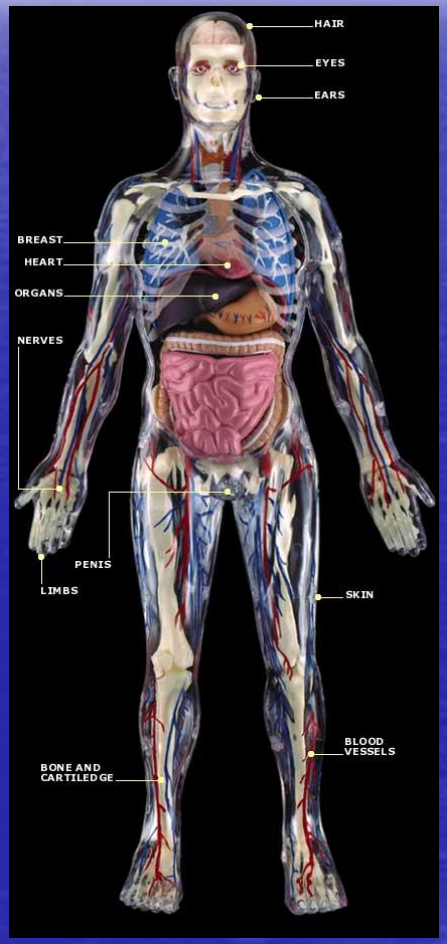
ΤΕΧΝΗΤΑ ΟΡΓΑΝΑ

- ΓΕΩΡΓΙΟΣ ΠΑ ΜΗΧΑΝΕΤΖΗΣ, ΕΔΙΠ

Εργαστήριο Εμβιομηχανικής κ Βιοϊατρικής Τεχνολογίας
Τμήμα Μηχανολόγων κ Αεροναυπηγών Μηχανικών
Πανεπιστήμιο Πατρών

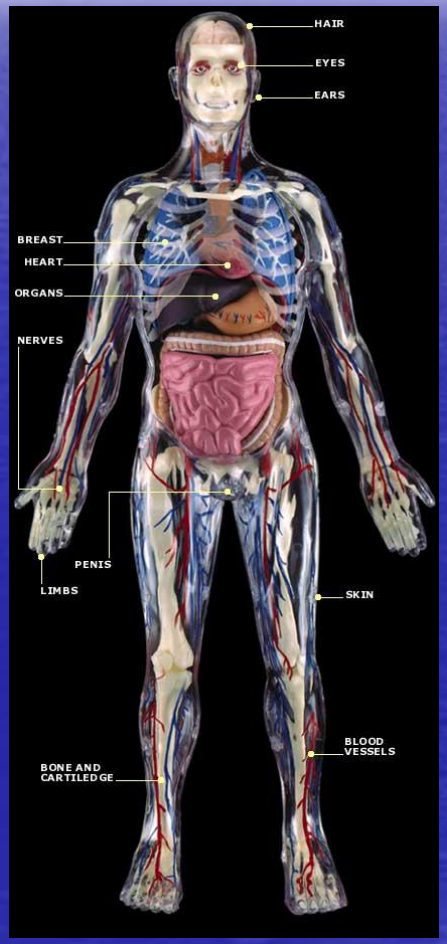
Artificial Organs

- Artificial organs fall into the area of assistive medical devices.
- They assist in making a patient s life better, sometimes the patient cannot live without them.



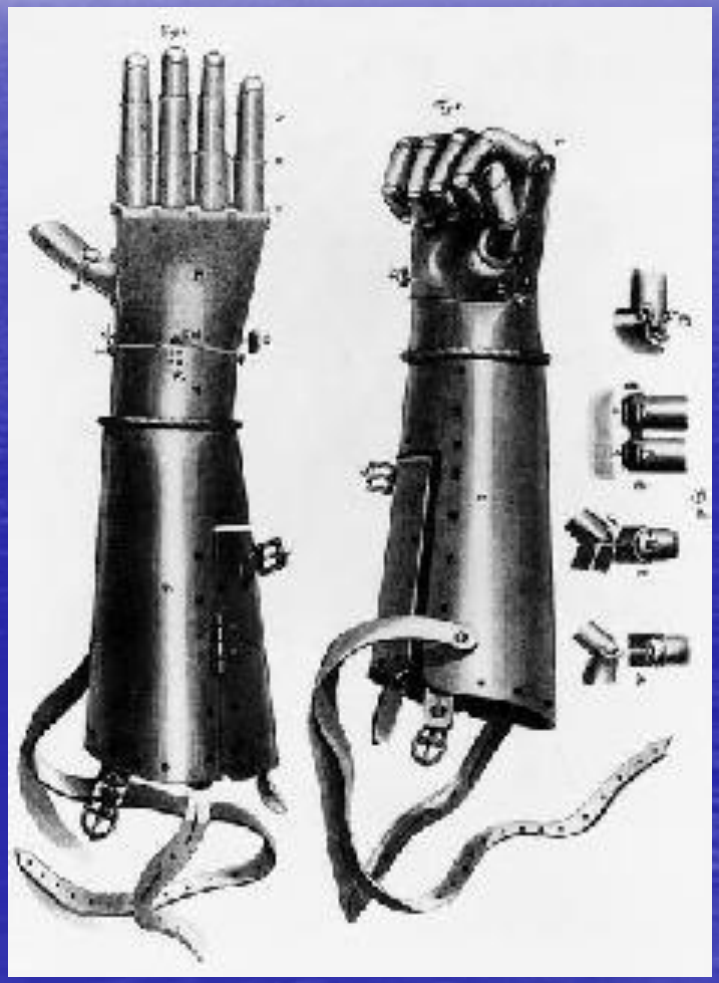
Artificial Organs

- The medical definition for an artificial organ is a man-made medical device integrated into a patient to replace a natural organ.



Prosthetic Limbs

- A person would need a prosthetic limb if they have an injury so severe that it requires amputation.
- Prosthetic limbs (or artificial limbs) have been around since 300 B.C.E.



Prosthetic Leg

- It replaces a leg amputated below the knee.
- Since the knee is retained, these amputees can regain normal leg movement faster than a transfemoral amputation.

Prosthetic leg (II)

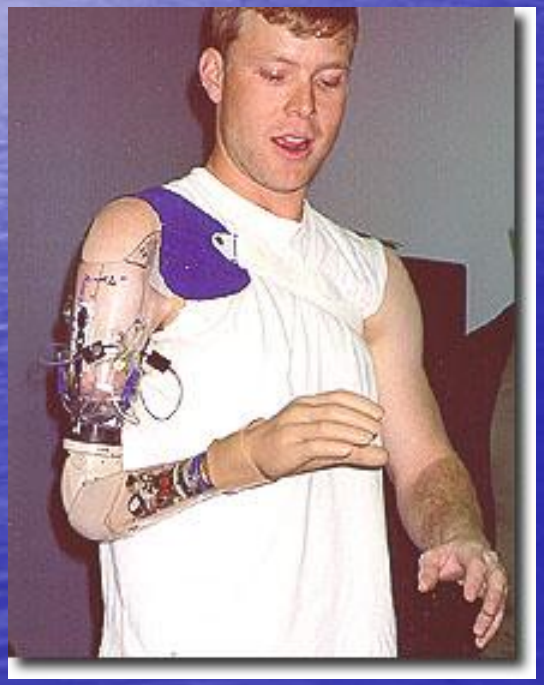
- This involves the replacement of a leg amputated above the knee.
- Since the knee is removed, the patient has major difficulty moving (use 80% more energy than a normal two legged walker!).
- Lots of occupational therapy is required

Prosthetic arm

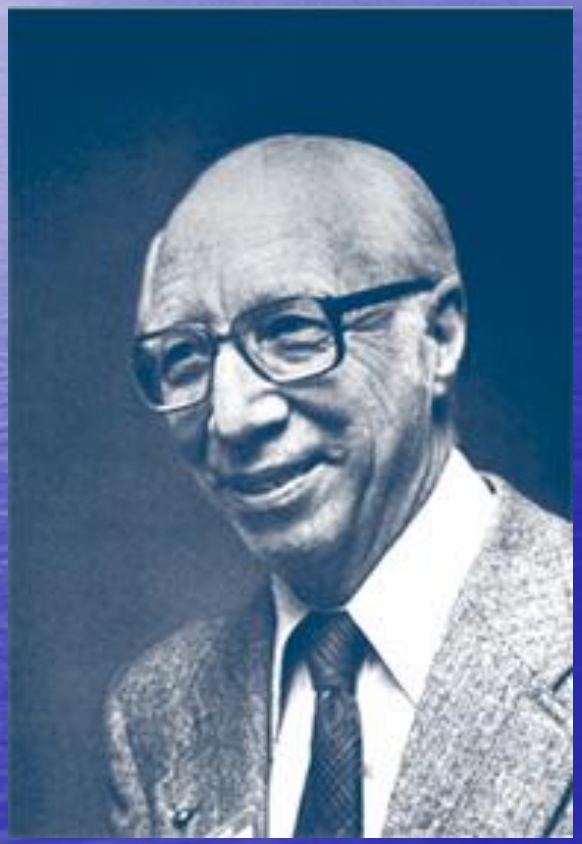
- Replaces an arm amputated below the elbow.
- Two types: cable operated and myoelectric.

Prosthetic arm (II)

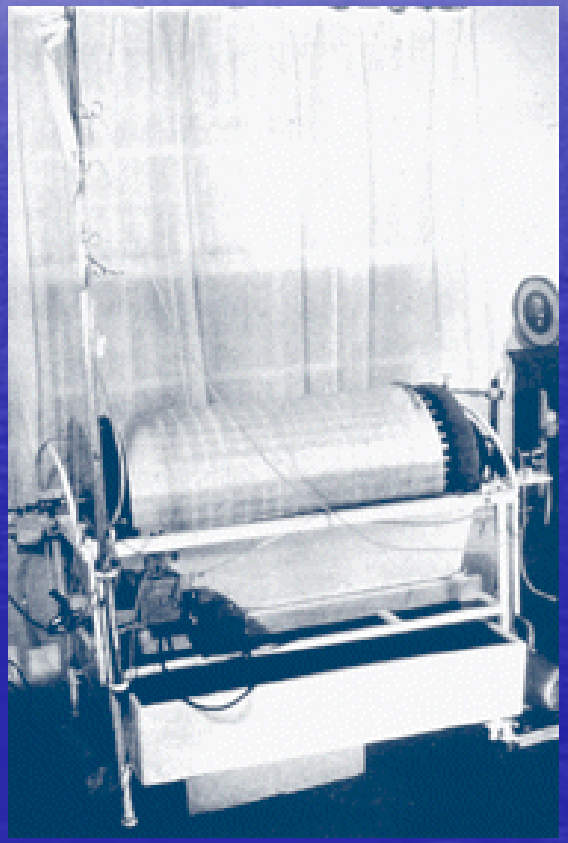
- Replaces an arm, amputated above the elbow.
- Since the elbow is gone, it is hard for these amputees to regain normal movement of the arm.
- Again, cable and myoelectric types.



