CHIMERA

/kʌɪˈmɪərə,kɪˈmɪərə/

noun

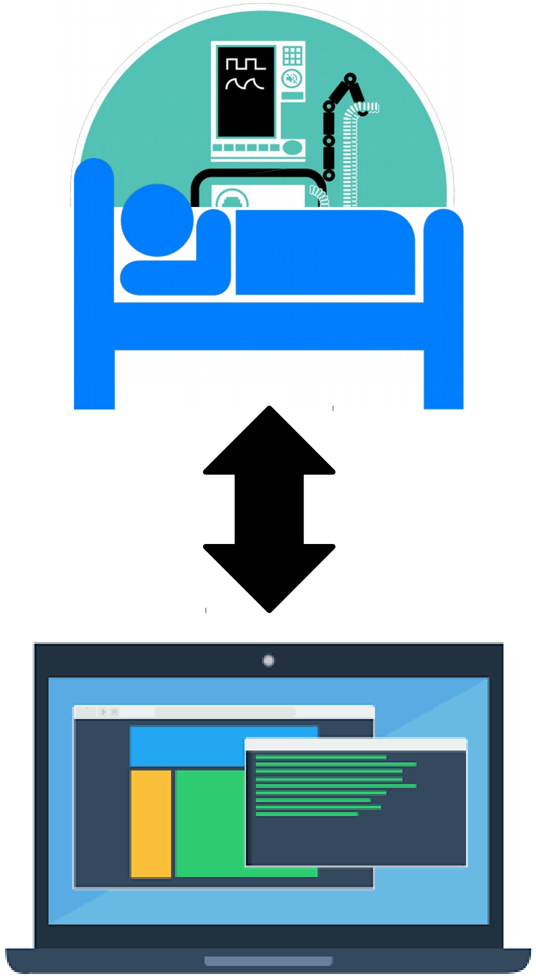
Collaborative Healthcare Innovation through Mathematics, EngineeRing and Artificial Intelligence

The Particular Problems of Critical Care

- Mechanical ventilation is the most important therapeutic intervention for patients with respiratory failure
- 100k ICU admissions undergo mechanical ventilation per year in the UK, with average daily cost of £1500
- Clinician workload is directly linked to patient outcomes. 1.7 human errors per patient per day, high mortality rates (30-40%)

Why use mechanistic models for respiratory illnesses?

- Very difficult to conduct clinical research on critically ill patients
- Many practical / ethical issues, clinical trials massively expensive, difficult to design, with high failure rates
- No single animal model typically replicates the complex pathophysiology of respiratory diseases
- Still difficult to “look inside” the lung
- Demand for more personalised treatment strategies
- Strong interest from Funding Agencies and Industry



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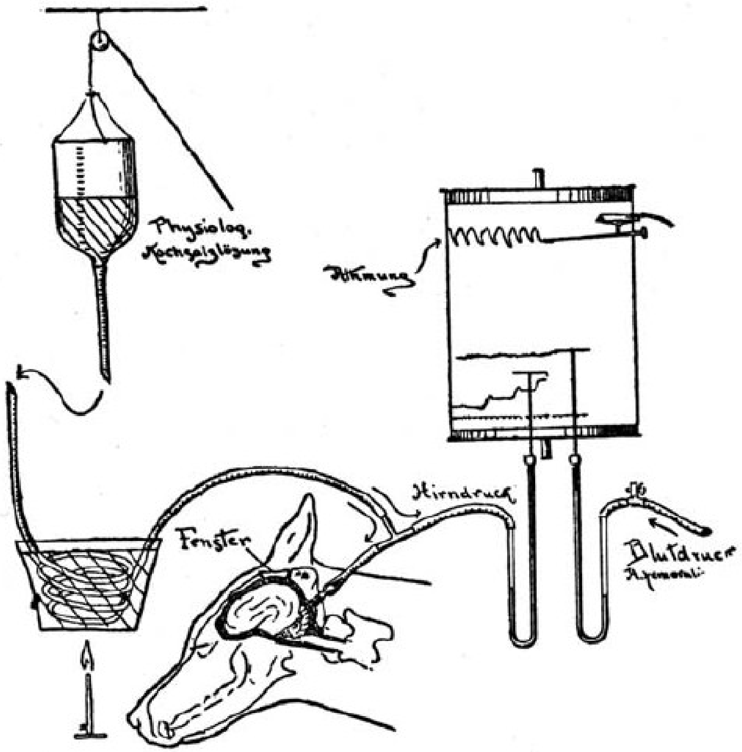
Physiology

UCL



Most physiology knowledge developed from animal experiments

This interpretation of physiology is applied to the complex environment of intensive care units

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Making use of data

Continuous data generation in ICU patients…

… but only fraction of data used to make treatment decisions

Admission Documents | Progress notes | Consult Notes | Discharge/Transfer | Child Protection Checklist | ECLS | ICU Chart | Cares | Ward Chart | Neonatal Care | RRT | Labs | Resus | Patient Monitoring | CATS flowsheet | Graphs | How To | MDT - Test | Test-Do not us

- Flowsheet (Paeds)
- Medication Administration Record
- Order Entry
- Order Reminders
- Orders Overview

Shift checklist
Vital signs
Ventilation
Spontaneous Breathing T...
Blood gases
Physio
Fluid Balance / Targets
Fluids & Dietary Intake
Colloids
Drugs - Continuous Infus...
Drugs - All Others
Drug Levels
Withdrawal score: Opioid...
Output
Pain
Calcs
PEWS

Flowsheet (Paeds)	04/04/2019 04:00	05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00
Weight (Working)	25.000	25.000	25.000	25.000	25.000	25.000	25.000	25.000	25.000	25.000	25.000	25.000	25.000
Height (Working)													
Head circumference (cm)													
Tri Weekly Weight (Kg)													
No. of Days on ITU	1	1	1	1	1	1	1	1	1	1	1	1	1
Date/Time Fit For Discharge													
Heart Rate	123	125	125	133	128	124	123	121	119	117	117	122	117
Heart Rhythm	NSR	NSR	NSR	Sinus tach	Sinus tach	NSR	NSR	NSR	NSR	NSR	NSR	NSR	NSR
Art BP	111/53 (68)	90/53 (66)	89/51 (63)	103/69 (81)	101/43 (58)	104/58 (70)	99/50 (62)	97/48 (60)	86/45 (56)	87/46 (57)	81/45 (55)	80/42 (54)	83/45 (55)
NBP	91/54 (64)												
Temp. 1	Oes. 37.0	Oes. 36.9	Oes. 36.9	Oes. 37.0	37.0	Oes. 37.0	Oes. 37.4	Oes. 37.4	Oes. 37.2	Oes. 37.2	Oes. 37.0	Oes. 36.9	
Temp. 2	Ax. 37.0					Ax. 37.4						Ax. 36.5	
Temp. 3													
Bair Hugger													
Respiratory Rate	22	25	25	25	22	22	20	18	20	18	18	18	17
Capillary Refill	2-3 Secs		2-3 Secs		2-3 Secs	< 2 Secs		< 2 Secs		< 2 Secs		< 2 Secs	
General Colour	Normal		Normal		Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
CVP													
Intra-abdominal pressure													
Cardiac Output													
Cardiac Index													
NIRS Channel Right Forehead													
NIRS Channel 3 Somatic													
Pupils, Left			2: Briskly		: Pinpoint	3: Briskly			3: Briskly			3: Briskly	
Pupils, Right			2: Briskly		: Pinpoint	3: Briskly			3: Briskly			3: Briskly	
Sedation Score		-5			-5	-5	-5	-5	-4	-4	-4	-3	-3

The broad aim

- Use real patient data
- Apply contemporary mathematical and computational techniques to develop an understanding of patient physiology during critical illness and recovery
- Improve methods for patient treatment
- Build an internationally-recognised, multidisciplinary and multisector Hub focused on these questions

Work packages

WP1 – statistical learning from clinical data

WP2 – iteratively testing and improving biomechanical models

WP3 - learning biophysical model structure and parameters with neural networks

WP4 – multidisciplinary workshops, clinical and industry engagement

WP5 – data curation, infrastructure, open source data and model platforms

WP6 – patient and public engagement, dissemination

The Team

Project partners and host institution

Management, partnership building, engagement, dissemination (WP4,5,6)

