Bayesian information-theoretic approach to determine effective scanning protocols of cancer patients

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ICERM

Joint work with

Dr. Allison Lewis (Lafayette Univ.)

Dr. Kathleen Storey (Univ. Minnesota)

Dr. Tin Phan (LANL)

Cho lab - Mathematics in Biomedical Application

1. Develop mathematical models of novel medical treatments

- Cell-based immunotherapy (adoptive T-cell)
- Neural stem cell treatments

2. Develop mathematical models using new biomedical data acquisition technologies.

- Single-cell gene sequencing data
- Spatiotemporal transcriptomic data

3. Develop framework to bring mathematical models to clinical practices

- Personalized patient scanning schedule
- Design experiments to infer cancer cell interaction

Clinical collaborators :

City of Hope™

Content

- Motivation and Problem set up

- Bayesian information-theoretic framework to determine patient scanning protocols
  - Mutual information
  - Mutual information with temporal penalty
  - Nonlinear mixture model for prior estimates

- Summary and Future work

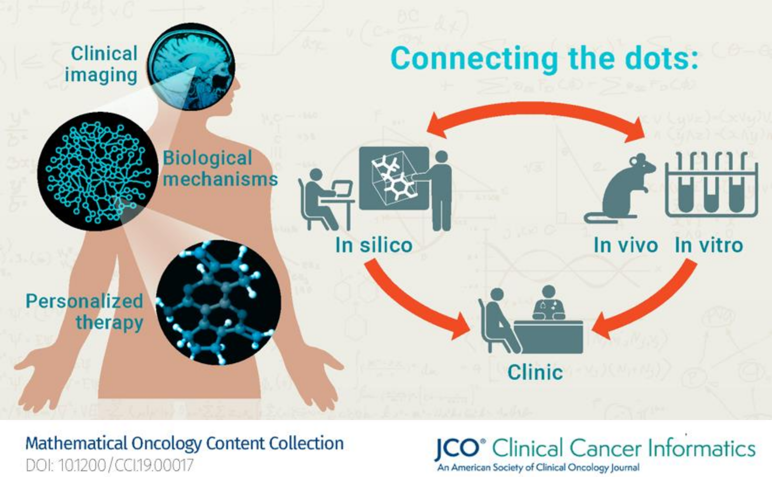
Joint work with

Allison Lewis (Lafayette College)

Katie Storey (University of Minnesota)

Tin Phan (LANL)

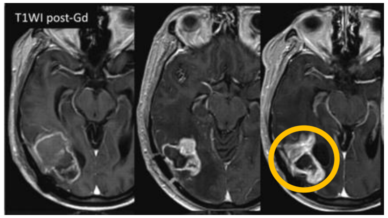
Motivating questions



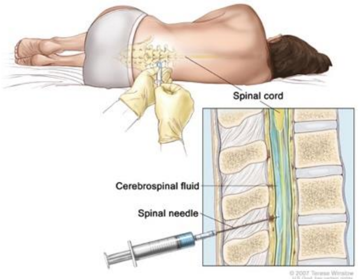
GOAL: Develop framework in which mathematicians can support decision-making in the clinic.

e.g. use mathematical models to predict the tumor growth and response to treatment of patients

- <u>Observable cancer patient data</u>
  - Imaging (MRI/CT/PET)
    : Tumor volume, Necrotic fraction, tissue structure, metabolism, …



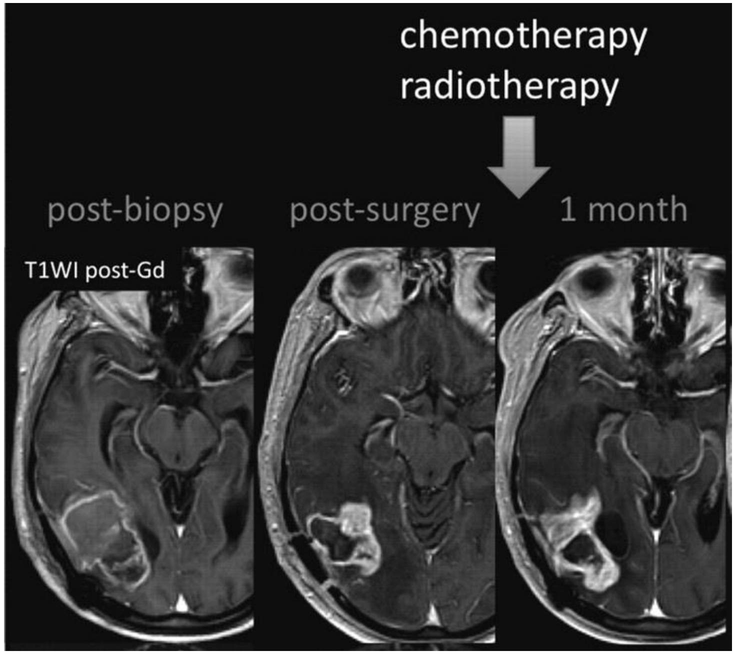
  - Tumor Biopsy, Cerebrospinal fluid (CSF) collection, Bone marrow biopsy, peripheral blood draw
    : Tumor composition, Genetics, Immune cell counts, Tumor antigens
  - Single-cell gene sequencing data
    : genetic profile, genetic mutation



→ Problem: collecting clinical data can be expensive and/or invasive

Limited temporal aspect is a challenge in model calibration using clinical data

For example, during 6-8 weeks of radiotherapy, patients receive 1-2 scan before treatment, and one more scan after 6-8 weeks treatment.



L.C. Hygino da Cruz, et al. 2011

*MRI-LINAC

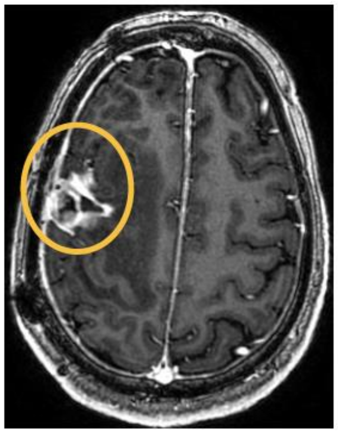
Questions:
Can we predict the treatment response earlier?

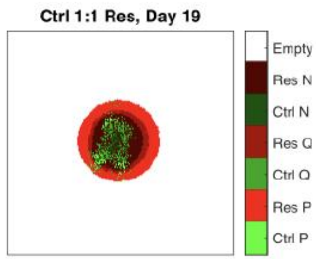
Can we determine the scan schedule in some optimal matter?

A simple set up of Model Calibration to Clinical Data

- Data $\{d_i\}$

- CT or MRI detectible tumor volume





* Note. We used synthetic data - hybrid Cellular Automata (CA) that track tumor growth in space with cell cycle and oxygen

- Model $\{Y(t_i;\theta)\}$

- Consider a dynamical system that tracks tumor volume $Y(t)$ in time

$$\frac{dY}{dt} = \lambda Y\left(1-\frac{Y}{K}\right) - \underbrace{(1-e^{-\alpha d-\beta d^2})u(t)Y}_{\text{cell kill due to radiotherapy}},$$

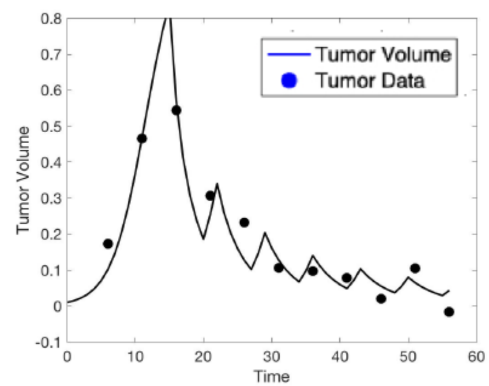
$$\theta = [\lambda, K, \alpha, \beta]$$

α, β: radiosensitivity
λ, K: growth and capacity

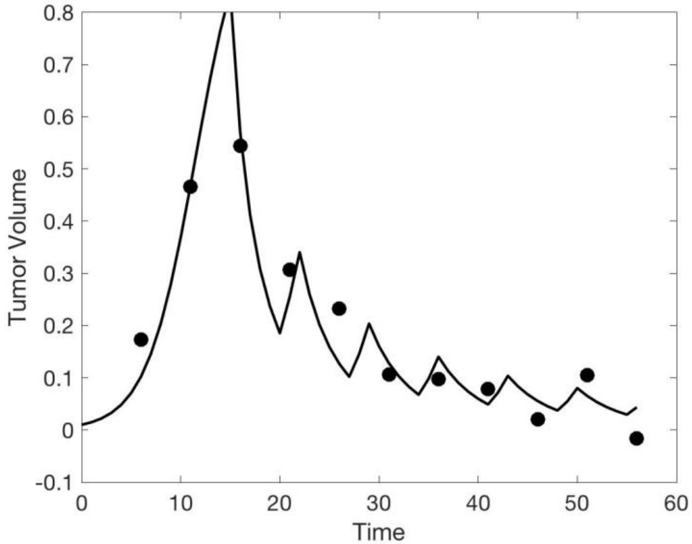
→ Model calibration using data

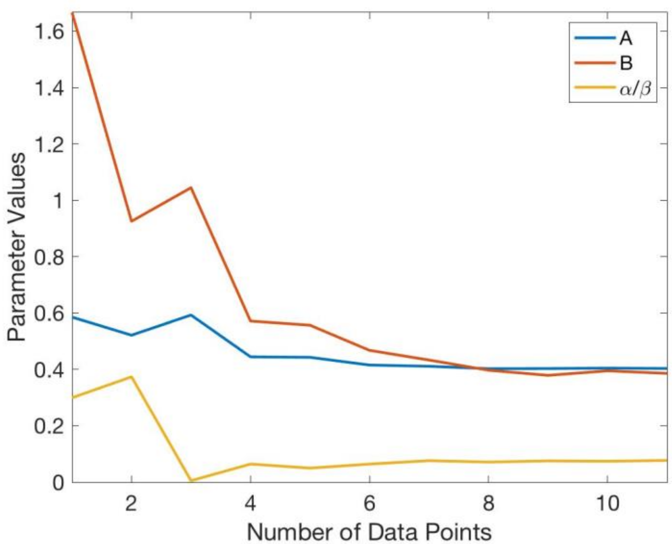
$$\theta^* = \mathrm{argmin}_\theta \left\| \vec{d} - Y(\vec{t};\theta) \right\|_2^2$$

$$p_{\text{post}}(\theta|d) = \frac{p(d|\theta)\, p_{\text{prior}}(\theta)}{p(d)}$$