1945: The first successful dialysis treatment

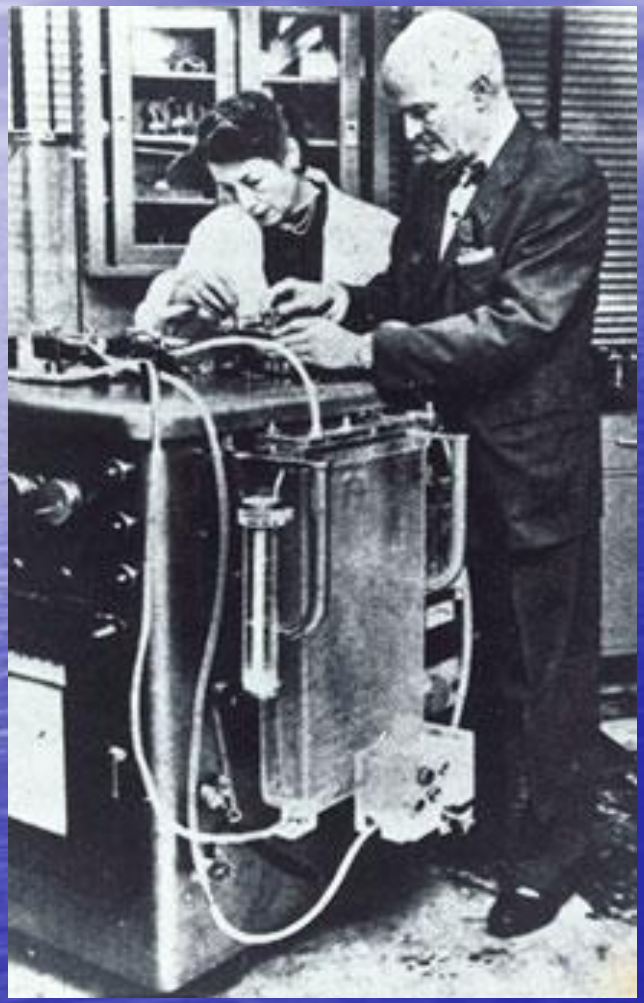


Willem Kolff



Kolff rotating drum kidney (1943)

1955: Gibbon's heart lung machine



John H. Gibbon, Mary H. Gibbon and heart-lung machine, u.d. (Art/Photo Collection, AG-054)

Artificial Heart

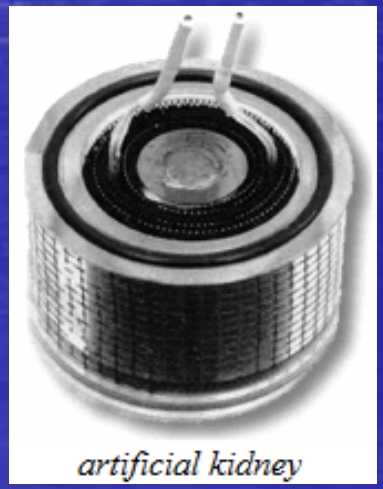
- The 1st artificial heart to be surgically implanted (Jarvik 7) into a human patient was in 1982.
- That patient lived for 112 days after.

Artificial kidney

How does it work ?

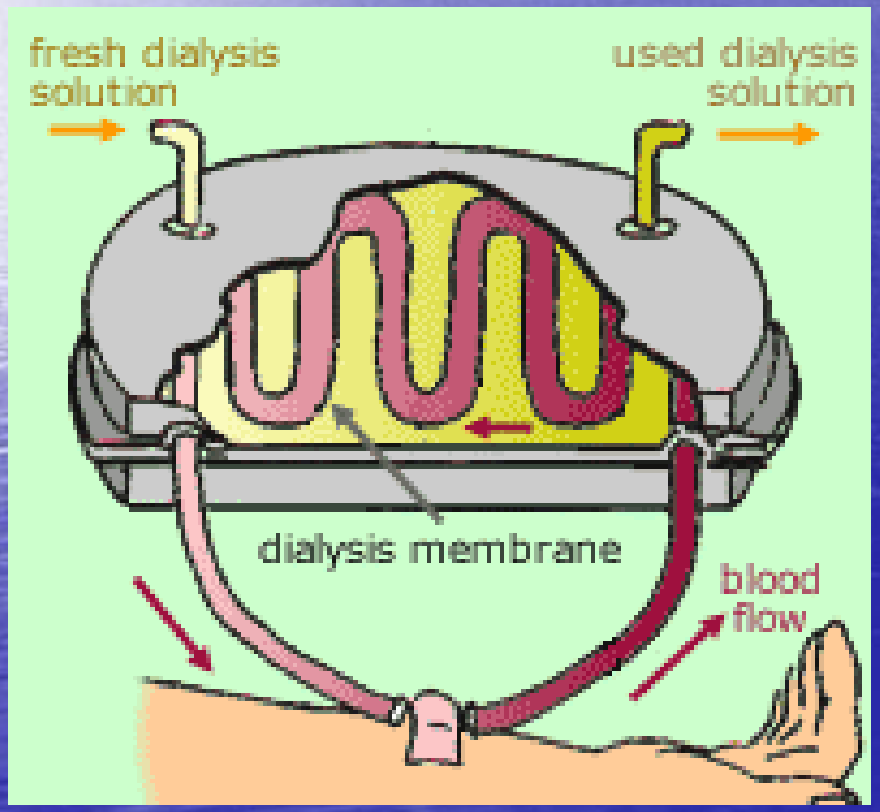
- The kidney removes waste material from the body, and when this is not achieved properly, the patient develops a kidney failure.

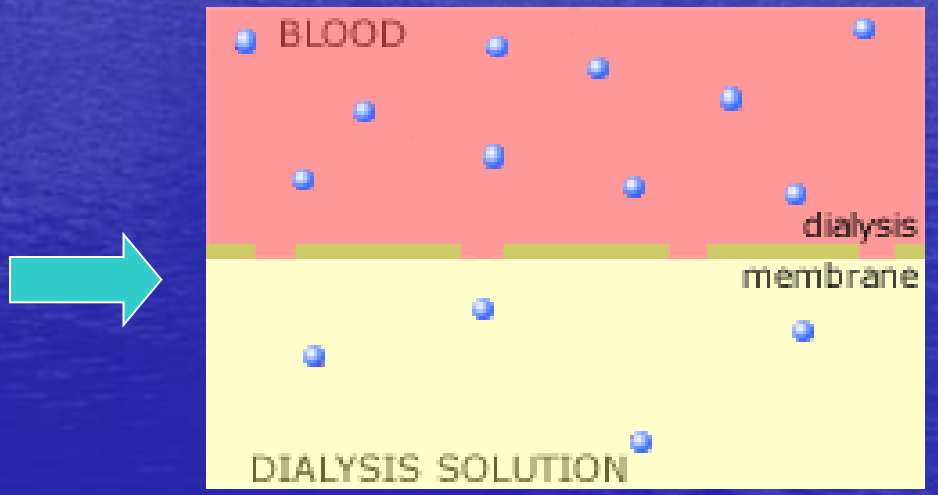
- The artificial kidney, or dialyzer, is a life support system designed to remove waste products from the patients body.



artificial kidney

How does it work ?





Dialysis machine

Artificial kidney

- The patient who undergoes a successful transplant can return to normal existence.
- Although a light work is preferable, there are no restrictions apart from taking drugs.
- Now, many patients with kidney failure stand a reasonable chance at a normal life with artificial kidney treatments and a well-matched transplant.

Artificial muscle

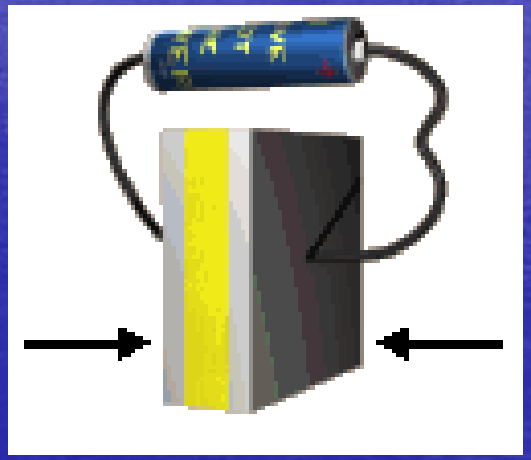
How does it work ?

- Polymer based artificial muscles may soon yield organs that work like real limbs.
- Polyacrylonitrile drastically contracts when its pH changes.
- The fibres are capable of holding four kilograms per square centimetre. A human biceps can lift a maximum of just over two kilograms per square centimetre.

Artificial muscle

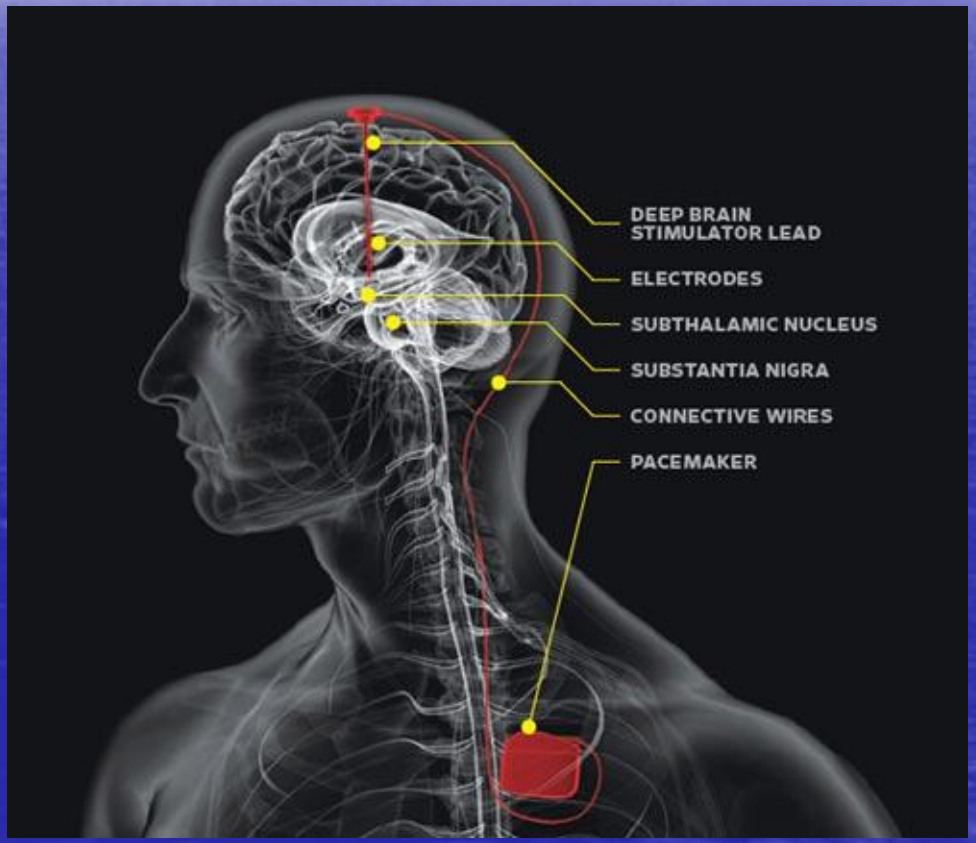
How does it work ?

- An electronically activated muscle will not dry or wear out over time.
- When electrodes are applied, the muscle contracts.
- Dielectric elastomers are still at a research level, but they have the potential to be produced at a low cost.



Brain Pacemaker

- These are inserted into the brain to send electrical signals used to stop things like depression, epilepsy and the tremors associated with Parkinson's.



Cochlear implants

- Implanted into the inner ear to improve hearing.

Where technology is going

- Some of the other possible artificial organs still in the testing phase include:
  - Artificial lungs
  - Artificial liver
  - Artificial eyes
  - Artificial pancreas
  - Artificial bone

BioArtificial Organs

What is the difference between Artificial and BioArtificial Organs?

Tissue Engineering

a) What is it?

b) How does it work?

c) Applications

What is it?

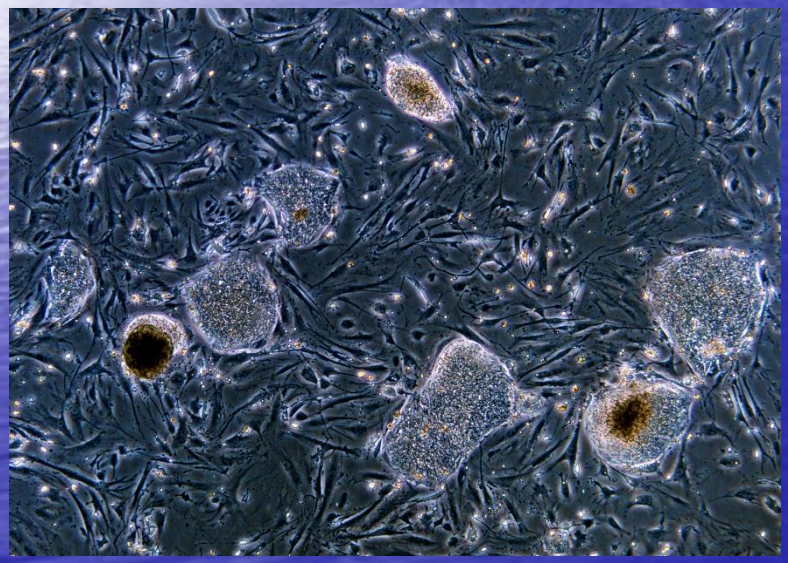
→ Regenerative Medecine

- New research field combining medicine, biology and engineering.
- Purposes: - to **regenerate**, repair or replace diseased tissues or organs **using living cells**.
  - find a new solution to the current problem of organ shortage and biomaterial failures**.**
- Applications: - skin, cartilage, bones diseases or injuries (ex: burns)
  - heart valves, blood vessels, corneas, ears, livers...

