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# Intention to submit document for the Work with US researchers BBSRC-NSF/BIO lead agency 2024 funding opportunity

# Enabling Naturalistic, Long-Duration and Continual Neuroscience Experimentation with Advanced Machine Learning

October 24, 2024

## 1 Summary

Word limit: 2 A summary is not required for this section, please write 'N/A' in the textbox. Please still include a title for your project.

N/A

# 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)
- specialist
- professional enabling staff
- research and innovation associate
- technician
- researcher co-lead (RcL)

Only list one individual as project lead.

The core team section must only contain details of the UK applicants. The US applicant information should be listed in the 'US applicants' section.

Find out more about UKRI's core team roles in funding applications.

**project lead (PL)** Prof. Maneesh Sahani

**project co-lead (UK) (PcL)** Prof. Tiago Branco, Prof. Thomas Mrsic-Flogel

**researcher co-lead (UK) (RcL)** Dr. Joaquin Rapela, Dr. Dario Campagner

# 3 Application questions

## 3.1 Research theme

Word limit: 5 Please state the research theme you are applying under. Choose one of the following research themes:

1. biological informatics
2. understanding host-microbe interactions
3. synthetic cells and cellular systems
4. synthetic microbial communities

biological informatics

## 3.2 Vision

Word limit: 500

What are you hoping to achieve with your proposed work?

What the assessors are looking for in your response

Your vision should clearly address:

- one of the opportunity research themes (biological informatics, understanding host-microbe interactions, synthetic cells and cellular systems or synthetic microbial communities)
- the remit of the BBSRC and the NSF/BIO division associated with your chosen research theme

References may be included within this section, but this will count towards your word count.

Images are not required for this section.

### 3.2.1 Context

Conventional systems neuroscience experiments are typically short in duration and often place significant constraints on subject behavior to simplify data analysis. However, these restrictions may limit our ability to observe critical aspects of brain function and behavior that only manifest in more naturalistic and extended conditions.

At the Sainsbury Wellcome Centre (SWC), we are pioneering Naturalistic, Long-Duration, and Continual (NaLoDuCo) foraging experiments in mice that span weeks to months. During these experiments, we collect high-resolution behavioural and neural recordings in naturalistic settings. In collaboration with the Gatsby Computational Neuroscience Unit (GCNU), we are developing novel analytical methods to interpret this data.

This novel experimental approach will enable researchers to explore neural mechanisms underlying naturalistic behavior over extended periods for the first time, offering the possibility of uncovering insights across a wide range of phenomena, including long-term behavioral adaptation, neural plasticity, and learning.

We aim to empower research centers worldwide to adopt this groundbreaking approach. However, the scale and complexity of the data generated pose significant challenges in data acquisition, visualisation, and analysis. In this proposal, we will address these challenges by sharing openly expertise and software to enable this transformative type of experimentation.

### 3.2.2 Focus areas

Below, we outline the key focus areas we aim to address. Challenges addressing these areas primarily revolve around the collection and analysis of continuously recorded, extremely large datasets–on the order of hundreds of terabytes–gathered from experiments spanning weeks to months.

While experiments in neuroscience that are naturalistic, long-duration, or continuous have been conducted in the past [e.g., 12, 16, 28], to the best of our knowledge, we are the first to integrate all three of these features in a single experimental paradigm. This combination introduces unprecedented complexities in data processing, as we aim to capture behavior and brain activity in their most ecologically valid, extended, and uninterrupted forms.

The focus areas of the proposed project are (Figure 1):

**Data Collection & Management** Efficiently gathering and organizing massive datasets over extended periods.

**Data Sharing** Providing global access to large-scale datasets.

**Data Visualization** Developing efficient web-based tools to visualize very large behavioral and neural datasets.

**Spike Sorting** Assigning spikes to neurons reliably and tracking individual neurons across long-periods of time in real time.

