TOPICS IN INTELLIGENT ENGINEERING AND INFORMATICS 8

János Fodor
Robert Fullér
Editors

Advances in Soft Computing, Intelligent Robotics and Control

Springer

Topics in Intelligent Engineering and Informatics

Volume 8

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Advances in Soft Computing, Intelligent Robotics and Control

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ISSN 2193-9411 ISSN 2193-942X (electronic)
ISBN 978-3-319-05944-0 ISBN 978-3-319-05945-7 (eBook)
DOI 10.1007/978-3-319-05945-7
Springer Cham Heidelberg New York Dordrecht London

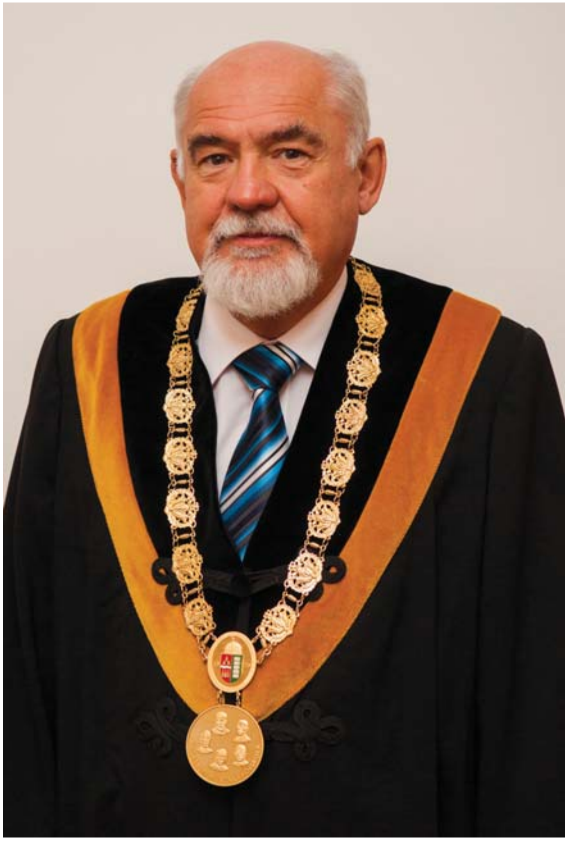
Library of Congress Control Number: 2014934569

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Dedication

The volume is dedicated to Prof. Dr. Imre J. Rudas on the occasion of celebrating his 65^{th} birthday and expressing our respect to his outstanding, high level achievements of 11 years rectorship.



Foreword

I am very pleased to have an opportunity to write a foreword to "Advances in Soft Computing, Intelligent Robotics and Control", dedicated to my esteemed friend, Imre J. Rudas on the occasion of his 65th anniversary. In the course of his long and distinguished career as a researcher, educator and administrator, Imre has contributed importantly to the advancement of our understanding of how to conceive, design and construct intelligent systems. Imre's work makes a skilled use of concepts and techniques drawn from a broad range of methodologies, principally soft computing, fuzzy logic and robotics. Imre is a man of vision and initiative. He is a true leader.

As my tribute to Imre, I should like to share with the readers of this Volume, some of my thoughts and ideas which relate to an issue which underlies much of Imre's work—achievement of human-level machine intelligence. My thoughts and views reflect my long-standing interest in machine intelligence, going back to the beginning of my teaching and research career. The beginning of my teaching and research career coincided with the debut of the computer age and the birth of artificial intelligence. It was my fortune to be able to observe at close distance, and participate in, the advent of the Information Revolution—a revolution which fundamentally changed the way we live and work today.

Back in the late forties and early fifties of last century, there were many exaggerated expectations of what was around the corner. It was widely predicted that human-level machine intelligence would become a reality in a few years' time. In a short paper published in 1950, entitled "Thinking machines—a new field in electrical engineering", I included some of the headlines which appeared in the popular press at that time. One of them read, "Electric Brain Capable of Translating Foreign Languages is Being Built". Today, we have fairly good translation programs, but nothing that can approach the quality of human translation. In 1948, on the occasion of inauguration of IBM's relay computer, Howard Aiken, Director of Harvard's Computation Laboratory, said, "There is no problem in applied mathematics that this computer cannot solve". What is remarkable is that Aiken made this claim about a relay computer which had a memory of about one thousand words. His claim could not be farther from truth.

Putting exaggerated expectations aside, tremendous progress has been made in our ability to construct machines which can process huge volumes of information at high speed and with high reliability. But achievement of human-level machine intelligence remains a challenging problem. In what follows, I will briefly address a basic question: Why achievement of human-level machine intelligence proved to be a much more difficult problem than it was thought to be at the dawn of the computer age?

