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Kinetic Analysis of Dynamic Positron Emission Tomography Data using Open-Source Image Processing and Statistical Inference Tools

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Abstract

In dynamic mode, positron emission tomography (PET) can be used to track the evolution of injected radio-labelled molecules in living tissue. This is a powerful diagnostic imaging technique that provides a unique opportunity to probe the status of healthy and pathological tissue by examining how it processes substrates. The spatial aspect of PET is well established in the computational statistics literature. This article focuses on its temporal aspect. The interpretation of PET time-course data is complicated because the measured signal is a combination of vascular delivery and tissue retention effects. If the arterial time-course is known, the tissue time-course can typically be expressed in terms of a linear convolution between the arterial time-course and the tissue residue. In statistical terms, the residue function is essentially a survival function - a familiar life-time data construct. Kinetic analysis of PET data is concerned with estimation of the residue and associated functionals such as flow, flux, volume of distribution and transit time summaries. This review emphasises a nonparametric approach to the estimation of the residue based on a piecewise linear form. Rapid implementation of this by quadratic programming is described. The approach provides a reference for statistical assessment of widely used one- and two-compartmental model forms. We illustrate the method with data from two of the most well-established PET radiotracers, $^{15}\text{O}\text{-H}_2\text{O}$ and $^{18}\text{F}\text{-fluorodeoxyglucose}$, used for assessment of blood perfusion and glucose metabolism respectively. The presentation illustrates the use of two open-source tools, AMIDE and R, for PET scan manipulation and model inference.

Introduction

The past fifty years have seen major advances in the quality of diagnostic imaging available for medical application. Exquisite anatomic detail on tissue X-ray attenuation and water composition can be recovered by computerised tomography (CT) and magnetic resonance (MR) scanning. But increasingly, it has been recognised that deeper functional biological characteristics of tissue have more medical significance. This has led to advances in the

development of nuclear medicine based imaging procedures and especially positron emission tomography (PET). There is an ever increasing range of clinical questions which can only be addressed at present by PET. This is especially true in oncology where PET scanning is established as standard practice in much of the “developed” world. A PET imaging study begins with the venous injection of a small (trace) amount of a substance containing radioactive (positron-emitting) isotope atoms. PET imaging involves using the externally measured emitted radiation to reconstruct an image of the source distribution of radioactive atoms in the field of view. The attenuation characteristics of tissue are critical to the reconstruction process. In early instruments PET-based transmission scans were used for attenuation measurement. Current PET/CT scanners use X-ray attenuation characteristics measured by CT for this. Similar to CT, the mathematical basis of emission tomography is the Radon transform¹². The reconstruction problem of PET has long been recognised as highly statistical¹⁹ and in recent years operational reconstructions can be seen to have an increased reliance on sophisticated statistically motivated algorithms, especially the expectation maximisation algorithm. Technology has improved with nominal clinical scanner resolution now at the millimeter level. But in a clinical setting, the major determinants of resolution include the injected dose and natural physiological variation (respiration, organ motion, subject movement). These place practical limits so the real resolution is perhaps on the order of several millimeters, which is unlikely to change, in the near future with improved electronics or reconstruction algorithms.

A major strength of PET is its ability to acquire dynamic data. Following the injection of the tracer, a series of scans can be taken. This allows the evolution of the tracer activity distribution to be evaluated and analyzed. However, with dynamic scanning, the underlying activity of the tracer decays over time and this has an impact on the statistical variation of scan data. The interpretation of PET (dynamic or static) data is complicated because the activity in the field of view at any time reflects a combination of vascular delivery of the tracer and its retention (metabolism) by tissue. The purpose of kinetic analysis is to separate these two components so that a deeper understanding of tissue can be obtained from the PET study. This problem is intrinsically statistical but is probably less familiar to the statistical community, than the basic PET image reconstruction problem. The purpose of this article is to review the methodology with focus on computational aspects of model fitting and inference. General modelling of PET time activity curves is presented in the next section. Various parametric and a novel nonparametric modelling strategies are then introduced. The inference involved in this modelling is discussed and then illustrated. We conclude with some discussion and suggested further reading.

