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Piece-Linear Aggregates for Formal Specification and Simulation of Hybrid Systems: Pharmacokinetics Patient-Controlled Analgesia

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Introduction

Computer aided simulations becomes more and more important in many study fields, from theoretical system characteristics research to practical engineering problem solving. There are two genuinely different ways to characterize and simulate continuous or hybrid systems. The most common is based on time discretization, the other one – by event discretization. The first method is well described in literature and has many use examples. But there are many disadvantages of using time discretization, especially in hybrid system simulations. Besides of high computation cost, which is needed to obtain high accuracy, the use of time discretization is inconvenient, when it is important to observe and react to system's state changes. There are two major formalisms dealing with discreet event systems – Piece Linear Aggregates formalism, and Discreet Event System specification formalism.

We need a method, which solves ODE and allows change function value or function differential instantaneously. To obtain such method we shall adapt Quantized State System, described in DEVS, for use in PLA formalism. Originally QSS method was created for solving ODE for continuous systems simulation. There is already technique of using QSS to solve ODE with instant differential changes, so we only need to add function value change functionality.

Previously described method is needed to create pharmacokinetic model. We need means to solve the ordinary differential equations system, which would allow us to simulate morphine concentration in plasma. Virtual patient behavior and drug injection pump models will be used to imitate the regulation of morphine concentration. This will allow us to calculate time-span, when morphine concentration was in desirable therapeutic level, and when wasn't. Obtained results will be used to evaluate and improve PCA.

Piece linear aggregates formalism

Piece Linear Aggregates is formalism for a discreet event system specification language [1,2]. The systems are represented as a set of interacting piece-linear aggregates. The aggregate object is defined by: Z – set of state values; X – set of input signals; Y – set of output signals; H – transition function; G – output generator function; E' – set of discreet events, where $E = \{E', E''\}$, E' – set of external events, E'' – set of internal events. The aggregate operates in time set $t \in T$. The structure of a state is: $z(t) = (v(t), z_v(t)) \in Z$; where $v(t)$ – discreet part of a state; $z_v(t)$ – continuous part of a state. It denotes the next time of internal event in the current state.

Events occur when system arrives to a determined time point when the next internal event is scheduled or when input signal arrives. Aggregate may give away output signal when internal or external event occur.

Discreet event systems specification formalism

Discreet Event System formalism is consanguineous to the PLA formalism. DEVS defines a systems whose input/output behavior is characterized by a sequence of events. DEVS model process input signal and depending on initial states generates output signals. An atomic DEVS model can be defined by: $M = (X, Y, S, \delta_{int}, \delta_{ext}, \lambda, ta)$, where: X – set of input signals; Y – set of output signals; S – set of state values; δ_{int} – set of internal events; δ_{ext} – set of external events; λ – output function; ta – time advance function.

Each possible state s ($s \in S$) has an associated Time Advance calculated by the Time Advance Function $ta(s)\left(ta(s): S \to \Re_0^+\right)$. The Time Advance is a non-negative real number saying how long the system remains in a given state in absence of input events. The new state is calculated as $s_2 = \delta_{\text{int}}(s_1)$. When the state goes from s_1 to s_2 an output event is produced with value $y_1 = \lambda(s_1)$. When an input event arrives the state changes instantaneously. The new state value depends not only on the input event value but also on the previous state value and the elapsed time since the last transition. No output signal is produced in external event [3].

Hybrid systems specification and simulation

To solve ODEs system we'll adopt and slightly modify Quantized State System method, which was defined by Ernesto Kofman [3]. QSS method computes function's value with a given differential at the fixed quantum grid. The next quantization level time-point is calculated based on given differential value with integrator object. Integrator and quantization function are defined in one aggregate, further Quantized State Integrator (QSI) aggregate. Objects, named f_i, are aggregates, calculating functions differentials from given functions values and input values vectors. The all compound of summation and QSI aggregates forms Quantized State System (Fig 1). Below is given QSI model specification in DEVS formalism:

$$M_1 = (X, Y, S, \delta_{\text{int}}, \delta_{ext}, \lambda, ta), \tag{1}$$

where $X = \Re \times \{inport\}$; $Y = \Re \times \{outport\}$; $S = \Re^2 \times Z \times \Re_0^+ \infty$;
$\delta_{\text{int}}(s) = \delta_{\text{int}}(x, d_x, k, \sigma) = (x + \sigma \cdot d_x, d_x, k + \text{sgn}(d_x), \sigma_1)$;
$\delta_{ext}(s, e, x_u) = \delta_{ext}(x, d_x, k, \sigma, e, x_v, port) = (x + e \cdot d_x, x_v, k, \sigma_2)$;
$\lambda(s) = \lambda(x, d_x, k, \sigma) = (Q_{k+\text{sgn}(d_x)}, outport)$;
$ta(s) = ta(x, d_x, k, \sigma) = \sigma$.

