Appendix of the ISCORN[1] consensus

on renal transit time measurements

authors [2]:

Emmanuel DURAND, MD, PhD*[1]
M. Donald BLAUFOX, MD, PhD[2]
Keith BRITTON, MD, FRCP[3]
Ove CARLSEN[4]
Philip COSGRIFF, M.Sc.[5]
Eugene FINE, MD, MS[2]
John FLEMING, PhD[6]
Cyril NIMMON, BSc[7]
Amy PIEPSZ MD, PhD[8]
Alain PRIGENT, MD, PhD[1]
Martin ŠAMAL, MD, PhD[9]

* corresponding author
Service de Biophysique et Médecine Nucléaire – CHU Bicêtre
78 rue du Général Leclerc
F94275 Le Kremlin-Bicêtre, France
Tel: +33 1 45 21 26 37
Fax: +33 1 45 21 21 12
e-mail: emmanuel.durand@u-psud.fr

1- Univ Paris-Sud, Department of Biophysics and Nuclear Medicine, Le Kremlin-Bicêtre, France.
2- Department of Nuclear Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY.
3- Department of Nuclear Medicine, St Bartholomew's Hospital and Barts and the London, Queen Mary School of Medicine and Dentistry, University of London, London, United Kingdom.
4- Department of Nuclear Medicine, Vejle Hospital, Vejle, Denmark
5- Medical Physics Department, Pilgrim Hospital, Boston, Lincolnshire, United Kingdom.
6- Southampton University Hospitals NHS Trust, Southampton, United
7- Department of Nuclear Medicine, St Bartholomew's Hospital, London, United Kingdom (retired).
8- Centre Hospitalo-Universitaire St Pierre, Brussels, Belgium
9- Department of Nuclear Medicine, Charles University Prague and the General Teaching Hospital, Prague, Czech Republic

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Note: in the main text, for clarity sake, the formulation of convolution was written in a slightly simplified way. Thus, the functions P and R have a meaning that is slightly different here and in the main text.
In this document, the functions are expressed as continuous, which corresponds to a physical or physiological point of view. When activities are measured with a camera with a finite frame rate, the functions become discrete and the formulation should be modified, taking into account the sampling rate (this is out of the scope of this document).

A Renal retention function

This paragraph is considered as common knowledge to help less familiarised readers to understand what follows. Readers may refer to papers by Lawson **(53)**, Peters **(11)**, Wyman **(212)** of Bassingthwaighte **(213)** for more detailed information.

Let us use the following notations:

- F is the renal plasma flow (assumed constant here)
- E is the extraction ratio
- EF is the renal clearance i.e. the individual function
- $P(t)$ is the plasma concentration of tracer over time
- s_K is the renal detection sensitivity (i.e. number of cpm divided by number of Bq)
- s_C is the cardiac detection sensitivity
- v_K is the renal blood volume in the ROI
- v_C is the cardiac blood volume in the ROI
- $K^0(t)$ is the tracer content of kidney
- $K(t)$ is the renogram corrected for interstitial activity
- $R^0(t)$ is the normalised retention function
- $R(t)$ is the scaled retention function
- $R^M(t)$ is the modified retention function, after removing the vascular phase
- $R^{M,0}(t)$ is the modified retention function, after removing the vascular phase and normalising the plateau to 1
- h is the transport function (transit time spectrum)
- h^0 is the normalised transport function (with an integral normalised to 1)
- $I(t)$ is the input function to the kidney (flow of activity)
- $U(t)$ is the activity that is leaving the kidney ROI through urine

- $C(t)$ is the activity in the cardiac ROI corrected for interstitial activity

The activity in the kidney is the sum of the vascular activity, plus the activity extracted by kidney minus the activity that has left the renal ROI. Indeed, the resolution of renal scan cannot separate vessels from parenchyma. Therefore:

$$K(t) = s_K \left[v_K P(t) + EF \int_0^t P - \int_0^t U \right] \qquad \text{<eq. 1>}$$

