

CHIMERA Progress Report January 2024



Executive summary

CHIMERA (Collaborative Healthcare Innovation through Mathematics, Engineering and AI) is an EPSRC funded centre based at UCL, launched in Autumn 2020.

Researchers at CHIMERA are examining anonymised data from patients at University College London Hospital (UCLH) and Great Ormond Street Hospital (GOSH), to develop a better understanding using mathematical modelling of how people's physiology changes during ill health and recovery. This new understanding will in turn provide new ideas for how critically ill patients can best be cared for.

In this report we present progress so far across the workstreams and many other strands of activity that have arisen organically from clinicians, mathematicians, statisticians and data scientists working together and talking to each other. While it has been an enormous challenge to set up the data sharing infrastructure, this is now in place and we are excited to launch a public facing website for the data platform within a few months. All of our workstreams are now progressing well and exciting new results and research projects are emerging.

Table of contents
Table of contents2
Executive summary1
Work package progress to date
WP1: Numerical Statistics, PI: Alejandro Diaz3
WP2: Iteratively Testing and Improving Biomechanical Models, PIs: Vanessa Diaz & Nick Ovenden5
WP3: Learning Biophysical Model Structure and Parameters with Neural Networks, PI: Simon Arridge
WP4: Multidisciplinary Workshops, Clinical and Industry Engagement, PI: Christina Pagel & Becky Shipley
WP5: Data Curation, Infrastructure, Open Source Data and Model Platforms, PI: Steve Harris8
WP6: Patient and Public Engagement, Dissemination, PI: Christina Pagel & Becky Shipley8
Additional CHIMERA activity9
1. Airway secretions. PI: Nick Ovenden, Simon Arridge, Claire Black
2. Obtaining better estimates of exercise intensity. PI: Alex Diaz, Claire Black
3. How much data do we actually need? PI: Sam Ray, Simon Arridge9
4. Oxygen in the blood. PI: Sam Ray9
5. Using mathematics for a better insight into CPR. PI: Mark Peters, Sam Ray, Alex Diaz, Nick Ovenden, Vanessa Diaz10
6. Predicting adverse outcomes during CAR-T cancer therapy: PI: David Brealey11
Other activity to date11
CHIMERA seminar series11
Publications to date12
Associated grants13
Academic talks given by CHIMERA team13
Other activity/public engagement/outreach14

WP1 - Computational Statistics, PI: Alejandro Diaz

A new algorithm for rare event simulation and Markov Chain Monte Carlo (MCMC) has been developed. It is designed to solve problems in Bayesian inference, model updating, reliability analysis and unconstrained optimisation (Figure 1).

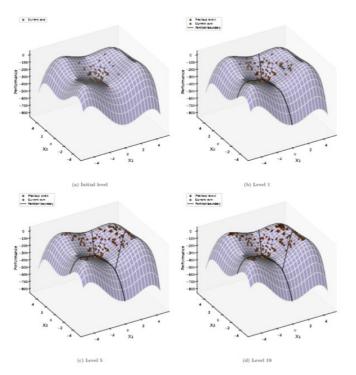


Figure 1. New rare-event simulation algorithm detects 4 modes, whereas a traditional algorithm would get stuck in local maxima.

One potential application that this new algorithm is being tested on is a Bayesian hierarchical model of the maximum aortic pressure in pigs during cardiopulmonary resuscitation recorded with pressure sensors, used to train first aiders (Figure 2, and Additional activity 5).

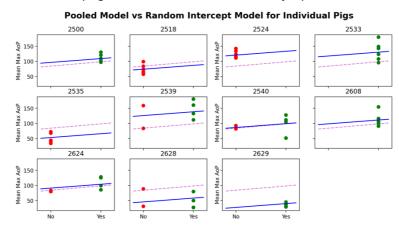


Figure 2. Preliminary results of a Bayesian hierarchical model using rare-event simulation.

Sequential Monte Carlo and history matching methods are being developed with the aim of calibrating dynamic simulators. Namely, models whose output depend on a constant stream of data. A reduced version of a new CHIMERA cardiorespiratory model is being calibrated (see workstream 2). Figure 3 shows how well the algorithm matches the target data values.

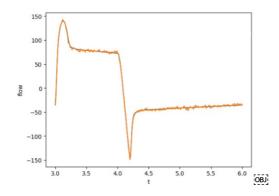


Figure 3. Calibration of model output through history matching (Cheng).

