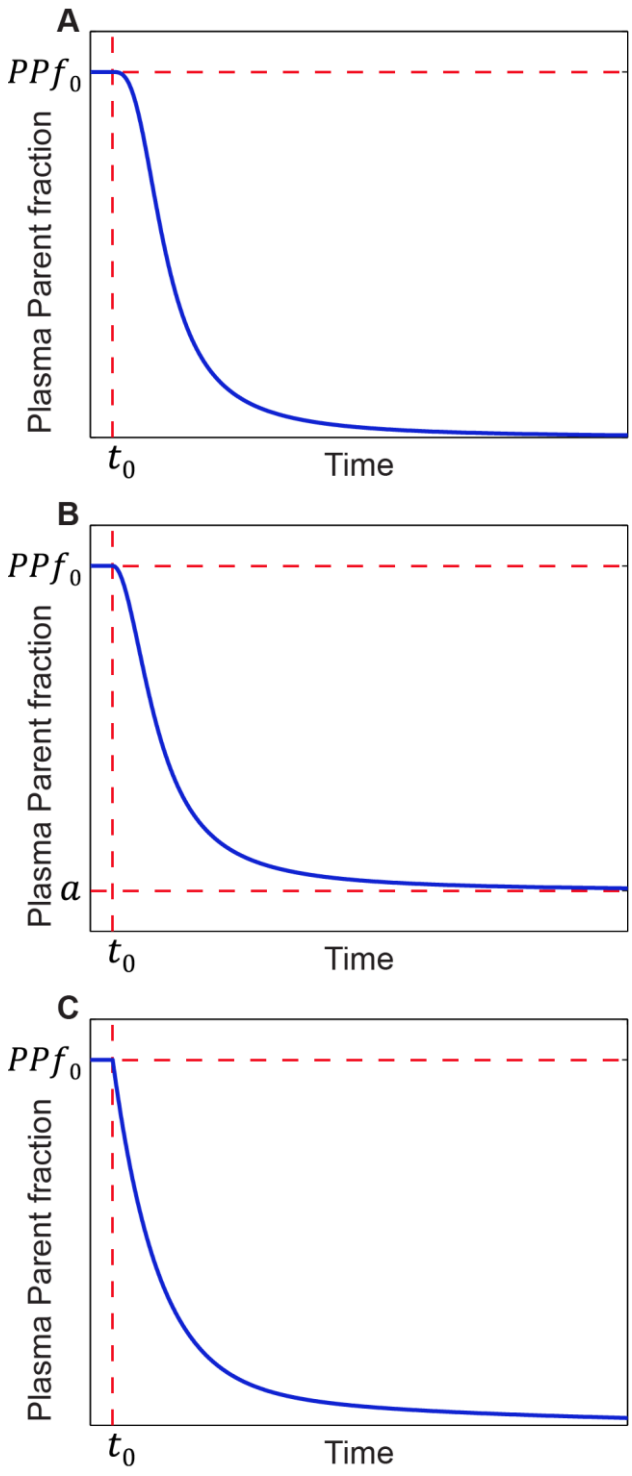
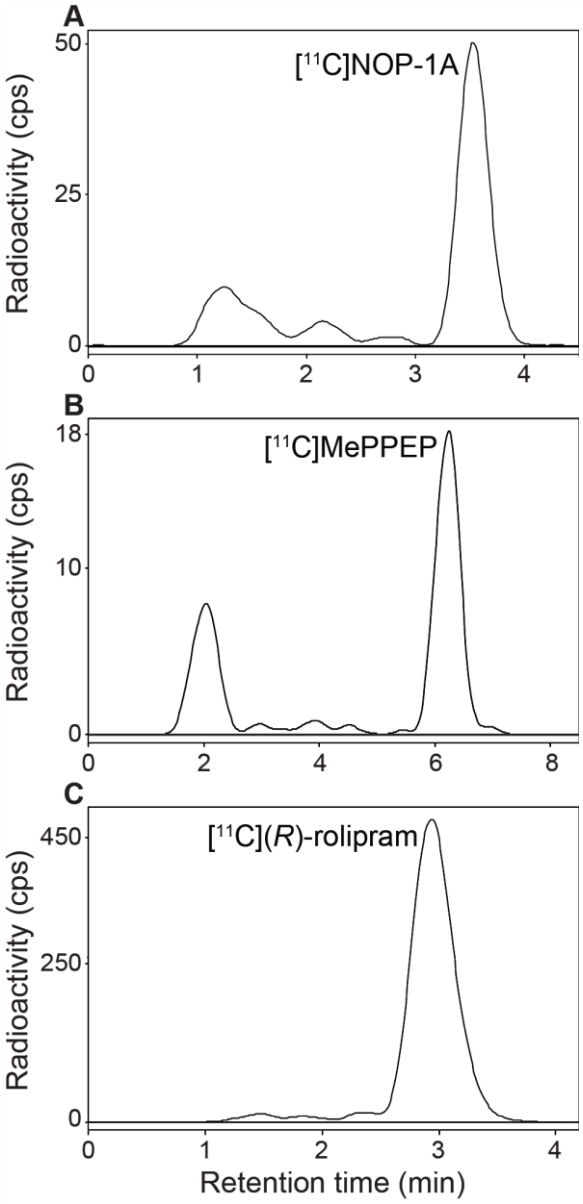
