Kinetic Model Based Factor Analysis of Cardiac $^{82}$Rb PET Images for Improved Accuracy of Quantitative Myocardial Blood Flow Measurement
Prologue

It wasn’t always like this. There were times when Jack’s heart was content. It was only in recent weeks that he started to sense that yurning - that desire. At first it was distant. It left him breathless. As the weeks rolled by the sensation became stronger and more frequent. Now it was impossible to ignore. Jack’s heart was not getting enough... blood.

- Coronary arteries deliver blood to the myocardium (heart muscle).
- Stenosis can lead to reduced blood supply, reduced heart function, damaging of heart muscle, and death.
- Coronary artery disease is the largest single cause of death in western society.

www.daviddarling.info/images
Jack is referred for a myocardial perfusion imaging (MPI) exam:

- Radioactive labeled material (tracer) is injected intravenously (e.g. $^{82}\text{Rb PET}$).
- After several minutes an image of the tracer distribution is acquired.
- Jack’s heart is then stressed (exercise / drug) and imaging is repeated.
- The images are then interpreted by a specialist doctor.
Dr. Heart receives Jack’s MPI data for interpretation. He follows a well rehearsed method:

- Reorient images to a standard left ventricle (LV) reference frame.
- Locate brightest region (highest uptake) and assume normal perfusion.
- Identify regions with reduced stress uptake as ischemic (reduced blood supply).
- Compare rest and stress images to interpret severity of stenoses.
Myocardial Perfusion Imaging

Normal

Short Axis (SA)
- Stress
- Rest

Vertical Long Axis (VLA)
- Stress
- Rest

Horizontal Long Axis (HLA)
- Stress
- Rest
Myocardial Perfusion Imaging

Myocardial Ischemia

Short Axis (SA)
Stress
Rest

Vertical Long Axis (VLA)
Stress
Rest

Horizontal Long Axis (HLA)
Stress
Rest
Quantitative MBF can detect multi-vessel disease and distributed disease of the micro-vasculature.
Description of highly automated MPI and MBF processing software.

Assessment of operator dependent variability for MPI, MBF, and flow reserve.

Image Reorientation

Camera reference frame

LV reference frame
LV + Blood Pool Segmentation

File p301
Study: p301-Rest.mat
SA angle: 0° (preset)
Kinetic Modelling

UPTAKE = 7e+004
FLOW = 1.1
K1 = 0.62
TBV = 0.46

High uptake regions

Activity [Bq/cc] vs Time [minutes]

K1 = 0.62 ± 0.012
TBV = 0.44 ± 0.01
Renkin-Crone

\[ K_1 = (1 - a \cdot e^{-b/MBF}) \cdot MBF \]

\[ C_m(t) = (1 - TBV)C_t(t) + TBV \cdot C_a(t) \]

\[ \frac{dC_t(t)}{dt} = K_1 \cdot C_a(t) - k_2 \cdot C_t(t) \]

\[ C_t(t) = C_a(t) \otimes m(t) \]

\[ m(t) = K_1 e^{-k_2 t} \]
Coronary Flow Reserve

Stress

Rest

Patient Name: Anonymous  08-Jul-2008

stressRubidium Flow

Defect Size: 202 (40.7% of LV)
Defect Mean: 1.05 (34.9% of max)
Defect Min: 0.343 (11.5% of max)
Defect Location: mid inferolateral
LV Mean: 2.02, LV Median: 2.4

stressRubidium / restRubidium

Defect Size: 270 (54.4% of LV)
Defect Mean: 1.8 (48.1% of max)
Defect Min: 0.507 (13% of max)
Defect Location: mid inferolateral
LV Mean: 2.63, LV Median: 2.83

restRubidium Flow

Defect Size: 314 (63.3% of LV)
Defect Mean: 0.646 (62% of max)
Defect Min: 0.449 (43.1% of max)
Defect Location: mid inferolateral
LV Mean: 0.753, LV Median: 0.728

stressRubidium - restRubidium

Defect Size: 240 (48.4% of LV)
Defect Mean: 0.566 (26.8% of max)
Defect Min: -0.336 (-15.9% of max)
Defect Location: mid inferolateral
LV Mean: 1.27, LV Median: 1.62
Operator Dependent Variability

Image Set (30 Rest+Stress Pairs)

Randomize

Operator 1
- Set1
- Set2

Intra-operator 1 (novice)

Operator 2
- Set1
- Set2

Intra-operator 2 (expert)

Inter-operator

- Rest MBF
- Stress MBF
- Stress MBF / Rest MBF
- Stress MBF - Rest MBF

Inter-Operator Stress MBF

RPC: 0.052 (2.3%)
CV: 1.2%

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Model Based FADS for Improved MBF Quantification

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• Experienced operator had less variability than novice operator.
• Stress-Rest less variable than stress/rest.
Conclusion

- Excellent operator dependent variability.
  - Comparison with reported results using other software programs
- Reduced variability with experience.
  - Need to train users, but fast learning curve.
- Importance of reports for quality assurance.
  - Ensuring that results are reliable.
- To Jack:
  - MBF quantification can detect multi-vessel disease + microvascular disease.
  - Diagnosis is not sensitive to operator variability.
Spillover Signal Contamination

Time Activity Curves

Activity (Bq/ml)

Time (min)

Myocardium
LV Blood
RV Blood

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Constrained Factor Analysis (Chapter 3)


- Description of new Minimal Factor Overlap factor analysis (MFO).
- Comparison of MFO to previously published Minimal Spatial Overlap factor analysis (MSO)
Factor Analysis

Structures  Factors

Recomposed Image Sequence

\[ \sum \]

Residue

Raw Image Sequence

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Image decomposition is not unique!

