mathematical models: conversations between minds and machines

2040 vision symposium on the occasion of George Stephanopoulos' 70th birthday and retirement from MIT, MIT, Cambridge, MA, June 2, 2017

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overview

• what is mathematical modeling?

• is modeling practical?

• is it significant?

• examples: discoveries on the aging brain

• conclusions and remarks
what is modeling?

(mathematical)
A set of equations corresponding to a physical, biological or economic prototype

(Tarski: Logic)
Possible realizations in which all valid sentences of a theory T are satisfied

(general)
A replacement of a theory-less domain of facts by another for which a theory is known
replacement of a theory-less domain by another (0,1)

decade system

2 + 3 = 5

binary world (AND/OR)

On tape initially: $0010$0011 // adding 2+3
When done: $0000$0101 // equals 5
model-based discovery and learning

**formulate**

(mind)

- A \( x = b \)
- \( f(x) = 0 \)
- \( \min_{x} f(x) \) s.t. \( h(x)=0 \)
- \( \dot{x} = Ax(t) + Bu(t) + C d(t) \)

**solve**

(machine)

- math model
- well-known theories
- \( X \)

**validate**

physical predictions

P, T, c

insight about prototype domain

unknown prototype

new process

prototype domain
formulating models is expensive

paper and pencil (mind)
The formulation is expensive.

- **COREX process (my thesis)**
  - 2 years code development in Fortran
  - perhaps faster with GAMS

- **Process flowsheet (Aspen):**
  - beginner level: 15 weeks x 3 hrs = 45 hrs
  - expert: 10 hrs

- **CFD model (Fluent):**
  - routine problem: Days/weeks
  - research level (PhD level): 1-2 years

**Cost/effort: weeks/year(s):**

- **formulate** = 4-200 k$ (200 $/hr)  
  = 10-450 k$ (500$/hr)

- **solve** = 0.5 k$
can machines* help formulate?

(*intelligent systems)
AGENT-BASED APPROACH TO A DESIGN SUPPORT SYSTEM FOR THE SYNTHESIS OF CONTINUOUS CHEMICAL PROCESSES

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INTELLIGENT SYSTEMS IN PROCESS ENGINEERING: A REVIEW

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MODEL.LA. A MODELING LANGUAGE FOR PROCESS ENGINEERING—I. THE FORMAL FRAMEWORK

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batch design-kit (BDK)
1994-1997

+Ajay Modi
+Kike Aumond

Enrique Salomone  Eleni Stephanopoulos  Shahin Ali  AL
BDK generates math models

**FLOW SHEET**
virtual representation of
• units
• material mixtures, compounds, phases
• process streams

**BATCH SHEET**
(formalized)-natural language input
= chemists’ dialect

• operational tasks
• schedule and sequencing
(parallel, sequential)
BDK language emulated experiments in a virtual lab

<table>
<thead>
<tr>
<th>Group of Operation</th>
<th>Name of Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material Transfer</td>
<td>Charge, Charge from Recycle, Transfer, Transfer-through-Heatexchanger, Transfer Intermediate</td>
</tr>
<tr>
<td>Heat Transfer</td>
<td>Cool, Heat, Heat and Reflux, Quench</td>
</tr>
<tr>
<td>Operations on Gases</td>
<td>Pressurize, Vacuum, Purge, Vent, Sweep</td>
</tr>
<tr>
<td>Operations on Solids</td>
<td>Centrifuge, Dry, Filter, Crystallize, Filter Continuously, Filter in Place, Wash Cake</td>
</tr>
<tr>
<td>Liquid Separations</td>
<td>Concentrate, Concentrate, Semicontinuously, Distill, Distill Continuously, Distill, Semicontinuously, Fractionation, Extract, Extract Continuously, Decant</td>
</tr>
<tr>
<td>Column Operations</td>
<td>Elusion, Loading, Regeneration</td>
</tr>
<tr>
<td>Reactions</td>
<td>Age, pH Adjustment, React, React in CSTR</td>
</tr>
<tr>
<td>Synchronization</td>
<td>Begin Parallel Operations, End Parallel Operations, Begin Sequential Operations, End Sequential Operations</td>
</tr>
</tbody>
</table>
BDK generated models .... and solved them

