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Next Generation Patient Monitor Powered by In-Silico Physiology

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Abstract

The goal of this paper is to introduce a next generation patient monitoring technology that relies on objective and continuous data analytics to alleviate the data overload in the critical care unit. The technology provides the foundation for increasing the consistency and efficacy of data use in clinical practice and improving outcomes. This paper presents results for applying the approach to the hemodynamic monitoring of infants immediately following cardiac surgery and demonstrates its efficacy of estimating the probability of inadequate systemic oxygen delivery, which is an essential risk attribute in the management of critically ill patients.

I. Introduction

Conventional monitoring of critical care patients involves dozens of continuously and intermittently tracked data streams. These data serve to inform a treatment strategy consisting of a multitude of medications and life support devices. At the center of the decision-making process is a multi-disciplinary team of nurses, physicians, and other providers performing an average of 180 actions on each individual patient daily [1]. The timing and efficacy of these interventions greatly affect the clinical outcome. In this extreme data intensive environment, data is exclusively processed by the clinician, establishing an enormous premium on attention, experience, and training. This paper introduces a next generation patient monitoring technology that relies on objective continuous data analytics, which alleviates the data overload in the critical care unit. Consequently, this work provides a foundation for increasing the consistency and efficacy of data use in clinical practice.

It is the opinion of the authors that model-based estimation targeted towards quantifying the actionable patient risks is uniquely suited to deliver this next generation patient monitoring technology. The model-based risk assessment approach provides a framework that is: *grounded on first principle mechanistic models of the human body* and is, thus, capable of incorporating existing medical knowledge and *scalable* to inclusively accommodate all available patient data. In addition, the framework is *refinable* to quantify an increasing set of patient risks and associated etiologies towards an evolving understanding of disease patterns and treatment effects.

Moreover, the value and utility of model-based estimation has been repeatedly demonstrated across multiple, diverse industries. In its original application dating back to the 1960s, model-based estimation was a key technology behind the guidance, navigation, and control of the Apollo missions [2]. In today's highly instrumented world, the approach is responsible for harnessing the power of data in a diverse set of industries such as weather prediction, autonomous vehicles, flight control systems, oil refining, and radar systems.

In this paper, the authors apply the model-based risk analytics approach to a particularly vulnerable set of patients - infants with congenital heart disease (CHD) who are post cardiac surgery. This patients experience approximately 10% mortality [3] while encumbering \$1.4B of health-care cost in the first year of life amongst survivors [4]. The focus of the discussed application is to continuously track the patient risk for inadequate oxygen delivery (*iDO2*) and the etiologies that drive this risk. Optimizing the balance between oxygen delivery and demand is possibly the most important objective in critical care medicine [5].

II. Model-based Risk Assessment Fundamentals

The international standard on risk management, ISO 31000, defines risk as “the effect of uncertainties on outcome”. Thus, a key component of risk assessment is the quantification of uncertainty. In clinical practice, uncertainties arise from multiple interrelated factors, both known and unknown, that are exclusively and subjectively processed by the clinician's mind to arrive at an understanding of the attributes that underlie a patient's condition. These factors can be classified into two categories according to their relationship to the patient: *exogenous* and *endogenous* factors.

The *exogenous* factors relate to the uncertainties introduced by the nature of the data gathering process. Medical data is subject to noise from multiple sources, either introduced by a human component (a mislabeled blood sample leads to an incorrect clinical lab result), by the accuracy of the medical device (e.g. calibration bias or thermal noise), or by the actions of the patient or care team (e.g. motion artifacts).

The uncertainty attributed to *endogenous* factors is introduced by the physiologic condition or disease processes within the patient itself and is influenced by variability between individual patients due to the complex interaction between different phenomes and genomes (e.g. heterogeneity of treatment effects), or through stochastic mechanisms within a single patient (e.g. an evolving pathophysiology).

The rest of this section describes the problem of risk assessment from two perspectives: clinical and mathematical. The clinical component is aimed at introducing *a)* the limitations of the current, largely subjective method of evaluating risks, and related uncertainties when assessing and treating critically ill patients, and *b)* how the model-based risk assessment approach impacts these processes. The mathematical portion defines a formal framework for constructing continuous real time analytics for assessing risk and quantifying uncertainty.

