# Modeling Approaches to Cardiac Perfusion Determination

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## Outline

- Myocardial Perfusion – Introduction
- Model-based Analysis of Time Curves
  - Dynamic PET
  - Dynamic MRI
- Model-based Blind Estimation of the Input Function
- Model-based Reconstructions



## Introduction

- Up to 85% coronary stenosis, no reduction in resting perfusion
- Perfusion Reserve: Ratio of "stress" perfusion to rest (baseline) perfusion
- X-ray angiography the gold standard for atherosclerotic disease? (WISE study, JACC, Feb. 2006)



## Introduction

**Echo**: Contrast agents, limitations.

**SPECT**: Over 8 million perfusion scans annually, ~80/80%

**PET**: Best established method.

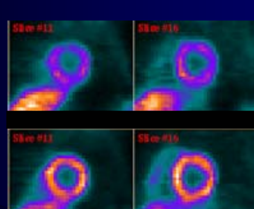
**MRI**: Possibility for subendocardial flow measurements. Usage increasing.



## Dynamic PET – summed frames

Rest

Adenosine Stress





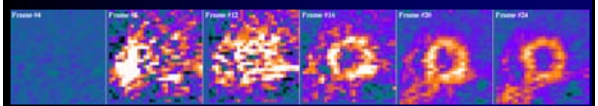
## Tracer Kinetics

How is perfusion measured from an injected tracer?

Characteristics of the tracer
- Extraction fraction
- Metabolism/diffusion
- Microspheres, the gold standard

Determinants of perfusion. A function of:
- Rate pressure product
- Capillary recruitment
- Coronary stenoses
- Microvascular disease

## Example of time series images



5 sec 5 sec 5 sec 10 sec 30 sec 30 sec

**Dynamic ammonia PET**

**5 second to 60 second time frames**



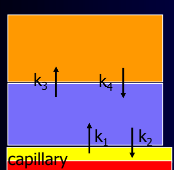
## Quantitating Perfusion

Quantitative imaging of regional cardiac perfusion (ml/min/g) valuable for assessment of coronary artery disease

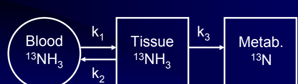
Why better?
- 3 vessel disease
- Longitudinal and population studies
- Inadequate stress
- Can be more sensitive
- Can be more robust



## Model for Ammonia, $^{13}NH_3$

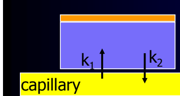



- Tissue - metabolized
- Tissue – free ammonia
- Vascular – free ammonia
- Vascular - metabolized






## Two Compartment Model



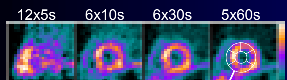

- Tissue - metabolized
- Tissue – Free ammonia
- Vascular – free ammonia ($C_b$)
- Vascular - metabolized

$$\frac{dC_t}{dt} = k_1 C_b - k_2 C_t \qquad k_1 = EF$$

$$C_t(t) = C_b \otimes k_1 e^{-k_2 t}$$

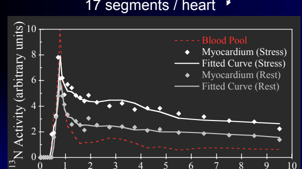


## Dynamic PET & Quantification of Myocardial Blood Flow




$$C_t(t) = (1-V_b)C_b \otimes k_1 e^{-k_2 t} + V_b C_b$$

17 segments / heart



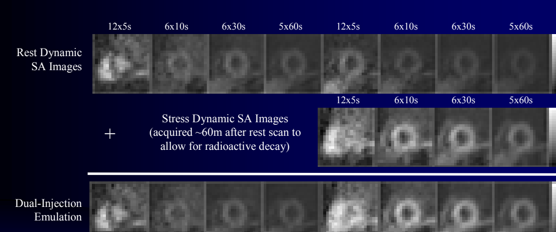

MBF estimates (mean ± s.d.)

