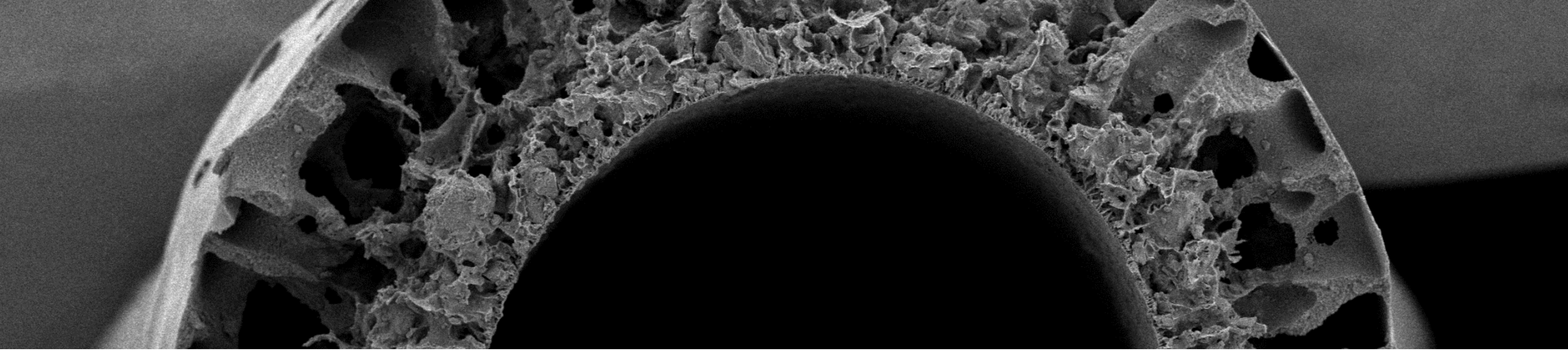


Onderzoek naar betere dialysefilters

Het NODIAL-project

dr. Odyl ter Beek - Advanced Organ bioengineering and Therapeutics (AOT)

UNIVERSITY OF TWENTE.

Advanced Organ bioengineering & Therapeutics

(Bio)Artificial Organs

Wetenschapsdag 2023

NIERSTICHTING

nvn nierpatiënten vereniging nederland

nieren.nl

Deze presentatie

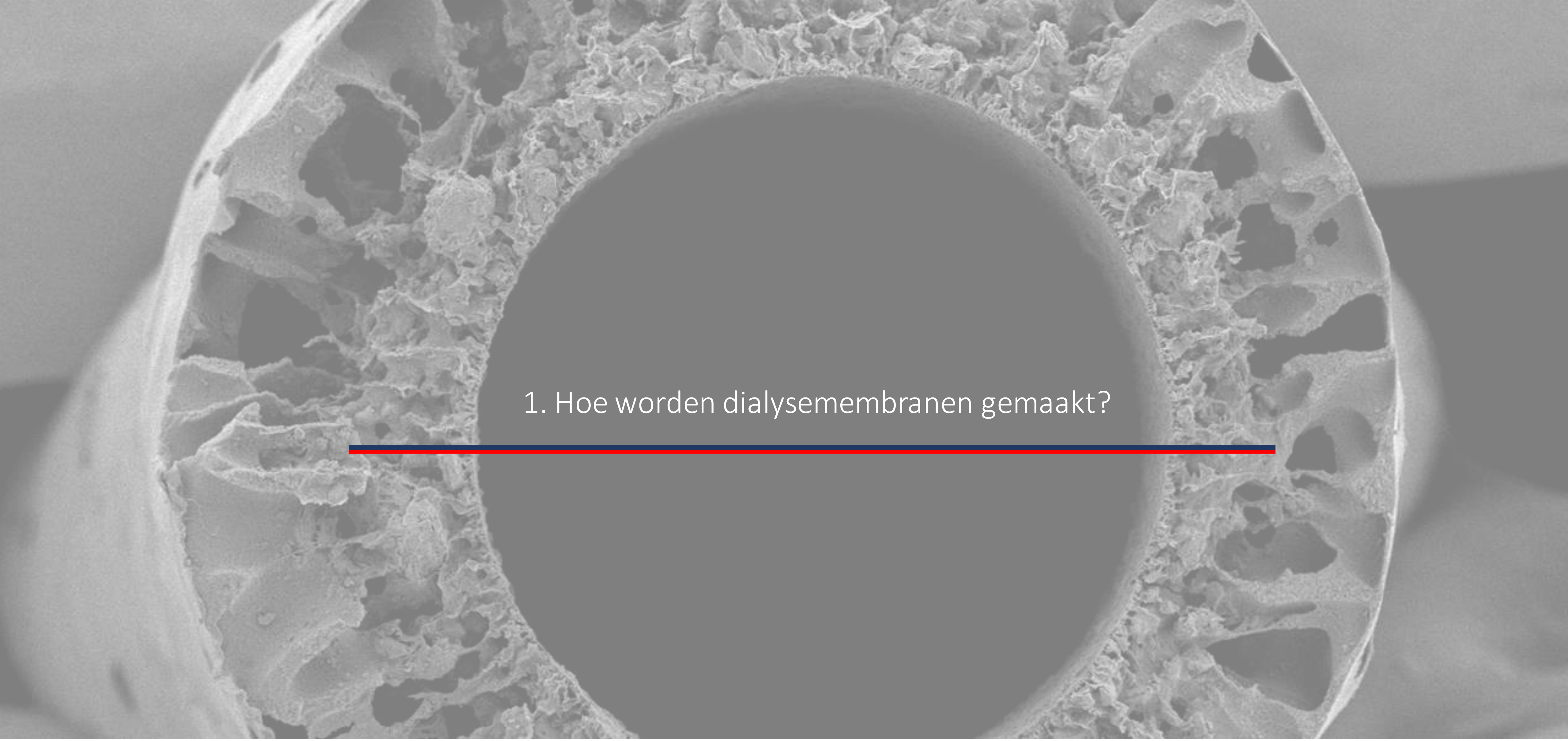
everydayhealth.com

1. Hoe worden dialysemembranen gemaakt?

2. Wat zijn de karakteristieken van dialysefilters?

3. Wat is er nieuw? – Het NODIAL project

1. Hoe worden dialysemembranen gemaakt?



UNIVERSITY OF TWENTE.

Advanced Organ bioengineering & Therapeutics

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Wetenschapsdag 2023

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nvn nierpatiënten vereniging nederland

nieren.nl

1. Hoe worden dialysemembranen gemaakt?

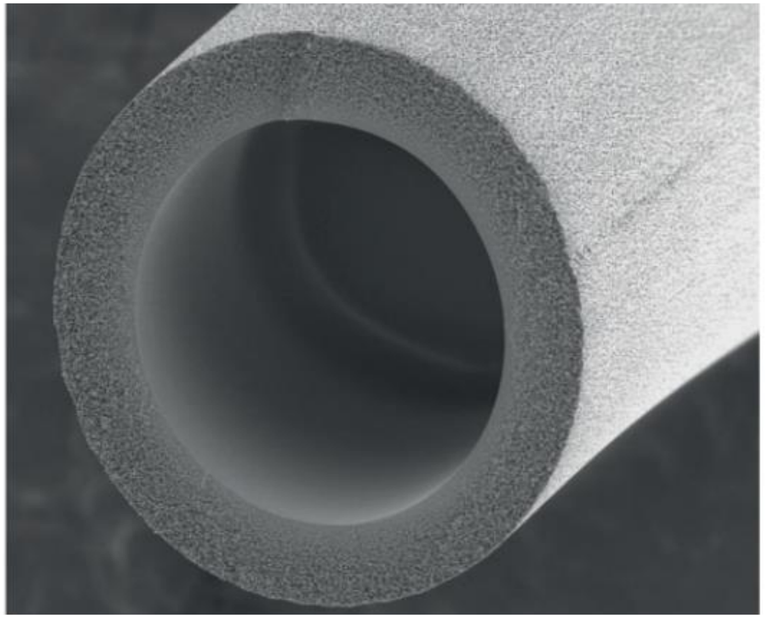
everydayhealth.com

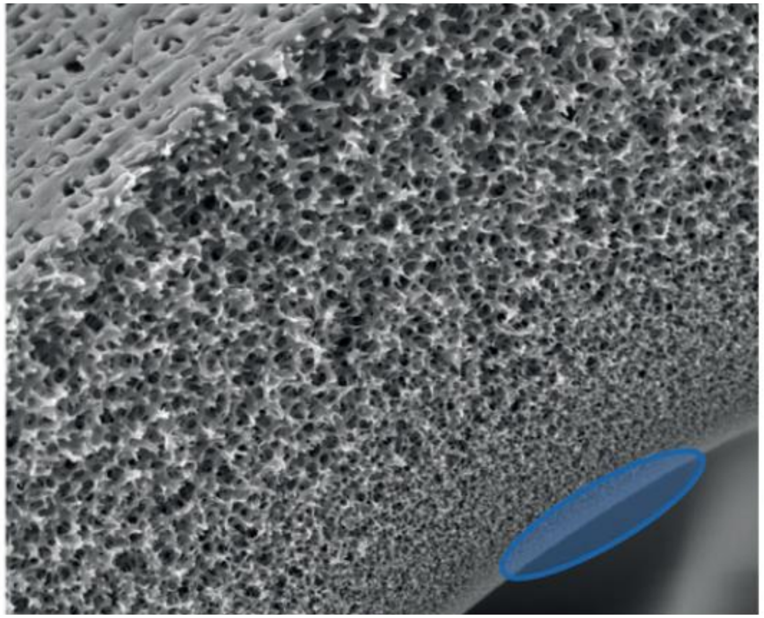
Stamatialis, D.F., et al., Journal of Membrane Science, ***308*** *(2008), p. 1-34.*

- Filter: 10.000 – 20.000 hollow fibers
- Effective surface area: 1,0 – 2,5 m^2

Canaud, B., Curr Opin Nephrol Hypertens ***30*** *(2021), p. 613-622.*

1. Hoe worden dialysemembranen gemaakt?





*Bowry, S.K. and Chazot, C., Clinical Kidney Journal, **14** (2021), suppl 4, i5-i16.*

- Hollow fiber
- Semipermeabel membraan
- Dunne, selectieve laag (skin layer, < 50 nm)

1. Hoe worden dialysemembranen gemaakt? – het aanbod

Baxter.com

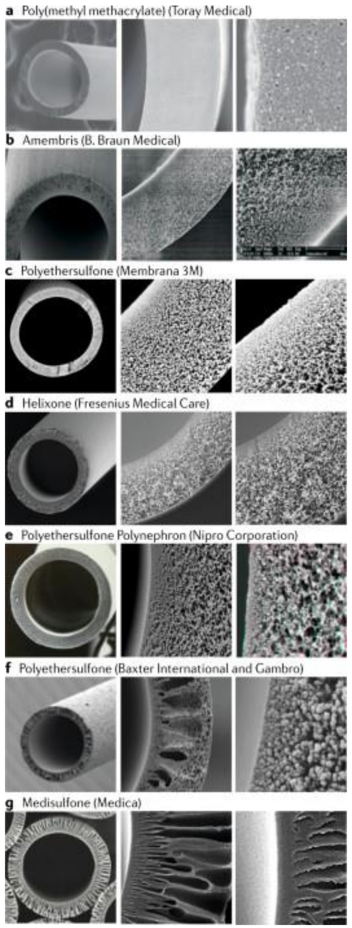
Fresenius.com

B.Braun.com

Table Commercial dialyzers in the current market.

Country	Dialyzer Series Name	Brand	Polymeric Material(s) [a]	Sterilization
Germany	FX-class	Fresenius	PSf (Helixone)	Inline steam
	F-series		PSf	Inline steam
	Hemoflow™		PSf	Ethylene oxide, steam or electron beam
	Purema	Membrana	PES	Gamma ray
The United States of America	Polyflux L	Baxter	PAES, PVP and PA	Steam
	Theranova		PAES and PVP blend BPA-free	Steam
	Revaclear		PAES and PVP blend BPA-free	Steam
	Xevonta	B Braun	PSf	Gamma
	Diacap Pro		α PSf pro	Oxygen free gamma
Japan	ELISIO S	Nipro	PES (polynephron)	Gamma ray
	Sureflux		CTA	Gamma ray
	Solacea™		CTA	Oxygen free gamma
	APS-U	Asahi	Asahi PSf	Gamma sterilized wet type
	ViE Series		Vitamin E-coated PSf	Gamma sterilized wet type
	Rexeed Series		PSf	Gamma ray and
	KF-201 Series		EVAL	Gamma ray
	Toraysulfone TS	Toray	PSf	Gamma ray
	Filtryzer		PMMA	Gamma ray
	Renak	Kawasumi	PSf	Gamma ray
China	F15	WEGO	PSf	Gamma ray
	HF15		PSf	Gamma ray

[a] BPA (bisphenol A); CTA (cellulose triacetate); EVAL (ethylene vinyl alcohol copolymer); PA (polyamide); PAES (polyarylethersulfone); PES (polyethersulfone); PMMA (polymethylmethacrylate); PSf (polysulfone); PVP (polyvinylpyrrolidone).



*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*
*Ronco, C. and W.R. Clark, Nature Reviews Nephrology, **14**(6) (2018), p. 394-410.*

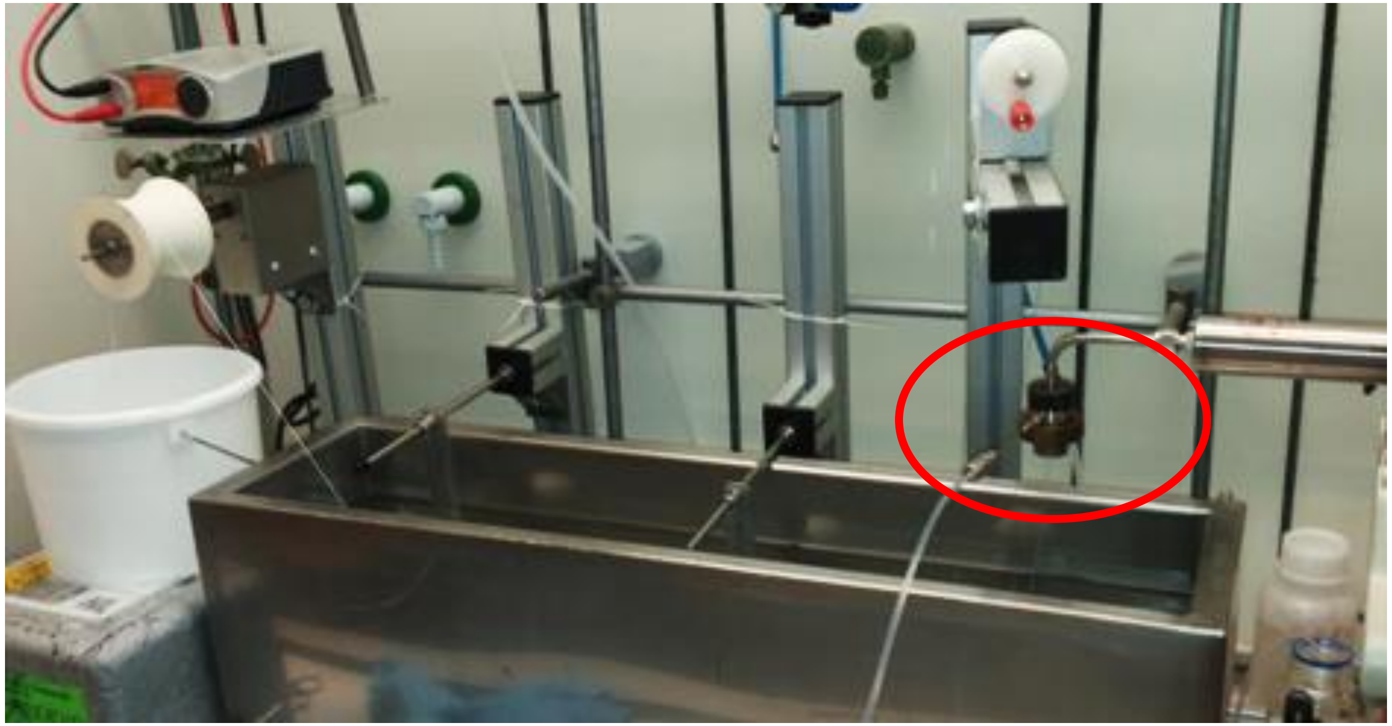
1. Hoe worden dialysemembranen gemaakt?

