#### Data to Knowledge: Understanding Dynamic Medical Images

Computer Science (CS) is the new language of science as Mathematics was until the Twentieth Century. CS generalizes mathematics toward being more versatile. In this talk we will focus on some problems in bio-medical science and discuss how our group views the challenges and how we try to address them computationally.

Tomography is the technology of combining data from multiple views (say, 2D camera snapshots) to create a comprehensive image (say, in 3D). In medicine tomography is used to gather knowledge about target organs or physiology inside patients without any probing surgery. In vivo molecular imaging, or gene expression analysis in real time, is a promised goal of functional imaging. However, it involves time-varying signals coming from inside the body. My talk is on some of the projects on nuclear imaging and fluorescent imaging data with different types of dynamics in order to elicit bio-medical information.

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#### Data to Knowledge: Understanding Dynamic Medical Images

**Debasis Mitra** 

Department of Computer Sciences Florida Institute of Technology

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Image credit: Mahmoud Abdalah and www

## Tomography: Non-invasive Probing of Human Body

Views from a rotating camera: Sinogram



Computed 3D Reconstructed Image



Cardiac reversible ischemia: stressed(A), rest(B) http://www.aipes-eeig.org/white-paper-spect-spect-ct.html

## Tomography: Non-invasive Probing of Human Body



Forward Problem: This is what the imaging system does P = S.V

P: Camera Views - input S: Camera model / System Matrix - computed V: Target object - unknown



*Inverse Problem*: This is what a reconstruction algorithm does  $V = S^{-1}.P$ 

### Types of Imaging

#### Anatomical Imaging

- Where is some organ located?
- Where is the tumor located?
- What is the bone density on spine?
- Example:
  - Absorption of X-ray: Computed Tomography (CT)

#### Functional Imaging

- Where is the targeted physiological function taking place?
- What is the strength of that function?
- How are the nerve cells functioning on heart muscles?
- Example:
  - Concentration of probing molecules, which emits gamma rays: Emission Tomography (SPECT and PET)

### Emission Tomography: Functional Imaging



## PET: Positron Emission Tomography





- Positron annihilates with electron
   ⇒ two gamma photons each at 511 keV leave at180°
  - Coincidence detection ("electronic collimation")

## SPECT: Gamma Emission Tomography (Single Photon Emission Computed Tomography)



γ-ray detectors

Resolution

100-200 keV



collimators

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### **Iterative Reconstruction**



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### **Dynamic Imaging**

- Dynamic Imaging: Target Image not stationery during scan

   e.g. Patient moved
- Dynamic Functional Imaging: As the target "function" is taking place:
  concentration is changing
  - e.g. nerve cells are picking up norepinephrine

### Dynamic Imaging: PET Project 1

3D x t

### Dynamic Imaging: PET Project 1



PET: views from all angles available at all instances.

#### PIB tracer binding on Alzheimer's studies

- Time-lapsed Reconstructed 3D images, a slice through human brain
- Tracer concentration is changing with time



#### Dimensions of the Problem

- V = 64x64x64 voxels => 262,000 => x4 bytes => 8 Mb
- T = 35 snapshots or views => 8 Mb x 35 => 280 Mb

#### F = 4 target functions

- upstream and downstream blood,
- reference specific tracer binding,
- non-specific binding

### Dynamic PET: Alzheimer's studies

#### **CIFA:** Cluster-Initialized Factor Analysis

Input: 4D images of possible Alzheimer's patient



**Output:** Detect affected tissues based on their tracer dynamics

Boutchko R, Mitra D, Baker S, Jagust W, and Gullberg GT. (April 2015) "Clustering Initiated Factor Analysis (CIFA) Application for Tissue Classification in Dynamic Brain PET." Journal of Cerebral Blood Flow & Metabolism – Nature, doi:10.1038/jcbfm.2015.69.

### **CIFA** Algorithm

**Problem:** Recognize 3 tissue types by tracer kinetics Carotid artery, Normal tissue, Alzheimer's affected tissue (PIB attached to beta-amyloid);

$$V_k(t) = \sum_{i=1}^{J} C_{k,j} f_{j,i}$$

 $\cup, j$ 

*f*: Time basis functions *C*: Coefficients of time basis functions
k: voxel index *J*: Number of time basis functions.

$$\arg\min_{C} \left\| Cf - V \right\|^2 + \text{Regularization} \right\}$$

Non-negative matrix factorization (NNMF): Alternating optimization for C and f

Seung HS, and Lee DD. (1999) "Learning the parts of objects by non-negative factorization." Nature.

