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An *in silico* physiologically-based pharmacokinetic (PBPK) study of the impact of the drug release rate on oral absorption, gut wall metabolism and relative bioavailability

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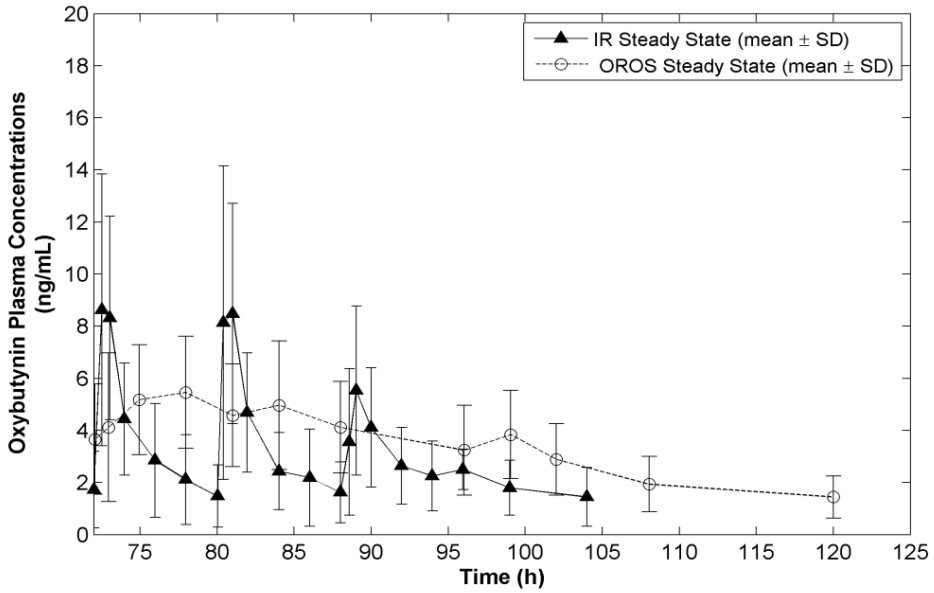
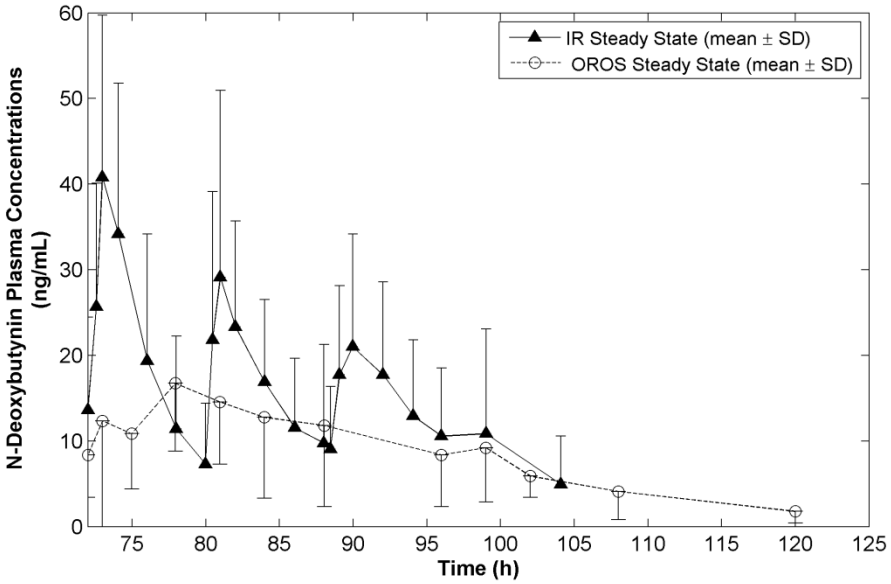
Controlled release (CR) formulations

- Intended to control the absorption rate
- Advantages compared to conventional dosage forms (IR):
  - ✓ Reduction in peak to trough fluctuations
  - ✓ Prolonged exposure (drugs with short half life)
  - ✓ Targeted drug delivery
- When developing a CR formulation the goal is to achieve similar exposure as the marketed formulation

