Improved kinetic modelling with cross-modality parameter coupling

Kjell Erlandsson, INM, UCL

PET/MRI Methodology Symposium: 21-23 September, 2016

Introduction

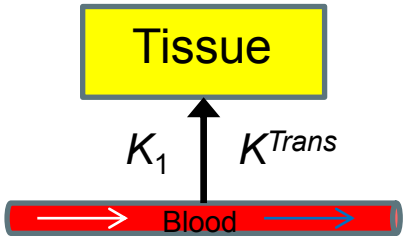
- Kinetic analysis of dynamic PET data can be used for estimation of various physiological or biochemical parameters.
- The kinetic models usually have to be simplified in order to allow robust parameter-estimation.
- Kinetic analysis can also be performed on dynamic MRI data.
- Some of the parameters could be transferable between the two modalities.
- This would allow for...
  - improved parameter estimation,
  - Improved input function estimation,
  - the use of simplified acquisition protocols,
  - the use of more complex and more realistic models.

Background

Combined PET/MRI dynamic studies

MRI	Brain	PET	Ref
ASL	+	R_1	Scott
DSC	+	AIF	Sari
DCE	-	F	Zhang
DCE	-	V_e	Erlandsson

Blood flow



The transfer of tracer from blood to tissue can be described as follows[1,2,3,4]

$$K_1 = F \cdot E = F\left(1 - e^{-PS/F}\right)$$

where F = blood flow,
E = extraction fraction,
P = permeability and
S = surface area

In MRI, K_1 is known as K^{Trans}.[5]

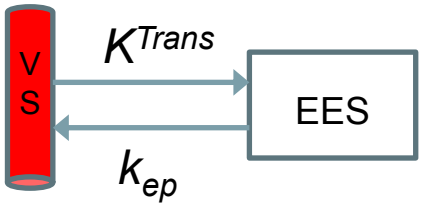
1) Kety SS, Schmidt CF (1948), J Clin Invest, 27:476-83.
2) Kety SS (1951), Pharmacol Rev, 3:1-41.
3) Renkin EM (1959), Am J Physiol, 197:1205-10.
4) Crone C (1963), Acta Physiol Scandinav, 58:292-305.
5) Tofts PS, et al. (1999), J Magn Reson Imaging, 10:223–32.

Blood flow

- Two studies have been performed by a group in Boston, combining DCE-MRI and [^{15}O]-H_2O PET in rabbit tumours.
  - 1) Zhang et al. measured *PS* of Gd-DTPA contrast agent, assuming *F* could be directly obtained from H_2O PET and was the same in both modalities.[1]
  - 2) Wilks et al. used joint modelling to improve the signal-to-noise ratio, and to extract true blood flow values on a voxel-wise basis. This joint estimation method constrains parameters which are shared between modalities, such as *F* and *S*. Additionally, a single global parameter was fit for the ratio of *P* between water and the contrast agent (Magnevist).

1) Zhang X, et al. (2015), *J Nucl Med*, **56**:644.
2) Wilks M, et al. (2016), *J Nucl Med*, **57**:436.

