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Anesthesiologist in the Loop and Predictive Algorithm to Maintain Hypnosis While Mimicking Surgical Disturbance

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Abstract: Many regulatory loops in drug delivery systems for depth of anesthesia optimization problem consider only the effect of the controller output on the patient pharmacokinetic and pharmacodynamic response. In reality, these drug assist devices are over-ruled by the anesthesiologist for setpoint changes, bolus intake and additional disturbances from the surgical team. Additionally, inter-patient variability imposes variations in the dynamic response and often intra-patient variability is also present. This paper introduces for the first time in literature a study on the effect of both controller and anesthesiologist in the loop for hypnosis regulation. Among the many control loops, model based predictive control is closest to mimic the anticipatory action of the anesthesiologist in real life and can actively deal with issues as time lags, delays, constraints, etc. This control algorithm is here combined with the action of the anesthesiologist. A disturbance signal to mimic surgical excitation has been introduced and a database of 25 patients has been derived from clinical insight. The results given in this paper reveal the antagonist effect in closed loop of the intervention from the anaesthesiologist when additional bolus intake is present. This observation explains induced dynamics in the closed loop observed in clinical trials and may be used as a starting point for next step in developing tools for improved assistance in clinical care.

Keywords: regulatory loops, predictive control, patient variability, anaesthesia, drug dosing control, antagonist effect, feedforward action, disturbance rejection

1. INTRODUCTION

Many regulatory loops address drug dosing problems, with applications varying among diabetes (Kovacs, 2017), anaesthesia (Copot and Ionescu, 2014), immunodeficiency (Popovic et al., 2015) and hormonal treatment (Churilov et al., 2009). Drug intake, uptake and clearance have been characterized using either compartmental models, either input-output filters by means of linear transfer functions. Compartmental models for drug kinetics are available in the literature from population data and are based on Gaussian normalized distributions (Pereira, 2010). Additional dynamic response in drug effect is added as a pharmacodynamic (PD) additional compartment, usually nonlinear. The pharmacokinetic (PK) and PD models then combined deliver the response to a drug input administered either oral or intravenous, of an average patient (Holford and Sheiner, 1999).

These average patient models are no longer valid in the framework of individualised treatment paradigm, irrespective of the medical application. It is therefore important to deliver models which are sufficiently accurate yet simple in structure such that adaptation may be obtained (Nino et al., 2009). To circumvent the complexity of compartmental models, input output models driven from online data have been proposed as transfer functions with poles and zeros identified for each patient (Soltesz et al., 2013; Dumont et al., 2009). Their time constants may be related to various residence times from different tissue properties and volumetric elements.

The complete regulatory paradigm is however much more complex that anything literature addresses from control engineering point of view. The computer based drug dosing optimisation is always limited in the information it receives from the system (i.e. vital signals from the patient). In general anaesthesia, the anesthesiologist must provide a cocktail of optimal dosages of various drugs to induce and maintain this complex physiological state in the patient, while avoiding under- and over-dosing, and coping with great patient variability (Ionescu et al., 2014; Copot and Ionescu, 2014). As such, anaesthesia is much of an art rather than a numerical problem. The expertise of the team of doctors and the unique patient response may play at times a role delimiting the fine line between life and death-threatening situations.

Rather than delivering control algorithms based on individualised patient models and optimal dosing protocols, in an effort to mimic the operation theater with the actors playing a role, fuzzy control seemed to be a good tool at hand for multiple variable control (Shieh et al., 2005). The fact that the controller was using a patient model

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based on neural network modelling with manifold of inputs to extract via nonlinear functions the response to specific drug input was clearly a step towards reality. However, the necessity to ensure stability and maintain constraints for patient well-being and safety required a control law which can provide an analytical solution. Furthermore, feedback based control loops have a drawback in their looking backward policy, whereas true anticipatory reactions of the anaesthesiologist require predictive control techniques, i.e. looking in the future policies (Ionescu et al., 2014).

