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DESIGN OF MICRO-FLUIDIC BIO-REACTORS USING TOPOLOGY OPTIMIZATION

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Abstract. *We address the design of optimal reactors for supporting biological cultures using the method of topology optimization. For some years this method have been used to design various optimal microfluidic devices [1, 2, 3, 4]. We apply this method to distribute optimally biologic cultures within a flow of nutrition. From this optimized distribution alone the metabolic rate in the reactor increase by close to a factor 20.*

1 BACKGROUND

The interest for developing microfluidic bio-reactors has increased greatly within the last decade, as they enable automation, parallel experimentation, and reduced use of resources, which ultimately will allow e.g. high-throughput screening of bacterial strains and rapid bio-process development [5].

On that basis we have studied how to optimally design bio-reactors for supporting immobilized biological cultures.

Having developed a versatile numerical tool for optimizing the topology of general microfluidic systems [4], it was natural to apply this method on the design of bio-reactors. We use a very simplified model of a metabolic process as even this model results in complex reactor-designs, but the method can easily be applied to more realistic and complex models.

2 THE MODEL

We imagine a reactor consisting of a rectangular box in which an immobilized biological culture is distributed in distinct patches across the horizontal extension of the reactor and extending vertically through the whole reactor-region. A buffer-fluid carries the nutrition, labelled A and with concentration $a(\mathbf{r})$, which are driven through the void spaces between the structures in the reaction-chamber by an applied pressure-drop Δp, and feed from a fluid inlet having constant concentration a_0.

To simplify the metabolism model as much as possible we only describe the consumption of nutrition and neglect waste-products. As our optimization of even the simplest metabolism-model give rise to complex reactor-designs, the consumption is modelled by a single first order isothermal reaction depending only on the local concentration of nutrition and cell-density[1].

We assume that the cells are immobilized by a porous material, where the total structure has a local porosity γ, defined as the local fluid-density inside the structure[2]. The scalar porosity-field $\gamma(\mathbf{r})$ can vary continuously in the interval $0 \leq \gamma \leq 1$ in the reaction region, where $\gamma = 0$ is the limit of solid material (no pores) and $\gamma = 1$ is the limit of pure fluid (channel bulk). This field is two-dimensional as the porous cell-supporting structures extend throughout the vertical (third) dimension of the reactor.

From an optimization point of view the situation is quite simple: The metabolic rate is high if the cells are densely distributed. However, a very dense structure slows down the pressure-driven feeding of the cells which results in a low metabolic rate. Inversely a very porous structure increases the feeding, but then the low cell-concentration results in a low metabolic rate. Consequently, the optimal design may involve an intermediate density, but with the aid of topology optimization we achieve a even much better metabolic rate by using an intricate distribution of cell-structures within the reactor.

The kinetics is given by the following steady-state advection-diffusion-reaction equation:

$$(\mathbf{u}(\gamma) \cdot \boldsymbol{\nabla}) a = D \boldsymbol{\nabla}^2 a - k_a \left(1 - \gamma\right) a \tag{1}$$

where the velocity-field $\mathbf{u}(\gamma)$ depends on the porosity γ and advects the nutrition A with diffusion coefficient D. The reaction is first order: $r_a = -k_a \left(1-\gamma\right) a$, where $(1-\gamma)$ should be interpreted as the local cell-density.

The variation of $\gamma(\mathbf{r})$ uniquely characterizes the reactor-design since it also affects the fluid flow, as the porous structures is assumed to give rise to a Darcy damping force $\mathbf{F}_{Da} = -\alpha(\gamma)\,\mathbf{u}$, where α is characterized as the local inverse permeability. In all the stationary Navier-Stokes equations, governing the fluid flow, becomes:

$$\begin{aligned} \rho(\mathbf{u} \cdot \boldsymbol{\nabla})\mathbf{u} &= -\boldsymbol{\nabla} p + \eta \nabla^2 \mathbf{u} - \alpha(\gamma)\,\mathbf{u} \\ \boldsymbol{\nabla} \cdot \mathbf{u} &= 0 \end{aligned} \tag{2}$$

