

Examiner Report Form

Doctoral Thesis Submission Post Viva

(Part II)



THE UNIVERSITY
of EDINBURGH

Examiners are requested to complete the form jointly and to return it
without delay (within two weeks of the oral examination),
as an email attachment to:

cmvmpgr-examinations@ed.ac.uk

(emailed reports need not be signed but will require verification)

Alternatively, a signed paper copy may be returned by post to:

College of Medicine and Veterinary Medicine, Graduate School: College Hub
The University of Edinburgh, The Chancellor's Building Room SU223
49 Little France Crescent, Edinburgh EH16 4SB

Please complete the form in typescript or block capitals

Name of student:	Benjamin Moore	UUN	S0810810
Title of thesis:	Unravelling higher order chromatin organization through statistical analysis		
Degree sought:	Doctorate		

Date of oral examination	18/11/2015
Name of external examiner (1)	Professor Cathal Seoighe
Name of internal examiner (1)	Dr Andrew Wood
Name of external examiner (2) (if required)	Click here to enter text.

Name of non-examining chair (if applicable)	Professor Chris Haley
Name of observer(s) (if present)	Click here to enter text.

Examiners are reminded that Part I and Part II reports can be requested and made available to students and their supervisor(s) after ratification by the College.

If examiners have any concerns about this they should contact the College Postgraduate Office.

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Comments made *after* the oral examination

Please indicate your assessment below by placing an “X” or tick in the appropriate box and adding your comments in the spaces provided. (*The space will expand as required in the electronic version. If using paper, please continue your comments on a separate sheet.*)

Report to the College Committee	
Were there any areas of significant disagreement between the examiners in their respective Part I reports?	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
If YES , please explain below how these differences were reconciled. If the Examiners are not in agreement (and are therefore completing separate copies of this report), please state below details of the disagreement and, where appropriate, relate them to the preliminary report.	
Click here to enter text.	

Please comment on how criticisms made in the initial reports were resolved or reinforced by the student's performance at the oral examination and any further criticisms that arose during the examiners' discussion or in the course of the oral examination.
The examiners did not identify any major areas of concern in the initial reports, and all minor issues were resolved in a satisfactory manner during the oral examination.

