane:
    - – Membranes with a pore size >200 nm produce *multilamellar* liposomes
    - – Membranes with a pore size ≤200 nm produce *unilamellar* liposomes with a low polydispersity.
  - ► *Mozafari's method:* A bottle with a baffled wall of the bottle is used to create multiple turbulences.
  - ► *Solvent injection method:* lipid dissolution in an organic solvent (ethanol or ether), and the injection of the solution into water.

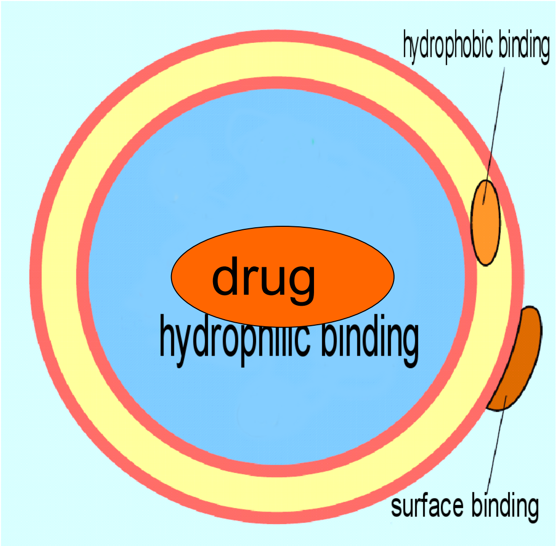




Ethanol injection method

Vyboishchikov (77)

- ***Drug delivery*** using liposomes:
  - ► *General advantages*:
    - A liposome encapsulates an aqueous solution inside; hydrophilic molecules cannot easily pass through the membrane.
      $\Rightarrow$ the solute *inside* (the *drug*) will not be lost;
      $\Rightarrow$ hydrophilic molecules from *outside* will not enter $\Rightarrow$ no damage to the drug
    - A liposome can carry both *hydrophobic* (*inside* the membrane) and hydrophilic (*inside* the bubble) molecules. A *surface binding* also exists.
    - Liposomes are not destroyed in heart, kidney, brain, nervous system $\Rightarrow$ low cardio-, nephro-, and neurotoxicity.
    - Still not absolute stable (destruction by *macrophages*, see page 80).

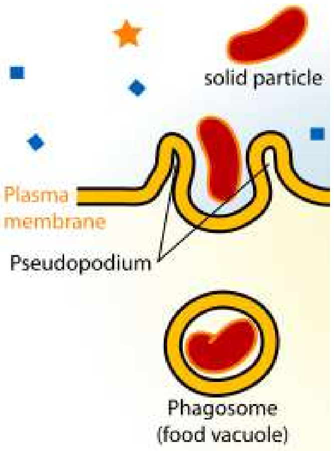


Vyboishchikov (78)

• ***Delivery approaches***:

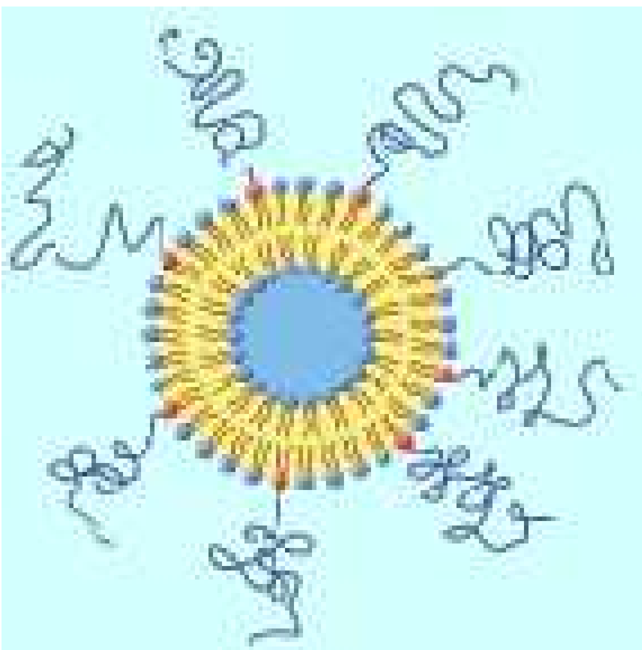
► Fusion of the liposome membrane with the cell membrane ⇒ the liposome content is delivered to the cell.
– Fusion of membrane bilayers is provoked by certain substances.

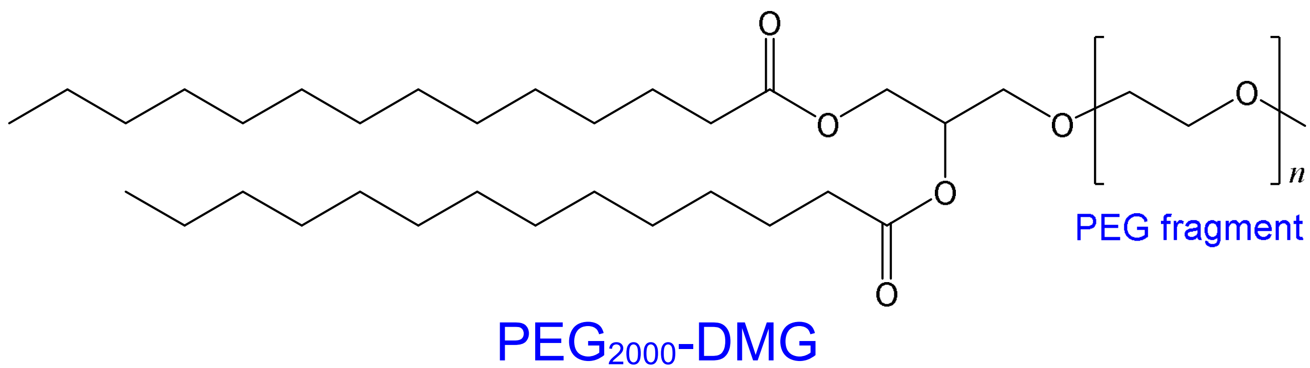
► Endocytosis/phagocytosis: the target cell ingests the liposome. The membrane invaginates the liposome in a pocket, closes the pocket, and the liposome is sealed off into a large (≥250 nm) vacuole (phagosome).



phagocytosis

- ***Problem*:**
  - ► Liposomes are not sufficiently stable in blood: destruction by *macrophages*, especially in liver, spleen, and bone marrow.
- ***Solution*:**
  - ► binding (covalently) polyethylene glycol (PEG) = polyethylene oxide (PEO) ($(-CH_2-CH_2-O-)_n$; $n = 25–80$) to the liposome
    $\Rightarrow$ antibodies do not attach to the liposome and the macrophage does not attack it ("*stealth liposomes*").





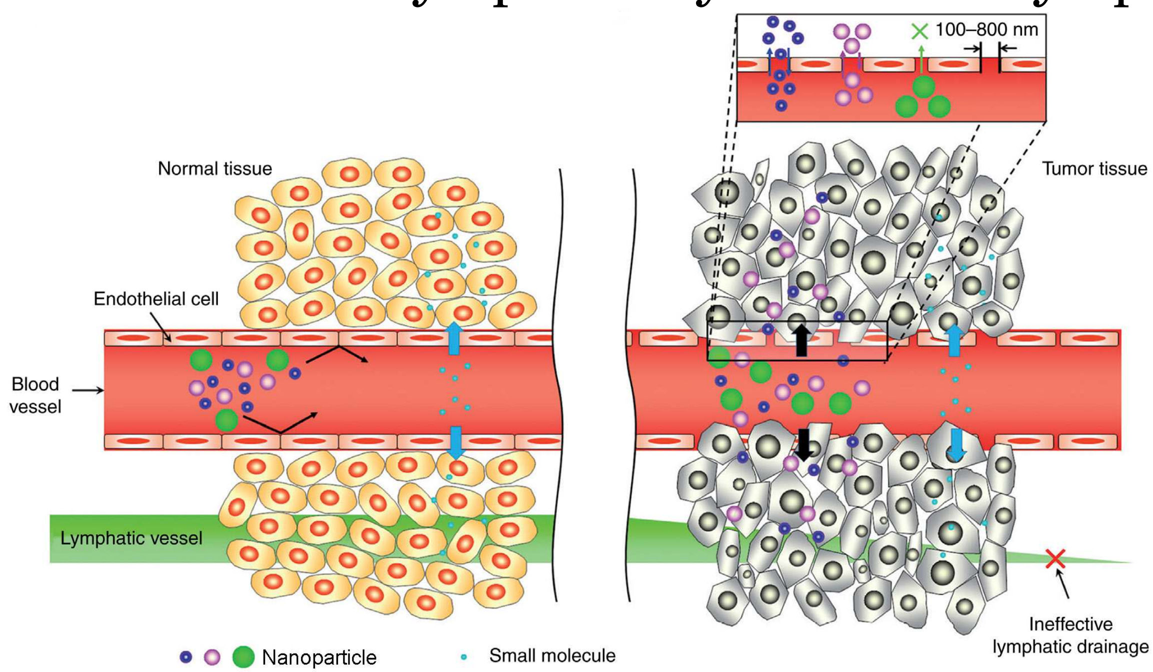
- ***Liposomes against cancer***:

  Liposomes (and some macromolecules) are accumulated in tumor tissue much more than they do in normal tissues – *Enhanced Permeability and Retention Effect (EPR)* (Matsumura and Maeda 1986):

► Even very small tumors (~0.2 mm) depend on the blood supply and have blood vessels.

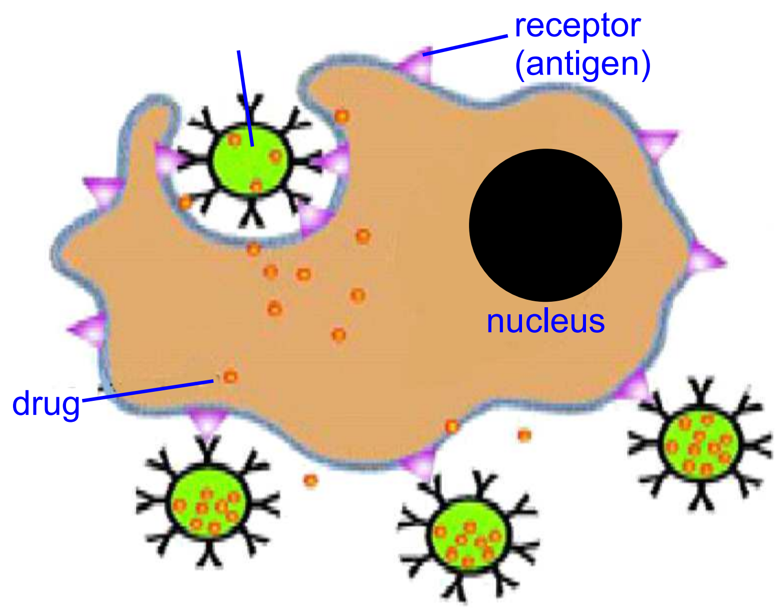
  – These blood vessels are abnormal: their endothelial cells are leaky (have pores ⌀100–300 nm), and nanoparticles (including liposomes) can enter tumor cells. However, in healthy tissue they are kept in the bloodstream by the endothelial wall.

► Tumors lack a well-defined lymphatic system ⇒ no lymphatic drainage.



Vyboishchikov (81)

- *Active* and *passive* ***targeting***:
  - ► Passive targeting: the use of EPR-effect.
    - – The EPR allows for selectively targeting cancer cell, while normal cell would not be penetrated into.
  - ► Active targeting: conjugation of *targeting moieties* (typically *antibodies*) and drugs to nanoparticles or polymers:
    - – Both the drug and an antibody are attached to the nanoparticle $\Rightarrow$ the nanoparticle will specifically attack only the cells that have the corresponding antigen;



    - – Antibody production: injecting antigens to an animal.
  - ► *Active* and *passive targeting*: these concepts apply not only to liposomes, but to drug delivery using other types of nanoparticles as well.

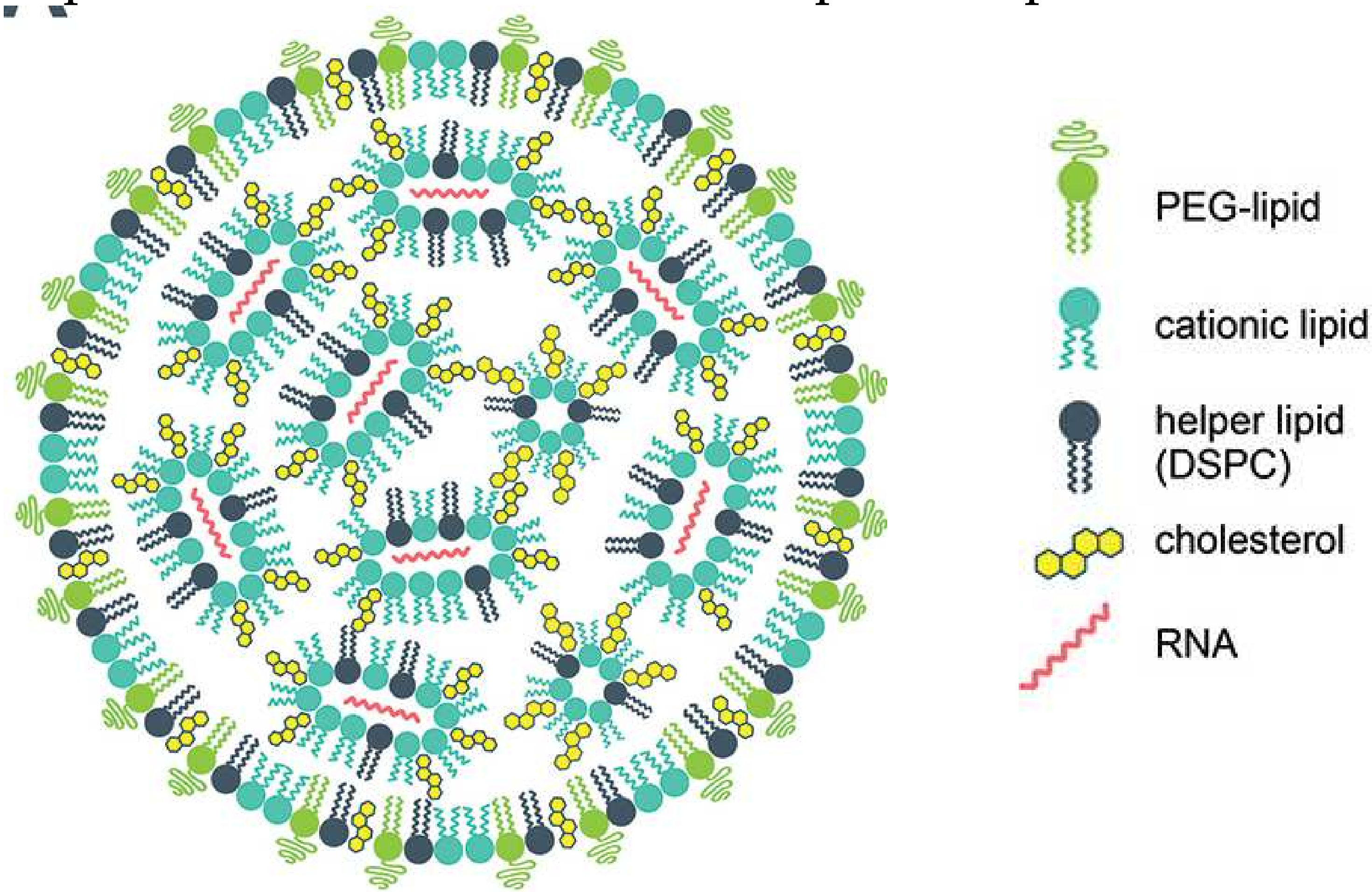
- Examples of liposomal anti-cancer therapy (clinically approved):
  - *Doxorubicin* (known from 1950): treatment of a wide range of cancers;
    - Doxil®: the first FDA-approved nanomedicine (1995): PEG-coated liposome-encapsulated form of doxorubicin;
  - *Daunorubicin* (isolated from soil bacteria in the 1950th): Kaposi's sarcoma (DaunoXome®: FDA 1996);
  - *Mifamurtid* (synthesized in the 1980): osteosarcoma (Mepact®: EMA 2009)
  - *Irinotecan* (Camptosar®): derivative of camptothecin – pancreatic cancer (Onivyde®: FDA 2015) PEG-coated.

- Liposome-based gene therapy:
  introducing mRNA fragments into cells to produce necessary proteins and eventually antibodies: cancer treatment (clinical trial).

- Liposomal nanovaccines:
  - Epaxal® for vaccination against hepatitis A; virus proteins linked to the liposome membrane ("virosome").
  - Inflexal V® for vaccination against influenza (approved by EMA and used in the EU but usage discontinued).

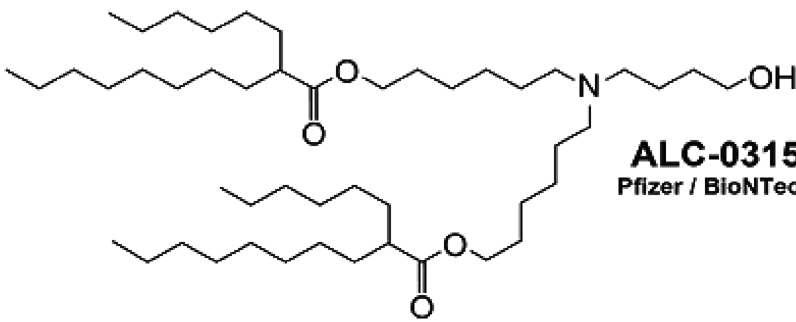
- Liposomes against fungal infection:
  amphotericin B (isolated from bacteria in 1955); toxic. Liposomal form (Ambisom®) is employed for preventing or treating invasive fungal infections (FDA 1997; also EMA).

- Nanovaccines against Covid-19:
  - ► *Lipid nanoparticles* (LNP) – *different from lliposomes:*
    - – LNPs have micells (or inverse micells) *inside*;
    - – less cytotoxicity when compared to liposomes;
    - – better encapsulation efficiency for RNA/DNA;
    - – Covid-19 nanovaccines: BioNTech/Pfizer and Moderna mRNA encapsulated in ionizable cationic lipid nanoparticles

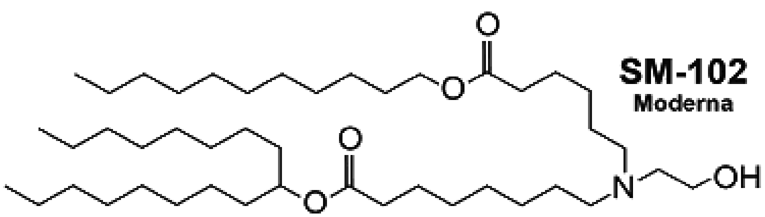


- Nanovaccines against Covid-19 – *continued*:
  - ► *Lipids used:*

Cationic Lipids



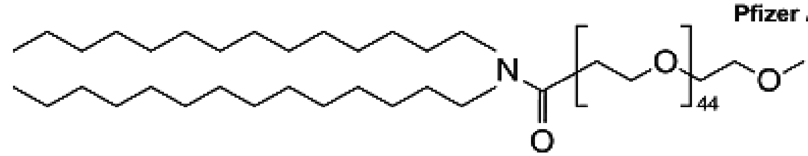
ALC-0315
Pfizer / BioNTech

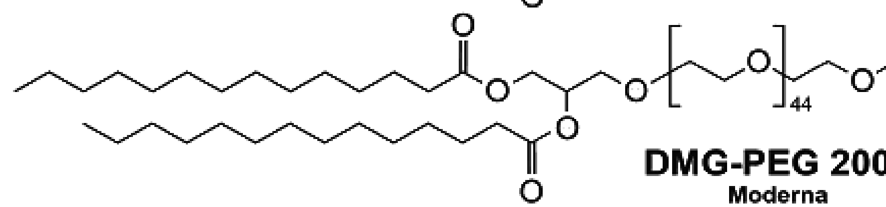


SM-102
Moderna

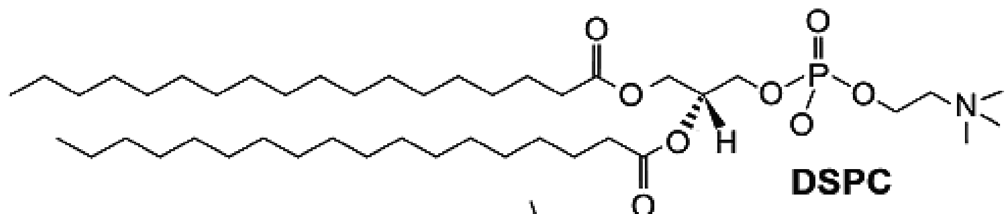
PEG-Lipids

ALC-0159
Pfizer / BioNTech



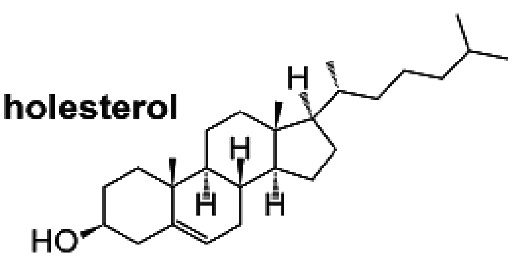


DMG-PEG 2000
Moderna

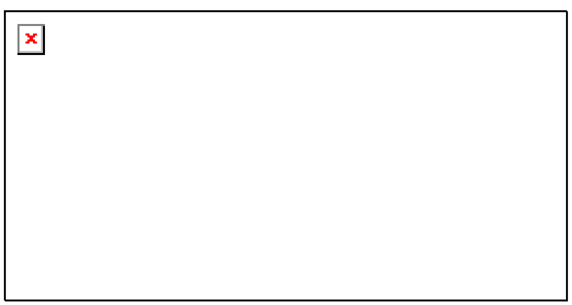


DSPC

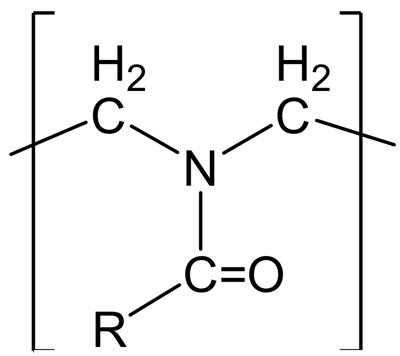
Cholesterol



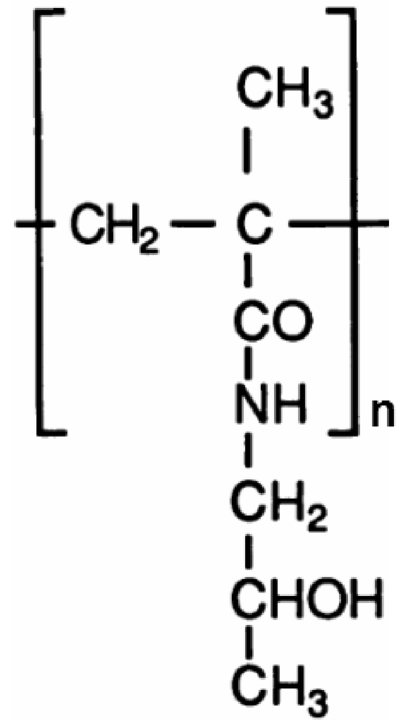
- ***Polymer-drug conjugates***: drugs and, possible, a targeting moiety is attached to a polymer.
  - ► Polymers used for conjugation must be:
    - – *hydrophilic*
    - – *non-immunogenic*
    - – *bio-compatible and bio-degradable*
  - ► Using polymers allows tuning molecular weight, and, thus, the size.
  - ► Examples of polymers used:
    - – polyethylene glycol (PEG): $(–CH_2–CH_2–O–)_n$;
    - – *N*-(2-hydroxypropyl) methacrylamide (HPMA) ;
    - – polyvinylpyrrolidone (PVP)



polyvinylpyrrolidone



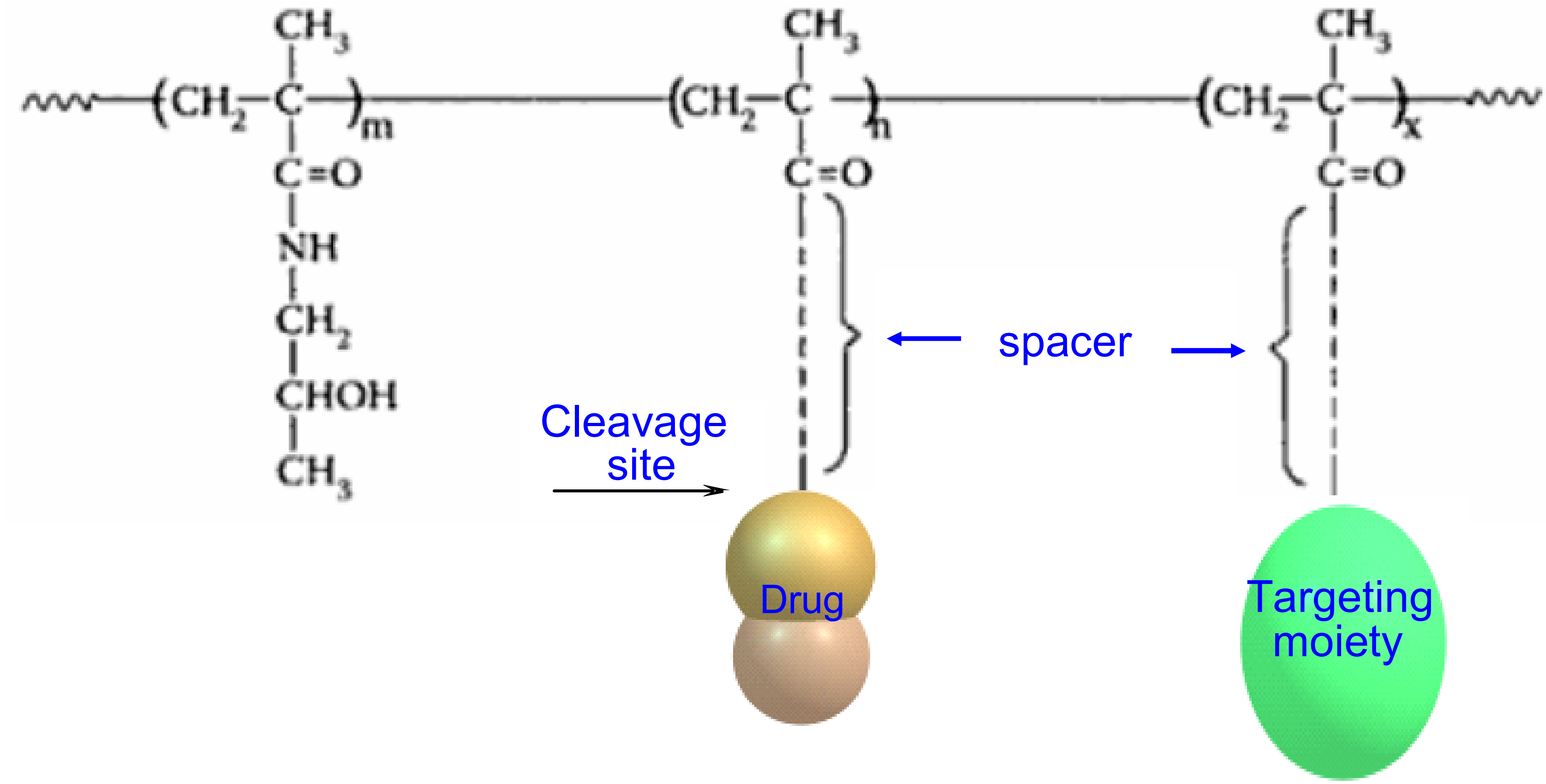
polyoxazoline



HPMA

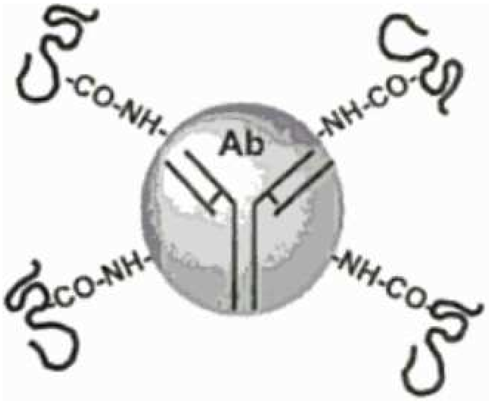
    - – various copolymers.

- ***Polymer-drug conjugates***:
  - ▶ Drug delivery system with an HPMA backbone:

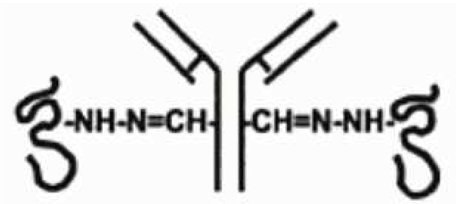


– Targeting moiety: typically an antibody.

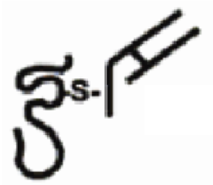
• ***Polymer-drug conjugates***: Linking a polymer to an antibody:



Random attachment
by **amide** linkage

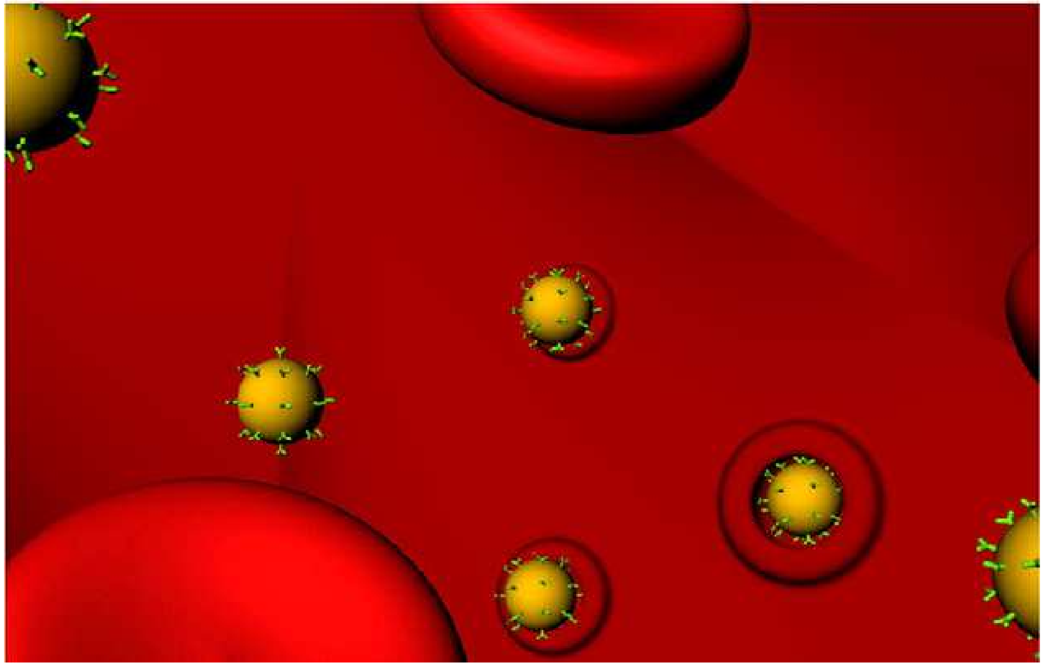


site-specific attachment
by **hydrazone** linkage
(via sugar chains)

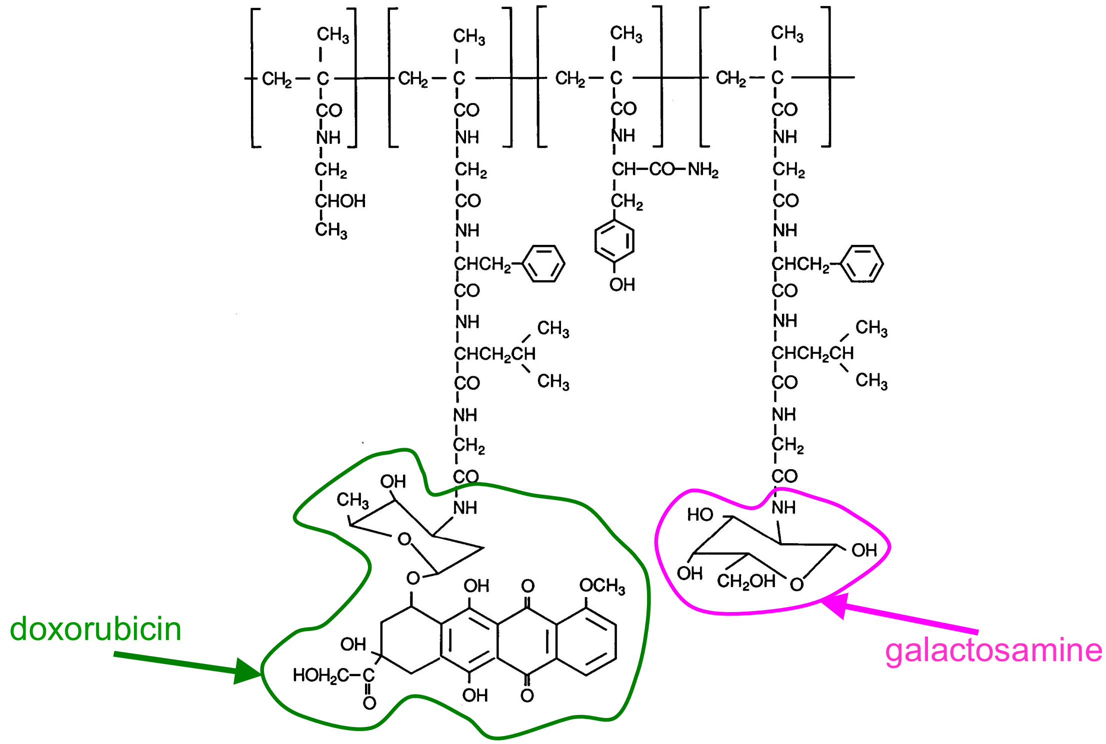


site-specific attachment
by **thioether** linkage
(via sulfhydril groups)

• Antibody-coated nanoparticles:

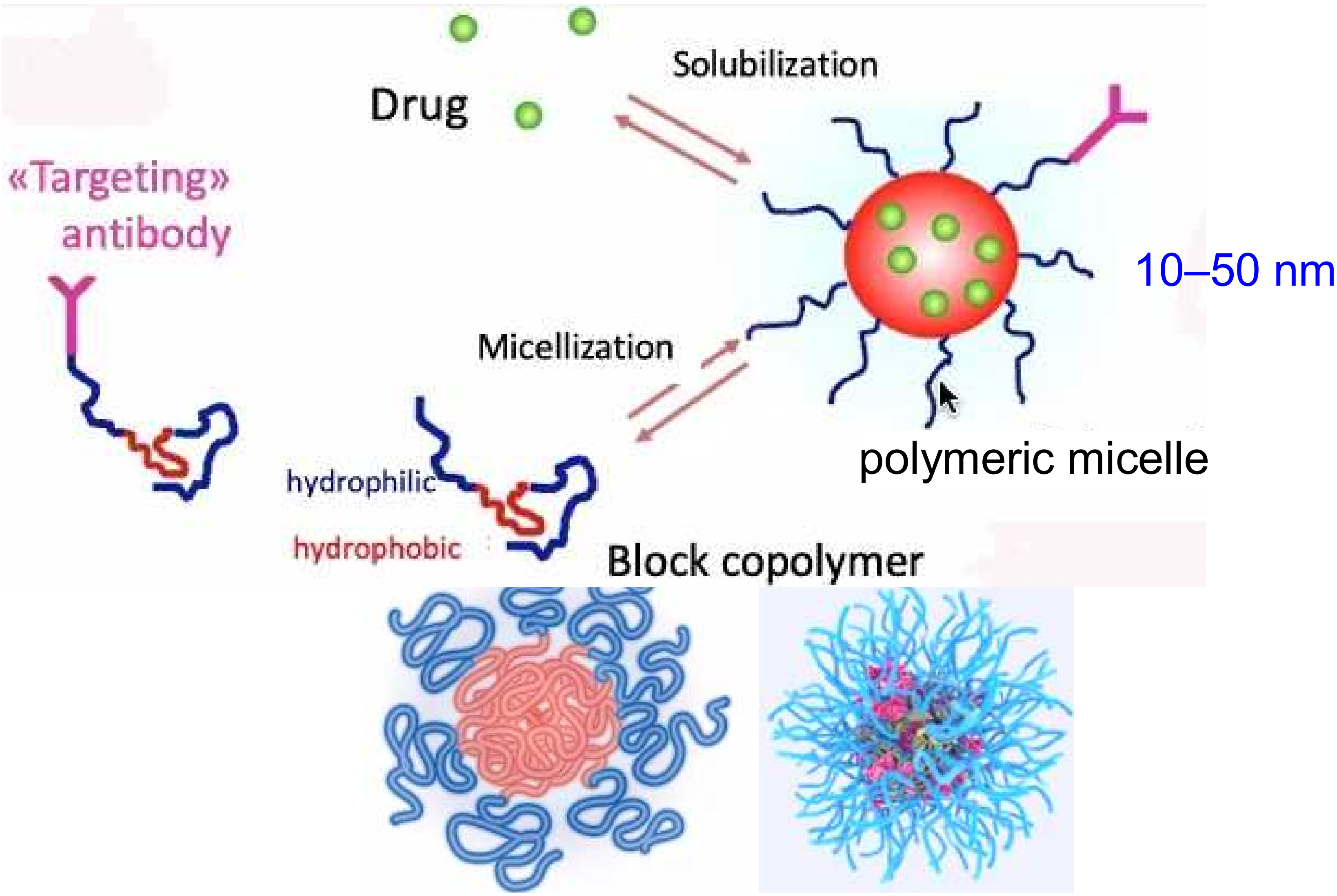


- ***Polymer-drug conjugates***: Example of HPMA usage: HPMA copolymer containing doxorubicin for liver cancer therapy:

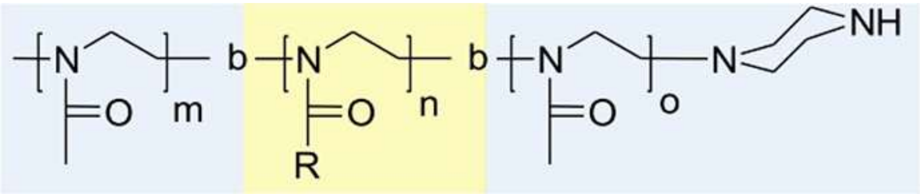


  - Paclitaxel (=taxol): lung/breast/pancreatic cancer; isolated in 1971 from the Pacific yew; now manufactured by semi-synthesis from European yew; *albumine*-bound (100–200 nm) taxol (Abraxane®) approved FDA 2005, EMA 2008 – the first non-liposomal anti-cancer nanodrug. *Widely used clinically!*
  - *Cyclosert-camptothecin* (natural alkaloid discovered in 1966): highly toxic; cyclodextrine-based copolymer (alternating subunits of cyclodextrin and PEG) nano-particle currently under clinical trial against leukemia.

