COLLEGE OF ENGINEERING
INDUSTRIAL & OPERATIONS ENGINEERING
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Operations Research in Medicine:

Past, Present, and Future

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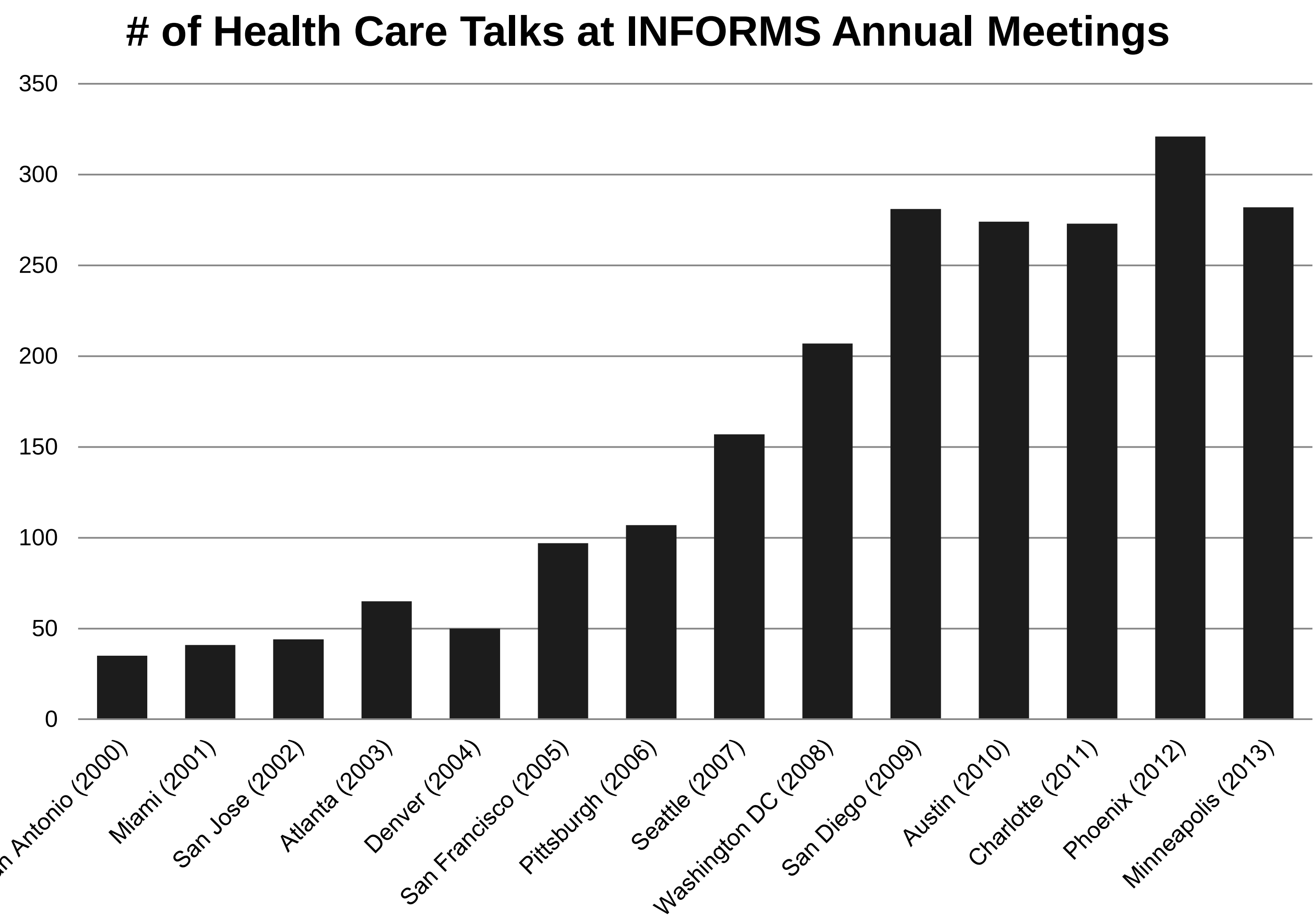
INFORMS



# of Health Care Talks at INFORMS Annual Meetings
350
300
250
200
150
100
50
0
San Antonio (2000)
Miami (2001)
San Jose (2002)
Atlanta (2003)
Denver (2004)
San Francisco (2005)
Pittsburgh (2006)
Seattle (2007)
Washington DC (2008)
San Diego (2009)
Austin (2010)
Charlotte (2011)
Phoenix (2012)
Minneapolis (2013)

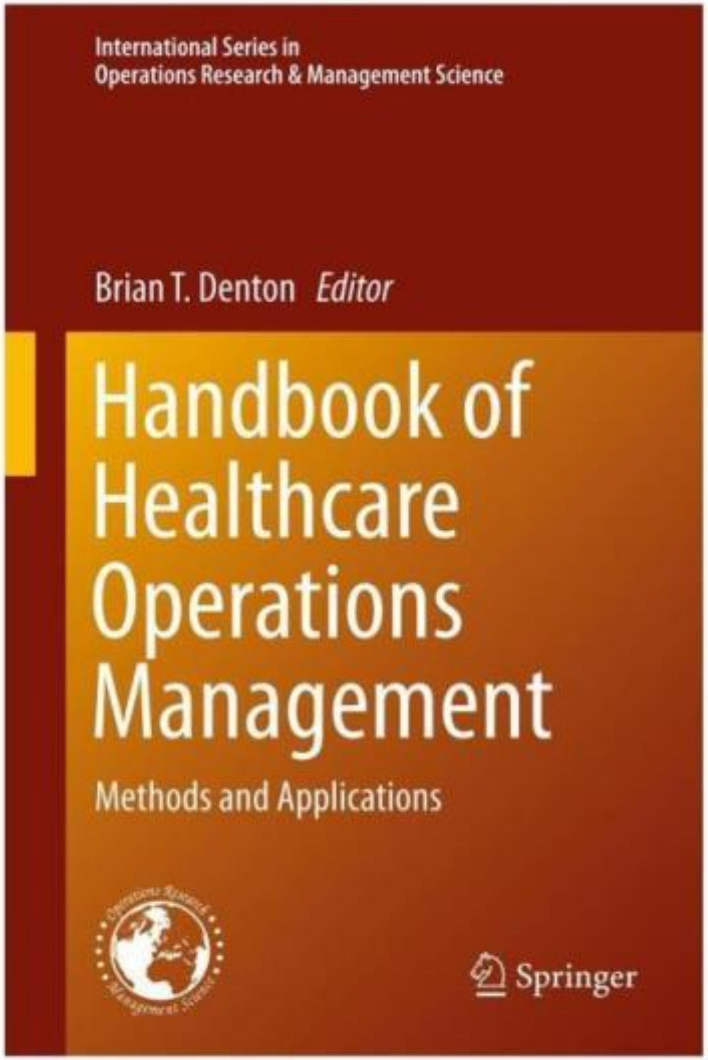
Operations Management

Nurse Scheduling

Ambulance Dispatching

Surgery Planning

Inventory Management

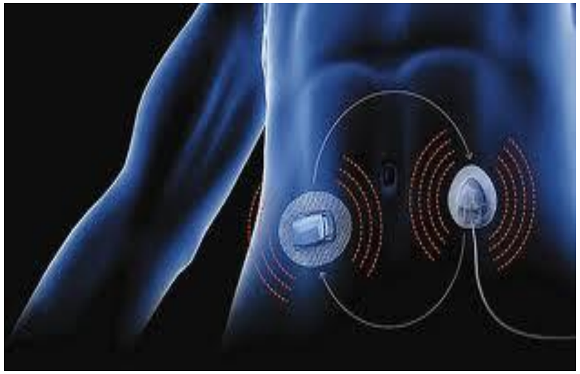


Carrie Chan
Linda Green
Diwakar Gupta
Bruce Golden
Mehmet Begen
Erik Demeulemeester
Jeff Kharoufeh
Steven Thompson
Hari Balasubramanian
Craig Froehle
Mark Lawley
Andrew Mason
Jeffrey Herrmann
Ken McKay
Bjorn Berg
Jonathan Patrick
Tom Rohleder
Julie Ivy
Sylvain Landry
Jessica McCoy
Jackie Griffin

