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Analogue tracers and lumped constant in capillary beds

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Abstract

The lumped constant is a proportionality factor for converting a tracer analogue's metabolic rate to that of its mother substance. In a uniform system, it is expressed as the ratio of the tracer analogue's extraction fraction (E^*) to the extraction fraction of its mother substance (E).

Here we show that, in capillary beds perfused by unidirectional blood flow, unequal concentration gradients of the tracer analogue and of the mother substance influence extraction fractions both locally and across the organ and that the direct proportionality of E^* and E must be replaced by $\ln(1-E^*)/\ln(1-E)$ to yield Λ , i.e. the lumped constant derived from first principles of bi-substrate enzyme and membrane kinetics. In other words, at a given capillary blood flow (F), the ratio of systemic clearances ($F E^*/F E$), often used in compartmental kinetic analysis, must be replaced by the ratio of the intrinsic clearances, $[-F \ln(1-E^*)]/[-F \ln(1-E)]$.

The conclusion is supported by 2- $[^{18}\text{F}]$ fluoro-2-deoxy-D-galactose removal kinetics in pig liver *in vivo* from previous publications by the dependence of E^*/E and the independence of Λ , respectively, on blood galactose concentration. Moreover, our corrections to the results of compartmental kinetics are quantified for comparing extraction fractions in different of regions of interest (e.g. by positron emission tomography) and for calculating Λ using whole-organ E^* and E measured by arteriovenous concentration differences.

Keywords

Microvascular tracer kinetics *in vivo*; Intrinsic clearance; 2- $[^{18}\text{F}]$ Fluoro-2-deoxy-D-glucose PET; Positron emission tomography; Bi-substrate enzyme kinetics

1. Introduction

Structural differences between natural sugars and their radioactive analogue tracers (the latter used in kinetic studies such as positron emission tomography (PET)) facilitate the

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study of regional metabolism by halting analogue metabolism after the phosphorylation step. However, this advantage comes at the cost of making the analogue inaccurate as tracer of its mother substance. To correct for this inaccuracy, the lumped constant is universally used to quantitatively convert the measured metabolic clearance of the tracer analogue to that of its mother substance.

In the simplest situation a radiolabelled analogue tracer is present at a concentration c^* and the mother substance at concentration c in the bathing fluid of a well-mixed suspension of cells that metabolize the tracer and the mother substance at steady metabolic rates v^* and v , respectively. The relationship between v^* , c^* , v and c as assessed by first principles of bi-substrate enzyme kinetics and membrane transport defines the lumped constant Λ [1,2]. For this calculation, compartmental kinetics is appropriate. *In vivo*, however, the cells line capillaries perfused by unidirectional flow at rate F , with inlet concentrations of mother substance (c_i) and tracer analogue (c_i^*). Then different concentration gradients of the two substrates form in the capillary along the flow direction, based on their respective intrinsic kinetic characteristics. Here we show that, in a capillary bed, the aforementioned Λ calculated from first principles of enzyme and membrane kinetics, is equal to the ratio of the intrinsic clearances $[-F \ln(1 - v/F c_i)]$ and $[-F \ln(1 - v^*/F c_i^*)]$ but not the ratio of the systemic clearances v/c_i and v^*/c_i^* . We demonstrate this by showing, both theoretically and experimentally, that when Λ is independent of the concentration of mother substance (as for galactose and 2- ^{18}F fluoro-2-deoxy-galactose ($^{18}\text{FDGal}$) in pig liver) then the ratio of intrinsic, but not of systemic, clearances is so independent.

If the ratio of systemic clearances is used in place of Λ in a capillary bed (as is commonly done), then inferences from the tracer analogue to the mother substance become semi-quantitative: we show that when Λ is greater (or smaller) than unity, then it is also greater (or smaller) than $(v^*/F c_i^*)/(v/F c_i)$. This inequality increases with the magnitudes of the clearances and with the deviation of Λ from unity. When $v^*/F c_i^*$ and $v/F c_i$ are small relative to unity, intrinsic and systemic clearances approach each other, as the compartmental kinetics become increasingly applicable with diminishing concentration gradients. The widespread use of the ratio of systemic clearance to approximate Λ in a capillary bed is acceptable in that limit [2].

