Introduction
Active efflux by P-glycoprotein (P-gp) has been suggested to increase drug exposure to Cytochrome P450 3A (CYP3A) metabolising enzymes in the gastrointestinal tract, through cycling drug in and out of the enterocyte via absorption and active efflux, leading to a reduced fraction of drug escaping gut wall metabolism (F_G) (Benet & Cummins, 2001). However, when examining the transporter metabolism interplay using the Segmental Segregated Flow Model (SSFM) no evidence was found to support the above under linear kinetics (Pang 2003), attributing any interplay to the nonlinear aspects of gut wall metabolism.

The ADAM model, within the Simcyp® Simulator, is a comprehensive physiologically-based pharmacokinetic model, based on the Compartmental Absorption and Transit (ACAT) Model (Yu & Amidon, 1999) incorporating further features as compared to the SSFM (Pang 2003), as described in detail by James et al. (2009).

Objectives
To examine the impact of systemic variation in parameters relating to gut metabolism and transporter efflux interplay through studying the endpoints F_G (fraction absorbed into the enterocyte) and F_G, utilising the ADAM model.

Method
Simulations were carried out using the ADAM model (see Figure 1) within the Simcyp Simulator (r 9.1). The star map shown in Figure 2 indicates the allocation of compounds within the Simcyp library to the four subdivisions of the Biopharmaceutics Classification System (BCS), relating to their estimated fraction absorbed into the enterocyte (F_G estimated from measured or calculated human effective gut permeability), and dose number (Do), a measure of solubility (Amidon et al., 1995).

Results
CL_{CYP3A4} and K_{Pgp} showed no effect on F_G under the studied conditions. However, a significant effect on F_G was observed throughout the range (CL_{CYP3A4}=0.01 to 2000 µL/min/mg) (Figure 4).

For a majority of Simcyp library compounds the effect of P-gp efflux on metabolism was negligible. The effect was limited to compounds such as saquinavir (Class III) and simvastatin (Class IV) (Figure 7).

Discussion and Conclusions
Results suggest that P-gp efflux decreases enterocytic drug concentration for drugs given at a reasonably high dose, which possess adequate passive apparent permeability, by desaturating CYP3A4 in the gut resulting in a lower F_G.

However, the P-gp / CYP3A4 interplay was observed in a very limited area of parameter space, matching very few therapeutic drugs expressing (Figure 7):

- High degree of CYP3A1 metabolism
- High affinity to P-gp efflux transporter
- Low permeability

The systematic approach enabled us to recognise the combination of parameter values where the potential interplay between metabolising enzymes and efflux transporters is expected to be highest, using a realistic range of parameter values taken from an intensive literature search.

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References