### **CIFA** is Cluster-initialized Factor Analysis

NNMF is very sensitive to initialization: Garbage in garbage out!

#### R-clustering to initialize NNMF R-clustering = Representative Clustering Just find out J number of representatives in data

*Input*:  $\{V\} = N$  time series (TS)  $V^n$  of length K each, the elements are denoted as  $V^n_k$ 

*Output*: *P* TS  $C^{p}_{k'}$  each representing a cluster

- **1.** Find the ensemble average  $M^A$  of all  $V^n$ ;
- // the first cluster is farthest from average
- 2. Find a fixed number J of TS in {V} that are furthest from  $M^A$ , denote those as set {F<sub>1</sub>};
- 3.  $C^1$  = average of { $F_1$ };
- 4. For p = 2 through P
- 5. Find a fixed number *J* of TS in {*V*} that are furthest from all  $C^{l}$ ,  $l \in \{1, P-1\}$ , denote those as set  $\{F_{p}\}$ ;
- 6.  $C^{p}$  = average TS of  $\{F'_{p}\}$ ; // end for;
- // refine clusters to be furthest from each other:

7. Repeat the loop 4-6, only this time the set  $\{F_p\}$  denotes *J* TS that are furthest away from all  $C^l$ ,  $l \in \{\{1, P\} \text{ excluding } p\}$ .

### Results from CIFA on Alzheimer's studies



Output 1: Time-activity curves (or f) for: i) Carotid artery, ii) Veins, iii) Normal tissue, and iv) Alzheimer's affected tissue (PIB attached to β-amyloid)

> Output 2: 3D views of Corresponding segments (coefficients C)





### Results from CIFA on Alzheimer's studies

Question: Recognize 3 tissue types by tracer kinetics i) Carotid artery and vein, ii) Normal tissue, iii) Alzheimer's affected tissue (PIB attached to beta-amyloid);



**Output 1: Time-activity curves** 



#### **Output 2: Corresponding segments**





3D view of above tissues

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### Dynamic Imaging: SPECT Project 2

 $2D x \theta x t$ 

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# **Dynamic Data with SPECT**



### Dynamic Imaging: SPECT Project 2

Only two projections for each time point: more difficult than PET

Time 1 I amiT First Rotation Sinogram Immediately after injection





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## **Dynamic Vs. Static Projections**

Static Sinogram

#### Dynamic Sinogram





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## SPECT Dynamic Imaging- Challenges

- III-posed Problem
  - less time for data acquisition on each view
  - Low counts high noise
- Underdetermined Problem
  - Fewer data in each time window after binning
  - Inconsistent sinogram

- Small animal imaging:
  - Low resolution & motion

#### **Dimensions of the Problem**

- V = 64x64x64 voxels => 262,000 => x4 bytes => 8 Mb
- P = 64x64 pixels per view x 120 views => 500,000
   => x4 b => 20 Mb
- System matrix, S = 8 x 20 => 160 Mb
- F, target functions = 3 to 4

## **Dynamic SPECT: Task**

 Goal: Estimation of tracer's temporal distribution in the imaged tissues directly from inconsistent projections

Input: Dynamic Sinogram

Output: Time Activity Curves (TACs)





## **Dynamic SPECT Model**

- Dynamic SPECT is modeled by:
- 4D volume is factored with J time basis functions:

K  $P_n(t) = \overset{-}{a} S_{n,k} V_k(t)$ k=1

i=1

*P*: Sinogram as function of time *S*: System Matrix *V*: 4D Imaged volume, as function of time. *n*: pixel index on the detector *k*: voxel index on the volume *f*: Time basis functions *C*: Coefficients of time *j*,*t* basis functions

J: Number of time basis functions.

 $P_n(t) = \overset{K}{\overset{J}{\text{a}}} S_{n,k} \overset{J}{\overset{J}{\text{a}}} C_{k,j} f_{j,t}$ k=1 *j*=1

 $V_k(t)$ 



# Static Image Reconstruction

• Optimize for V:

$$\arg \min_{V} \left\| SV - P \right\|_{w}^{2} + \text{Regularization} \right\}$$

**Existing Dynamic SPECT Image Reconstruction Methods** 

#### Spectral Methods:

 Select a set of representative time basis functions (Typically cubic bsplines) and optimize for coefficients.

