Active Surveillance of Prostate Cancer in the Context of Model Ambiguity

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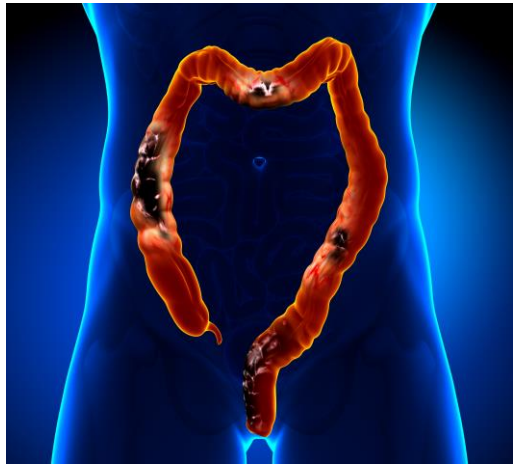
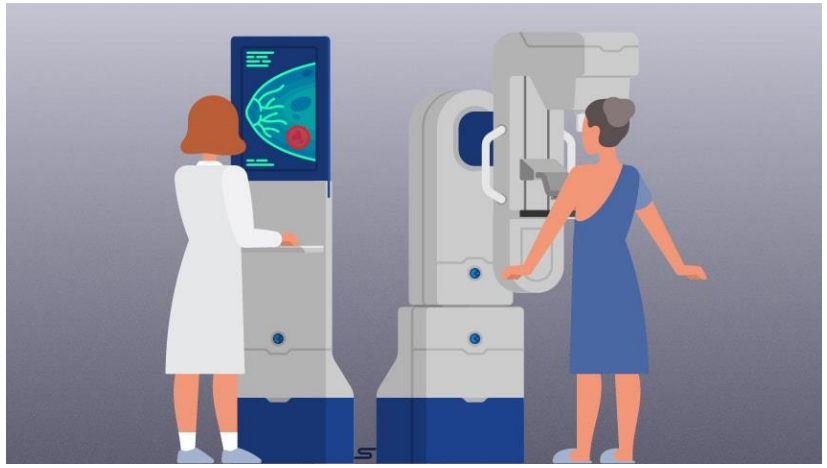
Early detection of cancer

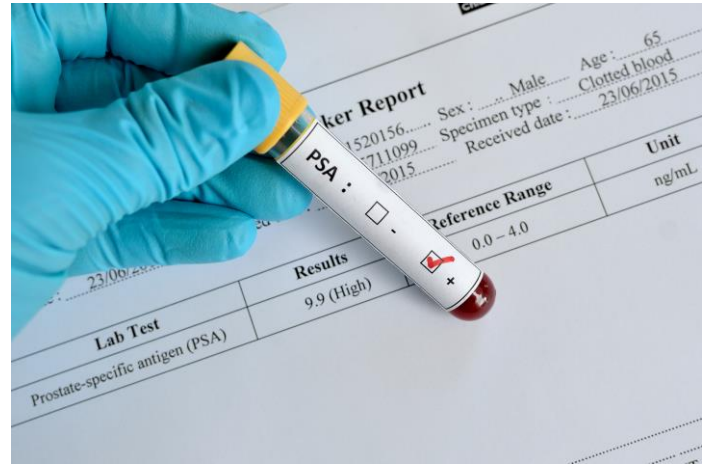
Early detection offers the opportunity for definitive treatment and cure, but many "low-risk" cancers are detected along the way



Colonoscopy Screening for Colorectal Cancer



Mammography Screening for Breast Cancer



Prostate-specific Antigen (PSA) Test for Prostate Cancer

Source: Harvard Health Publications + Michigan Health Lab

Cancer surveillance is challenging

- **Unobservable cancer state**, and stochastic transitions over time
- **Imperfect** diagnostic tests with false positive and false negative outcomes
- **Conflicting goals** to balance benefits and harms

