DETECTION OF TARGET MOLECULES USING SURFACE-BASED BIOSENSOR ARRAYS IN FLUID FLOWS

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ABSTRACT

In this paper, the concentration of target molecules in a fluid flow is estimated using an array of biosensors. The concentration evolves according to an advection-diffusion partial differential equation which is coupled with chemical reaction equations on the biosensor surface. An approximate characterization of the system is developed as a system of ordinary differential equations by exploiting the multiple-time scale behaviour of the system and using the divergence theorem. The estimate of target molecules is then obtained by solving a nonlinear least squares problem. An explicit expression for the asymptotic variance of the estimation error is obtained. To demonstrate the accuracy of proposed method, we illustrate our results on a novel biosensor built out of protein molecules.

Index Terms— Advection diffusion partial differential equation, multi-compartment model, protein-based biosensor array, concentration Estimation, least squares method

1. INTRODUCTION

The concentration of target molecules in a fluid flow over biosensors evolves according to an advection-diffusion partial differential equation(PDE) which is coupled with Dirichlet and Neumann boundary conditions and cannot be solved analytically. Therefore, estimating the concentration is considered as a challenging parameter estimation problem. Moreover, the measurement equation and the state equation are mutually coupled since the measurement process affects the system state since each biosensor grabs target molecules and changes the concentration in the flow. The main results of this paper are briefly stated as follows:

1. To facilitate estimation of the concentration of target molecules, Theorem 3.1 develops an approximation method to describe the dynamics of the problem by a system of ordinary differential equations (ODEs). The approximate model is derived by exploiting the multiple time-scale behaviour of the system and the divergence theorem. The proposed approximate model in this work is an improved version of the model in our previous work [1], where a new transport coefficient is obtained by using the divergence theorem and a multiple time-scale approach. Moreover, the order of approximation error is obtained in Theorem 3.1. It is shown that the obtained approximation error is valid in a certain range of the response time.

2. A novel biosensor constructed out of protein molecules is used as an actual example to illustrate our results.

3. The estimation of target molecule concentration is posed as a parameter estimation problem in terms of the derived ODE model. The estimate is computed numerically for the novel biosensor via nonlinear least squares method. It is shown that the estimator is asymptotically normal and its asymptotic variance is derived. Experimental results are provided to illustrate the accuracy of the derived expression for the estimation variance.

The general approach to address the estimation problem in a distributed system (infinite dimensional systems) is converting the system description from a distributed-parameter into a lumped-parameter form by methods for solving partial differential equations, such as finite-difference method, the finite-element method, and modal analysis [2]. However, these methods usually convert the PDE system to a highly nonlinear system of several ODEs, whereas the multi-compartment model converts the PDE model to only one ODE over each sensor. The multi-compartment model is developed by extending the two-compartment model which is used in modeling a variety of binding experiments influenced by mass transport [3].

In Sec.2, the PDE model for a biosensor is constructed. It is then followed by the approximate characterization of the system by the multi-compartment model in Sec.3 which is used for estimating the target molecular concentration. Sec.4 presents the results based on protein biosensors and Sec.5 concludes the paper.

2. PDE MODEL FOR THE FLUID FLOW

The aim is to estimate the concentration of target molecules in a fluid system where the dynamics are described by an advection-diffusion PDE model.

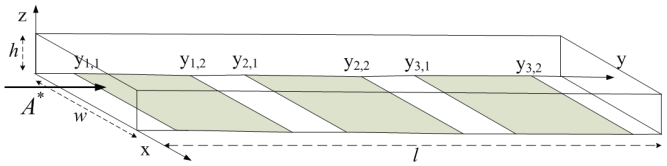

Fig. 1: An equally spaced linear array of three biosensors in a rectangular flow chamber. The fluid containing target molecules enters from the left side. The concentration of target molecules at the inlet is A^* as expressed in the boundary condition (4).

