Humphries Lab

Lab Manual

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Contents

1 Introduction

Hello reader, welcome to the Humphries' lab. We are a neural data lab: we analyse neuroscience data to test computational theories of how brains work. To do this, we often have to create new analysis approaches; and we build models of neurons and circuits to test the match between theories and data. As a purely computational lab, we are at liberty to have looser rules than our experimental colleagues. This manual lays out how the lab works, and the expectations of everyone within it.

The public faces of the lab can be found here:

- Lab website: https://humphries-lab.org
- Twitter: http://twitter.com/markdhumphries

Credit: ideas for the content have come from the lab manuals of Miriam Aly (whose Nature opinion piece inspired this manual), Jonathan Peelle and Maureen Ritchey.

2 Practical information: how the lab works day-to-day

How labs work evolves over time as they grow or shrink, as they change direction, or move institution. This is how we currently work:

Intra-lab communication We use Slack for all intra-lab communication. We use Slack precisely so that we do not have to turn on email to talk to each other. It ensures you can contact Mark easily. Each major project has its own channel in Slack. See below for our notifications policy.
Action: Install Slack on your work PC, and anything else you want to.

Lab scheduling The lab has a Google Calendar to track all scheduled lab events (meetings, visitors etc). It has two other main functions: for everyone to enter their holidays; and for adding interesting external events (local seminars, conferences etc).
Action: Ask Mark to give you access to the lab calendar.

Lab meetings : lab meetings are weekly*, from 12-1pm. Meeting content alternates: week 1 is a data club; week 2 is a journal club; both follow a rota so all members will present. Data clubs are a chance to present your latest results, your problems you want to solve, or plans. When in the midst of writing paper, data clubs are a chance to talk through the paper, explaining the figures in order. A useful guide to presenting work-in-progress papers in lab meetings is here: https://dreamingofchickens.com/2019/03/03/how-to-write-and-other-things-were-supposed-to-be-teaching-trainees/
* Weekly is an aspiration. Weeks will be missed when sufficient numbers of people are absent

Data storage Each major data analysis project will store its data in a separate folder on the lab's Sharepoint area: access via the 0365 interface. Ask Mark to add you to the Sharepoint group if you have no access.

Code We use Matlab by default; everyone is encouraged to use and/or learn Python. Mark does not know Python, as he is a dinosaur. We like the look of Julia, but have not been brave enough to dive in yet.
Action: Matlab should already be installed on your PC. Register your Nottingham email address with Mathworks, and the institutional license will let you install copies of Matlab

wherever you want.
Action: Learn Python. Install Anaconda https://www.anaconda.com/products/individual. Read "Neural Data Science: A Primer" (Nylen & Wallisch) for a great guide to both Python and the kinds of tools we use.

Code sharing We use GitHub for code sharing. Consequently, we use Git for version control when needed. We strive to upload all our computational models to ModelDB.

Writing We write all papers in LaTeX by default; for co-writing papers with collaborators who do not know LaTeX, we will use Word with gritted teeth. Or Google Docs like a sane person.

Graphics We currently prefer Inkscape for our main needs: laying out panels into figures; editing them; and making schematics.

Some useful information on when you are and are not supposed to be working:

University holidays : https://www.nottingham.ac.uk/about/keydates/index.aspx
Note in particular that UK universities close completely over Christmas.

UK public holidays : https://www.gov.uk/bank-holidays
p.s. the UK calls all public holidays "bank holidays".

3 Roles and responsibilities

Who does what, and what to expect of them – and yourself.

3.1 PI

You can expect me to do the following:

- Have a vision of where the lab is going.
- Be aware of where the field(s) are going.
- Care about your happiness.
- Create and submit funding applications to support the science in the lab.
- Support you in your career development, including:
  - helping you prepare for a successful career both in and out of academia
  - writing letters of recommendation
  - introductions to other scientists
  - funding trips to relevant conferences
  - funding training at advanced schools
  - promoting your work in talks
  - inviting you to jointly peer review papers
  - make available to you example grant applications, both successful and unsuccessful. Comparing the two will show the fine margins involved.

