Advancing Research in Mechanical Ventilation using Computational Modelling

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WARWICK

GLOBAL RESEARCH PRIORITIES
HEALTH

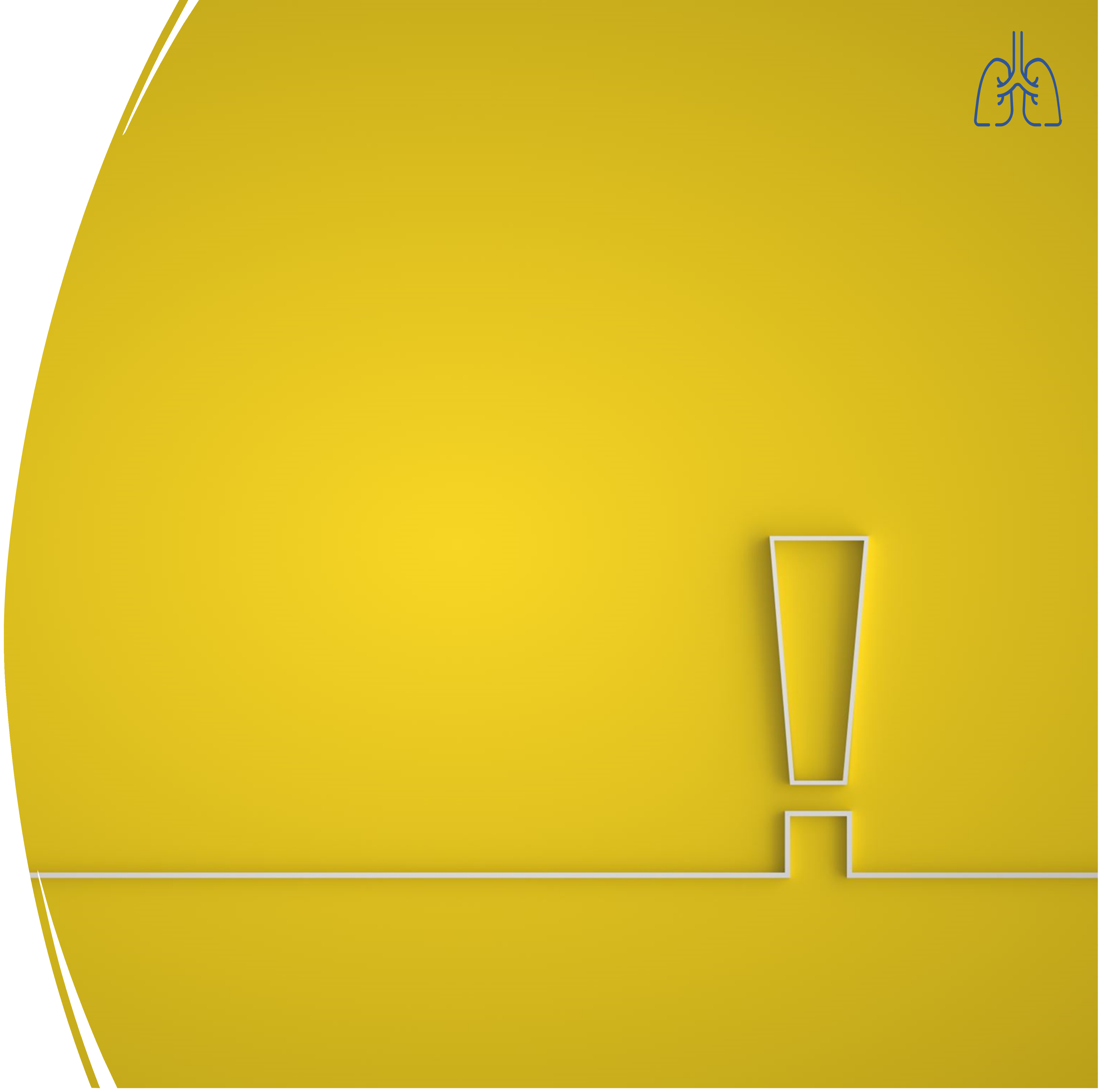
ICSM

Interdisciplinary
Collaboration
in Systems Medicine

Royal Academy of Engineering

Overview

- The Particular Problems of Critical Care
- Why mechanistic models?
- What can be done?
- What about AI!



