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Application of 3D-QSDAR for modeling of various biological and toxicity endpoints

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A 3D-quantitative spectral data-activity relationship (3D-QSDAR) approach utilizing fingerprints constructed from simulated NMR chemical shifts augmented with inter-atomic distances was used to model various endpoints. The partitioning of the abstract 3D-QSDAR space into regularly sized elements produced descriptors of integer bin occupancies. Depending on the grid density, data matrices with columns ranging from hundreds to tens of thousands can be generated. To avoid bias, each of the modeled datasets was split randomly into 100 training and hold-out test subsets. A PLS algorithm was employed to extract a fixed number of latent variables and to predict the hold-out test sets. At the end, consensus models based on the averaged predicted values for the hold-out test sets were proposed. The weights of the original bin occupancies can be used to decode the underlying structure-activity relationship.

3D-QSDAR was applied successfully to datasets of: i) 130 estrogen receptor binders; ii) 154 progesterone receptor binders and iii) 444 drugs tested for their ability to cause phospholipidosis. Average R2-s for the hold-out test sets of 0.56 and 0.51 for the estrogens and progesterons respectively were obtained. These compared favorably to earlier reports for the same or similar datasets. For the well balanced phospholipidosis dataset (~50% of the compounds were active) models with accuracy of 0.69, sensitivity of 0.69 and specificity of 0.68 were obtained.

Further comparison with classical descriptor types revealed that the efficiency of 3D-QSDAR descriptors to model biological phenomena lie in their ability to depict localized steric and electrostatic effects encoded in the fingerprints.

Biography

Richard D Beger received his Ph.D. in theoretical biophysics from Purdue University in 1991. He has been at the National Center for Toxicological Research (NCTR), US FDA, in Jefferson, AR for the last fourteen years and is currently the Director of the Biomarkers and Alternative Models Branch in the Division of Systems Biology. He is an author or co-author of over 100 publications including 6 book chapters. After arriving at the NCTR, he initiated research activities using NMR-based and MS-based metabolomics methods to identify non-invasive and tissue-based metabolic biomarkers of drug toxicity, drug efficacy, disease status, and individual susceptibility.

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