Advances in Quantitative MRI: Acquisition, Estimation, and Applications

Gopal Nataraj

Dissertation Proposal
May 15, 2017

Dept. of Electrical Engineering and Computer Science
University of Michigan

Quantitative MRI (QMRI)

Goal: rapidly and reliably localize biomarkers from MR data

Quantitative MRI (QMRI)

Goal: rapidly and reliably localize biomarkers from MR data

- biomarker   measurable tissue property (*e.g.*, elasticity) that characterizes a biological process (*e.g.*, sclerosis)

Quantitative MRI (QMRI)

Goal: rapidly and reliably localize biomarkers from MR data

- biomarker   measurable tissue property (*e.g.*, elasticity) that characterizes a biological process (*e.g.*, sclerosis)
- localize   produce quantitative MR images

Quantitative MRI (QMRI)

Goal: rapidly and reliably localize biomarkers from MR data

- biomarker — measurable tissue property (*e.g.*, elasticity) that characterizes a biological process (*e.g.*, sclerosis)
- localize — produce quantitative MR images
- rapidly — fast acquisition, fast estimation

Quantitative MRI (QMRI)

Goal: rapidly and reliably localize biomarkers from MR data

- biomarker — measurable tissue property (*e.g.*, elasticity) that characterizes a biological process (*e.g.*, sclerosis)
- localize — produce quantitative MR images
- rapidly — fast acquisition, fast estimation
- reliably — accurate signal models, precise estimation

Quantitative MRI (QMRI)

Goal: rapidly and reliably localize biomarkers from MR data

- biomarker — measurable tissue property (*e.g.*, elasticity) that characterizes a biological process (*e.g.*, sclerosis)
- localize — produce quantitative MR images
- rapidly — fast acquisition, fast estimation
- reliably — accurate signal models, precise estimation

Challenges (beyond conventional MRI):

- complicated, nonlinear signal models
- more data required, so longer scan times

Overview

Advances in Quantitative MRI:

- **Acquisition** [Ch. 4]
  How can we assemble fast, informative collections of scans to enable precise biomarker quantification?

Overview

Advances in Quantitative MRI:

- **Acquisition** [Ch. 4]
  How can we assemble fast, informative collections of scans
  to enable precise biomarker quantification?
- **Estimation** [Ch. 5]
  Given data from an informative acquisition,
  how can we rapidly and accurately quantify these biomarkers?

Overview

Advances in Quantitative MRI:

- **Acquisition** [Ch. 4]
  How can we assemble fast, informative collections of scans to enable precise biomarker quantification?
- **Estimation** [Ch. 5]
  Given data from an informative acquisition, how can we rapidly and accurately quantify these biomarkers?
- **Application** [Ch. 6]
  Using these tools, can we design a state-of-the-art biomarker?

Overview

Advances in Quantitative MRI:

- **Acquisition** [Ch. 4]
  How can we assemble fast, informative collections of scans to enable precise biomarker quantification?
- **Estimation** [Ch. 5]
  Given data from an informative acquisition,
  how can we rapidly and accurately quantify these biomarkers?
- **Application** [Ch. 6]
  Using these tools, can we design a state-of-the-art biomarker?

Signal Model

After reconstruction, single voxel y_d in dth image modeled as

$$y_d = s_d(\mathbf{x}; \boldsymbol{\nu}, \mathbf{p}_d) + \epsilon_d \tag{1}$$

• $\mathbf{x} \in \mathbb{R}^L$	latent free parameters
• $\boldsymbol{\nu} \in \mathbb{R}^K$	known parameters
• $\mathbf{p}_d \in \mathbb{R}^A$	acquisition parameters
• $s_d : \mathbb{R}^{L+K+A} \mapsto \mathbb{C}$	dth signal model
• $\epsilon_d \in \mathbb{C}$	noise $\sim \mathbb{C}\mathcal{N}\left(0, \sigma_d^2\right)$

Signal Model

A *scan profile* contains D voxels $\mathbf{y} := [y_1, \ldots, y_D]^\mathsf{T}$, modeled as

$$\mathbf{y} = \mathbf{s}(\mathbf{x}; \boldsymbol{\nu}, \mathbf{P}) + \boldsymbol{\epsilon} \tag{1}$$

- $\mathbf{x} \in \mathbb{R}^L$ — latent free parameters
- $\boldsymbol{\nu} \in \mathbb{R}^K$ — known parameters
- $\mathbf{P} := [\mathbf{p}_1, \ldots, \mathbf{p}_D]$ — acquisition parameter matrix
- $\mathbf{s} : \mathbb{R}^{L+K+AD} \mapsto \mathbb{C}^D$ — vector signal model
- $\boldsymbol{\epsilon} \sim \mathbb{C}\mathcal{N}(\mathbf{0}_D, \boldsymbol{\Sigma})$ — noise, with $\boldsymbol{\Sigma} := \mathrm{diag}\left(\sigma_1^2, \ldots, \sigma_D^2\right)$

Signal Model

A *scan profile* contains D voxels $\mathbf{y} := [y_1, \ldots, y_D]^\mathsf{T}$, modeled as

$$\mathbf{y} = \mathbf{s}(\mathbf{x}; \boldsymbol{\nu}, \mathbf{P}) + \boldsymbol{\epsilon} \tag{1}$$

- $\mathbf{x} \in \mathbb{R}^L$ latent free parameters
- $\boldsymbol{\nu} \in \mathbb{R}^K$ known parameters
- $\mathbf{P} := [\mathbf{p}_1, \ldots, \mathbf{p}_D]$ acquisition parameter matrix
- $\mathbf{s} : \mathbb{R}^{L+K+AD} \mapsto \mathbb{C}^D$ vector signal model
- $\boldsymbol{\epsilon} \sim \mathbb{C}\mathcal{N}(\mathbf{0}_D, \boldsymbol{\Sigma})$ noise, with $\boldsymbol{\Sigma} := \mathrm{diag}(\sigma_1^2, \ldots, \sigma_D^2)$

Task: design $\mathbf{P}$ to enable precise unbiased estimation of $\mathbf{x}$

Towards an Objective Function

When $\mathbf{s}$ is analytic in $\mathbf{x}$ (as is typical),
Fisher information characterizes unbiased estimator precision:

$$\mathbf{F}(\mathbf{x};\nu,\mathbf{P}) := (\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\nu,\mathbf{P}))^{\mathsf{H}}\mathbf{\Sigma}^{-1}\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\nu,\mathbf{P}). \tag{2}$$

Towards an Objective Function

When $\mathbf{s}$ is analytic in $\mathbf{x}$ (as is typical),
Fisher information characterizes unbiased estimator precision:

$$\mathbf{F}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}) := (\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}))^{\mathsf{H}}\boldsymbol{\Sigma}^{-1}\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}). \tag{2}$$

When $\mathbf{F}$ is invertible, Cramér-Rao Bound (CRB) [Cramér, 1946]
ensures covariance of unbiased estimates $\widehat{\mathbf{x}}$ of $\mathbf{x}$ satisfy

$$\mathrm{cov}(\widehat{\mathbf{x}};\boldsymbol{\nu},\mathbf{P}) \succeq \mathbf{F}^{-1}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}). \tag{3}$$

Towards an Objective Function

When $\mathbf{s}$ is analytic in $\mathbf{x}$ (as is typical),
Fisher information characterizes unbiased estimator precision:

$$\mathbf{F}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}) := \left(\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\boldsymbol{\nu},\mathbf{P})\right)^{\mathsf{H}}\boldsymbol{\Sigma}^{-1}\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}). \tag{2}$$

When $\mathbf{F}$ is invertible, Cramér-Rao Bound (CRB) [Cramér, 1946]
ensures covariance of unbiased estimates $\widehat{\mathbf{x}}$ of $\mathbf{x}$ satisfy

$$\mathrm{cov}(\widehat{\mathbf{x}};\boldsymbol{\nu},\mathbf{P}) \succeq \mathbf{F}^{-1}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}). \tag{3}$$

Maximum-likelihood (ML) estimates achieve CRB asymptotically
or equivalently (for Gaussian data) at sufficiently high SNR.