When now considering a single molecule of tracer, let us define R^0 as the normalised retention function i.e. as the probability that a molecule that entered the kidney at time 0 still remains at time t. This function R^0 is a probability so its values range from 0 to 1. If the molecule can have different pathways inside the kidney (vessels, nephrons,… do have various lengths), one can easily imagine that the time that it will stay in the renal ROI is not always the same so there is a distribution of transit time and the probability will have the pattern described in Figure 2 (see main text). This is for a single molecule. However, as the kidney will receive tracer with a varying concentration along time, the tracer in the renal ROI will be the sum of all individual contributions from the molecules that arrive. If the tracer were injected directly into the renal artery, as an elementary bolus, without any recirculation, the renal content would be given by R^0 times the injected activity. In real life, the kidney receives as an input (in the renal artery) a function I which can be described as a successive of infinitesimal bolus injections shifted in time. The kidney response to each of these small bolus injections will be the function R^0 scaled to the amount injected at each instant, and shifted in time. Therefore, the response to the input function I will be the sum of all these individual responses given by the following:

- sum over all injections, each one made at time τ
- the kidney response at this time is given by the function R^0
- to see what is the response at time t, R^0 must be taken at time t, shifted by $-\tau$ to take into account the fact that injection wad delayed by a time τ, this gives $R^0(t-\tau)$
- scale this response by the amount injected at time τ, which is $I(\tau)\cdot d\tau$

So K^0, the renal content of tracer in the ROI is expressed as a convolution product (see Figure 5 in main text):

$$K^0(t) = \left[R^0 * I \right](t) = \int R^0(t-\tau) \times I(\tau)\, d\tau \qquad \text{<eq. 2>}$$

One must take care that the convolution product is a product of functions (not numbers!) so the commonly encountered formulation $R^0(t) * I(t)$ is not correct **(214)**.

In this equation, K^0 is in Bq, I in Bq/s and R^0 is adimensional (the convolution product is an equivalent to integrating over time). In practice, one does not know K^0 but rather K, the detected activity in the ROI, i.e. the renogram. The relationship between K and K^0 is given by the detection sensitivity:

$$K = s_K \times K^0 \qquad \text{<eq. 3>}$$

where s_K is expressed in cps/Bq. The input function I is the product of the renal plasma flow by the concentration of tracer in the renal artery:

$$I = F \times P \qquad \text{<eq. 4>}$$

If we assimilate the renal artery concentration to the cardiac concentration, P can be assessed by the detected activity C in a cardiac ROI:

$$C = s_C \times v_C \times P \qquad \text{<eq. 5>}$$

where v_C is the blood volume detected in the ROI and s_C the corresponding detection sensitivity. From <eq. 2> to <eq. 5>, we infer:

$$K = \left[\frac{s_K}{s_C} \frac{F}{v_C} \right] C * R^0 \qquad \text{<eq. 6>}$$

A deconvolution process applied on the detected activities K and C will provide the scaled retention function R, i.e. the function defined by

$$K = R * C \qquad \text{<eq. 7>}$$

From <eq. 6> and <eq. 7>, we can infer the relationship between R and R^0:

$$R = \left[\frac{s_K}{s_C} \frac{F}{v_C} \right] R^0 \qquad \text{<eq. 8>}$$

Initially, all the tracer is inside the kidney. This initial vascular peak lasts a time VTT (vascular transit time). So, when $t < \mathrm{VTT}$, the value of R^0 is 1 so:

$$R(t) = R_V = \frac{s_K}{s_C v_C} F \qquad \text{<eq. 9>}$$

which is proportional to the RBF. Absolute knowledge of the RBF would however require to know s_C, s_K and v_C. Here, for clarity sake, we have supposed that the vascular transit time VTT is unique. In some papers, the first vascular plateau is considered as infinitely short (Dirac distribution). After the vascular peak, either the molecule has not been extracted (probability $1-E$) so it leaves the kidney, or it has been extracted (probability E) so it remains in the kidney during a time that is called RTT (renal transit time) when R stays at a plateau. Therefore when $t > \mathrm{VTT}$ and $t < \mathrm{TT_{min}}$, the value of R^0 is E so:

$$R(t) = R_K = \frac{s_K}{s_C v_C} EF \qquad \text{<eq. 10>}$$

The plateau value R_K is then proportional to the renal function. Thus, assuming that s_K is the same for both kidneys, the plateau value can be used to determine relative function (proved in comparison with Patlak **(13)**). This may however not be precise enough to warrant an acceptable function assessment **(49)**. When $t > \mathrm{TT_{min}}$, R starts to decrease again until no tracer remains in the renal ROI, so the general shape for R is given by Figure 3 in main text.

Note that here, due to the external detection technique, the measured RRF R and the true RRF R^0 are different (as expressed in equation 8). The "scaling factor" between the two has the dimensions of inverse time. However, whereas this point would be relevant to determine absolute renal function, it is irrelevant for transit times.

B Determining transit times

The VTT, RTT_{min} and RTT_{max} can be read directly from the curve. In order to determine the mean renal transit time RTT_{mean}, it is necessary to remove the vascular part from R, which can be done by back extrapolation of the plateau (see Figure 1). With this modified function, named R^M, it is easy to see that the mean transit time is given by:

$$TT_{min} = \frac{\int_0^\infty R^M}{R_K} \qquad \text{<eq. 11>}$$

where $R_K = \max\left(R^M\right)$. Instead of recording what is inside the kidney, one can record what has left the kidney: this is given by the function $H = R_K - R^M$. The derivative of H, known as the transport function, or also as transit time spectrum, is defined as:

$$h(t) = H'(t) = -R^{M'}(t) \qquad \text{<eq. 12>}$$

and gives the distribution of transit times. Then, convoluting the transport function with the input function gives the urinary organ output:

$$U = h * C \qquad \text{<eq. 13>}$$

The mean transit time can also be calculated from h by:

$$TT_{mean} = \frac{\int_0^\infty t \cdot h(t)\,dt}{\int_0^\infty h(t)\,dt} \qquad \text{<eq. 14>}$$

Since $\int h = R_K$, instead of using the functions R and h, one can use normalised variants**(215)**:

$$R^{M,0} = \frac{1}{R_K} \cdot R^M \qquad \text{<eq. 15>}$$

and

$$h^0 = \frac{1}{R_K} \cdot h \qquad \text{<eq. 16>}$$

for which $\max\left(R^{M,0}\right) = 1$ and $\int h^0 = 1$. This has the drawback of loosing the functional information but it slightly simplifies the calculations for the transit time; with these normalised functions:

$$TT_{mean} = \int R^{M,0} \qquad \text{<eq. 17>}$$

$$TT_{mean} = \int t \cdot h^0(t)\,dt \qquad \text{<eq. 18>}$$

Because the end of the plateau is not easy to determine, RTTmin can be defined by using the point when the RRF falls under 90% of the plateau value **(216)**.

