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Simulation of controllable permeation in PNIPAAm coated membranes

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ABSTRACT

Membranes separate fluid compartments and can comprise transport structures for selective permeation. In biology, channel proteins are specialized in their atomic structure to allow transport of specific compounds (selectivity). Conformational changes in protein structure allow the control of the permeation abilities by outer stimuli (gating). In polymeric membranes, the selectivity is due to electrostatic or size-exclusion. It can thus be controlled by size variation or electric charges. Controllable permeation can be useful to determine particle-size distributions in continuous flow, e.g. in microfluidics and biomedicine to gain cell diameter profiles in blood. The present approach uses patterned polyethylene terephthalate (PET) membranes with hydrogel surface coating for permeation control by size-exclusion. The thermosensitive hydrogel poly(N-isopropylacrylamide) (PNIPAAm) is structured with a cross-shaped pore geometry. A change in the temperature of the water flow through the membrane leads to a pore shape variation. The temperature dependent behavior of PNIPAAm can be numerically modeled with a temperature expansion model, where the swelling and deswelling is depicted by temperature dependent expansion coefficients. In the present study, the free swelling behavior was implemented to the Finite Element tool ABAQUS for the complex composite structure of the permeation control membrane. Experimental values of the geometry characteristics were derived from microscopy images with the tool ImageJ and compared to simulation results. Numerical simulations using the derived thermomechanical model for different pore geometries (circular, rectangle, cross and triangle) were performed. With this study, we show that the temperature expansion model with values from the free swelling behavior can be used to adequately predict the deformation behavior of the complex membrane system. The predictions can be used to optimize the behavior of the membrane pores and the overall performance of the smart membrane.

Keywords: Smart Membranes, Permeation Control, Hydrogels, Micromechanical Pore Valves, Particle Separation, Microfluidics, Simulation and Modeling, Finite Element Method

1. INTRODUCTION

This paper is about the design of a smart membrane structure with which we realize the natural selectivity and gating in a synthetic system. After an introduction about the general concept in chapter 1, the membrane system and its modeling is described in chapter 2. Here, also the design steps for the application as a filtering system are described. The step of pore geometry optimization in chapter 3 is the central part of the present work. It is followed by the synthesis of results in chapter 4.

1.1 Membranes

Membranes are entities to separate fluid compartments like the inner and outer of a cell or the up- and downstream side of a filtration device. They mostly comprise transport structures for their biological or technological function.¹ Biological transport structures are pores, channels or carriers which are formed by proteins embedded into the bilayer lipid membrane (BLM) of cells. Due to their molecular structure, carriers and channels allow selectivity in permeation for specific ionic species or macromolecules.² Conformational changes in this molecular structure due to external stimuli, like variations in membrane potential or transmitter concentrations, alter this behavior. The process is called gating,³ see figure 1.

Figure 1. A bilayer lipid membrane (BLM) is composed of amphiphilic phospholipids which self-assemble in water to form a structure. Transport structures like pores, channels or carriers are embedded into the layers. Selective permeation through channels and carriers can be stimuli-dependent, e.g. to membrane potentials $\Delta\Psi$, temperature differences ΔT , concentration changes Δc or mechanical membrane stresses σ_{Membrane} .

1.2 Mimicking Nature

Both selectivity and gating are promising for implementation in microfluidics to mimic e.g. the in vitro cell information processing. Selectivity can also be used to allow the separation of cells in a continuous flow for biomedical applications. An approach to copy the behavior of channels in technology is to use bilayer lipid membranes such as supported BLM⁴ and insert the biological protein structures, as it is done e.g. by Refs.^{5,6} As stated by the authors, channel proteins have to remain in a fluid BLM to maintain their functionality. This fact restricts the range of applications in technology. To circumnavigate the problems with fluidic membranes and to obtain long-term stable microfluidic devices, an approach with permeation control in polymeric membranes is better suited. Current developments in materials and fabrication methods allow first advances in this direction.

1.3 Smart Membranes

Smart materials like hydrogels can be used to control the permeation of particles with a size of $10 - 100\mu\text{m}$ through a polyethylene terephthalate (PET) membrane structure. The concept of Finite Element simulation of pore size changes is proven in previous work by the authors.⁷ Further advancement in fabrication precision is needed to reach the cellular size-level. Furthermore, the mechanical instability of biological cells, which allows a squeezing through pores smaller than the original cell size, poses problems. To better understand the ongoing processes in interaction between cells and smart membranes, several steps are still to go. The current work focuses on the aspect of pore geometry optimization.