Sequential model calibration procedure





: Parameter values "settle down" around the 4th data point

GOAL. Determine a patient specific data collection strategy (scanning schedule) that calibrates the model parameters early and accurately using limited number of scan budget?

Bayesian experimental design

- Experimental design problem

$$x^* = \underset{x \in \Xi}{\operatorname{argmax}} f(x)$$

where

- x represents the design or scenario of an experiment
- Ξ is all the possible designs or scenarios
- f is an objective function that quantifies the goal of the experiment

- Approaches

$$x_n = \underset{x \in \Xi}{\operatorname{argmax}} u(x; x_{1:n-1}, f_{1:n-1})$$

where u is the acquisition function.

- Model-based approach
  - Information-theoretic approach
  - Mean objective cost of uncertainty
- Data-driven approach (Gaussian process)
  - expected improvement (EI), probability of improvement (PI), upper-confidence bounds (UCB), entropy search (ES), …

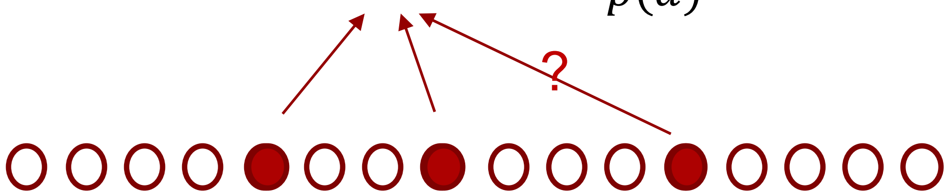
PART 1. Mutual Information

Application to Prostate Cancer with Radiotherapy

Bayesian Information-theoretic Calibration

❿ Bayesian calibration framework d: data $\boldsymbol{\theta}$: parameter

$$p_{\text{post}}(\theta|d) = \frac{p(d|\theta)\, p_{\text{prior}}(\theta)}{p(d)}$$



Possible scans (for example, daily)

Likelihood $p(d|\theta)$: Gaussian distribution

Estimate posterior using MCMC :

DRAM (Delayed Rejection Adaptive Metropolis Algorithm)

H. Haario et al. (2006) DRAM: Efficient adaptive MCMC, Stats. Comput.

- Sequential calibration : Given a data set of size $n-1$ (D_{n-1}), choose the n-th data d_n in an optimal manner.

$$d_n = \underset{d \in \Xi}{\operatorname{argmax}}\, u(d; D_{n-1}) \quad \text{for some acquisition function } u \,.$$

→ Take u as the reduction of model uncertainty via **mutual information**

Mutual Information Framework

Goal: Maximize Mutual Information between model parameter θ and future data d_n. (D_{n-1} is previously chosen $n-1$ scans)

Shannon Entropy:

$$H(\Theta|D_{n-1}) = -\int_\Omega p(\theta|D_{n-1})\log(p(\theta|D_{n-1}))d\theta$$

Utility Function:

$$U(d_n,\xi_n) = \int_\Omega p(\theta|d_n,D_{n-1})\log p(\theta|d_n,D_{n-1})d\theta - \int_\Omega p(\theta|D_{n-1})\log p(\theta|D_{n-1})d\theta$$

Mutual Information:

$$\begin{aligned} I(\theta;d_n|D_{n-1},\xi_n) &= \int_{\mathcal{D}} U(d_n,\xi_n)p(d_n|D_{n-1},\xi_n)dd_n \\ &= \int_{\mathcal{D}}\int_\Omega p(\theta,d_n|D_{n-1},\xi_n)\log\frac{p(\theta,d_n|D_{n-1},\xi_n)}{p(\theta|D_{n-1})p(d_n|D_{n-1},\xi_n)}d\theta dd_n \qquad (1)\end{aligned}$$

Given D_{n-1}, choose the n-th scan such that

$$\xi_n^* = \arg\max_{\xi_n\in\Xi} I(\theta;d_n|D_{n-1},\xi_n)$$

A. Kraskov et al., Estimating mutual information, PRE 69 (2004)
A Lewis, R Smith, et al. JCP (2018)

Algorithm – multi-fidelity simulation

d_ℓ Low-fidelity (in-silico, ODE) model prediction at design n

$\tilde{d}_n$ High-fidelity (experimental, patient) data collected at design n

Existing data: $D_{n-1} = \{\tilde{d}_1, \tilde{d}_2, \ldots, \tilde{d}_{n-1}\}$

Run MCMC (DRAM) Algorithm

Calibrate parameters of low-fidelity model: $d_\ell(\theta, \xi_n)$

Compute Mutual Information

Choose new design $\xi_n^* = \arg\max_{\xi_n \in \Xi} I(\theta; d_n | D_{n-1}, \xi_n)$ to reduce uncertainty in θ

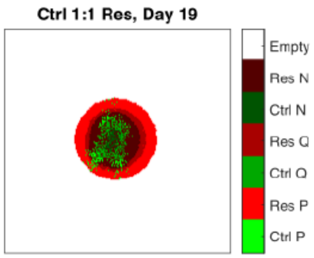
Collect High-Fidelity data

Add $\tilde{d}_n = d_h(\xi_n^*) + \tilde{\varepsilon}_n(\xi_n^*)$ to the data set

Simulation. Prostate cancer with radiotherapy treatment

❿ Data (synthetic data)

Prostate cancer patient treated with radiotherapy



* Note. We used synthetic data - hybrid Cellular Automata (CA) that track tumor growth in space with cell cycle and oxygen

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- Consider a dynamical system that tracks tumor volume $Y(t)$ in time

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α, β: radiosensitivity
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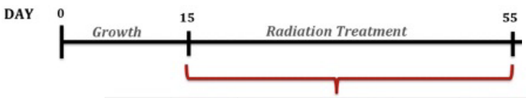
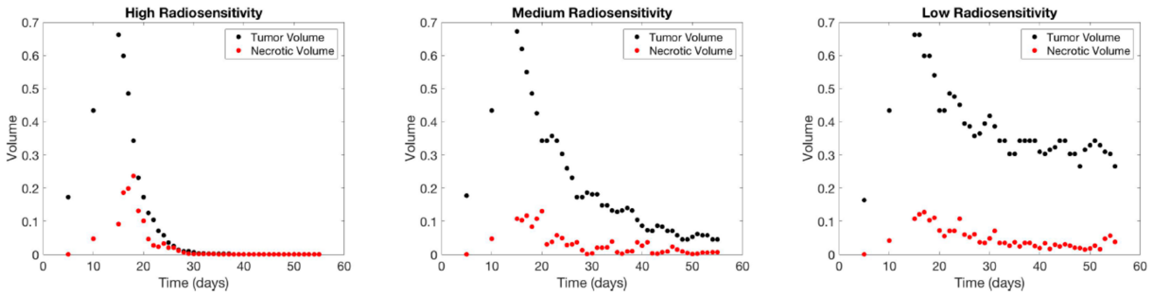
- Radiotherapy schedule



Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
X	X	X	X	X		

- Example patients depending on response levels:



