

Physiologically Based Pharmacokinetic – Quantitative Systems Toxicology and Safety (PBPK-QSTS) Modeling Approach Applied to Predict the Variability of Amitriptyline Pharmacokinetics and Cardiac Safety in Populations and in Individuals.

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Burch 1981 [9]		100	single	4	2	18 – 40																
Baumann 1986 [15]		75, 150	multiple	9	21	20 – 60																
Gupta 1998 [16]		75	multiple	16	8	19 - 49																
Gupta 1999 [3]		25	multiple	15	0	21 – 37																
Miljković 1996 [17]		150	multiple	3	3	31 - 59																
		75	multiple	3	6	39 – 56																
Schulz 1983 [18]		80	single	1	0	21																
		40	single	1	0	70																
Vandel 1993 [19]		125	multiple	7	10	24 – 69																
Pickup 1982 [20]		PBPK-QSTS	75	single	8	0		20-28		1.801 [21]	3.5 [22]	21.9 [22]	2.27 [23]	CSS default	CSS default	CSS default	10 / 8	default	1 / 2*	QTcB _i		
Upward 1988 [24]	150, 200		multiple	5	7	29 – 61	10 / 12	default									1	QTcB				
Warrington 1989 [25]	75		multiple	12	0	20-30	10 / 12	default										ΔQTI				
Zakynthinos 2000 [26]	PD model performance verification			0	1	44								480	1	1	QTcB					
Schmidt 2015 [27]				0	1	54								638								
Rudorfer 1982 [28]	PBPK-QSTS	7500	multiple	0	1	29	1111								10 / 1	1	1	462				
		3600	single	1	0	25												429				
		750	multiple	0	1	29												429				
		2500	multiple	0	1	67												517				
		350	single	0	1	19												500				

	1500	single	1	0	22									484		
	375	single	0	1	23									429		
	3000	single	0	1	39									400		
	1750	single	0	1	32									500		
	2000	multiple	1	0	25									556		
	1500	multiple	1	0	17									480		
	3000	single	0	1	19									476		
Erdem 2010 [29]	3750	multiple	1	0	24						2.9	136		429		QT
Kiyan 2006 [30]	300	multiple	0	1	33						CSS default	CSS default		500		QTcB
Paksu 2014 [31]	750	multiple	1	0	34						CSS default	137		500*		QTcB
Abeyaratne 2016 [32]	500	single	0	1	25						CSS default	CSS default		364		TdP occurrence

*40 individuals were simulated with the seed 1, and 40 with the seed 2; the file had to be divided because of technical issues, **There was no data on RR interval length in the publication. The individual RR were predicted in the E_{max} model. The mean of model-predicted RR was used as input value in CSS.

Table 1: The details of simulation scenarios and settings.

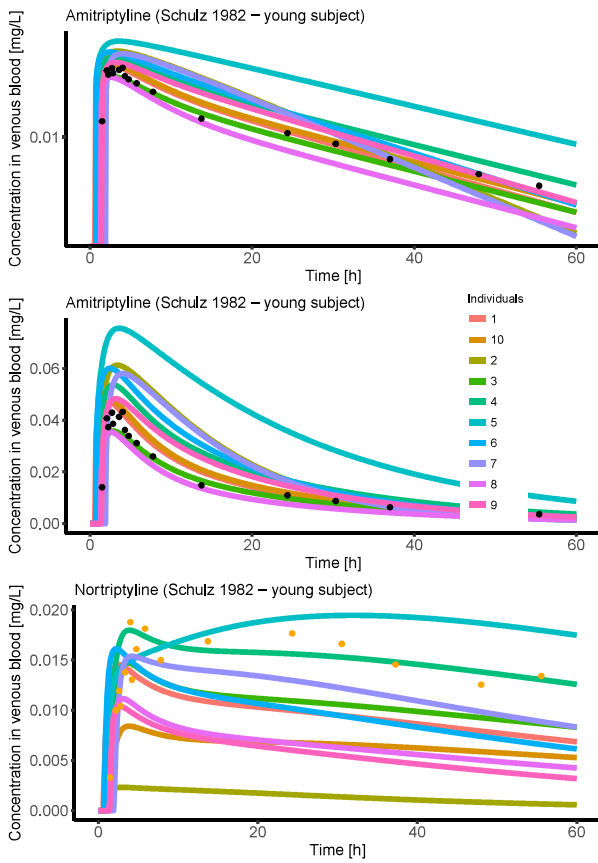
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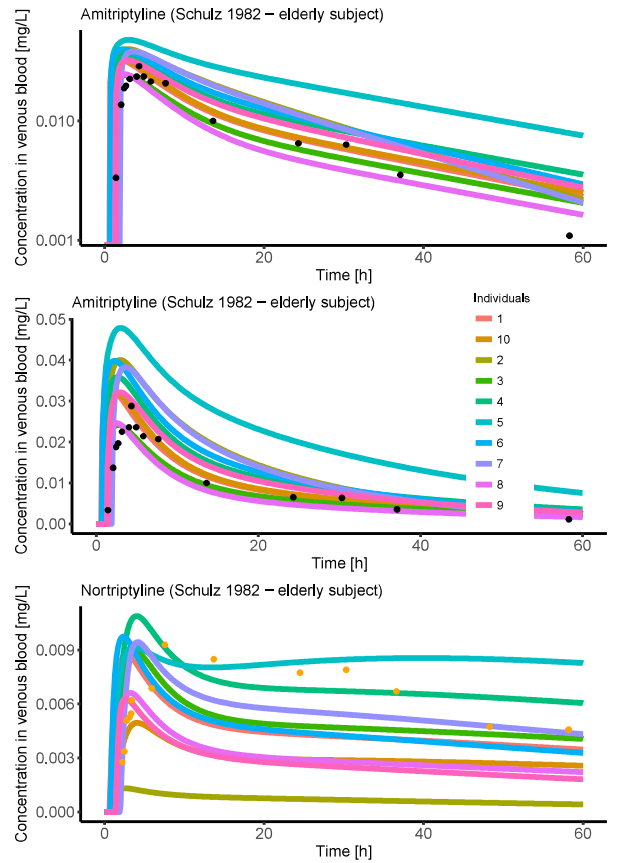
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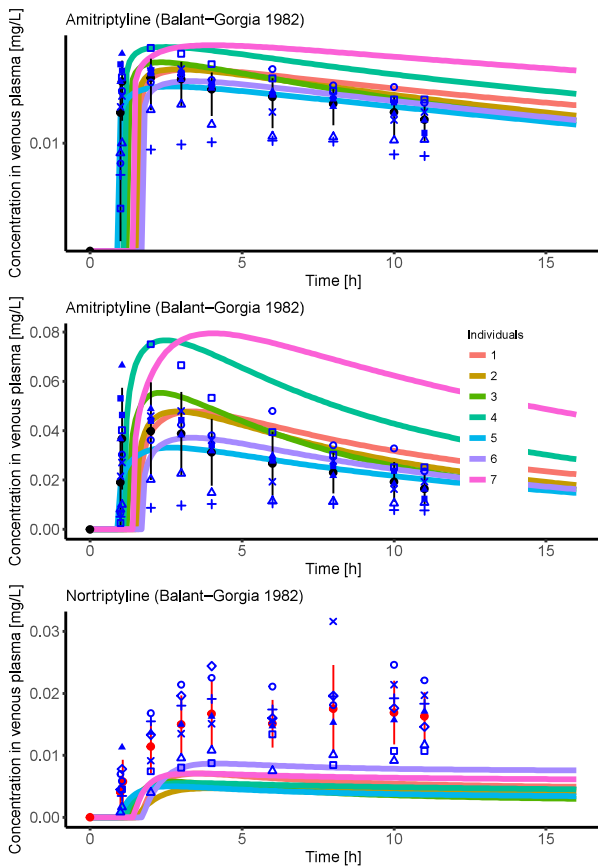
Figure 1: The simulated PK profiles along with AT and NT concentrations observed in clinic



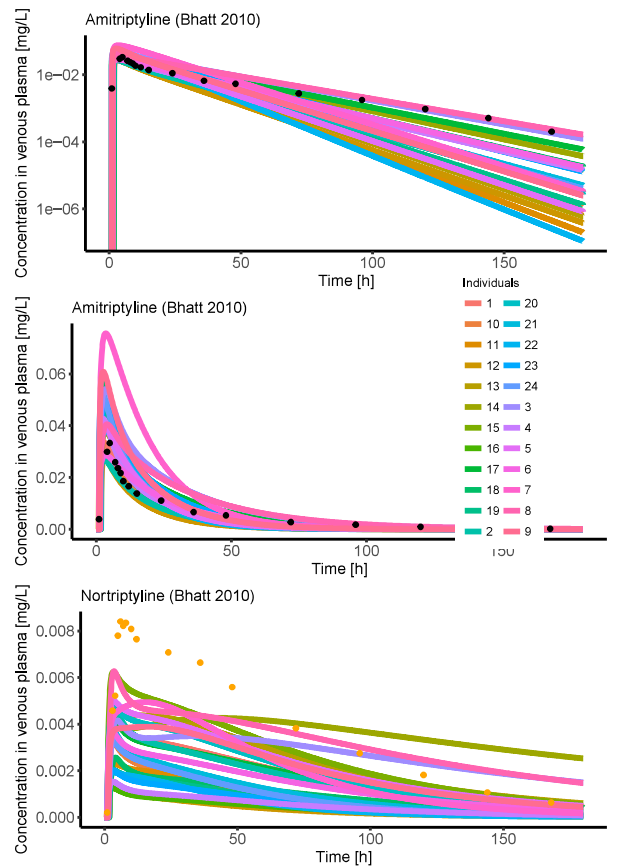
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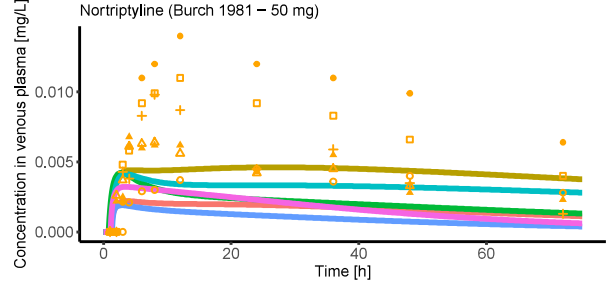
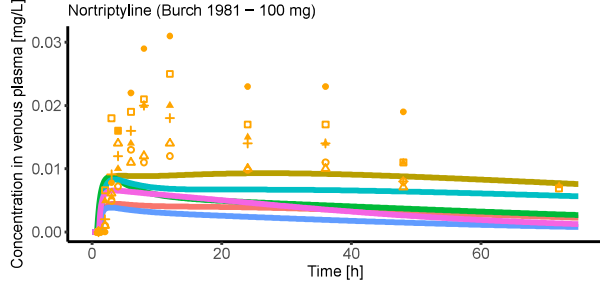
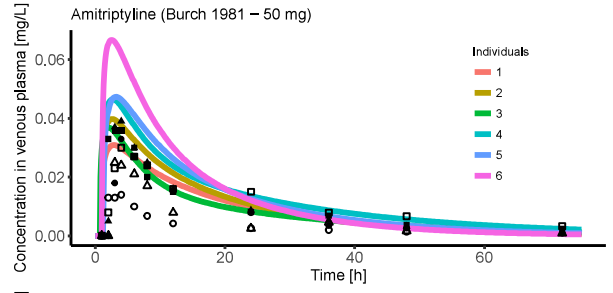
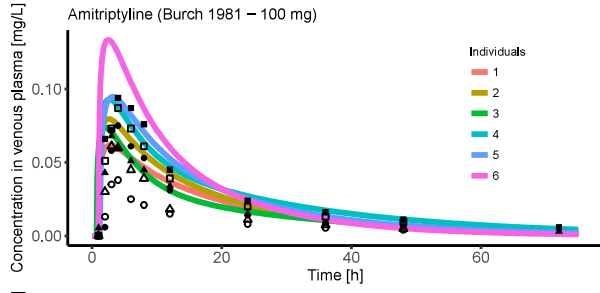
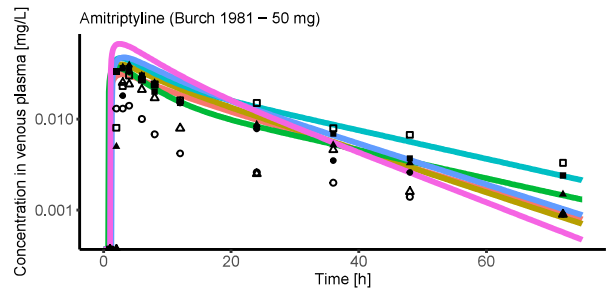
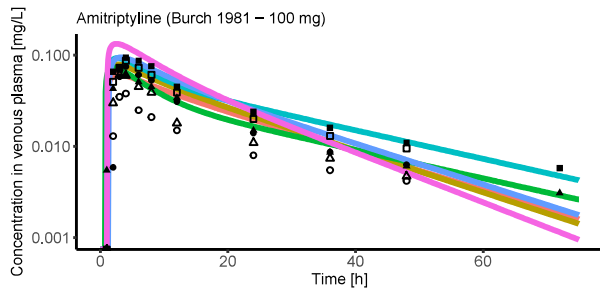


