Democratizing the use of modeling and simulation with InSilicoTrials' biosimulation platform

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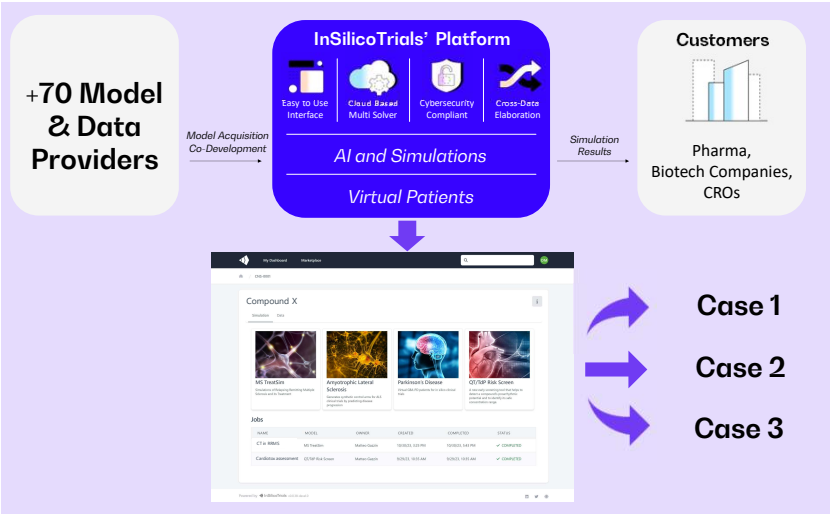
InSilicoTrials

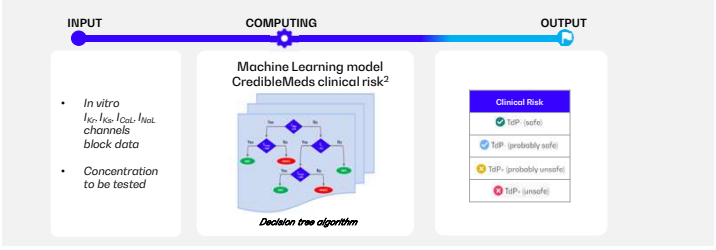
In silico trials are transforming medical research by simulating drug effects in virtual environments, thus reducing the need for traditional experimental approaches. The cloud-based InSilicoTrials' platform (insilicotrials.com) leverages this innovation, enhancing efficiency and ethical standards of drug development[1]. Supported by a global scientific network, the platform hosts healthcare simulation tools for various bench, preclinical and clinical evaluations, and for diverse disease areas. Model templates and simulation tools are seamlessly integrated into user-friendly online applications, allowing users to automatically set up trial scenarios, run simulations and process outcomes. The proposed platform embeds a variety of programming languages (e.g., C++, Python, R, Matlab) and simulation engines (e.g., NONMEM, ANSYS, Abaqus, CodeASTER, OpenFOAM) with no direct access to the solvers by the user. It is built on the Microsoft Azure cloud environment, in compliance with the highest standards of security and privacy (amongst others HIPAA Privacy and Security Rules; ISO/IEC 9001, 20000, 22301, 27017, 27018 and 27001; FDA 21 CFR Part 11 (GxP); Protection Directive 95/46/EC).



CASE1.
EARLY IN SILICO ASSESSMENT OF DRUG-INDUCED CARDIAC RISK

Among the platform tools for preclinical evaluations, the InSilicoTrials platform hosts a collection of complementary models for evaluation of Torsade des Pointes (TdP) risk. These tools require as inputs ion channel block data for each compound, and provide screening and evaluation of the TdP risk. The three tools comprising the suite:

- QT/TdP Risk Screen – A prediction tool combining clinical data, machine learning, and a model of the cardiomyocyte's electrophysiology, which outputs a prediction of clinical TdP risk.
- STrhiPS – A population of virtual human induced pluripotent stem cell derived cardiomyocytes, which outputs behavior of a population of up to 1774 virtual cells under treated conditions.
- CiPA in Silico – Evaluation of TdP risk based on Milnes protocol data on hERG and ion block channel for up to 6 other channels, following the Comprehensive in vitro proarrhythmia assay (CiPA) initiative's in silico protocol.



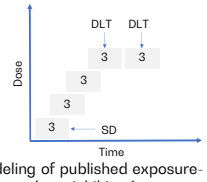
As a case study, ion block channel data for example compound X was entered into QT/TdP, together with data on a selection of the CiPA initiative's test compounds. QT/TdP provides as outputs a prediction of the TdP risk score as in the xx database. Compound X was found to be unsafe (see right).