with $\mathbf{u}$ being the velocity field, ρ and η the density and viscosity of the fluid buffer, and p the pressure. The coupling between the inverse permeability and the design-variable γ vary through this work depending on the kind of optimization applied, but have the following general form: $\alpha(\gamma) = \alpha_{max} f(\gamma)$, with $\alpha_{max} = \frac{\eta}{Da\, L^2}$ being the inverse permeability inside the cell-structures, characterized by the Darcy number Da. For the coupling function $f(\gamma)$ to be consistent, the limiting cases must be: $f(0) = 1$ having maximal damping

[1] In the following we imagine the biological culture as being a cell-culture even though bacteria may fit evenly well in this simplified model.

[2] The porosity is sometimes denoted ε in literature [6].

inside the cell-structures and $f(1) = 0$ where no damping is present in the bulk fluid and we return to the standard Navier-Stokes equations[4]. In this work Da is typically around 10^{-5}, resulting in an strong damping created by the porous structures.

The model is solved for a given design $\gamma(\mathbf{r})$, using the commercial numerical software-tool COMSOL[3], by first finding $\mathbf{u}(\gamma)$ from Eq.2 and then $a(\mathbf{r})$ from Eq.1.

Our aim is to optimize the metabolic rate, which corresponds to finding the optimal distribution of $\gamma(\mathbf{r})$ such as to maximize the reaction-term in Eq. 1. As a result we introduce an objective function Φ, which by convention has to be minimized:

$$\Phi = -\langle\, k_a\,(1-\gamma)\,a\,\rangle \tag{3}$$

Here the average is naturally taken over the reaction region.

3 THE OPTIMIZATION

Essential for the optimization problem is having the objective function Φ defined to guide the method towards the optimum, and often additional constrains on the design variable or other characteristics of the system have to be defined. In this work no constrains are needed as both the extreme cases of a completely empty or filled reactor are unfavorable, as described earlier.

3.1 Optimized simple design

To benchmark the topology optimized 2D reactors, we first optimize two simple reactor-designs which are shown in Figure 1. The left design we call the homogeneous model as the uniform porosity of the whole design-region is optimized, while the width δ of a porous band is optimized in the right design, called the band model. In both cases there is only one design-variable which is optimized using a brute-force optimization method [4].

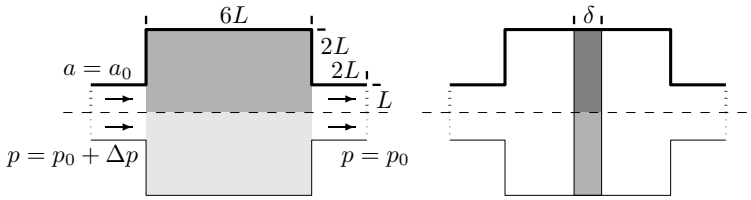

Figure 1: Illustration of the two simple reactor-setup. Because of symmetry, only the upper half of the reactor is solved, where the geometry is defined in terms of $L = 10^{-3}m$. In the "homogeneous model", to the left, the value of the homogeneous porosity is optimized, while the width δ is optimized in the "band model" to the right.

[3]COMSOL AB, Stockholm

[4]The MATLAB routine `fminbnd` minimizes a single variable using a golden section search and parabolic interpolation.

3.2 Topologically optimized design

We have used similar setup as for the simple 2D cases (left setup in Fig.1), but now with a locally varying $\gamma(\mathbf{r})$, and again we have assumed y-symmetry of the solutions[5].

The design-process is an iterative method starting from an initial design γ_0. Here we set the initial design to be an empty reactor, which is the most unfavorable state as no metabolism occurs. Given the nth design-configuration γ_n, at one point in the iteration-process, we first numerically solve the reactor-model and from the solution calculate Φ. Then we perform an sensitivity analysis by solving a related adjoint problem which in the end gives $\frac{\partial \Phi}{\partial \gamma}$ [4]. From this information we use the Method of Moving Asymptotes (MMA)[7] to obtain a new updated design-variable γ_{n+1}, and the process continuous until it has converged to a optimal design. A thorough description of the method is given in [2, 4].

