

## **Quantitative Systems Pharmacology & Machine Learning – A match made in heaven or hell?**

Marcus John Tindall<sup>1,2</sup>, Lourdes Cucurull-Sanchez<sup>3</sup>, Hitesh Mistry<sup>4</sup> and  
James W.T. Yates<sup>3</sup>

<sup>1</sup> Department of Mathematics and Statistics, University of Reading, Whiteknights, Reading,  
United Kingdom, RG6 6AX.

<sup>2</sup> Institute of Cardiovascular and Metabolic Research, University of Reading, Whiteknights,  
Reading, United Kingdom, RG6 6AA.

<sup>3</sup> GSK Medicines Research Centre, Stevenage, SG1 2NY, United Kingdom

<sup>4</sup> Pharmacy, Division of Pharmacy and Optometry, University of Manchester, Oxford Road,  
Manchester, United Kingdom, M13 9PL.

Corresponding author: Marcus Tindall, Department of Mathematics and Statistics, University of Reading, PO Box 220, Whiteknights, Reading, United Kingdom, RG6 6AX. E-mail:

[m.tindall@reading.ac.uk](mailto:m.tindall@reading.ac.uk)

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#### Non-standard abbreviations

ML – Machine Learning

QSP – Quantitative Systems Pharmacology

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## Abstract

As pharmaceutical development moves from early stage in vitro experimentation to later in vivo and subsequent clinical trials, data and knowledge are acquired across multiple time and length scales, from the subcellular to whole patient cohort scale. Realising the potential of this data for informing decision making in pharmaceutical development requires the individual and combined application of machine learning (ML) and mechanistic multiscale mathematical modelling approaches. Here we outline how these two approaches, both individually and in tandem, can be applied at different stages of the drug discovery and development pipeline to inform decision making compound development. The importance of discerning between knowledge and data is highlighted in informing the initial use of ML or mechanistic Quantitative Systems Pharmacology (QSP) models. We discuss the application of sensitivity and structural identifiability analyses of QSP models in informing future experimental studies, to which ML may be applied, as well as how ML approaches can be used to inform mechanistic model development. Relevant literature studies are highlighted and we close by discussing caveats regarding the application of each approach in an age of constant data acquisition.

### Significance statement

We consider when best to apply Machine Learning (ML) and mechanistic Quantitative Systems Pharmacology (QSP) approaches in the context of the drug discovery and development pipeline. We discuss the importance of prior knowledge and data available for the system of interest and how this informs the individual and combined application of ML and QSP approaches at each stage of the pipeline.

## 1. Introduction

The drug discovery and development pipeline offers great opportunities for combining mechanistic modelling and machine learning (ML) methodologies. Mechanistic mathematical modelling has played an important role in the development of pharmaceutical drugs over the past 50 years. Models in drug development have generally comprised compartmental pharmacokinetic and pharmacodynamics (PKPD) models, linking drug concentration in plasma to pharmacological responses. These models have been the cornerstone of dosing/scheduling decisions within drug development. They have also been expanded to include more realistic descriptions of human physiology (physiologically based pharmacokinetic; PBPK), which describe drug absorption, distribution, metabolism and excretion (ADME) within multiple organs in the body. Such models were initially conceived in the 1930's (Paalzow, 1995). Recently the focus has moved to more detailed models of pharmacodynamics which account for compound effects at the cellular and subcellular scales, leading to the advent of Quantitative Systems Pharmacology (QSP). Initiated within industrial settings, the focus of QSP has been to understand the way in which single cell to whole host models can be linked to create multiscale descriptions of drug action which account for basic physiology (via PBPK models) and molecular descriptions of drug action. Such multiscale models allow for variation between individuals to be considered and have led to in silico drug trials (Clancy et al., 2016).

Mathematical modelling of drug development has not only facilitated the understanding of data (e.g. the processes determining the pharmacokinetics of a drug) but also the generation of hypotheses (e.g. “these data could be explained if this drug is a CYP450 inducer”) and experimental design (e.g. proposing of a dose range and time points for observations to be made). The result has been that

mathematical modelling has had a considerable impact on drug research and development (Allerheiligen, 2014; Davies et al., 2020; Milligan et al., 2013; Visser et al., 2013; Visser et al., 2014; Wu et al., 2021). However, the ability to collect data from the subcellular to whole human scale, with increasing speed and automation has led to an explosion in recent years in the availability of data describing biological systems (Hafner et al, 2016). How researchers are able to make sense of the available data, given its often complex, multifactorial, multiscale (both in terms of space and time) nature has become a growing challenge.