The algorithm outputs a non-implausible set of values (figure 4) for each of the 6 parameters (3 resistances, 3 compliances). The samples are non-implausible in the sense that they are highly likely to provide a match between model output and target observed values and cannot be discarded after taking into account all sources of uncertainty.

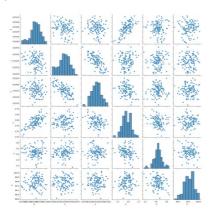


Figure 4. Pairwise non-implausible space for the six model parameters.

A high-dimensional respiratory model is currently being calibrated. The challenge with this model is that each of its 3N inputs contributes equally to the output. Here, N is the number of alveoli used to model gas exchange within the lungs. Dimension reduction techniques were not effective and instead the problem is being solved by decomposing the model into 2 components and using linked Gaussian processes. The emulation of the model is necessary due to its computational cost. The current approximation through emulation has low bias but high variance (figure 5). Once this procedure is refined, it will be used to calibrate the model using history matching and the number of alveoli can be scaled up to more realistic values.

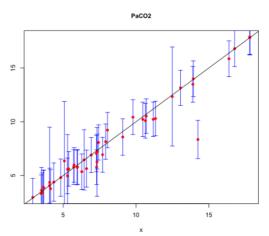


Figure 5. Simulated vs emulated values and uncertainty bounds for respiratory model. Most predictions have low bias around the 45-degree line but still exhibit variance that should be reduced.

Additional to history matching, other types of calibration are currently being tested, namely, generative models (e.g. autoencoders and diffusion models) coupled with evolutionary methods for optimisation (e.g. covariance matrix adaptation).

Missingness in data is being studied to predict pH in arterial blood (an important clinical quantity). Data from 14 patients is available and different techniques are being considered, amongst which are hierarchical models (Figure 6), deep Gaussian processes and generative models.

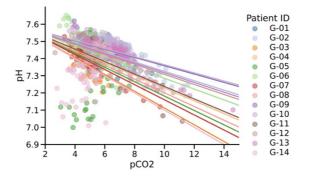


Figure 6. Partial pooling through hierarchical model to predict pH in arterial blood with missing data

WP2: Iteratively Testing and Improving Biomechanical Models, PIs: Vanessa Diaz & Nick Ovenden

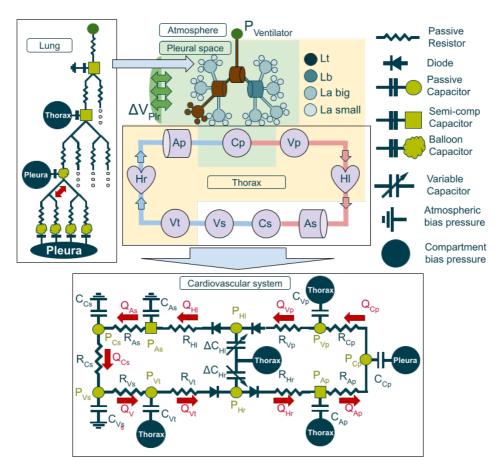


Figure 7. Schematic representation of our cardiopulmonary model with the equivalent electric circuits for the pulmonary and cardiovascular systems

The aim is to develop mechanistic models of the respiratory and cardiovascular systems of critically ill patients (see Figure 7). These patients typically suffer from multiple-organ failure so a 'system' model

that considers the main physiological interconnections between key organs/subsystems and breathing is being built. These models will be informed by large and unique clinical datasets, available from the intensive care units at GOSH and UCLH. Ultimately a digital twin model will be developed alongside virtual populations of critically ill patients, reproducing variability in the normal population.

This work progresses side-by-side with the Machine Learning and Data Science team to build classification tools based on these virtual populations that can shed some light on individual risk and key inter-patient variability markers.

A preliminary analysis on ventilator waveform data employing topological data analysis methods has been carried out (see Figures 8,9). A three-compartment lung model to mimic the respiratory mechanics of ventilation (airway pressures and flowrates) has been developed and is being validated using time-series ventilator data.

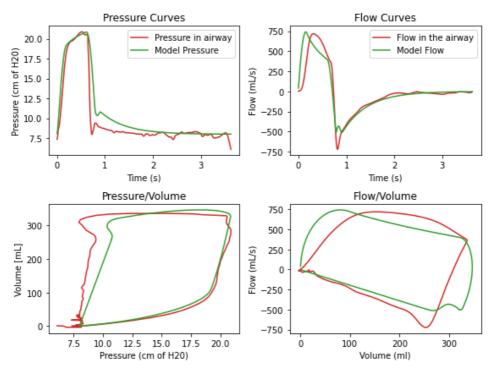


Figure 8. Fitting Respiratory Model to Ventilator Data

We have also developed a flexible, non-linear cardiopulmonary model that incorporates a novel alveoli opening strategy in a tree-like, non-symmetric branching lung structure that is capable of reproducing a whole range of physiological tests not covered by other models in literature. A poroelastic model of the lung incorporating gravity that can replicate ventilation and perfusion ratios according to the patient's body position is also under development (very relevant during the Covid pandemic when critically ill patients were often proned). We have recently take on another PhD student who will be working on modelling secretions in the lung.

