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Application to the BBR24 funding opportunity

Enabling the Next Generation of Naturalistic Long-Duration Neuroscience Experimentation with Advanced Machine Learning

April 26, 2024

1 Summary

Word limit: 550

In plain English, provide a summary we can use to identify the most suitable experts to assess your application.

Clearly describe your proposed work in terms of:

- context
- the research the infrastructure, facility or resource will enable
- aims and objectives
- potential user communities, applications and benefits

1.1 Context

The use of large amounts of data in image and speech recognition and more recently in large language models has generated breakthroughs in the capabilities of machine learning models. Yet, most animal experiments in Neuroscience still generate limited amounts of data, as animal behaviour is heavily constrained and the duration of experiments is short. Long-duration experiments, where animals can move freely in naturalistic environments, combined with advanced machine learning methods, could reveal new aspects of behaviour and brain function not evident in data generated in simpler experiments. At the Sainsbury Wellcome Centre (SWC) for Neural Circuits and Behaviour we are performing

long-duration and naturalistic foraging experiments. Here we propose to create a resource to share openly online and offline machine learning methods to process behavioural and neural data generated by these experiments. Every method shared in this resource will be demonstrated with data from the SWC foraging experiments.

1.2 The research the infrastructure, facility or resource will enable

Advanced machine learning software is essential to extract insights from the data generated by naturalistic and long-duration experiments. Thus, the software disseminated by our resource will be essential to extract insights from these experiments and could generate valuable findings.

In addition, the evaluation of different models on our foraging datasets should help researchers analysing long-duration and naturalistic experiments choose the best models for their needs, accelerating their research.

Our resource could also motivate research and development on novel machine learning methods for controlling and characterising long-duration and naturalistic experiments, as our foraging datasets could act as a testbed for methods comparison, and machine learning scientists may want to develop methods to excel in this comparison.

1.3 Aims and objectives

The first aim of the proposed resource is to enable a new type of long-duration and naturalistic animal experimentation, by sharing well-tested machine learning methods for online and offline processing of data generated by these experiments.

A second aim is to build a resource that is a reference where the best machine learning methods to control and characterise long-duration naturalistic experiments can be compared against each other on state-of-the-art foraging datasets.

1.4 Potential user communities, applications and benefits

The following user communities could benefit from the proposed resource:

research groups investigating data from long-duration naturalistic experiments could use the distributed machine learning software to analyse their data and generate scientific discoveries.

business entities using long-duration and/or naturalistic experiments could benefit from our distributed software and improve their processes. For example, pharmaceutical businesses are starting to use whole animal screening to test for side effects on drugs. They could use our distributed software to improve animal behavioural and neural monitoring.

machine learning methods developers could contribute their methods to the resource, so that they are evaluated on our foraging data, and become known to users of our repository.

2 Core team

List the key members of your team and assign them roles from the following:

- project lead (PL)
- project co-lead (UK) (PcL)
- researcher co-lead (RcL)
- specialist
- professional enabling staff
- research and innovation associate
- technician
- visiting researcher

Only list one individual as project lead.

A research technical professional or research software engineer can be listed as a project lead or project co-lead, provided that:

- their appointment is resourced from the central funds of their research organisation at the time of application
- their level of responsibilities and duties is appropriate to a person with substantial research experience
- their contract extends beyond the duration of the project

The researcher co-lead role has replaced the research co-investigator role previously used in Je-S grant applications. They will be an individual who merits appropriate recognition for making a substantial contribution to the formulation and development of the application and will be closely involved with the project.

project lead (PL) Dr. Joaquin Rapela

project co-lead (UK) (PcL) Prof. Tiago Branco, Prof. Maneesh Sahani, Prof. Thomas Mrcic-Flogel

researcher co-lead (RcL) Dr. Dario Campagner

specialist Dr. Nicholas Guilbeault

3 Application questions

3.1 Vision

Word limit: 1,700

What are you hoping to achieve with your proposed work?

