PEP-NET

Predictive Epigenetics:
Fusing Theory and Experiment

Call for Applicants – 14 Early Stage Researcher Positions available within the H2020-MSCA-ITN-2018 project (grant no. 813282) "PEP-NET" - Predictive Epigenetics: Fusing Theory and Experiment

Deadline: 30th April 2019

Applications are invited for 14 Early Stage Researcher (ESR) 3-year fixed-term positions to be funded by the Marie-Skłodowska - Curie Innovative Training Network "PEP-NET" (http://www.ringroselab.com) within the Horizon 2020 Programme of the European Commission. This network, led by Professor Leonie Ringrose (Humboldt University, Berlin), brings together 16 academic laboratories and companies who have pioneered the successful combination of theoretical and experimental epigenetics. Please read the information package provided on pages 9-16 of this document which contains details of host labs and of individual projects.

Benefits

The selected candidates will receive a 36-month, full-time employment contract as per Marie Skłodowska-Curie Actions (MSCA) regulations for early stage researchers. The monthly salary will be confirmed upon offer, paid in the currency of the host country, and with a correction factor applied to the host country. Marie Curie ITNs provide a highly competitive salary to the ESR, including a competitive monthly living and mobility allowance and (if eligible) a monthly family allowance. https://ec.europa.eu/research/mariecurieactions/

How to apply

Please fill out the application form on pages 1-8 of this document. Please send the following as a **single** pdf to pepnet.bio@hu-berlin.de

- Application form
- Transcripts and certifications from University: Bachelor and master degrees, including class ranking if possible
- Certificate of English qualification if appropriate
- Curriculum vitae of at most 3 pages. Europass C.V. format preferred (https://europass.cedefop.europa.eu/documents/curriculum-vitae)

Candidates selected for interview will be informed by 31.05.2019 at the latest. (Note the deadline and interview date may vary for each position, details are given in "application_info.pdf"

Education Requirements

Bachelors and Master Degree or equivalent in biochemistry, molecular biology, bioinformatics, computational biology, biological engineering, mathematics or physics. Master's degree or equivalent must be completed at the time of appointment. A high proficiency in spoken and written English is required.

Marie Skłodowska - Curie ITN eligibility requirements

- The positions are open to all nationalities.

- At the time of hiring (i.e. at the start of the contract), applicants may not have lived or carried out their main activity (work, studies) in the country in which they are hired, for more than 12 months in total in the 3 years immediately before the date on which they start their contract.

- Early-Stage Researchers (ESRs) must, at the date of starting their contract, be within the first four years (full-time equivalent research experience) of their research careers and have not been awarded a doctoral degree.

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Application form

Application form for recruitment of 14 3-year PhD fellowships in the EU-funded Marie Sklodowska Curie Innovative Training Network (ITN) "PEP-NET- Predictive Epigenetics: Fusing Theory and Experiment.

Please see pages 9 - 16 for detailed information on the individual projects

How to apply

Extract the application form (pages 1 to 8 of this document), complete all fields.

Please type your answers if possible. This is best done in Adobe Acrobat using "Tools>Content>Add or Edit Text Box". If you do not have Acrobat, please use CLEAR handwriting and scan the filled form.

Please submit the application form and all other required documents (see section 6) as a single pdf to pepnet.bio@hu-berlin.de.

Incomplete applications will not be considered.

1) Personal data

Submission date: _____

Surname: _____

First name: _____

Title: ❑ Ms. ❑ Mr. ❑ Other (please specify) _____ ❑ Rather not say

Street: _____

Postal code / city: _____

Country: _____

Phone (home or work) _____

Phone (mobile): _____

Email: _____

Date of birth: _____

Place of birth: _____

Nationality: _____

First language: _____

Preferred start date: _____

Country/ countries of residence since March 2016: (please give month and year of arrival and departure if you have moved)

2016 _____

2017 _____

2018 _____

2019 _____

Country/ countries of the labs to which you wish to apply (up to three, see section 3). Please note the EU mobility rule: As a PEP-NET fellow you cannot join a lab if you have lived in that country for more than 12 months (total) in the three years prior to starting your contract. Please do not apply to labs for which you are not eligible!

1st choice _____

2nd choice _____

3rd choice _____

❑ I affirm the correctness of all information and documents, and I herewith apply for the PEP-NET PhD Program

❑ I hereby confirm that all the information provided in this application is complete and give my permission that all data concerning my application may be distributed among the supervisors involved in the selection procedure. *If you do not agree, your application cannot be processed further according to German laws for protection of personal data*

2) Education

Masters degree

Dates: From _____ To _____

Title of the degree: _____

University / college: _____

Date of graduation: _____

Final score(s) if known: _____

Please briefly explain the grading system of the country in which you did this degree:

_____

_____

Title of thesis: _____

_____

Host lab: _____

Abstract:

If you do not have a Masters degree you may still be eligible for the program. Please list equivalent qualifications or experience here.

