Total-Body PET Kinetic Modeling and Applications

Guobao Wang
University of California Davis Health

October 16, 2021
Short-Course Agenda

• 08:00 a.m. Roger Gunn (Invicro & ICL):
  Basics of dynamic PET quantification / Compartment modeling

• 09:30 a.m. Marc Normandin (MGH):
  Graphical and linearized models / Reference-tissue modeling methods

• 11:15 a.m. Guobao Wang (UCD):
  Total-body PET kinetic modeling and parametric imaging / potential applications

• 12:30 p.m. Q&A
Disclosure

- University of California Davis has a revenue sharing agreement and a research agreement with United Imaging Healthcare (UIH)
Lecture Outline

I. Dynamic whole-body PET imaging on conventional short scanners
   – Whole-body Patlak parametric imaging

II. Total-body PET kinetic modeling and parametric imaging with long scanners
   – Benefits of total-body PET for kinetic modeling
   – Technical challenges and solution
   – Comparison of compartmental modeling with Patlak plot

III. Potential benefits/applications of total-body parametric imaging
Why Do We Need Whole-Body Imaging?

- Example: metastatic cancer

https://en.wikipedia.org/wiki/Metastasis

metastatic lesions
Axial Length of Standard Clinical PET Scanners

- Standard clinical PET scanners commonly have an axial length of 15-30 cm

<table>
<thead>
<tr>
<th>PET Scanner</th>
<th>Year coming into the market</th>
<th>Axial length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE Discovery 690</td>
<td>2010</td>
<td>15.9</td>
</tr>
<tr>
<td>Philips Vereos</td>
<td>2018</td>
<td>16.4</td>
</tr>
<tr>
<td>GE Discovery MI (5-ring)</td>
<td>2018</td>
<td>25</td>
</tr>
<tr>
<td>Siemens Biograph Vision</td>
<td>2018</td>
<td>26</td>
</tr>
<tr>
<td>Canon Cartesion Prime</td>
<td>2019</td>
<td>27</td>
</tr>
<tr>
<td>UIH uMI780</td>
<td>2019</td>
<td>30</td>
</tr>
</tbody>
</table>

- However, adult human height is about 1.5-2 m
Implementation for Whole-body PET Imaging

- A whole-body scan by a conventional PET scanner requires **multiple bed positions**

Each takes 2-3 minutes, resulting in a total of 10-20 minutes

Images courtesy of Dr. Ramsey Badawi
Dynamic Whole-Body (WB) PET Imaging

- Dynamic scan of whole body
  - Multi-bed positions
  - Two or multiple passes
  - Mainly late-phase dynamic data

- Blood input function
  - By a short dynamic scan (e.g., 6 minutes) with the bed fixed at the chest region
  - or by using a population-based input function

N Karakatsanis et al. PMB 2013; Rahmim et al EJNMMI 2019

Yao et al Med Phys 2020; Wu et al. Med Phys 2021
Dynamic WB PET Imaging: Advantages and Limitations

- **Advantages:**
  - Implementable on all existing commercial PET scanners

- **Limitations:**
  - Limited temporal resolution
  - Lost early-dynamic data for most organs
  - But it still enables whole-body Patlak parametric imaging

AH Dias et al. EJNMMI 2020
Patlak Graphical Plot

- Model equation (Patlak et al. JCBFM 1983):
  \[
  \frac{C_T(t)}{C_p(t)} = K_i \int_0^t \frac{c_p(\tau)d\tau}{C_p(t)} + b, \quad t > t^*.
  \]
  \[y(t) \quad x(t)\]

- No early-phase data of \(C_T(t)\) is needed

- Observations (Zhu et al. TMI 2014):
  - A linear inverse problem with two unknown kinetic parameters \((K_i, b)\)
  - In theory, only two time points are needed to solve the problem

- High temporal resolution is not necessary
Relative Patlak Plot

- Observation: Only the integral of the early phase of $C_p(t)$ is needed by the Patlak plot

\[
\frac{c_T(t)}{c_p(t)} = K_i \int_0^t c_p(\tau)d\tau + b, \quad t > t^*
\]

- Any error in the early-phase integral only introduces a global scaling factor in the Patlak slope image

- Relative Patlak plot

\[
\frac{c_T(t)}{c_p(t)} = K_i \int_{t^*}^t c_p(\tau)d\tau + b', \quad t > t^*
\]