- Additional constraints must be imposed.
  - Constraints should be representative of physical and physiological processes to ensure accurate solution.

Typical Constraints include:

- Non-negative factors and structures
- Minimal Structure Overlap (MSO)
  - Overlooks existence of arterial blood in the myocardium (tissue blood volume) and spillover due to limited spatial resolution.

Proposed Minimal Factor Overlap (MFO)

- No strict physiologic evidence to support assumption of maximally different temporal responses.

Physiologically accurate constraints still needed.
Kinetic Model Based Factor Analysis (Chapter 4)


➢ Description of new kinetic model-based factor analysis (MB).
➢ Comparison of MB to previously published minimal spatial overlap factor analysis (MSO)
RA+RV blood flows through the lungs en route the LA+LV resulting in a delay and mixing.

- Can be described by a Shifted – Gamma Variate Response Function

* K. Iwata, JNM, 1988 and M. T. Madsen, PMB, 1992
Blood from the LV flows to the myocardium (and other tissues)
- Can be described by an appropriate kinetic model
Instead of resolving 3 factors

3 X (17 time frames – 1) = 48 parameters

We can resolve

1 X (17 time frames – 1)

+ 2 parameters (gamma-variate function)

+ 1 parameter (1 compartment model)

Factors are tightly coupled.

More control over which factors are resolved.
**MSO and MB Factor Analysis**

**MSO**

Step 1 – Decomposition

\[
C_{MSO} = W_E |\epsilon| + W_{NF} f_{neg}(F') + W_{NS} f_{neg}(S')
\]

Step 2 – Rotation (MSO constraint)

\[
f_{tot}^{MSO} = f_{neg}(F'R') + f_{neg}(R'^{-1}S') + bf_{ovl}(R'^{-1}S')
\]

\[
f_{ovl}(X) = \sum_{p=1}^{P} \sum_{q=p+1}^{P} \sum_{i=1}^{N} \frac{x_{ip}}{\sqrt{\sum_{j=1}^{N} x_{jp}^2}} \frac{x_{iq}}{\sqrt{\sum_{j=1}^{N} x_{jq}^2}}
\]

**MB**

\[
C_{MB} = W_E |\epsilon| + W_{NF} f_{neg}(F) + W_{NS} f_{neg}(S) + W_{BR} f_{BR} + W_R f_R
\]

- Error Weight: \( W_E = 1 / |\epsilon| \)
- Non-negative Factor Weight: \( W_{NF} = 100 \)
- Non-negative Structure Weight: \( W_{NS} = 1 \)

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Model Based FADS for Improved MBF Quantification
Simulation Results

<table>
<thead>
<tr>
<th>Specie</th>
<th>MSO</th>
<th>MB</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Factor</td>
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<tr>
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<td>0.5%</td>
<td>0.2%</td>
<td>&lt;0.001</td>
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<tr>
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<tr>
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<td>4.7%</td>
<td>3.0%</td>
<td>&lt;0.001</td>
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<tr>
<td>Rat</td>
<td>6.7%</td>
<td>3.0%</td>
<td>&lt;0.001</td>
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Arterial Blood Sampling

[Image of arterial blood sampling apparatus]

- Graphs showing normalized activity over time for sampled blood and MB blood factors.

Blood Factor Validation

- Graph comparing RMSE (%) for MSO and MB factors, with p-value 0.027.

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Variable Infusion Durations

Blood structure agreement with CO image

Structure Reproducibility

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Scaling of factors.

MBF quantification using scaled blood factors.

Evaluation of MBF accuracy and polarmap uniformity.
Scaling of Factors and Structures

- Structure scaling based on total partial volume (TPV) = 1 inside heart region.
- Iteratively estimates the heart region and TPV.
MBF in Normals and Patients

![Graph showing MBF in Normals and Patients]

- **MBF [mL/min/g]**
- **Rest**
- **Stress**
- **CPT**

<table>
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<tr>
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<th>Normals</th>
<th>Patients</th>
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<tr>
<td>FARV</td>
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</table>

* indicates a significant difference
• Bland-Altman analysis with water imaging as a standard.
• No significant difference in accuracy between methods.
- Lateral region most uniform
- IDF and SOC have higher MBF in septum due to RV spillover.

Greater uniformity in normal population
MBF in Patients

Example case with good PM correspondence

Example case with poor PM correspondence

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Discussion and Future Direction (Chapter 6)

- **Benefit to Jack:**
  - More reliable diagnosis (comparison to databases)
  - Ability to detect smaller changes in longitudinal studies (follow up studies)
  - Detection of smaller regional variations (localization of stenoses)

- **Further Validation:**
  - Animal Studies:
    - Validation using invasive blood flow measurements (microspheres)
    - Blood sampling in larger animals (dogs, pigs)
  - Human studies
    - Various population cohorts
    - Application to other tracers (other physiologic functions)
THANK YOU FOR YOUR ATTENTION
Other Relevant Publications