MRI kinetics

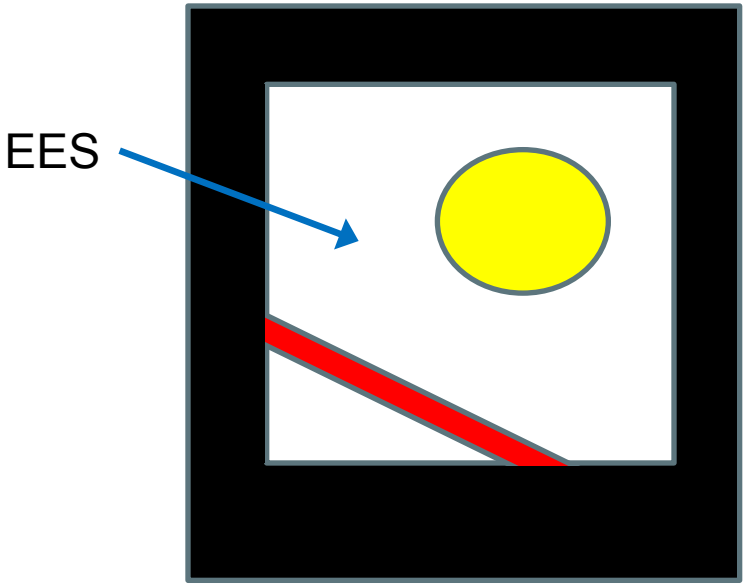


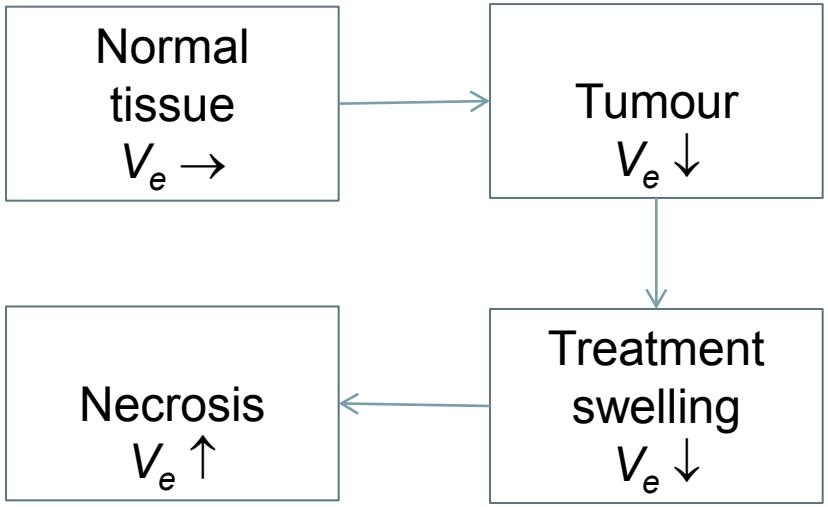
VS=vascular space,
EES=extra-vascular extra-cellular space

- With dynamic contrast enhanced (DCE) MRI, a 1TC/2k-model can be used[1] (i.e. with 1 tissue compartment and 2 rate constants)
- for estimation of the rate constants K^{Trans} and k_{ep}
  - representing transport between the vascular to the extra-vascular space.
- which are linked by the expression: $V_e = K^{Trans} / k_{ep}$
- *where* V_e is the extra-vascular extra-cellular volume of distribution.

1) Tofts PS, et al. (1999), J Magn Reson Imaging, 10:223–32.

Extra-vascular extra-cellular space (EES)

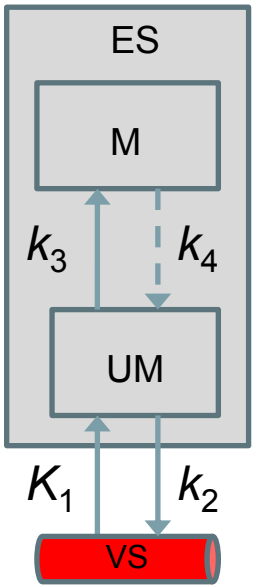




- EES is a physical space, independent of tracer binding.
- V_e can change; e.g. in tumours before and after treatment[1].

1) Koh D-M, Collins DJ (2007), *Am J Roentgenol*, **188**:1622-35.

Standard FDG model



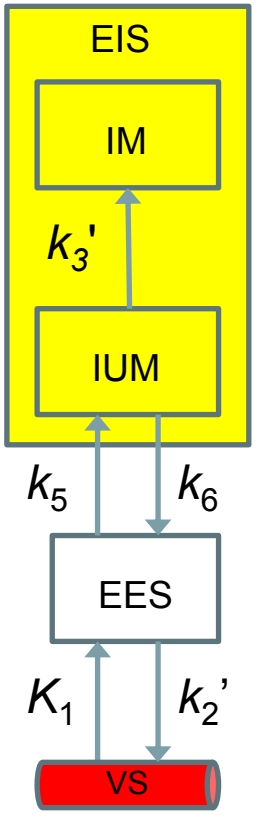
VS=vascular space,
ES=extra-vascular space,
UM=un-metabolised tracer,
M=metabolised tracer

- The standard 2TC/3k- or 4k- FDG models[1,2] are simplified models that do not make a distinction between the extra-vascular extra-cellular and intra-cellular spaces

1) Sokoloff L, et al. (1977), J Neurochem, 28:897–916.
2) Phelps ME, et al. (1979), Ann Neurol, 6:371–88.