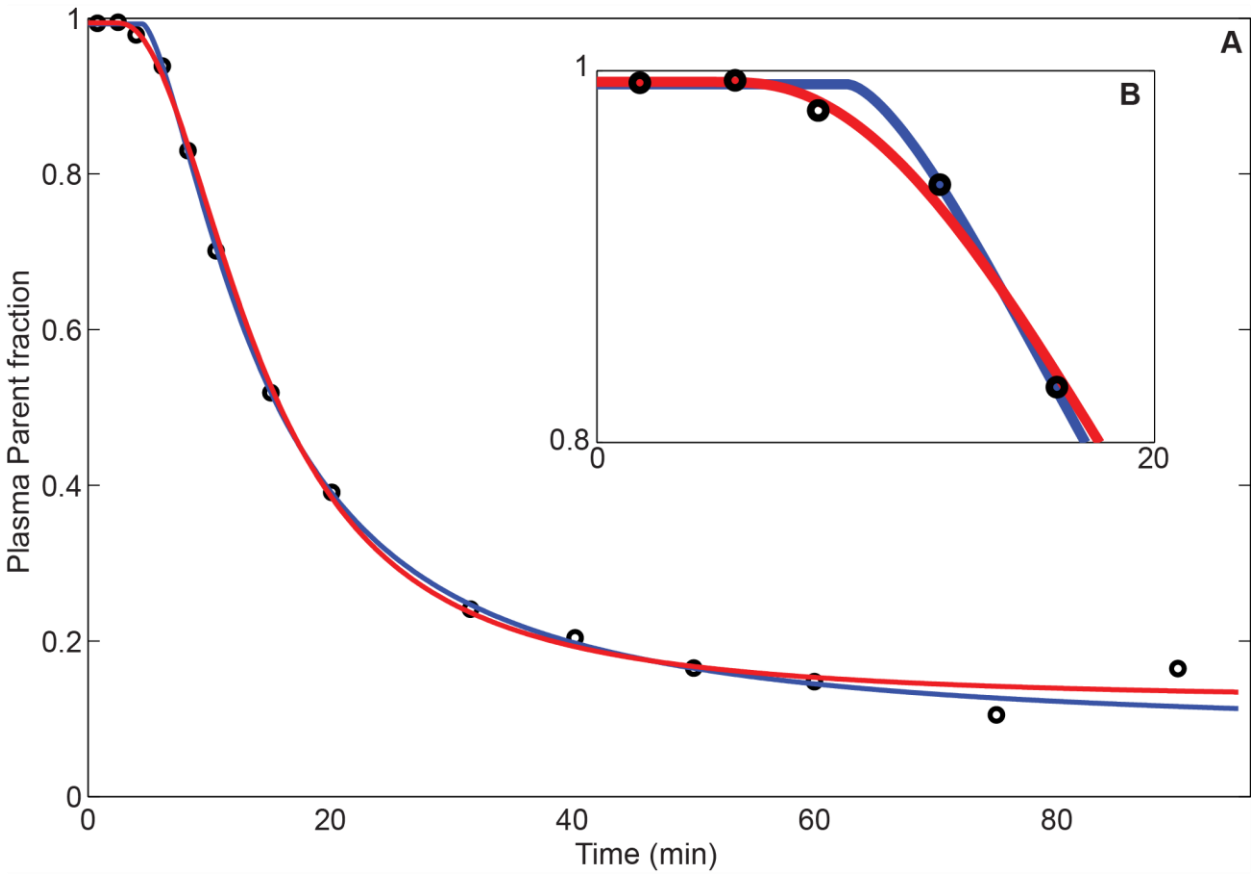