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 £1600**
- Clinician workload is directly linked to patient outcomes. **1.7 human errors** per patient per day, **high mortality rates (30-40%)**

The Guardian
Newspaper of the year

Coronavirus

Intensive care units: 'The point is to keep people alive'

Doctors on coronavirus frontline say admission to ICU is about giving patients chance to recover

- Find all our coronavirus coverage here
- Coronavirus - latest news and updates

An intensive care bed and respirator at the temporary NHS Nightingale hospital constructed in the ExCeL centre in London. Photograph: Reuters

Why mechanistic models?

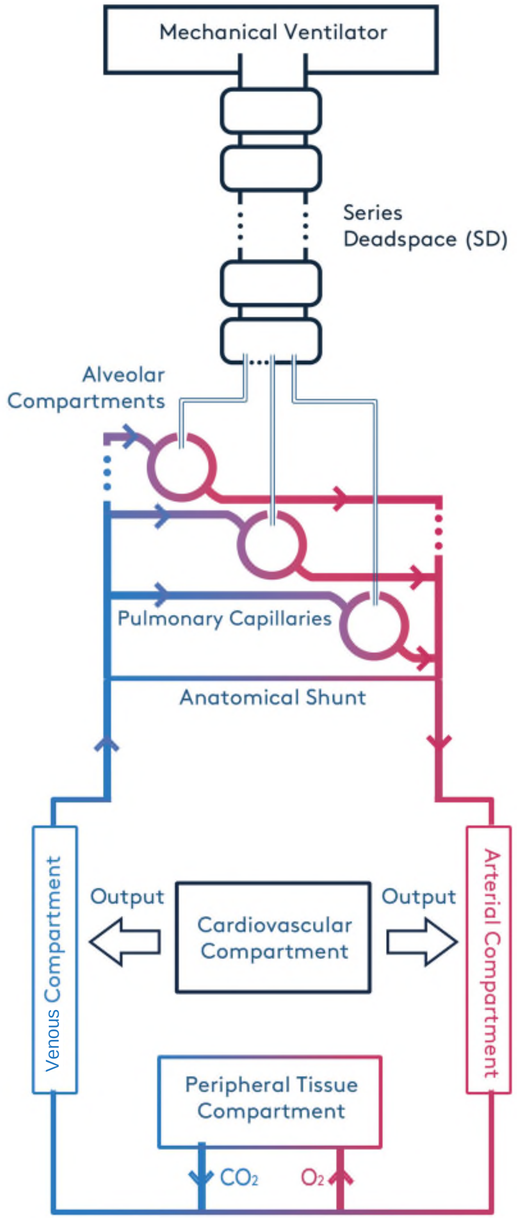
Arduous to conduct clinical research

Still difficult to “look inside” the lung

Demand for more personalised treatment strategies

Animal models not replicating complex pathophysiology of respiratory diseases

Strong interest from Funding Agencies and Industry



Cardiopulmonary simulator

- More than 25 years of continuous development
- A computational simulator that includes representations of multiple, interacting organ systems
- Multiple (100's), independent, viscoelastic, gas-exchanging alveolar compartments allow heterogeneous distributions of pulmonary ventilation and perfusion
- Every component based on well accepted physiological principles – no black boxes

What can be done?

Many things!

- Modelling drug delivery and effect
- Investigating guidelines and treatment strategies
- Help in better understanding of the disease/Pathophysiology
- Personalised treatment
- Automated mechanical ventilation
- …

THE IRISH TIMES Tue, Jul 2, 2019 Dublin

Reducing the risks associated with life-saving ventilation

Research shows dropping pressure can lessen lung damage without hurting treatment

Subscriber Only »

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OPEN

In Silico Modeling of Coronavirus Disease 2019 Acute Respiratory Distress Syndrome: Pathophysiologic Insights and Potential Management Implications