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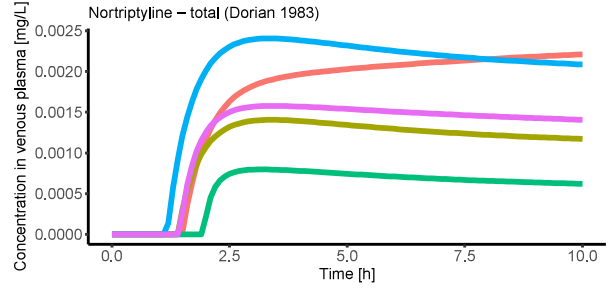
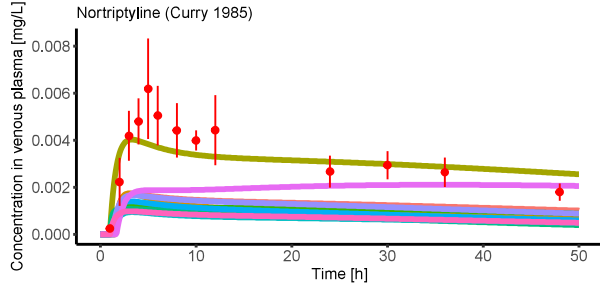
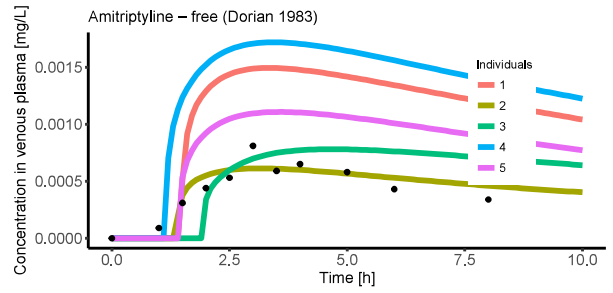
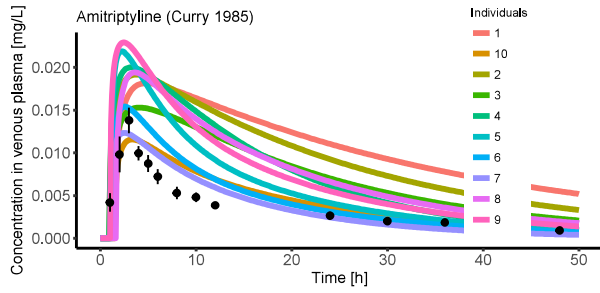
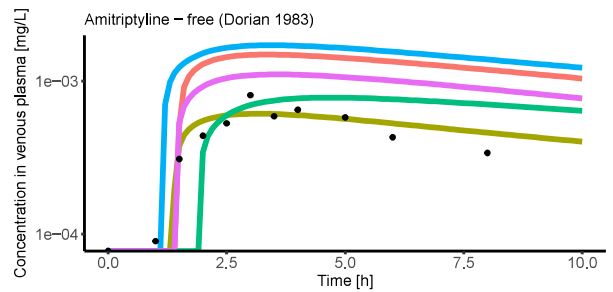
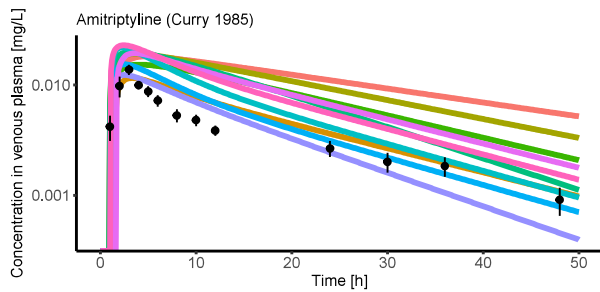
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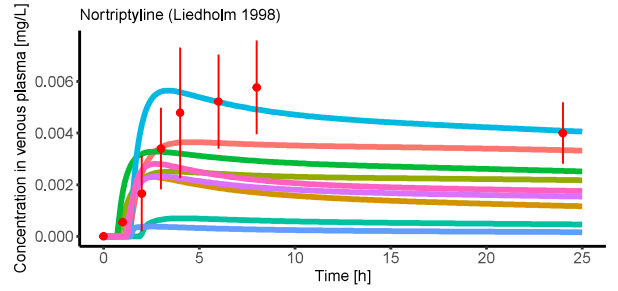
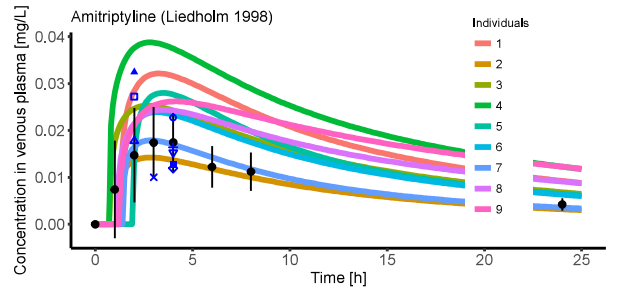
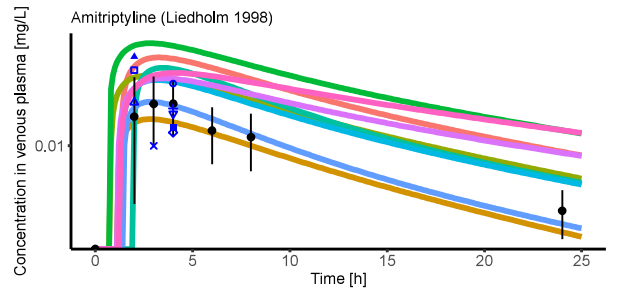
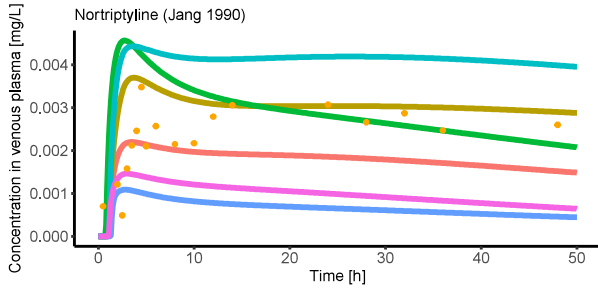
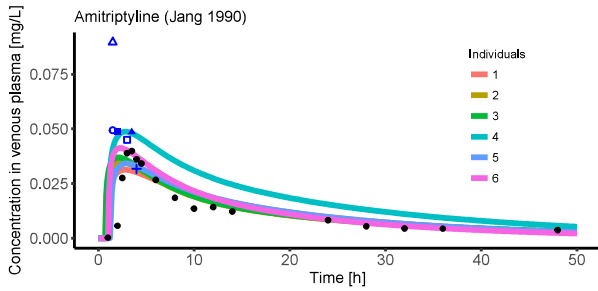
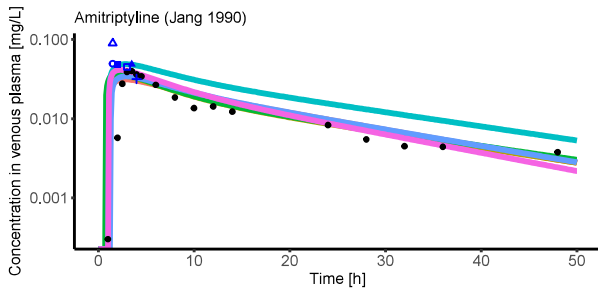
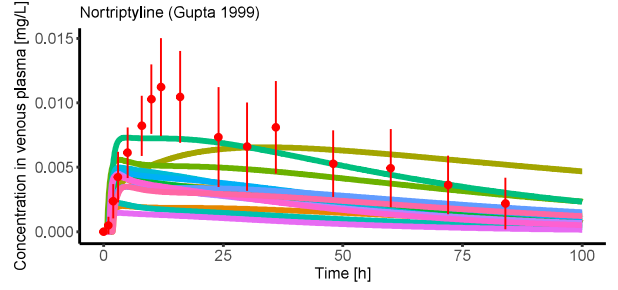
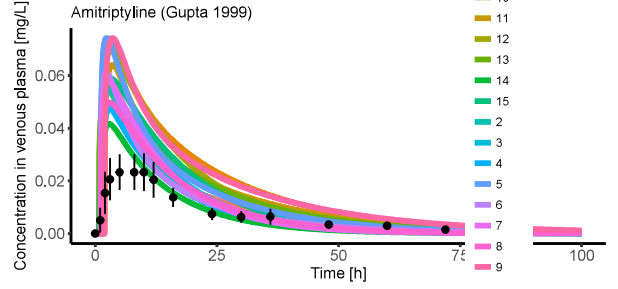
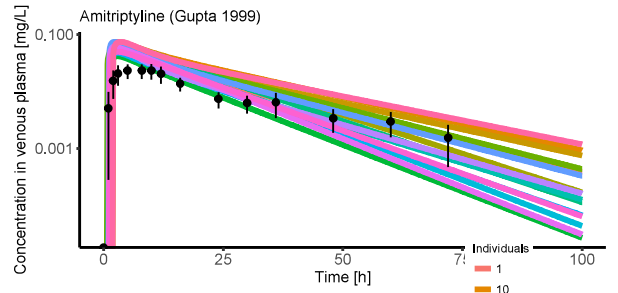
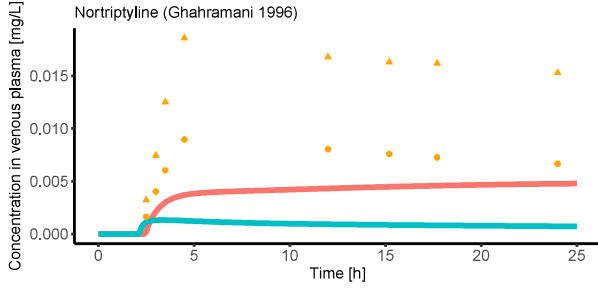
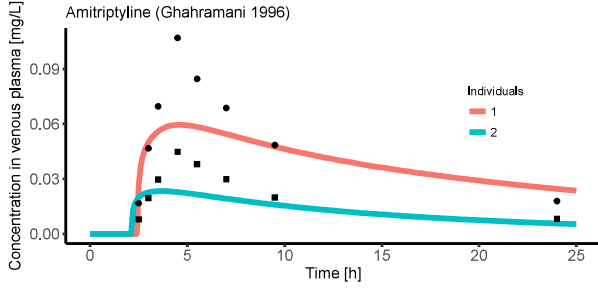
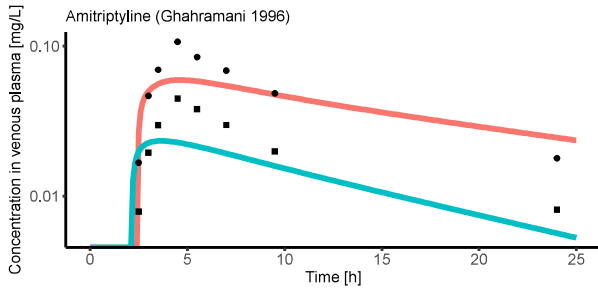
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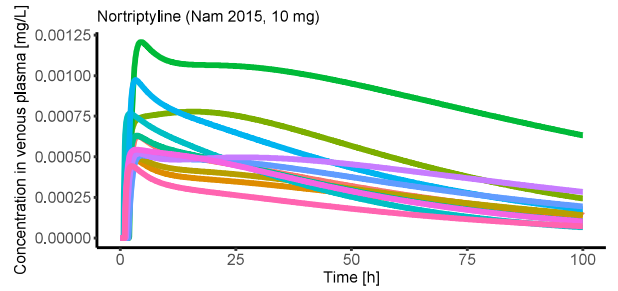
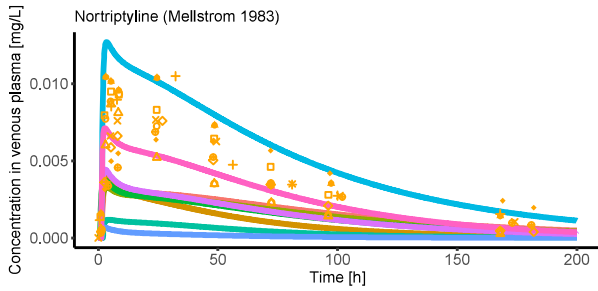
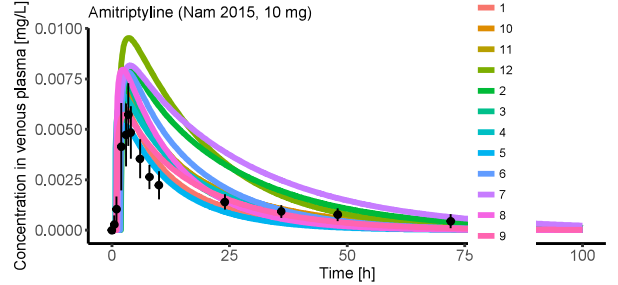
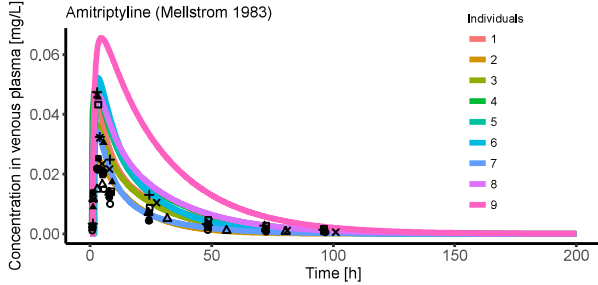
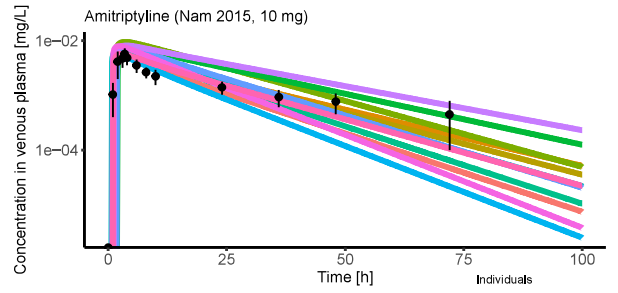
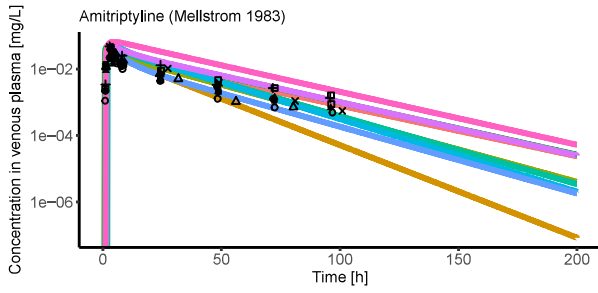
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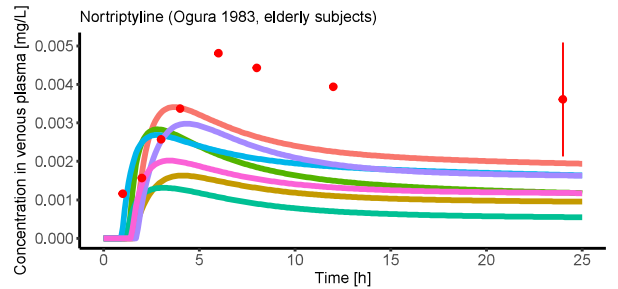
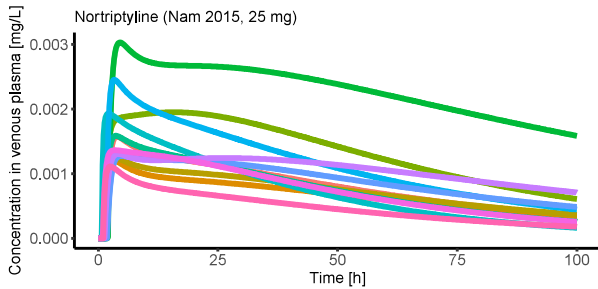
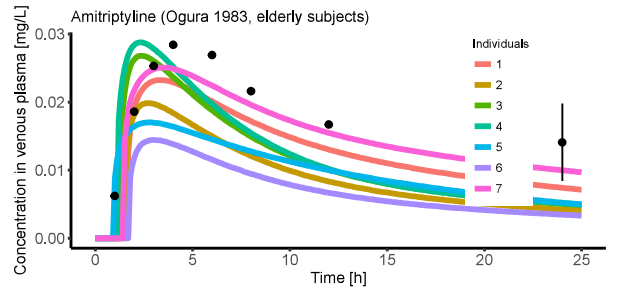
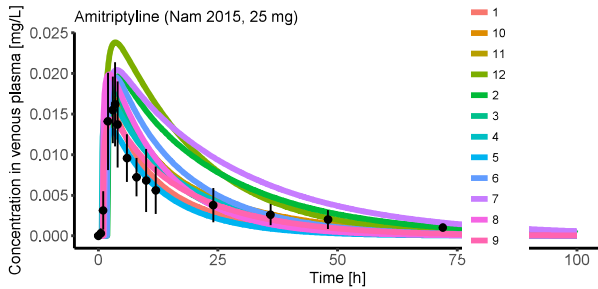
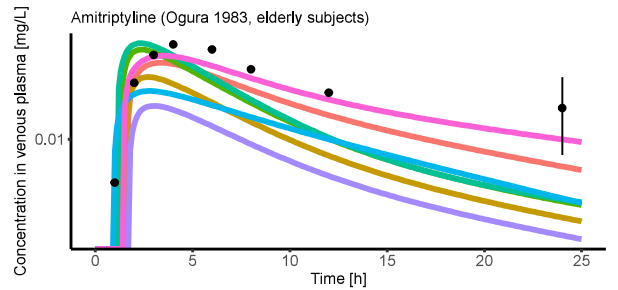
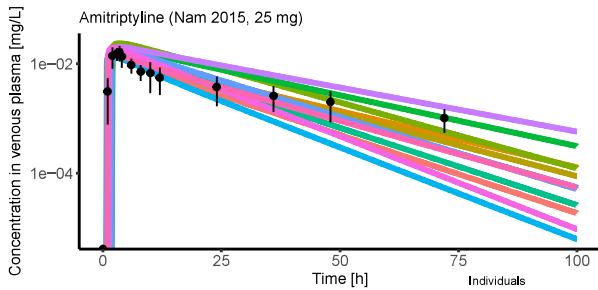
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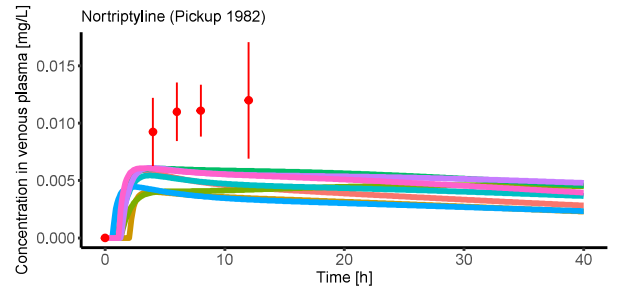
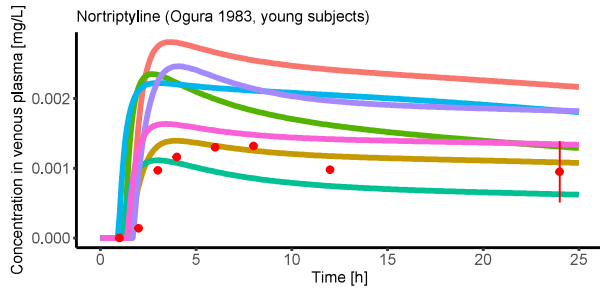
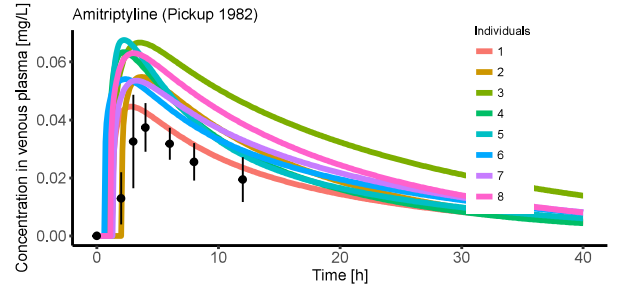
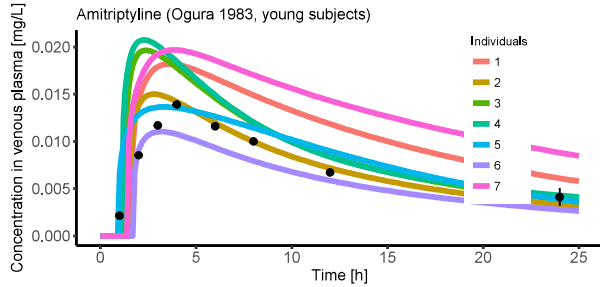
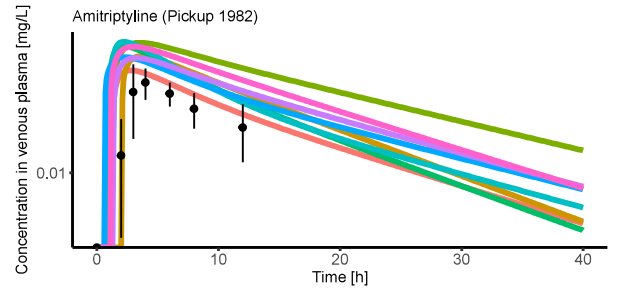
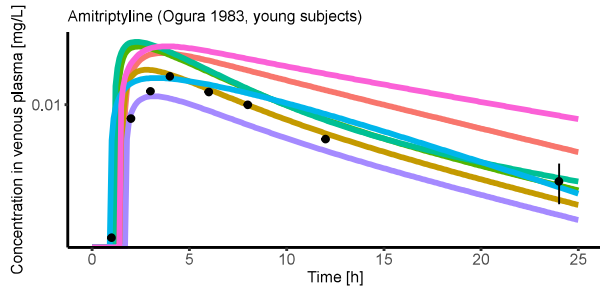
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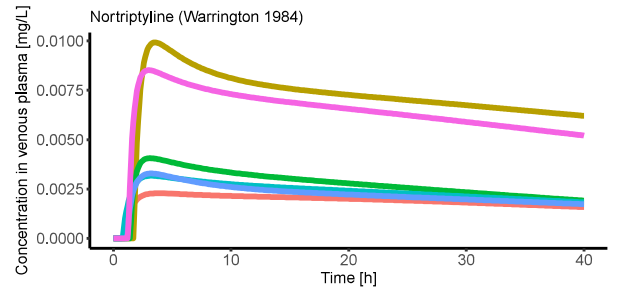
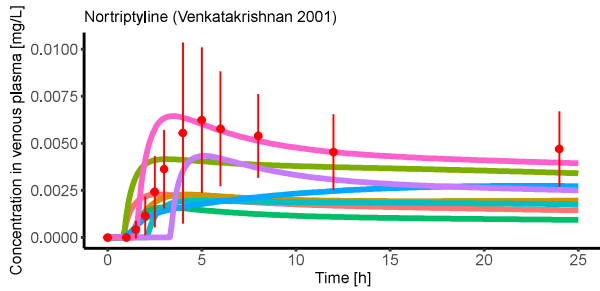
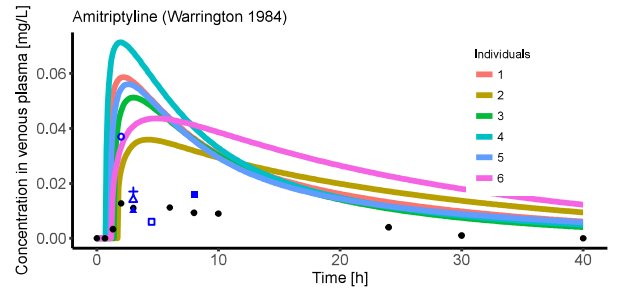
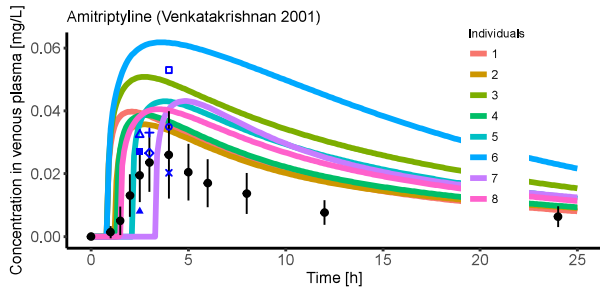
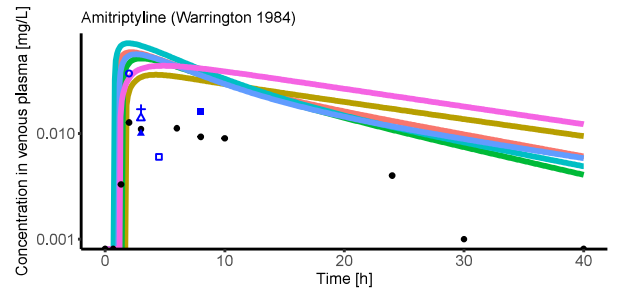
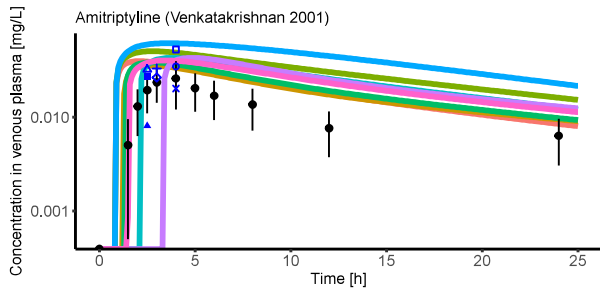
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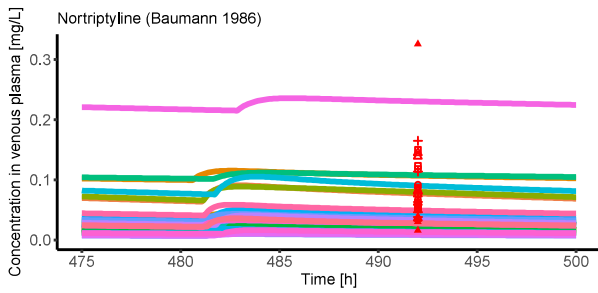
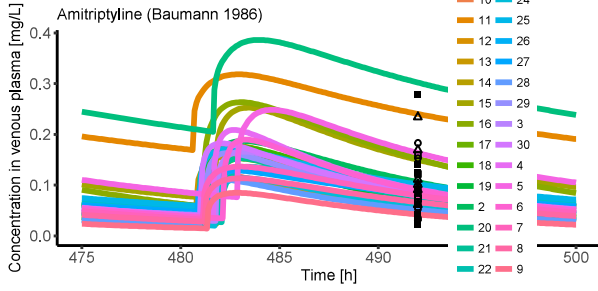
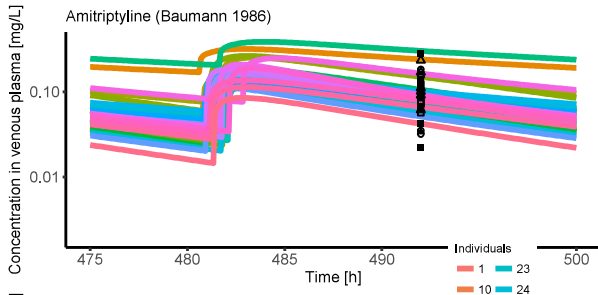
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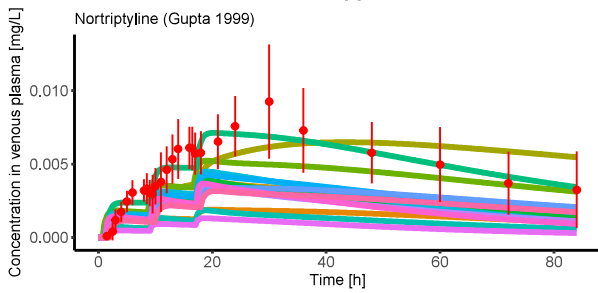
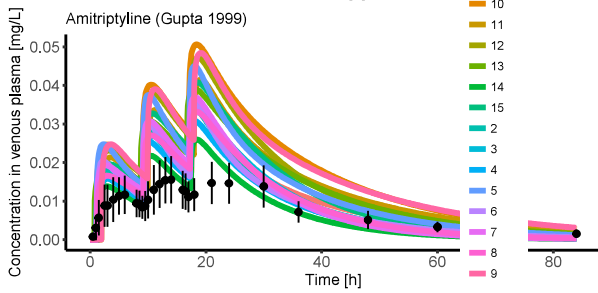
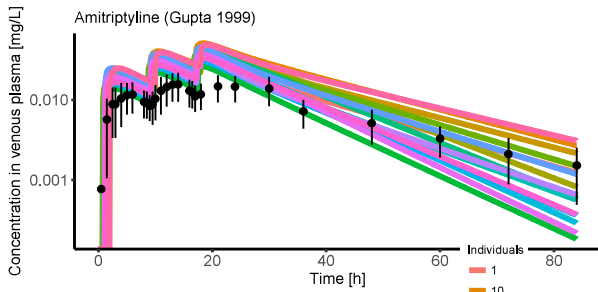
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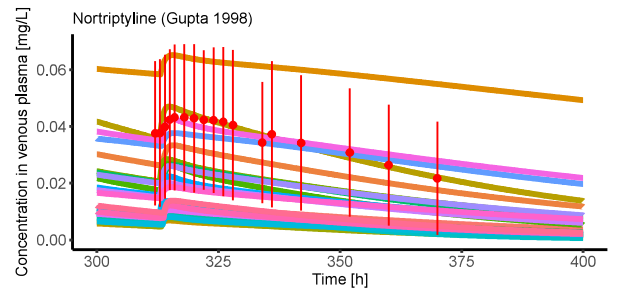
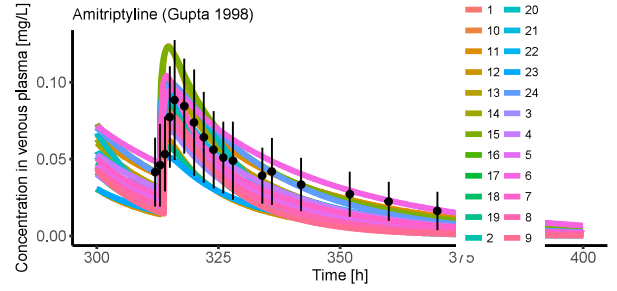
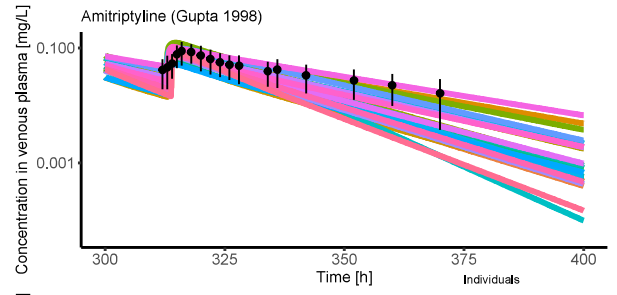
Figure 1 - Continued



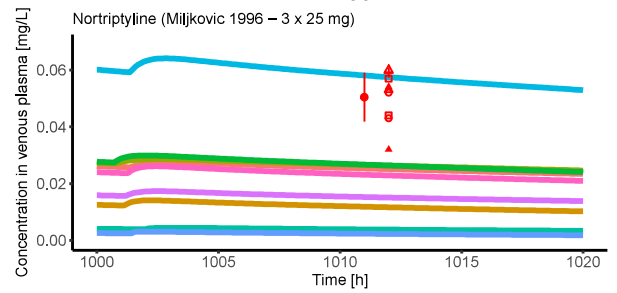
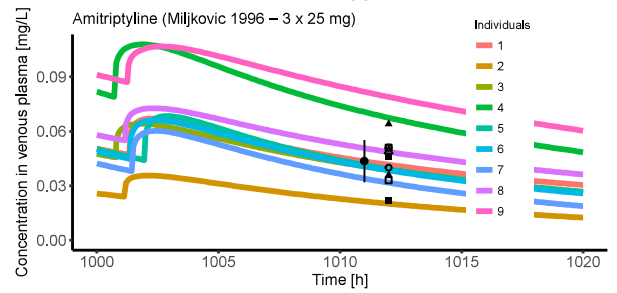
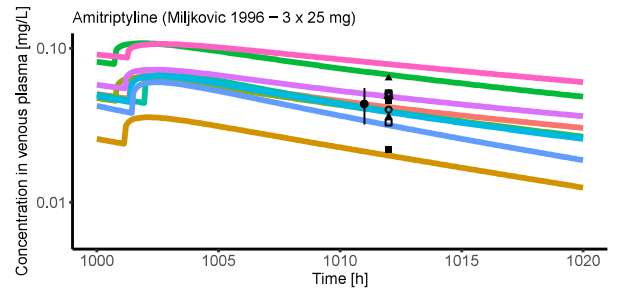
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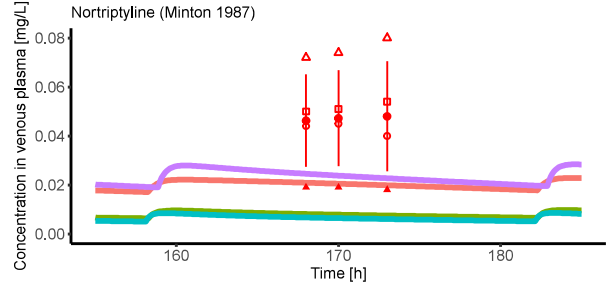
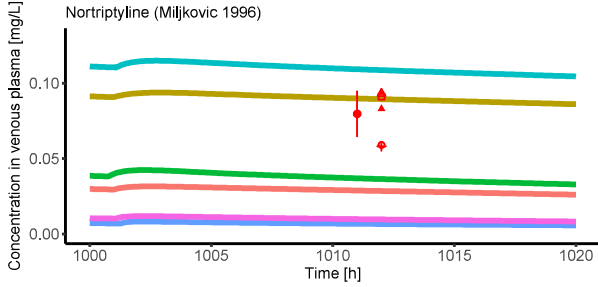
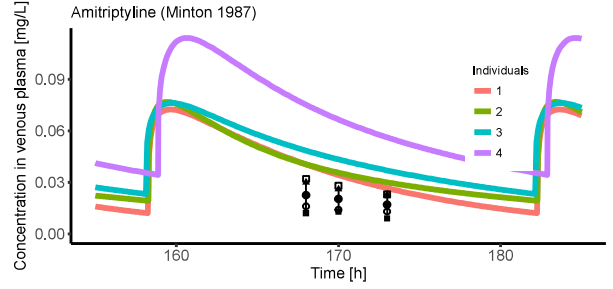
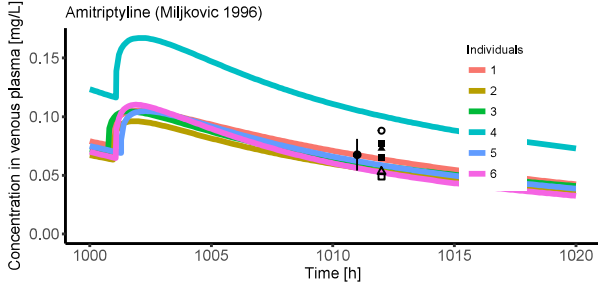
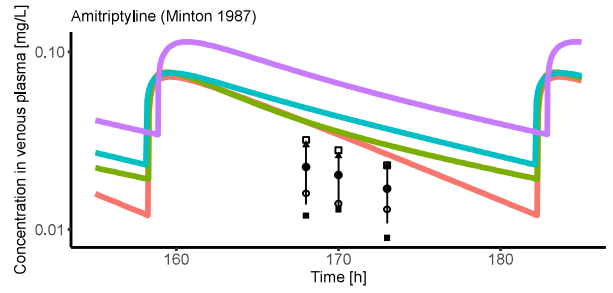
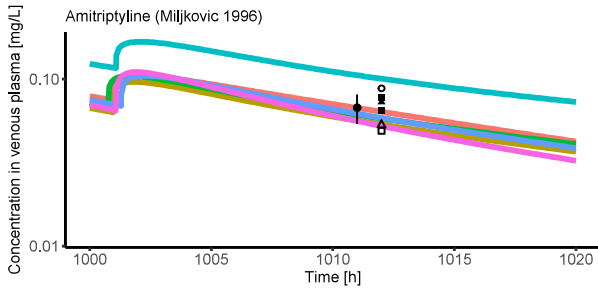


