# In-complex molecular switching: The need to address complexity in cell regulation

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The first few decades of signalling research were characterised by sustained oversimplification of cell regulatory systems. In particular the space-time compartmentalisation of these systems was dramatically underestimated. It has, though, now become clear in outline, if not yet in detail, how cellular regulatory and signalling systems are constructed. The essential machines are tightly localised protein complexes that effect regulatory decisions by undergoing internal changes of state. The knowledge now being won about the role of natively disordered polypeptide and short linear motifs, suggests that these protein modules are assembled into molecular switch devices within these complexes. Paradoxically these motif modules are both hugely abundant but difficult to research (Ref. 6; Fig. 1). So, despite the many successes in identifying short regulatory protein motifs, it is thought that only the “tip of the iceberg” has been exposed.

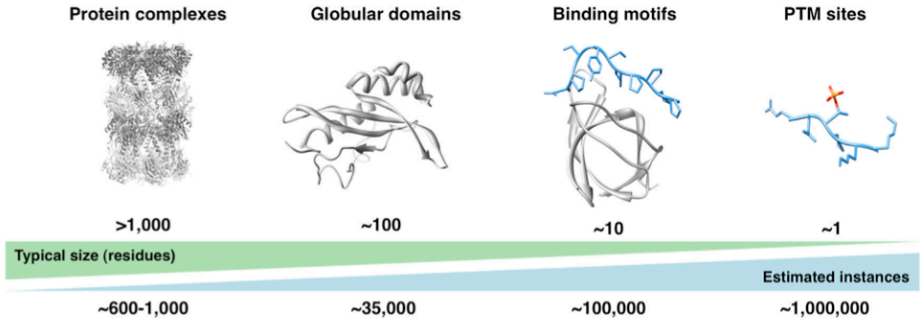


**Figure 1. Functional Modules of Proteins**
Modularity of protein function is manifest at distinct levels, from the recurrent use of whole-protein elements (complexes and structural domains [folds]) to protein parts (binding motifs and modification sites). The figure highlights their typical length scale and estimated number of instances in the human proteome, as outlined in detail in this manuscript.

In the talk, I will review and discuss the nature of cell regulation by in-complex molecular switching. In particular, it needs to be understood that protein complexes are units of biochemical function as are, at a different scale, the individual peptide modules (domains, motifs): Regulatory proteins themselves are not, however, meaningful units of biochemical function but are vehicles for bringing concatenated assemblies of functional peptide modules into the regulatory complexes. Until we face up to the full complexity that the cell can deploy, we will continue to be inefficient in our efforts to find new treatments for diseases of cell regulation.

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