SIMULATING A CLOSED LOOP CONTROLLER FOR LONG-TERM OXYGEN THERAPY

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Abstract: While Long-Term Oxygen Therapy (LTOT) is standard treatment in Chronic Obstructive Pulmonary Disease (COPD), optimal delivery of supplemental oxygen for patients remains uncertain. The fixed flow-rates set during LTOT are unresponsive to patients' fluctuations in oxygen requirement. In many COPD patients, arterial oxygen saturation (SpO_2) while receiving LTOT falls below an acceptable threshold (SpO_2<90%) for extended periods during routine daily activities. Using a closed-loop PID controller, we describe a method of actively varying flow-rates in response to the measured oxygen demand. We have demonstrated how SpO_2 measurements from pulse oximetry can be integrated into an automated flow-rate controller. Initial simulation findings indicate an optimized matching between oxygen supply and demand, maintaining SpO_2 above threshold to maximize therapeutic efficacy. The study illustrates the potential to significantly improve the efficacy and economic delivery of this widespread therapy.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is estimated to affect over 900,000 people living in the UK, with a combined annual direct and indirect cost to the NHS of approximately £982,000,000. Long-Term Oxygen Therapy (LTOT) has been shown to increase survival among patients with COPD. The 'Nocturnal Oxygen Therapy Trial' demonstrated that an average of 19 hours versus 12 hours of oxygen therapy per day led to a proportional reduction in mortality [1]. As well as an increased survival, other recognized benefits include a decrease in hypoxia-induced elevations of hemoglobin, increased stroke volume index, improved exercise tolerance, and improvement in quality of life [2,3]. Despite the positive benefits of LTOT, even short periods of hypoxemia can lead to right ventricular hypertrophy from increased pulmonary artery pressure and pulmonary vascular resistance [3].

As oxygen flow-rates remain fixed during LTOT, delivery will not respond to patients' fluctuations in oxygen demand. Several recent outpatient studies using ambulatory pulse oximetry confirmed the existence of hypoxemic periods during LTOT. Over the course of daily activities, corroborating studies revealed an average of approximately 25% of the monitored period spent with a SpO_2 <90% [4,5,6]. By eliminating these periods of hypoxemia there may be further proportional health, practical and economic benefits. We report preliminary results on a closed-loop controller capable of actively varying flow-rates during LTOT in response to the measured pulse oximetry.

Materials and Methods

Figure 1 illustrates the feedback system schematic. A microprocessor receives measurements from a pulse oximeter and automatically computes the optimum oxygen flow-rate. The controller outputs a signal to a flow regulator managing the delivery of oxygen to the patient. An oxygen saturation target of 91% is maintained by changing the flow-rate subject to feedback from the pulse oximetry. This control scheme has been preliminarily implemented in a computer simulation on Simulink™ via a close-loop proportional-integral-derivative (PID) algorithm. The controller is evaluated using a model developed to approximate the patient oxygen saturation response.

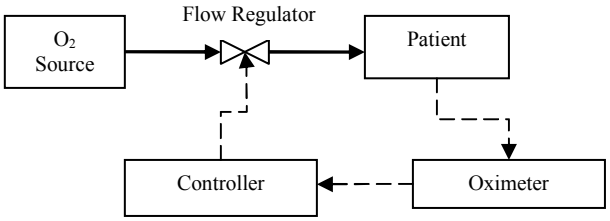

Figure 1: Active LTOT, close-loop schematic

The closed-loop simulation consists principally of two components, the Controller and Patient models as shown in Figure 2. The controller computes the error (E) between the target setpoint and measured oximetry value. It then determines the oxygen flow-rate output to the patient. The patient saturation is modelled as a composite value, dependent on the oxygen flow rate and a local arbitrary disturbance. Each of these two main components is discussed in detail below. The simulation also accounts for the discrete sampling from the pulse oximeter which is assumed to have a sampling rate of 1Hz.