Motivating example: Oxybutynin IR vs. CR



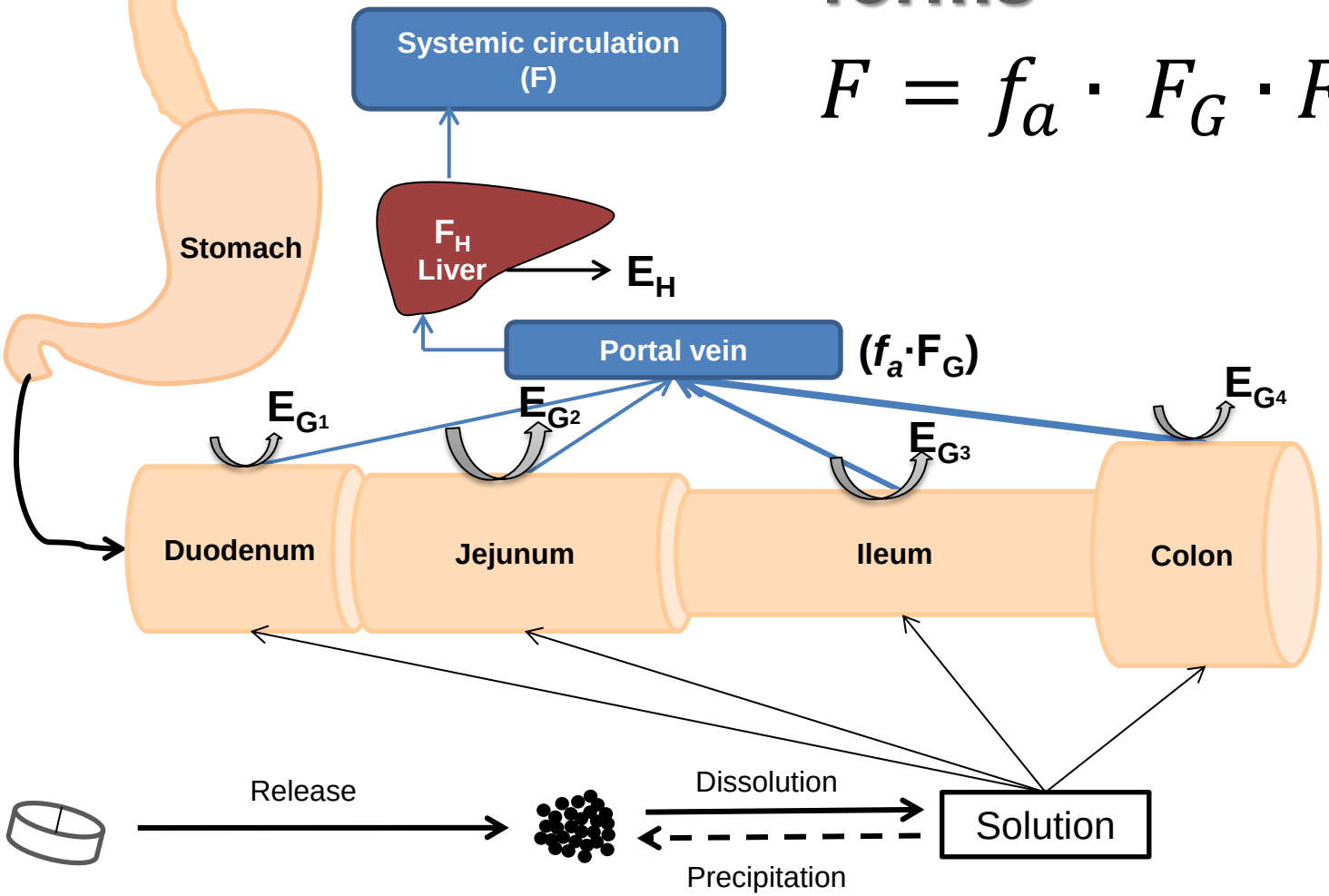


- Bioavailability of CR formulation ~50% higher than IR[1]
- Exposure of the main metabolite decreased by ~30%[1]
  - ✓ Improved safety profile (antimuscarinic side effects), but similar efficacy as the IR formulations[2,3]

[1]Gupta and Sathyan, 1999; [2]Gupta et al. 1999; [3]Sathyan et al. 2001

Oral absorption of solid dosage forms

$$F = f_a \cdot F_G \cdot F_H$$

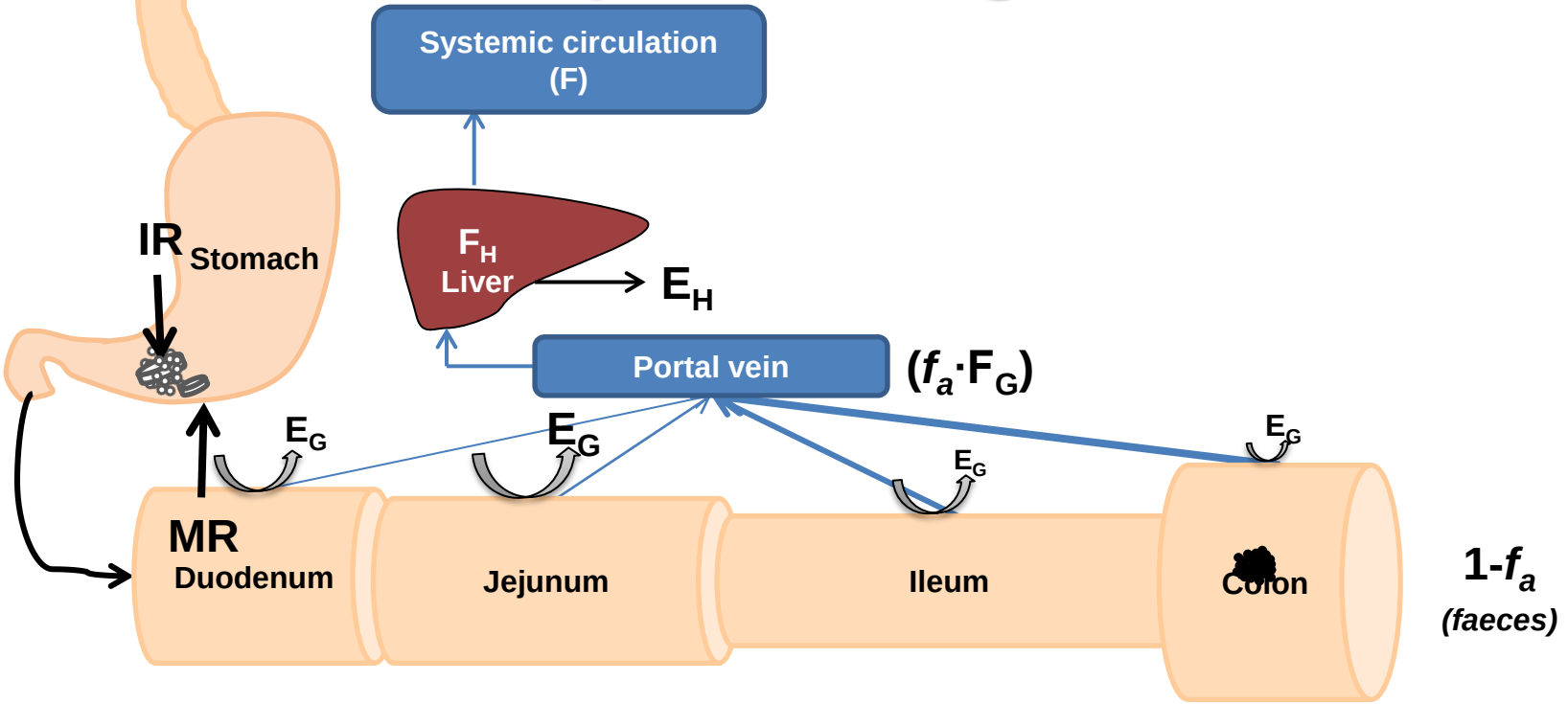


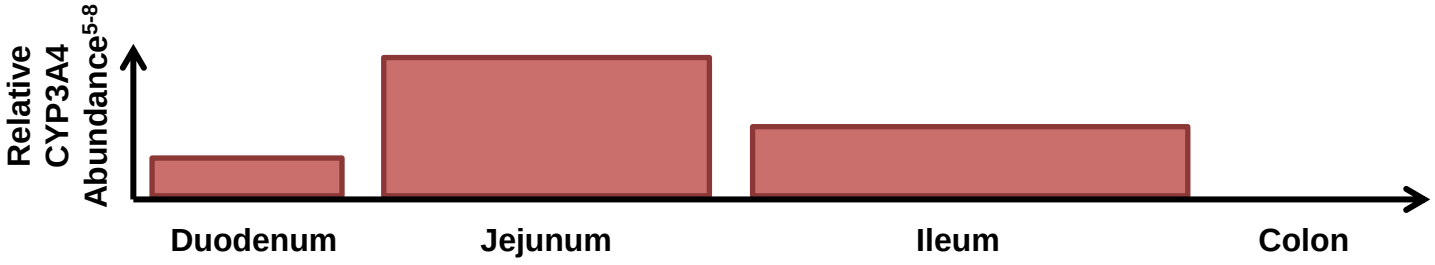
$F_H = 1\text{-}E_H$

$F_G = 1\text{-}\Sigma E_{Gi}$

$1\text{-}f_a$ ***(faeces)***

Possible interplay between absorption and gut wall metabolism





[4]Kolars et al, 1994; [5]Paine et al., 1997; [6]Zhang et al, 1999; [7]von Richter et al, 2004; [8]Bruyére, et al, 2010

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Project aims

- To investigate the impact of the interplay between drug release, physicochemical and biochemical properties on oral drug absorption and CYP3A4-mediated gut wall metabolism using a PBPK modelling and simulation (M&S) approach.

