A Population-based PBPK Model for the Prediction of Time-varying Bile Salt Disposition within GI Luminal Fluids – Toward a Mechanistic Model

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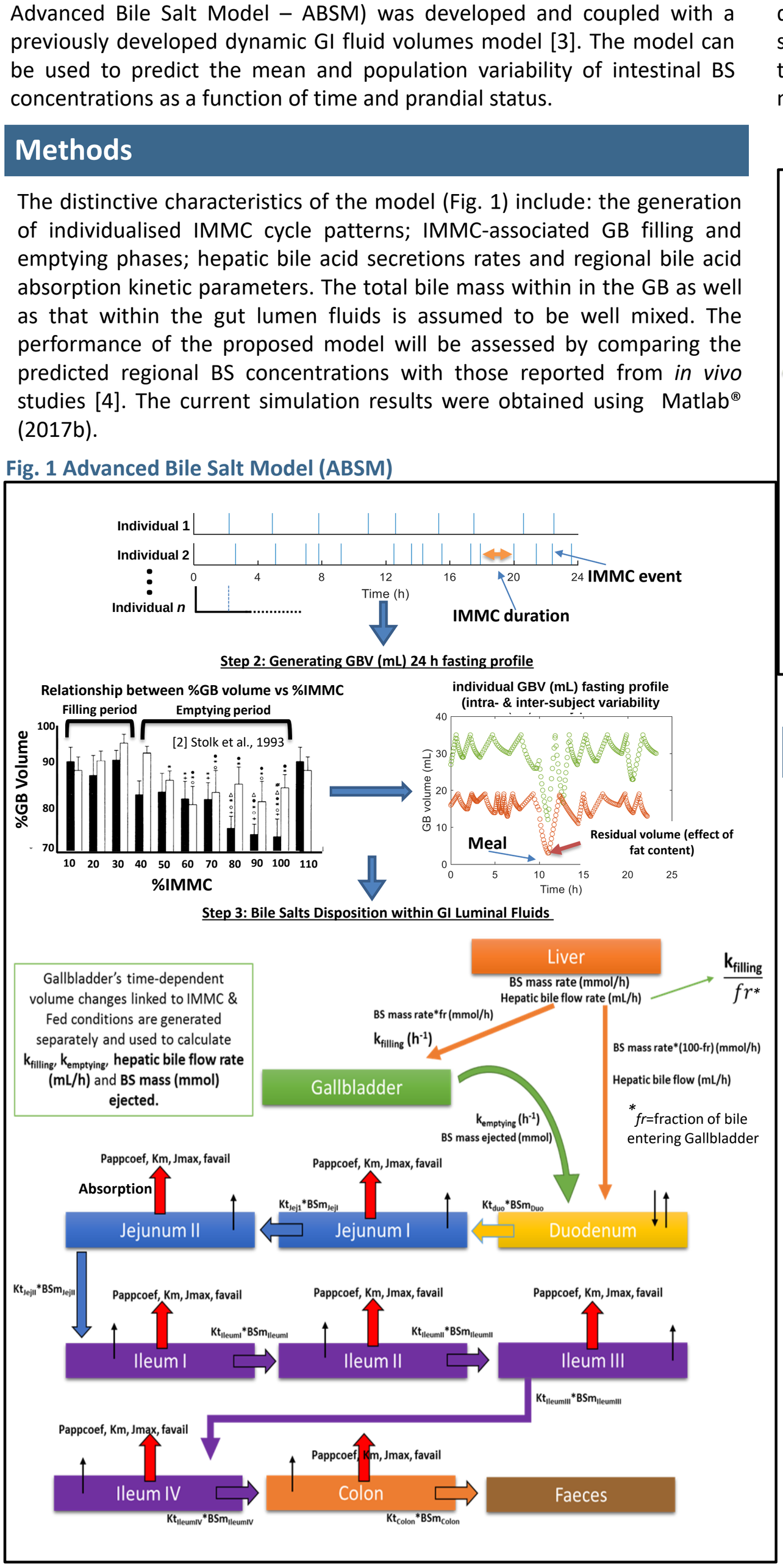
Background

Bile salts (BS) play a crucial role in the solubilisation and absorption of lipophilic and poorly soluble drug compounds. The concentration of BS, however, varies significantly within the GI tract due to factors such as the cyclic motility patterns of the gall bladder (GB) linked to the interdigestive migrating motor complex (IMMC) [1,2], dynamic changes of the GI luminal fluid volumes and most importantly the prandial state. As opposed to the fasted state, strong GB contractions empty a significant amount of BS in response to feeding events. Thus, a novel mechanistic BS model (the Advanced Bile Salt Model – ABSM) was developed and coupled with a previously developed dynamic GI fluid volumes model [3]. The model can be used to predict the mean and population variability of intestinal BS concentrations as a function of time and prandial status.

Methods

The distinctive characteristics of the model (Fig. 1) include: the generation of individualised IMMC cycle patterns; IMMC-associated GB filling and emptying phases; hepatic bile acid secretions rates and regional bile acid absorption kinetic parameters. The total bile mass within in the GB as well as that within the gut lumen fluids is assumed to be well mixed. The performance of the proposed model will be assessed by comparing the predicted regional BS concentrations with those reported from *in vivo* studies [4]. The current simulation results were obtained using Matlab® (2017b).

