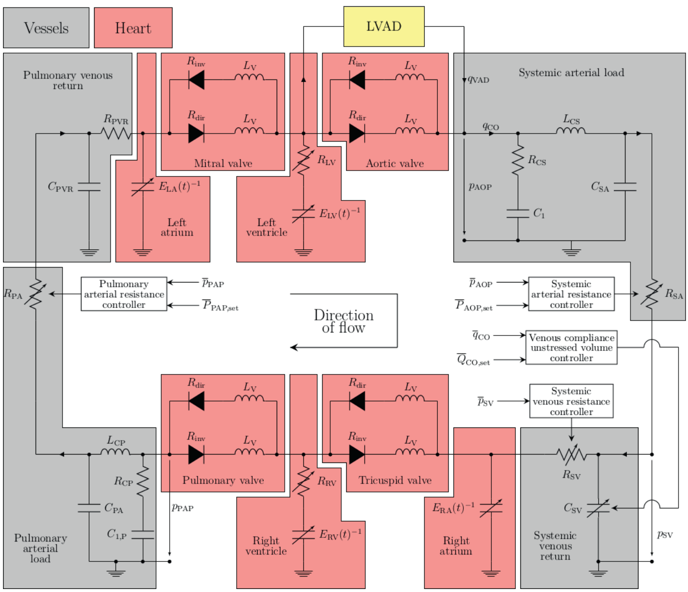
Band 54

Daniel Rüschen

Robust Physiological Control of Left Ventricular Assist Devices



Aachener Beiträge zur Medizintechnik

Herausgeber:

Univ.-Prof. Dr.-Ing. Dr. med. Dr. h. c. Steffen Leonhardt
Univ.-Prof. Dr.-Ing. Klaus Radermacher
Univ.-Prof. Dr. med. Dipl.-Ing. Thomas Schmitz-Rode

Robust Physiological Control of Left Ventricular Assist Devices

Von der Fakultät für Elektrotechnik und Informationstechnik der Rheinisch-Westfälischen Technischen Hochschule Aachen zur Erlangung des akademischen Grades eines Doktors der Ingenieurwissenschaften genehmigte Dissertation

vorgelegt von

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Robust Physiological Control of Left Ventricular Assist Devices

Ein Beitrag aus dem Lehrstuhl für Medizinische Informationstechnik
(Univ.-Prof. Dr.-Ing. Dr. med. Dr. h.c. Steffen Leonhardt).

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The question is what is the question

H. P. Baxxter

Acknowledgments

This thesis is the result of two interdisciplinary research projects I conducted during my time as a research associate in the Medical Information Technology (MedIT) group of the RWTH Aachen University. Since almost all the people I want to thank are native German speakers, the remainder of this section is written in German.

An erster Stelle danke ich Herrn Professor Steffen Leonhardt, der mich mit viel Engagement förderte und diese Arbeit mit unzähligen Impulsen prägte. Er gab mir genug Freiraum um meine eigenen Ideen zu verfolgen und war immer da, wenn ich ihn brauchte. Herr Professor Leonhardt hat die Rolle des Doktorvaters weit über die fachliche Betreuung hinaus ausgefüllt, dafür bin ich ihm sehr dankbar. Herrn Professor Oliver Nelles möchte ich für das große Interesse an dieser Arbeit und für die Übernahme des Korreferats danken.

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Abstract

Due to the increasing shortage of donor hearts, modern left ventricular assist devices (LVADs) have become a real alternative to heart transplantation in advanced heart failure therapy. Rotary blood pumps (RBPs) are often used as LVADs in order to relieve the weakened native heart and increase the cardiac output (CO). In clinical practice, RBPs are typically operated with fixed speed control which causes an insufficient adaption of the pump flow to the varying blood flow demand of the patient. This can lead to undesired or even dangerous operating conditions and prevents LVAD patients from living normal lives. There are numerous approaches to the demand-driven operation of LVADs, but there is still no agreement on two pivotal questions in control engineering: "what is the appropriate control variable?" and "what is the corresponding setpoint?".

