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A curved top-wall flow cell for improvement of response consistency in surface plasmon resonance array detection

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ABSTRACT

High spatially consistent responses are desired for the array-based biomolecular interaction analysis. The response consistency is dependent on the uniformity of mass transport rate. Based on theoretical analysis, we established a universal mathematical relation between the mass transport rate and the flow cell height. The optimal flow cell geometry for analyte distribution uniformity, $H(l) = 1/3 \cdot l^{-1/2}$, was derived from the mathematical relation. Using Poly(dimethylsiloxane) elastomer replica molding methods, the flow cell was fabricated. The actual flow regimes within the flow cell were confirmed by micro-PIV experiments and results agreed with expectations. To demonstrate the capability of this flow cell in improving spatial consistency of responses, goat-anti-rabbit IgG and rabbit IgG interaction experiments were performed on a home-built SPR imaging system. Results showed that the curved top-wall flow cell significantly reduced the coefficient of variance of association rate across the sensing surface.

1. Introduction

Biomolecular interaction analysis is a key part of drug development. To obtain the reliable interaction information efficiently, a label-free and high-throughput detection method is desired [1,2]. Surface plasmon resonance (SPR) imaging can realize real-time, label-free and high-throughput analysis of biomolecular binding events, and has emerged as the most promising tool in drug development [3–5]. Typically, these high-throughput SPR sensors require a large flow cell (at centimeter scales) to hold arrays of binding sites. Analyte transports by convection and diffusion to the sensor surface and then interacts with the immobilized receptors at each binding site. The uniformity of analyte distribution directly affects the response consistency. If the analyte distribution is nonuniform, binding responses obtained from even the same analyte–receptor interaction will be different. It has been a great challenge for the array-based SPR detection to improve the uniformity of analyte distribution and generate consistent binding responses [6–8].

Many researchers have explored the effects of mass transport and interaction on analyte distribution. Based on a two-compartment model and quasi-steady-state approximation [9–11], the concentration of analyte just above the sensing surface can be analytically expressed and it indicates that the analyte concentration, following the mass transport rate, decreases along streams. Researches also revealed that the mass transport rate is dependent on a number of design (geometrical) and operational parameters [12–14]. In case of sufficient analyte or detection sensitivity, the nonuniformity of analyte distribution, induced by the variation of mass transport rate, could be reduced by increasing the analyte flow rate or decreasing the receptor immobilization density [15–17]. Another method is to optimize the flow cell configuration, such as implementing actuators and incorporating structures within flow cell, to impose a secondary flow to increase analyte mixing. Implementing actuators such as electrothermal stirring and centrifugal mixing could actively mix analyte with high efficiency, but it increases the complexity of system [18,19]. In contrast, the passive mixing method incorporates structures such as slanted and herringbone grooves within the flow cell. By adding less complexity to the system, it can also acquire satisfying mixing efficiency [20–23]. Recently, much effort has been expended to improve the analyte mixing efficiency and reduce the complexity of system.

In order to achieve high mixing efficiency at minimum complexity, we propose a novel flow cell based on theoretical analysis of the relationship between the mass transport rate and flow cell geometry. The flow cell uses a curved-surface top wall, rather than arrays of microchannels, to eliminate the along-stream variation of analyte distributions. It is even less complex, more easily

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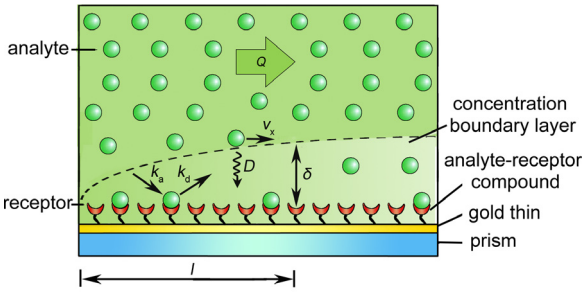

Fig. 1. Schematic of analyte–receptor interaction in the flow chamber (not to scale).

fabricated, and can also achieve comparable analyte mixing efficiency. The flow cell geometry was derived from the mathematical relation between the mass transport rate and flow cell geometry. It was fabricated by Poly(dimethylsiloxane) elastomer replica molding. Micro-PIV experiments were conducted and results confirmed that flow regimes in this optimized flow cell agree with expectations. Goat-anti-rabbit IgG and rabbit IgG interaction experiments were performed on a home-built SPR imaging system. Results showed that the coefficient of variance (CV) of association rate got a significant reduction in the curved top-wall flow cell.

