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Application

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2015-05256 **Medvedev, Alexander** **NT-14**

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Information about application

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Participants

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Descriptive data

Project info

Project title (Swedish)*

Styrning av Goodwins impulsiva oscillator

Project title (English)*

Control of the impulsive Goodwin's oscillator

Abstract (English)*

The purpose of this project is to build up a system-theoretical framework that enables controller design for a specific mathematical model known as impulsive Goodwin's oscillator. This model is proposed by the project group in 2007 to describe the oscillating hybrid dynamics that arise when a continuous plant is subject to an intrinsic impulsive feedback and has application in e.g. pulsatile endocrine regulation. In the latter case, controller design is interpreted as individualizing a model-based pharmacotherapy as the controller calculates the dosing and the administration schedule of a drug. The proposed research program is planned for three years and addresses the challenges of model-based control in a class of hybrid infinite-dimensional oscillating systems, underpinned by novel hybrid observers and model identifiability analysis. Mathematical methods from non-smooth, nonlinear, hybrid, and time-delay systems come in handy in design of control and state estimation in impulsive Goodwin’s oscillator. No biological data are handled in the project. A parallel study in cooperation with medical researchers in Endocrinology Clinic of Karolinska Institute, Huddinge is being set up focusing on the use of the proposed control techniques in normalization of testosterone regulation after anabolic steroids abuse. Other prospective applications of the anticipated project results are e.g. individualized prostate cancer and hormone replacement treatments.

Popular scientific description (Swedish)*

Reglerteknik studerar hur man använder återkoppling för att åstadkomma önskat beteende i dynamiska system, d v s system med minne. Levande organismer är också dynamiska system som reglerar sig själva genom ett stort antal biologiska kretsar som agerar på olika nivåer och i olika tidskalor. I människan, som hos andra högre djur, uppstår återkopplad reglering på cellnivå, organnivå och individnivå. För att i detalj förstå hur ett återkopplat system fungerar måste det i sin helhet beskrivas matematiskt.

Avvikelser och störningar i biologisk reglering hos människan leder ofta till sjukdomar som studeras inom medicinska vetenskaper. Beroende på vilka organ och system som drabbas kan det handla om endokrinologi, neurologi, kardiologi, eller något annat.

Hormoner är signalämnen som frisätts av endokrina körtlar och som sprids i blodet till celler i målorgan. Det mänskliga endokrina systemet styrs av komplexa återkopplingar och ansvarar för bl a tillväxt, metabolism och reproduktion. Kommunikation i endokrina kretsar uppstår genom att ett hormons molekyler stimulerar eller hämmar produktionen av ett annat hormon. Detta kan ske kontinuerligt (basalt) eller stötvis (icke-basalt). Frekvensen och amplituden hos hormonimpulserna vid stötvis frisättning av hormon har stor biologisk betydelse för det endokrina systemet. Goodwins impulsiva oscillator är den enda matematiska modellen för icke-basal hormonfrisättning som är validerad gentemot kliniska data.

Detta projekt syftar primärt till att studera hur Goodwins impulsiva oscillator kan styras med externa signaler men också hur icke-mätbara hormonhalter och frisättningstider kan skattas utifrån blodanalysdata. Styrning av endokrina system utförs genom läkemedelsbehandlingar där mängden av läkemedlet och tiderna då det skall ges beräknas av reglersystemet med den individualiserade matematiska modellen som underlag.

Behandlingar av prostatacancer, testosteronbrist och rehabilitering efter missbruk av anabola steroider är de medicinska huvudområden där den föreslagna individualiserade tekniken kan tillämpas. De reglertekniska lösningar som tas fram inom projektet kommer att testas i kliniska prov i samarbete med forskare vid Endokrinmottagningen, Karolinska Institutet, Huddinge.

Project period

Number of project years*

3

Calculated project time*

2016-01-01 - 2018-12-31

Classifications

Select a minimum of one and a maximum of three SCB-codes in order of priority.

Select the SCB-code in three levels and then click the lower plus-button to save your selection.

SCB-codes*	2. Teknik > 202. Elektroteknik och elektronik > 20202. Reglerteknik

Enter a minimum of three, and up to five, short keywords that describe your project.

Keyword 1*

hybrida system

Keyword 2*

pulsmodulerade system

Keyword 3*

biomedicinska tillämpningar

Keyword 4

Keyword 5

Ethical considerations

Specify any ethical issues that the project (or equivalent) raises, and describe how they will be addressed in your research. Also indicate the specific considerations that might be relevant to your application.

Reporting of ethical considerations*

This project does not use any biological data and is focused on system-theoretical problems with high relevance to biomedicine.

The project includes handling of personal data

No

The project includes animal experiments

No

Account of experiments on humans

No

Research plan

A Research plan

A.1 Purpose and aims

The purpose of this project is to build up a system-theoretical framework that enables controller design for systems described by a specific mathematical model known as an impulsive Goodwin's oscillator. This model is developed to describe the oscillating hybrid dynamics that arise when a continuous plant is subject to an intrinsic impulsive feedback and has application in e.g. pulsatile endocrine regulation. In the latter case, controller design is interpreted as individualizing a model-based therapy.

The present proposal will be paralleled by a clinical study carried out in cooperation with the Endocrinology Clinic of Karolinska Institutet, Huddinge, and funded from other sources. Only the agenda within the realm of systems and control is addressed in this project. Therefore it is *neither* a systems biology *nor* a biomedical engineering project as its scope is limited to the control and analysis of a certain mathematical model encountered in life science.

The proposal extends, to the area of control, the results previously achieved in research on mathematical modeling and estimation in endocrine systems funded by the Advanced Grant "Systems and signals tools for estimation and analysis of mathematical models in endocrinology and neurology" awarded by the European Research Council for the period 2010-2014 and the VR project "Mathematical modeling, analysis, and estimation in endocrine systems with pulse-modulated feedback" granted for 2012-2015.

A research program addressing the challenges of model-based control in a class of hybrid oscillating systems, with a prospective application to design of hormone therapies, is envisaged. The proposal topic, with emphasis on control of hybrid oscillating systems in living organisms, is not covered by any previous or on-going project.

The concrete aims are set as follows:

- Develop design and analysis methods for continuous-time controllers robustly modifying behaviors of the impulsive Goodwin's oscillator in a pre-defined manner;
- Propose impulsive control laws that exhort periodical action on the impulsive Goodwin's oscillator to achieve a given signal pattern of its state variables;
- Derive synchronization conditions between two coupled impulsive Goodwin's oscillators;
- Utilize the concept of integrate-and-fire output error feedback, to develop design methods for hybrid observers reconstructing the state of the impulsive Goodwin's oscillator;
- Establish identifiablity conditions for the intrinsic pulse-modulated feedback in the impulsive Goodwin's oscillator from measurements of its continuous output.