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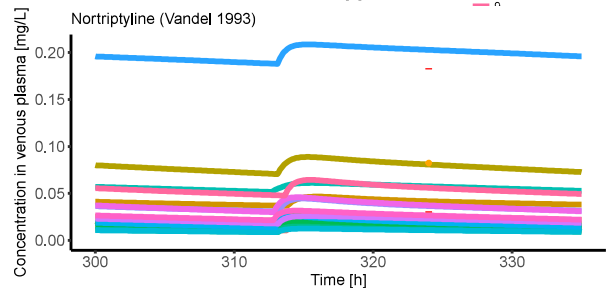
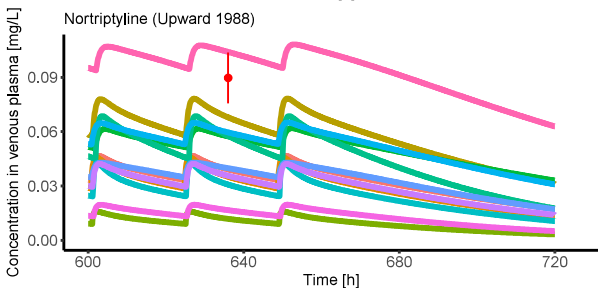
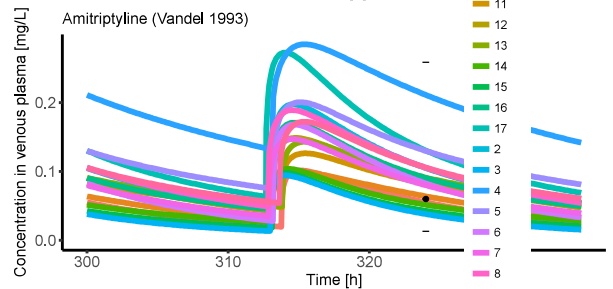
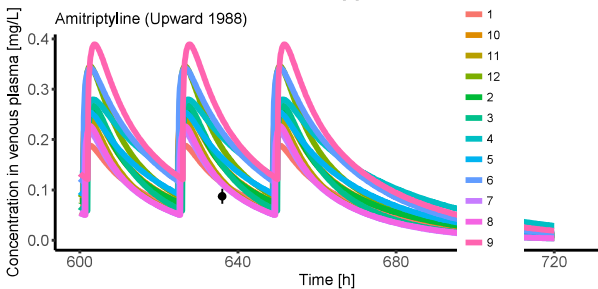
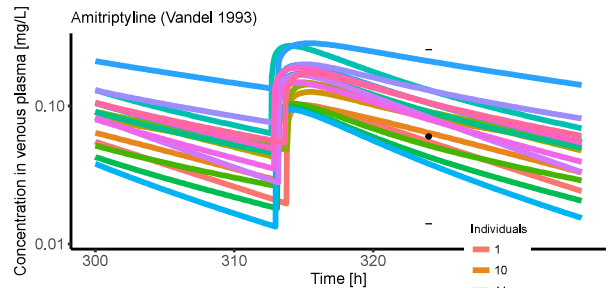
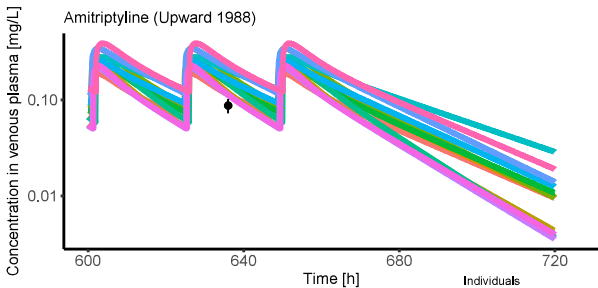
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Figure 1 - Continued



Y

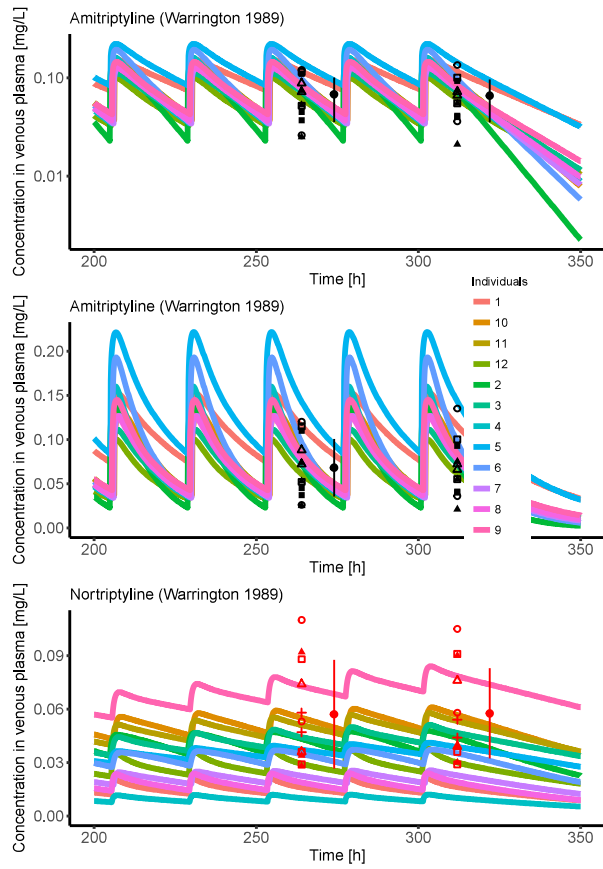
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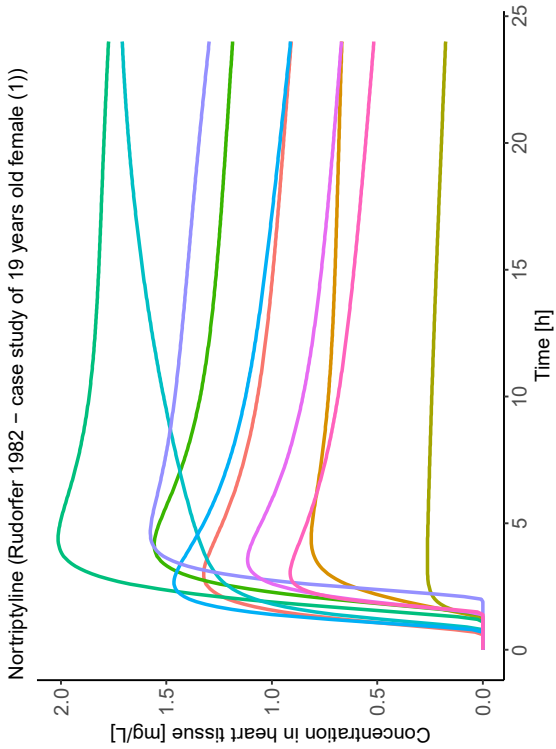
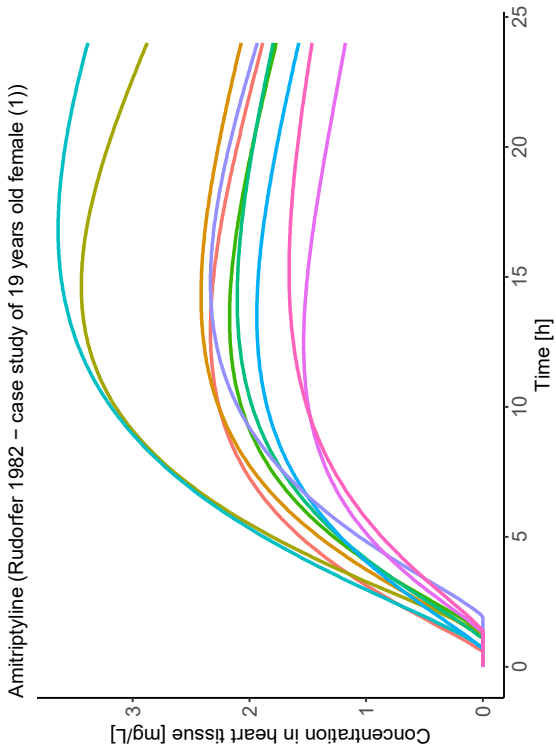
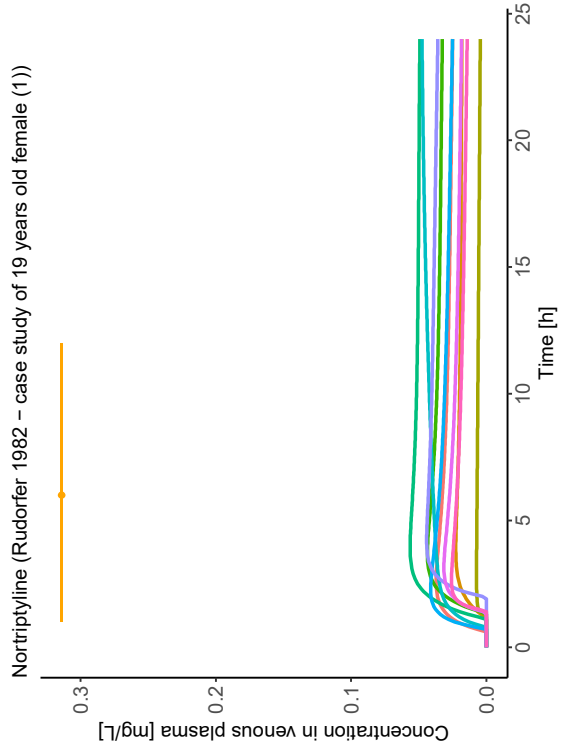
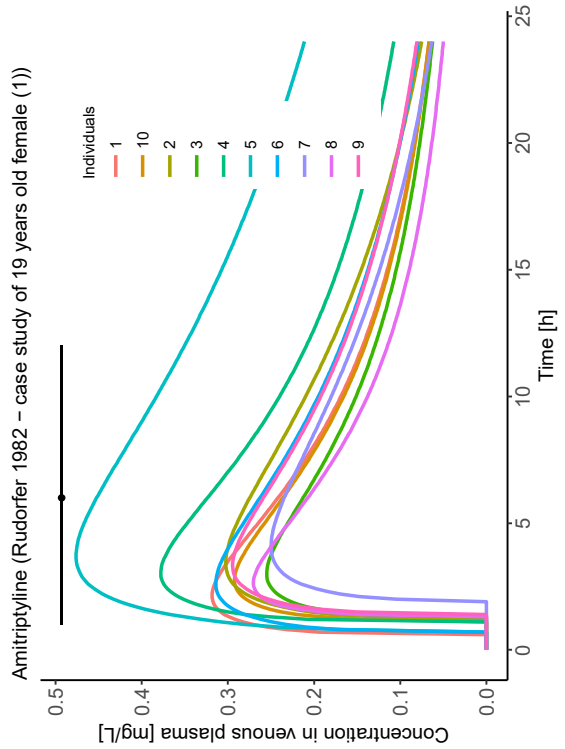
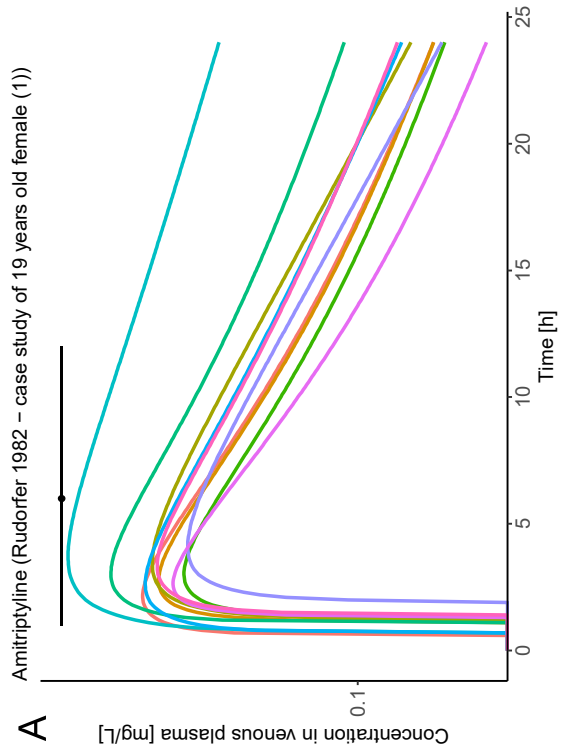
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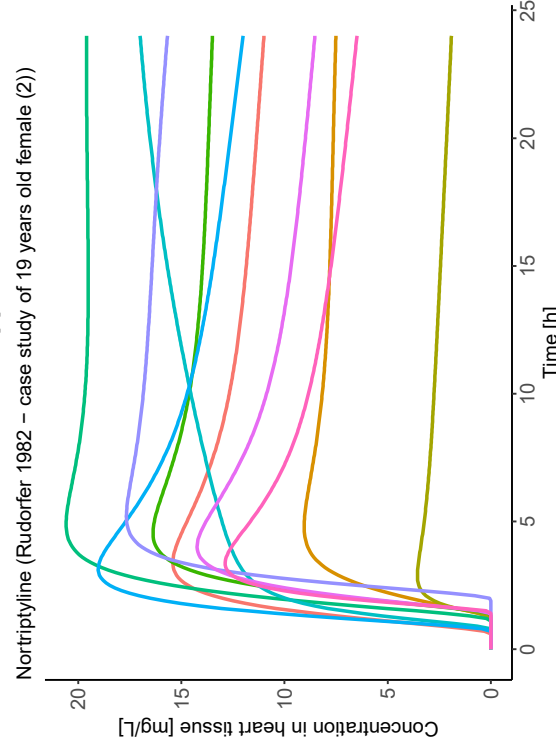
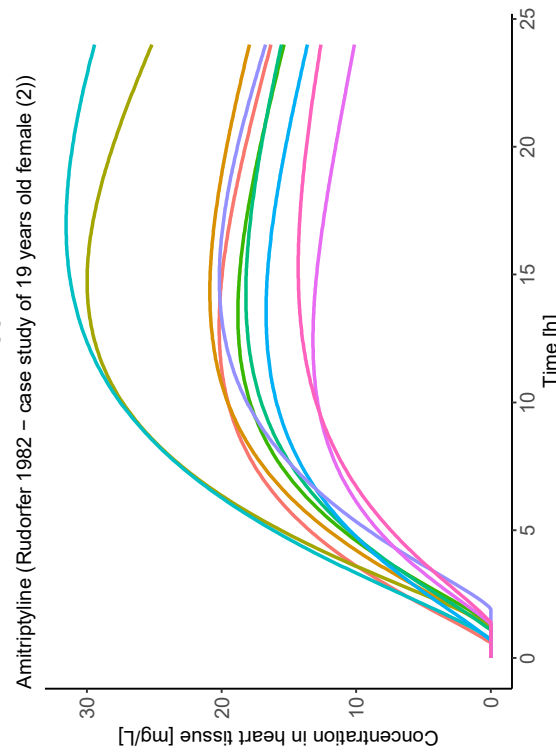
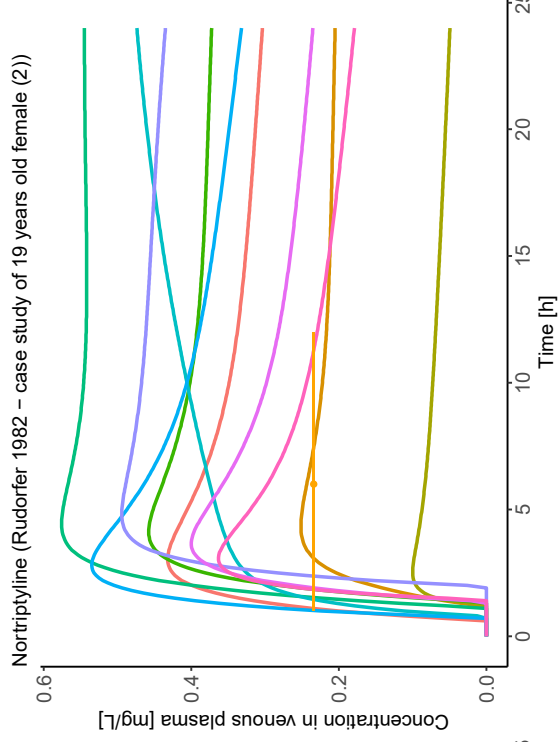
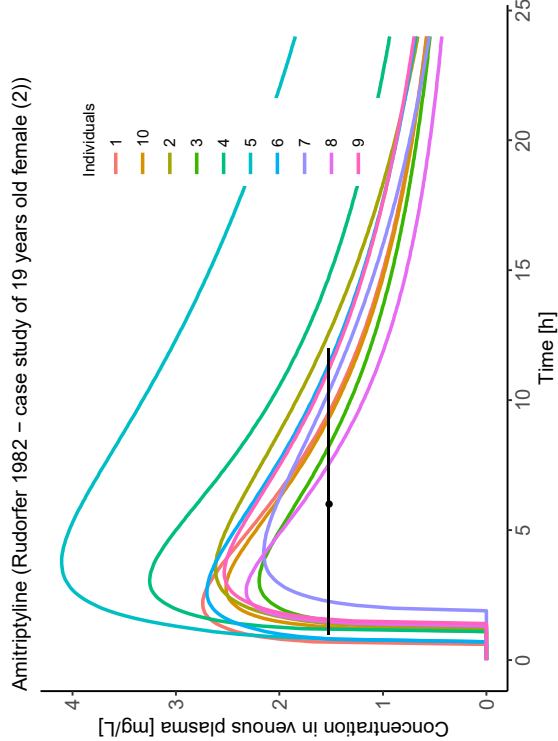
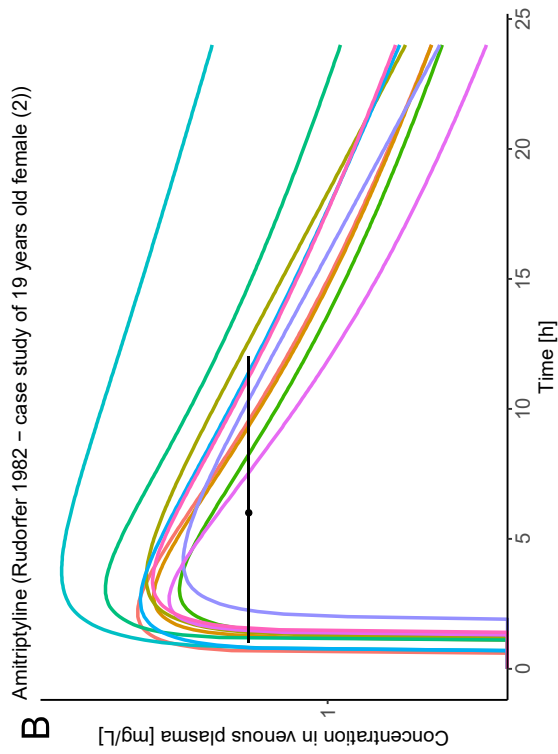
Figure 1 - Continued

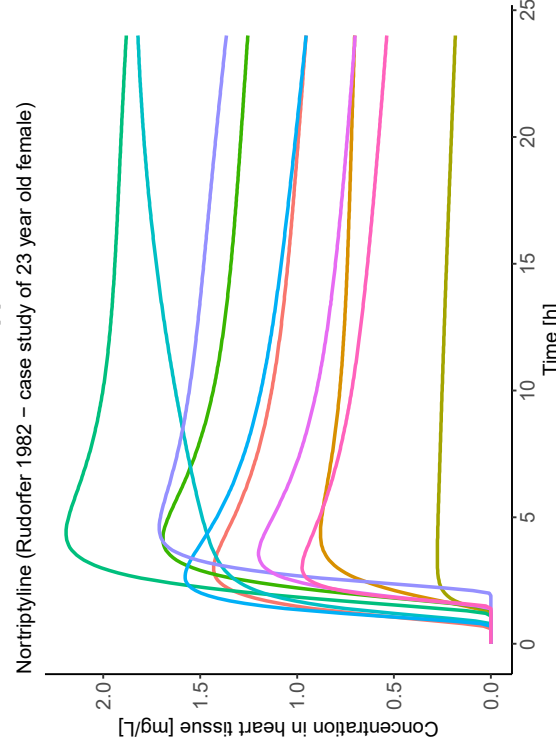
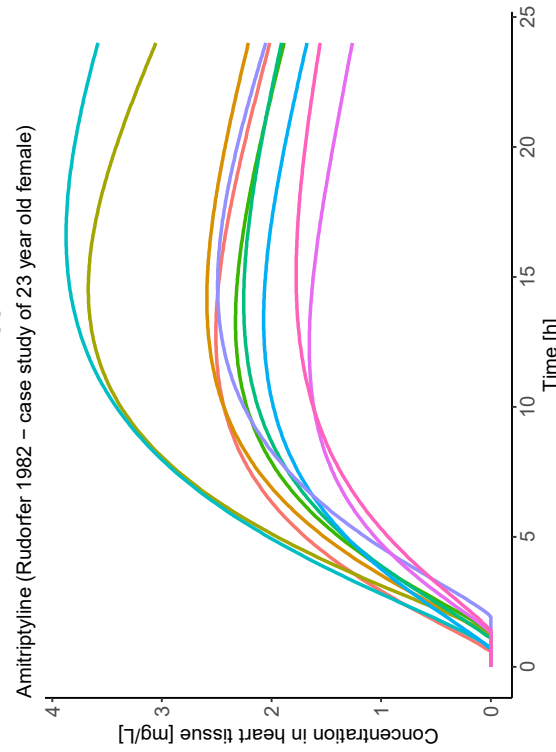
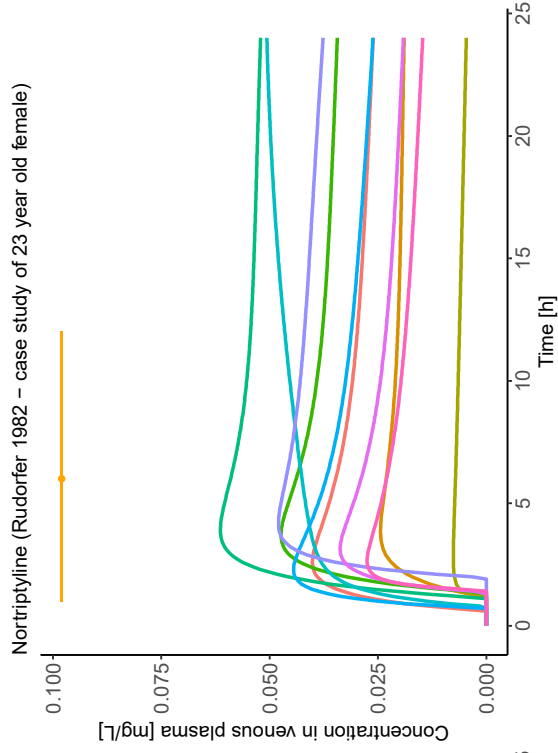
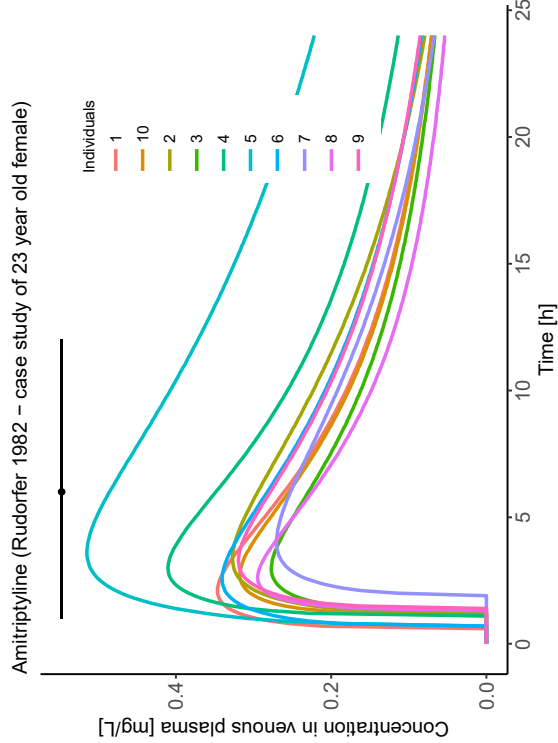
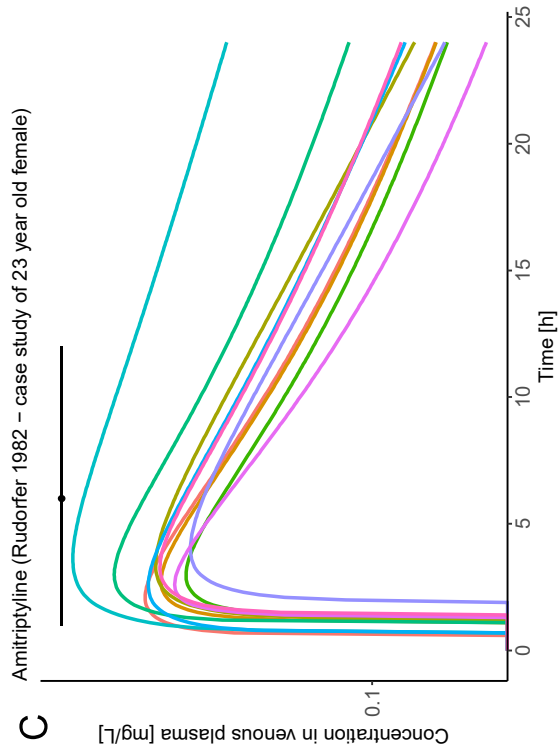


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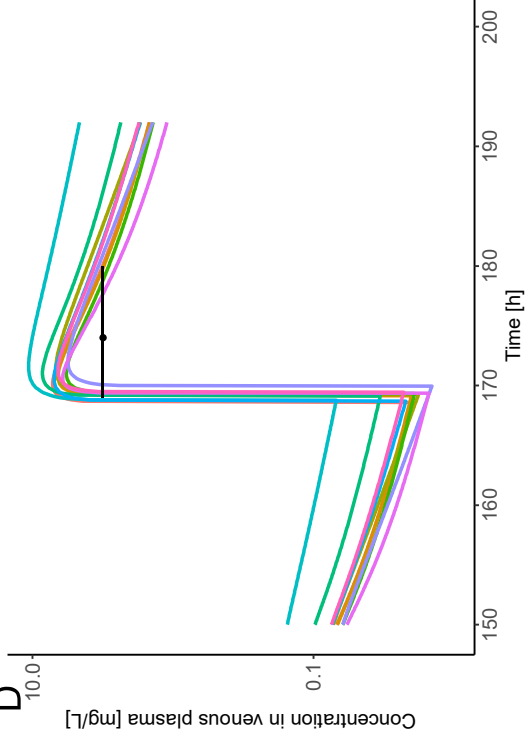
Figure 2 - The PK simulations' results of cases of AT intoxication (continued on nextpage).