ML has been used to interrogate and visualise complex data sets to gain insight that informs decisions in drug research. ML utilises algorithms to learn by interrogating data. This learning is then used to identify key descriptors or patterns within large data and image sets, where doing so without computing power would be infeasible given the large number of calculations required.

There has been an increase in combining mechanistic modelling with ML to provide insight into biological systems. Baker et al. (2018) considered the synergy between mechanistic modelling and ML in a general biological context, suggesting a cyclic interplay of the two approaches whereby ML finds important patterns and structures in the data and mechanistic approaches attempt to explain them by hypothesis generation. Others (Zhang et al., 2022b)] have discussed the application of QSP and ML approaches to drug discovery and development and considered possibilities for how they can be combined. Here we detail the importance of each approach in the context of knowledge and data, providing examples to date of their application in drug discovery and discuss areas in which both can be utilised together. We identify when ML and QSP approaches are best applied at the stages of drug discovery and development, based on the availability of data and knowledge

for their application. We close by discussing the issues and caveats of combining the approaches and opportunities for further exploring the integration of the two areas in the context of each stage of the drug discovery and development pipeline.

### **Data, knowledge and modelling**

A critical element in the application of QSP and ML within drug discovery and development is the distinction between knowledge and data. Knowledge can be defined as collection of facts or information about a system, in our case biological ones, which allows a mechanistic description of processes within the system to be formulated. In contrast, data is most often a collection of quantitative values (e.g. rate constants, protein expression levels, time course data), collected by experimentation. Data does not immediately infer knowledge - a system and its data needs to be analysed in order to gain knowledge. This difference between knowledge and data is important in recognising the distinction between mechanistic modelling approaches used in QSP versus those in ML, particularly given that prior knowledge is often available to inform a QSP model of the biological system being considered .

Knowledge and data is acquired during the drug discovery pipeline in a multiscale manner, working from the lower to higher length scales, starting initially at the cellular and subcellular scales during the early stages before moving into the higher organ and whole host scales and subsequent clinical studies. The ability of QSP modelling to infer knowledge by deduction, and of ML approaches to infer knowledge by induction, means each can be applied within and at different points in the drug discovery and development pipeline data acquisition process (see Figure 1).

Mechanistic models primarily rely upon first principles from chemistry, biology and physiology, scoped to the specific biological system processes of relevance, with the goal of inferring emerging system behaviours in hypothetical scenarios, such as therapeutic intervention, generated by perturbing the system (Figure 1, left). Examples of such behaviour include individual cell models of tissue (e.g. agent based), which allow the effect of molecular scale processes, cell-cell communication and extracellular factors on growth and development at the tissue scale to be evaluated. In this way, a mechanistic modeller can set model parameter values with prior quantitative data either directly or indirectly (e.g. from a related system). Where no such data is available, informed estimates from subject matter experts may be utilised as an initial starting point. This framework allows the modeller to extend the model to include and test multiple plausible hypotheses at the molecular level (for example a feedback loop in a cellular signalling pathway) that earlier experimentation at a cellular, tissue or in-vivo level has indicated may be possible. Depending upon prior data and knowledge of the system, model outcomes can be tested qualitatively and/or quantitatively, the latter not always available for biological systems due to cost and time limitations. In this way, mechanistic modelling can develop initial predictions of the system, without the need for information other than the hypothesised topology of the system. In the context of drug discovery questions which inform this may include (Morgan et al., 2012; Cook et al., 2014; Friedrich, 2016) for example:

1. Is the proposed drug target sufficiently linked to the disease indication that it is a viable therapeutic strategy?
2. Out of all the molecules developed and tested in discovery, which one has the highest potential to elicit a positive response from patients?
3. Which patients might benefit from this approach?

