Traditional and Automatic Drug Delivery System: A Review

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Abstract
Drug Delivery is a process of administrating a pharmaceutical compound in human beings to achieve theraputical effects. Drug can be delivered through many ways e.g. through mouth, skin (topical), nasal (transmucosal), and inhalation routes etc. It may include a target area in the body concerned with quantity and duration of drug presence. Drug Delivery methods become an important factors as this decides the important target area so user often chose a delivery method that gets them higher, faster. Automated Drug Delivery consists of electronic/mechanical instruments to provide and maintain rate of drug without the human intervention. Two methods may be applied for automated drug delivery system: Model Base (Open Loop Control) and Close Loop Control. Both Open and Closed Loop required a set point, but in Closed loop feed back signal is added along with set point as a control signal to achieve Target Concentration.

Keywords
Pharmacokinetic Model, Bispectral Index Sensor

I. Introduction

Drug Delivery is a process of administrating a pharmaceutical compound in human beings to achieve theraputical effects. Drug can be delivered through many ways e.g. through mouth, skin (topical), nasal (transmucosal), and inhalation routes etc. It may include a target area in the body concerned with quantity and duration of drug presence. As rate and amount of dose in the body must be carefully calculated so in the traditional drug delivery methods where dose rate is calculated and delivered manually any type of mishandling can lead to certain complications in a patient. The traditional drug delivery systems required 100% human intervention where chances of miscalculation were more. An Automated Drug Delivery System consists of electronic/mechanical instruments to calculate, provide and maintain rate of drug with 20-30% human intervention. Preprogrammed syringe/infusion pumps are normally used in automated drug delivery system. A preprogrammed syringe pump is consists of a microprocessor/microcontroller programmed with a drug delivery algorithm. Two methods may be adopted in automated drug delivery system:

- Model Base (Open Loop Control)
- Closed Loop Drug Delivery Systems.

A. Model Base Drug 7Delivery Methods

Model Base Drug Delivery is a form of Open Loop Control. Open Loop systems are also called externally regulated system. In Model Base drug delivery system Target Infusion or Plasma Concentration is set by clinician. This approach works well where feed back signals from patient are not measured and only appropriate model is available. Thus the performance of Open Loop system is highly dependent on the accuracy of the model on which it is based the modern concept of feedback was severely formulated in 1934 by Harold Black [2-3] with invention of the feedback amplifier. In those early days, repeater amplifiers for telephony were built from glass tubes that had nonlinear and uncertain characteristics with significant distortion.

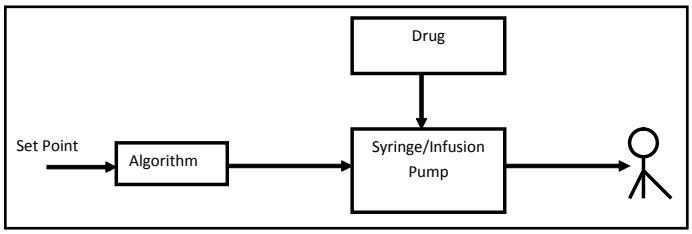

Fig. 1:

Black proposed a feedback amplifier with spectacular results, showing the feedback allows the design of good systems from components with poor performance characteristics. That invention by Black lead to a revolution in telecommunication. Closed Loop Drug Delivery is modern Drug Delivery method to provide precise amount of dose and works on a feedback mechanism. Both Open Loop and Closed Loop system required a set point. The feedback signal is the value that has resulted from the automated delivery system. Consequently the feedback signal and set point given as an input to drug delivery algorithm to generate control signals. The control signals direct the syringe pump to produce intervention to obtain set point. While vital sign such as Heart Rate (HR), mean arterial Pressure (MAP), and expired gases are commonly used to monitor patient status, measurements of these quantities do not provide an adequate indication of level of anesthetic depth, and additional indicators must be considered. For example, the electroencephalogram (EEG) has been considered as one measure of depth of hypnosis [4]. Recent work has demonstrated that a derivate of the EEG signal, the bispectral index (BIS), correlates with changes in consciousness. The BIS is a scalar measure ranging from 0 to 100, with the upper value of 100 corresponding to the awake state and the lower limit of 0 corresponding to isoelectrical EEG signal. The ease of BIS monitoring and its ready availability for use in the operating room, opens the possibility of closed-loop control of anesthetic drug administration, using the BIS as the performance and measurement variable [5]. The recent example of drug delivery system is CLADS (Closed Loop Anesthesia Delivery Systems) [6-7]. Closed-loop administration of anesthetics during surgery promises to provide a number of possible benefits, such as, tailoring and minimizing the overall amount of anesthetics required for individuals-leading to reduced costs and recovery time and allowing anesthesiologist to focus on more critical safety tasks [4].

