Cardiovascular Modelling and Identification in Septic Shock – Experimental validation

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Diagnosis and Treatment

- **Problem**: Cardiac disturbances difficult to diagnose and treat
  - Limited data
  - Reflex actions

  → experience and intuition (mental models)

- **Solution**: Minimal Model + Patient-Specific Parameter ID
  - Interactions of simple models to create complex dynamics
  - Primary parameters
  - Identification must use common ICU measurements
  - E.g. increased resistance in pulmonary artery → pulmonary embolism, atherosclerotic heart disease

- **However**: Identification for diagnosis requires fast parameter ID
  - Must occur in "clinical real-time"
  - Limits model and method complexity (e.g. parameter numbers, non-linearities, …)

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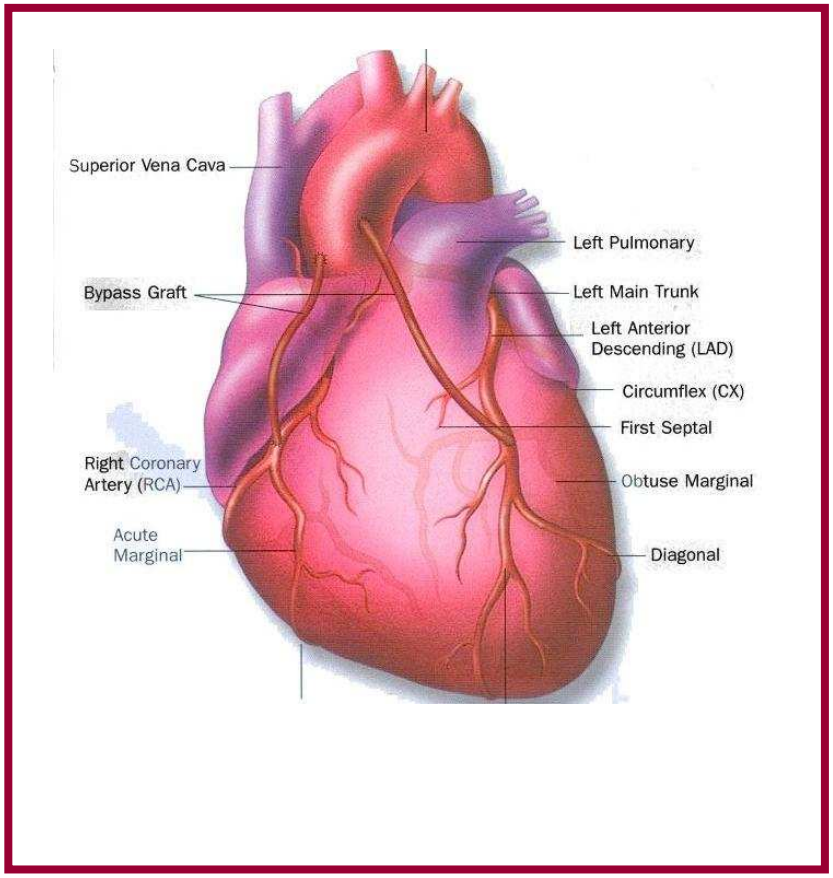
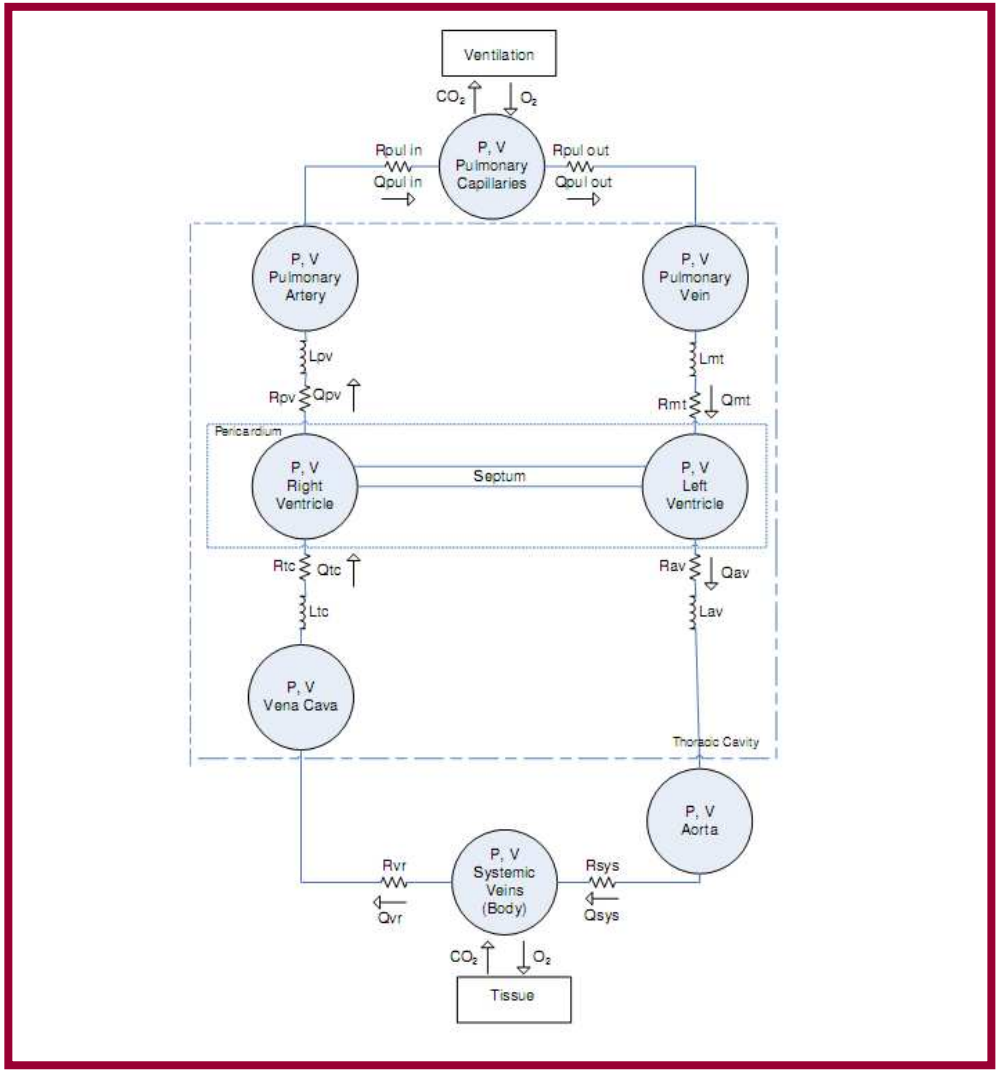
Heart Model