In this paper, we revisit our previous predictive control algorithms for hypnosis regulation to include and analyse the effect of anaesthesiologist in the loop (Ionescu et al., 2008, 2014, 2015; Nascu et al., 2015). Since these are merely assist devices, the clinical expert will always have a supervisory role and intervene whenever necessary. From a control engineering viewpoint, the action of anaesthesiologist is based on information which is not available to the controller. For instance, the controller sees only the hypnotic state of the patient, past values and past drug dosing samples, makes a prediction for optimizing the best suitable dosing scenario to reach/maintain the desired level of hypnosis. The anaesthesiologist, however, has a broader view of information, from the various sensing devices monitoring vital signs of the patient, e.g. heart rate, respiratory rate, distal oxygenation, and can anticipate effects in the hypnotic state from the information cocktail. Additional drugs to stabilise various other vital signs alter the information and the controller does not know this, i.e. in heart surgery patients medication alters heart rate and indication of elevated hypnosis may not be directly observable in the feedback signal (Ionescu et al., 2014).

The paper is organized as follows. Next section presents the materials and methods used, i.e. the PK-PD model used to simulate the patients. The surgical stimulation profile acting as a disturbance is also presented in the same section. Third section presents the control algorithm and the additional bolus intake protocol. The results and discussion thereof are given in the fourth section, and a conclusion section summarizes the main outcome of this work and points to further use.

2. PATIENT MODEL FOR HYPNOSIS

As an important part of the anaesthesia paradigm, hypnosis is characterized by unconsciousness, i.e. inability of the patient to recall intra-operatory events. In order to control the depth of anesthesia by means of model-based control strategies, a suitably defined model which captures the dynamics of the relation between drug uptake, drug effect and the patient is required (Nascu et al., 2015; Ionescu et al., 2015).

The selection of the model input and output variables is crucial for achieving optimal control (Dumont et al., 2009; Ionescu et al., 2014). The PK-PD model most commonly used for Propofol is the 4th order compartmental model described in (Schnider et al., 1998, 1999). A generic schematic representation of a PK-PD compartmental model is presented in Fig. 1.

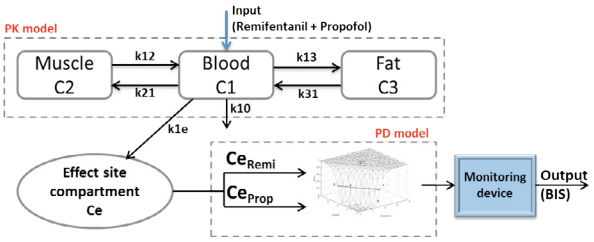

Fig. 1. A schematic representation of a compartmental model for PK and PD with two inputs and one output. For the purpose of this paper, only one input (Propofol) has been considered active and the second one (Remifentanil) is zero.

The ODEs characterizing the Propofol uptake as the PK model are given by the relations to the variation of concentrations x_i with $i = 1..3$ the respective compartments (i.e. blood, muscle, fat):

$$\begin{aligned}&\dot{x}_1(t) = k_{12}x_1(t) - k_{13}x_1(t) - k_{10}x_1(t) - \\ &k1_e x_1(t) \\ &-k_{21}x_2(t) + k_{31}x_3(t) + u(t)/V_1\end{aligned} \tag{1}$$

with $u(t)$ the input infusion rate of drug (Propofol, Remifentanil, or a combination of both).

$$\dot{x}_2(t) = k_{21}x_1(t) - k_{12}x_2(t) \tag{2}$$

$$\dot{x}_3(t) = k_{13}x_1(t) - k_{31}x_3(t) \tag{3}$$

with the parameters k_{ji} for ij, denoting the drug transfer frequency from the j^{th} to the i^{th} compartment and $u(t)$ $[mg/s]$ the infusion rate of the anaesthetic drug into the central compartment.

$$\dot{x}_e(t) = k_{1e}x_1(t) - k_{e0}x_e(t) \tag{4}$$

An additional hypothetical effect compartment represents the lag between drug plasma concentration and drug response. The amount of drug in this compartment is represented by x_e. The parameters of the PK models depend on age, weight, height and gender (Schnider et al., 1998, 1999) and can be calculated for Propofol as follows :

$$\begin{aligned}&V_1 = 4.27[l] \quad V_3 = 2.38[l] \\ &V_2 = 18.9 - 0.391 \cdot (age - 53)[l]\end{aligned} \tag{5}$$

The volumes V_1, V_2 and V_3 represent the compartmental volume, i.e. blood, muscle and fat.