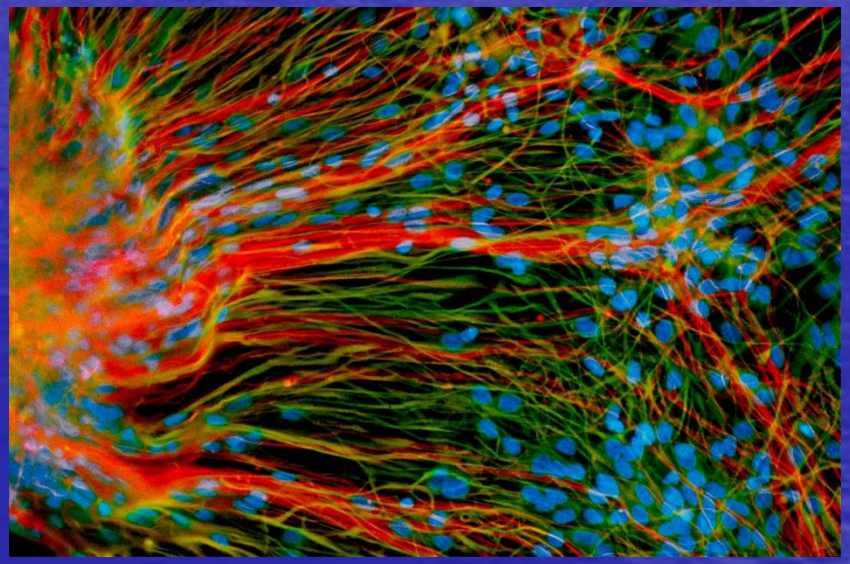
How does it work?

- Stem cells are able to generate every cell type in the body.

They may be used to create new tissues and organs.



View of a colony of undifferentiated human embryonic stems cells



Derived from human embryonic stem cells: mature neurons (red) and glial cells (green)

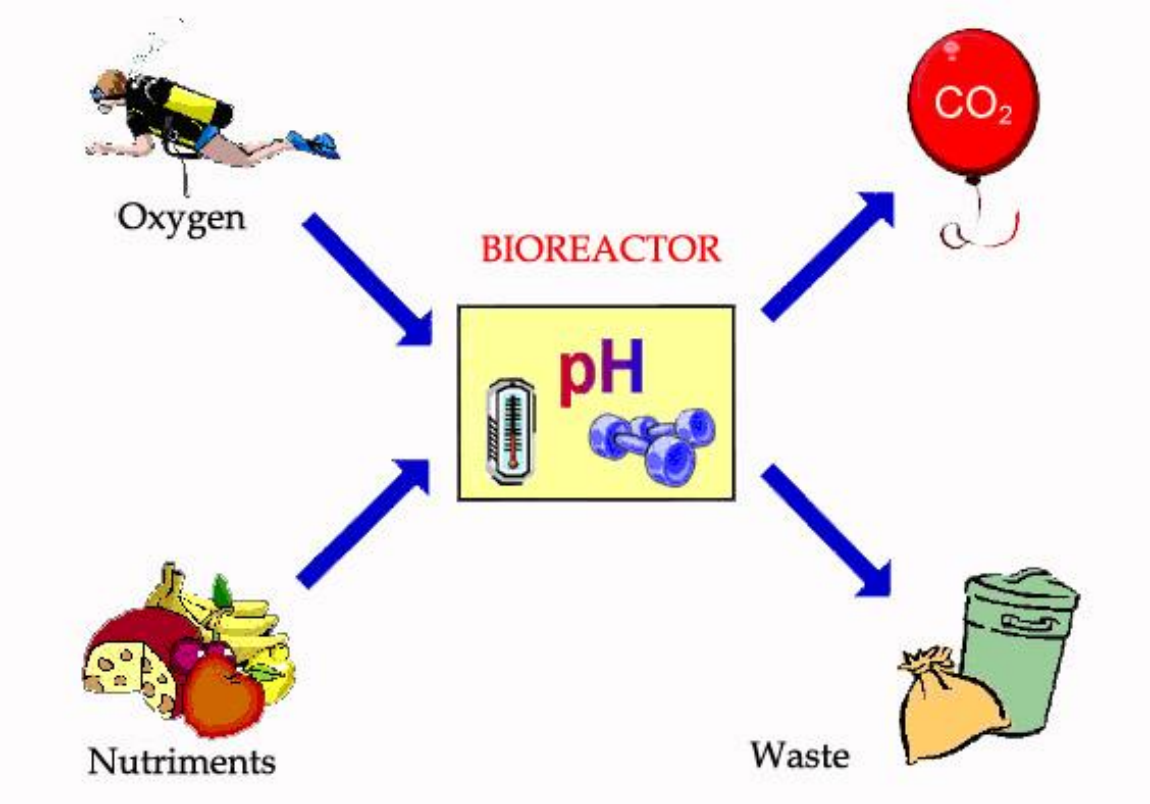
How does it work?

- To create an organ, cells need :

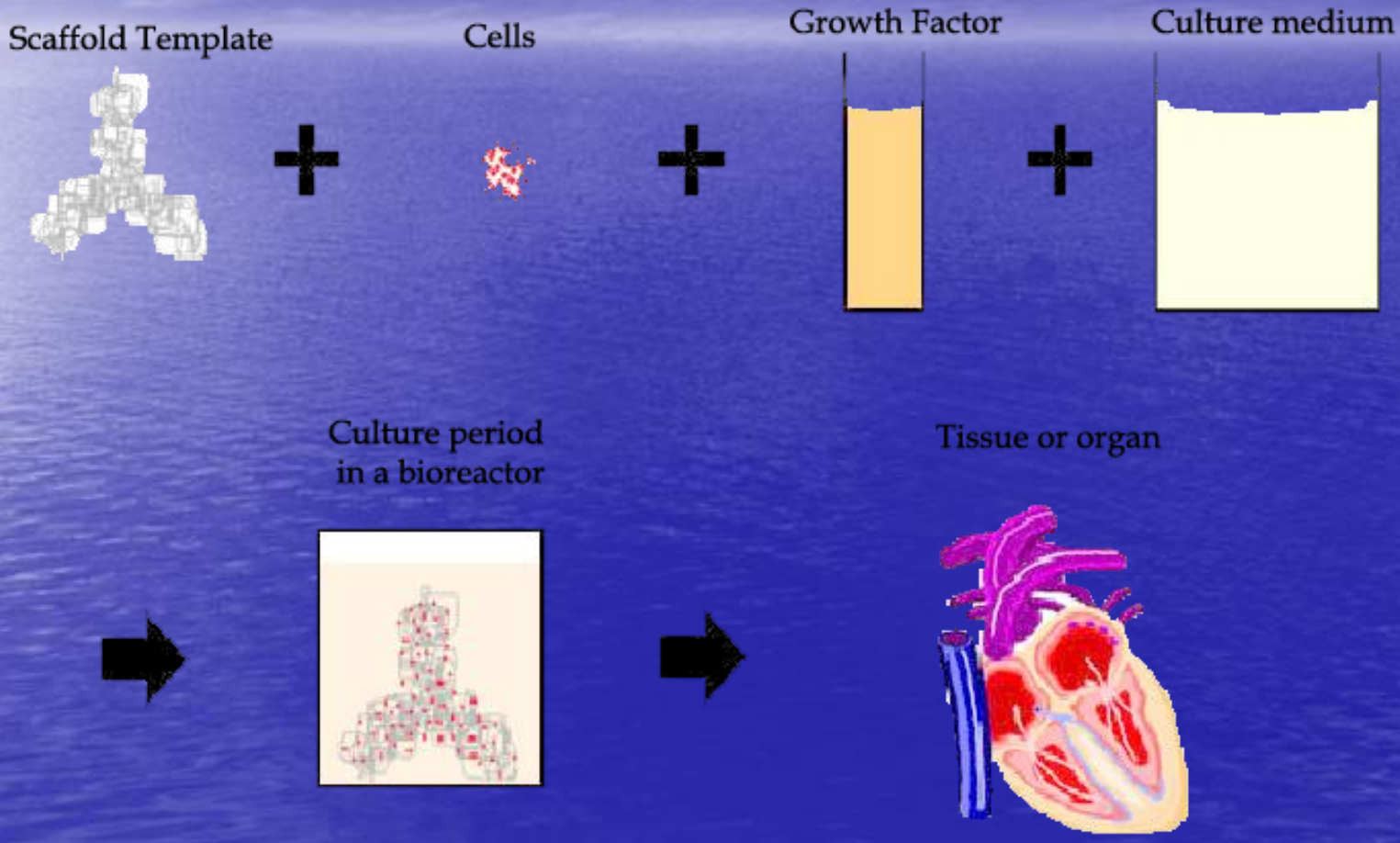
  - to be organised on a scaffold (= a structure)

Bioreactor

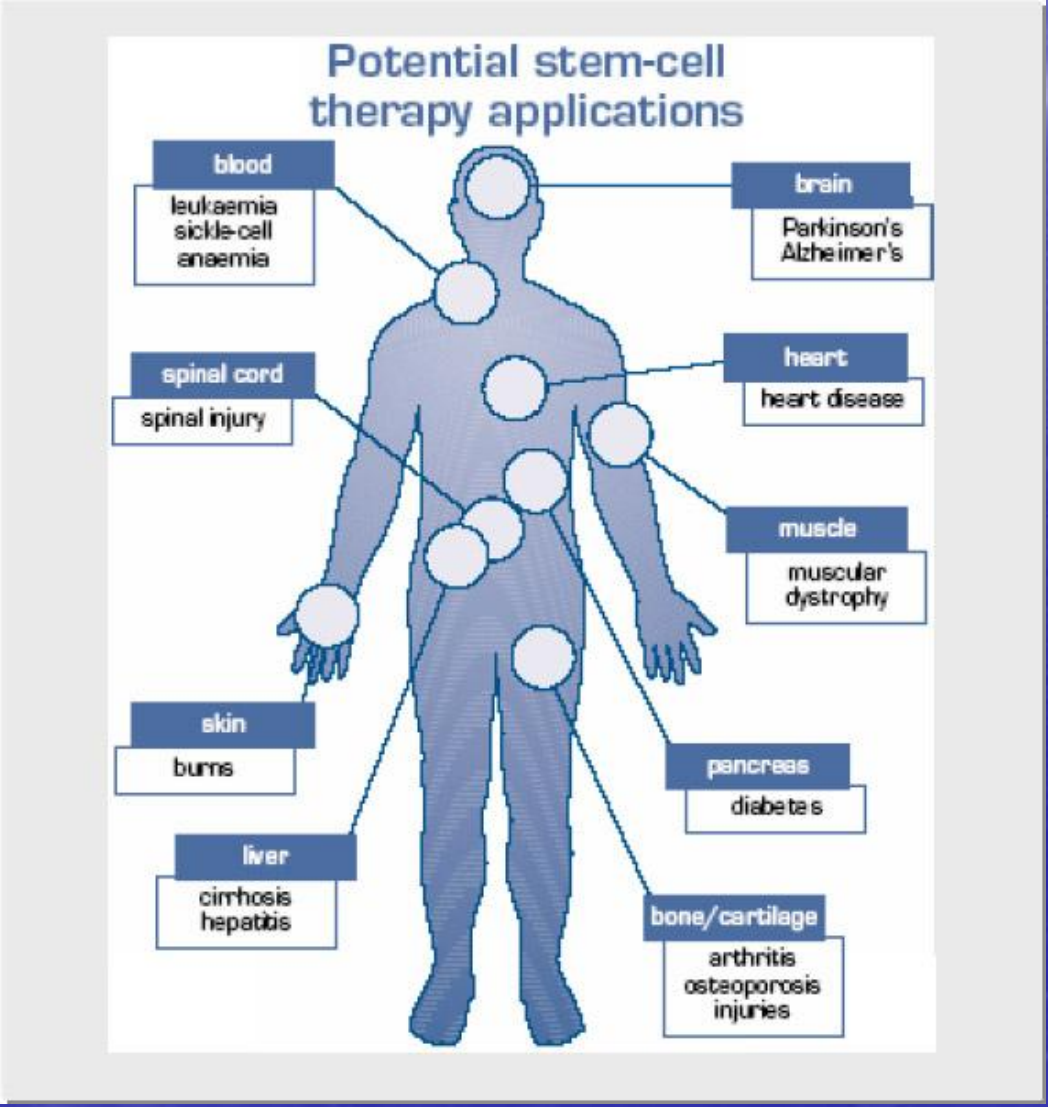
- to be placed in a culture medium with growth factor which will be placed in a bioreactor.



