**Proceedings of the 17th World Congress**
**The International Federation of Automatic Control**
**Seoul, Korea, July 6-11, 2008**

# Nonlinear model predictive control with moving horizon state and disturbance estimation - Application to the normalization of blood glucose in the critically ill

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**Abstract:** In this paper we present a nonlinear model predictive control (NMPC) strategy that can be used to tackle nonlinear control problems with changing model parameters, unknown disturbance factors and specifications on the rates of change of the inputs. The closed-loop performance of the proposed NMPC strategy is demonstrated by applying it to the problem of blood glucose normalization in critically ill patients. A nonlinear patient model, that is particularly developed for describing the glucose and the insulin dynamics of these patients, is used for online state and disturbance estimation and control under a realistic disturbance realization. The results are satisfactory both in terms of control behavior (set point tracking and the suppression of unknown disturbance factors) and clinical acceptability.
***Keywords:*** *control applications, model predictive control, output feedback control, physical models, parameter and state estimation.*

## 1. INTRODUCTION

Hyperglycemia (i.e., an increased glucose concentration in the blood) and insulin resistance (i.e., the resistance of the glucose utilizing tissues to insulin) are common in critically ill patients (even if they have not had diabetes before) and are associated with adverse outcomes. Tight glycemic control (between 80 and 110 mg/dl = target range) by applying intensive insulin therapy in patients admitted to the medical and the surgical intensive care unit (ICU) results in a spectacular reduction in mortality and morbidity (Van den Berghe et al. (2006, 2001)).

Currently, ICU patients are treated through a manual and rigorous administration of insulin (Van den Berghe et al. (2003)). We want to design a semi-automated control system for glycemia control in the ICU in order to reduce the workload for the medical staff. Moreover, this computer-aided control system may introduce the glycemia normalization concept in hospitals that are currently *not* making use of the manual intensive insulin protocol (Van den Berghe et al. (2003)), world-wide leading to a potential further reduction of mortality and morbidity (Van Herpe et al. (2006)).

Model predictive control (MPC) has emerged as a powerful and widely used control technique (particularly in the process industry) over the last two decades (Qin and Badgwell (1996)). MPC controllers are designed on the basis of a dynamical model of the system that has to be controlled and apply mathematical optimization techniques in order to obtain the optimal inputs to be applied to the system. Recently there has been growing interest in predictive control of *nonlinear systems* (Qin and Badgwell (2000)) and the properties of a variety of NMPC schemes have been investigated theoretically, see for example (Allgöwer et al. (1999); Nicolao et al. (2000)) for a review.

For the estimation of the current system state, unknown disturbances and parameters we propose a moving horizon estimator (MHE) (Diehl et al. (2006); Muske and Rawlings (1995); Rao et al. (2003)). Moving horizon estimation can be regarded as the dual of MPC: also in MHE a dynamical model of the system is employed and optimization over a finite window of data is performed (albeit a window in the past whereas MPC employs a future window). The numerical methods for the MHE scheme presented in this paper are based on the direct multiple shooting method for parameter estimation (Bock and Plitt (1984)).

In previous work (Van Herpe et al. (2007b)) a model predictive control strategy was presented for glycemia control in the ICU and a qualitative and quantitative assessment

was given for the proposed control strategy demonstrating its potential. In the work presented in this paper we have improved the numerical efficiency of the MPC implementation using a multiple shooting method (Bock (1981)) as opposed to the single shooting method previously used. Next, a moving horizon estimator for state and parameter estimation is presented capable of handling unknown disturbances, also using a multiple shooting method. Finally, target calculation is proposed to provide integral control. Thus, the focus of this paper is on the closed-loop control behavior using the nonlinear ICU Minimal Model (Van Herpe et al. (2007a)). The presented scheme is generally applicable to nonlinear systems described by first-principles models and with changing model parameters, unknown disturbance factors, and, specifications on the rates of change of the inputs.

This paper is structured as follows. In Section 2 the control system is presented and its components - model predictive control, moving horizon estimation and target calculation - are described in detail. Then, in section 3 the proposed control strategy is applied to the normalization of blood glucose in the ICU and the closed-loop performance properties are discussed. Finally, in section 4 conclusions are given and future work is outlined.

