How well does our machine behave like the body?

Fitting a physiological model to a mechanical afterload.

Harry Pigot

LUNDS UNIVERSITET

Contents

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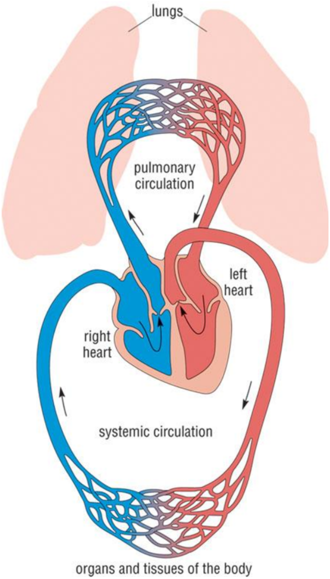
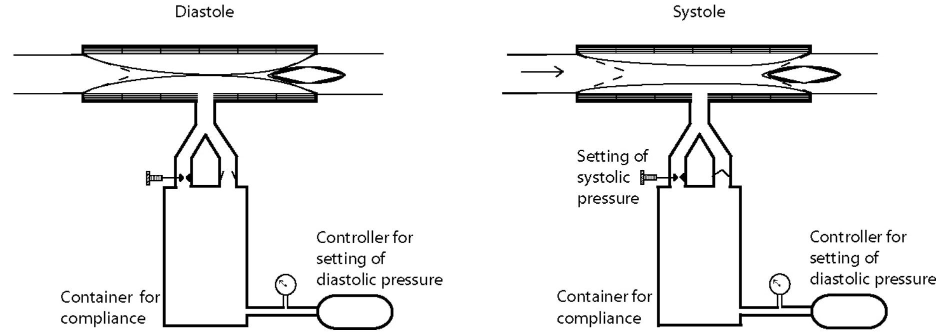
Contents

- goal: evaluate heart function outside of the body for safer (+ marginal) heart transplantation. To do this we use a mechanical load to represent the body.

Physiological afterload



Mechanical afterload

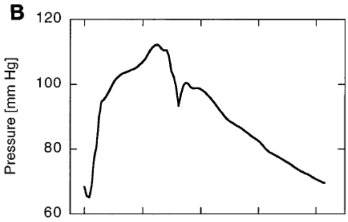


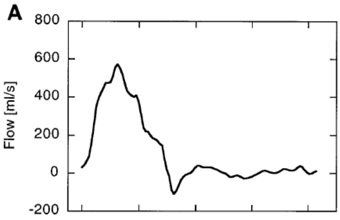
- Diastole: pressurized balloon stops blood flow
- Systole: “check valve” allows air out of balloon
- Measurement: balloon pressure
- Actuator: roller pump

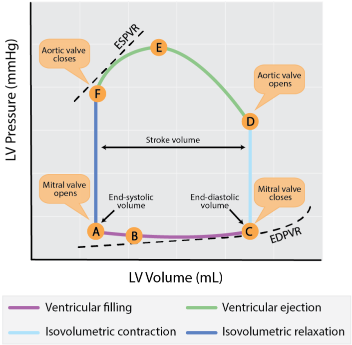
Mechanical afterload

redacted

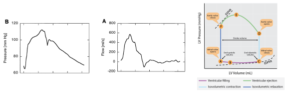
Motivation


B
120
100
80
60
Pressure [mm Hg]


A
800
600
400
200
0
-200
Flow [ml/s]

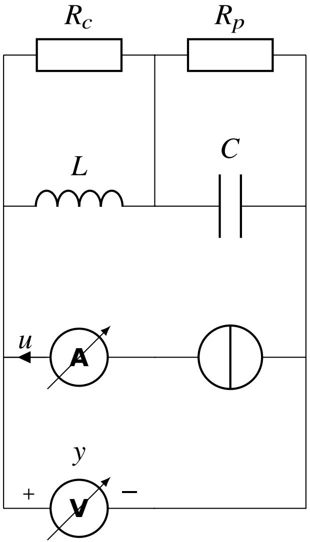

LV Pressure (mmHg)
LV Volume (mL)
ESPVR
EDPVR
Aortic valve closes
Aortic valve opens
Mitral valve opens
Mitral valve closes
Stroke volume
End-systolic volume
End-diastolic volume
A
B
C
D
E
F
Ventricular filling
Ventricular ejection
Isovolumetric contraction
Isovolumetric relaxation

Motivation

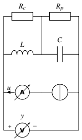


- So, how do we know that our load is physiologically representitive?
- We could look at P waveforms, but this is highly variable between individuals and conditions (same heart won't behave exactly the same in vivo and ex vivo).
- Alternatively, consider in PV loop (no more time info), another standard
- in the mechanical afterload, we can adjust the pressure (max,min,mean) and mean flow, but this doesn't necessarily translate to a physiologically accurate impedance.
- One idea is to use a well-established model of the load, with parameters that are widely considered to be physiologically interpretable, and fit that model to the measured data when using the mechanical load.

