Name	NICHOLAS LUSCOMBE
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2012

Career History

1996-2000: PhD in Structural Biology, UCL
2000-2004: Post-doctoral Research Associate, Yale University
2005-2012: Group Leader, EMBL European Bioinformatics Institute

Major Awards, Honours and Prizes

2019: Finalist (with Rickie Patani), Lancet Research Award 2019, Royal College of Physicians Excellence in Patient Care
2017: Winner, Best Public Sector Project, UK Cloud Awards 2017 (with eMedLab)
2015: Fellow of the Royal Society of Arts
2013: Elected member of the European Molecular Biology Organisation
2006 - 2011: Senior Research Fellowship, Wolfson College, Cambridge, UK

Membership of external committees, editorial boards, review panels, SABs etc

Academic committees
UCL Division of Biosciences IT Committee (Chair, 2015-2016)
MRC Skills Development Fellowships (2017-2020)
Wellcome Trust Expert Review Group (2017)
Finnish Academy of Sciences (2009-2011)
Academic reviews
Scientific Computing Review, Okinawa Institute of Science & Technology (Chair, 2016)
UCL Faculty of Life Sciences Computing Review (Chair, 2015)
Conference Organiser
Cold Spring Harbor Asia Computational Biology of the Genome, China (2020-present)
Winton-CRUK Conference Series on Big Data Analytics (2013-2018)
Wellcome Trust Functional Genomics & Systems Biology Meeting (2009-2015)
EMBO Meeting “Advances in Prokaryotic Genomics” Session (2010)
Bioinformatics & Genomics Workshop, Rio de Janeiro, Brazil (April 2008)
CSHL Functional Genomics & Systems Biology Meeting (2007)

Lab Name	***Bioinformatics & Computational Biology Laboratory***

Research programme and achievements

Past work

How do cells recognise and respond appropriately to diverse internal and external stimuli? By ensuring the correct gene expression at the right times and places, regulatory systems control diverse cellular behaviours. Our laboratory undertakes interdisciplinary approaches, using computational and statistical methods to quantify complex molecular and genomic measurements. In this way, we are able to address complex yet far-reaching questions in biology, particularly:

1. How do transcriptional and post-transcriptional regulatory mechanisms control gene expression? We answered such questions by building, for example, extraordinarily accurate and predictive statistical models for transcriptional regulation, which provide insights into molecular mechanisms.
2. How do these mechanisms regulate important biological systems? We explored the use of distal regulatory elements and mRNA splicing during cell-state transitions such as neural development.
3. How do regulatory systems interface with molecular evolutionary mechanisms? Specifically, we examined how mutation rates in genomes are influenced by interactions with components of the gene regulatory system.

In taking a genomic perspective, we uncover general principles that apply across many biological conditions; features unique to individual systems can then be understood within this context. Ultimately, we wish to achieve quantitative explanations of how regulatory systems interpret the information encoded in the genome; in doing so, we seek to predict and modulate the molecular mechanisms by which cellular decisions are made.

Future work

We have spent the last 12 months consolidating our computational work within a background of neural development and degeneration, specifically the development of motor neurones and their untimely destruction in amyotrophic lateral sclerosis (ALS). The availability of representative *in vitro* human and mouse models, combined with sensitive techniques such as single-cell measurements, means that high-resolution -omic investigations are now possible for the neural system and give hope for targeted molecular therapeutic development. We shall address the following questions in the next review period.

1. Can we quantitatively model and modulate transcriptional regulation during neural development?
2. What post-transcriptional systems are involved in neural development?
3. In what way do these mechanisms break down to cause ALS?

The three strands of work are anchored by the computational analysis of genomic datasets - for example, advanced integration of binding site measurements with functional readouts - and development of statistical models that are biologically interpretable. We will focus on close collaborations with James Briscoe (Crick), Jernej Ule (UCL, seconded to Crick) and Rickie Patani (UCL, seconded to Crick). I will continue with a laboratory of 12 researchers equally divided between the three subject areas; some will be wet/dry scientists co-supervised with one of our collaborators. Proteomics is a new area of particular interest throughout, which will give us orthologous insights into the nature and abundance of interacting molecules.

