DISCRETE EVENT SIMULATION OF THE PHARMACEUTICAL SYSTEM

Jelenka Savković-Stevanović

[1]University of Belgrade, Faculty of Technology and Metallurgy, Department of Chemical Engineering, 11000 Belgrade, Karnegijeva 4, Serbia

savkovic@tmf.bg.ac.yu (Jelenka Savkovic)

Abstract

This paper presents a new framework for simulation and modeling of pharmaceutical system. Discrete event simulation was employed. Discrete event formalism, one must specify basic models from which larger ones are built and how these models are connected together in hierarchical fashion. The basic models are defined by the structure of the set of external input event types, the sequential state set, the set of external event types generated as output, the internal transition function dictating state transitions due to internal events, the output function generating external events at the output, and the time advance function. To specify modular discrete event models requires that adopt a different view than that fostered by traditional simulation languages. As with modular specification in general a model should be viewed as possessing input and output ports through which all interaction with the environment is mediated. As a case study the medicine transport in the human body was used. An effective model for medicine transport simulation was developed and corresponding parameters were defined. Operation was simulated with derived simulation models. Simulation was carried out for various conditions. Steady state and unsteady state metabolite behaviors were simulated. The obtained results in this paper can be applied in the others engineering domain.

Keywords: Internal transition, Medicine, Biotransformation, Metabolite behavior.

Jelenka Savković-Stevanović. Full professor, University of Belgrade, Faculty Technology and Metallurgy, Serbia. Education. B.Sc. and M.Sc. degree, University of Belgrade, PhD Thesis Technishe Universitat Berlin (West)&University of Belgrade. Research Interest. Chemical Engineering and Process System Engineering; Modeling, Analysis, Synthesis, Design, and Optimization of Chemical Processes; Advanced Numerical Methods, Control and On-line Optimization; Computer Aided Process Operation and Optimization, Design, Safety and Risk analysis; Information System, Data Bases, Expert Systems, Learning Systems; Informatics, Management; Artificial Intelligence, Neural Network and Fuzzy Logic; Biosystems, Bioinformatics, Pharmaceutical Engineering etc.. Other Professional Activities**:** over 800 papers, 7 books, patentees in the field, Consultant in many companies, Member of many professional organizations, Reviewer of many journals, S.C Index over 100. She has cited in numerous monographs and list of the first 100 Scientists in the World 2007 by IBC-Cambridge.

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1 Introduction

A many number of methodologies and modeling/simulation systems have been developed to aid the modeling process in engineering domain[1,2]. On the model development side, the issue of knowledge representation in the form of systematic composition and quantity representation are developed. On the model analysis side, issues involving the automatic evaluation and presentation of simulation results via microcomputer are considered.

Discrete Event System specification formalism and its implementation was introduced last two decades[1-7].

Modelling of the biopharmaceutical system was used as a valuable tool for system operation [8].

In this paper the discrete event simulation model of the medicine transport in the human body was developed and corresponding parameters were defined.

2 Discrete event system modelling

Model construction process is begin by conceptualization, decomposition and specifying of components of the system being modeled. Discrete event formalism provides a means of specifying a entity called system. Basically, a system has a time base, inputs, states, outputs and functions for determining next states and outputs given current states and inputs. The insight provided by the discrete event system formalism is in the simple way that characterized how discrete event simulation specify discrete event system parameters. Having this abstraction, it is possible to design new simulation language with sound semantics that is easier to understand.

Discrete event simulation scheme, an implementation of the discrete event formalism in scheme (Prolog or Lisp dialect) supports building models in a hierarchical, modular manner. This is a system oriented approach not possible in popular commercial simulation languages such as Simscript, Simula, Gasp, Salm, all of which discrete event based.

2.1 Basic model

In discrete event system formalism one must specify basic model from which larger ones are built, and how these models are connected together in hierarchical fashion. In this formalism basic models are defined by the structure,

$$M = < X, S, Y, if, of, tf > \qquad (1)$$

where X is the set of external input event types, S is the sequential state set, Y is the set of external event types generated as output, if is the internal transition function dictating state transitions due to internal (external) events, of is the output function generating external events at the output, and tf is the time advance function.

To specify modular discrete event models requires that adopt a different view than that fostered by traditional simulation languages. As with modular specifications in general, a model should be viewed as processing inputs and outputs ports, through which all interaction with the environment is mediated. In the discrete event case, event determine values appearing on such ports.

More specifically, when external events, arising outside the model, are received on its input ports, the model description must determine how it responds to them. Also, internal events arising within the model change its state, as well as manifest themselves as events on the output ports to be transmitted to other model components.