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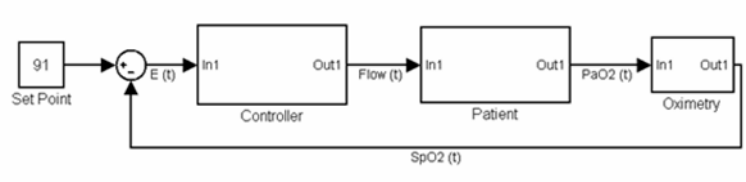

Figure 2: Top level Simulink block diagram

A PID controller constitutes the active subcomponent of the control algorithm. The PID function used extensively in controls is given in Eqn.1. Overall, the PID function endeavours to correct for any input errors (E). The response (U) of the PID function is characterized by the proportional (K_P), integral (K_I) and derivative (K_D) parameters. The output, U, can be viewed as the oxygen flow-rate in liters/minute. The PID function can also be expressed in terms of its Laplace transfer function as in Eqn.2.

$$U(t) = K_P E(t) + K_I \int E(t)dt + K_D \frac{dE(t)}{dt} \quad (1)$$

$$U(S) = \frac{K_D S^2 + K_P S + K_I}{S} \quad (2)$$

Since the simulation assumes a maximum sampling rate from the pulse oximeter of 1 Hz, a discrete filter has also been incorporated into the control algorithm. A Butterworth lowpass filter is used to screen out higher frequencies near the sampling rate. It also reduces the potentially detrimental affects of noise or spurious measurement from the pulse oximeter. In addition, the filter will ensure a stable flow-rate response from the control algorithm. The transfer function for the first order lowpass filter is presented below.

$$W(S) = \frac{A + AS^{-1}}{1 + BS^{-1}} \quad (3)$$

As a patient safety matter, the oxygen flow-rate must have a maximum and minimum limit. In the control algorithm this is accomplished via a non-linear saturation regulator. The minimum flow-rate limit is 0 l/min, and the maximum limit has been set to 5 l/min. Thus the flow controller can only output values within this predetermined range. The Simulink block diagram for the controller is depicted in Figure 3.

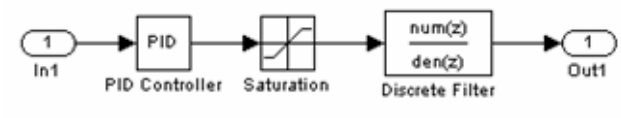

Figure 3: Simulink Flow Controller block diagram

The model representing the patient saturation response is best described mathematically. The function (Eqn.4) governing the patient's arterial pressure of oxygen has three distinct components: a baseline level (P_0), an arbitrary disturbance (D), and an oxygen flow-rate dependence (F). Combined together, their sum represents the patient PaO_2 in mmHg. P_0 can be considered the default value. In the absence of any disturbance or oxygen flow, this baseline level approximately yields a 91% saturation.

$$PaO_2(t) = P_0 + D(t) + F(t) \quad (4)$$

Where $P_0 \sim 60$mmHg

$$D(t) = -3 + 3\cos ine(2\pi f) \quad (5)$$

Where f = Frequency (Hz)

The arbitrary disturbance, D(t), introduces fluctuations from the baseline level. These fluctuations simulate the conditions possible in COPD patients during changing exertion or sleep. Negative disturbances will induce hypoxemia ($PaO_2 < 60$mmHg), while positive values raise the $PaO_2 > 60$mmHg. For the purpose of the simulation, D(t) is given by a cosine function with a bias of -3 and amplitude 3, oscillating between 0 and -6 mmHg. Nevertheless, any arbitrary input can be given to the system. Eventually the model could receive actual patient oximetry recordings.

Capturing the oxygen flow-rate dependence, F(t), requires a more complicated differential equation. A change in the fraction of inspired oxygen (F_IO_2), takes time to diffuse down to the blood capillaries where the pulse oximetry measures the oxygen saturation. This is known as the lung-to-capillary circulatory time. By looking at the response to a step change in F_IO_2 illustrated in Figure 4, two phases can be identified. The time from onset until a measurable change in saturation is know as dead time (T_1). The lag time (T_2) is approximately the time between the first measurable change and the final stable measurement.

