CeFEMA
Center of Physics and Engineering of Advanced Materials

TÉCNICO LISBOA

# Hemocompatible Nanostructured Membranes for Artificial Organs

Maria Norberta de Pinho
CeFEMA / Membrane and electrochemical processes
Departamento de Engenharia Química / Instituto Superior Técnico
Lisboa, Portugal

July 6, Ciência 2016 – Lisboa, Portugal

# Hemocompatible Nanostructured Membranes for Artificial Organs

## Project PTDC/CTM-BIO/6178/2014
## Financed by FCT
## May 1st, 2016 – April 30th, 2019

Research Team:


Maria Norberta Neves Correio de Pinho – CeFEMA, IST - ULisboa

Pedro José Oliveira Sebastião – CeFEMA, IST - ULisboa

Pedro Miguel Félix Brogueira – CeFEMA, IST – ULisboa

Maria Helena Godinho – CENIMAT, FCT - UNL

Vítor Geraldes – CeFEMA, IST – ULisboa

Viriato Semião – IDMEC, IST – ULisboa

1 BPD & 1 BI

# SCOPE

- **Membranes, Processes and Equipment Design in Membrane Devices with Extracorporeal Blood Circulation**

  **- Blood Oxygenators**

  **- Hemodialysers**

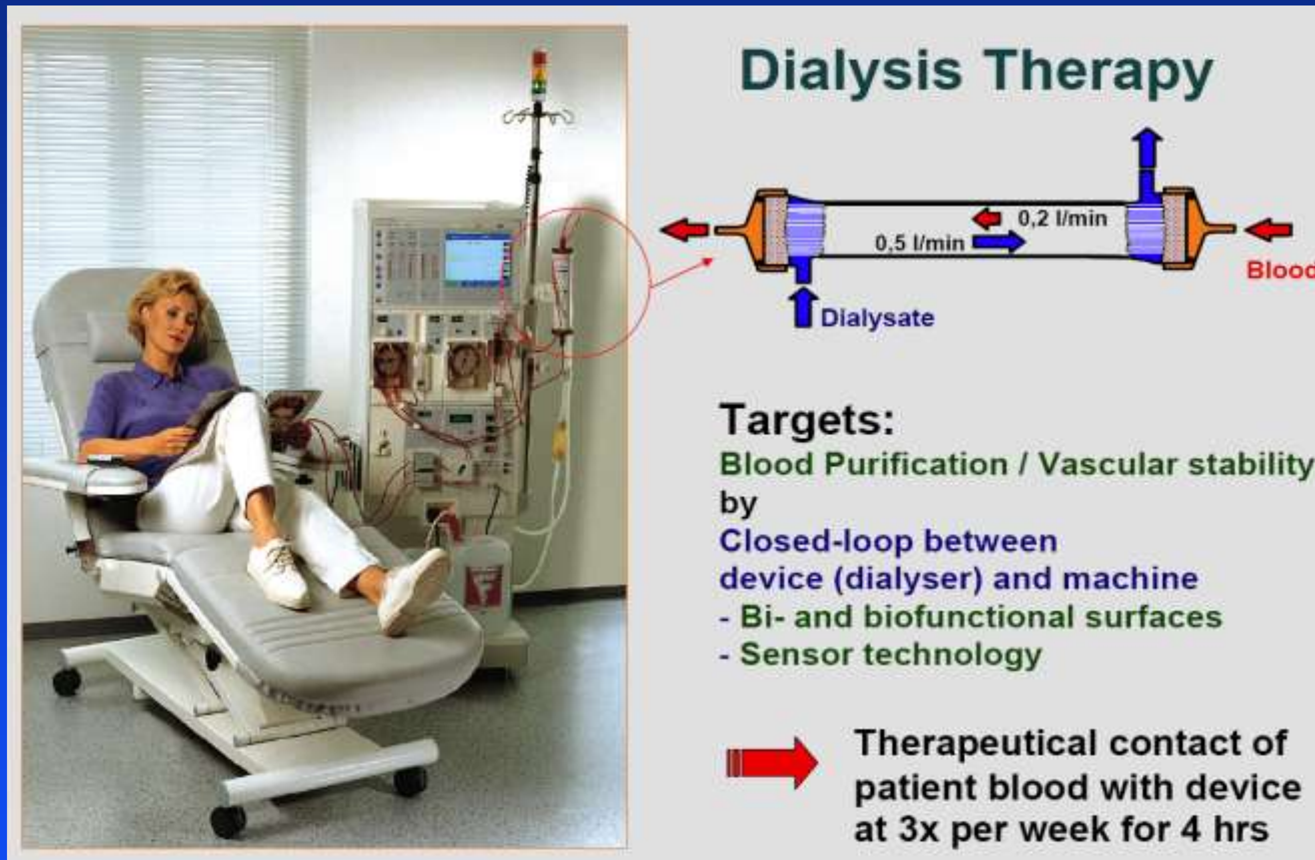
- **Challenges in Blood Oxygenators**
- **Challenges in Hemodialysis**
- **Challenges in Hemocompatible Membranes**

# Extracorporeal Artificial Organs

**Production of Membrane Medical Devices in 2002 (Krause *et al*, 2003).**

| **Membrane Operation** | **Millions of Devices/year** | **Membrane Surface Area [$m^2$]** |
|---|---|---|
| Hemodialysis | 110 | $230\times10^6$ |
| Blood Oxygenation | 0.75 | $2\times10^6$ |
| Perfusion | 1-2 | $<1\times10^6$ |
| Apheresis | 0.3 | $\sim 1\times10^5$ |
| Plasma Fraccionation | <12 | $<1\times10^5$ |