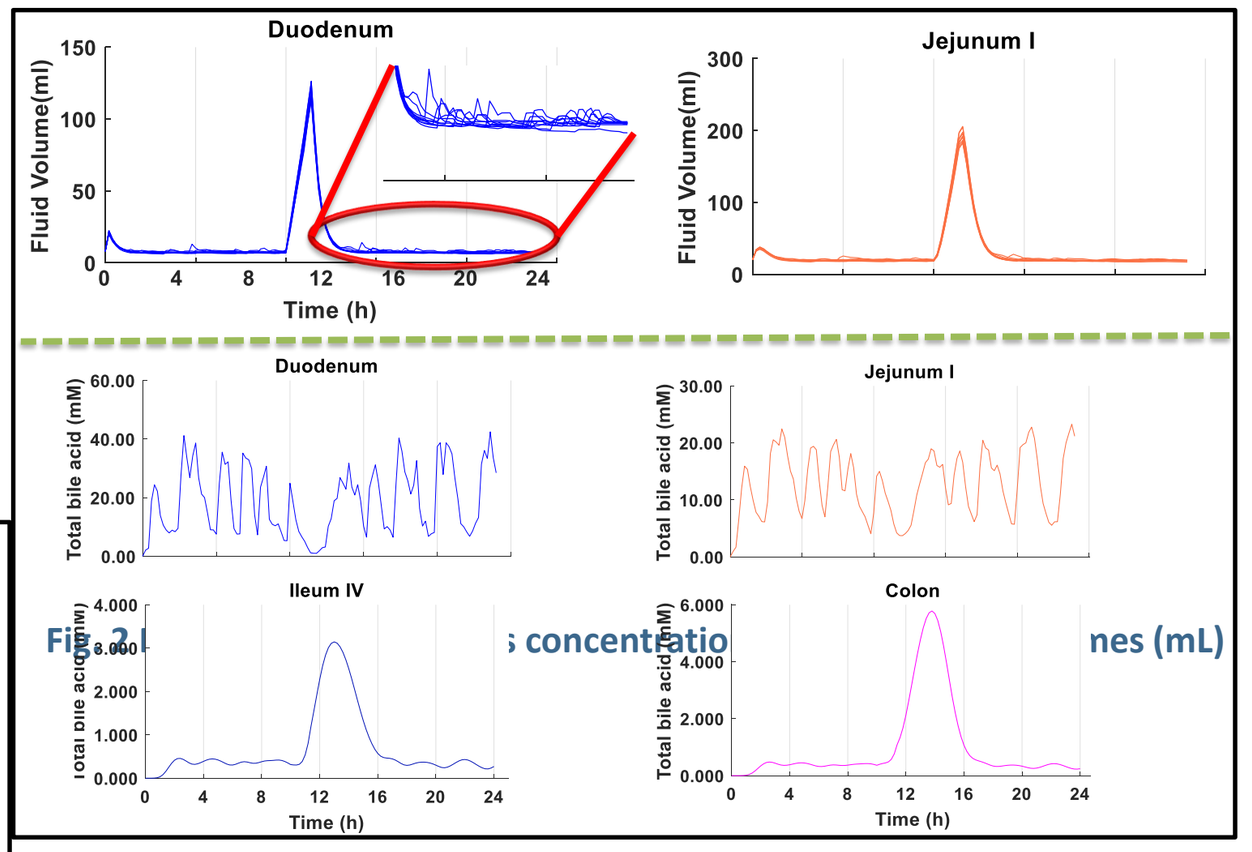
Fig. 1 Advanced Bile Salt Model (ABSM)



Results

Twenty-four hour fasted motility profiles of the GB were generated together with a meal ingested at a random time during this period. The preliminary results of the simulations using 1,000 virtual individuals showed cyclic fluctuations of BS concentration in the duodenum, with ranges of 0.25-37 mM (fasted) and 0.45-48 mM (fed) which is within reported in vivo ranges (fasted: 0.03-36.18 mM; fed: 0.74-86.14 mM, [4]).; Fig 2 shows an example of a single individual profile of BS concentration and luminal fluid volumes. Multiple minor peaks were also observed in the duodenal fluid volumes, following the discontinuous release of biliary secretions. Similar results have been reported from MRI studies, showing time-varying fluctuations of intestinal fluid volumes which at least in part might be attributed to the bile fluid dynamics [5, 6].

Fig. 2 An Example of a Single Individual Profile of BS Concentration



Conclusions

Quantitative estimation of time-varying BS concentration within the GI tract may be critical for the accurate prediction of oral drug absorption. *In vivo* measurements of BS duodenal concentrations have shown multiple BS peaks [1] which can be linked to coordinated GB and GI tract motility. The developed dynamic BS model, coupled with GI fluid volume dynamics, can describe the *in vivo* observations for the GB and also predict reasonably well the duodenal BS concentrations within known physiological ranges [4]. Further work is underway to fully validate the model for the whole intestine. The ABSM is to be integrated into the Simcyp Simulator where the bile flow patterns can also be used as part of a model for enterohepatic re-circulation of drug and/or metabolite(s).

References

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