Towards an Objective Function

When $\mathbf{s}$ is analytic in $\mathbf{x}$ (as is typical),
Fisher information characterizes unbiased estimator precision:

$$\mathbf{F}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}) := (\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}))^{\mathsf{H}}\boldsymbol{\Sigma}^{-1}\nabla_{\mathbf{x}}\mathbf{s}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}). \quad (2)$$

When $\mathbf{F}$ is invertible, Cramér-Rao Bound (CRB) [Cramér, 1946]
ensures covariance of unbiased estimates $\widehat{\mathbf{x}}$ of $\mathbf{x}$ satisfy

$$\mathrm{cov}(\widehat{\mathbf{x}};\boldsymbol{\nu},\mathbf{P}) \succeq \mathbf{F}^{-1}(\mathbf{x};\boldsymbol{\nu},\mathbf{P}). \quad (3)$$

Maximum-likelihood (ML) estimates achieve CRB asymptotically
or equivalently (for Gaussian data) at sufficiently high SNR.
Idea: choose $\mathbf{P}$ such that imprecision matrix $\mathbf{F}^{-1}$ “small”

Scan Design

Idea: choose $\mathbf{P}$ to minimize the objective

$$\Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P}) = \operatorname{tr}\left(\mathbf{W}\mathbf{F}^{-1}(\mathbf{x};\boldsymbol{\nu},\mathbf{P})\mathbf{W}^{\mathsf{T}}\right), \tag{4}$$

where $\mathbf{W} \in \mathbb{R}^{L\times L}$ is a pre-selected diagonal matrix of weights.

Scan Design

Idea: choose $\mathbf{P}$ to minimize the objective

$$\Psi(\mathbf{x}; \boldsymbol{\nu}, \mathbf{P}) = \mathrm{tr}\Big(\mathbf{W}\mathbf{F}^{-1}(\mathbf{x}; \boldsymbol{\nu}, \mathbf{P})\mathbf{W}^{\mathsf{T}}\Big), \qquad (4)$$

where $\mathbf{W} \in \mathbb{R}^{L \times L}$ is a pre-selected diagonal matrix of weights.

Challenge: $\mathbf{x}, \boldsymbol{\nu}$ vary spatially

Scan Design

Idea: choose $\mathbf{P}$ to minimize the objective

$$\Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P}) = \mathrm{tr}\Big(\mathbf{W}\mathbf{F}^{-1}(\mathbf{x};\boldsymbol{\nu},\mathbf{P})\mathbf{W}^{\mathsf{T}}\Big), \tag{4}$$

where $\mathbf{W} \in \mathbb{R}^{L\times L}$ is a pre-selected diagonal matrix of weights.

Challenge: $\mathbf{x}, \boldsymbol{\nu}$ vary spatially

Two problems considered:

- min-max scan design [Nataraj et al., 2017b]

$$\check{\mathbf{P}} \in \left\{ \arg\min_{\mathbf{P}\in\mathbb{P}} \max_{\substack{\mathbf{x}\in\mathbb{X}^{\mathrm{t}} \\ \boldsymbol{\nu}\in\mathbb{N}^{\mathrm{t}}}} \Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P}), \right\} \tag{5}$$

  where $\mathbb{X}^{\mathrm{t}} \subseteq \mathbb{R}^{L}$ and $\mathbb{N}^{\mathrm{t}} \subseteq \mathbb{R}^{K}$ are "tight" ranges of interest and $\mathbb{P}$ is defined by acquisition/timing constraints

Scan Design

Idea: choose $\mathbf{P}$ to minimize the objective

$$\Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P}) = \mathrm{tr}\left(\mathbf{W}\mathbf{F}^{-1}(\mathbf{x};\boldsymbol{\nu},\mathbf{P})\mathbf{W}^{\mathsf{T}}\right), \tag{4}$$

where $\mathbf{W} \in \mathbb{R}^{L \times L}$ is a pre-selected diagonal matrix of weights.

Challenge: $\mathbf{x}, \boldsymbol{\nu}$ vary spatially

Two problems considered:

- min-max scan design [Nataraj et al., 2017b]

$$\check{\mathbf{P}} \in \left\{ \arg\min_{\mathbf{P}\in\mathbb{P}} \max_{\substack{\mathbf{x}\in\mathbb{X}^{\mathrm{t}} \\ \boldsymbol{\nu}\in\mathbb{N}^{\mathrm{t}}}} \Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P}), \right\} \tag{5}$$

- Bayesian scan design [§6.3]

$$\check{\mathbf{P}} \in \left\{ \arg\min_{\mathbf{P}\in\mathbb{P}} \mathrm{E}_{\mathbf{x},\boldsymbol{\nu}}(\Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P})) \right\} \tag{6}$$

Scan Design

Idea: choose $\mathbf{P}$ to minimize the objective

$$\Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P}) = \operatorname{tr}\Big(\mathbf{W}\mathbf{F}^{-1}(\mathbf{x};\boldsymbol{\nu},\mathbf{P})\mathbf{W}^{\mathsf{T}}\Big), \tag{4}$$

where $\mathbf{W} \in \mathbb{R}^{L\times L}$ is a pre-selected diagonal matrix of weights.

Challenge: $\mathbf{x}, \boldsymbol{\nu}$ vary spatially

Two problems considered:

- min-max scan design [Nataraj et al., 2017b]

$$\check{\mathbf{P}} \in \left\{ \arg\min_{\mathbf{P}\in\mathbb{P}} \max_{\substack{\mathbf{x}\in\mathbb{X}^{\mathrm{t}} \\ \boldsymbol{\nu}\in\mathbb{N}^{\mathrm{t}}}} \Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P}), \right\} \tag{5}$$

- Bayesian scan design [§6.3]

$$\check{\mathbf{P}} \in \left\{ \arg\min_{\mathbf{P}\in\mathbb{P}} \mathrm{E}_{\mathbf{x},\boldsymbol{\nu}}\big(\Psi(\mathbf{x};\boldsymbol{\nu},\mathbf{P})\big) \right\} \tag{6}$$

Detailed Example Study

Task: design fast acquisition for precise estimation of relaxation parameters T_1, T_2 in white/gray matter (WM/GM) of brain

Detailed Example Study

Task: design fast acquisition for precise estimation of relaxation parameters T_1, T_2 in white/gray matter (WM/GM) of brain

- Consider scan profiles consisting of two fast pulse sequences
  - Spoiled Gradient-Recalled Echo (SPGR) [Zur et al., 1991]
  - Dual-Echo Steady-State (DESS) [Redpath and Jones, 1988]

Detailed Example Study

Task: design fast acquisition for precise estimation of relaxation parameters T_1, T_2 in white/gray matter (WM/GM) of brain

- Consider scan profiles consisting of two fast pulse sequences
  - Spoiled Gradient-Recalled Echo (SPGR) [Zur et al., 1991]
  - Dual-Echo Steady-State (DESS) [Redpath and Jones, 1988]
- For each scan profile feasible under total time constraint:
  1. Let $\mathbf{s}$ model corresponding single-component signal
     - $\mathbf{x} \leftarrow [m_0, T_1, T_2]^\mathsf{T}$, where m_0 is a scale factor
     - $\boldsymbol{\nu} \leftarrow$ flip angle variation
     - $\mathbf{P} \leftarrow$ nominal flip angles, repetition times
  2. Optimize $\mathbf{P}$ subject to flip angle, sequence timing constraints
     - $\mathbf{W} \leftarrow \mathrm{diag}(0, 0.1, 1)$ emphasizes T_1, T_2 est roughly equally
     - $\mathbb{X}^\mathrm{t}$ chosen to focus on WM/GM at 3T field strength
     - $\mathbb{N}^\mathrm{t}$ chosen to allow 10% flip angle variation

Scan Profile Comparison

(#SPGR, #DESS) Profiles	$(2, 1)$	$(1, 1)$	$(0, 2)$
SPGR nom. flip (deg)	(15, 5)	15	–
DESS nom. flip (deg)	30	10	(35, 10)
SPGR rep. times (ms)	(12.2, 12.2)	13.9	–
DESS rep. times (ms)	17.5	28.0	(24.4, 17.5)
Optimized Cost	4.0	4.9	**3.5**

Scan Profile Comparison

(#SPGR, #DESS) Profiles	$(2, 1)$	$(1, 1)$	$(0, 2)$
SPGR nom. flip (deg)	(15, 5)	15	–
DESS nom. flip (deg)	30	10	(35, 10)
SPGR rep. times (ms)	(12.2, 12.2)	13.9	–
DESS rep. times (ms)	17.5	28.0	(24.4, 17.5)
Optimized Cost	4.0	4.9	**3.5**

Main finding: 2 DESS sequences can yield T_1, T_2 WM/GM estimates that are at least as precise as T_1, T_2 estimates from SPGR/DESS scan profiles, under this competitive time constraint.

