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Closed-Loop Intravenous Drug Administration Using Photoplethysmography

GEORGE W. CARPENTER, III[1,2], HOLLY G. MYERS[3], ERIC A. SHERER[4], KATIE A. EVANS[1], AND D. PATRICK O'NEAL[3]

[1]Department of Mathematics and Statistics, Louisiana Tech University, Ruston, LA 71272, USA
[2]Department of Electrical and Computer Engineering, Texas A&M University at College Station, College Station, TX 77843-3120, USA
[3]Department of Biomedical Engineering, University of Utah, Salt Lake City, UT 84112, USA
[4]Department of Chemical Engineering, Louisiana Tech University, Ruston, LA 71272, USA

CORRESPONDING AUTHOR: D. P. O'NEAL (poneal@latech.edu)

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ABSTRACT An optically-based injection control system has been developed for preclinical use for an intravenous drug delivery application. Current clinical drug delivery for oncology typically provides for intravenous administration without an awareness of achieved plasma concentration, yet interpatient variability produces consequences ranging from toxicity to ineffectual treatments. We report a closed-loop injection system integrating a pulse-photoplethysmograph to measure the concentration of an injected agent in the circulating blood system using a previously described technique. A proportional-derivative (PD) controller manages the injection rate in real-time. The target function for the controller is the population estimate of the pharmacokinetic model developed using Bayesian statistics describing the injection phase of a calibration set of 22 injections in mice. The controlled set of eight injections showed a reduction in variance from the target injection phase concentration profile of 74.8%.

INDEX TERMS Absorbance, automated control, Bayesian statistical modeling, indocyanine green, intravenous, population pharmacokinetics, photoplethysmography, proportional-differential controller, population model, pulse oximetry, reduced variance.

I. INTRODUCTION

The administration of medication has been simplified to the five rights: right medication, right dose, right patient, right time, and right route as a first approximation of the appropriate use of drugs. This mantra neglects the variance observed between patients and between doses on the same patient in both pharmacokinetics (i.e., drug concentration dynamics) and pharmacodynamics (i.e., effects of these concentrations). Although the vast majority of drugs that receive Food and Drug Administration (FDA) approval have a broad therapeutic window – the range of doses at which a drug is effective without unacceptable adverse events – many drugs are available with a narrow therapeutic window because the potential benefits outweigh the side effects. For example, many chemotherapeutic agents fall into this category.

For drugs with a narrow therapeutic window, the concentration can be monitored over time to be within that window based on an individual patient's response. These adjustments can be made over a longer period of time based on the pharmacodynamics (e.g., titrating the dose of warfarin or adjusting the chemotherapy dose based on neutrophil counts) or over shorter time scales by adjusting the dose based on the pharmacokinetics. In theory, adjustments based on pharmacokinetics can be performed during clinical drug administration and the area of therapeutic drug monitoring has arisen to regulate the effects of narrow therapeutic index drugs by controlling the pharmacokinetics. However, one of the limitations of therapeutic drug monitoring is the logistics of measuring blood concentrations at regular intervals and providing timely feedback during a single dose. Clinical therapeutic drug monitoring is generally restricted to measuring the pharmacokinetics during a dose and then adjusting subsequent doses based on the measured, patient-specific pharmacokinetics. Herein, we demonstrate an enhancement of therapeutic drug monitoring in which the drug concentration is measured in real-time using optical

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sensing which allows for controlling the concentration of a drug during a dose rather than waiting for the next dose.

Recent previous reports have demonstrated the use of proportional-integral-derivative (PID) control [1]–[4] with pharmacometrics or fuzzy logic theories [5] to manage the dosing of anesthesia or drugs in a clinical setting. Control in this setting can refer to the ability to manage a physiological variable within a desirable range, such as heart rate or blood pressure or brain activity, as well as the restriction of a drug concentration in vivo within a therapeutic dosing window. A significant limiting factor towards implementing control was the availability, or the lack thereof, of an associated sensing system to track an instantaneously relevant physiological state.