WP3: Learning Biophysical Model Structure and Parameters with Neural Networks, PI: Simon Arridge

We are improving and extending existing cardiovascular models which reproduce observations on real data from the cardiovascular system. This includes a "grey box model" where parts of the model are learned from the data (see Figure 10). In contrast to previous work, the learned part has been associated with the ventricular interaction function which is conventionally solved with a non-linear optimisation technique. Our grey box model allows reproduction of the function of this interaction with a parsimonious learned model that is computationally faster.

Transitions in dynamical systems such as critical slowing down post extubation are often preceded by patterns of increased relaxation time (autocorrelation) and high amplitude fluctuations (variance). By studying signs of critical slowing down in the heart rate, respiratory rate and mean blood pressure measured in ICU datasets, evidence for autocorrelation of the heart rate has been found. Combining

these measures with mean values of the vital signs shows increased predictive power for failed extubation.

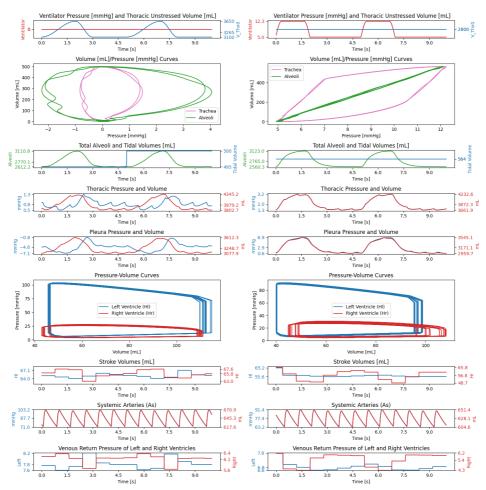


Figure 9. Comparison of simulations for an adult patient using Self Breathing (left side) vs Positive Pressure Ventilation (right side)

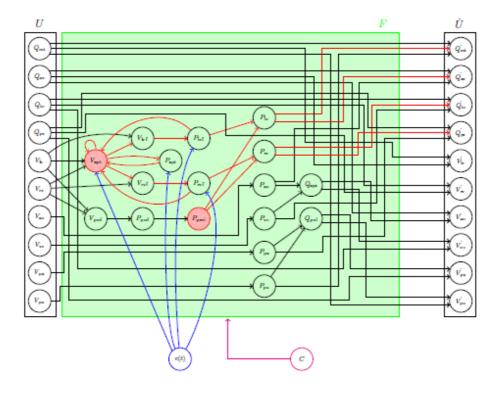


Figure 10. Computational graph representation of the cardiovascular model

The information content in vital signs and the exchange of information between them are known to indicate pathology. Here information theoretic measures can be used for extubation prediction. By studying the information content in measured ICU variables and how predictive they are of extubation failure. The sample and multiscale entropy measured from heart rate and multiscale entropy of the respiratory rate are significantly associated with extubation outcome. In addition, the mutual information between each of the heart rate, respiratory rates and mean blood pressure signals, as well as the transfer entropy between the respiratory rate and heart rate were also significantly linked to extubation outcome.

WP4: Multidisciplinary Workshops, Clinical and Industry Engagement, PI: Christina Pagel & Becky Shipley

It was decided to not hold a workshop until CHIMERA data becomes available. Data is now finally ready to come through the pipeline alongside access to Cardio-Pulmonary Exercise Testing (CPET) data. A Turing DSG (Data Study Group) using CPET data is scheduled for May 2024, looking at the cohort of patients who have had an operation to remove their bladder.

Forthcoming workshops will be used to generate ideas for future grants (small or large). CHIMERA funds attached to the workshop will fund a small writing day or two days to kickstart a grant application. We are currently scheduling two initial brainstorming sessions before Spring, with UCLH and GOSH clinicians respectively, to plan topics for (at least) two workshops later this year.