What the assessors are looking for in your response

Explain how your proposed work:

- is of excellent quality and importance within or beyond the field(s) or area(s)
- has the potential to advance current understanding, or generate new knowledge, thinking or discovery within or beyond the field or area
- is timely given current trends, context, and needs
- impacts world-leading research, society, the economy, or the environment

Include the following in your statement:

- the uniqueness and expected added value of the proposed resource to the UK bioscience research community and infrastructure landscape
- how the resource relates to past and current resources in the subject area in both the UK and abroad
- full details of the resource and an overview of the associated objectives. Details on how these objectives are delivered should be included in the Approach section
- a description of the types of research that will be enabled by the resource
- consideration of the potential impact on the scientific community and other possibly dependent resources if the resource did not exist
- only if applicable, relevance of the proposed work to the plant health spotlight

In your vision, you should also clearly identify which of the following categories your proposed resource falls under, and expand on the relevant points raised below:

- establishment of a new and innovative resource that will be beneficial to a broader BBSRC user base. Explain why a new resource is needed and what unique and important features it will offer
- maturation and subsequent maintenance of a project-based resource into a community-based one. Briefly explain the background to the resource, current usage, proposed changes and the benefits this will lead to for the research community

- further development or essential maintenance of an existing community resource, with well-established access mechanisms. Explain current usage and how this project will increase its relevance, quality and utility, for example:
 - by enabling the resource to support FAIR (findable, accessible, interoperable, reusable) principles
 - by enabling new uses, for example metadata enrichment for machine learning and AI approaches
- association, or integration, of distinct resources. Explain current usage and how the proposed plans will create an upgraded resource with a greater value than the sum of the parts

References may be included within this section.

You may demonstrate elements of your responses in visual form if relevant. Further details are provided in the Funding Service.

Conventional versus modern neuroscience experimentation

Conventional system neuroscience experiments heavily constrain the behaviour of their subjects in order to simplify behavioural and neural analysis. However, important aspects of brain function may not be expressed in these constrained behaviours and these aspects may only manifest in naturalistic experimental conditions.

Recent technological advances now allow to build complex naturalistic experiments, while measuring a large number of experimental variables and recording from a large number of neurons simultaneously. These advances allow unrestrained subjects behaviour with precise monitoring of what happens in the subjects' environment and brain.

Important examples of these experiments are naturalistic foraging experiments, where freely moving subjects search for food in unrestrained environments. Foraging studies are currently underway at major research centres around the world (e.g., the Allen Institute for Brain Research, Janelia Farm, the Max Plank Institute of Animal Behaviour).

A complication of naturalistic neuroscience experiments is extracting meaning from the plethora of data that they generate. Machine learning methods are specially helpful to address this problem. For example, they can be used to extract subjects' internal states from behavioural measurements, to extract low-dimensional latent variables from high-dimensional neural recordings, and to relate the inferred subjects' internal state to the neural latent variables.

The data generated by conventional system neuroscience experiments can be understood by just plotting a few of its variables. However, interpreting the output of naturalistic experiments is more difficult and machine learning methods become essential for this.

Long-duration and naturalistic SWC experiments

At the SWC we are performing a novel type of naturalistic and long-duration foraging experiments. Mice are housed in large arenas (two meters in diameter) equipped with a nest, where animals can rest and drink, and with food patches, where animals can get food pellets after moving a wheel for a fixed configurable distance. Mice live in the arena for extended periods of time. We monitor the behaviour of mice in detail with multiple high-resolution video cameras, to monitor the positions of mice body parts, ultrasound audio cameras, to monitor mice vocalisations, and a scale in the nest, to regularly measure mice weights. We record neural activity using Neuropixel probes with 5,000 channels, from which 384 channels can be selected for recording, and with 64-channel probes, equipped with an electrical stimulator and an optical stimulator. We are running foraging experiments with one or multiple mice per arena.

A unique feature of our foraging experiments is their long duration. We have already recorded behaviour and neural activity of mice continuously for 48 hours and by the end of 2024 we aim at recording continuously for two weeks.

These long-duration experiments are allowing us to address foraging questions that cannot be studied in shorter experiments. For example, scientifically these experiments allow us to ask how do mice foraging patterns change across days, and what are the neural mechanisms underlying these changes. Statistically, the large amount of data recorded in the new experiments allows us to estimate parameters of much more complex models than those that can be fitted to data from conventional system neuroscience experiments.

