Washington University in St. Louis
Office of Technology Management

RATIONAL DRUG DESIGN USING BOLTZMANN DOCKING

Bowman, Gregory

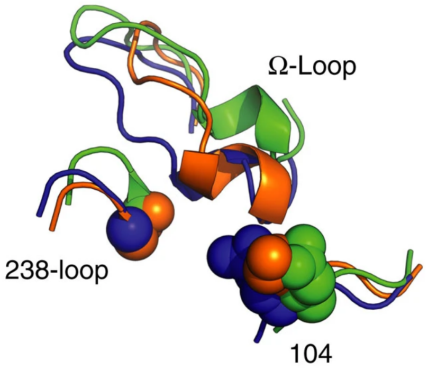
Markiewicz, Gregory

T-016234

Technology Description

Researchers in Greg Bowman's lab at Washington University have developed an improved method for rational drug and protein design called Boltzmann docking. This process better incorporates the dynamic structures of proteins to identify sites for binding that are not revealed in a static structure.

Boltzmann docking uses novel Markov state model (MSM) tools to develop a representative set of protein conformations. Compounds docked against these structures can be weighted for the probability a protein will adopt each structure.



Conformational comparison resulting from Boltzmann docking of TEM-1 β-lactamase showing the structural changes associated with cefotaxime resistance. Two structures from MSMs (non-cefotaximase in green, cefotaximase in orange) are compared to the crystal structure (blue).

Stage of Research

Researchers have developed and validated this technique *in silico*. The method was additionally validated experimentally by analyzing the structural basis for cefotaxime resistance in TEM-1 β-lactamase. Reduced Ω-loop flexibility was correlated with increased cefotaximase activity, a result confirmed by further experiments *in vitro* and *in vivo.*

Publications

- Hart KM, Ho CMW, Dutta S, Gross ML & Bowman GR. (2016). Modelling proteins' hidden conformations to predict antibiotic resistance. *Nature Communications*, 7: 12965.

Applications

- Rational drug and protein design

Key Advantages

- Higher probability of success in drug design
- More effective process for identifying allosteric sites

Patents: US20190147985

Related Web Links: Bowman Profile & Lab