- Polymeric micelles:
  - Genexol-PM® (Samyang) – taxol: breast, ovarian cancer (approved)

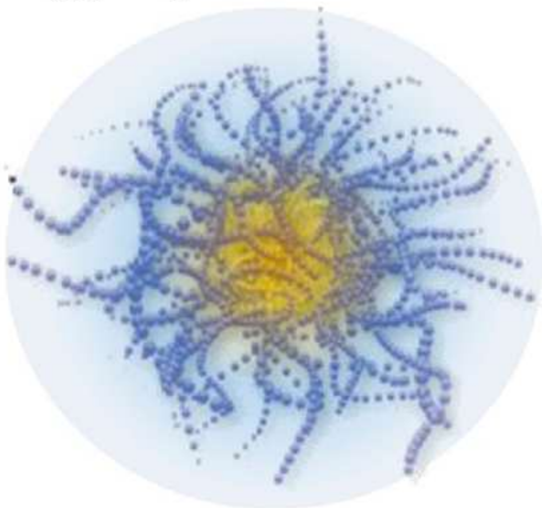


- Polymeric micelles – example – poly(2-oxazoline) block copolymer:



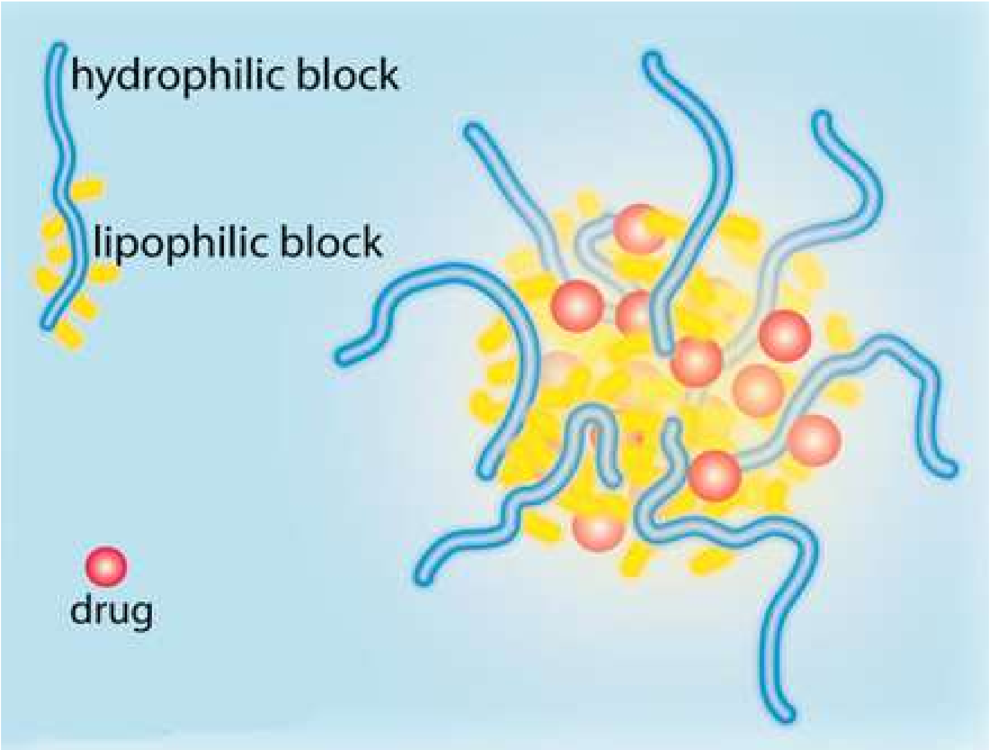
P1: R= $-(CH_2)_8CH_3$
P2: R= $-(CH_2)_3CH_3$

$\downarrow H_2O$

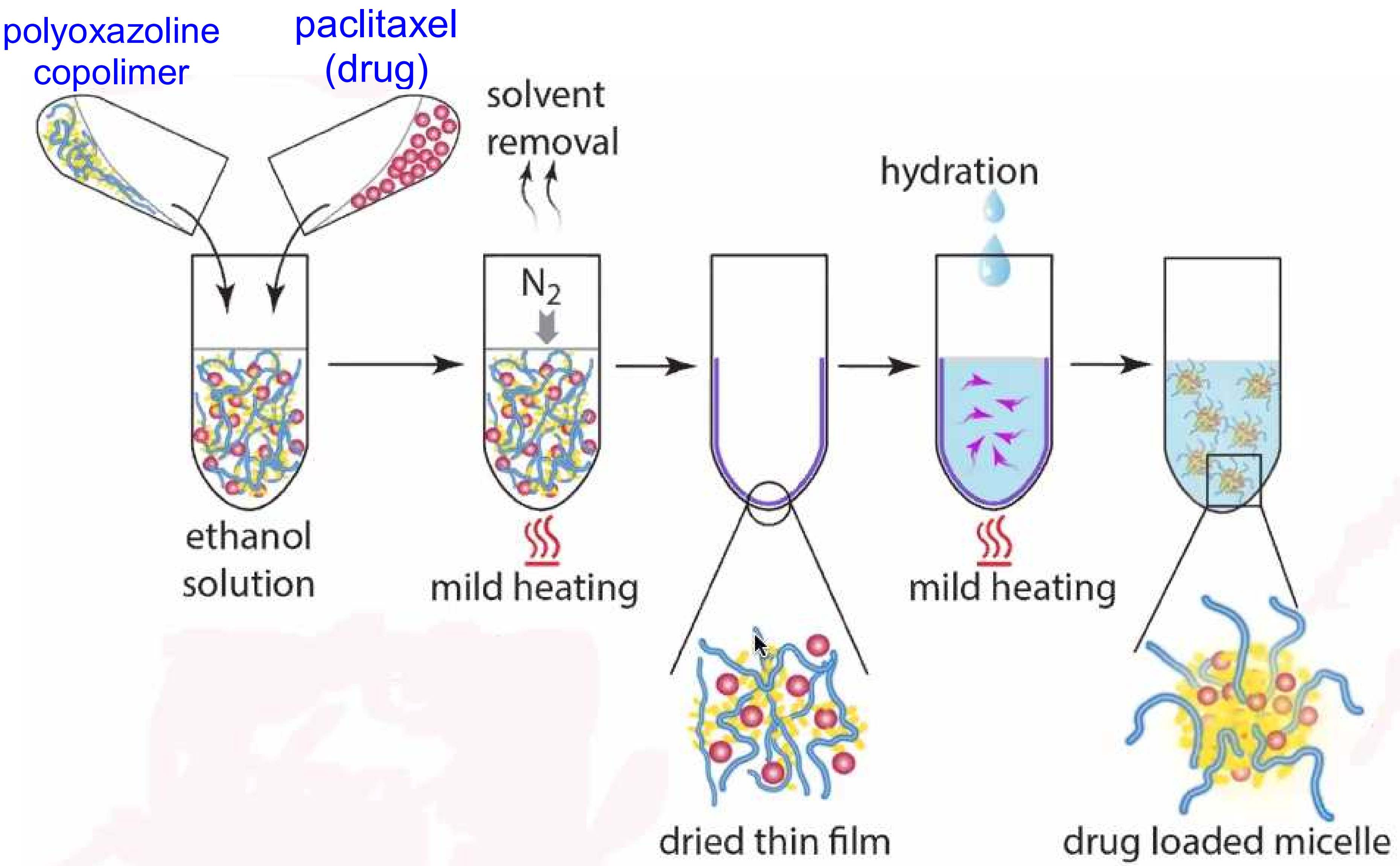


Longer alkyl substituents make the polymer block hydro*phobic*;

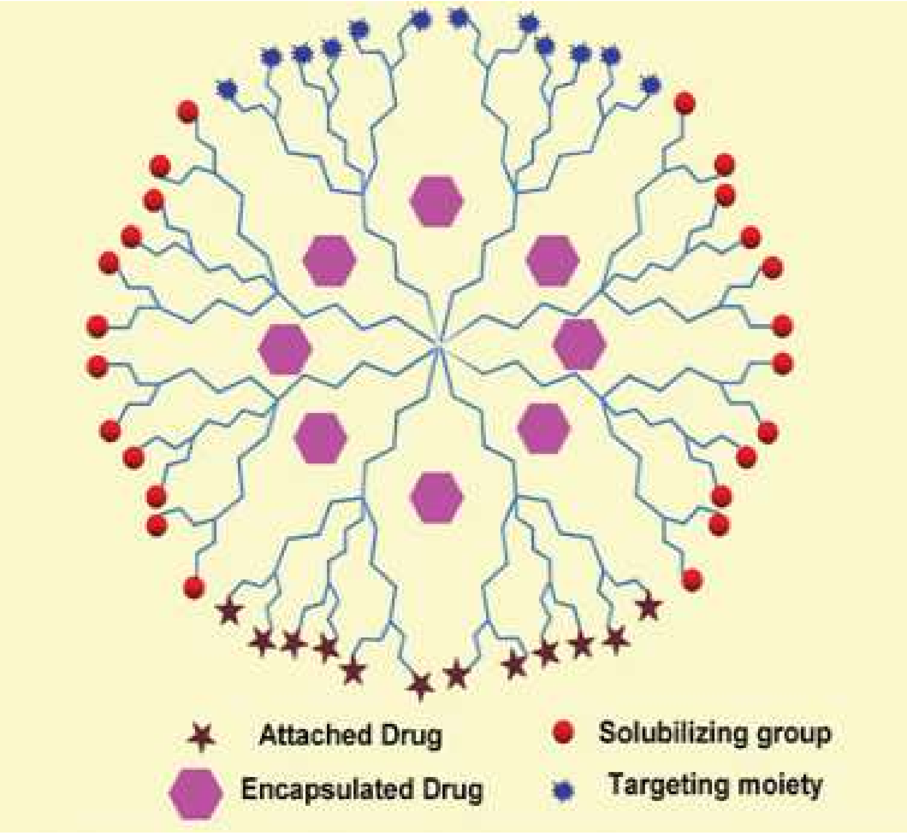
Shorter alkyl substituents (methyls) retain the polymer block hydro*phylic*.

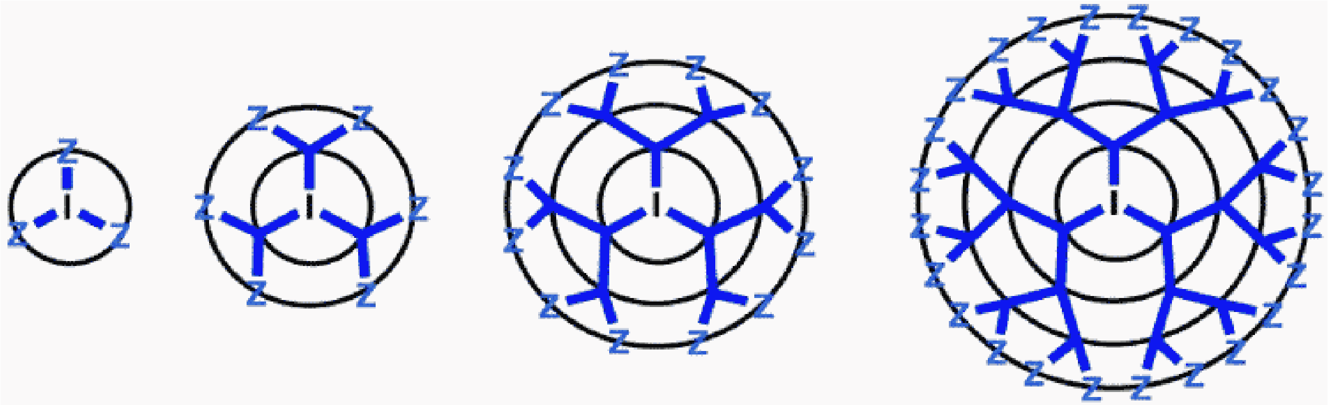


- Polymeric micelles – production – drug blending with block copolymer:

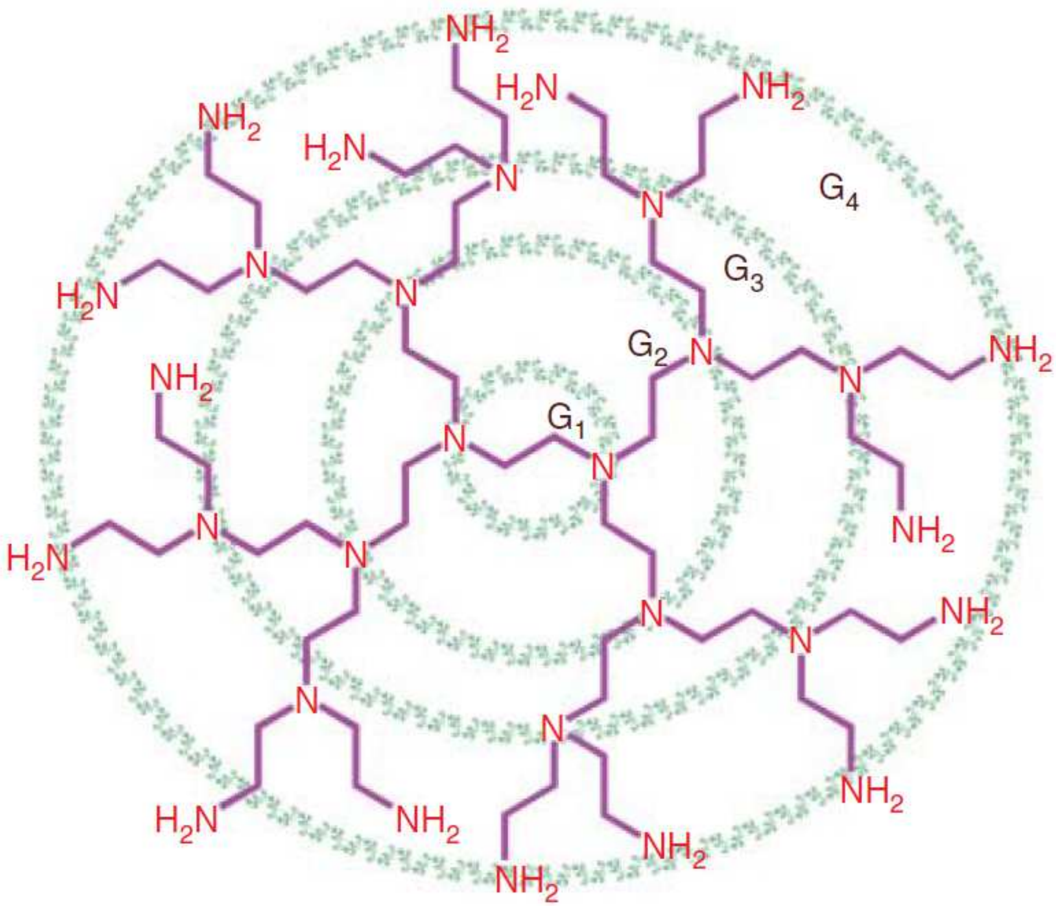


- ***Dendrimers***:
  - ▶ Dendrimers are tree-like macromolecules with branching reach out from a central core.
    - – Advantages:
      - Tailored and uniform size;
      - Highly-functionalized terminal surface;
      - Non-immunogenic;
      - Possibly biodegradable.

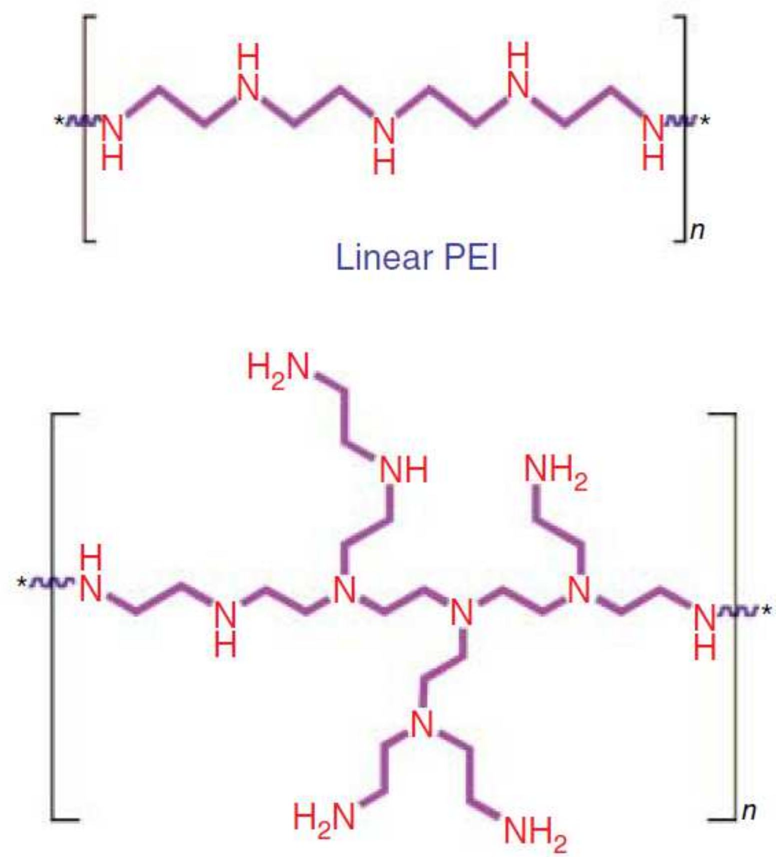




► Dendrimers – difference to polymers.

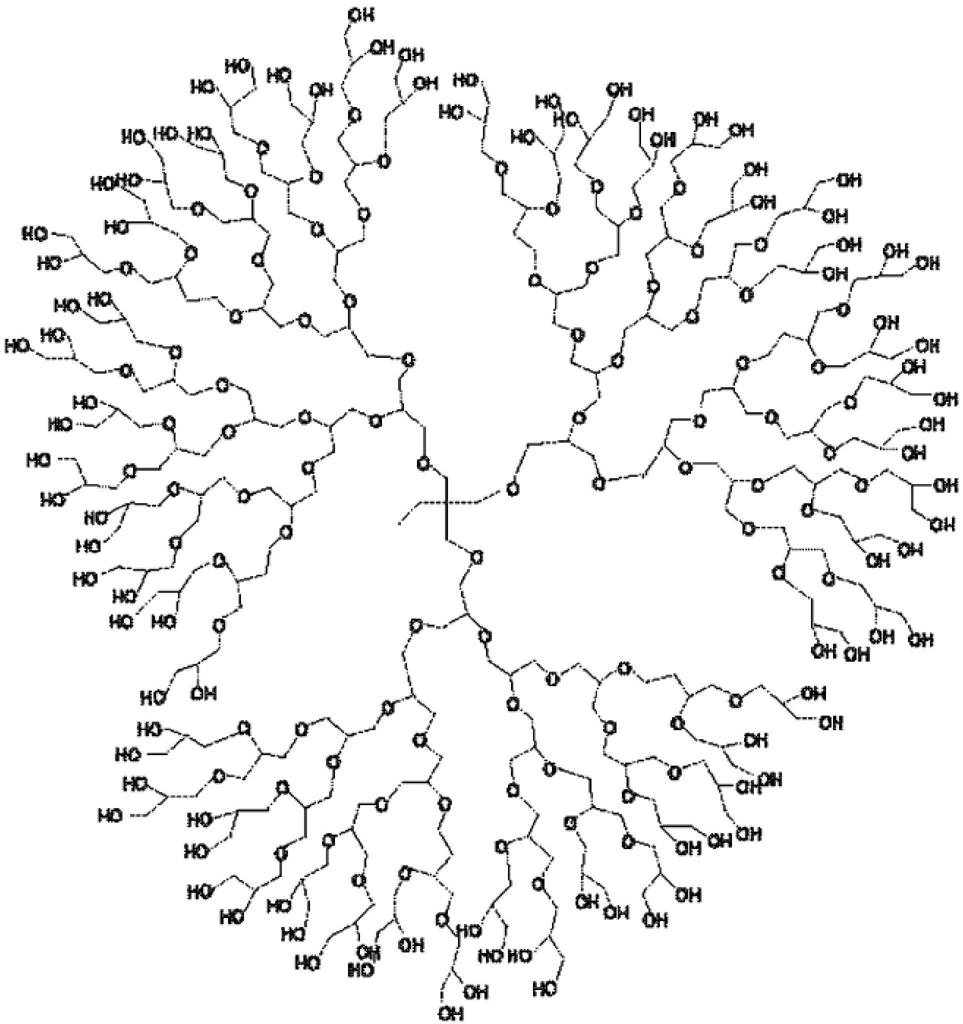


polyethylenimine (PEI) dendrimer

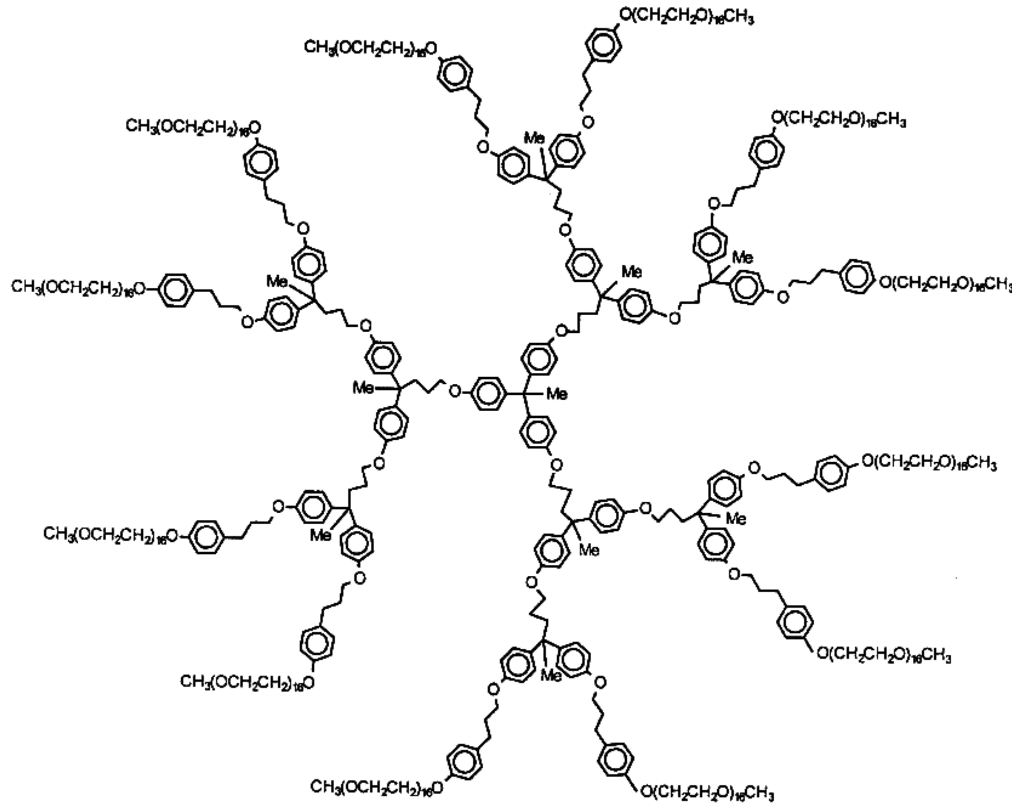


PEI branched polymer

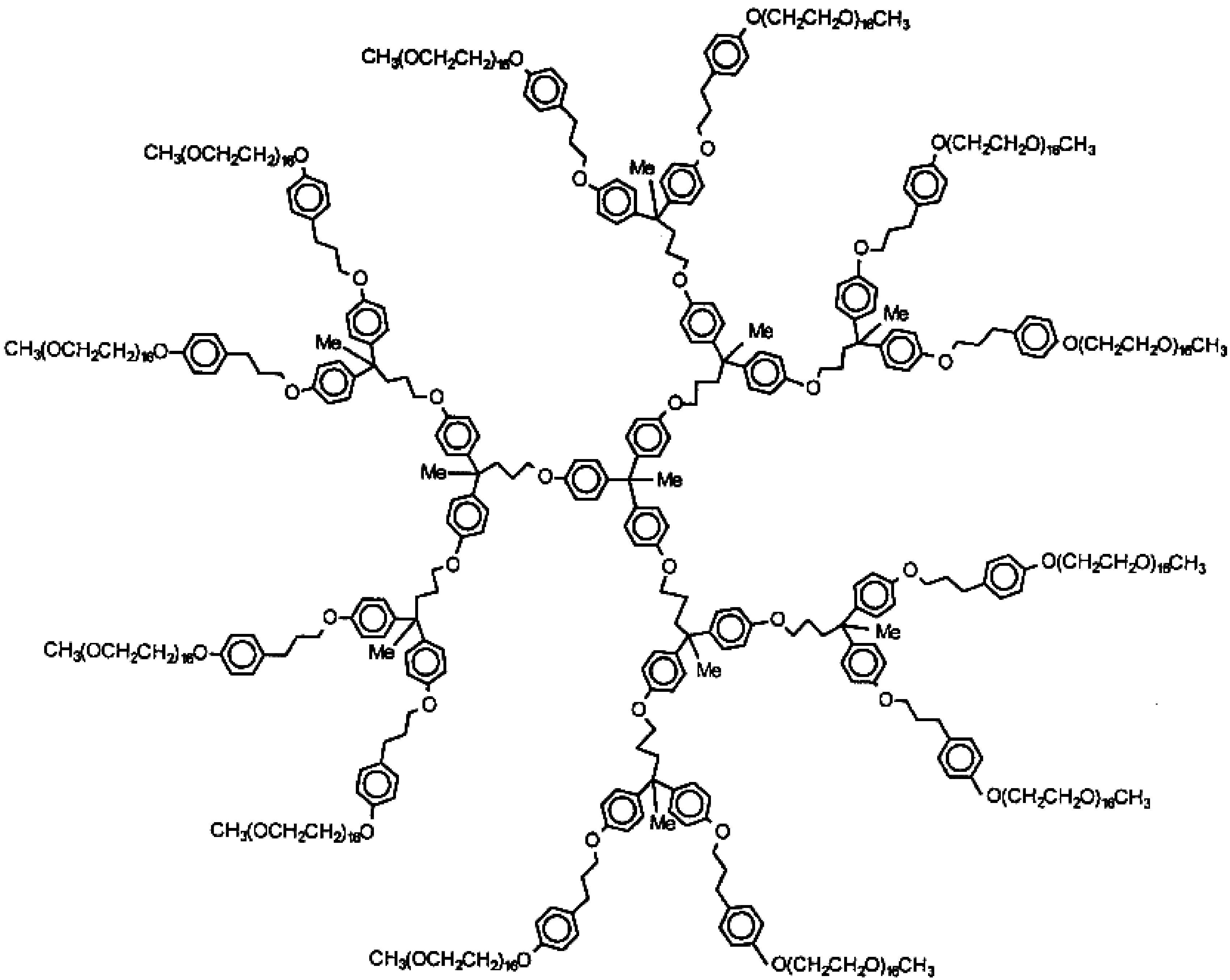
- ***Dendrimers***:



polyglycerol dendrimer



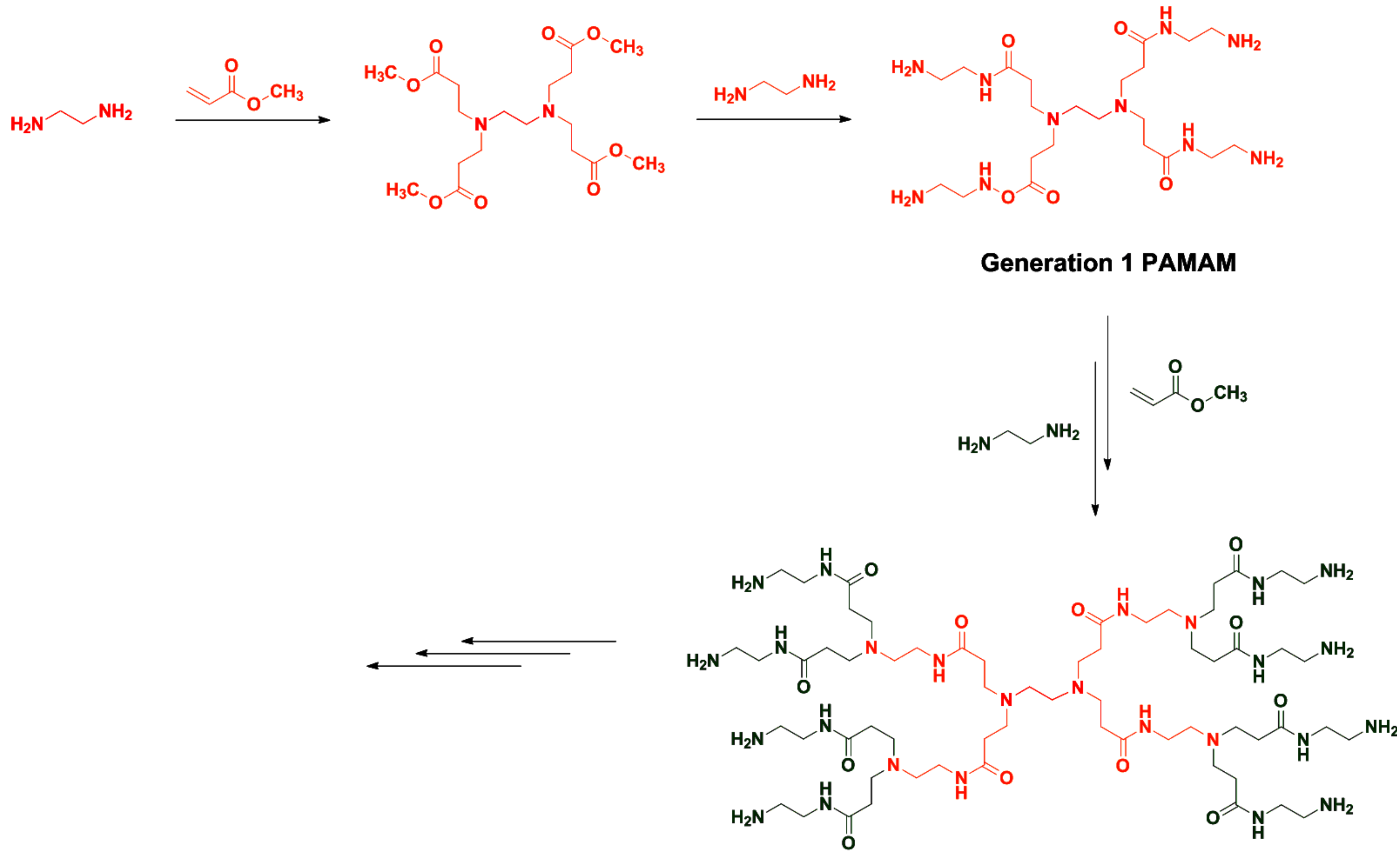
dendritic micelle based on 4,4-bis(4'-hydroxyphenyl)pentanol + PEG shell



dendritic micelle based on 4,4-bis(4'-hydroxyphenyl)pentanol + PEG shell

Vyboishchikov (97)

- ***Dendrimers***:
  - ► *Synthesis*: repetitive steps (“divergent synthesis”) from a central core.
    - – example (PAMAM – polyamidoamine):