- Support you in your personal growth by giving you flexibility in working hours and environment, and encouraging you to do things other than science.
- Be available to meet with you, to talk about your science, about your future plans, and any other issues you want to raise.
- Provide feedback in a timely manner on abstracts, posters, job and fellowship applications
- Work with you on your papers. Sometimes this will be comments on a manuscript; sometimes this will be redrafting; sometimes this will be working on code.

What does a PI do? For better or for worse, the best way to understand how a modern biomedical lab works is to picture it as a small tech start-up. It pitches projects to raise funds from investors, hires people to work on projects, and produces outputs from those projects (scientific ones: papers, techniques, and code). And just like a start-up, it has to deal with all the admin of a business: HR, accounting, marketing etc. A PI does all the things that a start-up CEO does: pitches; fund-raises; interviews and hires people; leads projects; advertising and marketing; accounting; quality control of products. Also, as they are employed by a University, they teach and sit on administrative committees. This is why succeeding in academia is about more than just being good at science.

3.2 Postdoc

Postdocs are research positions typically funded from research grants. As a postdoc in the lab you are expected to:

- Develop your own independent line of research. If funded from a specific project grant, the aims and ideas of that grant are your starting point, not the end-goals.
- Become the lab expert in your line of research, including reading the literature
- Regularly update Mark on your progress: from short messages on what problem you're tackling now, to in-person meetings on key results and decision points
- Challenge me (Mark) when I'm wrong or when your opinion is different
- Help train and mentor students in the lab (whether undergraduate, MSc, or PhD) when they need it – either because they ask, or because I ask you to
- Present your work: at local events; at other labs; and at conferences
- Plan your future, as appropriate:
  - Apply for jobs (academic, industry or third sector) when you're ready, but no later than 6 months before the end of your current postdoc contract. There are more, and in many ways better, jobs outside academia, for which you are well-qualified.
  - Apply for fellowships, well in advance of the end of your postdoc. For external funders (UKRI etc), the typical lag between submission deadlines and being able to start a Fellowship is a minimum of 10 months. Submission deadlines are at most three times a year; many schemes are once a year. Plan well in advance.
- Take responsibility for your career development: produce work in a timely fashion necessary to support your own career; where practicable, take advantage of the opportunities that arise from working in the lab

3.3 PhD student

- Develop a line of research for your thesis. Developed with Mark's help.
- Read the literature in your research area
- Regularly update Mark on your progress: from short messages on what problem you're tackling now, to in-person meetings on key results and decision points
- Present your work at local events and conferences
- Do some soulsearching as to what type of career you want to pursue, e.g., academic jobs that are research-focused or teaching-focused, nonacademic jobs like data science or science writing.
- Assist in training and supervising undergraduate students
- Stay up-to-date, and keep Mark up-to-date, on any deadlines that you need to meet to fulfil the training programme, School or Faculty requirements for your PhD.

3.4 MSc/undergraduate project student

The primary goal of a project student is to produce a quality piece of written work, that reflects a solid piece of research work.

- Work on your assigned research project
- Plan your research time according to the course's project deadlines
- Plan your writing time too.
- Stay up-to-date on your project deadlines, and inform Mark of them.
- Attend lab meetings if they fit into your course schedules.

3.5 Intern

The purpose of an internship is to find out how a lab works, and if their line of research is something you'd be interested in pursuing in future. Thus the expectations for an internship are:

- Find out what the other lab members are working on
- Work on your assigned research project
- Attend lab meetings

4 How we aspire to work: the lab principles

Lab motto: don't be afraid to be wrong.

We are, ultimately, theorists. George Box's aphorism "All models are wrong, some are useful" may be a cliche, but it doesn't stop it being true.

4.1 Strong inference

We are not committed to a single "true" idea or single "true" method of analysis. We can disprove our own ideas, and break our own methods.

