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# Backstepping Control with Radial Basis Function Network for a Nonlinear Cardiopulmonary System

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**Abstract:** Oxygen therapy plays a vital role to recover a patient from severe hypoxia as well as to minimize the risk of hypoxia in a critical situation. Based on this therapeutic technique, this article presents an application of backstepping control for the oxygenation in a cardiopulmonary system. A nonlinear multi-compartment system with unknown hysteresis is used as a human model in this study. With no a priori knowledge of the underlying system dynamics, a radial basis function (RBF) network is integrated into a closed-loop subsystem and trained to identify the unknown nonlinear functions. Consequently, a backstepping controller is designed based on the Lyapunov stability theorem for regulating oxygenation. The theoretical framework and simulation are presented and demonstrated in terms of stability and control performance under the presence of simulated physiological changes, possibly caused by pathophysiological effects in the cardiopulmonary system i.e. critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

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**Keywords:** backstepping control, radial basis function (RBF) network, nonlinear system with unknown hysteresis, cardiopulmonary system, closed-loop mechanical ventilation.

## 1. INTRODUCTION

Oxygen therapy is an effective technique of medical treatment for subjects or patients in various clinical conditions (such as aviation first aid, chronic obstructive pulmonary disease (COPD), infant respiratory distress syndrome (IRDS), or severe hypoxia) by providing supplementary oxygen concentration in the breathing air. The purpose of this technique is to reverse the adverse consequences of low oxygen in the blood so that oxygenation is improved and maintained at an appropriate target range. In this article, a cardiopulmonary system is considered based on the control input of a fraction of inspired oxygen ( $FiO_2$ ) and the output in terms of oxygenation, specifically arterial oxygen saturation ( $SaO_2$ ) or partial pressure of oxygen in arterial blood ( $PaO_2$ ). Based on a historical perspective, there were a number of different advanced control strategies nominating for the control of oxygenation, for example adaptive control (Sano and Kikucki (1985)), robust control (Dugdale et al. (1988)), an expert system (Waisel et al. (1995)), and a protocol-driven expert system (Pomprapa et al. (2017b, 2015)). The most distinctive application is for preterm infants (Pomprapa (2015)).

To control oxygenation, a mathematical model of the complex cardiopulmonary system was developed based on human hypoxia using a three-compartment model of lungs, brain, and lumped body tissue (Fincham and Tehrani (1983a)). In addition, the regulation of cardiac output and cerebral blood flow was modeled based on the use of Chebyshev polynomials (Fincham and Tehrani (1983b)). In this contribution, we design a controller based on this particular model, consisting of coupled linear models in the compartments, transport delay, first-order linear model of metabolism and nonlinear relationship of blood gas. This approach should be able to translate to the closed-

loop adjustment of  $FiO_2$  in a mechanical ventilator based on the concept of oxygen therapy (Pomprapa et al. (2017a)). On one hand the overall design should be able to handle hypoxia, but on the other hand, it should be able to avoid hyperoxia that leads to oxygen toxicity in other body tissues (Mach et al. (2011)). Therefore, it becomes a challenging task for the optimization of control input ( $FiO_2$ ) in a nonlinear cardiopulmonary system with unknown hysteresis and system dynamics.

Backstepping control has been introduced in the early of 1990s (Kokotovic et al. (1992)) as a systematic and recursive method to cope with a nonlinear system. The practical applications of backstepping control are numerous, for example, a power system (Jain and Khorrami (1995)), a nonholonomic mobile robot (Fierro and Lewis (1989)), chemical processes (Chen and Liu (2005)), flight dynamics (Xu et al. (2016)), and a pneumatic muscle actuator (Carbonell et al. (1995)). Therefore, it is motivated to investigate its feasibility for a biomedical system, in particular a nonlinear cardiopulmonary system for the control of oxygenation. With this control strategy, the virtual control laws are initially synthesized in small subsystems and progressively derived until reaching the final cascaded subsystem of the overall system based on the Lyapunov stability theorem (Krstic et al. (1995)).

