Automated Delivery of Inhaled Drugs through CPAP

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abstract

Treatment of concurrent diseases often involves the integration of multiple therapies. Individuals suffering from both obstructive sleep apnea and asthma are treated with continuous positive airway pressure (CPAP) to prevent apneic episodes during sleep. Our client would like to test the effects of delivering long-acting asthma medication in the early morning hours on the need for acute asthma therapy during the day. Dr. Teodorescu has requested a device capable of automated drug delivery in-line with the CPAP tubing. Optimal inhaler use requires synchronization of inhalation and drug release. The products of last semester included a mechanical prototype capable of agitating and actuating a metered-dose inhaler and a temperature-sensing thermistor circuit used to detect the onset of inhalation. This semester, a LabVIEW program and transistor circuits were developed to integrate existing mechanical and electrical components. Real-time data acquisition from the thermistor circuit, peak analysis/related calculations and electronic triggers were combined to provide power to the mechanical prototype with the end goal of synchronizing inhalation with actuation. Our system results in actuation during inhalation 90% of the time when the cam is reset to the upright position following each use. Infrequent errors in peak detection result in undesirable actuation during exhalation.

background

Motivation

Patients may have both obstructive sleep apnea (OSA) and asthma

OSA: Chronic airway blockage during sleep (Figure 1)

- Treated with CPAP: The use of compressed air as a stent to sustain open airway

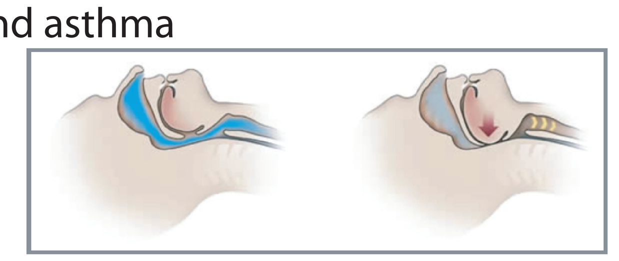


Figure 1. Illustrated effect of OSA on airway conformation: unobstructed breathing passage (left) becomes fully obstructed (right) due to the relaxation of muscles controlling anatomy in the nasal/oral cavities (fusionsleep.com).

Asthma: Constriction of airways due to inflammation, symptoms may worsen at night

- Treated with inhaled medication (long-acting and/or fast-acting)

Hypothesis: Combination of CPAP use and nighttime in-line delivery of asthma medication (over period of one month) may improve daytime asthma symptoms

Previous work

Fall 2007: Construction of mechanical prototype (Figure 2)

Development of circuit to create breathing waveform (algorithm trigger)

- Differential amplifier comparing breath and room temperatures

design criteria

- Agitate MDI to mix drug and propellant at specific time
- Detect breathing pattern to coordinate drug delivery w/ onset of inhalation (Figure 3)
- Depress inhaler to deliver one or more doses during sleep
- Deliver aerosolized drug through existing tubing
  > Utilize flow generated by CPAP machine
  > Administer drug orally using full face mask
- Size, weight and noise levels appropriate for clinical research (sleep studies)

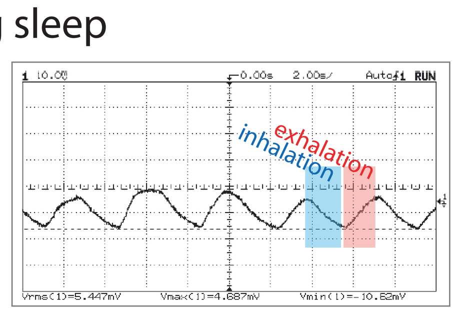


Figure 3. Oscilloscope screenshot illustrating phases of breathing within temperature waveform.

circuitry

- Output voltage varies with fluctuations in temperature of air leaving mouth port of mask
- Difference amplifier used to minimize effect of room temp. variation and provide gain (Figure 4).

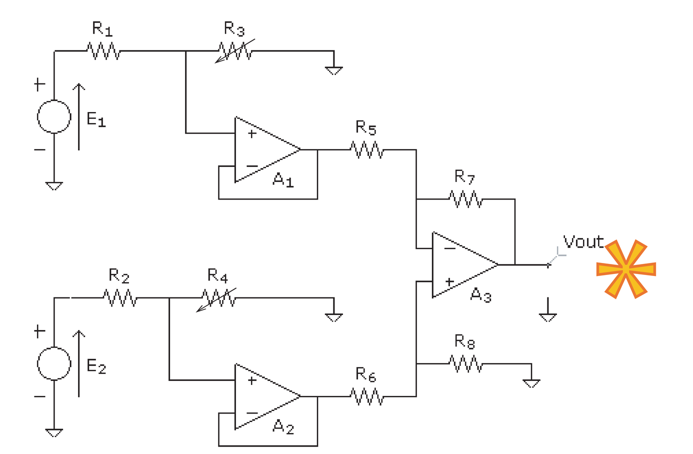


Figure 4. Diagram of differential amplifier circuit: R_3, R_4 correspond to thermistors (R_4: room temp., R_3: exhalation); R_1, R_2 ~10 kΩ; R_5, R_6 ~3.8 kΩ; R_7, R_8 ~ 82 kΩ.

