IEEE Sensors Letters Volume x(x) (2019)
Article Subject (Biosensor Interface)

Implantable Biosensor Interface Platform for Monitoring of Atherosclerosis

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Abstract— The drug-eluting stents (DESs) have been considered as an effective technique to reduce the severity of atherosclerotic stenosis. Recent technological advances have opened the door for developing new and innovative smart cardiovascular stents by integrating various electronics components and sensors to improve health monitoring and diagnosis. Rupture of atherosclerotic plaque represents the major cause of cardiovascular disease (CVD) such as heart attacks due to blockages of the arterial lumen. Pentraxin-3 (PTX3) is a novel localized inflammatory biomarker associated with the development of atherosclerosis and plaque vulnerability. In this paper, we propose a biosensor interface platform for monitoring the plaque vulnerability via detection and prediction of the inflammatory biomarker (PTX3). We propose mathematical and stochastic models using molecular communication paradigm for detection of Pentraxin-3 (PTX3) molecules in the atherosclerotic arterial wall using biosensor attached to a vascular stent inside the artery. The proposed platform and models can help in the localized sensing of the atherosclerotic biomarkers for monitoring of the plaque progression and for early warning of certain disorders such as heart attack.

Index Terms— Artery, Atherosclerosis, biosensor interface, molecular communication.

I. INTRODUCTION

Atherosclerosis is the most serious and common cardiovascular disease (CVD) and one of the leading causes of death in the world. Atherosclerosis blocks the artery and reduces the blood flow due to the accumulation of fatty deposits (plaque) in the arterial wall [1]. The plaques have a high risk of rupture when the fibrous cap thickness becomes very thin, e.g., <65µ, which may cause heart attacks, its known as vulnerable (unstable) plaques [2]. During the pathogenesis of atherosclerosis, several molecular biomarkers will be released by the inflammatory cells in the artery wall and the surrounding tissues [3, 4]. Some of these biomarkers may enter the blood, but usually, they may have a very low concentration in the blood and may be associated with other disorders in the body, which requires highly sensitive biosensing techniques. Unlike other inflammatory biomarkers, Pentraxin-3 (PTX3) is a biomarker which is more specific to the site of vascular inflammation rather than other systemic inflammation [4]. The PTX3 is mainly produced by the various cells in atherosclerotic lesions, e.g., macrophages, dendritic cells, and endothelial cells. The experimental and clinical studies showed that the PTX3 plays an important role in the process of plaque development and vulnerability even after implantation of the Drug-eluting stents (DES) [4, 5]. Therefore, it can be used as an early indicator for detection of the vulnerable plaques to avoid the high-risk events such as heart attacks.

Smart cardiovascular stents are currently being developed, which can integrate additional components and sensors for healthcare monitoring and diagnostic purposes [6-9]. The smart cardiovascular stents are being designed to wirelessly communicate with the external world to remotely access important information about the physiological conditions of the patients for early detection of diseases and disorders. Various biosensors have been developed for the detection of a wide range of CVD biomarkers, e.g., atherosclerotic biomarkers, to reduce the healthcare costs [10, 11]. In the literature, many drug transport models using DESs have been reported, e.g., [5, 12]. However, these models focused on drug release from the DES inside the artery lumen and drug distribution to the surrounding artery wall and thus they are out of the scope of this paper. To the best of our knowledge, no model or platform were reported in the literature for monitoring of atherosclerosis based on molecular biomarkers using localized implantable biosensor attached to cardiovascular stent.

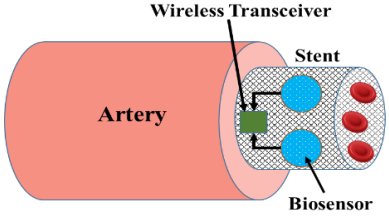

Fig. 1. Biosensor Interface on a cardiovascular stent in the artery.

In this paper, we propose a novel interface biosensing platform by attaching the biosensors to the cardiovascular stents before insertion in the artery, as shown in Fig. 1. This enables local measurement of the concerned biomarkers (e.g., PTX3) inside the arteries, and then the data can be wirelessly transmitted to an external transceiver to help clinicians for diagnosis and monitoring of atherosclerosis including development and vulnerability of the plaques. Therefore, the progression of atherosclerosis can be locally monitored for the

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Digital Object Identifier: 10.1109/LSEN.XXXX.XXXXXXX.

different parts of the diseased artery. Using molecular communication (MC) paradigm [13, 14], we develop mathematical and stochastic simulation models for transport and detection of the PTX3 biomarkers from the cellular sources (act as transmitters) located inside the artery wall (act as a channel) to the biosensor (act as receivers) on the artery stent. The communication link with the stents is already developed in the literature, e.g., [6-8], and it is out of the scope of this paper.