## 2. CLOSED-LOOP NONLINEAR CONTROL SYSTEM

### *2.1 Global set-up*

The complete closed loop control system is depicted in Figure 1. Its components will be described in detail in this section. Throughout this paper it is assumed that the system model is given by a system of nonlinear index-one ordinary differential equations of the form

$$\dot{x}(t) = f(x(t), u(t), w(t), d, p), \tag{1}$$

where $x$ are the differential states, $u$ the inputs, $w$ the system noise accounting for modeling errors, $d$ the unknown disturbances and $p$ the set of free parameters. We will also allow bounds on the variables

$$\begin{aligned} x_{\min} \leq x(t) \leq x_{\max}, \\ u_{\min} \leq u(t) \leq u_{\max}, \\ w_{\min} \leq w(t) \leq w_{\max}, \\ d_{\min} \leq d \leq d_{\max}, \\ p_{\min} \leq p \leq p_{\max}. \end{aligned}$$

The measurement data are generated as

$$y_k = h(x(t_k)) + v_k, \tag{2}$$

where $v_k$ represents measurement noise (sensor noise) and the subscript $k$ indicates the fact that measurements are obtained at discrete time instants.

Thus, the disturbances that enter the closed loop system can be summarized as

(1) process noise $w$, which is usually assumed to be zero-mean random noise but in the MHE-setting can also be regarded purely deterministic as bounded optimization variables with the only assumption that zero is contained in the feasible set,

(2) unknown model disturbance $d$ which is assumed to be slowly varying. In the presented application the unknown disturbance represents the effect of medication, to which we assigned a typical realization and which we assumed to have direct influence on the glycemic level,

(3) sensor noise $v$ which we will assume to be normally distributed with mean zero and known covariance matrix,

(4) unknown initial states, disturbance and parameters. We will assume that expected values for the states, disturbance and parameters ($\bar{x}_0$, $\bar{d}_0$ and $\bar{p}_0$ resp.) are given as well as the corresponding covariance $P_0$. After a transient, the effect of the initial conditions usually diminishes and the estimates converge to the true values provided that the measurements contain sufficient information.

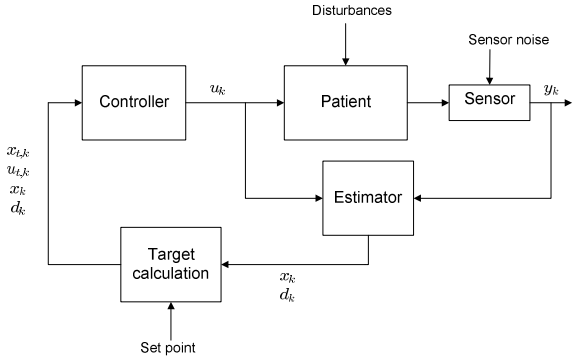


Fig. 1. Illustration of the closed loop control scheme.

### *2.2 Moving horizon estimation*

The idea of moving horizon estimation is to estimate the state using a moving and fixed-size window of data. When a new measurement becomes available, the oldest measurement is discarded and the new measurement is added. The philosophy is to penalize deviations between measurement data and predicted outputs. In addition - for theoretical reasons - a regularization term on the initial state estimate is added to the objective function. Two important characteristics distinguish MHE from other estimation strategies, such as the extended Kalman filter (EKF). First of all, prior information in the form of constraints on the states, disturbances and parameters can be included. Second, since MHE is optimization based it is able to handle explicitly nonlinear system dynamics through the use of approximative nonlinear optimization algorithms. In (Haseltine and Rawlings (2005)) MHE was shown to possess superior estimation properties compared to EKF.

The estimation problem to be solved at time $t_0$ is:

$$\min_{x(\cdot),w(\cdot),d,p} \left\| \begin{matrix} x(t_0-N)-\bar{x} \\ d-\bar{d} \\ p-\bar{p} \end{matrix} \right\|^2_{P^{-1}} + \int_{t_0-T}^{t_0} \|w(t)\|^2_{Q_e^{-1}} dt + \sum_{k=t_0-T}^{t_0} \|y_k - h(x(t_k))\|^2_{R_e^{-1}} \quad (3a)$$

s.t.

$$\dot{x}(t) = f(x(t), u(t), w(t), d, p), \quad (3b)$$
$$x_{\min} \le x(t) \le x_{\max}, \quad (3c)$$
$$w_{\min} \le w(t) \le w_{\max}, \quad t \in [t_0 - T, t_0] \quad (3d)$$
$$d_{\min} \le d \le d_{\max}, \quad (3e)$$
$$p_{\min} \le p \le p_{\max}. \quad (3f)$$

The weighting matrices $Q_e$ and $R_e$ are the covariance matrices for the process noise and measurement noise respectively. The matrix $P$ and vectors $\bar{x}$, $\bar{d}$ and $\bar{p}$ express a-priori information and are determined from one problem to the next by a discrete time EKF update.

