Biomedical Optical Imaging[1]

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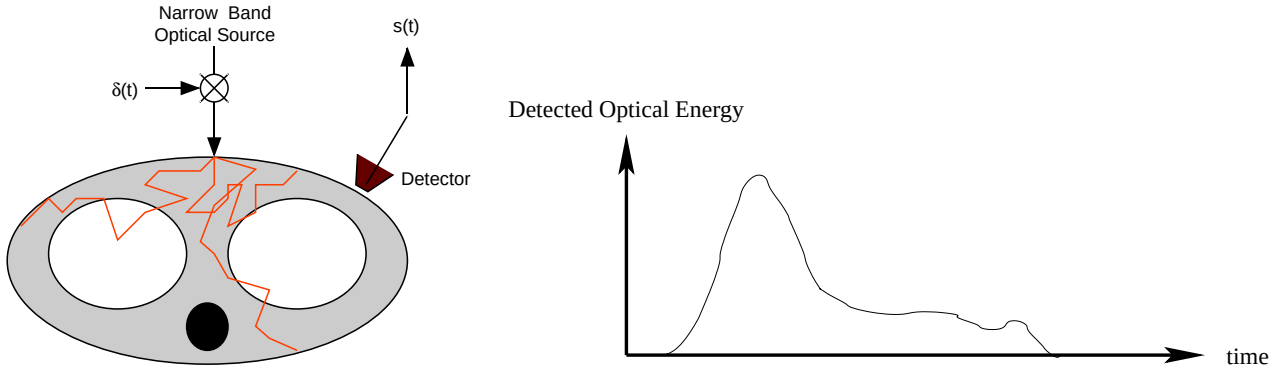
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Part II: Modeling and Image Formation for Biomedical Optical Imaging

1. Forward Model
   (a) ODT Forward Model
   (b) Fréchet Derivative
   (c) Adjoint Differentiation
2. Inversion of Forward Model
   (a) Bayesian Framework
   (b) Optimization Methods
      i. Conjugate Gradient
      ii. Iterative Coordinate Decent
      iii. Multigrid Algorithms
   (c) Linearized Approach
   (d) Source-Detector calibration
   (e) Shape-Based Reconstruction
3. Fluorescence ODT
   (a) Forward Model
   (b) Multifrequency inversion
   (c) Design Metrics

ODT Model: Time Domain



- The photon flux density, $\psi(r,t)$, obeys the **wave** equation

$$\frac{1}{c}\frac{\partial}{\partial t}\psi(r,t) - \nabla \cdot D(r)\nabla\psi(r,t) + \mu(r)\psi(r,t) = S(r,t)$$

$\psi(r,t)$ - photon flux density (photons per unit volume)

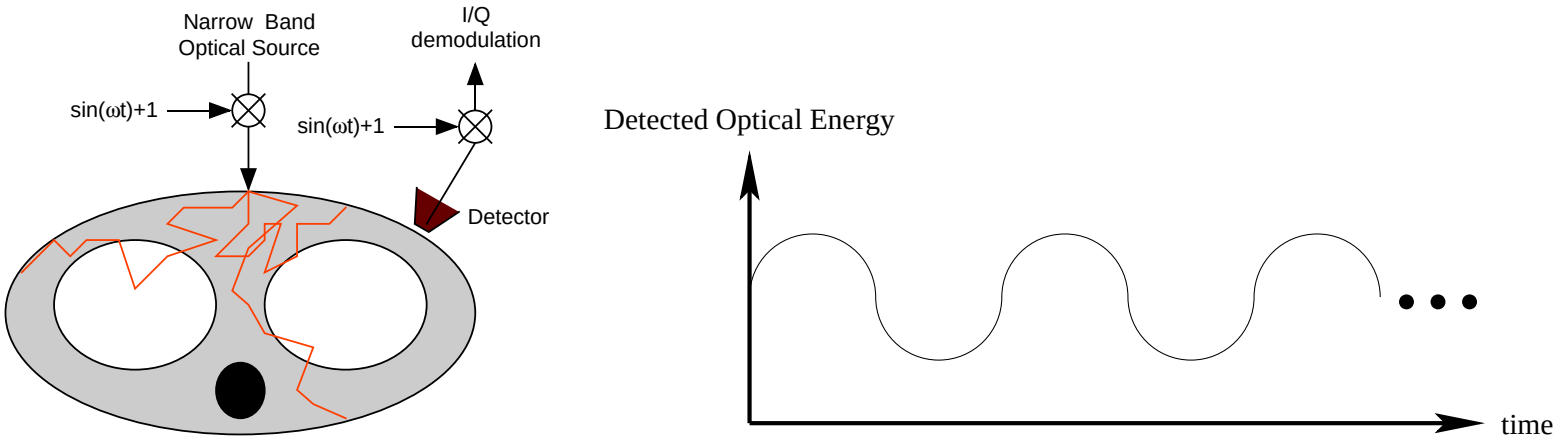
$D(r) = \frac{1}{3(\mu(r)+\mu_s'(r))}$ - Diffusion coefficient (cm)

$\mu(r)$ - absorption coefficient (cm^{-1})

$S(r,t)$ - Instantaneous power density of source at location r and time t

r, t - 3-D position and time

ODT Model: Frequency Domain



- If source is modulated by $e^{j\omega t}$, then

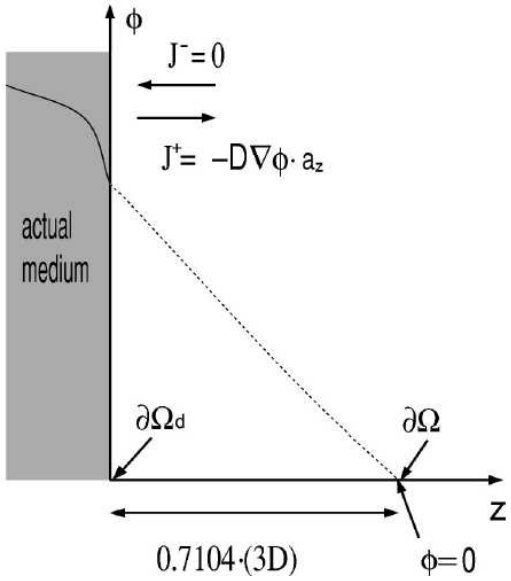
$$\begin{aligned} \psi(r,t) &= \phi(r)e^{j\omega t} \\ S(r,t) &= S(r)e^{j\omega t} \end{aligned}$$

Then the frequency modulated light, $\phi(r)$, obeys the elliptic PDE

$$\nabla \cdot D(r)\nabla\phi(r) - [\mu(r) + j\omega/c]\,\phi(r) = -S(r)$$

- Objective:
  - Measure: $\phi(r)$
  - Reconstruct: $\mu(r)$ and $D(r)$

ODT Model: Boundary Condition [1, 2]



- Basics

  $J = -D\nabla\phi \cdot n$ - photon current in direction n

  J^+ - Photon current leaving boundary

  J^- - Photon current entering boundary

  $D = \frac{1}{3(\mu+\mu_s')}$ - Reduced scattering constant μ_s'

  $l_s = 3D$ - Transport Length for randomization

- Boundary conditions

  $J^- = 0$ - No photons entering boundary

  $J^+ = -D\frac{\partial\phi}{\partial z}$ - Photons leaving boundary

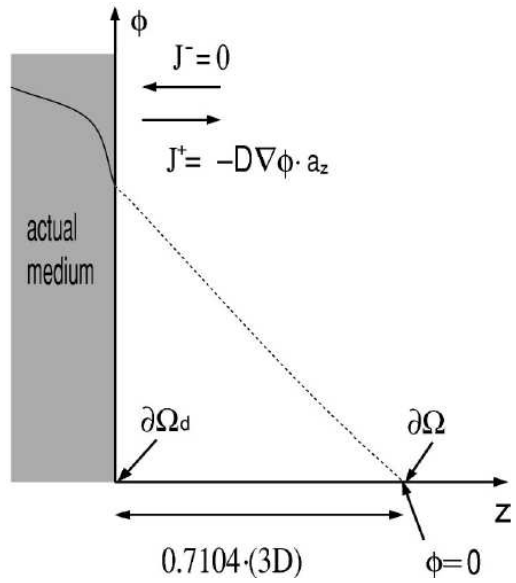
  $J = \frac{1}{3*(0.7104)}\phi$ - Photon current proportional to density ([1] p. 144)

- Boundary condition

$$\boxed{\phi = -(0.7104)3D\frac{\partial\phi}{\partial z}}$$

J. J. Duderstadt and L. J. Hamilton, *Nuclear Reactor Analysis*, Wiley, 1976.

ODT Model: Extrapolated Boundary [1]



Zero-flux condition

- Basics

  $J = -D\nabla\phi \cdot n$ - photon current in direction n

  J^+ - Photon current leaving boundary

  J^- - Photon current entering boundary

  $D = \frac{1}{3(\mu+\mu_s')}$ - Reduced scattering constant μ_s'

  $l_s = 3D$ - Transport Length for randomization

- Set boundary condition to $\phi = 0$ at extrapolated position of

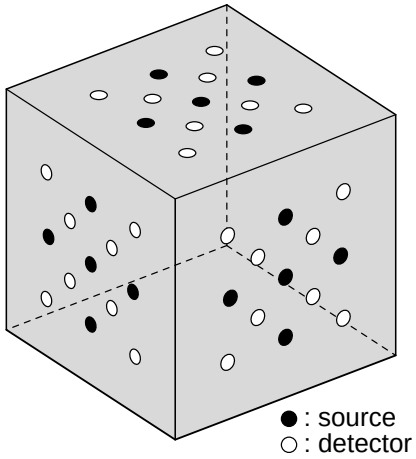
$$z_o = (0.7104)3D$$

- Approximates

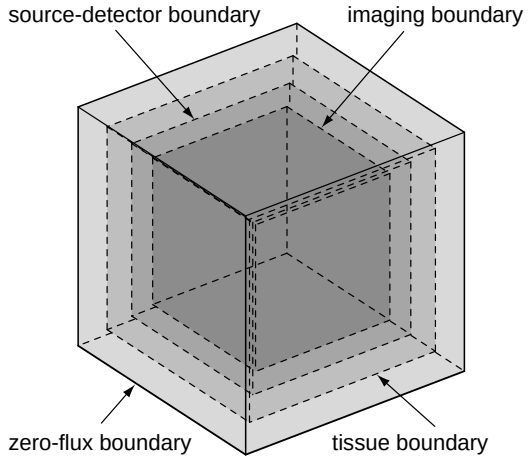
$$\phi = -z_o \frac{\partial \phi}{\partial z}$$

  Converts problem to Dirichlet boundary conditions

ODT Model: Source/Detector Location [1]



Sources and detectors

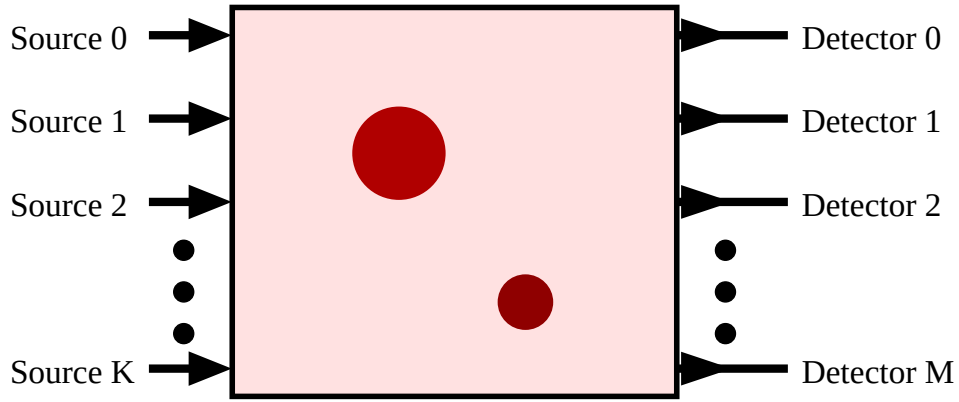


Imaging boundaries

- Computational source/detector locations should be inside tissue boundary
  - Located $l_s = 3D$ inside tissue boundary.
  - Models the distance light must travel to scatter
- Results in four boundaries
  - Zero-flux boundary - Flux set to zero to enforce boundary condition
  - Tissue boundary - Physical boundary of material being imaged
  - Source/detector boundary - Location of sources and detectors
  - Imaging boundary - Region for valid image reconstruction

ODT Model: Typical Measurement Configuration

- Typical assumptions
  - Sources 0 to $K-1$ at locations s_k
  - Detectors 0 to $M-1$ at locations d_m

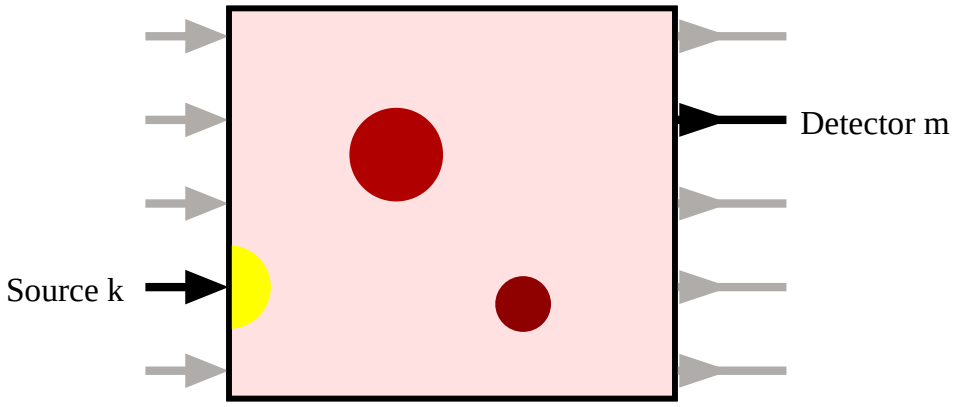


- Total of $P = MK$ measurements
  - Every combination of source and detector
  - Normally, each source must be used in sequence

ODT Model: Forward Operator

- $\phi_k(d_m)$ - The expected measurement between source k and detector m

$$\nabla \cdot D(r)\nabla\phi_k(r) - (\mu(r) + j\omega/c)\phi_k(r) = -S_k\delta(r - s_k)$$



- The full forward model is then

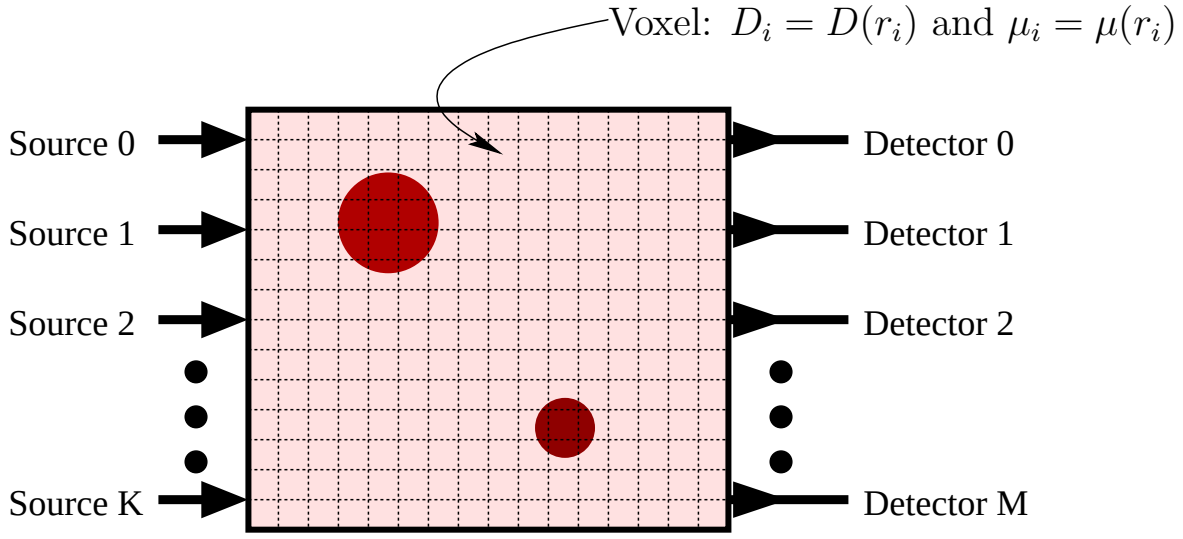
$$f(D,\mu) \triangleq [\underbrace{\phi_0(d_0),\cdots,\phi_0(d_{M-1})}_{\text{source } 0},\cdots,\underbrace{\phi_{K-1}(d_0),\cdots,\phi_{K-1}(d_{M-1})}_{\text{source } K-1}]^t$$

where

$$f_{k*M+m}(D,\mu) = \phi_k(d_m)$$

ODT Model: Discretizing Domain

- Let $r_1, r_2, \cdots, r_N$ be the voxel locations.



- Define the vectors D and μ so that

$$\begin{aligned} D &= [D(r_1), D(r_2), \cdots, D(r_N)] \\ \mu &= [\mu(r_1), \mu(r_2), \cdots, \mu(r_N)] \end{aligned}$$

- Then the forward model, $f(D, \mu)$, is a mapping from $\mathbb{R}^{2N} \rightarrow C^{KM}$

ODT Model: Computing Forward Operator

- Computing $f(D, \mu)$
  - Need to solve PDE K times (once for each source)
- Computing the gradients $\nabla_D f(D, \mu)$ and $\nabla_\mu f(D, \mu)$
  - Very important for computation of inverse
  - Both are $(MK) \times N$ matrices

$$[\nabla_D f(D, \mu)]_{k*M+m,i} = \frac{\partial \phi_k(d_m)}{\partial D_i}$$

$$[\nabla_\mu f(D, \mu)]_{k*M+m,i} = \frac{\partial \phi_k(d_m)}{\partial \mu_i}$$

  - These form the elements of a Fréchet derivative matrix operator

The Fréchet Derivative

- Question: How does ϕ depend on small changes in D and μ?

$$\begin{aligned} D(r) &\longrightarrow D(r) + \delta D(r) \\ \mu(r) &\longrightarrow \mu(r) + \delta\mu(r) \\ \phi(r) &\longrightarrow \phi(r) + \delta\phi(r) \end{aligned}$$

  Then, for small perturbations, the input/output must have the form

$$\delta\phi(r) = \int_\Omega H_D(r, r')\delta D(r')dr' + \int_\Omega H_\mu(r, r')\delta\mu(r')dr'$$

- The kernels are known as Fréchet derivatives

  $\frac{\delta\phi(r)}{\delta D(r')} = H_D(r, r')$ - Fréchet derivative of ϕ with respect to D

  $\frac{\delta\phi(r)}{\delta\mu(r')} = H_\mu(r, r')$ - Fréchet derivative of ϕ with respect to μ

- How do we compute these?

