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

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What's wrong with modern medicine?

THE RISE & FALL OF MODERN MEDICINE

Winner of the Los Angeles
Times book prize

'Excellent' *Financial Times*
'Brilliant' *Daily Mail*
'Fascinating' *Sunday Telegraph*

JAMES LE FANU

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”

1787 - 1872

Pierre Charles Alexander Louis

founder Médecine d'Observation

1813 - 1878

Schools of Medical Reasoning

Subject

Rationalism
The Individual

Empiricism
The Population

Model

Pathophysiologic

Probabilistic

Method

**Laboratory or bench
science**

**Large clinical trials
(of risk factor reduction)**

Benefits to the individual

Measurable

Immeasurable

Treatment of disease

People with disease

Outcome
(measurable)

Responders

Non-Responders

Continue treatment

Stop treatment

Rationalism

Treatment of risk

People at risk of disease

Outcome
(probabilistic)

Disease
prevented

Disease not
prevented

Disease was never
going to develop

Treatment
continues
indefinitely

Empiricism

So *engineers* are from Venus; *doctors* from Mars

Cockpit view A380

Built by engineers → rationalism

Rationalism

Critically ill patient

Managed by doctors → empiricism

Empiricism

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”*

1 Richard Smith, [http://en.wikipedia.org/wiki/Richard_Smith_\(editor\)](http://en.wikipedia.org/wiki/Richard_Smith_(editor))

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.skeptictoolbox.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?

They are in this room!

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....

McHUMOR by T. McCracken

I wish you'd come to me sooner

off the mark.com by Mark Parisi

Why computer engineers should not be surgeons

I think you should be more explicit here in step two

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

Its obvious why this wooden chopper won't fly....

...but in medicine why something works or why it doesn't work may not obvious *[or even intuitive]*

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"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

*Kress et al Daily Interruption Of Sedative Infusions In Critically Ill Patients
Undergoing Mechanical Ventilation N Engl J Med 2000;342:1471-7.*

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

de Wit et al. Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients Crit Care. 2008;12(3):R70. Epub 2008 May 20

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

Wiener-Kronish, 2001

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

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...

Agitation sensor

5 intermediate metrics

Chase JG, Agogue F, Starfinger C, Lam Z, Shaw GM, Rudge AD, Sirisena H. Quantifying agitation in sedated ICU patients using digital imaging. *Comput Methods Programs Biomed.* 2004 Nov;76(2):131-41.

User Interface

Real-Time Agitation Sensor

Patient
Name: **Franck**
Number: **FFF1234**

Patient State Update:
Date: **19/08/04** Time: **09:59:58**
Agitation Sedation
0 **0** **SET**

Start **Stop**

Video Pause

Video Resume

Patient image

Agitation Index
10

Init: successful!
video camera connected!
Backup File: DataFile_patient_FFF1234_190804_095740.bin
Real Time Agitation sensor on!
video 1 started!

Metrics
HR: **0**
HRD: **0**
SBP: **0**
BPD: **0**
MAI: **25.4**

Agitation Index

Time (min)	Agitation Index
0	20
5	15
10	25
15	35
20	45
25	50
30	55
35	60
40	55
45	60
50	55
55	60
60	50

System vs. Nurses: A continuous range

Agitation
Index

SAS
score

How do patients handle 'sedation'?

Pharmacokinetics

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

E_{Comb}

Morphine Effect-site Concentration

Midazolam Effect-site Concentration

Primary Equation

Stimulus

Cumulative effect of current and prior sedation

$$\frac{dA}{dt} = w_1 S - w_2 K_T \int_0^t E_{Comb}(\tau) e^{-K_T(t-\tau)} d\tau$$

Agitation Index

Combined drug effect

Rate of change of agitation depends upon relative magnitude of stimulus compared to cumulative effect of sedation

Controlled feedback (closed loop)

$$\dot{C}_c = -K_1 C_c + \frac{U}{V_d}$$

$$\dot{C}_p = -K_3 C_p + K_2 C_c$$

$$\frac{dA}{dt} = w_1 S - w_2 K_T \int_0^t E_{Comb}(\tau) e^{-K_T(t-\tau)} d\tau$$

$$U = K_p A + K_d \frac{dA}{dt}$$

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

dreamstime

dreamstime.com

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'

http://www.vetmed.wsu.edu/courses_vm551_crd/_archive/fluids/images/how_much.jpg

$\Sigma \rightarrow$ Suboptimal care :

Apologies to...

SERRE

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

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

* Desai 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.

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, +++ Desai et al., 2008; Starfinger et al., 2008b, Starfinger et al., 2008c, # Starfinger et al. 2008a