| | Rest | Stress |
|---|---|---|
| Subject #1 | 1.00 ± 0.20 | 3.35 ± 0.77 |
| Subject #2 | 0.74 ± 0.20 | 2.10 ± 0.39 |
| Subject #3 | 1.23 ± 0.16 | 4.88 ± 0.57 |
| Subject #4 | 0.93 ± 0.14 | 2.70 ± 0.70 |

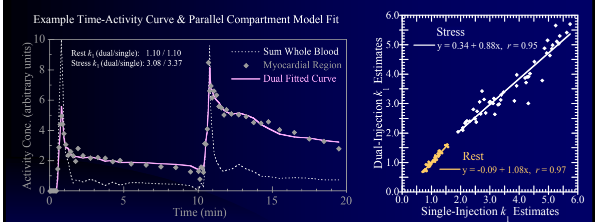
Coronary flow reserve (3.31 ± 0.75)



## Rapid rest/stress Ammonia PET



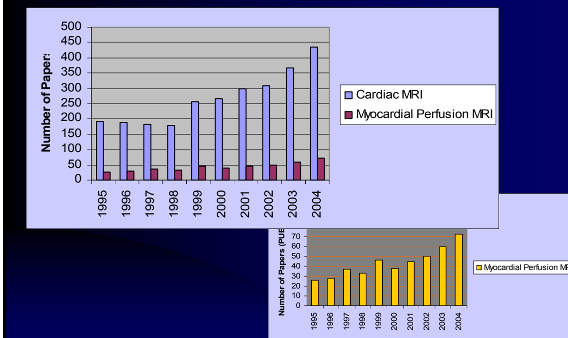
## Rapid rest/stress Ammonia PET




A Rapid Dual-injection Method for Quantification of Rest and Stress Myocardial Blood Flow using 13N-Ammonia PET
TC Rust; EVR DiBella; CJ McGann; PE Christian; JM Hoffman; DJ Kadrmas. Submitted to Soc Nucl Med 2006.

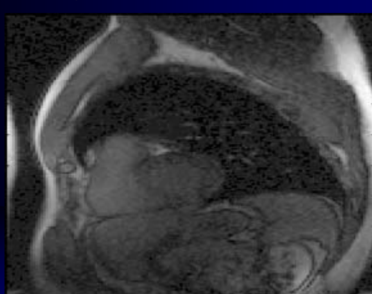


## Cardiac MRI



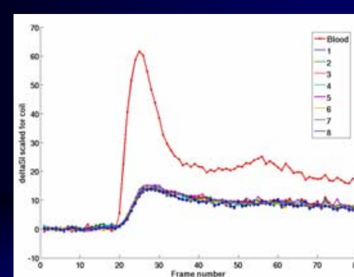



## Example of dynamic contrast MRI perfusion, 3T





## Myocardial Perfusion with Contrast MRI






## Dynamic Contrast MRI

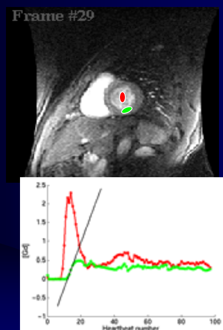
- Inject paramagnetic Gd-DTPA I.V. rapidly
- Acquire image per slice every heartbeat
- Extract regional time-varying signals
- Assume physiological model with parameters that can be related to local blood flow
- Fit contrast concentration as a function of time to the model; kinetic parameters (may) give flow.



## Challenges

1. Acquisition
   Temporal constraints
   Sequences, uniformity, poor SNR, motion, ECG issues
2. Processing
   Registration, segmentation to get 1D time curves
3. Modeling
   Conversion to Gd concentration
   Compartment models
   Input function

## Upslope model

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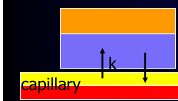
## Two Compartment Model




- Tissue - Intracellular
- Tissue - Interstitial ($C_{is}$)
- Vascular - plasma ($C_p$)
- Vascular - red blood cells (Hct)

$$\frac{dC_{is}}{dt} = kC_p - kC_{is}$$

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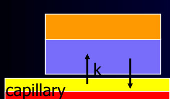
## Distribution volume




