

Implantable Pacemakers Control and Optimization via Fractional Calculus Approaches: A Cyber-Physical Systems Perspective

Paul Bogdan¹, Siddharth Jain², Kartikeya Goyal¹, and Radu Marculescu¹

¹Department of Electrical and Computer Engineering, Carnegie Mellon University, Pittsburgh, PA 15213, USA

²Department of Electrical Engineering, Indian Institute of Technology Kanpur, Kanpur, India - 208016

pbogdan@ece.cmu.edu, radum@ece.cmu.edu

Abstract—Managing cardiac disease and abnormal heart rate variability remain challenging problems with an enormous economic and psychological impact worldwide. Consequently, the purpose of this paper is to introduce a fractal approach to pacemaker design based on the constrained finite horizon optimal control problem. This is achieved by modeling the heart rate dynamics via fractional differential equations. Also, by using calculus of variations, we show that the constrained finite horizon optimal control problem can be reduced to solving a linear system. Finally, we discuss the hardware complexity involved in the practical implementation of fractal controllers.

Keywords - Cyber-physical systems, fractional calculus, optimal control, model predictive control, fractal behavior, non-stationary behavior, heart rate variability.

I. INTRODUCTION

Modern embedded systems enable a tight integration of sophisticated sensors monitoring real world processes (e.g., heart rate, cloud movement, temperature fluctuations, wind speed, volcanic activity, and terrestrial magnetism) and actuators able to control the environment. Consequently, these systems are expected to successfully integrate computation, communication and control with physical processes and are commonly referred to as cyber physical systems (CPS) [10][30][46]. The CPS paradigm is meant to drive the design of many technological systems ranging from smart transportation (e.g., autonomous collision avoidance for either roadway or air traffic corridors), to distributed energy (e.g., energy generation and transportation, zero-net energy buildings), and to health care (e.g., automated systems for health care monitoring and diagnosis, robust and noninvasive drug delivery systems, robotic surgery).

In addition to various engineering requirements (e.g., adaptiveness, autonomy, efficiency, functionality, reliability, safety, and usability), the health care CPS need to maximize the patients quality-of-life, while minimizing the intrinsic costs related to patient hospitalization. For instance, given that the cardiac diseases are among the most widespread medical conditions, it is necessary to have bio-implantable devices capable of monitoring the heart rate, communicating with medical experts/devices, and actuating some parameters in real time when the patient's heart is misbehaving. Despite this need for such systems, the biomedical system development lacks a coherent theory that coordinates the use of cyber and physical resources in a unique, efficient, and

robust approach. One such example of a CPS challenge is the artificial pacemaker¹ consisting of both analog (i.e., sense amplifiers to monitor information about the heart rate activity and pacing output circuitry) and digital components (i.e., microprocessors and memory blocks for actuating pacing events) [23][43].

Although the area of pacemaker design has a relatively long history, advanced approaches for pacemaker control gained significant attention only recently. More precisely, it has been observed that the heart rate variability of healthy individuals is neither periodic, nor fully chaotic, but instead characterized by fractal laws [19][20][21][28]. On the other hand, while ignoring the fractal characteristics of the heart rate variability, the proposed approaches for artificial pacing have focused mainly on employing classical linear system theory [14][32][37][38] or neural networks [50] to design various control algorithms.

However, pacemakers need pacing algorithms that rely on optimal control for heart stimulation that consider the characteristics of the individual heart rate on both short and long time scales, as well as adequate medical therapy [15][17]. As shown in Fig. 1, the role of the optimal control algorithm is to identify whether the heart rate is following a healthy trend or indicates a life threatening situation given the available information about the metabolic state (SO₂ level, respiration rate, etc.), human activity (rest/exercise), and measurement time (daytime /nighttime). The optimal controller can contribute not only to minimizing the risk of inadequate heart stimulation (that, in turn, may lead to other medical conditions), but also to maximizing the likelihood of detecting a malfunction in the pacemaker itself and improve the battery longevity.

Starting from these overarching ideas, our contribution is three fold: First, we propose a more accurate modeling of the heart rate dynamics via fractional differential equations. Second, we model the rate adaptive pacing as a constrained finite horizon optimal control problem with fractal state equations. Third, we compare and contrast various control approaches for pacemakers and give a sense of the hardware implementation complexity required by such fractal controllers.

The remainder of this paper is structured as follows: Section II summarizes the complex mechanism behind human heart rate generation and the main approaches for

¹ An artificial pacemaker senses the heartbeats and triggers electrical impulses to the heart in order to regulate the heart rhythm [24].

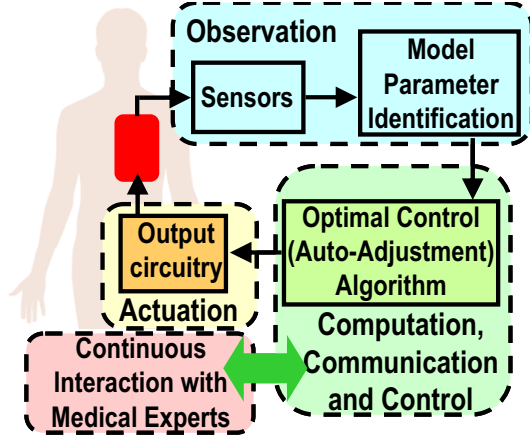


Figure 1. Cyber-physical system approach to pacemaker design: Accurate monitoring and continuous interaction with medical experts/devices allows for better modeling and control approaches of rate adaptive pacemakers.

building rate responsive pacemakers, and motivates the need for a fractal optimal control approach. Section III introduces the concept of fractional calculus and its applications to real problems. Section IV discusses a constrained finite horizon optimal control approach to regulate the dynamics of a fractal process (i.e., control of R-R intervals) considering two performance index functions. Section V presents the goodness-of-fit analysis for two modeling approaches (i.e., a non-fractal one based on classical integer order calculus and a fractal approach based on fractional order differential equation) and the performance analysis of the proposed solution. Finally, Section VI concludes the paper by pointing out future directions for dynamic optimization algorithms of such medical systems.

II. MOTIVATION AND PRIOR WORK

A. Cardiac Signals and the Role of Pacemakers

The human heart is a muscle-based organ divided into four chambers: two atria (top chambers holding the blood) and two ventricles (bottom thick-walled chambers meant to help pumping the blood into the circulatory system). When the myocardium and specialized fibers are resting, the heart collects de-oxygenated blood from the body in the right atrium and oxygenated blood from lungs in the left atrium. Then, with each heart beat (which results from a muscle contraction), the blood flows from the right ventricle into the lungs for oxygenation and from the left ventricle into the human body. This entire process of creating a heart beat is known as the *cardiac cycle* and is carefully preceded and controlled by a complex electrical mechanism [16]. As shown in Fig. 2, this activity can be recorded on an electrocardiogram as a P-wave (atrial depolarization), as well as QRS complex which corresponds to ventricles depolarization. The cardiac cycle ends with the ventricles repolarization, i.e., a small wave called the T-wave.

