Systems Engineering Methodology for Healthcare Information Highways, Hospital Management, Disease Biology and Modern Pharmaceuticals

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Healthcare, in all its forms and systems, is currently a major challenge for the whole world and for industrialized countries alike.

Healthcare systems around the world are facing unprecedented challenges -- issues are truly global.

Healthcare costs are rapidly increasing: rose 2.6% in 2013, accelerating to an average of 5.3% per year over 2014-2017, even higher in 2017-2022.

Unfortunately coverage and offered services are decreasing.

Economist Intelligence Unit (EIU) estimates that global health care spending as a percentage of Gross Domestic Product (GDP) will average 10.5 percent in 2014 (unchanged from 2013), with regional percentages of 17.4 percent in North America, 10.7 percent in Western Europe, 8.0 percent in Latin America, 6.6 percent in Asia/Australasia, and 6.4 percent in the Middle East/Africa.

Among developed nations, health is the second-largest category of government spending, after social protection (social assistance, health/unemployment insurance).

Four major issues that governments, health care providers, payers, and consumers face: aging population and chronic diseases; cost and quality; equality in access to care; technology; data and their availability and use.
Motivation – HealthIT

• Adoption of new **digital health information technologies (HIT)** such as electronic medical records (EMRs), telemedicine, mobile health (mHealth) applications, and electronic medical prescriptions is driving change in the way physicians, payers, patients and other sector stakeholders interact.

• These technology-based changes are shifting the power balance within the health care system and driving different dialogues along the value chain.

• **Health Information Technology** (Health IT) has great potential and promise to ameliorate these problems, and is being aggressively pursued in the US, Europe and many other countries. **Health IT is of central interest and importance for these problems.**

• There are **several fundamental reasons**: EHR, patients active partners, support heterogeneous sensors and tests, track quality and treatment effectiveness and costs, facilitate dialogue between patients and health care providers, can accumulate huge data sets and learn from them, support health care social networks, eliminate unnecessary hospital visits, incorporate learning in such systems.
HealthIT and Systems Engineering

- Broadband Hybrid Communication Networks with widely available access
- Universal patient records and dissemination
- Universal logistics support (insurance, databases, accounting, case management)
- Web-based services
- Mini-clinics and inexpensive tests and consultations
- Social, behavioral aspects
- Hospital information and management systems
- Multimedia systems, robotics, tele-surgery, new operating rooms
- Health care management systems
- Security, trust, authentication and privacy

“I would like more Systems Engineering principles for Health Care”
Harvey V. Fineberg, President of the Institute of Medicine
“Innovation in Medical Technology”, Whiting-Turner Lecture – 2009
• Despite great promises and potential, the deployment of Health IT has been very slow -- neither easily acceptable nor becoming indispensable
• Problems encountered are very complex and diverse and involve: human behavior and psychology, political challenges, regulatory and legal challenges, debates and contentions among the major shareholders: healthcare providers, health insurance providers, patients, technologists
• Health IT systems are complex systems and even systems of systems
• It is imperative that are modeled, designed, constructed and operated as systems -- taking a holistic and integrative systems view
• The challenge is even greater because humans of various capabilities, functionalities and roles are essential parts of health care systems
• What has been lacking in these developments, as emphasized in the report to President Obama [PCAST, May 2014] is a modern systems engineering approach to the modeling, design, construction, operation and maintenance of such systems.
UMD Rigorous Model-Based Systems Methodology and Framework
UMD MODEL-BASED SYSTEMS ENGINEERING PROCESS

PRODUCT: Integrated System Synthesis
Methods & Software Tool Suites

Iterate to Find a Feasible Solution / Change as needed

Change structure/behavior model as needed

Assess Available Information

Define Requirements
Effectiveness Measures

Create Behavior Model

Map behavior onto structure
Allocate Requirements

Specifications
Perform
TradeOff Analysis

Create Sequential
build & Test Plan

Create Structure
Model

Generate derivative
requirements and metrics

UML - SysML - GME - eMFLON
ANSYS Model Center
Rapsody
UPPAAL
MATLAB, MAPLE
Dassault Systemes Dymola, CATIA, PLM
CONSOL-OPTCAD
IBM CPLEX ILOG Optimization Studio
GUROBI
SIEMENS PLM, NX, TEAM CENTER

Apply this to: Design, Manufacturing, Operations and Management TO THE WHOLE LIFE-CYCLE ⇒ MBE
FOUR PILLARS OF SYSML

1. Structure

2. Behavior

interaction
state
machine
activity/
function

3. Requirements

4. Parametrics
SysML Taxonomy

System Architecture

OMG 2010
The Challenge & Need:
Develop scalable holistic methods, models and tools for enterprise level system engineering

Multi-domain Model Integration via System Architecture Model (SysML)

BENEFITS
- Broader Exploration of the design space
- Modularity, re-use
- Increased flexibility, adaptability, agility
- Engineering tools allowing conceptual design, leading to full product models and easy modifications
- Automated validation/verification

APPLICATIONS
- Avionics
- Automotive
- Robotics
- Smart Buildings
- Power Grid
- Health care
- Telecomm and WSN
- Smart PDAs
- Smart Manufacturing

**MBSE:**
Three key components.

**ADD & INTEGRATE**
- Multiple domain modeling tools
- Tradeoff Tools (MCO & CP)
- Validation / Verification Tools
- Databases and Libraries of annotated component models from all disciplines

"Master System Model"

Update System Model

ILOG SOLVER, CPLEX, CONSOL, OPTCAD

Tradeoff parameters

DB of system components and models
INTEGRATION OF CONSTRAINT-BASED REASONING AND OPTIMIZATION FOR TRADEOFF ANALYSIS AND DESIGN SPACE EXPLORATION

To enable rich design space exploration across various physical domains and scales, cyber domains and scales, human and social domains and scales
A Model-Based Systems Engineering Framework for Healthcare Management and a Medical Information Highway for Diabetes Mellitus
• Framework for Health Care Management Systems via MBSE
  – application to Diabetes Mellitus
  – desired architecture of such Health Care Management Systems
• Controlled Hidden Markov Chain model for diabetes disease progression
  – diagnostic tests and interventions
  – patient behavior profiles
• Metrics: Health Care Quality and Health Care Cost
• Methods for computing tradeoffs between health care cost and health care quality:
  – exhaustive Monte Carlo simulation
  – use multi-criteria optimization with full and partial disease state information
  – comparisons: latter obtain similar results at a fraction of the time of the first
• Demonstrate capabilities of framework via practical health care management examples
Motivation – Diabetes

- Chronic diseases are, by far, the leading cause of mortality in the world – 63% of all deaths
- Cancer and heart disease are becoming major killers
- Africa, the Middle East, Asia, and Latin America are experiencing epidemics in diabetes and cardiovascular illnesses
- China, with 92 million diabetics, has overtaken India (80 million) as the world leader in diabetes cases, according to International Diabetes Federation
- Selected as focus the modeling and management of Diabetes Mellitus (or Diabetes 2) -- problem of high impact affecting tens of millions of people world-wide
- 366 million people have diabetes and another 280 million are at identifiably high risk of developing diabetes. If nothing is done, by 2030 this number is expected to rise to 552 million with diabetes and an additional 398 million people at high risk. Three out of four people with diabetes now live in low- and middle-income countries.
• In the USA alone in 2012 29.1 million people, or 9.3% of the population, had diabetes, while the associated costs were estimated for 2012 at $245 billion
• Furthermore in the USA alone for the same time period 86 million adults (more than 1 out of 3) have pre-diabetes
• Across the world, health care systems are recognizing the need for innovation:
  − advances in health technologies and data management can help facilitate new diagnostic and treatment options
  − however, these same advances are likely to increase overall costs, prompting widespread efforts by public and private health care providers and insurers to contain expenditure by restructuring care delivery models and promoting more efficient use of resources
• Health care technology changes will be rapid and, in some parts of the world, disruptive to established health care models
• Some exciting advancements are taking place at the intersection of information technology and medical technology
Framework Based on MBSE

A framework that is:
- Scalable
- Expandable
- With learning ability
- Linkable
- Measurable

- MBSE framework to develop Health Care Management Systems (HCMS)
- Variety of connectivity to facilities, labs, hospitals, patients, doctors, insurance managers, etc.
- Under development in many countries – c.f. Massachusetts Medical Information Highway
• MBSE key for characteristics and capabilities needed:
  • Is scalable to millions of patients, tens of thousands of healthcare providers
  • Is expandable, in the sense that it can continuously accommodate new data and knowledge, new tests, new, models, new treatments
  • Is linkable to distributed medical databases
  • It has capabilities to “learn”
  • It can be easily used by healthcare providers, health insurance managers, and patients
  • It can operate in a distributed collaborative manner and be linked to extensive communication and data networks and large heterogeneous sensors and databases
  • It can provide quantitative answers to “what-if” type of questions such as: what is the effect of using modern monitoring wearable technology, what is the most effective test, what is the most effective treatment, what are the tradeoffs between costs and tests and treatments
Layered system

- Three logical layers
- Reasoning as the base layer
- The diagnostic and measuring mechanisms as the intermediate layer
- Medical interventions and implementations as the higher layer
Ontologies in HCMS for Diabetes II

- Components of the system have parent-child relationships between them and the subsystems.