A representative collection of optimal designs for different parameters are shown in Figure 2, with the upper row (A) showing the distribution of porous material in black together with a grey-scale indication of the flow-speed. Below in row (B) the upper half shows the concentration-field and the reaction-field below.

Comparing Φ between the simple and the topologically optimized reactors shows a more than ten-fold improvement for the last case. To investigate the nature behind this improvement, we note that mass-conservation leads to the following scaling of the objective function $\Phi \sim Q\,\mathcal{C}$, where Q is the flowrate through the reactor and $\mathcal{C}$ is the conversion of the reactant, defined by

$$\mathcal{C} \equiv \frac{a_0 - a_L}{a_0} = 1 - \frac{a_L}{a_0}$$

where a_0, a_L is the inlet, outlet concentration, respectively. Now we plot in Figure 3 the relative change in Q and $\mathcal{C}$ between the simple homogeneous optimizations and the other two optimizations for similar outer conditions. We have normalized by the results from the homogeneous model, and because it is presented in a log-log plot the contours of the relative improvement of Φ become straight lines, as showed by the dashed lines and the related factors in Figure 3. The normalized results from the band-model are shown by points and the results from the topology optimization are shown by diamonds. Figure 3 shows that topology optimization can increase the metabolic rate of the optimal reactors by nearly a factor 20, while the band-model only increase the rate by around 20%. Furthermore we see that the topology optimization achieve such impressive improvement by increasing the flow-rates at the expense of lower conversions. This efficient design-strategy emphases the value of the complex microfluidic channel-design in microreactor-design, which basically arise as to distribute the fluid over a large area at minimal pressure-loss.

[5]Throughout the optimizations, we use a mean mesh-size in the design-domain of $\approx 0.1\,L$

