# Les polymères au service de la pharmacologie


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# Pharmaceutical Treatment

**Common administrative ways:**

- **Oral treatment**

- **Injection (Intravenous, intramuscular, subcutaneous…)**

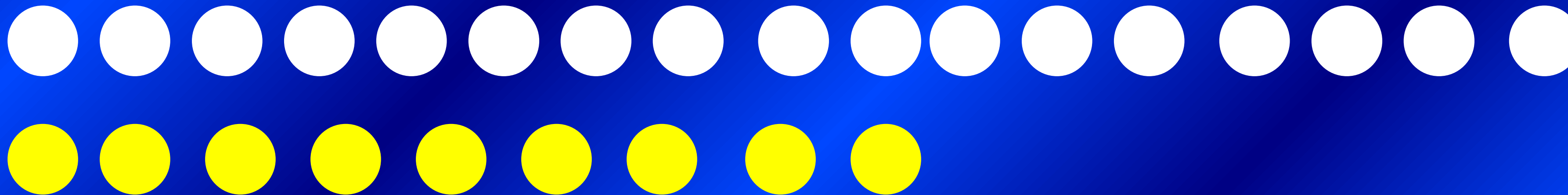
- **Inhalation**

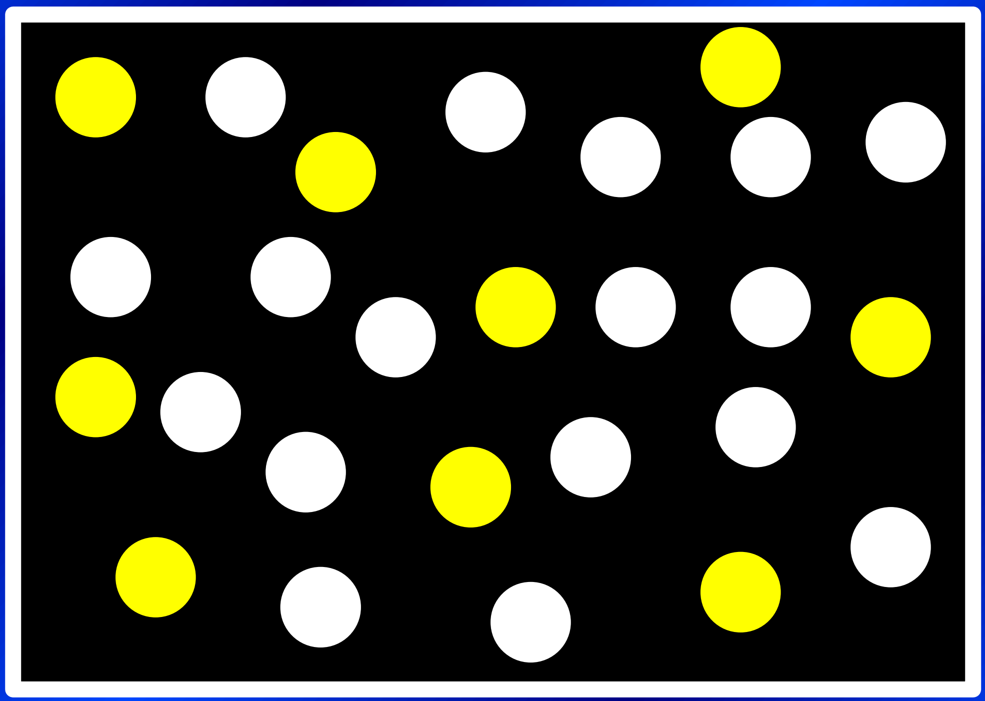
**Issues for intravenous injections:**

- **Solubility of the drug: in the blood for**
- **Degradation of the drug in the body**
- **Distribution of drugs in all the body and not only in the part of the body to be treated: higher amount of drug needed, risk of undesired secondary effects, low efficiency**
- **Rapid decrease of the amount of the drug at the part of the body to be treated ; several injections required**

# Solubility

**Let us consider 17 french people and 9 walloon people ?**

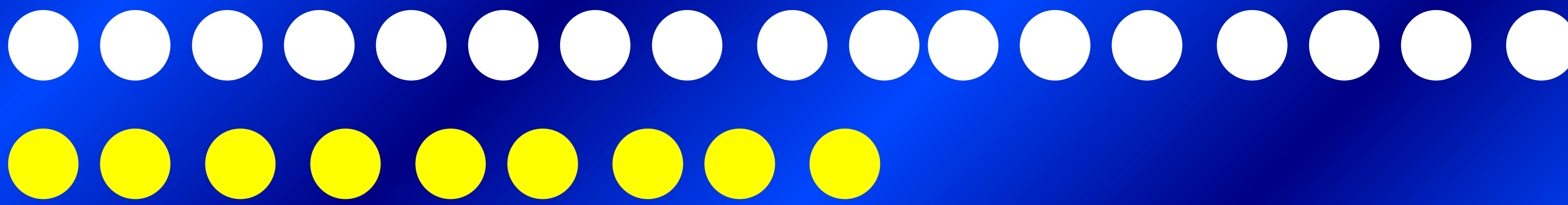


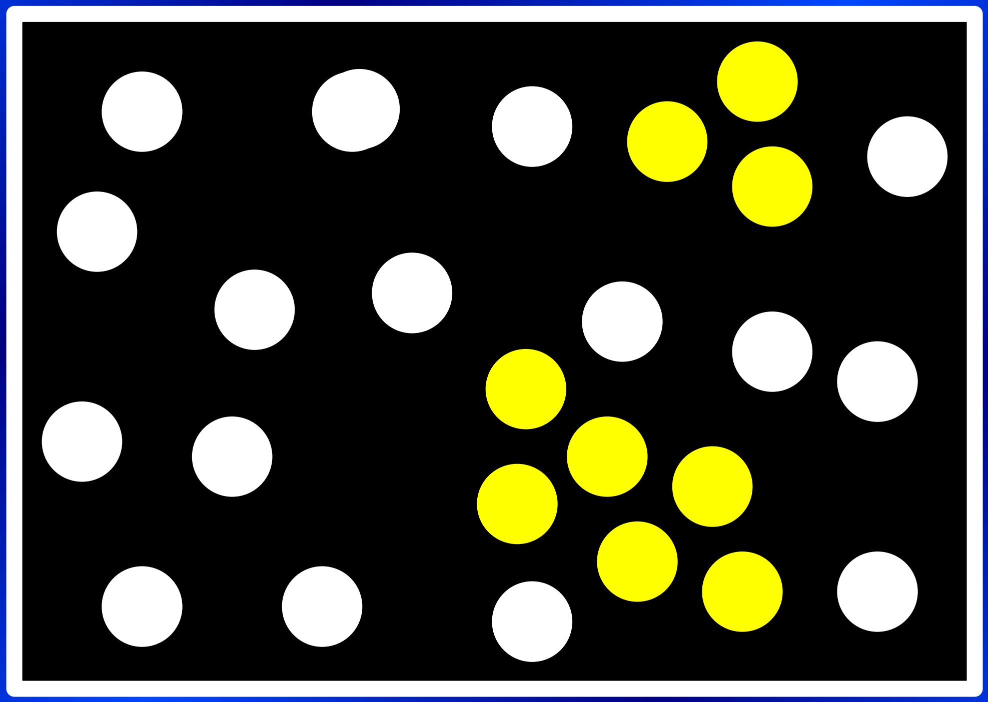


**They speak the same language and they scattered with no particular order**

# Solubility

**Let us consider 17 french people and 9 chinese people ?**





**They don't speak the same language and they don't understand each one another.**

**They will group in clusters.**

# Solubility

**The same behavior is observed in chemistry.**

**One has to consider chemical interaction between molecules rather than interaction through the language.**

**Natural trend : scattering of the drug molecules among the solvent molecules (entropic effect)**

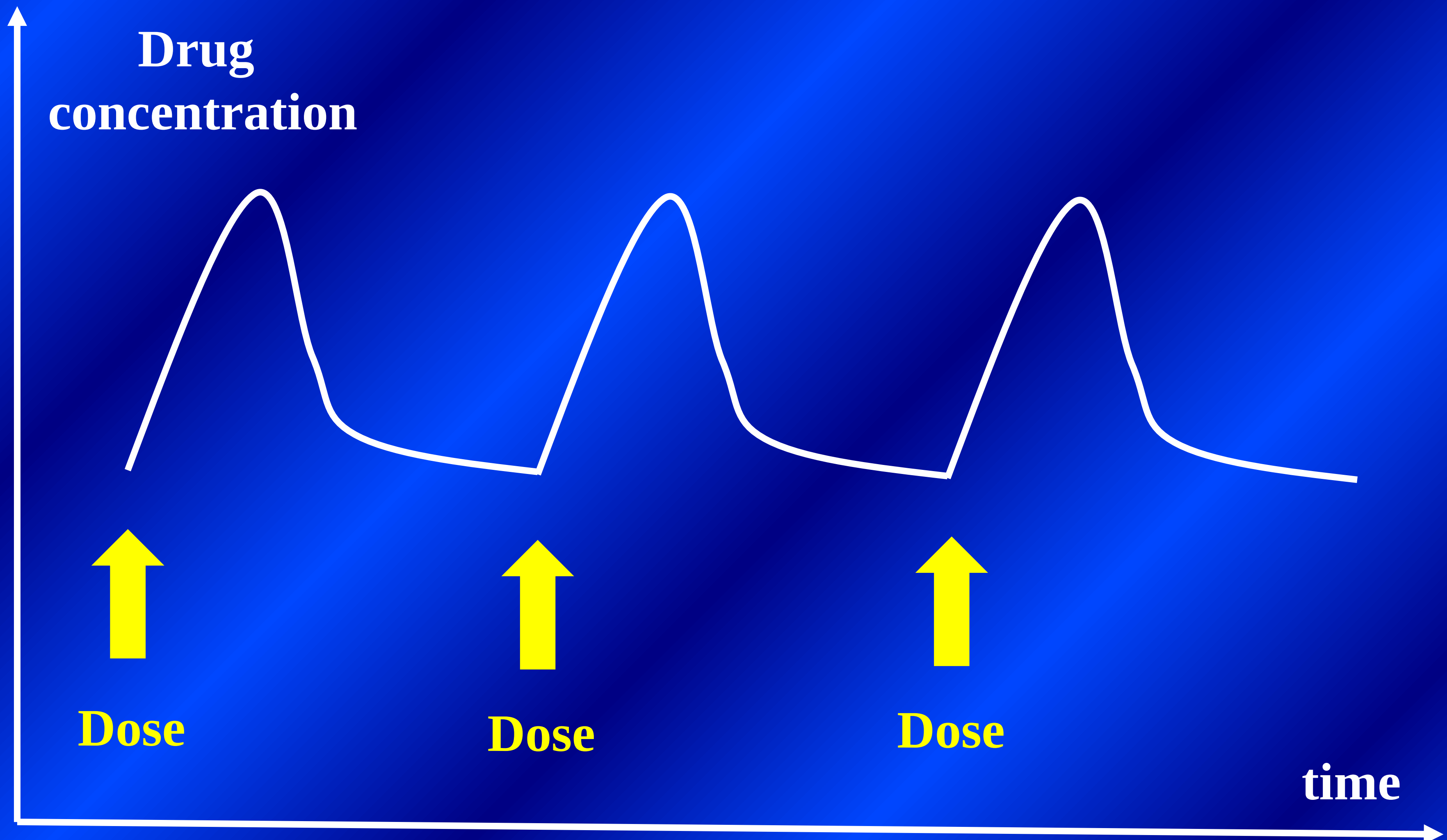
**→ Solubilisation of the drug**

**Nevertheless, some molecules prefers to interact with themselves rather than with the solvent (enthalpic effect)**

**→ Precipitation of the drug**

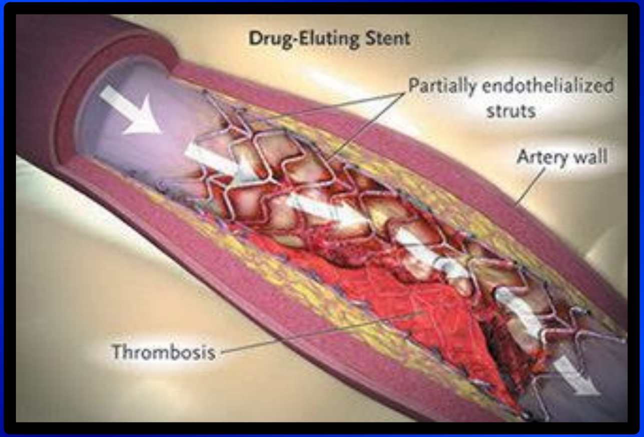
# Pharmaceutical Treatment

**Time distribution of drugs in the part of the body to be treated:**



# Drug Delivery and Polymers

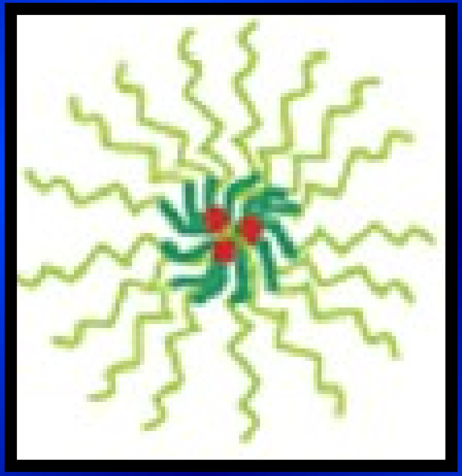
## Drug loaded implants




- Loading of drug in an implant
- Elution of the drug from the implant in the body
- The implant can be made up of a polymer or can be coated on a metal implant.

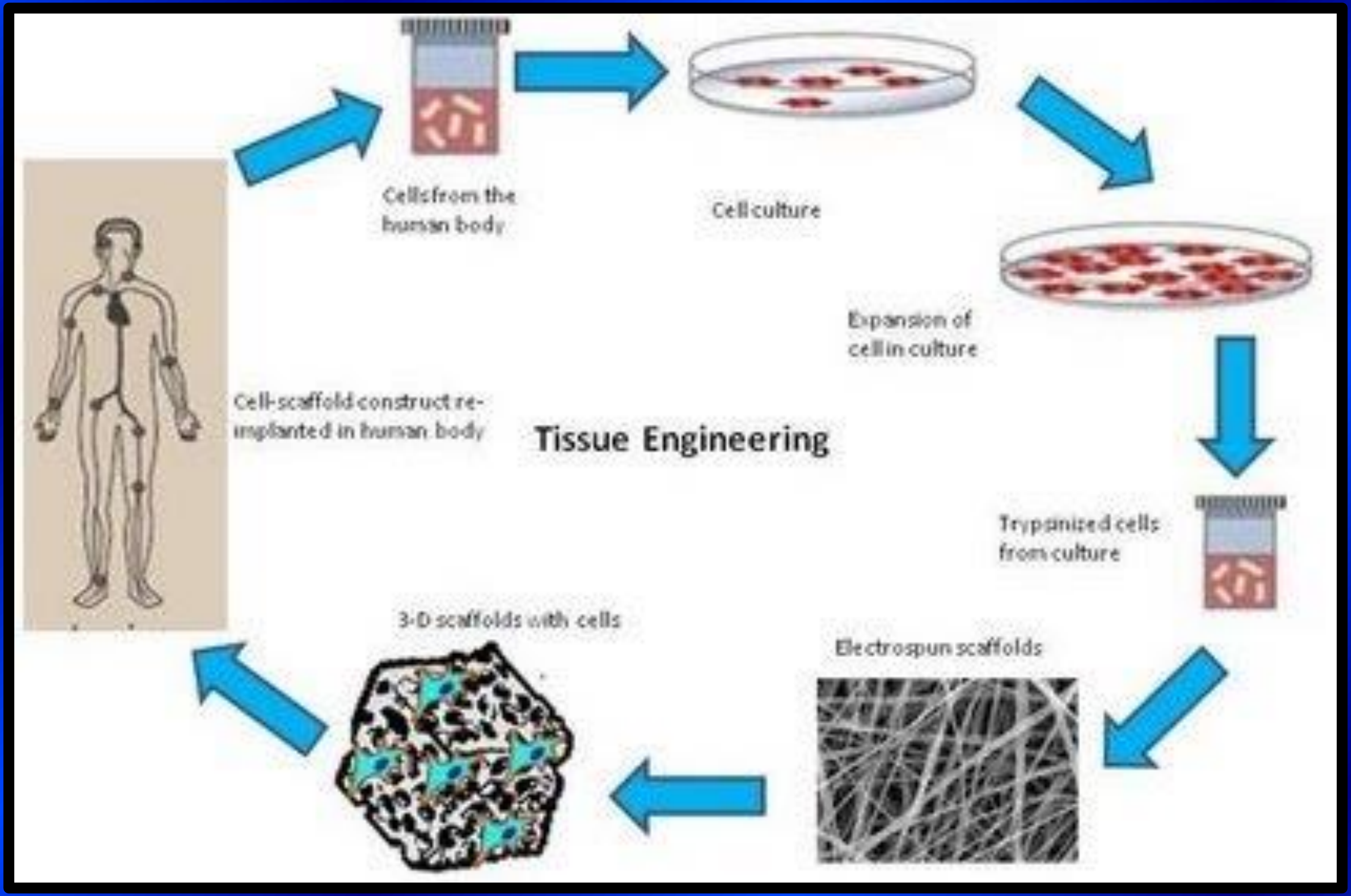
## Carriers based systems

- Polymer = carrier prone to solubilize, transport and protect the drug in a simar way a car transports and protects you.