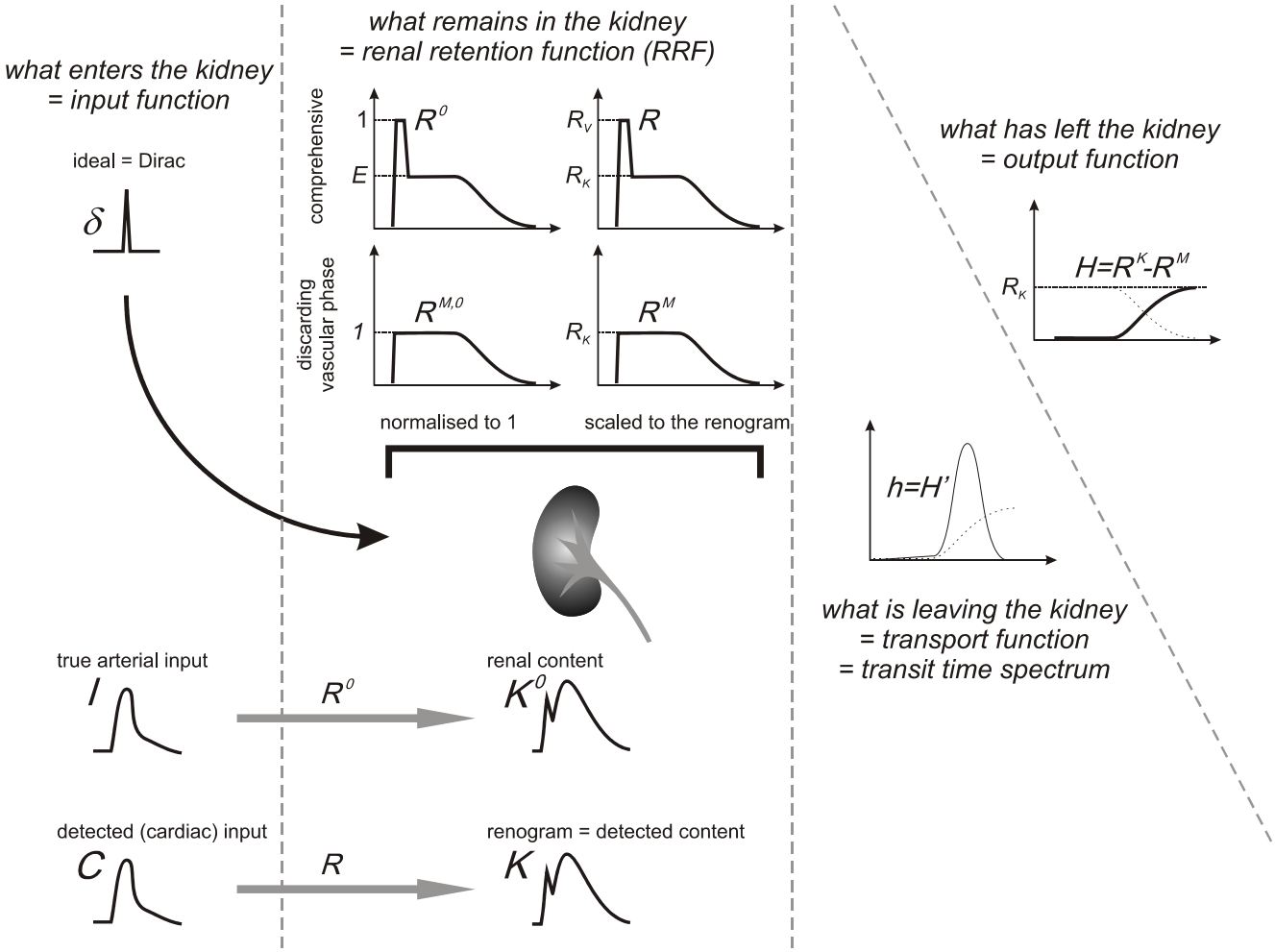

Figure 1 – Summary of the main functions used

B.1 Deconvolution techniques

In the equation $K = R * C$, the corrected renogram K and the corrected cardiac input C are known by renal scan. The continuous equation

$$K(t) = \int_{-\infty}^{+\infty} C(\tau) \times R(t-\tau)\, d\tau \qquad \text{<eq. 19>}$$

after sampling and considering a null activity before times zero, gives:

$$K_n = \sum_{k=0}^{k=\infty} C_k \times R_{n-k} \qquad \text{<eq. 20>}$$

where K_n stands for $K(n \times \Delta t)$, Δt being the sampling time. Assessment of transit requires inversion of this equation to get R. The process is called deconvolution. Continuous deconvolution leads to an integral equation with no general solution. However, deconvolution techniques exist for discrete data **(217)**. This could be performed by "exact" methods or by "non-exact methods". After deconvolution, RTT can be assessed on curve H as explained in paragraph 4.2.

