3D-QSAR: Machine Learning for Binding Affinity Prediction

Shyamal Nath[1] and Jingyi Chen[1]

[1]*OpenEye, Cadence Molecular Sciences, 9 Bisbee Court Suite D, Santa Fe, NM 87508*

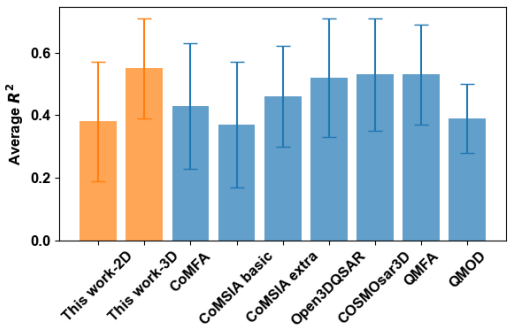
Summary:

- Building ML models featurized with shape, color and electrostatics
- Making predictions with associated confidence
- Using model interpretation to guide design of new molecules

Product Keywords: Orion®, 3D-QSAR, OE Affinity, ROCS®, EON, POSIT

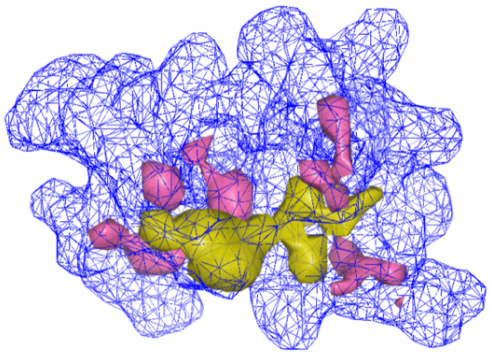
Abstract:

Estimating the binding affinity of small molecules to a protein target using machine learning or QSAR is an enduringly popular method in drug discovery. We have developed a QSAR methodology, 3D-QSAR, for predicting binding affinity that leverages the full 3D similarity of molecules, using shape (from ROCS) and electrostatics (from EON) as featurizations.



3D-QSAR's predictions are on-par with, or better than, published methods.

QSAR models can be limited when predicting beyond their training data. To address this, our 3D-QSAR predictions include error estimates, helping users focus resources on confidently predicted molecules and identify the experimental data that will have the most impact on improving the model. These estimates also guide whether more rigorous methods, like physics-based OE Affinity for free energy calculations, are needed.



Favorable regions for H-bond acceptor (magenta) and donor (yellow) in the binding site. The 3D-QSAR model also provides binding site interpretation of regions preferring specific interactions, which can be used to generate novel ideas for hit optimization.

Our results demonstrate that our models perform on par or even surpass the performance of other methods. Moreover, 3D-QSAR automatically provides prediction error to help users identify the right compounds for the right reasons.

Source: OpenEye CUP Presentation, March 2024, Santa Fe

info@eyesopen.com