Because the R-waves are always the most pronounced ones on an electrocardiogram, the distance between two consecutive R waves (i.e., the R-R interval) is used by

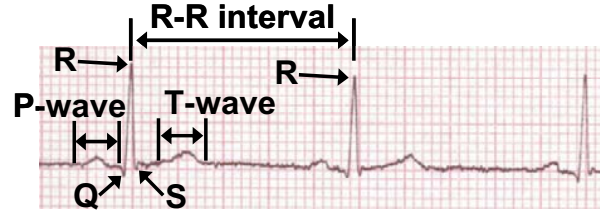


Figure 2: A short electrocardiogram showing the heart activity of three beats and the P-wave (atrial depolarization), QRS complex (ventricles depolarization) and T wave (ventricles repolarization). The R-R interval is the time interval between two consecutive heart beats represented in the electrocardiogram by two consecutive R-waves. The variability observed in the R-R intervals is essential for medical diagnosis.

physicians to determine the heart rate activity. Consequently, the study of heart rate variability is extremely important for medical diagnosis. This also motivates our optimal control approach seeking to regulate the magnitude of the R-R intervals. This is described in detail in Section IV.

B. Control-Based Approaches to Pacemaker Design

Since their invention in 1932, implantable pacemakers have evolved from fixed rate pacemakers (i.e., medical devices delivering an electrical pulse at fixed intervals of time) and demand pacemakers (i.e., medical device triggering an electrical impulse only if a heart beat is missing), to complex rate responsive pacemakers. The main distinction between the rate responsive pacemakers and their predecessors is that besides the sensory part responsible with sensing the heart beats, they also consist of a *control* part which is meant to adapt the pacing response as a function of the heart activity [51]. Therefore, designing the control algorithm for heart pacing is a very important and challenging task. For instance, the introduction of extra pacing to an already active heart can be lethal because heart chambers will not have enough time to refill with blood and thus will not provide the necessary amount of oxygenated blood throughout the body. On the other hand, missing heart beats can also lead to critical conditions.

Consequently, based on the characteristics of the proposed control approaches and the state variables which are optimized, the rate responsive pacemakers can be classified as open loop² [3][5][26][47], closed loop³ [18][22][23][25][27][31][38][50][53][52], metabolic⁴ [32][37][48][49], and autonomous nervous system⁵ (ANS) [37] controllers. For instance, Inbar et al. [18] describe a closed loop proportional (P) controller for optimal pacing, which maintains the venous oxygen saturation at a predefined level. Of note, the proposed P-controller relies on a postulated non-linear model that relates the venous oxygen saturation to the

² Pacing rate is determined only by the current state of heart rate by using a predefined model with no feedback from changes in the system and no observation of the output.

³ Pacing rate is determined by using feedback information from the output of the systems (in particular, the heart rate activity).

⁴ Pacing depends on metabolism and/or respiratory system.

⁵ Pacing is influenced by the autonomous nervous system activity.

heart rate. Along the same lines, Hexamer et al. [25] discuss a closed loop pacing approach based on regulating the atrial-ventricular conduction time (AVCT). At the heart of their approach lies the assumption that the dynamics of AVCT can be modeled as a linear time invariant system. Employing a similar closed-loop processes control, Zhang et al. [53] propose a classical proportional-integral derivative (PID) controller for ensuring that the entire system consisting of the heart rate activity and pacing pulse achieves a targeted R-R interval. More precisely, their PID controller uses the error difference between the monitored and the predefined target R-R interval to compute the necessary amplitude of the atrio-ventricular node vagal stimulation. Using the same error difference between the observed and targeted R-R interval, Tosato et al. [52] propose a proportional integral (PI) closed loop controller to determine the frequency of stimulation.

Along the same lines of focusing on timing behavior of the contractions between atria and ventricles, Sun et al. [50] propose a spiking neural network (SNN) based pacemaker device which predicts the pacing delays. The analog design of the SNN neurons uses a second order transfer function to determine the delays of the delivered impulses. More recently, Neogi et al. [38] assume that the heart rate activity can be modeled by a second order transfer function and present a proportional plus derivative controller for regulating the heart rate.

In parallel with the development of this body of work on control pacing algorithms, Jiang et al. [22] introduce a testing software platform. More precisely, the authors model the heart timing and electrical conduction properties via a timed automaton and interface it with a postulated pacemaker. Based on this closed loop infrastructure, the authors are able to identify a set of requirements that need to be satisfied in order to ensure safe and high efficiency for pacemaker operation.

Lopez et al. [32] propose nonlinear approach and a heart beat control algorithm that uses concepts of proportional gain and norm. Alternatively, Sugiura et al. [49] use the fuzzy control theory to regulate pacing while patient respiratory rate and temperature are used as state variables. In contrast to these approaches, Nakao et al. [37] uses an optimal control approach to regulate the heart rate and the sympathetic activity while assuming that the blood pressure is the state variable.

Despite this significant body of work, state-of-the-art pacing algorithms assume that the heart rate (and other relevant physiological processes) can be modeled via linear state equations. However, by relying on detrended fluctuation analysis [19], one can observe that the R-R intervals exhibit a fractal behavior and thus cannot be well approximated by such linear models. To overcome this limitation, we argue that the control algorithms of rate responsive pacemakers should rely on fractal dynamical equations using concepts from fractional calculus [10]. This is described in the following sections.

III. BASICS OF FRACTIONAL CALCULUS

The origins of fractional calculus date back to the correspondence between L'Hopital and Leibniz in which

they debated the meaning of a 0.5 order differentiation [42]. Over the years, fractional calculus has found applications in physics (e.g., viscoelasticity [34], dielectric polarization [39], heat transfer phenomena [6]) and engineering (e.g., control [40][42][1][2][36], bioengineering [33], traffic modeling [8], game theory [11]).

Broadly speaking, fractional (or fractal) calculus deals with functional differentiation and integration of arbitrary orders [35][42]. Unlike classical (i.e., integer order) calculus, fractional derivatives directly incorporate the dynamical characteristics (i.e., fractal behavior) of any target process $x(t)$ (e.g., R-R intervals, flow of oxygenated blood) through a weighted sum denoting the contribution of the previous events $x(\tau)$, for any $\tau \in [0, t]$:

$$\frac{d^\alpha x(t)}{dt^\alpha} = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_0^t \frac{x(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau, \quad (1)$$

where α is the fractional order of the derivative and $\Gamma(n-\alpha)$ is the Gamma function [35]. This continuous time definition of fractional derivative can also be written in discretized form via the Grunwald-Letnikov formula:

$$\frac{d^\alpha x(t)}{dt^\alpha} = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t^\alpha} \sum_{j=0}^{\lfloor t/\Delta t \rfloor} (-1)^j \binom{\alpha}{j} x(t-j\Delta t) \quad (2)$$

where Δt is the time increment, $\lfloor t/\Delta t \rfloor$ represents the integer part of the ratio between the t and Δt . Equations (1) (continuous) and (2) (discrete) capture directly the role of the power law observed in the time differences (i.e., $(t-\tau)^{n-\alpha-1}$) and allows not only for a more accurate description of the time dynamics of various physiological processes $x(t)$, but also for a better optimization; this issue is discussed in the next section.

IV. FRACTIONAL CALCULUS BASED MODELING AND OPTIMAL CONTROL OF HEART RATE ACTIVITY

In this section, we build a new theory based on the experimental observations that heart rate processes display a fractal behavior and model it via fractional differential equation. This represents a major departure from the traditional modeling approaches used in control (dynamic) optimization field. Our approach tries to bring the magnitude of R-R intervals to a given reference value from either very large or very small values which are signs of heart disease (i.e., bradycardia or tachycardia). Of note, although we illustrate the optimal control problem only for two different cost functions, the proposed formalism can be extended to other cost functions and control signals (e.g., magnitude of the pacing voltage applied to either atria or ventricles).