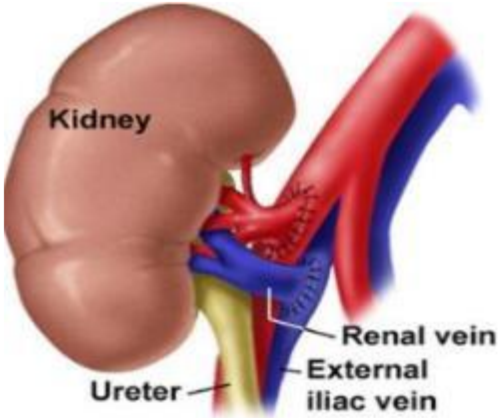
Medicine

Cancer

Diabetes



Kidney Failure



Glaucoma

Challenges

1. Medicine is complicated
2. The rate of discovery is fast
3. Privacy, ethics, and cost limit research

Medicine is complicated

Magnetic Resonance Cholangiography Technique. All ERCP procedures were completed within 24 hours of the preceding MRC. The examinations were performed using a General Electric Signa 1.5 Tesla MR scanner (Milwaukee, WI). Image acquisition was performed using a phase array torso multicoil. Two acquisitions each were performed in the axial and coronal planes using a single-shot fast-spin echo pulse sequence with a repetition time of infinity, average echo time equal to 90 milliseconds, matrix size equal to 256/256, and slice thickness of 5 mm with 0-mm skip. Each image slice required 2 seconds. Total breath-hold time averaged 20 seconds per patient. Multiple breath-hold scans were also performed to image the entire hepatic parenchyma if required. Three additional acquisitions were performed in the coronal plane and in planes approximately 45° oblique to the porta hepatis. A slice thickness of 5 cm, requiring a single 2-second breath hold, was used for the additional acquisitions.

MRC is a noninvasive imaging method, ERCP uses a tiny camera to take pictures of your bile duct

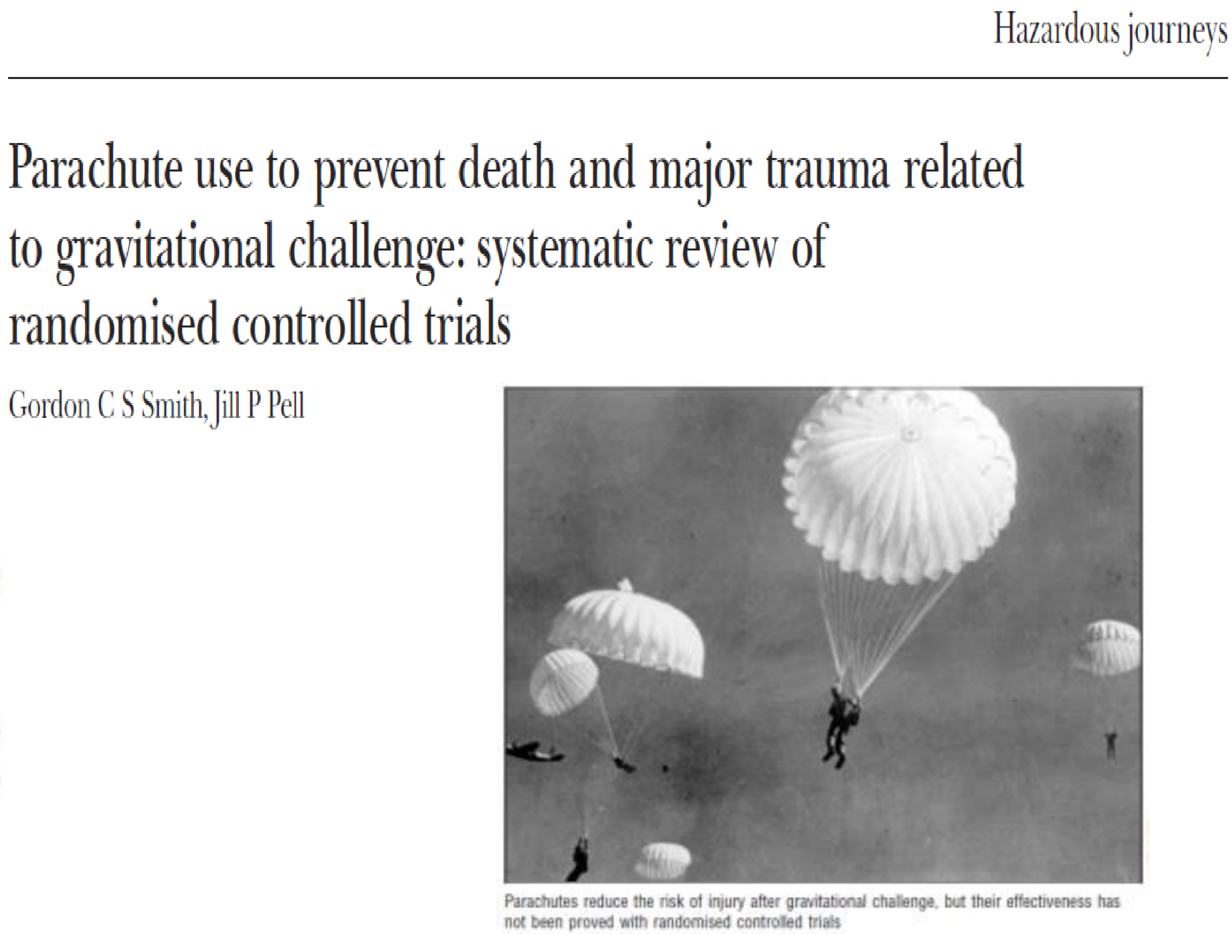
Fast rate of discovery

2013 Statistics:

- 146,367 articles on cancer
  - 18,966 articles on breast cancer
  - 9,271 articles on prostate cancer
- 49,333 articles on heart disease
- 34,263 articles on diabetes
- 16,253 articles on HIV
- 10,306 articles on ophthalmology
- 8,704 articles on allergies

Privacy, Ethics, and Cost

HIPAA



Hazardous journeys

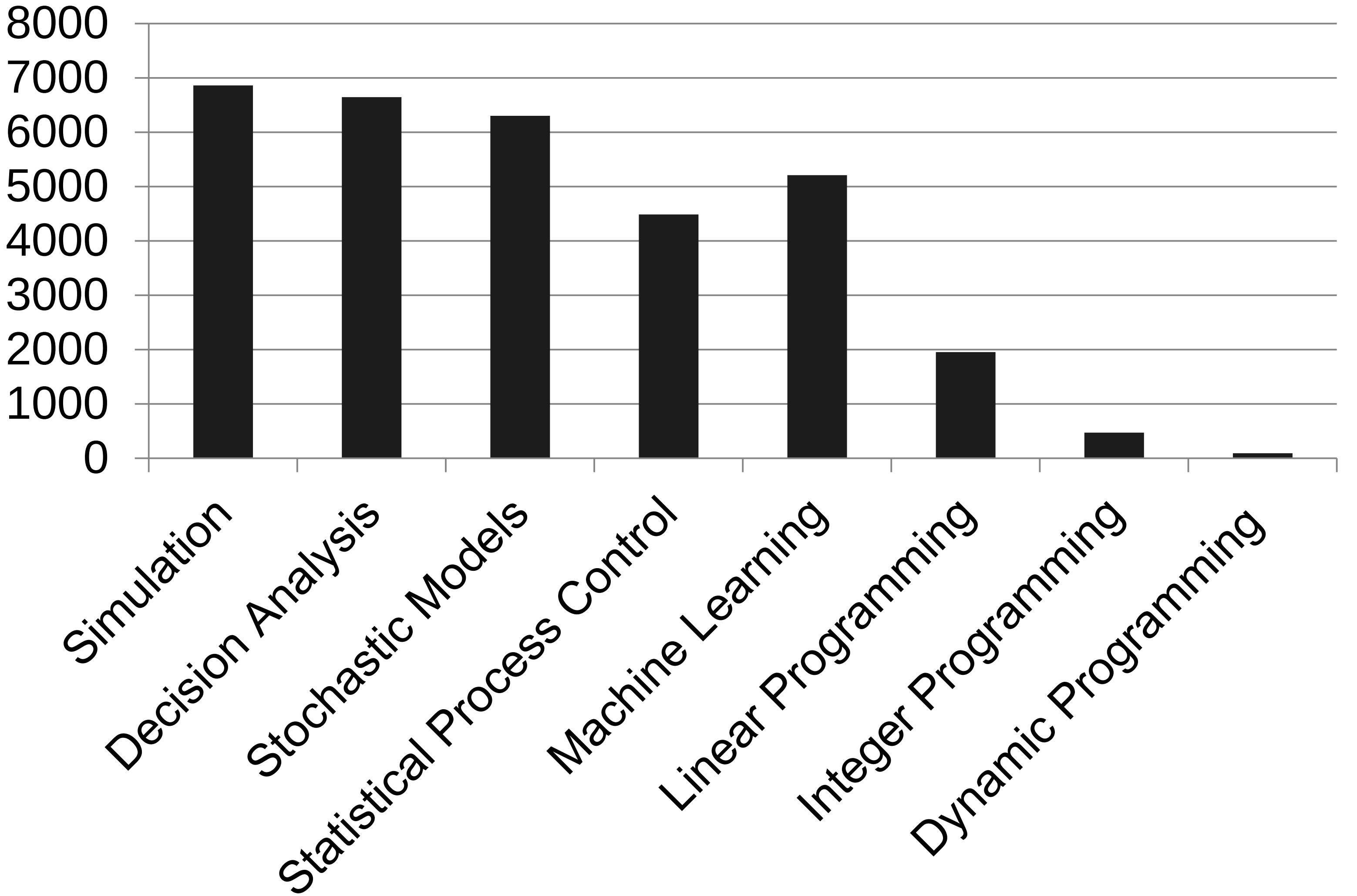
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

