FDA PCLC Symposium
Integrative Cardiopulmonary Mathematical Modeling Short Term Regulation

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innovation + you

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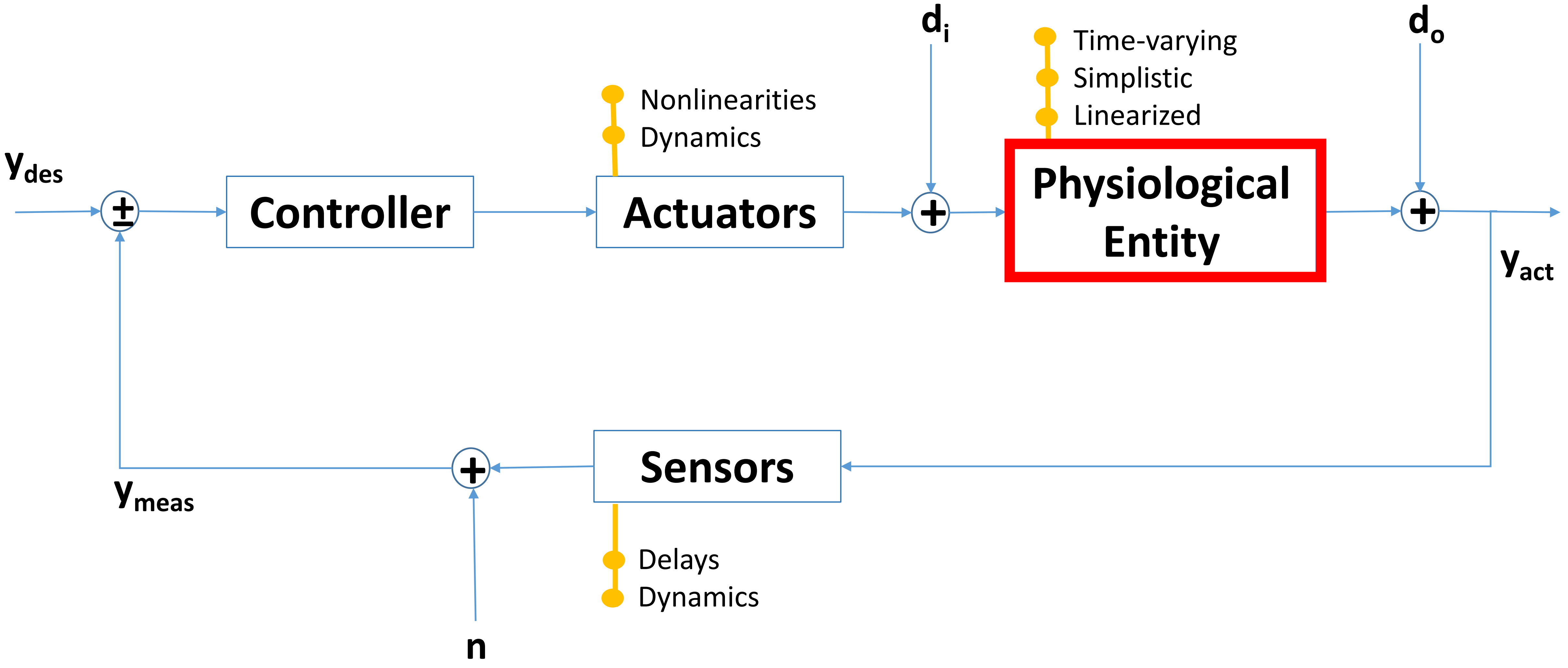
Physiological Closed-loop Control Medical Devices

- To implement a PCLC → need to design → need to simulate → need to model
- Need to model many blocks in a PCLC; this talk concentrates on the physiology
- The physiological entity that you plan to control need be understood
- Different rationales to model (why model?)
  - Ex: build PCLC, time scale of interest, what do you hope to capture
- Different ways of modeling (how to model?)
- Different uses of models (what model?)
  - prediction, what-if scenarios, detection, prognosis, education
- **Luckily**, well-established fields: steady-state models, dynamic models (ODEs, PDEs)