II. MODELLING OF BIOSENSOR INTERFACE

The target molecules (i.e., PTX3 biomarker) are assumed to be released from the molecular source (e.g., macrophage cells) located in the intima layer of the artery wall. Then, the molecules move across the atherosclerotic intima to finally react with the biosensor, as shown in Fig. 2. In the case of atherosclerosis, plaque builds up inside the intima, forming a thin layer (fibrous cap) and lipid core, which creates a significant change in the diffusion properties of the arterial wall. Atherosclerosis mainly affects the intima but may also affect the media layer in advanced stages.

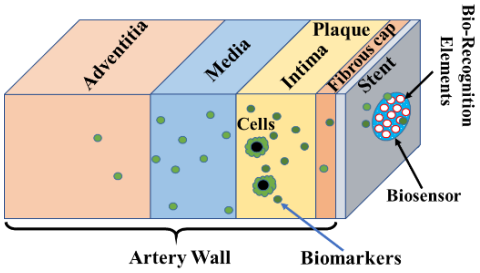

Fig. 2. Transport of the biomarkers from the molecular source to the biosensor through the atherosclerotic intima.

A. Analytical Model

The biological microenvironment between the molecular source and the biosensor is modelled as a multilayer medium with different characteristics, as shown in Fig. 2. The molecular diffusion through this medium is mathematically described as [15],

$$\frac{\partial C_i}{\partial t} = D_i \nabla^2 C_i \tag{1}$$

where C_i is the concentration of the biomarker (PTX3) in the i^{th} layer, ∇^2 is the Laplacian operator, D_i is the diffusion coefficient of PTX3 in the i^{th} layer, and i =1,2,...,N.

Following the mathematical technique presented in [16, 17], we derive an expression for the molecular concentration, i.e., the channel impulse response (CIR), for the multilayer MC channel. The Laplace domain expression of the molecular concentration in the i^{th} layer can be expressed as

$$C_i(s) = M_i(s) + W_i(s) \tag{2}$$

The concentration function $M_i(s)$ is the concentration expression in the Laplace domain due to the instantaneous release of the PTX3 molecules by a point-like source in unbounded medium. The function $M_i(s)$ can be obtained by converting the CIR expression, given in [18], to Laplace domain, as

$$M_i(s) = \frac{M_0}{4\pi D_i} \int_0^\infty \frac{1}{g_i} e^{-g_i|z-z_0|} J_0(\mathrm{R}\xi)\xi d\xi \tag{3}$$

where M_0 is amount of the released biomarker from the source in (ng), $J_0(\cdot)$ is the Bessel function of the first kind of order zero, $R = ((x-x_0)^2 + (y-y_0)^2)^{1/2}$, $g_i = (\xi^2 + \lambda_i^2)^{1/2}$, and $\lambda_i^2 = s/D_i$.

The function $W_i(s)$ is the solution of Eq. (4) that vanishes at t = 0 and makes Eq. (2) satisfy the boundary conditions (6)-(9).

$$\frac{\partial^2}{\partial R^2} W_i(s) + \frac{1}{R}\frac{\partial}{\partial R} W_i(s) + \frac{\partial^2}{\partial z^2} W_i(s) - \lambda_i^2 W_i(s) = 0 \tag{4}$$

Equation (4) is the Laplace transform of the diffusion equation given by [15, eq. (1.7)] but extended to multiple layers. The solution of (4) can be expressed as [16]:

$$W_i(s) = \int_0^\infty \left[A_i e^{-g_i z} + B_i e^{g_i z} \right] J_0(\xi R)\xi d\xi \tag{5}$$

where A_i and B_i are the weighting functions. The boundary conditions at the interfaces between the layers are extended for N-layer medium in the Laplace domain [15] as

$$D_j \frac{\partial C_j(s)}{\partial z} = D_{j+1} \frac{\partial C_{j+1}(s)}{\partial z} \tag{6}$$

$$C_j(s) = k_j C_{j+1}(s) \tag{7}$$

$$\lim_{z\to\infty} C_1(s) = 0 \tag{8}$$

$$\lim_{z\to-\infty} C_N(s) = 0 \tag{9}$$

The boundary condition (6) imposes continuity of the flux at the interfaces between the layers, while the boundary condition (7) allows for possible changes in the concentration at the interfaces. The boundary conditions (8)-(9) assume vanishing of the concentration at a very large distance in the first and last layers. The factor k_j is equal to the diffusivity ratio between the adjacent layers. The general expression for the concentration in any layer can be obtained by substituting (3) and (5) in (2) as follows:

$$C_i(s) = \int_0^\infty \left[\frac{M_0 \delta_{i1}}{4\pi g_i D_i} e^{-g_i|z-z_0|} + A_i e^{-g_i z} + B_i e^{g_i z} \right] J_0(\xi R)\xi d\xi \tag{10}$$