A.2 Survey of the field

This section is organized in two parts: The first part provides an overview of currently available results on Goodwin's oscillators and the second one briefly summarizes the potential medical applications that are important for understanding the inherent control limitations. It should be pointed out here that control of the impulsive Goodwin's oscillator is a new territory and never been treated before. This safeguards the novelty of the proposal.

A.2.1 Mathematical models of biological oscillators

Oscillating nonlinear systems are standard mathematical models in life science because they capture periodicity patterns in living organisms. Periodicity arises due to natural phenomena within the system but is also affected by signals from the environment. Relevant examples are presented by e.g. models of biological clocks that are instrumental in timing of all basic biological processes, see e.g [1].

Goodwin's oscillator A feedback mechanism is necessary for creating a self-sustained oscillation. An early and general mathematical construct to describe a simple periodical biological system is Goodwin's oscillator [2]. It was intended to portray an oscillation in a single gene that suppresses itself via the production of intermediate enzymes. From a control perspective, Goodwin's oscillator is just a third-order linear continuous-time system with a static nonlinear feedback parameterized by a Hill function. Already in this early model, two important properties shared by many mathematical models of biological oscillators have been heralded: One of them is a feedback nonlinearity exhibiting saturation and another one is the cascade (chain) structure of the linear part.

As further analysis has proven, Goodwin's oscillator has to incorporate a Hill function of order eight in order to possess sustained periodic solutions [3]. Since the order of the Hill function is usually interpreted as an upper bound for the number of ligand molecules that a receptor or enzyme can bind [4], eight appears to be a biologically infeasible number. The presence of a time delay in the closed loop of Goodwin's oscillator does not sufficiently alleviate the problem of producing sustained oscillations [5].

One of the applications that the concept of Goodwin's oscillator has found on the level of a system of organs is endocrine feedback regulation. A hormone is a chemical messenger from one cell to another. Hormones are produced by nearly every organ and tissue type in a multicellular organism. The endocrine system is an integrated chemical signal system based on release of hormones, using blood vessels as information channels. The endocrine system is instrumental in regulating the metabolism, growth and development, as well as the sexual function and the reproductive processes.

The original paradigm of Goodwin's oscillator fits well into the simplified structure of testosterone (Te) regulation in the male [6], where gonadotropin-releasing hormone (GnRH) produced in the hypothalamus stimulates the production of luteinizing hormone (LH) in hypophysis, which hormone, in its turn, stimulates the production of Te in the testes. The concentration of Te exhorts negative feedback on the concentration of GnRH by inhibiting its release. Goodwin's oscillator is often called the Smith model [7] in the context of endocrine regulation.

Impulsive Goodwin's oscillator Being a conceptual (phenomenological) model, Goodwin's oscillator, in its classical form, does not necessarily fit experimental data or capture the underlying biological mechanisms. In the endocrine regulation of Te, a significant difficulty is presented by the fact that GnRH secretion by the hypothalamic neurons is not continuous but rather episodic. In fact, synchronized GnRH neurons collectively produce bursts of hormone concentration [8] whose amplitude and frequency are dependent on the concentration of Te. This pulse-modulated mechanism has been established experimentally [9] and implements a negative feedback as the amplitude and frequency of the GnRH pulses decrease for increasing Te levels.

To bring Goodwin's oscillator (the Smith model) in agreement with the biological evidence, the original static nonlinear feedback of it is substituted with a frequency-amplitude pulse modulation mechanism in [10]. The resulting model is termed the impulsive Goodwin's oscillator. It possesses hybrid dynamics as the feedback is implemented by pulse modulation of the first kind [11] and thus introduces a first-order discrete subsystem in the closed loop of the oscillator.

The most prominent property of the impulsive Goodwin's oscillator is the lack of equilibria that together with boundedness of the solutions [10] agrees well with the original biological function of producing periodic temporal patterns. This is in contrast with what is experienced in the classical continuous-time version of the mathematical model. A diversity of signal shapes (hormone concentration profiles) is achieved through richness of the dynamics. Even for the impulsive Goodwin's oscillator without time delay, periodic solutions of high multiplicity as well as deterministic chaos are observed [12].

Time delays Time delays play an important role in biological oscillators, both depicting certain biological phenomena and extending the parameter space of sustained periodic solutions. They are sometimes pointed out as the sole reason of oscillations in biological networks [13]. As impulsive Goodwin's oscillator lacks equilibria, time delays are biologically motivated and describe lags due to either transport phenomena in the underlying endocrine system or effects related to synthesis of releasable hormone pools. Therefore, the involved time delays are subject to inter-individual and intra-individual variability. As any other feedback control system, the impulsive Goodwin's oscillator has to cope with uncertainty.

When the time delay is less than the minimal interval between two (subsequent) firings of the pulse-modulated feedback, no qualitative change in the dynamics of the impulsive Goodwin's oscillator occurs [14]. Thus, the pulse-modulated feedback adopted in the model to mimic a biological mechanism demonstrates significant robustness against time delay, a property that is highly desirable with respect to maintaining homeostasis over an organism population.

Once the time delay value increases over the least possible modulation period, the repertoire of dynamical behavior drastically enlarges and includes e.g. multistability and quasi-periodical oscillations [15]. Notice that these complex dynamics types are not observed in the whole parameter space. In fact, for model parameter values estimated from biological data [16], only a reduction in oscillatory behavior is observed in the impulsive Goodwin's oscillator for increasing values of the time delay. This reduction manifests itself via a bifurcation that decreases the multiplicity of cycles exhibited by the oscillator solutions.

A.2.2 Control interpretation of hormone therapy

Exogenous endocrine control Biomathematical studies of endocrine regulation are mostly concerned with capturing and analyzing the effects of endogenous feedback. Exogenous control is practiced only in specific areas of endocrinology and limited to prosthetic function, i.e. replacing the endogenous regulation originally implemented by a failing organ, e.g. the pancreas. The most promising replacement therapy for type 1 diabetes is a closed-loop artificial pancreas incorporating a continuous glucose sensor and an insulin pump. For instance, a proportional-integral-derivative insulin flow controller whose gains are to be individually trimmed to fit the patient is a typical solution for the artificial pancreas to sustain near-normal glucose concentrations, [17]. Yet, very relevant to the scope of this project, in [18], an impulsive algorithm employing the natural pulsatile pattern of insulin secretion and the oscillatory pattern of resting blood glucose levels is described and tested in diabetic pigs.

Testosterone therapies The abundance of research on artificial pancreas is contrasted by a sparse coverage of other hormone therapies that rely mainly on manual delivery and ad hoc optimization. With minor modifications, the insulin pumps are also used for delivery of synthetic GnRH in treatment of reproduction failure due to hypothalamic disorders in men and women [19]. However, the control function is simply reduced to periodic release of a pre-defined quantity of the medication without any attempt to treatment individualization reported in the literature.

