Title of Project:	Genetics, molecular biology and mathematical modelling applied to understand how mammalian cells deal with gene dosage in S-phase
Cell Mechanism Supervisor Name	Sara Buonomo
Quantitative Supervisor Name	Ramon Grima

Summary of project

Transcription is the process that transforms the sequence of the DNA into a messenger, the RNA, capable of directing the synthesis of the cellular working machine, the proteins. As one would intuitively expect, in bacterial cells the amount of transcriptional output is directly proportional to the amount of template DNA available. During DNA replication, therefore, newly replicated genes display a 2X amounts of transcripts. Unexpectedly, however, in eukaryotic cells, the situation is different, and there is some mechanism to avoid over-representation of proteins encoded by genes that are replicate first during S-phase [1]. However, very little is known about the mechanisms which make this possible, particularly in mammalian cells. In this project the student will combine both mathematical modelling and experimental work to tackle this question, integrating gene expression, replication timing and chromatin immunoprecipitation data from newly replicated DNA (ChOR-seq) [2]. The contribution of the timing of replication to this process will be analysed by Cas9/CRISPR-mediated deletion of key regulators of replication timing [3]. The student will build several different mathematical models of gene expression [4], each with a different plausible mechanism of gene dosage compensation. These models will then be used to design a set of perturbation experiments that can precisely distinguish between alternative mechanisms. The project will be jointly supervised by Dr Buonomo and Professor Grima who have extensive expertise covering all aspects of the experimental and computational methodology.

We are looking for an enthusiastic, flexible and hard-working candidate driven by curiosity and passion for science. A strong background in computer science, applied mathematics, informatics or physics is preferred, but a keen attitude towards experimental work is essential.

1. Bar-Ziv et al. *Trends in Genetics* 32.11 (2016): 717-723.
2. Reverón-Gómez et al. *Molecular cell* 72.2 (2018): 239-249.
3. Cornacchia et al. *The EMBO journal* 31.18 (2012): 3678-3690.
4. Skinner et al. *Elife* 5 (2016): e12175.

What quantitative skills will the student acquire or develop during their PhD project?

Cell biology skills: Mammalian cell culture, RNA isolation, Cas9/CRISPR genome engineering, Repli-seq.
Quantitative skills: Stochastic simulation methods, Mathematical model analysis, Statistical analysis of experimental data, Bayesian inference