Humans have a remarkable capability to reason with information which is imprecise, uncertain and partially true. In large measure, today's computers employ the classical, Aristotelian, bivalent logic. Bivalent logic is intolerant of imprecision and partiality of truth. It is my conviction that to simulate human reasoning, it is necessary to employ a logic in which the objects of reasoning and computation are classes with unsharp (fuzzy) boundaries. Bivalent logic is not the right logic for reasoning and computation with objects of this type. What is needed for this purpose is fuzzy logic. Basically, fuzzy logic is a system of reasoning and computation in which the objects of reasoning and computation are classes with unsharp (fuzzy) boundaries. In my view, human-level machine intelligence cannot be achieved without the use of fuzzy logic. What should be underscored is that this view is at variance with conventional wisdom.

A Litmus test of human-level machine intelligence is natural language understanding. In large measure, existing approaches to natural language understanding are based on bivalent logic and probability theory. In a natural language, a word, w, is typically a label of a class with unsharp (fuzzy) boundaries. In this sense, almost all words in a natural language have a fuzzy meaning. Examples. Tall, fast, heavy, beautiful, likely, etc. There are two choices in representing the meaning of a fuzzy word. First, as a probability distribution; and second, as a fuzzy set or, equivalently, as a possibility distribution. A problem which arises is: If the meaning of a word, w, is represented as a probability distribution, then not w cannot be represented as a probability distribution. By contrast, if the meaning of w is represented as a possibility distribution, then the meaning of not w is a possibility distribution which is very simply related to the possibility distribution of w. A more complex problem is that of composing the meaning of a proposition from the meanings of its fuzzy constituents. Traditional approaches to semantics of natural languages do not have this capability. Fuzzy logic has this capability because it is designed to compute with classes which have unsharp (fuzzy) boundaries.

In conclusion, I believe that to achieve human-level machine intelligence it will be necessary to employ fuzzy logic. This does not mean, however, that the use of fuzzy logic will necessarily lead to achievement of human-level machine intelligence. Many other problems will have to be solved. What is my conviction is that without the use of fuzzy logic, human-level machine intelligence cannot be achieved. As was stated earlier, this view is at variance with conventional wisdom. History will judge who is right.

The editors, Professors János Fodor and Róbert Fullér and the publisher, Springer, deserve our thanks and congratulations for producing a Volume which is a significant contribution to the literature of soft computing, fuzzy logic and robotics.

January 23, 2014

Lotfi A. Zadeh
Berkeley, CA

Preface

Soft computing, intelligent robotics and control, and some applied mathematical aspects – the main subjects of this volume – are in the core of interest of an illustrious and successful scientific researcher, an exceptional leader, and an incredibly great man. He is Professor Imre J. Rudas, the Rector of Óbuda University, Budapest, Hungary. He becomes 65 this April, and this fact motivated us to edit this volume. This is a token of appreciation and friendship of his colleagues, students and friends.

Professor Rudas's achievements are long-lasting both in science and in leadership. Because of space limitations we mention just a few facts and figures from his rich oeuvre. He has published more than 700 papers in books, scientific journals, and peer reviewed international conference proceedings, delivered more than 50 plenary talks at international conferences, and received more than 2000 independent citations for his publications. He founded Acta Polytechnica Hungarica, an international peer-reviewed scientific journal, which started to own impact factor after 6 years of its existence. He is the founder of seven IEEE sponsored international conference and symposium series. He is the only rector in the Hungarian higher-education who could establish a new university (Óbuda University) by upgrading an existing institution (Budapest Tech), through the fulfillment of high standards.

For those who do not know professor Rudas personally, we would like to picture him with the help of two appraisals.

Gyula Sallai (professor, Budapest University of Technology and Economics) writes as follows:

> "Imre J. Rudas is a prominent, distinguished personality of the Hungarian higher education, whose thoughts concentrate on strengthening the reputation and professional success of the organization directed by him, who is a strategist, professor and team builder in one person, who catches with keen insight:
>
> – the strategic opportunities,
> – the prospective breakthroughs in scientific research and
> – the effective professionals that can make stronger his team;

who establishes success of his institutional plans, and realizes them by

– firm faith, focusing on the objectives,
– carrying his smaller and larger collectives with him and
– receiving with recognition of the Hungarians within and beyond the frontier, and the wider international community;

who, nevertheless remains the man at all times, with whom it is good to be together, to turn an idea over in our mind or devise a plan, and to drink a glass of good wine."

János Dusza (professor at Óbuda University, Member of the Presidium of the Slovak Academy of Sciences, External Member of the Hungarian Academy of Sciences) writes:

"I first met Professor Rudas in 2011 in Kosice, Slovakia. Kosice is not just a city I call home but also where Prof. Rudas received his first Doctor Honoris Causa degree, conferred on him by the Technical University of Kosice.