A most recent and exciting clinical application of impulsive Te therapy is castration-resistant prostate cancer. A treatment based on rapid cycling between high and low (near-castration) testosterone levels results in declining prostate-specific antigen values and complete or partial response in tumor size [20]. This presents an ample opportunity for the use of impulsive control techniques.

Testosterone replacement therapy is prescribed when low Te levels are accompanied by clinical complaints e.g. such as fatigue, loss of muscle mass, and depression. An emerging field of Te therapies is rehabilitation of patients with history of anabolic steroids abuse that are estimated to constitute $1.5 - 2.0\%$ of all young males.

Exogenous Te is typically provided via injections or transdermally. In the former case, the therapy results in a periodical and impulse-like control action while, in the latter case, it contributes a constant offset. Oral administration has no place in Te therapy because of liver toxicity.

Due to the feedback action via GnRH that is secreted and released by neurons within the hypothalamus, there is a drop of the Te level below the normal range shortly before the next injection, leading to increased symptoms. This cyclical nature of highs and lows can be minimized by shortening the interval between injections, and lowering the dose. Despite these important insights, no attempts of optimizing Te replacement therapy by taking into account the pulsatile GnRH feedback can be found in the literature.

To summarize, there is a significant accumulated knowledge on how the dynamic mechanisms of endocrine systems can be described mathematically. The complexity of the models varies from high-order comprehensive simulation models to very simplistic qualitative ones that grasp the dominant dynamics of the studied phenomena. Such mathematical constructs and means of qualitative validation of physiological theories can be transformed into tools for estimating otherwise inaccessible-to-measurement biological parameters, as well as to tools for the development of new and optimization of existing strategies for medical interventions.

A.3 Project description

The project relies on control-theoretic methods, particularly for nonlinear, discontinuous, and hybrid systems, as well as concepts from system identification. The mathematical model under consideration, i.e. the impulsive Goodwin's oscillator, is given by

$$\begin{aligned} \frac{dx}{dt} &= A_0 x(t) + A_1 Q_t(x) + Gu(t), \qquad y = Cx, && (1) \\ t_{n+1} &= t_n + T_n, \qquad x(t_n^+) = x(t_n^-) + \lambda_n B, && (2) \\ T_n &= \Phi(y(t_n)), \qquad \lambda_n = F(y(t_n)), && \end{aligned}$$

were B is a column, C is a row orthogonal to B, (i.e. $CB = 0$), to guarantee that y is continuous despite the jumps in (2), and $Q_t(\cdot)$ is a hereditary operator capturing the lags in the closed-loop system. The control signal u acts on the continuous state variables x through the control matrix G specifying the accessible for manipulation variables. The impulsive Goodwin's oscillator possesses hybrid dynamics as the differential equation in (1) is subject to the first-order discrete dynamics of (2) implemented in the form of a pulse-modulated feedback given by the frequency $\Phi(\cdot)$ and amplitude $F(\cdot)$ modulation functions.

In the context of endocrine regulation, the continuous state vector x comprises the concentrations of the involved hormones and the discrete state variable t_n describes the firing times (jumps or impulses) of the neurally implemented feedback. The control signal u corresponds to a therapeutical intervention, a pharmacotherapy.

More specifically, the research is concentrated on three interconnected topics i) control of systems with intrinsic pulsatile feedback; ii) hybrid observers for systems with intrinsic pulsatile feedback, and iii) identifiability analysis.

The project group members possess complementing research profiles: Prof. Medvedev, who has track record and practical experience in all the target areas of the proposal (i.e. **T1,T2, T3**), is the PI of the research program. Prof. Wigren has expert knowledge of nonlinear identification (**T3**), as well in application to automatic drug delivery. Medvedev and Wigren co-authored several publications, collaborated in joint projects, and shared supervision of a PhD student (M. Silva), who successfully defended her thesis last year. Two current PhD students with Medvedev as main supervisor are involved in this proposal and both have multiple publications within the scope of the project. P. Mattsson has obtained his Licentiate degree last year with a thesis devoted to identification of impulsive Goodwin's oscillator. His doctoral thesis will be mostly on control of endocrine systems. D. Yamalova has studied hybrid observers for one and a half years and will carry on with this topic.

TX.Y refers to **Task Y** in **Topic X** described further in the proposal.

T1: Control of systems with intrinsic pulsatile feedback

Besides the well-studied case of artificial pancreas, exogenous feedback control of endocrine systems is not currently feasible due to the lack of reliable on-line hormone concentration measurements. Thus the control problems considered below are pertaining to open-loop control and aiming at a certain pre-defined modification of a stationary behavior exhibited by closed-loop system (1), (2) by means of the control signal u. Notably, only autonomous behaviors of the impulsive Goodwin's oscillator (i.e. $u \equiv 0$) have been studied so far.

T1.1: Static control signal This simplistic control strategy encompasses the traditional androgen replacement therapy with topical or transdermal delivery. Hormone deficiency is compensated with an agent administration over a prolonged period of time, i.e. $u(t) = \text{const}$. Due to the highly nonlinear dynamics of (1), (2), the effect of such intervention can be actually adverse. In Fig. 1, a positive bias imposed on $y(t)$ results in a significant drop in the mean value of the variable. Therefore, the intended elevation of the hormone replacement therapy would not be achieved despite the administered medication. The controller design methods developed here have to rely on individualized mathematical modeling and demand the following action points:

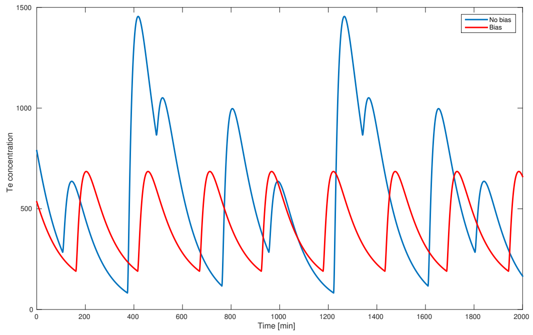

Figure 1: Example of continuos control in impulsive Goodwin's oscillator: No control (blue line) – 4-cycle with mean Te concentration 556 units ; An exogenous bias (e.g. Te patch) is introduced (red line) resulting in higher nadir points and 1-cycle is obtained with mean Te concentration 414 units. The decrease in Te is ≈ 26%.

T1.1.1 Develop Poincaré mappings capturing the impulse-to-impulse propagation of x in (1) for $u(t) \neq 0$.

T1.1.2 Establish conditions for existence of periodical solutions (n-cycles) in the controlled system.

T1.1.3 Based on bifurcation analysis, devise a numerical estimation procedure for basins of attraction of the feasible periodic behaviors.

T1.1.4 Study the effects of pointwise and distributed delays expressed in terms of a finite-memory convolution

$$Q_t(x) = \int_0^\tau K(s)x(t-s), \tag{3}$$

where $K(\cdot)$ is a continuous kernel function.

