Multiagent systems for cardiac pacing simulation and control

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Abstract. Simulating and controlling physiological phenomena are complex tasks to tackle. This is due to the fact that physiological processes are usually described by a set of partial models representing specific aspects of the phenomena and their adoption does not allow the achievement of an effective simulation/control system. A current open issue is the development of techniques able to comprehensively describe a phenomenon exploiting partial models. Simulation and control heavily rely on accurate modelling of physiological systems. In addition, since a large number of partial models of a single physiological phenomenon have been proposed over the years, the evaluation of their effectiveness and of their combinations is a fundamental task. In this paper we propose a multiagent paradigm, called anthropic agency, as a flexible tool to support and evaluate the combination of partial models embedded in agents. We present an agent negotiation paradigm, that improves the one we employed in our previous applications, as a flexible approach to combine optimally the partial models. We formally describe the negotiation protocol and we embed it in a FIPA agent interaction protocol. Furthermore, as an example of practical application, we describe how our paradigm can be a potential solution to the problem of adaptive cardiac pacing. Finally, we experimentally evaluate our approach and we discuss its properties and peculiarities.

1. Introduction

Physiological processes are characterized by high complexity and their satisfactory study and modelling is difficult to achieve [15]. This is mainly due to the fact that a physiological process usually emerges from the interaction of several elements belonging to an intricate network of relationships, where each element is involved in more processes [2]. Currently, several physiological phenomena are described by a set of partial models representing specific aspects of the phenomenon. However, the basis of the relationships among these partial models has not found yet a satisfactory description. The lack of comprehensive models of physiological processes usually imposes the adoption of a single partial model in the design of simulation/control systems, not allowing the achievement of precise and effective simulation/control. A typical example concerns the adaptive cardiac pacing: several partial models have been used in the attempt to mimic the natural regulatory system of heart rate, but the results are so poor that the use of such models in commercial pacemakers is still limited [17].

Hence, the combination of partial models is a fundamental problem to solve in order to improve the performance of simulation/control systems of physiological processes. In order to address such tasks, several questions need an answer: what are the models to take into account to have the best performance? what are the most effective combinations of partial models? and so on. Two aspects are crucial here: the definition of a paradigm to combine several models that can mimic the existing relationships between the corresponding phenomena and the provision of a flexible software tool to support the combination of the models and its evaluation. In literature several techniques are adopted to

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combine models; for instance, in cardiac pacing, attempts have been made with weighted average, model selection, and overdrive (i.e., the selection of the model that proposes the highest value for the control variable). They all exhibit two drawbacks: their overall performance is modest, and they are not supported by any flexible and general software tool to study and analyze their effectiveness.

In previous work [1], we developed a system based on the multiagent paradigm [31], called anthropic agency, able to integrate a number of partial models of a physiological phenomenon in order to globally produce a comprehensive model of the phenomenon. In anthropic agency, partial models are embedded in specific agents (called decisional agents) and the global model results from the interaction via a cooperative negotiation of these agents. In anthropic agency, negotiation offers a way to integrate partial models that goes beyond “putting pieces together”: it can account for secondary inter-effects between the partial models and it flexibly models physiological phenomena [7] according to an optimal decentralized control technique [5]. Anthropic agency provides a flexible infrastructure to analyze different model combinations, allowing dynamic insertion and removal of models (agents).

Starting from what presented in [1], in this paper we improve the negotiation mechanism and apply it in a new case study: the modeling of the heart rate regulatory system. The improvement of the negotiation mainly consists in a more precise specification of the protocol and in its implementation according to standard FIPA interaction protocols [12]. The choice of heart rate regulatory system modeling as a case study is due to the fact that in this field the partiality of the models is particularly evident. Many models have been proposed over the years [14,17], but each one of them is effective in emulating the normal sinus activity only under ideal and very restrictive conditions. Since these conditions are different for every model, a desirable solution would be to have a combined model in which every partial model prevails just when its ideal conditions are satisfied. Anthropic agency provides an effective approximation of such solution.

This paper is structured as follows. Section 2 describes the state of the art in simulation/control of complex systems via multiagent systems. Section 3 introduces the open issues in heart rate modeling. Section 4 describes our negotiation mechanism, and its applications to cardiac pacing. Section 5 describes the experimental evaluation of the negotiation mechanism. Finally, Section 6 concludes the paper.

2. Complex system simulation and control via multiagent system

Simulation and control of complex dynamical systems, such as systems exhibiting intricate interconnections, high dimensionality, multi-resolution, multi-representation, and uncertainty, are difficult tasks to tackle [4]. Physiological phenomena are a particular class of complex systems [15]. The idea of dealing with complexity by representing complex systems using different models according to several dimensions, such as at different scales, in different operating contexts, etc. is common in the literature [20]. The multi-modeling paradigm – introduced in [11] – was one of the first methodologies based on the adoption of a set of models to represent a single phenomenon. However, the adoption of a multiplicity of models of an unique phenomenon rises several issues regarding their coexistence. The most relevant issue to face concerns the combination and the synchronization of different models [22]. Traditional techniques such as weighted average, model selection (according to a confidence index of the model), fuzzy combination, and multimodeling itself do not solve the conflicts risen by the different models since they do not take into account any inter-effect between them.