Each workshop will have a clinical champion (ideally someone not already within CHIMERA) to discuss the background, the problem & knowledge gaps. The CHIMERA team would describe what CHIMERA has available (in terms data, existing physiological models & expertise) and then we have structured breakout activity to brainstorm potential ideas for grant proposals based on this. Attendees can be any UK academic or clinician or affiliated industry. Promising ideas are then invited to submit a 1–2-page proposal of a potential grant idea and then we offer funding for 1-2 day in person workshops for maybe 4-5 people each max to work up a grant proposal. We could potentially fund several workshops, but only with a sufficient number of promising ideas.

WP5: Data Curation, Infrastructure, Open Source Data and Model Platforms, PI: Steve Harris The principal aims are to provide electronic health record (EHR) and continuous wave form data (from ventilators, monitors etc.) to researchers to develop and validate their mathematical models. We have ethics approval to build this database, and local approvals at UCLH and GOSH. UCLH was approved in 2023 and GOSH was approved at the beginning of 2024 and will provide access to the T3 intensive care telemetry system (5 second resolution data) and associated health record data. The UCL Data Safe Haven (DSH) will be used as the Trusted Research Environment.

A pipeline to extract data from the ventilators on the ICU at UCLH as a stream of HL7 messages that can be processed into a high frequency digital waveform (up to 300Hz) has been built. The first data merge and extract from UCLH to support a piece of research examining blood gas data has been completed and (a) the CPET data, (b) GOSH electronic health record (EHR) and pig cardiovascular data are currently being processed.

In collaboration with UCLH-UCL Biomedical Research Centre, we are at an advanced stage of developing a front-end webpage to make CHIMERA data (appropriately anonymised and complying with all ethics requirements) available as a resource to the broader research community. We see this as key to building new collaborations and opportunities as a Hub (noting that researchers will still need to work in the UCL Data Safe Haven, with appropriate access arrangements in place e.g. via Honorary Contracts). We anticipate launching the website around Easter 2024, and using it extensively to support future workshops. Information for patients and the public will also be included.

WP6: Patient and Public Engagement, Dissemination, PI: Christina Pagel & Becky Shipley We are currently planning the first PPIE event together with UCLH intensive care patient liaison groups (slated for late Spring). UCLH Intensive Care follow up team are currently recruiting 2-5 previous intensive care patients to help us co-develop the PPIE event, with a meeting planned in late February or early March. We already have 3 former ICU patients interested in helping us plan. We have been producing regular newsletters. These are shared on the CHIMERA website.

Additional CHIMERA activity

1. Airway secretions. PIs: Simon Arridge, Claire Black, Nick Ovenden

Use of biomechanical models and machine learning techniques to improve the identification of airway secretion accumulation and evaluation of airway clearance techniques in intubated and ventilated patients in ICU. The goal is to identify consistent waveform alterations or combined loop (like pressure-volume) deviations that signify the clearance of airway secretions. Specifically, we want to ascertain whether there is any discernible difference in the waveform data for individual patients before and after the suctioning process.

A series of paired 30 second snapshots of high resolution (100Hz) ventilator data, that represent the airway waveforms before and after a suction intervention have been collected. A data pipeline from the Servo U ventilators to a SQL database on an NHS server that collects, converts and stores the flow volume and pressure waveform data has been setup. Waveform Data Analysis and Biomechanical Lung Models will now be developed.

2. Obtaining better estimates of exercise intensity. PIs: Claire Black, Martin Wiegand, Alex Diaz Exercise intensity during rehabilitation can be quantified by measuring a patient's rate of oxygen consumption, but these measurements are not available in all intensive care units. This project has applied statistical modelling techniques to establish ways to estimate oxygen consumption as a proxy for exercise intensity from parameters available in routine clinical ICU practice. We used data from an observational study which recorded breath-by-breath-gas-exchange measurements as mechanically ventilated ICU patients participated in various rehabilitation activities. This comprises 74,332 measurements from 37 patients and 103 rehabilitation sessions. Since the raw data is subject to considerable noise (a combination of patients coughing, airway secretions and machine error) work has focused on finding reliable ways to remove outliers and different approaches to modelling the data.

Additionally, Cardio-Pulmonary Exercise Testing (CPET) data has been acquired to validate feasibility findings and inform choices for additional predictors in the future. This data recorded oxygen consumption levels in patients scheduled to undergo surgery, as part of their risk assessment. The nature of these standardised exercise tests results in more accurate data with fewer outliers being collected, which may not be attainable in ICU settings.