- Tissue - Intracellular
- Tissue - Interstitial ($C_{is}$)
- Vascular - plasma ($C_p$)
- Vascular - red blood cells (Hct)

$$\frac{dC_t}{dt} = k_1 C_p - k_2 C_t$$

$$k_2 = \frac{k_1}{v_e} \qquad v_e = \frac{C_t}{C_b}(1 - Hct)$$

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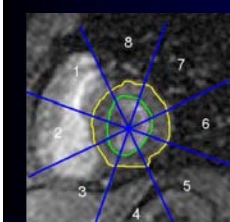
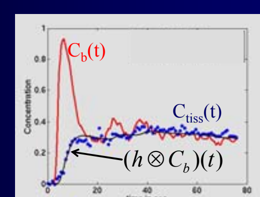
## Fit to Compartment Model




"Standard" division of left ventricle into 8 regions.




Example compartment model fit to regional time curve

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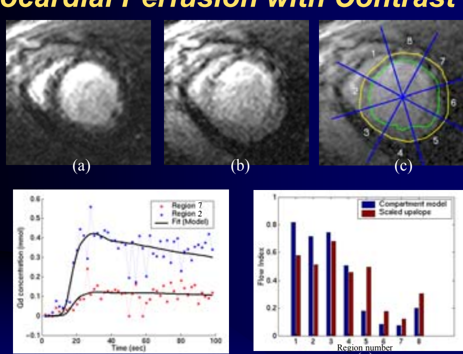
## Myocardial Perfusion with Contrast MRI

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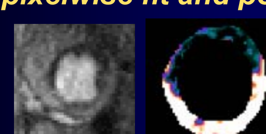
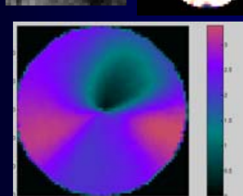
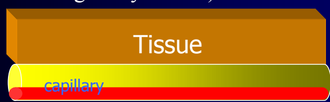
## Stress pixelwise fit and polar map





## Axial concentration gradient

Johnson-Wilson Model (JW Model). (Also called Tissue Homogeneity Model)




Vascular - plasma ($C_p$)

Vascular - red blood cells (Hct)

$$h(t)=\begin{cases} F & t<T_c \\ EFe^{(-EF(t-T_c)/v_e)} & t\ge T_c \end{cases}$$

$T_c$ = capillary transit time = $v_p/F_p$

St. Lawrence and Lee, *J Cerebral Blood Flow and Metab* 18:1365-1377, 1998.

## Different Models

$$C_t(t)=(1-p)\underline{K^{trans}\exp^{-(K^{trans}/v_e)t}\otimes C_b(t-t_0)}+V_bC_b(t-t_0)+pC_b(t)$$

$C_t(t)$ is the signal difference from the tissue of interest

$C_b$ is the signal difference from a region chosen in the left ventricular blood pool

$V_b$ is the (fractional) amount of blood signal from vasculature in the tissue

$t_0$ is a delay term

$p$ is the fraction of signal from the left ventricular blood pool that appears in the tissue region of interest

## Different Models

$$C_t(t)=(1-p)K^{trans}\exp^{-(K^{trans}/v_e)t}\otimes C_b(t-t_0)+V_bC_b(t-t_0)+pC_b(t)$$

#1 is a compartment model with all terms, #2 Same, $V_b=0$ and $p=0$

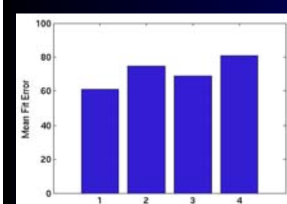
#3 Same as #1 but only a single delay term and $p=0$

#4 Fermi $\quad C_t(t)=\dfrac{F}{\exp^{k(t-T)}+1}\otimes C_b(t-t_0)$

#5 Upslope

E. DiBella, N. Pack, C. McGann "Kinetic models and blood signal modeling for dynamic cardiac MRI perfusion studies", to appear ISMRM 2006.