General FDG model (3TC/5k)

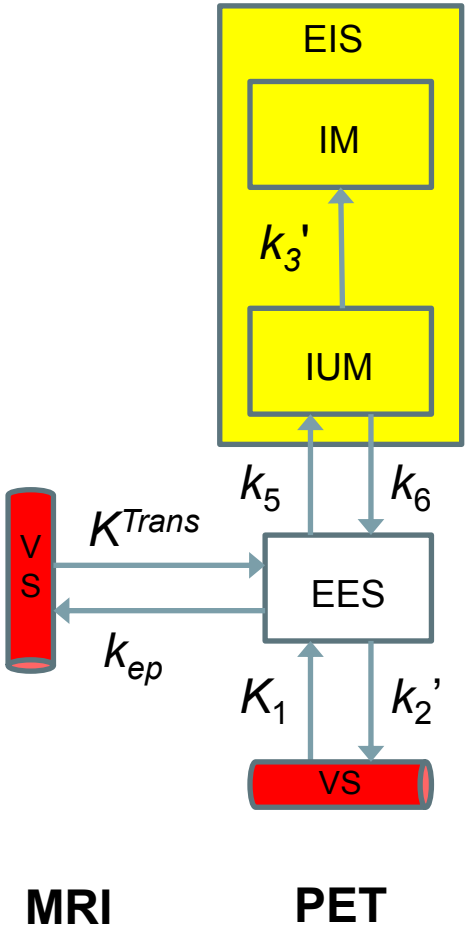
- The 3TC/5k-model distinguishes between extra- and intra-cellular space, and is more biologically realistic.
- However, it has too many parameters, which are normally not identifiable in practice.



VS=vascular space,
ES=extra-vascular space,
EES=extra-vascular extra-cellular space,
IUM=intra-cellular un-metabolised tracer,
IM=intra-cellular metabolised tracer

Combined PET/MRI model

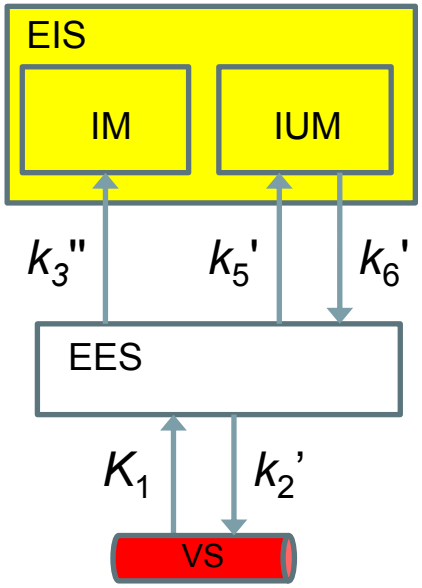
- We link the PET and MRI models by assuming V_e is the same in both.
- If V_e can be accurately obtained from e.g. DCE-MRI, the number of parameters in the PET model is reduced by 1.



$$\frac{K_1}{k_2'} = \frac{K^{Trans}}{k_{ep}} = V_e$$

VS=vascular space,
EES=extra-vascular extra-cellular space,
EIS=extra-vascular intra-cellular space,
IUM=intra-cellular un-metabolised tracer,
IM=intra-cellular metabolised tracer

Equivalent 3TC/5k-model (uncoupled)



VS = vascular space,
EES = extra-vascular extra-cellular space,
EIS = extra-vascular intra-cellular space,
IUM = intra-cellular un-metabolised tracer,
IM = intra-cellular metabolised tracer