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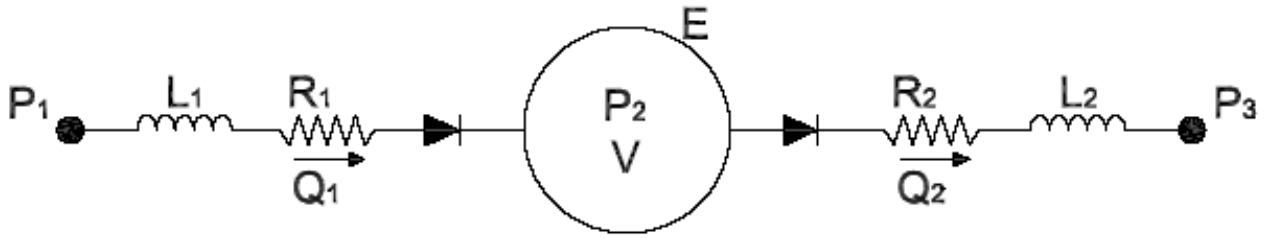
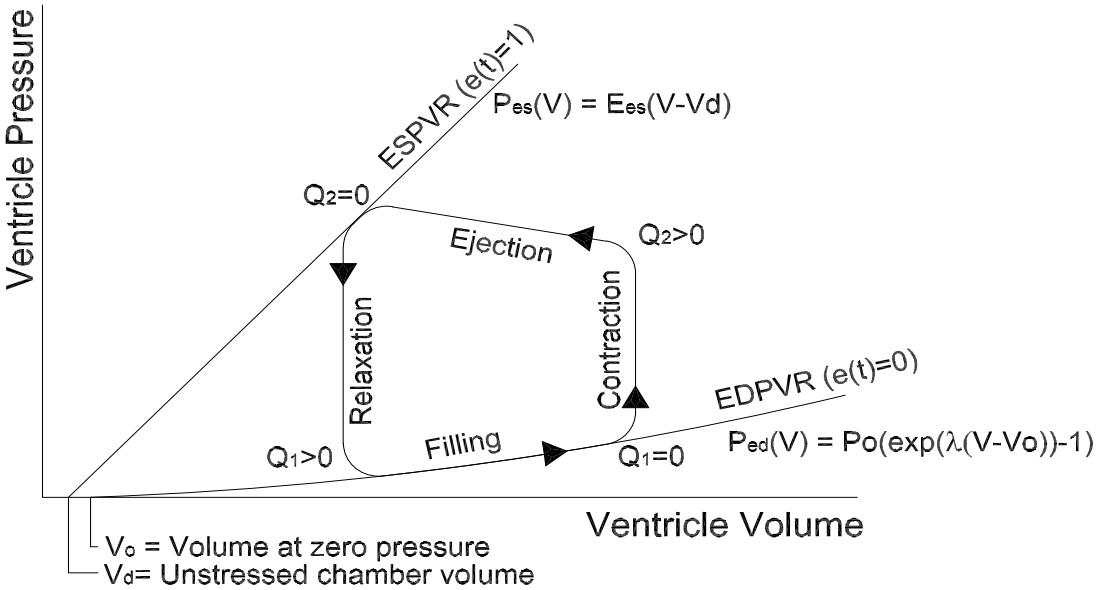
D.E.'s and PV diagram



- **Open on pressure, close on flow valve law**



$$\dot{V} = Q_1 - Q_2$$

$$\dot{Q}_1 = \frac{P_1 - P_2 - Q_1 R_1}{L_1}$$

$$\dot{Q}_2 = \frac{P_2 - P_3 - Q_2 R_2}{L_2}$$

$$P_2 = e(t)E_{es}(V - V_d) + (1 - e(t))P_0(e^{\lambda(V - V_0)} - 1),$$

$$e(t) = e^{-80\left(t - \frac{period}{2}\right)^2}$$

(Cardiac muscle activation)

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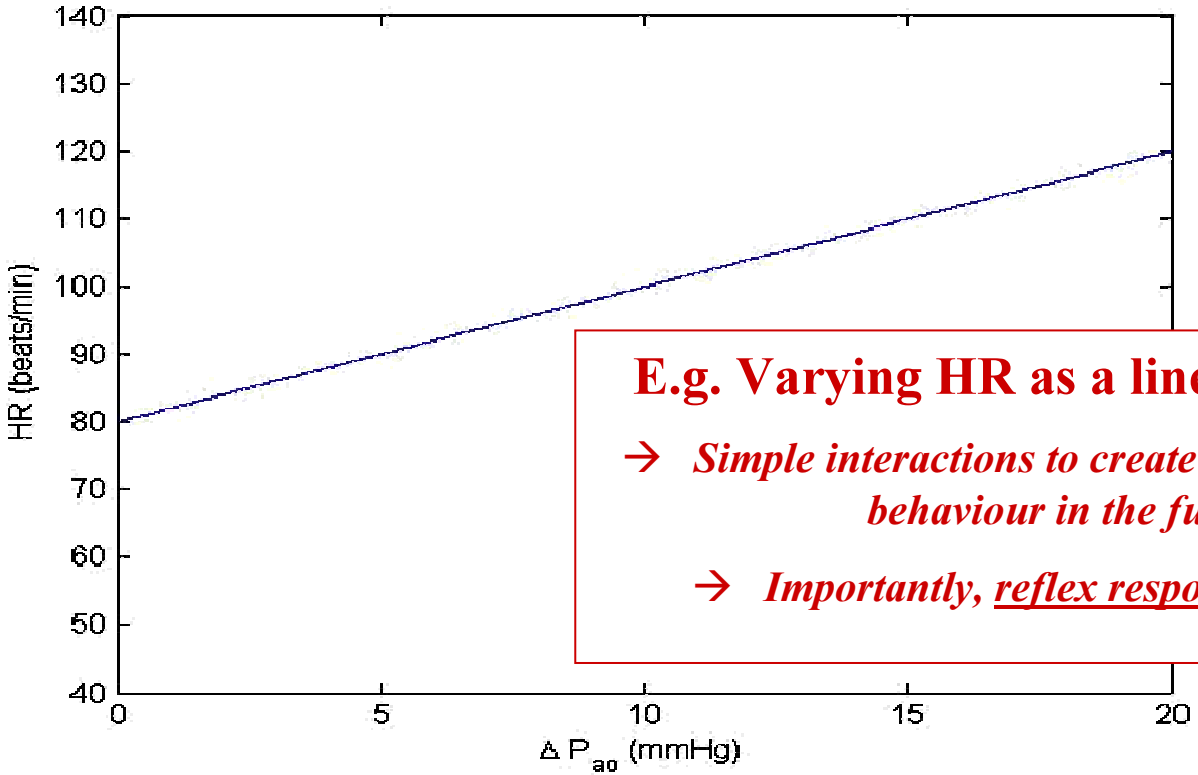
Reflex Actions