Numerical Simulation

- Simulated many WM-like, GM-like voxel realizations
- Studied sample statistics of T_1, T_2 ML estimates $\widehat{T}_1^{\mathrm{ML}}$, $\widehat{T}_2^{\mathrm{ML}}$

Numerical Simulation

- Simulated many WM-like, GM-like voxel realizations
- Studied sample statistics of T_1, T_2 ML estimates $\widehat{T}_1^{\mathrm{ML}}$, $\widehat{T}_2^{\mathrm{ML}}$

Profile	$(2,1)$	$(1,1)$	$(0,2)$	Truth
WM $\widehat{T}_1^{\mathrm{ML}}$	830 ± 17	830 ± 15	830 ± 14	832
GM $\widehat{T}_1^{\mathrm{ML}}$	$1330 \pm 30.$	1330 ± 24	1330 ± 24	1331
WM $\widehat{T}_2^{\mathrm{ML}}$	$80. \pm 1.0$	$80. \pm 2.1$	79.6 ± 0.94	79.6
GM $\widehat{T}_2^{\mathrm{ML}}$	$110. \pm 1.4$	$110. \pm 3.0$	$110. \pm 1.6$	110

Table 1: $\widehat{T}_1^{\mathrm{ML}}$, $\widehat{T}_2^{\mathrm{ML}}$ sample means $\pm$ sample standard deviations

Experimental Setup

Candidate $(2,1)$, $(1,1)$, $(0,2)$ SPGR/DESS scan profiles

- Prescribed optimized nominal flip angles, repetition times
- Used $256 \times 256 \times 8$ 3D matrix over $24 \times 24 \times 4$cm FOV
- Required **1m37s** scan time for each profile

Experimental Setup

Candidate $(2, 1)$, $(1, 1)$, $(0, 2)$ SPGR/DESS scan profiles

- Prescribed optimized nominal flip angles, repetition times
- Used $256 \times 256 \times 8$ 3D matrix over $24 \times 24 \times 4$cm FOV
- Required **1m37s** scan time for each profile

Reference scan profile

- Four inversion recovery (IR) scans for T_1 estimation
- Four spin-echo (SE) scans for T_2 estimation
- 256×256 matrix over $24 \times 24 \times 0.5$cm FOV
- Required **40m58s** scan time total

Experimental Setup

Candidate $(2,1)$, $(1,1)$, $(0,2)$ SPGR/DESS scan profiles

- Prescribed optimized nominal flip angles, repetition times
- Used $256 \times 256 \times 8$ 3D matrix over $24 \times 24 \times 4$cm FOV
- Required **1m37s** scan time for each profile

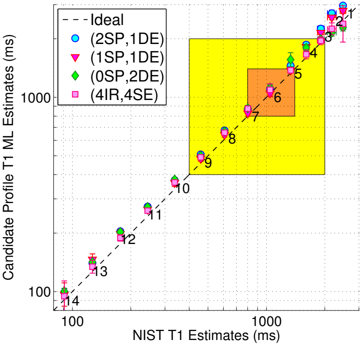
Reference scan profile

- Four inversion recovery (IR) scans for T_1 estimation
- Four spin-echo (SE) scans for T_2 estimation
- 256×256 matrix over $24 \times 24 \times 0.5$cm FOV
- Required **40m58s** scan time total

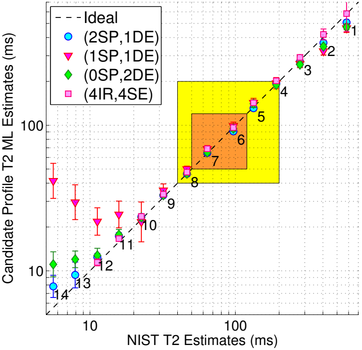
Bloch-Siegert (BS) acquisition for separate flip angle calibration

- Acquired 2 BS-shifted SPGR scans in 1m40s total
- Used for T_1, T_2 est from both candidate and reference profiles

Phantom Accuracy Results



(a) $\widehat{T}_1^{\mathrm{ML}}$ Estimates



(b) $\widehat{T}_2^{\mathrm{ML}}$ Estimates

Compared against NIST NMR measurements [Keenan et al., 2016]

Phantom Precision Results

- Repeated each profile 10 times
- Estimated T_1, T_2 std dev of typical voxel across repetitions

Phantom Precision Results

	(2, 1)	(1, 1)	(0, 2)
V5 $\widehat{\sigma}_{\widehat{T}_1^{\mathrm{ML}}}$	50 ± 12	$40 \pm 10.$	39 ± 9.4
V6 $\widehat{\sigma}_{\widehat{T}_1^{\mathrm{ML}}}$	70 ± 18	60 ± 15	70 ± 16
V7 $\widehat{\sigma}_{\widehat{T}_1^{\mathrm{ML}}}$	60 ± 13	50 ± 13	50 ± 13
V5 $\widehat{\sigma}_{\widehat{T}_2^{\mathrm{ML}}}$	2.6 ± 0.63	6 ± 1.4	3.5 ± 0.84
V6 $\widehat{\sigma}_{\widehat{T}_2^{\mathrm{ML}}}$	1.9 ± 0.46	5 ± 1.1	2.3 ± 0.54
V7 $\widehat{\sigma}_{\widehat{T}_2^{\mathrm{ML}}}$	1.4 ± 0.34	3.4 ± 0.80	1.5 ± 0.35

Table 2: Pooled sample standard deviations $\pm$ pooled standard errors of sample standard deviations (ms), from optimized SPGR/DESS profiles.

Phantom Precision Results

	(2, 1)	(1, 1)	(0, 2)
V5 $\widehat{\sigma}_{\widehat{T}_1^{\mathrm{ML}}}$	50 ± 12	$40 \pm 10.$	39 ± 9.4
V6 $\widehat{\sigma}_{\widehat{T}_1^{\mathrm{ML}}}$	70 ± 18	60 ± 15	70 ± 16
V7 $\widehat{\sigma}_{\widehat{T}_1^{\mathrm{ML}}}$	60 ± 13	50 ± 13	50 ± 13
V5 $\widehat{\sigma}_{\widehat{T}_2^{\mathrm{ML}}}$	2.6 ± 0.63	6 ± 1.4	3.5 ± 0.84
V6 $\widehat{\sigma}_{\widehat{T}_2^{\mathrm{ML}}}$	1.9 ± 0.46	5 ± 1.1	2.3 ± 0.54
V7 $\widehat{\sigma}_{\widehat{T}_2^{\mathrm{ML}}}$	1.4 ± 0.34	3.4 ± 0.80	1.5 ± 0.35

Table 2: Pooled sample standard deviations $\pm$ pooled standard errors of sample standard deviations (ms), from optimized SPGR/DESS profiles.

Similar trends across profiles of empirical vs. theoretical std dev!

In vivo Results

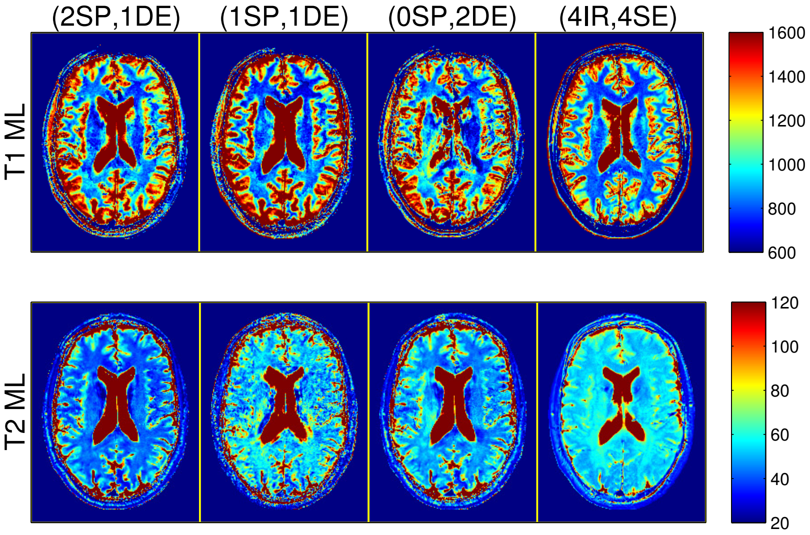


Figure 1: Colorbar ranges in ms.

Summary

Contributions

- MR scan design method for precise parameter estimation
- Fast SPGR/DESS scan profile for T_1, T_2 estimation in brain

Summary

Contributions

- MR scan design method for precise parameter estimation
- Fast SPGR/DESS scan profile for T_1, T_2 estimation in brain
  - Simulation and phantom results validate method
    as a predictor of unbiased estimation precision.