This basic model contains the following information:

- The set of input ports through which external events are received.
- The set of output ports through which external events are sent.
- The set of state variables and parameters.
- The time advance function which controls the timing of internal transitions.
- The internal transition function which specifies how the system will transit after the time given by the time advance function has elapsed.
- The external transition function which specifies how the system changes state when an input is received, the next state is computed on the bases of the present state, the input port and value of the external event, and the time that can elapsed in the current state.
- The output function which generates an external output just before an internal transition takes place.

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2.2 Multicomponent model

Basic models may be coupled in the discrete event system formalism to form a multicomponent model which is defined by the structure.

$$DN =< D, M_i, I_i, Z_{ij}, Select > \qquad (2)$$

where *DN* is a set of component names for each *i* in *D*, M_i is a component basic model, I_i is a set the influences of *i* and for each *j* in I_i, Z_{ij} is a function the i to j output translation. *Select* is a function the tie-breaking selector.

Multicomponent models are implemented in discrete event simulation scheme as coupled models. A coupled models tell how to couple (connect) several component models together to form a new model. This later model can itself employed as a component in a larger coupled model, thus giving to hierarchical construction. A coupled model contains the following information:

- the set of component,
- for each components its influences,
- the set of input ports through which external events are received,
- the set of output ports through which external event are sent,

The coupling specification consists of:

- The external input coupling which connects the input ports of the coupled model to one or more of the input ports of the components.
- The external outputs coupling which connects the output ports of components to output ports of the coupled model.
- The internal coupling which connects output ports of components to input ports of other components.
- The select function which embodies the rules of employed to choose which of the imminent components is allowed to carry out is next event.

A multicomponent model DN can be expressed as an equivalent basic model in the discrete event simulation formalism. Such a basic model can itself be employed in a larger multicomponent model.

The model construction process is being by conceptualizing decomposition and specialization of components of the system being modeled.

3 The medicine activities description

As a case study medicine influence effect in the human body was considered.

L (medicine) + R (receptor) ⟶

(LR) ⟶ stimulus ⟶ effect

Medicine transfer is consisted of resorbtion, distribution, metabolisms and eliminating process(Fg.1).

Resorbtion means transport medicine from environment into blood circulation. The libo soluble medicine, which do not dissociates resorbing very quickly after oral application and the others applications. In opposite hydrosoluble medicine and which dissociating, they resorbtion slow.

Process resorbtion is carried out mostly by *diffusion* through membrane and than *filtration* through the membrane pores between cells. One medicines group by active transport resorbs, over specific carrier.

After resorbtion medicine distributes non uniformly in tissue and organs. Medicine distribution depends of libosolubilty, ability protein plasma connection, and ability tissue connection.

Metabolism is medicine biotransformation in liver by enzymatic systems which it has decomposed and metabolite formed. These metabolite are soluble in water and so eliminating urine. The most important are oxidizes, esterase, transferases, flavin enzyme etc..

Individual dose can be minimal, maximal therapy dose as well as toxically dose. Dose increasing make numerous undesired effects of medicine.

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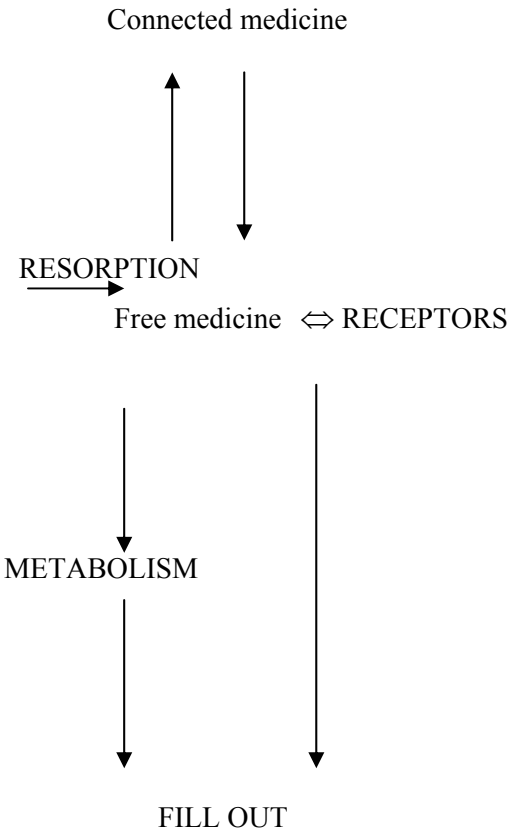

Fig.1 A medicine transport scheme

Medicine application can be in the liquid form, powder, tablet, drug and the others forms.