Simple scenario: One scan per week

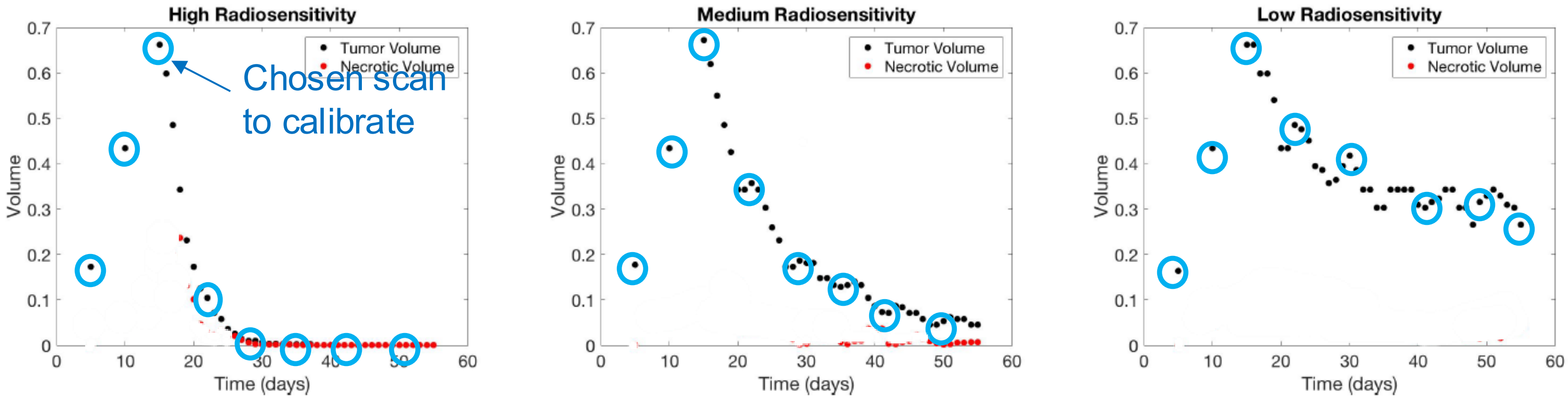
- Assume a budget of one scan per week during treatment

  Use MI to choose the most informative scanning day each week

  : [Mon Tue Wed Thurs Fri Sat Sun]

- Test on three different types of patients responding to radiotherapy

  : High, Medium, Low responder

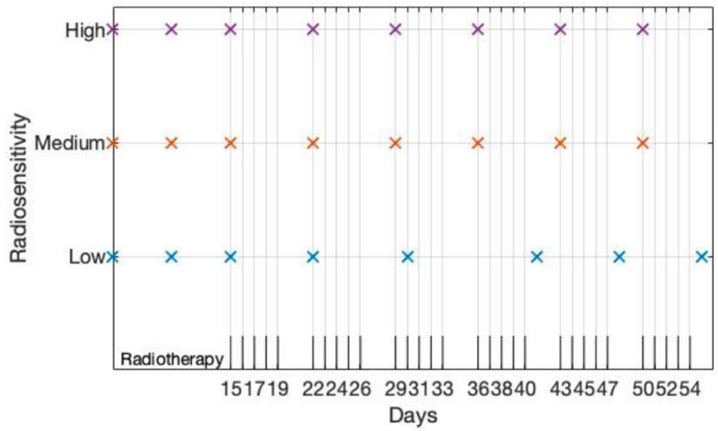


Simple scenario: Determine one scan per week

- Assume a budget of one scan per week during treatment.

  Use MI to choose the most informative scanning day each week

Figure. Selected scans



Result

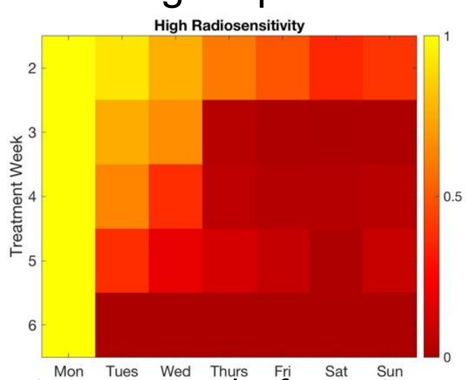
First week, scan on the first day,

Later weeks,

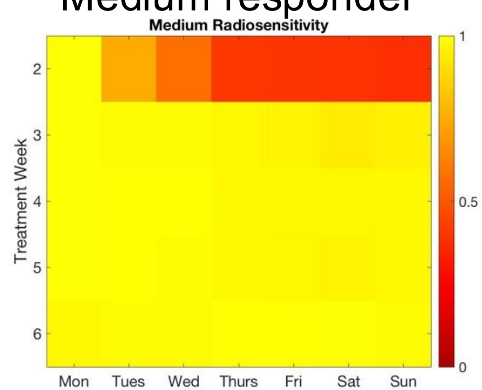
scan on the first day if patient is responsive,

scan any day if patient is not responsive

Strong responder



Medium responder



Weak responder

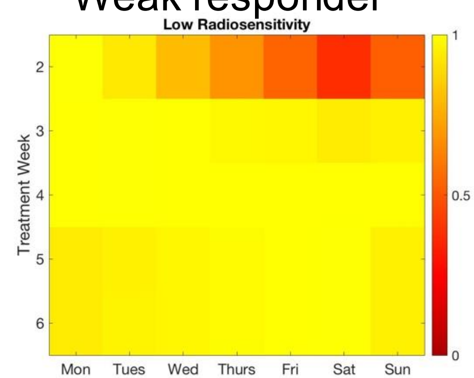


Figure. Mutual Information

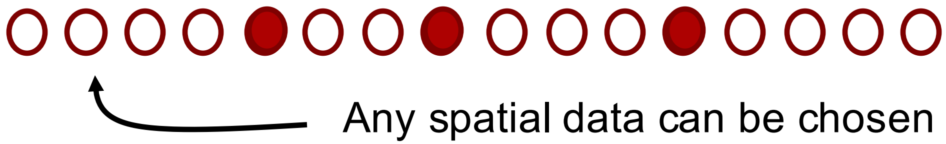
PART 2. Mutual Information with temporal penalty

Application to Prostate Cancer

1. Synthetic data of Radiotherapy
2. Clinical data of Androgen suppression treatment

Mutual information framework for temporal data

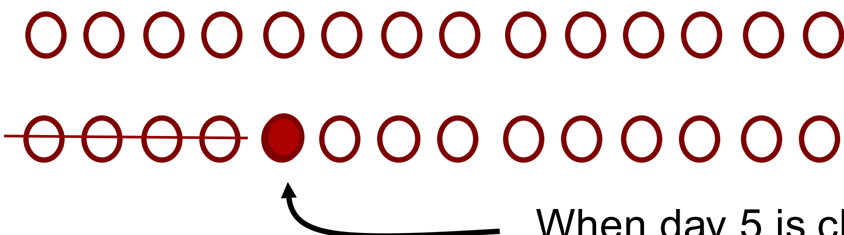
- General framework: available designs reduce by one



ex) Spatial sensor

Any spatial data can be chosen

- Temporal framework: lose prior designs

Day 1  Day 14

When day 5 is chosen, day 1-4 are gone.

➔ Strategy: Develop an object function that rewards large mutual information while <u>penalizing choice of scan at later times.</u>

Modified Mutual information with temporal penalty

- Objection (score) function with temporal penalty

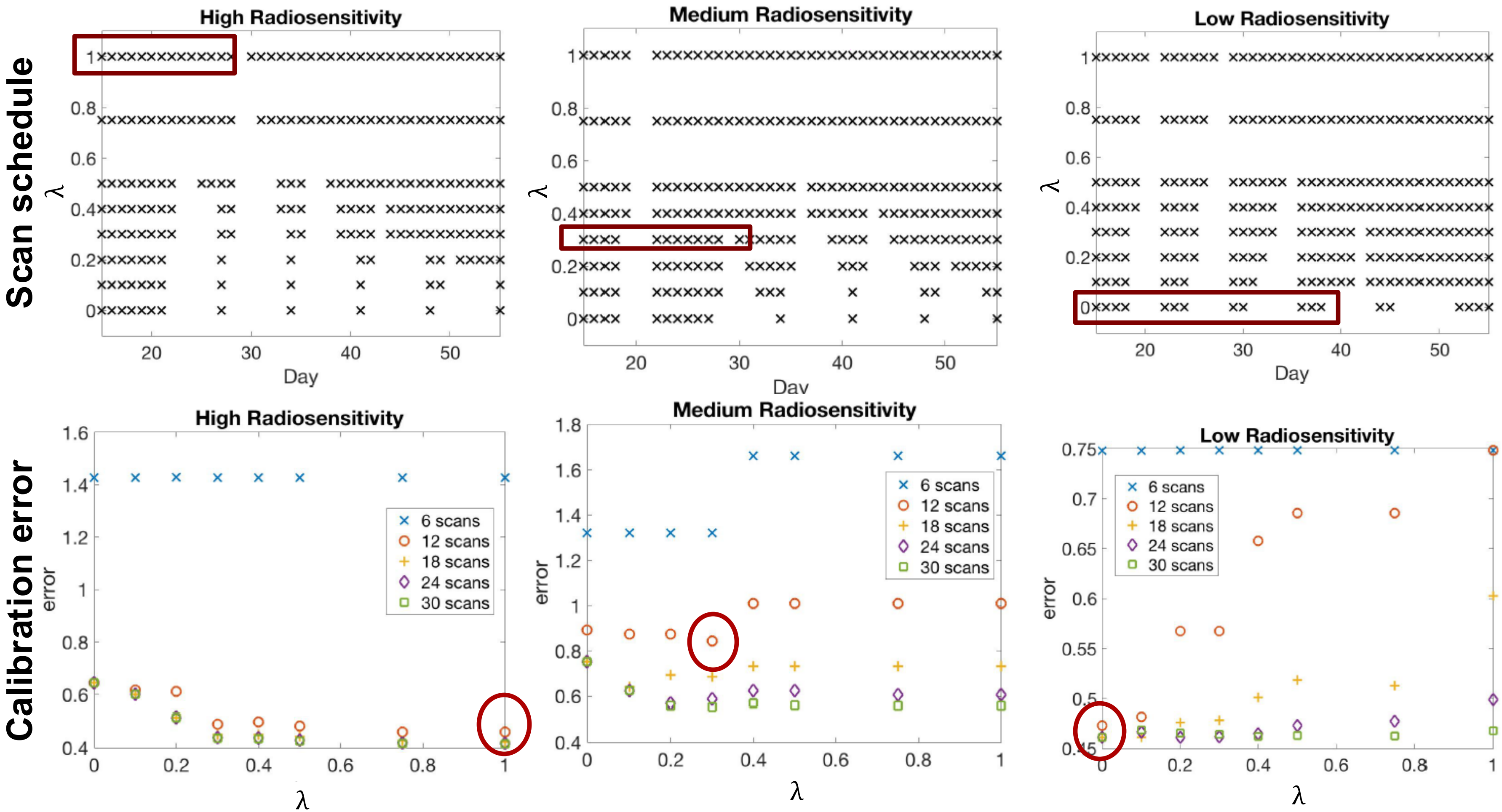
$$S_\lambda(i,r) = \underbrace{R(i,r)}_{\text{Rescaled MI}} - \lambda \underbrace{\boxed{\left(\frac{\sum_{j=r+1}^{i-1} R(j,r)}{\sum_{\ell=r+1}^{N} R(\ell,r)} \right)}}_{\text{Information Loss Ratio}},$$

