Royal Holloway Santander Travel Award Report

By Diego Galeano,
Ph.D. Candidate, 2nd year, Computer Science, RHUL.

The Royal Holloway Santander Travel Award, allowed me to accompany my supervisor, Prof. Alberto Paccanaro, and members of my lab (http://www.paccanarolab.org//people/), to the U.S. and join Gerstein Lab at Yale University for three months (February to April 2017). Prof. Mark Gerstein is Albert Williams Professor, co-director of the Yale Computational Biology and Bioinformatics program at Yale University. Gerstein lab is world leading in the field of structural bioinformatics, with important contributions to structural genomics and proteomics.

My Ph.D. research focuses on developing computational methods for drug repositioning. Drug repositioning aims at finding new therapeutic indication for approved drugs. The most famous case of repositioning through side effects is sildenafil. At first, sildenafil was intended to cure a heart disease but during pre-clinical trials showed an unexpected side effect: involuntary erections. Nevertheless, the drug was repurpose for sexual dysfunction. Most known as Viagra, the drug remains until today, one of the most profitable drugs in the market (revenue of £1.5 billion only in 2008).

Why is drug repositioning important? In short, to save time and money. The drug development pipeline is characterize mainly by the enormous cost (~£1.6 billion) and long-lasting process (~ 15 years). At the end, only one lucky candidate out of the millions of molecules tested will see the light into the market. In fact, recent studies show that high attrition rates occur during clinical testing in humans due to either lack of efficacy, i.e. the drug does not cure the disease; or safety, i.e. severe drug adverse effects.

Under my supervisor guidance, I have been developing constrained latent factor models for drug side-effect prediction, exploiting concepts from the machine learning area of recommendation systems. Although my method provided good performance, the disadvantage of my model was a set of hidden features lacking biological interpretation. A fundamental question to answer in order to understand drug activity at population-level.

The biological expertise of the post-doctoral researchers Dr. Shantao Li and Dr. Chengfei Yan at Gerstein lab helped me to formulate the first hypothesis about the biological meaning of these hidden features in my model. The features could be encapsulating pathways, cellular processes or even cross talk among organs. The answer was not obvious given the variability in drug activity and the incomplete understanding of their mechanism of action. In spite of these limitations, we found that the hidden features were relate to the main therapeutic action of the drug, e.g. only neural system drugs activates in feature 1 and only anti-cancer drugs activates in feature 2. We notice then that we could characterize each drug activity by a phenotypic signature. In fact, we went even further to show that the drug signatures are also related to molecular activity, drug indication, and even drug-drug interactions.

I have also collaborated in projects at Gerstein lab. I worked with the graduate students Mengting Gu, Mateo Torres and the Dr. Cheng Ye in Enhancer prediction. Enhancers are short regions of DNA that contribute to the activation of their target genes. Genome-wide prediction of enhancer regions is important for understanding the regulatory elements in the genome and the many biological processes occurring during gene transcription. We used eight histone marks from mouse hindbrain as features to predict the presence or absence of enhancers. We found that ensemble classifiers such as subspace discriminant analysis and neural network-based architectures perform the best. Besides, we are currently working on tuning our model to improve the performance of the prediction. In addition, I also participated in many discussion with the graduate student Bo Wang and the Dr. Prashant Emani on understanding the role of genetic variants in protein structure and ultimately in drug response.

The research visiting at Gerstein lab at Yale University was, without any doubt, an amazing experience as a Ph.D. student. I had the opportunity to discuss research projects with so many postdoctoral and doctoral students, leading researchers in their respective fields. I have also enjoyed the cultural diversity of the lab and the so many great facilities that Yale University provides to their students (fantastic library and gym!).