Research outputs

Ghahramani, A., Watt, F.M., and Luscombe, N.M. (2018) *Generative adversarial networks uncover epidermal regulators and predict single cell perturbations*. bioRxiv. DOI: 10.1101/262501

- A completely novel, orthogonal method for analysing single-cell RNA-seq data, inspired by developments in image-analysis algorithms.
- Trained models simulate realistic single-cell RNA-seq data that covers the full range of cell types.
- Internal parameters of the algorithm can be interpreted in multiple ways to provide biologically meaningful insights into the data.
- Most interesting interpretation is latent space interpolation, a general way to examine trajectories between two or more cells.

***Metzis, V., *Steinhauser, S., Pakanavicius, E., Gouti, M., Stamataki, D., Ivanovitch, K., Watson, T., Rayon, T., Mousavy Gharavy, S.N., Lovell-Badge, R., Luscombe, N.M., and Briscoe, J. (2018). *Nervous System Regionalization Entails Axial Allocation before Neural Differentiation*. Cell 175, 1105–1118.e17. DOI: 10.1016/j.cell.2018.09.040**

- Re-writes textbook model about the order of events in neural development.
- Examines enhancer accessibility, measured using ATAC-seq, as a sensitive method for defining cell types.
- Advanced statistical analysis and large-scale integration of public datasets identifies differentially accessible enhancers and the features that distinguish them from each other.
- Confirms distinguishing features *in vivo*.

***Luisier, R., *Tyzack, G.E., Hall, C.E., Mitchell, J.S., Devine, H., Taha, D.M., Malik, B., Meyer, I., Greensmith, L., Newcombe, J., Ule, J., Luscombe, N.M.+, and Patani, R.+ (2018). *Intron retention and nuclear loss of SFPQ are molecular hallmarks of ALS*. Nat Commun 9:2010. DOI: 10.1038/s41467**

- Amyotrophic lateral sclerosis (ALS) is incurable and invariably fatal, with a lifetime risk of 1 in 400. Avenues for treatment is desperately needed.
- Reveals the earliest molecular events that apply universally to familial and sporadic ALS.
- Detailed statistical analysis of RNA-seq data reveals ~200 transcripts that aberrantly retain long introns at a very early stage of neural development.
- Identifies RNA-binding proteins that regularly bind their own transcripts, mislocalise from the nucleus to the cytoplasm.
- Observations suggest the beginnings of protein aggregation observed at later disease stages, giving insights into possible early stage mechanism.

***Mifsud, B., *Tavares-Cadete, F., Young, A.N., Sugar, R., Schoenfelder, S., Ferreira, L., Wingett, S.W., Andrews, S., Grey, W., Ewels, P.A., Herman, B., Happe, S., Higgs, A., LeProust, E., Follows, G.A., Fraser, P., Luscombe, N.M.+, and Osborne, C.+ (2015). *Mapping long-range promoter contacts in human cells with high-resolution capture Hi-C*. Nat. Genet. 47, 598–606. DOI: 10.1038/ng.3286**

- Describes a new high-throughput HiC method that enriches for promoter regions.

- Identifies a regulatory network of physically interacting promoters and non-promoter regions; many of the latter have hallmarks of gene regulatory activity.
- Opens a new avenue for interpreting the mechanism of action for intergenic disease-associated SNPs.
- Many SNPs overlap with interacting enhancers, thus potentially altering the regulation of the partner gene.

Sugimoto, Y., Vigilante, A., Darbo, E., Zirra, A., Militti, C., D'Ambrogio, A., Luscombe, N.M.+, and Ule, J.+ (2015). ***hiCLIP reveals the in vivo atlas of mRNA secondary structures recognized by Staufen 1*****. Nature** ***519*****, 491–494. DOI: 10.1038/nature14280**

- Introduces a new method to measure RNA-RNA duplexes bound by a double-stranded binding protein.
- Identifies hundreds of previously unseen mRNA secondary structures, with many duplexes spanning thousands of intervening bases.
- Long-range duplex structures occur in mRNAs encoding for specific protein functions and have an effect on translational efficiency and transcript stability.