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Real-Time Physiological Simulation and Modeling toward Dependable Patient Monitoring Systems

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Abstract. We present a novel approach to describe dependability measures for intelligent patient monitoring devices. The strategy is based on using a combination of methods from system theory and real-time physiological simulations. For the first time not only the technical device but also the patient is taken into consideration. Including the patient requires prediction of physiology which is achieved by a real-time physiological simulation in a continuous time domain, whereby one of the main ingredients is a temporal reasoning element. The quality of the reasoning is expressed by a dependability analysis strategy. Thereby, anomalies are expressed as differences between simulation and real world data. Deviations are detected for current and they are forecasted for future points in time and can express critical situations. By this method, patient specific differences in terms of physiological reactions are described, allowing early detection of critical states.

Keywords: Physiological Simulation, Real-Time, Risk Assessment, Patient Specific Modeling, Dependability

1. Introduction

Physiological modeling and simulation are very useful for various purposes in the medical domain (e.g. medical education, medical training simulators, interventional planning and understanding of physiological phenomena therein; as well as for prognostic modeling). Due to the multidimensionality of the problem, normally the overall modeling is a complex task (>4000 variables for quantitative circulatory physiology (QCP) [1]). In addition there are substantial uncertainties in the modeling data. Due to computational complexity, many approaches only apply population models and thus restrict to statistical information. Applying individualized physiologically based models including metabolism and transportation for different organs and tissues, however, allows for individualized simulations. Compared with population model based simulations, these individualized approaches are thus expected exhibiting the same advantages as we see them when comparing physiological based pharmacokinetic (PBPK) [2] with population pharmacokinetic (PopPK) [3] approaches.

We provide a new hybrid approach by combining stochastic modeling with integrative system, which provides realistic, patient individual and real-time capable simulations of physiological reactions to induced events e.g. given by medication or interventions. We present a novel methodology how approaches from system theory and dependability analysis therein can be applied to use real-time physiological simulations for patient risk assessment based on standard monitoring of high frequency physiological vital parameter addressing intelligent monitoring systems in clinical workspace.

2. State of the Art

One can find various micro and macro models considering special physiological interactions in human body. The main strategy focuses on using integrative models formulated by systems of ordinary differential equations (ODE) [4]. By Physiome [5] and QCP [1] a substantial step towards a platform for overall physiological modeling was established. Additionally, by these platforms it was possible for combine different smaller models into overall physiological descriptions and a general modeling language is supported, which allows building model data bases. The disadvantages are the lack of supporting real-time simulation, overcome model complexity issues as well as uncertainty of model parameters.

Thus, stochastic approaches are considered in our ap-proach as well. Especially dynamic Bayesian networks (DBN) [6] (as generalization of Markovian decision processes) are selected for medical simulations [7]. As shown earlier, the combination of integrative and stochastic approaches are well suited for real-time and realistic physiological simulations [8], and thus are essential as a basis for our risk assessment approaches.

System dependability, considered as a mixture of availability, reliability, safety, confidentiality, integrity and maintainability [9], is, unfortunately, not defined uniquely in literature and often it is system and mission specific dealing with errors, faults and failures. For dynamic systems, dependability is formally specified by the description of system behavior, such that the system trajectory remains in a certain predefined region/boundary [10]. Due to the fact that human factor is an important part of a monitoring system [11], diverse approaches consider the human in the context of dependability analysis [12]. Yet, no approach considers the patient's dependability additionally to technical systems so far. Even in the concrete field of patient monitoring, recent work on risk analysis only considers the system without patient [13]. We consider this as a systematic weakness, which we want to address and overcome with our new methodology by applying methods from systems theory in combination with dynamic simulations to provide a better and sophisticated way for risk assessment. The feasibility of our dependability strategy is demonstrated in a simulator environment extending a vital parameter monitoring system from the intensive care unit (ICU).

3. Methods

3.1. General Framework

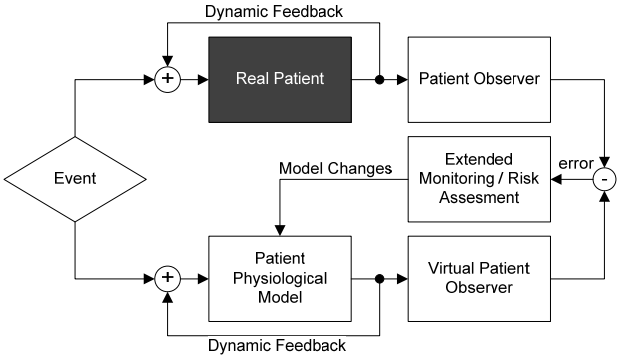

Fig. 1: System theoretical view: Event based real-time simulations have been used to simulate and predict the outcome of patient's vital signals, which can be measured/observed. The differences in signal outcome of the real and simulated patients have been used to describe dependability measures and provide an extended monitoring system.