# Tissue Engineering

**Biodegradable polymers = scaffold for cell regeneration and there is no need of another operation for removing the scaffold.**



# Polymers for Biomedical Applications

**How to chose polymers for biomedical applications?**

**Let us describe**

- **BIOcompatible polymers**
- **BIOdegradable polymers**
- **BIO-sourced polymers**

**BIO has thus different meanings.**

**What is the impact on environment ?**

# Biocompatible Polymers for Biomedical Applications

# Biocompatibility

**Let us define biocompatibility:**

- **the ability of a material to perform with an appropriate host response in a specific application. (Williams 1999, recommended)**

- **the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy. (Williams 2008)**

# Biocompatibility

**For biomedical applications, any polymer must be validated and must be of biomedical-grade (high purity).**

**Validation in USA: FDA : Food and Drug Administration**

**The number of polymers used for biomedical applications is limited.**

**The implementation of a brand new polymer for any biomedical application is very expensive, especially when not yet validated by the FDA.**

**Let us cite: polylactide, polyglycolide, poly(ethylene glycol)**

# (Bio)degradable polymers

# Esterification Reaction

**The esterification reaction is a reaction between a carboxylic acid and an alcohol into an ester:**


**carboxylic acid** **alcohol** **ester** **water**

**The reaction can take place in both directions at will:**

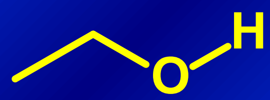
- **The esterification reaction can be used to synthesize chemical products**

- **The hydrolysis reaction of esters can be used to degrade them !!!**

# Esterification Reaction

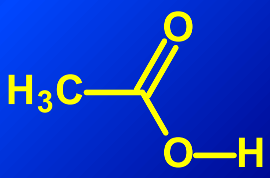
**Examples:**

- **Ethanol:**



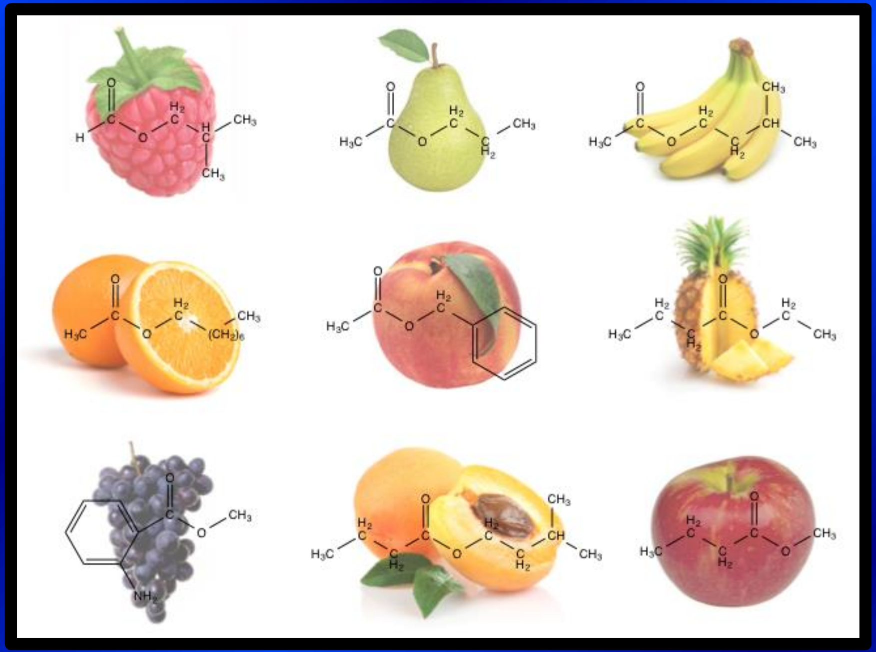


- **Vinegar or acetic acid:**





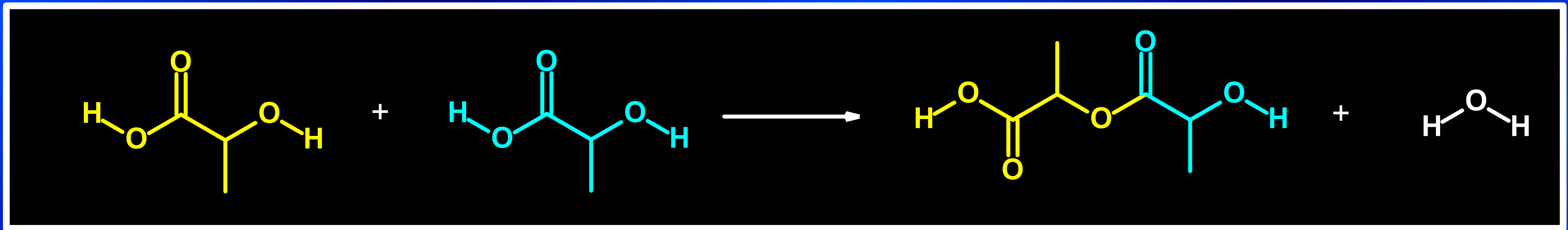
- **Esters: fruit smells:**

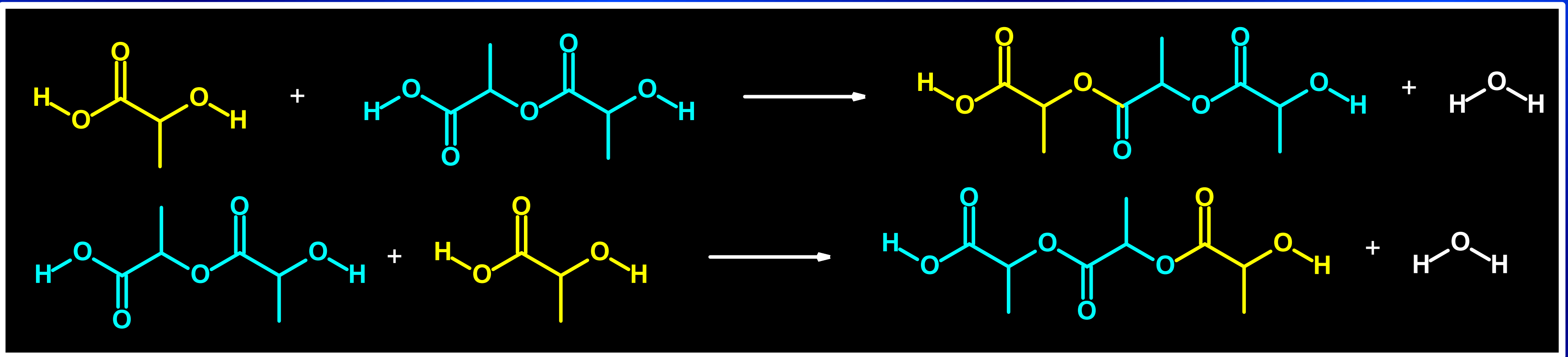


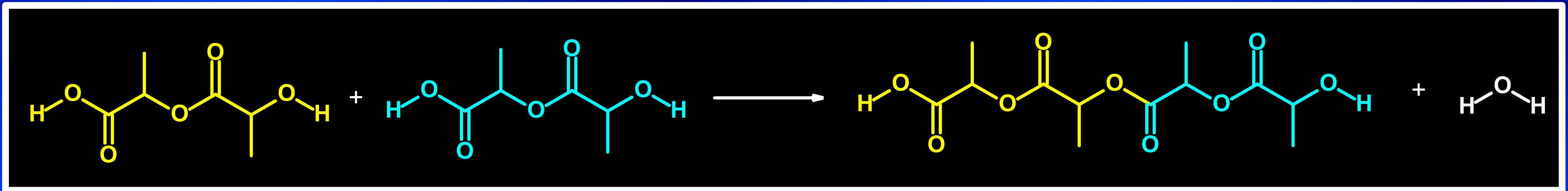
# Esterification Reaction: Polymerization

A polymer is made up of monomers attached to each one another to form a chain:

Let us take the example of lactic acid





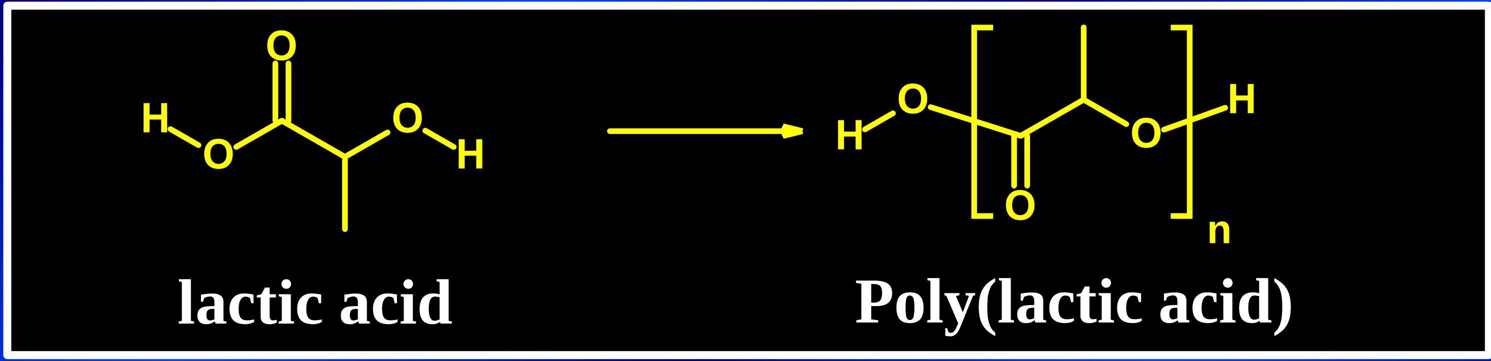


# Esterification Reaction: Polymerization

**Polymer = chain**

**Monomer = repeating unit = link**

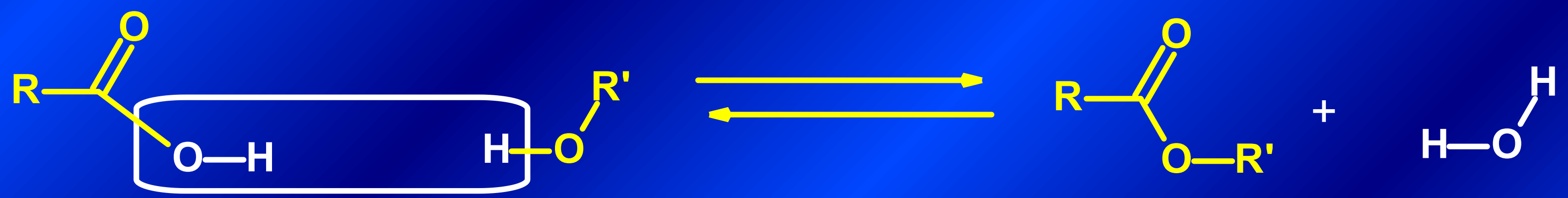
**Polymerization = chemical reaction allowing to attach links to form a chain. The higher is the number of consecutive reactions, the longer is the chain.**

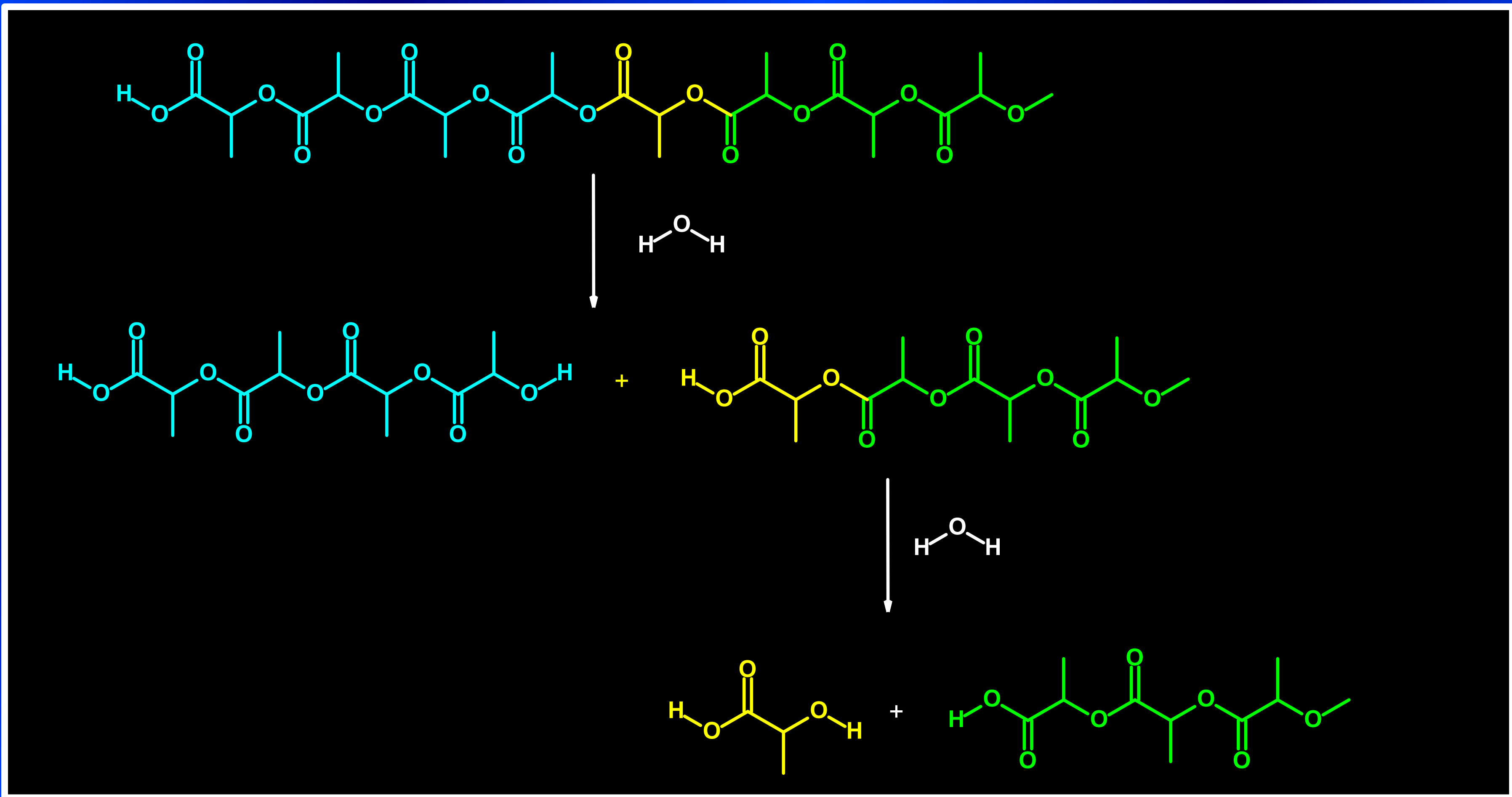



**Polymers are obtained from molecules at least di-functional. This technique of polymerization is reported as a step-growth polymerization. It is difficult to obtain very long chains by this technique. A mixture of chains of different length is obtained.**

# Hydrolytic Degradation of Polyesters

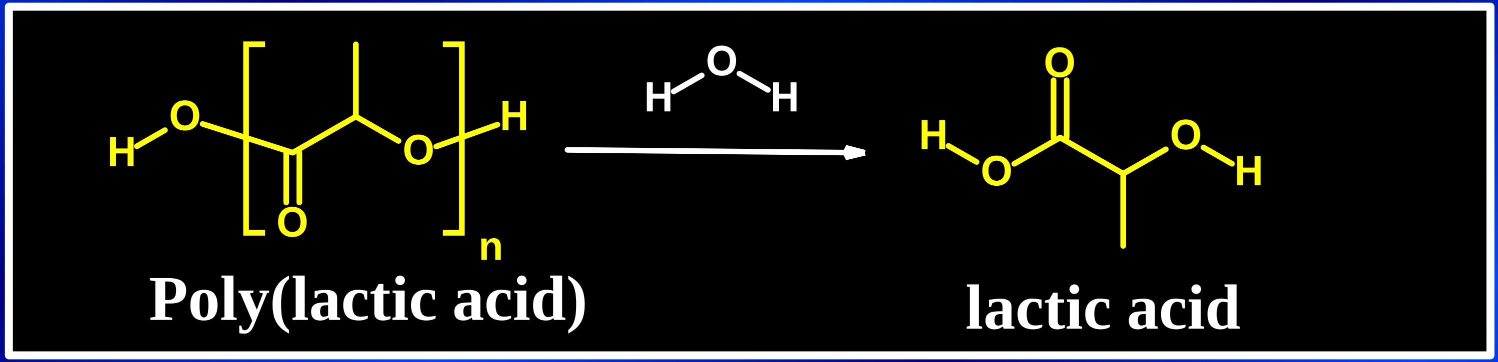
**Let us recall:**



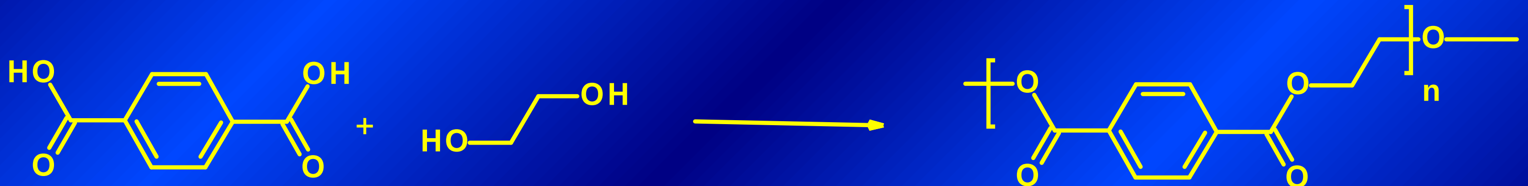



# Hydrolytic Degradation of Polyesters

**Polyesters in aqueous medium react with water and are degraded into their corresponding monomers (provided that the time left for degradation is long enough).**




**All polyesters do not degrade at the same speed. For instance the degradation of PET (used for drink bottles) is very slow.**



# (Bio)degradation

**Definition from the dictionary:**

**Biodegradability = capability of decaying through the action of living organisms.**

**This definition is to general because it does not take into account:**

- **the environment where the degradation takes place;**
- **the type of material and the duration of the degradation;**
- **the measured implemented to measure biodegradability;**
- **the possible impact on environment.**

# (Bio)degradation

**Degradable polymer materials :**

- **retain the same performances compared to conventional plastics during use.**
- **degrade after use into low molar masscompounds under**

  **- biological stimuli (naturally occurring microorganisms ; bacteria, fungi, algae, and/or enzymes)**

  **- physico-chemical stimuli (light, heat, oxygen and water)**

- **ultimately degrade into $CO_2$ and/or $CH_4$, $H_2O$, and biomass at comparable and commensurable rate and extent, as known for environmentally degradable materials like yard waste and paper, and leaves no persistent or toxic residues.**

# End of Life: (Bio)degradation

## Biodegradable polymer materials:

- retain the same performances compared to conventional plastics during use;

- degrade after use into low molar mass compounds under biological stimuli;

- ultimately degrade into $CO_2$ and/or $CH_4$, $H_2O$, and biomass at comparable and commensurable rate and extent, as known for environmentally degradable materials like yard waste and paper, and leaves no persistent or toxic residues.

