

## RESEARCH

# A data repository and analysis framework for spontaneous neural activity recordings in developing retina

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### Abstract

**Background:** During early development, neural circuits fire spontaneously, generating activity episodes with complex spatiotemporal patterns. Recordings of spontaneous activity have been made in many parts of the nervous system over the last 20 years, reporting developmental changes in activity patterns and the effects of various genetic perturbations.

**Results:** We present a curated repository of multielectrode array recordings of spontaneous activity in developing mouse and ferret retina. The data have been annotated with minimal metadata and converted into the HDF5 format. This paper describes the structure of the data, along with examples of reproducible research using these data files. We also demonstrate how these data can be analysed in the CARMEN workflow system. This article is written as a literate programming document; all programs and data described here are freely available.

**Conclusions:** 1. We hope this repository will lead to novel analysis of spontaneous activity recorded in different laboratories. 2. We encourage published data to be added to the repository. 3. This repository serves as an example of how multielectrode array recordings can be stored for long-term reuse.

**Keywords:** retinal waves; spontaneous activity; electrophysiology; HDF5; multielectrode arrays

### Background

The retina is the neural circuit within the eye responsible for converting light signals into neural activity. During at least the first postnatal week of life in the mouse, retinal ganglion cells (RGCs) are spontaneously active, generating waves of activity that propagate across the retina. These spontaneous activity patterns are thought to help refine the development of neuronal connections, as blocking or perturbing the activity leads to altered connectivity patterns. For reviews on the nature and role of spontaneous activity in the nervous system, see [1, 2].

Retinal waves can be studied both using imaging methods and with multielectrode arrays (MEAs). We have collected and annotated these recordings to allow researchers to compare the spatiotemporal properties of recordings obtained from different research groups. We have focused on curating recordings collected by MEAs, as although there are several types of array recording platforms available on the market, the underlying data after spike detection and sorting is simply a

set of event times denoting when an action potential was detected on a particular electrode.

This data paper describes the repository we have curated from many key papers investigating the nature of retinal spontaneous activity. We have converted these data files into a common format so that it can be easily shared with others, and provide some scripts to analyse these recordings. We created this repository for several reasons:

- 1 By building a repository from many sources we are able to effectively compare findings from laboratories acquired under different experimental conditions, and from different transgenic mice.
- 2 There are few public datasets of MEA recordings, although some are available accompanying research papers [3].
- 3 We hope this platform will encourage future researchers to contribute their data. Many funding agencies now require data to be archived/shared for several years, and we hope this will serve as an example of how to share data.
- 4 Converting data to a standard open format, such as HDF5, should ensure that they can be read for many years to come. By contrast, keeping old datasets in proprietary formats may mean that the data are effectively unreadable in a few years.
- 5 We have used these data as a demonstration for the workflow system in the CARMEN virtual laboratory.

This article is written as an example of “reproducible research”, in that the results should be reproducible by others in a straightforward manner, given the same software and data [4]. The notion of reproducible research is beginning to be practised quite widely in some areas, such as Computational Biology [5], but is not yet that common within most fields, including Neuroscience[6]. Figures and tables marked (Dynamic) in the legends of this article are regenerated dynamically, involving re-computation as needed. (Figures and tables marked (Static) are those that required no computation.) The source file for this article contains  $\LaTeX$  and R code, from which the paper is generated (see section “Availability of supporting data”). Links to all files required to regenerate the paper are provided on the accompanying website [7].

## Data Description

The project web page [7] contains links to the data and code, and will list any updates to the repository. The data are freely available on the CARMEN portal [8]. Free registration to the CARMEN system is required to access the data.

The data provided to us from different laboratories arrived in several text and binary formats. We converted them to one common format to promote their reuse. We chose the open format HDF5 [9] because it provides an efficient and portable framework for storing large datasets. It is supported by many popular computational environments, such as R, Python, Mathematica, Matlab and Julia, and is freely available on all major operating systems. HDF5 is used across many scientific disciplines and is well-tested.

HDF5 stores objects in a hierarchical tree that can be fully specified by the user. Our approach is to store the principal data items (spike times and electrode positions) for a recording in the top level of the tree. Relevant metadata about recordings (such as the age of the retina, and the species) are stored in objects under the `/meta/` group of the tree.

Data format for storage of MEA recordings

The following objects are stored in the root of the HDF5 data files:

- 1 `epos`: an  $N \times 2$  matrix, where  $N$  is the number of spike trains in the current recording. Row  $i$  stores the  $(x, y)$  location assigned to spike train  $i$  in this recording. The values  $x$  and  $y$  are specified in  $\mu\text{m}$ .
- 2 `sCount`: a vector of length  $N$ . `sCount[i]` stores the number of spikes included in spike train  $i$ .
- 3 `spikes`: a vector of length  $S$ , where  $S = \text{sum}(sCount)$ . These are the spike times (in seconds). The spike trains for each electrode are concatenated into one long vector, so that the spikes for electrode  $j \in [1, N]$  are stored in elements  $a$  to  $b$ , where  $a = \sum_{i=1}^{j-1} sCount[i]$  and  $b = a + sCount[j] - 1$ . Within each spike train, the spike times are sorted, smallest first.
- 4 `array`: a string describing the MEA used to record the activity. Table 7 lists the values used to date.
- 5 `names`: an optional vector of strings of length  $N$ ; `names[i]` stores the name assigned to spike train  $i$ .