4 Discrete event simulation

Multifacetted methodology denotes a modeling approach which recognizes the existence of multiplicities of objectives and models in any simulation project. It provides formal representation schemes that support the modeller in organizing the model construction process, in aggregating partial models, and in specifying simulation experiments. Modelling objectives drive tree fundamental processes in the methodology, they facilitate the representation of model's structures, retrieval, and manipulation of structures, the specification of model's behavior, and the specification of experimental conditions under which models are evaluated by a simulation study.

A model is synthesized from components stored in the model base. A synthesis specification is the results of pruning a substructure from the system entity structure. Pruning results in a model structure candidate for a best match to the set of modelling objectives. It can be viewed as a search through the space of candidate solutions to the problem. Production rules represent the knowledge consisting of modeling objectives, coupling constraints user's requirements and performance expectations. The aim of pruning is to recommend plausible candidates for an optimal solution to the problem with respect to the requirements and constraints.

To provide the rules that guide pruning of the system entity structure the following steps are required: specify of rules for selecting an entity for each specialization, for any entity with several aspects, specify rules for selecting a unique aspect, and for each aspect specify rules that ensure that the entities selected from specializations are configurable.

The above rule set constitute a knowledge base for the inference engine that prunes a system entity structure for a particular applications domain. Pruning generates a model composition tree, structure that contains all the information needed to synthesize a model in an hierarchical fashion from its segment model components. To support the model construction process a software tools need to use.

5 System entity structure specialization

A model described by the structure "M" represent an open system since it maintains flows across in its boundary as depicted in Fig.2.

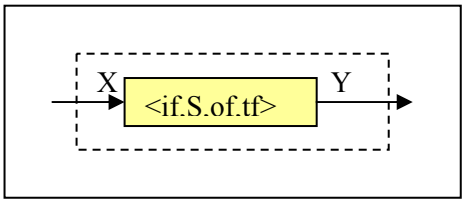

Fig.2 A stream segment

The input set X , where $X = (x_1, x_2, x_3, \ldots, x_n)$ and $x_i \in R$, represents the part of the interface through which the environment communicates with the system. The x_i elements of X are the transport characteristics downstream from a given segment. Conversely, the output set Y, where $Y = Y(y_1, y_2, y_3, \ldots, y_n)$ and $y_i \in R$, represents the part

of the interface through which the system communicates with the environment.

The inputs are mapped into system internal states represented by state variables, by the transition function:

$$if : X \rightarrow S$$

and are transformed outside the model by an output function:

$$of : S : tf \rightarrow Y$$

The model "M" can be called atomic or segment that indicate it is not further decomposed. In the system under study, the elements of X and Y can be, for example, medicine resorbtion, distribution, metabolism, filling out, indicators, and parameters characteristics. Transition X into S can be expressed in the form of a differential equation which returns the output Y.

At the higher level of system specification one can consider a number of segment models described by the M structure, coupled into the non-branching network of segment models as illustrated in Fig.3. Such a network forms a coupled model C which consists of segment models. Linking of segment models is realized by the interface mapping function. Circles symbolized the interface mappings.

At the next higher level of system specification, one can consider a number of coupled models, where each model represents a transport component of medicine, aggregated into a hierarchically coupled model. Such a model can represent a branching network of medicine route as illustrate in Fig.4.

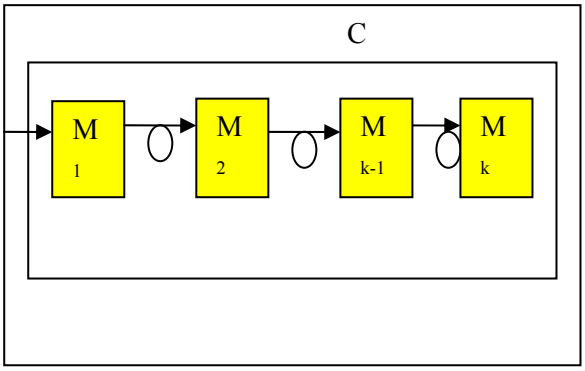

Fig. 3 Network structure for the coupled model C representing a single, non-branching stream

A coupled model of the system entity for the medicine transport can be defined as a structure:

$$C =< (X_i, Y_i, M_i) I_i, Z_{ij}, Select > \quad (3)$$

where X is the set of input sets, $X \in X_k$, Y is the set of the output sets $Y \in Y_k$, M is a set of models, where models can be of $M \in M_k$ and of coupled type C, $C \in C_k$, *I, Z, and Select* can be defined as a common interface mapping function. The role of the mapping function is to translate outputs into inputs.