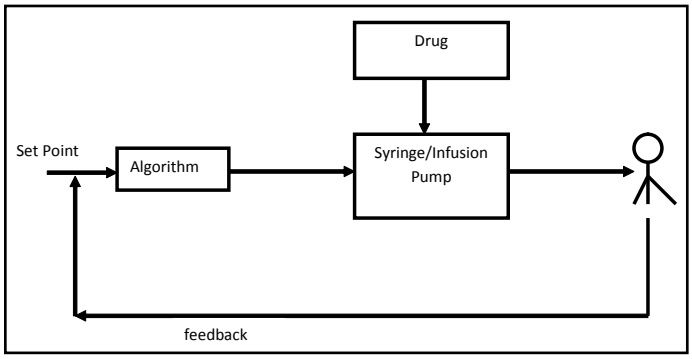

Fig. 2:

B. Depth of Anaesthesia

Advances in signal processing have allowed researcher to correlate anaesthesia depth. There has been a long standing interest in the use of electrocephalogram (EEG) as an objective, quantitative measure of consciousness. Recent work has demonstrated that a derivate of the EEG signal, the bispectral index (BIS), correlates with changes in consciousness [2]. The BIS is a scalar measure ranging from 0 to 100, with the upper value of 100 corresponding to the awake state and the lower limit of 0 corresponding to an isoelectrical EEG signal. The ease of BIS monitoring and its ready availability for the use in the operating rooms open the possibility of closed loop control of anaesthetic drug administration.

C. CLADS

Closed Loop Anesthesia Delivery System is a recent advancement in accurate titration of drug delivery and target control infusion. The goal of CLAD is to develop an automatic control system for anesthesia and to demonstrate its usefulness, safety and benefits in the operating room. In comparison with manual titration of drug delivery and target control infusion CLADS prove superior in maintaining adequate depth of anaesthesia [8].

CLADS system consists of a standard syringe/infusion pump which allows IV infusion at low flow rate. The syringe pump may be connected with PC on a serial or USB port. The CLAD system shown in the fig. 3 is connected with PC via serial cable. A personal Computer with a software to implement drug delivery algorithm (Typically pharmacokinetic models are used for administration). A Datex Ohmeda anesthesia monitor to measure Invasive/Non-Invasive Blood Pressure, Saturation, Pulse, ECG, EEG etc. The patient data is displayed on the screen of Datex Ohmeda Anesthesia monitor and also send to software stored in the PC as feedback.

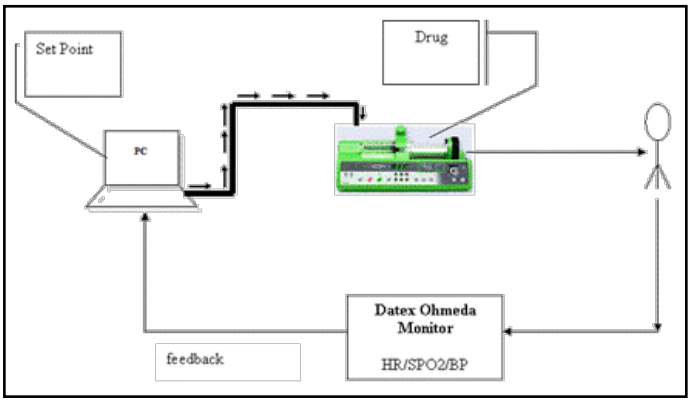

Fig. 3:

D. Working of CLADS

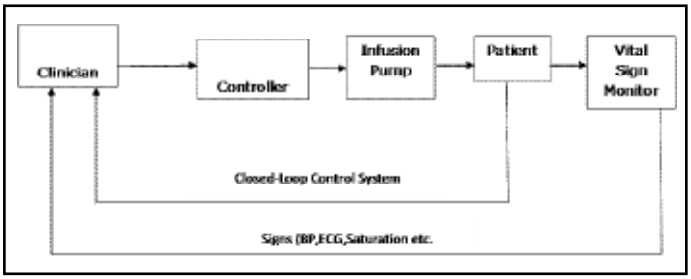

Fig. 4:

The CPU executes a program that incorporates pharmacokinetic model. Pharmacokinetic model becomes a commercial model for the administration of propofol (drug to deliver anesthesia). CPU is interacted with syringe/infusion pump. The anesthetist enters Target Concentration based on the knowledge of pharmacokinetic dynamic relationship of drug and patient. At regular interval (5-10 seconds) patient parameters are feed back as control signals to software, subsequently infusion rate is affected by the effect of control signals. A BIS (Bispectral Index Sensor) is used as a feed back. Now all the vital parameters like infusion rate of drug, BIS value were continuously recorded.

BIS was introduced in 1942 by Aspect Medical System and was approved by Food and Drug Administration in 1996 for accessing the hypnotic effects of general anesthetics and sedatives. A BIS monitor is required to BIS values, which ranges from 0 to 100 where 0 is equivalent to EEG silence and 100 is equivalent to fully awake/alert. The target of an anesthetist is to keep BIS value from 40 to 60 that indicates appropriate level of anesthesia. As a result a BIS monitor gives an idea to an anesthetist how deep a patient is under anesthesia. Overall a BIS is a parameter that allows an anesthetist to reduce the risk of anesthesia awareness during "High risk" surgeries. BIS is also used for critically ill patients during transportation.

Based upon Pharmacokinetic model the system calculates the rate of infusion after every 5-10 seconds. At each step it checks the safety parameters (e.g empty sryringe, air in line etc.). The total amount of drug delivered, current infusion rate, Target concentration and some other information that may be helpful for a clinician displayed on PC.

II. Conclusion

An Ultra Modern Dynamic Drug Delivery System can be developed, in which the detail parameters of a patient will be received by CPU and analyzed by specific software. After analyzing the detail parameters of a patient at the pre surgery stage, it can give instruction to Pump to deliver drug(s) to patient. After every dose the fresh parameters will be analyzed by the CPU and change the level of dose as per the report. Here both software and hardware act as dynamic and the number of slots can be increased as per need, change of drug is also allowed, but need to modify in program before delivery, drug slots can be increased but we have to give the detail within program before delivery.

The Ultra Modern Dynamic Drug Delivery System will be an expert system based drug delivery system along with analyzer data base. The patient parameter and drug rate should be stored in a database that could helpful as a case study for the researcher in the future. The Analyzer Database in Dynamic Drug Interface can be helpful to improve/judge the quantity, quality and efficiency of the medicine

References

[1] Arney, D., Pajic, M., Goldaman, J., Lee, I., Mangharam, R.,"Toward Patient Safety in Closed-Loop Medical Device Systems", Paper presented at the Cyber-Physical Systems (ICCPS), Stockholm, Sweden, April 13-14, 2010.

[2] Dumont, Guy A., Ansermino, Mark J.,"Closed Loop Control of Anesthesia: A Primer for Anesthesiologists.

[3] Huang, J.W., Lu,Y.Y., Nayak,A.,Roy,R.J.,"Depth of Anesthesia Estimation and Control", IEEE Transaction on BioMedical Engineering, 1999.

[4] Ling, Hui-Hing., Beck, Carolyn L., Bloom, Marc J.,"On the Use of Multivariable Piecewise-Linear Models for Predicting Human Response to Anesthesia", IEEE Transaction on BioMedical Engineering, 2004.