Y Zuo et al. PMB 2018; Yao et al Med Phys 2020
Difference between Standard and Relative Patlak Slopes: Global Scaling

Standard Patlak plot

Relative Patlak plot

$K_i$

$K'_i$

Y Zuo et al. PMB 2018
Patlak Parametric Imaging Became Available on Commercial PET Scanners

- Siemens implemented the whole-body Patlak parametric imaging (Hu et al. IEEE-TRPMS 2020)

- Scan protocol: multibed multi-pass scan (Karakatsanis et al. PMB 2013)

- Direct parametric reconstruction with the Nested EM algorithm (Wang & Qi PMB 2010)
Total-Body PET

(A) Conventional PET scanner
(Axial FOV: 15-30 cm)

(B) EXPLORER
(Axial FOV: 194 cm)

Total-body PET provides unprecedented photon detection sensitivity and enables simultaneous dynamic imaging of the entire body

Cherry et al. JNM 2018; Badawi et al. JNM 2019
Long Axial FOV PET Scanners

UIH uEXPLORER (installed at UC Davis in 2019)

Axial FOV: 194 cm
Spencer et al. JNM 2021

PennPET EXPLORER

Axial FOV: 112 cm (extended)
Karp et al. JNM 2020

Siemens Biograph Vision Quadra

Axial FOV: 106 cm
Alberts et al. EJNMMI 2021
Benefits of Total-Body PET for Dynamic Imaging and Kinetic Modeling

• Improved sensitivity
  – makes it more robust to estimate kinetic parameters
  – enables dynamic PET imaging with higher temporal resolution
  (Badawi et al JNM 2019; Zhang et al PNAS 2021)

• Total-body coverage
  – provides full time course of tracer activity for all organs

Clinical reliability
Probing physiology
Good image-derived input function
Total-body parametric imaging of macro- and micro-kinetic parameters
Benefits of Total-Body PET for Dynamic Imaging:
High Image Quality

Conventional PET (uMI 780)
8 beds, 2 mins/bed,
50 min p.i.

EXPLORER
20 min scan, 1 bed
82 min p.i.

Courtesy of Ramsey D. Badawi
Simultaneous Dynamic Imaging of the Entire Body on EXPLORER

Shown are MIP (maximum intensity projection) images.

- $t = 0.5-1$ min
- 1-2 min
- 10-12 min
- 30-35 min
- 55-60 min

Metastatic lesions
Benefits of Total-Body PET for Dynamic Imaging: High Temporal Resolution

Zhang et al. JNM 2020; Badawi et al. JNM 2019
Benefits of Total-Body PET for Kinetic Modeling: Extraction of Input Function

- Blood input function is conventionally obtained with invasive blood sampling

- For brain imaging, best available image-derived input function (IDIF) by conventional PET scanners is from the common carotid artery, which however suffers from severe partial volume effect

- With total-body PET, IDIF is available from a large blood pool, e.g., the left ventricle
Image-Derived Input Functions (IDIFs) in Total-Body Dynamic PET

Courtesy of Elizabeth Li
Example of Brain Parametric Imaging

Cerebral FDG $K_i$

with LV IDIF

with CC IDIF

E Li et al. 2019 SNMMI
Benefits of Total-Body PET for Dynamic Imaging:
Capturing the Full Time Course of Tracer Activity in All Organs

- Brain
- Lung
- Liver
- Tumor
- Myocardium
- Spleen
Total-Body Patlak Parametric Imaging on EXPLORER

Zhang et al. JNM 2020
Benefits of Total-Body PET for Kinetic Modeling: Parametric Imaging with Compartmental Models

- Compartmental model

\[
\frac{d}{dt} \begin{bmatrix}
C_f(t) \\
C_m(t)
\end{bmatrix} = \begin{bmatrix}
-k_2 + k_3 & k_4 \\
k_3 & -k_4
\end{bmatrix} \begin{bmatrix}
C_f(t) \\
C_m(t)
\end{bmatrix} + \begin{bmatrix}
K_1 \\
0
\end{bmatrix} C_p(t)
\]

- Differential equations

- Total activity that is measured by PET is

\[
C_T(t) = (1 - \nu_b)[C_f(t) + C_m(t)] + \nu_b C_b(t)
\]