This thesis aims to address these questions by presenting a robust control concept that ensures an adjustable load distribution between the native heart and an RBP. In order to quantify the distribution of cardiac workload, the assistance ratio is introduced. Intuitively, it is defined as the time-averaged ratio of RBP flow and total CO. By using this relative value as the control variable, the changes of the residual CO are amplified. If these changes are initiated by the remaining native physiological control loops, the combination of the damaged heart and an LVAD restores the functionality comparable to a healthy heart. For this purpose, a robust $\mathcal{H}_\infty$ controller was designed to cope with the uncertainty caused by inter- and intra-patient variability. The robustness of the closed-loop control system was analyzed using detailed mathematical models of the human cardiovascular system (CVS) and a transvalvular LVAD with uncertainties. In the final control system, the assistance ratio is determined from estimations of the pump flow and the aortic flow rate. For the latter, an extended Kalman filter is proposed which uses measurements provided by fiber-optic pressure sensors mounted on the pump inlet and outlet. Based on a μ analysis, the resulting closed-loop control system is robustly stable.

The assistance control strategy was successfully tested *in vitro* using a hydrodynamic CVS simulator as well as *in vivo* in two different animal studies with sheep suffering from acute heart failure. The evidence from these acute trials suggests that, if the native CO control loops are still intact, the assistance control strategy adequately maintains the systemic circulation. The assistance ratio offers an intuitive setting option for the responsible physician and allows the future definition of therapy protocols independently of a specific device or an individual patient. This could eventually lead to an improved rate of myocardial recovery and successful weaning in LVAD therapy.

Contents

Abbreviations and symbols

Mathematical notation and conventions

The following conventions are followed with regard to the style of mathematical notation: Scalar functions and time-varying signals are denoted by lowercase italic letters followed by their argument in parentheses, i.e. $f(t)$. In general, column vectors are printed in bold lowercase ($\mathbf{x}$), while matrices are represented by bold uppercase letters ($\mathbf{A}$). Functions that yield matrices are written calligraphically ($\mathcal{F}_1$) in order to distinguish them from matrices. If the argument of the function is either the time t or the LAPLACE variable s, it is often omitted. Parameters and constants are denoted by uppercase italic Latin letters (R) or exceptionally by lowercase greek letters, in cases where these are more common (i.e. τ). Moreover, vector spaces and fields are indicated by uppercase blackboard bold letters ($\mathbb{R}$), whereas normed vector spaces are denoted by uppercase calligraphic letters ($\mathcal{L}^\infty$).

The finite difference or change of a quantity is denoted by a preceding delta (Δp), while the first derivative with respect to time is marked by a central dot ($\dot{x}$). The asterisk is used to either mark constant peak values of a signal (V^*) or nonlinear (transfer function) matrices ($\mathbf{G}^*$). Furthermore, the mean value of an arbitrary signal or vector is identified by a horizontal bar above the respective symbol ($\overline{q}$). The only exception are singular values, for which the bar above or below indicates the maximum ($\overline{\sigma}$) or minimum ($\underline{\sigma}$). Usually, a hat symbol on top of a variable ($\hat{x}$) identifies estimated quantities. Variables associated with a balanced state-space realization will be marked by a tilde ($\tilde{x}$). Moreover, the real part of a complex variable is denoted by $\mathrm{Re}\{\cdot\}$. The notation regarding vectors and matrices is in accordance with PETERSEN and PEDERSEN [PP08].

As suggested by LEONHARDT and WALTER in [LW16], variables that represent physical quantities are denoted by their common symbols (i.e. p for pressure) and, in case there is a well-established medical term, it is used as an index (i.e. q_{CO} for cardiac output). Furthermore, all systems are multiple-input and multiple-output (MIMO), unless stated otherwise. Finally, the term physiological control will usually be used for a technical control system.

