Citation: CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e16; doi:10.1038/psp.2012.17

www.nature.com/psp

PERSPECTIVE

Has the Time Come for Predictive Computer Modeling in CNS Drug Discovery and Development?

H Geerts[1,2], A Spiros[1], P Roberts[1,3] and R Carr[1]

We discuss whether a new paradigm, quantitative systems pharmacology (QSP), based on computational neuroscience modeling combined with proper drug target engagement and pharmacology, human pathology, imaging studies, and calibration and validation using clinical studies in human subjects might improve the success rate of central nervous systems research and development (CNS R&D) projects. We suggest that an improved understanding of neuronal circuit interactions using a humanized computer-based integration of physiology and pharmacology knowledge can substantially de-risk new CNS projects.

CPT: Pharmacometrics & Systems Pharmacology (2012) **1,** e16; doi:10.1038/psp.2012.17; advance online publication 28 November 2012

WHY A NOVEL APPROACH IS NEEDED IN CNS R&D

The successful development of novel first-in-class therapeutic agents in the CNS has been lagging with respect to other disease areas. Moreover, only 8% of CNS drugs that enter phase 1 are approved,[1] with about 65% of the failures due to lack of efficacy or sufficient differentiation in phase III.[2] This high degree of failure is caused by the extreme complexity of the human brain neurobiology and the increasing realization that the clinical outcome is driven by emergent properties of neuronal circuits, rather than by a single target.

Complex translational problems that preclude simple animal model extrapolation[3] in CNS R&D include (i) fundamental differences in neurotransmitter circuitry between rodents and humans, (ii) the incomplete representation of the full human pathology, (iii) the absence of important functional genotypes in animal models, and (iv) the existence of unique pharmacologically active human metabolites. Many of these problems can in principle be reduced using humanized computer-based QSP, as suggested by a white paper (http://isp.hms.harvard.edu/wordpress/wp-content/uploads/2011/10/NIH-Systems-Pharma-White-paper-Sorger-et-al-2011.pdf). Application of QSP in CNS disorders is particularly appealing because of the large academic expertise in computational neuroscience since the seminal paper of Hodgkin and Huxley,[4] and due to the availability of the specialized software languages and the sharing of software modules (http://senselab.med.yale.edu/ModelDB/).

We will argue with a few examples that computer-based QSP (**Figure 1**) could be a powerful additional tool to reduce clinical attrition in psychiatry and Alzheimer's disease, although in principle, this approach can be applied to other CNS diseases, such as Parkinson's disease, Huntington's disease, and cognitive and negative symptoms in schizophrenia.

Re-engineering the drug discovery operation

There appears to be a fatalistic perception that we need to base our decisions for CNS projects solely on animal models even realizing that their predictability is limited.

In other successful industries with shorter cycle times and higher success rates such as microelectronics, aerodynamics, and petrochemistry, computer models are extensively used to test the effects of different experimental designs before actually building a prototype, saving significant amounts of money and time. Of course, data in biology are inherently noisier because of intrinsic variability in the human patient population and the limited accessibility and readout of specific experiments. However, the addition of a simple, yet incomplete computer model that is able to integrate many facts into a single predictive, quantifiable effect estimate will essentially include already a great deal of information that is not currently and easily accessible in any drug pipeline decision process. Current neuropharmacological treatment strategies and decisions are also "based" on a rational "qualitative understanding" of human biology and the impact of drugs and pathology on these interactions, usually using cartoon-based schematic drawings.[5]

We would therefore argue that a more quantitative computer-based mechanistic modeling and simulation, even with the current limited knowledge is a possible solution to increase the chances of clinical success.

A possible detailed implementation of such a QSP platform for schizophrenia is shown in **Figure 2** and is described in detail.[6]

With this model, the correlation between the simulated outcome of 76 different drug–dose combinations and their corresponding effects on clinical scales, such as Positive and Negative Scales in Schizophrenia total, is 0.56 as compared with a correlation coefficient of 0.18 with the simple D_2R occupancy calculation, the current gold standard for predictive pharmacokinetics/Parkinson's disease modeling. This suggests the computer model can explain much more of the biological variance