I was, prior to our first meeting, very aware of his reputation as an internationally recognized expert in the field of computational cybernetics, robotics with special emphasis on robot control, fuzzy control and fuzzy sets.

Being a scientist active in the field of advanced ceramics and coatings, I was concerned that we would find little of common scientific overlap. I was delighted to find that not only were there many conversational topics we enjoyed discussing, but the possibility of future collaborative projects also became obvious.

At first, it was the interdisciplinary research into the field of robotics with regard to advanced materials with exceptional tribological properties. Professor Rudas's overview, knowledge of the initial problems and further collaborative suggestions were particularly welcome and greatly appreciated.

Secondly it was the management of education and research. Without hesitation, I would say that Professor Rudas's understanding, foresight and experience in strengthening his University's core ethos and reputation during his leadership was unsurpassed in anyone I had met before, or since.

The third area was in international collaboration. He provided strong support to many young scientists and members of the Hungarian scientific community in the Carpathian Basin and throughout the world. I highly appreciate these activities and I am very happy to have been personally involved.

I would particularly like to emphasize Professor Rudas's ability to see unrecognized skills and talents in others and his desire to ensure that each individual's potential is fully realized.

Only our personal friendship has meant more to me than our work together and I look forward to developing both in the future."

The present volume is a collection of 20 chapters written by respectable experts of the fields. Professor Rudas's wide spectrum of interests is reflected in the variety of these contributions, dealing with three major topics.

The first part of the book addresses issues of intelligent robotics, including robust fixed point transformation design, experimental verification of the input-output feedback linearization of differentially driven mobile robot and applying kinematic synthesis to micro electro-mechanical systems design.

The second part of the book is devoted to fundamental aspects of soft computing. This includes practical aspects of fuzzy rule interpolation, subjective weights based meta learning in multi criteria decision making, swarm-based heuristics for an area exploration and knowledge driven adaptive product representations.

The last part concerns with different problems, issues and methods of applied mathematics. This includes perturbation estimates for invariant subspaces of Hessenberg matrices, uncertainty and nonlinearity modelling by probabilistic metric spaces and comparison and visualization of the DNA of six primates.

The editors are grateful to the authors for their excellent work. Thanks are also due to Dr. Péter Kárász for his editorial assistance and sincere effort in bringing out the volume nicely in time.

We do hope that readers will benefit from the content of this volume, and will find it intellectually stimulating and professionally rewarding.

January 27, 2014

János Fodor
Robert Fullér
Budapest, Hungary

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Part II: Soft Computing

Part III: Applied Mathematics

Model-Based Disease Treatment: A Control Engineering Approach

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Abstract. Computer engineering opens new ways in healthcare including a more exact treatment possibility of different diseases. By modeling the disease and using control engineering methods it is possible to refine the treatment, but also to seek for optimal solutions/therapies. The current work summarizes the results of model-based disease treatment researches in the field of physiological modeling and control carried out at the Physiological Controls Group of the Obuda University. The developed and presented optimal algorithms and strategies focus on three diseases with high public health impact: diabetes (the artificial pancreas problem), obesity (predicting obesity-related risks) and cancer (antiangiogenic therapy). The studies are done in strong collaboration with different Hungarian hospitals, from where measurement data were obtained.

1 Introduction

Development of computer science, control engineering and measurement theory gives the possibilities of the biomedical engineering interdisciplinary research field to spread. The aim of physiological control–a subdiscipline of biomedical engineering [1]–is to study, model and apply identification and control strategies in order to understand and help automated treatment of various diseases or injuries of the human body.

In many biomedical systems, external controllers provide biosignal input / inject given specific dosage substituting the internal, physiological procedure because patient's body cannot ensure it / produce it. The outer control might be partially or fully automated. The regulation has several strict requirements, but once it has been designed, it permits not only to facilitate the patient's life, but also to optimize (if necessary) the amount of the used dosage. The newly formed Physiological Controls Group of the Óbuda University together with the Control Engineering and Information Technology of the Budapest University of Technology and Economics and the Semmelweis University from Budapest are investigating the mentioned problem.

The current work summarizes three of our research tasks connected to modeling and control of diseases with high public health impact: diabetes, obesity and cancer [2].