Active surveillance of prostate cancer

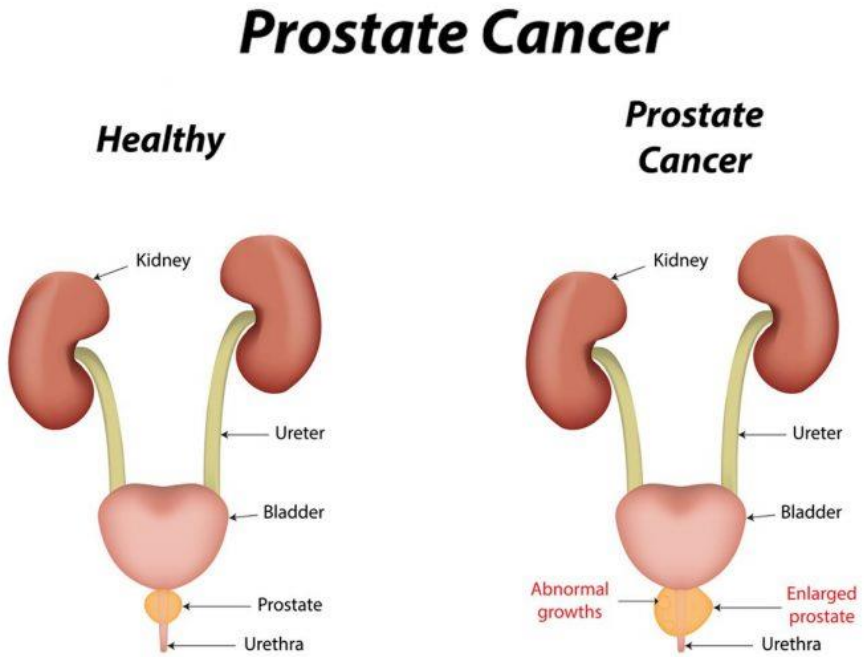
Active Surveillance (AS): monitoring “low-risk” patients with prostate specific antigen (PSA) tests and prostate biopsies

PSA Test

- Blood test with almost no direct harm
- Recommended every 6 months
- Very high rate of false positives and false negatives

Biopsy

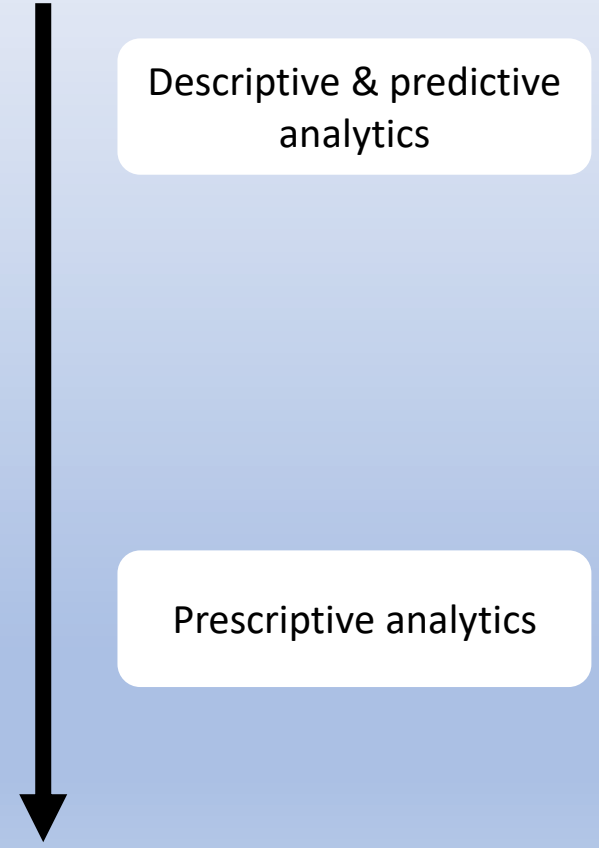
- Sampling the tissue with needles
- Painful and harmful
- Much more reliable than PSA test, but still imperfect



