COLLEGE OF ENGINEERING
INDUSTRIAL & OPERATIONS ENGINEERING
UNIVERSITY OF MICHIGAN

Optimization in Medicine

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Optimization

Optimization[1]: an act, process, or methodology of making something (as a design, system, or decision) as fully perfect, functional, or effective as possible.

$$max\ \{ f(x) \ \mid x \in C\}$$

- x: vector of decision variables
- f: objective function
- C: constraints

[1]Merriam Webster Dictionary

Operations Management

Nurse Scheduling

Ambulance Dispatching

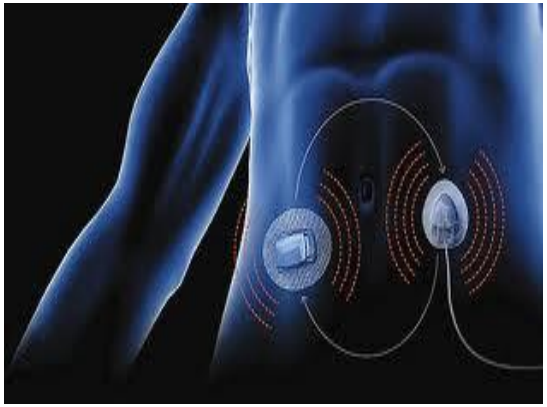
Surgery Planning

Inventory Management

Medicine

Cancer

Diabetes



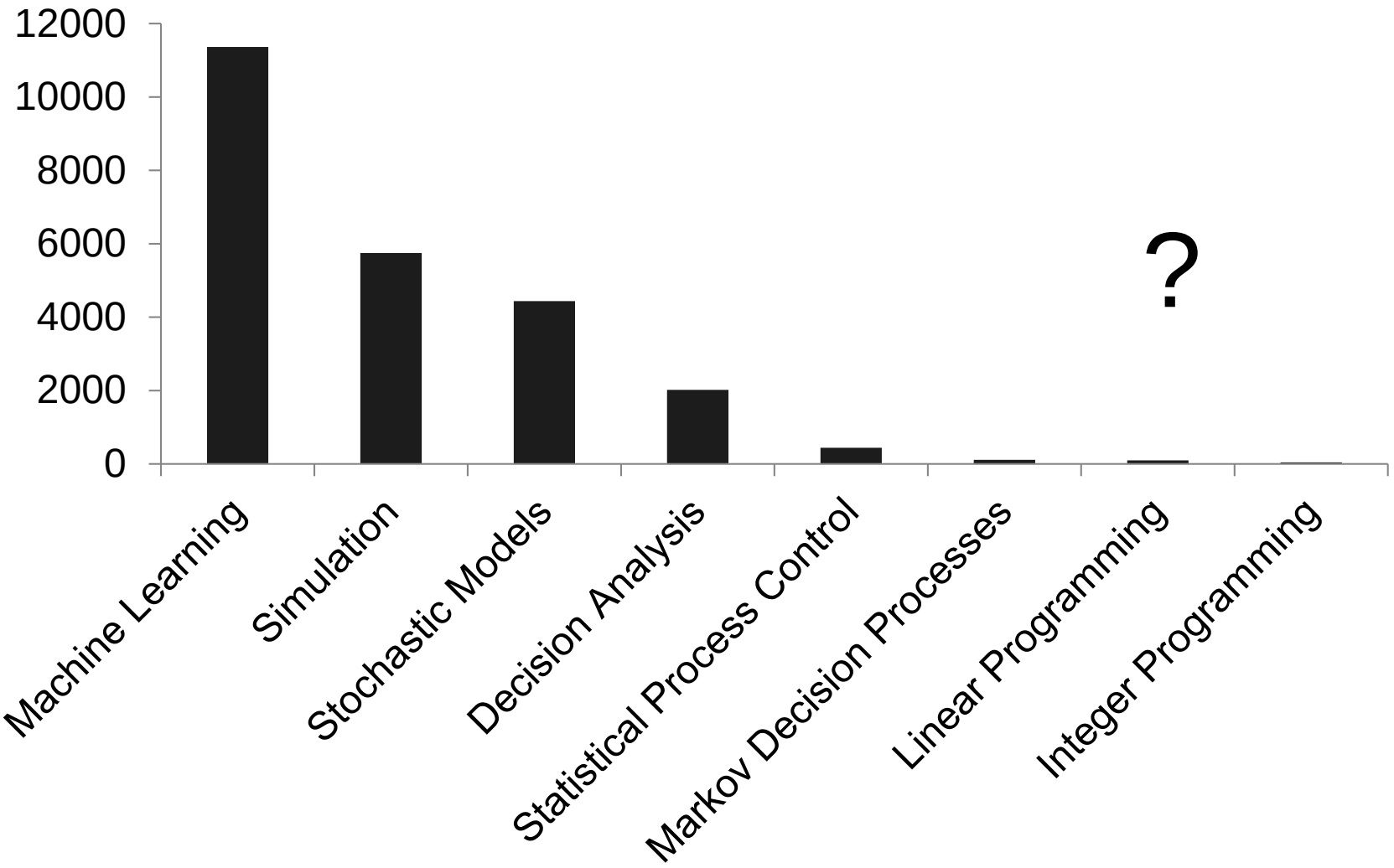
Kidney Disease

Heart Disease

Publications on PubMed in the last 10 years

- 1,426,842 articles on cancer
  - 169,076 articles on breast cancer
  - 79,662 articles on prostate cancer
- 474, 417 articles on heart disease and stroke
- 304,406 articles on diabetes
- 43,887 articles on kidney disease
- 2,935 articles on allergies