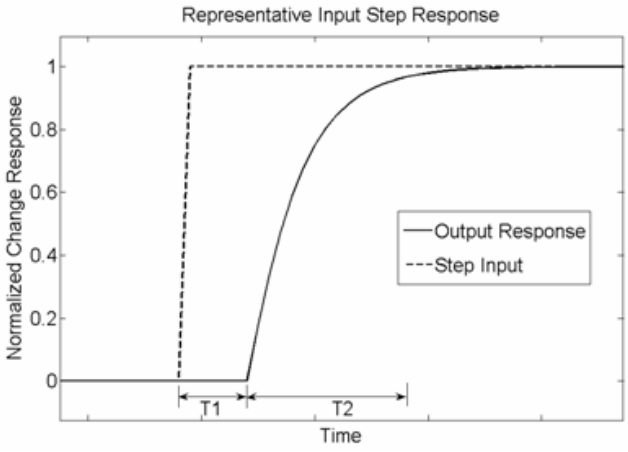

Figure 4: Flow-rate step response

Several studies have investigated the lung-to-capillary circulatory time based on pulse oximetry measurement [7,8]. It appears sensor placement is a key factor affecting the lung-to-capillary time. Pulse oximetry is commonly obtained from sensors at the foot, hand or ear. Overall, measurements from the ear

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displayed the shortest delay times. Ear sensor measurements also were the least sensitive to error from either exercise or cold [9]. Based upon these studies, T_1 and T_2 are approximately 6 and 15 seconds, respectively [10]. However, these values are certain to contain variability between patients from physiological parameters such as shunt fraction, respiratory rate, heart rate, cardiac output.

In order to model the lag time (T_2), F(t)* is given by the differential equations for a mass-spring-damper system. Eqn. 6 defines the dynamic behaviour as a function of oxygen flow-rate. M,B,K are all parameters given to the model to yield the appropriate lag time. Furthermore, the dead-time (T_1) is also included in corresponding transfer function, Eqn.7. Since F(t) must be in mmHg, a sensitivity factor α is utilized. This factor is derived from the following relationship. For each additional l/min of oxygen flow-rate provided, the F_IO_2 increases by approximately 3% [11].

$$F(t)^* = M\frac{d^2x(t-T_1)}{dt^2} + B\frac{dx(t-T_1)}{dt} + Kx(t-T_1) \quad (6)$$

$$F(S)^* = e^{-sT_1}\left[\frac{1}{MS^2+BS+K}\right] \quad (7)$$

$$F(t) = \alpha F(t)^* \quad (8)$$

Ultimately, the pulse oximeter measures the oxygen concentration in terms of percent saturation. The saturation can be calculated from the arterial oxygen pressure using the Severinghaus oxyhemoglobin dissociation relationship [12] shown in Figure 5. The combined patient saturation value is then feedback into the closed loop controller.

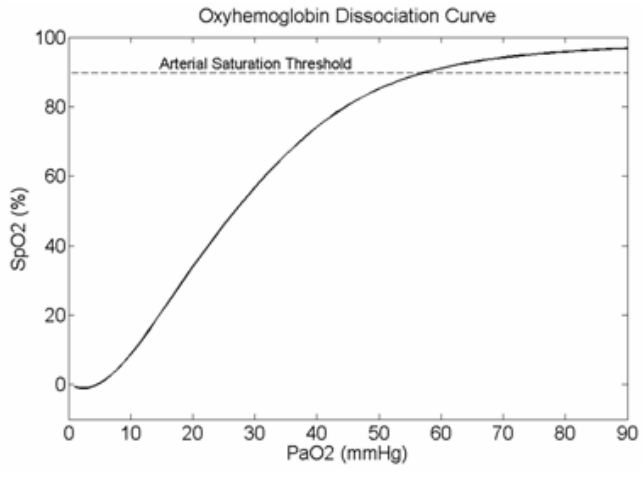

Figure 5: Oxyhemoglobin disassociation curve

The closed-loop system response is evaluated at frequencies between 10^{-3} to 10^{-1} Hz. A frequency sweep has been implemented across the disturbance function. Measurements can be made at any point throughout the simulation to evaluate variables of interest. Two variables are worth particular focus; the $SpO_2(t)$ as measured by the pulse oximeter, and the flow-rate(t) as output by the flow controller. These measurements will demonstrate the response and efficacy of the controller. Also, a deviation measurement is defined as the maximum difference between target saturation and the SpO_2 for a given disturbance frequency.

Futhermore, these values can be compared against an untreated patient model. In the untreated model, the disturbance will directly produce fluctuations in oximetry measurements. A ratio of the maximum deviation between the controlled model versus the untreated model can illustrate the attenuation provided by the closed-loop system. The untreated model also serves as the reference for any phase comparisons.