- Vaso-constriction - contract veins
- Venous constriction – increase venous dead space
- Increased HR
- Increased ventricular contractility



E.g. Varying HR as a linear function of ΔP_{ao}

→ *Simple interactions to create overall complex dynamic behaviour in the full system model*

→ *Importantly, reflex response is patient specific*

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Disease States

- **Pericardial Tamponade:**
  - Build up of fluid in pericardium
  - Decrease: dead space volume V0,pcd

- **Pulmonary Embolism:**
  - Increase: Rpul

Current Status:
- **Clinical results for Pulmonary Embolism**
- **Clinical results for Septic Shock and therapy intervention**
- **Clinical results for PEEP interventions**
- **Simulated results for others**

- **Cardiogenic shock:**
  - Not enough oxygen to myocardium (e.g. from blocked coronary artery)
  - Decrease: Ees,lvf, Increase: P0,lvf → A more complex set of changes/interactions

- **Septic shock:**
  - Blood poisoning
  - Decrease: Rsys = systemic resistance

- **Hypovolemic shock:**
  - Severe decrease in total blood volume = sum of individual volumes

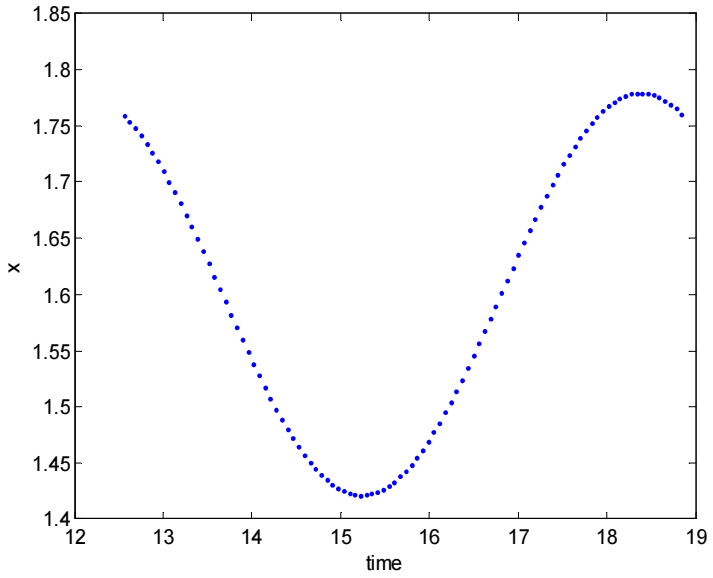
Integral Method - Concept

- $\dot{x} = ax + b\sin(t) + c, \quad x(0) = 1$

  $a = -0.5, \quad b = -0.2, \quad c = 0.8$

(simple example with analytical solution)

Discretised solution analogous to measured data



- Work backwards and find a,b,c
- Current method – solve D. E. numerically or analytically

$$x(t) = \frac{1}{(a^2+1)a}(e^{at}(a + c + ab + ca^2 + a^3) - (ab\cos t + ba^2 \sin t + ca^2 + c))$$

- Find best least squares fit of x(t) to the data

- Non-linear, non-convex optimization, computationally intense

- integral method

– reformulate in terms of integrals

– linear, convex optimization, minimal computation

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Integral Method - Concept

- Integrate $\dot{x} = ax + b\sin(t) + c$, both sides from t_0 to t ($t_0 = 4\pi$)

$$\int_0 \dot{x}\, dt = \int_0 (ax + b\sin(t) + c)\, dt$$

$$\Rightarrow x(t) - x(t_0) = a\int_0 x\, dt + b\int_0 \sin(t)\, dt + c\int_0 1\, dt$$

$$\Rightarrow \quad x(t) = x(t_0) + a\int_0 x\, dt + b(\cos(t_0) - \cos(t)) + c(t - t_0)$$

- Choose 10 values of t, between $t_0 = 4\pi$ and 6π form 10 equations in 3 unknowns a,b,c

$$a\int_{t_0} x\, dt + b(1 - \cos(t_i)) + c(t_i - t_0) = x(t_i) - x(t_0), \quad i = 1,\ldots,10$$

Integral Method - Concept

$$\begin{pmatrix} \int_{t_0}^{t_1} x\,dt & \cos(t_0)-\cos(t_1) & t_1-t_0 \\ \vdots & \vdots & \vdots \\ \int_{t_0}^{t_{10}} x\,dt & \cos(t_0)-\cos(t_{10}) & t_{10}-t_0 \end{pmatrix} \begin{pmatrix} a \\ b \\ c \end{pmatrix} = \begin{pmatrix} x(t_1)-x(t_0) \\ \vdots \\ x(t_{10})-x(t_0) \end{pmatrix}$$

