Gaussian process based online dynamic modeling of neuromuscular blockade

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Abstract: A non-parameter modeling methodology for the online dynamically modeling of nonlinear neuromuscular blockade (NMB) is presented in this paper. A big challenge of modeling NMB is the responses from muscular are quite different from people to people and the individual dynamic may change during the procedure of operation. Gaussian process (GP) is a kind of probabilistic and non-parametric modeling method in on need of any information about the plant structure. It just builds the data relationship between the input and output by statistical approaches. In order to tackle the difference in patients, an online dynamic GP modeling technique is used which can avoid the traditional static models' defects, i.e., it is only suitable for an individual patient and the controller designed based on the traditional model is not robust. Furthermore, a moving window technique is adopted in order to improve the local accuracy of Gaussian process model and reduce the calculation burden. The training data set size is fixed and the old ones are dropped as soon as the new data are available.

Key Words: Dynamic model, Gaussian process, Nonlinear system, Neuromuscular blockade

1 INTRODUCTION

Biological systems are non-stationary and nonlinear, besides they present a high degree of marked individual difference [1]. Anesthesia is a typical biological system, which is common occurred phenomenon in intensive care unit (ICU). A general requirement in anesthesia is to ensure a suitable level of muscle relaxation in the patient with minimal drug quantities and side effect [2]. The control of injected drug dosages is characterized by a very high degree of uncertainty due to the systems' dynamics [3], while the nature of the application involved requires a very reliable model for the controller design.

Anesthesia is composed of hypnosis, analgesia and NMB, hypnosis is considered as the loss of consciousness and the incapability of recalling the memories during surgical procedure, analgesia is defined as the loss of the pain, NMB means the incapability of movement. The purpose of anesthesia is to keep the patient in a state that is reversible of hypnosis, analgesia and muscle relaxation [4]. In this paper, we are focusing on the process of muscle relaxation, i.e., NMB, while muscle relaxation is caused by the blockade of neuromuscular, then the loss of moving ability is realized. Thus, from a control engineering viewpoint, such a requirement can be considered as a regulation problem where the plant to be regulated is the patient, the output is the patient's NMB level (%), which can be obtained from the response of a muscle, and the input is the drug (Atracurium) infusion rate [1]. In practice, the problem is complicated mainly due to the undesirable transients caused by the initial ignorance of the relevant patient dynamics. The key issue is the capacity of the modeling method to catch the large level of uncertainty associated with patient dynamics.

The paper is organized as follows. The previous works on the mechanism model of NMB is described in section 2. An online dynamic Gaussian process modeling method with fixed training data set size based on the moving window technique is presented in section 3. In section 4, GP dynamic models of NMB for one hundred patients are established and the model precision is analyzed. Conclusions are drawn in section 5.

2 MECHANISM MODEL OF THE NEUROMUSCULAR BLOCKADE

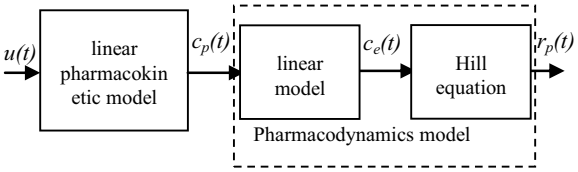

Fig.1 Mechanical structure of the neuromuscular blockade system

As shown in Fig.1, dynamic responses of the neuromuscular to the blockade drugs infusion rate $u(t)$ can be modeled by two parts in series. The linear pharmacokinetic model builds the relationship between $u(t)$ and plasma concentration $c_p(t)$ [5], and the nonlinear pharmacodynamics model reflects $c_p(t)$ to the final NMB level $r(t)$ [6]. Compartment model is a widely used mathematical model to analysis drug dynamic distribution regulations in vivo. A system can be divided into several compartments according to the internal drug distribution dynamics of the system. Here the patient dynamics have been divided into three comportments, a rich blood supplied tissue compartment, a relatively poor blood

This work is supported by the National Natural Science Foundation of China (61174128, 61473025, 61403017 and 61573050), the Beijing Natural Science Foundation (4132044) and the Fundamental Research Funds for the Central Universities of China (YS1404)

supplied tissue compartment and the effect site compartment in NMB system [7]. The description of linear pharmacokinetic model is made by the state space equation,

$$\dot{x}_1 = -\lambda_1 x_1(t) + a_1 u(t) \quad (1)$$

$$\dot{x}_2 = -\lambda_2 x_2(t) + a_2 u(t) \quad (2)$$

$$c_p(t) = \sum_{i=1}^{2} x_i(t) \quad (3)$$

where x_1, x_2 represent the drug concentration in the compartment of the rich blood supplied tissue and the poor part respectively, and λ_i, $a_i(i=1,2)$ are patient-dependent parameters. The nonlinear part pharmacodynamics response to the drug atracurium can be model by the Hill equation,

$$r(t) = \frac{100C_{50}^{\beta}}{C_{50}^{\beta} + c_e^{\beta}(t)} \quad (4)$$

where C_{50}, β are patient related parameters.