• BDK:
  • formalized-natural language input
  • model generation (synthesis of equations)
  • virtual representation of world-objects (material model)

• Current commercial tools
  • select icons form a palette
  • model equations are hard coded
  • representations remain hidden for the user
is model generation practical?
example 1

oxygen exchange and blood flow in the aging brain
model generation

models from medical images:
(mouse)

synthesis of vascular trees
(human)
generate network model of the cortical angio-architecture

2-photon microscopy  vectorized image  network adjacency matrix
network topology of primary somatosensory cortical mouse data sets
Biphasic Blood Flow

Volumetric Mass Conservation
\[ 0 = \nabla \cdot Q \quad \Delta P = Q \alpha = Q \cdot \frac{8 \mu L}{\pi R^4} \cdot \eta_{vivo} (R, H_d) \]

Kinematic Plasma Skimming Law
\[ 0 = \nabla \cdot (Q H_d) = Q_1 H_1 - Q_2 \theta_2 H^* - Q_3 \theta_3 H^* \]
\[ \theta_3 = \left( \frac{A_3}{A_1} \right)^{\frac{1}{M}} \]
\[ \theta_2 = \left( \frac{A_2}{A_1} \right)^{\frac{1}{M}} \]

Biphasic O2 Transport

RBC O2 Molar Flux Conservation
\[ 0 = \nabla \cdot D_{HbO_2} \nabla C_{HbO_2} - \mu_{RBC} \nabla C_{HbO_2} - \dot{R}_{R \rightarrow P} \]

Plasma O2 Molar Flux Conservation
\[ 0 = \nabla \cdot D_{plO_2} \nabla C_{plO_2} - \mu_{pl} \nabla C_{plO_2} + \dot{R}_{R \rightarrow P} - S_b \frac{U}{W_b} \left( C_{plO_2} - C_{BECO_2} \right) \]

Kinetic O2 Hemoglobin Dissociation
\[ \dot{R}_{R \rightarrow P} = H_t V_b k \left( C_{plO_2} - K_{eq} C_{HbO_2} \right) \]
\[ K_{eq} = \frac{C_{plO_2}}{\beta \cdot S \left( C_{plO_2} \cdot \alpha_{pl} \right)} \]
capillary blood flows like a bi-phasic suspension

Reference link: https://www.youtube.com/watch?v=pwmlP1hLJf0&feature=youtu.be
drift flux for bi-phasic blood flow

\[
H_2 = H_1 - \Delta H = \theta_2 \cdot H^* \quad H_3 = \theta_3 \cdot H^* \quad (9)
\]
\[
\theta_2 = \left( \frac{A_2}{A_1} \right)^\frac{1}{M} \quad \theta_3 = \left( \frac{A_3}{A_1} \right)^\frac{1}{M} \quad (10)
\]
\[
Q_1 H_1 = Q_2 H_2 + Q_3 H_3 = Q_2 \theta_2 H^* + Q_3 \theta_3 H^* \quad (11)
\]

**Figure 2.** Schematic of a bifurcating vessel carrying biphasic blood flow composed of RBC and plasma phase. Branch 3 receives more bulk blood, \( Q_3 \), and disproportionately more RBCs, \( Q_3 \cdot H_3 \), than the weaker branch 2.
predict microcirculatory blood flow and oxygen extraction
analyze microcirculation (in-silico brain)
key findings

- hemodynamic states are not uniform (=stabilization in space)

- tissue is supplied evenly

- pressure drop in capillaries
how is oxygen supplied to human brain?
generate network topology

Minimum tree volume optimization

$$\begin{align*}
\min \quad & V = \sum_{i=1}^{N} \frac{\pi}{4} d_i^2 \cdot l_i(x) \\
\text{s.t.} \quad & \Delta P = \alpha_i F_i \quad \forall \text{segments} - \ i \ \text{in Network}
\end{align*}$$

