You are cordially invited to a talk in the Edmond J. Safra Center for Bioinformatics Distinguished Speaker Series.
The speaker is Prof. Guy Sella, Department of Biological Sciences, Columbia University.

Title: "Quantifying selection and demographic effects on quantitative genetic variation: an application to human height"

Time: Thursday, June 23 2016, at 14:30 Sharp.

Place: Melamed Hall 007, Exact Sciences Faculty

Host: Prof. Eran Halperin, eranhalperin@gmail.com, School of Computer Science and Life Sciences Faculty.

Abstract: The genetic architecture of a quantitative phenotype (i.e., the number, frequency and effect size of alleles underlying variation in its value) arises from genetic and population genetic processes. Mutations affecting the trait appear at a rate that reflects the target size, and their trajectory through the population is determined by demographic processes and by the selection acting on them. Many phenotypes, including human height, appear to be under stabilizing selection, either because of selection on the trait itself or through the effects of genetic variation on other traits (i.e., via pleiotropy). With these considerations in mind, we introduce and solve a generative model for the genetic architecture of a continuous trait under direct and pleiotropic stabilizing selection. We derive simple and robust predictions for the distribution of additive genetic variation among loci. We then relate these predictions to observations from GWAS, accounting for how the power to detect a locus depends on its contribution to additive genetic variation.
This new theory allows us to make inferences about the population genetic processes that underlie genetic variation for height in Europeans. We find an extremely good fit to GWAS findings (Wood et al. *Nature Genetics* 2014): by fitting a single parameter, we are able to explain the distribution of additive genetic variation over the ~700 genome-wide significant associations. Accounting for the demographic history of European populations suggests that the current GWAS is well powered to identify only loci under moderate selection. This relatively weak selection explains why the majority of loci that have been associated with height in Europeans are also segregating in African populations. We estimate the target size and distribution of selection coefficients of mutations affecting height within the range in which the current GWAS is well powered. We then employ these estimates to predict the expected increase in explained heritability with GWAS size due to variants in this range. Our results also suggest how increasing study size will enable the discovery of loci experiencing a wider range of selection effects. The framework presented here can be applied much more broadly, to investigate the genetic and selection parameters governing variation in other quantitative traits.