Summary

Contributions

- MR scan design method for precise parameter estimation
- Fast SPGR/DESS scan profile for T_1, T_2 estimation in brain
    - Simulation and phantom results validate method as a predictor of unbiased estimation precision.
    - *In vivo* results reveal discrepancies (especially in T_2 estimates), suggesting sensitivity to model mismatch.

Summary

Contributions

- MR scan design method for precise parameter estimation
- Fast SPGR/DESS scan profile for T_1, T_2 estimation in brain
    - Simulation and phantom results validate method as a predictor of unbiased estimation precision.
    - *In vivo* results reveal discrepancies (especially in T_2 estimates), suggesting sensitivity to model mismatch.

How to address model mismatch?

- More complete *in vivo* signal models
- More scalable parameter estimation

Overview

Advances in Quantitative MRI:

- **Acquisition** [Ch. 4]
  How can we assemble fast, informative collections of scans to enable precise biomarker quantification?
- **Estimation** [Ch. 5]
  Given data from an informative acquisition, how can we rapidly and accurately quantify these biomarkers?
- **Application** [Ch. 6]
  Using these tools, can we design a state-of-the-art biomarker?

Quantitative MRI (QMRI) Parameter Estimation

Given: MR image sequence informative about a physical process

- flow
- diffusion
- multi-compartmental relaxation
- ...

Quantitative MRI (QMRI) Parameter Estimation

Given: MR image sequence informative about a physical process

- flow
- diffusion
- multi-compartmental relaxation
- ...

Task: estimate MR tissue properties characterizing the process

- flow velocity
- diffusivity
- compartmental relaxivity
- ...

QMRI Problem Statement

Given: at each voxel, image sequence $\mathbf{y} \in \mathbb{C}^D$ modeled as

$$\mathbf{y} = \mathbf{s}(\mathbf{x}, \boldsymbol{\nu}) + \boldsymbol{\epsilon} \tag{7}$$

- $\mathbf{x} \in \mathbb{R}^L$ latent free parameters
- $\boldsymbol{\nu} \in \mathbb{R}^K$ known parameters
- $\mathbf{s} : \mathbb{R}^{L+K} \mapsto \mathbb{C}^D$ signal model
- $\boldsymbol{\epsilon} \in \mathbb{C}^D$ noise $\sim \mathbb{C}\mathcal{N}(\mathbf{0}_D, \boldsymbol{\Sigma})$

QMRI Problem Statement

Given: at each voxel, image sequence $\mathbf{y} \in \mathbb{C}^D$ modeled as

$$\mathbf{y} = \mathbf{s}(\mathbf{x}, \boldsymbol{\nu}) + \boldsymbol{\epsilon} \tag{7}$$

- $\mathbf{x} \in \mathbb{R}^L$ latent free parameters
- $\boldsymbol{\nu} \in \mathbb{R}^K$ known parameters
- $\mathbf{s} : \mathbb{R}^{L+K} \mapsto \mathbb{C}^D$ signal model
- $\boldsymbol{\epsilon} \in \mathbb{C}^D$ noise $\sim \mathbb{C}\mathcal{N}(\mathbf{0}_D, \boldsymbol{\Sigma})$

Task: construct fast estimator $\widehat{\mathbf{x}}(\mathbf{y}, \boldsymbol{\nu})$

Prior Work

Task: construct fast estimator $\widehat{\mathbf{x}}(\mathbf{y}, \boldsymbol{\nu})$

Challenges:

- signal $\mathbf{s}$ often nonlinear in $\mathbf{x}$: non-convex inverse problems
- signal $\mathbf{s}$ might be difficult to write in closed form

Prior Work

Task: construct fast estimator $\widehat{\mathbf{x}}(\mathbf{y}, \boldsymbol{\nu})$

Challenges:

- signal $\mathbf{s}$ often nonlinear in $\mathbf{x}$: non-convex inverse problems
- signal $\mathbf{s}$ might be difficult to write in closed form

Conventional Approaches:

- gradient-based local optimization
  - initialization-dependent solution
  - requires signal gradients

Prior Work

Task: construct fast estimator $\widehat{\mathbf{x}}(\mathbf{y}, \boldsymbol{\nu})$

Challenges:

- signal $\mathbf{s}$ often nonlinear in $\mathbf{x}$: non-convex inverse problems
- signal $\mathbf{s}$ might be difficult to write in closed form

Conventional Approaches:

- gradient-based local optimization
  - initialization-dependent solution
  - requires signal gradients
- stochastic methods (*e.g.*, simulated annealing)
  - unclear convergence analysis [?]
  - several unintuitive tuning parameters

Prior Work

Task: construct fast estimator $\widehat{\mathbf{x}}(\mathbf{y}, \boldsymbol{\nu})$

Challenges:

- signal $\mathbf{s}$ often nonlinear in $\mathbf{x}$: non-convex inverse problems
- signal $\mathbf{s}$ might be difficult to write in closed form

Conventional Approaches:

- gradient-based local optimization
  - initialization-dependent solution
  - requires signal gradients
- stochastic methods (*e.g.*, simulated annealing)
  - unclear convergence analysis [?]
  - several unintuitive tuning parameters
- grid search *e.g.*, for MR fingerprinting [Ma et al., 2013]

Motivation

Grid search computational costs

	L	$\sim$number dictionary atoms
(1-compartment) relaxivity	3	$\sim 100^2$

Motivation

Grid search computational costs

	L	$\sim$number dictionary atoms
(1-compartment) relaxivity	3	$\sim 100^2$
flow velocity	4	$\sim 100^3$
diffusivity tensor	7	$\sim 100^6$
2-3 compartment relaxivity	6-10	$\sim 100^5 - 100^9$

Motivation

Grid search computational costs

	L	~number dictionary atoms
(1-compartment) relaxivity	3	$\sim 100^2$
flow velocity	4	$\sim 100^3$
diffusivity tensor	7	$\sim 100^6$
2-3 compartment relaxivity	6-10	$\sim 100^5 - 100^9$

Can we scale computation with L more gracefully?

Machine Learning for QMRI Parameter Estimation

Idea: learn a *nonlinear* estimator from simulated training data

Machine Learning for QMRI Parameter Estimation

Idea: learn a *nonlinear* estimator from simulated training data

- sample $(\mathbf{x}_1, \boldsymbol{\nu}_1, \epsilon_1), \dots, (\mathbf{x}_N, \boldsymbol{\nu}_N, \epsilon_N)$ from prior distributions
- simulate image data vectors $\mathbf{y}_1, \dots, \mathbf{y}_N$ via signal model $\mathbf{s}$

Machine Learning for QMRI Parameter Estimation

Idea: learn a *nonlinear* estimator from simulated training data

- sample $(\mathbf{x}_1, \boldsymbol{\nu}_1, \boldsymbol{\epsilon}_1), \dots, (\mathbf{x}_N, \boldsymbol{\nu}_N, \boldsymbol{\epsilon}_N)$ from prior distributions
- simulate image data vectors $\mathbf{y}_1, \dots, \mathbf{y}_N$ via signal model $\mathbf{s}$
- design *nonlinear* functions $\widehat{x}_l(\cdot) := \widehat{h}_l(\cdot) + \widehat{b}_l$ for $l \in \{1, \dots, L\}$ that map each $\mathbf{q}_n := [\mathrm{Re}(\mathbf{y}_n)^\mathsf{T}, \mathrm{Im}(\mathbf{y}_n)^\mathsf{T}, \boldsymbol{\nu}_n^\mathsf{T}]^\mathsf{T} \in \mathcal{Q}$ to $x_{l,n} \in \mathbb{R}$

Machine Learning for QMRI Parameter Estimation

Idea: learn a *nonlinear* estimator from simulated training data

- sample $(\mathbf{x}_1, \boldsymbol{\nu}_1, \boldsymbol{\epsilon}_1), \dots, (\mathbf{x}_N, \boldsymbol{\nu}_N, \boldsymbol{\epsilon}_N)$ from prior distributions
- simulate image data vectors $\mathbf{y}_1, \dots, \mathbf{y}_N$ via signal model $\mathbf{s}$
- design *nonlinear* functions $\widehat{x}_l(\cdot) := \widehat{h}_l(\cdot) + \widehat{b}_l$ for $l \in \{1, \dots, L\}$ that map each $\mathbf{q}_n := [\mathrm{Re}(\mathbf{y}_n)^\mathsf{T}, \mathrm{Im}(\mathbf{y}_n)^\mathsf{T}, \boldsymbol{\nu}_n^\mathsf{T}]^\mathsf{T} \in \mathcal{Q}$ to $x_{l,n} \in \mathbb{R}$

$$\left(\widehat{h}_l, \widehat{b}_l\right) \in \left\{ \arg\min_{\substack{h_l \\ b_l \in \mathbb{R}}} \frac{1}{N} \sum_{n=1}^{N} \left(h_l(\mathbf{q}_n) + b_l - x_{l,n}\right)^2 \right\}$$

