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Robust predictive control for respiratory CO_2 gas removal in closed-loop mechanical ventilation: An in-silico study

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Abstract: In this study a physiological closed-loop system for arterial CO_2 partial pressure control was designed and comprehensively tested using a set of models of the respiratory CO_2 gas exchange. The underlying preclinical data were collected from 12 pigs in presence of severe changes in hemodynamic and pulmonary condition. A minimally complex nonlinear state space model of CO_2 gas exchange was identified post hoc in different lung conditions. The control variable was measured noninvasively using the end-tidal CO_2 partial pressure. For the simulation study the output signal of the controller was defined as the alveolar minute volume set value of an underlying adaptive lung protective ventilation mode. A linearisation of the two-compartment CO_2 gas exchange model was used for the design of a model predictive controller (MPC). It was augmented by a tube based controller suppressing prediction errors due to model uncertainties. The controller was subject to comparative testing in interaction with each of the CO_2 gas exchange models previously identified on the preclinical study data. The performance was evaluated for the system response towards the following five tests in comparison to a PID controller: recruitment maneuver, PEEP titration maneuver, stepwise change in the CO_2 production, breath-hold maneuver and a step in the reference signal. A root mean square error of 2.69 mmHg between arterial CO_2 partial pressure and the reference signal was achieved throughout the trial. The reference-variable response of the model predictive controller was superior regarding overshoot and settling time.

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1 Introduction

In intensive care the need for patient-specifically adapting ventilation therapy options exists if high quality standards have to be ensured in presence of cost pressure and partial lack of highly qualified personnel. To guarantee safety in such automated systems, comprehensive testing is obligatory. This goal can be achieved by lab tests and subsequent extensive preclinical studies or by using appropriate physiological process models as reviewed by Parvinian et al., [1]. Such models might simplify and improve effectiveness of admission processes in the future. Therefore, data from preclinical studies providing a wide range of physiological state information could potentially help to reduce animal studies as required by basic medical research guidelines [2]. The main objective of this study was an extensive performance test of a closed-loop P_{aCO_2} control system interacting with a new ventilation mode, representing an extension of Adaptive Support Ventilation [3] to demonstrate robust behavior.

2 Materials and Methods

Overview: The proposed simulation approach relied on monitoring data recorded in 12 pigs included in a preclinical trial on regional pulmonary perfusion monitoring. A variety of pulmonary and hemodynamic conditions were covered. For further details regarding the protocol and animal preparation please refer to Bluth et al. [4]. An in-silico system model for benchmark tests including positive end-expiratory pressure (PEEP) and CO_2 production changes was developed. As shown in Fig. 1 it consisted of three main components, the model predictive controller (MPC), the actuator and the physiological process model. The alveolar CO_2 partial pressure represented the control variable. The output signal of the controller was the alveolar minute volume. Two

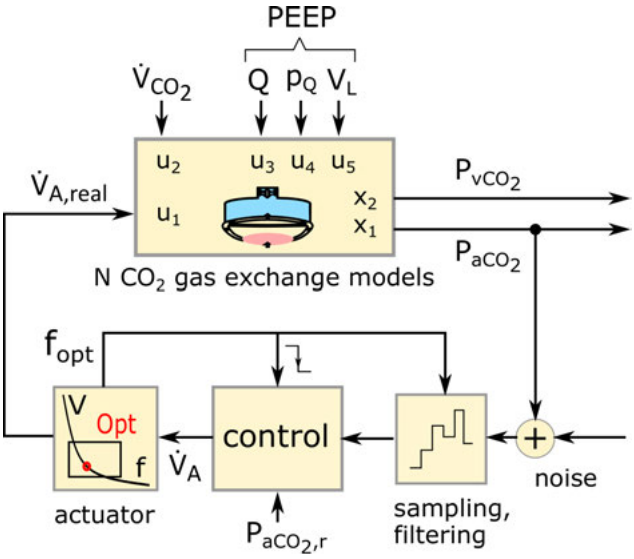


Fig. 1: Components of in-silico testing as described in Overview.

different parametrizations (***MPC fast***, ***MPC slow***) of the same predictive controller algorithm were compared to a PID controller design (***PIDC***). The alveolar minute volume was applied by a lung-protective ventilation mode, represented by the actuating element, the second component of the system model. The sampling frequency of the measurement signal is defined by the respiratory frequency continuously optimized in a lung-protective manner as displayed at the bottom. The alveolar minute volume $\dot{V}_A$ set by the actuator to $\dot{V}_{A,\text{real}}$ was used as input signal for a nonlinear human CO_2 gas exchange model described in the next section. The two compartment CO_2 gas exchange model is depicted with its input signals and their dependencies.