Fréchet Derivative: General PDE

- Consider a general linear PDE on the domain Ω [2]

$$\mathcal{D}_x \, \phi(r) = S(r)$$

  - $\mathcal{D}_x$ is a linear differential operator with linear coefficients x
  - Use Dirichlet boundary condition $\phi|_{\partial\Omega} = 0$ for all problems.

- Examples:

  If $\mathcal{D}_x = x(r)\nabla^2$, then the PDE is

$$x(r)\nabla^2\phi(r) = S(r)$$

  If $\mathcal{D}_x = \nabla \cdot x_1(r)\nabla + x_2(r)$, then the PDE is

$$\nabla \cdot x_1(r)\nabla\phi(r) + x_2(r)\phi(r) = S(r)$$

[2] This analysis can be extended to nonlinear PDE by linearizing the PDE about a solution.

Fréchet Derivative: Solution to General PDE

$$\mathcal{D}_x \, \phi(r) = S(r) \text{ with } \phi|_{\partial\Omega} = 0$$

- Let $g_x(r, r')$ be the Green's function for this PDE
  - The Green's function is the solution to

$$\mathcal{D}_x \, g_x(r, r') = \delta(r - r')$$

  - The solution to the PDE can be expressed as a convolution

$$\phi(r) = \int_\Omega g_x(r, r') S(r') dr'$$

Fréchet Derivative: Pertubational Analysis

- By definition, we know that

$$\mathcal{D}_x\,\phi(r) \;=\; S(r)$$

$$\mathcal{D}_{x+\delta x}\;(\phi(r)+\delta\phi(r)) \;=\; S(r)$$

- Subtracting these yields

$$\mathcal{D}_{x+\delta x}\;(\phi(r)+\delta\phi(r)) - \mathcal{D}_x\,\phi(r) \;=\; 0$$

  Simplifying and dropping high order terms yields

$$\mathcal{D}_x\,\delta\phi(r) = -\mathcal{D}_{\delta x}\,\phi(r)$$

- This is a PDE with forcing function $-\mathcal{D}_{\delta x}\,\phi(r)$. It can be solved using the Green's function as

$$\delta\phi(r) = -\int_\Omega g_x(r,r')\,[\mathcal{D}_{\delta x}\,\phi(r')]\,dr'$$

Fréchet Derivative: Application of Reciprocity

- If $\mathcal{D}_x$ is self-adjoint, then by reciprocity we know that

$$g_x(r, r') = g_x(r', r)$$

- For a detector at location d_m, we can write

$$\begin{aligned} g_m(r) &\triangleq g_x(d_m, r) \\ &= g_x(r, d_m) \end{aligned}$$

- So the perturbed solution has the form

$$\delta\phi(d_m) = -\int_\Omega g_m(r)\mathcal{D}_{\delta x}\,\phi(r)dr$$

where

$$\mathcal{D}_x\, g_m(r) = \delta(r - d_m)$$

Fréchet Derivative: For Diffusion Equation

- For the diffusion equation, we have

$$\mathcal{D}_{\delta x}\,\phi(r) = -\nabla\cdot\delta D\nabla\phi(r) + \delta\mu\phi(r)$$

- For source k and detector m, the perturbation is

$$\begin{aligned}\delta\phi_k(d_m) &= \int_\Omega g_m(r)\nabla\cdot\delta D\nabla\phi_k(r)dr - \int_\Omega g_m(r)\delta\mu\phi_k(r)dr\\ &= -\int_\Omega \nabla g_m(r)\cdot\nabla\phi_k(r)\,\delta D(r)dr - \int_\Omega g_m(r)\phi_k(r)\,\delta\mu(r)dr\\ &\quad + \oint_{\partial\Omega} g_m\delta D\nabla\phi_k\cdot ds\end{aligned}$$

- If $g_m(r) = 0$ and/or $\delta D(r) = 0$ on $\partial\Omega$, then we have

$$\delta\phi_k(d_m) = -\int_\Omega \underbrace{\nabla g_m(r)\cdot\nabla\phi_k(r)}_{H_D(d_m,r)}\,\delta D(r)dr - \int_\Omega \underbrace{g_m(r)\phi_k(r)}_{H_\mu(d_m,r)}\,\delta\mu(r)dr$$

Fréchet Derivative: Derivation of Integral Equality

Let u be a scalar field and v be a vector field on Ω. We know the standard vector identity

$$u\nabla \cdot v = \nabla \cdot (uv) - v \cdot \nabla u$$

Therefore using the divergence theorem, we have

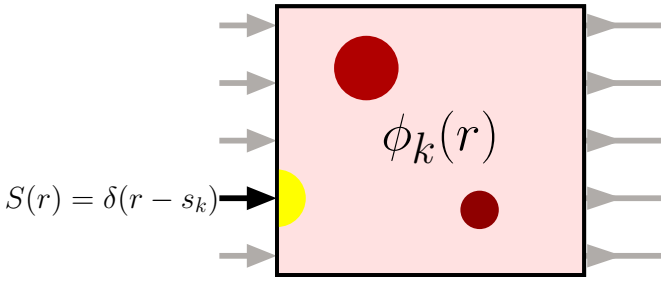
$$\begin{aligned} \int_\Omega u\nabla \cdot v dr &= \int_\Omega \nabla(uv) dr - \int_\Omega v \cdot \nabla u dr \\ &= -\int_\Omega v \cdot \nabla u dr + \oint_{\partial\Omega} uv \cdot ds \end{aligned}$$

For $u = g_m$ and $v = \delta D \nabla \phi_k$

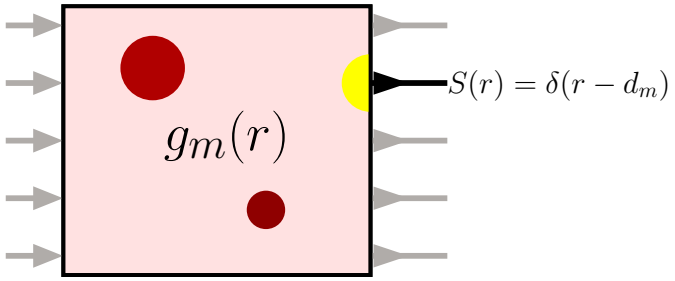
$$\int_\Omega g_m \nabla \cdot [\delta D \nabla \phi_k] \, dr = -\int_\Omega \delta D \nabla \phi_k \cdot \nabla g_m dr + \oint_{\partial\Omega} g_m \delta D \nabla \phi_k \cdot ds$$

Fréchet Derivative: Summary Form for ODT

- For each source, solve PDE for $\phi_k(r)$



- For each detector, solve PDE for $g_m(r)$



- Use solutions to form Fréchet derivative

$$\frac{\delta \phi_k(d_m)}{\delta D(r)} = -\nabla g_m(r) \cdot \nabla \phi_k(r)$$

$$\frac{\delta \phi_k(d_m)}{\delta \mu(r)} = -g_m(r)\, \phi_k(r)$$

Fréchet Derivative: Computing $\nabla f(D, \mu)$

- For each source, solve PDE for $\phi_k(r)$
- For each detector, solve PDE for $g_m(r)$



- Gradients of $f(D, \mu)$ can be computed from Fréchet derivative

$$\frac{\partial \phi_k(d_m)}{\partial D_i} = -\nabla g_m(r_i) \cdot \nabla \phi_k(r_i) V$$

$$\frac{\partial \phi_k(d_m)}{\partial \mu_i} = -g_m(r_i)\, \phi_k(r_i) V$$

where V is the volume of a voxel

Fréchet Derivative: Time/Memory Complexity



$$\begin{aligned}
\text{Time Complexity} &= \underbrace{KMN}_{\text{fill in matrix}} + \underbrace{KLN}_{\text{compute } \phi_k(r)} + \underbrace{MLN}_{\text{compute } g_m(r)} \\
&= KMN + (K+M)LN
\end{aligned}$$

$$\begin{aligned}
\text{Memory Complexity} &= \underbrace{KN}_{\text{store } \phi_k(r)} + \underbrace{MN}_{\text{store } g_m(r)} \\
&= (K+M)N
\end{aligned}$$

K - number of sources

M - number of detectors

N - number of voxels

L - iterations used to solve PDE

Adjoint Differentiation: A Method for Reducing Computational Complexity [3, 4, 5]

- If $M >> L$
  - # of detectors >> # of iterations used to solve PDE
  - Filling in matrix can dominate computation
  - Matrix size = (# of measurments)$\times$(# of voxels)
  - Matrix is fully populated

- Adjoint differentiation
  - Eliminate the explicit computation of $\nabla f(D, \mu)$
  - Based on superposition/duality
  - Applicable for methods such as conjugate gradient
  - General approach for chains of nonlinear systems

Adjoint Differentiation: Gradients of Functionals

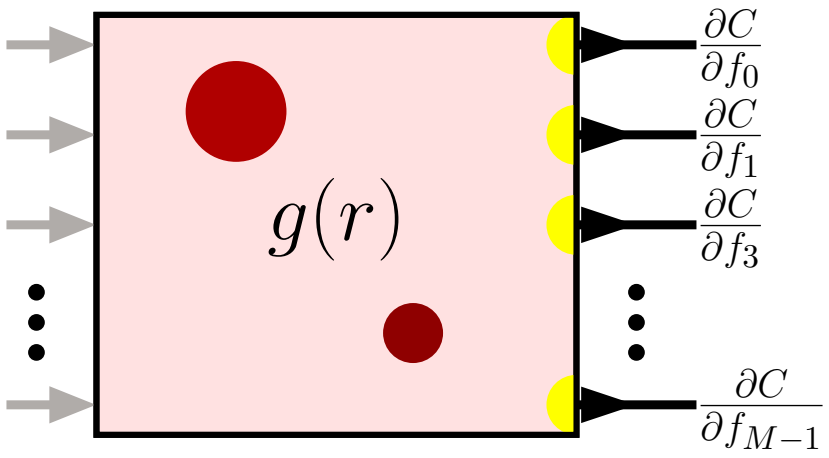
- For simplicity assume
  - $K = 1$ source
  - D known
- Consider a scalar cost functional such as $C(f(\mu)) = ||y - f(\mu)||^2$
  - Need to compute $\nabla C(f(\mu))$
  - Fréchet derivative is $\frac{\partial f_m}{\partial \mu_i} = -g_m(r_i)\,\phi(r_i)$
- By using chain rule

$$\begin{aligned}
\frac{\partial C}{\partial \mu_i} &= \sum_{m=0}^{M-1} \frac{\partial C}{\partial f_m} \frac{\partial f_m}{\partial \mu_i} \\
&= \sum_{m=0}^{M-1} -\frac{\partial C}{\partial f_m} g_m(r_i)\,\phi(r_i)\,V \\
&= -g(r_i)\,\phi(r_i)\,V
\end{aligned}$$

where

$$g(r) = \sum_{m=0}^{M-1} \frac{\partial C}{\partial f_m}\, g_m(r)$$

Adjoint Differentiation: Using Superposition



$$\frac{\partial C}{\partial \mu_i} = -g(r_i)\,\phi(r_i)\,V$$

- How to efficiently compute $g(r)$?

$$g(r) = \sum_{m=0}^{M-1} \frac{\partial C}{\partial f_m}\, g_m(r)$$

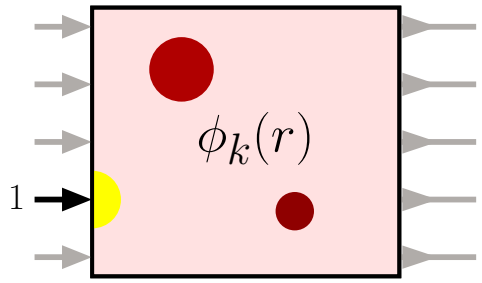
  - Inject signal into each detector location with amplitude

$$\frac{\partial C}{\partial f_m} = -2(y_m - f_m((\mu))$$

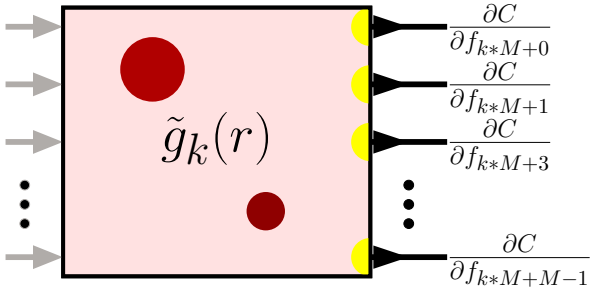
  - Exploits superposition of PDE
  - Reduces computation by factor of M

Adjoint Differentiation: Using Multiple Sources

- For each source, solve PDE for $\phi_k(r)$



- Solve one PDE for $g(r)$

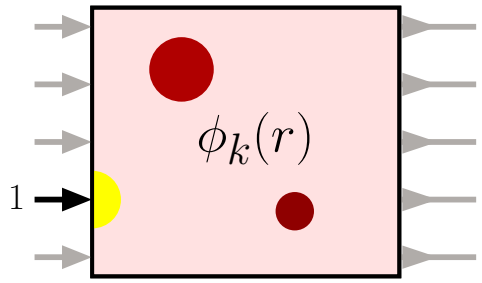


$$\frac{\partial C}{\partial \mu_i} = \sum_{k=0}^{K-1} -\tilde{g}_k(r_i)\,\phi_k(r_i)\,V$$

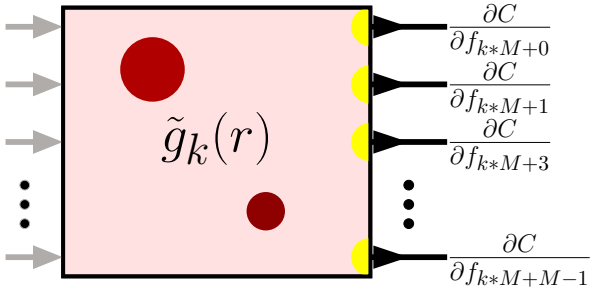
- Notice that $\tilde{g}_k$ is dependent on source index k
- Similar method possible for D

Adjoint Differentiation: Time/Memory Analysis

- For each source, solve PDE for $\phi_k(r)$



- Solve one PDE for $g(r)$



$$\text{Time Complexity} = \underbrace{KLN}_{\text{compute } \phi_k(r)} + \underbrace{KLN}_{\text{compute } \tilde{g}_k(r)}$$

$$\text{Memory Complexity} = \underbrace{KN}_{\text{store } \phi_k(r)} + \underbrace{KN}_{\text{store } \tilde{g}_k(r)}$$

K - number of sources

N - number of voxels

M - number of detectors

L - iterations used to solve PDE

Adjoint Differentiation: Time/Memory Complexity

- If (# of Detectors) << (# of Sources)
  - Reciprocity can be used to reverse roles of sources and detectors
  - Complexity formulae replace K with M

$$\text{Time Complexity} = \min\{K, M\}\, LN$$

$$\text{Memory Complexity} = \min\{K, M\}\, N$$

K - number of sources

M - number of detectors

N - number of voxels

L - iterations used to solve PDE

Direct Formulation of Inverse Problems

- Forward model $\quad x \xrightarrow{f(\cdot)} y = f(x)$

  x : image

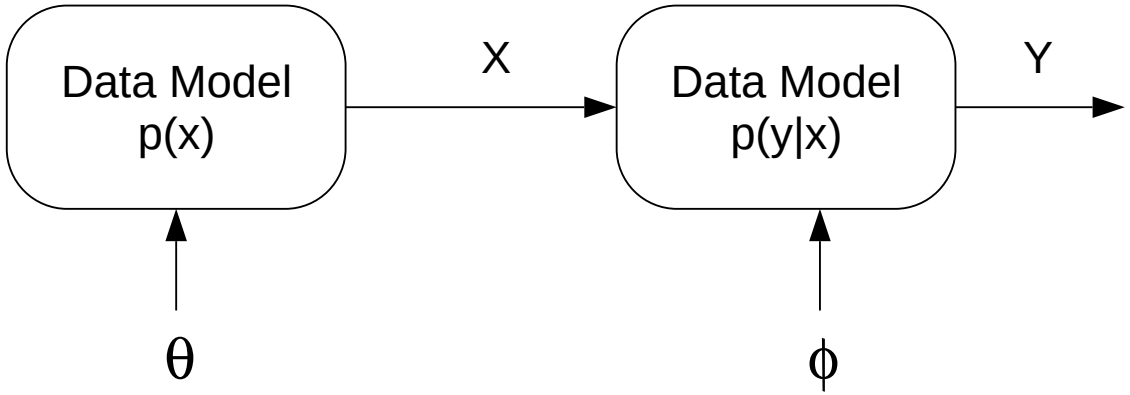
  y : measurement vector

- Inverse Problem $\quad y \xrightarrow{\text{How?}} x$

- Direct approach
  - Directly compute inverse $x = f^{-1}(y)$
  - Filtered back projection (FBP); convolution back projection (CBP); Gauss elimination
  - Computationally efficient
  - Inverse may not exist; may not be unique; may be noise sensitive
  - For non-linear problems, direct inverse may be impossible to compute

- Alternative: Search for x so that $f(x)$ approximately equals y

Bayesian Framework



- Data

  Y - Measured data: P-dimensional real random vector (or $P/2$ dimensional complex random vector)

