InSilicoTrials

InSilicoDISCOVERY

Target and Bioactivity Prediction

Identification of drug-target interactions is of fundamental importance in the discovery process of potential new medicines, as well as in the repositioning or off-target predictions of existing drugs.

Traditional in vitro experiments are time-consuming and costly, whereas in silico methodologies can detect drug-target interactions as efficiently, while cutting time and costs to bring new molecular entities to the preclinical and clinical development phases.

Multi-fingerprint similarity screening

The multi-fingerprint similarity screening algorithm identifies putative drug targets of a query compound based on a reference database extracted from ChEMBL [1]. In addition, it provides an estimation of the bioactivity in terms of Ki, IC50 and EC50 values.

The algorithm relies on the assumption that structurally similar compounds most likely will bind to the same biological targets [2]. The similarity between the query ligand and each of the ligands present in the ChEMBL database is based on the estimate of the Tanimoto scores on 13 unique molecular fingerprints resulting into the identification of similars [3].

Similars' activity predictions are obtained by estimating the most probable activity value and variance towards each relevant target with a well characterized experimental activity in the database.

Advantages

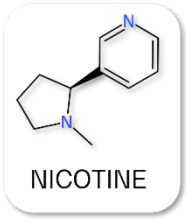
- Identify putative drug targets by screening a large database covering more than 3,000 biological targets and a chemical space based on more than 600,000 molecules
- Quantify drug bioactivity based on more than 1,000,000 activity records
- Repurpose existing drugs through new targets identification
- Detect off-target, potentially harmful drug-target interactions

How it works

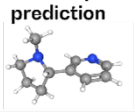
The multi-fingerprint similarity screening algorithm requires as input the structure of the query compound in SMILES notation and it provides as output:

1) The predicted targets ranked according to a global similarity score

2) The estimated bioactivity measures Ki, IC50 and EC50 for each predicted target ranked according to their precision



Bioactivity based screening for quantitative affinity prediction



Target	IC50	Ki	EC50	σ_p
Neuronal acetylcholine receptor; alpha4/beta2:Rattus norvegicus	84.1nM	36.9nM	225nM	1.1:Ki
Neuronal acetylcholine receptor; alpha4/beta2:Homo sapiens	630nM	23.3nM	845nM	1.2:Ki
Neuronal acetylcholine receptor protein alpha-7 subunit:Homo sapiens	3.62μM	345nM	974nM	1.2:Ki
Nicotinic acetylcholine receptor alpha 5 subunit:Musca domestica	1.28μM	4.58μM		1.2:Ki
...	...	...	...	...

Multi-fingerprint similarity-based screening of putative drug targets

Target	Score	Reliability
Neuronal acetylcholine receptor subunit alpha-4/beta-2:Mus musculus	13.00	yes
Acetylcholine receptor subunit beta-like 2:Drosophila melanogaster	13.00	yes
Nicotinic acetylcholine receptor alpha-4/beta-2:Mus musculus	13.00	yes
Neuronal acetylcholine receptor; alpha2/beta2:Homo sapiens	13.00	yes
Transient receptor potential cation channel subfamily A member 1:Homo sapiens	13.00	yes
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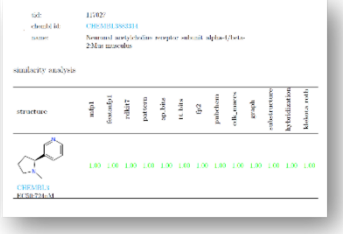

Why working with InSilicoTrials

TECHNOLOGY-ENABLED SERVICES

Ask us for support on technology integration, in silico trials planning, execution and reporting, in line with regulatory requirements

VIRTUAL PATIENTS

Design and accelerate your clinical trials with the virtual patient populations you need

ON DEMAND & CUSTOM

Ask us for the models and simulations you need, or ask us to evaluate where modeling and simulation can support you

SaaS

Buy tokens and use the online products of your choice among those available on the platform

In silico methods can innovate drug research and development

Today, the very long and expensive development and the complex registration processes for new drugs are becoming financially unsustainable.

Regulatory agencies have been encouraging the use of in silico methods in drug research and development for years [2] because the use of these methods can significantly reduce costs and greatly accelerate the go-to-market of new medicines, allowing companies to exploit patents for a longer period. Solvers, IT infrastructure and computational specialists require a continuous investment from companies.

To help solve these challenges, InSilicoTrials Technologies has developed a game-changing-solution. Our experts:

- Select computational models from excellence research centers around the world
- Integrate them in our cloud-based platform
- Make them available through user-friendly online products

This solution enables companies to leverage cutting-edge in silico methods at low costs without specific computational expertise, IT infrastructure and solvers investments requirements. On our cloud-based platform, users can select the online computational product of their choice in pay-per-use or ask us to build the digital product they need.

References:

[1] A. Gaulton et al., "ChEMBL: a large-scale bioactivity database for drug discovery," Nucleic Acids Res., vol. 40, no. Database issue, pp. D1100-1107, Jan. 2012, doi: 10.1093/nar/gkr777.
[2] D. Alberga, D. Trisciuzzi, M. Montaruli, F. Leonetti, G. F. Mangiatordi, and O. Nicolotti, "A New Approach for Drug Target and Bioactivity Prediction: The Multifingerprint Similarity Search Algorithm (MuSSeL)," J. Chem. Inf. Model., vol. 59, no. 1, pp. 586–596, Jan. 2019, doi: 10.1021/acs.jcim.8b00698.
[3] A. Bender and R. C. Glen, "Molecular similarity: a key technique in molecular informatics," Org. Biomol. Chem., vol. 2, no. 22, pp. 3204–3218, Nov. 2004, doi: 10.1039/B409813G.
[4] U.S. Department of Health and Human Services and Food and Drug Administration, "Innovation or stagnation? Challenge and Opportunity on the Critical Path to New Medical Technologies," 2004.