[1]Department of Biomedical Engineering, In Silico Biosciences, Berwyn, Pennsylvania, USA; [2]Department of Biomedical Engineering, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [3]Department of Biomedical Engineering, Oregon Health and Science University, Portland, Oregon, USA. Correspondence: H Geerts (Hugo-Geerts@In-Silico-Biosciences.com)
Received 29 August 2012; accepted 26 September 2012; advance online publication 28 November 2012. doi:10.1038/psp.2012.17

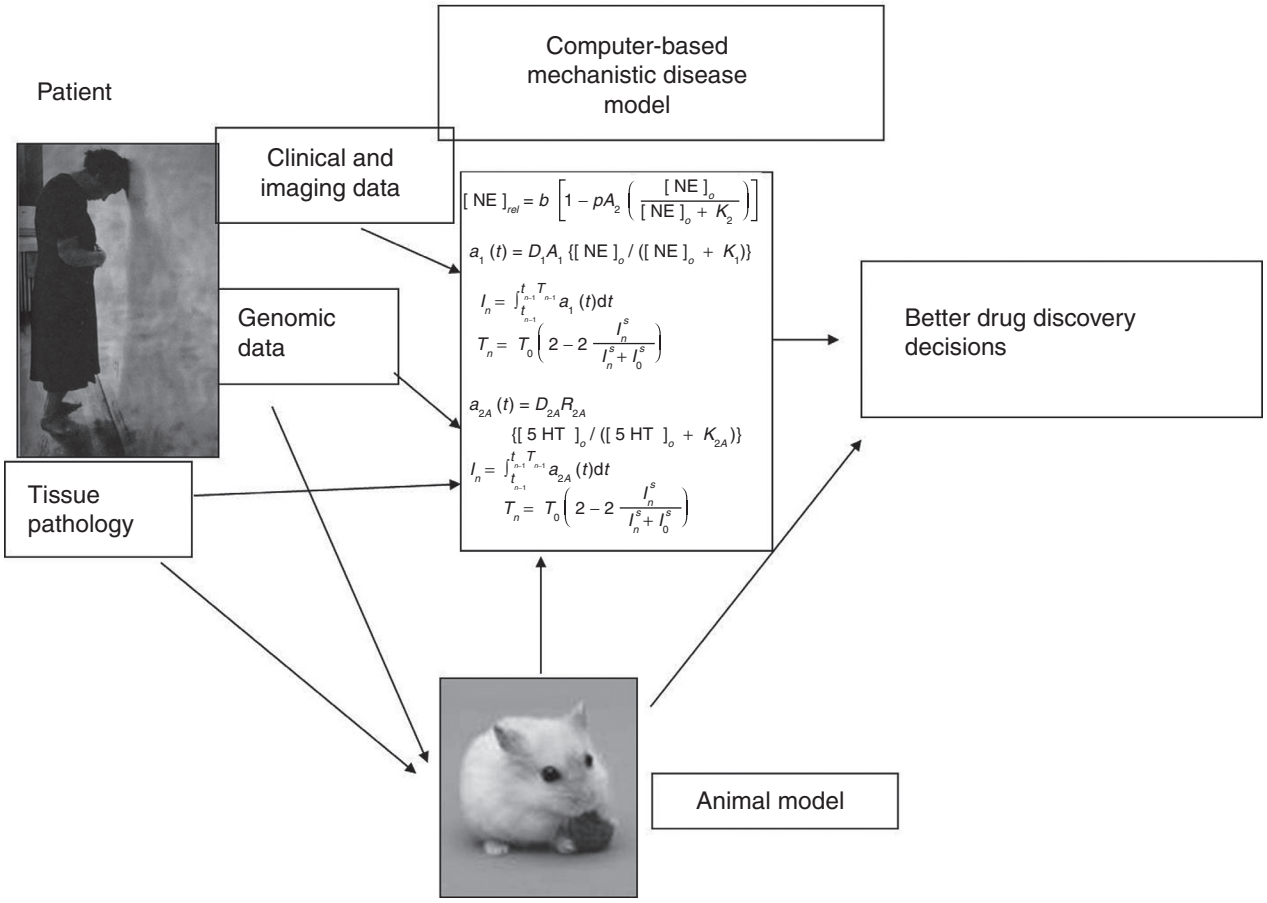

Figure 1 Computer-based quantitative systems pharmacology modeling of complex biological systems is based on the same set of preclinical rodent and primate neurophysiology, human tissue pathology, and genomics information that are used to inform preclinical animal models. However, in contrast to traditional drug discovery, there is a much larger emphasis on human clinical, pharmacological, genotype, and imaging data early on to drive the development of more humanized model systems and mathematical language substitutes for wet-lab research.

than the correlation with target engagement at one receptor. This is because the computer model simulates the off-target effects of antipsychotics at other receptors in a physiologically relevant way.

