Cross-Talk between modelling platforms: (A) Graphical Representation of PK/ PD models: Utility of the Systems Biology Graphical Notation

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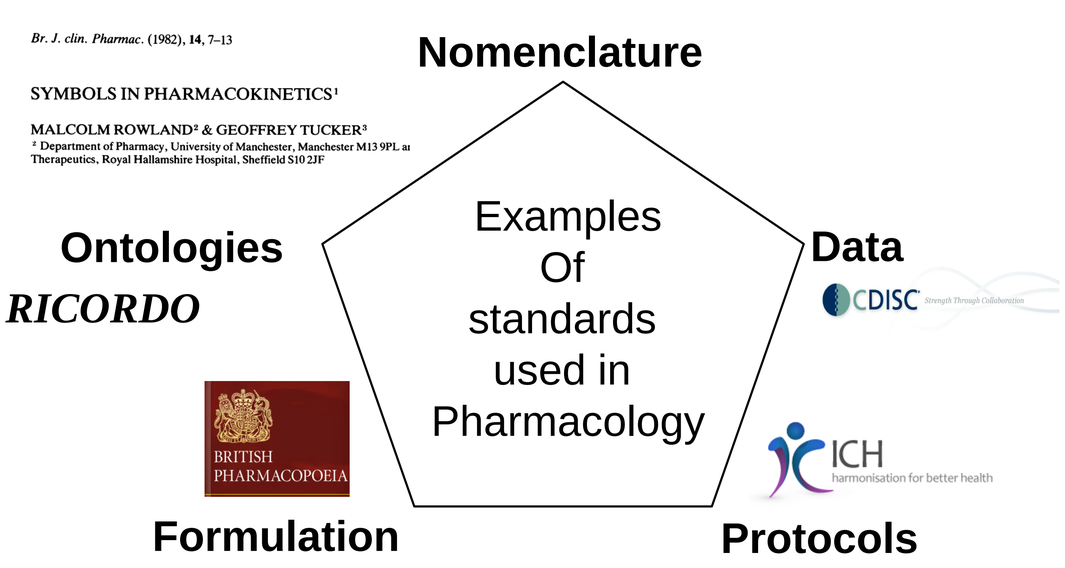
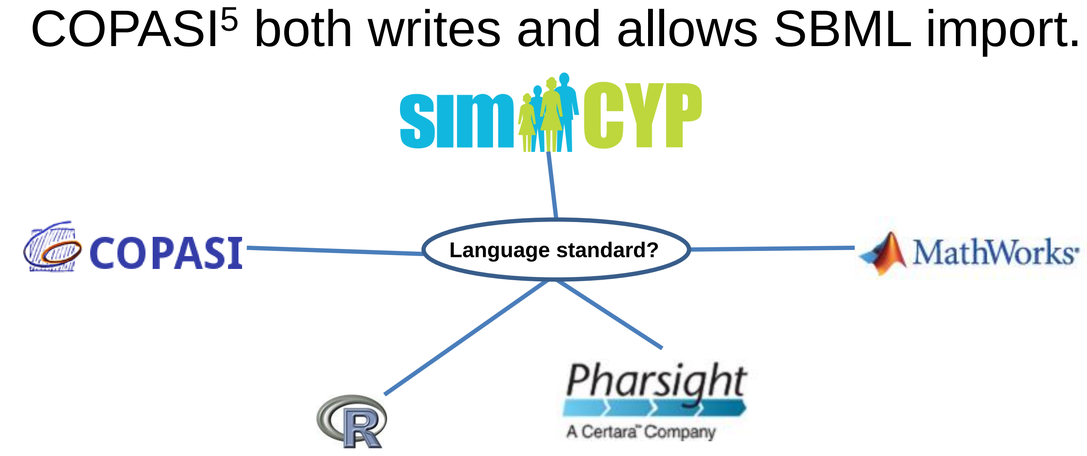
Standardisation in pharmacology

- Standards[1,2,3,13,14,15] adopted in the fields of pharmacology enable comparison of methods, measurements, data and ultimately the information derived from these experiments



Exchange of models

- Currently, the exchange of pharmacokinetic (PK) and pharmacodynamic (PD) *in silico* models between software platforms[4,5] is hampered by not having a universal language standard. However COPASI[5] both writes and allows SBML import.