4. What are the potential toxicities of engaging with this target/molecule?
5. What dose and dosing frequency would this drug candidate require for therapeutic benefit in humans?
6. Is combination therapy better than monotherapy?
7. What aspects of the biology requires further data/knowledge collection to be clear in progressing model development?

The mathematical predictions that can answer or inform these questions can be updated as new data and knowledge emerges at each stage of the drug discovery and development pipeline. This enables drug projects to predict from one compound to its back-up molecule in discovery, from nonclinical to first in human/patient at candidate selection, or from Phase 1 to subsequent phases during clinical development. It should be noted that rather than replacing the data, the simulations guide the design of studies (nonclinical or clinical) to generate the key data that will underpin decisions. Once that data has been generated, it can be used to assess the model performance and to refine/develop it further where needed. Given the granularity and multi-scale nature of QSP models, this approach brings some mechanistic insights into the system - a particularly advantageous trait given the many nonlinearities associated with biological systems, a result of interactions both within the same and across different spatial and time dependent scales.

In contrast, ML approaches require large and diverse enough amounts of data to be collected from the system in a consistent way, with the goal of inferring general patterns or rules about the system (Figure 1, right). In this way, ML approaches have been described as 'data hungry'. Data must also be of sufficient quality (strong signal to noise ratio), consistent (collected by reasonably similar experimental methods and protocols) and within scope (with some degree of diversity in the sampling of cases).



ML has been seen as method for learning about the structure of data, thus providing an opportunity to extract understanding and insights from it. Any application to similar types of data on the same problem, means algorithms can be used in a predictive capacity.

### **Machine Learning in drug discovery and development**

The use of ML has gained considerable traction within the healthcare (Erickson et al., 2017; Garcia-Vidal et al., 2019), biological (Mahmud et al., 2018) and pharmacological sciences (Jiménez-Luna et al., 2020) over the past few years, but there remain a number of caveats to its successful application. Most critical here is the quality and quantity of data to ensure algorithms are able to adequately learn and there is confidence in the resulting predictions (Chen et al., 2019). Indeed, issues have been highlighted around the use of ML in clinical studies (Liu et al, 2019; Nagendram et al., 2020), leading to recent efforts regarding the creation of guidelines on the use of AI methods in this area (Ibrahim et al., 2021). ML methods have also found a home in particularly high signal to noise ratio, but laborious, applications such as medical imaging where computers are quite capable of automatically segmenting images (Hosny et al., 2018).

Due to the challenges of understanding complex biological and chemical data, ML has found applications in drug discovery. Algorithms have been able to elucidate core elements in complex structures, e.g. protein-protein interaction cascades and identifying drug targets, protein structure and binding sites (Reed et al, 2017). ML has made significant progress (Callaway, 2020; Tunyasuvunakoo, 2021) with the seemingly intractable task of predicting the secondary and tertiary 3D structure of proteins based upon their amino acid sequence. Of particular note is the reported

use of ML approaches to discover resistance mechanisms by integrating CRISPR gene knock-out experiments and biological network information into knowledge graphs (Gogleva et al., 2022). Here empirical approaches are integrated with prior biological knowledge. There are a number of reported applications of ML to what many would recognise as classical PKPD analyses (Brunton et al., 2016; Sale & Sherer, 2015). Some of the applications to pharmacokinetics and PKPD modelling (Erickson et al., 2017; Gobburu & Chen, 1996) date quite far back and yet there has been little follow up until recently (Lu et al., 2021). As well as PKPD, there have also been reported applications of ML to pharmacometric analyses such as the clearance of monoclonal antibodies (Wang et al., 2020).

ML methods in pharmacology also include structure based property modelling of drugs (e.g. quantitative structure-activity relationship (QSAR) modelling) that uses structural descriptors to predict binding affinities (Jones et al., 2021) and pharmacokinetic properties (Soares et al 2022). Whilst ML methods have attracted focus in recent years, traditional statistical modelling approaches, such as linear regression, still have value for hypothesis generation from large scale data sets, for example generating hypotheses for mechanisms of toxicity (Munoz-Muriedas, 2021). Indeed, those looking to use ML approaches, should also be aware that they do not always provide superior solutions to those already available methods. An illustrative example is of a commercial ML parole system using 137 features of offender's history that was no better at predicting recidivism than lay-reviewers or a simple linear model based on two features (Dressel & Farid, 2018). Another example is within safety pharmacology, where prediction of Torsades de Pointes using a combined mechanistic/ML model was no better than linear regression (Mistry 2017).