The optimal decentralized approach [5] is emerging as the most effective technique to simulate/control systems by using different models. An optimal decentralized simulation/control task is formulated as a decentralized multi-objective problem where \( n \) independent decision makers operating on continuous variables are forced to cooperate to achieve a common goal [16]. More specifically, each decision maker \( i \) determines the optimal value for a vector variable \( u \) as the argument that minimizes/maximizes an objective function \( J_i \) under local and global constraints. Formally, let \( x_0 \) be the current state of the system, \( t \) the time, and \( u = [u_1, \ldots, u_m] \) the vector of variables, a decentralized multi-objective problem is (\( \forall i \in [1,n] \)):

\[
\begin{align*}
\text{arg min} / \text{max}_{u} & J_i(u_1(t), \ldots, u_m(t), x_0) \\
\text{s.t. } f_i(u) & \leq 0,
\end{align*}
\]

(1)

where \( f_i(u) \leq 0 \) represents the constraints of the decision maker \( i \). The solution of (1) is usually a non-trivial computational problem. In some special cases, involving linear or linearizable systems [28], traditional techniques of decentralized optimization can be adopted. In all other cases, including complex non-linear systems, ad hoc techniques are required.
In a large number of works in literature [10,22], market-based/economic techniques have been demonstrated effective at multi-objective optimization. Each decision maker \( i \) operates a local minimization/maximization of its own utility \( U_i \) (the economic analogue of the \( J_i \)) and a global optimum is achieved via a cooperative negotiation among them [26]. Thus, cooperative negotiation tries to solve the conflicts arising from the different objectives of the decision makers in order to, in an economic perspective, maximize the social utility \( U \) of the system (and, correspondingly, in an optimization perspective, maximize a global objective function \( J \)). The functions employed by the decision makers to negotiate are designed in order to maximize the social utility \( U \).

A requirement (as discussed in Section 1) is that the software system supporting model combination techniques be reconfigurable allowing the insertion and the removal of models at runtime. This means that, in a market-based perspective, the set of decision makers dynamically changes with time. In addition, since models can be developed by different designers, they can be heterogeneous in their paradigms. An approach for a reconﬁgurable integration of heterogeneous models is required to have an effective model combination.

The multiagent approach [31] is somehow a “natural” candidate to set up a reconﬁgurable framework for modeling based on market-based techniques. Several techniques for negotiation, aggregation of heterogeneous entities, and reconﬁgurability at runtime [3] have been deeply explored within multiagent system field. In particular, agents behave as decisional makers and negotiate to achieve a common agreement. Several works concerning the application of multiagent systems to ﬂexible decentralized optimization can be found in literature; they regard mainly the resource allocation ﬁeld. Two examples: in [19] a cooperative negotiation approach for real-time control of cellular network coverage is proposed and in [9] a cooperative negotiation approach is adopted to solve a distributed resource allocation problem in radar tracking of targets in an environment.

Anthropic agency [1,2] is a particular multiagent system that employs a decentralized multi-objective optimization via cooperative negotiation to model and control physiological processes. The anthropic agency paradigm has been adopted in [1] to implement a regulator for glucose-insulin metabolism in patients suffering diabetes. In this regulator two partial models coexist: the insulin response to the food adsorption and to the physical activity. The two models are embedded in two decisional agents that, once they have performed individual optimization according to the models they embed, negotiate amongst them via a mediator with the aim of achieving a global agreement.

A deeper analysis of the negotiation protocol of [1] identified some limitations [13]: it was not formal enough to be studied in order to prove some properties, such as the convergence of the agreement and the termination within a temporal deadline, and it was not parametric enough to be tailored on a specific patient. Nevertheless, the adoption of the multiagent paradigm and of the proposed negotiation protocol provide the anthropic agency with ﬂexibility towards the designer and towards the application. The designer can change the composition of the system by inserting and removing agents in order to determine the most effective combination of models that provides the most effective control for the application to be addressed. Thus, the designer can, within the anthropic agency framework, evaluate control algorithms, optimization algorithms, negotiation techniques, and their different combinations. In addition, anthropic agency exhibits ﬂexibility towards the application since the same infrastructure can be adopted to address different applications: the insulin-glucose metabolism regulation in [1], the pacing rate determination in this paper.