# End of Life: (Bio)degradation

**2 mechanisms of biodegradation can be distinguished:**

**Mineralization: biodegradation of polymers with ultimate release of $CO_2$, $H_2O$…**

**Bioassimilation: biodegradation of polymers into biomass.**

# End of Life: (Bio)degradation

**Disintegration: irreversible decomposition of a product into tiny pieces.**

**Biofragmentation: decomposition of polymers into oligomers or monomers by chemical cleavage of covalent bonds induced by biological agents.**

**Disintegration can take place without any biofragmentation. Nevertheless, disintegration can also be the consequence of the biofragmentation of a material.**

**Disintegration of a material brings about dramatic changes of physico-chemical properties in the absence of any mineralization / bioassimilation. The material is then not biodegradable !!!**

# End of Life: (Bio)degradation

**Polymer material after use**

Step 1

**Disinstegration** and/or **Biofragmentation**

Mechanical, UV, thermal

Bacteria, champignons, vers de terre, insects,…

Step 2

Increase of the contact surface with microorganisms

**Bioassimilation**

Digestion by microorganisms and enzymes

métabolites

$CO_2/CH_4$, $H_2O$

**Mineralization**

# End of Life: (Bio)degradation

## How is biodegradability determined?

- **In vitro:**

**measurement of the release of $CO_2$ (Sturm's test) and/or of methane, of the consumption of $O_2$ or the microbian growth (under controlled conditions).**

- **In situ:**

**measurement carried out on soil and compost (under known but not mastered conditions).**

# End of Life: (Bio)degradation

There is more than "meets the eye" in "biodegradation"! An entire army of microorganisms attacks the material to be broken down and the army differs according to the environment (the specific temperature, moisture content, pH, supply of oxygen, etc.) where biodegradation occurs.

A product's application determines the ideal biodegradation environment. Accordingly, Belgium has already introduced a law to decide that packaging may not be presented as biodegradable. After all, the idea is not to have packaging spread around on a massive scale like litter because it is "biodegradable".

http://www.okcompost.be/en/recognising-ok-environment-logos/ok-biodegradable-soil-amp-ok-biodegradable-water/

# End of Life: (Bio)degradation

## OK Biodegradable SOIL

**Biodegradability in the soil offers huge benefits for agricultural and horticultural products, as they can be left to break down in situ after being used. The OK biodegradable SOIL label is a guarantee a product will completely biodegrade in the soil without adversely affecting the environment.**

http://www.okcompost.be/en/recognising-ok-environment-logos/ok-biodegradable-soil-amp-ok-biodegradable-water/

# End of Life: (Bio)degradation

## OK Biodegradable WATER

**Products certified for OK Biodegradable WATER guarantee biodegradation in a natural fresh water environment, and thus substantially contribute to the reduction of waste in rivers, lakes or any natural fresh water. Note that this not automatically guarantees biodegradation in marine waters.**

**http://www.okcompost.be/en/recognising-ok-environment-logos/ok-biodegradable-soil-amp-ok-biodegradable-water/**

# End of Life: (Bio)degradation

## OK compost


**Packaging or products featuring the OK compost label are guaranteed as biodegradable in an industrial composting plant. This applies to all components, inks and additives. The sole reference point for the certification programme is the harmonised EN 13432: 2000 standard.**

**In any event any product featuring the OK compost logo complies with the requirements of the EU Packaging Directive ( 94/62/EEC).**

**http://www.okcompost.be/en/recognising-ok-environment-logos/ok-compost-amp-ok-compost-home/**

# End of Life: (Bio)degradation

**The EN 13432 standard: the need to recover packaging waste on the basis of industrial composting.**

**Requirements:**

- **Chemical composition: the standard sets the limits for volatile matter, heavy metals and fluorine;**

- **Biodegradation: at least 90% of the material has to be broken down into $CO_2$, water, minerals by biological action within 6 months;**

- **Desintegration: at least 90% of the material should be able to pass through a 2x2 mm mesh after 12 weeks;**

- **Quality of the final compost and ecotoxicity: the germination and biomass production of plants should not be affected by the influence of the composted packaging.**

**http://www.okcompost.be/en/recognising-ok-environment-logos/ok-compost-amp-ok-compost-home/**

# End of Life: (Bio)degradation

## OK compost HOME


Owing to the comparatively smaller volume of waste involved, the temperature in a garden compost heap is clearly **lower and less constant than in an industrial composting environment**. This is why composting in the garden is a more difficult, slower-paced process.

**The certification OK compost HOME from Vinçotte guarantees complete biodegradability in the light of specific requirements, even in your garden compost heap.**

http://www.okcompost.be/en/recognising-ok-environment-logos/ok-compost-amp-ok-compost-home/

# Origin of Polymers: Oil- and Bio-Sourced Polymers

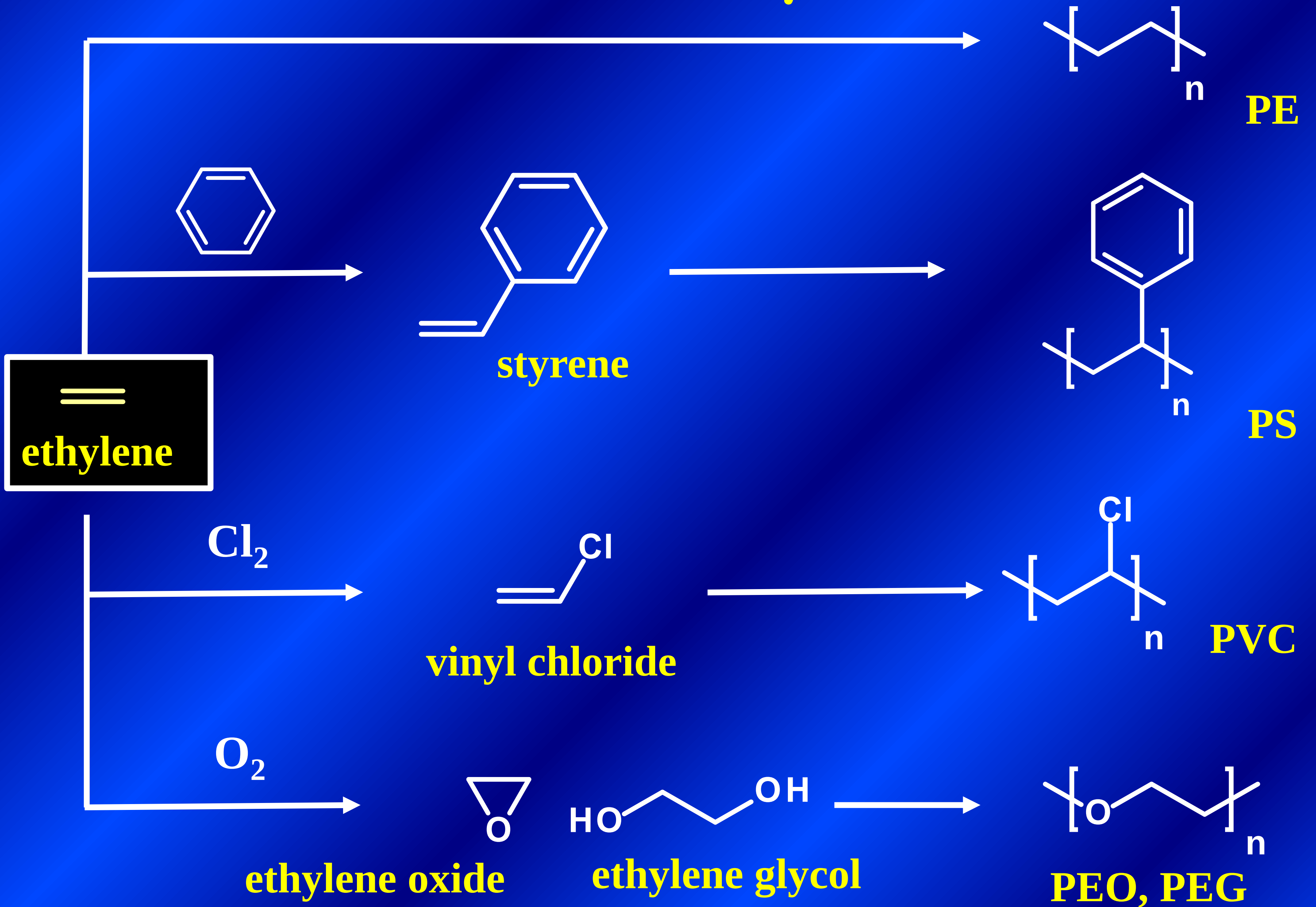
# Plastic Production

| Synthetic polymers | 1940 | 1950 | 1960 | 1970 | 1980 | 1990 | ~ 2000 |
|---|---|---|---|---|---|---|---|
| Thermoplastics | 0.2 | 2 | 8 | 32 | 55 | 95 | 140 |
| PE | - | 0.5 | 2 | 8 | 18 | 30 | 45 |
| PP | - | | - | 2 | 8 | 15 | 25 |
| PS | - | 0.5 | 2 | 10 | 12 | 20 | 25 |
| PVC | - | 1 | 3 | 10 | 12 | 20 | 30 |
| Miscellaneous | - | - | 1 | 2 | 5 | 10 | 15 |
| Themosets | 0.3 | 1 | 1.5 | 5 | 8 | 14 | 17 |
| Elastomers | | 1 | 2 | 5 | 8 | 11 | 16 |
| Fibers | 0.5 | 2 | 4 | 9 | 15 | 20 | 25 |

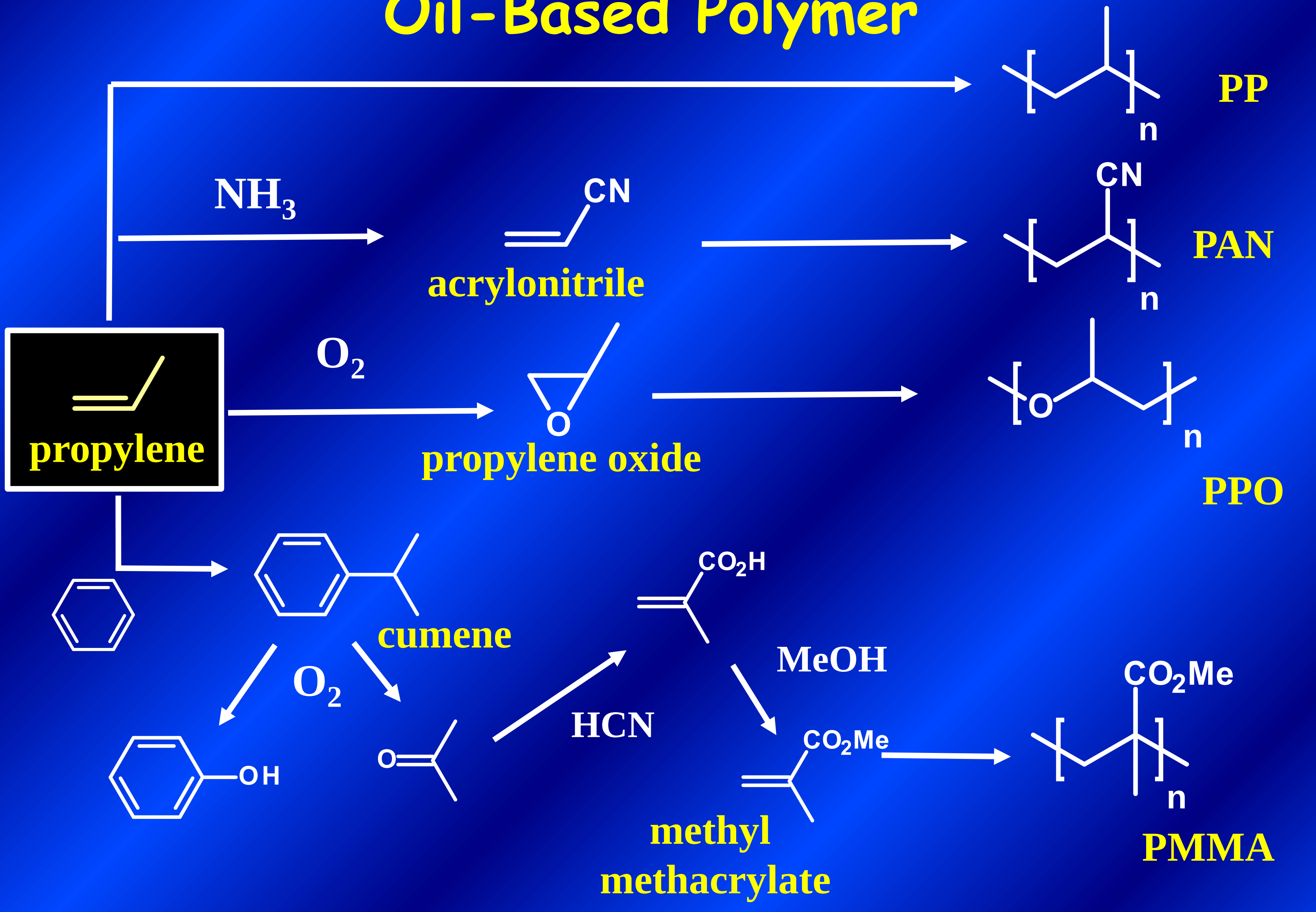
(millions of tons / year)