- To identify the drug and formulation specific factors associated with the higher relative bioavailability observed for some CR formulations of CYP3A substrates

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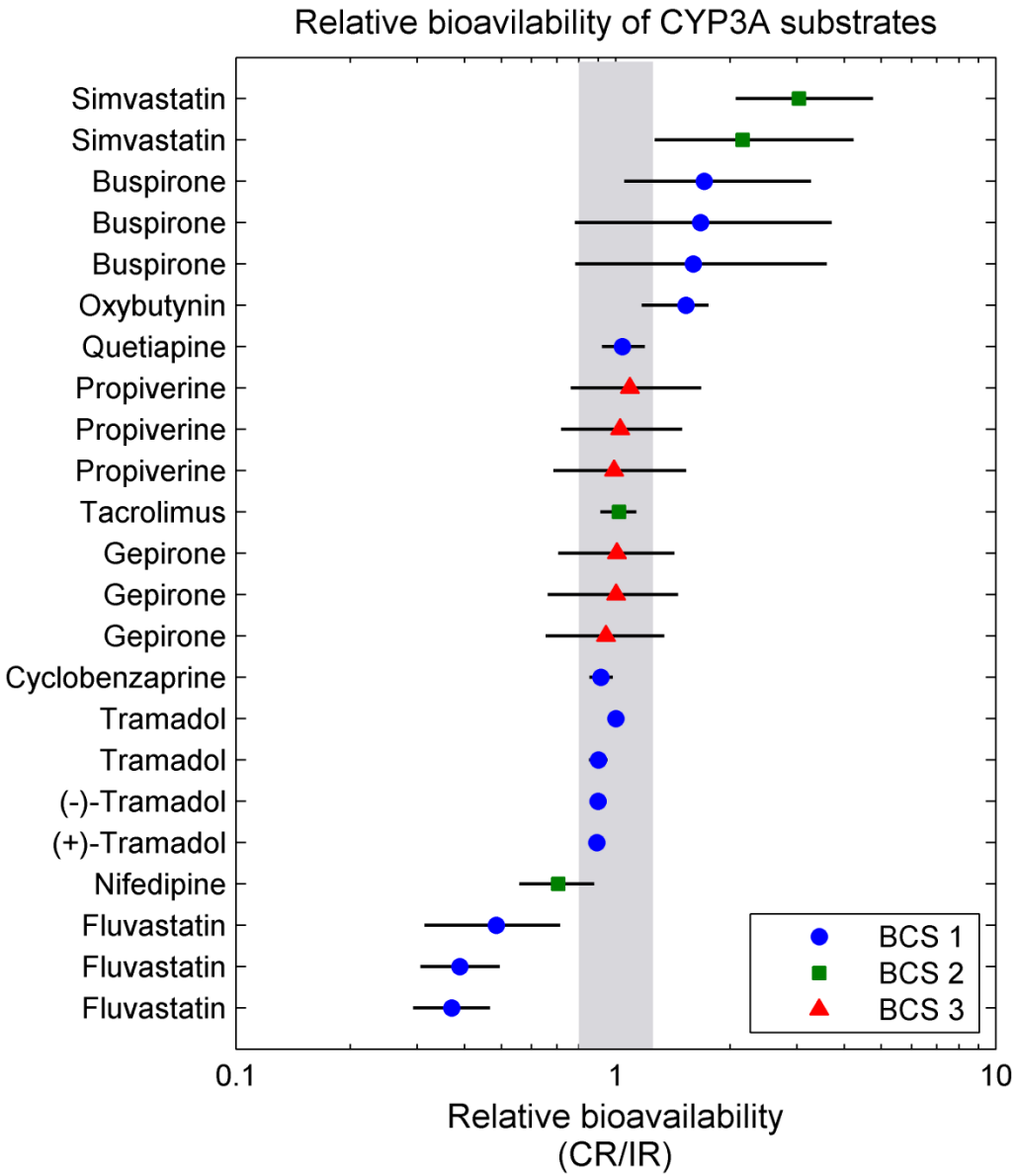
Is this common for other CYP3A substrates?



- ✓ IR and CR in the same sets of healthy adults volunteers
- ✓ Fasted

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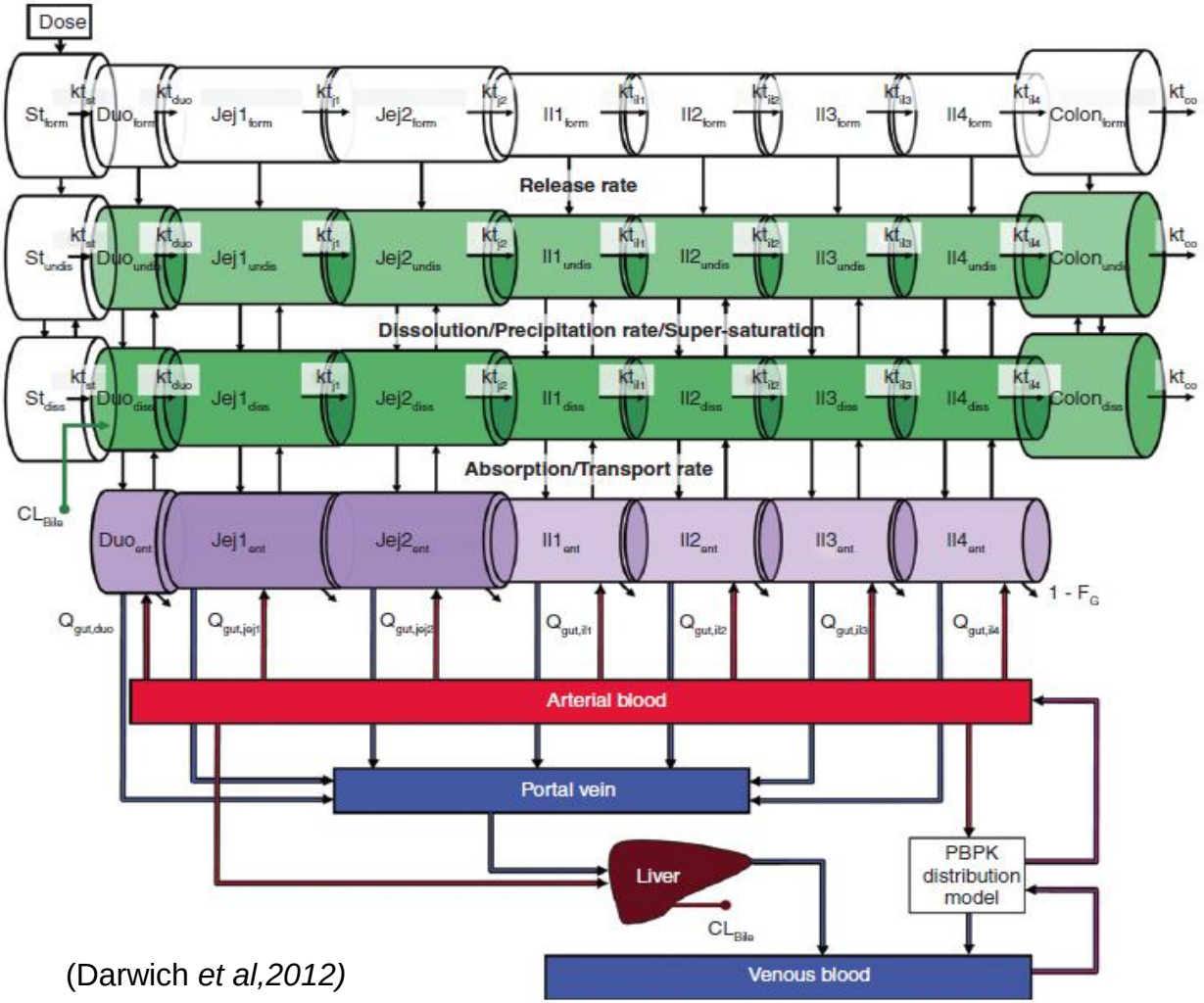
A PBPK M&S factorial study