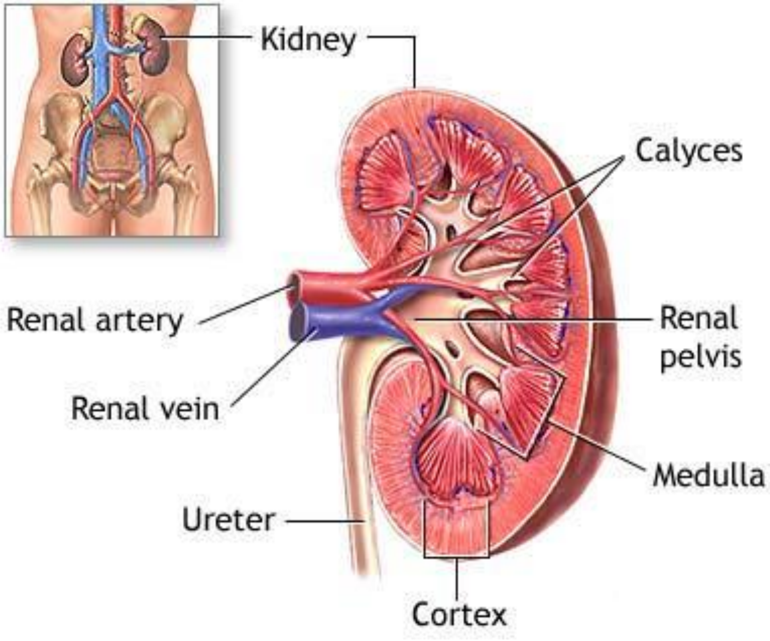

PRESENT
FUTURE
PAST

PubMed Search Results



Kidney Disease

- Principal treatment options:
  - Dialysis (home or clinic)
  - Transplant (live or deceased donor)
- More than 350,000 people are on dialysis and 80,000 waiting for transplant



Simulation

Simulation of medical decisions: Applications of SLN*

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and
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1001 West Tenth Street
Indianapolis, Indiana 46202

Please see "The Simulation of Logical Networks (SLN)" in this issue for authors' biographical sketches.

ABSTRACT

Simulation has been applied to several important medical decision problems using the SLN language. The applications to end-stage renal disease, chronic stable angina, renal artery stenosis, and treatment of hypertension and hypercholesterolemia are reviewed emphasizing the modeling considerations and results. These investigations support the utility of simulation in medical decisions and the applicability of SLN to these problems. The general applicability of simulation to medical decision problems must be evaluated in the context of available knowledge and data. The simulation of medical decisions does not produce dependence among observations so prevalent in discrete-event simulations, but to the extent that arbitrary criteria such as cost-effectiveness are estimated, statistical concerns remain. Simulation, particularly with SLN, can play an important role in medical protocol design.

INTRODUCTION

Fifty years ago the medical and financial impact of medical decisions was limited to individual patients. Minimal technology was available, so diagnosis and treatment were based on time-honored protocols offered by individual physicians. Today medical decisions are made in a far different environment. Expensive equipment and facilities have made economics a major consideration not only for individual patients but also for society, since costs are often shared by everyone through taxes, insurance, etc. The rapid growth in medical technology means that medical protocols must be revised often to include recent advances. Time-honored procedures cannot take advantage of the state-of-the-art developments in medicine. Complicating the problem further is that these new developments often offer a mixed set of benefits and costs. The practice of medicine itself reflects greater specialization so that individual physicians are increasingly unable to offer comprehensive care and cannot individually evaluate new developments.

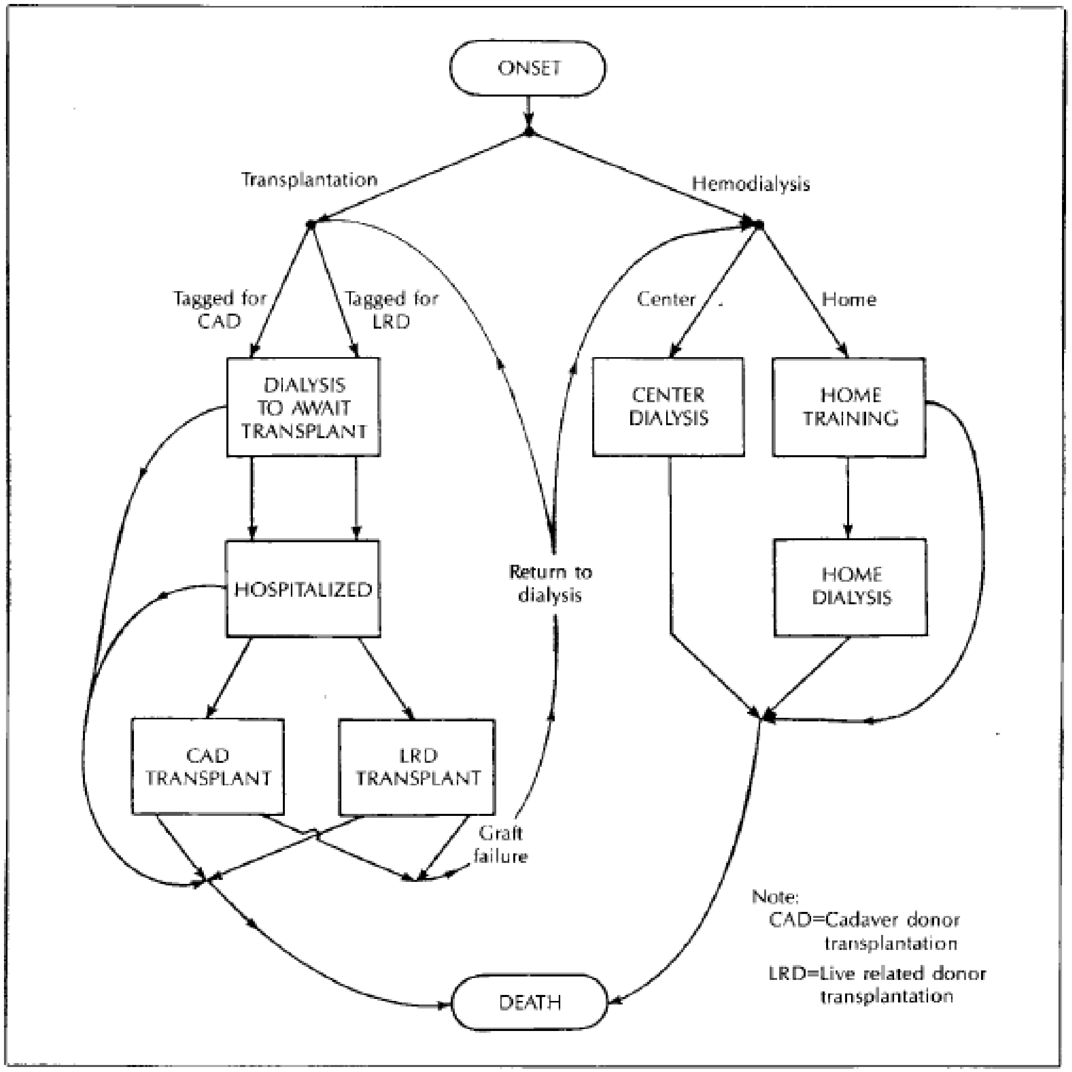
Traditional approaches to evaluating methods for diagnosis and treatment are limited. Clinical trials, the major source of clinical experience, must be confined to experimentally verifiable hypotheses. These are both expensive and intricate, usually requiring considerable time and commitment. The proliferation of alternatives, the timeliness of evaluation, the use of human subjects, and the cost of experimental procedures mean that clinical trials must be reserved for issues where actual experiments are the only method of evaluation. Clinical judgment may supplement or replace experimental findings since the state of the art is changing so rapidly. Yet judgment is now more difficult because of the complexities of the technology and environment.