- **Linear least squares (unique solution)**

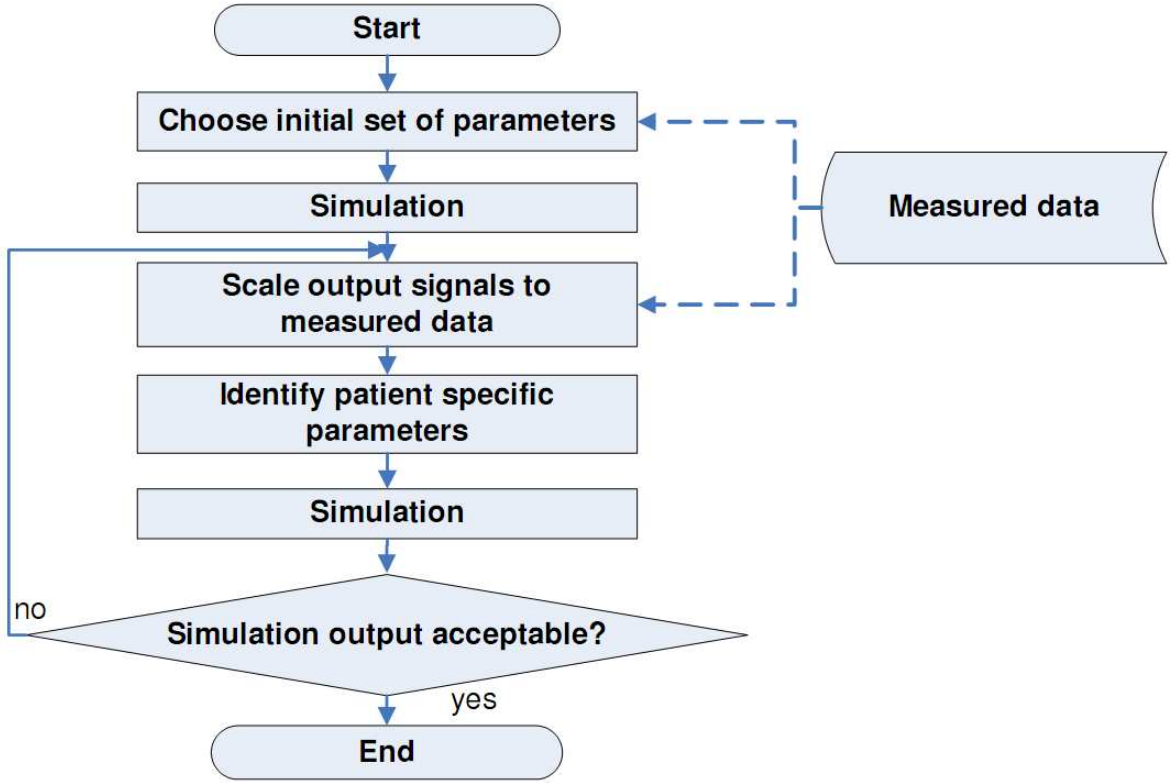
Method	Starting point	CPU time (seconds)	Solution
Integral	-	0.003	[-0.5002, -0.2000, 0.8003]
Non-linear	[-1, 1, 1]	4.6	[-0.52, -0.20, 0.83]
Non-linear	[1, 1, 1]	20.8	[0.75, 0.32, -0.91]

- **Integral method is at least 1000-10,000 times faster depending on starting point**
- **Thus very suitable for clinical application**

Integral method with discrete data

- If only given max and min, scale pre-computed waveforms (cts input)
- Requires typically several iterations – but fast convergence since integrals filter modelling error and noise

- "Simulation" can be replaced by closed form analytical approximations – immediate evaluation at steady state
- 10^5-10^6 times faster than standard methods (non-linear regression)



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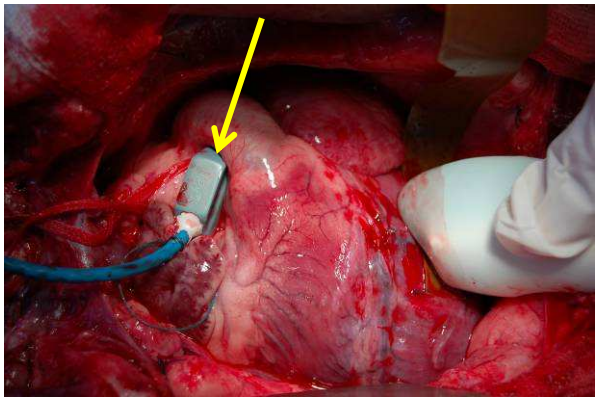
Clinical trials - Belgium

- **Septic shock** induced in pigs (collaborators in Liege, Belgium)
  - 0-30 minutes, endotoxin infusion, >60 minutes, hemofiltration, (5 pigs, 25-30 kg)

