Pharmacological profiling with universal Generative Topographic Maps

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Generative Topographic Mapping (GTM)[1] has already been proven as a versatile tool in QSAR modeling[2]. Universal Generative Topographic Maps (UGTM)[3] is a new approach that provides 2D representations of chemical space selected for their "polypharmacological competence", *i.e.* the ability to simultaneously represent meaningful classification models (activity landscapes), associated with many distinct targets. Several such UGTMs can be generated – each based on a different initial descriptor vector, encoding distinct structural features. While their average polypharmacological competence may indeed be equivalent, they may nevertheless significantly diverge with respect to the quality of each property-specific landscape.

Eight UGTMs[4] were employed as support for predictive classification landscapes, using more than 600 active/inactive ligand series associated with as many targets from the ChEMBL database (v.23). For nine of these targets, external sets featuring sufficient "actives" and "decoys" were extracted from the Directory of Useful Decoys (DUD) and subjected to a GTM-based virtual screening: each molecule was projected on every class landscape of a particular universal map, and its probability of being active against the corresponding target was estimated. However, consistently accurate predictions for each selected target could not be achieved by any individual map.

We demonstrated that any individual universal map may lack prediction accuracy on a given target-specific activity landscape, however, different UGTMs are complementary and behave in strongly synergistic manner. Consensus application of several maps significantly increases efficiency of virtual screening both in cross-validation and on external test sets on DUD.

Bibliography

[1] Bishop, C. M., Svensén, M., & Williams, C. K. Neural computation, 1998, 10(1), 215-234.
[2] Gaspar, H. A., Baskin, I. I., Marcou, G., Horvath, D., & Varnek, A. J. Chem. Inf. Mod., 2014, 55(1), 84-94.
[3] Sidorov, P., Gaspar, H., Marcou, G., Varnek, A., & Horvath, D. J. Computer Aided Molecular Design, 2015, 29(12), 1087-1108.
[4] Casciuc, I., Zabolotna, Y., Horvath, D., Marcou, G., Bajorath, J., & Varnek, A. J. Chem. Inf. Mod., 2018, 59(1), 564-572.