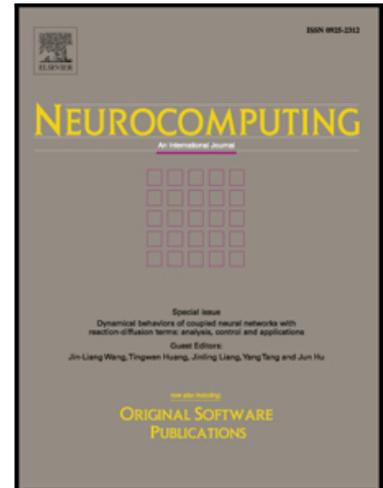


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Emulation of chemical stimulus triggered head movement in the *C. elegans* nematode

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Abstract

For a considerable time, it has been the goal of computational neuroscientists to understand biological nervous systems. However, the vast complexity of such systems has made it very difficult to fully understand even basic functions such as movement. Because of its small neuron count, the *C. elegans* nematode offers the opportunity to study a fully described connectome and attempt to link neural network activity to behaviour. In this paper a simulation of the neural network in *C. elegans* that responds to chemical stimulus is presented and a consequent realistic head movement demonstrated. An evolutionary algorithm (EA) has been utilised to search for estimates of the values of the synaptic conductances and also to determine whether each synapse is excitatory or inhibitory in nature. The chemotaxis neural network was designed and implemented, using the parameterization obtained with the EA, on the *Si elegans* platform a state-of-the-art hardware emulation platform specially designed to emulate the *C. elegans* nematode.

1 Introduction

Caenorhabditis elegans (*C. elegans*), is a 1 mm long, soil-dwelling nematode that is widely used as a model system in animal biology. The popularity of *C. elegans* is a consequence of it being the best characterised living entity [1] (including its nervous system and genome) and its development being understood at the single-cell level [2]. It also shares many of the essential biological characteristics that inform central problems of human biology [3]. This nematode has one of the simplest nervous and locomotor systems composed of 302 neurons, about 8000 synapses and 95 body wall muscles [3].

The aim of this paper is to simulate the behaviour produced by chemotaxis. *Chemotaxis* is the ability to move up or down a gradient of chemical attractants or repellents, to find food, avoid noxious conditions, develop

appropriately, and mate [4]. To achieve this, the nervous system generates motor commands which bias the movement and direct the animal toward higher attractant concentration or away from repellent concentration. In particular, *C. elegans* detects the presence of chemicals with a pair of sensory organs (amphids) at the tip of the nose, each containing multiple chemosensory neurons. The sensory neurons responsible for chemosensation, in *C. elegans*, are ASEL and ASER [3], situated at each side of the head. The *C. elegans* worm is attracted to NaCl when it is conditioned with food [5]; in this paper a NaCl concentration gradient is simulated.

Computational modelling and analysis are able to provide useful biological insights and predictions, as well as to explore other questions which are not easily accessible through experimentation [6]. The simulation of locomotion in *C. elegans* has been a common topic of research in recent years. The most common models are those based either on central pattern generators [7], oscillators [8] or artificial neural networks [9]–[12]. Previous research has considered chemosensory locomotion and behaviour, by either training a dynamic neural network to control muscle contraction in response to a chemical gradient [9], [11] or training an artificial neural network to produce the probability of forward motion, pirouette or rest [10].

The neurons ASEL and ASER are able to perceive the NaCl concentration changes and are typically used in the modelling of chemotaxis, providing inputs to the model [7], [9], [13].

One of the usual modelling assumptions is that the worm has the ability to sense the spatial gradient by ASEL and ASER. ASEL responds to positive changes in NaCl concentration and ASER responds to both positive and negative concentrations [14]. The network described in [7] used neuron pairs represented as single neurons, with ASE as the input and AVA and AVB, which regulate forward versus pirouette behaviour [15], as outputs (ASEL, ASER, AVA and AVB are neurons identified in the fully characterised neural connectome in [3] – see Fig. 4) This network was modelled as a fully connected network with recurrent self-connections. A different approach used a similar network [13], with ASER and ASEL as inputs, a series of interneurons, and the motor neurons DA and RMD as outputs. This network was built using the known connectome [4], with the sensory neurons responding to NaCl concentration changes. The network used in [13] is a simplification of [5], with only RMD neurons as motor neurons and the inclusion of muscles in the head and neck of the worm, and well established neuron and muscle models. Another network, [9], was built using ASEL and ASER as input neurons for food attraction, and motor neurons (RMD, SMB and SMD) as output neurons for head movements. The head movement is used here to achieve the decision making function and is used as control of the oscillation. The rest of the undulation is achieved with a different network, although a pattern generator can generate the rhythm of the locomotion in the rest of the body [16].