- All components use as medium different information and communication technologies.
Essential components of integration framework include: hardware models, software models, analysis models, verification, and requirements components.

Enterprise level systems engineering

Integration of multiple domain modeling tools, trade off tools, annotated databases and libraries, validation/verification tools, and domain component models required.

Benefits from proposed methodology include broader exploration of decision space, modularity, flexibility and agility.

Engineering tools used allow conceptual planning to lead to full strategy models with easy to implement modifications that are also traceable.

Proposed methodology enables monitoring and validation/verification integration with decision space exploration tools, through the aid of SysML integrated models.

Focused on Reasoning Engine component
Based on several models and clinical data

- Three states: **State 1** represents the *Healthy* (disease free) condition of a generic patient. **State 2** represents the *Pre-diabetic* condition of a generic patient. **State 3** represents the *Diabetic* condition of a generic patient.

- Our MBSE approach enables incremental improvement of disease models, parameters, the tests, interventions

- States determined by a variety of medical tests, described in the current medical diagnostic practice for disease.

- As the patient goes on with her/his life, various tests are performed periodically to determine the state of health of the patient regarding this particular disease, and various interventions (treatments) are recommended and followed, depending on both the test outcomes (measurements) and the state of health of the specific patient.

- In practice absolute description of the state of the disease does not exist in healthcare. State represents the collection of ranges in the outcomes of the various diagnostic tests performed – Hidden Markov Models better
Key Components for Modeling Diabetes II Disease Progression

- Incorporating medical tests and interventions
- Progression as a Controlled Hidden Markov Chain (CHMC), with three states
- Complexity based on detailed dynamics in disease and treatments clinical data and biochemical models
- Operational characteristics of tests; i.e. statistical errors
- Sequential disease state estimation schemes from tests
- Types of interventions (technology, diet, exercise, medication), and ten specific interventions from these types
- A strategy involves a sequence of interventions applied at various times as in OR and engineering
- Time horizon for the study denoted by $T$; in most of our experiments/simulations, $T$ is ten years
Typical Diagnostic Tests for Diabetes II

- **A1C Test**
  Blood test that reflects the average of a person’s blood glucose levels over the past 3 months and does not show daily fluctuations

- **Fasting Plasma Glucose (FPG) Test**
  Detects Diabetes and Pre-diabetes. Measures blood glucose in a person who has fasted for at least 8 hours, most reliable in the morning.

- **Oral Glucose Tolerance Test (OGTT)**
  Detects Diabetes, Pre-diabetes, and Gestational Diabetes. More sensitive than the FPG test, but less convenient to administer. Measures blood glucose after a person fasts for at least 8 hours and 2 hours after the person drinks a liquid containing 75 grams of glucose dissolved in water.

<table>
<thead>
<tr>
<th>State</th>
<th>A1C (percent)</th>
<th>Fasting Plasma Glucose (mg/dl)</th>
<th>Oral Glucose Tolerance Test (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>&gt; 6.5</td>
<td>&gt; 126</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>Pre-diabetic</td>
<td>5.7 to 6.4</td>
<td>100 to 125</td>
<td>140 to 199</td>
</tr>
<tr>
<td>Healthy</td>
<td>&lt; 5.7</td>
<td>99 or below</td>
<td>139 or below</td>
</tr>
</tbody>
</table>
Four types of interventions considered:

- **Technology** $u_{(1,2)}$: we assume that one therapy uses communication wireless technology (telemedicine, EHR), while the other intervention is not using such technologies.

- **Diet** $u_{(3,4,5)}$: we have three types of diets one that has as a target of losing 5% of weight, another with 10% and the last one with 15%.

- **Exercise** $u_{(6,7,8)}$: we assume that a person can burn with 30 minutes of daily exercise 100, 200, 300 calories respectively.

- **Medication** $u_{(9,10)}$: we have two interventions one that includes a light medication metformin and another one including strong insulin.

**Selection of interventions**

- If state is known, or, as is more appropriate estimated on the basis of diagnostic tests results, medical practice standards and the reasoning and experience of medical practitioners result in a selection process for these interventions.

- Selections is ranking the interventions in some order of preference.

- More general conditioning including more detailed information about the patient can be incorporated in the same manner.

- Our overall MBSE approach supports the incorporation of additional information, models and statistics.
Evaluation Metrics - Cost

\[ N_{T, \Delta} = \frac{T}{\Delta} \]

- Cost intervention function with total \( k \) (number of interventions) = 10
- Cost of diagnostics \( m \) with total different types \( l = 3 \)
- Total Cost of interventions for patient \( (i) \) for time period \( t \)
- Total Cost of diagnostic for patient \( (i) \) for time period \( t \)
- In these sums, the tests and interventions used at each time step of a time history are considered
• **Three types of patients** with respect to the attention and systematic care that they apply to their health care and to following the recommendations resulting from tests and visits with doctors, as well as following orderly the prescribed interventions: *Risk Averse, Risk Indifferent, Risk Taker*

• It is well a known, and unfortunately a well-documented fact, that many patients do not follow recommendations and interventions rigorously (and some not at all)

• Capture the different behavioral types of patients via weights representing the value (or significance) each patient places for being in each state of the model (Healthy, Pre-diabetic, Diabetic):

\[
V_1^i, V_2^i, V_3^i \quad V_1^i, V_2^i, V_3^i \in [0,1], \\
V_1^i + V_2^i + V_3^i = 1, \quad \forall i = 1, 2, ..., N_p
\]

• superscript \(i\) (we also use the superindex \(p_i\) to indicate patient \(i\)) is the index of a specific patient, while the subscript refers to the states 1, 2, 3
Patient Behavior Models

**Risk Averse**

\[ V^i_1 = 0.8, \ V^i_2 = 0.1, \ V^i_3 = 0.1 \]

**Risk Indifferent**

\[ V^i_1 = 0.6, \ V^i_2 = 0.2, \ V^i_3 = 0.2 \]

**Risk Taker**

\[ V^i_1 = 0.4, \ V^i_2 = 0.4, \ V^i_3 = 0.2 \]
• **Health Care Quality**: \( J_{hc} (i, m_i) \)

  first argument \( i \) is the index assigned to a specific patient, while the second argument \( m_i \) is the index assigned to a specific time history (the \( m^{th} \)) associated with patient \( i \)

• We compute and include in our quantitative model and evaluations the three counting statistics for each patient and each time history from our model:

  \[ O_1^i (m_i) = \text{number of periods, from } N_{T,\Delta} \text{ total, patient } i \text{ is at state 1 (i.e. is Healthy)} \]

  \[ O_2^i (m_i) = \text{number of periods, from } N_{T,\Delta} \text{ total, patient } i \text{ is at state 2 (i.e. is Pre-diabetic)} \]

  \[ O_3^i (m_i) = \text{number of periods, from } N_{T,\Delta} \text{ total, patient } i \text{ is at state 3 (i.e. is Diabetic)} \]

• The fractions

  \[ F_1^i (m_i) = O_1^i (m_i) / N_{T,\Delta}, \quad F_2^i (m_i) = O_2^i (m_i) / N_{T,\Delta}, \quad F_3^i (m_i) = O_3^i (m_i) / N_{T,\Delta}, \]

  as “probabilities” for patient \( i \) being in health state 1, 2, or 3, respectively

• **Health Care Quality metric**:

  \[ J_{hc} (i, m_i) = V_1^i \ast O_1^i (m_i) + V_2^i \ast O_2^i (m_i) + V_3^i \ast O_3^i (m_i) \]
• **Step 1**: Run the model for the number of patients, horizon, set of tests and interventions

• **Step 2**: Store results as triples of arrays: First contains sequence of health states, second sequence of tests used and third sequence of interventions used at each time step.

