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SLiM Pickings: Mining structural and sequence data for the prediction of short linear protein interaction motifs

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Short Linear Motifs (SLiMs) are short functional protein sequences that act as ligands to mediate transient protein-protein interactions (PPI) in critical biological pathways and signaling networks. SLiMs are short (3-15aa), generally tolerate considerable sequence variation and typically have fewer than five residues critical for function. These features result in a degree of evolutionary plasticity not seen in domains and SLiMs often add new functions to proteins by convergent evolution. They also present a challenge for computational identification, making it difficult to differentiate biological signal from stochastic patterns. Despite this, discovering new SLiMs is of great interest due to their potential as therapeutic targets.

In recent years, we have made great progress in SLiM discovery, particularly through development of the SLiMSuite package of bioinformatics tools. SLiMs generally occur in structurally disordered regions of proteins and exhibit evolutionary conservation relative to other disordered residues. SLiMFinder uses this knowledge and exploits patterns of convergent evolution to predict novel, over-represented motifs within a statistical framework with high specificity. Applying this approach to a comprehensive set of human PPI data has highlighted interactome complexity and quality as the next challenges for SLiM prediction. Our latest development, QSLiMFinder ("Query" SLiMFinder) tackles some of these issues by incorporating specific interaction data to restrict the motif search space, which improves both the sensitivity and biological relevance of predictions. We are now using QSLiMFinder to combine structurally defined domain-motif interactions with large-scale PPI data to perform large-scale de novo SLiM prediction.

Biography

Richard J. Edwards received his Ph.D. in genetics from the University of Nottingham before working as a postdoc in The Royal College of Surgeons in Ireland and University College Dublin on protein bioinformatics. He has been leading his own group at the University of Southampton for over five years, where he is now a Lecturer in molecular evolution and bioinformatics. In addition to more than 25 papers, Rich Edwards has written a number of open source bioinformatics tools available as part of the SLiMSuite and SeqSuite packages, including several webservers available at bioware.ucd.ie.

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