PubMed Results Over the Last 10 Years



Questions

1. Can optimization improve decision making in medicine?

2. What opportunities are there for future research?

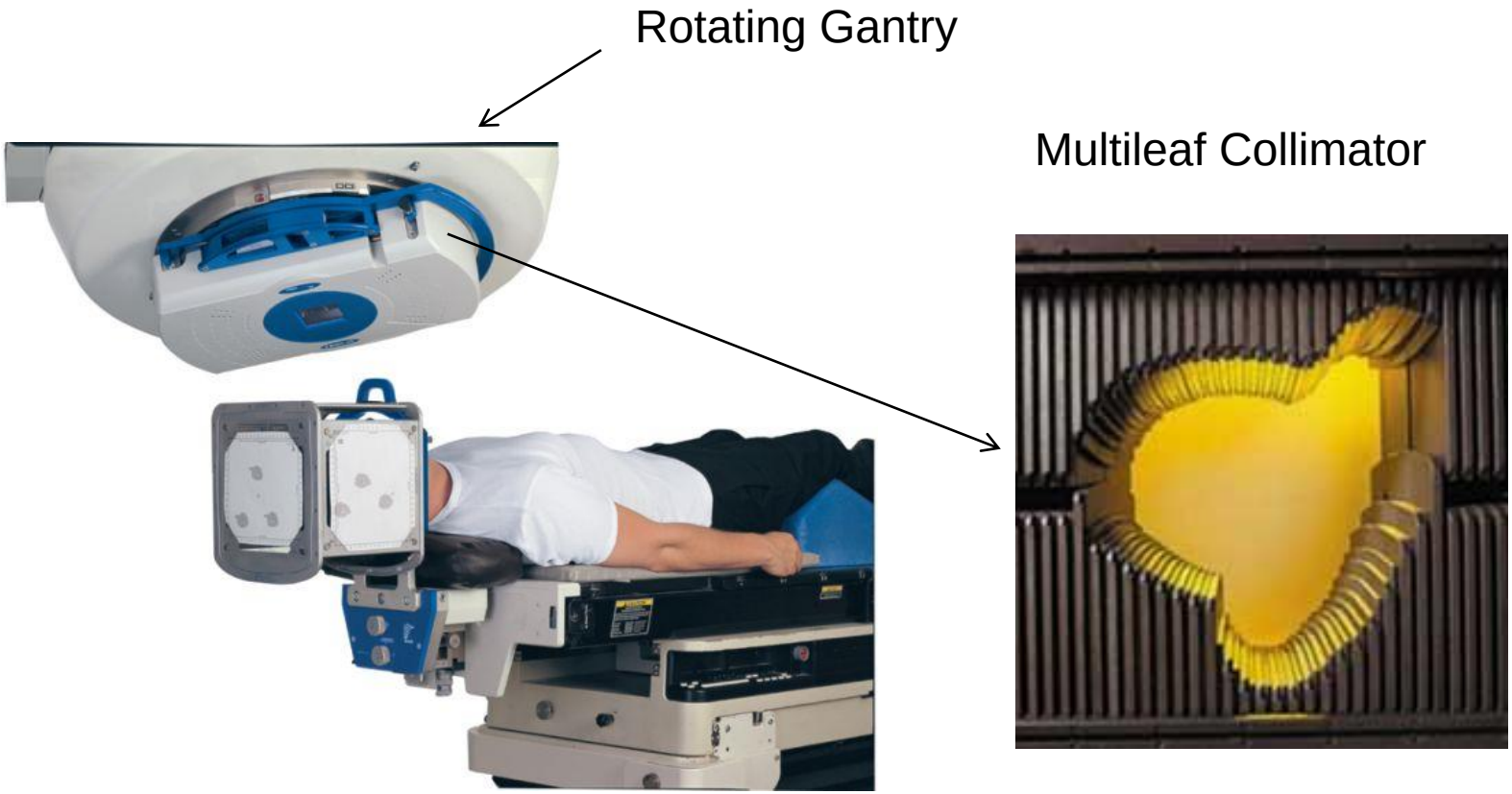
PRESENT
FUTURE
PAST

Radiation Treatment

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

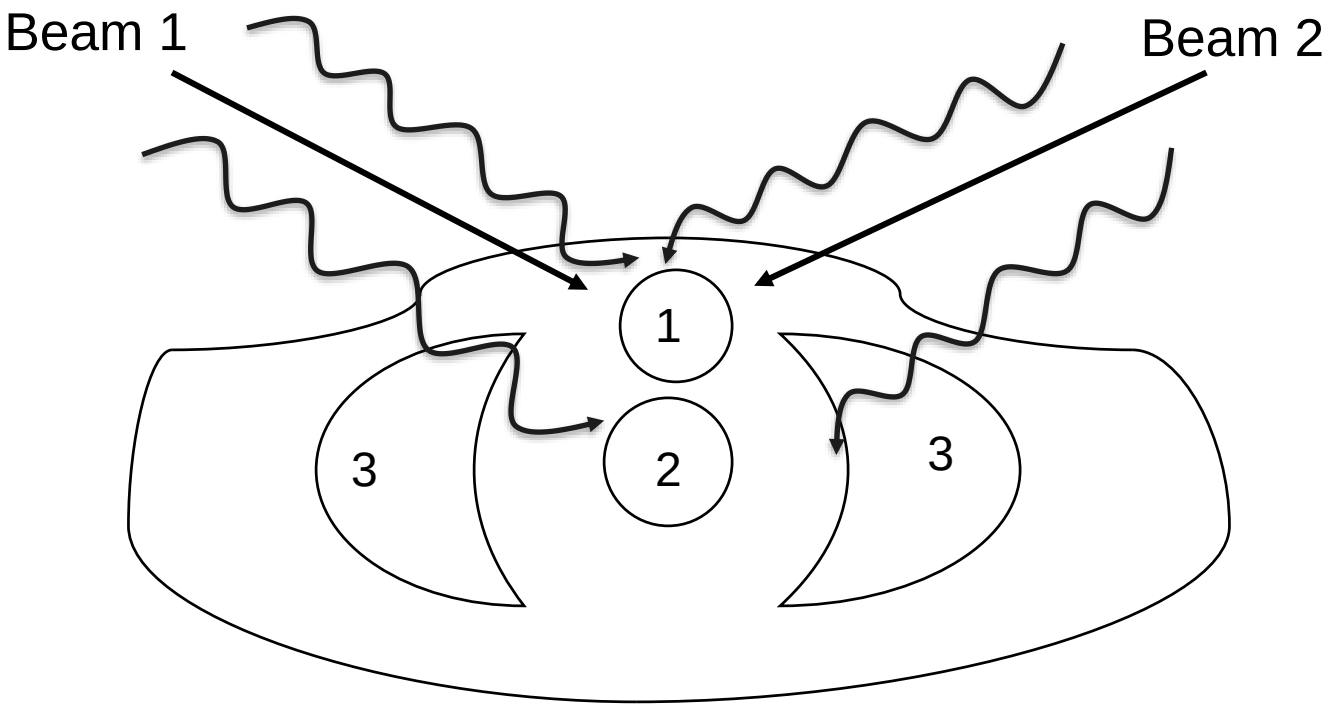
Bahr et al, 1968, The Method of Linear Programming Applied to Radiation Treatment Planning, *Radiology*, 91, 686-693

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



Example

1. Tumor
2. Spine
3. Brain

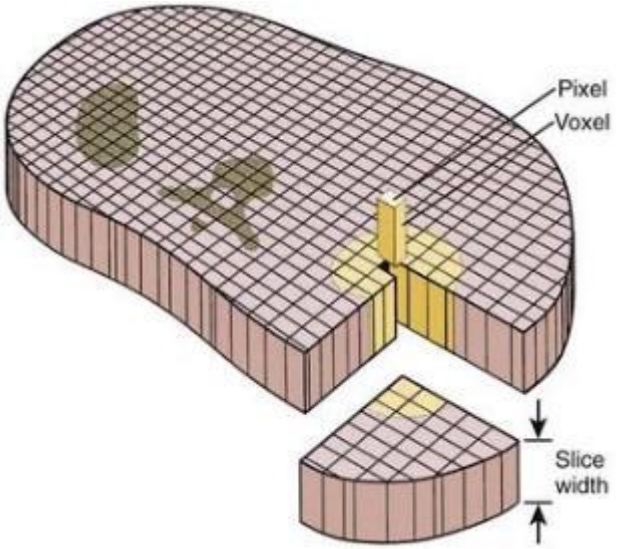


Linear Program

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

Area	Dose Absorbed		Restriction on Dosage in 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



$$Min \ \sum_{\ell \in L} G_\ell(z)$$

$$Subject\ to:$$

$$z_j = \sum_{k \in K} D_{kj} x_k, \qquad for\ all\ j\ in\ V$$

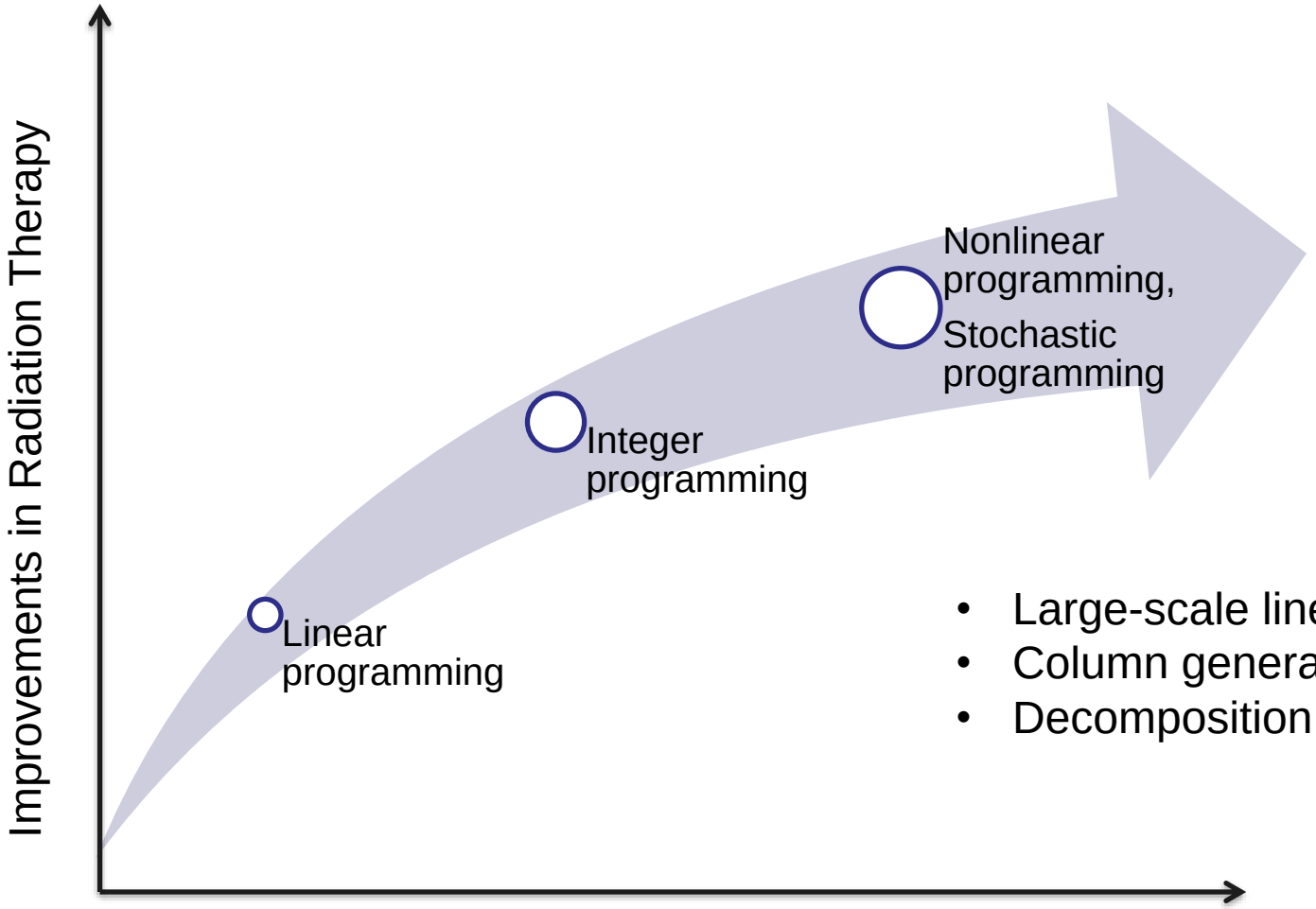
$$x_k \geq 0, \ \ k \in K, \ \ z_j \geq 0, \ j \in V$$

z_j: the dose delivered to voxel $j \in V$

x_k: the duration of beam $k \in K$

Romeijn & Dempsey. (2008). Intensity modulated radiation therapy treatment optimization. *TOP*, *16*(2), 215.