2. A SWITCHABLE COMPOSITE MEMBRANE

2.1 Theoretical Background

In the present work, a temperature expansion model for thermal swelling⁸ of poly(N-isopropylacrylamide) (PNI-PAAm) similar to Ref⁹ is derived. The model is based on the theory of continuum mechanics, consisting of the balance law, kinematic relations and constitutive equations.⁷

Mechanical balance The balances in transversal and rotational momentum lead to the symmetry of the stress tensor $\sigma_{kl} = \sigma_{lk}$ and to three partial differential equations

$$\sigma_{kl,k} + f_l = 0, \quad \sigma_{kl} = \sigma_{lk} \quad (1)$$

where f_l are volume loads and $()_{,k}$ denotes the partial derivative $\partial()/\partial x_k$.

Kinematic relation For small gradients of deformation u_k , the second order term $u_{k,l}u_{l,k}$ is negligible in comparison to first order derivatives of the deformation gradients. This leads to the technical strain measure ε_{kl}

$$\varepsilon_{kl} = \frac{1}{2}(u_{k,l} + u_{l,k}) \quad (2)$$

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Constitutive equations The material law of linear elasticity with the elasticity tensor E_{klmn} incorporates the homogeneous thermal expansion through the temperature dependent expansion coefficient $\alpha = \alpha(T)$. Here, δ_{mn} denotes the Kronecker symbol and ΔT the temperature difference with respect to a reference state.

$$\sigma_{kl} = E_{klmn} \underbrace{(\varepsilon_{mn} - \alpha \delta_{mn} \Delta T)}_{\varepsilon_{mn}^e} \quad (3)$$

Suitable jump and boundary conditions are prescribed. The model is consistent with the underlying physical problem of hydrogel swelling due to the stimulus. Model parameters are obtained by free swelling experiments which lead to $\alpha = \alpha(T)$. The developed methodology is used for opening simulation of the hydrogel pore system. These simulations show an excellent agreement with experimental results for a cross-shaped pore.⁷

2.2 Design steps for the construction of the pores

As stated in our previous work,⁷ the model described above can excellently predict the behavior of an arbitrary pore structure. Simulations on this basis can now be used to design a pore system with optimized properties for a possible application: A microfluidic cell separation system, allowing to detect the size distribution of cells in a blood sample using constant flow. Several interactions are still to be investigated in order to design the system. The steps are presented in the following.

Choice of smart material Hydrogels are a group of Electroactive Polymers (EAP) which undergo a volume swelling under varying stimuli due to their chemical properties.¹⁰ The material poly(N-isopropylacrylamide) (PNIPAAm) is responsive to temperature stimulus, see figure 2. At temperatures lower than the volume phase transition temperature 32 °C, it is in swollen state. Since in the composite membrane setup the gel forms an open structure, the deswelling at higher temperatures leads to a opening of the pore while a swelling at lower temperatures to a closing.

Figure 2. Deswelling of a PNIPAAm with rising temperature due to first order volume phase transition. The small pictures show actual microscopy images of a hydrogel-disk in swollen (left) and shrunken (right) state.

Different hydrogels can be used for the composite membrane system if it is possible to surface-polymerize them on a PET foil. The Temperature Expansion Model is not applicable to polyelectrolyte gels, where models describing the electro-chemo-mechanical fields must be used.¹¹ In the current work, PNIPAAm according to the recipe described in Ref⁷ is used.

Flow through the membrane The *membrane-fluid interaction* can be approximated as a rigid channel structure interacting with a fluid. Due to the microfluidic properties ($Re \ll 1$, creeping flow), the water flow is dominated by the channel rather than by impulse loss (outlet) or inlet. This fact was previously presented in Ref.¹²

Figure 3. Bending of the membrane composite structure consisting of the PET membrane and the surface polymerized PNIPAAm. It is weakened by the inserted pores.