### *2.3 Target calculation*

The goal of target calculation is to find a steady state of the closed loop system and a corresponding input that yields the output at the set point. This is an inverse problem that can be formulated as an optimization problem. Due to constraints or nonlinearities it might occur that no steady-state targets can be found corresponding to the set point. In that case we require the output target to be the closest output to the set point for which a steady state exists. If there are multiple steady states satisfying the output set point, the one that is closest to the previous input target is selected. At each time instant a new target must be calculated to account for changing parameters and integrated disturbances.

We formulate the target calculation as the following optimization problem (see Tenny (2002)):

$$\min_{x^t(t_0),u^t(t_0),\eta} \frac{1}{2}\eta^T \bar{Q}\eta + \bar{q}^T\eta + \frac{1}{2}(u^t(t_0) - u^t(t_{-1}))^T \bar{R}(u^t(t_0) - u^t(t_{-1})) \quad (4a)$$

subject to

$$x^t(t_0) = f(x^t(t_0), u^t(t_0), \hat{d}, \hat{p}), \quad (4b)$$
$$h(x^t(t_0)) - \eta \le y_{\text{set}} \le h(x^t(t_0)) + \eta, \quad (4c)$$
$$u_{\min} \le u^t(t_0) \le u_{\max}, \quad (4d)$$
$$x_{\min} \le x^t(t_0) \le x_{\max}, \quad (4e)$$
$$\eta \ge 0. \quad (4f)$$

Here $u^t(t_{-1})$ is the input target calculated in the previous time step. This is an exact penalty method (Fletcher (1987); Rao and Rawlings (1999)) which relaxes the problem in a $l_1/l_2^2$ sense if the set point is infeasible by introducing the *slack variable* $\eta$. In general, $\bar{q}$ is chosen to be relatively large and strictly positive and both $\bar{Q}$ and $\bar{R}$ are positive definite. By shifting the state and input targets, the target calculation accounts for modeling error and adjusts the model to remove offset from the closed-loop system.

### *2.4 Model predictive control*

Given the current state, disturbance and parameter estimates $\hat{x}(t_0)$, $\hat{d}$, $\hat{p}$ of the system at time $t_0$, NMPC predicts the future dynamic behavior of the system over a horizon $T$ and determines the future inputs such that an open-loop performance objective function is optimized. Due to disturbances and/or model-plant mismatch the true system behavior is different from the predicted behavior. Therefore, in order to incorporate feedback, only the first of this optimal input sequence is applied to the system. When a new measurement and new estimates are obtained the horizon is shifted and the previous steps are repeated.

The open-loop optimization problem we address is:

$$\min_{x(\cdot),u(\cdot)} \int_{t_0}^{t_0+T} \|\tilde{x}(t)\|^2_Q + \|\tilde{u}(t)\|^2_R \, dt \quad (5a)$$

subject to

$$x(t_0) = \hat{x}(t_0), \quad (5b)$$
$$\dot{x}(t) = f(x(t), u(t), \hat{d}, \hat{p}), \quad (5c)$$
$$c(x(t), u(t), \hat{d}, \hat{p}) \ge 0, \quad t \in [t_0, t_0 + T]. \quad (5d)$$

Here $\tilde{x}(t) = x(t) - x^t$ and $\tilde{u}(t) = u(t) - u^t$ with $x^t$ and $u^t$ the target state and input determined by the preceding target calculation. This approach of penalizing deviations from target states and inputs provides integral (offset free) control. In order to guarantee theoretical stability of the MPC controller, one should add to the above formulation either a terminal constraint, or a terminal cost, or both. We implemented a terminal constraint but it was found that in order to achieve guaranteed theoretical stability the control performance was deteriorated. Other stability measures are currently being investigated. For the stability theory of NMPC we refer to (Magni and Scattolini (2004)).

*Move blocking* A rule of thumb in control theory (and practice) states that the output should be sampled fast enough to capture all the important system dynamics. Often, however, the inputs are allowed to change only at a lower rate. In such cases integration time intervals for the state-space model are taken as short as necessary while the inputs are *blocked* during several time intervals. A strategy for *move blocking* of the inputs was added to the MPC formulation. For the glycemia control problem, integration time intervals of 5 min and a future horizon of $N_{\text{mpc}} = 240$ min are used, while the insulin flow input is allowed to change only every 60 min. This specification is imposed by the medical staff for clinical validation reasons.