The measurable output $r(t)$ is normalized between 0 and 100 in percent, where 0 means full paralysis and 100 indicates normal muscular activity [8]. The relationship of plasma drug concentration $c_p(t)$ and the effect compartment drug concentration $c_e(t)$ is associated by an auxiliary signal c.

$$\dot{c}(t) = -\lambda c(t) + \lambda c_p(t) \quad (5)$$

$$\dot{c}_e(t) = -\frac{1}{t} c_e(t) + \frac{1}{t} c(t) \quad (6)$$

where λ and τ are also patient related parameters.

In the system of NMB, all the parameters are associated with individual physical conditions. The individual related parameters are within the ranges shown in Table 1[9].

Table.1 patient related parameters variation range

Parameter	Min	Max	Units
a_1	0.0029	0.0581	kg·mL^{-1}
a_2	0.0031	0.0083	kg·mL^{-1}
λ_1	0.14	0.65	min^{-1}
λ_2	0.026	0.049	min^{-1}
λ	0.081	0.13	min^{-1}
C_{50}	0.59	0.72	μg·mL^{-1}
β	2.8	6.2	dimensionless
τ	0.42	14	min

As already mentioned that a major challenge of modeling NMB process is the patients' variability, then a hundred models were randomly chosen and induced by a bolus of 500$\mu g \cdot kg^{-1}$ of atracurium at t =0 min [10].

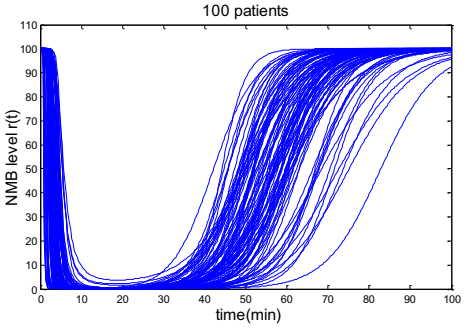

Fig.2 Responses (noise free) of a hundred models that represent 100 actual patients induced by a bolus of 500 μg·kg^{-1} atracurium at t = 0min.

It is shown in Fig. 2 that different people present a big difference in response to the same drug dosage. In traditional offline parameter modeling methods, lots of experiments need to be made to collect training data firstly. Then the structure of the model selected by experience or experiments, and the model parameters are estimated subsequently. Similar experiments have to be carried out in order to get another patient's NMB model, since different people show different responses to the same drug dosage. In addition, patient dynamics may change during the procedure caused by surgery scratch which might give rise to the controller's inaccuracy. In order to avoid the problems presented above, a probabilistic and nonparametric Gaussian Process (GP) online dynamic modeling method is presented here.

3 GAUSSIAN PROCESS BASED DYNAMIC MODELING OF NEUROMUSCULAR BLOCKADE

Gaussian process is a novel method in machine learning. It can be called either regression or classification based on the characteristics of the outputs. The problem of learning input-output mappings from empirical data is called regression if the outputs are continuous signals, otherwise it is called classification if the outputs are discrete [10]. The GP modeling method has been used in nonlinear system identification in many fields [11-15]. There are two ways to explain the theory of Gaussian process modeling: 1). function space, assuming that the target function's prior distribution is Gaussian process, then proceeding Bayesian inference about the Gaussian processes in function space; 2). weight space, assuming that the function can be represented by linear models and its input covariance function weight vector's prior distribution is Gaussian process, then proceeding Bayesian inference about the Gaussian processes in weight space.