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Joint recommendation

Please indicate your joint recommendation (refer to Postgraduate Assessment Regulations for Research Degrees). Please place an "x" or tick in the appropriate box.				
	Options:	Student Action:	Re-examination:	"X"
a	Award PhD/Doctorate: student meets the doctorate requirements without corrections.	<ul style="list-style-type: none"> Finalise hard-copy thesis submission for doctorate degree 	<ul style="list-style-type: none"> Nil 	<input type="checkbox"/>
b	Minor Corrections Needed: thesis is satisfactory apart from the rectification of editorial corrections or minor weaknesses.	<ul style="list-style-type: none"> Make specified corrections within 3 months 	<ul style="list-style-type: none"> Corrections to be certified by the Internal Examiner(s), and by the External Examiner (if requested) ** 	X
c	Additional Oral Examination Needed: student's oral defence of the thesis was inadequate in specified respects. *	<ul style="list-style-type: none"> Re-sit viva. 	<ul style="list-style-type: none"> Further oral examination of original thesis required. ** 	<input type="checkbox"/>
d	Additional Work on Thesis Needed - No Oral Re-Examination Needed: The thesis needs work above and beyond editorial corrections or minor weaknesses in order to meet one or more of the requirements for the degree, and this work may require further supervision * (<i>Examiners to specify period of corrections, usually up to 6 months, but exceptionally up to 12 months with recategorisation to (e)</i>)	<ul style="list-style-type: none"> Complete the thesis revision specified period. No thesis resubmission is required. 	<ul style="list-style-type: none"> Revisions are subject to certification by the Internal Examiner(s), and by the External Examiner (if requested) ** 	<input type="checkbox"/>
e	Substantial Work on Thesis and Oral Re-Examination Needed: Examiners may recommend resubmission within a further specified period of study, with reasons stated in their Part II report. * (<i>Examiners to specify period of corrections, usually up to 12 months, but exceptionally up to 24 months.</i>)	<ul style="list-style-type: none"> Rectify deficiencies and resubmit thesis within specified period. 	<ul style="list-style-type: none"> Oral examination of the resubmitted thesis required 	<input type="checkbox"/>
f	Award MPhil: thesis is deficient for doctoral award but meets the MPhil requirements without corrections.	<ul style="list-style-type: none"> Finalise hard-copy thesis submission for MPhil degree. 	<ul style="list-style-type: none"> Nil 	<input type="checkbox"/>
g	Award MPhil following Minor Corrections: thesis is inadequate for doctoral award but student is eligible for an MPhil degree if specified corrections are made.	<ul style="list-style-type: none"> Make specified corrections within 3 months 	<ul style="list-style-type: none"> Corrections are subject to certification by the Internal Examiner(s), and by the External Examiner (if requested) ** 	<input type="checkbox"/>
h	Substantial Work on Thesis Needed before Resubmission and oral examination for MPhil: thesis is inadequate for doctoral award but it may satisfy the requirements for an MPhil degree if student corrects deficiencies.	<ul style="list-style-type: none"> Rectify deficiencies and resubmit thesis within 12 months. 	<ul style="list-style-type: none"> Oral examination of the resubmitted thesis required 	<input type="checkbox"/>
i	Award Masters by Research: thesis is deficient for doctoral or MPhil degrees, but the work merits the award of Masters by Research.	<ul style="list-style-type: none"> Nil 	<ul style="list-style-type: none"> Nil 	<input type="checkbox"/>
j	Fail: the thesis is fundamentally deficient in regard to doctoral, MPhil or masters standards.	<ul style="list-style-type: none"> * Nil 	<ul style="list-style-type: none"> * Nil 	<input type="checkbox"/>

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* Specific Period recommended for corrections/re-sit viva by examiners (recommendation b, c, d or e)	3 months
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** Please tick if the external examiner has requested to certify corrections before the degree is awarded (recommendation b, c, d or g)	
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If resubmission is recommended, only one copy of the original thesis should be returned to the student. The other should be retained by the Internal Examiner to facilitate checking of revisions when the thesis is resubmitted.

Signature of external examiner (1)	
Signature of internal examiner (1)	
(Signature of external examiner (2))	

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Specific examination critique to be given to the student by the College Committee (always to be completed unless no thesis amendments are required)

Please complete the form in typescript or block capitals

Name of student:	Benjamin Moore	UUN	S0810810
Title of thesis:	Unravelling higher order chromatin organization through statistical analysis		
Degree sought:	Doctorate		

- The joint report must include any conclusions reached by the examiners as a result of the oral examination, particularly in any areas of concern identified in the individual reports.
- Where editorial corrections or modifications are required these should be specified in the joint report.
- If resubmission is recommended, only one copy of the original thesis should be returned to the student. The other should be retained by the Internal Examiner to facilitate checking of revision when the thesis is resubmitted.
- If the thesis is considered to be substantially deficient, the report should explain in detail which aspects of the thesis require revision to bring it up to the standard required. If the examiners recommend that no degree should be awarded, the main reasons for rejecting the thesis must be given.
- **If examiners pass information to students about recommendations they must make it clear that these are only provisional, as the final decision rests with the Examinations Committee.**

Critique to the student (the space will expand as required in the electronic version. If using paper, please continue your comments on a separate sheet.)

