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.
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:

- **Flow chamber:** Height = \( h \), Length = \( L \), Width = \( w \), (1)
- **Biosensors:** Length = \( L_i \), Spacing = \( d \),
- **Biosensor** \( i \) is located in the range \( y \in [y_{i,1}, y_{i,2}] \).

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

\[
\frac{\partial A}{\partial t} = \gamma \left( \frac{\partial^2 A}{\partial y^2} + \frac{\partial^2 A}{\partial z^2} \right) - 4\bar{v}(z/h)(1 - z/h) \frac{\partial A}{\partial y},
\]

\( A(t = 0, y, z) = 0, \quad y \in (0, 1), \quad z \in (0, h) \) \quad \text{(2)}

Here \( \gamma \) 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, 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:

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

\( R(A, \mathbf{u}_i) \) 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]

\[
A(t, 0, z) = A^*, \quad \frac{\partial A}{\partial y} \bigg|_{y=1} = 0, \quad \frac{\partial A}{\partial z} \bigg|_{z=h} = 0,
\]

\( \frac{\partial A}{\partial z} \bigg|_{z=0, y \notin \cup_{i=1}^N [y_{i,1}, y_{i,2}]} = 0 \).

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 \( g_i(A_1, t) \).

\[
g_i(A_1, t) = F \left( \bar{u}_1(t) \right), \quad \bar{u}_i(t) = \int_{y_{i,2}}^{y_{i,1}} \mathbf{u}_i(y, t) \, dy
\]

\( \text{Here, } F(\cdot) \) 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 \( t \) is denoted by \( m_i^k \), is

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

The noise samples \( n_i^k \) are independent normally distributed with zero mean and finite variance \( \sigma^2 \).

**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 time-scale 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 \( \bar{u}_i(t) \), satisfies

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

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

\[
A_i = \alpha A_{i-1}, \quad i = 2, \ldots, N, \quad \alpha = 1 - \frac{3\gamma L}{2h_0 \sqrt{\gamma}}, \quad A_1 = A^*.
\]

The implication of the above theorem is that the multi-compartment model provides an accurate description of the concentration of target molecules. In (8), \( A_i \) 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 \( i \) 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:

\[
\tilde{A}_1 = \arg\min_{A_1 \in \mathbb{R}^N} S^{-1} \sum_{i=1}^N \sum_{k=1}^S (m_k^i - g_i(A_1, t^{i,k}))^2,
\]

where \( N \) and \( S \) refer to the number of biosensors and the number of time samples, respectively. In (10), \( m_k^i \) refers to \( m_i(t^{i,k}) \) which, according to (7), is the measurement of biosensor \( i \) 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 \( F(\bar{u}_i(t^{i,k})). \) \( \bar{u}_i(t) \) is an implicit function of the initial concentration \( A_i \) 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

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

Here, \( g(A_1, t) \) 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 \( A_1 - A^* \), obtained by (10), is asymptotically normal as \( S \to \infty \):

\[
\sqrt{S} (\tilde{A}_1 - A^*) \to N(0, \sigma^2 / \Gamma),
\]

where \( \Gamma = \lim_{S \to \infty} \frac{1}{S} \sum_{k=1}^S \sum_{i=1}^N \alpha_i^{2i-2} \left[ \frac{\partial g}{\partial A}(\alpha_i^{-1} A^*, t^{i,k} - t_i) \right]^2 \),

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

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

\[
e_i(t) = |\tilde{D}_i(t) - \bar{D}_i^{\text{ODE}}(t)| / \bar{D}_i(t), \quad i = 1, \ldots, N.
\]

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).
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 $10 \mu$L/min. The length of the biosensors is $L = 2$ mm and their spacing is $d = 1$ mm.

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


