Probabilistic Description of Model Set Response in Neuromuscular Blockade

Conceição Rocha[1], João M. Lemos[2], Teresa F. Mendonça[1], and Maria E. Silva[3]

[1] Departamento de Matemática, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 4169-007 Porto, Portugal and Center for Research & Development in Mathematics and Applications (CIDMA), Universidade de Aveiro, Portugal
{mnrocha,tmendo}@fc.up.pt

[2] INESC-ID/IST, Technical University of Lisbon, Lisboa, Portugal
jlml@inesc-id.pt

[3] Faculdade de Economia da Universidade do Porto, Porto, Portugal, and Center for Research & Development in Mathematics and Applications (CIDMA), Universidade de Aveiro, Portugal
mesilva@fe.up.pt

Abstract. This work addresses the problem of computing the time evolution of the probability density function (pdf) of the state in a nonlinear neuromuscular blockade (NMB) model, assuming that the source of uncertainty is the knowledge about one parameter. The NMB state is enlarged with the parameter, that verifies an equation given by its derivative being zero and has an initial condition described by a known pdf. By treating the resulting enlarged state-space model as a stochastic differential equation, the pdf of the state verifies a special case of the Fokker-Planck equation in which the second derivative terms vanish. This partial differential equation is solved with a numerical method based on Trotter's formula for semigroup decomposition. The method is illustrated with results for a reduced complexity NMB model. A comparison of the predicted state pdf with clinical data for real patients is provided.

Keywords: Stochastic systems, state estimation, fokker-Planck equation.

1 Introduction

The physiologic effect induced by drug administration is described by deterministic pharmacokinetic and pharmacodynamic models that represent the interaction of the drug with the patient body. These models are of compartmental type [1] and describe, for a given drug dosage, the time evolution of the plasma concentration, C_p, and the effect concentration, C_e, of the drug. Their mathematical representation consists of a system of differential equations with several unknown parameters. These dynamic processes may also be represented by reduced complexity models that, although not being compartmental modes, have

J. Świątek et al. (eds.), *Advances in Systems Science*,
Advances in Intelligent Systems and Computing 240,
DOI: 10.1007/978-3-319-01857-7_39,

the advantage of leading to simpler controllers and to avoid identifiability problems because these last models have less unknown parameters [2].

Like in most practical dynamical systems, physiological effects induced by drug administration are subjects to stochastic disturbances, either internal or external. Furthermore, model parameters vary from patient to patient and, for both these reasons, anesthesia models are not deterministic. Thus, instead of computing the exact state of the system, a stochastic process that would vary from realization to realization, a probability density function (pdf) that reflects our knowledge that the state is contained in some region is to be computed. In this case, deterministic differential equations gives place to stochastic differential equations. In particular, we are interested in Markov diffusion processes modeled by stochastic differential equations and for which the pdf is a function of time that satisfies the Fokker-Planck equation (FPE) [3].

The Fokker-Planck equation is a partial differential equation (PDE) used in several fields of natural science and engineering [4–7]. In the context of Markov diffusion processes, the transition probability density of the process, *i.e.*, the time evolution of the probability density of finding the state at a given time, in a given point, is a fundamental solution of this equation.

The problem considered in this article consists of computing, as a function of time, the probability density function (pdf) of the state of a neuromuscular blockade (NMB) model given a pdf that encodes our knowledge about uncertain model parameters (that in this case depend on the patient population considered). This problem is addressed by enlarging the state with the uncertain parameter and solving a special case of the Fokker-Planck equation known as the Liouville equation [8] to propagate in time the state pdf. This PDF is solved numerically by using an algorithm that relies on Trotter's formula [9].

The contribution consists in the method to propagate the state pdf given the pdf of the uncertain parameters and its application to the NMB model. It is remarked that the method can be applied to other components of anesthesia and to other dynamic systems whose state equations depend on uncertain parameters.