As scientists, we cannot do deduction, only inference. We cannot infer proof, only disprove. Thus, we aspire to do strong inference (Platt, 1964). For each problem, ideally we will:

1. create alternative hypotheses;
2. devise a crucial analysis or model that will exclude one or more hypotheses; and
3. perform the analysis (or build the model) that will obtain a clean result

Then: (1') reiterate the procedure to refine the remaining possibilities.

In practice this means:

- Write down hypotheses, before starting analysis (or model building).
- Discuss them with others with constructive criticism (through informal chats, in lab meetings, or by sharing written text)
- Define outcomes expected of analysis testing (or models)
- Then analyse/build

4.2 Exploratory data analysis

What if we don't have any hypotheses yet? In the absence of specific, disprovable hypotheses, we always have an aim to our analysis. That aim is a testable proposition.

For example "brain area X contains two independent populations that encode Y and Z" is a proposition. It is not yet a disprovable hypothesis, as that depends on our definitions of "independent", "population", and "encode". Once we have defined those, then we can frame one or more hypotheses.

Exploratory data analysis is what we do to turn aims into hypotheses. At root, it is about constructing a model for the data, and using that model and its changes to generate hypotheses.

For example, we can define "independent populations" by using unsupervised clustering of neurons into groups based on their correlations. That idea contains two models. The first is a model of the relationships between independent time-series as a series of pairwise correlation measures. The second is a model of the relationships between those relationships: the clusters based on similar correlations. We might observe the existence of two strongly defined clusters of neurons, and define those as the basis for testing hypotheses about encoding. Disproving such hypotheses takes us back to Strong Inference.

4.3 Research collaboration care guide

We work with a lot of data directly from experimental labs. So that means we:

- Take care in all communication about private data. Discretion.
- Respect efforts of experimentalists in obtaining that data
- Treat their data with respect, and check it carefully
- Store their data well: multiple copies, backed-up. And we never ever work on the only copy of the data (see Section 5.1).

4.4 Open science

4.4.1 Open publication

We pre-print every paper on which it is our decision to make. Neuroscience papers go to bioRxiv. Technical papers to arXiv. Our policy is to submit pre-prints simultaneously with the initial submission to the journal at the latest. For some projects, it can make more sense to pre-print before initial submission. Pre-prints are then updated with every major revision to the manuscript that comes as a result of the reviews.

We publish open-access whenever possible, and always when essential. Both the UK Research Evaluation Framework and UK research funders have rules about making papers publicly available. For some journals, we do not need to publish open-access as either (a) their policy allows immediate posting of the post-print to a public repository (e.g. EuropePMC) or (b) they have an open archive, which falls within the rules. All papers have to be submitted to the University's own paper repository, to abide by REF rules.

4.4.2 Open code

A computational paper without code is just an advert. Sometimes adverts are fine: the model is the medium for the message, and the message is what counts. But normally a computational paper stands or falls on the details of its computation. And those are only accessible from the code.

In practice this means:

- Share code whenever asked
- Always release code with publication
- When suitable, develop in public too

4.4.3 Open data

As we openly share code, so we would like to openly share the data too. But often it is not our data. So we make it politely clear to our collaborators that we would like to share the data to accompany the shared code in this best of all possible worlds. And that we will do everything in our power to help to do so, if necessary. For example, we have been directly involved in making two data-sets open access:

- Voltage sensitive dye imaging data from the *Aplysia* pedal ganglion, as used in Bruno, Frost & Humphries (2017) eLife.
- Tetrode recordings in prefrontal cortex and behavioural data from rats learning rules in a Y-maze. Data from Adrien Peyrache and colleagures. Used in a range of papers, but made open access with us (we contributed the example analysis code to the repository) for Maggi, Peyrache & Humphries (2018) Nature Communications.

4.5 Who works on what

We aspire to this division of labour:

- Everyone in the lab will work on at least one project that belongs to them. This project (or projects) will be your day-to-day work.

