Research Article

ARACHNE: A neural-neuroglial network builder with remotely controlled parallel computing

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Abstract

Creating and running realistic models of neural networks has hitherto been a task for computing professionals rather than experimental neuroscientists. This is mainly because such networks usually engage substantial computational resources, the handling of which requires specific programing skills. Here we put forward a newly developed simulation environment ARACHNE: it enables an investigator to build and explore cellular networks of arbitrary biophysical and architectural complexity using the logic of NEURON and a simple interface on a local computer or a mobile device. The interface can control, through the internet, an optimized computational kernel installed on a remote computer cluster. ARACHNE can combine neuronal (wired) and astroglial (extracellular volume-transmission driven) network types and adopt realistic cell models from the NEURON library. The program and documentation (current version) are available at GitHub repository https://github.com/LeonidSavtchenko/Arachne under the MIT License (MIT).

Introduction

Neural network simulation remains an important and powerful tool to understand principles that underpin the functional organisation and multi-faceted activities of the human brain. There have been at least several dozen successfully implemented large-scale scale network simulators enabling the exploration of multicellular assemblies at various levels of organisational and functional detail. These include Topographica [1], Nest [2], Brian [3], ANNarchy [4], NEURON [5], Genesis [6], Auryn [7], Nengo [8], PyNN’s [9], NeuroManager [10]. Among such tools, it appears that Genesis [6] (new version in the development stage) and NEURON [5] have been most frequently employed by a wide neuroscience community. NEURON in particular provides a tool to create some highly realistic, experimentally tested cell models and their networks, with parallel computation add-ons. These features have been successfully
adopted by the Blue Brain project [11], the most ambitious attempt to recreate mammalian brain functions in silico. However, the degree of virtual reality that would satisfy a brain scientist (such as in Blue Brain) is a matter of having state-of-the-art supercomputers, the corresponding programming expertise, and the resources and skills for maintenance. These are not routinely available to experimental neuroscientists.

Among such modelling tools, NeuroManager [10] represents a simulation management software interfacing with other tools such as NEURON [12]; this normally requires professional knowledge of Python [3, 9], C++ [7] or Java [8]. Network modellers such as Brian, NEST, NEURON, GENESIS, Nengo, or Auryn focus on parallel simulations on shared memory systems (multi-core or multi-processor) or distributed systems (clusters) using either OpenMP (open multi-processing) or MPI (Message Passing Interface). Some of the more purpose-tuned neural simulators including GeNN1, MVAPICH [13], NeMo [14], and CARLsim [15] provide support for simulations on a single or multiple GPU architectures. Again, these diverse systems adapt the technical programming solutions specific to the task under study, which, in many cases, requires a specific programming language, often with a high degree of semantic and linguistic development. This in turn demands programming skills and experience. Furthermore, while reflecting the enormous complexity and diversity of brain circuits the narrow specialisation of the modelling paradigm can significantly narrow the users’ pool.

A somewhat different approach to neural network modelling refers to a brain machine that incorporates standard logic devices and mathematical operators mimicked by the integrate-and-fire cell circuits adapted to produce a desired response function or operation, be it a filter, integrator, attractor, or else [16]. This ‘top-down’ modelling method is capable of successfully reproducing some key recognition and memory functions, from perceptive input to motor output [16]. However, such models create and connect elements of artificial neural networks in order to perform a desired behaviour rather than reproducing real-world brain circuits with an aim to understand their function. Similarly, neural network algorithms underpinning industrial robots do not generally aim at understanding how the brain circuitry works. The latter nonetheless is what neuroscientists strive to achieve. In contrast, network models implementing synaptic plasticity rules [17, 18] could provide conceptual insights into the principles of synaptic circuit functioning.

Another principal complexity in the field has recently transpired. All well-established neural network simulators deal with excitable nerve cells communicating via individual cell-cell connections representing synaptic inputs. However, it has emerged that the other common type of brain cells—glia, and especially astroglia—can directly influence brain circuits [19–21]. Most astroglia are non-excitable cells that handle physiological signals through intracellular Ca$^{2+}$ waves [22, 23], occupy non-overlapping tissue domains (each hosting many thousands of synapses on different neurons) [24], and release a variety of signalling molecules into the extracellular space [25, 26]. Thus, astrocytes operate a diffuse, or ‘volume-transmitted’, type of extracellular signalling, which is qualitatively different from the ‘wired’ transmission underpinning classical neural networks [27]. When incorporated into the neural network, this volume-transmitted signals prompts neural network state transitions [28] which are yet to be understood. To our knowledge, there have been no systematic attempts to incorporate this (physiologically essential) type of cell–cell communication in the neural network software.