where δ_{i1} is the Kronecker Delta function. In general, for N-layer channel, the unknown functions A_i and B_i can be obtained by applying the boundary conditions (6)-(9) to Eq. (10), and then by solving the obtained equations for j = 1,2,.., N-1. Since the molecular source is assumed to be located in the first layer (i.e., intima) at the location (x_0,y_0,z_0), and the biosensor is located in the last layer (i.e., at the interface between lumen and fibrous cap), the function $M_i(s)$ vanishes for all the layers except in the first layer. The intima microenvironment consists of two layers, namely, layer-1 (plaque) and layer-2 (fibrous cap). Therefore, the concentration expression in the vicinity of the biosensor can be expressed as

$$C(s) = \int_0^\infty \left[A_2 e^{-g_2 z} + B_2 e^{g_2 z} \right] J_0(\xi R)\xi d\xi \tag{11}$$

The inverse Laplace transform of the concentration expression given in Eq. (11) can be evaluated using Zakian's method as

$$C_a(t) = \frac{2}{t}\sum_{m=1}^{5} Re\left[K(m)C(s)\right] \quad (12)$$

where $s = a(m)/t$ and *K(m)* and *a(m)*, are listed in Table 9.2 in [19]. The number of the received PTX3 molecules by the biosensor is significantly affected by the concentration in the vicinity of the biosensor.

B. Stochastic Simulation Model

We propose a stochastic simulation framework for transport and detection of the molecular biomarker (PTX3) in a 3-D multilayer channel between the molecular source and the biosensor. The simulation time T is divided into small time steps Δt. The molecules are released from the source at the first-time step via an impulse release. Then, the molecules move randomly in all directions following Brownian motion. The location of each molecule at each time step is updated and recorded as [20]:

$$(x_k, y_k, z_k) = (x_{k-1}, y_{k-1}, z_{k-1}) + (\Delta x_k, \Delta y_k, \Delta z_k) \quad (13)$$

where $k=1,\ldots,N_t$, N_t is the total number of time steps, (x_{k-1}, y_{k-1}, z_{k-1}) are the coordinates of the molecule at the previous time-step, (Δx_k,Δy_k,Δz_k) are the random displacements which follows the normal distribution with zero-mean and variance $\sigma_i^2 = 2D_i\Delta t$ for $i=1, 2,\ldots,N$.

If the molecules move to the adjacent new layer, the displacements will be influenced by the diffusion coefficient of the new layer. In order to predict the biomarker concentration in the vicinity of the biosensor, we monitored number of the molecules inside a virtual observer (volume) without hindering or absorbing the molecules. This can be used to compare the analytical results to verify accuracy of the simulation transport framework. The biomarker concentration in the vicinity of the biosensor in (μg/ml) can be expressed as

$$C_s(t_k) = M_0 \frac{\alpha(t_k)}{V_{obs}\ N_0} \quad (14)$$

where $\alpha(t_k)$ is number of the molecules inside the observer volume at the time-step t_k , N_0 is the total number of released molecules, and V_{obs} is the observer volume.

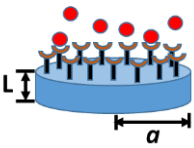

Fig. 3. Molecular reaction with the biosensor recognition elements.

For predicting number of the received molecules by the biosensor, the molecules that reach the biosensor will bind with the receptors (recognition elements) and thus will be removed from the environment, as shown in Fig. 3. The cumulative number of absorbed (received) molecules by the biosensor at the time-step t_k due to release an amount of PTX3 biomarker (M_0) can be written as

$$N(t_k) = \frac{M_0\ N_A\ \left[P(t_{k-1}) + P(t_k)\right]}{MW_{PTX3}\ N_0} \quad (15)$$

where $P(t_k)$ and $P(t_{k-1})$ are number of the received molecules at the time-steps t_k and t_{k-1}, respectively, due to release N_0 molecules by the source, N_A is the Avogadro number, and MW_{PTX3} is the molecular weight of PTX3 biomarker.

III. RESULTS

In this section, we present analytical and simulation results for prediction number of the received PTX3 biomarker by the biosensor and the concentration in its vicinity. The simulation parameters, e.g., the time-step and the number of released molecules, are chosen by performing a trial and error run with different values to examine the variations in the output received signal. We found that a time-step with values less than 1s, will not lead to significant variation in the simulation results. The effective diffusivity of PTX3 biomarker (D_{PTX3}) in the plaque and the fibrous cap are estimated using Eq. (16) by applying Stokes-Einstein equation based on the diffusivity and the molecular weight of the low-density lipoproteins (LDL) [2]. The system parameters used in the computations are summarized in Tables 1 and 2.

$$D_{PTX3} = D_{LDL} \times \left(\frac{MW_{PTX3}}{MW_{LDL}}\right)^{-1/3} \quad (16)$$

where D_{LDL} is diffusivity of the LDL.