2. Theoretical basis

As shown in Fig. 1, in the conventional flow cell, analyte is transported by horizontal convection and vertical diffusion to the sensing surface and then interacts with the immobilized receptors. The horizontal flow velocity v varies with the distance from sensing surface. Due to analyte diffusion and depletion, there exists a thin concentration boundary layer near the sensing surface. Its thickness δ can be calculated by equating the time $t_c \sim l/v(\delta)$ for analyte to flow past the length l, and the time $t_d \sim \delta^2/D$ for analyte to diffuse across the height δ. With the horizontal flow velocity at the layer edge simplified as $v(\delta) = 6Q\delta/H^2W$, the thickness of the concentration boundary layer can be obtained [12,24]

$$\delta = \sqrt[3]{\frac{DWH^2}{6Q}l} \tag{1}$$

where D is the analyte diffusion coefficient, W and H is the width and height of flow cell, and Q is the volumetric flow rate of bulk solution. It can be seen that the concentration boundary layer thickness δ increases monotonically along streams. Thus, the mass transport rate ($k_m \sim D/\delta$) will accordingly decrease along streams, and the analyte near the sensing surface dilutes downstream.

When the top wall of flow cell is tilted to be a curved surface, the flow regimes change to be a gradually varied flow. Analyte flows along curved streamlines, rather than horizontal movement. Based on the similarity theory, any intersection of streamlines with the concentration boundary layer satisfies:

$$\frac{z}{H(x)} = \frac{\delta(l)}{H(l)} \tag{2}$$

In this case, the convection time for analyte to flow past length l can be integrated as:

$$\begin{aligned} t'_c &= \int_0^l \frac{1}{v_x}\,dx \\ &= \frac{WH(l)}{6Q\delta}\int_0^l H(x)\,dx \end{aligned} \tag{3}$$

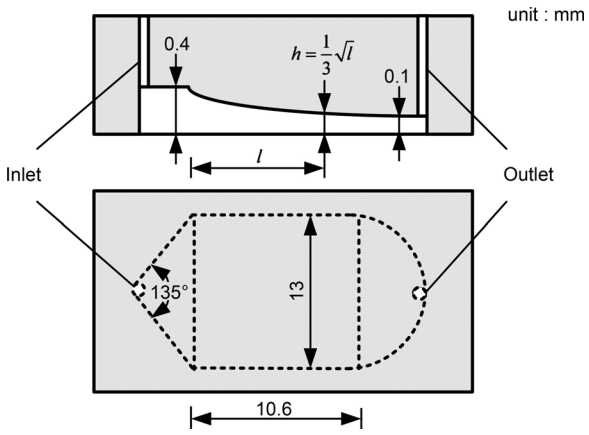

Fig. 2. Schematic drawing of the curved top-wall flow cell.

The thickness of the concentration boundary layer becomes

$$\delta = \sqrt[3]{\frac{DW}{6Q}H(l)\int_0^l H(x)\,dx} \tag{4}$$

It can be seen that the profile of the concentration boundary layer is dependent on the flow cell geometry. Actually, Eq. (4) equals to Eq. (1) in the special case where the flow cell height is invariant along streams. By optimizing the flow cell geometry, variations of the layer thickness and of the mass transport rate could be eliminated. Thus, consistent binding responses could be obtained.

3. Design and fabrication

Based on Eq. (4), the along-stream variation of the concentration boundary layer thickness can be eliminated when the height of flow cell satisfies $d\delta/dl = 0$, or

$$H(l) = \alpha \cdot l^{-1/2} \tag{5}$$

where α is an arbitrary constant. The less α gives rise to the thinner concentration boundary layer and accordingly the larger mass transport rate k_m. But too little α will increase the flow pressure and lead to device failure. The α was ultimately assigned to be 1/3. Furthermore, it is unrealizable for Eq. (5) near the inlet of flow cell, where l is so little that the flow cell height H approaches infinite. For practice, a tilting surface was used instead of the curved surface near the inlet. The geometrical parameters of the designed curved top-wall flow cell were shown in Fig. 2.

Because of the good bio-compatibility and easy-fabrication, Poly(dimethylsiloxane) (PDMS) has been widely used for biomolecular analysis devices [25,26]. So PDMS was used as the material of the flow cell. The replica molding method, as illustrated in Fig. 3, was used for the flow cell fabrication. The polymethylmethacrylate (PMMA) mold used for PDMS casting was designed in a computer-aided design (CAD) program and then cut by laser machine (Fig. 3A). The two pieces of the mold were clamped together by spring clamp bolts. Two needles were inserted into two holes on the mold to form the inlet and outlet (Fig. 3B). The PDMS prepolymer base and curing agent was thoroughly mixed in a 10:1 weight ratio and degassed in a desiccator with a mechanical vacuum pump for 30 min to remove air bubbles. Then the prepolymer mixture was poured into the mold from the cast hole (Fig. 3C). After curing at 80 °C for 60 min, the PDMS sheet was peeled off the mold. A photograph of the flow cell is presented in Fig. 3D.