De ingrediënten:

PES

PVP

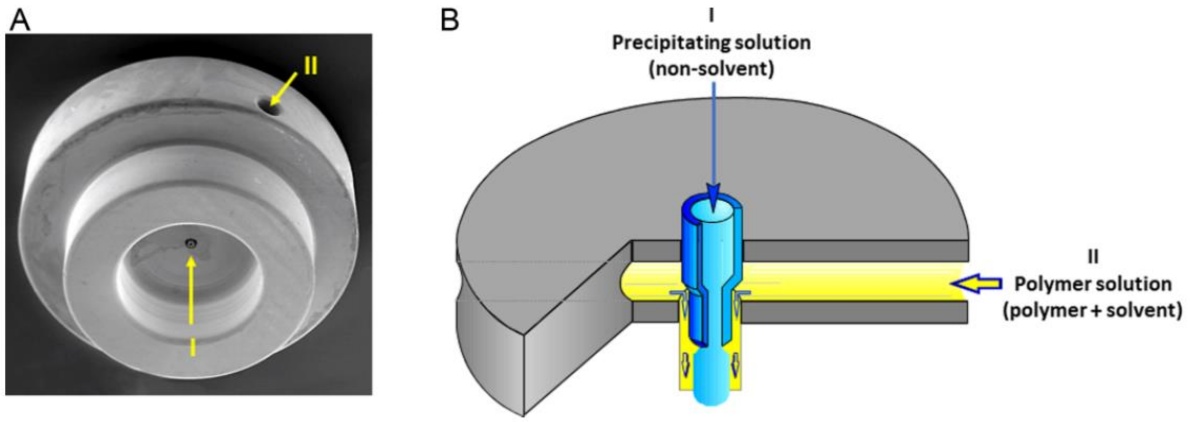
1. Hoe worden dialysemembranen gemaakt?



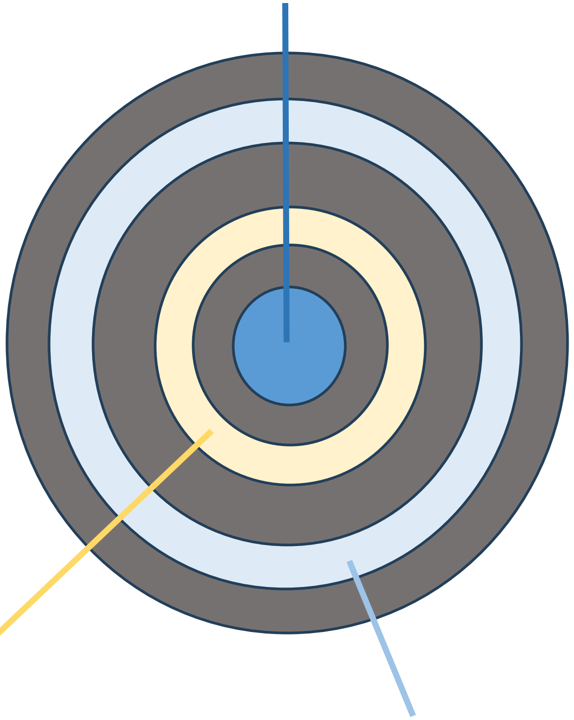
spinneret

hollow fiber membrane

1. Hoe worden dialysemembranen gemaakt? – wet spinning



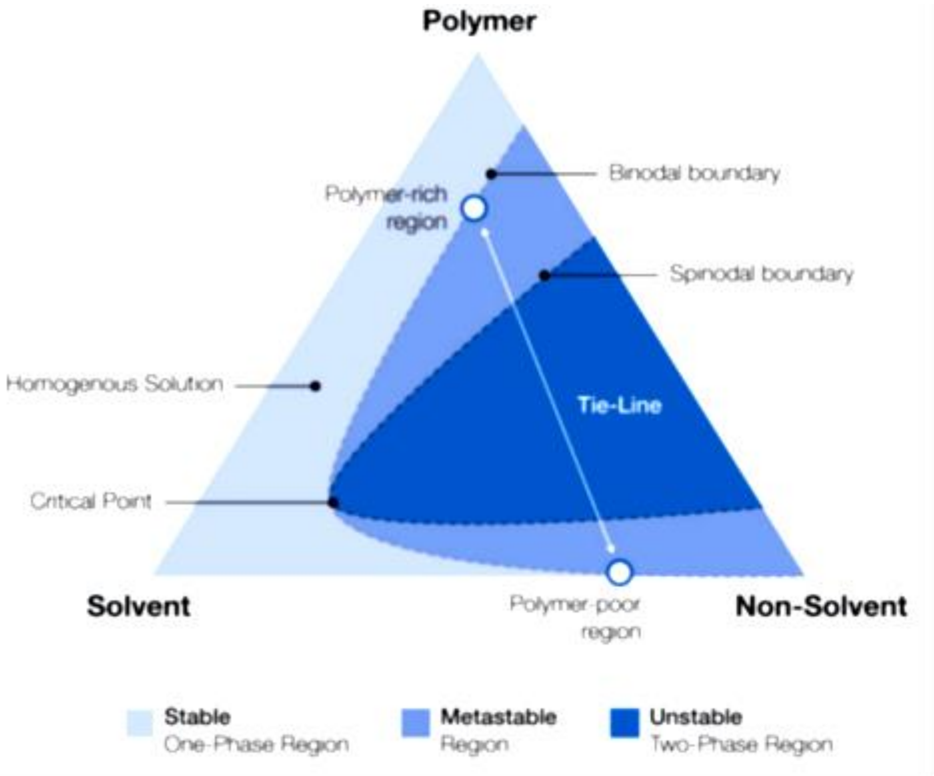
Bowry, S.K. and Chazot, C., Clinical Kidney Journal, **14** (2021), suppl 4, i5-i16.



1. Polymeeroplossing: PES & PVP opgelost in NMP
(polymeren) (oplosmiddel = solvent)

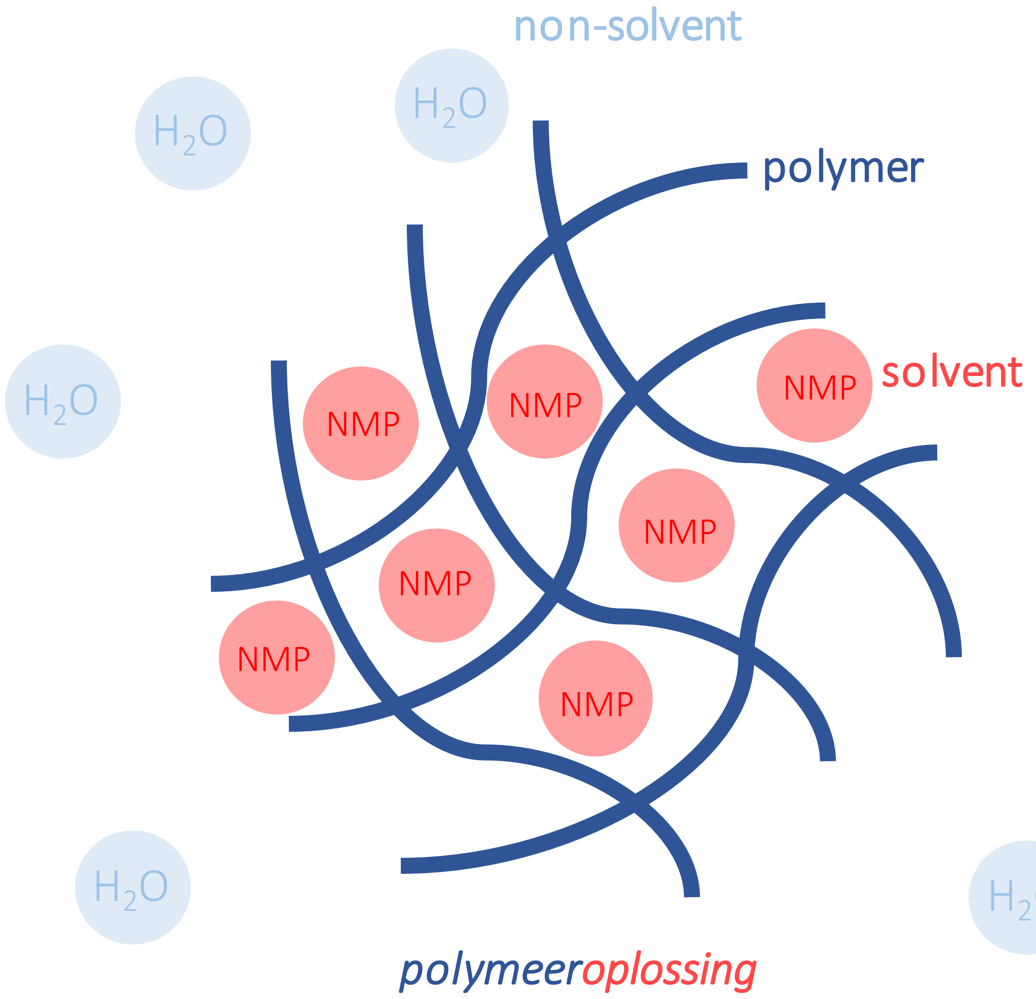
uitwisseling

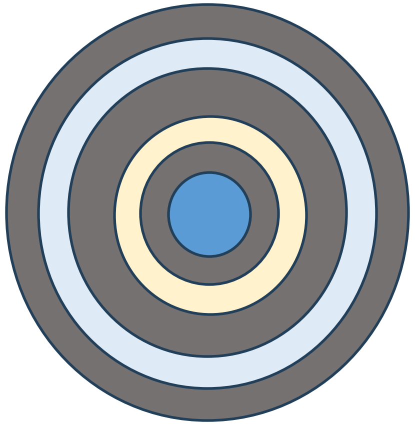
2. Bad & lumen: water
(non-solvent)



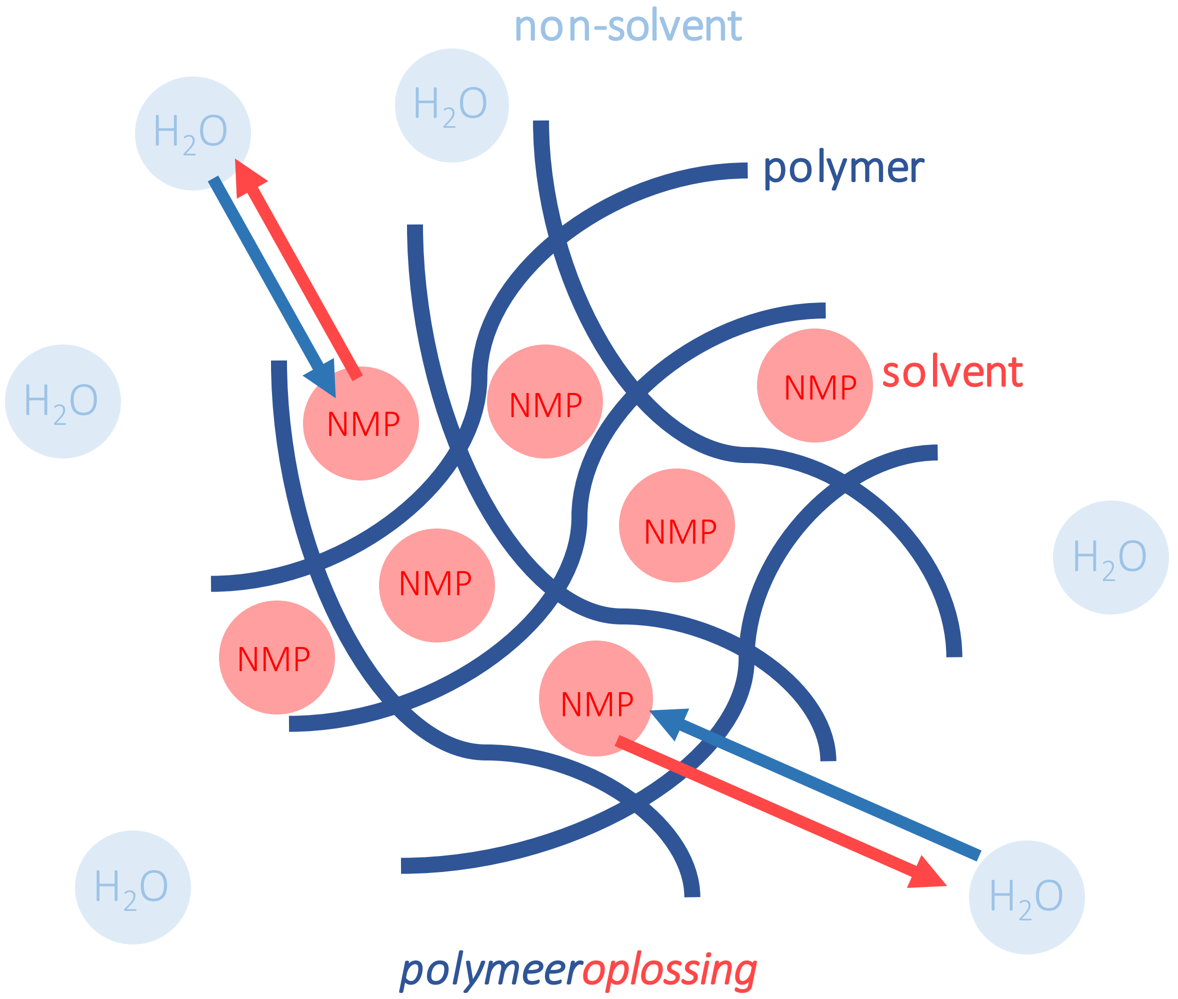
ternary phase separation system/ triangle

*Bowry, S.K. and Chazot, C., Clinical Kidney Journal, **14** (2021), suppl 4, i5-i16.*

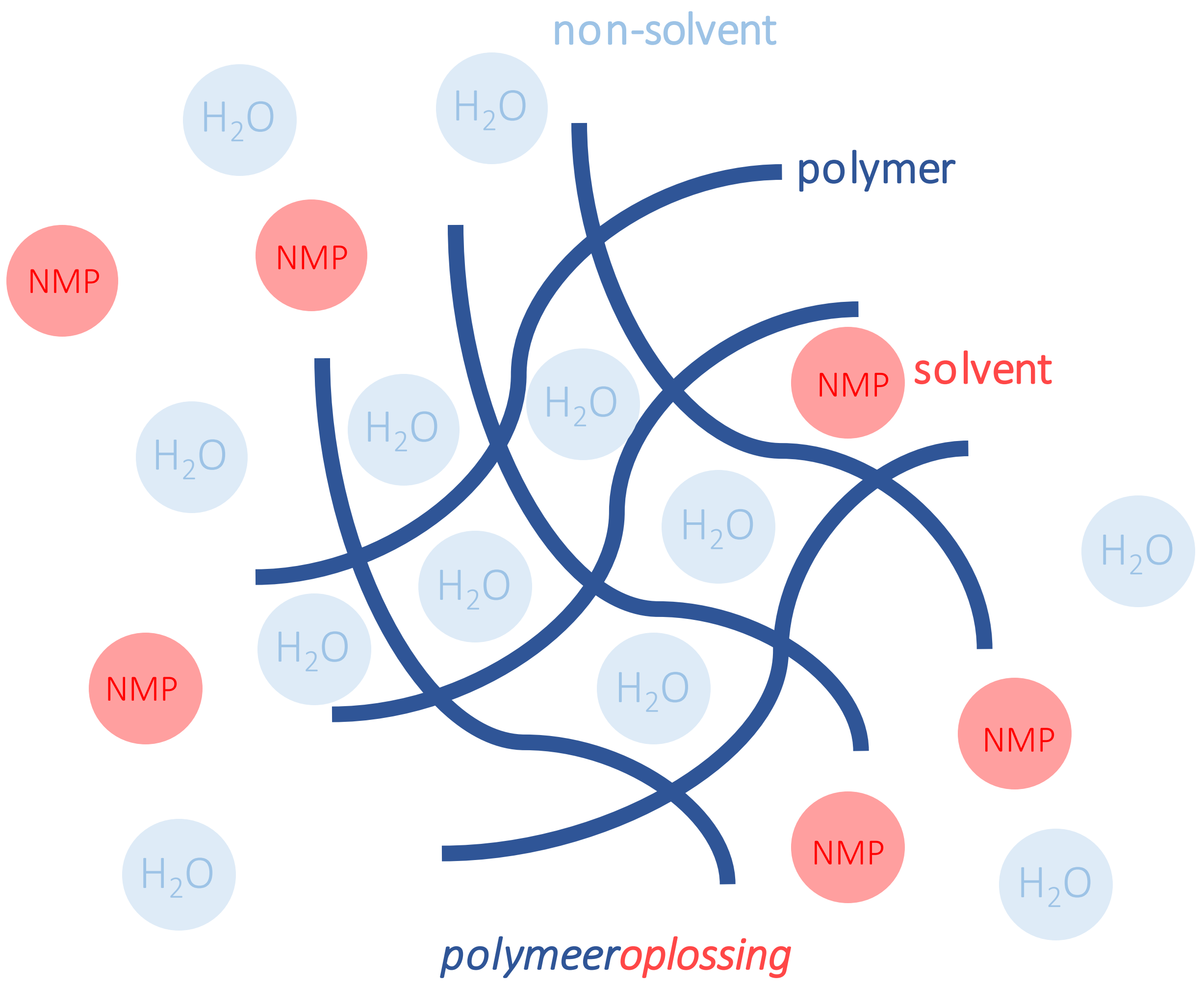

non-solvent
H_2O
H_2O
polymer
H_2O
NMP
NMP
NMP
solvent
NMP
NMP
NMP
NMP
H_2O
H_2O
H_2O
polymeeroplossing



