
Hugo Geerts¹, Athan Spiros¹, Giouliana Kadra², Richard Hayes², Robert Stewart²

¹ In Silico Biosciences, Berwyn, PA
² BRC Nucleus, Institute of Psychiatry, Psychology and Neurosciences, King’s College London

Objectives. In real clinical practice and in pharma-sponsored clinical trials patients are usually on polypharmacy. The pharmacodynamic interactions of these drug combinations are hard to predict. If there is a sufficiently deep calibration set available, bio-informatics approaches can build classifiers for classification. However as each case is unique, this severely limits the predictive value of various machine learning approaches.

Methods. We applied a mechanism-based computer model of a cortico-striatal-thalamocortical loop of the dorsal motor circuit that has been calibrated with clinical data on the prevalence of extrapyramidal symptoms after antipsychotic treatment in schizophrenia patients and therapeutic interventions in Parkinson’s patients[1]. The Quantitative Systems Pharmacology (QSP) model is based on the appropriate connections between basal ganglia regions and consists of 220 neurons (8 different cell types), 3500 synapses and implementations of 32 CNS active targets, based on their unique locations and coupling with intracellular pathways. Modulation of the various CNS targets were calculated on simulating the competition between the endogenous neurotransmitter and the two drugs at their appropriate concentrations and their affinity.

The model was challenged to blindly predict the extrapyramidal symptoms liability of 1,124 patients prescribed two antipsychotics for six or more months (772 unique combinations). Anonymised data were derived from South London and Maudsley NHS Foundation Trust (SLAM) electronic health records (EHR). Extrapyramidal side effects were captured in electronic health records and identified using a combination of Natural Language Processing and a bespoke algorithm [2]. Only names and doses of the two drugs were made available without any calibration set.

Results: Blind prediction of the outcomes using a Receiver Operating Characteristic curve with the QSP model resulted in an Area-Under-the Curve of 0.64 (p<0.01). Neither summation of the Ki or the sum of D2R occupancies of the individual antipsychotics achieved statistical significance.

Discussion: QSP is a powerful approach to predict PD-PD interactions in the absence of any calibration set or with limited and unique data. A major application is the simulation of pharmacodynamic interactions of comedication in clinical trials with novel compounds leading to possible better balance between the different treatment arms.

References