Figure 5. Logic flow executed by LabVIEW program; temperature data obtained from output of thermistor circuit, motors powered on through transistor circuits. Temperature waveform used to determine average time between breaths (t_{avg}). Subsequent calculations based on temp. waveform used to synchronize onset of inhalation with drug delivery.

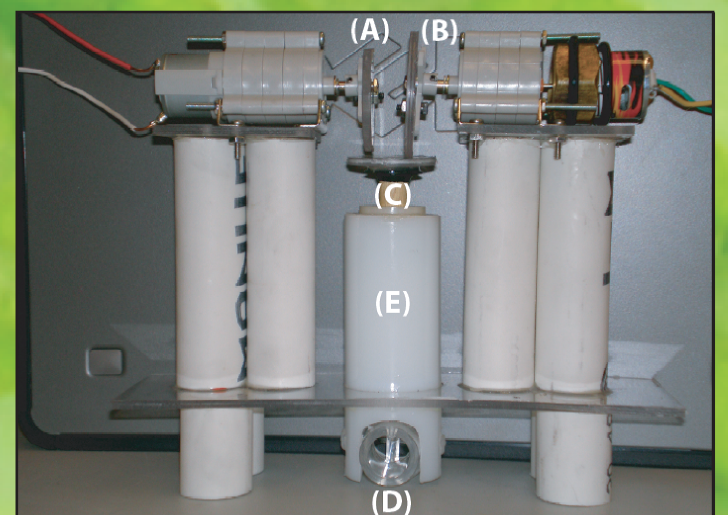
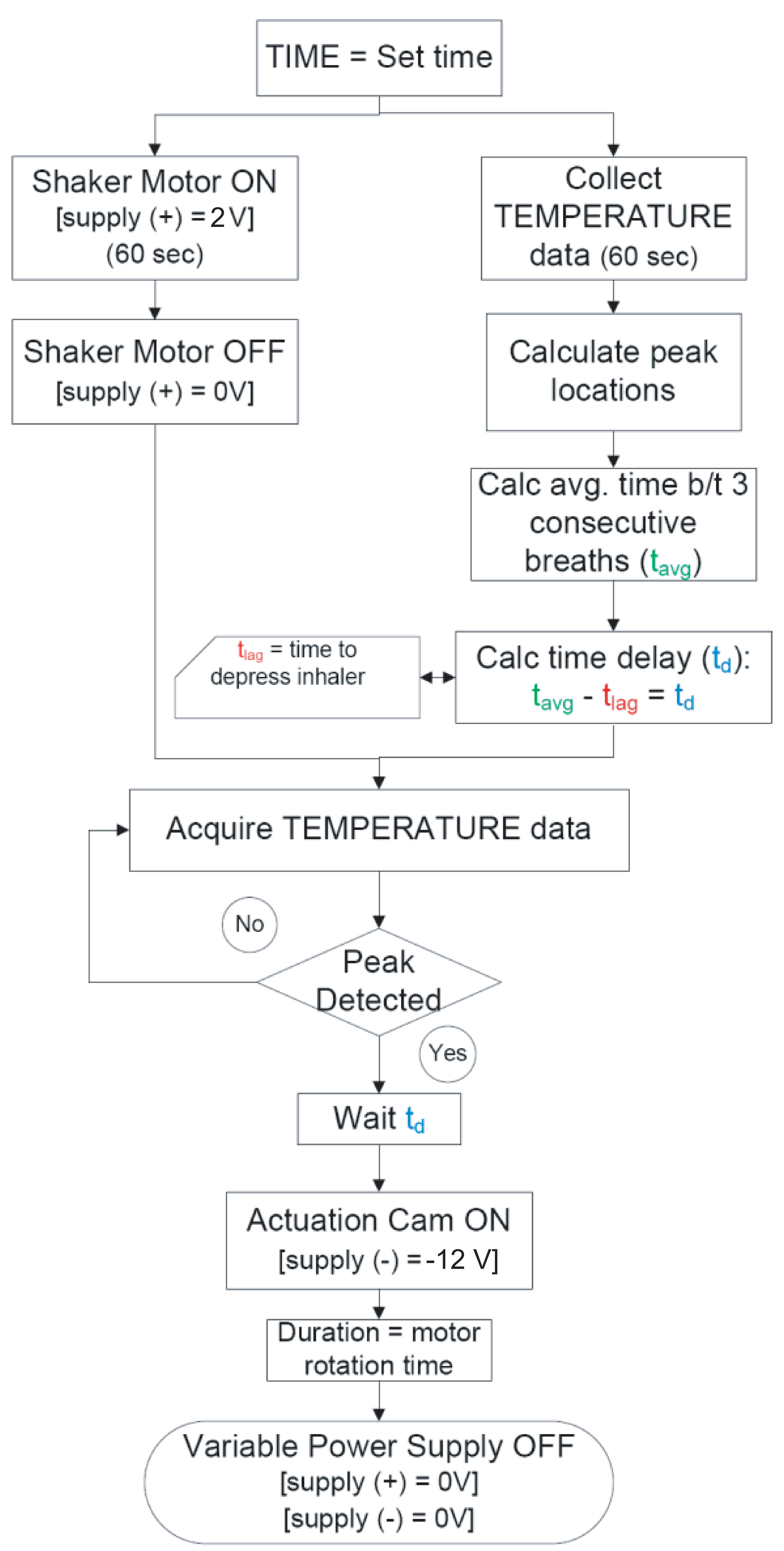