ACTIONABLE APPLICATIONS

A quantitative simulation study on aripiprazole and bifeprunox[7] found that the specific differences between primate and rodent striatal dopaminergic physiology and aripiprazole's unique human metabolite OPC1485 can account for a large part of their difference in clinical trials. The clinical development of bifeprunox was halted after 15 years of study and at an enormous financial and resource cost.

Using the complete human pharmacology of dimebon, an antihistaminergic compound with mitochondrial membrane protecting properties, a QSP failure analysis in Alzheimer's disease suggests strongly that the off-target effect at hD_1R significantly reduced cognitive benefits and that this effect is genotype-dependent.[8]

A similar computational approach has been proposed on the effect of AMPA modulation in complex neuronal networks in which changes in the kinetics of a ligand-based voltage channel after drug action have a major influence on the network behavior at different time scales.[9]

IS IT TIME TO INTRODUCE QSP IN THE CNS R&D OPERATION?

Currently, pharmacometric modeling and simulation becomes involved only in early clinical development with a compound and target that has been selected many years before. If either the target fails the drug or the drug fails the target, then the best that computational modeling and simulation can do is to find clinical trial solutions to mitigate these problems, which is often insufficient to rescue the project.

Of note, dosing mismatch was the only area in clinical drug development that has significantly improved between 1995 and 2004[10] likely as a consequence of improved pharmacometric modeling and simulation.