Thus the resulting static control design is in selecting such a value of u that yields a cycle of given multiplicity and with a sufficient basin of attraction to accommodate model uncertainty.

T1.2: Impulsive control signal The impulsive control signal case is instrumental in modeling a pharmacotherapy administered by injection. Both the timing and the dosing of the drug (aka drug regiment) are important and have to be properly selected to induce the intended therapeutic effect. The control signal is given by $u(t) = \bar{C}z(t)$, where z is the state vector of a dynamical system whose input is a weighted train of Dirac delta functions $\delta(\cdot)$

$$\dot{z}(t) = \bar{A}x(t) + \bar{B}\xi(t), \quad \xi(t) = \sum_{n=0}^{\infty} \bar{\lambda}_n \delta(t - \bar{T}_n). \tag{4}$$

The Dirac delta functions do not depict any physical or chemical phenomenon but are solely used for marking the injection times. The differential equation parametrized by $\bar{A}, \bar{B}$ describes the effect of an injection on the hormone concentration.To obtain a continuous control signal, $\bar{C}\bar{B} = 0$ should hold. The weights $\bar{\lambda}_n \geq 0$ correspond to the medication dose administered at the time instant $t - \bar{T}_n$. The signal $\xi(t)$ implements an implicit way of introducing jumps, cf. (2). In fact, when the pharmacotherapy is performed repeatedly, it is more suitable to model it by impulsive Goodwin's oscillator in a n-cycle, where n is the number of injections within a given period of time, e.g. a day.

A serious complication with impulsive control is the interaction of the intrinsic feedback impulses in the plant with those of the control signal. It is known [15] that the time delays in the impulsive Goodwin's oscillator lead to non-smooth dynamical phenomena when the delay value is greater than the least interval between the impulses. In the augmented system of (1), (2), (4), the interval between two consecutive impulses is no longer bounded from below by $\inf_y \Phi(y)$ as the instances t_n in (2) can be arbitrarily close to $t - \bar{T}_n$ in (4). Thus a non-smooth bifurcation may arise for a smallest possible delay τ in (3). The action points for this part of the project are:

T1.2.1 Derive the Poincaré mapping for the augmented system given by (1), (2), (4) and study its smoothness properties.

T1.2.2 Establish entrainment and synchronization conditions between a periodic sequence $\xi(t)$ in (4) and the resulting oscillations in the plant.

T1.2.3 For given $\bar{A}$, $\bar{B}$, study the conditions of achieving a periodic solution in (1), (2) maximizing the mean hormone concentration over the least period of the solution. It is hypothesized that such a solution is a 1-cycle with the weight equal to $\sup_y F(y)$.

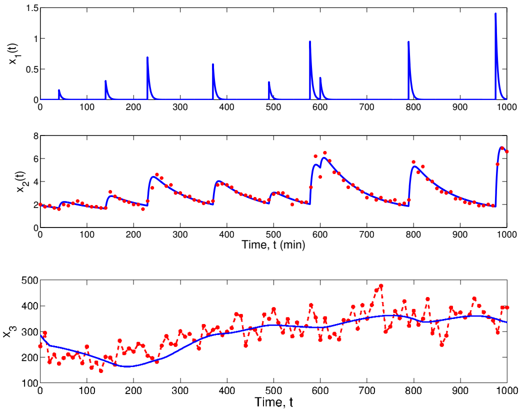

Figure 2: Identification of impulsive Goodwin's oscillator from clinical Te, LH data. Blue lines - model estimates, red lines - experimental data. From top down: pulses of GnRH estimated from LH data; LH data and the model estimate; Te data and the model estimate.

T2: State estimation in systems with intrinsic pulsatile feedback

The impulsive Goodwin's oscillator is a hybrid system and both the discrete state t_n in (2) and the continuous state vector $x(t)$ are needed to completely define the hybrid system state for $\tau = 0$. In presence of a non-trivial delay, the instantaneous state vector $[t_n \quad x^T(t_n^-)]^T$ has to be augmented with the function currently stored in the hereditary operator $Q_t(\theta), \theta \in [t_n^-, t_n^- - \tau]$. To reconstruct the state, only measurements of the continuous output $y(t)$ and the control $u(t)$ are available. This particular case is seldom encountered in hybrid observers where the discrete state vector is traditionally assumed to be available.

The following hybrid observer structure will be considered:

$$\dot{\hat{x}} = A\hat{x} + A_1 Q_t(x) + K(y - \hat{y}), \quad \hat{y} = L\hat{x}, \quad \hat{z} = C\hat{x}, \tag{5}$$

$$\hat{x}(t_n^+) = \hat{x}(t_n^-) + \hat{\lambda}_n B, \quad \hat{t}_{n+1} = \hat{t}_n + \hat{T}_n, \hat{\lambda}_n = F(\hat{z}(t_n)), \tag{6}$$

and

$$\hat{T}_n = \Phi(\hat{z}(\hat{t}_n) + K_f\{\hat{y}(\hat{t}_n) - y(\hat{t}_n)\}). \tag{7}$$

The observer design degrees of freedom are the continuous gain matrix K and, in general case, the hereditary operator $K_f\{\cdot\}$. The design problem of observer (5),(6),(7) is closely related to the problem of synchronization of two impulsive Goodwin's oscillators in **T1.2.2**. Indeed, for completely (phase) synchronized feedback pulses in the plant and the observer, the output residual is zero, i.e. $\hat{y}(t) - y(t) = 0, \forall t$. As suggested in [21], rendering this synchronized mode stable (i.e. providing some basin of attraction) by means of the design degrees of freedom yields a workable observer. Two performance issues remain for the existing observer structures: One is sluggish convergence, especially for the plant in a low-multiplicity cycle and another is unclear robustness properties. Besides, no hybrid observability analysis of (1), (2) has been carried out so far. The following problems will be targeted:

- **T2.1** Establish observability criteria for the discrete state t_n of impulsive Goodwin's oscillator from the continuous measurements $y(t)$.
- **T2.2** Devise a design procedure for observer (5),(6),(7) with a convolution type of discrete feedback operator $K_f\{\cdot\}$ (integrate and fire). Notice that using a static modulation function, similar to $\Phi(\cdot), F(\cdot)$, yields a solution vulnerable to measurement noise.
- **T2.3** Develop an observer structure capable of handling a general form of the hereditary operator $Q_t(\cdot)$ in (3).
- **T2.4** Generalize the observer structure of (5),(6),(7) to accommodate the effects of circadian rhythm and non-basal hormone secretion.

