



Optimal drug infusion profiles using a Particle Swarm Optimization algorithm

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ABSTRACT

The dynamic optimization of the administration of therapeutic drugs in simulated patients is proposed. The approach is based on a non-linear discontinuous cardiorespiratory model, which has been conceived to simulate the effect of inotropic and vasoactive drugs as well as anesthetic agents. A stochastic technique (Particle Swarm Optimization), within the context of the control vector parameterization approach, is adopted to identify the infusion profiles of various drugs in order to track, as close as possible, the set-points on several variables of medical interest. Two different medical procedures are investigated in order to test the efficiency and robustness of the algorithm: a congestive heart failure and the unclamping of an aortic vessel. Due to the conflicting nature of the different objectives, compromise solutions are obtained in all cases.

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1. Introduction

The most critical variables to be controlled in intensive care units are mean arterial pressure, mean pulmonary arterial pressure, cardiac output and depth of anesthesia. The control of such variables is achieved through the administration of various drugs and anesthetic agents. Drugs commonly used are sodium nitroprusside and phenylephrine to regulate mean arterial pressure, dopamine to control cardiac output, nitroglycerin to regulate mean pulmonary arterial pressure, propofol to induce anesthesia and isoflurane to maintain the anesthetic state.

In practice, physicians are responsible for adjusting the doses of drugs in order to keep the hemodynamic and anesthetic variables within acceptable levels, performing the task of a closed loop controller. The design of automatic controllers to assist physicians in this process has been addressed by the Process Systems Engineering community. For example, Yelneedi et al. (2009a,b) evaluated the robustness of advanced control strategies for the regulation of hypnosis with propofol in a broad range of patients. In general, the most popular control strategies considered are (Dua and Pistikopoulos, 2010; Gentilini et al., 2001; Gopinath et al., 1995; Isaka and Sebald, 1993; Kwok et al., 1997; Rao et al., 2000; Uemura et al., 2006; Yu et al., 1992): multirate model predictive

control, model predictive control, cascade internal model control and multi-parametric model based control, among others. Model based controllers use non-linear physiological models to simulate human processes such as blood circulation, respiration and distribution of substances among the organs (Yelneedi et al., 2009a,b; Yu et al., 1992). The performance criteria commonly adopted is the minimization of the settling times of the variables of interest. Some of the controllers have been tested with relative success on animals and on patients undergoing a specific disease (Dua and Pistikopoulos, 2010; Gentilini et al., 2001; Gopinath et al., 1995).

Knowing in advance the optimal infusion profiles of the drugs to be administered to a patient, provided by a dynamic optimization problem, can potentially improve the quality of the treatment in surgical and intensive care environments. Infusions can be designed in order to prevent exceeding concentration limits of the drugs which might impact, for example, on the time spent by the patient in the post-operative care unit recovering from anesthesia. A patient-specific physiological model within a dynamic optimizer can also be used by the anesthesiologists to carry out “what if” and failsafe analysis for various scenarios that may arise during surgery. In a closed loop framework, the optimal infusion profiles can be fed as set-points to the control system since the open-loop optimal controls are rarely applied directly in practice, due to the presence of uncertainty such as model mismatch, process disturbance and variation in initial conditions. Moreover, the knowledge in advance of an open-loop optimal control law for a given process can offer an estimate on how far the system is from the optimal operation and help to identify possible improvement actions (Chachuat, 2007).

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Nomenclature

Parameters

C_{a1}	1° systemic arterial capacitance
$C_d(\text{injectable})$	drug concentration in vein chamber
$C_d(\text{inhalable})$	drug concentration in lung chamber
$C_d(\text{organs})$	drug concentration in organ chamber
C_j	vessel elasticity in cardiovascular chamber j
C_{p1}	1° pulmonary arterial capacitance
C_{v1}	1° systemic venous capacitance
$C_{v1\text{BARO}}$	1° systemic venous capacitance influenced by the baroreceptor
C_{v2}	2° systemic venous capacitance
$\text{Eff}_{C_{a1}}$	effect of drugs on 1° systemic arterial capacitance
$\text{Eff}_{C_{p1}}$	effect of drugs on 1° pulmonary arterial capacitance
$\text{Eff}_{C_{v1}}$	effect of drugs on 1° systemic venous capacitance
$\text{Eff}_{E_{\max\text{lv}}}$	effect of drugs on the maximal left systolic elastance
$\text{Eff}_{R_{a2}}$	effect of drugs on 2° systemic arterial resistance
$\text{Eff}_{R_{a3}}$	effect of drugs on 3° systemic arterial resistance
$\text{Eff}_{R_{l1}}$	effect of drugs on 1° pulmonary venous resistance
$\text{Eff}_{V_{unv1}}$	effect of drugs on 1° systemic venous unstressed volume
$E_{\max\text{lv}}$	maximal left systolic elastance
$E_{\max\text{lv}\text{BARO}}$	maximal left systolic elastance influenced by the baroreceptor
$E_{\max\text{rv}}$	maximal systolic right ventricular elastance
H	heart rate
L_j	flow inertia in cardiovascular chamber j
P_{AA}	partial pressure of drug in alveoli
P_{CO_2}	partial pressure of CO_2 in alveoli
P_j	blood pressure in cardiovascular chamber j
P_{O_2}	partial pressure of O_2 in alveoli
Q_{a3}	flow rate at the systemic capillary section
Q_j	blood flow in cardiovascular chamber j
Q_{p3}	Flow rate at the pulmonary capillary section
R_{a1}	1° systemic arterial resistance
R_{a2}	2° systemic arterial resistance
$R_{a2\text{BARO}}$	2° systemic arterial resistance influenced by the baroreceptor
R_{a3}	3° systemic arterial resistance
$R_{a3\text{BARO}}$	3° systemic arterial resistance influenced by the baroreceptor
R_j	viscous loss term in cardiovascular chamber j
R_{l1}	1° pulmonary venous resistance
V_j	blood volume in cardiovascular chamber j
V_{unj}	unstressed volume in cardiovascular chamber j
V_{unv1}	1° systemic venous unstressed volume
$V_{unv1\text{BARO}}$	1° systemic venous unstressed volume influenced by the baroreceptor
V_{unv2}	2° systemic venous unstressed volume

Acronyms

BIS	Bispectral index
CO	Cardiac output
CVP	Control Vector Parameterization
DAEs	Differential-algebraic equations
DOA	Depth of anesthesia
DP	Dopamine
EEG	Electroencephalogram
ISO	Isoflurane
IVP	Initial value problem
MAP	Mean arterial pressure
MPAP	Mean pulmonary arterial pressure
NLP	Non-linear programming problem

NTG	Nitroglycerin
OF	Objective function
PFL	Propofol
PNP	Phenylephrine
PSO	Particle Swarm Optimization
SNP	Sodium nitroprusside
SQP	Succesive quadratic programming

The dynamic optimization approach is extensively used to aid in the design and operations of industrial systems (Adams and Seider, 2008; Balsa-Canto et al., 2005; Barton et al., 1998, 2000; Biegler, 2010; Carrasco and Banga, 1997; Galán and Barton, 1998; Vassiliadis et al., 1994). The most popular application is the determination of optimal operating policies in batch processes. Other applications include the design of operating procedures for process start-up, shut-down and changeover, the design of emergency shutdown systems, and the optimal design of inherently dynamic processes such as those operated in a batch, semi-continuous and/or periodic manner (Carrasco and Banga, 1997; Barton et al., 2000; Schlegel et al., 2005).

Besides its development, according to our knowledge there are practically no reports in the open literature on applications of the dynamic optimization strategy to physiological systems. In this article, the drug infusion optimization problem is formulated as a dynamic optimization problem (or open loop control problem) to find the input profiles of the manipulated variables (drug infusion rates) that minimize the off-sets of the hemodynamic and anesthetic variables with respect to appropriate set-points over a finite time interval. For this purpose, a detailed physiological simulation model is used and the Particle Swarm Optimization (PSO) strategy within a Control Vector Parameterization (CVP) approach is adopted to conduct the dynamic optimization. It is worth mentioning that the problem is inherently multi-objective, since it is desired to control several variables simultaneously.