Machine Learning for QMRI Parameter Estimation

Idea: learn a *nonlinear* estimator from simulated training data

- sample $(\mathbf{x}_1, \boldsymbol{\nu}_1, \boldsymbol{\epsilon}_1), \ldots, (\mathbf{x}_N, \boldsymbol{\nu}_N, \boldsymbol{\epsilon}_N)$ from prior distributions
- simulate image data vectors $\mathbf{y}_1, \ldots, \mathbf{y}_N$ via signal model $\mathbf{s}$
- design *nonlinear* functions $\widehat{x}_l(\cdot) := \widehat{h}_l(\cdot) + \widehat{b}_l$ for $l \in \{1, \ldots, L\}$ that map each $\mathbf{q}_n := [\mathrm{Re}(\mathbf{y}_n)^\mathsf{T}, \mathrm{Im}(\mathbf{y}_n)^\mathsf{T}, \boldsymbol{\nu}_n^\mathsf{T}]^\mathsf{T} \in \mathcal{Q}$ to $x_{l,n} \in \mathbb{R}$

$$\left(\widehat{h}_l, \widehat{b}_l\right) \in \left\{ \arg\min_{\substack{h_l \\ b_l \in \mathbb{R}}} \frac{1}{N} \sum_{n=1}^{N} \left(h_l(\mathbf{q}_n) + b_l - x_{l,n}\right)^2 \right\} \quad \text{ill-posed!}$$

Machine Learning for QMRI Parameter Estimation

Idea: learn a *nonlinear* estimator from simulated training data

- sample $(\mathbf{x}_1, \boldsymbol{\nu}_1, \boldsymbol{\epsilon}_1), \ldots, (\mathbf{x}_N, \boldsymbol{\nu}_N, \boldsymbol{\epsilon}_N)$ from prior distributions
- simulate image data vectors $\mathbf{y}_1, \ldots, \mathbf{y}_N$ via signal model $\mathbf{s}$
- design *nonlinear* functions $\widehat{x}_l(\cdot) := \widehat{h}_l(\cdot) + \widehat{b}_l$ for $l \in \{1, \ldots, L\}$ that map each $\mathbf{q}_n := [\mathrm{Re}(\mathbf{y}_n)^\mathsf{T}, \mathrm{Im}(\mathbf{y}_n)^\mathsf{T}, \boldsymbol{\nu}_n^\mathsf{T}]^\mathsf{T} \in \mathcal{Q}$ to $x_{l,n} \in \mathbb{R}$

$$\left(\widehat{h}_l, \widehat{b}_l\right) \in \left\{ \arg \min_{\substack{h_l \in \mathbb{H} \\ b_l \in \mathbb{R}}} \frac{1}{N} \sum_{n=1}^{N} \left(h_l(\mathbf{q}_n) + b_l - x_{l,n}\right)^2 + \rho_l \|h_l\|_{\mathbb{H}}^2 \right\} \quad (8)$$

Solution: solve a *kernel ridge regression* (KRR) problem

- restrict function space over which we optimize
- include function regularization

A Function Space over which Optimization is Tractable

Hilbert space: complete inner product function space

A Function Space over which Optimization is Tractable

Hilbert space: complete inner product function space

Reproducing kernel Hilbert space (RKHS)

Hilbert space $\mathbb{H}$ over input space $\mathcal{Q}$ with *reproducing property*

$$\langle h, k(\cdot, \mathbf{q}) \rangle_{\mathbb{H}} = h(\mathbf{q}), \qquad \forall h \in \mathbb{H}, \mathbf{q} \in \mathcal{Q}$$

for some $k : \mathcal{Q}^2 \mapsto \mathbb{R}$ called a reproducing kernel (RK)

A Function Space over which Optimization is Tractable

Hilbert space: complete inner product function space

Reproducing kernel Hilbert space (RKHS)

Hilbert space $\mathbb{H}$ over input space $\mathcal{Q}$ with *reproducing property*

$$\langle h, k(\cdot, \mathbf{q}) \rangle_{\mathbb{H}} = h(\mathbf{q}), \qquad \forall h \in \mathbb{H}, \mathbf{q} \in \mathcal{Q}$$

for some $k : \mathcal{Q}^2 \mapsto \mathbb{R}$ called a reproducing kernel (RK)

Relevant facts

- Bijection between RKHS $\mathbb{H}$ and RK k [Aronszajn, 1950]
- Function $k(\cdot, \mathbf{q}) \in \mathbb{H}$ called a *feature mapping*

Function Optimization over a RKHS

Choose: RK $k : \mathcal{Q}^2 \mapsto \mathbb{R}$, which induces choice of RKHS $\mathbb{H}$

Function Optimization over a RKHS

Choose: RK $k : \mathcal{Q}^2 \mapsto \mathbb{R}$, which induces choice of RKHS $\mathbb{H}$

- *Nonlinear* kernel corresponds to *nonlinear* estimation
- We use $k(\mathbf{q}, \mathbf{q}') \leftarrow \exp\left(-\frac{1}{2}\left\|\mathbf{\Lambda}^{-1}(\mathbf{q} - \mathbf{q}')\right\|_2^2\right)$

Function Optimization over a RKHS

Choose: RK $k : \mathcal{Q}^2 \mapsto \mathbb{R}$, which induces choice of RKHS $\mathbb{H}$

Solve: for each desired latent parameter $l \in \{1, \ldots, L\}$,

$$\left(\widehat{h}_l, \widehat{b}_l\right) \in \left\{ \arg \min_{\substack{h_l \in \mathbb{H} \\ b_l \in \mathbb{R}}} \frac{1}{N} \sum_{n=1}^{N} (h_l(\mathbf{q}_n) + b_l - x_{l,n})^2 + \rho_l \|h_l\|_{\mathbb{H}}^2 \right\} \quad (9)$$

Function Optimization over a RKHS

Choose: RK $k : \mathcal{Q}^2 \mapsto \mathbb{R}$, which induces choice of RKHS $\mathbb{H}$

Solve: for each desired latent parameter $l \in \{1, \ldots, L\}$,

$$\left(\widehat{h}_l, \widehat{b}_l\right) \in \left\{ \arg \min_{\substack{h_l \in \mathbb{H} \\ b_l \in \mathbb{R}}} \frac{1}{N} \sum_{n=1}^{N} \left(h_l(\mathbf{q}_n) + b_l - x_{l,n}\right)^2 + \rho_l \|h_l\|_{\mathbb{H}}^2 \right\} \quad (9)$$

- Optimal $\widehat{h}_l$ over $\mathbb{H}$ takes form [Schölkopf et al., 2001]

$$\widehat{h}_l(\cdot) \equiv \sum_{n=1}^{N} \widehat{a}_{l,n} k(\cdot, \mathbf{q}_n) \quad (10)$$

Function Optimization over a RKHS

Choose: RK $k : \mathcal{Q}^2 \mapsto \mathbb{R}$, which induces choice of RKHS $\mathbb{H}$

Solve: for each desired latent parameter $l \in \{1, \ldots, L\}$,

$$\left(\widehat{h}_l, \widehat{b}_l\right) \in \left\{ \arg \min_{\substack{h_l \in \mathbb{H} \\ b_l \in \mathbb{R}}} \frac{1}{N} \sum_{n=1}^{N} \left(h_l(\mathbf{q}_n) + b_l - x_{l,n}\right)^2 + \rho_l \|h_l\|_{\mathbb{H}}^2 \right\} \quad (9)$$

- Optimal $\widehat{h}_l$ over $\mathbb{H}$ takes form [Schölkopf et al., 2001]

$$\widehat{h}_l(\cdot) \equiv \sum_{n=1}^{N} \widehat{a}_{l,n} k(\cdot, \mathbf{q}_n) \quad (10)$$

- Plug (10) into (9); solve now instead for $\left(\widehat{a}_l, \widehat{b}_l\right)$; construct:

$$\widehat{x}_l(\cdot) = \sum_{n=1}^{N} \widehat{a}_{l,n} k(\cdot, \mathbf{q}_n) + \widehat{b}_l \quad (11)$$