T3: Identifiability of pulsatile feedback

In engineered systems, the dynamics of a controller are usually well-defined and typically assigned by the designer. The dynamics of the controlled plant are however assumed to be uncertain and captured only approximatively. The situation with the modeling of biological systems is, in particular with the impulsive Goodwin's oscillator, reversed. A major complication with biological feedback is that the involved control laws are nonlinear and often discontinuous. In the model in hand, the latter property appears because of e.g. pulsatile signaling. The fidelity in modeling of Te regulation by an impulsive Goodwin's oscillator is illustrated in Fig. 2. The fit is sufficiently good for many applications. Yet, the question of model identifiability remains so far unanswered. Therefore, the control strategy of **T1** that is built on model parameter estimates without any guarantee for their uniqueness would not be acceptable for individualized hormone therapy. Thus identifiability of impulsive Goodwin's oscillator will be studied in depth according to the following:

- **T3.1** Establish conditions for identifiability of pulsatile feedback from measured data reflecting the dynamic patterns of the endocrine system under homeostatic regulation. Even for linear systems under pulse-modulated feedback there are no known identifiability results. The recent results of [22] and [23] on identifiability for periodic nonlinear autonomous systems could provide a starting point for this analysis.
- **T3.2** Modify the analysis for Te regulation in [10] to take into account the effects of circadian rhythm and non-basal hormone secretion, see also **T2.4**.
- **T3.3** Develop identification algorithms to distinguish between distributed time delays (finite-memory convolutions), their cascade couplings with pointwise (lumped) delays and finite-dimensional dynamics.

A.4 Significance

This proposal raises new challenging system-theoretical problems motivated by demanding medical applications with significant impact on public health care. A recent overview by VR [24] points out that the borderline between automatic control and biomedicine has received less scope in Sweden, despite the internationally strong standing of automatic control. The project is expected to deliver novel and effective control and system modeling techniques for a class of oscillating hybrid systems and pertaining to: design of non-smooth nonlinear dynamics via bifurcation analysis, theory of systems with intrinsic pulse-modulated feedback, synchronization of hybrid oscillators, hybrid system identification, identification of systems with distributed and pointwise delays. The results will be of general character and mathematical in form, thus relevant to many other, also non-biological applications. Underpinned by the existing national and international collaborations with medical researchers, the developed solutions will be clinically tested in independently funded spin-off projects. The expected outcome is individualized endocrine intervention protocols within e.g. hormone replacement therapies, prostate cancer treatments, and treatments of anabolic steroid-induced hypogonadism.

A.5 Research Environment

During the last seven years, biomedical systems and signals research has become a dominating topic at the Division of Systems and Control, Information Technology, Uppsala University and has a high international standing. More than 70% of the senior staff are involved full or part time with projects on automatic and automated drug delivery, mathematical modeling of biomedical systems, signal processing for medical imaging, biomechanics, neuroscience, neuromodulation, etc. These activities are well integrated into the strategic development plan of the Department of Information Technology targeting Biomedical Information Technology as one of two priority areas. This is well in line with the strategy at the level of Uppsala University where the infrastructure for Biomedical Engineering and Technology is being set in partnership with Uppsala University Hospital.

A.6 Preliminary results

The mathematical model of impulsive Goodwin's oscillator was proposed by the project group in 2006, see [25]. The concept has become a game changer in mathematical modeling of biological oscillators due to the following crucial properties:

- It does not possess equilibria, while sustaining oscillations is a main concern in the classical version of Goodwin's oscillator;
- It explicitly implements the biologically motivated mechanism of pulse-modulated feedback that is the key element in merging continuous metabolism with primarily episodic neural activity in endocrine regulation;
- It successfully validates through system identification [26; 16] on clinical data of measured Te and LH concentrations in the human male;
- It exhibits significant robustness against time delay in the closed-loop, which property is consistent with the biological purpose of the regulation mechanism.

Within the scope of the present proposal, the main theoretical achievements stand as follows:

- Novel analysis tools based on discrete Poincaré maps have been developed for capturing and studying the hybrid dynamics of impulsive Goodwin's oscillator [10; 27];
- The proposed Poincaré maps have been instrumental in bifurcation analysis of complex nonlinear dynamics, revealing the occurrence of such phenomena as cycles of high periodicity, deterministic chaos [12], multistability, and quasi-periodical behaviors. In fact, there is compelling biological evidence of low-order chaotic attractors in endocrine systems;
- Hybrid observers estimating the firing times and weights of the pulse-modulated feedback have been developed based on the model with finite-dimensional [21] and infinite-dimensional continuous part [28].
- Analysis of the delay-induced effects on the dynamics of impulsive Goodwin's oscillator has been performed both for poinwise and distributed delays. The key findings are the following: The cascade structure of the continuous part of the model renders so-called "finite-dimensional reducibility" that significantly simplifies the analysis. All time delays under the least interval between the consecutive feedback firings do not

result in a new nonlinear behavior. The Poincaré map for an impulsive Goodwin's oscillator with a delay over this value is non-smooth.
- New results on identifiability of nonlinear systems in self-sustained oscillations have been developed in [22].

Being individualized by the identification methods in [16], the model closely follows the actual (closed-loop) endocrine data, cf. Fig. 2.

The theoretical and applied work of the project group on impulsive Goodwin's oscillator has been appreciated by both the control community and specialists in endocrinology. An anonymous reviewer of [15] has responded as "The theoretical contribution of the paper has major implications for the understanding of various biological mechanisms and, subsequently, for their control". Altogether, related to the topic of this proposal, eight journal papers, 25 conference papers, and one book chapter have been published. Four journal papers are submitted of which three are papers invited by Editors based on publications in conference proceedings.

Systems and Control at Uppsala University has a internationally prominent position in the fields of mathematical modeling of endocrine system, model-based automatic drug delivery, and biomedical signal processing. Numerous publications in leading control and signal processing journals are indicative of high research quality. Established national and international collaborations and joint publications with physicians and medical researchers are instrumental in safeguarding the clinical relevance and impact of the performed research.

A.7 International and national collaboration

In the fields of nonlinear, non-smooth, and hybrid dynamics, the project group enjoys close collaboration with Prof. Churilov (Saint Petersburg State University), Prof. Zhusubaliev (South West State University), Prof. Mosekilde (Technical University of Denmark). Within Uppsala University, a cooperation with Prof. Tucker, Department of Mathematics, has been initiated. The planned project activities will be discussed in workshops and seminars of U4 Group (`www.u4network.eu`) 'Biological Oscillators", established together with Prof. Cao (University of Groningen) and Prof. Aeyels (University of Ghent). An extra international dimension in dissemination of project results is added by IEEE Technical Committee on Systems Biology and IEEE Technical Committee on Medical and Healthcare, where the PI of this proposal is invited member and founding member, respectively.

The practical and societal impact and outreach of this research program are highly dependent on the availability of medical data, clinical experiments, and the dialogue with physicians and biologists. Although the research program does not directly include medical research, it will be underpinned and enabled by parallel and spin-off activities carried out by cooperating researchers in medicine engaged in independently funded theoretical and clinical projects. Currently, a clinical study on treatments of anabolic steroid-induced hypogonadism at Endocrinology Clinic of Karolinska Institute, Huddinge, under direction of its Head Dr. Arver, is being planned.