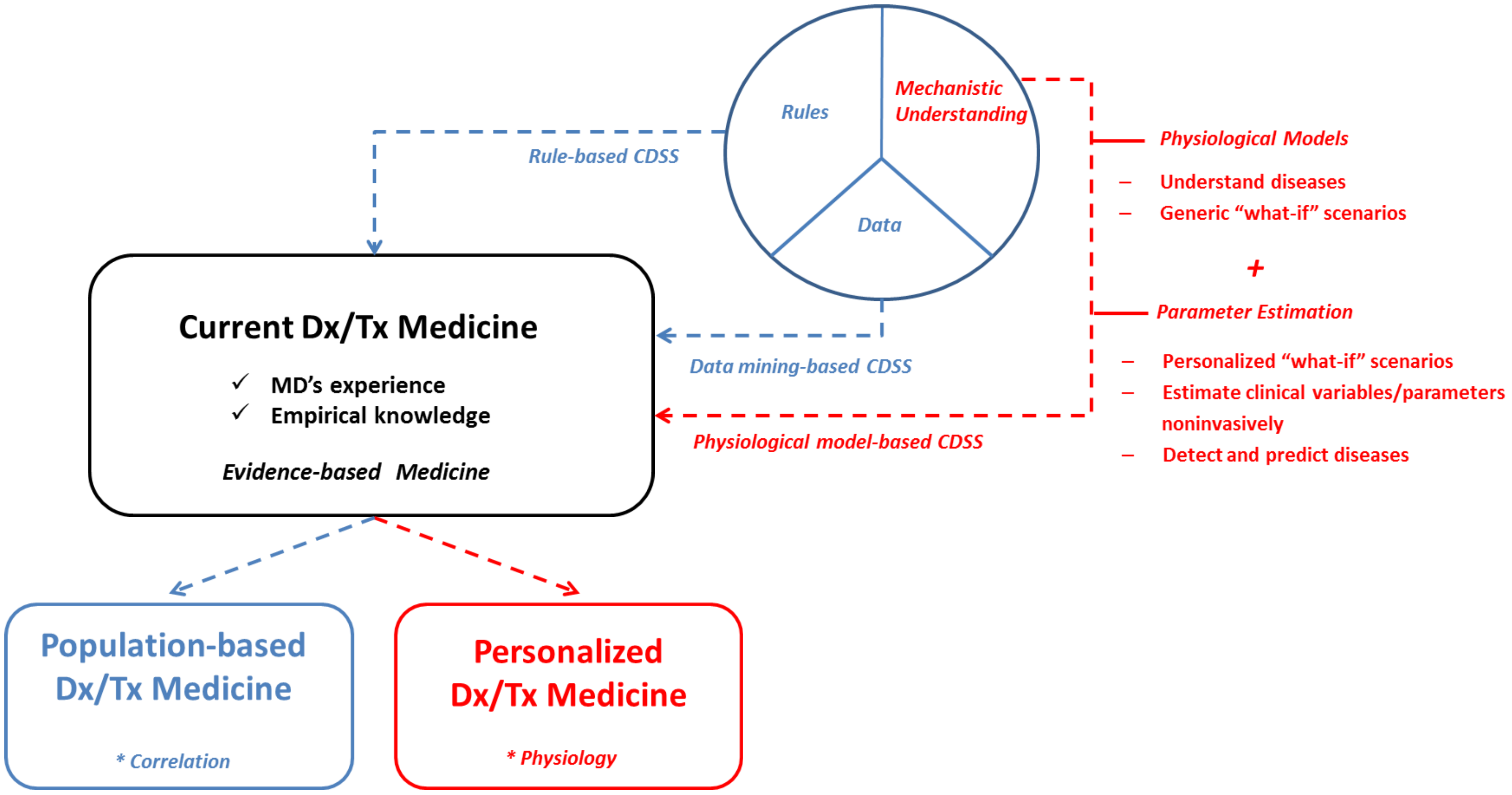
Physiological Closed-loop Control Devices