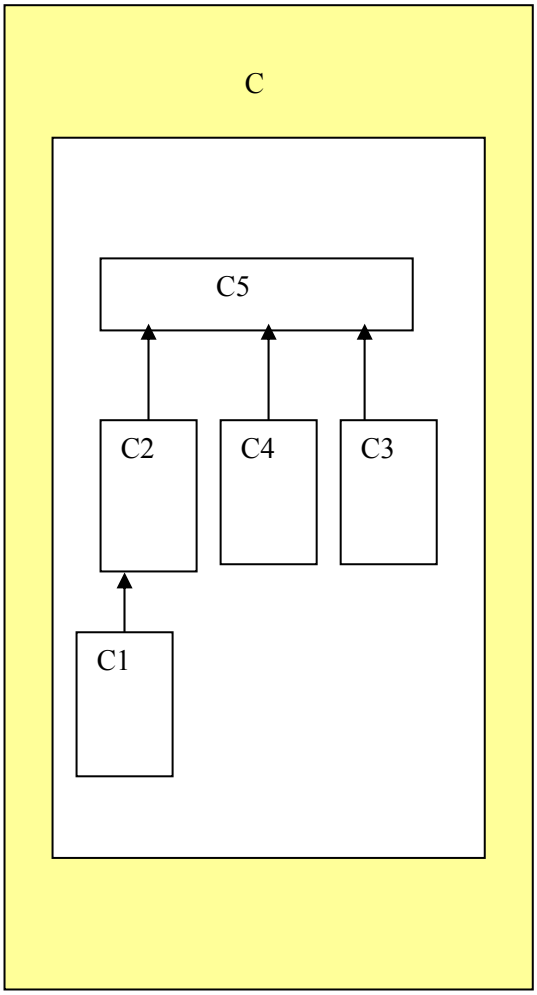

Fig.4 Coupled model C representing a tree structure of the branching network

The entity structure for a single constituent model represents a model space from which alternative configurations of a single constituent model can be derived.

Each specialized entity has the attached variable number of segment models which, together with the multiple specialization, represent the number of segments partitioning upon the segmentation criteria (topological, biological etc.) for a given

entity, and a number of single segment, single constituent model.

Each of four entities can be specialized into subentities denoting a constituent specify type of segment model. They are the primitives from which the model description of a system is assembled. The segment models can be expressed in a special formalism depending on the problem at hand. Typical specifications include differential equations, finite difference equations, or discrete event system specification. In the proposed approach of this paper it is employed the discrete event specification of segment models [1,2]. The discrete event formulated segment models are retrieved from the model base as the leaf entities of the composition tree. Linking of the retrieved segment model into in a system model is accomplished through coupling and is guided by constraints.

6 Selection an appropriate model

A coupled model of the system medicine transport can be defined as the following structure as shown in Fig.5.

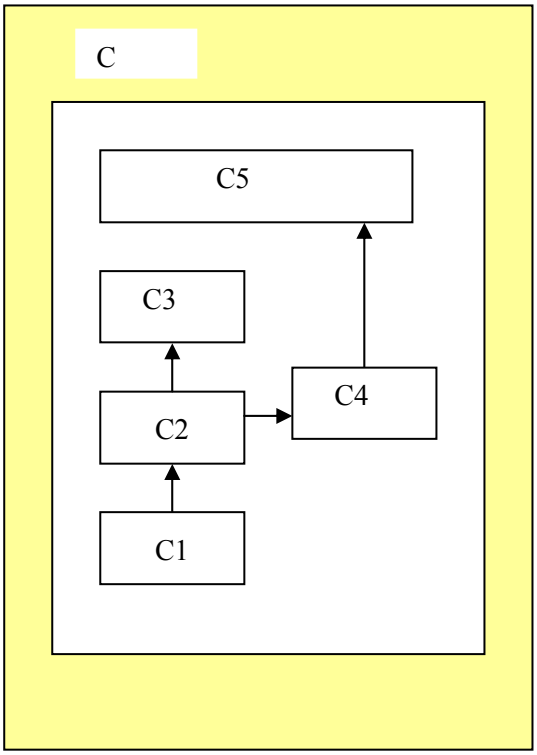

Fig.5 Coupled model C representing a tree structure of the branching network of a medicine transport

The base rules for model selection, and procedures for model coupling constitute the core of a rapid modeling environment in which a case specific model can be promptly built.

