Flatness-based control approach to drug infusion for cardiac function regulation

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Abstract: A new control method based on differential flatness theory is developed in this study, aiming at solving the problem of regulation of haemodynamic parameters. Actually control of the cardiac output (volume of blood pumped out by heart per unit of time) and of the arterial blood pressure is achieved through the administered infusion of cardiovascular drugs such as dopamine and sodium nitroprusside. Time delays between the control inputs and the system’s outputs are taken into account. Using the principle of dynamic extension, which means that by considering certain control inputs and their derivatives as additional state variables, a state-space description for the heart’s function is obtained. It is proven that the dynamic model of the heart is a differentially flat one. This enables its transformation into a linear canonical and decoupled form, for which the design of a stabilising feedback controller becomes possible. The proposed feedback controller is of proven stability and assures fast and accurate tracking of the reference setpoints by the outputs of the heart’s dynamic model. Moreover, by using a Kalman filter-based disturbances’ estimator, it becomes possible to estimate in real-time and compensate for the model uncertainty and external perturbation inputs that affect the heart’s model.

1 Introduction

A control method is developed for the regulation of haemodynamic parameters with the use of administered infusion of cardiovascular drugs. Control of haemodynamic parameters is important for patients suffering from cardiac diseases, for safe recovery of patients in post-operative conditions as well as for improved treatment of patients in intensive care units. Aiming at solving the problem of haemodynamic variables control, several approaches have been developed. In [1–4], linear control of haemodynamics has been proposed. In [5–9], adaptive and robust control approaches have been proposed for models of heart function. In [10–13], the problem of control of haemodynamic models under time delays has been treated. Moreover, in [14–17] intelligent control methods for the regulation of cardiac function have been proposed.

In this paper, a cardiac function’s model is considered in which the monitored variables are the cardiac output (CO), that is, the blood volume that is pumped out by heart per unit of time ΔCO and the arterial blood pressure ΔBP, while the control inputs are infused cardiovascular drugs such as dopamine (DP) and sodium nitroprusside (SNP). This model is characterised by time delays between the control inputs and the outputs [10–13]. Using Taylor series expansion the time-delay terms are linearised. Moreover, the principle of dynamic extension is applied, which means that certain control inputs and their time derivatives are considered to be additional state variables of the system. Thus, a state-space description of the model is obtained.

It is proven that the state-space model of the heart’s function is a differentially flat one. This means that all its state variables and its control inputs can be expressed as differential functions of two primary variables which are the system’s flat outputs [18–22]. The flat outputs are taken to be the CO ΔCO and the arterial BP ΔBP. By exploiting the differential flatness properties of the model, its transformation into a linear canonical and decoupled form becomes possible [23–26]. For the latter description of the system’s dynamics, the design of a stabilising feedback controller is achieved, assuring the asymptotic elimination of the state variables’ tracking error [27, 28]. Such a controller is shown to assure fast and accurate tracking of the heart’s model to the associated reference setpoints.

To implement feedback control by measuring only the system’s outputs, the Kalman filter is applied on the linearised model of the heart system [29, 30]. The Kalman filter’s optimality assures that state estimates of improved accuracy will be obtained for the model of the heart’s dynamics [31–33]. This use of the Kalman filter on the linear equivalent model of initially non-linear differentially flat systems is also known as derivative-free non-linear Kalman filter. Moreover, by designing the Kalman filter as a disturbances’ estimator it becomes possible to estimate in real-time and compensate for additive disturbance inputs that effect the cardiac function’s model [18–20]. Such perturbation inputs can be due to modelling uncertainty, approximate linearisation of the time-delay terms of the model, parametric variations or external disturbances affecting the drugs infusion. Simulation experiments are provided to confirm the excellent tracking performance and the robustness of the proposed flatness-based control scheme.

The structure of this paper is as follows: in Section 2, the multi-variable dynamic model of the heart’s function is introduced. In Section 3, a state-space form for the model of the heart’s dynamics is obtained after linearisation of its time-delay terms and after applying the dynamic extension principle. In Section 4, the differential flatness properties of the state-space model of heart’s function are proven. In Section 5, a flatness-based feedback controller is designed for the model of the heart’s dynamics and its stability properties are proven. In Section 6, a Kalman filter-based disturbance observer is introduced aiming at estimating and compensating for the additive disturbance inputs that affect the heart’s dynamic model. In Section 7, simulation tests are performed to evaluate the tracking performance and the stability features of the proposed control scheme. Finally in Section 8, concluding remarks are stated.
2 Dynamic model of the cardiac function

Next, the dynamic model of the cardiac function is formulated and a state-space model is formulated. The primary parameters that define cardiac function are: (i) the CO which is measured in ml/min kg and which expresses the volume of blood pumped out by heart per unit of time, subject to a normalisation with respect to the patient’s weight and (ii) the arterial BP which is measured in mmHg.