Basic feedback block diagram

Main design components



Physiological Modeling and… Personalized Medicine

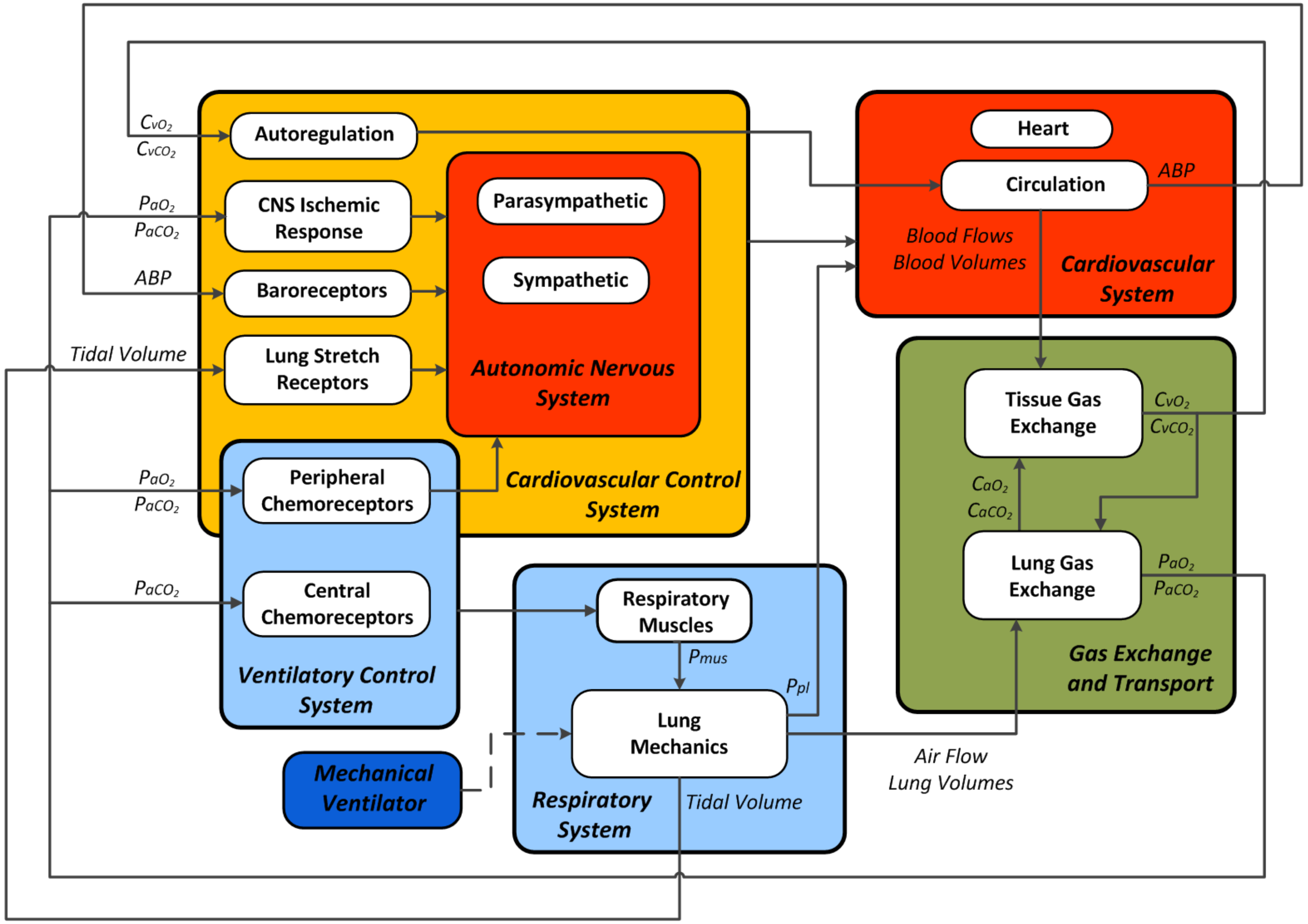


- Physiology-based models
- Parameter estimation

} ***Patient-specific models*** → ***Personalized Medicine***

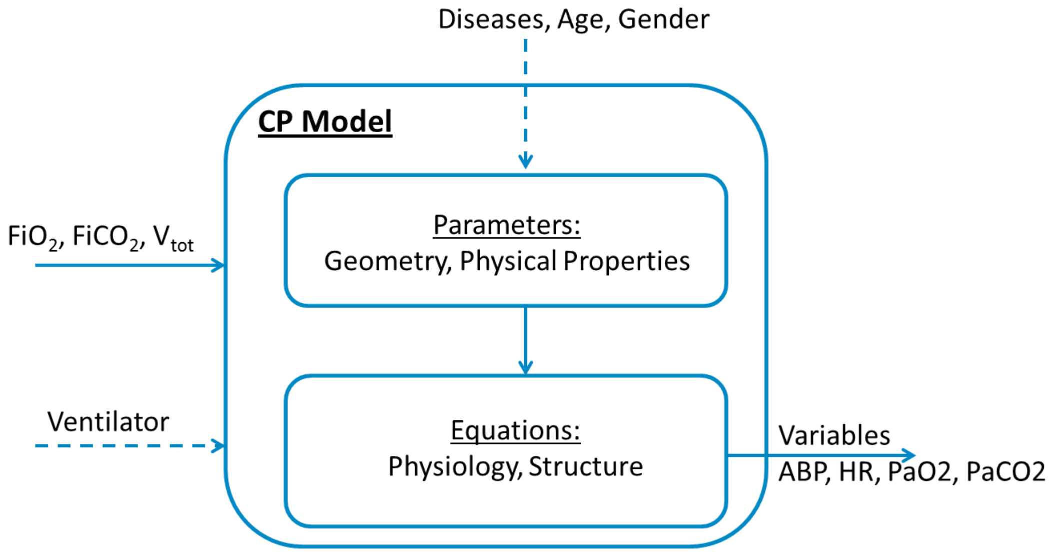
The Cardiopulmonary Model

Block Diagram



The Cardiopulmonary Model

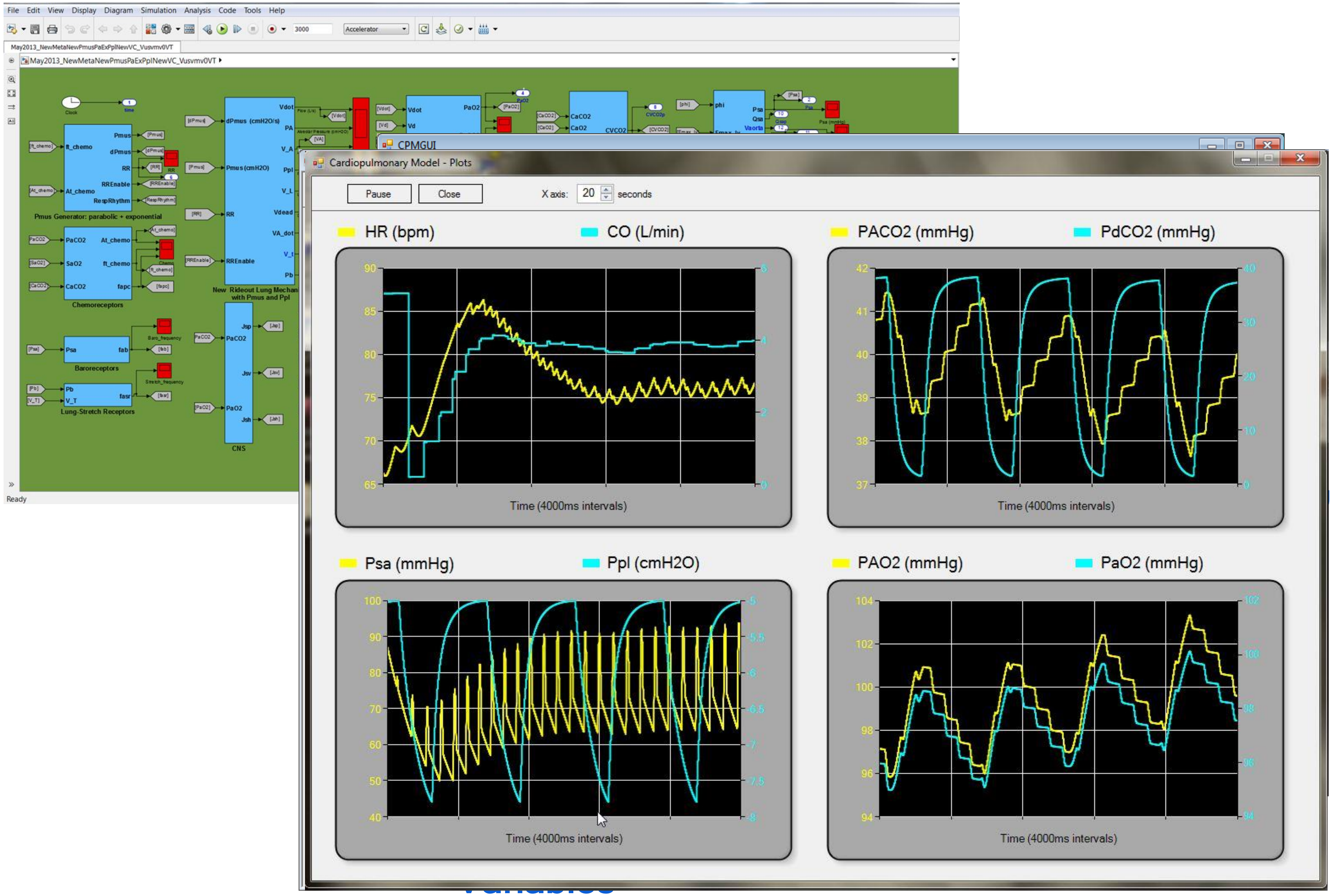
General Structure



NUMBER OF STATE VARIABLES, PARAMETERS AND OUTPUTS IN THE COMBINED CP MODEL