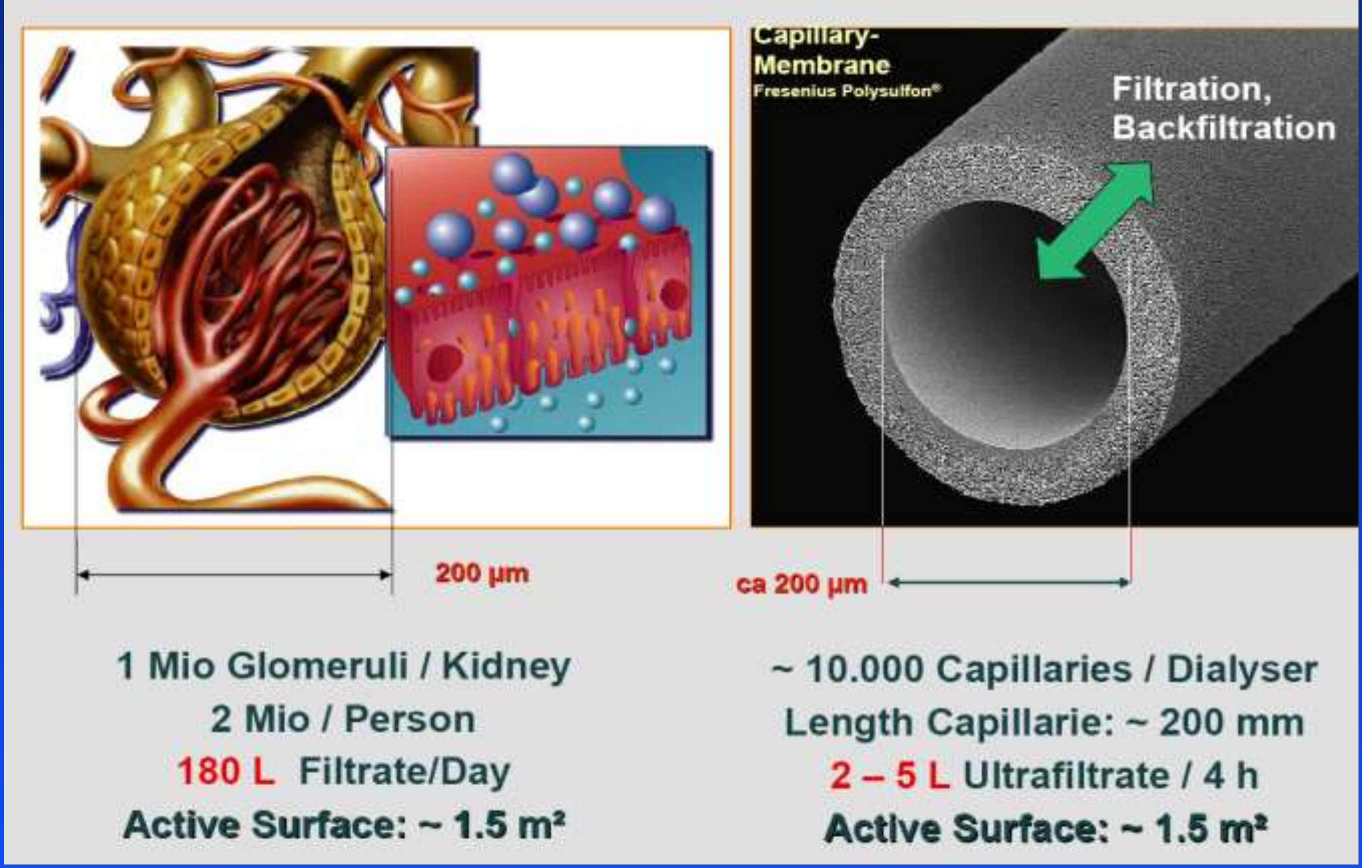
# Dialysis Therapy




Professor Vienken; Hemodialysis Conference in Membranes in Medicine, IST, Lisboa, February 2009.

European Network of excelence “Expanding membrane macroscale applications by exploring nanoscale materials properties” (NanoMemPro)

# Human & Artificial Kidneys




Professor Vienken; Hemodialysis Conference in Membranes in Medicine, IST, Lisboa, February 2009.

European Network of excelence "Expanding membrane macroscale applications by exploring nanoscale materials properties" (NanoMemPro)

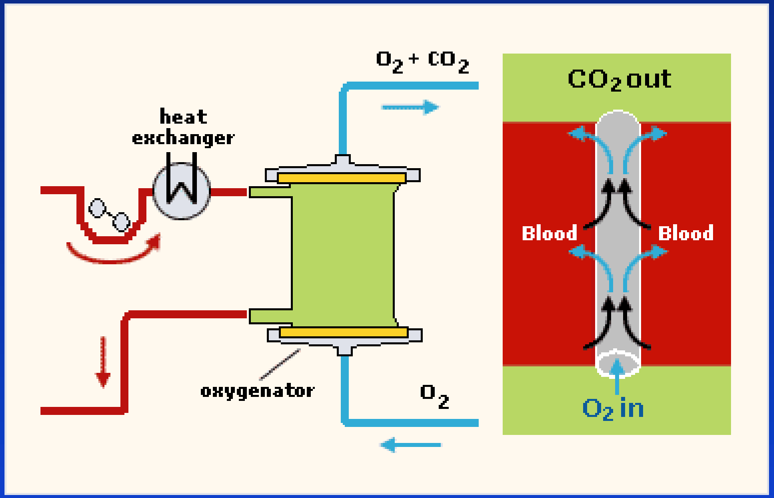
# Membrane Blood Oxygenators (MBO)

Disposable medical devices that take over the function of the heart and lungs to permit surgical operations on the heart and vessels

