Physiological Closed-Loop Control of Life Support

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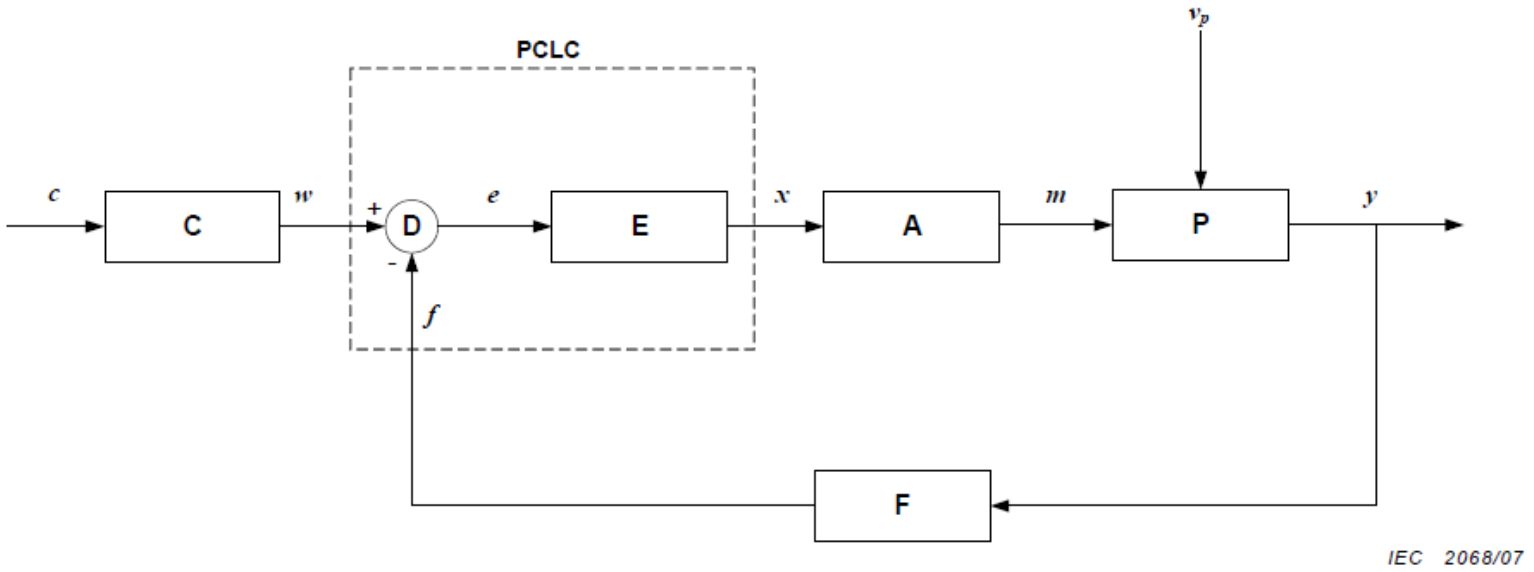
Conflict of Interest and Acknowledgements

- Acting Vice President
  ZOLL Medical Corporation
- The views expressed herein are mine and may not reflect the position of ZOLL
- We are developing equipment and technology related to this presentation
- The work is funded by:
  - U.S. DoD sources
  - Internal funds
- This is the work of many people

Physiological Closed-Loop Control



Elements		VARIABLES	
PCLC	PHYSIOLOGIC CLOSED-LOOP CONTROLLER		
A	ACTUATOR	m	MANIPULATED VARIABLE
C	COMMAND TRANSFER ELEMENT	w	REFERENCE VARIABLE
D	COMPARING ELEMENT	e	ERROR VARIABLE
E	CONTROL TRANSFER ELEMENT	x	CONTROLLER OUTPUT VARIABLE
F	MEASURING TRANSFER ELEMENT	f	FEEDBACK VARIABLE
P	PATIENT TRANSFER ELEMENT	y	CONTROLLED PHYSIOLOGIC VARIABLE
		v_p	PATIENT DISTURBANCE VARIABLE
		c	COMMAND VARIABLE