A. Clinical Limitations and Impact

The study by Tibby et al, [6], provides an illustrative example of the effect of uncertainty on risk assessment in clinical practice. In this study, a group of clinicians with various levels of experience were tasked to classify the cardiac output of ventilated children and infants based on clinical examination and physiologic data (e.g. clinical laboratory results and vital signs). The resultant assessment was then compared with thermodilution derived (gold standard) cardiac output measurements. The results showed a poor correlation between the subjective interpretation of the clinicians and the objective gold standard measurements regardless of the level of experience. The example illustrates that even a single hypothesis (e.g., the value of cardiac output), when evaluated subjectively through clinicians experiences and beliefs may lead to strikingly inaccurate conclusions.

Bayes' Theorem provides the fundamental mathematical formulation for evaluating hypotheses in light of available evidence (data). Specifically, given two hypotheses H_0 and H_1 and available independent evidences $\sigma_0, \sigma_1, \dots, \sigma_n$, one can express the probability of each one of these hypotheses being true as proportional to:

$$P(H_0|\sigma_0, \sigma_1, \dots, \sigma_n) \propto P(\sigma_0|H_0) \cdot P(\sigma_1|H_0) \cdots P(\sigma_n|H_0),$$

where $P(\sigma_i|H_0)$ expresses the probability of observing an evidence σ_i given that H_0 is true. In other words, Bayes' Theorem provides a formulation with which one can objectively assess the probability of various hypotheses given all available data, while incorporating the uncertainty of available evidence.

However, human perception introduces biases that limit the ability to optimally process evidence and objectively quantify such probabilities. *Confirmatory bias* is a well understood cognitive phenomenon in which people are more likely to use the available evidence in a way that confirms their original hypothesis, effectively skewing the probabilities $P(\sigma_i|H_j)$ [7]. Applied clinically, this means clinicians are more likely to use and interpret evidence in a way that conforms to their initial assessment, rather than in a way that disproves it. The clinical author of this paper has observed that in medical practice this initial belief is often informed by the most recent or a highly memorable experience (e.g. what has been observed in the last similar patient) potentially contributing as one of several types of cognitive errors during clinical decision-making.

Another cognitive bias is introduced by the limits of the data bandwidth of human perception [7]. This limit leads to a higher likelihood of using evidence that is perceived to be stronger (e.g. is expected to have higher impact on uncertainty), than evidence that is

hard to interpret (e.g. is noisy or complex). For example, although cerebral and somatic NIRS oximetry have been established as a viable proxy for mixed venous oxygen saturation [8], an important marker of tissue oxygen delivery, the variable and uncertain nature of this relationship has hindered its adoption as a noninvasive tool for hemodynamic assessment [9].

Fig. 1 illustrates the basic architecture of the model-based risk assessment methodology. At the center of the architecture is a model that captures both the human physiology and the effects by which the physiology produces medical data. The model incorporates the *endogenous* uncertainties by embedding parameter variability that captures the diversity within a particular patient population, and abstracts *exogenous* uncertainties by modeling mechanisms of sensor error (additive noise, sensor disconnects, line flushes, systemic error, etc).

The stochastic inference block is used to continuously ingest the acquired patient data by computing the likelihood of the data given a set of hypotheses such as possible patient states and their etiologies. Effectively, the stochastic estimator employs the model to generate the probable patient trajectories and then compares them with the observed data to assign a probability of each possible explanation of the patient's condition. Thus the physiology model provides an objective framework that is inclusive of all available clinical data (evidence) and is immune to human bias.

Consequently, direct measurements and parameter estimates derived from the continuous data stream feed the generation of discrete, clinically relevant questions that ultimately allow for instantaneous assessment of attributes of patient states that are related to important outcomes. Fig. 2 describes how the component attributes associated with the transition from a normal physiologic state to the state of inadequate oxygen delivery (iDO_2) can be abstracted as a chain. Controlling the risks associated with the illustrated outcomes is the main focus of treating critically ill patients.