$$\sigma_1 = \begin{cases} \dfrac{Q_{k+2} - (x + \sigma \cdot d_x)}{d_x}, & if\ d_x > 0, \\ \dfrac{(x + \sigma \cdot d_x) - (Q_{k+1} - \varepsilon)}{|d_x|}, & if\ d_x < 0, \\ \infty, & if\ d_x = 0, \end{cases} \tag{2}$$

$$\sigma_2 = \begin{cases} \dfrac{Q_{k+1} - (x + e \cdot x_v)}{d_x}, & if\ x_v > 0, \\ \dfrac{(x + e \cdot x_v) - (Q_k - \varepsilon)}{|x_v|}, & if\ x_v < 0, \\ \infty, & if\ x_v = 0. \end{cases} \tag{3}$$

Given QSS model is enough to simulate a system of ODEs. It can react to function differential values changes, depending on other function values and input signals – *u(t)* – and accordingly calculate function value trajectory.

In order to utilize QSS method for drug injection simulation, we need add function augmentation characteristic. To do that, we add new input vector *d(t)*, which carries function augmentation value. When augmentation of function occurs, function value changes accordingly

$$x_i(t) = x_i(t^-) + d_i(t). \tag{4}$$

The rest of the QSS model is left unchanged. Below is given modified QSS model specification in PLA formalization language:

1. Set of input signals – $X = \{x_v(t_m), y_r\}$ (where $x_v(t_m) \in R$ –function differential; $y_r \in R$ – function augmentation value).
2. Set of output signals – $Y = Q_j(t_m), j = 1 \ldots r$ (where $Q_j(t_m)$ – quantized function value).
3. Set of external events – $E' = \{e_1', e_2'\}$ (where e_1' – new differential value; e_2' – function augmentation value).
4. Set of internal events – $E'' = \{e_1''\}$ (where e_1'' – function reached next quantum step).
5. Discreet component of state – $v(t_m) = \{x(t_m), d_x(t_m), j(t_m), \varepsilon, \Delta Q\}$ (where $x(t_m) \in R$ - function value, $d_x(t_m)$ – current differential, $j(t_m) \in Z$ – number of quantized function value, ε – hysteresis window, $Q_k - Q_{k-1} = \Delta Q$ – quantum value.
6. Continuous part of state – $z_v(t_m) = \{w(e_1'', t_m)\}$ (where $w(e_1'', t_m)$ – time point of next internal event; $w(e_2'', t_m) = \begin{cases} < \infty, d_x(t_m) \neq 0; \\ \infty\ otherwise. \end{cases}$
7. Controlling sequences – $e_1' \mapsto \{\sigma_1\}$, $e_1'' \mapsto \{\sigma_2\}$.
8. Initial state – $v(t_0) = \{x(t_0), d_x(t_0), j(f(x(t_0)))\}$, $z_v(t_0) = \{t_0 + \sigma_2\}$.
9. Transfer operators: $H(e_1')$: (event - new differential value arrived), $x(t_{m+1}) = x(t_m) + e \cdot x_v$ (new function value calculated at the point of event using old differential value), $d_x(t_{m+1}) = x_v$ (new differential assigned), $j(t_{m+1}) = j(t_m)$ (new quantized value number), $w(e_1', t_{m+1}) = t_m + \sigma_1$, where:

$$\sigma_1(t_{m+1}) = \begin{cases} \dfrac{Q_{j(t_m)+1} - (x(t_m) + e(t_m) \cdot x_v)}{x_v}, & if\ x_v > 0, \\ \dfrac{(x(t_m) + e(t_m) \cdot x_v(t_m)) - (Q_{j(t_m)-1} - \varepsilon)}{|x_v|}, & if\ x_v < 0, \\ \infty, & if\ x_v = 0, \end{cases} \tag{5}$$

where $e(t_m)$ – elapsed time after previous event; $H(e_2')$: $x(t_{m+1}) = x(t_m) + e \cdot d_x + x_y$; $d_x(t_{m+1}) = d_x(t_m)$; $j(t_{m+1}) = j(t_m) + \lfloor (e \cdot d_x + x_y) / \Delta Q \rfloor$; $w(e_2', t_{m+1}) = t_m + \sigma_2$; $G(e_2')$: $y = Q_{j(t_m)} + \lfloor x_y / \Delta Q \rfloor$; $H(e_1'')$: $x(t_{m+1}) = x(t_m) + \sigma \cdot d_x(t_m)$; $d_x(t_{m+1}) = d_x(t_m)$; $j(t_{m+1}) = j(t_m) + \text{sgn}(d_x(t_m))$; $w(e_1'', t_{m+1}) = t_m + \sigma_2$.