When comparing local extraction fractions in two regions of interest (ROIs) within the same organ, for example, the brain [3], the inference from tracer analogue to mother substance is particularly simple when Λ is close to the ratio of the systemic clearances of the tracer analogue to the mother substance. In this case, the ratio of the systemic clearances of the mother substance in the two ROIs is then equal (by cancellation of Λ) to the ratio of tracer analogue clearances in these same two ROIs. We show how this equality is modified in capillary beds as a result of intrinsic clearances replacing systemic clearances. The need to distinguish systemic from intrinsic clearance signifies that microvascular elements have been incorporated into the model.

2. Lumped constant in a uniform system (cell suspension)

Consider an enzyme with Michaelis-Menten parameters $V_{\max}$ and K_m for a substrate of concentration c_c metabolised at the steady rate v (and, similarly, $V_{\max}^*$, K_m^* , c_c^* and v^* for a second, competing substrate, such as a radiolabelled tracer). Then [1]:

$$v = \frac{V_{\max} c_c}{c_c + K_m (1 + c_c^*/K_m^*)} \quad (1)$$

$$v^* = \frac{V_{\max}^* c_c^*}{c_c^* + K_m^* (1 + c_c/K_m)} \quad (2)$$

pertain to a well-mixed intracellular compartment that is in contact, via a permeable plasma membrane, with a well-mixed plasma compartment containing concentrations c and c^* of the two substrates.

Next, let the radiolabelled analogue be present in only tracer quantities. Neglecting c_c^*/K_m^* against unity, Eq. (1) and Eq. (2) then become:

$$v = \frac{V_{\max}/K_m}{1 + c_c/K_m} c_c \quad (3)$$

$$v^* = \frac{V_{\max}^*/K_m^*}{1 + c_c/K_m} c_c^* \quad (4)$$

Dividing Eq. (3) and Eq. (4) by the plasma concentrations c and c^* , respectively, yields the plasma clearances v/c and v^*/c^* :

$$v/c = \frac{V_{\max}/K_m}{1 + c_c/K_m} (c_c/c) \quad (5)$$

$$v^*/c^* = \frac{V_{\max}^*/K_m^*}{1 + c_c/K_m} (c_c^*/c^*) \quad (6)$$

Defining the lumped constant as:

$$\Lambda = \frac{V_{\max}^*/K_m^*}{V_{\max}/K_m} \left[\frac{c_c^*/c^*}{c_c/c} \right] \quad (7)$$

and dividing Eq. (5) by Eq. (6), we obtain:

$$\Lambda v/c = v^*/c^* \quad (8)$$

Note that the denominators $(1 + c_c/K_m)$ in Eqs. (5) and Eq. (6) have been cancelled out in Eq. (7) and Eq. (8).

3. The partition coefficients

Next, we consider the cell-plasma partition coefficients c_c/c and c_c^*/c^* in Eq. (7). At quasi-steady state, transport in and out of the cell take place at approximately constant rates described by:

$$PSc = P'S c_c + v \quad (9)$$

$$P^*Sc^* = P'^*Sc_c^* + v^* \quad (10)$$

where v and v^* are given by Eq. (3) and Eq. (4) with PS and $P'S$ being the permeability-surface area products for influx and efflux, respectively, across the cell membrane for the mother substance (and similarly, P^*S and P'^*S for the tracer). Substituting Eq. (5) for v in Eq. (9) yields:

$$\frac{c_c}{c} = \frac{PS}{P'S + \frac{V_{\max}/K_m}{1 + c_c/K_m}} \quad (11)$$

while substituting using Eq. (6) for v^* in Eq. (10) yields:

$$\frac{c_c^*}{c^*} = \frac{P^*S}{P'^*S + \frac{V_{\max}^*/K_m^*}{1 + c_c^*/K_m^*}} \quad (12)$$

where c_c/K_m on the right-hand sides of Eq. (11) and Eq. (12) can be expressed in terms of observed plasma concentration c by solving Eq. (12) for c_c .

For a highly permeable membrane, that is $P^*S \gg V_{\max}^*/K_m^*$ and $P'S \gg V_{\max}/K_m$, Eq. (11) and Eq. (12) are simplified:

$$c_c/c = PS/P'S \quad (13)$$

$$c_c^*/c^* = P^*S/P'^*S \quad (14)$$

and therefore Λ , as given by Eq. (7), becomes independent of the cold mother substance concentration. This is indeed the case for galactose and ^{18}F FDGal metabolism in the liver, as discussed below in Section 6, and possibly for the glucose analogue 2- ^{18}F fluoro-2-deoxy-D-glucose (^{18}F FDG).