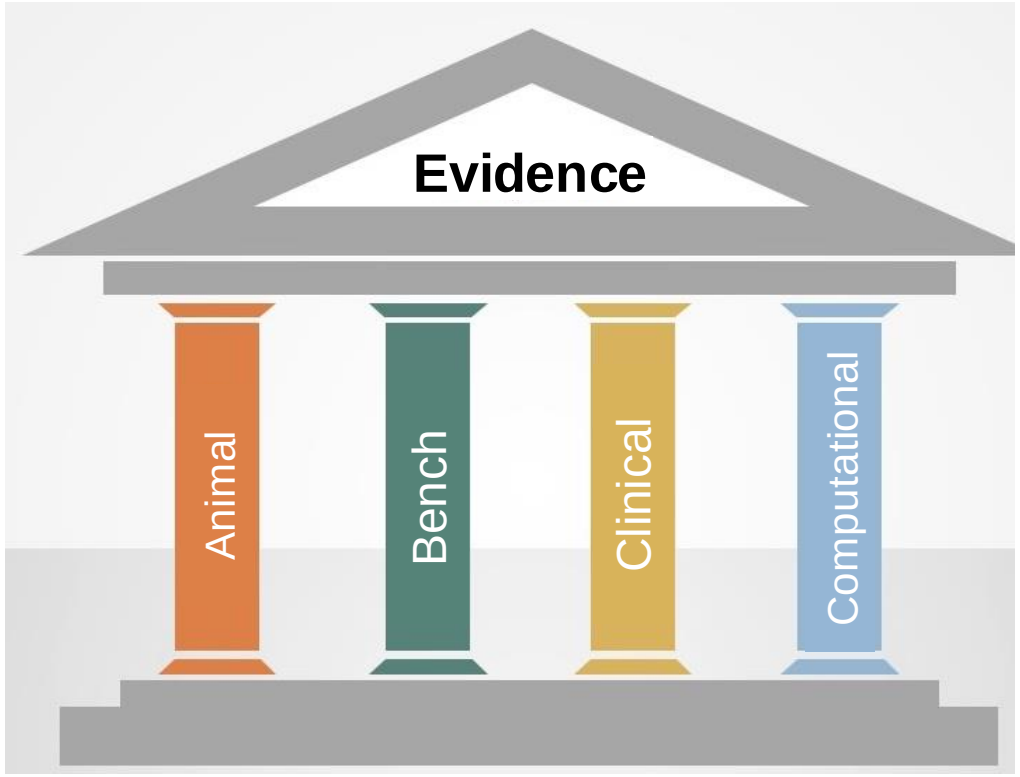
If practicable, the MANUFACTURER shall develop and use a mathematical model to characterize the PATIENT TRANSFER ELEMENT.

From IEC 60601-1-10 2020

Why Computational Modelling?

1. FDA requires computational modelling to evaluate PCLC systems (IEC 60601-1-10:2020[1])
   - Essential to receive Investigational Device Exemption (IDE)

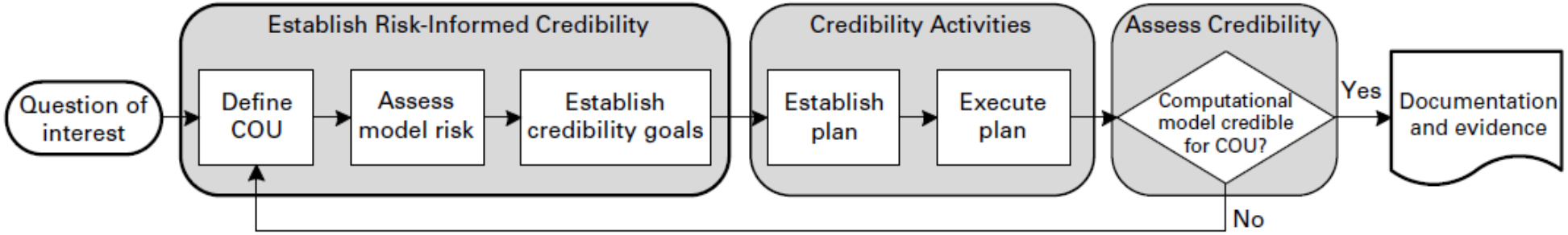
2. Before using a computational model, the *credibility of the model* must be assessed:
   - ASME V&V 40[2] / FDA Draft Guidance[3]