- Object function penalty weighted with relative tumor volume difference

$$S(i,r) = \underbrace{R(i,r)}_{\text{Rescaled MI}} - \underbrace{\boxed{\left| \frac{\tilde{d}_r - d_N}{\tilde{d}_r + d_N} \right|}}_{\text{Penalty Coefficient}} \cdot \underbrace{\left(\frac{\sum_{j=r+1}^{i-1} R(j,r)}{\sum_{\ell=r+1}^{N} R(\ell,r)} \right)}_{\text{Information Loss Ratio}}, \qquad (2)$$

d_r : previously chosen high-fidelity measurement,
d_N :expected final prediction using low-fidelity model

Optimized scanning schedule for three scenarios



- ➔ When scan budget is low as <10 scan (high as >15 scans), λ=0 (λ>0.3) will give optimal scan schedule.
- ➔ When 12 scan budget, start with λ =0.2~0.3, then increase (decrease) λ if patient is (not) responsive.

Simulation. Prostate cancer with radiotherapy treatment

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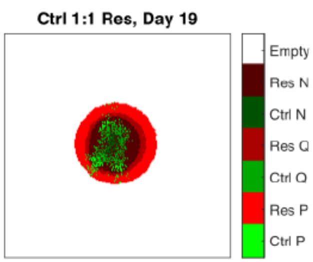

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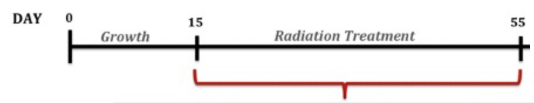
$$\theta = [\lambda, K, \alpha, \beta]$$

α, β: radiosensitivity
λ, K: growth and capacity

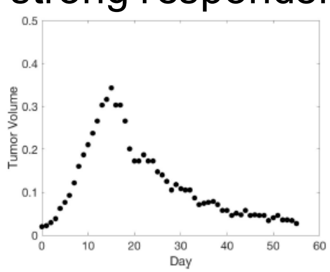
- Radiotherapy schedule



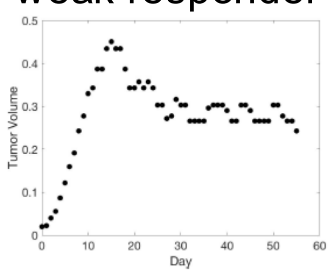
Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
x	x	x	x	x		

- Virtual patients depending on response levels:

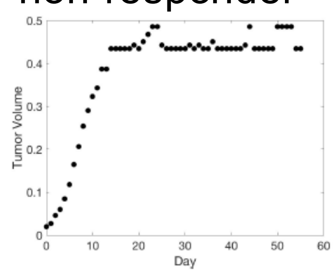
strong responder



weak responder

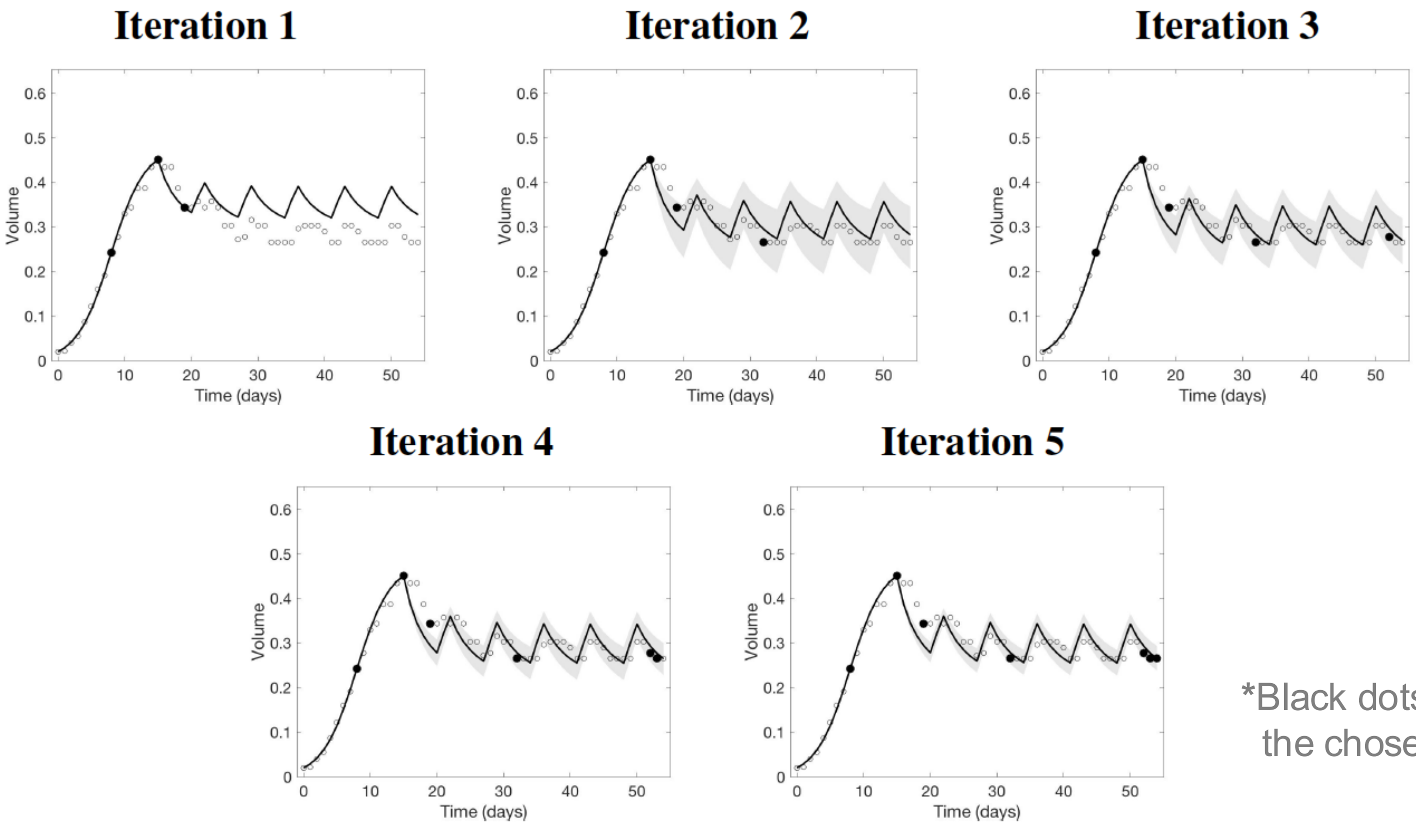


non-responder



Simulation 1. Prostate cancer with radiotherapy treatment

❿ Sequential calibration with chosen scans - weak responder.