4. Formal introduction of extraction fractions in compartmental analysis

In a uniform system (such as a well-mixed cell suspension), an extraction fraction cannot be defined. In compartmental analysis, a conventional next step introduces extraction fractions by dividing v and v^* through with F :

$$v/(Fc_i) = E \quad \text{and} \quad v^*/(Fc_i^*) = E^* \quad (15)$$

where the replacement of c and c^* with the inlet (arterial) concentrations c_i and c_i^* hints at concentration differences without specifying them. From PET data, local systemic clearance v^*/c_i^* is estimated. Using Eq. (15), we can express the ratio of systemic clearances formally as E^*/E , without explicit reference to concentration gradients although their implicit presence has the consequence that E^*/E is not equal to Λ , as we show next (see also the end of Section 5).

5. Lumped constant in a capillary bed

In the presence of substrate concentration gradients, Eqs. (5)–(8) can be applied to each infinitesimal volume element, thereby contributing the metabolic rates dv and dv^* to total metabolism:

$$\Lambda \frac{dv}{c} = \frac{dv^*}{c^*} \quad (16)$$

which is the infinitesimal counterpart of Eq. (8), with Λ given by Eq. (7).

In an organ perfused from inlet to outlet through a manifold of functionally parallel capillaries (the so-called “convective spaghetti” [4]), we put the x -axis along the flow from inlet at $x = 0$ to outlet at $x = L$. The volume element between x and $x+dx$ extends into adjoining cells, in which metabolism takes place at substrate concentrations c_c and c_c^* , but the substrates are assumed to be transported in the x -direction only by the convective fluxes Fc and Fc^* (Fig. 1). Then:

$$dv = -Fdc \quad (17)$$

$$dv^* = -Fdc^* \quad (18)$$

so that, from Eq. (16):

$$\Lambda dc/c = dc^*/c^* \quad (19)$$

Thus, the modelling of single-substrate saturation kinetics in a capillary bed [5–8] is extended here to a pair of substrates. The minimum size of a PET region-of-interest (ROI) ensures that the ROI contains predominantly complete capillaries with their substrate gradients.

Integrating Eq. (19) from inlet [$x = 0$: $c(0) = c_i$, $c^*(0) = c_i^*$] to the outlet [$x = L$: $c(L) = c_o$, $c^*(L) = c_o^*$], we find:

$$\Lambda \ln \frac{c_o}{c_i} = \ln \frac{c_o^*}{c_i^*} \quad (20)$$

Using extraction fractions, now fully defined by

$$E = 1 - \frac{c_o}{c_i}, \quad E^* = 1 - \frac{c_o^*}{c_i^*} \quad (21)$$

we obtain:

$$\Lambda = \frac{\ln(1 - E^*)}{\ln(1 - E)} \quad (22)$$

Thus, in this simplest description of metabolism in a capillary bed, Λ given by Eq. (7) is the constant of proportionality between the intrinsic clearances $[-F \ln(1-E^*)]$ and $[-F \ln(1-E)]$. Note that, whereas the intrinsic clearance expression is confined to first-order kinetics, Eq. (22) holds for two substrates governed by Michaelis-Menten kinetics, if the saturation kinetics is dominated by one of them.

Making use of the expansion in positive terms

$$-\ln(1-E) = E + \frac{1}{2}E^2 + \frac{1}{3}E^3 + \dots \quad \text{where } 0 < E < 1$$

(e.g., Abramowitz and Stegun [9]), we can then write Eq. (22) as:

$$\Lambda = \left(\frac{E^*}{E} \right) \frac{1 + \frac{1}{2}E^* + \frac{1}{3}E^{*2} + \dots}{1 + \frac{1}{2}E + \frac{1}{3}E^2 + \dots} \quad (23)$$

and deduce that if $\Lambda > 1$, then $E^* > E$, and therefore $\Lambda > E^*/E$. If $\Lambda < 1$, then $E^* < E$, and therefore $\Lambda < E^*/E$. Hence the use of E^*/E in place of Λ in a capillary bed renders inferences drawn from the analogue tracer and applied to the mother substance only semi-quantitative. This same conclusion holds for the use of E^*/E when Λ is calculated experimentally by determining whole-organ extraction fractions [Eq. (21)] from inlet and outlet samples of the analogue and mother substance.