$$\begin{aligned}&C_{l1} = 1.89 + 0.0456(weight - 77) - \\ &0.0681(lbm - 59) + +0.0264(height - 177)[l/min]\end{aligned} \tag{6}$$

$$C_{l2} = 1.29 - 0.024(age - 53)[l/min] \tag{7}$$

$$C_{l3} = 0.836[l/min] \tag{8}$$

$$\begin{aligned}&k_{10} = \frac{C_{l1}}{V_1}[min^{-1}]; k_{12} = \frac{C_{l2}}{V_1}[min^{-1}] \\ &k_{13} = \frac{C_{l3}}{V_1}[min^{-1}]\end{aligned} \tag{9}$$

$$\begin{aligned}&k_{21} = \frac{C_{l2}}{V_2}[min^{-1}]; k_{31} = \frac{C_{l3}}{V_3}[min^{-1}] \\ &k_{e0} = 0.456[min^{-1}]\end{aligned} \tag{10}$$

where lbm represent the lean body mass, C_{l1} is the rate (called also clearance rate) at which the drug is cleared

from the body, C_{l2} and C_{l3} are the rates at which the drug is removed from the central compartment to the other two compartments by distribution. The lbm for man and women necessary in (6) is calculated using the following expressions:

$$lbm_m = 1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2} \quad (11)$$

$$lbm_f = 1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2} \quad (12)$$

The relation between the effect site concentration and the measured effect in the brain, i.e. the Bispectral Index (BIS) is modelled as a nonlinear sigmoid Hill curve scaled between 0%-100%, with 100% denoting fully awake patient:

$$BIS(t) = E_0 - E_{max} \frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + C_{50}^{\gamma}} \quad (13)$$

where E_0 is the BIS value when the patient is awake; E_{max} is the maximum effect that can be achieved by the infusion of Propofol; C_{50} is the Propofol concentration at half of the maximum effect and γ is a parameter which together with the C_{50} determines the patient sensitivity to the drug. E_0 and E_{max} are considered equal to the value of 100. This signal has proved most suitable in clinical trials for regulatory closed loops in hypnosis (Sakai et al., 2000; Absalom et al., 2002; Absalom and Kenny, 2003). The ODE model has been shown to be approximated by linear transfer functions, more practical from control engineering point of view, while still related to compartmental physiology, as in Soltesz et al. (2013). An important factor in the origin of great uncertainty in patient PD model is the great patient variability (Ionescu et al., 2016; Padula et al., 2016; Ionescu et al., 2011), which require the additional actions of the anesthesiologist.

3. PROPOSED ANALYSIS PROTOCOL

3.1 Controller-Based Regulation

The typical closed loop control is depicted in Fig. 2. This involves the control strategy receiving feedback information from the state of the system, i.e. the patient BIS level in our case, followed by an optimization algorithm to compute the best suitable Propofol infusion profile. Since the regulatory loop has a model based predictive control algorithm, it considers past inputs (Propofol), past outputs (BIS), a cost function based on required performance (desired BIS). Along with a forecasting procedure, it computes then the optimal infusion rate over a predefined time interval in the future (prediction horizon) to reach the desired output. The method has various features, being able to cope with a manifold of control system challenges, e.g. constraints, nonlinearities, time delays and disturbance profiles. For the objectives of this work, the time delay effect has been neglected.

The EPSAC (Extended Prediction Self-Adaptive Control) algorithm has been employed hereafter. The method has been developed in the early 80s (De Keyser and Van Cauwenberghe, 1981) and tailored later for regulatory loops in anaesthesia (Ionescu et al., 2008, 2014, 2015; Nascu et al., 2015). For details on the control algorithm, the reader is thus referred to the references mentioned above.

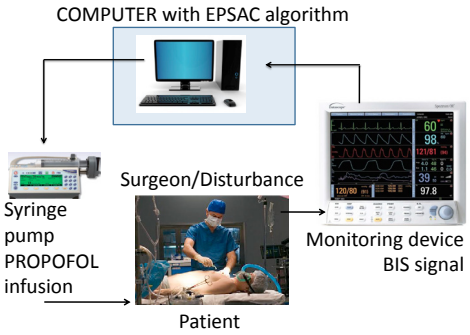

Fig. 2. The computer based hypnosis regulatory loop.