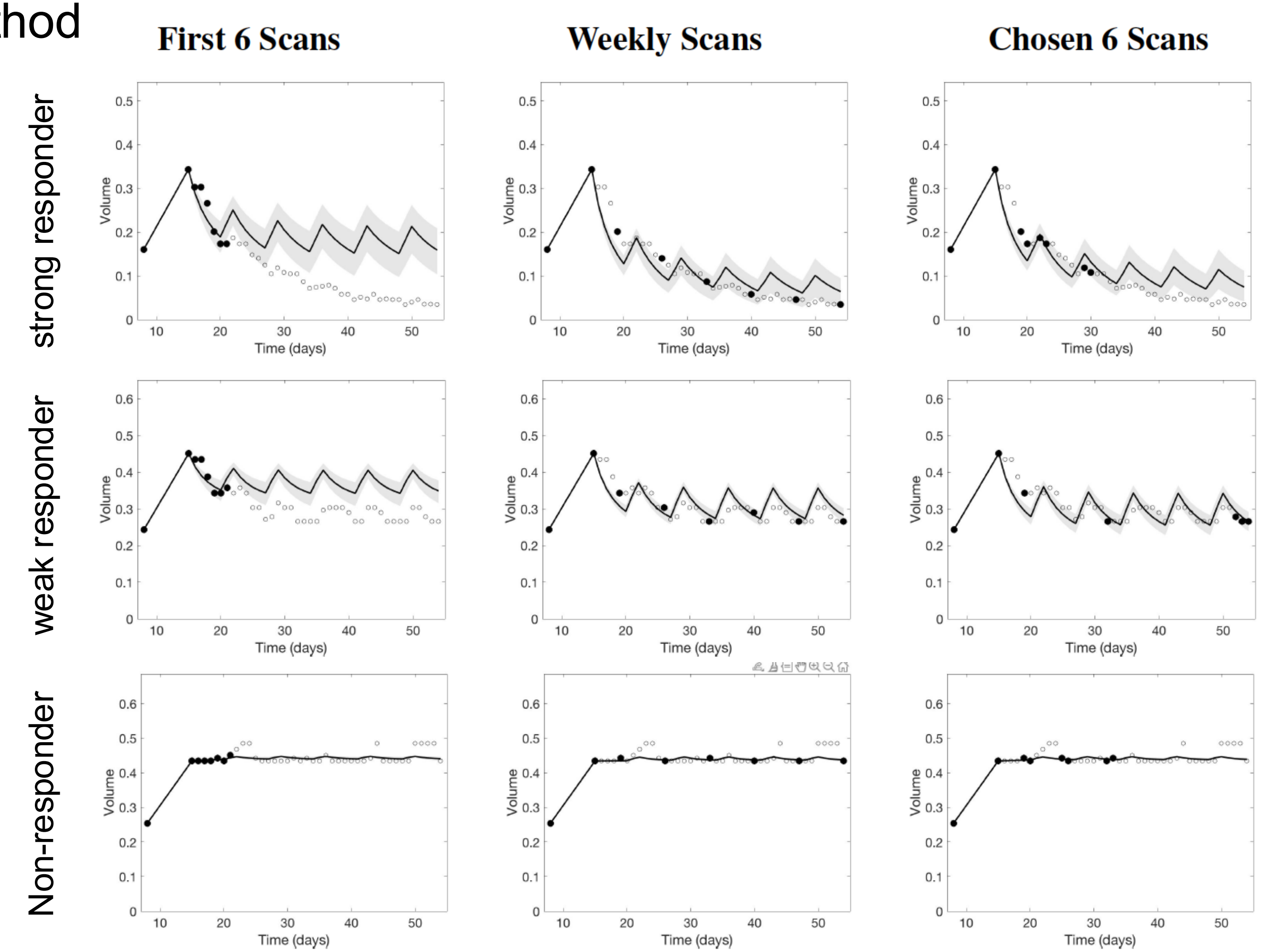
*Black dots are the chosen scans

→ Let us compare the following with 6 (+1-2 for initial growth) scans budget :

1. First 6 scans (Mon-Sat on week 1)
2. Weekly scans (Fridays for 6 weeks)
3. Chosen schedule of **6 scans** with our framework

Simulation 1. Prostate cancer with radiotherapy treatment

❿ Comparison between 1) First 6 scans, 2) Weekly scans, 3) our method



Simulation 1. Prostate cancer with radiotherapy treatment

❿ Comparison between 1) First 6 scans, 2) Weekly scans, 3) our method

		First Scans	**Weekly Scans**	**Chosen Scans**
Strong	**Error**	0.0102	0.0013	0.0017
	Uncertainty	3.5445	2.4024	2.4587
Weak	**Error**	0.0056	0.0012	0.0010
	Uncertainty	2.0207	1.2887	1.7847
Non	**Error**	0.0003	0.0003	0.0003
	Uncertainty	0.3412	0.2649	0.2409

Error : mean square error : $\frac{1}{n}\sum_{i=1}^{n}(y_i - f(x_i;\theta))^2$

Uncertainty : area of 95% credible intervals

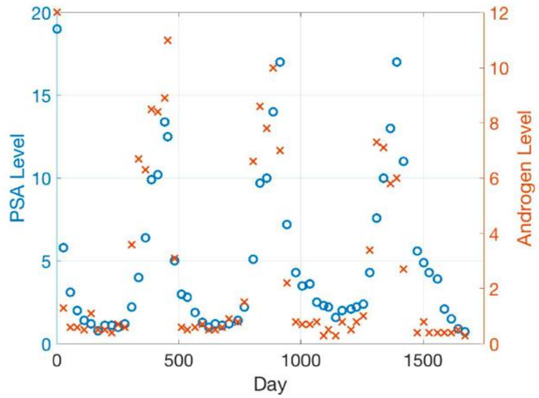
➔ Our chosen scan schedule is doing comparable to the equally spaced scan schedule in terms of the accuracy and uncertainty,

Simulation 2. Prostate cancer with androgen treatment

❿ Data (clinical data)

Prostate cancer patient treated with intermittent androgen suppression therapy

- Prostate-Specific Antigen (PSA) level
- Serum Androgen level



Data from N. Bruchovsky et al (2006)

❿ Model

$$
\begin{aligned}
\frac{dx_1}{dt} &= \max\left(\mu\left(1-\frac{q_1}{Q}\right)x_1, 0\right) - dx_1(x_1+x_2) - c\frac{K}{Q+K}x_1\\
\frac{dx_2}{dt} &= \max\left(\mu\left(1-\frac{q_2}{Q}\right)x_2, 0\right) - dx_2(x_1+x_2) + c\frac{K}{Q+K}x_1\\
\frac{dQ}{dt} &= m(A-Q) - \frac{\mu(Q-q_1)x_1 + \mu(Q-q_2)x_2}{x_1+x_2}\\
\frac{dA}{dt} &= \gamma_1 u(t)\left(1-\frac{A}{A_0}\right) + \gamma_2 - \delta A\\
\frac{dP}{dt} &= bQ + \max\left(\sigma_1\left(1-\frac{q_1}{Q}\right)x_1, 0\right) + \max\left(\sigma_2\left(1-\frac{q_2}{Q}\right)x_2, 0\right) - \epsilon P,
\end{aligned}
$$

-$x_1(t)$, $x_2(t)$: prostate cancer population
- P(t): Prostate-Specific Antigen(PSA) level
- A(t): Serum Androgen level
- Q(t): Intermediate Androgen level

[Dr. Kuang group] W Meade, et al. (2022)

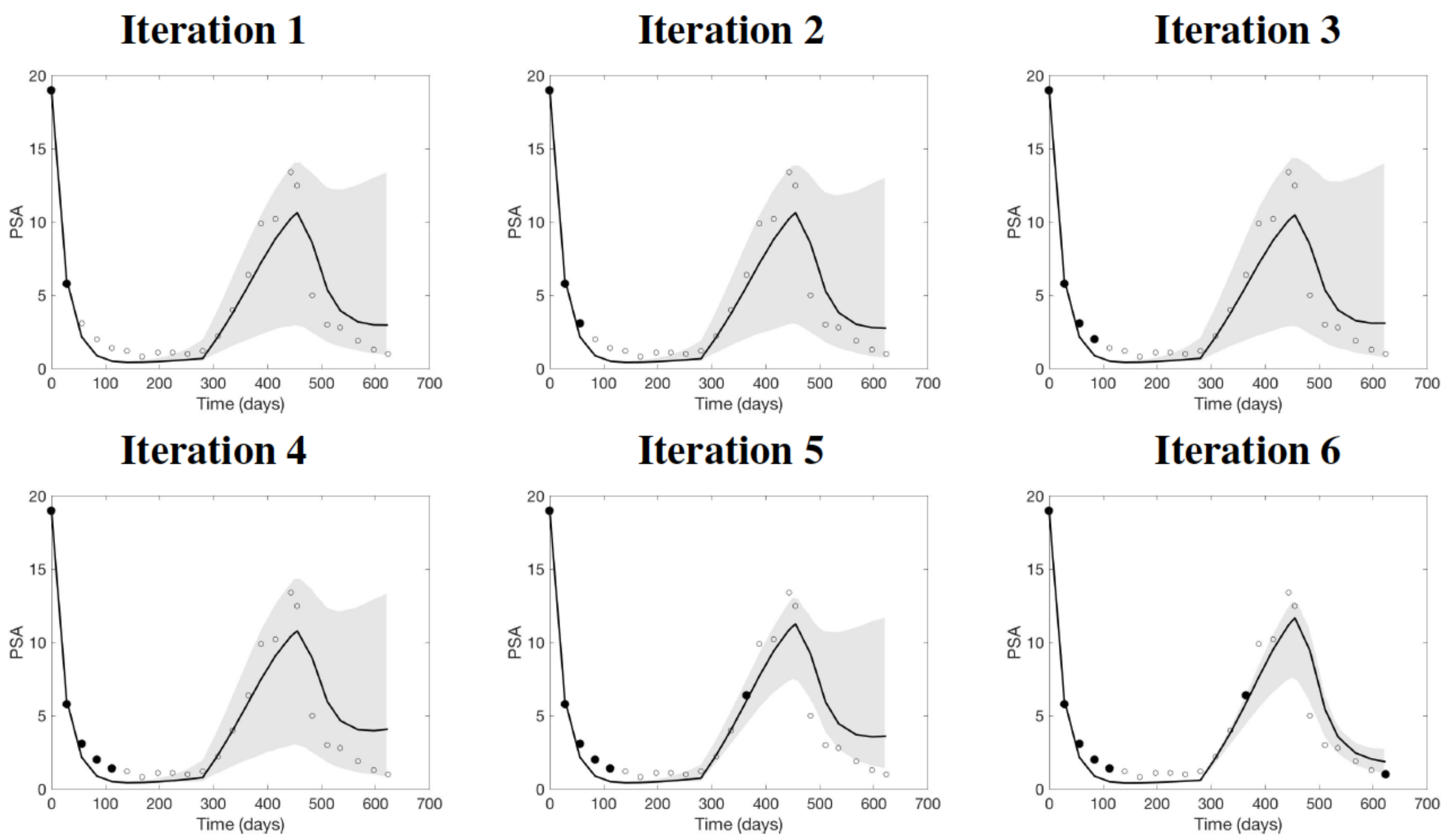
❿ Collect data for 1.5 cycle to predict 3.5 cycle