The Simcyp's Advanced Dissolution, Absorption and Metabolism (ADAM) model



(Darwich *et al,2012)*

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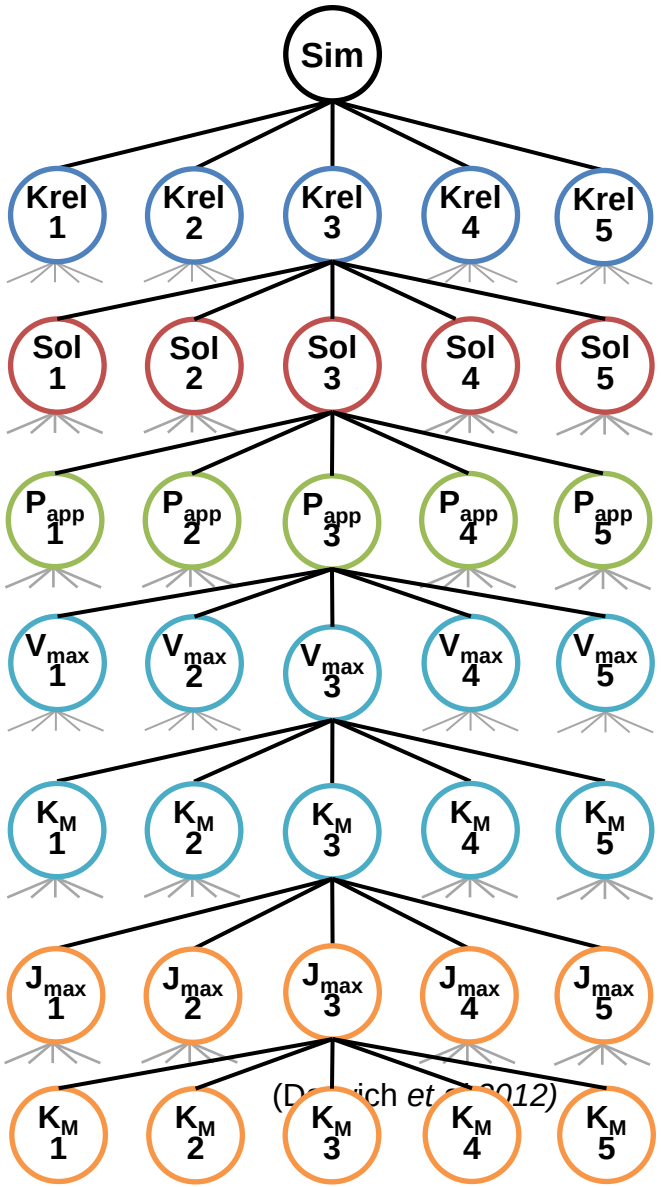
A PBPK M&S factorial study



(D... ich *et al* 2012)

Value (Percentile)	1 (1st)	2 (25th)	3 (50th)	4 (75th)	5 (99th)
k_{rel} (h^{-1})	4.6	2.3	0.38	0.19	0.096
Solubility (mg/mL)[9]	0.001	0.1	1	10	100
$P_{app\ (Caco-2)}$ (10^{-6} cm/s) [10,11]	0.01	0.5	5	10	80
$V_{max\ CYP3A4}$ (pmol/min/mg)[12]	1	100	500	2,500	10,000
$K_{M\ CYP3A4}$ (μM)[12]	1	10	50	100	10,000
$J_{max\ P\text{-}gp\ (Efflux)}$ (pmol/min)[13]	1	30	300	500	1,500
$K_{M\ P\text{-}gp}$ (μM)[13]	1	50	150	300	2,000

([9]Benet et al, 2011; [10]Lennernas 2007; [11]Sun et al 2002; [12]Bu, 2006; [13]Troutman and Thakker, 2003)

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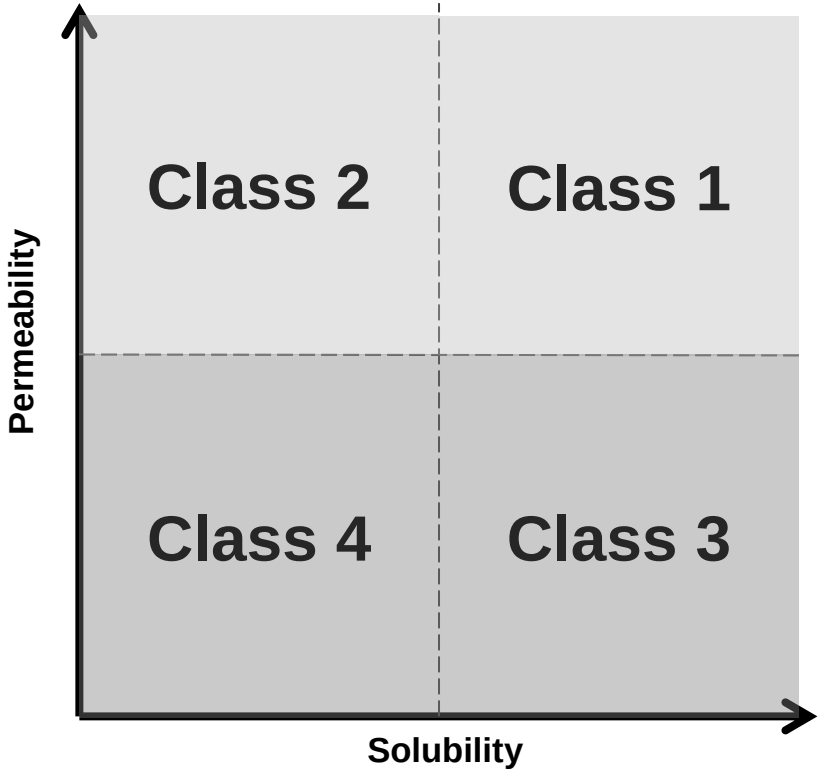
How to analyse such large dataset?

