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Towards the CFD model of flow rate dependent enzyme-substrate reactions in nanoparticle filled flow microreactors

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ABSTRACT

Measurable kinetic parameters of enzyme-substrate reactions in the presence of immobilized biocatalysts in flow microreactors show remarkable dependence on the substrate flow rate. This paper presents a computational model that operates with a flow rate dependent K_M value. CFD simulations and actual measurements were carried out in a chip microreactor, investigating the chemical process of deamination of phenylalanine by the model enzyme *Pf*XAL attached to the surface of magnetic nanoparticles, forming packed bed reactors in the microfluidic chip. The reactor geometry has been varied in order to examine the flow rate dependence of the reaction. Experimental results suggested a moderate flow rate dependence of the examined kinetic parameters. The volumetric product concentration distribution was calculated in the reactors by CFD simulations, created with the open source software OpenFOAM, to enable further optimizations of the chip structure, enabling the design of more reliable flow reactors.

1. Introduction

Immobilized enzymes in microfluidic structures have promising advantages in diagnostics and synthetic, or in analytical applications [1]. In our microfluidic microreactors the enzyme, or other catalytic biomolecules are covalently attached to the surface of small magnetic nanoparticles (MNPs) which have an average diameter of a few hundred nanometres (see Fig. 1/a). The nanoparticles therefore have biocatalytic activity due to the enzymes on their surface. The MNPs can be brought into the microchambers (microreactors) with the fluid flow as a suspension. Special microfluidic devices (e.g. Spinsplit MagneChip) have controllable magnets which can be positioned over each chamber. By using the magnetic field of these magnets the MNP suspension can be anchored in the chambers, i.e. the continuous fluid flow cannot sweep them away (see Fig. 1/b). After filling the chambers with MNPs the substrate S let it flew through the reactor as an aquatic solution. As the substrate S goes through the suspension, it reacts with the enzyme E generating some product P. The product concentration $[P]$ is measured after the chambers with an appropriate detector. This biofunctionalised packed-bed microreactor offers the feasibility of several variations of the biocatalysts [2]. Investigating an enzymatic reaction with the MNP filled microreactors has several advantages because of the reduced size. The small size scale of the microfluidic structure requires reduced quantities of the expensive reagents [3]. In our case one microchamber has a volume of only $V = 0.73$ µl. Further benefits of the reduced size are the high surface-to-volume ratio, reduced mixing times and the precise temperature control [4,5]. The measurement of high number of different samples can be facilitated by automation or parallelization. This means that a measurement cycle requires less manpower compared to the traditional batch chemistry methods (see section Experimental). The variable parameters are mainly the substrate concentration $[S]$, temperature T or the type of the substrate. After performing several measurements one get the enzyme kinetics data (Fig. 1/c).

The enzyme-substrate reactions are found to be flow rate dependent in flow-through packed-bed reactors [6]. The dependence was shown using microfluidic devices of various authors [3,7]. This means that the reaction has a dependence on the flow velocity. Therefore the homogenization of the flow field in the MNP filled microchamber is needed to get reliable and precise results. In the absence of this the different parts of the microreactor perform the reaction differently due to the inhomogeneous velocity distribution (see Fig. 2/d). To get rid of this problem recently we designed various enhanced microreactor geometries in order to homogenize the velocity field [8]. The chip layout containing microreactors with the original cylindrical geometries is shown in Fig. 2.

In this paper first the flow field simulation results for the original and the new enhanced geometries are presented based on [9,8]. It will be shown that based on these simulations the flow field is more homogeneous in case of the new geometries. Therefore they are more

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Nomenclature

δ	Constrictivity
ε	Porosity
ν	Kinematic viscosity [m^2s^{-1}]
τ_f	Tortuosity
[C]	Molar concentration of substance C [mmol l^{-1}]
D_C	Diffusivity of C [m^2s^{-1}]
D_{visc}	Viscous resistance [m^{-2}]
k_{cat}	Turnover number [s^{-1}]
K_M	Michaelis constant [mmol l^{-1}]
p	Pressure [Pa]
Q	Flow rate [m^3 s^{-1}]
Re	Reynolds number
T	Temperature [°C]
v	Velocity [m s^{-1}]
v_r	Reaction velocity [mmol l^{-1} s^{-1}]
CFD	Computational fluid dynamics
IPA	Isopropanol
MNP	Magnetic nanoparticle

applicable for the investigation of the flow rate dependent reactions. Then experimental results with a given enzyme-substrate reaction are presented. Finally the investigated reaction will be simulated, where the simulation model is based on the Michaelis-Menten kinetics. The used model is based on our previous work in [10].