**Main origin:**
**Oil, a non-renewable resource**

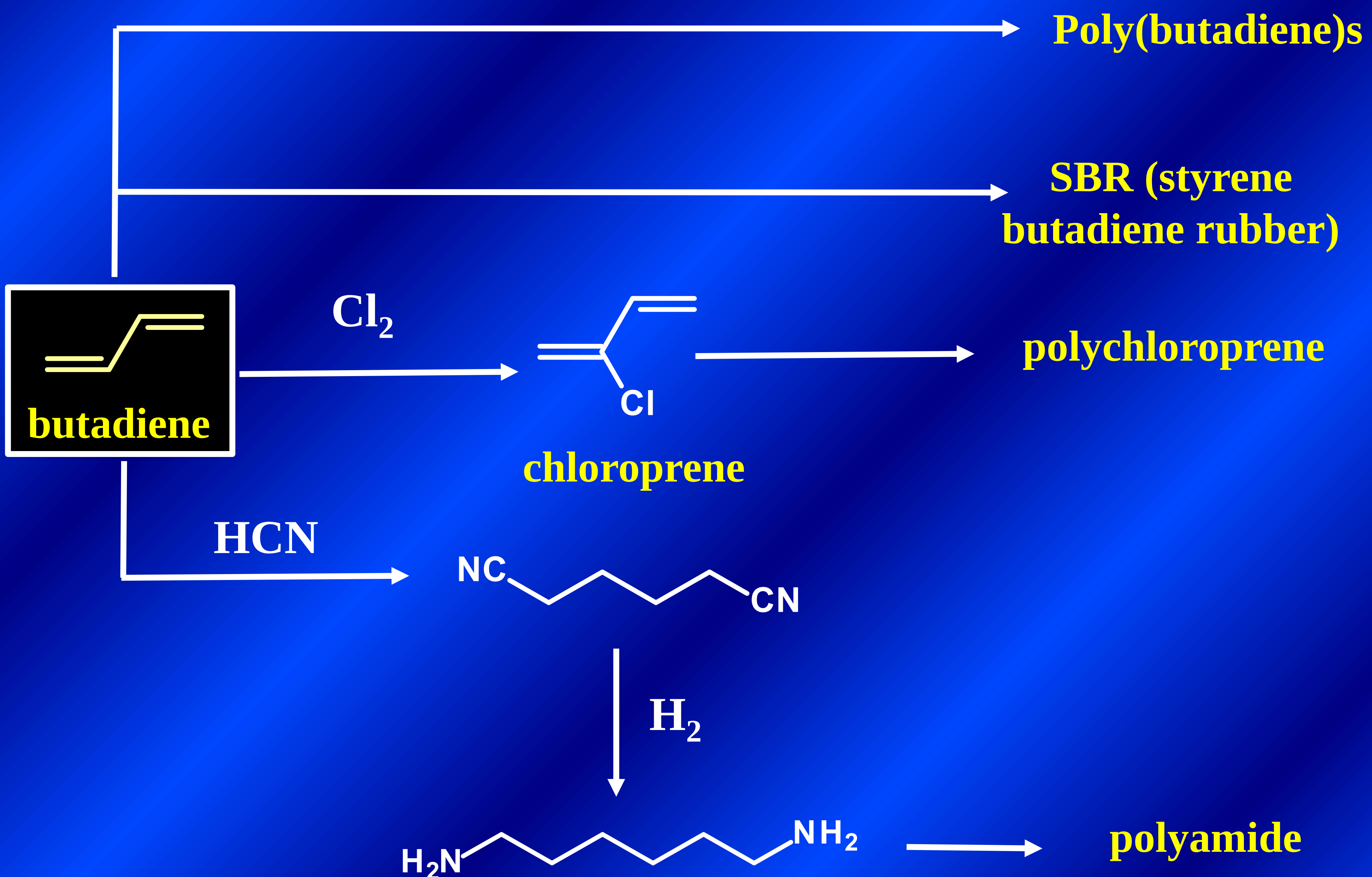
# Oil-Based Polymer



# Oil-Based Polymer



# Oil-Based Polymer



# Oil-Based Polymer

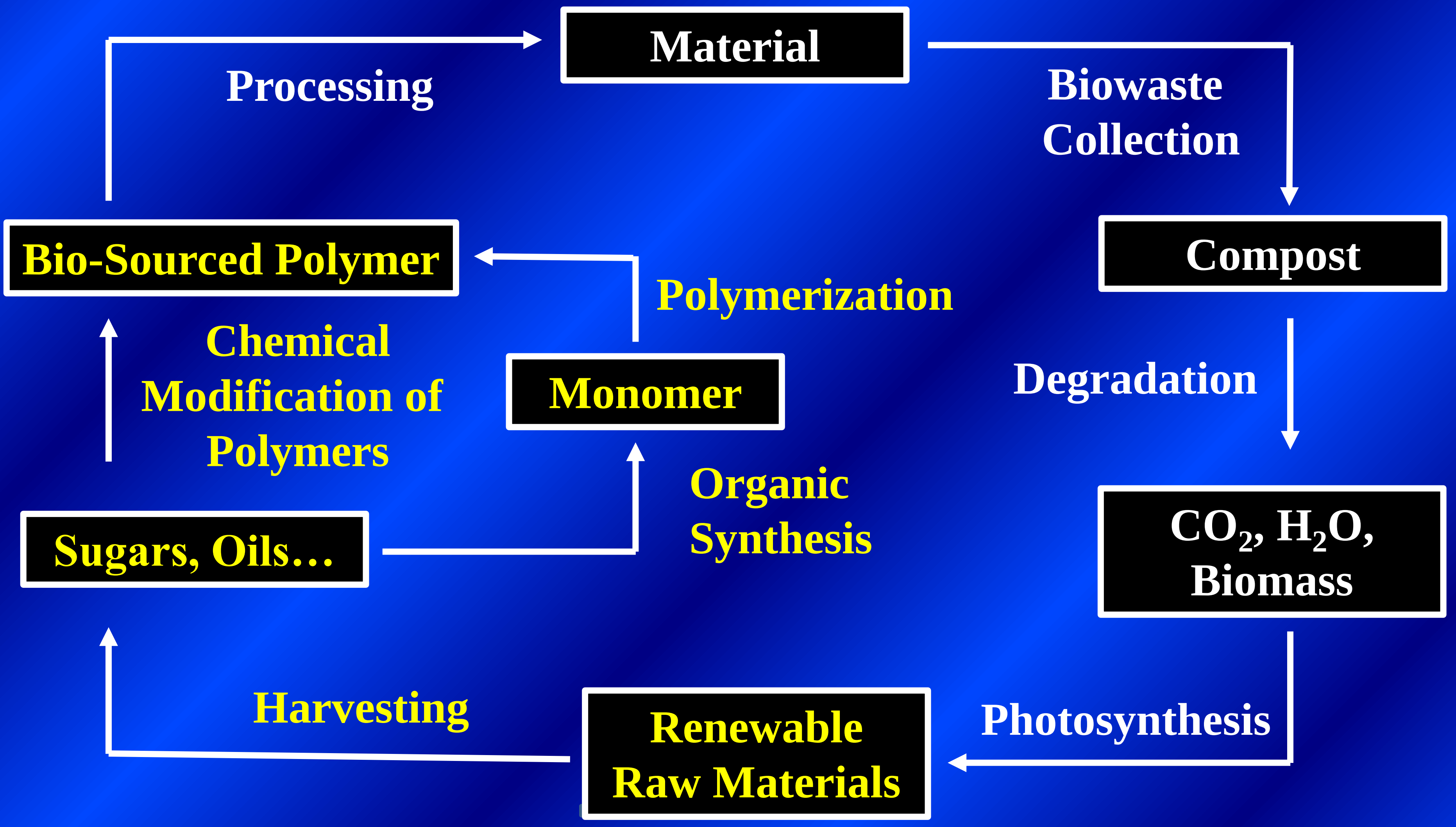
OIL
100 %

- Road Diesel
  Domestic fuel oil
  70 %
- Fuel Oil
  20 %
  - Combustible for cars
    13 %
  - Petrochemical
    Starting materials
    7 %
    - **POLYMERS**
      **4 %**
    - Other chemicals
      3 %
- Miscellaneous
  10 %

# Bio-Based Polymers

# Bio-Based Biodegradable Polymers

**Let us focus on the synthesis of bio-sourced biodegradable polymers:**



# Biorefinery

# Biorefinery

**Biorefinery = processing plant where biomass feedstocks are converted and extracted into a wide range of valuable products.**

**Biorefinery = facility that integrates biomass conversion processes and equipment with the aim to produce from biomass:**

- **Fuel**
- **Power**
- **Chemicals** ➡ **Polymers**

# 1st Generation Biorefinery

**1st generation biorefineries are based on direct utilization of classical forms of agricultural biomass:**

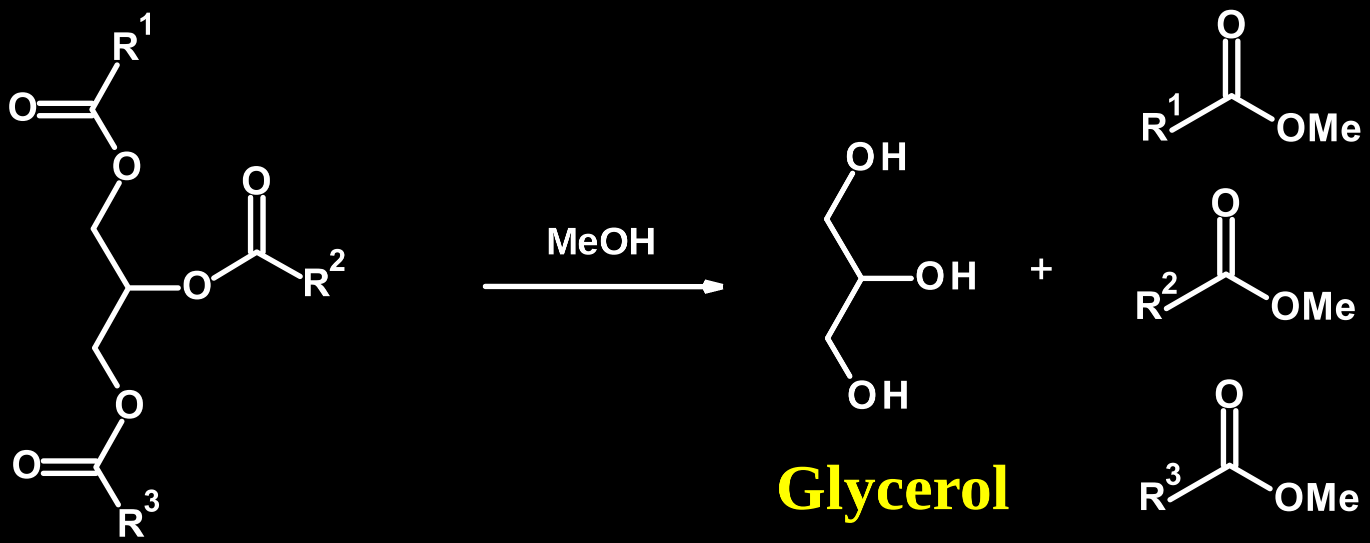
**Agricultural + forestry products: biomass used as food**

**One can distinguish two types of 1st generation biorefinery processes:**

- **Conversion processes of oil-rich biomass by transesterification for bio-fuel production**
- **Conversion processes of sugar-rich biomass by fermentation for bio-ethanol production.**

# 1st Generation Biorefinery: Biofuel

**Biofuel is obtained by the transesterification reaction of oils (lipids) by methanol (or ethanol):**




**Triglyceride: triester of glycerol and fatty acids**

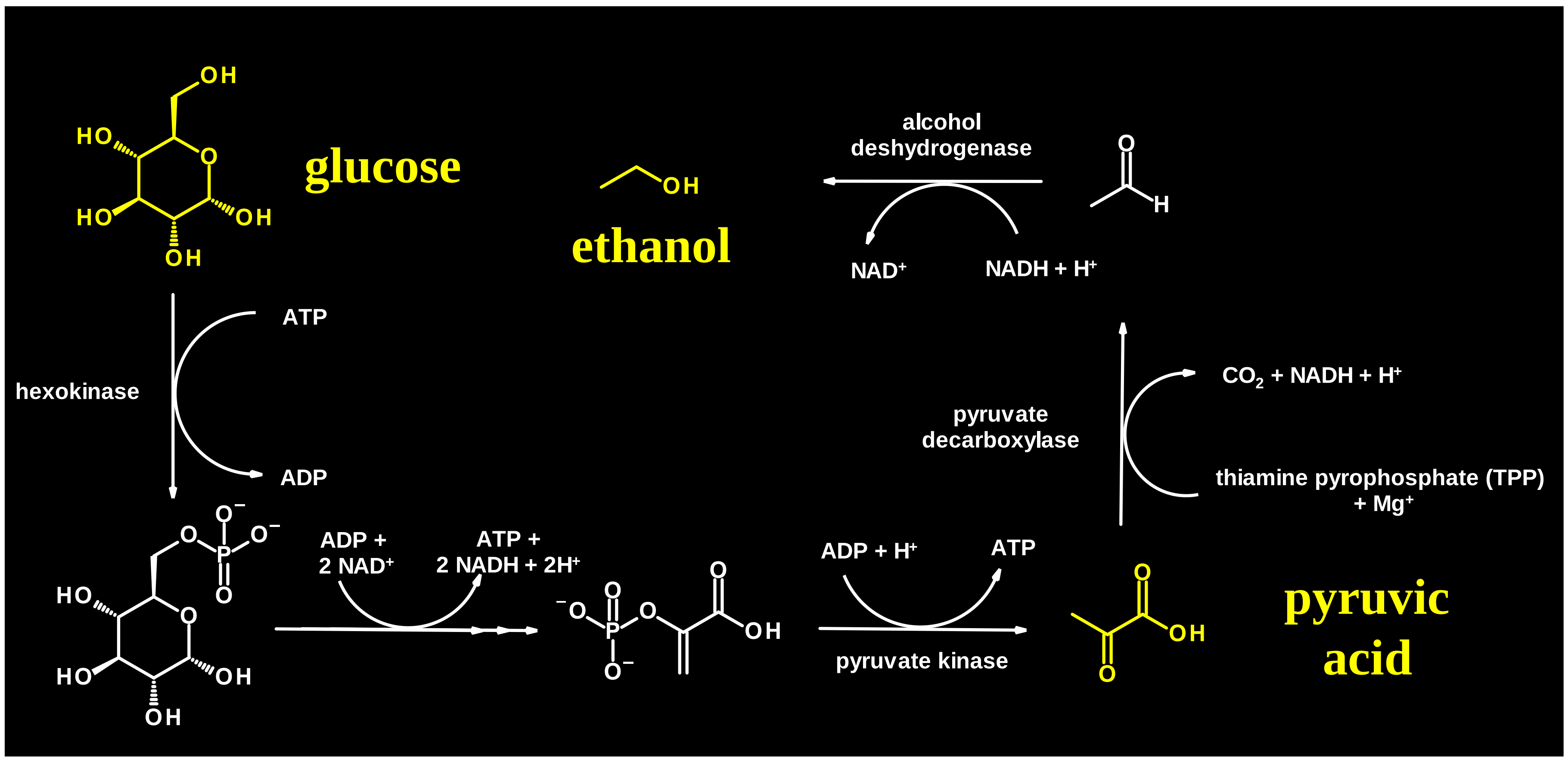
**Glycerol**

**Fatty Acid Methyl Esters**

**Natural oils from various origin could be used. Let us cite: rapeseed (colza); soy (soja); coconut (noix de coco); sunflower (tournesol) hemp (chanvre); palm tree (palmier), chinese tallow tree (suif chinois)**

# 1st Generation Biorefinery: Ethanol Fuel

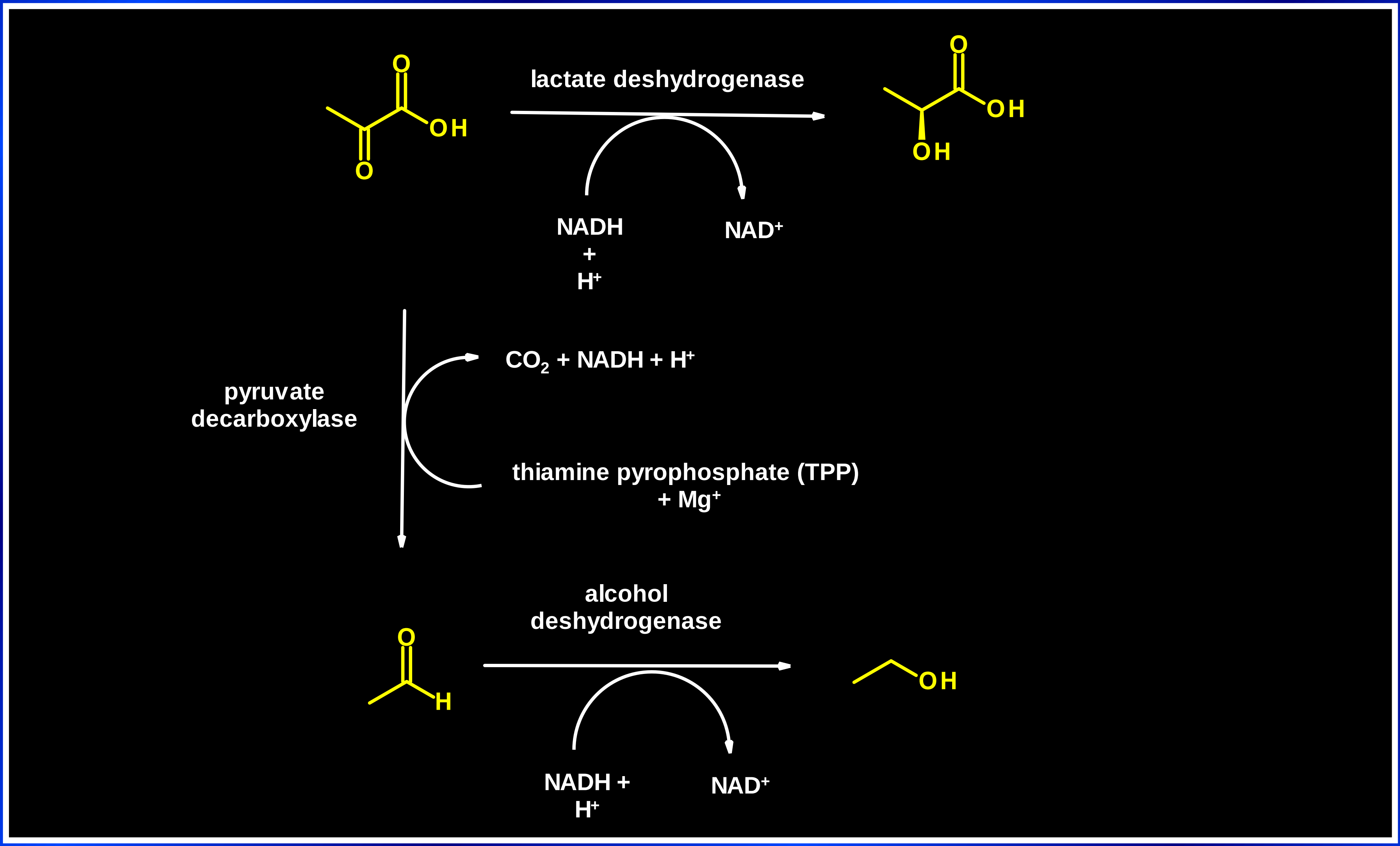
**Ethanol fuel is produced by the fermentation of glucose and other sugars:**



