Unveiling the Water Coupled Conformational Dynamics of Thromboxane and Prostacyclin Synthases by Molecular Dynamics Simulation and Small-Angle X-ray Scattering

Hsiao-Ching Yang (楊小青)*[1] , Cheng-Han Yang (楊承翰)[1] , Ming-Yi Huang (黃明怡)*[1], Shang-Wei Lin (林尚緯) [1],Jyh-Feng Lu (盧志峰)[2] , Jinn-Shyan Wang (王進賢)[2] , Yi-Qi Yeh (葉奕琪)[4] and U-Ser Jeng (鄭有舜)[3,4]

[1]*Fu Jen Catholic University, Department of Chemistry, New Taipei city 24205, Taiwan*
[2]*Fu Jen Catholic University, School of Medicine, New Taipei city 24205, Taiwan*
[3]*National Tsing Hua University, Department of Chemical Engineering, Hsinchu 30013, Taiwan*
[4]*National Synchrotron Radiation Research Center, Hsinchu Science Park, Hsinchu 30076, Taiwan*

A combination of molecular dynamics (MD) simulations and X-ray scattering (SAXS) has emerged as the approach of choice for studying protein structures and dynamics in solution. This approach has potential applications for membrane proteins that neither are soluble nor form crystals easily. We explore the water-coupled dynamic structures of thromboxane synthase (TXAS) and prostacyclin synthase (PGIS) from scanning HPLC-SAXS measurements combined with MD ensemble analyses. Both proteins are heme-containing enzymes in the cytochrome P450 family, known as prostaglandin H_2 (PGH_2) isomerase, with counter functions in regulation of platelet aggregation. Currently, the X-ray crystallographic structures of PGIS are available, but those for TXAS are not. The use of homology modeling of the TXAS structure with ns-ms explicit water solvation MD simulations allows much more accurate estimation of the configuration space with loop motion and origin of the protein behaviors in solution. In contrast to the stability of the conserved PGIS structure in solution, the pronounced TXAS flexibility has been revealed to have unstructured loop regions in connection with the characteristic P450 structural elements. The MD-derived and experimental-solution SAXS results are in excellent agreement. The significant protein internal motions, whole-molecule structures, and potential problems with protein folding, crystallization, and functionality are examined.

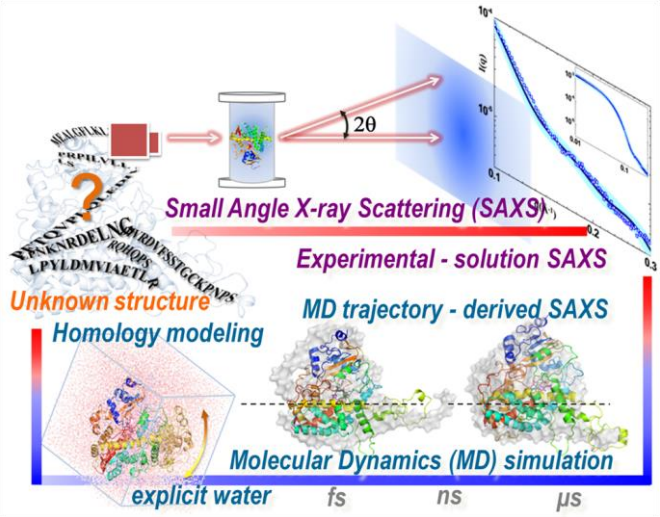

Figure 1: Emerging theorem and approach in the molecular dynamics simulation and small-angle x-ray scattering of water-coupled protein dynamics.

References

[1] Hsiao-Ching Yang et al. ACS Catal. **2018**, *8*, 2534.
[2] Hsiao-Ching Yang et al. J. Phys. Chem. B **2017**, *121*, 11229.
[3] Hsiao-Ching Yang, Jinn-Shyan Wang, and Pi-Tai Chou et al. J. Am. Chem. Soc. **2011**, *133*, 18870.
[4] Hsiao-Ching Yang, and Pi-Tai Chou et al. Nature Communications, **2013**, *4*, 2611.
[5] Hsiao-Ching Yang, and Jinn-Shyan Wang et al. Biochemistry, **2013**, *52*, 6, 1113.