Open chest

Ventilated and sedated

12 Electrode Conductance Catheter
(Vlv,Vrv,Plv,Prv)



Also measure
Pao,Ppa

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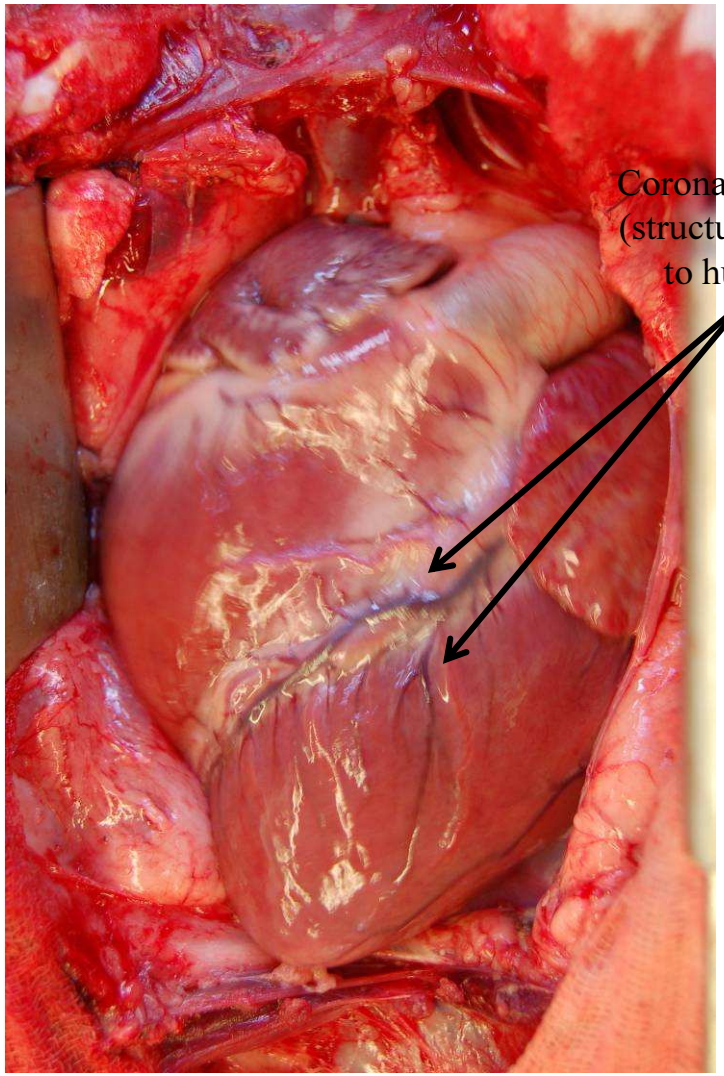
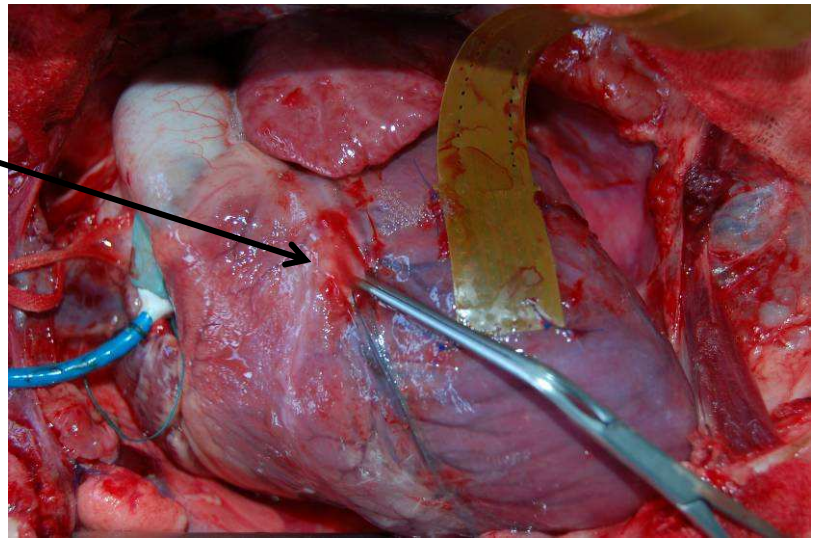
More pictures



Coronary arteries (structure similar to humans)

Ischemia



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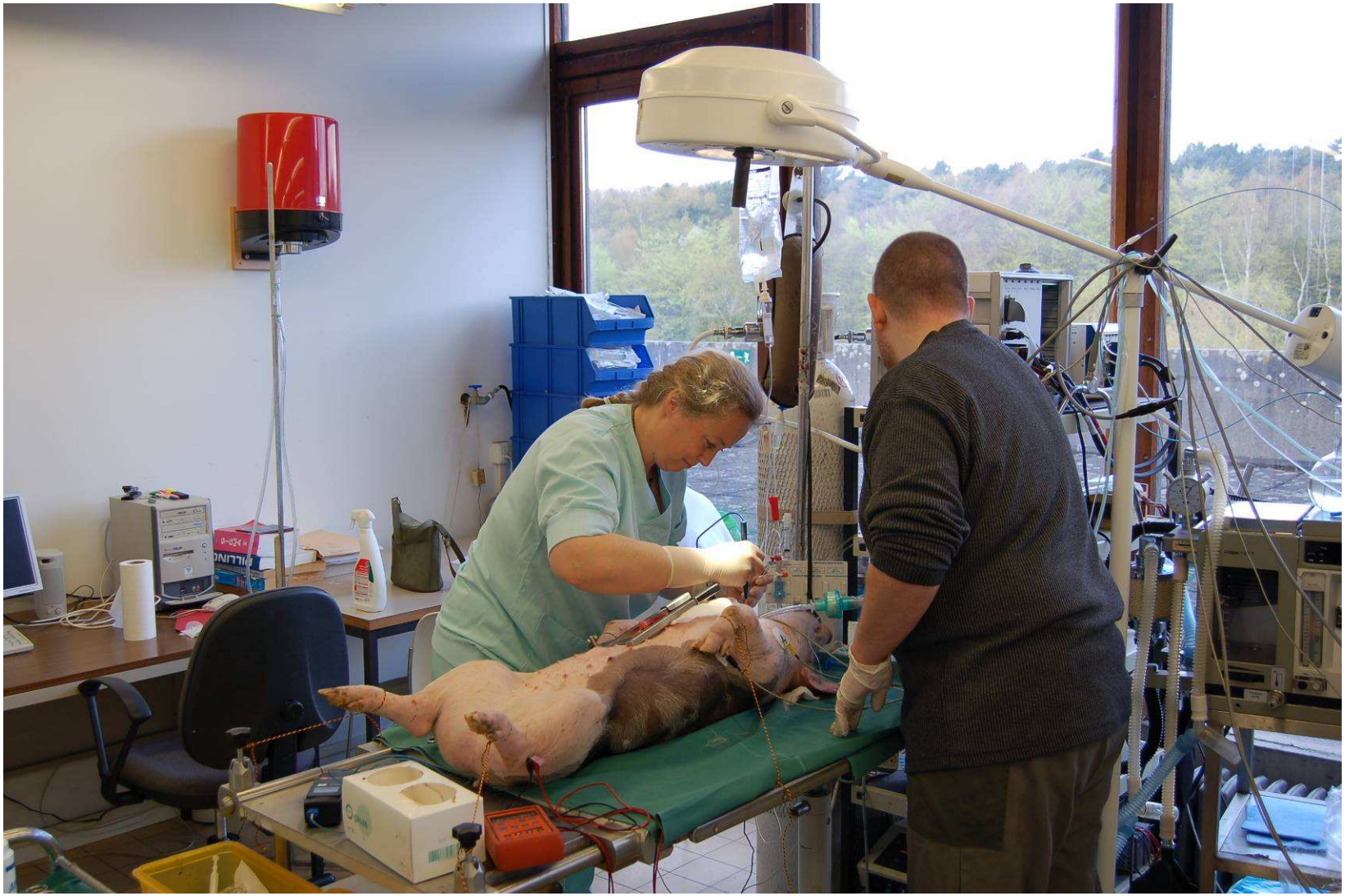
Clinical setting