3.1 What is Gaussian Process model?

Assuming a training data set $D=\{(\boldsymbol{x}_i, y_i)|i=1,\ldots,N\}$ where $\boldsymbol{x}_i$ is the input vector and y_i is the output or goal value, N is the training data set size, $\boldsymbol{X}=(\boldsymbol{x}_1, \boldsymbol{x}_2,\ldots, \boldsymbol{x}_N)^{\mathrm{T}}$, $\boldsymbol{y}=(y_1, y_2,\ldots, y_N)^{T}$. The standard linear regression model with Gaussian noise is described as $f(x)=\boldsymbol{x}^{\mathrm{T}}\boldsymbol{w}+\varepsilon$. Assuming that the additive noise is Gaussian distribution of zero mean and variance σ_n^2, i.e., $\varepsilon \sim N(0,\sigma_n^2)$. From the noise assumption and the standard linear regression models, likelihood of the observed objective values can be achieved. When the training data set and prior distribution of parameters based on training set are given, the probability density of the observations, i.e., objective values y, can be got,

$$\begin{aligned} p(\boldsymbol{y}\,|\,\boldsymbol{X},\boldsymbol{w}) &= \prod_{i=1}^{N} p(y_i\,|\,\boldsymbol{x}_i,\boldsymbol{w}) \\ &= \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi}\sigma_n} \exp\left(-\frac{(y_i - \boldsymbol{x}_i^T\boldsymbol{w})^2}{2\sigma_n^2}\right) \\ &= \frac{1}{(2\pi\sigma_n^2)^{\frac{N}{2}}} \exp\left(-\frac{1}{2\sigma_n^2}\left\|\boldsymbol{y} - \boldsymbol{X}^T\boldsymbol{w}\right\|_2^2\right) \\ &\sim N(\boldsymbol{X}^T\boldsymbol{w}, \sigma_n^2\boldsymbol{I}) \end{aligned} \quad (7)$$

where $\|\cdot\|$ denotes the Euclidean length of a vector or matrix, I denotes the identity matrix.

The prior probability distribution over weights should be defined in order to infer a bayesian linear model. Generally, the weight is a zero mean Gaussian prior with covariance matrix Σ_P , i.e., $\boldsymbol{w}\sim N(0, \Sigma_P)$.

Given the input and output data, posterior distribution over the weights can be computed by,

$$p(\boldsymbol{w}\mid \boldsymbol{y},\boldsymbol{X}) = \frac{p(\boldsymbol{y}\mid \boldsymbol{X},\boldsymbol{w})p(\boldsymbol{w})}{p(\boldsymbol{y}\mid \boldsymbol{X})} \tag{8}$$

and the marginal likelihood is obtained

$$p(\boldsymbol{y}\mid \boldsymbol{X}) = \int p(\boldsymbol{y}\mid \boldsymbol{X},\boldsymbol{w})p(\boldsymbol{w})d\boldsymbol{w} \tag{9}$$

The posterior in eq. (8) united the prior and the likelihood, and acquired everything we know about the parameters. The relationship that the posterior distribution is in proportion to the product of likelihood and prior can be obtained from eq. (7) and (8),

$$\begin{aligned} &p(\boldsymbol{w}\mid \boldsymbol{X},\boldsymbol{y}) \\ &\propto \exp\left(-\frac{(\boldsymbol{w}-\bar{\boldsymbol{w}})^T}{2}(\frac{\boldsymbol{X}\boldsymbol{X}^T}{\sigma_n^2}+\Sigma_p^{-1})(\boldsymbol{w}-\bar{\boldsymbol{w}})\right) \end{aligned} \tag{10}$$

where $\bar{\boldsymbol{w}} = \sigma_n^{-2}(\sigma_n^{-2}\boldsymbol{X}\boldsymbol{X}^T+\Sigma_p^{-1})^{-1}\boldsymbol{X}\boldsymbol{y}$. It can be known from eq. (10) that the form of the posterior distribution is Gaussian with mean $\bar{\boldsymbol{w}}$ and covariance matrix A^{-1}.

$$p(\boldsymbol{w}\mid \boldsymbol{X},\boldsymbol{y}) \sim N\left(\bar{\boldsymbol{w}} = \frac{1}{\sigma_n^2}\boldsymbol{A}^{-1}\boldsymbol{X}\boldsymbol{y}, \boldsymbol{A}^{-1}\right) \tag{11}$$

where $\boldsymbol{A} = \sigma_n^{-2}\boldsymbol{X}\boldsymbol{X}^T+\Sigma_p^{-1}$.