1. **IEC 60601-1-10-2020**: General requirements for basic safety and essential performance – Collateral Standard: Requirements for the development of physiologic closed-loop controllers
2. **ASME V&V 40-2018**: Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices.
3. Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions. **FDA Draft Guidance** issued December 2021.

ASME V&V 40-2018: Assessing Credibility of Computational Modeling through V&V: Application to Medical Devices

- "Risk-Informed Credibility Assessment Framework"



Question of Interest

What does your controller do?

Context of Use

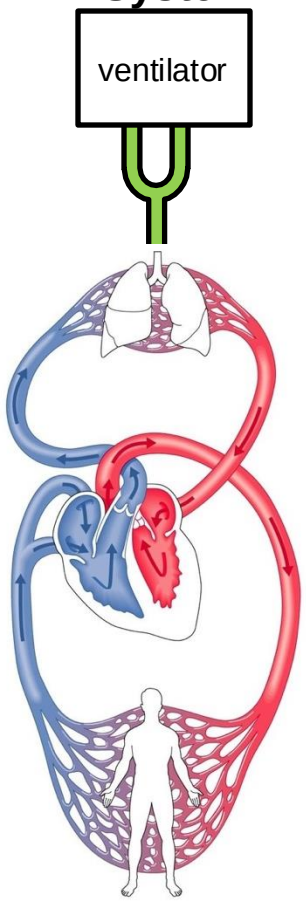
- Who are the users?
- What is the clinical environment?
- Who are the patients?

Model Risk Matrix

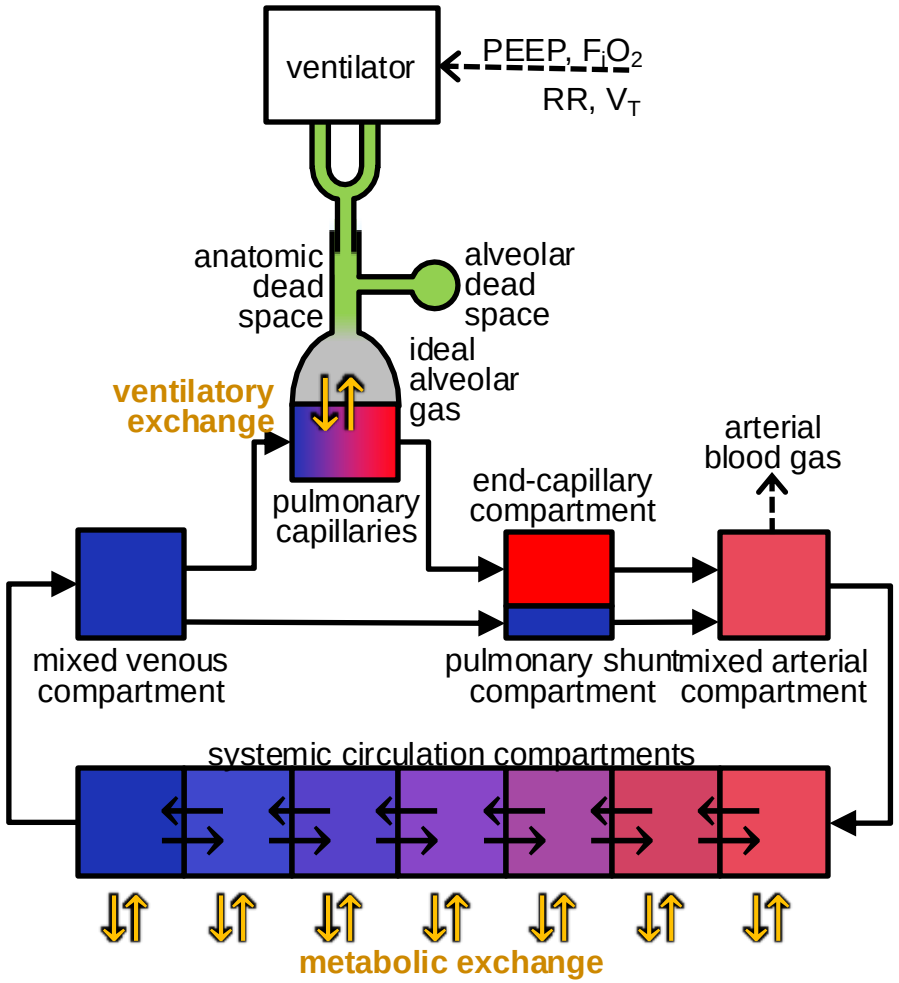
Decision Consequence				
	HIGH	3	4	5
	MEDIUM	2	3	4
	LOW	1	2	3
		LOW	MEDIUM	HIGH
		Model Influence		

