MEDINFO 2015: eHealth-enabled Health
I.N. Sarkar et al. (Eds.)

doi:10.3233/978-1-61499-564-7-549

A Baseline Patient Model to Support Testing of Medical Cyber-Physical Systems

Lenardo C. Silva[a], Mirko Perkusich[b], Hyggo O. Almeida[a], Angelo Perkusich[c], Mateus A. M. Lima[c], Kyller C. Gorgônio[a]

[a] *Embedded Systems and Pervasive Comp. Lab, Federal University of Campina Grande, Campina Grande, Brazil*
[b] *Federal Institute of Paraíba, Monteiro, Brazil*
[c] *Electrical Engineering Department, Federal University of Campina Grande, Campina Grande, Brazil*

Abstract

Medical Cyber-Physical Systems (MCPS) are currently a trending topic of research. The main challenges are related to the integration and interoperability of connected medical devices, patient safety, physiologic closed-loop control, and the verification and validation of these systems. In this paper, we focus on patient safety and MCPS validation. We present a formal patient model to be used in health care systems validation without jeopardizing the patient's health. To determine the basic patient conditions, our model considers the four main vital signs: heart rate, respiratory rate, blood pressure and body temperature. To generate the vital signs we used regression models based on statistical analysis of a clinical database. Our solution should be used as a starting point for a behavioral patient model and adapted to specific clinical scenarios. We present the modeling process of the baseline patient model and show its evaluation. The conception process may be used to build different patient models. The results show the feasibility of the proposed model as an alternative to the immediate need for clinical trials to test these medical systems.

Keywords:

Baseline Patient Model; Statistical Analysis; Simulation; Testing; Medical CPS.

Introduction

In the health care domain, traditional clinical scenarios are seen as *closed-loop systems* in which the caregivers are the *controllers*, medical devices act as *sensors* and *actuators*, and patients are the "*physical*" *plants*. *Medical Cyber-Physical Systems* (MCPS) modify this vision by introducing additional computational entities that help the caregiver control the "*plant*", i.e., decision support [1].

Due to the insufficient understanding of human body dynamics in response to any treatment, MCPS development is more complex than traditional systems [1]. Since patient safety is the main concern of an MCPS, they must be carefully tested before being released to the market. However, to allow a MCPS to be directly tested with real patients, it is necessary to have an alternative solution for developers to identify critical errors and prevent serious harm to test patients. Therefore, a pre-validation step must be added to the validation process to anticipate the identification of these errors.

Nowadays, MCPS designers, more specifically the manufacturers of medical devices, use documents provided by regulatory agencies related to health, such as the FDA[1]. They specify standards for safety and performance to minimize design risks and to ensure the effectiveness of products.

The importance of having a formal patient model is the capability of generating relevant test cases to validate an MCPS. This process aims to examine if the therapies provided by these systems are adequate and ensure patient safety by adapting their behavior given the patient's current state [2].

The concept of a *virtual patient* described by Agur [3] is related to a complex set of mathematical models and a set of parameters that represent the dynamics of biological, pharmacological, and pathological processes in the body of a patient under medication. In the literature, we can find some related work about computational modeling of patients. For instance, Jiang et al. [2] provide an environment for closed-loop testing, whose patient model, specifically a formal model of the human heart, is the control center of a cardiac pacemaker system. The goal is to evaluate the device's operation safety and effectiveness based on the patient condition.

Other recent research is presented by Van Heusden et al. [4], which proposes an artificial pancreas model for patients with type 1 diabetes mellitus based on control theory. Its goal is to improve glucose control in such patients. One of its advantages is that it incorporates the patient's medication (insulin) reaction.

Lastly, Khan et al. [5] present a glucose control system to prevent hypoglycemia as a consequence of medication administration. In this work, the patient model (i.e., an artificial pancreas) establishes a relationship between certain vital signs such as heart rate and skin impedance in the blood glucose level control.