The article is organized as follows. In section 2, and in order to make the text self-contained, basic notions about Markov diffucion processes, the Foker-Plank equation and Trotter's formula are reviewed. Section 3 describes the NMB model as a stochastic differential equation with uncertainty in the initial conditions corresponding to the parameter, writes the corresponding Fokker-Planck equation and presents its numeric solution. Finally, section 4 draws conclusions.

2 Diffusions and the Fokker-Planck Equation

In this section, and for the sake of clarity, the definitions as well as restrictions to the application of some of the models or equations used in the next section are presented.

2.1 Diffusion Processes

Let $\boldsymbol{X}(t)$ be a Markov process in n dimensions, described by the multi-dimensional stochastic differential equation (SDE) defined in the Itô sense

$$d\boldsymbol{X}(t) = \boldsymbol{f}(\boldsymbol{X}(t), t)dt + \boldsymbol{G}(\boldsymbol{X}(t), t)d\boldsymbol{W}(t), \tag{1}$$

with

$$\boldsymbol{X}(t_0) = \boldsymbol{c}, \;\; t_0 \leq t \leq T,$$

where $\boldsymbol{G}$ is $n \times d$ matrix valued function; $\boldsymbol{W}$ is an $\mathbb{R}^d$ -valued Wiener process, *i.e.*, all the coordinates $W_i(t)$ are independent one-dimensional Wiener processes; $\boldsymbol{X}$, $\boldsymbol{f}$ are n-dimensional vector valued functions and $\boldsymbol{c}$ is a random variable independent of $\boldsymbol{W}(t) - \boldsymbol{W}(t_0)$ for $t \geq 0$ [3].

Teorema 1 (Existence and Uniqueness[10]). *If the following conditions are satisfied*

1. *Coefficients are locally Lipschitz in* $\boldsymbol{x}$ *with a constant independent of* t*, that is, for every* T *and* N*, there is a constant* K *depending only on* T *and* N *such that for all* $|\boldsymbol{x}|$,$|\boldsymbol{y}| \leq N$ *and all* $0 \leq t \leq T$

$$|\boldsymbol{f}(\boldsymbol{x}, t) - \boldsymbol{f}(\boldsymbol{y}, t)| + |\boldsymbol{G}(\boldsymbol{x}, t) - \boldsymbol{G}(\boldsymbol{y}, t)| < K\,|\boldsymbol{x} - \boldsymbol{y}|\,,$$

   then for any given $\boldsymbol{X}(0)$ *the strong solution to SDE is unique.*
2. *The linear growth condition holds*

$$|\boldsymbol{f}(\boldsymbol{x}, t)| + |\boldsymbol{G}(\boldsymbol{x}, t)| \leq K_T(1 + |\boldsymbol{x}|),$$

   $\boldsymbol{X}(0)$ *is independent of* $\boldsymbol{W}$*, and* $E\,|\boldsymbol{X}(t_0)|^2 < \infty$,

then the strong solution exists and is unique on $[t_0, T]$.

If the conditions of the above existence and uniqueness theorem are satisfied for the SDE (1) and in addition the functions $\boldsymbol{f}$ and $\boldsymbol{G}$ are continuous with respect to t, the solution $\boldsymbol{X}(t)$ is a n-dimensional diffusion process on $[t_0, T]$ with drift vector $\boldsymbol{f}$ and diffusion matrix $\boldsymbol{b} = \boldsymbol{G}\boldsymbol{G}^T$, with $\boldsymbol{G}^T$ denoting the transposed of $\boldsymbol{G}$.

2.2 Fokker-Plank Equation

A property of diffusion processes is that their transition probability is, under certain regularity assumptions, uniquely determined merely by the drift vector and the diffusion matrix.