Increasingly, simulation modeling is being used in the analysis of health care decisions to synthesize available information.[7] Models can combine existing knowledge with clinical judgment to gain insight into the problems of diagnosis and treatment. Decision analysis has played a particularly central role in the modeling activity.[12] Stochastic modeling[6] and optimization of decision trees[2] are among other recently applied analytical techniques.

Simulation also provides a suitable vehicle for the analysis of medical decisions and can promote insight into the design of diagnostic and therapeutic protocols. Simulation, unlike its more analytical alternatives, places fewer requirements on the decision system and can accommodate a greater variety of problems. The simulation language, SLN (Simulation of Logical Networks), was designed especially to facilitate modeling and analysis of decision systems and has been applied in particular to medical decisions. SLN has been described in a companion paper.[9] In this paper, we will review a number of the medical decision applications of SLN and describe some of the general experiences from these simulation studies.

*This work was supported in part by grant 18-P-97515-03 from Health Care Financing Administration, Department of Health and Human Services.

Discrete Event Simulation

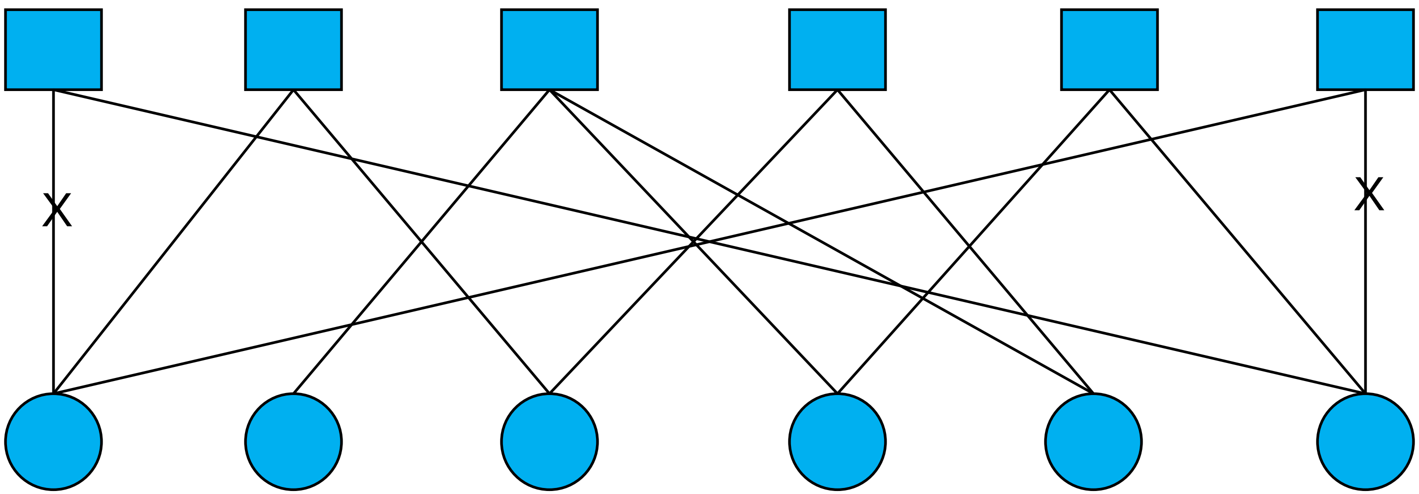


- Inputs: kidney supply, survival probabilities, costs, decision rules
- Outputs: quality adjusted lifespan, cost of treatment

Optimization

Kidney Exchange

Donors

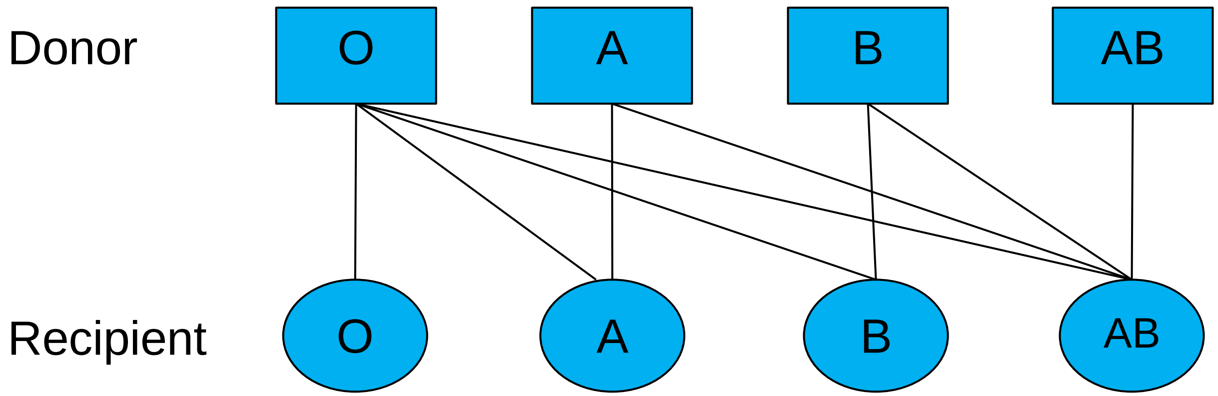


Recipients

Compatibility is determined by two primary factors:

- Blood type
- Tissue antibodies

Blood type compatibility



Criteria

- Number of matches
- Number of priority matches
- Immunologic concordance
- Travel requirements

Example

Objective: To maximize the number and quality of donor-to-recipient matches

Only certain matches are allowable. The “cost” defines a measure of risk associated with performing the transplant

	Recipient 1	Recipient 2	Recipient 3	Recipient 4
Donor 1	**0.2**	**M**	**M**	**0.01**
Donor 2	**M**	**0.5**	**0.01**	**0.2**
Donor 3	**0.3**	**0.1**	**0.4**	**M**
Donor 4	**M**	**0.01**	**0.3**	**0.2**

Example

$$\text{Min } Z = 0.2x_{11}+Mx_{12}+Mx_{13}+0.01x_{14}+Mx_{21}+0.5x_{22}+0.01x_{23}+0.2x_{24}$$
$$+0.3x_{31}+0.1x_{32}+0.4x_{33}+Mx_{34}+Mx_{41}+0.01x_{42}+0.3x_{43}+0.2x_{44}$$

S.T.: $x_{11}+x_{12}+x_{13}+x_{14} = 1$ (Donor Constraints)

$x_{21}+x_{22}+x_{23}+x_{24} = 1$

$x_{31}+x_{32}+x_{33}+x_{34} = 1$

$x_{41}+x_{42}+x_{43}+x_{44} = 1$

$x_{11}+x_{21}+x_{31} +x_{41}= 1$ (Recipient Constraints)

