PROBABILISTIC BEHAVIORAL MODEL FOR THE DETECTION OF CRITICALITIES WHEN USING MORPHINE AND FENTANYL PCA

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ABSTRACT

When patient controlled analgesia (PCA) was originally introduced, the belief was that frequency of analgesic demand uniquely reflects the level of patient's pain. However frequency of the demand is a random process that has its own distribution with a unique shape and parameters. We used this distribution to simulate the risk of drug concentration exceeding critical threshold.

We used quantized state system model to create hybrid aggregate model of PCA. We investigated two randomly selected, real data based, unidentified morphine and fentanyl PCA logs. Based on this data we generated model of the random process that approximated real demand data and created 500 virtual PCA logs. These logs allowed pharmacokinetic simulation of the effect compartment concentration.

The proposed methodology allows an estimation of frequency and duration of critical episodes, when target concentration exceeds critical threshold. These estimations might be used to evaluate patient specific risk of postoperative opiate overdose.

Keywords: patient controlled analgesia, hybrid aggregate model, time series, probabilistic distribution.

1. INTRODUCTION

Research suggests (Grass, 2005), that different persons show different demand pattern when using PCA (Dahan, Aarts and Smith, 2010). This behavioral pattern varies depending on the variety of simultaneously occurring factors (Boom et al. 2013), including the level of pain, drug concentration in plasma and the effect site, various side effects (e.g., nausea, sedation, respiratory depression), or even the psychological state of the patient, such as anxiety or cognitive impairment. All these simultaneous factors (Woodhouse and Mather, 2000) introduce randomness in the behavioral dose demand pattern and therefore demand sequence could be thought of as a random process what allows utilizing autoregression moving average model ARMA(p,q), commonly used in time series forecasting (Makridakis and Hibon, 1997).

However, for the analysis of random process with arbitrary degree of precision, there must also be available time series of random process of arbitrary length. In our publication here we describe one of the ways of how to generate and analyze time series of PCA demand of arbitrary length.

2. HYBRID AGGREGATE MODEL OF PATIENT CONTROLED ANALGESIA

2.1. Hybrid aggregate model

For simulation of patient controlled analgesia we used hybrid systems simulation method based on PLA formalism (Pranevicius et al. 2011).

PLA is a special case of automaton models. In the application of the PLA approach for system specification, the system is represented as a set of interacting piece-linear aggregates. The PLA is taken as an object defined by a set of states Z, input signals X, and output signals Y. Behaviour of an aggregate is considered in a set of time moments $t \in T$. States $z \in Z$, input signals $x \in X$, and output signals $y \in Y$ are considered to be time functions. Transition and output operators, H and G correspondingly, must be known as well.

The state $z \in Z$ of the piece-linear aggregate is $z(t) = \left(v(t), z_v(t)\right)$, where $v(t)$ is a discrete state component taking values on a countable set of values; and $z_v(t)$ is a continuous component comprising of $z_1(t), z_2(t), \dots, z_{v_k}(t)$ coordinates.

When there are no inputs, an aggregate state changes as follows: $v(t) = const$, $\frac{dz_v(t)}{dt} = -a_v$, where $a_v = \left(a_{v_1}, a_{v_2}, \dots, a_{v_k}\right)$ is a constant vector.

For hybrid aggregate model (Pranevicius et al. 2011) continuous coordinate's model is described by the ordinary differential equations (ODE):

To solve ODEs system we'll adopt Quantized State System (QSS) method, which was defined by Ernesto Kofman (Kofman 2004).

Considering ODE system:

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

where $x(t) \in R^n$ is the static vector, $u(t) \in R^n$ is an input vector, which is a known piecewise constant function.

The QSS method simulates an approximate system, which is called quantized state system:

$\frac{dx(t)}{dt} = f[q(t), u(t)]$,

where $q(t)$ is a vector of quantized variables which are quantized versions of the state variables $x(t)$. Each component of $q(t)$ is related to the corresponding component of $x(t)$ by a hysteretic quantization function. A generic Quantized State System can be represented by the block diagram of Figure 1.