B. Formal definitions and computation architecture

As described in the previous subsection, the goal of the model-based risk assessment approach is to quantify the probability of various possible patients states. It is assumed that a patient state is identifiable by a set of physiologic attributes. Formally, a *physiologic attribute* is defined as $A_i \in \mathcal{A}_i$ where the set $\mathcal{A}_i$ is finite and discrete $\mathcal{A}_i \equiv \{a_i^1, a_i^2, \dots, a_i^{n_i}\}$. It is assumed that given a particular patient population there exist a finite number of physiologic attributes $A_1, A_2, \dots, A_N$ that ultimately inform the clinical management. For example, given a cardiac population, the attributes may be focused on specifying different manifestations of impaired cardiac function and its etiologies.

The *patient state* is then defined as a subset of the domain spanned by all physiologic attributes:

$$S_j \subseteq \mathcal{D} \equiv \mathcal{A}_1 \times \mathcal{A}_2 \times \dots \times \mathcal{A}_N.$$

The intuitive interpretation of this definition is that the patient state represents a particular collection of attributes which in medical practice specify the patient condition and its underlying causes. For example, the attribute *inadequate tissue oxygen delivery* together with the attribute *low cardiac output* can be interpreted as the patient state: *inadequate oxygen delivery caused by reduced cardiac output*.

Consequently, given a particular set of physiologic attributes, all clinically relevant interpretations of the patient data can be abstracted as a partition of a domain $\mathcal{D}$:

$$\mathcal{S} = \{S_1, S_2, \dots, S_q\},$$

i.e. $S_i \cap S_j = \emptyset, \forall S_i, S_j \in \mathcal{S}$ and $\bigcup_{S_i \in \mathcal{S}} S_i = \mathcal{D}$.

Let $\mathbf{z}_t \in \mathbb{R}^m$ correspond to all measurements collected at some time t , and $\mathbf{z}_{[0,t]} = \{\mathbf{z}_0, \mathbf{z}_1, \dots, \mathbf{z}_t\}$ correspond to all measurements collected between the patient admission and the time t . Then the uncertainties in the interpretation of the measurements can be abstracted as a conditional probability distribution function:

$$P(S|\mathbf{z}_{[0,t]}) := P_t(S),$$

where $S \in \mathcal{S}$. As a result, the clinical risk to the patient at a particular time t can be defined as the set $R = \{P_t(S_1), P_t(S_2), \dots, P_t(S_q)\}$.

It is further assumed that each attribute can be uniquely defined through a particular physiologic variable, e.g. the attribute ventricular dysfunction can be defined as cardiac contractility below a particular critical value. By this formulation, given a set of physiologic variables $\mathbf{x}(t) \in \mathbb{R}^n$, there exist an indicator function $J: \mathcal{S} \times \mathbf{x} \rightarrow \{0, 1\}$, such that $J(S_i, \mathbf{x}) = 1 \Leftrightarrow \mathbf{x}$ implies the attributes defining S_i . Consequently, assuming a probability density function, $p(\mathbf{x}|\mathbf{z}_{[0,t]})$, the function $P_t(S)$ can be defined as:

$$P_t(S_i) = \int_{\mathcal{X}} J(S_i, \mathbf{x}) p(\mathbf{x}|\mathbf{z}_{[0,t]}) d\mathbf{x}. \quad (1)$$

Note that the formulation $p(\mathbf{x}|\mathbf{z}_{[0,t]})$ is amenable to recursive estimation techniques (e.g. Kalman Filter) as will be discussed in the next section.

III. Hemodynamic risk assessment

The basic motivation for applying model-based risk assessment approach toward hemodynamic monitoring is illustrated in Fig. 2, and discussed in Sec. II-A. This section discusses the physiology model and inference scheme designed to quantify the probability of inadequate oxygen delivery ($P(S_{IDO_2})$) and the probabilities of the etiologies that cause this patient state. As a foundation of future development, the work focuses on defining and validating the computation of $P(S_{IDO_2})$, and leaves the definition and validation of the etiologies of this patient state for further development.