The Basic Equation of Dynamic PET

The key assumptions underlying most radiotracer imaging with PET is linearity and time-invariance of the biological response to the injected dose. These assumptions allow the concentration of tracer atoms in a tissue region $C_T(t)$ to be expressed as a convolution involving the arterial input $C_P(t)$ and the tissue impulse response function, which is necessarily positive and monotonically decreasing. As the measurement of the arterial $C_P(t)$ is typically made at a site (radial artery or heart) which is remote from the tissue region, a delay term (Δ) is included. Thus the fundamental equation of dynamic PET radiotracer imaging is

$$C_T(t) = v_B C_P(t - \Delta) + K \int_0^t R(t - s) C_P(s - \Delta) ds \quad (1)$$

where $C_T(t)$ is measured as activity per unit volume (KBq/cm³) and $C_p(t)$ is activity per millilitre (ml) of blood; K has units of flow (ml per unit time) and v_B is in units ml of blood per unit volume of tissue. By analogy with indicator dilution terminology, $R(t)$ is the tissue residue function, normalised to have unit height at time zero. If $R(t)$ is differentiable, it can be expressed in terms of a residence function h as

$$R(t) = 1 - \int_0^t h(\tau) d\tau$$

where h describes the distribution of travel times for radiotracer atoms. Note this distribution may not be proper, i.e. integrate to 1, since it is possible for tracer atoms to be retained by tissue and consequently have infinite travel times. Because the duration of the PET study is finite, say over a time-interval $[0, T_e]$, at best $R(t)$ can be determined over $[0, T_e]$, where T_e is the end time of the scan, although a model form can be used for extrapolation. This is a familiar aspect of survival analysis. The apparent rate of retention of tracer is assessed by Ke where $e = R(T_e)$ is the extraction fraction. Ke is the apparent flux. The mean transit time (MTT) of non-extracted tracer is obtained by integration of the renormalised residue

$$MTT = \int_0^{T_e} \frac{R(t) - R(T_e)}{1 - R(T_e)} dt.$$

The volume of distribution (v_D) of non-extracted tracer is defined by the product $v_D = K.MTT$, based on the central volume theorem¹⁴. The collection of parameters describing flow, flux, mean transit time, volume of distribution and blood volume (K , Ke , MTT , v_D , v_B) are most commonly used to summarise the kinetic interaction of tracer atoms with the tissue.

Modelling the Tissue Residue Function

Although more sophisticated modelling constructs are available¹, in PET there is substantial reliance on compartmental models as a means to summarise kinetics. Detailed treatment of these models can be found in Zaidi²¹. We discuss the most popular ones: the one-compartment (1C) Kety-Schmidt model used for analysis of PET studies with ¹⁵O-H₂O and the two-compartment (2C) Sokolov-Huang model used with ¹⁸F-fluorodeoxyglucose (FDG).

One-Compartment Model

Kety and Schmidt⁷ proposed this for the analysis of perfusion tracers (tracers that do not get retained in tissue cells). A schematic of their model is shown in Figure 1. The model formulation is based on balance between the concentration of tracer in the large arteries ($C_p(t - \Delta)$) and the concentration ($C_1(t)$) (outside of that) in tissue. The state equation is

$$\dot{C}_1(t) = K_1 C_p(t - \Delta) - k_2 C_1(t) \quad (2)$$

where K_1 and k_2 (both positive) represent influx into and efflux out of the tissue compartment. The total tissue concentration is a weighted sum of large vascular and extravascular elements $C_T(t) = v_B C_p(t - \Delta) + (1 - v_B) C_1(t)$. In terms of Equation 1, $K = (1 - v_B) K_1$. The residue for Equation 2 is given by

$$R(t)=e^{-k_2 t}. \quad (3)$$

The model allows extrapolation of the residue beyond the measurement period (T_e) and since $R(t) \downarrow 0$ as $t \uparrow \infty$, the asymptotic extraction and flux are zero, while the limiting mean

transit time is k_2^{-1} and the limiting volume of distribution is $\frac{K}{k_2}$.