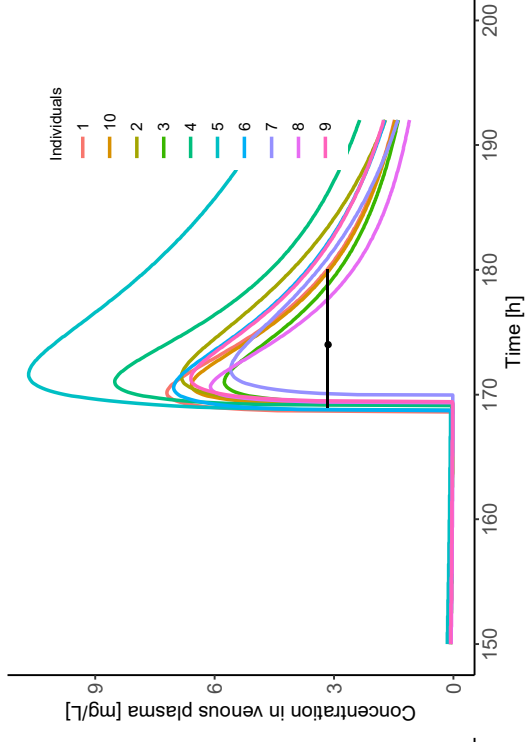




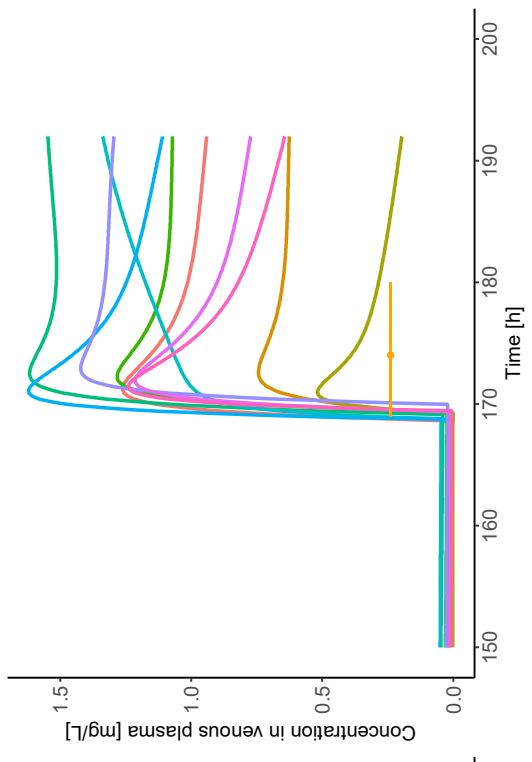
D Amitriptyline (Rudorfer 1982 - case study of 29 years old female (1))



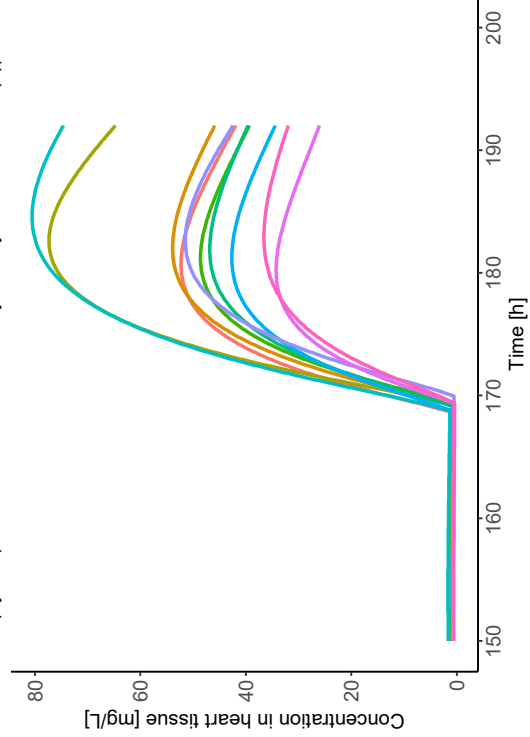
Amitriptyline (Rudorfer 1982 - case study of 29 years old female (1))



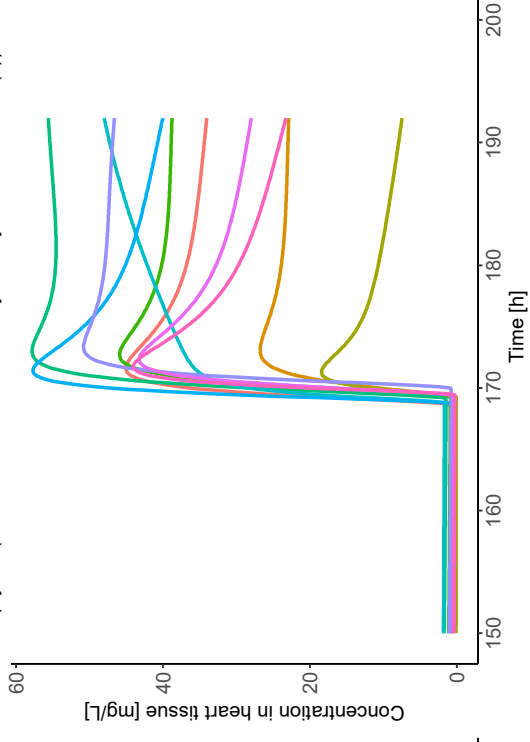
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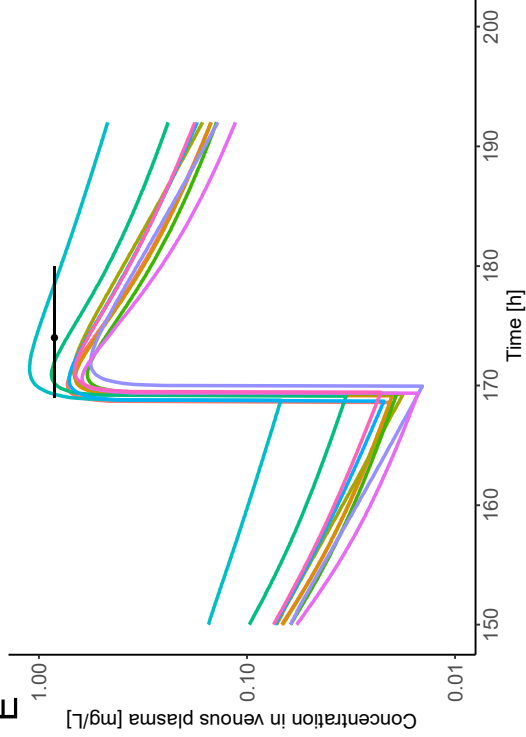
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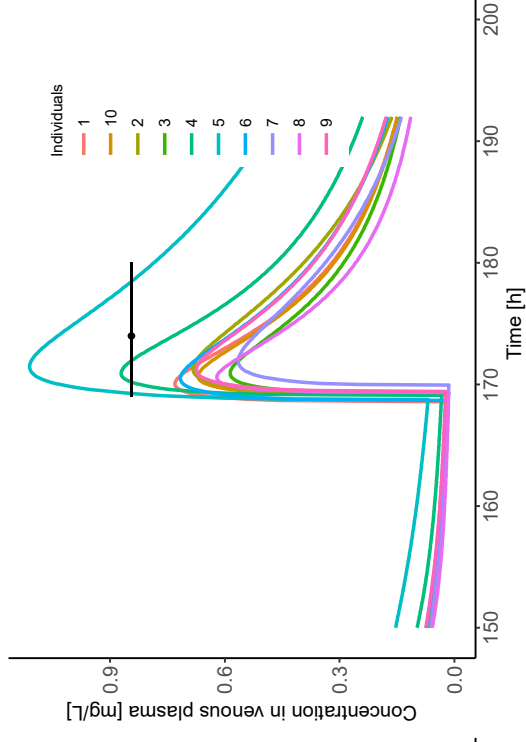
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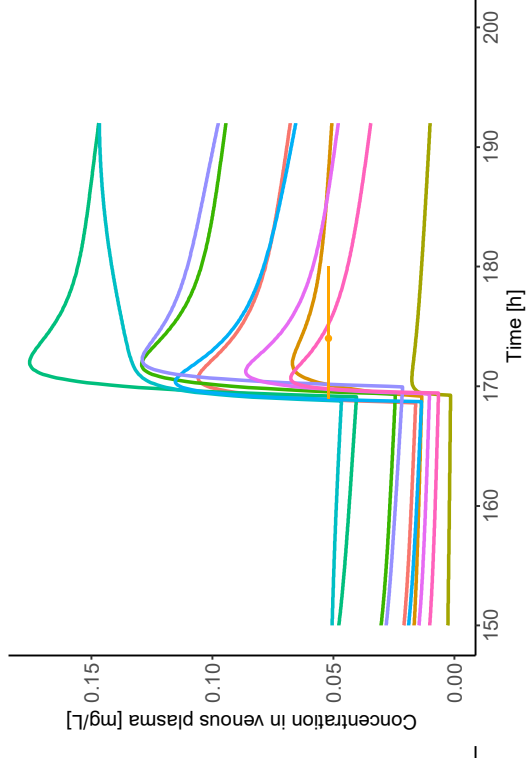
E Amitriptyline (Rudorfer 1982 - case study of 29 years old female (2))



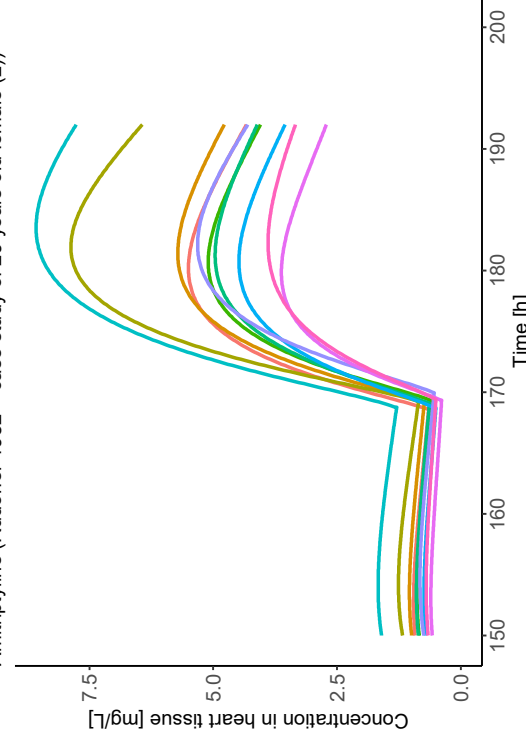
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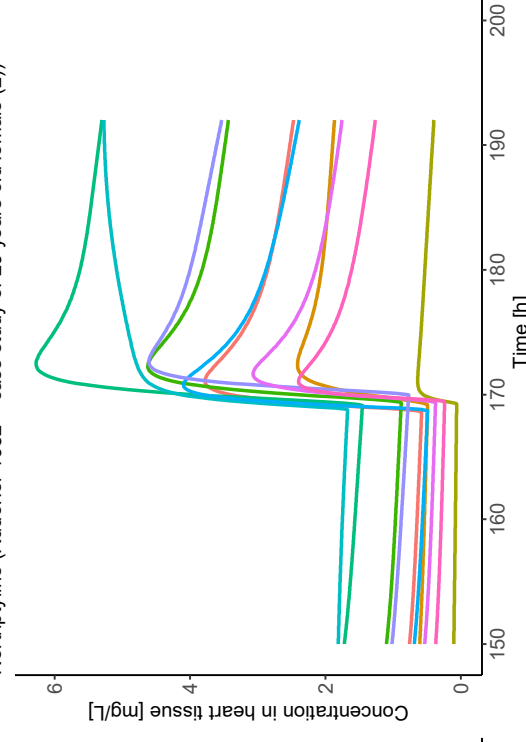
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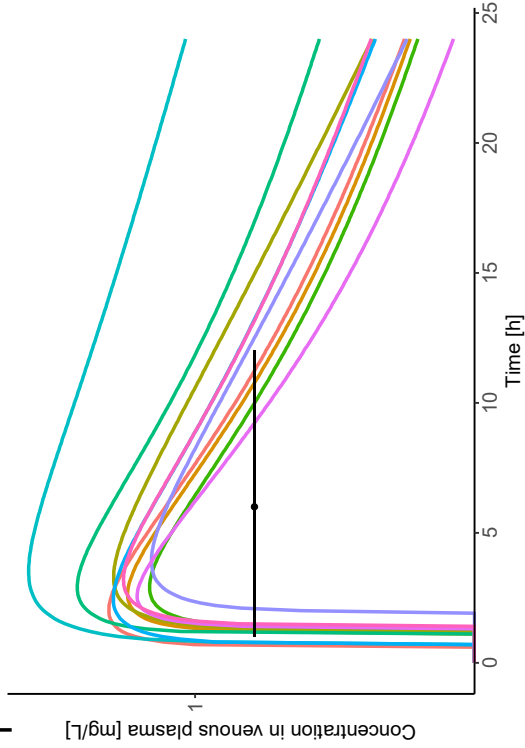
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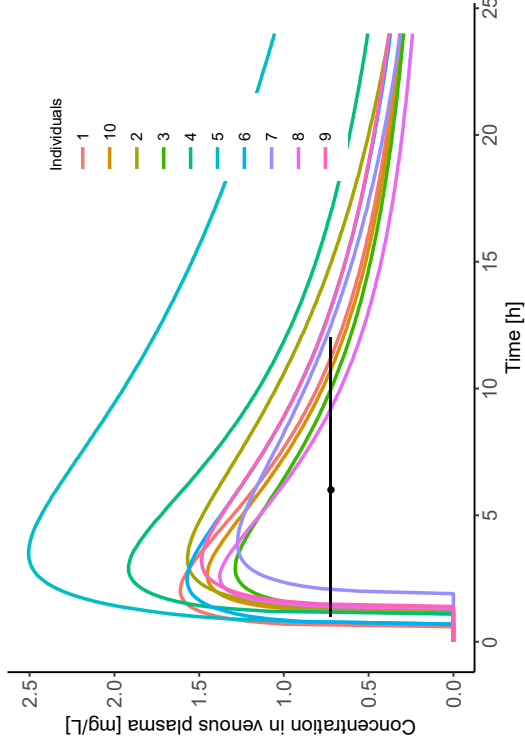
Nortriptyline (Rudorfer 1982 - case study of 29 years old female (2))



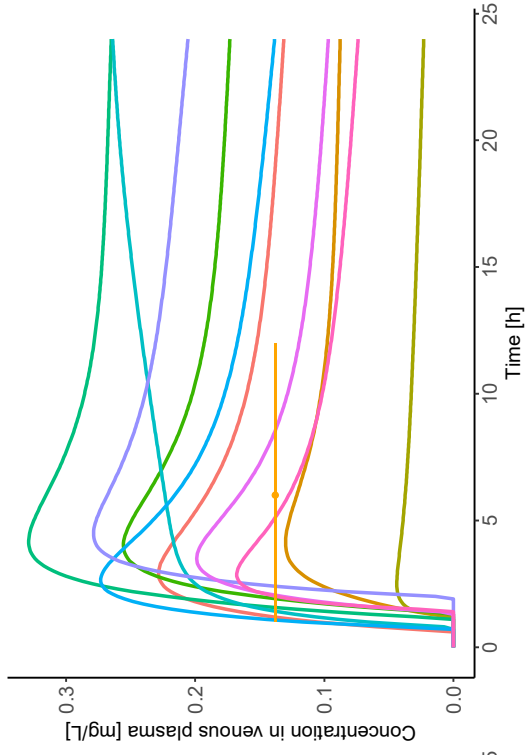
F Amitriptyline (Rudorfer 1982 – case study of 32 year old female)



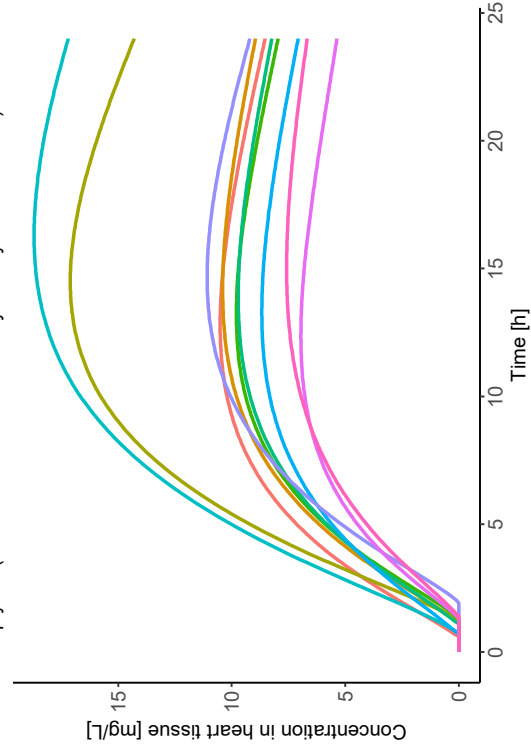
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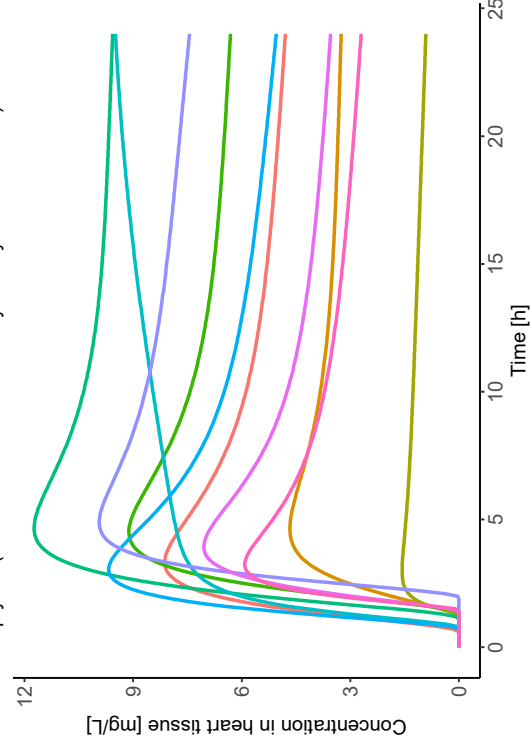
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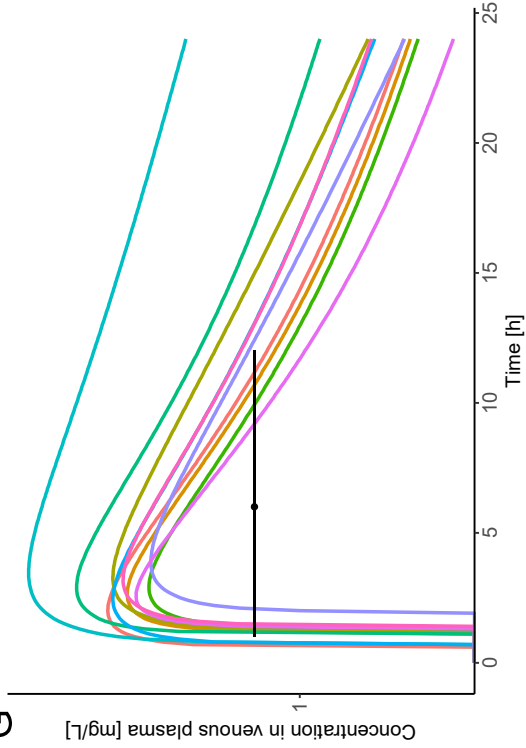
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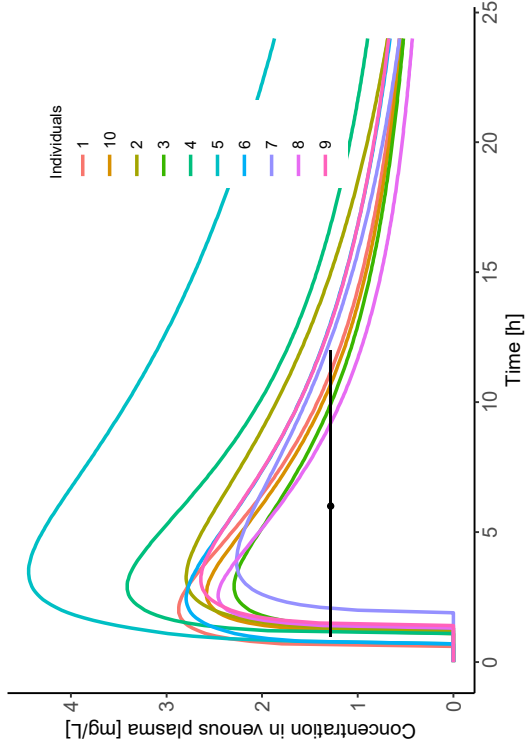
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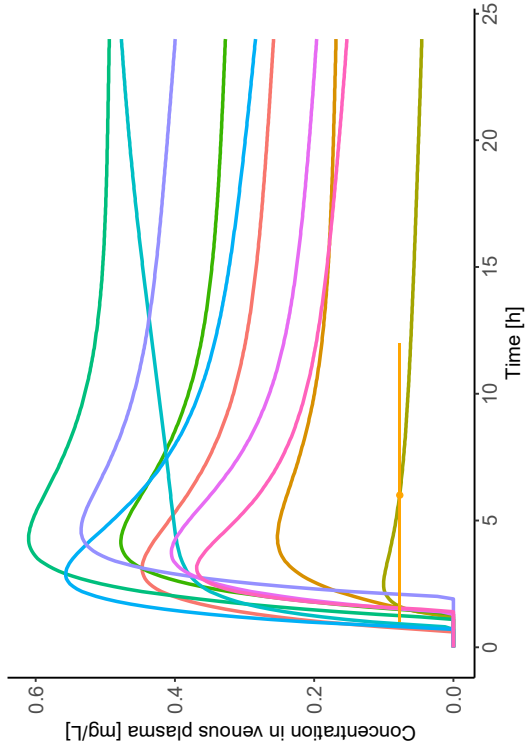
G Amitriptyline (Rudorfer 1982 – case study of 39 year old female)



