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Bridging gaps in the chemical interaction matrix via biclustering across activity-modulated feature space

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In the decade since science first scratched the surface of comprehensive biochemistry via complete characterization of human coding DNA, new paradigms have emerged as more practical platforms for future medical discovery. Prominent among these are chemical genomics and chemical proteomics which collectively embody small molecule / biochemical target interaction knowledge arising from general associative and receptor-specific binding characterization. This complete interaction space might theoretically provide humanity with all requisite knowledge from which to optimize personal therapeutics with minimized side effects, but this matrix of millions of distinct target isoforms crossed by millions of known, potentially bioactive organic molecules is unattainable *in vitro*. Fortunately, representative subsets of the encompassing data (such as are accruing in PubChem) should enable well-crafted informatics techniques to bridge the expanse. Unlike machine learning methods that pursue bioactivity classification across supersets of general ligand and target features, we have found it productive to assess relationships via clustering techniques (wherein activity is treated as a feature rather than an endpoint) that elucidate analogies among subsets of active ligand-target pairs while functionally distinguishing mechanistically unrelated instances. We have developed a protocol to pursue this based on biclustering across an activity-modulated feature space. Our preliminary test cases yield insight with respect to two mechanistically convoluted assays: cytotoxicity within the IEC-6 intestinal epithelial cell line, and human oral bioavailability profiling. The method has natural extensions to mechanistic clustering across target families, with applications to target selectivity optimization and side-effect prediction.

Biography

Gerry Lushington is a chemical informatics research scientist with more than 130 peer-reviewed publications addressing diverse foci including protein structure prediction, structure-based drug design, QSAR, molecular diversity profiling, molecular pathway analysis and proteomics profiling. Lushington has a long track record of cross-disciplinary collaboration and is currently the principal consultant at LiS Consulting. He is the informatics section editor for the journal Combinatorial Chemistry & High Throughput Screening, and is an advisory board member for the Journal of Clinical Bioinformatics, BioMed Central, the Enzyme Inhibition Journal and Current Bioactive Compounds.

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