An example of this, with $\Lambda > 1$, is provided by a study in human skeletal muscle [10]. Arterial and venous blood samples of ^3H -glucose and the glucose analogue ^{18}F FDG were used to determine whole-organ extraction fractions E and E^* , both of which varied between 0.1 and 0.7 upon insulin dosing. The ratio E^*/E was found to be constant at 1.2 (range, 1.1 – 1.3), whereas Λ calculated as $[\ln(1-E^*)]/[\ln(1-E)]$ varies from 1.1 (at low extraction fraction) to 1.5 (at the highest observed extraction fraction). Kelley et al. [10] concluded that the lumped constant (which they calculated as E^*/E) was unaffected by insulin dose, but Λ has a larger range and it is thus likely that an effect of insulin was missed by E^*/E . The inequality between Λ and E^*/E is due to unequal concentration gradients of ^{18}F FDG and ^3H -glucose along the capillary flow. This mismatch is eliminated only when $\Lambda = 1$ or when extraction fractions are small relative to unity.

The integration step from Eq. (19) to Eq. (20) clarifies the problematic transition from spatially uniform clearances in Eqs. (5) and (6) to Eqs. (15) in Section 5. By integrating Eq. (19) explicitly from inlet to outlet,

$$\Lambda \int_{c_i}^{c_o} \frac{dc}{c} = \int_{c_i^*}^{c_o^*} \frac{dc^*}{c^*}$$

we can deduce the compartmental use of E^*/E as the lumped constant only by the unjustified replacement of the variable denominators of the integrands with the constant lower integration limits: $c = c_i$, $c^* = c_i^*$, along the entire length of the perfused capillaries (“arterial equilibration” assumption).

6. Dependence of E^*/E , but not of Λ , on the concentration of mother substance

Does Λ depend on the plasma concentration of mother substance, and if so, how? This question is important for the use of analogue tracer, especially when an endogenous concentration cannot be adequately controlled, as in the case of glucose in humans.

To uncover the essentials, we turn to the limits of relatively high membrane permeability [Eq. (13) and Eq. (14)], so that the partition coefficients c_c^*/c^* , c_c/c in each volume element, and Λ are all independent of the concentration of the mother substance. These limits are firmly established for galactose and ^{18}F Gal in intact pig liver in references [7,11–12] containing the data to which the following calculation will be applied. We take the anti-logarithm of Eq. (20):

$$\frac{c_o^*}{c_i^*} = \left(\frac{c_o}{c_i} \right)^\Lambda \quad (24)$$

Then, introducing the kinetics described by Eq. (3) into a bed of functionally identical capillaries (sinusoids) acting in parallel, with steady state metabolic rate of substrate (v) according to the sinusoidal perfusion model [6–7]:

$$1 - E = \frac{c_o}{c_i} = e^{-\frac{V_{\max} - v}{FK_m}} = e^{-\frac{V_{\max}/(FK_m)}{1 + \hat{c}/K_m}} \quad (25)$$

where

$$v = F(c_i - c_o) \text{ and } \hat{c} = \frac{c_i - c_o}{\ln(c_i/c_o)} \quad (26)$$

$\hat{c}$ is the logarithmic mean of c_i and c_o and accounts for the decreasing substrate concentration along the capillary (sinusoid) as used in the Michaelis-Menten relation *in vivo* between v and $\hat{c}$ [6–7].

From Eq. (21), Eq. (24) and Eq. (25):

$$1 - E^* = \frac{c_o^*}{c_i^*} = e^{-\Lambda \frac{V_{\max}/(FK_m)}{1 + \hat{c}/K_m}} \quad (27)$$

From Eq. (25) and Eq. (27):

$$\frac{E^*}{E} = \frac{1 - e^{-\Lambda \frac{V_{\max}/(FK_m)}{1 + \hat{c}/K_m}}}{1 - e^{-\frac{V_{\max}/(FK_m)}{1 + \hat{c}/K_m}}} \quad (28)$$

