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Development and characterization of nanofibrous membrane for the treatment of congenital diaphragmatic hernia

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Abstract

Congenital Diaphragmatic Hernia (CDH) is a rare malformation, a hole in the diaphragm is formed early in the embryogenesis. For the most severe cases of CDH, a prosthesis is necessary to fill the hole in the diaphragm. The major issue is that the currently used prosthesis cannot follow the growth of the child. Their mechanical properties are not suitable in terms of stretchability and rigidity, leading to the break of the stretches and recidivism of the hernia. We aim to change the paradigm by designing a biocompatible prosthesis adapted to the disease with two distinct faces: one smooth side to impair the intestine adherence on the abdominal side and one fibrous side to enhance the cellular colonization to improve the integration of the prosthesis to the diaphragm. To follow the growth of the child, the mechanical specifications are the following: a 300 % minimum stretchability and a rigidity similar to the muscle. A medical grade elastomeric thermoplastic polyurethane (TPU) was processed using electrospinning. A semi-diluted entangled polymer solution is stretched in a jet-like form, under a strong electric field, leading to the formation of a nano-fibrous membrane on a grounded collector. Electrospinning formulation and process parameters, using a 4-needles set-up, were studied to obtain fibrous membranes. Then, the preparation of bilayered membrane with a smooth film layer and a rough fibrous layer was investigated. To avoid delamination between the two layers, the membranes were fabricated in a continuous process by varying the flow rate of the solution during electrospinning. A 4-needles emitter was used to increase the production yield and its translation was optimized to ensure the thickness homogeneity of the membrane (Figure 1). It was shown that mechanical properties are impacted by the ratio of film to total thickness. A panel of membranes was thus designed varying this ratio from 0 (only fibers) to 1 (only film) allowing to modulate the mechanical properties of the membrane (tensile strength, elongation at break, Young modulus, Figure 2). The membrane exhibiting the best mechanical properties was compared with the current prosthesis. The specifications in terms of stretchability were successfully doubled (600 %) and the rigidity was considerably lowered (2.5 MPa). Further biological and mechanical tests, such as uniaxial tensile tests on the stretched membrane or bi-axial tensile tests, are currently ongoing to complete the study.

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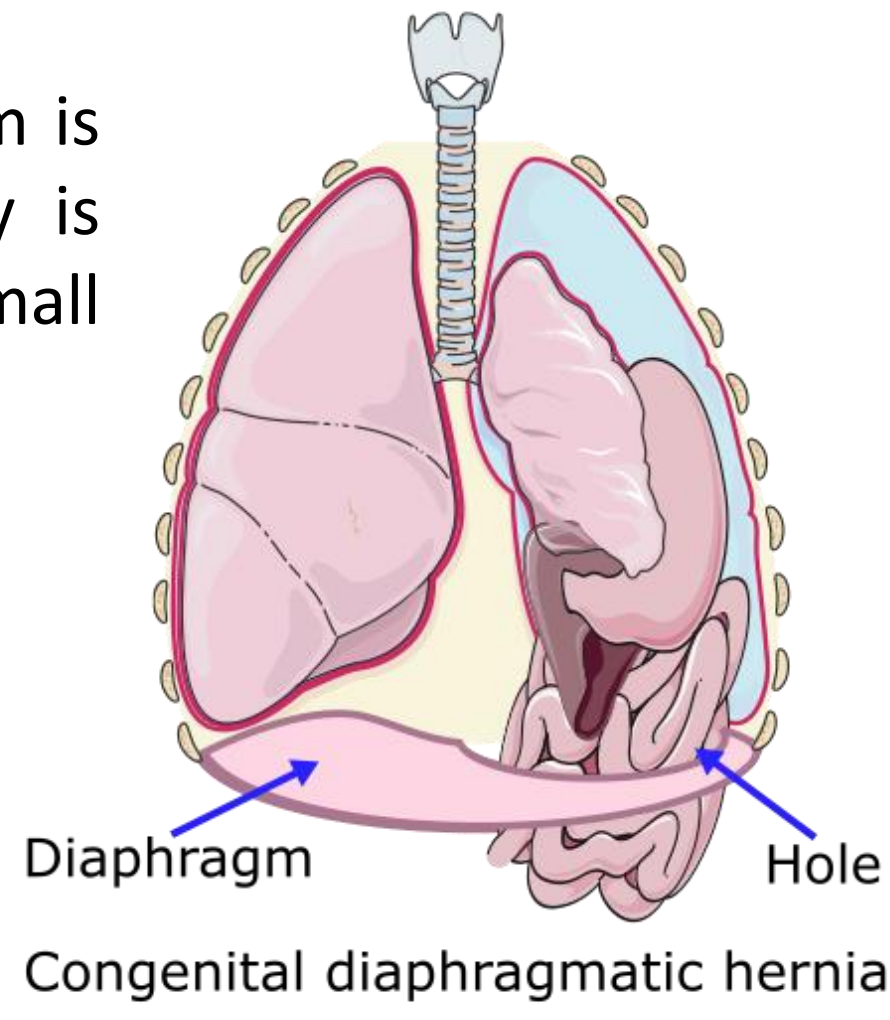