  X - Unknown Image: N dimension random vector

- Models

  $p(y|x)$ - System model: Incorporates physical properties of system and noise

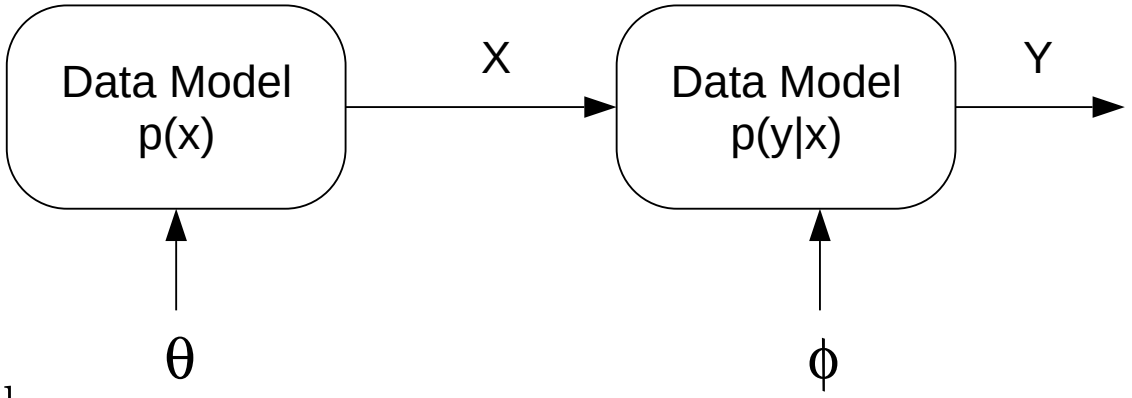
  $p(x)$ - Prior model: Incorporates assumptions of smoothness in image

- Unknown parameters

  ϕ - Unknown parameters of system

  θ - Unknown parameters of prior model

Bayesian Framework: Inversion



- Bayes Rule

$$p(x|y) = \frac{p(y|x)\ p(x)}{p(y)}$$

- Maximum *a posteriori* (MAP) estimation

$$\begin{aligned} \hat{x} &= \arg\max_x p(x|y) \\ &= \arg\max_x \{\log p(y|x) + \log p(x)\} \end{aligned}$$

- Joint MAP estimation of x, θ, and ϕ (with uniform prior)

$$\begin{aligned} \hat{x} &= \arg\max_x \max_{\theta,\phi} p(x|y,\theta,\phi) \\ &= \arg\max_x \max_{\theta,\phi} \{\log p(y|x,\phi) + \log p(x|\theta)\} \end{aligned}$$

Bayesian Framework: Forward Noise Models

- The deterministic component of forward model is $f(x)$, so

$$E[Y|X] = f(X)$$

- Gaussian model with covariance $\alpha\Lambda^{-1}$

$$p(y|x) = \frac{1}{(2\pi\alpha)^{P/2}}|\Lambda|^{1/2}\exp\left\{-\frac{1}{2\alpha}||y - f(x)||^2_\Lambda\right\}$$

where
α : measurement noise factor
$\Lambda \propto$ (measurement covariance)$^{-1}$
P : number of (real valued) dimensions to y

- Poisson model

Bayesian Framework: Generalized Gaussian Markov Random Field (GGMRF) Prior [6]

- We use the generalized GMRF (GGMRF) model

$$\log p(x) = -\frac{1}{p\sigma^p} \sum_{\{i,j\} \in \text{Neighbor}} b_{i-j} |x_i - x_j|^p + \text{constant}$$

  where

  $1 \leq p \leq 2$ controls the degree of edge smoothness

- Properties
  - $p = 2$ - Gaussian case (penalizes image edges)
  - $1.2 \approx p$ - Preserves sharp discontinuities
  - $p > 1$ Strictly convex function
  - ML estimate of σ^p

$$\hat{\sigma}^p = \frac{1}{N} \sum_{\{i,j\} \in \text{neighbor}} b_{i-j} |x_i - x_j|^p$$

Bayesian Framework: MAP Estimate with Noise Gain Estimation

$$\hat{x}_{MAP} = \arg\max_{x\geq 0} \max_{\alpha} \{\log p(y|x,\alpha) + \log p(x)\}$$

$$= \arg\max_{x\geq 0} \max_{\alpha} \left\{ -\frac{1}{2\alpha}||y - f(x)||^2_\Lambda - \frac{P}{2}\log\alpha - \frac{1}{p\sigma^p} \sum_{\{i,j\}\in\mathcal{N}} b_{i-j}|x_i - x_j|^p \right\}$$

$$= \arg\min_{x\geq 0} c(x)$$

where

$$c(x) = \frac{P}{2}\log\left(||y - f(x)||^2_\Lambda\right) + \frac{1}{p\sigma^p} \sum_{\{i,j\}\in\mathcal{N}} b_{i-j}|x_i - x_j|^p$$

- Comments:
  - Automatically adjusts for unknown noise gain α
  - Estimation of α makes global convergence more robust
  - Intuition: Scaling of α preserves relative sizes of data and prior terms

Bayesian Framework: Reconstruction Strategy

- What needs to be done?
  - Formulate function $f(x)$ using PDE model of ODT
  - Specify Gaussian noise model through choice of Λ
  - Specify prior model through choice of p, σ, and b_{i-j}
  - Minimize cost functional

$$c(x) = \frac{P}{2}\log\left(||y - f(x)||_{\Lambda}^2\right) + \frac{1}{p\sigma^p}\sum_{\{i,j\}\in\mathcal{N}} b_{i-j}|x_i - x_j|^p$$

- Optimization strategy

$$\text{Step 1: } \hat{\alpha} = \frac{1}{P}||y - f(\hat{x})||_{\Lambda}^2$$

$$\text{Step 2: } \hat{x} = \arg\min_{x\geq 0}\left\{\frac{1}{2\hat{\alpha}}||y - f(x)||_{\Lambda}^2 + \frac{1}{p\sigma^p}\sum b_{i-j}|x_i - x_j|^p\right\}$$

Step 2 is difficult part

Optimization: Major Issues and Choices

- Some Choices:
  - Levenberg-Marquardt
  - Gradient descent, steepest descent
  - Conjugate gradient, preconditioned conjugate gradient
  - Iterative coordinate descent/Gauss-Seidel
  - Multiresolution, wavelet based, and multigrid
- Major Issues:
  - Per iteration computation
  - Number of iterations to convergence
  - Enforcement of convex (e.g. positivity) constraints
  - Convergence to local and (approximate) global minimum
  - Parallel implementation

Optimization: Selected Publications

- Nonlinear optimization
  - Nonlinear conjugate gradient [7, 4, 5, 8, 9, 3, 4, 10, 11]
  - Truncated Newton [12, 13, 10]
  - Levenberg-Marquardt method [14, 15, 16, 17, 18, 19]
  - Quasi-Newton [20]
- Multigrid
  - Seminal [21]
  - General [22, 23, 24, 25, 26, 27, 28]
  - Image reconstruction [29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40]
  - Matching derivative [30, 31, 41, 42]
- Linearized optimization
  - Backprojection: [43, 44, 45, 46, 47, 48]
  - Perturbation approach: Conjugate gradient [49]

Optimization: Conjugate Gradient (CG): Algorithm [50]

- To solve

$$\hat{x} = \arg\min_x c(x)$$

Apply the following algorithm

Initialize x and $g = -\nabla c(x)$ and $h = g$
Repeat until converged {

$g_{old} \leftarrow g$ /* store old gradient */

$g \leftarrow -\nabla c(x)$ /* evaluate new gradient */

$\gamma \leftarrow \dfrac{(g - g_{old})^t g}{g_{old}^t \, g_{old}}$ /* Polak-Ribiere */

$h \leftarrow g + \gamma h$ /* compute conjugate */

$\hat{\xi} \leftarrow \arg\min_{\xi} c(x + \xi h)$ /* line search */

$x \leftarrow x + \hat{\xi} d$

}

Optimization: CG: Issues to Consider

- Advantages:
  - Can exploit adjoint differentiation
  - Rapid convergence for quadratic cost functionals
  - Preconditioning can speed convergence
- Disadvantages:
  - Each update requires a line search:

$$\hat{\xi} = \arg\min_{\xi} c(x + \xi\, d)$$

  - Convex constraints (positivity) requires bending or soft constraint region
  - May behave less predictably on nonquadratic cost functionals e.g. non-Gaussian priors

Optimization: CG: Time/Memory Complexity

- Complexity per iteration

$$\begin{aligned}
\text{Time Complexity} &= \underbrace{\min\{K, M\}\, LN}_{\text{Adjoint Differentiation}} + \underbrace{ILN}_{\text{Line Search}} \\
&= (\min\{K, M\} + I)\, LN \\
\text{Memory Complexity} &= \min\{K, M\}\, N
\end{aligned}$$

K - number of sources

M - number of detectors

N - number of voxels

L - iterations used to solve PDE

I - iterations per line search

Optimization: Iterative Coordinate Decent (ICD) [51, 52]

- Sequentially minimize cost functional with respect to each pixel

Order the voxels from 1 to N, i.e. $x_1, x_2, \cdots, x_N$
Repeat until converged {
  For $i = 1$ to N {
    $x_i \leftarrow \arg\min_{x_i \geq 0} c\left(x_1, \cdots, x_{i-1}, x_i, x_{i+1}, \cdots, x_N\right)$
  }
}

- Each voxel update might be for more than one parameter (e.g. μ and D)
- Algorithm for update is unspecified
- Each update monotonically reduces the cost functional
- ICD algorithm must converge to local minimum

Optimization: ICD: Efficient Update

$$c(x) = -\frac{1}{2\hat{\alpha}}||y - f(x)||_{\Lambda}^2 - \frac{1}{p\sigma^p}\sum_{\{i,j\}\in\mathcal{N}} b_{i-j}|x_i - x_j|^p$$

Initialize x and set $e \leftarrow y - f(x)$
Repeat until converged {

$A \leftarrow \nabla f(x)$ /* Compute Fréchet derivative */

For $i = 1$ to N {

$x_{old} \leftarrow x_i$

$\theta_1 \leftarrow -2Re\left\{A_{*,i}^H \Lambda e\right\} \quad / * \theta_1 = \dfrac{\partial c(x)}{\partial x_i} * /$

$\theta_2 \leftarrow 2A_{*,i}^H \Lambda A_{*,i} \quad / * \theta_2 \cong \dfrac{\partial^2 c(x)}{\partial x_i^2} * /$

$$x_s \leftarrow \arg\min_{\tilde{x}_i \geq 0}\left[\theta_1(\tilde{x}_i - x_i) + \frac{\theta_2}{2}(\tilde{x}_i - x_i)^2 + \frac{1}{p\sigma^p}\sum_{j\in\mathcal{N}_i}|\tilde{x}_i - x_j|^p\right]$$

$e \leftarrow e + A_{*,i}(\tilde{x}_i - x_{old})$

}

}

Optimization: ICD: Update Analysis

Initialize x and set $e \leftarrow y - f(x)$
Repeat until converged {

$A \leftarrow \nabla f(x)$ /* Compute Fréchet derivative */
For $i = 1$ to N {

$x_{old} \leftarrow x_i$

$\theta_1 \leftarrow -2Re\left\{A_{*,i}^H \Lambda e\right\}$

$\theta_2 \leftarrow 2A_{*,i}^H \Lambda A_{*,i}$

$$x_i \leftarrow \arg\min_{\tilde{x}_i \geq 0} \left[\theta_1(\tilde{x}_i - x_i) + \frac{\theta_2}{2}(\tilde{x}_i - x_i)^2 + \frac{1}{p\sigma^p}\sum_{j \in \mathcal{N}_i} |\tilde{x}_i - x_j|^p\right]$$

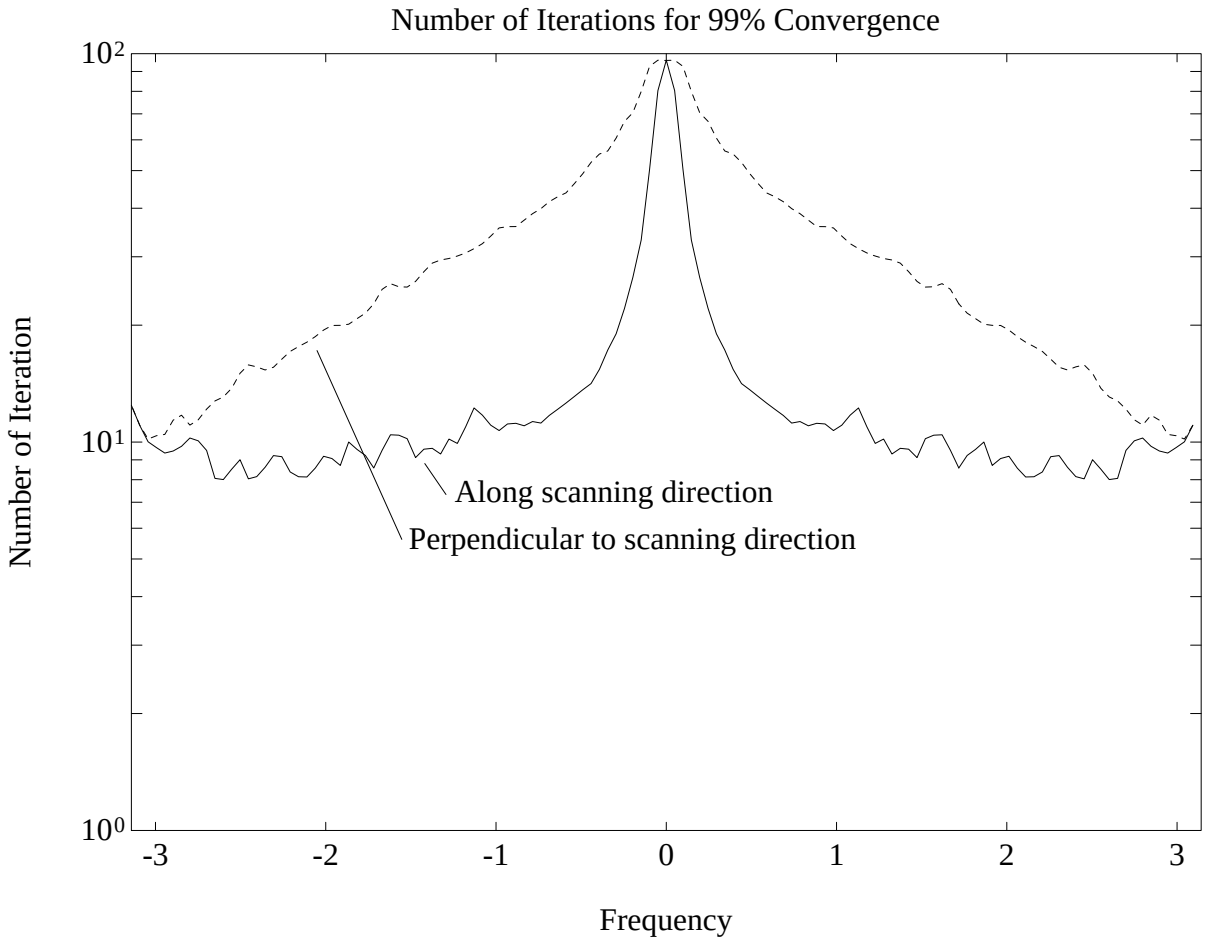
$e \leftarrow e + A_{*,i}(\tilde{x}_i - x_{old})$

}
}

- A is Fréchet derivative
- $A_{*,i}$ is i^{th} column of A
- $e = y - f(x)$ - forward error
- $\theta_1 = \frac{\partial c(x)}{\partial x_i}$
- $\theta_2 \cong \frac{\partial^2 c(x)}{\partial x_i^2}$

- Updates of θ_1, θ_2, and e dominate computation
- Voxel minimization can be done with simple numerical search
- Easy to implement positivity constraints
- Easy to incorporate non-Gaussian priors
- Can be easily extended to Poisson noise model [53]

Optimization: ICD: Convergence Analysis



- Example of convergence behavior for traditional tomography
- Low frequencies tend to converge more slowly
- Can be important to have good low frequency initial condition

Optimization: ICD: Time/Memory Complexity

- Complexity per iteration

$$\text{Time Complexity} = \underbrace{KMN}_{\text{voxel updates}} + \underbrace{(K+M)LN}_{\text{Fréchet derivative}}$$

$$\text{Memory Complexity} = (K+M)N$$

K - number of sources

M - number of detectors

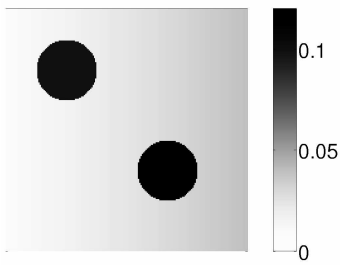
N - number of voxels

L - iterations used to solve PDE

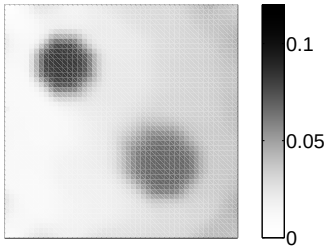
I - iterations per line search

- CG versus ICD?
  - Which is greater $(K+M) \gtrless (\min\{K,M\} + I)$?
  - Non-Gaussian priors and positivity constraints favor ICD

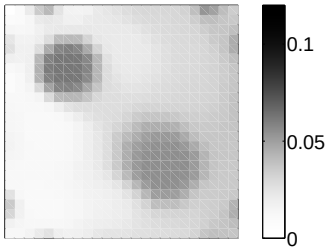
Optimization: Multigrid Inversion: The Problem



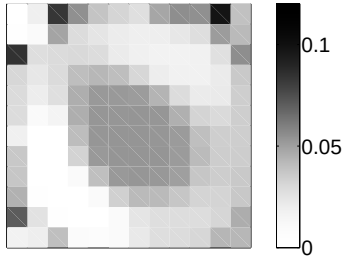
True phantom



$65 \times 65 \times 65$ Recon.



$33 \times 33 \times 33$ Recon.



$17 \times 17 \times 17$ Recon.