The success of such models [10], [13], however, is limited by the many unknown parameters, variables and simplifications of the model system, including the variety of neurotransmitters and modulation pathways or the extra synaptic circuit mechanisms [17]. Furthermore, nervous systems have the ability to perform the same function even if they are structurally different or have different parameters [18].

Other research has attempted to devise a neural network model for *C. elegans*' behaviour by considering the physical behaviour of its body [17], [19]–[21]. In these papers the simulated neural networks have some motor-neurons that activate the muscles, making the worm move. The simplest methods use a row of segments, each one acting as a muscle [19], [22]. Others use reproductions of the nematode in 2D, where two rows of muscles enclose the whole body of the worm [20], [21]. In recent years, 3D simulation has been

used in order to obtain a more realistic anatomical reproduction of the animal [23], [24], taking into account the *C. elegans*' muscles' small asymmetry, not implemented in simpler models.

In this paper, we report on the results of simulations of the neural network in *C. elegans* that responds to chemical stimulus, and show how such stimuli result in realistic head movement. To address the problem of unknown parameters, variables and modulation pathways, an evolutionary algorithm (EA) has been developed to estimate the values of the synaptic conductances and whether they produce an excitatory or inhibitory synapse. Although there are and have been previous attempts to use EAs to train the entire connectome to respond to specific stimuli [12] there is still no definitive answer into what are the parameters, and what might be missing, to fully simulate *C. elegans* behaviour.

The results presented in Section 3 were obtained by running experiments on the *Si elegans* open-access platform for the accurate emulation of the *C. elegans* nervous system [25]. This platform provides a sophisticated emulation environment, exploiting an advanced design environment where users can design their own custom neuron models, or use models from a model library, to run and visualise the results on a unique 3D Virtual Arena (VA). The emulation runs on a parallel hardware architecture based on Field Programmable Gate Arrays (FPGAs) [26].

The remainder of this paper is structured as follows. Section 2 describes the methodology and approach, including muscle and synaptic models, the genetic algorithm, the physics engine and force calculations, and the hardware implementation on the *Si elegans* platform. Section 3 presents the results and discussion of network optimisations, the simulations and the FPGA performance. Section 4 presents the conclusion of the work.

2 Materials and Methods

The chemosensory network was initially designed and tested in software and later implemented and tested on the *Si elegans* platform. A brief overview of the *Si elegans* platform, the models, the genetic algorithm used, the physics engine, forces calculations, and details of the FPGA implementation are given below.

2.1 The *Si elegans* platform

The *Si elegans* platform is open access and provides a unique environment, specifically designed to accurately emulate the *C. elegans* nematode, where users (such as neuroscientists and modellers) can design and run their own experiments [27]. The platform (Fig. 1) provides an advanced design environment, including a User Interface (UI) for selecting pre-designed neuron models from the model library or designing custom neuron models, defining network topology, parameterizing neuron and muscle models or controlling the experiment and readback results [28], [29].

The platform is supported by a cloud-based server providing storage space (for simulation related data) and the functionality of sharing experimental results and/or neuron models within the *Si elegans* community. Different types of interactions between the virtual worm and the surrounding environment can be designed in a web-based 3D VA. Simulation information set by the user in the VA is transferred to the Physics Engine (PE) that is located in a Lab Server (LS). The PE is responsible for computing the virtual worm's locomotion, creation of runtime stimuli and management of the muscle results, based on data communicated from the

core computing facility (Fig. 1). Section 2.4 explains in more detail the operation of the PE. Finally, once the results of the experiment are collected, they are transferred to the VA, where they can be visualized.

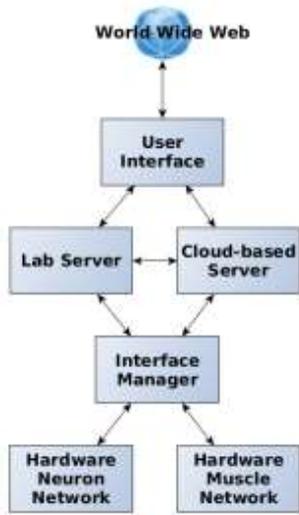


Fig. 1 *Si elegans* platform architecture

The *Si elegans* platform runs on top of a High Performance Computing (HPC) facility based on FPGA technology, utilised as neuromorphic hardware that can be freely reconfigured by users [26]. This HPC FPGA cluster facility is composed of 375 Terasic TR5 FPGA development kit [30] (Fig. 2 and Fig. 3) equipped with a powerful Intel (formerly Altera) Stratix 5SGXAB FPGA device (Table 1 lists the most important features available on the Stratix 5SGXAB device).