Fig. 1 shows an extended patient monitoring represented in a system theoretic way. The upper part of the diagram shows *real patient* block, being a black box model and including some observable and non-observable internal states. This block describes the physiology (behavior) of the patient, in other words the patient's health states, which could be multiparametric. According to system dynamics – subsequent patient states are correlated to earlier ones – a *dynamic feedback* loop is necessary. As mentioned before, we are unable to observe and measure all patient internal parameters, which is depicted by a *patient observer* block. In the lower part of the diagram a corresponding network is found, which is a description of the virtual model, being a simulation model of the real patient. This system is, again, composed of *patient model* block, a *dynamic feedback*, and an *observer* block. The patient model may be any mixture of time-invariant dynamic systems even containing non-stationary probabilistic temporal models.

If the virtual model is mimicking/simulating the real world perfectly, there will be no difference in both observations. A difference, however, is interpreted as error given by the simulation, which – as depicted in the intermediate layer – allows extending the monitoring by providing more knowledge about patient states and even extend to patient dependability and risk analysis. Normally, if the virtual patient model is accurate and well suited, the error is a significant sign for a deviation between real patient states and virtual patient states. Such a deviation may be interpreted as a deviation from safety boundaries and hints towards possible safety critical situations.

3.2. Physiological Simulation Framework

As mentioned earlier, for the simulation engine a mixture of deterministic and probabilistic methods have been used, which provides better modeling capabilities especially by including stochastic causal influences, which can also have dynamic character. For this purpose, in addition to compartment models (Figure 2. left) DBNs (Figure 2. right) have been applied [16]. A DBN is a pair *(G,P)*, where *G* is a directed acyclic graph which nodes correspond to a set of random variables *x* of a stochastic time dependent process $X=\{X_t: t \in T\}$. $P=P(X)$ is the joint probability distribution (JPD) of variables of the random process X. Essentially, *G* describes the dependency by how far a variable is conditional or unconditional to other variables, i.e. a representation for causal influences between variables. The strength of influence is given by the conditional probability distribution CPD, which can be described for discrete and continuous space. For discrete space, the CPD can be specified by a finite conditional probability table (CPT), which is not restricting the CPD to predefined distributions e.g. a Gaussian. The main aspect of BN/DBN is the probabilistic inference, i.e. if the probability of a certain variable/node – called evidence variable/node – is known to affect the conditional probability of other variables/nodes. Various algorithms exist for performing exact inference, mainly based on applying Bayesian rule and d-separation on the JPD. On the contrary, approximate inference additionally supports large BN/DBNs and additionally operates on incomplete evidence in the network. In case of DBNs, the inference of nodes of future temporal slices corresponds to the prediction of future outcome and is therefore called temporal reasoning.

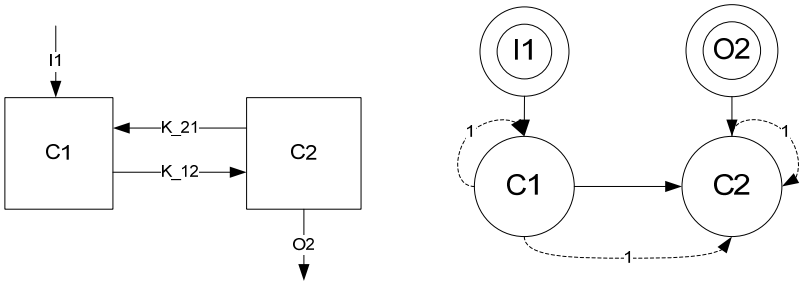

Fig. 1. Left: A 2-Compartment model. Right: The corresponding BN/DBN mixture containing static anchor nodes I1 and O2 from BN and two dynamic nodes C1, C2 from DBN.

