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A set of diagnostic bench tests leads to the development of accurate flexible docking algorithms

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Introduction: An X-ray based geometry force field was applied to PDB data to produce a consistent set of 11.03 all atom binding site models. Geometries are conserved in regions with sharp electron density, elsewhere small movements lead to geometries and energies found at atomic resolution. These models contain multiple complexes for 3,900 unique proteins and are a rich source of information on ligand-induced binding site changes.

Methods: The data is split into learning sets which focus on different challenges to docking prediction: 1) flexible ligand-fixed site; 2) ligand dependent water bridging; 3) predicting side-chain movement. These bench tests can detect and track docking errors. Examination of 3D-images of docked/target poses is also helpful.

Results: These tests are being successfully used to develop new algorithms for QXP. 1) Tests for flexible ligand docking suggested changes which result in large increases in successful predictions (RMS to experimental <0.3 A) . 2) Addition of bridging water improved the numbers of accurate predictions. The algorithm for computing water coordinates was based on the X-ray force field and atomic resolution X-ray data. 3) Side-chain movement: A data base of pairs of structures suitable for cross-docking has been developed. Preliminary results of cross-docking studies will be reported.

Biography

Colin McMartin is currently the CEO of Thistlesoft. He obtained Degree in Chemistry at Cambrige University, England in 2012.

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