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1 Intention to submit document for the Work with
2 US researchers BBSRC-NSF/BIO lead agency
3 2024 funding opportunity

4 Enabling Naturalistic, Long-Duration and
5 Continual Neuroscience Experimentation with
6 Advanced Machine Learning

7
8 October 26, 2024

9 **1 Summary**

10 Word limit: 2 A summary is not required for this section, please write 'N/A' in
11 the textbox. Please still include a title for your project.
12 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

professional enabling staff Dr. Adam Tyson

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

1 3.2 Vision

2 Word limit: 500

3 What are you hoping to achieve with your proposed work?

4 What the assessors are looking for in your response

5 Your vision should clearly address:

- 6 • one of the opportunity research themes (biological informatics, under-
7 standing host-microbe interactions, synthetic cells and cellular systems or
8 synthetic microbial communities)
- 9 • the remit of the BBSRC and the NSF/BIO division associated with your
10 chosen research theme

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

13 Images are not required for this section.

14 3.2.1 Context

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

20 At the Sainsbury Wellcome Centre (SWC) and Gatsby Computational Neu-
21 roscience Unit (GCNU) we are pioneering Naturalistic, Long-Duration, and
22 Continual (NaLoDuCo) foraging experiments in mice that span weeks to months.
23 During these experiments, we collect high-resolution behavioural and neural
24 recordings in naturalistic settings.

25 This novel experimental approach will enable researchers to explore neural
26 mechanisms underlying naturalistic behaviour over extended periods for the
27 first time, offering the possibility of uncovering insights across a wide range
28 of phenomena, including long-term behavioural adaptation, neural plasticity,
29 and learning. The data generated from NaLoDuCo experiments represent an
30 entirely new resource in neuroscience, with the potential to drive breakthroughs
31 and discoveries that are beyond the reach of traditional experiments.

32 While experiments in neuroscience that are naturalistic, long-duration, or
33 continuous have been conducted in the past [e.g., 12, 16, 28], to the best of our
34 knowledge, we are the first to integrate all three of these features in a single
35 experimental paradigm.

36 Our US collaborator, the Allen Institute for Neural Dynamics (AIND) is
37 also investigating foraging, but using head-fixed mice. Key to their mission
38 is distributing very large Neuroscience datasets, and providing functionality to
39 process them on the cloud.

40 Since the project started in 2021, our UK business partner, NeuroGEARS
41 Ltd. has been contracted by the SWC to lead the implementation of the NaLo-
42 DuCo experimental framework. It also provides services to the AIND.

1 The extremely large datasets—on the order of hundreds of terabytes—gath-
2 ered from experiments spanning weeks to months pose significant challenges
3 in data acquisition, visualisation, and analysis. Together, the GCNU, SWC,
4 AIND and NeuroGEARS will address these challenges, co-develop this new
5 type of experimentation, share expertise and build software infrastructure to
6 help scientistis around the world perform NaLoDuCo experiments.

7 **3.2.2 Focus areas**

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

9 **Data Collection & Management** Efficiently gathering and organising mas-
10 sive datasets over extended periods.

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

12 **Data Visualisation** Developing efficient web-based tools to visualise very large
13 behavioural and neural datasets.

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

16 **Data Analysis** Characterising behavioural and neural recordings (Figure 2).

17 **Inference-Driven Experimentation** Creating a new type of experimenta-
18 tion driven by real-time behavioural and neural inferences.

19 **3.2.3 Cross fertilisation**

20 The foraging experiments at the AIND are different from those at the SWC.
21 They do not probe freely moving and naturalistic behaviour, but are able to per-
22 form electrophysiological recordings more densely than those at the SWC. These
23 experimental approaches to foraging are complementary and this collaboration
24 will greatly benefit both of them.

25 Currently, both GCNU and AIND are independently developing methods
26 to address the focus areas outlined in Figure 1. We will joint forces to co-
27 develop these areas and our foraging research programs, leveraging our combined
28 expertise for greater impact.