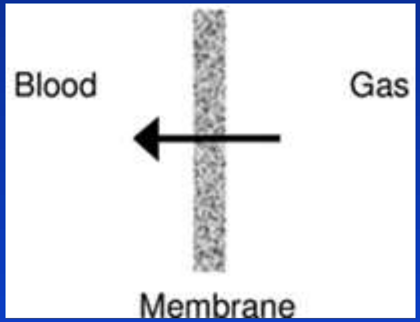


“Aplicações biomédicas de membranas poliméricas” (Cap. 26), Maria Norberta de Pinho e Nuno Reis, “Biomateriais: Conceitos e Aplicações”, Eds. Maria Helena Gil e José Paulo Sardinha

# Membrane Blood Oxygenators (MBO)




Membranes for $O_2/CO_2$ permeation:




- Membrane development requires:

1. In a MBO with membrane surface area ~2m$^2$ at a gas feed pressure of 76cmHg the membranes should exhibit $CO_2$ and $O_2$ permeances of approximately 0.22×10$^{-5}$cm$^3$(STP)/cm$^2$scmHg and 0.27×10$^{-5}$cm$^3$(STP)/cm$^2$scmHg, respectively.

2. Blood Compatibility

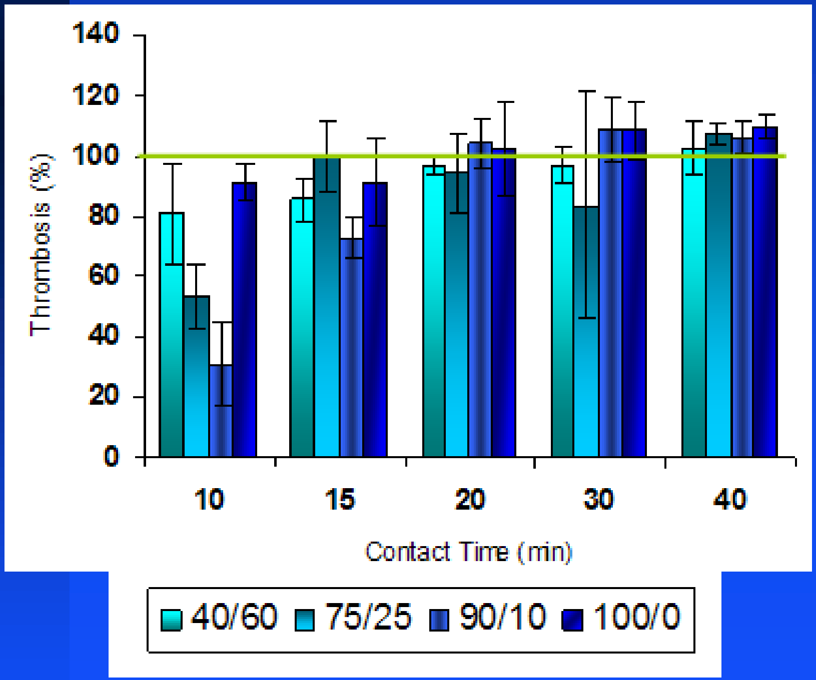
"Synthesis and Characterization of Bi-Soft Segment Poly (Ester Urethane Urea) Membranes for Extracorporeal Blood Oxygenation Devices", Mónica Faria, Pedro Brogueira, Maria Norberta de Pinho,
XXXVIII Congress of the European Society for Artificial Organs (ESAO 2011) and
IV Biennial Congress of the International Federation on Artificial Organs (IFAO 2011), Porto - Portugal

# Background of Bi-Soft Segment Poly (Ester Urethane Urea) Symmetric Membranes

<u>Blood compatibility</u>

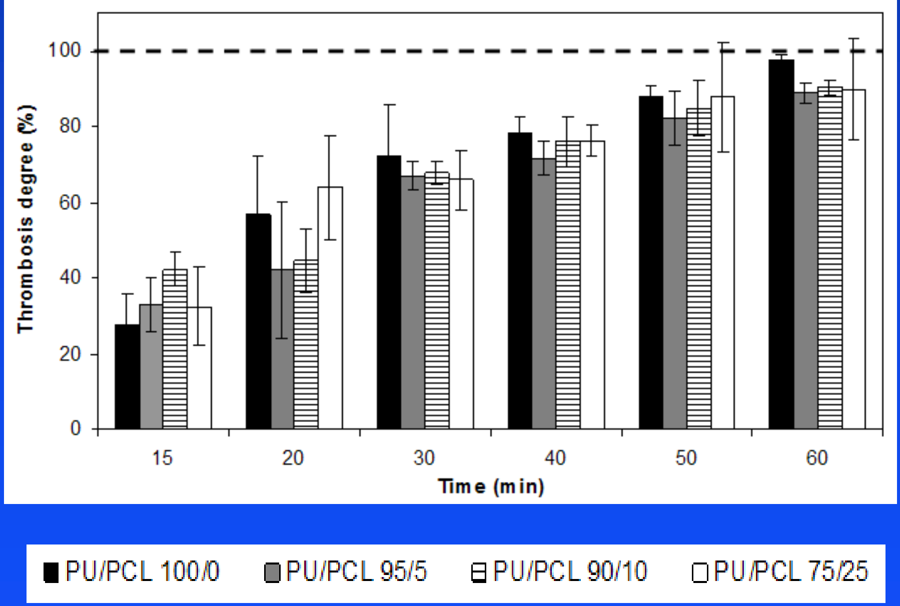
- Thrombosis versus blood contact times:

Polyurethane/Polybutadiene (PU/PBDO)