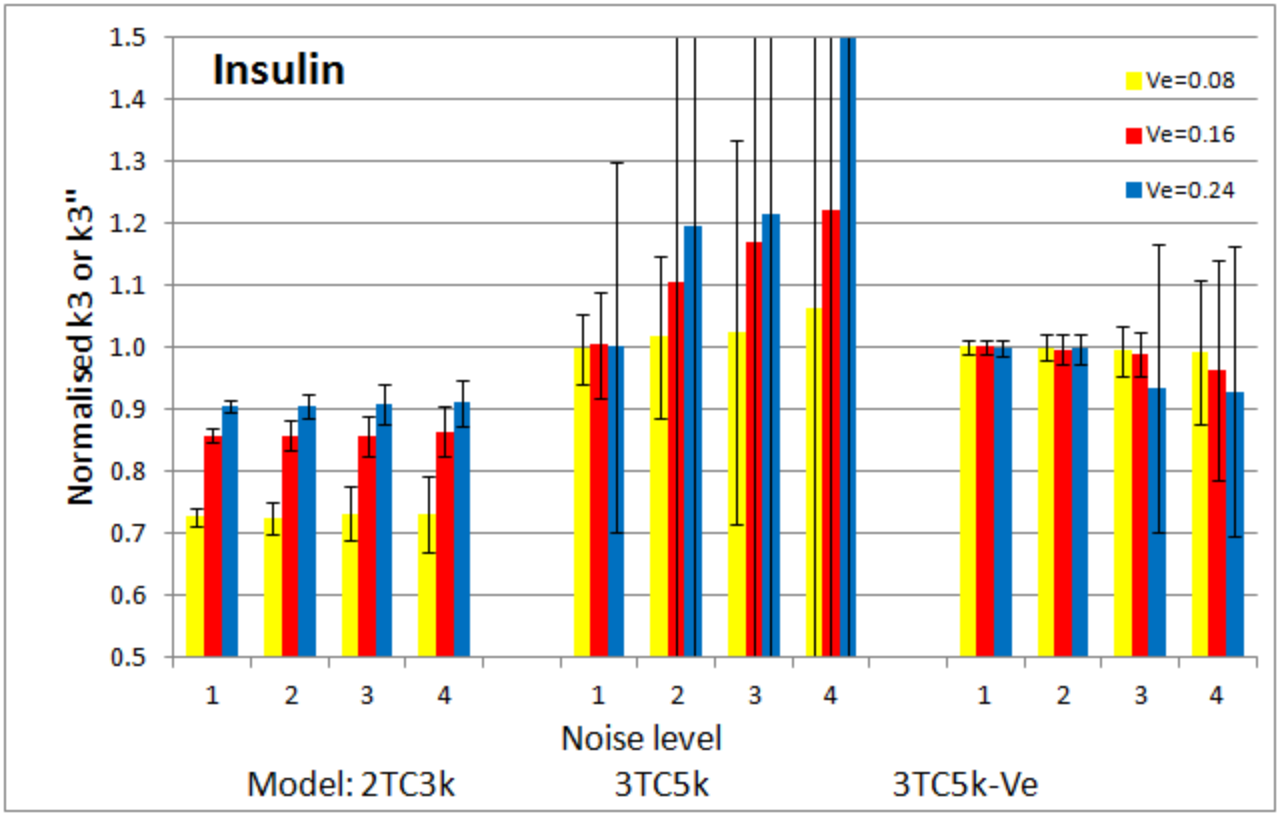
- The un-coupled model is numerically more stable than the coupled one.
- k_3'' represents a combination of transport across the cellular membrane and phosphorylation.

Evaluation

- The method has been evaluated using simulated data.
- Time-activity curves (TACs) were generated with the coupled 3TC/5k-model with rate constants for [^{18}F]-FDG in skeletal muscle[1] and also for [^{18}F]-FMISO[2] using the COMKAT software[3].
- For FDG, data were simulated with 3 different V_e values (0.08, 0.16 and 0.24 mL/mL).
- Noise was added, and 100 noise- realisations were generated.
- The data were fitted with the standard 2TC/3k model, and with the uncoupled 3TC/5k model, with and without fixed V_e.
- Mean and SD values were calculated across noise-realisations.

1) Bertoldo A, et al. (2001), *Amer J Physiol Endocrinol Metab*, **281**:E524–36.
2) Erlandsson K, et al. (2016), *J Nucl Med*, **57**:371.
3) Muzic, Cornelius (2001), *J Nucl Med*, **42**:636-45.

FDG results



1) Erlandsson K, et al. (2016), *IEEE Trans Nucl Sci*, in press.

Conclusions

- With simultaneous PET and MRI dynamic imaging, it is possible to obtain improved estimation of parameters which are common to the two modalities, such as blood flow, by using simultaneous modelling.
- Also, new parameters can be estimated by the use of a more complex model, which can provide more specific information regarding tracer uptake and retention.
  - On the other hand, the estimation of macro-parameters, such as K_i, will not be improved, since it just represents a combination of all the steps involved (delivery, extraction, transport and trapping).
- Alternatively, common kinetic parameters can be used for obtaining an improved input function or developing a simplified scanning protocol.

The End

- **Acknowledgements**
  - This work was supported by by the EPSRC (grant number EP/K005278/1) and the National Institute for Health Research University College London Hospitals Biomedical Research Centre.