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Chapter

Enhancement of SARS-CoV-2 Detection Time for Integrated Flow Confinement Microfluidic Biosensor

Sameh Kaziz

Abstract

The performance of the microfluidic biosensor with integrated flow confinement for the detection of SARS-CoV-2 was analyzed numerically by the finite element method. First, the numerical model was validated by comparison with experimental data reported in the literature. Then, the influence of some parameters on the binding reaction was investigated, such as the flux confinement rate and the amount of analyte supplied to the microchannel inlet. Results showed that flow confinement enhances the convection and diffusion transport of target analytes to the reaction surface and significantly reduces device detection time as well as target sample consumption.

Keywords: biosensor, SARS-CoV-2, flow confinement, detection time

1. Introduction

The new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is the coronavirus disease virus (COVID-19), has quickly emerged around the world since the end of December 2019 and caused a lot of deaths [1]. As a result, various measures have been taken by WHO and researchers in different fields to limit the outbreak of the virus and its damage. The rapid detection of the virus to control the pandemic situation was, therefore, a real challenge. Microfluidic biosensors played an important role in the fight against the disease, nevertheless, the low rate of diffusion of target analytes toward the sensitive surface generates a long response time and therefore limits their uses [2, 3]. The binding reaction between the analytes and the ligands immobilized on the sensitive surface leads to the creation of analyte-ligand complexes on this surface, the concentration of which has a determining part in the detection process [4, 5]. Quantitative real-time polymerase chain reaction (qRT-PCR) is currently the most used method for the detection of viruses in respiratory infections. This method can detect very small amounts of viruses [3] but requires well-sophisticated laboratories, a long detection time, and above all, it can be prone to errors [6]. Other methods of diagnosis such as point-of-care (POC) technologies remain, despite some disadvantages, hopeful ways for sensitive, rapid, and inexpensive diagnosis [7]. As, at the microscopic scale, mass transport of analytes is very
difficult because the Reynolds number is low (Re < 1) and the fluid flow is always laminar [8], the binding kinetics of the analyte-ligand reaction, as well as the response time of such detection devices, are generally limited. Currently, several mechanical and physical effects have been used to enhance mass transport in microfluidic networks, such as magnetic effect [9], AC electrokinetic effect (ACEK) [10, 11], and optical forces [12]. Other studies have shown that several design parameters can be adjusted to improve the performance of biosensors [13–17]. In this context, we achieved a 2D finite element numerical simulation on the kinetics of SARS-COV-2 to optimize the performance of a microfluidic biosensor with integrated flow confinement. To determine the degree of influence of some input factors on the biosensor detection time, a main flow of water mixed with analytes connected to a perpendicular flow of pure water has been studied numerically. The make-up flow contributes to the confinement of the target analytes in a thin layer above the biosensor and thus increases the rate of the binding reaction.

2. Physical model

2.1 Microfluidic biosensor setup

As illustrated in Figure 1, the 2D configuration of the microfluidic biosensor with flow confinement studied has a length, L, of 250 μm and a height, H, of 40 μm. The reaction surface, of 20 μm in length, is positioned on the bottom border of the microchannel. The carrier fluid, mixed with the analytes (SARS-CoV-2) enters the microchannel (sample flow) from left to right. Ligands having constant concentration, $B_{max}$, are initially immobilized on the reaction surface. The sample flow is correlated to the confinement flow in the vertical direction. The confinement flow traps analytes to a thin layer over the detection area.

2.2 Velocity field modeling

The fluid, supposed to be Newtonian and incompressible, flows in a laminar and isothermal regime. The Navier-Stokes equations are thus used to determine the pressure and velocity fields of the fluid in the microchannel (Eqs. (1) and (2)):
∇ \cdot \mathbf{u} = 0 \quad (1)
\rho (\mathbf{u} \cdot \nabla) \mathbf{u} = -\nabla p + \mu \nabla^2 \mathbf{u} \quad (2)

where \( \mathbf{u} \) is the flow velocity field, \( \rho \) and \( \mu \) are, respectively, the fluid’s density and dynamic viscosity, and \( p \) is the pressure.

### 2.3 Analyte concentration modeling

The transport of aimed analytes by diffusion and convection is modeled by the following Fick’s second law (Eq. (3)):

\[
\frac{\partial [A]}{\partial t} + \mathbf{u} \cdot \nabla [A] = D \Delta [A] \quad (3)
\]

where \([A]\) and \(D\) designate the concentration and the diffusion coefficient of the target analyte, respectively.

### 2.4 Analyte-ligand concentration modeling

The first-order Langmuir–Hinshelwood adsorption model [18, 19] was employed to calculate the concentration of analyte-ligand complexes formed on the reaction surface (Eq. (4)):

\[
\frac{\partial [AB]}{\partial t} = k_{\text{on}} [A_{\text{surf}}] [B_{\text{max}} - [AB]] - k_{\text{off}} [AB] \quad (4)
\]

where \([AB]\) is the bound analyte-ligand concentration and \(B_{\text{max}}\) is the immobilized ligand concentration on the reaction surface. \([A_{\text{surf}}]\) is the concentration of analytes at the reaction surface, \(k_{\text{on}}\) is the adsorption rate constant and \(k_{\text{off}}\) is the desorption rate constant.