Bachelors degree

Dates: From _____ To _____

Title of the degree: _____

University / college: _____

Date of graduation: _____

Final score(s): _____

Please briefly explain the grading system of the country in which you did this degree, if different from your Masters:

_____

_____

Title of bachelors thesis or final project: _____

_____

Host lab: _____

Honours, publications and awards:

Honours and awards: _____

Travel grants and scholarships: _____

Publications (give PUBMED ID). : _____

_____

English proficiency

To be accepted for this program you need to have a good command of the English language. Please indicate which formal English test you have attended and how you scored. Alternatively. Please make other comments about your English skills (e.g, Native language, Education in English etc)

3) Interest in specific projects

You may apply for up to three positions from the list below (see pages 9-18 of this document for more information on projects, supervisors and host institutions). If you apply to more than one position, please indicate the preferred order (use the box on the left to indicate your preference, with 1 indicating first choice.) Please send only one application to the central PEP-NET coordinator pepnet.bio@hu-berlin.de

For **ESR2 only**, please also send your pdf to pepnet.bio@hu-berlin.de AND to Edda Schulz edda.schulz@molgen.mpg.de

- ☐ **ESR 1** (Humboldt University Berlin, Germany)
  Visualising and modelling Polycomb/Trithorax (PcG/TrxG) regulation in real time
- ☐ **ESR 2** (Max Planck Institute for Molecular Genetics, Berlin, Germany)
  Model-driven quantitative dissection of a bistable epigenetic switch in X-chromosome inactivation
- ☐ **ESR 3** (John Innes Centre, Norwich, UK)
  Combining analogue and digital modes of gene regulation
- ☐ **ESR 4** (University of Copenhagen, Denmark)
  Modeling cellular memory governed by the Polycomb and Trithorax group (PcG/TrxG) proteins.
- ☐ **ESR 5** (Friedrich Miescher Institute, Basel, Switzerland)
  Three- dimensional chromatin organisation and transcriptional regulation in single cells.
- ☐ **ESR 6** (Humboldt University Berlin, Germany)
  DNA sequence determinants of Polycomb targeting in flies and vertebrates.
- ☐ **ESR 7** (Humboldt University Berlin, Germany)
  Polycomb Targeting in the context of 3D chromatin organisation.
- ☐ **ESR 8** (IGBMC, Strasbourg, France)
  Modelling transcription factor mitotic bookmarking in adynamic chromatin structure
- ☐ **ESR 9** (San Raffaele Hospital, Milan, Italy)
  Transcription factor search mechanism, chromatin mobility and organisation upon DNA damage
- ☐ **ESR 10** (Max Delbrück Centre for Molecular Medicine, Berlin, Germany)
  Investigating long-range chromatin contacts during early cell fate decisions in mouse embryos
- ☐ ~~**ESR 11** (University of Oxford, UK)~~ This position has been filled and is no longer available
  ~~Relating the 3D organisation of chromatin to antisense transcription~~
- ☐ **ESR 12** (University of Naples Frederico II, Italy)
  Understanding chromatin 3D organisation and its underlying physical mechanisms
- ☐ **ESR 13** (Diagenode, Liege, Belgium)
  Developing technologies for analysis of long non-coding RNAs and investigation of their role in long-range chromatin contacts
- ☐ **ESR 14** (Diagenode, Liege, Belgium)
  Computational methods for chromatin conformation investigation
- ☐ **ESR 15** (University of Oxford, UK)
  Modelling parameters for resetting higher order chromatin structures

4) Research interests and motivation

For each project to which you wish to apply, please briefly explain why you are interested in that project, and what relevant skills and experience you have.

Rank	ESR No.	Supervisor/ Country	Motivation/ relevant experience (max. 150 words per project)
1st choice			
2nd choice			
3rd choice			

Please briefly explain why you want to join the PEP-NET PhD training program, and how you think the program will help your future career (200 words max)

Write a short essay (200 words max) on a relevant scientific paper of your choice

Which of your undergraduate courses did you find most inspiring and why? (100 words max):

5) References

Please give contact details of at least two referees who have agreed to provide a reference for you. We will contact you referees if you are being considered for an interview.

First referee

Name and title:_____

Email: _____

Institution: _____

Phone: _____

Association with the candidate (e.g, Undergraduate advisor, Masters supervisor, colleague etc).

_____

Second referee

Name and title:_____

Email: _____

Institution: _____

Phone: _____

Association with the candidate (e.g, Undergraduate advisor, Masters supervisor, colleague etc).

_____

Supplementary information: How did you hear about this program?