A. Finite Time Fractal Optimal Control with Integral of Squared Tracking Error (ISE) Criterion

In this section, we introduce a constrained finite horizon fractal optimal control approach to heart rate regulation

problem. More precisely, given an initial time t_i and a final time t_f , the goal of the controller is to find the optimal control signal, i.e., the frequency of the pacing events, which minimizes the quadratic cost of observing deviations in either the magnitude of R-R intervals or heart rate activity from a predefined reference value, as well as the magnitude of pacing frequency, as shown below:

$$\min_{f(t)} \int_{t_i}^{t_f} \left\{ \frac{w}{2} [y(t) - y^{ref}(t)]^2 + \frac{z}{2} f^2(t) \right\} dt \quad (3)$$

subject to the following constraints:

$$\frac{d^\alpha y(t)}{dt^\alpha} = a(t)y(t) + b(t)f(t), \quad 0 \leq y^{\min} \leq y(t) \leq y^{\max} \leq 1 \quad (4)$$

$$y(t_i) = y_0, \quad y(t_f) = y_0 \quad (5)$$

$$f^{\min} \leq f(t) \leq f^{\max} \quad (6)$$

where $y(t)$ represents the heart rate activity seen as a state variable, $y^{ref}(t)$ denotes the reference values that need to be achieved in terms of heart rate activity, $f(t)$ is the pacing frequency, w and z are the weighting coefficients for the quadratic error and magnitude of the control signal, respectively, in the cost function, α is the exponent of the fractional order derivative characterizing the dynamics of the heart rate activity $y(t)$, $a(t)$ and $b(t)$ are weighting coefficients for the heart activity and pacing frequency, y^{\min} and y^{\max} are the minimum and maximum bounds on heart rate activity $y(t)$, $y(t_i)$ is the initial condition, $y(t_f)$ is the final condition, f^{\min} and f^{\max} are the minimum and maximum allowed bounds on pacing frequency $f(t)$.

By focusing on the squared difference between the actual and the reference value in (3), the optimal controller minimizes the chances of getting either positive or negative deviations from a predefined reference. In other words, the cost functional in (3) penalizes any deviations from the reference value and large magnitudes in the control signal. The use of the integral of squared difference between the actual and the reference heart rate is also attractive because of two reasons: First, it simplifies to linear equations when evaluating the optimality conditions. Second, the integral of squared error is in general robust to parameter variations. Note that unlike other general formulations of optimal control, in this setup we have to deal with very specific initial and final values summarized in (5). Consequently, the role of the controller is to determine the right pacing frequency which drives the system from one initial state (labeled as life-threatening) to a final state (labeled as safe).

Note also that in both equations (4) and (6), we impose minimum and maximum bounds on the accepted R-R intervals and the delivered pacing frequencies. These bounds are necessary because they prevent the optimal control algorithm from driving the heart muscle system at excessive pacing rates.

To solve the above optimal control problem, we use concepts from the optimization theory and construct first the

Lagrangian functional, $L(y, f, \lambda, \beta_1, \xi_1, \beta_2, \xi_2)$ (consisting of the initial cost function in (3) and the constraints in (4), (5) and (6) multiplied by Lagrange multipliers), as follows:

$$L = \int_{t_i}^{t_f} \left\{ \frac{w[y(t) - y^{ref}(t)]^2}{2} + \frac{zf^2(t)}{2} + \beta_1(f - f^{\min} - \xi_1) - \lambda \left[\frac{d^\alpha y(t)}{dt^\alpha} - a(t)y(t) - b(t)f(t) \right] + \beta_2(f^{\max} - f - \xi_2) \right\} dt \quad (7)$$

where λ , β_1 , and β_2 are the Lagrange multipliers associated with the dynamical state equation for $y(t)$ and the constraints imposed on the control variable f , ξ_1 and ξ_2 are the slack variables needed to transform the inequality bounds into equality constraints on the control variable f . The reason for introducing the Lagrange multipliers λ , β_1 , and β_2 and encapsulate the constraints (4), (5), and (6) into a single optimization function is to transform the constrained problem into an unconstrained minimization.

By expanding the Lagrange function in (7) via the Taylor formula and considering that it attains its minimum in the vicinity of $\tau = 0$, i.e., $\partial L / \partial \tau = 0$, we obtain the following relations:

$$\frac{\partial L}{\partial y} + {}_t D_{t_f}^\alpha \frac{\partial L}{\partial {}_t D_{t_f}^\alpha y} = 0, \quad \frac{\partial L}{\partial f} = 0, \quad \frac{\partial L}{\partial \lambda} = 0, \quad \frac{\partial L}{\partial \beta_1} = 0, \quad \frac{\partial L}{\partial \beta_2} = 0 \quad (8)$$

where ${}_t D_{t_f}^\alpha$ and ${}_t D_{t_i}^\alpha$ are the fractional derivatives operating backward and forward in time, respectively.

In order to solve the relations in (8), we discretize the interval $[t_i, t_f]$ into N intervals of size $\Delta t = (t_f - t_i) / N$ and use the formula in (2) to construct a linear system as follows:

$$\sum_{i=0}^k \frac{(-1)^i}{\Delta t^\alpha} \binom{\alpha}{i} y((k-i)\Delta t) - a(k\Delta t)y(k\Delta t) + \frac{b(k\Delta t)}{z(k\Delta t)} \lambda(k\Delta t) + \frac{b(k\Delta t)}{z(k\Delta t)} \beta_1(k\Delta t) - \frac{b(k\Delta t)}{z(k\Delta t)} \beta_2(k\Delta t) = 0, \quad k = 1, \dots, N \quad (9)$$

$$\frac{\beta_2(k\Delta t) - \beta_1(k\Delta t) - b(k\Delta t)\lambda(k\Delta t)}{z(k\Delta t)} - \xi_1(k\Delta t) = f^{\min}, \quad k = 1, \dots, N \quad (10)$$

$$\frac{\beta_2(k\Delta t) - \beta_1(k\Delta t) - b(k\Delta t)\lambda(k\Delta t)}{z(k\Delta t)} + \xi_2(k\Delta t) = f^{\max}, \quad k = 1, \dots, N \quad (11)$$

$$\sum_{i=0}^{N-k} \binom{\alpha}{i} \frac{(-1)^i \lambda((k+i)\Delta t)}{\Delta t^\alpha} - w(k\Delta t) [y(k\Delta t) - y^{ref}(k\Delta t)] - a(k\Delta t)\lambda(k\Delta t) + \frac{\lambda(\Delta t N) (t_f - t_i - k\Delta t)^\alpha}{\Gamma(1-\alpha)} = 0, \quad k = N-1, \dots, 0 \quad (12)$$

In summary, the constrained finite horizon fractal optimal control defined in (3) through (6) can be reduced to solving a linear programming problem (given by (9), (10), (11), and (12)) and so it does not add a significant complexity compared to classical linear system theory approaches. In addition, this constrained finite horizon fractal optimal control can address some of the American Heart Association desideratum [15] for optimal control algorithms that find the right pacing frequency, output voltage, pulse width, or atrio-ventricular delays that can improve the patient quality-of-life and battery longevity.