3.3. Dependability and Risk Assessment Model

In clinical monitoring, a p*atient observer* (Fig. 1) analyzes and monitors patient's vital parameters, especially heart rate, blood pressure, oxygen saturation. Usually, these parameters are defined in a signal space *S*. By definition, monitoring devices adjust alarms, when a parameter exceeds a certain limit or boundary in the signal space. This procedure induces a subspace $\zeta \leq S$, where the signal is representing a non-critical and safe state. If ζ is time invariant with regard to the system dynamics it represents a constant interval, which is well-known from given alarm boundaries of

patient monitoring devices. We define the window dependability of a signal trajectory as shown in Eq. (1). t_w is describing the time window of interest and $\varepsilon_\zeta^2(t)$ is the squared error given by the Euclidian distance of the signal value and a given boundary ζ.

$$D_{t_w} = 1 - \frac{1}{t_w} \int_{t_0}^{t_0+t_w} \varepsilon_\zeta{}^2(\tau) d\tau \tag{1}$$

This formalism has two impacts; on the one hand the boundary ζ does not need to be a constant and on the other hand the integrative window shows how the boundary error is behaving over time. Additionally, dependability is defined with respect to a special mission [[9]]. In our case, stabilizing a patient's health state by an intervention or a medication is describing exactly such a mission and corresponding mission trajectories. For such a case, we define the mission dependability as given in Eq. (2). t_m is describing the mission time which is given by the time for an intervention or a medication. $\varepsilon_\partial^2(t)$ is the quadratic error, which is given by the Euclidian distance of the real signal value and the simulated virtual signal value.

$$D_m = 1 - \underbrace{\frac{1}{t} \int_{t_0}^{t} \varepsilon_\partial{}^2(\tau) d\tau}_{past} - \underbrace{\frac{1}{t_w} \int_{t}^{t+t_w} \varepsilon_\xi{}^2(\tau) d\tau}_{future} \tag{2}$$

Hereby, one focus is on the dependability during a certain event based mission (from a starting time t_0 to an actual time t). The second focus lies on predicting dependability in future (from the actual time t to the prediction horizon t_w). Thus, the formula consists of two parts; one error-formula for the past and one for the future. The error formula for the past can be interpreted on one hand as a measure for the quality of the simulation model. If the model is not simulating the real world accurately the error is large and the model is not well suited. By adding additional knowledge e.g. changing model parameters one adapts the model to the real world. This is either realized by user interaction or by applying multivariate optimization techniques. On the other hand if the model is designed well for healthy patients. The error term for the past is thus a good measure for the health state of a patient, taking time-variant information into account as well. Deviations to the health state is considered as reduced dependability like in system theory.

In our architecture, as shown in Fig. 1, we assume that there is a model which simulates and predicts the dynamic time-invariant changes of a monitored signal. Generally, such models are rare, because one needs to know the trajectory of the system states as well as the environmental influences. Therefore, probabilistic models are typically used to allow prediction of future system (in our case patient) states.

3.4. Quality of Service

According to our proposed architecture, it is possible to update the internal states of the dynamic system model by the knowledge of the real world observation. This process (which is called "smoothing" for probabilistic dynamic systems) will lead to

another prognosis for the next prognosis time window horizon t_w [[13]]. Assuming that we can apply N_w updates on the patient model within the time window t_w will result in a measure for the quality of the predictions for future outcome, as shown in Eq. (3). The quadratic error $\varepsilon^{(i)}{}_{\partial}{}^{2}(t)$ is given by the Euclidian distance of the signal value and the predicted value $\partial^{(i)}(t)$ at time t for $i=1..N_w$ model updates (smoothing) within in the prediction horizon. One has to consider that the entropy for probabilistic inference and thus the amount of uncertainty is increasing with the amount of reasoning steps N_w and the prediction time t_w [[14]]. Generally, in our terms this will lead automatically to worst quality of service for the predictive model.

$$Q = 1 - \frac{1}{t_w N_w} \sum_{i=1}^{N_w} \int_{t_w}^{t} \varepsilon^{(i)}{}_{\partial}{}^{2}(\tau) d\tau \tag{3}$$