Fig. 2: Front and side view of the HPC FPGA cluster

Hodgkin-Huxley type dynamics and the computational efficiency of integrate-and-fire neurons [32]. It may be described by a system of differential equations of the form:

$$v' = 0.04v^2 + 5v + 140 + I(t) \quad (1)$$

$$u' = a \cdot (b \cdot v - u) \quad (2)$$

$$\text{If } v \geq 30 \text{ mV, then } \begin{cases} v = c \\ u = u + d \end{cases} \quad (3)$$

In these equations, the variables v and u represent the membrane potential and the recovery variable respectively, I is the injected direct current, a is the time scale of the recovery variable, b is the sensitivity of the recovery variable, c is the after-spike reset value of the membrane potential caused by high-threshold potassium conductance and d is the after-spike reset value of the membrane potential caused by low-threshold potassium conductance.

The equations of the Izhikevich model were first implemented in software using Python and then using the Very Large Scale Integration (VLSI) Hardware Description Language (VHDL) for hardware (FPGA) implementation. Further details about the FPGA implementations are presented in section 2.5.

2.2.2 Muscle model

A second order linear model (LMM) was used to model the isometric force, since linear models are attractive due to their simplicity and ease of analysis for muscle force modelling [34]. However, such models have to be considered carefully, as they may lead to loss of information and may not provide a good description of muscle force [35]. A second order ordinary differential equation (ODE) describes the linear model of the muscle force in Eq. (4).

$$\theta_3 \ddot{F}(t) + \theta_2 \dot{F}(t) + \theta_1 F(t) = \theta_0 u(t) \quad (4)$$

Where $F(t)$ is the muscle force as a function of time, θ_i are the model parameters and $u(t)$ is the input spike train coming from the motor neurons.

2.2.3 Synapse model

An instantaneous rise and single-exponential decay [36] model was used to simulate the synapses. This is a simple model that assumes an instantaneous rise of the synaptic conductance $g_{syn}(t)$ from 0 to \bar{g}_{syn} at time t_0 followed by an exponential decay with constant τ (5).

$$g_{syn}(t) = \bar{g}_{syn} e^{\frac{-t+t_0}{\tau}} \quad (5)$$

The synapse was then modelled as follows:

$$I_{syn} = g_{syn}(t)[V(t) - E_{syn}] \quad (6)$$

where I_{syn} is the postsynaptic current, $V(t)$ is the voltage potential of the postsynaptic current, E_{syn} is the postsynaptic neuron reverse potential or 0 depending whether it's an inhibitory or excitatory synapse, \bar{g}_{syn} is the channel conductance (measured in Siemens, S), t and t_0 the current time and the time from the last spike (both in seconds) and τ is the time constant [36]. In this implementation, $\tau=0.017s$ for all synapses [36].

2.3 Genetic algorithm to train the network

Knowledge of the connectivity of the neurons in the nervous system of *C. elegans* (Fig. 4) is insufficient to enable accurate simulations of how the system behaves under varying circumstances. This is because the specific details of all the synapses are not known, i.e. the strength of the transmitter release, the type of transmitter used or, even, its directionality (inhibitory or excitatory). One is thus required to explore a large search space to determine suitable combinations of parameter values to obtain observable, realistic behaviour in the worm. To expedite this, a well-known computational intelligence search optimisation method, an evolutionary algorithm (EA), was used to tune the values of the synapses, simulating the training of the weights of an artificial neural network (ANN). To achieve this, the connectivity of the network was set as specified in the worm connectome [37], but optimal conductance values of the synapses, along with E_{syn} , indicating an excitatory or inhibitory connection, were sought using the EA. Values of the conductance's range were constrained to lie between zero and one, while E_{syn} was determined to be either 0 or -80 mV, indicating either excitatory or inhibitory connections. The parameters of the neuron models are set as default to tonic spiking conditions ($a = 0.02$, $b = 0.2$, $c = -65$ mV and $d = 6$), while the muscle model parameters were set after the network was trained.

Evolutionary Algorithms create a set of different solutions to a problem (through a representation) and varies them (via mutation and recombination) to create new ones iteratively (generations). The process of eliminating the worst solutions (competition) and preserving the best ones (evaluation and parent selection) converges into an optimal solution. A particular type of evolutionary algorithm is used, Evolutionary Programming [38], where all the components are present with the exception of recombination (representation, evaluation, population, parent selection, mutation and competition), since it has been indicated that recombination does improve the performance of the algorithm in neural networks [39]. The details of this algorithm are described as follows.