The aforementioned patient models either focus on variables of interest for specific clinical scenarios or neglect the relationship between the four human being's vital signs: heart and respiratory rates, blood pressure, and body temperature. Therefore, the absence of these aspects contradicts the actual behavior of human beings. So, these models have limited applicability to other scenarios.

In this paper, we propose a formal patient model to be used as a basis for developers to validate MCPS solutions without risking compromising patients' health if the system fails. Our model provides parameters to define patient profiles, and correlates the main vital signs to simulate the patient's health condition. The vital signs are represented by statistical regression models which were integrated to provide the patient's model dynamics.

[1] United States Federal Food and Drug and Administration - http://www.fda.gov/

The key feature of the baseline patient model is the ability to be adapted to various specific clinical scenarios, promoting reuse. The main contribution of this paper is to present the conception process used to develop the baseline patient model of the model-based architecture proposed by Silva et al. [6].

Materials and Methods

The vital signs and physiological parameters provided by our patient model are based on thresholds. They are generated by regression models. We established the parameters that defined the thresholds in accordance with Clinical Guidelines, such as [7-9]. These clinical guidelines also were used to help identify the probable regression model predictor variables for each vital sign considered in our baseline patient model. Also, we applied some rules on the real patient data obtained from the *MIMIC II Clinical Database v2.6*, whose access was authorized by the PhysioNet.org [10]. This data set contains clinical data from Intensive Care Unit (ICU) patients and the rules were applied to characterize the population of interest for study. The baseline patient model conception process consists of: (1) Statistical analysis and (2) Computational modeling.

Statistical Analysis

We used the same database to characterize a population of individuals. We applied inferential statistical techniques such as a *Generalized Linear Model* (GLM) to obtain regression models. These models are used to predict the observed signs to be incorporated in the baseline patient model.

In the GLM, is assumed that the response variable follows the exponential family distribution, and the predicted values are calculated from a link function [11].

The population contained 38,141 observations from 2,245 patients, in which approximately 37.4% were female and 62.6% male. From this population, we obtained a sample with one observation of each patient in the moment they were admitted to the ICU. We present a summary of the process to characterize the population of interest and sampling procedure in Figure 1, whose sample size represents only approximately 0.001% of total population. Table 1 presents descriptive statistics about the data set extracted from this process.

Table 1 – Statistics of the Population of Interest

Variable	Mean	Std. Dev.	CV [a]	Min.	Max.
hr	86.863	14.473	0.167	42.00	150.00
sbp	115.447	20.403	0.177	62.00	205.00
rr	17.552	5.619	0.320	8.00	38.00
pt	36.926	0.879	0.024	31.70	41.44
gl	129.631	30.444	0.235	47.00	188.00
weight	83.727	20.826	0.249	33.00	200.00
height	169.781	10.427	0.061	124.50	231.10

[a] Coefficient of Variation; Std. Dev. = Standard Deviation, Min = minimum, Max. = Maximum.

We selected eight variables for the statistical analysis: *gender*, *weight* and *height* as demographic variables; heart rate (*hr*), respiratory rate (*rr*), systolic blood pressure (*sbp*), and body temperature (*pt*), as vital signs; and blood glucose level (*gl*), as a physiological parameter. It is worth mentioning that a variable for diastolic blood pressure was not used in this analysis because it depends on *sbp* variable. The strong correlation between these variables may cause a multicollinearity problem [12].