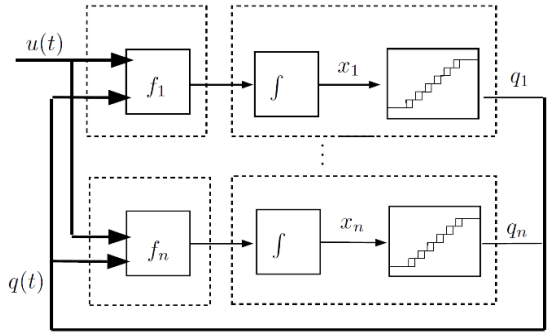

Figure 1: Block diagram representation of a QSS (Kofman 2004)

QSS method was implemented using PLASim simulation library created in our department (Pranevicius , Pilkauskas and Guginis, 2006). The PLASim is an object-oriented library for discrete-event simulation of models created using aggregate formalism. The PLASim's current version written in C# for NET Framework 4.0 and has packages that support random number generation, statistical collection, basic reporting with data visualization and discrete-event simulation. The development of a simulation model is based on sub-classing the SimlationModel class that provides the primary recurring actions within a simulation and event scheduling and handling.

We upgraded module of this library PLASimInternalEvents which implements internal event classes:

InternalWEvent– class of the internal event; ContinuousCoordinate– abstract of the continuous coordinate;

WlSum– class of the controlling sum;

ControlSequence – class of the controlling sequence;

InternalEventHandler – handler (delegate) of the internal event.

Controlling sums (ControlSum) initiate internal event of the aggregate -- CreateInternalEvent(w). Timing of the internal event is determined by the the parameter w. Determination of the parameter w can be done using object from the ControlSequence class. Generated internal event is placed on the list of internal events internalEventQuque. Internal event for the processing is selected using SimulationModel method. The processing method itself is called up using NextInternalEvent() and InternalEventHandler.

Additional classes were added to construct QSS events:

InternalHEvent– class of QSS events;

InternalHEventList list for QSS events;

Hsum – class of QSS events control sum.

2.1.1. Modeling PCA by using hybrid aggregate model

A three compartmental model of drug distribution between the serum and the brain tissue (effect compartment) was used to describe fentanyl and morphine pharmacokinetics/pharmacodynamics, as is shown in Figure 4.

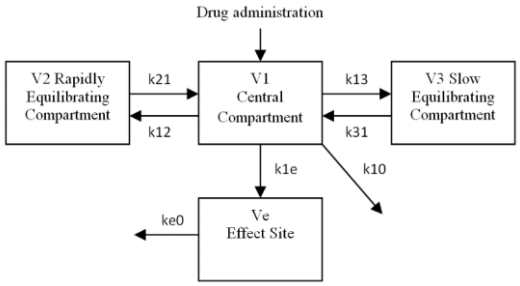

Figure 2: Three compartment pharmacokinetic model

The central compartment (V1) represents a distribution volume and includes rapidly mixing portion of the blood. The peripheral compartments (V2, V3) are composed of tissues and organs, where drug distributes at a slower rate. The effect site is the hypothetical compartment that relates the time course of plasma drug concentration to the time course of drug effect.

Pharmacokinetic model is described by four differential equations:

$$\begin{cases} \frac{dx_1}{dt} = k21 \cdot x_2 - k12 \cdot x_1 + k31 \cdot x_3 - k13 \cdot x_1 \\ \qquad -k10 \cdot x_1 + u(t) \\ \frac{dx_2}{dt} = k12 \cdot x_1 - k21 \cdot x_2; \\ \frac{dx_3}{dt} = k13 \cdot x_1 - k31 \cdot x_3; \\ \frac{dx_e}{dt} = ke0 \cdot x_1 - ke0 \cdot x_e, \end{cases}$$

where x_1 , x_2, x_3 and x_e are the amounts of drug in the central, second, third and effect site compartments, respectively, and k10, k12 , k13 , k21, k31, and ke0 are the constants defining the elimination and inter-compartmental transfer rates, and $u(t)$ the function describing drug delivery.

Aggregate scheme of patient controlled analgesia aggregate model is presented in Figure 5.