These two examples highlight the importance of doing comparisons to simpler approaches to understand the value of ML.

### **QSP modelling**

The term Systems Pharmacology or Quantitative Systems Pharmacology was first coined in 2008 (Allerheiligen, 2010; Jusko et al., 2008) and fully established in 2012 through a white paper jointly written by systems biologists and pharmacologists (Sorger et al., 2011). Focusing on elucidating drug action at the individual cell and subcellular scales in pre-clinical stages of development, the field has come to encompass not only detailed temporal models of genetic regulatory and associated protein-protein interaction processes at the cell scale, but the integration of such information into higher organ and individual host scale models allowing for the development of virtual population models (Cheng et al., 2022). Models have primarily been formulated using the theory of nonlinear ordinary differential equations (ODEs), but also other approaches such as stochastic models including agent-based methods (Cosgrove et al., 2015) have been employed. Both have generally only accounted for temporal phenomena. Spatiotemporal approaches to drug discovery and development have been used to incorporate descriptions of drug diffusion into the surrounding tissue (McGinty & Pontrelli, 2015) although the application of partial differential equation models, accounting for temporal and spatial detail, is ripe for further exploitation in QSP. All of these approaches allow dynamical predictions of the system behaviour to be made from which new understanding can be gained and hypotheses tested: for example understanding the pharmacokinetic properties required of a drug to gain a therapeutic benefit from binding to a target by an early model based assessment of target pharmacology (Chen et al., 2022).

A highly interdisciplinary field bringing together mathematical modellers, computer scientists, pharmacological scientists and biologists, to tackle specific problems, QSP models seek to integrate information and data obtained at the earlier stages of the drug discovery and development pipeline, typically obtained from in vitro experiments and in vivo scale animal models. Multiscale QSP models allow the effect of compound dosing at the individual host scale to be examined at the cellular/subcellular level. In turn the cellular functional outcomes affected by the compound can then be evaluated at the organ and whole host scale. In this way QSP models have the ability to link across varying spatial and temporal scales, which allows for emergent behaviour at particularly the lower spatial scales (e.g. multicellular level) to be evaluated at the tissue scale.

The ability to combine early-stage knowledge and data in the drug discovery and development pipeline along with combining processes across spatial and temporal scales, means QSP models are well placed for also considering variability not only within individuals, but also across populations. In this way QSP models can be used to run in silico clinical trials for a particular compound, long before any possible actual clinical trials take place.

The QSP approach is also helpful in cases where data or knowledge of the compound is not available for its known or proposed biological mechanisms of action. A mechanistic model does not need a full data set describing the full system for modelling to be initiated. Models can be formulated which take account of known information, using available data from the same cellular system or ones similar to it to both inform and test the model predictions, whilst utilising knowledge of any remaining parameters to inform the model. Knowledge and data for building and parameterising QSP models may take a variety of forms and include the following: (i)

models (or reduced versions thereof) can be fitted to available data to obtain estimates of the required model parameters; (ii) parameters from previously published mathematical models directly or indirectly related to the system being modelled; (iii) estimates of model parameter values utilising informed upper and lower bounds as to what values the parameters may obtain; or (iv) a combination of (i), (ii) and (iii). In this way QSP models do not need access to large amounts of experimental data for an initial set of predictions to be made. The initial predictions can be assessed both qualitatively and quantitatively against known experimental data and knowledge gained to date of the system, e.g. if the concentration of a specific entity lies within a given known range. Analysis of the model, either analytical or computational (e.g. sensitivity analysis) can then be used to identify parameters critical to the model outcomes of interest. Where critical parameters are identified for which more knowledge of that parameter is required (by combining the results of structural identifiability and sensitivity analysis), then experimental work can be explored/undertaken to do so. In this way, mechanistic modelling helps both inform our understanding of the biological system and/or test hypotheses whilst helping to direct future experimental work.