Source: joshya - Fotolia

Progression of Data-Driven Models for Active Surveillance of Prostate Cancer

- **Natural history modeling by HMM**
- **POMDP for individualized sequential decision-making**
- **Multi-POMDP model for addressing model ambiguity**



Urologists disagree on the best strategy for when to biopsy patients

Study	Recommended Biopsy Plan
Johns Hopkins (JH)	Annual biopsy
University of California, San Francisco (UCSF)	Biopsy 1 year after diagnosis, then every 1 to 2 years
Prostate Cancer Research International Active Surveillance (PRIAS) / University of Toronto (U of T)	Biopsy 1 year after diagnosis, then every 3 years

Data from surveillance studies

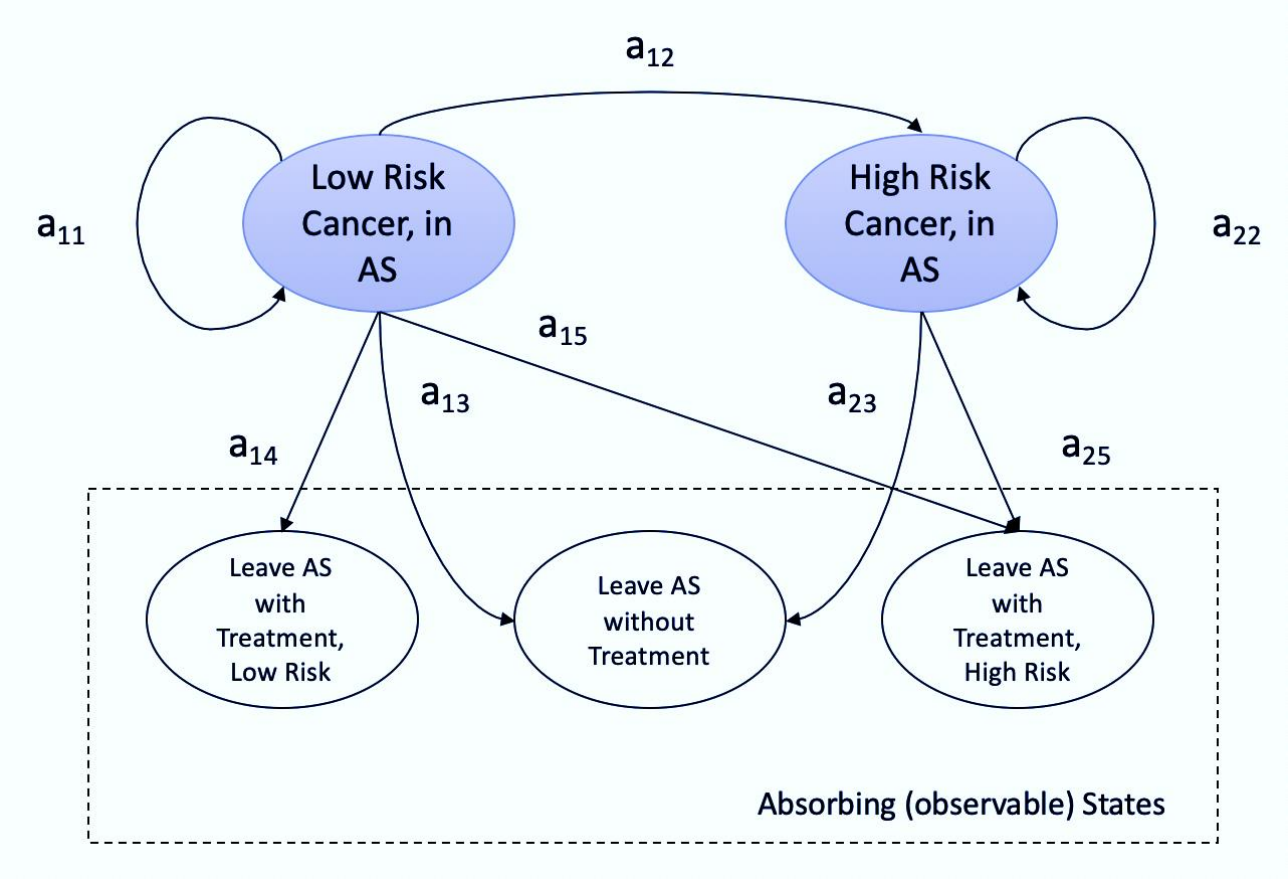
Movember Global Prostate Cancer Database:

- Includes 15,101 patients from 25 established AS cohorts worldwide
- Longitudinal observations of patients' clinical and demographic data

We picked 4 major AS cohorts (9,021 patients):

- Johns Hopkins (JH) Hospital
- University of California San Francisco (UCSF) Medical Center
- University of Toronto (U of T) medical center
- Prostate Cancer Research International Active Surveillance (PRIAS) project

Hidden Markov Model



- Time periods: annual time periods from the start to the end of the AS
- Initial distribution (at diagnosis)
  $$\phi = (\phi_1, 1 - \phi_1)$$
- Transition probability matrix:
  $$P = [\mathbb{P}(s_{t+1}|s_t)]$$
- Observation at time t:
  $$O_t = (X_t, Y_t)$$ (PSA, Biopsy)
- Observation probability
  $$F = [\mathbb{P}(o_t|s_t)]$$

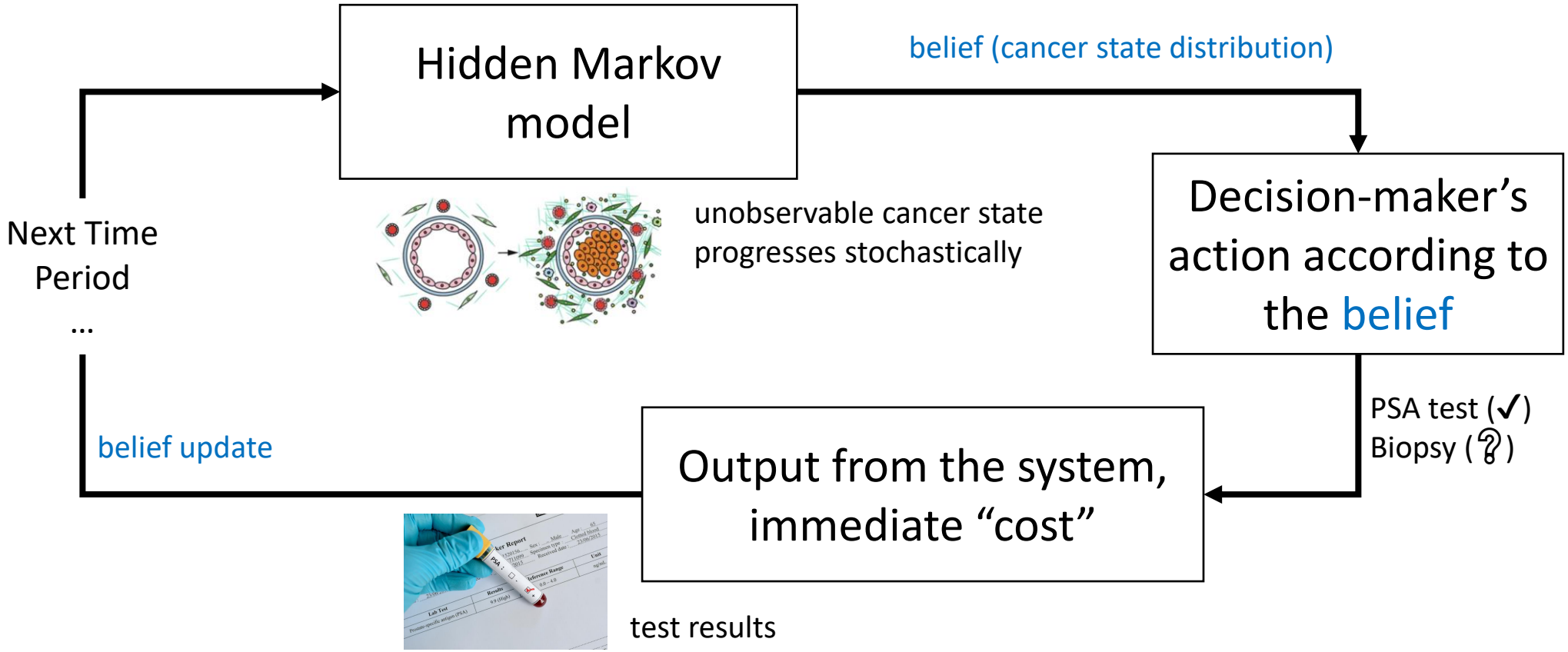
HMM model estimates for 4 different studies