Number of simulations = $Levels^{Factors} = 5^7$

Biopharmaceutics classification system (BCS)



(Amidon et al, 1995)

$$Dn = \frac{Dose/250\ ml}{Solubility} \qquad f_a = 1 - e^{-\frac{2P_{eff}}{R}T_{SI}}$$

Scenarios of interest (one-at-at-time)

$Dn < 1$ $f_a \geq 0.9$

1. *Release and CYP3A4*
2. *Release, CYP3A4 and P-gp*

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Impact on absorption, first pass metabolism and systemic exposure

SIMULATION OUTCOME

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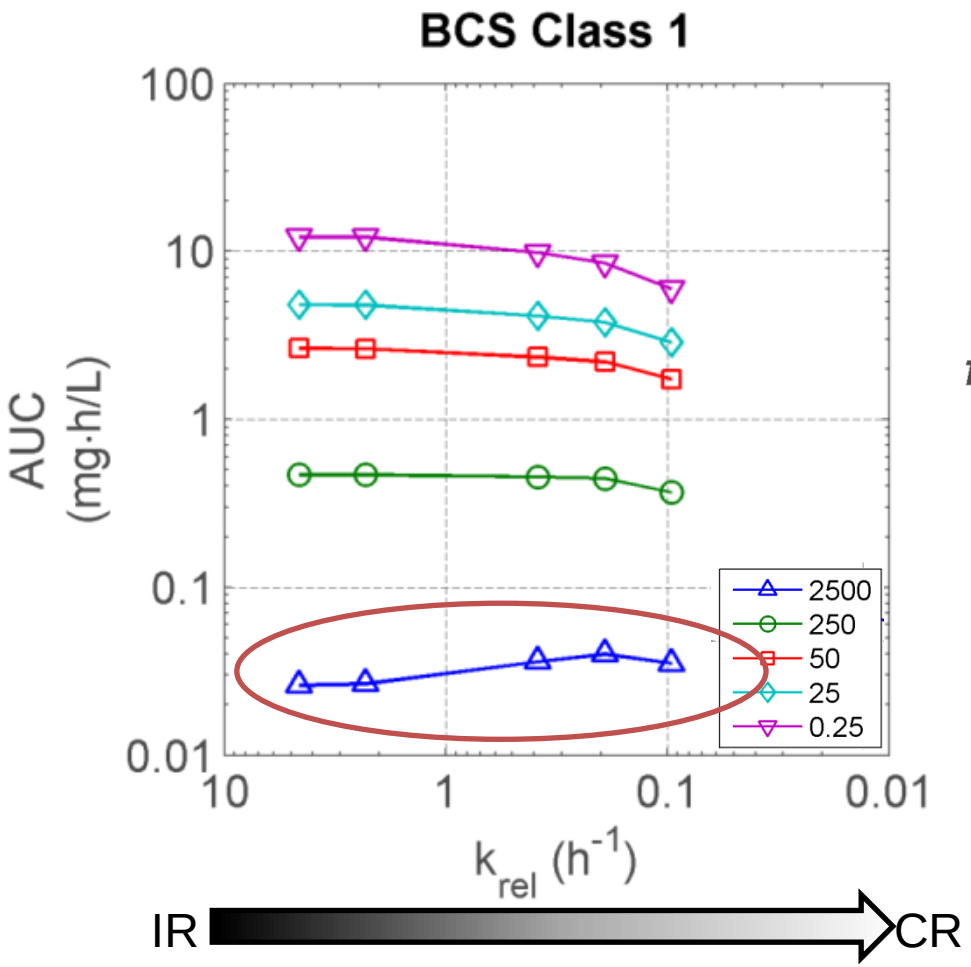
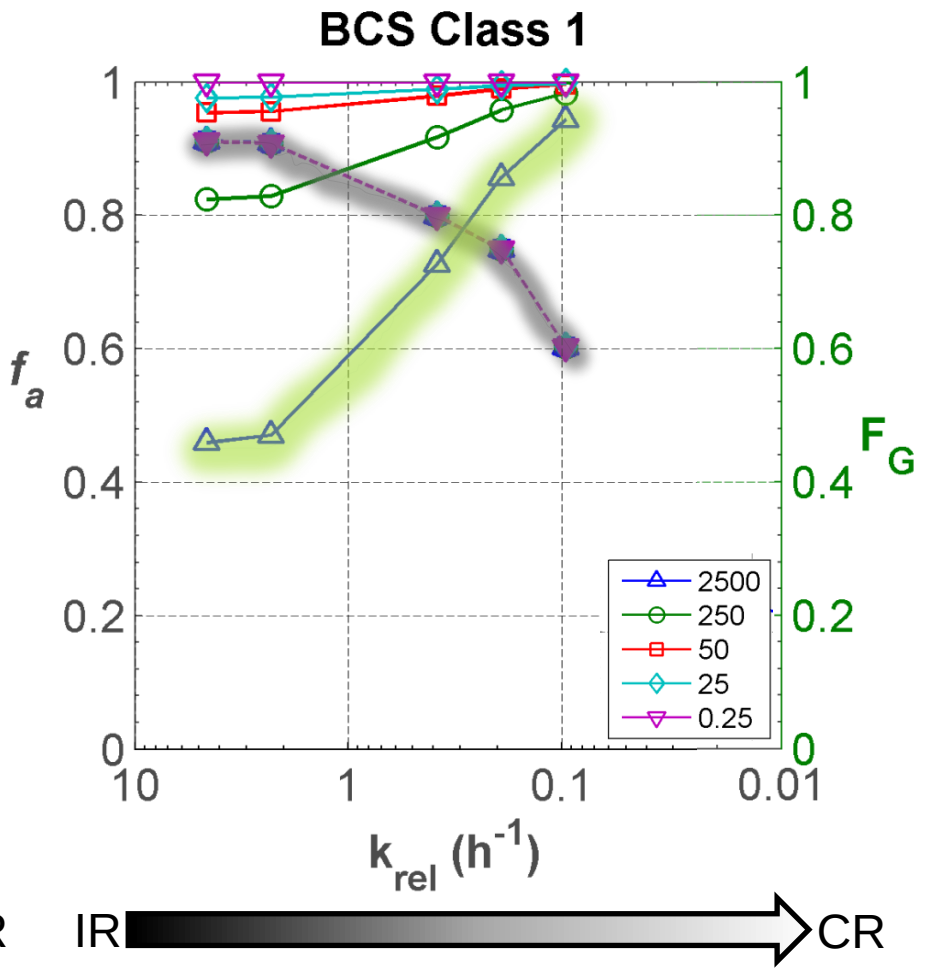
1. Release & CL_{CYP3A4}