Two-Compartment Model

This model was originally developed by Sokolov¹⁷ for the analysis of ^{14}C -labelled glucose. Its special status in PET arises from its proposed use for evaluation of cerebral glucose metabolic rates from FDG-PET data¹⁵. For instance when working with FDG, the model considers tracer atoms in three states: the vasculature ($C_p(t - \Delta)$), extra-vascular tissue as FDG, and extra-vascular tissue in a metabolised form known as FDG-6-phosphate. The total extra-vascular activity is a sum of unmetabolised and metabolised tracer concentrations $C_1(t)$ and $C_2(t)$. Mass-balance of $C_1(t)$ and $C_2(t)$ (Figure 2) gives

$$\begin{aligned} \dot{C}_1(t) &= K_1 C_p(t - \Delta) - (k_2 + k_3) C_1(t) + k_4 C_2(t) \\ \dot{C}_2(t) &= k_3 C_1(t) - k_4 C_2(t). \end{aligned} \quad (4)$$

By standard use of Laplace transform techniques²¹, the tissue residue for Equation 4 is the mixture of two exponentials

$$R(t) = \pi e^{-\varphi_1 t} + (1 - \pi) e^{-\varphi_2 t}$$

$$\text{where } \varphi_{1,2} = \frac{k_2 \pm \sqrt{k_2^2 - 4k_2 k_4}}{2} \text{ for } k = k_2 + k_3 + k_4 \text{ and } \pi = \frac{k_3 + k_4 - \varphi_1}{\varphi_1 - \varphi_2}.$$

Flow is $K = (1 - v_B) K_1$ and flux, extraction and mean transit time at T_e can be derived from these. As $k_4 \downarrow 0$, φ_2 becomes negligible and $\varphi_1 \approx k_2 + k_3$. Here

$$R(t) \approx \frac{k_2}{k_2 + k_3} e^{-(k_2 + k_3)t} + \frac{k_3}{k_2 + k_3}$$

where the asymptotic ($T_e \uparrow \infty$) flux is $\frac{K k_3}{k_2 + k_3}$ and v_D is $\frac{K}{k_2 + k_3}$.

Piecewise Constant Residue

As the residue is a survival function, it is not unreasonable to approximate it by a piecewise constant form over the observation window $[0, T_e]$. Let $0 = \tau_0 < \dots < \tau_J < T_e$ be a collection of $J + 1$ points and let I_j^+ be the indicator for the set $[\tau_j, \infty)$. For $\alpha = (\alpha_1, \dots, \alpha_J)^T$, a vector

with non-negative components satisfying $\sum_{j=1}^J \alpha_j \leq 1$, a piecewise constant residue can be defined over $[0, T_e]$ by

$$R_{\alpha}(t)=1-\sum_{j=1}^J\alpha_jI_j^+(t). \quad (5)$$

The residence density corresponding to this residue is discrete with mass α_j concentrated at τ_j . The mean transit time is a weighted average of these times and the extraction fraction also has a simple form:

$$MTT=\frac{\sum_{j=1}^J\alpha_j\tau_j}{\sum_{j=1}^J\alpha_j}; \quad \varepsilon=1-\sum_{j=1}^J\alpha_j.$$

Unlike compartmental models, there is no basis for extrapolation of the above residue outside of the observation window. A potential advantage of the piecewise constant approach is that a detailed compartmental assumption is not required. This can be difficult to justify in cases where the tissue is heterogeneous.