List of abbreviations

Abbrev.	Meaning
AHA	American Heart Association
AHF	acute heart failure
AV	aortic valve
AWU	anti-windup
BAI	blood assist index
BIBO	bounded-input bounded-output
BiVAD	biventricular assist device
BTC	bridge to candidacy
BTD	bridge to decision
BTR	bridge to recovery
BTT	bridge to transplantation
CAN	controller area network
CO	cardiac output
CVS	cardiovascular system
DT	destination therapy
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
EDPVR	end-diastolic pressure volume relationship
EDV	end-diastolic volume
EKF	extended Kalman filter
ESC	European Society of Cardiology
ESPVR	end-systolic pressure volume relationship
ESV	end-systolic volume
GP	gear pump
HF	heart failure
HR	heart rate
IABP	intra-aortic balloon pump
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
KF	Kalman filter
LA	left atrium
LFT	linear fractional transformation

Abbrev.	**Meaning**
LMI	linear matrix inequality
LV	left ventricle
LVAD	left ventricular assist device
MAF	moving average filter
MCL	mock circulatory loop
MCS	mechanical circulatory support
MIMO	multiple-input and multiple-output
MV	mitral valve
NP	nominal performance
NS	nominal stability
NYHA	New York Heart Association
ODE	ordinary differential equation
PAL	pulmonary arterial load
PCLCS	physiologic closed-loop control system
PI	proportional-integral
PR	power ratio
RA	right atrium
RBP	rotary blood pump
RMSE	root-mean-square error
RP	robust performance
RS	robust stability
RV	right ventricle
RVAD	right ventricular assist device
SAL	systemic arterial load
SISO	single-input single-output
SSV	structured singular value
SV	stroke volume
SW	stroke work
TAH	total artificial heart
VAD	ventricular assist device
VCA	voice coil actuator

List of Latin symbols

Symbol	Unit	Meaning
$a(t)$	[%]	assistance ratio
$\hat{a}(t)$	[%]	estimated assistance ratio
$\mathbf{A}$		state-space system matrix, generic matrix
$\mathbf{B}$		state-space input matrix
$\mathbf{C}$		state-space output matrix
C	$[\mathrm{mL\,mmHg^{-1}}]$	compliance
$\mathbb{C}$		field of complex numbers
$\mathbb{C}^n$		n-dimensional complex vector space
$\mathbb{C}^{n\times m}$		space of complex $n \times m$ matrices
$\mathbf{d}(t)$		disturbance
$\det(\mathbf{A})$		determinant of a square matrix $\mathbf{A}$
$\mathbf{D}$		state-space feedthrough matrix
$\mathbf{e}(t)$		control error
$\overline{e}_{\mathrm{rel}}$	[%]	average relative error
e_{rms}	$[\mathrm{L\,min^{-1}}]$	root-mean-square error
E	$[\mathrm{mmHg\,mL^{-1}}]$	elastance
$f(\cdot)$		generic function
f_{HR}	$[\mathrm{min^{-1}}]$	heart rate
$\mathbf{F}(\boldsymbol{\Delta})$		uncertain closed-loop transfer function
$\mathbf{F}_\infty$		optimal state feedback gain matrix
$\mathcal{F}_\mathrm{l}(\mathbf{P},\mathbf{K})$		lower linear fractional transformation
$\mathcal{F}_\mathrm{u}(\mathbf{N},\boldsymbol{\Delta})$		upper linear fractional transformation
$\mathbf{G}(j\omega)$		frequency response matrix
$\mathbf{G}(s)$		nominal plant model, generic transfer function matrix
$\mathbf{G}_d(s)$		disturbance model
$\mathbf{G}_\mathrm{p}(s)$		particular perturbed plant model
$\mathbf{G}^*_{\mathrm{VAD}}$		nonlinear VAD system model
$\mathcal{H}_\infty$		HARDY space on the closed right half of the complex plane
i		index