Generation 1 PAMAM

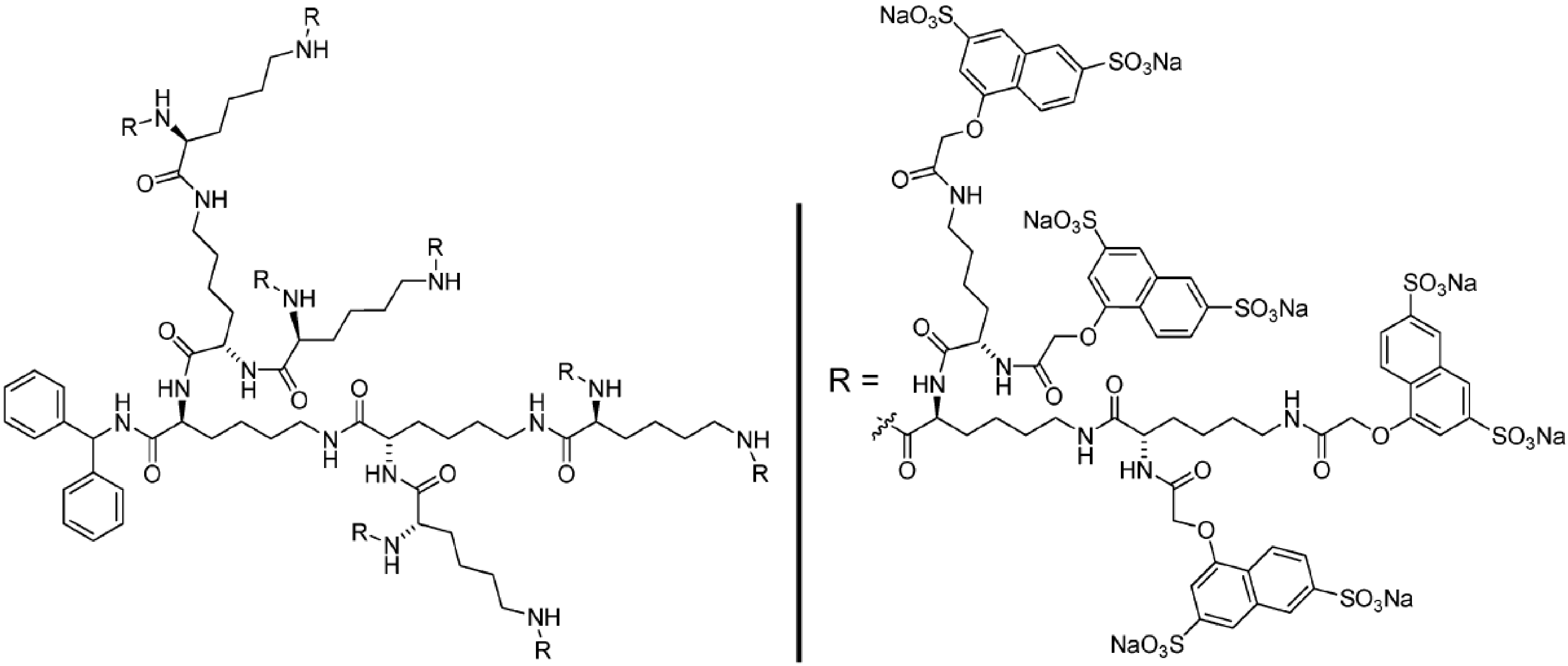
Generation 2 PAMAM

- ***Dendrimer** application*:

► Starpharma VivaGel® :

– polylysine dendrimer: antiviral and antibacterial activity;

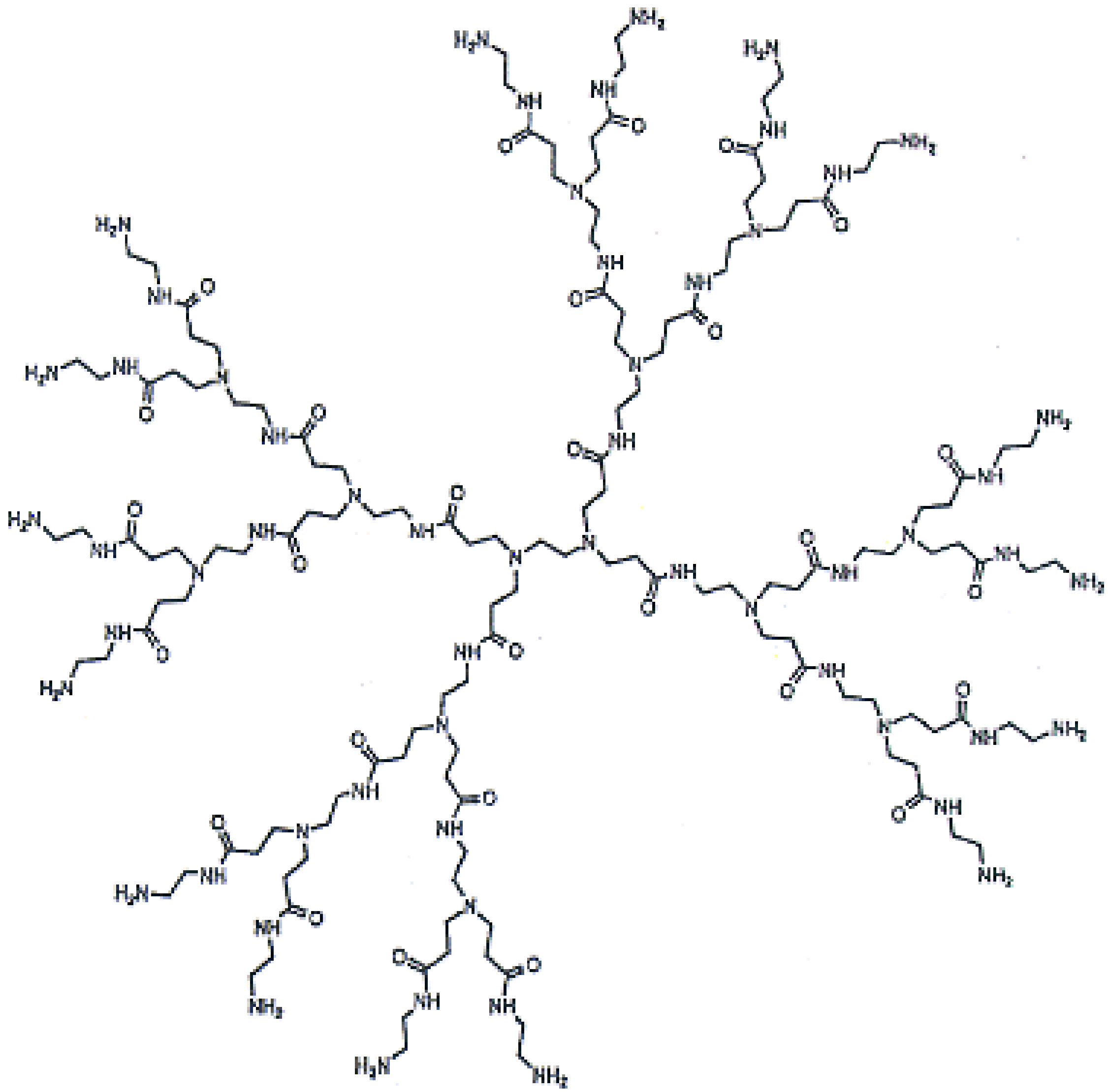
– VivaGel® BV for bacterial vaginosis: in clinical use since 2019



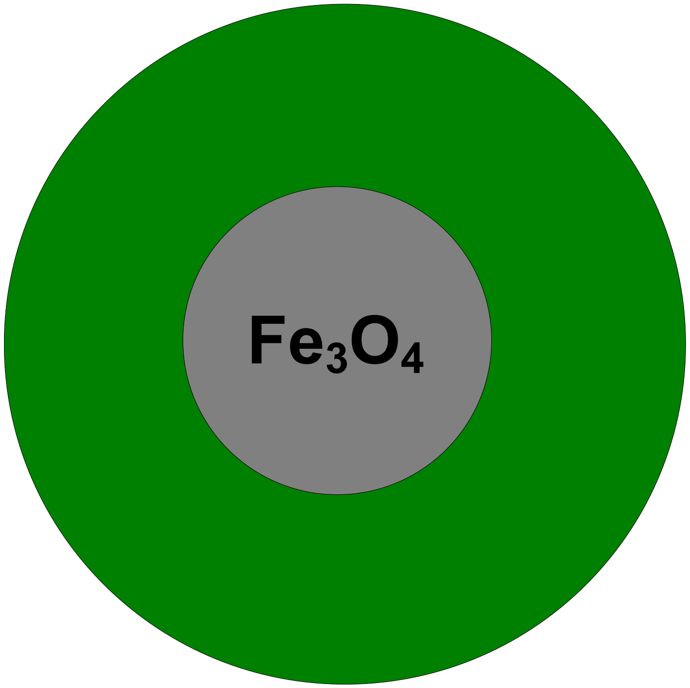
- ***Dendrimer*** *application (continued)*:

  ► Folic acid–PAMAM dendrimers with *methotrexate*: epithelial cancer;

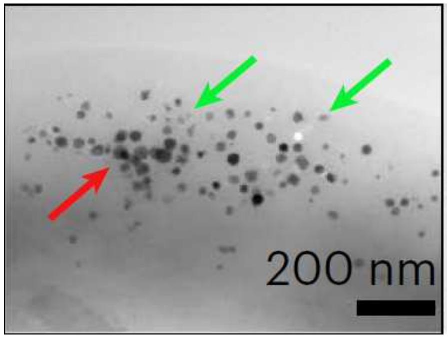
  ► PEG-polylysine dendrimers with *Chloroquine phosphate*: malaria.;



- ***Magnetic nanoparticles***: (10–20 nm size)
  - ▶ Superparamagnetism: different from ferro-, para-, and diamagnetism.
  - ▶ Mostly used are Fe_3O_4 (magnetite) nanoparticles.
  - ▶ Also used are γ-Fe_2O_3 (maghemite), Fe, Co, Ni, and FeCo nanoparticles.
  - ▶ Thick hydrophilic coating is used for magnetic nanoparticles employed in bio-systems to avoid aggregation and achieve bio-compatibility:
    - – SiO_2-coating
    - – surfactant coating
    - – polysaccharide coating.
    - – hydrophilic polymer coating.



- **Fabrication** of Fe_3O_4 nanoparticles (10–20 nm size) by co-precipitation:
  - $2\,FeCl_3\,(aq) + FeCl_2\,(aq) + 8\,NH_3\,(aq) + 4\,H_2O \rightarrow Fe_3O_4 + 8\,NH_4Cl\,(aq)$
  Stirring Fe_3O_4 with PEG (polyethylene glycol) and sodium oleate (≈soap).
  - Centrifugating and fractioning in the magnetic field;
  - Can be used for preparing *ferrofluids* (magnetic liquids) by dispersion in a non-aqueous medium.
- *Biofabrication using bacteria:*
  - *Magnetotactic* bacteria naturally synthesize *magnetosomes* (intracellular magnetic Fe_3O_4 particles covered by a lipid bilayer; biomagnetism). There genes can be transferred into non-magnetic bacteria.



B. viridis with magnetosomes

- Fabrication of magnetic *metal* nanoparticles:
  - From a zerovalent complex precursor ($Fe(CO)_5$ for iron nanoparticles; $Ni(cyclooctadiene)_2$ for nickel nanoparticles) by a soft H_2 treatment.

- ***Magnetic nanoparticles*** – application:

► *Magnetic hyperthermia* (NanoTherm™ therapy – in clinical use) :

– (Superpara)magnetic nanoparticles produce heat in alternating magnetic field.

– If inside a tumor in the alternating magnetic field, the tumor is heated and eventually killed (T > 45 °C).

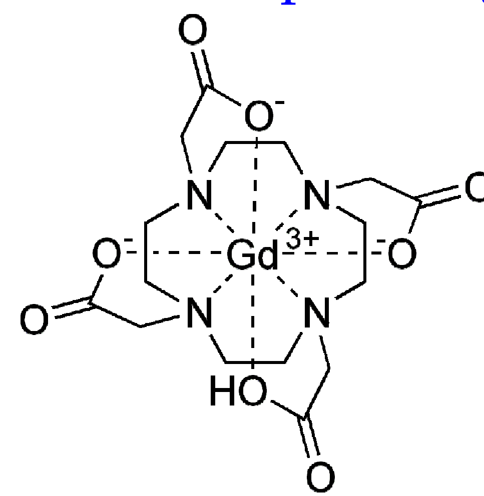
► For NMR imaging: (superpara)magnetic nanoparticles as a paramagnetic contrast agent (clinically approved):

– Feridex®/Endorem®: 120–180 nm (core size: ~7 nm) $FeO_{1.44}$, dextran-stabilized

- *production discontinued*

– Resovist®: ~50 nm size (core size: ~4 nm)

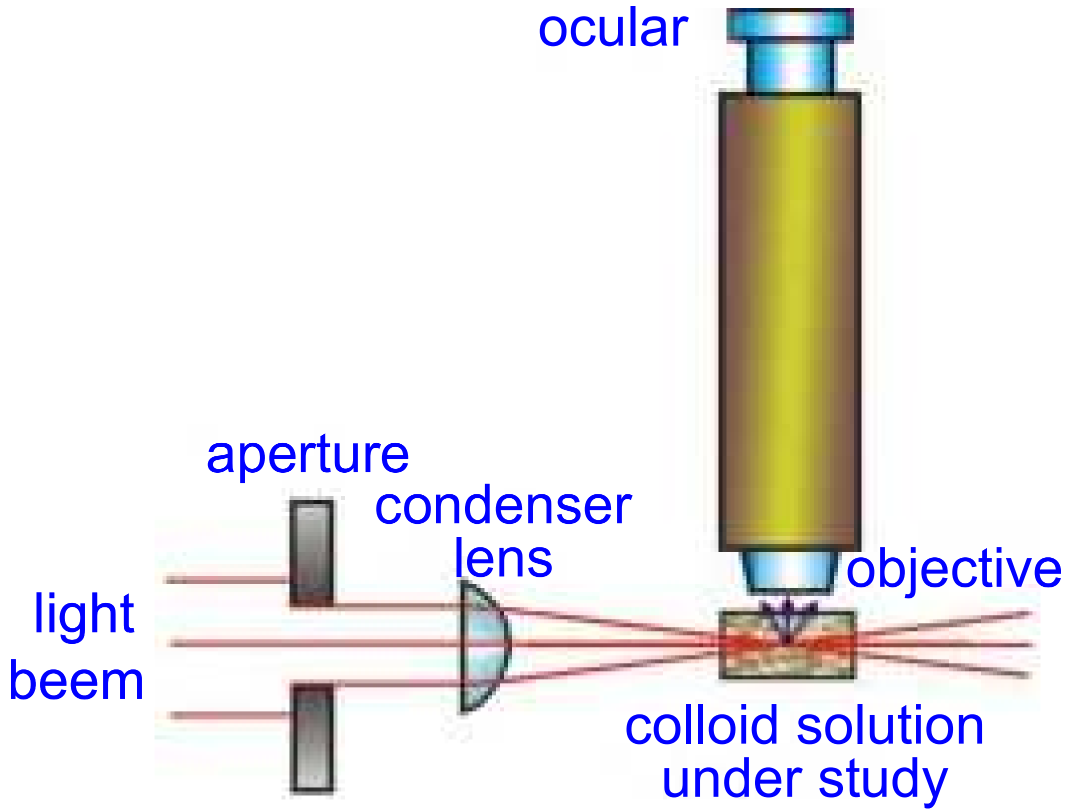
- *production discontinued*



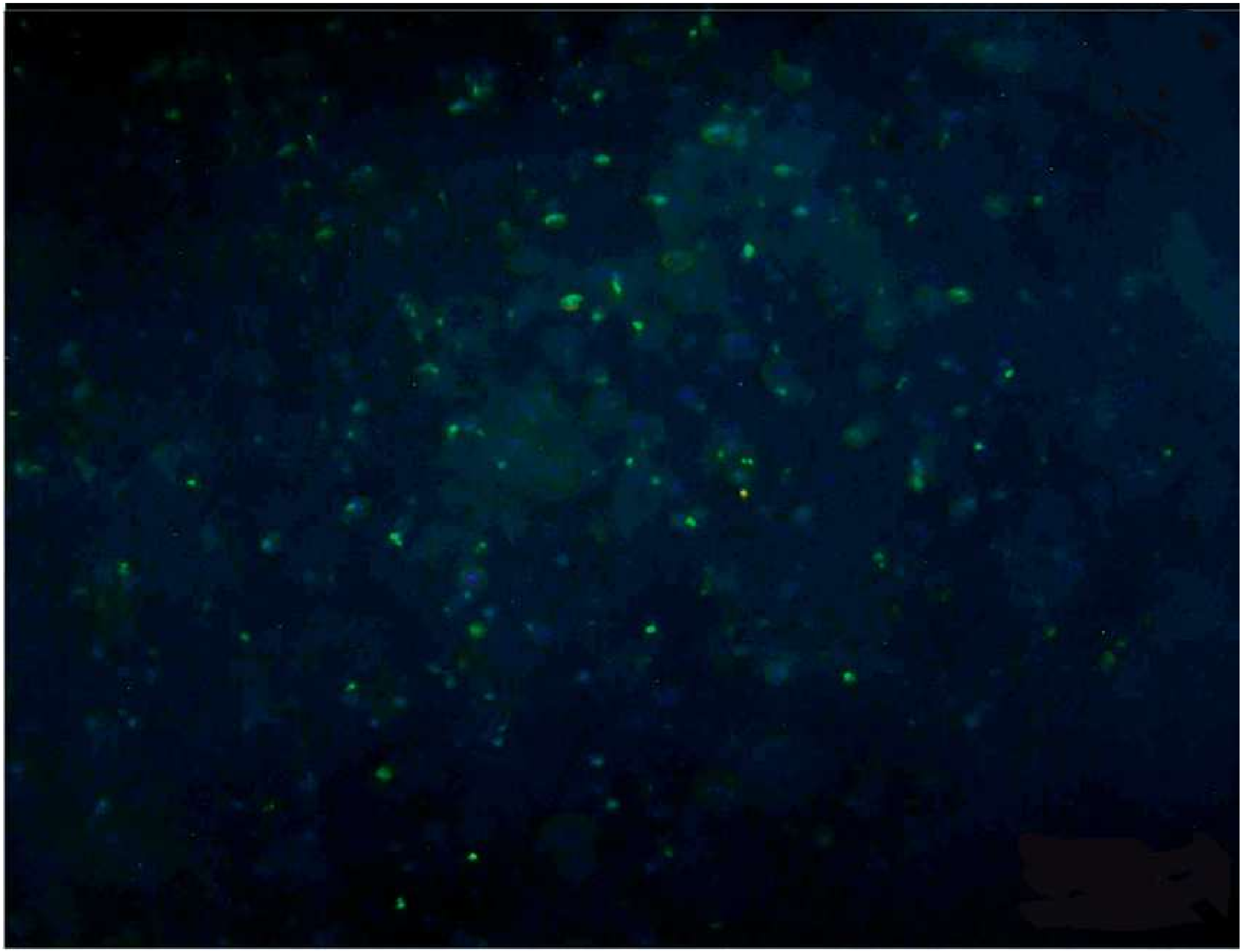
Example of a non-nanotechnology based paramagnetic contrast agent

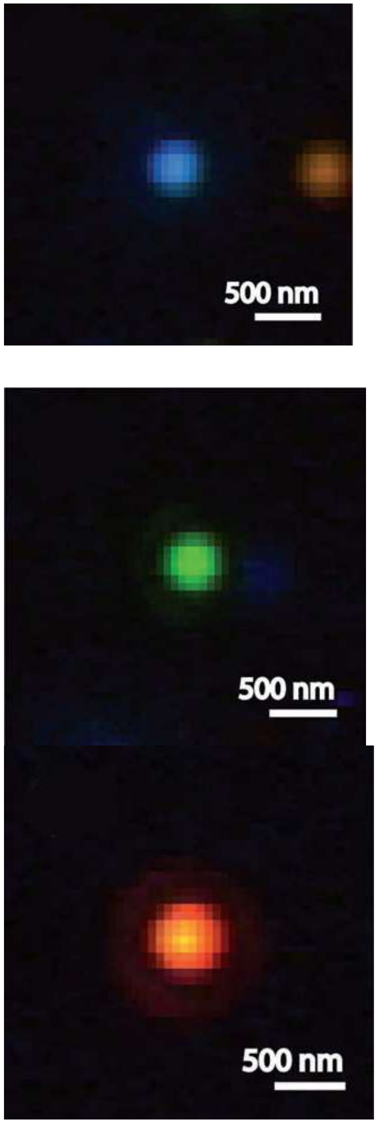
- **Methods** available for studying nanoparticles and nanostructures:
  - Ultramicroscopy
  - Transmission Electron Microscopy (TEM)
  - Scanning Electron Microscopy (SEM)
  - Atomic Force Microscopy (AFM)
  - Scanning Tunneling Microscopy (STM)
  - Surface Plasmon Resonance and Localized Surface Plasmon Resonance
  - Stimulated Emission Depletion Microscopy (STED)
  - Piezoresponse Force Microscopy
  - Methods of determining particle size:
    - Sieve analysis
    - Laser diffraction
    - Dynamic light scattering
    - Eyecon

- **Ultramicroscope**
  - Siedentopf & Zsigmondy 1903; Nobel prize to Zsigmondy 1925;
  - Indivudual colloidal particles can be observed and counted; their size can be often determined, but *not* their their shape;
  - The observation of the scattered light is done in direction perpendicular to the light beam (Tyndall effect) ⇒ diffraction spots are observed.
  - Observation of nanoparticles of up to 10–20 nm size is possible.



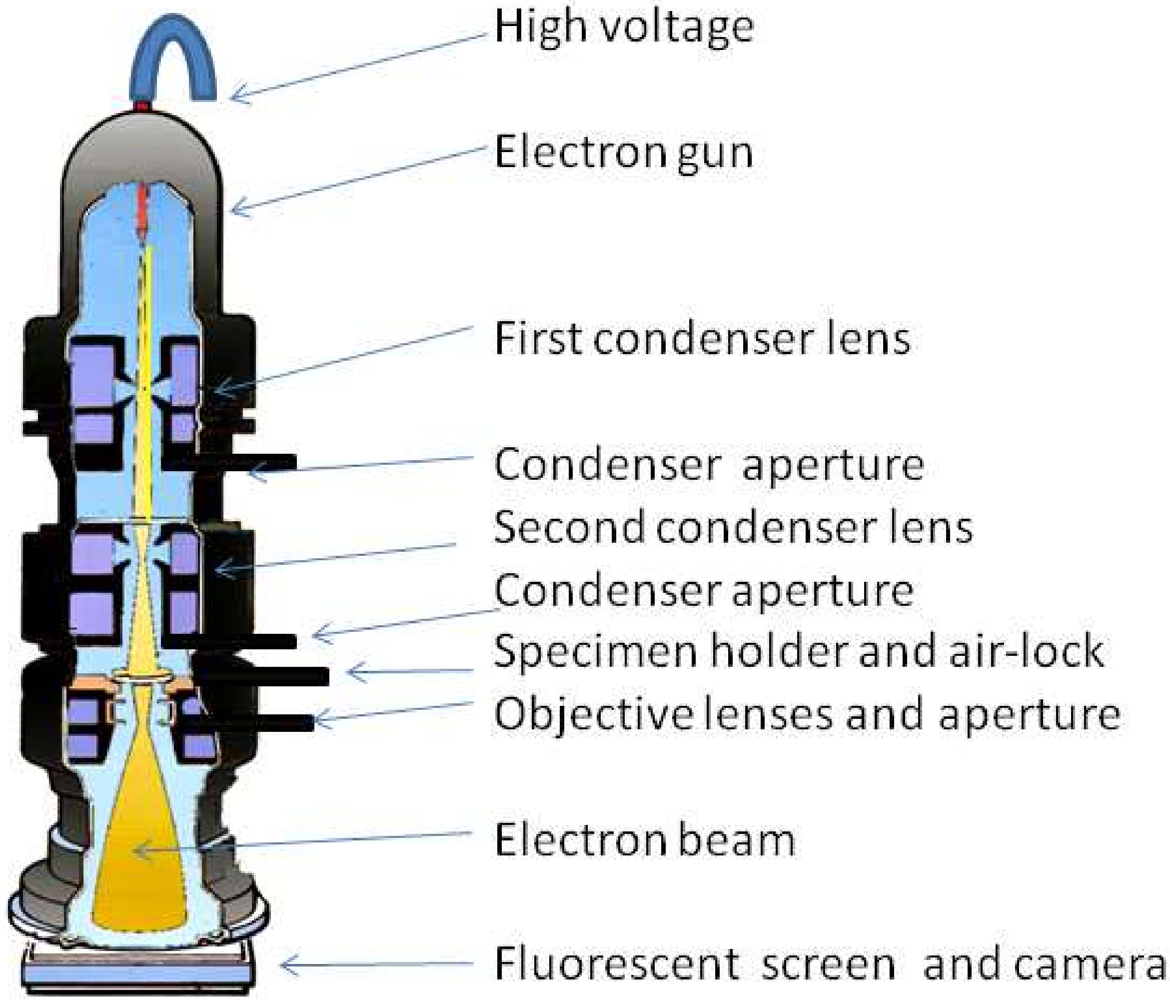
- **Ultramicroscope**





silver nanoparticles

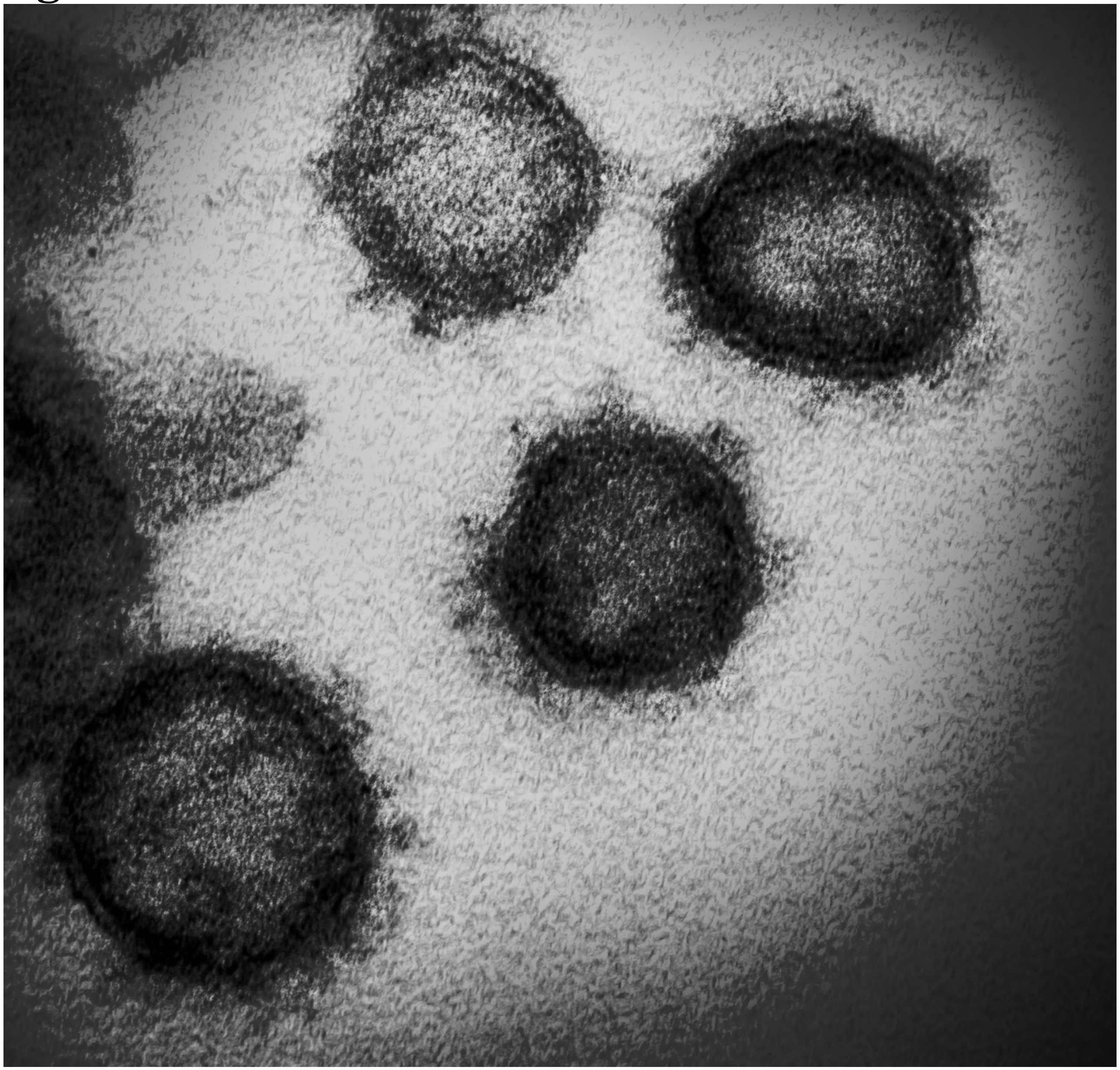
- **Transmission electron microscope (Ruska 1933)**
  - ►Uses high-energy electron beams instead of light; voltages ~ 50–130 kV;
  - ►Magnification of up to 1 million times, resolution of up to 0.2 nm;
  - ►De Broglie wavelength λ of an electron can be much smaller than of a photon;
  - ►Sophisticated sample preparation; very thin samples (30–60 nm) are needed. A device called *ultra-microtome* is used for this.



$$\lambda = \frac{h}{mv}$$

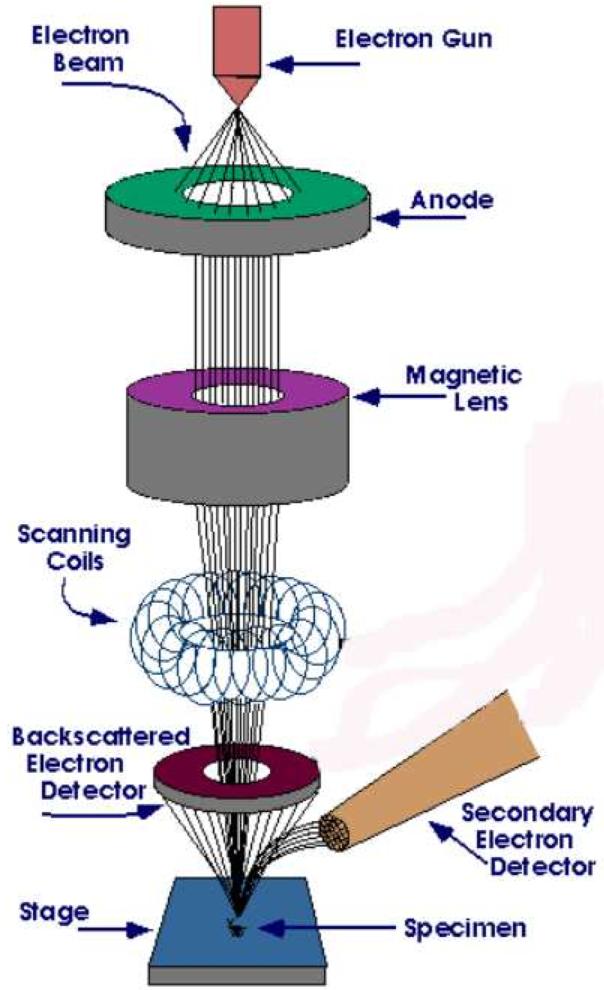
Energies: 40–400 eV

- **Transmission electron microscope**
  - ▶ Typical image:



COVID-19 viruses

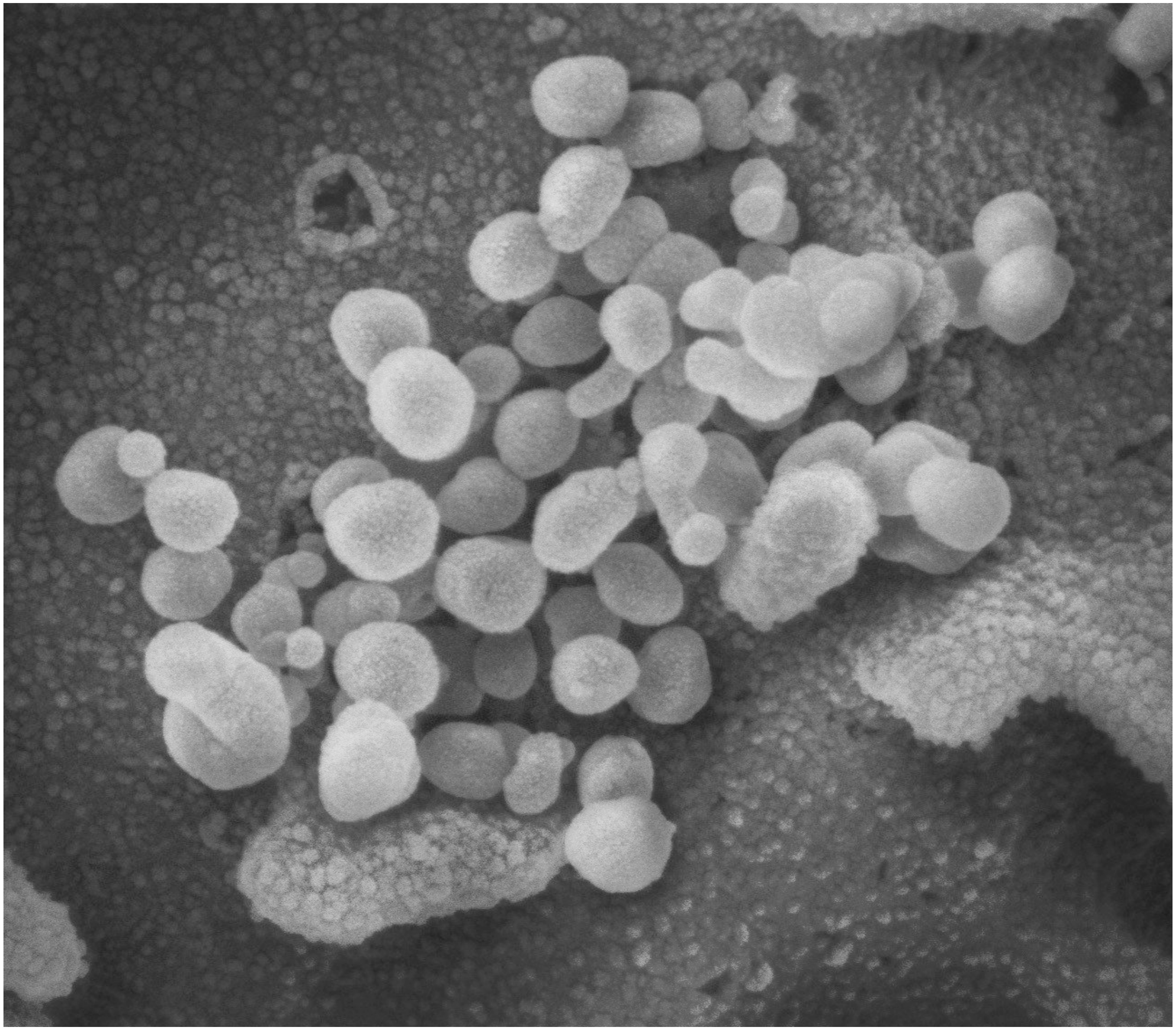
• Scanning electron microscope (von Ardenne 1937)



- Sample surface is scanned with an electron beam in a *raster scan* pattern.
- High electron energies: 1000–40 000 eV
- Detection:
  - *Back-scattered* (high-energy) electrons (BSE) are "reflected" by the specimen; heavier atoms "reflect" stronger;
  - *secondary electrons* (low-energy) are emitted by the specimen.
  - *flat* sample surface mostly absorb electrons; *tilted* surfaces produce more secondary electrons ⇒ topographic information is obtained.
- *Magnification* of 10 to 500 000 times – up to 1 nm resolution and even lower – atomic resulution is possible;
- *3D images* are possible;
- Conducting surfaces are usually needed ⇒ sophisticated sample preparation (gold or carbon coating etc.) is required.