A population of random neural networks is created and their outputs, described here as the currents feeding the muscles, are calculated. The stimulus added is based on the concentration of the chemical NaCl, although in this simulation it is represented as an input current in mA. This stimulus is added to either the left or right ASE. In the real behaviour of the neurons [14], ASEL is known activate only with positive NaCl gradients and ASER with both positive and negative. In our model, we have made the simplifying assumption that the stimulus is added to either the left or right ASE, where the left ASE is assumed to activate with a NaCl gradient towards the left and the right ASE with a rightward gradient. This type of assumption has been made in previous works [9], [13], [15]. Since the worm is lying on its side, to turn left or right the dorsal or ventral muscles need to be contracted. The convention is that to turn left the dorsal muscles are contracted and to turn right the ventral muscles are contracted.

The chromosome of the *C. elegans* is a table of values containing, for each synapse, the value of the conductance and a 1 or a 0 to indicate whether it is an excitatory or inhibitory synapse. For this particular algorithm, no crossover has been included since their application tends to destroy features found during the evolutionary process [39].

Using the Izhikevich and synapse models the, currents and voltages across the network were calculated from the stimulus in the sensory neurons to generate the input currents reaching the muscles. These currents are used to calculate a simple point-based fitness function, where a positive point is given if the current reaches

the correct muscles and a negative point is given if it reaches the wrong muscles or if it's zero in the correct muscles. The best performing network will be the one with the higher score in their fitness function.

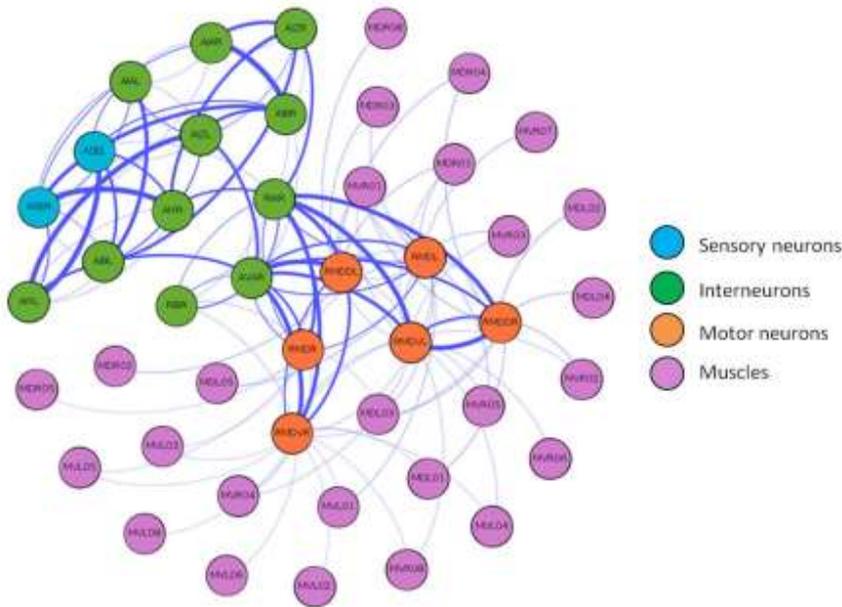


Fig. 4 Network used to represent the chemotaxis response in *C. elegans* [13]. The strength of the connections is shown as the width of the links

With the exception of the network with the highest fitness value, all networks were mutated at the end of each generation. The mutation function adds a random value to the conductance of the connections, which can be positive or negative. There is a 50% chance of mutation. If the conductance value is mutated, it is added a random value from a uniform distribution between -0.1 to 0.1. The type of the synapse was also mutated in the EA, with a 50% chance of reversing from inhibitory to excitatory and vice versa. This process was repeated for all networks iteratively for 1000 generations. At that point it was assumed that the optimal network (relative to computational efficiency) had been found; this should be a network where, given the right stimulus, the ventral muscles contract and with a left stimulus the dorsal muscles contract and vice versa.

The currents feeding the muscles were then used to calculate the muscle forces using the linear muscle model (LMM) (described in Section 2.2.2). This way the parameters of the muscles can be tuned independently of the EA. It is assumed that all muscles have the same dynamics and therefore the same parameterization is used in all the muscles, since all the body wall muscle cells are the same [40].

Having determined the optimal parameters, using these muscle forces, the emulated movement was run in the simulation arena (computed in the physics engine and visualised in the virtual arena results GUI). This showed the behaviour of the worm in the platform. More details on the physics engine are presented in the following section.

2.4 Physics Engine and Forces calculation in the VA

C. elegans is composed of 95 body wall muscles divided in 4 longitudinal bundles located in 4 quadrants: dorsal left (DL), dorsal right (DR), ventral left (VL) and ventral right (VR). All 4 bundles have 24 muscles except for VL that has 23 [40]. Each quadrant is divided in two rows, medial and lateral. One of the main goals of the work described in this paper is to improve upon the widespread symmetric model (with 96 muscles) to a more realistic model with 95 muscles.