	State Variables	Parameters	Outputs
Cardiovascular System	17	74	43
Respiratory System	5	19	8
Gas Exchange and Transport	26	29	9
Cardiovascular Control	26	104	8
Respiratory Control	4	14	2
Total	78	240	70

Model Implementation

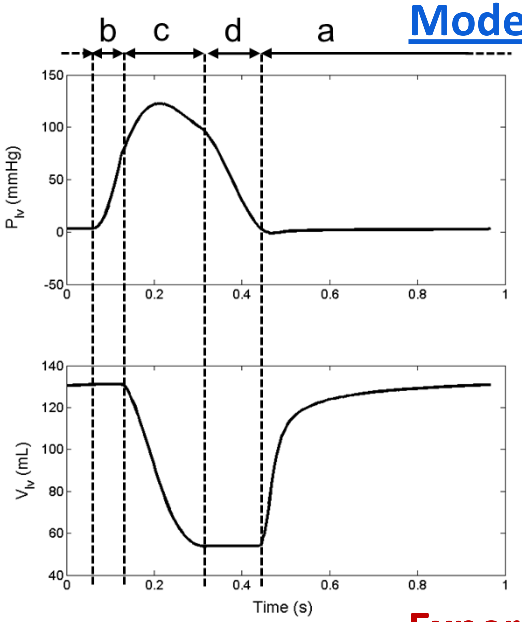


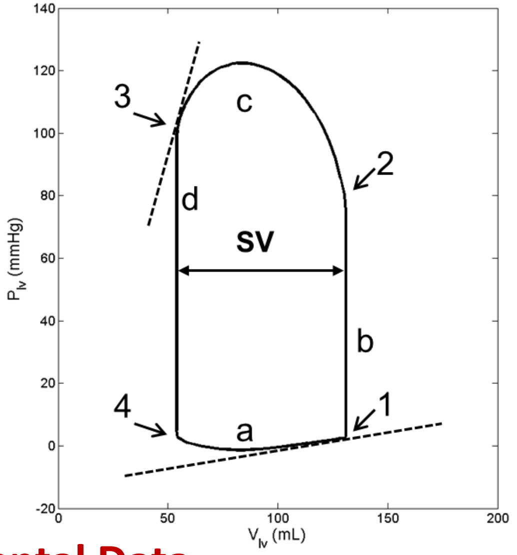
Model Verification and Validation

- Single set of parameters (240)
  - Average 70 Kg healthy subject
- Normal conditions
- Hypercapnia
- Hypoxia

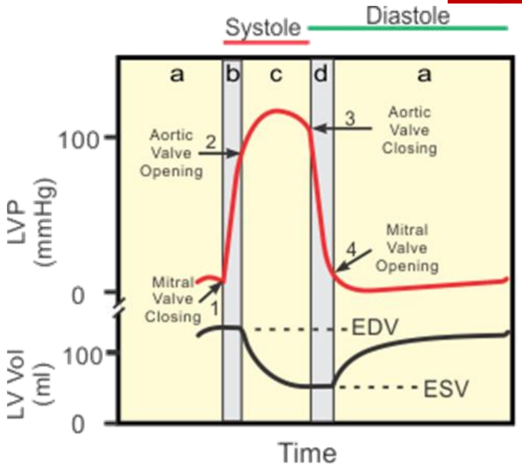
Normal Conditions: Cardiovascular Variables