Clinical partners

Statistical analysis and learning (WP1)

Biomechanical modelling (WP2)

Machine learning (WP3)

Critical care, clinical data (WP4,5)

Alan Turing Institute

UCL-University College London Hospital (UCLH) Biomedical Research Centre (BRC)

Great Ormond Street (GOS) Hospital & UCL-GOS-Institute of Child Health BRC

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Claire Black
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(UCLH BRC funded)

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Engineering, UCL

- Hugh Kinnear (PhD, Oct 2020 – Sep 2023) (Funded: UCL Mathematics)
- Sam Jackson (PDRA, Jan 2021 – Aug 2021) (Funded: EPSRC) – Replaced by Victoria Volodina starting Nov 2021
- Federico Ricciardi (Mar 2021 – Feb 2024) (Funded: UCLH BRC) (Leaving Dec 2021)

- Abigail Smith (PhD, Oct 2020 - Sep 2023) (Funded: UCL Mathematics)
- Manuel Teixeira Cabeleria (PhD Sep 2021 – Aug 2024) (Funded UCL Mech Eng)
- Sina Saffaran (PDRA, Feb 2021 - Jan 2023) (Funded: EPSRC)

- Gevik Grigorian (PhD, Oct 2020 - Sep 2023) (Funded: UCL Mechanical Engineering)
- James Stainer (PhD, Oct 2020 – Sep 2024) (Funded: UCL-EPSRC CDT for AI Enabled Healthcare)
- Sandip Varkey George (Aug 2021 – Jul 2023) (Funded: EPSRC)

Progress so far

- Officially started in Jan 2021
- PhDs and PDRAs all recruited
- Weekly meetings of investigator team since August 2020
- Fortnightly multidisciplinary meetings of full team in place since August 2020
- Monthly seminar series established – internal and external speakers
- UCL website: https://www.ucl.ac.uk/chimera/; Twitter: @uclchimera
- Have already developed new collaborations internal and external to UCL
- Meetings with other EPSRC Maths in Healthcare Hubs including ECR conference
- Events and workshops being held in 2022 – Turing Engagement Event, Clinical Engagement Event
- Established Research Data Services platform for data sharing of deidentified clinical data within UCL/ UCLH/ GOSH
- Ongoing developments in data governance and ethics approvals with UCLH and GOSH.

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WP1 Blood Gas Project

1. Constructed a Dynamic Bayesian Network to analyse the oxygen affinity state, represented by p50, in critically ill patients.

2. The proposed approach relates the control factors (lactate, ph, PCO_2) to each other and to p50 over adjacent time steps.

3. Demonstrated the importance of comprehensive uncertainty treatment, i.e. through the probabilistic coupling we have propagated the uncertainty about the control factors and accounted for this uncertainty in the predictions of the oxygen affinity state.

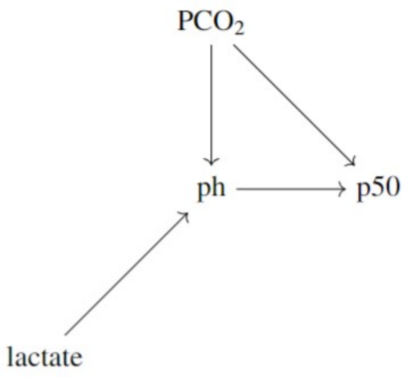

Figure: Directed acyclic graph to analyse the oxygen affinity state. Arrows represent causal effects.

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WP1 Blood Gas Project

- For individual patient, let $Y_t(i)$ be the value of clinical variable i at time t and the set $pa\big(Y_t(i)\big)$ is the set of parents of $Y_t(i)$, these variables have an arrow to $Y_t(i)$.

The joint density for the whole network can be decomposed:

$$f(\boldsymbol{y}) = \prod_{t=1}^{T}\prod_{i=1}^{n} f\big(y_t(i)|pa\big(y_t(i)\big), D_{t-1}\big),$$

where D_{t-1} denotes the information available at $t-1$. To model individual variables conditioned on its parents set, we use a Dynamic Linear Model.

To produce the short-term forecast, we propose to only consider the first two moments:

$$E[Y_t(i)|D_{t-1}] = E\big[E\big(Y_t(i)|pa\big(Y_t(i)\big), D_{t-1}\big)\big|D_{t-1}\big]$$
$$V[Y_t(i)|D_{t-1}] = E\big[V\big(Y_t(i)|pa\big(Y_t(i)\big), D_{t-1}\big)\big|D_{t-1}\big] + V\big[E\big(Y_t(i)|pa\big(Y_t(i)\big), D_{t-1}\big)\big|D_{t-1}\big]$$

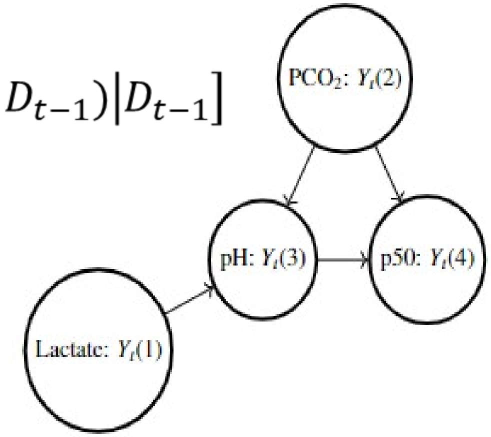

Figure 2: Naive DAG for the analysis of oxygen affinity state in ICU patients.

Future work

Incorporate information about medical treatment by suitable intervention into the model to explain abrupt structural changes.

If such information is not available, modify the network model to handle these events automatically.

Specifying a Bayesian inverse problem to improve p50 values produced by a blood gas analyser machine for clinically ill patients.

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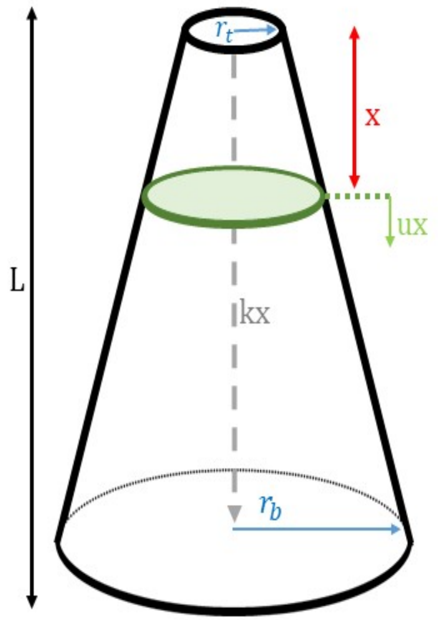
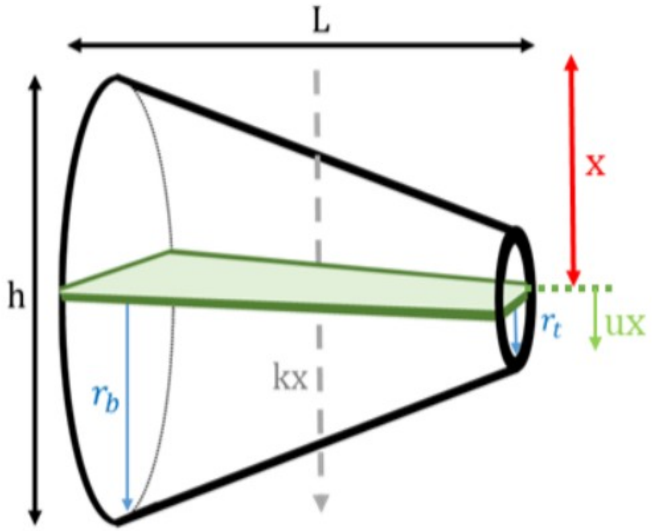
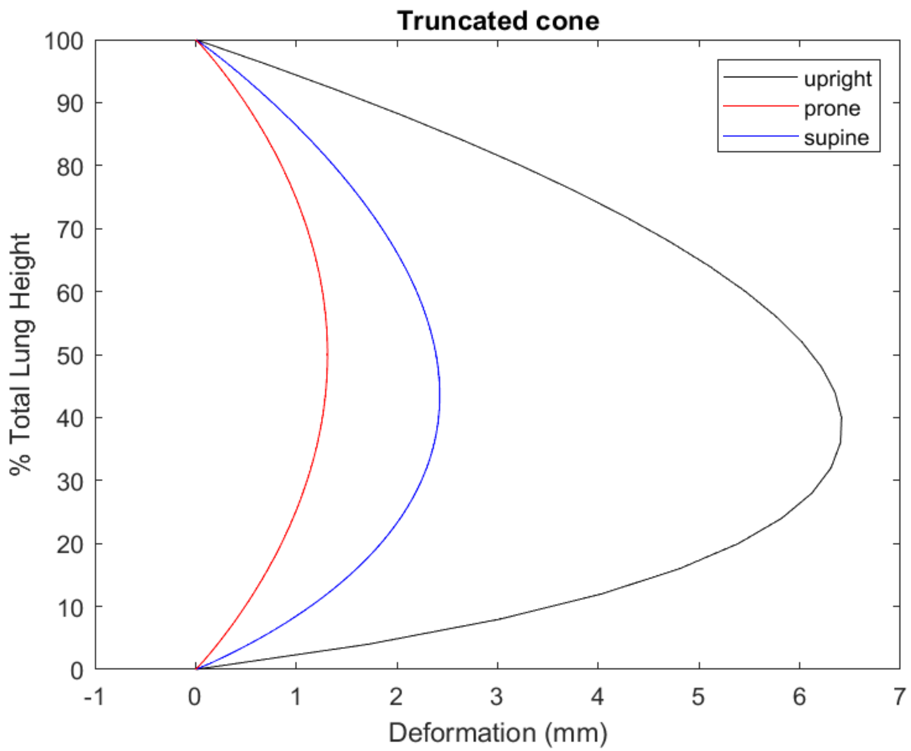
WP2 The effects of gravity and patient positioning on pulmonary mechanics for use in clinical care.