Anup Das, PhD[1]; Sina Saffaran, PhD[1]; Marc Chikhani, FFICM[2]; Timothy E. Scott, PhD[3,4]; Marianna Laviola, PhD[5];

ARTICLE

Inhaled sGC Modulator Can Lower PH in Patients With COPD Without Deteriorating Oxygenation

Sina Saffaran[1], Wenfei Wang[1], Anup Das[1], Walter Schmitt[2], Eva-Maria Becker-Pelster[2], Jonathan G. Hardman[3],

High risk of patient self-inflicted lung injury in COVID-19 with frequently encountered spontaneous breathing patterns: a computational modelling study

Liam Weaver, Anup Das, Sina Saffaran, Nadir Yehya, Timothy E. Scott, Marc Chikhani, John G. Laffey, Jo

Utility of Driving Pressure and Mechanical Power to Guide Protective Ventilator Settings in Two Cohorts of Adult and Pediatric Patients With Acute Respiratory Distress Syndrome: A Computational Investigation

Sina Saffaran, MSc[1]; Anup Das, PhD[1]; John G. Laffey, MD[2]; Jonathan G. Hardman, PhD[3];

Citation: CPT Pharmacometrics Syst. Pharmacol. (2018) 00, 00; doi:10.1002/psp4.12308

ARTICLE

Inhaled sGC Modulator Can Lower PH in Patients With COPD Without Deteriorating Oxygenation

Sina Saffaran[1], Wenfei Wang[1], Anup Das[1], Walter Schmitt[2], Eva-Maria Becker-Pelster[2], Jonathan G. Hardman[3], Gerrit Weimann[2] and Declan G. Bates[1*]

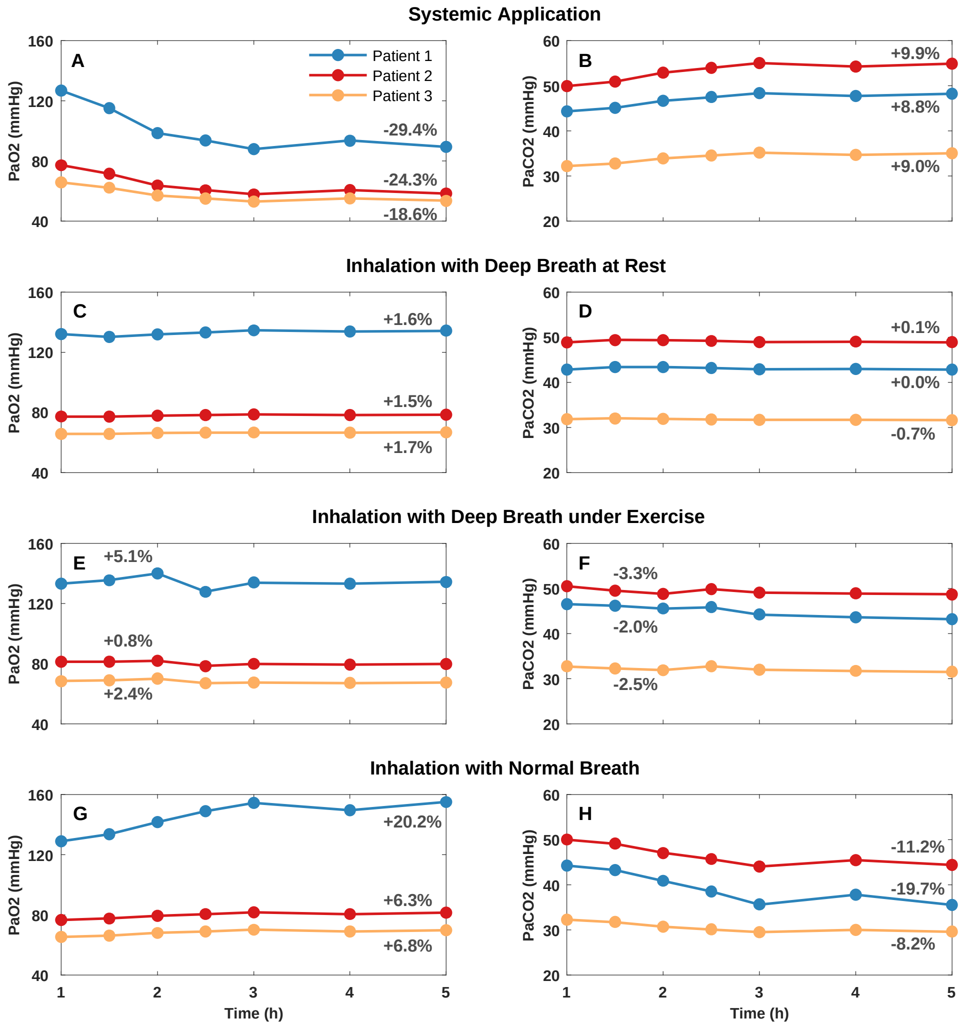
This study uses a highly fidelity computational simulator of pulmonary physiology to evaluate the impact of a soluble guanylate cyclase (sGC) modulator on gas exchange in patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH) as a complication. Three virtual patients with COPD were configured in the simulator based on clinical data. In agreement with previous clinical studies, modeling systemic application of an sGC modulator results in reduced partial pressure of oxygen (PaO_2) and increased partial pressure of carbon dioxide ($PaCO_2$) in arterial blood, if a drug-induced reduction of pulmonary vascular resistance (PVR) equal to that observed experimentally is assumed. In contrast, for administration via dry powder inhalation (DPI), our simulations suggest that the treatment results in no deterioration in oxygenation. For patients under exercise, DPI administration lowers PH, whereas oxygenation is improved with respect to baseline values.
CPT Pharmacometrics Syst. Pharmacol. (2018) **00**, 00; doi:10.1002/psp4.12308; published online on 0 Month 2018.