Considering that the cardiac function parameters exhibit an exponential decay response to stimulus provided by drug infusion, and also that there exist time delays between the drug inputs and their effect on the levels of the aforementioned parameters, a multi-input–multi-output (MIMO) model of cardiac function has been proposed [10–13]. The coupling between the model’s inputs and outputs is shown in Fig. 1. The model is expressed in the s-frequency domain, using transfer function matrices

\[
\begin{align*}
\Delta CO(s) & = \frac{K_{12}e^{-T_{12}s}}{\tau_{12}s + 1} \left( \frac{K_{12}e^{-T_{12}s}}{\tau_{22}s + 1} \right) \left( DP(s) \right) \\
\Delta BP(s) & = \frac{K_{21}e^{-T_{12}s}}{\tau_{12}s + 1} \left( \frac{K_{21}e^{-T_{12}s}}{\tau_{22}s + 1} \right) \left( SNP(s) \right)
\end{align*}
\]

Indicative values for the parameters of this model are [10–13]: \( K_{12} = 5 \) ml/μ, with variation ranges between 1.0 and 12 ml/μ, \( \tau_{12} = 150 \) s, with variation ranges between 70 and 600 s, \( T_{12} = 60 \) s, with variation ranges between 15 and 60 s.

Additionally: \( K_{12} = 12 \) ml/μ, with variation ranges between \(-15 \) and 25 ml/μ, \( \tau_{12} = 40 \) s, with variation ranges between 30 and 60 s, \( T_{12} = 60 \) s, with variation ranges between 15 and 60 s.

Moreover, \( K_{21} = 3 \) ml/μ, with variation ranges between 0 and 15 ml/μ, \( \tau_{21} = 40 \) s, with variation ranges between 30 and 60 s, \( T_{21} = 60 \) s, with variation ranges between 15 and 60 s.

Finally, \( K_{22} = -15 \) ml/μ, with variation ranges between \(-1 \) and \(-50 \) ml/μ, \( \tau_{22} = 40 \) s, with variation ranges between 30 and 60 s, \( T_{22} = 60 \) s, with variation ranges between 15 and 60 s.

The variation ranges for the control inputs are usually: (i) for DP, \( DP \in [0, 10] \) mg/min kg and (ii) for SNP \( SNP \in [0, 10] \) mg/min kg. By denoting as system outputs \( y_1 = \Delta CO \) and \( y_2 = \Delta BP \) and as system inputs \( u_1 = DP \) and \( u_2 = SNP \) one obtains

\[
\begin{align*}
y_1(s) & = \frac{k_{11}e^{-T_{12}s}}{\tau_{11}s + 1} u_1(s) + \frac{k_{12}e^{-T_{12}s}}{\tau_{22}s + 1} u_2(s) \\
y_2(s) & = \frac{k_{21}e^{-T_{12}s}}{\tau_{11}s + 1} u_1(s) + \frac{k_{22}e^{-T_{12}s}}{\tau_{22}s + 1} u_2(s)
\end{align*}
\]

From (2) one obtains (see (3))

Next, linearisation of the model is performed through Taylor series expansion (see (4))

By substituting (4) into (3) one obtains

\[
\begin{align*}
[(\tau_{11} + T_{12}s) + (\tau_{12} + T_{12}s + 1)(1 + (T_{11} + T_{12}s))u_1(s) & = K_{11}(\tau_{22}s + 1)(1 + (T_{12}s + T_{22}s)u_1(s) + K_{22}(\tau_{21}s + 1)(1 + (T_{21}s + T_{22}s)u_2(s)
\end{align*}
\]

Next, by performing intermediate operations one gets

\[
\begin{align*}
\left((T_{11} + T_{12})(\tau_{11} + T_{12}s) + (T_{11} + T_{12})(\tau_{12} + T_{12}s) + (T_{12} + T_{12}s)\right) & = K_{11}(\tau_{12} + T_{12}s) + (\tau_{12} + T_{12}s + 1)u_1(s) + K_{22}(\tau_{21}s + 1)(1 + (T_{21}s + T_{22}s)u_2(s)
\end{align*}
\]