*D.P.Queiroz, I.M.Pinto, M.C.F.Besteiro, A.F.M.Silva, M.H.Gil, A.J. Guiomar, M.N.de Pinho, Internacional Journal of Artificial Organs, 29(2006), 866-872*

Polyurethane/Polycaprolactone (PU/PCL)

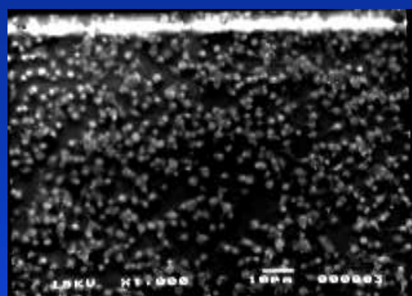



*Mónica Faria, António Jorge Guiomar, C.A. Gonçalves, V. Bairos, Maria Norberta de Pinho, Maria Helena Gil, Journal of Biomedical Materials Research – Part A, 93A (2009), 954-964*

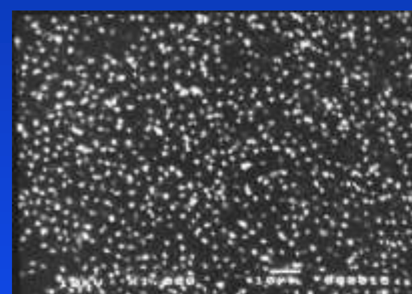
# Background of Bi-Soft Segment Poly (Ester Urethane Urea) Symmetric Membranes

<u>Blood Compatibility</u>

- Platelet Adhesion on PU/PCL symmetric membranes:

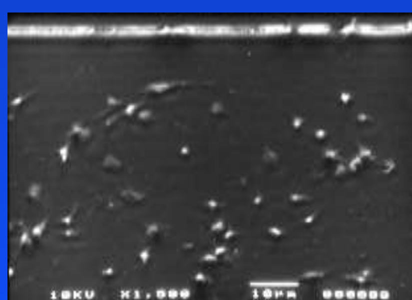


PU/PCL 100/0



glass

PU/PCL 95/5



PU/PCL 90/10

PU/PCL 75/25

- PU/PCL symmetric membranes exhibit much lower gas permeation than the required for MBOs

*Mónica Faria, António Jorge Guiomar, C.A. Gonçalves, V. Bairos, Maria Norberta de Pinho,Maria Helena Gil, Journal of Biomedical Materials Research – Part A, 93A (2009), 954-964*

# State of the Art of Bi-Soft Segment Poly (Ester Urethane Urea) Symmetric Membranes

**PU/PBDO membranes**

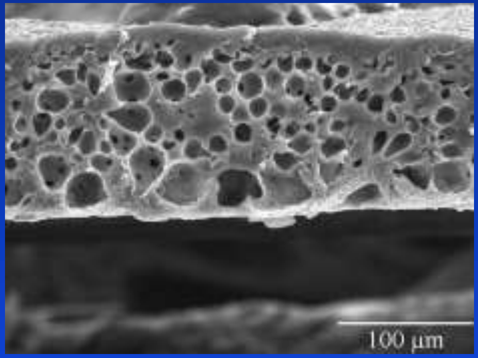
- Good Gas Permeation Rates: 50 – 800 Barrer
- Thrombosis degrees approximately 100% for contact times above 20 minutes

**PU/PCL membranes**

- Very very low Gas Permeation Rates: Questionable technical feasibility
- Thrombosis degrees below 60% for contact times of 20 minutes
- Platelet adhesion depends on PCL content and can be minimized.

# How to Go Beyond the State of the Art?

HOW TO COMBINE MEMBRANE HEMOCOMPATIBILITY WITH HIGH PERMEATION FLUXES ?




*Process of Synthesis of Asymmetric Polyurethane Based Membranes with Hemocompatibility Characteristic and Membranes by Said Processes, PCT/IB2007/003340.*

- Bi-soft segment Integral Asymmetric Polyurethane Membranes:

  PCL as a second soft segment

  Asymmetric cross-sections

  Tailoring of blood contacting surface morphologies

  Tailoring of the active layer thickness (minimization of gas permeation resistance)