3. How much data do we actually need? PIs: Simon Arridge, Sam Ray

Patients are monitored continuously on the intensive care unit, with their vital signs being displayed continuously by the bedside. These vital signs are used to aid clinical decision making. However, typically they are recorded hourly, with much of the information being lost having been displayed in real-time. Although clinical practitioners may be able to draw inferences from the on-screen values, these are rarely analysed objectively.

This work is trying to understand the information held within these vital signs, and the relationships between them, using high frequency (every 5-second) data from the intensive care units at Great Ormond Street Hospital. Also using defined clinical events (extubation, the removal of the breathing tube when thought to be clinically appropriate by the clinical team, or the use of fluid boluses for shock) to understand whether information held within the vital signs can predict this with accuracy. Despite the time-series data being sparsely labelled, apart from when the event of interest occurred and basic demographic data, the aim is to understand whether hidden signals in high-frequency data can inform clinical decision making. So far, we have tested this to see if there is an association between the information between vital signs and successful liberation from the ventilator, and survival.

4. Oxygen in the blood. PI: Sam Ray

Haemoglobin in red blood cells is the main carrier of oxygen around the body, with oxygen binding to haemoglobin at the blood-lung interface and oxygen being released at the tissues for oxygen to diffuse into cells along a concentration gradient. The binding properties of oxygen to haemoglobin varies according to the surrounding chemical environment, a property which is vital for oxygen to be released

when it is needed the most. The affinity between haemoglobin and oxygen is defined by the oxygen dissociation curve (ODC).

Siggaard-Anderson proposed a mathematical algorithm (model) to derive the position of the curve based on recorded measures such as haemoglobin-oxygen saturation, pH, CO2 and temperature. Like many other mathematical models, Siggard-Anderson's model suffers from several sources of inaccuracy. For example, parameters of this mathematical model were estimated using the data from healthy subjects, which raises the question how accurate and informative the results of this model are for critically ill patients.

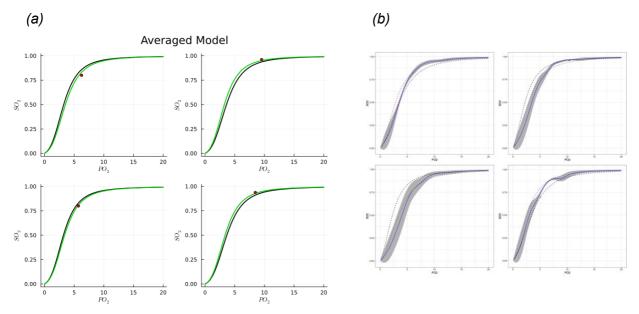


Figure 11. (a) Individual samples of haemoglobin-oxygen saturation measurements (SaO2) and partial pressure of oxygen in arterial blood (PaO2) measurements can be used to identify the space within which the ODC curve lies. This allow us to account for sources of uncertainty within the Sigaard-Anderson algorithm. (b) averaging these over a population of measurements via symbolic regression, we can improve the estimates of the ODC curve position (green line) based on SaO2 and PaO2 measurements, compared to those generated by the current Sigaard-Anderson algorithm (black line).'

In this project, we are interested in applying methods in statistics (Bayesian calibration) and machine learning (scientific-machine learning) to estimate the model parameters and learn about the missing model components using data from critically ill patients and current clinical knowledge. Based on these results, the Siggaard-Andersen algorithm can be updated, which will make it more relevant to criticalillness. Therefore, more accurate estimates of the ODC position may inform personalised treatment in critically-ill patients, since blood gas analyser machines based on Siggaard-Andersen model are widely used in ICU on critically ill patients.

5. Using mathematics for a better insight into CPR. PI: Mark Peters, Sam Ray, Alex Diaz, Nick Ovenden, Vanessa Diaz

Cardio-pulmonary resuscitation (CPR) is used as emergency treatment when a patient goes into cardiac arrest. The aim of CPR is to provide circulation to the organs of the body whilst in cardiac arrest. This includes circulating blood to the heart itself so it can resume spontaneous activity. Research to understand the optimum way to deliver CPR is difficult in live patients due to the emergent and unpredictable nature of cardiac arrest. Therefore, data must be collected from animals under experimental conditions and extrapolated across to patients, or under uncontrolled observations in humans.

Depth and rate recommendations largely come from observed data from humans, based on favourable outcomes. Previous work (outside of CHIMERA) developed a mechanical sensor that can be placed on the chest of a patient received CPR, to measure the force, depth and rate at which chest compressions are being delivered during CPR. This can allow the person resuscitating to adjust their compressions to the recommended depth and rate. However, this is the only known force sensor developed for this purpose.