This article is organized as follows. It starts with the description of a nonlinear cardiopulmonary system based on oxygen dynamics of a human model in section 2, followed by a design of backstepping control using an integrated RBF network in section 3. Simulation results in various clinical scenarios are then presented in section 4 in order to evaluate stability and control performance. In addition, a discussion is provided in section 5 and this article ends with the conclusion in section 6.

## 2. SYSTEM DESCRIPTION

The model configuration of a cardiopulmonary system is presented in Fig. 1, based on a three-compartment model of lungs, brain, and lumped body tissue based on linear differential equations (Fincham and Tehrani (1983a)). The control mechanisms for cardiac output and cerebral blood flow using Chebyshev polynomials (Fincham and Tehrani (1983b)) are integrated into the system modeling. In addition, metabolism and transport delay between heart and brain tissue ( $T_d=10$  s) are included to represent a human model.

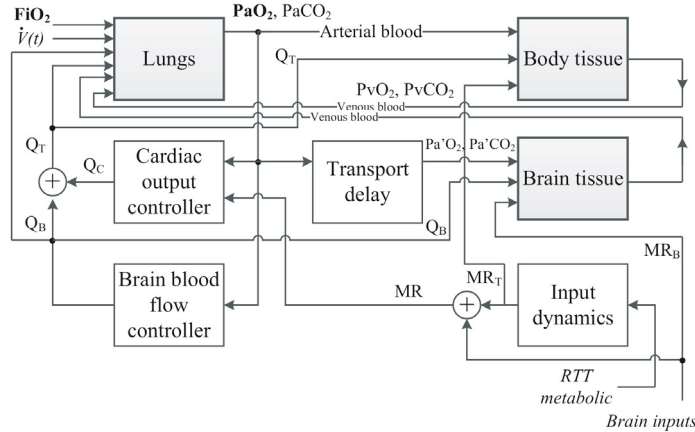


Fig. 1. A three-compartment model of a cardiopulmonary system with integrated cardiac output and cerebral blood flow controllers.

A fraction of inspired oxygen ( $FiO_2$ ) serves as a control input for the system. The internal states (such as partial pressure of oxygen in arterial blood ( $PaO_2=z_1$ )) are assumed to be accessible and oxygen saturation in arterial blood ( $SaO_2=z_2$ ) is the control output, which is governed by a nonlinear relationship, providing in eq. (1) with a unit in percent [%] (Tehrani (1992)).

$$SaO_2 = (1 - e^{-0.046 \times PaO_2})^2 \times 100 \quad (1)$$

The dynamical behavior of this nonlinear system was simulated and verified in the previous work under the condition of hypoxia (Pomprapa et al. (2014a)). The overall cardiopulmonary system can also be presented in the nonlinear strict-feedback form with input saturation as follows:

$$\dot{x}_1 = f_0(x_1, t) + g_0(x_1, t) \cdot z_1 \quad (2a)$$

$$\dot{z}_1 = f_1(x_1, z_1, t) + g_1(x_1, z_1, t) \cdot z_2 \quad (2b)$$

$$\dot{z}_2 = f_2(x_1, z, t) + g_2(x_1, z, t) \cdot \text{sat}(u(t)) \quad (2c)$$

$$y(t) = z_2(t), \quad (2d)$$

where  $\mathbf{x}$  represents a state vector ( $= [x_1 \ z_1 \ z_2]^T = [SaO_{2ref} \ PaO_2 \ SaO_2]^T$ ),  $\mathbf{z} = [z_1 \ z_2]^T$ , and  $f_i(\mathbf{x}, t)$  and  $g_i(\mathbf{x}, t)$  are the nonlinear functions with a subscript  $i \in \{0, 1, 2\}$ , representing each particular subsystem.  $u(t)$  is a control input and a saturation function of  $u(t)$  is defined by eq. (3).

$$\text{sat}(u(t)) = \begin{cases} 0.21 & \text{if } u(t) < 0.21 \\ u(t) & \text{if } 0.21 \leq u(t) \leq 1 \\ 1 & \text{if } u(t) > 1 \end{cases} \quad (3)$$

## 3. CONTROL SYSTEM DESIGN

### 3.1 Radial Basis Function Network

Radial basis function (RBF) network is used to approximate the unknown nonlinear functions  $f_i(\mathbf{x}, t)$  and  $g_i(\mathbf{x}, t)$  with the idea of learning kernels in the distinct shape, yielding the approximate functions  $\hat{f}_i$  and  $\hat{g}_i$ , respectively (Schilling et al. (2001)). Its architecture consists of input layer, hidden layer, and output layer in a cascade structure, presented in Fig 2.