- Choosing a discretization resolution
  - Coarse grid $\Rightarrow$ fast
  - Fine grid $\Rightarrow$ accurate
- Approach
  - Move back-and-forth between resolutions
  - Better speed and accuracy
- Some existing multigrid methods
  - Nonlinear multigrid solvers[21, 54]
  - Tomographic reconstruction[29, 36]

- **Opportunity:**
  - Robust convergence to optimum
  - Fast and accurate
  - Use any fixed grid optimizer

- **Challenge:**
  - Fine and coarse scale cost functions are not consistent
  - Dynamically adjust cost functions for consistency

Optimization: Multigrid Inversion: Approach[31, 35, 55]

- Formulate a cost functional at scale q

$$c^{(q)}(x^{(q)}; y^{(q)}, r^{(q)}) = \frac{P}{2} \log ||y^{(q)} - f^{(q)}(x^{(q)})||^2_{\Lambda} + S^{(q)}(x^{(q)}) - r^{(q)} x^{(q)}$$

  $f^{(q)}(\cdot)$ - coarse scale **forward** model

  $x^{(q)}$ - coarse scale solution

  $S^{(q)}(\cdot)$ - coarse scale stabilizing functional

  $y^{(q)}$ - coarse scale measurement

  $r^{(q)}$ - adjustment factor at scale q

- **Key issues:**
  - Coarse discretization of **forward** model reduces computation
  - $y^{(q)}$ and $r^{(q)}$ can be dynamically selected at each scale
  - Novel optimization based approach [31, 41]

Optimization: Multigrid Inversion: Simplified Recursion

$x^{(q)} \leftarrow \text{MultigridV}\left[\, c^{(q)}\left(x^{(q)}; y^{(q)}, r^{(q)}\right)\,\right]\,\{$

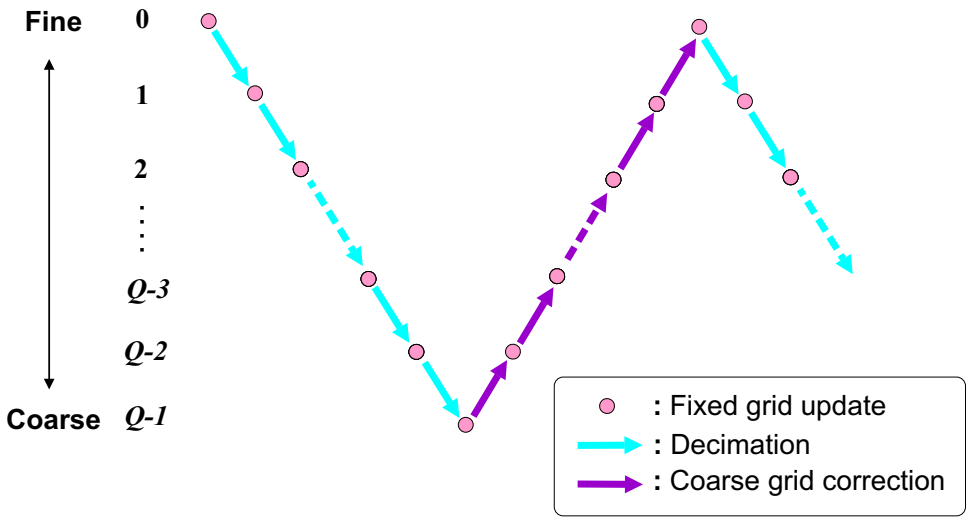
Select $y^{(q+1)}$ and $r^{(q+1)}$ /* But, how? */

$x^{(q+1)} \leftarrow \text{MultigridV}\left[c^{(q+1)}\left(x^{(q+1)}; y^{(q+1)}, r^{(q+1)}\right)\right]$

Correct $x^{(q)}$ by using $x^{(q+1)}$

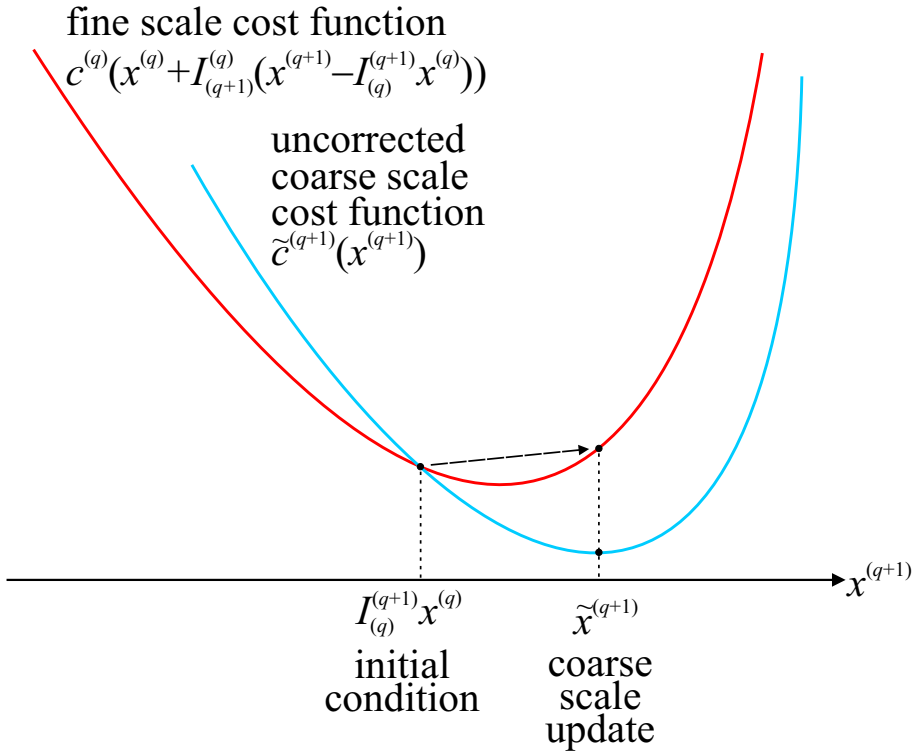
Apply fixed grid optimizer to $x^{(q)}$

$\}$

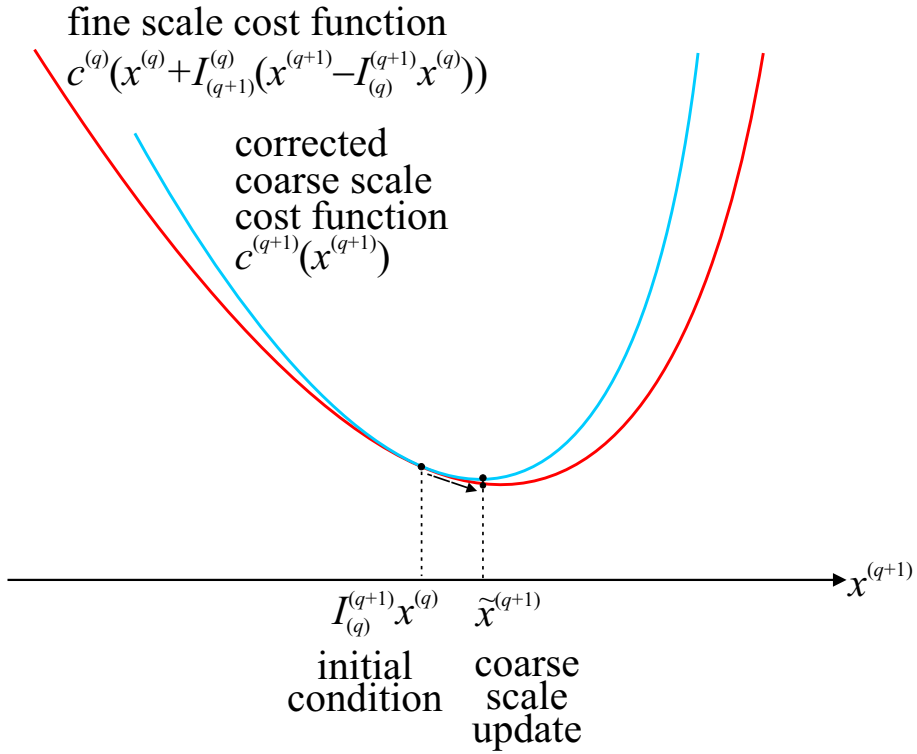


- MultigridV recursion
  - MultigridV calls itself
  - Moves from fine to coarse to fine
- Questions
  - How are $y^{(q+1)}$ and $r^{(q+1)}$ selected?
  - How is $x^{(q)}$ corrected using $x^{(q+1)}$?

Optimization: Multigrid Inversion: Graphical Interpretation of Consistent Cost Functionals



Inconsistent Update



Consistent Update

- Choose $y^{(q+1)}$ and $r^{(q+1)}$ so that coarse scale cost function should:
  - Be tangent to fine scale cost functional at initial solution
  - Upper bound fine scale cost functional

Optimization: Multigrid Inversion: Choosing $y^{(q+1)}$ and $r^{(q+1)}$

- Match error in data term at coarse and fine scales

$$y^{(q+1)} \leftarrow y^{(q)} - \left[f^{(q)}(x^{(q)}) - f^{(q+1)}(I_{(q)}^{(q+1)} x^{(q)}) \right]$$

- Match derivatives in cost function at coarse and fine scales

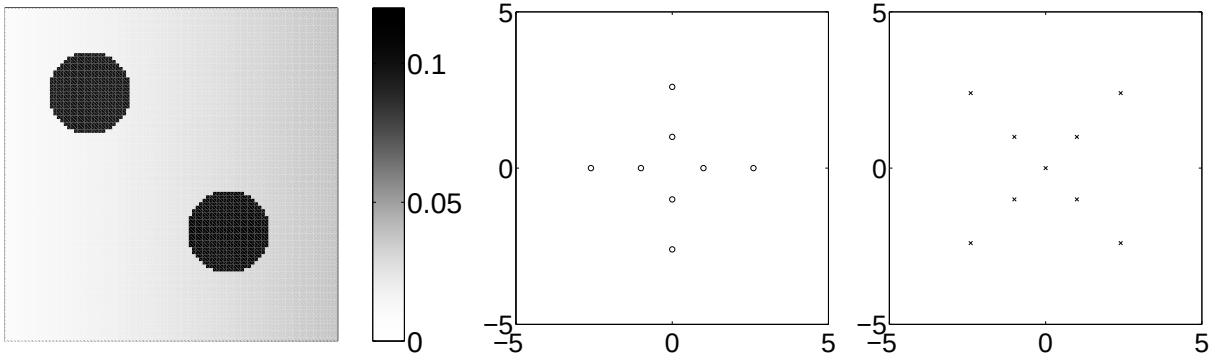
$$r^{(q+1)} \leftarrow \nabla \tilde{c}^{(q+1)}(x^{(q+1)})\Big|_{x^{(q+1)}=I_{(q)}^{(q+1)} x^{(q)}} - \left(\nabla \tilde{c}^{(q)}(x^{(q)}) - r^{(q)} \right) I_{(q+1)}^{(q)}$$

where

$$\tilde{c}^{(q)}(x^{(q)}) \triangleq \frac{P}{2} \log ||y^{(q)} - f^{(q)}(x^{(q)})||_{\Lambda}^2 + S^{(q)}(x^{(q)})$$

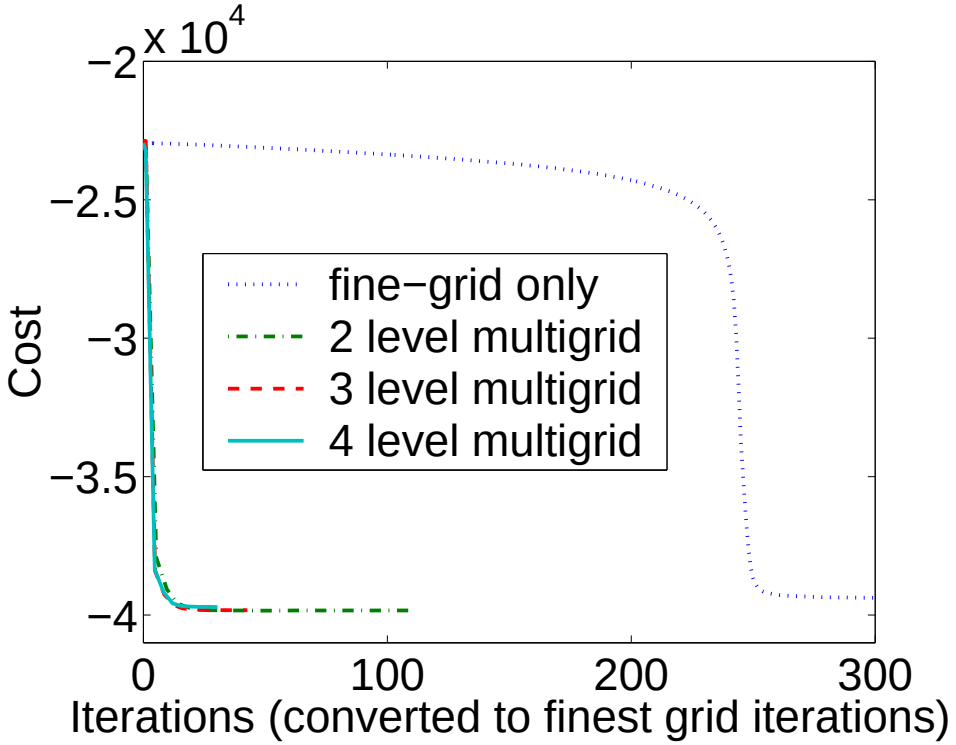
- Theorem: If the difference between cost functionals is convex, then multigrid iterations generate monotone decreasing cost.

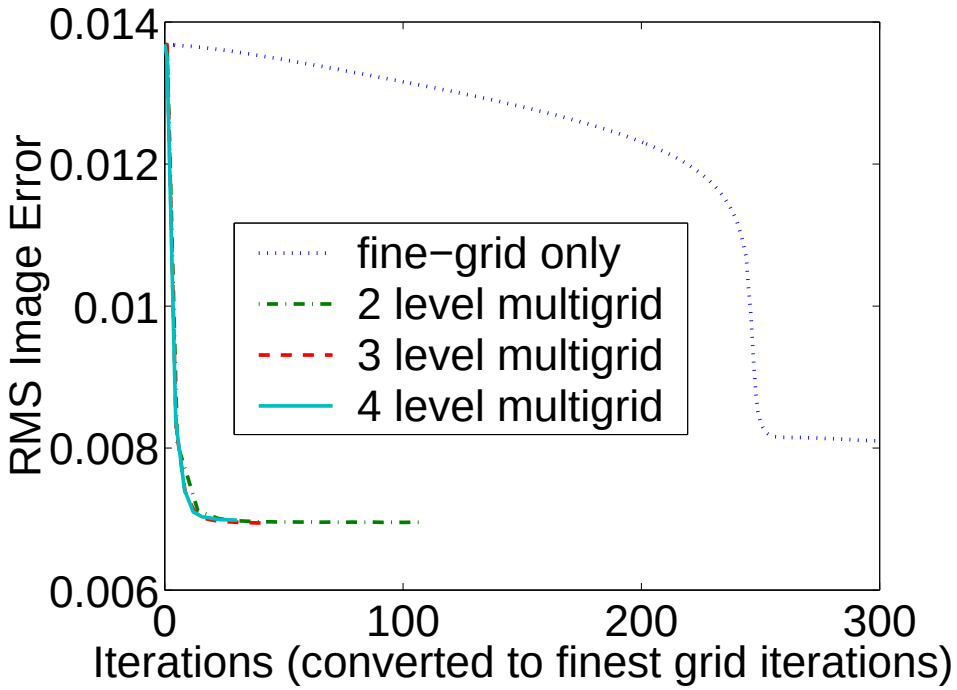
Optimization: Multigrid Inversion: Simulation



- Phantom
  - 10cm $\times$ 10cm $\times$ 10cm cube
  - Linearly varying background: $\mu = 0.01\text{cm}^{-1}$ to 0.04cm^{-1}
  - Two spherical inhomogeneities with diameters of 1.85cm with $\mu = 0.10\text{cm}^{-1}$ and $\mu = 0.12\text{cm}^{-1}$
  - Diffusion coefficient, D, is constant
- Model
  - Sources and detectors on all 6 faces using 100MHz modulation frequency and 35dB average SNR
  - GGMRF with $p = 1.2$ and $\sigma = 0.018\text{cm}^{-1}$

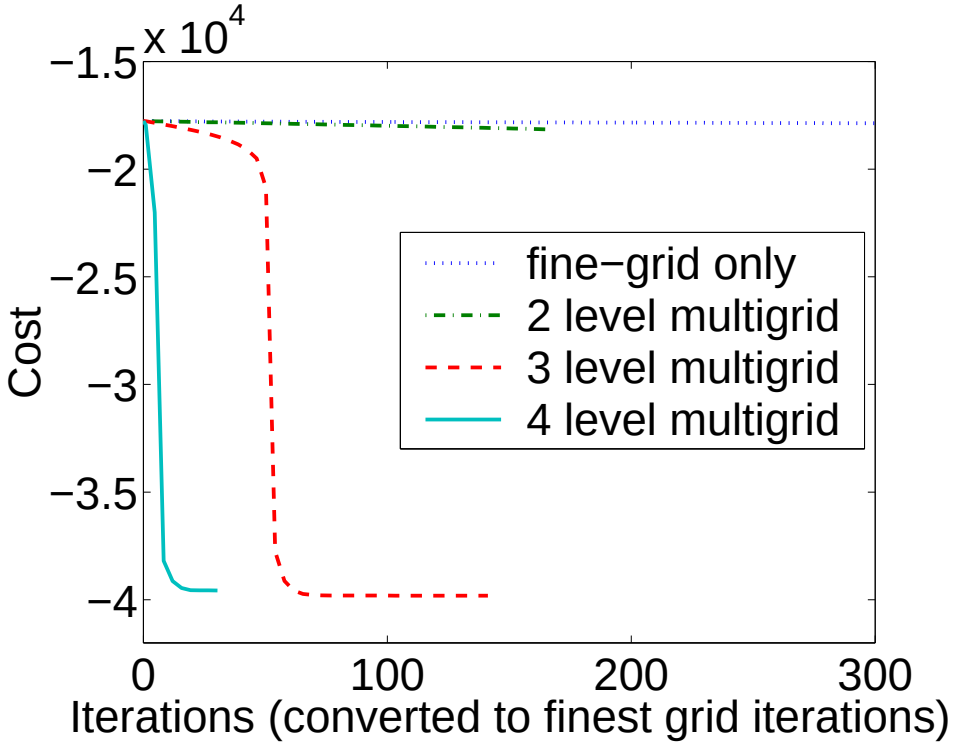
Optimization: Multigrid Inversion: Convergence Speed for $65 \times 65 \times 65$ Reconstruction with Good Initial Condition