This device was tested in laboratory conditions on pigs who underwent induced cardiac arrest followed by CPR. Data was collected from the device and from invasive monitoring of the animals. These high-frequency data (every 10ms) give rich information about the physiology of CPR and the measured force, depth and rate of chest compressions delivered. Using these data for each compression, the impact of the presence of feedback can be assessed. In addition, these compression-by-compression data provide an understanding of the haemodynamic effects of each of these components of CPR. Potentially, this could be harnessed to provide personalised real-time recommendations for resuscitators to optimise surrogate haemodynamic end-points for chest compressions.

Thus far work with the statistical modelling team using Bayesian hierarchical modelling to both understand the effect of sensor feedback on aortic pressure in pigs, and to find the compression parameters using time-series data to optimise aortic pressure, has been carried out, with very promising results.

6. Predicting adverse outcomes during CAR-T cancer therapy: PI: David Brealey, Cols: Alex Diaz, Christina Pagel, Rebecca Shipley

UCLH pioneered CAR-T therapy for cancer, revolutionising the management of B-cell malignancies. However, the treatment is associated with significant toxicities, particularly hyper-inflammation manifesting as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and sepsis. About 20% of patients undergoing CAR-T therapy require ICU admission for these complications, worsening mortality, morbidity and costs. Early recognition and treatment of these adverse events will improve outcomes.

Using a novel wireless wearable monitor attached to CAR-T patients, the primary objective of this work is to continuously analyse subtle changes in waveforms to predict the onset of these hyperinflammatory syndromes before symptoms develop. This proof-of-concept study could lead to dynamic risk stratification, identifying not only those likely to deteriorate and eligible for pre-symptomatic intervention, but also those at low-risk and thus eligible for early discharge.

The project will monitor 50 patients for 14 days post-infusion or ICU admission, whichever occurs first. The leads recognise the difficulty in embedding this technology within complex ward environments. We will work with haematology and outreach teams to ensure an educational package and a workflow that suits their needs. CHIMERA is providing expertise around data analysis and modelling (including funded of Martin Wiegand to complete the work), as well as patient data infrastructure/ pipelines.

This project is funded by the UCL/UCLH BRC Infection, Immunopathology and Immunotherapeutics Theme, with additional support from the Healthcare Engineering and Imaging Theme.

Other activity to date

CHIMERA seminar series

We run regular online seminars with internal and external speakers. We normally get between 10 and 30 attendees at each talk, which often generate vibrant discussion.

- 1. December 2023: Ken Li An Explainable Al-driven Method for Real-time Mortality Prediction in Critically III Children during Emergency Transports
- 2. November 2023: Maarten van Smeden Uncertainty in Al
- 3. October 2023 Mark Peters The Oxy-PICU trial of Conservative vs Liberal Oxygenation Targets in Critically ill Children
- 4. July 2023: Padmanabhan Ramnarayan High-Resolution Vital Sign Measurements from Continuous Monitoring during Paediatric Critical Care Support
- 5. June 2023: Derek Hill More Meaningful Measures of Patient Function by Combining Activity and Position
- 6. April 2023: Payam Barnaghi Remote Monitoring and Machine Intelligence for Dementia Care
- 7. March 2023: Miquel Aguirre Data-Driven Computational Modelling for Cardiovascular Medicine Applications

- 8. January 2023: Dirk Husmeier Parameter estimation and uncertainty quantification in cardiac mechanics
- 9. December 2022: Philip Pearce Multi-scale modelling of blood flow in sickle cell disease
- 10. July 2022: Patty Kostkova 'There's An App for That': How digital technologies and social media shape our health
- 11. June 2022: Waty Lilaonitkul and Alireza Mani Interdisciplinary research in network physiology: Lessons from hypoxia
- 12. March 2022: Terry O'Neill, Knowledge Transfer Network
- 13. November 2021: Elizabeth Stokoe The softness of hard data
- 14. September 2021: Tony Bagnall and Markus Löning sktime: a toolkit for machine learning with time series
- 15. July 2021: Tom Lawton and Yan Jia Gaps between theory and the real world: Safety and the Al Clinician
- 16. May 2021: Andrey Kormilitzin, University of Oxford Unreasonable effectiveness of the path signature representations for electronic health records
- 17. April 2021: Stephanie Hyland, Microsoft Research in Cambridge Predicting near-term circulatory failure in the ICU with machine learning
- 18. March 2021: Aldo Faisal, Imperial College London Towards deployment of the Al Clinician in critical care: Risk, Prediction and Off-Line Learning

