Challenges in structural modeling based on XL-MS data

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Cross-linking and mass-spectrometry (XL-MS) is a low-resolution structural method, which finds pairs of residues that are spatially close in protein complexes. Protocols and software for identifying cross-linked residues in MS data are now fairly established. Yet, means to turn this information into useful structural models are much less established and largely depend on the availability of other structural inputs. In my talk I will present two examples of modeling based on XL-MS that we employed to determine the architecture of the transcription pre-initiation complex. The first example, which was assisted by homologous crystal structures, led to an all-atom model of the WH domain of Tfg2 on the promoter DNA. The second model, which was less constrained, suggested a rough arrangement of the subunits in the TFIIE and TFIIH transcription factors. These very different modeling scenarios illustrate the challenges of using XL-MS data and call for creative approaches to solve them.