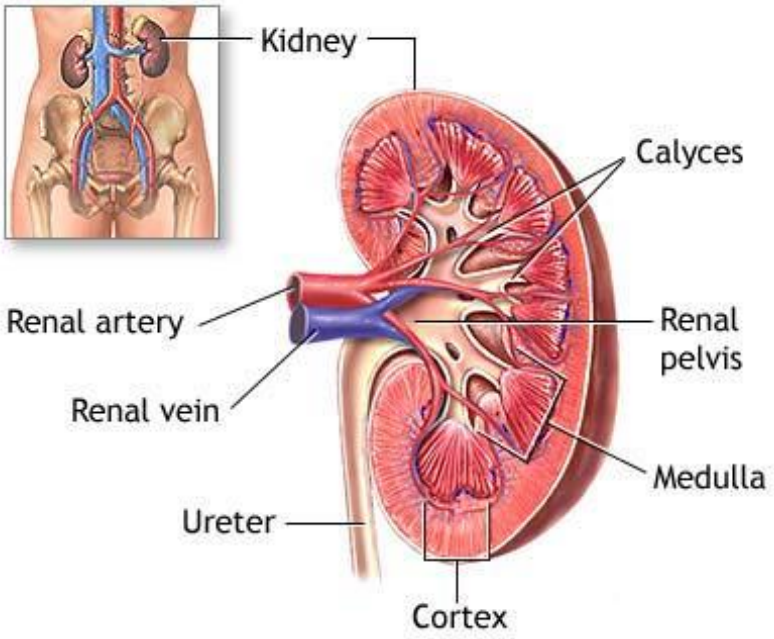
Path from Research to Implementation



Kidney Disease

- Principal treatment options:
  - Dialysis (home or clinic)
  - Transplant (live or deceased donor)

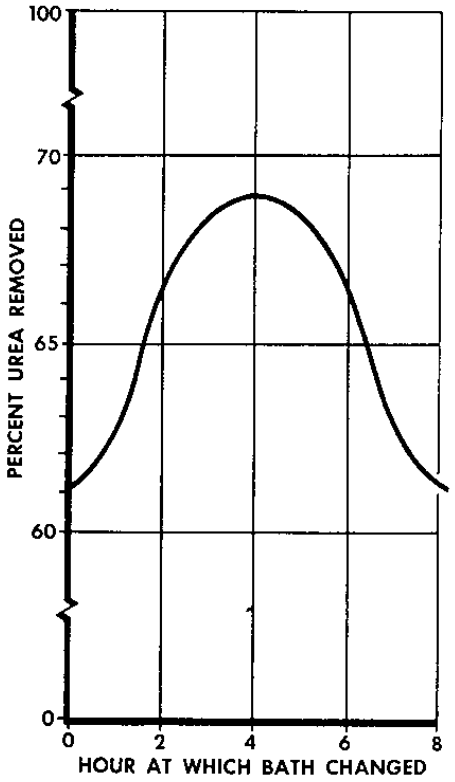
- More than 350,000 people are on dialysis and 80,000 waiting for transplant



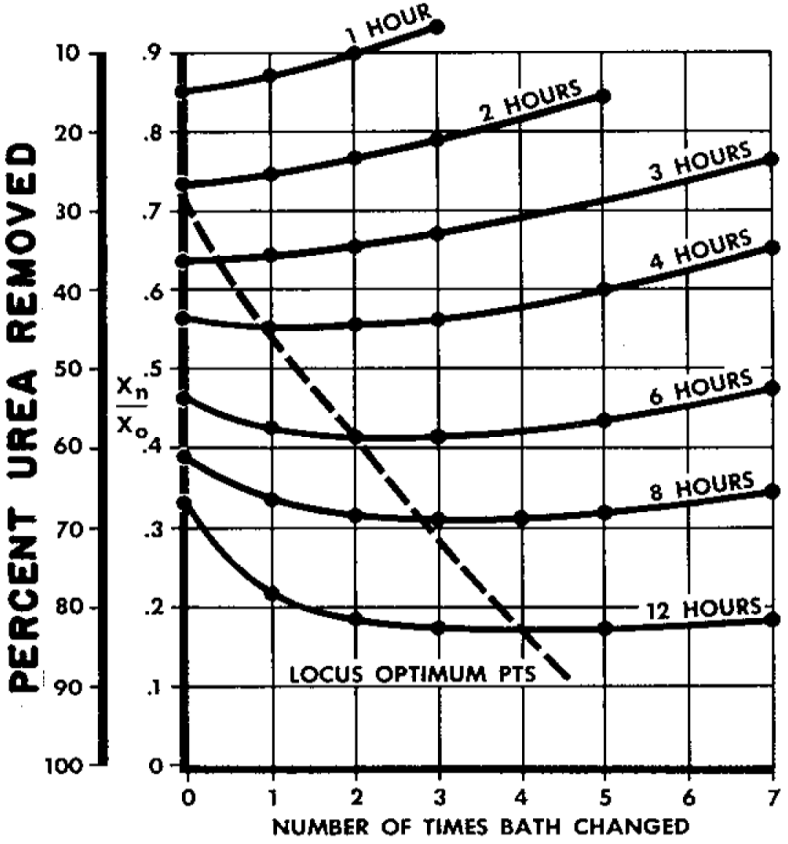
Nonlinear Optimization

Miller, J.H. et al., 1960, Optimization of Certain Parameters in Hemodialysis, Transactions - American Society for Artificial Internal Organs, 6(1); 68-75

Optimal time to change bath



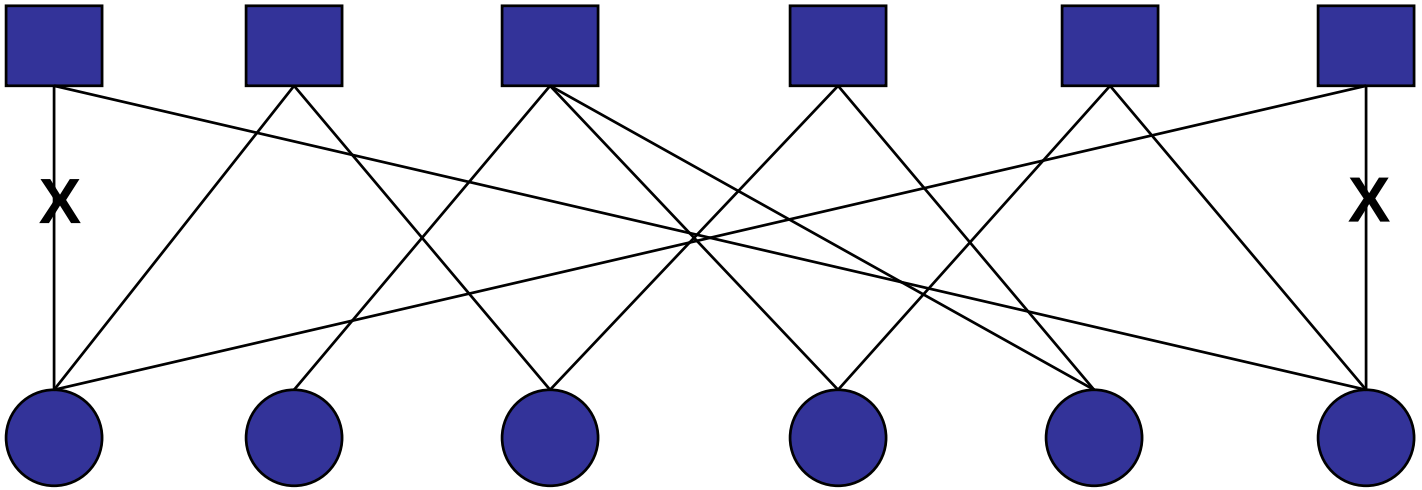
Optimal time to change bath



Optimization of Kidney Transplants

Kidney Exchange

Donors



Recipients

Criteria

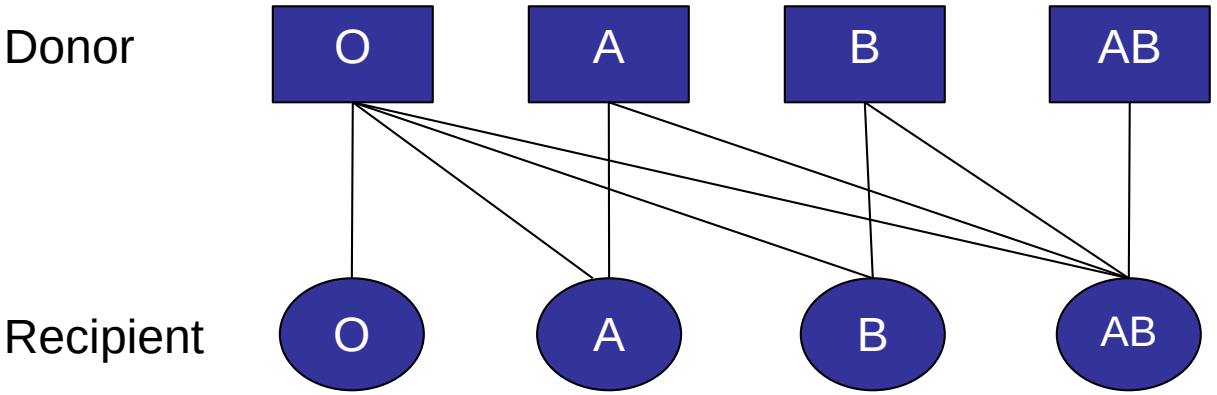
- Number of matches
- Number of priority matches
- Immunologic concordance
- Travel requirements

Constraints

Compatibility is determined by two primary factors:

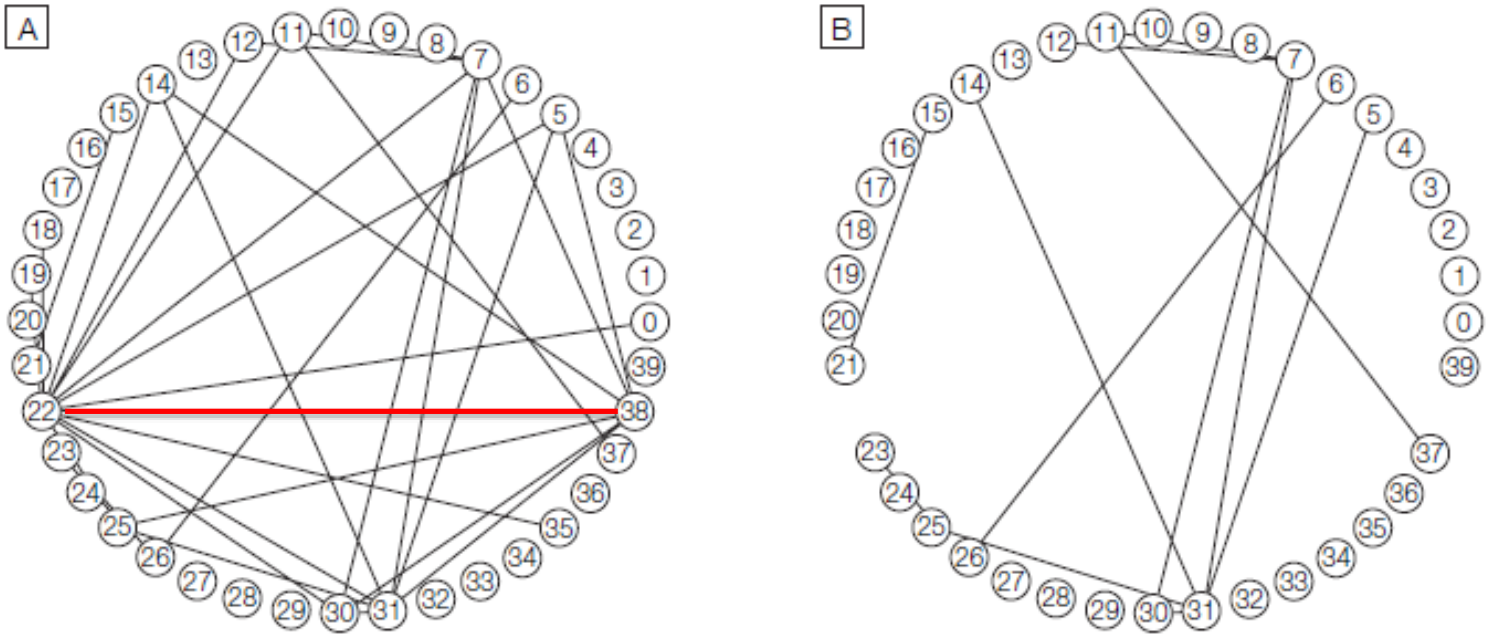
- Blood type
- Tissue antibodies

Blood type compatibility



Paired Matching

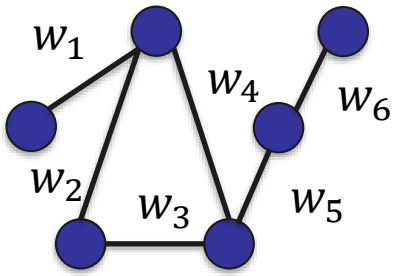
Figure 1. Graph Theory Model of Donor/Recipient Nodes, With Links Indicating Compatible Matches

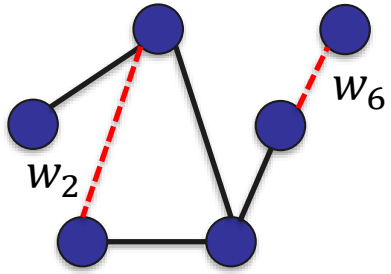


Segev, D, Gentry, S.E., Warren, D.S, Reeb, Montgomery, RA, 2005, Kidney Paired Donation and Optimizing the Use of Live Donor Organs, *JAMA,* 293(15), 1883-1890.

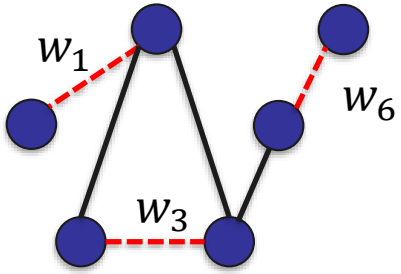
Maximum Edge Weight Matching

Given a graph $G(V, E)$ a *matching* is a set of pairwise nonadjacent edges.





2 matches



3 matches

A maximal edge-weight matching is a set of non-adjacent edges with maximum total weight among all matches.

Maximum Edge Weight Matching

A matching problem for a graph $G(V, E)$ can be expressed as an *integer program*

$$Max \ \sum_{e \in E} w_e x_e$$

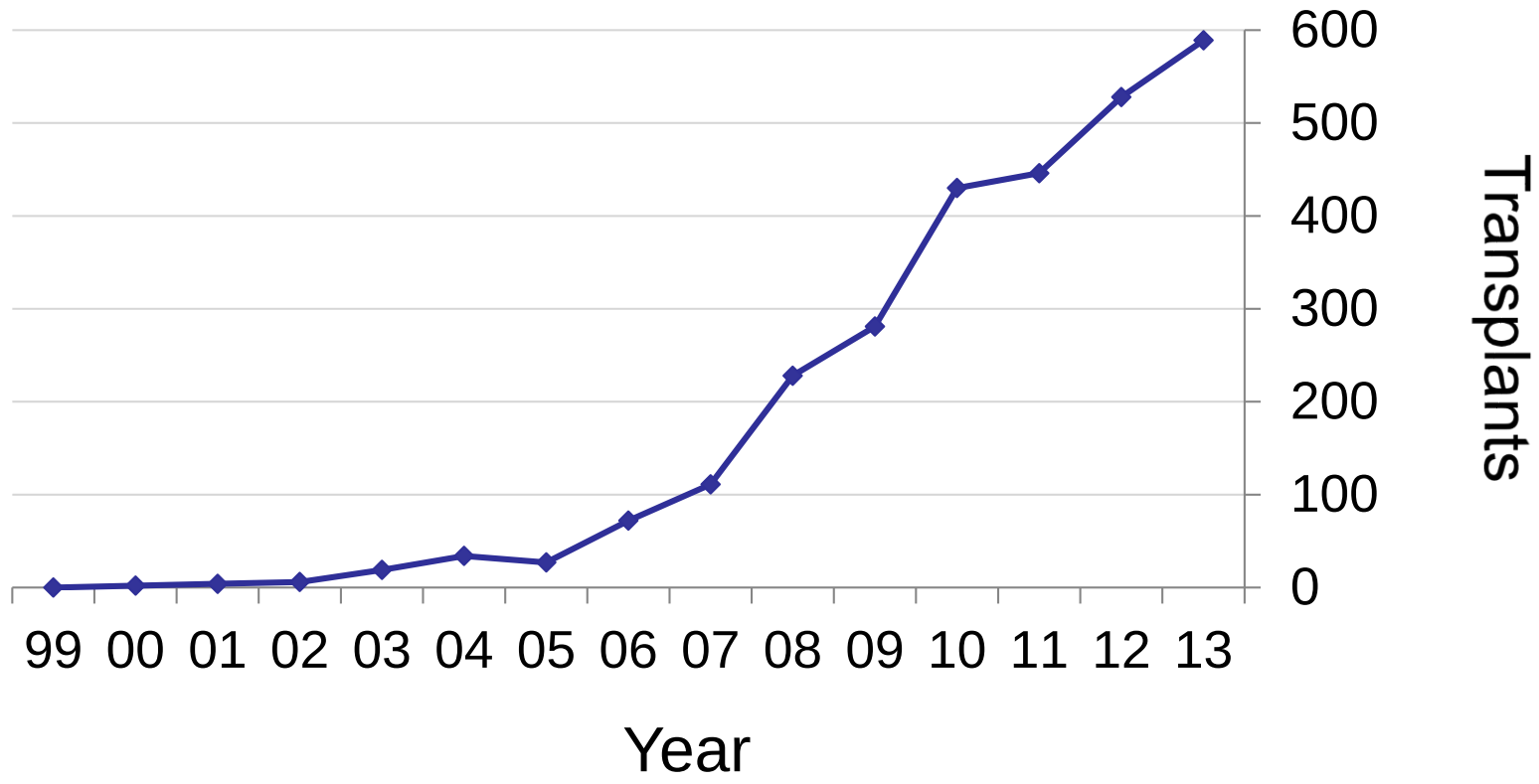
$$Subject\ to:$$

$$\sum_{e \sim v} x_e \leq 1, \ \ for\ all\ v \in V$$

$$x_e \in \{0,1\}, \ for\ all\ e \in E$$

Edmonds, J. 1965. "Paths, trees, and flowers". Canadian J. Math. 17: 449–467.