## Data sources

Table 2 lists the main studies included in the repository, and the number of files in each collection. A key challenge in creating the repository was writing functions to parse the various formats of source data from the different research groups. This has now been done for each of the major formats. When each data set was converted, tests were performed to check that our results matched those presented in the original publications; some of these checks are discussed later. First we describe each of the key studies included in the repository:

*Blankenship2011* This study investigated the impact of knocking out two connexin isoforms (Cx36 or Cx45) upon spontaneous activity [10]. Recordings of wild-type, single or double (Cx36 and Cx45) knockouts were performed at postnatal day 11/12 (P11/12).

*Demas2003* Recordings over an extended period (P9–P42) were made in wild-type mice, along with mice reared in the dark [11]. This study also served as a baseline for subsequent recordings in transgenic mice [12].

*Demas2006* This set contains data recorded from *nob* mutant mouse, where retinal waves persist at late developmental stages [12].

*Hennig2011* A set of eight recordings investigating the effects of chronic bicuculline application at two critical ages when the effect of GABA upon RGCs switches from excitatory to inhibitory [13].

*Kirkby2013* Recent recordings from wild-type and  $\beta 2$  KO mice recorded in the first postnatal week [14].

*Stacy2005* A set of further control recordings in wild-type mice are provided [15]. In this study, retinal waves were also recorded in transgenic mice where cholinergic neurotransmission was inhibited in most of the retina. However, recordings from the transgenic animal could not be found post-publication.

*Stafford2009* A detailed set of recordings at one age (P6) showing that  $\beta 2$  KO mice do still generate correlated waves [16]; see also [17]. A directional bias in control waves was also reported for the first time.

*Sun2008* Two different versions of the  $\beta 2$  KO transgenic mice were studied, and in comparison to earlier studies [18], shown to have correlated activity extending over larger distances than wild type. Although the key paper [17] focuses on postnatal days 4 and 5, recordings from a range of days are provided, and were analysed separately [19].

*Torborg2004* This key summarises data that appeared in several publications [18, 20–22]. These were the first MEA recordings of spontaneous activity in the  $\beta 2$  KO mouse, and showed that although individual RGCs were spontaneously active, the correlations in firing of neighbouring RGCs were strongly reduced. There are also recordings combining the  $\beta 2$  KO line with a gap junction knockout (CX36), and recordings under different pharmacological conditions.

*Wong1993* This is the first MEA recording of retinal waves, in ferret at different developmental ages. This was the first paper to introduce the key measure of correlated activity, the correlation index, that has been subsequently used in most studies. Although the recordings are relatively short, they highlighted strong distance-dependent correlations gradually decaying with age. (Conversion of these files was complicated as they were binary files, so we converted them through a custom macintosh program written for these data by Markus Meister.)

*Xu2011* To investigate further the effect of cholinergic neurotransmission, transgenic line (where  $\beta 2$ -nAChR was expressed in just RGCs of  $\beta 2$  KO mice) was generated [23]. In this  $\beta 2$ (TG) line, waves were restored, although the spatial extent of correlations was reduced.

#### Citing the data

We are grateful to our colleagues for sharing their recordings. If you use any of these data sets, we request that you acknowledge the relevant authors by citing the corresponding papers (listed in Table 2).

#### Minimal metadata

Our approach to metadata is deliberately minimal, simply describing what we think are some of the essential features of the recordings, such as developmental

age, and genotype. This of course means that many details are missing, but in most cases we hope that they can be extracted (manually) from the corresponding publications. We store the metadata as named items in the HDF5 file, under the `/meta/` group. For example, the developmental age of the recording is stored in `/meta/age`. Table 1 describes the metadata that are included in the HDF5 files.

## Analyses

We now provide some examples of reproducible research using the repository. The aim is to summarise the main features of the repository, rather than to provide novel analyses of these data.

### R package

We have used the R programming environment to develop a package of tools for the analysis of spontaneous activity. R, however, is not required to use these data files. This R package (called `sjemea`) was created in 2001 (to support work subsequently published [11]) and is still under development. The package primarily focuses on the batch analysis of data; other open tools more suitable towards interactive analysis are available [24, 25]. We now give several examples of analysing the repository using code from this R package.

### Overview of the repository

Figure 1 provides an overview of the repository, showing that recordings range from just a few minutes to many hours. In particular, we see that two different groups recorded waves continuously for up to eight hours [13, 15]. Most recordings contain fewer than 100 spike trains because they were made on MEAs consisting of 60 or 64 electrodes. (Most recordings have been spike sorted, so that more than one neuron can be detected on each electrode.) There is also a clear group of recordings with around 500–1000 neurons which were all recorded from the 512-electrode array [16].

### Fourplot

The “fourplot” is our one page summary plot of a recording which we use as an initial screen to check its quality. Figure 2 shows one such example. This plot allows us to quickly evaluate the recording using the features described in the figure legend. The accompanying website has a gallery section showing the fourplot for each datafile in the repository.

### Correlation indices in neonatal ferret

Retinal waves induce correlations in the firing patterns of neighbouring RGCs. This was first demonstrated in the analysis of ferret retinal waves using the correlation index measure [26]. The correlation index measures the degree that two neurons spike together within some small time window (typically 50 ms). Figure 3 shows the correlation index as a function of the distance separating any given pair of electrodes. This figure almost exactly replicates Figure 8 of the prior study [26], with the only exception that we also show correlation indices for pairs of neurons with zero distance separating them.