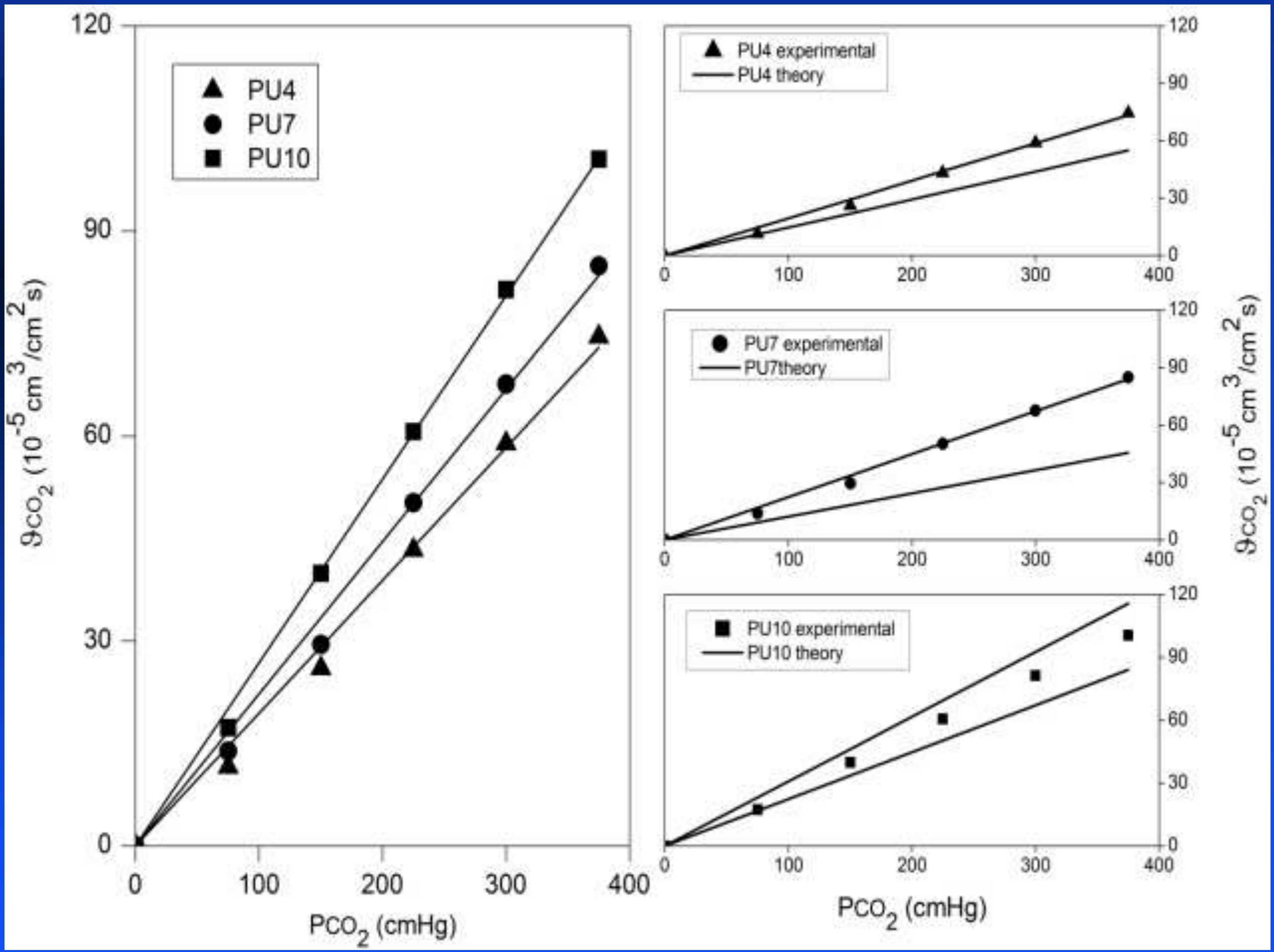
# Integrally Skinned PU/PCL Asymmetric Membranes

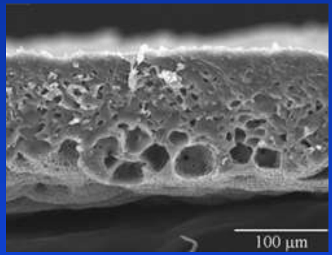
- $CO_2$ permeation fluxes. Experimental versus Theoretical Predictions

Theoretical Predictions (solution/diffusion model) based on:

Skin layer thicknesses processed by SEM & ImageJ, NIH

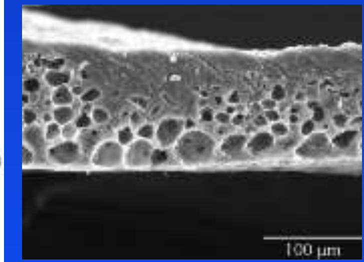
PU10 $CO_2$ permeance measurement (0,26×10-5cm3/(cm2scmHg))