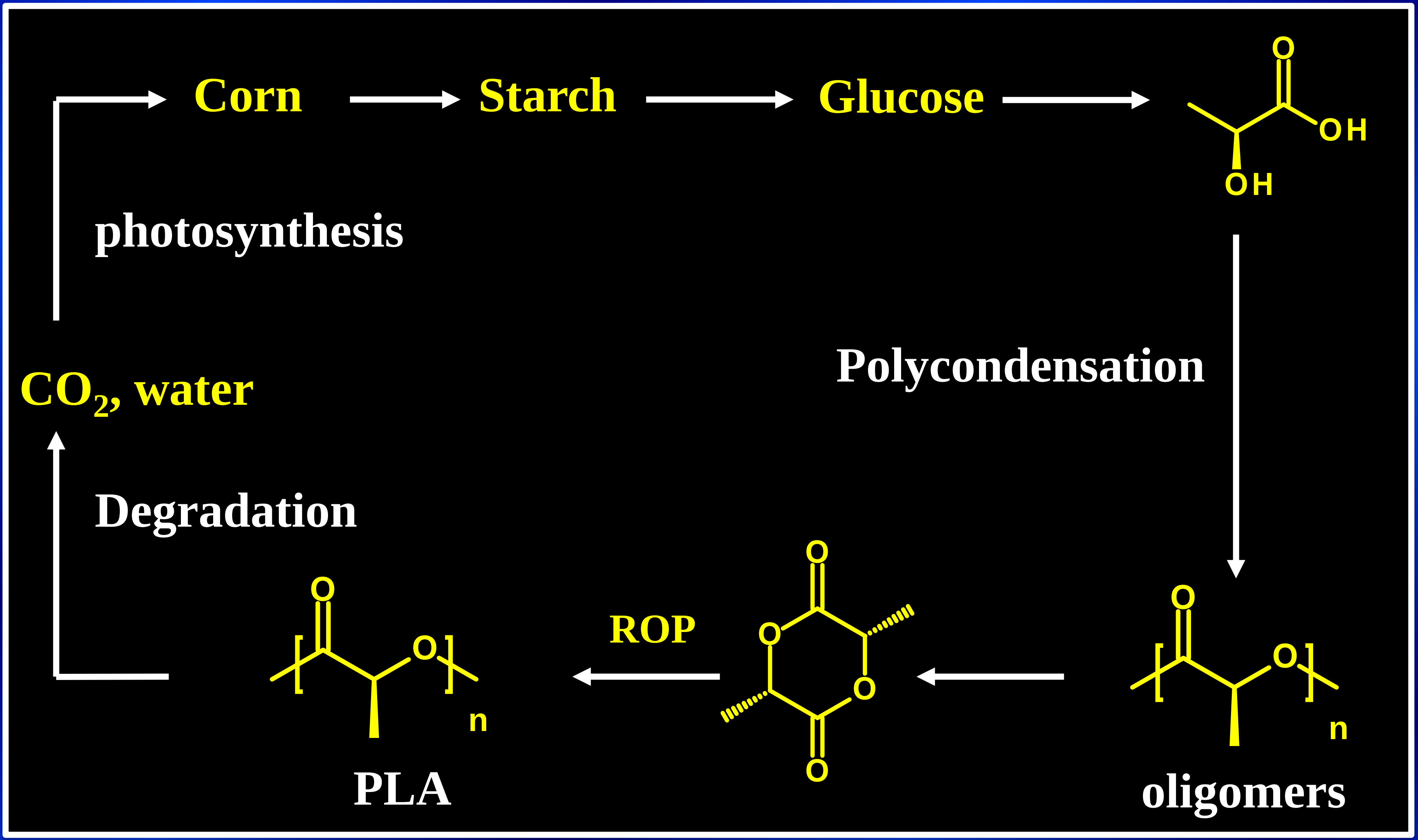

**The nature of the formed products depends on the conditions (presence of oxygen) and on the presence of the suitable enzymes.**

# 1st Generation Biorefinery: Pyruvic Acid

## Pyruvic acid is an important intermediate:



# Poly(L-Lactide): Industrial Synthesis



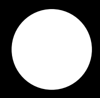

= Cargill process

# Chain-Growth Polymerization

The polymerization takes place through three steps (at least)

➢ **Initiation:** formation of the active species.

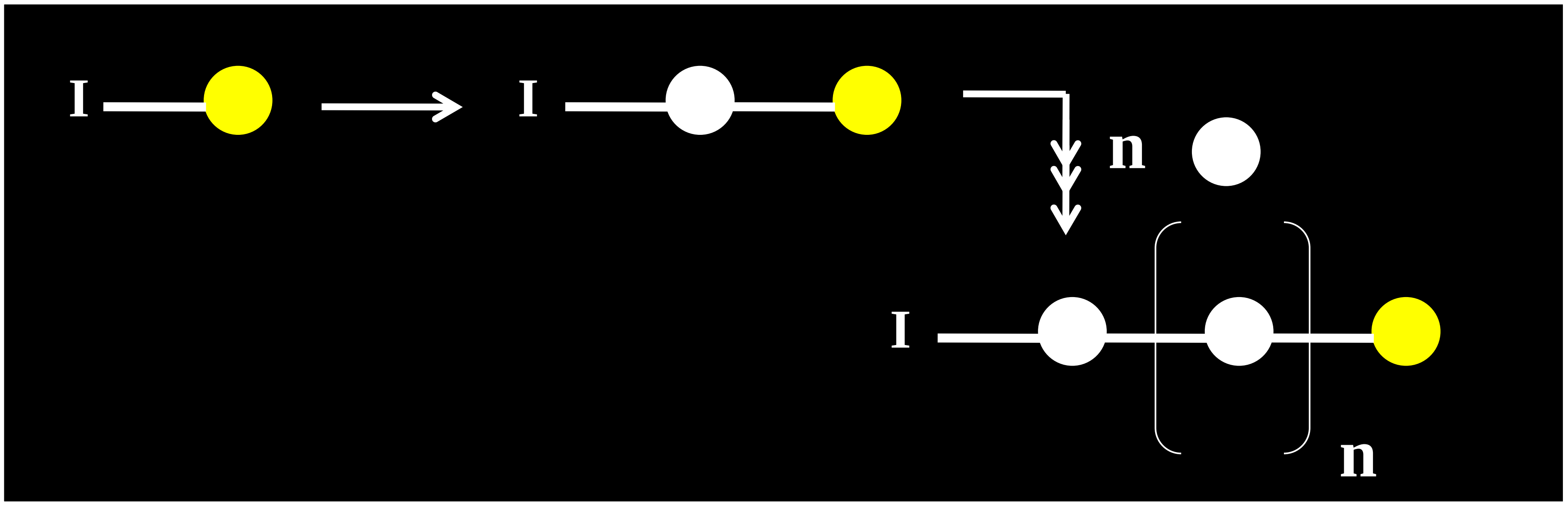

I = radical, anion, cation, carbene, organometallic species.

 = monomer and I = initiator

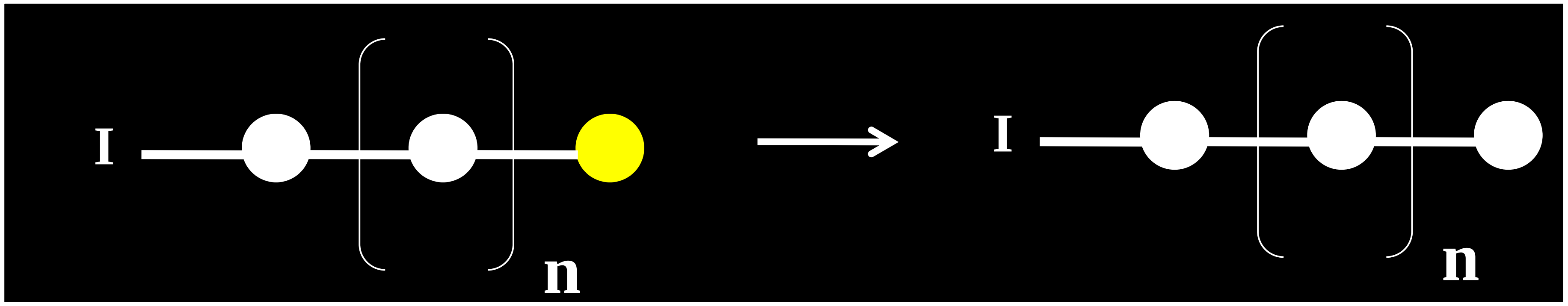
The species highlighted in yellow bear the active propagating species ;
the species highlighted in white do not bear any active propagating species.

# Chain-Growth Polymerization

- **Propagation:** extension of the chains (increase of the DP).



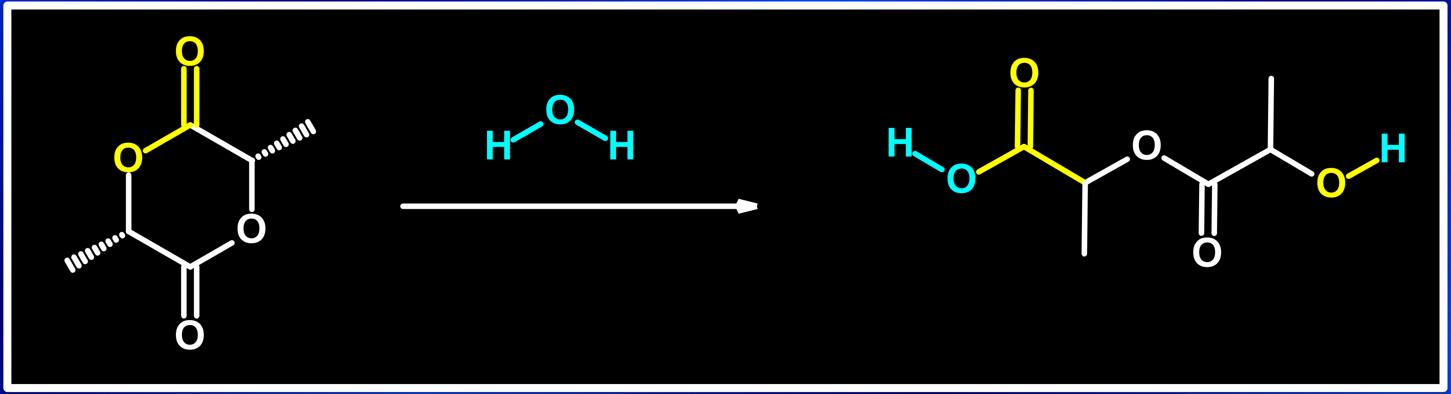

- **Termination:** the active species at the chain-end of chains are killed.



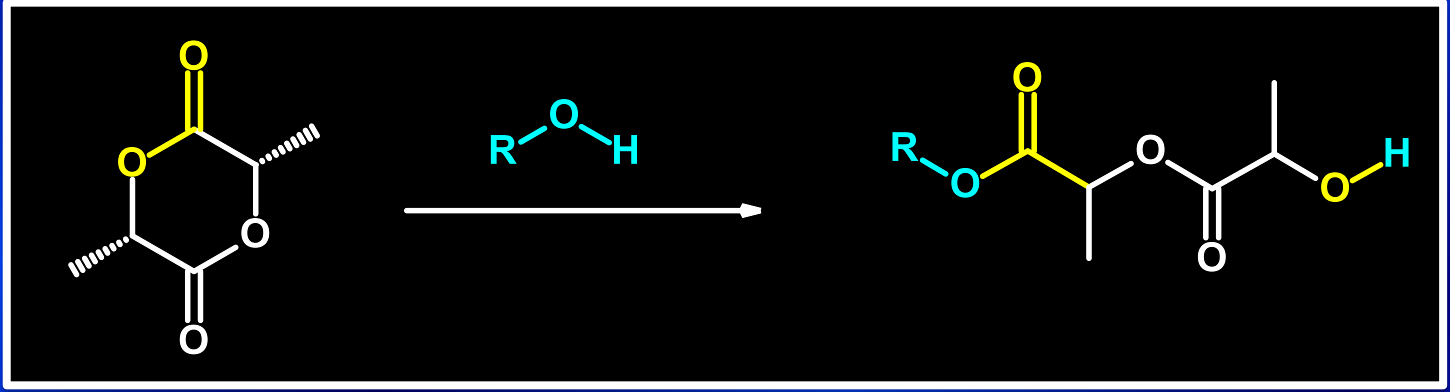
# ROP of Cyclic Esters

**Let prepare polyesters by chain-growth polymerization by using cyclic esters.**

**Firstly, let us write the hydrolysis reaction of one ester function:**

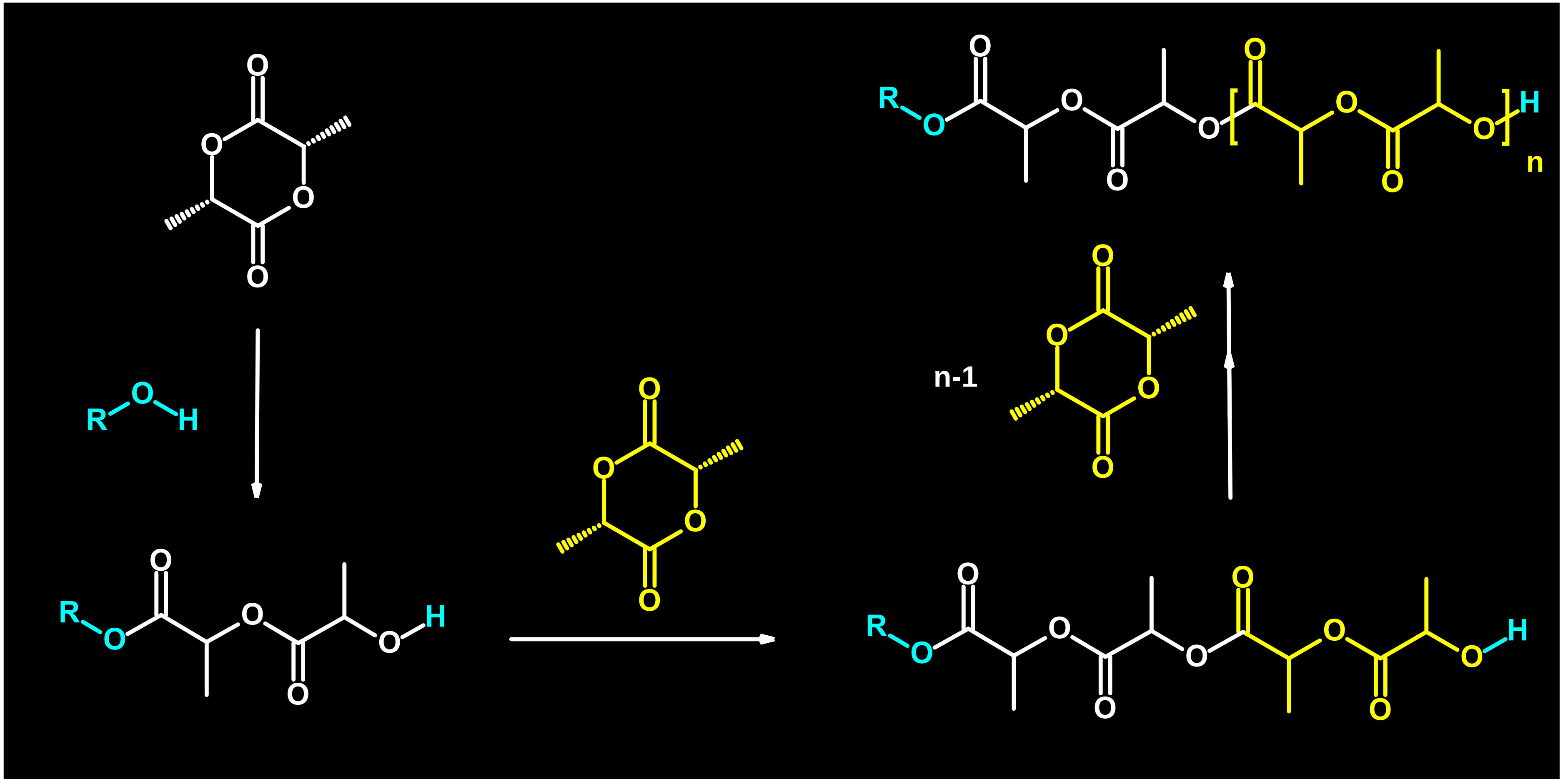


**Let us achieve the similar reaction by using an alcohol rather than water:**



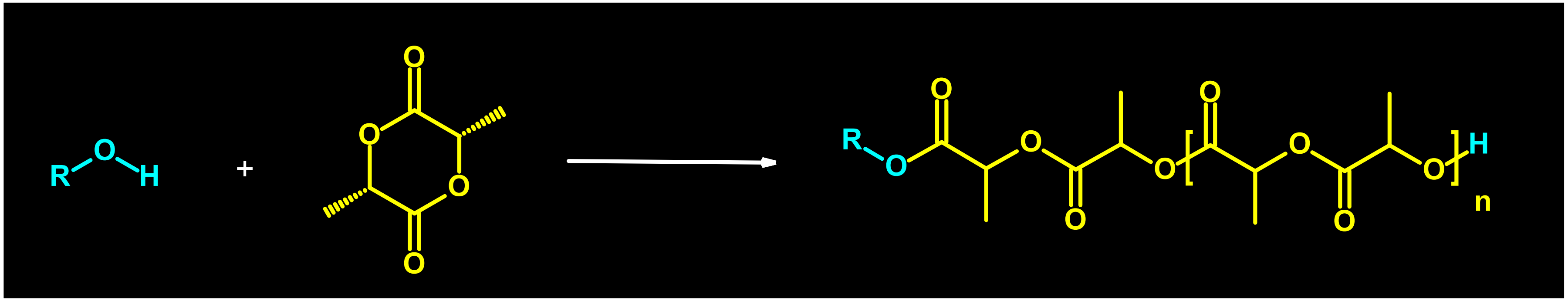
# ROP of Cyclic Esters

**One just found the initiation. The product is end-capped by a OH function and can be used to start a second reaction and to start the propagation:**