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\[\{(T_{11} + T_{12})(\tau_{11} + \tau_{12})\}^3 + (T_{21} + T_{22})(\tau_{21} + \tau_{22})\}^3 + (T_{11} + T_{12})\] 
+ (\tau_{11} + \tau_{12})^2 + 1)\psi_z(s) + 
K_{11}(\tau_{11} + \tau_{12})u_1 + K_{12}(\tau_{11} + \tau_{12})u_2 + K_{21}u_1 + 
K_{22}(\tau_{11} + \tau_{12})u_2 (7)

which after grouping polynomial terms of the same order becomes

\[\{(T_{11} + T_{12})(\tau_{11} + \tau_{12})\}^3 + [(T_{11} + T_{12})(\tau_{11} + \tau_{12})\}^3 + (T_{11} + T_{12})\]
+ [(T_{11} + T_{12}) + (\tau_{11} + \tau_{12})\}^3 + 1 - y_1 = 
K_{11}(\tau_{11} + \tau_{12})u_1 + K_{12}(\tau_{11} + \tau_{12})u_2 + K_{21}u_1 + 
K_{22}(\tau_{11} + \tau_{12})u_2 (8)

\[(T_{21} + T_{22})(\tau_{21} + \tau_{22})\}^3 + [(T_{21} + T_{22})(\tau_{21} + \tau_{22})\}^3 + (T_{21} + T_{22})\]
+ [(T_{21} + T_{22}) + (\tau_{21} + \tau_{22})\}^3 + 1 - y_2 = 
K_{11}(\tau_{21} + \tau_{22})u_1 + K_{12}(\tau_{21} + \tau_{22})u_2 + K_{21}u_1 + 
K_{22}(\tau_{21} + \tau_{22})u_2 (9)

By defining the coefficients \(a_{11} = (T_{11} + T_{12})(\tau_{11} + \tau_{12})\), \(a_{12} = [(T_{11} + T_{12})(\tau_{11} + \tau_{12})\}^3 + (T_{11} + T_{12})\]
+ [(T_{11} + T_{12}) + (\tau_{11} + \tau_{12})\}^3 + as well as \(b_{11} = K_{11}(\tau_{11} + \tau_{12})\), \(b_{12} = K_{12}(\tau_{11} + \tau_{12})\)
+ \(b_{21} = K_{21}\) and \(b_{22} = K_{22}\) and also by defining the coefficients \(a_{21} = (T_{21} + T_{22})(\tau_{21} + \tau_{22})\), \(a_{22} = [(T_{21} + T_{22})(\tau_{21} + \tau_{22})\}^3 + (T_{21} + T_{22})\]
+ [(T_{21} + T_{22}) + (\tau_{21} + \tau_{22})\}^3 + \(a_{21} = 1\) as well as \(b_{11} = K_{11}(\tau_{21} + \tau_{22})\), \(b_{12} = K_{12}(\tau_{21} + \tau_{22})\)
+ \(b_{21} = K_{21}\), \(b_{22} = K_{22}\) one arrives at the following description of the system’s dynamics

\[a_{11}y_1 + a_{12}y_2 + a_1y_1 = b_{11}u_1 + b_{12}u_1 + b_{21}u_2 + b_{22}u_2 \] (10)

\[a_{21}y_1 + a_{22}y_2 + a_2y_2 = b_{21}u_1 + b_{22}u_2 \] (11)

or equivalently

\[y_1^{(3)} = -\frac{a_{21}}{a_{11}} y_1 - \frac{a_{31}}{a_{11}} y_1 - \frac{a_{41}}{a_{11}} y_1 \]
+ \(b_{11} u_1 + b_{12} u_1 + b_{21} u_2 + b_{22} u_2 \)
+ \(b_{21} u_2 + b_{22} u_2 \) (12)

\[y_2^{(3)} = -\frac{a_{21}}{a_{12}} y_2 - \frac{a_{32}}{a_{12}} y_2 \]
+ \(b_{11} u_1 + b_{12} u_1 + b_{21} u_2 + b_{22} u_2 \) (13)

Next, the following state variables are defined: \(z_1 = y_1\), \(z_2 = y_2\), \(z_3 = y_3\), \(z_4 = y_4\), \(z_5 = y_5\), \(z_6 = y_6\), \(z_7 = y_7\). Moreover, by following the concept of dynamic extension, the control inputs and their derivatives are considered as additional state variables, that is, \(z_7 = u_1\), \(z_8 = u_1\), \(z_9 = u_2\), \(z_{10} = u_2\). Finally, new control inputs are defined as \(\tilde{u}_1 = v_1\) and \(\tilde{u}_2 = v_2\).