In the next section the used physiological model is described. In Section 3 the basic concepts of dynamic optimization problems are presented followed by the description of the PSO algorithm (Section 4). In Section 5 implementation details of the proposed approach are presented. In Section 6, the results of the addressed case studies are detailed followed by a conclusions and future work section.

2. Physiological model

The adopted physiological simulation model is built up on models available in the literature for the following processes: cardiovascular dynamics, baroreflex, respiration, transport and distribution of substances and pharmacologic effects of drugs. The integrated model, reported in Montain et al. (2014), provides the time profiles of the main hemodynamic and pharmacodynamic variables under many different scenarios of drug infusion for therapeutic purposes. A brief description of each sub model and the corresponding references are provided below. In Fig. 1, the interconnection among the sub models is depicted.

2.1. Cardiovascular and baroreflex model

The cardiovascular system model is a lumped pulsatile model that captures the main features of the blood circulation. The different organs are represented by a series of interconnected elastic chambers, representing the pumping heart and vascular systems (systemic and pulmonary circulation). For a complete description of this model see Ottesen et al. (2004).

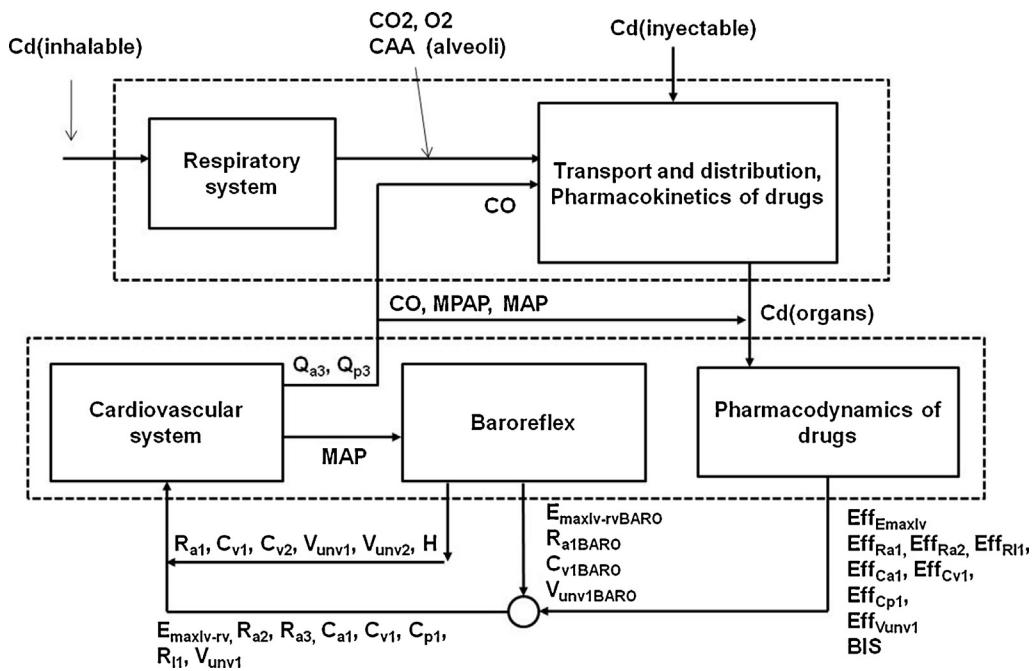


Fig. 1. Block diagram of the physiologic model comprising the sub systems: cardiovascular, baroreflex, respiratory, transport and distribution of substances and pharmacodynamics of drugs. The flow of information between models is also depicted.

The heart is made up of four elastic chambers to model left and right atria and ventricles. Regarding the vasculature, arteries are represented by three elastic chambers for each section, systemic and pulmonary, while veins are lumped into two elastic chambers per section.

Each chamber is described in terms of a mass balance. The volume represents the dynamic state of the chamber. In the atria and ventricles, where the inertial effects are important, a momentum balance is also required. The flow rate is the corresponding state variable in such cases. For all chambers, a linear relationship between pressure and volume is adopted. In order to model the pumping effect of the ventricles, a sinusoidal driving function provides the time varying elastances of such chambers. The cardiac valves are represented as switches between two models depending on upstream and downstream pressures.

Every vascular chamber is described by the following parameters: viscous loss term (R_j), flow inertia (L_j), vessel elasticity (C_j) and unstressed volumes (V_{unj}). Index j denotes a particular chamber. For the heart chambers, the parameters that characterize the ventricular contractility are the maximum and minimum elastances (E_{\max}, E_{\min}).

The variables provided by the cardiovascular model are: blood volumes (V_j), blood pressures (P_j) and blood flows (Q_j). The mean arterial pressure (MAP) and the mean pulmonary arterial pressure (MPAP) are obtained through the temporal integration of the pressure of the first chambers corresponding to the systemic and pulmonary arterial sections, respectively, divided by the cardiac period. The cardiac output (CO) is obtained by performing the integration over time of the blood flow of the left ventricle.

The baroreflex system has influence on some cardiovascular variables since it monitors changes in MAP to provide short-term pressure regulation. The pressure control is achieved through the manipulation of the following cardiovascular parameters: maximum elastances of the ventricles (E_{\maxlv}, E_{\maxrv}), systemic arterial resistances (R_{a1}, R_{a2}, R_{a3}), unstressed volumes of the systemic venous section (V_{unv1}, V_{unv2}), capacitance of the systemic venous section (C_{v1}, C_{v2}) and heart rate (H).

2.2. Respiratory system

The proposed physiological model also includes the respiration process. The sub model of the respiratory system was taken from Christiansen and Dræby (1996) and represents the transport of gaseous components from the atmosphere or a respiratory mask to the alveoli, where the exchange of matter with blood takes place. The states of the model are the pressures in the different sections of the airways from the nasal and oral cavities to the alveolar sacs, together with the molar fractions of oxygen, carbon dioxide and, eventually, inhalable anesthetic agents. The gases perfuse through the lung membrane to the capillaries and reach the circulatory system from where they distribute to the body organs.

2.3. Transport and distribution System (pharmacokinetics)

In order to study the distribution of the different substances within the organs, the body is divided into several compartments: liver, kidney, brain, heart, and remaining organs; connective tissue; muscles and adipose tissue. The circulatory system is also divided into blood pools: central arterial pool, central venous pool, adipose venous pool, lean venous pool, viscera venous pool and capillaries (Christiansen and Dræby, 1996).

The different drugs and gases in the system are consumed at specific rates in each organ depending on their concentration in blood. Mass balances model the concentration profiles of each component. Therefore, in every division of the transport and distribution sub system the pressures and concentrations of these substances are available. Also, dissociation functions are needed to relate the tensions of the substances in the blood and tissue with their corresponding concentrations. The dissociation functions of oxygen and carbon dioxide are complex nonlinear relationships which depend on the blood pH. The dissociation functions of drugs are usually linear.

2.4. Pharmacodynamic system

The pharmacodynamic system describes the effect of the drugs on the physiological variables (Dua and Pistikopoulos, 2010; Dua

Table 1

Main effects of drugs on cardiovascular parameters (Teiken et al., 2000).