The simulation is based in a Finite Element Method (FEM) model. The method uses a set of tetrahedra that represent the muscles and the rest of the body of the worm, enclosed by its cuticle (shown in Fig. 5). The 3D representation of *C. elegans* that was created within the Virtual Worm Project [40] has been tetrahedralised. The nodes that compose tetrahedral were transformed by internal and external forces to obtain locomotion. The cuticle (semi-transparent in Fig. 5) has 330 nodes; each individual muscle is defined by 24 inner nodes and contains 32 tetrahedra; the rest of the body that fills the space between the muscles and the cuticle is composed of 7340 tetrahedra.

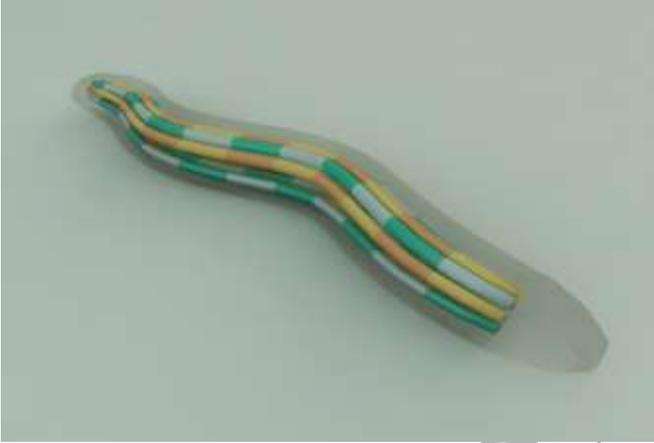


Fig. 5 The cuticle and the muscles of our 3D reproduction of *C. elegans*

The material of the muscles and the interior part of the cuticle has been modelled by the Saint Venant-Kirchhoff model [41]. It describes the behaviour of a simple hyperelastic material by considering the following equation:

$$\mathbf{S} = \lambda \text{tr}(\mathbf{E}) \mathbf{1} + 2\mu \mathbf{E} \quad (7)$$

Where \mathbf{S} is the second Piola–Kirchhoff stress, \mathbf{E} is the Lagrangian Green strain, λ and μ are the Lamé constants and $\mathbf{1}$ is the second order unit tensor. These constants are obtained from the Young's modulus and the Poisson's ratio of the specific material and, in our case, they were obtained from [42] for both materials (body and muscles).

The motion in three dimensions of the nodes that compose the body of *C. elegans* is controlled by Newton's second law of motion:

$$M\mathbf{u}''(t) + C\mathbf{u}'(t) + K\mathbf{u}(t) = F(t) \quad (8)$$

Where $\mathbf{u}(t)$ describes the deformation of the nodes of the worm, M represents the mass matrix, C is the damping matrix, K is the stiffness matrix and $F(t)$ are the external forces applied to the nodes of the worm.

The forces that are used for the simulation of the locomotion of *C. elegans* are the internal pressure of the worm, elasticity of the cuticle, external and muscle induced forces. The first two are simulated as part of the simulation of the material of different parts of the body, since the body is stiff enough to impede the collapse of the body structure (internal pressure) and is strong enough to recover the rest position after a transformation (elasticity of cuticle). The rest position is the straight position of the worm. At the moment, apart from forces that come from collisions with objects of the environment and gravity, friction is the only external force applied. This is the key force that allows the nematode to move forward.

The last force, the activation of muscles, is guided by the signals that come from the motor neurons as described in previous sections. At each time step, each muscle receives from the neural network a signal between 0 and 1 and consequently applies forces in every simulation node of the muscle.

$$F_{ij} = \delta_k \lambda_i F (p_{i+1,j} - p_{i,j}) \quad (9)$$

The magnitude of the force exerted in the node located in the i th ring and in row j (Fig. 6) of the muscle k depends on the signal that comes from the neural network, δ_k , a parameter that depends on the ring where the node is located and increases when moving away from the centre of the muscle, λ_i , and a constant that regulates the forces in the whole simulation, F . The direction of the force F_{ij} is given by the following node in the j th row, $(p_{i+1,j} - p_{i,j})$. Note that, in order to obtain contraction in all nodes of the muscle, once the middle of the muscle is passed, the direction is the opposite, $(p_{i-1,j} - p_{i,j})$.