Moreover, one can define

\[f_2(z) = -\frac{a_{21}}{a_{12}} z_3 - \frac{a_{31}}{a_{12}} z_3 - \frac{a_{41}}{a_{12}} z_3 + \frac{b_{11}}{a_{12}} z_8 + \frac{b_{12}}{a_{12}} z_8 + \frac{b_{21}}{a_{12}} z_{10} + \frac{b_{22}}{a_{12}} z_{10} \] (14)

\[g_{11} = \frac{a_{21}}{a_{11}} g_{12} = \frac{a_{22}}{a_{12}} \] (15)

\[f_2(z) = -\frac{a_{21}}{a_{12}} z_6 - \frac{a_{31}}{a_{12}} z_6 - \frac{a_{41}}{a_{12}} z_6 + \frac{b_{11}}{a_{12}} z_9 + \frac{b_{12}}{a_{12}} z_9 + \frac{b_{21}}{a_{12}} z_{10} + \frac{b_{22}}{a_{12}} z_{10} \] (16)

\[g_{11} = \frac{a_{21}}{a_{12}} g_{12} = \frac{a_{22}}{a_{12}} \] (17)

Thus one obtains the state-space equations

\[\dot{z}_1 = z_2 \quad \dot{z}_2 = z_3 \quad \dot{z}_3 = f_1 + g_{11} v_1 + g_{12} v_2 \]
\[\dot{z}_4 = z_5 \quad \dot{z}_5 = z_6 \quad \dot{z}_6 = f_2 + g_{21} v_1 + g_{22} v_2 \]
\[z_7 = z_8 \quad \dot{z}_8 = v_1 \]
\[\dot{z}_9 = z_{10} \quad \dot{z}_{10} = v_2 \] (18)

which can also be written in the following matrix form

\[
\begin{pmatrix}
\dot{z}_1 \\
of(z) = 
\dot{z}_2 \\
of(z) = 
\dot{z}_3 \\
of(z) = 
\dot{z}_4 \\
of(z) = 
\dot{z}_5 \\
of(z) = 
\dot{z}_6 \\
of(z) = 
\dot{z}_7 \\
of(z) = 
\dot{z}_8 \\
of(z) = 
\dot{z}_9 \\
of(z) = 
\dot{z}_{10} \
\end{pmatrix}
= 
\begin{pmatrix}
0 & 0 \\0 & 0 \\0 & 0 \\0 & 0 \\
0 & 1 \\0 & 0 \\0 & 0 \\
\end{pmatrix}
\begin{pmatrix}
\epsilon_1 \\
\epsilon_2 \\
\epsilon_3 \\
\epsilon_4 \\
\epsilon_5 \\
\epsilon_6 \\
\epsilon_7 \\
\epsilon_8 \\
\epsilon_9 \\
\epsilon_{10} \
\end{pmatrix}
\] (19)

By defining the state vector \(z = [z_1, z_2, ..., z_{10}]^T\) and the control inputs vector \(v = [v_1, v_2]^T\) one arrives at the state-space description

\[z = F(z) + G(z)v \] (20)

3 Linearised state-space form of the system

The system of (20), describing the cardiac function, can be also written in the common linear state-space form

\[\dot{x} = Ax + Bu + \tilde{d} \] (21)

where (see equation (22) at the bottom of the next page)

where \(\tilde{d}\) is the disturbances’ vector due to the approximate linearisation of the system.

4 Differential flatness properties of the cardiac function model

By proving differential flatness properties for a dynamical system, its transformation to an equivalent linear canonical form is possible. Using the latter description, the solution of the control and state estimation problems is enabled. A dynamical system in state-space form is considered to be differentially flat if (i) all its state variables and its control inputs can be expressed as differential functions of specific algebraic variables which in turn depend on only a subset of its state vector elements and (ii) the flat outputs and their derivatives are not connected between them through a relation of the form of an ordinary differential equation [18–20]. The dynamics of the cardiac function is given by (see equation (23) at the bottom of the page)

The system exhibits zero dynamics. Actually, one can describe it by
two potentially decoupled subsystems of the form

\[ z_1^{(3)} = \begin{pmatrix} a_{11} & a_{12} \\ a_{11} & a_{12} \end{pmatrix} \begin{pmatrix} z_1 \\ z_2 \end{pmatrix}, \]

or equivalently

\[ z_1^{(3)} = \begin{pmatrix} a_{11} & a_{12} \\ a_{11} & a_{12} \end{pmatrix} \begin{pmatrix} z_1 \\ z_2 \end{pmatrix} + \begin{pmatrix} b_{11} & b_{12} \\ b_{11} & b_{12} \end{pmatrix} \begin{pmatrix} \dot{z}_1 \\ \dot{z}_2 \end{pmatrix} \]

\[ \begin{pmatrix} z_3 \\ z_4 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} \\ a_{11} & a_{12} \end{pmatrix} \begin{pmatrix} z_3 \\ z_4 \end{pmatrix} + \begin{pmatrix} b_{11} & b_{12} \\ b_{11} & b_{12} \end{pmatrix} \begin{pmatrix} \dot{z}_3 \\ \dot{z}_4 \end{pmatrix} \]  

\[ \begin{pmatrix} z_5 \\ z_6 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} \\ a_{11} & a_{12} \end{pmatrix} \begin{pmatrix} z_5 \\ z_6 \end{pmatrix} + \begin{pmatrix} b_{11} & b_{12} \\ b_{11} & b_{12} \end{pmatrix} \begin{pmatrix} \dot{z}_5 \\ \dot{z}_6 \end{pmatrix} \]