UC BIOMEDICAL ENGINEERING



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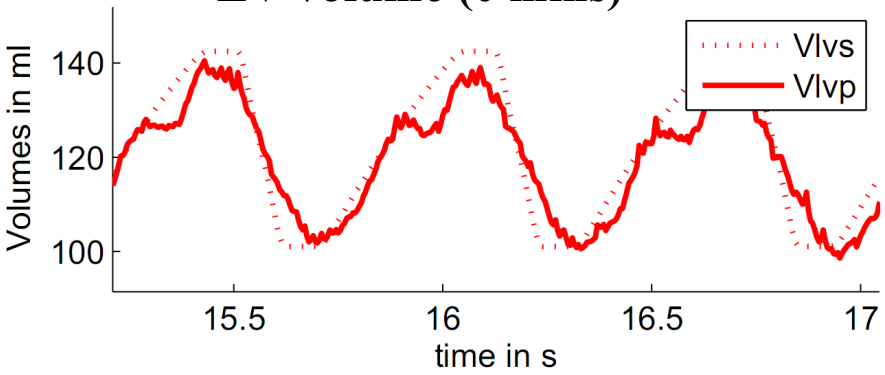
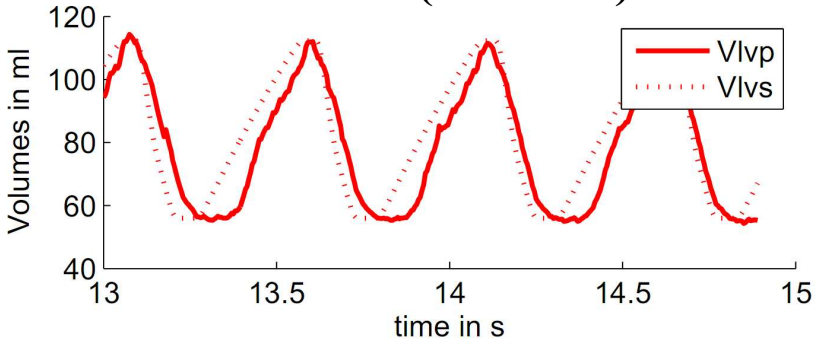
Clinical Results

- Use only: Pao, Ppa, min/max(Vlv, Vrv) to ID all parameters
- Measurements available in an ICU

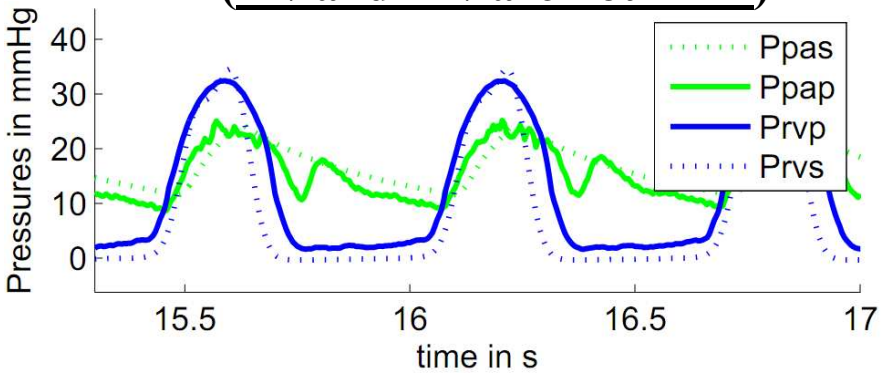
LV volume (0 mins)



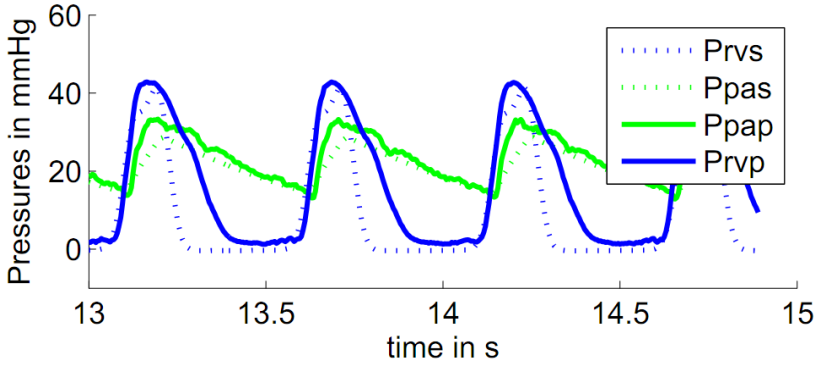
LV volume (120 mins)



RV pressures (0 mins)
(Plv and Prv are not in ID)



RV pressures (120 mins)