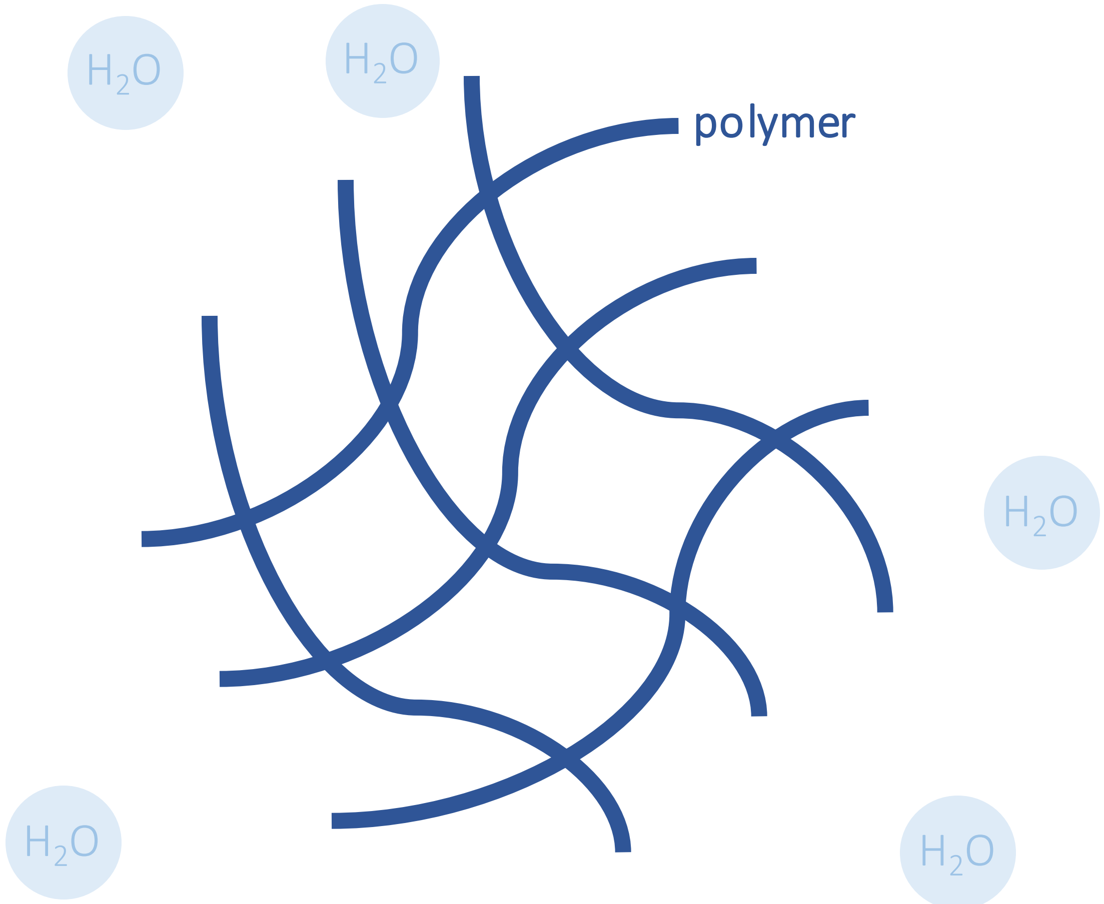
 phase inversion / phase separation



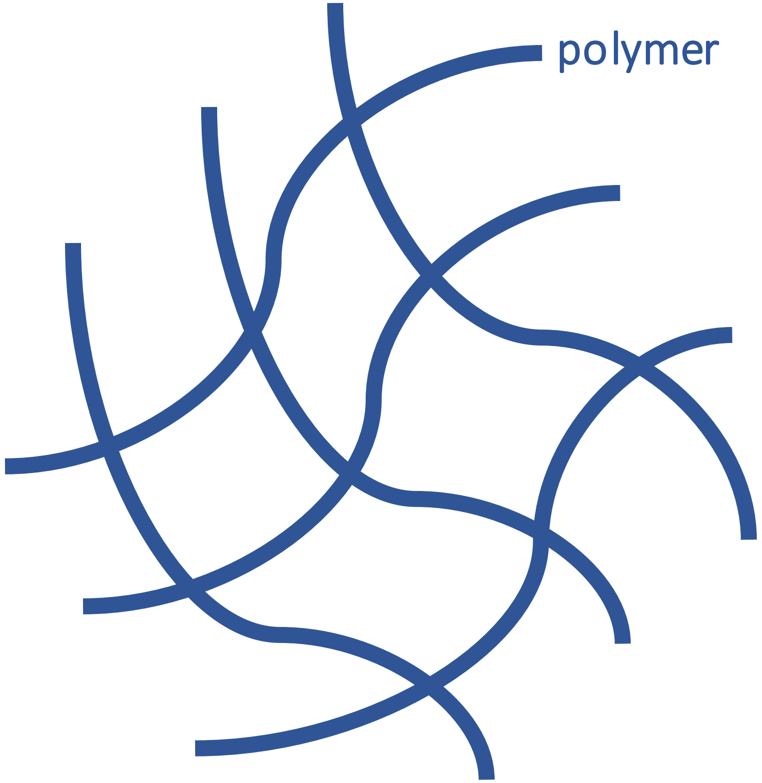
1. Hoe worden dialysemembranen gemaakt? – **phase inversion / phase separation**

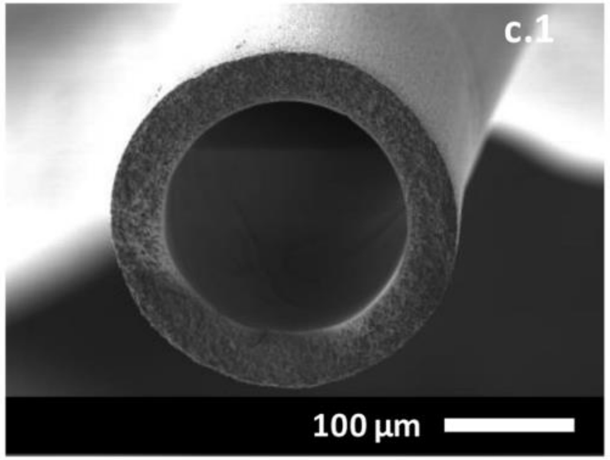


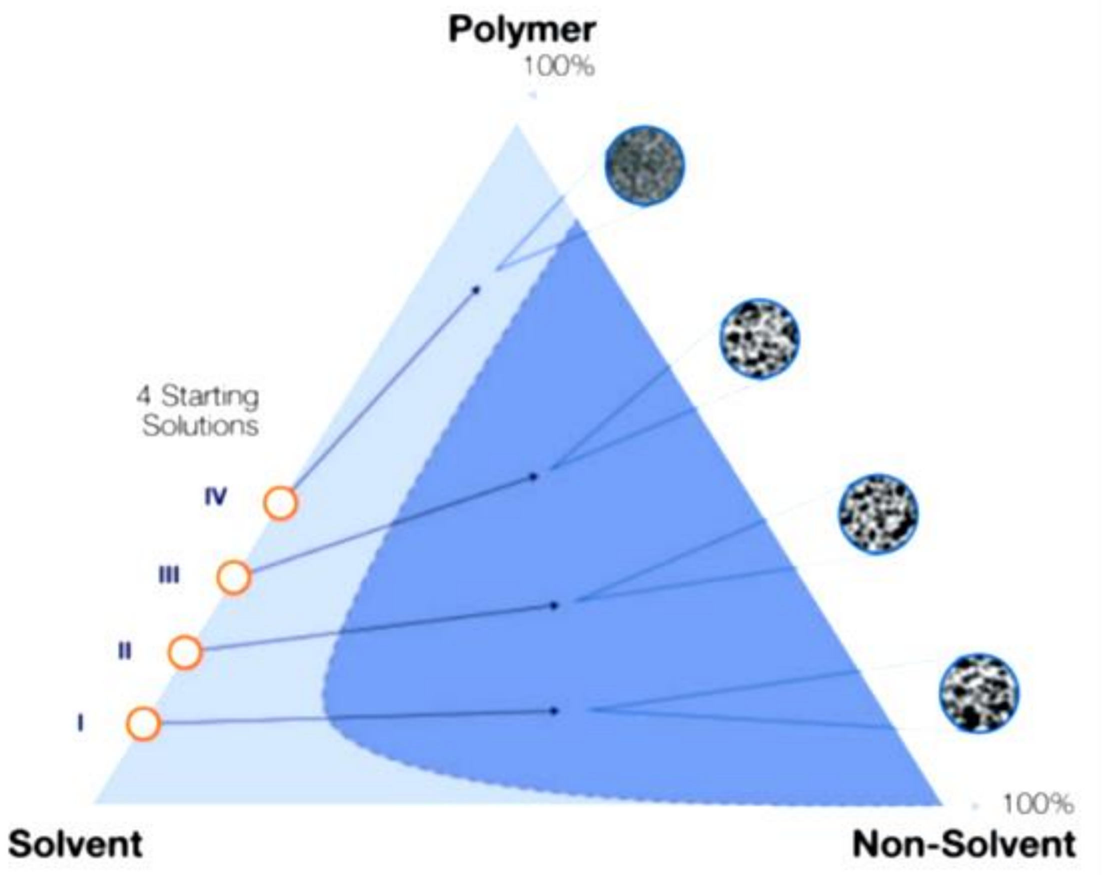
1. Hoe worden dialysemembranen gemaakt? – phase inversion / phase separation



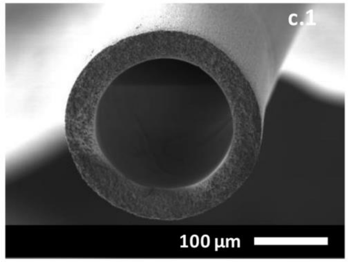
 – phase inversion / phase separation



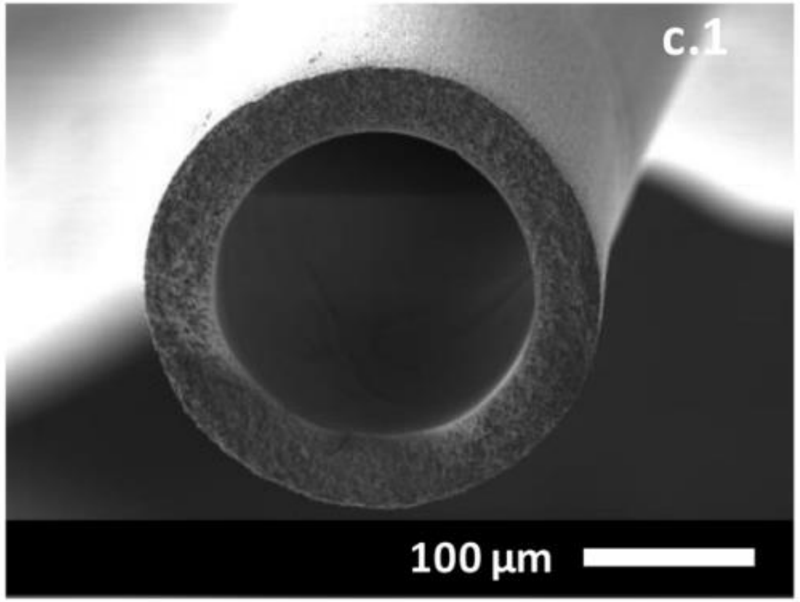




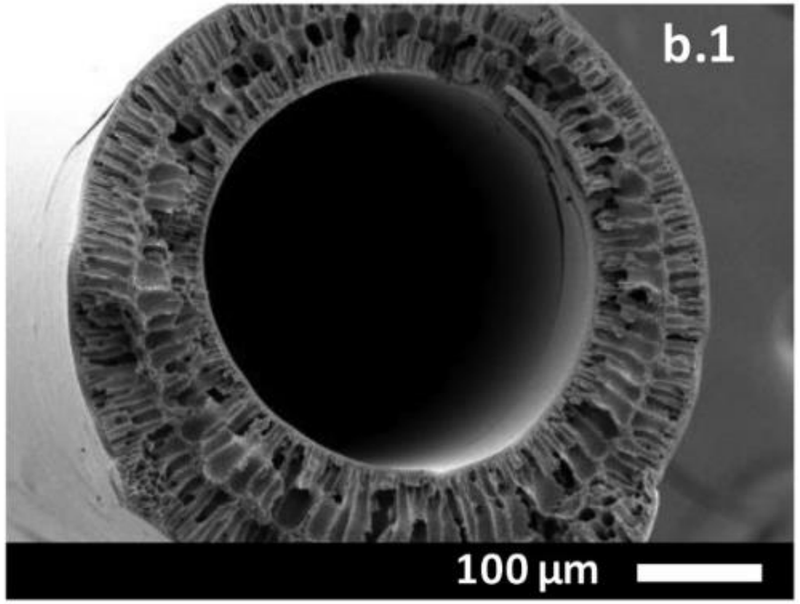
Bowry, S.K. and Chazot, C., Clinical Kidney Journal, **14** (2021), suppl 4, i5-i16.



 phase inversion / phase separation

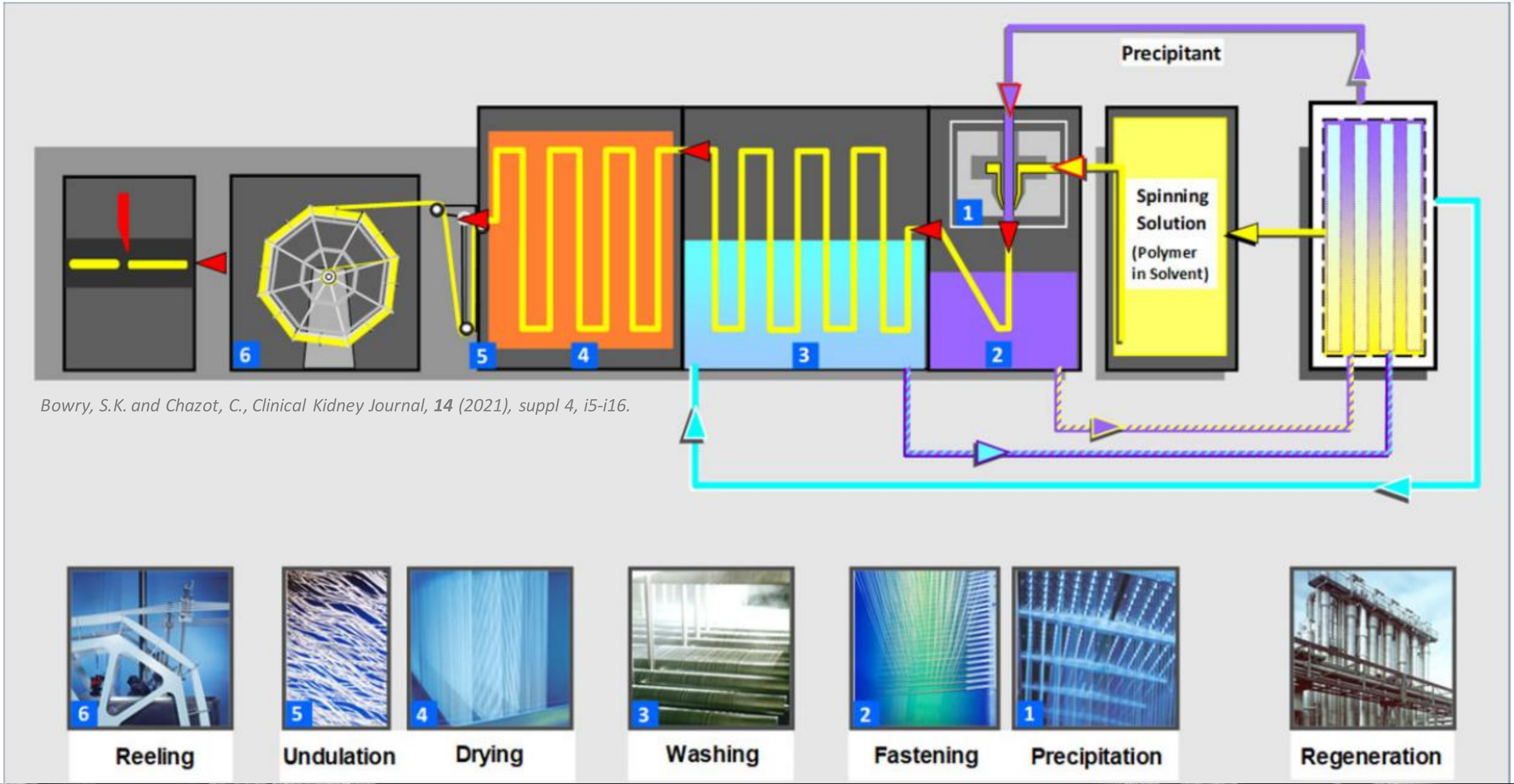


sponge-like structure



finger-like macrovoids

1. Hoe worden dialysemembranen gemaakt?



Bowry, S.K. and Chazot, C., Clinical Kidney Journal, ***14*** *(2021), suppl 4, i5-i16.*

2. Wat zijn de karakteristieken van dialysefilters?

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2. Wat zijn de karakteristieken van dialysefilters?

