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Hybrid machine learning / molecular modeling approaches for design of compounds with desired activity profile: Application to Wnt pathway inhibitors

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One of the major challenges in current drug discovery is the rational design of compounds with desired polypharmacology or selectivity profiles requiring reliable prediction or ranking of activities towards multiple relevant targets. The available molecular modeling approaches such as docking scoring functions or affinity estimates based on molecular dynamics simulations (e.g., MM-PBSA) are often not sufficiently accurate for this purpose. We show that the quality of predictions can be significantly enhanced by using hybrid machine learning models (especially Deep Neural Networks) based on the molecular modeling data. These approaches were successfully applied to the design of the dual target inhibitors of PI3Kα and tankyrase, promising targets for the colorectal cancer therapy.
The molecular docking-based virtual screening workflow can be significantly enhanced by the machine learning approach to the development of target-specific scoring functions. Using the empirical potential values derived from the Smina scoring functions as descriptors, the Deep Neural Network classification models achieve high external test AUC ROC values.
To predict binding affinities from the analysis of short molecular dynamics trajectories, they can be considered as multidimensional time series represented by 2D tensors containing the ligand-protein interaction descriptor values for each timestep. The convolutional neural network models trained on a relatively small dataset provide the best predictive power, outperforming the commonly employed molecular docking and MM-PBSA scores. Thanks to its relatively low computational complexity and the increasing GPU power, this approach can be used as an advanced virtual screening filter for compound prioritization.

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