The dependence of E^*/E on $\hat{c}/K_m$ in Eq. (28) is illustrated in Fig. 2 for different values of Λ and $V_{\max}/(F K_m)$. As $\hat{c}$ increases from zero concentration of mother substance to $\hat{c} \gg K_m$, then E^*/E goes from:

$$(E^*/E)_{\hat{c}=0} = \frac{1 - e^{-\Lambda V_{\max}/(FK_m)}}{1 - e^{-V_{\max}/(FK_m)}} \quad (29)$$

to:

$$(E^*/E)_{\hat{c} \gg K_m} = \Lambda \quad (30)$$

as compartmental kinetics approaches microvascular kinetics at near-saturation. Given that Λ is in fact independent of $\hat{c}$ in the case under consideration, this variation of E^*/E with $\hat{c}$ invalidates the use of E^*/E as lumped constant. The red curve in Fig. 2 illustrates this conclusion using *in vivo* parameters for removal kinetics in pig liver of FDGal [12] and galactose [11], for which the simplifications stated in Section 3 hold. From Eq. (29), $(E^*/E)_{\hat{c}=0} = 0.45$ which is three times larger than $(E^*/E)_{\hat{c} \gg K_m} \approx \Lambda = 0.15$ in Eq. (30), whereas $\ln(1-E^*)/\ln(1-E) = 0.15$, independent of $\hat{c}$.

7. Comparing regional metabolic rates

Comparing metabolic activities in regions within the same organ is of interest both in normal physiology (e.g., regional cerebral glucose utilization rates) and in pathophysiology (e.g., PET of tumour areas with an increased metabolic rate visible as *hotspots* compared to the metabolic rate in surrounding reference tissue).

If in two regions of interest (ROIs), the metabolic rates of the tracer analogue v_1^* and v_2^* have been measured, E_1^* and E_2^* follow from Eqs. (15). For a common influx $F c_i$ into the two ROIs, the expression $E_2^*/E_1^* = v_2^*/v_1^*$ holds for the ratios. We wish to deduce the ratio E_2/E_1 for the mother substance from E_2^* and E_1^* .

Isolating E from Eq. (22) and taking the ratio E_2/E_1 pertaining to the two ROIs:

$$E_2/E_1 = \frac{1 - (1 - E_2^*)^{1/\Lambda}}{1 - (1 - E_1^*)^{1/\Lambda}} \quad (31)$$

Thus, E_2/E_1 depends on Λ and on E_2^* and E_1^* separately. However, when $E_2^* \ll 1$ and $E_1^* \ll 1$, or when $\Lambda \approx 1$, Eq. (31) simplifies to:

$$E_2/E_1 = E_2^*/E_1^* \quad (32)$$

independent of Λ . This attractive simplification is commonly used beyond its range of validity. For example, cerebral glucose utilization rate in monkeys has been found to be four times higher in the inferior colliculus than in the hypothalamus [3] from E_2^*/E_1^* using Eq. (32). Given that the glucose and analogue extraction fractions by the whole brain, which were used to calculate the lumped constant by their ratio, were small in contrast to some regional values, we adopted the published value for Λ of 0.34 [3]. Assuming $E_1^* = 0.1$ and $E_2^* = 0.4$ yields E_2/E_1 of 4 from Eq. (32), but only 2.9 from Eq. (31). Thus, comparisons of metabolic activities in different regions of a capillary bed that are based on Eq. (32) are semi-quantitative.

In general, the ratio of higher to lower regional extraction fractions of the analogue tracer underestimates the ratio of extraction fraction of the mother substance in the same ROIs when $\Lambda > 1$, and overestimates the ratio when $\Lambda < 1$. A proof of this is provided in the Appendix.

8. Discussion

Since ROIs from PET recordings provide data in the form of average activities, compartments appear to be natural elements of modelling regional metabolism. However, compartmental models are unable to account fully for the effects of concentration gradients of substrate in a capillary bed resulting from interactions of its metabolism with its convective transport by blood perfusion [13]. Such effects are better handled with physiologically based microvascular models of the whole perfused organ, which interpret data sampled from its artery and vein but are unable to infer metabolic rates in local regions of interest. The present work aims at bridging this gap between the compartmental and microvascular approaches.

The limitation of compartmental modelling of metabolic rates in perfused organs becomes apparent when relating metabolic rates of a pair of substances (such as a mother substance and its tracer analogue) that interact differently with their common microvascular environment. The lumped constant Λ , developed to enable inferences from radiolabelled analogue to mother substance, is a case in point. As derived from first principles in Section 2, Λ is the proportionality constant between the systemic clearance of the mother substance and analogue in a uniform system, such as a cell suspension, and between their intrinsic clearances in a capillary bed. The quantitative effects of introducing these microvascular elements increase with the magnitudes of extraction fractions and with the deviation of Λ from unity, reflecting the mismatch between concentration profiles of tracer analogue and mother substance along the blood flow.

