Nonlinear Identification of Individualized Drug Effect Models of the Neuromuscular Blockade in Anesthesia

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Outline

1. Closed-loop drug delivery
2. Mathematical model of closed-loop NMB
3. Control loop analysis
4. Surgery room scenario
5. Simulation experiment
6. Patient model estimation
7. Estimation algorithms
8. Experiments
   1. Synthetic data
   2. Clinical data
9. Conclusions
This talk is a nutshell

A method to control slowly varying Wiener systems by PID without oscillations
This talk is a nutshell

1. A method to control slowly varying Wiener systems by PID without oscillations

2. Particle filter is the best way of estimating Wiener models of drug administration.
Closed-loop drug delivery

Automatic dosing of the drug by a feedback controller from quantified symptoms:

- Individualization of treatment
Closed-loop drug delivery

Automatic dosing of the drug by a feedback controller from quantified symptoms:

- Individualization of treatment
- Intrinsic monitoring of the patient state

Prerequisites:

- Sensor (monitor) quantifying the symptoms
- Controller guaranteeing that the symptoms closely follow the set point prescribed by medical personnel
- Drug dosing device (pump, dispenser, vaporizer, etc.)
Closed-loop drug delivery

Automatic dosing of the drug by a feedback controller from quantified symptoms:

▶ Individualization of treatment
▶ Intrinsic monitoring of the patient state
▶ Automation of tedious dose adjustment
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NMB – neuromuscular blockade; EMG – blockade level measured by electromyogram; muscle relaxant — atracurium; reactive and predictive control of blockade level by anaesthesiologist
Anesthesia: KMG NMB sensor

KMG NMB sensor: The electrical stimulation of the adductor pollicis muscle is performed via the two electrodes on the wrist of the patient and the response is measured by the motion of the thumb. Unrelated with the NMB measurement, there is a finger oximeter placed on the middle finger of the patient.
Closed-loop Anesthesia: PID

NMB – neuromuscular blockade; EMG – blockade level measured by electromyogram; muscle relaxant — atracurium; PID – proportional, integral and derivative controller
Closed-loop drug delivery

Challenges

- Difficulties in translating control performance into clinical outcome
Closed-loop drug delivery

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- High inter-patient and intra-patient variability

- Implementation of predictive action
- Oscillations: interchanging underdosing and overdosing episodes
- Underdosing: insufficient drug effect
- Overdosing: risk of side effects
- Oscillation: both of the above
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Closed-loop drug delivery

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## Closed-loop drug delivery

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<table>
<thead>
<tr>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Difficulties in translating control performance into clinical outcome</td>
</tr>
<tr>
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<tr>
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</tbody>
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Closed-loop drug delivery: PID-control of BIS

Oscillations in PID-controlled anesthesia. Appropriate BIS level for general anesthesia is from 40 to 60. From Méndez et al, Computer Methods in Biomechanics and Biomedical Engineering Vol. 12, No. 6, December 2009, pp. 727–734
Closed-loop drug delivery

Avoiding oscillations

- How far is the closed loop from oscillation?
Closed-loop drug delivery

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Closed-loop drug delivery

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## Closed-loop drug delivery

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Closed-loop drug delivery

Avoiding oscillations

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Accurate pharmacodynamic-pharmacokinetic models are necessary.
Mathematical modeling: The patient model

The system (PK/PD) is modeled by a Wiener model:

- The linear block is of third order, with the parameter $\alpha$

\[
\begin{align*}
\dot{x}_1 &= -\alpha k_3 (x_1 - u(t)), \\
\dot{x}_2 &= \alpha k_2 (x_1 - x_2), \\
\dot{x}_3 &= \alpha k_1 (x_2 - x_3),
\end{align*}
\]

- The nonlinearity is a Hill function of order $\gamma \in \mathbb{R}^+$

\[
y(t) = \frac{100 C_5^\gamma}{C_5^\gamma + x_3^\gamma(t)}.
\]