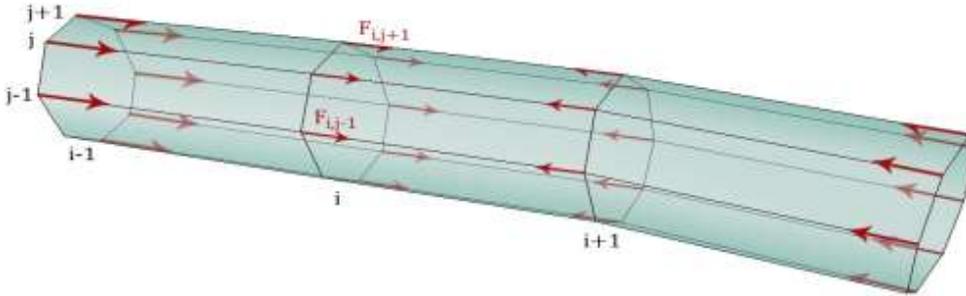


Fig. 6 Forces exerted in the simulation nodes of a muscle

Since the neural network described above only activates the muscles of the head and the worm needs activation in its whole body to obtain proper locomotion, a central pattern generator (CPG) has been created in the Physics Engine to control the body movements of the worm. This way, a combination of normal locomotion obtained via the CPG and the head steering using the neural network is obtained. In other words, the CPG makes the worm move forward and the neural network fixes the forward direction of the worm, going towards the attractant or going away from a repellent.

Thus, another activation signal is added to the activation signal of the muscle in Eq. (9) δ_k :

$$\delta_k = \frac{\sin\left(\frac{3\pi m}{24} + \theta_r \frac{\pi}{2} + \frac{2\pi t}{P}\right) + 1}{10} \quad (10)$$

Where m is the number of the muscle in its row of muscles, θ_r is -1 for muscles in ventral rows and 1 for dorsal ones, t is the current time and P the period of activation. Note that in Eq. (9) i and j refer to the row and the ring of nodes inside a specific muscle (Fig. 6) and in Eq. 10, m and r refer to the position and the row of a whole muscle in the body (Fig. 5). The first summand inside the sinusoidal function makes the wave propagate through the body of the worm. The second summand makes the muscles on one side of the body (ventral) contract while the opposite muscles (dorsal) relax and vice versa. The third summand contains the shape change through time, representing the period P .

2.5 Hardware implementation of models

FPGAs are advanced computational devices with a substantial amount of uncommitted hardware resources, which can be freely reprogrammed by the user after manufacture. Theoretically, any electronic circuit can be implemented on an FPGA as long there are available resources [43]. At the present time, FPGAs exhibit significant speed, lower power consumption, built-in Intellectual Property (IP) blocks, a substantial number of Digital Signal Processing (DSP) blocks, increased built-in memory and large numbers of digital Inputs/Outputs (I/Os). Each model neuron was implemented on an individual Terasic TR5 development board, equipped with an Altera Stratix V GX FPGA, with one neuron per FPGA. This allowed for the implementation of models of massive complexity, while retaining the high computational speed of an FPGA based computing cluster and the re-programmability of FPGAs, mimicking biological plasticity. This approach presents major improvements over a conventional computing cluster in terms of retention of true parallelism. Each model was described in VHDL, simulated in Mentor Graphics QuestaSim v1.04 and then tested using a test bench in Python, prior to generating a configuration bitfile for each FPGA. The test bench configured the model described on the FPGA, ran the simulation and collected the results via the serial port. The hardware results were then compared with the software results.

2.5.1 Neuron Model

The results from the simulation of VHDL in QuestaSim obtained for the Izhikevich model are presented in Fig. 7. For this particular behaviour, the Izhikevich parameters were set to: $a = 0.02$, $b = 0.238$, $c = -50.0$ and $d = 2.2$.