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6) Required documents

Please compile **a single pdf document** comprising:

1) The completed application form (pages 1 to 8 of this pdf)
2) Transcripts and certifications from University: Bachelor and master degrees, including class ranking if possible
3) Certificate of English qualification if appropriate
4) Curriculum vitae of at most 3 pages. Europass C.V. format preferred (https://europass.cedefop.europa.eu/documents/curriculum-vitae)

Send your pdf to (pepnet.bio@hu-berlin.de)

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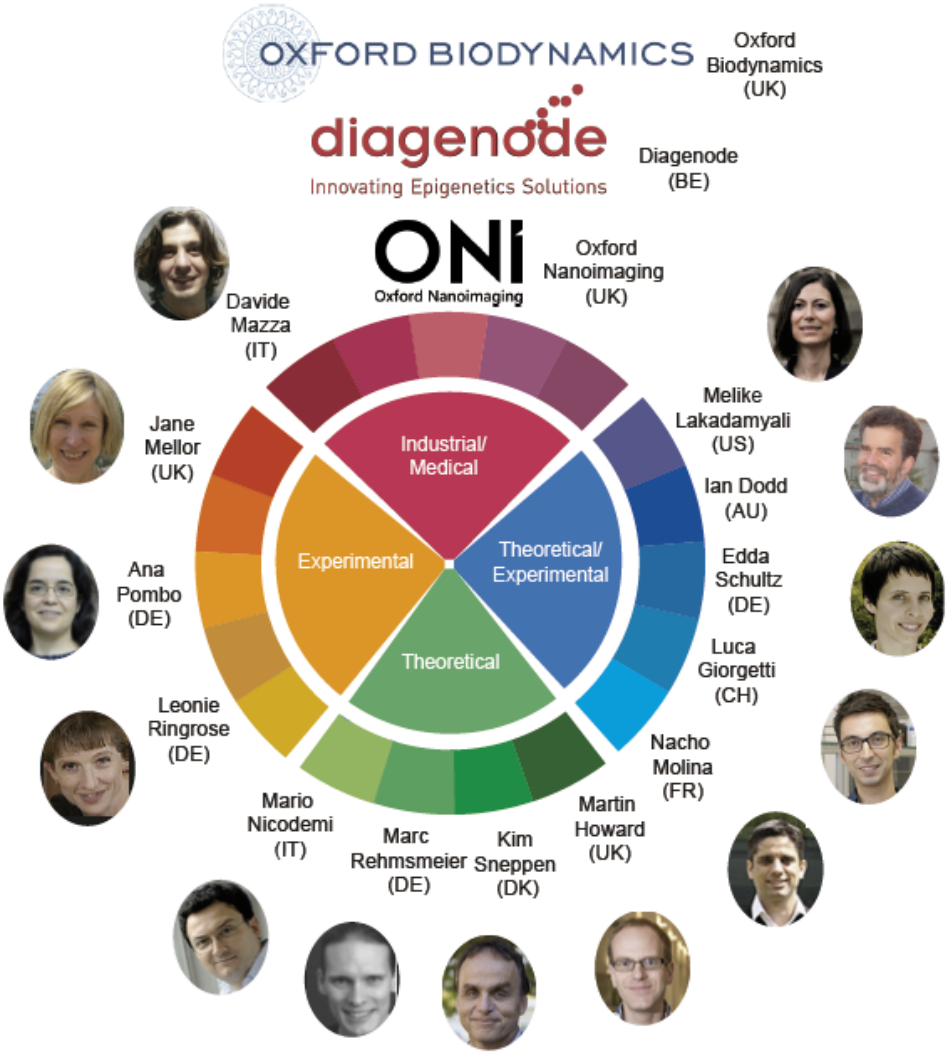
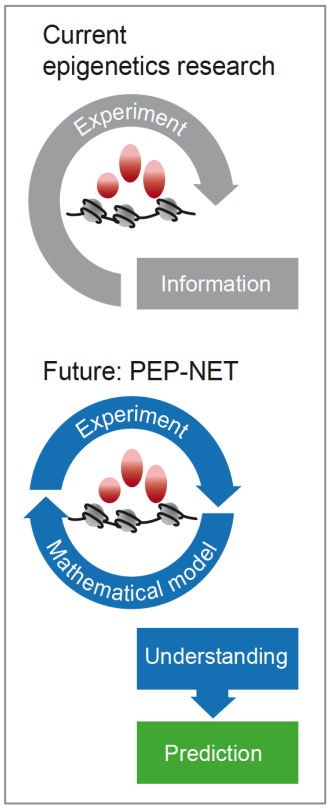