$x_{12}+x_{22}+x_{32} +x_{42}= 1$

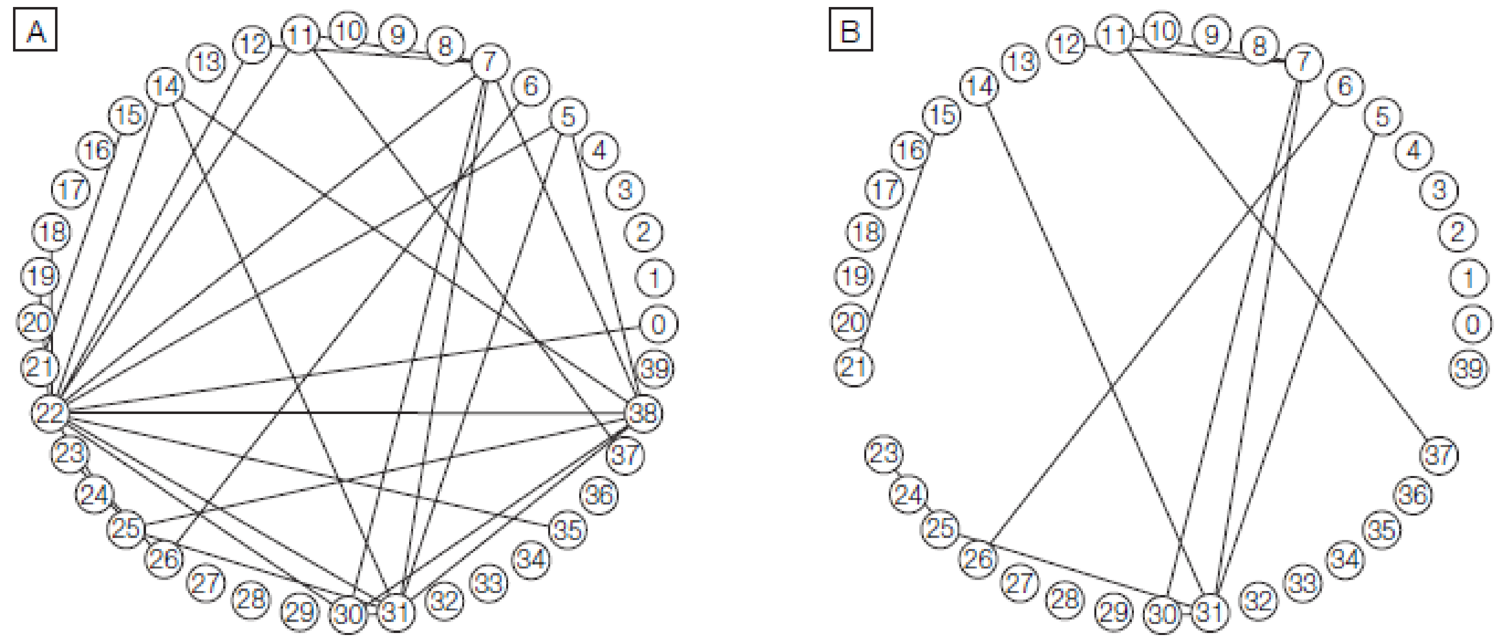
$x_{13}+x_{23}+x_{33} +x_{43}= 1$

$x_{14}+x_{24}+x_{34} +x_{44}= 1$

$x_{ij} \geq 0$ (i= 1,2,3; j= 1,2,3,4)

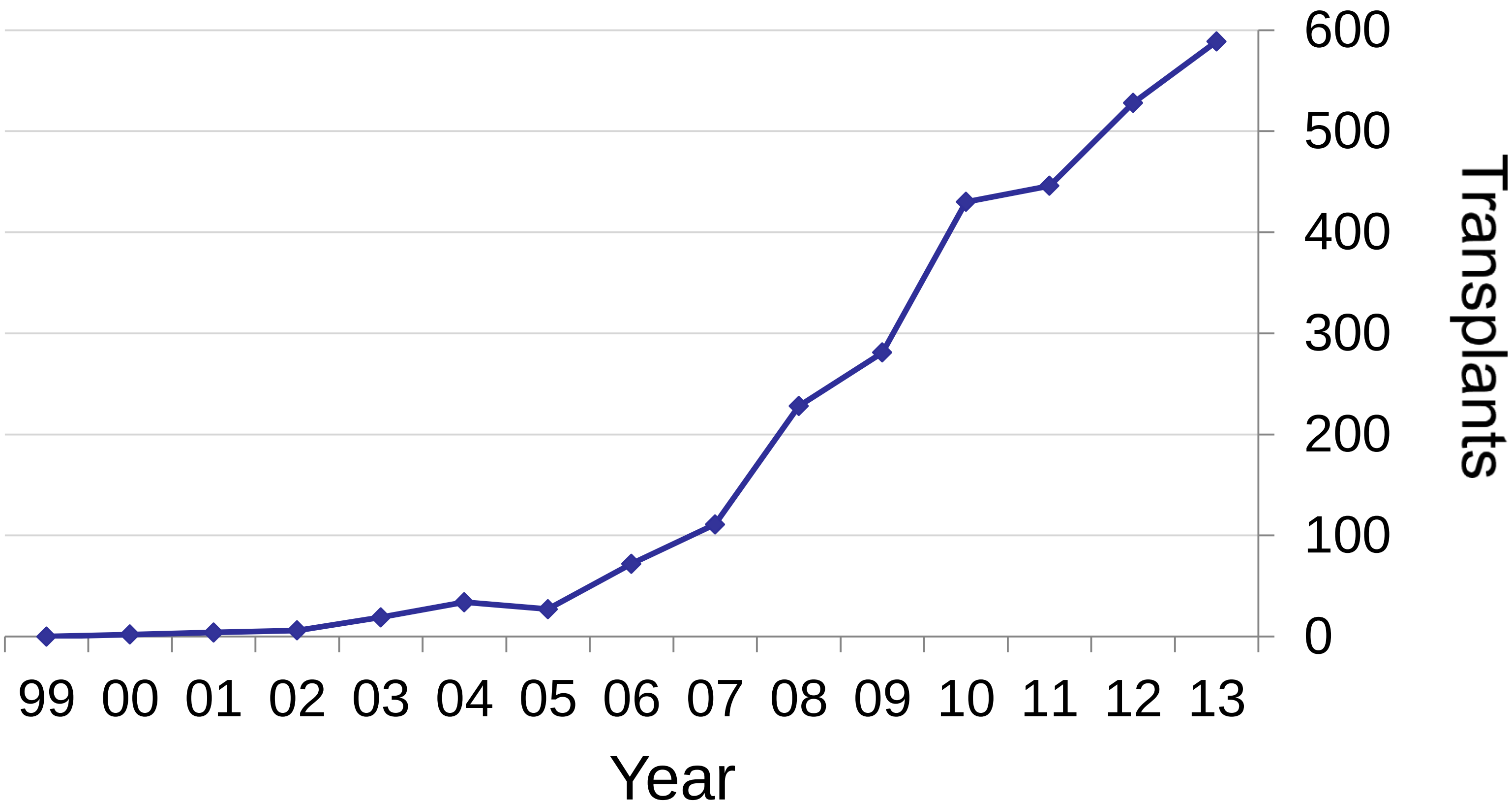
Paired Matching

Figure 1. Graph Theory Model of Donor/Recipient Nodes, With Links Indicating Compatible Matches



Segev, D, Gentry, S.E., Warren, D.S, Reeb, Montgomery, RA, 2005, Kidney Paired Donation and Optimizing the Use of Live Donor Organs, *Journal of the American Medical Association,* 293(15), 1883-1890.