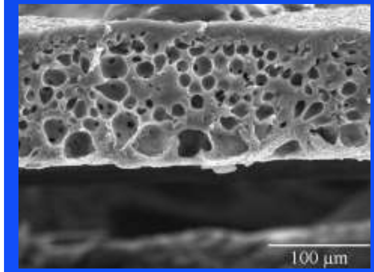

PU4

ℓ = 24±6µm




PU7

ℓ = 20±3µm

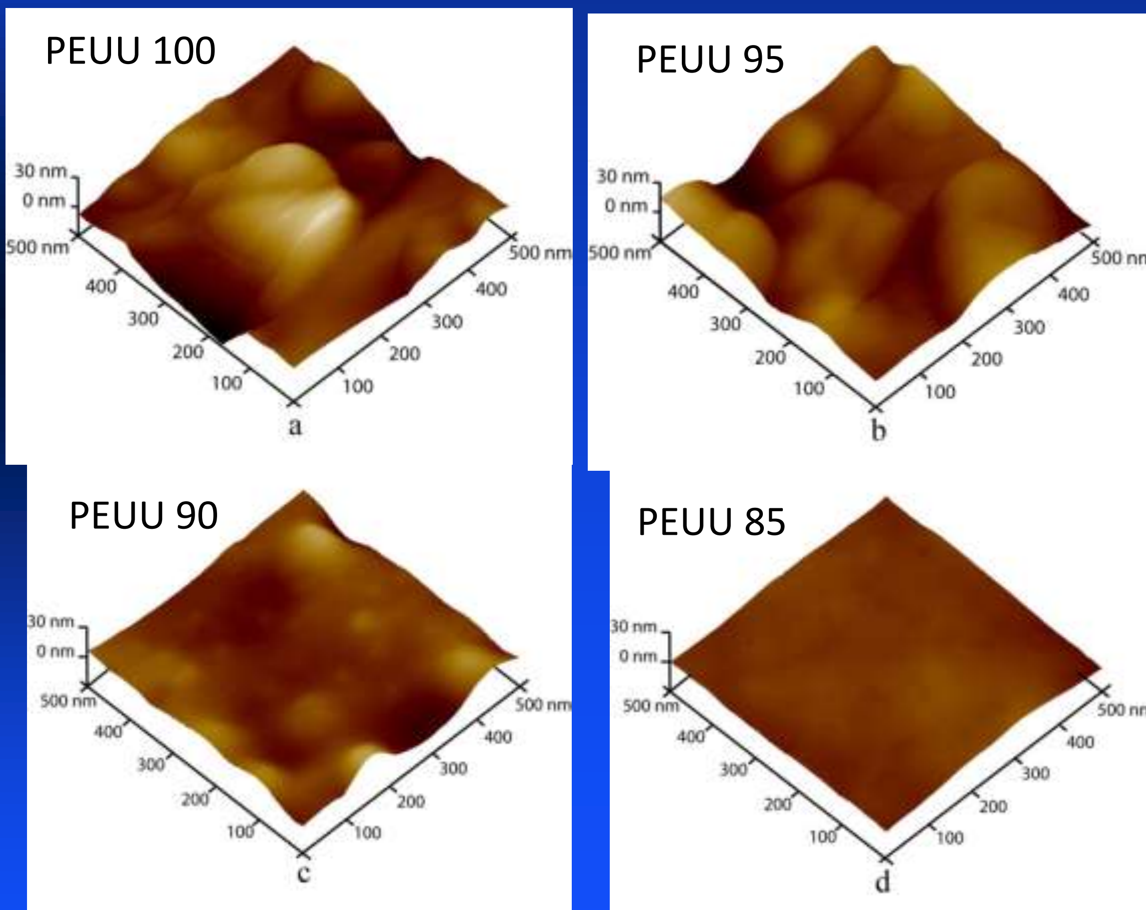



PU10

ℓ = 13±2µm

# Integrally Skinned PU/PCL Asymmetric Membranes

- AFM Characterization of Blood Contacting Surfaces at the sub-micron scale. Scanning areas: 500 nm x 500 nm

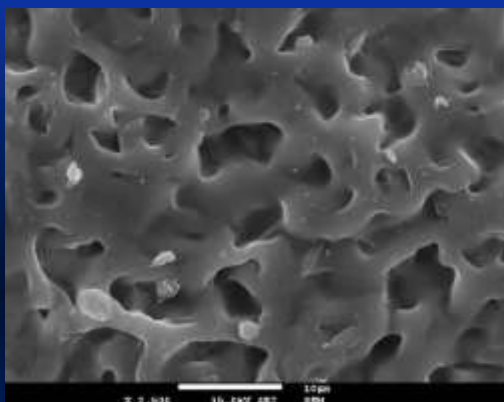



| Dense Layer | Z (nm) | Ra (nm) | Rq (nm) |
|---|---|---|---|
| PEUU 100 | 52 ± 5 | ~5.7 | ~7.5 |
| PEUU 95 | 34 ± 3 | ~4.1 | ~5.5 |
| PEUU 90 | 19 ± 3 | ~2.3 | ~3.2 |
| PEUU 85 | 11 ± 4 | ~1.2 | ~1.6 |

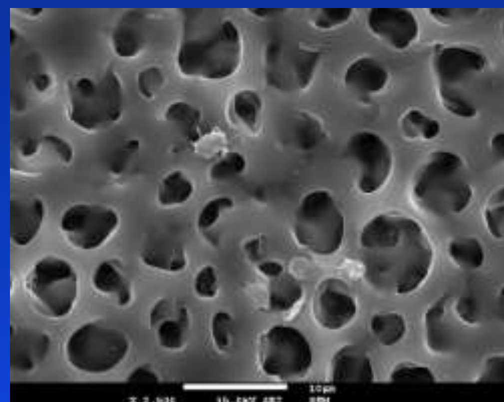
# Integrally Skinned PU/PCL Asymmetric Membranes

- Hemocompatibility. Platelet Adhesion on Blood Contacting Surfaces. Platelet Deposition and Coverage

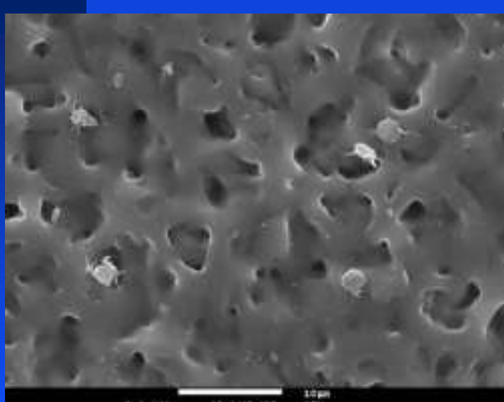
PEUU 100



PEUU 95



PEUU 90



PEUU 85

* original enlargement 2500×

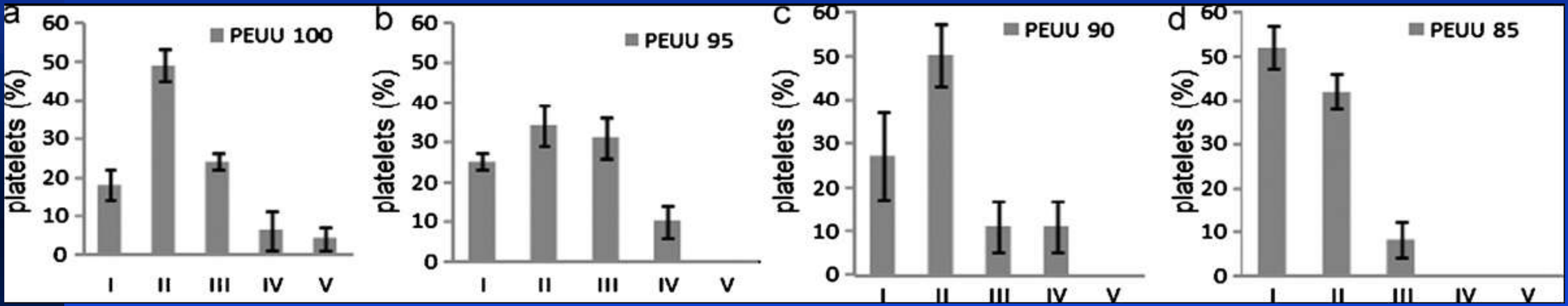
SEM images of top dense surfaces of PEUU membranes after contact with PRP (platelet rich plasma).

