perform a fast 3D prescreen. The more effective the prescreen is at eliminating false positives, the faster the overall searching time.

Finally, a database screen may return different levels of information, depending on the capabilities of the software and the user's requirements. When the pharmacophore-based screen is being done as a precursor to docking, the user may need to know only the identities of the molecules that match the query. In other cases, the user may wish to see each matching structure aligned to the pharmacophore model. If multiple conformers are searched, a given molecule may yield more than one match, and the user may wish to examine some or all of them. Sorting of matches according to some fitness measure is also common, which allows the user to focus only on what he considers to be a reasonable number of high-ranking hits.

CONCLUSIONS

The past few decades have seen extensive innovation in pharmacophore modeling and continual expansion in its scope of applicability. Thus while a substantial portion of modeling efforts remain devoted to structure-based design, pharmacophore methods continue to be relied on for analysis of complex SAR data, elucidation of key ligand/receptor interactions when crystallographic data are unavailable, measurement of 3D similarity, rapid screening of large chemical libraries, and as a powerful means of combining structure-based and ligand-based knowledge.

The sheer diversity of available pharmacophore methods is a tremendous asset to modern drug discovery, but recognizing the limitations of a particular technique is absolutely critical to its successful application. Likewise, it is important to have realistic expectations about what can and cannot be achieved. A given pharmacophore method may provide any number of plausible solutions to the structure/activity problem, but it rarely points a user directly to the most correct solution. Nor is there any guarantee that all factors governing activity can be embodied in a pharmacophore model, so the picture one obtains is not always complete. Yet if the advantages are leveraged appropriately in light of the limitations, pharmacophore methods are indispensable tools in the drug discovery paradigm.

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