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State-Space Modeling for Graphene FET Biosensor Dynamic Response

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Abstract

Graphene field effect transistor (G-FET) biosensors exhibit high sensitivity due to their high electron/hole mobilities. However, G-FET biosensors often undergo baseline drift as a result of their instability under aqueous environments, which makes it difficult to analyze the sensor response against target molecules. Here, we present a computational approach to build state-space models (SSMs) for time-series data of G-FET biosensors, which can separate the response against target molecules from the drift. The drain current (I_{DS}) was continuously measured, while sensing the influenza virus (H1N1) as target molecules. The obtained time-series data including I_{DS} change induced by the virus and the drift was modeled by the proposed SSMs. The parameters were estimated by using Markov chain Monte Carlo (MCMC) methods. The models were evaluated by using widely applicable Bayesian information criterion (WBIC). Our models fit the time-series data of the G-FET biosensors well, and extracted the sensor response to target molecules from the baseline-drift data. This study would enable one to accurately analyze the sensor response.

1. Introduction

Graphene, a two-dimensional (2D) sheet of hexagonally arranged carbon atoms, offers an ideal sensing platform owing to its high electron/hole mobilities and 2D nature. Indeed, there have been reports on Graphene field effect transistor (G-FET) biosensors showing detections of ions [1], biomolecules [2], and others. However, G-FET biosensors exhibit baseline drift [3], which makes it difficult to estimate concentration of target molecules properly. Here, we presented state-space models (SSMs) to describe time-series data of G-FET biosensors. SSMs have been widely used in time-series analysis, for example gravimetric chemical sensors [4], to understand the systems that can generate the time-series data. Our proposed SSMs demonstrated that the time-series data of G-FET biosensors was separated into the sensor response to target molecules and the drifted baseline.

2. Results and Discussions

CVD graphene films were used for making G-FETs. The G-FETs were functionalized with sialoglycans as described elsewhere [2]. The sialoglycans can specifically bind influenza virus, and then transconductance of G-FET will change due to the surface charge of the virus (Fig.1).

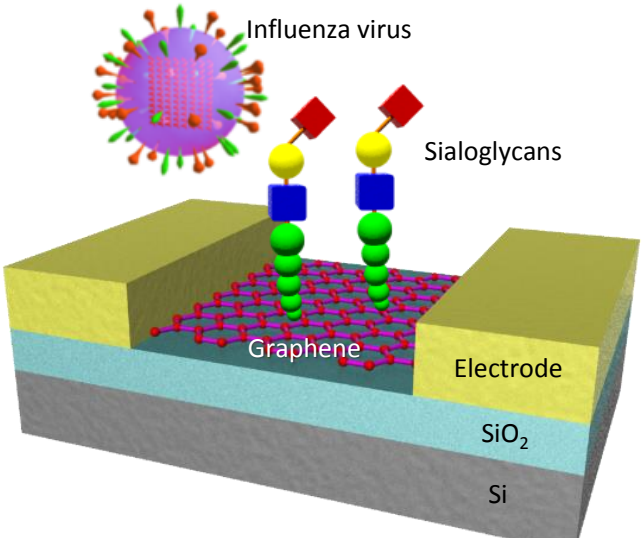

Fig. 1 Schematic of sialoglycan-functionalized G-FET.

A fixed top-gate voltage (V_{GS} = - 0.35 V) was applied in Dulbecco's phosphate-buffered saline (D-PBS) solution (150 mM, pH 7.4) via a Ag/AgCl reference electrode, and the drain current (I_{DS}) was measured with the bias voltage (V_{DS}) of 0.1 V. Influenza virus (H1N1) was intermittently piped onto the sensor, with changing the virus concentration ranging from 0 to 256 HAU in D-PBS solution. In the dynamic response of the sensor, I_{DS} changed correspondingly when the virus concentration changed (Fig. 2(a) (b)). In addition, the dynamic response also showed apparent baseline drift as I_{DS} sequentially changed even without virus.

The obtained time-series data was modeled as follows (eqs. (1) - (5)).

$$I_{DS,t} = x_t + q_t + \varepsilon_t \quad (1)$$

$$q_t = \sum_{i=1}^{11} \Delta q_i \quad (2)$$

$$\Delta q_i = \begin{cases} 0 & (t < t_i) \\ (Q_i - Q_{i-1})\left\{1 - exp\left(-{t - t_i}/{\tau_i}\right)\right\} & (t \geq t_i) \end{cases} \quad (3)$$