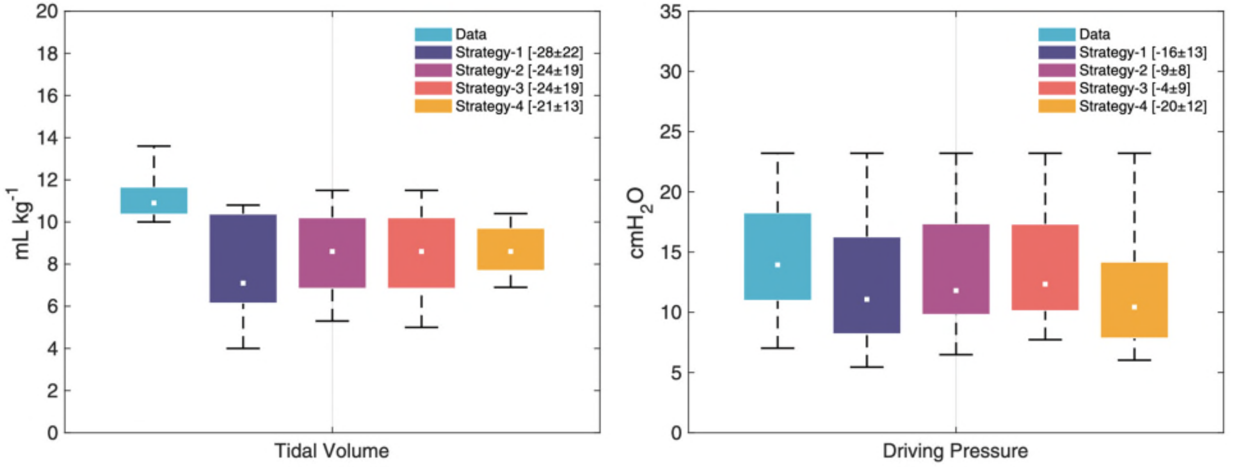
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Using a high-fidelity pulmonary simulator, calibrated to data from three patients with COPD involved in a previous clinical trial, we showed that administering an sGC via DPI can reduce PH without deteriorating oxygenation, particularly when administration is combined with exercise.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

☑ Our results highlight the potential advantages of administering sGCs to patients via DPI, rather than systemically.





1–2 years) and 2 (initial $V_T > 10$ mL/kg), with test cohort 2 showing the greatest potential for lung-protective ventilation (Figs. 1, S7, S8).

