# Towards a Systems Pharmacology Ontology: the use of state-machines paradigm

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**Abstract**

Identification of potential Adverse Drug Reactions (ADRs) can be facilitated via the engagement of emerging data sources, including pharmacological Mechanism of Action information. Biochemical, genetic, pharmacogenomics and especially signaling pathway information can be part of this emerging data sources ecosystem. Systems Pharmacology (SP) could be the knowledge link, providing the means to integrate heterogeneous data via models supporting computational needs. We propose the development of the States Pharmacology Ontology (SPO), an ontological model that could facilitate the representation of systems pharmacology information, focusing on state-based machine paradigm.

**Keywords**

Systems Pharmacology, Ontological Modelling, State Machines, Signaling Pathway Information

## 1. Introduction

Systems Pharmacology (SP) is defined as "*a hybrid, multi-scale modelling approach that seeks to combine systems or network-based structures with basic principles of pharmacokinetics and pharmacodynamics (PK/PD)"* [1]. SP paradigm refers to the use of multi-scale models, i.e. from low-level biochemical information regarding the behaviour of molecular structures, to more abstract information potentially regarding pharmacokinetic/pharmacodynamic behaviour of the drug, or even its phenotypic results. The goal of SP is to facilitate in-silico application of algorithmic approaches, e.g. simulations or the use of Machine Learning (ML). The use of in-silico tools could significantly reduce costs and time needed for various drug development aspects [2], e.g. drug repurposing, the identification of Adverse Drug Reactions (ADRs). SP models focusing on networks of interacting components have being used to describe the complex patterns of drug action (i.e. synergy, oscillatory behaviour) and disease progression (i.e. episodic disorders) [3]. PV has been identified as a prominent application of SP modelling approaches such as mechanism-based drug safety evaluations [4]. The ultimate goal of modelling SP information using an ontological model combining state-based approaches, is the potential development of a neuro-symbolic ML tool to identify novel signaling pathways for ADRs.

## 2. State-based Models

Typically, SP focuses on the use of differential equations modelling PK/PD behaviours (e.g. concentration of the active substance), also referred as Quantitative Systems Pharmacology (QSP) computational models. State-based models (SBMs) which are defined modelling states and transitions, are not frequently used in the context of SP. Since SBMs can "naturally" represent transitions, they can be combined with probabilistic approaches and the use of time as principal modelling dimension to

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facilitate SP knowledge representation. The concepts of *state, input* and *transition* fit with the paradigm of drug administration acting as a triggering event *(input)* causing a biochemical turbulence (*transition*) leading to a new biochemical (or physiological) *state*. These sequences of various "states" can be aligned with signaling pathway information thus, they can be used to elucidate drugs' MoA.

We argue that SBMs have an advantage compared to typical QSP models, as they do not necessarily depend on quantitative information (e.g. differential equations) which are very difficult to produce and validate, but they could still be included as part of the overall states transition model when available. SBMs can also be used to exploit non-quantitative or empirical expert knowledge regarding biological systems, bypassing the need for the quantification of such biochemical processes.

## 3. States Pharmacology Ontology

Computationally, such models could enable the merge of ML and Description Logics (DL) based reasoning, combining the two paradigms along the lines of neuro-symbolic AI.

While such a data model could have additional applications unrelated to drug safety, ADR detection is highlighted as an exemplar application due to its high clinical importance and the existence of data evidence from multiple (and potentially heterogeneous) data sources. The main objectives are to:

1. Facilitate data integration that enable both symbolic and non-symbolic reasoning approaches
2. Provide semantic/syntactic interoperability, to ease data sharing/reuse via FAIR principles
3. Use open, non-proprietary data exchange standards, to facilitate application in various software engineering platforms and enable seamless adoption in real-world applications
4. Facilitate the computational exploitation of SP and SBMs, with minimal data transformation.

The proposed States Pharmacology Ontology (SPO) could provide a practical way to support the relative data sources integration in one Knowledge Graph and investigate the respective computational advantages. SPO enables the representation of the main SBMs concepts and models in a systematic manner, thus facilitating the combination of DL and SBMs in one computational framework. We envisage using signaling pathway information (i.e. *REACTOME*), pharmacogenomics (i.e. *PharmGKB*) and gene-disease relationships (i.e. *Comparative Toxicogenomics Database*). The ultimate goal would be to build a Knowledge Graph, based (at least partly) on SPO to combine the power of DL reasoning with the SM modelling to identify potential ADRs based on personal data (e.g. lab tests, genetic profile etc.) and also the underlying ADR MoA.

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