Our group previously implemented a three-wavelength photoplethysmograph (PPG) which measures the absorbance (which is related to concentration through Beer's Law) of optically active compounds in circulation, which was employed in this report to provide for real-time feedback. This device was used to measure the concentration of a circulating dose of optically absorptive gold nanoshells (a $\sim$100 nm diameter particle) used in medical applications such as cancer therapy [6] as well as two drugs: amphotericin B [7] and quinine [8]. The probe is physically similar to a pulse oximeter and uses a finger or murine tail/leg clip. The precision of the instrument to provide a point estimate of concentration of these nanoparticles, relative to the measurement via off-line external blood draws, was reported to be $\pm$20% in the relevant concentration ranges.

The primary objective of this manuscript is to demonstrate a system that controls the shape of the concentration versus time curve of a drug during injection by varying the injection rate of the drug in response to real-time concentration measurements. This system controls the infusion rate thus providing the recommended drug concentration. Receiving the recommended concentration is more likely to result in an effective treatment (by ensuring under-exposure does not occur) with fewer adverse side effects (by ensuring over-exposure does not occur). To achieve this objective, we calibrated a population model for the selected drug, indocyanine green (ICG) on a BALB/c mouse model; developed a proportional-differential feedback control system (PDCS) that uses real-time absorbance measurements from the PPG as feedback; and then quantified the total delivered dose and verified we could track a target concentration versus time curve through the implementation of the control system on BALC/c mice to ensure it was effective in fulfilling its purpose of reducing variance within the therapeutic window.

II. MATERIALS AND METHODS

All experiments were performed using BALB/c mixed gender mice. The care and handling of mice followed the Louisiana Tech University Institutional Animal Care and Use Committees protocol. Prior to injection, each mouse was kept under specific temperature control (35-39°C) to facilitate intravenous cannulation and to maintain consistency with drug delivery protocols designed to promote profusion. Isoflurane inhalation (3% for induction and 2% for maintenance) anesthesia was used to immobilize a mouse during the injections; this aided in the collection of data [2].

A. INJECTIONS OF ICG IN MICE

A fresh ICG solution was prepared each day with a target concentration of 156 mg/mL which, according to Beer's Law ($A = \varepsilon cd$), has an absorbance of 300; the actual absorbance of ICG used varied from 197 absorbance to 318 absorbance. Stability of the solution at this high concentration necessitated the use of DMSO (10% by volume) and spectrographic analysis to ensure that the peak at 780 nm was dominant in the stock solution [9].

ICG injections were given with the intent to reach one of three pre-specified points of maximum absorbance in the animal: small (2.25 absorbance), medium (3.00 absorbance), and large (3.75 absorbance). Each mouse was kept at approximately 36°C for the duration of the experiment in the presence of a space heating fan, and placed on a heating pad set to that temperature. The injections were carried out intravenously via tail vein using a custom catheter system fashioned from a 28 gauge needle tip and 2-french tubing. The method of injection was through a syringe pump (New Era Pump Systems, Inc. Farmingdale, NY. Model # NE-1010) which was programmed to inject the provided ICG solution at an initial rate of 15 μL/min. During the course of all injections, the data was collected by the PPG data probe, placed near the base of the mouse's tail.

B. THE PHOTOPLETHYSMOGRAPH

The PPG is a non-invasive optical monitoring device that can detect an optically active compound in the blood stream by measuring the optical extinction at three different wavelengths of light [10]. The PPG consists of an optical probe, analog signal modification circuitry and a LabVIEW DAQ which feeds all the received data into the created LabVIEW program for processing, monitoring, and cataloguing. Given the optical similarity of ICG dye to previous types of nanoparticles used, the probe was implemented unchanged using optical extinction measurements at 660 nm, 805 nm, and 940 nm. This probe detects the pulsatile blood signal in a tissue mass and calculates the concentration of ICG according to AC805/DC [7].