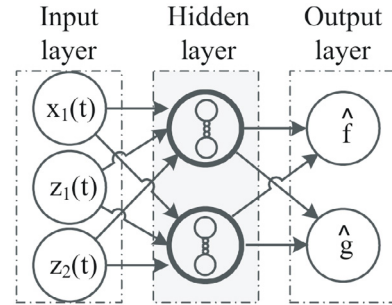


Fig. 2. Architecture of a RBF network.

Based on its topology, the stimulus input vector ( $\mathbf{x}$ ) is used in the hidden layer and is defined by a RBF with Gaussian function ( $\varphi(\mathbf{x}) : \mathbb{R}^n \rightarrow \mathbb{R}$ ), which can be expressed by

$$\varphi_j(\mathbf{x}) = \exp\left(-\frac{\|\mathbf{x} - \mu_j(t)\|^2}{2\sigma_j^2}\right); \quad j = 1, \dots, n \quad (4)$$

where  $\mu_j(t)$  represents a center vector for neuron  $j$  whilst  $\sigma_j$  is called a width of neuron  $j$  and  $\|\cdot\|$  denotes the Euclidean norm. The symbol “ $n$ ” denotes the overall number of nodes in the hidden layer. In this work, 5 hidden nodes were chosen.

The unknown nonlinear functions  $f$  and  $g$  can be approximated by RBF networks in the hidden layers, which can be expressed in eq. (5).

$$f_i = \sum_{j=1}^n W_{fij}^T \cdot \varphi_j + \varepsilon_{i1} \quad (5a)$$

$$g_i = \sum_{j=1}^n W_{gij}^T \cdot \varphi_j + \varepsilon_{i2}, \quad (5b)$$

where  $W_{fij}$  and  $W_{gij}$  denote the weights of  $f$  and  $g$  at output layer for a subsystem  $i$  and  $\varepsilon_{i1}$  and  $\varepsilon_{i2}$  represent the modelling errors of functions  $f_i$  and  $g_i$ , respectively. Moreover, functions  $f_i$  and  $g_i$  are assumed to be smooth and  $g_i \neq 0$ .

The model approximation  $\hat{f}_i$  and  $\hat{g}_i$  can then be computed using the RBF functions, as follow:

$$\hat{f}_i = \sum_{j=1}^n \hat{W}_{fij}^T \cdot \varphi_j \quad (6a)$$

$$\hat{g}_i = \sum_{j=1}^n \hat{W}_{gij}^T \cdot \varphi_j. \quad (6b)$$

A weighting error matrix  $\tilde{W}_i$  is specified by

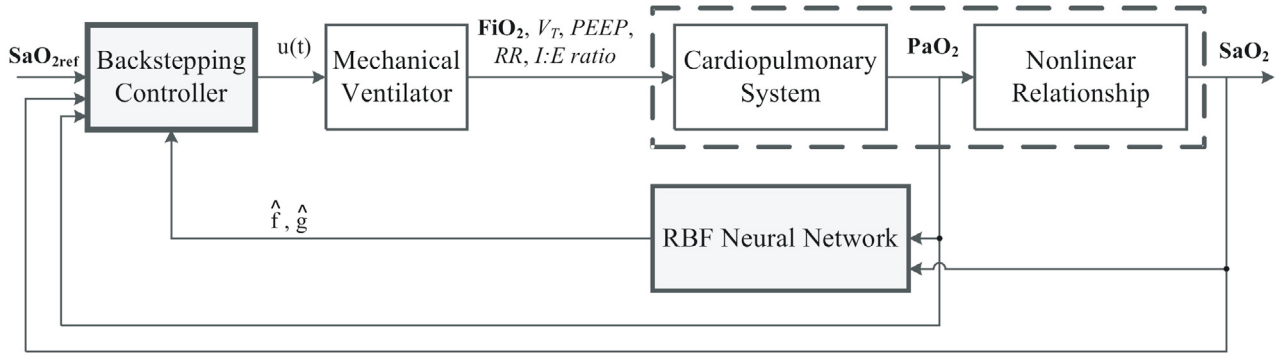


Fig. 3. Block diagram of the closed-loop backstepping control technique with the RBF neural network for oxygen therapy.

$$\tilde{\mathbf{W}}_i = \begin{bmatrix} W_{fi1} - \hat{W}_{fi1} & W_{fi2} - \hat{W}_{fi2} \\ W_{gi1} - \hat{W}_{gi1} & W_{gi2} - \hat{W}_{gi2} \end{bmatrix} \quad (7)$$

and a neural network functional reconstruction error vector  $\xi_i = [\varepsilon_{i1} \ \varepsilon_{i2}]$  will be used to formulate the Lyapunov function ( $V$ ), which is defined by

$$V = \frac{1}{2} \xi_i^T \xi_i + \frac{1}{2} \text{tr}(\tilde{\mathbf{W}}_i^T \Gamma_i^{-1} \tilde{\mathbf{W}}_i), \quad (8)$$

where  $\Gamma_i$  is a positive definite matrix. With an assumption, the desired trajectory and its derivatives are bounded. The adaptive mechanism for tuning the weighting error matrix can be provided by the following dynamical equation.

$$\dot{\tilde{\mathbf{W}}}_i = \Gamma_i \varphi_i \xi_i^T - k_w \Gamma_i \|\xi_i\| \tilde{\mathbf{W}}_i, \quad (9)$$

where  $k_w$  represents a scalar positive constant. The stability analysis lies on the assumption of bounded ideal weight under the Frobenius norm and its proof of stability was provided in Kwan and Lewis (2000).

### 3.2 Backstepping control design

Given the block diagram in Fig. 3, the control objective is to stabilize the whole system via state feedback and to control the output value of oxygenation based on  $\text{SaO}_2$  using a backstepping controller with a RBF network. To design a backstepping control, a repetitive process is carried out for the synthesis of the virtual inputs in the subsystems as well as the control input  $u(t)$  in the nonlinear cardiopulmonary system based on Lyapunov stability analysis (Khalil (2015)).

Step 1:  $z_1$  is defined by the virtual input and  $z_{1d}$  represents the desired virtual input. We can then formulate eq. (10).

$$\dot{V}_1 = \frac{\partial V_1}{\partial x_1} \frac{\partial x_1}{\partial t} = \frac{\partial V_1}{\partial x_1} (f_0 + g_0 \cdot z_1) \quad (10a)$$

$$= \frac{\partial V_1}{\partial x_1} (f_0 + g_0 \cdot z_{1d}) + \frac{\partial V_1}{\partial x_1} g_0 (z_1 - z_{1d}) \quad (10b)$$

$$\leq -\mathbb{W}(\mathbf{x}) + \frac{\partial V_1}{\partial x_1} g_0 (z_1 - z_{1d}), \quad (10c)$$

where  $e_1 = z_1 - z_{1d}$  and  $\mathbb{W}(\mathbf{x})$  denotes a positive definite function, provided in eq. (11).