3. Cardiac pacing

Since the 1960s, permanent cardiac pacing has been used as an effective and reliable therapy for speciﬁc pathological alterations of the cardiac rhythm (arrhythmia) [14]. The physiological mechanism underlying cardiac pacing is simple: the cardiac pacemaker applies a pulse of electrical current to the ventricular wall, through a set of electrodes. The electrical stimuli cause a ventricular contraction that can be considered identical to a ventricular contraction occurring during a “natural” heart beat. Clearly, the heart rate is a vital factor in determining the amount of blood reaching the end organs per second, and a pathological alteration of the heart rate can have serious consequences on the patient’s health and well-being. When implanted, a cardiac pacemaker partially or totally takes over the function of the sinoatrial node, that, under normal conditions, initiates every heart contraction, and hence determines the heart rate. Different types of cardiac pacemakers have been used in clinical applications [17]: asynchronous (fixed pacing frequency, set by physicians), synchronous (fixed pacing frequency, but the
stimulation is activated just when needed), adaptive (pacing frequency is a function of some physiological parameters measured by the device).

Nowadays, asynchronous pacing is the standard therapy for many arrhythmia situations. However, some pathologies affecting the functionality of the sinoatrial node (e.g., Sick Sinus Syndrome) require adaptive stimulation. In rate-adaptive pacemakers, the control system determining the pacing frequency must mimic adequately the heart rate regulatory system of a healthy subject.

Many researchers have been looking for an optimal solution to the problem of rate-adaptive cardiac pacing. The common goal is to develop a multi-sensor heart rate regulatory system that effectively emulates the normal sinus activity. Many different combinations of physiological parameters, sensors, and algorithms have been proposed over the years [14,17]. Many studies [17] have shown that single-sensor pacemakers emulate effectively the normal sinus activity only under very specific conditions. These conditions change depending on the sensor and the algorithm used. It therefore seems rather unlikely that a single-sensor pacemaker will ever be able to regulate heart rate effectively under every possible physiological condition and the changing requirements caused by activities of daily life. In order to overcome these limitations, different strategies and combinations of algorithms have been pursued (overdrive, cross-checking, weighted mean) [14]. Such strategies have also been implemented in commercial dual-sensor pacemakers. Unfortunately, there is no comprehensive literature available about the efficacy of these combined techniques. Comparative studies between single-sensor and dual-sensor pacemakers showed that many subjects do not perceive benefits (in terms of general wellness) in using multi-sensor based regulatory systems, and some prefer a single-sensor based approach [29]. Moreover, the technologies used in dual-sensor pacemakers are more expensive and energy-consuming. Furthermore, the increased complexity of parameter setup in a multi-sensor approach have made some cardiologists to question about the future of multi-sensor based regulatory systems [6,29].

There is an evident need for a software instrument to compare different combinations of heart rate regulation algorithms. This instrument should match the properties of functionality, versatility, and effectiveness, and it is desirable that the technique it uses to combine algorithms be more efficient than the ones used so far.

4. Pacing controllers combination with anthropic agency

The anthropic agency paradigm [1] involves several classes of agents. In this paper we deal just with decisional agents that embed the partial models to combine and behave as decision makers. In addition, according to a decentralized approach, a mediator guides the negotiation. The decisional agents interact among them indirectly via the mediator. In what follows, “decisional agents” will be simply called “agents”.

In this section we concentrate on the negotiation paradigm of the anthropic agency. We introduce the new version of the negotiation protocol and we describe how it can be adopted for multi-sensor rate-adaptive pacing. Two phases of optimization are involved in model combination via anthropic agency: the agent optimization phase and the agency optimization phase.

4.1. Agent optimization phase

4.1.1. Partial models and agents

In order to apply the anthropic agency paradigm to the problem of heart rate regulation, we need a simulator of the physiological system to regulate. The input of the simulator is a 24-hours long ECG signal; the outputs are three parameters that are extracted from the ECG: QT interval length1, ECG derived respiratory signal [23], and heart rate. Obviously the open-loop nature of our approach (the output of the simulator will not be modified by the output of the control system) is a heavy simplification of the physiological reality. However, an open-loop approach is adequate in the initial part of our research, that has the purpose to preliminarly verify and test the performances and the properties of the anthropic agency paradigm applied to heart rate regulation.

We have taken into account two partial models that relate the heart rate (beats per minute) to two different variables: the length of QT interval (ms) and the respiration rate (cycles per minute). The first control model relates the heart rate (HR) to the length of QT interval as proposed by Sarma et al. in [27]:

\[
HR = - \frac{q_1}{\log \frac{q_2}{q_3 - QT}}, \tag{2}
\]

1QT interval can be defined as the time interval between the beginning of the QRS complex and the end of the T wave in the ECG.
while the second control model relates the heart rate (HR) to the respiration rate (RR) and is a slight refinement of the model proposed by Voukydis and Krasner in [30]:

\[ \text{HR} = r_1 \cdot \arctan(r_2 \cdot \text{RR} - r_3) + r_4, \]  

(3)

where \(q_i\) and \(r_i\) are parameters that must be tailored to the specific person. Both the models are approximation of the heart rate determination but, individually taken, do not describe appropriately the physiological system.

We embed in an agent, called QT agent, the model described by (2), and in another agent, called RR agent, the model described by (3). Figure 1 shows the system.