When using the PPG, a strict inclusion criteria was maintained on all collected data. A data point was created by the system by averaging data collected over 5 seconds. The criteria for retaining each data point was that it had a standard deviation of less than 0.03 mV, that the mouse heart rate calculated from the observations of the three system wavelengths each be within 20% of the computed mean heart rate, and that the voltage peak-to-peak of the AC portion be greater than 1.5 mV [11].

C. PHARMACOKINETIC MODEL IDENTIFICATION

The one compartment model, given by Equation (1) or (2), provided an excellent fit to the available data based on the measured absorbance. The concentration of the therapeutic agent in the mouse bloodstream was available in the form of experimental data from the PPG [11].

$$\frac{dA}{dt} = -\frac{\mathrm{CL}}{\mathrm{V}}A + \frac{\mathrm{RATE}\,(t)}{\mathrm{V}}; \quad A(0) = 0 \tag{1}$$

$$A\,(t) = \left[\frac{-\mathrm{RATE}(t)}{\mathrm{CL}}\right] e^{-\frac{\mathrm{CL}}{\mathrm{V}}t} + \frac{\mathrm{RATE}(t)}{\mathrm{CL}} + \varphi_0 \tag{2}$$

In equations (1) and (2), A is the absorbance (as an analogue for concentration), CL is the clearance rate, V is the volume of distribution, φ_0 represents the absorbance shift from baseline, RATE(t) is the injection rate over time, and t is time.

The population pharmacokinetic model was identified by comparing the absorbance versus time data and pharmacokinetic model predictions using the WinBUGS software. The covariate free one compartment model structure selected for use in this study was determined by observing the deviance information criteria of different pharmacokinetic models. The following model components were evaluated: inter-mouse variability and inter-trial variability on clearance and volume of distribution; additive, proportional, and combined residual error models; and covariate effects of heartrate, O_2 level, and mouse weight on clearance and volume of distribution. A non-informative normal distribution was used as the prior distribution for these pharmacokinetic model parameters. Inverse gamma distributions were used for the precision of normally distributed error [11].

An ICG pharmacokinetic model for BALB/c mice was identified based on concentration versus time measurements from the PPG for a total of 22 injections divided into three injection size categories: small (7 injections), medium (9 injections), and large (6 injections) (see Fig. 1).

Once the final population pharmacokinetic model was identified, we used the posterior distribution of parameters from WinBUGS as the population model parameters. These are the parameters applied to the pharmacometric model set equation (Equation 2) for developing the control system.

D. CONTROL SYSTEM AND TUNING

A proportional-derivative (PD) control system was used to control the error between the pharmacokinetic model predictions (the set equation) and the current concentration measurement (system signal). This PD system is a reduction of a proportional-integral-derivative (PID) control design. This reduction from PID to PD was used as a method of reducing the complexity of the overall system as to help maintain the aspect of proof-of-concept.

Although data points from the system were digital, not analog, the PD control system worked in much the same manner as would an analog PD control system: it numerically differentiated the error signal rather than using the analog derivative. The PPG collected data once every 5 seconds so

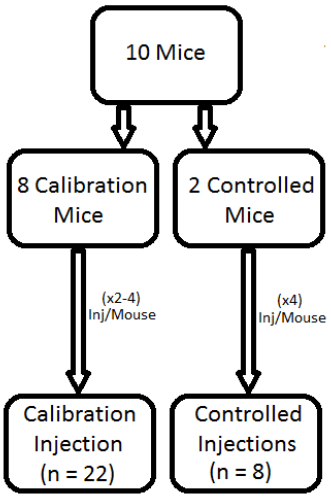

FIGURE 1. Flow chart describing distribution of mice within experimentation parameters.

the signal was discrete rather than continuous. This influenced the controller because the error signal was discrete as well. We used a continuous time solution to the differential equation for the set equation and then input the current time index of the received PPG data from the injection. This avoided any discrepancy between the analog-discrete setup we created because it allowed the analog differential equation to be used at the discrete points of data. As seen in the equation (3), the system error, e(t), is calculated and used by the PD error equation.

$$u\,(t) = k_p e\,(t) + k_d \frac{de(t)}{dt} \tag{3}$$

The values $k_p = 124.56$ and $k_d = 48.91$ were obtained using the Zeigler-Nichols tuning rule, where u(t) is the controller [12].