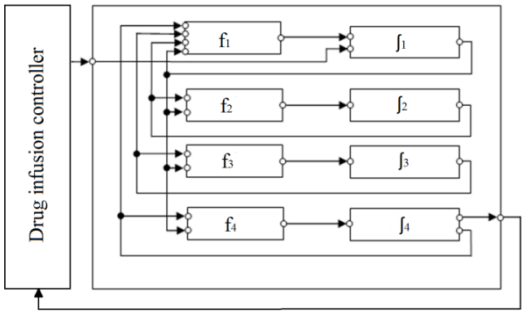

Figure 3: Aggregate scheme of the pharmacokinetic model

3. PATIENT'S BEHAVIORAL MODEL

We used two random real data logs from PCA device, one with a prescription for morphine and one for fentanyl. We analyzed the length of time period (in minutes) between the two consecutive drug requirements.For building of a suitable model we used SPSS and MATLAB statistical tools.

3.1. Analysis of morphine PCA demands

Analysis of correlograms shows (see Fig. 4 and Fig. 5), that neither the values of autocorrelation, nor the values of partial autocorrelation function are statistically significant.

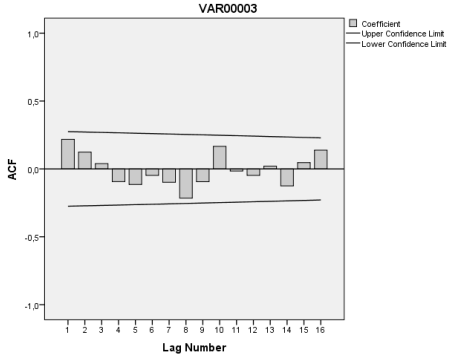

Figure 4: Values of autocorrelation function for morphine PCA log

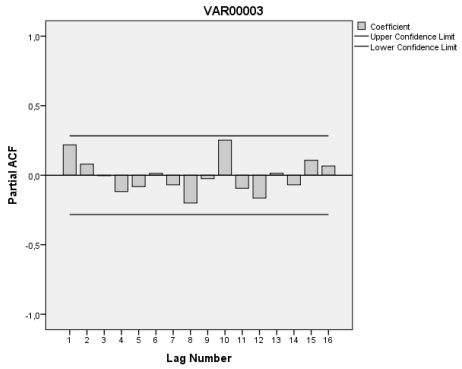

Figure 5: Values of partial autocorrelation function for morphine PCA log

We compared 25 different ARMA(p,q) models, with values of p and q ranging form 0 to 4, and chose the model with lowest value of Bayesian Information Criterion (BIC). BIC, unlike e.g. R squared value, "punishes" models with higher number of parameters, thus it favors more parsimonious models. The values of BIC with different ARMA models are presented in Table 1:

Table 1: BIC values of different ARMA(p,q) models (morphine PCA)

	MA(*q*)				
AR(*p*)	0	1	2	3	4
0	7,180	7,249	7,341	7,437	7,518
1	7,245	7,343	7,440	7,542	7,560
2	7,342	7,442	7,457	7,531	7,659
3	7,441	7,467	7,531	7,659	7,725
4	7,523	7,555	7,658	7,687	7,783

Data form Table 1 shows, that ARMA(0,0) has lowest BIC value, which is consistent with the values of autocorrelation and partial autocorrelation functions. This suggests that the following model is optimal:

$y_t = \mu + kt + \varepsilon_t,$

where $\varepsilon_t \sim WN(0, \sigma^2)$, i.e., identically distributed independent white noise, with mean 0 and variation σ^2. Parameter estimates are presented in Table 2.

Table 2: Parameter estimates for ARMA(0,0) model (morphine PCA)

Parameters	Estimate	Significance
Constant: μ	21,029	0,034
Numerator: k	0,407	0,222

Parameter estimates of this model suggest, that lag numerator k is not statistically significant, thus optimal model for morphine data is

$y_t = \mu + kt + \varepsilon_t,$

where $\varepsilon_t \sim WN(0, \sigma^2)$, i.e., identically distributed independent white noise, with mean 0 and variation σ^2.

Parameter estimates (see Table 2) of this model suggest, that lag numerator k does not differ from 0 significantly, thus optimal model for time periods y_t between two drug requirements during morphine analgesia can be modeled simply as: $y_t = \varepsilon_t$, where $\varepsilon_t \sim WN(0, \sigma^2)$.

Thus, it seems reasonable to model time periods between two drug requirements as identically distributed independent random numbers. In order to choose the best probability distribution function, we used MATLAB distribution fitting tool.