**Assumption:** A Lyapunov function  $V$  exists and satisfies the following condition to ensure a stability in this particular subsystem.

$$\frac{\partial V_1}{\partial x_1} [f_0 + g_0 z_{1d}] \leq -\mathbb{W}(\mathbf{x}) \quad (11)$$

Step 2: Let's determine  $V_2(\mathbf{x}) = V_1(x_1) + \frac{1}{2} e_1^2$ .

$$\dot{V}_2 \leq -\mathbb{W}(\mathbf{x}) + \frac{\partial V_1}{\partial x_1} g_0 e_1 + e_1 \dot{e}_1 \quad (12a)$$

$$= -\mathbb{W}(\mathbf{x}) + e_1 \left[ \frac{\partial V_1}{\partial x_1} g_0 + \dot{e}_1 \right] \quad (12b)$$

$$= -\mathbb{W}(\mathbf{x}) + e_1 \left[ \frac{\partial V_1}{\partial x_1} g_0 + f_1 + g_1 z_2 - \frac{\partial z_{1d}}{\partial x_1} (f_0 + g_0 z_1) \right] \quad (12c)$$

$z_2$  is the virtual control and  $z_{2d}$  is provided in eq. (13) and defined so that the second term of eq. (12c) is negative.

$$z_{2d} = \frac{1}{g_1} \left[ \frac{\partial z_{1d}}{\partial x_1} (f_0 + g_0 z_1) - f_1 - \frac{\partial V_1}{\partial x_1} g_0 - k_1 e_1 \right], \quad (13)$$

where  $e_2 = z_2 - z_{2d}$  and  $k_1 \in \mathbb{R}^+$  is required as a designed parameter to stabilize the subsystem.

Step 3: Similarly as in Step 2, the backstepping control law for the cardiopulmonary system in terms of oxygen therapy can then be designed by

$$u(t) = \frac{1}{\hat{g}_2} [z_{2d} - \hat{f}_2 - e_1 \hat{g}_1 - k_2 e_2]. \quad (14)$$

The backstepping control procedure with RBF network is a repetitive process in analyzing the subsystems based on Lyapunov functions in order to synthesize the virtual control inputs and control input  $u(t)$ . Its derivation remains unchanged even in the presence of parametric and nonparametric uncertainties. Thereby, it can be classified as a robust and adaptive control scheme in order to cope with a nonlinear system with no a priori knowledge of system dynamics and unknown hysteresis in a cardiopulmonary system. In eq. (14), the control input  $u(t)$  can therefore be designed based on the estimation of nonlinear functions ( $\hat{g}_1, \hat{g}_2$ , and  $\hat{f}_2$ ) using the RBF network, derivative of virtual input, errors in the subsystems ( $e_1$  and  $e_2$ ), and the designed parametric gain ( $k_2$ ). Based on this control design, it yields

$$\dot{V}_2 \leq -\mathbb{W}(\mathbf{x}) - k_1 e_1^2 - k_2 e_2^2, \quad (15)$$

$k_2 \in \mathbb{R}^+$ , which guarantees that the overall closed-loop system is asymptotically stable under the bounded tracking error for the control of oxygenation.

#### 4. SIMULATION RESULTS

Based on the proposed human model (Fincham and Tehrani (1983a) and Fincham and Tehrani (1983b)), the dynamical response of oxygenation can be simulated using MATLAB with Simulink (The MathWorks Inc., Natick, MA, USA). To prove the effectiveness of control performance, a clinical scenario of possible pathophysiological change was also simulated at different conditions of atelectasis or loss of lung volume by changing alveolar ventilation per breath ( $\dot{V}_A$ ) as given in eq. (16).

$$\dot{V}_A(t) = \begin{cases} 0.027 \text{ l/s} & \text{if } t < 300 \text{ s} \\ 0.037 \text{ l/s} & \text{if } 300 \leq t < 600 \text{ s} \\ 0.047 \text{ l/s} & \text{if } 600 \leq t < 900 \text{ s} \\ 0.057 \text{ l/s} & \text{if } 900 \leq t < 1200 \text{ s} \end{cases} \quad (16)$$

The closed-loop control performance is demonstrated as shown in Fig. 4 for its nonlinear behavior and controller interactions in the cardiopulmonary system, presenting  $\text{SaO}_2$ ,  $\text{SaO}_{2\text{ref}}$ ,  $\text{PaO}_2$  and  $\text{FiO}_2$ , respectively. It should be noted that the respiratory rate was fixed at 15 breaths per minute (bpm).