Symbol	Unit	Meaning
$i_{\mathrm{arm}}(t)$	[A]	armature current
$\mathbf{I}_n$		identity matrix $\in \mathbb{R}^{n\times n}$
j		unit imaginary number
J_{rot}	$[\mathrm{kg\,m^2}]$	moment of inertia of the rotor and impeller
k		time step
$\mathbf{K}(s)$		controller
$\mathbf{K}_{\mathrm{c}}(s)$		central controller
K_{e}	$[\mathrm{V\,s\,rad^{-1}}]$	back-EMF constant
K_{f}	$[\mathrm{N\,m\,s}]$	viscous friction constant
K_{pump}	$[\mathrm{mmHg\,s^2\,rad^{-2}}]$	pump constant
K_{t}	$[\mathrm{N\,m\,rad\,A^{-1}}]$	motor torque constant
l	[m]	ventricular wall thickness
$\mathbf{L}(s)$		loop transfer function
$\mathbf{L}_\infty$		optimal state observer gain matrix
L	$[\mathrm{mmHg\,s^2\,mL^{-1}}]$	inertance
L_{arm}	[mH]	armature inductance
L_{fluid}	$[\mathrm{mmHg\,s^2\,mL^{-1}}]$	hydraulic pump inertance
L_{ves}	[m]	length of a blood vessel
$\mathcal{L}^p(\mathbb{R})$		normed space consisting of signals with finite p-norm
$\mathcal{L}^p_n(\mathbb{R})$		extension of $\mathcal{L}^p(\mathbb{R})$ to n-dimensional vectors
$\mathcal{L}^\infty(\mathbb{R})$		normed space consisting of signals with finite ∞-norm
$\mathcal{L}^\infty_n(\mathbb{R})$		extension of $\mathcal{L}^\infty(\mathbb{R})$ to n-dimensional vectors
$\min_{\mathbf{x}} f(\mathbf{x})$		minimum of function f with respect to $\mathbf{x}$
$\mathbf{M}(s)$		transfer function matrix for robust stability analysis
$\widehat{\mathbf{M}}(s)$		transfer function matrix for internal stability analysis
n		constant integer
$\mathbf{n}(t)$		measurement noise

Symbol	**Unit**	**Meaning**
$\mathbf{N}(s)$		transfer function matrix for robust performance analysis
p		real number
$p(t)$	[mmHg]	pressure
$p_{\mathrm{A}}(v(t))$	[mmHg]	atrial pressure
$p_{\mathrm{AOP}}(t)$	[mmHg]	aortic pressure
$p_{C_{\mathrm{SA}}}(t)$	[mmHg]	systemic arterial compliance pressure
$p_{\mathrm{diastolic}}$	[mmHg]	diastolic pressure
$p_{\mathrm{EDPVR}}(v(t))$	[mmHg]	end-diastolic pressure volume relationship
$p_{\mathrm{ESPVR}}(v(t))$	[mmHg]	end-systolic pressure volume relationship
$p_{E_{\mathrm{V}}}(v(t),t)$	[mmHg]	pressure generated by the ventricular elastance
$p_{\mathrm{LA}}(t)$	[mmHg]	left atrial pressure
$p_{\mathrm{LVP}}(t)$	[mmHg]	left ventricular pressure
$p_{\mathrm{PAP}}(t)$	[mmHg]	pulmonary arterial pressure
$p_{\mathrm{PVR}}(t)$	[mmHg]	pulmonary venous return pressure
$p_{\mathrm{RA}}(t)$	[mmHg]	right atrial pressure
$p_{\mathrm{RV}}(t)$	[mmHg]	right ventricular pressure
$p_{\mathrm{SV}}(t)$	[mmHg]	systemic venous pressure
p_{systolic}	[mmHg]	systolic pressure
$\mathbf{P}(s)$		generalized plant model
$q(t)$	$[\mathrm{mL\,s^{-1}}]$	flow rate
$q_{\mathrm{AV}}(t)$	$[\mathrm{mL\,s^{-1}}]$	aortic valve flow rate
$q_{\mathrm{CO}}(t)$	$[\mathrm{mL\,s^{-1}}]$	aortic flow rate
$q_{C_{1,\mathrm{P}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	pulmonary compliance flow rate
$q_{C_{\mathrm{PA}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	pulmonary arterial compliance flow rate
$q_{C_{\mathrm{PVR}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	pulmonary venous compliance flow rate
$q_{C_{\mathrm{SA}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	systemic arterial compliance flow rate
$q_{\mathrm{LA}}(t)$	$[\mathrm{mL\,s^{-1}}]$	left atrial flow rate
$q_{\mathrm{LV}}(t)$	$[\mathrm{mL\,s^{-1}}]$	left ventricular flow rate
$q_{L_{\mathrm{CP}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	pulmonary inertance flow rate
$q_{L_{\mathrm{CS}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	systemic inertance flow rate
$q_{\mathrm{MV}}(t)$	$[\mathrm{mL\,s^{-1}}]$	mitral valve flow rate