Drug	Effect	Parameters modified	Infusion range
SNP	↓ MAP	R_{a2}, R_{a3}, V_{unv1}	3–10 $\mu\text{g}/\text{kg}/\text{min}$
DP	↑ CO	E_{maxlv}	4–10 $\mu\text{g}/\text{kg}/\text{min}$
		$E_{maxlv}, R_{a2}, R_{a3}$	>10 $\mu\text{g}/\text{kg}/\text{min}$
PNP	↑ MAP	R_{a2}, R_{a3}, C_{v1}	10 $\mu\text{g}/\text{kg}/\text{min}$
NTG	↓ MPAP	R_{l1}, C_{p1}	<4 $\mu\text{g}/\text{kg}/\text{min}$
		$R_{l1}, C_{p1}, R_{a2}, R_{a3}, V_{unv1}$	>4 $\mu\text{g}/\text{kg}/\text{min}$
PFL	↓ MAP	C_{a1}	200 $\mu\text{g}/\text{kg}/\text{min}$
			induction of anesthetic state
ISO	↓ BIS ↓ MAP	$R_{a2}, R_{a3},$	1, 1.5, 2 MAC Maintenance of anesthetic state
	↓ BIS		

MAC (minimum alveolar concentration) is the concentration of isoflurane in the alveoli needed to prevent movement (motor response) due to a surgical stimulus (pain). It was established that MAC = 1 represents an alveolar concentration of 1.15% of isoflurane (Malan et al., 1995).

and Pistikopoulos, 2005; Gopinath et al., 1995; Larsen et al., 1988; Leier et al., 1978). Six drugs are considered in this work: sodium nitroprusside (SNP) which is a vasodilator, dopamine (DP) which is used in the inotropic range to enhance cardiac performance, phenylephrine (PNP) an arterial vasoconstrictor, and nitroglycerin (NTG) a veno dilator. Propofol (PFL), an intravenous anesthetic agent, and isoflurane (ISO) an inhalable anesthetic agent, are used to control the depth of anesthesia (DOA) monitored through the Bispectral Index (BIS). The BIS is an indirect measure of the effects of anesthetics and sedatives on the brain. It is based on the bispectral analysis of the electroencephalogram (EEG) of the patient and is the only measure clinically accepted to monitor hypnosis (Gopinath et al., 1995). BIS ranges between 0 and 100, where 100 is associated with patient awake state and 0 denotes an isoelectric EEG signal, associated to unconsciousness. In Table 1, the cardiovascular parameters modified by each drug are detailed. The effects described depend on the drug concentration in the arteries.

2.5. Integrated system

The different physiological processes described by the sub models of the previous sections were integrated in a single framework to dynamically simulate the system. As previously mentioned the complete model, together with simulation and validation studies, has been presented in Montain et al. (2014). The variable that connects the cardiovascular sub system with the transport sub system is basically the heart flow rate (cardiac output), that at the pulmonary section is represented by flow rate Q_{p3} , and at the systemic level, by flow rate Q_{a3} . Each organ is fed with a fraction of the blood flow rate taken from Q_{a3} . The transport sub system is in turn connected to the respiratory sub system by means of the partial pressures of the gaseous components, which are exchanged at the pulmonary capillaries and the alveoli (P_{CO_2} , P_{O_2} , P_D).

If the drug is administered via the respiratory system, it is modeled as a gaseous component that reaches the transport and distribution sub system through the alveoli-capillaries interphase in the lungs. Whether the drug is infused intravenously, C_d (injectable), or via the respiratory system, C_d (inhalable), it is distributed according to a particular kinetics among the different organs through the transport system, where the concentration of the drug, C_d (organs), evolves according to the corresponding mass balance. The arterial blood concentrations of drugs that have hemodynamic effects modify certain parameters of the cardiovascular sub system ($Eff_{E_{maxlv}}$, $Eff_{R_{a2}}$, $Eff_{R_{a3}}$, $Eff_{R_{l1}}$, $Eff_{C_{a1}}$, $Eff_{C_{v1}}$, $Eff_{C_{p1}}$, $Eff_{V_{unv1}}$). The effects on these parameters are quantified through the pharmacodynamic system and typically impacts on MAP resulting

in a feedback loop (Loop A in Fig. 1). Moreover, since the baroreflex system controls MAP by manipulating some of the cardiovascular parameters that also are influenced by the drugs ($E_{maxlvBARO}$, $R_{a2-a3BARO}$, C_{v1BARO} , $V_{unv1BARO}$), the changes in both effects combine to give the new parameters E_{maxlv} , R_{a2} , R_{a3} , C_{v1} , C_{p1} , R_{l1} , V_{unv1} leading to a second feedback loop (Loop B in Fig. 1). The new parameters, together with those that are only modified by the baroreflex sub system (R_{a1} , H , E_{maxrv} , C_{v2} , V_{unv2}), are fed to the cardiovascular system (Loop C in Fig. 1). Finally, the concentration in a specific compartment, of the drugs with anesthetic effects can be used to quantify the depth of anesthesia through the bispectral index (BIS).

Although a particular drug affects a specific variable, since the physiological model is a closed circuit of interconnected chambers and presents feedback action due to the baroreflex activity (Fig. 1), all the variables end up being affected to a greater or lesser extent. For example, PNP has influence on the resistance of the arteries, causing an increase in MAP. However, due to the change in pressure, the baroreflex sub system affects other parameters of the circulatory system, and therefore CO and MPAP are also modified.

From a mathematical point of view, the model has several challenging properties due to the significant non linearity present in almost every equation and the discontinuity introduced by the cardiac valves and the unidirectional events taking place in the respiration. These discontinuities give rise to the so called "state events" which confer a hybrid nature (continuous/discrete) to the model (Bahl and Linnenger, 2000; Gopal and Biegler, 1997; Mao and Petzold, 2002; Pantelides, 1988; Park and Barton, 1996). A state event defines "a change" in the model equations triggered by some state variables reaching a specific condition. For example, a cardiac valve is open when the upstream pressure is greater than the downstream pressure. In this situation the corresponding flow rate is quantified by the momentum balance. When the downstream pressure is larger than the pressure in the heart chamber, the valve closes and the flow rate is set to zero. This phenomenon is particularly intense in the integrated model due to the sinusoidal nature of the driver functions of the cardiovascular and the respiratory system.

3. Dynamic optimization problem

The general formulation of a dynamic optimization problem can be expressed as follows:

$$\min \phi(\mathbf{y}(t_f), \mathbf{u}(t_f), t_f) + \int_{\mathbf{u}(t), t_f}^{t_f} L(\mathbf{u}, \mathbf{y}, t) dt \quad (1)$$

Subject to:

$$\mathbf{f}(\mathbf{y}, \dot{\mathbf{y}}, \mathbf{u}, t) = 0 \quad \forall t \in [0, t_f] \quad (2)$$

$$\mathbf{h}(\mathbf{y}, \dot{\mathbf{y}}, \mathbf{u}, t) = 0 \quad \forall t \in [0, t_f] \quad (3)$$

$$\mathbf{g}(\mathbf{y}, \dot{\mathbf{y}}, \mathbf{u}, t) \leq 0 \quad \forall t \in [0, t_f] \quad (4)$$

$$\mathbf{k}_p(\mathbf{y}, (t_p), \dot{\mathbf{y}}(t_p), \mathbf{u}(t_p), t_p) \leq 0 \quad \forall p \in \{0, \dots, n_p\} \quad (5)$$

In Eq. (1) $\Phi(\cdot)$ represents a steady state component of the objective function evaluated at $t = t_f$, while $L(\cdot)$ is related to the transient response of the system. In Eqs. (1)–(5) $\mathbf{y}(t)$ are the state variables and $\mathbf{u}(t)$ the manipulated variables. $\mathbf{f}(\cdot)$ represents the DAEs describing the system dynamics, while $\mathbf{h}(\cdot)$ is the set of equality constraints. $\mathbf{g}(\cdot)$ in Eq. (4) is the set of path inequality constraints that must be satisfied over the entire time horizon and $\mathbf{k}_p(\cdot)$ are point constraints at a finite set of times, including the initial and the end-points.

The Control Vector Parameterization (CVP) approach is a very popular choice to solve dynamic optimization problems due to its high efficiency and ease of implementation compared with other options.

