Modelling, computation and parameter estimation tools for studies of G-protein coupled receptor signalling dynamics

Lloyd Bridge\(^1\), Lauren May\(^4\), John King\(^2\), Stephen Hill\(^3\)

\(^1\)Department of Engineering Mathematics, University of Bristol, Queen’s Building, University Walk, Bristol BS8 1TR, UK, \(^2\)School of Mathematical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, UK, \(^3\)School of Biomedical Sciences, University of Nottingham, Queen’s Medical Centre, Nottingham NG7 2UH, UK, \(^4\)Department of Pharmacology, Monash University, Clayton, Victoria 3800, Australia

In the literature on G-protein coupled receptor (GPCR) mediated signal transduction pathways, much experimental data and mathematical modelling has been presented which assumes equilibrium conditions. There is significantly less detailed study on the signalling kinetics of such pathways. Recent studies have provided new insights into the kinetics of ligand-receptor interactions and G-protein activation by detailed numerical analysis of a dynamic cubic ternary complex model (Woodroffe et al, 2009 & 2010). Our analysis reveals the appearance of a peak active G-protein (alphaGTP) response at early times after agonist stimulation, followed by reduction to a plateau level. Numerical analysis of the dynamic models highlights parameters which control key reaction steps such as receptor pre-coupling prior to agonist addition, and peak-plateau responses at later times. Asymptotic analysis facilitates a separation of the time scales in each model, giving a clear picture of dominant reaction steps over each time scale — for the parameter regimes studied, agonist binding and receptor activation typically dominate over short times, whereas the full G-protein cycle comes into play over the longest time scale.

The characteristic features of the peak-plateau dynamic response of alphaGTP following agonist administration may be significantly altered by the presence of a second, competing ligand such as an antagonist or inverse agonist. The variety of dynamic responses observed in simulations of agonist-inhibitor competition is far greater than for equilibrium models, and dynamic models represent a means for more detailed characterisation of ligand-receptor interactions. In particular, an agonist-antagonist competition model may simultaneously predict surmountable antagonist effect for equilibrium conditions and insurmountable antagonism for dynamic responses (Bridge et al, 2010). Simulations of inverse agonist effects on constitutively active systems reveal previously unreported potential dynamic response behaviour including undershoots in alphaGTP time courses (Bridge, 2010).

Mathematical modelling has further been employed to quantify ligand-receptor interactions in terms of dynamic binding and cooperativity parameters for adenosine A3 receptor homodimers (May et al, 2011), where we show simulation and computational parameter estimation to be powerful tools for recovering pharmacologically interesting parameters (ligand on and off rates and agonist/agonist, agonist/antagonist and antagonist/antagonist cooperativity factors) from experimental time course data and revealing a range of possible kinetic behaviours.

We conclude that dynamic modelling and parameter estimation have the potential to become invaluable tools for GPCR and pharmacological analysis, to generate experimentally testable predictions and to recover dynamic rate constants from real data. With this in mind, we discuss a work in progress – the development of GPCR Toolbox, a new software package which will implement simulation and parameter estimation routines for a catalogue of ligand-GPCR-pathway models. It is hoped that this toolbox, designed specifically for the pharmacologist rather than the mathematician, will become a computational package of choice within the community.

References:


This work is supported by BBSRC and the Wellcome Trust.