• Scanning electron microscope (SEM)

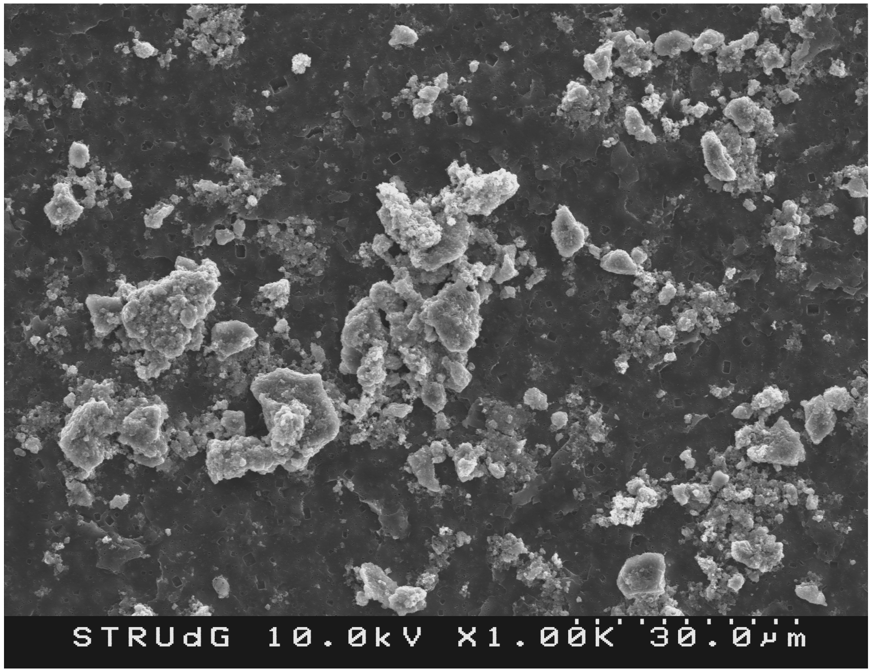
▶ Typical image.



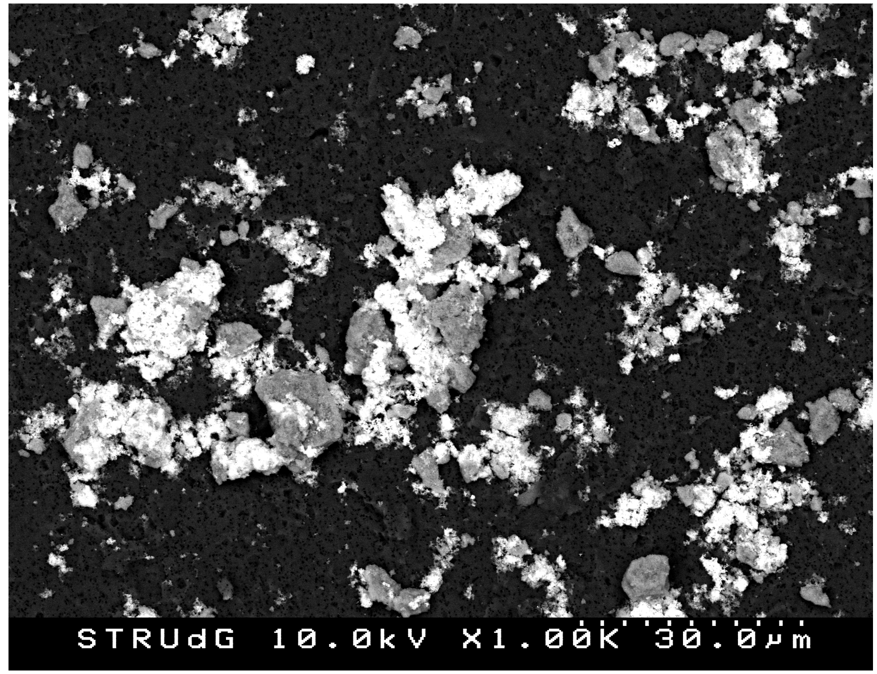
COVID-19 viruses

METHODS – SEM

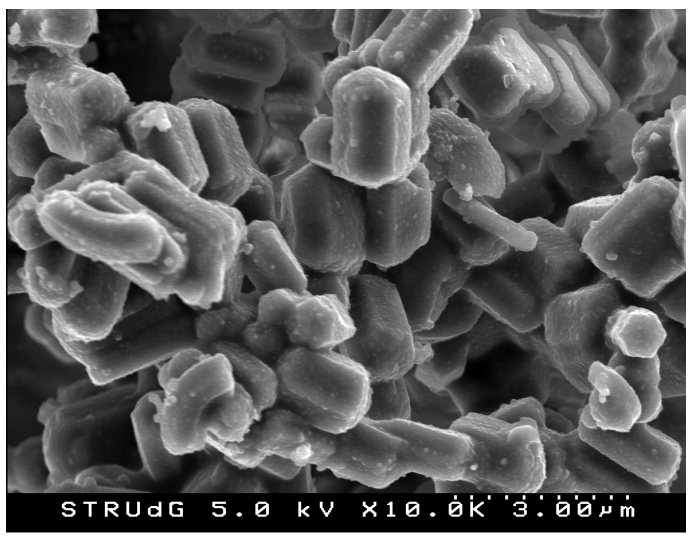
- **Scanning electron microscope (SEM):** Typical images



Ni_3B on $MgSiO_3$
(secondary electrons)



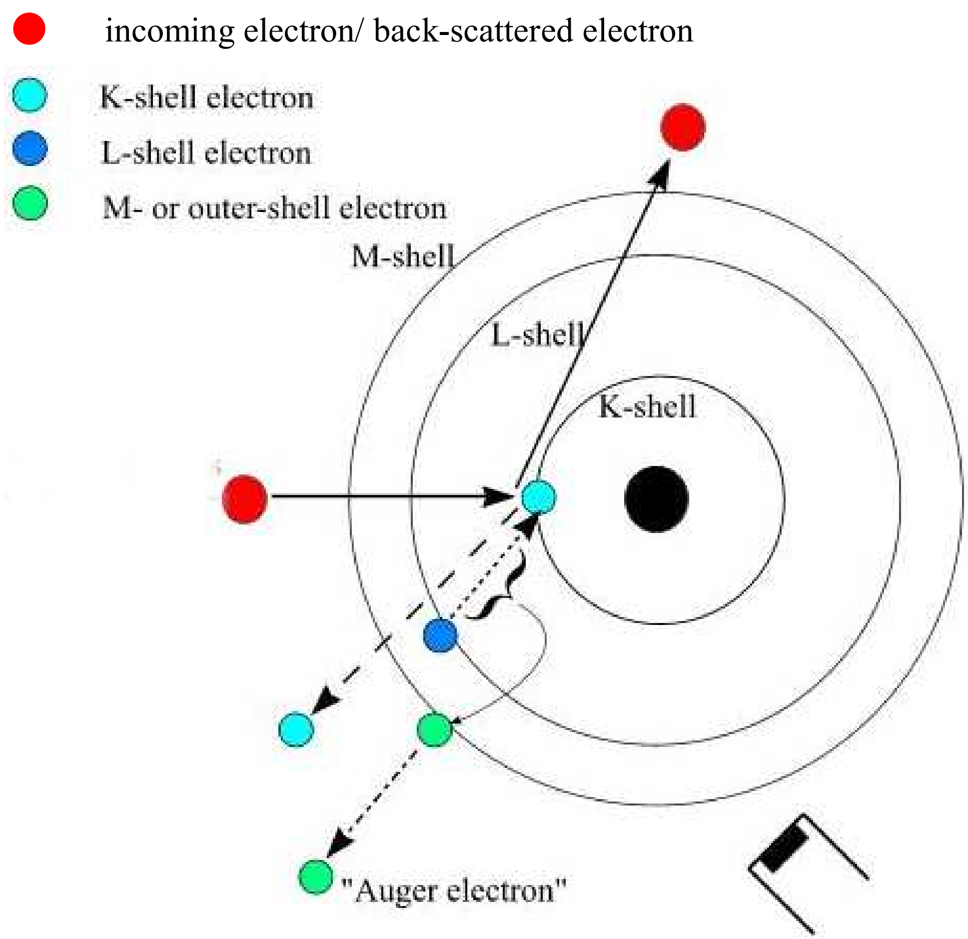
Ni_3B on $MgSiO_3$
(back-scattered electrons)



pure MCM-41 (secondary electrons)

Vyboishchikov (111)

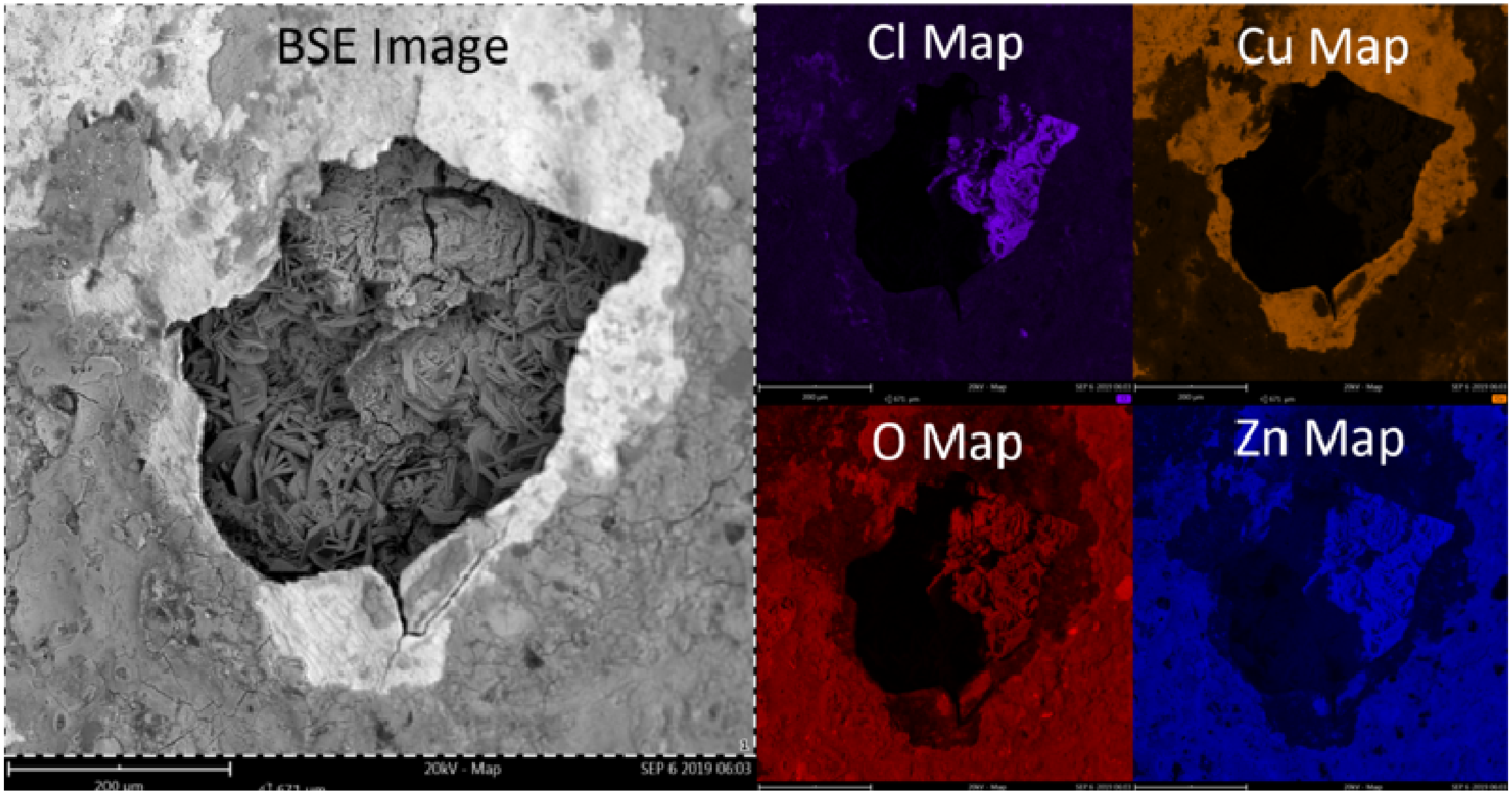
- **SEM/EDS:‡ Scanning electron microscopy with X-ray microanalysis**
  - ► Secondary *X-ray radiation* produced by the surface atoms is analyzed.
    - – The X-rays produced so are specific to the element



Principles of X-ray spectroscopy

‡ EDS stands for *Energy Dispersive X-ray Spectroscopy*.

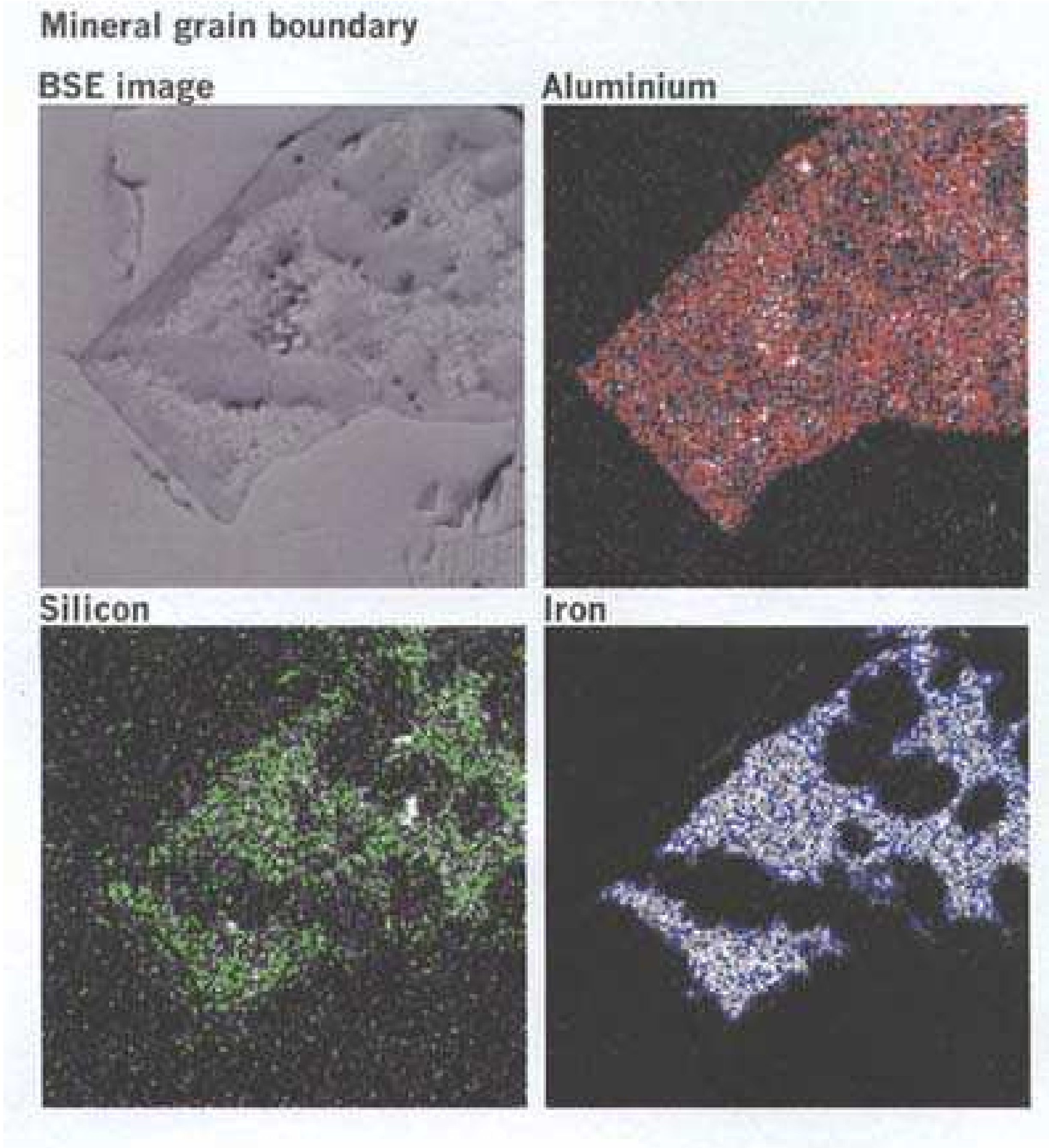
- **SEM/EDS: Scanning electron microscopy with X-ray microanalysis**
  - ► Typical SEM/EDS image. The coloring is automatic and based on X-ray microanalysis



SEM image of a coin surface (back-scattered electrons)

Elemental EDS mapping

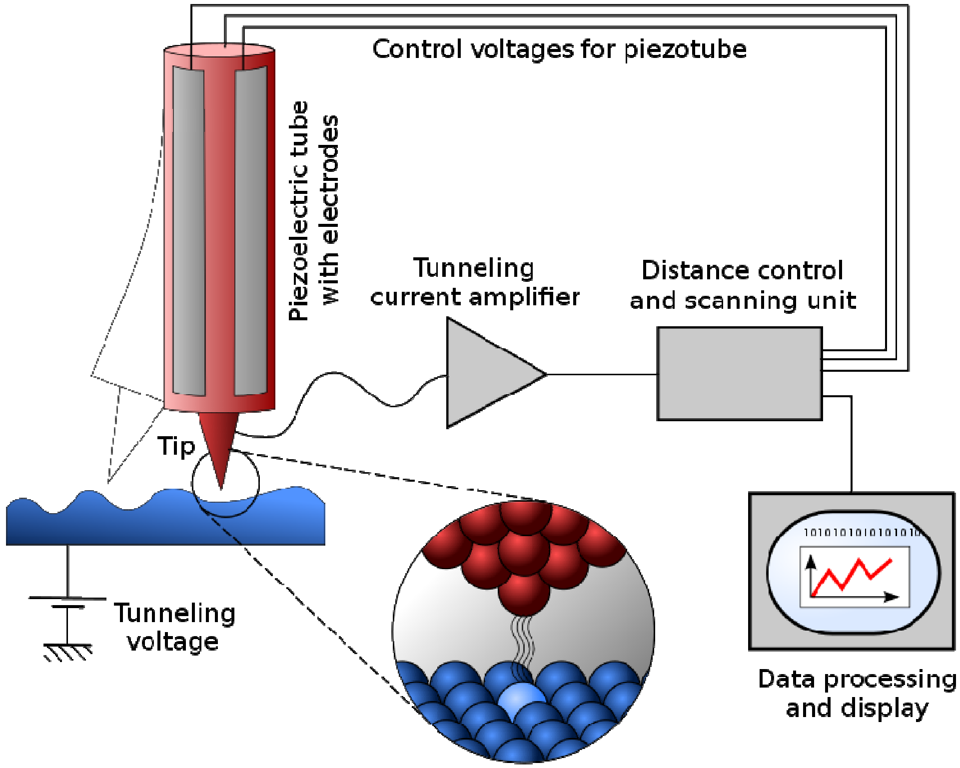
- ► Limitation of SEM/EDS:
  - – Limited detection of elements below Na in the periodic table
  - – No detection of elements below C in the periodic table

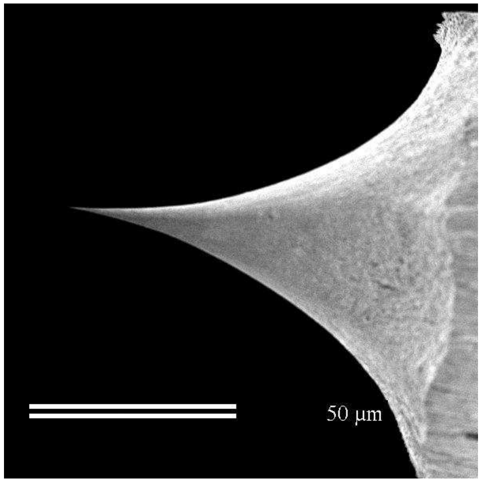


Elemental EDS mapping

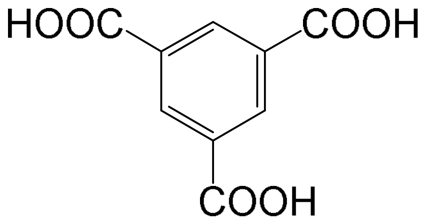
• STM: Scanning tunneling microscope (Binnig & Rohrer 1981)

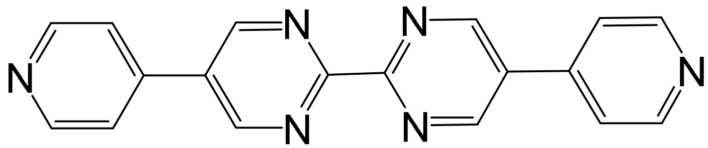
- ▶ A very fine conducting tip is moved along the surface to be studied.
  – Tip preparation: electrochemical etching of a W wire by 8% NaOH.
- ▶ *Tunnel current* between the tip and the surface is measured – a quantum effect ⇒ conducting surfaces only;
- ▶ Operating modes:
  – *constant current mode* (more common) – the tip is moved vertically, maintaining constant tunnel current;
  – *constant height mode:* the tip moves strictly horizontally.
- ▶ Atomic or nearly atomic resolution;
- ▶ Dynamic studies of surface processes are possible (imaging rates of up to 25 frames/s and more).

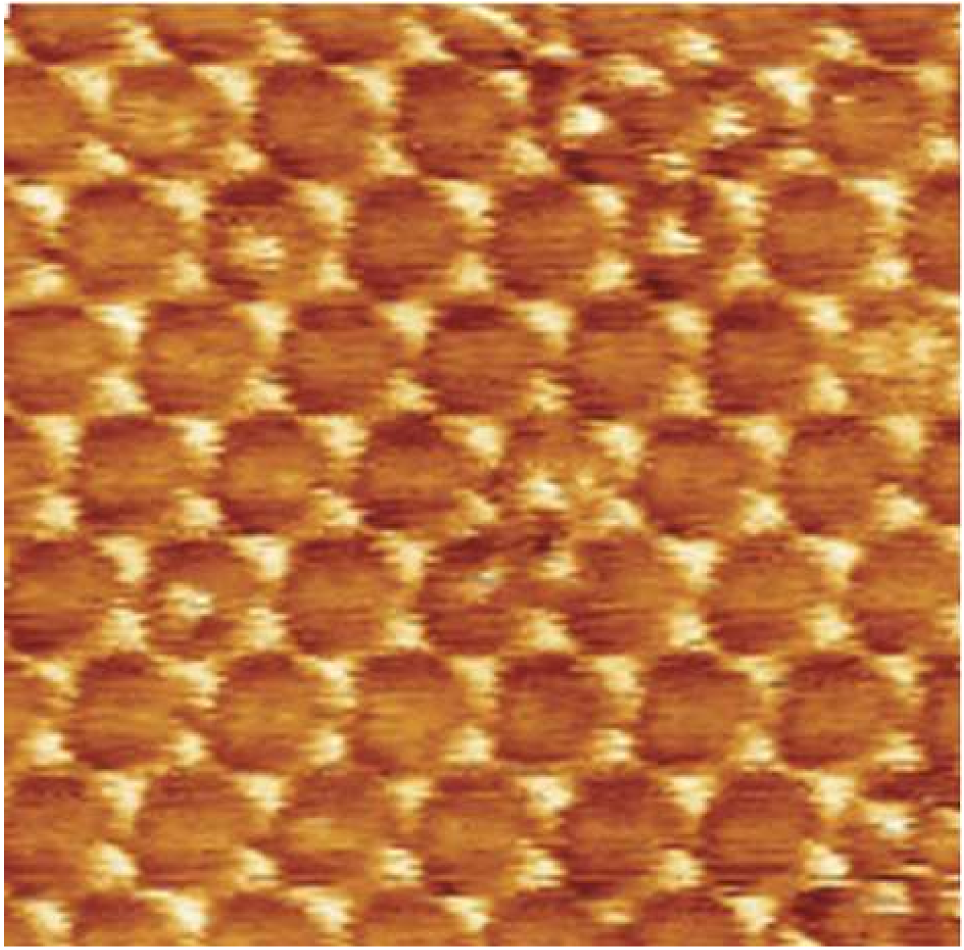




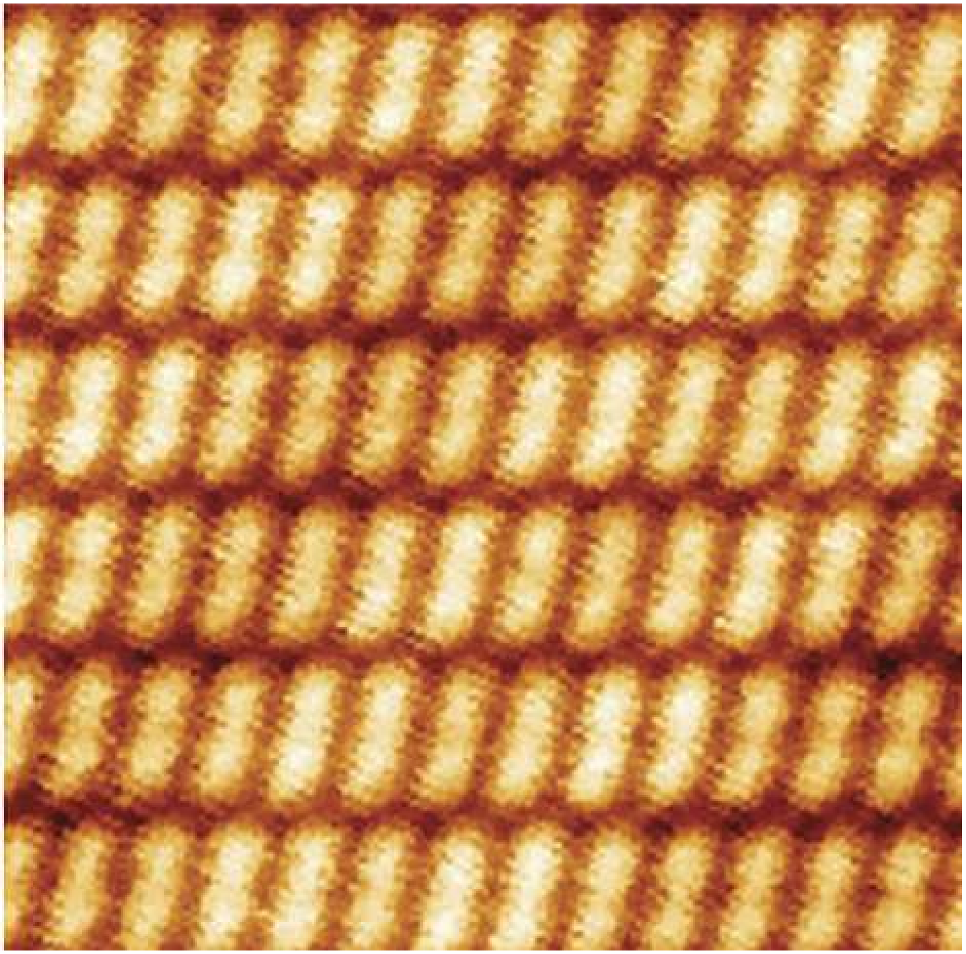
- **STM: Scanning tunneling microscope**
  - ► Typical images – self-assembling monolayers of adsorbates:



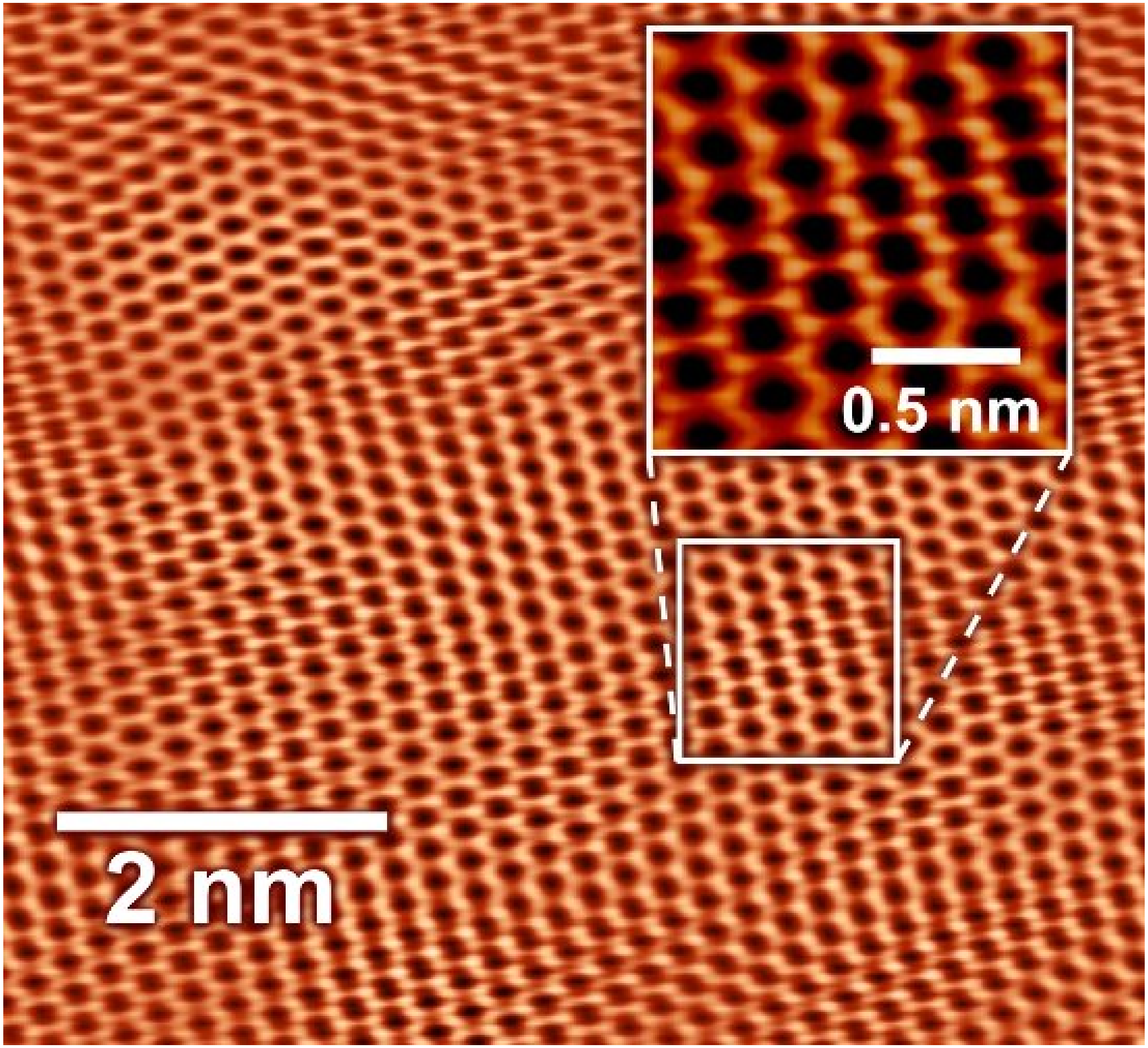




trimesic acid honeycomb network (12×12 nm)

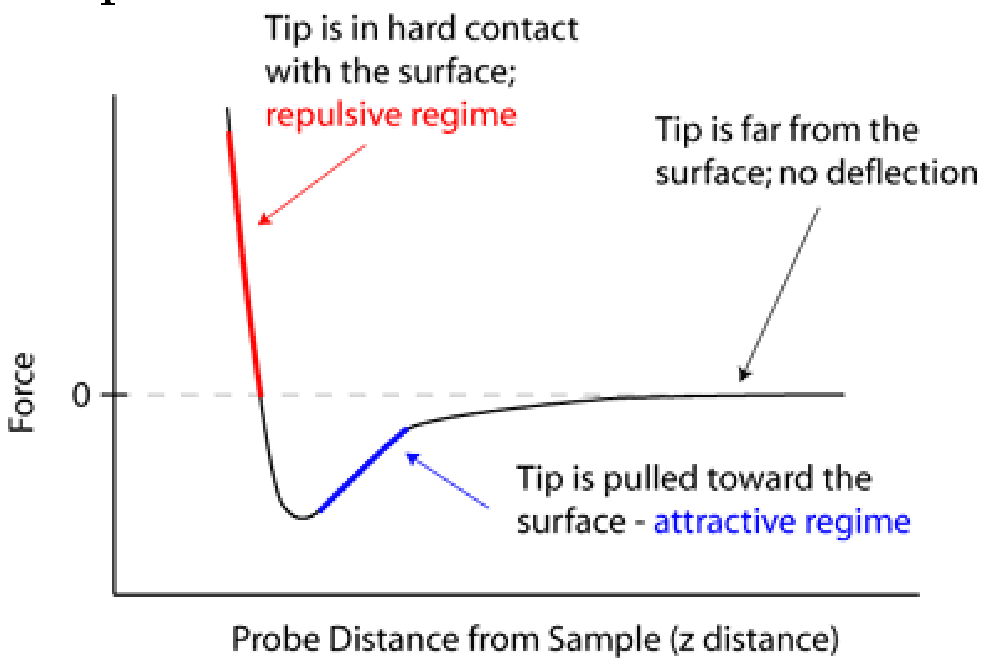


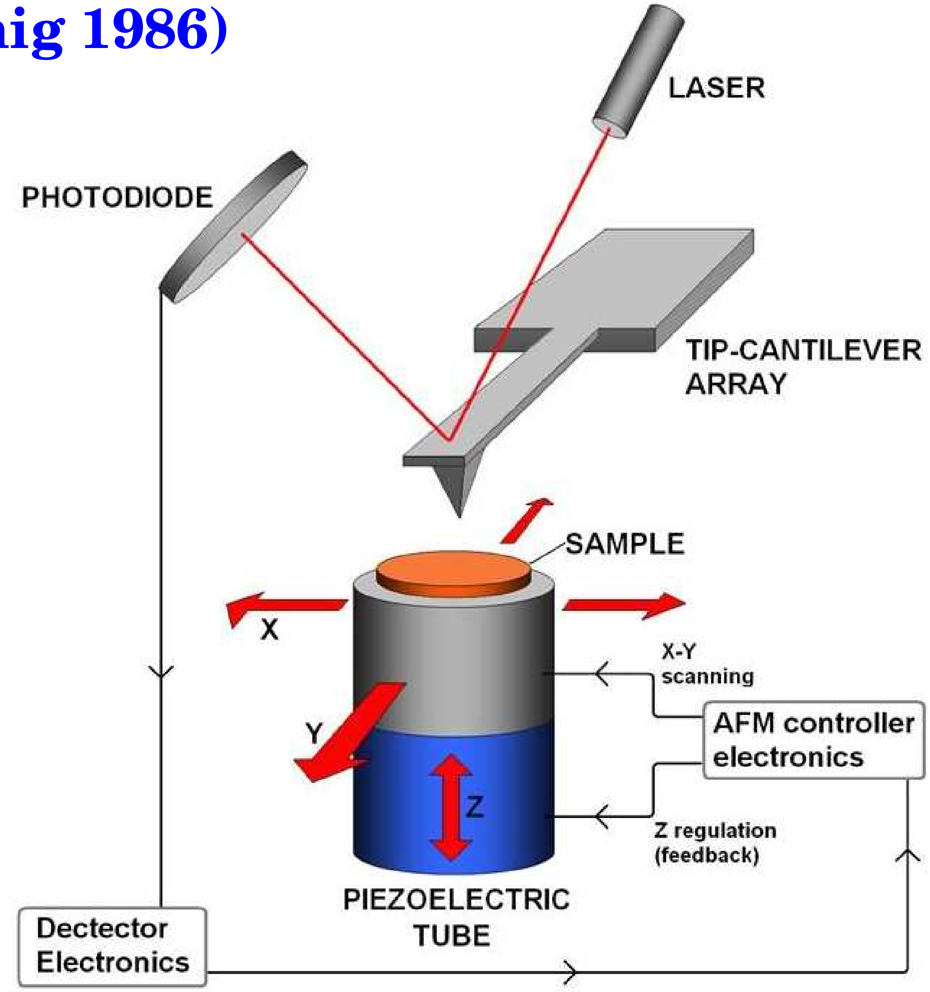
bis-pyridyl-bipyrimidine (8×8 nm) on Au(111) surface



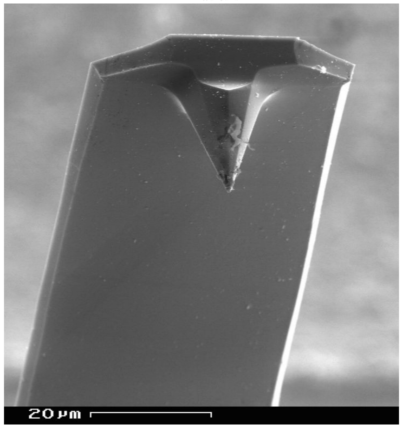
Atomically resolved STM image of graphite

- **AFM: Atomic force microscope (Binnig 1986)**
  - ▶ Based on the *van der Waals force* measurement between the surface and the tip:





  - ▶ The tip is placed on a *cantilever*; bending of the cantilever is measured by reflected laser light.
    – cantilivers are typically made of Si or Si_3N_4.