Correlation indices in wild-type and transgenic mice

Cholinergic neurotransmission is required for the generation of retinal waves in early development [27, 28]. One key transgenic line has been global knockout of the  $\beta 2$  subunit of the nicotonic acetylcholine receptor (nAChR), termed  $\beta 2$  KO here. Initial reports suggested that  $\beta 2$  KO mice lack retinal waves [18, 29], but subsequent studies reported retinal waves in these mice [16, 17]. These differences might have occurred because of different recording conditions, notably temperature and bath medium [16]. Given the importance of these results, we have collected and curated most of the key recordings published to date that quantify spontaneous activity in  $\beta 2$  KO mice.

The effects of transgenically rescuing  $\beta 2$ -nAChR into just RGCs, leaving it knocked out in the rest of the nervous system, were recently investigated [23]. In this genetic manipulation, termed  $\beta 2$ (TG), retinal waves were correlated over shorter distances than waves in wild-type mice (Figure 1G of [23]). We have recreated that result by recalculating the correlation indices. Figure 4 has the same key properties as previously reported with the notable exception that the correlation indices in both wild-type and  $\beta 2$ (TG) mice are about half the magnitude compared to those originally reported. The shape of the two groups, and the overall conclusions, are unaffected however. The discrepancy between the two results is likely to be an artifact of the method previously used [23], although their code is no longer available to confirm this.

CARMEN application: burst analysis

We have made our data freely available in the CARMEN system [30]. The CARMEN Virtual Laboratory is a collaborative online facility for neuroscientists. Data can be uploaded to a repository, and shared with other neuroscientists. Extensive metadata [31] can be attached to the data, and a search facility allows data to be located in the repository. The system is currently targeted towards electrophysiology data, and predominantly MEA and EEG data.

Useful neuroscience analysis routines can be converted into CARMEN services [32]. Service code can be written in a range of programming languages (including Matlab, Python, R, C/C++, Java), and can be easily wrapped into a service using the CARMEN Service Builder tool. Metadata attached to each service provides information for the user and the system. Once a service has been registered with the CARMEN system, users can run them via the portal, using any available data on the repository. The service is executed within the CARMEN system's execution environment, which is a private cloud of heterogeneous servers. The execution environment can support multiple execution server environments; currently these are Windows Server, Centos5 Linux and Scientific Linux 4 platforms. The execution details are hidden from the user.

The CARMEN portal also deploys a workflow tool within the browser, to allow users to tie services together into a processing pipeline. To support the interaction of services, a common data standard for all data types is used; the Neural Data Translation Format (NDF). NDF provides a standard format for neural time series data, segment data, and event data [33] and has a rich metadata header which provides a detailed description of the data contents, and which supports the addition

of annotations and other relevant attachments (e.g. visual or audio files). A workflow editor provides a graphical means to construct and edit workflows. A workflow enactment engine allows the workflow to be run over the execution servers. The heterogeneous nature of the service infrastructure means that a workflow can be constructed from services that are written using different programming languages and for differing platforms.

To demonstrate the virtual laboratory workflows on these data, three services were built in Matlab and compiled into a standalone executable for inclusion into the service framework:

- 1 HDF5 to NDF converter — This reads in the HDF5 file and converts it into an NDF neural event data file.
- 2 A burst detection service — This finds bursts independently within each spike train of a recording [13]. The service takes input data in the form of an NDF neural event file.
- 3 A graphing service to plot burst durations of multiple input files.

The CARMEN workflow facility (Figure 5) chains these services together so that given an input file, it is first converted into NDF and then the burst times are computed. The output from the independent burst analysis services are then compared to generate a plot such as Figure 6. This figure demonstrates that median burst duration is around 0.1 s and there is good agreement between recordings from different laboratories, albeit with one recording showing a few bursts longer than 2 s.

## Discussion

*Role of the repository* Given the ongoing debate about whether neuronal activity instructs the development of neuronal circuits [34, 35], we believe it is important to understand the spatiotemporal properties of waves in different recordings. This repository provides a framework for systematic studies of spontaneous activity, looking for example at the effects of particular mutations, such as the  $\beta 2$  KO. Furthermore, we can now begin to study the variability between laboratories when recording spontaneous activity in the retina, as has already been reported for cortical cultures [36]. We hope this repository will also lead to increased data reuse.

*Collecting new data* We hope that the repository will prove useful and we encourage investigators to provide recordings of spontaneous activity. We typically require just spike times (rather than voltage traces) and a description of how to map neurons to positions on the array. The minimal metadata is also required, typically in a spreadsheet. It is preferable if the data have already been presented in an article, so that we can refer to that article. Unpublished data can also be accepted as long as the investigator is aware that the data are made freely available.

The current focus of the repository is on collecting spontaneous activity from developing retina. Since spontaneous activity is present in other systems, we also anticipate extending the repository to include data from e.g. cortical and hippocampal cultures [37].

*Generating new standards* To date, there are no established standards for storing spike trains recorded from MEAs; there are a range of data formats from different hardware vendors which our R package can process. However, one key aim of the datasharing program of the International Neuroinformatics Coordinating Facility (INCF) is to establish such standards. We hope that the data provided here can be used as a useful test case for evaluating any proposed standards [38]. Given the relatively simple format in which our data are currently provided, we imagine that changing the data files to accommodate any new standards should be straightforward.

## Methods

All data reported in this paper have been previously published, see Table 2. Details of the experimental procedures are available in those articles. None of the recordings have previously been made freely available. In all cases, recordings of spike times (rather than voltage traces) were provided. Files were then converted into the common HDF5 framework described in this paper. During this conversion, data were checked where possible with previous reports, e.g. descriptions of mean firing rates. Metadata were validated using a separate script. The fourplot (Figure 2) for each recording was also checked. In a few instances this led to discussions with the original authors, or some data being excluded.