Publications to date

- G.A.L. Jones, M. Wiegand, S. Ray, D.W. Gould, R. Agbeko, K. Thomas, I. Chang, M. Orzol, L. O'Neill, C. Au, E. Draper, L. Elliot-Major, E. Giallongo, L. Lampro, J. Lillie MD, J. Pappachan, P. Ramnarayan, K.M. Rowan, D.A. Harrison, P.R. Mouncey, M.J. Peters (for the Oxy-PICU Investigators* of the Paediatric Critical Care Society Study Group) (PCCS-SG) (2024). Ethnicity and observed oxygen saturations, fraction of inspired oxygen and clinical outcomes: a post-hoc analysis of the Oxy-PICU trial of conservative oxygenation. Submitted to Pediatric Critical Care Medicine.
- 2. M. T. Cabeleira, D.V. Anand, N.C. Ovenden, V. Diaz_Zuccarini V (2024). Comparing physiological impacts of positive pressure ventilation versus self-breathing via a versatile cardiopulmonary model incorporating a novel alveoli opening mechanism (pre-print imminent and submission to Journal of Royal Society Interface)
- 3. G. Grigorian, V. Volodina, J. Chen, S. Ray, S., F.A. DiazDelaO, S. Arridge (2024). Grey-box modelling with uncertainty quantification of oxygen dissociation curve (advanced stage of preparation).
- 4. S. Jackson, D. Ming, F.A. DiazDelaO, S. Saffaran (2024). Calibration of a nearly symmetric respiratory simulator (in preparation)
- 5. G. Grigorian, S.V. George, S Lishak, R.J. Shipley, S. Arridge (2024). A hybrid neural ODE model of the cardiovascular system. Under revision, Journal of the Royal Society Interface.
- 6. H.J. Kinnear, F.A. DiazDelaO (2024) Branching subset simulation, <u>https://arxiv.org/abs/2209.02468</u>. Under review, Applied Mathematical Modelling.
- 7. D. Ming, D. Williamson, S. Jackson, F.A. DiazDelaO, S. Saffaran (2024). Linked deep Gaussian process for model networks (under review, Technometrics)
- 8. A. Septiandri, T. Jendoubi, D.A. DiazDelaO (2024). Handling missing data in healthcare scenarios (advanced stage of preparation).
- 9. S. Ray et al (2024), Redefining model discrepancy in calibration: learning missing model components from observations, in preparation for Phil Trans B (special issue)
- 10. S. Ray, M. Peters, H. Kinnear, F.A. DiazDelaO, et al (2024). Pilot in-vivo study of chest compression quality with CPR-feedback using a small chest sensor potentially suitable for infants and children. (In preparation)

- 11. S. Lishak, G. Grigorian, S.V. George, N.C. Ovenden, R.J. Shipley, S. Arridge (2023). A variable heart rate multi-compartmental coupled model of the cardiovascular and respiratory systems. Journal of the Royal Society Interface 20:20230339. doi.org/10.1098/rsif.2023.0339
- 12. L. Khalil, S.V. George, K. Brown, S. Ray, S. Arridge (2023). Transitions in intensive care: investigating critical slowing down post extubation. Submitted to PLOS Digital Health.
- 13. T. Peros, F. Ricciardi, J. Booth, S. Ray, M.J. Peters. Evaluation of blood pressure trajectories and outcome in critically ill children with initial hypertension on admission to Paediatric Intensive Care. Anaesth Crit Care Pain Med. 2022 Dec;41(6):101149.
- 14. M Peters, RJ Shipley, 2020. Clinical Classification of Cold and Warm Shock: Is There a Signal in the Noise? Pediatric Critical Care Medicine, 21(12):1085-1087.

Associated grants

- Digital Health: A Digital Twin to improve holistic community-based diagnosis of heart disease. EPSRC (Sep 2022 - Aug 2024). PI: Tim Chico (University of Sheffield). Co-I: Vanessa Diaz (UCL), Richard van Arkel (Imperial College), Faith Matcham (U. of Sussex), Oliver Buckley (University of East Anglia), Joan Condell (University of Ulster). £503,424
- UCLH-UCL Biomedical Research Centre, Flagship Programme: Patient Monitoring Technologies (including CHIMERA funding for sepsis-prediction modelling, ICU physiology bed) (£173K), 2023-2024
- UCLH-UCL Biomedical Research Centre. Pre-Symptomatic Detection of Deterioration in CAR-T Patients (£40,850, PI: David Brealey, Co-Is: Alex Diaz, Christina Pagel, Rebecca Shipley), 2024-2025
- 4. EPSRC Centre for Doctoral Training in Digital Health Technologies (£8.7M, PI: Rebecca Shipley). UCL-Ulster University alongside 30 project partners across healthcare and industry, 2024-2032 (embargoed, announcement pending)