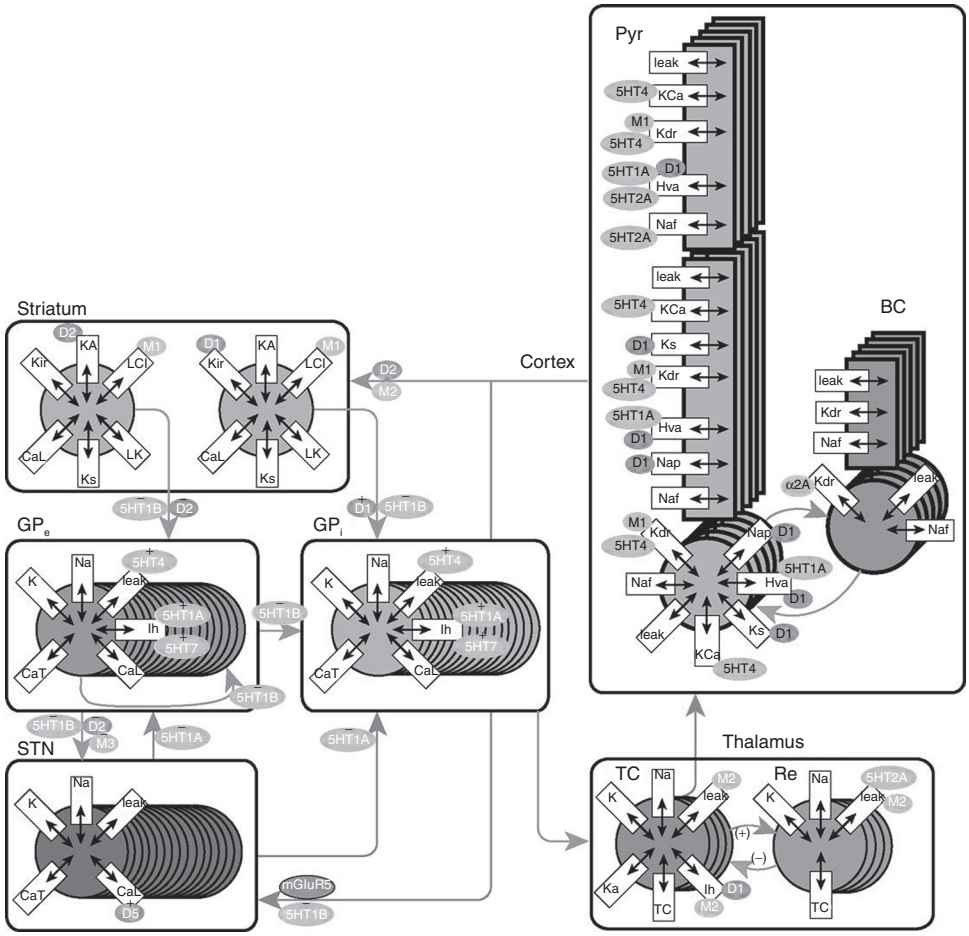

Figure 2 The quantitative system pharmacology approach for a schizophrenia model is based on actual preclinical neurophysiology and human neuroanatomy. For instance, the different types (direct vs. indirect pathway projecting) of striatal medium spiny neurons (MSN) are driven by cortical afferents, gated by the amygdala and hippocampal projections and their activity is modulated by dopaminergic afferents from the ventral tegmentum area (in the case of the N accumbens), cholinergic input from local tonically active interneurons, serotonergic afferents from dorsal raphe, and noradrenergic projections from the locus coeruleus. All these processes modulate the MSN membrane potential that further define the timing of the action potential train into the other subcortical regions and ultimately through the thalamus back to the cortex. The model output is calculated as an information content (i.e., bandwidth) from the action potential spike train in the MSN (see text for a detailed description). A larger cortical network of 120 neurons (80 pyramidal cells and 40 inhibitory interneurons) simulates the cortical pathology and pharmacology that drives the MSN activity. The D_1-mediated direct pathway MSN then further projects into GP_i; the D_2-mediated indirect pathway projects to the GP_e and STN before converging in the GP_i and further projecting to thalamic nuclei. The number of circles reflect the total number of cells simulated in the network except for the cortical model (where there are 120 neurons). There are 16 neurons in the GP_e, GP_i, and STN and four excitatory and four inhibitory cells in the thalamic nuclei. At various positions in the circuit, different types of neuromodulatory receptors (29 in total) mediate the effect of various neurotransmitters on the membrane excitability and subsequently the nature of the emergent network properties. These receptors are indicated by tags like D_1 (dopamine D_1), M_1 (muscarinic M_1 receptor), and $5HT_4$ (serotonin-receptor type 4), and affect various ion channels (indicated by K_{ir} (indirect rectifier K^+ channel), Na_p (persistent Na^+-channel), Hva (high-threshold activated Ca^{++}-channel), leak (leak current), etc.). The specific interaction between neuromodulatory receptors and voltage-gated ion-channels is derived from the preclinical literature data. By virtue of their pharmacology, drugs might affect certain postsynaptic receptors as they enter in competition with the endogenous neurotransmitter and affect neuronal membrane excitability through changes in appropriate ion-channel conductances. BC, basket cell interneuron; GP_e, globus pallidus externa, GP_i, globus pallidus interna; Pyr, pyramidal cell; RE, reticular (inhibitory) cell; STN, subthalamic nucleus; TC, thalamocortical cell.

QSP as an alternative

The QSP computational approach as described here was inspired by the seminal work of the late Leif Finkel and further developed as "computational neuropharmacology." Taking into account the limitations of this model, proper use of these humanized computer models could significantly reduce the dependence of the go/no-go decisions on traditional and less-predictive animal models and substantially de-risk CNS projects. In fact, the approach lends itself very naturally to the concept of learn-and-confirm; when the prediction of the model is not confirmed in a clinical trial, we can identify what assumptions are needed to be changed and the model parameters that can be improved so as to better reflect the actual clinical outcomes.

The mechanistic disease computer-based model can further function as a useful biological knowledge repository with a common universal language (mathematics). The availability of a uniform and well-defined mathematics-based

language will naturally improve communication between scientists active in CNS drug R&D and make comparisons between different laboratoria and experimental conditions much easier.

A computer model explicitly lists the biological assumptions in a decision process, and provides a framework to discuss the validity of those assumptions. In R&D, such a model can act as a bridge and discussion platform between groups and opinions within the decision process and is helpful in situations where different preclinical models have different outcomes for the investigative drug. A computational model can then provide an independent test for each opinion in the process by quantifying specific mechanisms and pathways that lead to the specific result and then provide an integrative tool for decision-making process.