**Data Analysis** Characterizing behavioral and neural recordings (Figure 2).

**Inference-Driven Experimentation** Creating a new type of experimentation driven by real-time behavioral and neural inferences.

We are a unique team to implement this project. The SWC is a world leader in experimental neuroscience, and the GCNU is an authority in computational neuroscience and machine learning. Both institutions share the same building and have been collaborating extensively since 2005. NeuroGEARS Ltd. has been a key business partner for the implementation of the NaLoDuCo experimental framework since the project started in 2021, while Catalyst Neuro has played a pivotal role in developing and operating the DANDI archive, in collaboration with Dr. Jeremy Magland, an expert in spike sorting, data visualization, and cloud computing.

## 3.3 Approach

Word limit: 500

How are you going to deliver your proposed work?

What the assessors are looking for in your response

Your approach should give an overview highlighting:

- a clear description of the objectives and methodology for the proposed work, including the contributions of the UK and US teams
- the potential outputs and outcomes of the proposed work

References may be included within this section, but this will count towards your word count.

Images are not required for this section.

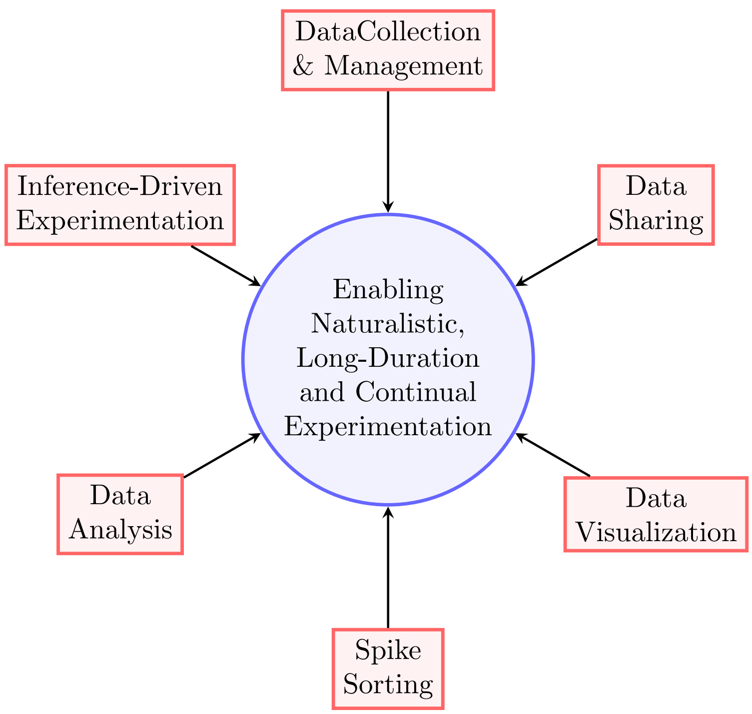



Figure 1: Project theme (blue) and focus areas (red).