• **Step 3**: Using these arrays compute: health care costs, counting statistics and healthcare quality metric

• **Step 4**: Plot for each patient and time history pair, the pair of values:
  - vertical axis (y-axis) Health Care Cost and
  - horizontal axis (x-axis) Health Care Quality, and **determine Pareto points**
• Approach and methodology can be used to compute other metrics

\[Q_{3 \rightarrow 1}^{p_i}(m_{p_i}) = \text{Number of transitions from state 3 to state 1 in time-history } m_{p_i}\]

\[Q_{3 \rightarrow 2}^{p_i}(m_{p_i}) = \text{Number of transitions from state 3 to state 2 in time-history } m_{p_i}\]

\[Q_{2 \rightarrow 1}^{p_i}(m_{p_i}) = \text{Number of transitions from state 2 to state 1 in time-history } m_{p_i}\]

\[Q_{\text{good}}^{p_i}(m_{p_i}) = Q_{3 \rightarrow 1}^{p_i}(m_{p_i}) + Q_{3 \rightarrow 2}^{p_i}(m_{p_i}) + Q_{2 \rightarrow 1}^{p_i}(m_{p_i})\]

\[Q_{\text{tr}}^{p_i}(m_{p_i}) = [Q_{1 \rightarrow 1}^{p_i}(m_{p_i}), Q_{1 \rightarrow 2}^{p_i}(m_{p_i}), Q_{1 \rightarrow 3}^{p_i}(m_{p_i}), Q_{2 \rightarrow 1}^{p_i}(m_{p_i}), Q_{2 \rightarrow 2}^{p_i}(m_{p_i}), Q_{2 \rightarrow 3}^{p_i}(m_{p_i}), Q_{3 \rightarrow 1}^{p_i}(m_{p_i}), Q_{3 \rightarrow 2}^{p_i}(m_{p_i}), Q_{3 \rightarrow 3}^{p_i}(m_{p_i})]\]

• or create a reward vector

\[R = [R_{1 \rightarrow 1}, R_{1 \rightarrow 2}, R_{1 \rightarrow 3}, R_{2 \rightarrow 1}, R_{2 \rightarrow 2}, R_{2 \rightarrow 3}, R_{3 \rightarrow 1}, R_{3 \rightarrow 2}, R_{3 \rightarrow 3}]\]

and use it to create a Reward metric

\[R_{pi}(m_{p_i}) = R_{2 \rightarrow 1}Q_{2 \rightarrow 1}^{p_i}(m_{p_i}) + R_{3 \rightarrow 1}Q_{3 \rightarrow 1}^{p_i}(m_{p_i}) + R_{3 \rightarrow 2}Q_{3 \rightarrow 2}^{p_i}(m_{p_i})\]
Tradeoff Analysis as Reasoning Engine

• Reasoning Engine of the HCMS, based on these disease models
• First method, Evaluation by Monte Carlo Simulation (EMCS),
• The second method Fully Observable Multi-Criteria Optimization (FOMCO)
• The third Partially Observable Multi-Criteria Optimization (POMCO),
Output from the EMCS Method

- 32 runs for 10,000 patients

- Typical 2-D graphs produced by our EMCS based Reasoning Engine that gives the Pareto frontier for a typical risk averse and risk indifferent patients (Pareto points in red)
• 9 runs for 100,000 patients

• Typical 3-D graphs produced by our EMCS based Reasoning Engine that gives the Pareto frontier for a typical risk averse and risk indifferent patients (Pareto points in red)
• Health Care metric is the same
• Health Care Quality metric is now:

\[ E[J_{hc}(i, m_i)] = \bar{J}_{hc}(i, \mu, u) = \sum_{m=1}^{n_x} \sum_{t=0}^{N_{T,\Delta}} V_m \Pr\{x(t) = m | \mu, u\} \]

• Investigated both scalarization method and the \( \varepsilon \)-method
• Results were similar, but scalarization was much faster
• Normalized metrics to avoid numerical range problems
• Normalized scalarization method (FOMCO-SN) solves the optimization problem:

\[
\max_{\mu, u} \left[ \lambda \bar{J}_{hc}^{r,n}(i, \mu, u) + (1 - \lambda)(-C_{total}^{\mu,n}(i, \mu, u)) \right]
\]

• \( \lambda \in (0, 1) \) The pair \((\mu^*, u^*)\) is a Pareto point
• Used **Dynamic Programming** to solve it
• 32 runs for 10,000 patients

• Typical 2-D graphs produced by our FOMCO-SN Reasoning Engine that gives the Pareto frontier for a typical risk averse and risk indifferent patients (Pareto points in red)
Collect and Analyze Available Information

- From medical databases, disease models, clinical databases, human agents
- Through information and communication technologies
- Or from knowledge bases and ideas from multiple disciplines, that are relevant to this complex system problem
- It happens and is assessed continuously and “learns” – c.f. efforts by the IBM Watson team
<table>
<thead>
<tr>
<th>Use case ID</th>
<th>Use Case Name</th>
<th>Primary Actor</th>
<th>Scope</th>
<th>Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Receive test</td>
<td>Population</td>
<td>in</td>
<td>High</td>
</tr>
<tr>
<td>2</td>
<td>Receive intervention</td>
<td>population</td>
<td>in</td>
<td>high</td>
</tr>
<tr>
<td>3</td>
<td>Provide test</td>
<td>lab</td>
<td>in</td>
<td>med</td>
</tr>
<tr>
<td>4</td>
<td>Provide intervention</td>
<td>Doctors nurses</td>
<td>in</td>
<td>med</td>
</tr>
<tr>
<td>5</td>
<td>Provide transition metric</td>
<td>hospital</td>
<td>in</td>
<td>high</td>
</tr>
</tbody>
</table>
## Use Case 4

<table>
<thead>
<tr>
<th>Use case element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use case number</td>
<td>4</td>
</tr>
<tr>
<td>Application</td>
<td>MBSE for Diabetes Type two (Mellitus)</td>
</tr>
<tr>
<td>Use case Name</td>
<td>Doctor Provides Intervention</td>
</tr>
<tr>
<td>Use case Description</td>
<td>Doctor suggests test and based on the interpretation of the test results suggests an intervention</td>
</tr>
<tr>
<td>Primary Actor</td>
<td>Doctor</td>
</tr>
<tr>
<td>Precondition</td>
<td>Doctor is informed about Diabetes Mellitus health states, and has received information about the transition probabilities matrix</td>
</tr>
<tr>
<td>Trigger</td>
<td>The results from Diabetes Mellitus test are positive and the state of the patient results in a recommendation to receive one of the 10 suggested interventions</td>
</tr>
</tbody>
</table>
| **Basic Flow**   | 1. Doctor receives test results from patient and the results map the patient’s health state in the 2nd or 3rd state  
2. Doctor consults the guidelines, the health state definition and the state transition matrix and suggests an intervention  
3. Doctor informs hospital for the period of the therapy  
4. Doctor assigns a nurse to patient for a period until the next screening test period for the patient |
| **Alternate Flows** | 1. Hospital receives the results from lab  
2. Hospital assigns a doctor to interpreting the results, consult the patient  
3. Doctor makes a decision and informs the patient to follow a specific intervention  
4. Doctor informs hospital about his health strategy |
Structure Diagram of HCMS for Diabetes 2
Structure Diagram of part of the EMCS Subsystem of the Reasoning Engine of HCMS
Behavior Diagram of Reasoning Engine Subsystem of HCMS
Behavior Diagram of EMCS Subsystem of Reasoning Engine
Requirements Diagram of EMCS Subsystem

Constructed Requirements Tables and Traceability Matrices
These capabilities and analytics derive from the MBSE methodology applied: linkage of efficient and powerful tradeoff analysis methods and algorithms for design space exploration, with effective system dynamic models of disease progression that incorporate tests, interventions, and many system and system-environment parameters.