## Availability of supporting data

The HDF5 files are available as a zip file [8]; accompanying code is linked to from the project web page [7]. This article is an example of a literate programming document. It has been created in R using the `knitr` package [39]. All the figures and tables in this paper are generated dynamically as the document is compiled. Several R packages are required to run the analysis. Full details are given on the “Code” section of the accompanying website.

## List of abbreviations used

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CARMEN	Code Analysis, Repository and Modelling for E-Neuroscience
CDF	Cumulative Distribution Function
CRAN	Comprehensive R Archive Network
EEG	Electroencephalography
HDF5	Hierarchical Data Format, version 5
INCF	International Neuroinformatics Coordinating Facility
MEA	multielectrode array
NDF	Neural Data Translation Format
P <sub>n</sub>	Postnatal day <i>n</i> , e.g. P5 for Postnatal day 5.
RGC	retinal ganglion cell

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## Competing interests

The authors declare that they have no competing interests.



## Authors' contributions

- Conceived and designed the project: SJE, ES.
- Collected data from groups: SJE, JDS.
- Curated and processed data: SJE.
- Contributed code: SJE.
- CARMEN workflow analysis: MJ, TJ, MW.
- Wrote the manuscript: SJE, TJ, ES, MW.

All authors read and approved the final manuscript.