Congenital diaphragmatic hernia

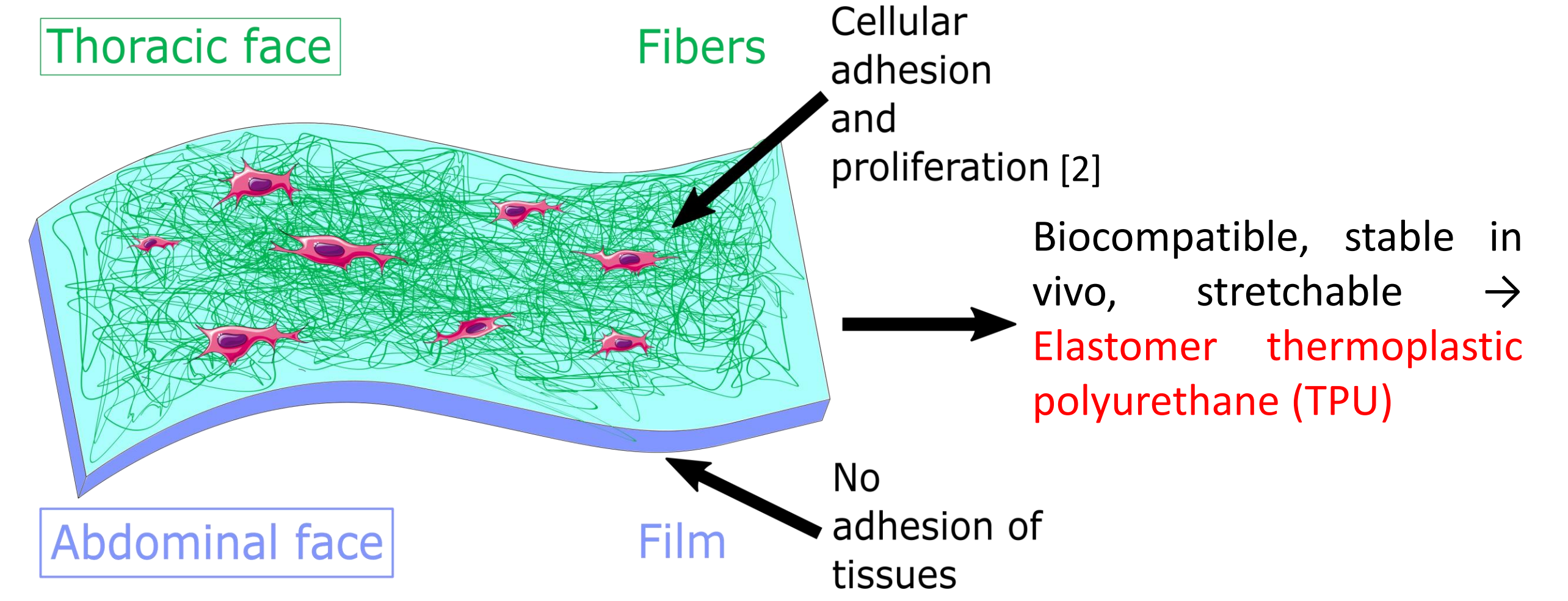
Congenital Diaphragmatic Hernia is a rare disease: a hole in the diaphragm is formed early in the embryogenesis. When the child is born, a surgery is required to fill the hole in the diaphragm → Stiches are done if it's small enough, otherwise a prosthesis is required

Currently used prosthesis:

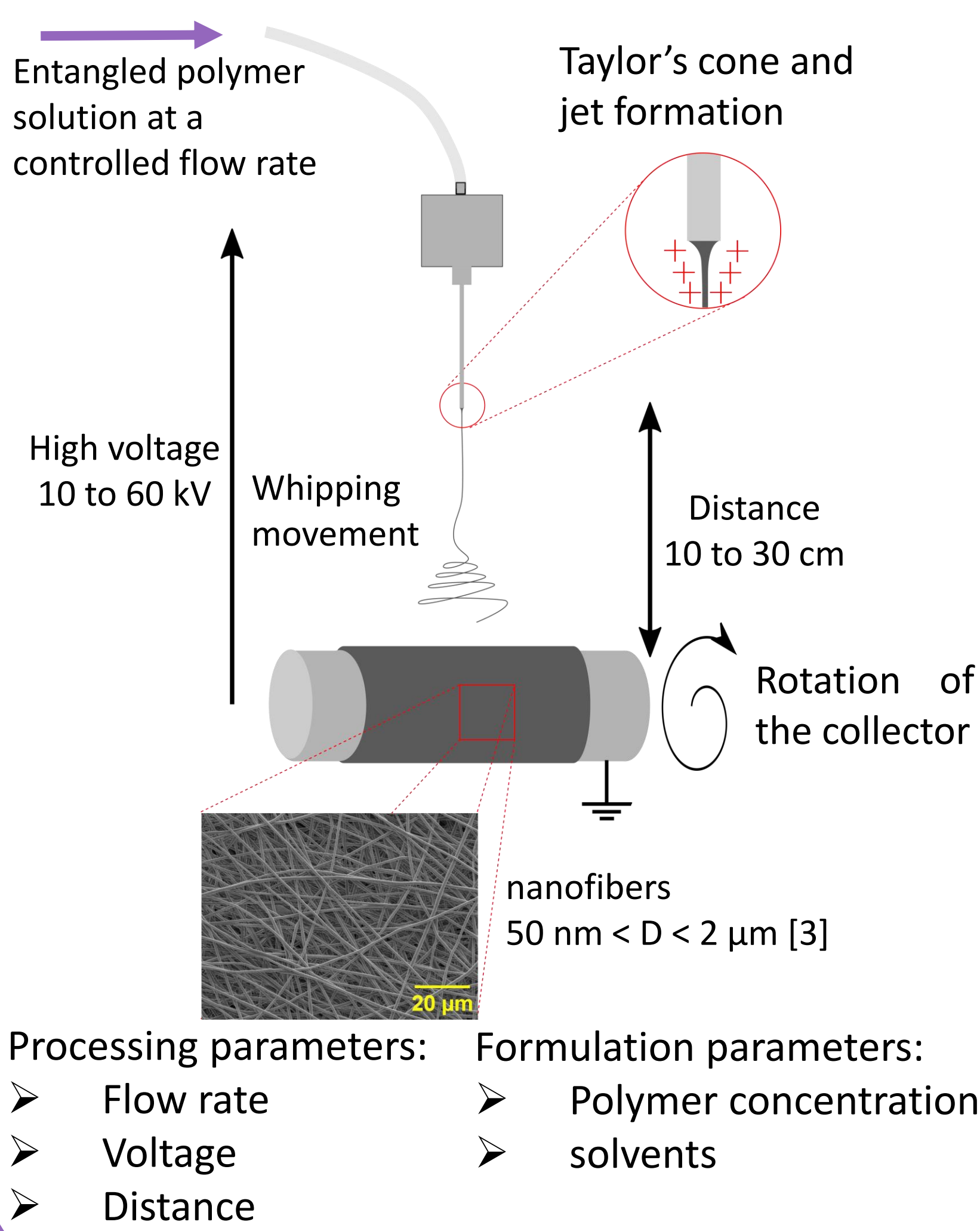
- Too stiff
 - Cannot follow the growth of the diaphragm (x4) → Rupture of the prosthesis [1] → Another surgery required
 - Weak cellular adhesion and proliferation
- Dualmesh, Gore® (e-PTFE)