4.1.2. Agent utility functions

In an optimization perspective a utility/objective function to minimize (see Section 2) is needed. We define the utilities \(U_{QT}\) and \(U_{RR}\), where \(U_i : \mathbb{R}^2 \rightarrow \mathbb{R}\). In particular, \(U_{QT} : A_{QT} \rightarrow \mathbb{R}\) where \(A_{QT} \equiv \text{HR} \times \text{QT}\), and \(U_{RR} : A_{RR} \rightarrow \mathbb{R}\) where \(A_{RR} \equiv \text{HR} \times \text{RR}\). The state of the agent QT can be described by a pair of values \(\langle \text{hr}, \text{qt} \rangle\), and the state of the agent RR by a pair of values \(\langle \text{hr}, \text{rr} \rangle\). In addition, we call \(A \equiv A_{QT} \cup A_{RR}\), a vector \(p \in A\) (i.e., \(\langle \text{hr}, \text{qt}, \text{rr} \rangle\)) describes the state of the entire system. Note that qt and rr are given by the simulated sensors and hr is estimated by negotiation. Given a point \(q \in A_{QT}\) (respectively, \(A_{RR}\)) and calling \(d(q)\) the Euclidean distance of \(q\) from the curve (2) (respectively, (3)) \(U_{QT}(q)\), (respectively, \(U_{RR}(q)\)) is calculated as:

\[ U_{QT}(q) = \begin{cases} \frac{d(q)^2}{10} & d(q)^2 < 20 \\ 20 + 10 \cdot \log \frac{d(q)^2}{10} - 20 + 1 & d(q)^2 \geq 20. \end{cases} \]  

(4)

The formulas (4) have been experimentally determined after several trials in order to define steep potential functions that assign high values to the points that are far from the optimal curves. These functions are also
piecewise convex, to avoid local minima. In Fig. 2, $U_{QT}$ and $U_{RR}$ are shown.

We note that utility $U_i$ is defined similarly to a potential function where the points that satisfy (2) and (3) have the minimum value of potential (equal to 0). This is coherent with the idea that states of optimal functioning of the heart (represented by the points satisfying (2) and (3)) should be associated with low potential, and that other points of heart functioning should be associated to higher values of potential, according to the distance of such points from the points satisfying (2) and (3). Indeed, the optimal curves are the only information we have on the physiological phenomenon: we can reasonably assume that when a state is far from an optimal curve, then the performance of the heart is far from optimal; this aspect is captured in the above steep potential function. We note also that in our proposal the maximum utility corresponds to the minimum value of $U_i$.

The goal of each agent is to change the heart rate in order to drive the system to the minimum potential state nearest to the current state, according to its own potential-based model. This interpretation of the heart rate regulatory system is consistent with the idea that the autonomic nervous system, which is the main natural regulatory system of the heart rate, performs a synergy between homeostatic and allodynamic regulation [8].

4.1.3. Agent optimization algorithm
Given the vector $\langle hr, qt, rr \rangle$ representing the current state of the phenomenon, the two agents read the information about their states ($p_{QT} = \langle hr, qt \rangle$ and $p_{RR} = \langle hr, rr \rangle$). Then, the agents assign to $p_0^i$ the result of a local optimal search (with a function MINIMIZATION, see Section 4.4) performed on the objective function $U_i(\cdot)$ under their specific constraints $f_i$:

$$p_0^i = \arg \min_{p_i} U_i(p_i) \quad \text{s.t.} \quad f_i(p_i) = 0.$$

In our approach, we assume that the constraints are: $f_{QT} = \Delta QT = 0$ and $f_{RR} = \Delta RR = 0$, in other words the values of QT and RR cannot change during the local search. Potential functions $U_i(\cdot)$ constructed as described above do not have local minima (see Fig. 2); thus we can assume, without loss of generality, that hill-climbing-like techniques efficiently find the global minimum of $U_i(\cdot)$ (namely $U_i(p_0^i) = 0$). Hence, agent optimization phase eventually results in two vectors, $p_{QT}^0 = \langle hr_1, qt \rangle$ and $p_{RR}^0 = \langle hr_2, rr \rangle$.

4.2. Agency optimization phase: negotiation

4.2.1. Negotiation sessions
A negotiation session is a sequence of interleaved proposals of the agents to the mediator $e (p_{i \rightarrow e}^t)$ and counter-proposals of the mediator to the agents ($p_{e \rightarrow i}^t$), starting at time 0 and ending at time $\tau$. For example, the portion of a negotiation session regarding agent $i$ can be represented as follows:

$$p_{i \rightarrow e}^0 \succ p_{e \rightarrow i}^0 \succ p_{i \rightarrow e}^1 \succ \cdots \succ p_{e \rightarrow i}^\tau.$$

Each agent makes (with a function PROPOSE) its proposal by sending the following pair to the mediator: $\langle p_{i \rightarrow e}^t, U_i(p_{i \rightarrow e}^t) \rangle$. The initial proposal of an agent is $p_{i \rightarrow e}^0$ calculated as in Section 4.1.3.