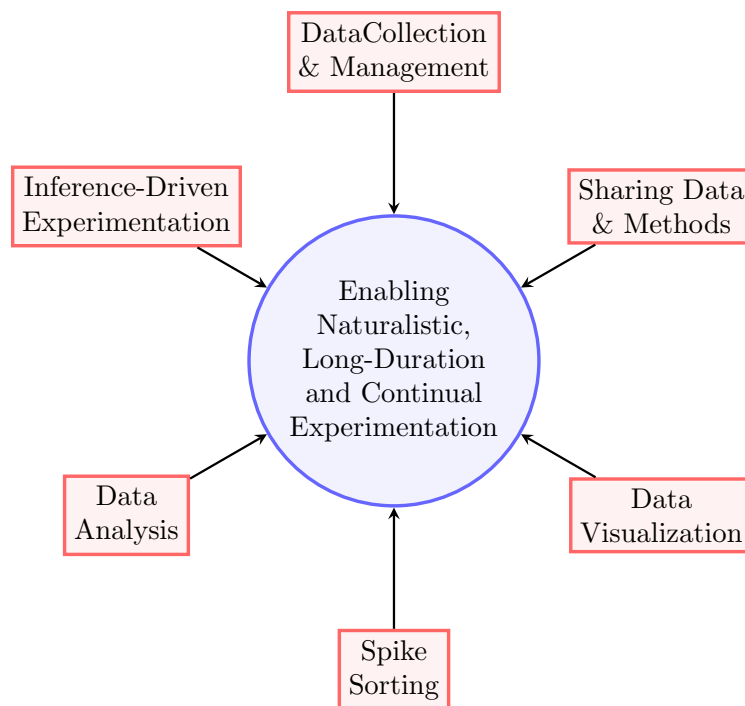


Figure 1: Project theme (blue) and focus areas (red).

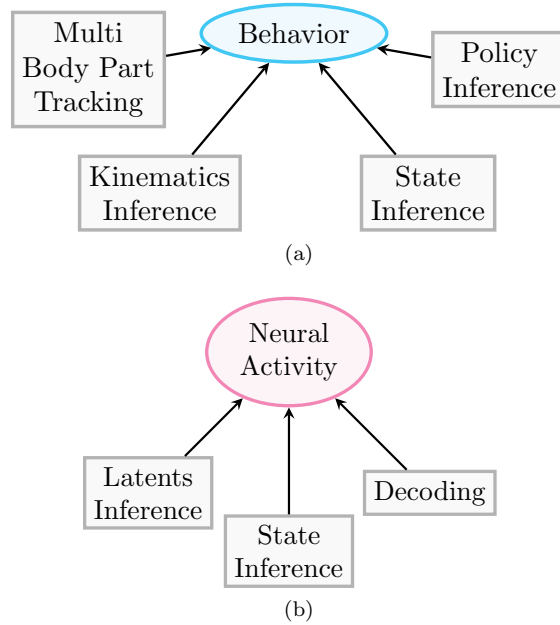


Figure 2: Behavioural (a) and neural (b) data analysis problems to address.

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.

3.3.1 Data collection & management

We have developed an innovative platform for housing of mice in large arenas (>2m diameter) enabling precise behavioural manipulation and high-resolution monitoring [Figure 3, 2]. We have openly shared software for supporting data acquisition [9] and management [10] in this arena. Additionally, the platforms supports continuous, long term monitoring of neural activity with Neuropixels probes, capable of recording from thousands of neurons simultaneously spanning

1 the entire brain depth. This setup has allowed us to collect several week-long
2 datasets with single and multiple mice per arena.

3 To facilitate the replication of our experimental setup by other groups, we
4 will share instructions for building foraging arenas, as well as specifications of
5 hardware used in them, and we will improve the documentation of the software
6 repositories for data acquisition and management.

7 **3.3.2 Sharing data and methods**

8 NaLoDuCo experiments produce vast datasets, often exceeding hundreds of ter-
9 abytes, making traditional methods of data distribution inefficient and imprac-
10 tical. Instead, users will interact with the data directly where it is stored. The
11 maturation of cloud technologies now enables scalable and efficient solutions for
12 handling such large volumes of data.

13 We will leverage the Distributed Archives for Neuroscience Data Integra-
14 tion (DANDI), which utilizes Amazon S3 storage, for hosting the data. Addi-
15 tionally, we will provide software to visualize and analyze data using Amazon
16 EC2 instances, thereby minimizing the need for costly and time-consuming data
17 transfers.

18 Handling and sharing continuous behavioral and neural recordings of this
19 scale presents unique challenges. For instance, analyzing such large datasets ef-
20 ficiently is a key concern. We will assess the computational performance of the
21 methods used to address the problems in Figure 2. If we encounter unaccept-
22 able delays, we will explore advanced optimization strategies, such as parallel
23 processing and resource-efficient cloud configurations.