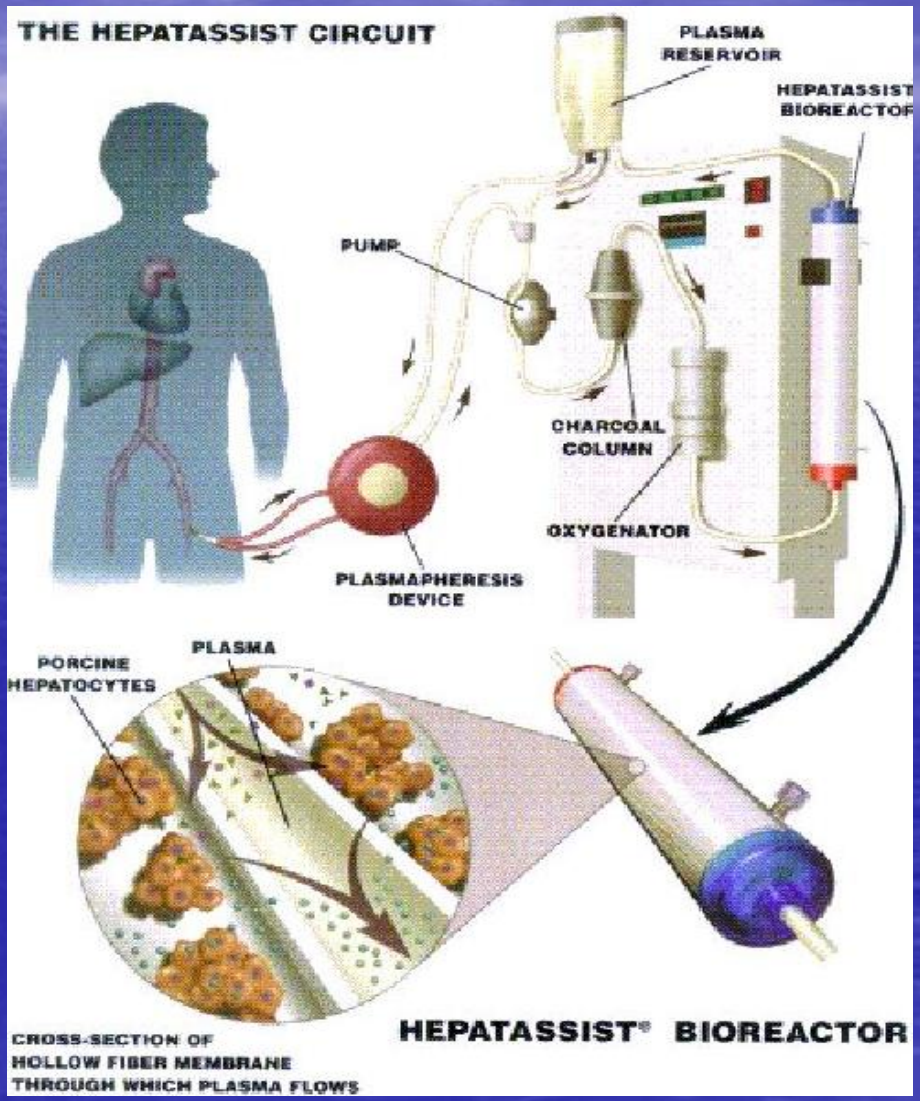
How does it work?



Applications

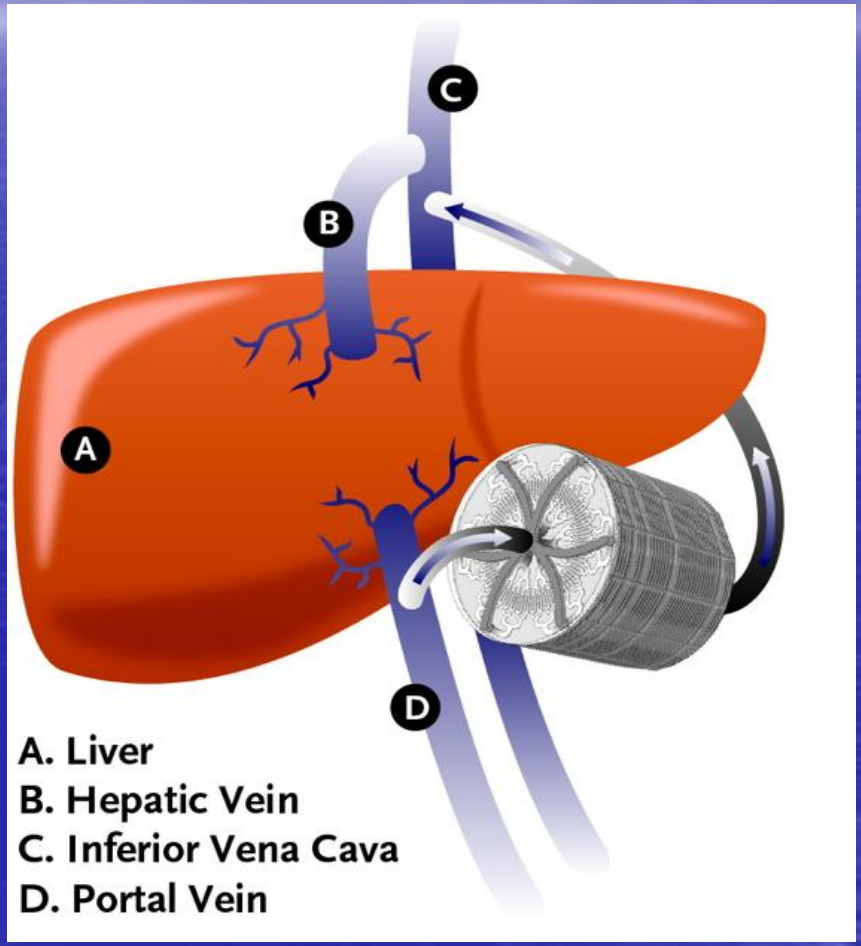


BioARTIFICIAL LIVER



Bio Engines Implantable BioArtificial Liver

- Designed to take place of a liver or a portion of the liver
- Polymer grid-like mesh used as artificial vasculature resembling that of an actual liver
- Patterned silicon wafers serve as molds for polymer sheets
- Currently being tested on pigs
- Clotting issues



Challenges

- Bio-artificial livers should be able to provide at least 10% of liver functioning
  - This requires approximately 10^{10} hepatocytes
- Controversy over the use of porcine cells due to possible transmission of infections
- Hepatocytes and plasma have very different physio-chemical properties
  - Hepatocytes do not perform well when in contact with plasma
  - Have a very high oxygen uptake rate
- Hepatocyte cells undergo a lot of stress inside of bio-artificial liver
  - Any stress above 5 dyn/cm^2 renders cells useless
- Limited volume of the bioreactor
  - maximum blood/plasma that can be safely drawn out of liver failure patient is one liter
  - Difficult to achieve 10% of liver functioning within 1 liter
- Makes Bio-artificial liver designing very difficult

Artificial pancreas

How does it work ?

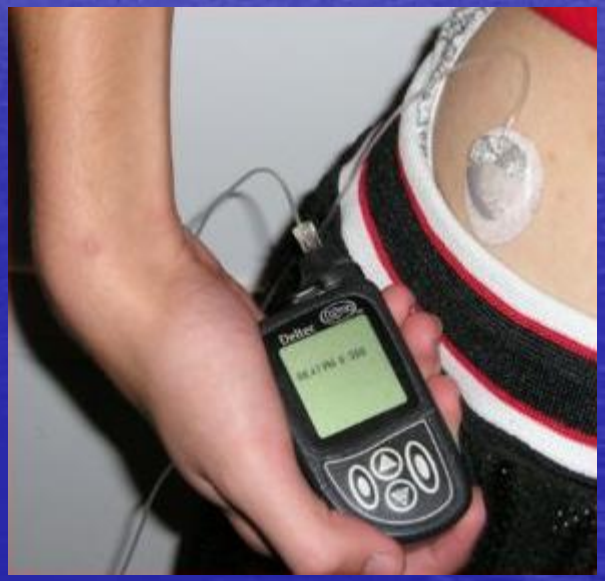
- The artificial pancreas is a promising technology in development to help diabetic persons automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.

- There are two approaches : the medical equipment approach and the bio-engeenering approach.

Artificial pancreas

The medical equipment approach

- In type 1 diabetes, insulin-producing cells in the pancreas are killed by the body's own immune system.
- The prototype system comprises : a glucose sensor, a handheld computer, and an insulin pump.



Artificial pancreas

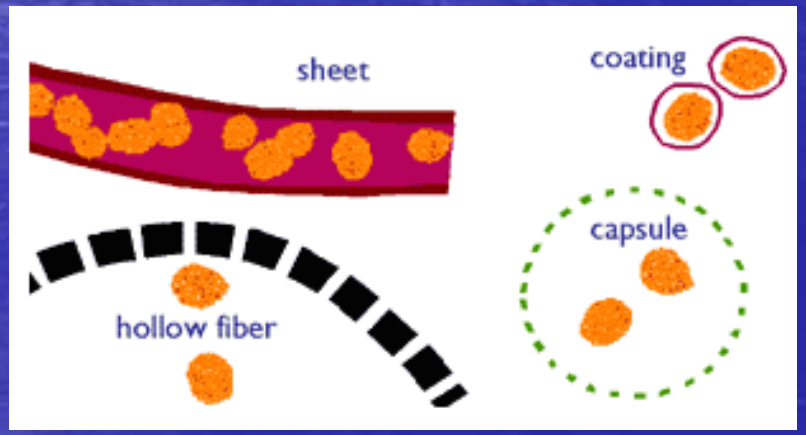
Drawbacks :

- The implantable sensor is inserted into a neck vein leading to the heart.
- The sensor accurately measures glucose in 95% of cases.
- The sensors stop working after an average of nine months.
- The mathematical programs needs to be refined.

