Cross-Talk between modelling platforms: (B) application of the SBGN standard to a minimal PBPK model.

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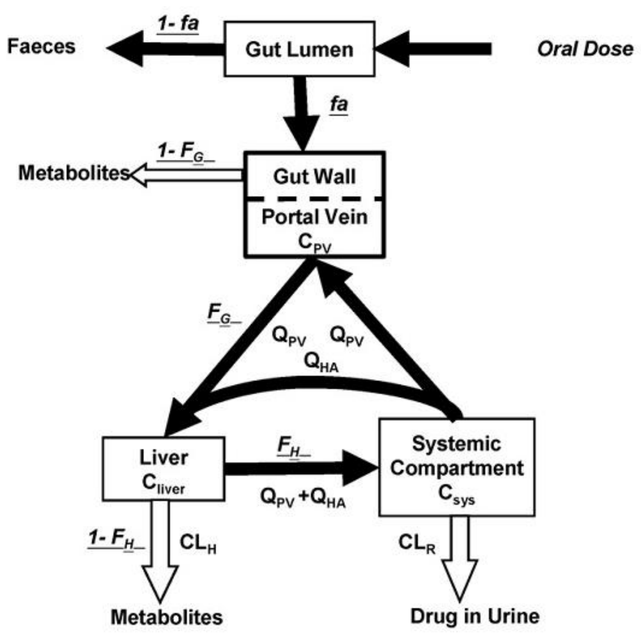
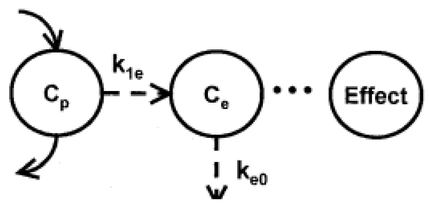
Informal graphical model representation

- Despite their mathematical rigour, the diagrammatic representation of pharmacokinetic[1] (PK) and pharmacodynamic[2] (PD) models has largely been informal.

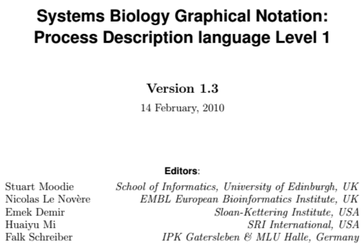




Representations of minimal PBPK and PK/PD models

Use of the SBGN standard

- In a complementary abstract we detail the progress made in applying a set of standards within the Systems Biology community (SB).
- The systems biology graphical notation (SBGN)[3] provides an existing standard that bridges understanding and unambiguously represents a PK and / or PD model semantics.