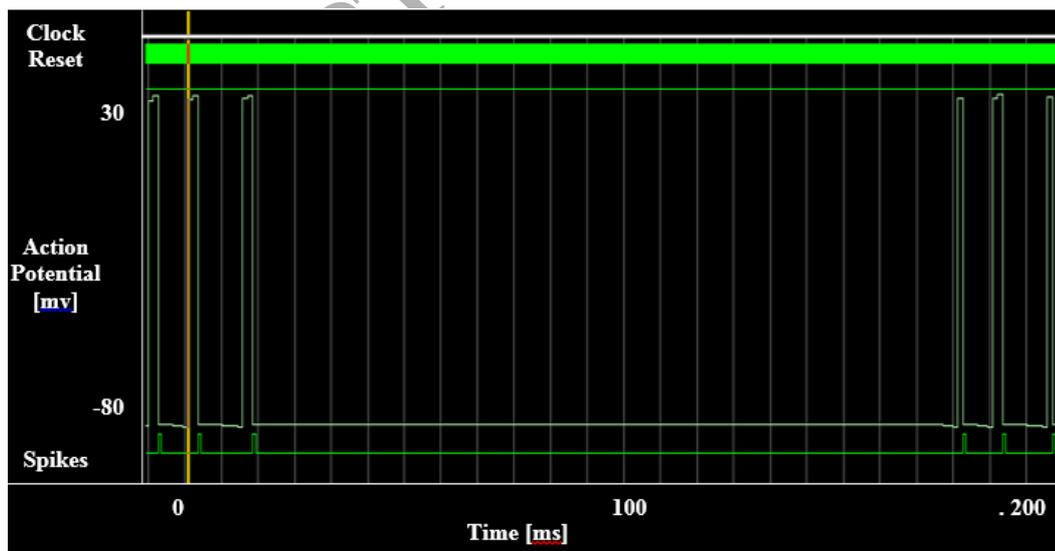


Fig. 7 Simulation results of the Izhikevich in QuestaSim. Starting from the top, the first row shows the clock, second row the reset signal, third row the action potential and the fourth row shows the spikes.

Once the VHDL code has been tested in QuestaSim , a configuration bitfile for each FPGA is generated. The experimental results obtained from the implementation of the Izhikevich models on an FPGA are depicted in Fig. 6.

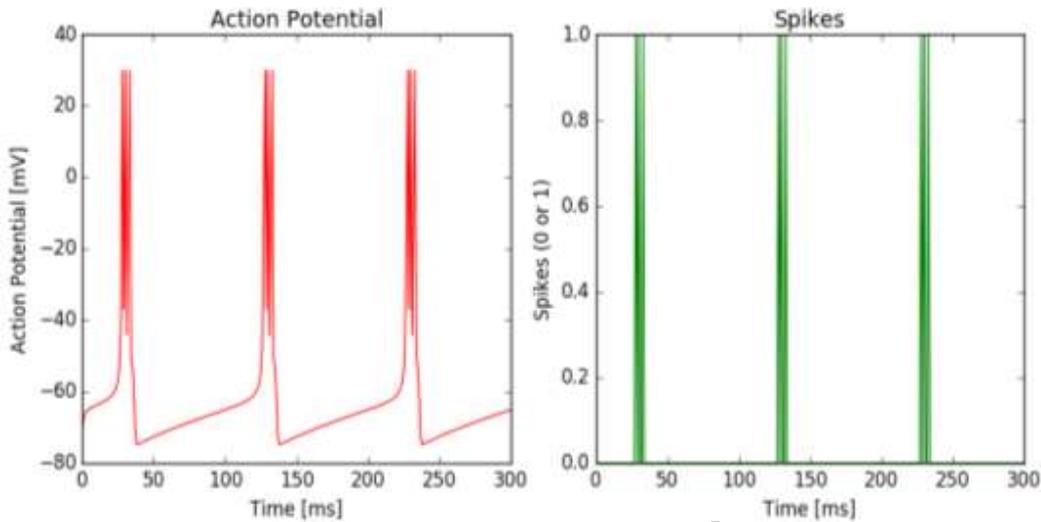


Fig. 8 Experimental results of the Izhikevich neuron model running on the FPGA.

The first plot (in red) shows the membrane potential (in mV) versus time (in ms), the second plot (in green) shows the spikes (0 if no spike otherwise 1) versus time (in ms). For this particular behaviour (the tonic bursting) the Izhikevich parameters were set to: $a = 0.02$, $b = 0.238$, $c = -50.0$, $d = 2.2$ and constant input current of 2mA.

2.5.2 Muscle Model

The same procedure was adopted to implement, simulate and test the Linear Muscle Model. In Fig. 9 the simulation results obtained in QuestaSim are presented.

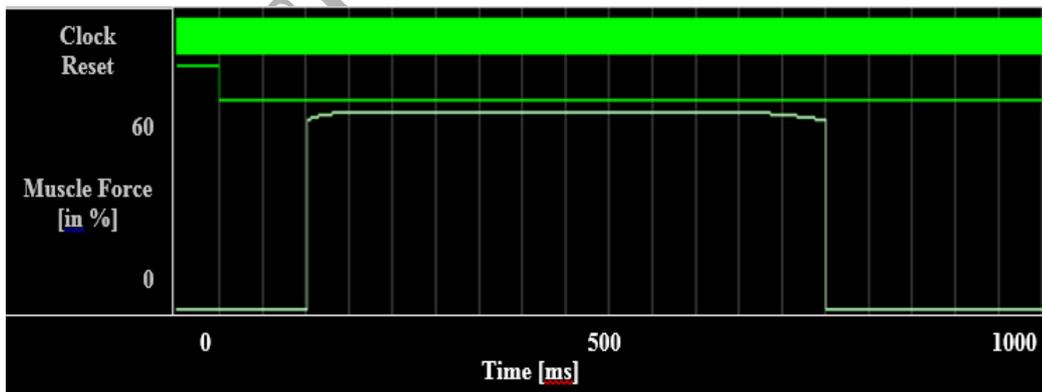


Fig. 9 Simulation results of the LMM in QuestaSim.