Figure 2. Photograph of current mechanical prototype: vibration cam (A), actuation cam (B), plunger (C), in-line MDI actuator (D), tube (E).

algorithm



- LabVIEW program sets SUPPLY (+) to 2V; transistor acts as electronic switch to turn on agitation motor (Figure 6).

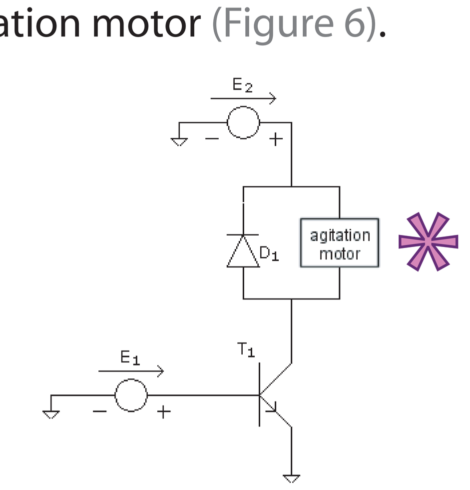
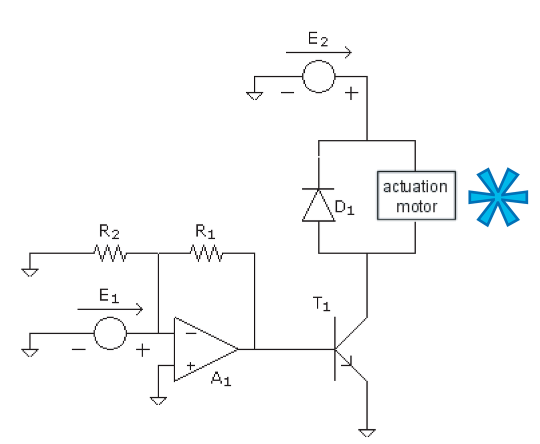


Figure 6. Diagram of transistor circuit used to control power to agitation motor. E_1 corresponds to SUPPLY (+) (variable power supply on NI ELVIS breadboard), ~ 2 V; E_2 corresponds to 3 V battery combination; D_1 serves as a protection diode; T_1 is a TIP 41C transistor. Providing +2 V to T_1 saturates transistor, allowing current flow through motor.

Figure 7. Diagram of FET circuit used to control power to actuation motor. E_1 corresponds to SUPPLY (-) (variable power supply on NI ELVIS breadboard), ~ -12 V; E_2 corresponds to 6 V lantern battery, providing up to 4 A required current; D_1 serves as a protection diode; T_1 is a FET (field-effect transistor). Inverting op amp (A1 = 1, R1 = R2) switches sign of input voltage; providing +12 V to T_1 saturates transistor, allowing current flow through motor.



- LabVIEW program sets SUPPLY (-) to -12 V; inverting op amp provides +12 V to FET (transistor), FET acts as electronic switch to turn on actuation motor (Figure 7).

testing

Tube length testing

Characterized behavior of drug + propellant spray when tubing conformation was changed.

Conclusion: Spray exits straight and bent tubes almost instantaneously (<0.1 sec) after actuation.

Accuracy & Reliability

Cam rotation

Measured offset angle after actuation (Figure 8).

Conclusion: Cam must be reset if outside specific range in order to guarantee actuation (Figure 9).