A. Model of Physiology

Fig. 3 summarizes the basic features of the physiology model employed for the estimation of $P(S_{IDO_2})$ and the captured effects. The model presented and discussed here is a simplification and modification of the model originally described by Guyton in [10]. We note that the complexity of the model prohibits the detailed derivation of the modifications and the simplifications in the constraints of this paper and reserve an expanded discussion for a follow up journal paper. A major simplification worth noting is that the model abstracts the systemic circulation, with future work intended to expand the model to incorporate the pulmonary tract.

Following Fig. 3, the notation W_x signifies a first order differential equation and, accordingly, the functions W_{HR} , W_{SVR} , and W_{V_u} signify the dynamics of physiologic auto-regulation, where HR is heart rate, SVR is systemic vascular resistance, and V_u is the unstressed blood volume. The auto-regulation is approximated by a closed-loop controller that commands the dynamics to set point values HR_{AR} , SVR_{AR} , and $V_{u,AR}$. These values are based on mean arterial blood pressure (MAP) (baro-reflex), and arterial oxygen saturation, SaO_2 (chemo-receptor reflex) connected to all three of the regulated variables, and mixed venous oxygen saturation, SvO_2 , connected to SVR (active hyperemia - local organ perfusion control based on metabolic demand). The variables HR^+ and SVR^+ , are assumed to evolve according to a random process, and capture baseline variations of the nominal state introduced either by inter-patient variability or by the effect of applied treatment.

Figs. 4 and 5(a) show HR , V_u , and SVR as functions of mean arterial blood pressure for three different values of SaO_2 . It can be observed that lower blood pressure is compensated through an increase in heart rate, a decrease in unstressed volume, and an increase in systemic vascular resistance. In nominal conditions the increase in HR increases cardiac output, Q_s , since $Q_s = HR \times SV$. Similarly a decrease in V_u leads to a higher Q_s , since the reduction in unstressed volume occurs through redistribution of blood volume from capacitance venous vessels to the central veins, thereby increasing filling pressure (central venous pressure $CV P$) which leads to increase in stroke volume, SV . The described autonomic regulation also captures the effects of desaturation (low SaO_2), which results in higher blood pressure, heart rate, and vascular resistance.

Fig. 5(b) shows the modulation of systemic vascular resistance based on a reduction of mixed venous oxygen saturation. This models the effects of local organ perfusion regulation based on metabolic demand and the loss of vascular tone as oxygen delivery fails to meet demand.

Referring back to Fig. 3, the SV is a function of $CV P$, HR , MAP , and π . The relationship between SV , $CV P$, and HR captures the dependence of end-diastolic volume to filling pressure and filling duration. Similarly, the dependence of SV on MAP relationship expresses the modulation of end-systolic volume. The ventricular dysfunction factor, $\pi \in (0, \infty)$, captures possible evolving pathology, with $\pi = 1$ corresponding to nominal condition and $\pi < 1$ signifying heart failure.

On the vascular side, $CV P$ is determined as a function of total blood volume V , the unstressed blood volume V_u , and $M A P$, where the relationship is driven by the capacitance of both the arterial and the venous vascular beds [11].

Note that the *endogenous* uncertainties are captured by the random nature of the ventricular dysfunction factor, π , total blood volume, V , oxygen consumption, $V O_2$, hemoglobin concentration, $H g b$, and the heart rate and the systemic vascular resistance baseline deviations, $H R^+$, $S V R^+$. The steady-state probability density function of these variables determines the total variability attributed to the patient population, and enables a framework within which these parameters can be estimates and adjusted given data specific for individual patients.

Absent from Fig. 3 is an important relationship between the described physiologic variables and systolic and diastolic blood pressures, which is used to inform the model. Specifically, this relationship can be derived from the Windkessel formulation in the form $S A P - D A P = f(S V R, Q_s, t_{sys}, \eta_{dyn})$, where $S A P$ and $D A P$ are systolic and diastolic blood pressures, respectively, and t_{sys} and η_{dyn} are variables capturing the duration of systole and dynamic arterial compliance, which are assumed to be random variables with their distributions centered around nominal values.