B.1.1 "Exact" (or analytic) methods

All the following methods aim at finding the retention function that, when convoluted with the input function, would recreate the renogram. Accuracy could be considered as the goal and these methods considered as ideal. However, one should keep in mind that the primary goal is to assess a physiological parameter in a patient, not to solve a mathematical equation. Indeed, if the acquired data are imperfect – which they are – this could lead to a result that is much farther from the truth than with other (non-exact) methods **(53)**. Also, even if they are "exact", edge effects, choice of a given matrix… may induce differences between the results provided by these methods. The term 'exact' must be understood here as 'free of any *a priori* information'.

B.1.1.1 *Matrix inversion*

The principle of the matrix method is simple: because nothing was injected before time 0, I only takes non-null values for positive indices; the same is true for H because the kidney response needs to be causal. Therefore, one can write:

$$\begin{cases} K_0 = R_0 I_0 \\ K_1 = R_0 I_1 + R_1 I_0 \\ K_2 = R_0 I_2 + R_1 I_1 + R_2 I_0 \\ K_3 = R_0 I_3 + R_1 I_2 + R_2 I_1 + R_3 I_0 \\ \vdots \end{cases}$$

This is a set of N equations with N unknowns, which can be written with the matrix formalism as:

$$\begin{pmatrix} K_0 \\ K_1 \\ K_2 \\ K_3 \\ \vdots \end{pmatrix} = \begin{pmatrix} I_0 & 0 & 0 & 0 & \cdots \\ I_1 & I_0 & 0 & 0 & \cdots \\ I_2 & I_1 & I_0 & 0 & \cdots \\ I_3 & I_2 & I_1 & I_0 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix} \times \begin{pmatrix} R_0 \\ R_1 \\ R_2 \\ R_3 \\ \vdots \end{pmatrix}$$

This equation can be solved in an exact way by inverting the second matrix, which is easy even for very large numbers because it is triangular. However, the result may be strongly dependent on the first values so any error in the beginning of K or I will propagate and be amplified. This method is therefore very sensitive to noise **(53)**. Indeed, because of this sensitivity this method is called ill-conditioned. This means that a very slight variation of the input data, especially in the first points, could result in a huge variation of the result **(214,215)**. This method has been widely used, maybe because of its simplicity (the basic algorithm taking just a few lines of program code). Some authors chose to cut off any leading point before the maximum activity point in the input function, which increases the deconvolution stability.

B.1.1.2 *Fourier-transform method*

From the equation $K = I * R$, by Fourier-transformation, one obtains $\mathsf{F}\ K = \mathsf{F}\ I * \mathsf{F}\ R$ where F designs the Fourier-transform. Therefore, R can be easily obtained by inverse-Fourier transform:

$$R = \mathsf{F}^{-1}\left(\frac{\mathsf{F}\ K}{\mathsf{F}\ I}\right)$$

This also is an exact transform. However, in practice, Fourier-transform is usually performed on powers of 2. This implies to zero-pad the original functions and induces truncation artefacts **(24)**, with rapid oscillations. One may use some 'cut-off' level to remove high frequency noise. Moreover, windowing the data entails periodising it for Fourier transform **(218)**. Therefore, this method does not provide the same results as the matrix inversion. Data truncation is associated to high sensitivity to noise **(24)**. To avoid this, it is recommended to apodise (filter) the function at its end **(219)**. Therefore, though Fourier transform method is, from a theoretical point of view, an exact method, in practice, the results obtained may differ from those obtained by the matrix method. A comparison between Fourier and matrices showed that the results were very close together **(220)**.