Study	Mis-classification Error at Diagnosis	Annual Grade Progression Rate	Biopsy Sensitivity (True Pos.)	Biopsy Specificity (True Neg.)
JH	5.83% (0.74%)	6.91% (0.43%)	71.84% (0.53%)	99.72% (0.61%)
UCSF	8.09% (0.75%)	12.17% (0.85%)	74.31% (0.89%)	99.25% (0.80%)
U of T	7.74% (0.83%)	10.16% (0.79%)	79.49% (0.69%)	99.62% (0.75%)
PRIAS	6.53% (0.44%)	8.41% (0.73%)	76.14% (0.72%)	99.20% (0.95%)

Estimated parameters (and bootstrapped standard errors) by the HMMs in different studies.

Li, W. Denton, B.T., et al. “Comparison of biopsy under-sampling and annual progresssoin using hidden Markov models to learn fom prostate cancer active surveillance studies,” *Cancer Medicine*, 2020

POMDP for sequential decision-making



Goal: Minimize the weighted sum of harm from biopsies and delays in detection of high-risk cancer

Cancer Progression Figure by Alice Santi

Optimal value function & policy

The optimal policy $\pi^* = (\pi_0^*, \dots, \pi_T^*)$ achieves the maximum value function

$$V_t^{\pi^*}(b_t) \coloneqq \arg\max_{\pi} \mathbb{E}^{m,\pi}\left[\sum_{k=t}^{T} \gamma^{k-t} r^m(s_k, a_k, o_k) | b_t^m\right], \forall b_t, \forall t < T, \forall m$$