Cardiopulmonary Model

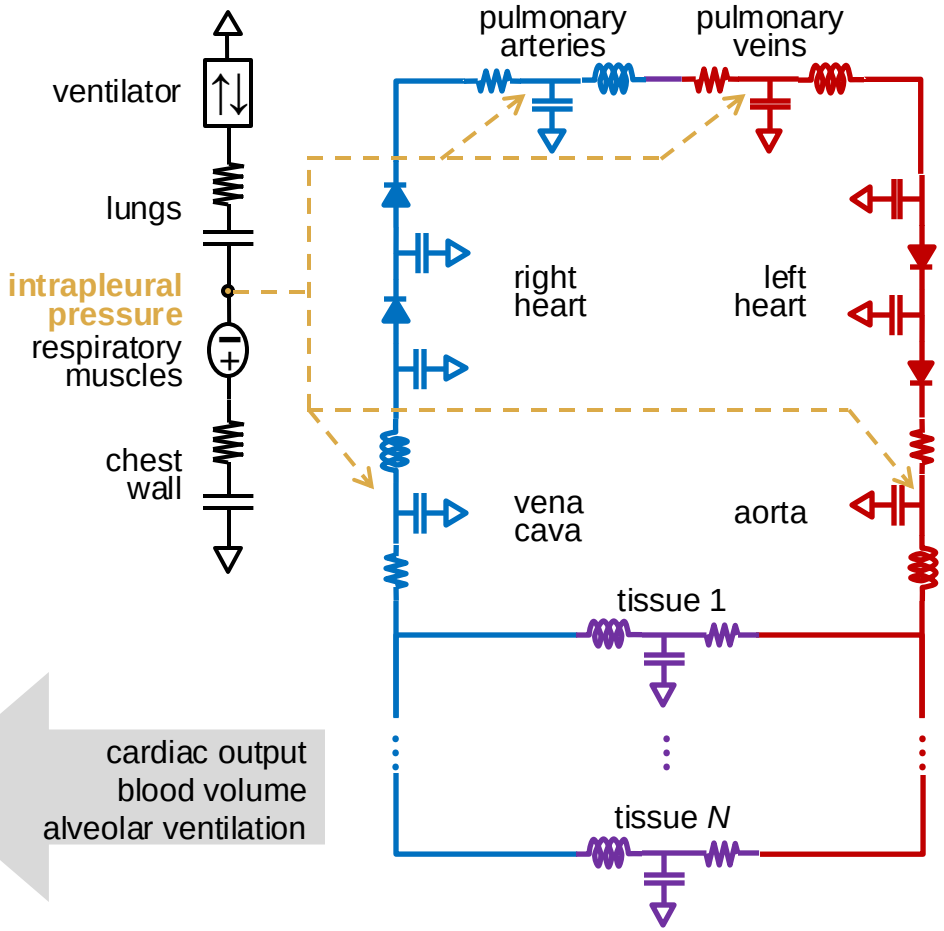
A. Patient-Ventilator System



B. Gas Exchange Model