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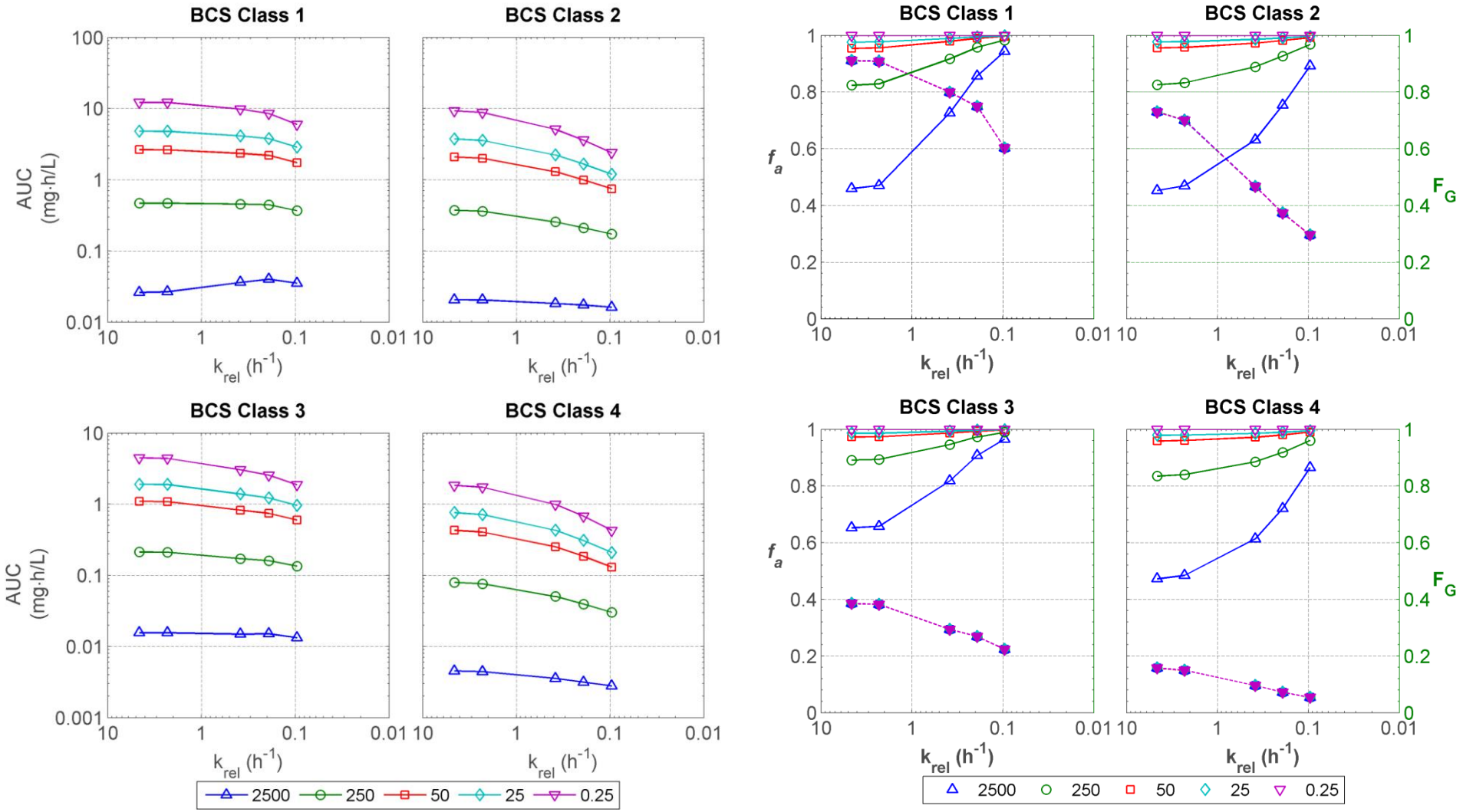

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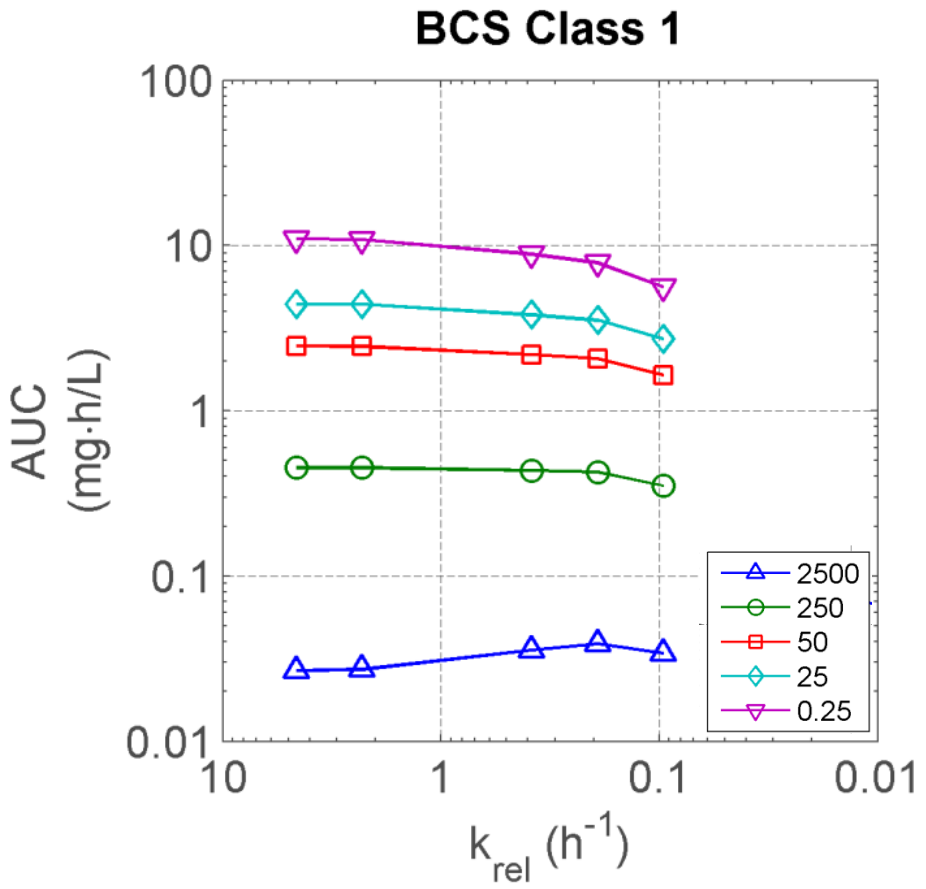
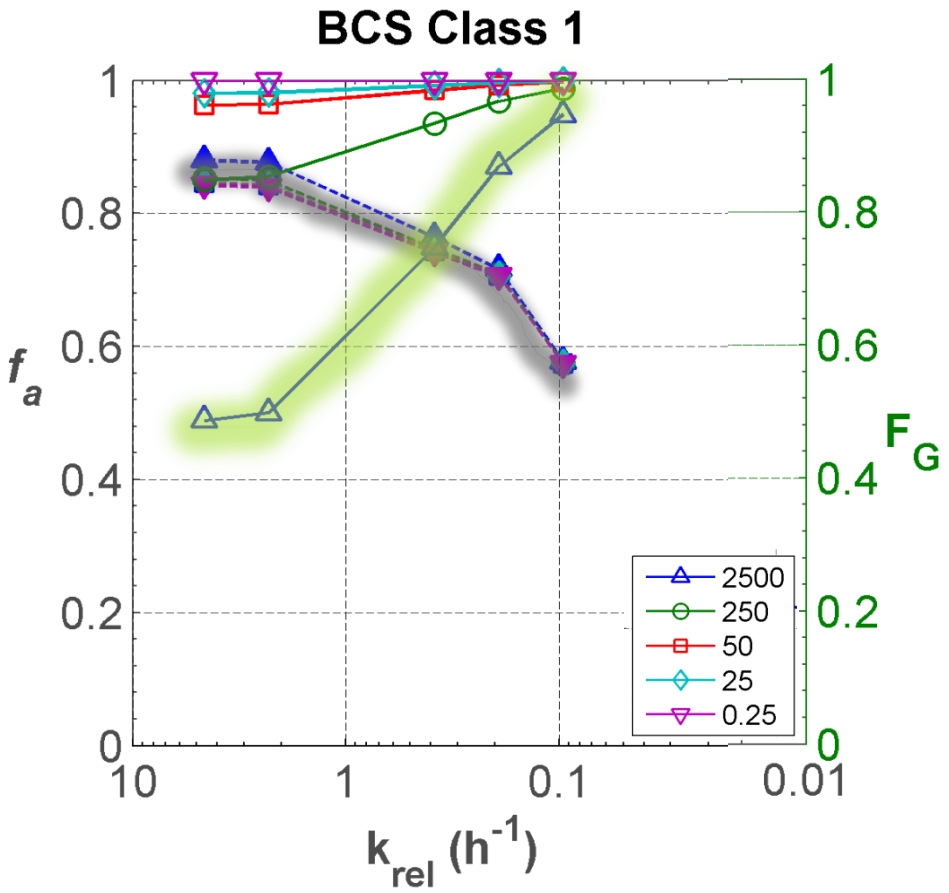
2. Release, CL_{CYP3A4} and $CL_{P\text{-}gp}$(fixed)