Proposed resource

Here we propose to create a resource to share openly machine learning software implementations of methods to process behavioural and neural data generated by long-duration naturalistic experiments. Whenever possible we will distribute offline and online implementations of a distributed method. The software in our resource will be thoroughly demonstrated with data from our foraging experiments.

We will initially distribute in the resource methods that we have used in our foraging experiments. For most functionalities we have used more than one method, and we will distribute all of them. In this way experimental neuroscientists around the globe would be able to compare the functionality of different distributed methods and choose the one more suitable for their experimental data.

We will also welcome contributions from machine learning method developers interested in applying their methods to the data generated by our foraging experiments. In this way, our foraging experiment will become a testbed for machine learning methods for the characterization of foraging experiments, which could motivate machine learning method developers to contribute better and better methods to our resource.

Intelligent experimental control with Bonsai

Bonsai is a reactive visual programming environment developed by NeuroGEARS Ltd that is widely used in Neuroscience for controlling sophisticated neuroscience experiments. Reactive programs are very different from procedural ones (like C or Python). The main entity of a reactive program is stream and a reactive program is a sequence of stream transformations that get an input stream and transform it an output one. Reactive programs are ideal to process online data, like that generated in animal neuroscience experiments.

Funded by a BBR award¹ we at the SWC, GCNU and NeuroGEARS are adding machine learning methods to Bonsai. A central goal is to allow Bonsai to control neuroscience experiments based on inferences performed online on behavioral and neural data.

Not all algorithms that we propose to distribute in this resource admit and online implementation, however most of them do. Whenever possible, we will distribute online versions of the distributed methods implemented in Bonsai.

Resource background

In October 2021? the SWC began building hardware and software infrastructure to record behaviour and neural activity of freely moving mice foraging in large arenas. Our initial focus was on monitoring behavior for extended periods of time. We have been able to monitor mice positions, their food consumption and weight for up to xx weeks in experiment with different food delivery policies.

More recently we have been able to record behavior (as described above) and neural activity (Neuropixel array, four shanks, 384 electrodes per shank) for up to 48 hours.

We have developed computer vision methods to track the center of mass of foraging mice, linear dynamical methods to infer mice kinematics (e.g., velocity and acceleration) from tracked positions and Hidden Markov Models to infer mice states from kinematics inferences. We have also linear and nonlinear regression models to predict mice patch visit durations from inferred kinematics and states.

We have not yet processed neural recordings from the foraging experiment. However, at the GCNU we have extensive experience developing and applying advanced statistical models for neural recordings, which will expedite our processing of neural foraging data.

We expect that a position paper describing our foraging experiments will be published by ??/????

Why is the proposed resource unique and timely

Long-duration and naturalistic experimentation is the future of neuroscience. Animal foraging is a central neuroscience problem today, and multiple groups

¹<https://gow.bbsrc.ukri.org/grants/AwardDetails.aspx?FundingReference=BB%2FW019132%2F1>

around the world are working on this topic (e.g., Allen Institute for Neural Dynamics, Janelia Farm, Max Plank Institute of Animal Behavior). It is imperative for the UK to become a leader on this new type of experimentation.

The foraging data that we are creating, and the machine learning methods that we propose to distribute, are key elements to enable world-class foraging research. We (the SWC, GCNU and NeuroGEARS) are an excellent team to develop the proposed resource. The SWC is at the forefront of experimental neuroscience research. Specifically, it has been building mice foraging experiments for more than three years. The GCNU is a leader in computational neuroscience and machine learning, with ample experience in building methods to characterize neural data, and more recently in distributing openly machine learning methods. And NeuroGEARS has more than a decade building high-quality software for experimental neuroscience.

3.2 Approach

Word limit: 4,400

How are you going to deliver your proposed work?