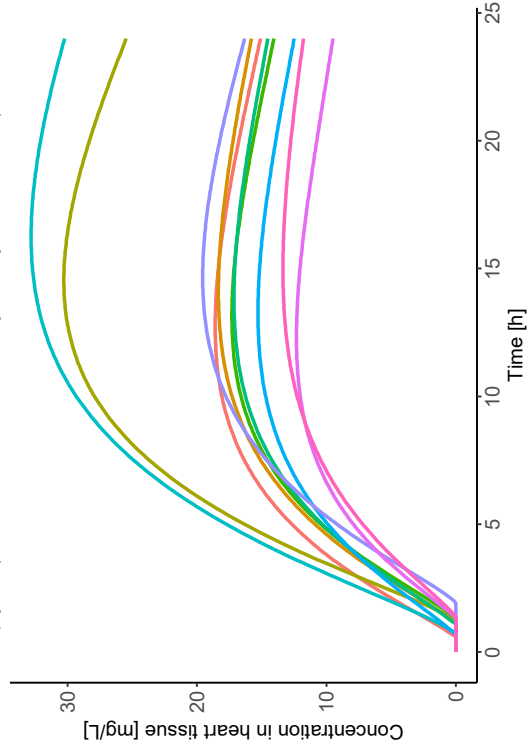
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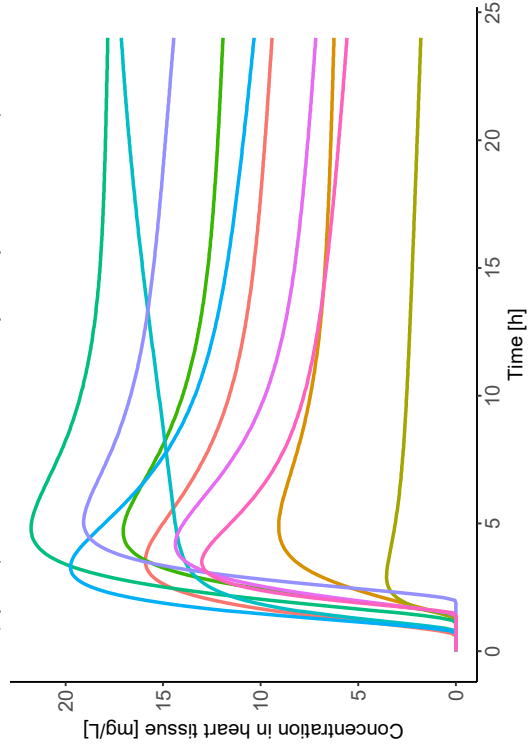
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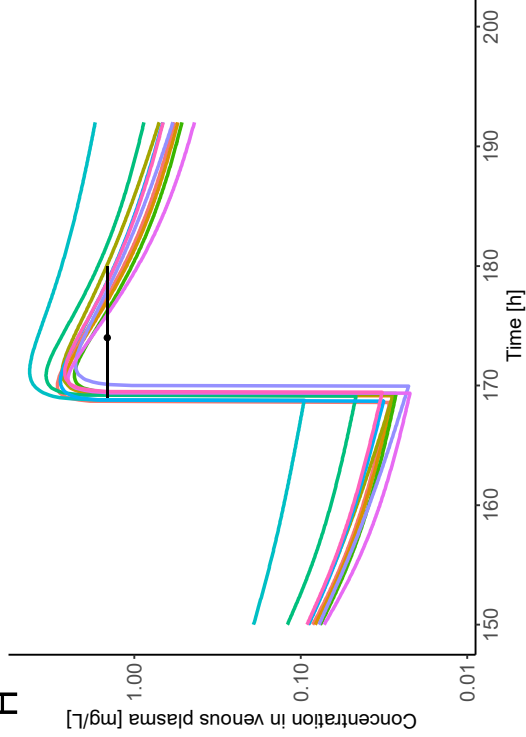
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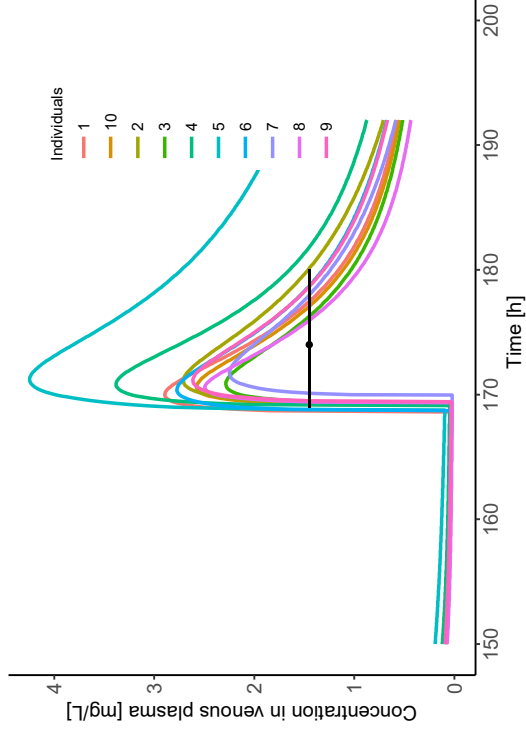
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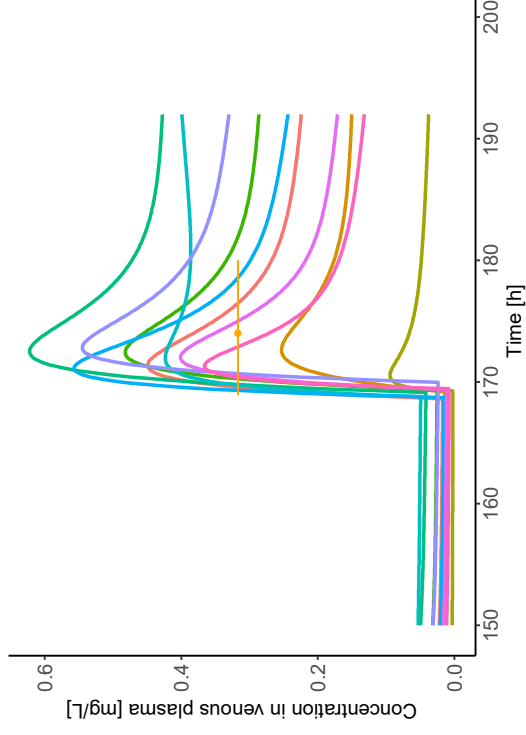
H Amitriptyline (Rudorfer 1982 - case study of 67 years old female)



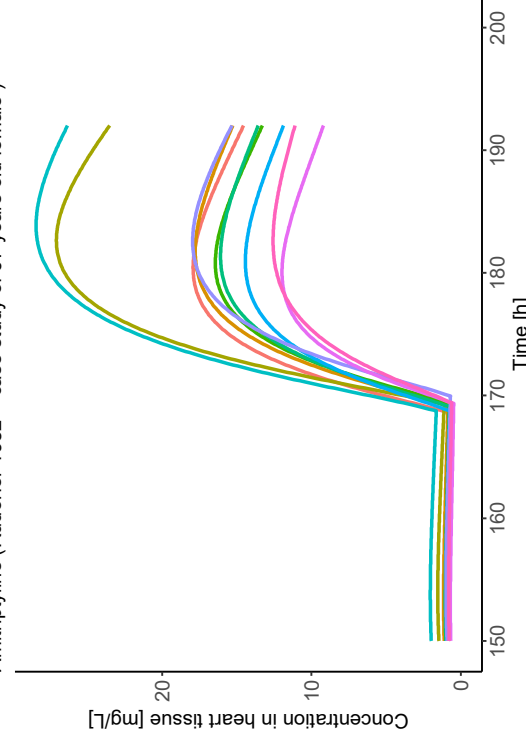
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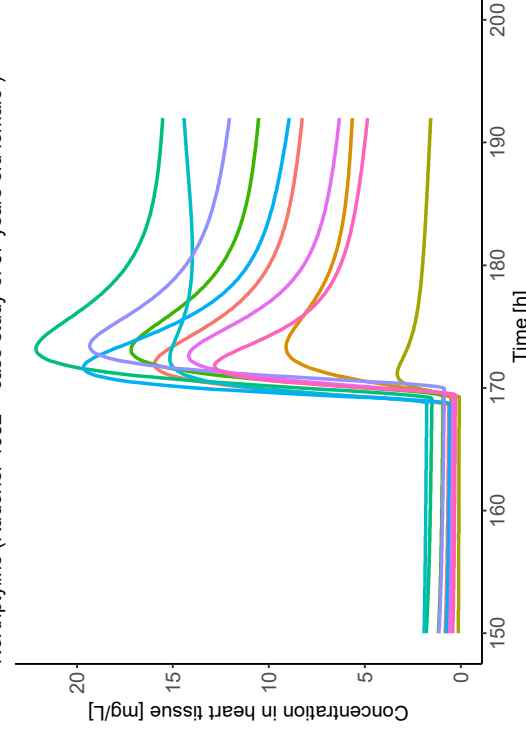
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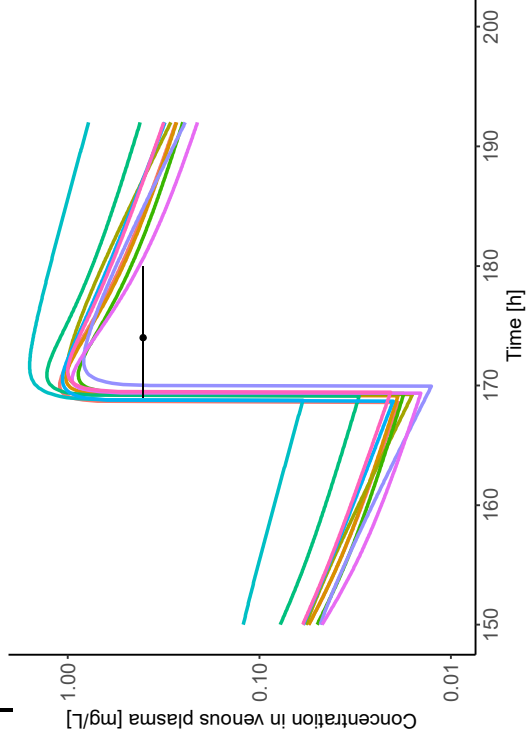
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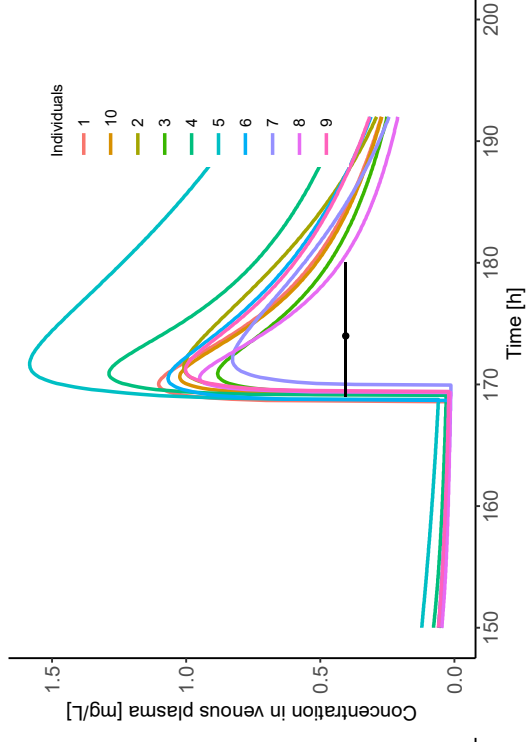
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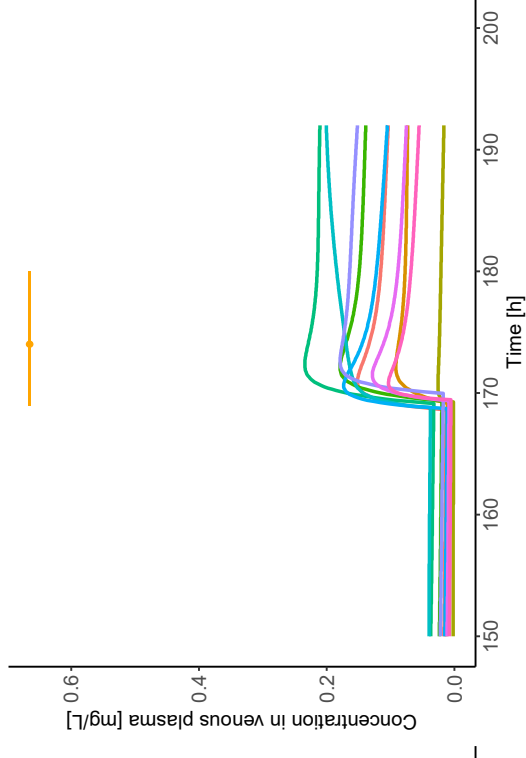
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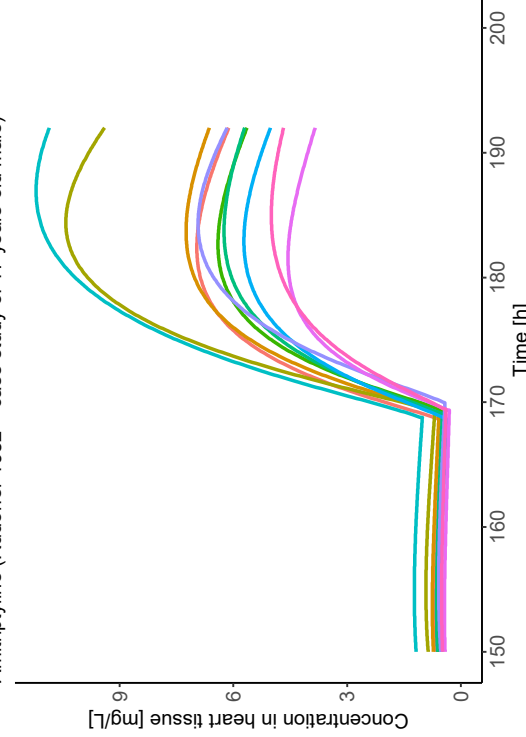
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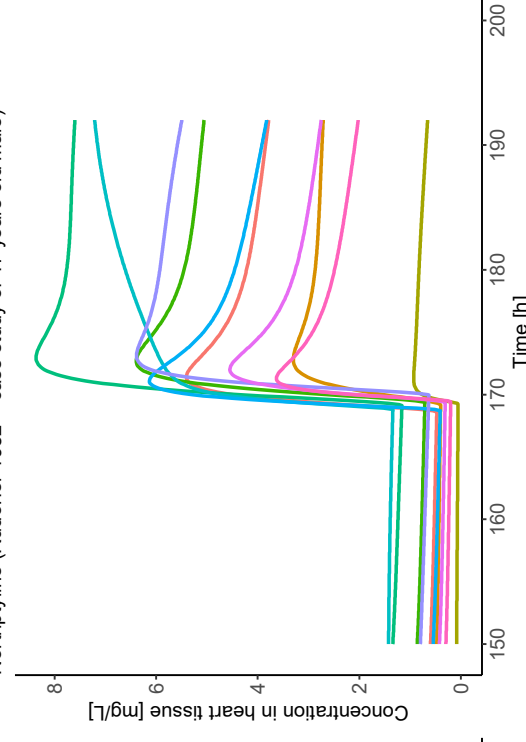
Nortriptyline (Rudorfer 1982 - case study of 17 years old male)



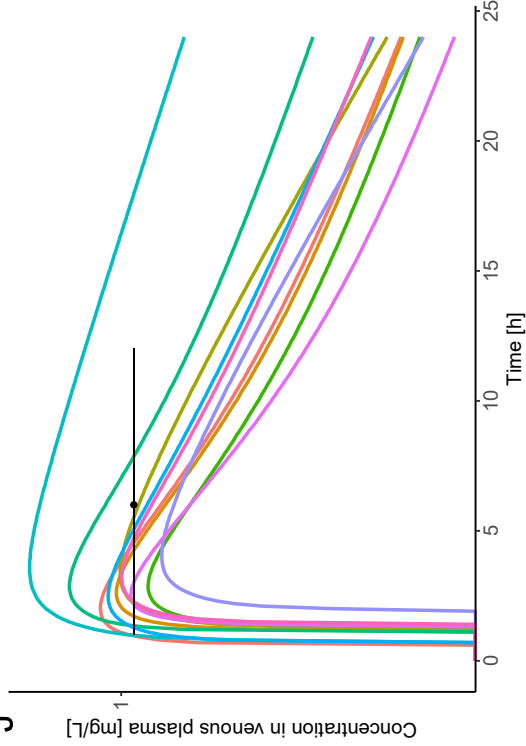
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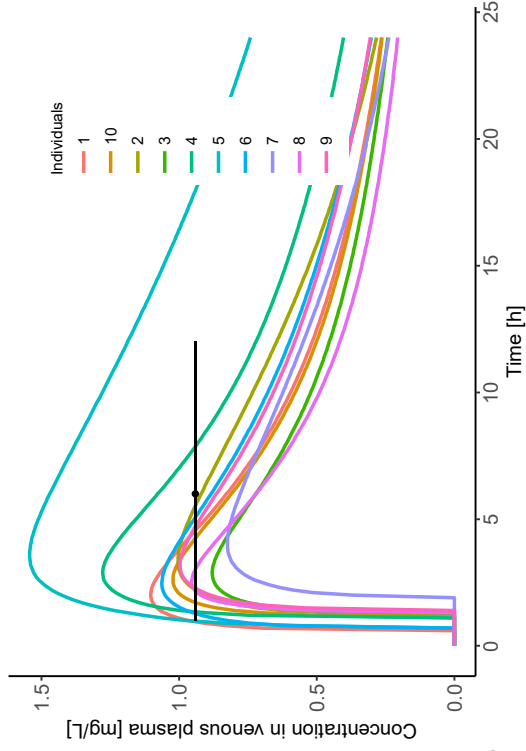
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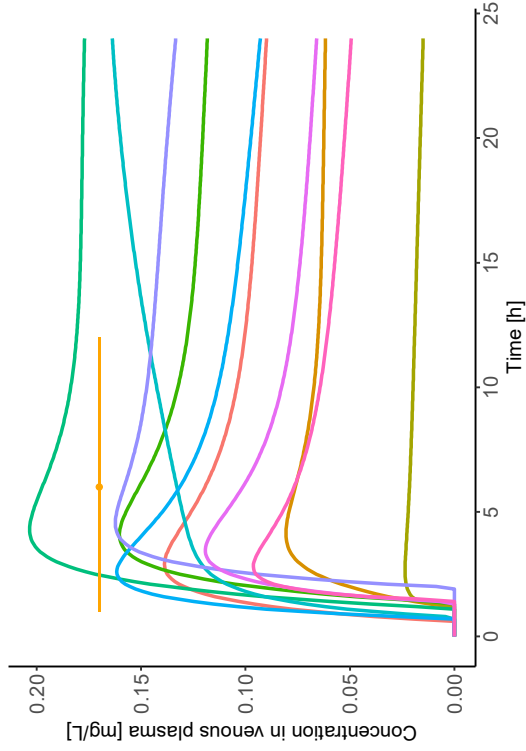
J Amitriptyline (Rudorfer 1982 - case study of 22 year old male)



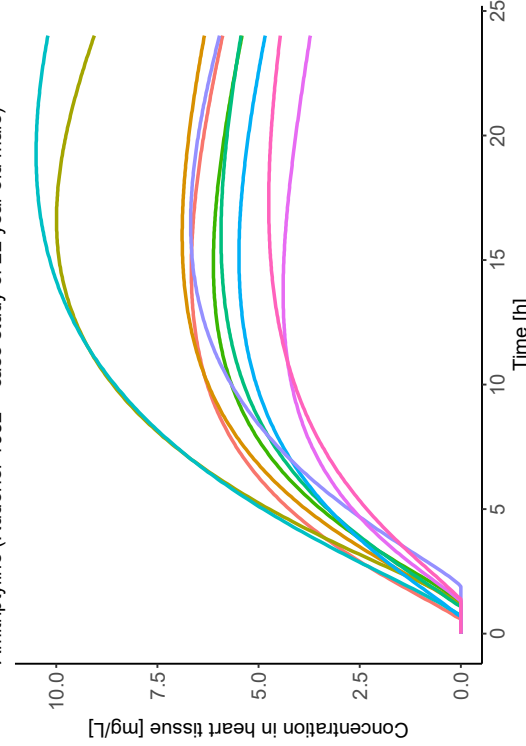
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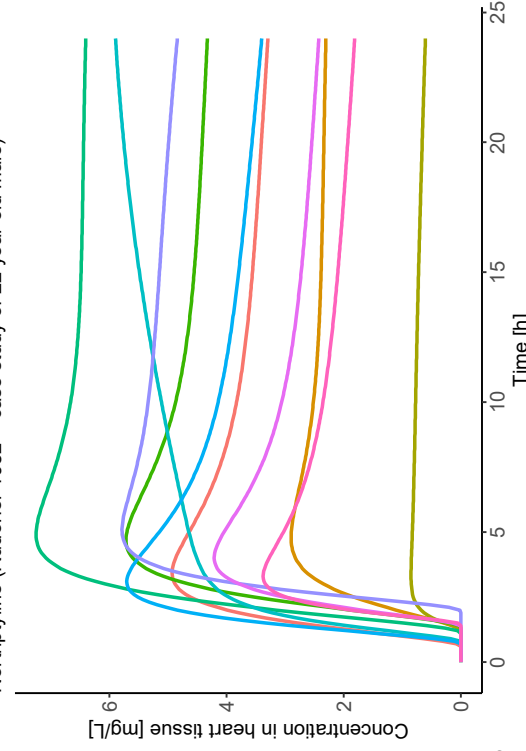
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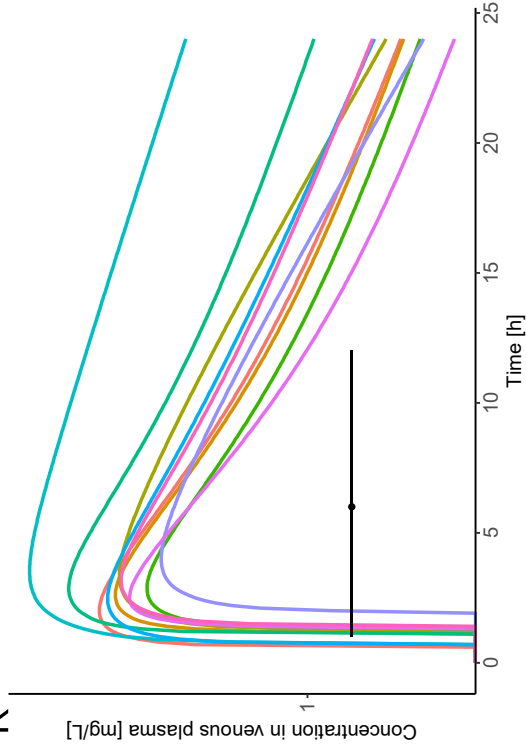
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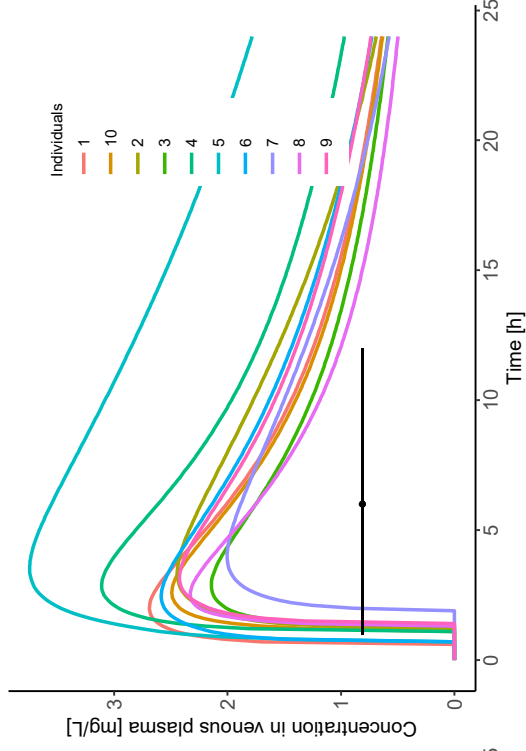
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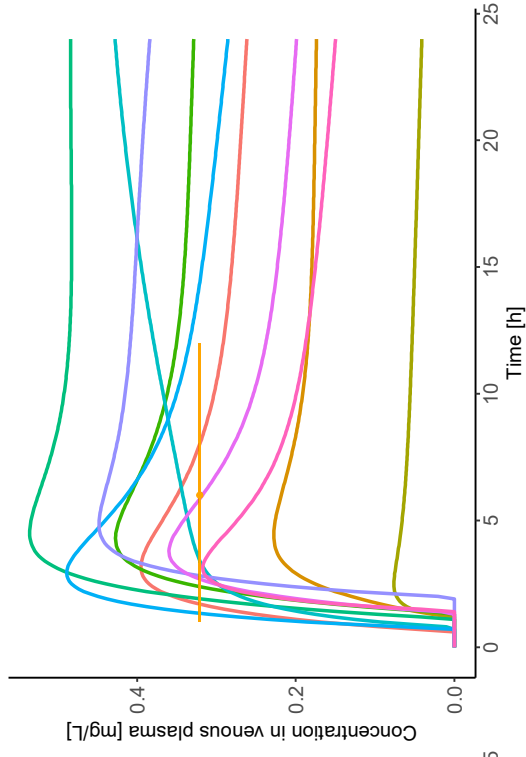
K Amitriptyline (Rudorfer 1982 - case study of 25 year old male (1))