Problem: what is the best set of basis functions?

$$\arg \min_{c} \left\| SCf - P \right\|_{w}^{2} + \text{Regularization} \right\}$$

#### Factor Analysis of Dynamic Structures (FADS):

Initialize and optimize both time basis functions and coefficients.
 Problem: what to initialize with?

$$\arg\min_{c,f} \left\{ \left\| SCf - P \right\|_{w}^{2} + \text{Regularization} \right\}$$

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### **Our Approach: Spline-initialized FADS (SIFADS)**

### **Enhancements:**

- Combined those two types of optimization
- Imposed Data-driven Prior information as constraints in optimization

### **Consequence:**

Reduced dependence on initialization

Abdalah M, Boutchko R, Mitra D, and Gullberg GT. "Reconstruction of 4-D Dynamic SPECT Images From Inconsistent Projections Using a Spline Initialized FADS Algorithm (SIFADS)." IEEE Transactions in Medical Imaging, 34(1): 216-228, 2015.

### **Innovation 1– Hybrid Optimization**

• Spline-Initialized FADS (SIFADS) algorithm



### **Innovation 2-** Impose Prior information

- Reconstruction of later frames is segmented
- Segments are used to impose regularization functions:

1. An anisotropic total variation  $\Theta(C) = |ATV(C)|_1$ 2. Coefficients mix prevention  $W(C) = |\vec{C_j} \cdot \vec{C_i}|_1 \quad j \neq i$ 3. Curves' smoothness constraint  $F(f) = |\nabla f|_1$ 

$$arg\min\left\{\left\|SCf - p\right\|_{w}^{2} + \frac{1}{2}Q(c) + \frac{1}{2}W(c) + \frac{1}{3}F(f)\right\}$$

Spatial Regularization Temporal Regularization

## **Innovation 2– Masking**



### **Innovation 3– Data-driven dynamic update of Regularization Parameters**

$$argmin\{\|SCf - p\|_{w}^{2} + /_{1}O(c) + /_{2}W(C) + /_{3}F(f)\}$$

• Weighting parameters are dynamically updated at each iteration by:  $\|SC^{[k]}f^{[k]} - p\|^2$ 

$$\int_{1}^{[k+1]} \frac{1}{g^{[k]}} \frac{\|SC^{[k]} - P\|_{w}}{Q(c^{[k]})}$$

$$\int_{2}^{[k+1]} \frac{1}{g^{[k]}} \frac{\|SC^{[k]} f^{[k]} - p\|_{w}^{2}}{W(c^{[k]})}$$

$$\int_{3}^{[k+1]} \frac{1}{g^{[k]}} \frac{\|SC^{[k]} f^{[k]} - p\|_{w}^{2}}{F(f^{[k]})}$$

• Where  $\underline{\gamma^{[k]}}$  is estimated by:

$$\mathcal{Q}^{[k]} = \mathcal{G}_0 \sqrt[4]{\frac{\left\|SC^{[k]}f^{[k]} - p\right\|_w^2}{0.05 \left\|p\right\|_w^2}}$$

I. Kazufumi et. al., 2011.

## **SIFADS** Algorithm

#### SIFADS Algorithm //STEP 1: Initialization: Spectral //B-Splines fitting 1: $f^0 \leftarrow \{B - Spline functions\};$ 2: $C^0 \leftarrow 0;$ 3: $C^1 \leftarrow \arg\min_c \left\{ \left\| SC^0 f^0 - p \right\|_w^2 \right\}$ // Estimating initial Curves and Coefficients: nitial Guess Preparation 4: $V(t) \leftarrow C^1 f^0;$ 5: $f^1 \leftarrow Ave(segment(V(t));$ 6: $C^2 \leftarrow \arg\min_{C} \left\{ \left\| SC^1 f^1 - p \right\|_w^2 + \lambda_1 \Theta(C^1) + \lambda_2 \Omega(C^1) + \lambda_3 \Phi(f^1) \right\}$ // STEP 2: FADS Refinement Refinement 7: $(C^*, f^*) \leftarrow \arg\min_{C} \left\{ \left\| SC^2 f^1 - p \right\|_w^2 + \lambda_1 \Theta(C^2) + \lambda_2 \Omega(C^2) + \lambda_3 \Phi(f^1) \right\}$ FADS // Estimate and Output Final Curves: $V(t) \leftarrow C^* f^*;$ 8: $f \leftarrow Ave(segment(V(t));$ 9:

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## MAP Algorithm for coefficients estimation

$$C \leftarrow 1;$$
  
for i = 1 to N do  

$$U(C^{[i]}) \leftarrow \lambda_1 \Omega(C^{[i]}) + \lambda_2 \Theta(C^{[i]});$$

$$\nabla U(C^{[i]}) \leftarrow \frac{\partial U}{\partial C^{[i]}};$$

$$C^{[i+1]} = \frac{C^{[i]}}{\sum Sf + \nabla U(C^{[i]})} \sum \frac{P}{\sum SC^{[i]}f} Sf;$$
end for  
return C

## MAP Algorithm for coefficients and factors estimation

for i = 1 to N do // Coefficient minimization:  $U_1(C^{[i]}) \leftarrow \lambda_1 \Omega(C^{[i]}) + \lambda_2 \Theta(C^{[i]});$   $\nabla U_1(C^{[i]}) \leftarrow \frac{\partial U_1}{\partial C^{[i]}};$  $C^{[i+1]} = \frac{C^{[i]}}{\sum Sf^{[i]} + \nabla U_1(C^{[i]})} \sum \frac{P}{\sum SC^{[i]}f^{[i]}} Sf^{[i]};$ 

$$\begin{array}{l} \text{// Factor minimization:} \\ U_2(f^{[i]}) \leftarrow \lambda_3 \Phi(f^{[i]}); \\ \nabla U_2(f^{[i]}) \leftarrow \frac{\partial U_2}{\partial f^{[i]}}; \\ f^{[i+1]} = \frac{f^{[i]}}{\sum SC^{[i+1]} + \nabla U_2(f^{[i]})} \sum \frac{P}{\sum SC^{[i+1]} f^{[i]}} SC^{[i+1]}; \\ \text{end for} \\ \text{return } C, f \end{array}$$

## **Validation with Simulation**

#### Coefficients used for simulation (NCAT phantom) 0.4 Blood Cavity +Myocardium Blood Pool Liver Activity 7.0 Myocardium NCAT Phantom 0 21 1 11 31 41 51 71 81 61 Time Sec. Liver

#### Generated projections with Poisson noise



### **Results: Drawback of Pure Spline-method**



#### Drawback:

Very sensitive to initial time basis function

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#### **Results: Drawback of Arbitrarily Initialized FADS-method**

Blood Cavity

Mvocardium

\*Liver





41 51 61 71 81

Time Sec.



$$\arg\min_{c,f} \left\{ \left\| SCf - p \right\|_{w}^{2} + \operatorname{Reg} \right\}$$

Drawback: Very sensitive to initialization

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### **Spline vs. SIFADS results**



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## **FADS vs. SIFADS Results**



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## **Real Data: Rat heart**

- Dynamic, pinhole SPECT study, rat's heart
- Collimators:1.5×2 mm tungsten pinholes
- GE VG3 Millennium Hawkeye camera
- Acquisition started with injection of 7 mCi <sup>123</sup>I-MIBG
- 30 rotations, 90 one-second views, per rotation
- Detector pixel: 4.42 mm, recon voxel 0.8 mm



#### Original projections:

## **Results from the Rat Study**



## Estimated rat TACs from the first inconsistent rotation:

## Estimated projections by forward projecting dynamic reconstruction:





**RAT TACs** 

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## **Results from a Canine Study**

- GE Millennium VG3Hawkeye SPECT/CT camera
- Two detectors, H-mode, parallel LEHC collimators, 4.42 mm pixel resolution
- <sup>99m</sup>Tc-teboroxine stress study of a canine subject
- 24 rotations, 72 one-second views per rotation



## **Summary on SIFADS**

- Segmentation according to TACs
- Several regularization functions proposed and imposed using anatomical information.
- Hybrid optimization procedure (SIFADS) developed to reduce the initialization issue

TACs as a new biomarker?