IR → CR

IR → CR

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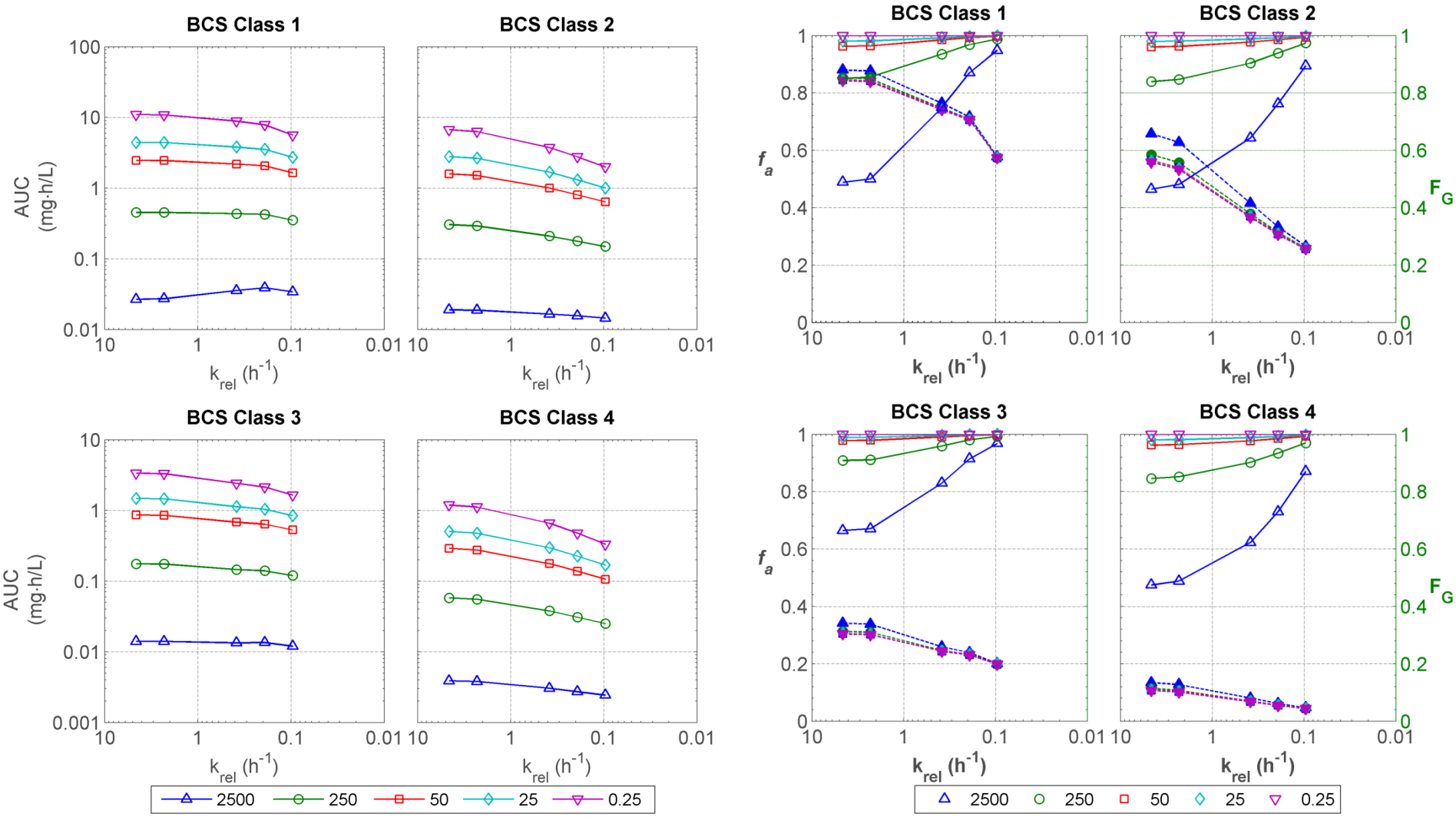