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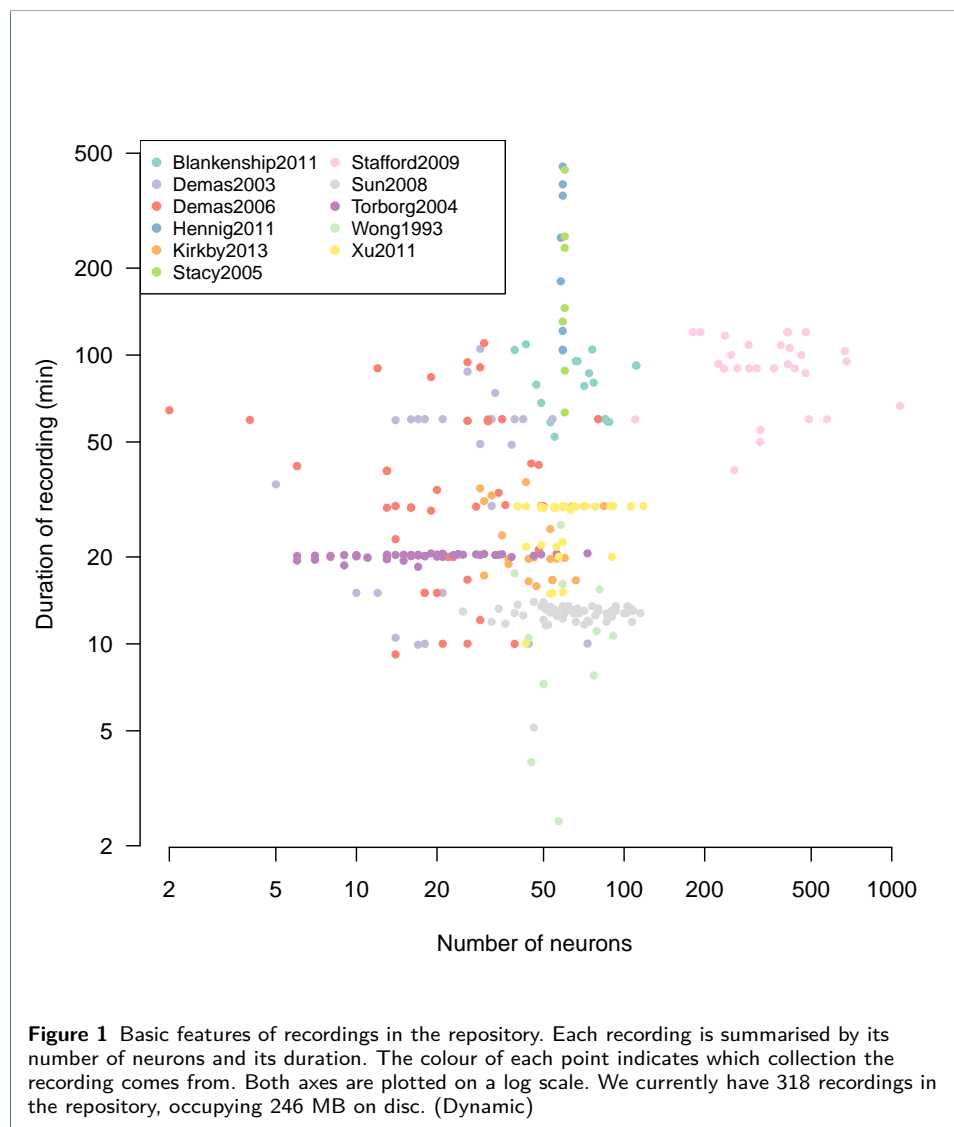
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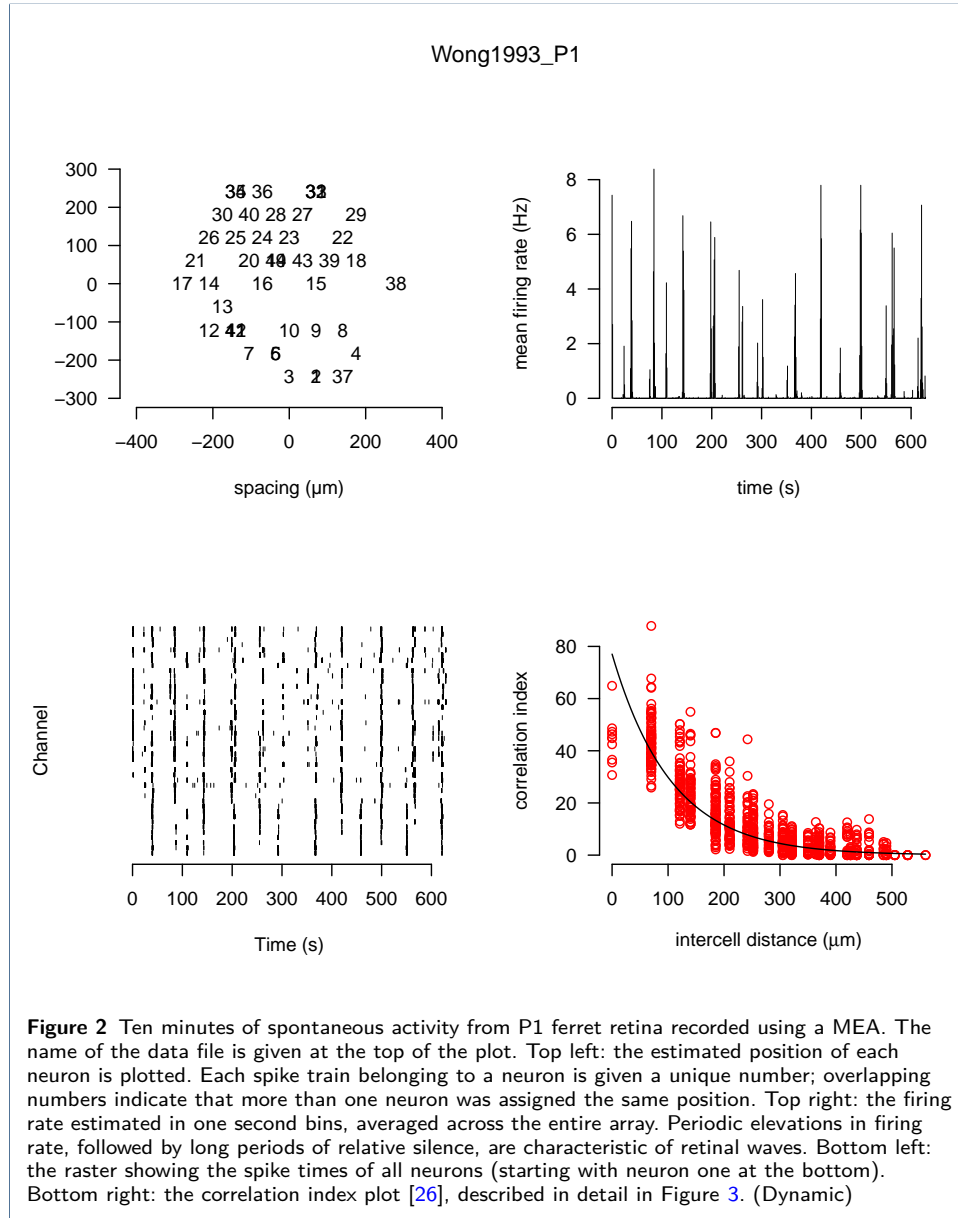