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Interdisciplinarity

My application is interdisciplinary

☐

An interdisciplinary research project is defined in this call for proposals as a project that can not be completed without knowledge, methods, terminology, data and researchers from more than one of the Swedish Research Councils subject areas; Medicine and health, Natural and engineering sciences, Humanities and social sciences and Educational sciences. If your research project is interdisciplinary according to this definition, you indicate and explain this here.

Click here for more information

Scientific report

Scientific report/Account for scientific activities of previous project

Project title: ”Mathematical modeling, analysis and estimation in endocrine systems with pulse-modulated feedback.”

Budget: 2.550.000 SEK

Project period: 2013-01-01—2015-12-31

Systems and Control at Uppsala University has an internationally prominent position in the fields of mathematical modeling of endocrine system, model-based automatic drug delivery, and biomedical signal processing. Numerous publications in leading control and signal processing journals are indicative of high research quality. Established national and international collaborations and joint publications with physicians and medical researchers are instrumental in safeguarding the clinical relevance and impact of the performed research.

During the past decade, with the funding provided by SysTEAM Advanced Grant from ERC (2010-2014) and individual grants from VR, the project group has had a sustained research activity in the area of biomedical system modeling, control, and signal processing. Currently, 17 researchers are involved full or part-time in biomedical projects at Systems and Control, UU. Within the scope of the present report, the main achievements stand as follows:

- A mathematical model for pulsatile endocrine regulation by pulse-modulated feedback is developed and its dynamical properties are extensively explored with novel analysis tools based on Poincaré mappings.
- For the case of testosterone regulation, the model is shown to explain numerous biological facts such as the signal form and type of hormone concentration temporal profiles as well as empirically observed chaotic behaviors.
- Being individualized by the identification methods developed in the project, the model closely follows the actual (closed-loop) endocrine data. It is the only closed-loop model of testosterone regulation that is validated on clinical data.
- Tools for analyzing the impact of pointwise and distributed time delays on the closed-loop dynamics of the mathematical model have been devised and successfully applied to testosterone regulation case with small and large time delays.
- It has been shown that once the delay value surpasses the least interval between the feedback pulses, the corresponding Poincaré mapping becomes non-smooth, which phenomenon results in completely new range of complex dynamical behaviors such as multistability and quasiperiodicity.
- Hybrid observers estimating the firing times and weights of the pulse-modulated feedback have been developed based on the model with finite-dimensional and infinite-dimensional kinetics.

The proposed research program is aimed at maintaining and enhancing the internationally leading research profile in biomedical systems established by the project group. The current proposal is a logical continuation of this line of research that makes use of the already developed tools and takes them further in order to solve control problems in endocrine systems.

The concept of biological (endogenous) feedback is central in explicating the way in which nature sustains biological function in a living organism. Feedback malfunction often manifests itself in a disease or disorder. Furthermore, exogenous feedback is instrumental in computer-assisted medical treatments as well as in data processing for diagnostics and staging of disease. Dosing (titration) of medication can also be cast as an exogenous feedback incorporating quantification of symptoms and medical decision making. A recent overview by VR points out that the borderline between automatic control and systems biology has received less scope in Sweden, despite the internationally strong standing of automatic control.

Control of hybrid oscillators subject to intrinsic pulse-modulated feedback has never been addressed before. The problems arising in this area akin to those in oscillators in general (networks of firing neurons, Kuromoto oscillators, Goodwin's oscillators) and can be formulated as entrainment and synchronization. Those already challenging research topics become even more complicated when the involved oscillators exhibit hybrid dynamics.

Budget and research resources

Project staff

Describe the staff that will be working in the project and the salary that is applied for in the project budget. Enter the full amount, not in thousands SEK.

Participating researchers that accept an invitation to participate in the application will be displayed automatically under Dedicated time for this project. Note that it will take a few minutes before the information is updated, and that it might be necessary for the project leader to close and reopen the form.

Dedicated time for this project

	Role in the project	Name	Percent of full time
1	Applicant	Alexander Medvedev	30
2	Participating researcher	Torbjörn Wigren	20
3	Other personnel without doctoral degree	Diana Yamalova	80
4	Other personnel without doctoral degree	Per Mattsson	80

Salaries including social fees

	Role in the project	Name	Percent of salary	2016	2017	2018	Total
1	Applicant	Alexander Medvedev	30	334,350	334,375	334,400	1,003,125
2	Other personnel with doctoral degree	Torbjörn Wigren	20	222,750	222,775	222,800	668,325
3	Other personnel without doctoral degree	Diana Yamalova	80	415,800	415,810	418,815	1,250,425
4	Other personnel without doctoral degree	Per Mattsson	80	418,830	0	0	418,830
5	Other personnel without doctoral degree	Ny doktorand	80	0	415,500	415,800	831,300
	Total			1,391,730	1,388,460	1,391,815	4,172,005

Other costs

Describe the other project costs for which you apply from the Swedish Research Council. Enter the full amount, not in thousands SEK.

Premises

	Type of premises	2016	2017	2018	Total
1	kontorsrum, 30%	12,000	12,000	12,000	36,000
2	kontorsrum, 20%	8,000	8,000	8,000	24,000
3	doktorandkontor, 80%	20,000	20,000	20,000	60,000
4	doktorandkontor, 80%	20,000	20,000	20,000	60,000
	Total	60,000	60,000	60,000	180,000

Running Costs

	Running Cost	Description	2016	2017	2018	Total
1	Resor	konferenser	75,000	75,000	75,000	225,000
2	Datorer		20,000	10,000	10,000	40,000
3	Mjukvara		10,000	10,000	10,000	30,000
	Total		105,000	95,000	95,000	295,000

Depreciation costs

Depreciation cost	Description	2016	2017	2018

Total project cost

Below you can see a summary of the costs in your budget, which are the costs that you apply for from the Swedish Research Council. Indirect costs are entered separately into the table.

Under Other costs you can enter which costs, aside from the ones you apply for from the Swedish Research Council, that the project includes. Add the full amounts, not in thousands of SEK.

The subtotal plus indirect costs are the total per year that you apply for.

Total budget

Specified costs	2016	2017	2018	Total, applied	Other costs	Total cost
Salaries including social fees	1,391,730	1,388,460	1,391,815	4,172,005		4,172,005
Running costs	105,000	95,000	95,000	295,000		295,000
Depreciation costs				0		0
Premises	60,000	60,000	60,000	180,000		180,000
Subtotal	1,556,730	1,543,460	1,546,815	4,647,005	0	4,647,005
Indirect costs	449,019	445,038	446,044	1,340,101		1,340,101
Total project cost	2,005,749	1,988,498	1,992,859	5,987,106	0	5,987,106

Explanation of the proposed budget

Briefly justify each proposed cost in the stated budget.