An important concern we held in developing a control system for use as a therapeutic device was the potential danger of an erratic or poorly tuned system to the patient. In the event the controller were to over predict and inject more than required of a therapeutic agent, the patient would be at risk of toxicity. Therefore, we developed the controller with an intentional negative bias to ensure we were below the population pharmacokinetic curve and reducing the risk of toxicity by turning off the pump if the measured concentration was above the target.

E. CONTROL SOFTWARE

The control software was the primary component for enacting the objective of this project: controlling the drug concentration with time. The control software was written in the Python programing language, version 3.3.0, and - implementing the serial, numpy, matplotlib, tkinter, time, os, and math libraries - it controls the ICG injections based on the real time absorbance measurements from the PPG. The set equation implemented for the PD control

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system (2) was the identified Bayesian population pharmacokinetic model. The system enacted its changes through use of serial communication with the injection pump, calculating a new injection rate based on the current system error. Displaying all available mouse data (heart rate, O_2, absorbance, injection rate, and total volume injected), and allowing for emergency system stop, the software was self-contained; given a concentration of ICG and valid injection endpoint, the system would run the injection to completion, auto-stop the pump, and then continue monitoring after injection.

To validate that the control system could follow a desired concentration versus time profile, the tuned system with pharmacokinetic model parameters and the PD control values were set within the software. This was then applied to a total of 8 injections on BALB/c mice, generating the controlled set. These injections were performed with 3 in the small, 3 in the medium, and 2 in the large target absorbance group. The data collected from these injections was used to determine if control based medication was a valid option in future treatments.

F. ANALYSIS OF CONTROLLED INJECTIONS

The viability of the controller was demonstrated using the error between the measured absorbance of each data point and the corresponding population pharmacokinetic model prediction. The primary outcome was the reduction in variance in the average error between data points in the calibration injections versus the controlled injections.

III. RESULTS

A. DATA INCLUSION CRITERIA

The PPG absorbance measurements were verified using the standard data metric for the device; any data collected during experiments was held to this metric to ensure reduced variability. An example of this metric for an uncontrolled injection is in the test output in Fig. 2. The applied inclusion criteria was developed by a previous project from this lab, when the PPG was developed for use with gold nanoparticles [10] (see The Photoplethysmograph subsection of Materials and Methods).

B. POPULATION PHARMACOKINETIC MODEL

A single compartment model provided an accurate and unbiased fit to the calibration data (22 injections performed on 8 mice at 3 maximum absorbance levels). There were no significant covariate effects on any of the model parameters. The resulting population pharmacokinetic model parameters are shown in Table 1.

The half-life from the calibration injections (1.89 min) agrees with a previously published report (2-4 min) [13].

C. ANALYSIS OF CONTROLLED INJECTIONS

The primary outcome is that there was a 74.8% reduction in variance of the controlled group (Fig. 3). As can be seen, not only was the controlled group less varied on an individual basis of the injections, but the overall spread of the injection around the average was smaller as well. This data definitively displays the reduced variability of the controlled injections.

A demonstration of the controller in action can be seen in Fig. 4. The system is corrected by increasing the injection rate when the measured concentration was below the target to better fit the provided target model.

With the controller in place, we had a variance comparable to that seen in the clearance rates and cardiac output metrics obtained in clinical studies employing ICG, using pulse dye densitometry [14], [15]. As seen in Fig. 5 the control group