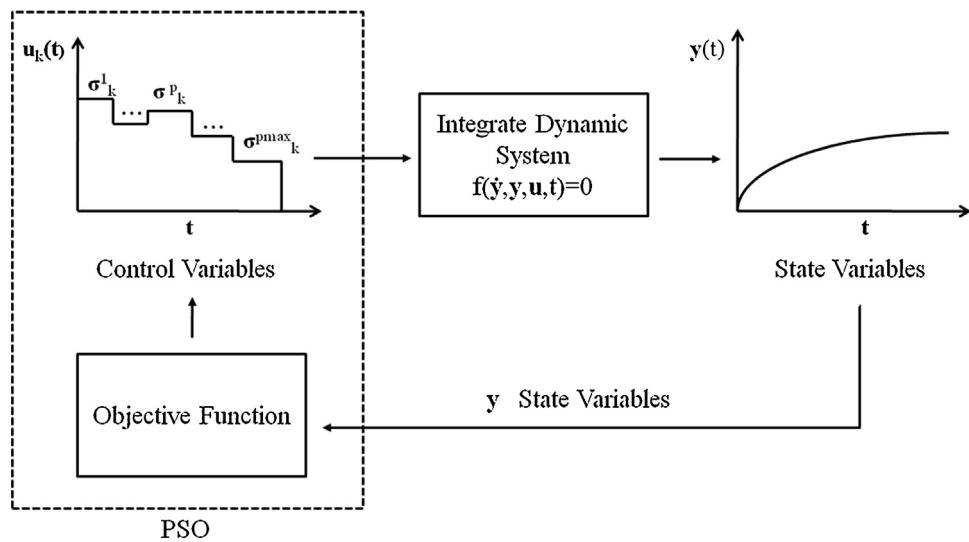


Fig. 2. Control parameterization approach for dynamic optimization using PSO algorithm.

CVP reduces the infinite dimensional dynamic optimization problem (Eqs. (1)–(5)) to a finite dimensional problem through the approximation of the manipulated variables profiles $\mathbf{u}(t)$ by a discrete set of basis functions (for example, piecewise linear functions) characterized by a finite number of invariant parameters σ . Therefore the objective function and the point constraints are expressed as composite functions of parameters σ , which allows the decomposition of the dynamic optimization problem into two subproblems:

- 1) A Master subproblem, given by a non-linear programming problem (NLP) in terms of σ :

$$\min_{v, t_f} \phi(\mathbf{y}(\sigma, t_f), \mathbf{u}(\sigma, t_f), t_f) + \int_0^{t_f} L(\mathbf{u}(\sigma, t), \mathbf{y}(\sigma, t), t) dt \quad (6)$$

Subject to:

$$k_p(\mathbf{y}(\sigma, t_p), \dot{\mathbf{y}}(\sigma, t_p), \mathbf{u}(\sigma, t_p), t_p) \leq 0 \quad \forall p \in \{0, \dots, n_p\} \quad (7)$$

- 2) An Initial Value subproblem (IVP), which is the numerical integration of Eqs. (2)–(4) for given values of the parameters σ which yields:

$$\mathbf{y}(\sigma, t), \dot{\mathbf{y}}(\sigma, t) \quad \forall t \in [0, t_f] \quad (8)$$

The master NLP may be solved with either gradient based approaches (e.g. successive quadratic programming SQP) or gradient-free approaches such as direct or stochastic search.

Specifically, stochastic techniques present the following advantages over their deterministic counterparts: ease of implementation, global convergence properties, good computational efficiency, and ease of extension to multiple-objective problems (Carrasco and Banga, 1997; Reyes-Sierra and Coello Coello, 2002). In particular, in the last years, among the many proposed stochastic techniques, the Particle Swarm Optimization (PSO) approach has been successfully implemented in many research and application areas providing better results in a faster and cheaper way compared to other stochastic methods (Reyes-Sierra and Coello Coello, 2006).

In this contribution, the stochastic search algorithm PSO is adopted to solve the master problem.

As shown in Fig. 2, the optimization procedure based in the CVP and PSO approaches is as follows: the control profiles $\mathbf{u}(t)$ are discretized into p_{\max} piecewise constant functions (subdivisions characterized by σ_k^p with $p=1\dots p_{\max}$). The manipulated variables profiles proposed by the stochastic algorithm in iteration k are

fed to the dynamic model to calculate the state variables through numerical integration. The system response is used to compute the corresponding objective function (OF). A new set of control variables profiles is calculated with that information in iteration $k+1$ until convergence is achieved.

4. Particle Swarm Optimization (PSO)

The PSO method was proposed by Kennedy and Eberhart (1995). This heuristic search technique simulates social behaviors as that of a flock searching for food. In this algorithm, the individuals move within the search space and a fitness value (objective function, OF) is associated to each individual according to its position. This individual information is exchanged with the rest of the population members along the search process.

Mathematically, the search process can be described by the following formulas, where \mathbf{x} represents the position and \mathbf{v} the velocity of each particle (individual):

$$\mathbf{x}_{k+1}^i = \mathbf{x}_k^i + \mathbf{v}_{k+1}^i \quad (9)$$

$$\mathbf{v}_{k+1}^i = w_k \mathbf{v}_k^i + c_1 r_1 (\mathbf{z}_k^i - \mathbf{x}_k^i) + c_2 r_2 (\mathbf{z}_k^g - \mathbf{x}_k^i) \quad (10)$$

In Eqs. (9) and (10):

- \mathbf{z}_k^i is the position with the best value of the objective function visited so far for the i th particle.
- \mathbf{z}_k^g is the position with the best value of the objective function found so far by any particle of the swarm (following a star topology (Van den Bergh and Engelbrecht, 2006)).
- The inertia weight, w , is employed to control the impact of the previous history on the current velocity of a given particle.
- c_1 is the cognitive learning factor and c_2 is the social learning factor. They represent the attraction that a particle has toward its own success and toward the success of the swarm, respectively.
- The control step factors r_1, r_2 ensure a variable step size of the particle within the search space to avoid “falling in a routine”. They are random values selected in the range $(0, 1]$.

Velocities are usually clamped following Eqs. (11)–(13):

$$\mathbf{v}_k^i = \min(\mathbf{v}_k^i, \mathbf{v}^{\max}) \quad (11)$$

$$\mathbf{v}_k^i = \max(\mathbf{v}_k^i, -\mathbf{v}^{\max}) \quad (12)$$

$$\mathbf{v}^{\max} = \gamma(\mathbf{U} - \mathbf{L}) \quad (13)$$

v^{\max} is the maximum allowed velocity, \mathbf{U} and \mathbf{L} are the upper and lower bounds of the variables, respectively, and γ is a user selected parameter in the range $(0, 1]$ which may vary from problem to problem (Adams and Seider, 2008).

In order to confer better convergence properties to the algorithm, Eberhart and Shi, (2001), Shi and Eberhart (1998a,b) introduced the inertia weight w . As can be seen from Eq. (10), this factor weighs the contribution of the previous velocity, controlling how much of the previous flight direction will influence the new velocity.

Eberhart and Shi (2000) proposed the use of a linear decreasing value of w , in order to increase the exploration of the parameter space during the initial search iterations and increase the exploitation of the parameter space during the final steps of the search.

Typically, a dynamic inertia factor is implemented using a linear function with two thresholds: w_{end} , w_{start} which usually take the values 0.4 and 0.9, respectively. Eqs. (15) and (16) present decreasing and increasing inertia weight schemes, respectively.

$$w_k = \frac{(k_{\max} - k) \cdot (w_{\text{start}} - w_{\text{end}})}{k_{\max}} + w_{\text{end}} \quad (15)$$

$$w_k = \frac{(k) \cdot (w_{\text{start}} - w_{\text{end}})}{k_{\max}} + w_{\text{end}} \quad (16)$$

The adopted convergence criterion of the algorithm is satisfied when the objective function (*OF*) in the k th iteration has no improvement with respect to that of the k -10 generation.

Finally, death penalty is generally used to reject infeasible individuals. This is probably the easiest way to handle constraints and it is also computationally efficient, because as soon as a certain solution violates a constraint, it is immediately rejected while the corresponding *OF* assigned with an unfavorable value to discourage revisiting that position (Coello Coello, 2002).

5. Implementation issues

In this section, several implementation details concerning the use of the PSO algorithm within the CVP approach to optimize the drugs flow rate profiles along medical procedures are presented.