Use of solid mechanics to simulate tissue deformation in the lung under its own weight.

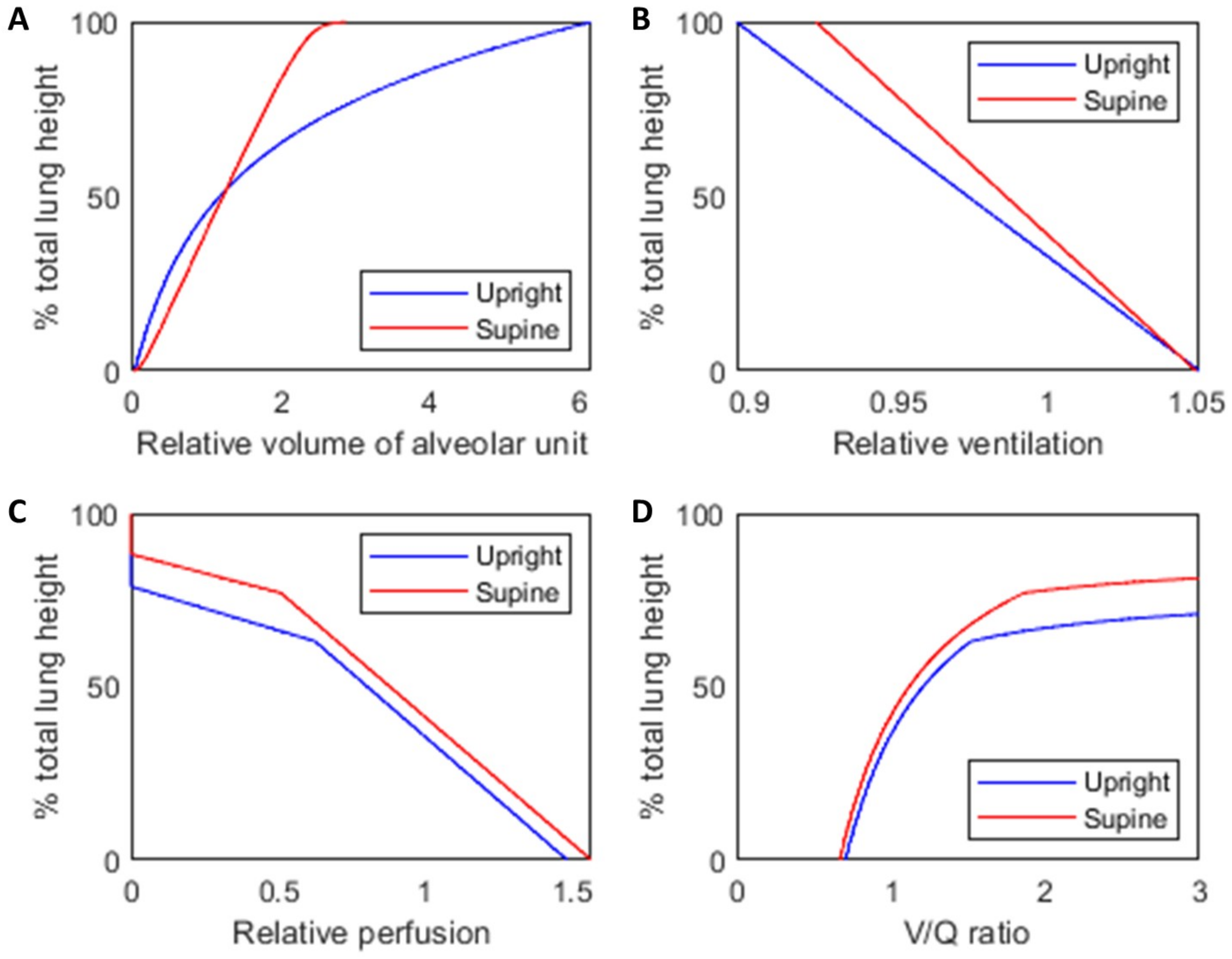


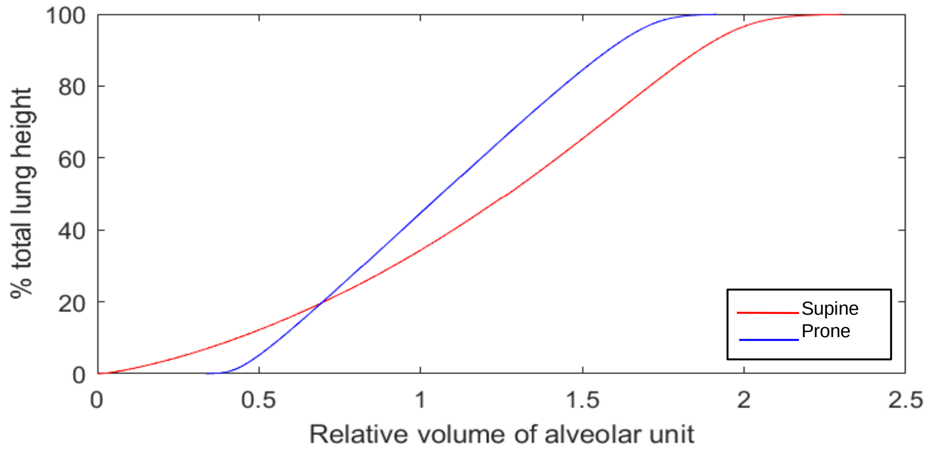


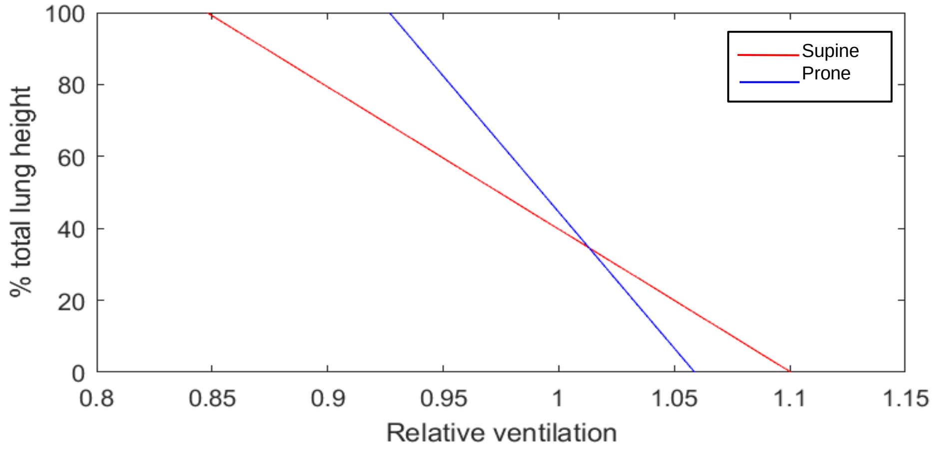


WP2 The effects of gravity and patient positioning on pulmonary mechanics for use in clinical care.