Fig. 6(a) describes the relationship between $CV P$ and $S V$ derived from computing the nullclines of the closed loop auto-regulation model derived from two different perspectives, the vasculature and the ventricle. The intersection of the two curves determines the steady state operating condition of the patient. Figs. 6(b) and 6(c) show how this relationship is modulated through the introduction of cardiac dysfunction $\pi < 1$ with no treatment (Fig. 6(b)) and with a treatment of a fluid bolus (increase in V) and vasopressor support ($S V R^+$) (Fig. 6(c)). This relationship is further demonstrated in the time domain in Fig. 7, which was created by simulating the model (i.e. simulating a virtual patient) under progression from a normal state, through a ventricular dysfunction state, to ventricular dysfunction with treatment.

B. Stochastic Estimation

Following the basic data flow of the model-based risk assessment introduced in Sec. II, the physiology model captures the physiologic relationships, and endogenous uncertainties pertaining to the patient's state. This section introduces the estimation scheme which is tasked with employing this model in computing the probability density $p(\mathbf{x}|\mathbf{z}_{[0,t]})$ from which the probability of possible patients states $P_t(S_i)$ will be derived (See (1)). Specifically, the focus of the reported work is to compute the probability of inadequate oxygen delivery $D O_2$, which is defined as the probability that an ideal mixed venous oxygen saturation measurement yields a value that is less than or equal to 40%. We note that the definition of inadequate $D O_2$ in this way may be considered restrictive. In reference [12], we establish the clinical value of this definition in terms of predicting the important outcomes illustrated in Fig. 2. We also note that the provided model-based estimation framework is expandable to accommodate etiologies of inadequate $D O_2$ and refinement of its definition.

To accommodate for the nonlinearities in the model, we employ an Extended Kalman Filter (EKF), a version of the Kalman Filter that uses first-order approximations to capture the nonlinear effects [13]. We note that the EKF is a well studied algorithm, with predictable behavior, that is more computationally tractable than other nonlinear estimation techniques, such as particle filtering.

The EKF approximates the conditional probability density, $p(\mathbf{x}_t|\mathbf{z}_{[0,t]})$, as a Gaussian density, $\mathcal{N}(\hat{\mathbf{x}}_{t|t}, \Sigma_{t|t})$, where $\hat{\mathbf{x}}_{t|t}$ and $\Sigma_{t|t}$ are the current conditional mean and covariance given all prior and current measurements. The tasks of propagating this density over time, and incorporating new measurement information is accomplished using basic linear algebra. For this purpose the physiology model described above is abstracted in the form of a nonlinear, partially observed, stochastic system:

$$\begin{aligned}\dot{\mathbf{x}}(t) &= f(\mathbf{x}(t), t) + \mathbf{w}(t) \\ \mathbf{z}_t &= h(\mathbf{x}(t), t) + \mathbf{n}(t),\end{aligned}$$

where $\mathbf{x}(t)$ is the continuous time $n \times 1$ state vector of physiologic variables, and $\mathbf{z}_t$ is the discrete time sampled $m \times 1$ measurement vector. The functions $f()$ and $h()$ describe the nonlinear dynamics and observational relationships between variables and measurements. The vectors $\mathbf{w}(t)$ and $\mathbf{n}(t)$ are random processes, representing uncertainties, described with the power spectral density matrix $\mathbf{Q}$ and noise covariance $\mathbf{R}$, respectively.

The state vector $\mathbf{x}$ consists of two components, $\mathbf{x} = \{\mathbf{x}_\phi, \mathbf{x}_m\}$. The component $\mathbf{x}_\phi$ consists of the physiologic variables described by Fig. 3, while the component $\mathbf{x}_m$ captures the effects of systematic errors (i.e. *exogenous* uncertainties) corrupting the available physiologic data, i.e. exogenous effects on uncertainty.

The measurement vector, $\mathbf{z}_t$, includes the following patient data streams:

$$\mathbf{z}_t = [SpO_2, SaO_{2_{abg}}, SvO_{2_{vbg}}, MAP_i, MAP_{ni}, PP_i, \dots, PP_{ni}, CVP_i, RAP_i, HR_{ecg}, HR_{pulse}, hgb_{cbc}]^T,$$

where the index *abg* signifies arterial blood gas, *vbg* venous blood gas, *i* invasive measurement by intra-vascular catheter, *ni* non-invasive measurement by pressure cuff, *cbc* complete blood count. The different measurements of *HR* come from electrical activity, *ecg*, and optically from the *SpO₂* monitor. Note, that some of these measurements are acquired persistently (i.e. *HR*, *SpO₂*, invasive blood pressures), while others are acquired intermittently (i.e. arterial and venous blood gases, hemoglobin and non-invasive blood pressure).