Consider a flow chamber with a rectangular cross section as shown in Fig.1. A flow of target molecules flows past N identical surface-based biosensors along the length of the chamber in the y-axis direction. Biosensor i, for $i = 1, 2, \ldots, N$, is located in the range $[y_{i,1}, y_{i,2}]$ along the y-axis and $[0, w]$ along the x-axis. The inlet of the flow chamber lies in the xz plane. The dimensions of the flow chamber and biosensors are:

$$\begin{aligned} &\text{Flow chamber: Height} = h, \ \text{Length} = l, \ \text{Width} = w, \quad (1)\\ &\text{Biosensors: Length} = L, \ \text{Spacing} = d,\\ &\text{Biosensor } i \text{ is located in the range } y \in [y_{i,1}, y_{i,2}]. \end{aligned}$$

The concentration of target molecules in the flow chamber (1), denoted by $A(t, y, z)$, is governed by [4]

$$\begin{aligned} &\frac{\partial A}{\partial t} = \gamma \left(\frac{\partial^2 A}{\partial y^2} + \frac{\partial^2 A}{\partial z^2} \right) - 4\bar{v}(z/h)(1 - z/h)\frac{\partial A}{\partial y}, \quad (2)\\ &A(t = 0, y, z) = 0, \quad y \in (0, l), \quad z \in (0, h) \end{aligned}$$

Here γ is the diffusion constant of the target molecule and $\bar{v}$ is the maximum velocity in a fully developed parabolic velocity profile [3] in y direction. When target molecules in the solution arrive at the biosensors, chemical reactions are initiated which result in a change in impedance that is translated to change in the measured current. On the surface of biosensor i, the adsorption flux of target molecules is equal to the rate of consuming target molecules by the reactions which is described as the following boundary condition:

$$\gamma \frac{\partial A}{\partial z}\bigg|_{z=0, y \in [y_{i,1}, y_{i,2}]} = R(A(t, y, z = 0), \mathbf{u}_i(t, y)), \quad (3)$$

where the vector $\mathbf{u}_i(t, y)$ contains the values of concentration of chemical species at time t and location y on biosensor i. $R(A, \mathbf{u}_i)$ is the rate of adsorption of target molecules per unit area on the biosensor. The concentration at the inlet of the flow chamber is constant during the estimation process and equal to A^*. The boundary conditions are [4]

$$\begin{aligned} &A(t, 0, z) = A^*, \ \frac{\partial A}{\partial y}\bigg|_{y=l} = 0, \ \frac{\partial A}{\partial z}\bigg|_{z=h} = 0, \quad (4)\\ &\frac{\partial A}{\partial z}\bigg|_{z=0, y \notin \cup_{i=1}^{N} [y_{i,1}, y_{i,2}]} = 0. \end{aligned}$$

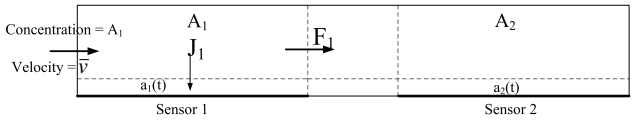

Fig. 2: Four-compartment model for two biosensors.

The dynamics of $\mathbf{u}_i(t, y)$, for $y \in [y_{i,1}, y_{i,2}]$, are described as

$$\frac{d\mathbf{u}_i(t, y)}{dt} = G(\mathbf{u}_i(t, y), A(t, y, 0)), \quad t > t_i, \ \mathbf{u}_i(t_i, y) = u_0. \quad (5)$$

Here, $G(\cdot)$ is specified by the rate law of reactions on the biosensor. The response of biosensor i commences at $t = t_i$. The response of biosensor i at time t for the inlet concentration A_1 is an implicit function of A_1 denoted by $g_i(A_1, t)$. It can be written that

$$g_i(A_1, t) = F(\bar{\mathbf{u}}_i(t)), \quad \bar{\mathbf{u}}_i(t) = \frac{\int_{y_{i,1}}^{y_{i,2}} \mathbf{u}_i(y, t)\, dy}{y_{i,2} - y_{i,1}}. \quad (6)$$

Here, $F(\cdot)$ is the transducer function which translates the concentration quantities on the biosensor to a corresponding electrical signal. The measurement taken at biosensor i at time $t^{i,k}$, denoted by m_i^k, is

$$m_i^k = g_i(A^*, t^{i,k}) + n_i^k, \quad i \in \{1, 2, \ldots, N\}. \quad (7)$$

The noise samples n_i^k are independent normally distributed with zero mean and finite variance σ^2.

