“We've got no money, so we've got to think”

The conundrum of dwindling supply and increasing demands for healthcare the 21st century

Geoffrey M Shaw  FANZCA, FCICM, Hon FIPENZ
Adjunct Prof Dept of Mech Eng Univ Canterbury
Assoc Prof Dept of Anaesthesia Univ Otago
You can't tell faculty what to do... it's like herding cats.

Challenges:
- Global race for talent
- Lack of research funding
- Valley of death

Energy and healthcare:
- We need more focus and investment.

It's all about the people:
- A magnet for innovation

China's growth is 10x faster than the US.

Some of the best work is not done in fancy offices.

But in a trailer.

Make sure you know the right questions to ask.

Always think about the big picture.

The innovation ecosystem health.
Two broad areas in healthcare innovation

...where would you put your money?

Harm/waste reduction through systems/quality improvement

(e.g. Safety initiatives, better informatics)

Improved efficacy through biotechnology investment

(e.g. Coronary artery stents, tissue engineering)

http://i.imgur.com/Rg6CQlu.jpg
“30% of healthcare spending is waste”!

In 2012, a panel of experts convened by Institute of Medicine estimated 30% health care spending is “wasted on unnecessary or poorly delivered services and other needless costs”

Supply-demand matching in real time
20 ICU patients: *demands on nursing time*

![Bar chart showing FTE required for each ICU patient.](image-url)
20 ICU patients: \textit{demands on nursing time}
20 ICU patients: *demands on nursing time*
Clinical Activity Tracking System--CATS

No Image Data Recorded --- Privacy Protected --- Approved by Research Office
Informatics

Data
People
Systems

Data ↔ Information ↔ Knowledge
Model-based therapeutics

- Process of care ("skills")
- Drugs and devices ("tools")
- Patient organ system behaviours
“Humans are horribly variable”

Diagnosis, treatment and outcome prediction are EXTREMELY hard

“..easier to play dot-to-dot than generate meaningful models of physiology.”

[International Journal of Clinical & Medical Imaging]
Model-based therapeutics in Critical Care

Some of the basic things that we do...

- Glucose control and nutrition
- Mechanical ventilation
- Sedation
- Cardiovascular management:
  - “tropes and fluids”
The bread and butter of ICU:

Intuition and experience, provides the fundamental basis of care delivered to the critically ill; it is specific to the clinician, but it is not specific to the patient.

The result:

- Highly variable and over customised care
- Poor quality and increased costs of care,

What are needed:

- Treatments that are patient specific and independent of clinician variability and bias
- A “one model”, not “one size”, fits-all approach
A glycaemic control wish list

- What will happen if I add more insulin?
- What is the hypoglycemia risk?
- How good is my control?
- Should I change nutrition?
  - Many if not all protocols are “carbohydrate blind” and thus BG is a very poor surrogate of response to insulin
- Is patient condition changing? What happens if it changes between measurements?
Model based therapeutics ➔ “MBT”

First, we describe the physical systems to analyse
Model based therapeutics ➔ “MBT”

Next, we build up a mathematical representation of the system

\[
G = -p_x G(t) - S_j G(t) - \frac{Q(t)}{1 + \alpha_j Q(t)} + \frac{\min(d, P_2, P_{\text{min}}) + EGR - \text{CNS} + PN(t)}{V_o}
\]

\[
\dot{Q} = n_j (I(t) - Q(t)) - n_i \frac{Q(t)}{1 + \alpha_j Q(t)}
\]

\[
I = -\frac{n_j I(t)}{1 + \alpha_j I(t)} - n_i I(t) - n_j (I(t) - Q(t)) + \frac{u_{\text{in}}(t)}{V_i} + (1 - x_j) \frac{u_{\text{in}}(G)}{V_i}
\]
Finally, we use computational analysis to solve these equations to help us design and implement new, safer therapies.
At the bedside....