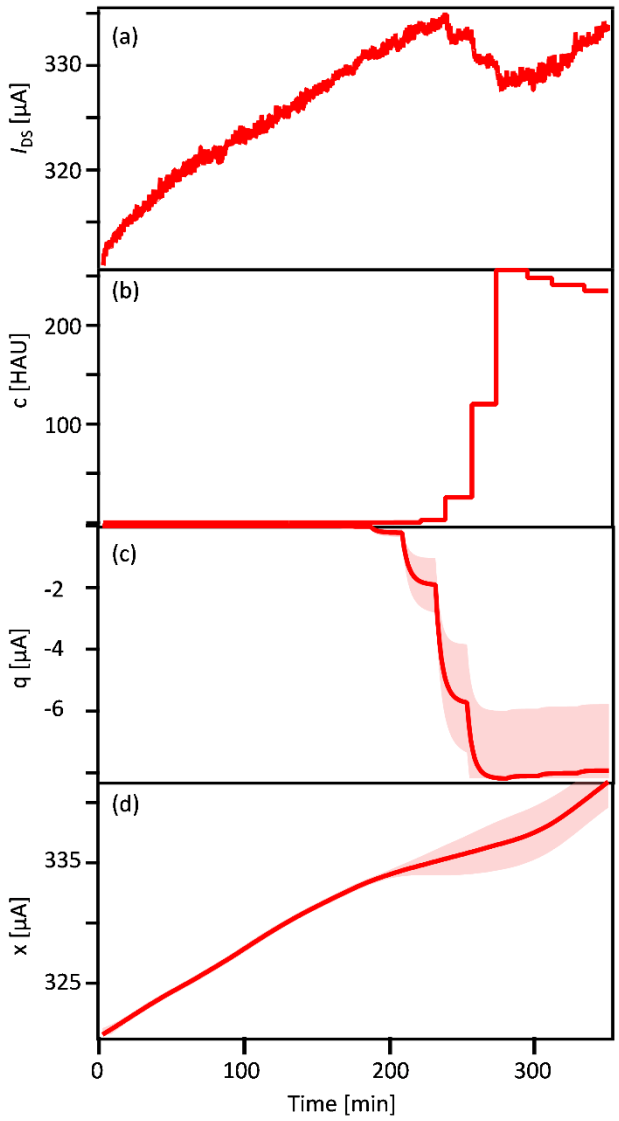

Fig. 2 (a) Dynamic response of G-FET biosensors. (b) The corresponding concentration of influenza virus on the G-FET. (c)(d) The sensor response regarding the virus (c) and the baseline (d) extracted from (a) by using the SSM. The shades in (c) (d) indicate 95% Bayesian credible interval.

$$Q_i = \frac{ac_i}{K_D + c_i} \quad (4)$$

$$x_t - x_{t-1} = x_{t-1} - x_{t-2} + \omega_t \quad (5)$$

Eq. (1), which is called the observation equation, denotes that I_{DS} is summation of the baseline (x_t), regression component regarding virus (q_t), and the observation noise ($\varepsilon_t \sim N(0, \sigma_\varepsilon)$). The regression component (q_t) is described according to two ideas: (i) q_t is cumulative sum of signal changes at each virus piped point (Δq_i), where i indicates virus piped indices (eq. (2)), and (ii) each Δq_i follows exponential decay after the virus piped, where t_i corresponds to the time of virus piped (eq. (3)), and finally Δq_i reaches to plateau following Langmuir adsorption model as a function of the concentration (c_i) with coefficients of dissociation constant (K_D) and a (eq. (4)). Eq. (5), which is called the state equation, assumes that the baseline (x_t) follows a quadratic trend with the system noise ($\omega_t \sim N(0, \sigma_\omega)$). The parameters were estimated using Markov chain Monte Carlo (MCMC) methods implemented in Python and Stan's probabilistic programming languages. After the estimation, R_{hat}, which is an indicator of MCMC convergence [5], was smaller than 1.1 for all parameters, indicating that the parameters were properly estimated in the model. According to the model and the estimated parameters, the time-series data in Fig. 2(a) was clearly separated into the signal related to the virus (q_t, Fig. 2(c)) and the baseline (Fig. 2(d)). The parameters of K_D in eq. (4), and τ_i in eq. (3) were estimated to be 155 [HAU] (95% Bayesian credible interval: 68 - 501) and 3.1 [min] (95% Bayesian credible interval: 1.81 - 4.6) in this experiment, respectively.

Finally, we compared the developed model through eqs. (1)-(5) (Langmuir model with exponential decay and a quadratic trend; *model 1*) with two simplified models: Langmuir model with a linear baseline (*model 2*), and Langmuir model with a quadratic trend (*model 3*). Widely applicable Bayesian information criterion (WBIC), which is an information criteria [6], was calculated for three models (Table I). The list shows that WBIC for *model 1*, is the lowest value among the candidates, indicating that *model 1* is the best one to describe the obtained G-FET dynamic response.

Table I Comparison of WBIC for three models

	model 1	*model 2*	*model 3*
WBIC	-860	-819	-846

3. Conclusions

We developed the SSM to describe the dynamic response of G-FET biosensors against influenza virus. The parameter estimation was conducted by using MCMC methods. The dynamic response fitted well to the model, and was separated into the virus response and the baseline drift. The model proposed here enables one to accurately analyze the sensor response.

Acknowledgements

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