## Comparison of Models



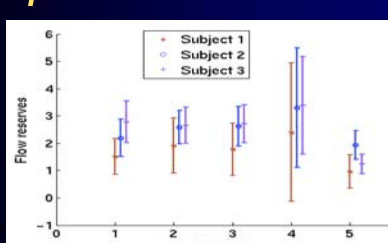


#1 is a compartment model with all terms, #2 is the same but $V_b=0$ and $p=0$, #3 is the same as #1 but only a single delay term and $p=0$, #4=Fermi.

Averaged over the rest and stress flows in the 6*3*3=54 regions and does not use the flow reserve data.

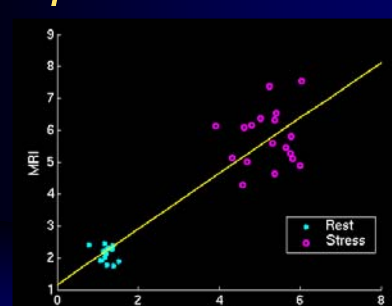


## Comparison of Models

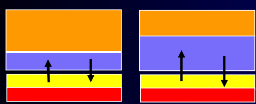





## Comparison of MRI and PET



## Infarct - volume of distribution changes

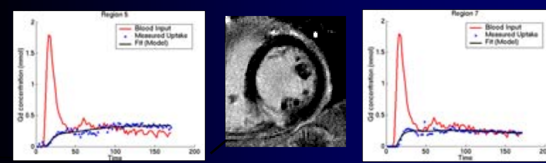



- Tissue - Intracellular
- Tissue - $v_e$
- Vascular - plasma ($C_p$)
- Vascular - red blood cells

$$\frac{dC_t}{dt} = k_1 C_p - k_2 C_t \qquad k_2 = \frac{k_1}{v_e}$$

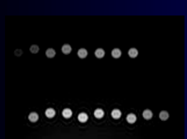


## Myocardial viability

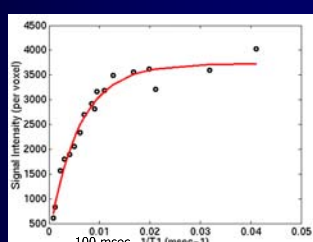




## Part 2: Input Function



Vials in a water bath

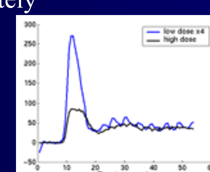



[Gd] = (1/T1 - $1/T1_{init}$) / R



## Arterial Input Function

- Measuring $C_p(t)$ accurately
  - Saturation
  - Flow effects




- Dynamic PET and SPECT
  - Blood binding
  - Temporal sampling

## Cross Relations

Xu et al. IEEE TSP Dec. 1995.

$$y_1(t) = b(t) \otimes h_1(t)$$
$$y_2(t) = b(t) \otimes h_2(t)$$
$$h_2(t) \otimes y_1(t) = \underbrace{h_2(t) \otimes b(t)}_{} \otimes h_1(t)$$
$$y_1(t) \otimes h_2(t) = y_2(t) \otimes h_1(t)$$
$$y_m(t) \otimes h_n(t) = y_n(t) \otimes h_m(t)$$



## Frequency Domain perspective

$$Y_1(v) = H_1(v) C_p(v)$$

$$Y_1(v) H_2(v) = Y_2(v) H_1(v)$$
$$Y_1(v) H_3(v) = Y_3(v) H_1(v)$$
$$Y_2(v) H_3(v) = Y_3(v) H_2(v)$$

- # of independent equations $\approx T(M-1)$
- Importance of blood input frequencies

## Theory, continued

- Not possible to solve uniquely as is

$$Y_1(v)/Y_2(v) = H_1(v)/H_2(v)$$

## Solution: Parameterize h()

- Two compartment model

$$y(t) = b(t) \otimes k_1 \exp(-k_2 t)$$



## Limitations of Approach

- Scale factor:

$$y_1(t) \otimes sh_2(t) = y_2(t) \otimes sh_1(t)$$

- Conditions on input
  - Blood input must have sufficient spectral components
- Conditions on *h()* (different)



## Advantages

- No blood sampling or blood ROI selection or associated corrections needed
- May permit larger doses, giving increased SNR
- May allow for relaxation of temporal sampling requirements



## Implementation

Constrained optimization

$$y_1(t) \otimes h_2(t) - y_2(t) \otimes h_1(t) = 0$$

$$\min \sum_{m,n} \left\| y_n \otimes k_1^m e^{-k_2^m t} - y_m \otimes k_1^n e^{-k_2^n t} \right\|^2$$

E.V.R. DiBella, R. Clackdoyle, and G.T. Gullberg 1999 "Blind Estimation of Compartmental Model Parameters", *Phys. Med. Biol.*, 44(3) 765-780.