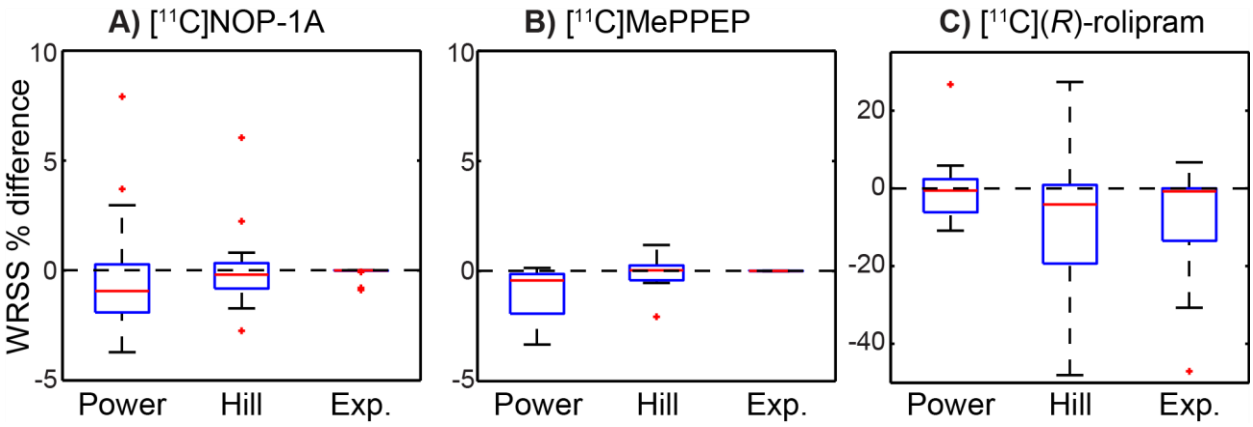
Supplementary figure 1: Classification of main plasma parent fraction modelling approaches. A-C represent the *Power*, *Hill*, and *Exponential* models for plasma parent fraction modelling respectively. All models allow accounting for the metabolite delay (t_0) and non-unitary initial plasma parent fraction value (PPf_0). In addition, the Hill model allows accounting for the final plateau (a).