Membrane mechanics When the membrane is exposed to a pressure difference $\Delta p > 0$ from upstream to downstream side, it will be deflected in flow direction. Depending on the pore geometry, opening degree and actual hydrogel stiffness, the composite system is weakened in comparison to the simple PET membrane, see figure 3. In addition, due to the actuated layers and the much stiffer PET support, internal stresses occur. This combined behavior has both impact on the pore geometry and the permeation abilities. It can lead as far as loss of separation functionality due to widening of the pore. A means to investigate this behavior is the Classical Laminate Theory (CLT) which also includes thermal strains in layers of the composite. The temperature expansion model can therefore be used for simulations on this model basis, which will be done in subsequent investigations.

Particle membrane interaction When particles are separated in an analytical flow, the underlying process is depth-filtration. This is in contrast to the field of process engineering, where much higher particle loads are used and the filtration behavior is dominated by screen-filtration due to the formation of so-called *filter cakes*.¹³ Thus dealing with a very small amount of particles, the flow characteristics of a pore, when it is blocked by a particle, are of importance, see figure 4. If a pore is blocked, this is expressed in the bypass stream, see section 3.1. In addition, a force governed by the drag of the particle in the stream is exercised onto the membrane. This effect can be investigated by means of fluid-structure interaction simulations and will be addressed in future research.

Figure 4. When a pore of arbitrary geometry (e.g. triangle-pore) is blocked by a particle, the bypass-flux can be calculated with the bypass-area A_{bypass} . For blocked particles of different sizes, A_{bypass} is always governed by the largest particle, that can pass the pore (here: Particle I), i.e. the passage diameter d^{passage} . Particle II only governs the flux in the immediate surrounding of the channel inlet.

Soft particle influences Cells are soft particles and thus are heavily influenced in their form by pressure differences, wall contact and agglomeration. Due to the fluid properties of their bilayer lipid membrane described by the Fluid Mosaic Model,¹⁴ they can squeeze through holes, which are smaller than their undisturbed diameter. This effect, as well as the interaction with the hydrogel, which can be equally soft depending on actual swelling degree and synthesis conditions, will be part of future works.

Pore geometry The shape and size of the pore is important for all other design steps. For this cause, different pore geometries and their individual performances are compared in the following section.

3. PORE GEOMETRY OPTIMIZATION

The geometry of the pore cut into the hydrogel embedded in the PET occurs to be the substantial fact for the design of our system. This section will point out the main criteria which make the pore system applicable to rigid and soft particle separation.

3.1 Influencing variables

The geometry must be optimized with respect to the following main criteria in order to achieve a working separation system. A change of hydrogel pore material is not taken into account since we focus on the geometric relationship.

- The **Passage Diameter** d^{Passage} is the diameter of the biggest spherical particle that can pass through the shape, see figure 4. It governs which particles are blocked through size-exclusion.
- The **Closing Multiplier** denotes the quotient of opening and closing passage diameter $d_{\text{max}}^{\text{Passage}}/d_{\text{min}}^{\text{Passage}}$. It must mirror the range of particle-sizes expected in the flow to allow the capturing of the particle distribution.
- The **Overall Water Permeation** is determined by the Poisson's equation of laminar flow in a channel. It governs the overall speed of the filtration process.
- The **Bypass Flow** is the volume flux occurring, when a pore is blocked by a particle and thus plays a role in filtration speed as well.
- The **Bypass Diameter** d^{Bypass} is the maximum diameter of particles that can pass through a blocked pore. Only when smaller particles with $d < d^{\text{Passage}}$ can pass through the pore which counts *closed* particles with $d > d^{\text{Passage}}$, a full size profile can be achieved.
- The **Weakening Influence** of the pore geometry is the reduction in the bending resistance of the composite membrane for a geometry.

In order to make different pore geometries comparable, different criteria can be hold equal. From the process engineer's point of view, the overall flow through the membrane should be the same. This can be achieved by using geometries sharing the hydraulic diameter $d_h = d_{h,0}$. A much simpler approach would be to use the same area $A = A_0$ for all pore geometries. From the angle of permeation control, a same closing multiplier would be desirable to separate the properties of a geometry from the performance of the smart material. In the present research, the criterion of the same hydraulic diameter $d_h = 85.8447 \mu\text{m}$ is used to gain comparable geometries.