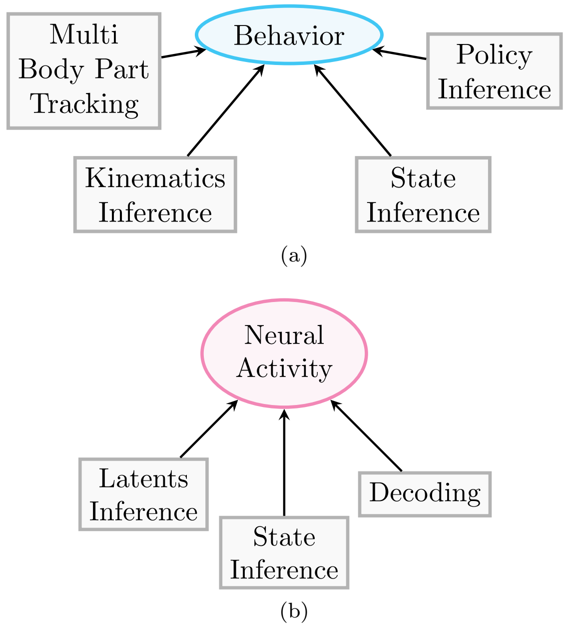


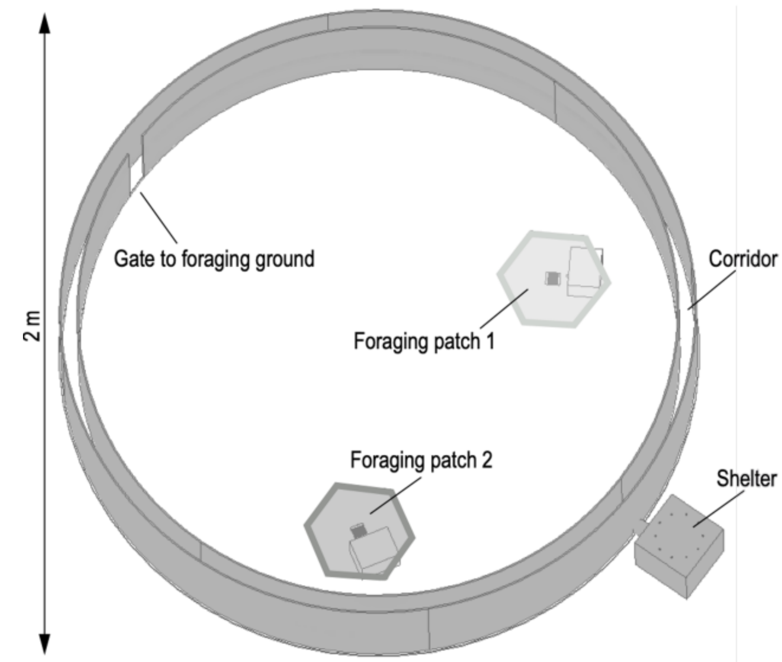

Figure 2: Behavioral (a) and neural (b) data analysis problems to address.

### 3.3.1 Data collection & management

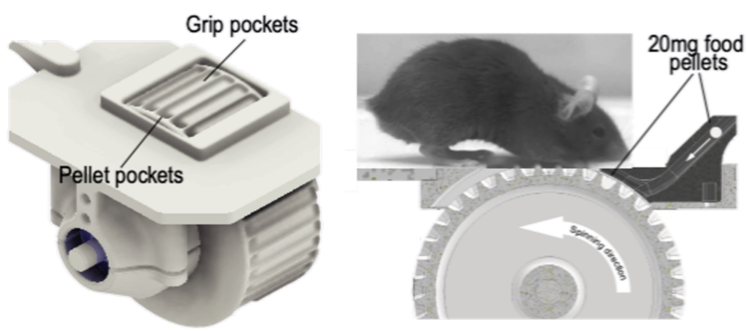
We have developed an innovative platform for housing of mice in large arenas (>2m diameter) enabling precise behavioral manipulation and high-resolution monitoring [Figure 3, 2]. The software for data acquistion [9] and management [10] has been openly shared. Additionally, the platforms supports continuous, long term monitoring of neural activity with Neuropixels probes, capable of recording from thousands of neurons simultaneously spanning the entire brain depth. This setup has allowed us to collect several week-long datasets with single and multiple mice per arena.

### 3.3.2 Data sharing

The large dataset sizes generated by NaLoDuCo experiments, on the order of hundreads of terabytes, make it impractical to distribute data to users, and require to bring users to data. Fortunately, cloud technologies are now mature to allows this. We will store data in the Distributed Archives for Neuroscience Data Integration (DANDI), which uses Amazon S3 buckets, and we will provide software to visualize and analyze data in Amazon EC2 instances, to avoid costly data transfers.




(a)




(b)

Figure 3: Foraging Arena (a) and Feeder (b). The arena is composed of tessellated hexagonal tiles (a), each featuring a newly designed underground feeder (b). Pellets are dispensed onto a foraging wheel once the mouse has spun it for a pre-defined programmable distance threshold using its forepaws (fictive digging). The arena contains up to six scale-equipped nesting modules that allows housing of mice in the arena and weight monitoring. Behavioural monitoring is achieved by an array of high-speed cameras (up to 15), by which mouse location, mouse identity and body parts can be track in real time.