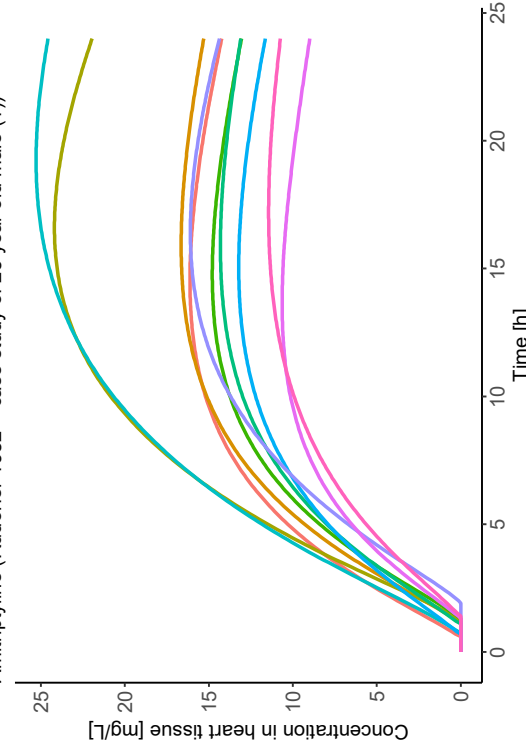
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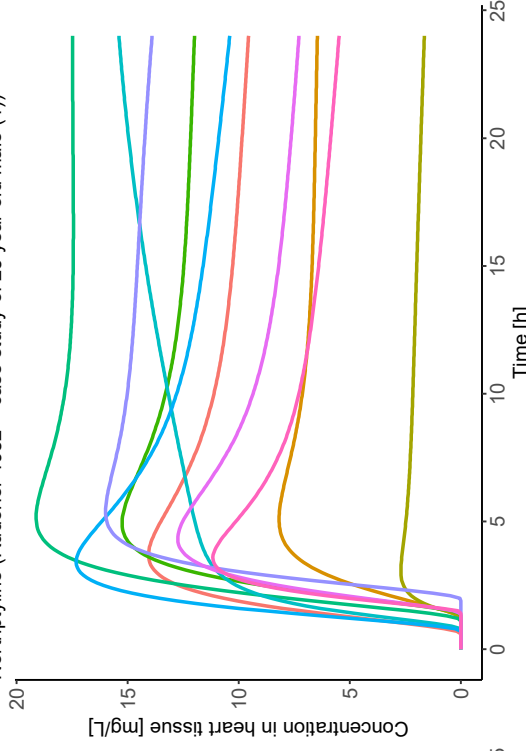
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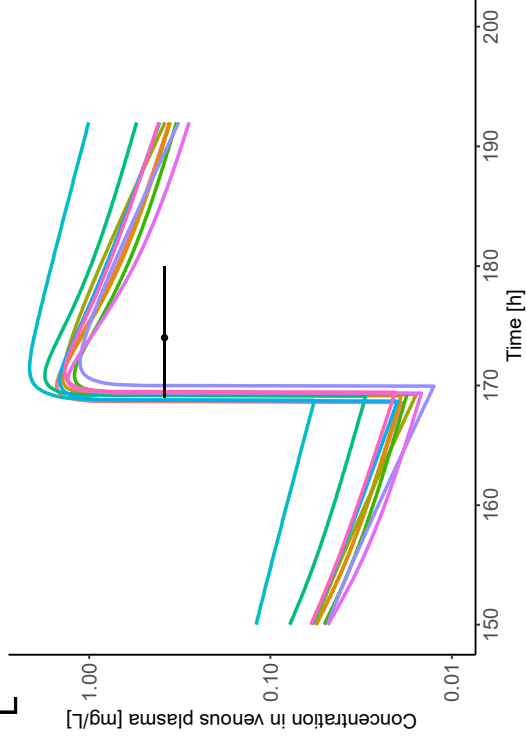
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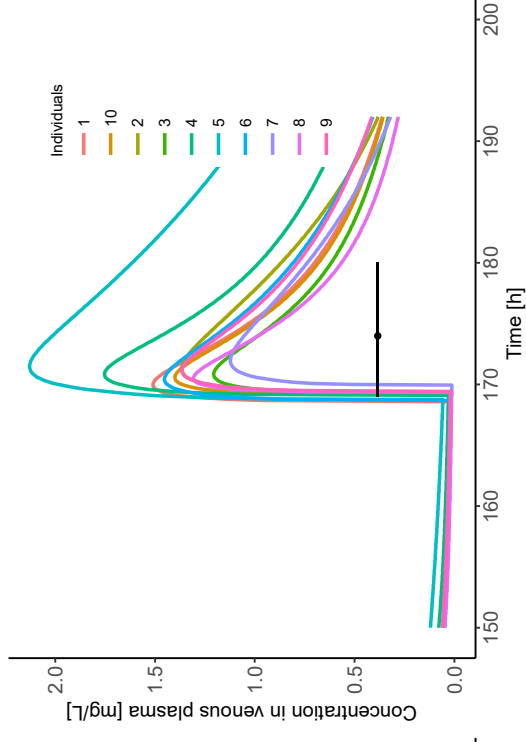
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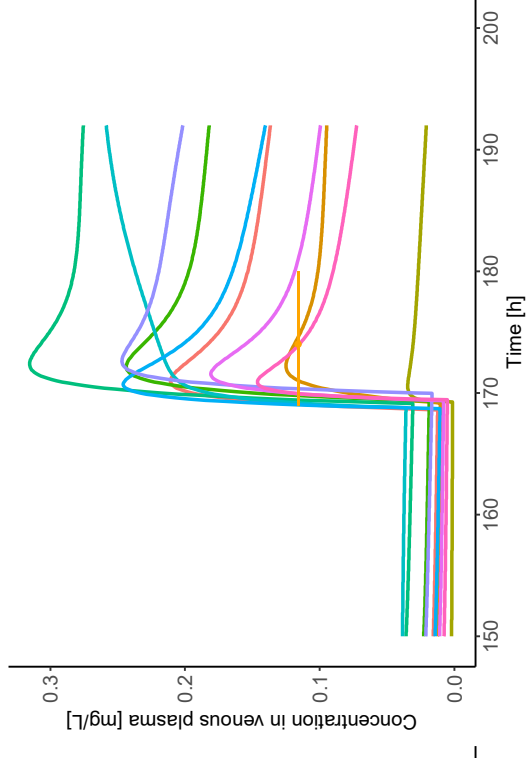
Amitriptyline (Rudorfer 1982 - case study of 25 years old male (2))



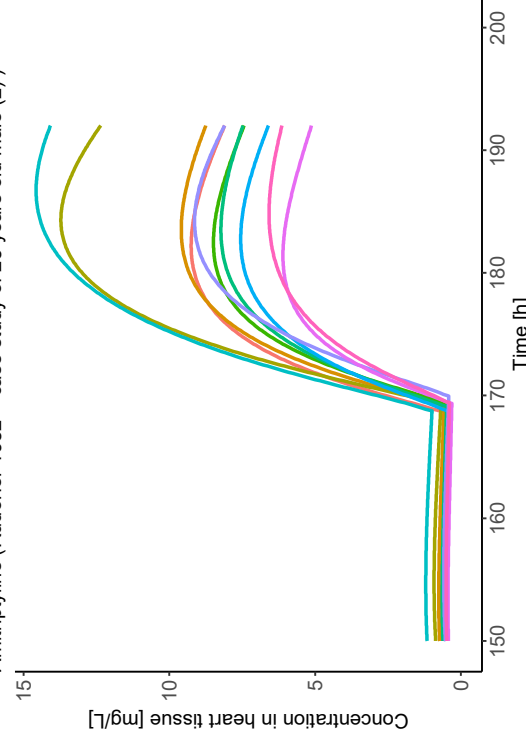
Amitriptyline (Rudorfer 1982 - case study of 25 years old male (2))



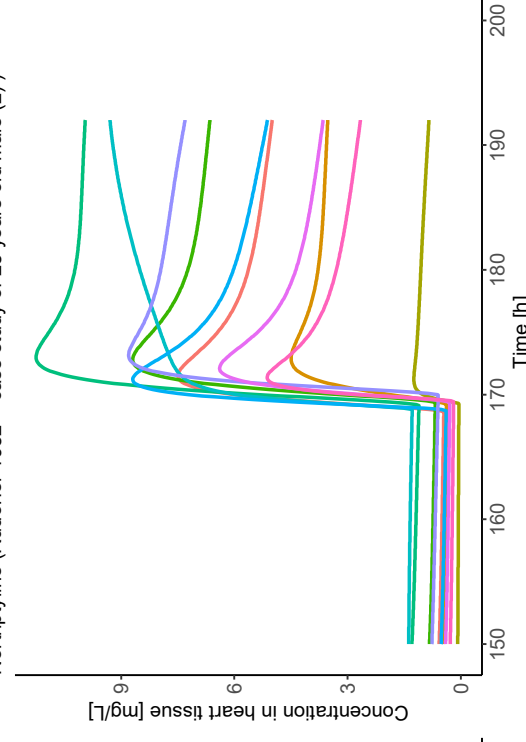
Nortriptyline (Rudorfer 1982 - case study of 25 years old male (2))

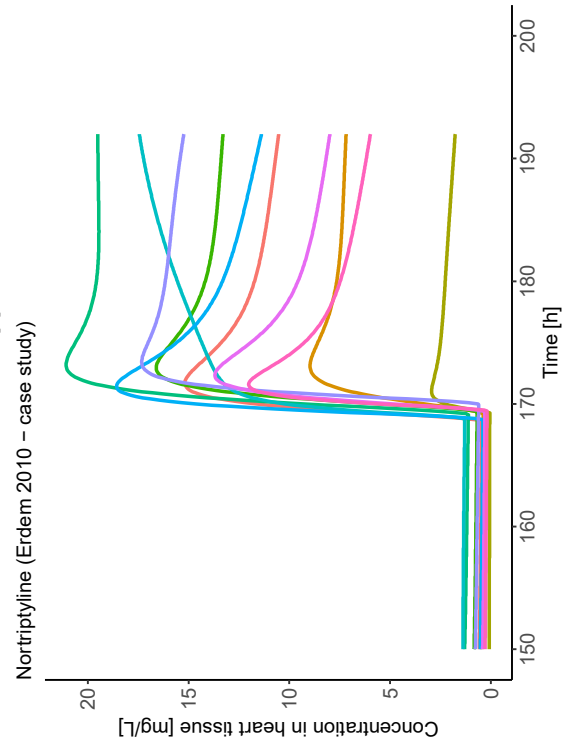
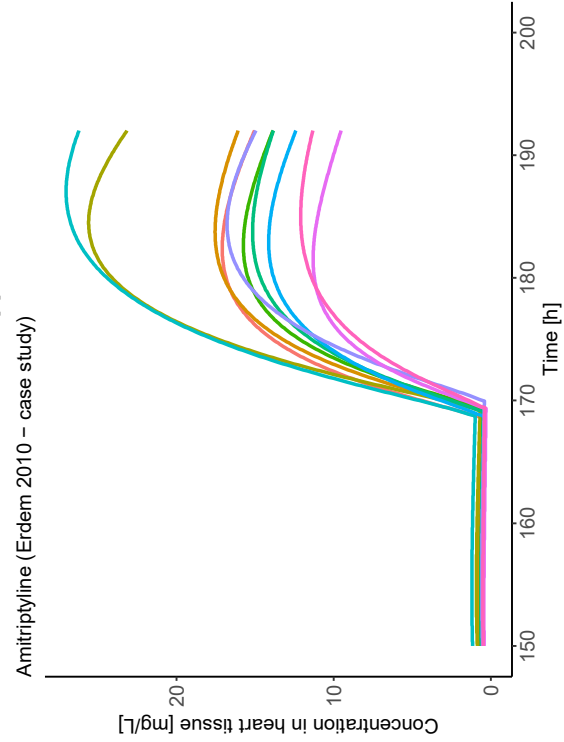
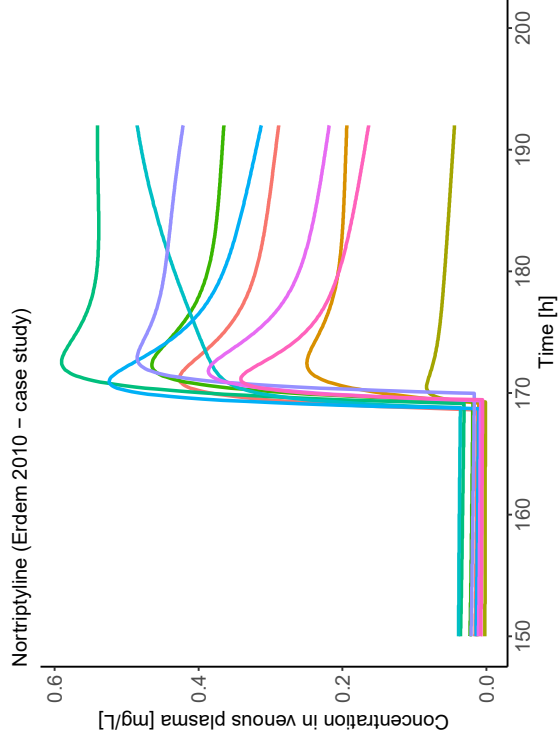
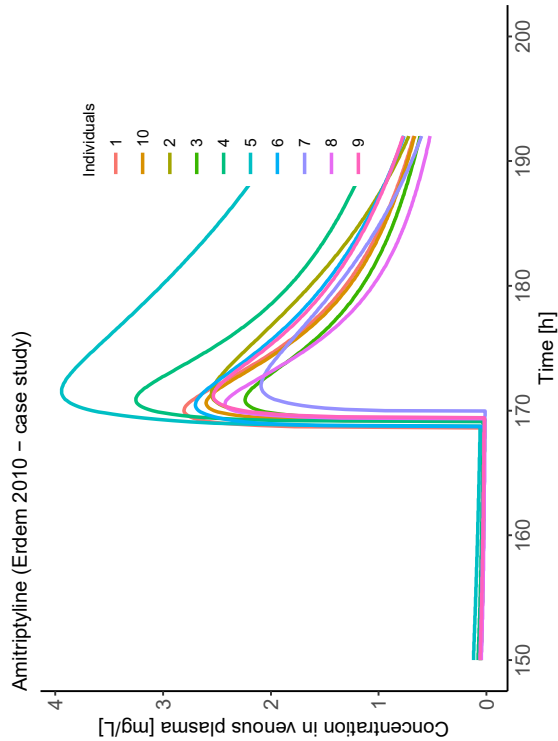
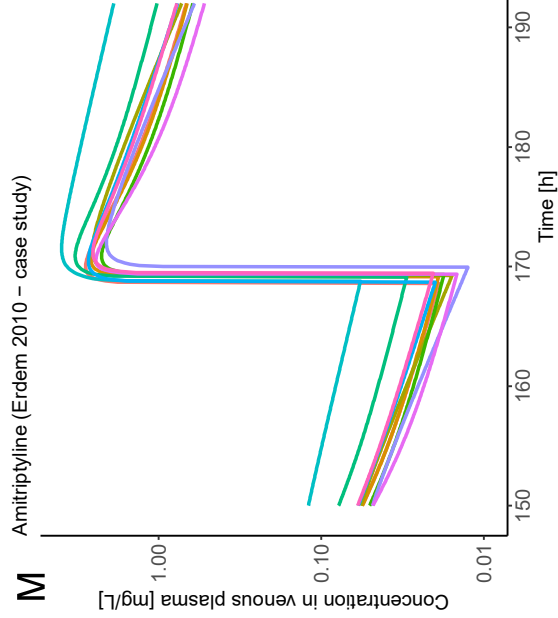


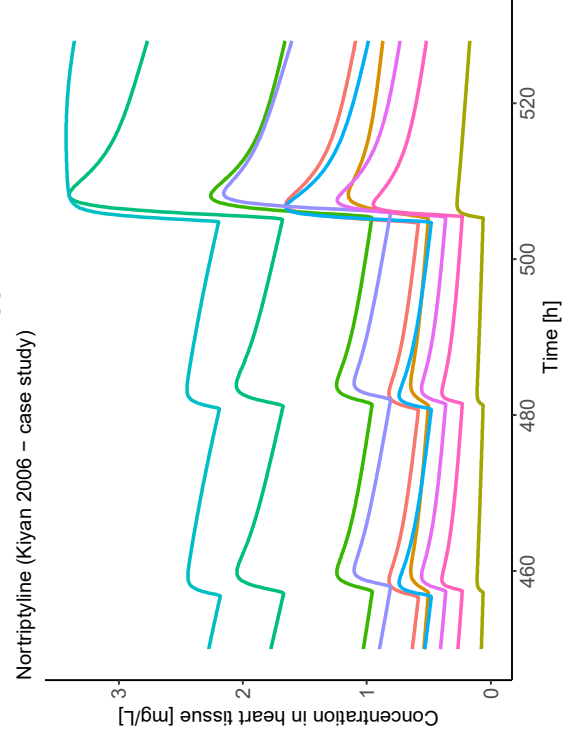
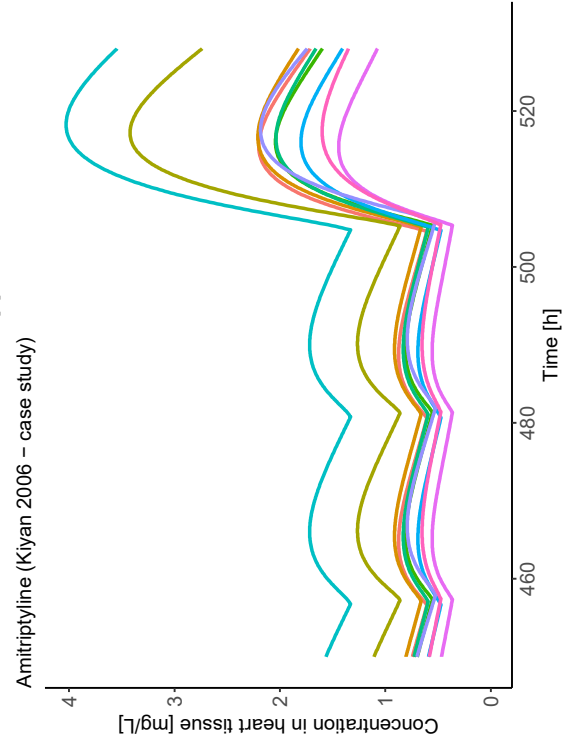
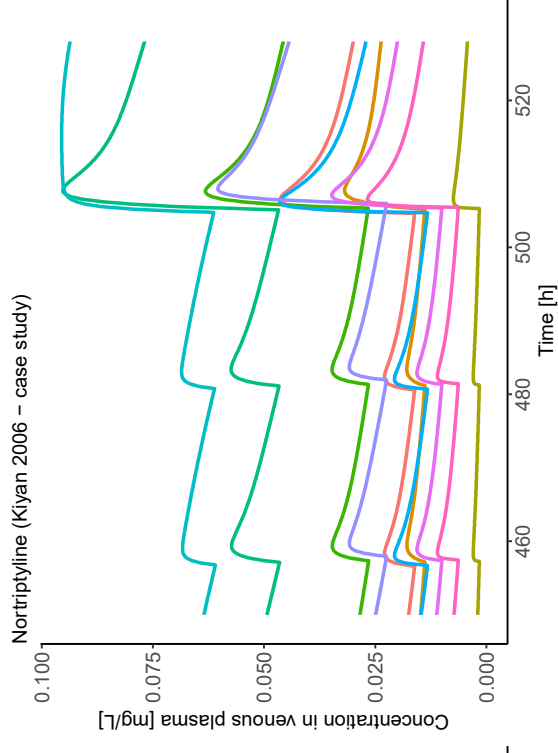
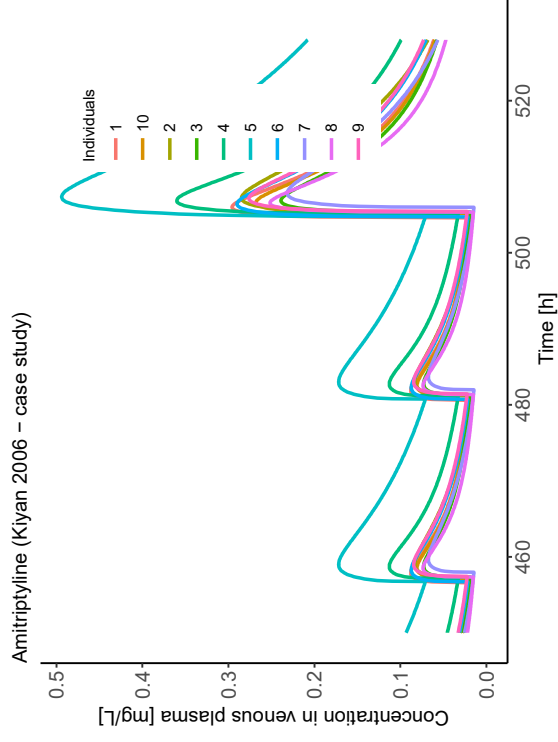
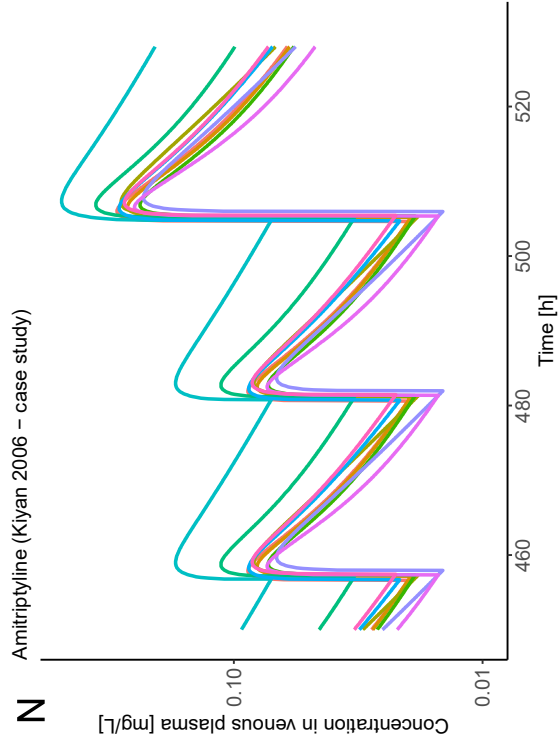
Amitriptyline (Rudorfer 1982 - case study of 25 years old male (2))

