Pharmacophylogenomics: Developing phylogenies as predictive tools in drug discovery

Supervisory team:
Main supervisor: Prof Davide Pisani (University of Bristol)
Second supervisor: Dr Tom Crabbe (UCB)
Dr Parmeggiani Fabio (University of Bristol)

Host institution: University of Bristol

Project description:

The Project: Drug targets are proteins encoded in our genomes that can interact with drugs, triggering physiological responses. The pairing of targets and their targeting drugs is at the core of drug discovery and is accomplished with a combination of bioinformatics and biochemical approaches. Evolutionary principles (e.g. homology1) underpin bioinformatic methods, and it has been argued that an explicit inclusion of phylogenetic methods2 in drug discovery pipelines, the Pharmacophylogenomic approach3, should increase their power. Protein families increase in size by duplication1, and the duplication of a protein that is also a drug target will generate two targets. Phylogenetic methods2 are routinely used to resolve the relationships of duplicated proteins1, including drug targets3. Intriguingly, phylogenetic methods could also be used to predict novel drug targets by phylogenetic implication2, improving the predictive power of drug discovery pipelines. However, this promising area of research is currently underdeveloped.

Your Role: You will use Bayesian methods2 to generate highly accurate phylogenies for all protein families in the human genome. You will use drug-target databases [e.g. 4] to identify drug targets on these phylogenies, and Bayesian character mapping2 to predict new targets. You will model the structure of new drug targets5 and assess drug binding in silico by docking. You will use protein expression data6 to predict the tissues and organs where newly identified drug targets are expressed, which will help delimiting potential area of application and side effects of given drugs. Finally, you will investigate the application of your results to real drug discovery pipelines at UCB Pharma's Slough research site, where you will bring your new approach into the world of a drug-discovery organisation and work within the separate but aligned New Targets, Bioinformatics and Genetics teams to learn through training how to optimise the process with other datasets and tailor it to the standard required for the launch of a hypothetical new portfolio project.

What will you learn: You will gain strong (transferrable) backgrounds in bioinformatics, comparative genomics and pharmacology. You will gain research experience in both the academic and industrial sectors, placing you in an ideal place to pursue a successful career after your PhD.

References: 1. Ohno 1970 Evolution by Gene Duplication. Springer-Verlag, Berlin. 2. Chen et al. 2014. Bayesian Phylogenetics. CRC Press. 3. Searles 2003. Nat Rev Drug Discovery 2:613-23. 4. http://db.idrblab.net/ttd/ 5. Jumper et al. 2021. Nature 596, 583–589. 6. https://www.proteinatlas.org