Starting with initial distribution $p(\mathbf{x}_0) = \mathcal{N}(\mu_{\mathbf{x}_0}, \Sigma_{\mathbf{x}_0})$, the EKF recursively computes $\hat{\mathbf{x}}_{t|t}$ and $\Sigma_{t|t}$ for each consecutive measurement $\mathbf{z}_t$. For a more in-depth treatment of the Extended Kalman Filter, the reader is referred to [13].

To ensure robustness against faulty measurements, such as those caused by the use of invasive intra-vascular lines for blood draws or fluid infusions, the filter utilizes a data monitoring technique, known as a χ^2 test, in which a χ^2 test statistic is computed for each measurement residual and compared to a threshold value, $\chi_{95\%}^2$. If $\chi_i^2 > \chi_{95\%}^2$, then the measurement is rejected. $\chi_{95\%}^2$ is the χ^2 value with which 95% of the measurement residual values should fall within. For more on this technique, the reader is referred to [14].

To compute the probability of inadequate oxygen delivery, $P(S_{iDO_2})$, we define the set of feasible physiologic states $\mathbb{D} \subseteq \mathbb{R}^n$, as the states that are achievable given the patient physiology. By restricting $\mathbf{x}_t \in \mathbb{D}$, we effectively reject values for the physiologic variables that are not possible given the patient physiology, e.g. $SaO_2, SvO_2 \notin (0,100]$.

In these terms, the indicator function, $J(S_{iDO_2}, \mathbf{x}_t)$ is defined as follows:

$$J(S_{iDO_2}, \mathbf{x}_t) = \begin{cases} 1 & \text{if } \mathbf{x}_t \in \mathbb{D} \cap SvO_2 \leq 40\%, \\ 0 & \text{otherwise.} \end{cases} \quad (2)$$

Then, by utilizing the Gaussian approximation, we compute the density, $p(\mathbf{x}_t | \mathbf{z}_{[0,t]}) = \mathcal{N}(\hat{\mathbf{x}}_{t|t}, \Sigma_{t|t})$, which yields:

$$P(S_{iDO_2}) = \frac{\int_{\mathbb{D}} J(S_{iDO_2}, \mathbf{x}_t) p(\mathbf{x}_t | \mathbf{z}_{[0,t]}) d\mathbf{x}_t}{\int_{\mathbb{D}} p(\mathbf{x}_t | \mathbf{z}_{[0,t]}) d\mathbf{x}_t},$$

where the denominator is a normalization factor, which accounts for the fact that the integration is performed over the feasible set $\mathbb{D}$.

IV. Results

This section reports results on the retrospective assessment of the technology on a sample of 479 neonates who have had cardiac surgery between January 2011 and March 2014 at Boston Children's Hospital. Data collected by the Etimetry™ T3 Monitor™, which included standard monitoring data and labs was used under Institutional Review Board approval for exempt retrospective review. After excluding patients with weight $< 2kg$, those requiring intraoperative ECMO, and those undergoing surgery without CPB, 312 patients were analyzed to assess the efficacy of the model-based risk analytics in computing the probability of inadequate oxygen delivery.

Fig. 8 shows a Receiver Operating Characteristic (ROC) curve of using the $P(S_{iDO_2})$ to predict a mixed venous oxygen saturation measurement below 40% immediately prior to a blood draw. The Area Under the Curve for this study was 0.79 (0.76 – 0.82), where the range was assessed through a bootstrap method. These results confirm the ability of the risk-based estimation to correlate a continuous assessment of $P(S_{iDO_2})$ with intermittent measurements. We note that the measurement methodology for SvO_2 creates systematic uncertainty that limits its utility as a gold standard. Blood can be drawn from various access

points such as the superior vena cava, intracardiac, central line catheters, etc., each one with its own mechanisms of error. Therefore, the current AUC may be considered as a conservative estimate of the system's performance.