Results

The system is first evaluated analytically through the study of its transfer functions. This will give insight into the dynamic response and stability of the controller. The linear transfer function (Eqn.9) can be simply derived from the system diagram in Figure 6. It relates the oximetry output (O_2) to both the target input (T) and disturbance function (D). Since the target input (T) does not vary with time, the equation can be rewritten as in Eqn.10. This form of the equation yields the system output in terms of an input disturbance function (D). It should be noted that the analytical transfer function only applies while the system remains linear. At high frequencies, the saturation regulator introduces a non-linear response.

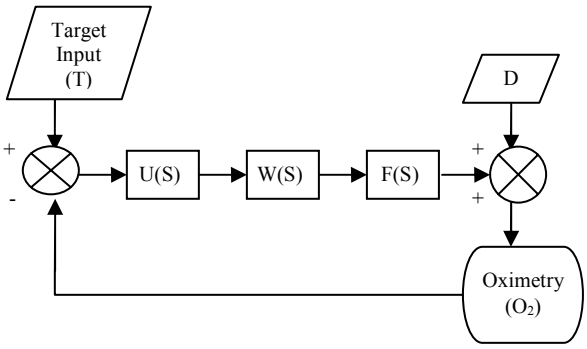

Figure.6: Transfer function diagram

$$(T - O_2)\times UWF + D = O_2 \quad (9)$$

$$-O_2 \times UWF + D = O_2$$

Where T = 0

$$O_2 \times (1 + UWF) = D$$

$$\frac{O2}{D} = \frac{1}{1+UWF} \quad (10)$$

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Figure 7 is a Bode plot of the theoretical system response across a range of disturbance frequencies. This plot gives the magnitude of attenuation in Decibels. The negative magnitudes demonstrate a decrease in the O_2 fluctuation with respect to the disturbance signal. However, positive values indicate an amplification in the disturbance. For frequencies less than 10^{-2} Hz, the analytical predictions are acceptable. The flow controller is successful in significantly attenuating the disturbance. Nevertheless, the linear transfer function solution reveals an undesirable region of amplification around $10^{-1.8}$ Hz. This feature is due to the limitations of the 1 Hz pulse oximeter sampling rate. Furthermore, the controller must account for the time delay from the lung-to-capillary circulatory time. Together, these effects limit the systems ability to effectively manage disturbance with a period close to the lag time. This region of amplification is eliminated in the controller through the use of the non-linear saturation regulator. At this time, the non-linear element is not easily incorporated into the analytical evaluation.

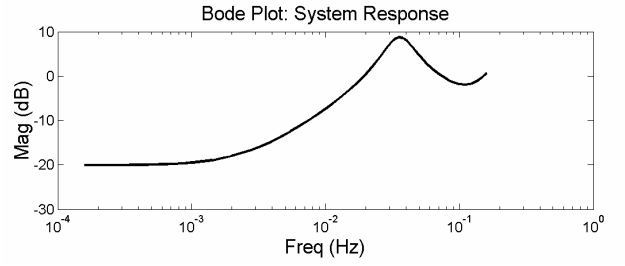

Figure 7: System Transfer Function

Hence the following results are taken directly from the simulation results. A plot of the simulated flow controller's effectiveness is given in Figure 8. Corroborating the theoretical results, the attenuation increases in relation to the period of the disturbance. At steady state or at rest, the controller will automatically provide the optimum therapeutic oxygen flow-rate. It can then significantly suppress disturbances with periods greater than a couple of minutes. Even for high frequency disturbances, the flow controller will still correct the bias offset. Notice the stable dynamic behaviour illustrated in the simulated controller effectiveness (Figure 8). Unlike the analytical solution from the system transfer function, there is no region of amplification as in Figure 7.