Symbol	Unit	Meaning
$q_{\mathrm{PV}}(t)$	$[\mathrm{mL\,s^{-1}}]$	pulmonary valve flow rate
$q_{\mathrm{RA}}(t)$	$[\mathrm{mL\,s^{-1}}]$	right atrial flow rate
$q_{\mathrm{RV}}(t)$	$[\mathrm{mL\,s^{-1}}]$	right ventricular flow rate
$q_{R_{\mathrm{CS}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	characteristic systemic resistance flow rate
$q_{R_{\mathrm{PA}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	pulmonary arterial resistance flow rate
$q_{R_{\mathrm{PVR}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	pulmonary venous resistance flow rate
$q_{R_{\mathrm{SA}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	systemic arterial resistance flow rate
$q_{R_{\mathrm{SV}}}(t)$	$[\mathrm{mL\,s^{-1}}]$	systemic venous resistance flow rate
$q_{\mathrm{TV}}(t)$	$[\mathrm{mL\,s^{-1}}]$	tricuspid valve flow rate
$q_{\mathrm{VAD}}(t)$	$[\mathrm{mL\,s^{-1}}]$	left ventricular assist device flow rate
q_{valve}	$[\mathrm{mL\,s^{-1}}]$	directional valve flow rate
$\mathbf{Q}(s)$		stable proper transfer function, YOULA parameter
$\mathbf{Q}_{\mathrm{EKF}}$		extended KALMAN filter process noise covariance
$\mathbf{Q}_{\mathrm{KF}}$		KALMAN filter process noise covariance
$\mathbf{r}(t)$		reference input
r	$[\mathrm{m}]$	radius
$r_{\mathrm{BAI}}(\omega)$	$[\%]$	blood assist index
r_{EF}	$[\%]$	ejection fraction
$r_{\mathrm{PR}}(t)$	$[\%]$	power ratio
R	$[\mathrm{mmHg\,s\,mL^{-1}}]$	hydraulic resistance
R		measurement noise covariance
R_{arm}	$[\mathrm{m\Omega}]$	armature resistance
R_{fluid}	$[\mathrm{mmHg\,s\,mL^{-1}}]$	hydraulic pump resistance
R_{lam}	$[\mathrm{mmHg\,min\,L^{-1}}]$	laminar flow resistance
R_{turb}	$[\mathrm{mmHg\,min^2\,L^{-2}}]$	turbulent flow resistance
$\mathbb{R}$		field of real numbers
$\mathbb{R}^n$		n-dimensional real vector space
$\mathbb{R}^{n\times m}$		space of real $n \times m$ matrices
$\mathcal{RH}_\infty$		proper and real rational functions in $\mathcal{H}_\infty$
s	$[\mathrm{s^{-1}}]$	LAPLACE variable
$S_{\mathrm{O_2}}$	$[\%]$	Oxygen saturation