For a new test input data, the GP model is used to predict its corresponding output. Suppose the test data is $\boldsymbol{x}^*$, the predictive output $f(\boldsymbol{x}^*)$ can be calculated eq.(12)

$$\begin{aligned} &p(f(\boldsymbol{x}^*)\mid \boldsymbol{x}^*,\boldsymbol{X},\boldsymbol{y}) \\ &= \int p(f(\boldsymbol{x}^*)\mid \boldsymbol{x}^*,\boldsymbol{w})p(\boldsymbol{w}\mid \boldsymbol{X},\boldsymbol{y})d\boldsymbol{w} \\ &\sim N(\sigma_n^{-2}\boldsymbol{x}^{*T}\boldsymbol{A}^{-1}\boldsymbol{X}\boldsymbol{y}, \boldsymbol{x}^{*T}\boldsymbol{A}^{-1}\boldsymbol{x}^*) \end{aligned} \tag{12}$$

The posterior distribution is based on the assumption of the Bayesian linear model, which is limited in expressiveness. A common way to tackle this problem is to map the inputs into some high dimensional space and then implement the linear model in this space instead of the original inputs themselves. Specifically, $\boldsymbol{\phi}(\boldsymbol{x})$ is defined as a function of $\boldsymbol{x}\epsilon R^L$, which maps a L-dimensional input vector x into an D dimensional feature space. Furthermore a matrix $\Phi(x)$ is introduced as the aggregation of columns $\boldsymbol{\phi}(\boldsymbol{x})$. Now the model is $f(\boldsymbol{x})= \boldsymbol{\phi}(\boldsymbol{x})^T\boldsymbol{w}$, then the predictive distribution becomes

$$\begin{aligned} &p(f(\boldsymbol{x}^*)\mid \boldsymbol{x}^*,\boldsymbol{X},\boldsymbol{y}) \\ &= \int p(f(\boldsymbol{x}^*)\mid \boldsymbol{x}^*,\boldsymbol{w})p(\boldsymbol{w}\mid \boldsymbol{X},\boldsymbol{y})d\boldsymbol{w} \\ &\sim N(\boldsymbol{\phi}(\boldsymbol{x}^*)^T(\Phi(\boldsymbol{X})\Phi(\boldsymbol{X})^T+\sigma_n^2\Sigma_p^{-1})^{-1}\Phi(\boldsymbol{X})\boldsymbol{y}, \\ &\quad \boldsymbol{\phi}(\boldsymbol{x}^*)^T\sigma_n^2\left(\Phi(\boldsymbol{X})\Phi(\boldsymbol{X})^T+\sigma_n^2\Sigma_p^{-1}\right)^{-1}\boldsymbol{\phi}(\boldsymbol{x}^*)) \end{aligned} \tag{13}$$

Generally, the matrix inverse formulation is,

$$(M+NL)^{-1} = M^{-1}-M^{-1}N(I+LM^{-1}N)^{-1}LM^{-1} \tag{14}$$

So the reversal term in eq. (13) can be calculated as,

$$\begin{aligned} &(\Phi(X)\Phi(X)^T+\sigma_n^2\Sigma_p^{-1})^{-1} \\ &= \sigma_n^{-2}\Sigma_p-\sigma_n^{-2}\Sigma_p\Phi(X)(\sigma_n^2I+K)^{-1}\Phi(X)^T\Sigma_p \end{aligned} \tag{15}$$

where $K = \Phi(X)^T\Sigma_p\Phi(X)$. Thus

$$\begin{aligned} &\boldsymbol{\phi}(\boldsymbol{x}^*)^T(\Phi(X)\Phi(X)^T+\sigma_n^2\Sigma_p^{-1})^{-1}\Phi(X)\boldsymbol{y} \\ &= \boldsymbol{\phi}(\boldsymbol{x}^*)^T\Sigma_p\Phi(X)(\sigma_n^2I+K)^{-1}\boldsymbol{y} \end{aligned} \tag{16}$$

$$\begin{aligned} &\boldsymbol{\phi}(\boldsymbol{x}^*)^T\sigma_n^2(\Phi(X)\Phi(X)^T+\sigma_n^2\Sigma_p^{-1})^{-1}\boldsymbol{\phi}(\boldsymbol{x}^*) \\ &= \boldsymbol{\phi}(\boldsymbol{x}^*)^T\Sigma_p\boldsymbol{\phi}(\boldsymbol{x}^*) \\ &-\boldsymbol{\phi}(\boldsymbol{x}^*)^T\Sigma_p\Phi(X)(\sigma_n^2I+K)^{-1}\Phi(X)^T\Sigma_p\boldsymbol{\phi}(\boldsymbol{x}^*) \end{aligned} \tag{17}$$

let $k(\boldsymbol{x},\boldsymbol{x}') = \boldsymbol{\phi}(\boldsymbol{x})^T\Sigma_p\boldsymbol{\phi}(\boldsymbol{x}')$, where $\boldsymbol{x}$ and $\boldsymbol{x}'$ are in either the training or the test sets , then

$$k(\boldsymbol{x},X) = \boldsymbol{\phi}(\boldsymbol{x}^*)^T\Sigma_p\Phi(X) = \boldsymbol{k}^* \tag{18}$$

$$k(\boldsymbol{x}^*,\boldsymbol{x}^*) = \boldsymbol{\phi}(\boldsymbol{x}^*)^T\Sigma_p\boldsymbol{\phi}(\boldsymbol{x}^*) = k \tag{19}$$