[5] Hayakawa, Tomohisa., Haddad, Wassim M., Bailey, James M., Hovakimyan, Naira,"Passivity-Based Neural Adaptive

Output Feedback Control for Nonlinear Nonnegative Dynamical Systems", 2005.
[6] Aggarwal, J., Puri, G.D., Mathew, P.J.,"Comparison of closed vs. manual administration of propofol using the Bispectral index in cardiac surgery", PubMed-Index for MEDLINE, 53(3), pp. 390-7, 2009.
[7] Michel M.R.F.Struys, Tom De Smet,M.SC, Linda F.M. Versichelen,, Atijn Van de Velde,"Comparison of Closed-loop Controlled Administration of Propofol Using Bispectral Index as the Controlled Variable versus,"Standard Practice" Controlled Administration", Anesthesiology, 2001 Jul, 95(1), pp. 6-17.
[8] Puri GD, Kumar B, Aveek J.,"Closed loop anaesthesia delivery system (CLADS) using bispectral index: A performance assessment study", Anaesth Intensive Care. 2007, 35, 357–62. [PubMed], 2007.
[9] Puri, G.D, Jayant, A., Tsering, M., Dorje, M., Tashi, M., "Closed loop anaesthesia at high altitude (3505 above sea level) :performance level characteristics of an indigenously develop closed loop anaesthesia delivery system", Indian J Anaesth, 56(3), pp. 238–242, 2012.
[10] Simanski, O., Schubert, A., Kaehler, R., Janda, M., Bajorat, J., Hofmockel, R., Lampe, B.,"Automatic Drug Delivery in aneshesia: From the begining untill now", IEEE Xplore, pp. 1-6, 2007.
[11] Siql, JC., Chamoun NG,"An Introduction to bispectral analysis for the electroencephalogram", pp. 392-404 [PubMed], 1994.
[12] Glass, P.S., Bloom, M., Kearse, L., Rosow, C., Sebel, P., Manberg, P.,"Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurance and alfentanil in normal volunteers", pp. 836-847, 1997.
[13] Mortier, E., Struys, M., Smet, T.D., Versichelen, L., Rolly, G.,"Closed-loop controlled administration of propofol using bispectral analysis", pp. 749-754, 1998.
[14] Leslie, K., Sessler, D.I., Schroeder,M.,Walter,K., "Propofol blood concentration and the bispectral index predict suppression of learning during propofol/epidural anesthsia in volunteers", vol. 81, pp. 1269-1274, 1995.
[15] Gibbs, G.A., Gibbs, E.L., Lennox, W.G.,"Effect on the electroencephalogram of certain drugs which influence nervous activity" Arch int Med. Vol. 60, pp. 154-166, 1997.
[16] Struys, M.M., Desmet, T., Versichelen, L.F.,"Comparison of closed loop controlled administration of propofol using Bispectral Index as the controlled variable versus "standard practice" controlled administration", 2001.
[17] Liu, N., Chazot, T., Genty, A., Landais, A., Restoux, A., McGee, G., Laloe, P.A, Trillat, B., Fischler, M.,"Titration of propofol for anaesthetic induction and maintenance guided by the Bispectral Index: Closed-loop versus manual control- a propective, randomized, multicenter study", Anesthesiology pp. 686-695, 2006.
[18] Absalom, A.R., Sutcliffe, N., Kenny, G.N.,"Closed-loop control of anaesthesia using bispectral index", Anesthesiology pp 67-73, 2002.
[19] Leslied, K., Absalom, A., Kenny, G.N.,"Closed-loop control of sedation for colonoscopy using Bispectral index", pp. 55, pp. 693-697, 2002.
[20] Morley, A., Derrick, J., Mainland, P., Lee, B.,"Closed loop control of anaesthesia: An assessment of bispectral index as the target of control", 55, pp. 955-959, 2000.
[21] Coetzee, J.F., Glen, J.B., Wium, C.A,"Pharmacokinetic model selection for target controlled infusion of propofol: assessment of three parameter sets", Anaesthesiology, 82, pp. 1328-1345, 1995.
[22] Glass, P.S., Bloom, M., Kearse, L., Rosow, C., Sebel, P., Manberg, P.,'Bispectral analysis measures sedation and memory effects of propofol, midazolan, isoflurane and alfentanil in healthy volunteers".

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