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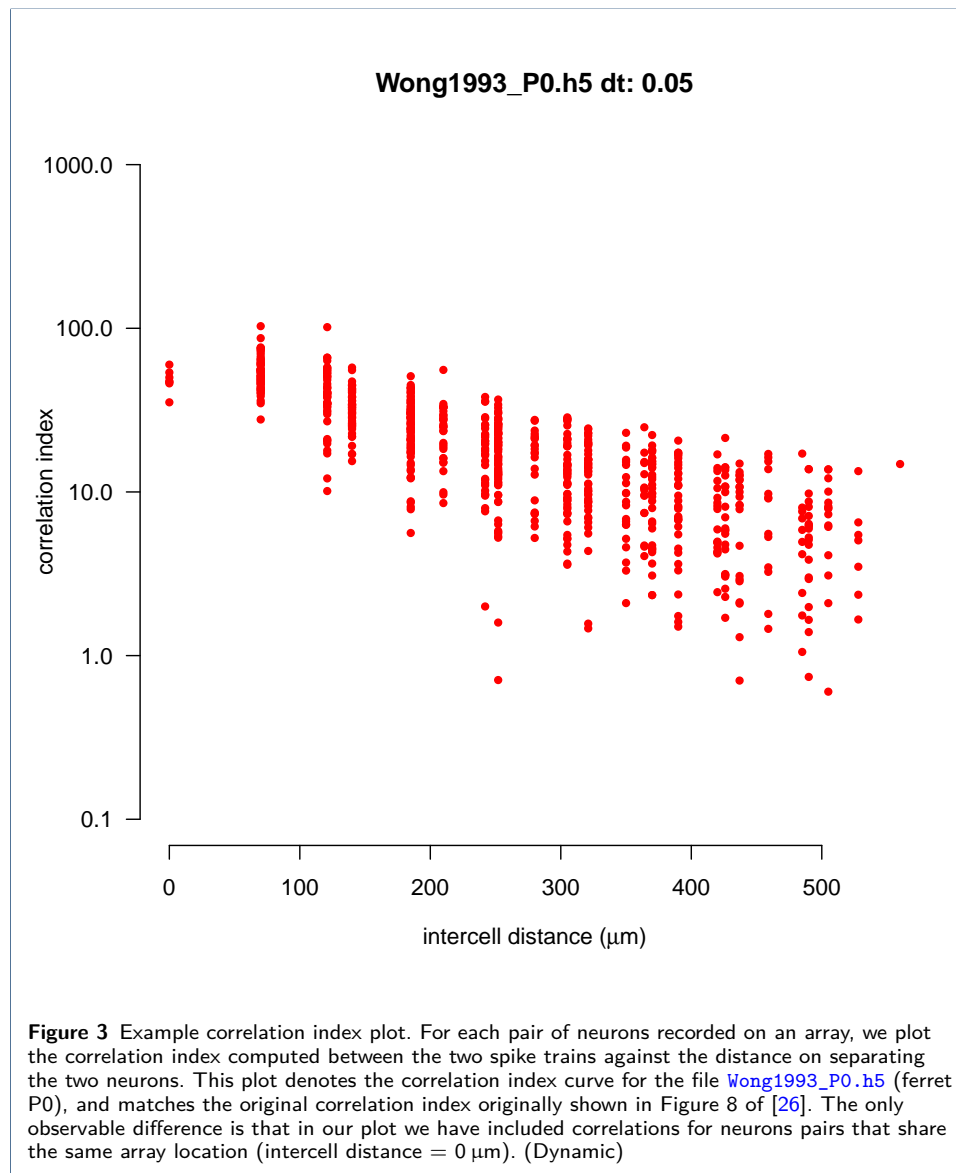
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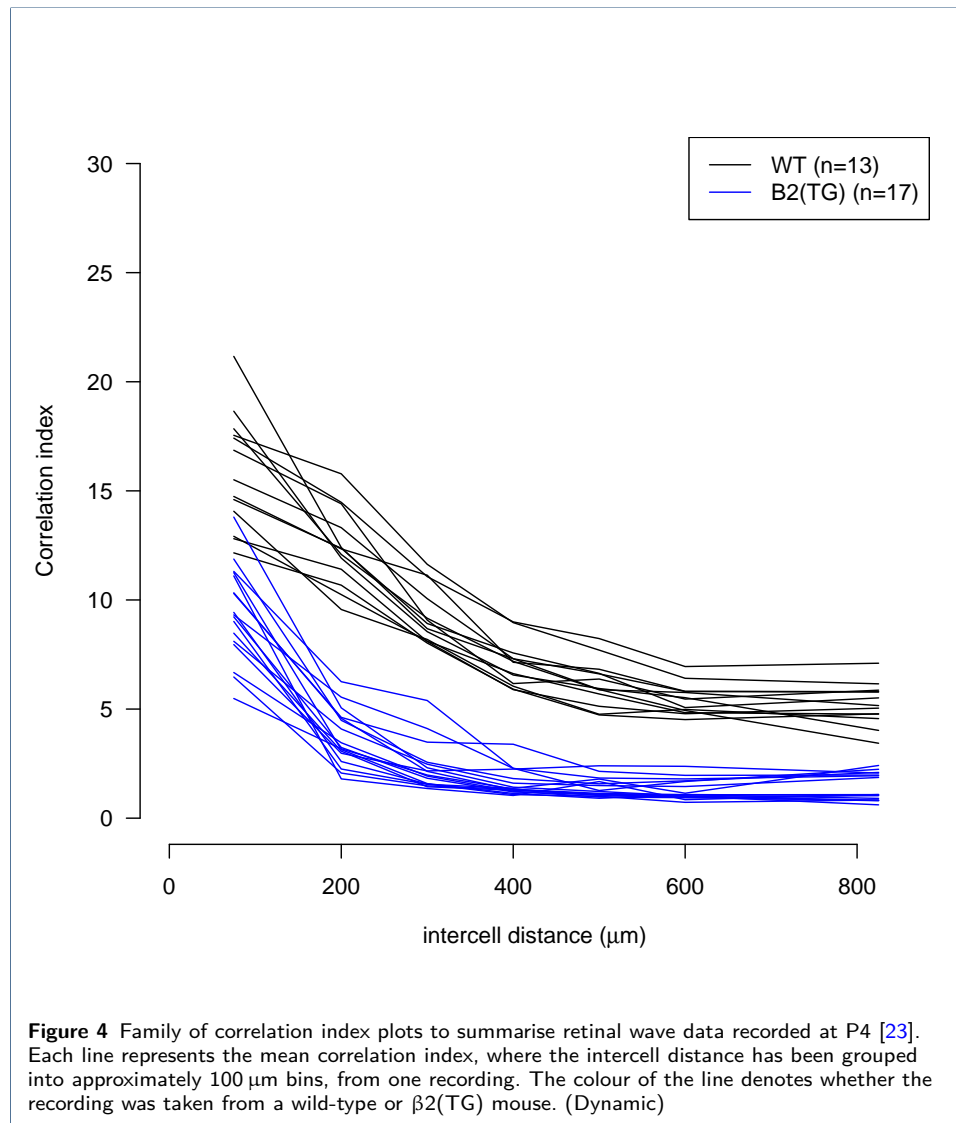