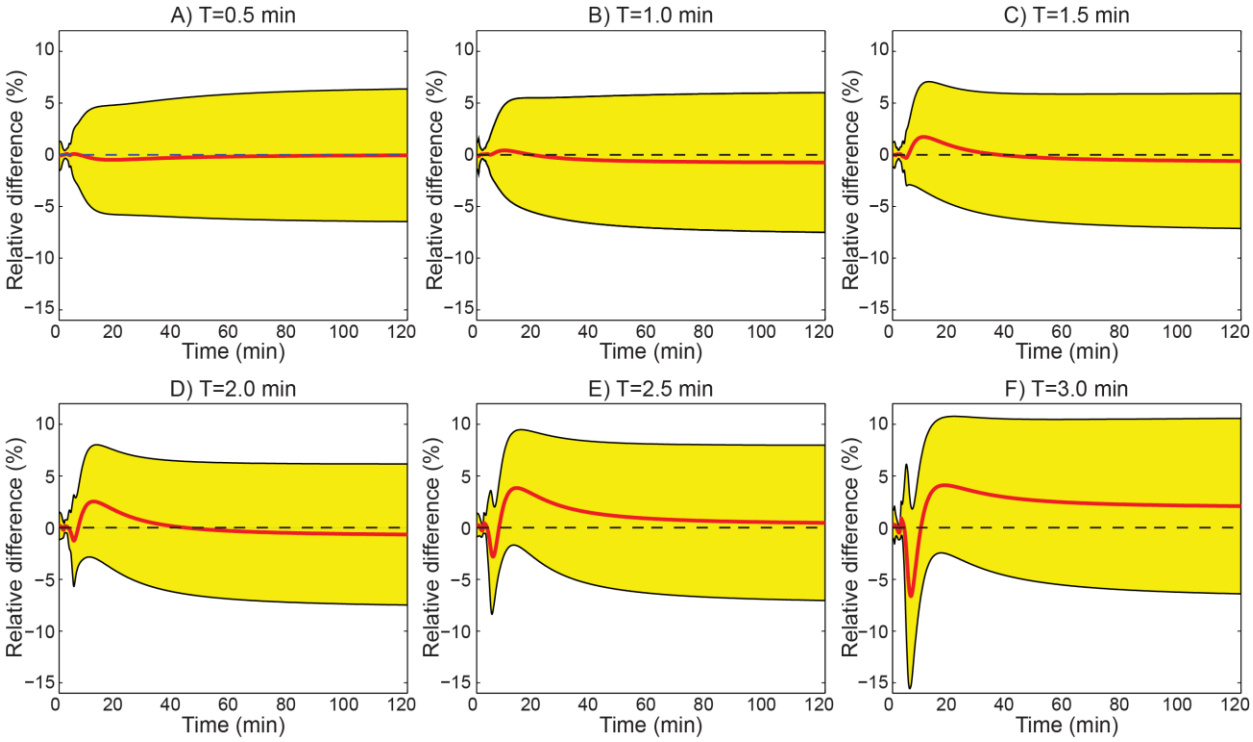
Supplementary figure 2: Radiochromatograms obtained from the HPLC. A) Human plasma sample (#15) at 10 min after the intravenous injection of [^{11}C]NOP-1A (733 MBq). There are at least four radiometabolites A & B= 22.1%; C = 6.5%; D = 2.4%; and parent = 69%. The parent radioligand eluted at 3.55 min and was well separated from the rest of the radiometabolites. Mobile phase was Methanol : water : triethylamine (80:20:0.1 by vol.) as previously described in [17]. B) Human plasma sample (#11) at 10 min after the intravenous injection of [^{11}C]MePPEP (625 MBq). There are at least five radiometabolites A = 29.6%; B = 2.0%; C = 3%; D = 18.8%; and parent = 62.6%. The parent radioligand eluted at 6.37 min and was well separated from the rest of the radiometabolites. Mobile phase was Methanol : water : triethylamine (80:20:0.1 by vol.) as previously described in [25]. C) Human plasma sample (#13) at 6 min after the intravenous injection of [^{11}C](*R*)−Rolipram (744 MBq). There are three radiometabolites A = 2.34%; B = 1.42%; C = 2.05%; and parent = 94.2%. The parent radioligand eluted at 2.95 min and was well separated from the rest of the radiometabolites. Mobile phase was Methanol : water : triethylamine (65:35:0.1 by vol.) as previously described in [26]. All the radio analysis were done according to methodology detailed in [14].