Whilst the size and complexity of QSP models can vary, simple models can be insightful and explanatory, alongside larger scale, more detailed ones (Stein & Looby, 2018; Mistry & Orrell, 2020). This is both the case when data and knowledge are plentiful or sparse. Indeed, simple models capturing gross complexity can provide overall understanding of the system dynamics, helping to improve knowledge (Mistry, 2018). At whichever scale the modeller chooses to work, as models move into the clinic, it is important they are informed and tested with appropriately sized patient samples, to ensure predictions are meaningful and can be trusted (Riley et al., 2020).

## **Combining ML and QSP in drug discovery and development**

Drug discovery and development offers opportunities for combining ML and QSP. A key consideration here is observing the outcomes and outputs that each approach has that can inform the use of the other one. Particular thought should be given to the richness and type of data available in the context of the overall question at each stage of the pipeline. At each stage of drug discovery and development, there may be the opportunity to either use each method in its own right and/or combine both at the same stage.

As shown in Figure 1, integration between QSP and ML can happen in two possible ways: (1) by extracting patterns from a collection of QSP emerging behaviours with ML methods, or (2) by using the rules derived from ML methods as first principles feeding into QSP models. Whilst Zhang and colleagues have recently identified ways and examples of unifying ML and QSP approaches in drug discovery and development (Zhang et al., 2022b), here we provide details on how the methods can be combined at each stage of drug discovery and development, given the knowledge and data available as a compound moves down the pipeline, and noting recent successes in the literature relevant to each case. In each case “Data rich” refers to cases where enough experimental data is available so meaningful insight can be gained using ML approaches, and thus they may be a good first step. “Data poor” indicates inadequate or insufficient experimental data is available for ML approaches to be insightful and thus mechanistic QSP approaches should be considered. References to current examples are provided and an overview of how the combination of each approach applies to the drug discovery development pipeline is shown in Figure 2.

### Discovery/preclinical development

**ML to QSP (Data rich):** Here ML methods can be used to interrogate experimental data sources to: (i) identify patterns and relationships upon which mechanistic QSP models can be built (e.g. searching for signals in 'omics data associated with disease (Kolluri et al., 2022; Menden et al., 2019; Vamathevan et al., 2019;); and (ii) parameterise QSP models, e.g. analysis of computational QSAR models to inform PBPK model parameters (McComb et al., 2021).

**QSP to ML (Data poor):** Here QSP models are created when limited good quality experimental data is available. In this case, no QSAR models are available to inform the QSP parameters, so models can be informed using parameter values from similar systems or with a known level of uncertainty based on current knowledge. Models initially formulated at the subcellular genetic regulatory/protein-protein interaction level can be integrated with PKPD/PBPK ones to create patient cohort level multiscale predictive models that pre-empt between patient variability: for example the PBPK tool SimCyp with its detailed knowledge of variations in physiological parameters for different patient populations to predict variability in pharmacokinetics (Zhang et al., 2022a). Such Digital Twin style models (Agur et al., 2020) can be used to provide cohort predictions of drug efficacy/toxicity before clinical trials are undertaken, identifying potential issues and which clinical trial data is critical to improving model predictions. ML approaches can then be applied to identify patterns within the simulated virtual patient populations, to inform decisions relevant to the design of specific disease/drug response studies (Koch et al., 2013). They may also be applied to identify parameters and thus mechanisms responsible

for certain outcomes in mechanistic models as demonstrated by McGillen and colleagues (McGillen et al, 2014).

### Clinical trial phases 1 to 3

**ML to QSP (Data rich):** Here 'omics data can be interrogated with ML methods during a clinical trial to uncover potential biomarkers of response (Agur et al. 2020). This information can be used to test multiscale QSP model predictions. Others have utilised ML analysis of high-throughput in vitro drug combination data to predict and prioritise drug combinations (Menden et al., 2019) for clinical investigation using only single drug potency data by incorporating prior mechanistic biological knowledge. This information can then be applied to develop relevant PKPD/PBPK models of the various combinations.