3.2 Combined Anesthesiologist-Controller Based Regulation

A more realistic view on the actual regulatory loop is given in Fig. 3. In this case, the anaesthesiologist may decide to intervene with additional bolus of Propofol infusion, as to anticipate the presence of disturbances. It is important to realize that the information sources for the anaesthesiologist and computer-controlled hypnosis actually differ.

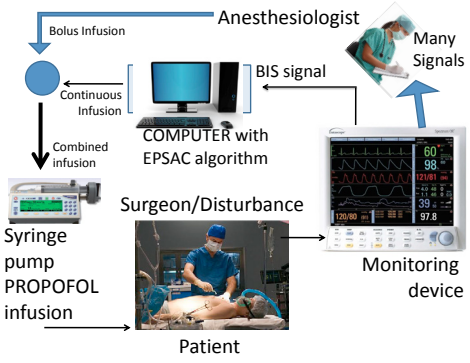

Fig. 3. The combined anesthesiologist in the loop and computer based hypnosis regulatory loop.

The operation theater is a collection of monitors delivering information upon the vital signs of the patient undergoing general anaesthesia and surgical intervention. The anaesthesiologist is but one actor of the many playing a role in maintaining patient well-being during and after the medical objective has been achieved. During the surgery, a constant interval of BIS (40-60) is required for safe operation. Values BIS¿70 suggest a light sedated patient with imminent awakening profile, whereas values BIS¡30 are deep anaesthesia with complex post-surgical side effects. Both outliers should be avoided, and reduce risk for over- and under-dosing.

For the anaesthesiologist in the loop protocol, a fixed amount of bolus infusion has been set to 10 mg/ml during 10 seconds.

3.3 Surgical Stimulation Profile

Literature presents a disturbance signal mimicking surgical stimulation profile, as depicted in Fig. 4. Each segment corresponds to a typical step in most of the procedures.

However, the assumption that the signal changes abruptly in one sample instant is highly unlikely. Instead, a finely tuned smooth profile can be considered, as given in the same figure referenced as above.

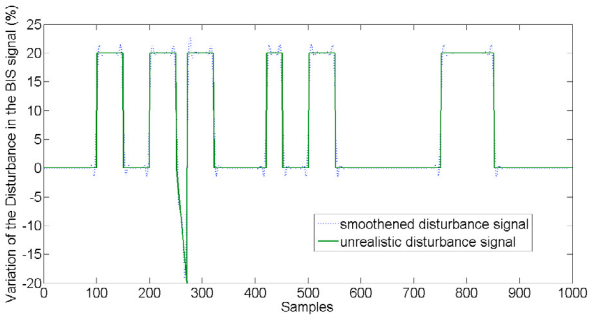

Fig. 4. The original disturbance profile from literature and its smoothed version. The stimulus represents, in order, the following events: intubation; surgical incision followed by a period of no surgical stimulation (i.e. waiting for pathology result); an abrupt stimulus after a period of low level stimulation; onset of a continuous normal surgical stimulation; short-lasting, larger stimulation within the surgical period; and withdrawal of stimulation during the closing period.

For the controller-based regulation protocol, the disturbance signal is not known in advance, and thus enters the system through the feedback loop information flow.

When the protocol is enhanced with the intervention of the anaesthesiologist, an additional input signal is delivered to the system. This additional input signal is depicted in Fig. 5 along with the disturbance signal, where one may recognize the anticipatory action of the anaesthesiologist to compensate in part the expected disturbance profile.

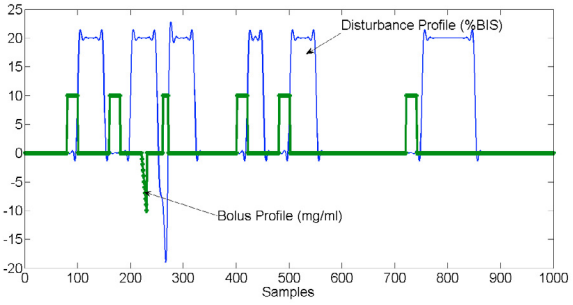

Fig. 5. The signal used for bolus infusion as a result of the anticipatory action of the anesthesiologist to the expected disturbance profile.

3.4 Numerical Simulation from Artificial Patient Database

Given our past expertise and studies in cooperation with Ghent University Hospital Belgium and University Medical Center Groningen The Netherlands, a database of patient profiles has been artificially created to mimic as close as possible reality. The details for the PK-PD models are given in table 1 (Ionescu et al., 2008).