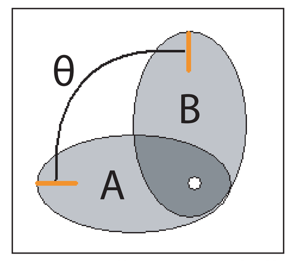


Figure 8. Illustration of offset angle (θ) formed when cam is rotated (A), not upright (B).

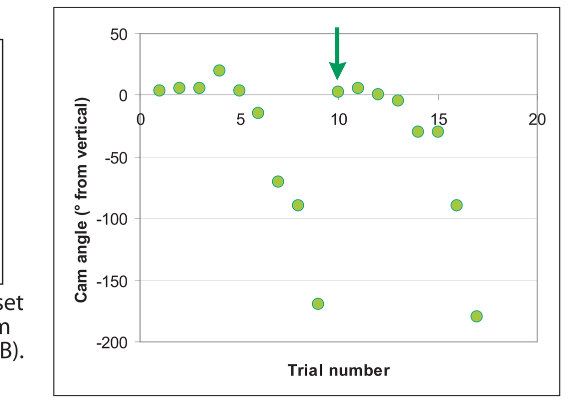


Figure 9. Cam offset angle recorded during each of 17 trials. Cam was reset to upright after trial 9; initial offset angle for trial 10 was 0°(green arrow).

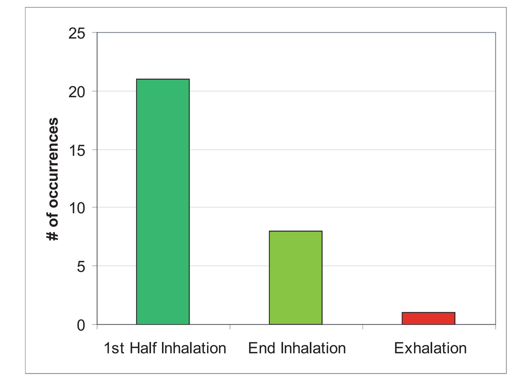


Figure 10. Number of trials during which actuation occurred within the following time periods: beginning/middle of inhalation, end of inhalation, or exhalation (n = 30).

Cam reset (± 45°)

When offset angle was > 45°, cam was manually reset (30 trials).

Results:
- Ideal actuation time (beginning/middle of inhalation) = 70%
- Acceptable actuation time (end of inhalation) = 27%
- Unacceptable actuation time (exhalation) = 3% (Figure 10).

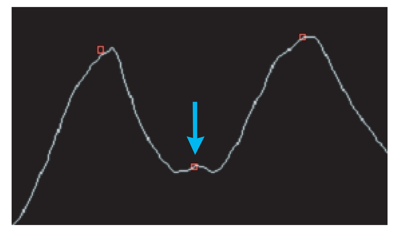
Consistent cam reset + motor correction

Cam was manually reset after each trial (10 trials). Additional lag time due to ELVIS/transistor delay was also added to algorithm.

Results: 90% success rate (Figure 11).

Single failure trial resulted from error in peak detection (Figure 12).

Figure 12. Screenshot displaying error (blue arrow) in peak detection within temperature waveform (thermistor circuit output). Erroneous peak leads to shorter peak-to-peak time, resulting in actuation during exhalation.



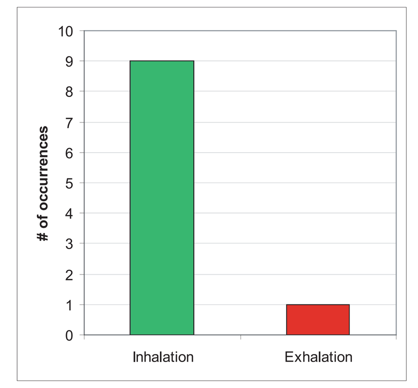


Figure 11. Number of trials during which actuation of the inhaler occurred within either inhalation (9 out of 10) or exhalation (1 out of 10).

future work

- Rebuild mechanical prototype:
  > Simplify wiring for use in clinical research setting
  > Cam design: Fabricate cams from aluminum, plunger top from Teflon®
  > Professionally manufactured/re-designed to be smaller and quieter
- Translate high-level LabVIEW software to lower-level code for microcontroller implementation:
  > Eliminate need for NI ELVIS and other large, expensive hardware
  > Facilitate development of in-home system (minimize user/engineer interaction)
- Make program "smarter"/increase accuracy:
  > Run sleep studies to acquire ideal temperature data to test algorithm
  > Develop robust error detection (ignore abnormal breaths)
- Test for proportion of drug reaching patient's lungs
  > Radiolabeled-particle study in collaboration with clinician
  > Determine appropriate # of actuations needed / night

acknowledgments

We would like to extend our sincerest gratitude to Amit Nimunkar and L. Burke O'Neal for their continued assistance in the bioinstrumentation laboratory this semester.