

[P49] Protein active site comparison with SiteHopper: phylogeny to polypharmacology

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There is a long history of using sequence alignment data to understand evolutionary relationships [1]. More recently attempts to use sequence alignment and comparison to predict cross-reactivity and polypharmacology have been made with varying degrees of success [2]. We present a new method, SiteHopper, which rapidly aligns and compares a three-dimensional representation of protein active or binding sites. This method is expected to show superior performance to sequence comparison in compound cross-reactivity/polypharmacology versus sequence because it directly compares the shape and underlying chemistry of different protein binding sites. Case studies will be presented to show that SiteHopper is able to find similarity between binding sites for targets with very different sequences (Figure 1).

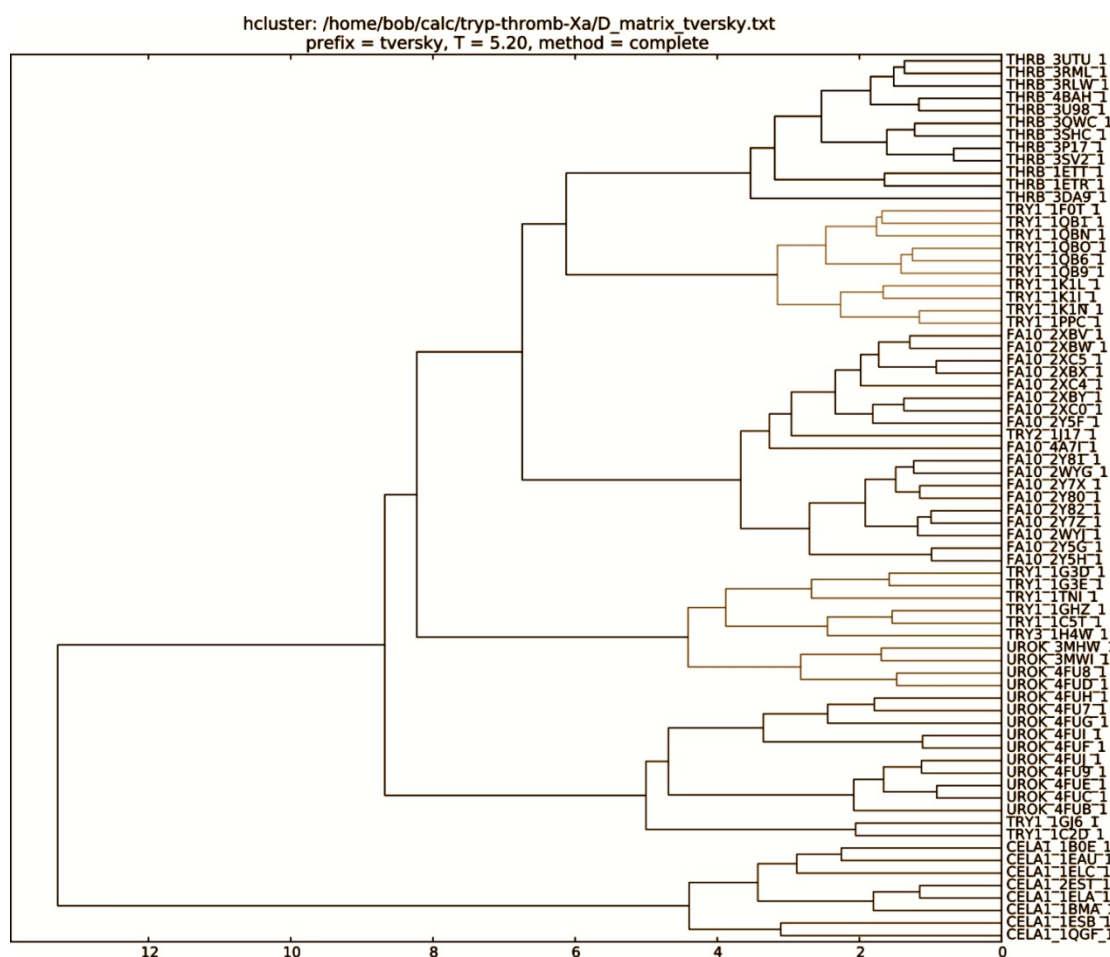


Figure 1: Successful hierarchical clustering of protein active sites from 5 different protein classes based of shape similarities

[1] Lotytynoja, A.; Goldman, N. Science, 320 (2008), 1632–1635.

[2] Kalinina, O.V. et al. Nucleic Acids Res., 2004, 32 (Web Server issue), W424–W428.