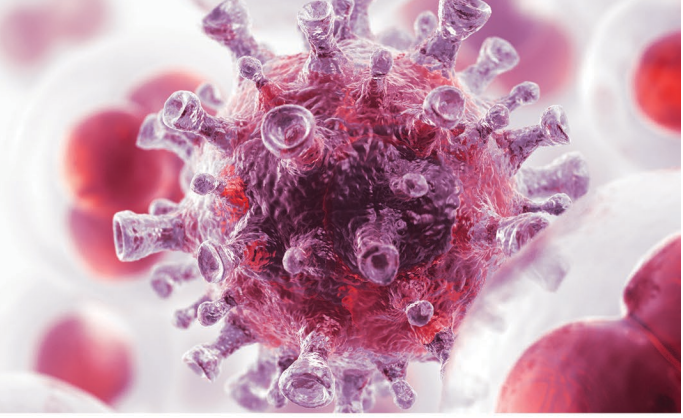
Griffith UNIVERSITY
Institute for Glycomics
Queensland, Australia



2021 Lecture Series

Dr Billy Williams-Noonan

Postdoctoral Researcher,
RMIT University, Melbourne

will present a seminar entitled

Computational free energy methods to assist drug design efforts targeting: (1) HIV-1 integrase (2) influenza virus N2 neuraminidase (3) SARS-CoV-2 s-protein adhesion

Friday 4 June 2021, 11am

Institute for Glycomics
Lecture Theatre (G26 4.09)

(No food or drink allowed in the lecture theatre)

Abstract

The use of computational methods to assist rational drug design projects is becoming increasingly mainstream in medicinal chemistry. Particularly common are molecular dynamics-based free energy methods which can be used to predict the binding free energy of biological complexes, thereby allowing for the prediction of the dissociation constant (K_D). Reliable computational predictions of K_D are useful and have the potential to expedite rational drug design projects by decreasing the laboratory work required. We complement existing evidence for the potential of computational methods in drug discovery projects, and apply free energy methods to assist drug design efforts for three viral drug targets. The targets discussed are: (1) human immunodeficiency virus-1 (HIV-1) integrase, (2) influenza virus N2 neuraminidase and (3) the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein (s-protein) interaction with the host cell. Specifically, we use allosteric HIV-1 integrase ligand complexes as test systems for the comparison of common computational free energy methods that are available, reporting more methods for comparison than in previous works. Using the best method from this comparative study, in a separate study, we predict the binding of the glucuronic acid-based inhibitors of N2 neuraminidase reported by the von Itzstein group and other researchers. We show strong correlations between predicted and experimental measures of N2 neuraminidase inhibition strength ($R^2 = 0.92$, $F = 150$, $p < 0.0001$). Finally, due to the global pandemic caused by the novel coronavirus, SARS-CoV-2, there is an urgent need for viable therapeutic agents for those infected. We report here evidence of a mechanism for potential anti-SARS-CoV-2 therapeutics. By molecular dynamics simulations and free energy analysis, we show that a bound active site inhibitor of angiotensin converting enzyme-2 (ACE2), moderately perturbs the interaction strength of SARS-CoV-2 s-protein adhesion with host cell bound ACE2. This marginal reduction in binding strength is proposed to be due to the induced conformational lability in the ACE2 s-protein binding site when the ACE2 active site inhibitor, MLN-4760, is bound. Future work will aim at quantifying the conformational disorder in the ACE2 s-protein binding site induced by other active site inhibitors of ACE2.

For further information, contact

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