A key output from our MBSE system, are the Pareto points that describe succinctly the relative value of treatments and tests vs the overall health care quality of a patient's time history.

Generated the following data sets:
(a) 100,000 patients, 9 runs, with 3 metrics (Performance, Cost, Reward);
(b) 10,000 patients, 32 runs with 2 metrics (Performance, Cost).
Examples of Questions

▪ One can compare tests and interventions.
▪ Which test for each type of patient has the best impact on the patient time history?
▪ How one can use the data to try to evaluate this type of a question? For example one can select from the data the time histories where there was a reversal of the disease progression. That is the patient became diabetic at some time in the horizon we use and then became healthy in the end of the horizon. One can rank this subset of the time histories according to the time steps it took to reverse the disease. The smaller number it took the better the health care represented in this time series.
▪ Can you identify the tests that were used in the best three subsets of such time histories?
<table>
<thead>
<tr>
<th></th>
<th>Risk Averse</th>
<th>Risk Indifferent</th>
<th>Risk Taker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Health Performance</td>
<td>Cost</td>
<td>Health Performance</td>
</tr>
<tr>
<td>Top 20% percentiles</td>
<td>0.736081</td>
<td>2577.8</td>
<td>0.51180556</td>
</tr>
<tr>
<td>Health Perf., Cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average of</td>
<td>0.81251</td>
<td>2506.111</td>
<td>0.53248</td>
</tr>
<tr>
<td>Health Perf., Cost,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>over $P_{V_i}^{HHP20%}$</td>
<td>0.579465</td>
<td>2769.3</td>
<td>0.44885666</td>
</tr>
</tbody>
</table>

Comparison of Health Performance vs Costs for subsets of Pareto points clustered by patient type and percentile statistics of Health Performance and/or Cost
### Decision Making and Analytics Capabilities

Comparison of Health Performance vs Costs vs Reward for subsets of Pareto points clustered by patient type and percentile statistics of Cost

<table>
<thead>
<tr>
<th>Type of patient</th>
<th>Averages</th>
<th>Cost</th>
<th>Reward</th>
<th>H.C P</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>No Thresholds</td>
<td>2802.042</td>
<td>0.674</td>
<td>0.489</td>
</tr>
<tr>
<td>V1</td>
<td>20%</td>
<td>2381.882</td>
<td>1.076</td>
<td>0.722</td>
</tr>
<tr>
<td>V1</td>
<td>10%</td>
<td>2294.143</td>
<td>1.134</td>
<td>0.766</td>
</tr>
<tr>
<td>V1</td>
<td>90%</td>
<td>2714.318</td>
<td>0.735</td>
<td>0.765</td>
</tr>
<tr>
<td>V2</td>
<td>No Threshold</td>
<td>2840.575</td>
<td>0.648</td>
<td>0.490</td>
</tr>
<tr>
<td>V2</td>
<td>20%</td>
<td>2416.192</td>
<td>1.028</td>
<td>0.696</td>
</tr>
<tr>
<td>V2</td>
<td>10%</td>
<td>2344.154</td>
<td>1.079</td>
<td>0.737</td>
</tr>
<tr>
<td>V2</td>
<td>90%</td>
<td>2756.184</td>
<td>0.704</td>
<td>0.523</td>
</tr>
<tr>
<td>V3</td>
<td>No threshold</td>
<td>2817.58</td>
<td>0.663</td>
<td>0.485</td>
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<td>20%</td>
<td>2405.583</td>
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<td>0.697</td>
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<tr>
<td>V3</td>
<td>10%</td>
<td>2335.583</td>
<td>1.072</td>
<td>0.737</td>
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<tr>
<td>V3</td>
<td>90%</td>
<td>2734.252</td>
<td>0.724</td>
<td>0.512</td>
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</table>
## Decision Making and Analytics Capabilities

<table>
<thead>
<tr>
<th>Model and Method used</th>
<th>Patient type</th>
<th>Interventions</th>
<th>Number of times implemented specific intervention</th>
<th>Number of improvement times</th>
<th>Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMCS (2 variables)</td>
<td>V1</td>
<td>6</td>
<td>711</td>
<td>129</td>
<td>18%</td>
</tr>
<tr>
<td>EMCS (2 variables)</td>
<td>V2</td>
<td>8</td>
<td>26</td>
<td>6</td>
<td>23%</td>
</tr>
<tr>
<td>EMCS (2 variables)</td>
<td>V3</td>
<td>8</td>
<td>28</td>
<td>6</td>
<td>21%</td>
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<tr>
<td>EMCS (3 variables)</td>
<td>V1</td>
<td>7</td>
<td>53</td>
<td>19</td>
<td>36%</td>
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<td>V2</td>
<td>8</td>
<td>36</td>
<td>16</td>
<td>44%</td>
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<tr>
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<td>V3</td>
<td>8</td>
<td>38</td>
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<td>FOMCO</td>
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<td>53%</td>
</tr>
<tr>
<td>FOMCO</td>
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<tr>
<td>FOMCO</td>
<td>V3</td>
<td>6</td>
<td>n/a</td>
<td>n/a</td>
<td>75%</td>
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</tbody>
</table>

Best performed intervention for V1, V2, and V3 risk type of patients
## Evaluation of diagnostic test for specific improved health state transitions, for each patient type

<table>
<thead>
<tr>
<th>Type of patient</th>
<th>Improvement between states a to b</th>
<th>Type of test</th>
<th>Times of intervention used in the therapy</th>
<th>Times of improvement</th>
<th>Efficiency</th>
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</thead>
<tbody>
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<td>Risk averse</td>
<td>2 to 1</td>
<td>2</td>
<td>769</td>
<td>80</td>
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<tr>
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<td>1</td>
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<td>89</td>
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<tr>
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<td>3 to 2</td>
<td>3</td>
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<tr>
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<td>3 to 1</td>
<td>1</td>
<td>690</td>
<td>12</td>
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<tr>
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<td>3 to 1</td>
<td>3</td>
<td>503</td>
<td>9</td>
<td>2%</td>
</tr>
<tr>
<td>Risk taker</td>
<td>2 to 1</td>
<td>1</td>
<td>689</td>
<td>87</td>
<td>13%</td>
</tr>
<tr>
<td>Risk taker</td>
<td>3 to 2</td>
<td>2</td>
<td>681</td>
<td>27</td>
<td>4%</td>
</tr>
<tr>
<td>Risk taker</td>
<td>3 to 2</td>
<td>3</td>
<td>493</td>
<td>22</td>
<td>4%</td>
</tr>
<tr>
<td>Risk taker</td>
<td>3 to 1</td>
<td>1</td>
<td>689</td>
<td>14</td>
<td>2%</td>
</tr>
<tr>
<td>Risk taker</td>
<td>3 to 1</td>
<td>2</td>
<td>681</td>
<td>13</td>
<td>2%</td>
</tr>
<tr>
<td>Risk taker</td>
<td>3 to 1</td>
<td>3</td>
<td>493</td>
<td>10</td>
<td>2%</td>
</tr>
</tbody>
</table>
Comparison of two Methods

- **Key output** form our Reasoning Engine of a HCMS, are the **Pareto points** (or **Pareto frontiers**) that describe succinctly the relative value of treatments and tests vs the overall health care quality of a patient’s time history.
- Running EMCS with two metrics (and 2-D graphs) for 10,000 patients and 32 runs, took for the whole experiment 783 sec.
- Running ECMS with three metrics (and 3-D graphs) for 100,000 patients took for the whole experiment 1,385 sec.
- FOMCO outputs directly the Pareto-points and other related information and is **very fast -- two or more orders faster time**.
- For the same problems our Second Method (FOMCO-SN) took only 2.36 sec on the same laptop.
- For the same problems POMCO implementations took only twice the time of FOMCO.
- The Pareto points and frontiers computed are very similar to those computed with EMCS.
• Investigated the value of Model Based System Engineering (MBSE), as a basis for a framework for the development of Health Care Management Systems (HCMS) for chronic diseases
• Used Diabetes Mellitus as a driving specific case
• Developed such a framework and demonstrated the value of a MBSE approach
• **Focused on** the development and evaluation of the **Reasoning Engine component** of a HCMS
• **Showed that tradeoff analysis methods linked with integrated models of disease progress** that incorporate diagnostic tests and interventions provide a powerful foundation for such a Reasoning Engine, as it allows the investigation of a rich variety of “what-if” type questions
• Following modern MBSE, developed Use Case, Structure, Behavior, Requirements Diagrams and Requirements Traceability Matrix for components of the Reasoning Engine
• Developed a Controlled Markov Chain model for the progression of Diabetes Mellitus, with three states, three diagnostic tests and ten interventions
Conclusions and Future Directions