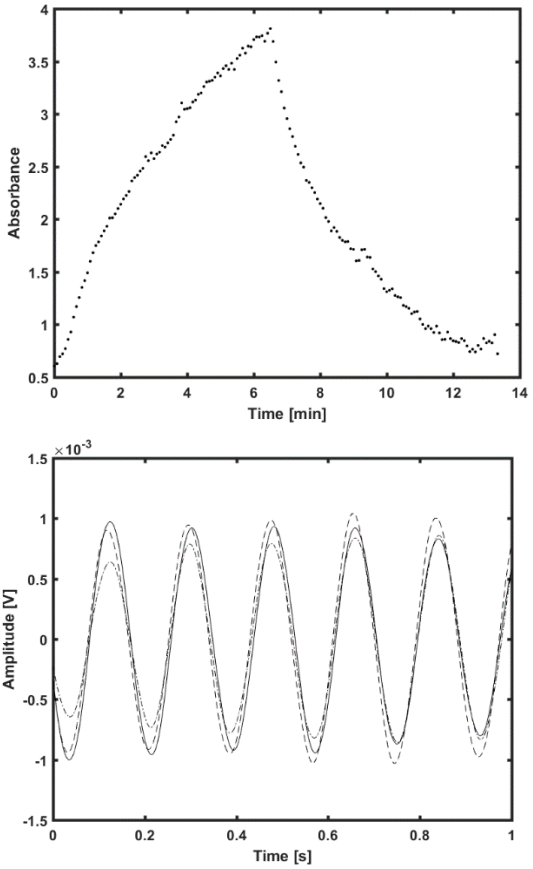

FIGURE 2. (Top) Example photoplethysmograph output of absorbance vs. time from mouse injection for an uncontrolled injection. (Bottom) Corresponding heartrate data over a 1 s interval.

TABLE 1. Population pharmacokinetic model parameters based on calibration trials (n = 22).

Median Parameter (95% Credible Interval)		
Clearance	CL	1.10 (0.920 – 1.28) mL/min
Volume of Distribution	V	3.01 (2.69 – 3.34) mL
Shift	φ_0	0.663 (0.558 – 0.769)
Inter Mouse Variability (95% Credible Interval)		
Clearance	CL	0.412 (0.313 – 0.581) mL/min
Volume of Distribution	V	0.752 (0.568 – 1.07) mL
Shift	φ_0	0.241 (0.183 – 0.341)
Residual Variability (95% Credible Interval)		
σ	-	0.0906 (0.0884 – 0.0929)

TABLE 2. Comparison between expected dose (Exp) and achieved dose injected (Inj) necessary to achieve a target absorbance in validation experiments.

Comparison between expected dose (Exp) and achieved dose injected (Inj) necessary to achieve a target absorbance in validation experiments								
Injection #	Target Absorbance	Stock Conc (mg/mL)	**Exp Vol (uL)**	**Exp Time (min)**	**Exp Dose (mg)**	Inj Vol (uL)	Inj Time (min)	Inj Dose (mg)
1	2.25	1.56	**31.20**	**2.08**	**0.05**	36.14	2.08	0.06
2	2.25	1.26	**72.45**	**2.83**	**0.09**	121.33	4.83	0.15
3	2.25	1.26	**57.45**	**2.83**	**0.07**	91.92	3.83	0.12
4	3.00	1.56	**68.70**	**3.92**	**0.11**	87.77	4.58	0.14
5	3.00	1.56	**68.70**	**3.92**	**0.11**	87.47	4.58	0.14
6	3.00	1.56	**73.80**	**3.92**	**0.12**	84.62	4.92	0.13
7	3.75	2.19	**63.75**	**3.50**	**0.14**	82.62	4.25	0.18
8	3.75	2.19	**91.20**	**3.50**	**0.20**	138.27	6.08	0.30