New adapted prosthesis

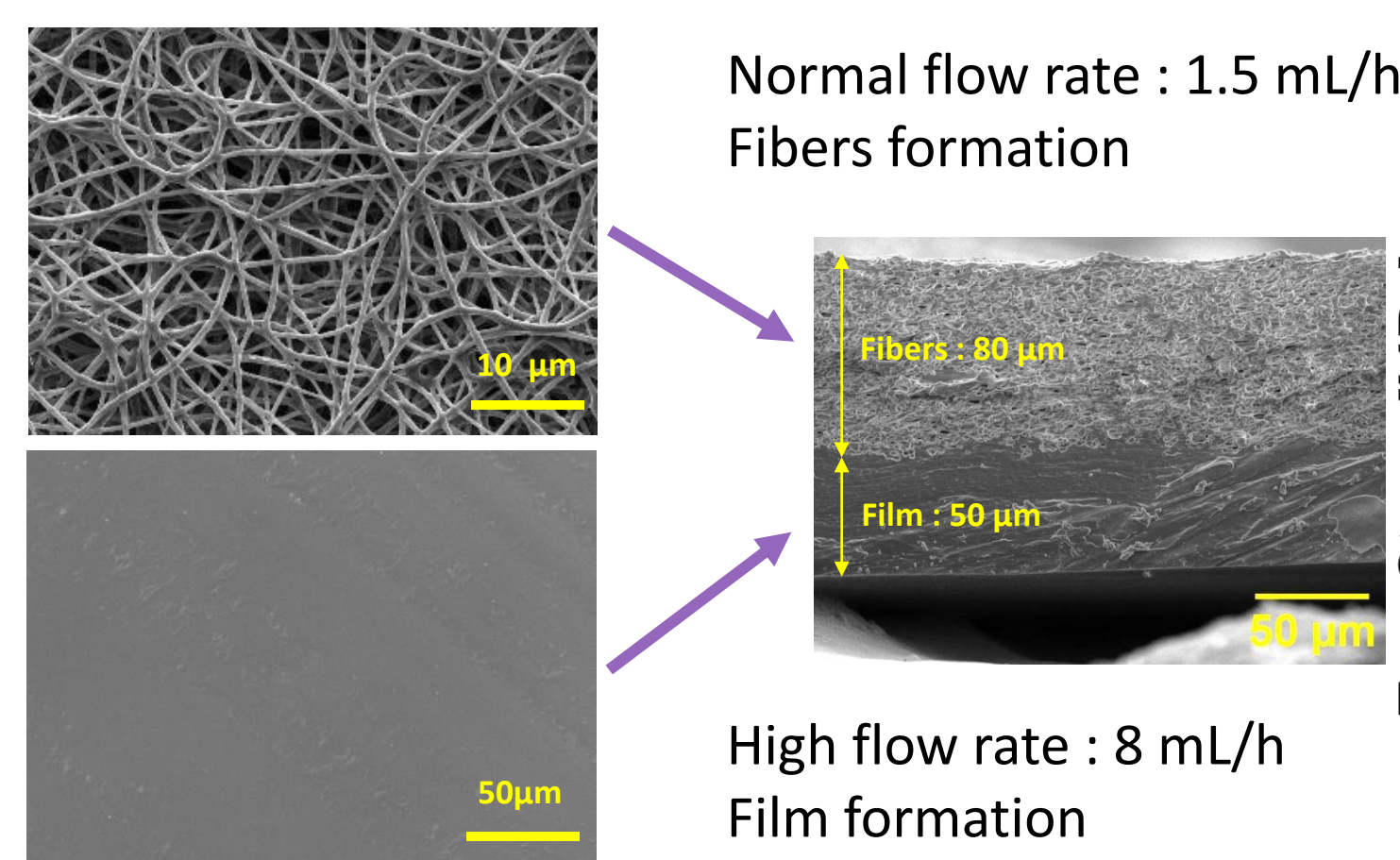


Electrospinning