Here, in developing the modelling tool ARACHNE our aim was therefore to enable experimental neuroscientists to build, run and explore complex, realistic cellular networks incorporating neurons (wired connections) and astroglia (extracellular diffuse signalling), with little computational expertise and little computational resource available on site. In some respects, ARACHNE follows the logic of “neuroConstruct” [29], a neuroscientist-friendly shell (add-on) helping to create 3D networks of realistic cells using NEURON or GENESIS, but with an
advantage of having its own computational kernel. We thus sought to build a simple interface for model creation and running combined with a powerful simulation tool adapted to extensive resources for parallel computing. To enable realistic cell representations, ARACHNE was to provide direct upload of membrane biophysical mechanisms from the NEURON library. This option allows an inexperienced user to take advantage of the NEURON database and the tools of ARACHNE in setting up a realistic cellular network. Finally, the interface was to enable full computational control of network simulations from a mobile device.

**Design and implementation**

The host application is running under Windows. It can be launched from the same machine or a remote mobile device (Android or iOS). The HPC kernel (C++) operates under either Linux or Windows.

Currently ARACHNE provides four configuration types:

- (GUI) Windows → (kernel) Windows,
- (GUI) Windows → (kernel) Linux,
- (CLI*) Android → (No GUI) Windows → (kernel) Windows,
- (CLI*) Android → (No GUI) Windows → (kernel) Linux,

where *CLI—Command Line Interface.

ARACHNE also supports a silent mode in which the GUI is not used, and all the input parameters are transferred to the host entry point in a “struct” of MATLAB.

The Linux operating kernel was tested on a remote, ad hoc-built 12-node cluster [30], which we have previously used and optimized for Monte Carlo simulations [28, 31–35]. The kernel performs numerical integration of a massive system of ODEs describing the biophysical states and the topology of cell networks (Fig 1).

The GUI enables the user (a) to create a network model, (b) to control simulations, and (c) to keep all the network configurations, the input data and the results on a local drive using only the GUI. At this stage, the design of neuronal networks does not require programming skills. The user generates an input file (input.mat) via the GUI, including parameters of the network and settings for computation (S1 File, Supplementary Material). Once the input.mat has been sent to the cluster to execute computations, the user can either employ the interface-cluster link to monitor the computation process or disconnect it altogether. The input.mat file is small enough to be sent through a limited bandwidth connection such as 3G networks. Once the simulations have been completed, the results (output.mat) are sent to the interface computer and stored on the cluster for further analyses. The system architecture has sufficient provisions for a mobile applet that would enable general public sourcing and migration to cloud to help building realistic networks. The requirement to the cluster is the presence of either Linux or Windows and the availability of “Open MPI C++ wrapper compiler” and MATLAB for simple compilation.

Various hosts may interact with the same cluster sequentially. In brief, communication between the local computer and the remote cluster uses the SSH network protocol (Fig 1). We use PuTTY applications to execute commands on a remote computer and to exchange files in between. In particular, we use Plink (a command-line interface to the PuTTY back ends) and PSCP (a SCP client, i.e. command-line secure file copy). In the current version of software, we do not provide an interface to TORQUE, which enables control over batch jobs and distributed computing resources. ARACHNE currently assumes no simultaneous access of multiple users to a single cluster but allows individual access in a queue. Several users can monitor one simulation (i.e. visualise intermediate results on different local machines), but cannot run more than one simulation on the cluster at the same time. The software fully manages the communication between local MATLAB host and remote C++ worker, no user action required.
Fig 1. Structure of ARACHNE and simulated network types. (A) General diagram of the ARACHNE simulator. In brief, local computer generates the model and the HPC configuration as input.mat file, which is sent to the remote computer with master and slaves N clusters. Each slave computer has M processors. After
the parallel computation has run the results recorded in output.mat file are sent back to the local computer. (B) Diagram depicting three key network types: principal neurons (e-neurons), interneurons (i-neurons) and astrocytes (a-cells); $R_n$ and $R_i$, the network size (radius), respectively. (C) A network fragment depicted by dotted area in (B): different types of cell-cell signalling types are indicated including an aa connection reflecting (mostly) astrocyte gap junctions.