Firstly, based on medical considerations (Table 1), the involved variables have to verify the following constraints (Eqs. (19)–(24)):

$$0 \leq \sigma SNP_k^{i,p} \leq 10 \mu\text{gkg}^{-1}\text{min}^{-1} \quad (19)$$

$$0 \leq \sigma PNP_k^{i,p} \leq 0.7 \mu\text{gkg}^{-1}\text{min}^{-1} \quad (20)$$

$$4 \leq \sigma DP_k^{i,p} \leq 10 \mu\text{gkg}^{-1}\text{min}^{-1} \quad (21)$$

$$0 \leq \sigma NTG_k^{i,p} \leq 4 \mu\text{gkg}^{-1}\text{min}^{-1} \quad (22)$$

$$0 \leq \sigma PFL_k^{i,p} \leq 200 \mu\text{gkg}^{-1}\text{min}^{-1} \quad (23)$$

$$0 \leq \sigma ISO_k^{i,p} \leq 2 MAC \quad (24)$$

Eqs. (25) and (26) prevent large fluctuations on the manipulated variables:

$$\begin{aligned} \sigma SNP_k^{i+1,p} - \sigma SNP_k^{i,p}, \sigma PNP_k^{i+1,p} - \sigma PNP_k^{i,p}, \sigma NTG_k^{i+1,p} \\ - \sigma NTG_k^{i,p} \leq 0.2 \mu\text{gkg}^{-1}\text{min}^{-1} \end{aligned} \quad (25)$$

$$\sigma DP_k^{i+1,p} - \sigma DP_k^{i,p} \leq 0.5 \mu\text{gkg}^{-1}\text{min}^{-1} \quad (26)$$

Death penalties are introduced to the PSO algorithm when violation of constraints (27)–(30) occurs:

$$MAP < 20 \text{ mmHg}, MAP > 110 \text{ mmHg} \quad (27)$$

$$MPAP < 5 \text{ mmHg} \quad (28)$$

ALGORITHM

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a. Initialize  $x_k^i$  randomly
b. Initialize  $v_k^i$  randomly with an upper bound  $v^{\max}$  (Eq 13).
c. Do kmax iterations.
   For each particle i:
      1. Evaluate the objective function at  $x$ .
      2. When the current objective is the best that an individual has experienced, remember the location  $z_k^i$ , and the objective function value.
      3. When the objective is the best that any particle has experienced, remember the location  $z_k^g$  and the objective function value.
   For each particle i and subdivision p:
      1. Set  $v^{i,p}_{k+1}$  Eq. (10)
      2. Set  $v^{i,p}_{k+1} = \min(v, v^{\max})$ . (Eq. 11)
      3. Set  $v^{i,p}_{k+1} = \max(v, -v^{\max})$ . (Eq. 12)
      4. Set  $x^{i,p}_{k+1}$  Eq. (9)
         If  $abs(x^{i+1,p}_{k+1} - x^{i,p}_{k+1}) > \Delta Drug$  (Eqs. 25,26)
            Set  $x^{i+1,p}_{k+1} = x^{i,p}_{k+1} \pm \Delta Drug$ 
         If  $x^{i,p}_{k+1} > U$  (Eqs. 19-24)
            Set  $x^{i,p}_{k+1} = U$ 
            Set  $v^{i,p}_{k+1} = 0.1 v^{i,p}_{k+1}$ 
         If  $x^{i,p}_{k+1} < L$ 
            Set  $x^{i,p}_{k+1} = L$ 
            Set  $v^{i,p}_{k+1} = 0.1 v^{i,p}_{k+1}$ 
      5. Next subdivision
      6. Next particle
      Next iteration

```

(Adams and Seider, 2008; Kennedy and Eberhart, 1995)

Fig. 3. Pseudo code of the PSO algorithm.

$$BIS < 10 \quad (29)$$

$$CO < 0.0251/\text{s} \quad (30)$$

Regarding the dynamic optimization problem, the time profile of each manipulated variable is represented by the components of the vectors of Eqs. (9) and (10), i.e., the position \mathbf{x} of a particle i in iteration k is defined as follows:

$$\mathbf{x}_k^i = [\mathbf{PFL}_k^i, \mathbf{ISO}_k^i, \mathbf{DP}_k^i, \mathbf{PNP}_k^i, \mathbf{NTG}_k^i, \mathbf{SNP}_k^i]$$

In addition, each time profile is constituted by a sequence of p_{\max} constant segments. For example, the PFL and DP infusions are represented as follows:

$$\mathbf{PFL}_k^i = [\sigma PFL_k^{i,1}, \sigma PFL_k^{i,2}, \dots, \sigma PFL_k^{i,p_{\max}}, \sigma PFL_k^{i,p_{\max}}]$$

$$\mathbf{DP}_k^i = [\sigma DP_k^{i,1}, \sigma DP_k^{i,2}, \dots, \sigma DP_k^{i,p_{\max}}, \sigma DP_k^{i,p_{\max}}]$$

In Fig. 3, the pseudo code of the implemented PSO algorithm is shown.

The addressed optimization problem is necessarily multi-objective since it is desired to simultaneously control several variables of medical interest, which present conflicting behaviors. There exist different techniques to solve multi-objective optimization problems with stochastic algorithms (Reyes-Sierra and Coello Coello, 2006). The aggregated functions approach is adopted here, which combines, in a weighted fashion, all the objectives of the problem in a single objective function (*OF*):

$$OF = \sum_p \left[w_{BIS} (BIS_d - BIS_k^p)^2 + w_{CO} (CO_d - CO_k^p)^2 + w_{MAP} (MAP_d - MAP_k^p)^2 + w_{MPAP} (MPAP_d - MPAP_k^p)^2 \right] \quad (31)$$

BIS_d , CO_d , MAP_d , and $MPAP_d$ are the desired set-points for BIS , CO , MAP , and $MPAP$, respectively (Eq. (31)). The total time of the procedure is divided in intervals of 30 s characterized by superscript p . Therefore BIS_k^p , CO_k^p , MAP_k^p and $MPAP_k^p$ are the evaluations of the variables at the end of interval p in iteration k , provided by the physiological model in response to the infusion proposed by the PSO algorithm. Parameters w_{BIS} , w_{CO} , w_{MAP} and w_{MPAP} weigh the different objectives through χ_{BIS} , χ_{MAP} , χ_{MPAP} and χ_{CO} which scale the terms involving variables MAP , $MPAP$ and CO to be comparable with the BIS value as follow (Eqs. (32)–(35)):

$$w_{CO} = \chi_{CO}(BIS_d/CO_d)^2 \quad (32)$$

$$w_{MAP} = \chi_{MAP}(BIS_d/MAP_d)^2 \quad (33)$$

$$w_{MPAP} = \chi_{MPAP}(BIS_d/MPAP_d)^2 \quad (34)$$

$$w_{BIS} = \chi_{BIS} \quad (35)$$

Since the objective of the procedure is to take the system from a certain initial condition to a situation close to the recommended set-points, experiences with different values of the weighting factors were carried out in order to identify a convenient choice from the point of view of the final approximation to the desired state. For weighting factors of similar magnitudes, it was observed that the BIS variable ended far from its desired set-point. In order to avoid this undesirable behavior, several parameterizations were tried by modifying χ_{BIS} while assigning an equivalent importance to the hemodynamic objectives ($\chi_{CO} = \chi_{MAP} = \chi_{MPAP}$). The following parameter configuration was considered the most convenient regarding the quality of the approximations to the set-points of the involved variables: $\chi_{BIS} = 85$ and $\chi_{CO} = \chi_{MAP} = \chi_{MPAP} = 5$.

Table 2
 γ parameter values.

	γ_{SNP}	γ_{DP}	γ_{PNP}	γ_{NTG}	γ_{ISO}	γ_{PFL}
Case 1	–	1	0.14	0.14	0.14	1
Case 2	0.1	0.375	0.056	0.14	0.14	1

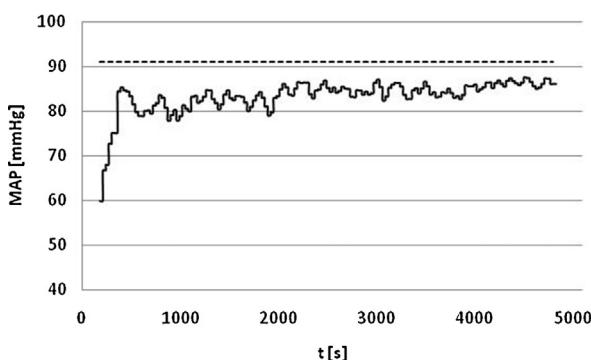
The physiological model and the PSO strategy were computationally implemented using the Fortran language. Each iteration of the algorithm is carried out in approximately 1 min and 20 s of CPU time, using an Intel® Core™ i5-2500 3.3 GHz with 4 GB RAM computer desktop. The used number of particles was 50 (i_{\max}) and the maximum number of iterations was set in 30 (k_{\max}).

6. Results and discussion

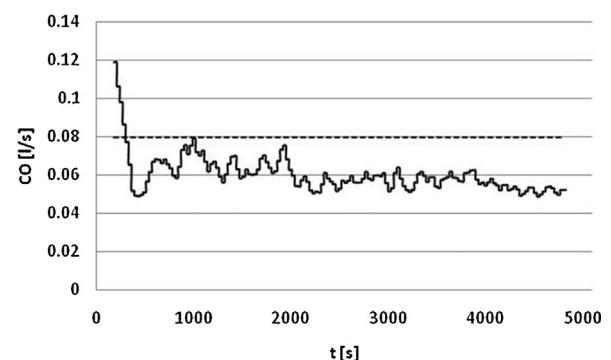