• Developed several metrics in our new framework and focused on two: Health Care Quality and Cost metrics
• Considered three types of patient behavior: Risk Averse, Risk Indifferent and Risk Taker
• Developed two basic methods for tradeoff analysis and developed, implemented and tested the associated algorithms, that were incorporated in the Reasoning engine of the HCMS
• Evaluation by Monte Carlo Simulation (EMCS) generates all possible patient time histories with all possible test and intervention sequences, and then computes Pareto points by direct comparison.
• Fully Observable Multi-criteria Optimization (FOMCO) is based on the use of Dynamic Programming (DP) for multi-criteria optimization.
• **Lack of real data a problem and limitation in our studies**
• Currently finalizing POMCO (partially observed case)
• The model we developed is stochastic. So how should we compare the cost vs the health care value?
• **Can these results be used for “learning”** and then used to improve the model and the medical recommendations? How should we implement this feedback?
A Model-Based Systems Engineering Framework for Healthcare Management of an Intensive Care Unit (ICU)
MBSE uses Models to Identify and Evaluate Improvements

Healthcare operations

Monitor performance, generate ideas, implement changes

Build models, analyze operations, predict changes
A Cost and Revenue Model can Evaluate Financial Impact of Changes

• **Focus**: treatment of patients with severe traumatic brain injury (STBI) in an intensive care unit (ICU).

• **Approach**:
  – Identify the phases (states) of the patient’s condition;
  – Estimate the one-time and recurring costs (staffing, medications, procedures, supplies) associated with each state;
  – Model the progression of the condition and estimate time in each state;
  – Combine with unit fixed costs (infrastructure);
  – Determine revenue (from payers) associated with patients of this type.

• **Example**: how would using an intra-abdominal pressure (IAP) measuring device, which should reduce the occurrence of complications, affect patient length of stay, the costs (expensive monitor, but fewer complications), and the revenue (more patients per year)?
Using **System Architecture Model** as a MODEL Integration Framework

**MATLAB, Scheduler, COQ, Planning, Fault Analysis, Cost Estimation**

**Geometry-Layout**
- AUTOCAD, Architecture,

**Patient, Equipment, Personnel**
- (Nurses-Doctors)

**VMS, UPPALL, IF, BIP, COQ**

**UML, UPPALL ARTIST, MAPLE, Policies-Rules**
Analysis of Intensive Care Unit (ICU)

- Efficient and cost effective operation of an ICU
- Dispatcher allocates arriving patients to the appropriate bed.
- Patients are modeled as classes of discrete phase type distributions.
- Each state of the patient chain is associated with an associated cost vector.
- Blocking probability given by the probability that all the beds are full.
- Expected cost per unit time evaluated as a function of the stationary distribution.
- Major challenge – exponential components due to huge states set.
Arrival Machine

- Only one parameter $r$, the probability of an arrival occurring in the current timeslot.
- Behavior independent of other chains.
- Exponential arrivals reported as a good model in literature, but more complex distributions can be accommodated.
Dispatch

• Having $2^N$ states, corresponding to the occupied / unoccupied status of each bed.

• When Arrival is in the Arrival state:
  – If there is an unoccupied bed switches the status of the bed to occupied.
  – Otherwise rejects a patient (this is rare, but can occur in practice).

• When an occupied bed is in the Discharge state, switches the status of the bed to unoccupied.

• Has its own two state variable reflecting bed state for each bed but does not directly alter the state of the Bed machines.
- Patient class modeled after arrival to bed by a probability mass function.
- In addition to patient states, Bed has states **unoccupied** and **discharge**.

$s$ is information from Dispatch. It is 0 if this bed is **unoccupied** and 1 if this bed is **occupied**.

† These are exiting transitions from the classes with well defined probabilities possibly representing multiple exit paths.
Patient Class

- Discrete phase type distributions.
- Time evolving Bayesian Network (reducible to finite state Markov chain).
- Each state associated with some cost vector.

UMMC STC protocols can be used here, but need **further data on transition probabilities, timing and cost information**.
Patient Progression Model

- Finite state Markov chain
- States associated with patient clinical stage
- Each state associated with some cost vector
• [Litvak 2009] describes the cost of nursing as dependent on the occupancy in the following manner.
  – Nurses are staffed to maintain a constant ratio with the varying ICU occupancy.
  – Nurses may be either
    • roster nurses, who are constantly employed, independent of demand
    • or supplementary nurses, who ~4x more.

• The stationary occupancy distribution can be computed from Dispatch states.

• Each occupancy level is associated with a cost based on the above so expected cost can be computed from the occupancy distribution.

• Nurse model can depend on several other parameters
Cost Evaluation

- Determine the stationary distribution of the Markov chain, giving the probabilities of each state
- This leads to the expected cost
- *Alternatively* we can use “operational” analysis, i.e. non stochastic models – this allows time varying models
- Operational analysis also links cost models with patient states and progression
State Space Explosion

• Composition of Markov chains creates enormous state spaces (from patients, nurses, doctors, equipment …)

• For example
  – Assume we are composing $N$ Markov chains.
  – Assume each chain has $|Q|$ states.
  – There are then $|Q|^N$ states in the composed machine.

• This is an exponential dependence between the number of components and the complexity the resulting system.

• Storing or performing any computations on such large systems is difficult.
Systems Engineering Approach to Complexity Management

- Use the *local structure and separation of interests* to perform calculations.

- Abstraction *hides information* that is irrelevant to current queries resulting in simpler models.

- Hierarchy an effect of tree topologies

- **Summary propagation** over semirings entails many problems, optimization, logical and probabilistic inference, AI, …

- A methodology from reasoning / planning / decision making

- Can be used to combine states when performing a query on the model (e.g., What is the nurse utilization? What is the expected cost?)
Complexity of System Analysis

- Decomposition: a fundamental problem in systems engineering.
- Decomposition methods from software community
  - Computation is exponential in \textit{treewidth} and linear in overall system size
- Generalize this to \textit{structured} networks of communicating dynamic systems
  - Physical in nature: sparsity and structure in communication graph, implying low treewidth.

Dynamic Bayesian networks (DBNs)

- DBNs model complex dynamic systems effectively.
- The linear scaling in system size means that very large systems can be analyzed as long as they are sufficiently sparse and well structured.
- Summation (projection) and product (composition)
Dynamic Bayesian Networks

• A conceptual example of a dynamic Bayesian network
  – Tree
  – Node

• Steps
  1. Analyze a component a time
  2. Take local products and projecting out unnecessary intermediate information
  3. Use summary propagation

• Summary propagation: a methodical approach to analyze a system using mathematically defined abstraction and composition operations
Abstraction as a Tool for Complexity Management

• Summary propagation is a technique for computing the expression $\sum \cdots \sum f(X)$ where $f(X)$ is a product having a special form.

• Abstraction occurs when lower level details of the model are aggregated away. The summation operator is an aggregation technique not restricted to addition of real numbers.