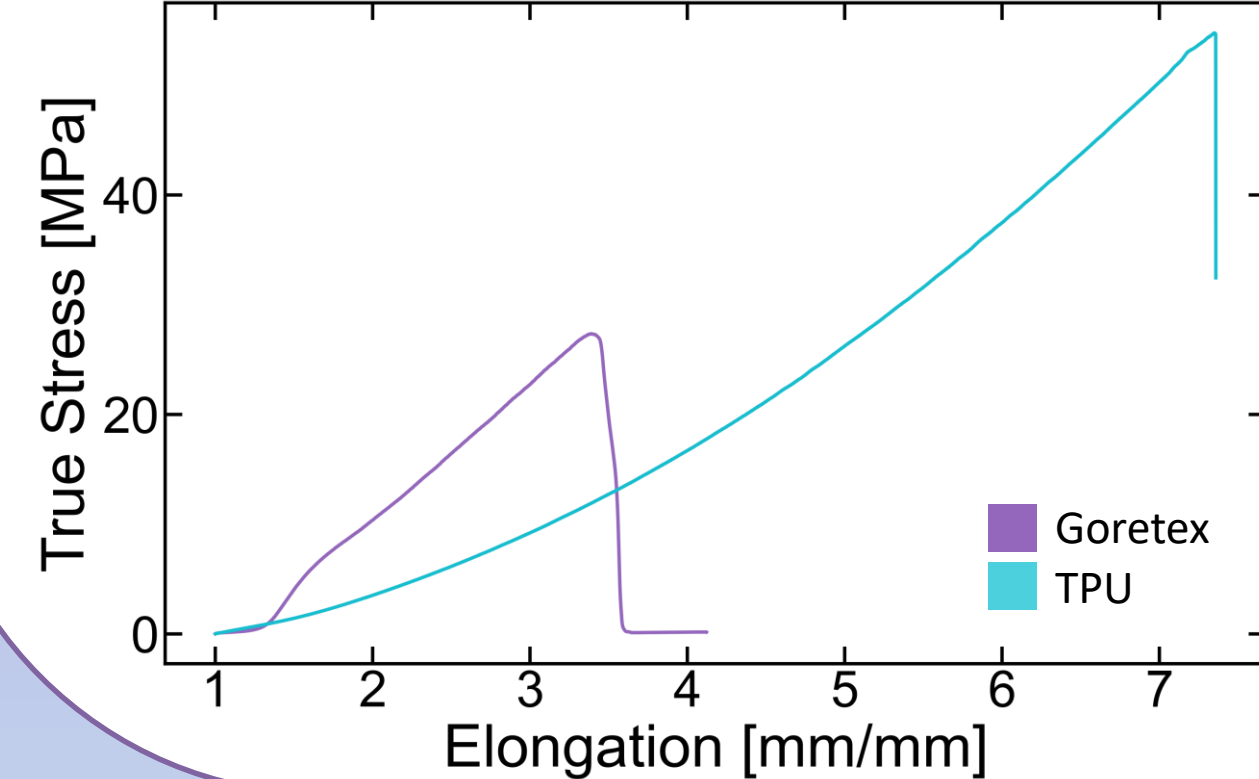
Mechanical characterization

Bilayered membranes:

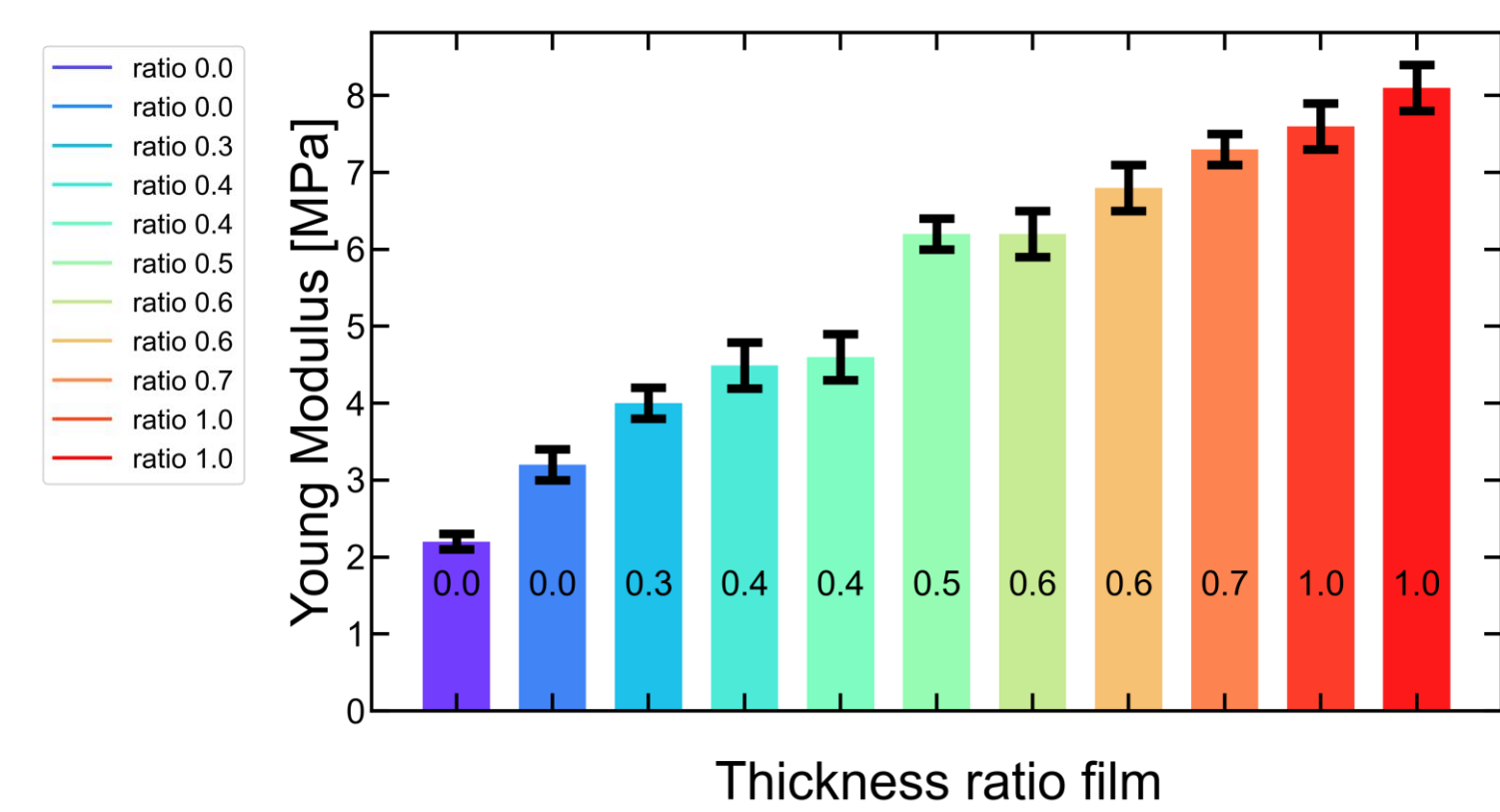
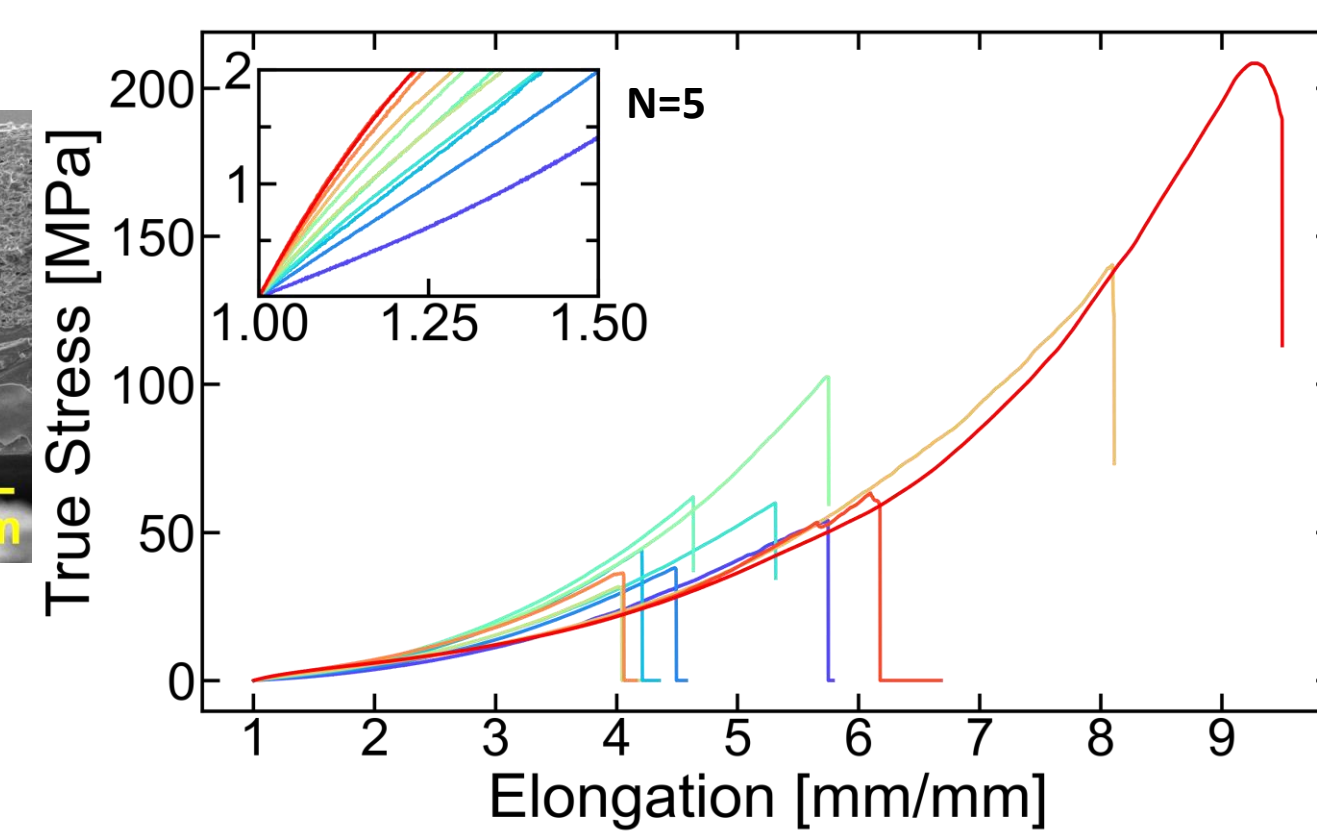


