**University of Leicester**

**BBSRC MIBTP Studentship Project 2025-6 entry.**

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**Section 2 – *Project Information***

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| **Project Title** | Unravelling age-related gene expression dysregulation through system biology and mathematical modelling. |
| **Project Summary** | |
| Transcription of a human protein-coding gene by RNA polymerase II (RNAPII) is a complex process requiring multiple steps, including transcription initiation, RNAPII pausing and pause release, transcription elongation, and transcription termination (**Figure A**). In addition, transcription is associated with co-transcriptional processes, such as capping, splicing, and cleavage and polyadenylation, and modifications of the chromatin environment. A key factor of transcription regulation is the RNAPII elongation rate, which corresponds to the speed RNAPII is transcribing across the gene body, that has a strong influence on the fidelity of transcription and on co-transcriptional processes. The transcription elongation rate as currently measured experimentally provides a picture averaging multiple confounding variables, including premature termination of transcription (RNAPII not going to the end of the gene), random fluctuations as a consequence of a small number of transcribing RNAPII, and RNAPII stalling, backtracking, and congestion. A better understanding and quantification of these confounding variables is therefore required for improving measurement of RNAPII speed but also for the development of novel mathematical models of transcription.    Dysregulation of transcription activity frequently occurs in disease, including cancer and some developmental disorders, but is also a cause and consequence of ageing. Indeed, several research groups have found that ageing is associated with a reduced chromatin compaction and higher RNAPII elongation rate and RNAPII backtracking [1]. However, the exact contribution of the multiple confounding variables in transcription and how they could contribute to the increased RNAPII elongation rate in ageing remain poorly understood. We are therefore in need of quantitative measurements and mathematical models of transcription regulation to inform on the influence and weight of different factors controlling the transcriptional output observed in genome-wide experiments and how these factors change during ageing.  The two major aims of the project are to:  1. Quantify the contribution of the different confounding variables to RNAPII elongation speed using genome-wide datasets (RNA-seq, ChIP-seq, MNase-seq, and nascent transcription techniques such as PRO-seq) and bioinformatics approaches.  2. Develop new mathematical models of regulation of gene expression that explain these quantitative measurements [2, 3] (**Figure B and C**).  The project will therefore be of interest to a student with biology/bioinformatics, computational, mathematics, or physics background who wants to gain expertise in next generation sequencing data analysis and mathematical modelling of gene expression data. The PhD project will provide important insights into how RNAPII transcription becomes dysregulated during ageing, which could open new approaches to counter ageing-related dysregulation of gene expression.  Techniques that will be undertaken during the project  The project will combine bioinformatics analyses of multiple genome-wide datasets, including ChIP-seq, RNA-seq, and nascent transcription techniques (PRO-seq, mNET-seq, POINT-seq), with mathematical modelling. Depending on focus and student’s background and interests, a range of numerical methods can be applied for this project including statistical analyses, mechanistic modelling, and physics-informed AI. If the student is interested in the experimental side of the project, but it is not a requirement, there will be opportunities to perform experiments (cell culture, generation of genome-wide datasets, and other molecular and cellular techniques as needed). | |
| **References** | |
| [1] Papadakis A, et al (2023). Age-associated transcriptional stress due to accelerated elongation and increased stalling of RNAPII. Nature Genetics (and references wherein).  [2] Cavallaro, M et al (2023). Bayesian inference of polymerase dynamics over the exclusion process. Royal Soc. Open Sci.  [3] Yazdani A et al (2020). Systems biology informed deep learning for inferring parameters and hidden dynamics. PLoS Comput Biol. | |