$$\sigma_2(t_{m+1}) = \begin{cases} \dfrac{Q_{j(t_m)+2} - (x(t_m) + \sigma(t_m) \cdot d_x(t_m))}{d_x(t_m)}, \text{ if } d_x(t_m) > 0; \\ \dfrac{(x(t_m) + \sigma(t_m) \cdot d_x(t_m)) - (Q_{j(t_m)-1} - \varepsilon)}{|d_x(t_m)|}, \text{ if } d_x(t_m) < 0; \\ \infty, \quad \text{if } d_x(t_m) = 0. \end{cases} \quad (6)$$

$$G(e_1''): \; y = Q_{j(t_m)+\mathrm{sgn}(d_x(t_m))} \cdot \quad (7)$$

Pharmacokinetics model specification and simulation

When drug enters the body, numerous processes begin to work on the drug. Pharmacokinetics describes how absorption, distribution, metabolism and elimination influences drug in human body. Different body parts and tissues are represented as sections. The drug distribution between sections is marked as arrows with rate constants [4].

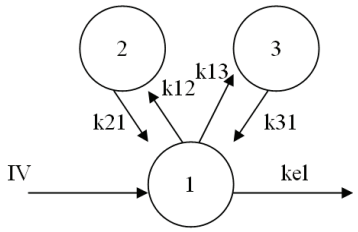

Fig 1. A three compartment pharmacokinetics model; IV – drug intravenous injection, kel – drug elimination constant; 1-compartment is called central compartment

The rate constants shows how quickly drug move from one compartment to another. The drug concentration change is described in first order process:

$$\begin{cases} \dot{X}_1 = k21 \cdot X_2 - k12 \cdot X_1 + \\ \quad + X_3 \cdot k31 - X_1 \cdot k13 - kel \cdot X_1, \\ \dot{X}_2 = k12 \cdot X_1 - k21 \cdot X_2, \\ \dot{X}_3 = k13 \cdot X_1 - k31 \cdot X_3. \end{cases} \quad (8)$$

The values X_1, X_2 and X_3 are drug concentration in blood plasma. The given ODEs system can be easily modeled using QSS model. Additionally, using function augmentation feature (1), drug injection can be implemented. The actual increment value is calculated depending on bolus dose and compartment volume. Drug injection is executed by drug pomp model. Drug demand is executed using virtual patient model with exponential impatience function (3):

$$wait = \begin{cases} e^{2C/C_B}/K + \xi, & \text{if } C < C_B, \\ e^{((C-C_B)/(C_T-C_B)+2)}/K + \xi, & \text{otherwise}, \end{cases} \quad (9)$$

where C – drug concentration in observed compartment; C_B – bottom of therapeutic level of drug concentration; C_T – top of therapeutic level of drug concentration; K – adjustment constant. Virtual patient periodically sends signals to the pump, which are based on current concentration level. It has to be noted, that therapeutics level is not constant and during the day changes. ξ - normal distribution random value from 0 to 80, mean=40

For model simulation used pharmacokinetics parameters: *kel=0.158, k12=0.385, k13=0.233, k21=0.228, k31=0.021*. Central section volume *V=13l*, bolus dose – *1 mg*. Concentration increment on injection, when injection is distributed to 10 parts $\Delta C = 1mg \div 13l \div 10 = 7.69 \mu g / ml$. Pomp lockout – *10 min*. simulation precision – ΔQ*=0.1* [5]. The simulation is performed using Power DEVS 1.0 environment [6]. Time scale showed in minutes.