• We assume that $f(X)$ is a tree -- In the current model, this does apply.
Factor Graph Representation

• As mentioned on the previous slide, $f(X)$ is a product and it is assumed to be a tree.

$$f(X) = f_A(x_1)f_B(x_2)f_C(x_1, x_2, x_3)f_D(x_3, x_4)f_E(x_3, x_5)$$
• The graphs below are only graphical reorganizations of the previous graph.
Summary Propagation

\[ g(x_1, \ldots, x_5) = f_A(x_1) f_B(x_2) f_C(x_1, x_2, x_3) f_D(x_3, x_4) f_E(x_3, x_5) \]

Compute the **marginal** function \( g_1(x_1) = \sum_{\sim \{x_1\}} g(x_1, \ldots, x_5) \)

\[ g_1(x_1) = f_A(x_1) \times \sum_{\sim \{x_1\}} \left( f_B(x_2) f_C(x_1, x_2, x_3) \times \left( \sum_{\sim \{x_3\}} f_D(x_3, x_4) \right) \times \left( \sum_{\sim \{x_3\}} f_E(x_3, x_5) \right) \right) \]

(a) Local computation  (b) Factor graph  (c) Expression tree
\[ f(\mathcal{X}) = \bigotimes_{k=1}^{m} f_k(\mathcal{X}_k), \text{ where } \mathcal{X} = \{x_1, \ldots, x_N\} \text{ and } \mathcal{X}_i \subseteq \mathcal{X} \]

\[ \bigoplus_{x_1 \in D_1} \ldots \bigoplus_{x_N \in D_N} f(\mathcal{X}) \]
Our Approach in General

• Complexity

\[
\text{compute } \bigoplus_{x_1 \in D_1} \cdots \bigoplus_{x_N \in D_N} f(\mathcal{X}) \nRightarrow \nRightarrow
\text{explore all } \langle x_1, \ldots, x_N \rangle \text{ combinations}
\]

• Construct the factor graph for \( f(\mathcal{X}) \)
  – Tree \(\Rightarrow\) Summary propagation
  – Graph \(\Rightarrow\) Tree \(\Rightarrow\) Summary propagation

Our tool: transform a general graph into a tree
Markov Chains

- Each Markov chain in the original model comprises one variable.
- The Markov chain, described as a transition matrix, maps time traces of the variables to a probability.
- Gives rise to a factor graph that looks something like what’s on the left.

The factor graph is *loopy* even though the system topology is a tree!
Traces as Cliques in Markov Chains

Consider a simpler topology for example. The transition behavior is shown below.

- Treating each trace as a variable restores the original tree topology.
- The potential functions are weighted relations on sets of traces.
Labeled Markov Chain Formalism

- Every state of the Markov Chain is associated with a label or vector of labels in general.
- Every component of the label defines a partition of the states.
- Label may be associated with cost or with control state.

![Diagram of a labeled Markov chain](image)

Use c to split b.

1. 1, 2 lead to c with p=1
2. 3 leads to c with p=0.5
3. 4 leads to c with p=0
Product and Summation Operations

- The product of two Markov chains is the natural composition.
  - Form every possible pairwise combination of states.
  - Label vectors are grouped into a set
    - For example \{\langle a, a \rangle, \langle \alpha, \alpha \rangle \}.
  - Transition probabilities are given by the product.
    - Consistency (summing to one) of products can be proven to be a consequence of consistency of factors.
- The summation over a Markov chain is the elimination of a label.
  - A Markov chain is a mapping from initial state $\times$ traces of labels to probabilities.
  - Removing a label means summing the probabilities of traces that become indistinguishable.
Intensive Care Unit (ICU) Model

- Discrete Markov chain consisting of communicating subchains.
- **Time is discretized.**
- Interarrival times are **geometrically distributed.**
- Dispatcher allocates arriving patients to the appropriate bed.
- Patients are modeled as classes of discrete phase type distributions.
- Each state of the patient chain is associated with an **associated cost vector.**
- **Blocking probability** given by the probability that all the beds are full.
- **Expected cost per unit time** evaluated as a function of the **stationary distribution.**
Utilization Querying using Summary Propagation

- To answer the question about nurse overflow, we label the dispatch chain with utilization levels.
- We sum out, one at a time, via summary propagation all other labels (this discards things like costs, patient state labels, etc.)
- We are left with a Markov chain that moves only over utilizations which we can solve for the stationary distribution.
We include a cost label on Bed\textsubscript{1}.

Apply summary propagation.

The result is a Markov chain moving between costs on a single bed.

By symmetry, we can multiply by $N$ to get the cost for the ICU.
Implementation

• The model is specified using extended UML activity diagrams or a DSL implemented with ANTLR.

• We use the export function of Papyrus to produce XMI which is then translated using XSLT to another format for our tool.
Implementation (cont.)

Dynamic ICU Model

Multidimensional Markov Chain (MMC)

described using

UML Profile

UML Activity Diagram

Domain Specific Language (DSL)

Analysis Engine

Logical Inference Engine (Java)

(Multiple | Binary) Decision Diagram

ROMDD / MTBDD

Resolution Methods

Numerical Analysis (Matlab)

DOM parsed

exports

translates into

DTD Specified XML

XML Metadata Interchange (XMI)

XSLT (Xalan)
Multi-dimension Markov Chain Patient Progression Model

- UML2 for Eclipse is used to describe the Markov chain.
- We parse the XMI exported from this tool.
- This *should* mean that we can easily parse the XMI generated by other UML tools.
Results

- Measure the overflow probability, the occupancy and the expected cost.

Stationary distribution of one bed

DBN used to query occupancy – observer added

Stationary occupancy distribution as observed by occupancy observer
### Cost Components for each state

Values are daily cost of caring for patient in that state.

<table>
<thead>
<tr>
<th>Cost Components</th>
<th>Init LOW</th>
<th>HIGH ICP</th>
<th>LOW ICP</th>
<th>Other</th>
</tr>
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<tr>
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<tr>
<td><strong>Taxes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Property</td>
<td>38.71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interest</td>
<td>21.65</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ventilation (incl. cpns, masks, NIV)</td>
<td>38.71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salaries</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nursing</td>
<td>1134.5</td>
<td>1134.5</td>
<td>1134.5</td>
<td></td>
</tr>
<tr>
<td>Medical Staff</td>
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<td>757.75</td>
<td>757.75</td>
<td></td>
</tr>
<tr>
<td>Professional allied to medicine</td>
<td>116.91</td>
<td>116.91</td>
<td>116.91</td>
<td></td>
</tr>
<tr>
<td><strong>Non HCP Cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing administration</td>
<td>25.98</td>
<td>25.98</td>
<td>25.98</td>
<td></td>
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<tr>
<td>Maintenance</td>
<td>8.66</td>
<td>8.66</td>
<td>8.66</td>
<td></td>
</tr>
<tr>
<td>Catering</td>
<td>4.33</td>
<td>4.33</td>
<td>4.33</td>
<td></td>
</tr>
<tr>
<td>Laundry</td>
<td>4.33</td>
<td>4.33</td>
<td>4.33</td>
<td></td>
</tr>
<tr>
<td>General Admin</td>
<td>17.32</td>
<td>17.32</td>
<td>17.32</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3953.33</td>
<td>4330.00</td>
<td>3953.33</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Spreadsheet Implementation (cont.)

- **Inputs to Cost and Revenue Model**
  - **Fraction of time each bed is in each state**
    - Init Low: 0.4389
    - High ICP: 0.0944
    - Low ICP: 0.0661
    - Other: 0.4006
  - **Number of beds in unit**: 3 beds
  - **Patient arrival rate (expected number per day)**: 0.46
  - **Average revenue per arrival**: $31,353
  - **Period length**: 30 days
  - **Fraction of time for each occupancy level**
    - 0: 0.0566
    - 1: 0.2942
    - 2: 0.4438
    - 3: 0.2054

- **Occupancy**
  - Expected number of occupied beds: 1.80
  - Expected utilization of each bed: 0.60

- **Financial Performance**
  - Expected revenue per period: $432,671.40
  - Expected cost per period: $216,466.53
  - Expected profit per period: $216,204.87

- **Snapshot of computed output about cost**
Use of UMMC data

- Approximately 600 patients with severe traumatic brain injury who were in the Shock Trauma Center Neurotrauma critical care unit (NTCC) entering on or after January 1, 2010, and departing on or before June 30, 2011.
- These patients have ICD 9 codes in the range 851.0 through 854.9, which correspond to traumatic brain injury, and an Abbreviated Injury Scale (AIS) code that is at least 4.
- Data from patient medical records will provide frequency and timing of medical procedures and medications and measurements of patient condition variables.
- Data from financial system will provide revenue, direct variable, fixed, and indirect costs per patient.
State reduction achieved

Number of states as a fcn of number of steps in inference
Sawtooth pattern is the result of the project-compose pattern

Appropriate definition of summation and multiplication yields significant reductions in this problem.
Summary Product Works

- It reduces the number of states of the machines tested by several fold.
  - One ICU model tested was reduced from 17496 to 3071 states.
  - The reduction was achieved this primarily by symmetry reduction.
  - The models are input as products of identical patient state machines.
  - This is simple for the user to input, but leads to redundancy in the model.
  - We verified the stationary distribution computed by the eigenvector of the reduced machine against Monte Carlo simulation and the results were very close.