The mathematical approach emphasizing neuronal networks and circuits also forces the scientists to explicitly formulate their assumptions in a quantitative way, leading to a better understanding of the human brain biology, often going beyond the single target they are interested in.

Limitations of QSP

Technological barriers include the limit on the complexity of the neuronal networks we can simulate; however, hardware and software advantages together with the availability of cloud computing allow these boundaries to be pushed out considerably. "Big-Science" initiatives such as the Human Connectome and the Human Brain Atlas from the Allen Institute can help build increasingly complex computer models using the human neurophysiology and neuroanatomy information.

QSP will never be able to simulate the complete human brain in detail, but even with incomplete biological implementations, we have shown that this approach can already be successful. Due to the top–down nature, processes with the biggest impact on the clinical outcomes tend to be selected. After all, engineers did not wait for the Grand Unified Theory to be completely solved to develop the transistor.

Other more conceptual limitations include the defeatist nature of the industry ("failure is inherent to the business"), the risk aversiveness of introducing new, untested, and unfamiliar technologies ("why should we embrace new technologies with steep learning curves?"), the milestone-driven nature of drug discovery and limited time horizon of R&D projects ("we have to get a clinical candidate within xx months"). Full acceptance and understanding of this technology necessitates also a new generation of scientists; mathematical-savvy individuals with a clear broad understanding of network physiology, pharmacology, biology, and drug discovery, as opposed to the individuals trained in reductionist-focused educational programs such as molecular biology and genetic analysis.

The QSP as presented here is slightly different from the more traditional systems biology approach. The latter is aimed at interrogating large, omics databases using statistical data mining techniques in a target-agnostic way and uses generic techniques, i.e., the same approach can be used in different indications. Both approaches are complementary, in that systems biology can help identify potential new pathways, that can then be implemented in a more physiological and anatomical rational context on a QSP platform.

In summary, because of the unsustainable failure rate of drugs in clinical development, the pharma industry is forced to embrace new out-of-the-box processes. We believe the time has come to introduce computer-based mechanistic QSP more into the early stages of drug discovery and development to ensure that the best clinical candidate can be advanced using the most efficient clinical trial design for the right patient population.

Acknowledgments. We are indebted to the late Professor Leif Finkel (University of Pennsylvania) who inspired us to develop this platform to find new and better drugs for CNS diseases.

Conflict of interest. H.G., A.S., P.R., and R.C. are employees of In Silico Biosciences that funded the research.

1. Kola, I. & Landis, J.. Can the pharmaceutical industry reduce attrition rates?. *Nat. Rev. Drug Discov.* **3**, 711–715 (2004).
2. Arrowsmith, J. Trial watch: Phase II failures: 2008–2010. *Nat. Rev. Drug Discov.* **10**, 328–329 (2011).
3. Geerts, H. Of mice and men: bridging the translational disconnect in CNS drug discovery. *CNS Drugs* **23**, 915–926 (2009).
4. Hodgkin, A.L. & Huxley, A.F. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.)* **117**, 500–544 (1952).
5. Grasela, T.H. & Slusser, R. Improving productivity with model-based drug development: an enterprise perspective. *Clin. Pharmacol. Ther.* **88**, 263–268 (2010).
6. Spiros, A., Roberts, P., & Geerts, H. A Quantitative systems pharmacology computer model for schizophrenia efficacy and extrapyramidal side effects. *Drug Dev. Res.* **73**, 1098–1109 (2012).
7. Spiros, A., Carr, R. & Geerts, H. Not all partial dopamine D(2) receptor agonists are the same in treating schizophrenia. Exploring the effects of bifeprunox and aripiprazole using a computer model of a primate striatal dopaminergic synapse. *Neuropsychiatr. Dis. Treat.* **6**, 589–603 (2010).
8. Geerts H., Roberts, P., & Spiros, A. Failure analysis of dimebon using mechanistic disease modeling: lessons for clinical development of new AD therapies. *Alzheimer's & Dementia* **8** (suppl.311), P1–307 (2012).
9. Bouteiller, J.M. et al. Integrated multiscale modeling of the nervous system: predicting changes in hippocampal network activity by a positive AMPA receptor modulator. *IEEE Trans. Biomed. Eng.* **58**, 3008–3011 (2011).
10. Hurko, O. & Ryan, J.L. Translational research in central nervous system drug discovery. *NeuroRx* **2**, 671–682 (2005).