### 2.5 Boundary and initial settings

Table 1 and Figure 2 recapitulate all the boundary settings used in this study. For the laminar flow, the inlet fluid flows inside the main microchannel with a parabolic profile where the average velocity, \(u_{\text{ave}}\), was set at 50 µm/s, that which enters through the confining channel, its velocity was set to \(u_{\text{conf}}\) and at the outlet, the flow was

<table>
<thead>
<tr>
<th>Type</th>
<th>Velocity ((\mathbf{u}))</th>
<th>Concentration (([A]))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walls</td>
<td>(u = 0)</td>
<td>(\frac{\partial [A]}{\partial t} = 0)</td>
</tr>
<tr>
<td>Reaction surface</td>
<td>(u = 0)</td>
<td>(\frac{\partial [A]}{\partial t} = -\frac{1}{2} \frac{\partial [AB]}{\partial t})</td>
</tr>
<tr>
<td>Inlet sample Flow</td>
<td>(u_{\text{ave}})</td>
<td>(c_0)</td>
</tr>
<tr>
<td>Inlet confinement Flow</td>
<td>(u_{\text{conf}})</td>
<td>(\bar{n} (D \nabla [A]) = 0)</td>
</tr>
<tr>
<td>Outlet</td>
<td>(\bar{n} = 0)</td>
<td>(\bar{n} (D \nabla [A]) = 0)</td>
</tr>
</tbody>
</table>

Table 1. Boundary settings of velocity field and concentration of analyte for the reaction surface, walls, inlets, and outlet.
assumed fully developed. For mass transport, a constant concentration of analytes $c_0$, was imposed at the inlet of the microchannel and the outlet the condition $\bar{n} \cdot (D \nabla [A])$ was applied. Considering the non-interaction of the analyte with the rest of the walls, the homogeneous Neumann condition was used [17]. On the sensitive surface, the diffusive flux condition generated by the binding adsorption reaction between analytes and ligands was employed.

Initially the velocity of the fluid within the microchannel, the bulk analyte concentration, $[A]_0(t=0)$, and the complex concentration formed on the reaction surface, $[AB]_0(t=0)$, were assumed to be zero. All the parameters used in the modeling [20] are presented in Table 2.

### Table 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho$</td>
<td>Fluid density</td>
<td>1000</td>
<td>kg/m$^2$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Dynamic viscosity</td>
<td>$1.08 \times 10^{-3}$</td>
<td>Pa.s</td>
</tr>
<tr>
<td>$k_{am}$</td>
<td>Adsorption constant</td>
<td>$10^4$</td>
<td>m$^3$/Mol.s</td>
</tr>
<tr>
<td>$k_{off}$</td>
<td>Desorption constant</td>
<td>$10^{-2}$</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$D$</td>
<td>Diffusion constant</td>
<td>$10^{-11}$</td>
<td>m$^2$/s</td>
</tr>
<tr>
<td>$B_{max}$</td>
<td>Ligand concentration</td>
<td>$3.310^2$</td>
<td>$\mu$mol/m$^2$</td>
</tr>
<tr>
<td>$c_0$</td>
<td>Analyte input concentration</td>
<td>$10^{-3}$</td>
<td>$\mu$mol/m$^3$</td>
</tr>
</tbody>
</table>

Figure 2.

*Boundary conditions. (a): boundary conditions for the velocity field. (b): boundary conditions for analyte concentration.*
2.6 Numerical method

The proposed model equations were solved using Galerkin finite element analysis [21]. We used 1923 triangular geometric elements for the complete 2D domain, including the refined elements of the reaction surface. To prove that the convergence is reached and that the calculated results are independent of the mesh, the profile of the velocity field at $x = 140 \mu m$ of the microchannel was plotted, in Figure 3, for several meshes (1328, 1923, 1958, and 2612 elements). The variations obtained by using different numbers of elements are significantly the same. All the stages of the model resolution are recapitulated as presented in Figure 4. The pressure and the velocity fields were calculated by solving stationary Eqs. (1) and (2) at once. The concentration of analytes and that of the analyte-ligand complexes, appearing on the binding area, were simulated from the coupled time-dependent Eqs. (3) and (4).