J. Fodor and R. Fullér (eds.), *Advances in Soft Computing, Intelligent Robotics and Control,* Topics in Intelligent Engineering and Informatics 8,
DOI: 10.1007/978-3-319-05945-7_3,

Diabetes is named by the World Health Organization (WHO) as the "disease of the future" [3]. Statistics of the International Diabetes Federation (IDF) show that the European Region has the highest number and the highest incidence rate of type 1 diabetes (T1DM) in children from any other region worldwide [4]. Diabetes is diagnosed if for some reasons the human body is unable to control the normal glucose-insulin interaction (e.g. glucose concentration level is constantly out of the 70-110 mg/dL range). The consequences of diabetes are mostly long-term: cardiovascular diseases, neuropathy, retinopathy [5]. Hence, diabetes is a serious metabolic disease, which should be artificially controlled, and from engineering point of view its treatment can be represented by an outer control loop, to replace the partially or totally deficient blood glucose control system of the human body. Our approach was to design robust optimal control algorithms to maintain the normoglycaemic blood glucose range and in this way to extend the applicability of individualized therapies formulated in the literature [6].

Obesity is named by the WHO the "disease of today" as it is considered an endemic in the most part of the developed world [7]. In Hungary, according to [8], 1.5 million Hungarian are definitely obese, whilst an additional 2.7 million can be considered overweight. Together, this is almost the half of the Hungarian population. In the last few decades, increased occurrence of several morbidities were casually linked to obesity, such as non-insulin dependent diabetes mellitus (T2DM), stroke, ischemic heart disease (IHD), immunological and reproductive dysfunctions and certain neoplasms [9]. From these, stroke and IHD is amongst the first three in the list of mortality rates in Hungary [10]. These all confirm that obesity poses a significant risk. Hence, early intervention is needed to prevent the onset of obesity and obesity-associated comorbidities. Early, focused intervention presumes however an efficient screening method which can select those people who are prone to obesity even when they are healthy otherwise. Hence, our approach focused on the investigation of new ways in which obesity-related risks can be assessed.

Regarding the third mentioned disease, *cancer* is one of the most destructive illness nowadays, which is lethal in most cases. According to recent statistics, 1.3 million people of the European Union is estimated to die from cancer in 2013 [11]. Unfortunately, Hungary is the leading country of the European Union (and also in top ten in the world) in mortality data of all types of cancer [12,13]. There are classical therapies, such as chemotherapy and radiation therapy, but chemical agents and ionizing radiation have effects on certain healthy cells of the patient as well. Treatments which are based on specific molecules that target a signalling pathway in the growth and development of a tumor cell are called targeted molecular therapies (TMTs). Antiangiogenic therapy [14] is a type of TMTs, which inhibits angiogenesis (forming new blood vessels). Preventing tumor cells from grow and develop, the tumor can be kept in a dormant state, where the cellular proliferation rate balanced by the apoptotic rate, thus the tumor will be unable to grow in size beyond a few milimeters [14]. Consequently, our aim was to combine the advantages of control theory with the antiangiogenic therapy in order to optimize the treatment.

2 Modern Robust Control Algorithms for Type 1 Diabetes

The quest for artificial pancreas can be structured in three different tasks [6]: continuous glucose sensor for measurements, insulin pump for infusion and control algorithm problem.

To design an appropriate control, an adequate model is necessary. From the many models appeared in the literature [15] and the wide palette of control strategies [6], it become evident that modeling of the glucose-insulin system and controlling its behavior are two tightly connected questions that cannot be separated. Model predicted control proved to be an efficient solution for individualized treatment of type 1 diabetes [6], but due to insulin sensitivity and patient variability hard constraints are also beneficial [16,18].

Hence, we have focused on one of the most complex model (the Sorensen-model) [17] and developed a nonlinear model based robust control algorithm [18]. The nonlinear model-based approach was realized using LPV (Linear Parameter Varying) methodology capturing the validity of the Sorensen-model inside a polytopic region and building up the LPV model as a linear combination of the linearized models derived in each polytopic point [18,19].

The LPV based robust controller was developed to minimize the meal disturbance level over the performance output for all possible variation of the parameter within the determined polytope:

$$\min_K \|G\| = \min_K \sup_{\varrho \in F_p} \sup_{\|d\| \neq 0} \frac{\|z_{y1}\|}{\|d\|}, \tag{1}$$

where d denotes the meal disturbance input and z describes the glucose variation. G represents the transfer function of the system and K the H_∞ controller in question. A priori information is injected to the controller throughout the augmentation of the nominal plant (Fig. 1) with extra dynamics, called weighting functions and Δ unstructured uncertainty blocks [18,19]:

- W_p the performance weighting function;
- W_m the disturbance (glucose) input weighting function;
- W_i, W_{im} the input multiplicative uncertainty weighting functions;
- W_u the control input weighting function;
- W_o the output multiplicative uncertainty weighting function;
- W_{n1}, W_{n2} the sensor noise weighting functions.