# ROP of Cyclic Esters

Let us summarize:



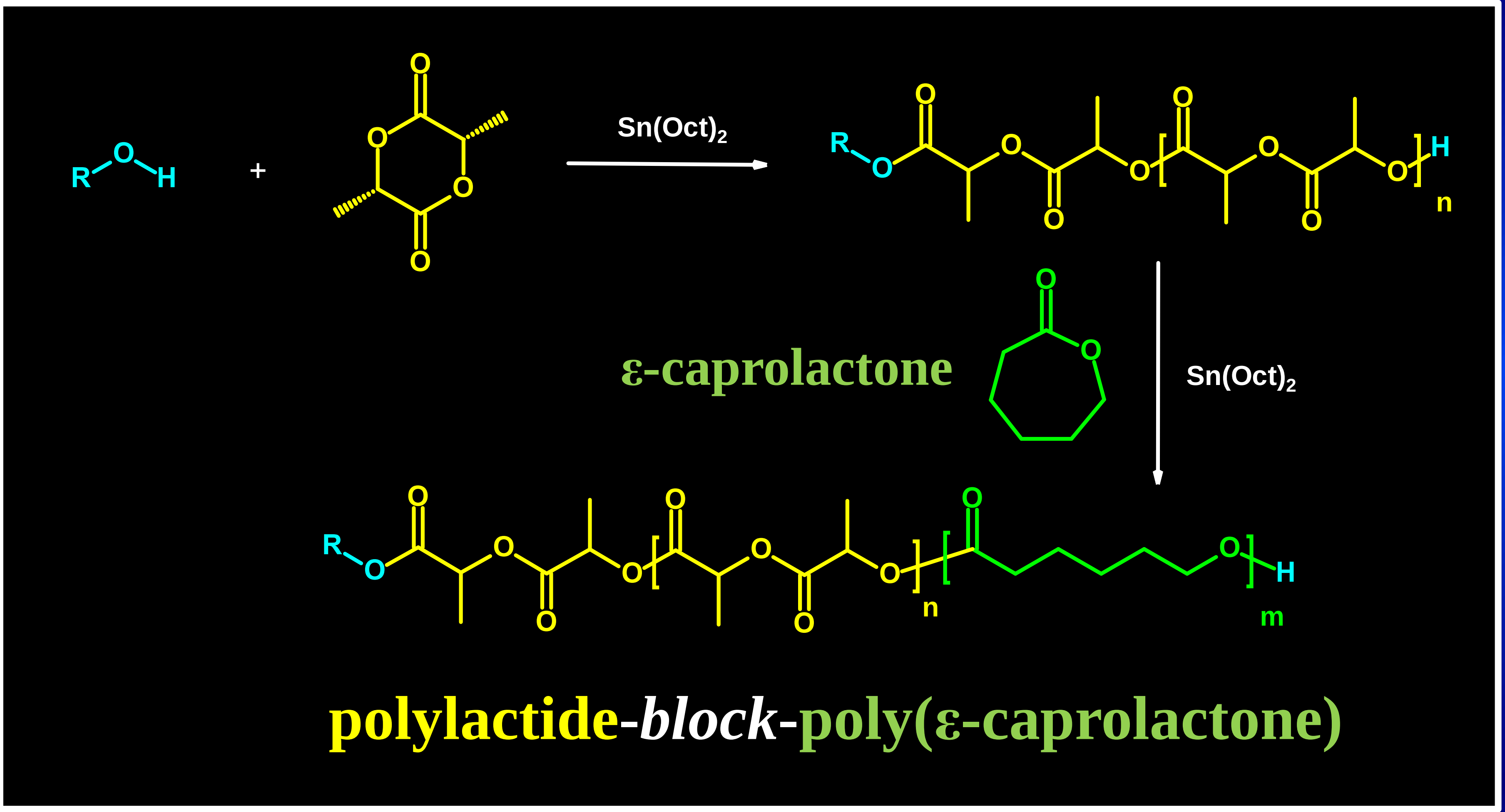

Unfortunately, this reaction is not efficient. Nevertheless, chemists finds tricks and catalysts to increase the reactivity either of the alcohol or of the cyclic ester. Under optimized, conditions, it works !!!

Usual catalyst accepted by the FDA: $Sn(Oct)_2$ (used in industry)

Advantages:

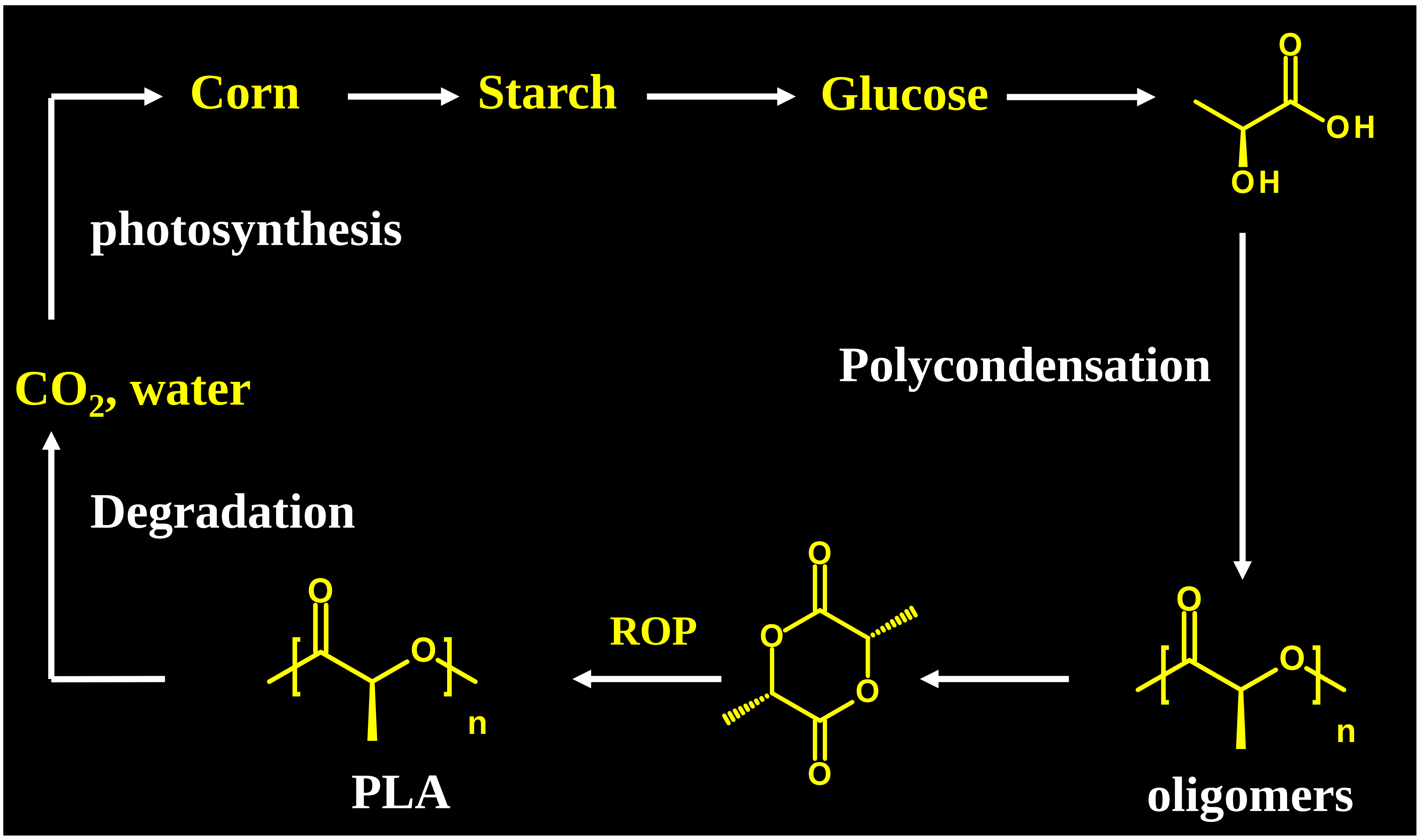
- Control of the length and narrow length distribution
- High molar mass easily reached
- Possibility to synthesize block copolymers by sequential addition of two different monomers

# ROP of Cyclic Esters: Block Polyesters




**They are many possibilities and one can vary at will the composition of the copolymers and thus their properties, which can be exploited in many applications, and thus also biomedical applications.**

# Poly(L-Lactide): Industrial Synthesis




= Cargill process

# 1st Generation Biorefinery

**Issues:**

- **Risk of an excessive consumption of food crop**
- **Risk of deterioration of organic quality and mineral content of soil**
- **Excessive utilization of fertilizers and pesticides to improve production levels**
- **Competition between food industry and biorefineries**
- **Risk of deforestation on the long-run**

# 2nd Generation Biorefinery

**2nd generation biorefinery utilizes lignocellulosic biomass as a raw material (straw, wood and wastes…).**

**The principal advantage of this class of biorefinery is:**

- **recovery of the most abundant source of renewable carbon on the planet.**
- **Reduces the dependence on food crops.**
- **Improvement of energy and environmental cycles.**
- **Improved output and cost of production**

**Lignocellulosic biomass is made up of polymers of plant cell walls (French: parois des cellules végétales):**

- **Cellulose**
- **Hemicellulose**
- **Lignins (aromatic derivatives)**

# 3rd Generation Biorefinery

**3nd generation biorefineries have the advantage of utilizing agricultural residues as well as forestry, petrochemical, and urban waste.**

**The adavantages are:**

- **recovery of the most abundant source of renewable carbon on the planet.**
- **Reduces dependence on food crops.**
- **Improvement of energy and environmental cycles.**
- **Improved output and cost of production**

# Life Cycle Assesment

# Life Cycle Assesment

**Life Cycle Assessment (LCA)**

**compilation and evaluation of all inputs and outputs**

**“from cradle to grave”**

**(analyses and the interpretation of the LCI in terms of environmental impact)**

# Life Cycle Assessment

**LCA (as defined in ISO 14040 thru 14043) in 4 steps:**

1. **Goal and Scope definition**
2. **Inventory analyses with system boundaries, data cut-off, and allocation (multi-use) resulting in lists of input and output (emissions)**
3. **Impact assessment (with selection of method):**
   - a. **classification (making groups of substances for each impact)**
   - b. **characterization (creating “equivalent” emissions)**
   - c. **normalization (comparing the equ.em. to the total in a country)**
   - d. **grouping**
   - e. **weighting (adding the relative importance)**
4. **Interpretation, with conclusions and recommendations.**

# Life Cycle Assessment: Plastic Bag

**The Life Cycle Assessment (LCA) is a recognized technique used to quantify the environmental impact of products during their entire life cycle as an international standard-setting process via the ISO 14040 series (1997 and revised in 2006).**

**cradle**

**Extraction and processing of raw materials**

**Manufacturing**

**Packaging**

**Transportation and distribution**

**Useful life, maintenance of the product and reuse**

**recycling**

**Disposal as waste at the end of its useful life**

**grave**

# Life Cycle Assessment

**Are biodegradable polymers good for environment?**

**Are bio-sourced polymers good for environment?**

**No definite answer can be given because one can not consider one step but the whole life cycle of the product.**

**!!!** **A common mistake is to consider just one step for assessing the environmental impact of polymers on environment !!!**

**For each application, the whole life cycle has to be considered and the answer can be different depending on the considered application !!**

**Many industries develop bio-sourced polymer because nature provides a broad range of new monomers polymerizable into new polymers with original properties for applications**

# Polymers Nanocarriers for Drug Delivery

# Amphiphilic Polymers

Let us consider intravenous injections. Let us use polymers as carriers.

What is the behavior of a polymer in water? They are two possibilities:

not soluble in water
precipitates

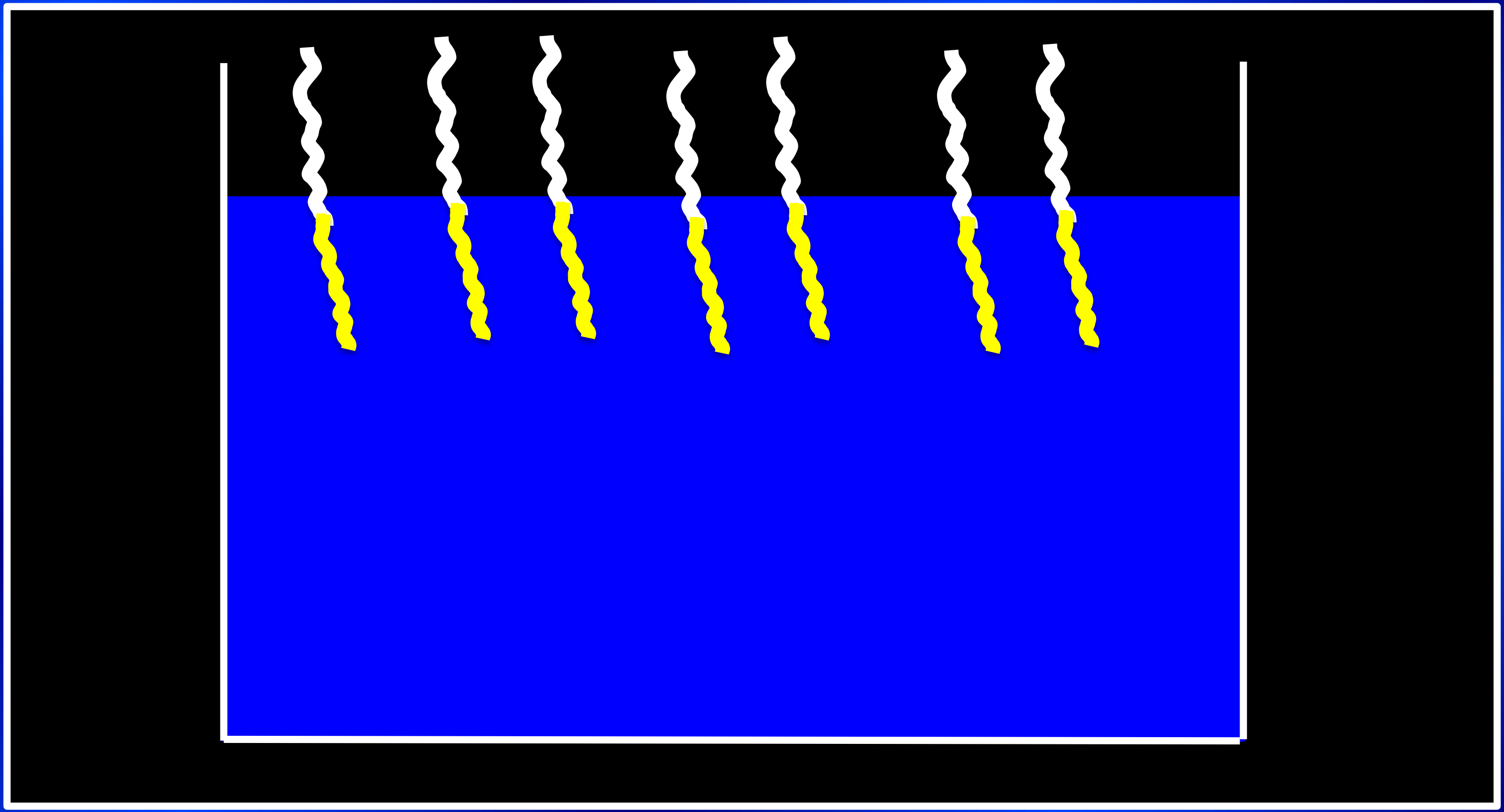
soluble in water

What is the behavior of a diblock copolymer made up of one soluble block and one second insoluble block?