#### Primal-Dual (PD) Optimization - to improve efficiency: Canine study

#### MLEM

#### **Conjugate Gradient**

PD







#### **Convergence:**







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Chen S, Pan H, Abdalah M, Boutchko R, Mitra D, and Gullberg GT. (2014) "Image reconstruction with a primal-dual algorithm," SNMMI, Seattle, Washington

2D x t

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#### FRET: Fluorescence Resonance Energy Transfer New Technology for quantifying gene expression in live single cells



 $\frac{A(i) - F^{D}(i) \cdot R_{D} - F^{A}(i) \cdot R_{E}}{F^{A}(i)}$  $E_A(i) = \frac{r}{r}$ 

Three channels for each Time-frame: Donor emission ( $F^D$ ), Acceptor Emission ( $F^A$ ), D-to-A Excitation emission ( $F^{DA}$ )

> "Imaging biochemistry inside cells" TRENDS in Cell Biology, 11(5): 203-211, 2011 Wouters, Verveer and Bastiaens



Input: Frames of the time-lapsed 2D image from a confocal microscope



Output: Same frames after tracking by scale-space segmentation

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Scale Space Algorithm: Handles varying sizes of cells

Problems: Live cells move in 3D – across the frame, in-out of focal plane; cells also divide!

How to track a cell from frame to frame?

Semi-solved ("threading"): Search around a cell in next frame for similar average intensity



Tracking a cell from frame to frame by threading algorithm



A sample cell's average intensity variation over time-lapsed frames. Three colored curves represent three channels:

Cy3 excitation-Cy3 emission, Cy5 excitation-Cy5 emission, and Cy3 excitation-Cy5 emission.

SPIE Medical Imaging Conference, February 2015, Orlando, Debasis Mitra, Rostyslav Bouthcko, Judhajeet Ray, and Marit Nilsen-Hamilton

### **Rigid Motion in SPECT Projections**

Project 4

Conventional Perfusion studies with Static Imaging: Step and shoot mode, consistent projection, but patient moves during scan



**Motionless Dataset** 

**Motion-Corrupted Dataset** 4/15/2016 • 50

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## **Corrections for motion with** SinoCor



Eiland D, Mitra D, Abdalah M, Butchko R, and Gullberg GT. (2012) "SinoCor: Inter-frame and Intra-frame motion correction tool," Conf. Record IEEE Nuclear Science Symposium and Medical Imaging Conference, Anaheim, CA.

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## Future

#### Improving Algorithm:

- Optimization (Primal-Dual)
- Parallelization (using High-performance Computing)
- Removing Manual Intervention: Automatic Segmentation for Masking
- Better basis function (Spline-Wavelet)
- Motion compensation
  - Rigid motion of patient (SinoCor)
  - Beating heart (Blind deconvolution)
  - Respiratory motion (Rank optimization)

# Multiple-modality data-fusion for better reconstruction in both

- Machine learning (Cross-modality reconstruction with prior knowledge infusion across different modalities)
- Data management to keep track of metadata across modalities (Research Medical Imaging database: ReMI.lbl.gov)

### Imaging Beyond Medicine: Problems with similar mathematics -

Linear Algebra, Statistics, Numerical Optimization, ...

Spread the cost of imaging research across multiple agencies

• Muon tomography:

cosmic ray-generated muon scattered from heavy metals

• Cosmology:

Structure of universe from telescopic observations

• Electron Microscopy:

3D view of a virus or molecule, & in action

• Seismic:

Acoustic waves from earthquake or artificial source to study subsurface structure & activities

#### Quantifying nuclear threats with muon tomography algorithms Kim Day

Faculty Advisor: Dr. Debasis Mitra, Dept. of Computer Science, Florida Institute of Technology

#### Abstract

The Florida Tech High Energy Physics Group A led by Dr. Marcus Hohlmann has been developing a prototype muon tomography station (MTS) for identifying shielded nuclear materials. The MTS typically requires days of data taking in order to reconstruct objects. Since waiting for days will not be an option in practical use, this study focused on developing algorithms that could work with small amounts of data for identifying suspect materials. Focus was put on finding "clear" areas that did not contain high density materials. The algorithm was able to identify a 2cm block of uranium in the prototype station within an hour's worth of data.

#### Motivation

- Millions of packages enter the US every day, but only a small percentage can be scanned without slowing down the process.
- Nuclear material smuggling can be easily done by using lead shielding to hide the radiation.
- There is a need for a method that can see through lead shielding without being intrusive or time consuming.