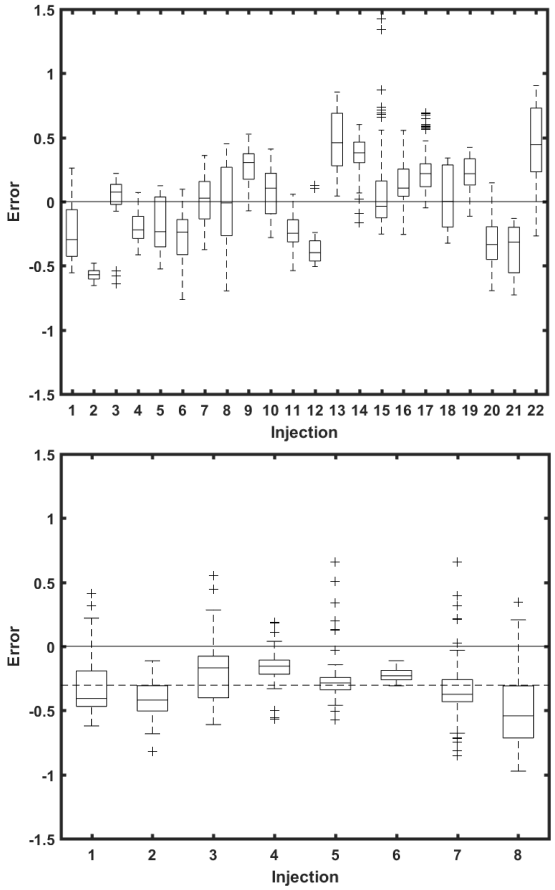

FIGURE 3. (Top) model comparison error of 22 injections from the controlled group represented as a standard box plot about the average (solid line) approximately 0. (Bottom) model comparison error of 8 injections from the controlled group as a standard box plot about the average (dashed line) approximately −0.3, calibration average (solid line) provided for comparison.

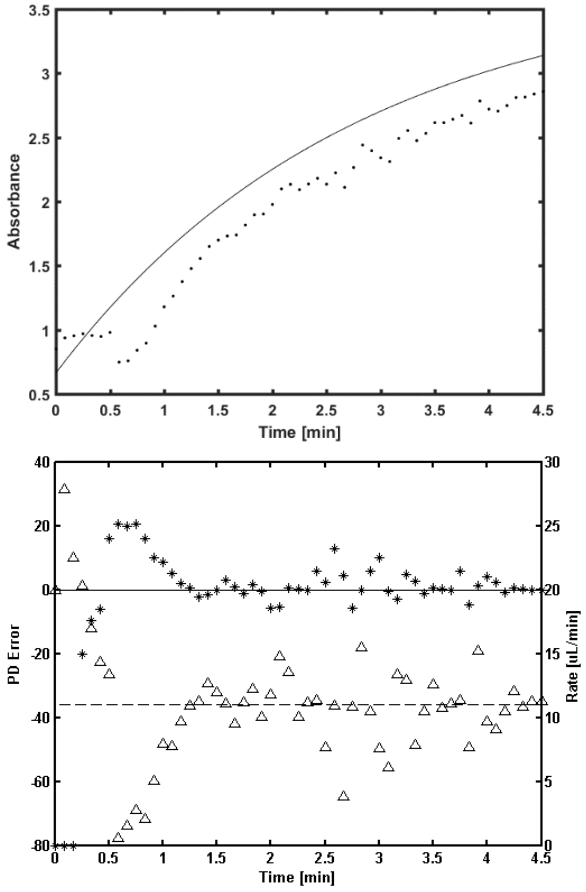

FIGURE 4. (Top) Example absorbance with time, with injection control. The solid line is the population pharmacokinetic model. (Bottom) Corresponding PD error, triangles, and calculated injection-phase rate change, stars. The dashed line is an asymptote of error (averaged), and solid line is asymptote of injection rate (averaged).

injections are displayed in comparison to the population pharmacokinetic model to represent this.

Because the goal of this project was the reduction in variability of injections of a therapeutic agent, we also analyzed the delivered dosage generated by the controller for each injection (Table 2). While the control system may be given a certain termination point in time or absorbance, it was not calculating or using the area under the curve, or AUC, as is standard in many pharmacological studies. This is due to the systems feedback mechanism. Data collected by the PPG was optical absorbance, and therefore keeping the system simple and operating on this variable was ideal as this was only a proof of concept.