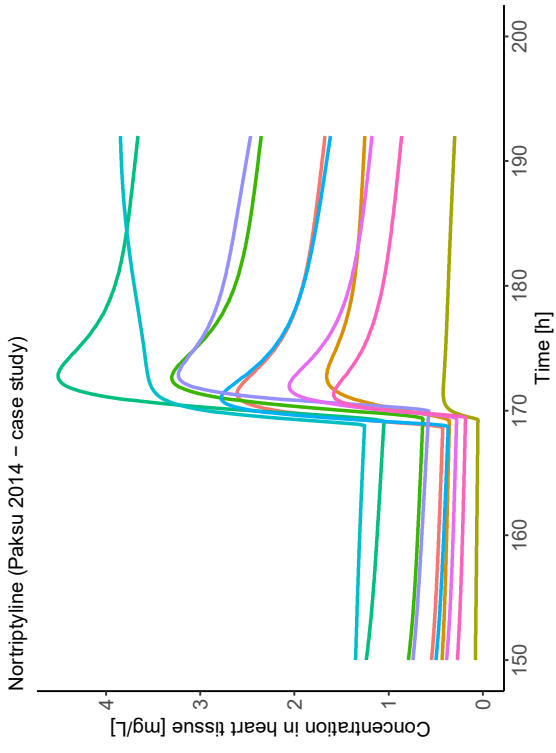
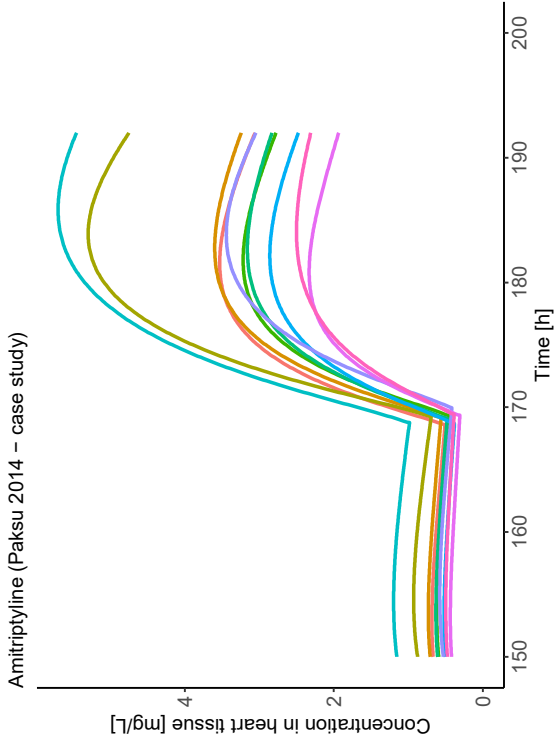
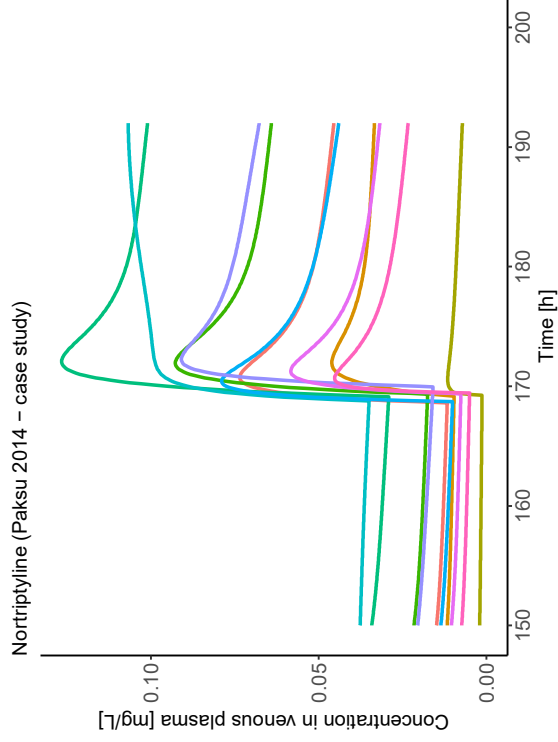
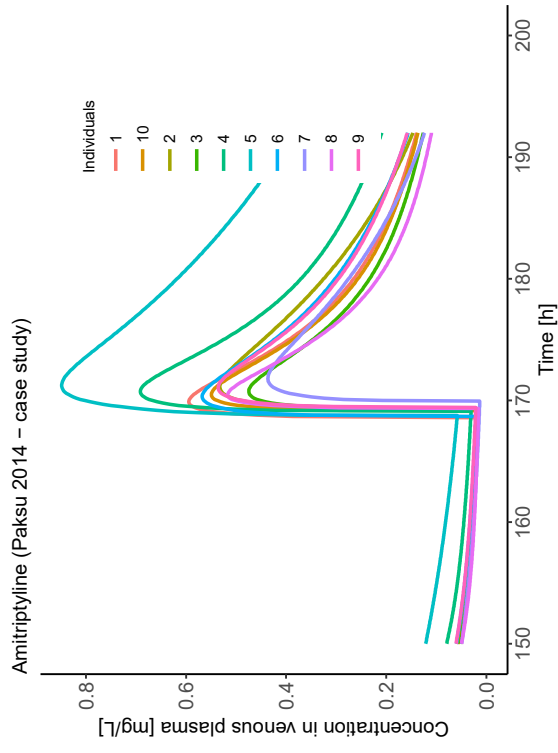
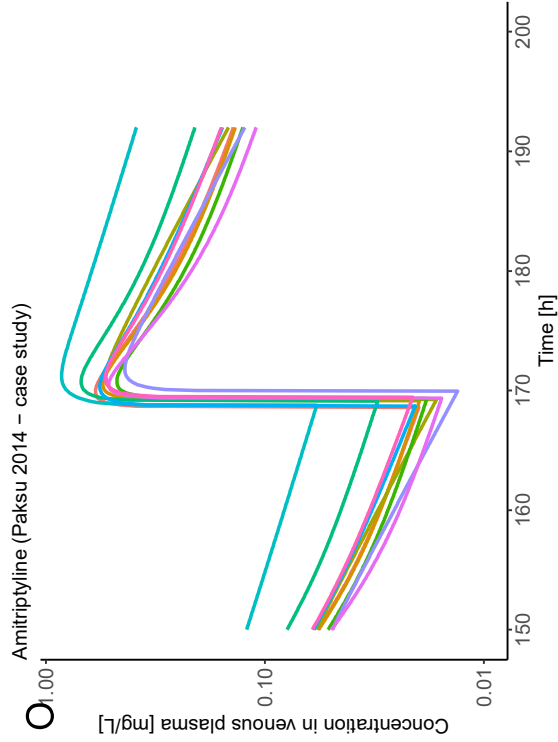


Nortriptyline (Rudorfer 1982 - case study of 25 years old male (2))

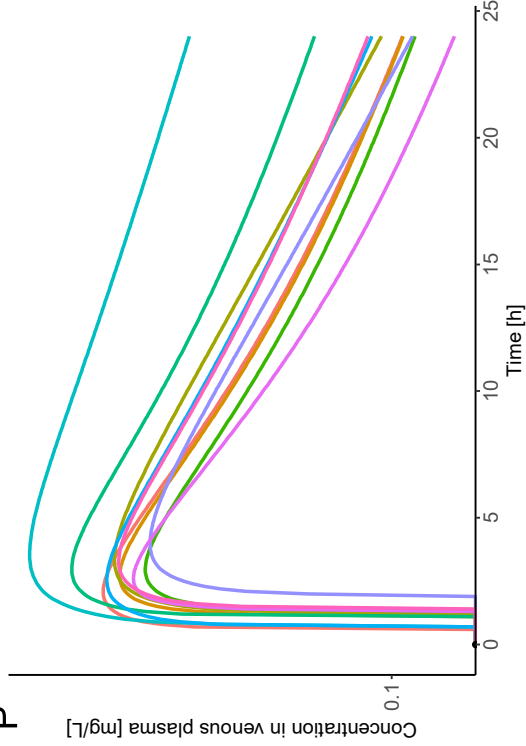




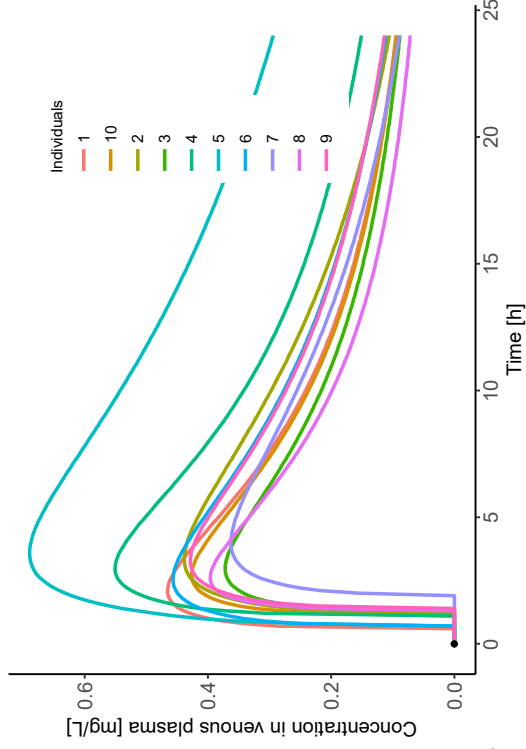




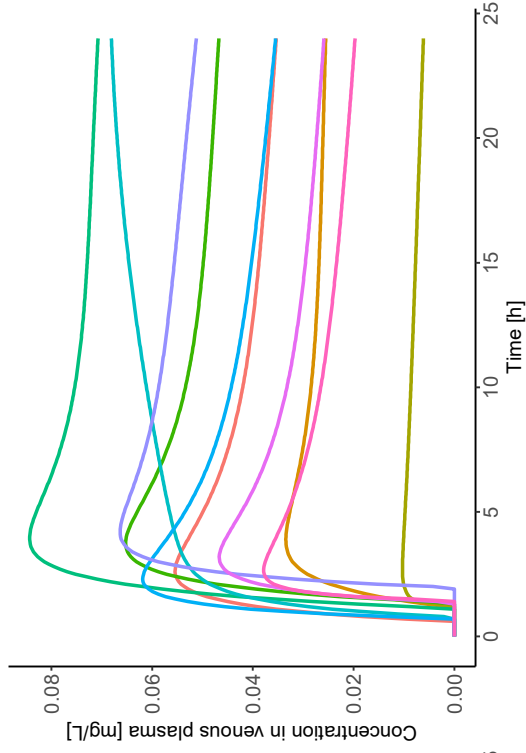
P Amitriptyline (Abeyaratne 2016 - case study of 25-year old female)



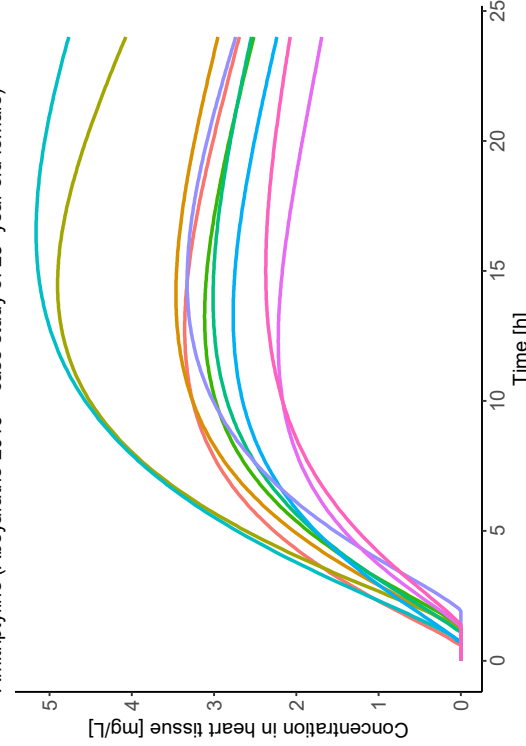
Amitriptyline (Abeyaratne 2016 - case study of 25-year old female)



Nortriptyline (Abeyaratne 2016 - case study of 25-year old female)



Amitriptyline (Abeyaratne 2016 - case study of 25-year old female)



Nortriptyline (Abeyaratne 2016 - case study of 25-year old female)

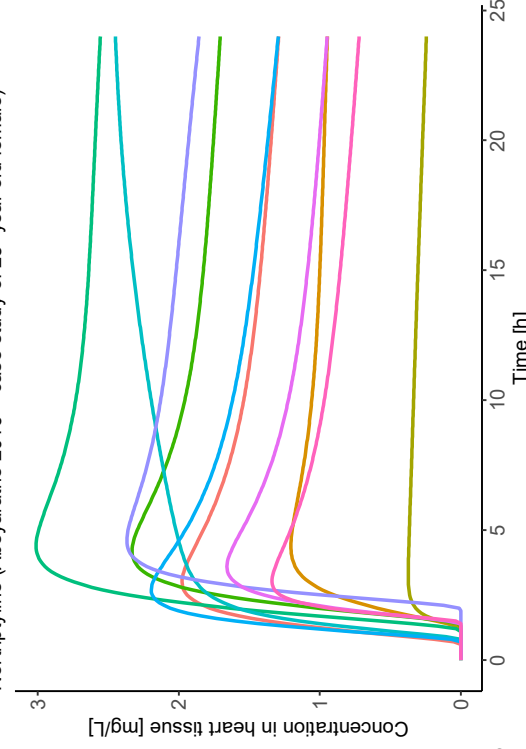


Figure 3 - The simulated QT or QTc for each of the cases in 10 virtual patients (1 - 10) along with clinical observations (obs). The triangle means virtual arrhythmia occurrence.

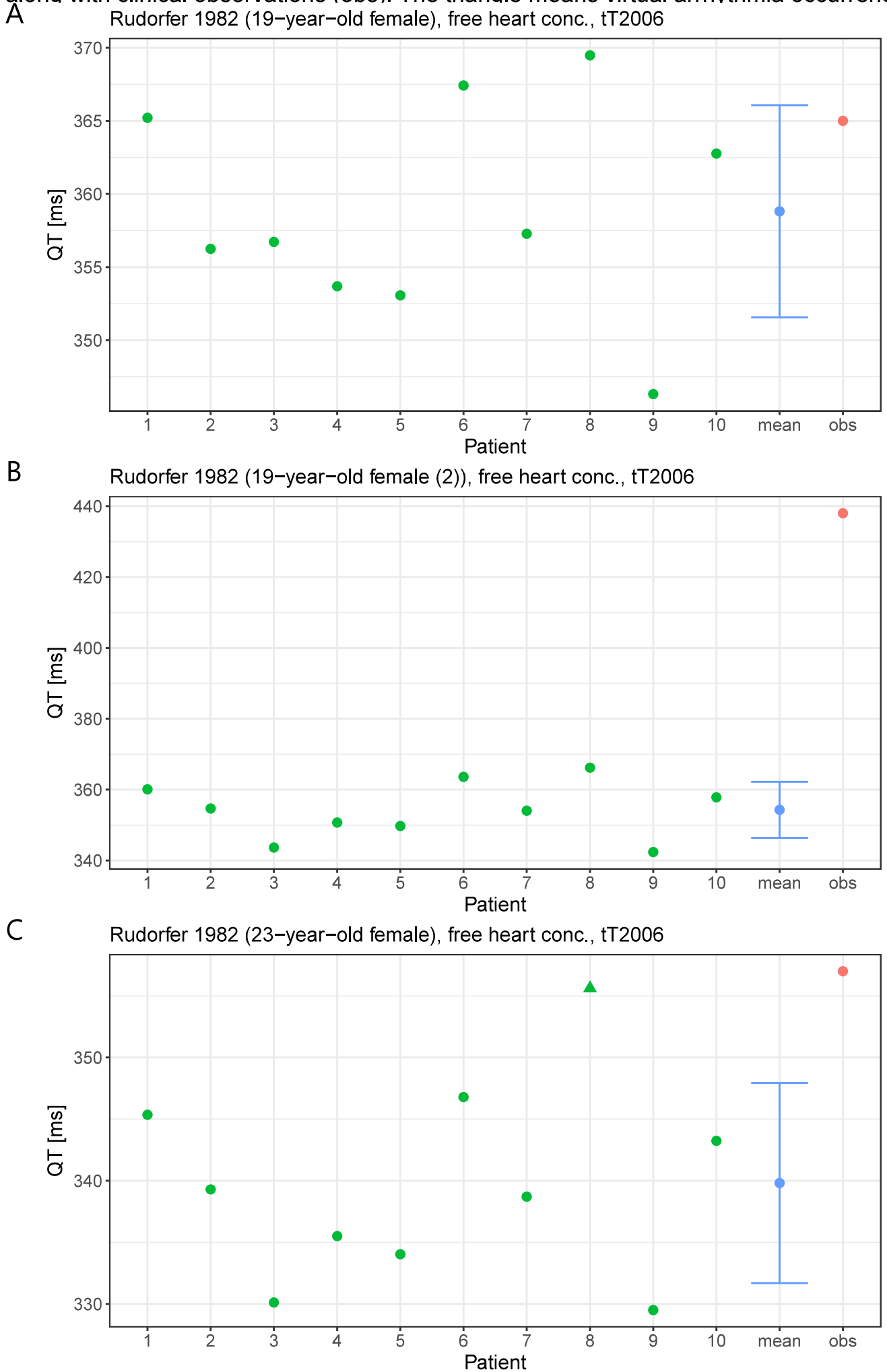
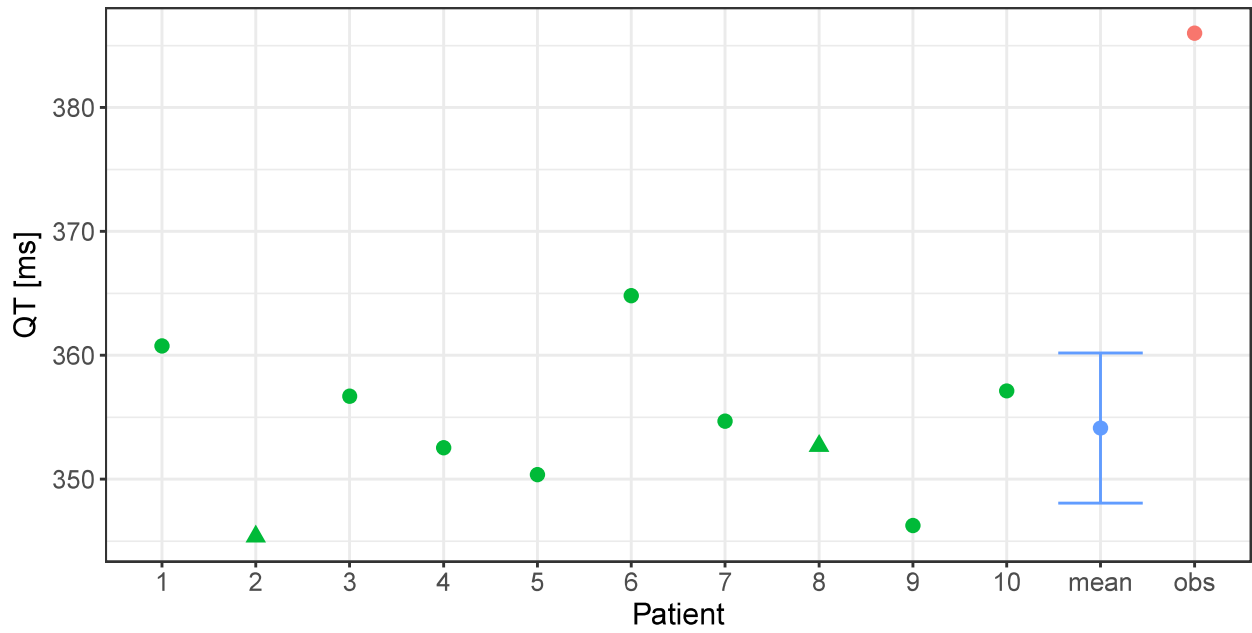


Figure 3 - Continued

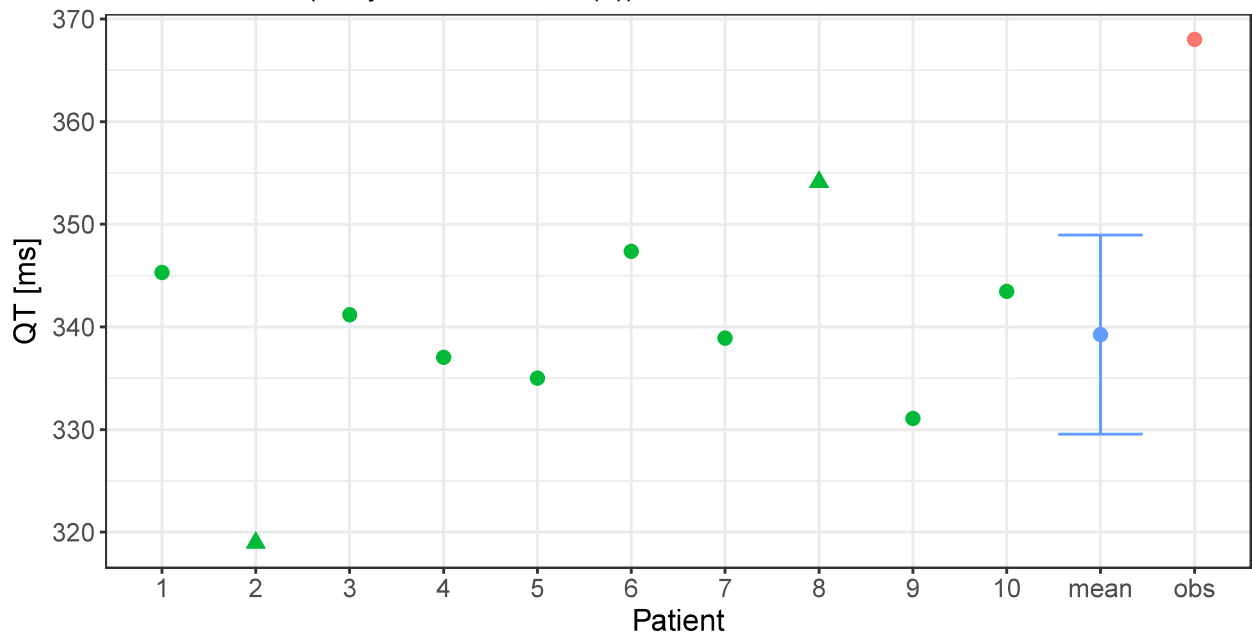
D

Rudorfer 1982 (29-year-old female (1)), free heart conc., tT2006



E

Rudorfer 1982 (29-year-old female (2)), free heart conc., tT2006



F

Rudorfer 1982 (32-year-old female), free heart conc., tT2006

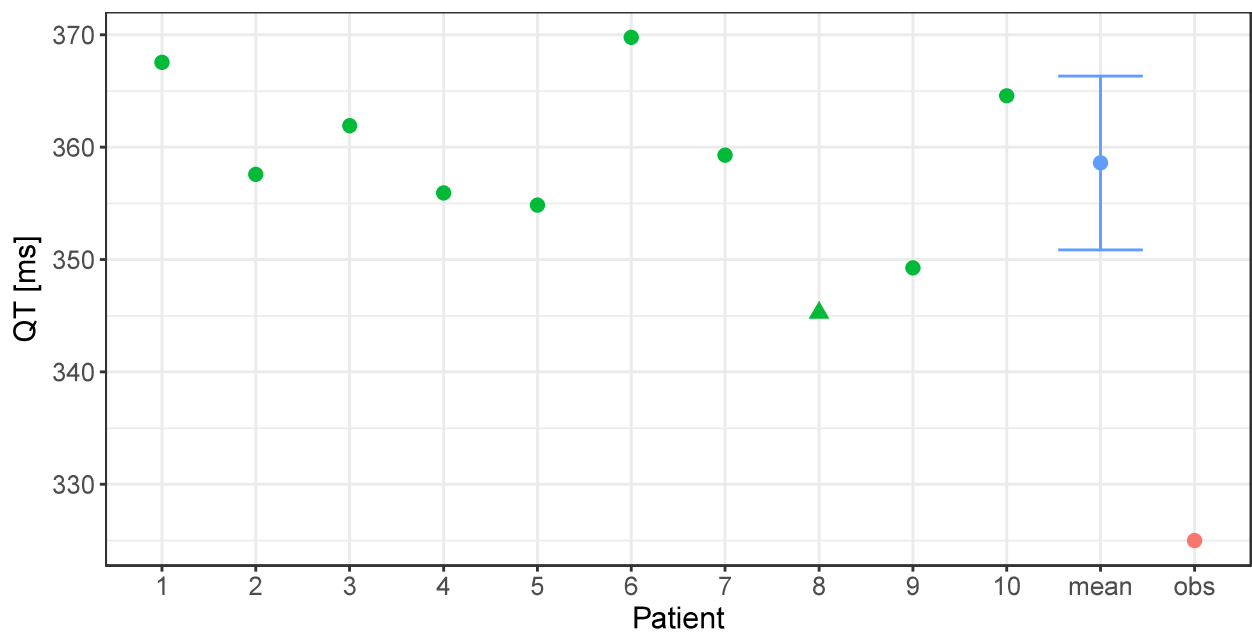
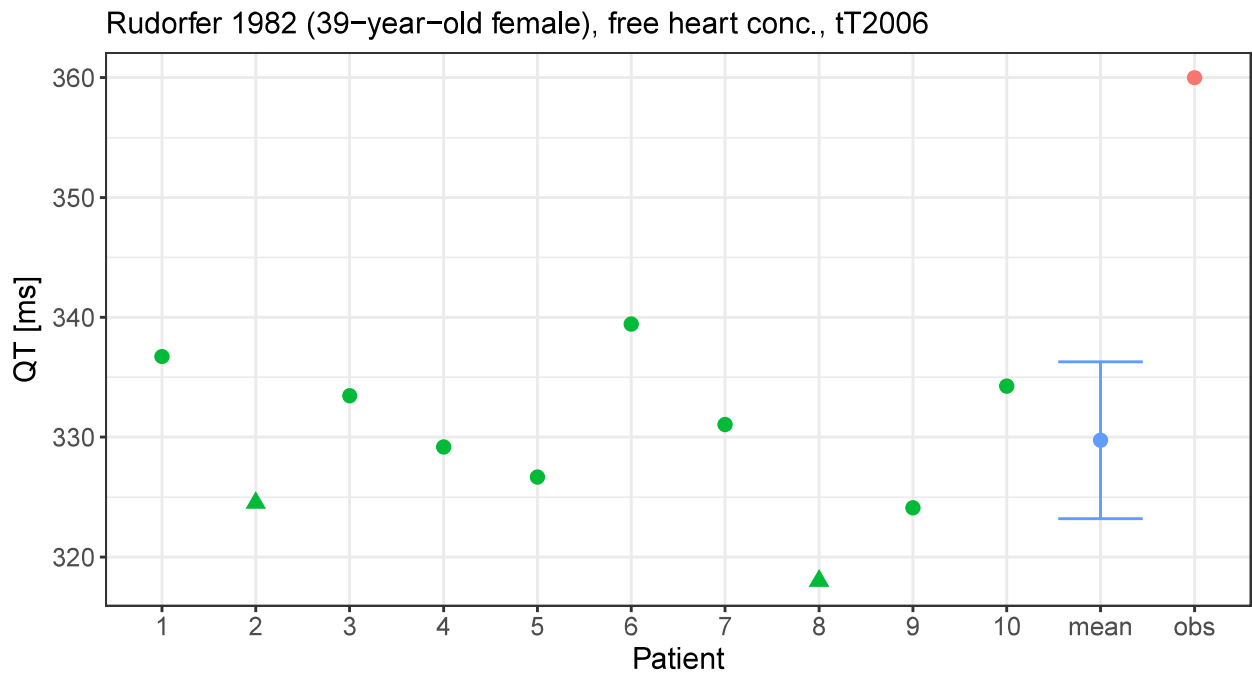
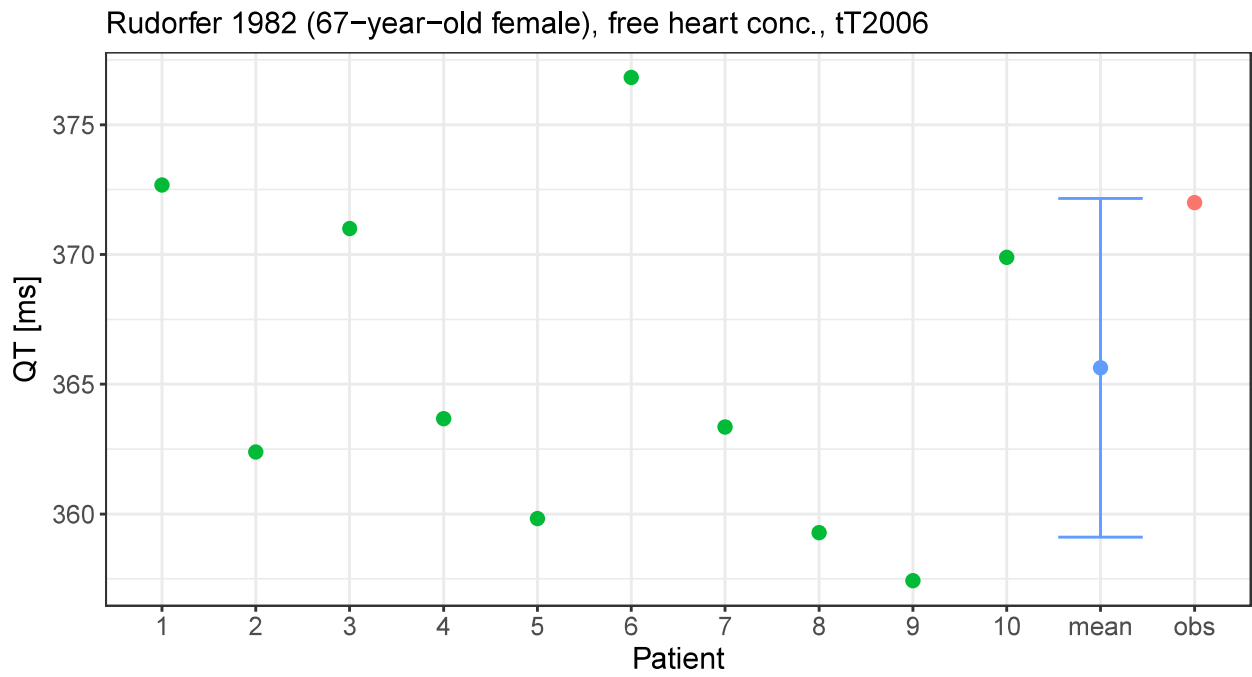