Explanation of the proposed budget*

The project is led by two senior researchers A. Medvedev who will be involved 30% of time and T. Wigren who will spend 20% on it. Two PhD students are already participating in the project activities but P. Mattsson will defend his PhD thesis during 2016. A new PhD student will take his places. Two or three conference trips are planned each year targeting high-quality fora such as CDC/ACC/ECC. Computer costs are inflicted by the laptops to be purchased for the group members.

Other funding

Describe your other project funding for the project period (applied for or granted) aside from that which you apply for from the Swedish Research Council. Write the whole sum, not thousands of SEK.

Other funding for this project

Funder	Applicant/project leader	Type of grant	Reg no or equiv.	2016	2017	2018

CV and publications

CV

I PERSONAL DATA

Name:	Alexander Medvedev
Date of birth:	18 of June 1958
Citizenship:	Swedish
Living address and telephone number:	Junkervägen 11A, 187 36 Täby +46 8 768 40 21

II Employment

Position	*Employer*	*Period*
Professor	Uppsala University	October 2001– present
Professor	Luleå University of Technology	January 1998- April 2003
Acting Professor	Luleå University of Technology	October 1996 - December 1997
Associate Professor	Luleå University of Technology	September 1991-September 1996
Visiting Professor	Åbo Akademi	September 1990 - August 1991
Associate Professor	Leningrad Electrical Engineering Institute (LEEI)	January 1991 - August 1991
Assistant Professor	LEEI	1982-1991
System Programmer	LEEI	1981-1982

III Education

Degree	*University*	*Year*
Ph. D., Control Engineering	LEEI	1987
M. Sc. *cum laude* Automatic and Remote Control	Leningrad Electrical Engineering Institute (LEEI)	1981

IV Academic titles

Title	*University*	*Year*
Professor, Control Engineering	Uppsala University	2002
Professor, Control Engineering	Luleå University of Technology	1998
Docent, Control Engineering	Luleå University of Technology	1996
Docent, Control Engineering	LEEI	1991

V Formerly supervised doctoral students

Name	*University*	*Year, PhD*	*Year, Lic*
Olov Rosén	Uppsala University	2015	2013
Margarida Silva	Uppsala University	2014	
Egi Hidayat	Uppsala University	2014	2012
Magnus Evestedt	Uppsala University	2007	2005
Mikael Stocks	Luleå University	2006	2002
Claes Olsson	Uppsala University	2005	
Benny Stenlund	Luleå University		2002
Michael Bask	Luleå University		2001
Wolfgang Birk	Luleå University	2002	1999
Andreas Johansson	Luleå University	2001	1999
Britta Fischer	Luleå University	1999	1997
Caj Zell	Luleå University		1996

Main supervisor for 4 PhD students at Uppsala University. One is to obtain PhD in the fall of 2015.

VI Publications

Author and co-author of more than 220 peer reviewed journal and conference papers.

VII Awards

Co-PI to Petre Stoica in an Advanced Grant from European Research Council; Best Paper Award from IEEE-sponsored 6th International Congress on Ultra Modern Telecommunications and Control Systems, Saint Petersburg, Russia, October 2014; A PhD student of mine received Best Student Paper Prize from International Symposium on Computational Models in Life Sciences, Sydney, Australia, November 2013.

VIII Editorial boards

Member of Editorial Board	EURASIP Journal on Signal Processing and Bioinformatics	Springer	2009 - until now
Member of Editorial Board	International Journal of Systems, Signals, Control and Engineering Applications	Medwell Journals Publishing	2008
Member of Editorial Board	Automation Technology in Practice	Oldenbourg Verlage, Germany	2005

IX Other

External expert to appointment boards (”sakkunnig”) Research fellowship in Automatic Control, Luleå University of Technology, 2013; Professorship in Automatic Control, Linköping University, 2013; Research fellowship in Automatic Control, Chalmers University of Technology, 2010; Professorship in Automatic Control, Royal Institute of Technology, 2009; Readership in Automatic Control, Lund University, 2008; Professorship in Network-based Automatic Control, Royal Institute of Technology, 2006; Professorship in Control Engineering, Linköping University, 2002; Professorship in Mechatronics, Chalmers University of Technology, 2001.

Opponent at PhD thesis defense Luleå University of Technology, automatic control, 2011; Åbo Akademi, automatic control, 2009; Royal Institute of Technology, Electrical machines and Power Electronics, 2006; Lund University, industrial automation, 2002; Åbo Akademi, heat engineering, 2002; Chalmers University of Technology, control engineering, 1999.

Opponent at Licentiate thesis defense Linköping University, vehicle technology, 2013; Luleå University of Technology, automatic control, 2013; Linköping University, control engineering, 2006; Linköping University, control engineering, 2002; Lund University, computer science, 2000; Åbo Akademi, heat engineering, 2000.

Member of examination board (”betygsnämnd”) Chalmers University of Technology: 2012, 2004, 2003, 2002; Royal Institute of Technology: 2011, 2008; Uppsala University, 2014, 2008, 2002; Lund University: 2013, 2006; Karlstad University: 2004; Linköping University: 2015, 2014, 2013, 2003; Mälardalen University: 2014, 2002; Luleå University of Technology: 2000, 1999.

Miscellaneous assignments **International Program Committee member:** Indian Control Conference 2016; IEEE Global Conference on Signal and Information Processing, Orlando, Florida, 2015; 9th IFAC Symposium on Medical and Biological Systems, Berlin, 2015; International Conference on Smart Portable, Wearable, Implantable and Disability-oriented Devices and Systems, Brussels, 2015; **Technical Committee Member:** IEEE Technical Committee on Systems Biology, member, invited by Committee Chair, 2015; IEEE Technical Committee on Medical and Health Care Systems, founding member 2013; **Administrative functions:** Director of program in Automatic Control, Uppsala University, 2013; Professor in charge of the PhD program in Automatic Control, Uppsala University, 2012; Elector for the area Science and Technology, Uppsala University, Deputy elector for the area Science and Technology, Uppsala University, 2007 (three years appointment); Vice chairman of Recruitment Committee, Information technology, Uppsala University, 2006; 2004 (three years appointment); **External Evaluator:** External PhD thesis evaluator (2 theses), University of Jyväskylä, 2013; External evaluator for Executive Agency for Higher Education, Research, Development and Innovation Funding, Romania, 2011-2012; External PhD thesis evaluator, Åbo Akademi, 2009; External PhD thesis evaluator, Åbo Akademi, 2006; External evaluator for a Senior Researcher position of the Swedish Research Council, 2005; National expert for European Commission, spring 2002;

Curriculum Vitae for Torbjörn Wigren

Academic parts

1. M.Sc

Master of Science, Engineering Physics, Uppsala University	1985

2. Ph.D

Doctor of Technology, Automatic Control, Uppsala University, Title: Recursive Identification Based on the Nonlinear Wiener Model. Supervisor: Prof. Torsten Söderström	1990

3. Postdoctoral positions

None.