C. Pneumatic & Hydraulic Circuit Models
(electrical analogy)

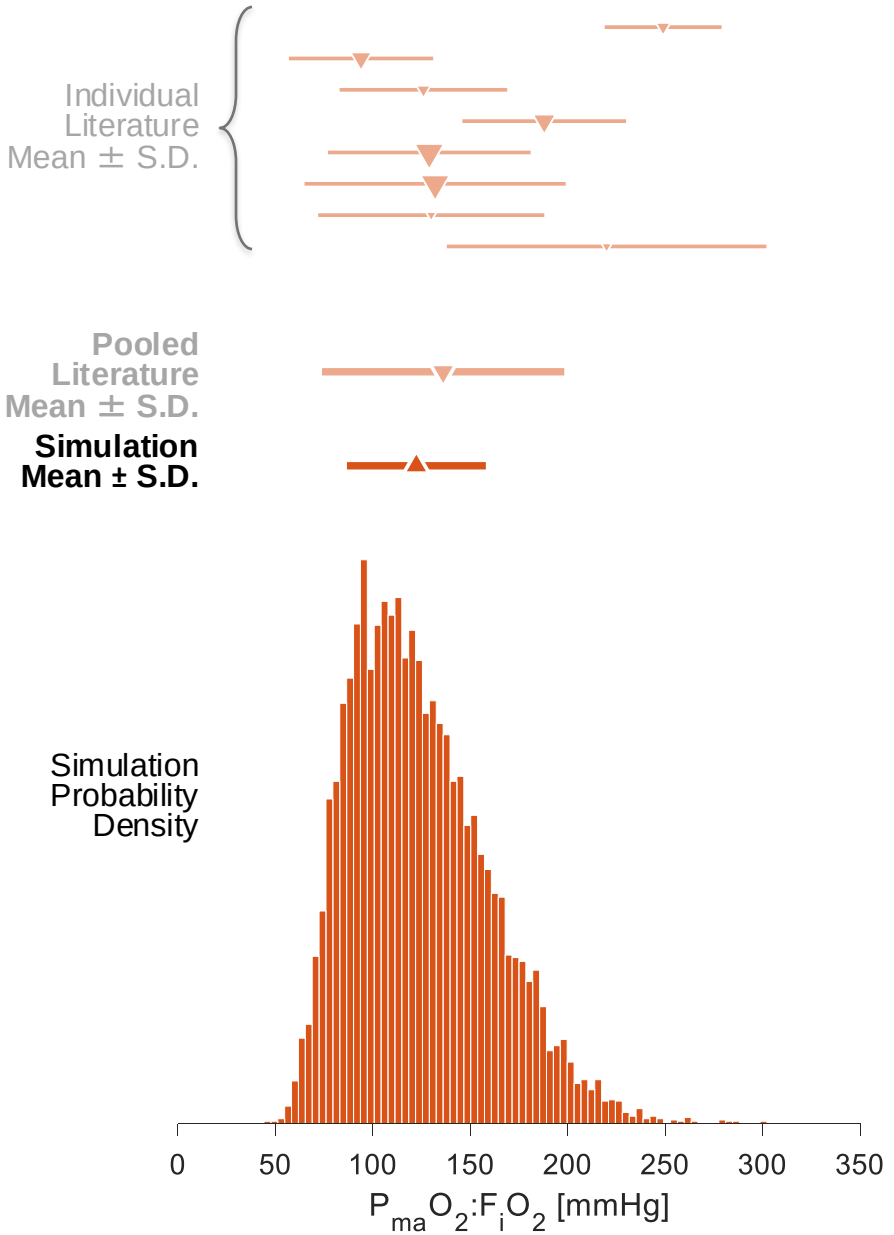


cardiac output