Our data suggests that PARDS patients are routinely over-ventilated and there is scope for achieving protective ventilation without compromising gas exchange.

Intensive Care Med
https://doi.org/10.1007/s00134-019-05559-4

LETTER

High-fidelity computational simulation to refine strategies for lung-protective ventilation in paediatric acute respiratory distress syndrome

Sina Saffaran[1], Anup Das[1], Jonathan G. Hardman[2], Nadir Yehya[3*] and Declan G. Bates[1*]

Dear Editor,

Mechanical ventilation in paediatric acute respiratory distress syndrome (PARDS) is less studied than in adults, with guidelines for ventilation adapted from adult ARDS. However, PARDS has a distinct epidemiology, and adult ARDS guidelines may not be appropriate in children. As an example, clinical trials suggest that lower tidal vol-

collection (see Supplement), we developed and tested four lung-protective strategies for reducing either V_T (strategies 1–3) or ΔP (strategy 4). Strategy 1 reduced V_T maintaining constant minute ventilation, strategy 2 reduced V_T maintaining alveolar ventilation with a fixed ratio of inspiratory time to total cycle time, strategy 3 reduced V_T maintaining alveolar ventilation with fixed

Weaver *et al. Ann. Intensive Care* (2021) 11:109
https://doi.org/10.1186/s13613-021-00904-7

Annals of Intensive Care

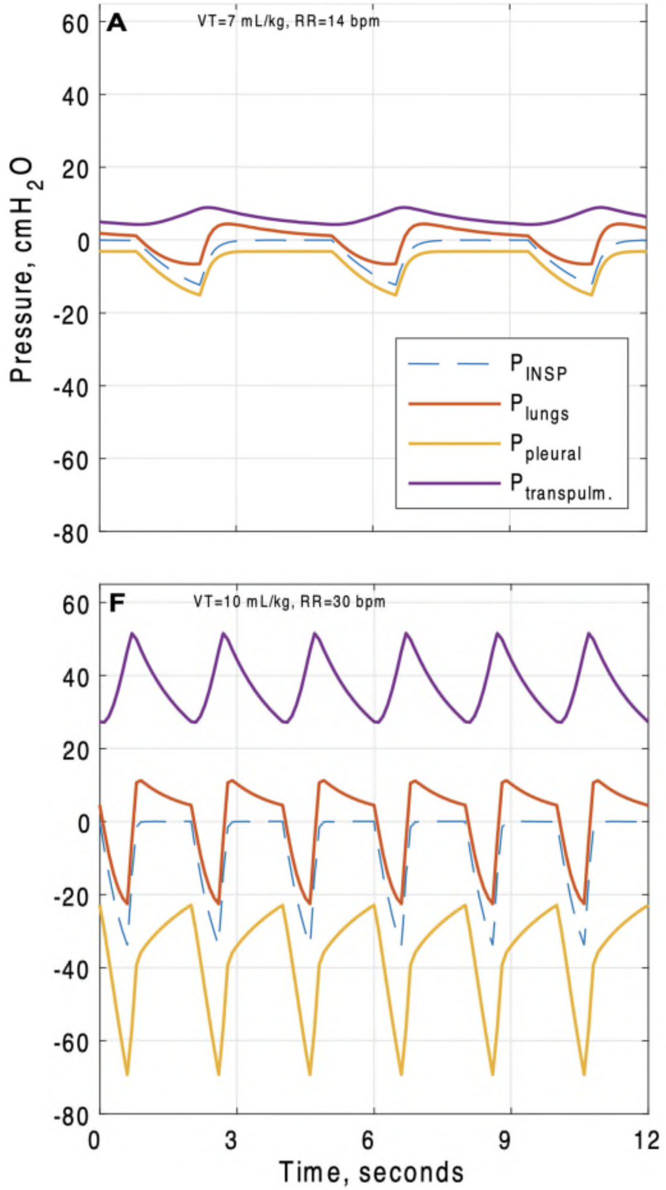
RESEARCH **Open Access**

High risk of patient self-inflicted lung injury in COVID-19 with frequently encountered spontaneous breathing patterns: a computational modelling study