During the H_∞ control design and using γ-iteration algorithm, based on the weighing functions presented in [18], $\gamma = 1.0096$ solution was obtained (the tolerance for the algorithm was set to 0.01).

During the controller design sensor noise and input and output multiplicative uncertainty were taken into account. The obtained γ value represents the upper limit of the robust performance criterion, which means that the formulated system requirements are quite severe. However, this could be an advantage in the

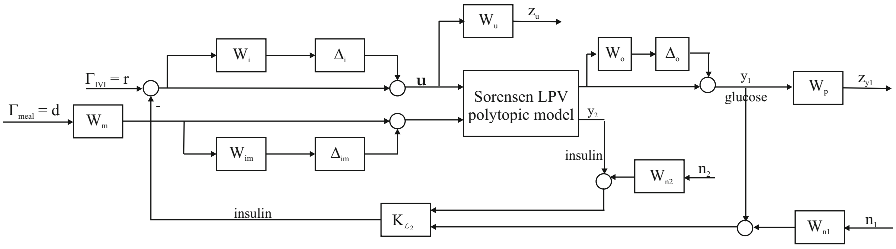

Fig. 1. The augmented nonlinear model based robust control system

validation process. Simulations were tested on the reference value taken from the literature, and proven that hyperglycaemia is avoided [18,19].

Consequently, in the next validation step the obtained controller was tested on real patient data, by using glucose absorption of the well-known and largely approved model of [20].

Minimum 1 week's real data of 83 type 1 diabetic patients (aged between 6–52 years) obtained from different insulin pump centers of Hungary were taken under investigation [21] using real data obtained from Medtronic's insulin pumps. In all of the cases hypoglycemia is avoided and less hyperglycemic episodes can be observed (77.16% less then in case of clinically measured (real) data). It also turned out that blood glucose values were kept 94.6% in the 3.9-7.8 mmol/L normoglycaemic interval [21].

From the investigated cases, results of one case are presented in the following. Fig. 2 compares results of three days of the developed controller with real data of a 43 year old woman (she is on insulin pump for three years being noted with moderate compliance). It can be seen that the output of the controller kept the blood glucose level almost all the time in the normal 3.9-7.8 mmol/L range, avoiding hypoglycemic episodes.

3 Laboratory Results Based Automatic Classification of Obesity in Adolescents

Measuring and predicting obesity and overweight is a complex task, hindered significantly by the varying definitions. However, it is accepted that both states are characterized by elevated quantities of fat tissue, but we are still lacking exact, strict, widely used diagnostic criteria.

While indirect indicators, such as body mass index (BMI) or waist circumference (WC) are widely used [22], their predictive power is limited and they are especially unfit to predict obesity-related risk. Direct indicators, such as dual-emission X-ray absorptiometry (DXA) or bioelectric impedance analysis can precisely characterize fat distribution on the other hand, giving a sound estimation of obesity-related risk. However, they are simply unfit for screening in wider populations, mostly due to radiation exposure they cause and their expensiveness [23].

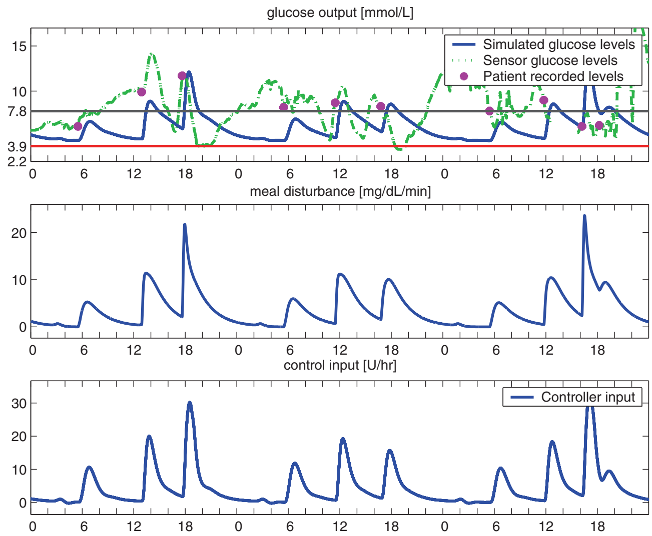

Fig. 2. Comparison of simulated robust controller output (solid line) and sensor real data (dashed line) using absorption scenario of [7]. Blood glucose levels measured from fingertips (dots) are also shown.

Hence, our aim was to resolve this problem by investigating new ways in which obesity-related risks can be assessed. The combination of usual clinical techniques (anthropometric measurements, laboratory parameters) and bioelectric impedance analysis were taken into account. The research is focused on adolescent population (aged 14-18 years) being the optimal target population on which early intervention could and should be performed to best prevent the adverse health consequences. The project included a multicenter clinical study of healthy and obese population. Such study has not yet been performed on Hungarian adolescent population from this aspect.