PEP-NET vision: Epigenetics needs mathematics



Epigenetic mechanisms of gene regulation are profoundly implicated in human health and disease. However, we are still far from a complete mechanistic understanding of many epigenetic processes. Without an understanding of mechanisms we cannot fully understand function in healthy cells, in disease states, and the effects and side effects of therapeutic interventions. This severely limits the development of healthcare strategies. Research in epigenetics has typically been based on experiments and not on theory (Fig. 1). Although this has delivered large amounts of information, information alone is not sufficient. Further progress urgently needs a paradigm shift in the way in which we study epigenetics, namely: **epigenetics needs mathematics.** Mathematical models are essential to capture and understand the complex, dynamic and stochastic nature of epigenetic regulation. These models are immensely powerful because they identify unifying concepts and enable predictions of system properties. **Modelling epigenetic processes not only holds the key to a deep mechanistic understanding, but also ultimately, to drug response predictions, patient-specific diagnoses and new therapies.** One of the greatest challenges to uniting biology and mathematics is the barrier between disciplines, because education in each field has traditionally been mono-disciplinary. **The PEP-NET ITN will overcome these barriers by uniting 16 outstanding European academic laboratories and companies who have pioneered the successful combination of theoretical and experimental epigenetics.** PEP-NET will train a new cohort of 15 European researchers to combine quantitative experiments with predictive theoretical models, and to apply this knowledge to basic and applied questions of epigenetic function.

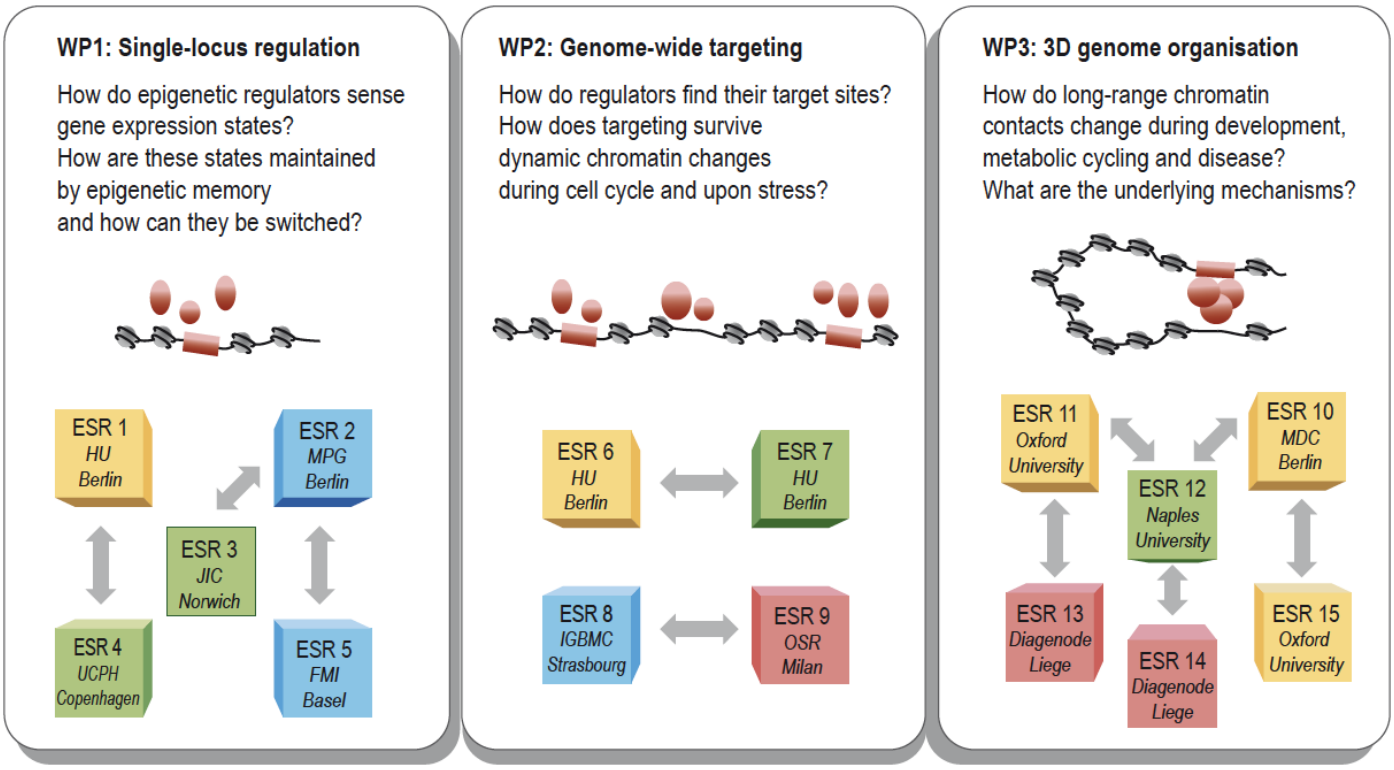
Figure 1. Epigenetics needs mathematics. Current epigenetics research is mainly experimental (top). PEP-NET will unite theory and experiment (bottom).