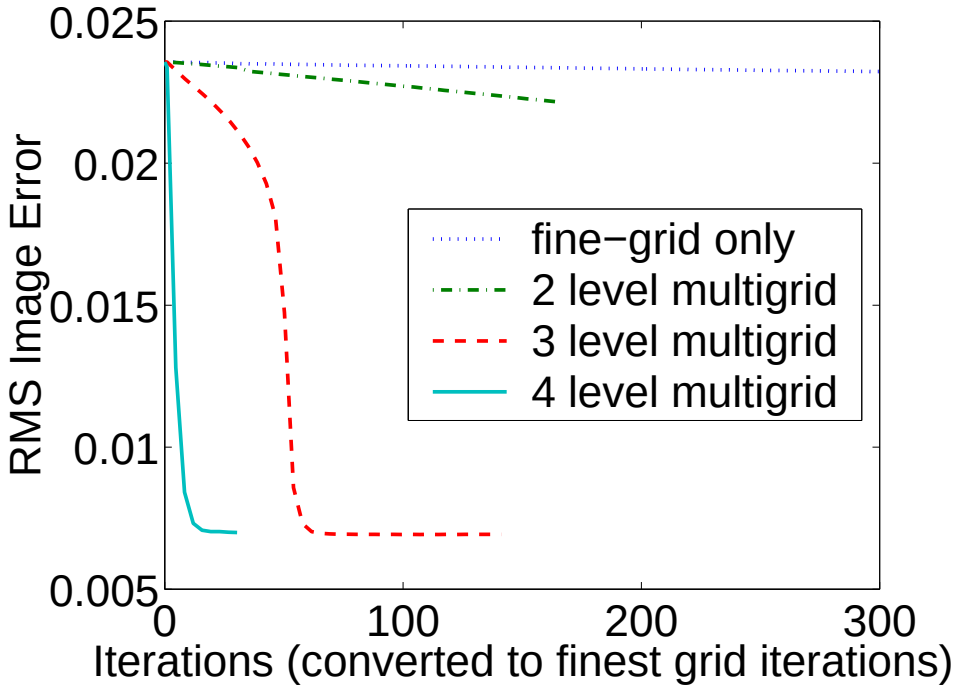




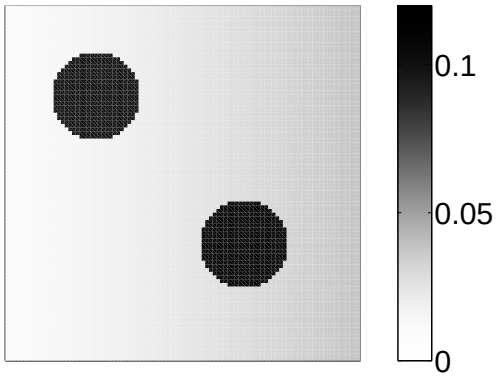
- All iterations in units of a single fixed grid iteration

Optimization: Multigrid Inversion: Convergence Speed for $65 \times 65 \times 65$ Reconstruction with Poor Initial Condition

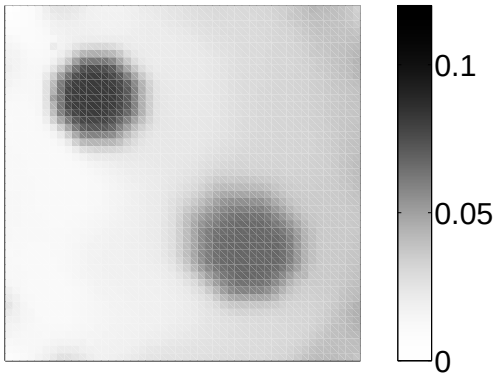




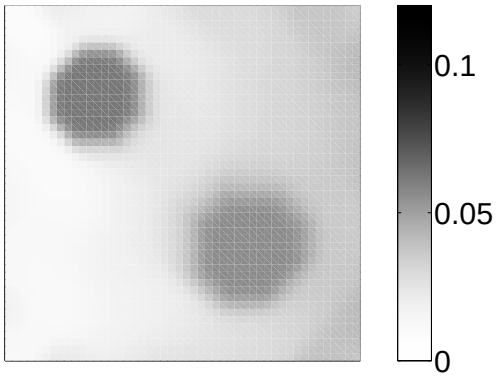
Optimization: Multigrid Inversion: Reconstruction Quality for Multigrid and Fixed Grid Algorithms



True phantom



4 level multigrid
(25.6 iter.)



Fixed-grid
(300 iter.)

Linearized Approach: Viewpoint

- Perturbation can be approximated by linearization using Fréchet derivative

$$\delta\phi_k(d_m) = \sum_{i=1}^{N} \frac{\partial\phi_k(d_m)}{\partial\mu(r_i)}\delta\mu(r_i) + \sum_{i=1}^{N} \frac{\partial\phi_k(d_m)}{\partial D(r_i)}\delta D(r_i)$$

- This can be viewed as

$$\tilde{y} \cong A \begin{bmatrix} \delta\mu \\ \delta D \end{bmatrix}$$

...or as

$$\min_{\mu,D} \left\{ \frac{1}{2\alpha} \left\| \tilde{y} - A \begin{bmatrix} \delta\mu \\ \delta D \end{bmatrix} \right\|_{\Lambda}^{2} - \frac{1}{p\sigma^p} \sum_{\{i,j\}\in\mathcal{N}} b_{i-j}|x_i - x_j|^p \right\}$$

where $\tilde{y} = y - f(\mu, D)$

- The solution is then $\mu + \delta\mu$ and $D + \delta D$

- Question: How do we choose μ and D?

Linearized Approach: Specific Form

- Perturbation can be approximated by linearization

$$\delta\phi_k(d_m) = \sum_{i=1}^{N} \frac{\partial \phi_k(d_m)}{\partial \mu(r_i)} \delta\mu(r_i) + \sum_{i=1}^{N} \frac{\partial \phi_k(d_m)}{\partial D(r_i)} \delta D(r_i)$$

- Can be formulated as a linear equation

$$\begin{bmatrix} \delta\phi_1(d_1) \\ \vdots \\ \delta\phi_1(d_M) \\ \delta\phi_2(d_1) \\ \vdots \\ \delta\phi_K(d_M) \end{bmatrix} = \underbrace{\begin{bmatrix} \frac{\partial \phi_1(d_1)}{\partial \mu(r_1)} & \cdots & \frac{\partial \phi_1(d_1)}{\partial \mu(r_N)} & \frac{\partial \phi_1(d_1)}{\partial D(r_1)} & \cdots & \frac{\partial \phi_1(d_1)}{\partial D(r_N)} \\ \frac{\partial \phi_1(d_2)}{\partial \mu(r_1)} & \cdots & \frac{\partial \phi_1(d_2)}{\partial \mu(r_N)} & \frac{\partial \phi_1(d_2)}{\partial D(r_1)} & \cdots & \frac{\partial \phi_1(d_2)}{\partial D(r_N)} \\ \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \frac{\partial \phi_1(d_M)}{\partial \mu(r_1)} & \cdots & \frac{\partial \phi_1(d_M)}{\partial \mu(r_N)} & \frac{\partial \phi_1(d_M)}{\partial D(r_1)} & \cdots & \frac{\partial \phi_1(d_M)}{\partial D(r_N)} \\ \frac{\partial \phi_2(d_1)}{\partial \mu(r_1)} & \cdots & \frac{\partial \phi_2(d_1)}{\partial \mu(r_N)} & \frac{\partial \phi_2(d_1)}{\partial D(r_1)} & \cdots & \frac{\partial \phi_2(d_1)}{\partial D(r_N)} \\ \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \frac{\partial \phi_K(d_M)}{\partial \mu(r_1)} & \cdots & \frac{\partial \phi_K(d_M)}{\partial \mu(r_N)} & \frac{\partial \phi_K(d_M)}{\partial D(r_1)} & \cdots & \frac{\partial \phi_K(d_M)}{\partial D(r_N)} \end{bmatrix}}_{A} \underbrace{\begin{bmatrix} \delta\mu(r_1) \\ \vdots \\ \delta\mu(r_N) \\ \delta D(r_1) \\ \vdots \\ \delta D(r_N) \end{bmatrix}}_{\begin{bmatrix} \mu \\ D \end{bmatrix}}$$

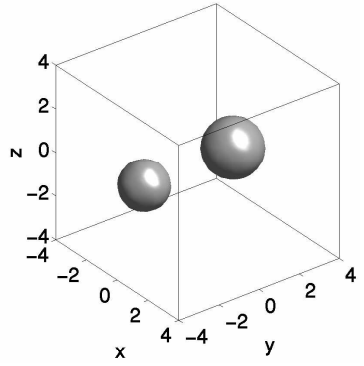
Linearized Approach: Reconstruction

- Direct methods
  - Singular value decomposition (SVD) [56, 57, 58]
- Iterative methods
  - Algebraic reconstruction techniques (ART) and simultaneous iterative reconstruction technique (SIRT) [57]
  - Conjugate gradient (CG) [57]
  - Saves re-computation of Green's functions
- Back-projection algorithm
  - Widely used in tomographic imaging systems (e.g. CT, PET)
  - Works well for "ideal" projections with negligible scatter
- Limitations
  - Requires the selection of baseline values for μ and D
  - Results can be seriously affected by erroneous choice of μ and D
  - Quantitative imaging of spatially varying optical properties is very difficult due to linearization error [59]

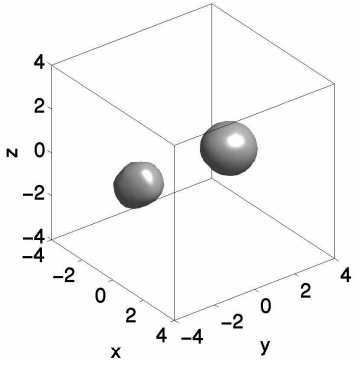
Source-Detector Calibration: Coupling Variability

- Variability in practical ODT imaging systems
  - Excitation strength of sources
  - Collector efficiency of detectors
  - Effective position of sources and detectors
- Variability can be modelled with source-detector coupling parameters [60]
- Calibration of these unknown parameters is essential for effective imaging
- Importance of calibration [61]

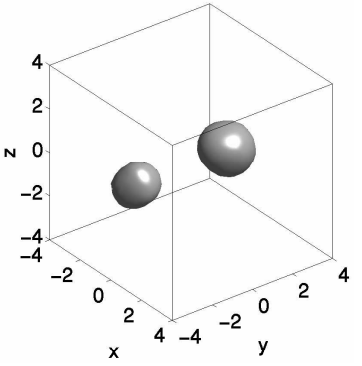
True phantom



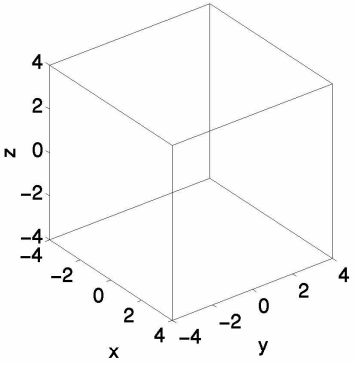
Calibration



True weights



Average weights



S-D Calibration: Approaches

- No calibration: Assume known weights (e.g. use $1 + 0j$ for all weights)
- Preprocessing
  - Compare prior measurements for a homogeneous medium with the corresponding computed values [62, 63, 64, 65, 66, 67]
  - Minimize the error between the measurements for the given inhomogeneous phantom and the computed values with an assumed homogeneous medium [68]
- Simultaneous reconstruction and calibration [60, 61, 69, 70]
  - Forward model

$$f_{kM+m}(x, \beta_k, \gamma_m) = \beta_k \gamma_m \phi_k(\gamma_m; x)$$

    β_k: source excitation
    γ_m: detector collection efficiency
  - Estimate β_k's and γ_m's while reconstructing image x
  - We will focus on this approach!

S-D Calibration: Joint MAP Estimation [61, 69]

- Data likelihood function $p(y|x,\beta,\gamma,\alpha)$ involves weights β and γ

$$\log p(y|x,\beta,\gamma,\alpha) = \frac{1}{\alpha}||y - f(x,\beta,\gamma)||^2_\Lambda + constant$$

- MAP estimate for both the image and unknown model parameters results in single cost function for both image and weights

$$\begin{aligned}(\hat{x}_{MAP},\hat{\beta},\hat{\gamma},\hat{\alpha}) &= \arg \max_{x\geq 0,\beta,\gamma,\alpha} \{\log p(y|x,\beta,\gamma,\alpha) + \log p(x)\} \\ &= \arg \max_{x\geq 0,\beta,\gamma,\alpha} c(x,\beta,\gamma,\alpha)\end{aligned}$$

  $p(x)$: image prior model

- Coordinate descent optimization of the single cost function

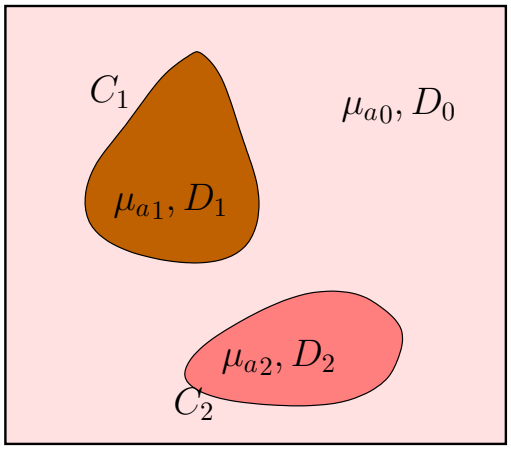
For each iteration {

$$\begin{aligned}\hat{\alpha} &\leftarrow \arg\min_{\alpha} c(\hat{x},\hat{\beta},\hat{\gamma},\alpha) \\ \hat{\beta} &\leftarrow \arg\min_{\beta} c(\hat{x},\beta,\hat{\gamma},\hat{\alpha}) \\ \hat{\gamma} &\leftarrow \arg\min_{\gamma} c(\hat{x},\hat{\beta},\gamma,\hat{\alpha}) \\ \hat{x} &\leftarrow ICD_update_x\ c(x,\hat{\beta},\hat{\gamma},\hat{\alpha})\end{aligned}$$

}

Shape-Based Reconstruction

- Estimate region parameters directly from data

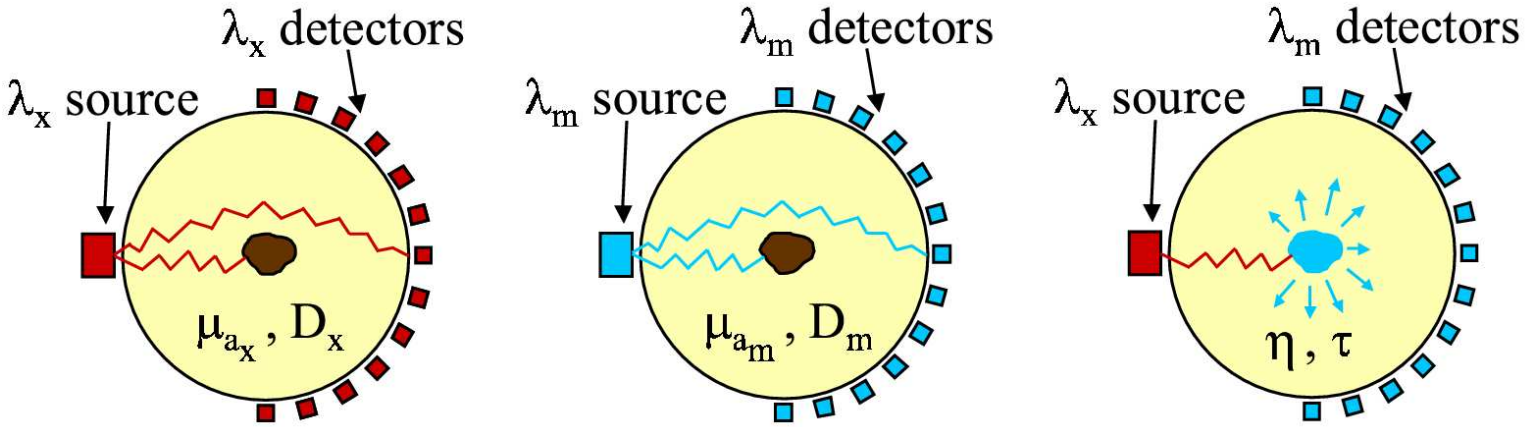


  - Boundary parameters $C_0, \ldots, C_N$
  - Optical parameters $\mu_0, \ldots, \mu_N$, $D_0, \ldots, D_N$

- Useful for identifying localized anomalies e.g. Breast tumor detection
- Reduced number of parameters $\Rightarrow$ higher SNR
- Regions may also vary in space or time [71]
- Regions may be parameterized by:
  - 2-D: B-spline [72], Fourier series [73, 74, 75]
  - 3-D: ellipsoid [76]
  - Level set methods [77, 78]
  - Dynamic methods [71]

Fluorescence ODT (FODT)[67]

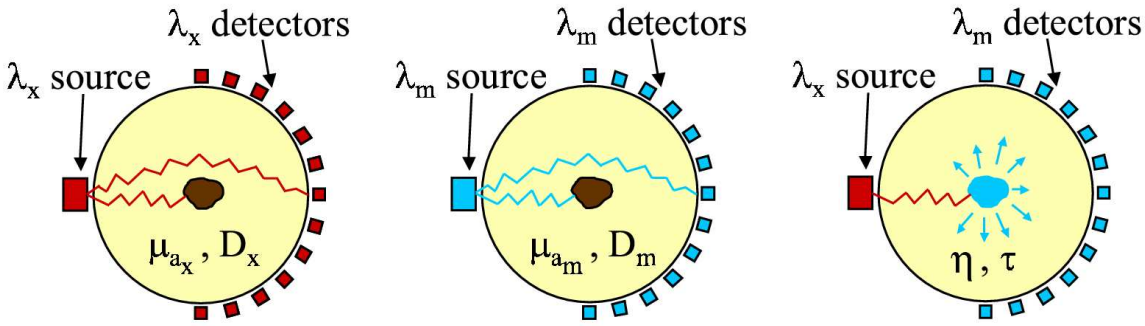
- Basic concept fluorescent tagging
  - Fluorophore provides enhanced contrast
  - With targeted delivery $\rightarrow$ site-specific imaging (e.g. tumors)
  - Fluorophore absorbs energy at excitation wavelength, λ_x
  - Fluorophore re-emits at emission wavelength, λ_m



