

## The influence of sequence alignment length of template on the accuracy and quality of homology modelling: Human cytochrome P450 2D6 (CYP2D6)

### Abstract:

Homology modelling is one of the important alternative techniques to X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy in structural determination of protein. CYP2D6 drug metabolizing enzymes have extensively studied prior to the successful determination of its 3D structure using X-ray crystallography. This study is one of the earlier works being carried out before the crystal structure was solved. The enzyme is polymorphic and more than 80 different alleles have been identified. The aim of this study is to identify possible criteria to improve the quality of 2D6 model. Four mammalian crystal structures CYP2C8, CYP2B4, CYP2C9 and CYP2C5 were selected from protein databank as template for CYP2D6 model. Multiple sequence alignment between the selected target and template was performed. Secondary structure prediction was generated using CYP2D6 sequence and the 3D models built based on each template. The quality of the models was evaluated using Ramachandran's plot. The final models were superimposed with CYP2D6 crystal structure. The result shows that not only the sequence identity is important for the template selection but also the alignment length of sequence. The secondary structure prediction of CYP2D6 sequence was found significantly matched the secondary structure prediction of the 3D structures of CYP2D6 models. The stereochemical quality of CYP2D6 models were found adequately satisfied the Ramachandran.plot requirements and comparable to the stereochemical quality crystal structure proteins used as templates and CYP2D6 crystal structure. The criteria set shows that CYP2C8 is the better template for homology modelling of CYP2D6 since it has scored lower E-value and longer alignment length, high sequence identity provided by ClustalW . In addition the secondary structure prediction of the model better matched the consensus and satisfy the criteria of Ramachandran's plot as well it retained lowest RMSD value from the crystal structure. The study concludes to that the length of the sequence alignment is a critical factor in template selection it is also shows the important primary and secondary structure prediction.