Growth in Paired Transplants



From 1 in 1999, to nearly 600 in 2013, KPD now comprises 10% of living kidney donations**

**Figure courtesy of Sommer Gentry, US Naval Academy; www.optimizedmatch.com

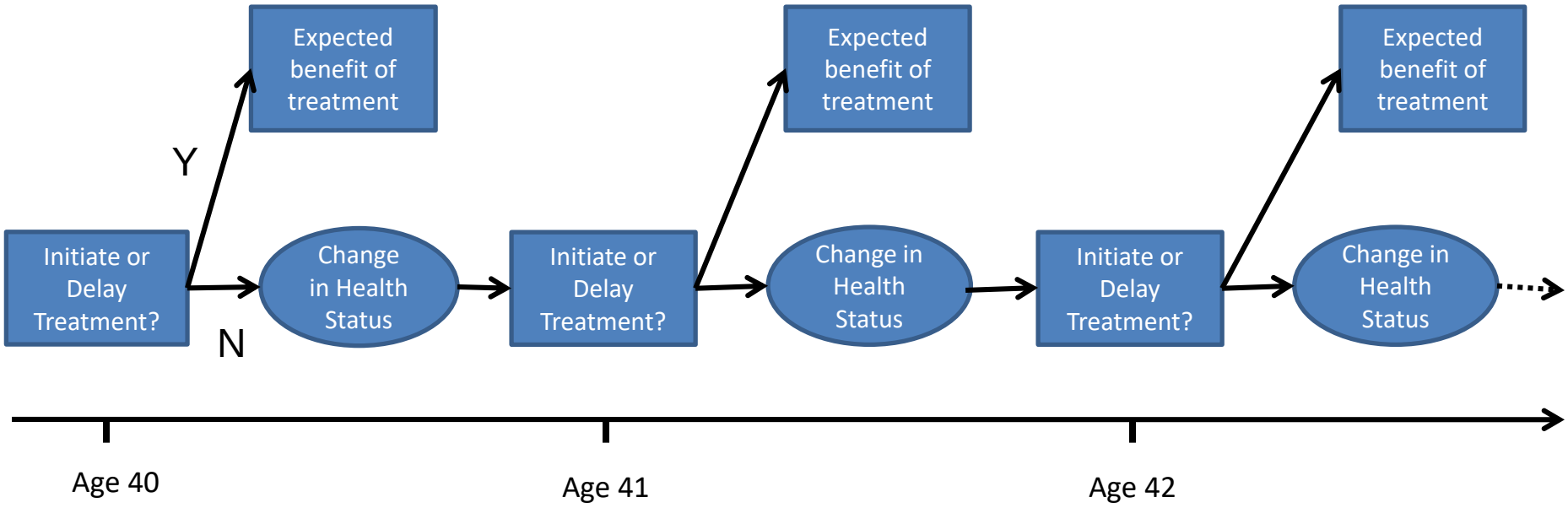
Diabetes

- 29 million people have diabetes in the U.S.
  - 9% of the U.S. population
  - 90% have type 2 diabetes
- Two out of three people with diabetes will die from cardiovascular diaesse
- Cholesterol and blood pressure control are an important for prevention of cardiovascular disease

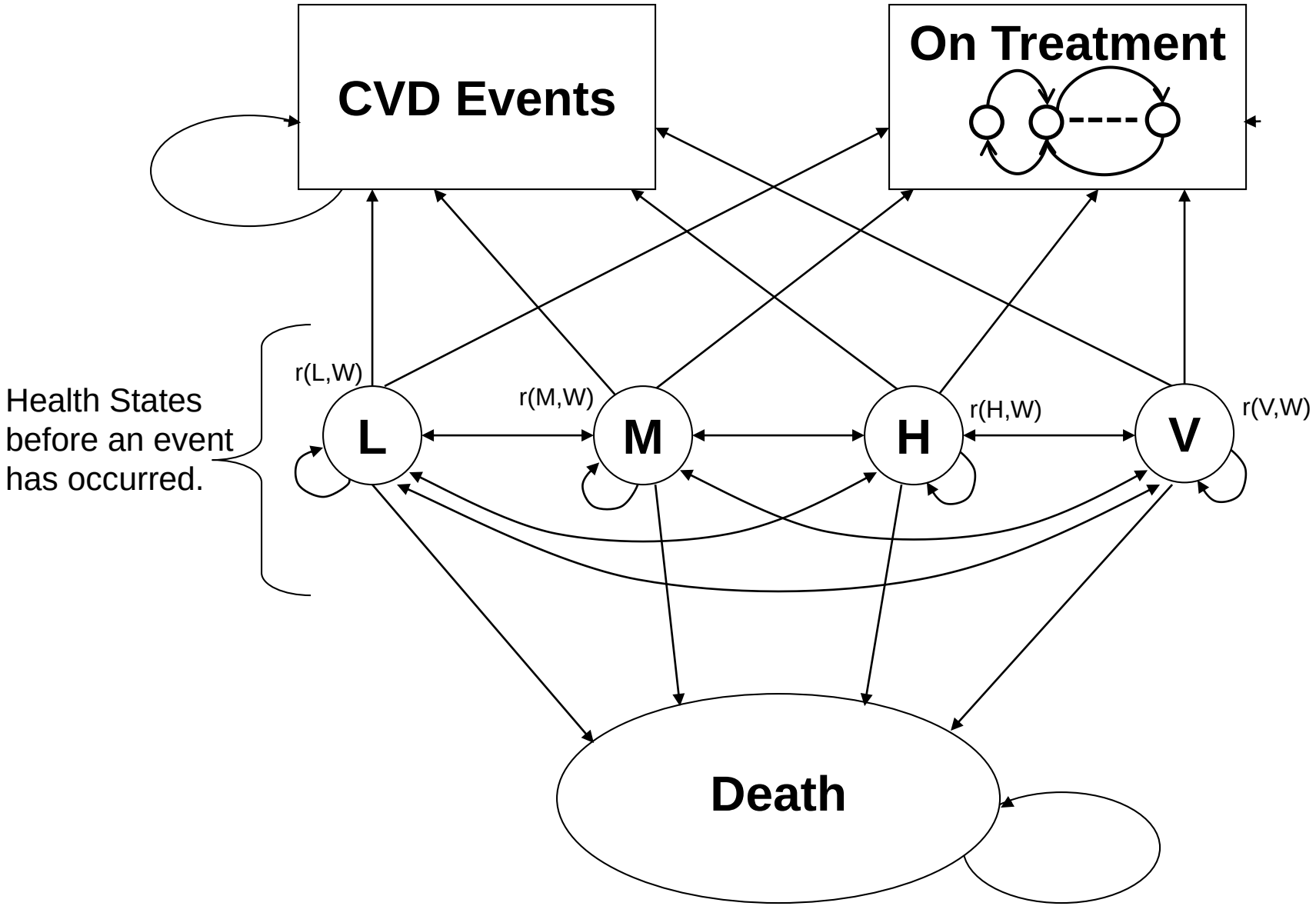
Mason, J.E. et al. 2014. Optimizing the Simultaneous Management of Blood pressure and Cholesterol for Type 2 Diabetes Patients. European Journal of Operational Research; 233(3) 727-738.

Sequential Decision Making

- Choose the best action each time period to maximize long term expected rewards



State Transition Diagram



Markov Decision Process

- Health status: $s_t \in S \equiv \{1,2,3,\ldots..L, L+1\}$
- Treatment decision in state s_t: $a(s_t) \in A(s_t)$
- Optimality Equations for all $s_t, t = 1, \ldots, T-1$:

Optimal Reward to Go in Health State s_t

Period t Reward

Discounted Expected Future Reward

$$v_t(s_t) = \max_{a_t}\{r(s_t, a_t) + \lambda \sum_{\forall s_{t+1}} p(s'_t|s_t, a_t) v_{t+1}(s'_t)\}$$