Artificial pancreas

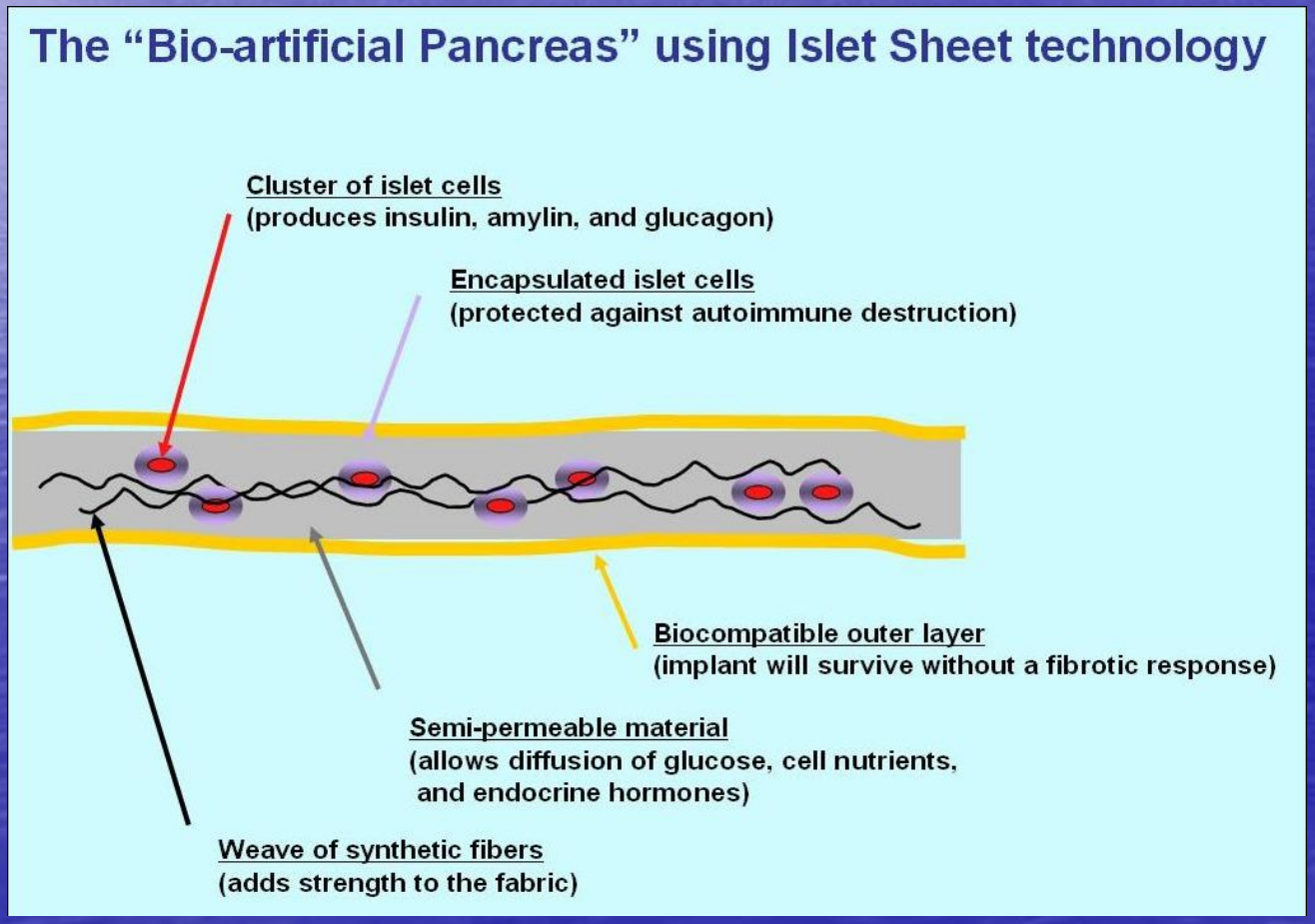
The bio-engineering approach

- Bio-artificial pancreas designs come in four physical types : hollow fibers, capsules, coatings and sheets.



Artificial pancreas

The bio-engeenering approach



LABORATORY of BIOMECHANICS and BIOMEDICAL TECHNOLOGY

Dept of Mechanical Engineering and Aeronautics
University of Patras, Patras, GREECE

EXPERIMENTS AND APPLICATION OF COMPUTATIONAL FLUID DYNAMICS IN THE DESIGNING OF A HEPARIN-ADSORBING DEVICE (H.-A.D.)

By
A.K.M. Podias and Y.F. Missirlis

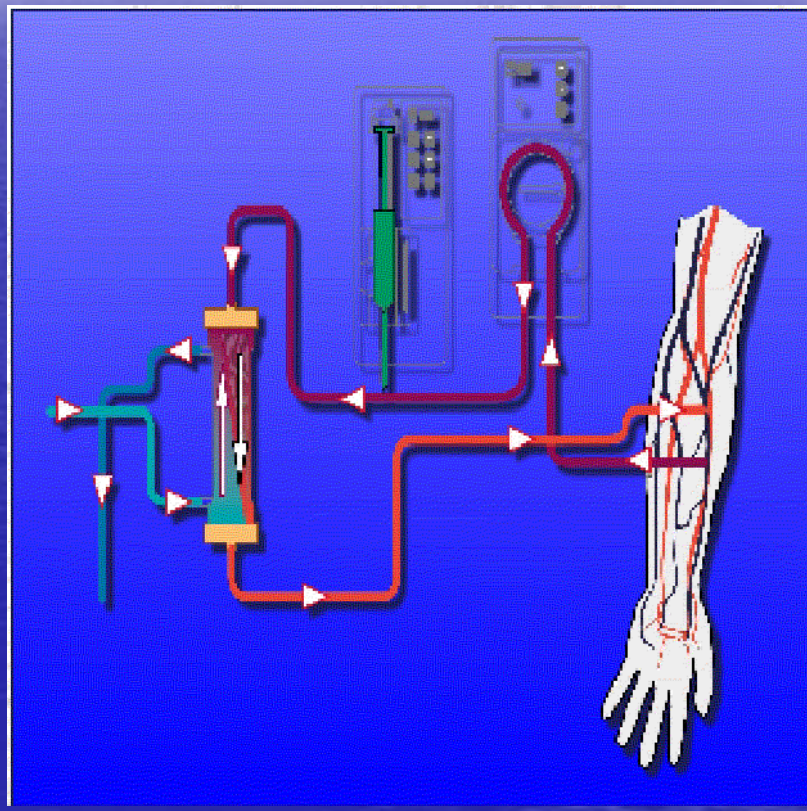
Biomedical Engineering Laboratory
Mechanical Engineering & Aeronautics Department
University of Patras, Ellas

BRITE EURAM II project No. 7516

Motivation of the present study

- There is a need to heparinize patients undergoing extracorporeal therapy (Artificial kidney, Pump Oxygenator). Many of them are incapable of sustaining any of the heparin because given its permanent bleeding condition it often leads to haemorrhagic complications.

- There is a definite need for heparin elimination just before heparinized blood returns to the patient's circulation.



Heparin-Adsorbing Device Concept

- It is our intention to contribute in such a way by the development of a heparin-adsorbing device (H.-A.D.), located at the effluent of the extracorporeal haemodialysis filter unit, just before blood returns to the patient

- This H.-A.D. operates as a liquid-solid particulate fluidized bed, and constitutes an extracorporeal circuit that allows ex vivo deheparinization by means of a polycationic ligand that binds heparin molecules

Objectives

- The experimental evaluation of the fluid mechanical characteristics involved in the fluidization process
- The experimental evaluation of the heparin adsorption kinetics during fluidization
- The development of a mathematical model to describe heparin transport & its removal by the dispersed polymeric particles contained in the heparin-adsorbing device

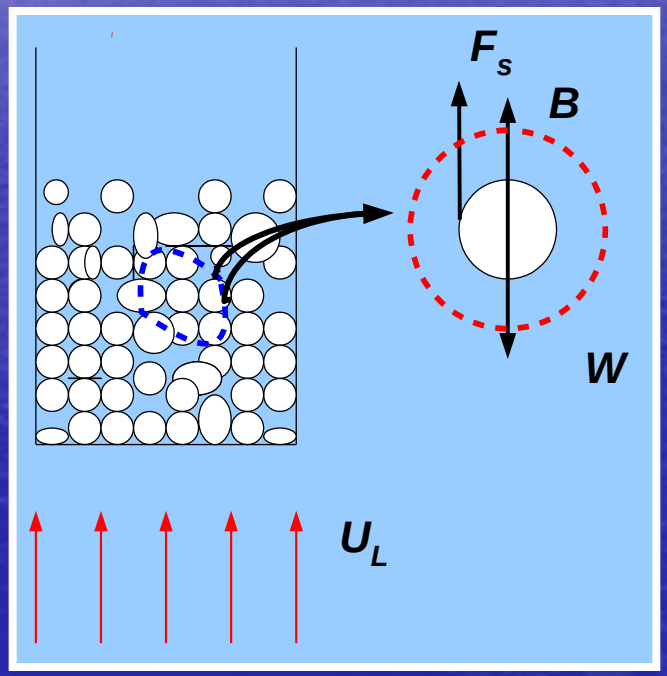
Examined parameters

- Particle size distribution
- Particle configurations with respect to the polysaccharide layers and the surface grafted poly (amido-amine) (PAA), as well as, to the rigid core of the examined beads
- Fluidized Bed Design characteristics

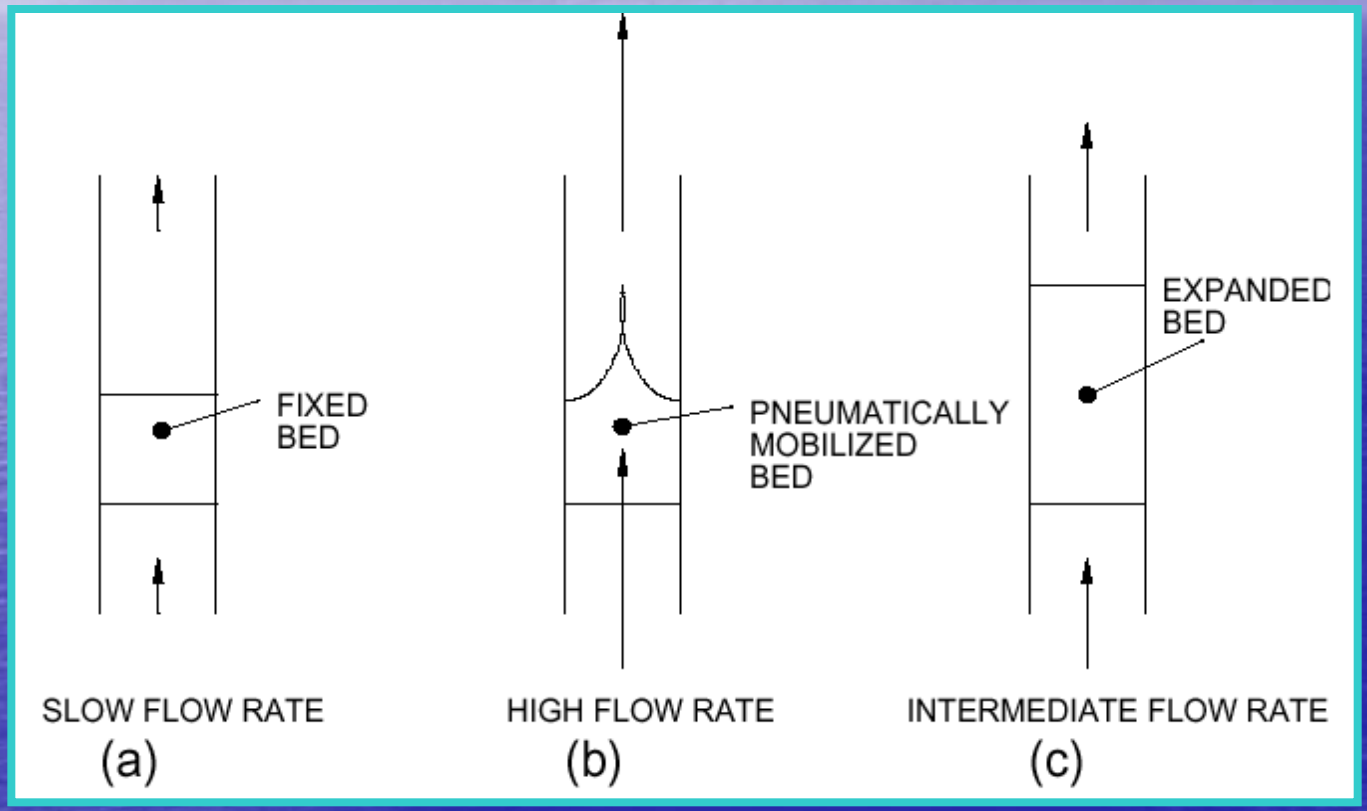
  One Columnar (CFB) and two Tapered (TFB) Fluidized Beds with angle of tapering, θ, 5° and 10° were used for that purpose

What is a Liquid-Solid Fluidized Bed ? When is the Fluidization regime established ?

- A fluidized bed is formed when the particles in the bed are in dynamic equilibrium. The gravitational force pulls the particles downward, whereas the fluid drag force and the buoyancy force are exerted in the upward direction (*Davidson and Harrison*, (1971).
- This drag force is constant at any position within a CFB of uniform particles, whereas it decreases in the upward direction when TFB is considered, as the superficial velocity of the fluid decreases also.
- The particle phase is comprised of Biosil-Dextran-Poly(amido amine) particles, whose diameters ranged from 125 to 1000 *μm*. The liquid phase is a saline solution or the heparinized whole human blood.



