Computational simulation of patients with respiratory disease - what is it good for?
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Talk Overview

Introduction to Systems Medicine

Simulators as systems engineering tools for therapeutic optimisation

Protective ventilation in acute respiratory distress syndrome (ARDS)

Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

Optimising paediatric / neonatal critical care
Introduction to Systems Medicine

Systems Medicine:

Fuses disciplines underlying medicine (biology, physiology, pathology, pharmacology, epidemiology and therapeutics) with computer science, mathematics, and engineering

Exploits the development of computational models that map the (mal)functioning of the human body, its processes and interactions across multiple levels of structural and functional organisation - from molecular reactions, to cell-cell interactions in tissues, to the physiology of organs and organ systems
Key drivers:

Data avalanches (at all scales)

Dramatic increases in computational power (and re

Patient demand for more personalised treatment strategies

Faltering industrial drug development pipeline – too slow, too expensive, not enough new targets, too many failed clinical trials

Reduction, refinement & replacement of animal models

Attention of regulatory agencies
Strong interest from funding agencies:

THE CASyM ROADMAP
Implementation of Systems Medicine across Europe

Implementation strategy for Systems Medicine

The ten key areas for a successful implementation of Systems Medicine:

1. Improving the design of clinical trials
2. Methodology and technology development including modeling
3. Data generation
4. Technological infrastructure
5. Patient stratification for a more personalized medicine
6. Working with industry
7. Ethical and regulatory issues
8. Multidisciplinary training
9. Stakeholder engagement: Community building, networking and disseminating the Systems Medicine concept
10. Integration of national efforts in Systems Medicine and within the EU
Strong interest from industry:

“Virtual patients” allow novel treatment strategies to be investigated across different types of patients in a safe, cost-effective and reproducible *in silico* environment.

Entelos: asthma, obesity, Type 1 and Type 2 diabetes, rheumatoid arthritis, cholesterol metabolism, cardiovascular, skin sensitization, etc.

Bio-Simulation Market to exceed $2B by 2020

US FDA starting to explore use of simulators for certification
Simulators as systems engineering tools for therapeutic optimisation

The problem:

Treatment strategies for critical lung disease essentially based on mechanical ventilation to restore physiological flows and tissue oxygenation

Despite numerous studies:
Mortality rate of ICU patients has not changed significantly over the past 30 years
Still at about 35%
Little progress in shortening the period of time spent on the ventilator

Joint work with Prof. Jon Hardman,
Simulators as systems engineering tools for therapeutic optimisation

The problem:

Very difficult to conduct clinical research on critically ill patients – many practical / ethical issues

Animal models not fit for purpose

Limited understanding of the human/machine interface

Difficult to “look inside” the lung

Clinical trials massively expensive and difficult
Simulators as systems engineering tools for therapeutic optimisation

A computational simulator that includes representations of multiple, interacting organ systems (cardiac, vascular, pulmonary, etc)

Multiple, independent, viscoelastic, gas-exchanging alveolar compartments

Interdependent blood-gas solubilities

Pulsatile blood flow generated by a multi-chamber heart

Heterogeneous distributions of pulmonary ventilation and perfusion
A systems engineering approach to validation of a pulmonary physiology simulator for clinical applications

A. Das¹, Z. Gao², P. P. Menon¹, J. G. Hardman³ and D. G. Bates¹,*

¹College of Engineering, Mathematics and Physical Sciences, University of Exeter, UK
²Department of Electrical Engineering and Electronics, University of Liverpool, UK
³Division of Anaesthesia and Intensive Care, University of Nottingham, UK

Verification & Validation:
Statistical clinical approaches + formal engineering methods
Essential to convince clinicians and regulatory authorities

Simulators as systems engineering tools for therapeutic optimisation
Optimising ventilator settings

Optimal settings are different for different disease states

Combinatorial complexity of the problem defeats clinical intuition

Protective ventilation in acute respiratory distress syndrome (ARDS)