Supplementary figure 3: Comparison of model fit. Panel A shows the measured PPf (black circles) of a representative [^{11}C]NOP-1A subject. Blue and red lines represent the data fits obtained with the standard and convoluted Hill model respectively. Panel B contains the zoomed version of the same curves in the interval from 0 to 20 min.



Supplementary figure 4: Effects of radioligand injection on plasma parent fraction modelling in the downsampled datasets. The figure reports the boxplots of the Weighted Residual Sum of Squares (WRSS) percentage difference, computed between convoluted PPf modelling (accounting for the radioligand injection time) and standard PPf modelling (applied without any information about radioligand injection time). A-C refer to [^{11}C]NOP-1A, [^{11}C]MePPEP, and [^{11}C](*R*)−rolipram analysis, respectively. Positive values means that the WRSS of the standard model is lower than the corresponding WRSS of the convoluted model (i.e. standard model performs better than convoluted one). The opposite for negative values.



Supplementary figure 5: Error generated in PPf model description when radioligand injection length is not taken into account. The figure reports the effect of using a standard Hill model to fit a PPf curve generated with a convoluted model. The mean (red line) and standard deviation (yellow band) of the relative difference between the simulated and estimated curves are shown across time. Panels A-F show how the error varies depending on the increasing simulated injection lengths, from T = 0.5 min (A) to T = 3 min (F).

Supplementary table 1: indices for the optimal PPf model selection for standard (st) and convoluted (conv) models

		CV [a]					Outliers[b]	zero-line crossing[c]	*WRSS*[d]
		a	b	c	PPf_0	t_0			
[^{11}C] NOP-1A	Power st	51% ± 39%	188% ± 205%	174% ± 194%	0,3% ± 0,2%	298% ± 194%	10%	0,37	1,94E-04 ± 1,67E-04
	Hill st	19% ± 22%	13% ± 6%	68% ± 29%	0,2% ± 0,1%	23% ± 20%	5%	0,46	1,20E-04 ± 1,03E-04
	Exp st	13% ± 11%	23% ± 15%	163% ± 149%	0,2% ± 0,1%	7% ± 6%	19%	0,51	2,75E-04 ± 2,44E-04
	Power conv	61% ± 51%	199% ± 206%	191% ± 193%	0.3% ± 0.1%	242% ± 132%	5%	0.37	2.24E-04 ± 2.16E-04
	Hill conv	10% ± 80%	13% ± 6%	82% ± 42%	0.2% ± 0.1%	34% ± 22%	5%	0.48	1.00E-04 ± 9.81E-05
	Exp conv	12% ± 10%	20% ± 12%	170% ± 155%	0.2% ± 0.1%	6% ± 3%	24%	0.46	2.19E-04 ± 1.95E-04
[^{11}C] MePPEP	Power st	47% ± 41%	181% ± 173%	167% ± 161%	0,2% ± 0,1%	364% ± 328%	0%	0,45	3,06E-05 ± 2,66E-05
	Hill st	15% ± 8%	10% ± 6%	45% ± 29%	0,1% ± 0,0%	19% ± 15%	0%	0,59	2,05E-05 ± 1,43E-05
	Exp st	10% ± 5%	32% ± 24%	111% ± 120%	0,2% ± 0,1%	18% ± 17%	10%	0,59	1,04E-04 ± 9,88E-05
	Power conv	38% ± 35%	140% ± 127%	129% ± 116%	0.2% ± 0.1%	336% ± 299%	0%	0.46	3.03E-05 ± 2.66E-05
	Hill conv	14% ± 80%	10% ± 5%	52% ± 40%	0.1% ± 0.1%	53% ± 149%	0%	0.60	1.77E-05 ± 1.27E-05
	Exp conv	70% ± 50%	24% ± 26%	89% ± 60%	0.2% ± 0.1%	14% ± 18%	15%	0.61	5.44E-05 ± 5.62E-05
[^{11}C] (*R*)−rolipram	Power st	184% ± 239%	54% ± 68%	167% ± 193%		35% ± 53%	4%	0,53	1,41E-05 ± 4,08E-05
	Hill st	19% ± 19%	11% ± 6%	22% ± 11%		14% ± 44%	0%	0,49	1,44E-05 ± 4,29E-05
	Exp st	16% ± 15%	31% ± 31%	36% ± 75%		5% ± 3%	17%	0,52	3,39E-06 ± 5,65E-06
	Power conv	96% ± 122%	79% ± 152%	123% ± 149%		48% ± 67%	17%	0.56	1.11E-05 ± 4.31E-05
	Hill conv	22% ± 20%	13% ± 7%	22% ± 12%		8% ± 6%	0%	0.54	1.38E-05 ± 4.41E-05
	Exp conv	15% ± 10%	26% ± 20%	21% ± 22%		5% ± 3%	22%	0.51	3.29E-06 ± 5.48E-06

[a] Coefficient of Variation of the parameter estimates (mean ± SD); reflects estimate reliability.
[b] the percentage of subjects over the total who reported at least one parameter with a corresponding $CV > 1000\%$ (excluding t_0).
[c] number of times that weighted residuals cross the zero line over the total number of residuals. The value reported is the mean between subjects, (excluding outliers).
[d] Weighted Residuals Sum of Squares (mean ± SD).