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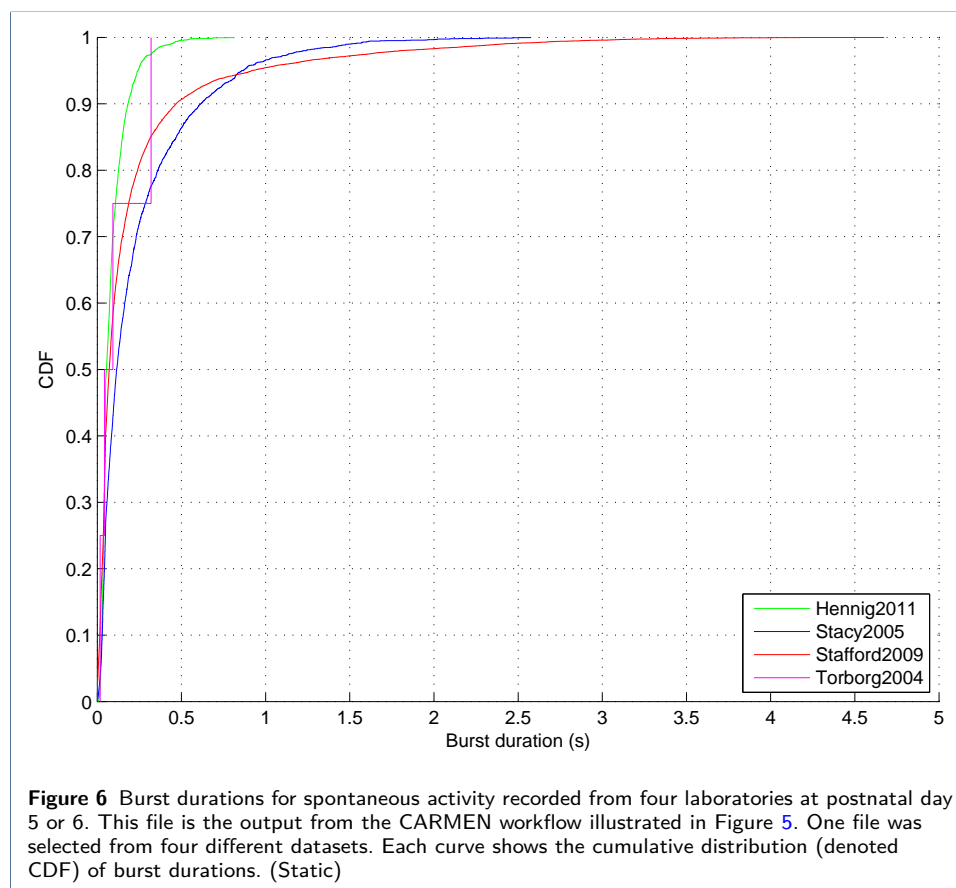
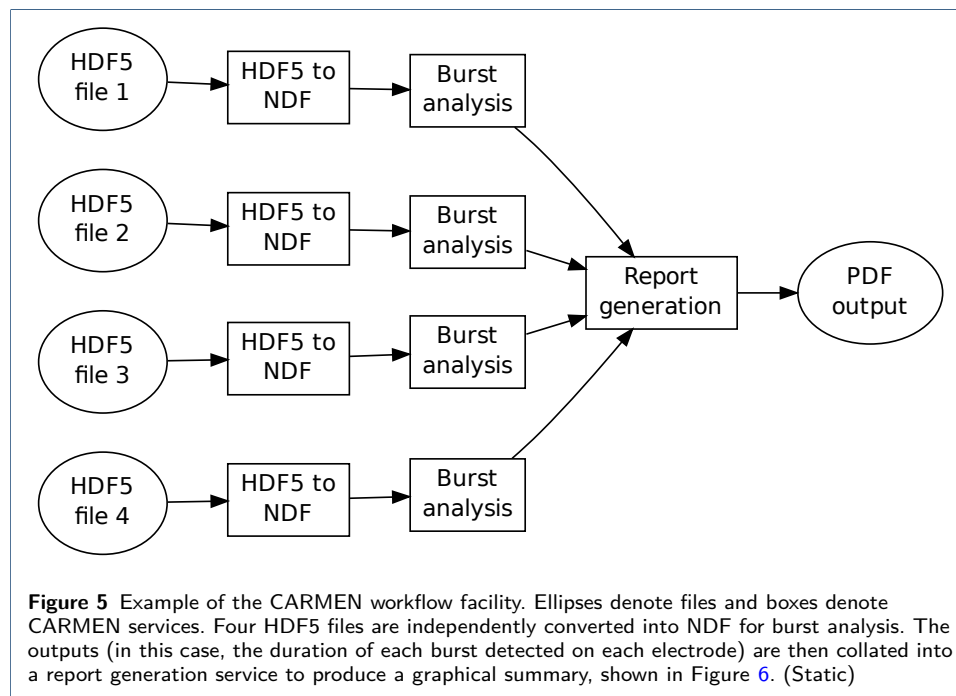
## Figures