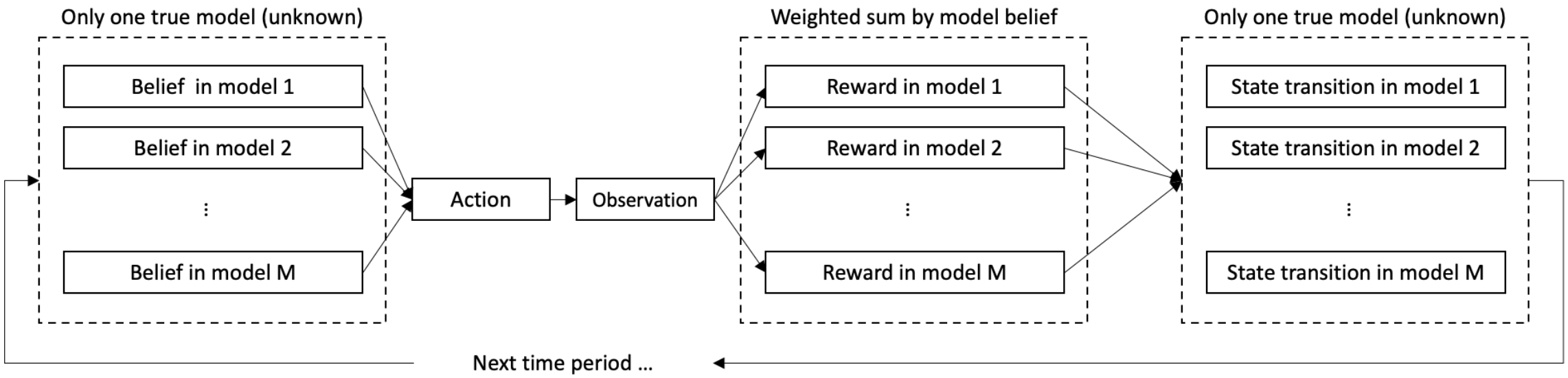
with the boundary condition

$$V_T^{\pi^*}(b_T) \coloneqq \arg\max_{\pi} r(b_T, \pi(b_T)), \forall b_T$$

where $\gamma \in [0,1]$ is a discount factor for future rewards.

Li W., Denton B.T., Morgan T.M.. "Optimizing Active Surveillance for Prostate Cancer Using Partially Observable Markov Decision Processes," *European Journal of Operational Research,* 2022.

Multi-Model POMDP



- True model is unknown
- A single policy is sought to minimize weighted costs

Results

- Objective: find the optimal timing of biopsies when the true model of each patient is unknown

- Cost function: weighted sum of
  1. number of biopsies to conduct
  2. delay time in detecting cancer progression

- non-informative prior model weights: $\lambda_1 = \lambda_2 = \lambda_3 = \lambda_4 = 1/4$

Comparison of the optimal policies when applying different models

Center	Minimum cost of the optimal policy (regret %)				
	JH model	UCSF model	U of T model	PRIAS model	MPOMDP model
JH	2.74 (0)	2.92 (6.50%)	3.84 (40.42%)	3.01 (9.89%)	2.87 (4.80%)
UCSF	2.54 (5.35%)	2.41 (0)	2.95 (22.45%)	2.68 (11.33%)	2.49 (3.33%)
U of T	2.65 (12.34%)	2.42 (2.39%)	2.36 (0)	2.77 (17.54%)	2.40 (1.72%)
PRIAS	2.59 (4.19%)	2.63 (5.54%)	3.11 (24.71%)	2.49 (0)	2.54 (2.03%)

Table 4.7: The optimal value (minimum cost) function in different AS studies when applying different policies.

- For each study center, the best model is always the “true” POMDP
- For each study center, the MPOMDP model dominates all “wrong” POMDPs
- The regret of a “wrong” model can be very high

Take Away Messages

- Be careful relying on a single study; you might pick the “wrong horse”
- Model ambiguity is much more important than statistical variation in model parameters
- See this working paper for more details: →

