X-ray crystallography is routinely used to determine the structures of small molecules (ligands) bound to proteins. Extended studies such as fragment screening probe the protein surface and elucidate information regarding the protein’s flexibility, potentially stabilising rare alternative conformations, identifying allosteric sites or revealing cryptic pockets. However, ligand identification and modelling in X-ray crystallography remains subjective and error-prone: disordered solvent molecules give rise to uninterpretable or misleading density, and ordered solvent may obscure the binding of a low-occupancy ligand. The PanDDA method [1] enables weak signal to be objectively identified in crystallographic datasets though the simultaneous analysis of an ensemble of electron density maps from different crystals. In the case of ligand screening, the PanDDA method enables the identification of weakly-bound ligands by contrasting individual datasets against the background of “ground-state” datasets. After applying a correction to remove this background “noise”, the density for partial-occupancy ligands is revealed, enabling weakly-bound ligands to be confidently modelled. The PanDDA method has been extensively tested in the context of crystallographic fragment screening at the XCHM facility at Diamond Light Source, and greatly increases the amount of structural information that can be derived from these experiments, compared to traditional data-analysis methods.