24 **3.3.3 Data visualisation**

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

30 **3.3.4 Spike sorting**

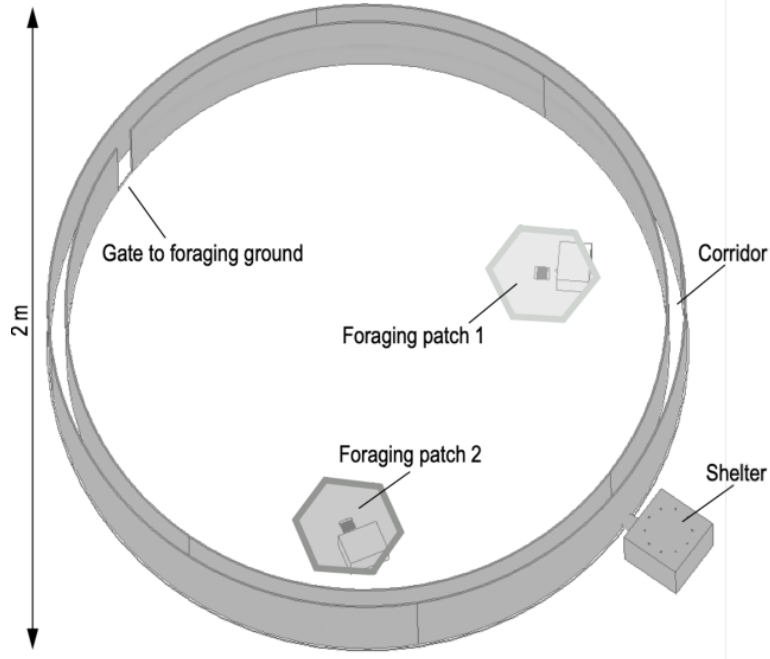
31 Spike sorting is specially challenging in NaLoDuCo experimentation since we
32 want to track individual neurons of freely moving mice for weeks to months.

33 In addition, we need online spike sorting, to allow experiments driven by
34 real-time machine learning inference, as described below.

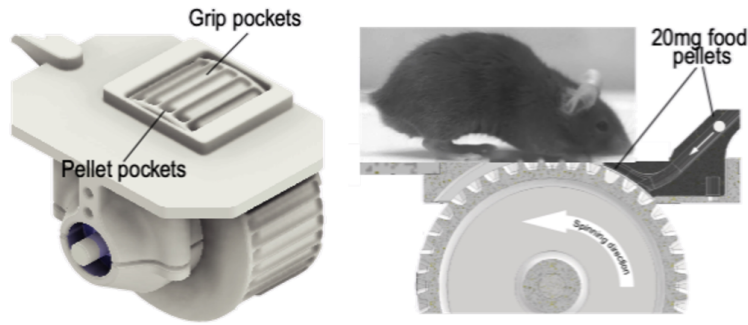
35 We will evaluate methods for tracking neurons over long periods of time [e.g.,
36 31, 27] and for online sorting [e.g., 23, 25].

37 **3.3.5 Data analysis**

38 The very large size of NaLoDuCo experimental data, the fact that the statis-
39 tics of these data change across time, and the requirement for real-time and



(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.

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 behavioural data, we will evaluate methods to:

- track multiple body parts of animals [e.g., 17, 20, 1, and a switching-linear-dynamical method using RFIDs that we will develop],
- infer kinematics of foraging mice [e.g., 21, 3],
- segment behaviour into discrete states [e.g., 30, 11, and a hierarchical HMM that we will develop],
- infer the rules that govern mice behaviour from behavioural 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 behavioural 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 behaviours. We would first check that a pattern of neural activity always precedes a given foraging behaviour. We would then detect the occurrence of the pattern and in real time optogenetically inactivate the neurons responsible for the pattern. If the behaviour disappears 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].

1 3.4 US applicants

2 Word limit: 200

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

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

9 Please also indicate who the lead US applicant will be.
10 NSF will use this information to confirm applicant eligibility.
11 Please do not include details of US applicants in the ‘Core team’ section.

12 1. Sakia de Vries

13 **institute** Allen Institute for Neural Dynamics
14 **job title** Associate Director, Data and Outreach
15 **role in the project** project lead
16 **email** saskiad@alleninstitute.org

17 2. David Feng

18 **institute** Allen Institute for Neural Dynamics
19 **job title** Sr. Director, Scientific Computing
20 **role in the project** project co-lead
21 **email** david.feng@alleninstitute.org

1 3.5 Resources

2 Word limit: 200

3 Please provide the following:

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

8 The overall budget should be below the maximum £2 million combined fun-

9 der contribution

10 If there is more than one UK or US team associated with the application,

11 please combine their estimates together.

12 A detailed calculation and breakdown of resources is not required at this

13 stage, nor is a justification of costs.

14 The following is an example of how this might look.

15 UK Resources:

16 Total cost estimate: £600,000

17 Research council contribution: £480,000

18 0.2 FTE time, 1.0 FTE PDRA, 0.5 FTE technician

19 US Resources:

20 Total cost estimate: \$300,000

21 1.0 FTE PDRA or 1.0 FTE doctoral researcher

22 Total funder contribution estimate:

23 £716,475 (£480,000 + £236,475 (\$300,000 at exchange rate 0.79))

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