Research showed, that exponential distribution with parameter λ = 1/31.4 (i.e., mean value 31.4) provided the best fit, according to the value of log likelihood, which was -222.34 in this case. Histogram and fitted probability distribution function is presented in Figure 3.

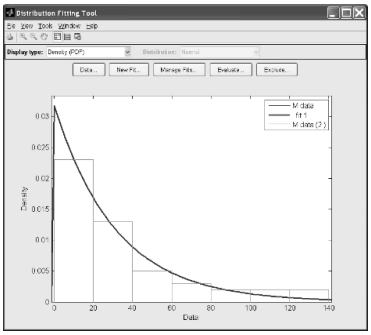

Figure 6: Distribution fitting for data obtained from morphine PCA

Since p value 0.6912 is above 0.05, chi square criterion does not reject the null hypothesis, making exponential distribution a reasonable fit for the data.

```
>> [h,p,s] = chi2gof(M,'CDF',pd)
h =     0
p =  0.6912
s = chi2stat: 0.7387
edges:[4.9407e-324  12.40  24.80  37.20
124.0000]
O: [17 9 9 15]
E: [16.3128 10.9906 7.4049 15.2917]
```

Exponentially distributed random variables can be generated by using standard functions (e.g., function exprnd() in MATLAB), or by the inverse function method. If r is basic random number (i.e., uniformly distributed in interval [0;1]), exponentially distributed number ε can be generated as $\varepsilon = -\frac{\ln r}{\lambda}$.

3.2. Analysis of fentanyl PCA demands

Analyzing correlograms of data, obtained from fentanyl PCA, suggests that it can not be assumed to be the white noise. Autocorrelation function damps cyclically, while partial autocorrelation cuts at level 2, which suggests that some kind of ARMA(2,q) process might be suitable.

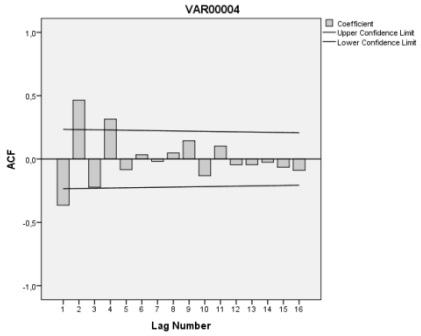

Figure 7: Values of autocorrelation function for fentanyl PCA log

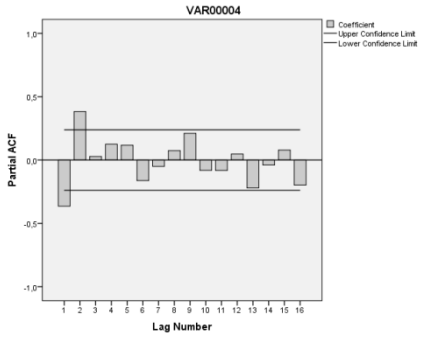

Figure 8: Values of partial autocorrelation function for fentanyl PCA log

Additional research supports this hypothesis, since BIC value is lowest with ARMA(2,0), i.e. AR(2), process suits best (see Table 2.), though it's squared value 0.306 explains smaller part of total variation among data.

Table 3: BIC values of different ARMA(p,q) models (fentanyl PCA)

	MA(*q*)				
AR(*p*)	0	1	2	3	4
0	6,511	6,459	6,427	6,495	6,484
1	6,371	6,360	6,422	6,496	6,514
2	6,354	6,423	6,498	6,534	6,554
3	6,426	6,452	6,530	6,626	6,641
4	6,490	6,528	6,584	6,642	6,720

Residuals of AR(2) model shows no significant autocorrelation, which suggests that residuals are not significantly different from the white noise.

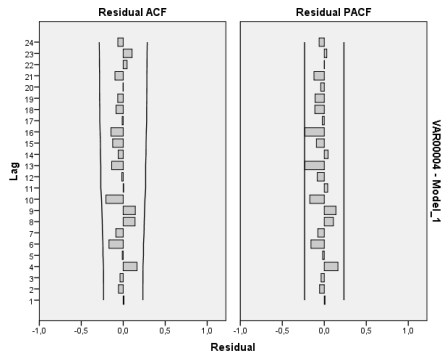

Fig. 9. Values of residuals from fitted ARMA(2,0) model (fentanyl PCA)

Actual five values of patients drug requirements also fitted well into predicted 95 percent confidence intervals, thus ARMA(2,0) might be a reasonable model for the fentanyl analgesia data.