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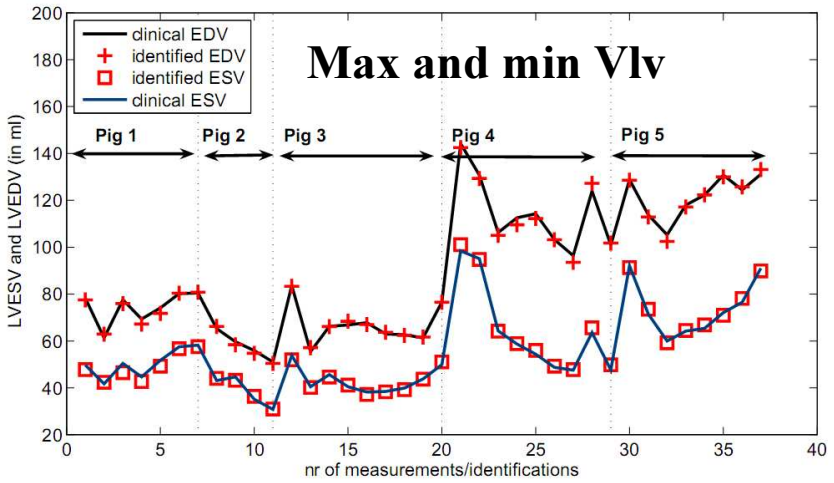
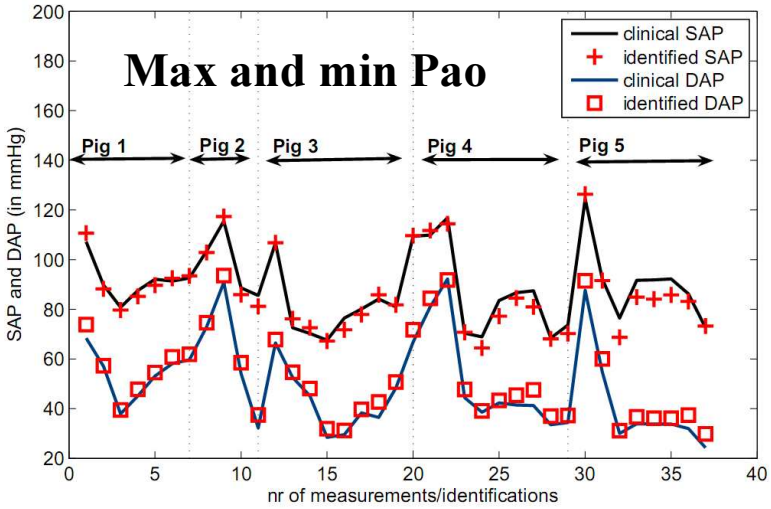
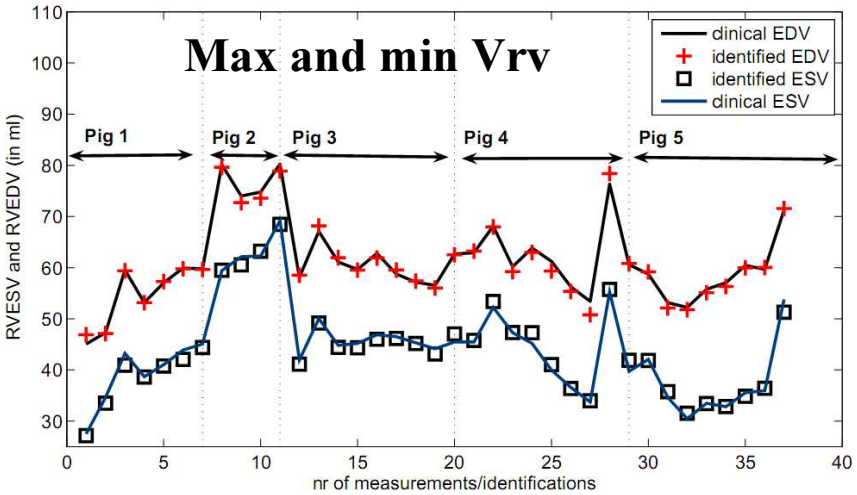
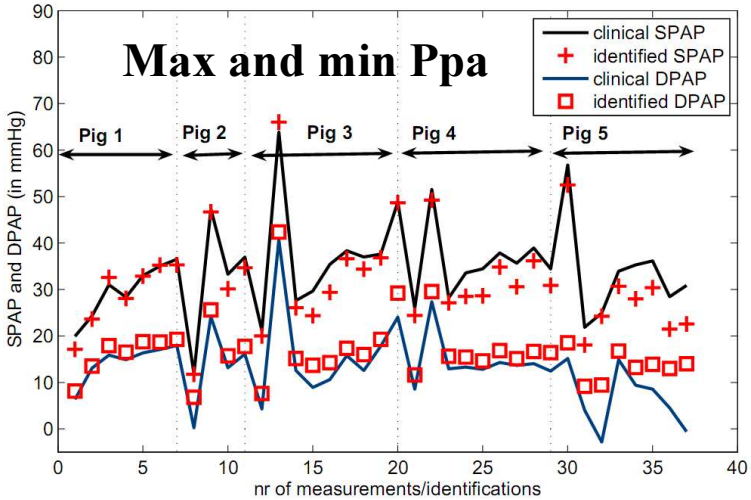
Animal Model Results – all pigs