## 3. APPLICATION TO BLOOD GLUCOSE CONTROL IN THE CRITICALLY ILL

### *3.1 ICU Minimal Model (ICU-MM)*

The presented model structure originates from the known *minimal* model that is developed by (Bergman et al. (1981)). In (Van Herpe et al. (2007a)) the original minimal model was extended to the ICU minimal model (ICU-MM) by taking into consideration some features typical of ICU patients. The new model was also validated on a real-life clinical ICU data set. The ICU-MM is presented as follows:

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b + \frac{F_G}{V_G} + F_M, \quad (6a)$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3(I_1(t) - I_b), \quad (6b)$$

$$\frac{dI_1(t)}{dt} = \alpha \ \max(0, I_2) - n(I_1(t) - I_b) + \frac{F_I}{V_I}, \quad (6c)$$

$$\frac{dI_2(t)}{dt} = \beta \ \gamma \ (G(t) - h) - nI_2(t), \quad (6d)$$

where $G$ and $I_1$ are the glucose and the insulin concentration in the blood plasma. The second insulin variable, $I_2$, is a purely mathematical manipulation such that $I_2$ does not have any direct clinical interpretation. The variable $X$ describes the effect of insulin on net glucose disappearance and is proportional to insulin in the remote compartment. $G_b$ and $I_b$ are the basal value of plasma glucose and plasma insulin, respectively. The model consists of two input variables: the intravenously administered (exogenous) insulin flow ($F_I$) and the parenteral carbohydrate calories flow ($F_G$). The glucose distribution space and the insulin distribution volume are denoted as $V_G$ and $V_I$, respectively. There is an unknown disturbance input that we ascribe to administered medication ($F_M$) and which directly influences the glucose concentration. This to the MPC unknown input could also account for other unknown disturbance factors.

The coefficient $P_1$ represents the glucose effectiveness (i.e., the fractional clearance of glucose) when insulin remains at the basal level; $P_2$ and $P_3$ are the fractional rates of net remote insulin disappearance and insulin dependent increase, respectively. The endogenous insulin is represented as the insulin flow that is released in proportion (by $\gamma$) to the degree by which glycemia exceeds a glucose threshold level $h$. The time constant for insulin disappearance is denoted as $n$. In case glycemia does not surpass the glucose threshold level $h$, the first part of 6c (that represents the endogenous insulin production) equals 0. In order to keep the correct units, an additional model coefficient, $\beta = 1$ min, was added. Finally, the coefficient $\alpha$ amplifies the mathematical second insulin variable $I_2$.

The units of all used variables and parameters and their values are represented in Table 1. These values are taken from an estimation process applied to a real-life data set of 19 critically ill patients (Van Herpe et al. (2007a)). The parameter and state values after the first 24 hour estimation for an arbitrary patient were chosen. Proceeding in this way the control system could be assessed using a realistic parameter realization.

*Smoothing discontinuities* The nonlinear model (6) contains a discontinuity in the form of a *max* term. In order to avoid problems with differentiability the *max* term was smoothed using exponential smoothing $\max(0, I_2) \sim s \ln(1 + \exp(\frac{I_2}{s}))$ with weighting $s = 0.1$.

### 3.2 Results and discussion

*Closed-loop control performance* In Figure 2 the simulated glucose course with added measurement noise and the administered known and unknown input flows are illustrated. Starting from a high initial blood glucose concentration, the closed-loop control system is able to

Table 1. Units and initial values of the state variables, units of the input variables and units and values of the parameters applicable in the ICU minimal model. These values are taken from an estimation process applied to a real-life data set of 19 critically ill patients (see Van Herpe et al. (2007a)).