blood volume
alveolar ventilation

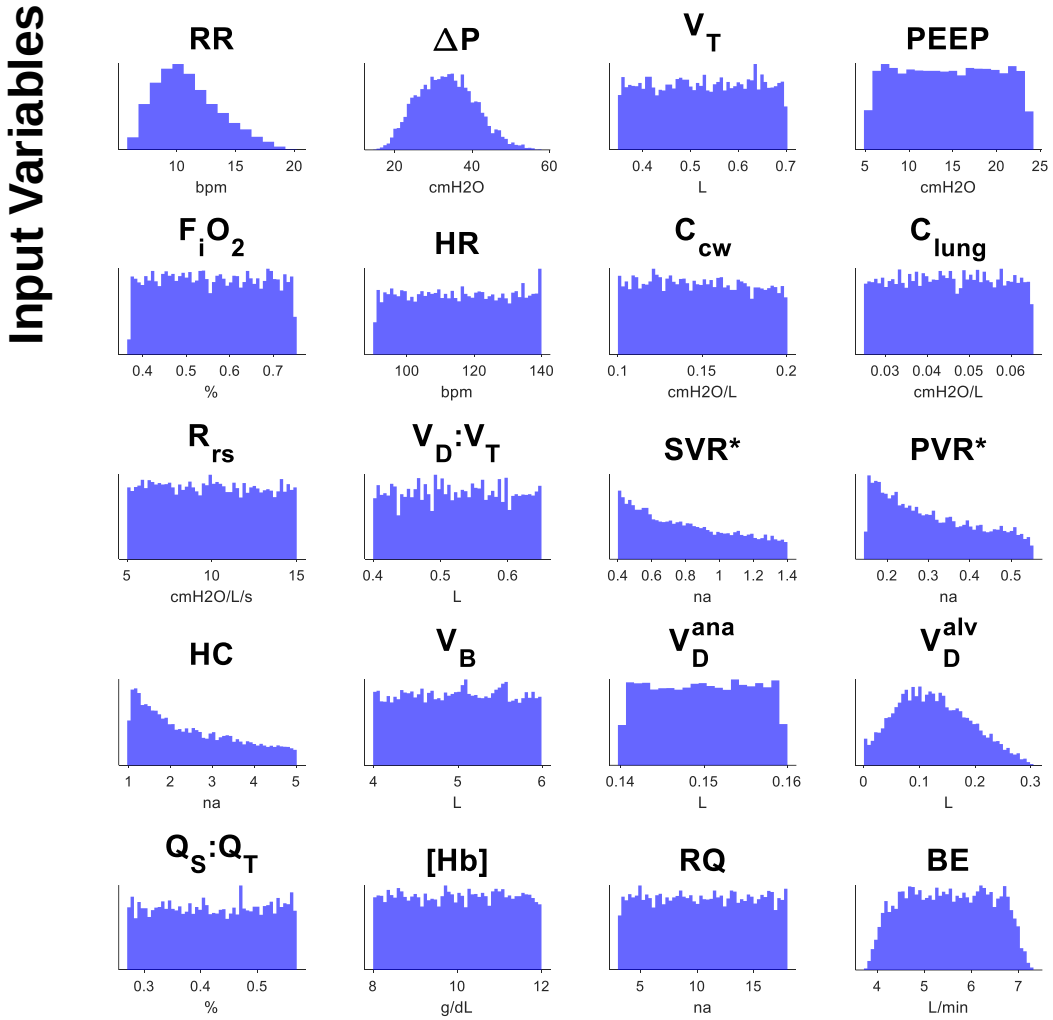
Mihiret Redhi, Jacob Herrmann, David Kaczka Ulowa