Teorema 2 ([3]). *Let $\boldsymbol{X}(t)$, for $t_0 \leq t \leq T$, denote a n-dimensional diffusion process with a transition density $p(s, \boldsymbol{x}, t, \boldsymbol{y})$. If the derivatives $\partial p/\partial t$, $\partial(f_i(t, \boldsymbol{y})p)/\partial y_i$ and $\partial^2(b_{ij}(t, \boldsymbol{y})p)/\partial y_i \partial y_j$ exist and are continuous functions, then, for fixed s and $\boldsymbol{x}$ such that $s \leq t$, this transition density is a fundamental solution of the Fokker-Planck equation*

$$\frac{\partial p}{\partial t} + \sum_{i=1}^{n} \frac{\partial(f_i(t, \boldsymbol{y})p)}{\partial y_i} - \frac{1}{2} \sum_{i=1}^{n} \sum_{j=1}^{n} \frac{\partial^2(b_{ij}(t, \boldsymbol{y})p)}{\partial y_i \partial y_j} = 0. \tag{2}$$

The boundary condition for Eq.(2) is given by $\lim_{t \to s} p(s, \boldsymbol{x}, t, \boldsymbol{y}) = \delta(\boldsymbol{y} - \boldsymbol{x})$.

This partial differential equation (PDE) has an analytical solution only in some special cases and, in general, numerical methods are need to solve it. In this work a method based on Trotter's formula for semigroup decomposition, explained below, is used.

2.3 Semigroup Definition

Consider the Banach space $\boldsymbol{X}$ of continuous functions equipped with the supremum norm.

Definition 1 ([11]). *A semigroup of operators of class C_0 is a family of operators T_t defined in $\boldsymbol{X}$ and indexed by the parameter $t \in \mathbb{R}$ (time) such that:*

1. *T_t is defined $\forall t \geq 0$;*
2. *T_t satisfies the* semigroup condition*:*

$$\forall_{s,t \in \mathbb{R}}\, T_{t+s} = T_t T_s \tag{3}$$

3. *T_t satisfies the continuity condition*

$$\lim_{t \to \infty} T_t \boldsymbol{x} = \boldsymbol{x}\ \forall_{\boldsymbol{x} \in \boldsymbol{X}}$$

4. *T_t is bounded $\forall t \geq 0$:*

$$\exists_{c \in \mathbb{R}} : \forall_{\boldsymbol{x} \in \boldsymbol{X}} \left\| T\boldsymbol{x} \right\| \leq c \left\| \boldsymbol{x} \right\|$$

Definition 2 ([11]). *The* infinitesimal generator *of the semigroup T_t is the operator defined by*

$$A = \lim_{t \to 0} t^{-1}(T_t - I)$$

where I is the identity operator.

Remark 1. *The set $B(\boldsymbol{X})$ of bounded linear operators in a Banach space $\boldsymbol{X}$ is itself a Banach space with respect to the norm induced by the norm defined in $\boldsymbol{X}$:*

$$\|T_t\| \triangleq sup \left\{ \frac{\|T_t \boldsymbol{x}\|}{\|\boldsymbol{x}\|} = \boldsymbol{x} \in \boldsymbol{X} \;\; \{0\} \right\}$$

Under this norm, definition 2 states that the semigroup T_t satisfies the following so called evolution equation

$$\frac{d}{dt}T_t = AT_t \tag{4}$$

with the initial condition $T_0 = I$. The solution T_t of (4) is referred to as the integral operator corresponding to a A.

2.4 Trotter's Formula

Consider the situation in which A is the sum of two operators A_1 and A_2. Let T_t^1 and T_t^2 be the corresponding integral operators (semigroups), *i. e.*, assume that

$$\frac{d}{dt}T_t^i = A_i T_t^i,\ i = 1,2 \tag{5}$$

with T_t satisfying the evolution equation

$$\frac{d}{dt}T_t = (A_1 + A_2)T_t. \tag{6}$$

In general, it is not true that T_t results from the composition of T_t^1 and T_t^2. However, this is approximately true for small t, meaning that T_t can be approximated by the iterated composition of T_Δ^1 ans T_Δ^2 over small intervals of time Δ. This is stated in the following theorem:

Teorema 3 ([9]). *Let T_t^1 and T_t^2 satisfy the* norm condition*:*

$$\exists_{w\in\mathbb{R}} : \forall_{t>0} \left\|T_t^i\right\| \leq e^{w_i t},\ i = 1,2$$

and that $D(A_1 + A_2) = D(A_1) \cap D(A_2)$ is dense in $\boldsymbol{X}$, where $D(A)$ denotes the domain of A. Then, (the closure of) $A_1 + A_2$ generates a semigroup of class C_0 iff (the closure) $R(\lambda I - A_1 - A_2)$ is dense in $\boldsymbol{X}$ for some $\lambda > w_1 + w_2$, where $R(A)$ denotes the range of A. If $A_1 + A_2$ (or its closure) generates a semigroup of class C_0, this is given by

$$T_t = \lim_{\Delta\to 0}(T_\Delta^1 T_\Delta^2)^{\lceil t/\Delta \rceil} \tag{7}$$

where $\lceil t/\Delta \rceil$ represents the greatest integer that does not exceed t/Δ.

Expression (7) is commonly known as Trotter's formula. It embodies an approximation that may be extended to a finite sum of operators.

3 Transition Probability in NMB

The neuromuscular blockade dynamics can be represented by a Wiener model comprising a linear state-space model and a nonlinear output equation. The influence of the parameter uncertainty on NMB state and output (the NMB level) is studied hereafter using the method previously described.

3.1 NMB Dynamics

Recently a reduced complexity model for the neuromuscular blockade induced by *Atracurium* was proposed [2] that has compartmental features and is represented by

$$\begin{cases} \dot{x}_1 = -k_3\alpha x_1 \\ \dot{x}_2 = \ \ k_2\alpha x_1 \ \ -k_2\alpha x_2 \\ \dot{x}_3 = \qquad\qquad\quad k_1\alpha x_2 \ \ -k_1\alpha x_3 \end{cases} \tag{8}$$

Here the dot denotes the time derivative; k_1, k_2 and k_3 are known process parameters; x_1, x_2 and x_3 are state variables; and α is an unknown model parameter. The advantage of this model consists in the fact that the description of inter-patient variability is reduced to the unknown parameter α, considered to be a random variable described by a probability density function. Therefore, all state variables are random outputs and the system can be rewritten as a stochastic system with a state enlarged by the parameter, as

$$\begin{cases} \dot{x}_1 = -k_3\alpha x_1 \\ \dot{x}_2 = \ \ k_2\alpha x_1 \ \ -k_2\alpha x_2 \\ \dot{x}_3 = \qquad\qquad\quad k_1\alpha x_2 \ \ -k_1\alpha x_3 \\ \dot{\alpha} = \qquad 0 \end{cases} \tag{9}$$

or

$$d\boldsymbol{X} = \boldsymbol{f}(\boldsymbol{X}(t), \alpha(t), t)dt \tag{10}$$

with $\boldsymbol{f}$ defined from (9), and

$$d\alpha = 0dt \tag{11}$$

with initial conditions $\boldsymbol{X}_0 = [x_1(t_0), x_2(t_0), x_3(t_0)]^T$ and $\alpha = \alpha(t_0)$ a random variable with a known pdf.

Since the conditions of theorem 1 (Existence and Uniqueness) are verified and the functions f_i are continuous, an equivalent description can be given in terms of a three-dimensional Fokker-Planck equation, and the time propagation of the probability density function of state variables obtained

$$\frac{\partial p}{\partial t} = k_3\alpha(p + x_1\frac{\partial p}{\partial x_1}) + k_2\alpha(p - (x_1 - x_2)\frac{\partial p}{\partial x_2}) + k_1\alpha(p - (x_2 - x_3)\frac{\partial p}{\partial x_3}) \tag{12}$$

with boundary condition $\lim_{t\to 0} p(x_1, x_2, x_3, \alpha, t) = p(x_1, x_2, x_3, \alpha, 0)$.