- Projects and their progress and especially the lack thereof due to problems should be discussed openly in the lab.
- We look for collaborative projects that will involve many or all of the lab members (most likely the senior members, PhD and above). Work on such projects will likely revolve around all-day hackathons, each hackathon focused on tackling a specific problem by harnessing the different skills and expertise within the lab. Our "spectral rejection" paper was based on work created during 5 hackathons spread over 6 months.

5 Policies

5.1 Scientific conduct

Thanks to the replication and reproducibility crises, and the ever-growing awareness of the mis(use) of statistics, the scientific conduct of researchers is more scrutinised than ever. These are our basic policies for conducting science:

Experimental data are sacrosanct We do not alter the content of experimental data. There should always be a complete, untouched set of any data files we obtain. Never load the only copy of any data set. Any changes to the formatting of data (e.g. changing from arrays to tables) are saved as copies.

Simulations should be replicable Every simulation in a paper should be replicable in principle: the same code run again with the same parameters should produce the same results. Hint: always save parameters from any simulation code that will be used for a paper. That includes the random number generator seed.

Document your work Use whatever works for you, but document your work. That could be a lab book, whether paper or tablet, with notes on each analysis or each simulation. Or typing notes. Or exporting key plots to Powerpoint, Google Docs etc. Or using a Jupyter notebook or RMarkdown to encapsulate what you've done, if you're comfortable with those things. Do something, so that you can give *accurate* answers to: what have you been working on? And: what have you found?

Every file is duplicated Your computer will die. All working files on your computer should be replicated elsewhere, at all times. At minimum, use an automated program to back up to an external hard-drive. Better, use cloud-based storage - this will also let you sync work across machines.

A Just Culture As scientists we are always learning: about new ways of analysing data, about our own findings, about new models, about new published research. And learning is inherently about making mistakes and errors, in order to correct our skills and knowledge. So the lab operates a "Just Culture", not a blame culture: mistakes and errors are expected; mistakes are not blamed on the individual; and mistakes are used as opportunities for learning by the lab: how to adjust our approaches to catch errors in the future.

An example of Mark's mistakes. Chapters 4 and 5 of my PhD thesis contain a spiking neuron model of the feedback loop between the globus pallidus (GP) and the subthalamic nucleus (STN). As thrilling as it sounds. This is a negative feedback loop: the GP inhibits the STN; the STN excites the GP. However, in the midst of writing up Chapter 4, I discovered

my code had a tiny but crucial error: the STN input to the GP had a minus sign in front of it. It was inhibiting, not exciting, GP. Already past the end of my funding, I had to ditch all the simulations that were to make up Chapters 4 and 5, and ran them all again from scratch. The lesson for the future: when coding connections between neurons, don't write the sign of the connection into the arithmetic (Input = A - w.B); always write the sign into the weights: (e.g. Inputs = A + w.B, and w = -1). That way, a quick glance down the parameter values at the top of the code will show up any errors.

5.2 Authorship

Until we reach that bright future where papers are no longer the de facto currency of academia, and/or where author names are solely linked to contributions like film credits, authorship will remain a tricky subject. Who gets their name on the paper, and where it goes on the list of authors, can cause problems. Our criteria are simple, and similar in spirit to the criteria of the ICMJE guidelines:

1. Substantial intellectual contribution to the content of the paper, AND
2. Contribute to the written content of the manuscript in a meaningful way [by contributing text and/or substantial editing; and approving the final manuscript]

The usual model is that the postdoc or PhD student leading the research project will be first author on publications from that project; and Mark will be listed as the senior author.

Authorship is open to discussion. Especially when we co-author with collaborators outside the lab, there will be discussions based on the balance of contributions, from e.g. the collection of data versus the analysis of data.

The badge of "corresponding author" can carry weight: it is the author taking ultimate responsibility for all the content of the paper, on behalf of all other authors. Typically this will be Mark. But this will be discussed if it is clear the intellectual contribution of the lead author merits being the corresponding author.

5.3 Work/life balance

Working hours Scientific research is target-based, not hour based. If you are producing a constant, evident stream of work - dead-ends and all - then you're doing it right. Core hours for the lab are 10am - 4pm. All lab meetings will be within those hours.