| State variables | Units | Initial value |
|---|---|---|
| $G$ | mg/dl | 207 |
| $I_1$ | $\mu$U/ml | 58.0 |
| $X$ | 1/min | 0.0005 |
| $I_2$ | $\mu$U/ml | 1.49 |
| **Input variables** | **Units** | |
| $F_I$ | $\mu$U/min | |
| $F_G$ | mg/min | |
| $F_M$ | mg/dl/min | |
| **Parameters** | **Units** | **Value** |
| $V_G$ | dl | 116.8 |
| $V_I$ | ml | 8760 |
| $G_b$ | mg/dl | 95 |
| $I_b$ | $\mu$U/ml | 10.7 |
| $P_1$ | 1/min | -1.71 $10^{-2}$ |
| $P_2$ | 1/min | -2.24 $10^{-2}$ |
| $P_3$ | ml/(min$^2$$\mu$U) | 2.5 $10^{-3}$ |
| $h$ | mg/dl | 107.4 |
| $n$ | 1/min | 0.2623 |
| $\alpha$ | 1/min | 0.35 |
| $\beta$ | min | 1 |
| $\gamma$ | $\frac{\frac{\mu U}{ml}\frac{dl}{mg}}{min^2}$ | 1.4001 $10^{-4}$ |

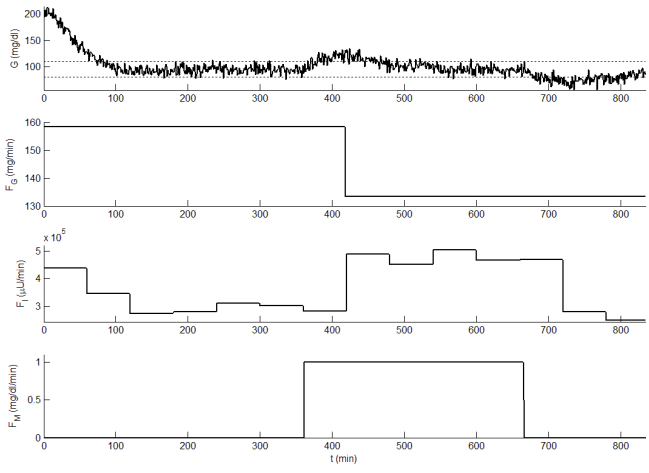


Fig. 2. The top panel shows the evolution of the simulated glycemia $G$ with added sensor noise (solid line) and the target range of $80-110$ mg/dl (dashed lines). The flow of the carbohydrate calories $F_G$ (second panel) is the known disturbance factor whereas the insulin rate $F_I$ (third panel) is the insulin sequence that is proposed by MPC controller. A fictitious medication disturbance factor $F_M$ (that is unknown to the MPC) is visualized in the bottom panel.

regulate to the normoglycemic range ($80 - 110$ mg/dl) in a considerably short time span by administering a still clinically acceptable insulin flow. The MPC controller was precisely tuned to obtain both good control performance and clinical acceptability. Furthermore, the control system is able to suppress the unknown disturbance input. When the rather large disturbance (i.e., medication) enters, the glycemic level is raised into the *modest* hyperglycemic range, after which the insulin flow is adjusted and the glycemic level is steered to the normoglycemic range again. Further on, a *slight* hypoglycemic event occurs when the large disturbance suddenly drops. This result shows the potential of the proposed control system to normalize the blood glucose exploiting the nonlinear model dynamics and taking into consideration unknown disturbance factors that are omnipresent in the ICU.

*Moving horizon estimation* In Figure 3 the courses of the four states and their estimates are depicted as well as the unknown disturbance and its estimate. The measurements are corrupted with zero-mean random noise with standard deviation $\sigma = 7.5$ mg/dl. For the estimator a time horizon of $N_{\text{mhe}} = 5$ min was employed. The true initial state of the system was $x_0 = [207\ 58.0\ 0.0005\ 1.49]$ (see Table 1) while the estimator was initialized with $\bar{x}_0 = [180\ 20\ 0\ 0]$. Despite this rather large initial error a fast convergence to the true state values could be obtained leading to a minimal impact of initial error on the closed loop performance. Furthermore, also the unknown disturbance could be perceived with reasonable accuracy from the output measurements.

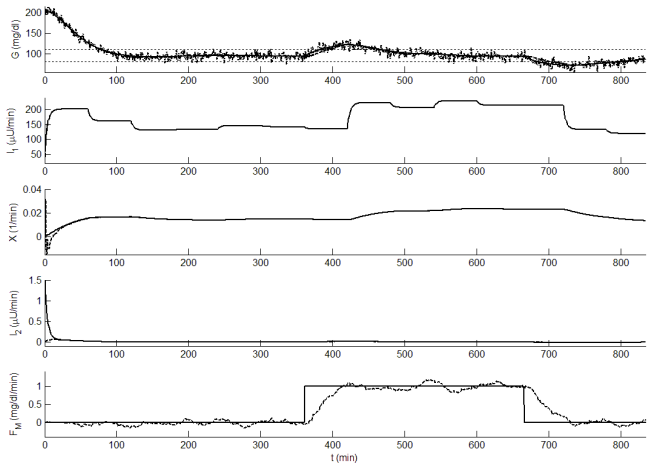


Fig. 3. The four top panels show the evolution of the true states (solid lin) and its estimates (dashed line). The bottom panel shows the true (solid line) and estimated (dashed line) unknown disturbance input.