$$\text{Ratio} = \frac{t_{\text{film}}}{t_{\text{film}} + t_{\text{fibre}}}$$

Comparison with current prosthesis



Mechanical properties depending on the ratio of film and fibers of TPU membranes:

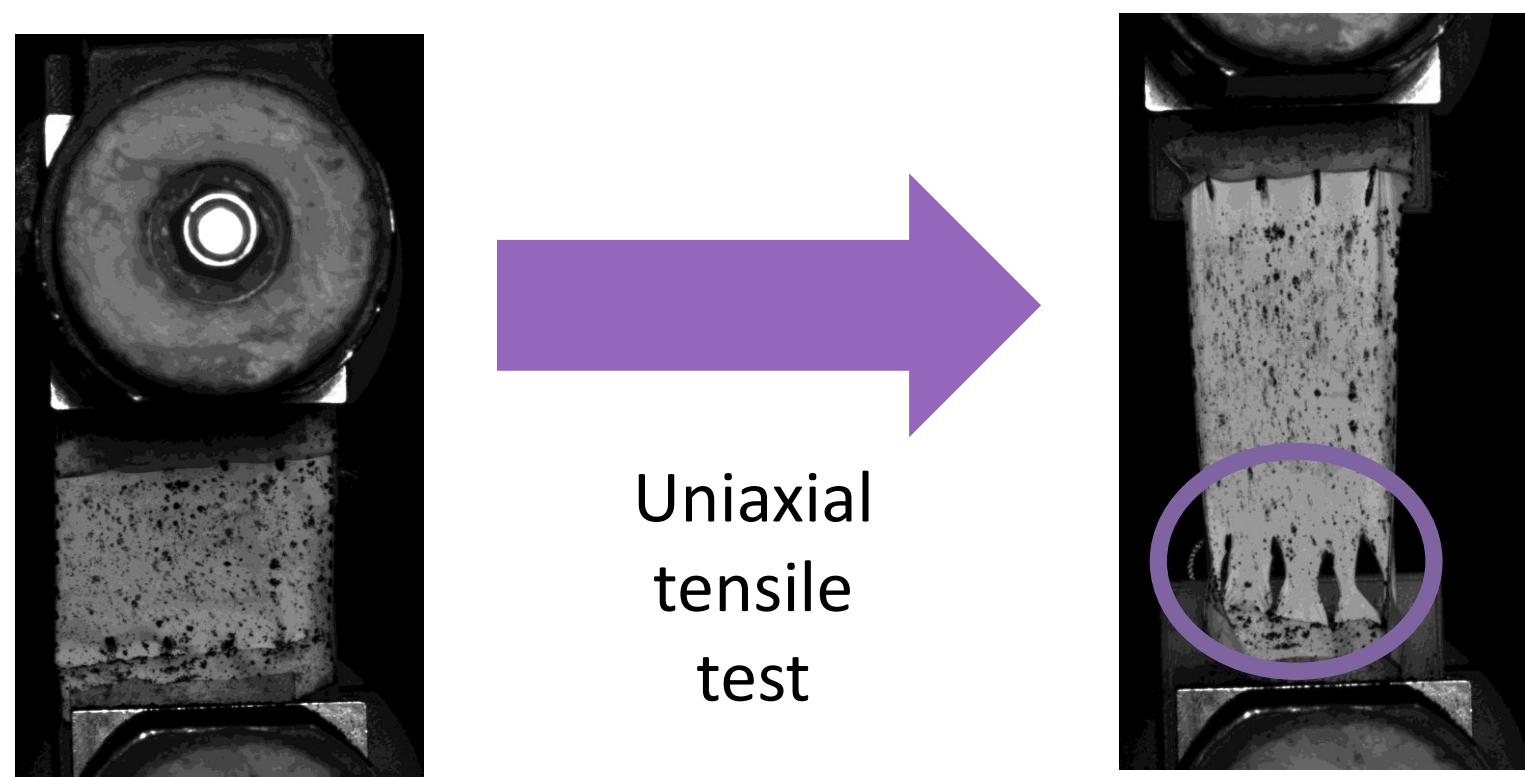


The TPU membranes are less stiff and can be far more elongated. The mechanical properties of the membrane can be tuned by increasing the film ratio.

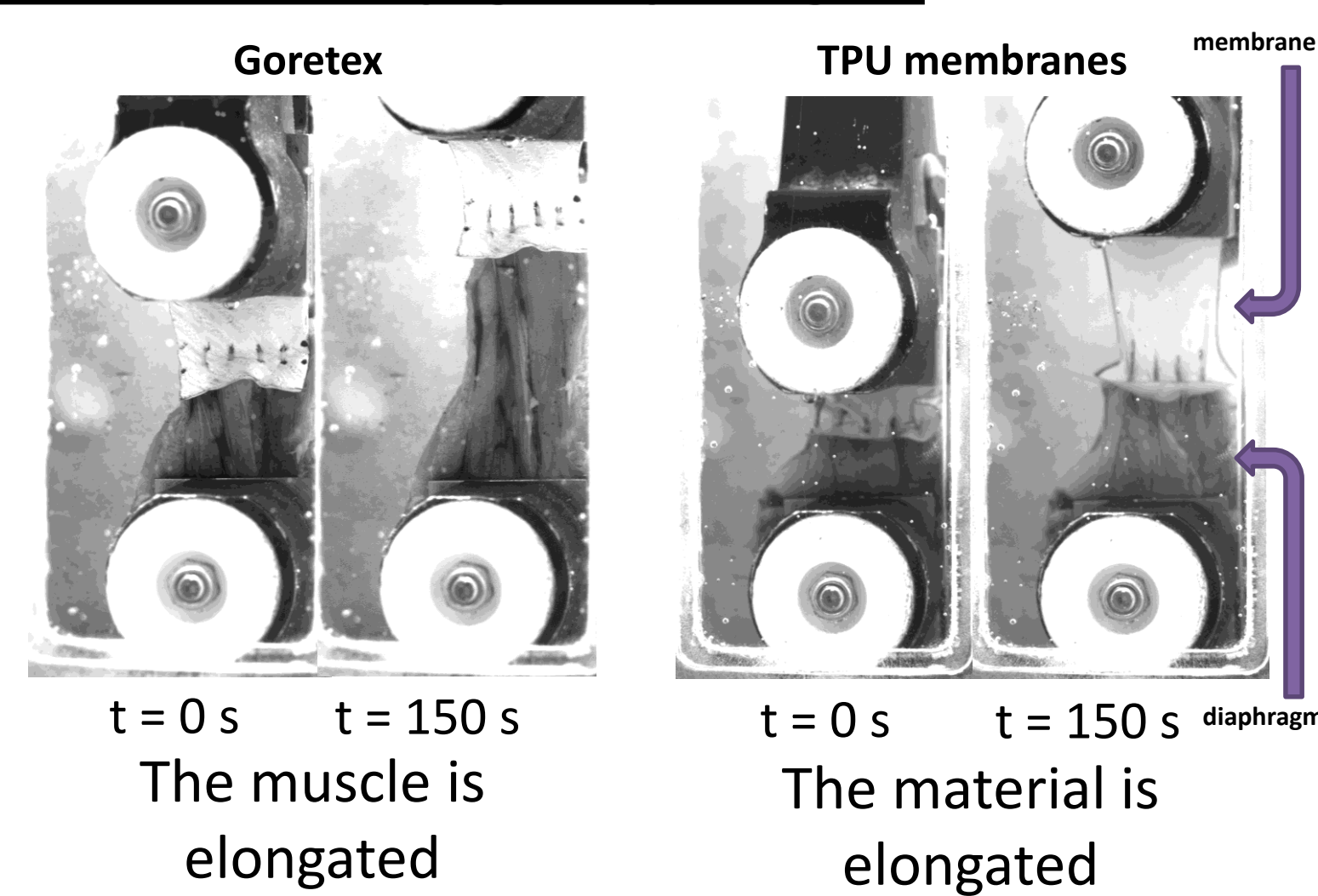
Prosthesis	Young Modulus (MPa)	Maximal deformation (%)	Thickness (μm)
Goretex (Current prosthesis)	22.3 ± 2.4	130 ± 45	≈ 850
Best prototype	2.5 ± 0.2	600 ± 30	≈ 185