Table 8. Performance comparison of selected commercial PSf dialyzers on the market.

Dialyzer Brand		**Asahi**			**Baxter**			**Fresenius**			**Toray**		
Product Name		**REXEED**			**Revaclear-400**			**FX80**			**Toraysulfone**		
Blood Flow (mL/min)		200	300	400	200	300	400	200	300	400	200	300	400
[a] Clearance in vitro (mL/min)	Urea	198	280	330	198	281	338	197	276	362	198	277	332
	Creatinine	194	265	309	191	267	315	189	250	287	196	264	308
	Phosphate	190	250	289	185	255	297	185	239	272	196	258	297
	Vitamin B_{12}	152	183	197	158	191	213	148	175	190	162	202	226
	nulin (Q_b = 200 mL/min)	92	-	-	84	-	-	112	125	133	131	162	182
K_oA (mL/min)		1415			1439			1394			1035		
K_{uf} (mL/h.mmHg)		81			54			59			51		

karakteristieken

Table 8. *Cont.*

Dialyzer Brand		**Asahi**	**Baxter**	**Fresenius**	**Toray**
Product Name		**REXEED**	**Revaclear-400**	**FX80**	**Toraysulfone**
Effective surface area (m^2)		1.8	1.8	1.8	1.8
Sieving coefficient	Inulin	1.0	1.0	1.0	0.9
	β_2-M	0.8	0.95	0.7	0.7
	Myoglobin	0.4	0.68	0.1	0.2
	Albumin	0.001	0.0027	<0.001	<0.001

[a] The in vitro performances were evaluated with blood flowrate varied in the range of 200–400 mL/min while dialysate flowrate was fixed at 500 mL/min. Testing temperature is 37 °C.

*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

Classificatie commerciële filters

(A) Permeabiliteit (K_{UF})

(B) Flux (toxin clearance)

(C) Mass transfer-area coëfficiënt (K_0A)

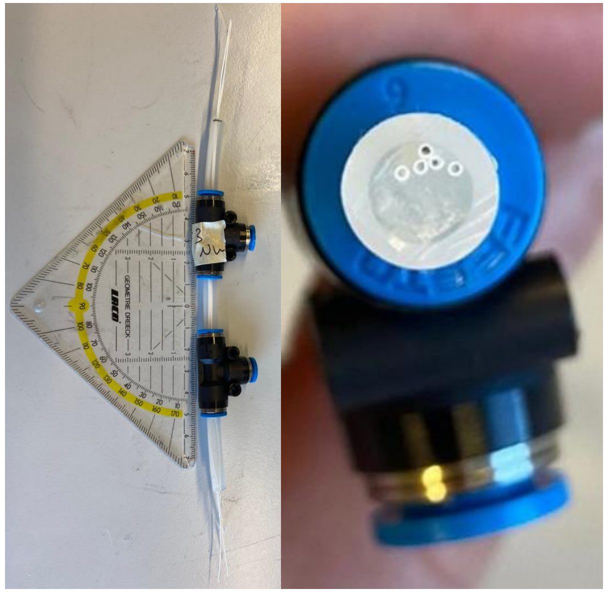
(D) Hemo(in)compatibiliteit

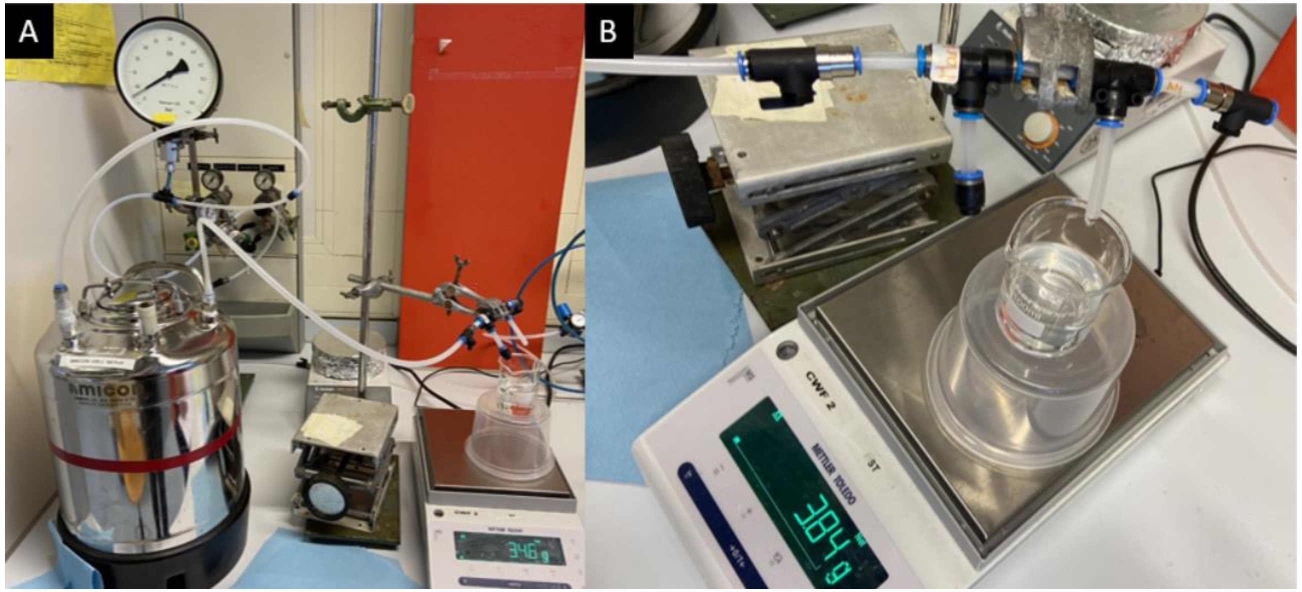
*Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.*

2. Wat zijn de karakteristieken van dialysefilters?

(A) Permeabiliteit (K_{UF})

- Water permeance
- The ultrafiltration coefficient, **K_{UF}** (mL/h·mmHg)





2. Wat zijn de karakteristieken van dialysefilters?

(A) Permeabiliteit (K_{UF})

Class	[a] Ultrafiltration Coefficient, K_{UF} (mL/h/mmHg)	β_2-Microglobulin (β_2-M)		Albumin		Ref
		[b] Clearance (mL/min)	[c] Sieving Coefficient	[d] Loss into Dialysate (g)	[c] Sieving Coefficient	
Low flux	<10	<10	-	0	0	[24]
High flux	20–40	20–80	<0.7–0.8	<0.5	<0.01	[24]
Medium cut-off	40–60	>80	0.99	2–4	<0.01	[28]
Protein leaking	>40	>80	0.9–1.0	2–6	0.01–0.03	[28]
Super high flux	40–60	-	1.0	9–23	<0.2	[29]

[a] The coefficient is a specific property that characterizes a "clean" membrane, i.e., unfouled membrane. [b] For conventional hemodialysis with a blood flow rate of 200–400 mL/min. [c] In vitro for 1.5 m^2 dialyzer. [d] For 4 h conventional hemodialysis.

*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

2. Wat zijn de karakteristieken van dialysefilters?

(A) Permeabiliteit (K_{UF})

- ↑ K_{UF} → ↑ verlies van albumine (grotere membraanporiën)

Class	[a] Ultrafiltration Coefficient, K_{UF} (mL/h/mmHg)	β_2-Microglobulin (β_2-M)		Albumin		Ref
		[b] Clearance (mL/min)	[c] Sieving Coefficient	[d] Loss into Dialysate (g)	[c] Sieving Coefficient	
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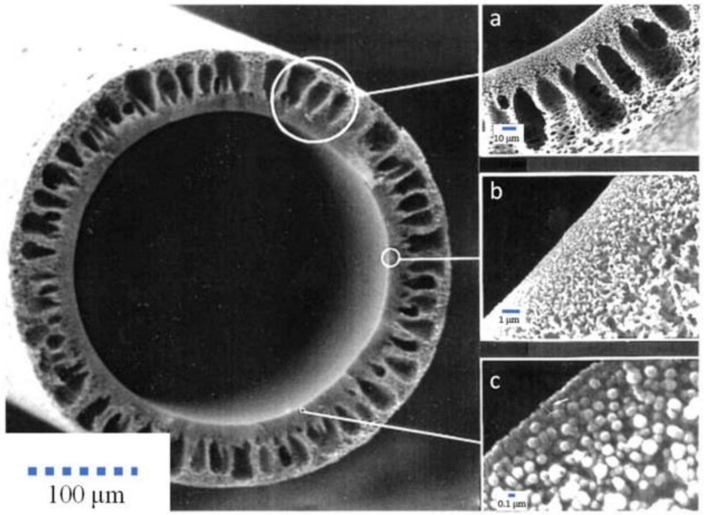
*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

 – 1) Low flux dialyzers



Polyflux L dialyzer (Baxter)
*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

Baxter.com

- **Voordelen:**

  - lage K_{UF}, lagere flow van vloeistoffen

  - geschikt voor pediatrische patiënten

- **Verwijdering:**

  - diffusie

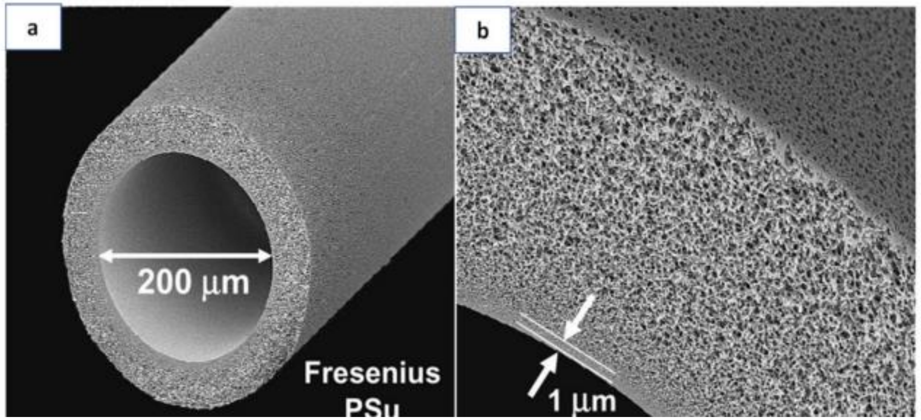
  - kleine, wateroplosbare afvalstoffen

- **Nadelen:**

  - niet geschikt voor verwijdering 'middle molecules', afvalstoffen met een hoger moleculair gewicht en eiwitgebonden afvalstoffen

- **Voorbeelden:** e.g. Polyflux L (Baxter), Hemoflow (Fresenius)

 – 2) High flux dialyzers



Fresenius Helixone dialyzer
*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

Fresenius.com

- **Voordelen:**

  - hoge K_{UF}, hogere flow van vloeistoffen

- **Verwijdering:**

  - diffusie (en convectie)
  - kleine, wateroplosbare afvalstoffen, middle molecules
  - water

- **Nadelen:**

  - hoge flow dialysevloeistof → endotoxines in bloed
  - verlies albumine

- **Voorbeelden:** e.g. Helixone, FX100 (Fresenius), Polyflux H (Baxter)

2. Wat zijn de karakteristieken van dialysefilters? – 3) Andere dialyzers

Theranova
Baxter.com

BK-F series
Toray.com

Eliso HX series
Nipro.com

3) Medium cut-off:

- convectie
- verwijdering van grotere middle molecules

- verlies van albumine

4) Protein leaking:

- verwijdering van kleine, eiwitgebonden afvalstoffen

- relatief nieuw, meer clinical trials nodig om voordelen te onderzoeken

5) Super high flux:

- convectie
- sepsis, AKI
- verwijdering cytokinen

- verlies albumine, hormonen en vitamines

2. Wat zijn de karakteristieken van dialysefilters?

(B) Flux (toxin clearance)

- **Toxin clearance** (mL/min) =

hoeveel toxins in mL, worden er bij een bepaalde flow rate van bloed (Q_b), verwijderd door het dialysefilter?

FX high-flux dialyzers

FX high-flux dialyzers	**FX 50**
Ultrafiltration coefficient (ml/h x mmHg)	33
Clearance: QB: (200ml/min)	
Urea	189
Creatinine	170
Phosphate	165
Vitamin B12	115
Inulin	76

Clearance: QB: (300ml/min)	
Urea	250
Creatinine	210
Phosphate	201
Vitamin B12	130
Inulin	81

freseniusmedicalcare.com

2. Wat zijn de karakteristieken van dialysefilters?

(B) Flux (toxin clearance)

- Flux is **opnieuw gedefinieerd** a.d.h.v. **β_2-M clearance** (reports of improved outcomes from middle molecule removal)

Class	[a] Ultrafiltration Coefficient, K_{UF} (mL/h/mmHg)	β_2-Microglobulin (β_2-M)		Albumin		Ref
		[b] Clearance (mL/min)	[c] Sieving Coefficient	[d] Loss into Dialysate (g)	[c] Sieving Coefficient	
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*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

*Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.*

2. Wat zijn de karakteristieken van dialysefilters?

(C) Mass transfer-area coëfficiënt (K_0A)

- **Mass transfer-area coefficient, K_0A** (mL/min) =

  maximale, theoretische clearance van een afvalstof door diffusie,

  bij oneindige flow rates voor bloed (Q_b) en dialysevloeistof (Q_d)

→ K_0 = mass transfer coëfficiënt

→ A = membraanoppervlak

*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

*Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.*

2. Wat zijn de karakteristieken van dialysefilters?

(C) Mass transfer-area coëfficiënt (K_0A)

- Filter met **$K_0A \leq 500$ mL/min** → small patients
- Filter met **K_0A 500-700 mL/min** → moderate efficiency for high-flux dialyzer
- Filter met **$K_0A \geq 700$ mL/min** → patients with large body size, to achieve high-efficiency dialysis for 4h

*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

*Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.*

2. Wat zijn de karakteristieken van dialysefilters?

(C) Mass transfer-area coëfficiënt (K_0A)

- ↑ K_0A → ↑ **efficiënter filter**

  → pore density

  → pore size distribution

  → resistance to toxin passage

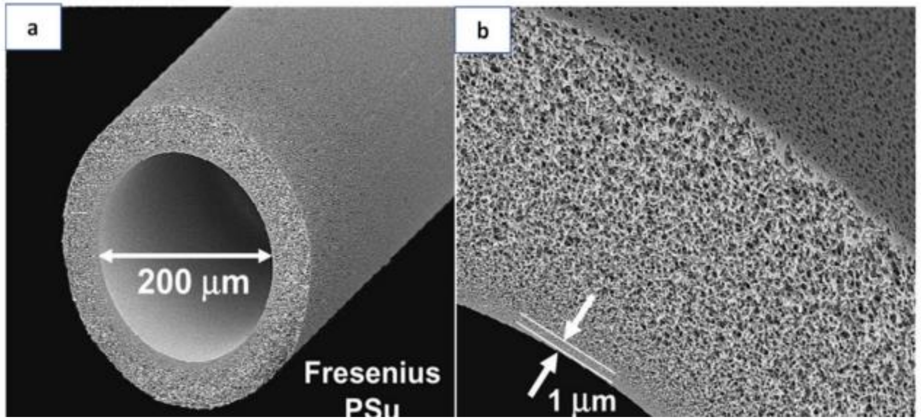
- Membraanstructuur: meer kleine poriën, dan grote poriën

  → **small toxins (urea):** 'makkelijk' transport door al deze poriën

  'flow rate-afhankelijk'

  → **larger toxins (β_2-M):** alleen door de grotere poriën

  'membraanafhankelijk'



*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

*Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.*

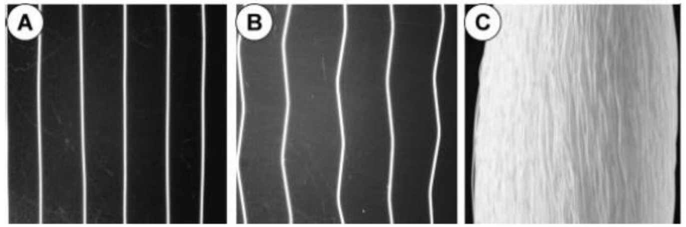
Fresenius Helixone dialyzer
*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

(C) Mass transfer-area coëfficiënt (K_0A)

- Voor de **optimalisatie van toxin clearance** → is het belangrijk om de efficiëntie van het filter te verbeteren, door **Q_b en Q_d te manipuleren**.
- *Hoe?*
- Dialyzer K_0A ↑ → ↑ Q_b en Q_d

  want, een hogere flow rate (Q) → ↓ dikte van stagnerende vloeistoflaag

  → ↓ weerstand voor toxin-transport



Fiber corrugation increases local mixing

- ↑ K_0A → **Q_d heeft grotere impact** dan Q_b !!