❿ Test cases :

1. Collect PSA data only for 1.5 cycle
2. Collect both PSA and Androgen data for 1.5 cycle

Simulation 2. Prostate cancer with androgen treatment

❿ Sequential calibration procedure of only PSA data for 1.5 cycle



→ Let us compare the following with 5 (+2 for initial calibration) scans budget :

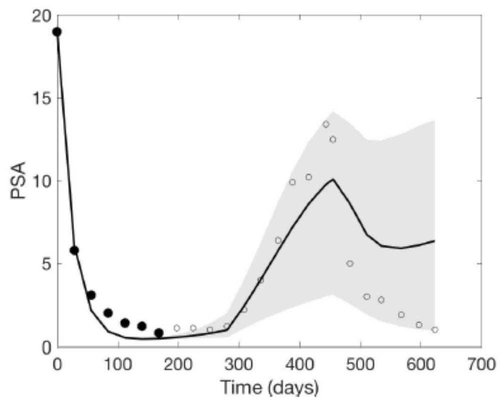
1. First 5 scans (every 28 days)
2. Evenly-spaced scans (every 140 days)
3. Chosen schedule of **5 scans** with our framework

*Black dots are the chosen scans

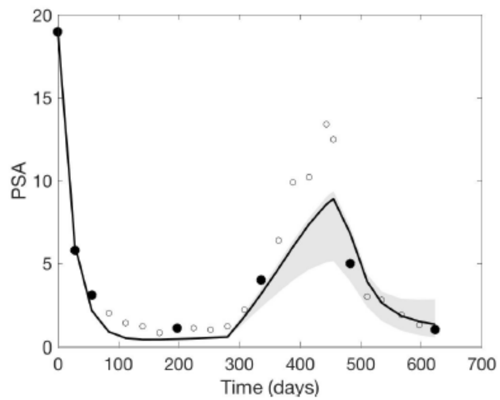
Simulation 2. Prostate cancer with androgen treatment

❿ Comparison of PSA data only collection for 1.5 cycle

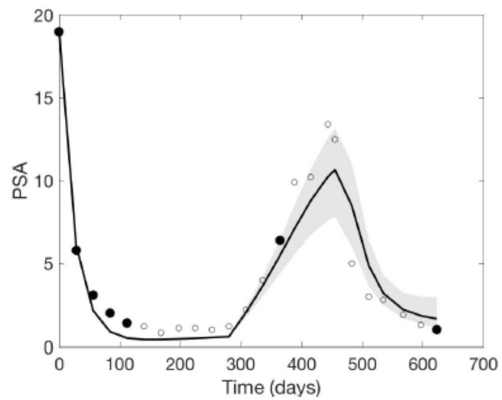
First 5 Scans



Evenly-Spaced 5 Scans



Chosen 5 Scans

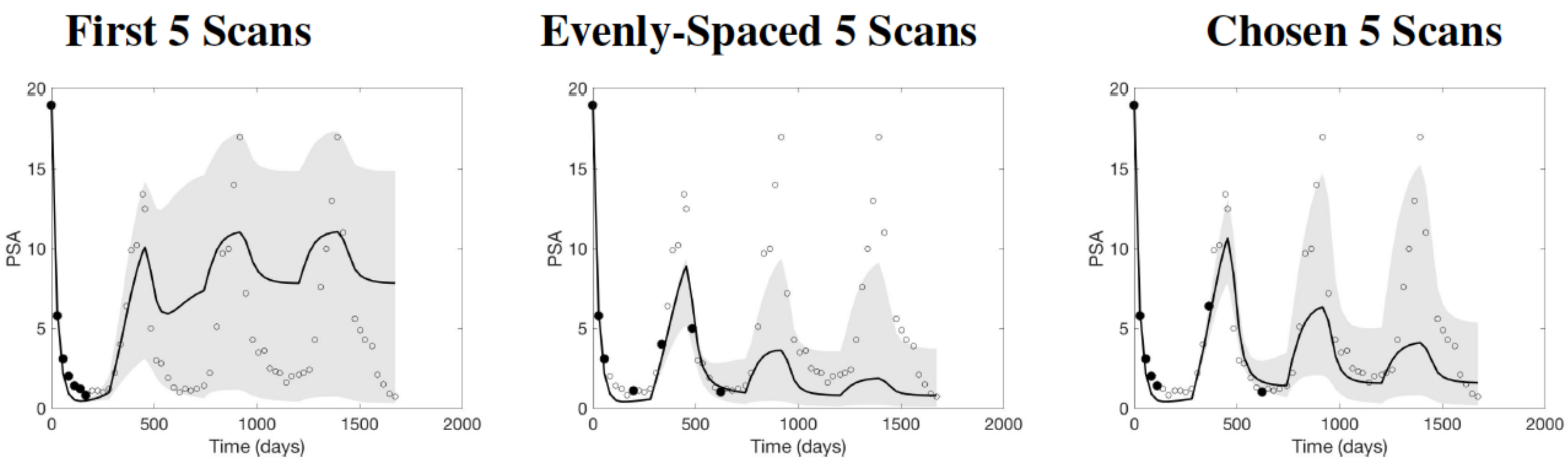


	First Scans	Evenly-Spaced Scans	Chosen Scans
Error	5.80	3.04	1.92
Uncertainty	126.54	31.18	36.13

➔ Our adaptive scan schedule gives most accurate result.

Simulation 2. Prostate cancer with androgen treatment

❿ Comparison of PSA data only collection, prediction up to 3.5 cycle



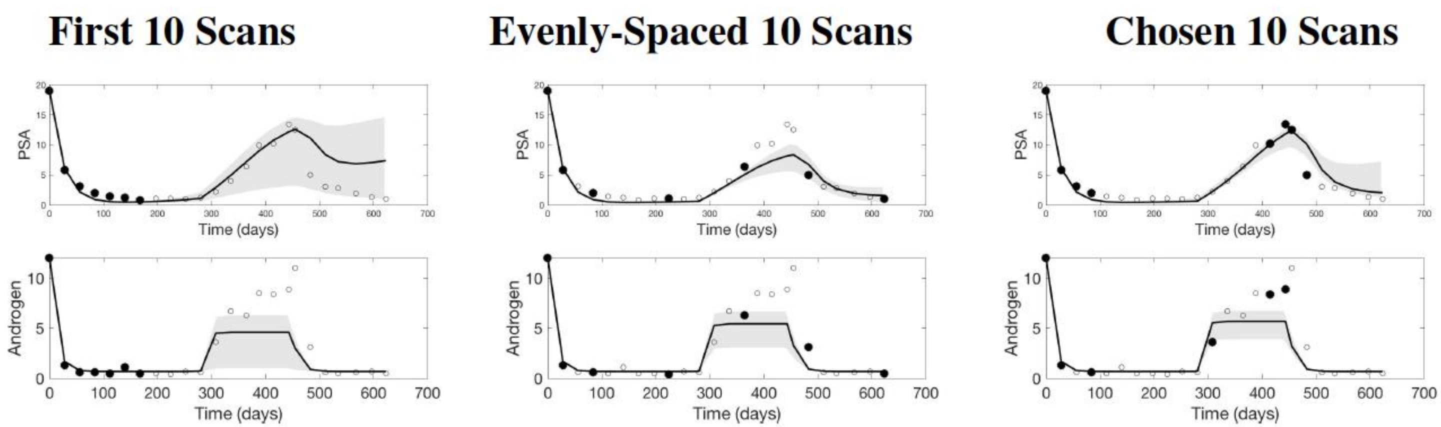
	First Scans	Evenly-Spaced Scans	Chosen Scans
Error	17.98	18.41	10.85
Uncertainty	665.15	212.81	297.95

➔ Our adaptive scan schedule gives most accurate result.