4.2.2. Agreement determination
All the agents send at time $t$ their proposals $p_{i \rightarrow e}^t$ to the mediator. Then the mediator computes (with a function CALCULATE_AGREEMENT) the weighted average of the received proposals; formally:
\[ m^t = \frac{\sum_{i=1}^{n} p_i \cdot (1 + U_i(p_{i,e}))}{\sum_{i=1}^{n} (1 + U_i(p_{i,e}))}. \] (5)

\( m^t \) is the agreement reached in the negotiation session at time \( t \). Note that \( m^t \) is a point in \( A \); in the above formula, the sum at the numerator is intended to sum only the corresponding elements of the vectors (for example, \( \langle hr_1, qt \rangle + \langle hr_2, rr \rangle = \langle hr_1 + hr_2, qt, rr \rangle \)).

The mediator communicates to the agents its counter-proposals \( p^t_{i,e} \), that are the projections of \( m^t \) on the \( A_i \), by sending to each one of them the value \( \langle p^t_{i,e} \rangle \).

The negotiation is stopped by the mediator when the proposals of the two agents are close enough. We define the distance \( \text{dist} \) between the proposals as:

\[ \text{dist} = \sqrt{\frac{\sum_{i=1}^{2} \| p^t_{i,e} - m^t \|^2}{2}}, \]

and we formulate the termination condition as \( \text{dist} < \text{th} \). \( \text{dist} \) is calculated by a function \text{CALCULATE_DIST}.

In our experiments we set \( \text{th} = 0.5 \). An error of one beat per minute is tolerable for our application.

### 4.2.3. Agent proposal determination

Since we have not any information about the relationships between the two models, we cannot define the social utility/global objective function \( U_i/J \) in the design phase. We define a parametric negotiation paradigm and we determine the most effective parameters calibrating the negotiation to the specific patient.

In such a way, as discussed in Section 2, we implicitly determine the social utility by finding the negotiation parameters that bring the agents to precisely mimic the behavior of the physiological phenomenon. In designing the functions that produce the proposals of the agents we take into account two principles: the first principle is social, and requires that the agents accommodate the society, the second principle is selfish, and requires that the agents try to maximize their own utilities. We design the functions that determine the proposals of the agents as a combination of these two principles.

After receiving the counter-proposal \( p^t_{i,e} \) from the mediator, every agent \( i \) computes (with a function \text{CALCULATE_PROPOSAL}) its new proposal \( p^{t+1}_{i,e} \) as:

\[ p^{t+1}_{i,e} = p^t_{i,e} + \| p^t_{i,e} - p^t_{i,e} \| \alpha_i(p_i)u^{t+1}_i + \beta_i(p_i)w^{t+1}_i, \] (6)

where \( \alpha_i(\cdot) \) and \( \beta_i(\cdot) \), called negotiation parameters, are two functions on \( A_i \) to \( \mathbb{R} \). \( \| \cdot \| \) is the vector norm, and \( u^{t+1}_i \) and \( w^{t+1}_i \) are the two versors defined below. The new proposal is then sent to the mediator.

Considering the vector connecting \( p^{i}_{t,e} \) to \( p^{t}_{i,e} \) and normalizing it results in:

\[ u^{t+1}_i = \frac{p^{i}_{t,e} - p^t_{i,e}}{\| p^{i}_{t,e} - p^t_{i,e} \|}. \]

This versor is headed towards the agreement (in \( A_i \)) at time \( t \) (see Fig. 3). From (6), it can be seen that the next proposal of the agent \( i \) gets closer to the last agreement of the negotiation by a quantity \( \alpha_i(p_i)\| p^{i}_{t,e} - p^{t}_{i,e} \| \), proportional to the distance between the last proposal of agent \( i \) and the last agreement. Versor \( u^{t}_i \) is produced by a function \text{CALCULATE_U}.

Considering the vector along the direction of the gradient of \( U_i(\cdot) \) in \( p^{t}_{i,e} \) and normalizing it, we obtain the following versor:

\[ v^{t+1}_i = \frac{\nabla U_i(p^{t}_{i,e})}{\| \nabla U_i(p^{t}_{i,e}) \|}. \]

This versor points towards the direction of maximum increasing of \( U_i(\cdot) \) and every vector orthogonal to \( v^{t+1}_i \) is tangent to an iso-potential curve (Fig. 3). Versor \( v^{t+1}_i \) is produced by a function \text{CALCULATE_V}. Furthermore, a versor orthogonal to the gradient direction (and thus tangent to the level curves of the potential space) is defined as (Fig. 3):

\[ w^{t+1}_i = \frac{u^{t+1}_i - (v^{t+1}_i \cdot u^{t+1}_i)v^{t+1}_i}{\| u^{t+1}_i - (v^{t+1}_i \cdot u^{t+1}_i)v^{t+1}_i \|}. \]

From (6), it can be seen that the next proposal of an agent tries to keep constant the potential value in the direction of the last agreement, namely it moves in the direction of \( w^{t+1}_i \) by a quantity \( \beta_i(p_i)\| p^{i}_{t,e} - p^{t}_{i,e} \| \). Among the infinite vectors orthogonal to the gradient direction, we choose \( w^{t+1}_i \) as the one that minimizes the angle with \( u^{t+1}_i \). This choice is justified by the fact that \( w^{t+1}_i \) has a component that is added to \( u^{t+1}_i \) and another component that is in the direction of the iso-potential curve on which the last proposal was. Versor \( w^{t}_i \) is produced by a function \text{CALCULATE_W}.