4. Docent Competence

Docent, Electrical Engineering, Uppsala University	2002

5. Present Academic Employment

Adjunct Professor of Automatic Control, 20%, Uppsala University	2012-2018

6. Previous Academic Employments

Adjunct Professor, Systems Modeling, 20%, Uppsala University	2006-2012
Adjunct Professor, Automatic Control, 20%, Uppsala University	2000-2006
PhD-student, Uppsala University, Department of Automatic Control	1989-1990

7. Interruption in research

None.

8. Supervision

Margarida da Silva (up to Licentiate)	2012

9. Other information of relevance for the application

Academic Awards and Memberships

Outstanding reviewer, Automatica 2010-2011,	2013-05-01
Senior Member AIAA	2009
DARPA Coin 505	2003
Senior Member IEEE	1998

Industrial CV

Present Employment

Systems engineer, Ericsson AB, LMR System, LTE L1 & L2	2014-

Previous Employments

Systems engineer, Ericsson AB, WCDMA RAN Systems, L1	2012-2014
Senior specialist, Ericsson AB, WCDMA RAN Systems, RRM	2010-2012
Systems engineer, Ericsson AB, WCDMA RAN Systems	2001-2010
Staff scientist, SAABTech Electronics AB, automotive radar group	1999-2001
Staff scientist, CelsiusTech Systems AB, sensor data processing group	1995-1999
Research engineer, Ericsson Radio Systems, R&D department	1991-1995
Group manager, Bofors Aerotronics AB, systems section	1990-1991
Group manager, Bofors Aerotronics AB, image processing section	1988
Development engineer, Bofors Aerotronics AB, image processing section	1985-1987

Industrial Awards

Ericsson Key Contributor	2012
Ericsson Key Contributor	2011
Ericsson Key Contributor	2010
Ericsson Inventor of the Year Award (10000 Euro awarded)	2007

Publication list

1 Publications by Alexander Medvedev, 2007-2014

Journal articles

[1] Z. Zhusubaliyev, E. Mosekilde, A. Churilov, and A. Medvedev, “Multistability and hidden attractors in an impulsive Goodwin oscillator with time delay,” *The European Physical Journal Special Topics*, 2015, accepted for publication.

[2] M. Silva, A. Medvedev, T. Wigren, and T. Medonça, “Modeling the effect of intravenous anesthetics: a path towards individualization,” *IEEE Design & Test*, 2015, accepted for publication.

[3] Z. Zhusubaliyev, A. Medvedev, and M. Silva, “Bifurcation analysis of pid controlled neuromuscular blockade in closed-loop anesthesia,” *Journal of Process Control*, vol. 25, pp. 152–163, January 2015.

[4] D. Jansson, A. Medvedev, and O. Rosen, “Parametric and nonparametric analysis of eye-tracking data by anomaly detection,” *IEEE Transactions on Control Systems Technology*, October 2014.

[5] A. Churilov and A. Medvedev, “An impulse-to-impulse discrete-time mapping for a time-delay impulsive system,” *Automatica*, vol. 50, no. 8, pp. 2187–2190, August 2014. *

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[7] O. Rosen, A. Medvedev, and T. Wigren, “Parallelization of the Kalman filter for banded systems on multicore computational platforms,” *Control Engineering Practice*, vol. 21, no. 9, pp. 1188–1194, September 2013.

[8] Z. Zhusubaliyev, A. Churilov, and A. Medvedev, “Bifurcation phenomena in an impulsive model of non-basal testosterone regulation,” *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 22, pp. 013 121–1–013 121–11, 2012. [8 citations] *

[9] A. Churilov, A. Medvedev, and A. Shepeljavyi, “State observer for continuous oscillating systems under intrinsic pulse-modulated feedback,” *Automatica*, March 2012, http://dx.doi.org/10.1016/j.automatica.2012.02.044. [11 citations] *

[10] E. Hidayat and A. Medvedev, “Laguerre domain identification of continuous linear time delay systems from impulse response data,” *Automatica*, vol. 48, no. 11, pp. 2902–2907, November 2012. [13 citations]

[11] O. Rosen and A. Medvedev, “Efficient parallel implementation of state estimation algorithms on multicore platforms,” *Control Systems Technology, IEEE Transactions on*, vol. PP, no. 99, pp. 1 –14, 2011. [7 citations]

[12] A. Medvedev and H. Toivonen, “Directional sensitivity of continuous least-squares state estimators,” *Systems & Control Letters*, vol. 59, no. 9, p. 571–577, 2010. [4 citations]

[13] M. Evestedt and A. Medvedev, “Model-based slopping warning in the ld steel converter process,” *Journal of Process Control*, vol. 19, no. 6, pp. 1000–1010, 2009. [8 citations]

[14] A. Medvedev and M. Evestedt, “Elementwise decoupling and convergence of the Riccati equation in the SG algorithm,” *Automatica*, vol. 45, no. 6, pp. 1524–1529, 2009.

[15] M. Stocks and A. Medvedev, “Linear-quadratic optimal time-varying observers with time-varying guaranteed convergence rate,” *IET Control Theory & Applications*, vol. 3, no. 2, p. 181188, 2009.

[16] Alexander Churilov, Alexander Medvedev, and Alexander Shepeljavyi. Mathematical model of non-basal testosterone regulation in the male by pulse modulated feedback. *Automatica*, 45(1):78–85, 2009. [36 citations]

*

[17] Magnus Evestedt and Alexander Medvedev. Model-based slopping warning in the LD steel converter process. *Journal of Process Control*, 19(6):1000–1010, 2009.

[18] Alexander Medvedev and Magnus Evestedt. Elementwise decoupling and convergence of the Riccati equation in the SG algorithm. *Automatica*, 45(6):1524–1529, 2009.

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Dissertation title (swe)

Dimensionering och utveckling av predikterande regulatorer för system med tidsfördröjningar

Dissertation title (en)

Design and development of predictive controllers for time-delay systems

Organisation	Unit	Supervisor
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Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
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Dissertation title (swe)

Rekursiv identifiering baserad på den olinjära Wiener modellen

Dissertation title (en)

Recursive identification based on the nonlinear Wiener model

Organisation	Unit	Supervisor
Uppsala universitet, Sweden Sweden - Higher education Institutes	Inst för informationsteknologi	Torsten Söderström

Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
20202. Reglerteknik	91-554-3640-9	1990-12-07

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Medvedev, Alexander has not added any publications to the application.

Publications

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Gender: Male	**Employer:** No current employer

Wigren, Torbjörn has not added any publications to the application.

Register

Terms and conditions

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