Estimated ARMA(2,0) with linear trend model parameters are presented in Table 4.

Table 4: Parameter estimates for ARMA(2,2) model fitted for data from fentanyl analgesia

Parameter		Estimate	Significance
Constant		11,570	0,26
AR	Lag 1	-0,302	0,12
	Lag 2	0,203	0,11
Numerator	Lag 0	0,264	0,38

All values are statistically significant under standard 0.05 level, so we chose the following model to simulate time period y_t between two consecutive patient requirements for fentanyl dose by the following process:

$y_t = 11{,}57 + 0.264t - 0.302y_{t-1} + 0.203y_{t-2} + \varepsilon_t,$

where $\varepsilon_t \sim WN(0, \sigma^2)$ i.e., it is identically (though not necessary normally) distributed independent random variables, with mean 0 and variation σ^2.

Our analysis suggests that generalized extreme values distribution, with parameters k= -0.021633, s=16.521 and m=-9.426 provides the best fit for AR(2) model residual, according to the likelihood criterion (the value is equal to -306.101). Histogram and fitted probability distribution function is presented in Fig. 7.

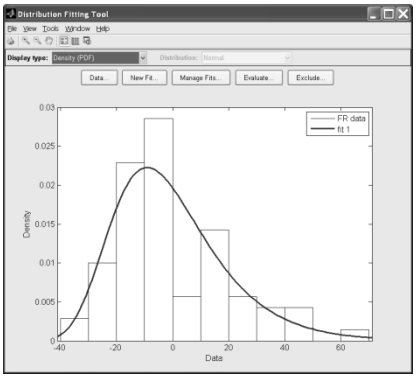

Figure 7: Distribution fitting for residual of ARMA(2;0) model (fentanyl PCA)

Chi square test does not reject our null hypothesis, that residuals are distributed according to a generalized extreme value distribution, since the p value is above the standard 0.05 value.

```
>>pd = fitdist(FR,'GEV')
pd =
generalized extreme value
distribution
    k = -0.021633
sigma = 16.5207
mu = -9.42619
>> [h,p,s] = chi2gof(FR,'CDF',pd)
h = 0
p = 0.0586
s =
chi2stat: 5.6748
edges:[-38.89 -18.42 -8.18 2.05 12.29
22.5260 63.47]
O: [11 15 21 6 6 11]
E: [12.5611 15.1296 14.9153 11.1766
7.1537 9.0636]
```

Moreover, we compared residuals from fitted ARMA(2,0) model with the data generated randomly, that have generalized extreme values distribution with already estimated parameters. Kolmogorov-Smirnov test for both data sets also did not reject the hypothesis that ARMA model residuals have the same distribution as data generated randomly.

```
>> [h,p,s]=kstest2(FR,FRand)
h = 0
p = 0.7246
s = 0.1143
```

The values of generalized extreme values distribution can be generated by the standard functions (e.g., function gevrnd() in MATLAB), or by the use of an inverse function method.

Generalized extreme values distribution with parameters k, s and m has the following cumulative distribution function:

$$F(x;k,s,m) = \exp\left\{-\left[1 + k\left(\frac{x-\mu}{\sigma}\right)\right]^{\frac{1}{k}}\right\}.$$

Thus, the value of random variable ε, having generalized extreme value distribution, can be generated by the following transformation of standard random number r:

$$\varepsilon = s\frac{(-\ln r)^{-k}-1}{k} + m.$$

4. SIMULATION OF PCA USING REAL PATIENT DATA

4.1. Simulation protocol

Simulation of morphine and fentanyl PCA was performed according to aggregate scheme presented in Fig 3. Drug infusion controller simulates patients' behavioral according to models, presented in section 2.

Pharmacokineticsof morphine and fentanyl was simulated by three compartment model. We used the following parameters for simulation of morphine pharmacokinetics:

Central compartment volume = 17.8 l,
Time to deliver the bolus dose = 40 sec,
Bolus dose = 1 ml.

Morphine micro rate constants were chosen from (Dahlstrom et al. 1990).

We used the following parameters for the simulation of fentanyl PCA:

Central compartment volume = 6.09 l,
Time to deliver the bolus dose = 40 sec,
Bolus dose = 1 ml.