Systems Biology Graphical Notation:
Process Description language Level 1

Version 1.3
14 February, 2010

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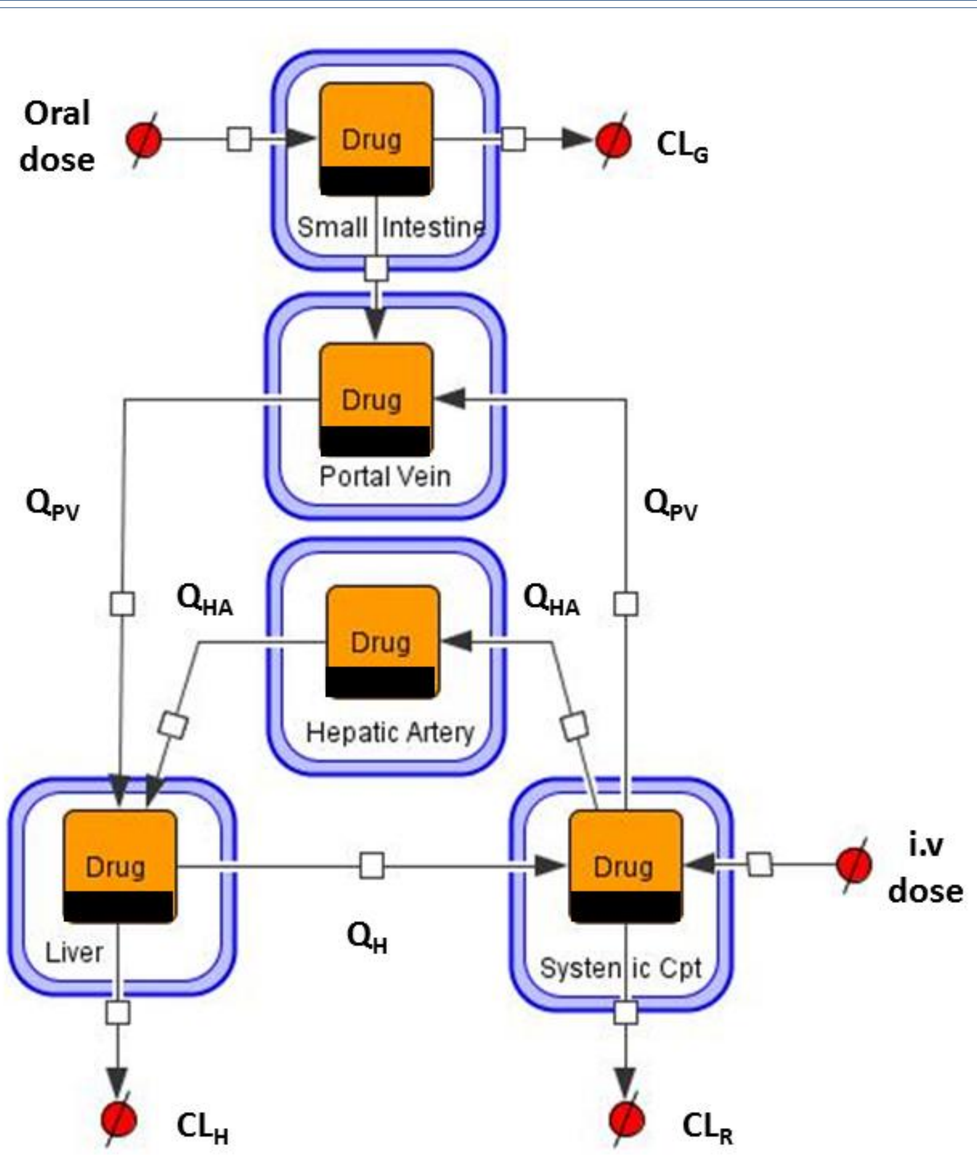
- Our aim was to render a minimal physiologically based pharmacokinetic model (mPBPK) in SBGN compliant notation.

Methods

- A pre-existing model that was rendered within the Simcyp simulator[4,5] was adopted and converted to an SBGN process description language level 1[6] diagram using the Cell Designer (v 4.3) software[7].



SBGN Process-Description language (level 1) [6] diagram describing a minimal PBPK model of substrate (drug) absorption, distribution, metabolism and excretion within different tissues and physiological compartments.
Compartments are represented as thickly-bordered *container nodes*.
Source/Sink *glyphs* (i.e. red circle with a cross through it) represent the administration of a dose or the elimination of drug.
Nodes are presented as either *entity pool nodes* – specifically *macromolecules* (i.e. drug) or as a *process node* (i.e. a square box) and *connecting arc* (i.e. line terminating in an arrow).
Note that the drug nodes also have the *clone marker* attribute (i.e. a dark band across their base), this denotes multiple occurrences of this *entity pool node*.
Italicised entries in this text refer to SBGN compliant nomenclature.
Labelling of dose, flows and clearances is non-compliant

Conclusion

- Adopting the SBGN standard can provide a semantically unambiguous and immediate understanding of a models utility and limitations. The use of software packages that 'write' the underlying SBML[8] mark-up allow for the exchange of these models and the emerging PharmML[9] standard aims to support SBML file import that would allow visualisation.
- Nevertheless, using entities or amounts (e.g. a drug / substrate) within PK models is challenging, as traditionally concentration (itself a derived parameter) is most often used.

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