History and Challenges of Automatic Feedback Control of Oxygenation

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Abstract. *The necessity for automatic feedback control of oxygenation became very visible during the COVID-19 pandemic. Insufficient and overworked clinical staff were unable to provide optimal therapy to patients suffering respiratory failure. This paper describes the history of automatic feedback control of oxygenation and highlights challenges in modelling the patient, synthesis of feedback controller, and validation methods. It should serve as a foundation for future work on this topic.*

Keywords

Physiological Closed-Loop Control, Mechanical Ventilation, Respiratory Modelling, Controller Synthesis.

1. Introduction

Precise regulation of oxygen levels during mechanical ventilation is vital for patients suffering from respiratory failure. The general approach to regulating the oxygen level during mechanical ventilation is for the clinician to manually adapt mechanical ventilator settings based on measurements of the oxygen level. This *clinician-in-the-loop* approach remains workforce intensive and requires well-informed clinicians. At the height of the COVID-19 pandemic, this proved a considerable bottleneck and prevented many patients from receiving optimal care.

Automatic feedback control of oxygenation presents an alternative to the *clinician-in-the-loop* and has been researched for over half a century. It allows a control algorithm to automatically adapt ventilator settings to keep a patient within a defined oxygenation target range - without the clinician being present. As is shown in the block diagram in Figure 1, the system has a feedback loop containing a sensor and a controller. In this paper, we take a closer look at the system to be controlled (the patient) and available models thereof, past and present sensors for measuring oxygen, and control topologies used. A brief discussion on available commercial systems and future possibilities is given.

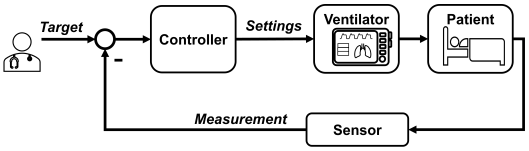

Fig. 1. Block diagram of the closed-loop oxygenation control.

2. Modelling the Oxygen Cascade

The survival of aerobic organisms is conditional upon the presence of sufficient oxygen and expulsion of excess carbon dioxide. Oxygen enters the body through the lungs, diffuses into the blood, and is transported to the tissue, where the synthesis of adenosine triphosphate (ATP) - the cellular energy currency - occurs. Excess oxygen and the by-product carbon dioxide are then transported back to the lungs, where carbon dioxide is expelled, and oxygen uptake restarts. A block diagram of the process is shown in Figure 2. Since the highest oxygen levels are present in the lungs and the lowest in the returning venous blood, the process is called the *oxygen cascade* [1].

In the lungs, adequate gas exchange is heavily reliant on the cooperation of three processes, namely 1) ventilation, 2) perfusion, and 3) diffusion. Equally important is the ability of blood to transport large amounts of oxygen. Instead of physically dissolved oxygen (which accounts for less than $2\,\%$), the oxygen is chemically bound to haemoglobin molecules. This non-linear relationship is given by the oxygen dissociation curve and is dependent on temperature, pH, and carbon dioxide levels in the blood - the chemical composition (or acid-base) status of the blood.

Modelling the cardio-pulmonary system has been the subject of much research. Grodins et al. first described a dynamic model of the cardiopulmonary system in 1954 [2]. Interest and expertise in the modelling and simulation of dynamic biological systems increased rapidly with computing capabilities [3, 4]. These new models included multiple compartments (such as the lungs, brain, and tissue) and considered the ability of the body to regulate internal variables by changing cardiac output and ventilation. The extensions also included chemical buffering, gas transport (Haldane and Bohr effects) and described the many transport delays [4]. Fincham and Tehrani extended this model to include respira-

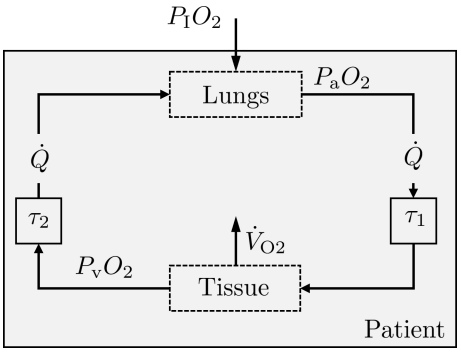

Fig. 2. Simplified representation of the cardiopulmonary model to show the oxygen cascade. The oxygen levels are expressed by partial pressure of oxygen in the inspired air (P_IO_2), arterial blood (P_aO_2) and venous blood (P_vO_2). The $\dot{Q}$ is the cardiac output, $\tau_{1,2}$ refer to transportation delays and $\dot{V}_{O2}$ is the oxygen consumption in the cells.

tory work output, the Hering-Breuer reflex, and increased the timing resolution of the model showing intra-breath states [5].