Kinetic Parametric Estimation by Full Time Activity Curve (TAC) Fitting

- Micro-kinetic parameters (e.g., $K_1$, $k_2$, ...) are estimated from TAC fitting
- Macro kinetic parameters can be calculated, e.g., for FDG:

\[
\text{Net influx rate } K_i = \frac{K_1k_3}{k_2+k_3}; \quad \text{Initial volume of distribution } V_0 = \frac{K_1k_2}{(k_2+k_3)^2}
\]
Challenges of Total-Body Kinetic Modeling and Parametric Imaging

- Time delay and dispersion correction
- Modeling of dual blood supplies (in liver, lung)
- Parent fraction correction
- Metabolite correction

- Model selection
  - Identifiability
  - ...

- Huge dataset
  - Motion
  - Local minimum
  - ...

**Blood Input Function**

- Graph showing activity vs. scan time (min.)

**Kinetic Model**

- Diagram illustrating various parameters and components

**Tissue TACs and Fitting**

- Graph showing measured and fitted activity vs. scan time (min.)

Key Components
Time Delay of the Blood Input Function

(A) IDIF extracted in left ventricle
(B) actual arrival in a tissue

Commonly Neglected in Parametric Imaging

- $K_i$ estimation is more dominated by the late phase instead of early phase of a dynamic scan

- Within a limited axial FOV of 15 cm of conventional PET, time delay can be just a few seconds

- Temporal resolution of dynamic PET was limited (e.g., 10-40 s/frame)

- Mainly considered to be important for estimation of fast kinetics (e.g., cerebral blood flow imaging using $^{15}$O-water)

Importance for Total-Body Kinetic Modeling

- Time delay in a tissue distant from the left ventricle can be up to 50 seconds

- Metastatic lesions spread to distant organs, which can be far away from the blood pool where a blood input function is extracted

- May significantly affect the estimation of $v_b$, $K_1$ and $K_i$
Time-Delay Correction by Joint Estimation

- Model TAC **without** time delay

\[ C_T(t) = (1 - v_b) \text{IRF}(t; \boldsymbol{\kappa}) \otimes C_P(t) + v_b C_b(t) \]

- Model TAC **with** time delay correction

\[ C_T(t) = (1 - v_b) \text{IRF}(t; \boldsymbol{\kappa}) \otimes C_P(t - t_d) + v_b C_b(t - t_d) \]

- \( \boldsymbol{\theta} = [\boldsymbol{\kappa}^T, v_b, t_d]^T \) is jointly estimated via nonlinear least-square fitting:

\[ \hat{\boldsymbol{\theta}} = \arg \min_{\boldsymbol{\theta}} \text{RSS}(\boldsymbol{\theta}), \quad \text{RSS}(\boldsymbol{\theta}) = \sum_{m=1}^{M} w_m [\hat{C}_T(t_m) - C_T(t_m)]^2 \]
Example of Fitting a Lesion TAC

A. no time-delay correction

B. with time-delay correction
Fractional blood volume $v_b$

FDG delivery rate $K_1$

w/o with

w/o with
Time-Delay Correction (TDC) Also Impacts on FDG $K_i$

Estimated time delay

$K_i$ (without TDC)  $K_i$ (with TDC)

(s)  (mL/min/cm$^3$)

+50  0.009  0.018
+30
+10
0.009  0.018

-10
0.000
Impact of Time Delay Correction Correlates with Blood Volume Fraction

Results from 19 lesions from 5 patients with metastatic genitourinary cancer
Why Time-delay Correction May Impact $K_i$ Estimation?

$$C_T(t) = (1 - \nu_b) \text{IRF}(t; \kappa) \otimes C_p(t - t_d) + \nu_b C_b(t - t_d)$$

$C_{ev}(t)$

A. No time delay estimation

B. With time delay estimation

---

**Graph 1:**
- Total tissue: $C_p(t)$
- Estimated vascular: $\nu_b C_b(t)$
- Estimated extravascular: $C_{ev}(t)$

**Graph 2:**
- Total tissue: $C_p(t)$
- Estimated vascular: $\nu_b C_b(t)$
- Estimated extravascular: $C_{ev}(t)$
• Conventionally a fixed model is commonly used in organ-specific parametric imaging, e.g.,
  – Brain
  – Myocardium

• Total-body parametric imaging
  – Many different organs
  – Each may follow a different compartmental model
Example of Candidate Compartmental Models

A. 2T

\[ \begin{align*}
C_p(t) & \xrightarrow{K_1} C_f(t) \\
& \xrightarrow{k_2} C_p(t) \\
C_f(t) & \xrightarrow{k_3} C_m(t)
\end{align*} \]

B. 1T

\[ \begin{align*}
C_p(t) & \xrightarrow{K_1} C_t(t) \\
& \xrightarrow{k_2} C_p(t)
\end{align*} \]

C. 0T

\[ C_p(t) \] (blood voxels)
Which Model Is the Best?

