De novo and Fast-Follower Design of Novel Therapeutic Compounds using Cosmos™

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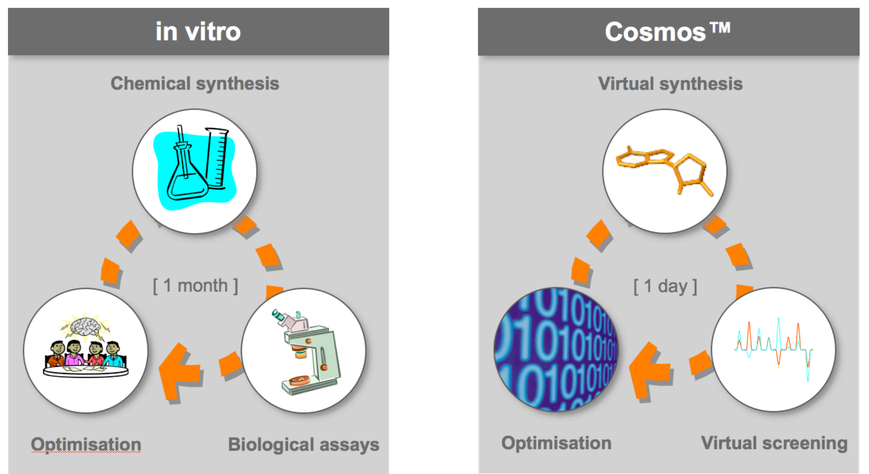
Abstract

Cosmos™ is a proprietary genetic programming suite for the design of lead- and drug-like compounds of novel chemistry. Cosmos™ is based on the combination of innovative virtual synthesis and optimization algorithms with commercially available, as well as proprietary scoring algorithms, such as protein docking and ligand similarity software.

Given this flexibility, Cosmos™ is speeding up the drug discovery process by generating novel compounds in a fast-follower strategy if a reference ligand is known, or by designing entirely new classes of compounds if information about the protein target is known.

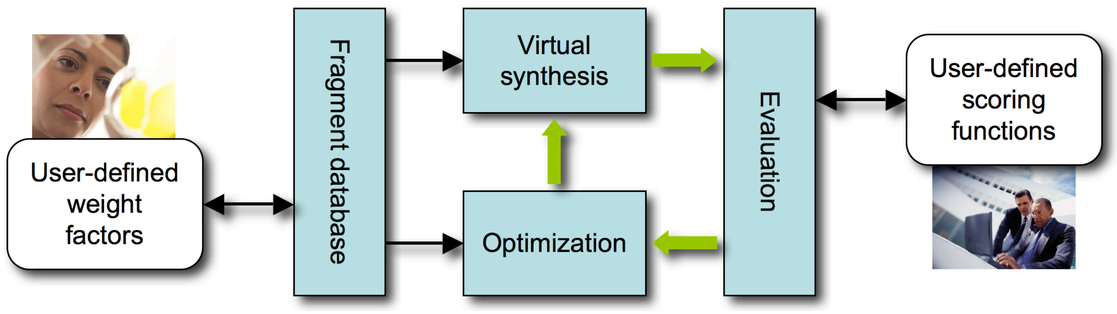
Purpose

The purpose of Cosmos™ is to provide an ***in silico*** alternative for the design of lead- and drug-like compounds. It can be seen as an **idea generator** with great emphasis on **flexibility** and **robustness**.