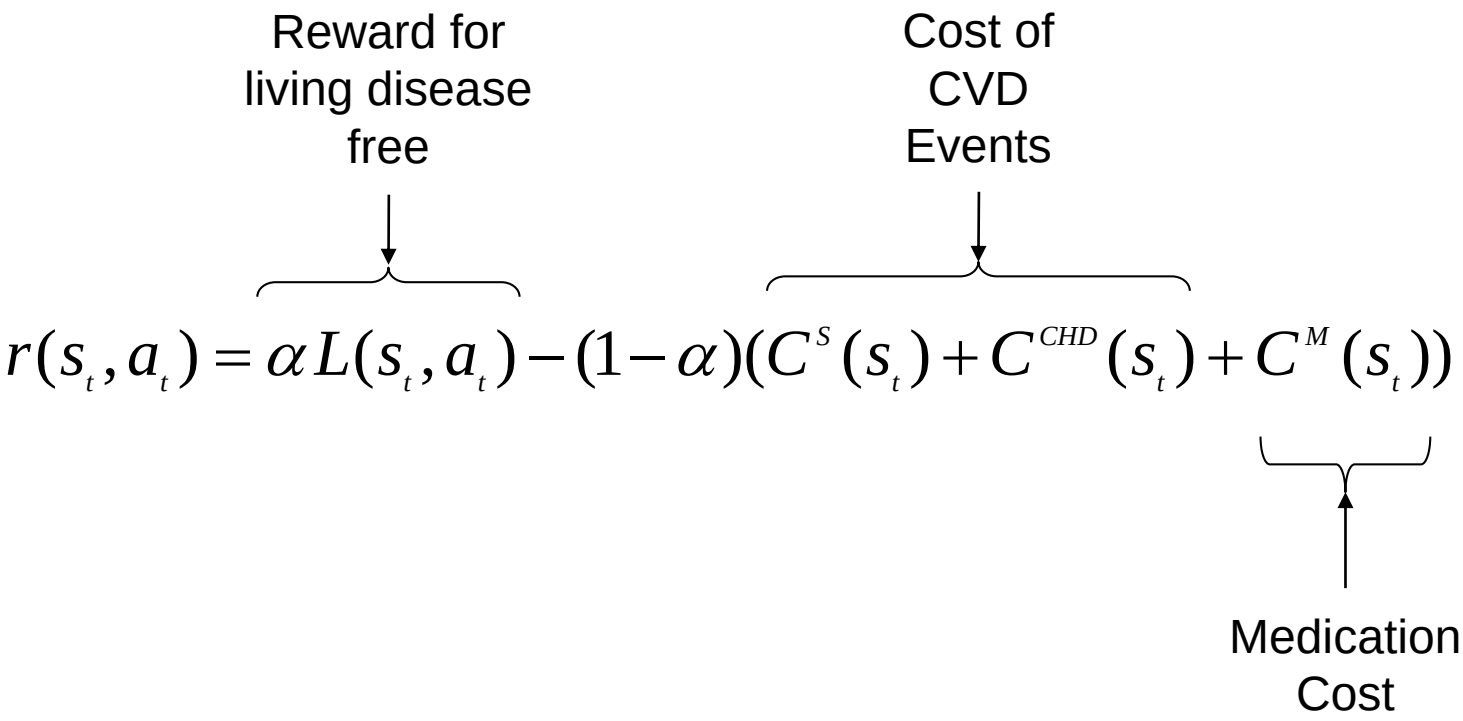
Transition probabilities

$$v_T(s_T) = r(s_T)$$

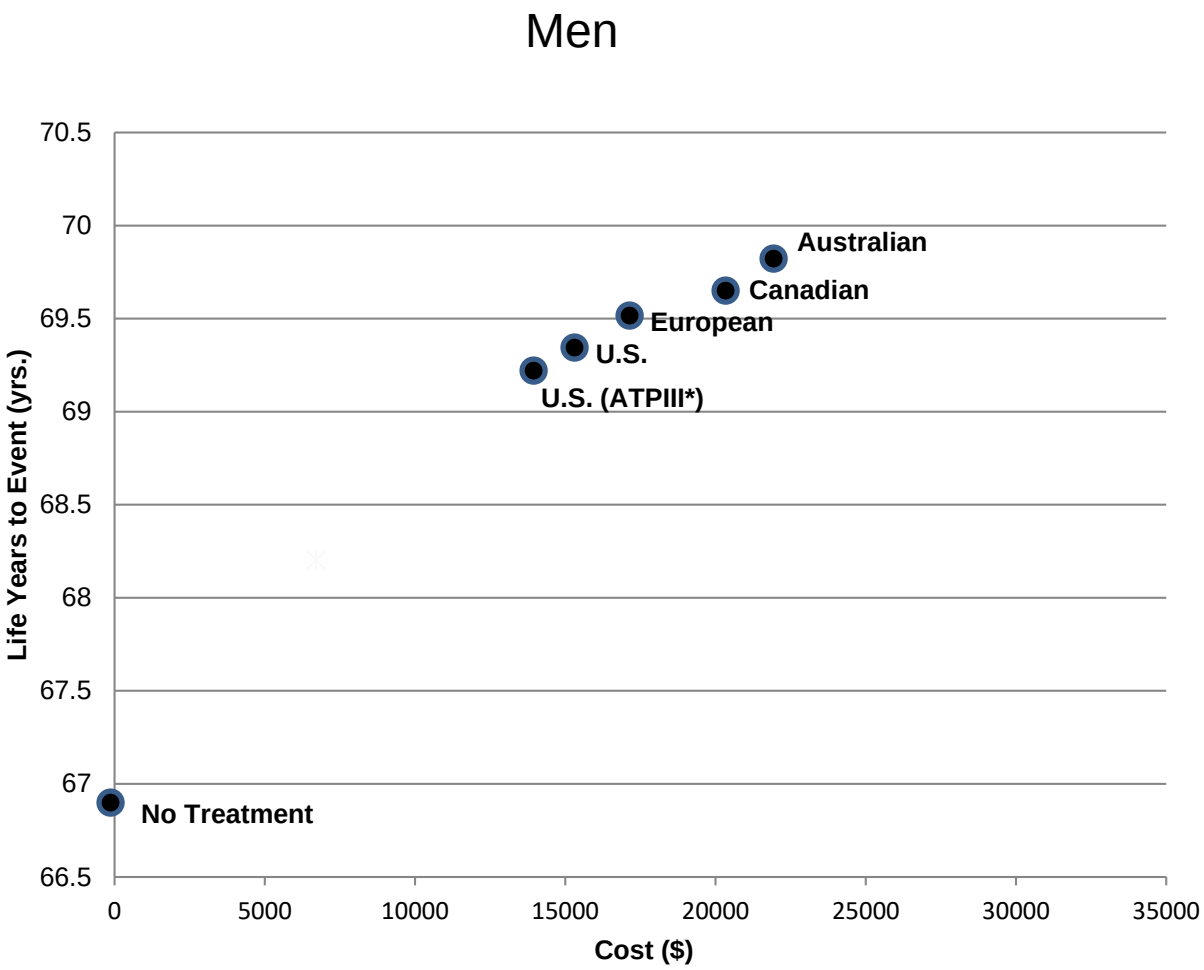
Boundary condition

Reward Function

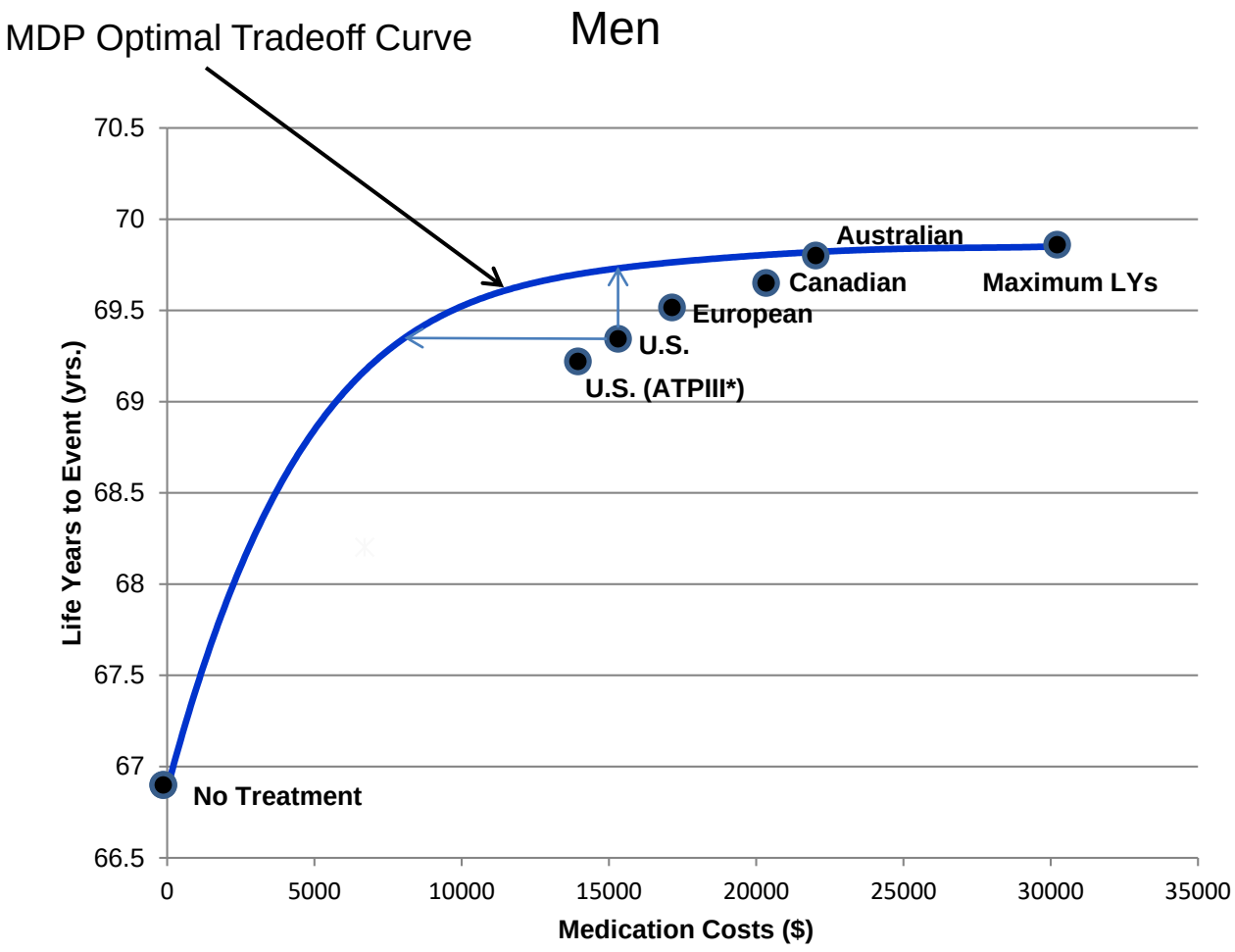
Rewards for each state action pair define the objective function for a Markov decision process