Lower risk of lung injury

Better gas exchange

Sweet Spot


Protective ventilation in acute respiratory distress syndrome (ARDS)

Optimising ventilator settings:

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Marcelo B.P. Amato, M.D., Maureen O. Meade, M.D., Arthur S. Slutsky, M.D.,
Laurent Brochard, M.D., Eduardo L.V. Costa, M.D., David A. Schoenfeld, Ph.D.,
Thomas E. Stewart, M.D., Matthias Briel, M.D., Daniel Talmor, M.D., M.P.H.,
Alain Mercat, M.D., Jean-Christophe M. Richard, M.D.,
Carlos R.R. Carvalho, M.D., and Roy G. Brower, M.D.

BACKGROUND
Mechanical-ventilation strategies that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes ($V_t$), and higher positive end-expiratory pressures (PEEPs) can improve survival in patients with the acute respiratory distress syndrome (ARDS), but the relative importance of each of these components is uncertain.

PEEP: pressure in the lungs at the end of expiration
ΔP: plateau pressure minus PEEP
Optimising ventilator settings:

Driving Pressure and Respiratory Distress

Marcelo B.P. Amato, M.D., Maureen O. Laurent Brochard, M.D., Eduardo L.V. C Thomas E. Stewart, M.D., Matthias Bri Alain Mercat, M.D., Jean-Christophe Carlos R.R. Carvalho, M.D.

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Figure 1. Relative Risk of Death in the Hospital across Relevant Subsamples after Multivariate Adjustment — Survival Effect of Ventilation Pressures.
Optimising ventilator settings:

Driving Pressure and Respiratory Risk

Background
Mechanical-ventilation strategies that use lower pressures, lower tidal volumes \( (V_t) \) (PEEPs) can improve survival in patients with Acute Respiratory Distress Syndrome (ARDS), but the relative importance of tidal volume and positive end-expiratory pressure \( (PEEP) \) is currently unclear. The study aims to determine the optimal ventilator settings for patients with ARDS.

Optimising ventilator settings:


Driving Pressure and Survival in the Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

Mechanical-ventilation strategies that use lower end-inspiratory (Pl): pressures, lower tidal volumes (V_T), and higher positive end-expiratory (PEEPs) can improve survival in patients with the acute respiratory distress (ARDS), but the relative importance of each of these components

Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

COPD:

A leading cause of mortality and disability

Predicted to be the 3rd greatest cause of death worldwide by 2020

Causes: smoking (mainly), long-term exposure to irritants such as industrial dust and chemical fumes, preterm birth, inherited factors

A progressive disease, associated with increasing frequency and severity of exacerbations
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

What we want to match: Measured outputs + V/Q curves

Ventilation and Perfusion must be matched at the alveolar capillary level – ideal V/Q ratio is 1
Diseased lung

Disease increases number of alveoli with low and high V/Q ratios (shunt and dead space, respectively)
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

Automated matching to patient V/Q curves:

50 compartments

100 compartments

Need sufficient model complexity to represent individual patients

Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

The problem:

Pulmonary Hypertension (PH)

One of the most serious complications of COPD

A progressive and debilitating condition associated with a sustained increase in:

- mean pulmonary artery pressure (mPAP)
- pulmonary vascular resistance (PVR)
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

The problem:

Various drugs with different modes of action investigated as potential PH-specific therapies in clinical studies.

Generally aim for a dilation or relaxation of the pulmonary arterial vessels, thus reducing the arterial pressure.