Statistical Inference

While the radiotracer atom emission process is Poisson, the statistical structure of reconstructed PET scans is more complex. A variety of theoretical and empirical calculations have shown reconstructed data to have a pseudo-Poisson character^{2,9,13}. That is to say, the variance is approximately proportional to the mean and over homogeneous regions the total activity tends to scale linearly with the size of the region considered. Although post-scan time-binning is an option on some scanners, it is almost always the case that the time-binning is not adapted to the subject. Rather in dynamic PET studies a standard time-binning protocol is used. The individual scans are sometimes referred to as time-frames or time-bins. The time-bins for a set of N dynamic scans will be denoted (t_{sk}, t_{ek}) for $k=1, 2, \dots, N$. Raw counts reconstructed over the k 'th time-bin represent the integrated activity in the field of view over the acquisition period. These counts are adjusted for decay. To obtain values in units proportional to activity (KBq/cm³), counts must also be adjusted for tissue attenuation, time-bin duration and volume. The machine sensitivity is taken into account by calibration of reconstructed activity using the activity of known sources placed in the scanner. Based on these considerations, if y_k is the raw reconstructed count for a volume over a time-bin $[t_{sk}, t_{ek}]$, the corresponding activity value is given by

$$z_k=y_k\frac{e^{\lambda t_k}}{t_{ek}-t_{sk}}c\equiv y_kf_kc$$

where c is a factor taking account of attenuation, volume and calibration, t_k is the mid-point of the time-bin and λ is the rate of decay of the isotope (half-life is $\ln(2)\lambda^{-1}$). The expected value of z_k corresponds to the underlying tissue activity function $C_T(t_k)$. Exploratory plots of z_k versus t_k are an essential step in data analysis. On this basis the approximate Poisson character of the counts y_k , the variance of z_k values is given by

$$\begin{aligned} \text{Var}(z_k) &= \text{Var}(y_k)(f_k c)^2 \approx \varphi E(y_k) f_k^2 c^2 \\ &= \varphi E(y_k f_k c) f_k c \\ &\approx \bar{\gamma} C_T(t_k) f_k \equiv \bar{\gamma} w_k^{-1} \end{aligned}$$

where $\bar{\gamma} = \varphi c$ and $\varphi(>0)$ reflects the extra-Poisson variation induced by reconstruction⁹. Using the model constructs for the residue and Equation 1, a form for the tissue concentration is obtained as $C_T(t|\theta)$, where θ is the set of model parameters. Specifically for the one- and two-compartmental models, $\theta = (\Delta, v_B, K_1, k_2)$ and $\theta = (\Delta, v_B, K_1, k_2, k_3, k_4)$ respectively, while $\theta = (\Delta, v_B, K, a_1, a_2, \dots, a_j)$ for the piecewise constant residue model. As there may be biological and other sources of deviation between the model and the data, the deviation of the data from the model is considered a sum of measurement and biologic error. Thus a reasonable statistical model for the data is

$$z_k = C_T(t_k|\theta) + \sigma \eta_k(\theta)^{-1/2} \epsilon_k \quad (1.1)$$

where $\eta_k(\theta)^{-1} = (1 + C_T(t_k|\theta) f_k)$ and $\sigma^2 \gamma = \bar{\gamma}$. In practice both σ and γ are unknown and the ϵ_k 's are modelled as a random sample from a standard normal distribution. Note, since η_k depends on the underlying tissue concentration, we have included its dependence on θ in Equation 6. The Poisson nature of the underlying emissions makes the assumption of independence not unreasonable and when the expected counts are large (a function of injected dose), a Gaussian approximation of the Poisson process is also reasonable. Based on Equation 6, conditional on γ , inference for parameters is based on the weighted residual sum of squares (WRSS)

$$\text{WRSS}(\theta) = \sum_{k=1}^N \omega_k(\theta) [z_k - C_T(t_k|\theta)]^2.$$