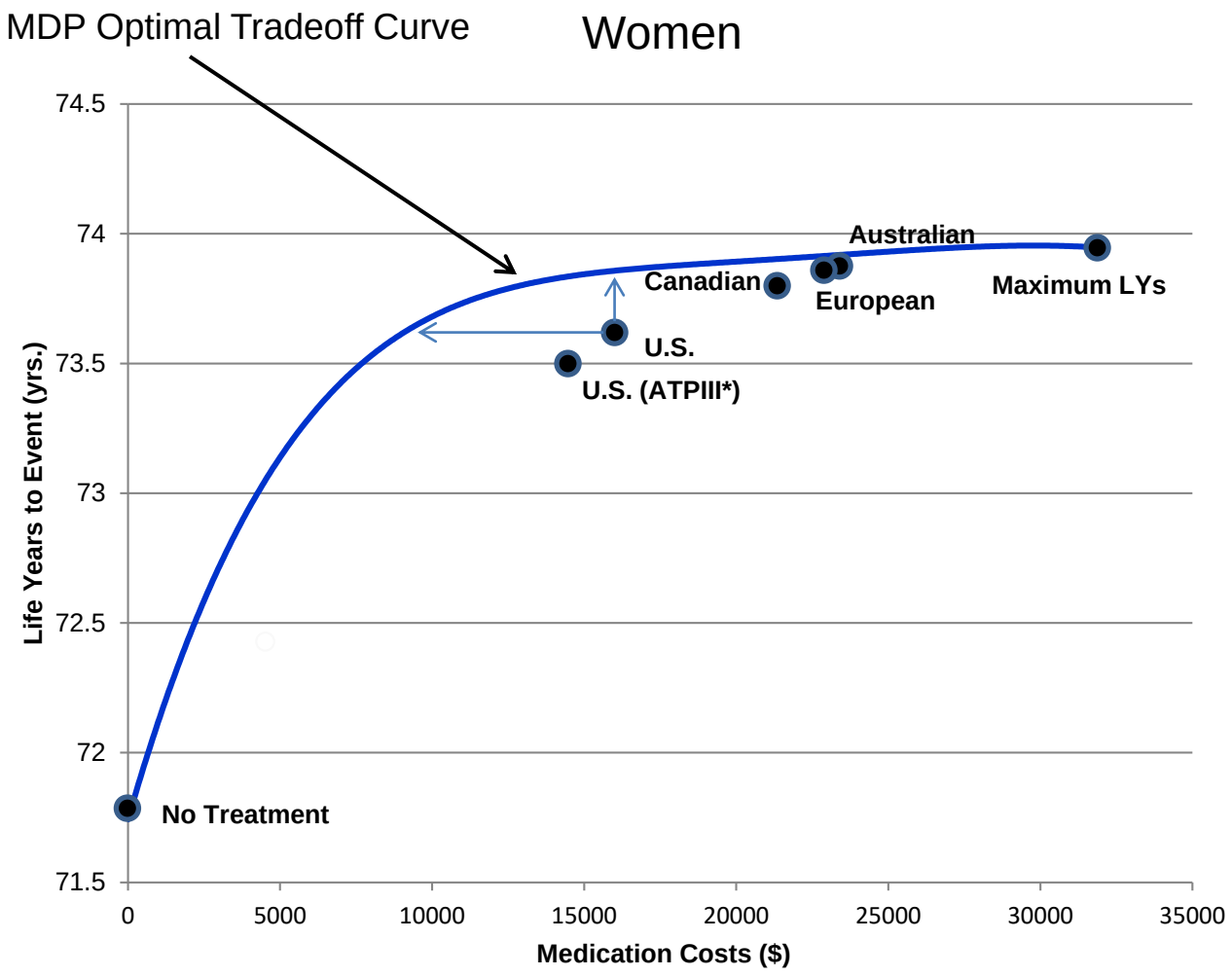
Policy Evaluation



Optimal Policy vs Guidelines



Optimal Policy vs Guidelines



Other Work

- Liver Transplants: Alagoz, Maillart, Schaefer, Roberts, *Management Science*, 2004
- Breast Cancer: Maillart, Ivy, Ransom, Dielhl, *Operations Research*, 2008
- HIV: Shechter, Schaefer, Roberts, *Operations Research*, 2008
- Prostate Cancer: Zhang, Denton, Balasubramanian, Shah, *M&SOM* 2012
- Adherence Screening: Ayer, Alagoz, Stout, Burnside, Management Science, 2015
- Colorectal Cancer: Erenay, Alagoz, Said, *M&SOM* , 2014

Markov Decision Processes for Screening and Treatment of Chronic Diseases

Markov Decision Processes in Practice pp 189-222

Part of the International Series in Operations Research & Management Science book series (ISOR, volume 248)

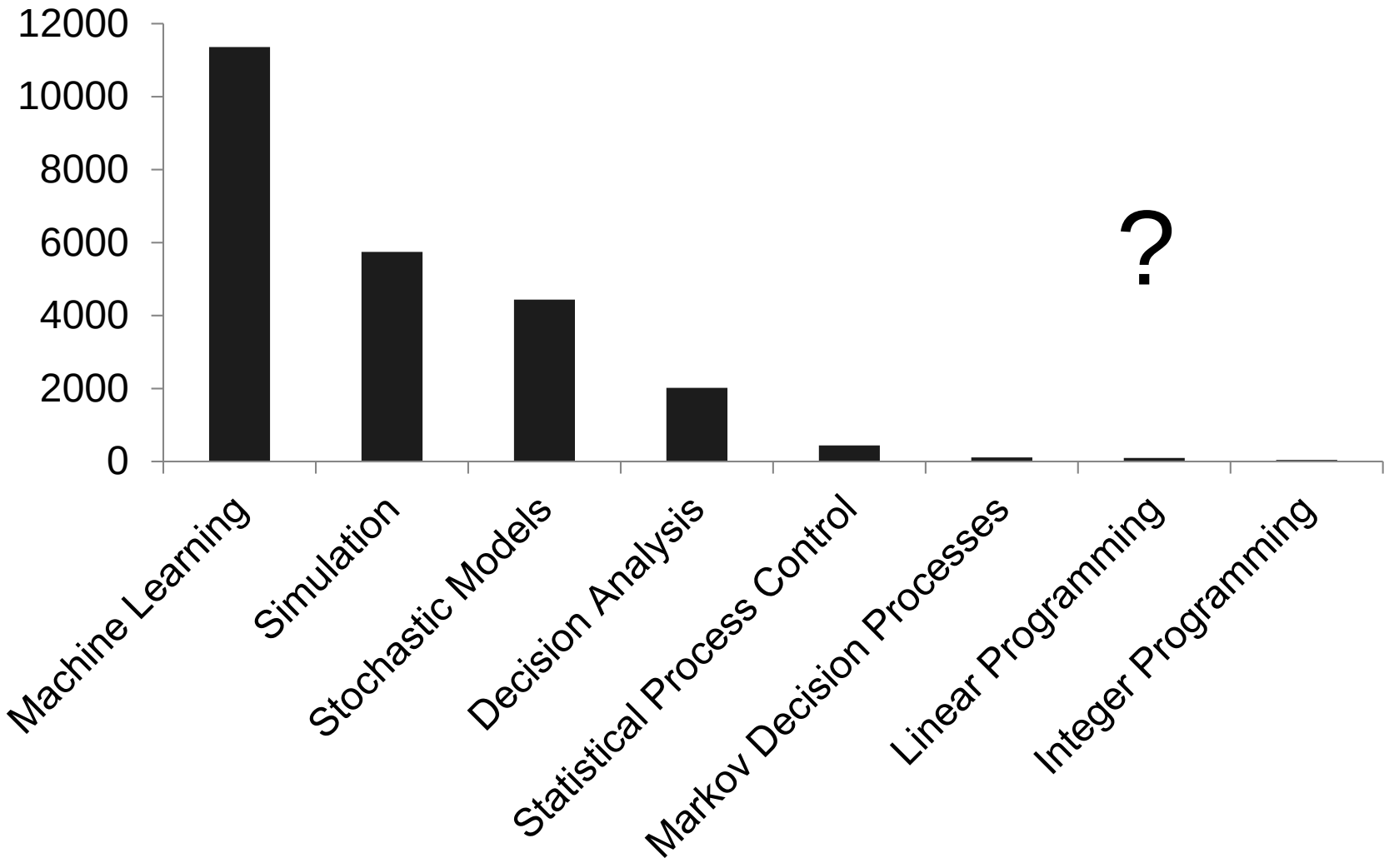
- Lauren N. Steimle (1) Email author (steimle@umich.edu)
- Brian T. Denton (1)

1. Department of Industrial and Operations Engineering, University of Michigan, Ann Arbor, USA

IOE 512: Dynamic Programming, Fall Semester

Optimization in Medicine: Future Opportunities

PubMed Search Results



Sequential Decision Making

Research Questions:

- When to screen for diseases? Which biomarkers to use?
- When to use diagnostic tests?
- When to initiate treatment?