What the assessors are looking for in your response

Explain how you have designed your approach so that it:

- is effective and appropriate to achieve your objectives
- is feasible, and comprehensively identifies any risks to delivery and how they will be managed
- uses a clearly written and transparent methodology (if applicable)
- summarises the previous work and describes how this will be built upon and progressed (if applicable)
- will maximise translation of outputs into outcomes and impacts
- describes how your, and if applicable your team's, research environment (in terms of the place and relevance to the project) will contribute to the success of the work

Include the following when describing your approach:

- measurable targets against which the outcome of the work will be assessed
- significant technical details for the development, maintenance or enhancement of the resource, indicating how this is of internationally exceptional quality
- any proposed research efforts and how they directly facilitate development of the resource (if applicable)
- if the focus is on maintaining an existing resource instead of suggesting further development, provide evidence of why significant upgrades are not required at this time and detail why the resource needs continued support to maintain world-leading functionality (if applicable)

Describe the specific contribution of each applicant to the proposed resource:

- their scientific contributions, for example, research field and specialist knowledge, experience, resource management expertise, technical and data analysis expertise
- their role and responsibilities, for example, managerial, leadership, mentoring
- references to specific work packages are recommended
- highlight where applicants will work collaboratively to deliver specific project requirements

- include clear time commitments for each applicant

There is no need to duplicate information included in the ‘Applicant and team capability to deliver’ section.

References may be included within this section.

You may demonstrate elements of your responses in visual form if relevant. Further details are provided in the Funding Service.

A project Gantt chart is compulsory and should be inserted as an image at the very end of this section. The Gantt chart should identify appropriate deliverables, responsibilities and time points for each objective.

The proposed resource will distribute machine learning methods to process behavioural data and neural data, to perform simulations and to compress behavioral and neural data. The resource will also distribute data from our foraging experiments that will be used to evaluate the functionality of all methods distributed by us and of those contributed by external developers.

3.2.1 Methods to process behavioral measurements

Linear dynamical systems models Linear dynamical systems (LDS) models are used to characterize time-varying observations as a function of hidden (i.e., latent) state variables that vary over time. It assumes that both state and observed variables are Gaussian. The Kalman filter algorithm can be used to infer the probability distribution of latent variables given observations. More information about LDS can be found in (Durbin and Koopman, 2012, part I).

We have developed an implementation of LDS models and used it to infer denoised positions, velocities and accelerations of foraging mice from noisy and incomplete position measurements [offline](#) and [online](#) with Bonsai.

Nonlinear and non-Gaussian dynamical systems models The LDS model is very versatile and can be used to model a wide range of time-series observation. However, there are cases where this model does not apply and nonlinear and non-Gaussians extensions are needed, like extended Kalman filter, the unscented Kalman filter and the particle filter (Durbin and Koopman, 2012, part II).

We have created the Poisson Linear Dynamical System model (PLDS) to characterize count observations (Macke et al., 2015) and distributed a Matlab implementation². This is an offline implementation, and we have not yet produced an online one. We have neither use PLDS to model behavioral or neural foraging data.

Hidden Markov models The hidden Markov model (HMM) is a latent variable model similar to the LDS model, but in the HMM states are discrete (? , Chapter 13). It is used to assign discrete states to time series observations.

We have developed an offline [implementation](#) of the HMM, used it to find repeatable states in epileptic seizures of human subjects, from unique Utah

²https://bitbucket.org/mackelab/pop_spike_dyn

array recordings of their neural activity (?). We have also used the HMM to infer mouse foraging states from kinematic inferences from the LDS model. We are currently building an online implementation of the HMM.

Generalized linear models Generalized linear models (GLMs) are regression models for observations with diverse noise distributions (i.e., noise distributions in the exponential family). For example, they can be used to estimate a linear regression model with spike count as the observation variable.

We have used a Gaussian GLM (i.e., a standard linear regression model) to study which of a large set of regressors (e.g., average speed or acceleration before entering a patch, amount of reward obtained in the previous visit to the current patch, amount of reward obtained in the previous visit to the other patch, weights). We have used a Bonsai implementation of online Bayesian linear regression to estimate receptive fields of cells in the primary visual cortex.

Deep neural networks

Switching linear dynamical systems models

Pose estimation methods

3.2.2 Methods to process neural measurements

Latent variable models

Gaussian linear dynamical systems

Poisson linear dynamical systems

Gaussian process factor analysis

Sparse variational Gaussian process factor analysis

Latent factor analysis via dynamical systems (LFADS)

CEBRA

3.2.3 Methods to simulate foraging data

3.2.4 Methods for compressing behavioral and neural measurements

3.2.5 Data sharing

3.3 Community demand: letters (or emails) of support

Letters (or emails) of support demonstrating community demand are mandatory for BBR.