Given that the population of interest was defined and one sample was obtained, we extracted four regression models, one for each vital sign in study. The regression models were evaluated using the following statistical measures: (a) determination coefficient (R^2); (b) square of the linear

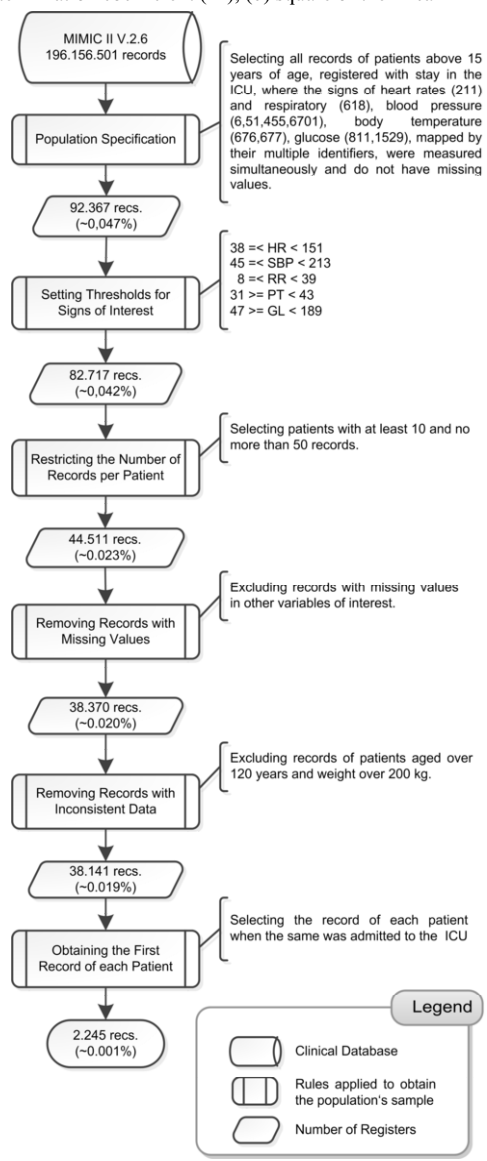


Figure 1 – Process to characterize the population of interest

correlation coefficient (R^{2*}) between response variable and adjusted values. Both measures were used to indicate the data variability explained by the regression model. Table 2 presents the results for each model, with confidence level of 95%.

Table 2 – Metrics to Evaluation of the Regression Models

Regression Model	R^2	R^{2*}
GLM_HR	0.310	0.332
GLM_SBP	0.477	0.511
GLM_RR	0.414	0.489
GLM_PT	0.480	0.480

R^2 = Determination Coefficient, $R^{2*} = COR(y, \hat{\mu})$

As human beings have many variables to be observed, and different individuals react differently to the same drug [13], we believe the results are satisfactory.

It is noteworthy that to predict the respiratory rate we used a *Normal Inverse Model* in the form of Equation (1) with canonical link function defined in Equation (2):

$$\hat{\mu} = \hat{\eta}^{-\frac{1}{2}} \quad (1)$$

where μ is the mean frequency of respiratory rate that we want to model and

$$\hat{\eta} = \hat{\beta}_0 + \sum_{i=1}^{4} \hat{\beta}_i X_i + \sum_{j=2}^{4} \hat{\beta}_{5j} X_{5j} + \sum_{i=6}^{7} \hat{\beta}_k X_k . \quad (2)$$

is the systematic component where β_0 corresponds to the intercept and $\beta_{1\text{-}7}$ to the coefficients of the variables *hr*, *sbp*, *pt*, *gl* and *group*, as well as the interactions between *hr*·*sbp* and *hr*·*gl*, respectively. The *group* variable is used according to the patient classification, given the values of the other predictor variables. Therefore, the X_{5j} variable assumes the value *1* according to the *j* value that specifies the patient group, and the value *0* for all other possible *j* values.

The usage of the *Normal Inverse Model* means that the higher the value of the systematic component, the lower the value of the average estimated respiration rate. Hence, higher values of variables with positive coefficients lead to lower values of *rr*. On the other hand, higher values of variables with negative coefficients, lead to higher values of *rr*.

For the remaining regression models, we used a *Gamma Linear Regression Model* given by Equation (3), whose variance function is more restrained than the *Normal Inverse Model*:

$$\hat{\mu} = \hat{\eta}^{-1} \quad (3)$$

Where μ is the mean frequency of vital signs that we want to model; in this case *hr*, *sbp* and *pt*. Since the workflow to create regression models for all vital signs is similar, these regression models were omitted.