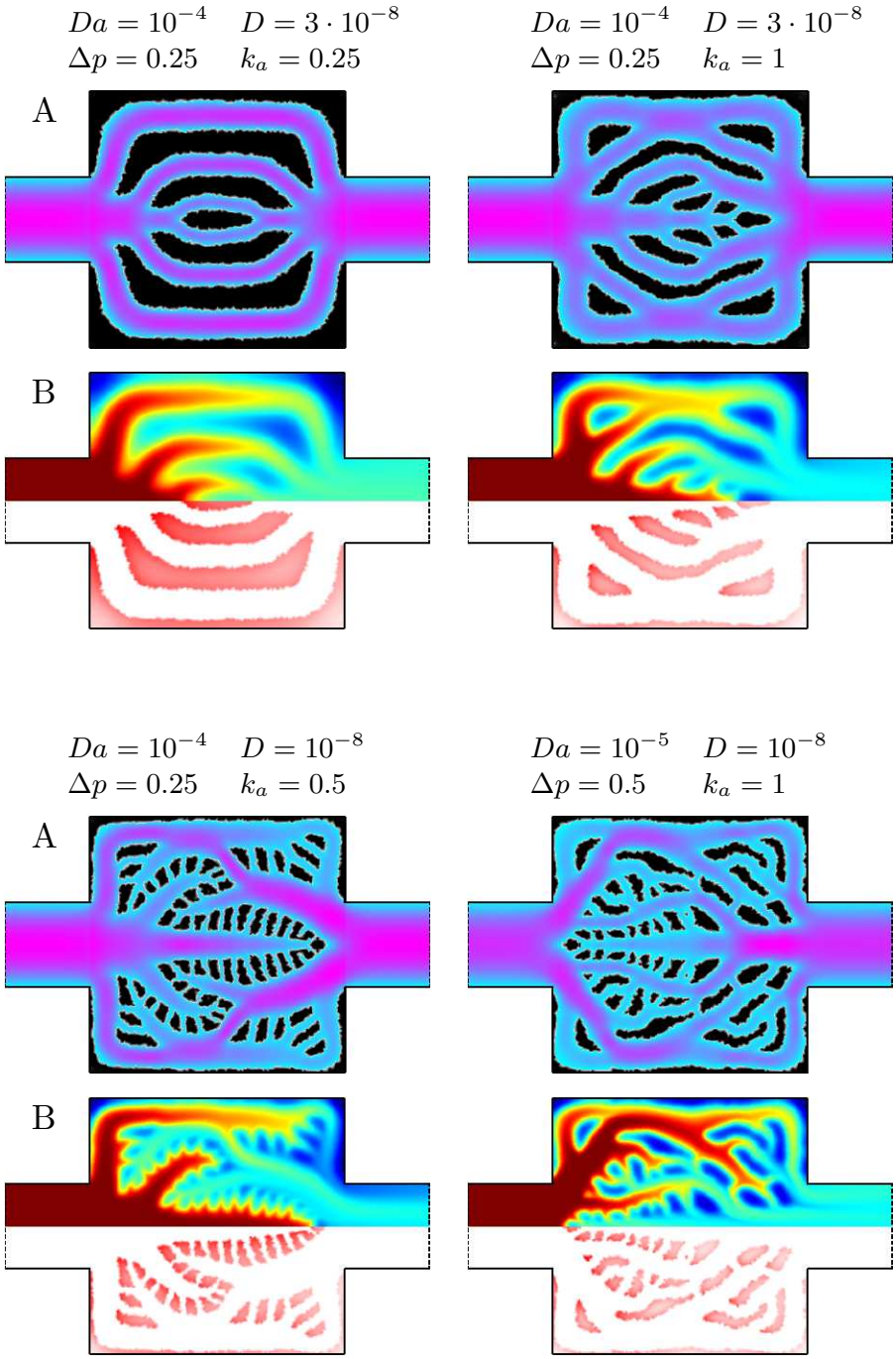

Figure 2: Representative collection of optimal reactor-designs. The upper row (A) shows the distribution of porous material in black together with a grey-scale indication of the flow-speed. Below in row (B) the upper part shows the concentration-field and the reaction-field below.

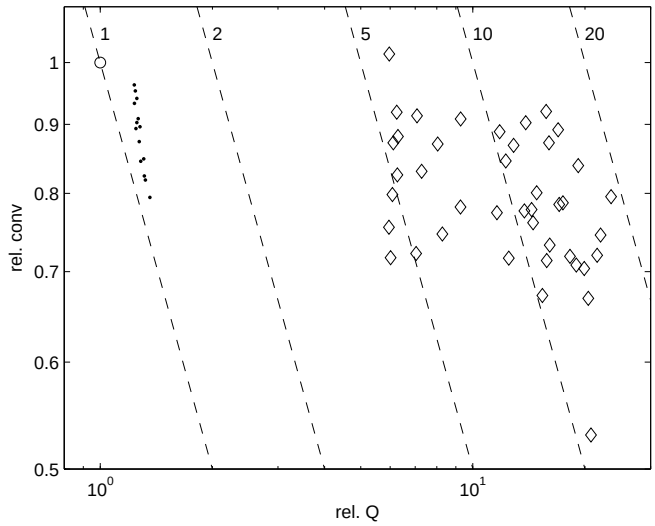

Figure 3: Comparing the improvement of the objective function Φ by relating the flow rate and the conversion for the different optimal designs at similar outer conditions.

4 CONCLUSION AND PERSPECTIVES

- We have optimized microfluidic bio-reactors for supporting biological cultures.
- By distributing optimally the immobilized cultures within a nutrition-flow, we have shown that the metabolic rate can increase by close to a factor 20.
- The main reason for this improvement comes from an efficient distribution of the nutrition to the biological cultures.
- This method of optimizing micro-reactors have been generalized to cover a hole class of catalytic reactions[8].

4.1 Acknowledgements

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