Fentanyl micro rate constants were chosen from the previous publications (Shafer et al. 1990).

4.2. Evaluation of increased risk

For the evaluation of critical periods during PCA operation, we generated 500 patients demand logs (according to models presented in section 2) and used hybrid simulation technique to estimate drug plasma and effect compartment concentrations, that was done according to the pharmacokinetic multi-compartmental models. Increased risk event was defined as the time when effect compartment concentration exceeded critical (toxic) threshold. From that, cumulative risk could be defined as the time above this threshold and may correlate with the duration and severity of respiratory depression. We chose the following critical concentration thresholds: 0.02 mcg/l for morphine and 0.07 mcg/l for fentanyl; these levels were chosen arbitrarily for the demonstration purposes only. Two parameters were evaluated: the number of times critical concentration threshold was exceeded during 24 hour simulation period and the duration of the periods when concentration exceeds critical threshold.

4.2.1. Evaluation increased risk periods for morphine

500 simulation sessions were performed that modeled morphine concentration at the effect site during 24 hours period; simulations were performed by using personal patients behavioral model (presented in section 2.1) together with pharmacokinetic compartmental model (Dahlstrom et al., 1978). Average number of times that increased risk concentration was reached, was relatively small – 1.78. Histogram (see Fig. 8) resembles geometric distribution, but statistical test rejected the null hypothesis.

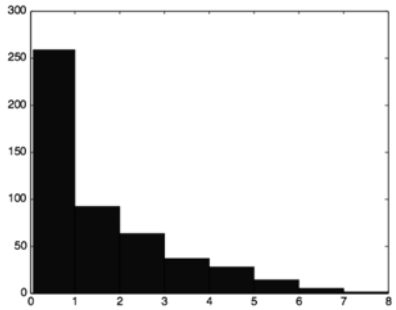

Figure 8: Histogram of the number of increased risk periods during simulated morphine analgesia

The time period spent above critical level is rather lengthy – about 109 minutes on average. More than half (256) of all increased risk periods were longer than 30 minutes. The histogram is presented below in fig.9:

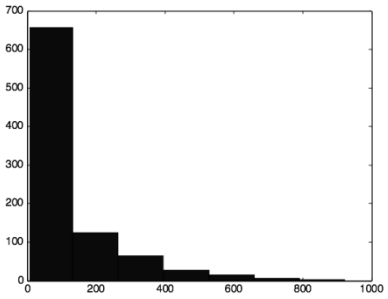

Figure 9: Histogram of the length of increased risk periods during simulated morphine analgesia

Overall proportion of time spent above the critical concentration during morphine PCA simulations was on average about 13.7 percent.

We also compared the estimated effect site morphine concentration from the original demand log with simulated morphine PCA logs (see Fig 10.):

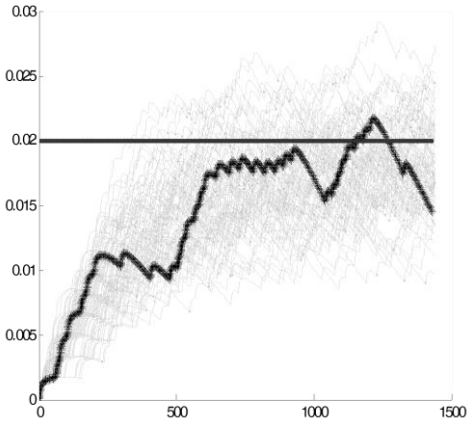

Figure 10: Comparison of estimated patients' drug concentration at the effect site (bold line) using 500 simulated morphine PCA logs. (Critical threshold 0.02)

It appears that the real patients' data fits the pattern of simulations.

4.2.2. Evaluation increased risk periods for fentanyl

500 simulation sessions were performed that modeled fentanyl concentration at effect site during 24 hours period; simulation was done using patients' random behavioral model (presented in section 2.2) together with previously described three compartmental pharmacokinetics model (Shaffer et al., 1990).