As introduced before, the next proposal of an agent takes into account two components, the first one pulls...
Fig. 3. The versors $u^i_t$, $v^i_t$, $w^i_t$ in a bi-dimensional space.

Figures 4.3. Comparison with traditional approaches

It is important to point out that the negotiation paradigm presented in this paper can be seen as a generalization of the techniques commonly used to combine partial models of heart rate regulation. In fact, it can be shown that when $\alpha_i = 0$, $\beta_i = 0$, $U_i = \omega_i$ where $\omega_i$ is the weight of the model embedded by agent $i$, the negotiation produces a weighted average combination. Similarly, when $\beta_i = 0$ and either (a) $\alpha_i = 0$ and $U_i = 0$ if the HR value proposed by agent $i$ is less than that proposed by other agent $j$ or (b) $U_j = 1$ otherwise, an overdrive mechanism is present.

In [13] we studied the stability of the negotiation protocol by determining, for each agent, the ranges of negotiation parameters that assure the stable convergence of the agreement to a value.

4.4. Agent interaction protocols

In this section we show how the agents can interact according to FIPA standards [12] in order to implement the negotiation paradigm described above. We specify a negotiation session as a FIPA iterated contract net (ICN), where the mediator is the initiator of the protocol and the agents are the participants. (Note that ICN is the only FIPA interaction protocol that supports an iterated negotiation.) The initiator implements the Protocol 4.1: it performs the performative CFP (call for proposals) in which it asks the agents to assign values to HR, then it waits (WAIT) for the proposals of the agents. Once the mediator has received the proposals, it computes the agreement (CALCULATE_AGREEMENT) and the current value of $dist$ (CALCULATE_DIST).
Then, if the time is over or the distance is less than \( t_h \), the mediator accepts the proposals with the performative ACCEPT_PROPOSAL, otherwise it rejects the proposals with the performative REJECT_PROPOSAL and performs a new CFP. The temporal deadline is introduced to force the negotiation to always return a value. The ICN (namely, a negotiation session) is repeated each 2 s.

Protocol 4.1.

\[
\text{ICN_INITIATOR}(\text{time})
\]
\[
t := 0;
\]
\[
\text{agreement} := \text{empty};
\]
\[
do \text{CFP(\text{agreement});}
\]
\[
\text{proposals} := \text{WAIT(all_proposals)};
\]
\[
\text{agreement} := \text{CALCULATE_AGREEMENT} (\text{proposals});
\]
\[
\text{dist} := \text{CALCULATE_DIST} (\text{proposals}, \text{agreement});
\]
\[
\text{if } (t > \text{time} \lor \text{dist} < \text{th}) \text{ then}
\]
\[
\text{ACCEPT_PROPOSAL} (\text{proposals});
\]
\[
\text{terminated} := \text{true};
\]
\[
\text{else}
\]
\[
\text{REJECT_PROPOSAL} (\text{proposals});
\]
\[
\text{end}
\]
\[
\text{while} (!\text{terminated})
\]

Each participant implements the Protocol 4.2: it waits for a CFP from the mediator, then, if the object of the CFP, namely, the agreement, is empty, the agent computes its initial proposal (MINIMIZATION), otherwise the agent computes the three versors \( u_i \), \( v_i \), \( w_i \) (CALCULATE_U, and so on) and its proposal (CALCULATE_PROPOSAL). Then it accomplishes a performative PROPOSE for sending the value it proposes to assign to HR.

Protocol 4.2.

\[
\text{ICN_PARTICIPANT}
\]
\[
\text{agree} := \text{WAIT(CFP)};
\]
\[
\text{old_proposal} := \text{proposal};
\]
\[
\text{if } (\text{agree} == \text{empty}) \text{ then}
\]
\[
\text{proposal} := \text{MINIMIZATION}(\text{state});
\]
\[
\text{else}
\]
\[
\text{u} := \text{CALCULATE_U}(\text{old_proposal}, \text{agree});
\]
\[
\text{v} := \text{CALCULATE_V}(\text{old_proposal}, \text{agree});
\]
\[
\text{w} := \text{CALCULATE_W}(\text{old_proposal}, \text{agree});
\]
\[
\text{proposal} := \text{CALCULATE_PROPOSAL}(\text{old_proposal}, \text{agree}, \text{u}, \text{w});
\]
\[
\text{end}
\]
\[
\text{PROPOSE} (\text{proposal}, \text{GET_WEIGHT}(\text{proposal}));
\]

5. Experimental activities

In order to evaluate the negotiation protocol described above in the cardiac pacing application, we compared it with other techniques for partial model combination. The proposed negotiation paradigm has been implemented in C in order to quickly evaluate it; then it has been wrapped and introduced in the anthropic agency software platform (written in JAVA).