PEP-NET goals

- To break interdisciplinary barriers between theorists and experimentalists
- To advance our understanding of fundamental epigenetic mechanisms in health and disease
- To train our PhD students in theoretical and experimental research skills
- To train our PhD students in transferrable skills and provide experience of both academic and industrial environments

PEP-NET work packages

PEP-NET research will combine mathematical modeling with quantitative experiments to address fundamental and applied questions in epigenetics. The 15 ESRs are assigned to three work packages (WP), each of which addresses a different scale of epigenetic regulation. Yellow: Host laboratory is mainly experimental. Green: Host laboratory is mainly theoretical. Blue: host laboratory is both theoretical and experimental. Red: Host laboratory is medical or industrial. Exchange visits between laboratories are indicated by arrows. Additional exchanges between work packages are envisaged, and each ESR will spend time in both academic and non- academic laboratories either via secondment or on training courses.



PEP-NET projects

Details of each project are given on the following pages. Please note that the application deadline for all projects is 30th April 2019, **except for ESR 10 (deadline 31st March 2019).**

How to apply

Please use the application form provided on pages 1-8 of this document, following the instructions given on page 1.

ESR 1

Host institution: Humboldt University Berlin, Germany
Project title: Visualising and modelling Polycomb/Trithorax (PcG/TrxG) regulation in real time
Objectives: (i) To establish single molecule tracking of tagged Polycomb and Trithorax (PcG and TrxG) group proteins in living *Drosophila*. (ii) To measure residence times of tagged PcG and TrxG proteins and variants thereof at loci of defined transcriptional status in living *Drosophila* (e.g., RNA pol II domains, tagged reporter gene). (iii) To derive stochastic mathematical models describing PcG and TrxG binding at loci of defined status.
We have previously quantified absolute molecule numbers, average binding rates and residence times for members of the Polycomb and Trithorax regulatory system in living *Drosophila*. ESR1 will now employ single molecule tracking (SMT) of individual molecules and their binding at defined transgenic loci, whose identity and transcriptional status are known and manipulable. In combination with stochastic modelling, this study will provide a coherent theoretical and experimental framework to understand the Polycomb/Trithorax system with unprecedented accuracy.
Required background and skills: Masters' degree or equivalent in biological sciences, with practical experience in molecular biology and/ or biochemistry. Programming skills and experience of mathematical modelling are desirable.
Main supervisor: Leonie Ringrose http://www.ringroselab.com/

ESR 2:

Host institution: Max Planck Institute for Molecular Genetics, Berlin, Germany
Project title: Model-driven quantitative dissection of a bistable epigenetic switch in X-chromosome inactivation
Objectives: (i) Analyze the quantitative input-output relationship of X-dosage dependent Xist expression to assess threshold behavior and bistability. (ii) Develop alternative models on how feedback loops in epigenetic regulation can generate threshold and potentially associated epigenetic memory. (iii) Distinguish alternative models based on quantitative perturbation data in mouse embryonic stem cell.
Gene-regulatory networks process quantitative information and elicit the appropriate cellular response. To understand the principles that govern quantitative information processing in biological networks, we study how X-chromosomal dosage ensures the female-specificity of X-chromosome inactivation. X dosage transmits information on the cellular sex and controls a bistable epigenetic switch to lock in the initial molecular decision. The project will combine quantitative measurements with mathematical modeling to dissect the underlying gene-regulatory network (see also Mutzel et el, BioRxiv, 2017, doi.org/10.1101/204909).
Required background and skills: Master's degree or equivalent qualification in Life Sciences or physics. Either experience in molecular biology and/or in mathematical modeling.
Main supervisor: Edda Schulz
https://www.molgen.mpg.de/molgen/en/Forschung/Otto-Warburg-Laboratorium/networks_stem_cells

ESR 3

Host institution: John Innes Centre, Norwich, UK
Project title: Combining analogue and digital modes of gene regulation
Objectives: (i) To precisely segment single cells in the *Arabidopsis* root and extract the corresponding FLC mRNA and protein levels. (ii) To develop an unbiased ordinary differential equation model of FLC transcriptional dynamics with analogue and digital components. (iii) To link the observations and model to antisense mediated gene regulation.
Preliminary experimental evidence indicates that constitutive downregulation of *Arabidopsis* FLC expression by the Autonomous pathway involves two methods: state switching (i.e. dynamic digital switching from ON to OFF expression states) and analogue down-regulation (i.e. smoothly decreasing transcription in the ON state). ESR3 will dissect how this regulation is achieved through the development of unbiased ODE models quantifying the importance of the two mechanisms. These models will also incorporate the dynamics of the long non-coding RNA COOLAIR, providing mechanistic insight into antisense-mediated gene regulation.
Required background and skills: Master's degree or equivalent qualification in Life, Natural or Mathematical Sciences. Prior experience in biological physics or mathematical/computational biology is desirable but not essential.
Main supervisor: Martin Howard https://www.jic.ac.uk/people/professor-martin-howard/

