**Project 1: studying epistatic interactions in rare hereditary disease**

Suited for: bachelor or short master projects in technical domains (bioinformatics, applied mathematics/computer science, systems biology)

Background: many rare diseases are caused by well-known mutations in one or a few specific genes. However, we often see that the phenotype still is different between patients carrying the mutation, and the penetration of the trait is less than a hundred percent. In some cases, patients may even be without symptoms.

These differences can be caused by differences in environmental factors, influencing the outcome by gene-environment interactions. Also, these differences can be caused by the effects of modifier genes that have epistatic, or gene-gene, interactions, with the disease causing gene(s). This is not unexpected as they may affect the expression of the disease causing genes, their products may form protein interactions with the mutated proteins of function in complexes, and so on.

The study of gene-gene interactions is far from easy: where for single gene effects we already deal with multiple testing situations, which lead to a high risk of false positives, and with issues related to degrees of freedom (more variables than samples), this is even more prominent for interactions. When for single genes we may have to study 30,000 genes (ignoring alternative splicing), for pairwise interactions we have to study 30,000^2 combinations. Using non-dedicated methods, this is hardly possibly.

Kristel van Steen’s group at the Université de Liège has developed dedicated analysis methods for the study of epistatic interactions, called MB-MDR. These methods can even be applied to search for epistatic interactions on a genome-wide scale, which requires substantial computational power and a powerful server. When applying to rare disease, where we would have to look for interactions of only one or a few genes with all genes in the genome, the required computational power, however, is much lower: we go back from degree two polynomial complexity, to degree one.

Project: In this project we want to join efforts and combine data from human inherited diseases under study at BiGCaT, UM with the computational tools developed at ULg. As a first disease of interest, we plan to study Rett syndrome (RTT), a rare neurological disease leading to a range of symptoms, mostly in girls. Symptoms include problems with growth, movement and coordination, language, and breathing. Rett syndrome is caused by mutations in the X-chromosomal MECP2 gene, but modifying genes may partially explain differences in severity of symptoms. For this study we will collaborate with experts from the Rett Expertise Centre of the MUMC+ in Maastricht. Alternatively, depending on data availability, other rare diseases may be studied. Supervision will be shared between both universities, with daily supervision at UM, and co-supervision from ULg. Your stand will be at Maastricht University, at BiGCaT.

Contact details: Lars Eijssen - [l.eijssen@maastrichtuniversity.nl](mailto:l.eijssen@maastrichtuniversity.nl) / Kristel Van Steen – [kristel.vansteen@ulg.ac.be](mailto:kristel.vansteen@ulg.ac.be)

Keywords: Genetics, Bioinformatics, Epistasis, Genomics, Rare hereditary disease