Heterogeneous Tissue Model For Leucine

We have developed a heterogeneous tissue model for the behavior of leucine (Fig S1) in which we assume that each tissue is composed of two homogeneous subregions, e.g., (*a*) gray and (*b*) white matter. Activity in the tissue as a whole can be expressed as a convex linear combination of activity in its subregions (*a* and *b*) as

$$C_T^*(t)=(1-V_b)\left\{w_a[C_{Ea}^*(t)+P_a^*(t)]+w_b[C_{Eb}^*(t)+P_b^*(t)]+V_D C_c^*(t)\right\}+V_b C_b^*(t) \qquad [1]$$

where w_a and w_b are the relative weights of subregions ($w_a+w_b=1$), and V_b is the fraction of the region's volume occupied by blood.

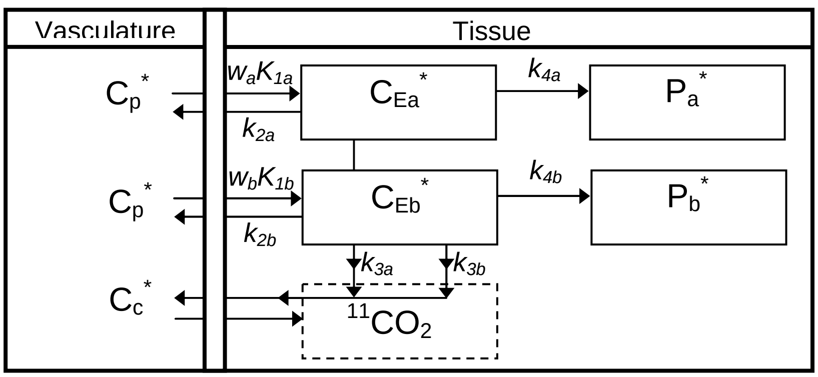

Fig S1. Heterogeneous Tissue Model for Leucine

If subregions *a* and *b* are characterized by parameter sets $\{K_{1a},k_{2a}+k_{3a},k_{4a}\}$ and $\{K_{1b},k_{2b}+k_{3b},k_{4b}\}$, respectively, then

$$\begin{aligned}C_T^*(t;\boldsymbol{\rho})=(1-V_b)\Bigg\{&\left(\frac{w_aK_{1a}(k_{2a}+k_{3a})}{k_{2a}+k_{3a}+k_{4a}}\right)\int_0^t C_p^*(\tau)e^{-(k_{2a}+k_{3a}+k_{4a})(t-\tau)}d\tau\\&+\left(\frac{w_bK_{1b}(k_{2b}+k_{3b})}{k_{2b}+k_{3b}+k_{4b}}\right)\int_0^t C_p^*(\tau)e^{-(k_{2b}+k_{3b}+k_{4b})(t-\tau)}d\tau\\&+\left(\frac{w_aK_{1a}k_{4a}}{k_{2a}+k_{3a}+k_{4a}}+\frac{w_bK_{1b}k_{4b}}{k_{2b}+k_{3b}+k_{4b}}\right)\int_0^t C_p^*(\tau)d\tau+V_DC_c^*(t)\Bigg\}+V_bC_b^*(t).\end{aligned} \qquad [2]$$

For this model, the parameter vector is $\boldsymbol{\rho}=[w_aK_{1a},w_bK_{1b},k_{2a}+k_{3a},k_{2b}+k_{3b},k_{4a},k_{4b},V_b]$. Only six parameters can be estimated from Eq [2] – three integral coefficients, two exponents, and V_b. (V_D is assumed known *a priori*). The single constraint that λ_a=λ_b, motivated by the observation that regional variation in λ is small (Bishu *et al,* 2008), allows all seven parameters to be estimated. Weighted average rCPS in the region can be calculated as

$$\text{rCPS} = \left(\frac{w_a K_{1a} k_{4a}}{k_{2a}+k_{3a}} + \frac{w_b K_{1b} k_{4b}}{k_{2b}+k_{3b}}\right) C_p \qquad [3]$$

and lambda as

$$\lambda = \frac{k_{2a}+k_{3a}}{k_{2a}+k_{3a}+k_{4a}} = \frac{k_{2b}+k_{3b}}{k_{2b}+k_{3b}+k_{4b}}. \qquad [4]$$

The weighted average influx rate constant for the mixed tissue, K_1, can also be determined as $w_a K_{1a}+w_b K_{1b}$, but averages of k_2+k_3 and k_4 are not identifiable from estimated parameters since w_a and w_b are not independently known.