B. Finite Time Fractal Optimal Control with Integral of Squared Time Multiplied by Squared Tracking Error (ITSE) Criterion

Despite its analytical tractability, the finite time optimal control problem with integral of the squared difference between the actual and reference value of the process has the drawback that in some cases it can present large overshoots and oscillations. In addition, besides the magnitude of the error existing between the actual and the reference values, also the *time* at which this error occurs is of significant importance. As an alternative to the integral of the difference between the actual and the reference values, we consider next an optimization criterion involving the integral of the squared time multiplied by the squared tracking error (ITSE). This approach is meant to penalize any overshoot or oscillation that might appear in the cost function close to the final time t_f . Consequently, the augmented finite horizon fractal optimal control problem seeks to minimize the following cost function:

$$\min_{f(t)} \int_{t_i}^{t_f} \left\{ \frac{w}{2} [y(t) - y^{ref}(t)]^2 + \frac{z}{2} f^2(t) \right\} dt \quad (13)$$

subject to the following constraints:

$$\frac{d^\alpha y(t)}{dt^\alpha} = a(t)y(t) + b(t)f(t), \quad 0 \leq y^{min} \leq y(t) \leq y^{max} \leq 1 \quad (14)$$

$$y(t_i) = y_0, \quad y(t_f) = y_0 \quad (15)$$

$$f^{min} \leq f(t) \leq f^{max} \quad (16)$$

where $y(t)$ represents the heart rate activity seen as a state variable, $y^{ref}(t)$ denotes the reference values that need to be achieved in terms of heart rate activity, $f(t)$ is the pacing frequency, w and z are the weighting coefficients for the quadratic error and magnitude of the control signal, respectively, in the cost function, α is the exponent of the fractional order derivative characterizing the dynamics of the heart rate activity $y(t)$, $a(t)$ and $b(t)$ are weighting coefficients for the heart activity and pacing frequency, y^{min} and y^{max} are the minimum and maximum bounds on heart rate activity $y(t)$, $y(t_i)$ is the initial condition, $y(t_f)$ is the final condition, f^{min} and f^{max} are the minimum and maximum allowed bounds on pacing frequency $f(t)$.

Employing concepts from the theory of constrained optimization and calculus of variations and discretizing the optimality conditions (i.e, differential equations), we obtain the following system of equations:

$$\sum_{i=0}^k \frac{(-1)^i}{\Delta t^\alpha} \binom{\alpha}{i} y((k-i)\Delta t) - a(k\Delta t)y(k\Delta t) + \frac{b(k\Delta t)^2}{z(k\Delta t)} \lambda(k\Delta t) + \frac{b(k\Delta t)\beta_1(k\Delta t)}{z(k\Delta t)} - \frac{b(k\Delta t)\beta_2(k\Delta t)}{z(k\Delta t)} = 0, \quad k = 1, \dots, N \quad (17)$$

$$\sum_{i=0}^{N-k} \binom{\alpha}{i} \frac{(-1)^i \lambda((k+i)\Delta t)}{\Delta t^\alpha} - w(k\Delta t)(k\Delta t)^2 [y(k\Delta t) - y^{ref}(k\Delta t)] - a(k\Delta t)\lambda(k\Delta t) + \frac{\lambda(\Delta t N)(t_f - t_i - k\Delta t)^\alpha}{\Gamma(1-\alpha)} = 0, \quad k = N-1, \dots, 0 \quad (18)$$

$$\frac{\beta_2(k\Delta t) - \beta_1(k\Delta t) - b(k\Delta t)\lambda(k\Delta t)}{z(k\Delta t)} - \xi_1(k\Delta t) = f^{min}, \quad k = 1, \dots, N \quad (19)$$

$$\frac{\beta_2(k\Delta t) - \beta_1(k\Delta t) - b(k\Delta t)\lambda(k\Delta t)}{z(k\Delta t)} + \xi_2(k\Delta t) = f^{max}, \quad k = 1, \dots, N \quad (20)$$

As one can observe from equations (17), (18), (19), and (20), the optimal control problem reduces to solving a linear program which computes the y and λ values for a predefined set of discretization steps. Of note, the size of the linear program depends on the number of discretization steps.

V. EXPERIMENTAL RESULTS

An important requirement of optimal control approaches is to rely on accurate models of the dynamical system or state variables of interest to the designer. Consequently, in this section we first estimate the parameters corresponding to a non-fractal and a fractal model and analyze the goodness-of-fit of each approach. More precisely, we perform a hypothesis testing by investigating whether or not the observed data can be modeled via a specific model. In this context, the goodness-of-fit measures (via the P-value⁶) the discrepancy between the real measurements and the model predictions. Next, we provide a complete numerical analysis of the proposed fractal optimal control problems introduced in Section IV.

A. Parameter Identification of Fractional Calculus Models

To make the discussion more concrete, we consider two types of models: First, we model the heart rate through a first order differential equation, estimate the corresponding parameters (i.e., a and b), and compute the goodness-of-fit between the actual measurements and the obtained model. Second, we assume that over a finite time interval the heart

⁶ The P-value is a goodness-of-fit metric. A small P-value (below the significance value) allows us to reject the null hypothesis (the data follows a certain distribution or can be modeled via an ARMA type with specific parameters).

TABLE I. COMPARISON BETWEEN A NON-FRACTAL MODEL (1-STEP ARMA) AND A FRACTAL MODEL (SEE (4)) IN TERMS OF THE ESTIMATED PARAMETERS AND THE GOODNESS-OF-FIT OBTAINED FOR FIVE TIME SERIES OF HEART RATE ACTIVITY. THE R-R INTERVAL TIME SERIES ARE OBTAINED FOR HEALTHY INDIVIDUALS [41]. EXCEPT THE TIME SERIES WITH ID 3, ALL OTHER HEART RATE ACTIVITY SERIES CAN BE MODELED THROUGH A FRACTIONAL ORDER DIFFERENTIAL EQUATION OF THE TYPE PRESENTED IN (4). THIS IS JUSTIFIED BY THE ESTIMATED P-VALUES AND TEST STATISTICS.

Heart Rate Time Series ID	Classical (Non-Fractal) Model				Fractal Model				
	Parameters of the model		Goodness-of-fit		Parameters of the model			Goodness-of-fit	
	a	b	P-value	Test statistic	α	a	b	P-value	Test statistic
1	0.9665	0.0267	0	61.127	0.6226	0.1613	-0.1284	1	0.2754
2	0.979	0.0193	0	30.031	0.7762	0.0355	-0.0326	1	0.2564
3	0.9513	0.0403	0	120.880	0.707	0.1255	-0.1038	0.51	0.3182
4	0.9525	0.0409	0	73.945	0.7258	0.1105	-0.0951	1	0.2544
5	0.9663	0.0286	0	88.339	0.699	0.0643	-0.0546	1	0.2714

rate can be modeled through a fractional order differential equation similar to the one presented in (4), estimate the parameters α , a , and b and report its goodness-of-fit.

Table 1 summarizes the estimated parameters and the goodness-of-fit results for both non-fractal and fractal models proposed to model the heart rate dynamics of healthy individuals. To discriminate in terms of accuracy between the two models, we use the goodness-of-fit described in [7] at 0.05 statistical significance level. This implies that we perform a null hypothesis testing against each model and if the P-value computed for the considered model is below 0.05 level, then with 95% confidence we reject the model as a good fit for the data. Note that this statistical approach proves to be a more robust way of validating models than relying on mean square method [7]. By comparing the P-values in the fourth and ninth columns, we can draw the following conclusions:

- The modeling approach of heart rate processes via a fractional differential equation (as shown in (4)) cannot be rejected. The model is superior to the one based on first order derivative for all five heart rate times both in terms of P-values and test statistics.
- The modeling of heart rate dynamics via a first order derivative type of model is strongly rejected by the observed null P-values and high test statistic results.