Upload a single PDF of maximum 8MB containing a maximum of 10 letters or emails of support. These should be uploaded in English or Welsh only. Enter the words ‘attachment supplied’ in the text box.

What the assessors are looking for in your response

The letters should give an indication of community demand for the resource in question, demonstrating the breadth of research and the high-quality science relevant to BBSRC remit that the resource would underpin.

Add the following details for each letter:

1. the organisation name (searchable via a drop-down list or enter the organisation’s details manually, as applicable)
2. contact name of the signatory

Letters of support aimed at demonstrating community demand should:

1. outline the uniqueness and expected added value of the proposed resource to the UK bioscience research community and infrastructure landscape
2. clearly explain the impact and benefit of the proposed resource on the writer’s research and the associated community
3. if possible, explain where this supported research has already demonstrated or could have potential for particular scientific, economic or societal impact
4. help to demonstrate the breadth of the relevant user community

Letters of support that fail to do so, in particular template letters indicating generic support without identifying a particular usage, are of negligible value for the assessment and should not be submitted. Carefully chosen letters containing relevant evidence of the requirement or benefit to be gained, are of greater value than large numbers of letters.

The Funding Service will provide document upload details when you apply.

3.4 Applicant and team capability to deliver

Word limit: 1,650

Why are you the right individual or team to successfully deliver the proposed work?

What the assessors are looking for in your response

Evidence of how you, and if relevant your team, have:

- the relevant experience (appropriate to career stage) to deliver the proposed work
- the right balance of skills and expertise to cover the proposed work
- the appropriate leadership and management skills to deliver the work and your approach to develop others
- contributed to developing a positive research environment and wider community

You may demonstrate elements of your responses in visual form if relevant. Further details are provided in the Funding Service.

The word count for this section is 1,650 words: 1,150 words to be used for R4RI modules (including references) and, if necessary, a further 500 words for Additions.

Use the Résumé for Research and Innovation (R4RI) format to showcase the range of relevant skills you and, if relevant, your team (project and project co-leads, researchers, technicians, specialists, partners and so on) have and how this will help deliver the proposed work. You can include individuals' specific achievements but only choose past contributions that best evidence their ability to deliver this work.

Complete this section using the R4RI module headings listed. Use each heading once and include a response for the whole team, see the UKRI guidance on R4RI. You should consider how to balance your answer, and emphasise where appropriate the key skills each team member brings:

- contributions to the generation of new ideas, tools, methodologies, or knowledge
- the development of others and maintenance of effective working relationships
- contributions to the wider research and innovation community
- contributions to broader research or innovation users and audiences and towards wider societal benefit

Additions

Provide any further details relevant to your application. This section is optional and can be up to 500 words. You should not use it to describe additional

skills, experiences, or outputs, but you can use it to describe any factors that provide context for the rest of your R4RI (for example, details of career breaks if you wish to disclose them).

Complete this as a narrative. Do not format it like a CV.

There is no need to duplicate information included in the ‘Approach’ section.

UKRI has introduced new role types for funding opportunities being run on the new Funding Service.

For full details, see [Eligibility as an individual](#).

References may be included within this section.

3.5 Project partners

Add details about any project partners' contributions. If there are no project partners, you can indicate this on the Funding Service.

A project partner is a collaborating organisation who will have an integral role in the proposed research. This may include direct (cash) or indirect (in-kind) contributions such as expertise, staff time or use of facilities.

Add the following project partner details:

- the organisation name and address (searchable via a drop-down list or enter the organisation's details manually, as applicable)
- the project partner contact name and email address
- the type of contribution (direct or in-direct) and its monetary value

If a detail is entered incorrectly and you have saved the entry, remove the specific project partner record and re-add it with the correct information.

For audit purposes, UKRI requires formal collaboration agreements to be put in place if an award is made.

3.6 Project partners: letters (or emails) of support

Upload a single PDF containing the letters or emails of support from each partner you named in the Project Partner section. These should be uploaded in English or Welsh only.

Enter the words ‘attachment supplied’ in the text box, or if you do not have any project partners enter N/A.

What the assessors are looking for in your response Each letter or email you provide should:

- confirm the partner’s commitment to the project
- clearly explain the value, relevance, and possible benefits of the work to them
- describe any additional value that they bring to the project

The Funding Service will provide document upload details when you apply. If you do not have any project partners, you will be able to indicate this in the Funding Service.