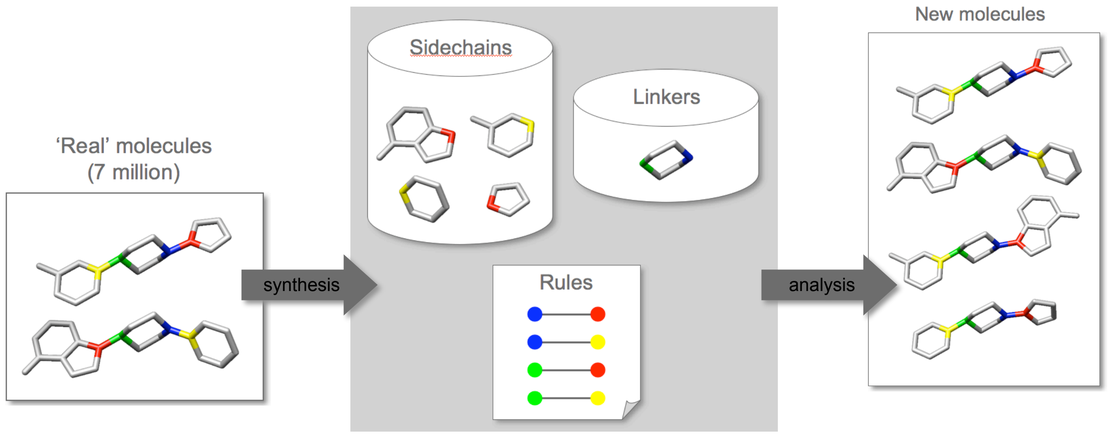
Flexible Design

- User-defined scoring functions
  - Interface via scripts
  - Protein-based evaluation: Fred, Gold, FlexX, ...
  - Ligand-based evaluation: Rocs, Fingerprints, Spectrophores™, ...
- User-defined fragment weighting
- Include additional experimental information
- Guide optimisation process



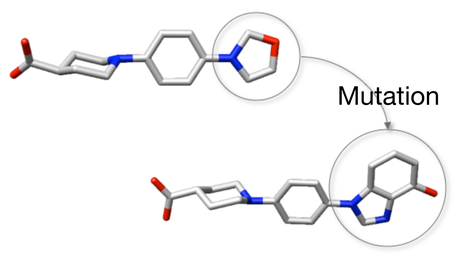
Virtual Synthesis

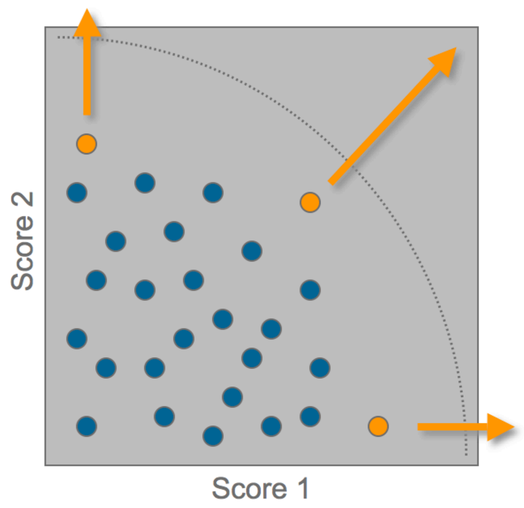
Novel molecules are generated from a set of predefined **fragments** and **connectivity rules**. Both these building blocks and connectivity rules have been extracted from existing compounds, thereby increasing the likelihood that the designed virtual compounds are indeed **synthetically accessible**.



Optimisation

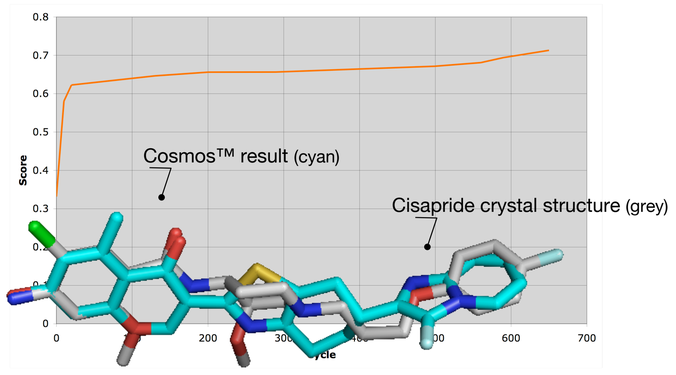
Cosmos™ tries to optimise a population of molecules. When only a **single objective** is given, a standard Genetic Algorithm [GA] is used. For the more complex case of **multiple objectives** (for example, ADME/Tox incorporation) the 'Non-dominated Sorting Genetic Algorithm' [NSGA][1] has been implemented.





Example: Cisapride

To illustrate the process, Cosmos™ was employed to design **novel compounds** having a large shape similarity to **Cisapride**, but with the additional constraint that the resulting compounds should be conformational **less flexible** than the original Cisapride structure. This was achieved by imposing larger **weight factors** to the entire set of ring fragments contained in the fragment database of Cosmos™.



1. Deb, K. et al., A fast and elitist genetic algorithm for multi-objective optimization: NSGA-II. IEEE Trans. Evol. Comp., 2002, 6(2), 182-197.