CCO, Schreiner et al.
recursive
network
generation
The Basal Ganglia

Selection of Desired Areas
computer-generated anatomical model for humans match mouse
oxygen maps in humans
prediction of blood flow and oxygen exchange in a 3x3x3 mm section

FIGURE 5. Visualization of a relatively large 27 mm$^3$ subsection of the secondary cortex with computed steady state blood pressure, volumetric flow rate, and oxygen profiles projected onto the vessel architecture. Top row—larger vessels (capillary bed without showing small vessels, d < 10 $\mu$m). Bottom row—all vessels, including capillary bed, are shown. (a) Blood pressure, (b). Oxygen tension, and (c). Volumetric blood flow value profiles.
is model generation significant?

Knowledge discovery in the aging brain
brain diseases are a world-wide health burden

Total European 2010 cost of brain disorders was €798 billion (2010)

• Average cost per inhabitant was €5,550.
• mood disorders 113.4;
• dementia 105.2;
• stroke 64.1; and
• headache 43.5;

*Nature Medicine 12, 780 - 784 (2006)*

Alzheimer disease is the most common cause of dementia.

• An estimated 37 million people worldwide currently have dementia;
• Alzheimer disease affects about 18 million of them\(^1\).
Information Technology and Innovation Foundation (ITIF).

**Mental Disorders Top The List Of The Most Costly Conditions In The United States:**

$201 BillionHealth Aff 10.1377/hlthaff.2015.1659;
WASHINGTON—In addition to significant human costs, mental and neurological disorders and diseases
Cost to U.S. economy: >$1.5 trillion per year—8.8% GDP

Policy Recommendations:
• Expand funding for the National Institute of Health’s (NINDS).
• Encourage biopharmaceutical companies to invest more in research

**World health report**

Mental disorders affect one in four people

Geneva, 4 October—One in four people in the world will be affected by mental or neurological disorders at some point in their lives. Around 450 million people currently suffer from such conditions, placing mental disorders among the leading causes of ill-health and disability worldwide.
parkinson’s disease = disturbed dopamine metabolism

NINDSD - US is at least 500,000. Actual number is higher
Cost: USA: $6-10 billion per year (NINDS); Europe: €13.9 billion.

alzheimer’s disease = nerve cells break down

USA: 5.4 million people in the US have Alzheimer’s disease (AD).
Cost: Worldwide: 115.4 million people by 2050.
    USA: $200 billion per year, as of 2012. $1.1 trillion per year by 2050.
aging brain-models generate first promising insights

1.2 Lymphocyte Blockage

<table>
<thead>
<tr>
<th>Normal</th>
<th>5%</th>
<th>10%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
example 2

hemodynamic risk factors in human arterial tree
virtual endovascular intervention planning
example 3
rational design of gene delivery to the CNS
conclusions

modeling accelerates discovery about complex systems
  o aging brain
  o drug and gene delivery
  o systems biology***

formulation is expensive so that machine generation is both lucrative (cost) & effective (faster revision cycle)

intellectual demand calls for (systems engineering) research

more on model generation: http://lppd.bioe.uic.edu
is model generation effective?
replacement of a theory-less domain of facts by another for which a theory is known

pure (mathematical) property exploration yield less about the prototype than sharpened formulation

formulating models is communication&composition task

... good narrative induces a ‘sense’ about the process
a ‘model’ for modeling

formulation/modeling == language (formal or natural)

language requires grammar/syntax (mathematical properties)
composition requires good reading practice
students need to compose, synthesize

Application: math modeling as a “language course”
biological systems analysis course (bio310, bio532)

“reading” exercises
“translate” physical prototypes into quantitative expressions
“compose” with multi-physics phenomena
“interpret” physical model behavior

*** genetics/systems biology?
Happy birthday George

Best luck for a new stage in your life

MIT, Cambridge, MA, June 2, 2017