The input reference ( $\text{SaO}_{2\text{ref}}$ ) was applied to excite the system and used to determine a desired physiological output response of ( $\text{SaO}_2$ ). The excitation was a sinusoidal wave with an amplitude of 1% so that its control operation was in the nonlinear region. The backstepping controller interacts with the nonlinear cardiopulmonary system, yielding acceptable control performance with the bounded error ( $e(t) = \text{SaO}_2 - \text{SaO}_{2\text{ref}}$ ). The output of  $\text{SaO}_2$  is also in a clinical safety region ( $> 88\%$ ) (ARDSNetwork (2000); Pomprapa et al. (2017b)) under the

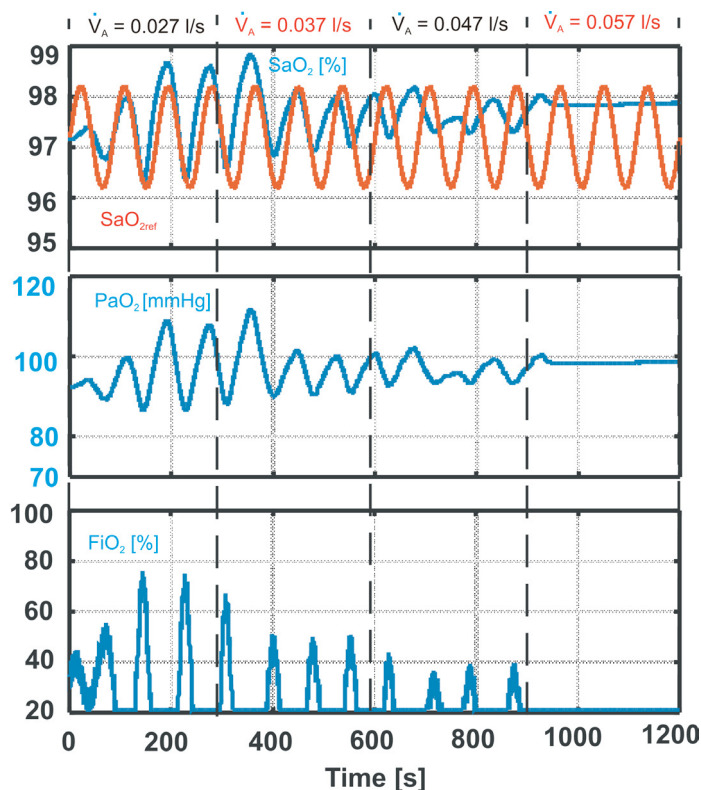


Fig. 4. Closed-loop control performance under the presence of step variation in alveolar ventilation, reflecting possible lung collapse due to a pathophysiological change.

severe condition of the simulated sudden change of alveolar ventilation, namely the loss of lung volume or atelectasis.

The backstepping controller can react in a closed-loop ventilation system to cope with the risks of hypoxia and hyperoxia by computing and adjusting the control variable  $\text{FiO}_2$  using the proposed neural-based adaptive control configuration of state feedback structure. Additionally,  $\text{PaO}_2$  in mmHg was also presented in Fig. 4, which is based on the nonlinear mathematical relationship, given in eq. (1).  $\text{PaO}_2$  and  $\text{SaO}_2$  have a direct dependence, specifically when  $\text{PaO}_2$  variable increased so was the  $\text{SaO}_2$ . Conversely, when  $\text{PaO}_2$  variable decreased, the  $\text{SaO}_2$  variable declined as well.

Based on the simulation result in Fig. 4, the control performance can be evaluated under various pathological conditions with an abrupt change of the condition in every 300 s. Four phases of different pathological conditions were designed with  $\dot{V}_A = 0.027 \text{ l/s}$ ,  $0.037 \text{ l/s}$ ,  $0.047 \text{ l/s}$ , and  $0.057 \text{ l/s}$ , respectively, represented the severe condition for 52% loss of tidal volume, 35% loss of volume, 17.5% loss of volume and normal healthy condition in the respiratory system. In all phases, oxygen therapy was able to reverse the condition of hypoxia. At the last phase of  $\dot{V}_A = 0.057 \text{ l/s}$ , it was not able to control  $\text{SaO}_2$ . In other words, no tracking performance was achievable because the system operated under normal tidal volume. Therefore,  $\text{PaO}_2$  and  $\text{SaO}_2$  remained constant at the lowest physical limitation of  $\text{FiO}_2 = 0.21$ . For the other phases from phase I to phase III, the condition of the tidal volume was gradually improved and the backstepping controller was able to stabilize oxygenation in the safe operating region.