The Windessel heart afterload model



The Windessel heart afterload model



- That model is the Windkessel model.
- The heart is represented as a current source, with model input being flow and the output being pressure measured in the aorta (alt. pulmonary artery).

The Windessel heart afterload model

Parameter	Unit	Name
R_c	mmHg/(L/min)	Central resistance
R_p	mmHg/(L/min)	Peripheral resistance
C	L/mmHg	Compliance
L	mmHg min/(L/min)	Inertance

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- Note that the central resistance R_c contributes to flow impedance only during acceleration of blood through the system.

Model formulation

The circuit model yields the transfer function

$$G_c(s|\theta) = R_c + \frac{R_P}{1 + sCR_p} - \frac{R_c}{1 + sL/R_c}$$

from u to y, parameterized in

$$\theta = [R_c \; L \; C \; R_p]^\top \succ 0.$$

Model fitting

With parameter set The optimal parameter set is given by

$$\theta^{o} = \arg\min_{\theta \succ 0} J(\theta), \quad (1)$$

where

$$J(\theta) = \frac{1}{2}\epsilon(\theta)^{\top}\epsilon(\theta) \quad (2)$$

with output error of the model against the sampled system

$$\epsilon(\theta) = y - \hat{y}(\theta) \quad (3)$$

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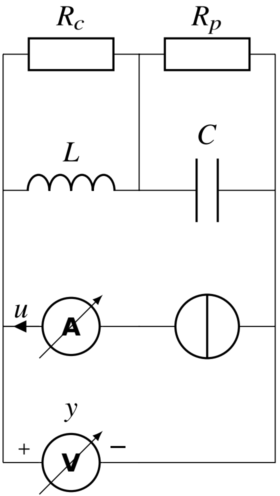
- minimize the squared error with Newton’s method
- Using the Optim package in Julia
- We identify the CT parameters directly (the ZOH operator is included within the optimized function). Guarantees that the DT system that’s solved maps back to our CT system.

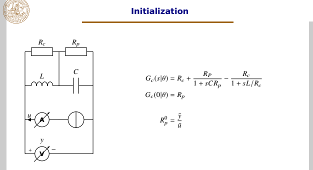
Initialization



$$G_c(s|\theta) = R_c + \frac{R_P}{1 + sCR_p} - \frac{R_c}{1 + sL/R_c}$$

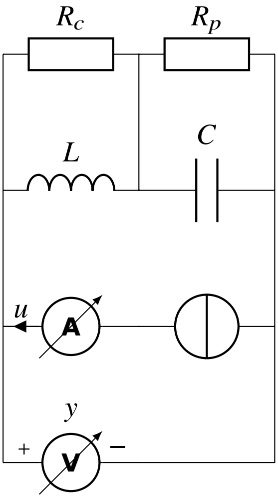
$$G_c(0|\theta) = R_p$$

$$R_p^0 = \frac{\bar{y}}{\bar{u}}$$



- multiple initialization
- One of four parameters (Rp) well approximated mean(P)/mean(Q)
- Otherwise, uniform positive distributions (0.001:10)

Initialization

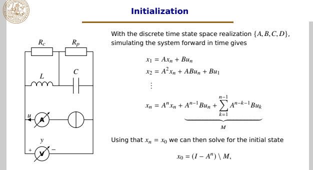


With the discrete time state space realization $\{A, B, C, D\}$, simulating the system forward in time gives

$$
\begin{aligned}
x_1 &= Ax_n + Bu_n \\
x_2 &= A^2 x_n + ABu_n + Bu_1 \\
&\vdots \\
x_n &= A^n x_n + \underbrace{A^{n-1}Bu_n + \sum_{k=1}^{n-1} A^{n-k-1}Bu_k}_{M}
\end{aligned}
$$