Calculation of regional ventilation and perfusion.







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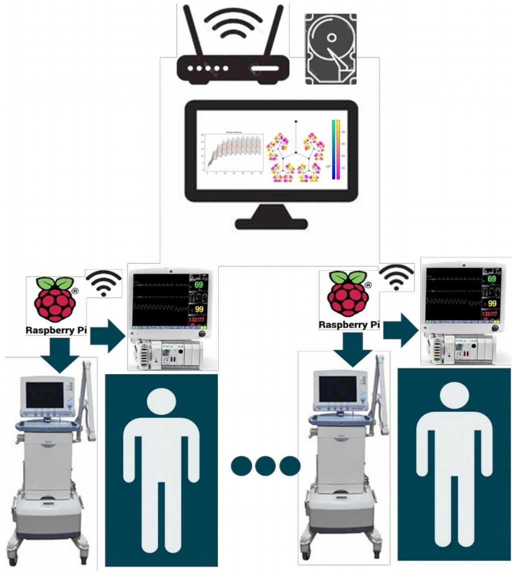
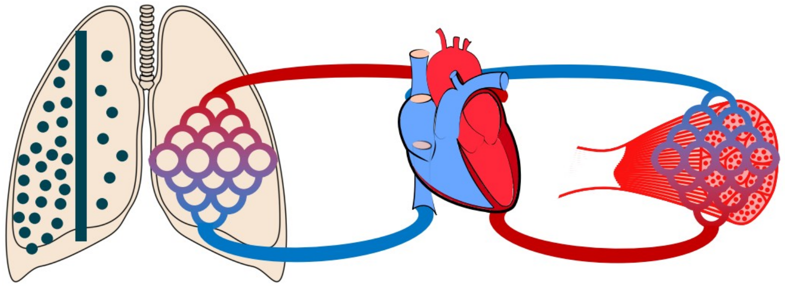
WP2 My ICU Twin - A Patient-Specific Cardio/Respiratory Model

- A software that can be used at the bedside
- Implements a mathematical model of the cardiorespiratory system, optimised to the patient
- The effects of treatments can be simulated in real-time prior to being applied to the patient
- The evolution of the patient during ICU stay can be monitored
- Parameter estimation in real-time (ex. Blood gases and pH)





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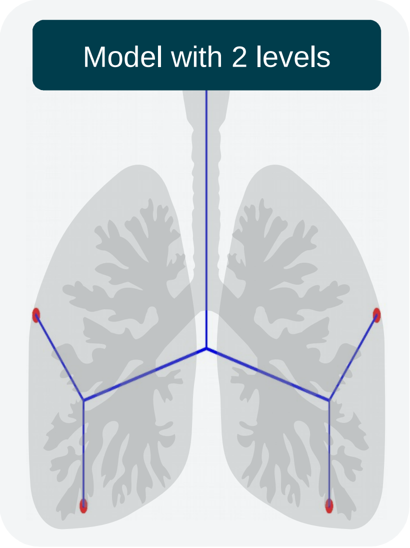
WP2

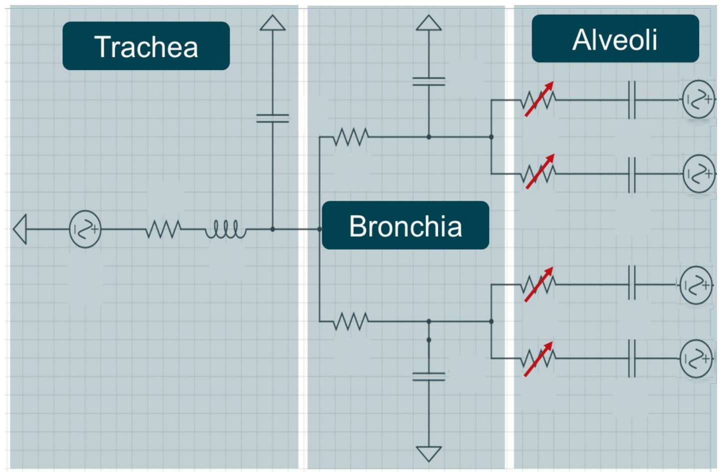
My ICU Twin - A Patient-Specific Cardio/Respiratory Model

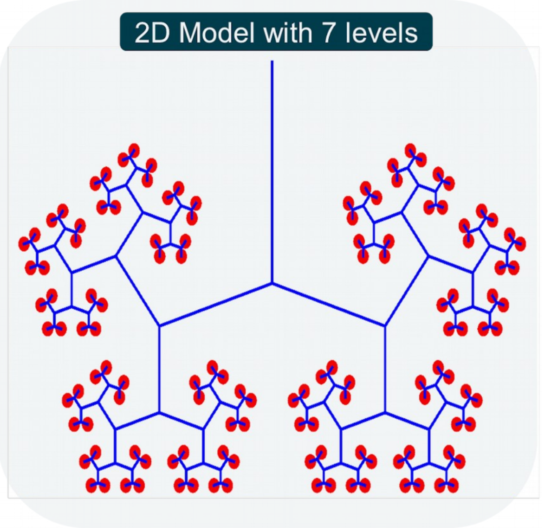
Lung Model

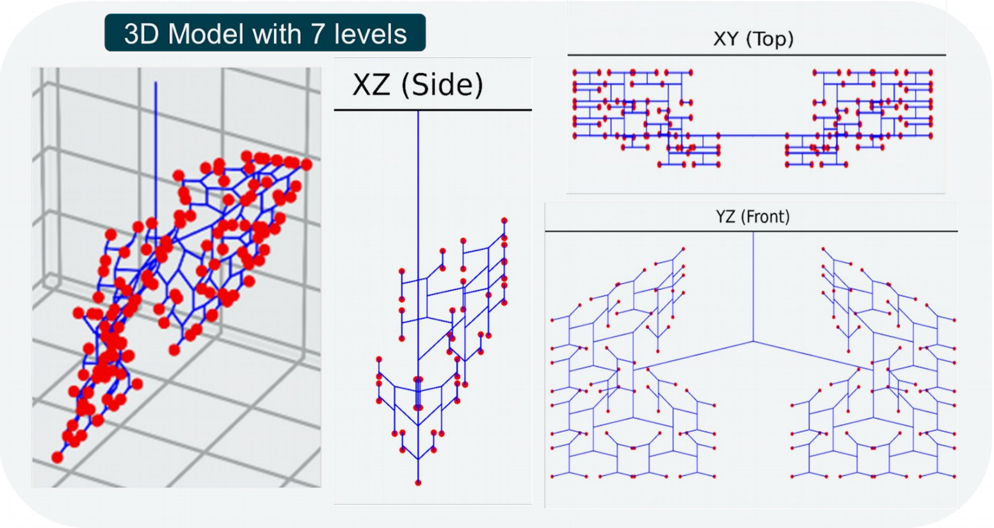
- Lumped parameter model of the lung incorporating branching of the bronchia,
- Systems of equations and 2D/3D models are generated automatically using a set of initial conditions:
    - # Levels, Length and Radius of the trachea, Branching angle, Length decay, Min/Max R and C

- The model can be imbued with extrinsic pressures at the alveoli level to simulate the effect of gravity and autonomic control features