Growth in Paired Donations



From 2 in 2000, to nearly 600 in 2013, KPD now comprises 10% of living kidney donations

**Courtesy of Sommer Gentry, US Naval Academy

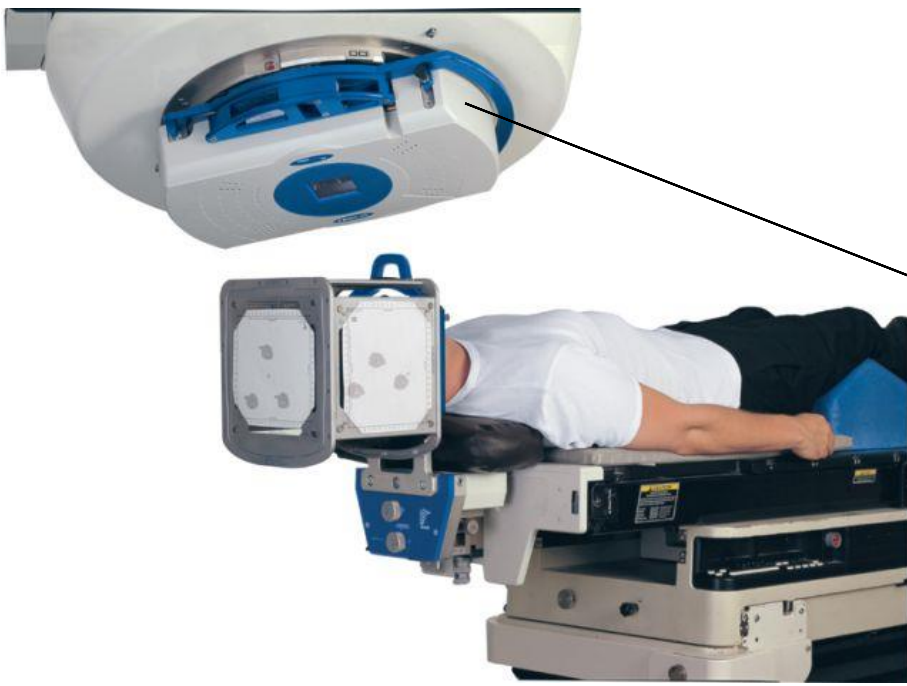
Radiation Treatment

- External beam radiation is passed through the body harming cancerous and healthy tissue
- Goal is to minimize damage to healthy tissue while delivering required dose to cancer tissue

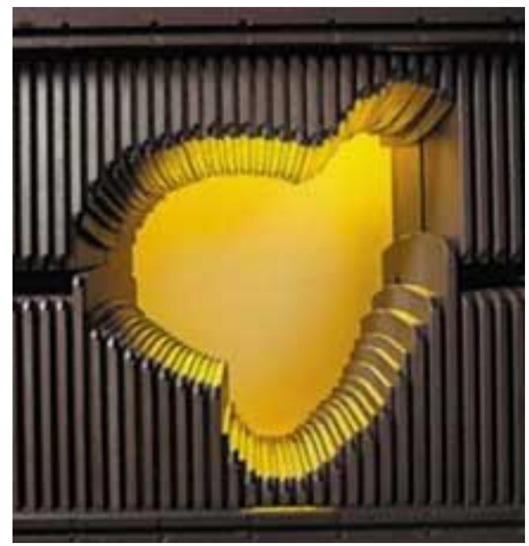
Bahr et al, 1968, The Method of Linear Programming Applied to Radiation Treatment Planning, *Radiology*, 91, 686-693

Radiation is delivered via a rotating gantry with a multi-leaf collimator

Rotating Gantry

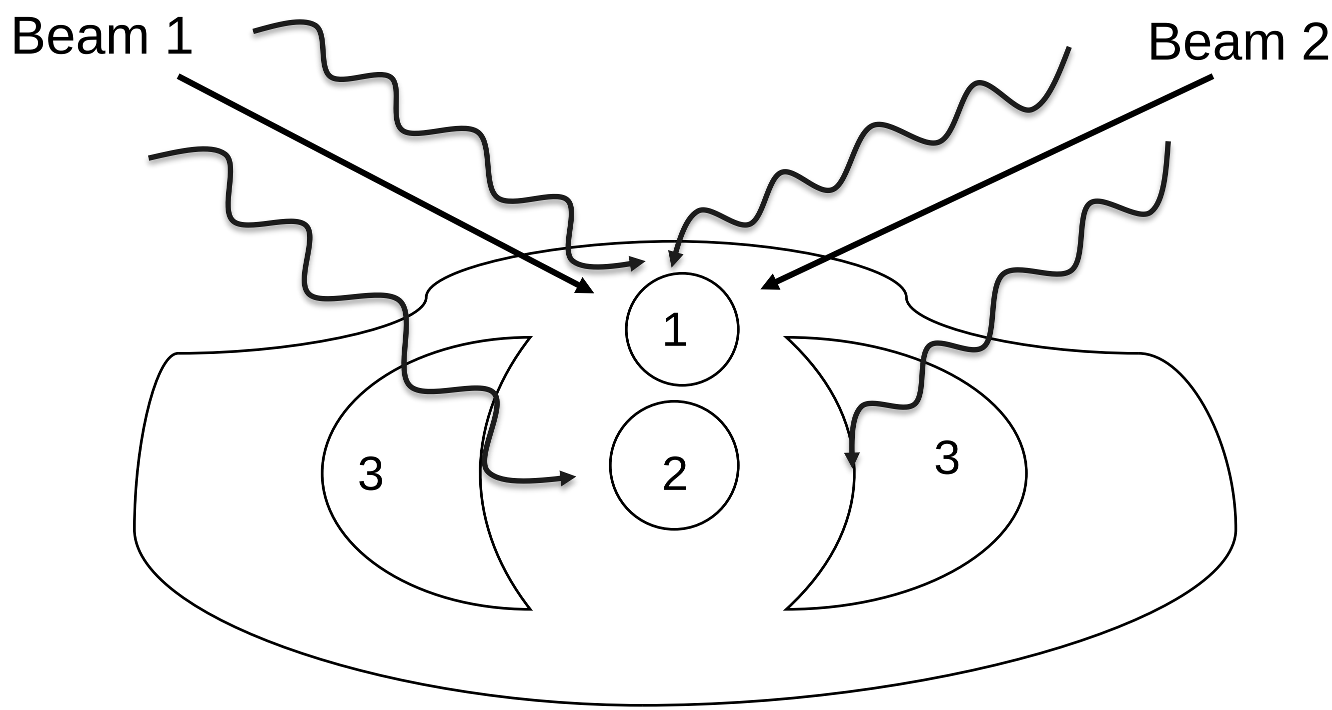


Multileaf Collimator



Example

1. Tumor
2. Spine
3. Brain



Data

Decision Variables: Exposure times for beams 1 and 2 (x_1, x_2)

Area	Dose Absorbed per unit time (ms)		Restriction on Total Average Dosage, Kilorads
	Beam 1 Dose	Beam 2 Dose	
Brain	0.4	0.5	Minimize
Spine	0.3	0.1	$\leq$ 2.7
Tumor	0.5	0.5	$=$ 6
Center of tumor	0.6	0.4	$\geq$ 6

Linear Program

Minimize $$Z = 0.4x_1 + 0.5x_2$$

s.t. $$0.3x_1 + 0.1x_2 \leq 2.7$$

$$0.5x_1 + 0.5x_2 = 6$$

$$0.6x_1 + 0.4x_2 \geq 6$$

$$x_1 \geq 0, x_2 \geq 0$$

Peng, F, Jia, X, Gu, X, Epelman, MA, Romeijn, EH, Jiang, SB. 2012. A new column-generation-based algorithm for VMAT treatment plan optimization, *Physics in Medicine and Biology*, 57(14)

Personalized radiation treatment

Research Question:

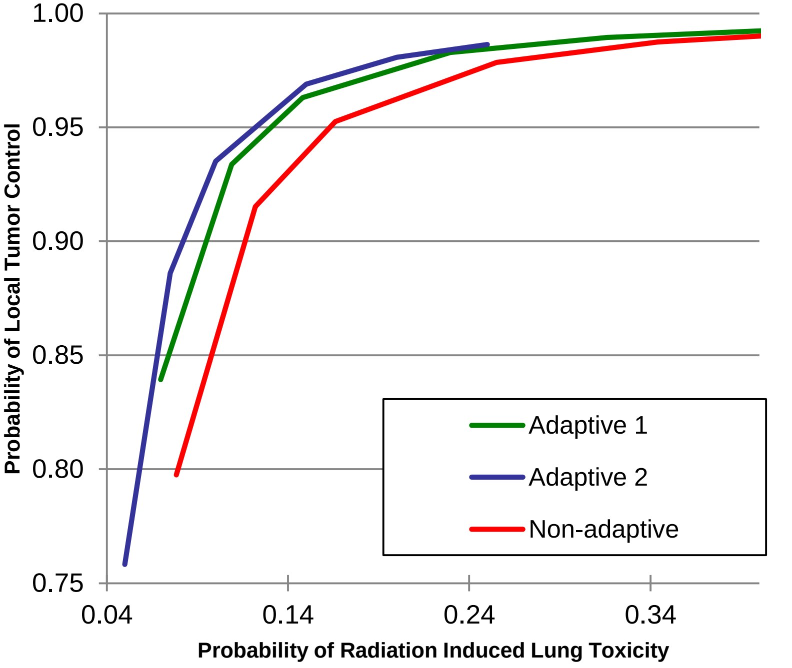
Can biomarker information be used to improve outcomes of radiation treatment for cancer patients?