Fixed – Mobilized – Expanded Beds

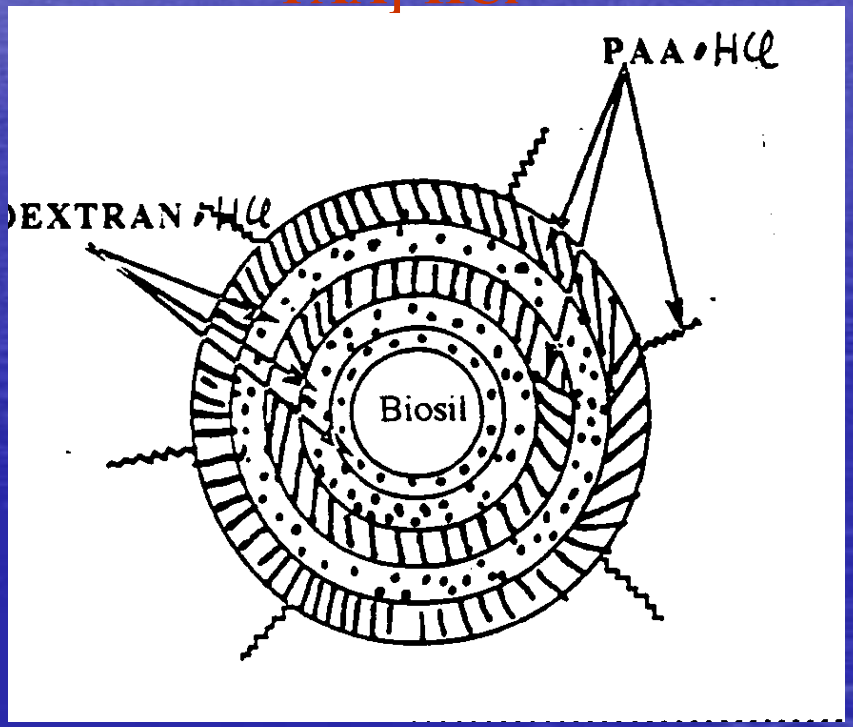


Experimental part
Materials and methods

- Polymeric particles……..

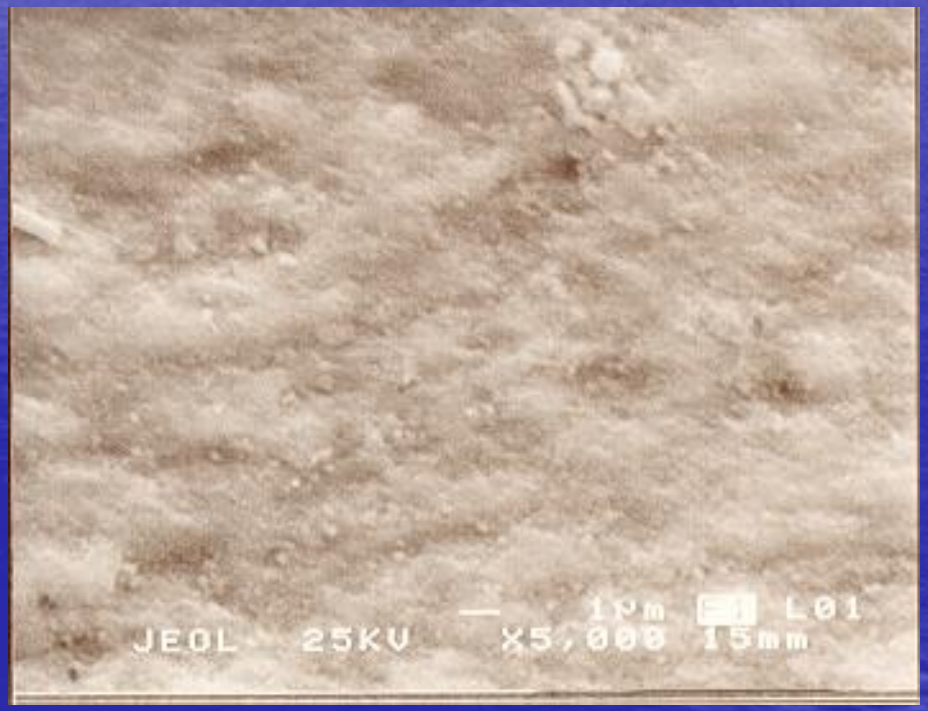
A=Biosil-NH2;
B=Biosil-Dextran;
C=Biosil-OH;
D=Biosil-DextranT70-NH_2;
E=Biosil-[Dextran-PAA-Dextran-PAA]-HCl;
F=Biosil-[Dextran-PAA]-HCl;
G=Glass Beads-OH;
H=Glass Beads-DextranT10-500;
I=Glass Beads-Dextran-NH_2-500;
J=Controlled Porous Glass beads;
K=Chromosorb-aw-DextranT10-300

E=Biosil-[Dextran-PAA-Dextran-PAA]-HCl

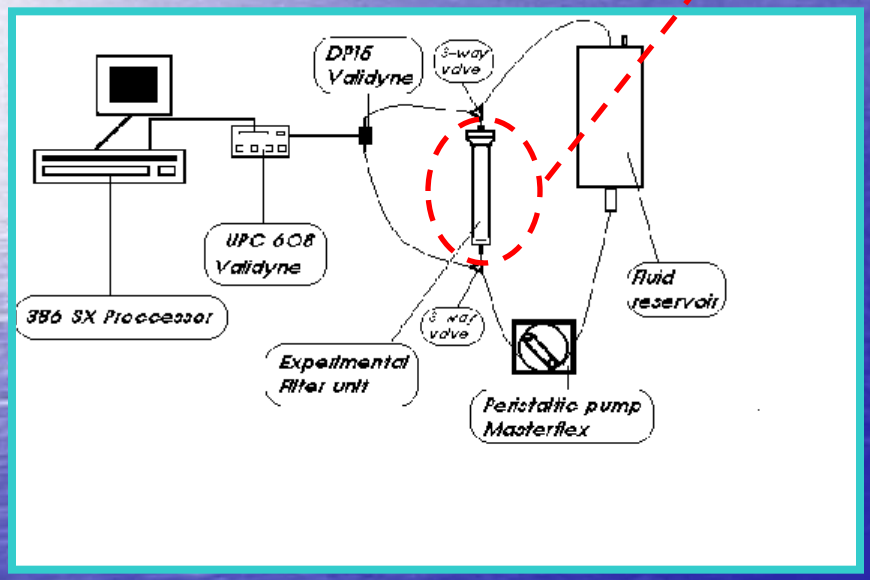


E=Biosil-[Dextran-PAA-Dextran-PAA]-HCl beads

Optical microscopic and SEM images

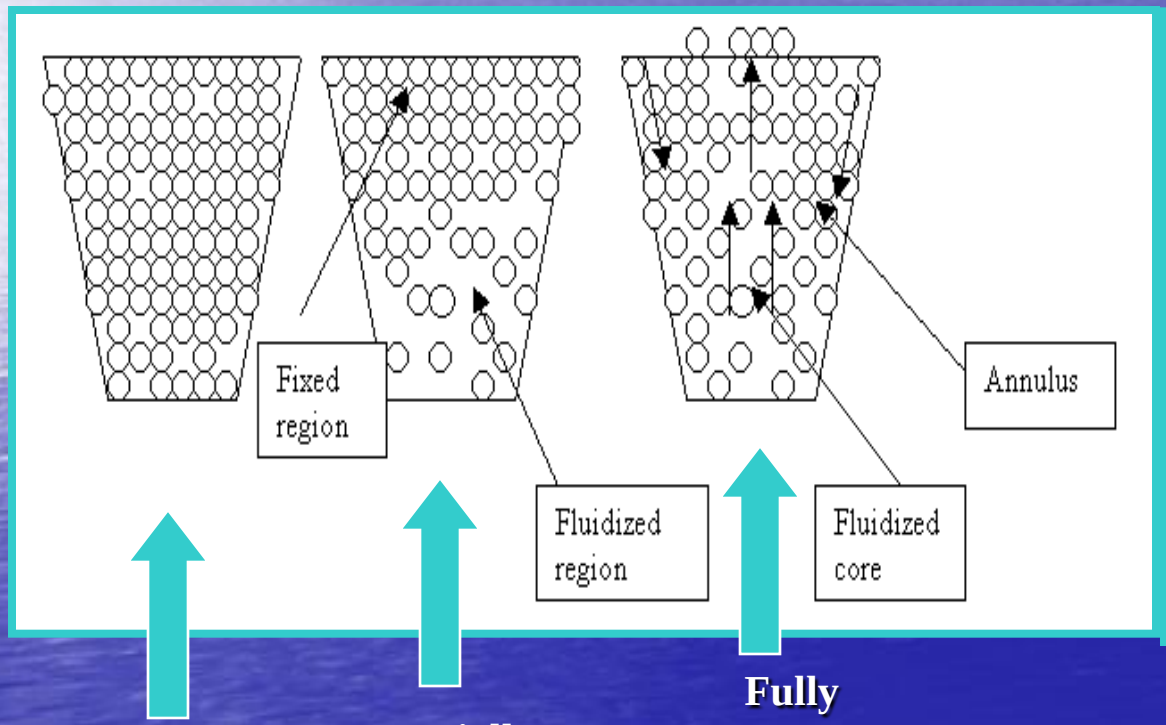


Experimental set-up and the fluidized bed adsorbers used



- Columnar Bed
- Tapered Bed ($\theta=5^{o}$)
- Tapered Bed ($\theta=10^{o}$)

Tapered Fluidized Bed flow regimes & Typical pressure drop results



Fixed bed

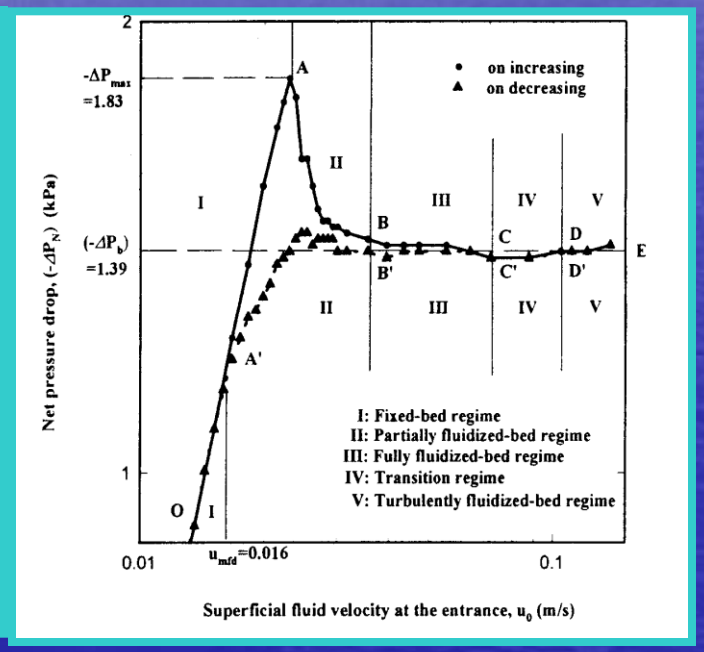
O-A; A'-O

Partially Fluidized bed

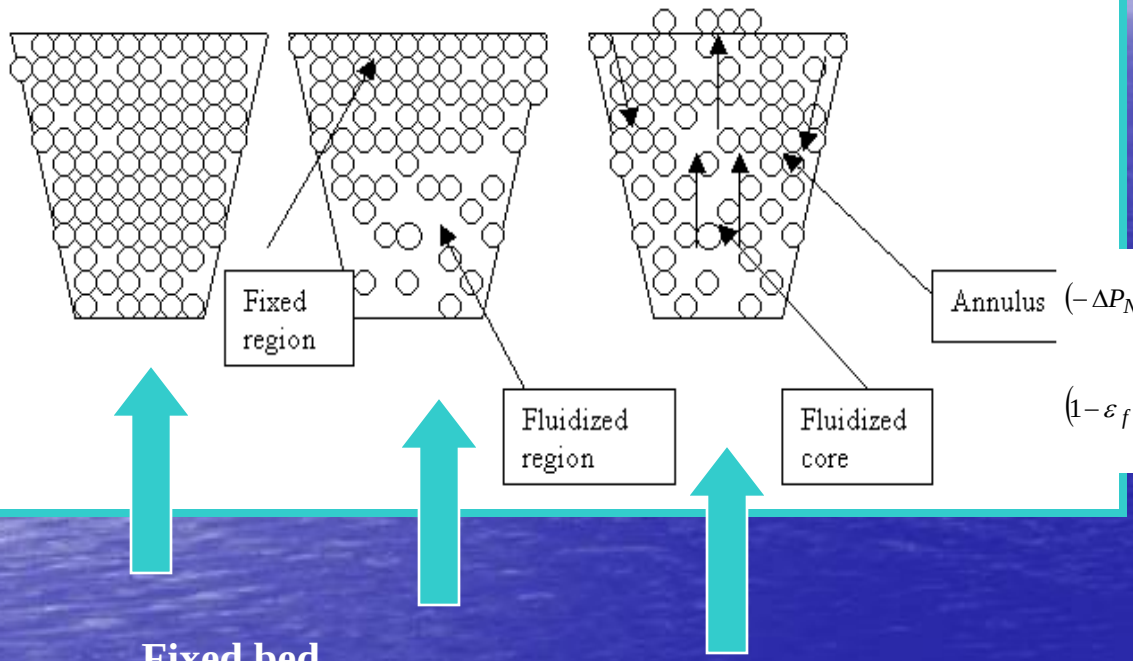
A-B; A'-B'