or equivalently

\[ z_3^{(3)} = f_3(z) + g_{11} v_1 + g_{12} v_2 \]

\[ z_4^{(3)} = f_4(z) + g_{21} v_1 + g_{22} v_2 \]

in which state variables \( z_7, z_8, z_9, z_{10} \) are not related to state variables \( z_1-\dot{z}_6 \) or to the measured outputs of the system \( z_1-\dot{z}_4 \). The system can be also written in matrix form as

\[ \begin{pmatrix} \dot{z}_1^{(3)} \\ \dot{z}_2^{(3)} \end{pmatrix} = \begin{pmatrix} f_1(z) \\ f_2(z) \end{pmatrix} + \begin{pmatrix} g_{11} & g_{12} \\ g_{21} & g_{22} \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} \]

The flat output of the cardiac function’s model is taken to be the vector \( \hat{Y} = [z_1, z_2, z_3, z_4]^T \). It holds that

\[ z_1 = \begin{pmatrix} 1 & 0 & 0 & 0 \end{pmatrix} \hat{Y}, \quad z_2 = \begin{pmatrix} 0 & 1 & 0 & 0 \end{pmatrix} \hat{Y}, \quad z_3 = \begin{pmatrix} 0 & 0 & 1 & 0 \end{pmatrix} \hat{Y}, \quad z_4 = \begin{pmatrix} 0 & 0 & 0 & 1 \end{pmatrix} \hat{Y} \]

Moreover, it holds that \( z_2 = \dot{z}_1, z_3 = \dot{z}_2, z_4 = \dot{z}_3 \) and \( z_5 = \dot{z}_4 \) and additionally \( z_8 = \dot{z}_7 \) and \( z_{10} = \dot{z}_9 \). Therefore, state variables \( z_2, z_3, z_5, z_6, z_8, z_{10} \) are differential functions of the flat output.

To remain consistent with the requirement that the dimension of the inputs of the system should be equal to the dimension of the flat outputs vector one can define additional (virtual) control inputs, e.g. \( v_1 = (b_{11}/a_{11}) \) and \( v_4 = (b_{12}/a_{12}) \). Moreover, from (28) one obtains

\[ z_1^{(3)} = f_1(Y, \dot{Y}, \ddot{Y}) + g_{11} v_1 + g_{12} v_2 \]

\[ z_4^{(3)} = f_4(Y, \dot{Y}, \ddot{Y}) + g_{21} v_1 + g_{22} v_2 \]

which in matrix form is written as

\[ \begin{pmatrix} z_1^{(3)} \\ z_4^{(3)} \end{pmatrix} = \begin{pmatrix} f_1(Y, \dot{Y}, \ddot{Y}) \\ f_4(Y, \dot{Y}, \ddot{Y}) \end{pmatrix} + \begin{pmatrix} g_{11} & g_{12} \\ g_{21} & g_{22} \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} \]

Thus, after solving with respect to \( v_1 \) and \( v_2 \) one obtains

\[ \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} g_{11} & g_{12} \\ g_{21} & g_{22} \end{pmatrix}^{-1} \begin{pmatrix} z_1^{(3)} \\ z_4^{(3)} \end{pmatrix} - \begin{pmatrix} f_1(Y, \dot{Y}, \ddot{Y}) \\ f_4(Y, \dot{Y}, \ddot{Y}) \end{pmatrix} \]

Consequently, the control inputs \( v_1, v_2 \) are also expressed as differential functions of the flat output. Therefore, the cardiac function’s model is a differentially flat one.

5 Design of a stabilising flatness-based controller

A stabilising feedback control input for the previous description of (28) of the system is described as follows: (see equation (33) at the bottom of the next page)

by defining the tracking error \( e_1 = z_1 - z_{1*,d} \) and \( e_4 = z_4 - z_{4*,d} \), the application of the feedback control law of (33) into (28) results in

\[ \dot{z}_1 = z_2 \]

\[ \dot{z}_2 = z_3 \]

\[ \dot{z}_3 = -a_{11} z_3 - a_{12} z_2 + b_{11} z_1 + b_{12} z_4 + a_{11} \dot{z}_1 + a_{12} \dot{z}_2 + b_{11} \dot{z}_1 + b_{12} \dot{z}_4 \]

\[ \dot{z}_4 = z_5 \]

\[ \dot{z}_5 = -a_{11} z_5 - a_{12} z_4 + b_{11} z_3 + b_{12} z_6 + a_{11} \dot{z}_3 + a_{12} \dot{z}_4 + b_{11} \dot{z}_3 + b_{12} \dot{z}_6 \]