- The patient model is parameterized in two parameters $\alpha, \gamma$. 
PID controller with time-varying gain

\[ u(t) = K(t) \left( e(t) + \frac{1}{T_i} \int e(s) \, ds + T_d \frac{de(t)}{dt} \right), \]

with

\[ \dot{K}(t) = -\xi (K(t) - K_*) . \]

- \( e(t) = y_r - y(t) \) is the control error
- \( y_r \) is the reference to be followed.
The mathematical model of the closed-loop NMB

\[ \frac{dx}{dt} = f(x), \]

\[ x = (x_1, x_2, x_3, x_4, x_5)^T, \]

\[ f(x) = (f_1, f_2, f_3, f_4, f_5)^T, \]

with

\[ f_1 = -\alpha k_3 x_1 - \alpha^2 k_1 k_3 T_d x_5 \Phi'(x_3)(x_2 - x_3) \]
\[ + \alpha k_3 x_5 (y_r - \Phi(x_3)) + \frac{\alpha k_3}{T_i} x_4 x_5, \]

\[ f_2 = \alpha k_2 (x_1 - x_2), \quad f_3 = \alpha k_1 (x_2 - x_3), \]

\[ f_4 = y_r - \Phi(x_3), \quad f_5 = -\xi (x_5 - K_\star), \]

\[ \Phi'(x_3) = -\frac{\gamma x_3^{\gamma-1}}{100 C_{50}^\gamma} \Phi^2(x_3). \]
The closed-loop system has a single equilibrium state $\mathbf{x}^* = [x_1^*, x_2^*, x_3^*, x_4^*, x_5^*]^T$, where

$$x_1^* = x_2^* = x_3^*, \quad x_4^* = \frac{T_i}{K_*} x_3^*, \quad x_3^* = C_{50} \left( \frac{100}{yr} - 1 \right)^{\frac{1}{\gamma}}, \quad x_5^* = K_*.$$

The local stability of $\mathbf{x}^*$ is determined by the eigenvalues of

$$Df(\mathbf{x}^*) = \left[ \frac{\partial f_i}{\partial x_j} \right]_{1 \leq i \leq 5; 1 \leq j \leq 5},$$

- Real part: the rate of growth in response to perturbation away from the equilibrium point
- Imaginary part: the angular frequency of an oscillatory component of the dynamics
Analysis: distance to bifurcation

Andronov-Hopf bifurcation

The transition in which a pair of complex conjugated eigenvalues simultaneously crosses the imaginary axis from the left to the right complex half-plane.
Analysis: distance to bifurcation

Andronov-Hopf bifurcation

The transition in which a pair of complex conjugated eigenvalues simultaneously crosses the imaginary axis from the left to the right complex half-plane.

The surface in the parameter space \((T_d, T_i, K_*, \alpha, \gamma)\)

\[
\chi(T_i, T_d, K_*, \alpha, \gamma) = b_3^2 - b_1 b_2 b_3 + b_1^2 b_4 = 0
\] (2)
defines the stability boundary of the equilibrium.

\[
b_1 = \alpha (k_1 + k_2 + k_3),
\]

\[
b_2 = \alpha^2 (k_1 k_2 + k_1 k_3 + k_2 k_3)
+ \alpha^3 k_1 k_2 k_3 K_* T_d \Phi'(x_3^*),
\] (3)

\[
b_3 = \alpha^3 k_1 k_2 k_3 \left[ 1 + K_* \Phi'(x_3^*) \right],
\]

\[
b_4 = \frac{\alpha^3 k_1 k_2 k_3 K_*}{T_i} \Phi'(x_3^*).
\]
Analysis: distance to bifurcation