2.1 Process Model

Patient model:

The CO_2 gas exchange dynamics were described by a nonlinear state space model with the arterial CO_2 partial pressure (P_{aCO_2}) and the mixed-venous CO_2 partial pressure (P_{vCO_2}) as state variables. The CO_2 dissociation curve was replaced by its linearisation $C_{xCO_2} = \alpha P_{xCO_2} + \beta$ with $x = a, v$ in accordance with Khoo et al., [5].

A nonlinear CO_2 gas exchange model derived from CO_2 mass balance as described in Kim et al. [6] was extended to the following system of first order differential equations

$$V_L \dot{P}_{aCO_2} = \dot{V}_A \left[P_{ICO_2} - P_{aCO_2} \right] + \alpha \lambda p_Q Q \left[P_{vCO_2} - P_{aCO_2} \right] \quad (1)$$

$$V_B \dot{P}_{vCO_2} = Q p_Q \left[P_{aCO_2} - P_{vCO_2} \right] + \frac{\dot{V}_{CO_2}}{\alpha}. \quad (2)$$

A parameter identification for the parameters blood volume V_B, lung volume V_L and shunt fraction $(1 - p_Q)$ was carried out for all pigs and the respective lung state. The constant $\lambda = 863\,\text{l}_{\text{BTPS}}/\text{l}_{\text{STPD}}$ was set according to [6, 7]. The lung volume was described as linearly dependent on PEEP. As a surrogate for alveolar CO_2 partial pressure (P_{aCO_2}), which equals arterial CO_2 partial pressure, end-tidal CO_2 partial pressure was derived from capnography. In contrast to previous work the cardiac output Q was not assumed to be constant. A continuous cardiac output estimation was computed with a novel pulse contour analysis approach. Inspiratory CO_2 partial pressure (P_{ICO_2}) was set to zero. The metabolic activity ($\dot{V}_{CO_2}$) and physiological dead space were considered as constant but individual for each pig and lung state computed based on volumetric capnography data, [8]. Each of these models represented a sufficiently good description of the system dynamics.

MPC model:

The nonlinear CO_2 gas exchange model was linearized to design a robust model predictive controller. Therefore, one single operating point $P_{aCO_2,ss} = 35\,\text{mmHg}$, $p_{Q,ss} = 0.9$, $Q_{ss} = 7\,\frac{\text{l}}{\text{min}}$ and $\dot{V}_{CO_2,ss} = 0.27\,\frac{\text{l}}{\text{min}}$ was chosen and a fixed model with parameters $V_L = 5\text{l}$, $V_B = 6\text{l}$ and $p_Q = 0.95$ was derived. Steady state equations were used to set $\dot{V}_{A,ss}$ and $P_{vCO_2,ss}$. The dead space fraction f_{ds} was included as $f_{ds} = 0.07$. The difference state space model

$$\begin{pmatrix} \Delta\dot{P}_{aCO_2} \\ \Delta\dot{P}_{vCO_2} \end{pmatrix} = A \begin{pmatrix} \Delta P_{aCO_2} \\ \Delta P_{vCO_2} \end{pmatrix} + B\,\Delta\dot{V}_A + E \begin{pmatrix} \Delta\dot{V}_{CO_2} \\ \Delta\dot{V}_A\,\Delta P_{aCO_2} \end{pmatrix} \quad (3)$$

with the system matrices

$$A = \begin{pmatrix} -\frac{1-f_{ds}}{V_L}\,\dot{V}_{A,ss} & 0 \\ 0 & 0 \end{pmatrix} + Q_{ss} \cdot p_{Q,ss} \cdot \begin{pmatrix} -\frac{\alpha\lambda}{V_L} & \frac{\alpha\lambda}{V_L} \\ \frac{1}{V_B} & -\frac{1}{V_B} \end{pmatrix},$$

$$B = \begin{pmatrix} \frac{(1-f_{ds})\,P_{aCO_2,ss}}{V_L} \\ 0 \end{pmatrix} \text{ and } E = \begin{pmatrix} 0 & -\frac{1-f_{ds}}{V_L} \\ \frac{1}{\alpha V_B} & 0 \end{pmatrix}$$

approximated the system behavior of the control signal to the system states. Taking E into account, errors on the system states due to discrepancies in metabolic activity and the nonlinear dynamics were estimated. Physiological limits to these errors were used to find an applicable robust control law.