**QSP to ML (Data poor):** Classically this is the stage at which mechanistic PKPD/PBPK models have been applied to inform drug dosing and understand compound effects at the whole organ scale. There is a growing trend of applying ML approaches to PKPD/PBPK models to identify subpopulations with varying pharmacokinetics and response to treatment within clinical data sets (McComb et al, 2021). Others are utilising ML analysis of patient data in response to therapeutics to derive PKPD like models (Lu et al, 2021). This work demonstrated that the application of ML does not necessarily lead to better results than those captured by the initially formulated PKPD model. Indeed, the analysis detailed in Lu et al. (2021) does not follow the natural flow of data creation in clinical trials – the authors consider phase 3 data when the greatest utility of the modelling (PKPD or ML) would be to inform movement from phase 1 to phase 2 trials.



## Life Cycle Management

Whilst we are not currently aware of any studies looking at the individual or combined use of mechanistic and ML approaches once a pharmaceutical has received regulatory approval, it is probably fair to state that this later stage of big, complex data, is ripe for the application of ML approaches such as in pharmacovigilance. Here individual adverse reaction reporting of pharmaceuticals in the community can be analysed using ML approaches to identify plausible patterns in reporting. Such results can then be used to inform future post-approval PKPD/PBPK modelling to address these findings, for instance, the formulation and parameterisation of a model based on an observed drug-drug interaction.

## **Summary and conclusions**

There is growing interest in applying QSP mechanistic approaches and more recently ML to inform decision making in drug discovery and development, the overall goal being to inform compound development earlier in the drug discovery and development pipeline, thus reducing compound attrition at later stages. The application of both approaches relies greatly on the knowledge and data available to develop a model of the biological system of interest.

Given the flow of data collection in the drug discovery and development pipeline and the need to assimilate knowledge at different spatial and time scales, it is becoming increasingly clear that the application of QSP and ML approaches should not be considered in isolation. Both approaches can be used to progress compound development. What is important in this marriage is the relevant context for their application and the appropriate sequence of application: the right tool for the right

job. For instance, where data may be lacking to make meaningful use of ML approaches, a QSP approach can be applied to begin postulating how the system may behave, thus helping to inform future experimental data collection to improve model predictions. Such data collection may require the application of ML approaches to subsequently inform and test the QSP model. Likewise, when data sources are large and beyond the scale of humans being able to extract meaningful relationships, ML approaches can be particularly helpful at informing relationships in data, upon which mechanistic models can be built.

As more data at molecular scales becomes publicly available we are moving to a stage where early stage drug discovery and development can be informed using such information, before further experimentation is undertaken. Within this data rich age we are fortunate that we can utilise ML approaches to bring understanding to large datasets or where such understanding is difficult or not meaningful, we can turn to mechanistic style QSP models to progress research and development. With both tools available and growing understanding and data, barriers to informing earlier stage drug discovery and development, which in turn informs decision making in later stages, are being reduced.

Whilst data is becoming more readily available to researchers, the application of both approaches needs to account for the reproducibility issues within the scientific literature (Baker, 2016; Voelkl et al, 2018). The analysis of data and its subsequent interpretation where reproducibility is questionable, can lead to incorrect conclusions and subsequent incorrect or misinformed drug development, regardless of whether ML or QSP approaches are applied independently or together. Data collection and

providence needs to account for the required scale and relevance to the overall question being asked about the development of the compound. For instance, to meaningfully inform and test a QSP model multiscale (subcellular to organ scale) longitudinal data may be required to uniquely and accurately inform parameters within the model. As such, the need to conduct reproducible experiments for a given cellular system, to improve confidence in model predictions, is and will continue to become increasingly important as reliance on model predictions for directing future experiments becomes greater. In contrast, to simply begin a study when limited system specific data is available for informing model development, researchers may be satisfied to utilise data from different cell systems in order to make progress. Each case very much depends upon the model application and the model uncertainty modellers and their teams are willing to work with. Overall, the quality and completeness of data in each case, is something which both ML and QSP approaches, individually and collectively, can help with in progressing the development of future pharmaceuticals.

The success of combining ML and QSP models will be assessed on the overall ability of the combined approach to make as much progress on a given problem, minimising time and cost to do so (Androulakis, 2022). For instance, in the case of a project where no or limited experimental data has been collected, but mechanistic knowledge of processes is available then a model should be formulated, parameterised and used to direct any future experimental work. In such a case it would be counterproductive to initially undertake large scale experimentation, when this option is available, Likewise, when large scale data sets are available and no

causal relationships between processes are known, ML approaches should be used first to then inform QSP model development (Putnins, 2022).