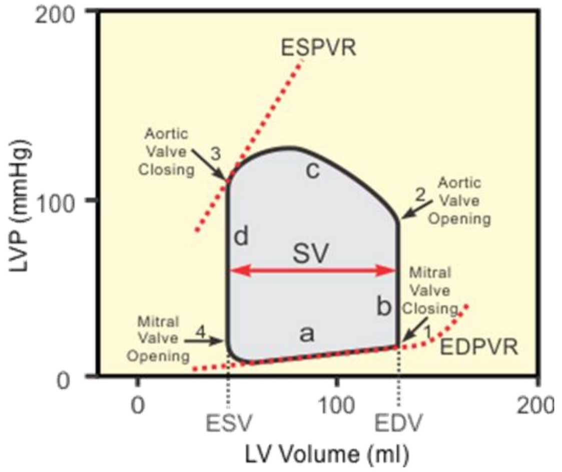
Model Simulations





Experimental Data

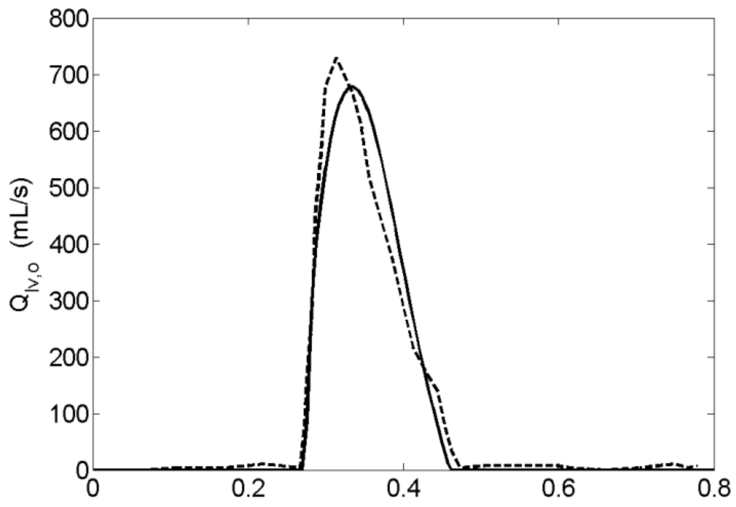


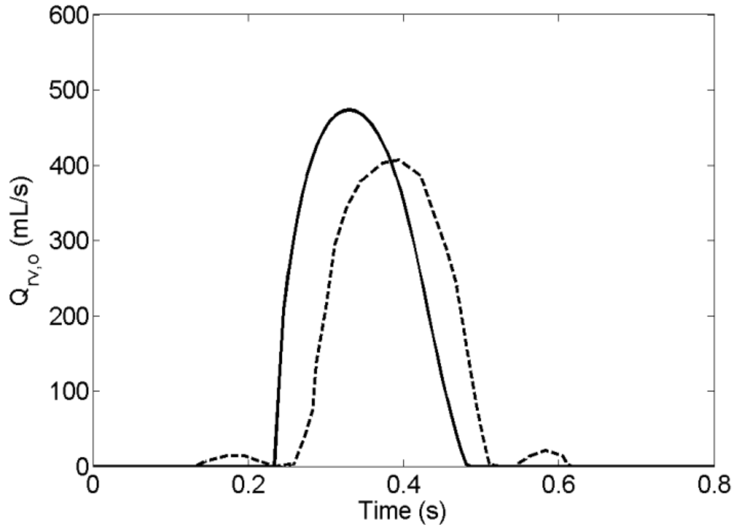


Normal Conditions: Cardiovascular Variables

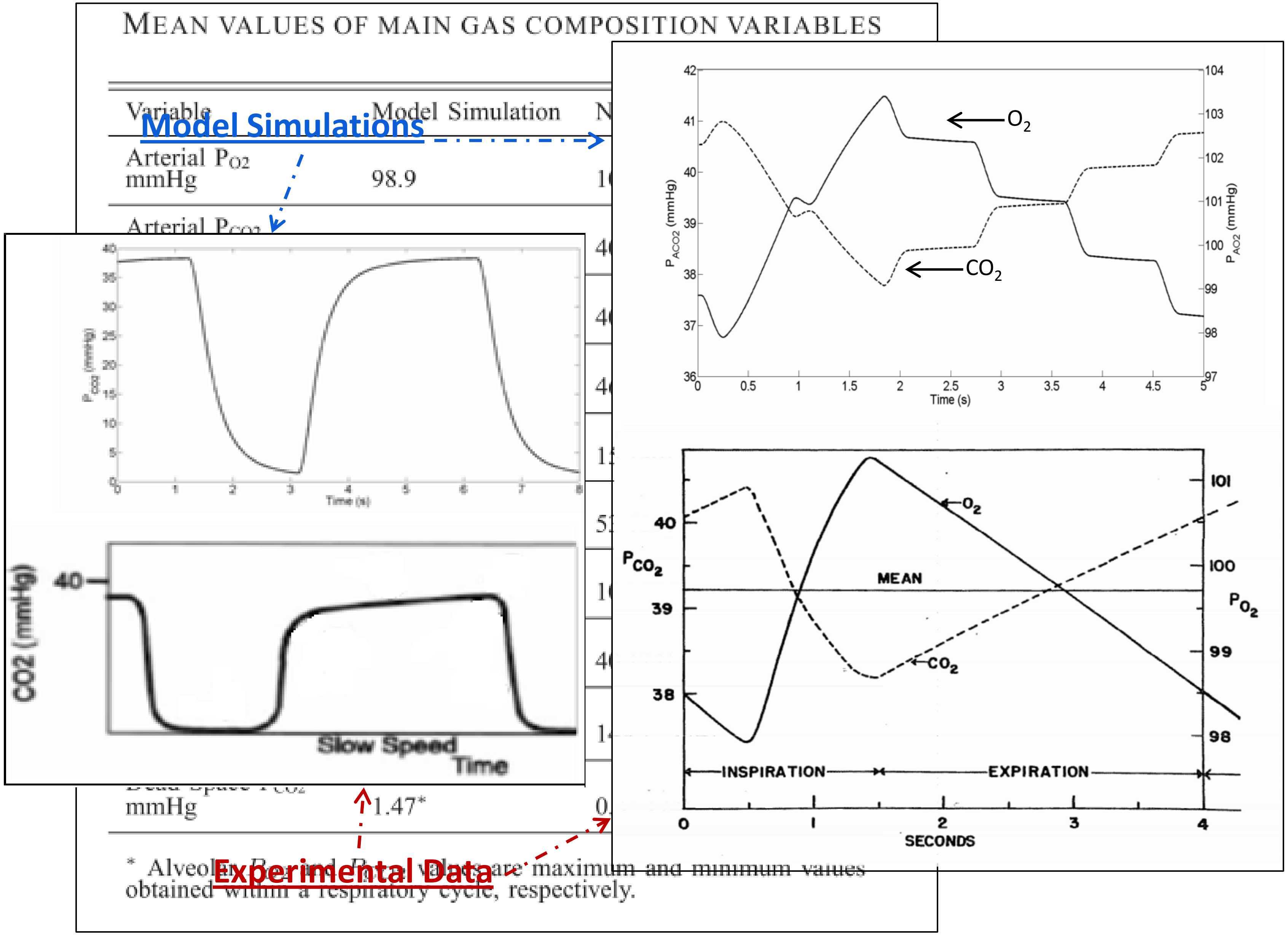
STATIC VALUES OF MAIN HEMODYNAMIC VARIABLES