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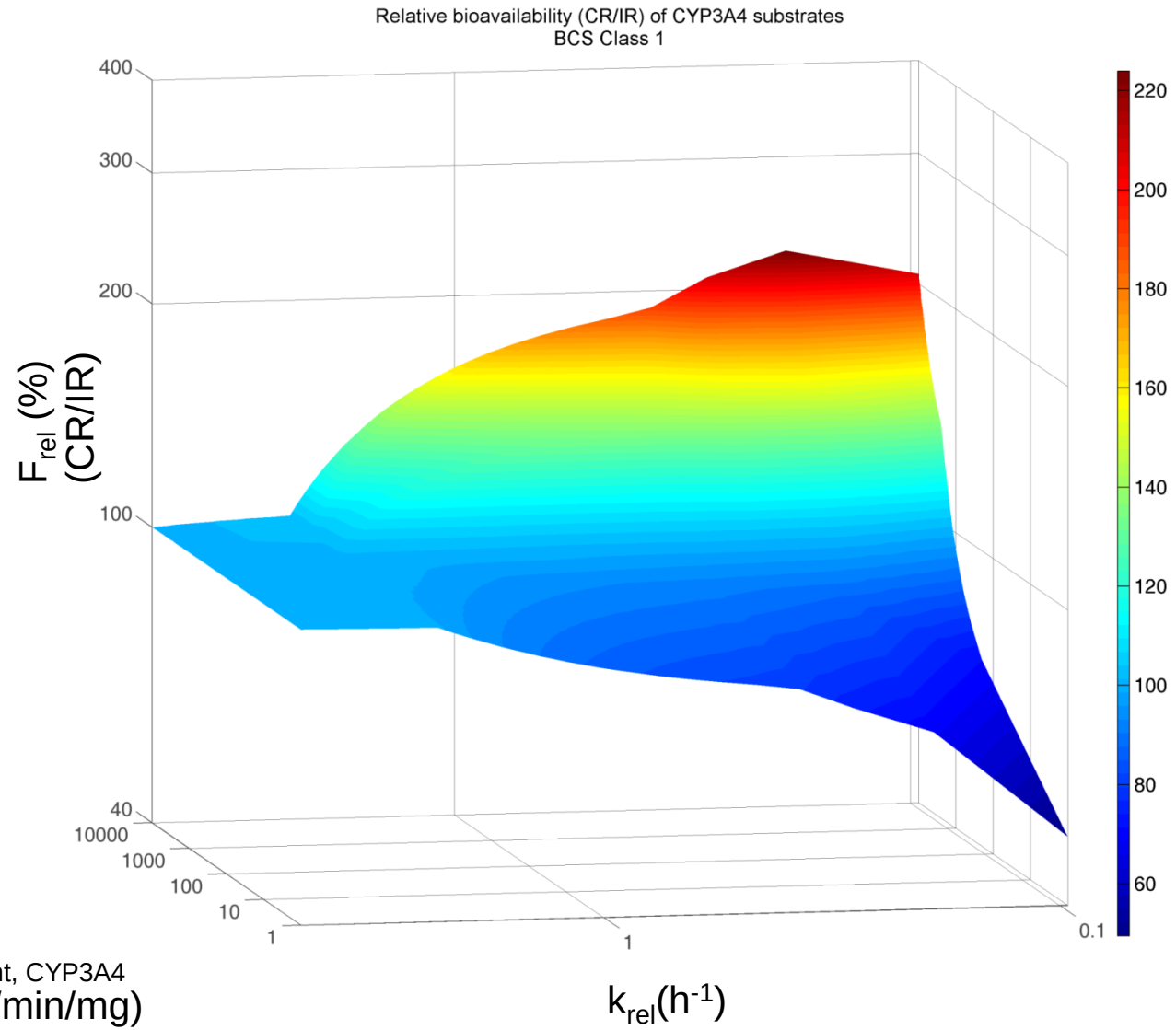
Higher relative bioavailability: Parameter space



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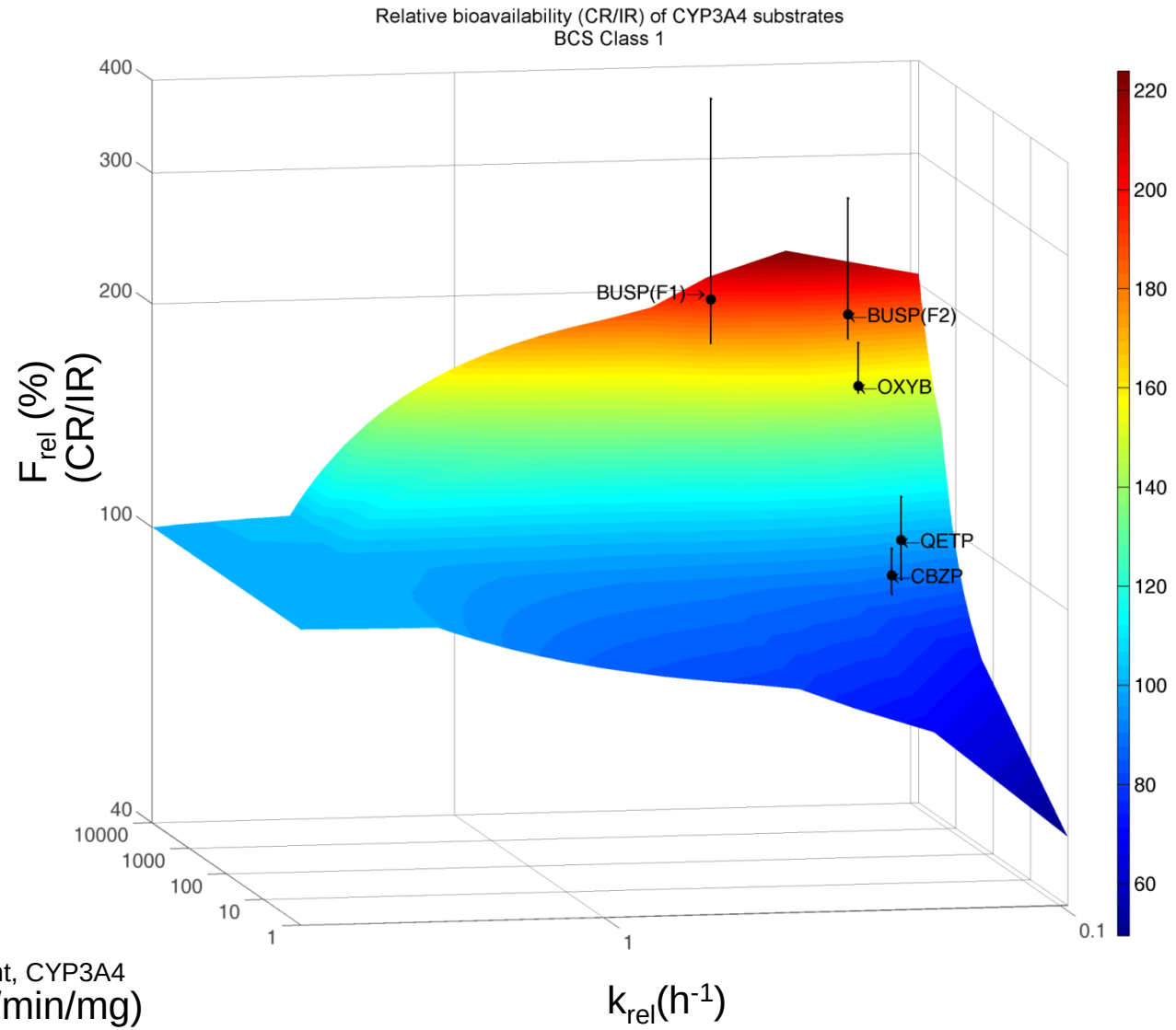
Simulations vs. observed data



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Conclusions

- The use of an absorption PBPK model allowed the simultaneous consideration of both formulation and drug-specific properties and their impact on oral bioavailability

- In almost all the cases, a reduced absorption, *i.e.* reduced f_a, was observed when employing a CR formulation. However, in some cases this was compensated by a reduction on intestinal metabolism (higher F_G), thus leading to a net increase in systemic exposure.

- CR formulations of highly permeable and highly CYP3A4 –cleared compounds are more likely to display higher relative bioavailability than the IR formulations. This can be used as an advantage when developing and CR formulation

Acknowledgments

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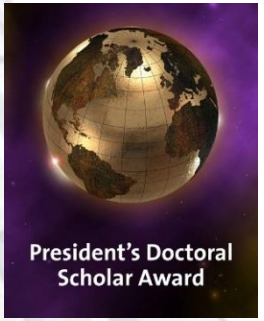
- The University of Manchester



Thank you all for listening!