- Possible measurement scenarios
  - Source at λ_x and detect at $\lambda_x \Rightarrow$ ODT model
  - Source at λ_m and detect at $\lambda_m \Rightarrow$ ODT model
  - Source at λ_x and detect at $\lambda_m \Rightarrow$ Coupled ODT model

A. B. Milstein, *et al.*, "Fluorescence Optical Diffusion Tomography", *Applied Optics,* 2003.

FODT: Time Domain Model at λ_x



- The photon flux density, $\psi_x(r,t)$, obeys the diffusion equation

$$\frac{1}{c}\frac{\partial}{\partial t}\psi_x(r,t) - \nabla \cdot D_x(r)\nabla\psi_x(r,t) + \mu_x(r)\psi_x(r,t) = S_x(r,t)$$

- Quantities at excitation wavelength

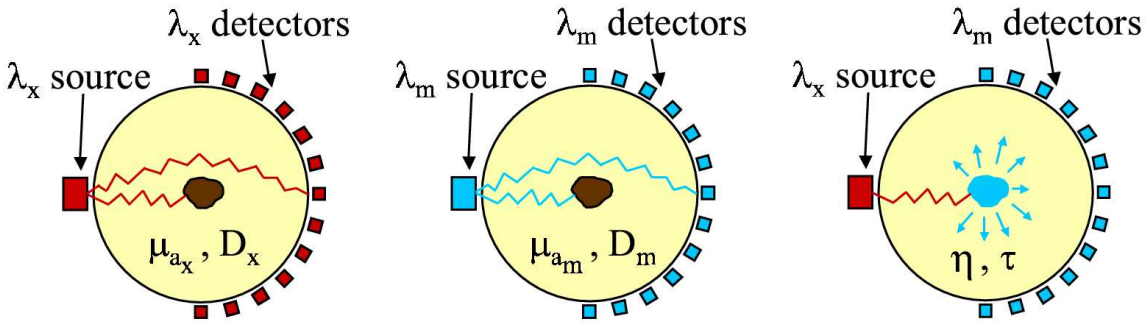
  $\psi_x(r,t)$ - photon flux density

  $D_x(r)$ - Diffusion coefficient

  $\mu_x(r)$ - absorption coefficient

  $S_x(r,t)$ - Source power at location r and time t

FODT: Time Domain Model Re-emission at λ_m



$$\frac{1}{c}\frac{\partial}{\partial t}\psi_x(r,t) - \nabla \cdot D_x(r)\nabla\psi_x(r,t) + \mu_x(r)\psi_x(r,t) = S_x(r,t)$$

- Light is re-emitted at wavelength λ_m as ($*$ denotes time-domain convolution)

$$\psi_x(r,t) * \left\{\frac{\eta(r)}{\tau(r)}e^{-t/\tau(r)}\right\}$$

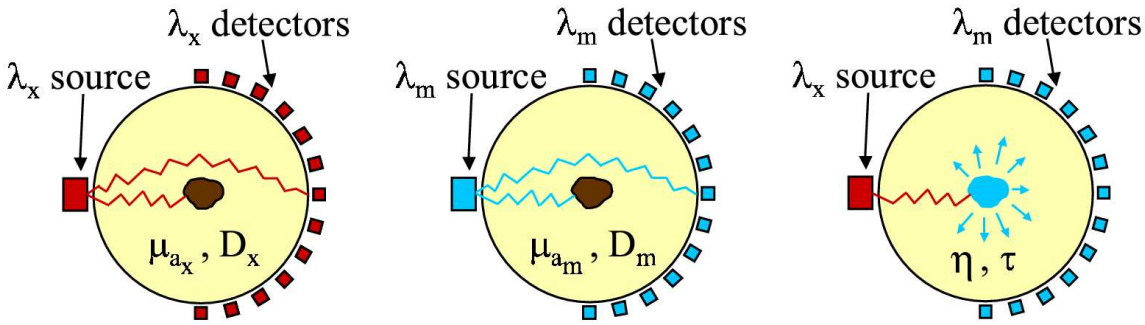
$\psi_x(r,t)$ - photon flux density at excitation wavelength

$\eta(r)$ - fluorescent yield

$\tau(r)$ - fluorescent lifetime

- Models fluorescent impulse response as exponential with time constant τ

FODT: Time Domain Model at λ_m



$$\frac{1}{c}\frac{\partial}{\partial t}\psi_m(r,t) - \nabla\cdot D_m(r)\nabla\psi_m(r,t) + \mu_m(r)\psi_m(r,t) = \underbrace{\psi_x(r,t) * \left\{\frac{\eta(r)}{\tau(r)}e^{-t/\tau(r)}\right\}}_{\text{fluorescent source}} + S_m(r,t)$$

- Quantities at emission wavelength

  $\psi_m(r,t)$ - photon flux density

  $D_m(r)$ - Diffusion coefficient

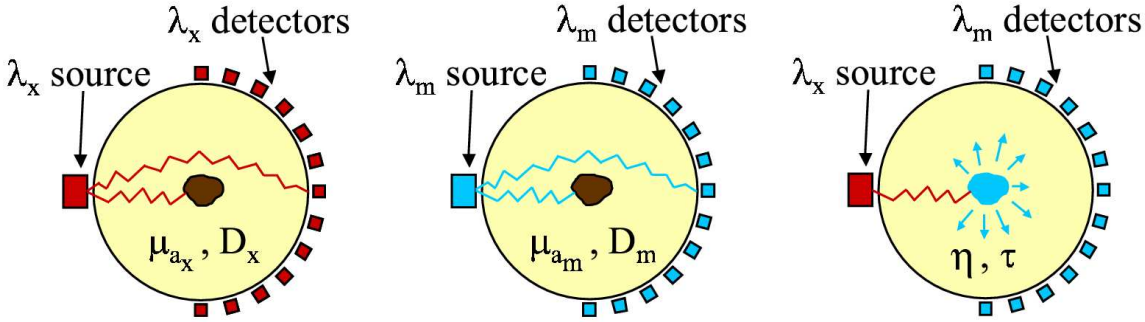
  $\mu_m(r)$ - absorption coefficient

  $S_m(r,t)$ - Source power at location r and time t

  $\eta(r)$ - fluorescent yield

  $\tau(r)$ - fluorescent lifetime

FODT: Frequency Domain Model



Source terms:

$$S_x(r,t) = S_x(r)e^{j\omega t}$$
$$S_m(r,t) = S_m(r)e^{j\omega t}$$

Photon density terms

$$\psi_x(r,t) = \phi_x(r)e^{j\omega t}$$
$$\psi_m(r,t) = \phi_m(r)e^{j\omega t}$$

Fluorescent re-emission term

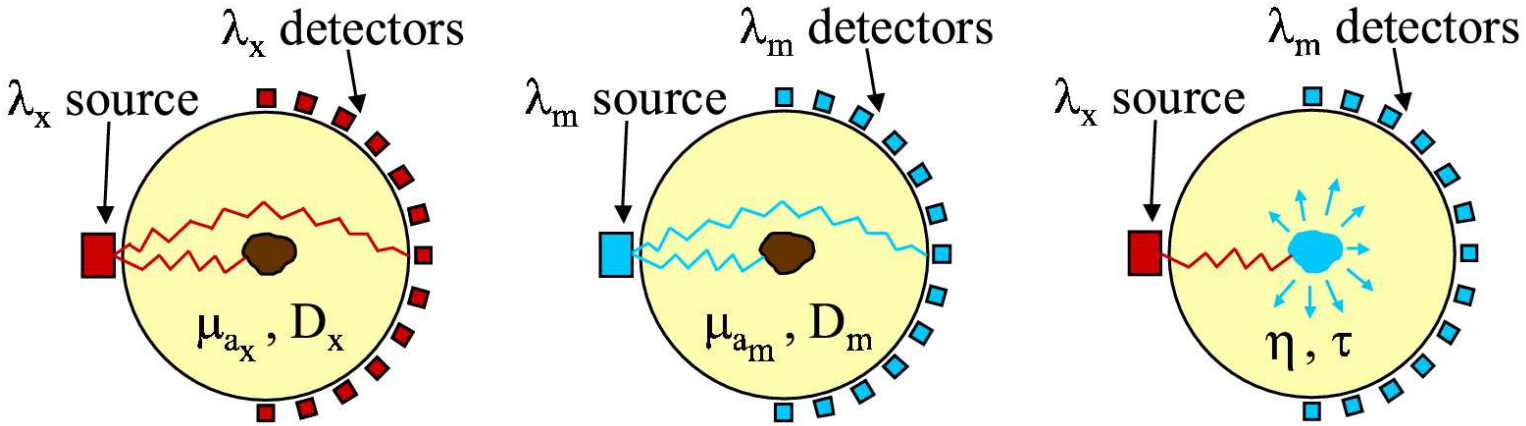
$$\psi_x(r,t) * \left\{ \frac{\eta(r)}{\tau(r)} e^{-t/\tau(r)} \right\} = \phi_x(r) \frac{\eta(r)\left[1 - j\omega\tau(r)\right]}{1 + \left[\omega\tau(r)\right]^2} e^{j\omega t}$$

- Then the frequency modulated light obeys the coupled elliptic PDEs

$$\nabla \cdot D_x(r)\nabla\phi_x(r) - \left[\mu_x(r) + j\omega/c\right]\phi_x(r) = -S_x(r)$$

$$\nabla \cdot D_m(r)\nabla\phi_m(r) - \left[\mu_m(r) + j\omega/c\right]\phi_m(r) = -\phi_x(r)\frac{\eta(r)\left[1 - j\omega\tau(r)\right]}{1 + \left[\omega\tau(r)\right]^2} - S_m(r)$$

FODT: Measurement Approach



Source λ	Detector λ	Unknown Image	Observation
λ_x	λ_x	$x_x = [D_x, \mu_x]$	y_x
λ_m	λ_m	$x_m = [D_m, \mu_m]$	y_m
λ_x	λ_m	$x_f = [\eta, \tau]$	y_f

- Reconstruction strategy
  - Use y_x to determine x_x and ϕ_x
  - Use y_m to determine x_m
  - Use y_f, ϕ_x, and x_m to determine x_f

FODT: MAP Inversion

- For each image, joint MAP estimation of x and α

$$\begin{aligned}
\hat{x}_x &= \arg \max_{x_x \geq 0, \alpha_x} \{ \, p(x_x | y_x, \alpha_x) \, \} \\
\hat{x}_m &= \arg \max_{x_m \geq 0, \alpha_m} \{ \, p(x_m | y_m, \alpha_m) \, \} \\
\hat{x}_f &= \arg \max_{x_f \geq 0, \alpha_f} \{ \, p(x_f | y_f, \alpha_f, \hat{x}_x, \hat{x}_m) \, \}
\end{aligned}$$

- Estimation of α improves robustness of convergence
- Iterative optimization scheme:
  alternate updates with respect to α and x

$$\text{Step 1: } \hat{\alpha} = \frac{1}{P} ||y - f(\hat{x})||_{\Lambda}^2$$

$$\text{Step 2: } \hat{x} = \arg \min_{x \geq 0} \left\{ \frac{1}{2\hat{\alpha}} ||y - f(x)||_{\Lambda}^2 + \frac{1}{p\sigma^p} \Sigma \, b_{i-j} |x_i - x_j|^p \right\}$$

FODT: Multifrequency: Inversion of η and τ [79]

- Problem: η and τ are nonlinearly related to fluorescent re-emission

$$\phi_x(r)\frac{\eta(r)\left[1-j\omega\tau(r)\right]}{1+\left[\omega\tau(r)\right]^2}$$

- Solution for single frequency case
  - Reparameterize $\{\eta,\tau\}$ as $\{\gamma,\tau\} = \{\frac{\eta}{1+[\omega\tau]^2},\tau\}$
  - $\{\gamma,\tau\}$ are linearly related to fluorescent re-emission
- Solution for multiple frequency case
  - Parameterize using $\{\eta,\tau\}$
  - Use parametric ICD (PICD) to decouple nonlinearity
  - Compute θ_{1,ω_q} and θ_{2,ω_q} for frequencies $\omega_1,\cdots,\omega_q$
  - Perform numerical optimization of η τ at each voxel

FODT: Multifrequency: Parametric ICD (PICD) Optimization[79]

$[\omega_1, \cdots, \omega_Q]$ - the Q different frequencies used

$x_s = [\eta_s, \tau_s]$ - the unknown values at voxel s

- Define the functions

$$h(x_s) \triangleq \left[\frac{\eta_s(1 - j\omega_1\tau_s)}{1 + (\omega_1\tau_s)^2}, \cdots, \frac{\eta_s(1 - j\omega_Q\tau_s)}{1 + (\omega_Q\tau_s)^2}\right]^t$$

$$\Delta h(\tilde{x}_s, x_s) \triangleq h(\tilde{x}_s) - h(x_s)$$

- Generalize the concept of θ_1 and θ_2 to

$$\theta_1 \triangleq [\theta_{1,1}, \cdots, \theta_{1,Q}] \qquad \theta_2 \triangleq [\theta_{2,1}, \cdots, \theta_{2,Q}]$$

- Then update of voxel $x_s = [\eta_s, \tau_s]$ is given by:

$$x_s \leftarrow \arg\min_{\tilde{x}_s \geq 0} \left\{\theta_1 \Delta h(\tilde{x}_s, x_s) + \frac{1}{2} \left\|\Delta h(\tilde{x}_s, x_s)\right\|_{\theta_2}^2 + \frac{1}{p\sigma^p} \sum_{j \in \mathcal{N}_s} |\tilde{x}_s - x_j|^p\right\}$$

FODT: Multifrequency: Mutual Information Design Metric [79]

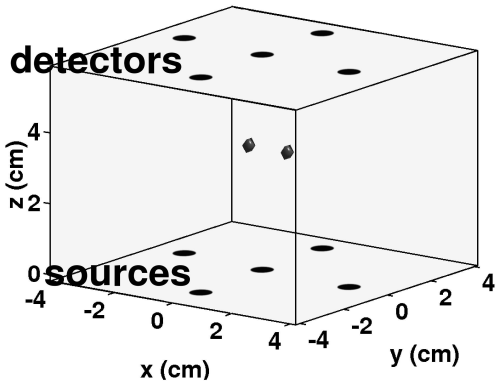
- Previously, singular value analysis has been used to evaluate measurement geometries[80]
- Information theory provides statistical framework for evaluating tomography system and reconstruction quality
- Mutual information concept: $I(X;Y)$ is the reduction in uncertainty of X due to knowledge of Y
- Consider the model

$$p_X(x) = \frac{1}{\sqrt{(2\pi)^N |C|}} \exp\left\{-\frac{1}{2}||x||_C^2\right\}$$
$$p_{Y|X}(y|x) = \frac{1}{\sqrt{(2\pi\alpha)^P |\Lambda^{-1}|}} \exp\left\{-\frac{1}{2\alpha}||y - Ax||_\Lambda^2\right\}$$

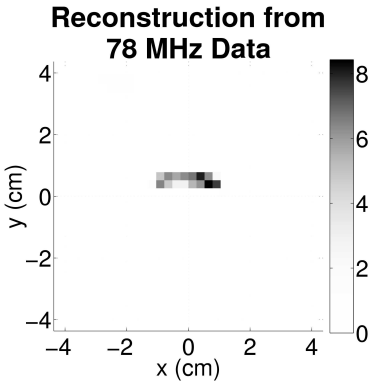
  A is the forward operator

- Then $I(X;Y) = \frac{1}{2}\log\left|I + \frac{1}{\alpha}\Lambda A C^{-1} A^H\right|$

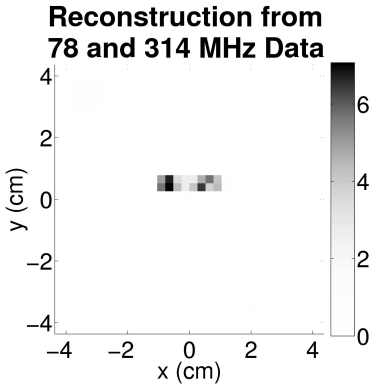
FODT: Multifrequency: Mutual Information Comparison



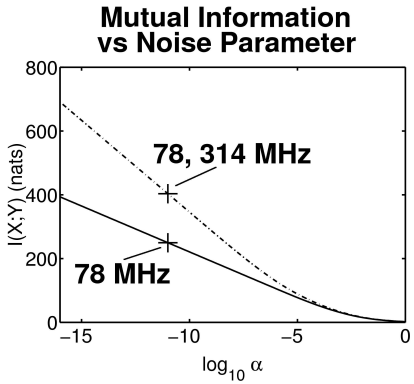
(a)



(b)



(c)



(d)

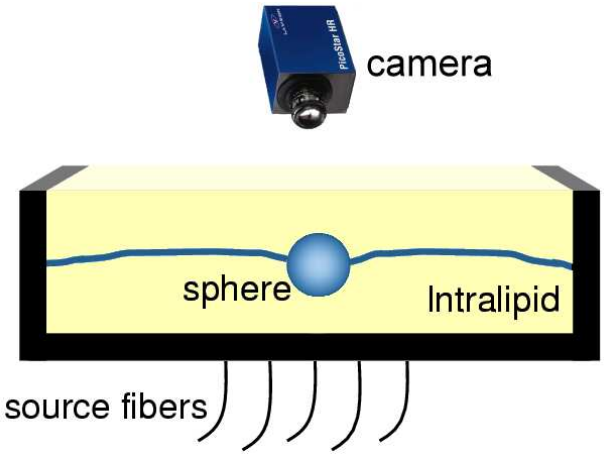
21.2dB avg. SNR at 78.4 MHz

14.7dB avg. SNR at 314 MHz

- Reconstructed 2 small, nearby objects from sparse, noisy data
- Multiple frequencies improves quality, as predicted by $I(X;Y)$