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The host automatically packages the data, uploads it to the cluster and tells the remote cluster to begin execution. This occurs once the user has set up simulation parameters in the GUI and clicked the “OK” button. ARACHNE is thus organised in such a way that it enables an untrained user to create a large network and to operate computation on and communication with the cluster. The GUI has a special option called HPC where the user can easily change the parameters of cluster computation.

The kernel solves the set of differential equations related to the membrane potential of neurons Eq (1) and intracellular calcium dynamics Eq (2) for astrocytes. When a new cellular mechanism is added to the kernel, the corresponding C++ code has to be appended and recompiled as required.

In order to expand the modelling capabilities, the ARACHNE GUI can incorporate membrane mechanisms from the NEURON database (mod-files). The incorporation of new mechanisms requires recompilation of C++ code of the HPC kernel located on the cluster.

To reduce computation time for a newly designed neural network, we have envisaged two distinct operating modes for the kernel. Mode I is designed for the optimization of any newly configured network. The key goal here is to determine how best to parallelise the network, and how much memory should be allocated in order to increase the speed and the accuracy of calculations. Mode II applies to the exploratory computations with a fixed cluster configuration. Here, users may also employ various nodes of the cluster at their discretion. This mode is highly suitable for exploring the parameter space for a given neural network architecture.

The biophysical basis: A case study

ARACHNE includes basic pre-set parameters reproducing local cellular networks in hippocampal area CA1, a well-explored subject of neural modelling [36, 37]. Unlike previous models consisting of inter-connected neurons only, ours also incorporated astroglia (enabling a diffuse, volume-transmission extracellular signalling mechanism acting at subgroups of neighbouring neurons). Thus, each of the three cellular networks (Fig 1B)—e-neurons (excitatory neurons), i-neurons (inhibitory neurons), and a-cells (electrically non-excitable astrocytes)—was equipped with a specific set of biophysical, architectural and topological features. Biophysical parameters describe known physiological mechanisms present in each cell type, such as ion channels and pumps [38–40], ion diffusion, receptor currents, etc (S2 File).

The basic dynamic variables represent the main cellular communication mechanisms in the network: these are membrane potential $V$ for neurons (1) and the intracellular calcium concentration for astrocytes. The dynamics of $V$ for both types of neurons is described by a set of equations with the Hodgkin–Huxley formalism:

$$C_m \frac{dV}{dt} = \sum I_n + I_{syn}$$

(1)

where $C_m$ is a membrane capacitance and $\sum I_n$ is a sum of transmembrane currents (S2 File) and $I_{syn}$ is synaptic current from nearby neurons with plasticity mechanisms allowing self-organization of network connections with the bottom-up approach similar to that described earlier [17].
Astrocyte network

Astrocytes, electrically non-excitable cells, can modify release probability of nearby synapses in tissue volume \[41\], likely by releasing signalling molecules ('gliotransmitters') in a Ca\(^{2+}\) dependent manner \[42\]. In turn, neurotransmitters released by neurons influence Ca\(^{2+}\) dynamics in astroglia \[43\]. The basic feedback between neurons and astrocytes has thus been incorporated in ARACHNE, in which astrocytes occurring next to an e-cell alter adjacent synapses (Fig 1C) \[44\]. For the sake of simplicity, the relationship between astrocyte calcium concentration \(Ca\) and neurotransmitter release probability at affected synapses, \(p\), has been described with the simple formulism based on earlier suggestions \[45\] (S2 File); this relationship could be modified in accord with experimental data.

The dynamics of astrocyte calcium follows the equation

\[
\frac{dCa}{dt} = -\sum J_n
\]

where \(J_n\) are intracellular Ca fluxes \[45\]. The basic interaction between astroglial Ca\(^{2+}\) and synaptic circuitry modulation, which is implemented here mainly for illustration purposes, can be modified in accord with the emerging experimental data on astroglia-neuron communication.

Results

Optimizing the model configuration

A newly created network model designed for a multiprocessor cluster with a parallel algorithm will require an initial optimisation step. The outcome of such optimisation is the number of cluster workers that provides the fastest possible computation. To explore and illustrate this optimisation strategy, we have tested three identical neural networks with the unchanged, 'basic set' of parameters (S2 File) but with different numbers of neurons (100, 1000 and 4000). The examples of optimization (Fig 2) illustrate a search for the number of cluster workers that provides the highest frequency of execution, for a given network (Fig 2).