The predictive distribution can be written as

$$\begin{aligned} &p(f(\boldsymbol{x}^*)\mid \boldsymbol{x}^*,X,\boldsymbol{y}) \\ &\sim N\left(\boldsymbol{k}^*(\sigma_n^2I+K)^{-1}\boldsymbol{y}, k-\boldsymbol{k}^*(\sigma_n^2I+K)^{-1}\boldsymbol{k}^{*T}\right) \end{aligned} \tag{20}$$

Inference could be made if a new input data is given. Its corresponding predictive output is $\boldsymbol{k}^*(\sigma_n{}^2I+K)^{-1}\boldsymbol{y}$, and the uncertainty of the prediction given by variance of the Gaussian distribution k-$\boldsymbol{k}^*(\sigma_n{}^2I+K)^{-1}\boldsymbol{k}^{*T}$.

Considering making inference directly in function space, we can get the same results as weight space. Before using Gaussian processes to describe functions' distribution, assumptions should be made that the real process $f(\boldsymbol{x})$ is defined by mean function $m(\boldsymbol{x})$ and covariance function $k(\boldsymbol{x}, \boldsymbol{x}')$,where $\boldsymbol{x}$ and $\boldsymbol{x}'$ are in either the training or the test sets

$$\begin{aligned} &m(\boldsymbol{x}) = E\left(f(\boldsymbol{x})\right) \\ &k(\boldsymbol{x},\boldsymbol{x}') = E\left((f(\boldsymbol{x})-m(\boldsymbol{x}))(f(\boldsymbol{x}')-m(\boldsymbol{x}'))\right) \end{aligned} \tag{21}$$

Then we can write the Gaussian process as

$$f(\boldsymbol{x}) \sim GP(m(\boldsymbol{x}),k(\boldsymbol{x},\boldsymbol{x}')) \tag{22}$$

Assume a Bayesian regression model as $f(\boldsymbol{x})=\boldsymbol{\phi}(\boldsymbol{x})^T\boldsymbol{w}$, and $\boldsymbol{w}\sim N(0,\Sigma_p)$, we can get the mean and covariance,

$$\begin{aligned} &E\left(f(\boldsymbol{x})\right) = \boldsymbol{\phi}(\boldsymbol{x})^T E(\boldsymbol{w}) = 0 \\ &E\left(f(\boldsymbol{x})f(\boldsymbol{x}')\right) = \boldsymbol{\phi}(\boldsymbol{x})^T E(\boldsymbol{w}\boldsymbol{w}^T)\boldsymbol{\phi}(\boldsymbol{x}') \\ &= \boldsymbol{\phi}(\boldsymbol{x})^T\Sigma_p\boldsymbol{\phi}(\boldsymbol{x}') \end{aligned} \tag{23}$$

Here $f(\boldsymbol{x})$ and $f(\boldsymbol{x}')$ are submit to the jointly Gaussian distribution with mean 0 and covariance $\boldsymbol{\phi}(\boldsymbol{x})^T\Sigma_p\boldsymbol{\phi}(\boldsymbol{x}')$. For any pairs of random variables, the covariance is specified by the following covariance function

$$\begin{aligned} &\mathrm{cov}\left(f(\boldsymbol{x}_p), f(\boldsymbol{x}_q)\right) = k(\boldsymbol{x}_p,\boldsymbol{x}_q) \\ &= v_1\exp\left(-\frac{1}{2}\sum_{d=1}^{D}w_d(\boldsymbol{x}_p(d)-\boldsymbol{x}_q(d))^2\right)+v_0\delta(p,q) \end{aligned} \tag{24}$$

where $x_p(d)$ is the dth element of D-dimensional input vector x_p, the vector of hyperparameters is $\boldsymbol{w}=[v_1,w_1,\ldots,w_D,v_0]^T$ and $\delta(p,q)$ is the Kronecker operator which is defined by,

$$\delta(p,q) = \begin{cases} 1 & p=q \\ 0 & p\neq q \end{cases} \tag{25}$$

To establish a Gaussian process model, the model structure, i.e., the covariance function, needs to be selected first. The condition in the covariance function selection is to make sure that all covariance matrix are nonnegative definite for all the data in the training set [11].