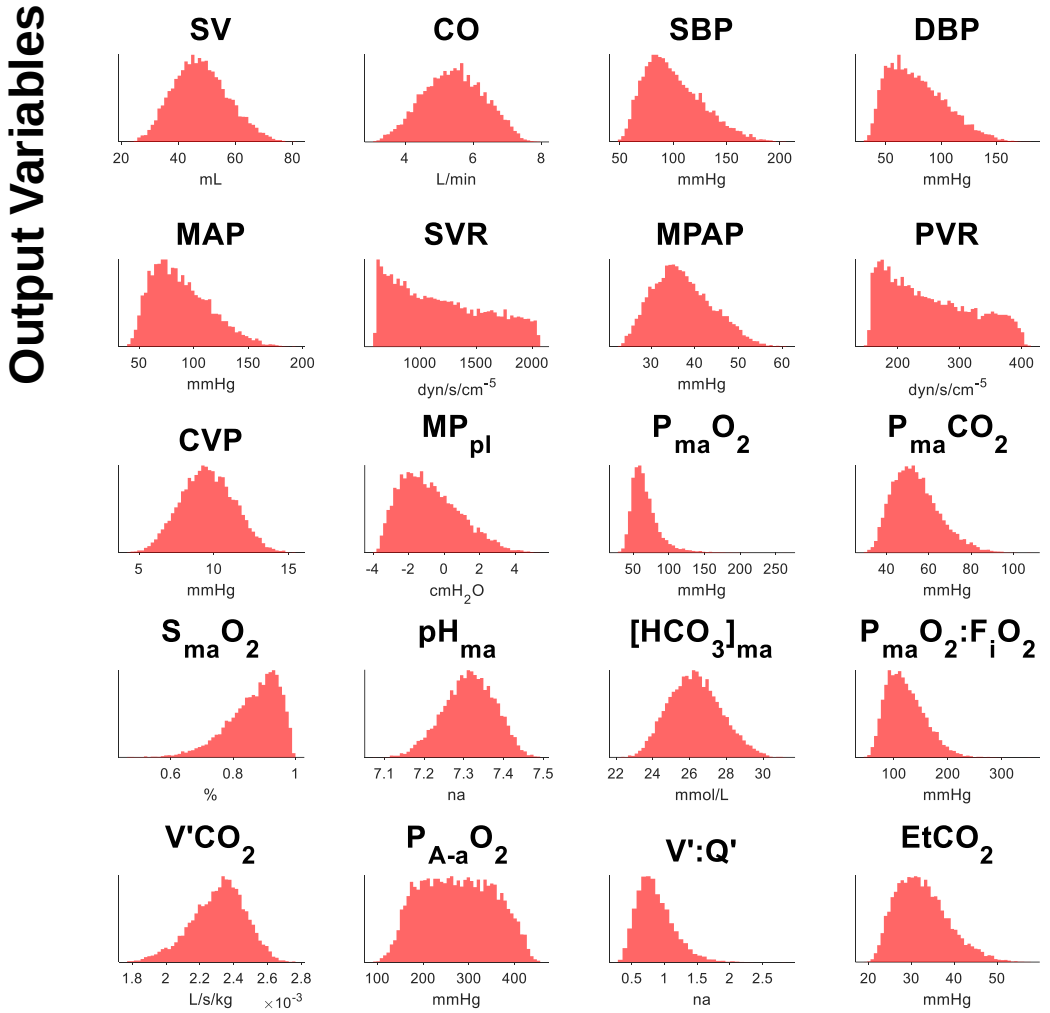
Clinical Validation

- Models only contain physiology that the developer includes
- The problem is over-specified, so the model should be able to create any desired set of clinical values
- Significant and poorly understood inter-patient variability