Figure: (a) Andronov-Hopf bifurcation boundary in the parameter space \((T_i, T_d, K_*)\) for \(\alpha = 0.0364\) and \(\gamma = 4.24358\): \(A\) is the equilibrium stability domain, \(B\) is the region of unstable equilibrium. Point 1 belongs to \(A\). (b) Andronov-Hopf bifurcation boundary in the parameter space \((T_i, T_d, K_*)\) for \(\alpha = 0.021435\) and \(\gamma = 4.24358\). Now Point 1 is in \(B\).
Figure: Histogram of the distance to bifurcation, at time $t = 40$ min, over the 48 cases in the synthetic database, assuming PID control. Note the log-scale on the x-axis. Three cases are at high risk of oscillations.
The eigenvalues of the Jacobian matrix are determined by

\[
\det (Df(x_*) - sl) = \\
= (s^4 + b_1 s^3 + b_2 s^2 + b_3 s + b_4)(s + \xi) = 0.
\]

The factor \((s + \xi)\) is independent of the system parameters.
Analysis: the impact of $K(t)$

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$$\det(Df(x_*) - sI) =$$

$$(s^4 + b_1 s^3 + b_2 s^2 + b_3 s + b_4)(s + \xi) = 0.$$  

The factor $(s + \xi)$ is independent of the system parameters.

No new nonlinear dynamical behaviors arise due to the time-varying PID controller.
The surgery room scenario

- A Wiener individualized NMB model is estimated from a drug bolus response.
The surgery room scenario

- A Wiener individualized NMB model is estimated from a drug bolus response.
- From the desired controller convergence rate and distance to bifurcation, the gains of the PID controller $K_0, T_i, T_d$ are calculated, see [JPC2015].
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- When the estimated distance to bifurcation goes under a given threshold, of the PID controller is re-designed giving $K_{ref}$. 
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- The recovery controller is activated for $K_0 \rightarrow K_{ref}$. 
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Simulation experiment: parameter changes

Figure: Time-domain changes in $\alpha$ and $K$, for $\xi = 0.1$. The red square depicts the value of $K_{\text{bif}}$. 

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Simulation experiment: system output

Figure: Time-domain behavior of $x_3$ and output $y$. The red dashed line indicates $1.2 \ x_3^*$, with $x_3^*$ as the steady state value of the state variable $x_3$ for $t > t_2$. 
Estimation algorithms

The model

\[
x_{t+1} = \begin{bmatrix} \Phi(\alpha_t) & 0_{3 \times 2} \\ 0_{2 \times 3} & I \end{bmatrix} \begin{bmatrix} \bar{x}_t \\ \alpha_t \\ \gamma_t \end{bmatrix} + \begin{bmatrix} \Gamma(\alpha_t) \\ 0_{2 \times 1} \end{bmatrix} u_t + v_t
\]

\[
\equiv f(x_t, u_t) + v_t,
\]

\[
y_t = \frac{100 C_{50}^{\gamma_t}}{C_{50}^{\gamma_t} + (C x_t)^{\gamma_t}} + e_t \equiv h(x_t) + e_t,
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State-of-the-art nonlinear recursive estimation algorithms:

- Extended Kalman Filter (EKF)
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State-of-the-art nonlinear recursive estimation algorithms:

- Extended Kalman Filter (EKF)
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Estimation algorithms

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State-of-the-art nonlinear recursive estimation algorithms:

- Extended Kalman Filter (EKF)
- Particle Filter (PF)
  - Sampling importance resampling (SIR PF)
  - Orthogonal basis particle filter (OBPF)
Estimation algorithm: EKF

The nonlinear model is used with state updates calculated from linearized dynamics

\[
H_t = \left. \frac{\partial h(x)}{\partial x} \right|_{x=\hat{x}_{t|t-1}}
\]

\[
K_t = P_{t|t-1} H_t^T [H_t P_{t|t-1} H_t^T + R]^{-1}
\]

\[
\hat{x}_{t|t} = \hat{x}_{t|t-1} + K_t [y_t - h(\hat{x}_{t|t-1})]
\]

\[
P_{t|t} = P_{t|t-1} - K_t H_t P_{t|t-1}
\]

\[
\hat{x}_{t+1|t} = f(\hat{x}_{t|t}, u_t)
\]

\[
F_t = \left. \frac{\partial f(x, u_t)}{\partial x} \right|_{x=\hat{x}_{t|t}}
\]

\[
P_{t+1|t} = F_t P_{t|t} F_t^T + Q.
\]
Estimation algorithm: PF

Sampling importance resampling (SIR) PF:

- $x^{(i)}$ denote a particle, $i = 1, 2, \ldots, N$
- $w^{(i)}$ the corresponding weight
- $N$ the number of particles
- $v^{(i)}_t$ is a draw from $p_v(v)$, the process noise distribution
- $p_e(e)$ is the measurement noise distribution

\[
\begin{align*}
\tilde{x}^{(i)}_{t+1} &= f(x^{(i)}_t, u_t) + v^{(i)}_t \\
\tilde{w}^{(i)}_{t+1} &= w^{(i)}_t p_e(y_t - h(\tilde{x}^{(i)}_t, u_t)) \\
w^{(i)}_{t+1} &= \tilde{w}^{(i)}_{t+1}/\sum_{j=1}^N \tilde{w}^{(j)}_{t+1} \\
\hat{x}_{t+1} &= \sum_{j=1}^N w^{(j)}_{t+1} x^{(j)}_{t+1}.
\end{align*}
\]
Estimation algorithm: OBPF

- The OBPF follows the steps of the PF
- An orthogonal series is fitted to the particle set in the resampling step

\[
p(x_t|Y_t) \approx \sum_{k \in K} a_t^{(k)} \phi_k(x_t),
\]

where \(a_t^{(k)}\) is the coefficient for the basis function \(k\).

- The Hermitian basis functions are used. In the one-dimensional case

\[
\phi_0(x) = \pi^{-1/4} e^{-x^2/2}, \quad \phi_1(x) = \sqrt{2} x \phi_0(x),
\]

\[
\phi_k(x) = \sqrt{\frac{2}{k}} x \phi_{k-1}(x) - \sqrt{\frac{k-1}{k}} \phi_{k-2}(x).
\]
Estimation algorithm: OBPF

Figure: A set of 50 weighted particles (gray stems) and the fitted series expansion (black solid line) using the first 7 Hermite functions.
Estimation algorithm: OBPF

- The OBPF is developed for efficient computations on parallel platforms.
- The global information on the estimated quantity expressed by the particles is compressed to a few expansion coefficients.
- The OBPF exhibits higher parallelizability and estimation accuracy of compared to the SIR PF and the Gaussian PF.
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Experiments

The EKF, the SIR PF, and the OBPF have been evaluated on

- **Synthetic data**: 48 synthetic data sets generated from real cases
- **Clinical data**: 48 data sets collected during PID-controlled administration of atracurium under general anesthesia

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- $0 < t \leq 10$ min, induction (initial bolus), open loop
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Anesthesia phases:
1. \(0 < t \leq 10\) min, induction (initial bolus), open loop
2. \(10 < t \leq 30\) min, P-controller
3. \(30 < t \leq 75\) min, from the beginning of the recovery from the initial bolus until the reference reaches its final value of 10%, PID-controller

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4. $75 < t \leq$ end, steady state, PID-controller
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4. \(75 < t \leq \text{end}\), steady state, PID-controller

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Anesthesia phases:

1. $0 < t \leq 10$ min, induction (initial bolus), **open loop**
2. $10 < t \leq 30$ min, **P-controller**
3. $30 < t \leq 75$ min, from the beginning of the recovery from the initial bolus until the reference reaches its final value of $10\%$, **PID-controller**
4. $75 < t \leq \text{end}$, steady state, **PID-controller**