  - ▶ The surface does not need to be conducting.

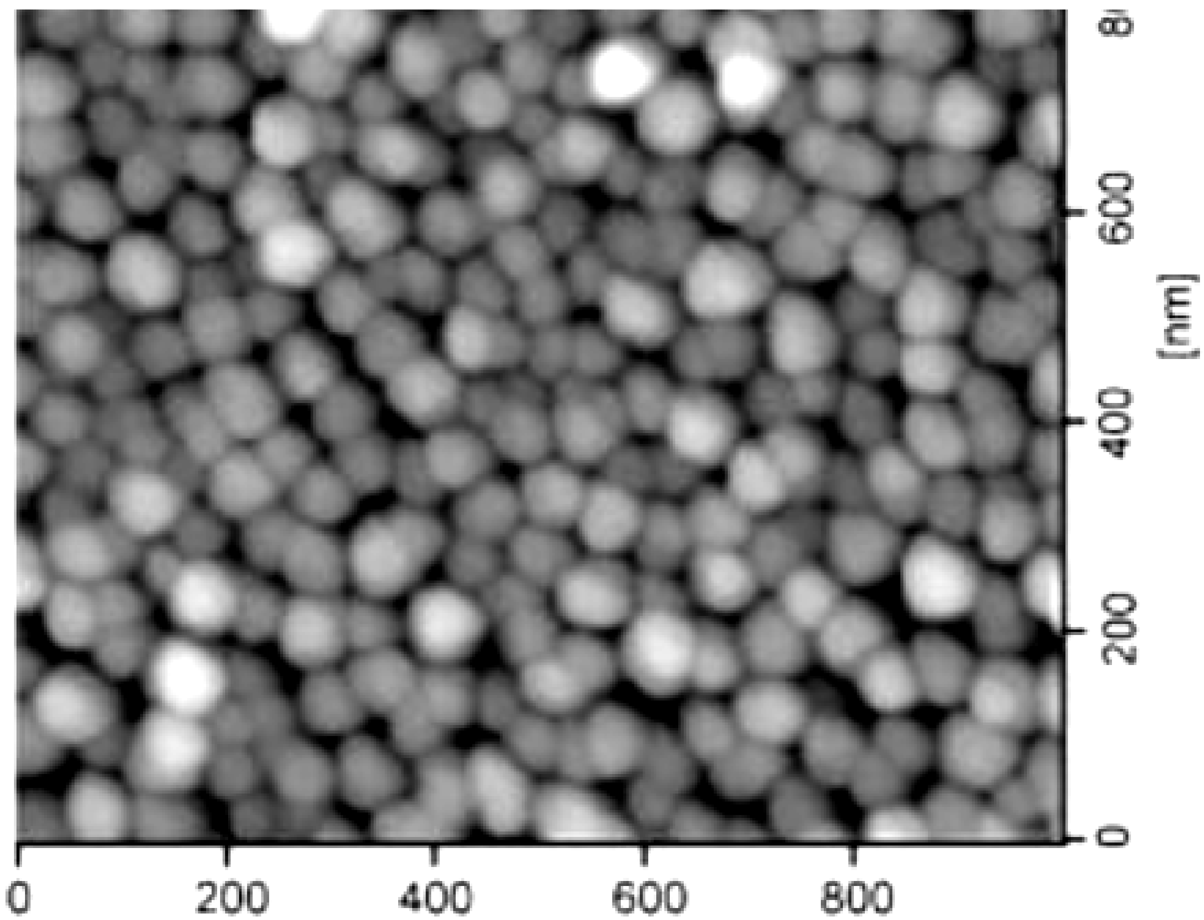
• Atomic force microscope

► Operating modes https://www.ntmdt-si.com/resources/spm-principles/atomic-force-microscopy/contact-afm

– *constant force mode*: registering the signal (position) from the scanner;

– *constant height mode*: registering the signal (force) from the cantilever;

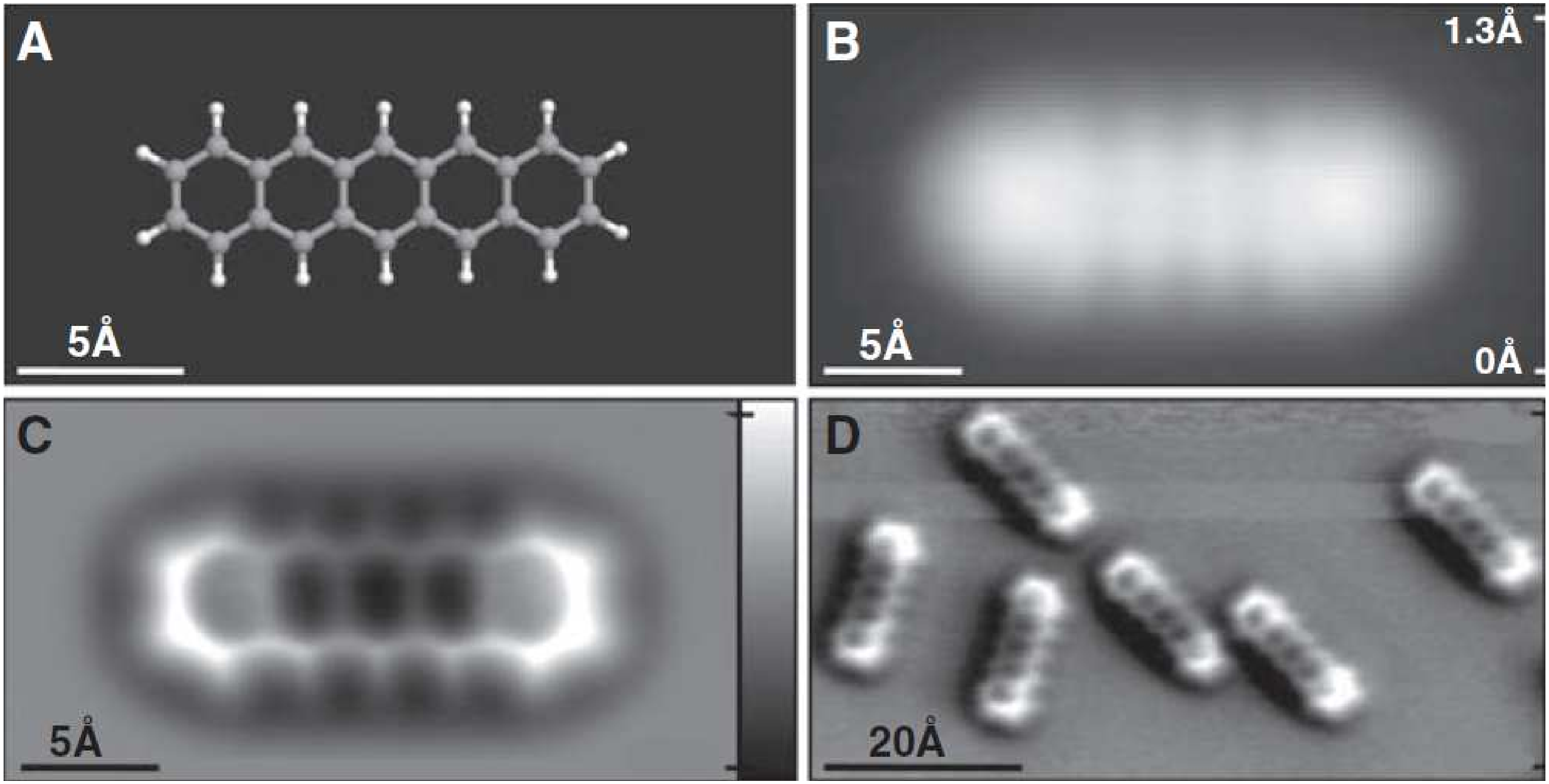
► Typical image:



gold nanoparticles

• Atomic force microscope

► Atomic resolution is possible (Gross *et al.*, DOI: 10.1126/science.1176210):



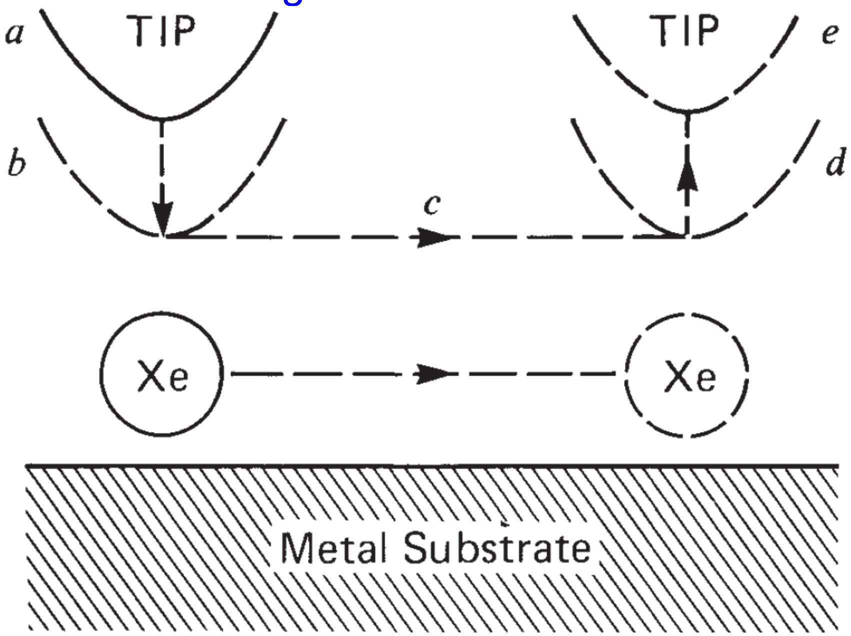
A: Pentacene ball-and-stick model

B: Constant-current STM;

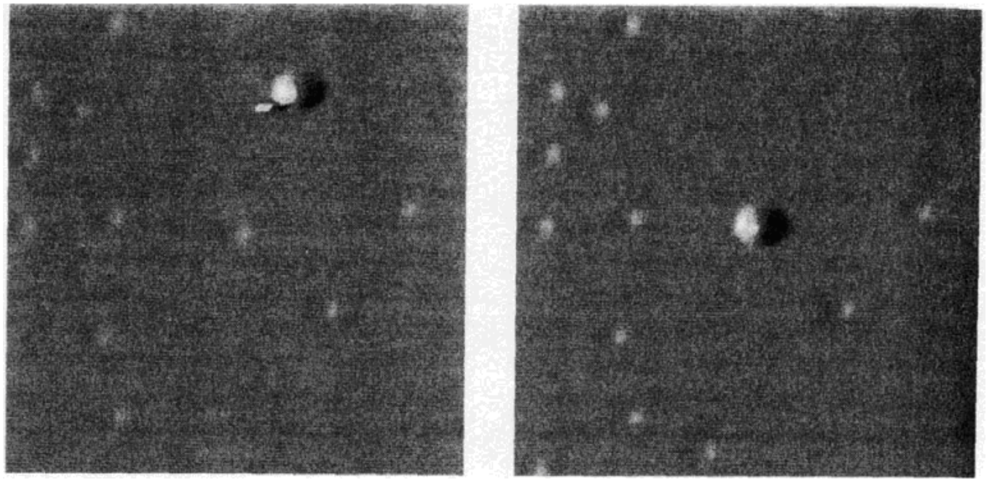
C and **D**: constant-height AFM with a CO-modified tip.

► *Writing "atom by atom"*: using a *Scanning Tunneling Microscope* or an *Atomic Force Microscope* to move atoms directy:

sliding adatoms with STM



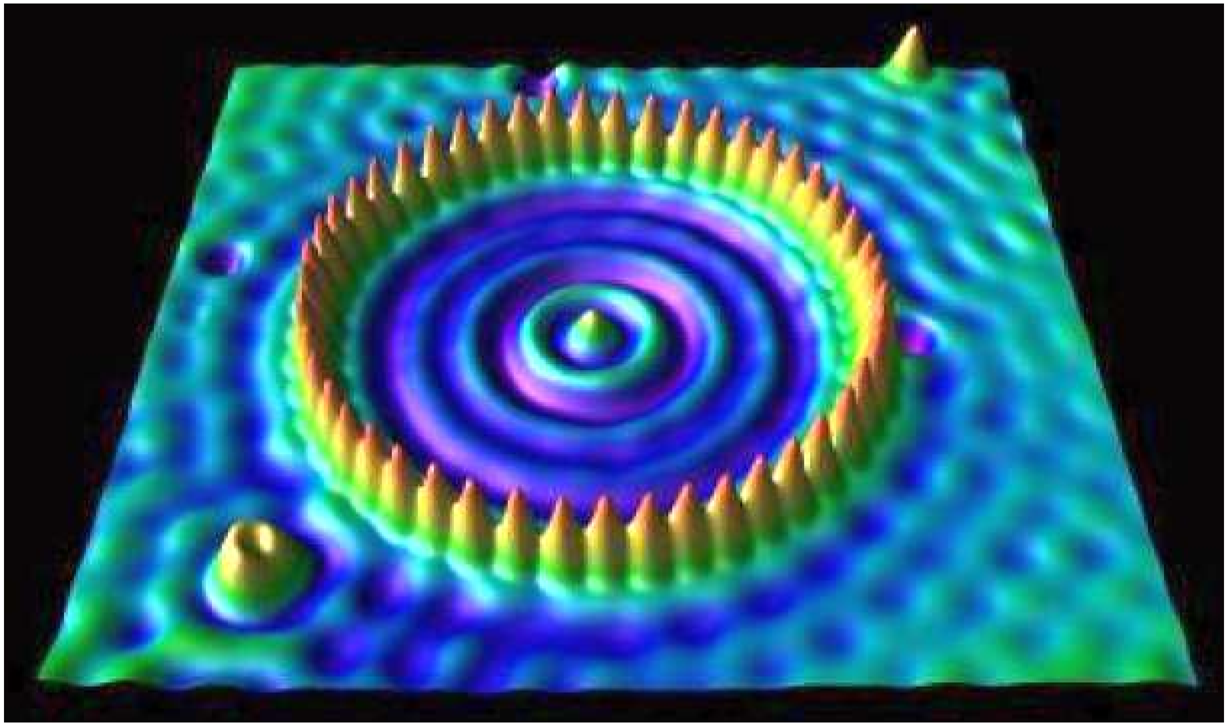
the first atom moved with STM – Xe on Pt



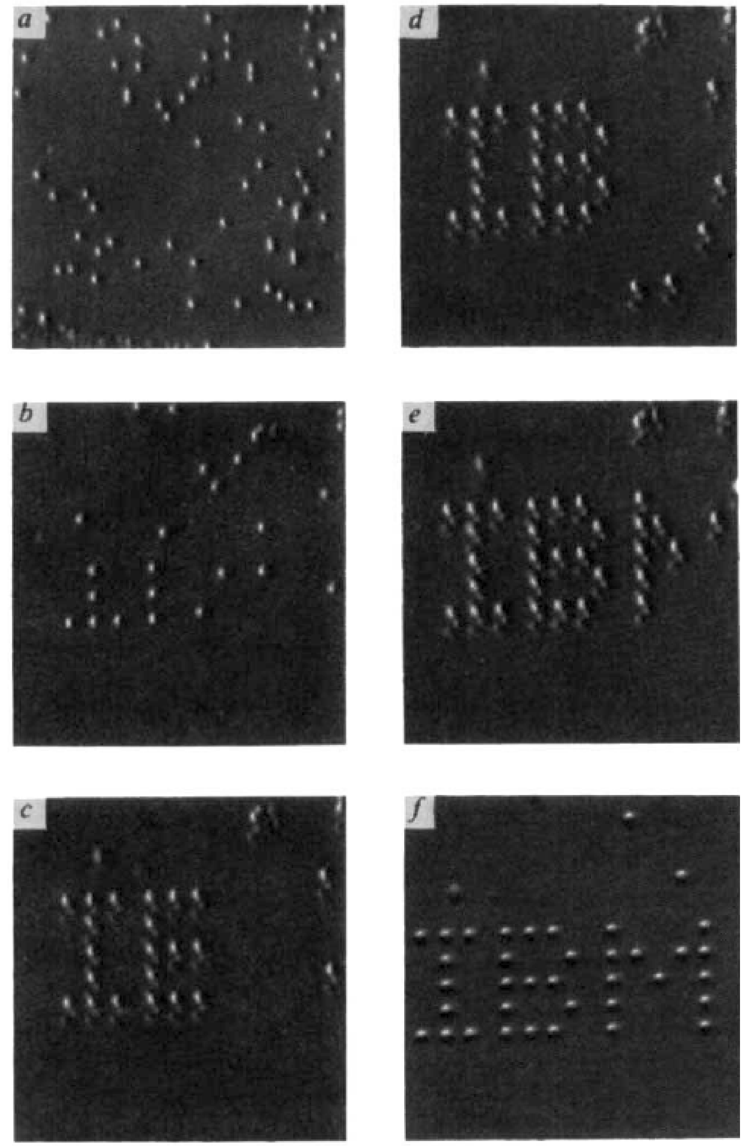
The tip is placed above the Xe atom (a), then lowered (b) to a height at which the attractive interaction between the tip and the Xe atom is sufficient to pull the Xe atom along the surface (c). When the Xe atom is moved, the tip raises back. D.M. Eigler, E.K. Schweizer, *Nature* **344**, 524 (1990) doi:10.1038/344524a0

NANOMATERIALS – FABRICATION – BOTTOM-UP

► *Writing "atom by atom"* – more pictures:



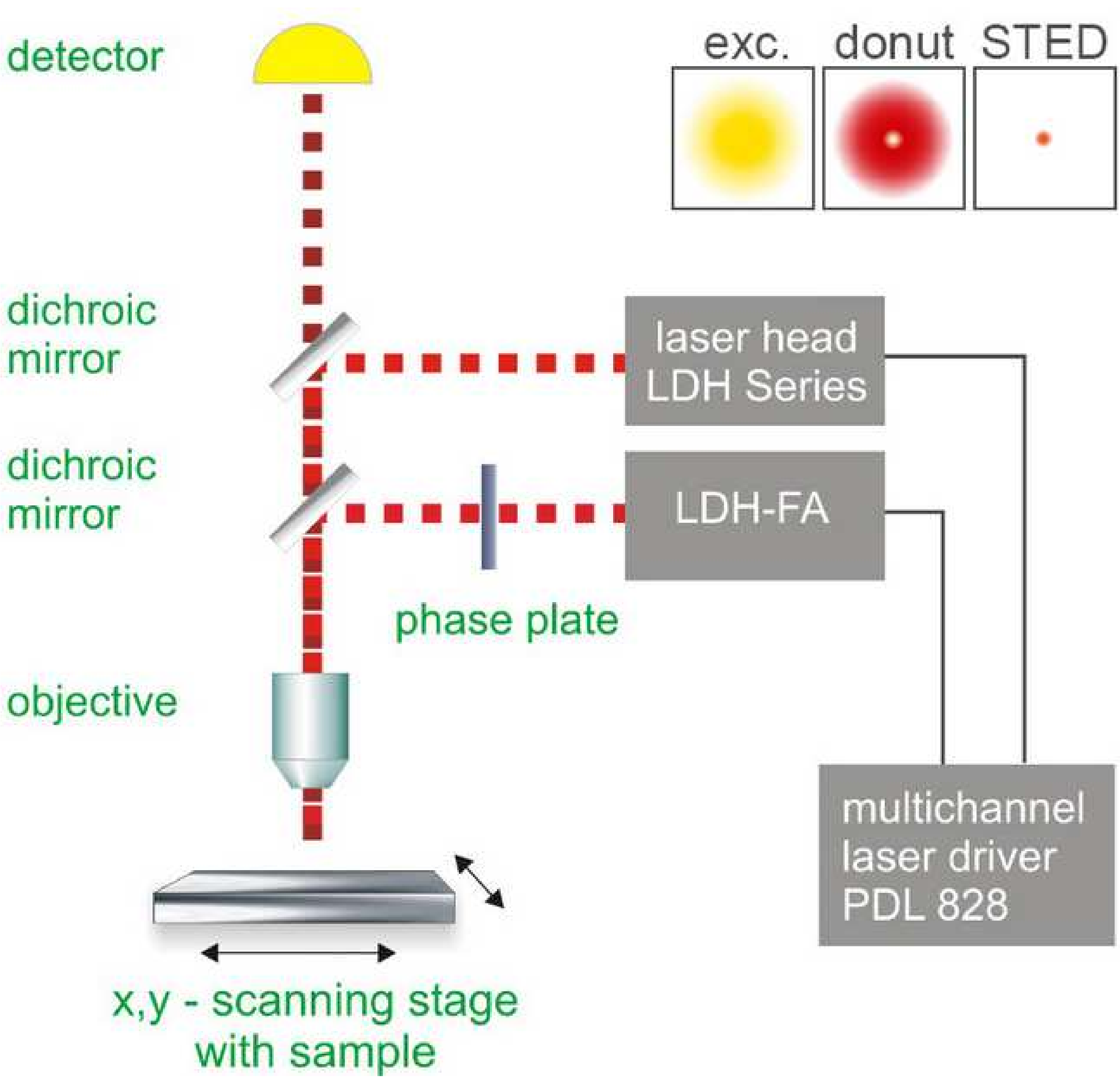
Artificial structure created from 48 Fe atoms on a Cu surface

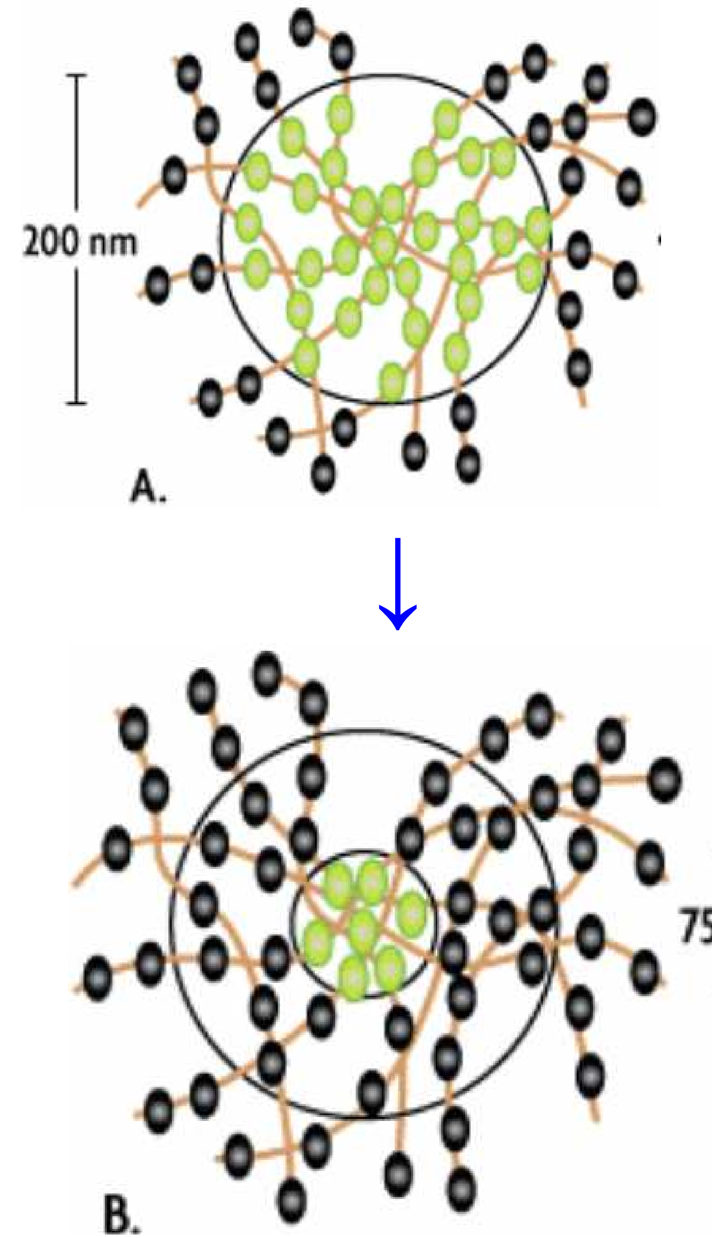


Xe atoms on Ni surface

- **Stimulated emission depletion microscopy (STED)**
  - ▶ Nobel prize 2014 to Betzig, Hell, and Moerner;
    - – discovered by Hell and Wichmann in 1994;
  - ▶ Based on *photoluminiscence* (luminiscent substance (dye) is needed;
    - – The object is scanned by laser puls (luminiscence is excited;
    - – A second laser puls depletes (red-shifts) the luminscence; the depletion is weaker in the center (the resulting luminiscence spot is smaller (higher resolution)
  - ▶ A scanning technique
  - ▶ Typical resolution: 30–80 nm.

- **Stimulated emission depletion microscopy (STED)** *continued*

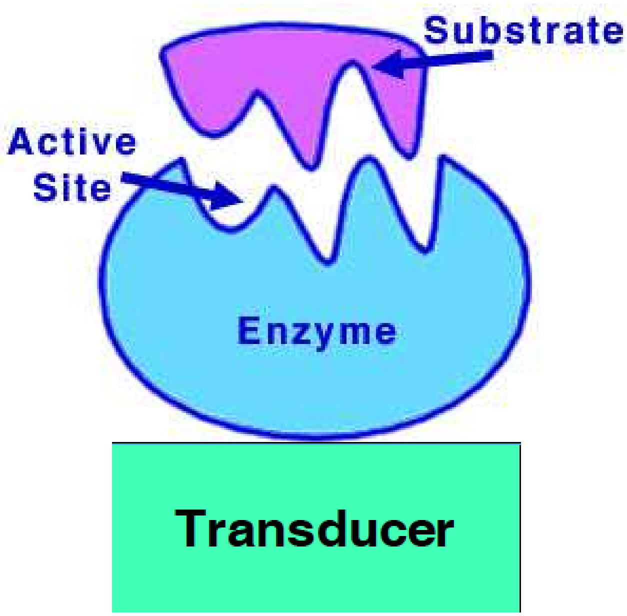




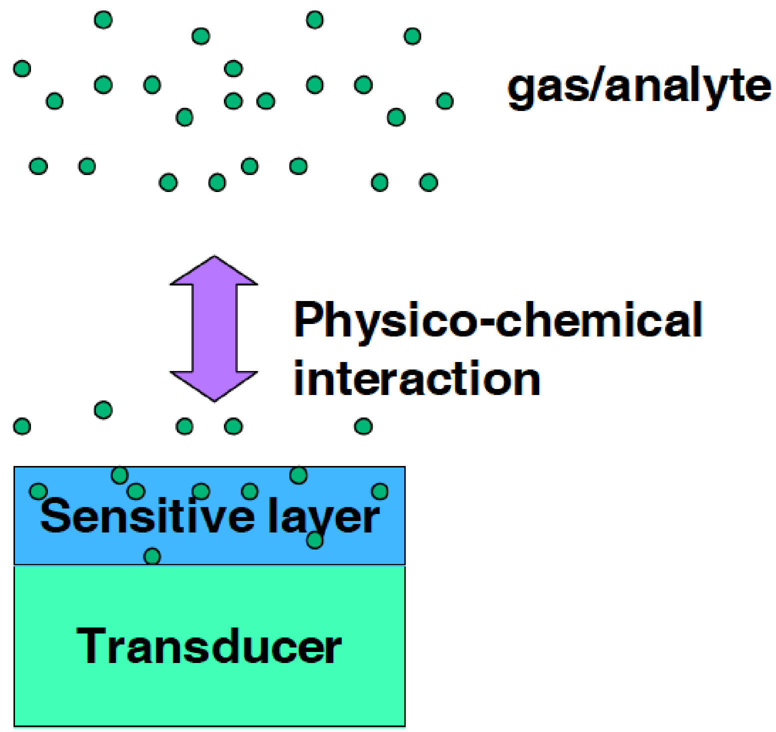
- **Sensors –** *definition*
  - ► A *sensor* is a device for recognizing a specific chemical species and "signaling" it in a quantifiable manner.
  - ► Terminology: *sensor* ≈ *transducer*
    - – A more accurate definition:
      A *sensor* is the *sensing element* itself;
      A *transducer* is the *sensor* + any device for *transfering* the sensor signal to a human-readable form
  - ► *Chemical* sensors measure and characterize chemical compounds:
    - – gas sensors;
    - – conductometric sensors;
    - – catalytic sensors.
  - ► *Bio*sensors measure and characterize biological materials:
    - – enzyme sensors
    - – antibody- or aptamer-based sensors
    - – DNA-based sensors

- ***What can be measured?***
  - magnetic and electric fields
  - resistance
  - capacitance
  - inductance
  - frequency
  - optical properties

biosensor:



chemical sensor:



SENSORS

- Metal-oxide ***chemiresistor*** gas sensors: example of a SnO_2-based CO sensor

  Conductance of SnO_2: $\sigma = \sigma_0 + k[CO]^{0.5}$

  σ is the conductance of the SnO_2

  k is a sensitivity coefficient (empirical)

► Other metal oxides used:

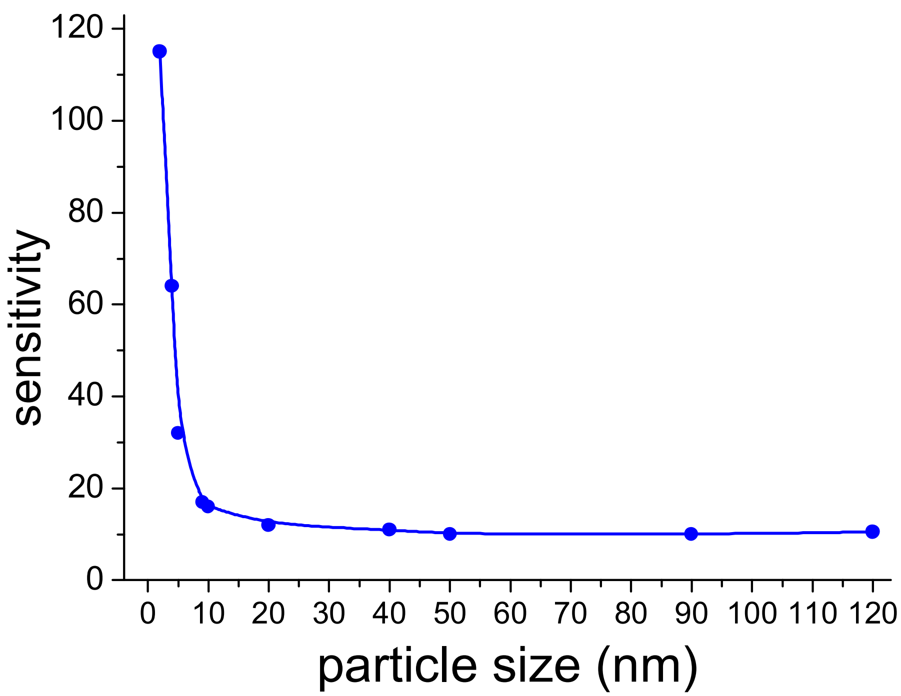
Ga_2O_3: for O_2, CO

In_2O_3: for ozone (O_3)