Platelet Deposition (PD) and Platelet Coverage (PC) parameters for the top dense surfaces of the PEUU membranes

| Membrane | PD (nº adherent platelets / 10000 $\mu m^2$) | PC (%) |
|---|---|---|
| PEUU 100 | 70 ± 1.4 | 8 ± 0.1 |
| PEUU 95 | 33 ± 1.8 | 6 ± 0.3 |
| PEUU 90 | 29 ± 1.0 | 5 ± 0.3 |
| PEUU 85 | 17 ± 1.2 | 2 ± 0.1 |

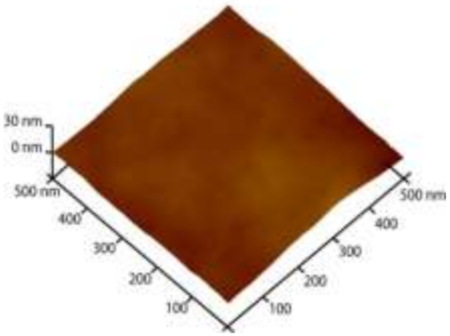
# Integrally Skinned PU/PCL Asymmetric Membranes

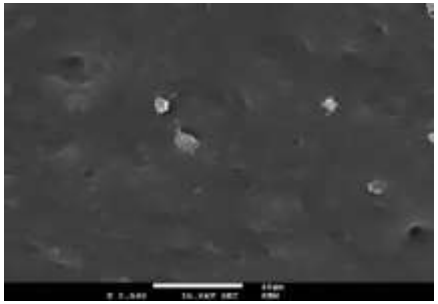
- Hemocompatibility. Platelet Activation on Blood Contacting Surfaces.



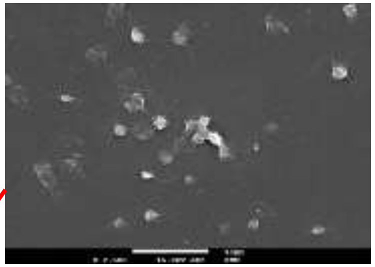
# Integrally Skinned PU/PCL Asymmetric Membranes

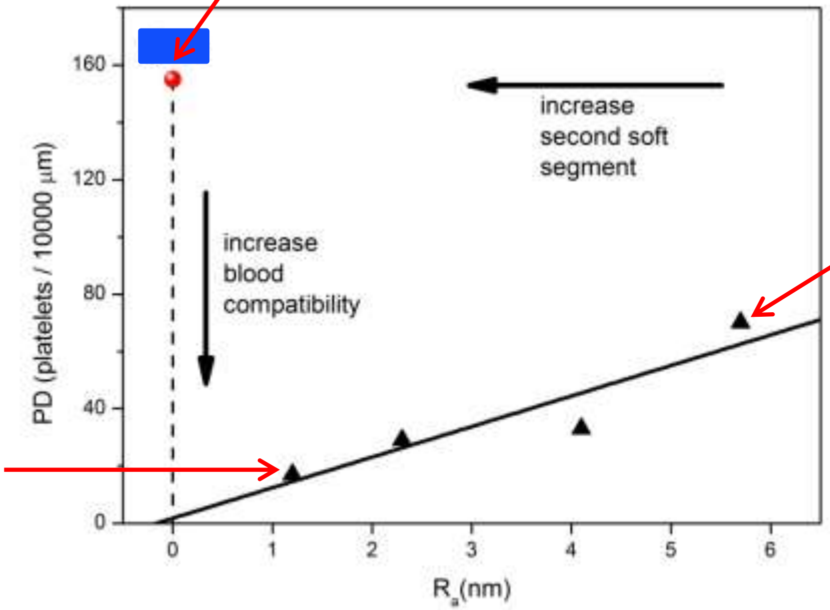
## Platelet Deposition vs Sub-micron roughness ($R_a$ (nm))

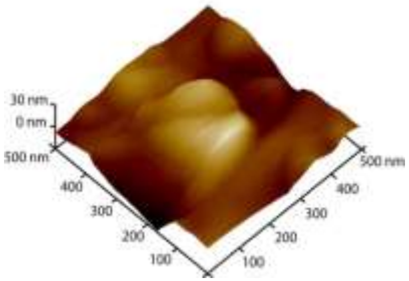


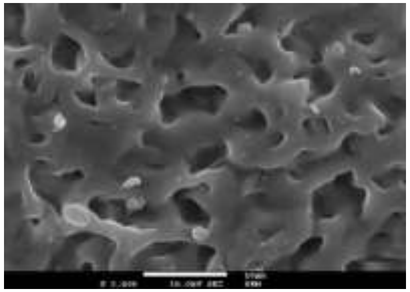



smoothest membrane
minimal platelet
deposition and inhibition
of extremes stages of
platelet activation





roughest membrane
maximum platelet
deposition and
extremes stages of
platelet activation