- As anticipated, the occupancy query is slightly more complex than the others. The blocking probability query and the cost query are identical except in the last step because the queries are the same except that the blocking probability query projects out the last patient’s cost information while the cost query does not.
Possible future studies

- Currently, the STC does not routinely monitor the intraabdominal pressure (IAP) of STBI patients.
- Intraabdominal hypertension (IAH) can cause increases in intracranial pressure (ICP).
- A pressure monitoring kit with a pressure transducer is approximately $15.
- How much would it cost to monitor the IAP of every STBI patient?
- Would IAP monitoring lead to interventions that reduce IAP and avoid elevated ICP?
- How would this affect patient length-of-stay?
- How would this impact total cost and revenue of unit?
Future Work

• Models for broader set of patients – in collaboration with Med School and Trauma Center
• Models of patient treatment processes
• Models for nursing and other personnel
• Models of equipment/instruments and consumable med supplies
• Develop an integrated (couple model of the above)
• NEED DATA to POPULATE these
• Develop more detailed cost, revenue models
• Link these models to the unit level models a above
• DATA NEEDED HERE as well
• Apply to more complex and real life use cases and evaluate the impact and recommendations
• Develop a more complete implementation to handle large problems
• Link to ML and AI methods and software
A Systems Biology Model for Alzheimer’s Disease
Systems Biology

Goal of systems biology:
To integrate information on:
- Genes
- Proteins
- Molecular interactions
- Metabolism
- Other biological systems/networks

... in order to improve our understanding of the physiology of cells and organisms.

SYSTEMS BIOLOGY – THE ULTIMATE SYSTEMS CHALLENGE

Integrative approach in which scientists study pathways and networks will touch all areas of biology, including drug discovery.

Requires
- Quantitative models of properties of components and their interactions
- Computational methods to manage complexity
What is Alzheimer’s Disease (AD)?

- Memory loss
- Behavioral abnormalities
- Decreased brain volume
- Beta amyloid & ApoE, Tau proteins pathology
Pathological Characteristics

• ↑ levels of:
  – Aβ
  – Inflammatory markers (IL-1, TNFα)

• Abnormalities in:
  – lipid metabolism
  – energy metabolism

Extensive:
  – Neuron loss
  – Neuroinflammation
  – ↑ Aβ

Dysfunction in:
  – Cholesterol metabolism
  – mitochondria

Mild AD (2-4 yrs)

• ↑ Aβ
• Mild neuron/synapse loss
• Continued ↑ in IL-1, abnormal lipids
• NFTs/τ pathology

Moderate AD (2-10 yrs)

Severe AD (1-3+ yrs)
Motivation for Studying AD....

- Most common form of dementia
  (60-80% of all dementias)
- **1 in 8** individuals over 65 affected
- Current treatment costs: Over $140 billion/yr
- Projected # affected by 2050: 12 million Americans
  (only 6 million are currently affected)

Currently no treatment/unknown pathogenesis
Our Contributions

• Studied effect of simvastatin treatment on LRP and ApoE levels, in addition to changes in Aβ
• Developed a mathematical model that integrates energy & lipid metabolism, the inflammatory response & expression of key proteins
• Model results were verified using results from experiments
**Amyloid Cascade Hypothesis**

- **Evidence for:**
  - High Aβ toxic to neurons & synapses
  - Aβ activates inflammation & reactive astrocytes
- **Evidence against:**
  - Location of plaques does not correspond to neuron/synapse loss \(^1\)
  - Oligomeric Aβ more toxic than plaques
  - Decrease in cognitive function before plaque formation

**Inflammation**

- **Evidence for:**
  - Key characteristic of AD
  - Microglial activation occurs early in pathogenesis \(^2\)
  - NSAIDs reduce AD risk \(^3,4\)
- **Evidence against:**
  - NSAIDS cannot stop or cure AD

**Zlokovic Hypothesis**

- **Evidence for:**
  - RAGE expression levels increase, LRP1 decrease with aging
- **Evidence against:**
  - Aβ plaques are neuronally-derived
  - Increase in RAGE not unique to AD

**Cholesterol Hypothesis**

- **Evidence for:**
  - Epidemiological & experimntal data shows altered cholesterol metabolism
  - Cholesterol modulates Aβ
  - Interacts w/ inflammatory pathway
- **Evidence against:**
  - Cholesterol alterations not unique to AD
  - Statin treatment not efficacious to ↓ Aβ
**Forefront of AD Research**

*Interplay between lipid metabolism & inflammation*

**apoE:**
- Coordinates re-distribution of cholesterol.

**IL-1:**
- Pro-inflammatory cytokine.
- Expressed by microglia in response to:
  - Stress
  - ↑ Aβ
  - ↑ Glutamate
- Functions:
  - ↑ neurotransmitter turnover rate
  - ↓ activation threshold for HPA axis
  - Causes hypoglycemia
  - ↑ Acetylcholinesterase activity → ↓ ACh
- Synapse formation
- Co-localizes w/ Aβ plaques

**LRP-1:**
- Transport of Aβ to blood
- Transfer of cholesterol to neurons & other CNS cells via apoE carrier binding
Previous Math Models for AD

• Kinetic models of Aβ fibrillogenesis\textsuperscript{1, 2}
• Chemotactic signaling in AD\textsuperscript{3,4}
• Cellular network model\textsuperscript{5}
• Precedence to use networks in biology\textsuperscript{6}

No previously developed model has used systems biology nor multi-level networks to study AD

**Specific Aim 1:**

1) Study the effect of simvastatin on:
   - level of plasma & brain cholesterol
   - Aβ, ApoE & LRP expression levels

2) Trends from these experiments will be used to help designate network connectivity.
Hypothesis 1

• **Objective:** To measure the level of Aβ following a chronic decrease in brain cholesterol levels

• **Animals:**
  – C57BLK mice on a mixed background (n= 44)
  – B6C3-Tg(APPswe, PSEN1dE9)85Dbo/J mice (n=13)
  – Mice ages: 29-59 weeks of age (plaques appear at 24 weeks)

• **Treatment**, short-term (2 week) or long-term (8 weeks):
  • Control: Tween-20 in peanut butter, orally, once/day
  • Experimental: simvastatin (100 mg/kg) in Tween-20 + peanut butter, orally, once/day
**Hypothesis 1**

**Methods:**
- Obtain plasma/brains & assay:
  - Aβ/APP levels: Western blot
  - Aβ plaque density: Immunohistochemistry
  - Cholesterol levels: Amplex Red Cholesterol Kit

**Expected Results for simvastatin-treated mice:**
- ↓brain cholesterol
- ↑brain Aβ
Conclusion on Hypothesis 1: Treatment of mice with simvastatin led to a statistically significant increase in Aβ plaque density as measured by IHC.
Hypothesis 2

- **Objective**: To measure expression levels of LRP-1 & ApoE following a decrease in brain cholesterol, and to quantify the distribution of these proteins within different cell types
- **Methods**:
  - Same animal experimental design as H1
  - Obtain brains & assay:
    - LRP-1 & apoE levels: Western blot
    - Distribution of proteins: IHC
- **Expected Results**:
  - ↓ LRP-1 expression in AD group more significant
  - ↑ ApoE in treated groups
Conclusion on Hypothesis 2: Data suggests that 2 week treatment of mice with simvastatin leads to ↑ ApoE & LRP, ↑ trend for 8 week treatment.
Specific Aim 2: To develop a systems biology mathematical model for Alzheimer’s disease to help study the roles of cholesterol, LRP, ApoE and inflammation in disease pathogenesis.
Two-level hierarchal network used to model our system. In this model, the brain has been modeled as a two-level hierarchal network. The higher level consists of the cellular network (neurons (N), astrocytes (A), microglia (M) and brain endothelial cells (EC). Each of these cell types also has a sub-cellular network that models lipid metabolism (L), protein metabolism (P), energy metabolism (M) and regulatory pathways (R).
Directed Graph for Neurons