Variable	Model Simulation	Normal Range
Arterial Pressure mmHg		
Mean	90.74	70-105 [86]
Systolic	122.79	90-140 [49]
Diastolic	78.86	60-90 [49]
Venae Cavae Pressure mmHg		
Systolic	3.79	2-14 [49]
Diastolic	2.72	0-8 [49]
Right Atrium Pressure mmHg		
Mean	0.7	2-6 [86]
Right Ventricle Pressure mmHg		
Systolic	24.45	15-28 [49]
Diastolic	-1.2	0-8 [49]
Pulmonary Artery Pressure mmHg		
Systolic	24.41	15-28 [49]
Diastolic	7.38	5-16 [49]
Left Atrium Pressure mmHg		
Mean	4	2-6 [86]
Left Ventricle Pressure mmHg		
Systolic	122.79	90-140 [49]
End-diastolic	0.2	4-12 [49]

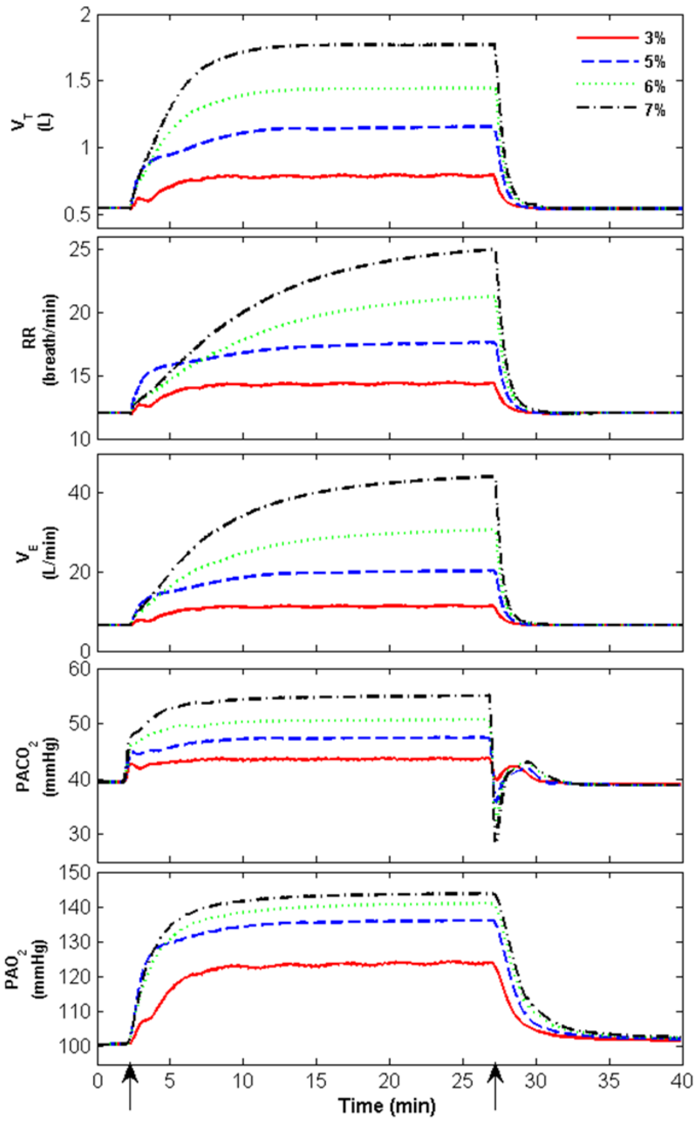


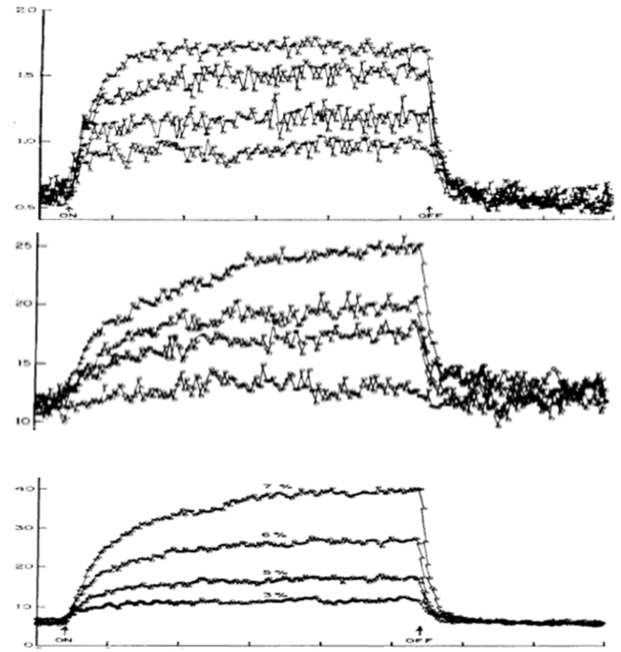


Normal Conditions: Gas Exchange Variables



Hypercapnia: Respiratory Variables





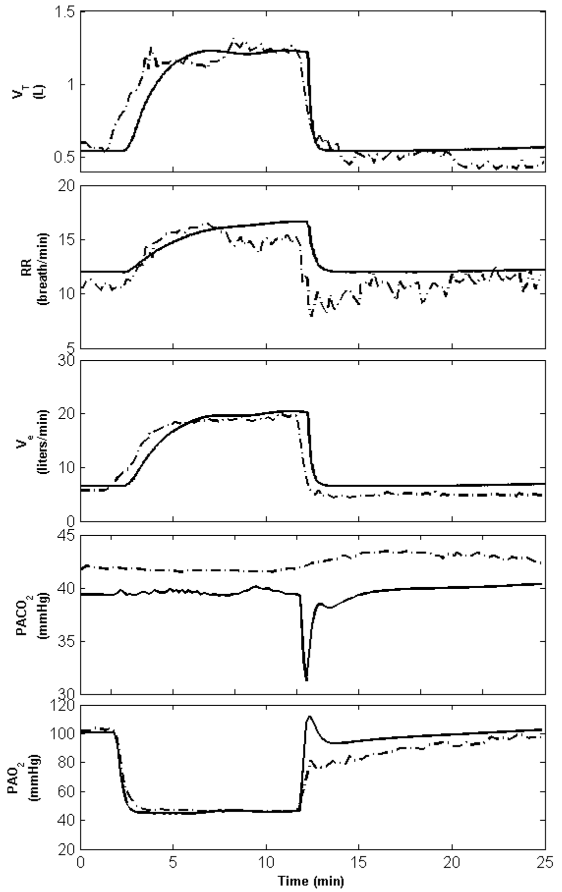
* Reynolds *et al.* (*J Appl Physiol*, 1972)
Averaged data from 15 subjects

Hypercapnia: Cardiovascular Variables

	7% CO_2		8% CO_2	
	Model	Kiely et al. (Chest, 1996) 10 subjects	Model	Mengesha (Ethiop J Health Dev, 2000) 8 subjects
Mean ΔHR (beat/min)	13.5 (+20%)	9.8 (+13.1%)	17.7 (+26.5%)	9.7
Mean ΔCO (L/min)	0.6 (+11.4%)	0.8 (+14.3%)	.86 (+16.2%)	
Mean ΔMAP(mmHg)	7.9 (+8.5%)	8.5 (+10.6%)	11.0 (+11.8%)	12.5
Mean ΔSBP(mmHg)	6.9 (+5.6%)	11 (+9.6%)	10.1 (+8.2%)	
Mean ΔDBP (mmHg)	8.4 (+10.8%)	6.4 (+10.1%)	11.4 (+14.6%)	
Mean ΔTPR ($mmHg*s*L^{-1}$)	0 (0%)	~0	-0.004 (-.44%)	