Figure 3 - Continued

G



H



I

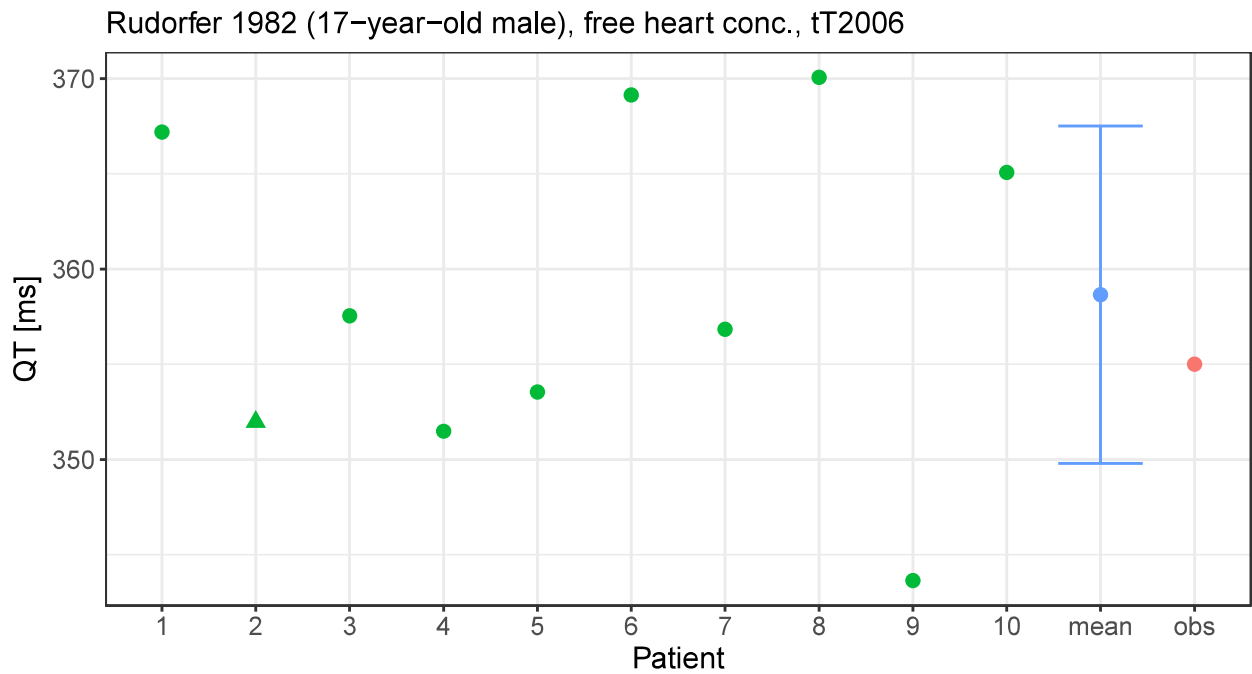


Figure 3 - Continued

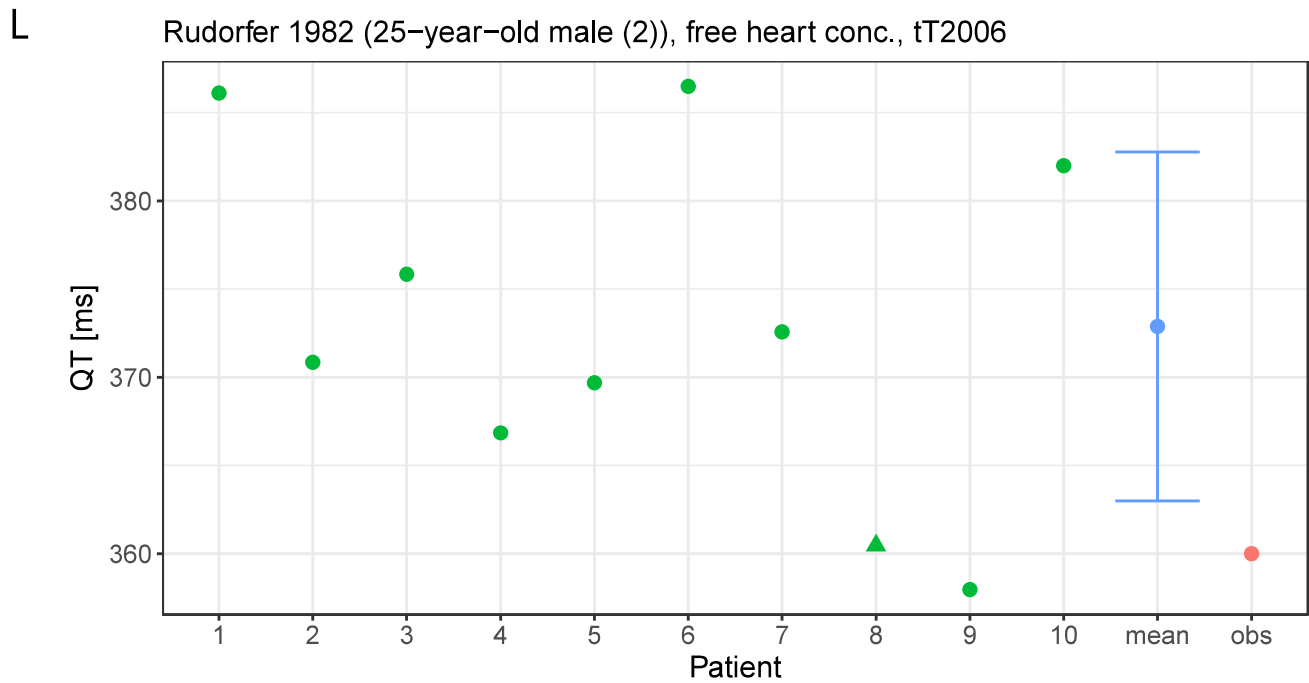
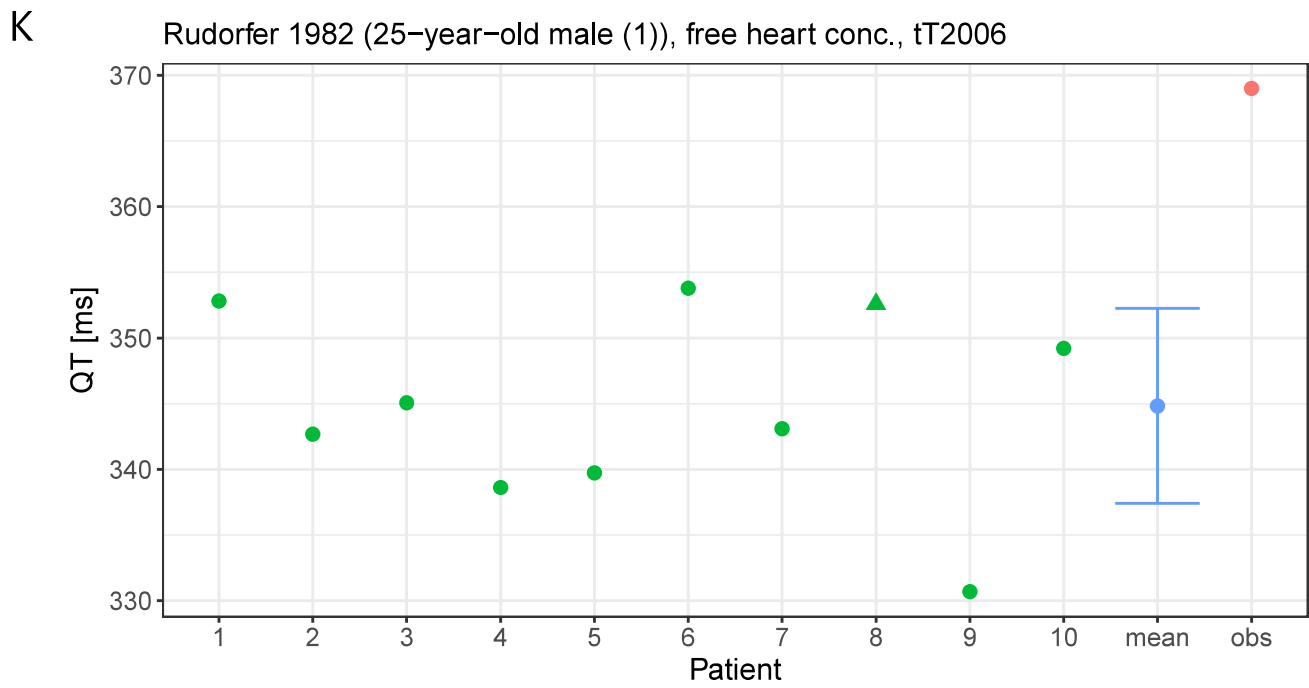
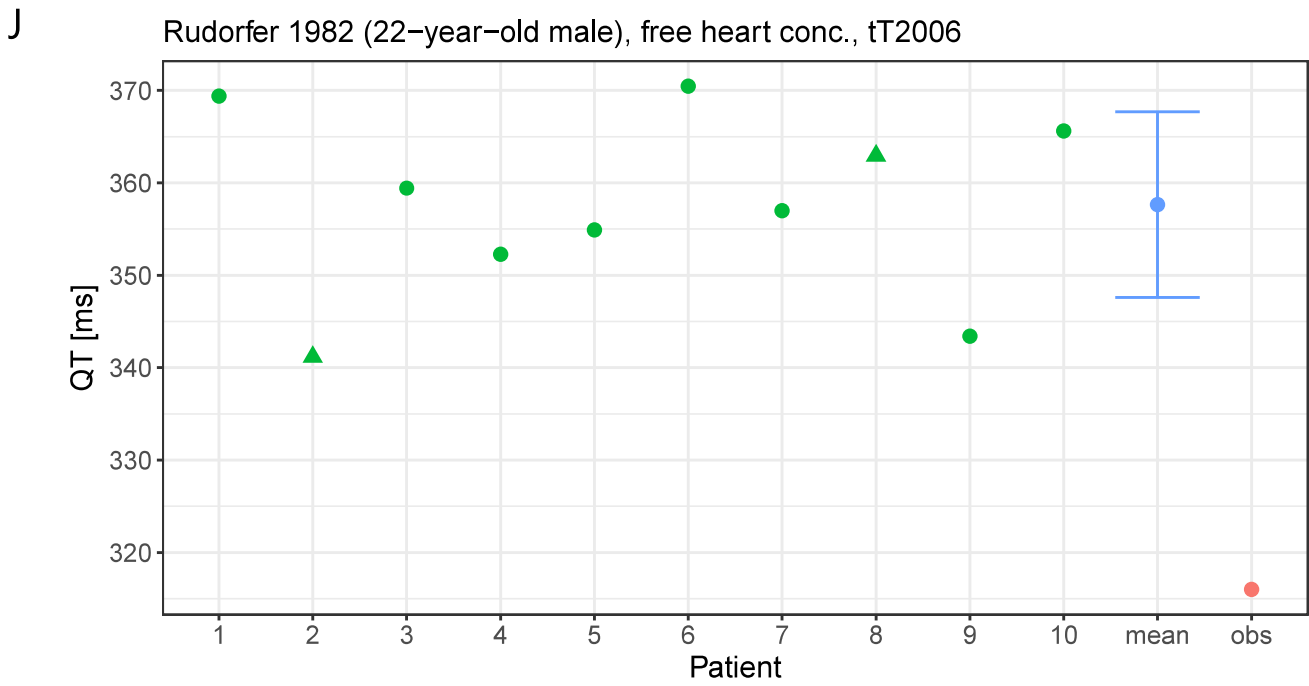
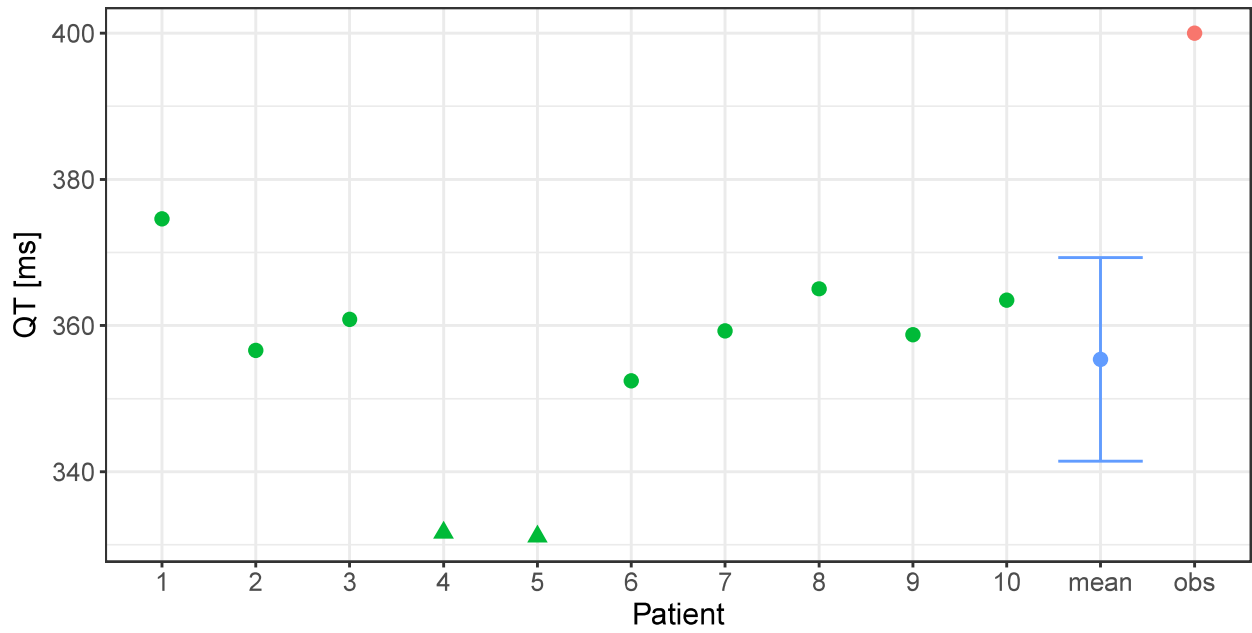


Figure 3 - Continued

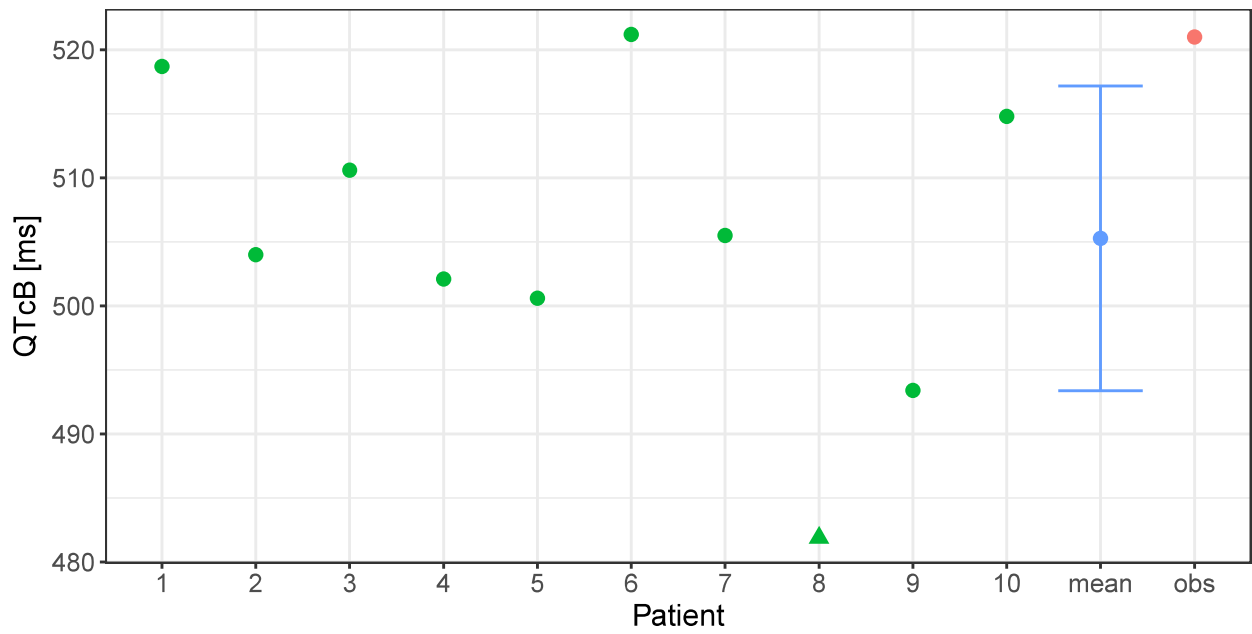
M

Erdem 2010 (24-year-old male), free heart conc., tT2006



N

Kiyan 2006 (33-year-old female), free heart conc., tT2006



O

Paksu 2014 (34-year-old female), free heart conc., tT2006

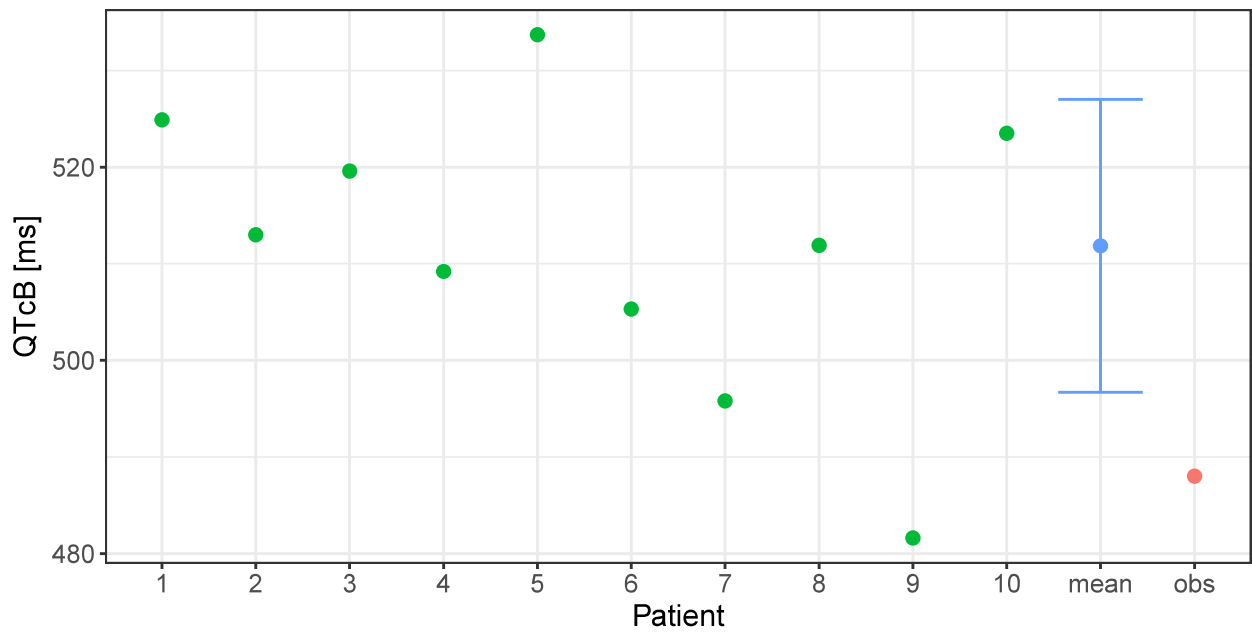
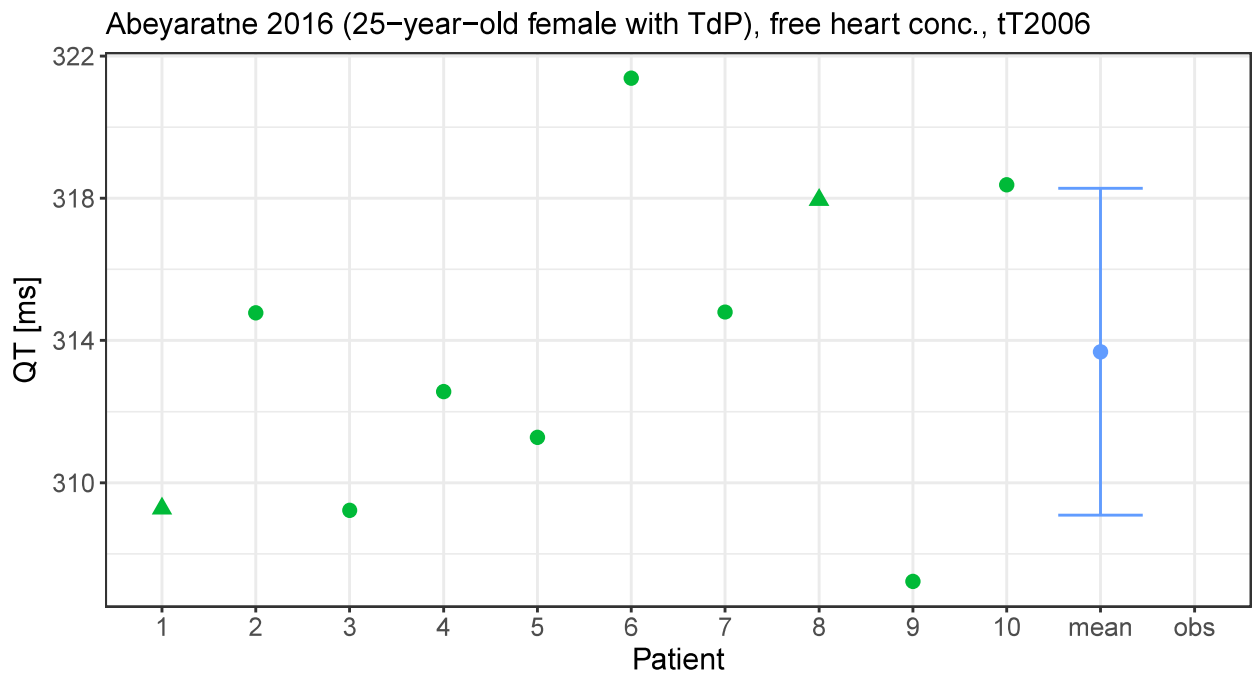


Figure 3 - Continued

P



Q



R