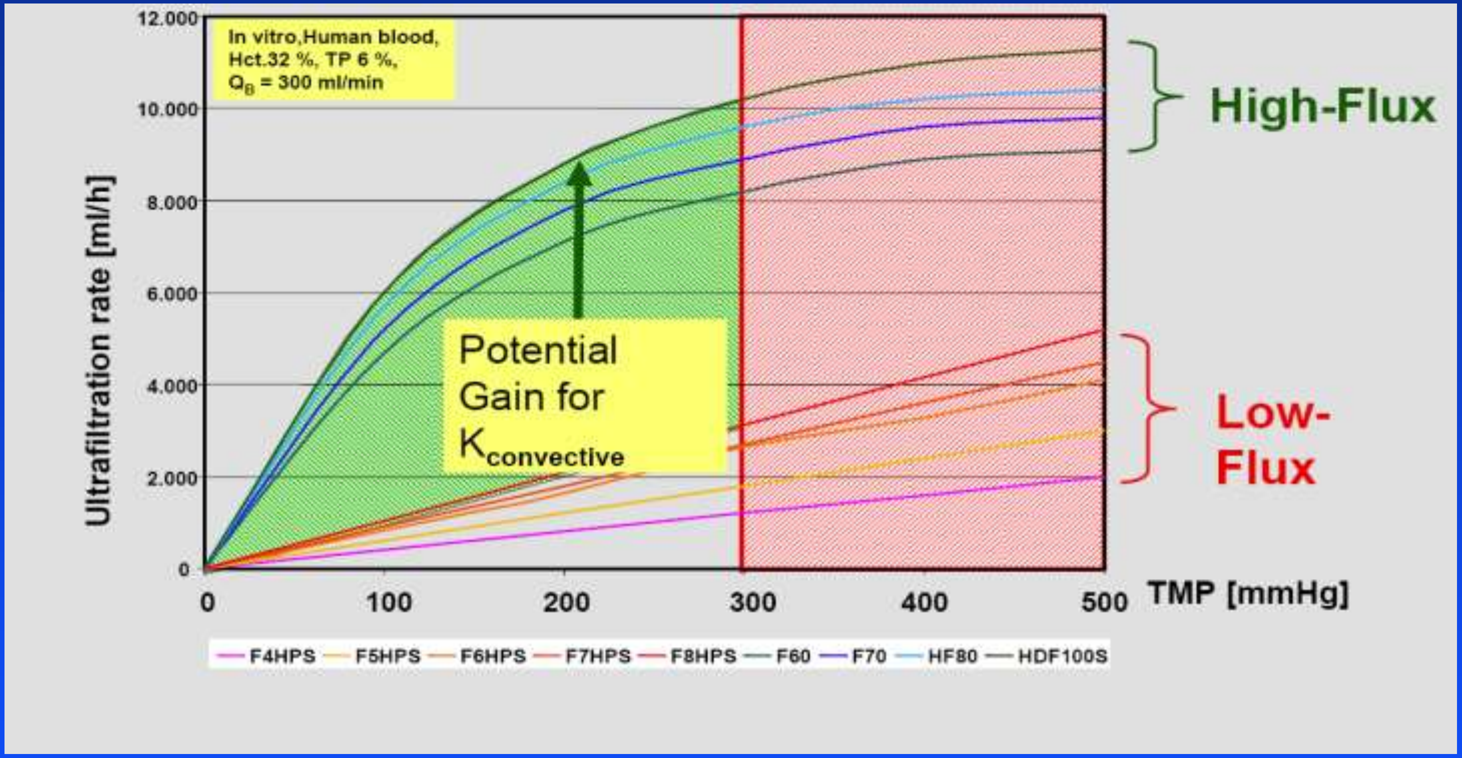
*M. Faria, P. Brogueira, M. N. de Pinho, Colloids and Surfaces B: Biointerfaces 86 (2011) 21–27*

# Integrally Skinned Asymmetric Membranes

- Enhancement of HEMOCOMPATIBILITY through tailoring of PEUU membrane surface morphologies: The Platelet Deposition, PD, increases linearly with the sub-micron roughness, $R_a$.
    - The average sub-micron roughness decreases monotonically by a factor of five to ~ 1 nm when the PCL content varies from 0 to 15%
    - The smoothness of the blood contacting surface leads to inhibition of extreme stages of platelet activation: PEUU 85, $R_a$=1.2nm, the smoothest membrane does not trigger extreme stages of platelet activation (IV and V).
- Enhancement of $CO_2$ and $O_2$ permeation fluxes through the tailoring of the skin layer thickness (13-24 µm).
    - $CO_2$ permeance of 0,26×10-5cm3/(cm2scmHg) for the membrane with the thinner skin layer of 13±2 µm

# Challenges for Hemodialysis

## Low *vs* High- Flux Dialysers



# High Flux Dialysis

- More Efficient Removal of Middle Molecules ranging from 1000 to 15000 Da.
- Removal of $ß_2$ – Microglobulin ($ß_2$M) – 11800 Da.

# Challenges in Hemocompatible Membranes

## Hemocompatibility

HEMOCOMPATIBLE MEMBRANES? THE ON GOING ISSUE….

Inability to initiate thrombogenic phenomena

Inability to cause any hemolysis or activate the complement system

Minimization of platelet adhesion and activation

No chronic inflamatory response

No direct or indirect toxicity of products extracted by biological medium in contact with the material

# Challenges in Mass Transfer

Optimization of blood circulation conditions for minimization of mass transfer resistances

- Membrane module arrangement
- Blood flow circulation

# Acknowledgments


- FCT Fundação para a Ciência e a Tecnologia (Portugal):

  Projects:

  POCTI/FCB/47661/2002

  REEQ1764/EQU/2005

  FCT/PTDC/CTM/099595/2008

  PTDC/CTM-BIO/6178/2014

Maria Norberta de Pinho would like to thank

- Professor Edward Leonard for hosting a sabbatical leave at the Artificial Organs Research Laboratory (AORL), Department of Chemical Engineering, Columbia University, New York
- FCT for the sabbatical scholarship SFRH/BSAB/1401/2014