2.2 Controller design

Notation: The quadratic norm of a weighted with the matrix $A \in \mathbb{R}^{n\times n}$ is written $\|a\|_A = a^T A\, a$. A polyhedron

P is the intersection of a finite number of halfspaces $P = \{x \mid Ax \leq b\}$, a polytope is a closed bounded polyhedron. The Minkowski-Sum on the Sets $\mathcal{A}$ and $\mathcal{B}$ is defined as $\mathcal{A} \oplus \mathcal{B} \coloneqq \{a+b \mid a \in \mathcal{A}, b \in \mathcal{B}\}$. The Pontryagin set difference for $\mathcal{A}$ and $\mathcal{B}$ is defined as $\mathcal{A} \ominus \mathcal{B} \coloneqq \{a \mid a + \mathcal{B} \subseteq \mathcal{A}\}$.

To guarantee robust behavior a tube based MPC approach was applied to the control problem similar to the one previously presented by Georg Männel based on previous work of Mayne et al. and an extension to reference tracking from Alvarado et al., [9–11]. Therefore the system (3) needed to be transformed to the discrete state space representation

$$x(k+1) = A\,x(k) + B\,u(k) + w(k). \tag{4}$$

where $w \in \mathcal{W}$ summons all disturbances and system uncertainties and $\mathcal{W}$ is a polytopic set. The system states x are elements of a given set $\mathcal{X}$. The set $\mathcal{U}$ includes all admissible control signals u for the application. In all simulations the alveolar minute volume was limited by the interval $[0\,\frac{\mathrm{l}}{\mathrm{min}}, 12\,\frac{\mathrm{l}}{\mathrm{min}}]$. If the error dynamics of the system trajectory x and the nominal system trajectory $\bar{x}$ of the nominal system $\bar{x}(k+1) = A\,\bar{x}(k) + B\,\bar{u}(k)$ is stabilized by the linear quadratic controller K,

$$e(k) = x(k) - \bar{x}(k): \quad e(k+1) = (A + BK)\,e(k) + w, \tag{5}$$

there exists a robust invariant set $Z \in \mathcal{X}$ so that

$$\forall e \in Z: \quad (A + BK)\,e + w \subset Z. \tag{6}$$

For the system states x holds

$$x(k+1) \in \bar{x}(k+1) \oplus Z, \tag{7}$$

if the control law

$$u = \hat{u} + K(x - \bar{x}) = \hat{u} + Ke \tag{8}$$

is applied. This control law, if applied constantly, guarantees that the actual system trajectory x is forced to a neighborhood of the nominal system trajectory $\bar{x}$. The uncertainty of the system trajectory x depends on the limits of the system disturbances covered by $\mathcal{W}$. This control law was implemented while $\hat{u}$ is the optimal control signal computed by the predictive controller. The problem solved as a predictive control problem over the horizon H_p was

$$J^*(\hat{x}, x_r, u_r) = \min_{\hat{u}}\ J(\bar{x}, \bar{u}, x_s, u_s, x_0, x_r, u_r) \tag{9}$$

$$s.t.\ \ \bar{x}(i+1) = A\,\bar{x}(i) + B\,\bar{u} \tag{10}$$

$$\bar{x}, x_s \in \mathcal{X} \ominus Z \tag{11}$$

$$\bar{u}, u_s \in \mathcal{U} \ominus K\,Z \tag{12}$$

$$\bar{x}(H_p) \in \mathcal{X}_f \tag{13}$$

$$\bar{x}(0) - x_0 \in Z. \tag{14}$$

The robust invariant set of final states for the nominal system is denoted as $\mathcal{X}_f$. The constraint (13) guarantees asymptotic convergence. The cost function J is then defined as

$$\begin{aligned} J(\bar{x}, \bar{u}, x_s, u_s, x_0, x_r, u_r) = &\sum_{i=0}^{H_p-1} \|\bar{x}(i) - x_s\|_Q \\ &+ \|\bar{u}(i) - u_s\|_R + \|\bar{x}(H_p) - x_s\|_P + \|x_s - x_r\|_T \\ &+ \|u_s - u_r\|_T + \|\bar{x}(0) - x_0\|_F. \end{aligned} \tag{15}$$

This formulation guarantees feasibility. The state reference x_r in this application is set by the signal $P_{aCO_2,r}$ and a corresponding u_r is computed from steady state conditions. The artificial state x_s with corresponding u_s are introduced for reference tracking. If x_r and u_r do not satisfy the conditions (11) and (12), x_s and u_s are chosen to be as close as possible to the reference values while keeping the problem feasible. Thus, the system is driven to the reference while the conditions for robust behavior are still satisfied. For further details please refer to Alvarado et al. [11].