Liam Weaver[1†], Anup Das[1†], Sina Saffaran[2†], Nadir Yehya[3], Timothy E. Scott[4], Marc Chikhani[8], John G. Laffey[6], Jonathan G. Hardman[5,8], Luigi Camporota[7*] and Declan G. Bates[1*]

Conclusions

Our results indicate that transpulmonary and pleural pressure swings, and levels of driving pressure, lung strain and mechanical power that have been associated with VILI during mechanical ventilation can develop in spontaneously breathing patients with COVID-19 acute respiratory failure, at levels of respiratory effort that are being frequently encountered by clinicians. Respiratory efforts in these patients should be carefully monitored and controlled to minimise the risk of lung injury.



AI & Mechanistic Models

BIOLOGY LETTERS

rsbl.royalsocietypublishing.org

Opinion piece

Check for updates

Cite this article: Baker RE, Peña J-M, Jayamohan J, Jérusalem A. 2018 Mechanistic models versus machine learning, a fight worth fighting for the biological community? *Biol. Lett.* **14**: 20170660. http://dx.doi.org/10.1098/rsbl.2017.0660

Received: 20 October 2017
Accepted: 22 April 2018

Subject Areas:
bioengineering, bioinformatics, biomechanics, biotechnology

Keywords:

Biomechanics

Mechanistic models versus machine learning, a fight worth fighting for the biological community?

Ruth E. Baker[1,2], Jose-Maria Peña[4], Jayaratnam Jayamohan[5] and Antoine Jérusalem[3]

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Ninety per cent of the world's data have been generated in the last 5 years (*Machine learning: the power and promise of computers that learn by example*. Report no. DES4702. Issued April 2017. Royal Society). A small fraction of these data is collected with the aim of validating specific hypotheses. These studies are led by the development of mechanistic models focused on the causality of input–output relationships. However, the vast majority is aimed at supporting statistical or correlation studies that bypass the need for causality and focus exclusively on prediction. Along these lines, there has been a vast increase in the use of machine learning models, in particular in the biomedical and clinical sciences, to try and keep pace with the rate of data generation. Recent successes now beg the question of whether mechanistic models are still relevant in this area. Said otherwise, why should we try to understand the mechanisms of disease progression when we can use machine learning tools to directly predict disease outcome?

AI & Mechanistic Models

diagnostics MDPI

Article

Developing an Artificial Intelligence-Based Representation of a Virtual Patient Model for Real-Time Diagnosis of Acute Respiratory Distress Syndrome

Chadi S. Barakat [1,2,3,*], Konstantin Sharafutdinov [3,4], Josefine Busch [1], Sina Saffaran [5], Declan G. Bates [5], Jonathan G. Hardman [6], Andreas Schuppert [3,4], Sigurður Brynjólfsson [2], Sebastian Fritsch [1,3,7,†] and Morris Riedel [1,2,3,†]