Actually, (12) is a degenerate form of the Fokker-Planck equation (Liouville Equation [8]) because the second derivative term associated to diffusion is assumed to vanish. The solution of (12) represents how the state pdf is influenced by the pdf of the parameter α and evolves along time. A numerical method based on Trotter's formula is applied hereafter in order to approximate the solution of (12). For that purpose, (12) is rewritten as

$$\frac{\partial p(x_1, x_2, x_3, \alpha, t)}{\partial t} = (L_1 + L_2 + L_3 + L_4)p(x_1, x_2, x_3, \alpha, t) \tag{13}$$

where the infinitesimal generators L_1, L_2, L_3 and L_4 are defined by

$$L_1 p(x_1, x_2, x_3, \alpha, t) = (k_1 + k_2 + k_3)\alpha p(x_1, x_2, x_3, \alpha, t) \tag{14}$$

$$L_2 p(x_1, x_2, x_3, \alpha, t) = k_3 \alpha x_1 \frac{\partial p(x_1, x_2, x_3, \alpha, t)}{\partial x_1} \tag{15}$$

$$L_3 p(x_1, x_2, x_3, \alpha, t) = k_2 \alpha (x_2 - x_1) \frac{\partial p(x_1, x_2, x_3, \alpha, t)}{\partial x_2} \tag{16}$$

$$L_4 p(x_1, x_2, x_3, \alpha, t) = k_1 \alpha (x_3 - x_2) \frac{\partial p(x_1, x_2, x_3, \alpha, t)}{\partial x_3} \tag{17}$$

The operators T_t^i generated by the infinitesimal generators L_i, $i = 1, 2, 3, 4$ are given by

$$T_\Delta^1 p(x_1, x_2, x_3, \alpha, t) = e^{\alpha(k_1+k_2+k_3)\Delta} p(x_1, x_2, x_3, \alpha, t) \tag{18}$$

$$T_\Delta^2 p(x_1, x_2, x_3, \alpha, t) = p(x_1 e^{-k_3 \alpha \Delta}, x_2, x_3, \alpha, t) \tag{19}$$

$$T_\Delta^3 p(x_1, x_2, x_3, \alpha, t) = p(x_1, x_1 + e^{-k_2 \alpha \Delta}(x_2 - x_1), x_3, \alpha, t) \tag{20}$$

$$T_\Delta^2 p(x_1, x_2, x_3, \alpha, t) = p(x_1, x_2, x_2 + e^{-k_1 \alpha \Delta}(x_3 - x_2), \alpha, t) \tag{21}$$

Since all the operators satisfy the conditions of definition 1 as well as the norm condition of theorem 3 is valid to apply Trotter's formula. Accordingly, the solution of (12) is approximated by

$$p(x_1, x_2, x_3, \alpha, t + \Delta) \approx T_\Delta^1 T_\Delta^2 T_\Delta^3 T_\Delta^4 p(x_1, x_2, x_3, \alpha, t), \tag{22}$$

meaning that

$$\begin{aligned} p(\boldsymbol{x}, \alpha, t + \Delta) \approx e^{\alpha(k_1+k_2+k_3)\Delta} & p(x_1 e^{-k_3 \alpha \Delta}, \\ & x_1 + e^{-k_2 \alpha \Delta}(x_2 - x_1), x_2 + e^{-k1 \alpha \Delta}(x_3 - x_2), \alpha, t). \end{aligned} \tag{23}$$

3.2 State Uncertainty Characterization

In order to illustrate the results, start by addressing a simplified one-dimensional case. Two parameter distributions are considered, namely the *lognormal* (LN) and the *uniform* distribution (U) defined as:

- For the *lognormal* distribution

$$f(\alpha) = \frac{1}{\sqrt{2\pi}\sigma\alpha} exp \left\{ -\frac{(ln(\alpha) - \mu)^2}{2\sigma^2} \right\}$$

  with $\mu = -3.287$ and $\sigma = 0.158$.
- For the *uniform* distribution

$$f(\alpha) = \begin{cases} 1/(b-a) \ , & for \quad a \leq \alpha \leq b \\ \quad 0 & , \ for \ \alpha < a \ or \ \alpha > b \end{cases} ,$$

  with $a = 0.027$ and $b = 0.052$.