## Matrix vector form

$$y_m = \mathbf{H}_m \mathbf{b} + \boldsymbol{\varepsilon}_m$$

$$\mathbf{H}_m = \begin{bmatrix} h_m(0)\ 0 \ldots & \\ h_m(1)\ h_m(0) \ldots. & \\ \vdots & \end{bmatrix}$$

$$\mathbf{y} = \mathbf{H}\mathbf{b} + \boldsymbol{\varepsilon}$$

D. Y. Riabkov and E. V. R. DiBella, "Estimation of kinetic parameters without input functions: Analysis of three methods for multichannel blind identification," *IEEE Trans Biomed Eng*, vol. 49, pp. 1318-1327, 2002.



## Model-based Blind Estimation

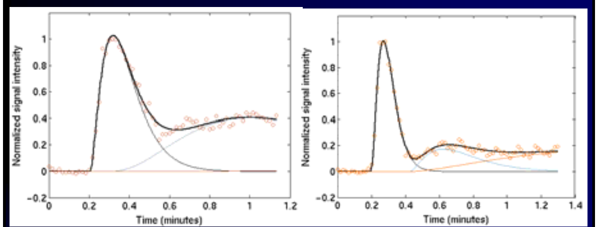
$$\underset{\mathbf{H},\mathbf{b}}{\arg\min} \left\| \mathbf{y} - \mathbf{H}\mathbf{b} \right\|_2^2$$

Parameterize "model" b:

$$b(t) = \sum_{i=1}^{3} S_{0_i} \frac{t^{\alpha_i} e^{-t/\tau_i}}{e^{-\alpha_i} (\tau_i \alpha_i)^{\alpha_i}}, t > \Delta_i$$

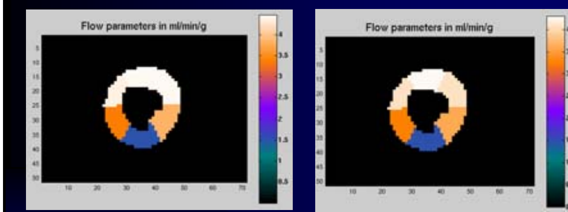
$$b(t) = 0, t < \Delta_i$$

## Arterial Input Function Model






## Model-based Blind Flow Estimation




AIF peak $S_{01}$ set to 170. Closed chest canine study at stress, 3T scanner



## Part 3: Model-Based Reconstruction

Want faster acquisition

- Improved coverage of LV
- Improved resolution
- Fewer motion artifacts
- Don't want to give up SNR



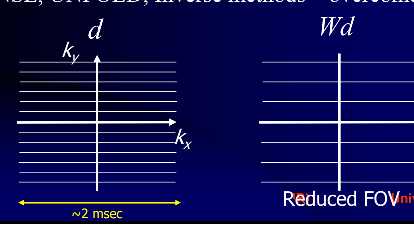
## Rapid imaging – reduced FOV

Standard Cartesian imaging

Frequency encoding ($k_x$) - fast

Phase encoding ($k_y$) – slow

SENSE, UNFOLD, Inverse methods – overcome aliasing






## Model-Based Reconstruction

$$m = \arg\min\left[\left\|WFm - Wd\right\|^2 + \alpha\sum_{r=1}^{N_m}\nabla_t m_r^2\right]$$

m - image (all frames)

d - frames in k-space

F - Fourier transform

W- weighting function describing data reduction

$N_m$ - number of total pixels

$$or\ \ \alpha\sum_{r=1}^{N_m}\frac{\nabla_t m_r^2}{\nabla_t m_r^2+\gamma^2}$$

Done independently for each coil; could combine with multi-coil speedup methods.