In Fig.5 a prototype of the entity structure tree for the medicine transport model is shown. The root entity named "medicine transport" denotes a single constituent model a section of it. It is specialized into four entities: resorbtion, distribution, metabolite formation and separation.

In order to choose the appropriate segment model for each given segment, can be employed rule based pruning. The following variables expressed by attached variables are used in this process:

- medicine concentration in the body D_b,

- medicine concentration which existing as a metabolite in the body, D_m,

- medicine concentration which eliminating in metabolite form D_{me},

- over concentration which eliminating ,D_e .

The four attached variables can take on the following values:

- medicine concentration in the body <low, high>,

- medicine concentration which existing as a metabolite in the body (low, high),

-medicine concentration which eliminating in metabolite form <low, high>,

-over medicine concentration which eliminating <low, high).

The heuristics involving the combinations of values received by the attached variables can be conveniently expressed in production rules. Production rules comprising the rule base on the model management system prototype are used pruning of the entity structure tree. Some pruning rules can be specified as follows:

Rule#1

IF medicine concentration in the body <low>

AND over medicine concentration eliminating <low>

THEN "Medicine transport" segment- model =

metabolite model.

Rule#2

IF medicine concentration which existing as a metabolite in the body <low>

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AND over medicine concentration which eliminating <high>

THEN medicine concentration which eliminating in metabolite form<high>

AND recommended segment- model=eliminate model.

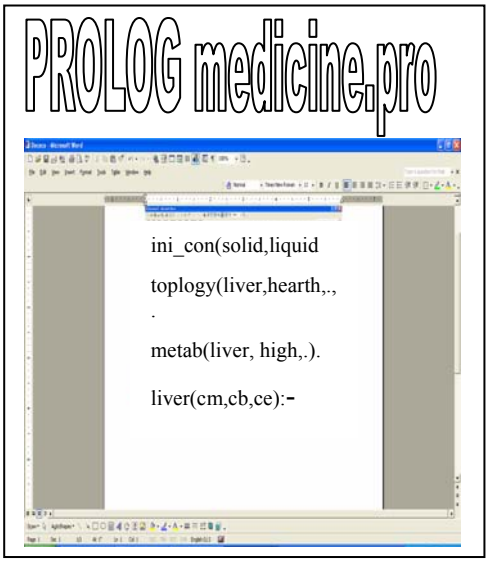

Fig.6 Production rules implementation by predicate in *Prolog*

7 Implementation

The entity structure tree modeling of stream or its section was implemented in the *Prolog* software environment. A segment-model template employed to calculate discrete values of variables and indicators for a given segment.

The scheme captures the following three relationships: decomposition, taxonomy, and coupling. Decomposition knowledge means that the structure has schemes for representing the manner in which an object is decomposed into components. Taxonomic knowledge is a representation of the kinds of variants that are possible for an object. The synthesis (coupling) constraints impose a manner in which components identified in decompositions can be connected together. The selection constraints limit choice of variants of objects determined by taxonomic relations.

Beyond this, procedural knowledge is a available in the form of production rules realized in *Prolog* environment (Fig.6). They can be manipulate the elements in the system domain by appropriately selecting and synthesizing the domain's components, it is called pruning. Pruning results is a recommendation for a model composition tree or the set of hierarchically arranged entities corresponding to model components. A composition tree is generated from the system entity structure by selecting a unique component for specializations and a unique decomposition for an entity with several decompositions.

The final step in the framework is the evaluation of models derived from composition tree. The model construction process involves the specification of the static and dynamic structure.

Performance of models is evaluated through simulation.

8 Simulation results

Simulation was run to assess the performance of a discrete event scheme based specification for medicine transport models. The results of simulation runs were then compared with the observed values of drug concentration changes versus time.

9 Conclusions

The aim of this paper has been a framework construction for modelling support of medicine release in the human body. A discrete event model for medicine transport simulation was derived.

Models have several submodels represented and managed by the system entity structure. The goal driving pruning of the structure is the basis for model selection and composition.

The potential application of this framework can be used the others areas in pharmaceutical engineering.

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Notation

D-concentration (dilution)

DN -component names

I_i - set the influences

if - internal transition function

L- medicine

M_i- component basic model

of- output function

R-receptor

S-sequential state set

Select-tie breaking selector

tf - time advance function.

X - set of external input event types

Y- set of external event generated as output

Z_{ij} -function of output translation

Subscript

b- body

m-metabolite

e-eliminated

me-eliminated metabolite

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