Methods:

Logistic regression, stochastic programming, simulation

Findings:

Biomarker tests prior to and during treatment can be used to enable adaptive optimization to improve tradeoffs between chance of cure and side-effects



**Courtesy of Marina Epelman and Edwin Romeijn, IOE, UM

Prostate Cancer Staging

- Staging involves determining if the cancer has spread

- Imaging studies (CT and Bone Scan) are done to detect the spread of cancer:

    - Benefits: increased accuracy of cancer staging

    - Harms: incidental findings, radiation exposure, cost

Imaging Guideline Optimization

$G(\vec{a})$ is a classification function based on patient attributes, $\vec{a}$

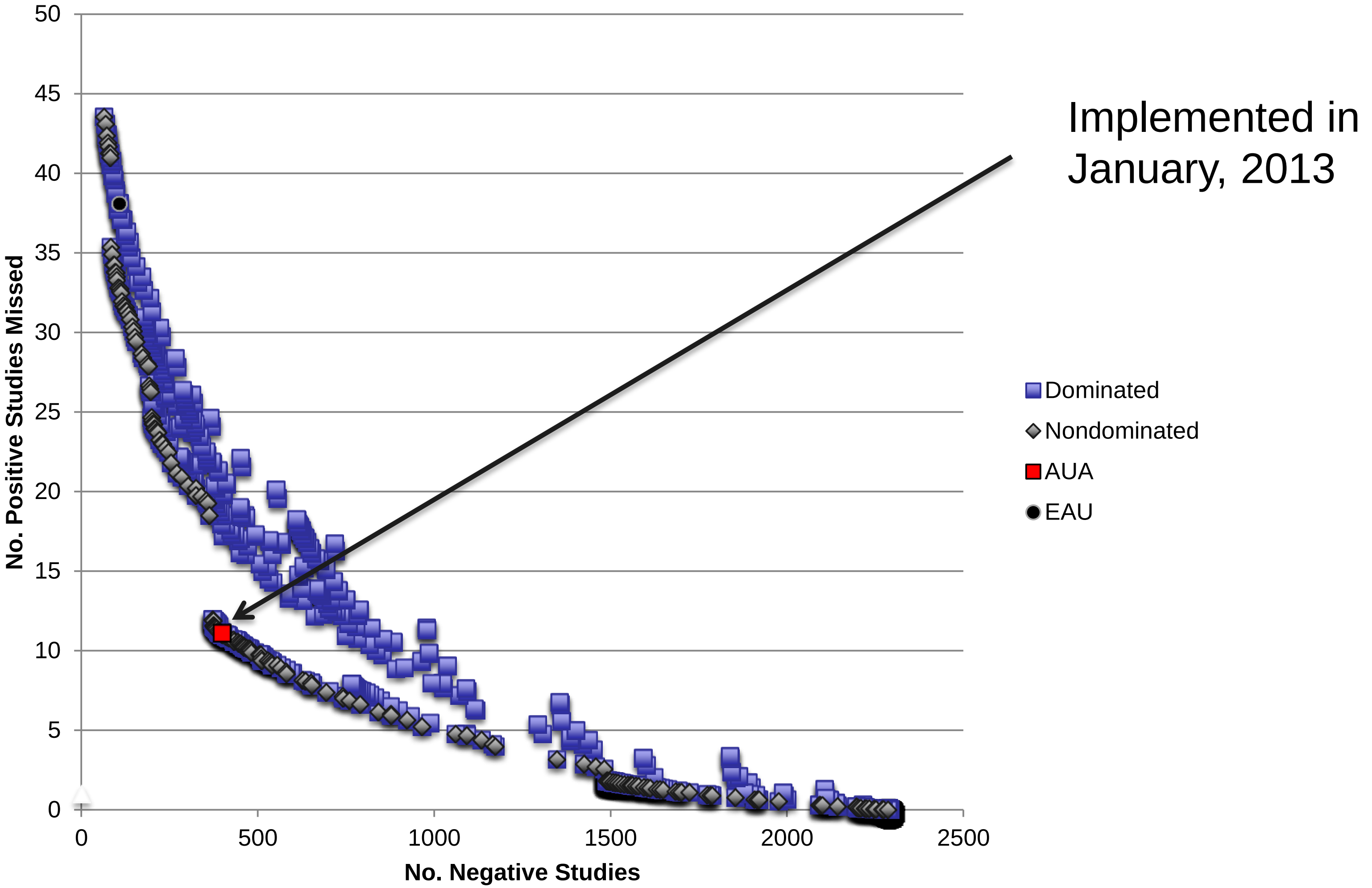
$$G(\vec{a}) \;=\; \begin{cases} 1 & if\ the\ guideline\ is\ satisfied \\ 0 & otherwise. \end{cases}$$

Criteria:

- Number of positive studies missed
- Number of negative studies

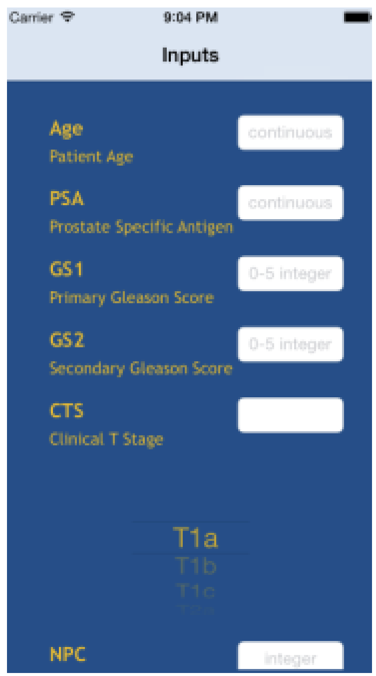
$$\min_{G}\{\alpha E_G[+\,studies\ missed] + (1-\alpha)\ E_G[-\,studies]\}$$

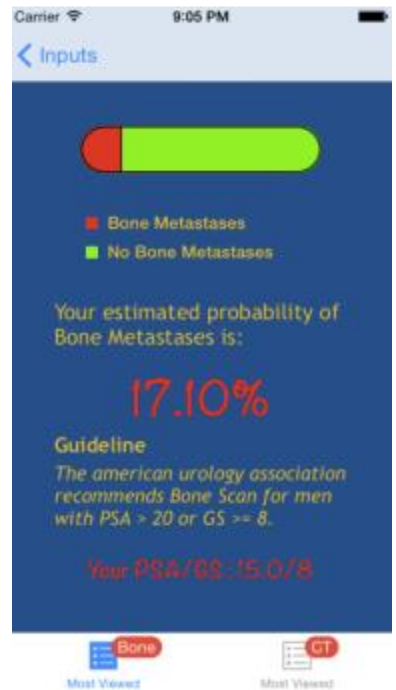
Guideline Implementation

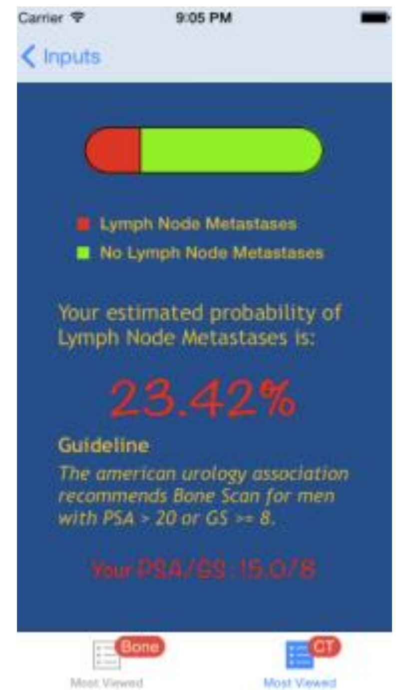


Imaging App

Logistic regression models validated for use in MUSIC using boot strapping to estimate statistical measures of discrimination and calibration







Merdan, S., Womble, P.R., Miller, D., Barnett, C., Ye, Z., Linsell, S., Montie, J., Denton, B.T., "Toward Better Use of Bone Scans Among Men with Early-Stage Prostate Cancer," Urology (in press), 2014.