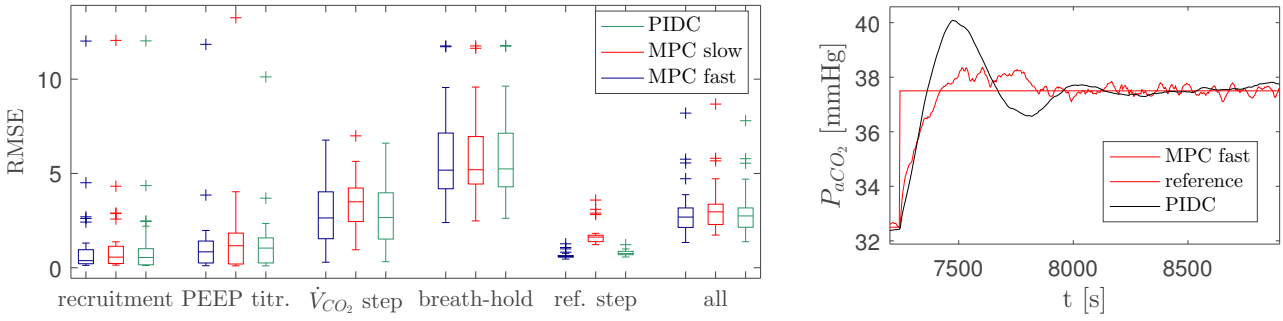
Actuator element: The actuator module is modeling the behavior of a lung-protective ventilation mode continuously optimizing the respiratory frequency. The operating point of the ventilator in terms of respiratory frequency, tidal volume and the pressure rise time set in response to the alveolar minute volume demand represents a minimum of the mean rate of inspiratory work of breathing (WOB). This functional is a clinically accepted criterion for lung protective ventilation, [12–14]. This adapting optimal breathing frequency defined then the sampling frequency of the measurement signal.

2.3 Testing Procedure

The MPC controller were tested in comparison to a PID controller with an anti-windup structure regarding five interventions: **1.** A recruitment maneuver with a PEEP step from 5 mbar to 15 mbar (recruitment), **2.** A PEEP ramp and PEEP titration maneuver in 5 mbar steps up to 25 mbar (PEEP titr.), **3.** A step in the CO_2 production ($\dot{V}_{CO_2}$) of 75 % of the mean CO_2 production measured in the preclinical study ($\dot{V}_{CO_2}$ step), **4.** A breath-hold maneuver (breath-hold) and **5.** A 5 mmHg step in the reference signal (ref. step).

3 Results and Conclusions

Results:
The controller performance was compared in a variety of situations and in parts even close to the limits of the underlying



(a) RMSE between reference signal and P_{aCO_2}; time segment of 1400 s

(b) Exemplary step responses ***PIDC*** and ***MPC fast***

Fig. 2: Results of in-silico testing. The row named all compares all interventions in series.

ventilation mode. The root mean squared error (RMSE) between the reference signal and the P_{aCO_2} signal was chosen as a general criterion for comparison. In Fig. 2a the results for the controllers tested on all 30 model parameter sets are shown. The outliers are caused by a single patient model with very high blood volume in combination with a high metabolic activity. In this case the maximum value of the alveolar minute volume of the actuator was still just not sufficient. Comparing the performance based on the RMSE the robust behavior of the closed-loop system was optimal. But this measure is not entirely suitable to justice performance details. While ***MPC slow*** reacted slowly on the disturbances ***MPC fast*** and the ***PIDC*** design caused almost alike errors to the reference signal. Still ***MPC fast*** was superior to ***PIDC*** regarding performance in less overshoot and minimizing oscillation as shown in Fig. 2b.

Conclusions:

This study contributes to current developments in physiological closed-loop systems [15]. In contrast to decision support systems previously presented for example by Becher et al., the proposed control structure was designed to counteract disturbances with fast reaction requirements, [16]. Demonstrating robust performance this work points out a start for an P_{etCO_2} based P_{aCO_2} control development ready for admission process.

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