### 3.3.3 Data visualisation

Our visualisation tools need to display very large datasets at different temporal scales, from milliseconds to weeks and months, and they need to be web based. We will use multi-resolution visualization techniques, which store data at various resolutions, and use the approriate resolution for each zoom level. Web-based visualisation will be optimized using web workers [6].

### 3.3.4 Spike sorting

Spike sorting is specially challenging in NaLoDuCo experimentation since we want to track individual neurons of freely moving mice for weeks to months. In addition, we need online spike sorting, to allow experiments driven by real-time machine learning inference, as described below.

We will evaluate methods for tracking neurons over long periods of time [e.g., 31, 27] and for online sorting [e.g., 23, 25].

### 3.3.5 Data analysis

The very large size of NaLoDuCo experimental data, the fact that the statistics of these data change across time, and the requirement for real-time and close-loop inference create new challenges to conventional machine learning data analysis methods. We will evaluate existing methods targeting the experimental problems in Figure 2 and, if necessary, modify them, or create new ones, to address the previous challenges.

For behavioral data, we will evaluate methods to:

- track multiple body parts of animals [e.g., 17, 20, 1, and a switching-linear-dyanamical method using RFIDs that we will develop],
- infer kinematics of foraging mice [e.g., 21, 3],
- segment behavior into discrete states [e.g., 30, 11, and a hierarchical HMM that we will develop],
- infer the rules that govern mice behavior from behavioral observations only (i.e., policy inference) [e.g., 33, 32].

For neural data, we will evaluate methods to:

- estimate low-dimensional continual representations of neural activity (i.e., latents inference) [e.g., 15, 7, 29, 19, 24],
- segment neural activity into discrete states [e.g., 4, 8],
- decode environment variables from neural activity [e.g., 5, 13, 26].

### 3.3.6 Inference-driven experimentation

We call inference-driven experimentation to a type of experimentation driven by machine learning inferences on neural or behavioral data, where the result of these inferences can change the experiment in real time.

We will apply inference-driven experimentation to test if patterns of neural activity are causally related to foraging behaviors. We would first check that a pattern of neural activity always precedes a given foraging behavior. We would then detect the occurence of the pattern and in real time optogenetically inactivate the neurons responsible for the pattern. If the behavior dissapears the causality argument would be supported.

For this we will use the Bonsai ecosystem for experimental control [14] and online machine learning functionality that we are adding to Bonsai [22], funded by a BBSRC award [18].

## 3.4 US applicants

Word limit: 200

Please provide the following details of the US applicants on this application:

1. name
2. institute
3. job title
4. role in project (for example, project lead or project co-lead)
5. email address

Please also indicate who the lead US applicant will be.

NSF will use this information to confirm applicant eligibility.

Please do not include details of US applicants in the 'Core team' section.

## 3.5 Resources

Word limit: 200

Please provide the following:

- overall estimates for costings and staffing full time equivalent (FTE) for both the UK and US components
- clear separation of UK and US costings, in pounds sterling and US dollars (USD) respectively

The overall budget should be below the maximum £2 million combined funder contribution

If there is more than one UK or US team associated with the application, please combine their estimates together.

A detailed calculation and breakdown of resources is not required at this stage, nor is a justification of costs.

The following is an example of how this might look.

UK Resources:

Total cost estimate: £600,000

Research council contribution: £480,000

0.2 FTE time, 1.0 FTE PDRA, 0.5 FTE technician

US Resources:

Total cost estimate: $300,000

1.0 FTE PDRA or 1.0 FTE doctoral researcher

Total funder contribution estimate:

£716,475 (£480,000 + £236,475 ($300,000 at exchange rate 0.79))

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