The study included the recording of routine blood test parameters of both obese and healthy subjects. The question rose whether these parameters could be used to discriminate the two groups. We have collected data from $n = 393$ adolescents, including both healthy and obese ones during our study [24].

The healthy control group consisted of volunteers from several Hungarian secondary schools. Every involved child participated with full written informed consent and the study was pre-authorized by the Hungarian Regional Bioethical Commission. Participants were required to show up for fasting examination early in the morning.

Examinations of the healthy volunteers included anthropometrical measurements, body composition analysis (with InBody 3.0 multi-frequency bioelectric impedance analyzer), blood sample drawing for standard laboratory parameters and recording of anamnesis. Measurements were carried out by doctors and nurses of the Heim Pál Children's Hospital, Budapest, Hungary [25].

The obese group consisted of children treated in the Heim Pál Children's Hospital, with their main diagnosis being E66.9 (according to ICD-10) "Obesity, unspecified", with no comorbidity or significant other illness.

We have performed a complex statistical analysis on the recorded parameters with special focus on the 27 laboratory variables. Statistical analysis was performed with R statistical program package (version 2.9.0), including custom scripts. Additional calculation was done with PASW/SPSS (version 18.0) and gretl (version 1.8.7) statistical program packages. Univariate and multivariate analysis was performed. We have investigated the distributions of the different laboratory results and we have examined the effect of obesity on them. It was shown that many laboratory parameter significantly differ according to state; we have interpreted these differences from the medical point of view [25].

Cluster Analysis and Principal Component Analysis (PCA) / Factor was also performed [25,26]. They allowed us to group the laboratory values into well-separated groups: RBC (Red Blood Cells) count, hemoglobin and hemotocrit formed the "macroscopic RBC descriptors" cluster; MCV (Mean Cell Volume) and MCH (Mean Cell Hemoglobin) the "microscopic RBC descriptors" cluster; liver enzymes GOT, GGT and GPT can also be grouped in separate cluster, while absolute neutrophil granulocyte count, absolute monocyte count and CRP formed the "inflammation" cluster; finally serum sodium and serum chloride grouped the "inorganic serum components" cluster, while serum total protein and serum albumin formed the "organic serum components" one. Many interesting observation can be made by comparing such correlational connections between healthy and obese subjects, for example total cholesterol and triglyceride levels are associated with the "macroscopic RBC descriptors" group in healthy children, but are moving largely independently from that in obese subjects [25].

Finally, logistic regression was applied in order to model our investigations about the discriminatory power of laboratory results, now in a multivariate sense. In case of males, the final model used only 6 variables and had an overall classification rate of 89.6%. (Negative predictive value: 89.0%, positive predictive value: 90.3%.) In case of females, the logistic regression classification model even topped the male ones: it used only 5 variables, and still had an overall classification rate of 87.7%. (Negative predictive value: 87.9%, positive predictive value: 87.5%.) This model is given in Table 1 as an example [25,26].

Table 1. Logistic regression model to classify females into obese/healthy groups

	β	S.E.	Wald	df	Sig.	$\exp(\beta)$
RBCCount	2.367	1.099	4.641	1	0.031	10.669
MCV	0.188	0.123	2.348	1	0.125	1.207
MCH	−0.975	0.311	9.834	1	0.002	0.377
CRP	0.281	0.105	7.171	1	0.007	1.324
Triglycerides	2.593	0.748	12.026	1	0.001	13.364
Constant	−3.020	9.720	0.097	1	0.756	0.049

4 Optimal Control of Tumor Growth Using Antiangiogenic Chemotherapy

Clinical aspects of angiogenic inhibition are discussed more detailed in [27] and [28]. A model for tumor growth under angiogenic inhibition was presented in [29], and validated using experiments on mice with lungs cancer. This model represented the starting point of the model-based antiangiogenic investigations giving direct connection to control theory. Optimal bang-bang control was designed on a simplified model in [30]. Anti-angiogenic therapy combined with radiotherapy was discussed in [31].

The model of [29] meant the starting point of our research. In antiangiogenic therapy the most efficient drug is endostatin [32]. The disadvantage of the therapy is the high cost of the drug; hence, its utilization should be optimized. As a result, we have started to design optimal model-based cancer algorithms in terms of drug usage.

Optimal control has a wide literature in control theory and date back to the revolutionary work of Pontryagin [33]. It has implications in classical control theory [34], modern control theory [19], soft computing applications [35] or even biomedical applications [36].