The examiners were in agreement that the thesis constitutes a substantial body of high quality work, which has advanced the field of higher order chromosome structure. The thesis is beautifully written, the figures are clearly presented, and an appropriate level of detail is included in the introduction and discussion sections. Ben defended his thesis with confidence and humility and it was evident that he had read widely and thought deeply about his chosen subject. Importantly, he was also aware of the limitations associated with many of the approaches taken. We are happy to recommend the award of a Doctorate, subject to completion of the following minor corrections:

1. The Chi-squared tests for calling TADs are potentially strongly affected by read depth (increasing power to call a TAD with increasing sequencing depth). Given the differences in sequencing depth between samples, this issue should be discussed. Does the HMM method help to mitigate this? The thesis should include some discussion of the impact of read depth and statistical power on TAD calling (e.g. in reference to Fig. 16 – though it may be preferable to include a figure showing TAD

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sizes in the different cell lines to illustrate this effect more explicitly)

2. To provide evidence that compartments called by the novel HMM method are superior to compartments based on eigenvectors alone, boundaries that are shared between the two methods should be compared to boundaries that are unique to the eigenvector only compartment calls. If the boundaries called by the eigenvector alone lack the distinguishing features of compartment boundaries discovered in this work that would provide support for the use of the HMM method instead of eigenvector sign changes alone to call compartments.
3. Statistical tests described in section 2.9 and reported in section 3.7 should be repeated with the chromosome treated as the statistical unit (and an appropriate test to compare between inner and outer chromosomes).
4. Remove any plots from Figures 44 & 45 to which the shared y-axis does not apply (e.g. GERP)
5. Plots involving A/B compartment boundaries should be oriented consistently (e.g. A on the left B on the right). Plots of TAD boundaries should be oriented if there is a natural way to orient them, or otherwise folded over (to show distance from the boundary instead of up and downstream distance, if this distinction is not meaningful).
6. In the Discussion Section 7.2, consideration should be given to the reasons underlying the strong association found between active transcription and domain boundaries (eg. Figure 46). Does this association have mechanistic significance (eg. enhanced flexibility of the chromatin fibre in regions of histone acetylation facilitating the formation of loop anchors) or could there be greater selective pressure to evolve boundary function within gene-dense regions?

The following typographical errors should be corrected:

- p.1 advent DNA should be 'advent of DNA'
- p.1 phrase 'wherein distinct... thought to occupy' should 'wherein' be 'which'?
- p.2 'your fragments of interest' -> 'the fragments of interest'
- p.6 'in order to increase' -> 'increasing'
- p.6 downstream-biased -> downstream bias
- p.14 and p.15 suggest avoid using terms like 'huge' and 'vast' if possible
- p.20 were build
- p.22 where thresholded
- p.29 should 'classes of variable' be 'classes of sample'?
- p.30 'involve the constrained' -> 'involves the constrained'
- p.30 source of the personal communication should be indicated if possible.
- p.31 'contact lamin'
- p.33 'peak maxima' -> 'peak maximum'
- p.34 'acts to reduces'
- p.41 'distribution of these boundary differences'
- p.45 legend of Fig. 15 'density' should be 'distribution'
- p.68 correct use of 'Conversely' here?
- p.88 'associations these features' -> 'associations between these features'
- p.88 'in 40kb' should be 'to 40kb resolution' ?

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p.94 speciality -> specificity
p.126 'Two different approaches could be used'
p.126 'first develop'
p.127 Lead -> Led

The following changes are optional suggestions, which are not essential prior to resubmission of the thesis.

p.49 Show the result indicated as 'data not shown' and indicate what algorithms were used here.
p.54 Explore the effects of gene length as a confounder in gene set analysis – e.g. using GOSeq
p.67 Repeat the assessment of the accuracy of compartment calling using Random Forest classification directly (instead of random forest regression, followed by compartment calling based on the predicted eigenvector)
p.95 Consider performing clustering analysis of boundaries to explore more generally whether there exist different classes.

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Signature of external examiner (1)	
Signature of internal examiner (1)	
(Signature of external examiner (2))	
Date:	23/11/2015

FOR COLLEGE USE ONLY

Date received:

Document control

Related policies/regulations:

www.docs.sasg.ed.ac.uk/AcademicServices/Regulations/PGR_AssessmentRegulations.pdf

If you require this document in an alternative format please email Academic.Services@ed.ac.uk or telephone 0131 650 2138.

Date last reviewed:
15.05.15

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