Email policy Turn it off. Keep your focus. We use Slack precisely so that you do not have to check email to keep intra-lab communications going. Check your email when you need to use it yourself; or when you have time to execute on whatever is there. Strongly advise that you do not have work email on your phone.

Slack policy Set notifications to only arrive during core work hours (10am - 4pm). Mark will occasionally send out of hours, as I sometimes have to shuffle email/Slack around other commitments; and when I remember stuff that needs sorting. There is no expectation to respond until the core work hours.

Holidays Take some. Take a day off to recharge after intense bouts of work. Take a week or two off to get away from research. Mark takes a non-negotiable two weeks off at Christmas, and turns down all requests for work, reviews, grants etc to do so. It's awesome.

5.4 Behavioural conduct

All lab members are expected to abide by the University of Nottingham's policies for behavioural conduct. Briefly, these are:

- The Dignity at Nottingham policy. That everyone has a right to work in a positive, supportive environment, where harassment and bullying are unacceptable.
- Equality and Diversity policies. That diversity across age, gender, race, culture, physical and mental ability, religion are to be celebrated.

6 Who we work with

It's good to know who we know. These are the lab's collaborators across the world. Some of these labs are where the data comes from. Some of them we share code with. Some of them we work with informally, exchanging ideas. Some we've been working with a long time; some we've only just started down the road with.

Collaborations are a great example of the concept of "X-teams": a team created to solve a problem or do a task by bringing together experts from across different, permanent teams. With no line management or hierarchy, such X-teams can be challenging to manage, but are great for solving problems we can't tackle alone.

6.1 Local

Tobias Bast (Psychology). Tobias' lab works on the role of prefrontal cortex in learning and decision-making. They train rodents on tasks, and do pharmacological manipulations of prefrontal cortex; they also do *ex vivo* electrophysiology of PfC slices. Paula Moran is also onboard some of these projects. We work with Tobias on analysing the rats' behaviour.

Nottingham computational neuroscience community Our immediate colleagues include Mark van Rossum (Psychology and Maths); Nikos Gekas (Psychology); Matias Ison (Psychology); Chris Madan (Psychology); Steve Coombes (Maths); and Ruediger Thul (Maths).

Nottingam's Precision Imaging Beacon Nottingham has a venerable tradition in human imaging: it is both the birthplace of MRI, and currently home to the first wearable MEG system. The Beacon is the visible entity for co-ordinating that work, and we are a member. The Beacon has its own dedicated computing cluster (to which we have access), and considerable funding (for fellowships and pilot projects).

6.2 National

NeuraxiS (Nottingham and Sheffield) A joint initiative between the computational neuroscience communities at Nottingham and Sheffield Universities. Its role is to help co-ordinate the work in both universities. Its first major output is the joint bid to the Wellcome Trust DTP programme in 2019; its second will be the 2019 national conference for computational neuroscience. Mark founded the initiative, and steers it alongside Hannes Saal, Robert Schmidt and Stuart Wilson (all Sheffield). See https://sites.google.com/view/neuraxisuk for more.

Matt Jones (Bristol) Matt's lab studies prefrontal-hippocampal circuits, particularly at the intersection of learning and sleep (e.g. consolidation and replay). He is Director of Neuroscience at Bristol. Mark is a named collaborator on Matt's Wellcome Trust Senior Fellowship. We work with a substantial data-set from Matt's lab on rats learning rules in a double-ended T-maze (or H-maze). Other datasets are available to the lab.

Tom Gilbertson (University Hospital, Dundee) Tom is a clinical neurologist, specialising in dystonia. We collaborate with Tom in analysing and modelling behavioural data from his patient cohort.

Rasmus Petersen (Manchester) Rasmus' lab studies the brain's sensory processing using the rodent whisker system as a model. Rasmus and Mark held three joint grants during their time together in Manchester; two with Rasmus as PI, one with Mark as PI. We work with Rasmus on the analysis of large-scale imaging data from mouse barrel cortex [Data are from Karel Svoboda's lab at Janelia Farm; Rasmus is our main contact with Janelia].

