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e-Newsletter
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No.17, december 2014

Research highlights

Fragment-based molecular evolution for drug design and discovery

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Evolutionary algorithms are actively used for computerized molecular design. But the method often results in many unfavorable structures that contain invalid hetero–hetero atomic bonds such as O–O and N–F.

For this reason, it is required to explore candidate molecules that are expected to have desirable drug actions as well as being chemically feasible.

Yoshimasa Takahashi at Toyohashi Tech and colleagues at Kaken Pharmaceutical Co. Ltd. have reported a similarity-driven simple evolutionary approach to producing candidate molecules that are structurally similar to a reference molecule and yet somewhat different in peripheral chains and/or scaffolds.

The method employs a known active molecule of interest as the reference molecule which is used to navigate a huge chemical space. The initial set of individual structures is prepared with seed fragments and additional fragments using the connection rules defined in advance. The fragment library is preferably prepared from a collection of known molecules related to the target of the reference molecule. New individuals are produced by the crossover and the fragment mutation with the fragment library. In the work, a total of 97,084 bioactive molecules with 313,980 assays recorded in GPCR SARfari of ChEMBL were used to prepare the fragment library.

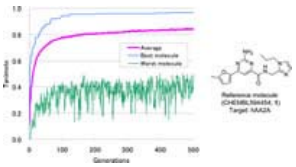

Fig1: Fitness curve in the computational trials of the molecular evolution for the target of hAA2A with the reference molecule 1. The red line shows the total average of the ten trials. The blue line shows that for the best molecule and the green for the worst molecule.

Computer experiments for exploring GPCR ligands with their own fragment library verified the feasibility of this approach to drug discovery.

The method could be used to explore chemically feasible candidate molecules and scaffolds in the huge chemical space for the discovery of a new drug of interest.

Reference:

- Authors: Kentaro Kawai[1], Naoya Nagata[1] and Yoshimasa Takahashi[2].
- Title of original paper: De novo design of drug-like molecules by a fragment-based molecular evolutionary approach
- Journal, volume, pages and year: *J. Chem. Inf. Model.*, **54**, 49-56 (2014).
- Digital Object Identifier (DOI): 10.1021/ci400418c
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- Department website: http://www.cs.tut.ac.jp/