Academic talks given by CHIMERA team

- 1. February 2024: "Redefining model discrepancy in calibration: learning missing components from observations", SIAM-UQ Minisymposium on Gaussian Process Modelling for Inverse Problems)
- 2. 19 February 2024: "Branching subset simulation for unconstrained optimisation", by Alejandro Diaz at University of Birmingham.
- 3. 28 February 2024: "Calibration of a high-dimensional simulator through linked Gaussian processes", by Alejandro Diaz, SIAM UQ Conference 2024, Trieste, Italy.
- 4. 28 February 2024: "Branching subset simulation for uncertainty quantification", by Hugh Kinnear, SIAM UQ Conference 2024, Trieste, Italy.
- 5. 28 February 2024: "Dynamic History Matching for a cardiorespiratory model", poster presentation by Jun Cheng.
- 6. Jan 2023, Invited public lecture, Rebecca Shipley, Institute of Physics and Engineering in Medicine, Hiding in Plain Sight: The Unseen Impact of Engineering in Healthcare
- 7. 10 March 2023: "Calibration of models for clinical research", by Vanessa Diaz, UCL Department of Statistical Science
- 8. 4 6 July 2023: poster, "Application of Scientific Machine Learning for Time-Series Predictions of Biomedical Signals" by Gevik Grigorian, Sandip George, Simon Arridge, Rebecca J. Shipley, presented at Conference on Deep Learning for Computational Physics, UCL
- 9. 14 August 2023, "Calibration of a digital twin. Learning model discrepancy", Joint RRes-Exeter Digital Twin Workshop)
- 10. Nov 2022 Invited talk, Rebecca Shipley, Australian & New Zealand Intensive Care Society Paediatric Study Group
- 11. 13 June 2022: "Dynamic linear modelling for ICU data" by Victoria Volodina, ECR Conference for the EPSRC Maths in Healthcare Hubs, UCL
- 12. 13 June 2022: "Acid Base Balance in Critical Care Medicine" by Ali Septiandri, ECR Conference for the EPSRC Maths in Healthcare Hubs, UCL

- 13. 26 July 2022: talk on CHIMERA by Nick Ovenden at INI Gateway Cambridge Mathematics of Information in Healthcare Hub (CMIH) Academic Engagement Event
- 14. 30 August 2022: "Branching Subset Simulation. European Conference on Safety and Reliability", by Hugh Kinnear, European Conference on Safety and Reliability
- 15. 30 August 2022: "Bayesian updating with reliability methods: stopping conditions", by Vanessa Diaz, European Conference on Safety and Reliability
- 16. 9 September 2022: "The CHIMERA Hub" by Vanessa Diaz, Cambridge Centre for AI in Medicine Summer School
- 17. September 2022: CHIMERA ECR workshop during BIOMEDENG22. Led by Nick Ovenden with talks by Abigal Smith, Manuel Teixeira-Cabeleira, Sandip George, Victoria Volodina, and Ali Septiandri.
- 18. 5 October 2022: "Calibration of a respiratory model at CHIMERA", by Vanessa Diaz, BIOREME webinar series
- October 2022: poster:, "Using complexity details of ICU monitor data to study extubation outcome", by Sandip V George, Samiran Ray, Simon Arridge presented at Conference on Complex systems, Mallorca

Other activity/public engagement/outreach

- 1. 23 October 2023: an ECR (workstream 2) attended SeCRET Competition on cardiac modelling organised by Glasgow Hub
- 2. June 2022: ECR Conference for the EPSRC Maths in Healthcare Hubs (leads: Christina Pagel, Rebecca Shipley)
- 3. July 2022: CHIMERA / Alan Turing Institute Workshop (leads: Sina Saffaran, Nick Ovenden)
- 4. September 2022, CHIMERA hosted two school students, Paul Curuia and Lucinda Khalil as part of the in2research programme.
- 5. 13 15 September 2022: an ECR (workstream 2) attended a Time-series workshop at the University of Lancaster
- 6. June 2020: Video introducing the CHIMERA Mathematics in Healthcare Hub published on UCL Dept of Mathematics YouTube Channel (leads Alex Diaz and Nick Ovenden)