Portniaguine O, Bonifasi C, DiBella E, Whitaker R. Inverse methods for reduced k-space acquisition. *Proc. Intl. Soc. Mag. Reson. Med.*, p. 481, Toronto, Canada; 2003.

*Heart image*

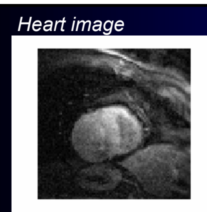
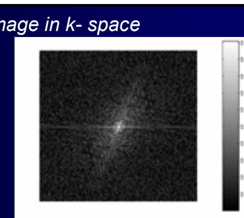
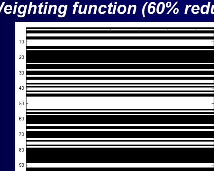


*Image in k- space*



***Weighting function (60% reduction)***



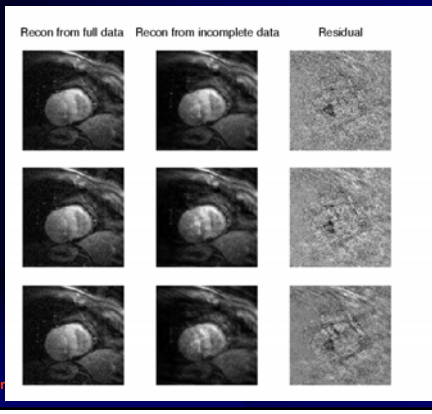
## Comparison of originals and reconstructions (2)

Level of Discard

80%

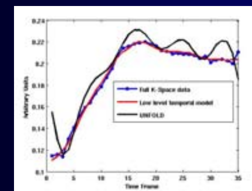
90%

95%



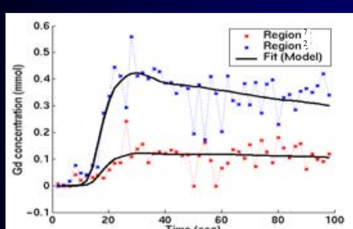

Utah Center for

## Model-based Reconstruction




Full k-space | Temporal Model, R=4 | UNFOLD, R=4

## Model-based Registration




Use model fit to estimate rigid translations

## Alternate (linear) formulation

$$\frac{dC(t)}{dt} = K^{trans} C_p(t) - \frac{K^{trans}}{v_e} C\ (t)$$

$$C(t_i) = K^{trans} \int_0^{t_i} C_p(\tau)d\tau - \frac{K^{trans}}{v_e} \int_0^{t_i} C(\tau)$$

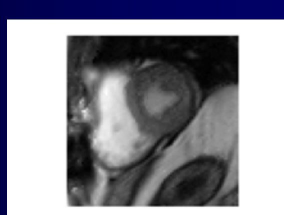
$$A = \begin{bmatrix} \int_0^{t_1} C_p(\tau)d\tau & -\int_0^{t_1} C(\tau)d\tau \\ \int_0^{t_2} C_p(\tau)d\tau & -\int_0^{t_2} C(\tau)d\tau \end{bmatrix}$$

$$C = AK$$

*Murase MRM 51:858-862, 2004*

## Model-based Registration

Original post-contrast frame



Model-based image

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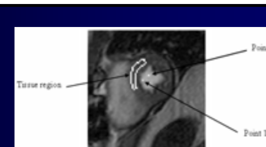
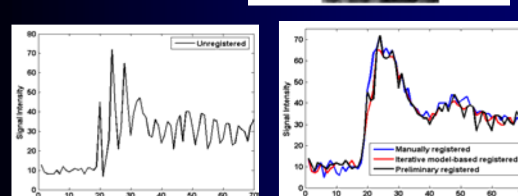
## Model-based Registration



## SUMMARY

- Modeling is an essential part of quantitative myocardial perfusion
  - Rich literature on modeling approaches for cardiac perfusion
- Using a model of the input function may improve blind estimation of kinetic model parameters
- Model-based reconstruction of sparse perfusion data can offer significant advantages



## Students, Post-docs and Collaborators

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