5.1. Experimental set-up

We used five 24-hours long ECGs taken from [24] and relative to five patients (respectively, 16265, 16273, 16420, 17052, and 17453). From each ECG signal, we extracted the beat-to-beat HR and the QT interval length using [25], and we extracted RR from the ECG-derived respiratory signal using [23] obtaining three temporal sequences of data: HR, QT, and RR. We extracted samples (uniformly distributed with respect to the frequency domain) from these temporal sequences in order to calibrate the parameters of the models (2) and (3). In the calibration process we used a non-linear least-square technique [21]. We report in Table 1 the parameters resulted from this calibration process for each track.

Every 2 s the agents read the values of QT and RR extracted them from the temporal sequences and produce a value of HR as a result of their cooperative negotiation.

5.2. Experimental results

We took into account some techniques (single model, weighted average) that are currently adopted to combine partial models in rate-adaptive pacing and we compared them with the proposed negotiation. In order to compare and evaluate the effectiveness of the different combination of models, we considered the average \( E[err] \) and the variance \( var[err] \) of the error \( err \).

<table>
<thead>
<tr>
<th>Track</th>
<th>HR-QT model</th>
<th>HR-RR model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( q_1 )</td>
<td>( q_2 )</td>
</tr>
<tr>
<td>16265</td>
<td>8.2</td>
<td>1930</td>
</tr>
<tr>
<td>16273</td>
<td>9.0</td>
<td>1931</td>
</tr>
<tr>
<td>16420</td>
<td>9.5</td>
<td>1920</td>
</tr>
<tr>
<td>17052</td>
<td>9.2</td>
<td>1930</td>
</tr>
<tr>
<td>17453</td>
<td>10.0</td>
<td>1931</td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>Track</th>
<th>$\alpha_{QT}$</th>
<th>$\alpha_{RR}$</th>
<th>$\beta_{QT}$</th>
<th>$\beta_{RR}$</th>
<th>$E[err]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>16265</td>
<td>0.010</td>
<td>0.152</td>
<td>0.010</td>
<td>0.240</td>
<td>2.918</td>
</tr>
<tr>
<td>16273</td>
<td>0.010</td>
<td>0.125</td>
<td>0.008</td>
<td>0.120</td>
<td>2.604</td>
</tr>
<tr>
<td>16420</td>
<td>0.010</td>
<td>0.075</td>
<td>0.009</td>
<td>0.005</td>
<td>4.031</td>
</tr>
<tr>
<td>17052</td>
<td>0.010</td>
<td>0.057</td>
<td>0.010</td>
<td>0.050</td>
<td>5.174</td>
</tr>
<tr>
<td>17453</td>
<td>0.010</td>
<td>0.100</td>
<td>0.000</td>
<td>0.080</td>
<td>4.812</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>$\alpha_{QT}$</th>
<th>$\alpha_{RR}$</th>
<th>$\beta_{QT}$</th>
<th>$\beta_{RR}$</th>
<th>$E[err]$</th>
<th>$\text{var}[err]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.010</td>
<td>0.152</td>
<td>0.010</td>
<td>0.240</td>
<td>2.918</td>
<td>6.794</td>
</tr>
<tr>
<td>0.010</td>
<td>0.150</td>
<td>0.010</td>
<td>0.248</td>
<td>2.918</td>
<td>6.808</td>
</tr>
<tr>
<td>0.010</td>
<td>0.150</td>
<td>0.010</td>
<td>0.250</td>
<td>2.918</td>
<td>6.814</td>
</tr>
<tr>
<td>0.010</td>
<td>0.154</td>
<td>0.010</td>
<td>0.244</td>
<td>2.918</td>
<td>6.816</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>$\alpha_{QT}$</th>
<th>$\alpha_{RR}$</th>
<th>$\beta_{QT}$</th>
<th>$\beta_{RR}$</th>
<th>$E[err]$</th>
<th>$\text{var}[err]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.010</td>
<td>0.152</td>
<td>0.000</td>
<td>0.000</td>
<td>3.005</td>
<td>6.987</td>
</tr>
<tr>
<td>0.010</td>
<td>0.150</td>
<td>0.000</td>
<td>0.000</td>
<td>2.980</td>
<td>7.006</td>
</tr>
<tr>
<td>0.010</td>
<td>0.150</td>
<td>0.000</td>
<td>0.000</td>
<td>3.032</td>
<td>6.938</td>
</tr>
<tr>
<td>0.010</td>
<td>0.154</td>
<td>0.000</td>
<td>0.000</td>
<td>3.013</td>
<td>7.112</td>
</tr>
</tbody>
</table>

as performance indexes. $err$ is defined as the absolute value of the difference between the real value of HR (as read from the ECG) and the value of HR estimated by the system (see Fig. 1) in beats per minutes (bpm). The choice of $E[err]$ follows the approach adopted in [18] where a centralized system is compared with a decentralized one.