The four parameters used in the two distributions are the maximum likelihood estimates for a real database of patient data with 48 samples. To apply Trotter's formula the interval Δ is made constant and equal to 0.1 minute.

One Dimensional Case. Before computing the impact of the state uncertainty on the system output (measured NMB level), and for the sake of illustration in a simple case, consider the one-dimensional case, in which

$$k_1 = 0,\ k_2 = 0 \text{ and } k_3 = 10$$

and the initial condition is $x_1(0) = 500k_3\alpha$ with initial probability density function

$$p(x_1, \alpha, 0) = f_\alpha(\alpha)\delta(x_1 - x_1(0))$$

where $f_\alpha(\alpha)$ is the probability density function of the parameter α.

First, the time evolution of the probability density function induced by each one of the two operators used in the Fokker-Planck equation is computed separately. Then, the approximated solution yielded by Trotter's formula, *i.e.*, the time evolution of the probability density function induced by the two operators, is represented and discussed.

The operator L_1 acts in the transition probability by means of one factor that depends on the value of α. This action deforms the transition probability by increasing pointwise the pdf, but does not change the position of the pdf to which it is applied, with respect to the values of x_1. Instead, the operator L_2 acts in the transition probability by causing a shift and a change of the independent variable *i.e.*, this operator replaces x_1 by $x_1 e^{-k_3\alpha t}$. When the two operators are applied in sequence, the result is represented on figure 1.

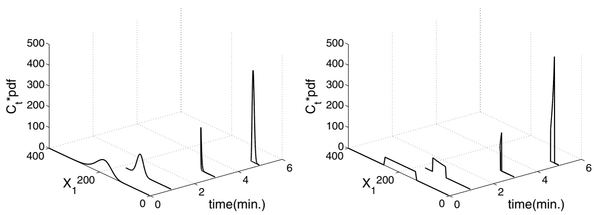

Fig. 1. Action of both operators, $L_1 + L_2$-parameter distribution LogN (left) and uniform distribution (right)

Neuromuscular Blockade. The NMB level is computed from the state variable using the output equation. This equation is nothing more than a static function that allows to compute the NMB level r as function of one of the state variables [2]. Therefore, the NMB signal pdf as a function of time t is computed using a pdf transformation associated to the output function.

Figure 2 shows the NMB pdf at 6 different time instants. In the plane $[r, t]$ a set of responses from 13 real patients (clinical results) are also plotted.

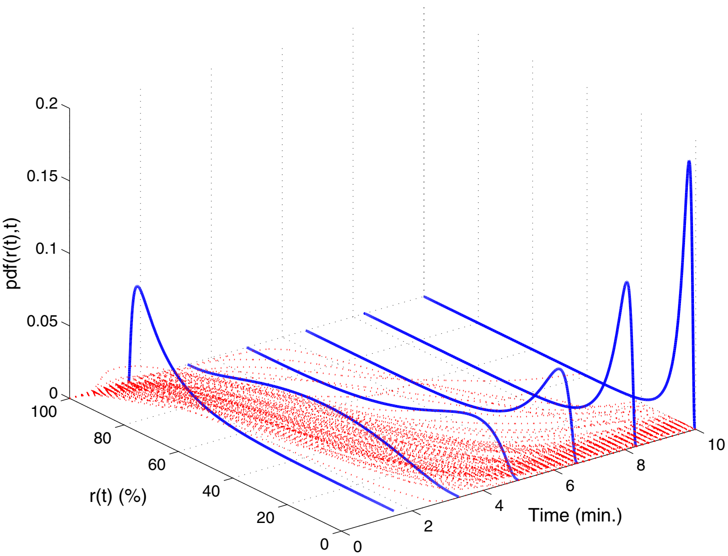

Fig. 2. Neuromuscular blockade pdf as computed from the model and a set of 13 responses from real patients

4 Conclusions

This work allows to see that the physiological effect induced by *atracurium* administration has different density transition probability for different parameter distribution. Moreover, the range of values for the state variables that may occur depends not only of the parameter distribution but also on the instance under consideration.