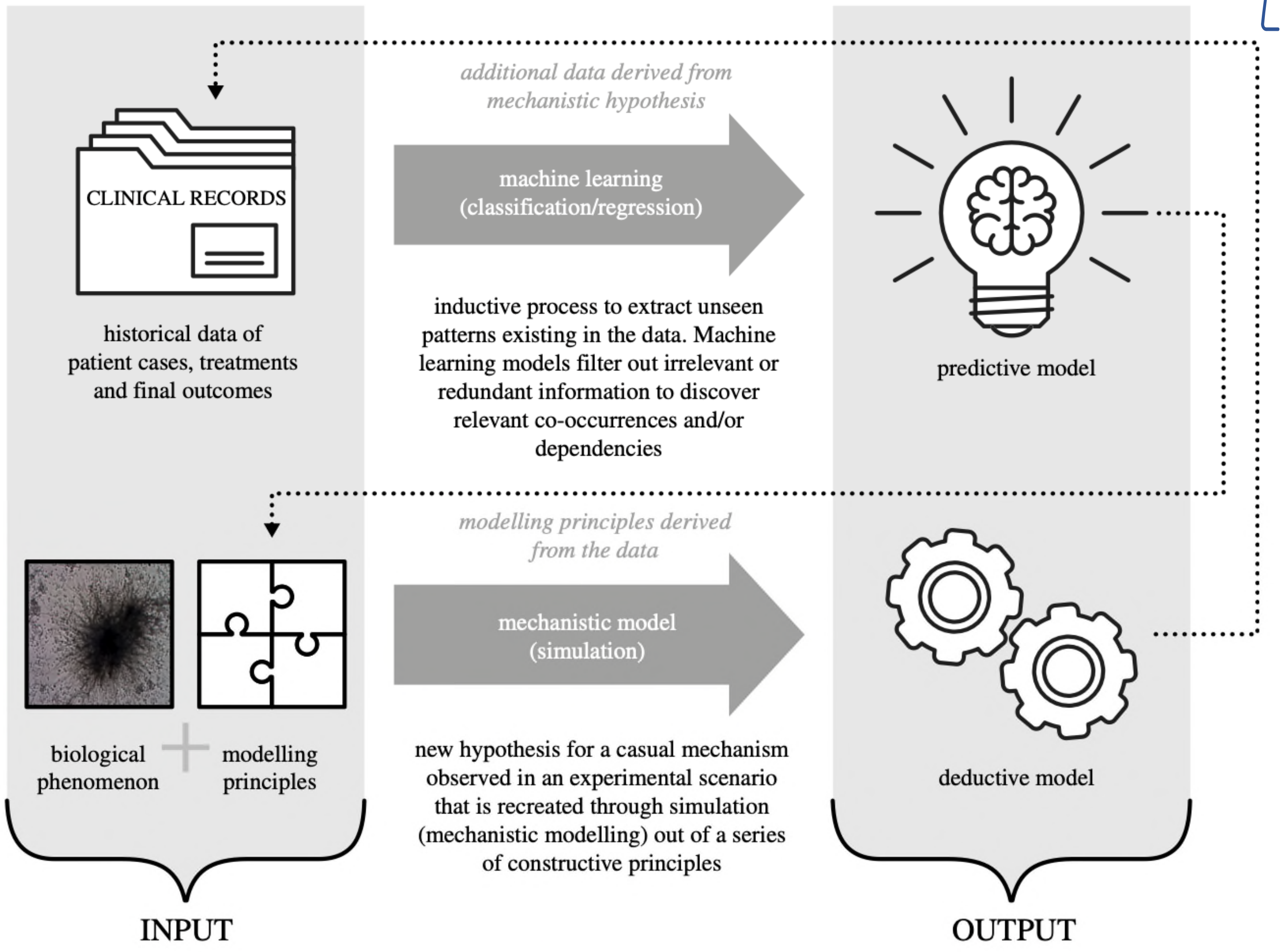
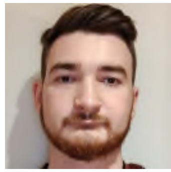


Figure 1. The inputs and outputs from machine learning and mechanistic modelling approaches, and the potential for synergy between the two.

The Interdisciplinary Collaboration in Systems Medicine Team

University of Warwick:
Professor Declan Bates – ICSM Co-leader
Dr Sina Saffaran
Sonal Mistry – PhD Student
Liam Weaver – PhD Student
Hossein Shahmohammadi – PhD Student




University of Nottingham:
Professor Jonathan Hardman – ICSM Co-leader
Dr. Marianna Laviola
Professor Don Sharkey



Guy's & St. Thomas' Hospital London: Professor Luigi Camporota

Children's Hospital of Philadelphia: Professor Nadir Yehya

Galway University Hospital, Ireland: Professor John Laffey

Royal Centre for Defence Medicine, Birmingham:
Surgeon Commander Tim Scott

Funding:

NC3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

Royal Academy of Engineering

BAYER Science For A Better Life

Fisher & Paykel HEALTHCARE

EPSRC Pioneering research and skills

bbsrc biotechnology and biological sciences research council

MRC Medical Research Council

NSF

“All models are wrong, but some are useful”

George E. P. Box

Thank You!