Hypoxic Respiratory Responses

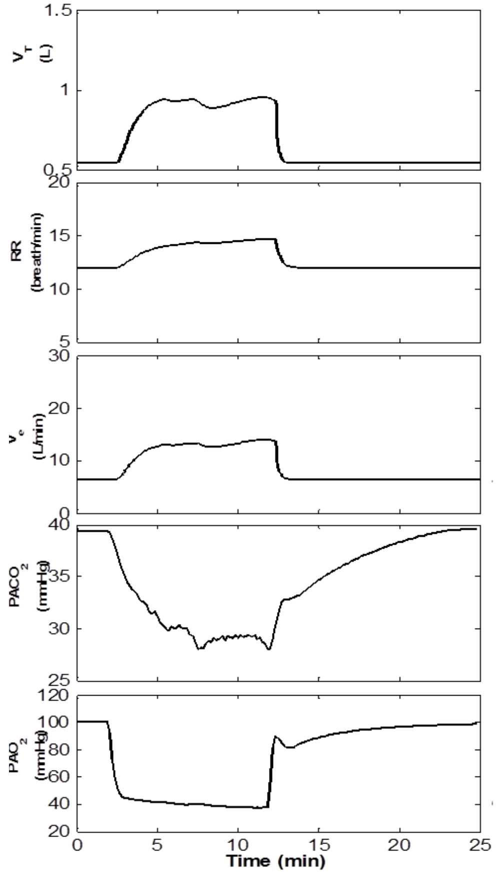
8% O_2 with controlled P_aco_2

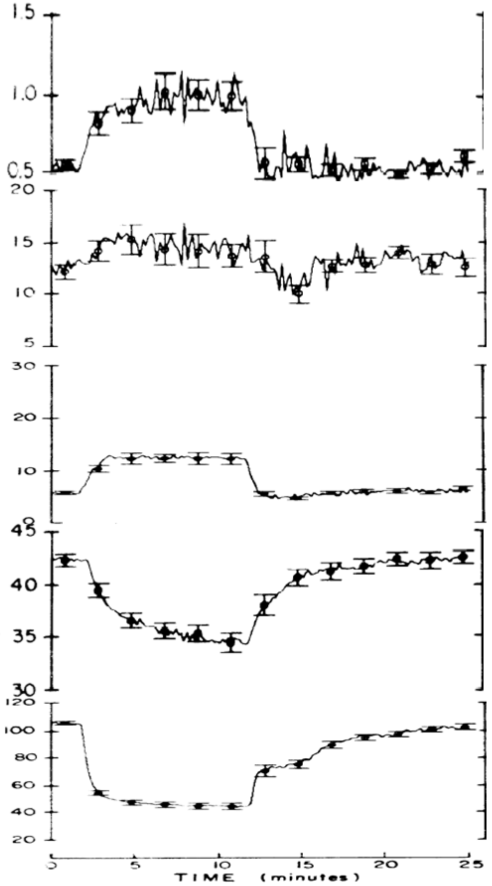


Model

Reynolds and Milhorn (*J Appl Physiol*, 1973)
Averaged data from 10 subjects

8% O_2 with uncontrolled P_aco_2





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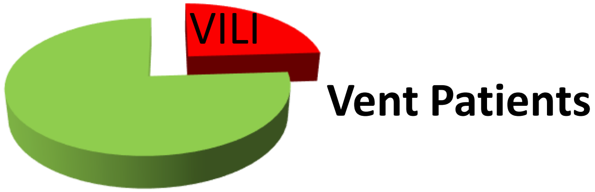
Averaged data from 10 subjects

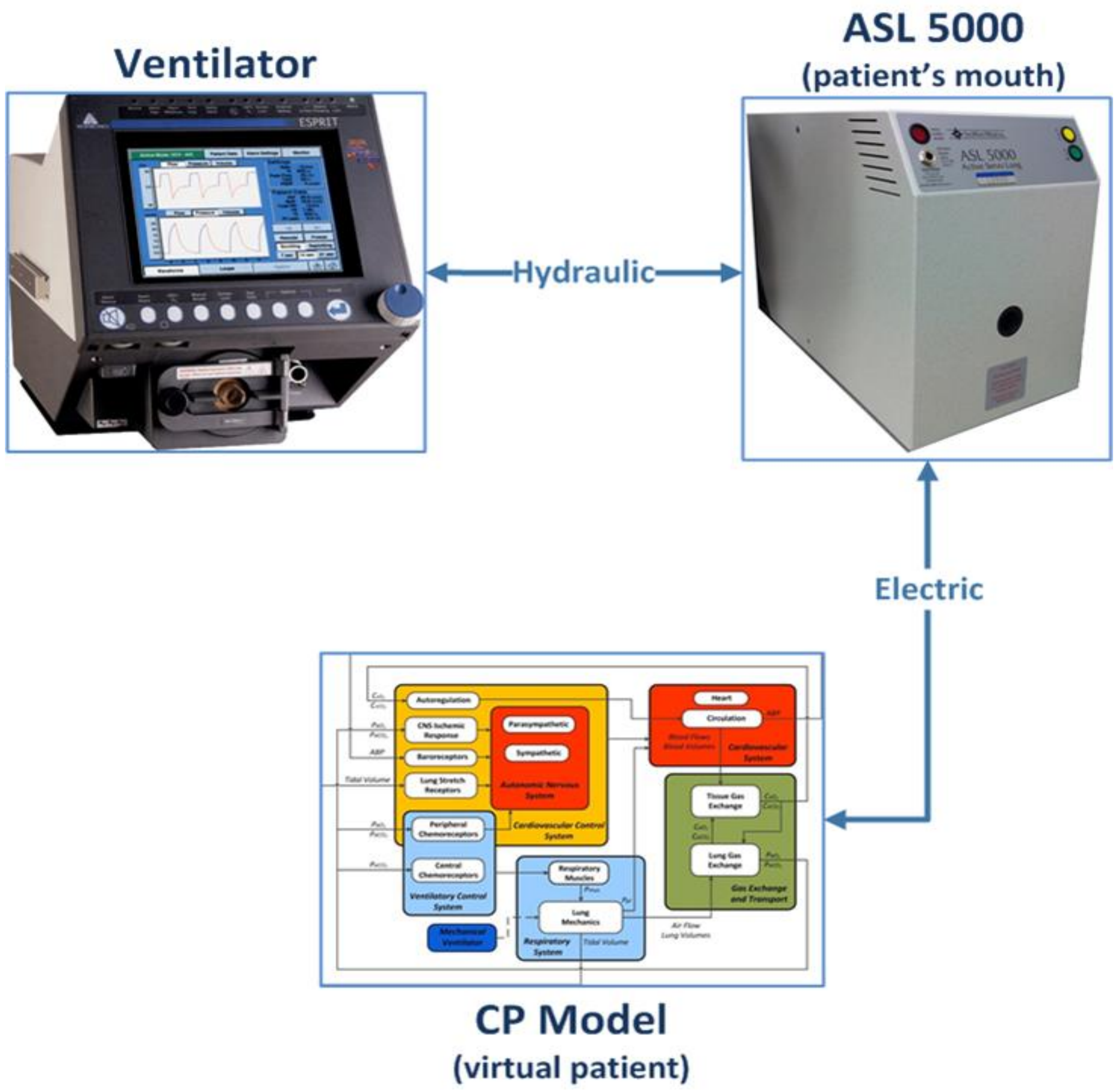
Ventilators (in the ICU)

- People are put on invasive ventilators:
  - After a surgery
  - Respiratory failure
- Mechanical ventilation: life saving procedure
- Need to minimize time on ventilator
- 6,000 new pts on ventilators daily in US (several days)
- 100,000 worldwide
- Improper ventilator settings →
  - Lung is 5 micron thin
  - Need right amount of pressure and flow
  - Settings are left for long periods
  - Patient conditions change
- Helping hand to the physician



Application of the CP Model

The Patient Emulator



Video of Patient Emulator on a Ventilator

Next Steps

Continue work on Physiologic Modeling

Continue research work on RT Parm Estim/System ID

Continue seeking clinical applications (baby steps)

Multi-institution Effort?

Thank you for your attention!

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