Mechanical trials with stiches

Stiches on both side:



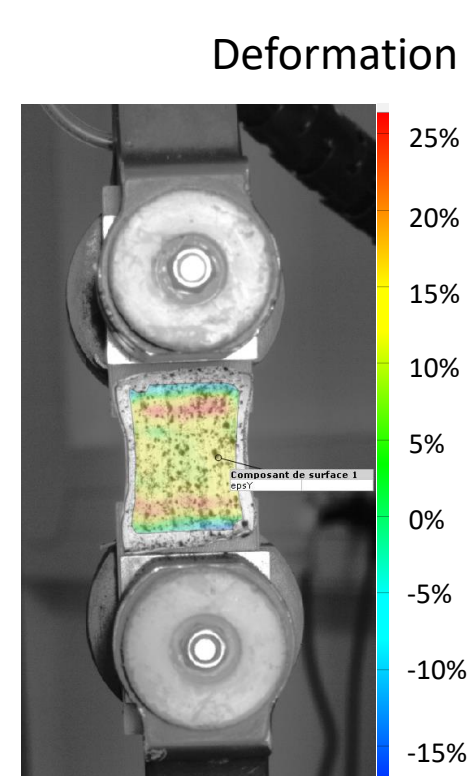
Stiches on a pig diaphragm:



With stiches, TPU membranes are 2-3 times more stretchable than Goretex. Moreover when grafted on a pig diaphragm the TPU membrane gets elongated because of the lower stiffness.

Prosthesis	Deformation at break (%)
Goretex (Current prosthesis) (N=3)	30 ± 5
Best prototype ratio ≈ 0.15 (N=2)	101 ± 0

The local and mean deformation of the material is evaluated by image correlation.

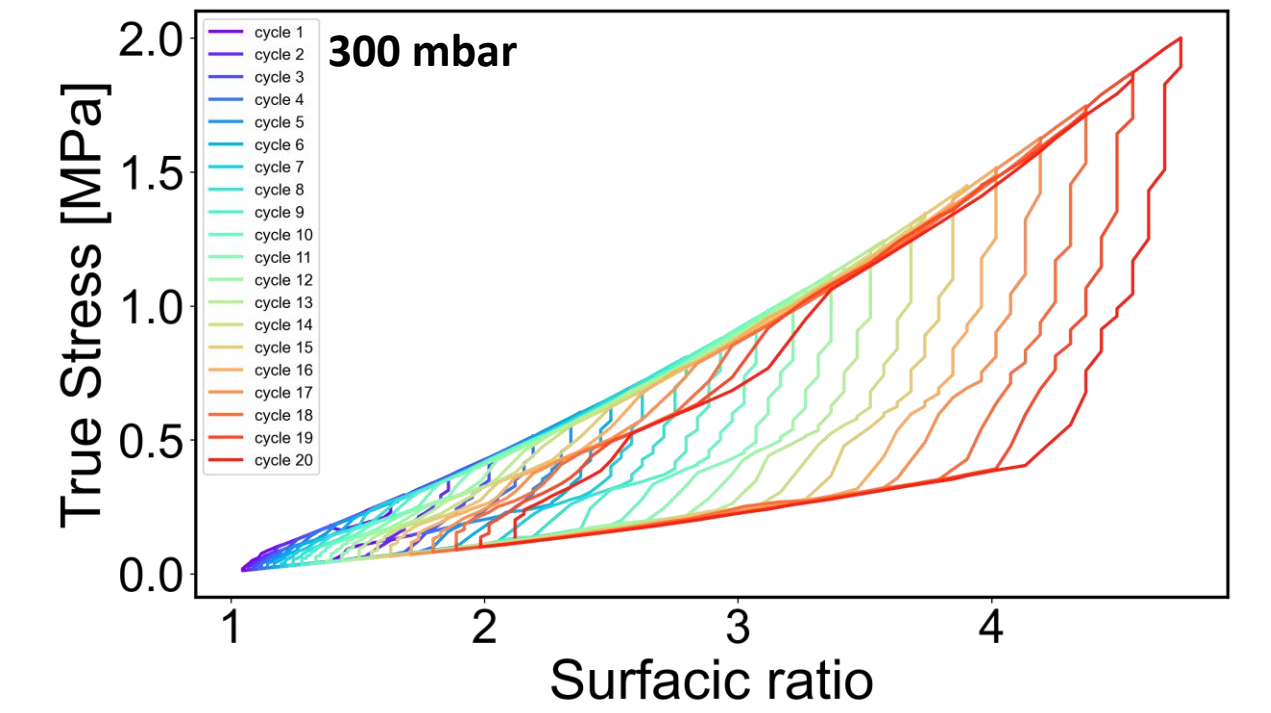
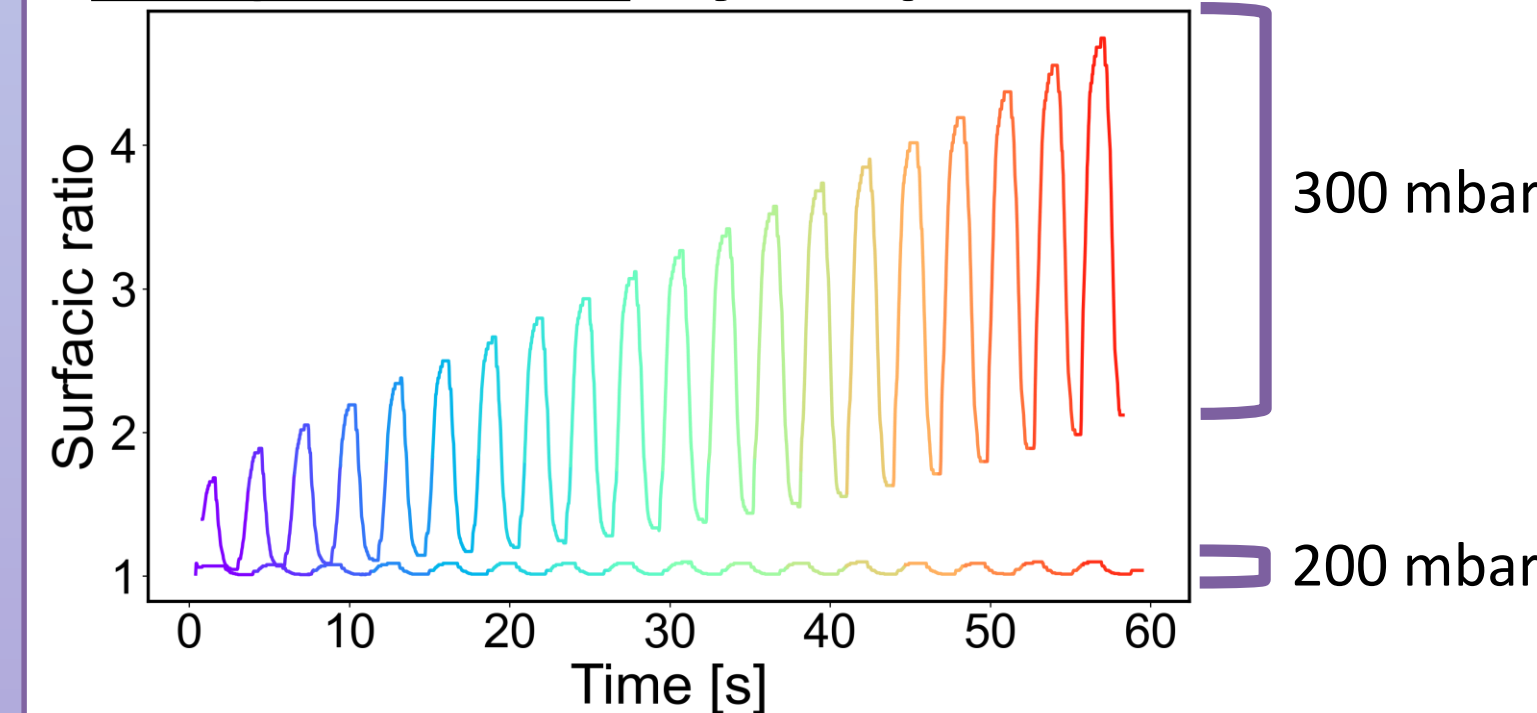