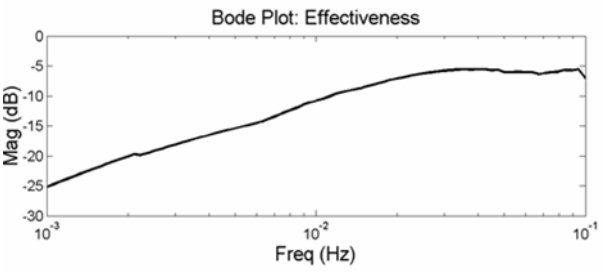

Figure 8: Attenuation in SpO_2 fluctuations

In terms of clinical effectiveness, the controller response must be analyzed in context of the oxygen flow-rate output to the patient. The controller suppresses a measured disturbance in the pulse oximetry by regulating the oxygen flow to the patient. In order to correct for a deviation in SpO_2, the oxygen flow-rate must be adjusted in phase and with the proper magnitude. This will attenuate the deviations in SpO2 away from the target value. Three representative simulation results are provided in Figures 9, 10, & 11 They demonstrate the controller response and effectiveness for disturbance frequencies at $10^{-2.5}$, 10^{-2} and $10^{-1.5}$ Hz respectively.

As predicted, the flow controller proved most effective for low frequency disturbances below 10^{-2} Hz. The upper plot in Figure 9 compares the oxygen saturation of the untreated model (No-LTOT) against the Active-LTOT. From the lower plot in Figure 9, it is evident that the oxygen flow-rate follows closely in phase with the disturbance function at low frequencies. The result is very minor deviations from the target saturation of 91% using Active-LTOT. In this example, the disturbance with a period of five minutes is suppressed by better than -17 dB.

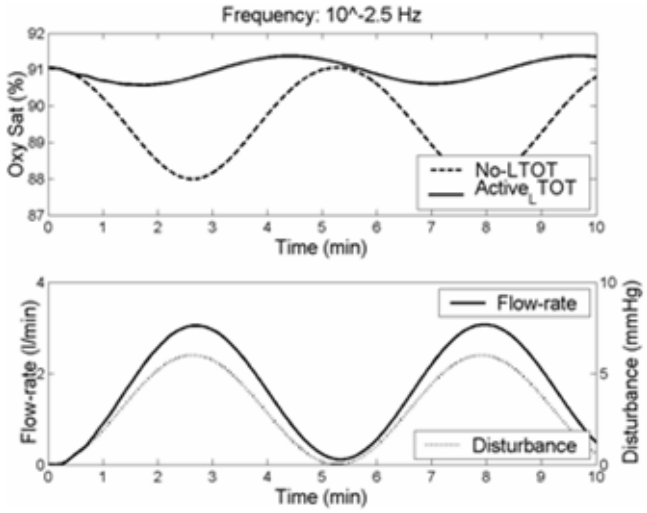

Figure 9: Simulation Results for $10^{-2.5}$ Hz disturbance,
Attenuation. = -17dB
Top: SpO_2 for Active-LTOT and No-LTOT
Bottom: O_2 Flow-rate plotted with Disturbance

As the period of the disturbance decreases, the observed suppression also diminishes. Figure 10 is the simulation results for a disturbance frequency of 10^{-2} Hz with a period of about 1.5 minutes. While the oxygen flow-rate still tracks the disturbance function, there is greater discrepancy in the phase and magnitude of the flow controller response. The resulting attenuation for this disturbance frequency is approximately -10 dB.

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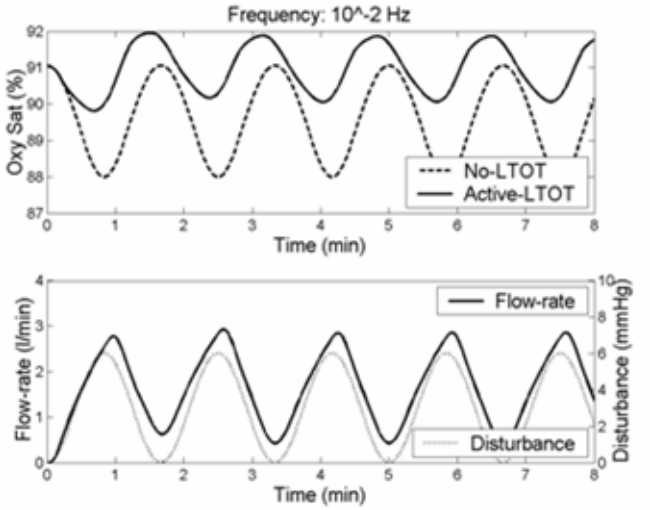

Figure 10: Simulation Results for 10^{-2} Hz disturbance,
Attenuation. = -10dB
Top: SpO_2 for Active-LTOT and No-LTOT
Bottom: O_2 Flow-rate plotted with Disturbance