IV. DISCUSSION

Our group developed a population pharmacokinetic model for the therapeutic agent ICG to study the feasibility of using

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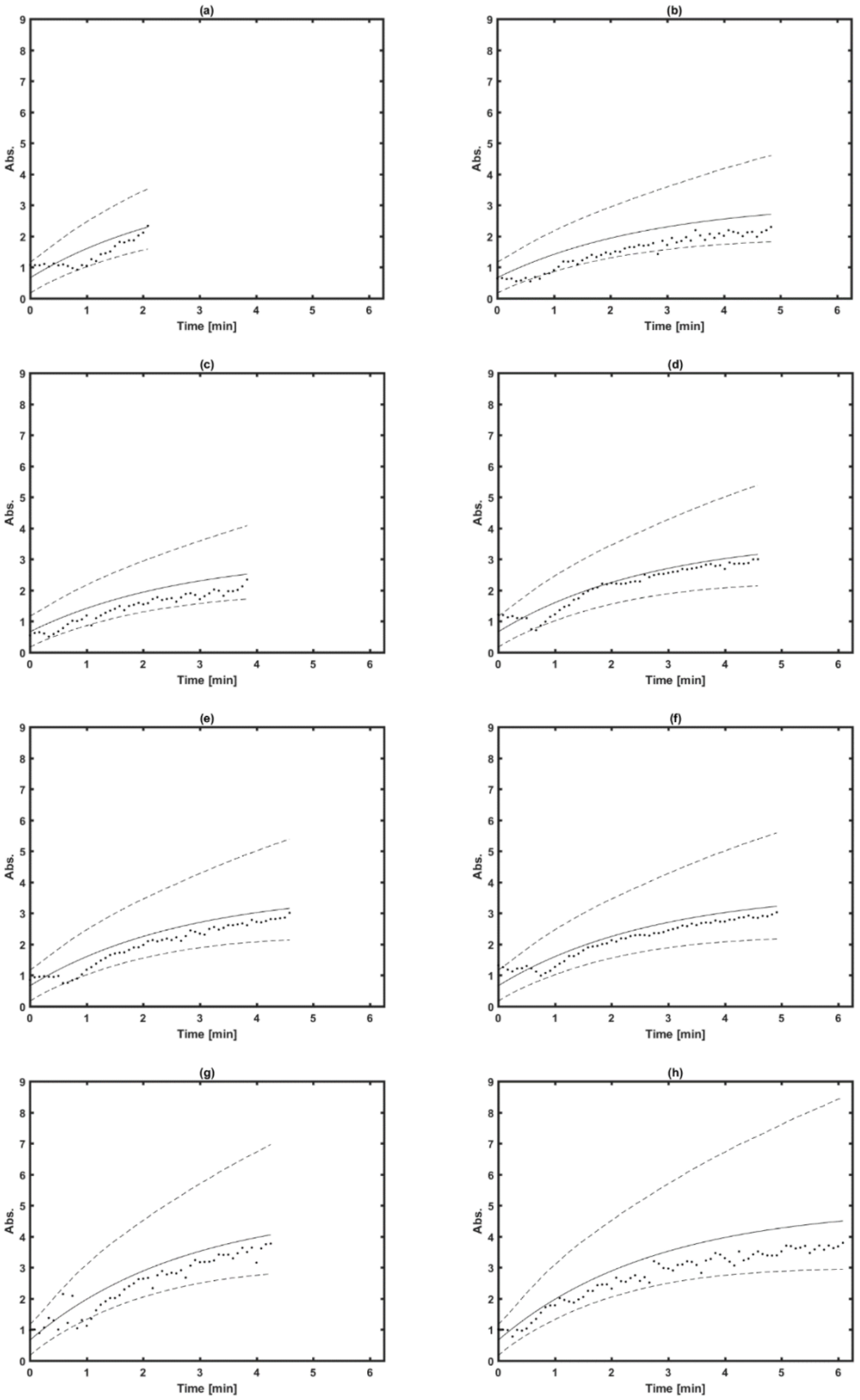

FIGURE 5. **Injections from Controlled Data Set (dots) with target model (solid line) and 95% confidence interval (dashed line), absorbance vs. time. Figures (a) – (c) have a final absorbance target of 2.25, figures (d) – (f) have a final absorbance target of 3.00, and figures (h) – (g) have a final absorbance target of 3.75.**

a closed-loop PD control system for tracking a desired concentration profile during intravenous administration of drugs. We found that closed-loop control of ICG reduces variance from the target injection concentration profile by 74.8%.