For completeness, in Table 2, we investigate the goodness-of-fit between a non-fractal model (i.e., first order differential equation) and a fractal one (based on fractional derivative as shown in (4)) for an individual suffering from atrial fibrillation. As one can notice, although the magnitude of the P-values increases compared to the healthy individuals, their values are smaller than the 0.05 significance level allowing us to reject the hypothesis that we can model such heart activity time series via a non-fractal equation. In contrast, the P-values for the fractional order derivative based model are significantly higher allowing the possibility of being a good fitting model.

B. Performance Analysis of Constrained Finite Horizon Fractional Optimal Control for Heart Rate Signals

To illustrate the performance and efficiency of the proposed optimal controller for regulating the pacing frequency of an artificial pacemaker, we consider the heart

rate of an individual suffering from atrial fibrillation⁷ (see Fig. 3.a). To better emphasize the abnormal behavior in the length of R-R intervals, we also plot the minimum (black solid line, corresponding to 0.667 seconds) and maximum (blue dotted line, corresponding to 1 second) bounds for a normal heart rhythm. In addition, we assume that the measured heart rate comes from a CPS infrastructure where the normalized pacing frequency was set to 1 for a fixed time interval of 56 seconds corresponding to 100 recorded beats. Both the natural and artificial pacing led to an elevated average heart rate of 108 beats per minute. The elevated heart rate is frequently experienced as heart palpitations and can cause fainting and dizziness leading to major injuries. Thus, the role of an adaptive CPS pacemaker is to regulate the pacing frequency in conjunction with the natural pacing coming from the brain in order to keep the heart rate between 60 and 90 beats per minute.

The first step in the analysis is to check which of the two modeling approaches (i.e., the non-fractal one represented by a first order differential equation and the fractal one given by a single fractional order differential equation) is more suitable to be used for capturing the heart rate characteristics exhibited for over 390 heart beats or an interval of time of 235.36 seconds. By relying on the goodness-of-fit algorithm presented in [7], the P-value and test statistics for the integer first order differential equation based model are 0.0018 and 0.3845, respectively. Since we performed the null hypothesis testing at 0.05 significance value, based on small P-value of 0.0018 we can reject the integer order differential equation as being a good model. In contrast, by applying the same goodness-of-fit algorithm, the P-value and the test statistic for a fractional single order differential equation type of model are 0.8471 and 0.2949, respectively. This shows that for this interval of time, the heart rate and implicitly the R-R intervals can be better modeled via a fractional order differential equation.

Once the parameter identification and goodness-of-fit analysis is completed (and validate or invalidate one type of model), the role of the optimal controller in equations (3)

⁷ Atrial fibrillation is a common example of irregular heart beat activity characterized by very high heart rate or very short R-R intervals. These short R-R intervals may precede congestive heart failures.

TABLE II. COMPARISON BETWEEN A NON-FRACTAL MODEL AND A FRACTAL MODEL (SEE (4)) IN TERMS OF THE ESTIMATED PARAMETERS AND THE GOODNESS-OF-FIT OBTAINED FOR FIVE TIME SERIES OF HEART RATE ACTIVITY. THE R-R INTERVAL TIME SERIES ARE OBTAINED FOR INDIVIDUALS SUFFERING FROM ATRIAL FIBRILLATION [41]. ALL THE ABOVE TIME SERIES CAN BE MODELED THROUGH A FRACTIONAL ORDER DIFFERENTIAL EQUATION AS IN (4). THIS IS JUSTIFIED BY THE ESTIMATED P-VALUES AND TEST STATISTICS.

Heart Rate Time Series ID	Classical (Non-Fractal) Model				Fractal Model				
	Parameters of the model		Goodness-of-fit		Parameters of the model			Goodness-of-fit	
	a	b	P-value	Test statistic	α	a	b	P-value	Test statistic
1	0.0407	-0.0245	0.0018	0.3845	0.6597	0.5827	0.3508	0.8471	0.295
2	0.0007	-0.0005	0.0031	0.3806	0.6841	0.7302	0.5853	0.4296	0.3224
3	0.0050	0.0055	0.0036	0.3795	0.6371	0.7862	0.8697	0.5523	0.3153
4	0.0289	0.0167	0.0017	0.3851	0.6307	0.8082	0.4659	0.226	0.3354
5	-0.0225	0.0142	0.0144	0.3681	0.6516	0.6850	0.4316	0.5098	0.3178

through (6) is to determine the optimal pacing frequency for which the R-R intervals can be increased from the observed 0.20 seconds to 0.80 seconds which would correspond to a normal heart rate of 75 beats per minute. Fig. 3.b shows the impact of considering various discretization steps (i.e., $N = 30, 40, 100, 500,$ and 1000 steps) on the R-R intervals for a finite control horizon of 0.1 second. Note that the controller was constrained to find the control signal such that the R-R intervals are between 0.6 and 1, and the pacing frequency between 0.5 and 1. The w and z coefficients in the performance index function shown in (3) were set to 0.1.

One can clearly see that even for a small number of discretization steps, the optimal controller is able to bring the R-R interval from 0.20 to 0.80 seconds for the predefined control horizon. In addition, Fig. 3.c shows the control signal (pacing frequency) needed to be followed in parallel with the natural pacing coming from the brain to achieve a 0.8 R-R interval or a heart rate of 75 beats per minute. For completeness, the final frequency as a function of the considered number of discretization steps is as follows: 0.8745 for 1000 steps, 0.8732 for 500 steps, 0.8689 for 100 steps, 0.8658 for 40 steps and 0.8647 for 30 steps.

Consequently, the loss in accuracy of computing the normalized pacing frequency from fewer discretization steps is approximately 1.1%.

Besides the importance of the number of discretization steps, the constrained finite horizon fractal optimal controller also depends on the choice of ratio between the w and z coefficients in (3). To investigate how the controller depends on this ratio, we fix the number of discretization steps and the z coefficient to 300 and 1, respectively. Next, we consider four values (i.e., 1, 5, 10, and 15) for the w coefficient and solve the optimal control problem assuming that the R-R interval state variable is constrained to be between 0.6 and 1 and the pacing frequency varies between 0.1 and 1. We also set the initial and final values for the R-R interval state variable to 0.4 and 0.8. As we can see from Fig. 4, increasing the magnitude of the w coefficient makes the state variable $y(t)$ get closer to the reference value for the considered finite control horizon. This implies that depending on the medical conditions, the optimal controller can be customized to be more or less sensitive to deviations by adjusting the coefficients in the performance index in equation (3).