3. MULTI-COMPARTMENT APPROXIMATION AND CONCENTRATION ESTIMATION

Given the measurement equation of (7) and the PDE model of Sec.2, defined by (2)-(5), the aim is to estimate the concentration A^* at the boundary in (4). To estimate A^* in (4), a multi-compartment ODE model is introduced that approximates the PDE by a system of ODEs.

The multi-compartment model is an extension of the existing two-compartment model for mass transport-binding experiments [3]. Its derivation is based on the multiple timescale behaviour of the system [5] and the divergence theorem. In this model, the flow chamber is partitioned into a series of two-compartment blocks above biosensors since the concentration in the bulk is varying faster than that in the vicinity of the biosensor surface. The two-compartment blocks are connected by middle compartments as shown in Fig.2. The concentration in the outer compartment above the first biosensor achieves equilibrium fast and is set equal to the concentration A^* at the inlet of the flow chamber. By applying the divergence theorem to the advection-diffusion PDE of (2) in the outer compartment associated with each biosensor, the concentration in the outer compartment above the next biosensor is obtained. The following theorem describes the multi-compartment characterization. Its proof can be found in [6].

Theorem 3.1 *Consider a flow of target molecules over an equally spaced linear array of N identical biosensors in the flow chamber (1). Suppose the concentration of target molecules at the inlet of the flow chamber is a constant denoted by A^*. The concentration of target molecules $A(t,y,z)$ and chemical species are described by the PDE model (2)-(5). As $\gamma \to 0$, there exists a time instant t^* such that for $t \in (t_i, t^*)$, the dynamics of the average of the surface concentration of chemical species on biosensor i, denoted by $\bar{\boldsymbol{u}}_i(t)$, satisfies*

$$\begin{aligned} h_0 \frac{d\bar{a}_i(t)}{dt} &= \frac{\gamma}{h_0}\left(A_i - \bar{a}_i(t)\right) - R(\bar{a}_i(t), \bar{\boldsymbol{u}}_i(t)) + O(\gamma^{4/3}), \\ \frac{d\bar{\boldsymbol{u}}_i(t)}{dt} &= G(\bar{\boldsymbol{u}}_i(t), \bar{a}_i(t) + O(\gamma^2)), \quad t \in (t_i, t^*), \\ \bar{a}_i(t_i) &= 0, \quad \bar{\boldsymbol{u}}_i(t_i) = u_0, \quad i = 1, \ldots, N. \end{aligned} \tag{8}$$

Recall γ in (8) denotes the diffusion constant. The concentration in the flow chamber for $y \in (y_{i-1,2}, y_{i,2})$, $z \in (h_0, h - h_0)$, and $t \in (t_i, t^*)$ can be expressed as $A(t,y,z) = A_i + O(\gamma)$. Here h_0 is defined as $h_0 = \frac{1}{1.464}\left[\frac{\gamma h L}{\bar{v}}\right]^{1/3}$. A_i is a constant obtained by the following recursion:

$$A_i = \alpha A_{i-1},\ i = 2, \ldots, N,\ \alpha = 1 - \frac{3\gamma L}{2h_0 \bar{v} h},\ A_1 = A^*. \tag{9}$$