Supplementary table 2: indices for the optimal PPf model selection for standard (st) and convoluted (conv) models in the downsampled dataset

		CV [a]					Outliers[b]	*WRSS*[d]
		a	b	c	PPf_0	t_0		
[^{11}C] NOP-1A	Power st	50% ± 38%	189% ± 206%	175% ± 194%	0,3% ± 0,2%	299% ± 194%	10	1,94E-04 ± 1,67E-04
	Hill st	2% ± 2%	14% ± 7%	85% ± 47%	0,2% ± 0,2%	28% ± 21%	0	1,08E-04 ± 1,02E-04
	Exp st	13% ± 11%	22% ± 16%	170% ± 175%	0,2% ± 0,1%	5% ± 3%	38	1,92E-04 ± 1,35E-04
	Power conv	54% ± 38%	208% ± 205%	193% ± 194%	0,3% ± 0,1%	261% ± 119%	5	2,24E-04 ± 2,16E-04
	Hill conv	2% ± 2%	13% ± 7%	83% ± 41%	0,2% ± 0,1%	38% ± 40%	0	1,09E-04 ± 1,03E-04
	Exp conv	13% ± 11%	22% ± 16%	170% ± 175%	0,2% ± 0,1%	5% ± 3%	38	1,91E-04 ± 1,34E-04
[^{11}C] MePPEP	Power st	129% ± 63%	495% ± 232%	468% ± 196%	8,9% ± 18,8%	545% ± 344%	45	6,58E-06 ± 6,10E-06
	Hill st	1% ± 1%	7% ± 5%	34% ± 32%	0,4% ± 0,9%	49% ± 131%	0	2,85E-06 ± 3,21E-06
	Exp st	4% ± 4%	7% ± 6%	33% ± 32%	0,1% ± 0,0%	3% ± 2%	55	3,70E-06 ± 2,30E-06
	Power conv	116% ± 62%	448% ± 217%	427% ± 184%	7,4% ± 16,0%	582% ± 389%	45	6,52E-06 ± 6,08E-06
	Hill conv	1% ± 1%	7% ± 5%	33% ± 30%	0,4% ± 0,8%	54% ± 130%	0	2,85E-06 ± 3,21E-06
	Exp conv	4% ± 5%	11% ± 18%	24% ± 29%	0,1% ± 0,0%	3% ± 3%	45	3,12E-06 ± 2,44E-06
[^{11}C] (*R*)−rolipram	Power st	163% ± 227%	67% ± 129%	152% ± 173%		40% ± 64%	13	1,09E-05 ± 4,20E-05
	Hill st	23% ± 21%	13% ± 8%	24% ± 12%		15% ± 44%	0	1,39E-05 ± 4,26E-05
	Exp st	15% ± 16%	30% ± 33%	59% ± 101%		13% ± 32%	22	1,33E-05 ± 3,88E-05
	Power conv	137% ± 193%	65% ± 126%	132% ± 152%		47% ± 68%	17	1,10E-05 ± 4,31E-05
	Hill conv	23% ± 21%	14% ± 7%	22% ± 12%		8% ± 6%	0	1,38E-05 ± 4,41E-05
	Exp conv	15% ± 11%	45% ± 55%	15% ± 9%		8% ± 9%	17	1,18E-05 ± 3,76E-05

[a] Coefficient of Variation of the parameter estimates (mean ± SD); reflects estimate reliability.
[b] the percentage of subjects over the total who reported at least one parameter with a corresponding $CV > 1000\%$ (excluding t_0).
[c] number of times that weighted residuals cross the zero line over the total number of residuals. The value reported is the mean between subjects, (excluding outliers).
[d] Weighted Residuals Sum of Squares (mean ± SD).