Fully Fluidized bed

B-C; B-C'



Calculations at the different flow regimes



$$(-\Delta P_N) = C_1 H \frac{D_0}{D} U_0 + C_2 H \frac{D_0\left(D_0{}^2 + D_0 D + D^2\right)}{3D^3} U_0{}^2 + \frac{1}{2}\left(\frac{U_0}{\varepsilon_0}\right)^2 \left[\left(\frac{D_0}{D}\right)^4 - 1\right]\rho_f$$

$$(-\Delta P_N) = C_1 (H - H_b) \frac{D_0^2}{D D_b} U_0 + C_2 (H - H_b) \frac{D_0^4\left(D_b{}^2 + D_b D + D^2\right)}{3D^3 D_b^3} U_0{}^2 + (1-\varepsilon_f)(\rho_s - \rho_f) g H_b + \frac{1}{2} U_0^2 \left[\left(\frac{1}{\varepsilon_0}\right)^2 \left(\frac{D_0}{D}\right)^4 - \left(\frac{1}{\varepsilon_f}\right)^2\right]\rho_f$$

$$(-\Delta P_N) = (1-\varepsilon_{mf})(\rho_s - \rho_f) g H + \frac{1}{2}\left(\frac{U_0}{\varepsilon_{mf}}\right)^2 \left[\left(\frac{D_0}{D}\right)^4 - 1\right]\rho_f$$

Fixed bed

Partially Fluidized bed

Fully Fluidized bed

Columnar Fluidized Bed experiment

Characteristic fluidization velocities and pressure drop

Particle Properties	**ρ_s=1990 Kg/m^3 // d_p=600 µm // φ_s=0.86 TFB [D_o=17 mm, D=26 mm, H=52 mm, θ=10^o, ε_o=0.38]**			
Fluidization Parameters	$U_1 x10^3$ m/s	$U_{mf} x10^3$ m/s	$U_2 x10^3$ m/s	$(-\Delta P_{max})$ Pa	$(-\Delta P_{mf})$ Pa
Blood ρ=1056 kg/m^3 μ=3.45 mPa s	0.525	0.757	0.324	406.10	308.62
PBS ρ=999 kg/m^3 μ=1.01 mPa s	2.0	3.0	1.0	390.78	331.82
Particle Properties	ρ_s=1990 Kg/m^3 // d_p=600 µm // φ_s=0.86 CFB [D=26 mm, H=52 mm, ε_o=0.38]			
Fluidization Parameters	$U_1 x10^3$ m/s	$U_{mf} x10^3$ m/s	$U_2 x10^3$ m/s	$(-\Delta P_{max})$ Pa	$(-\Delta P_{mf})$ Pa
Blood ρ=1056 kg/m^3 μ=3.45 mPa s	0.323	0.323	0.323	382.68	308.62
PBS ρ=999 kg/m^3 μ=1.01 mPa s	1.0	1.0	1.0	341.91	331.82

Experimental Observations & Conclusions

- Comparison of the pressure drop / flow rate (or velocity) curves for fluidization and the reverse process (de-fluidization) suggests that the operation of liquid / solid tapered fluidized beds is history dependent.
- The occurrence of hysteresis is inevitable in a TFB. It is observed that the pressure drop peaks at the minimum velocity of partial fluidization. The magnitude of $(-\Delta P_{max})$ far exceeds the pressure drop under fully fluidized conditions.
- It is shown that this excess increases as the tapering angle, θ, increases.

Experimental Observations & Conclusions

- An indicative feature of the TFB, especially an advantage over the CFB is that, the velocity of the fluidizing medium is relatively high at its lower part ensuring fluidization of large particles, and it is relatively low at the top, preventing entrainment of the particles. So, we can operate the TFB with particles whose size distribution is wide.
- **When blood used as the flowing medium, fluidization regime has reached at lower velocities with increased pressure drop compared to saline-polymeric particles experiments, for all three fluidized beds used in our study.**

Biomedical applications of the presented numerical study

- The deposition of cells onto surfaces in biological processes.
- The controlled release of drugs.
- The elimination of hazardous substances in, or from biological fluid streams.
- The adsorption of plasma proteins on to particles with specific ligands in therapeutic or preparative aphaeresis.

Standards in Biomaterials Testing
Set of documents 10993 (FDA's version #G95-1):

- 10993-1: "Guidance on Selection of Tests."
- 10993-2: "Animal Welfare Requirements."
- 10993-3: "Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity."
- 10993-4: "Selection of Tests for Interactions with Blood."
- 10993-5: "Tests for Cytotoxicity—In Vitro Methods."
- 10993-6: "Tests for Local Effects after Implantation."
- 10993-7: "Ethylene Oxide Sterilization Residuals."
- 10993-9: "Degradation of Materials Related to Biological Testing."
- 10993-10: "Tests for Irritation and Sensitization."
- 10993-11: "Tests for Systemic Toxicity."
- 10993-14: "Materials Evaluation."

Haemocompatibility Testing of Membranes Developed for BioArtificial Organs Applications

Georgios PA Michanetzis and Yannis F Missirlis

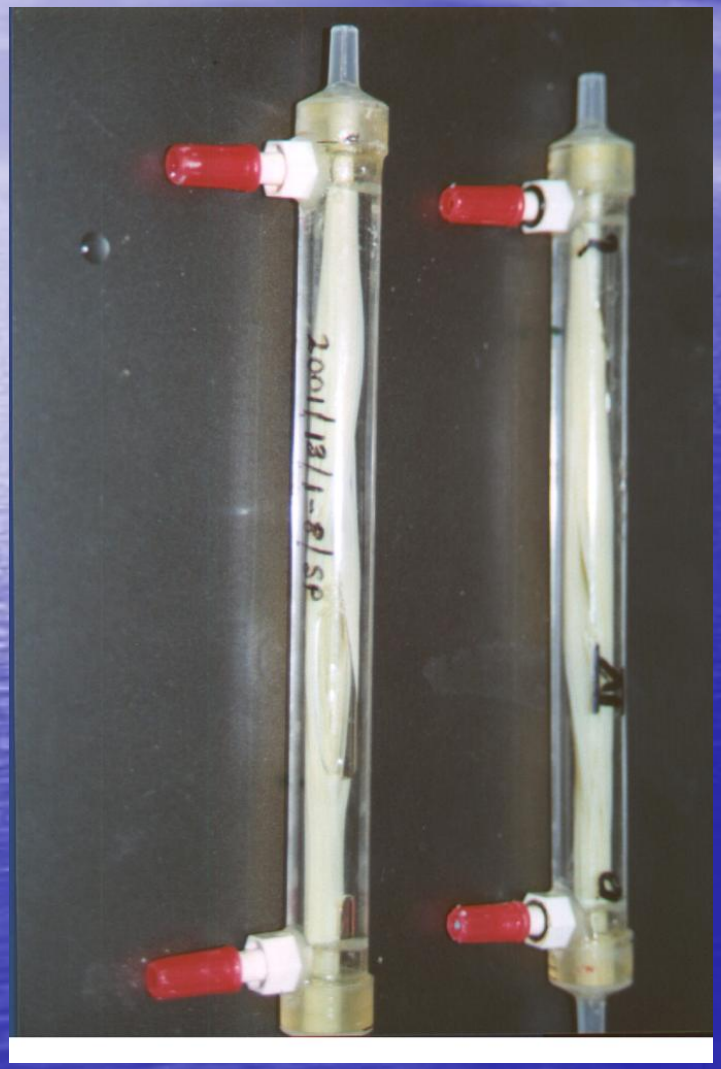
Project Brite-Euram II

Haemocompatibility Testing of Membranes Developed for BioArtificial Organs Applications

- Parameters:
  - –protein adsorption
  - –platelet adhesion, activation, aggregation
  - –activation of the coagulation system
  - –complement, contact activation
  - –haemolysis, toxicity testing

- Methods:
  - -static conditions
  - -dynamic (steady / pulsatile flow) conditions

ARTIFICIAL ORGANS: BIOARTIFICIAL LIVER/KIDNEY HOLLOW FIBER MODULES / PROTOTYPE



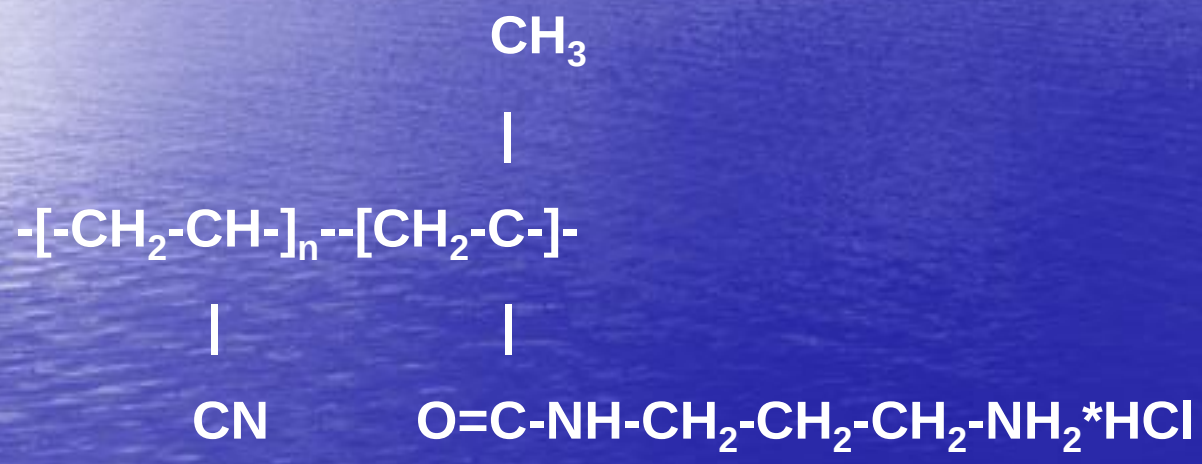
Modules were designed and constructed by US-BU.

A fast setting polyurethane resin was used for potting (PUR725A+PUR725BF, Rohm and Haas) with centrifugation to minimize wicking.

Fiber length was 136 mm and the number of fibers was 35 having an id of 500 µm giving an internal fiber surface area of 75 cm^2.

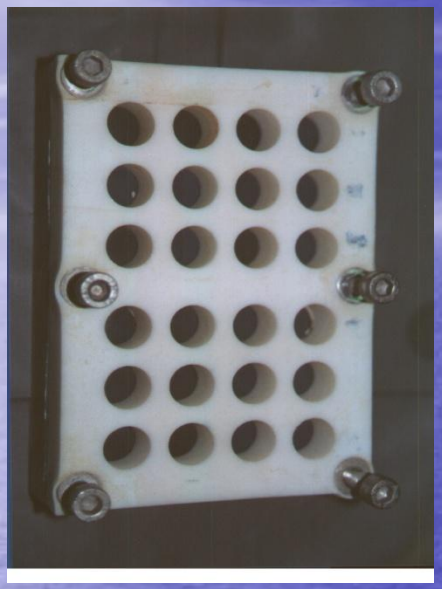
ARTIFICIAL ORGANS - POLYMER SYNTHESIS

Polymers (both membrane and hollow fiber format) were synthesised by GKSS using an acrylonitrile copolymer with 3-aminopropyl-methacrylamide hydrochloride (APMA) comonomer for reactive amine groups according to the following polymer structure formula:



Membrane cut-off was 61 kD suited for exclusion of proteins in a bioartificial liver unit.