When using only the QT model, we obtain $E[err] = 5.6 \pm 2.1$ bpm (this means that the average error $E[err]$ for the five patients is in the range $[3.2, 8.0]$) and $\text{var}[err] = 15.6 \pm 8.12$ bpm$^2$. When using only the RR model, we obtain $E[err] = 11.2 \pm 4.2$ bpm and $\text{var}[err] = 16.2 \pm 9.1$ bpm$^2$.

We then combined the proposals of the two models using weighted average. The result is: $E[err] = 4.6 \pm 1.3$ bpm and $\text{var}[err] = 8.6 \pm 3.0$ bpm$^2$. Each track requires specific weights for QT and RR models. We performed an exhaustive search for finding the values of $\omega_{QT}$ (keeping $\omega_{RR} = 1$) that minimize $E[err]$. We found: $\omega_{QT} = 7.8$ and $\omega_{RR} = 1$ for track 16265, $\omega_{QT} = 7.5$ and $\omega_{RR} = 1$ for track 16273, $\omega_{QT} = 5.7$ and $\omega_{RR} = 1$ for track 16420, $\omega_{QT} = 4.5$ and $\omega_{RR} = 1$ for track 17052, and $\omega_{QT} = 8.1$ and $\omega_{RR} = 1$ for track 17453.

Finally, we applied the negotiation protocol presented in this paper to combine the proposals of the agents. The negotiation parameters of the agents that minimize $E[err]$ in the five tracks are reported in Table 2 and have been determined by using an exhaustive search with the constraints $\alpha_i \in [0, 2]$ and $\beta_i \in [-1, 1]$ and a variable quantization between $10^{-1}$ and $10^{-3}$, reducing the quantization around the values that provide the best performance. For these combinations of parameters: $E[err] = 3.9 \pm 1.3$ bpm and $\text{var}[err] = 6.8 \pm 1.2$ bpm$^2$. These results improve those obtained using weighted average combination of about 15.2% for $E[err]$ and 20.1% for $\text{var}[err]$.

5.3. Negotiation analysis

Two main issues emerged during the analysis of the experimental results: the relationship between the weights of a weighted average and the negotiation parameters and the role of $\beta_i$ in the negotiation. For simplicity, for an analysis of such issues we consider only track 16265.

Comparing the values of the weights in a weighted average with the values of the negotiation parameters ($\alpha_i, \beta_i$) for a track, it is hard to find transformation formulas that bind weights to negotiation parameters. Nevertheless, it is evident that the agent with the higher weight $\omega_i$ (7.8 for QT model vs. 1 for RR model in our example) exhibits the lower sensitivity to changes in the weight values than it is the negotiation to changes in the negotiation parameters. For track 16265, varying $\alpha_i$ and $\omega_i$ around the values that give the best performance (i.e., $\alpha_{QT} = 0.01$ and $\omega_{QT} = 7.8$) of $\pm 100\%$ and keeping constant all the other parameters (namely, $\alpha_{QT} \in [0.0, 0.02]$ and $\omega_{QT} \in [0.0, 15.6]$), $E[err]$ increases of 2.7% on average in the negotiation approach and of 7.3% on average in the weighted average approach. Furthermore, the farther the values of the parameters from the optimal value, the larger the difference in performance between negotiation and weighted average.

Considering the role of $\beta_i$ during the negotiation (for track 16265), in Table 3 we report some negotiation parameters that minimize $E[err]$ and, in Table 4, we report the results corresponding to the same values for parameters $\alpha_{QT}$ and $\alpha_{RR}$ but with $\beta_{QT} = \beta_{RR} = 0$. It is clear that $\beta_i$, introducing the contribution of $w_i^{t+1}$, helps to improve the reliability of the model.
6. Conclusions

In this paper we have described the use of an agent negotiation paradigm to combine physiological models of cardiac pacing. We introduced a negotiation paradigm, structured in two phases: the agent optimization (performed by the single agents) and the agency optimization (performed by a negotiation between the agents in order to achieve a global agreement). We experimentally evaluated the negotiation paradigm in comparison with traditional techniques. We found that the presented negotiation protocol is a generalization and an improvement of the methods previously used to combine partial models of heart rate regulation. The negotiation paradigm gives to the anthropic agency system the properties of flexibility towards the designer – allowing the evaluation of different combinations of models embedded by the agents – and towards the application, since two different applications, the glucose metabolism regulation and the heart rate regulation, have been addressed by using the same methodology.

In the future our intention is to add other models to the system (e.g., the relationship between HR and physical activity measured by an accelerometer); to change the properties of the regulatory system when the subject is sleeping; and to estimate the optimal delay between atrial and ventricular stimulation (for pacemakers with double pacing mode). Moreover, the negotiation analysis evidenced the need of learning methods for the automatic calibration of the negotiation parameters to the patients.

References