  $Q_d \geq 2x\ Q_b$ → hoge concentratiegradiënt blijft behouden tussen bloed- en dialysevloeistofcompartimenten

*Said, N. et al., Membranes, **11**(767) (2021), p. 1-38.*

*Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.*

Stamatialis, D. (2022).

2. Wat zijn de karakteristieken van dialysefilters?

(D) Hemo(in)compatibiliteit

- **Alle interacties** tussen bloed en het dialysemembraan

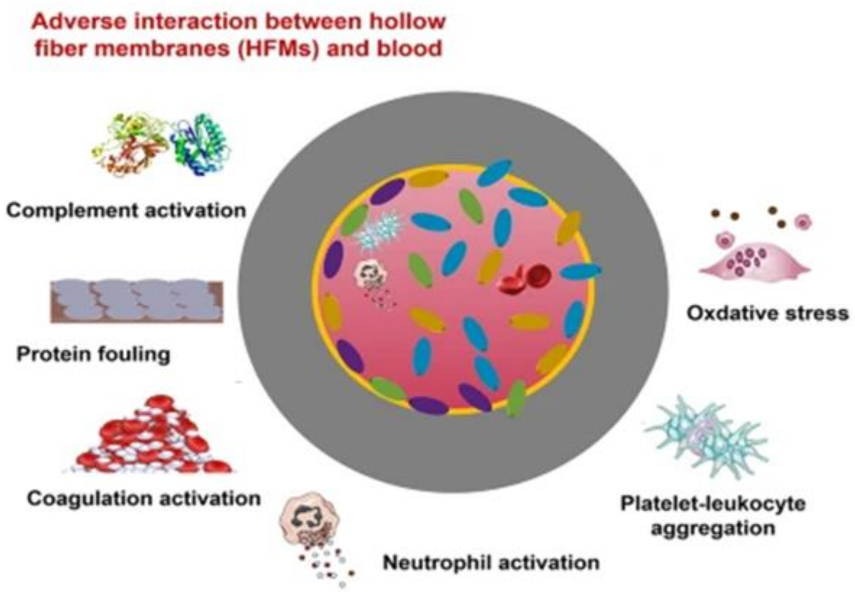
→ Lage binding van eiwitten aan membraanoppervlak/ in poriën (fouling)

→ Lage trombinegeneratie en coagulatie

→ Geen allergische reacties

→ Geen interacties met toegediende medicijnen

→ …



Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.

Adapted from Ji, H., et al., Advanced Fiber Materials, **5**, (2023), p. 1198-1240.

2. Wat zijn de karakteristieken van dialysefilters? – de nadelen

A. Wegwassen van materiaal

&

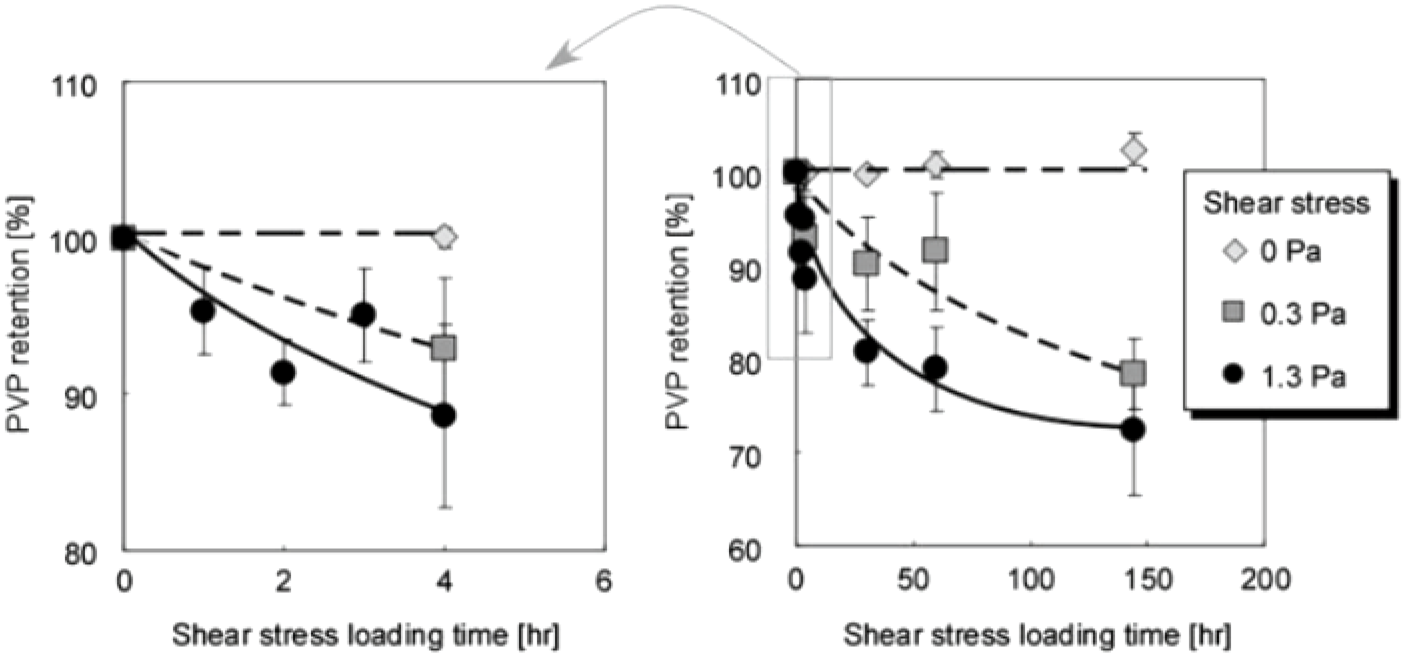
B. Verstopping van dialysefilters

&

C. Verwijdering van eiwitgebonden afvalstoffen

(hippuurzuur, indoxylsulfaat)

A. Wegwassen van materiaal



*Matsuda, M. et al., J. Artif. Organs, **11**(2008), pp. 148-155.*

B. Verstopping van dialysefilters

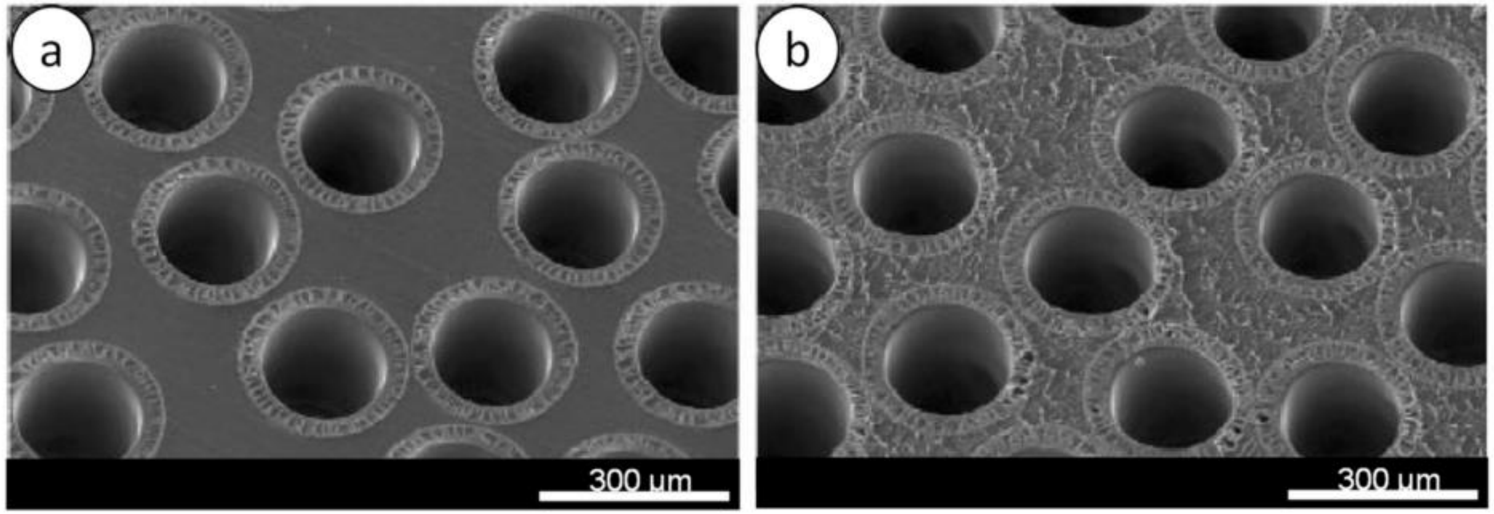
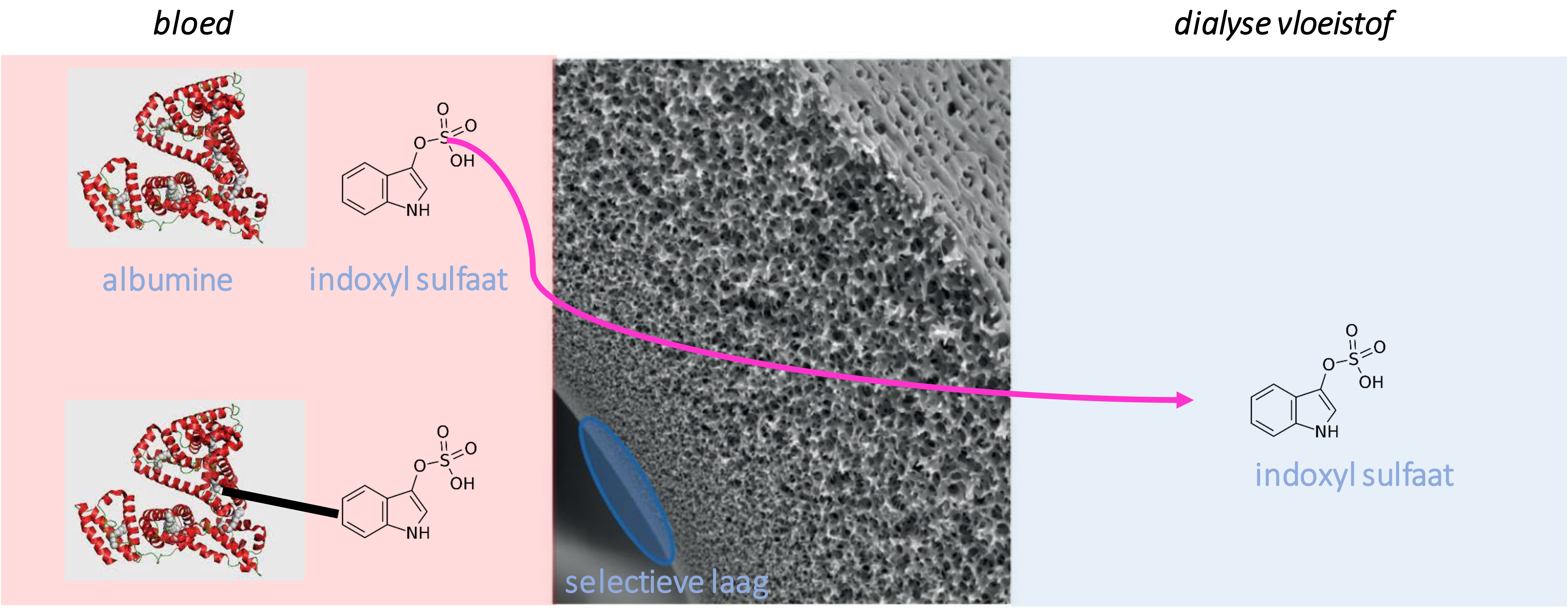


Figure 9. SEM images of the cutting surfaces of two dialyzers, (**a**) smooth blood contacting surface and (**b**) rough blood contacting surface [118].

*Dukhin, S.S., et al. Journal of Membrane Science, **464**(2014), p. 173-178*

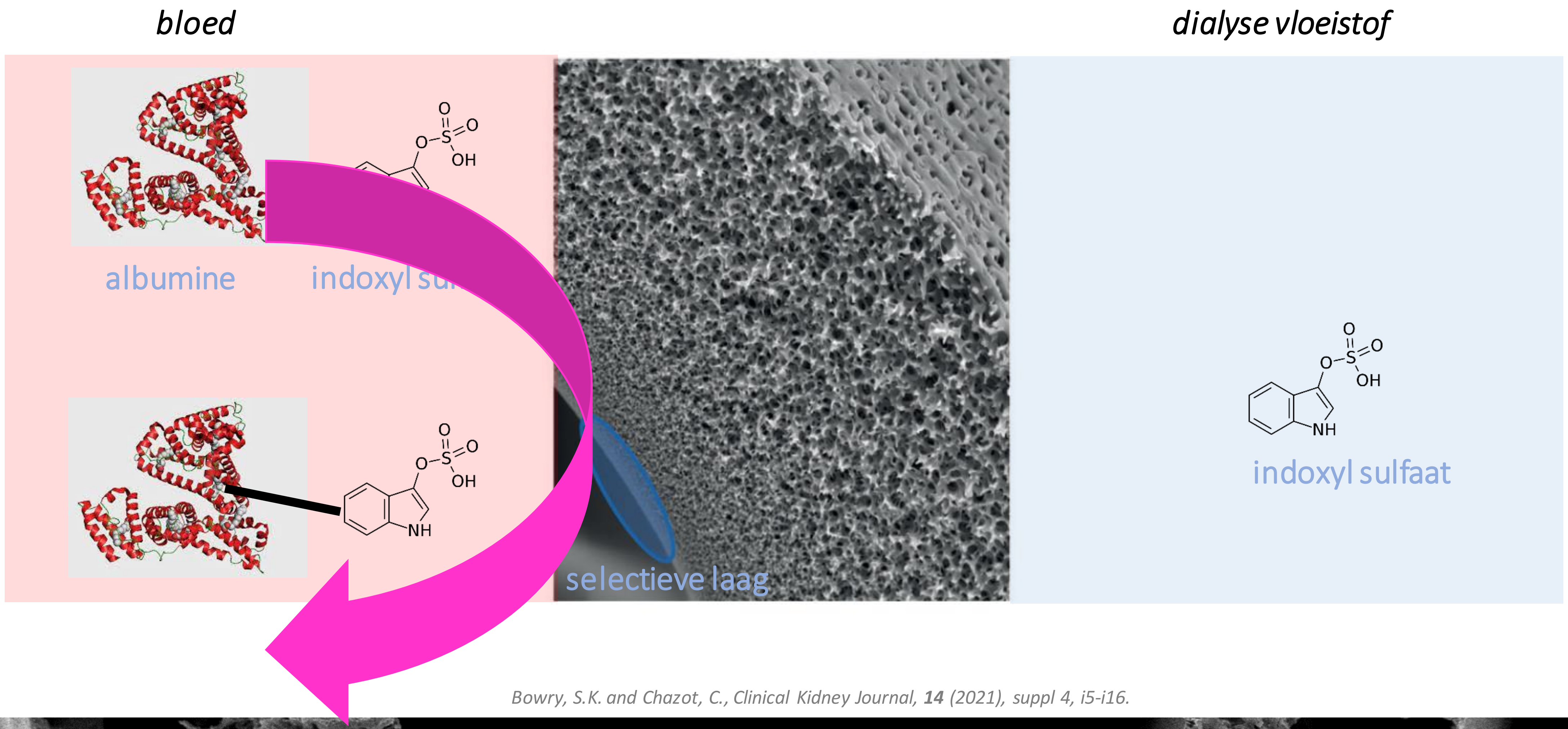
*Haroon, S. and A. Davenport, Hemodialysis International, **22**, (2018), p. S65-S74.*

C. Verwijdering van eiwitgebonden afvalstoffen



Bowry, S.K. and Chazot, C., Clinical Kidney Journal, ***14*** *(2021), suppl 4, i5-i16.*

