A Clinician’s View of Engineering and Technology in Intensive Care - Model-based Therapeutics and Patient Outcomes

Geoffrey Shaw¹
J Geoffrey Chase²
Chris Hann³

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1 Intensive Care Specialist, Christchurch Hospital
Clinical Senior Lecturer, Department of Anaesthesia, University of Otago, Christchurch
Adjunct Associate Professor, Department of Mechanical Engineering, University of Canterbury

2 Professor, Department of Mechanical Engineering, University of Canterbury

3 Lecturer, Department of Electrical Engineering, University of Canterbury
What’s wrong with modern medicine?

From mid 1940s onwards, the combination of clinical science, fortuitous drug discovery and innovative technology - together with the human virtues of imagination, perseverance and hard work impelled medicine.

By the late 1970’s these dynamic forces had become exhausted, creating the *intellectual vacuum* that was filled by the two radical but ultimately unsuccessful approaches of *The Social Theory* and the *New Genetics*.
What’s wrong with modern medicine?

Modern medicine simply stopped delivering to the expectations it was creating...

The “intellectual vacuum” occurred because medicine had reached its limits in its ability to understand disease processes through deductive rationalism.
To understand ..we need to look at the “Schools of Medical Reasoning”

Claude Bernard
“homeostasis”

Pierre Charles Alexander Louis
founder Médecine d’Observation

1787 - 1872

1813 - 1878
## Schools of Medical Reasoning

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<th>Empiricism</th>
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<td>Method</td>
<td>Laboratory or bench science</td>
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<td>Benefits to the individual</td>
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Treatment of disease

People with disease

Outcome (measurable)

Responders
Continue treatment

Non-Responders
Stop treatment

Rationalism

Treatment of risk

People at risk of disease

Outcome (probabilistic)

Disease prevented
Disease was never going to develop

Disease not prevented

Treatment continues indefinitely

Empiricism
So engineers are from Venus; doctors from Mars.

Cockpit view A380

Built by engineers ➔ rationalism

Managed by doctors ➔ empiricism

Rationalism

Empiricism

Critically ill patient
The medical research paradigm:
Empiricism and the Randomised Controlled Trial (RCT)

‘You don’t need to know how something works, you just need to do the RCT’ [to see if it works]¹

1 Richard Smith*, WCICCM Sydney 2001 in a discussion about clinical research

*Previous editor of British Medical Journal; CE BMJ Publishing Group,
The branding:
Evidence based medicine (EBM)

The results of RCTs are *branded* as “EBM”

*but the problem of pursuing a purely empiric approach is:*
“...medical journals have become ‘creatures of the drug industry,’ rife with fraudulent research and packed with articles ghost written by pharmaceutical companies”

The fallacy:

“No test based upon a theory of probability can by itself provide any valuable evidence of the truth or falsehood of a hypothesis...”

Jerzy Neyman and Egon Pearson  Philos Trans R Soc Lond A 1933

When doctors only consider EBM they risk manufacturing knowledge from statistical inference
The backlash:

Science based medicine [SCM] vs Evidence based medicine [EBM]

www.sciencebasedmedicine.org

*EBM simply looks at the published clinical research and accepts the findings*

*SBM considers preclinical research, prior probability, consistency with the rest of the body of scientific knowledge, and the fallibility of most research*

**SBM = EBM + CT [critical thinking]**

“Tooth Fairy Science and Other Pitfalls: Applying Rigorous Science to Messy Medicine”
Harriet Hall, MD http://www.skepticstoolbox.org/hall/
Empiricism it’s too easy...?
Lack of critical thinking and “black boxes”

The “Student” after years of medical education
The “Resident”

...after years of burn out....
The “Specialist”
“Easy-think” has dominated medical reasoning?! 

Doctors are gazumped by an enormous amount of information. There is simply no time to think .. “Why?”

The problems are too hard for doctors and ‘traditional’ allied professionals e.g. biostatisticians, physiologists to solve

If innocence is the first casualty of war, then critical reasoning has become the first casualty of modern medicine
“Problems cannot be solved by the same level of thinking that created them.”

A Einstein

The solutions to many clinical problems can not be solved using our current level of understanding.

Robust physiological models of the cardiovascular, respiratory, renal, neurological, and metabolic systems require dynamic systems modelling, smart people and fast [cheap] computers.

It’s taken 30 years for the technology,

............. but who/where are the “smart” people?
Physiological modelling of disease conditions can be used to guide individual, patient-specific therapies.

MODEL-BASED THERAPEUTICS [MBT]

A ‘one model fits all approach’
Key to success: collaboration amongst...

The “doctors”

The “engineers”

The “scientists”
Our intensive care environment is...