MRI Parameter Estimation via KRR

Non-iterative closed-form solution, for $l \in \{1, \ldots, L\}$:

$$\widehat{x}_l(\cdot) = \mathbf{x}_l^{\mathsf{T}} \left(\frac{1}{N}\mathbf{1}_N + \mathbf{M}(\mathbf{K}\mathbf{M} + N\rho_l \mathbf{I}_N)^{-1} \left(\mathbf{k}(\cdot) - \frac{1}{N}\mathbf{K}\mathbf{1}_N \right) \right) \quad (12)$$

- $\mathbf{x}_l := [x_{l,1}, \ldots, x_{l,N}]^{\mathsf{T}}$ training pt regressands

MRI Parameter Estimation via KRR

Non-iterative closed-form solution, for $l \in \{1, \dots, L\}$:

$$\widehat{x}_l(\cdot) = \mathbf{x}_l^\mathsf{T} \left(\frac{1}{N} \mathbf{1}_N + \mathbf{M} (\mathbf{K}\mathbf{M} + N\rho_l \mathbf{I}_N)^{-1} \left(\mathbf{k}(\cdot) - \frac{1}{N} \mathbf{K} \mathbf{1}_N \right) \right) \quad (12)$$

- $\mathbf{x}_l := [x_{l,1}, \dots, x_{l,N}]^\mathsf{T}$ training pt regressands
- $\mathbf{K} := \begin{bmatrix} k(\mathbf{q}_1, \mathbf{q}_1) & \cdots & k(\mathbf{q}_1, \mathbf{q}_N) \\ \vdots & \ddots & \vdots \\ k(\mathbf{q}_N, \mathbf{q}_1) & \cdots & k(\mathbf{q}_N, \mathbf{q}_N) \end{bmatrix}$ Gram matrix

MRI Parameter Estimation via KRR

Non-iterative closed-form solution, for $l \in \{1, \dots, L\}$:

$$\widehat{x}_l(\cdot) = \mathbf{x}_l^\mathsf{T} \left(\frac{1}{N} \mathbf{1}_N + \mathbf{M}(\mathbf{K}\mathbf{M} + N\rho_l \mathbf{I}_N)^{-1} \left(\mathbf{k}(\cdot) - \frac{1}{N} \mathbf{K} \mathbf{1}_N \right) \right) \quad (12)$$

- $\mathbf{x}_l := [x_{l,1}, \dots, x_{l,N}]^\mathsf{T}$ training pt regressands
- $\mathbf{K} := \begin{bmatrix} k(\mathbf{q}_1, \mathbf{q}_1) & \cdots & k(\mathbf{q}_1, \mathbf{q}_N) \\ \vdots & \ddots & \vdots \\ k(\mathbf{q}_N, \mathbf{q}_1) & \cdots & k(\mathbf{q}_N, \mathbf{q}_N) \end{bmatrix}$ Gram matrix
- $\mathbf{M} := \mathbf{I}_N - \frac{1}{N} \mathbf{1}_N \mathbf{1}_N^\mathsf{T}$ de-meaning operator

MRI Parameter Estimation via KRR

Non-iterative closed-form solution, for $l \in \{1, \dots, L\}$:

$$\widehat{x}_l(\cdot) = \mathbf{x}_l^\mathsf{T} \left(\frac{1}{N} \mathbf{1}_N + \mathbf{M}(\mathbf{K}\mathbf{M} + N\rho_l \mathbf{I}_N)^{-1} \left(\mathbf{k}(\cdot) - \frac{1}{N} \mathbf{K} \mathbf{1}_N \right) \right) \quad (12)$$

- $\mathbf{x}_l := [x_{l,1}, \dots, x_{l,N}]^\mathsf{T}$ training pt regressands
- $\mathbf{K} := \begin{bmatrix} k(\mathbf{q}_1, \mathbf{q}_1) & \cdots & k(\mathbf{q}_1, \mathbf{q}_N) \\ \vdots & \ddots & \vdots \\ k(\mathbf{q}_N, \mathbf{q}_1) & \cdots & k(\mathbf{q}_N, \mathbf{q}_N) \end{bmatrix}$ Gram matrix
- $\mathbf{M} := \mathbf{I}_N - \frac{1}{N} \mathbf{1}_N \mathbf{1}_N^\mathsf{T}$ de-meaning operator
- $\mathbf{k}(\cdot) := [k(\cdot, \mathbf{q}_1), \dots, k(\cdot, \mathbf{q}_N)]^\mathsf{T}$ nonlin kernel embedding

MRI Parameter Estimation via KRR

Non-iterative closed-form solution, for $l \in \{1, \dots, L\}$:

$$\widehat{x}_l(\cdot) = \mathbf{x}_l^\mathsf{T} \left(\frac{1}{N} \mathbf{1}_N + \mathbf{M}(\mathbf{K}\mathbf{M} + N\rho_l \mathbf{I}_N)^{-1} \left(\mathbf{k}(\cdot) - \frac{1}{N}\mathbf{K}\mathbf{1}_N \right) \right) \quad (12)$$

- $\mathbf{x}_l := [x_{l,1}, \dots, x_{l,N}]^\mathsf{T}$ training pt regressands
- $\mathbf{K} := \begin{bmatrix} k(\mathbf{q}_1, \mathbf{q}_1) & \cdots & k(\mathbf{q}_1, \mathbf{q}_N) \\ \vdots & \ddots & \vdots \\ k(\mathbf{q}_N, \mathbf{q}_1) & \cdots & k(\mathbf{q}_N, \mathbf{q}_N) \end{bmatrix}$ Gram matrix
- $\mathbf{M} := \mathbf{I}_N - \frac{1}{N}\mathbf{1}_N\mathbf{1}_N^\mathsf{T}$ de-meaning operator
- $\mathbf{k}(\cdot) := [k(\cdot, \mathbf{q}_1), \dots, k(\cdot, \mathbf{q}_N)]^\mathsf{T}$ nonlin kernel embedding

Can we scale computation with L more gracefully?

- Yes, in fact (12) separable in $l \in \{1, \dots, L\}$ by construction

MRI Parameter Estimation via KRR

Non-iterative closed-form solution, for $l \in \{1, \ldots, L\}$:

$$\widehat{x}_l(\cdot) = \mathbf{x}_l^\mathsf{T} \left(\frac{1}{N} \mathbf{1}_N + \mathbf{M}(\mathbf{K}\mathbf{M} + N\rho_l \mathbf{I}_N)^{-1} \left(\mathbf{k}(\cdot) - \frac{1}{N} \mathbf{K} \mathbf{1}_N \right) \right) \quad (12)$$

- $\mathbf{x}_l := [x_{l,1}, \ldots, x_{l,N}]^\mathsf{T}$ — training pt regressands
- $\mathbf{K} := \begin{bmatrix} k(\mathbf{q}_1, \mathbf{q}_1) & \cdots & k(\mathbf{q}_1, \mathbf{q}_N) \\ \vdots & \ddots & \vdots \\ k(\mathbf{q}_N, \mathbf{q}_1) & \cdots & k(\mathbf{q}_N, \mathbf{q}_N) \end{bmatrix}$ — Gram matrix
- $\mathbf{M} := \mathbf{I}_N - \frac{1}{N} \mathbf{1}_N \mathbf{1}_N^\mathsf{T}$ — de-meaning operator
- $\mathbf{k}(\cdot) := [k(\cdot, \mathbf{q}_1), \ldots, k(\cdot, \mathbf{q}_N)]^\mathsf{T}$ — nonlin kernel embedding

Can we scale computation with L more gracefully?

- Yes, in fact (12) separable in $l \in \{1, \ldots, L\}$ by construction
- However, explicitly computing $\mathbf{K}$ may be undesirable...