There are several advantages to closed-loop control of injections for tracking a desired concentration profile. These are primarily due to the applied control system's application of system error when calculating the next move to make. For example, our approach has the potential to reduce acute toxicity by ensuring that the actual concentration is below the population pharmacokinetic model. Another example may be seen in the application of closed-loop control to a highly sensitive therapy. Take for example one which needs to be maintained in a tight therapeutic window for an extended period. Keeping the patient within this window is a considerably less difficult task as the system can be designed to maintain the window rigorously with the application of feedback control to the drug delivery system. Still another advantage seen in applying a closed-loop control system is perhaps the most poignant caveat of control and automation systems in general. Control systems allow the designer to choose the operation and response time as well as the method and number of system reactions to a specific stimulus as relayed in the system error. Meaning, it is up to the designer in what way and how fast any form of system error is processed. Thus, the controller provides a more dynamic and robust platform upon which to expand any system. This cannot be accomplished without system feedback, and therefore cannot occur without the closed-loop.

In going from a target absorbance of 2.25 (Inj #1) to an absorbance of 3.75 (Inj #8) required 5 times the dose. Injection #1 appears to require a below average dose to achieve the desired concentration so the administration of the expected dose may lead to over-dose. On the other hand, Injection #8 required an above average dose to achieve the desired concentration so administering the expected dose may not be effective.

The best case of this can be seen in the overall error response of the Controlled group, where the error is centered below the marginal average of zero. This is due to the system design. As previously mentioned considered the potential threat of therapeutic toxicity, we therefore implemented a negative bias as a precautionary measure. While this increases system response time, this has two benefits; it allows our system to run longer and therefore approach the asymptotic PD error margin of zero, as well as reduces the potential threat to the patient from a system malfunction caused by over injection.

Beyond this initial impact in reducing the variability of patient treatment, this study is an important step in the direction of fully-automated therapeutic systems. We demonstrate that the idea of self-sustained and self-controlled treatment systems is not only practical, but closer than other current work would seem to suggest. Overall, our study shows that interpatient variability need not influence the outcome of a clinical study, and by the same token, personalized medicine is in the near future.

It should be noted that this study did not include the pharmacodynamics when considering our control system. This is reflected primarily in the choice of our style of control; i.e. a PD control system. Classically PID and all related modes of control are utilized in situations in which there are a plethora of unknown and or unmeasurable variables. The general idea behind a PID being to tune the error signal to a prespecified series of results in order to achieve the desired system convergence. In doing so, we focused entirely on meeting the goal of reduction of inter-patient variability and left all other system variation up to the control system. Thus, having designed our system around these aspects of the pharmacokinetics, no considerations had been made for the effect which the drug was having on the patients.

The main limitation is the system's undershooting of the population pharmacokinetic curve, though this is a measure to protect the patient from toxicity, (a potentially realistic concern in our overstepping of pharmacodynamics). In the future, a more finely calibrated control system, made with a more sensitive PPG, would not have this concern, and thus not need to undershoot. It should also be noted that the use of absorbance as the target and general pharmacokinetic model standard in our study is not the clinical tradition.

Although this project focused on the use of optically-based controller feedback, the system need not have any specific type of sensory feedback. In future work, an exploration into other clinical metrics such as glucose, neurotransmitters, and hormone level therapeutic applications could be explored.

V. CONCLUSION

Controller based medical therapy is a new and developing field. As shown in our work it holds promise in reducing inter-patient variability. The future application of controllers to the many forms of medical treatment is the key to resolving the current issues held in the medical field which limit treatments based on small margins of population effectivity and will allow physicians to be more certain of the reliability of medical treatment overall. Control based medication holds potential as a means to broaden the availability of medical treatments to the global populous.

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