C. Verwijdering van eiwitgebonden afvalstoffen

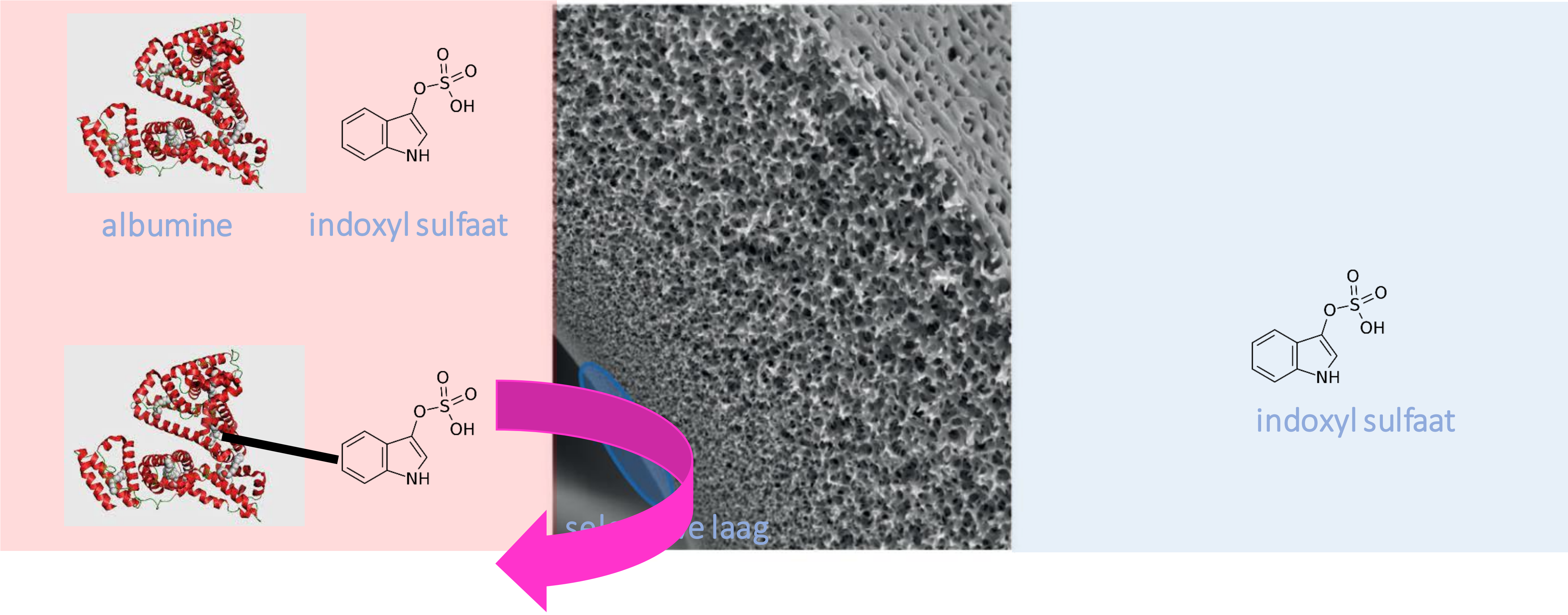


Bowry, S.K. and Chazot, C., Clinical Kidney Journal, **14** (2021), suppl 4, i5-i16.

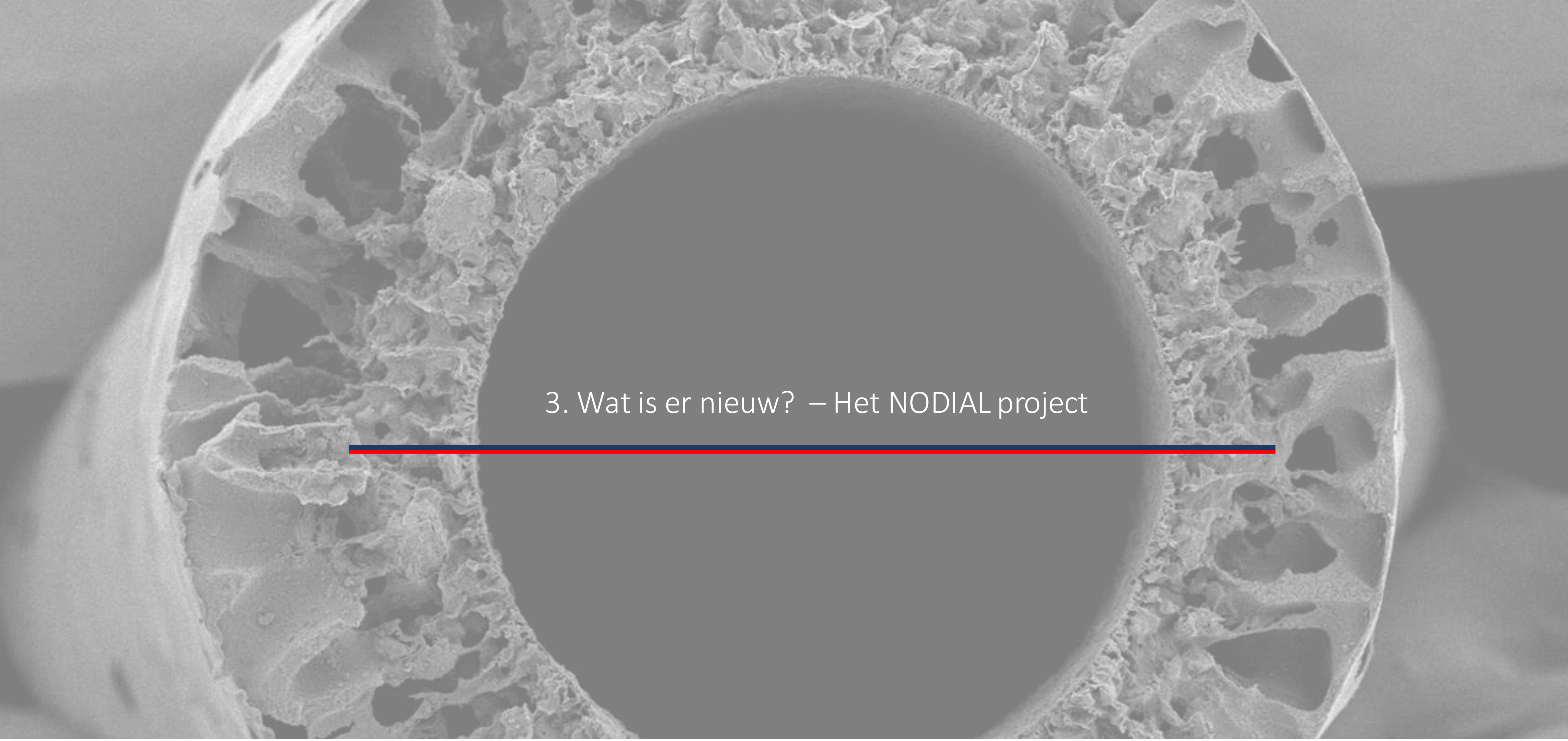
C. Verwijdering van eiwitgebonden afvalstoffen

bloed

dialyse vloeistof



*Bowry, S.K. and Chazot, C., Clinical Kidney Journal, **14** (2021), suppl 4, i5-i16.*



3. Wat is er nieuw? – Het NODIAL project

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Wetenschapsdag 2023

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nieren.nl

Betere dialysefilters – Het NODIAL project

→ **NODIAL** = **NO**vel membrane **DIAL**yzers for portable/artificial kidney devices

Universiteit Twente

David Ramada

Universiteit Twente

Dimitrios Stamatialis

Radboud UMC

Johan van der Vlag

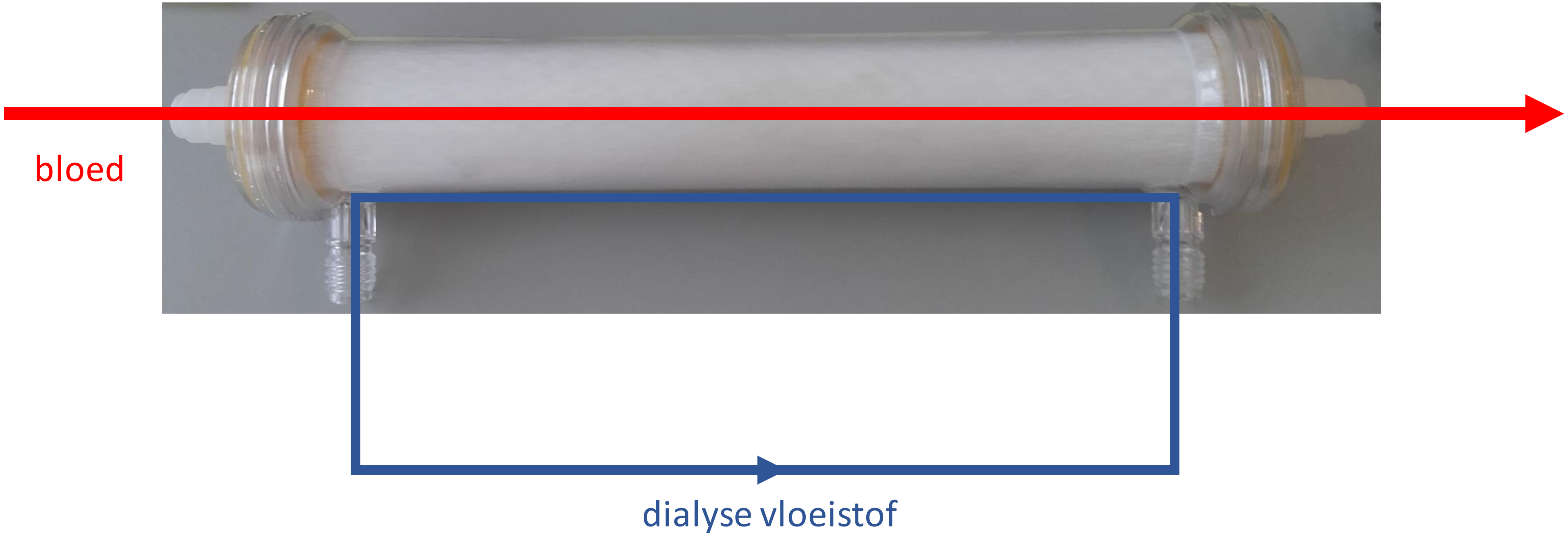
NIERSTICHTING
Leven gaat voor.

NovaFlux

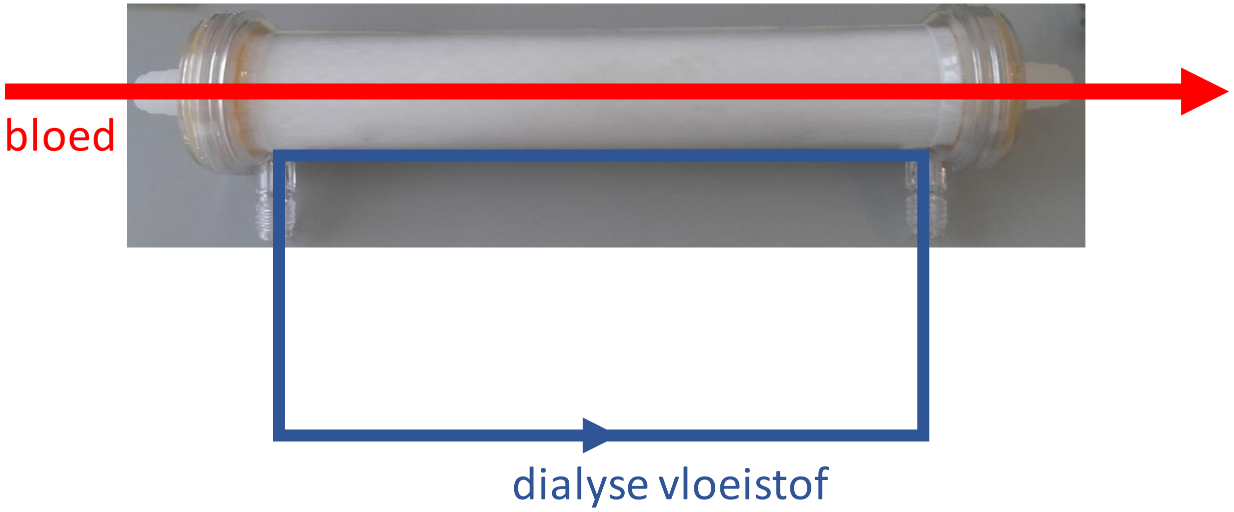
Betere dialysefilters – Het NODIAL project