KRR as High-Dimensional Affine Regression

Suppose there exists "approximate feature mapping" $\tilde{\mathbf{z}} : \mathcal{Q} \mapsto \mathbb{R}^Z$ such that $\tilde{\mathbf{Z}} := [\tilde{\mathbf{z}}(\mathbf{q}_1), \ldots, \tilde{\mathbf{z}}(\mathbf{q}_N)]$ has for $\dim(\mathcal{Q}) \ll Z \ll N$

$$\mathbf{K} \approx \tilde{\mathbf{Z}}^{\mathsf{T}} \tilde{\mathbf{Z}}. \tag{13}$$

KRR as High-Dimensional Affine Regression

Suppose there exists“approximate feature mapping” $\tilde{\mathbf{z}} : \mathcal{Q} \mapsto \mathbb{R}^Z$ such that $\tilde{\mathbf{Z}} := [\tilde{\mathbf{z}}(\mathbf{q}_1), \dots, \tilde{\mathbf{z}}(\mathbf{q}_N)]$ has for $\dim(\mathcal{Q}) \ll Z \ll N$

$$\mathbf{K} \approx \tilde{\mathbf{Z}}^\mathsf{T} \tilde{\mathbf{Z}}. \tag{13}$$

Plugging (13) into KRR solution (12) and rearranging gives

$$\widehat{x}_l(\cdot) \approx \frac{1}{N} \mathbf{x}_l^\mathsf{T} \mathbf{1}_N + \frac{1}{N} \mathbf{x}_l^\mathsf{T} \mathbf{M} \tilde{\mathbf{Z}}^\mathsf{T} \left(\frac{1}{N} \tilde{\mathbf{Z}} \mathbf{M} \tilde{\mathbf{Z}}^\mathsf{T} + \rho_l \mathbf{I}_Z \right)^{-1} \left(\tilde{\mathbf{z}}(\cdot) - \frac{1}{N} \tilde{\mathbf{Z}} \mathbf{1}_N \right)$$

KRR as High-Dimensional Affine Regression

Suppose there exists "approximate feature mapping" $\tilde{\mathbf{z}} : \mathcal{Q} \mapsto \mathbb{R}^Z$ such that $\tilde{\mathbf{Z}} := [\tilde{\mathbf{z}}(\mathbf{q}_1), \ldots, \tilde{\mathbf{z}}(\mathbf{q}_N)]$ has for $\dim(\mathcal{Q}) \ll Z \ll N$

$$\mathbf{K} \approx \tilde{\mathbf{Z}}^\mathsf{T} \tilde{\mathbf{Z}}. \tag{13}$$

Plugging (13) into KRR solution (12) and rearranging gives

$$\widehat{x}_l(\cdot) \approx \widehat{m}_{x_l} + \widehat{\mathbf{c}}_{x_l \tilde{\mathbf{z}}}^\mathsf{T} \left(\widehat{\mathbf{C}}_{\tilde{\mathbf{z}}\tilde{\mathbf{z}}} + \rho_l \mathbf{I}_Z \right)^{-1} (\tilde{\mathbf{z}}(\cdot) - \widehat{\mathbf{m}}_{\tilde{\mathbf{z}}}) \tag{14}$$

which is regularized ("ridge") Z-dimensional affine regression!

KRR as High-Dimensional Affine Regression

Suppose there exists "approximate feature mapping" $\tilde{\mathbf{z}} : \mathcal{Q} \mapsto \mathbb{R}^Z$ such that $\tilde{\mathbf{Z}} := [\tilde{\mathbf{z}}(\mathbf{q}_1), \ldots, \tilde{\mathbf{z}}(\mathbf{q}_N)]$ has for $\dim(\mathcal{Q}) \ll Z \ll N$

$$\mathbf{K} \approx \tilde{\mathbf{Z}}^\mathsf{T} \tilde{\mathbf{Z}}. \tag{13}$$

Plugging (13) into KRR solution (12) and rearranging gives

$$\widehat{x}_l(\cdot) \approx \widehat{m}_{x_l} + \widehat{\mathbf{c}}_{x_l \tilde{\mathbf{z}}}^\mathsf{T} \left(\widehat{\mathbf{C}}_{\tilde{\mathbf{z}}\tilde{\mathbf{z}}} + \rho_l \mathbf{I}_Z \right)^{-1} (\tilde{\mathbf{z}}(\cdot) - \widehat{\mathbf{m}}_{\tilde{\mathbf{z}}}) \tag{14}$$

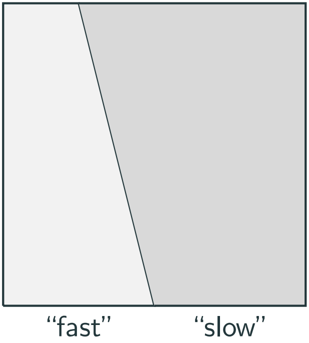
which is regularized ("ridge") Z-dimensional affine regression!

Does such a $\tilde{\mathbf{z}}$ exist and work well in practice?

- Yes, *e.g.* for "shift invariant" kernels (like our Gaussian) of form $k(\mathbf{q}, \mathbf{q}') \equiv k(\mathbf{q} - \mathbf{q}')$ [Rahimi and Recht, 2007]
- In such cases, can reduce from $\sim N^2$ to $\sim NZ$ computations

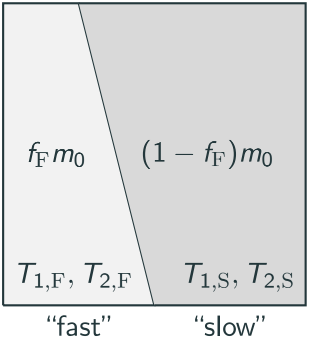
Application: Myelin Water Fraction (MWF) Imaging

simple two-compartment model



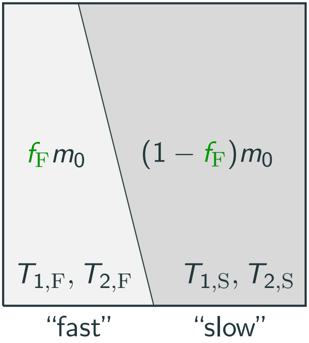
Application: Myelin Water Fraction (MWF) Imaging

simple two-compartment model



Application: Myelin Water Fraction (MWF) Imaging

simple two-compartment model



Goal: rapidly estimate f_{F} (proxy for MWF) in white matter (WM)

Application: MWF Imaging

Problem dimensions (per voxel)

- $\mathbf{x} \leftarrow [f_{\mathrm{F}}, T_{1,\mathrm{F}}, T_{2,\mathrm{F}}, T_{1,\mathrm{S}}, T_{2,\mathrm{S}}, m_0]^\mathsf{T}$
- $\boldsymbol{\nu} \leftarrow$ flip angle variation
- $\mathbf{y} \leftarrow$ voxel values from 10 datasets [Nataraj et al., 2017a]

Application: MWF Imaging

Problem dimensions (per voxel)

- $\mathbf{x} \leftarrow [f_{\mathrm{F}}, T_{1,\mathrm{F}}, T_{2,\mathrm{F}}, T_{1,\mathrm{S}}, T_{2,\mathrm{S}}, m_0]^{\mathsf{T}}$
- $\nu \leftarrow$ flip angle variation
- $\mathbf{y} \leftarrow$ voxel values from 10 datasets [Nataraj et al., 2017a]

Use KRR to estimate just f_{F}

- Separable prior on $\mathbf{x}$: f_{F}, m_0 uniform; others log-uniform
- $N \leftarrow 10^6$ training points
- $Z \leftarrow 10^3$ kernel approximation order

Application: MWF Imaging

Problem dimensions (per voxel)

- $\mathbf{x} \leftarrow [f_{\mathrm{F}}, T_{1,\mathrm{F}}, T_{2,\mathrm{F}}, T_{1,\mathrm{S}}, T_{2,\mathrm{S}}, m_0]^{\mathsf{T}}$
- $\nu \leftarrow$ flip angle variation
- $\mathbf{y} \leftarrow$ voxel values from 10 datasets [Nataraj et al., 2017a]

Use KRR to estimate just f_{F}

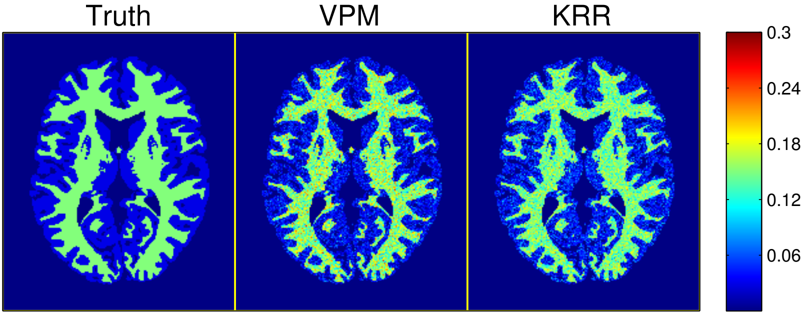
- Separable prior on $\mathbf{x}$: f_{F}, m_0 uniform; others log-uniform
- $N \leftarrow 10^6$ training points
- $Z \leftarrow 10^3$ kernel approximation order

Compare against grid search

- unconstrained search would require $\sim 100^5$ dictionary atoms
- we artificially constrain search here to limit computation