The simplified model of [29] and presented in [30] assumed that the tumor volume and the endothelial volume move together. Hence, we went further, and our theoretical investigations on the model proved that we can assume the administered inhibitor concentration by the simple differential equation [37,38]:

$$\dot{g} = -\lambda_3 g + u \tag{2}$$

where g is the administered inhibitor concentration, λ_3 is the drug's clearance, and u is the inhibitor administration rate. In this way the Dirac delta type rates, which means that the drug was given to the patient in the form of injections was changed by step function input types corresponding to infusion treatment. These assumptions were demonstrated by symbolic computations made on steady state and dynamic analysis [39].

Tumor growth can be examined on Fig. 3 where the simulation starts from $x_1 = 200\ \text{mm}^3$ tumor volume, $x_2 = 200\ \text{mm}^3$ endothelial volume and the control input $u = 0$ for the whole time during the simulation [38].

The tumor grows rapidly in the first two months then reaches its steady-state in about four months. The endothelial cell volume grows faster, as the difference between the endothelial cell volume and tumor cell volume is the motor of the tumor growth. Other dominant parameter in tumor growth speed is the tumor growth rate parameter, which is the feature of the tumor, so we can only affect the total tumor cell volume by decreasing the total endothelial cell volume.

After examining the working point linearization of the nonlinear model together with linear control characteristics (observability and controllability), a Linear Quadratic (LQ) controller and an observer based on pole-placement was designed on the considered model [39,40].

A saturation block was also placed in the control structure with zero lower bound as negative input has no physiological meaning [40].

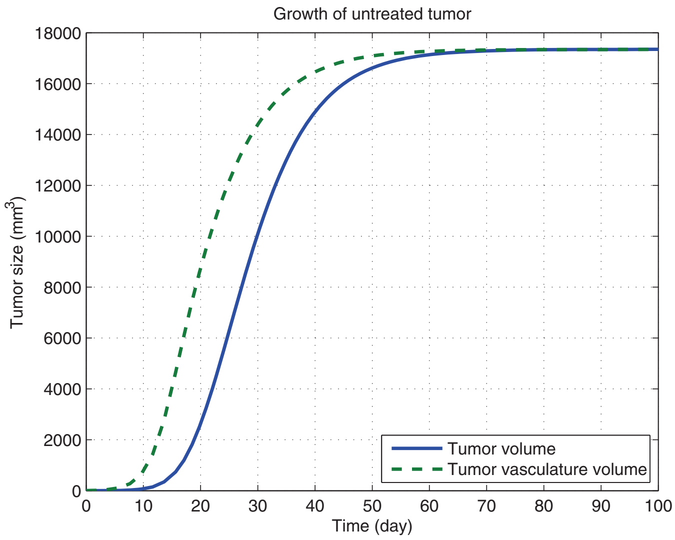

Fig. 3. Tumor and endothelial cell growth with no control input

In case of LQ design, the weighting matrix R was chosen to have a great value ($R = 10^5$), since the administered inhibitor (as the material used for the control) is quite expensive, while Q was chosen to select the energy of the tumor volume (x_1) and the administered inhibitor (x_3) [40]:

$$Q = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} . \tag{3}$$

In case of upper limit of the saturation block, we have made an iterative search to obtain its optimal value. We have started with 200 mg/kg/day, and decreased the upper limit with 1 unit step size until the control became inefficient. The simulations were run with 120 days treatment period. For each simulation result we calculated the total concentration of endostatin used in the treatment period, and treat this quantity as a cost function to be minimized. It has resulted that the cost function has a minimum at 79 units of saturation [38].

Fig. 4 depicts the simulation results for the optimal treatment. The tumor volume decreases rapidly and reaches 69 mm^3 in about 40 days. It can be seen that the input has two main periods. At the first period, the saturated input is at the maximum 79 units, and at the second period it is at 14.73 units [40].

The characteristics of the input are the same for the other simulation setups as well. They start with the maximum value and then they drop to a constant input at 14.7 units. The main role of the designed controller is to determine the switching time, when the maximal input is switched to the steady-state value [40].

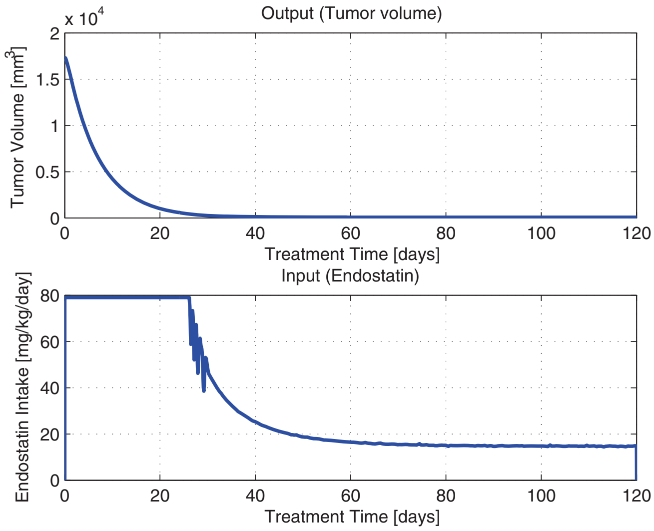

Fig. 4. Simulation results with the upper limit of 79 units on the input saturation

5 Conclusions

The current work summarized the results of model-based disease treatment researches in the field of physiological modeling and control carried out at the Physiological Controls Group of the Óbuda University.