3.2 Pore Shapes

The geometries used in the present research are all fabricable in an adequate precision with the methods described by the authors.⁷ They all have their individual advantages and disadvantages, which will be presented hereby. The name of the form derives from the actual shape of the outline in reference state with $T^{\text{ref}} = 32^\circ\text{C}$. When the environmental conditions are changed, i.e. when the stimulus leading to actuation of the smart material is given, the shape will change. We suppose, that our model described in section 2 is accurate and can be used to predict this shape change. The shapes can be varied with a slenderness-factor λ , which will be introduced for every single form, see figure 5. In the following, four different pore shapes are investigated:

1. Round pore/cylinder
2. Rectangle pore/parallelepiped
3. Cross pore
4. Isosceles triangle pore

Figure 5. The four shapes that are investigated in the current work: Round (I), Rectangle (II), Cross (III), Triangle (IV). For simulation in ABAQUS, symmetry can be considered to reduce computational cost. While the behavior of the round pore (I) can be analytically derived, geometries II and III are simulated as quarter-pores and IV as half-pore.

3.2.1 Case I: Round pore/cylinder

In the simplest, i.e. round, pore form (figure 6), all parameters can be calculated analytically in any state of actuation induced closing. The hydraulic diameter of this form is equal to the actual diameter of the circle-outline. There are no possibilities to vary the shape with a slenderness-factor and no water or particle bypass occurs, when the pore is blocked.

The swelling behavior of the PNIPAAm round pore under temperature stimulus can directly be derived by solving the disc-equation with rotation-symmetry and temperature-load with the temperature-dependent expansion coefficient $\alpha(T)$ ⁷

$$\left[\frac{1}{r} (r u_r)' \right]' = (1 + \nu) \alpha(T) (\Delta T)' \quad (4)$$

where ΔT is the temperature difference to the reference state and $()' = \partial()/\partial r$. The boundary conditions are (1) fixed outside $u_r(r = r_o) = 0$ and (2) free boundary inside $\sigma_r(r = r_i) = 0$. The solution depends on the Poisson's ratio ν which may also depend on the temperature. For the following simulations, $\nu = 0.2$ is assumed hence it yields the best resemblances to the experiments in our previous work.⁷ The round pore with $d = d_h = 85.8447 \mu\text{m}$ serves as a reference state for the other cases.

Figure 6. Circular pore outline (left). Passage diameter $d_{\text{Passage}} = d_{\text{max}}$ versus temperature for different Poisson's ratios (right). The outer circular disk with hole is fixed to the PET membrane (see figure 5) on the outside and free at the inside.

3.2.2 Case II: Rectangle pore/parallelepiped

The rectangle shaped channel is an archetype of non-circular channels. The hydraulic diameter and the slenderness-parameter can be calculated directly from the height and width of the pore.

$$d_h = 4 \frac{wh}{2w + 2h} \quad \lambda_{\text{Rectangle}} = \frac{w}{h} \quad (5)$$

The limiting factor for a particle to pass through a rectangle-shaped pore is the width or height, whichever is the lower. In figure 7, the analytically derived change of passage diameter is depicted.

Figure 7. With the rectangle shaped outline, a parallelepiped-formed pore is created. The slenderness of this structure $\lambda_{\text{Rectangle}} = w/h$ is defined with the height and width of the rectangle.

To investigate the change in passage diameter of different slendernesses, the following cases were used for a rectangle pore: *Square* for $\lambda_{\text{Rectangle}} = 1$ with $w = h = 85.8447 \mu\text{m}$ and *rectangle* for $\lambda_{\text{Rectangle}} = 2$ with $w = 128.7671 \mu\text{m}$ and $h = 64.3835 \mu\text{m}$.

Numerical simulations with the Temperature Expansion Model yield as an output the pore shape for every temperature in the range $T \in [23^\circ\text{C}; 38^\circ\text{C}]$. The maximum diameter can be found through an algorithm minimizing the maximal distance to wall contact from every point inside the open pore (figure 8). For the closing pore with $T < 32^\circ\text{C}$, the circle can be found at the sides rather than in the middle of the structure. The simulation results for square and rectangle are depicted and compared in figure 14.

Figure 8. Rectangle-pore at different states ($T = 23^\circ\text{C}$ (left), $T = 32^\circ\text{C}$ (middle), $T = 38^\circ\text{C}$ (right)) of opening and closing as simulated with the Temperature Expansion Model by using the finite element tool ABAQUS. Only a quarter of the pore is shown, i.e. there is symmetry at the x - and y -axis. The red circles depict actual points exported from the deformed FE model.