The optimisation tests reveal that a computer with a large number of processor cores appears computationally optimal for relatively small networks (Fig 2A). As the network size increases (Fig 2B and 2C) the optimal number of computers tends to rise keeping the optimal computation. ARACHNE enables the user to specify the maximum size of the network for a given set of parameters and the size of the computer cluster. Parallelisation is critical for improving computational performance. At first glance, calculations are quicker and more accurate with larger computer numbers. In fact, our tests indicate that this is not always the case, in line with the Amdahl’s law \[46\].

Exploration example: Network size versus network dynamics

The network size and the distribution of synapses could strongly affect the network activity, even when all other settings remain unchanged. To explore this relationship we focused on the network main spiking frequency (Fig 3A) and synchronization (Fig 3B) as readout parameters \[35\]. The network ‘main’ frequency was calculated as the average frequency \(F = \frac{1}{T} \sum_{i=1}^{N} f_i\) of all neurons \(N\) with an individual frequency \(f_i\) during the computation time \(T\). Synchronization was calculated as a correlation between spike timing for all neurons in the network during time \(T\). The raster plots were therefore obtained for four characteristic cases: (i) the base network configuration (Fig 3C), (ii) doubled size (Fig 3E), (iii) increased numbers of neurons.
In the brain, the synaptic strength appears to depend on the distance between cortical neurons [47]: to recapitulate this observation, the model provides two complementary types of connectivity. The first type, termed bell-shaped strength (BSS) model, incorporates a Gaussian distribution of synaptic weights $w$ (centred at the ‘presynaptic’ cell, standard deviation $\sigma$) with the uniform connection density between the nearest 50% of all network neurons (S2A Fig). The second type, a ‘bell-shaped’ connection density (BSD) model, incorporates uniform distribution of synaptic weights $w$ but a Gaussian distribution of cell-cell connection density (S2B Fig), with the number of connections decreasing with distance from the ‘presynaptic’ cell.

**Exploration example: Network memorisation and recall**

The network memory formation is reflected in a change in the connectivity matrix (Fig 4C) resulting from an external input (Fig 4A). In this respect, ARACHNE includes two scenarios, one of memorisation (Fig 4B, i and iii) and the one of recall (Fig 4B, ii and iv). The modelled networks can in fact incessantly memorise and recall: the sequence of such events is shown in Fig 4.
The first scenario (Fig 4B, stage i and ii) deals with the memorisation of the external pattern (EP) only. When EP₁ (Fig 4A) is applied to e-cells, both networks begin to generate action potentials (APs). This prompts activity-dependent plastic changes in synaptic connections depending on the correlations between the APs of presynaptic and postsynaptic neurons. After a memorisation period, the synaptic weights are stabilised, thus forming a new memory matrix, such as the example ee-matrices that formed in response to EP₁ and EP₂ (Fig 4C).

The second scenario (Fig 4B, stage ii) was designed to simulate a recall process. In this mode, the mechanism of synaptic modification was switched off. When either EP₁ or EP₃ activates the networks the neurons start to generate a pattern of APs, with the matrix of synaptic weights remaining unchanged. At this stage, the model calculates the difference between two patterns of APs (Fig 4B, ii and iv; and i and iii, correspondingly) of the network dynamics to determine the recall quality C (Fig 4B). The initial pattern of APs is formed by the EP during
the first stage of the network configuration, and the another pattern occurs in response to a new EP.

These examples reveal the following. When the memorised synaptic matrix is associated with the EP₁ (Fig 4C, stages i and ii) which is used for the memory formation, the quality of recall of the same EP₁ is perfect, $C = 1$ (Fig 4B, stage ii). In case of EP₂ is used during memorisation, the quality of recall is relatively poor, $C = 0.6$, when EP₃ is used for the association (Fig 4B stage iii).

When the astrocyte calcium dynamics (Fig 4D, left) is on and the functional relationship between the astrocyte Ca²⁺ concentration and the e-cells synapses is active (Fig 4D, right), astrocytes begin to modify release probability of excitatory synapses (Fig 4D, middle). The correlation between the astrocyte calcium dynamics and the neuronal dynamics is increased and synchronized (Fig 4D, left and middle spiking raster plots). This mode of ARACHNE enables
exploration of the interaction between astrocytes and neurons networks, including the role of astroglia in memory formation.