Simulation 2. Prostate cancer with androgen treatment

❿ Comparison of PSA & Androgen data collection for 1.5 cycle

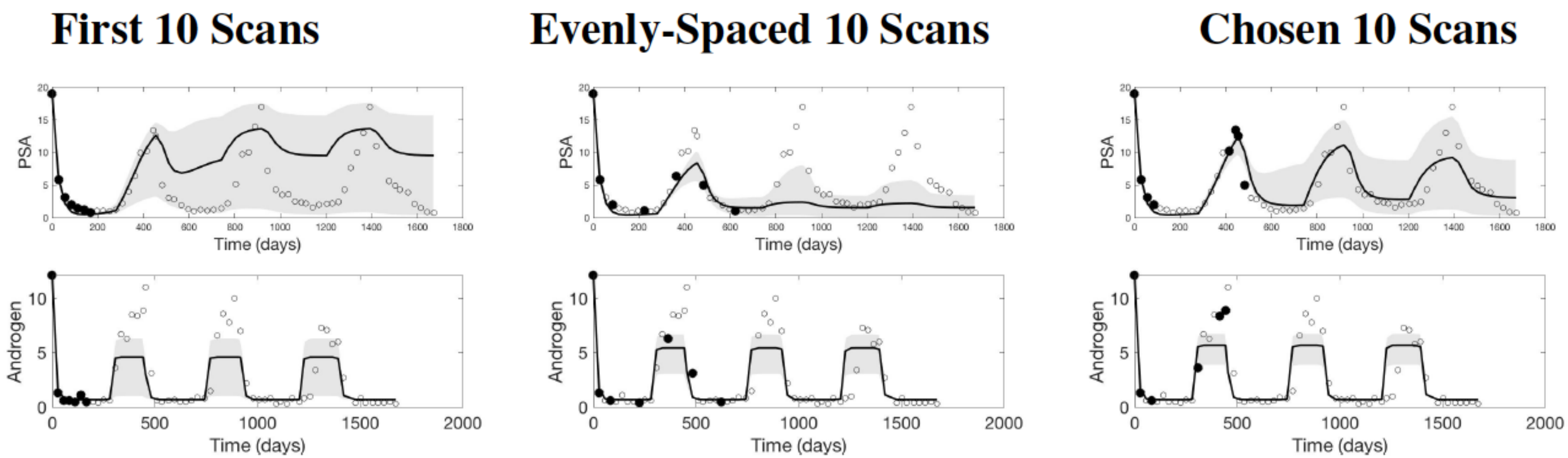
	0	28	56	84	112	140	168	197	224	252	280	308	336	364	388	415	443	455	483	511	535	567	597	623
PSA	x	x	x	x												x	x	x	x					
Androgen	x	x		x								x				x	x							



	First Scans	Evenly-Spaced Scans	Chosen Scans
Error	13.29	7.42	6.05
Uncertainty	4231.66	1413.62	1575.57

Simulation 2. Prostate cancer with androgen treatment

❿ PSA & Androgen data collection, prediction up to 3.5 cycle



	First Scans	Evenly-Spaced Scans	Chosen Scans
Error	33.47	22.45	7.62
Uncertainty	22510.54	7223.40	12741.40

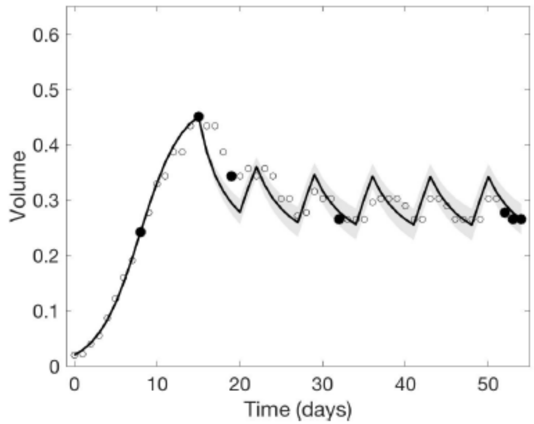
➔ Our adaptive scan schedule gives most accurate result.

PART 3. Further ideas to reduce # of scans

Application to Prostate Cancer with Radiotherapy

Simulation. Prostate cancer with radiotherapy treatment

❿ Example of selected scans in weak responder case



- Model $\{Y(t_i,\theta)\}$
- Consider a dynamical system that tracks tumor volume $Y(t)$ in time

$$\frac{dY}{dt} = \lambda Y\left(1 - \frac{Y}{K}\right) - \underbrace{(1 - e^{-\alpha d - \beta d^2})u(t)Y}_{\text{cell kill due to radiotherapy}},$$

$$\theta = [\lambda, K, \alpha, \beta]$$

α, β: radiosensitivity
λ, K: growth and capacity

3 scans required for initial estimate of parameters

➔ Use parameter prior distribution estimated from population

Last scans are redundant

➔ Check convergence criteria of parameter value and posterior

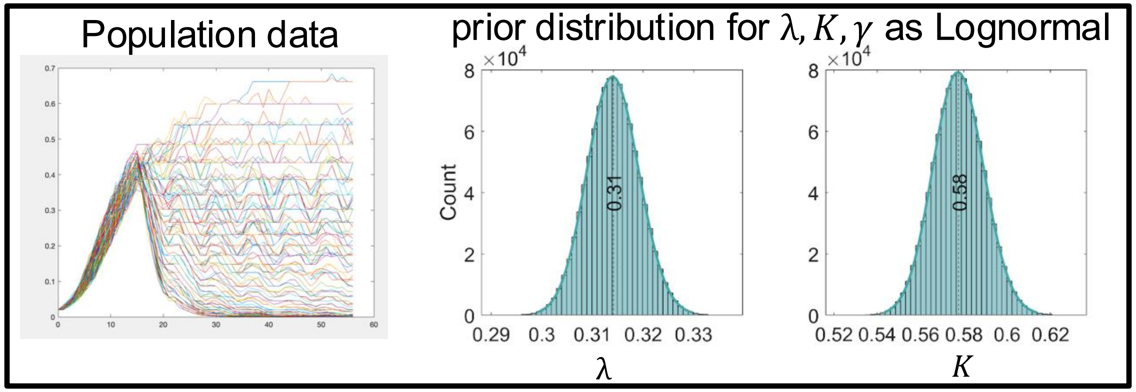
Workflow of patient scanning protocols

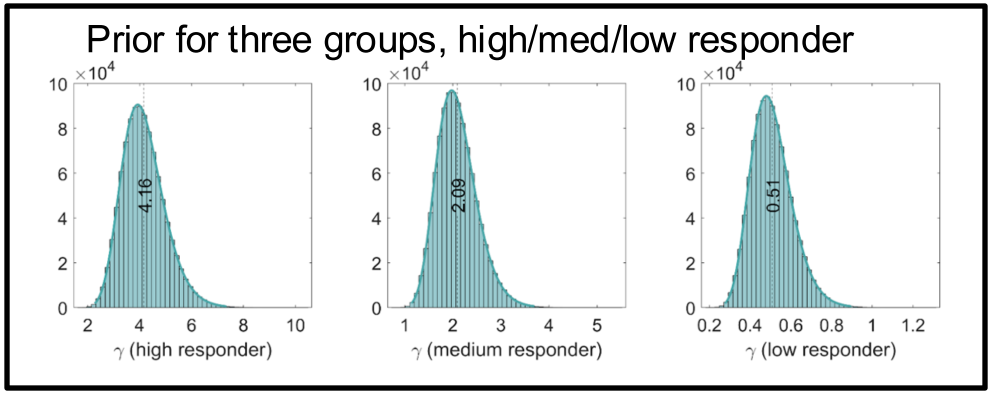
Pre-estimate population-level prior distribution

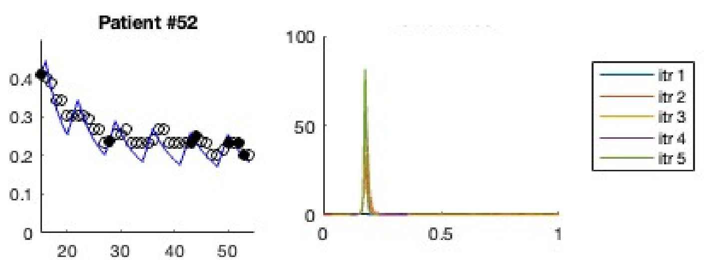
Select next scan using one data point

Based on the next scan, update prior among groups

Continue to select scans until Max budget OR convergence of posterior distribution



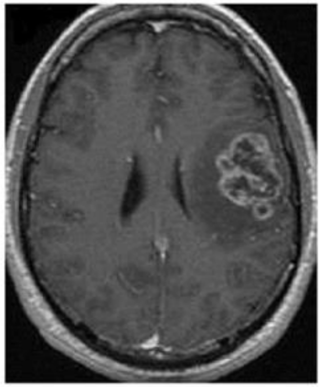




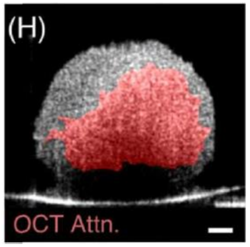
- Prior distribution computed by Monolix (nonlinear mixed-effects model)

More data - Adding model complexity

• Imaging necrotic region
: data of total tumor and necrotic volume →



MRI, L. Han et al, MBE (2019)



Y. Huang et al, Optical Coherence Tomography Detects Necrotic Regions and Volumetrically Quantifies Multicellular Tumor Spheroids, *Cancer Res (2017)*

• Model :
Dynamical system tracking tumor (V) and necrotic (N) volume

$$\frac{dV}{dt} = \lambda V\left(1 - \frac{V}{K}\right) - \eta V$$
$$\frac{dN}{dt} = \eta V - \zeta N$$

- Reference demonstrating that <u>tracking dead matter</u> is important in radiotherapy

T.D. Lewin, H.M. Byrne et al. The importance of dead material within a tumour on the dynamics in response to radiotherapy. Physics in Medicine and Biology (2019).
T.D. Lewin, P.K. Maini et al. A three-phase model to investigate the effects of dead material on the growth of avascular tumours. Mathematical Modelling of Natural Phenomena (2019).