Computational Modeling

To design the baseline patient model we used the AOD paradigm, i.e., a design methodology based on components called *actors* [14]. This methodology represents a formal model of concurrency in which an *actor* is a computational agent that has an independent thread of control and communicates through asynchronous message exchange. We used the *Ptolemy II* modeling tool, which is an extensible AOD-based software framework that supports experimentation, to build the models. Its emphasis is in concurrent components, using well-defined computation models that govern the interaction among these components [15].

The baseline patient model considers the four main vital signs: heart rate (*hr*), respiratory rate (*rr*), arterial blood pressure (*bp*) and peripheral body temperature (*pt*). This patient model consists of the integration among the regression models that represent each one of these vital signs. Such regression models in the AOD paradigm may be modeled as shown in Figure 2, whose regression model is for respiratory rate (*GLM_RR*).

We integrated the regression models to the baseline patient model (see Figure 3) to allow interaction among them and provide the behavioral dynamics to the patient's model. Thus, the user may change the value of a specific vital sign during simulation and automatically the values of other vital signs will be modified according to their respective regression models.

We present part of the elaborated model that incorporates the patient characteristics and the regression models of the four vital signs in Figure 3a. We have highlighted the following key elements: **(1)** the patient model configuration parameters,

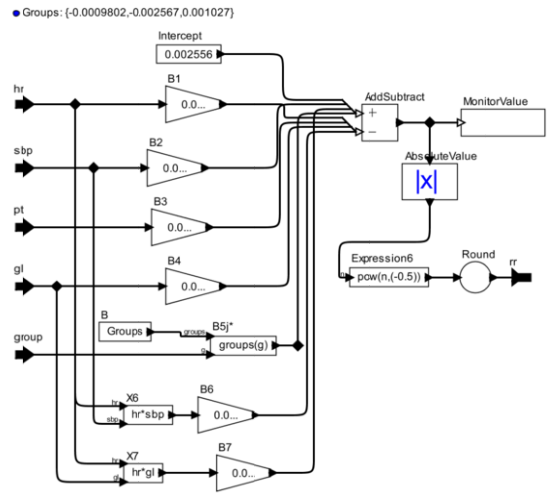


Figure 2 – GLM_RR for the Patient Model

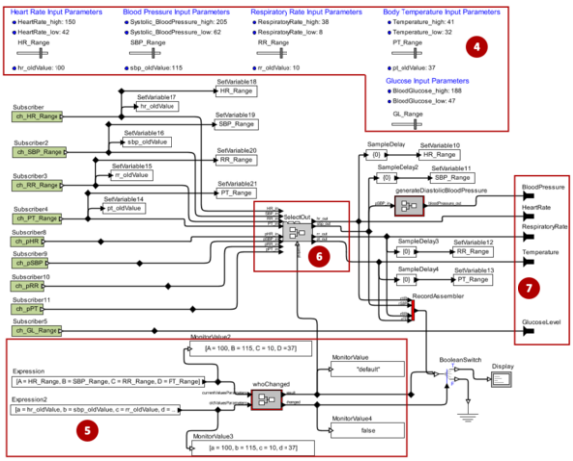
including the *Continuous Director* element that determines their execution semantics; **(2)** the substructure of the model that specifies the vital signs' initial values and physiological parameters represented in the model; **(3)** the elements labeled by the *GLM_<vital_sign>* pattern that denote the regression models for each vital sign modeled. The model parameters are the basis for generating the values for the vital signs provided by the patient model. Moreover, the specifications of the thresholds of each vital sign allow the developer to manipulate them during the simulation, to represent different health conditions for the patient's model. Consequently, the behavior analysis of the MCPS may be carried out for various situations.