- Similar fits, but very different $K_i$ results
Akaike Information Criteria (AIC)

• Definition

\[
\text{AIC} = M \ln \left( \frac{\text{RSS}}{M} \right) + 2n
\]

where RSS denotes the residual sum of squares

\[
\text{RSS} = \sum_{m=1}^{M} w_m \left[ \tilde{C}_T(t_m) - C_T(t_m) \right]^2
\]

with \( M \) the number of frames and \( n \) the number of unknown kinetic parameters.
AIC for Small Sample Size

• Correction for small sample size:

\[
\text{AICc} = \text{AIC} + \frac{2n(n + 1)}{M - n - 1}
\]

• AIC includes \( n \), thus the first-order estimate of the information loss

• AICc includes \( n^2 \) and is a second-order estimate

• Lower value of AIC (or AICc) indicates a better fit

Extra penalty to avoid overfitting
Test for Fitting a Blood TAC

2T fit: $K_i = 0.02$

0T fit: $K_i = 0.00$

AIC comparison:

- 0T: -20
- 1T: -15
- 2T: -10
Impact of Model Selection on $K_i$ Imaging of Lesions

Model selection map

No model selection (2Ti)

With model selection (0T, 1T, 2Ti)
Impact of Model Selection on Myocardial $K_i$ Imaging

No model selection

With model selection
Example of Total-Body PET Multiparametric Imaging Using Compartmental Modeling (CM)

FDG net influx rate

\[ K_i \] mL/min/cm^3

0.020

0.018

0.016

0.014

0.012

0.010

0.008

0.006

0.004

0.002

0.000

FDG delivery rate

\[ K_1 \] mL/min/cm^3

1.0

0.9

0.8

0.7

0.6

0.5

0.4

0.3

0.2

0.1

0.0

Fractional blood volume

\[ v_b \] mL/cm^3

1.0

0.9

0.8

0.7

0.6

0.5

0.4

0.3

0.2

0.1

0.0

Volume of distribution

\[ V_0 \] mL/cm^3

1.0

0.9

0.8

0.7

0.6

0.5

0.4

0.3

0.2

0.1

0.0
Comparison of 2T CM with Patlak Plot

Irreversible 2T CM

\[ C_T(t) = (1 - \nu_b) \text{IRF}(t; \kappa) \otimes C_p(t) + \nu_b C_{wb}(t) \]

Patlak plot

\[ \frac{c_T(t)}{c_p(t)} = K_i \int_0^t \frac{c_p(\tau)d\tau}{c_p(t)} + b, \quad t > t^* \]

• Pros

  – Better modeling of the blood component (\( \nu_b \))
  – The Patlak slope is not exactly equal to \( K_i = \frac{K_1k_3}{k_2+k_3} \) of the 2T model, but \((1 - \nu_b)K_i\)
  – Allowing parametric imaging of micro-kinetic parameters (e.g., \( K_1, \nu_b \))

• Cons

  – Computationally less efficient
  – Additional corrections are needed in order to explore the benefits
When Similar and When Different Between Compartmental Modeling and Patlak Plot?
The Relationship Depends on Vascular Fraction

- Compartment modeling allows separate estimation of $K_i$ and $v_b$
- Patlak slope $\approx (1-v_b)K_i$, which does not make the separation
- The difference becomes nonnegligible if $v_b$ is large
Patlak Underestimation Correlates with Blood Volume

Patlak plot underestimates $K_i$ but highly correlates with it

The underestimation is increased as blood volume increases

$r = 0.97$
$P < 0.0001$

$r = -0.85$
$P < 0.0001$

19 lesions from 5 patients with genitourinary cancer
Potential Benefits of Total-Body Multiparametric Imaging