\[ \dot{z}_6 = -a_{11} z_6 - a_{12} z_5 + b_{11} z_4 + b_{12} z_7 + a_{11} \dot{z}_4 + a_{12} \dot{z}_5 + b_{11} \dot{z}_4 + b_{12} \dot{z}_7 \]

\[ \dot{z}_7 = z_8 \]

\[ \dot{z}_8 = v_1 \]

\[ \dot{z}_9 = z_{10} \]

\[ \dot{z}_{10} = v_2 \]
the tracking error dynamics
\[ \begin{align*}
&\dot{e}_1^{(3)} + k_1^1 \dot{e}_1 + k_1^2 e_1 + k_1^3 e_1 = 0 \\
&\dot{e}_4^{(3)} + k_4^1 \dot{e}_4 + k_4^2 e_4 + k_4^3 e_4 = 0
\end{align*} \tag{34} \]
by selecting the coefficients (feedback gains) \( k_i^j \) \( i = 1, 2, 3 \) and \( k_i^4 \) \( i = 1, 2, 3 \) so as the associated characteristic polynomials to be Hurwitz stable one assures that
\[ \lim_{t \to \infty} e_1(t) = 0 \quad \lim_{t \to \infty} e_4(t) = 0 \]
\[ \lim_{t \to \infty} z_1(t) = z_{1,d} \quad \lim_{t \to \infty} z_4(t) = z_{4,d} \tag{35} \]

6 Design of a disturbances’ estimator

Disturbances affecting the control loop of cardiac’s function can be estimated and compensated with the use of a disturbance observer. In case of additive disturbance inputs (which may represent modelling and linearisation errors or external perturbations), the previous linearised and decoupled description of the system is rewritten as
\[ \begin{align*}
\dot{x}_1^{(3)} &= f_1(z_1) + g_{11} q_1 + g_{12} q_2 \\
\dot{x}_2^{(3)} &= f_2(z_2) + g_{21} q_3 + g_{22} q_4
\end{align*} \tag{36} \]

The effect of such disturbances can be compensated with the use of a Kalman filter-based disturbances estimator [18–20]. In such a case, one can also consider the disturbances and their derivatives as state variables of the system. The state variables of the model are redefined as: \( q_1 = z_1, q_2 = z_1, q_3 = z_1, q_4 = z_4, q_5 = \dot{z}_1, q_6 = \dot{z}_1, q_7 = \dot{z}_1, q_8 = \dot{z}_1, q_9 = \dot{z}_1, q_{10} = \dot{z}_1 \). By defining \( \dot{d}_1 = \dot{f}_1 \) and \( \dot{d}_2 = \dot{f}_2 \) and by defining the extended state vector \( \tilde{q} = [q_1, q_2, \ldots, q_{10}]^T \), the following state-space form is obtained
\[ \begin{pmatrix}
\dot{q}_1 \\
\dot{q}_2 \\
\dot{q}_3 \\
\dot{q}_4 \\
\dot{q}_5 \\
\dot{q}_6 \\
\dot{q}_7 \\
\dot{q}_8 \\
\dot{q}_9 \\
\dot{q}_{10}
\end{pmatrix} =
\begin{pmatrix}
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
\begin{pmatrix}
q_1 \\
q_2 \\
q_3 \\
q_4 \\
q_5 \\
q_6 \\
q_7 \\
q_8 \\
q_9 \\
q_{10}
\end{pmatrix} +
\begin{pmatrix}
\frac{\dot{d}_1}{f_1} \\
\frac{\dot{d}_2}{f_2}
\end{pmatrix} \tag{37}
\]
\[ \begin{pmatrix}
q_{1,m} \\
q_{4,m}
\end{pmatrix} =
\begin{pmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
\begin{pmatrix}
\tilde{q}
\end{pmatrix} \tag{38}
\]
where \( q_{1,m} \) and \( q_{4,m} \) are the measured outputs of the system. Thus the extended dynamics of the system is written in the form
\[ \dot{\tilde{q}} = A_{\tilde{q}} \tilde{q} + B_{\tilde{q}} \bar{v} \]
\[ \tilde{q}'' = C_{\bar{q}} \tilde{q} \tag{39} \]
The associated disturbances estimator is based on the following state-space description
\[ \dot{\tilde{q}} = A_{\tilde{q}} \tilde{q} + B_{\tilde{q}} \bar{v} + K_{\tilde{q}} [\tilde{q}'' - \tilde{q}'] \]
\[ \tilde{q}'' = C_{\tilde{q}} \tilde{q} \tag{40} \]
where \( \tilde{q} \) is the estimated state vector and \( \tilde{q}'' \) are the elements of the estimated state vector which are used for computing the innovation that is the difference to the measurements obtained from the real system. Moreover, for the matrices appearing in the observer’s equation one has \( A_{\tilde{q}} = A_{q'}, C_{\tilde{q}} = C_{q} \) and
\[ B_{\tilde{q}}' = \begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{pmatrix} \tag{41} \]