Identify and utilise “immeasurable” patient parameters
For insulin sensitivity (SI)

“Nurse-in-the-loop” system. Standard ICU equipment and/or low-cost commodity hardware.
So where does this go?

- Insulin
- Glucose
- Sedation
- Steroids and vaso-pressors
- Inotropes
- And many many more ...

Doctors clinical experience and intuition

- Glucose levels
- Cardiac output
- Blood pressures
- SPO2 / FiO2
- HR and ECG
- And many more...

- Insulin Sensitivity
- Sepsis detection
- Stroke volume
- Agitation level
- A better picture of the patient-specific physiology in real-time at the bedside

- Optimise glucose control
- Manage ventilation
- Diagnose and treat CVS disease
- And many other things...

- And many many more ...
Variability, not physiology or medicine...

Models offer the opportunity to **identify, diagnose and manage variability** directly, to guaranteed risk levels.
Models, Variability and Risk

Stochastic model predicts SI

Forecast BG percentile bounds: A predicted patient response!

Iterative process targets this BG forecast to the range we want: = optimal treatment found!

Patient response forecast can be recalculated for different treatments
Maximum 5% Risk of BG < 4.4 mmol/L

Stochastic model predicts SI

Blood glucose

Patient response forecast can be recalculated for different treatments

Forecast BG percentile bounds: A predicted patient response!

Iterative process targets this BG forecast to the range we want: = optimal treatment found!

Maximum 5% Risk of BG < 4.4 mmol/L

Stochastic model shows the bounds (5th – 95th percentile) for insulin sensitivity variation over next 1–3 hours from the initially identified level.

For a given feed+insulin intervention an output BG distribution can be forecast using the model.

5th, 25th, 50th (median), 75th, 95th percentile bounds for $S(t)$ variation based on current value.

SI percentile bounds + known insulin + system model = ...

Stochastic model predicts SI

Insulin sensitivity

Blood glucose

$t_{\text{now}}$  

$t_{\text{now}}+(1-3)hr$

5th
75th
50th
25th
5th
25th
50th
75th
95th

Patient response forecast can be recalculated for different treatments

Iterative process targets this BG forecast to the range we want: = optimal treatment found!
Why this approach?

• Model lets us guarantee and fix risk of hypo- and hyper-glycemia

• Thus, one can optimise the dose under all the normal uncertainties
  – No risk of “unexplained” hypoglycemia

• We fix a 5% risk of BG < 4.4 mmol/L which translates to less than 1/10,000 (interventions) risk of BG < 2.2 mmol/L (should be about 2% by patient)
  – Fyi, this is how airplanes are designed and how Christchurch's high rises should have been designed!
Some Results to Date

<table>
<thead>
<tr>
<th>Workload</th>
<th>STAR Chch</th>
<th>STAR Gyula</th>
<th>SPRINT Chch</th>
<th>SPRINT Gyula</th>
</tr>
</thead>
<tbody>
<tr>
<td># BG measurements:</td>
<td>1,486</td>
<td>622</td>
<td>26,646</td>
<td>1088</td>
</tr>
<tr>
<td><strong>Measures/day:</strong></td>
<td><strong>13.5</strong></td>
<td><strong>12.8</strong></td>
<td><strong>16.1</strong></td>
<td><strong>16.4</strong></td>
</tr>
</tbody>
</table>

| Control performance | | | |
|---------------------|-----------|-----------|-------------|--------------|
| **% BG in target range)** | **89.4** | **84.1** | **86.0** | **76.4** |
| % BG > 10 mmol/L | 2.48 | 7.7 | 2.0 | 2.8 |

| Safety | | | |
|---------|-----------|-----------|-------------|--------------|
| **% BG < 4.0 mmol/L** | **1.54** | **4.5** | **2.89** | **1.90** |
| % BG < 2.2 mmol/L | 0.0 | 0.16 | 0.04 | 0 |
| **# patients < 2.2 mmol/L** | **0** | **1 (started hypo)** | **8 (4%)** | **0** |

| Clinical interventions | | | |
|------------------------|-----------|-----------|-------------|--------------|
| Median insulin (U/hr): | 3 | 2.5 | 3.0 | 3.0 |
| Median glucose (g/hr): | 4.9 | 4.4 | 4.1 | 7.4 |