We present the second part of the baseline patient model in Figure 3b. The highlighted elements are: **(4)** the parameters that define thresholds for each signal so that these signals remain within the range of values considered in the conception of regression models; **(5)** the logic used to identify which vital sign was changed by the user at a given time during the model simulation; **(6)** the component developed to select the model's correct output according to user intervention; and **(7)** ports that provide the patient model communication interfaces with the medical devices models for data acquisition from these devices.

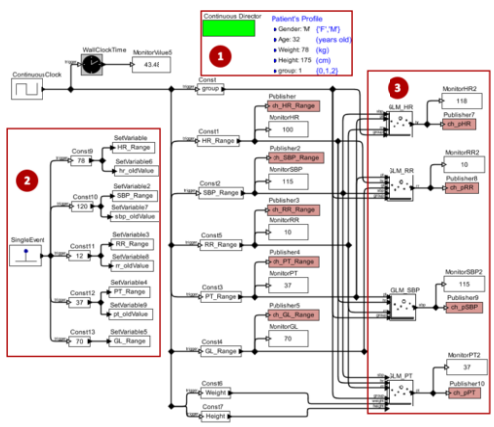
Notice that the patient model only has *output ports* for vital signs and physiological parameters. To receive *feedback control actions* from actuator models, *input ports* must be added to the patient model through the *Ptolemy II* framework. Additionally, the patient model must be adapted to represent the pharmacokinetic model's dynamic behavior corresponding to the drug type to be administered.

Results and Discussion

We used *Diagnostic Plots* to assess the regression models. In Figure 4 we present the envelope (*Normal Q-Q Plot*), leverage points, influential points and residuals versus fitted values plot for *rr*. Due to space constraints, we omit the results from the other vital signs.



(a) Regression models to estimate vital signs data



(b) Submodel to provide information to the medical devices' models

Figure 3 – Baseline Patient Model

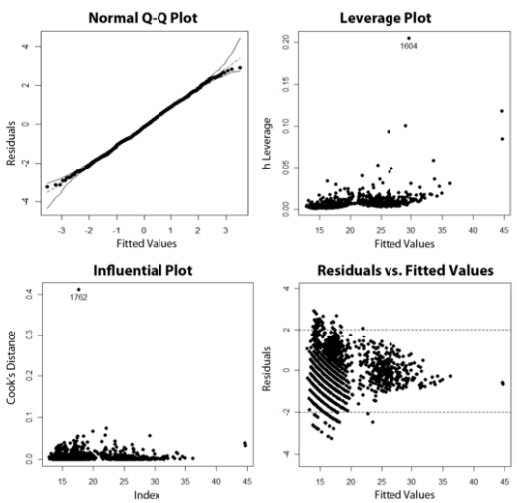


Figure 4 – Diagnostic Plots for the GLM_RR

Envelope plots are useful to check the regression models' fit. Leverage points may interfere in adjusted values close to them and regression coefficients estimate. Influential points may interfere in the model parameters' estimated values. The residuals versus fitted values plot is useful to assess the assumptions of the regression model (e.g., any visible trends would show a dependence of errors on the predictor variable).

After analyzing the diagnostic plots of each regression model, we concluded that the obtained models reasonably explain the vital sign they represent. Thus, the regression models were statistically validated. This means that the synthetic data generated by the patient computational model are compatible with the sample used in statistical analysis. The simulation of the proposed patient model in a specific clinical scenario is out of the scope of this paper.

Conclusion

In this paper, we presented a formal model to provide context information (e.g., profile and vital signs) of a patient, the so-called baseline patient model. We used regression models to generate a set of vital signs (heart rate, respiratory rate, blood pressure and body temperature) that compose the patient model.

The use cases of this patient model are to simulate patients' health conditions to support testing of MCPS. With its extension, it will be possible incorporate it to the context of specific clinical scenarios. This will provide the developer an important tool to identify failures in the system, and will also assist health experts in the strategy planning in the treatment of patients. However, its extension depends on the experience of the MCPS developer, as well as the knowledge of the medical expert that may help in this process.