After discretisation, the observer’s matrices are substituted by their discrete-time equivalents, that is, \( A_{\tilde{q}}', B_{\tilde{q}}', C_{\tilde{q}} \). The estimator’s gain can be computed through the Kalman filter recursion. The Kalman filter is applied to the linearised equivalent model, which was obtained by exploiting the differential flatness properties of the initially non-linear description of the system. This filtering procedure is also known as derivative-free non-linear Kalman filter [18–20]. The filter’s algorithm is formulated through a measurement-update and a time-update stages [31–33]

Measurement update
\[ K_{\tilde{q}}(k) = P(k)C_{\tilde{q}}[C_{\tilde{q}}'P(k)C_{\tilde{q}} + R(k)]^{-1} \]
\[ \tilde{q}(k) = \tilde{q}''(k) + K_{\tilde{q}}(k)[\tilde{q}''(k) - C_{\tilde{q}}' \tilde{q}(k)] \]
\[ P(k) = P(k) - K_{\tilde{q}}(k)C_{\tilde{q}}'P(k) \]

Time update
\[ P'(k + 1) = A'_{\tilde{q}}P(k)A'_{\tilde{q}} + T(k) \]
\[ \tilde{q}''(k + 1) = \tilde{A}_{\tilde{q}} \tilde{q}(k) + \tilde{B}_{\tilde{q}} \bar{v}(k) \]

Considering, that the disturbances’ estimates are provided through the state variables \( \tilde{z}_1 = \dot{d}_1 \) and \( \tilde{z}_2 = \dot{d}_2 \), to annihilate the disturbances’ effects, the feedback control input should be defined as follows: (see (44))

Remark 1: Differential flatness properties are proven to hold for the extended state-space description of the system, that is, the model obtained after defining as additional state variables specific control inputs. To provide the feedback control scheme with robustness, the Kalman filter is designed as a disturbance observer. This enables to estimate perturbation terms affecting the model of the cardiac function. These perturbations can be either due to model uncertainty or due to external disturbances. Once disturbances are identified they can be compensated with the inclusion of an
additional term in the control signal. The stability properties of the control scheme that makes use of the disturbance estimator are those of linear quadratic Gaussian (LQG) control.

7 Simulation tests

To further confirm the stability and robustness properties of the proposed control scheme simulation experiments have been performed. The obtained results are presented in Figs. 2–11. The problem of tracking of different reference setpoints has been considered. The real state variables of the system of heart dynamics are depicted with the light grey lines. The estimated state variables as provided by Kalman filtering are depicted with the green line. The reference setpoints are depicted with the dark grey line. It can be observed that through flatness-based control, fast and accurate tracking of the reference setpoints was succeeded. The convergence of the monitored haemodynamic

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**Fig. 2** Flatness-based control of haemodynamic parameters when tracking setpoint 1

- a Convergence of state variables $x_1$ (ACO) and $x_4$ (ABP) to the reference setpoints
- b Convergence of state variables $x_2$ and $x_5$ to the reference setpoints

**Fig. 3** Flatness-based control of haemodynamic parameters when tracking setpoint 1

- a Convergence of state variables $x_3$ and $x_6$ to the reference setpoints
- b Estimation of disturbances $d_1$ and $d_2$ by the disturbance observer
parameters, that is, of the cardiac output ($\Delta CO$) and of the arterial blood pressure ($\Delta BP$) to the desirable levels was fast and the associated transients were satisfactory. For the case of tracking of five different setpoints, this has been presented in Figs. 2a, 4a, 6a, 8a and 10a.

The simulation experiments have also confirmed the robustness of the control method. Modelling uncertainties, parametric variations and external perturbations affecting the heart’s function model were represented by additive input disturbances $\tilde{d}_1$ and $\tilde{d}_2$. These were dynamically identified by the proposed Kalman filtering method that was applied on the linearised model of the system (derivative-free non-linear Kalman filter). As shown in Figs. 3b, 5b, 7b, 9b and 11b, the Kalman filter was capable of estimating in real-time disturbance terms. By knowing the values of these perturbation variables their compensation was also possible after including an additional control term in the feedback control input.