1. Improved lesion contrast

2. Exploring micro kinetic parameters (e.g., $K_1$) for multiparametric imaging

3. Multiorgan quantification in systemic disease
Benefit 1: Parametric Image of $K_i$ Can Improve Lesion Contrast

- FDG $K_i$ can clean background signal in the liver and blood pool
Results from Whole-body Patlak Imaging on Conventional PET Scanners

Improved tumor-to-background ratio (TBR)

AH Dias et al. EJNMMI 2020
Initial Results from Total-Body Parametric Imaging with Compartmental Modeling on EXPLORER

Results from 19 lesions from 5 patients with metastatic cancer

$P < 0.0001$
Example of Liver Lesions

SUV

CR=1.6
COV=8%

FDG influx rate $K_i$

CR=5.8
COV=13%
Example of Abdominal Lesions

Contrast-enhanced CT

SUV

FDG $K_i$

Peritoneal mass

para-aortic lesion

g/mL

mL/min/cm³

0

0.025
Benefit 2: Exploring Micro-kinetic Parameters for Multiparametric Imaging

- SUV and $K_i$ characterize glucose metabolism
- FDG delivery rate $K_1$ generally reflects a mix of blood flow and glucose transport
- Many potential applications of FDG $K_1$:
  - Serve as a surrogate of blood flow
  - Independent imaging biomarker
  - Create lesion contrast
Cancer: FDG $K_1$ May Highly Correlate with Tumor Blood Flow

- Due to generally high extraction fraction of $^{18}$F-FDG in tumors
- Enabling single-tracer imaging of tumor flow-metabolism mismatch

FDG flow: Mullani et al, JNM 2008; Tseng et al JNM 2004;
Flow-metabolism mismatch: Komar et al CCR 2009; Mankoff et al CCR 2009
Heart: Measuring Myocardial Blood Flow (MBF) Using FDG K₁

- FDG K₁ is closely associated with blood flow in the myocardium
- Correlation of FDG-derived MBF with Rb MBF after the nonlinearity correction

Pilot study using Rb-82 PET on a conventional scanner

\[ K₁ = MBF \times (1 - 0.8 \times e^{-0.63/MBF}) \]

\[ r = 0.94 \]
\[ p = 6.4 \times 10^{-5} \]

Liver: FDG $K_1$ May Be a Potential Biomarker of Liver Inflammation

• Decreased liver FDG $K_1$ is associated with increased liver inflammation

Sarkar et al CGH 2021; Sarkar et al. AJR 2019; Zuo et al. PMB 2019; Wang et al. PMB 2018;
Brain/Skull: FDG $K_1$ Has Potential to Better Detect Tumors

Wang et al. unpublished EXPLORER data
Benefit 3: Enabling Multi-Organ Evaluation in Systemic Disease

• Simultaneous evaluation of myocardium in cancer patients?

• **Problem**: 30-40% of standard oncological FDG-PET scans do not show visible myocardium

• Parametric imaging can help
Simultaneous Visualization of Myocardium by Parametric Imaging

Example A

SUV

Example B

K_i
Allowing Evaluation of Perfusion-Metabolism Coupling/Mismatch

Example A

Example B
Putting All Puzzles Together

Single-tracer ($^{18}$F-FDG) Multiorgan Multiparametric Evaluation by EXPLORER

Multi Organs
- Myocardium
- Liver
- Lung
- Brain
- Bone marrow
- Spleen
- Kidney ...

Multiparametric Imaging
- Glucose metabolism
- Glucose transport / perfusion
- and potentially more
• Metabolite correction using total-body compartmental modeling
• Motion correction for total-body parametric imaging
• High-temporal resolution (e.g., 1s/frame) kinetic modeling
• 4D parametric imaging with cardiac/respiratory modulation
• Total-body dual-tracer and multi-tracer dynamic imaging
• Total-body organ network analysis and connectomes
• and many more …
Thank you for your attention!

Questions?
Acknowledgements

Simon R Cherry
Ramsey D. Badawi
Jinyi Qi
Terry Jones
Abhijit Chaudhari
Ben Spencer
Xuezhu Zhang
Yang Zuo
Elizabeth Li
Yiran Wang

Lorenzo Nardo
Yasser Abdelhafez
Souvik Sarkar
Javier Lopez
Chong-xian Pan
Primo N. Lara
Mamta Parikh
Rashimi Verma

UC Davis EXPLORER Molecular Imaging Tech Team

All UC Davis MiPET Group members