In this simulation, we treated the overall system as a single-input and single-output (SISO) system for oxygen therapy. The control input  $\text{FiO}_2$  reacts to stabilize the unknown cardiopulmonary system and is used to maintain the system output  $\text{SaO}_2$  at the body compartment based on the computation from the backstepping controller in a timely manner, which could avoid hypoxia and hyperoxia by automatic adjustment of  $\text{FiO}_2$ . In this study with a constant setting of the respiratory rate, the increment of oxygen concentration in the inspired air ( $\text{FiO}_2$ ) is sufficient to reverse the adverse effect of hypoxia. In addition, the automated setting of  $\text{FiO}_2 = 0.21$  suppressed the oxygenation in terms of  $\text{SaO}_2$  as well as  $\text{PaO}_2$  with the prominent effect of time delay in the cardiopulmonary system. It should also be noted that we require less amount of  $\text{FiO}_2$  given to the patient when the condition of lungs was recovered. Last but not least, if we introduced a low amplitude of the excited sinusoidal signal ( $=0.1$ ), the operating point would be in a linear region of the saturation curve. The backstepping controller was also able to stabilize the oxygenation and to keep the error bounds within 2%.

As presented in Fig. 4, nonlinear saturation limits and time delay among the compartments degrade the overall control performance and it becomes the challenge in dealing with this particular system. Based on its physiological aspect of oxygenation, we deal with the underlying unknown oxygen exchange and oxygen transport in the cardiopulmonary system using a multi-compartment model of body tissues, heart, lungs. The limitation of oxygen bonding, the reserved number of hemoglobin, metabolism, and transport delay (by blood circulation and blood storage) for each individual patient play a vital role in the control of oxygenation and they also act as an unknown constraint in the system. The proposed control

design should be able to stabilize the oxygenation and prevent the unexpected severe events at the bedside for the unexpected events of atelectasis.

## 5. DISCUSSION AND OUTLOOK

The backstepping control strategy offers a recursive and systematic approach for the control of oxygenation with no required accurate patient model. Its closed-loop configuration is categorized by a state-feedback control structure. In this particular setup, online identification of unknown nonlinear functions is carried out with the aid of a radial basis function (RBF) network. The tuning of the neural network has no learning phase involved, and it should provide us a practical solution in the real implementation. It is of great advantage for this control configuration, which saves time for system identification and requires no precise mathematical model, especially in the critical situation with a time constraint to stabilize and maintain oxygenation at the target range. The analysis of backstepping control laws is relatively tedious and requires the formulation of Lyapunov functions in the subsystems. The control signals can be synthesized based on the guaranteed stability in each particular subsystem. Therefore, the boundedness of the tracking error and weight updates can be achievable in the closed-loop control system by synthesizing the optimal control input  $\text{FiO}_2$  to prevent hypoxia as well as to avoid hyperoxia during oxygen therapy.

Typically, backstepping control works well for the system with linear unknown parameters. However, in this work, we deal with a system with linear and nonlinear unknown parameters (Fincham and Tehrani (1983a)) and this control strategy can also provide a satisfactory control performance with bounded error under saturation input for  $\text{FiO}_2$  in different clinical complication such as atelectasis and variable cardiac outputs. Based on the simulation results, we showed that this control strategy is promising and realizable for the control of oxygenation. Therefore, it should be stable and safe when we implement this control strategy in real clinical practice with unknown uncertainties and with limited variation in the cardiopulmonary system.