If the ratio E^*/E of extraction fractions was regarded as the definition of the lumped constant then, in a capillary bed (with E^* and E not small relative to unity), the lumped constant so defined would not be equal to Λ in Eq. (7), and it would vary with the concentration of the cold mother substance (Section 6) and with the choice of region of interest (Section 7), whereby the usefulness of tracer analogue for quantitative inferences about its mother substance would be lost.

The present model assumes functionally identical capillaries acting in parallel and neglects the effects of capillary heterogeneity of length, diameter and flow velocity [14]. We thereby adopted the simplest possible assumption which succeeds in bringing microcirculation quantitatively into the picture without introducing any additional parameters.

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List of Symbols

* indicates a radiolabelled tracer

c_c, c_c^*

Intracellular concentration (mmol/L)

c, c^*	Plasma concentration (mmol/L)
c_i, c_i^*	Inlet plasma concentration (mmol/L)
c_o, c_o^*	Outlet plasma concentration (mmol/L)
$\hat{c}$	Logarithmic mean of c_i and c_o (mmol/L)
F	Plasma flow rate (L/min)
E, E^*	Extraction fraction
Λ	Lumped constant
v, v^*	Rate of metabolism (mmol/min)
$V_{\max}, V_{\max}^*$	Maximum rate of metabolism (mmol/min)
K_m, K_m^*	Michaelis constant (mmol/L)
$v/c_i, v^*/c_i^*$	Systemic clearance (L/min)
$V_{\max}/K_m, V_{\max}^*/K_m^*$	Intrinsic clearance (L/min)
PS, P^*S	Permeability-surface area product, plasma-to-cell (L/min)
P^*S, P^*S	Permeability-surface area product, cell-to-plasma (L/min)
x, y, z	Mathematical symbols

References

1. Dixon, M.; Webb, EC. Enzymes. 3. Bungay; Longman, UK: 1979.
2. Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem.* 1977; 28:897–816. [PubMed: 864466]
3. Sokoloff, L. The radioactive deoxyglucose method: Theory, procedure, and applications for the measurement of local glucose utilization in the central nervous system. In: Agranoff, BW.; Aprison, MH., editors. *Advances in Neurochemistry*. Vol. 4. Plenum Publishing Corporation; 1977. p. 1-82.
4. Lassen, NA.; Perl, W. *Tracer Kinetic Methods in Physiology*. Raven press; New York: 1979.
5. Goresky CA, Bach GG, Nadeau BE. On the uptake of material by the intact liver. *J Clin Invest.* 1973; 52:975–1025. [PubMed: 4573355]
6. Bass L, Keiding S, Winkler K, Tygstrup N. Enzymatic elimination of substrates flowing through the intact liver. *J Theor Biol.* 1976; 61:393–399. [PubMed: 979305]
7. Keiding S, Johansen S, Winkler K, Tønnesen K, Tygstrup N. Michaelis-Menten kinetics of galactose elimination by the isolated perfused pig liver. *Am J Physiol.* 1976; 230:1302–1313. [PubMed: 1275072]
8. Goresky CA, Bach GG, Rose CP. Effects of saturating metabolic uptake on space profiles and tracer kinetics. *Am J Physiol.* 1983; 244:G215–232. [PubMed: 6337505]
9. Abramowitz, M.; Stegun, IA. *Handbook of Mathematical Functions*. New York: Dover; 1972.
10. Kelley DE, Williams KV, Price JC, Goodpaster B. Determination of the lumped constant for [^{18}F]fluorodeoxyglucose in human skeletal muscle. *J Nucl Med.* 1979; 40:1798–1804. [PubMed: 10565773]
11. Keiding S, Johansen S, Winkler K. Hepatic galactose elimination kinetics in the intact pig liver. *Scand J clin Lab Invest.* 1982; 42:253–259. [PubMed: 7134810]
12. Sørensen M, Munk OL, Mortensen, Aa FV, Olsen K, Bender D, Bass L, Keiding S. Hepatic uptake and metabolism of galactose can be quantified in vivo by 2-[^{18}F]Fluoro-2-deoxy-galactose

positron emission tomography. Am J Physiol Gastrointest Liver Physiol. 2008; 295:G27–36. [PubMed: 18483186]

13. Munk OL, Keiding S, Bass L. Capillaries within compartments: microvascular interpretation of dynamic positron emission tomography data. J Theor Biol. 2003; 225:127–141. [PubMed: 14559065]
14. Bass L, Robinson P, Bracken AJ. Hepatic elimination of flowing substrates: the distributed model. J Theor Biol. 1978; 72:161–184. [PubMed: 661331]

Appendix

As compartmental kinetics does not hold in capillary beds, the ratio E_2^*/E_1^* of two local extraction fractions of tracer analogue is not equal to the corresponding ratio E_2/E_1 of the mother substance. Under what circumstances does E_2^*/E_1^* overestimate or underestimate E_2/E_1 ?