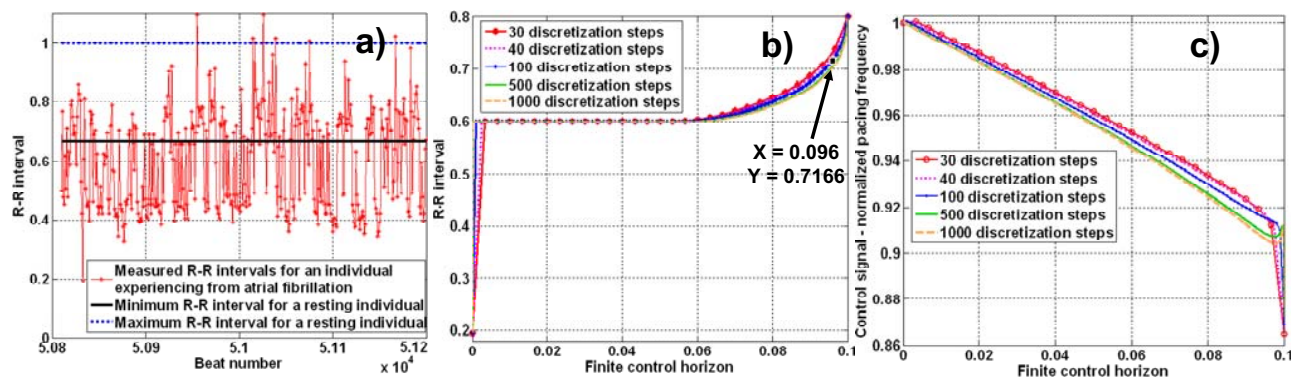


Figure 3. a) Comparison between the measured R-R intervals of an individual suffering from atrial fibrillation and the minimum and maximum bounds on the R-R intervals for a healthy individual at rest. One can clearly observe that the R-R intervals have the tendency of exhibiting small magnitudes. For instance, the first 100 beats exhibit on average R-R intervals of 0.55 seconds with a standard deviation of 0.14 seconds. This can lead to palpitations and so fainting and dizziness. b) Applying the fractal optimal controller, the R-R interval is increased from 0.19 to 0.80 (corresponding to a healthy heart rate of 75 beats per minute) in a finite control horizon of 0.1 seconds. c) Control signal - pacing frequency - necessary to be followed by the optimal control module of the pacemaker to increase the R-R intervals and reduce the heart rate from approximately 100 to 75 beats per minute.

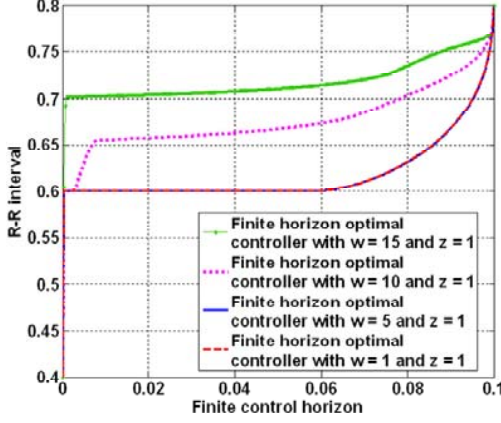


Figure 4. Impact of the w coefficient in the performance index in (3) on solving the constrained finite horizon fractal optimal control problem for 300 discretization steps and $z = 1$. Increasing the magnitude of w makes the error in the cost function larger and brings the state variable closer to the predefined reference value.

To fully understand the impact of the constraints on the convergence of the controller, we consider the fractal (optimal) controller defined in equations (3) through (6) for 100 discretization steps under four test cases:

- coefficients w and z set to 1, state variable $y(t)$ constrained between 0.79 and 1, control signal $f(t)$ constrained between 0.01 and 1, initial value for the control signal set to 0.3, initial and final values on the state variable to 1.5 and 0.8, respectively;
- coefficients w and z set to 1 and 0.01, respectively, state variable $y(t)$ constrained between 0.79 and 1, control signal $f(t)$ constrained between 0.01 and 1, initial value for the control signal set to 0.3, initial and final values on the state variable to 1.5 and 0.8, respectively;
- coefficients w and z set to 1, state variable $y(t)$ constrained between 0.66 and 1, control signal $f(t)$ constrained between 0.01 and 1, initial value for the control signal set to 0.3, initial and final values on the state variable to 1.5 and 0.8, respectively;
- coefficients w and z set to 1 and 0.01 respectively, state variable $y(t)$ constrained between 0.79 and 1, control signal $f(t)$ constrained between 0.01 and 1, initial value for the control signal set to 0.3, initial and final values on the state variable to 1.5 and 0.8, respectively.

As one can observe from Fig. 5, decreasing the magnitude of z makes the error between the state variable and the reference value more significant and so contributes to a higher rate of convergence. Moreover, by comparing the green (dotted) line with the blue (star markers) curve, we can observe that the magnitude of z coefficient plays a more important role than the constraints.

Next, we also investigate the performance of the fractal optimal controller defined by equations (13) through (16) (where the cost function integrates the product between the time and the error between the actual and the reference R-R

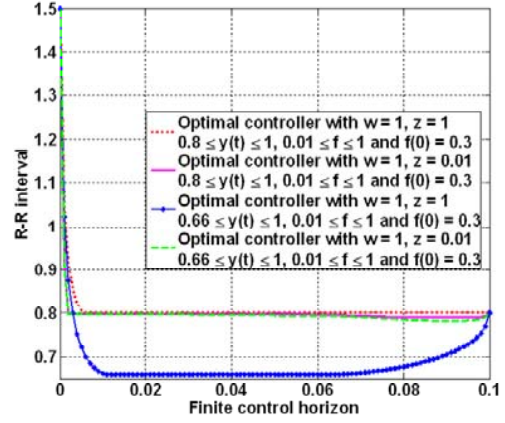


Figure 5. Impact of the z coefficient in the performance index in (3) and the constraints imposed on the state variable $y(t)$ while solving the constrained finite horizon fractal optimal control problem for 100 discretization steps and $w = 1$. Decreasing the magnitude of z makes the error in the cost function more important and brings the state variable closer to the predefined reference value. Also, the constraints on state variable can influence the convergence of the controller to the reference value.

interval) is influenced by the number of discretization steps N . Note that the controller was constrained to find the control signal such that the R-R interval is kept between 0.6 and 1 seconds and the pacing frequency is between 0.5 and 1. The w and z coefficients in the performance index function shown in (3) were set to 0.1. Fig. 6 shows that the optimal controller is able to bring the R-R interval from 0.2 to 0.8 seconds in the predefined finite horizon for various discretization steps (i.e., $N = 30, 40, 100, 500,$ and 1000 discretization steps). Due to the time multiplication of the error between the actual and the reference R-R interval, this controller exhibits a slightly faster convergence to the predefined reference value.

For completeness, Fig. 7 shows the control signal (pacing frequency) needed to be followed by the optimal controller in addition to the natural pacing coming from the brain to achieve a 0.8 R-R interval or a heart rate of 75 beats per minute. In this setup, the final optimal pacing frequency is as follows: 0.8473 for 30 discretization steps, 0.8487 for 40 discretization steps, 0.8527 for 100 discretization steps, 0.8576 for 500 discretization steps, and 0.8591 for 1000 discretization steps. Consequently, by reducing the number of discretization steps from 1000 to 30 which also reduce the computational time complexity, the penalty in accuracy is less than 1.4%.

C. Hardware Complexity of Fractal Optimal Control

In this subsection, we investigate the hardware complexity (i.e., area overhead) of implementing the fractal controller by building an FPGA prototype. Consequently, we consider its implementation on a Xilinx Virtex4 FPGA (Device: XC5VLX30 and Package: FF324). Xilinx's SXT is used for synthesis, and Xilinx's Isim is used for the simulations. Table III summarizes the area overhead of the controller design in terms of slice, LUT, and register utilization. In this design, the worst case time to solve a

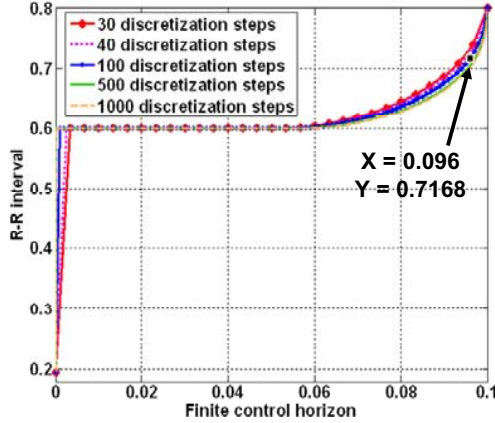


Figure 6. Applying the fractal optimal controller described in equations (13) through (16); the R-R interval is increased from 0.19 to 0.80 (corresponding to a healthy heart rate of 75 beats per minute) in a finite control horizon of 0.1 seconds. Of note, the effect of multiplying the error between the initial and final reference value with the time it occurs forces the process to converge to the target rate a bit faster.