In this problem, Trotter's formula provides an adequate approximation for the transition probability given by the solution of the Fokker-Planck equation for this stochastic system.

The time evolution of the transition density probability to the administration of an *atracurium* bolus of 500 $\mu g/kg$ (that corresponds to the usual procedure at the beginning of a general anesthesia), given by the solution of the Fokker-Planck equation is in accordance with the expected. This means that, for the same drug dosage applied, different patient have states that evolve in time in a different way. Nevertheless, all the states will converge for zero, and that is also expected since the drug will be eliminated from the body of the patient.

This work shows that the parameters uncertainty has an important role in the states uncertainty, and it is immediately after the drug administration that it is most noted. For further work the authors intend to study the influence of the parameters uncertainty over time, assuming that the unknown parameter instead of being constant in time is affected by disturbances. This may be seen as a stochastic approach to the on-line parameter identification problem.

Acknowledgment. This work was supported by *FEDER* funds through *COMPETE*–Operational Programme Factors of Competitiveness and by Portuguese funds through the *Center for Research and Development in Mathematics and Applications* (University of Aveiro) and "FCT–Fundação para a Ciência e a Tecnologia", within projects PEst-C/MAT/UI4106/2011 with COMPETE number FCOMP-01-0124-FEDER-022690, PEst-OE/EEI/LA0021-/2013 and GALENO - Modeling and Control for personalized drug administration, PTDC/SAU-BEB/103667/2008. Conceição Rocha acknowledges the grant SFRH/BD/61781 /2009 by FCT/ESF.

References

1. Bailey, J., Haddad, W.: Drug dosing in clinical pharmacology: paradigms, benefits, and challenges. IEEE Control Syst. Mag. 25(2), 35–51 (2005)
2. Silva, M.M., Wigren, T., Mendonça, T.: Nonlinear identification of a minimal neuromuscular blockade model in anesthesia. IEEE Transactions on Control Systems Technology 20(1), 181–188 (2012)
3. Arnold, L.: Stochastic Differential Equations: Theory and Applications. John Wiley & Sons, New York (1974)
4. Fall, C., Marland, E., Wagner, J., Tyson, J. (eds.): Computational Biology. Springer, New York (2002)
5. Grindrod, P.: The Theory and Applications of Reaction-Diffusion Equations – Patterns and Waves. Clarendon Press, Oxford (1996)
6. Mukherjee, A., Strikwerda, J.C.: Analysis of dynamic congestion control protocols – a fokker-planck approximation. In: Proc. ACM Sigcomm, Zurich, Switzerland, pp. 159–169 (1991)
7. Lemos, J.M., Moura, J.M.F.: Time sampling of diffusion systems using semigroup decomposition methods. In: MTNS 2004, 16th Int. Symp. on Mathematical Theory of Networks and Systems, Leuven, Belgium (2004)
8. Brockett, R.: Notes on the Control of the Liouville Equation. In: Cannarsa, P., Coron, J.-M. (eds.) Control of Partial Differential Equations, ch. 2. Springer (2010)
9. Trotter, H.F.: On the product of semigroups of operators. Proc. American Mathematical Society 10(4), 545–551 (1959)
10. Klebaner, F.C.: Introdution to Stochastic Calculus With Applications. Imperial College Press, London (2005)
11. McBride, A.C.: Semigroups of linear operators: An introdution. Longman Scientific & Technical, London (1987)