ESR 4

Host institution: University of Copenhagen, Denmark
Project title: Modelling cellular memory governed by the Polycomb and Trithorax group (PcG/TrxG) proteins
Objectives: (i) To aggregate existing literature into a map of possible states and transitions in a system of nucleosomes that are governed by the Polycomb-Trithorax groups of proteins. (ii) To build a dynamic stochastic model for the above system, formulated in terms of known read-write enzymes and nucleosome modifications. (iii) To investigate whether the above model can exhibit bi-stability, and investigate the role of bivalent states. We expect to formulate a new quantitative dynamic model for Polycomb/Trithorax system and implement this in-silico. The model

should reproduce epigenetic features of known experimental systems and allow us to explore bivalent states (co occurrence of H3K4me and H3K27me).
Required background and skills: Master's degree or equivalent qualification in Life, Natural or Mathematical Sciences. Prior experience in biological physics or mathematical/computational biology is desirable. Ability to implement simple dynamical models on computer is a requirement.
Main supervisor: Kim Sneppen https://cmol.nbi.ku.dk/people/

ESR 5
Host institution: Friedrich Miescher Institute, Basel, Switzerland
Project title: Three - dimensional chromatin organisation and transcriptional regulation in single cells
Objectives: (i) To quantify the correlation between the amount of nascent transcription from a promoter and the physical distance that separates it from known regulatory sequences, using live imaging. (ii) To build quantitative and predictive models of enhancer-promoter interactions, to interpret the experimental data and predict the outcome of independent experiments.
We have previously shown that in mouse embryonic stem cells, cell-to-cell differences in gene expression correlate to difference in the three-dimensional conformation of the chromatin fibre in the genomic region surrounding the gene and containing its long-range regulatory sequences. ESR5 will now use single-cell fluorescence microscopy to explore the relationship between the three-dimensional conformation of chromatin and transcription at a large number of chromosomal loci, and build multi-state stochastic models of promoter operation in the presence of enhancer looping.
Required background and skills: Masters' degree or equivalent in biological, physical or natural sciences, with practical experience in molecular biology, biochemistry and/or biophysics. Experience with programming, image analysis or mathematical modelling will be considered a plus but are not mandatory.
Main supervisor: Luca Giorgetti https://www.fmi.ch/research/groupleader/?group=134

ESR 6
Host institution: Humboldt University Berlin, Germany
Project title: DNA sequence determinants of Polycomb targeting in flies and vertebrates.
Objectives: (i) To establish an editable reporter gene in *Drosophila* at an endogenous Polycomb target locus, and use it to evaluate contribution of specific DNA motifs to Polycomb Response Element (PRE) activity. (ii) To optimise existing high throughput reporter assay in mouse ESCs using NGS and barcoding, and use it to evaluate contribution of specific DNA motifs to PRE activity. (iii) To refine machine learning approaches based on the outcome of these experiments.
We have previously developed a machine learning approach in collaboration with Marc Rehmsmeier, for prediction of Polycomb response elements (PREs) in *Drosophila*. The same approach is currently being applied to the mouse genome. The model makes several predictions in fly and mouse about which DNA sequence motifs are required for PRE function. ESR6 will test these predictions in fly and in mouse cell culture, both by genome editing and by high throughput reporter assays using ChIP-seq, and barcoding. Mouse ESC differentiation protocols will be used to reveal developmental aspects of mammalian PRE activity. The results will be used to refine the model and reiterate predictions and testing.
Required background and skills: Masters' degree or equivalent in biological sciences, with practical experience in molecular biology and/ or biochemistry. Programming skills and experience of bioinformatics or computational biology are desirable.
Main supervisor: Leonie Ringrose http://www.ringroselab.com/

ESR 7
Host institution: Humboldt University Berlin, Germany
Project title: Polycomb Targeting in the context of 3D chromatin organisation.
Objectives: (i) To map PRE-target gene interactions genome-wide in the fly and in the mouse using genome architecture mapping (GAM). (ii) To assess whether statistical search-space reduction through GAM can identify statistically weak PREs. (iii) To assess whether a combination of PRE prediction and GAM can distinguish between PRE and non-PRE Polycomb Group binding events in genome-wide profiling data.
We have previously developed a machine learning approach for the identification of Polycomb Response Elements (PREs). Our collaborators in the Pombo lab have developed the genome architecture mapping (GAM) method. Given a set of PREs, ESR7 will identify their target genes by GAM. Given a set of Polycomb target genes, ESR7 will identify by GAM candidate regions that might contain targeting PREs and use PRE prediction to identify those PREs.
Required background and skills: Master's degree or equivalent qualification in Life or Natural Sciences, Mathematics or Computer Science, with a focus on Bioinformatics or Computational Biology; experience in programming.
Main supervisor: Marc Rehmsmeier http://www.ringroselab.com/