These polymers are reported as amphiphlic

# Amphiphilic Polymers

**Let us add amphiphilic polymer in a cup of water.**



**Beyond a critical amount of polymer, they self-organize into nanoparticles made up of a insoluble core and a water-soluble corona.**

# Amphiphilic Polymers

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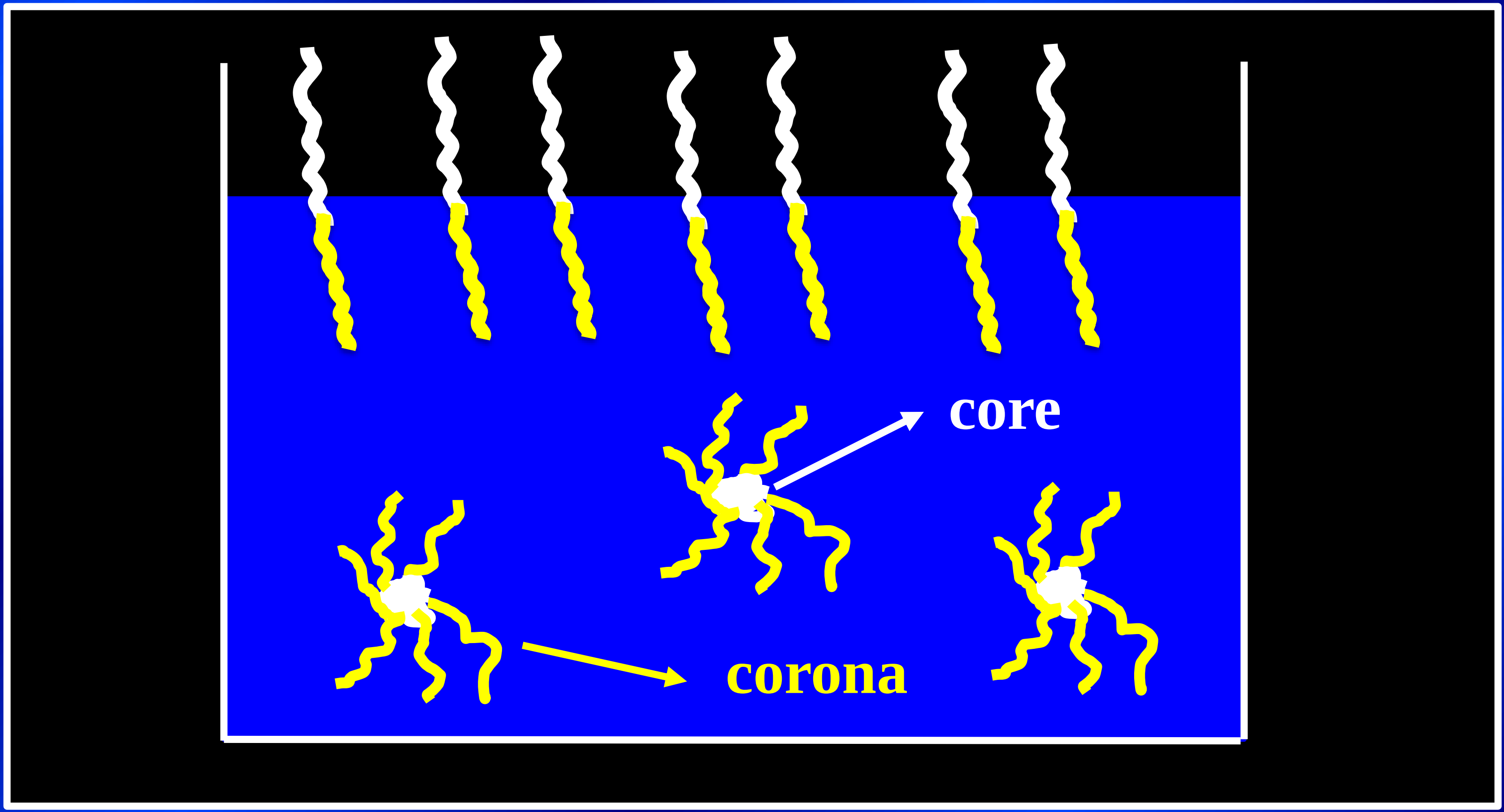
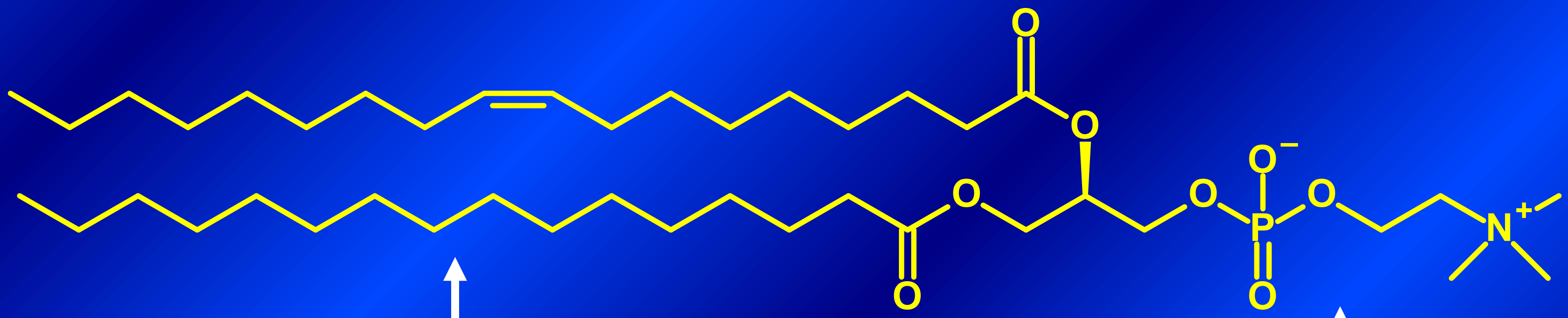



Beyond a critical amount of polymer, they self-organize into nanoparticles made up of a insoluble core and a water-soluble corona.

# Mayonnaise


Water and oil are not soluble. In order to disperse water in oil, one has to add a **surfactant**.
This is the principle of **mayonnaise**.

The egg yolk contains an amphiphilic molecule made up of a water soluble head and a non water soluble tail:



Non water-soluble tail
(hydrophobic tail)

Water-soluble head
(hydrophilic)

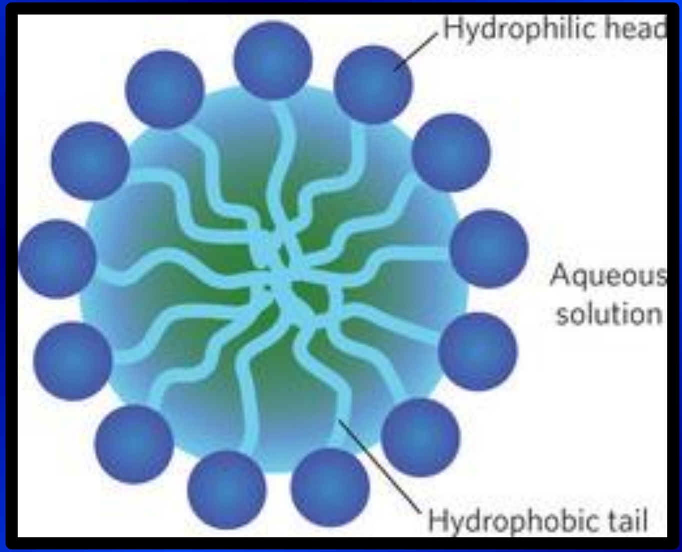
This molecule is a **surfactant** and allows to **stabilize** an **emuslion of an oil in water** to obtain mayonnaise:

# Soap

Soaps are also made up of an amphiphilic molecule:


hydrophobic tail hydrophilic head

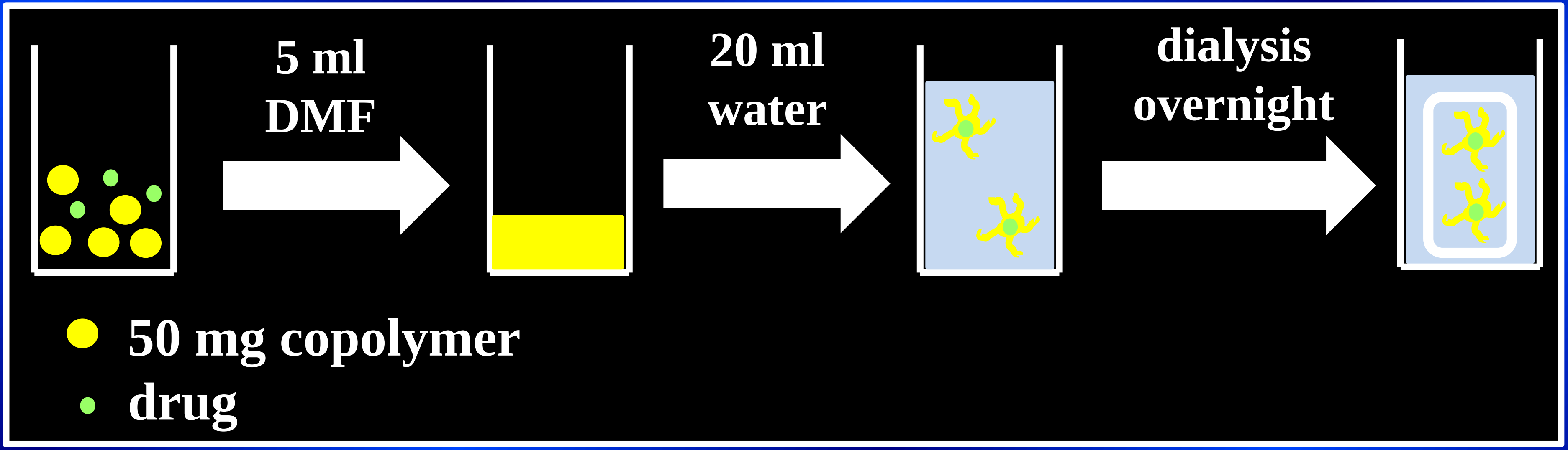

Soaps are used to get rid of non polar molecules such as grease, which is encapsulated inside the core of the micelles (nanoparticles).




In a similar way, let us use amphiphilic molecules based on polymers to load hydrophobic drugs in the core of polymer nanoparticles, in order to use them as vehicles for drug delivery applications.

# Nanoparticle: Drug Loading

Let us show the preparation of nanoparticles: 2 miscible solvents are involved. Each blocks of the amphiphilic copolymers are soluble in DMF. The PEO block is the only one soluble in water.

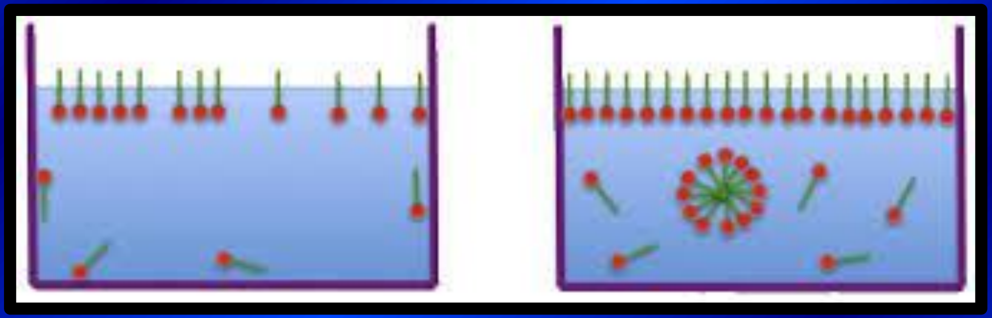



When the experiment is carried out in the presence of an hydrophobic drug, the drug is loaded in the hydrophobic core of the nanoparticles with a given efficiency.

The size of nanoparticles is measured by dynamic light scattering. After injection of micelles in the body, the drug is released by a given kinetics due to diffusion from the core or degradation of the polyester.

# Critical Micellar Concentration

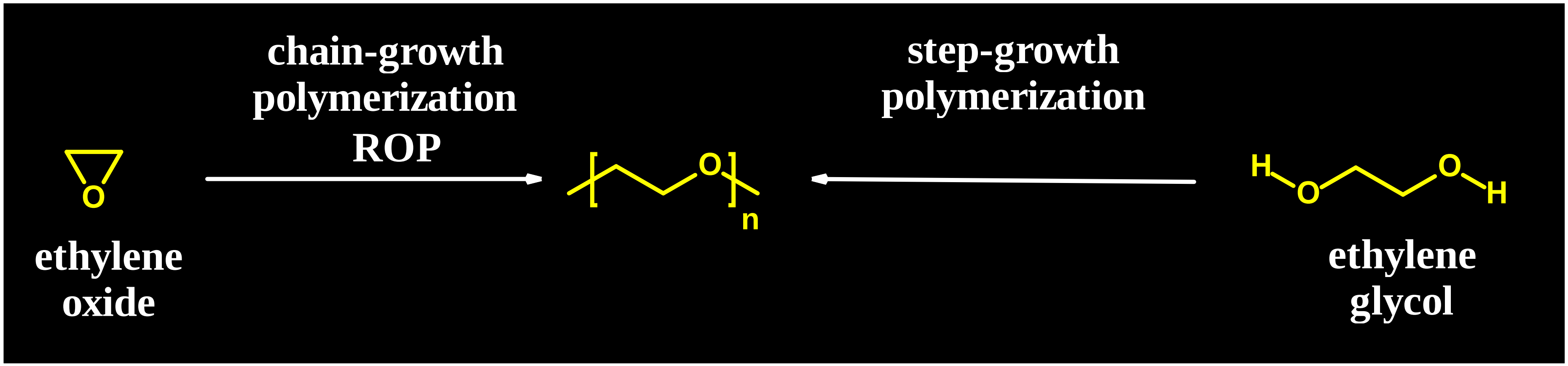
At very low concentration, amphiphilic copolymers diffuse to the interface to decrease the interfacial energy. Beyond a critical concentration, the interface is saturated and the aggregation of chains in water results in the formation nanoparticles :



Polymer nanoparticles are often referred as micelles and the critical concentration is referred as the critical micellar concentration (cmc). After injection of loaded micelles in the body, dilution below the cmc results in the disassembly of micelles and the premature release of the drug. Cross-linking of the core of micelles allows to prevent disassembly from taking place but crosslinking has an impact of the kinetics of the drug release by diffusion !

It is essential to measure the cmc of amphiphilic polymers in water (by dynamic light scattering, diffusion NMR, fluorescence (probe: pyrene).

# Poly(Ethylene Oxide) or Poly(Ethylene Glycol)



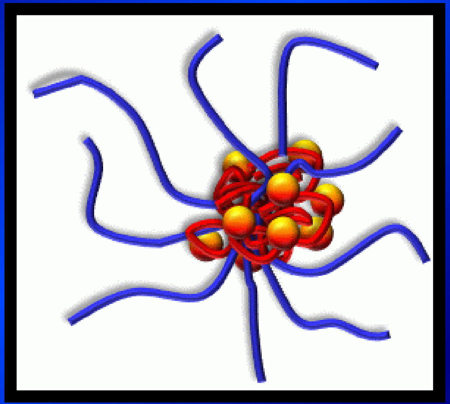

**This polymer is made up of the same repeating unit and it can be synthesized either by step-growth polymerization of ethylene glycol or by chain-growth polymerization of ethylene-oxide. The chain-ends depends on the chosen synthesis process.**

**When the nomenclature is based on the origin of the polymer (thus the name of the monomer), the same polymer has two different names [poly(ethylene oxide) (PEO) or poly(ethylene glycol) (PEG)]. There is a lot of confusion because, many times, the user does not know exactly how is prepared and thus from which monomer.**

# Poly(Ethylene Oxide) (PEO)

PEO has remarkable properties. Indeed, PEO is:

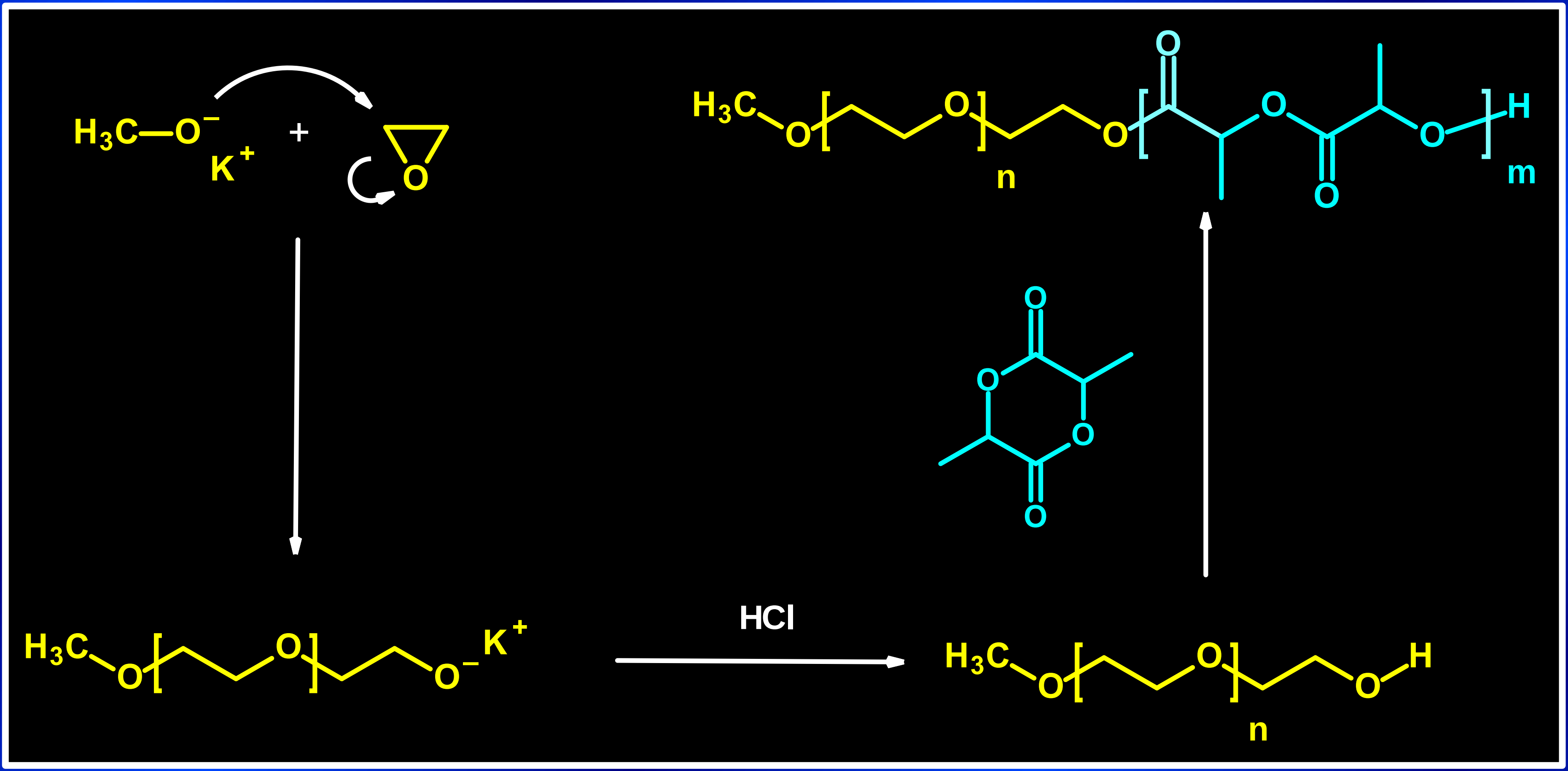
- flexible
- semi-crystalline.
- hydrosouble (which is not the usual rule for polyethers)
- biocompatible
- bioelliminable from the body
- protein-repellent