QT/TdP Risk Screen Results

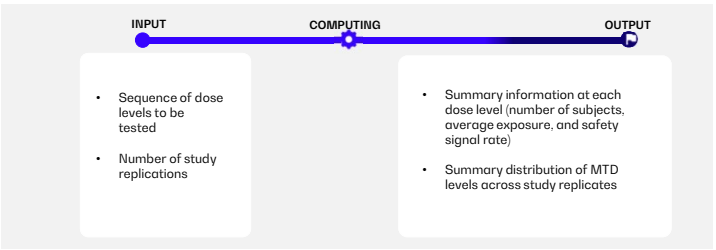
	Cmax (nM)	QT/TdP risk screen
Astemizole	0.26	unsafe
Chlorpromazine	38	probably unsafe
Cisapride	2.6	unsafe
Dofetilide	2	unsafe
Compound X	**1448**	**unsafe**
Ranolazine	1948.2	unsafe
Verapamil	81	safe

CASE 2.
SIMULATING DOSE-FINDING ONCOLOGY TRIALS

The platform incorporates a web-based clinical trial simulator, which allows simulations of dose-finding studies for cytotoxic oncology products. Such studies typically employ a 3+3 dose escalation approach, which determines the maximum tolerated dose (MTD) by enrolling successive cohorts of three patients[3].



The implemented trial simulator was successfully tested with the modeling of published exposure-response data of neutropenia grades from a FIH study of a thymidylate synthase inhibitor[4].

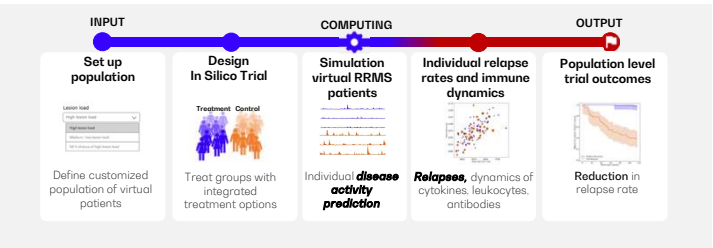


Of 1000 study replicates, the majority (48.8%) were in agreement with the MTD established in the real dose-escalation study[4], providing evidence of the simulator's capability at reproducing real trial scenarios, allowing to explore alternative dose escalation schemes, to assess the impact of variability and sample size on the probability of establishing a MTD, and to compare candidate drugs with different anticipated safety profiles.

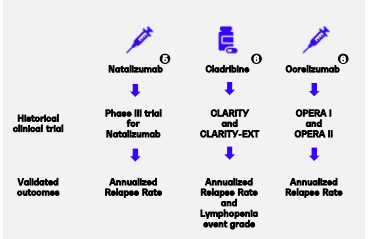
Dose (mg/m²)	MTD probability
20	2.6
30	36.8
40	48.8
50	11.4
60	0.4

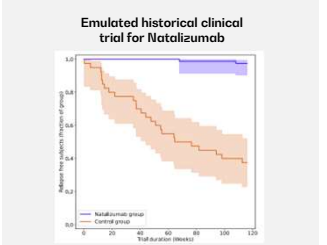
CASE 3. IN SILICO CLINICAL TRIALS WITH RELAPSING-REMITTING MULITPLE SCLEROSIS VIRTUAL PATIENT SIMULATOR MS TREATSIM

The InSilicoTrials platform also incorporates detailed virtual patients representing the pathophysiology and disease progression of individual patients. In MS TreatSim, our virtual relapsing-remitting Multiple Sclerosis simulator, detailed and individualized virtual patients are leveraged to perform large scale in silico studies, emulating a clinical trial or observational study. The treatment effect of a compound is evaluated following integration into MS TreatSim via its Mechanism of Action. Currently, MS TreatSim includes a variety of treatment options, including IFNβ-1a, teriflunomide, natalizumab, ocrelizumab, and cladribine. Novel treatments can be integrated in a custom version of the tool. MS TreatSim's main outcome measure is the occurrence of relapses. However, due to the detailed underlying model, the user is also able to evaluate the effects on immune system components such as populations of T or B cells, or cytokine levels.



As a case study, clinical trials for three of the included treatments (cladribine, ocrelizumab and natalizumab) were recreated with MS TreatSim. In all cases, the changes to relapse rates between treatment and comparator arms were mirrored well by MS TreatSim.





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