As early as 1949, Riley et al. proposed a static three-compartment model for the pathological lung [6]. Their model included three compartments: the alveolar dead-space compartment (ventilation but no perfusion), shunt compartment (perfusion but no ventilation - also known as venous admixture), and the ideal alveolar compartment (matched ventilation and perfusion). Therefore, only the portion of the blood flowing past the ideal alveolar compartment is oxygenated. The other portion of deoxygenated venous blood is mixed with the newly oxygenated blood to give the arterial blood oxygen concentration.

Chiari et al. [7] used the shunt and dead-space compartment and improved descriptions of the acid-base levels in their extension of the Grodins model [4]. Vidal-Meto et al. considered the effect of diffusion impairment and expanded on the description of heterogeneous ventilation-to-perfusion ratios ($\dot{V}/\dot{Q}$-mismatch) in their model [8].

An important extension of the Riley model was presented independently by Roe et al. [9] and Karbing et al. [10]. They split the ideal alveolar compartment into seven [9] or two [10] compartments to better simulate the $\dot{V}/\dot{Q}$-mismatch present in the lung. These models are only applicable to steady-state simulation; however, they bring crucial diagnostic information. They have therefore also been used in decision support systems for the intensive care unit [11].

2.1. Linear and Reduced Order Models

The above described mathematical models are complex, higher-order, and are difficult to accurately parameterize. As such, for controller synthesis, linearisation and reduced-order models were used instead. The most common model is the first-order plus dead time (FOPDT) system, which simplifies the input-output relationship for small input signal variations (ΔFiO_2) to:

$$G(s) = \frac{\Delta SpO_2}{\Delta FiO_2} = \frac{K}{\tau \cdot s + 1} \cdot e^{-s \cdot T_d} \quad , \qquad (1)$$

where K is the open-loop gain, τ is the time constant and T_d is the dead time. The open-loop gain of the linearised system can vary greatly and depends on the operating point chosen for the linearisation. Furthermore, the time constant and dead time depend on different factors, such as patient size and cardiac output, and include the measurement dynamics, as shown in the next section.

As an extension of the simple FOPDT representation, a Hammerstein model can be used to couple the static non-linear models of Roe [9] or Karbing [10] with a linear dynamic model. In this case, the gain was determined by non-linearity.

3. Measurement of Oxygen Levels

The clinical standard for measuring oxygen levels is the partial pressure of arterial oxygen (P_aO_2). P_aO_2 is only measurable invasively and is currently limited to discrete blood gas analysis. Previously, intravascular sensors, such as the umbilical arterial oxygen electrode sensor, were available for the continuous measurement of P_aO_2 in preterm infants [12]. The use of intravascular sensors has ceased (due to slow reaction time and lack of commercial systems) and was replaced by non-invasive sensors such as the transcutaneous gas sensor (on-the-skin) (tcO_2) or the pulse oximeter to measure peripheral oxygen saturation (SpO_2), which is the most common feedback sensor.

However, these sensors include an increased and highly variable transportation path, from the aorta to the periphery, as well as the diffusion from peripheral arteries to the vascular epithelium [13]. The considerable variation in transport time is also well documented for the SpO_2 measurement. Studies showed that the measurement site (forehead, ear, finger, or toe), the body temperature of the patient, and the perfusion at the measurement site all significantly impact the reaction time of the sensor [14]. In addition, pulse oximeters guarantee an accuracy of ± 2-3% SpO_2 in a range of 70-100%. The accuracy degrades below 70% due to the absence of data for the empirical calibration process.

The limited accuracy and increased transport delay of the measurement need to be considered in the design of the automated system.

4. Control Topologies

As explained above, the non-linear and time-varying dynamics of the cardio-pulmonary system, as well as the inter-patient variability in characteristics of respiratory fail-

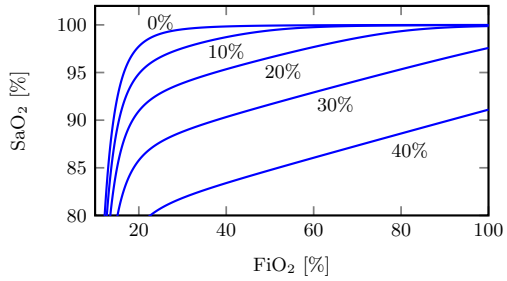

Fig. 3. Static non-linear relationship of FiO_2 to SpO_2 for different shunt fractions.