2. Theoretical background

2.1. Laminar flow

The flow is assumed to be laminar at the used flow rates ($Q \leq 200$ µl min^{-1}). The used liquid is water, isopropanol (IPA), or aquatic solution of tris(hydroxymethyl) aminomethane (TRIS), both of them are treated as incompressible. The flow and the reaction will be modelled as steady-state.

2.2. MNP suspension as porous media

The MNP suspension is modelled as porous media based on the previous measurement results in [1,8]. In the porous media the gradient of the pressure is proportional with the velocity

$$\text{grad } p = -\mu \cdot D_{visc} \cdot v, \tag{1}$$

where μ is the dynamic viscosity, and D is the viscous resistance. The viscous resistance can be direction dependent. In our case it is assumed to be equal to all direction because of the spherical shape of the nanoparticles. The value of the viscous resistance was determined based on previous measurements [1]:

$$D_{visc} = 2.071 \cdot 10^{10} \text{m}^{-2}. \tag{2}$$

2.3. Velocity calculations

As it was mentioned above, our initial goal was to design new chamber geometries, in which the velocity field is more homogeneous than in the original cylindrical chamber (shown in Fig. 2). To compare the different cases, we will calculate the volume weighted average velocity and the volume weighted velocity deviation for each geometries at the same flow rate. The volume weighted average velocity is calculated as

$$\bar{v} = \frac{1}{V_{MNP\_sus}} \sum_i V_i \cdot v_i, \tag{3}$$

where V_{MNP_sus} is the total volume of the MNP suspension, while V_i and v_i are the ith computational cell's volume and velocity in the MNP suspension, respectively. The volume weighted velocity deviation is

$$\sigma_v = \sqrt{\frac{1}{V_{MNP\_sus}} \sum_i V_i (v_i - \bar{v})^2}. \tag{4}$$

After calculating both quantities, the homogeneity of the flow field is measured as the ratio of the deviation to the average velocity. This ratio is decreased in the enhanced chamber geometries compared to the ratio for the original one in Fig. 2.

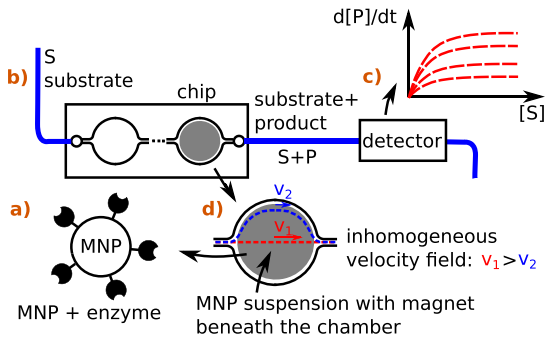

Fig. 1. Measurement schematic of an enzymatic reaction in the MNP filled microchambers.

2.4. Enzyme-substrate reaction

The simplified form of the investigated reaction is

$$E + S \underset{k_{1r}}{\overset{k_{1f}}{\rightleftharpoons}} ES \underset{k_{2r}}{\overset{k_{2f}}{\rightleftharpoons}} P + E, \tag{5}$$

where E is the enzyme, S is the substrate, ES is the enzyme-substrate complex and P is the generated product. The k values are the reaction rates. In the given reaction the ES term actually notes more components, which turn into one another in a cascade-reaction.

From modelling point of view, we try to give a simplified model which is based on the Michaelis-Menten kinetics (see e.g. in [11]). Using the kinetics the reaction velocity, i.e. the generation speed of the product can be calculated with the following formula:

$$v_r = \frac{\text{d}[P]}{\text{d}t} = v_{r\_max} \cdot \frac{[S]}{K_M + [S]}, \quad v_{r\_max} = k_{cat}[E], \tag{6}$$

where v_{r_max} is the maximum reaction speed, K_M is the Michaelis-constant and k_{cat} is the turnover number. In the kinetics, both values are constant and can be identified from the measurements (e.g. from the measured $v_r([S])$ dependence).

The investigation of enzyme reactions in flow-through systems has been reported in numerous articles. In these papers it was found that the K_M value is flow rate dependent [3]. In [12] and [13] a theoretical

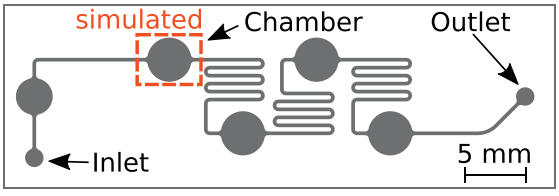

Fig. 2. The original microfluidic chip layout from a top view. The black circles note the microchambers each with one inlet and one outlet channel. In the modelling the flow field of only one chamber is simulated (noted with a dashed red rectangle). The chamber diameter is $D = 3600$µm, the channel width is 300 µm, while the height of the structure is 110 µm.

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