Methods:

- Markov decision processes
- Partially observable Markov decision processes
- Multi-stage stochastic programming
- Reinforcement learning

Example

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

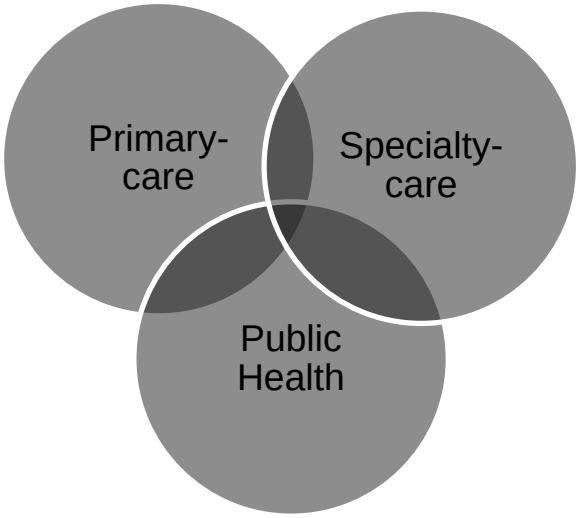
- Difficult real time optimal control problem
- Must maintain glucose levels within a defined range
- Current glucose state difficult to predict

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

Resource Constrained Decision Making

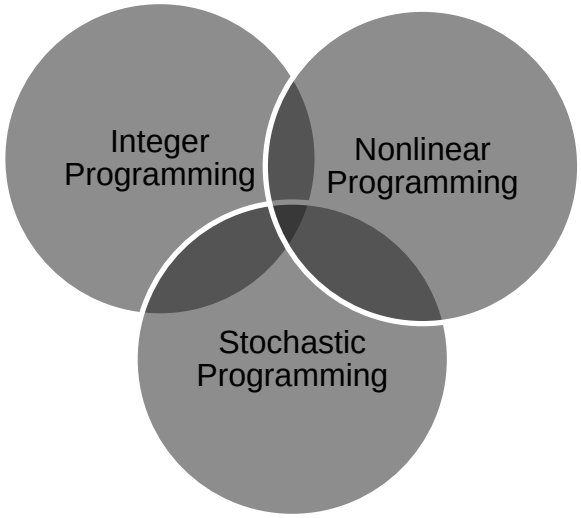
Research Questions:

- Coordination across medical “silos”
- Prioritizing treatment in resource constrained settings:
  - High value health care
  - Constrained burden on patients



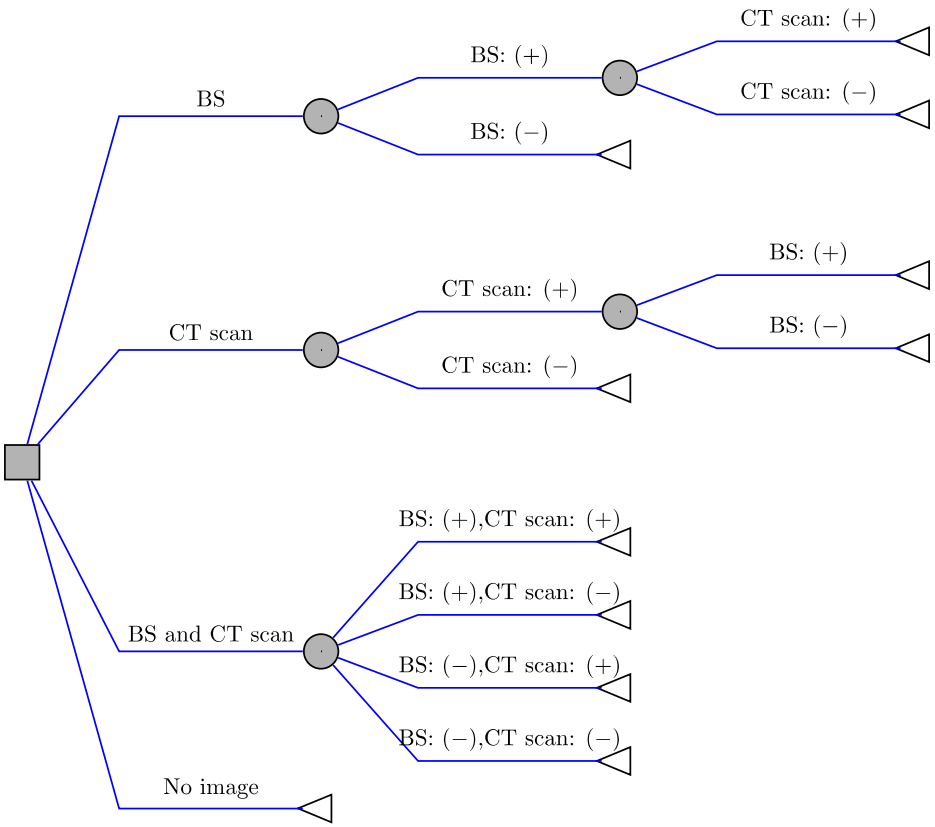
Methods:

- Discrete optimization
- Stochastic and robust optimization
- Convex approximations



Example

Optimizing the coordination of imaging decision for cancer staging



Statistical variation

$$\min \sum_{\forall j} \sum_{\forall p} n_{kp} z_{jp}$$

$$Subject\ to:$$

$$\sum_{\forall j} \sum_{\forall p} m_{jp} z_{jp} \leq \alpha$$

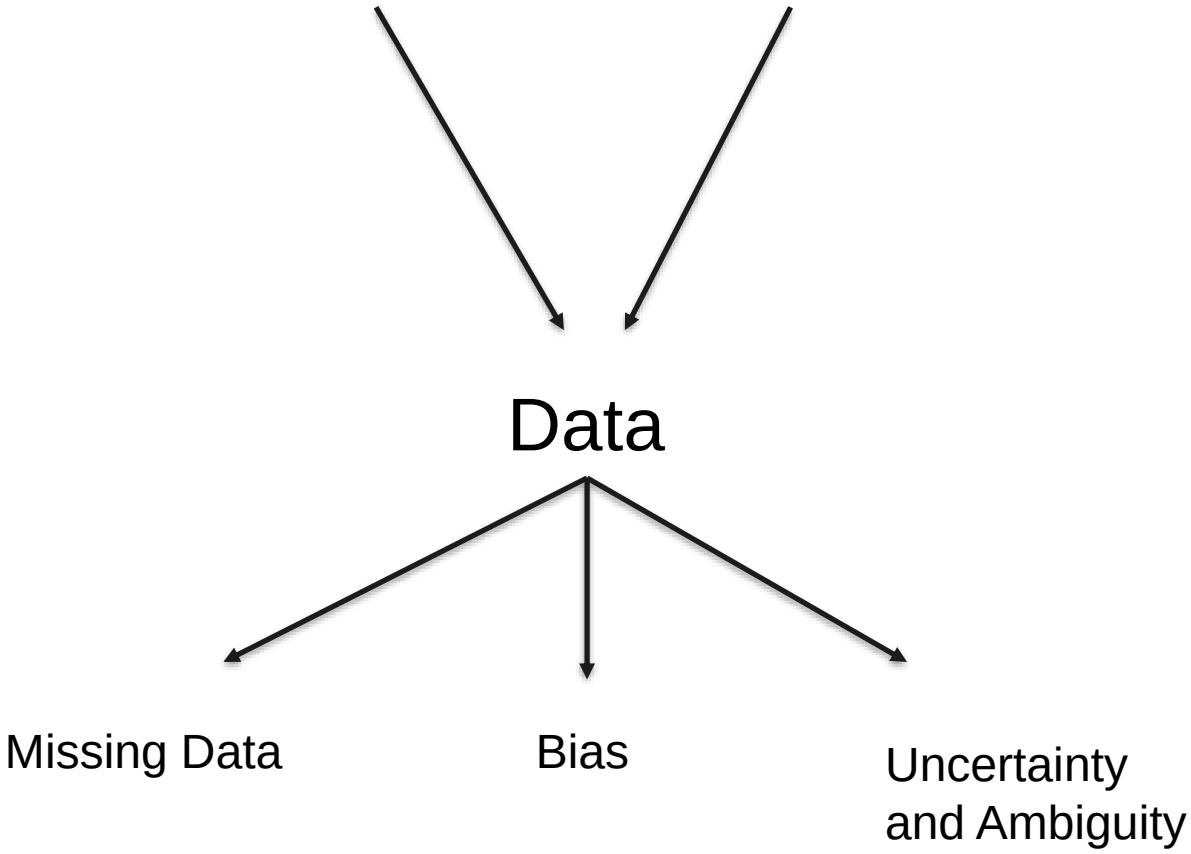
$$\sum_{\forall p} z_{jp} = 1, \qquad \forall j$$

$$z_{jp} \in \{0,1\}, \quad \forall j, p$$

Research with Selin Merdan, IOE PhD Candidate, UM

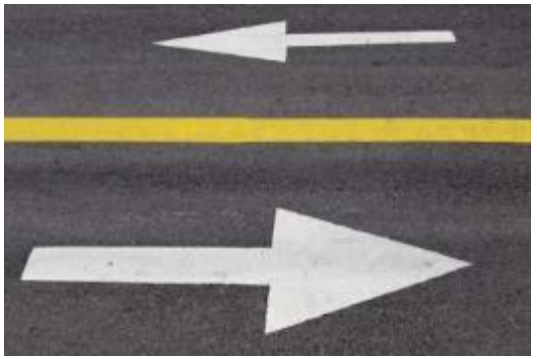
Intersection of Optimization and Statistics

$$max\ \{ f(x) \ \ | x \in C \}$$



Takeaways

- Optimization can improve medical decision making and vice versa but…



- It is underutilized and there are many challenges and unexplored opportunities

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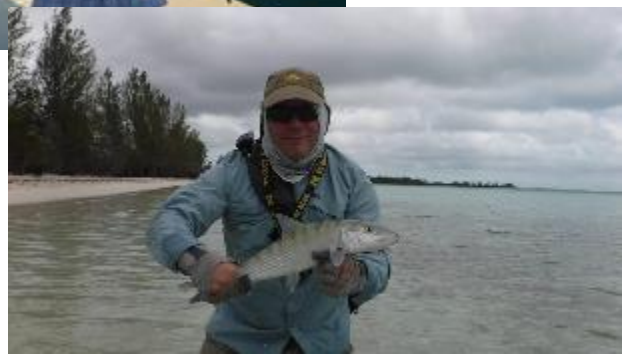

These slides are on my website:

http://umich.edu/~btdenton