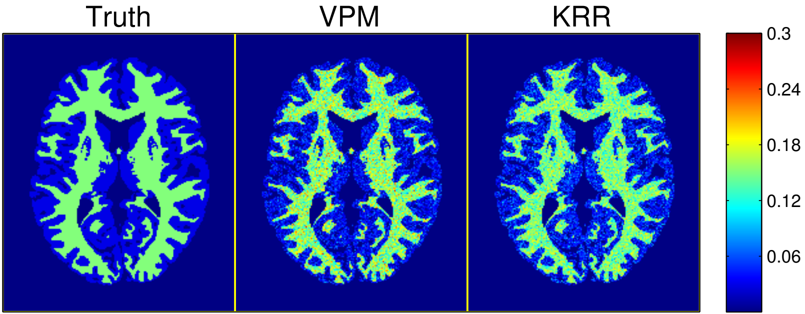
MWF Imaging: Simulation Result

Fast-fraction f_{F} estimates, in simulation:



MWF Imaging: Simulation Result

Fast-fraction f_{F} estimates, in simulation:



$\sim$4h 40s training, 2s testing

MWF Imaging: Proof-of-concept In Vivo Result

Fast-fraction f_{F} estimates, from 3D Cartesian data

MWF Imaging: Proof-of-concept In Vivo Result

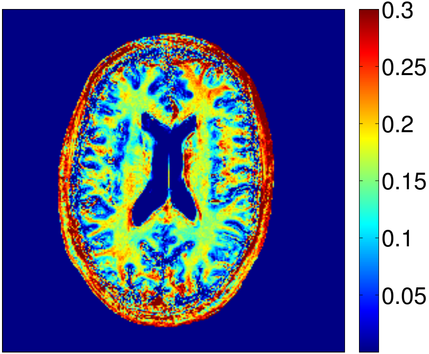
Fast-fraction f_{F} estimates, from 3D Cartesian data

- Full-scale grid search intractable on typical desktop

MWF Imaging: Proof-of-concept In Vivo Result

Fast-fraction f_{F} estimates, from 3D Cartesian data

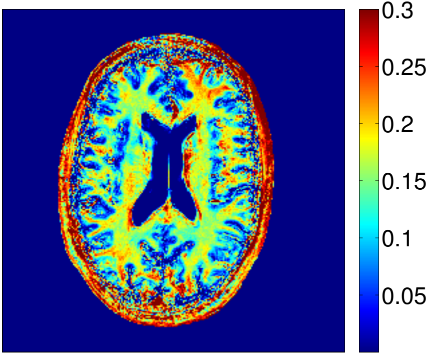
- Full-scale grid search intractable on typical desktop
- KRR estimates in single slice took about **70s**



MWF Imaging: Proof-of-concept In Vivo Result

Fast-fraction f_{F} estimates, from 3D Cartesian data

- Full-scale grid search intractable on typical desktop
- KRR estimates in single slice took about **70s**
- KRR MWF estimates in WM comparable to literature



Summary

Contributions

- Fast KRR method for nonlin MRI multiparameter estimation

Summary

Contributions

- Fast KRR method for nonlin MRI multiparameter estimation
  - Key insight: even with complicated MR signal models, can simulate training points “for free”

Summary

Contributions

- Fast KRR method for nonlin MRI multiparameter estimation
  - Key insight: even with complicated MR signal models, can simulate training points "for free"
  - Convert *nonlinear estimation* problem into *nonlinear regression* problem that we solve in closed-form with kernels

Summary

Contributions

- Fast KRR method for nonlin MRI multiparameter estimation
  - Key insight: even with complicated MR signal models, can simulate training points "for free"
  - Convert *nonlinear estimation* problem into *nonlinear regression* problem that we solve in closed-form with kernels
- Proof-of-concept *in vivo* application to MWF imaging

Summary

Contributions

- Fast KRR method for nonlin MRI multiparameter estimation
    - Key insight: even with complicated MR signal models, can simulate training points "for free"
    - Convert *nonlinear estimation* problem into *nonlinear regression* problem that we solve in closed-form with kernels
- Proof-of-concept *in vivo* application to MWF imaging

Ongoing work

- Conceptual: model selection, performance analysis
- Experimental: validation studies

Summary

Contributions

- Fast KRR method for nonlin MRI multiparameter estimation
  - Key insight: even with complicated MR signal models, can simulate training points "for free"
  - Convert *nonlinear estimation* problem into *nonlinear regression* problem that we solve in closed-form with kernels
- Proof-of-concept *in vivo* application to MWF imaging

Ongoing work

- Conceptual: model selection, performance analysis
- Experimental: validation studies

Backup: An Overview of Model Selection

Some model parameters **require manual selection**...

- Kernel shape $\quad k(\mathbf{q}, \mathbf{q}') \leftarrow \exp\left(-\frac{1}{2}\left\|\boldsymbol{\Lambda}^{-1}(\mathbf{q} - \mathbf{q}')\right\|_2^2\right)$

Backup: An Overview of Model Selection

Some model parameters **require manual selection**...

- Kernel shape $\quad k(\mathbf{q}, \mathbf{q}') \leftarrow \exp\left(-\frac{1}{2}\left\|\mathbf{\Lambda}^{-1}(\mathbf{q} - \mathbf{q}')\right\|_2^2\right)$
- Prior on $\mathbf{x}$ $\quad$ from tissue properties
- N, Z $\quad$ empirical methods

Backup: An Overview of Model Selection

Some model parameters **require manual selection**...

- Kernel shape $\quad k(\mathbf{q},\mathbf{q}') \leftarrow \exp\left(-\frac{1}{2}\left\|\boldsymbol{\Lambda}^{-1}(\mathbf{q}-\mathbf{q}')\right\|_2^2\right)$
- Prior on $\mathbf{x}$ $\quad$ from tissue properties
- N, Z $\quad$ empirical methods

...but others **tuned automatically**

- Kernel smoothing length-scale $\quad \boldsymbol{\Lambda} \leftarrow \mathrm{diag}\left(\sum_{n=1}^{N} \mathbf{q}_n\right)$
- Regularization parameters $\quad \rho_l \leftarrow \frac{1}{N^2}\mathbf{x}_l^\top \mathbf{M}\mathbf{x}_l$
- Prior on known $\boldsymbol{\nu}$ $\quad$ density estimation

Overview

Advances in Quantitative MRI:

- **Acquisition** [Ch. 4]
  How can we assemble fast, informative collections of scans
  to enable precise biomarker quantification?
- **Estimation** [Ch. 5]
  Given data from an informative acquisition,
  how can we rapidly and accurately quantify these biomarkers?
- **Application** [Ch. 6]
  Using these tools, can we design a state-of-the-art biomarker?

References i

Cramér, H. (1946).
Mathematical methods of statistics.
Princeton Univ. Press, Princeton.

Aronszajn, N. (1950).
Theory of reproducing kernels.
Trans. Amer. Math. Soc., 68(3):337–404.

Keenan, K. E., Stupic, K. F., Boss, M. A., Russek, S. E., Chenevert, T. L., Prasad, P. V., Reddick, W. E., Cecil, K. M., Zheng, J., Hu, P., and Jackson, E. F. (2016).
Multi-site, multi-vendor comparison of T1 measurement using ISMRM/NIST system phantom.
In *Proc. Intl. Soc. Mag. Res. Med.*, page 3290.

Ma, D., Gulani, V., Seiberlich, N., Liu, K., Sunshine, J. L., Duerk, J. L., and Griswold, M. A. (2013).
Magnetic resonance fingerprinting.
Nature, 495:187–93.

Nataraj, G., Nielsen, J.-F., and Fessler, J. A. (2017a).
Myelin water fraction estimation from optimized steady-state sequences using kernel ridge regression.
In *Proc. Intl. Soc. Mag. Res. Med.*, page 5076.
To appear.

Nataraj, G., Nielsen, J.-F., and Fessler, J. A. (2017b).
Optimizing MR scan design for model-based T1, T2 estimation from steady-state sequences.
IEEE Trans. Med. Imag., 36(2):467–77.

Rahimi, A. and Recht, B. (2007).
Random features for large-scale kernel machines.
In *NIPS*.

Redpath, T. W. and Jones, R. A. (1988).
FADE-A new fast imaging sequence.
Mag. Res. Med., 6(2):224–34.

Schölkopf, B., Herbrich, R., and Smola, A. J. (2001).
A generalized representer theorem.
In *Proc. Computational Learning Theory (COLT)*, pages 416–426.
LNCS 2111.

Zur, Y., Wood, M. L., and Neuringer, L. J. (1991).
Spoiling of transverse magnetization in steady-state sequences.
Mag. Res. Med., 21(2):251–63.