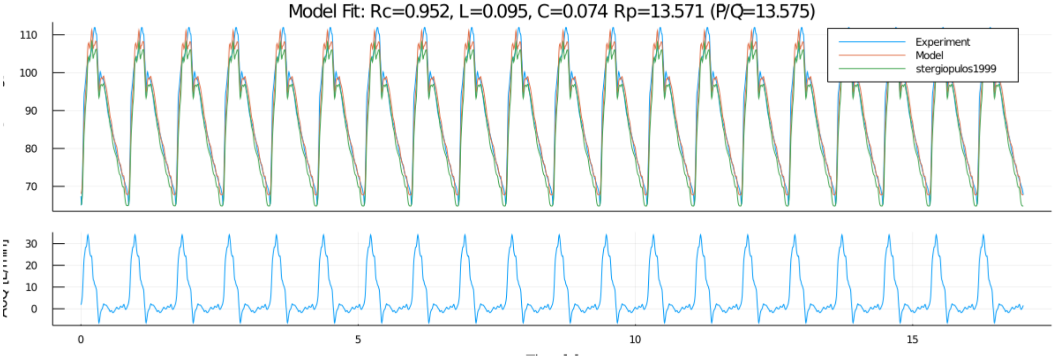
Using that $x_n = x_0$ we can then solve for the initial state

$$x_0 = (I - A^n) \setminus M,$$



- here we enforce the periodic stationarity condition, that the initial state is the same as the final state for a given periodic input. x0 = xn
- alternatively we could run a longer experiment and ignore the model output until the transient caused by our x0 guess fades. This could be long depending on the dynamics of the system.
- Here we instead solve for x0 directly using this periodic stationarity assumption (quite close to the truth for this system).

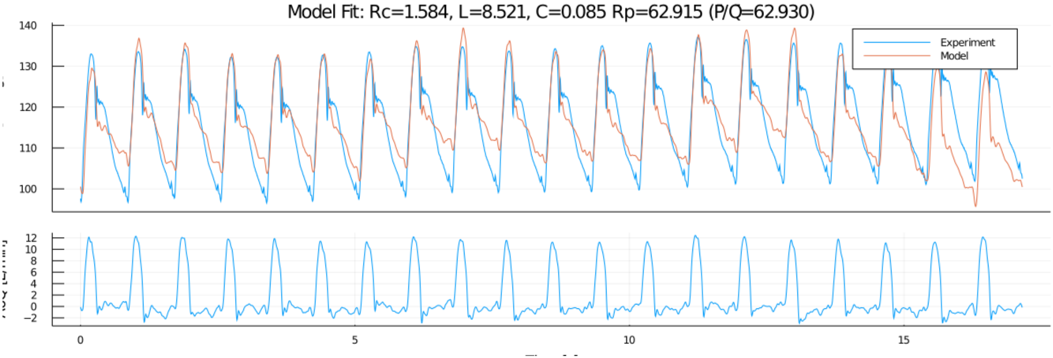
Fitting data from a previous publication



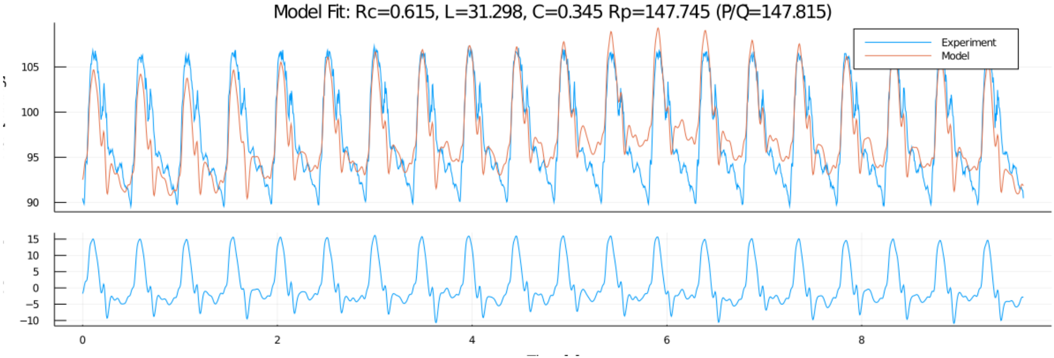
$$\theta = [0.93\ 0.085\ 0.073\ 13.2]^\top$$

$$\hat{\theta} = [0.95\ 0.095\ 0.074\ 13.6]^\top$$

In vivo measurements



Ex vivo measurements



Comparison of parameters

Data source	R_c	L	C	R_p	MSE
stergiopulos1999	0.95	0.095	0.074	13.6	0.029
in vivo	1.6	8.5	0.085	62.9	0.15
in vivo	1.6	4030	0.088	62.9	0.15
ex vivo	0.61	31	0.34	148	0.036

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- 1999: result closely matches fit from paper
- invivo: notably poorer MSE, but reasonable ranges
- invivo: similar MSE for vastly different L... low sensitivity and high uncertainty in that parameter
- exvivo: better MSE
- an advantage of this fitting method is that it allows for exact evaluation of the Hessian, facilitating sensitivity analysis.