→ Combinatie van **'outside-in' configuratie** & **Mixed Matrix Membranen**

Het NODIAL project – ‘outside-in’ configuratie

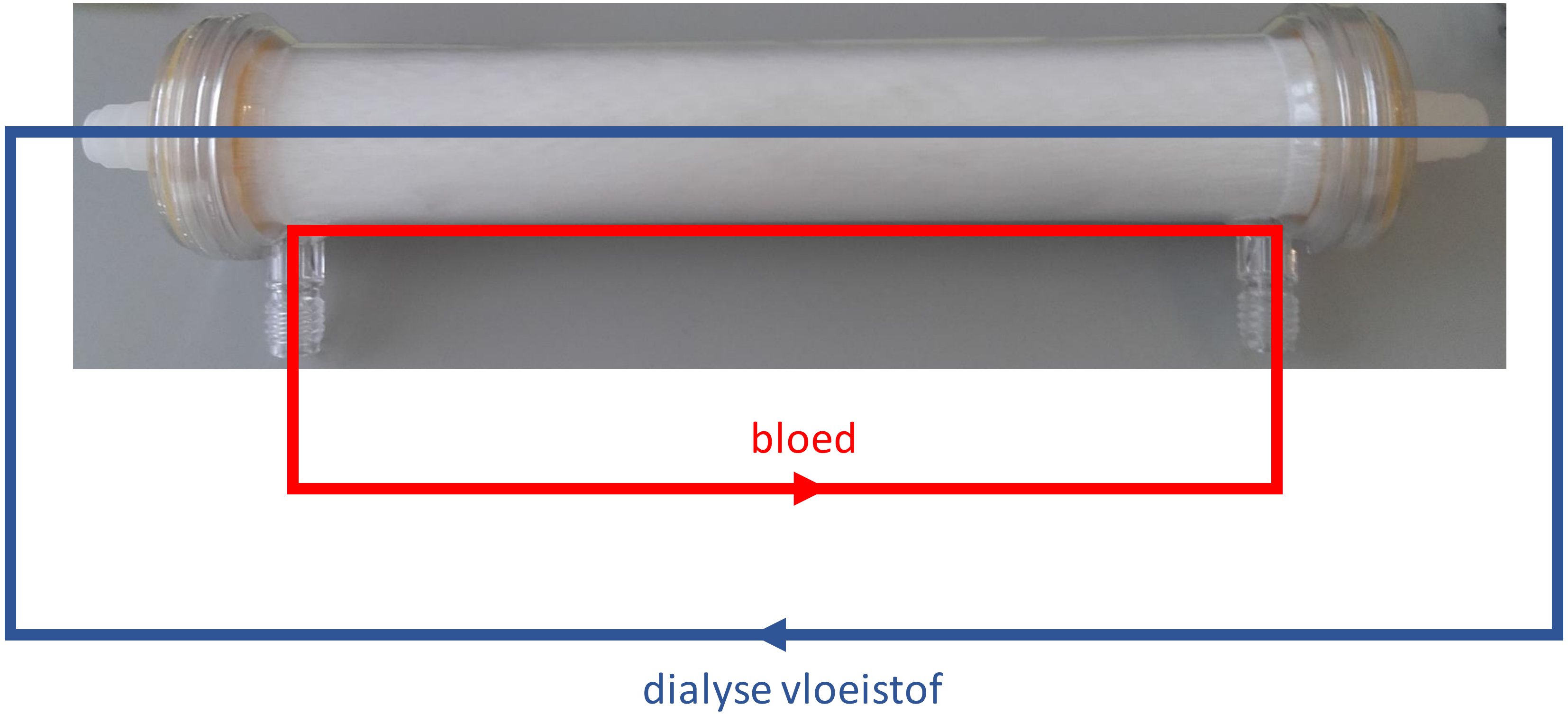


Het NODIAL project – 'outside-in' configuratie

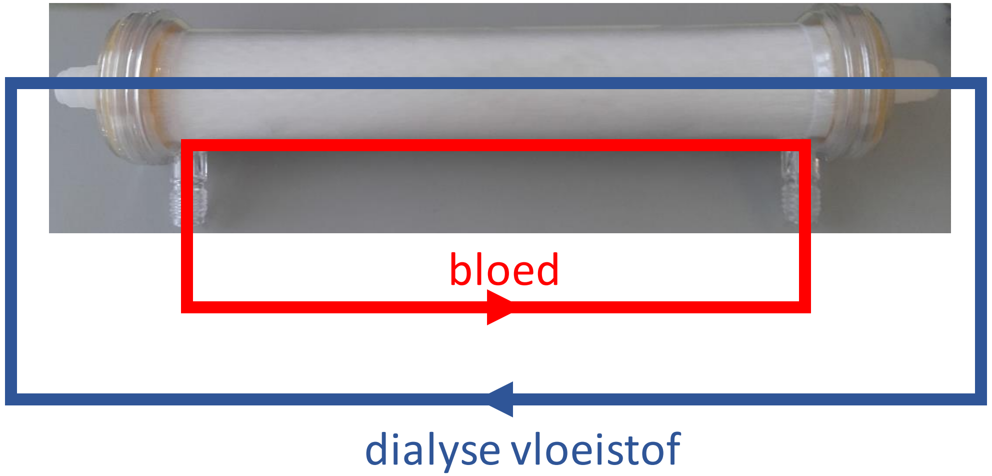


Dukhin, S.S., et al. Journal of Membrane Science, ***464****(2014), p. 173-178*

Het NODIAL project – ‘outside-in’ configuratie

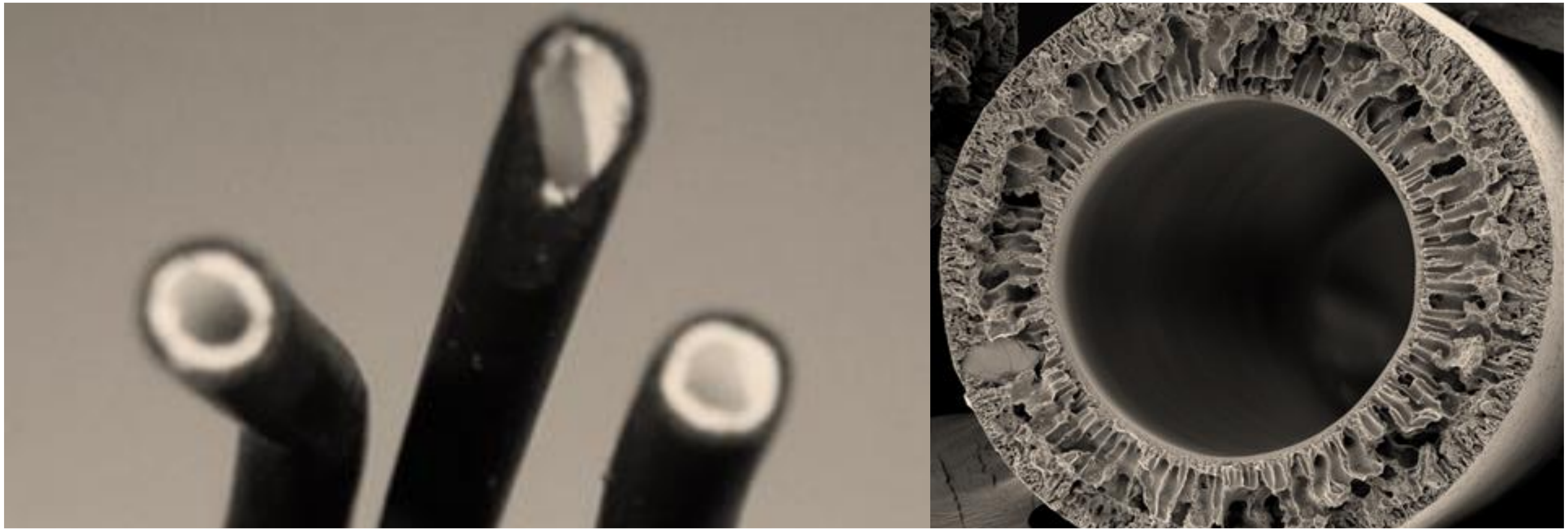


Het NODIAL project – ‘outside-in’ configuratie



Dukhin, S.S., et al. Journal of Membrane Science, ***464****(2014), p. 173-178*

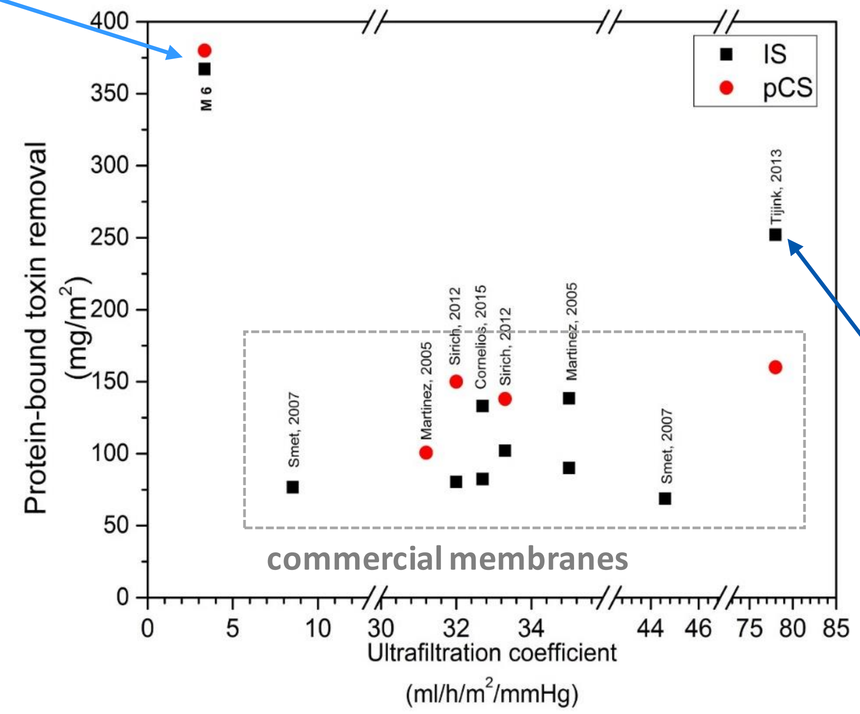
Het NODIAL project – Mixed Matrix Membranen



Het NODIAL project – Mixed Matrix Membranen

MMM 2.0

K_{uf} = 5
No albumin leakage



MMM 3.0

PBUT removal = 500 mg/m²
K_{uf} = 100
No albumin leakage

MMM 1.0

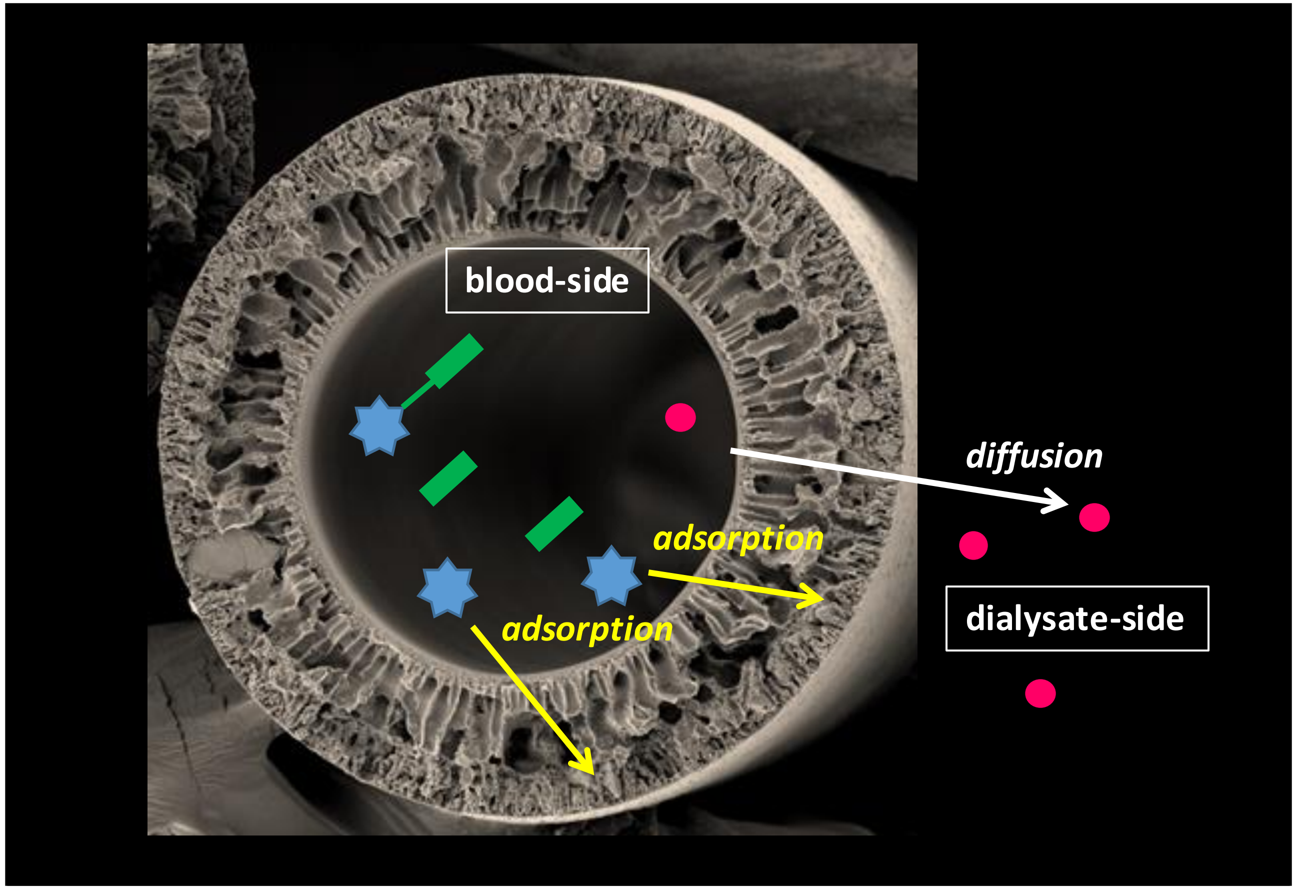
K_{uf} = 75
Albumin leakage

Pavlenko et al., Nat. Sci. Reports (2016)

Hoe werkt een dialysefilter?

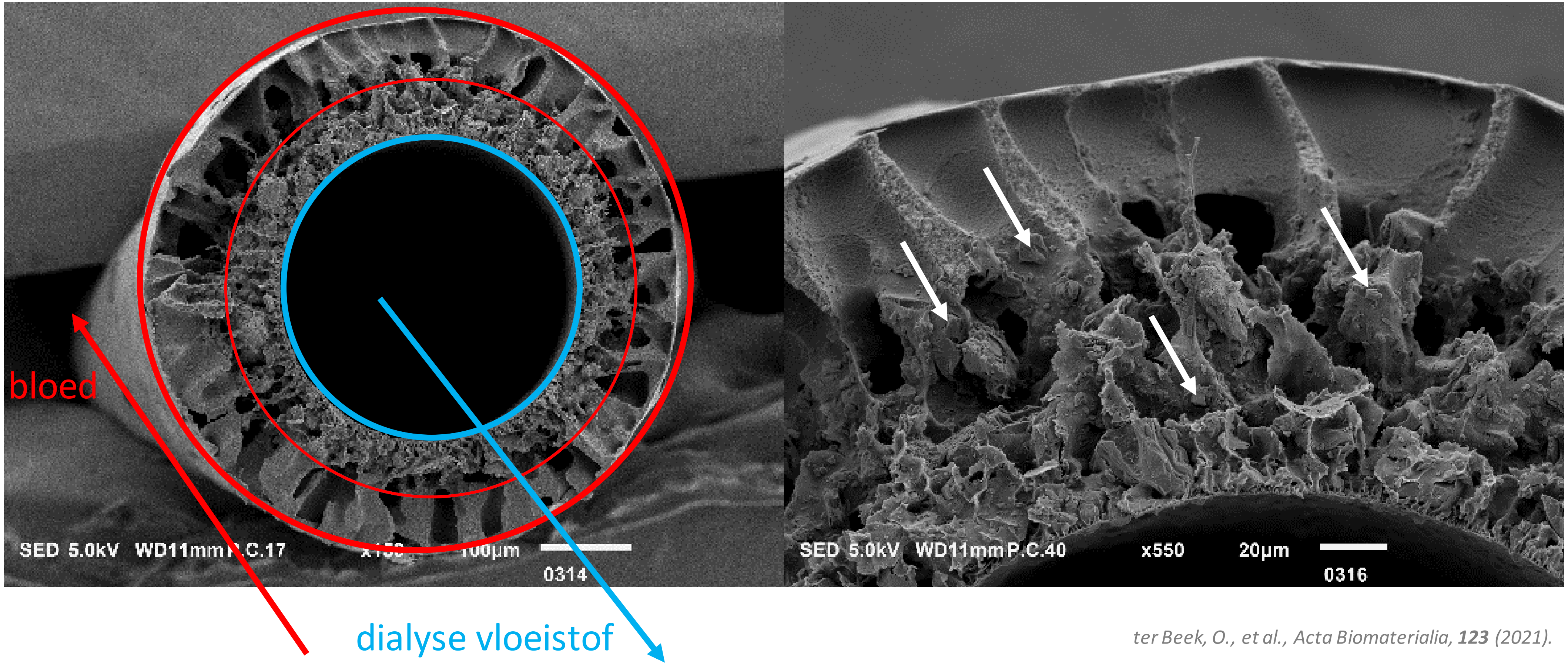
(opstelling dialyse)

Het NODIAL project – Mixed Matrix Membranen



$$\text{protein-bound toxins} \underset{}{\overset{\textit{adsorption}}{\rightleftarrows}} \text{proteins} + \text{toxins}$$

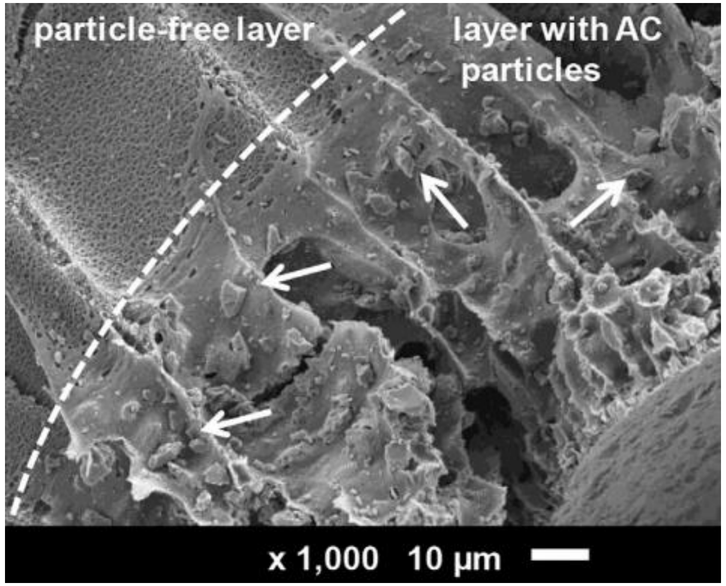
Het NODIAL project – MMM voor OIF



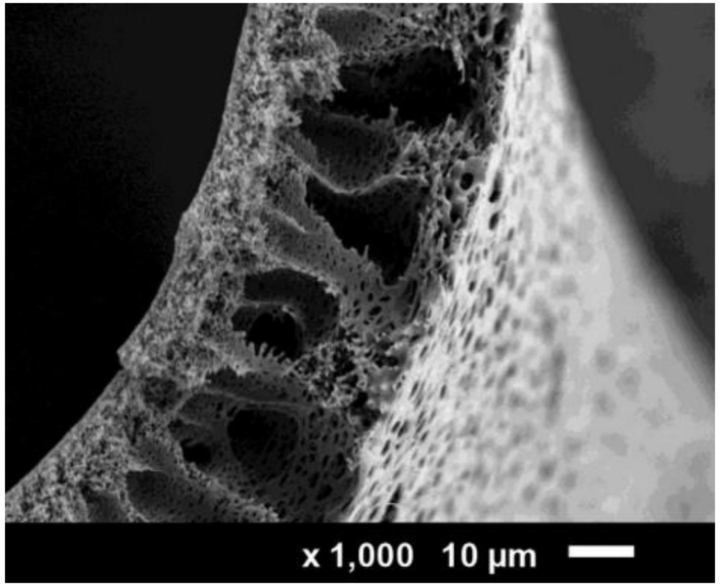
ter Beek, O., et al., Acta Biomaterialia, ***123*** *(2021).*

Het NODIAL project – MMM voor OIF

'Outside-in MMM'