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Experiments: synthetic data

Case # 7

Figure: Estimated $\alpha$ (upper plot) and $\gamma$ (bottom plot) for the Orthogonal Basis PF (OBPF), Sampling Importance Resampling PF and EKF for case number 7 in the synthetic database. The settling time instants are marked by the arrows.
**Figures:** The true $\alpha$ and $\gamma$ vs. estimation bias $b_\alpha$ and $b_\gamma$, respectively, for the 48 cases in the synthetic database. EKF – green circles, PF – blue crosses.
Experiments: synthetic data

**RMSE**

Figure: Root mean square error $R = \sqrt{\frac{1}{T} \sum_{t=0}^{T} (x_t - \hat{x}_t)^2}$ for $\alpha$ (upper plot) and $\gamma$ (lower plot) as a function of the number of particles $N$. 
Experiments: synthetic data
PDF estimation by PBPF

Figure: Marginal distribution for $\alpha$ at time $t = 5$ min. The true PDF is shown in dashed black line. The approximations obtained by the OBPF with approximation orders from 0 to 4 are shown in colored solid lines.
Experiments: clinical data
Case # 39

Figure: Estimated model parameters for the EKF, in dashed green, and the PF, in solid blue, over time for a case number 39 in the real database.
### Experiments: clinical data

#### Output error

**Table:** Output error (absolute value) of estimation for the EKF, the PF and the OBPF, during the four phases of anesthesia; **Best, Worst.**

<table>
<thead>
<tr>
<th>Phase</th>
<th>EKF mean</th>
<th>EKF stdv</th>
<th>EKF [min,max]</th>
<th>PF mean</th>
<th>PF stdv</th>
<th>PF [min,max]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.16</td>
<td>0.62</td>
<td>[2.58,5.42]</td>
<td>0.95</td>
<td>0.47</td>
<td>[0.24,2.34]</td>
</tr>
<tr>
<td>2</td>
<td>0.49</td>
<td>0.17</td>
<td>[0.16,0.85]</td>
<td>0.58</td>
<td>0.39</td>
<td>[0.14,1.97]</td>
</tr>
<tr>
<td>3</td>
<td>0.31</td>
<td>0.16</td>
<td>[0.08,0.98]</td>
<td>0.30</td>
<td>0.16</td>
<td>[0.13,0.77]</td>
</tr>
<tr>
<td>4</td>
<td>0.25</td>
<td>0.16</td>
<td>[0.04,0.97]</td>
<td>0.25</td>
<td>0.13</td>
<td>[0.07,0.76]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OBPF(0)</th>
<th>OBPF(5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>mean</td>
</tr>
<tr>
<td>1</td>
<td>0.87</td>
</tr>
<tr>
<td>2</td>
<td>0.52</td>
</tr>
<tr>
<td>3</td>
<td>0.31</td>
</tr>
<tr>
<td>4</td>
<td>0.26</td>
</tr>
</tbody>
</table>

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Computational complexity of PF

Figure: RMSE as a function of the number of floating-point operations per second (FLOPS) required for filter execution.
Conclusions

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PID design procedure in terms of \((R, L)\). The model parameters \(\alpha = 0.027\), \(\gamma = 2.4395\). Design specifications: \(r^* = 40\%\), \(T_{\text{conv}}^* = 30\) min. The shaded area corresponds to the designs with \(T_{\text{conv}} \leq T_{\text{conv}}^*\). The top side of the boundary \(\chi(\alpha_{\text{min}}, L, R) = 0\) (blue line) determines the region of controller robustness over \(r^* = \frac{\alpha_{\text{min}}}{\alpha}\). The red star depicts an admissible design \((L = 8.3, R = 0.02)\) with \(r = 42.178\%\) and \(T_{\text{conv}} = 26.8\) min.
Manual administration rocuronium. Upper plot: First twitch of a TOF stimulation normalized by the reference twitch, quantifying the NMB level. Bottom plot: rocuronium bolus. The circle marks the time when a bolus of atropine and neostigmine is intravenously administered to fasten the recovery from the NMB.