- Or contact me at btdenton@umich.edu

Acknowledgments

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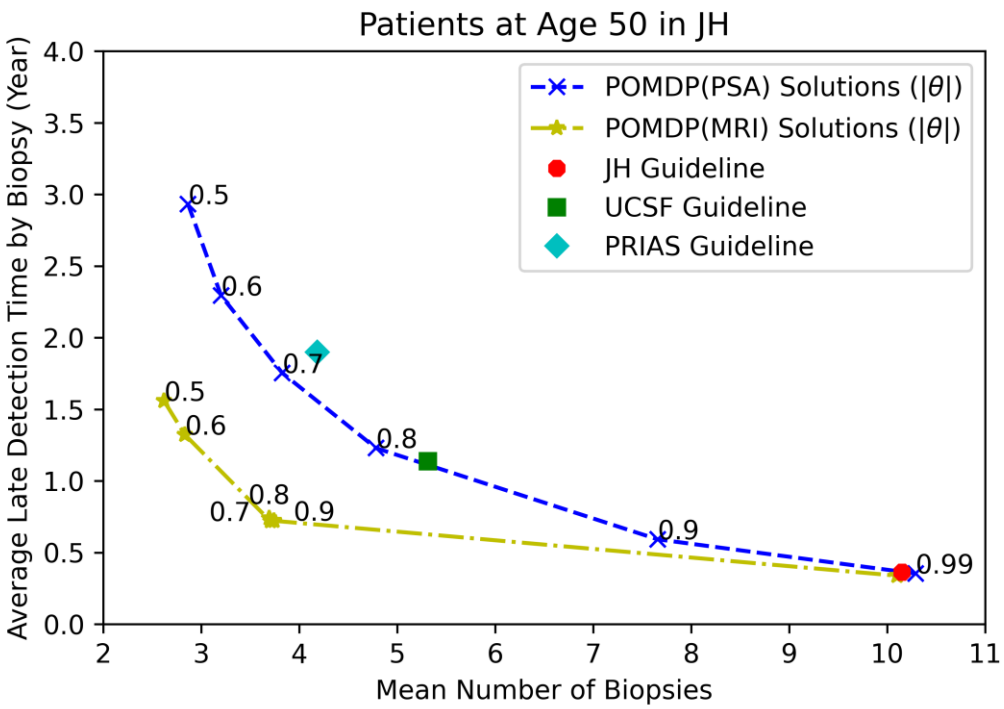
Backup slides

Bonus Example!

- Magnetic resonance imaging (MRI), is being adopted by some centers

- We conducted an experiment using MRI with the PSA test to show its potential impact.



The comparison between policies given by two AS-POMDP (PSA and MRI) models and current biopsy guidelines in the JH center.

Approximate methods: initialization with a lower bound

At each time t, recall the optimal value function

$$V_t(b_t) = \max_{\alpha \in \mathcal{A}} b_t \cdot \alpha, \forall b_t, \forall t$$

Instead of solving it for all $b_t \in [0,1]^M$, only sample a subset of belief points $B_t \subset [0,1]^M$, and solve $V_t(b_t)$ for $b_t \in B_t$, which gives the lower bound $\bar{V}_t, \ \forall t$.