We first note that when $E_2^* > E_1^*$, then $E_2 > E_1$, (and *vice versa*), so that the qualitative inference from $E_2^*/E_1^* < 1$ to $E_2/E_1 < 1$ (and *vice versa*) holds in a capillary bed. To prove this, we apply Eq. (22) to two ROIs having the same Λ and re-arrange:

$$\frac{\ln(1 - E_2^*)}{\ln(1 - E_1^*)} = \frac{\ln(1 - E_2)}{\ln(1 - E_1)} \quad (\text{A1})$$

Since $\ln(1-E)$ is a monotonic (rising) function of E , the desired inequalities follow.

We next show that when (without loss of generality) $E_2^* > E_1^*$, then:

$$\frac{E_2/E_1}{E_2^*/E_1^*} > 1 \text{ when } \Lambda > 1 \quad \text{and} \quad \frac{E_2/E_1}{E_2^*/E_1^*} < 1 \text{ when } \Lambda < 1 \quad (\text{A2})$$

as stated in Section 7. Dividing Eq. (31) through with E_2^*/E_1^* we obtain:

$$\frac{E_2/E_1}{E_2^*/E_1^*} = \frac{\left[1 - (1 - E_2^*)^{1/\Lambda}\right]/E_2^*}{\left[1 - (1 - E_1^*)^{1/\Lambda}\right]/E_1^*} \quad (\text{A3})$$

We consider the function:

$$y(x) = \frac{1 - x^z}{1 - x}, \text{ for } 0 \leq x \leq 1, \quad z > 0 \quad (\text{A4})$$

As x grows from 0 to 1 when $z > 1$, x^z remains below x , $1 - x^z$ remains above $1 - x$, so that y increases monotonically from 1 to z . For example $y = 1 + x$ for $z = 2$. As x grows from 0 to 1 when $z < 1$, x^z remains above x , $1 - x^z$ remains below $1 - x$, so that y falls monotonically from 1 to z . For example, $y = 1/(1 + \sqrt{x})$ for $z = 1/2$.

Setting $x = 1 - E^*$ and $z = 1/\Lambda$ in Eq. (A4), we see that y is the numerator of Eq. (A3) when $E^* = E_2^*$ and the denominator when $E^* = E_1^*$. For $\Lambda < 1$ ($z > 1$), y decreases monotonically as $E^* = 1 - x$ increases, so that $E_2^* > E_1^*$ gives $(E_2/E_1)/(E_2^*/E_1^*) < 1$ from Eq. (A3). For $\Lambda > 1$ ($z < 1$), y increases monotonically with increasing E^* , so that $E_2^* > E_1^*$ gives $(E_2/E_1)/(E_2^*/E_1^*) > 1$ from Eq. (A3). This completes the proof of Eq. (A2).

Highlights

- The lumped constant is a proportionality factor used to convert the metabolic rate of a tracer analogue to that of its mother substance.
- *In vivo*, the lumped constant in a capillary bed equals $\ln(1-E^*)/\ln(1-E)$ and not the frequently used E^*/E , where E and E^* are the extraction fractions of the mother substance and tracer analogue, respectively.

Fig. 1.
Concentration gradients of tracer and its mother substance along the length of a capillary perfused by blood flow from $x=0$ (inlet) to $x=L$ (outlet), see text.

Fig. 2.

The ratio of extraction fractions of analogue tracer to mother substance (E^*/E) as a function of the logarithmic mean concentration of mother substance relative the Michaelis constant of the mother substance ($\hat{c}/K_m$) (Eq. 28) for a range of Λ and $\alpha = V_{\max}/F K_m$ of mother substance as indicated in the figure. The red curve is calculated for experimentally determined mean values in pig livers *in vivo* of the lumped constant $\Lambda = 0.15$ [12] and $V_{\max}/F K_m = 4$ [11].