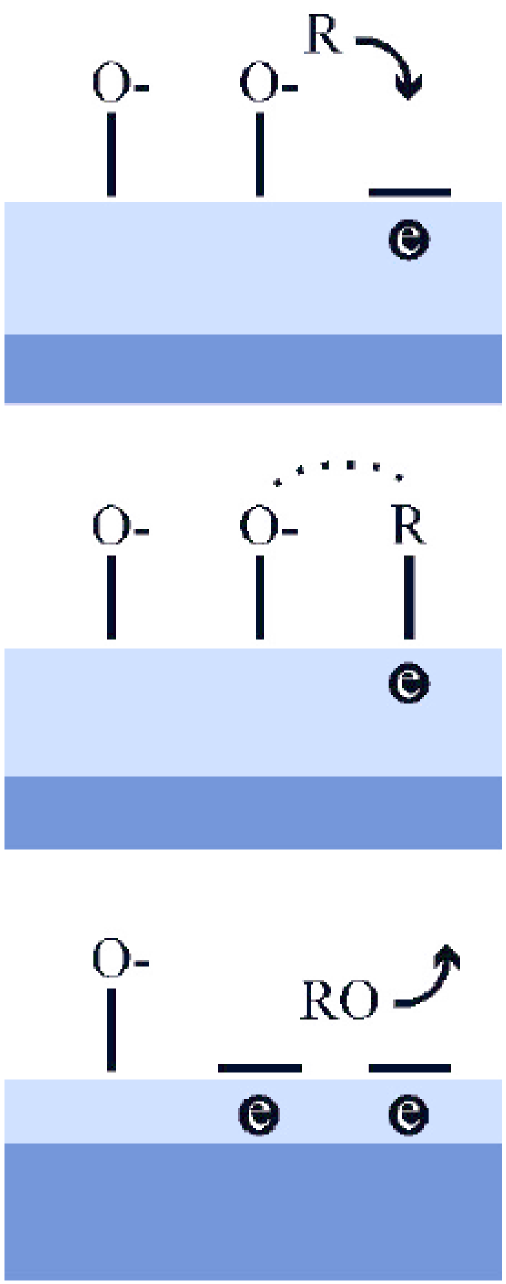
MoO_3: for NH_3

WO_3: for NO_2

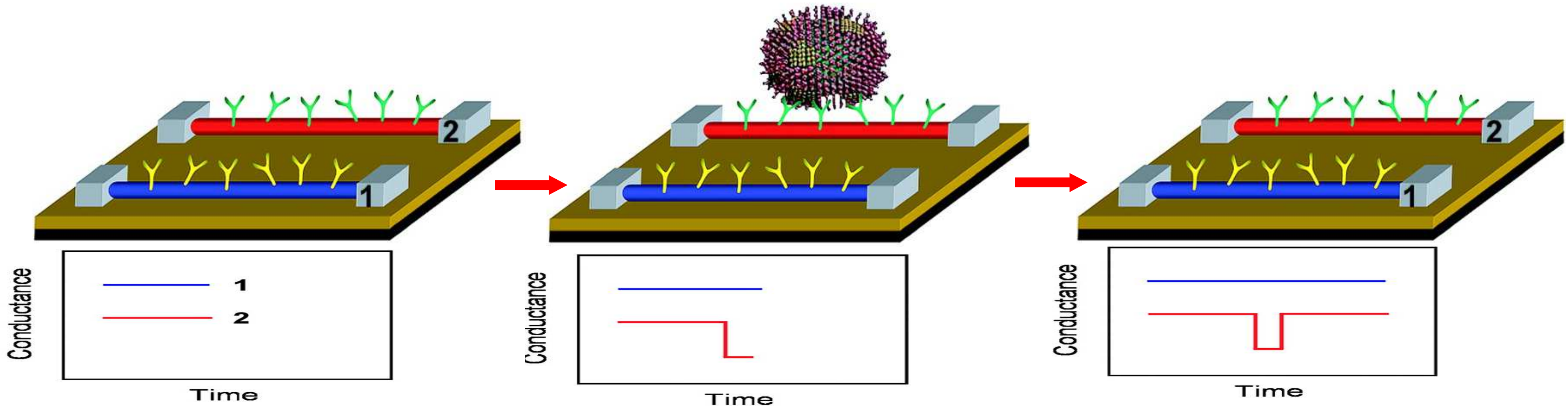
Cr_2TiO_5: for H_2S



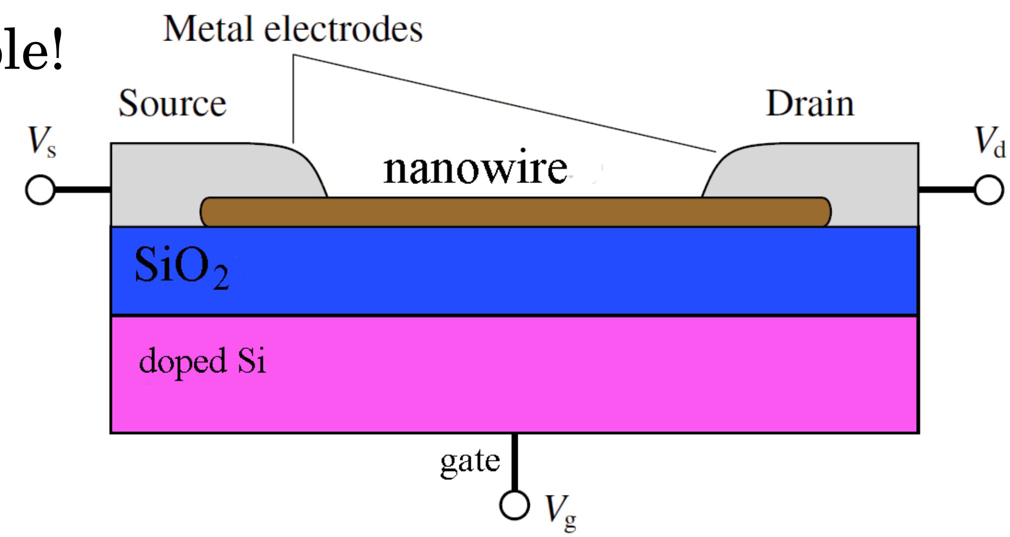
~20 €



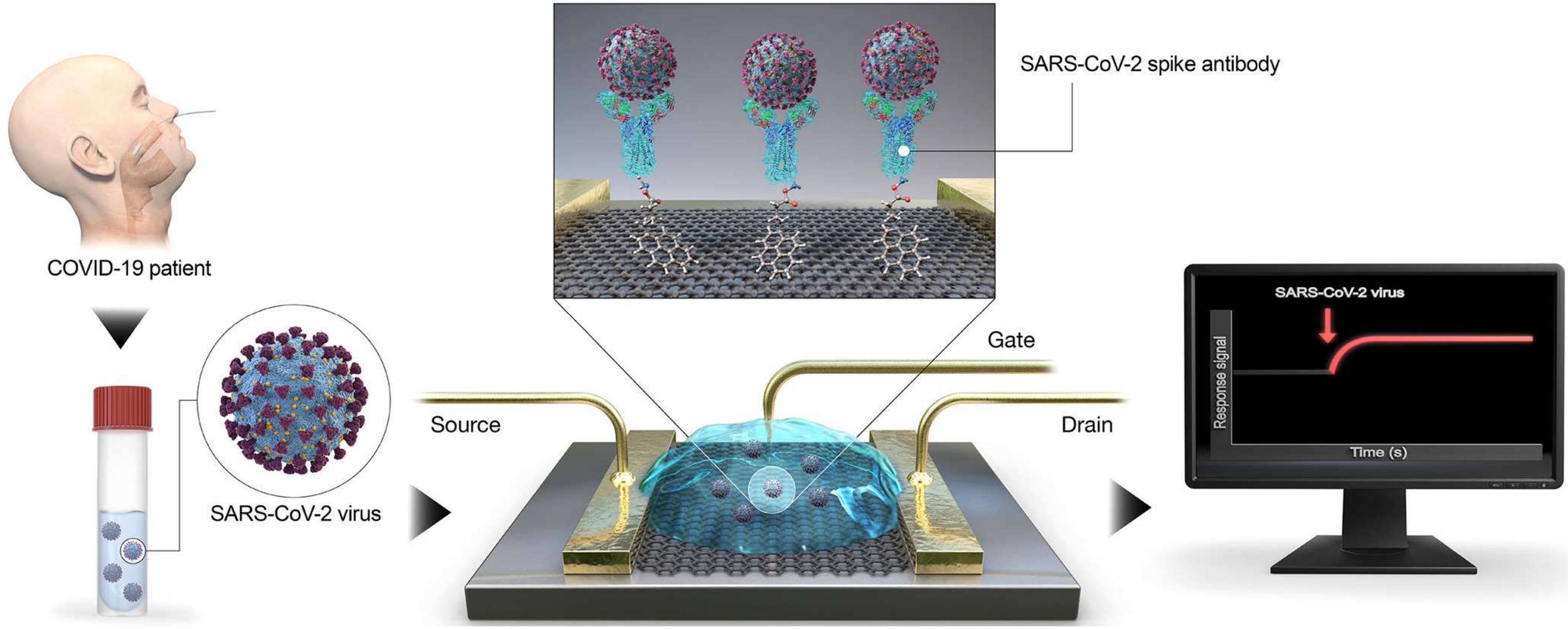
- **Electrical detection of viruses** (Patolsky *et al*. *PNAS*, *101*, 14017–14022 (2004))
  - B-doped Si nanowires are produced by *chemical vapor deposition* from SiH_4 on Au nanoparticles as catalyst in the presence of B_2H_6.
  - The nanowire is modified by $(CH_3O)_3SiCH_2CH_2CHO$; then, influenza *antibodies* are coupled to the aldehyde-terminated nanowire surface.
  - Conductance of the nanowire is measured.



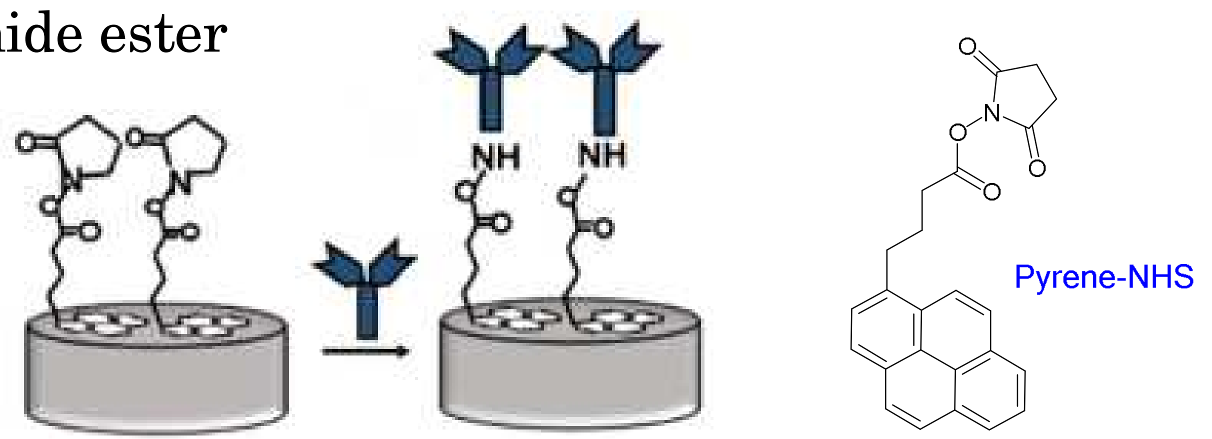
- Detection of a single virus is possible!
- Measurement scheme: a nanowire field-effect transistor (FET) →



• Electrical detection of viruses (Seo *et al.* *ACS Nano, 14*, 5135–5142, (2020))

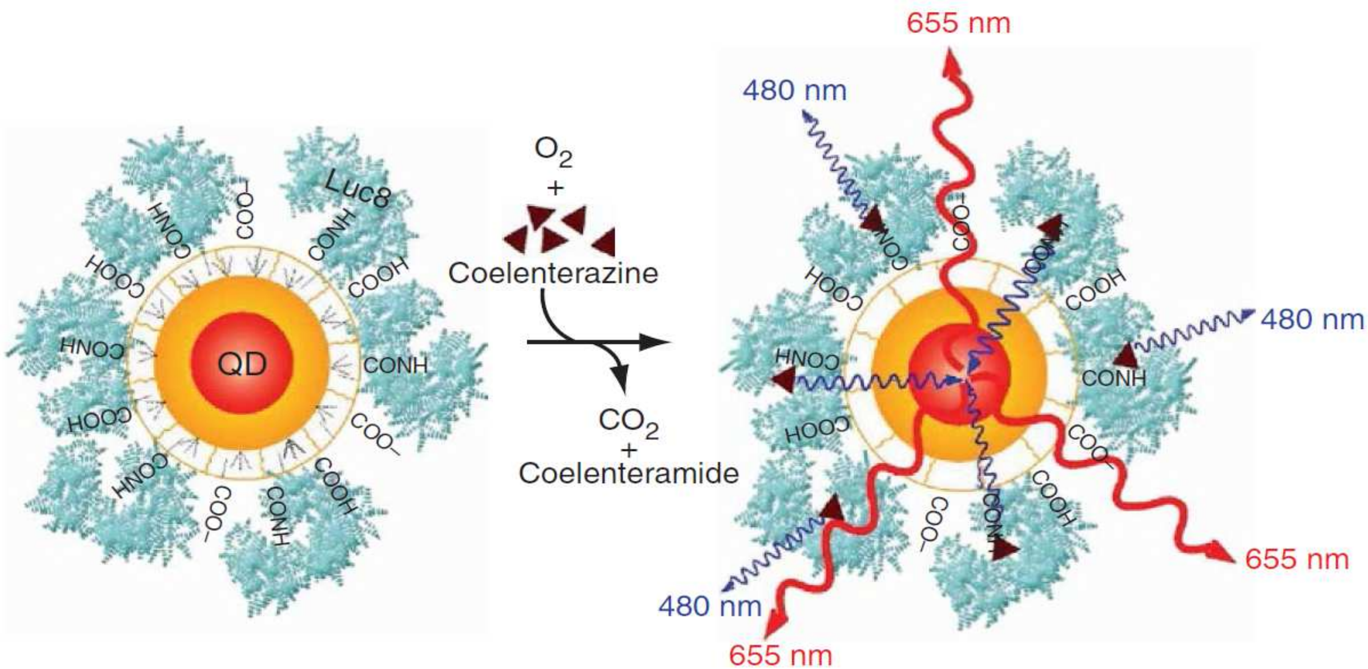


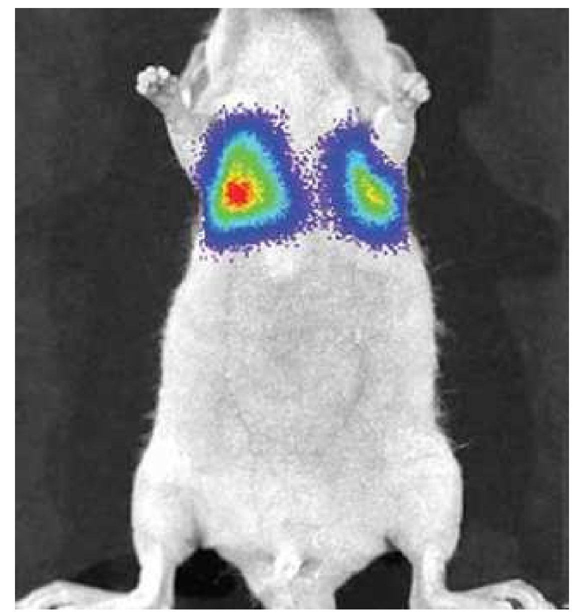
– Measurement scheme: a graphene-base field-effect transistor (FET) SARS-CoV-2 spike antibody is conjugated to graphene via 1-pyrenebutyric acid N-hydroxysuccinimide ester (= Pyr-NHS, which is also used for fluorescent labeling of proteins)



SENSORS

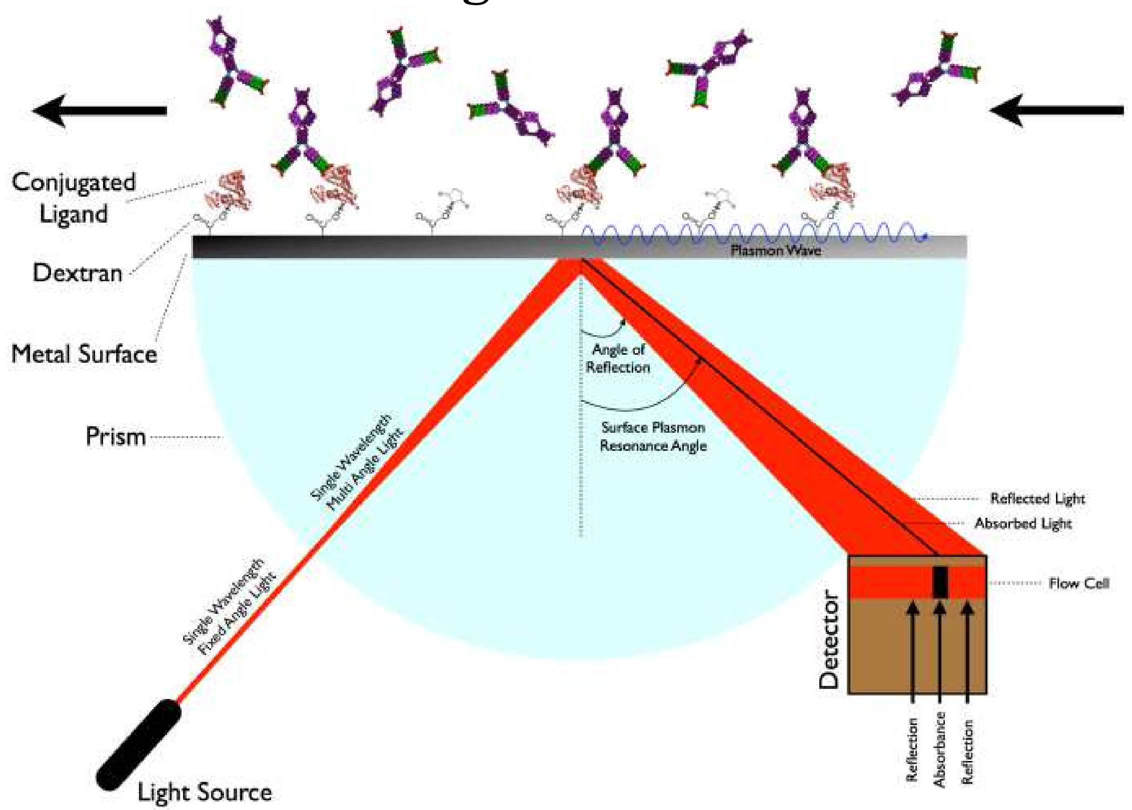
- ***Quantum dot***-bases biosensors:
  - ► Quantum dots coated with a polymer and covalently linked ("conjugated") to antibodies;
    - – The fluorescence is *specific* for the target and *brighter* and more *photo-stable* than comparable organic dyes.
  - ► Self-illuminating quantum dot conjugates for cancer diagnosis: Coelenerazine (a luceferine) and *quantum dots* coupled to luceferase are injected into the body. Bioluminescence energy of luceferase-catalyzed oxidation of coelenterazine is transferred to QD $\Rightarrow$ QD emission.





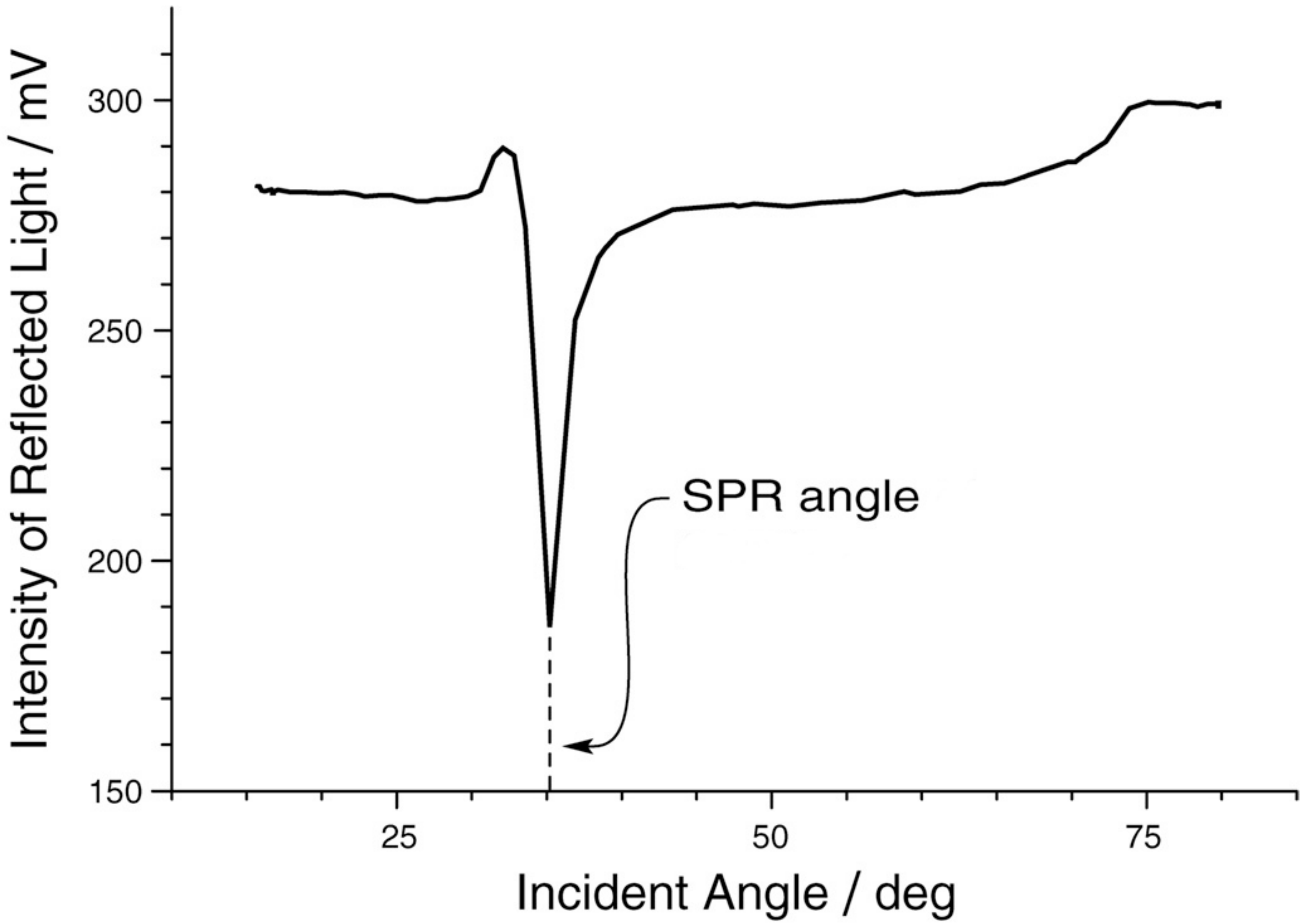
  - ► More examples: immunofluorescent labeling of breast cancer marker HER2 and prostata cancer marker PSMA; both *in vitro* and *in vivo*.

- **Surface plasmon resonance (SPR)**
  - ▶ *Surface plasmons* are collective oscillations (waves) of electrons on a conductor surface at a specific frequency.
  - ▶ Surface plasmons are responsible for observable metal color (golden for gold etc.)
  - ▶ For a macroscopic single crystal, surface plasmons are *delocalized* over the entire surface.
  - ▶ Surface plasmons strongly interact with incident light. Under certain conditions, a *resonance* occurs.
  - ▶ Experimental setup (Kretschmann) →
    - – Gold thin layer (500–100 nm) is often used;
    - – Total internal reflection is disrupted due to the plasmon resonance at a certain incidence angle (SPR angle).
    - – Resonanse conditions are sensitive to adsorption ⇒ even monolayers are detectable



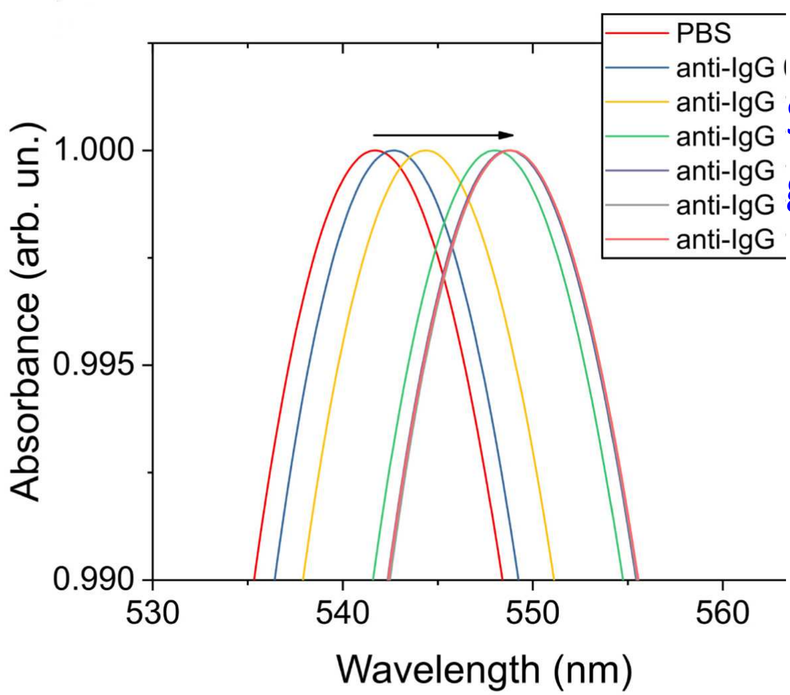
https://www.youtube.com/watch?v=sM-VI3alvAI

► A typical SPR curve:



► The SPR angle is very sensitive to adsorption on the gold surface. Measuring variation in the SPR angle allows analyzing very small concentrations of molecules in the solution.

- **Localized surface plasmon resonance (LSPR)**
  - ▶ Surface plasmons on a surface of a *nanoparticle* are different from those on a surface of a macroscopic crystal – *localized surface plasmons.*
  - ▶ Localized surface plasmons are *standing* waves, unlike the usual surface plasmons which are *propagating* waves.
  - ▶ If the incident light frequency concides with the plasmon frequency, *resonance* occurs ⇒ light is absorbed;
  - ▶ The resonance frequency is sensitive to the nanoparticle chemical *nature*, *size*, *shape*, and the *refractive index* of the environment;
  - ▶ Sensors based on the absorption wavelength *shift* are possible.

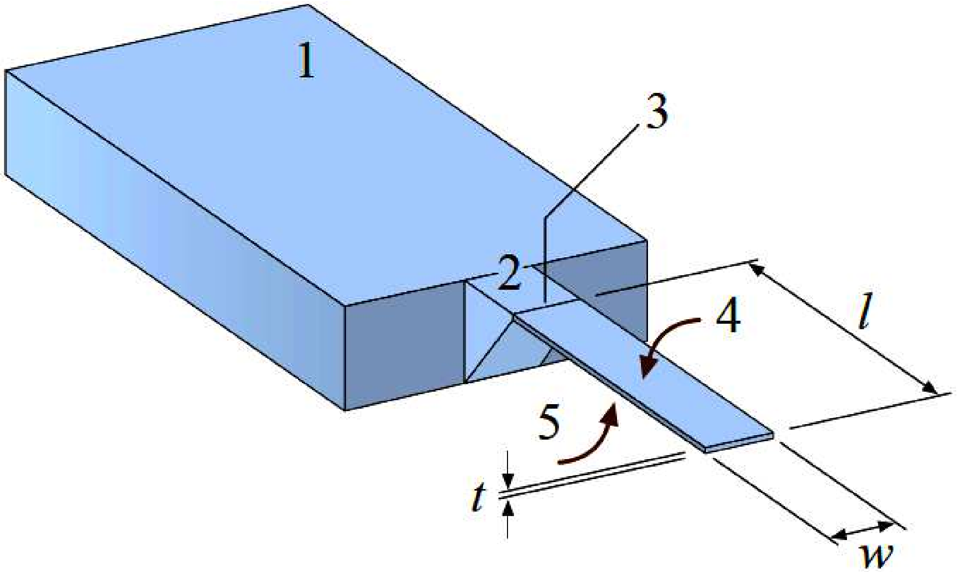


SARS-CoV-2 antibody detection on functionalized gold nanoparticles

DOI: 10.1016/j.bios.2020.112578

• *Nanomechanical cantilever array sensors*

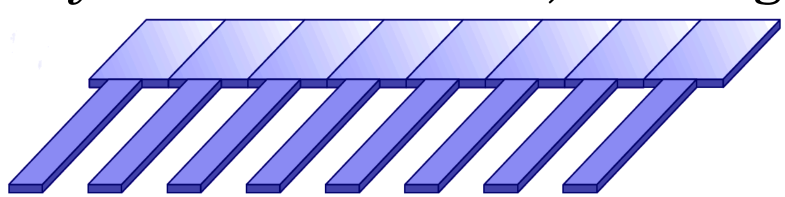
cantilever:



(1) rigid chip body;
(2) solid cantilever-support structure;
(3) hinge of cantilever;
(4) upper surface of the cantilever: usually functionalized with a sensor layer for detection of molecules,
(5) lower surface of the cantilever, usually passivated in order not to show affinity to the molecules to be detected.

► Cantilever sensors *concept*:
- Two non-equivalent surfaces: *functionalized* and *passivated*
- The formation of molecular layers on the cantilever surface generates surface stress, eventually resulting in a *bending* of the cantilever,
- Often *thiol-coated* gold is used; a specific functionalization is attached to the thiols.

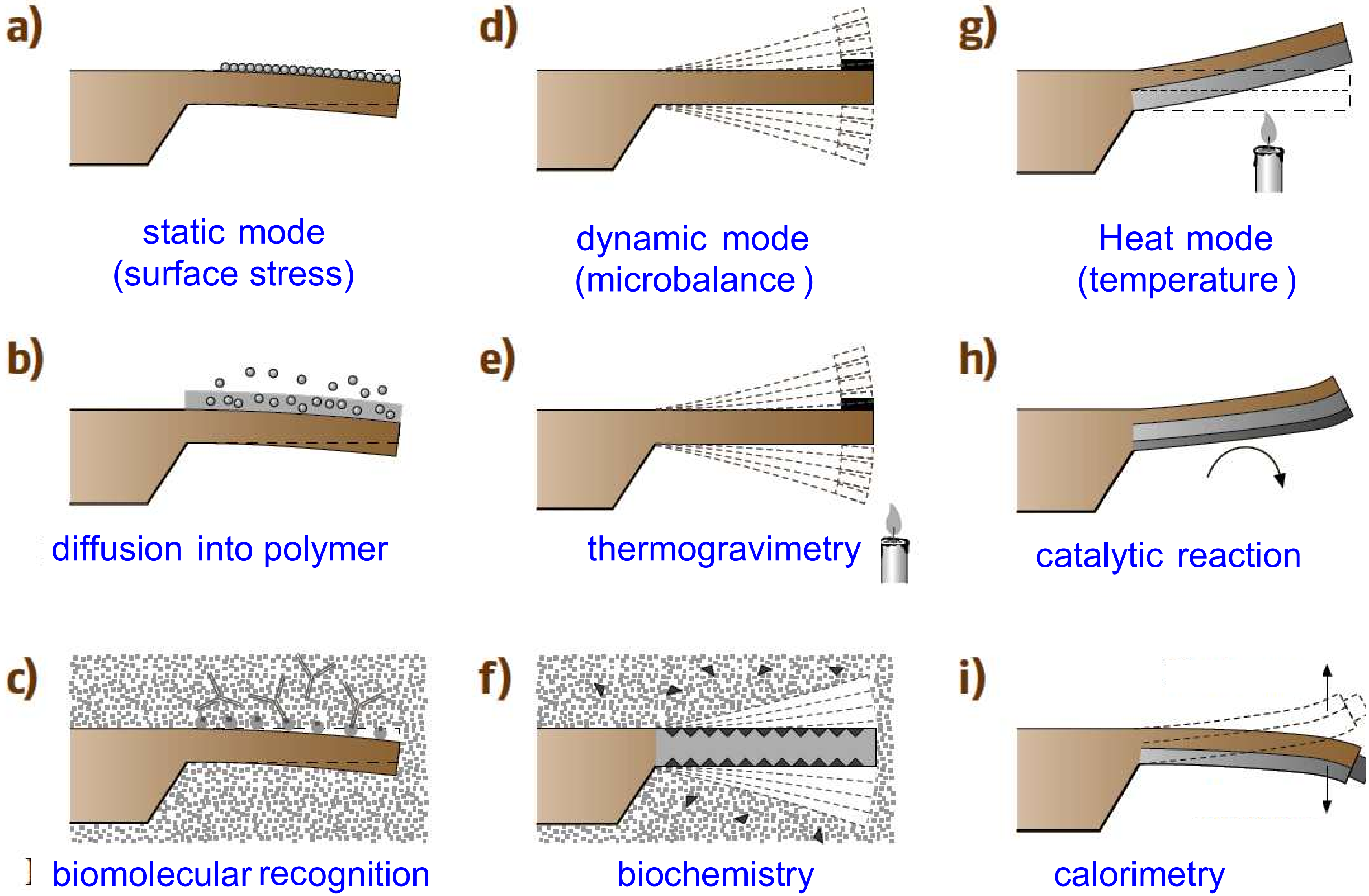
► Usually cantilever *array* sensors are used, not single cantilevers:



SENSORS

- ***Nanomechanical cantilever array sensors*** *(continued)*

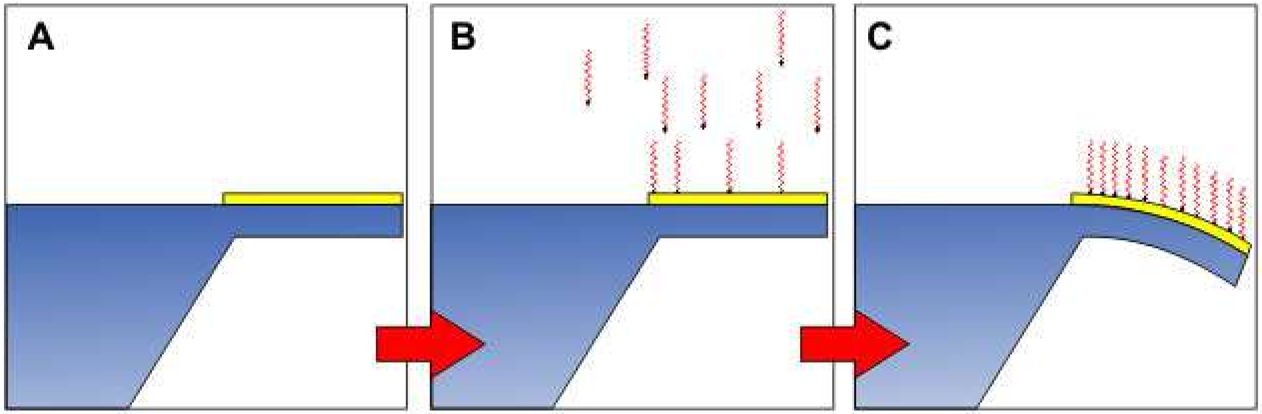
► Modes of operation:



comments see next page

• ***Cantilever operation modes*** *(comments):*

(a) *Static* bending of a cantilever on adsorption of a molecular layer.



(b) *Diffusion* of molecules into a polymer layer leads to *swelling* (*cat*. inflament) of the polymer and eventually to cantilever bending.

(c) Highly specific molecular recognition of biomolecules by receptors changes the surface stress on the upper surface of the cantilever and results in cantilever bending.

(d) *Oscillation* of the cantilever at its *resonance frequency* (dynamic mode) provides information on mass changes taking place on the cantilever surface (application as a microbalance).

(e) Changing the mass with changing the temperature of the sample attached to the apex of the cantilever provides information on a decomposition or oxidation process. Typical sample mass: $\sim 10^{-7}$ g, typical mass changes $\sim 10^{-12}$ g.

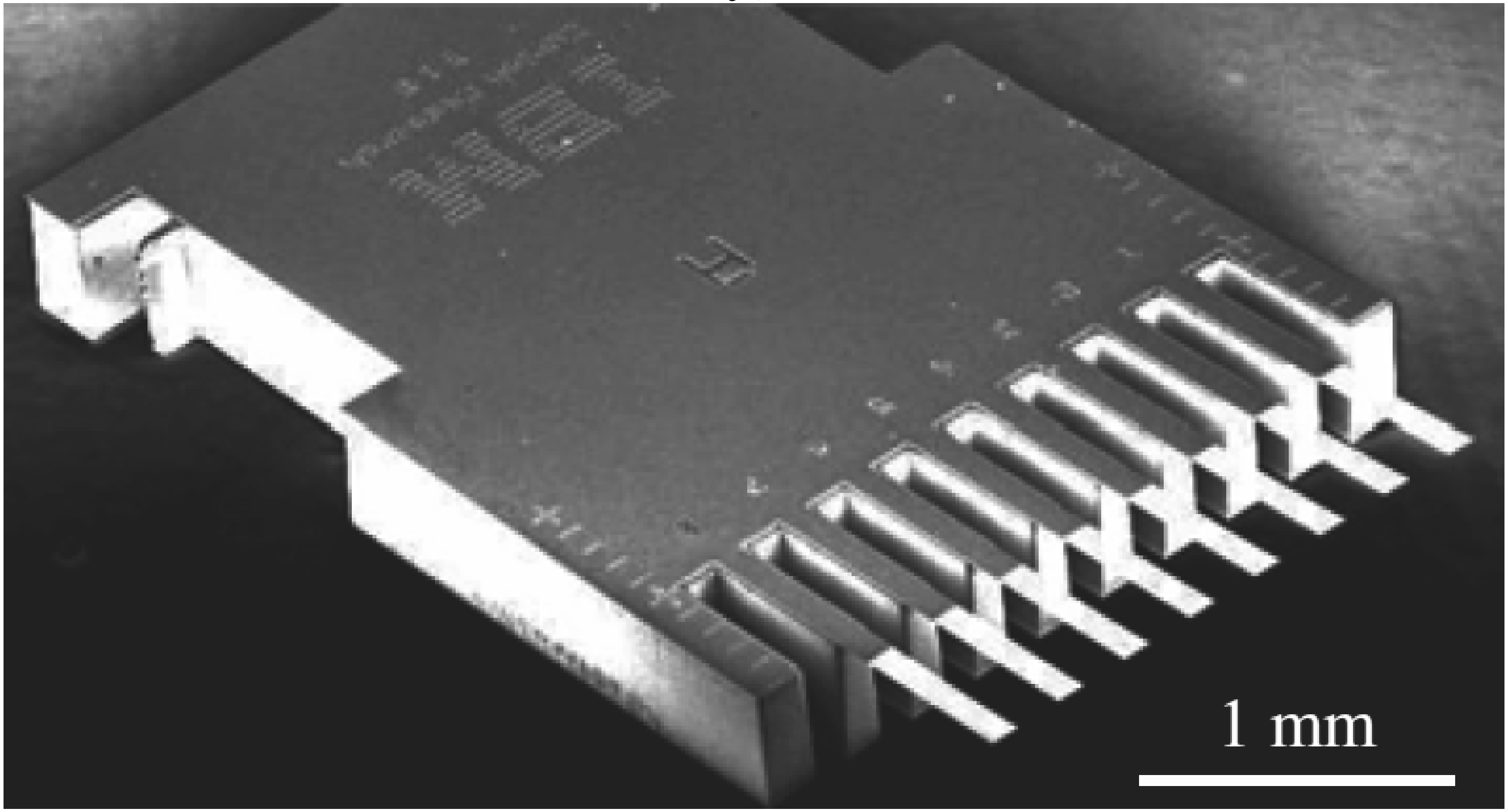
(f) Dynamic-mode measurements in liquids yield details on mass changes during biochemical processes.