Parameter sensitivity

$$J(\theta^o + \delta) - J(\theta^o) \approx \frac{1}{2}\delta^\top H \delta = \frac{1}{2}\delta^\top V \Sigma V^\top \delta,$$

Source	$\frac{\Sigma_{max}}{\Sigma_{min}}$	$V[1]^\top$	$V[4]^\top$
sterg1999	3e3	$\begin{bmatrix}-0.02 & 0.02 & -1 & 0\end{bmatrix}$	$\begin{bmatrix}1 & -0.28 & -0.21 & -0.01\end{bmatrix}$
in vivo	1e7	$\begin{bmatrix}0 & 0 & -1 & 0\end{bmatrix}$	$\begin{bmatrix}0 & 1 & 0 & 0\end{bmatrix}$
in vivo	3e14	$\begin{bmatrix}0 & 0 & 1 & 0\end{bmatrix}$	$\begin{bmatrix}0 & -1 & 0 & 0\end{bmatrix}$
ex vivo	3e9	$\begin{bmatrix}-1 & -0.07 & 0 & 0\end{bmatrix}$	$\begin{bmatrix}0 & 1 & 0 & 0\end{bmatrix}$

$$\theta = [R_c \; L \; C \; R_p]^\top$$

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ex vivo	3e9	$[-1\ \ -0.07\ \ 0\ \ 0]$	$[0\ \ 1\ \ 0\ \ 0]$

$$\theta = [R_c\ L\ C\ R_p]^\top$$

- Unitary vectors but I've rounded here for visibility.
- compare back to table (low confidence in L gives two close MSEs but vastly different params in in vivo case)
- ster + in vivo: most sensitive to C (highest certainty)
- ster least sensitive to Rc
- in vivo least sensitive to L, corresponding to vastly different L values on previous slide (same MSE)
- ex vivo most sensitive to Rc, least sensitive to L

State space form

In continuous time,

$$\dot{x}_c = \underbrace{\begin{bmatrix} -\frac{1}{CR_p} & 0 \\ 0 & -\frac{R_c}{L} \end{bmatrix}}_{A_c} x_c + \underbrace{\begin{bmatrix} 1 \\ R_c \end{bmatrix}}_{B_c} u_c$$
$$y_c = \underbrace{\begin{bmatrix} \frac{1}{C} & -\frac{R_c}{L} \end{bmatrix}}_{C_c} x_c + \underbrace{\begin{bmatrix} R_c \end{bmatrix}}_{D_c} u_c \tag{4}$$

As $L \to \infty$,

$$G_c(s|\theta) = R_c + \frac{R_P}{1 + sCR_p} \tag{5}$$

State space form

In continuous time,

$$\begin{aligned} \dot{x}_c &= \underbrace{\begin{bmatrix} -\frac{1}{CR_p} & 0 \\ 0 & -\frac{R_c}{L} \end{bmatrix}}_{A_c} x_c + \underbrace{\begin{bmatrix} 1 \\ R_c \end{bmatrix}}_{B_c} u_c \\ y_c &= \underbrace{\begin{bmatrix} \frac{1}{C} & -\frac{R_c}{L} \end{bmatrix}}_{C_c} x_c + \underbrace{\begin{bmatrix} R_c \end{bmatrix}}_{D_c} u_c \end{aligned} \quad (4)$$

As $L \rightarrow \infty$,

$$G_c(s|\theta) = R_c + \frac{R_P}{1 + sCR_p} \quad (5)$$

- as L -> infinity the model reduces to single order system, 3-element Windkessel.

Future work

- Investigate fit across the parameter space
- PV loop measurements
- in vivo and ex vivo measurements on the same heart
- investigate why identifiability is poor on some parameters in this model

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- Investigate fit across the parameter space
- PV loop measurements
- in vivo and ex vivo measurements on the same heart
- investigate why identifiability is poor on some parameters in this model

- This gives a local approximation of the optium parameters... try method more widely across the parameter space
- unreliable measurements, repeat with more reliable hardware
-
- identify an error model as well (not just Gaussian distribution as assumed here)

Thanks for listening!

References

- Total arterial inertance as the fourth element of the windkessel model
  Nikos Stergiopulos, Berend E. Westerhof, and Nico Westerhof
  American Journal of Physiology-Heart and Circulatory Physiology 1999 276:1, H81-H88
- heart diagram, Ben Himme
  https://www.pathwayz.org/Tree/Plain/CIRCULATORY+SYSTEM