EXPERIMENTAL SETUP



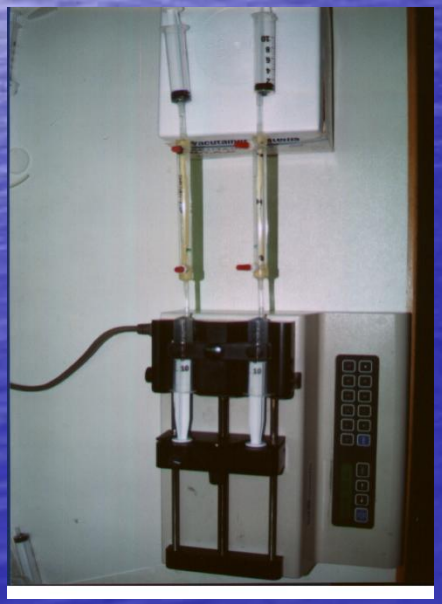
STATIC CONDITIONS - MEMBRANES:

Contact time : 30 min

Medium : PRP/PPP (2 ml/well)

Parameters: Platelet retention and activation, activation of the coagulation system.

4 experiments per material



DYNAMIC CONDITIONS - MODULES:

Contact time : 60 min

Mode : Continuous (5 ml)

Shear Rate : 250 / sec

Medium : PRP/PPP (10ml)

Parameters: Platelet retention, activation of the coagulation system.

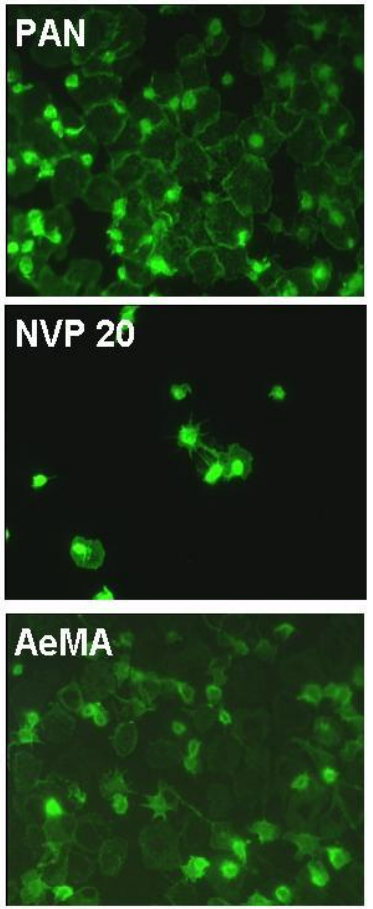
3 experiments per material

Chemical Modification to improve the Blood Compatibility of Polymers

- base copolymer: polyacrylonitrile (PAN)
  - NaMAS (negatively charged)
  - NVP (hydrophilic)
  - AeMA (amine group surface)

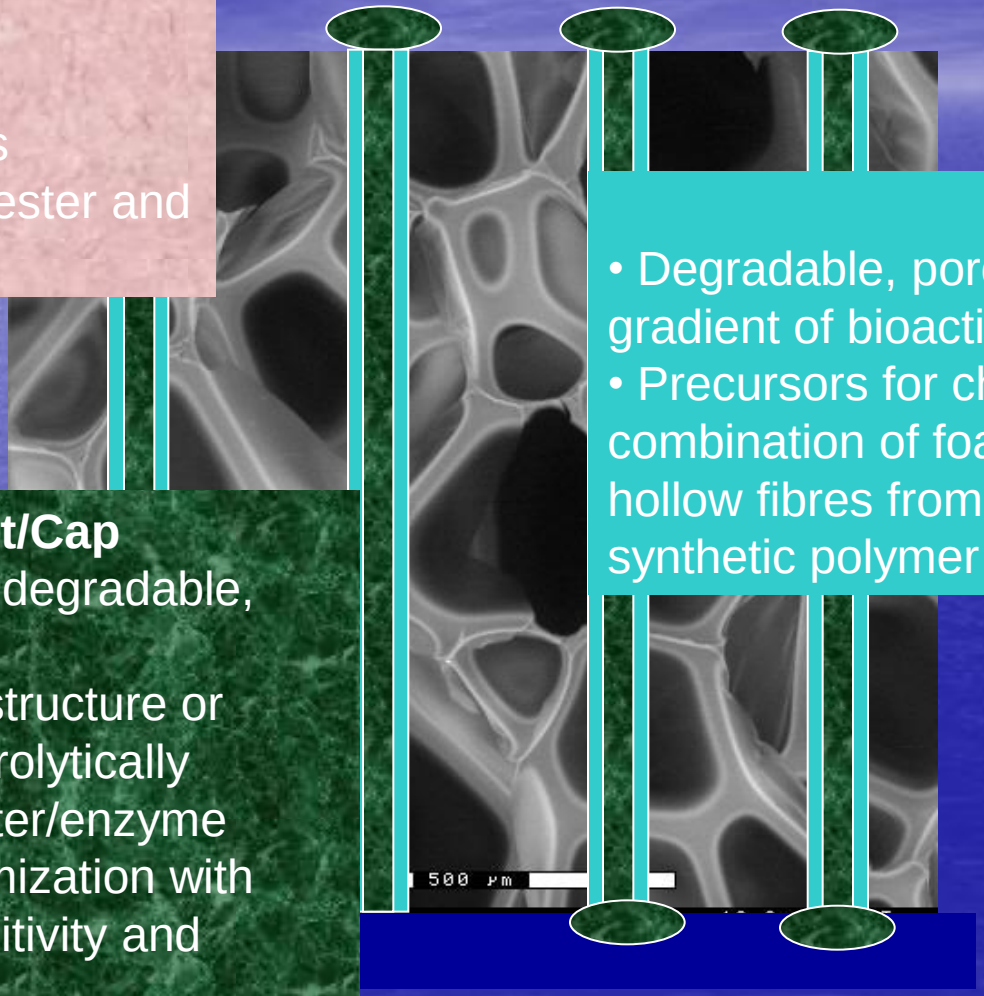
- EPO Patent : AN EP 1115145.3

  Membranes made from P(AN/NVP) - copolymers with both haemo and tissue compatibility and their application in the medical field



VASCUPLUG: "Bioreactive Composite Scaffold Design for Improved Vascular Connexion of Tissue-Engineered Products"

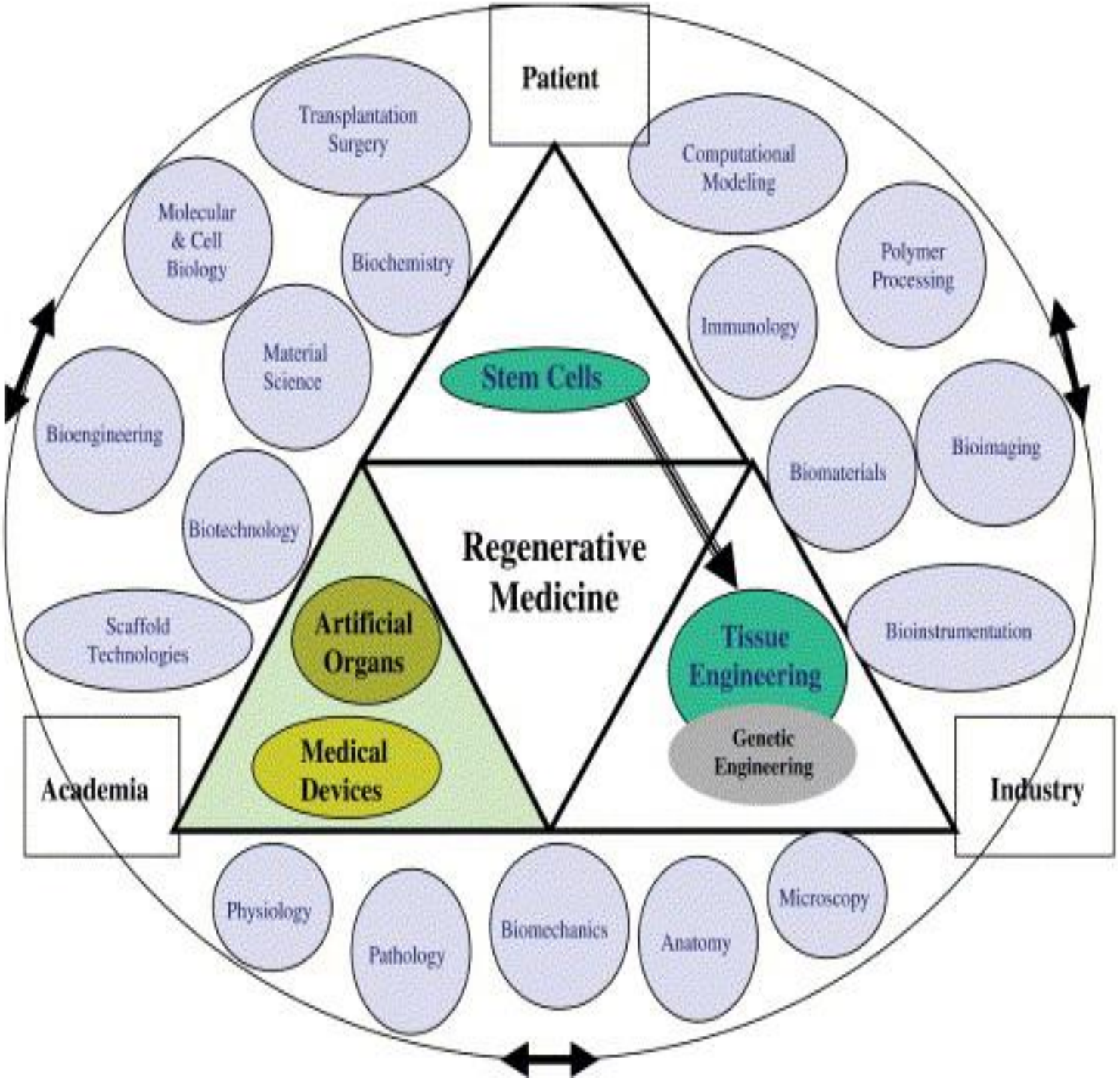
Foam
- Degradable, porous scaffolds with large interconnecting pores
- Biodegradable polyester and polyetherester



Tubes
- Degradable, porous, biocompatible, gradient of bioactive substances
- Precursors for channel-like structure by combination of foaming technology and hollow fibres from a biodegradable synthetic polymer

Filament/Cap
- Stimuli-sensitive, degradable, biocompatible
- pH sensitive gel structure or fast degrading hydrolytically degradable polyester/enzyme combination - optimization with respect to pH-sensitivity and degradation

Composite scaffold formed from three components:


Patient
Transplantation Surgery
Computational Modeling
Molecular & Cell Biology
Biochemistry
Polymer Processing
Immunology
Material Science
Stem Cells
Bioengineering
Biomaterials
Bioimaging
Biotechnology
Regenerative Medicine
Scaffold Technologies
Artificial Organs
Tissue Engineering
Bioinstrumentation
Genetic Engineering
Academia
Medical Devices
Industry
Physiology
Pathology
Biomechanics
Anatomy
Microscopy

ΒΙΒΛΙΟΓΡΑΦΙΑ

- Alan Golde: The Bio-Artificial Liver
  www.ele.uri.edu/Courses/bme181/S13/3_AlanG_1.pdf
- Assistive Devices
  schools.alcdsb.on.ca/hcss/.../Assistive%20Devices.ppt
- Vital Therapies: Hybrid Liver
  https://canvas.brown.edu/courses/773684/.../download?...
- Yannis F. Missirlis : Biomaterals – Tissue Engineering
  https://mecanobio2014.files.wordpress.com/.../biomateri...
- Kevin Warwick: Bionics 2 https://cw.fel.cvut.cz/wiki/_media/.../bionics_2.ppt
- Andreas K.M. Podias and Yannis F. Missirlis: Experiments and Computational Fluid Dynamics in the Designing of a Heparin-Adsorbing Device. 6th International Workshop on Mathematical Methods in Scattering Theory and Biomedical Engineering
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- Groth, Th., Fey-lamprecht, F., Seifert, B., Mihanetzis, G.,Missirlis, Y., Paul, D. Development of membranes for bioartificial organs ASAIO journal 46(2), pp. 217, 2000.
- Groth, T., Seifert, B., Albrecht, W., Michanetzis, G., Missirlis, Y., Engbers, G. Development of polymer membranes with improved haemocompatibility for biohybrid organ technology Clinical Hemorheology and Microcirculation 32(2), pp. 129-143, 2005.