Risko, R., Merdan, S., Womble, P.R., Montie, J., Barnett, C., Ye, Z., Linsell, S., Miller, D., Denton, B.T., "Clinical Predictors and Recommendations for Staging CT Scan Among Men with Prostate Cancer," Urology (in press), 2014.

Glaucoma Monitoring

Research Question

- When should glaucoma patients be monitored?

Methods

- Dynamic state space models of multidimensional disease state
- Confidence region approach on the maximum probability of progression
- Cross validated using 2 large randomized clinical trials

Results

- Solutions outperform current protocol
- Closed form solution enables implementation on physician's computer
- IRB obtained to start retrospectively testing algorithm on Kellogg patients

**Courtesy of Helm, Lavieri, Stein, Van Oyen, Musch

Drug Treatment Decisions for Type 2 Diabetes

Research Question:

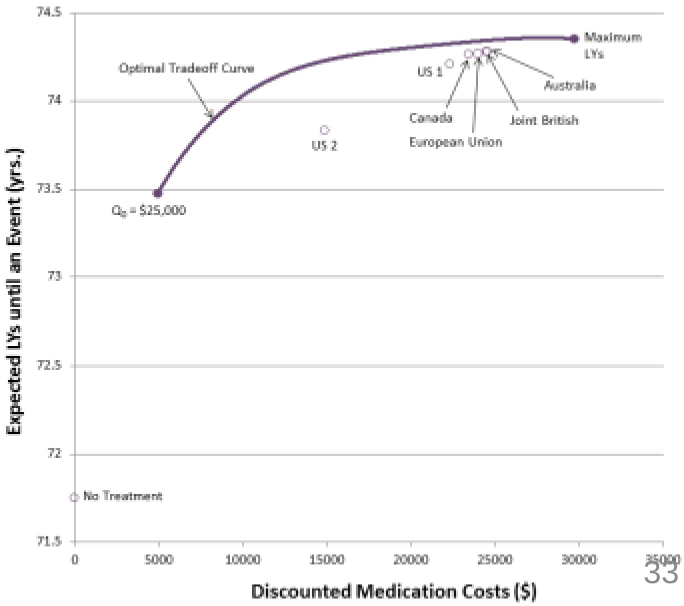
What is the optimal drug treatment plan to control the risk of diabetes complications?

Methods:

Markov decision processes and monte-carlo simulation

Findings:

Optimal control of risk factors can simultaneously increase lifespan and lower cost for type 2 diabetes



Denton, B.T., Kurt, M., Shah, N.D., Bryant, S.C., Smith, S.A., “A Markov Decision Process for Optimizing the Start Time of Statin Therapy for Patients with Diabetes,” *Medical Decision Making*, 29(3), 351-367, 2009

OR and the Future of Medicine

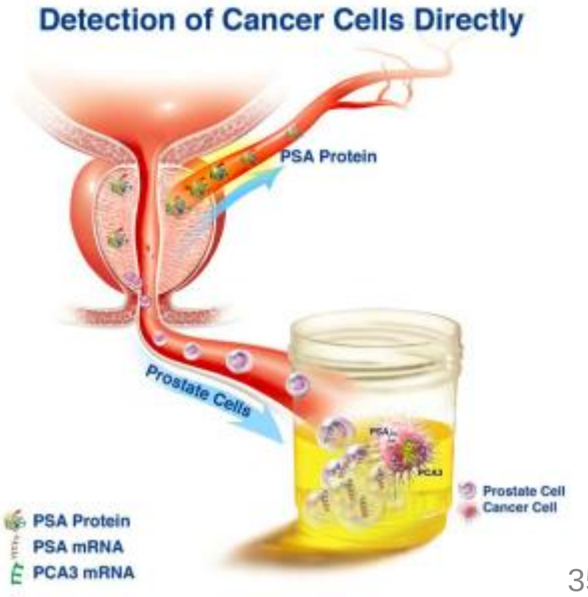
Biomarkers

Benefits:

- Early detection of diseases
- Predictors of disease severity
- Minimally invasive

Challenges:

- Partial observability
- Imperfect sensitivity and specificity
- Many biomarkers to choose from



Complex Patients

Patients over the age of 65 often have multiple chronic conditions

Example:

- Diabetes
- Heart disease
- Kidney Failure
- Hypertension
- Hyperlipidemia

Challenges: Dozens of medications, with uncertain benefits and harms, medication conflicts, and varying rates of adherence.

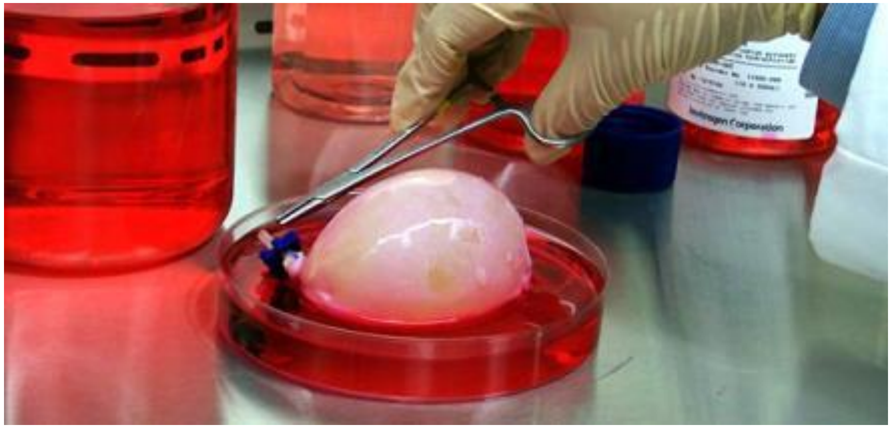
Automated Treatment

UVA's Continuous Closed-Loop Artificial Pancreas Powered by Android Smartphone

- Difficult real time optimal control problem
- Must maintain glucose levels within a defined range
- Current glucose state difficult to predict

Cobelli, C, Renard,E., Kovatchev, B. 2011. Artificial Pancreas: Past, Present, Future, *Diabetes*, 60, 2682 - 2682

Regenerative Medicine



Wake Forrest Institute for Regenerative Medicine:

- Heart valves
- Livers
- Kidneys
- Muscles
- Bladders
- Ears

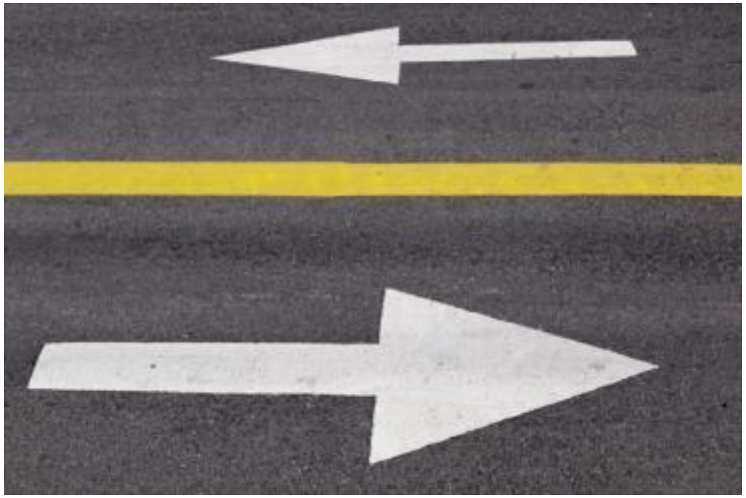
OR Methods: Simulation and stochastic models

TED Talk: Growing New Organs
http://www.ted.com/talks/anthony_atala_growing_organs_engineering_tissue

**Courtesy of Steve Roberts and Sean Carr, NC State University

Conclusions

- There is a long history of Operations Research in Medicine
- Operations Research is improving medical decision making and vice versa



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Rachel Risko, UM

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