Fig. 9 shows the estimated versus measured central venous pressure for a single patient of the study. The results shown in the figure demonstrate the ability of the χ^2 test to successfully identify artifacts in the central venous measurements due to line use for blood draws, line flushes, or fluid boluses. The statistical test rejects the faulty data, and only allows the non-corrupted data to inform the estimate.

Fig. 10 further demonstrates the robustness of the model-based estimation by showing the consistency with which the system accounts for bias between measured and actual arterial oxygen saturations. The dashed red line represents continuous measurements from a pulse oximeter, which are known to be inaccurate in lower saturation regions. The black diamonds represent arterial blood gas measurements. The figure clearly shows that the estimated arterial saturation, shown with the blue line, utilizes the blood gas measurements to account for the pulse oximeter inaccuracies, correcting for larger error in the low saturations, and smaller error in the higher saturations, when the two measurement sources are in better agreement.

Fig. 11 shows the contribution of *endogenous* uncertainties in the estimate of non-observable physiologic variables, specifically the systemic vascular resistance, SVR , and the ventricular dysfunction factor, π . One can observe the probability density function at each discrete time and the associated uncertainty with each of these physiologic variables. The figure shows that this uncertainty changes throughout time, depending on the measurement sources available at the time.

Finally, Fig. 12 demonstrates how the uncertainty in the estimation of SvO_2 is transformed into a probability of inadequate DO_2 . As defined by the indicator function in (2), the more of the SvO_2 probability density that resides below 40%, the larger the probability of inadequate DO_2 is. The figure also shows the venous blood gas measurements (black diamonds). The increasing trend of these measurements is confirmed by the decreasing value of $P(S_{IDO_2})$ over time.

V. Conclusion

The present work showed results on applying a novel model-based approach for transforming physiologic data into actionable information. Grounded on first physiologic principles the technology ingests real-time data to continuously assess patient risks and support clinical decision making. Specifically, the results demonstrated the tracking of the probability of inadequate tissue oxygen delivery relative to objective clinical markers. This work supports the viability of the proposed approach and creates the rationale for its deployment into clinical practice. Future work will aim to establish prospectively that the risks computed and presented to clinicians by this next generation monitoring technology are modifiable, and thus the technology can lead to improved clinical outcomes.

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Fig. 1.

The basic data flows of the model-based estimation technique; transforming physiologic data into actionable risks (e.g. probability of possible patient states).

Fig. 2. Pathways to inadequate oxygen delivery and consequent outcomes

Fig. 3.

Physiology effect abstracted by the model. Red connections signify feedback control loops that model auto-regulation.

Fig. 4.

The set points for heart rate, unstressed blood volume, and systemic vascular resistance as a function of mean arterial blood pressure for three different values of arterial oxygen saturation (60%, 80% and 100%).

(a) *SVR* % of nominal, for different values of SaO_2 . (b) *SVR* % of nominal, for different values of SvO_2 .

Fig. 5.

The set point of systemic vascular resistance as a function of mean arterial pressure for three different values of SaO_2 and SvO_2 .

(a) Nominal neonatal patient

(b) Ventricular dysfunction, no treatment

(c) Ventricular dysfunction with treatment

Fig. 6.

Nullclines derived by computing steady-state dynamics from vasculature and ventricle perspectives for different pathologies and treatment.

Fig. 7.

Vital signs derived from simulating the physiology model for progression from normal ventricular dysfunction state, with triangles corresponding to the timestamps of the change in the patient state.

Fig. 8. The computed Area Under the Curve (AUC) for predicting an SvO_{2vbg} 40%

Fig. 9. Probability density function, maximum likelihood estimate, and measured value of Central Venous Pressure.

Fig. 10. Probability density function, maximum likelihood estimate, and measured values (SpO_2 and $SaO_{2_{abg}}$) of arterial oxygen saturation.

Fig. 11. The probability density function of systemic vascular resistance and the ventricular dysfunction factor, π

Fig. 12.
The probability density function of SvO_2 and the derived probability of inadequate DO_2