Improved prediction error with necrotic volume scan

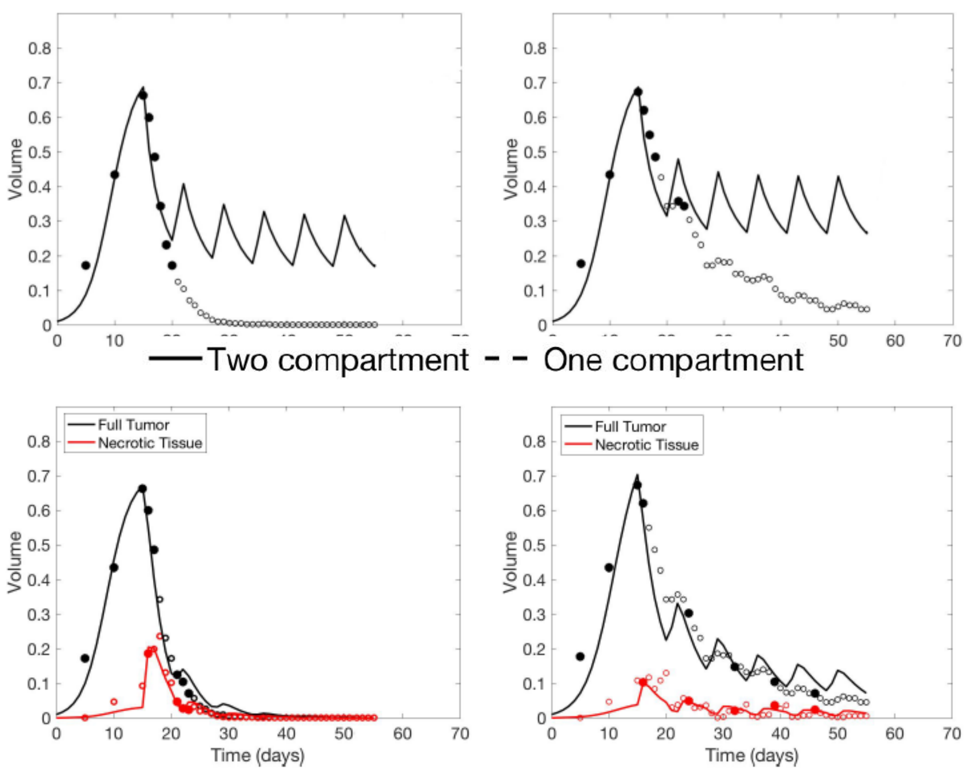
- With fixed 6 scan budget (+ 2 for initial growth)

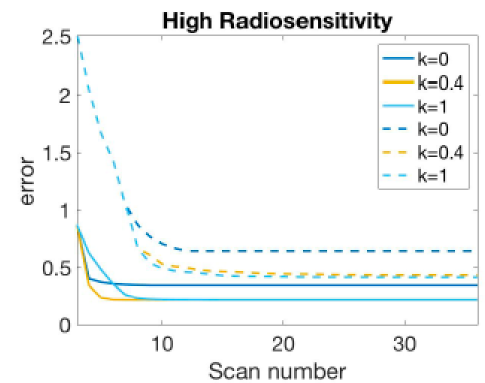
High Radiosensitivity $\lambda = 0.4$

Medium Radiosensitivity $\lambda = 0.0$

Tumor volume model

Tumor +necrotic volume model





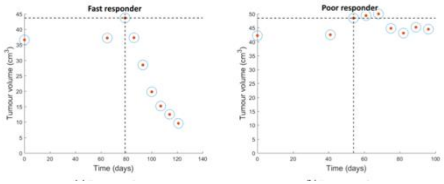
- - - - Tumor model

_____ Tumor+necrotic

➔ Measuring necrotic volume in addition to tumor volume, and proposed scan schedule gives much accurate calibration only with 6 scans after treatment.

Current/Future work

- Validation to more clinical data!
- Incorporate multiple collection modes of data
  - MRI imaging, Cerebrospinal fluid (CSF) collection,
    Bone marrow biopsy, blood draw



Radiotherapy Patient data (Lewin et al., 2022)

- Incorporate multiple models with different fidelity levels
  - Hierarchy of ODE and PDE models

- Develop efficient and accurate theoretical and computational approaches for conditional mutual information.

- Other Bayesian optimization methods for experimental design

- H Cho, A. Lewis, K Storey (2020)) J. Clin. Med. 9, 3208
- H Cho, A. Lewis, K Storey, et al. (2023) Math. Bio. Eng., 20(10)

Joint work with

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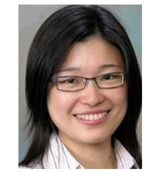

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UC RIVERSIDE

Application/Simulation to Prostate Cancer

1. Synthetic data of Radiotherapy
2. Clinical data of Androgen suppression treatment

kNN estimate of Mutual Information

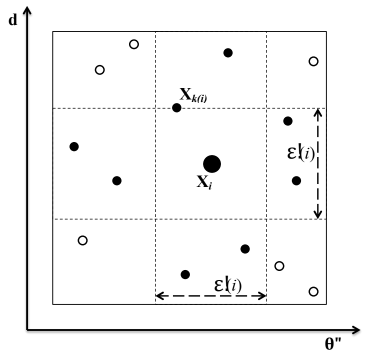
$$I(\theta; d_n|D_{n-1}, \xi_n) = \int_{\mathcal{D}} \int_{\Omega} p(\theta, d_n|D_{n-1}, \xi_n) \log \frac{p(\theta, d_n|D_{n-1}, \xi_n)}{p(\theta|D_{n-1})p(d_n|D_{n-1}, \xi_n)} d\theta dd_n$$

Methods for approximating MI:

- Monte Carlo sampling - prohibitively expensive for moderate to high-dimensional problems!

- k^{th}-Nearest Neighbor (kNN) estimate

  Kraskov et al. (2004) Estimating mutual information, Phys. Rev. E



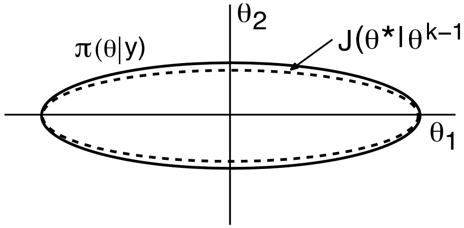
$$I(\theta; d_n|D_{n-1}, \xi_n) \approx \psi(k) - \frac{1}{N}\left[\sum_{i=1}^{N} \psi(n_\theta(i)+1) + \sum_{i=1}^{N} \psi(n_d(i)+1)\right] + \psi(N)$$

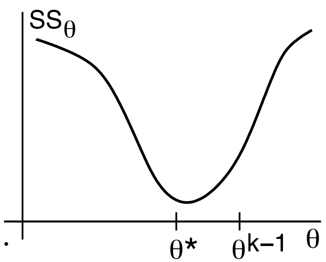
Delayed Rejection Adaptive Metropolis Algorithm

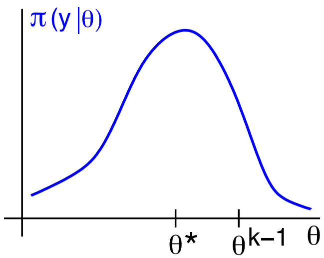
1. Determine $\theta^0 = \arg\min_\theta \sum_{i=1}^{N} [y_i - f(t_i, \theta)]^2$.
2. Construct covariance estimate V.
3. For $k = 1, ..., M$
   (a) Construct candidate $\theta^* \sim N(\theta^{k-1}, V)$.
   (b) Compute
   $$SS_{\theta*} = \sum_{i=1}^{N} [y_i - f(t_i, \theta^*)]^2,$$
   $$\pi(y|\theta) = \frac{1}{(2\pi\sigma^2)^{n/2}} e^{-SS_\theta/2\sigma^2}.$$
   (c) Compute $\alpha(\theta^*|\theta^{k-1}) = \min(1, e^{-[SS_{\theta*} - SS_{\theta^{k-1}}]/2\sigma^2})$.
   (d) Accept θ^* with probability α.

Proposal Distribution

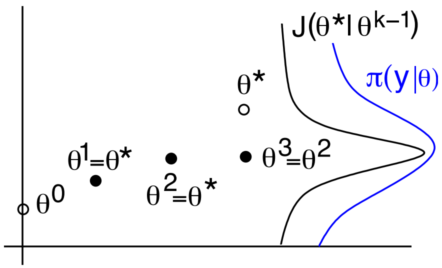
$$J(\theta^*|\theta^{k-1}) = N(\theta^{k-1}, V)$$







Note: Minimizing the SSQ function is equivalent to maximizing the likelihood



H. Haario et al. (2006) DRAM: Efficient adaptive MCMC, Stats. Comput.