Regarding diabetes, the Hungarian artificial pancreas research topic was briefly summarized. The developed nonlinear model-based LPV robust controller was created on the most complex Sorensen-model and our quasi in-silico results were tested and compared on real data of 83 type 1 diabetes patient. The developed framework kept the blood glucose level more than 90% of the time inside the 70-120 mg/dL interval (without any recalibration of the algorithm) proving its robustness. Hypoglycemia (not caused from physical activity) is efficiently avoided. The research proved that there is a real hope in developing a general (robust) framework, which could keep by hard constraints blood glucose level inside a defined interval; moreover, it is not sensitive to different meal intake profiles. Hence, it could efficiently support individualized control (ex. model predictive control (MPC)) protocols appeared in the literature [6].

It is planned to extend the robust framework with hard constraints regarding different life-style situations (physical activity, stress) as well as increasing number of simulated test cases on real data provided by pump centers members of the newly created Hungarian Artificial Pancreas working group associated to the Hungarian Diabetes Association.

Regarding obesity, we performed a clinical study to investigate the connections of obesity and laboratory results, and its implications in screening on Hungarian adolescent population, which was never before examined from this aspect. We could confirm that obesity causes systematical changes in the laboratory parameters. Differences between the means of these parameters of obese and healthy children also support the view of obesity as a chronic inflammation state. These differences also make the idea plausible to use the laboratory results for the classification of individuals. The true classification rate of 85-90% in both sexes of the logistic regression-based model could be in fact used to classify adolescents and also to be used in our risk prediction investigation.

Finally, regarding our investigations in the field of model-based cancer treatment, simulation results showed that even a simple optimal therapy can be beneficial. Our first obtained results show that an optimal therapy could start with an intense period, where the tumor volume is compressed, followed by a maintaining period, where the minimal value of inhibitor is given to the patient. This maintaining period can be continued till the remaining tumor cells are destroyed by another type of antitumor therapy. The main significance of the controller is in the allocation of the switching time, when the intense period should be terminated, and the maintaining period should be started.

Further investigations will be focused on other the application of other optimal control strategies (nonlinear control, modern robust control) as well as on model identification, model verification and biostatistic evaluation based on mice experiments in cooperation with clinical experts.

Acknowledgment. Levente Kovács was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences. This work was partially supported by the National Development Agency's GOP-1.1.1-11-2012-0055 project titled "DIALOGIC – Mathematical model-based decision support system to improve diabetes health management". The research work was also supported by the European Union and co-funded by the European Social Fund, project title: "Telemedicine-focused research activities in the field of Mathematics, Informatics and Medical Sciences", project number: TÁMOP-4.2.2.A-11/1/KONV-2012-0073.

The author thanks the members of the Physiological Controls Group, PhD students Péter Szalay, György Eigner, István Péter Sas for their work in the artificial pancreas problem, Dr. Tamás Ferenci for his work in the biostatistical investigation regarding obesity, PhD student Johanna Sápi for her work in the antiangiogenic tumor treatment. Special thanks are given to Dániel András Drexler and Dr. István Harmati from the Budapest University of Technology and Economics for their support in the model-based cancer treatment investigations.

The author say special thanks to the Hungarian Artificial Pancreas working group's insulin pump centers for the real data provided to validate the nonlinear model-based type 1 diabetes robust control algorithm as well as for Prof. Dr. László Barkai, president of the Hungarian Diabetes Association for his continuous support.

The author thank the secondary schools involved in obesity classification project: Fazekas Mihály (Budapest), Leövey Klára (Budapest), Puskás Tivadar (Budapest) and Esze Tamás (Mátészalka) Primary and Secondary Grammar

Schools. We say special thanks to Bétéri Csabáné for her cooperation in organizing the study at Mátészalka.

Finally, regarding the antiangiogenic research task, the authors say special thanks to Dr. Zoltán Sápi, deputy head of the 1st Department of Pathology and Experimental Cancer Research Institute from Semmelweis University Budapest, for his precious medical comments regarding the interpretation of the obtained results.

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