3.2.3 Case III: Cross

The cross pore is composed by two orthogonal rectangle shapes. The slenderness

$$\lambda_{\text{Cross}} = \frac{w_A}{l_A} \quad (6)$$

is defined with by the arm length l_A and arm width w_A of the cross's arms. For $l_A \rightarrow 0$ and therefore $\lambda_{\text{Cross}} \rightarrow \infty$, the form is a square. The threshold, where the diagonal of the inner square is no longer dominating the maximum in-circle is $\lambda_{\text{Cross}} = 2/(\sqrt{2} - 1) = 4.8284$. It figure 9, the variation of this shape is depicted.

Figure 9. With a cross-shaped outline, a more complex parallelepiped-formed pore is created. The structure's slenderness-factor $\lambda_{\text{Cross}} = w_A/l_A$ is here defined by the arm length and width.

The exported structures from the numerical simulations with the Temperature Expansion Model for different temperatures are depicted in figure 10. The same effect for the closing pore and the in-circle can be found as for the rectangle shape. The shape change is in excellent agreement with microscopic experimental pictures depicted in our previous work.⁷

Figure 10. Quarter of the cross-pore at different temperatures ($T = 23^\circ\text{C}$ (left), $T = 32^\circ\text{C}$ (middle), $T = 38^\circ\text{C}$ (right)). The x - and y -axes are symmetry axes.

3.2.4 Case IV: Isosceles Triangle

The outline is an isosceles triangle is defined by its base b and height h , which form the slenderness

$$\lambda_{\text{Triangle}} = \frac{b}{h}. \quad (7)$$

For $\lambda_{\text{Triangle}} = 2/\sqrt{3} = 1.1547$ the triangle is equilateral (see figure 11). Because of the definition of the hydraulic diameter as $d_h = 4A/P$ with the area $A = r_i s$ and perimeter $P = 2s$, it is always equal to the diameter $2r_i$ of the in-circle of a triangle. Thus, the passage diameter is constant for a fixed hydraulic diameter and any $\lambda_{\text{Triangle}}$. The following geometry is used for numerical investigation: Equilateral triangle for $\lambda = 1.1547$ and $b = 148.6874 \mu\text{m}$, $h = 128.7671 \mu\text{m}$

Figure 11. The slenderness factor $\lambda_{\text{Triangle}} = b/h$ for the triangle structure is formed by its base and height.

Simulations for the triangle pore are performed with a half-pore setup. The results of the equilateral triangle are depicted and compared to the other geometries in figure 14. The closing of the pore under temperature stimulus is depicted in figure 12.

Figure 12. Half-pore of the equilateral triangle pore for different temperatures ($T = 23^\circ\text{C}$ (left), $T = 32^\circ\text{C}$ (middle), $T = 38^\circ\text{C}$ (right)). The symmetry axis is the y -axis. During deswelling at $T \approx 33^\circ\text{C}$, the structure is very near to a round shape.

3.2.5 Comparison of the shapes

In figure 13, the above described shapes are compared according to their passage diameter in reference state for equal hydraulic diameter. It can be seen, that for $\lambda_{\text{Cross}} \rightarrow \infty$, the cross pore passage diameter converges to that of the square (rectangle at $\lambda_{\text{Rectangle}} = 1$), which is also the in-circle diameter of the triangle-shape $\forall \lambda_{\text{Triangle}}$. The triangle diameter is by definition equal to the hydraulic diameter.

Figure 13. Comparison of the different shapes' passage diameters. The shapes are equal in respect to the hydraulic diameter. The slenderness factors are $\lambda_{\text{cross}} = w_A/l_A$, $\lambda_{\text{Rectangle}} = w/h$ and $\lambda_{b/h}$

4. SYNTHESIS OF ANALYTICAL AND NUMERICAL STUDIES

The shapes of four different simulated pore geometries are compared in respect to the performance criteria defined in section 3.1. In figure 14, the change in passage diameter over the temperature is depicted.

Circular Pore The circular pore preserves its shape for opening and closing. The passage diameter varies directly with the flow diameter. There is no bypass flux or particles, hence the structure can only be used for a filtration system with two particle sizes. Since total blocking of the water can occur, a membrane with a large number of pores in the order of magnitude of the fluid particle concentration would be necessary. The weakening influence to the membrane is equally high.