Inflation trials

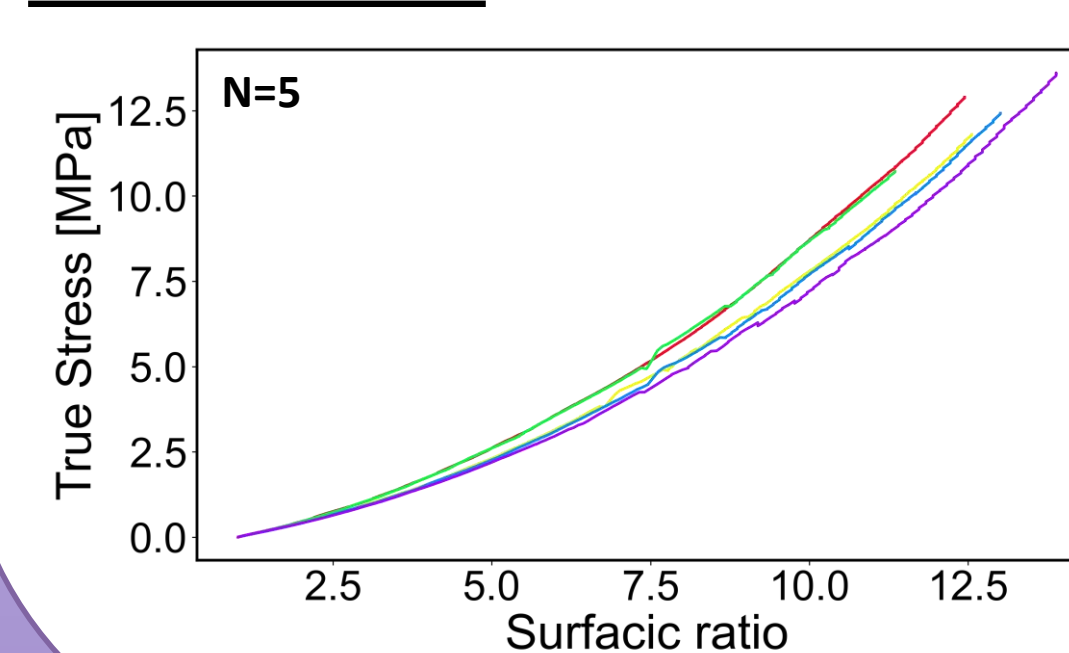
Membranes are inflated through air pressure (ratio ≈ 0.5)



Fatigue trials: Cyclic pressure



Burst trials: Pressure increase until burst



The membranes burst at 395 ± 17 mbar when the surface is multiplied by 12.6 ± 0.6 which is 2 to 3 time the specifications. Elastic deformations occur under 200 mbar but become inelastic at 300 mbar, the mean respiratory pressure is approximately 130 mbar. [4]

Conclusion

The aim of the project is to design a new adapted prosthesis for the treatment of congenital diaphragmatic hernia. Electrospinning is used to create a bilayered nanofibrous TPU membrane that allows cellular colonization and able to follow the growth of the child. The mechanical properties of the TPU membranes are adapted to the application with their low stiffness and a very high stretchability. When stitched, the TPU membranes exhibit better results than the current prosthesis, even if the stiches cause an anticipated breaking. Under inflation, the membranes exhibit an elastic behaviour at higher pressure than mean value for an adult. In burst trial, the surface was multiplied by 12.6, which is much higher than the initial objective meaning the membranes should be able to follow the entire growth of the child.



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