6.3 International

Bill Frost (Chicago Medical School, RFUM) Bill's lab studies the motor systems of molluscs, particularly sea-slugs, with high-resolution voltage-sensitive dye imaging. We work together on understanding how the dynamics of neural populations controls movement.

Adrien Peyrache (Monteral Neurological Institute) Adrien's lab works on the prefrontal-hippocampal system, currently with a particular focus on the head-direction system. We work together on Adrien's data on population activity in the prefrontal cortex of rats learning rules in a Y-maze.

Jakob Dreyer (Lundbeck A/S, Copenhagen) Jakob is perhaps the world's leading modeller of dopamine release, diffusion and re-uptake. We informally work with Jakob on ideas about how the release of dopamine is related to its role in reward processing, and its effects on the basal ganglia

Jose Obeso (HM-CINAC, Madrid) Jose is a world-leading movement disorder neurologist, who heads a joint clinic and experimental lab at HM-CINAC hospital. Jose is sympathetic to the insights available from computational models. We work informally with Jose on his ideas for why dopamine neurons are lost in Parkinson's, and consult with him on the clinical relevance of computational work.

7 Who funds us

Where does the money come from? To date, the bulk of our funding has come from the Medical Research Council (MRC). But we sit at the intersection of many fields, so have previously applied for funding to the BBSRC, EPSRC, and the Wellcome Trust.

Major funds include, or will shortly include:

2012-2020 MRC Senior non-Clinical Fellowship (to Mark). "Networks of neural dynamics". Includes collaborations with Rasmus Petersen, Adrien Peyrache and Sid Wiener, and Constance Hammond

2020-2023 MRC Project Grant (NMHB). "The Neural Basis of Movement Transitions". Mark sole PI. Data and support from the labs of Bill Frost and Lee Miller (also Chicago, by coincidence).

2020-2025 BBSRC Project Grant (PI: Mark Buckley, Oxford; us, Co-I, 5% time). "Spatiotemporal neuronal system dynamics underlying hierarchical visual representations of objects and faces for primate perception and discrimination". Massive experimental data-set of population recordings from macaque prefrontal cortex during decision making tasks.

Previous projects have included:

2017-2019 MRC Project Grant (NMHB). "Resolving the size and nature of neocortical population codes". PI. With Rasmus Petersen (Co-I) and Mat Evans (named PDRA).

The UK funding landscape. Government funding for scientific research is overseen by UKRI (UK Research and Innovation). UKRI acts both as direct funder of research (via fellowships at the moment), and as the umbrella organisation which co-ordinates the seven research councils. Of the seven, the most relevant to us are the Medical Research Council (MRC); the Biology and Biotechnology Research Council (BBSRC); and the Engineering and Physical Sciences Research Council (EPSRC). These councils all directly fund personal awards (fellowships) and research-led awards (project and programme grants). All applications work much the same way: the proposal is assessed by at least 3 reviewers; the proposal, reviews and any responses allowed are considered by the relevant grant panel (which means three of the panel will have read in-depth and report to the panel); the panel ranks all proposals and funds those above the cut-off.

Third sector funding plays a big role in UK research, The UK is fortunate to be the home of the Wellcome Trust, which funds around £1 billion of research each year. The Wellcome mainly funds personal awards and clinical trials. Other major charities of relevance to us include The Leverhulme Trust and Parkinson's UK.

Historically, the UK has been the most successful of all EU nations at winning funding from the EU funding bodies, both from the large projects supported by the EU Framework funds (e.g. Horizon2020) and the personal awards from the European Research Council. We await our fate there.

8 Useful reading

This is a collection of key pieces for the lab, both on the doing of science, and on working in science.
Doing science:

- Platt, J. R. Strong Inference Science, 1964, 146, 347-353

Working in science:

- Bela Z Schmidt What 50 principal investigators taught me about my failure to land tenure. Nature, 12 February 2019.
- Richard Hamming You and Your Research. Transcript of talk given in 1986. Essential reading.