The implication of the above theorem is that the multi-compartment model provides an accurate description of the dynamics of the concentration of target molecules. In (8), Theorem 3.1, h_0 is the height of the inner compartment above each biosensor and $\bar{a}_i(t)$ denotes the spatial average of concentration in the inner compartment of biosensor i. The non-negative constant A_i denotes the concentration in the outer compartment of biosensor i. The intuition behind the relation between A_i and A_{i-1} in (9) is that a fraction of molecules is grabbed by sensor $i-1$ and therefore a smaller amount of concentration arrives at the next biosensor. With the above multi-compartment characterization, the estimation of the initial concentration A^* is formulated as the following least squares problem for the multi-compartment model:

$$\hat{A}_1 = \underset{A_1 \in R^+}{\arg\min}\, S^{-1} \sum_{i=1}^{N} \sum_{k=1}^{S} \left(m_i^k - g_i(A_1, t^{i,k})\right)^2, \tag{10}$$

where N and S refer to the number of biosensors and the number of time samples, respectively. In (10), m_i^k refers to $m_i(t^{i,k})$ which, according to (7), is the measurement of biosensor i taken at time $t^{i,k}$. Regarding (6), $g_i(A_1, t^{i,k})$ is the response of biosensor i at time $t^{i,k}$ which is equal to $F(\bar{\mathbf{u}}_i(t^{i,k}))$. $\bar{\mathbf{u}}_i(t)$ is an implicit function of the initial concentration A_1 through the multi-compartment model (8). Thus, the estimate is the solution of the optimization problem (10) together with (8). According to (8), there is a common functional relation between the response of each biosensor and the concentration in its outer compartment expressed as

$$g_i(A_1, t) = g(A_i, t - t_i) \quad \text{for} \quad i = 1, \ldots, N \tag{11}$$

Here, $g(A_i, t)$ denotes the response of each biosensor when the concentration in its outer compartment is A_i. Recall the time shift t_i in (11), is the response delay of biosensor i.

Based on the results of [7] on the asymptotic properties of non-linear least squares estimators and Theorem 3.1, it is proved in [6] that the estimation error $\hat{A}_1 - A^*$, obtained by (10), is asymptotically normal as $S \to \infty$;

$$\begin{aligned} &\sqrt{S}\left(\hat{A}_1 - A^*\right) \to N(0, \frac{\sigma^2}{\Gamma}), \\ &\Gamma = \lim_{S\to\infty} \frac{1}{S} \sum_{k=1}^{S} \sum_{i=1}^{N} \alpha^{2i-2} \left[\frac{\partial g}{\partial A}(\alpha^{i-1}A^*, t^{i,k} - t_i)\right]^2, \end{aligned}$$

where $g(A,t)$, defined in (11), is the response of each biosensor when the concentration in its outer compartment is A. $\partial g(\alpha^{i-1}A^*, t^{i,k} - t_i)/\partial A$ is the value of $\partial g(A,t)/\partial A$ at $A = \alpha^{i-1}A^*$ and $t = t^{i,k} - t_i$. The noise variance is denoted by σ^2. Recall that α is defined in (9). The variance of the estimator $\hat{A}_1$ with finite number of samples S and N sensors, denoted by $\sigma^2_{S,N}$, can be approximated as

$$\sigma^2_{S,N} \approx \frac{\sigma^2}{\sum_{i=1}^{N} \alpha^{2i-2} \sum_{k=1}^{S} \left[\frac{\partial g}{\partial A}(\alpha^{i-1}A^*, t^{i,k} - t_i)\right]^2}. \tag{12}$$

4. RESULTS OF A CASE-STUDY: ION CHANNEL BIOSENSOR

In this section, the multi-compartment model of Sec.3 is evaluated for a protein-based biosensor, namely the ion channel switched (ICS) biosensor that was constructed and described in [8]. This biosensor incorporates artificial ion channels in a lipid bilayer. The flow of ions through a channel only occurs when a mobile channel in the outer layer aligns to a fixed channel in the inner layer to form a conducting dimer. The arrival of target molecule anchors the channels distant, on average, from their inner layer partners. The expected number of dimers is thus decreased. The conductance of the biosensor is proportional to the concentration of the dimers.