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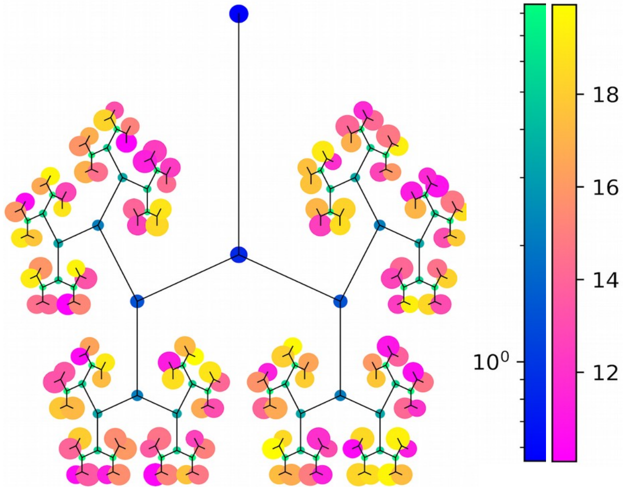
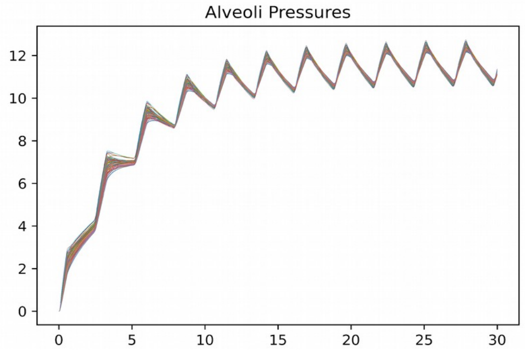
WP2

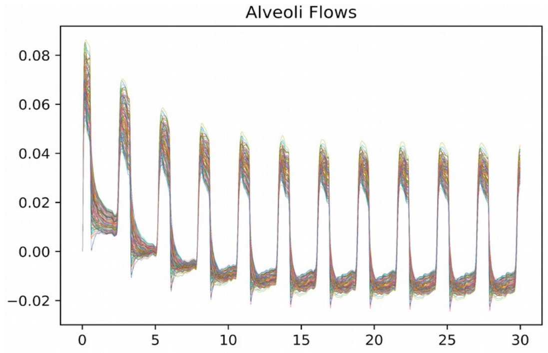
My ICU Twin - A Patient-Specific Cardio/Respiratory Model

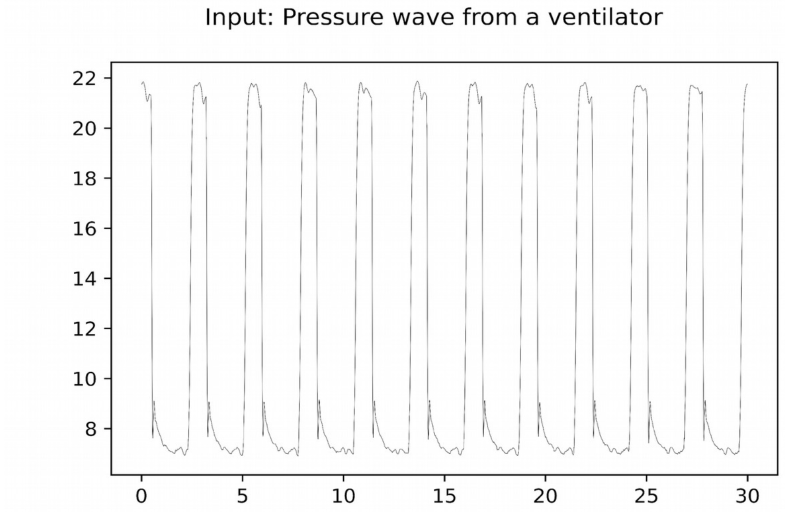
Preliminary Results

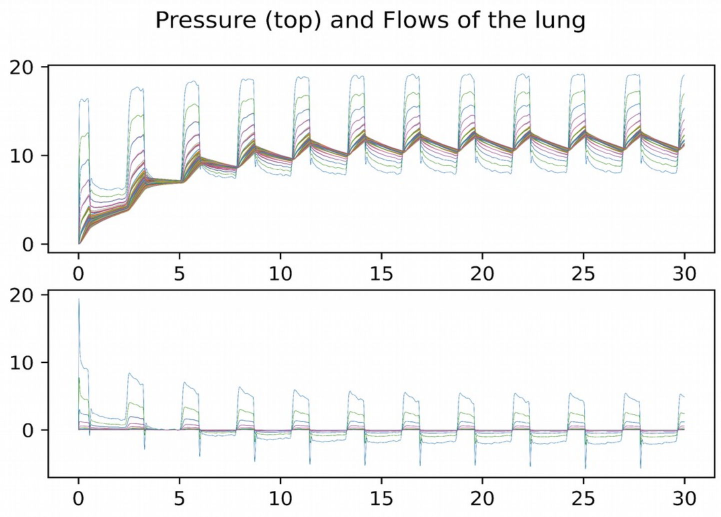
- length: 0.12
- radius: 0.01
- maxLevels: 7
- branchAngle: pi/2.5
- lengthDecay: 1.6
- mode: random
- resStart: 10
- resEnd: 20
- capStart: 0.01
- capEnd: 0.02

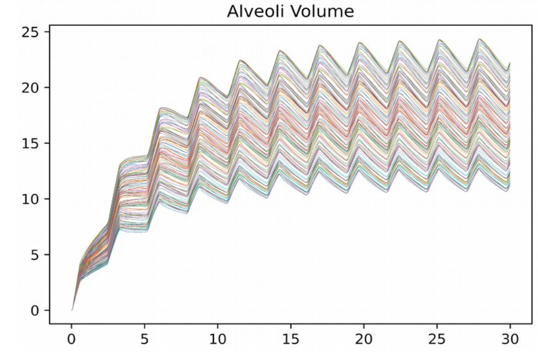






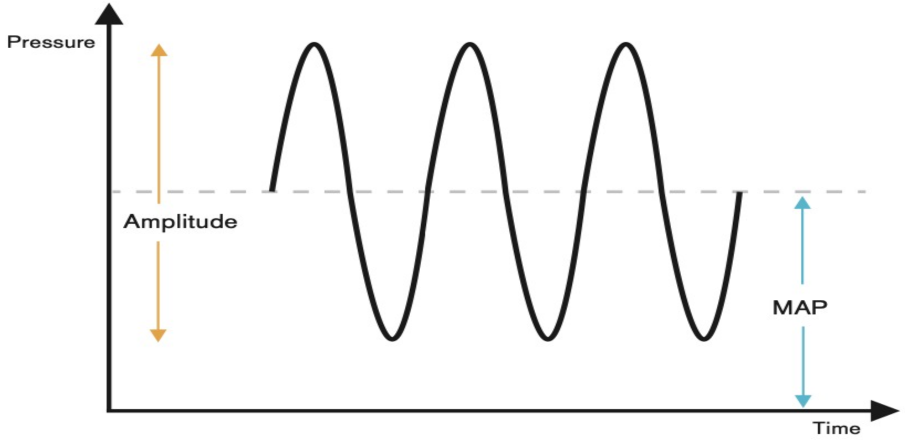






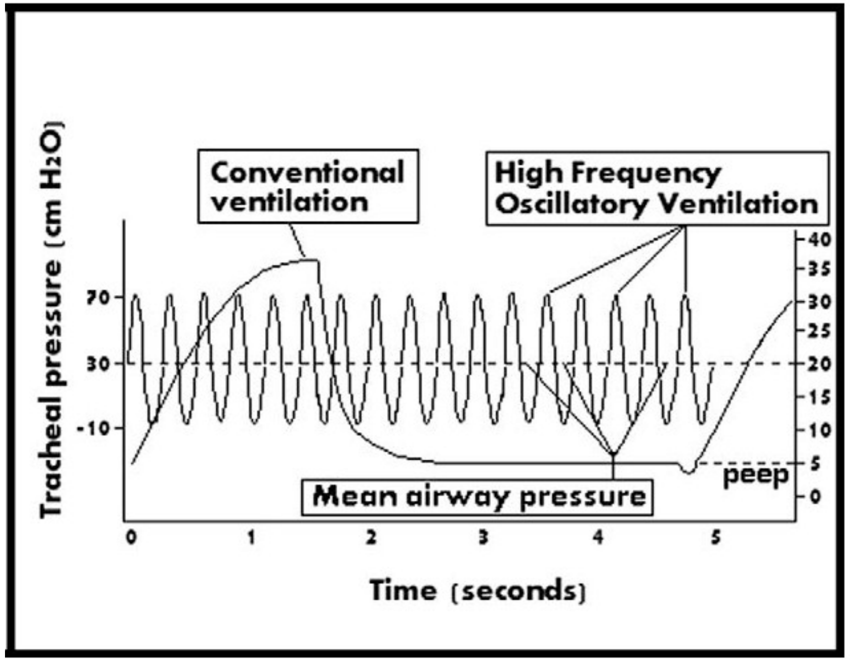
WP2 High Frequency Oscillatory Ventilation (HFOV)

- HFOV is an alternative method of mechanical ventilation which can be used as a **‘lung protective strategy’** in the management of some severe lung conditions.



