A philosophical framework for integrating quantitative systems pharmacology models into pharmacometrics

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Objectives: There is a natural tension between the deductive empirically driven (“top-down”) approach that requires pharmacometric models to fit data and the inductive quantitative system pharmacology (QSP) based approach (“bottom-up”) in which the system is defined based on a priori evidence. Science dictates that a process must be falsifiable in order to create evidence which is not thought to be directly applicable to the QSP approach. This paper proposes a framework for integrating QSP and standard pharmacometrics modelling.

Methods: The framework was developed by considering the known limitations of the top-down approach. Box [1] coined the phrase “All models are wrong but some are useful”. Four reasons were proposed for why models may be wrong: (1) the model is an approximation, (2) the model is built from data and cannot account for unobserved data, (3) the data includes an unexpected recursion and (4) the model is right for the one purpose.

Results: Parsimony guides the modelling process in order to get the minimal model by deductive reasoning that contains the features necessary to describe the data at hand. The injection of semi-mechanistic functional groups (e.g. receptor occupancy) provides some buffer to wrongness but does not eliminate all cause wrongness and therefore does not alleviate Box’s concern. In contrast, the QSP approach specifically addresses these four wrongs. In the proposed QSP framework both inductive (bottom up) and deductive (hypothesis testing) approaches are naturally involved (Figure 1). A QSP model, however, cannot be rejected by hypothesis testing, but rather evidence is presented that can satisfy or falsify sub-theories which can then be rebuilt and retested.

Conclusions: QSP provides a natural scientific framework to build evidence to understand systems and the data that arises. Importantly, it naturally includes both bottom-up and top-down approaches.