- Cluttered
- Complex
- Confusing
• ICUs create an illusion of technology but have the **lowest uptake** of any medical speciality in new technologies
• Nothing really useful has been added in the last 30 years

• Why??
Our current approach to solving some fundamental problems in critical care medicine is simply not working.

It's obvious why this wooden chopper won't fly....

...but in medicine why something works or why it doesn't work may not always be obvious [or even intuitive].
“It’s OK, this is a teaching hospital. Some people just have to learn the hard way”
Clinical applications in model based therapeutics
AGITATION!
A BIG problem in ICU
Agitation-Sedation management is all over the place

Consequences:

Cost of drugs...$$

Yearly cost in US of sedatives & analgesics in ICU is $0.8-1.2B US  *Fraser and Riker, 2001*

Resource utilisation.....

Landmark study of sedation interruption showed significant reduction in:

mechanical ventilation: 4.9 vs 7.3 days

median length of stay: 6.4 vs 9.9 days

Recent studies you may have thought about?
...cos if we don’t get it right....

Daily interruption of sedation might be bad..?

- increased death, MV, SOFA duration, LOS, Hosp LOS

Study was terminated by DSMB


Or it might not be?

Awakening and Breathing Controlled trial

Sedation Interruption + Spontaneous Breathing Trial

- increased breathing w/o assistance, & 12mth survival
- earlier discharge

Girard et al Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial Lancet. 2008 Jan 12;371(9607):126-34
Business case for getting sedation right..

435,000 ICU bed days in Australia & NZ
50% ventilated at $4000 /d ➔ $870M/y
10% wasted ➔ $87M/y

Global health impact $87M x 200 ➔ $17B/y
Business case for getting sedation right...

Our annual waste = :
12,000 ICU “bed years”
(time since end of the last ice age)

more $ than age of universe
What causes agitation?

**AND**

Why are we giving sedation??
Problem #1..

We often treat *all* forms of agitation the same way.

We pray for a ‘*drug cure*’ instead of looking for the underlying causes of agitation and managing this appropriately.
Current state of the “Art” → poor control

Subjective measures of agitation

Inconsistency between nurses

“over-customised care” and frequent over-sedation

… primarily due to a lack of a consistent measure of agitation

Wiener-Kronish, 2001
What we need....

A real, engineered and calibrated agitation sensor

Validated models of agitation-sedation dynamics

... Leading to well-understood infusion protocols

Hence quantitative analysis is needed...
User Interface

Patient image

Agitation Index

10
System vs. Nurses: A continuous range

Agitation Index

SAS score
How do patients handle ‘sedation’?

Infusion site + heart etc

Pharmacokinetics

Brain

Arms & Legs

Receptors
Pharmacodynamics

- Response surface modeling [Minto et al, 2000]
- Dual sigmoid
- Incorporates effect saturation
- Captures synergism
- Non-linear representation of the concentration-effect relationship
- Models the combined sedative effect of the drugs on the brain
Primary Equation

\[ \frac{dA}{dt} = w_1S - w_2K_T \int_0^t E_{Comb}(\tau)e^{-K_T(t-\tau)} \, d\tau \]

Rate of change of agitation depends upon relative magnitude of stimulus compared to cumulative effect of sedation
**Controlled feedback (closed loop)**

\[
\begin{align*}
\dot{C}_c &= -K_1 C_c + \frac{U}{V_d} \\
\dot{C}_p &= -K_3 C_p + K_2 C_c \\
\frac{dA}{dt} &= w_1 S - w_2 K_T \int_0^t E_{Comb}(\tau) e^{-K_T(t-\tau)} d\tau
\end{align*}
\]

\[
U = K_p A + K_d \frac{dA}{dt}
\]
Summary-sedation

It is possible to **quantify agitation**

Models of agitation-sedation dynamics allow **patient-specific** drug delivery

Improved, infusion protocols, based on dynamic models of drug effect and agitation response should **NOW** be the focus of new research
Model based cardiovascular diagnosis and therapy
The problem...

Cardiovascular diseases are extremely common and claimed nearly 1 million lives in the US in 2004, which equals 36.6% of all deaths*

More than 50% of postoperative deaths are caused by cardiac events+

Managing these patients is challenging:

Cardiac disease state is highly patient-specific: every patient has an unique expression of a given disease or dysfunction

* American Heart Association, Cardiovascular Disease Statistics
+ Mangano, 1994; Ramsey, 1999
Clinical challenges

Problems and Challenges:

All patients are different and may have different responses towards the same treatment and therapy
Multitude of interacting mechanisms and various disease states can change physiological relationships

Integration of diverse clinical data into a complete and accurate assessment of patient state.
Issues (1)

Wrong treatment choices based on incorrect paradigms!