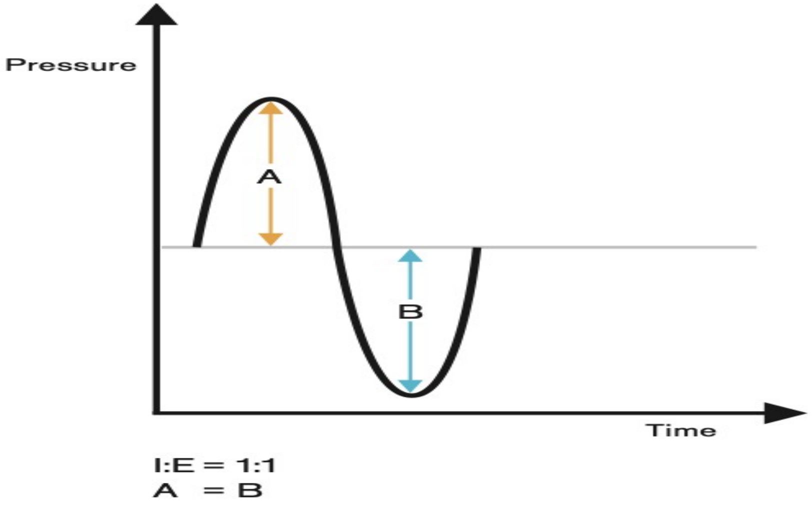
- How it works?

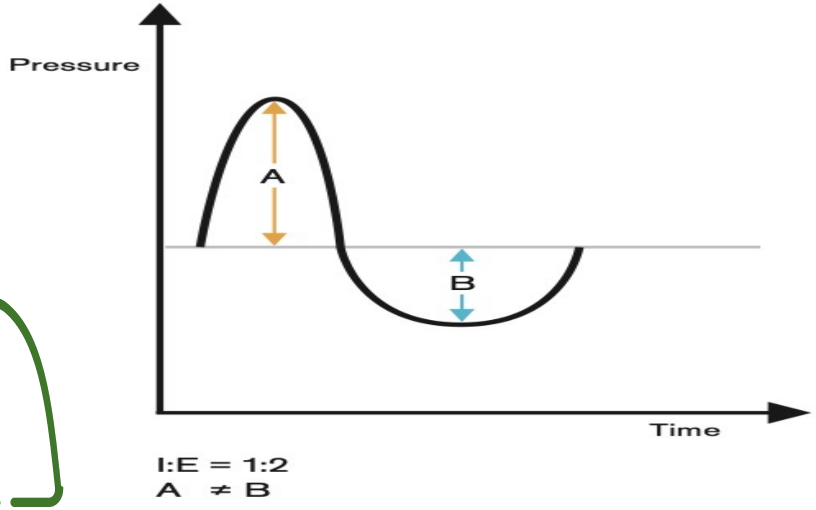
  A constant distending airway pressure (MAP) is applied, over which small tidal volumes (less than dead space) are superimposed at a high respiratory frequency (3-15 Hz).

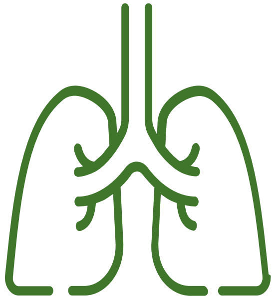


WP2 High Frequency Oscillatory Ventilation (HFOV)

- Gas mixing during CV is primarily dependent on direct ventilation, requiring tidal volumes larger than the deadspace.
- In sharp contrast to CV, HFOV offers highly effective oxygenation and clearance of waste gas, despite use of sub-deadspace tidal volumes.
- The efficiency of HFOV in ventilating the lung at very low tidal volumes is attributed to highly effective mixing of fresh and exhaled gases in the airways and alveolar compartment.







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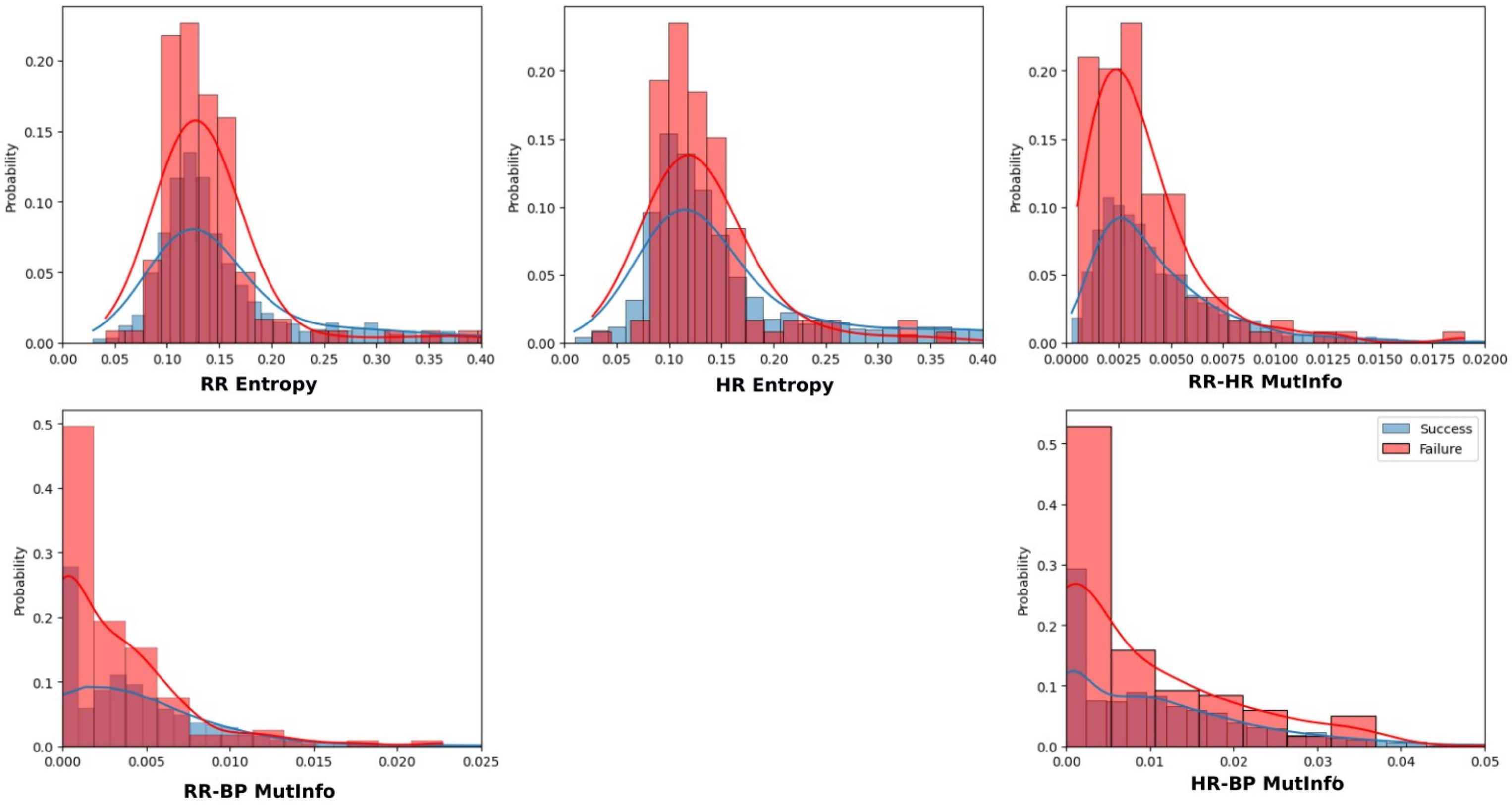
WP3 Using complexity measures of ICU time series for predicting extubation