3.2 GP dynamic model of neuromuscular blockade

Assume NMB process is defined as

$$y(k) = f(u(k)) + \varepsilon(k) \tag{26}$$

where k is an integer index, f is a function depend on u, y is the single output polluted by an uncorrelated Gaussian white noise with variance v_0 and u is the single input. The training data were collected from (25) and in the form of GP as

$$\boldsymbol{x}(k) = \left[y(k-1)...y(k-l)\,u(k-d)...u(k-d-h)\right] \tag{27}$$

$$y_m(k) = \mathrm{gp}(\boldsymbol{x}(k)) \tag{28}$$

where l and h are the relative output and input orders, respectively. d is delay steps, x(k) is current GP model input and y_m(k) is the corresponding output, gp represents the map function of GP model [12].

The training data set can be written as

$$\boldsymbol{X} = \left[\boldsymbol{x}(k)\quad \boldsymbol{x}(k+1)\ldots\boldsymbol{x}(k+N-1)\right]^T \tag{29}$$

$$\boldsymbol{y} = \left[y(k)\,y(k+1)\ldots y(k+N)\right]^T \tag{30}$$

Then we can get the output joint Gaussian distribution from eq.(7), as the output and input data are known, posterior distribution over the weights is get from eq.(8). The likelihood function is [13]

$$L(\boldsymbol{w}) = -\frac{1}{2}\boldsymbol{y}^T K^{-1}\boldsymbol{y} - \frac{1}{2}\log|K| - \frac{N}{2}\log(2\pi) \tag{31}$$

where K is the covariance function calculated by function (23), then we can get the hyperparameters w through maximum likelihood estimation.

$$\boldsymbol{w} = [v_1, w_1, ..., w_D, v_0]^T \tag{32}$$

Now the whole GP modeling steps were accomplished, then we can use it to predict the future output. The GP model gives not only the predict output y_m^* for a new input x^*but also the uncertainty σ_m^{2*} of this prediction [14]

$$y_m^* = \boldsymbol{k}^{*T} K^{-1}\boldsymbol{y} \tag{33}$$

$$\sigma_m^{2*} = k' - \boldsymbol{k}^{*T} K^{-1}\boldsymbol{k}^* \tag{34}$$

where $k' = k(\boldsymbol{x}^*, \boldsymbol{x}^*)$ and $\boldsymbol{k}^* = k(\boldsymbol{x}^*, X)$ are calculated from eq.(24).

Moving window is a technique that the training set is updated when a new data is obtained and delete the oldest one simultaneously, i.e., the size of the moving window is fixed. Suppose the training set window size is N and the hyperparameters are identified with related to the training window. Once the training set is updated, a set of new hyperparameters are calculated by the time. Specifically, the hyperparameters are calculated according to the training set window eq. (28) and (29) at sample time k. Then in the next sample time k+1, a new data is available and the training set window eq. (28) and (29) are updated, the hyperparameters will be recalculated simultaneously.

4 RESULTS

In the process of NMB controller design, a model aimed at each individual should be established before controllers design in traditional offline methods [9, 10]. Though the offline model is formed, the patient dynamics may be changed during the procedure of operation, which may cause side effects on patient's recovery or operation. Due to the inter- and intra-individual variability of biomedical systems, traditional offline modeling methods is no longer satisfactory for high precision controllers design. So a dynamic nonparametric GP model is used to solve the robust modeling problem.

As mentioned in section 3, the selection of the regression structure along with the covariance function is the key to GP model. During the modeling of NMB process, hyperpameters of the covariance function were chosen by maximizing the likelihood function over the training data [1]. The input structure is selected as

$$\boldsymbol{x}(k) = \left[r(k-1)\,r(k-2)\,r(k-3)\,u(k-1)\,u(k-2)\right] \tag{35}$$

In order to determine the moving window training data size N, a hundred patients were initially excited by the same bolus of atracurium 500μg/kg at t=0min. Then a small pseudorandom scalar drawn from the standard uniform distribution on the open interval (0, 3) was used to excite the patients at t= 30min. The corresponding responses from one hundred patients are shown in Fig.3.