(g) In the heat mode, a bimetallic cantilever is employed. Here bending is due to the difference in the thermal expansion coefficients of the two materials.

(h) A bimetallic cantilever with a catalytically active surface bends due to heat production during a catalytic reaction.

(i) A tiny sample attached to the apex of the cantilever is investigated, taking advantage of the bimetallic effect. Tracking the deflection as a function of temperature allows the observation of phase transitions in the sample in a calorimeter mode.

- ***Cantilever deflection detectors***:
  - ► An optical or electrical system:
    - – lasers with collimation lenses and a position-sensitive detector;
    - – piezoresistors.
- ***Nanomechanical cantilever array sensors***
  - – each cantiliver coated differently;



Scanning electron micrograph of a cantilever sensor array

- **Microelectronics**

Transistor size: ~5 cm (1948) → 10 μm (1971) → 600 nm (1990) → 45 nm (2007) → 14 nm (2014) → 10 nm (2016) → 7 nm (2018) → ...

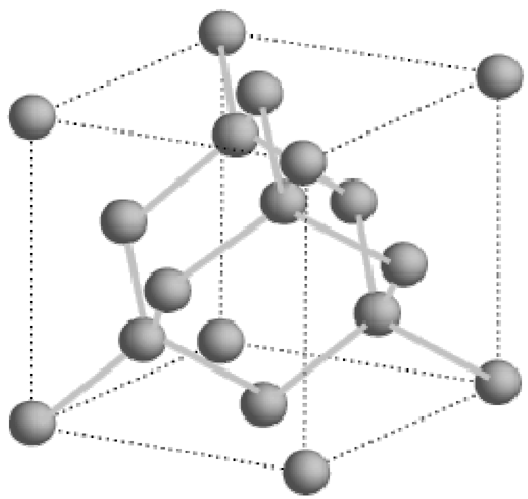
Intel I5 processor: ~ 1.3 billion transistors on a 150–200 mm^2 die.

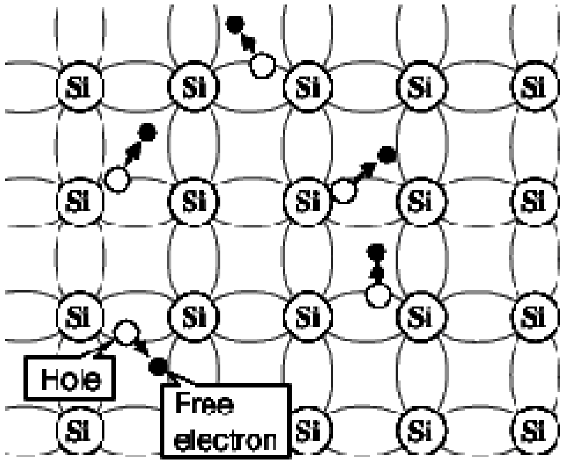
► Modern microelectronics is based on ***integrated circuits***. An *integrated circuit* is a device built on a single semiconductor chip containing many *transistors* and other electronic elements (diodes, capacitors, resistors...).

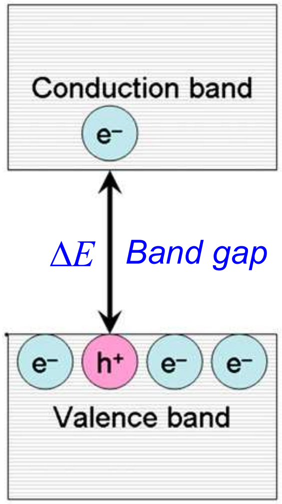
► *Moore's law* (1965, perhaps no longer valid as of 2024): the number of transistors in an integrated circuit *doubles* about every *two* years.

► A *transistor* is a key element of modern microelectronics. To understand what a transistor is and how it works, let's learn the basics of the semiconductor theory.

- **Semiconductors**
  - ▶ Typical semiconductors – silicon and germanium – consist of tetra-coordinate atoms in a diamond-like crystalline lattice:







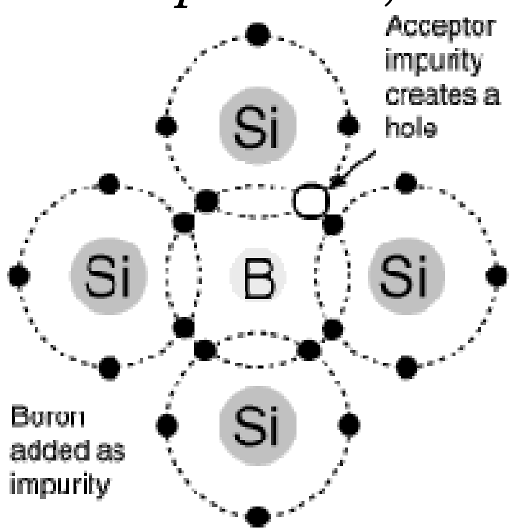
▶ Electric conductivity of pure Si and Ge is low, because the covalent bonds are localized and there are almost no free electrons.

▶ An electron sometimes can be knocked loose from its position, leaving behind an electron deficiency referred to as a "*hole*"; at room temperature it happens only to ~10^{-19} Si atoms or ~10^{-12} Ge atoms.

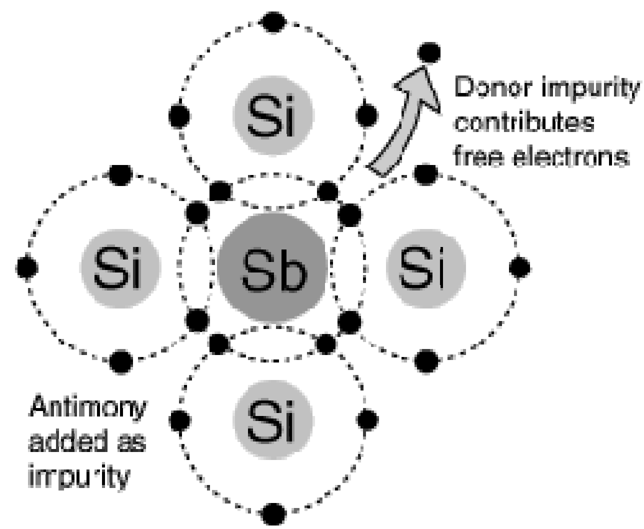
- This generates *free electrons* and *electron holes*. Their number is small but increases with increasing temperature;
- Both free electrons and holes can be charge carriers;
- Free electrons and holes can recombine (*dynamic equilibrium*).

▶ Band gaps (in eV): Si: 1.1; Ge: 0.7; GaAs: 1.4; InP: 1.3; GaN: 3.4; ZnS: 3.5.

- **Doped semiconductors**
  - ▶ If a small admixture of a *pentavalent* element (Sb, As, P) is added to Si or Ge, the crystal structure remains unaltered, but the (fifth) extra electron will be a free electron ⇒ free electron concentration increases ⇒ conductivity increases ⇒ ***n-type*** semiconductor (electrons are in excess over holes).
  - ▶ Similarly, admixture of a *trivalent* element (B, Al, Ga, In) creates a deficit of electrons ⇒ the hole concentration increases ⇒ conductivity increases ⇒ ***p-type*** semiconductor (holes are in excess over electrons).
    - – ***p*** stands for *p*ositive, ***n*** for *n*egative.



p-type



n-type

- – Typical doping: 0.0001–0.1%

- ***p–n* junction: a diode**

▶ Let an ***n***- and a ***p***-type semiconductors be in close contact:

– Electron diffusion $n \to p$;

– Hole diffusion $p \to n$;

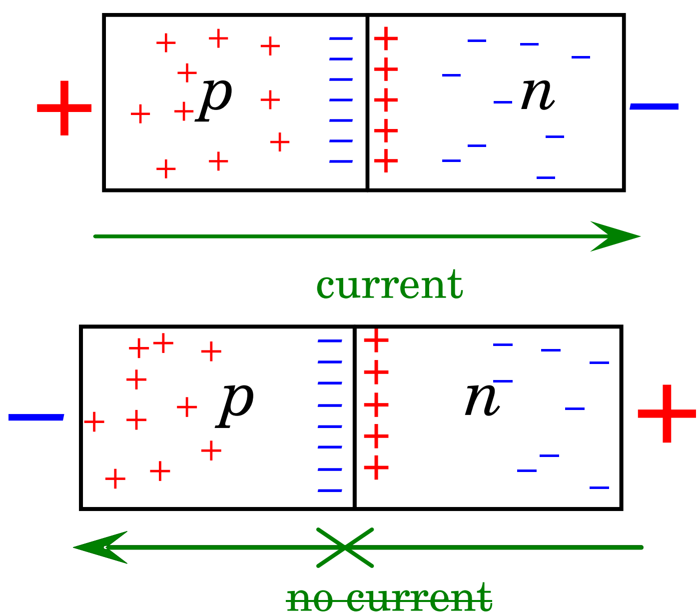
$\Rightarrow$ electron & hole annihilation $\Rightarrow$ charged double layers in the border region;

– Charges prevent more diffusion

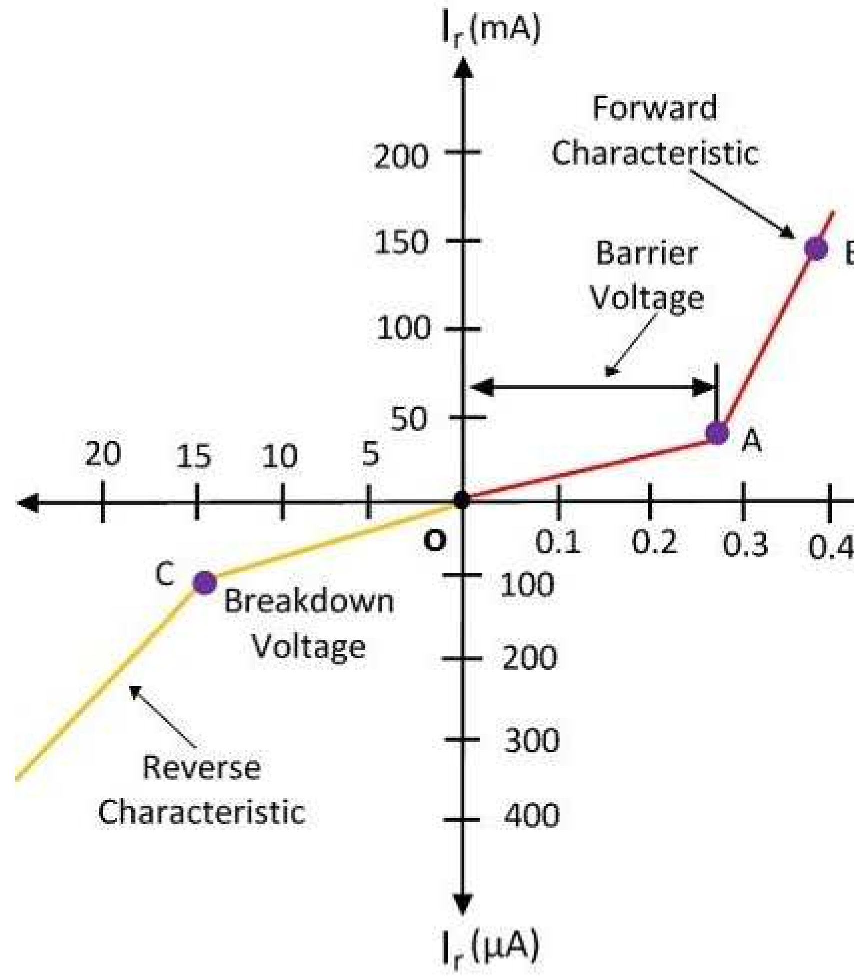
$\Rightarrow$ equilibrium, no current.

– electron and hole *depletion* near the border area

▶ Let us apply external voltage:

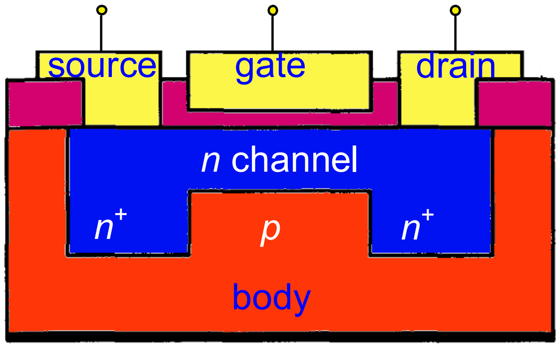


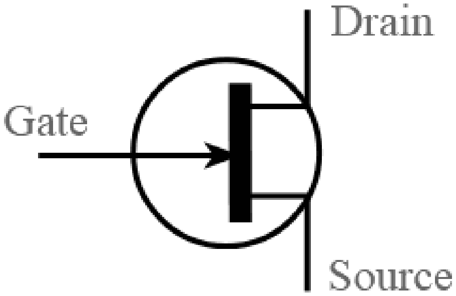
because charge transfer is blocked by the junction



volt-ampere characteristics

- **Field-effect transistor (FET):**

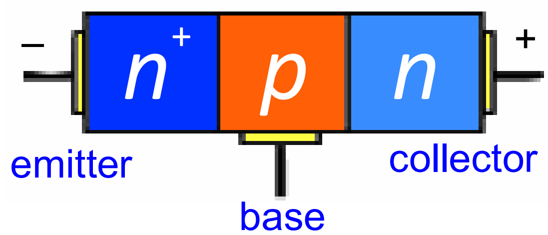


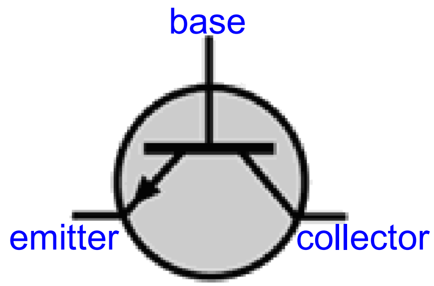


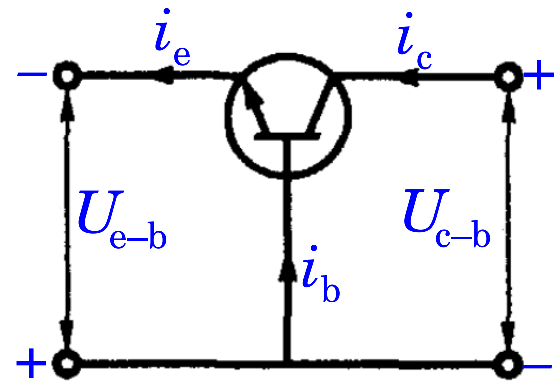
▶ The thin insulator layer (■) can be SiO_2 or Si_3N_4, or a metal oxide.
Gate potential (voltage) changes the electron concentration in the channel
⇒ the source-drain current is managed by the gate potential.

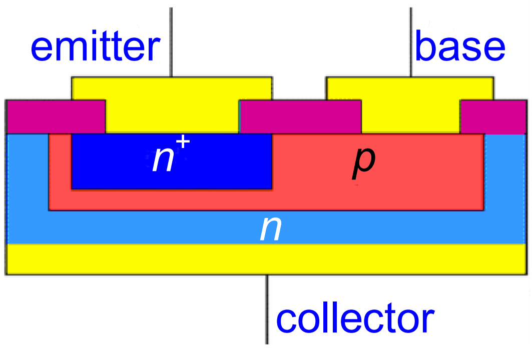
▶ In computer memory elements, one or several transistors are needed to store 1 bit of information.

- **Bipolar transistor:**









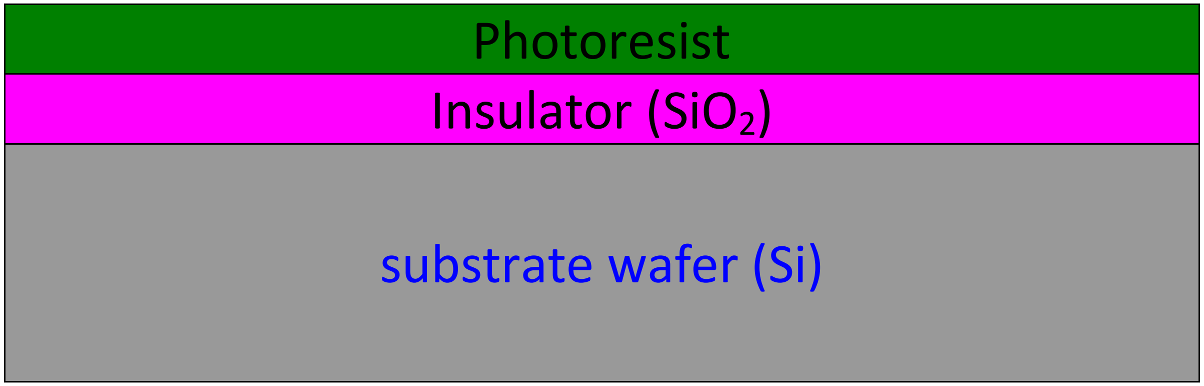
← a real NPN bipolar transistor:
- the *base* is *narrow* and has a low hole concentration;
- the *emitter* has a *higher* electron concentration than the collector;

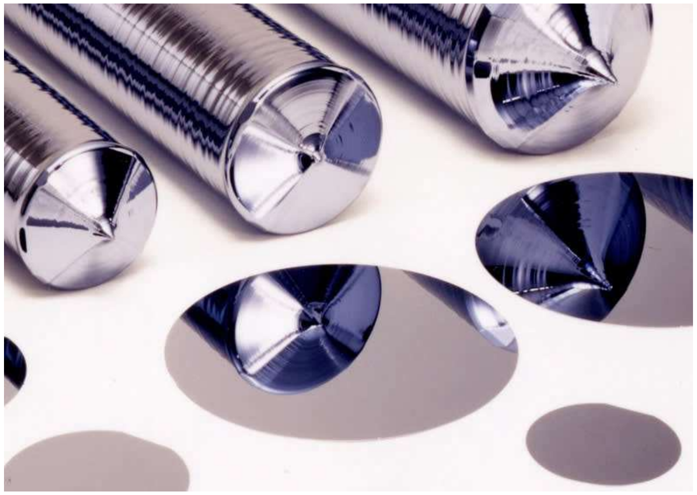
▶ If an emitter–collector voltage (emmiter: –, collector: +) is on, electrons are injected into the base. The base (previously hole-conducting) now becomes electron-conducting, and electrons can pass from emitter to collector.

▶ The base current i_b affects the hole concentration in the base and thus the conductivity between the collector and the emitter.
- A *small* current i_b can control a much *higher* collector-emitter current $\Rightarrow$ *amplification* (crucial for tape recorders, radios etc.)

▶ Unlike the gate in a FET (page 143), the *base* in not insulated: base→collector works as a diode.

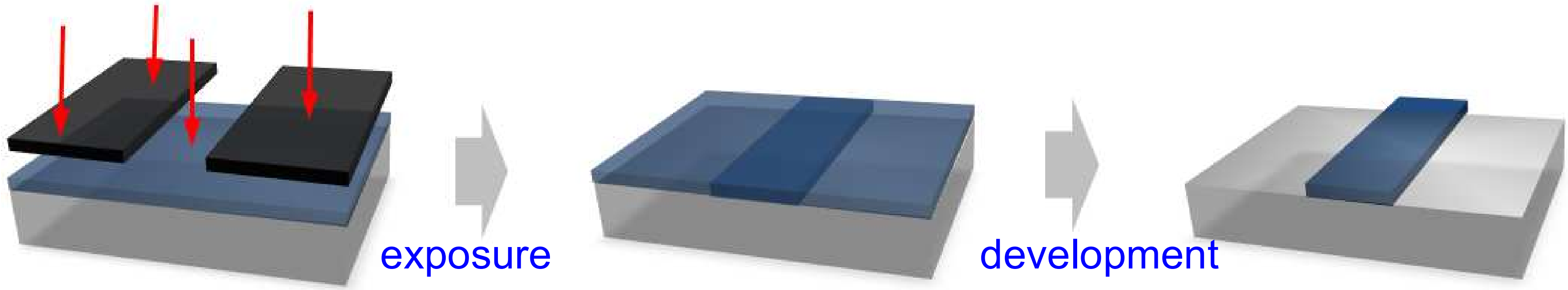
- **Fabrication in microelectronics**
  - ► General philosophy:
    - – Conducting, semiconducting, and insulating materials are deposited layer by layer on a Si *chip* (*die*, *wafer*) – "bottom-up" technologies;
    - – Parts of the layer are selectively removed (*etched*) to create the desired pattern – "top-down" technologies;



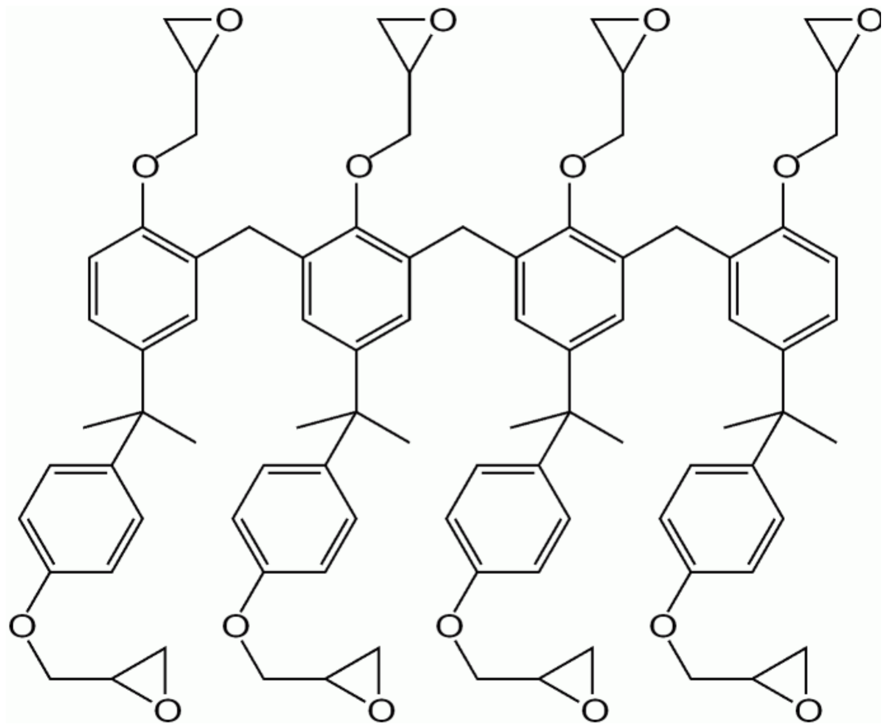


Photoresist is a light-sensitive polymer; a ~1000 nm layer put by spin-coating with subsequent baking (~60 °C). Its role is to protect the selected parts of the surface.

► ***Negative*** photoresist:



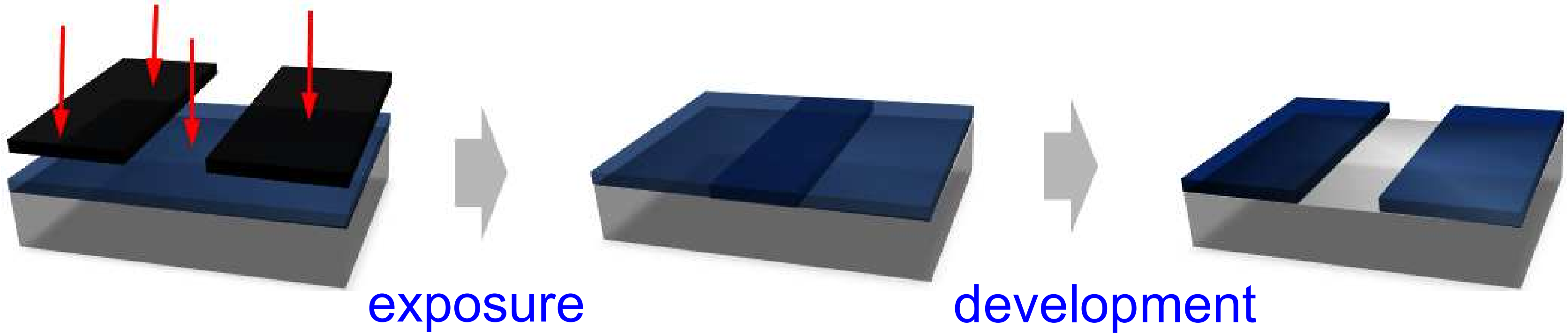
– Example of a *negative* photoresist: the SU-8 polymer:



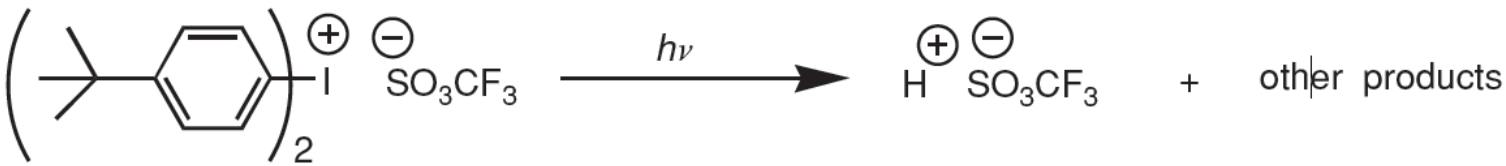
When *irradiated*: becomes hypercrosslinked due to breaking of epoxy-rings and formation of new O–C bonds ⇒ *insoluble*.

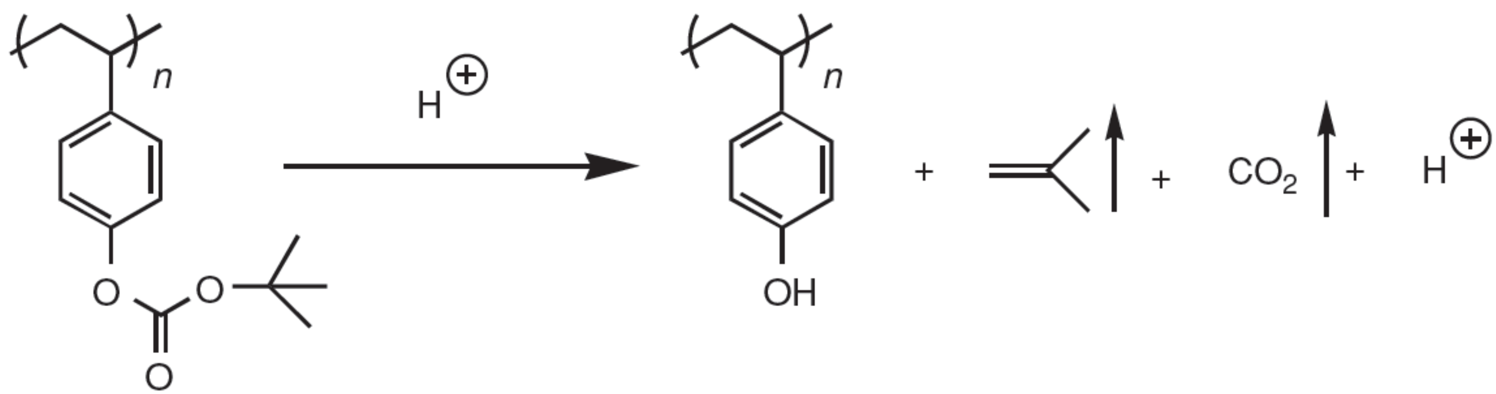
Unexposed parts remain unaltered ⇒ *soluble* in certain organic solvents (which acts as *developer*)

► ***Positive*** photoresist:



– Example of a *positive* photoresist:





A strong acid is formed due to UV irradiation ⇒ the polymer hydrolyses ⇒ *exposed* parts become *soluble* in certain organic solvents (which acts as *developer*).

- **Chemical vapor deposition (CVD)**

▶ A *precursor* is evaporated, transported to a substrate, *and*
 – thermically decomposes on the substrate (*pyrolisis*, 600–1200°C) *or*
 – reacts chemically with the substrate or with another precursor.

▶ *Semiconductor* deposition:

$$SiH_4 \rightarrow Si + 2H_2$$
$$SiCl_4 + 2H_2 \rightarrow Si + 4HCl$$

▶ *Conductor* deposition (no commercially feasible Cu deposition):

$$Ni(CO)_4 \rightarrow Ni + 4CO$$
$$2WF_6 + 3Si \rightarrow 2W + 3SiF_4$$

▶ *Insulator* deposition:

$$Si(OC_2H_5)_4 + 8O_3 \rightarrow SiO_2 + 10H_2O + 8CO_2$$
$$SiCl_2H_2 + 2N_2O \rightarrow SiO_2 + 2N_2 + 2HCl$$
$$3SiH_4 + 4NH_3 \rightarrow Si_3N_4 + 12H_2$$

▶ Producing an *insulator* (SiO_2) by *oxidation* of silicon:

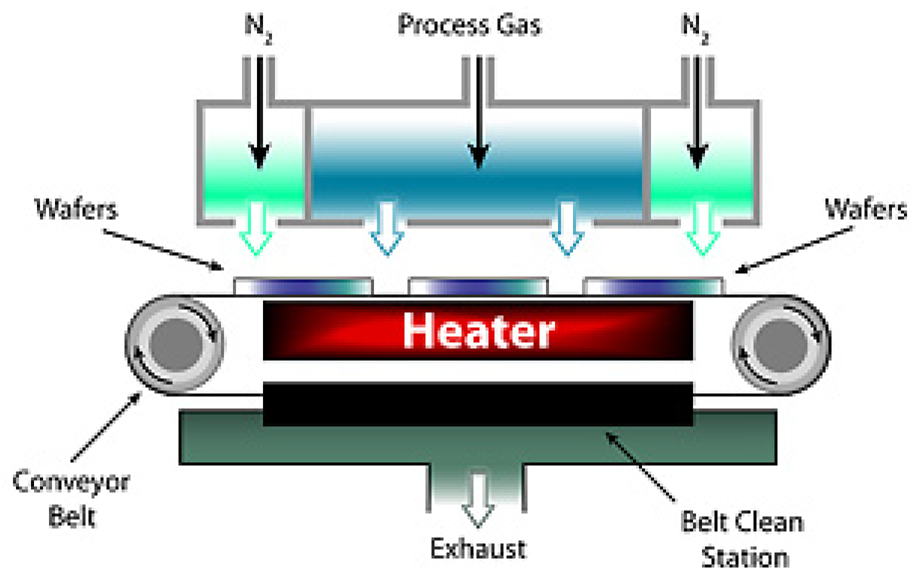
$$Si + O_2 \rightarrow SiO_2$$ (“dry oxidation”)

$$Si + 2H_2O \rightarrow SiO_2 + 2H_2$$ (“wet oxidation”)

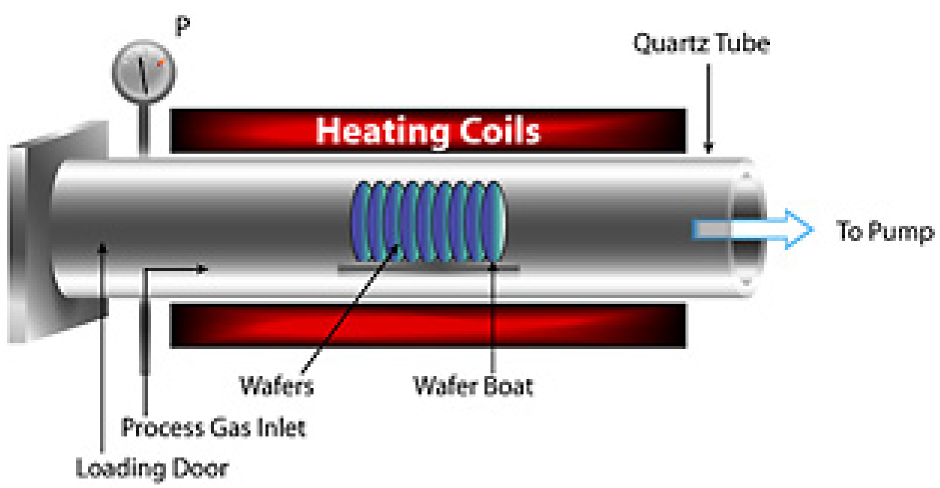
– Insulators are needed, e.g., for producing capacitors, field-effect transistors (see page 143) etc.