The Optimal Value Function

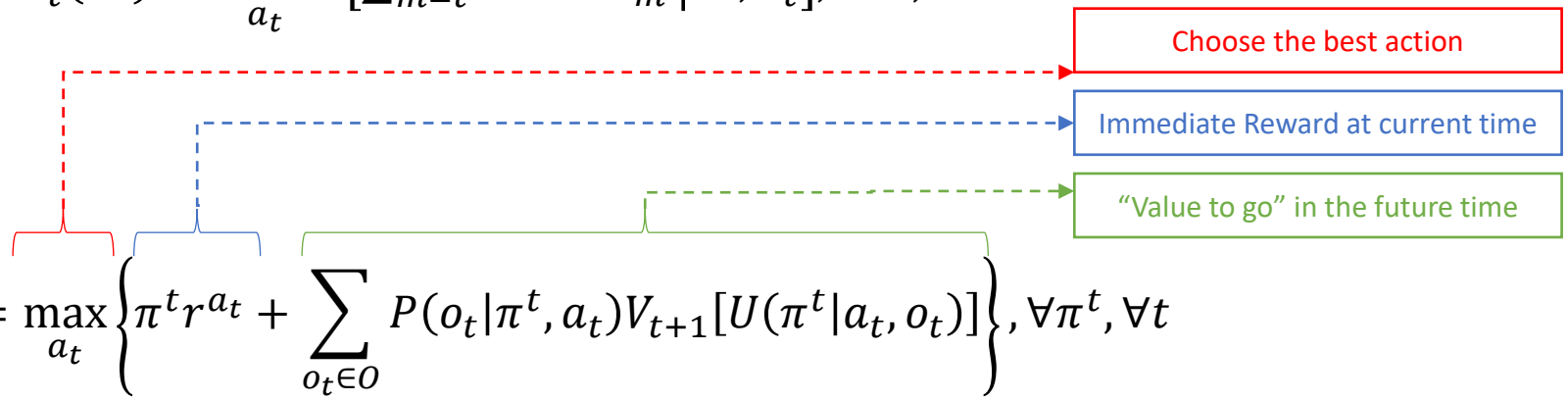
- Belief in high-risk cancer state

$$\pi^t \coloneqq P(S_t = \text{High Risk}), \forall t$$

- Optimal value function

$$V_t(\pi^t) \coloneqq \max_{a_t} \mathrm{E}\left[\sum_{m=t}^{\text{End}} \text{Reward}_m \,\middle|\, \pi^t, a_t\right], \forall \pi^t, \forall t$$

- Optimal equation



$$V_t(\pi^t) = \max_{a_t} \left\{ \pi^t r^{a_t} + \sum_{o_t \in O} P(o_t|\pi^t, a_t) V_{t+1}[U(\pi^t|a_t, o_t)] \right\}, \forall \pi^t, \forall t$$

where $U(\pi^t|a_t, o_t)$ is the updated belief calculated by the *Bayes formula*

- *Incremental pruning* algorithm (with approximation) to solve the POMDP (Cassandra et al. (1997))

Reference: Cassandra, A., Littman, M.L. and Zhang, N.L., 1997, August. Incremental pruning: A simple, fast, exact method for partially observable Markov decision processes. In *Proceedings of the Thirteenth conference on Uncertainty in artificial intelligence* (pp. 54-61). Morgan Kaufmann Publishers Inc..

The optimal individualized strategy

For each patient at time $t+1$, given the belief in high-risk cancer state $b_t, \forall t$:

1. Choose the optimal action given by:

value function

$$a_t^*(b^t) = \arg\max_{a_t} \mathrm{E}\left[\sum_t^{\mathrm{End}} \mathrm{Reward}_t \,\middle|\, b^t, a_t\right],$$

and observe the output o_t

2. Update his belief of being in high-risk cancer state: $b^{t+1} = P(S_{t+1} = \mathrm{high{-}risk} | b^t, a^t, o_t)$

… → previous belief b_t → choose action $a_t^*(b_t)$ → observe test results o_t → update belief b_{t+1} → …

Some related work in optimization under parameter ambiguity

- Robust optimization
  - e.g., robust DP (Iyengar 2005), Robust MDP (Nilim et al. 2005)
  - over conservative by optimizing the worst-case performance
- Multistage stochastic programming
  - e.g., Birge 2011 (textbook)
  - hard to tackle when the number stages increases
- Multi-model MDP
  - e.g., Steimle et al. 2018
  - only works for fully observable Markov processes

Weighted Value Problem

The objective is to find the optimal policy that performs well over all M POMDP models:

$$\max \sum_{m=1}^{M} \lambda_m \times \underbrace{\mathbb{E}[\text{future rewards in model } m | \text{curent beliefs, policy}]}_{\text{value function in POMDP models}}$$

There could be other risk measures:

- maximize the worst-case reward (robust optimization)
- minimize conditional value-at-risk (CVaR)
- probability measures

Baum-Welch Algorithm for Parameter Estimation

Given the observation sequences

$$O^{(1)} = \left(O_1^{(1)}, \dots, O_{T_1}^{(1)}\right), \dots, O^{(N)} = \left(O_1^{(N)}, \dots, O_{T_N}^{(N)}\right),$$

Baum-Welch algorithm, or equivalently *the EM (expectation-maximization) algorithm* estimates the model

$$\lambda = (A, B, \phi, c, \mu, \sigma)$$

that locally maximizes the likelihood function

$$P(O|\lambda) = \prod_{k=1}^{N} P(O^{(k)}|\lambda)$$

Note: The estimated parameters quantify the most important factors in AS, which are the essential elements for decision making.

Reference: Rabiner, Lawrence R. "A tutorial on hidden Markov models and selected applications in speech recognition." Proceedings of the IEEE 77, no. 2 (1989): 257-286.