16x16 linear program is 1190 clock cycles. Although some further optimization can be obtained via a dedicated ASIC implementation of the fractal optimal controller, this shows that the proposed approach can be implemented in silicon quite effectively. Further optimizations should also consider reducing the computational speed to save power.

TABLE III. CONTROLLER AREA REQUIREMENTS IN TERMS OF THE NUMBER OF SLICES, REGISTERS, LUTS.

Problem size	Registers	LUTs	RAM/FIFO	DSP48Es
16	243	239	1	6
128	340	618	29	6

VI. CONCLUSIONS

In this paper, we presented a constrained finite horizon optimal control approach to R-R interval regulation in implantable pacemakers. Towards this end, we have investigated the goodness-of-fit of a fractal approach to modeling the dynamics of R-R intervals and the performance of two controllers under parameters estimated from individuals suffering from atrial fibrillation and bradycardia. In addition, we have also analyzed the feasibility of implementing such a controller by reporting the area overhead obtained from a real FPGA implementation.

As future work, we plan to investigate the impact of cost functions that depend on higher order moments and the controller stability in the presence of uncertainties. Another line of research would be to investigate the implications and clinical benefits of various cost functions on cardiac pacing.

ACKNOWLEDGMENT

The authors would like to thank to anonymous reviewers for their constructive comments and helpful suggestions.

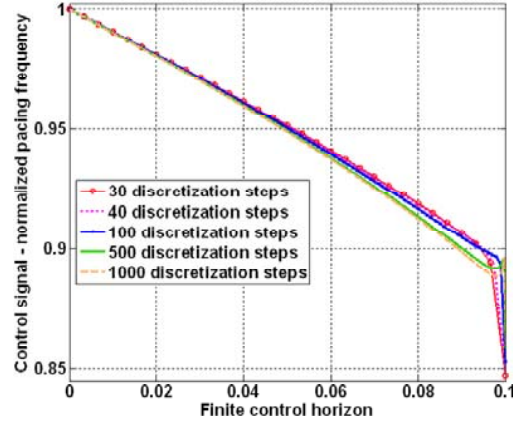


Figure 7. Control signal - pacing frequency - necessary to be followed by the optimal controller module (described by equations (13) through Eq. (16)) of the pacemaker in order to increase the R-R intervals and reduce the heart rate from approximately 100 to 75 beats per minute.

This research was supported in part by the National Science Foundation under grant CCF-0916752.

REFERENCES

- [1] O.P. Agrawal, "Formulation of Euler-Lagrange Equations for Fractional Variational Problems," *J. Math. Anal. Appl.*, 272(1):368–379, 2002.
- [2] O. P. Agrawal, O. Defterli, and D. Baleanu, "Fractional Optimal Control Problems With Several State and Control Variables," *J. of Vibration and Control*, pp. 1-10, May, 2010.
- [3] E. Alt, M. Matula and H. Theres, "The Basis for Activity Controlled Rate Variable Cardiac Pacemakers: An Analysis of Mechanical Forces on the Human Body Induced by Exercise and Environment", *Pacing Clin. Electrophysiol.*, pp. 1667–1680, 1989.
- [4] Autonomic Rate Response for Real-World Living, BIOTRONIK, <http://www.biotronik.de/en/us/4830>
- [5] D.W. Bacharach, T.S. Hilden, J.O. Millerhagen, B.L. Westrum and J.M. Kelly, "Activity-based Pacing: Comparison of a Device Using an Accelerometer versus a Piezoelectric Crystal," *Pacing Clin Electrophysiol*, 15, pp. 188–196, 1992.
- [6] J. L. Battaglia, L. Le Lay, J.-C. Batsale, A. Oustaloup, O. Cois, "Heat Flow Estimation Through Inverted Non Integer Identification Models," *Journal of Thermal Science*, 39(3), 374-389, 2000.
- [7] J. Beran, *Statistics for Long-Memory Processes*, 1994.
- [8] P. Bogdan and Radu Marculescu, "Statistical Physics Approaches for Network-on-Chip Traffic Characterization," in *Proceedings of the 7th IEEE/ACM International Conference on Hardware/software codesign and system synthesis (CODES+ISSS '09)*, pp. 461-470, 2009.
- [9] P. Bogdan and R. Marculescu, "Towards a Science of Cyber-Physical Systems Design", in *Proceedings of the 2011 IEEE/ACM Second International Conference on Cyber-Physical Systems (ICCPs '11)*, pp. 99-108, April 2011.
- [10] P. Bogdan and R. Marculescu, "Cyberphysical Systems: Workload Modeling and Design Optimization," *IEEE Design & Test of Computers*, vol.28, no.4, pp.78-87, July-Aug. 2011.
- [11] P. Bogdan and R. Marculescu, "A Fractional Calculus Approach to Modeling Fractal Dynamic Games," in *Proceedings of 50th IEEE Conference on Decision and Control and European Control Conference (CDC-ECC)*, Orlando, Florida, USA, December 2011.
- [12] M. Coenen, K. Malinowski, W. Spitzer, A. Schuchert, D. Schmitz, M. Anelli-Monti, S.K. Maier, W. Estlinbaum, A. Bauer, H. Muehling, F. Kalscheur, K. Puerner, J. Boergel and S. Osswald, "Closed Loop Stimulation and Accelerometer-based Rate Adaptation: Results of the PROVIDE Study", *Europace*. vol. 10, 2008.