In order to illustrate the performance of the algorithm this section presents results for two case studies described in Rao et al. (2000) involving anesthetic and hemodynamic procedures (Case 1 and Case 2). In both cases the model parameterization corresponds to an average healthy individual. Dysfunctions are simulated by modifying certain parameters from their nominal values.

Different values for the γ parameter (Eq. (13)) were analyzed for both experiences aimed at identifying those that provided the fastest convergence. The adopted values are reported in Table 2. The analysis was performed with a decreasing w_k (Eq. (15)).

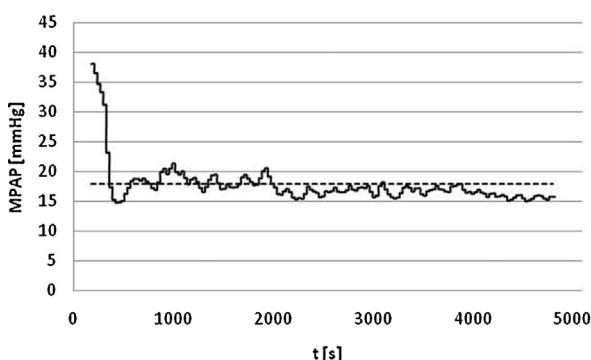
In Table 3 the slopes of the physiological variables observed when the drugs are administered one at a time are summarized. These results, obtained from “open loop” simulation experiments, are provided only to illustrate the indirect relationship existing



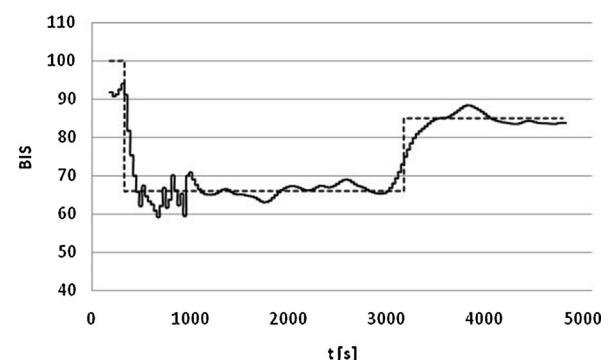
a. MAP vs t .



b. CO vs t .



c. $MPAP$ vs t .



d. BIS vs t .

Fig. 4. Optimal variables. Dashed line: Variable set-point. Solid line: Variable response.

Table 3

Individual effect of each drug over MAP, CO and MPAP.

Drug	Doses	Directly affects	ΔMAP (mmHg)	ΔCO (l/s)	$\Delta MPAP$ (mmHg)
PFL	100 $\mu\text{g}/\text{kg}/\text{min}$	MAP	≈ -7	≈ -0.0088	≈ -7
ISO	1 MAC	MAP	≈ -30	≈ 0.09	≈ 17
PNP	0.0175 $\mu\text{g}/\text{kg}/\text{min}$	MAP	≈ 16	≈ -0.0304	≈ -4
NTG	2 $\mu\text{g}/\text{kg}/\text{min}$	MPAP	≈ -5	≈ -0.0056	≈ -4
SNP	6 $\mu\text{g}/\text{kg}/\text{min}$	MAP	≈ -16	≈ 0.0291	≈ 2.5
DP	8 $\mu\text{g}/\text{kg}/\text{min}$	CO	≈ 10	≈ 0.0219	≈ -5

between the drugs and the variables to be optimized. For example, the administration of 0.0175 $\mu\text{g}/\text{kg}/\text{min}$ of PNP causes an increase of 16 mmHg in MAP directly, while CO and MPAP are indirectly decreased in 0.0304 l/s and 4 mmHg, respectively. This trends will be used later to analyze the obtained solutions.

6.1. Case 1: Congestive heart failure

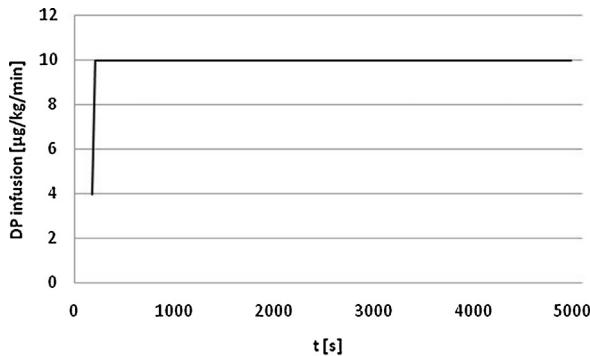
It is desired to maintain the anesthetic and hemodynamic state of a patient under congestive heart failure. The disease is simulated by decreasing $E_{\max,lv}$ in 40% from the normal value in order to reproduce a systolic dysfunction, and increasing $E_{\min,lv}$ in 40% to reproduce the diastolic dysfunction. As result, the physiological model settles in lower values of MAP and CO, and in a higher value for MPAP (60 mmHg, 0.12 l/s and 37 mmHg, respectively) relative to those of a healthy individual. PNP, NTG and DP are administered to lead the hemodynamic variables to their normal values: 91 mmHg for MAP, 0.08 l/s for CO and 18 mmHg for MPAP. PFL is supplied during the first 10 min to induce the anesthetic state,

followed by the administration of ISO to maintain unconsciousness. Both anesthetic agents help to decrease the BIS value from 100 to 66. At $t = 50$ min, the BIS set-point is increased to 85 to raise the consciousness level of the patient. The total duration of the procedure is 80 min.

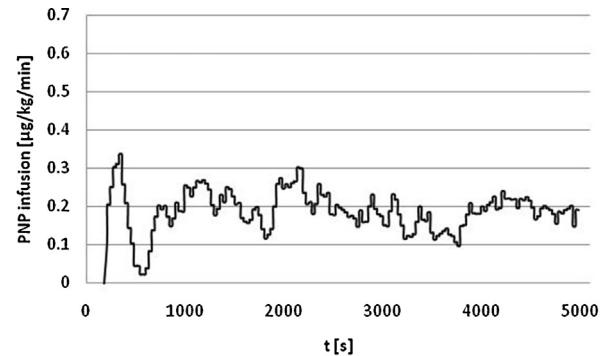
Results for Case 1 are presented in Figs. 4 and 5:

It should be mentioned that at $t = 0$ the changes on the parameters to simulate the dysfunction from a healthy initial condition are introduced. Then a period 180 s is allowed for the model to settle in the abnormal condition. This transient is not shown in the figures for clarity sake. After the 180 s period, the infusion of the different substances is allowed to pursue the desired controlled state.

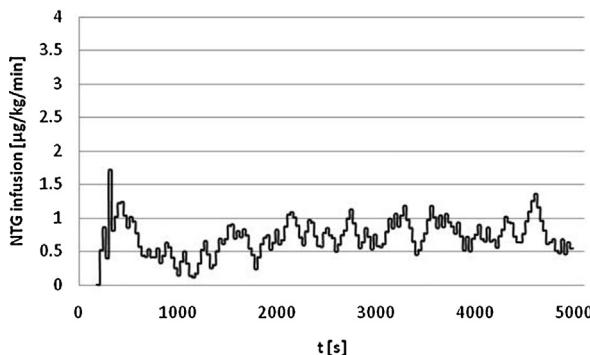
Fig. 4c and d (solid line) shows that the goals set for MPAP and BIS are quite closely met, while for CO and MAP relative off-sets of 20% and 5% are observed, respectively (Fig. 4a and b, solid line). It can be seen from Fig. 5a, that the infusion of DP reaches the constraint established by Eq. (21) at the beginning of the procedure. This drug is supplied to increase CO but the proposed (feasible) infusion is



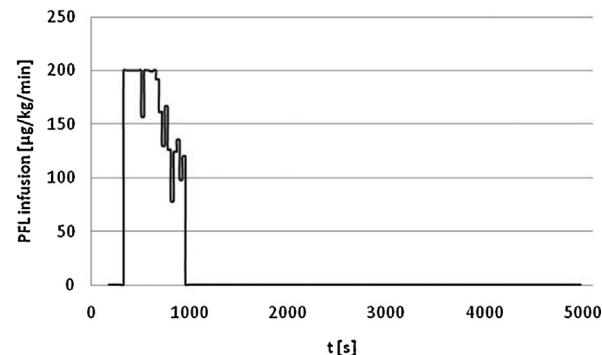
a. DP vs t .



b. PNP vs t .



c. NTG vs t .



d. PFL vs t .

Fig. 5. Optimal drug infusion profiles.

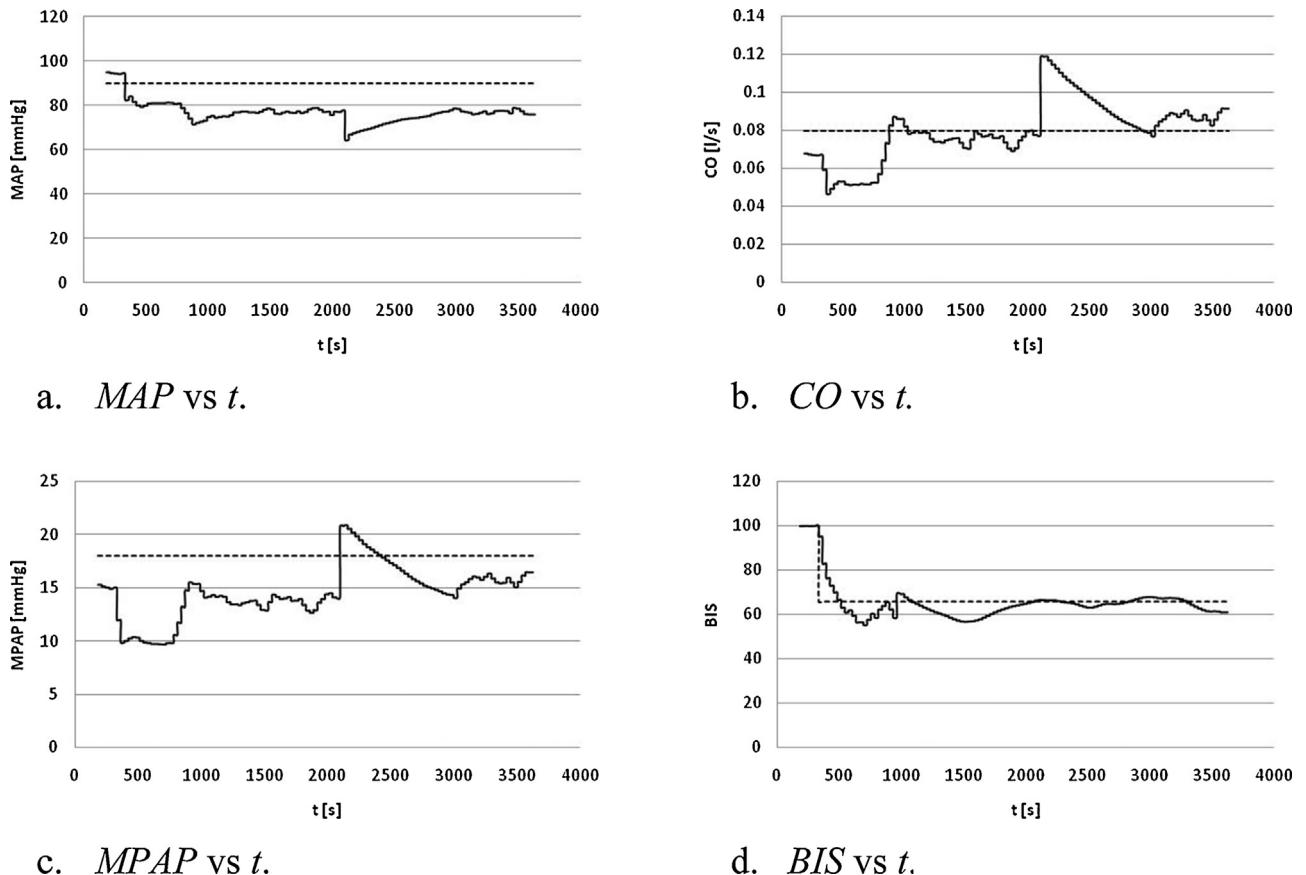


Fig. 6. Optimal variables. Dashed line: Variable set-point. Solid line: Variable response.

not enough to compensate the changes produced by drugs PFL, PNP and NTG responsible for decreasing CO (Table 3). The off-set in MAP cannot be further reduced without compromising variable CO since, in order to increase MAP , it is necessary to infuse more PNP which will decrease CO .

As mentioned, drug PFL is used to induce anesthesia in the first ten minutes of the procedure and then inhalable agent ISO is administered to maintain the unconsciousness state. The change of anesthetics is achieved in a proper manner with a small oscillatory behavior on BIS in period $t = 700 - 1000$ s (Fig. 4d, solid line). Finally, the BIS set-point change from 66 to 85 is accomplished by lowering the administration of ISO at $t = 3100$ s (not shown), which led to the adjustment of the infusion of the remaining drugs to maintain the hemodynamic states (Fig. 5).

6.2. Case 2: Unclamping of an aortic vessel