B.1.1.3 *Laplace Transform method*

Laplace transform method is a similar technique when Fourier transform is replaced by Laplace-transform.**(9)**. If the input function is expressed as a sum of exponentials, the calculation can be made analytically and the exponential fitting removes noise from the input function, which makes the calculation of MTT robust to noise **(221, 222)**. Exponential fitting the input function entails neglecting the initial ascending part of the blood curve, which may be a source of error **(223)**. Indeed, an input function on kidney (with recirculation) does not look like a sum of exponentials**(56, 224)**; indeed, it is usually taken from a so-called "gamma-fit" at its beginning **(225)**. Unlike the Fourier method, the Laplace method does not assume periodicity so it is quite immune to late oscillation of RRF. It is also more noise proof than unfiltered matrix method **(220)**

B.1.1.4 *Orthogonal polynomials*

Like the Fourier and Laplace techniques, this method projects the data onto a basis, which is here a series of Legendre polynomials. The original paper claimed this technique more robust than matrix inversion or Fourier inversion technique **(226)** but this method was not reassessed in further published studies.

B.1.1.5 *z-transform method*

Neufeld developed a formalism with the z-transform, noticing that it is the discrete version of Laplace transform and that it can be considered as division of polynomials **(227)**. Berehi also proposed to use the z-transform for deconvolution but showed that this method reduces to the matrix inversion **(228)**.

B.1.2 Non-exact (or approximate) methods

The four previous methods can be called « exact-methods » because they aim at delivering the function H that, when convoluted with the function I, will give you back the function K. However, one must keep in mind that this is a mathematical point of view, neglecting any errors on the measured functions K and I. In real life, these functions are only known with errors (biases and Poissonian noise) so the aim is not to get the function H that will fit the best the equation, but the function H that will match the best the behaviour of the kidney. It was shown by simulation that, except when noise is very low, unfiltered "exact methods" perform very poorly in producing reliable results **(216)**. Indeed, small uncertainties in the measured data may lead to considerable error. This is analogous to the 'butterfly effect' and occur when the problem is ill-conditioned. Filtering is one solution. Other methods can also be used, that will provide "less-exact" results from a purely mathematical point of view, but more realistic results from a physiological point of view. All of these methods inject some *a priori* information into the model to avoid to get an unrealistic solution. The result is not the more probable solution in the absolute (which is given by unfiltered "exact" methods) but it is

the more probable solution given some *a priori* assumptions in a Bayesian approach. This technique is called regularised inversion or constrained solutions **(53, 218)**.

B.1.2.1 *Model-Fitting (constrained least-squares)*

These methods also consist in solving the equation $K = I * R$, i.e. finding R but here, this is performed by optimisation (iterative process), under physiological constraints.(i.e. the renal retention function R must be positive and monotonic (decreasing) **(72, 229)**, or may be "smooth" or may use a constraint based on noise distribution) **(216, 230)**. Such a model-fitting would be preferable than exact deconvolution for low-count data such as vascular transit time **(18)**. This technique also proved more reliable to assess MTT than exact solutions when transit was slow **(216)**.

B.1.2.2 *Rutland's methods without deconvolution*

In the Patlak-Rutland approach, the renogram can be expressed as:

$$K(t) = aP(t) + EF\int_0^t P - U(t) \qquad \text{<eq. 21>}$$

where $U(t)$ is the output (what has left the renal ROI). Therefore, after determination of a, it is easy to get a corrected renogram:

$$K_C(t) = K(t) - aP(t) = EF\int_0^t P - U(t) \qquad \text{<eq. 22>}$$

By making the assumption that the transit time is unique, of value T , then the output in just the input shifted in time by T:

$$U(t) = EF\int_{-T}^{t-T} P \qquad \text{<eq. 23>}$$

$$K_C(t) = EF\int_{t-T}^{t} P \qquad \text{<eq. 24>}$$

It is then easy to find T from K_C and P **(231)**. This could be done for any point of the curve. In a further article, it was even proposed to compute T for various times t to obtain a RRF $T(t)$ **(232)**. This however is not coherent with the assumption of a single transit time upon which this technique relies. This technique was shown to provide only an approximation of transit time **(212, 233)**.