- [13] S. Dell'Orto, P. Valli, E.M. Greco, "Sensors for Rate Responsive Pacing" *Indian Pacing and Electrophysiology Journal*, 2004.
- [14] F. J. Doyle III, B. W. Bequette, R. Middleton, B. Ogunnaik, B. Paden, R. S. Parker and M. Vidyasagar, "Control in Biological Systems", *The Impact of Control Technology*, 2011.
- [15] A.E. Epstein, J.P. DiMarco, K.A. Ellenbogen, et al. "ACC/AHA/HRS 2008 Guidelines for Device-based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices)", *J Am Coll Cardiol.*, 51, pp.1–62, 2008.
- [16] A.S. Fauci, E. Braunwald, S.L. Hauser, D.L. Longo, J. Jameson, J. Loscalzo, *Harrison's Principles of Internal Medicine*, McGraw-Hill, 2008.
- [17] D.L. Hayes, C.D. Swedlow, and P.A. Friedman, "Chapter 8: Programming", *Cardiac Pacing Defibrillation and Resynchronization: A Clinical Approach*, edited by D.L. Hayes and P.A. Friedman, Mayo Foundation for Medical Education and Research, 2008.
- [18] G. F. Inbar, R. Heinze, K. N. Hoekstein, H. D. Liess, K. Stangl, and A. Wirtzfeld, "Development of a Closed-Loop Pacemaker Controller Regulating Mixed Venous Oxygen Saturation Level," in *IEEE Trans. Biomed. Eng.*, vol. 35, pp.679-690, 1988.
- [19] P. Ch. Ivanov, M. G. Rosenblum, C.-K. Peng, J. Mietus, S. Havlin, H. E. Stanley and A. L. Goldberger. "Scaling and Universality in Heart Rate Variability Distributions", *Proceedings of Bar-Ilan Conference, Physica A* 249, pp. 587-593, 1998.
- [20] P. Ch. Ivanov, A. Bunde, L. A. N. Amaral, S. Havlin, J. Fritsch-Yelle, R. M. Baevsky, H. E. Stanley and A. L. Goldberger, "Sleep-wake Differences in Scaling Behavior of the Human Heartbeat: Analysis of Terrestrial and Long-Term Space Flight Data", *Europhys. Lett.* 48, pp. 594-600, 1999.
- [21] P. Ch. Ivanov, L. A. N. Amaral, A. L. Goldberger, S. Havlin, M. G. Rosenblum, H. E. Stanley, Z. R. Struzik, "From 1/f Noise to Multifractal Cascades in Heartbeat Dynamics", *Chaos*, 11, 2001.
- [22] Z. Jiang, M. Pajic and R. Mangharam, "Model-based Closed-loop Testing of Implantable Pacemakers", in *Proc. of the ACM/IEEE Intl. Conf. on Cyber-Physical Systems*, Chicago, April 2011.
- [23] S. A. P. Haddad, R. P. M. Houben and W. A. Serdijn, "The Evolution of Pacemakers", *IEEE Eng. Medicine & Biology*, 2006.
- [24] *Heart Pacemakers*, The Journal of the American Medical Association, <http://jama.ama-assn.org/content/286/7/878.full.pdf>
- [25] M.P.R. Hexamer, M. Meine, A. Kloppe and E. Werner, "Rate-Responsive Pacing based on the Atrio-Ventricular Conduction Time", *IEEE Trans. on Biomedical Engineering*, vol.49, 2002.
- [26] D.P. Humen, W.J. Kostuk and G.J. Klein, "Activity-Sensing, Rate-Responsive Pacing: Improvement in Myocardial Performance with Exercise", *Pacing Clin Electrophysiol.*, 8, pp. 53–59, 1985.
- [27] G.K. Hung, "Application of the Root Locus Technique to the Closed Loop SO₂ Pacemaker-Cardiovascular System", in *IEEE Trans. on Biomedical Engineering*, vol. 37, 6, pp. 549-555, 1990.
- [28] K. Kiyono, Y. Yamamoto and Z. R. Struzik, "Statistical Physics of Human Heart Rate in Health and Disease", in *Understanding Complex Systems*, Springer, pp. 139-154, 2009.
- [29] F. Kusumoto, N. Goldschlager, N. F. Goldschlager, *Cardiac Pacing for the Clinician*, Springer 2008.
- [30] E. A. Lee, "CPS Foundations", in *Proceedings of the 47th Design Automation Conference (DAC '10)*, 2010.
- [31] S.Y. Lee, C.J. Cheng, M.C. Liang, "A Low-Power Bidirectional Telemetry Device with a Near-Field Charging Feature for a Cardiac Microstimulator", *IEEE Trans. Biom. Circ. and Syst.*, 2011.
- [32] M. J. Lopez, A. Consegliere, J. Lorenzo and L. Garcia, "Computer Simulation and Method for Heart Rhythm Control Based on ECG Signal Reference Tracking", *WSEAS Trans. on Syst.*, 2010.
- [33] R.L. Magin, *Fractional Calculus in Bioengineering*, Begell House Publishers, 2006.
- [34] F. Mainardi, *Fractional Calculus and Waves in Linear Viscoelasticity*, Imperial College Press, 2010.
- [35] B. B. Mandelbrot, *Gaussian, Self-Affinity and Fractals*, 2002.
- [36] C. A. Monje, Y. Chen, B. M. Vinagre, D. Xue, V. Feliu, *Fractional-Order Systems and Controls: Fundamentals and Applications*, Springer 2010
- [37] M. Nakao, T. Takizawa, K. Nakamura, N. Katayama and M. Yamamoto, "An Optimal Control Model of 1/f Fluctuations in Heart Rate Variability", *IEEE Engineering in Medicine and Biology Society*, vol. 20, Issue 2, pp. 77-87, March-April 2001.
- [38] B. Neogi, R. Ghosh, U. Tarafdar and A. Das, "Simulation Aspect of An Artificial Pacemaker", in *Intl. J. of Information Technology and Knowledge Management*, vol. 3, 2, pp. 723-727, 2010.
- [39] B. Onaral and H. P. Schwan, "Linear and Nonlinear Properties of Platinum Electrode Polarization, Part I, Frequency Dependence at Very Low Frequencies," *Medical Biological Engineering Computation*, 20, pp. 299-306, 1982.
- [40] A. Oustaloup, *La Derivation Non Entiere: Theorie, Synthese et Applications*, Hermes, Paris, 1995.
- [41] *PhysioNet - The Research Resource for Complex Physiologic Signals*, Available online: <http://www.physionet.org/>
- [42] I. Podlubny, *Fractional Differential Equations. An Introduction to Fractional Derivatives*, Academic Press, 1999.
- [43] R. S. Sanders and M. T. Lee, "Implantable Pacemakers", in *Proc. of IEEE*, 84(3), pp.480–486, 1996.
- [44] M. Schaldach "What is Closed Loop Stimulation?", *Prog Biomed Res.* vol. 3 (2), pp. 49-55, 1998.
- [45] E.N. Simantirakis, E.G. Arkolaki and P.E. Vardas, "Novel Pacing Algorithms: Do They Represent a Beneficial Proposition for Patients, Physicians, and the Health Care System?", *Europace*, vol. 11, pp. 1272-1280, 2009.
- [46] J. A. Stankovic, I. Lee, A. Mok and R. Rajkumar, "Opportunities and Obligations for Physical Computing Systems", *Computer* 38, 11, pp. 23-31, November 2005.
- [47] K. Stangl, A. Wirtzfeld, O. Lochschmidt, B. Basler and A. Mittnacht, "Physical Movement Sensitive Pacing: Comparison of Two "Activity"-triggered Pacing Systems", *Pacing Clin Elec.* 1989.
- [48] T. Sugiura, Y. Nakamura and S. Mizushina, "A Temperature-Sensitive Cardiac Pacemaker", *J. Med. Eng. Technol.*, 7, 1983.
- [49] T. Sugiura, S. Mizushina, M. Kimura, Y. Fukui and Y. Harrada, "A Fuzzy Approach to the Rate Control in an Artificial Cardiac Pacemaker Regulated by Respiratory Rate and Temperature: A Preliminary Report", in *J. of Medical Engineering & Technology*, vol. 15, No. 3, pp. 107-110, May/June 1991.
- [50] Q. Sun, F. Schwartz, J. Michel and R. Rom, "Implementation Study of an Analog Spiking Neural Network in an Auto-Adaptive Pacemaker", in *Proc. of the Circuits and Systems*, pp. 41-44, 2008.
- [51] R. Sutton, L. Ryden and I. Bourgeois, *The Foundations of Cardiac Pacing*, Futura Publishing, Armonk NY, 1999.
- [52] M. Tosato, K. Yoshida, E. Toft, V. Nekrasas, and J.J. Struijk, "Closed-loop Control of the Heart Rate by Electrical Stimulation of the Vagus Nerve, *Medical and Biological Engineering and Computing*, Vol. 44, No. 3, pp. 161-169, 2006.
- [53] Y. Zhang, K.A. Mowrey, S. Zhuang, D.W. Wallick, Z.B. Popovic and T. N. Mazgalev, "Optimal Ventricular Rate Slowing During Atrial Fibrillation by Feedback AV Nodal-Selective Vagal Stimulation", *Am J Physiol Heart Circ Physiol*, 1102-1110, 2002.