➔ mistakes...!!
Issues (2) The Knowledge Gap

"Here's where you made your mistake."

http://www.negotiationlawblog.com/mistake.jpg
Issues (3) Guess work; ‘superstition’
Σ → Suboptimal care:

Apologies to...
If you engineered it ...

Goals:

Physiologically validated minimal CVS model*
Highly efficient model implementation method+
Integral-based parameter identification method#

Combination of rapid patient-specific parameter identification and fast accurate forward simulation enables the potential for real-time diagnosis and therapy selection decision support in the ICU.

* Smith, 2004; Smith et al., 2004; + Hann et al., 2005; # Hann et al., 2006
CVS Model: ID from bedside measures to get a patient-specific model

- AO = Aorta
- IVC = Inferior vena cava
- LA = Left atrium
- LPA = Left pulmonary artery
- LPV = Left pulmonary vein
- LV = Left ventricle
- RA = Right atrium
- RPA = Right pulmonary artery
- RPV = Right pulmonary vein
- RV = Right ventricle
- SVC = Superior vena cava

- Rpv = Pulmonary Capillaries
- Rpul in = Pulmonary Capillaries Inflow
- Rpul out = Pulmonary Capillaries Outflow
- Rpul in = Pulmonary Capillaries Inflow
- Rpul out = Pulmonary Capillaries Outflow
- Lpv = Pulmonary Capillaries
- Lmt = Left Ventricle Mass
- Ltc = Left Ventricle Tissue
- Lav = Left Ventricle Inflow
- Qpv = Pulmonary Capillaries
- Qmt = Right Ventricle Mass
- Qtc = Right Ventricle Tissue
- Qav = Right Ventricle Inflow
- Qsys = Systemic Inflow
- Qvr = Right Ventricle
- Qav = Right Ventricle
- Qmt = Vena Cava
- CO2 = Carbon Dioxide
- O2 = Oxygen

- Thoracic Cavity
- Septum
- Pericardium

- Capillary beds in lungs
- Capillary beds in head
- Capillary beds in body
Results

Porcine Data:
* Pulmonary Embolism (PE) Experiment
  PEEP Titration Experiment
  Septic Shock Experiment

Human Data:
* Adrenaline Studies
Pulmonary Embolism Experiment

Diagnosing PE accurately is very difficult and results in over-investigation.

The mortality rate of acute PE patients is higher than in patients with acute myocardial infarction, exceeding 10% at 30 days and 16% at 3 months.

As PE is potentially lethal, a fast and accurate diagnosis is essential.

* Website of the Society of Vascular Surgery (SVS)
+Goldhaber et al., 1999
Experimental Protocol

PE was induced in 7 pigs with autologous blood clots*

Blood clots injected every two hours

$P_{ao}$, $P_{pa}$, $V_{lv}$ and $V_{rv}$ were measured continuously during the experiment, from 0 to 240 minutes

* Desaive et al., 2005; Ghuysen et al., 2007
Results - PE

Pulmonary vascular resistance increasing over time

* Starfinger et al., 2007b
Effect of adrenaline in humans

Study 1 – Effects of Age on Cardiovascular Responses to Adrenaline in Man:

14 young normotensive subjects (age 21-40 years, mean 30± 2 years; 8 male, 6 female)
18 older normotensive subjects (age 50-73 years, mean 60± 2 years; 6 male, 12 female)

Rested 60 minutes
Adrenaline given at 20, 40, 80, 120 and 160 ng/kg/min
(or until the heart rate had increased by 20-25 beats/min or the diastolic blood pressure decreased by 15 mmHg)

Each dose was infused for 8 mins.

* White & Leenen, 1997
Results – Adrenaline ID

For all 3 studies, the median identification percentage errors are < 9%.

Model output (circle), Clinical data (solid)  
* Starfinger et al., 2008a
Conclusions

Extension of original CVS model* to include heart-lung interactions and volume infusions/ blood losses

Application of integral-based parameter identification methods** to real-time clinical applications

Validated on Porcine Experiments of PE+, PEEP/Volume Titrations++, Septic Shock+++ and Human Adrenaline Studies#

→ Identification: Assist Device for Diagnosis

→ Prediction towards interventions: Therapy Guidance and Decision Support

* Smith et al. 2004, ** Hann et al, 2006, + Starfinger et al, 2007, ++ Starfinger et al., 2008d, Starfinger et al., 2008e, +++ Desaive et al., 2008; Starfinger et al., 2008b, Starfinger et al., 2008c, # Starfinger et al. 2008a