- ▶ Atmospheric-pressure CVD (APCVD)
- ▶ Low-pressure CVD (LPCVD)
- ▶ Plasma-enhanced CVD (PECVD)

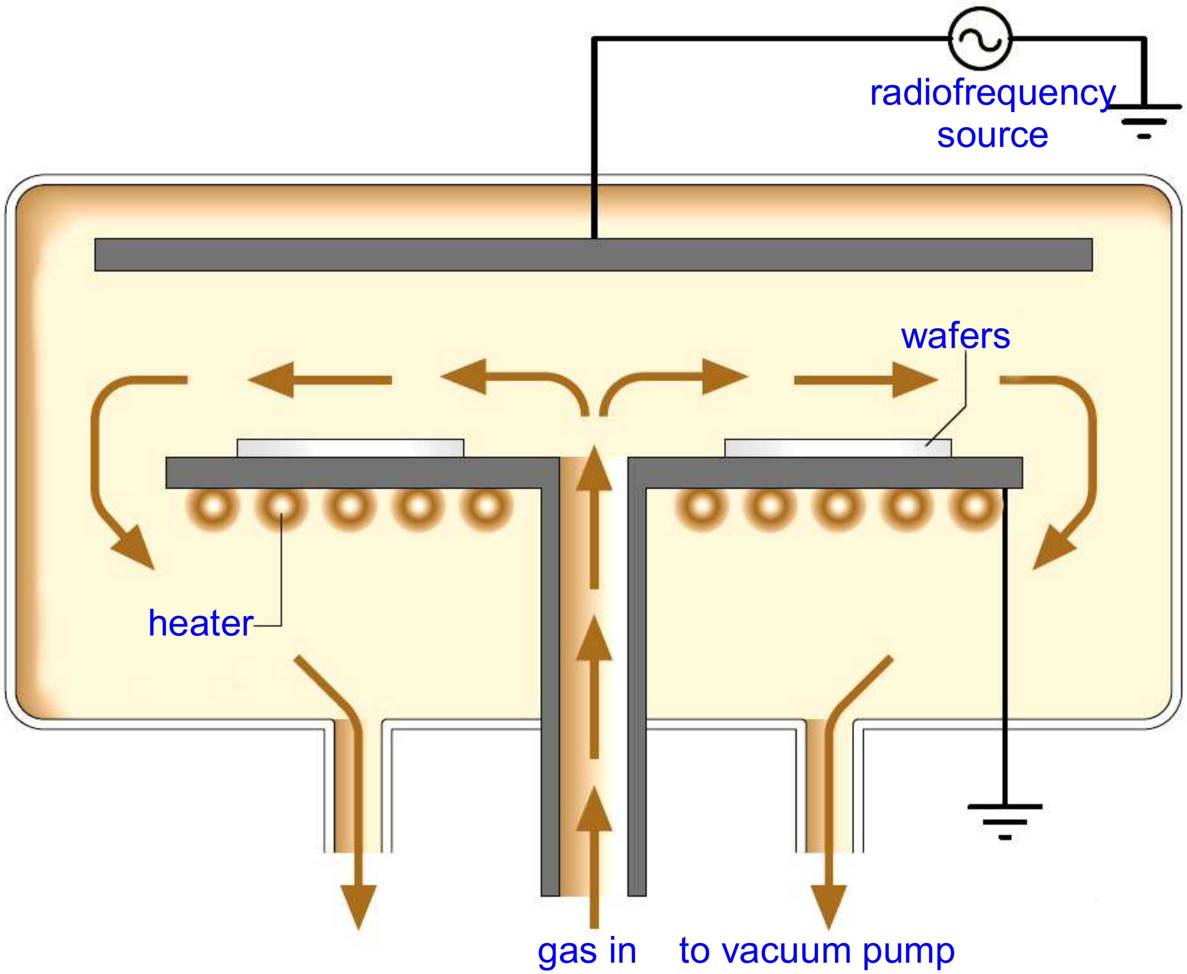
- **Atmospheric-pressure CVD** (APCVD):
  + fast deposition;
  – poorer coverage, contamination



- **Low-pressure CVD** (LPCVD): electrically heated tubes at 10^{-4}–10^{-3} atm.

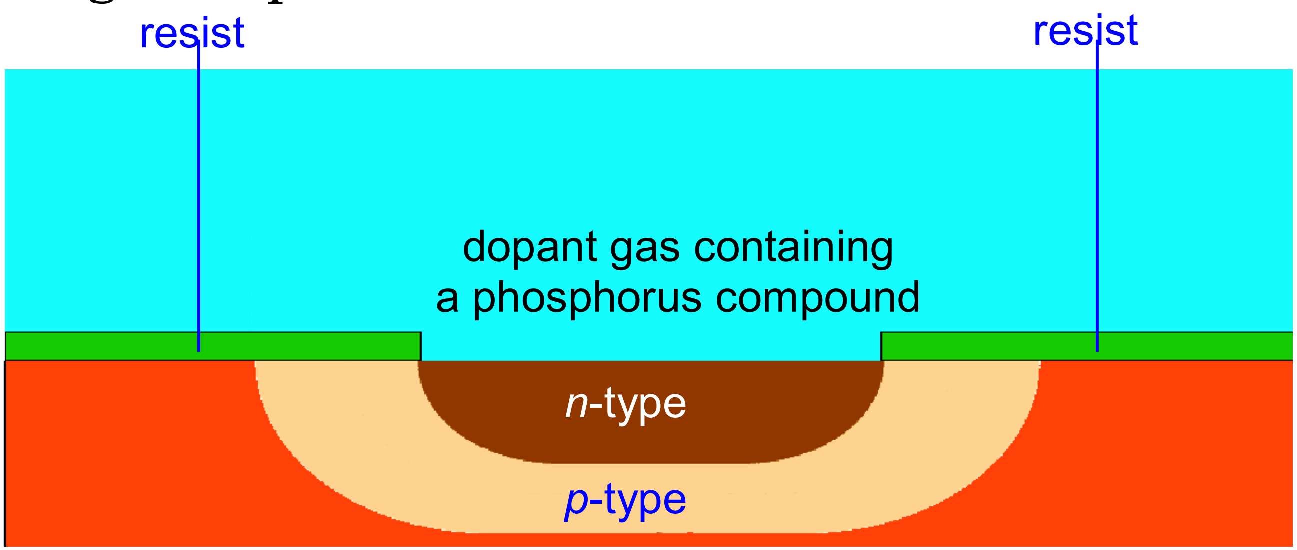


- **Plasma-enhanced CVD** (PECVD): electrically heated tubes at 10^{-4}–10^{-3} atm.



- ► Radiofrequency radiation (typically $\nu \approx 15$ MHz, $\lambda \approx 20$ m) creates highly reactive species in plasma, which allows for lower substrate temperatures (100–400 °C)
- ► Used to deposit thin films on a wafer: SiO_2, Si_3N_4, and *amorphous* Si films.

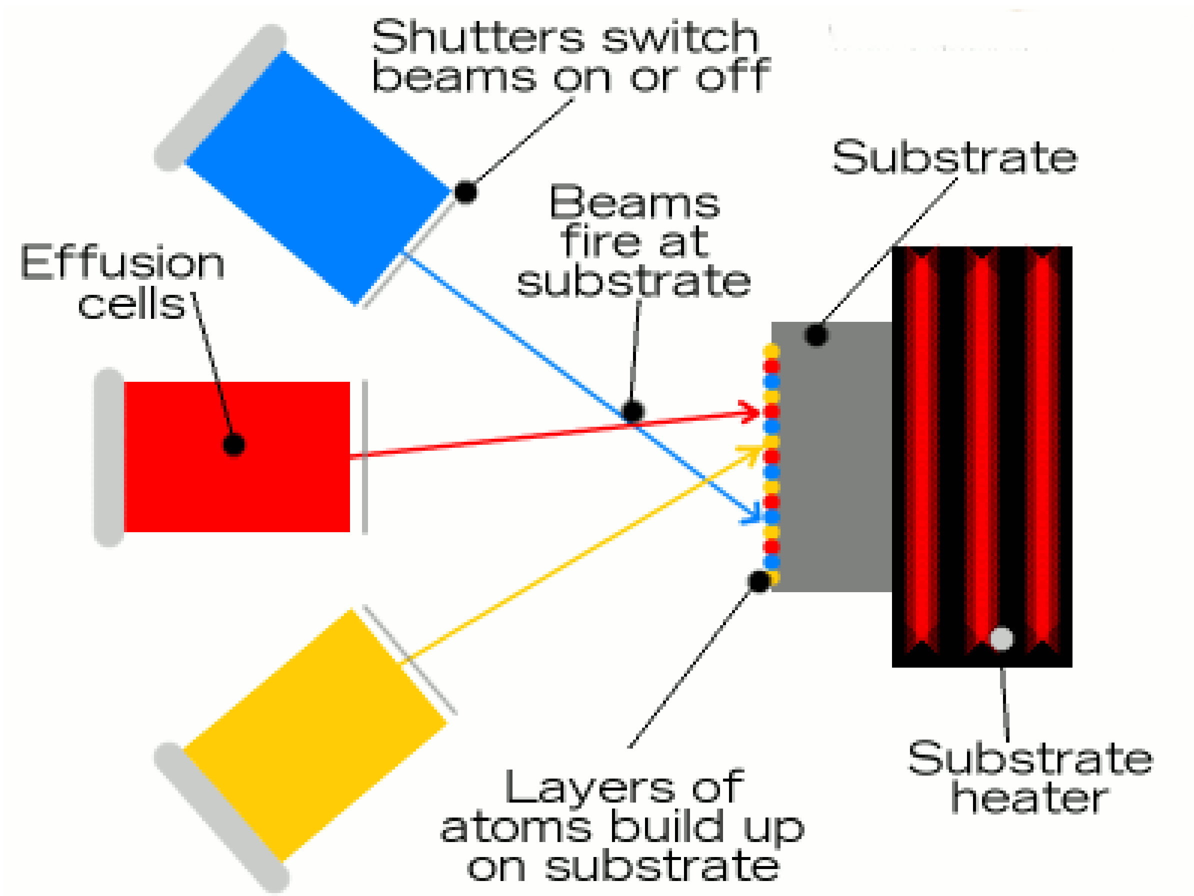
- **Doping** (see page 141)
  - ▶ Diffusion at high temperatures (~800 °C):



Creating an *n*-type region by diffusion of phosphorus into a *p*-type substrate

  - – *Dopant gas* containing a phosphorus compound: e.g. PH_3 for *n*-type doping; (partial pressure 1–20 mmHg).
  - – *Resist* is the masking layer.
- ▶ Other techniques:
  - **–** *Ion implantation:*
    - During ion bombardment, ions are implanted into irradiated substrate
    - Impurities (doping) are ionized and accelerated towards the semiconductor surface by electric field.
  - – *Epitaxial growth* (page 152 – *optional*): a doped semiconductor layer is created by molecular beams.

- **Molecular beam epitaxy (MEB):**
  - ► Molecular beams interact on a heated crystalline substrate under ultra-high vacuum (~10^{-13} atm) to produce a *single-crystal film*.
    - – Sophisticated process control and monitoring systems needed:

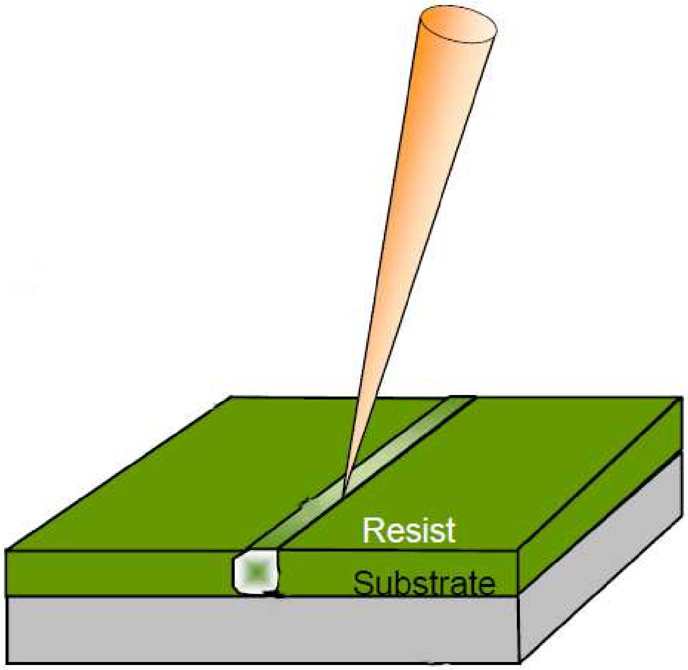


- **Masked *vs*. maskless approach**

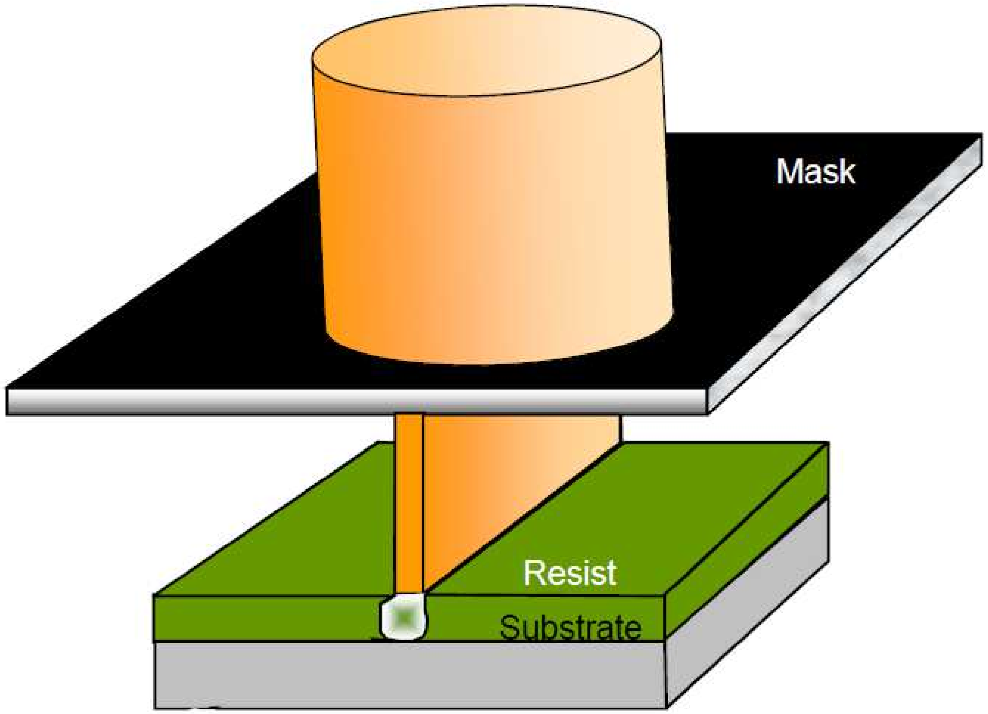
maskless (scanning)
directly writes the patterns serially into the resist

masked
copies the pattern from a mask into the resist

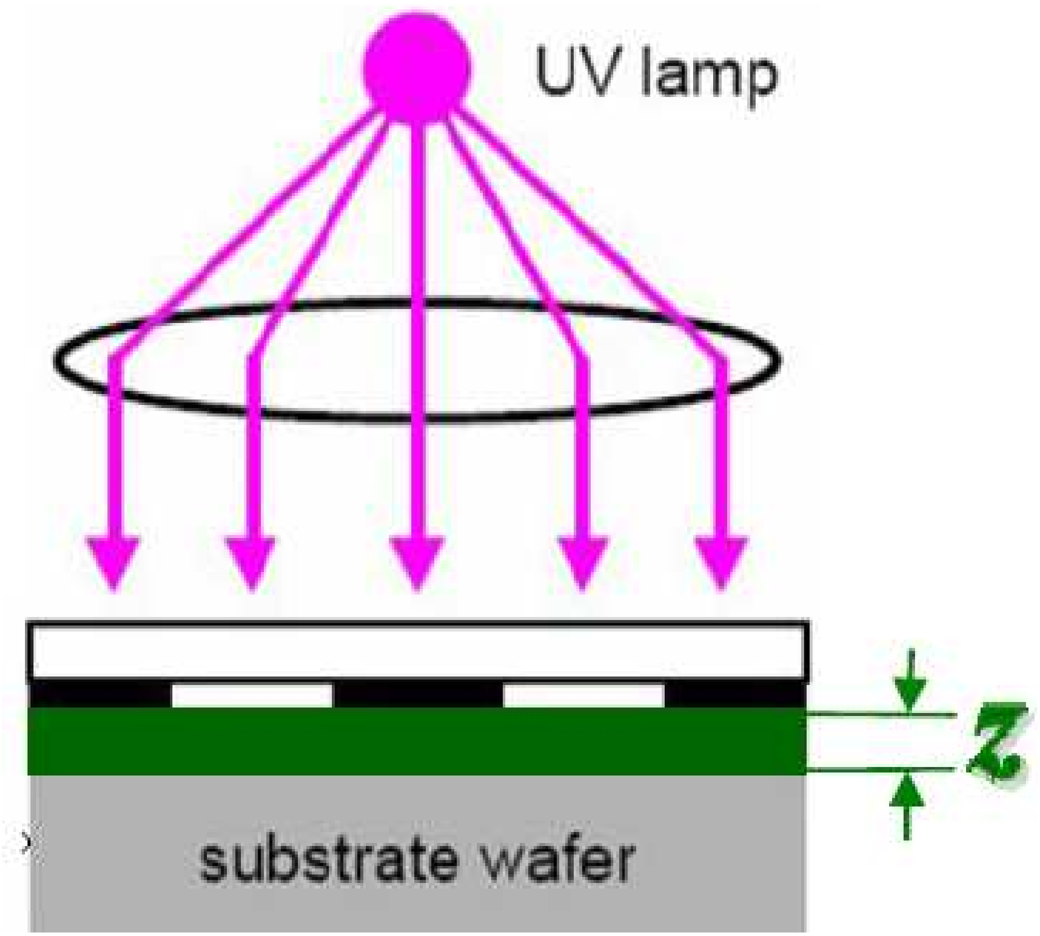
focused or shaped beam



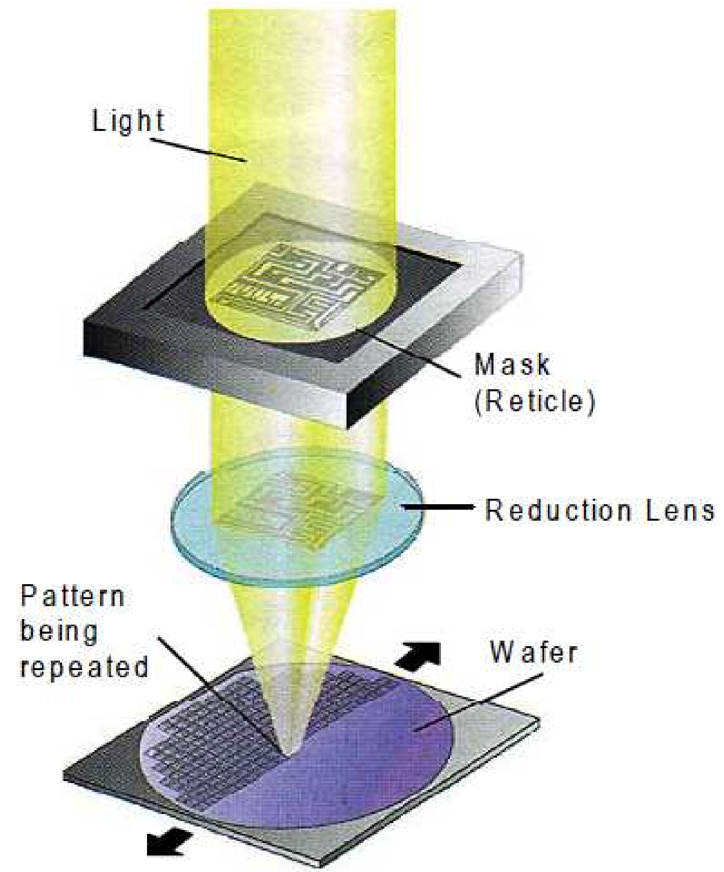
wide beam



- **Photolithography (masked)**



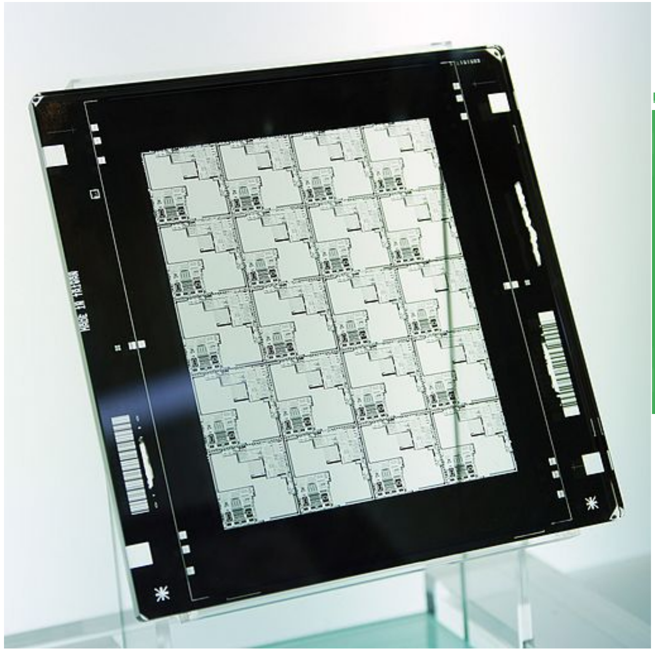
contact or proximity printing

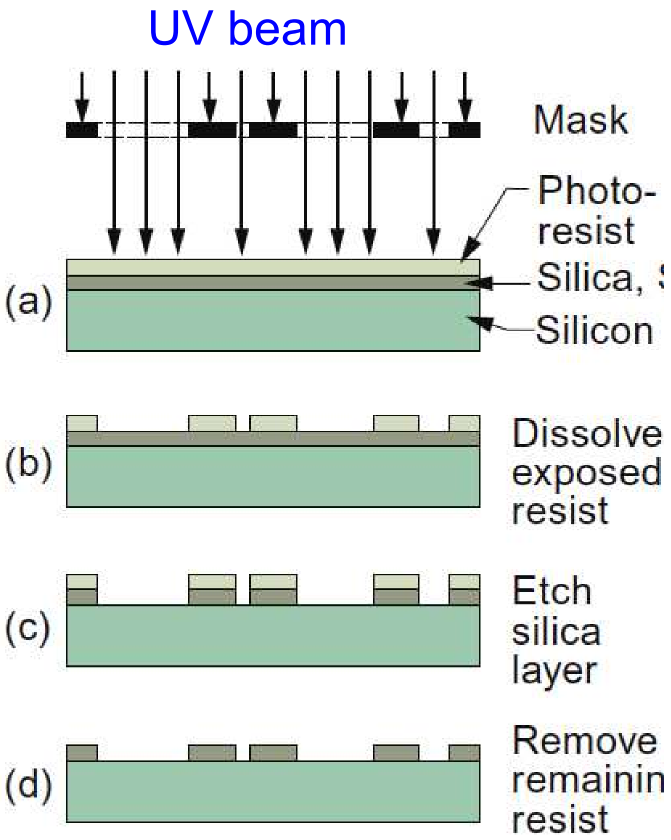


projection printing

- **Photolithography (masked)**
  - ▶ **Photolithography** is removing *selected* portions of thin films

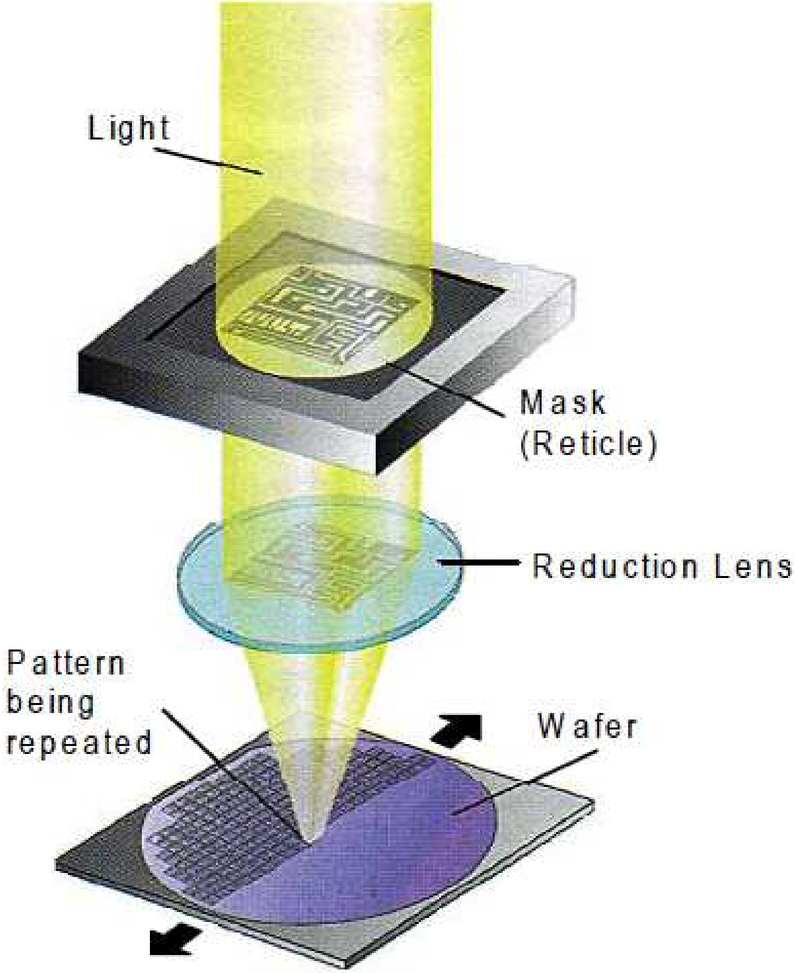
Substrate is typically a Si wafer.
Silica (SiO_2) is formed by oxidation (page 148).
Photomask:





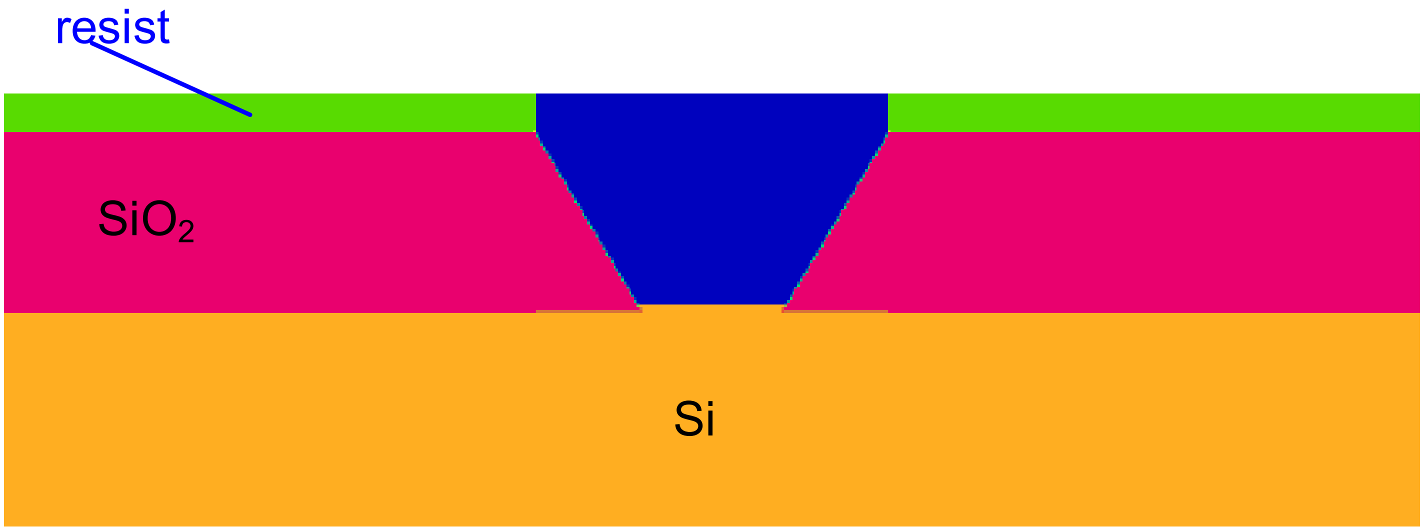
mask with *additional assist features*

- **Photolithography**: Exposure system – irradiates photoresist through a mask
  - ►Sophisticated optics is usually employed.
  - ►Up to 30 nm resolution is possible when using *deep ultraviolet* ($\lambda \leq 200$ nm).



▶ ***Etching:***

– *Chemical etching* ("wet etching"): typical etching agents are acids and bases.



• Typical etchants for Si is hydrofluoric acid HF:

$SiO_2 + 6\,HF \rightarrow H_2SiF_6 + 2\,H_2O$,

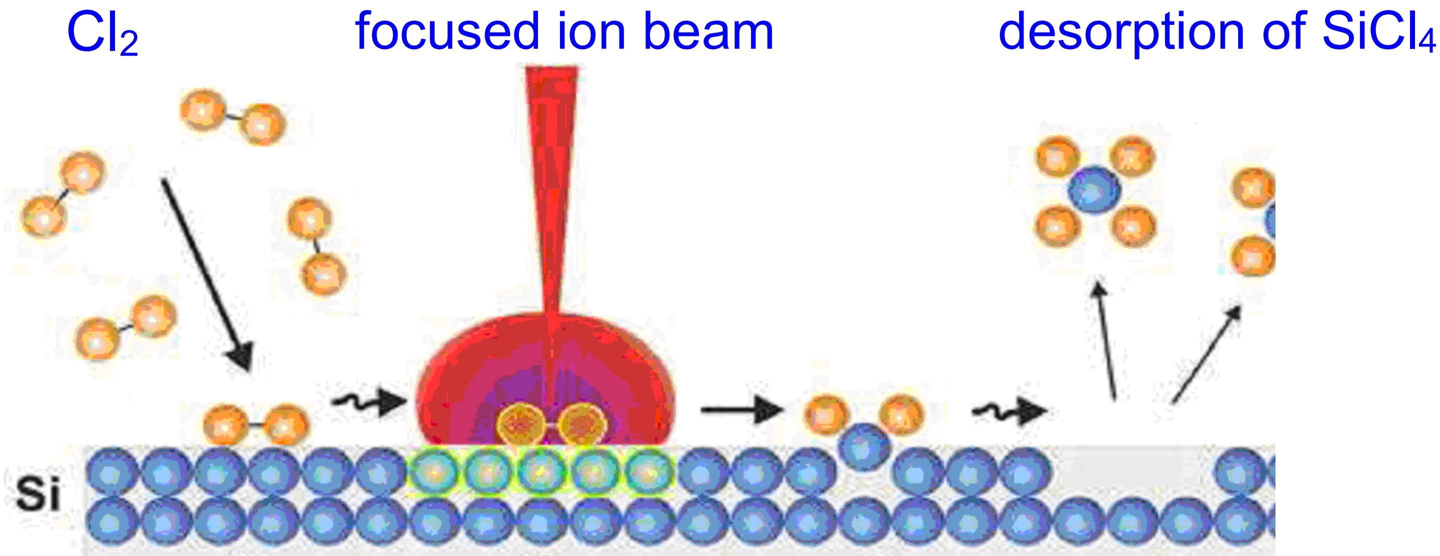
but also KOH, $[NMe_4]OH$.

– "*Dry etching*":

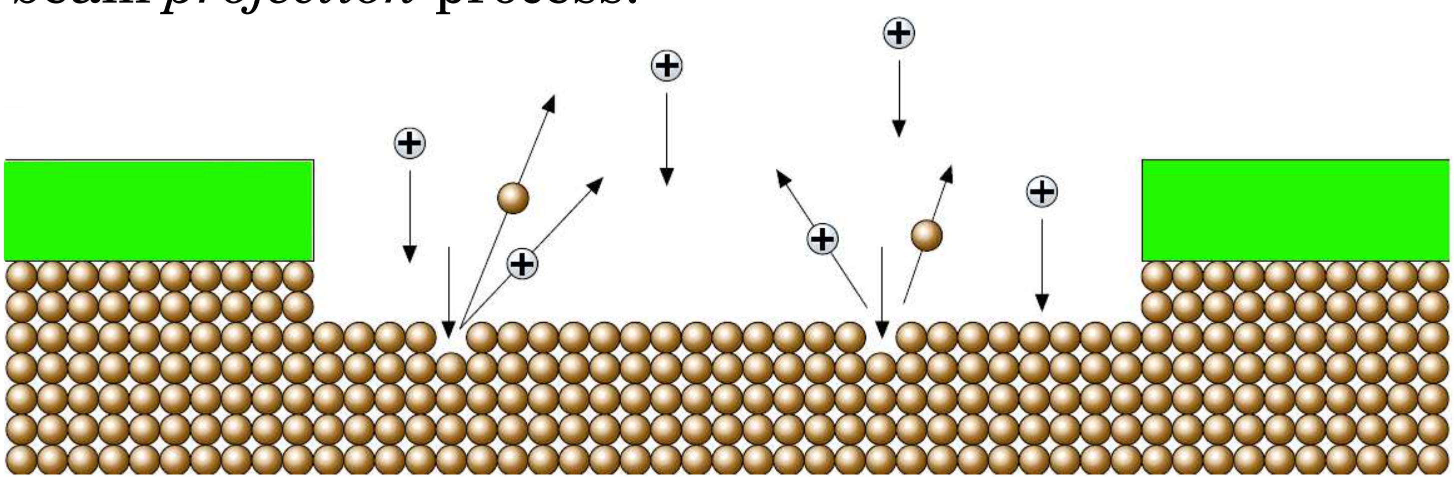
• Etching of Si with XeF_2; etching of SiO_2 with gaseous HF.

• *Ion-beam* etching (see page 158 below)

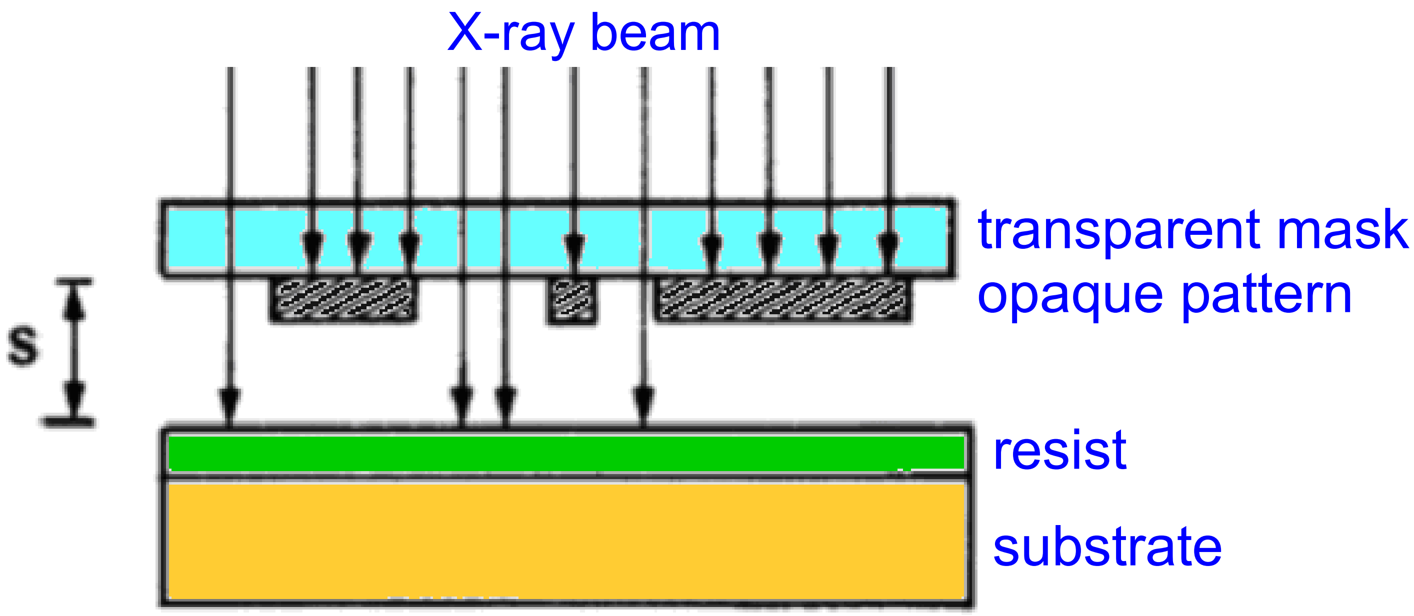
- ***More etching methods:***
  - ▶ *Ion beam etching:*
    - – Ions beams (usually Ar^+, He^+, H^+) knock atoms out of the surface
    - – can be both masked and maskless:
      - *maskless:* Focused Ion Beam (FIB):



      - ion beam *projection* process:



- **Other *masked* lithography techniques**:
  - ► *Projection Electron-Beam Lithography* (PEBL)
    - – uses electron beams instead of light: equipment similar to that of an electron microscope (electron lenses) is needed;
    - – A *resist* is still needed
  - ► *X-ray Lithography*
    - – uses soft X-rays ($\lambda \sim 0.1$–5 nm) instead of light;
    - – Problems with X-rays: almost no refraction or reflection (no lenses are possible, hence proximity printing only, no projection printing.



- Masks have to be prepared using some other nanotechnology, such as CVD or ion implantion.