## Tables

Name	Type	Default	Description	Table
key	string	—	A primary key to indicate the study that the file is associated with. This is typically of the form <i>Wong1993</i> , i.e. surname of first author and year of main paper [26].	Table 2
species	string	—	Species name; most recordings are from mouse, but we also have ferret recordings [26]. Although ages for both animals are given in postnatal days, ferret and mice have different gestational periods, and so cannot be directly compared.	Table 3
age	integer	—	Postnatal age of the animal. For one study [26], adult recordings were represented as age 500 days. (There are currently no embryonic recordings, but these could be represented by negative values; zero is the day of birth.)	Table 4
genotype	string	“wt”	genotype (of the mouse), with the default “wt” indicating a wild-type mouse.	Table 5
cond	string	“ctl”	A brief description of the conditions under which the spontaneous activity were made. e.g. some recordings were made in dark reared (“dr”) mice, and sometimes pharmacological agents were used. If no condition is supplied, control (“ctl”) is assumed.	Table 6

**Table 1** Metadata items stored in the repository. Values with no default are compulsory. The final column refers to subsequent tables for more details on each name. (Static)



key	n	citation
Blankenship2011	17	[10]
Demas2003	37	[11]
Demas2006	41	[12]
Hennig2011	8	[13]
Kirkby2013	22	[14]
Stacy2005	7	[15]
Stafford2009	29	[16]
Sun2008	62	[17]
Torborg2004	54	[20]
Wong1993	11	[26]
Xu2011	30	[23]

**Table 2** Names and citations of the data sources in the repository. n is the number of files associated with each key. (Dynamic)

species	n
ferret	11
mouse	307

**Table 3** Numbers of recordings for each species. (Dynamic)

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	15	21	30	42	500
Blankenship2011	0	0	0	0	0	0	0	0	0	0	0	17	0	0	0	0	0	0	0
Demas2003	0	0	0	0	0	0	0	0	0	2	0	5	0	3	9	8	0	10	0
Demas2006	0	0	0	0	0	0	0	10	0	0	0	0	10	0	8	13	0	0	0
Hennig2011	0	0	0	0	0	2	2	0	0	2	2	0	0	0	0	0	0	0	0
Kirkby2013	0	0	0	0	2	7	10	3	0	0	0	0	0	0	0	0	0	0	0
Stacy2005	0	0	0	0	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0
Stafford2009	0	0	0	0	0	0	29	0	0	0	0	0	0	0	0	0	0	0	0
Sun2008	0	1	3	2	13	17	3	4	4	4	2	6	1	2	0	0	0	0	0
Torborg2004	0	0	0	2	12	9	0	1	3	0	16	11	0	0	0	0	0	0	0
Wong1993	1	1	0	0	1	1	0	0	0	0	0	0	1	0	2	2	1	0	1
Xu2011	0	0	0	0	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0

**Table 4** Numbers of files from each study (rows) for each postnatal age (columns). (Dynamic)

	Beta2 KO	Beta2 KO/Cx36 KO	Beta2 Picciotto	Beta2(TG)	Beta2 Xu	Cx36 KO	Cx36 KO/Cx45 KO	Cx45 KO	nob	wt
Blankenship2011	0	0	0	0	0	2	6	4	0	5
Demas2003	0	0	0	0	0	0	0	0	0	37
Demas2006	0	0	0	0	0	0	0	0	25	16
Hennig2011	0	0	0	0	0	0	0	0	0	8
Kirkby2013	11	0	0	0	0	0	0	0	0	11
Stacy2005	0	0	0	0	0	0	0	0	0	7
Stafford2009	0	0	0	0	0	0	0	0	0	29
Sun2008	0	0	21	0	18	0	0	0	0	23
Torborg2004	11	7	0	0	0	19	0	0	0	17
Wong1993	0	0	0	0	0	0	0	0	0	11
Xu2011	0	0	0	17	0	0	0	0	0	13

**Table 5** Numbers of recordings of each genotype included in the repository. Note that Wong1993 data are from ferret.(Dynamic)

cond	n
10 microM forskolin	1
25 microM APV + 25 microM CNQX; wash then 50 microM Mecamylamine	1
25 microM APV + 50 microM CNQX	1
2.88 microM FPL	2
2 microM forskolin	2
2 microM strychnine	1
50 microM Carbenoxolone	1
bic	4
ctl	284
dr	19
wash	2

**Table 6** Pharmacological and environmental conditions under which spontaneous activity were recorded. Where possible, the descriptions of the conditions follow those provided with the original data. (Dynamic)

array	n	description
MCS_8x8_100um	154	60 electrodes in square lattice (corners missing) with 100 $\mu$ m spacing (Multi Channel Systems).
MCS_8x8_200um	70	60 electrodes in square lattice (corners missing) with 200 $\mu$ m spacing (Multi Channel Systems).
litke_hex_60um	29	512 electrodes on hexagonal lattice with 60 $\mu$ m spacing (AM Litke, UCSC)
EJC1_hex_60um	54	61 electrodes on hexagonal lattice with 60 $\mu$ m spacing (EJ Chichilnisky, Salk)
stanford_hex_60um	11	61 electrodes on hexagonal lattice with 60 $\mu$ m spacing (Stanford).

**Table 7** Descriptions of the MEA layouts in the repository, along with their name and number (n) of recordings. (Dynamic)

*Session information*

- R version 3.0.2 (2013-09-25), x86\_64-pc-linux-gnu
  - Locale: LC\_CTYPE=en\_GB.UTF-8, LC\_NUMERIC=C, LC\_TIME=en\_GB.UTF-8, LC\_COLLATE=en\_GB.UTF-8, LC\_MONETARY=en\_GB.UTF-8, LC\_MESSAGES=en\_GB.UTF-8, LC\_PAPER=en\_GB.UTF-8, LC\_NAME=C, LC\_ADDRESS=C, LC\_TELEPHONE=C, LC\_MEASUREMENT=en\_GB.UTF-8, LC\_IDENTIFICATION=C
  - Base packages: base, datasets, graphics, grDevices, methods, parallel, stats, utils
  - Other packages: knitr 1.5, RColorBrewer 1.0-5, rhdf5 2.4.0, sjemea 0.39, xtable 1.7-1
  - Loaded via a namespace (and not attached): digest 0.6.3, evaluate 0.4.7, formatR 0.9, highr 0.2.1, stringr 0.6.2, tools 3.0.2, zlibbioc 1.6.0
- Paper Revision: 1.43