- **dopamine**
- **serotonin**
- **glucose**
- **glycolysis**
- **pyruvate**
- **PhosphoChol**
- **choline**
- **AcetylCoA**
- **TCA**
- **MalonylCoA**
- **IL-1**
- **Aβ**
- **APP**
- **sAPPa**
- **cholesterol**
- **24SOH**
- **LRP**
Overall Conclusions

• Studied effect of simvastatin treatment on LRP and ApoE levels, in addition to changes in Aβ
  – Showed ↑ Aβ, ApoE & LRP in response to simvastatin treatment (↓ brain cholesterol)
• Developed a mathematical model that integrates energy & lipid metabolism, the inflammatory response & expression of key proteins
  – Model showed:
    • Elevated levels of ApoE, LRP & Aβ following inflammatory pulse
    • ↑ Aβ when glucose ↓
    • ↑ Aβ when HmgCoA → mevalonate ↓
• Model results were verified using results from experiments
  – Model results agreed both w/ experimental work & literature
Systems Biology and MBSE for Lab-on-a Chip
Revolutionizing Drug Manufacturing: Organ-on-a Chip -- Biochips

Wyss-Lung on a chip -- 2010

Wyss-Gut on a chip -- 2012
Revolutionizing Drug Manufacturing: Organ-on-a Chip – Biochips -- 2023

Organ-on-a-Chip Technology Reaches New Dimensions with Chip-A1™
Novel features of Chip-A1 include:

- An accessible culture chamber that enables users to create extracellular matrices up to 3 mm thick for modeling a wide variety of organs and tissues, including skin, lung, and the tumor microenvironment.
- A hinged lid that provides users direct access to the culture chamber for topical or aerosolized drug treatments.
- A tissue-vascular interface that enables the creation of an air-liquid interface.
- Full integration into the Human Emulation System for automated culture conditions, including fluid flow in both channels and cyclic stretch.
Revolutionizing Drug Manufacturing: Organ-on-a Chip – Biochips -- 2023
Revolutionizing Drug Testing

- Rapidly approaching untenable situation in human health -- Blockbuster drugs, which cure major diseases afflicting huge populations, are being pulled from the shelves (e.g., Vioxx) for unforeseen side-effects.
- They are being replaced by drugs that have smaller market potential and more localized impact (subpopulations, e.g., FluMist).
- Current cost of developing a drug and getting it to market exceeds $1B and process takes over ten years.
- These competing forces cannot be resolved without truly transformational changes in the way drugs are discovered, developed, and approved.
- This need is exacerbated by the emergence of personalized medicine – a natural outcome of high throughput sequencing technologies.
Personalized Medicine

Use of genetic and non-genetic molecular information to individualize prevention, diagnosis, treatment and prognosis for each person with greater precision.

The paradigm of personalized medicine, PMC
personalizedmedicinecoalition.org
Integration of UMD Rigorous Model-Based Systems Methodology with Data-Driven Methods (ML and AI) for Systems Engineering and PLM
Integrated Data-Driven & Model-Based Systems Engineering

PROBLEM ADDRESSED AND SIGNIFICANCE

Systematic Methodology and Software Tool Suite for Trustworthy Autonomous Systems

Critical need for many defense and commercial applications

HOW

MBSE – Static, known Requirements, Verifiable

MBSE defeated by complexity and diversity of autonomous systems

Large Data Sets Driven ML - AI to the rescue: simulations, experiments, operations

Design space exploration via tradeoffs to prioritize potential investments from portfolio of modules: sensors, actuators, cyber chips, materials, engines, architectures, algorithms, new technologies, etc.

NOVELTY and VALUE

Integrating large data sets makes feasible the design of high performance trustworthy autonomous systems through empirical (DD) and formal (MBSE) validation, with changing requirements and scenarios.

Not possible otherwise. Currently major open problem.
Main Goal and Focal Use Case

• Answer “what if?” “what is the impact if?” questions
• Address whole systems engineering life cycle: design, manufacturing/implementation, operations, policies
• Allow easy integration with domain specific tools
• Easy to learn and use
• Allow analysis and answers at various levels (from high level management to low level engineering)
• We now have massive data from simulations and testbeds, and powerful computational tools for data science and DATA DRIVEN methods (i.e. ML and AI)
• HOW TO MAKE EFFICIENT USE OF THESE ADVANCES?
• Critical use case: Trustworthy Autonomous Systems, Single or Multiple collaborating (self-monitor, self-adjust, self-learn)
How to Do System PLM on Autonomous Systems/Agents?

Autonomous Systems – Agent Architecture

- Situation Awareness
  - Perception
    - Interpretation of sensory information
    - Obstacles
  - Reflection
    - Construction/Update of environment model
- Knowledge Repository
  - Concepts
  - Properties
  - Methods
- Self-learning
  - Knowledge emergence
  - Goal emergence
- Decision Making
  - Goal Management (Strategy)
  - Planning (Tactics)

Abstraction – source: J. Sifakis 2023
UMD MODEL-BASED SYSTEMS ENGINEERING PROCESS

PRODUCT: Integrated System Synthesis
Methods & Software Tool Suites

Iterate to Find a Feasible Solution / Change as needed

Change structure/behavior model as needed

- Define Requirements
  - Effectiveness Measures

- Assess Available Information

- Create Behavior Model

- Map behavior onto structure
  - Allocate Requirements

- Specifications
  - Perform TradeOff Analysis

- Create Sequential build & Test Plan

Generate derivative requirements and metrics

Apply this to: Design, Manufacturing, Operations and Management
TO THE WHOLE LIFE-CYCLE

⇒ MBE

Tools:
- UML - SysML - GME - eMFLON
- ANSYS Model Center
- Rapsody
- UPPAAL
- MATLAB, MAPLE
- Dassault Systemes Dymola, CATIA, PLM
- CONSOL-OPTCAD
- IBM CPLEX ILOG Optimization Studio
- GUROBI
- SIEMENS PLM, NX, TEAM CENTER
PRODUCT – Proposed DATA DRIVEN ENHANCEMENTS

Scalable holistic methods, models, tools for enterprise level SE

- Multi-domain Model Integration
- System Modeling Transformations via System Architecture Model (SysML)

BENEFITS
- Broader Exploration of the design space
- Modularity, re-use
- Increased flexibility, adaptability, agility
- Engineering tools allowing conceptual design, leading to full product models and easy modifications
- Automated validation/verification

APPLICATIONS
- Avionics
- Automotive
- Robotics
- Smart Buildings
- Power Grid
- Healthcare
- Telecomm and WSN
- Smart PDAs
- Smart Manufacturing

Machine Learning & Artificial Intelligence
The Integrated Data-Driven MBSE Framework

Design Feasibility Check, Make Adjustments, Iterate.

Refine Architecture/Behavior as required

Use Case Modeling

Architectural Models

Behavioral Models

Requirements

Behavior Mapping, Requirements Allocation

IDDMB Digital Twin

Design Optimization and Trade-off Analysis

Verification and Validation

Real-world Deployment

Data

ROS

Autonomy Stack Modeling
FMI for Model Exchange and Co-Simulation

FMI 3.0 (2022) — Support for Directional Derivatives! Unlocks the potential for hybrid data & model-based methods.

FMI for Model Exchange

FMI for Co-Simulation
Enable rich design space exploration across various physical domains and scales, as well as cyber domains and scales.

FMI 3.0 (2022)—Support for Directional Derivatives & Automatic Differentiation (of simulation or data driven “models”)! Opens up the potential for hybrid data & model-based methods. It allows computation of sensitivities (key for tradeoffs)!
Advancing Rigorous Foundations of ML and AI

- Rigorous Mathematics for Deep Networks – Universal Architecture emerging
- Non von-Neumann computing – do not separate CPU from Memory – Synaptic NN, in-memory processing -- HTM
- Universal ML -- Integrate Deep NN and Synaptic NN
- Knowledge Representation and Reasoning: Integrate Knowledge Graphs and Semantic Vector Spaces
- Progressive Learning, Knowledge Compacting
- Link Machine Learning with Knowledge Representation and Reasoning
- Inspirations from neuroscience: attention, memory, time scales
Thank you!

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Questions?