Symbol	Unit	Meaning
$\mathbf{S}(s)$		sensitivity function
t	[s]	continuous time variable
T	[s]	cardiac cycle length
T_s	[s]	sample time
$\mathbf{T}$		generic transformation matrix
$\mathbf{T}(s)$		complementary sensitivity function
$\mathbf{u}(t)$		control signal, plant input
$\mathbf{u}_\Delta$		perturbation output
$\mathbf{v}(t)$		controller input
$v(t)$	[mL]	volume
v_arm	[V]	armature voltage
v_EDV	[mL]	end-diastolic volume
v_ESV	[mL]	end-systolic volume
v_LAEDV	[mL]	left atrial end-diastolic volume
v_LAESV	[mL]	left atrial end-systolic volume
$v_\mathrm{LV}(t)$	[mL]	left ventricular volume
v_LVEDV	[mL]	left ventricular end-diastolic volume
v_LVESV	[mL]	left ventricular end-systolic volume
v_RAEDV	[mL]	right atrial end-diastolic volume
v_RAESV	[mL]	right atrial end-systolic volume
$v_\mathrm{RV}(t)$	[mL]	right ventricular volume
v_RVEDV	[mL]	right ventricular end-diastolic volume
v_RVESV	[mL]	right ventricular end-systolic volume
v_SV	[mL]	stroke volume
$\mathbf{w}(t)$		exogenous input
w_PE	[mmHg mL]	potential energy of the cardiac muscle
w_PVA	[mmHg mL]	systolic pressure-volume area
w_SW	[mmHg mL]	stroke work
$\mathbf{W}_1(s)$		weighting function for **S** in mixed sensitivity synthesis
$\mathbf{W}_2(s)$		weighting function for **KS** in mixed sensitivity synthesis
$\mathbf{W}_3(s)$		weighting function for **T** in mixed sensitivity synthesis

Symbol	Unit	Meaning
$\mathbf{W}_{\mathrm{a}}(s)$		additive uncertainty weighting function
$\mathbf{W}_{\mathrm{c}}$		controllability Gramian
$\mathbf{W}_{\mathrm{ia}}(s)$		inverse additive uncertainty weighting function
$\mathbf{W}_{\mathrm{if}}(s)$		input feedback uncertainty weighting function
$\mathbf{W}_{\mathrm{im}}(s)$		input multiplicative uncertainty weighting function
$\mathbf{W}_{\mathrm{o}}$		observability Gramian
$\mathbf{W}_{\mathrm{of}}(s)$		output feedback uncertainty weighting function
$\mathbf{W}_{\mathrm{om}}(s)$		output multiplicative uncertainty weighting function
$\mathbf{W}_{\mathrm{P}}(s)$		performance weighting function
$\mathbf{x}(t)$		state, generic continuous time signal
$\mathbf{X}_{\infty}$		positive definite solution of a matrix RICCATI equation
$\mathbf{y}(t)$		plant output, generic continuous time signal
$\mathbf{y}_{\mathrm{m}}(t)$		measured plant output
$\mathbf{y}_{\Delta}$		perturbation input
$\mathbf{Y}_{\infty}$		positive definite solution of a matrix RICCATI equation
$\mathbf{z}(t)$		exogenous output

List of Greek symbols

Symbol	Unit	Meaning
α		generic scalar
γ		upper bound of $\mathcal{H}_\infty$ norm
γ_{min}		minimum value of $\mathcal{H}_\infty$ norm
δ		norm bounded real perturbation
$\boldsymbol{\Delta}$		norm bounded complex perturbation matrix
Δp	[mmHg]	differential pressure
Δp_{d}	[mmHg]	difference between left ventricular and aortic pressure
Δp_{pump}	[mmHg]	differential pressure generated by the RBP
Δv	[mL]	change of volume
η	[Pa s]	dynamic viscosity
$\Theta(x)$		unit step function
$\lambda_i(\mathbf{A})$		eigenvalue of a square matrix $\mathbf{A}$
$\mu_{\boldsymbol{\Delta}}$		structured singular value with respect to $\boldsymbol{\Delta}$
π		3.141 592 653 589 793 238 462 643 . . .
Π		set of possible perturbed plant models
ρ		PEARSON correlation coefficient
$\rho(\mathbf{A})$		spectral radius of a square matrix $\mathbf{A}$
σ_i		singular value
$\underline{\sigma}$		minimum singular value
$\overline{\sigma}$		maximum singular value
$\sigma_{\mathrm{H},i}$		HANKEL singular value
σ_{wall}	[mmHg]	ventricular wall stress
$\widetilde{\boldsymbol{\Sigma}}$		Gramian of a balanced realization
τ	[s]	time constant, continuous time variable
$\tau(\omega, q_{\mathrm{VAD}})$	[N m rad]	load torque
ω	[rad s^{-1}]	continuous circular frequency variable, rotational speed
ω_{set}	[rad s^{-1}]	rotational speed setpoint