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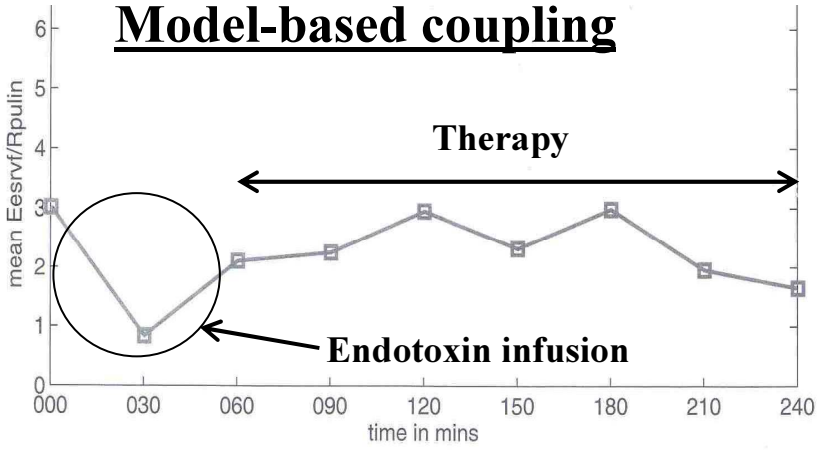
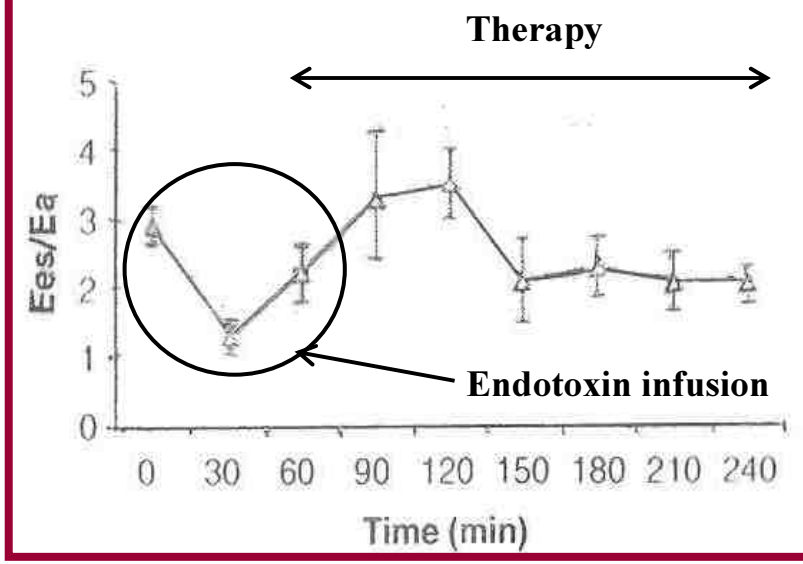
RV-vascular coupling

$$\text{Coupling} = \frac{\text{Contractility}}{\text{Afterload}}$$

Model-based coupling



Measured coupling



- Five pigs - Endotoxin infusion over first 30 minutes
- **Therapy** ➔ large-pore membrane Hemofiltration from 60-240 minutes
- Model accurately matches all hemodynamic response < 8% error
- Preserved coupling validated with invasive rapid vena cava occlusion maneuver

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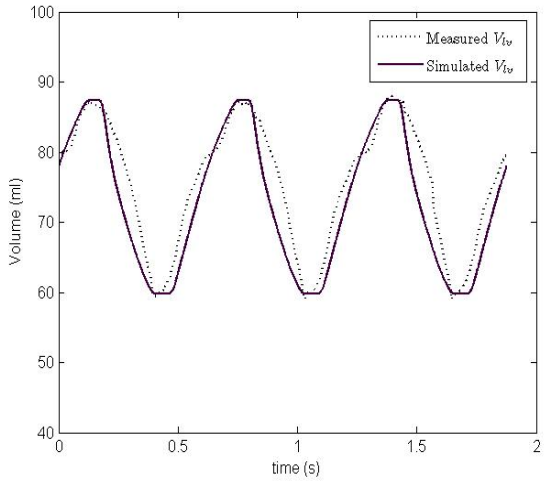
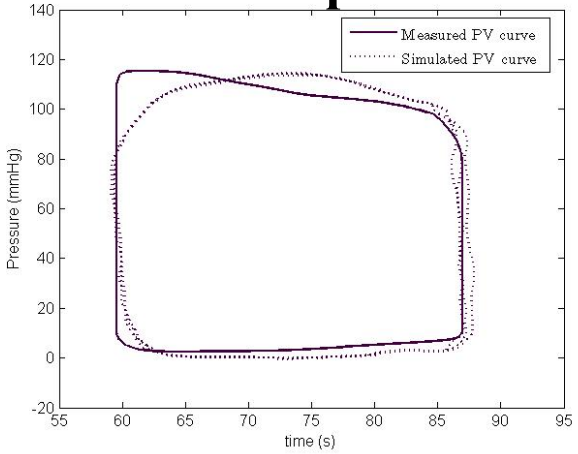
New results for IFAC

- Using extra measurement of ECG ➔ systolic, diastolic timings
- Experimentally derived, driver function shape (Plv/Vlv)

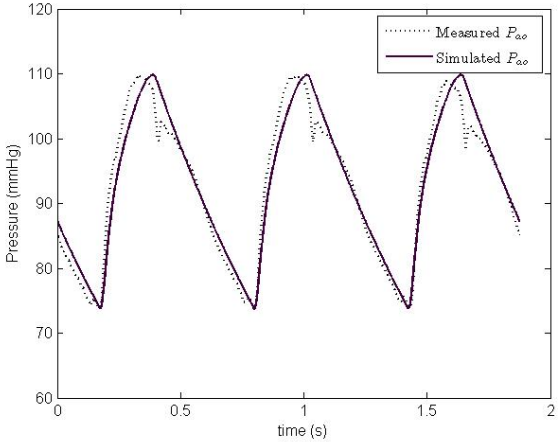
Vlv



PV loop



Pao



- Don't need max and min Vlv and Vrv. Replace by SV's (much easier to measure!)
- <10% change in fitted parameters (including volumes), improved ID of valvular resistances (trade off a little with Ees, significantly with preload parameters, e.g. Ppu)

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Conclusions and summary

- **Minimal cardiac model** → simulate time varying disease states
  - Accurately captures physiological trends and magnitudes
  - Accurately captures a wide range of dynamics
  - Very Fast simulation methods available

- **Integral-based parameter ID** → patient specific models
  - Simulation: ID errors from 0-10%, with 10% noise
  - Animal models: Pulmonary embolism, septic shock (with and without hemofiltration)
    Pressures (Total Error) < 8%
    Volumes (Total Error) < 5%
  - PEEP Therapy prediction: within 10% error

- **Identifiable using a minimal number of common measurements**
  - Rapid ID method, easily implemented in Matlab
  - Rapid ID = Rapid diagnostic feedback

- **Future Work = septic shock, ischemia, human trials and other disease states (2008-)**

Acknowledgements

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Questions ???

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