*4-8mmol/L
Cumulative time in glycaemic band: 1700 ICU patients [NZ and 7 EU countries]

Survival Odds Ratio

- **4.0 – 7.0**
- **5.0 – 8.0**
- **4.0 – 8.0**

Tighter target range

- cTIB > 50%
- cTIB > 60%
- cTIB > 70%
- cTIB > 80%

Better control

Day (1-14)
Hospital mortality SPRINT/Pre-SPRINT

LOS ≥ 1 day  LOS ≥ 2 days  LOS ≥ 3 days  LOS ≥ 4 days  LOS ≥ 5 days

P=0.244  P=0.077  P=0.023  P=0.012  P=0.010

The horizontal blue line shows the mortality for the retro cohort.

The green line is the total mortality of SPRINT patients against total number of patients treated on the protocol.
SOFA scores reduce faster with SPRINT and do so from day 2
Organ failure free days: SPRINT = 41.6% > Retro = 36.6% (p<0.0001)
Number of organ failures (% total possible) defined as SOFA > 2 for 1 SOFA score component: SPRINT = 16% < Retro = 19% (p<0.0001)

At ... *yesterday's cost*...

Pfeifer L, Chase JG, Shaw GM, “What are the benefits (or costs) of tight glycaemic control? A clinical analysis of the outcomes,” Univ of Otago, Christchurch, Summer Studentship 2010
Summary (1)

Model-based methods to control dysglycaemia in ICU:

- Better survival
- Reduced cost
- Improved safety
Mechanical Ventilation
Acute lung injury /respiratory distress syndrome

ICU doctors use positive pressure (PEEP) at the end of a breath to stop damaged lungs from collapsing. But no one knows how much to use!

Model-based PEEP selection

During each breath, if collapsed parts of the lungs open up, then lung stiffness will fall:

⇒ “RECRUITMENT”

If there is no fall in stiffness:

⇒ “NO RECRUITMENT”

Hence recruitment and potential lung injury can be balanced by selecting PEEP at minimal stiffness

http://www.youtube.com/watch?v=oKH7CtsEgHw
CURE in the ICU

1. Patient breathing is monitored by ventilator
2. Pressure and flow data recorded by laptop
3. CURE system analyses pressure and flow data in real time, and recommends PEEP based on minimum elastance
4. Clinician sets ventilator PEEP
5. Ventilator applies PEEP to patients

Spontaneous breathing:
Ventilation Dyssynchrony

Initial recruitment manoeuvre:
Recruitable Lung

Post recruitment:
Recruited Lung
In all but one patient (pt 2), clinically-selected PEEP was significantly less than a model-based estimate using minimal elastance.
In summary (2)...

**Optimisation of mechanical ventilation**
- Trend changes in condition
- Alerts to unexpected changes
- Aids diagnosis of changes in lung condition
- Prevention of ventilation-induced lung injury

**Clinical Use of Respiratory Elastance (CURE)**
- Semi-automated
- Real-time
- Improved confidence and performance
Randomised controlled trials test interventions amongst \textit{populations} of highly complex biological systems (aka humans).

However, the statistical process depends on us \textit{NOT knowing individual differences}.

RCTs can only tell us about the \textit{“climate”, but can’t tell us the “weather”; e.g. will it rain tomorrow? Or is a cyclone coming?}

RCTs \textit{cannot predict individual responses}
RCTs regard all patients as “black boxes”
Model-based therapeutics

Creates new knowledge and understanding
Customises care to patients and makes predictions about their response to treatments, which were previously only guessed at.
Can tell us if it is going to “rain, hail or snow”
Pondering the Future

IS THERE A **NURSE** IN THE HOUSE?