Standard iterative re-weighted least squares is used for estimation. For the compartmental models, the optimisation is implemented in R using the NLS function of Bates and DebRoy¹⁶. But even when weights are known, care must be taken as there are often multiple minima and the NLS process is quite sensitive to initialisation. For the piecewise constant residue model, apart from Δ , the unknowns enter linearly and so conditional for fixed weights, the estimation process is reduced to quadratic programming. With $\beta = (v_B, K, Ka_1, Ka_2, \dots, Ka_j)$ so $\theta = (\Delta, \beta)$ and

$$C_T(t_k|\Delta, \beta) = X_{k1}\beta_1 + X_{k2}\beta_2 + \dots + X_{k(j+2)}\beta_{j+2}$$

where $X_{k1} = C_P(t_k - \Delta)$, $X_{k2} = \int_0^{t_k} C_P(s - \Delta) ds$ and $X_{k(j+2)} = \int_0^{\max(t_k - \tau_j, 0)} C_P(s - \Delta) ds$ for $j=1, 2, \dots, J$. The components of β are non-negative and satisfy the linear constraint $\sum_{j=2} \beta_j = \beta_2$. Thus for any fixed Δ , a standard quadratic programming code can be used to obtain the unique optimal β -value. The implementation of this in R⁵ is highly efficient.

The weighted residuals are $r_k = \sqrt{\hat{\eta}_k}(z_k - \hat{z}_k)$, where $\hat{z}_k = C_T(t_k|\hat{\theta})$ and $\hat{\eta}_k = 1/(1 + C_T(t_k|\hat{\theta}) f_k)^{1/2}$ for $k = 1, \dots, N$. Asymptotic Normal approximation of sampling distributions via the Fisher

information matrix and subsequent propagation of error is quite unreliable. This arises from the parameter constraints which limit the Gaussian approximation and due to computational instability of the Hessian for compartmental models produced by the NLS routine in R. Thus sampling distributions for estimated model parameters and more particularly the derived quantities of interest (flow, flux, v_D , etc.) are best obtained by direct simulation, using Equation 6. This process provides estimates for standard errors and biases for parameter values⁴. The simulation approach is also recommended for model comparison^{3,20}. This avoids reliance on F-distributions for interpretation of weighted extra sums of squares statistics. Computational implementation of these in R is straightforward.

Considering that Equation 1 represents the time-course data as a convolution, one can appreciate that the most informative input function for identification of the residue is an idealised Dirac δ -function²⁰. But even then, the acquisition time-bins of dynamic scanning are incapable of resolving the within time-bin structure of the residue, and so there is no basis to prefer one pattern over another. This type of ambiguity is familiar with life-time data and the standard approach used is a piecewise constant form (e.g. the Kaplan-Meier estimator). Motivated by this, we take a residue function which is constant over acquisition time-bins as the fully nonparametric (NP) or saturated residue model. Since the acquisition time-bins are contiguous ($t_{sj} \equiv t_{s(j-1)}$ for $j = 2, \dots, N$), the NP residue is readily computed. We take $\tau_j = t_{s(j+1)}$ for $j = 1, \dots, N-1$. Under the sampling model in Equation 6, the piecewise constant residue can be shown to be consistent in dose (with parametric convergence). With an idealised Dirac input, the time-frames can be allowed to increase with dose and still achieve parametric convergence in dose. If the input is non-ideal, the convergence can still be guaranteed but the rate may not be parametric. NP estimates of flow, flux, v_D , etc., can be obtained from the NP residue, and sampling variation (standard errors and biases) derived by simulation.