#### About muon tomography

- Muon tomography is a 3D visualization method that uses naturally occurring muon showers to reconstruct objects.
- When a muon passes through a dense material, it will scatter slightly in its trajectory.
- A muon tomography station (MTS) can record the incoming and outgoing paths of all the muons that pass through it.
- The point of scattering can be found by finding where the incoming and outgoing rays intersect.
- Analyzing the high-angle scattered points will show where the densest materials are.
- A prototype cubic foot detector has been built at Florida Tech (figure 1).

#### Algorithm description

- The algorithm divides the volume inside the station into an array of voxels (3D pixels). Then, it counts the number of straight muon tracks that pass through each voxel.
- Since muons will pass straight through clear areas without scattering, voxels that contain a high straight track count are more likely to be clear of nuclear material.
- Scattered tracks were also used to show which voxels contained scattered points (less likely to be clear).



Figure 1 (left): The Florida Tech prototype cubic foot muon tomography station (left) Figure 2 (right): Visualization of the voxel grid inside the station. The green voxels are more likely to be clear since a straight track passes through them, while the red voxel is less likely since it contains a scattering point.

#### Sources

US Customs and Border Protection cargo security http://www.cbp.gov/border-security/ports-entry/cargosecurity

Los Alamos initial research paper on muon tomography http://scienceandglobalsecurity.org/archive/sgs16morris.p

#### Findings

- Tested on the "5 target" scenario: an arrangement of five 2cm blocks of different densities (figure 3).
- Able to see high density materials (Z >= 50) with 1 hour's worth of data taking (6000 tracks, figure 4).
- Taking data for 2-3 hours (12000/18000 tracks, figures 5-6) allowed for visualizing the shapes of the blocks.



**Figure 3 (left):** The "5 target" arrangement of 2 cm blocks (lead, tungsten, tin, iron, and uranium). **Figure 4 (right):** 2D output of the algorithm showing a horizontal slice through the center of the blocks after 1 hour. Red = threat, green = clear, blue = unknown.



Figures 5 & 6: Output of the algorithm using 2 hours (left) & 3 hours (right) of

#### Conclusion

The clearing algorithm developed for this project was able to identify high density blocks and narrow down much of the search area using 1 hour of data. This is promising for practical use, although the algorithm still requires work on noise reduction and parallelization for increasing the analysis speed. ACKNOWLEDGEMENT:

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### Data Management for Raw Acquisition Data: remi.lbl.gov

#### **RELATIONAL META-DATABASE**

#### Metadata Structure

- information on imaging technology and protocol
- information about subject
- data source information
- content specifications
- Core Entity: Experiment



#### <u>System</u>

**Architecture** 

#### **Privacy and Security**

- all patient-identifying data are removed before the upload
   upload only by registered users using secured protocols
- upload only by registered users using secured protocols

### Improving Efficiency with GPU: MLEM with Simulation data

256 <sup>2</sup> x 60 SPECT sinogram with 1 pinhole	Ray tracing (sec)	Average per iteration (sec)	Average forward projection (sec)	Average back projection (sec)	Total reconstruction (sec)	Normalized- mean-sqr difference: CPU to GPU images
CPU	2.13	5.91286	1.95625	2.8691	1188.41	
GPU	0.529756	0.286561	0.0951198	0.110944	60.1003	
Ratio CPU/GPU	4.02	20.633	20.56617	25.86	19.773	1.67
128 <sup>2</sup> x 60 SPECT sinogram with 4 pinholes						
CPU	7.34	3.979	1.564	2.044	49.51	
GPU	0.797533	0.0920357	0.0426326	0.0474005	4.01172	
Ratio CPU/GPU	9.203	43.233	36.685	43.121	12.341	1.65
128 <sup>2</sup> x 600 CT sinogram						
CPU	5.32	33.1364	10.169	19.081	340.79	
GPU	0.415884	0.818518	0.306646	0.477997	26.88	
Ratio CPU/GPU	12.792	40.483	33.16	39.9186	12.678	1.57

### **Reducing communication with CPU** improves speed



Reorganizing data over local memory has further improved a reconstruction time from 30.55 sec to 24.84 sec

We plan further improvement by holding more data longer time on local memory



# Thanks Questions

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