Sildenafil – PDE 5 inhibitor

Riociguat - soluble guanylate synthase (sGC) stimulator
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

In recent clinical trials:

Systemic (oral) administration of **Riociguat** resulted in:

- Improved 6-minute walk distance
- Significant reductions in mPAP and PVR

But

Deterioration of V/Q matching and oxygenation

Why?
Hypoxic vasoconstriction

Natural physiological response that reduces blood flow to hypoxic (unoxygenated) regions of the lung

Systemic (oral) administration of Riociguat inhibits hypoxic vasoconstriction by increasing blood flow throughout the whole lung.
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

Hypoxic vasoconstriction

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PaO2 reduced by 13%
PaCO2 increased by 4%
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

What if the drug was administered via inhalation?

Now the drug should only be deposited in those regions of the lung that are oxygenated

Could achieve same level of PVR reduction without worsening oxygenation?
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

Model matching:

### Table 1 Patient Matching Results

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<td>0.1&lt;V/Q&lt;10, %</td>
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PVR reduction due to drug:

Mean change of PVR from baseline over time in patients receiving single dose of riociguat 2.5 mg [Ghofrani2015]
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

Assuming the same PVR reduction, we modelled systemic drug application and administration via dry powder inhalation (DPI)

DPI is associated with a deep breath and hence a transitory reduction in airway resistance:

Resistance variation before and after a deep breath [Thorpe03]
Treating pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

Results

**Systemic Application**

- **Patient 1:** Decrease in PaO2 by -29.4%, PaCO2 increase by +9.9%.
- **Patient 2:** Decrease in PaO2 by -24.3%, PaCO2 increase by +8.8%.
- **Patient 3:** Decrease in PaO2 by -18.6%, PaCO2 increase by +9.0%.

**Inhalation with Deep Breath at Rest**

- **Patient 1:** Increase in PaO2 by +1.6%, PaCO2 decrease by -1.5%.
- **Patient 2:** Increase in PaO2 by +1.7%.
- **Patient 3:** Increase in PaO2 by +1.5%.

**Inhalation with Deep Breath under Exercise**

- **Patient 1:** Increase in PaO2 by +5.1%, PaCO2 decrease by -3.3%.
- **Patient 2:** Increase in PaO2 by +2.4%, PaCO2 decrease by -2.0%.
- **Patient 3:** Increase in PaO2 by +0.8%, PaCO2 decrease by -2.5%.

Deterioration in oxygenation after systematic application matches that seen in clinical trials.

No deterioration in oxygenation when drug administered via DPI.

Even better under exercise.

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Two new collaborations with paediatric intensive care clinicians:

Nadir Yehya, MD

Nadir Yehya, MD, is an attending physician in the Pediatric Sepsis Program and the Division of Critical Care Medicine at Children's Hospital of Philadelphia.

Areas of Expertise: Ventilation strategies
Locations: Main Campus

Don Sharkey

Clinical Associate Professor of Neonatal Medicine, Faculty of Medicine & Health Sciences

University of Nottingham
School of Medicine

Optimising paediatric / neonatal critical care

Simulator adapted to paediatric physiology:

## Optimising paediatric / neonatal critical care

Table 1. Patient characteristics and mechanical ventilator settings for each individual patient, and as mean and standard deviations (SD) across the cohort.

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<th>Weight (kg)</th>
<th>FIO₂</th>
<th>RR (bpm)</th>
<th>V₁ (mL/kg)</th>
<th>PEEP (cmH₂O)</th>
<th>PF</th>
<th>OI</th>
<th>PaO₂</th>
<th>P₅₇°C (mmHg)</th>
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<td>30.2</td>
<td>15.9</td>
</tr>
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<td>0.2</td>
<td>6.0</td>
<td>1.6</td>
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<td>12.2</td>
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<td>7.7</td>
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</table>
Lowering tidal volumes during mechanical ventilation decreases mortality in adult ARDS patients

No randomized trials to determine appropriate tidal volumes in paediatric ARDS

Average reductions in tidal volume of 21% could be safely achieved in 22/30 simulated patients.
Synthetic Biology:
Jack Bowyer, Nuno Paulino, Mathias Foo, Alex Darlington, Iulia Gherman Wilson Wong (Boston)
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