**Fig. 4** Flatness-based control of haemodynamic parameters when tracking setpoint 2

a Convergence of state variables $x_1$ ($\Delta CO$) and $x_4$ ($\Delta BP$) to the reference setpoints

b Convergence of state variables $x_2$ and $x_5$ to the reference setpoints

**Fig. 5** Flatness-based control of haemodynamic parameters when tracking setpoint 2

a Convergence of state variables $x_3$ and $x_6$ to the reference setpoints

b Estimation of disturbances $d_1$ and $d_2$ by the disturbance observer
Remark 2: The model of response of the cardiac function ($\Delta$BP and $\Delta$CO) to the infusion of medication (SNP and DP) is a non-trivial one. This is because it describes a multi-variable (MIMO) dynamics and because time delays between the inputs and the outputs stand for strong non-linearities which impose additional difficulty to the stabilisation of the control loop. Besides the considered system exhibits the so-called zero dynamics which means that the outputs are not affected only by the control inputs but are also determined by the derivatives of these inputs. By following the concept of dynamic extension, that is, by defining as additional state variables certain control inputs and their derivatives one arrives at a modified states-space description of the system which is shown to be differentially flat and consequently which can be transformed through a diffeomorphism into the linear canonical (Brunovsky) form. For the latter description, the solution of the control and state estimation problem becomes possible. Besides, for the latter description a disturbance observer can be designed, allowing to estimate and compensate for model

Fig. 6 Flatness-based control of haemodynamic parameters when tracking setpoint 3

a Convergence of state variables $x_1$ (ACO) and $x_4$ (ABP) to the reference setpoints
b Convergence of state variables $x_2$ and $x_3$ to the reference setpoints

d Convergence of state variables $x_5$ and $x_6$ to the reference setpoints

e Estimation of disturbances $d_1$ and $d_2$ by the disturbance observer

Fig. 7 Flatness-based control of haemodynamic parameters when tracking setpoint 3

a Convergence of state variables $x_1$ and $x_2$ to the reference setpoints
b Estimation of disturbances $d_1$ and $d_2$ by the disturbance observer
uncertainty and perturbation inputs affecting the cardiac function's model.

Remark 3: Flatness is a property of only the state if the system is 0-flat. A dynamical system which is not differentially flat in its initial state-space description can be shown to satisfy differential flatness properties in its extended state-space model. The latter model can be obtained after applying the principle of dynamic extension, that is, after defining specific control inputs of the system as additional state variables. To demonstrate differential flatness, the following properties should hold: (i) all state variables and the control inputs of the model should be expressed as differential functions of a subset of state variables which define the flat output of the system and (ii) the flat output and its derivatives are differentially independent, which means that they are not coupled to each other through a relation in the form of a non-linear differential equation. Obviously, in the case of the
The extended state-space model of the cardiac function, both conditions (i) and (ii) hold and thus this model is a differentially flat one.

Remark 4: The differential flatness properties of the model of cardiac function have been confirmed and this enabled the transformation of the system's dynamics into the linear canonical form. Regarding the effects of time delays, these have been approximated through the Taylor series expansion of the delay term while the remaining terms in this expansion are perceived as disturbances which are estimated by the robustness of the control algorithm. The proposed control scheme has been proven to assure elimination of the disturbance and model uncertainty terms and to assure global asymptotic stability for the control loop.

Remark 5: Differential flatness properties are proven to hold for the extended state-space description of the system, that is, the model
obtained after defining as additional state variables specific control inputs. To provide the feedback control scheme with robustness, the Kalman filter is designed as a disturbance observer. This enables to estimate perturbation terms affecting the model of the cardiac function. These perturbations can be either due to model uncertainty or due to external disturbances. Once disturbances are identified they can be compensated with the inclusion of an additional term in the control signal. The stability properties of the control scheme that makes use of the disturbance estimator are those of LQG control.

8 Conclusions
This paper has presented a differential flatness theory-based solution to the problem of regulation of haemodynamic parameters such as the cardiac output and the arterial blood pressure. The control inputs to this model were provided by the infusion of the cardiovascular drugs such as Dopamine and Sodium Nitroprusside. Through approximate linearisation of the time-delay terms that appear in the model of the heart’s dynamics and by applying the principle of dynamic extension a state-space description of the heart’s dynamics was obtained. Next, the differential flatness properties of this state-space description were proven and this enabled the transformation of the model into a linear canonical and decoupled form. Using the latter representation of the system’s dynamics, a stabilising feedback controller was designed. It was proven that this controller assures fast and accurate convergence of the model’s state variables to the reference setpoints.

Additionally, to implement feedback control by measuring only the two aforementioned outputs of the heart’s model, the Kalman filter has been used. Moreover, by redesigning the Kalman filter as a disturbance observer it has become possible to estimate in real-time and compensate for additive disturbance terms that affect the heart’s dynamics. Such perturbation inputs can be due to modelling uncertainty, parametric variations, approximate linearisation of the time-delay terms of the model or external disturbances that affect the infusion of the cardiovascular drugs. With the use of the Kalman filter as a disturbance estimator, the robustness of the control loop was further improved. Finally, simulation experiments have been performed to evaluate the stability and robustness features of the control method.

9 References
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