ESR 8

Host institution: IGBMC, Strasbourg, France
Project title: Modelling transcription factor mitotic bookmarking in a dynamic chromatin structure
Objectives: (i) To develop a mathematical model of chromatin condensation-decondensation based on Hi-C maps around the cell cycle. (ii) To extend our previous stochastic reaction-diffusion model of TF dynamics in the context of a dynamic chromatin structure. (iii) To validate the model using available FRAP and ChIP-seq data around the cell cycle for Sox2, Oct4, Nanog and Esrrb.
We have previously derived a model to describe the nuclear diffusion of TFs taking into account the chromatin structure. ESR8 will now extend the model to incorporate the dynamics of the chromatin structure in the context of the cell cycle. Statistical Mechanics techniques will be used to simulate a bead-spring polymer fibre upon which the structural constraints observed in HiC data from mitotic cells are imposed. The main result will be to understand and predict mitotic bookmarking by pluripotent TFs. In addition, ESR8 will investigate the power of mitotic bookmarking to maintain a specific gene regulatory landscape through the cell cycle.
Required background and skills: Master's degree or equivalent qualification in Physics, Mathematics, Computational Biology or Life Sciences. Strong background in mathematical or biophysical modelling and good programming skills are required. Experience analysing large-scale genomic data and/or microscopy images will be a plus.
Main supervisor: Nacho Molina http://www.igbmc.fr/molina/

ESR 9

Host institution: San Raffaele Hospital, Milan, Italy
Project title: Transcription factor search mechanism, chromatin mobility and organisation upon DNA damage
Objectives: (i) To quantify chromatin reorganisation in response to genotoxic stress by microscopy and/or biochemistry. (ii) To quantify chromatin mobility in response to genotoxic stress by single molecule imaging. (iii) To model and validate the combined effect of connectivity and chromatin mobility on TF search by single molecule imaging.
We have developed methods to quantify the diffusion and binding of TFs to chromatin in living cells by single molecule tracking, and applied it to the tumour-suppressor p53 a key TF activated by genotoxic stress. Here ESR9 will determine how modifications in chromatin structure and mobility induced by DNA damage can affect the efficient targeting of TFs to responsive elements. In combination with mathematical modelling of the TF search mechanism, using Monte-Carlo simulations of TF search mechanism in environments with heterogeneous crowding, we aim to identify how the physical epigenetic state of the cell can direct TFs to subsets of putative responsive elements.
Required background and skills: Master's degree or equivalent qualification in Physics, Biophysics, Life or Natural Science, with a focus on biophysical analysis of cellular and molecular biology data. Previous experience in advanced fluorescence microscopy will be considered a plus.
Main supervisor: Davide Mazza
http://research.hsr.it/en/centers/experimental-imaging-center/live-cell-single-molecule-microscopy.html

ESR 10

Host institution: Max Delbrück Centre for Molecular Medicine, Berlin, Germany
Project title: Investigating long-range chromatin contacts during early cell fate decisions in mouse embryos
Objectives: (i) To produce genome architecture mapping (GAM) datasets in early mouse embryos. (ii) To compare GAM datasets from early mouse embryos with embryonic stem cells. (iii) To validate chromatin contacts using single cell imaging approaches.
We have produced a GAM dataset in mouse ESCs, quantified the probability of 3D chromatin interactions genome-wide, and identified specific pairwise contacts between active genes and enhancer regions. To expand our understanding of chromatin contacts in vivo, we will apply GAM at different stages of development in wild type mouse embryos (E3.5 and E4.5), and in Nanog and Gata6 knockout embryos. In combination with mathematical and polymer modelling (NAPOLI), we will produce a coherent framework to understand the dynamics of promoter-enhancer contacts at the single cell level during early development.
Required background and skills: Masters' degree or equivalent qualification in life sciences or computational biology. Previous experience in gene and/or epigenetic regulation, mammalian cell culture, molecular biology and/or genomics approaches are preferred.
Main supervisor: Ana Pombo ~~https://www.mdc-berlin.de/pombo~~

ESR 11 This position has been filled and is no longer available

Host institution: University of Oxford, UK
Project title: Relating the 3D organisation of chromatin to antisense transcription
Objectives: (i) To map 3C interactions during the yeast metabolic cycle. (ii) To demonstrate the consequences of ablating pervasive antisense transcription on local 3D organisation. (iii) To derive stochastic mathematical models describing the effect of pervasive antisense transcription on the 3D architecture and associated sense transcription.