*Target calculation* Figure 4 shows the target input (insulin flow) and the corresponding optimal input computed by the MPC controller. The target input is influenced by the estimated unknown disturbance input and (less noticeable) by the changing carbohydrate calories flow. The MPC computed input is expected to track the big changes of the target but not the fast fluctuations, which is reasonably well achieved as can be seen from the figure. The effect of move blocking can be seen when a change in the influencing parameters occurs, for example at time instants $t = 360$ min and $t = 665$ min a sudden change in the unknown disturbance occurs, which is detected (estimated) shortly thereafter. Due to move blocking of the input the controller is not able to instantly react to these changes, leading for instance to a short hypoglycemic event around time $t = 750$ min (see Figure 2).

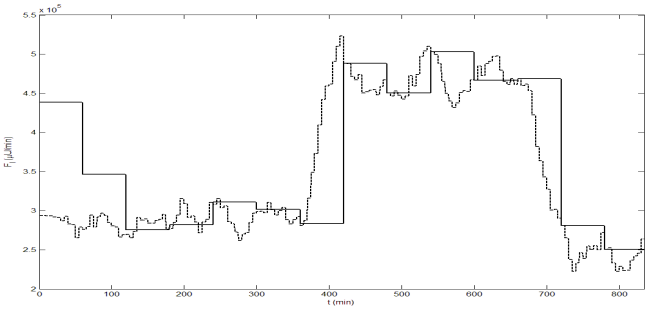


Fig. 4. Evolution of the computed target input (dashed line) and the optimal input proposed by the MPC controller (solid line).

## 4. CONCLUSIONS AND FUTURE WORKS

In this paper we present a nonlinear MPC strategy that can be used to tackle nonlinear control problems with changing model parameters, unknown disturbance factors, and, specifications on the rates of change of the inputs. Using a moving horizon estimator, accurate estimates of the true states that generated the output, can be obtained from noisy output measurements. The MHE is able to recover quickly from a wrong initial guess of the state vector. A target calculation is proposed to remove the effect of disturbances and changing parameters. The ability of the closed-loop control system to regulate to the normoglycemic range in a short time span and to suppress disturbances is shown for a realistic disturbance realization. The proposed control system is potentially suitable to control glycemia in the ICU and will be soon tested in real-life.

Future research can proceed along several avenues. First, online joint parameter, state and unknown disturbance estimation will be explored in detail and its predictive capacity will be analyzed. Second, the objective of the model predictive controller can be reformulated to explicitly account for the different glycemic ranges. Finally, exponential smoothing of the discontinuity that is presently used, might be avoided by using a recently proposed method for detecting and handling implicit switches or discontinuities (Kirches (2006)).

## 5. ACKNOWLEDGMENTS

Niels Haverbeke and Tom Van Herpe are research assistants at the Katholieke Universiteit Leuven, Belgium. Niels Haverbeke is supported by the IWT-Vlaanderen. Moritz Diehl is an associate professor at the COE Optimization in Engineering (OPTEC) of the Katholieke Universiteit Leuven. Bart De Moor and Greet Van den Berghe are full professors at the Katholieke Universiteit Leuven.

Research supported by Research Council KUL: GOA AM-BioRICS, CoE EF/05/006 Optimization in Engineering, several PhD/postdoc & fellow grants; Flemish Government: FWO: PhD/postdoc grants, projects, G.0407.02 (support vector machines), G.0197.02 (power islands), G.0141.03 (Identification and cryptography), G.0491.03 (control for intensive care glycemia), G.0120.03 (QIT), G.0452.04 (new quantum algorithms), G.0499.04 (Statistics), G.0211.05 (Nonlinear), G.0226.06 (cooperative systems and optimization), G.0321.06 (Tensors), G.0302.07 (SVM/Kernel, research communities (ICCoS, ANMMM, MLDM); IWT: PhD Grants, McKnow-E, Eureka-Flite2; Belgian Federal Science Policy Office: IUAP P6/04 (Dynamical systems, control and optimization, 2007-2011); EU: ERNSI.

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