Since the controller is model based, a patient model is required for the computer-based regulatory loop. A hypothetical patient model has been used in the controller for optimization purposes, with values simplifying the dynamics from the PK and PD models. The patients from table 1 denote the real patient, i.e. different from the model used in the controller, as to mimic inter-patient variability and test the robustness of the closed loop.

4. RESULTS AND DISCUSSION

The PK model (1)-(4) with values from the patient database in table 1 delivers a transfer function model for each patient. Analysis of these models reveals a pole-zero mapping of dominant pair of real valued poles ranging from -0.9 to -0.4. These are linked to the dynamic uptake and clearance from the compartments, specific to each patient through the biometric values (Soltesz et al., 2013).

The closed loop simulations have been performed with a sampling period of 1 second, a prediction horizon in the EPSAC algorithm of 40 samples and a prediction model with two real poles at -0.7 and unitary gain. Although the disturbance filter in EPSAC may be used to augment the prediction model (De Keyser and Ionescu, 2003), it has not been used, except in its default form, i.e. an integrator, to ensure zero steady state error to desired BIS values.

The greater variability among the patient response is coming not from the PK model, but from the PD model, i.e. the c_{50} concentration varies greatly from one patient to another. This has been in-depth analysed and presented in (De Keyser et al., 2015). In fact, it has been established in previous studies that this represents the gain of the patient model and its variability can be as high as 300% (Copot and Ionescu, 2014; Nino et al., 2009; Ionescu et al., 2016; De Keyser et al., 2015). The variability may be observed in the induction phase, when both regulatory loops have same conditions for simulation, as in Fig. 6.

Table 1. Artificial Patient Database with PK Model Biometric Values and PD Model Sensitivity Values.

Index -	Age (yrs)	Height (cm)	Weight (kg)	C_{50} (mg/ml)	γ -
1	74	164	88	2.5	3
2	67	161	69	4.6	2
3	75	176	101	5	1.6
4	69	173	97	1.8	2.5
5	45	171	64	6.8	1.78
6	57	182	80	2.7	2.8
7	74	155	55	1.7	3.5
8	71	172	78	7.8	2.9
9	65	176	77	2.9	1.88
10	72	192	73	3.9	3.1
11	69	168	84	2.3	3.1
12	60	190	92	4.8	2.1
13	61	177	81	2.5	3
14	54	173	86	2.5	3
15	71	172	83	4.3	1.9
16	53	186	114	2.7	1.6
17	72	162	87	4.5	2.9
18	61	182	93	2.7	1.78
19	70	167	77	6.8	3.1
20	69	168	82	9.8	1.6
21	69	158	81	3.2	2.1
22	60	165	85	5.1	2.51
23	70	173	69	3.67	3.1
24	56	186	99	5.8	2.3

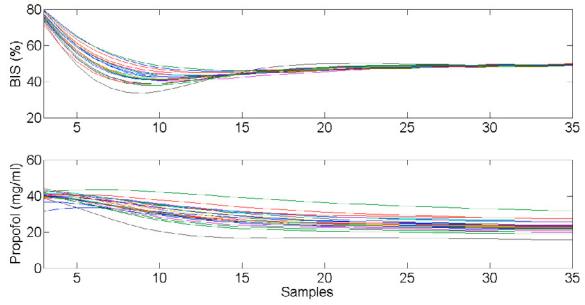

Fig. 6. Induction profiles for hypnosis regulation. Results reported as output (BIS) and input (Propofol) profiles.

The result for the computer based regulatory loop is given in Fig. 7 and the combined regulatory loop with the additional bolus infusion in Fig. 8. The result is reported by means of output (BIS) and input (Propofol) profiles. Both protocol loops violate now and then the maintenance interval for $45 < BIS < 55$. A closer look using histograms in Fig. 9 reveals that the case when the anesthesiologist in the loop is active, a higher number of violations above/below this maintenance interval occurs. The number of occurrences counted from simulated data is given in Fig. 10. It can be then concluded that the anesthesiologist in the loop combined regulatory loop has more wobble in the BIS values.