Concluding remarks

Our aim here was to develop a neuroscientist-friendly simulation tool that would enable the design and exploration of realistic brain networks of arbitrary complexity incorporating neurons and astroglia. The flexibility and ease of use by experimental neuroscientists was among the main goals in creating ARACHNE. An important distinction of the design is the physical separation of the model management and model computations. A standard low-cost host computing device can therefore be used for the model administration including the network synthesis, the formation of input and output files, and of visual presentation of the results. Once the network configuration has been prepared, it can be uploaded onto a remote cluster. The user remains within its familiar host computing environment throughout the computations and is free to break the link to the remote computer during computations. One of the key objectives was therefore to create computational algorithms, including optimal parallelisation, which would run equally efficiently for the models of varied complexity without having a complex model interface or without engaging in any architectural programming adjustments.

Anticipating a high demand for computational power, we thus separated the programming (as well as physical) environment of model management from that of model computation. Another key feature of ARACHNE is the ability for multiple users to connect to the remote cluster from a variety of computing devices, including mobile devices, using a conceptually simple user-interface. Different participants can thus share the same low-level kernels for their own calculations, store the result locally or remotely in different files, and continue their computations from any point of the previous run. This design significantly enhances the flexibility for users to manipulate the data according to the needs of their calculations.

ARACHNE appears to be one of the first modelling tools recognising an important role of astroglia in modifying the signal transfer across synaptic circuits of the brain. Much unlike the point-to-point, ‘wired’ communication mode operated by synaptic circuitries, extracellular molecular signals generated by astrocytes are transmitted diffusely through the local tissue volume thus engaging multiple synapses on multiple neighbouring cells [48]. To date, only a few attempts have been made to introduce this type of volume-transmitted, astroglia-type signalling to the computational models of classical, wired neural networks [28].

An important trait of the ARACHNE is that it provides the ability of the neuron-astroglia networks explorations using the host GUI only, without changing the computational kernel located on the remote cluster. Thus, when the size and the topology of the network changes the system could, in principle automatically, optimise the entire computational process.

Parallel remote computations are emerging as an important direction for the computational exploration of complex biological systems. To account for this, ever advancing scientific quest, the present builder provides a flexible functionality to the user. We thus emphasise that ARACHNE as described here is not a final software product but a tool to advance one’s exploration of the neural and neural-astroglia networks.

Availability and future directions

ARACHNE is available online at GitHub with the explanatory documentation at https://github.com/LeonidSavtchenko/Arachne. The program is made available with an MIT license. ARACHNE is written in a way that allows users to run it with all common remote platforms. Whilst the program is designed for the MATLAB interface, the skeleton code provided in the
package allow users to modify it for Python platform. We plan to untangle kernel and the graphical interface to use the GUI or the kernel with other tools such as NEURON or PyNN.

**Supporting information**

**S1 File. Text Box.** The boot file of communication between host and remote computers. (DOCX)

**S2 File. Biophysics of model.** A detailed description of the biophysical model of a neural-neuroglial network, the mathematical formalism and parameters. (DOCX)

**S1 Fig. Graphic user interface.** Example of GUI table of model parameters. (TIF)

**S2 Fig. Rules of network and synaptic engagement.** (a) BSS type includes a non-uniform density of synaptic weights (red line) and a uniform density of connections. (b) BSD type includes a uniform distribution of synaptic weights (red line) and non-uniformly distributed connections. (c) EP for large networks has been drawn in a graphic editor. (d) EP for small networks is prepared by the dynamic matrix. (e) (Top) Diagram of synaptic connections for STDP mechanisms. (Bottom) Examples of static rules of STDP. (f) (Top) Diagram of synaptic connections for the frequency dependent plasticity. (Bottom) Examples of rules for the frequency dependent plasticity. (TIF)

**S1 Code. The code of ARACHNE, all versions.** (ZIP)

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**Author Contributions**

**Conceptualization:** DAR LPS.

**Funding acquisition:** DAR.

**Investigation:** LPS KZ.

**Methodology:** LPS.

**Software:** SGA LPS KZ.

**Supervision:** DAR LPS.

**Validation:** KZ.

**Writing – original draft:** SGA.

**Writing – review & editing:** DAR LPS.

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