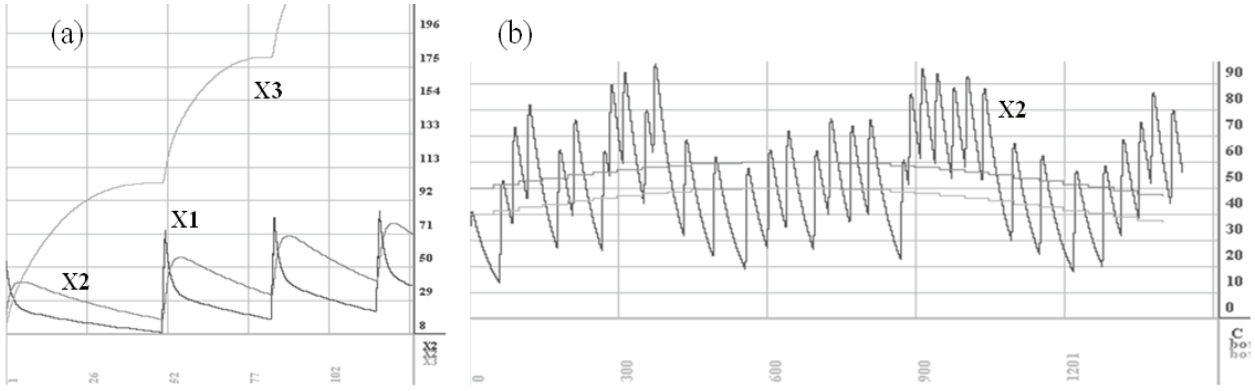

Fig. 2. a) drug concentrations in all apartments; b) drug concentration in 2-nd compartment corresponding to therapeutic level.

Conclusions

QSS method was proved to be convenient for pharmacokinetics model simulation. Slightly modified Quantized State System was easily implemented in PowerDEVS environment. Simulation results shows, that it is very hard to maintain steady drug concentration in therapeutic level using intravenous bolus injections (Fig 2b). During 24 hours period, high concentration's overdrafts detected – up to 100% from therapeutic level. It is possible, that patient demand is inaccurate, so further virtual patient model development needed. In order to get

better simulation efficiency, implementation of QSS2 and QSS3 methods is recommended.

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Piece Linear Aggregates formalism (PLA) for specification and simulation of hybrid systems, when continuous components are described in ordinary differential equations (ODEs). PLA is used to create Quantized State System (QSS) model. QSS is integration based method, created for ODE solving. Since QSS method first was introduced for use in Discreet Event Systems (DEVS) formalism, we adapted it for PLA formalism, which is fundamentally consanguineous to DEVS formalism. Pharmacokinetics model is used as example of hybrid system. Pharmacokinetics is a branch of pharmacology which describes administered drug absorption and distribution in human body. In pharmacokinetics drug distribution is described using ODE. In order to use drug injection in pharmacokinetics model, we have to modify standard QSS model and add some specific capabilities. Result**:** modified QSS method was obtained and used for pharmacokinetic model specification. Simulation of morphine concentration in plasma was performed using real pharmacokinetics data to test Patient-Controlled Analgesia (PCA) method effectiveness. Ill. 2, bibl. 6 (in English; abstracts in English and Lithuanian).

H. Pranevičius, L. Simaitis, M. Pranevičius, O. Pranevičius. Hibridinių sistemų formalus specifikavimas ir imitavimas atkarpomis tiesiniais agregatais: paciento valdomos analgezijos farmakokinetinis modelis // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2011. – Nr. 4(110). – P. 81–84.

Pateikiamas atkarpomis tiesinių agregatų formalizavimas (angl. PLA) hibridinėms sistemoms specifikuoti bei imituoti, kai tolydinės sistemos komponentai yra aprašomi įprastomis diferencialinėmis lygtimis (ĮDL). PLA metodas taikomas kuriant kvantuotų būsenų sistemos (KBS) modelį, kuris yra naudojamas sprendžiant ĮDL. KBS metodą, kuris pirmą kartą buvo panaudotas diskrečioms įvykių sistemoms formalizuoti (angl. DEVS), adaptavome PLA formalizuoti, kuris yra giminingas DEVS formalizmui. Farmakokinetinis modelis straipsnyje naudojamas kaip hibridinio modelio pavyzdys. Farmakokinetika yra farmakologijos šaka, kuri nagrinėja vaistų absorbciją ir pasiskirstymą žmogaus kūne. Vaistų pasiskirstymas aprašomas naudojant ĮDL. Tam, kad būtų galima aprašyti vaistų injekcijas, KBS modelis yra praplėstas. Gauti rezultatai: modifikuotas KBS modelis buvo panaudotas farmakokinetiniam modeliui specifikuoti. Sukurtas imitacinis modelis buvo panaudotas paciento valdomos analgezijos (angl. PCA) metodo efektyvumui tirti. Il. 2, bibl. 6 (anglų kalba; santraukos anglų ir lietuvių k.).