MODEL-BASED CARDIOVASCULAR THERAPEUTICS: CAPTURING THE PATIENT-SPECIFIC IMPACT OF INOTROPE THERAPY

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General problem

- Cardiovascular disturbances are difficult to diagnose and treat
  - Large range of possible dysfunctions
  - Reflex actions can mask the symptoms
    - Conflicting clinical data
    - Medical professionals often rely on experience and intuition to optimize the hemodynamics in the critically ill
Solution

- Physiological, identifiable and validated computer model
  - Minimal Model + Patient-Specific Parameter ID process
  - Identification must use common clinical measurements

- Application: study the effect of inotrope therapy prior to first human trials
Cardiovascular system model

- **Minimal CVS model:**
  - Physiologically validated
  - Capable of capturing patients dynamics commonly seen in the Intensive Care Unit (ICU)
  - Using a relatively small number of physiological variables
  - Minimal, typically available ICU measurements are all that is required to ID model

Suitable for rapid diagnostic feedback
Mathematical model

P-V diagram

One chamber model

\[ \dot{V} = Q_1 - Q_2 \]

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

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

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

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

B. W Smith et al., *Medical Engineering & Physics*, 26(2), 131-139, 2004
Clinical data

- Three clinical studies already published
  - Effects of age on cardiovascular responses to adrenaline in man\(^1\): 24 data sets
  - Effects of adrenaline in patients with myocardial dysfunction after CABG\(^2\): 8 data sets
  - Effects of epinephrine in septic shock\(^3\): 5 data sets

**Total = 37 data sets**

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Integral based parameter identification

- Previously validated
- Accurately identify almost the entire parameter set in the presence of noise
- Limited data and minimal computation
  - Very suitable for clinical applications
Adrenaline-specific parameters

- Left and right ventricular end-systolic elastances (contractility ↑)
- Arterial elastances (pulse pressure ↑)
- Systemic resistance (vasoconstriction ↑)

Changes in these parameters are used for predicting the response towards a change in dose of adrenaline or over time.
Method: Linear Prediction Rules

- Use reported patient specific response to capture drug affect in model
- Then ID model parameters
- Run model
- Compare model outputs of resulting MAP, SAP, DAP etc to clinical measurements to see if model captures the effect

Linear prediction rules for $Eeslvf$ (upper panel) and $Eesrvf$ (lower panel) for studies 2 (Heringlake et al., solid line) and 3 (Levy et al., dashed line).
Results: simulations

Study 1: **Clinical** mean systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure (solid lines) vs **simulated** pressures (circles).

Study 3: **Clinical** mean arterial (MAP), mean pulmonary artery (MPAP) pressure and cardiac index (CI) (solid lines) vs **simulated** pressures and CI (circles).

- All median identification percentage errors are less than 9%.
- This value is within or near expected measurement errors.
Conclusions

- Clinically accurate prediction of the impact of adrenaline (adrenaline specific parameters)

- This work represents a further clinical validation of the underlying fundamental CVS model and methods, and their use for cardiovascular diagnosis and therapy selection in critical care.

- These results are presented as (further) justification for (beginning) human trials of this model-based diagnostic and therapeutic approach.
A Note on Prior Validation Studies

- **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**
  - Error on max/min pressures/volumes < 5%
  - Identification needs a minimal number of common measurements
  - Rapid ID = Rapid diagnostic feedback

- **Pulmonary Embolism (PE) and the affect of PEEP:**
  - Hemodynamics successfully captured over time
  - Physiological responses to pulmonary embolism also captured

- **Septic shock (w/ and w/o fluid resuscitation):**
  - Hemodynamics and trends captured (including measurements not used in the ID process)
  - Further reduced data sets successful minimising patient-invasiveness and extra catheters
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