![Figure 3. Velocity field at $x = 140 \mu m$ of the microchannel for different mesh grids.](image)

![Figure 4. Model simulation flowchart.](image)
3. Results and discussion

3.1 Model validation

First, the numerical model was tested by comparison with experimental existing data of Berthier and Silberzan [18], as shown in Figure 5. The time-normalized surface concentration during the adsorption phase was calculated using the same experimental parameters [18], for a microfluidic of 10 mm in length and 1 mm in height without flow confinement. The flow rate of the transporter fluid is $10^{-6}$ m$^3$/s, the inlet concentration of the target molecules is $2.5 \times 10^{-6}$ Mol/m$^3$, the diffusion constant is $7 \times 10^{-11}$ m$^2$/s, and the density of ligands initially immobilized on the reaction surface is $1.668 \times 10^{-8}$ Mol/m$^2$. The association and dissociation constants are, 75 m$^3$/Mol·s and $10^{-2}$ 1/s, respectively. We can note that our results are in good agreement with the experimental data and that the average error between the two results is very small, which confirms the validation of the model.

3.2 Flow confinement impact

Succeeding the successful model validation, this section aims to show how to flow confinement can improve the kinetic response of SARS-CoV-2. Figure 6 shows the binding reaction with and without flow confinement for a biosensor configured, as shown in Figure 1. An enhancement of the binding reaction and thus the detection time (22%), was seen in the case where the flow confinement was employed (Table 3). This shows the effectiveness of confinement in improving biosensors immunoassays. Admittedly, this improvement can be explained by a local condensation of the analyte over the reaction surface. In fact, the flow confinement increases the fluid velocity in the vicinity of the sensitive membrane which decreases the thickness of the analyte concentration diffusion boundary layer formed at the adsorption phase, as illustrated in Figure 7. Also, it is noted that the thickness of the analyte concentration diffusion boundary layer decreases with increasing flow confinement rate.
Figure 6.
Impact of the flow confinement on the variation of the normalized surface concentration, $AB/C_2/C_3$, over time.

<table>
<thead>
<tr>
<th>Case</th>
<th>Detection time (s)</th>
<th>Drop percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Confinement</td>
<td>16,050</td>
<td>—</td>
</tr>
<tr>
<td>With Confinement</td>
<td>12,475</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 3.
Detection time and drop percentage for the microfluidic biosensor with or without flow confinement.

Figure 7.
Analyte concentration diffusion boundary layers in the adsorption phase with and without flow confinement effect. (a): Without flow confinement. (b): With flow confinement ($u_{conf} = u_{ave}$) and (c): With flow confinement ($u_{conf} = 3u_{ave}$).
3.3 Flow confinement velocity impact

To find the optimum flow confinement rate, beyond which the improvement of the binding kinetics becomes insignificant, the progression of the complex concentration for various flow confinement velocities has been plotted in Figure 8. It is evident that by increasing the flow confinement velocity from \( u_{\text{ave}} \) to \( 4u_{\text{ave}} \), the binding kinetics are improved (Table 4). Rapid flow confinement can, therefore, significantly improve the response time and therefore the performance of biosensor devices. However, beyond an optimal value (\( \sim 3u_{\text{ave}} \)) the improvement becomes insignificant. In summary, flow confinement confines the analyte molecules to a thin layer over the sensitive surface and thus raises the rate of the binding reaction.

3.4 Analyte mass minimization with flow confinement

Increasing the mass of the sample delivered to the inlet of the microfluidic channel can mitigate the lack of analyte consumed near the binding surface [22]. However, we show in this study that this lack of analyte can be solved by adding flow confinement in front of the sensitive surface which gives a significant improvement to the binding reaction. Figure 9 shows the time progression of the normalized complex concentration without and with confinement flow at the adsorption phase for two amounts of

![Figure 8](image-url)

*Figure 8.* Time advancement of the normalized surface concentration with different flow confinement velocities.

<table>
<thead>
<tr>
<th>Confinement coefficient ( (\alpha = \frac{U_{\text{conf}}}{U_{\text{ave}}}) )</th>
<th>Detection time (s)</th>
<th>Drop percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14,200</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>12,475</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>10,800</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>10,550</td>
<td>34</td>
</tr>
</tbody>
</table>

*Table 4.* Detection time and drop percentage for the microfluidic biosensor with various flow confinement rates.
analyte at the microchannel inlet. In the case of a biosensor with a confinement effect, although the concentration of analyte at the entrance is reduced \(10^{-5} \text{ μmol/m}^3\), an improvement in the binding reaction has been observed.

4. Conclusion

This work focuses on optimizing the performance of integrated flow confinement microfluidic biosensors for the immunoassay of SARS-CoV-2. Detection is based on the efficiency of the reaction kinetics of SARS-CoV-2 under the effect of certain parameters such as the inlet rate of the flow confinement and the inlet concentration of the analyte. The confining flow improved the transport of the analyte to the reaction surface of the biosensor and significantly reduced the mass consumption of the sample. Increasing the flow velocity by flow confinement can effectively decrease the thickness of the diffusion boundary layer and therefore increase the association and dissociation rates of the virus in question. This study helps to improve future designs of microfluidic biosensors that can be used for rapid virus detection.
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References


electrothermal force. Microfluidics and Nanofluidics. 2021;25:86