It is shown that the multi-compartment model (8) yields an excellent approximation to the flow dynamics. To this end, the response obtained by the multi-compartment model (8), for an array of ICS biosensors, is simulated using a Rosenbrock method for solving the ODEs. The response of the PDE model (2)-(5) is obtained using the COMSOL Multiphysics software which is based on finite element methods. The multi-compartment response is then compared with the PDE response using the normalized error

$$e_i(t) = \left|\bar{D}_i(t) - \bar{D}_i^{\text{ODE}}(t)\right| / \bar{D}_i(t), \quad i = 1, \ldots, N. \tag{13}$$

In (13), $\bar{D}_i(t)$ is the average dimer concentration on biosensor i, obtained by the PDE model (2)-(5) and $\bar{D}_i^{\text{ODE}}(t)$ is the corresponding response from the multi-compartment model (8).

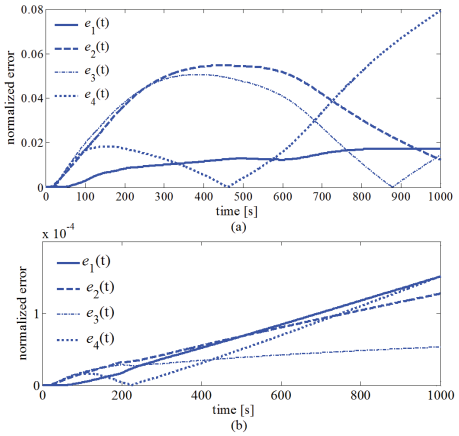

Fig. 3: The multi-compartment ODE model (8) is compared with the PDE model (2)-(5) by plotting the normalized error (13) for four biosensors for $A^* = 10^{-8}$ Mol/m^3 (a) and $A^* = 10^{-11}$ Mol/m^3 (b). The flow rate is 10 μL/min. The length of the biosensors is $L = 2$ mm and their spacing is $d = 1$ mm.

Table 1: Comparison between the simulated and approximate value (12) for the variance $\sigma^2_{S,N}$ of $\hat{A}_1$ (10): The simulated and analytical values of the standard deviation $\sigma_{S,N}/A^*$ for $S = 300$ time samples are shown. The sampling rate is 1 sample/s. $A^* = 10^{-8}$ Mol/m^3. The ratio of initial dimer concentration squared to the noise variance is equal to 10 dB.

	$\sigma_{S,N}/A^*$	
	Simulated	Analysis (12)
N=1	0.0971	0.0943
N=2	0.0611	0.0651
N=3	0.044	0.051

Fig.3 shows the normalized error (13) versus time for two values of concentration $A^* = 10^{-11}$ and $A^* = 10^{-8}$ Mol/m^3. It can be seen that the error during 1000 seconds of simulation time is less than 0.015% for $A^* = 10^{-11}$ Mol/m^3 and less than 8% for $A^* = 10^{-8}$ Mol/m^3. The height and width of the flow chamber are $h = 0.1$ mm and $w = 2$ mm. The length of each biosensor is $L = 2$ mm and the spacing between biosensors is $d = 1$ mm. The diffusion constant is equal to $\gamma = 10^{-6}$ cm^2/s and the flow velocity is 10μL/min.

The results are then compared with the approximate value (12) for verification. The standard deviation of $\hat{A}_1$ for different number of biosensors is shown in Table 1. The variance is obtained when $S = 300$ samples with sampling rate 1 sample/s are used for estimation. The actual value of the concentration is $A^* = 10^{-8}$ Mol/m^3. The ratio of initial dimer concentration squared to the noise variance is 10 dB.

5. CONCLUSIONS

In this paper, a multi-compartment approximation model is introduced by Theorem 3.1 in order to model the dynamics of a flow of molecules over multiple surface-based biosensors. The multi-compartment model (8) suggests that the response of each biosensor has a similar functional relationship with the concentration at the inlet of the flow chamber. This relationship is exactly reflected in the expression derived for the estimation variance in (12). This is an interesting result which enables us to analyse the estimation improvement obtained by using multiple biosensors. This capability distinguishes the multi-compartment method from other efficient methods such as boundary element methods. In future, the estimation improvement with multiple biosensors can be optimized by adjusting the dimensional proportions and biosensor parameters and using the multi-compartment model.

6. REFERENCES

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