Histogram demonstrating the number of times that effect site concentration exceeded critical threshold presented below in fig.11:

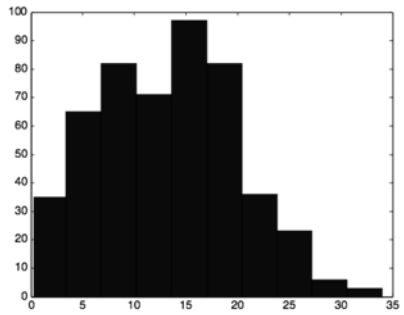

Figure 11: Histogram of the number of increased risk periods during simulated fentanyl analgesia

Average number of times exceeding critical threshold (13.22) is much higher than that of the morphine PCA. Data analysis showed that no standard discrete distribution was suitable to model these data.

However, mean length of the time above the critical threshold is much shorter than that of simulated morphine PCA - only about 6 minutes on average. Histogram is presented below in fig. 12 (no standard distribution was suitable to model the data):

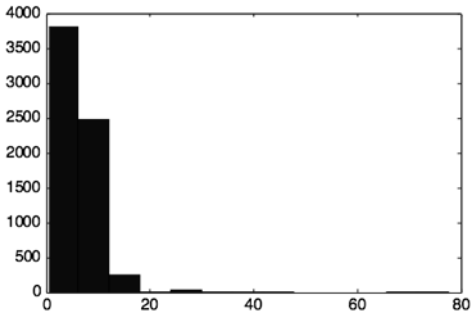

Figure 12: Histogram of the length of periods above critical threshold during fentanyl analgesia simulations

On an average, the time spent above the critical threshold was shorter, about 5.5 percent that of time when comparing morphine analgesia.

We also compared the estimated fentanyl concentration at the effect site obtained from the original demand log with the results obtained from simulated fentanyl PCA (see Fig 13):

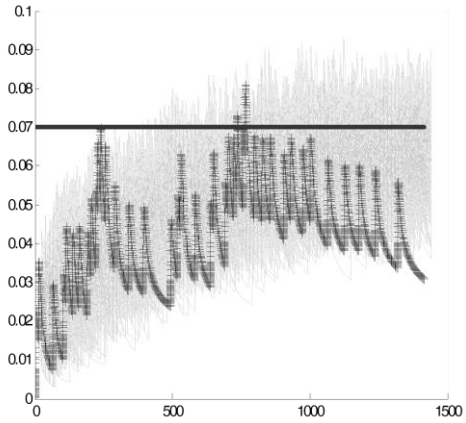

Figure 13: Comparison of the estimated patients' drug concentration at the effect site (bold line) and the results obtained from simulated fentanyl PCA. (Critical threshold 0.07)

As it is shown, patients' data matches simulated drug concentration levels reasonably well.

5. DISCUSSION

Although patient's demands for analgesia may be affected by a multiple factors, they can be reasonably approximated by the autoregressive moving average model of a stochastic process. To estimate the parameters of autoregressive moving average model we used the real data logs from PCA device, with duration in excess of 24. It provided ~50 data points in both morphine and fentanyl analgesia, which slightly exceeds a rule-of-thumb minimum sample size of 30 (Box, Jenkins 1994). Estimated model parameter can also be updated once new data (e.g. from PCA log) have arrived.

Even with limited patient's demand data, frequency and duration of the rare events — when effect compartment concentration exceeds critical threshold — can be predicted. Moreover, analysis of PCA logs allowed to uncover the fact, that periods of concentration exceeding critical threshold are more common, but of a shorter duration, when using fentanyl as a drug, not morphine, what corresponds to well known respiratory depression patterns of these two medications (Wong, 2013). Clinical investigation of these findings is warranted in order to establish individual critical concentration threshold for the respiratory suppression.

Our simulations assumed that starting drug concentration equals zero (figs. 10, 13). However, this is usually not the case, as patients commonly receive loading dose in order to achieve therapeutic concentration fast. This frequent clinical scenario was not accounted for in our simulations, although it is important to keep in mind, that the effect of a loading dose is negligible after two to three half-times of the drug.

Moreover, in current analysis we did not investigate whether or not the stochastic demand

process depends on the average concentration in the effect compartment; we intend to do that in the future.

6. CONCLUSION

The time between analgesia demands can be viewed as a random variable. Time series of a random process of such variable can be expanded to an arbitrary length, even from the limited real data logs; then these series can be analyzed utilizing autoregression moving average model ARMA(p,q) , commonly used in time series forecasting.

Modeling results suggest that periods above critical (toxic) concentration threshold of morphine are less frequent, but of a longer duration as compared to Fentanyl.

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