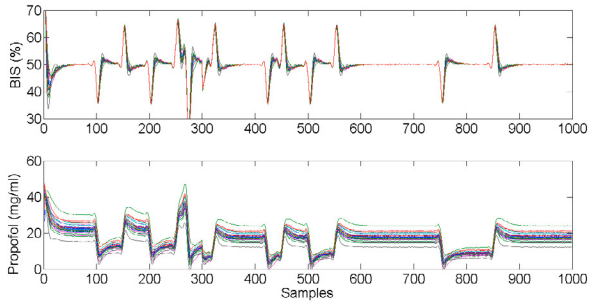

Fig. 7. Results obtained with the computer based protocol only.

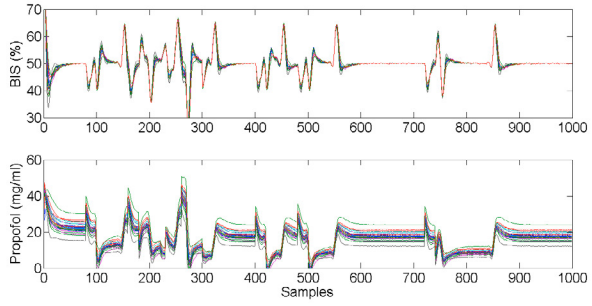

Fig. 8. Results obtained with the combined infusion from computer and from anesthesiologist in the loop.

Clearly, the comparison between the two protocols must be performed with care. As depicted in Fig. 3, the anesthesiologist receives more information from the state of the patient than the computer based regulatory loop in Fig. 2. This is reality in operation theaters and unfortunately,

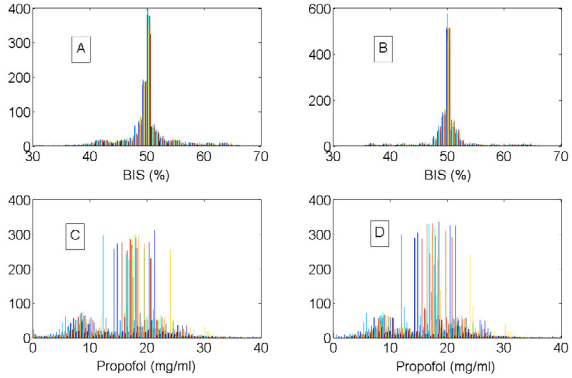

Fig. 9. Histograms of the BIS value distribution for the computer only loop (A) and the combined loop (B), with corresponding input distributions (C) and (D), respectively.

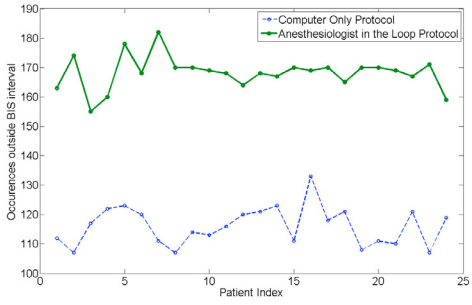

Fig. 10. Number of occurrence values outside the $45 < BIS < 55$ interval in both protocols.

today's computer based systems provide a limited amount of information they process. When the anesthesiologist anticipates the disturbance effect and takes feedforward action, this acts as an input disturbance in the controller optimization procedure. The controller does not understand the reason for this additional infusion augmentation, hence it decreases its own computed infusion rate, creating thus additional wobble in the input variable, later translated into the output variable. The result is then a decrease in the overall performance.

When discussing the complex depth of anesthesia paradigm, one needs to take into account multiple inputs and multiple outputs to reach the necessary minimum degree of information required by optimal drug management (Ionescu et al., 2014; Shieh et al., 2005).

5. CONCLUSION

This paper proposed to offer an explanation for the decrease in performance of regulatory closed loops in hypnosis observed as a result of the anesthesiologist anticipatory actions. These may have de-stabilising effects (oscillations) the computer-based closed loop due to the limited feedback information received by the controller and care must be exercised when comparison is made against various situations.

Ideally, assist devices for drug delivery systems in general, must have a mechanism which allows a multitude of

heterogeneous signals to be processed to distill useful information for the control algorithm. Both continuous as well as dis-continuous variables, boolean, logical operators and text input from the medical staff can be incorporated in one console for interfacing and centralizing the great amount of information available currently in the operation theaters at no extra cost.

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