- Calculate nonlinear measures of ICU time series 24 hours before extubation.
- Compare between failed and successful extubation groups
- ICU time series data
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Blood pressure (BP)
- Nonlinear measures
  - Fractal dimension
  - Multiscale entropy
  - Mutual information
- 5 of 9 measures showed a difference between the groups.
  - Entropy of RR and HR
  - Mutual information between
    - HR and RR
    - HR and BP
    - RR and BP



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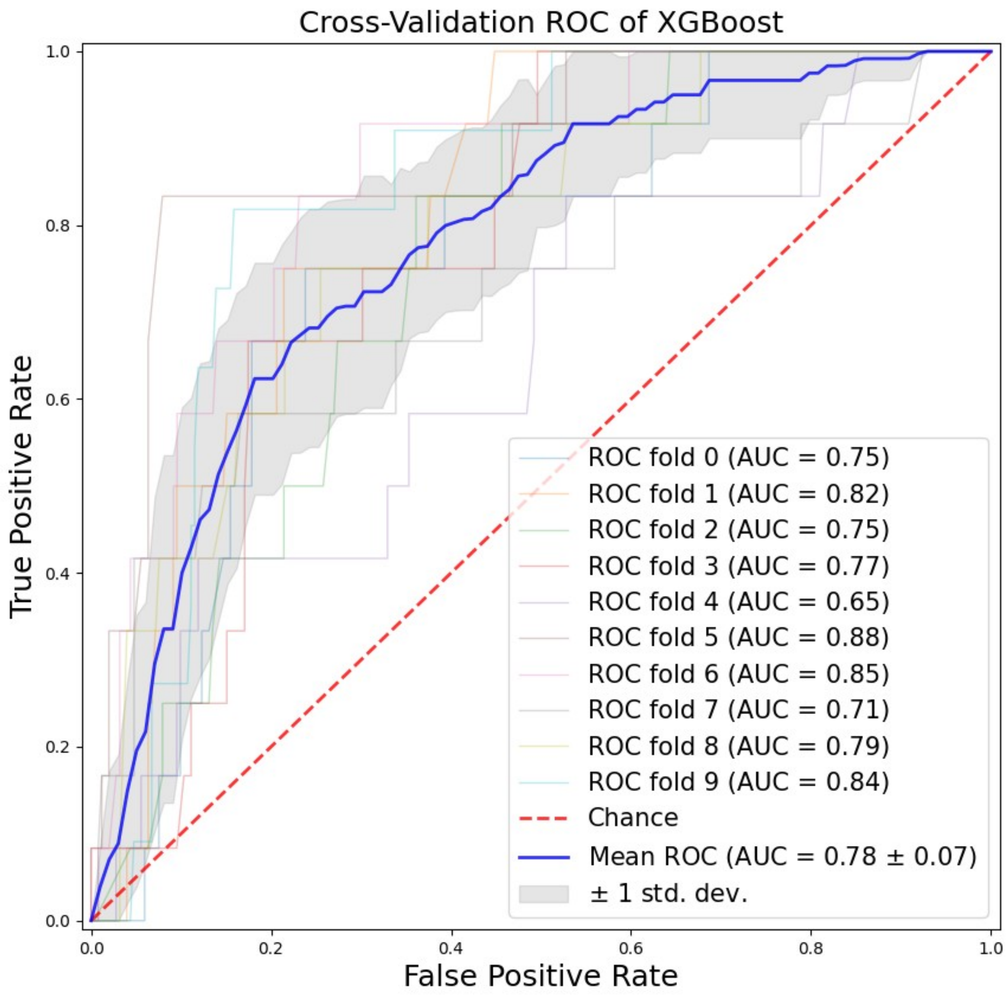
WP3 Using complexity measures of ICU time series for predicting extubation

- Predict extubation outcome using machine learning models
- Models compared between feature sets
  - Without complex measures (Basic)
  - With complex measures (Added)

Model	AUC (Basic)	AUC (Added)
Support vector machine	.73 ± .04	**.74 ± .04**
Artificial neural network	.72 ± .05	**.74 ± .01**
Random Forest	.74 ± .05	**.75 ± .05**
Light Gradient Boosting Machine	.77 ± .04	.77 ± .04
Exteme Gradient Boosting Machine	.74 ± .01	**.78 ± .07**



WP3 Grey-Box Models

When and How to Use Grey-Box Models

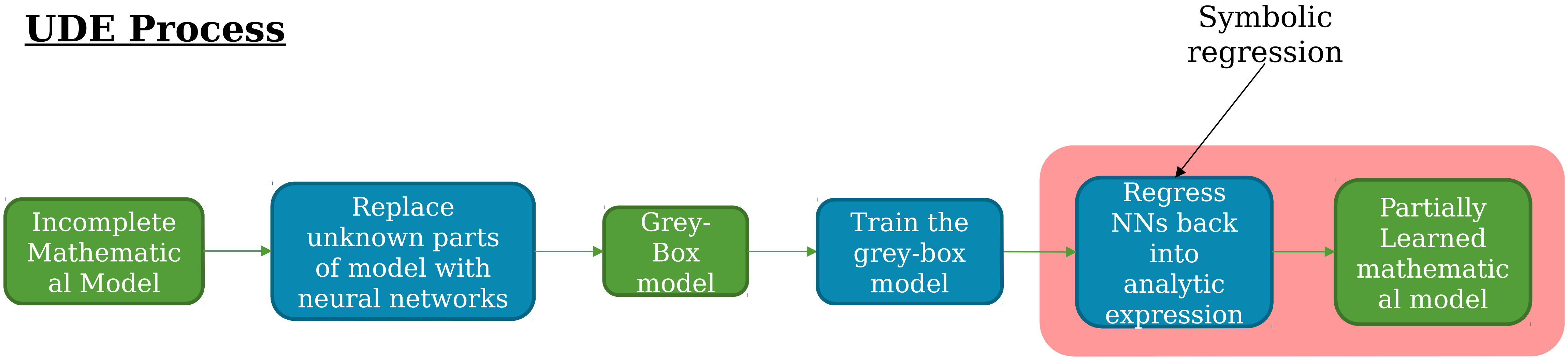
- Complex mathematical models can be incomplete due to difficulties in calculating certain parameter values and/or gaps in existing knowledge.
- For incomplete models, it is possible to **replace the unknown parts of the mathematical model with neural networks**. This is a grey-box model.
- Most of the structure of the dynamics (equations) are still known, so the grey-box model doesn’t require as much data as the black-box neural network → data efficient.
- This is a powerful tool for long term prediction when the mathematical model is incomplete.

WP3 Grey-Box Models

Universal Differential Equations:

1. Replace unknown terms in a system of ODEs with neural networks.
2. Regress trained neural networks back into mechanistic form.