Ensure you have prior agreement from project partners so that, if you are offered funding, they will support your project as indicated in the project partners’ section.

For audit purposes, UKRI requires formal collaboration agreements to be put in place if an award is made.

3.7 Management strategy

Word limit: 500

How do you plan to manage the resource?

What the assessors are looking for in your response

1. resources will be expected to have governance arrangements appropriate for the oversight and successful delivery of the project's complexity
2. provide details about the project's management and advisory structure
3. provide details of the approach to project and risk management, and the monitoring strategy for tracking progress of the proposed programme
4. provide details on how demand and access requests will be managed, and what support will be provided to the users of the resource
5. an advisory board is required for all projects, which is independent from both the academic institutions and project partners involved in the proposal. Provide information on the proposed membership of this advisory board and how it will be used
6. provide details on how the resource user perspective and their needs will be considered, including how feedback will be sought and subsequently used to inform the management of the resource

You may demonstrate elements of your responses in visual form if relevant. Further details are provided in the Funding Service.

3.8 Data management and sharing

Word limit: 1,500

How will you manage and share data collected or acquired as part of the proposed resource?

What the assessors are looking for in your response

Provide a data management plan using the [BBR DMP template](#) (PDF, 161KB) structure that clearly details how your proposed resource will comply with UKRI's published [data sharing policy](#), which includes detailed guidance notes.

3.9 Trusted Research and Innovation (TR&I)

Word limit: 500

Does the proposed work involve international collaboration in a sensitive research or technology area?

What the assessors are looking for in your response

Demonstrate how your proposed international collaboration relates to trusted research and innovation, including:

- list the countries your international project co-leads, project partners and visiting researchers, or other collaborators are based in
- if international collaboration is involved, explain whether this project is relevant to one or more of the 17 areas of the UK National Security and Investment (NSI) Act
- if one or more of the 17 areas of the UK National Security and Investment (NSI) Act are involved, please identify which areas

If your proposed work does not involve any international collaboration, answer 'n/a' here.

We may ask you to provide additional information about how your proposed project will comply with our approach and expectation towards TR&I, identifying potential risks and the relevant controls you will put in place to help proportionately reduce these risks.

3.10 Resources and cost justification

Word limit: 1,000

What will you need to deliver your proposed work and how much will it cost?

What the assessors are looking for in your response

Justify the application's more costly resources, in particular:

- project staff
- significant travel for field work or collaboration (but not regular travel between collaborating organisations or to conferences)
- any equipment that will cost more than £10,000
- any consumables beyond typical requirements, or that are required in exceptional quantities
- all facilities and infrastructure costs
- all resources that have been costed as 'Exceptions'

Assessors are not looking for detailed costs or a line-by-line breakdown of all project resources. Overall, they want you to demonstrate how the resources you anticipate needing for your proposed work:

are comprehensive, appropriate, and justified

- represent the optimal use of resources to achieve the intended outcomes
- maximise potential outcomes and impacts
- evidence appropriate consideration for alternative long-term sustainability options beyond BBSRC funding

3.11 Your organisation’s support

Word limit: 500

Provide details of support from your research organisation and project co-lead research organisations.

What the assessors are looking for in your response

Provide a statement of support from all participating research organisations detailing why they are best placed to support the proposed project. This should include details of any matched funding that will be provided to support the activity and any additional support that might add value to the work.

Assessors will be looking for a strong statement of commitment from your research organisations.

BBSRC recognises that in some instances, this information may be provided by the Research Office, the Technology Transfer Office (TTO) or equivalent, or a combination of both.

You must also include the following details:

- a significant person’s name and their position, from the TTO or Research Office, or both
- office address or web link

Upload details are provided within the service on the actual application.

We do not require separate institutional letters of support as attachments. By submitting your application to us, you are confirming that your institutions are supportive of and committed to your project.

References

- Durbin, J. and Koopman, S. J. (2012). *Time series analysis by state space methods*, volume 38. OUP Oxford.
- Macke, J. H., Buesing, L., and Sahani, M. (2015). *Estimating state and parameters in state space models of spike trains*, page 137–159. Cambridge University Press.