4. Results

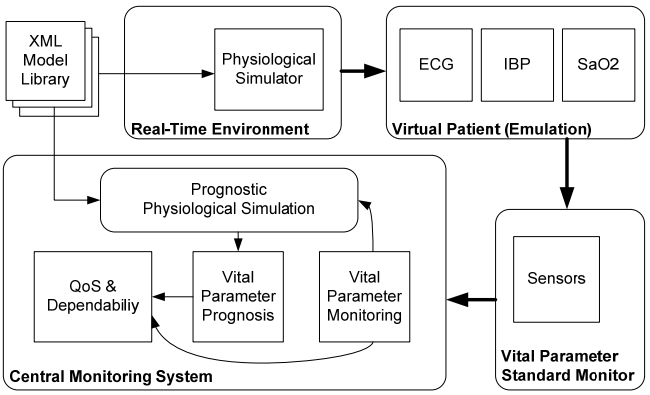

Fig. 2: Emulated vital parameter signals (ECG, IBP, SaO2) are detected by a monitoring system. An extended monitoring is supported due to the proposed methodology. Dependability and quality of service (QoS) are the major impacts of this method.

Our system developed for real-time-physiological simulations is using a hybrid approach applying ODEs and DBN for simulation of physiological interactions [5]. It is based on a hierarchical model description such that basic models for circulatory can be connected with e.g. models for drug interaction or interventional models as well. This system has been used to show the feasibility of the suggested approaches in a central monitoring environment.

We prepared a setup for a virtual ICU monitoring environment, as one can see in Fig. 3. A simulator dummy can simulate a real patient whose dynamics are represented by a set of models (e.g. circulatory system, medication, respiration defined in a XML model library) and patient specific parameters.

A similar simulation model is running virtually on the central monitoring system, while here the model parameters could be others. The virtual model updates internal states due to real measurements, emulated by the simulator dummy. The model

prognosis is analyzed regarding quality of service as well as dependability aspects for risk assessment.

In Fig. 4 we use a case study to show the feasibility of our methods on a medication with epinephrine, which is e.g used for the treatment of bardycardia. On the one hand a simulation (basic circulatory system in combination with simple 3-compartment PBPK) is running to forecast a prognosis for the effects on the heart rate (HR), on the other hand a similar simulation is running on the physiological simulator dummy to simulate the vital parameter in real-time. The measured data are processed by a monitoring system and emulate real data, although they are not from real patients. The error between forecasted and real data is used to compute the dependability value for the HR, given by the induced medication event. In fact, the error here is due to different parameter (clearance factor) given by the patient physiological model.

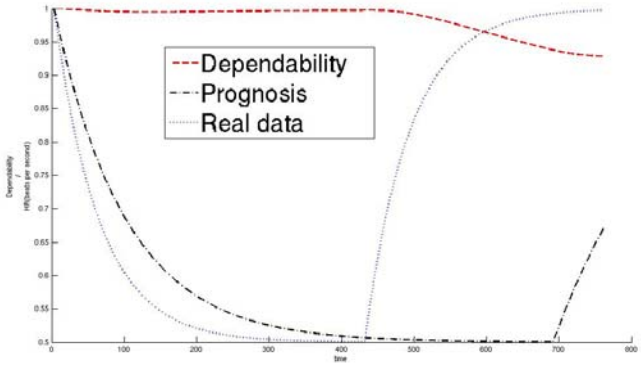

Fig. 3 Case Study: Effect of epinephrine on heart rate (HR) changes. One can see the forecasted HR due to the medication (Prognosis) and the real data extracted from the monitoring system. The error leads to a decreasing dependability value.

5. Conclusion and Future work

Applying dependability analysis on the human patient leads to interesting new methods for clinical monitoring. Physiological simulations are playing a key role in the proposed architecture, as far as they are addressed to take into account patient individual parameters as well as model updating and reasoning abilities. Once such models are available, the reasoning of events as medication or intervention for a specific patient based on the monitoring of vital parameter and other knowledge e.g. history, age and gender can be used for an individual risk assessment.

A general framework to access the dependability of patient states without forcing fault-tree modeling or similar approaches known from the reliability/dependability analysis have been provided by our methodology. The dependability measure for future risk and past model differences is a new view on patient's critical situations, which also considers dynamic attributes in addition to static ones, given by the well known alarm borders. Additionally the quality of service is a measure for the applicability of the virtual physiological model, which is currently in use.

We are preparing in vivo experiments on rats to test our methodology for vital parameter monitoring based on dedicational injection, showing how such a system

can be used to develop better and more specific models for drug interactions and provide a proof for the suggested concepts. By now, the applicability in terms of modeling and computational feasibility has been demonstrated as shown in Figure 4.

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