We have shown that the μ3C 3D architecture of the yeast genome is related to pervasive antisense transcription but it is not known whether the relationship is causal or if so, whether it is the act of transcription or the non-coding transcripts that play a role in the formation of μ3C interactions. Using an established stochastic model, coupled to simulations of experimental data, developed to describe the relationship between antisense and sense transcription, ESR11 will develop the model to address causal relationships. ESR 11 will exploit the temporal resolution of the yeast metabolic cycle (YMC), quantitative nascent transcript and μ3C events, and the dCas9 CRISPRi system to ablate selected well-characterised antisense transcription events, to derive data to populate the model and describe these relationships.
Required background and skills: Masters degree or equivalent in biological sciences, with practical experience in molecular biology and/ or biochemistry. Programming skills and/or experience of mathematical modelling are an advantage.
Main supervisor: Jane Mellor https://www.bioch.ox.ac.uk/research/groups/prof-jane-mellor

ESR 12
Host institution: University of Naples Frederico II, Italy
Project title: Understanding chromatin 3D organisation and its underlying physical mechanisms
Objectives: (i) To develop the analysis of genome architecture (GAM) high-throughput chromatin contact data. (ii) To develop polymer models to understand the underlying molecular mechanisms.
By combining Statistical Physics polymer models, computer simulations, and epigenomics high-throughput data analysis, we aim to understand genome-wide chromatin contact data produced by Hi-C based and our novel GAM technology (developed with Ana Pombo, also in this consortium). In particular, we expect to derive an understanding of the general mechanisms of chromosome folding and of the specific molecular factors acting in model loci (e.g, Hox loci) linked to human phenotypes (Sox9, Epha4, etc.) and embryo development.
Required background and skills: Master degree (or equivalent) in Physics, Math, Computer Sciences or Engineering, ideally with a background in Statistical Physics or Computational Biology and programming.
Main supervisor: Mario Nicodemi http://people.na.infn.it/~nicodem/

ESR 13
Host institution: Diagenode, Liege, Belgium
Project title: Developing technologies for analysis of long non-coding RNAs and investigation of their role in long-range chromatin contacts
Objectives: (i) Development and optimization of a method for library preparation of RNA, especially long non- coding RNA (lncRNA). (ii) Application of this methodology to investigate the role of lncRNAs in long-range chromatin contacts.
Diagenode is expert in wet lab and dry lab chromatin immunoprecipitation and methylation analysis, marketing kits and reagents but also offering service to external customers. Recently, the company has expanded its product portfolio to include kits for library preparation on RNA using CATS, a template switch-based method. ESR13 will further developp the CATS method in order to improve the analysis of lncRNAs. In addition, the CATS will be optimized to deal with limited amounts of RNA. ESR13 will then apply the optimized CATS method to investigate how lncRNAs are involved in higher order chromatin structure via secondment to the Mellor lab.
Required background and skills: A masters' degree or equivalent in biological sciences, with experience in molecular biology and/ or biochemistry.
Main supervisor: Céline Sabatel https://www.diagenode.com/en

ESR 14
Host institution: Diagenode, Liege, Belgium
Project title: Computational methods for chromatin conformation investigation
Objectives: (i) To develop a Hi-C bioinformatics pipeline. (ii) To learn wet lab techniques to understand where experimental biases potentially lie.
Diagenode is expert in wet lab and dry lab chromatin immunoprecipitation and methylation analysis, marketing kits and reagents but also offering service to external customers. The company has plans to expand its product portfolio to chromatin conformation analysis. ESR 14 will develop dry-lab Hi-C data analysis, first using datasets from the public sector and the consortium, then from in-house generated data from ESR 13. Specialised sequencing data alignment/peak calling and advanced statistical analysis will form the backbone of the bioinformatics pipeline required for efficient Hi-C data processing.
Required background and skills: Masters' degree or equivalent in life sciences or bioinformatics with experience in command line programming, linux environment and ideally epigenetic software tools.
Main supervisor: Céline Sabatel https://www.diagenode.com/en

ESR 15

Host institution: University of Oxford, UK

Project title: Modelling parameters for resetting higher order chromatin structures

Objectives: (i) To use selected glioma (e.g. BT142) and leukemic (e.g. EOL-1) cell lines and matched controls, treated with and without receptor tyrosine kinase inhibitors (RTKI), to define metabolism, gene expression, CTCF binding (DNA methylation), and targeted 3C interactions focusing on RTK oncogenes such as *PDGFRA* and *c-KIT*. (ii) To develop a stochastic model for feedback regulation of 3C interactions by the inhibited RTK via control of the chromatin environment.

Tyrosine kinase inhibitors (TKIs) such as the ATP mimetic Imatinib are being developed to treat chronic malignancies by targeting the activated enzyme. Higher order structures in chromatin (3C interactions) change in these diseases and accurately stratify patients suitable for TKI treatment. In addition to reducing RTK activity, our preliminary data suggests that TKIs may also function by resetting the higher order structures in chromatin, explaining why single doses of these TKIs are often successful in treating these conditions. Stochastic modelling and simulations of coding and non-coding transcripts can be used to predict parameters leading to switching of higher order structures. ESR15 will use tyrosine kinase inhibitors to monitor chromosome conformations and the associated changes to gene expression, metabolism and chromatin over time. By integrating time resolved molecular changes and modelling positive and negative feedback loops, this study will provide mechanistic and regulatory insights into the disease process and its treatment.

Required background and skills: Masters degree or equivalent in biological sciences, with practical experience in molecular biology and/ or biochemistry. Experince in 3C and/or programming skills are an advantage.

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