In the Figure 11, the disturbance frequency is $10^{-1.5}$ Hz with a period of about 30 seconds. Here the amplitude of the flow-rate response no longer corresponds with the disturbance function. Instead the flow-rate settles around an elevated average value. For high frequency disturbances above $10^{-1.5}$ Hz, the attenuation approaches -6 dB. Note that the SpO_2 fluctuates with the same amplitude in Figure 11 despite the Active-LTOT. However, the flow-controller does manage to correct the bias of the disturbance to be around 91%. Even with high frequency disturbances, the flow controller achieves a mean saturation near the target saturation value.

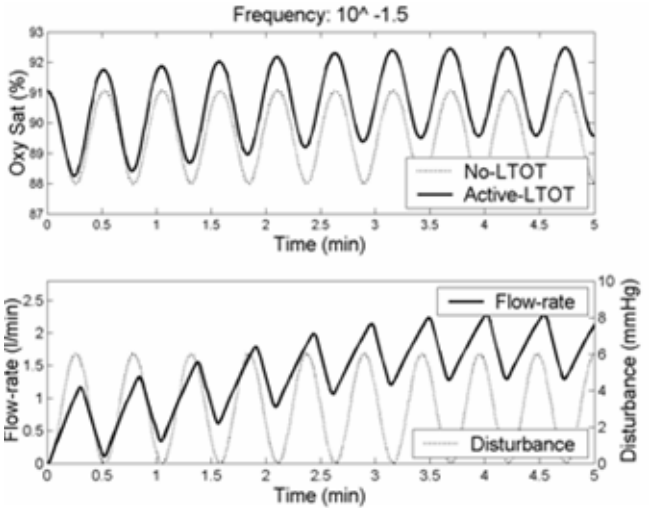

Figure 11: Simulation Results for $10^{-1.5}$ Hz disturbance
Attenuation. = -6dB
Top: SpO_2 for Active-LTOT and No-LTOT
Bottom: O_2 Flow-rate plotted with Disturbance

For high frequencies, the controller design is intended to reject the input signal. Combining the lowpass Butterworth filter with the non-linear saturation element, successfully regulates the flow-rate output. As previously mentioned, large fluctuations in flow-rate are potentially detrimental if their frequency exceeds the patient's respiratory rate. Alternatively, the simulation results indicate the flow controller attempts to find an optimum stable average flow-rate.

The plots in Figures 9 - 11 illustrate the transition in flow controller's dynamic response between lower to higher disturbance frequencies.

Discussion

The simulation results demonstrate the overall effectiveness of the Active-LTOT. The flow controller provides beneficial improvement in oxygen saturation, throughout the range of possible disturbance frequencies. Eliminating the need for a single prescription flow-rate, the Active-LTOT can automatically respond to a patient's changing needs.

The controller parameters have been iteratively tuned through trial and error to provide the best overall response. These preliminary results provided are representative of the controller behaviour. With additional refinement the dynamic response may yield further improvement. However, it is expected the system parameters will have to be somewhat modified to better accommodate patient variability not present in the current simulation. One step towards bridging the gap would be to input patients' real-time pulse oximetry as the disturbance function in the simulation. Measurements taken during different activities, such as exercise and sleep, might provide further insight into the effectiveness of the controller. Even basic information regarding the various frequency components present in the real-time signals would be beneficial towards iterating the control algorithm and parameters.

While the simulation may approximate the effectiveness of the Active-LTOT, there remains a question as how patients will adapt to the responsive therapy. In actuality, patients can not be viewed as strictly static components. As the oxygen saturation fluctuates within the body, the patient will naturally attempt to compensate. The dynamic interaction between the flow controller and the patients' instinctive response will be particularly interesting to study.

Conclusions

The aim is to develop the first automated closed-loop, flow-rate control device for patients with COPD undergoing treatment with LTOT. Simulation results indicate the benefit for this method to actively regulate LTOT. As part of the next phase in development, The PID parameters will next be validated against a database of patient oximetry trend measurements. True physiological measurements contain a wide range of signal frequencies as well as a significant amount of

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noise and artefacts. Before moving towards clinical implementation, the controller will have to demonstrate an appropriate response using actual patient measured input signals.

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