FODT: Experiment: Fluorophore in Lipid Suspension

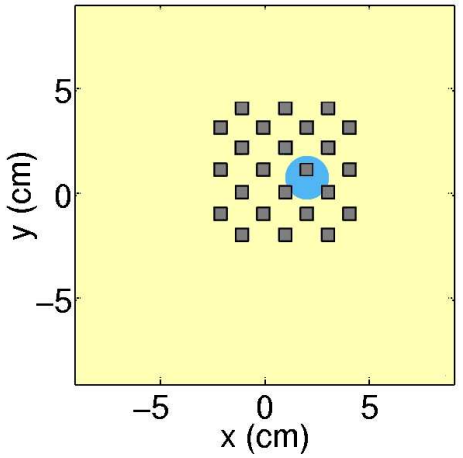
- 0.125 μM indocyanine green (ICG) in 1% Intralipid suspension
- MaiTai tunable, ultrafast Ti:sapphire source, and PicoStar intensified CCD detector
- $\lambda_x = 780$ nm, $\lambda_m = 830$ nm



Instrument



Measurement Box



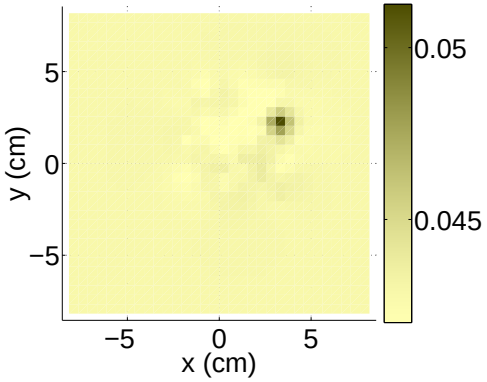
Source/Detection Positions

FODT: Experiment: Parameters

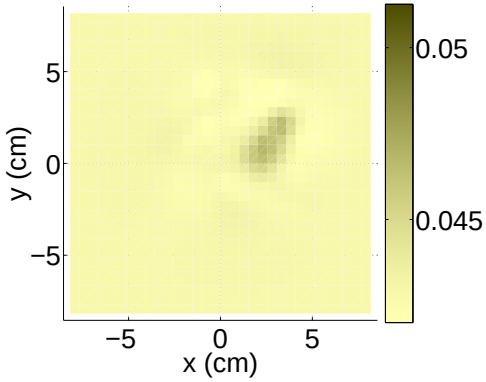
- Impulse responses from 24 source fibers, 24 detection positions
- $\mu_{a_{x,m}}$ data: 250 ps time step, 75 ms acquisition time/measurement, lower intensifier gain
- η, τ data: 500 ps time step, 1 s acquisition time/measurement, higher intensifier gain
- From FFT, 78, 314 MHz, and 627 MHz data used
- 16 cm $\times$ 16 cm $\times$ 5.7 cm domain modeled
- $p = 2.0$ for all reconstructions

σ used	Parameter
0.005 cm^{-1}	μ_a
0.1 ns	τ
0.00005 AU	η

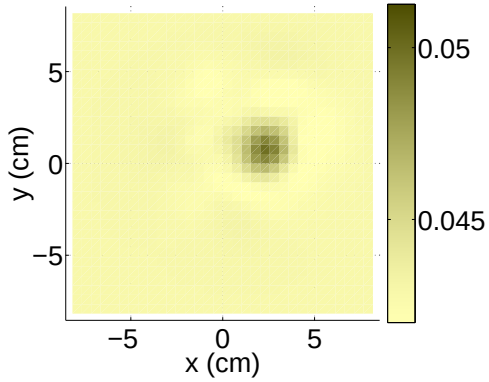
FODT: Experiment: Results - μ_x ($\mathbf{cm}^{-1}$)



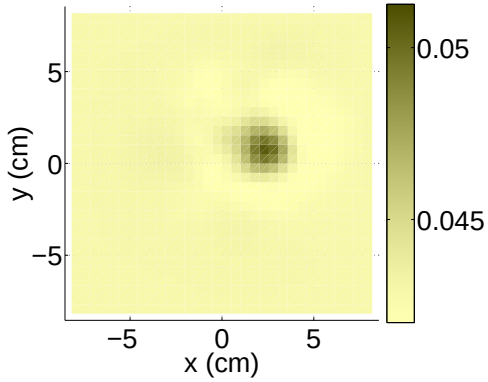
$z = 0.58$ cm



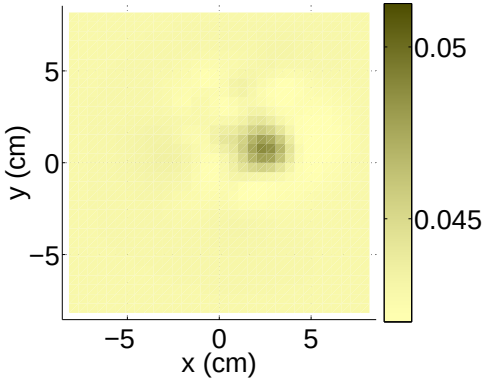
$z = 1.34$ cm



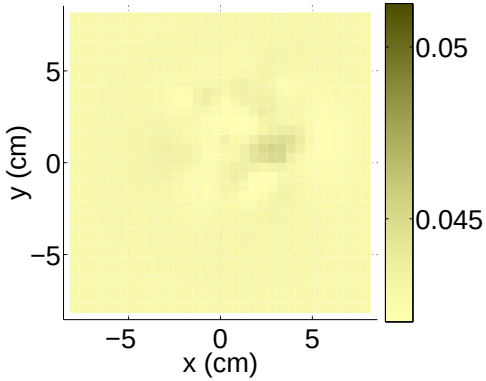
$z = 2.09$ cm



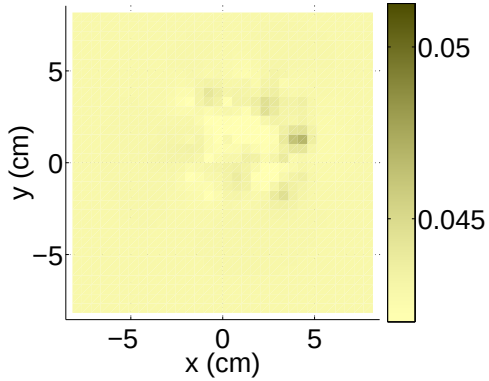
$z = 2.85$ cm



$z = 3.61$ cm

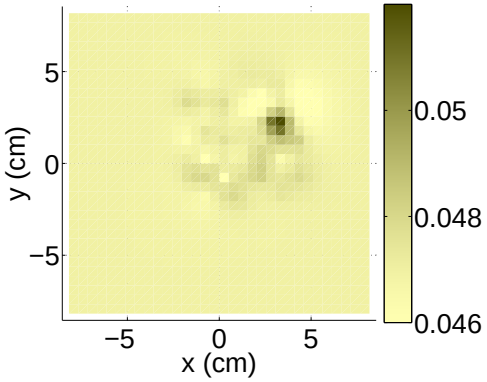


$z = 4.37$ cm

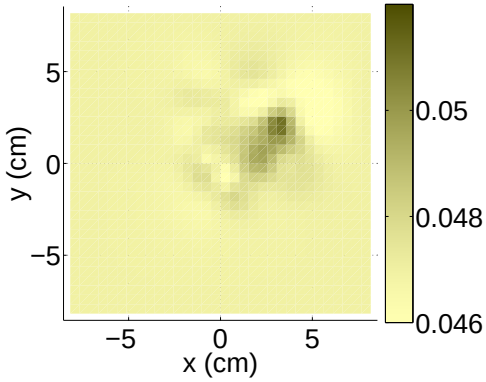


$z = 5.12$ cm

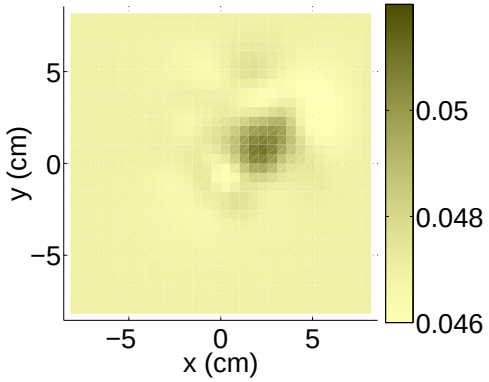
FODT: Experiment: Results - μ_m ($\mathbf{cm}^{-1}$)



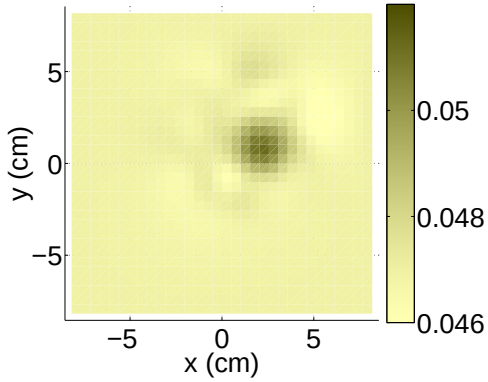
$z = 0.58$ cm



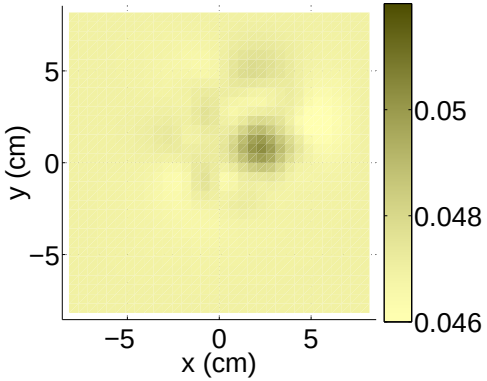
$z = 1.34$ cm



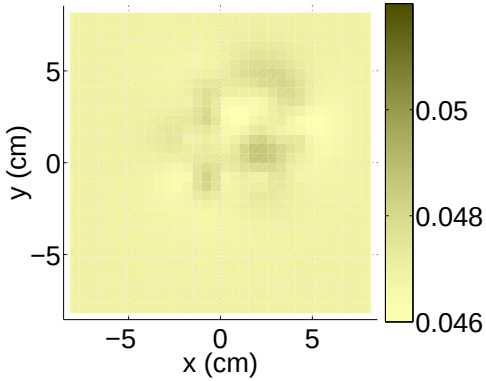
$z = 2.09$ cm



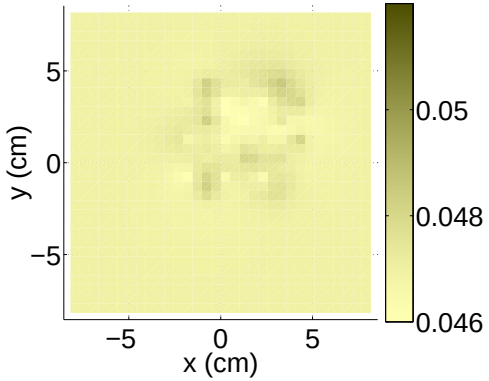
$z = 2.85$ cm



$z = 3.61$ cm

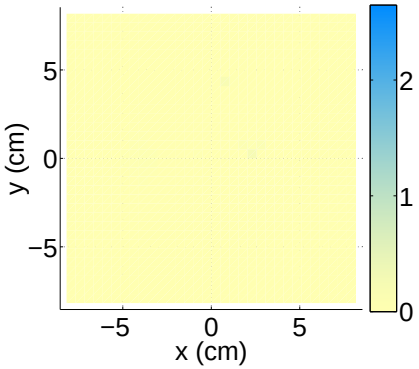


$z = 4.37$ cm

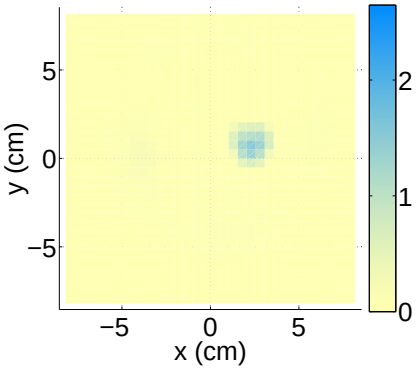


$z = 5.12$ cm

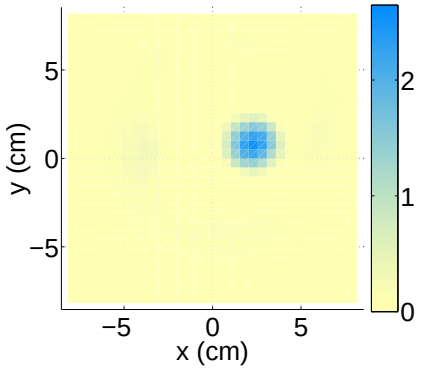
FODT: Experiment: Results - η (AU)



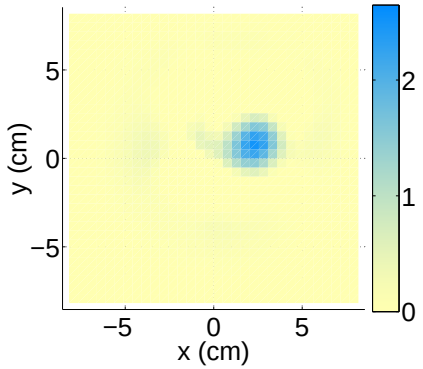
$z = 0.58$ cm



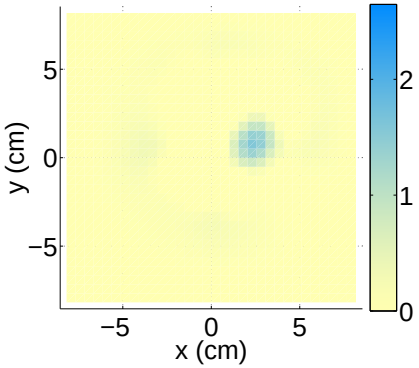
$z = 1.34$ cm



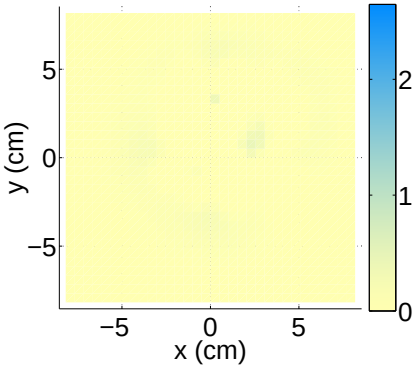
$z = 2.09$ cm



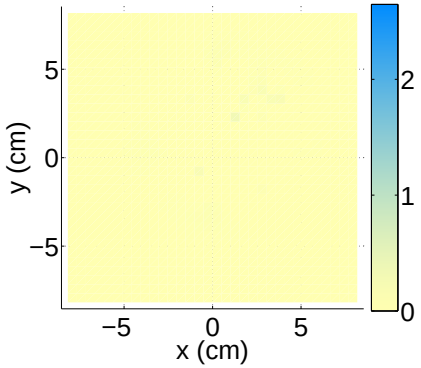
$z = 2.85$ cm



$z = 3.61$ cm

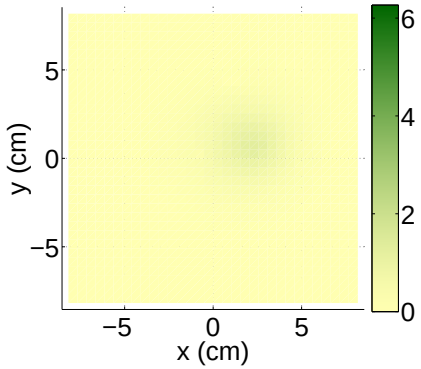


$z = 4.37$ cm

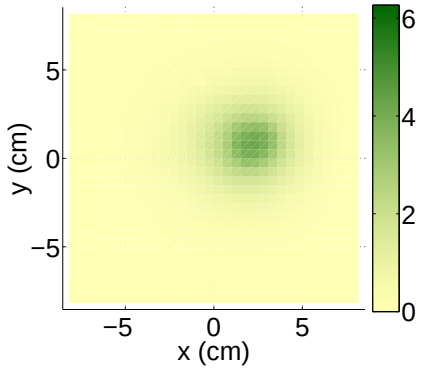


$z = 5.12$ cm

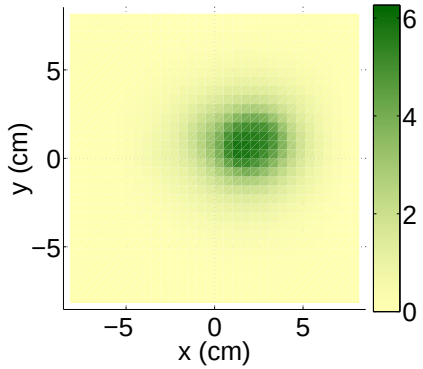
FODT: Experiment: Results - τ (1×10^{-10} s)