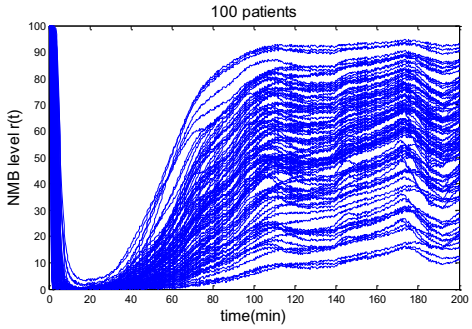

Fig.3 Corresponding responses of NMB levels r(t) for 100 patients

The input and output data of one hundred patients are collected and used to establish 100 patients' GP models with moving window technique. Here the window size are selected as N=10, 20, 30, 40, 50, 60, 70, 80, 90, 100, respectively. The mean square errors for 100 patients' model for different window size N are shown in Table.2.

Table.2 the mean square errors（MSE） corresponding to training data size, 100 patients.

N	MSE	N	MSE
10	0.0392	60	0.0166
20	0.0502	70	0.0167
30	0.0993	80	0.0167
40	0.0194	90	0.0168
50	0.0172	100	0.0168

In consideration of MSE and the burden of calculation, window size N=60 is chosen as the size of modeling data capacity.

For further verification, four typical patients were selected to test the result we get. A sinusoidal input signal is used to induce the patients and using the same way to establish their corresponding dynamic GP models. The selected patients are representing the extremes (corresponding to M3 and M4) and average (corresponding to M1 and M2) NMB dynamics

induced by a bolus of atracurium shown in Fig5. The four patients' parameters are shown in the following Table.3.

Table.3 four selected patients parameter values

Parameters	M1	M2	M3	M4
a_1	0.0529	0.0488	0.0463	0.0389
a_2	0.0061	0.0073	0.0081	0.0079
λ_1	0.3227	0.1664	0.3086	0.1758
λ_2	0.0270	0.0450	0.0471	0.0262
λ	0.1046	0.1062	0.1143	0.0898
C_{50}	0.6459	0.6403	0.6409	0.6039
β	4.1241	5.0827	3.8703	5.2487
τ	6.8852	10.4335	1.1499	12.4469

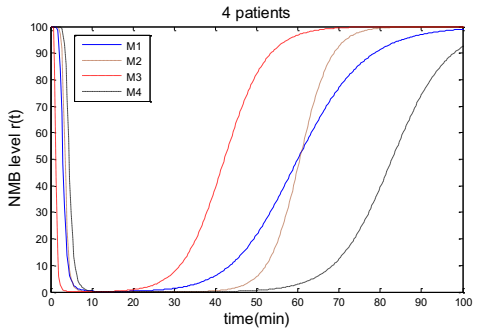

Fig.4 Four selected patients responses induced by a bolus of 500 $\mu g \cdot kg^{-1}$ atracurium at t = 0min

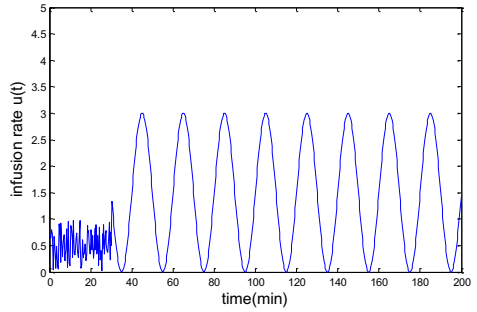

Fig.5 Test sinusoidal input signal for N=60's modeling verification.

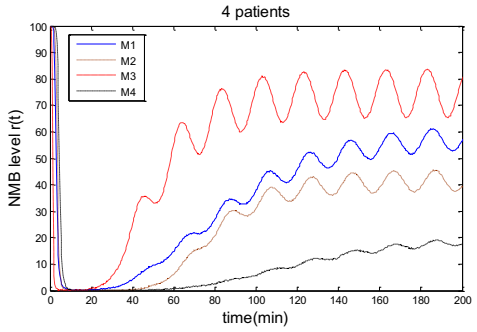

Fig.6 Corresponding response NMB level $r(t)$ induced by the test sinusoidal signal $u(t)$

Sinusoidal input signals, shown in Fig.6 were used to induce the four typical patients and their corresponding responses are shown in Fig.6. Using the same way to establish models of the four typical patients, the modeling performances are shown in Fig.7 and the modeling mean square errors are shown in Table.4. In terms of the table same conclusion could be drawn that N=60 is the best moving window size.

Table.4 Mean square errors（MSE）corresponding to the window size N with related to M1~M4.