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Wrote or contributed to the writing of the manuscript: Tindall M, Cucurull-Sanchez L, Mistry H, Yates J.

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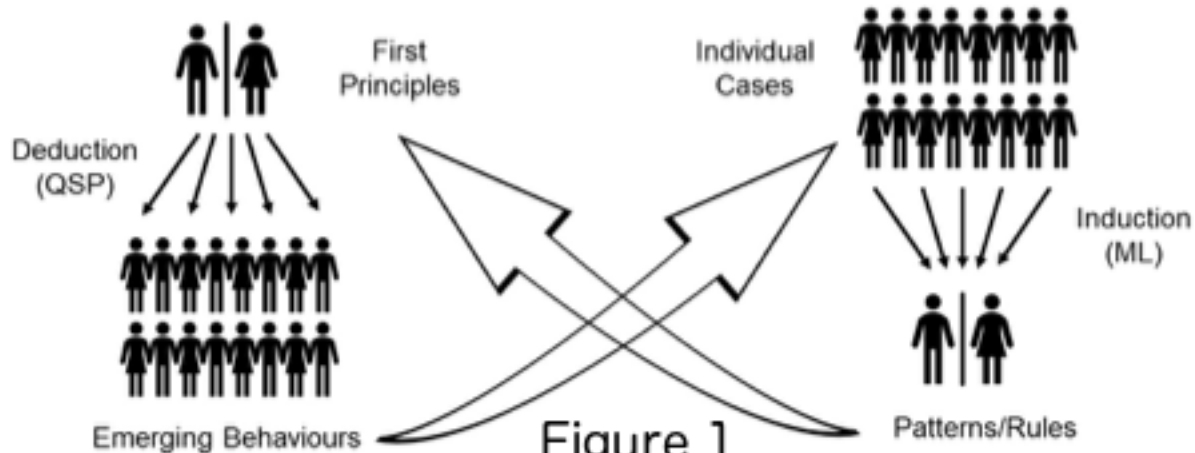
### Figure captions

**Figure 1. QSP and ML modelling methods.** QSP methods lead to knowledge by applying first principles to a specific context and allowing the exploration of new emerging behaviours when that context is perturbed (deductive method, left). On the other hand, ML methods lead to knowledge by extracting patterns or rules from a collection of data representative of multiple possible scenarios (individual cases) for the same system (inductive method, right). Therefore, integration between QSP and ML can happen in two possible ways: (1) by extracting patterns from a collection of QSP emerging behaviours with ML methods; or (2) by using the rules derived from ML methods as first principles feeding into QSP models.

**Figure 2: A summary of ML, QSP and ML and QSP combined approaches applied to each stage of the drug discovery and development pipeline.**







QSP

Multiscale (subcellular to individual/cohort scale).

"Population" PKPD including safety.

Using classifiers (e.g random forests) to identify areas of parameter space with different behaviour [3,4].

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ML to augment the utility of PBPK models [9].

ML & QSP

ML and Pharmacometrics [10].

ML in pharmacometrics including ANN PKPD models [6].

QSAR models to predict QSP model parameters e.g. PBPK.

Combination prediction – ML & cell signalling networks.

Imaging and pathology – remove issue of subjective human derived data.

ML

New indications.

'Omics for biomarker discovery of responding patient population/ drug effect [8].

Signal search genetic ('omics in general) association with disease [1,2].

Emerging safety (e.g. patient yellow card reporting) [5].

Discovery/ Preclinical development

Clinical trial phases 1 to 3

Life cycle management



[1] Vamathevan et al. (2019)	[6] McComb et al. (2021)
[2] Kolluri et al. (2022)	[7] Garcia-Vidal et al. (2019)
[3] Sorger et al. (2011)	[8] Agur et al. (2020)
[4] McGillen et al. (2014)	[9] Bose et al. (2020)
[5] Chen et al. (2019)	[10] Wang et al. (2020)

Figure 2