Table 1. System Parameters.

Parameter	Value
Simulation time (T)	5 h
Time step (Δt)	1 s
No. of released molecules (N_0)	1×10^5
Amount of released PTX3 (M_0)	1×10^{-4} ng/cell [21]
Radius of Biosensor (a)	0.5 mm
Thickness of Biosensor (L)	10 μm
Molecular Weight of LDL (MW_{LDL})	2500 kDa
Molecular Weight of PTX3 (MW_{PTX3})	45 kDa
Source Location (x_0, y_0, z_0)	(0, 0, 25) μm
Number of iterations	100

Table 2. Parameters of the atherosclerotic intima [2].

Parameters	Plaque (Lipid Core)	Fibrous cap	
		Vulnerabl	Stable
Thickness (μm)	650	(30, 65)	100
D_{LDL} (μm²/s)	0.011	0.45	0.45
D_{PTX3} (μm²/s)	0.043	1.72	1.72

The PTX3 concentration in the vicinity of the biosensor is plotted in Fig. 4 for different thicknesses of the fibrous cap layer. The analytical concentration results show perfect match with the stochastic simulation results. The PTX3 concentration increases with the time to reach the peak value and then it begins to decrease to very low level. The PTX3 concentration in the biosensor vicinity has a higher value

in the case of the vulnerable (unstable) plaque, i.e., with fibrous cap thickness (L = 30μm), compared to the stable plaque, i.e., L= 100μm. The results show that, as the fibrous cap thickness increases, the PTX3 concentration decreases while the peak time increases. This coincides with the clinical studies which showed that the systemic PTX3 levels in blood were significantly higher in patients with thin fibrous cap [22]. Also, the clinical studies revealed that the PTX3 level is inversely related to fibrous cap thickness.

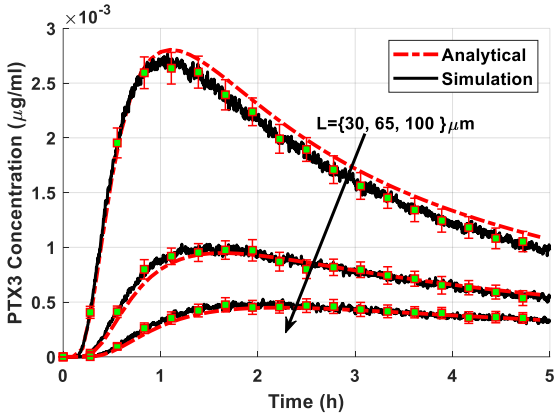

Fig. 4. The PTX3 concentration in the vicinity of the biosensor for different fibrous cap thickness (L) with 95% confidence interval.

The accumulative number of received PTX3 molecules by the biosensor is obtained using the stochastic particle-based simulator for both vulnerable (L = 30μm) and stable plaques, as shown in Fig. 5. As expected, the number of the received (absorbed) PTX3 molecules in the case of the vulnerable plaque is higher than that for stable plaque. This happens because the concentration of PTX3 biomarker near the biosensor is higher in the case of the vulnerable plaque as indicated in Fig. 4. The characteristics of the molecular received signal can provide critical information about the disease progression as well as the composition and thickness of the plaque and fibrous cap.

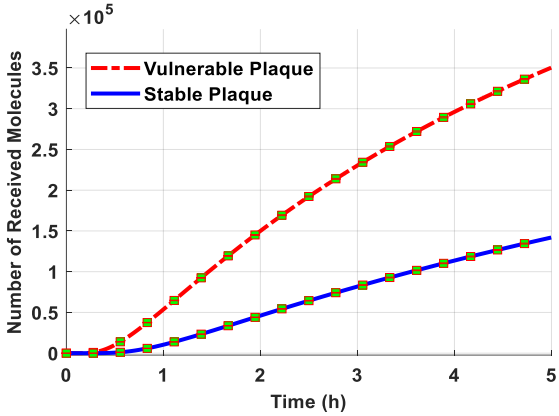

Fig. 5. The cumulative number of received PTX3 molecules by the biosensor for vulnerable (L= 30μm) and stable plaques with 95% confidence interval.

IV. CONCLUSIONS

In this paper, we propose a novel biosensing interface platform and models using MC paradigm for prediction of the inflammatory PTX3 biomarker associated with atherosclerosis. In the proposed platform, the biosensor is assumed to be attached to a cardiovascular stent inside the artery to act as an interface between the molecular world inside the body and external monitoring/control systems via the wireless link. We propose mathematical and stochastic models for capturing and prediction of the PTX3 biomarker level produced from the artery wall. The molecular received signal by the biosensor can help in monitoring and detection of atherosclerosis, particularly, the characteristics and vulnerability of the plaque. The proposed models could be useful for design smart cardiovascular stents for early warning of certain disorders such as heart attack.

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