The learning ability of the radial basis function (RBF) network will boost the overall system stability and robustness for the strict-feedback nonlinear system. The parameters of RBF network based on centers, widths, and weights are updated with guaranteed stability by minimizing the neural network functional reconstruction error vector ( $\xi_1$ ) (Kwan and Lewis (2000)). The learning process with guaranteed parameter convergence was verified in simulated clinical scenarios with complications of atelectasis and variable cardiac outputs based on a human cardiopulmonary system (Fincham and Tehrani (1983a,b)). The key merit of the neural network is to provide real-time learning for the modeling of a complicated nonlinear system with uncertainties, particularly in the presence of pathophysiological states, which may have sudden or gradual changes in internal states.

From the application perspectives, we may extend the use of this control strategy in the intensive care unit (ICU) for patients with acute respiratory distress syndrome (ARDS) or with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), home-based mechanical ventilation for elders and emergency devices to rescue the patients in need of oxygen therapy. However, the critical implementation is on the realizable assessment of internal state variables such as  $\text{PaO}_2$  and  $\text{SaO}_2$ . Further

sensor technique and failure handling of state measurement is of great interest in the overall development of the mechanical ventilator in a closed-loop physiological system. In addition, the sensor settings should be placed at reliable physiological positions in order to achieve continuous signals with the best signal quality. An excessive time delay should be avoided because it may introduce instability into the overall closed-loop system. This can be realizable by proper positioning of sensors and stabilizing ambient temperature to minimize the temperature gradient that may worsen the signal quality during the measurement of oxygenation.

Backstepping control has successfully been implemented in a number of applications, especially for a mechatronic system such as a vehicle with active suspension (Yagiz and Hacıoglu (2008)). However, based on our literature survey in a biomedical system, the applications of backstepping controller were still limited and focused merely on numerical simulations, for instance tracking control of coronary artery system (Li (2009)), MRI-guided therapeutic microrobot in blood vessels (Arcese et al. (2010)), functional electrical stimulation (FES) of agonist-antagonist muscles (Koo and Leonessa (2011)), and blood glucose control for type I diabetes (Parsa et al. (2014)). Hence, the translation from numerical simulation to real clinical practice should be the next challenging task for the control community in order to realize such a closed-loop system with the proposed neural-based adaptive backstepping controller. Based on our knowledge, there is a growing interest in the implementation of this control method in the medical assistive device i.e. an exoskeleton for human upper limbs (Li et al. (2015)).

For our future work, the backstepping control algorithm with the aid of the RBF network should, therefore, be implemented in order to evaluate the control performance with unknown system dynamics in practice. The RBF network will perform the online identification for estimating the underlying unknown nonlinear functions of an individual patient. With this control configuration, it promotes a generalized solution for a patient with cardiopulmonary diseases by no requirement of a priori knowledge of the system. In addition, further implementation of multivariable control for gas exchange in terms of oxygenation and carbon dioxide ( $\text{PaCO}_2$  or pH value), in which the Henderson-Hasselbalch equation will play a role in the nonlinear bicarbonate buffer system (Pomprapa et al. (2014b)). This should thereby be carried out using the backstepping control in order to have a complete regulation of gas exchange during respiration including inspiration and expiration phases. Additionally, it would be a challenge to integrate this control algorithm for oxygen therapy to patients with SAR-COV-2 (Tu et al. (2020)) in order to support and stabilize oxygenation.

## 6. CONCLUSION

Backstepping control is applicable for a system with multiple dynamics and with mismatched uncertainties. Based on the proposed backstepping control scheme with a combination of the RBF network, we do not require a priori knowledge of the system dynamics for the control of oxygenation. Using the multi-compartment model of a human cardiopulmonary system with unknown parameters, hysteresis effect and time delay, we present the feasible design of Lyapunov based control laws and we evaluate the closed-loop stability and the overall control performance through simulations of unexpected clinical complications for critically ill patients with acute respiratory

distress syndrome (ARDS) or with SAR-COV-2 in the presence of uncertainties such as variable loss of tidal volumes. For stabilizing and controlling oxygenation in the cardiopulmonary system, the proposed control technique guarantees the bounded error at the acceptable safety region. Therefore, this control strategy would be an alternative for closed-loop control of oxygenation.

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