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Computational investigation of the binding characteristics of β-amyloid fibrils

Ephraim Felix Marondedze[a], Krishna Kuben Govender[a,b], Penny Poomani Govender[a,*]

[a] Department of Chemical Sciences, University of Johannesburg, P. O. Box 17011, Doornfontein Campus, 2028 Johannesburg, South Africa

[b] Council for Scientific and Industrial Research, National Integrated Cyber Infrastructure, Centre for High Performance Computing, 15 Lower Hope Road, Rosebank, Cape

Town 7700, South Africa
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Abstract

Timely and accurate diagnosis of Alzheimer's disease (AD) remains a major challenge in the medical arena. β-amyloid (Aβ) imaging techniques such as positron emission tomography and single photon emission computed tomography require the use of an imaging probe. To date, only flutemetamol, florbetaben and florbetapir have been approved for clinical use as imaging probes. Design of imaging probes requires a detailed understanding of disease mechanism(s) and receptor-ligand interaction. In this study, molecular docking, molecular dynamics and binding free energies were used to investigate the multiple binding sites exhibited by β-amyloid fibrils. Protein atomic models 2BEG, 5KK3, 2M4J, 2LMN, 5OQV, 2NAO, 2MVX and 2MXU (protein databank codes) were used to investigate the nature and location of binding sites and binding profiles of selected molecules with known affinities. Although amyloid fibrils are known to have multiple binding sites, we demonstrated that model 2MXU possesses one site which is druggable and can bind with common scaffolds currently being used in the imaging of amyloid fibrils. Models 2NAO, 5KK3 and 2M4J revealed that even though multiple sites may be available in some fibrils, the entire protein may not have a druggable site. Molecular dynamics revealed atomic models 2MXU and 2MVX to be the least flexible among the list. The outcomes of this investigation can be translated to assist in designing novel molecules that can be used for brain imaging in Alzheimer's disease.