Rectangle Pore Two variants, square and rectangular, were investigated. It is found that the more $\lambda_{\text{Rectangle}}$ differs from 1, the better closing multiplier can be achieved. At the same time, d_0^{Passage} in reference state decreases. In comparison to the round pore, a water and particle bypass is possible. The overall bypass area is split into two non-connected areas $A^{\text{bypass}} = A_{\text{left}} \cup A_{\text{right}}$. Their shapes allow the passage of particles, hence fewer pores are needed than in the circular case. This leads to less weakening of the structure. For higher temperatures and respective opening, the rectangle shape is lost and nears a circle.

Figure 14. Comparison of the simulated opening and closing behavior of the different cases. The simulation starts at reference state $T = T_{\text{ref}} = 32^\circ\text{C}$ and varies in steps of 0.01 K to $T_{\text{max}} = 38^\circ\text{C}$ and down to $T_{\text{min}} = 23^\circ\text{C}$.

Cross Pore The cross shaped pore offers the largest range of passage diameters combined with a high bypass flow. Also, particles and water are allowed to bypass in the reference and slightly opened state. While other geometries reach the round shape very early, the cross keeps a more clover-like shape preserving this ability. Through a smaller λ_{Cross} , i.e. longer cross-arms, more bypass can be achieved with the downside of a reduced passage diameter. The geometry change in the cross's arms is comparable to the single rectangle described above.

Triangle Pore The equilateral triangle shaped pore offers an intermediate change in passage diameter. Water and particle bypass are lower than the cross but higher than circular and rectangle pores. When the triangle pore opens it nears the circular outline with the above described downsides. On closing, the outer edges immediately get in contact with each other. While this preserves the triangle-shape throughout closing, it blocks all bypass in this region. The three bypass area fragments $A^{\text{bypass}} = A_{\text{top}} \cup A_{\text{left}} \cup A_{\text{right}}$ are themselves nearly triangle-shaped, which leads to a fractal distribution of the passage diameter with $d_{\text{Passage}}^{\text{Level } n} / d_{\text{Passage}}^{\text{Level } n+1} \approx 3.03$.

Comparison of the shapes For opening of the pores, a shape very similar to the circular one is achieved in all tested geometries. This is due to the round structures in the PET membrane, wherein the hydrogel geometries are fixed. Since the round pore offers the least favorable performance in respect to the defined parameters, the pores must be designed such as less maximal opening is achieved. This can be achieved by reducing the amount of material between the pore outline and the outer fixing, i.e. smaller holes in the PET membrane. The downside is a decreasing performance in the closing direction. When closing, sides of the pore outline get in contact and block the passage. In table 1, the shapes are compared in respect to the performance criteria for the cell separation system.

5. CONCLUSION

The developed model offers an easy and efficient approach to obtain insights into the behavior of complex smart membrane structures under varying stimuli. Based on the microfluidic model, the flow through a membrane with multiple pores can be simulated. This leads to an optimized design of microfluidic membrane devices, which can be used e.g. for chemical information processing or biomedical applications. Four different geometries

Table 1. Performance of different geometries in respect to different parameters. Here, + denotes favorable properties for the cell separation system, - disadvantageous behavior and o neutral features.

	Round	Square	Rectangle	Cross	Triangle

Passage diameter	o	+	++	+++	++
Closing multiplier	2.31	3.02	7.88	10.82	4.49
Overall flow	o	+	++	++	++
Bypass flow	--	o	+	++	+
Bypass diameter	--	o	+	++	+
Weakening influence	-	o	+	+	+

for the outline of the pores in the membrane were compared. The circular shape serves as an analytical base for the rectangle and cross shapes which show very similar behavior and the triangle. Important performance parameters are defined in respect to the envisioned application of the smart membrane: a microfluidic device for the controlled filtration of cells in order to achieve a cell-size distribution. The performance parameters feature the shape change due to swelling, the associated particles and water bypass as well as the mechanical weakening of the overall structure. From the four described and investigated geometries, the cross shape offers the best results. Future investigations regarding the other design steps might lead to a reevaluation of these abilities. Especially the fluid properties of cell-membranes and their interaction with the deforming smart composite membrane play a major role in future evaluations.

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