Our solution can adapt and be used in a variety of clinical scenarios. These scenarios can simulate different medical contexts, helping in the validation process of medical systems. The approach applied to build the baseline patient model may be used to create different patient model types, but will require the use of different samples or clinical data sources. Furthermore, it might be necessary to define other patient use cases to validate the MCPS given that the patient model presented was built using only data of ICU patients.

A potential limitation of this patient model is its restriction to the input values for predictor variables. Whenever these values exceed their thresholds, the accuracy of the regression models used to generate the synthetic data for vital signs might decrease.

In the future, we will show how to extend the patient baseline model for specific clinical scenarios. This will require the incorporation of dynamics of the action of drugs in the patient's body to the model. Thus, the medical device models may act on patients' behavior, causing it to react to such actions. Lastly, we will request that health experts perform external validation of the patient model.

Acknowledgments

The authors would like to thank to CAPES, PPgCC-COPIN and IFPB for the financial support of this research, as well as LANEST-UFCG for the statistical consultancy service.

References

[1] Lee I, Sokolsky O, Chen S, Hatcliff J, et al. Challenges and Research Directions in Medical Cyber-Physical Systems. Proceedings of the IEEE 2012: 100(1): 75-90.

[2] Jiang Z, Pajic M, and Mangharam R. Cyber-Physical Modeling of Implantable Cardiac Medical Devices. Proceedings of the IEEE 2012: 100(1): 122-37.

[3] Agur Z. Interactive clinical trial design. In Faltin F, Kenett R, Ruggeri F, eds. Statistical Methods in Healthcare: John Wiley & Sons, Ltd., 2012; pp. 78-102.

[4] Van Heusden K, Dassau E, Zisser HC, Seborg DE, and Doyle FJ. Control-Relevant Models for Glucose Control Using a Priori Patient Characteristics. IEEE Transactions on Biomedical Engineering, Jul 2012; pp. 1839-1849.

[5] Khan SH, Khan AH, and Khan ZH. Artificial Pancreas Coupled Vital Signs Monitoring for Improved Patient Safety. Arabian Journal for Science and Engineering, Nov 2013; pp. 3093-3102.

[6] Silva LC, Perkusich M, Bublitz FM, Almeida HO, and Perkusich A. A Model-based Architecture for Testing Medical Cyber-physical Systems. In Proceedings of the 29th Annual ACM Symposium on Applied Computing 2014; New York: NY, USA: ACM; pp. 25-30.

[7] Buxton AE, Calkins H, Callans DJ, DiMarco JP, others.

[8] Chobanian AV, Bakris GL, Black HR, Cushman WC, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003: 42(6): 1206-52.

[9] McGee SR. Evidence-based physical diagnosis. In. St. Louis: Saunders Elsevier, 2007; pp. 187-202.

[10] PHYSIONET. Physionet.org. [Online].; 2012 [cited 2012 Nov. 05. Available from: http://physionet.org/mimic2.

[11] Paula GA. Modelos de Regressão com Apoio Computacional São Paulo: IME-USP, 2010.

[12] Gavish. B, Ben-Dov IZ, and Bursztyn M. Linear relationship between systolic and diastolic blood pressure monitored over 24 h: assessment and correlates. J Hypertens 2008: 26(2): 199-209.

[13] Katzung BG, Masters SB, Trevor AJ, eds. Basic & Clinical Pharmacology. 12th ed.: McGraw-Hill, 2012.

[14] Agha G. Actors: a model of concurrent computation in distributed systems Cambridge: MA, USA: MIT Press, 1986.

[15] Berkeley UC. The Ptolemy Project: heterogeneous, modeling and design. 2012.

Address for correspondence

Lenardo Chave e Silva, Embedded Systems and Pervasive Computing Lab., UFCG, 882 Aprígio Veloso Street, Universitário, Campina Grande, PB, Brazil. Email: lenardo.silva@embedded.ufcg.edu.br.