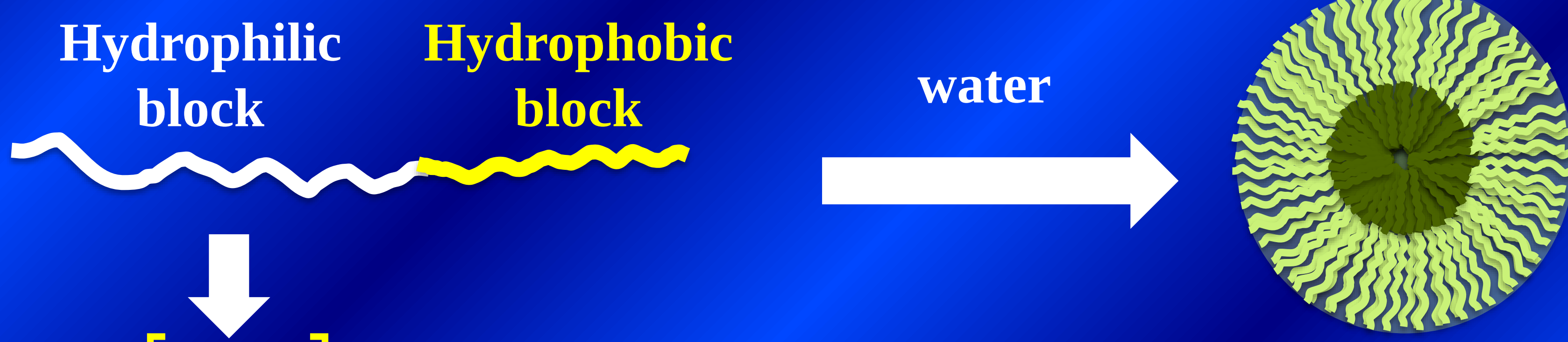
PEO is widely used for biomedical applications, for instance for the synthesis of stealthy micelles for drug delivery applications.

# PEO-*block*-Polylactide: Synthesis

**The monomethoxy-poly(ethylene oxide) (MeO-PEO-OH) is used as a macroinitiator for the ROP of lactide.**

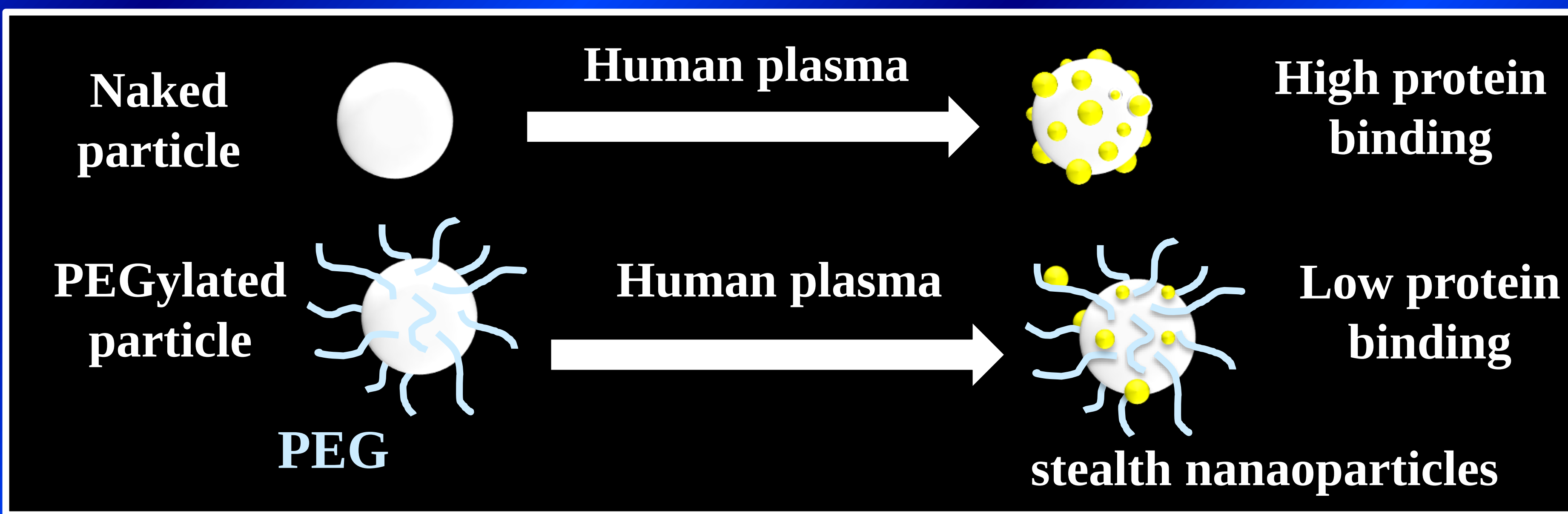


# PEO-*b*-Polyester Stealthy Nanoparticles

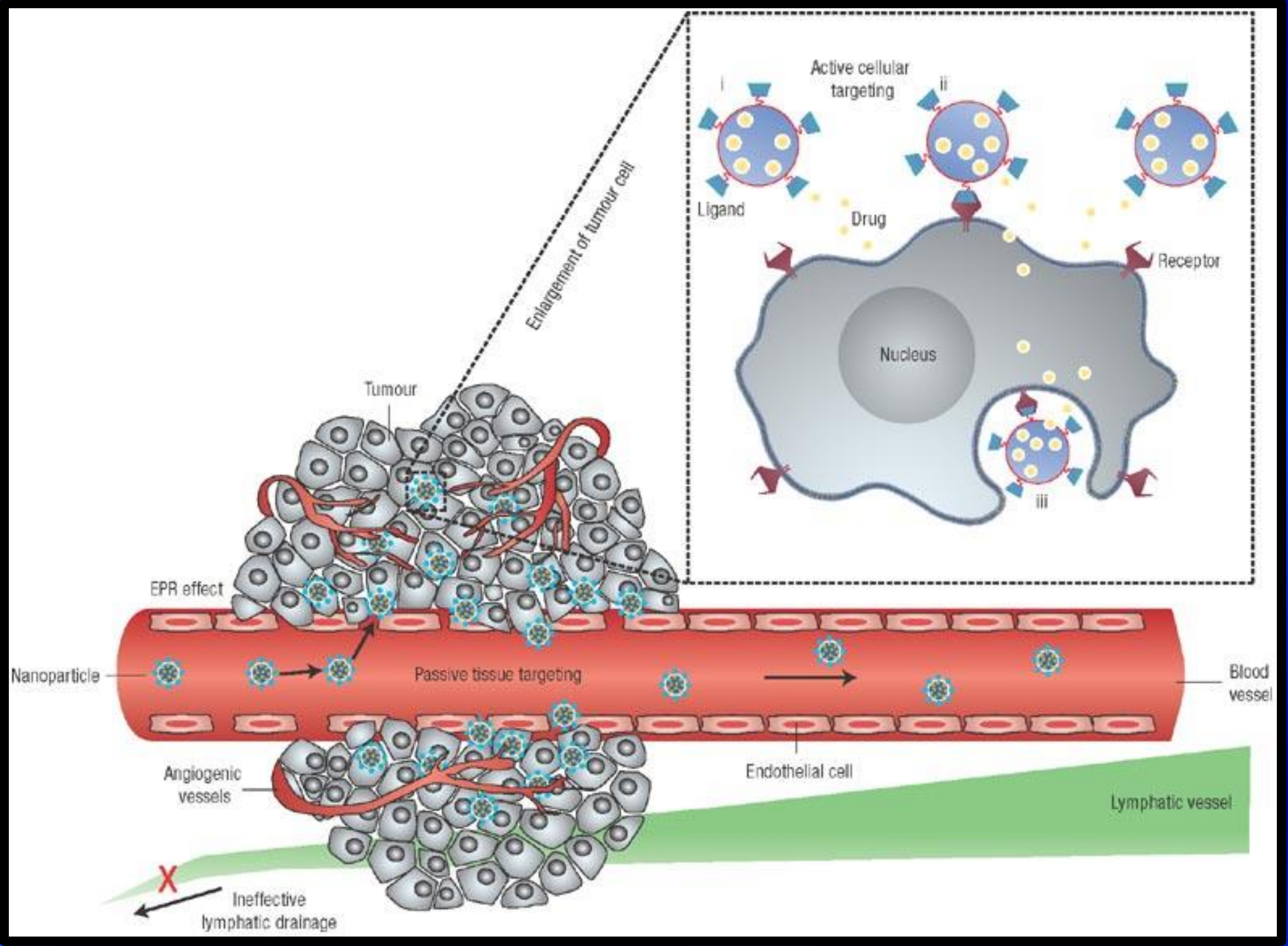



PEO
PEG


**PEO/PEG is soluble in water and has a low intrinsic toxicity that renders the polymer ideally suited for biomedical applications**



# Passive and Active Targeting



# Passive and Active Targeting

**Passive tissue targeting through the EPR effect: extravasation of nanoparticles through**

- **increased permeability of the tumour vasculature**
- **ineffective lymphatic drainage (retention effect).**

**Active cellular targeting:**

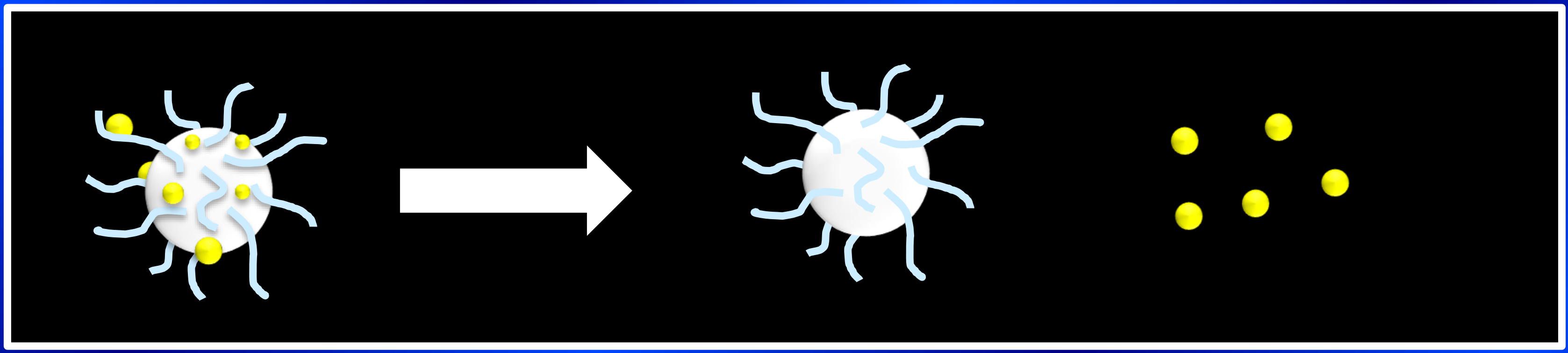
- **achieved by functionalizing the surface of nanoparticles with ligands that promote cell-specific recognition and binding.**

**When nanoparticles reach the organ to be treated, they can:**

- **release their contents in close proximity to the target cells;**
- **attach to the membrane of the cell and act as an extracellular sustained-release drug depot;**
- **internalize into the cell.**

# Drug Release

**Once the drug is transported to the organ to be treated, the drug has to be released from the core of the nanoparticle**



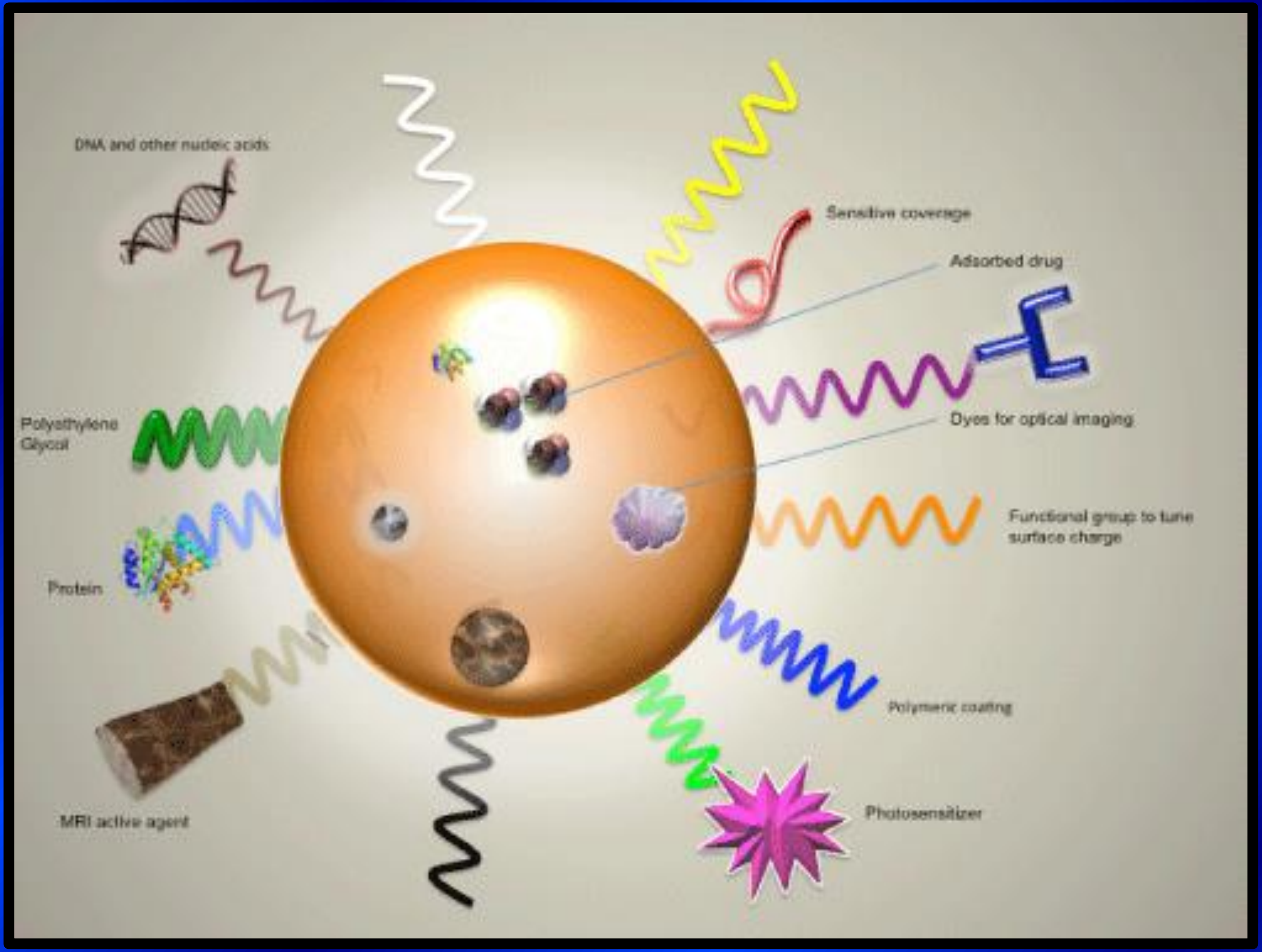
**The drug release can take place by**

- **simple diffusion of the drug out of the core of the nanoparticle**

- **Degradation of the (bio)degradable polyester according kinetics depending on the chemical structure of the polymer and on the environment (pH, temperature…).**

# Theranostic

**Theranostic nanomedicine focus on nanosystems, capable of diagnosis, drug delivery and monitoring of therapeutic response**



# Smart Nanoparticles

**One design the nanoparticles in such a way they are sensitive to a stimuli:**

- **Temperature**
- **pH**
- **Electrical field**
- **Magnetic field**

**The idea is to facilitate the release of the drug due to the presence of a given stimuli akin to the organ to treat (for instance: more acidic pH) or to an applied stimuli. Many research works are carried out at the time being.**

**Let us conclude that:**

**medicine = drug + excipients (polymer)**