Examples

We present kinetic analyses for two cerebral PET studies (one with ^{15}O -H₂O and the other with ^{18}F -FDG) conducted on a GE Advance scanner at the University of Washington, Seattle^{11,18}. The ^{15}O -H₂O study has $N = 36$ scans following a bolus venous injection over 6 seconds: ten 3-second scans, ten 6-second scans and ending with sixteen 9-second scans. The FDG study has $N = 30$ scans following a 1-minute infusion: four 20-second, 40-second, 1-minute, and 3-minute scans, and ending with fourteen 5-minute scans. Both studies here have direct arterial sampling. The arterial time-course for FDG shows that the tracer is retained in the blood for an extended period. The raw data (and variance) adjustment factor (f_k) for the ^{15}O -H₂O study increases much more dramatically than for FDG - see graph of variance factor f_k . This is due to the much shorter (2.07 minutes) half-life of ^{15}O in comparison to the 108 minute half-life of ^{18}F . AMIDE⁸ is an open-source medical image data examiner available for Windows, OS-X and Linux. Its flexible interface allows importation of data in raw DICOM and many other formats. There are convenient tools for co-registration with MR or CT data, if that is available. AMIDE has a simple 3-D region of interest (ROI) tool set, which allows extraction of ROI time-course data in dynamic studies and the ability to export that information for more detailed analysis in other environments. Figure 3 displays total tracer uptake in our ^{15}O -H₂O and FDG studies. ROIs for grey matter (^{15}O -H₂O) and a hypoglycaemic tumour region (FDG) were considered for analysis. The left-most plots show the time-course and directly sampled arterial data (adjusted for decay).

The illustrative kinetic analysis of the time-course data indicates that although the one-compartment model would typically be used for analysis of ^{15}O -H₂O and the two-compartment model for ^{18}F -FDG, these are found inadequate. Residual analysis and more formal assessment by simulation of the improvement in fit³, measured by the weighted sum

of squares, favours (p-values < 0.05) an NP approach for FDG and either the two compartment model or the NP analysis for $^{15}\text{O-H}_2\text{O}$. Estimates of key functional parameters (adjusted for bias) for both studies are shown. Standard errors for these are not substantially affected by whether a compartmental or NP approach is used. For $^{15}\text{O-H}_2\text{O}$ the values align with literature values for normal grey matter; the FDG kinetics indicate a much reduced flux, consistent with the post-treatment hypoglycaemic status of the tumour.

Conclusion

There is an expanding role for PET imaging in diagnostic radiology and this is set to continue, particularly in oncology. Dynamic PET studies offer the potential to obtain a detailed quantitative evaluation of metabolic processes associated with the interaction of the local tissue with the tracer molecule. Kinetic analysis is essential for this. The statistical elements of kinetic analysis involve the fitting of non-linear models for the tissue residue function -- a survival function construct which goes back to the work of Meier and Zierler¹⁰ on indicator dilutions. While one- and two-compartmental models are often used for kinetic analysis, a nonparametric approach is also feasible and indeed has some key advantages. PET time-course data often relate to tissue regions which are heterogeneous and this violates a central assumption of the compartmental modelling approach. Also the nonparametric approach can be expressed in terms of quadratic programming which greatly simplifies numerical evaluation. In practical terms, the analysis of dynamic PET studies relies on software tools for interaction with the image sets and for fitting relevant models. The possibility to use inexpensive (free) analytical tools like AMIDE and R could encourage a broader scientific interest in kinetic analysis of PET data. There are a number of research opportunities. Exceptions to the basic equation of dynamic PET arise in certain receptor imaging contexts, when the tracer may need to compete for a reduced set of available receptors. For further reading we suggest^{1,6,14,15,21}.

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Figure 1.
One-Compartment (1C) Model.

Figure 2.
Two-Compartment (2C) Model.

Figure 3.

Kinetic analysis of dynamic PET brain studies with ^{15}O -H₂O (top) and ^{18}F -fluorodeoxyglucose (FDG) (bottom). Left: AMIDE view of the tracer uptake data (colour) together with a co-registered T1-weighted MR scan for ^{15}O -H₂O and a PET tissue attenuation scan for FDG. The AMIDE ROIs for a grey matter region and tumour region are outlined in orange. Middle: ROI data and NP fit (grey line). Fitted compartmental and NP residue functions scaled by flow. Right: details of kinetic analysis. The measured arterial input (C_p) and the data weighting factor for decay and time-binning (f_k in section on statistical inference). Boxplots of weighted residuals from compartmental and NP models. Key parameter values (bias-corrected) with estimated standard errors. Reference histogram (yellow) for improvement in fit of the NP over compartmental model-observed value (vertical black line).