UDE Process



WP3 Grey-Box Models

UCL

Experiment: Lorenz Equations

Original Model

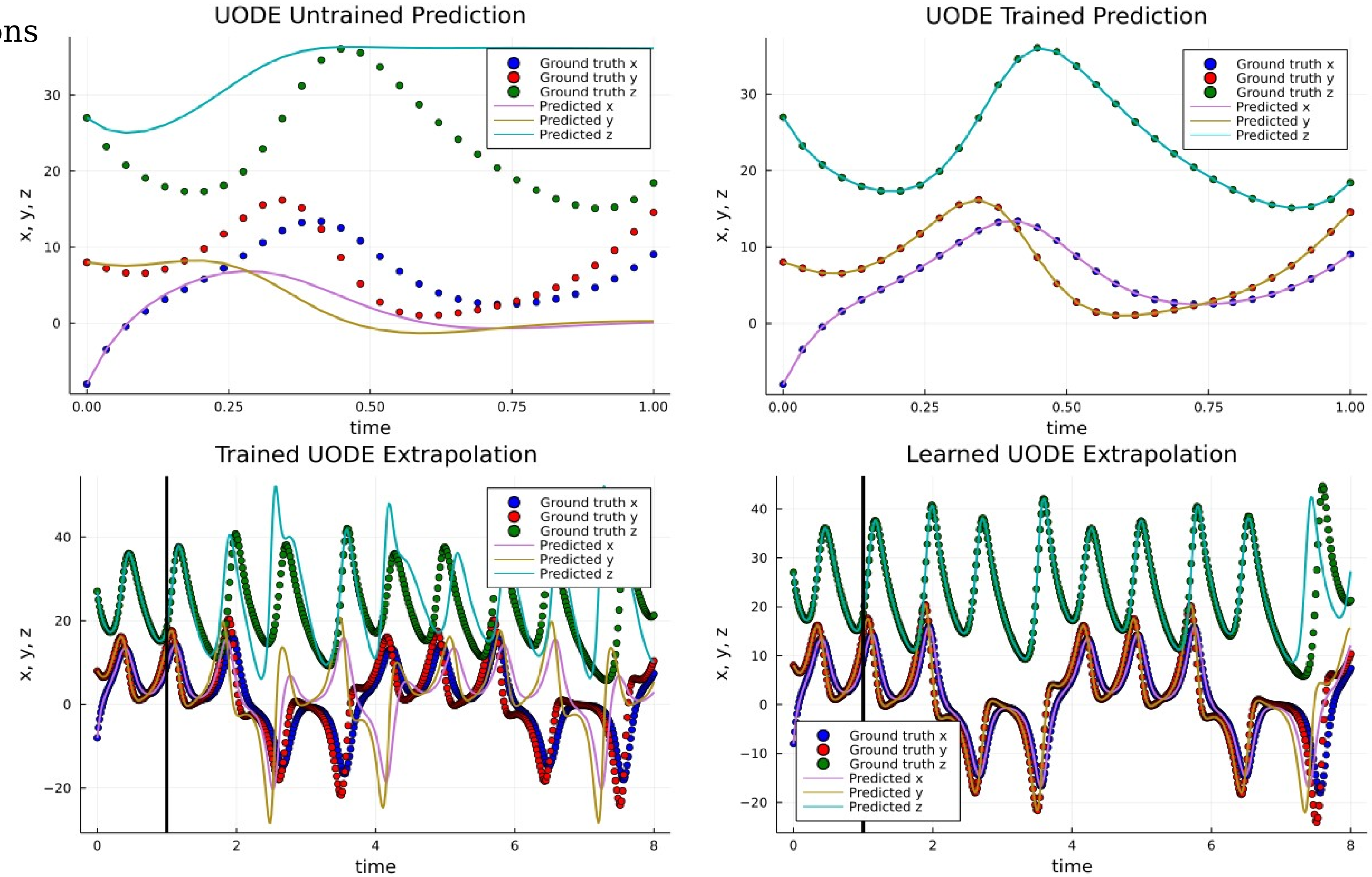
$$\frac{dx}{dt} = 10(y - x)$$
$$\frac{dy}{dt} = x(28 - z) - y$$
$$\frac{dz}{dt} = xy - \frac{8}{3}z$$

Grey-Box Model

$$\frac{dx}{dt} = 10(y - x)$$
$$\frac{dy}{dt} = x(28 - z) + NN_1$$
$$\frac{dz}{dt} = xy + NN_2$$

Learned Terms

$$NN_1 \rightarrow -0.9990727y$$
$$NN_2 \rightarrow -2.6667087z$$

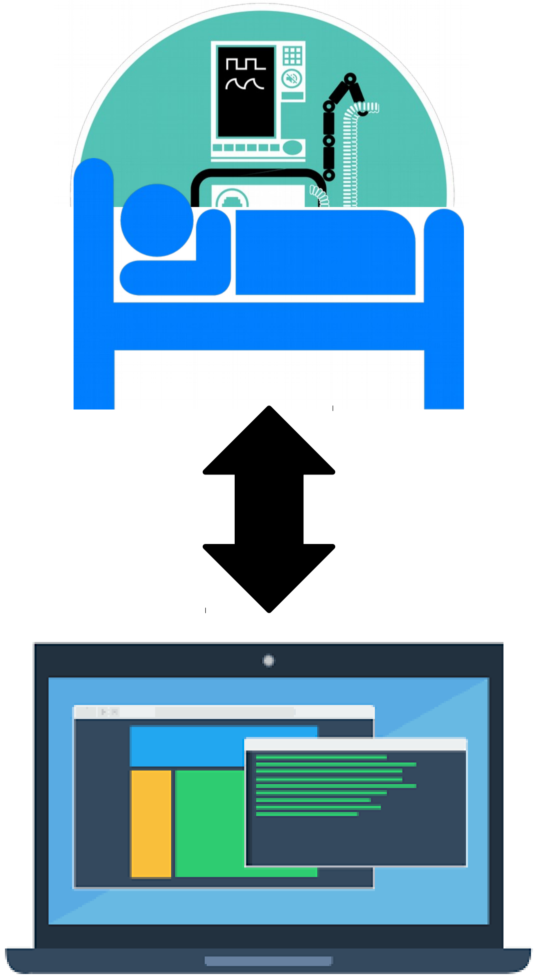


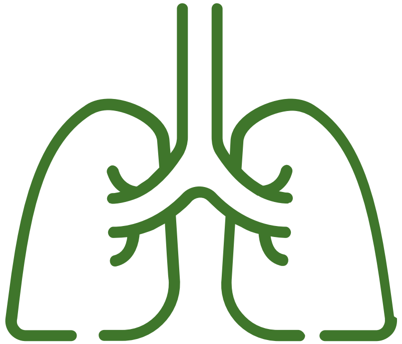
Connecting WPs

- **WP1 and WP2:** Employing emulators and history matching to speed up performance of parameter fitting.

- **WP2 and WP3:** Using the grey box approach to determine suitable biomechanical twin model components that mimic given patient data.

- **WP1 and WP3:** Predictive tools using complexity measures.





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CHIMERA

Project timeline

		Year 1	Year 2	Year 3	Year 4
	Work Packages				
WP1	**Statistical Learning from Clinical Data (A Diaz)**				
WP1.1	Missing data				
WP1.2	Sequential parameter estimation				
WP1.3	Hierarchical modelling				
WP2	**Testing and Improving Biomechanical Models through an Iterative Learning Loop (Ovenden/ V Diaz)**				
WP2.1	Initial assessment of biomechanical models				
WP2.2	Validation and selection via tracking observations				
WP2.3	Classify patient risk through machine learning				
WP3	**Learning Biophysical Model Structure and Parameters with Neural Networks (Arridge)**				
WP3.1	Framework for learned coupled non-linear differential equations				
WP3.2	Learned network model for electro-mechanical cardiac dynamics				
WP3.3	Learned network model incorporating other organs				
WP4	**Multidisciplinary Workshops, Clinical and Industry Engagement (Shipley/ Pagel/ Aviles/ Cade/ Ray/ Peters/ Harris)**				
WP4.1	Distribution of partnership resource				
	Co-production of selection process for allocation of partnership resource				
	Project panels for allocation of PDRA and PhD resource				
	Project panels for allocation of seedcorn funding				
WP4.2	Multidisciplinary workshop programme engaging new clinical, academic and industry partners (including ATI DSG in year 3)				
WP4.3	Funding bids by investigator team, project partners to grow the CHIMERA base and support long-term vision				
WP5	**Data Curation, Infrastructure, Open Source Data and Model Platforms (Shipley/ Arridge/ Ray/ Peters/ Harris)**				
WP5.1	Data curation and infrastructure development				
WP5.2	Open source data libraries, synthetic data and model platform development				
WP6	**Patient and Public Engagement, Dissemination (Pagel/ Shipley/ Cade/ Aviles)**				
WP6.1	Patient and public involvement (PPI) - workshops (year 3/4), researcher training, hosting blogs, Twitter live chats				
WP6.2	Dissemination of hub outputs - publications, conferenceswebsite, newsletter series, social media, seminar/ webinar series				