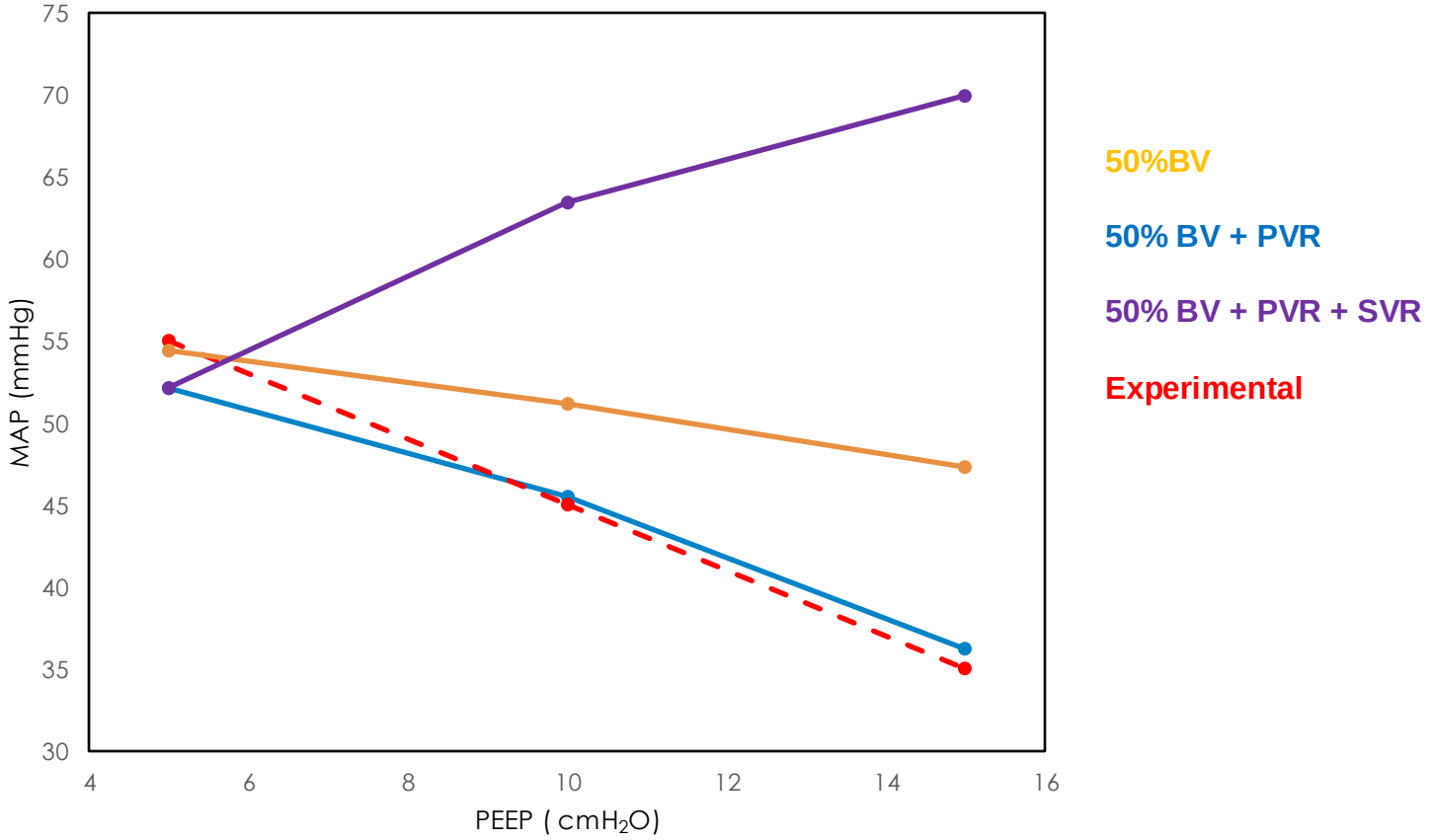
Digital Clinical Trials





Exploring Ventilation during Hemorrhage using modeling

- Animals were bled to a MAP of 55 mmHg and provided mechanical ventilation at PEEP values of 5, 10, or 15 cmH_2O
- Simulations included
  - 50% blood loss
  - 50% blood loss and increased pulmonary vascular resistance
  - 50% blood loss and increased pulmonary and systemic vascular resistance



Some Final Thoughts

- PCLC medical devices will be force multipliers
- Clinicians vs Machines and regulatory agencies
- Regulatory agencies need to be an early part of the discussion
- Academic – Industry – Government collaboration is necessary to break new ground

THANK YOU