Accurate, Precise and Reliable Binding Affinity Predictions for G Protein-Coupled Receptors

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Abstract

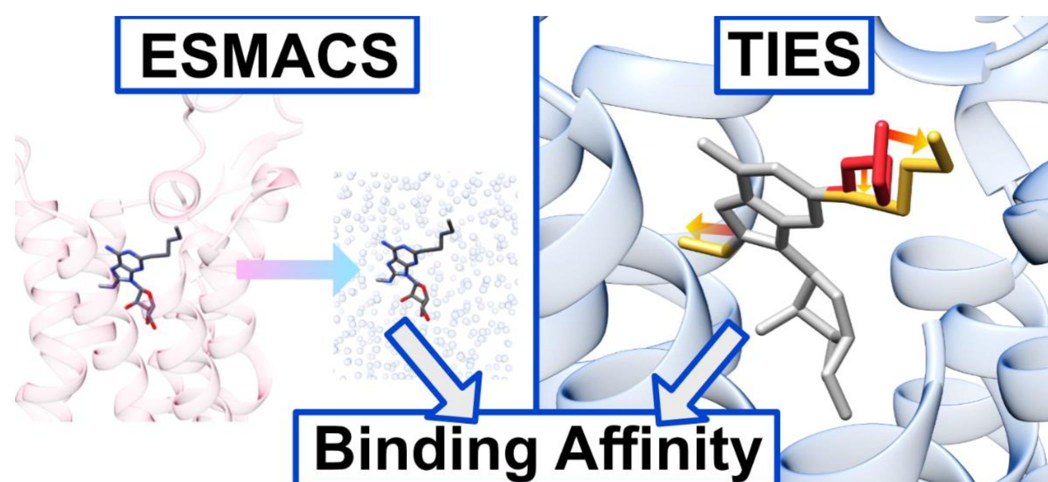

Figure 1: Diagram of the two different protocols, ESMACS and TIES, used to predict binding affinities of GPCR ligands.

There is an urgent need in the pharmaceutical industry for approaches and tools that are able to accurately, rapidly predict binding affinity values. Previous work[1-2] has demonstrated the inability of 'one-off' simulations to accurately, reliably and reproducibly predict the overall conformational states and dynamics of biological systems over a finite period of time. Thus, the use of enhanced sampling techniques is essential for accurate descriptions of binding between a receptor and its ligands. We investigate the application of Enhanced Sampling of Molecular Dynamics with Approximation of Continuum Solvent (ESMACS), and Thermodynamic Integration with Enhanced Sampling (TIES) for computing the binding affinities (see Figure 1) of a series of experimentally verifiable ligands to the A_1 and A_{2A} adenosine receptors (see Figure 2), members of a subclass of the GPCR superfamily.

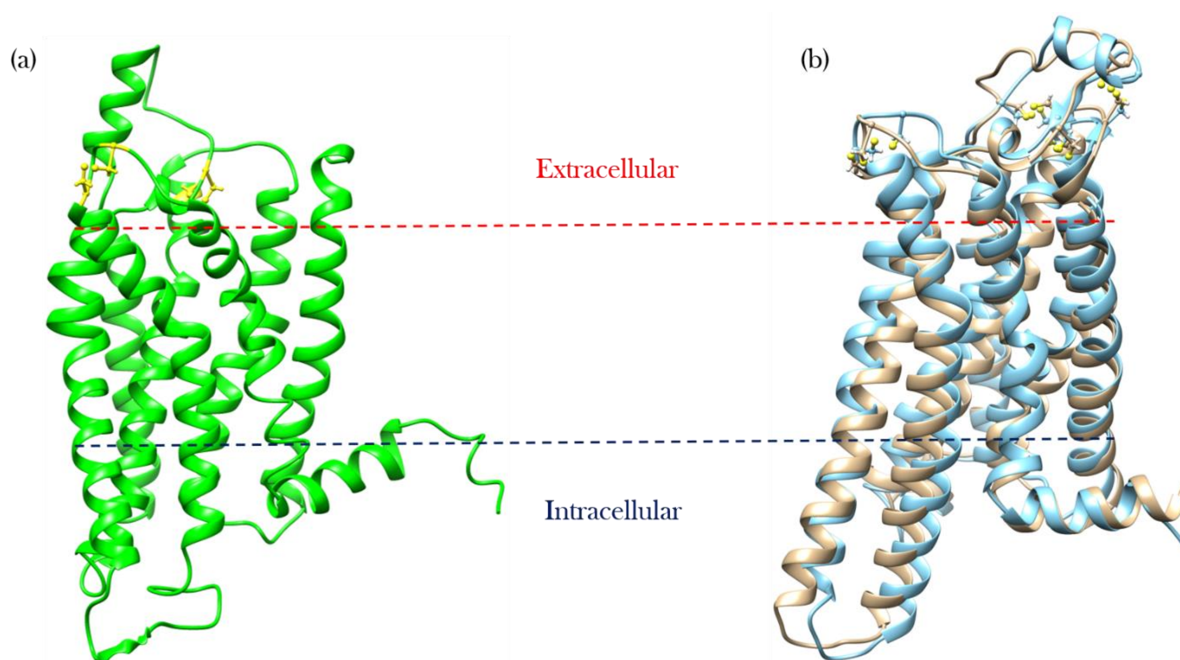

Figure 2: Structures of the (a) inactive A_1 and (b) inactive (beige) and active (blue) A_{2A} receptors in cartoon representation. The cysteine residues involved in disulphide bonds are shown in ball and stick representation.

Both protocols' calculated binding affinity correlates strongly with experimentally-determined binding values. Furthermore, we demonstrate the use of ESMACS to accurately quantify receptor subtype selectivity. In addition, the implementation of configurational entropy in our study allows us to describe the true nature of these receptors and their flexibility. We also show how disulphide bonds influence receptor architecture, activity and function. These results directly correlate with previous experiments[3-4]. Furthermore, we highlight the influence of ligand components on various activities in a receptor through residue fluctuation analyses. The fluctuating residue regions match exactly those previously reported[5]. We show that ESMACS and TIES can be used for the determination of reliable and experimentally-verifiable binding affinities for adenosine receptor subtypes and provide insight into conformational

changes taking place within the receptor during ligand binding, which can inform structure-based drug discovery. We propose that our methodology be extrapolated further within the GPCR superfamily and to other small molecule-receptor protein systems, which are experimentally difficult to investigate.

References

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