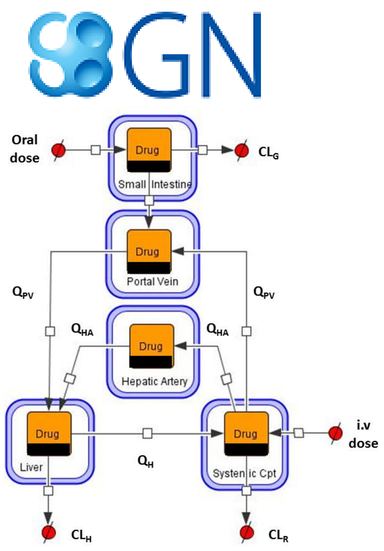
- The largest repository of Systems Biology (SB) models is the Biomodels database[12]

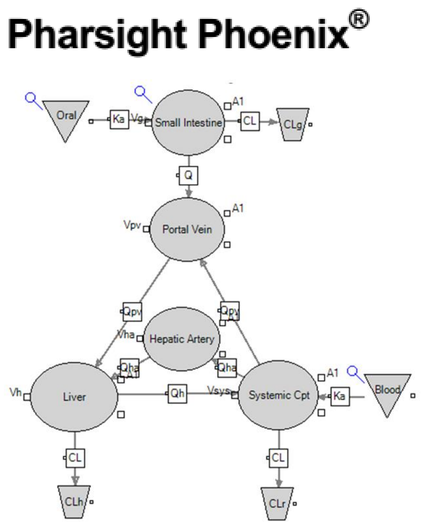
Existing standards

- Much progress has been made within the systems biology (SB) community to enable and develop existing standards[6,7]; notably the SB graphical notation (SBGN)[8].
- Currently, pharmacometrics mark-up language[13] (PharmML; a work package component of DDMoRe) is an emerging standard to describe the encoding of pharmacometric models that aims to enable their seamless exchange between platforms.

Graphical model representation

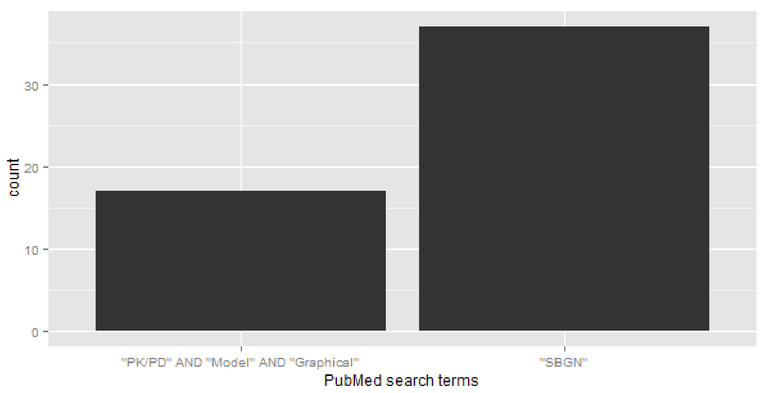
- The utility of graphical model representation (e.g. SBGN, Phoenix Modelling Language) is in making the semantics (e.g. drug 'A' is transported from compartment 1 to 2) transparent to expert and non-expert audiences alike.





Current graphical representation

- PubMed search reveals (24.01.14) there are 37 records that contained either "SBGN" OR "Systems Biology Graphical Notation". Examination of 61 records (("Pharmacokinetic" OR "Pharmacodynamic") AND ("Model" AND ("Graphical" OR "Diagram")) revealed 17 publications that mentioned graphical analysis.



Conclusion

- The proximity of SB and PK/PD model descriptions mean that these "parallel universes" have much in common. Adopting the existing SBGN standard using tools such as CellDesigner[10] means that the underlying semantics are represented within the SBML markup[6,9].
- An example of a minimal PBPK model represented as an SBGN process description is shown in a complementary abstract. An enhanced understanding of M&S approaches will furnish a greater appreciation and support of this work amongst lay and expert audiences alike.

Acknowledgments

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References

1 Rowland M & Tucker G. J Pharmacokinet Biopharm. 1980;8(5):497-507.
2 Anonymous. International Conference on Harmonization. 2014 [cited 2014 27th January 2014]; Available from: http://www.ich.org/.
3 Office UKS. British Pharmacopoeia 2013: STATIONARY OFFICE; 2012.
4 Jamei M, *et al.* Expert Opin Drug Met. 2009;5(2):211-23.
5 Hoops S, *et al.* Bioinformatics. 2006;22:3067-74.
6 Hucka M, *et al.* Bioinformatics. 2003;19(4):524-31
7 Le Novère N, *et al.* Nat Biotechnol. 2005;23(12):1509-15.
8 Le Novère N, *et al.* Nat Biotechnol. 2009;27(8):735-41.
9 Kell DB & Mendes P. J Theor Biol. 2008 Jun 7;252(3):538-43.
10 Funahashi A, *et al.* Biosilico. 2003;1:159-62.
12 BioModels Database: http://www.ebi.ac.uk/biomodels-main/
13 PharmML website: http://pharmml.org/
14 Ricordo website: http://www.ricordo.eu/
15 CDISC website: http://www.cdisc.org