PROJECTED SHORTAGE OF REGISTERED NURSES IN CALIFORNIA

![Graph showing projected shortage of registered nurses in California](http://www.papermasters.com/images/nursing-shortage.gif)

**Demand Forecast** vs **Supply Forecast**

*Source: Center for California Health Workforce Studies; University of California, San Francisco*
Problem: *We are not rich enough to pay for the care we want*
Solution: *Either get richer, or make healthcare more affordable*
Get richer?....yeah right!

“We've got no money, so we’ve got to **innovate**!”

“Get richer?....yeah right!”

Ernest Rutherford

“We've got no money, so we’ve got to **innovate**!”

...otherwise we could just ration...

...and leave it to these (non-thinking) guys
THE GIANT COLON...

HAVE IT CHECKED OR CANCEROUS GROWTHS CAN TAKE OVER!

The Christchurch Press, 5th June 2014
So who are the innovators?
Percent of Requests to advisory Board for Technology Evaluation

INnovators

<table>
<thead>
<tr>
<th>Field</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Radiology</td>
<td>26%</td>
</tr>
<tr>
<td>Cardiology</td>
<td>23%</td>
</tr>
<tr>
<td>Surgery</td>
<td>15%</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>13%</td>
</tr>
<tr>
<td>Oncology</td>
<td>11%</td>
</tr>
</tbody>
</table>

UNnovators

<table>
<thead>
<tr>
<th>Field</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosciences</td>
<td>5%</td>
</tr>
<tr>
<td>Anaesthesiology</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Intensive Care</td>
<td>&lt;&lt;1%</td>
</tr>
</tbody>
</table>
### Why?

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intensive care</th>
<th>Cardiology</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Heterogeneous population</td>
<td>Discreet syndromes</td>
</tr>
<tr>
<td></td>
<td>Wide age distribution</td>
<td>Single organ system</td>
</tr>
<tr>
<td></td>
<td>Multiple syndromes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple organ systems</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Culture</th>
<th>Advances in care mainly due to improved safety; Risk averse culture</th>
<th>Advances in care are due to innovative technologies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Managed risk</td>
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</table>

<table>
<thead>
<tr>
<th>System</th>
<th>Very high labour costs (esp. nursing)</th>
<th>Moderate labour costs</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Industry engagement</th>
<th>Poor alignment with industry; Low investment</th>
<th>Strong alignment with industry; Significant investment</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Industry</th>
<th>Cheap (“static”) technologies (e.g. capital cost of a ventilator = $50/patient)</th>
<th>High cost (“evolving”) technologies ($2500 - $4800 USD / patient*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very poor return on investment</td>
<td>$5B global market</td>
</tr>
</tbody>
</table>

*BERKELEY CENTER FOR HEALTH TECHNOLOGY
Innovate or die (or just be poor)

Comparison of annual income (median compensation) by physician subspecialty.

Where would you invest?

Acute / intensive / ward-based care?
➡ Little competition, but an opportunity?

Vs.

The greyhounds of innovation:
radiology / cardiology/ orthopaedics
➡ Highly competitive , possibly a risk?
Getting into bed with industry might be a good thing for everyone!

Cos investment in healthcare seems the only thing likely to save it!

From: “A Very Long Engagement”
http://4.bp.blogspot.com/-w4eSnNEGwRiM/UhouvY2urmOl/AAAAAAAADog/Wjg08faJB78/s1600/A+Very+Long+Engagement+1.jpg
"I don't have to be smart, because someday I'll just hire lots of smart people to work for me"
Acknowledgements

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Ulrike Pielmeier
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Dunedin

The Danes

The Belgians

Hungarians

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Some guy named Geoff

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... And all the clinical staff at over 12 different ICUs
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Richard Fernando
Laura Badcock
Sarah Poole
James Williams
eTIME (Eng Tech and Innovation in Medicine) Consortia

4 countries, 7 universities, 12+ hospitals and ICUs and 35+ people
Thank you!!

I HAVE NOTHING FURTHER TO SAY

1907 - 2007