B.1.2.3 *Patlak-Rutland plot differentiation or "database deconvolution"*

In Patlak-Rutland plot, the experimental points are initially aligned to form a straight line. When some tracer starts getting out of the ROI, this model is no longer true. By deriving this plot, one will obtain a constant value before minimal transit time and a decreasing value after. This has a behaviour that is very close to RRF. Rutland suggested that deriving the Patlak-Rutland plot would provide an estimation of RRF. The similarity between the two would become identity if the input function were a constant **(234)**. The advantage is that it only requires simple calculations (a spreadsheet software suffices)**(234)**. However, only correlation (not agreement) was shown between the deconvolution method and this new method **(231)**. Indeed, this method is a (fair) estimation of RRF **(233) (235)**. In fact, in case of a perfectly monoexponential function, this method equals the RRF. When the input function is not monoexponential, this method only gives the RRF in its first part, before the minimum transit time **(236)**.

B.1.2.4 *Singular Value Decomposition*

This technique is based on the assumption that R is limited in time; indeed, for normal kidneys, RRF falls to zero after a few minutes. On the contrary, the renogram, containing information on K and I lasts usually for a longer time. Therefore, the system is over determined. One can take the opportunity to draw only the more relevant part of information contained in K and I using a technique used Singular Value Decomposition **(237)**, which is quite similar to factorial analysis. In fact, this method proved applicable even for increased transit times.

B.1.3 Filtering (curve smoothing)

Because of Poissonian and physiological noise, exact methods are quite sensitive to noise so filtering is recommended to avoid error amplification. Contrarily, the constrained least squares techniques do not require any smoothing. Either input function, renogram or RRF could be filtered. Diffey proposed an adaptive filter to improve deconvolution by the matrix method **(20, 238)**. However, **(239)**, with the matrix method, after comparing a linear filter and an adaptive filter on the RRF, they conclude that the linear filter provides better results. The classical filter is a linear 1-2-1 filter, applied several times, which reduces to 1-4-6-4-1, 1-6-15-20-15-6-1 and so on. Non-linear adaptive filters were also proposed **(146, 238, 240)**. A drawback of filtering is loss of temporal resolution. Thus, intensive smoothing smears out the vascular component of H and makes the determination of the plateau harder **(24)**.

B.1.4 Comparison between methods

The use of different deconvolution methods (along with variations in choice of including background subtraction and, smoothing protocols…) can result in RRF with very different shapes **(230, 241)**. However, the MTT seems rather robust and does not depends much on the deconvolution technique **(53, 222, 230, 241)**. Indeed, the MTT only depends on the plateau level and the area under the curve. In dogs, no difference in MTT was found between the 3 following methods: matrices, Fourier and constrained least square **(241)**. However, data is lacking about robustness of dispersion parameters such as PTTI. In situations where noise is very low, exact techniques, such as the matrix method, perform better**(216)**. Conversely, when the data are very noisy, constrained least square methods perform better **(216)**. If retention functions are to be displayed, the output of the matrix algorithm will tend to be noisy and some additional smoothing may be advantageous**(48)**. Contrarily, the output of the constrained least squares technique will be better-behaved for this purpose.

C Other Transit indices

Other transit indices have been reported, without further validation.

C.1.1 Pelvic Excretion Efficiency (PEE)

This index is very close to OE but with an additional (probably minor in practice) correction for vascular activity **(242)**:

$$K(t) = \underbrace{c\int_0^t P}_{uptake} + \underbrace{b \times P(t)}_{vascular} - \underbrace{O(t)}_{drainage}$$

$$PEE(t) = \frac{drainage}{uptake} = \frac{K(t) - c\int_0^t P - b \times P(t)}{c\int_0^t P}$$

Normal is above 86%.

C.1.2 Elimination Index (EI)

The elimination index was defined as the ratio of A3/A20 or (if peak < 3 min) Apeak/A20 **(243)** with a normal above 3.

C.1.3 Carlsen's method

A transit time index, expressed in time units, without deconvolution, was also recently proposed and tested by simulation in adult data **(244)**.

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