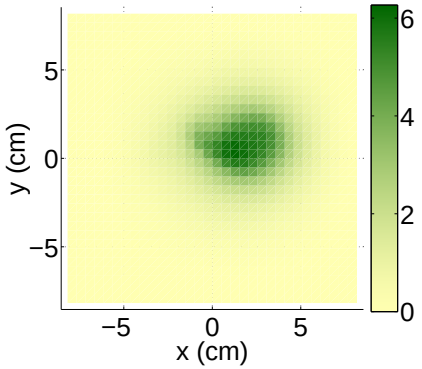
$z = 0.58$ cm



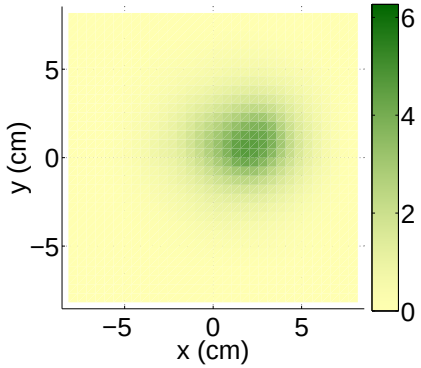
$z = 1.34$ cm



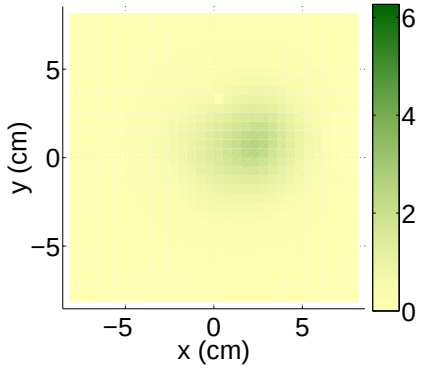
$z = 2.09$ cm



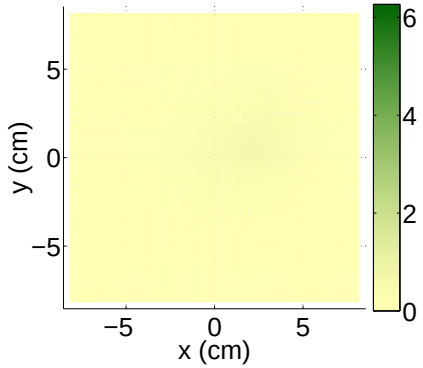
$z = 2.85$ cm



$z = 3.61$ cm



$z = 4.37$ cm

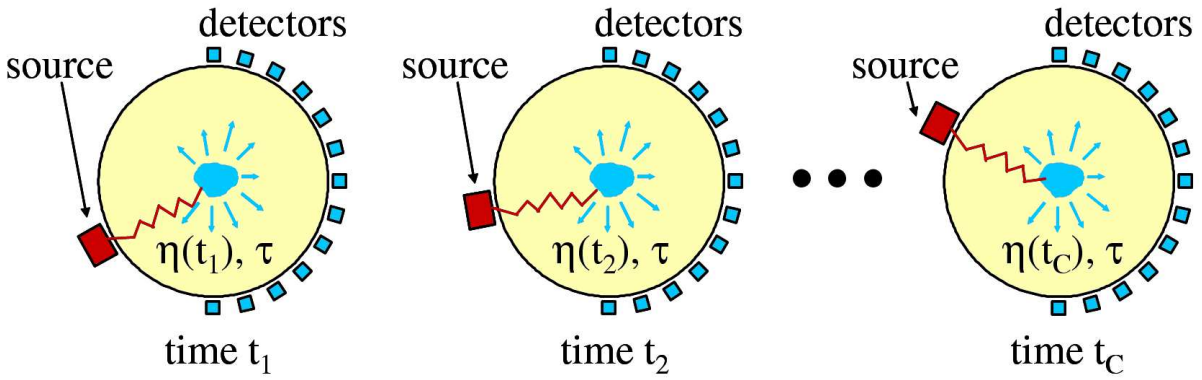


$z = 5.12$ cm

Kinetic Parameter Models in FODT

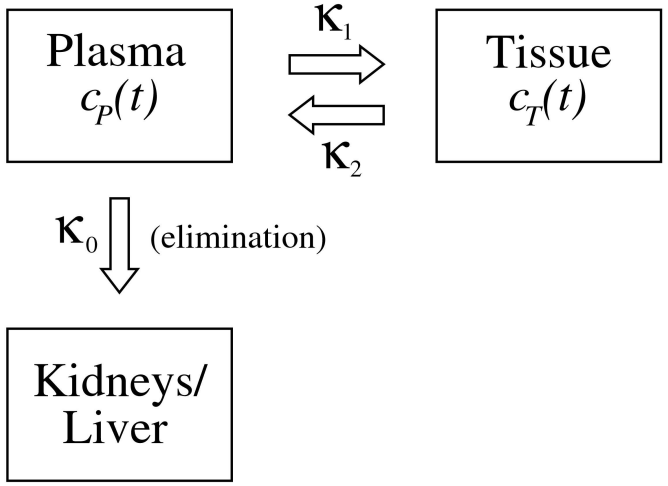
- Recent advances in targeted fluorescent probes have paved the way for molecular imaging
- Several groups have measured dynamic behavior of optical contrast agents in human or animal subjects [81, 82]
- Uptake rate of targeted dyes may form a basis for distinguishing diseased and healthy tissue

Kinetic FODT: Approach [83, 84]



- Problem
  - Would like to extract kinetic parameters for each voxel
  - Source position is typically moving
  - Insufficient data to reconstruct at each time
- Solution: Directly reconstruct kinetic parameters for each voxel
- Advantages
  - Only reconstruct one image of parameters
  - Account for time varying illumination
  - Reduced number of parameters
  - Increased SNR

Kinetic FODT: Compartment Model for Each Voxel



$$c_P = A\exp(-\kappa_3 t)$$
$$\frac{dc_T}{dt} = \kappa_1 c_P - \kappa_2 c_T$$

c_P: concentration in plasma
c_T: concentration in tissue
κ_1: rate to enter tissue
κ_2: rate to leave tissue
κ_3: exponential parameter for c_P
κ_O: rate of elimination into kidneys

- $\eta(r,t)$ is proportional to a weighted sum of c_P and c_T, with the form:

$$\eta(r,t) = \gamma_1(r)\exp[-\gamma_4(r)t] - \gamma_2(r)\exp[-\gamma_3(r)t].$$

- Parameters for voxel are

$$x_s = [\gamma_{1,s}, \gamma_{2,s}, \gamma_{3,s}, \gamma_{4,s}]$$

Kinetic FODT: Bayesian Approach with PICD Optimization

- At each time t_c, forward operator is linear with respect to $h_{t_c}(x) = \frac{\eta(t_c)}{1+j\omega\tau}$,
- Optimization of x may be written:

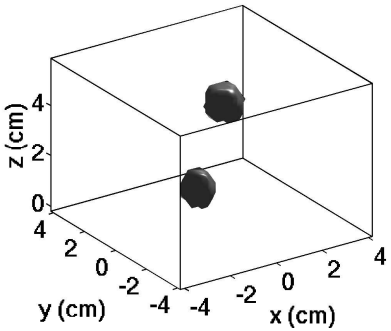
$$\hat{x} = \arg\min_x \left\{ \frac{1}{2\hat{\alpha}} \sum_{c=1}^{C} ||y_{t_c} - J_{t_c} h_{t_c}(x))||^2_{\Lambda_{t_c}} - \log p(x) \right\}$$

- We update voxels of τ and $\gamma_1 \cdots \gamma_4$ using nonlinear line search, with constraints $x \geq 0$, $\gamma_1 \geq \gamma_2$, and $\gamma_3 \geq \gamma_4$:

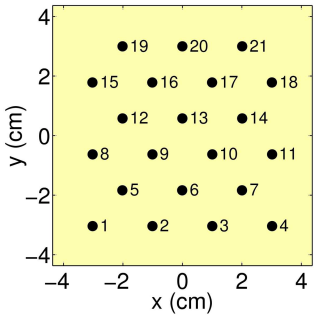
$$\hat{x}_i \leftarrow \arg\min_{x_i} \left\{ \sum_{c=1}^{C} \left(\theta_{1,t_c}[h_{t_c}(x_i)] + \frac{1}{2}\theta_{2,t_c}[h_{t_c}(x_i)]^2 \right) - \log p(x_i) \right\}$$

Simulation - Two Objects with Different Uptake

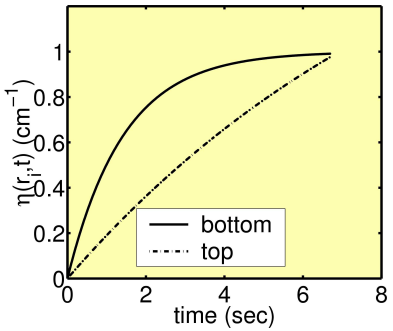
- Synthetic time series of data generated from cube-shaped phantom with two heterogenieties
- Objects have same τ, but different γ_1, γ_2, and γ_3.
- Sources illuminated one at a time in raster order, with each source used once
- Average signal/noise: 28 dB



Two Objects



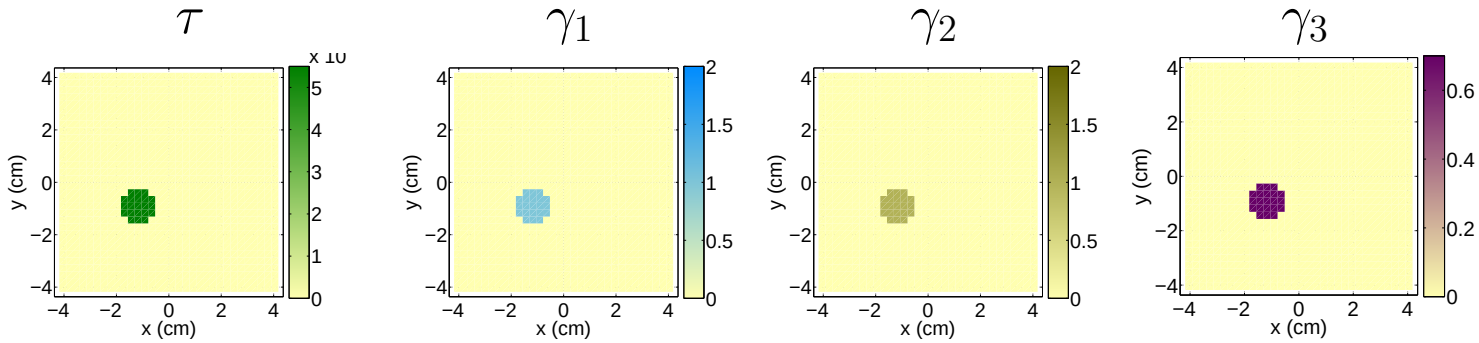
Sources



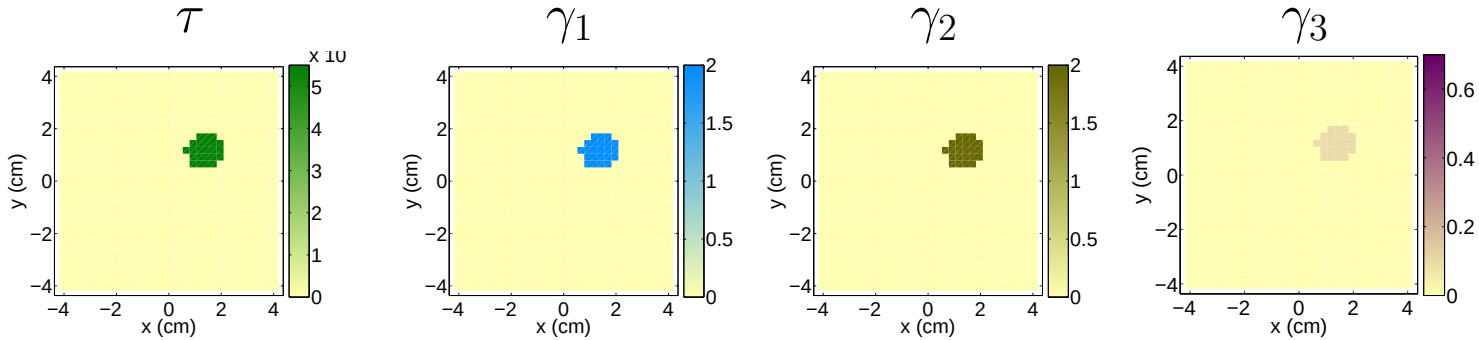
η vs. Time

Kinetic FODT: Simulation - True Phantom

Bottom: $z = 2.1$ cm

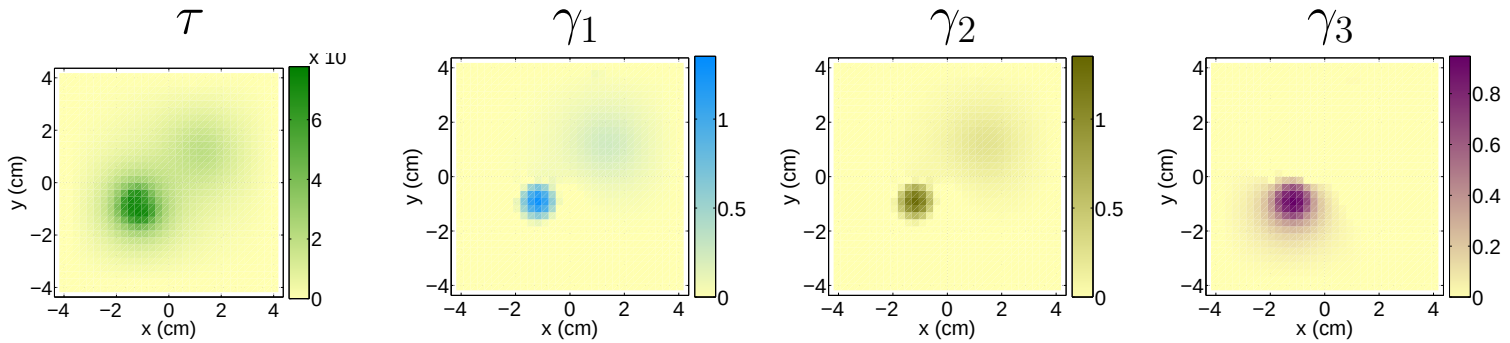


Top: $z = 4.0$ cm

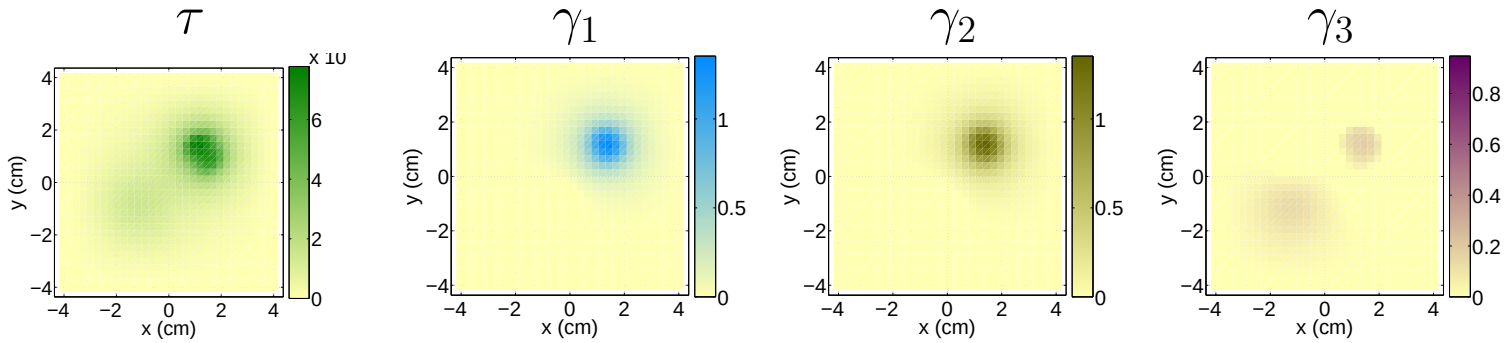


Kinetic FODT: Simulation - Reconstruction

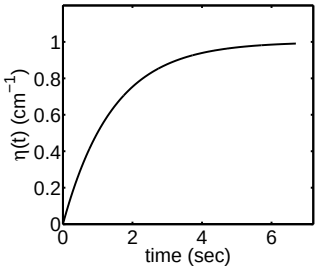
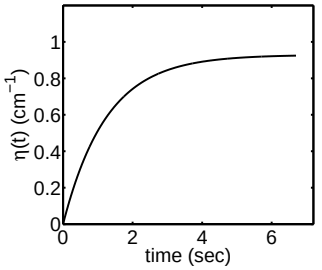
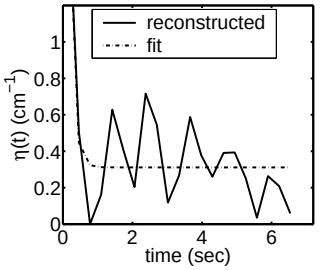
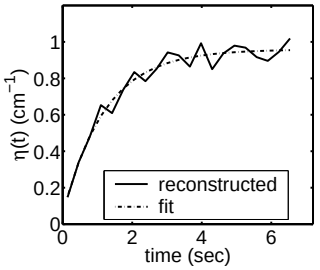
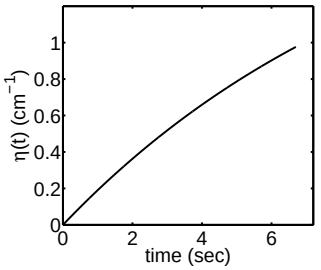
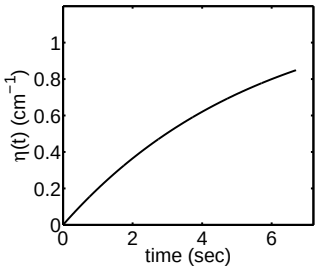
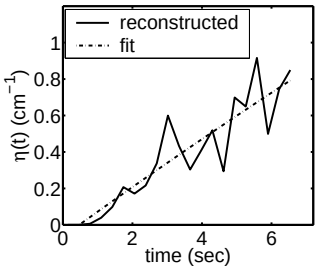
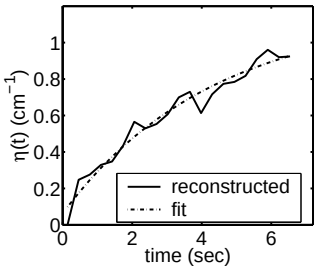
Bottom: $z = 2.1$ cm



Top: $z = 4.0$ cm



Kinetic FODT: Simulation - Plots of $\eta(t)$ and Reconstructions

	True	Reconstruction	Frame-by-frame	Frame-by-frame (21× more data)
Bottom: $z = 2.1$ cm				
Top: $z = 4.0$ cm				

Frontiers

- Research applications
  - Molecular imaging
  - Drug development
  - Molecular probes
  - Hyperspectral imaging
- Clinical applications
  - Breast imaging
  - Neuroimaging
  - Kinetics
  - Multimodal imaging (resolution/specificity)
- What will be the "Killer App"?

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Dr. J. Stott

Purdue University, Department of Chemistry
Prof. Philip S. Low
Dr. Michael Kennedy

University of Canterbury
Prof. Rick P. Millane

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