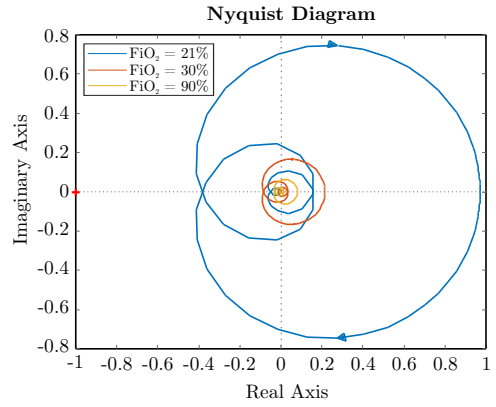

Fig. 4. Nyquist plot for the linearised models at a shunt of 25 %.

ure make designing a stable and performant controller very challenging.

As an illustrative example, the patient is modelled using the Hammerstein model mentioned above. The static non-linearity is shown in Figure 3 for a shunt fraction of 25 %. The linear dynamics are described by a FOPDT, with unit gain, a nominal time constant of 25.4 sec and a dead time of 22 sec. Assuming we linearise the system at discrete values of FiO_2 the open-loop system can be estimated.

The Nyquist plot for the resulting linear open-loop models is shown in Figure 4. Clearly, the closed-loop response will vary greatly, possibly even becoming unstable if the controller is synthesised for the wrong linearisation point. Importantly, this illustrative example only includes the effect of an uncertain open-loop gain. The effect of an uncertain time constant and dead time make matters considerably worse. In particular, the uncertain dead time can lead to problematic decreases in controller performance.

The earliest feedback control of oxygenation was proposed by Mitamura et al. in 1975, but the controller was a simple *on-off* relay control for the oxygen mixer [15].

The proportional-integral-derivative controller, which is the industrial standard for feedback control, was used by several researchers for the control of oxygenation [16]. Since the standard form of the PID-controller does not allow large uncertainties in system parameters, an offline identification for each subject was performed, with the subsequent tuning of the PID-values [17]. Whilst this approach worked in animal trials, it is unrealistic to transfer it to an intensive care unit. The use of gain-scheduling was applied by Raemer et al., which partially compensated for the variation in open-loop gain [18]. However, the initial tuning also required a manual identification to be performed.

An adaptive controller varies the control law depending on the online-identified system. Yu et al. employed a multiple-model adaptive control to match the current system model to a controller from the *a priori* tuned controller bank [19]. Dugdale et al. used a robust controller to guarantee stability for the worst-case open-loop gain, time constant and dead time [20]. Whilst this is a safe option, control action is normally very conservative and no dynamic response is presented in their paper. A combination of adaptive and robust controllers was used by Sano et al. [13]. An extensive review of the feedback control of oxygenation in presented by Claure et al. [21].

An alternative to the classical and modern controllers are the simple rule-based systems. Here, clinical protocols and clinical thinking are mimicked by rules. These were successfully applied by Waisel et al. [22] and Pomprapa et al. [23], but their decisions are based on quasi-static feedback signals.

5. Discussion

There has been much research both in the dynamic modelling of the cardio-pulmonary system and automatic feedback control of oxygenation. However, many of the complex, higher-order models are not directly useful for the synthesis of controllers. In addition, most of the models have not been independently validated [24].

As such, most researchers have relied on the simple first-order plus dead time model to design the controllers. Whilst early results for simpler controllers, such as the PID-control, show some merit, a complete analysis of the robustness - both in performance and stability - has yet to be performed. Sano et al. [13] and Yu et al. [19] applied the most modern controller designs with varying degrees of success. At the same time, the increased complexity does not allow for transparency and understanding. This limits the ability to transfer the concepts to the intensive care unit.

The final and true test for automatic feedback control of oxygenation remains a clinical study, and the availability of commercial systems for closed-loop control of oxygenation in neonates is making this possible [25]. Early results show that patients spend more time in the target zone than *clinician-in-the-loop* systems [21].

In summary, despite the many advances in modelling and feedback control, the real breakthrough for modern control theory to be applied to automatic control of oxygenation

is yet to occur. It requires more structured model analysis from the control engineering viewpoint and the availability of large, time-series datasets from patients in the intensive care unit. Based on these validated models, a thorough controller synthesis and robustness analysis needs to be performed. In addition, the transparency of controllers needs to be increased, such that clinical staff understand and trust them.

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