In this case the unclamping of an aortic vessel is studied. The clamp is simulated by reducing the systemic resistances (R_{a1} , R_{a2} and R_{a3}) 50% relative to those of a healthy individual. When the unclamping occurs, the resistance values are slowly ramped up for 10 min to mimic natural stabilization. Due to the unclamping in $t = 35$ min, MAP decreases and CO increases. Therefore, PNP and SNP are used to regulate MAP while CO is controlled through DP and NTG is infused to drive $MPAP$ to normal values. PFL and ISO are administered as in Case 1 to induce and maintain the anesthetic state. The physiological model initializes with the following values for MAP , CO and $MPAP$: 98 mmHg, 0.07 l/s and 15 mmHg, respectively and is desired to lead them to $MAP = 91$ mmHg, $CO = 0.08$ l/s and

$MPAP = 18$ mmHg. The BIS set-point is 66 for the entire procedure which lasts 60 min.

For Case 2, Figs. 6 and 7 illustrate the variable responses and infusion profiles provided by the PSO algorithm, respectively.

The BIS variable shows a close track of set-point (Fig. 6d, solid line), while for the remaining variables rather significant off-sets are exhibited during the procedure. As can be seen from Figs. 6a and 7d, the off-set in MAP could have been overcome if less SNP had been administered, but since this drug helps to raise variable CO , such objective would have worsen. Therefore, for the selected objective function weights, the algorithm allowed small off-sets in both variables rather than a big one in one of them.

When the unclamping occurs at $t = 2100$ s, it can be observed slight increases in the flow rates of drugs PNP and NTG (Fig. 7a and c) aimed at increasing MAP and lowering $MPAP$. As can be seen from Table 3, DP helps to raise MAP , which in this circumstance was located far from the target value.

The administration of ISO is lowered when the unclamping occurs due to a raise in CO , i.e., more blood carrying ISO is delivered and therefore it is necessary to lower the ISO concentration in blood to maintain the BIS value.

As in the previous experience, the change of anesthetic agents was successfully achieved.

Regarding the algorithm progress, it can be seen from Fig. 8 a progressive decrease in the OF value along iterations, although significant improvements are produced only within the first 10 iterations for both cases.

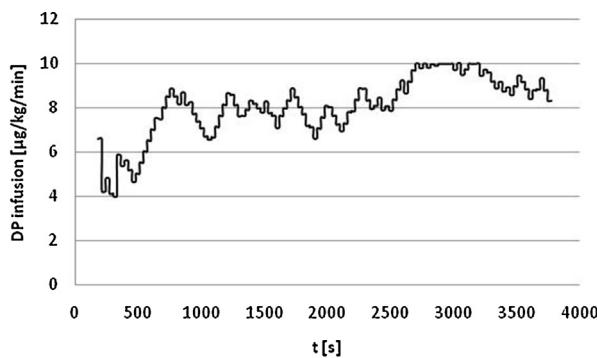
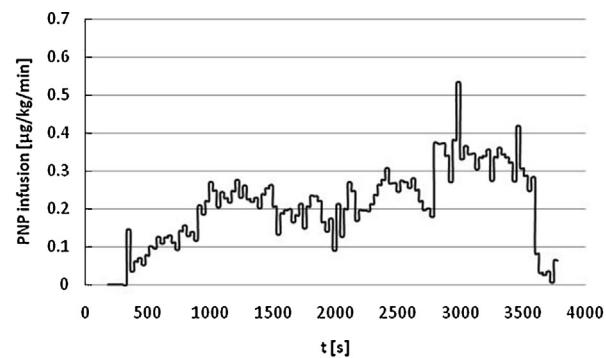
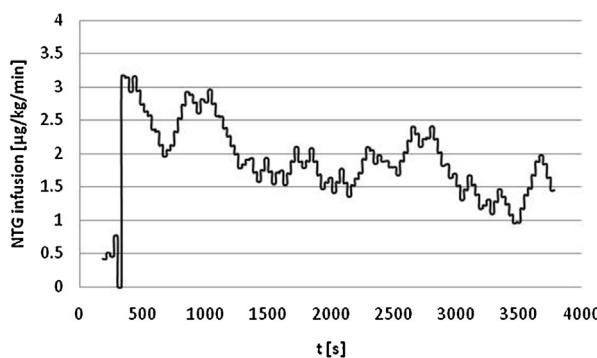
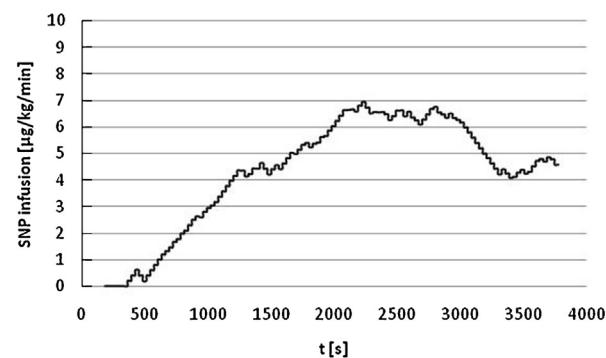
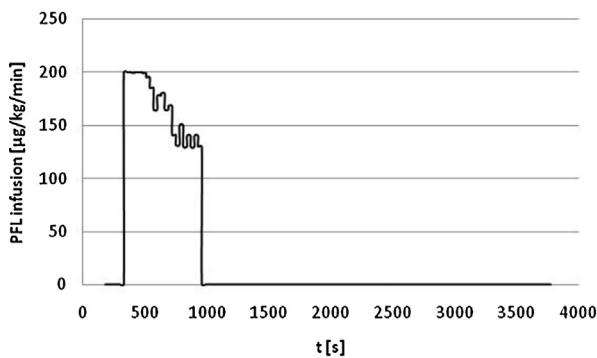
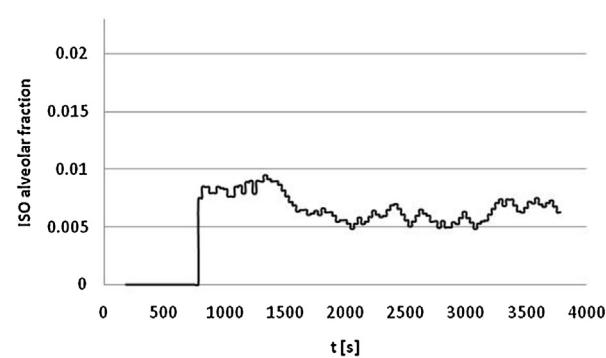
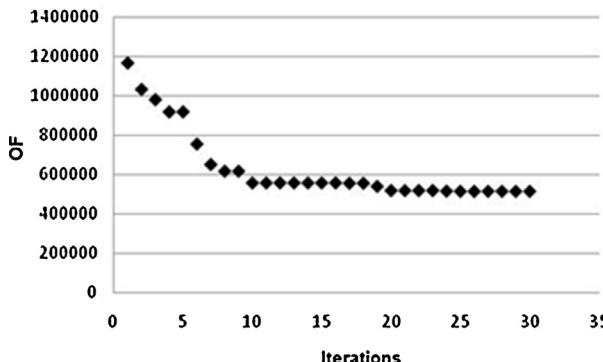
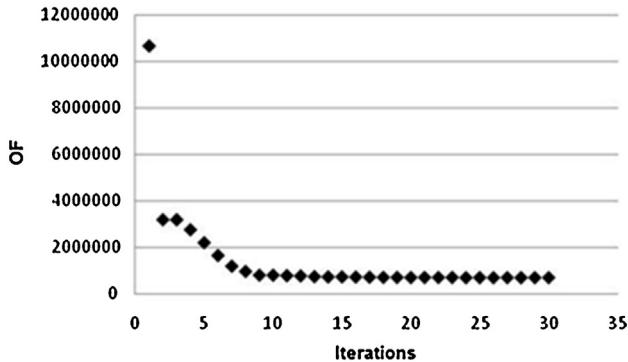
a. DP vs t .b. PNP vs t .c. NTG vs t .d. SNP vs t .e. PFL vs t .f. ISO vs t .

Fig. 7. Optimal drug infusion profiles.



Case 1



Case 2

Fig. 8. OF vs iterations.

7. Conclusions and future work

A dynamic optimization strategy was presented to control anesthetic and hemodynamic variables in simulated patients. The proposed approach could be considered as part of a control structure, where controllers, measurement devices, alarms and physicians are the main components of the loop.

The implemented physiological model used to simulate the pharmacological effect of drugs and to design optimal infusion schemes, presents nonlinearity and discontinuities. The aggregated functions approach making use of weights to tune the relative importance of the different objectives was adopted to solve the multi-objective optimization problem. The efficacy of the PSO strategy was tested for two cases study consisting of simulated patients under congestive heart failure (*Case 1*) and under the unclamping of an aortic vessel (*Case 2*), treated with typical drugs.

For *Case 1* the optimization led to a satisfactory result for the variables *BIS* and *MPAP*, while *MAP* and *CO* had a relative off-set of 5% and 20%, respectively. For *Case 2*, just the set-point set for the *BIS* variable was closely met. In general, is not possible to obtain the best result for every single variable since the best individual objective is achieved at the expense of the detriment of the other targets. In this sense, the algorithm is capable to select the drugs infusions that minimize the set-point of the variables given weights X_{CO} , X_{MAP} , X_{MPAP} and X_{BIS} .

The proposed methodology can be improved in a number of ways. For example, the aggregated functions approach was adopted as a practical way of dealing with the conflicting nature of the different objectives, boosted by an involved underlying nonlinear dynamics. However, more sophisticated approaches (Reyes-Sierra and Coello Coello, 2006) could be considered to study specific trade-offs among the different objectives.

Additionally, path constraints can be explicitly imposed on any variable. For example, the physiological model includes the breathing process. In this context, oxygen tissue saturation and output concentration of carbon dioxide could be explicitly monitored to provide control on the state of the artificial ventilation.

In all cases, the parameters of the optimization algorithm have to be properly tuned to achieve a fast convergence.

Finally it should be stressed that in order to consider this approach for practical purposes, the underlying physiological model should be adequately parameterized for the specific individual/patient. Parameter estimation of physiological models, currently under development, is a very complex activity which requires sensitivity analysis, appropriate technology to address the mean squares optimization problem and adequate amount of good quality experimental information.

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