N	MSE	N	MSE
10	0.1638	60	0.0472
20	0.1248	70	0.0490
30	0.1709	80	0.0512
40	0.0785	90	0.0508
50	0.0761	100	0.0545

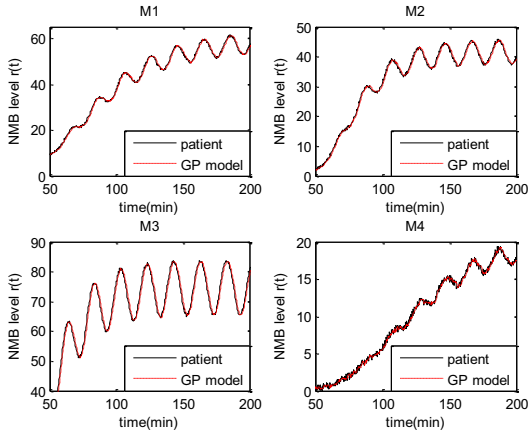

Fig.7 GP models of the four selected patients induced by sinusoidal input signal, N=60.

Furthermore, a 10-step-ahead prediction is implemented to illustrate the predictive ability of GP models. The prediction inputs can be obtained by the following types at time step k,

$$\begin{aligned}
\boldsymbol{x}(k) &= [r(k-1)\ r(k-2)\ r(k-3)\ u(k-1)\ u(k-2)] \\
\boldsymbol{x}(k+1) &= [\hat{r}(k)\ r(k-1)\ r(k-2)\ u(k)\ u(k-1)] \\
&\vdots \qquad\qquad \vdots \\
\boldsymbol{x}(k+9) &= [\hat{r}(k+8)\ \hat{r}(k+7)\ \hat{r}(k+6)\ u(k+8)\ u(k+7)]
\end{aligned}$$

where $\hat{r}$ is the predicted output that is calculated by (32).

The test input u is shown in Fig.8 and the corresponding outputs $r(t)$ are shown in Fig.9. 10-step-ahead prediction variance σ^2 are shown in Fig.10. The results show a good degree of accuracy between the prediction and the actual values for all the simulations. In addition in these simulations most of the actual values lie within the prediction confidence region.

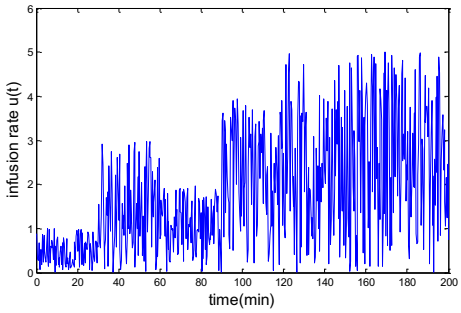

Fig.8 Input for 10-step ahead prediction simulation test

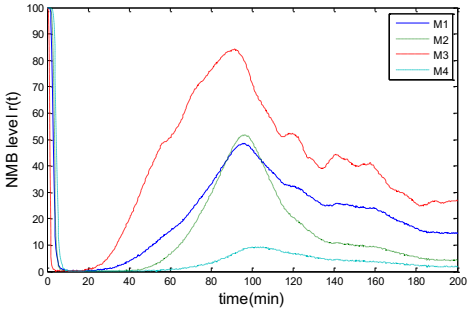

Fig.9 Response of the patients for 10-step ahead prediction

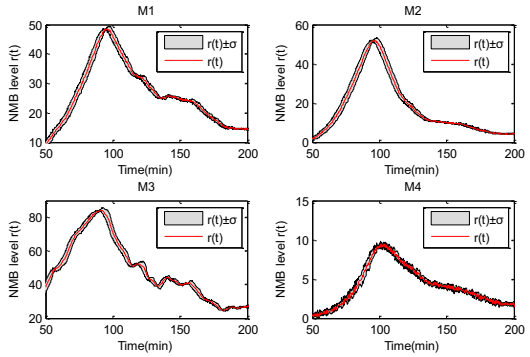

Fig11. GP model with 10-step-ahead prediction and its variance

Fig.10 shows the results of the proposed modeling method, where the grey area boundary means the predictive output plus and minus predictive variance σ and the middle region means the confidence interval. From the figure, conclusions can be made that most of the actual values lie in the area of confidence, which suggest that the referred modeling way perform a good performance of simulation results.

5 CONCLUSIONS

This paper is focusing on the study of GP modeling framework based on the Bayesian theory. An online dynamic GP modeling method is presented to simulate the NMB process. First, one hundred patients' data were collected to acquire the best dynamic modeling moving window size N. Then further efforts were made to confirm that the selected N is the best size for online dynamic modeling. As the purpose of modeling is to predict future output, a ten-step-ahead prediction test was taken to validate the established models' ability. It turns out that the established models perform a good predictive performance.

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