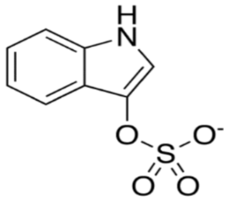


Polyflux 2H



*ter Beek, O., et al., Acta Biomaterialia, **123** (2021).*

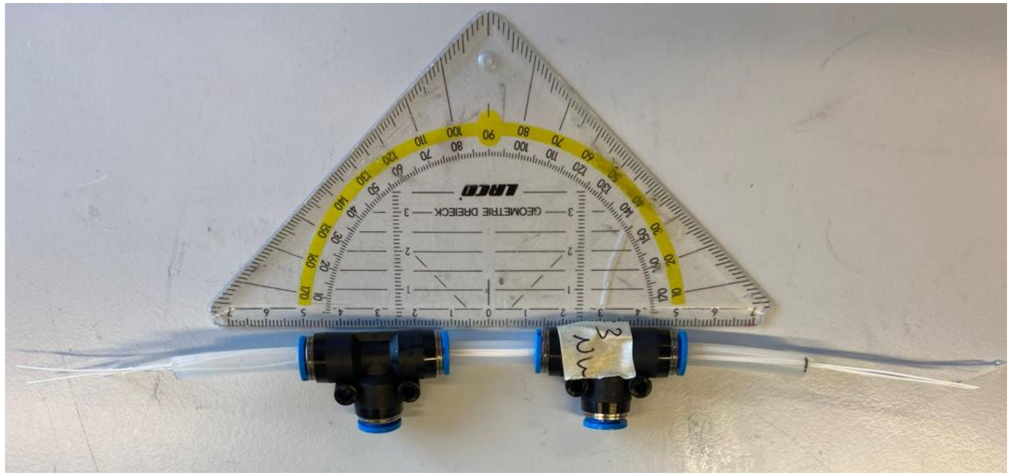
	MMM – OIF mode	Polyflux 2H – IOF mode	Polyflux 2H – OIF mode
Total IS removal - 4h (mg/m^2)	**860 ± 112**	374 ± 12	366 ±16



indoxylsulfaat (IS)

Het NODIAL project – De volgende stap …

Onze 'mini dialysefilters'

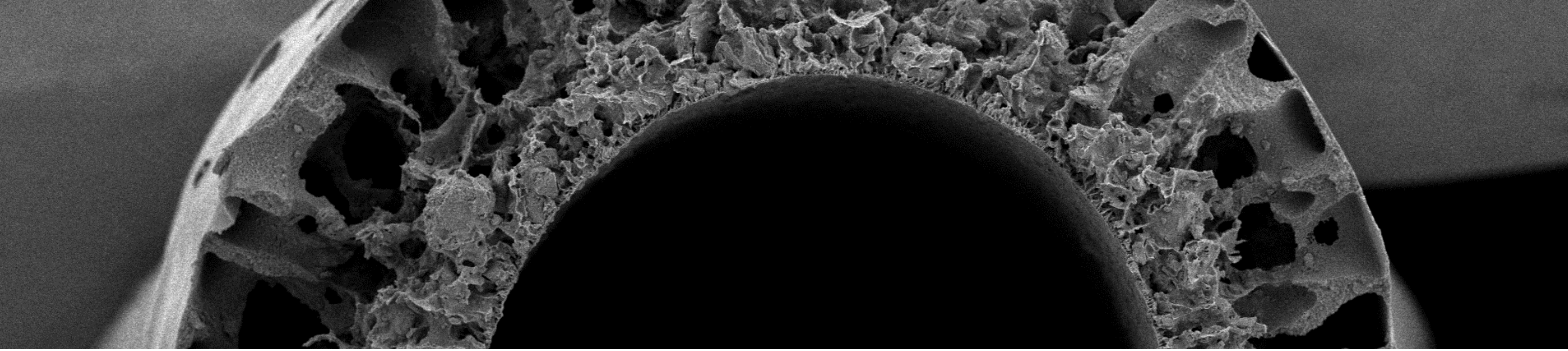


$0{,}001\ m^2$

Dialysefilters

Fresenius

$0{,}2\ m^2$ - $2{,}0\ m^2$



Onderzoek naar betere dialysefilters

Het NODIAL-project

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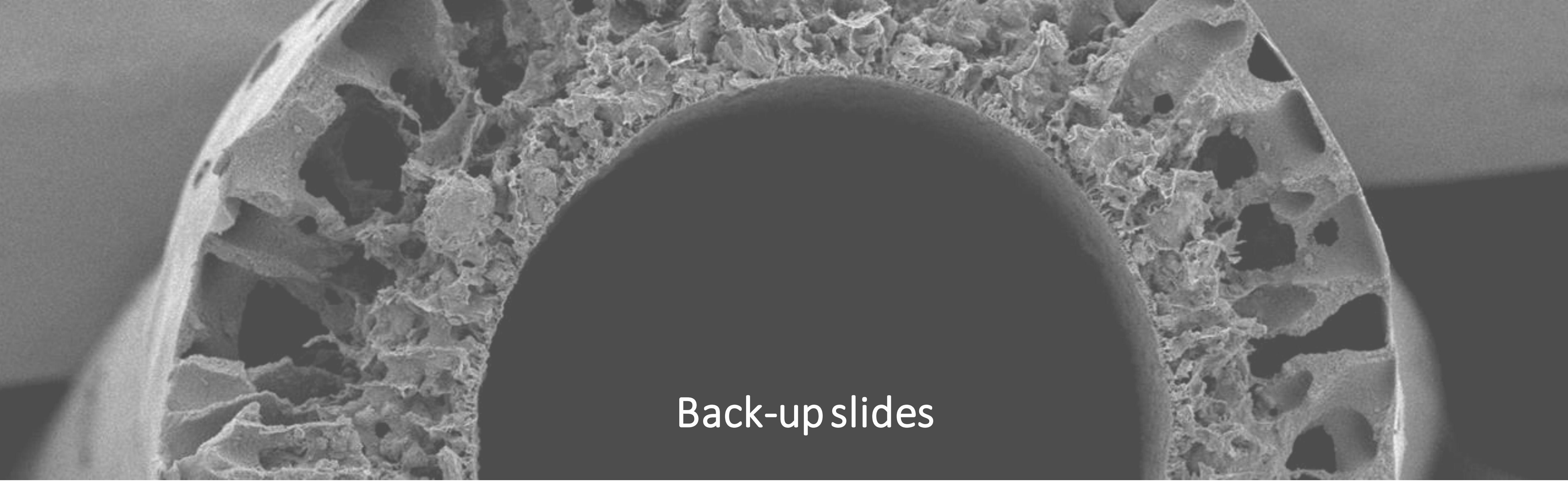

Back-up slides

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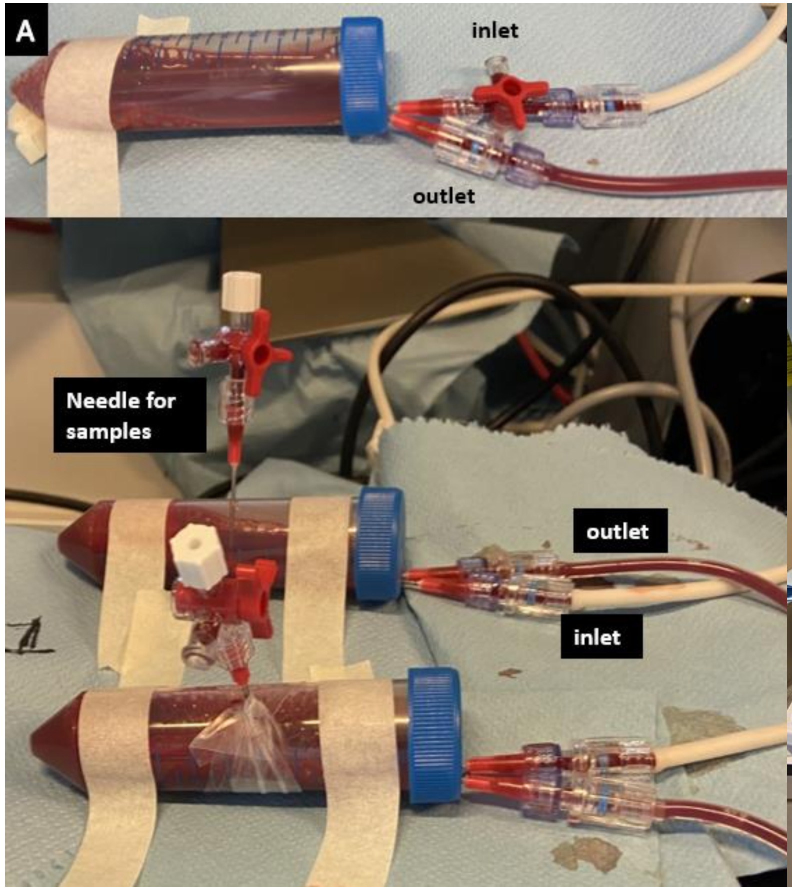
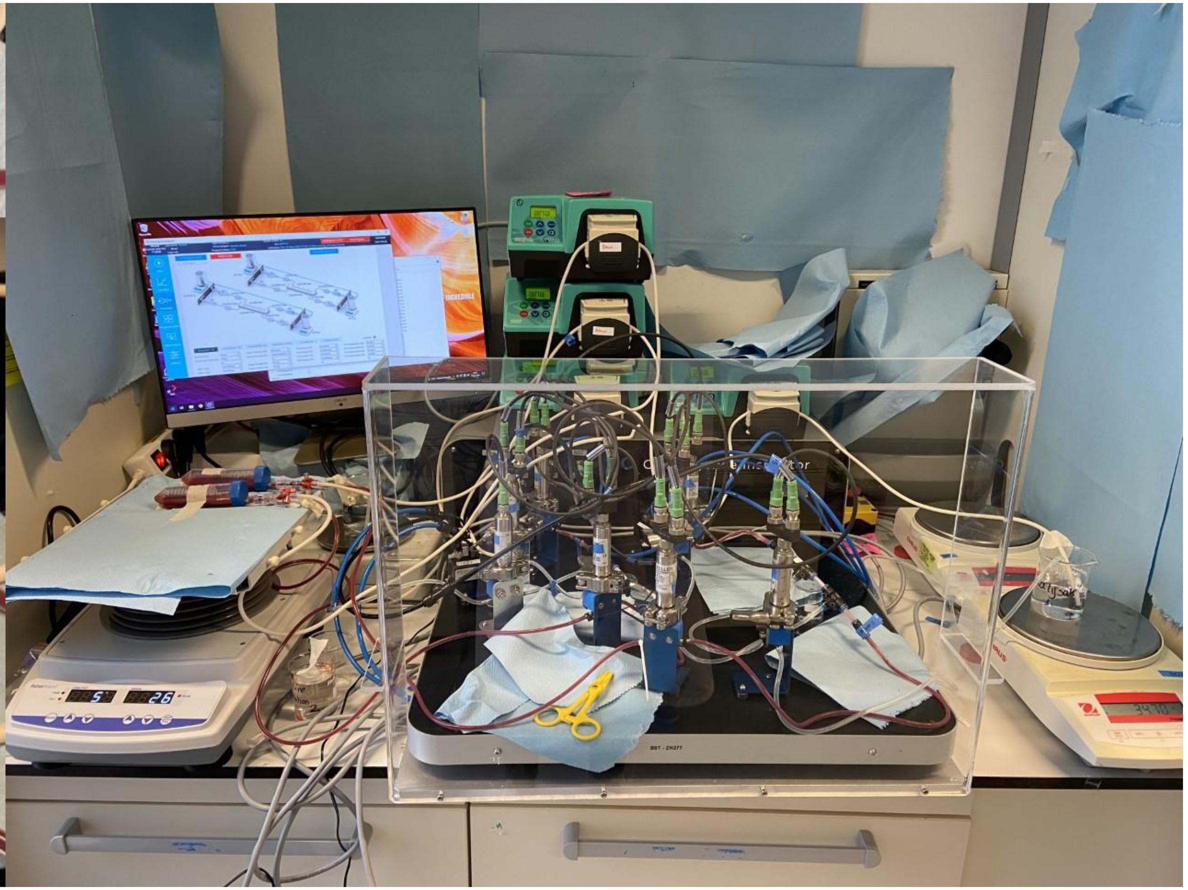
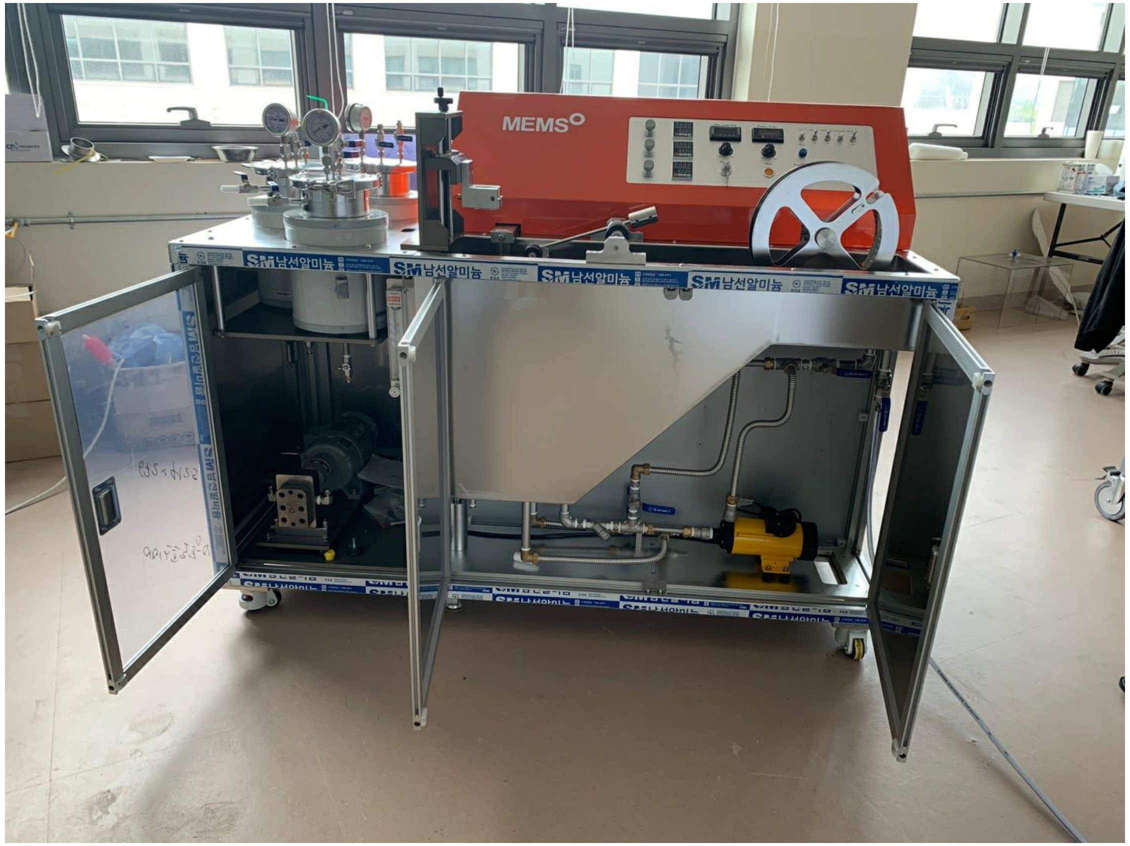
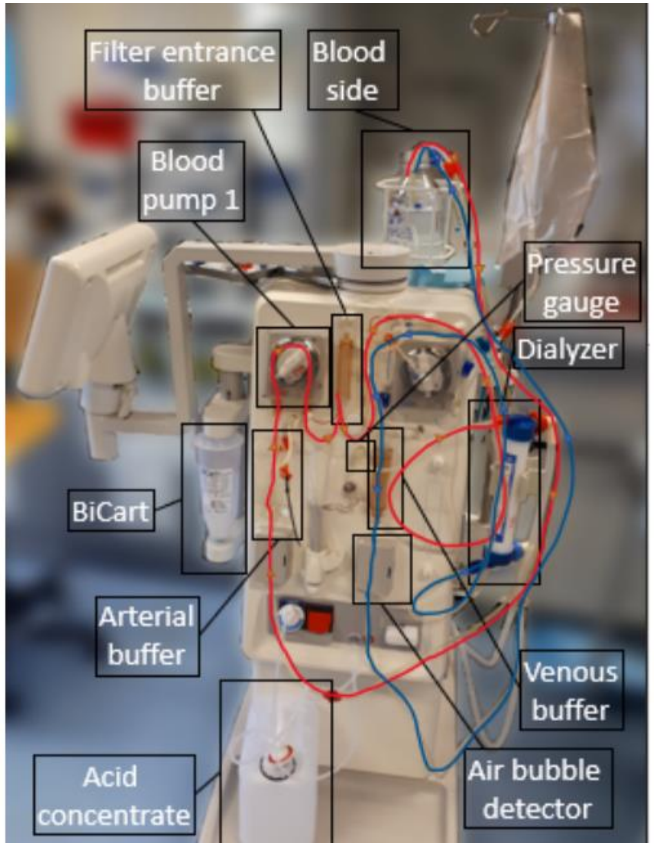

A
inlet
outlet
Needle for samples
outlet
inlet




MEMS


Filter entrance buffer
Blood side
Blood pump 1
Pressure gauge
Dialyzer
BiCart
Arterial buffer
Venous buffer
Acid concentrate
Air bubble detector