Starting from the top, the first row shows the clock, the second row shows the reset signal and the third row shows the contraction force (in a scale of 0% to 100%).

The results obtained from the implementation of the LMM on the FPGA are depicted in Fig. 10. The plot (in red) is the contraction force (in a scale of 0 to 100%) versus time (ms).

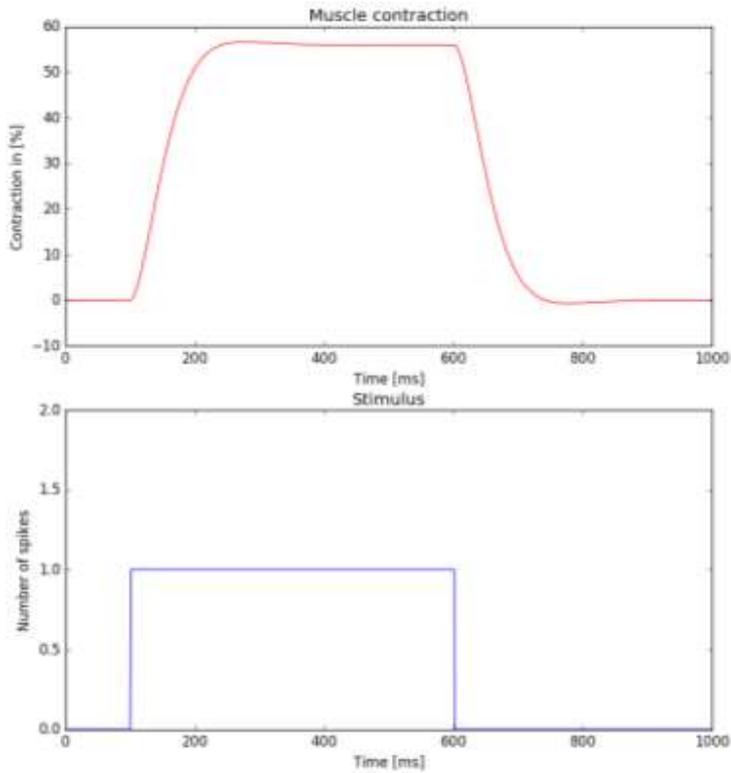


Fig. 10 Experimental results of the LMM running on the FPGA.

2.5.3 Synapse Model

The synapse implementation was performed using the same procedure described in Section 2.5.1. In Fig. 11 the simulation results obtained in QuestaSim are presented. The first row shows the clock, the second row shows the reset signal, the third row shows the spikes and the fourth shows the current generated by the synapse in mA.

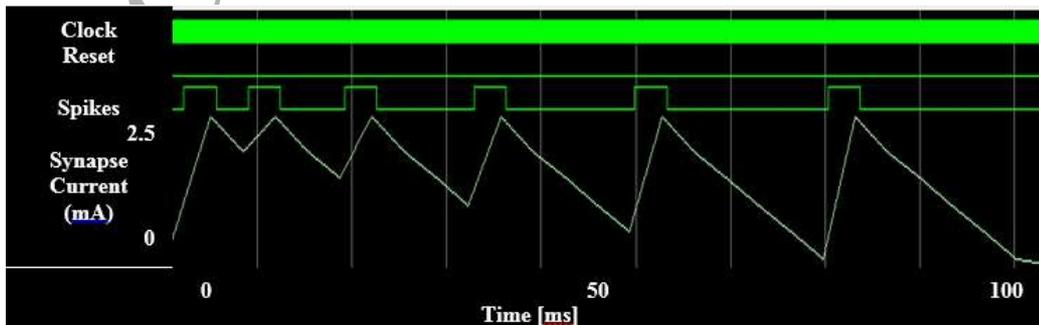


Fig. 11 Simulation results of the synapse model in QuestaSim.

The synapse model was part of each neuron/muscle model. Synapses can be configured as inhibitory/excitatory depending on the parameterization used. The exponential decay was implemented in hardware using look-up tables (LUT) to reduce the on-chip resource utilisation.

3 Results and Discussion

This description of results is divided into three sections, namely the network simulation; muscle, force and movements simulation, and FPGA performance.

3.1 Network simulation

The EA was run for 1000 generations to obtain the gain and the activation on the right motor neurons with a stimulus applied on the right side and vice versa, gain and activation on the left motor neurons in response to a stimulus on the left side.

When the stimulus is applied in ASEL, the signal is propagated throughout the network until it activates the left RMD motor neurons (Fig. 12), which are connected to the neck muscles on the left side, causing them to contract and activate a turn to the left side. When the stimulus is applied in ASER, the right RMD neurons are activated, producing a contraction towards the right side.

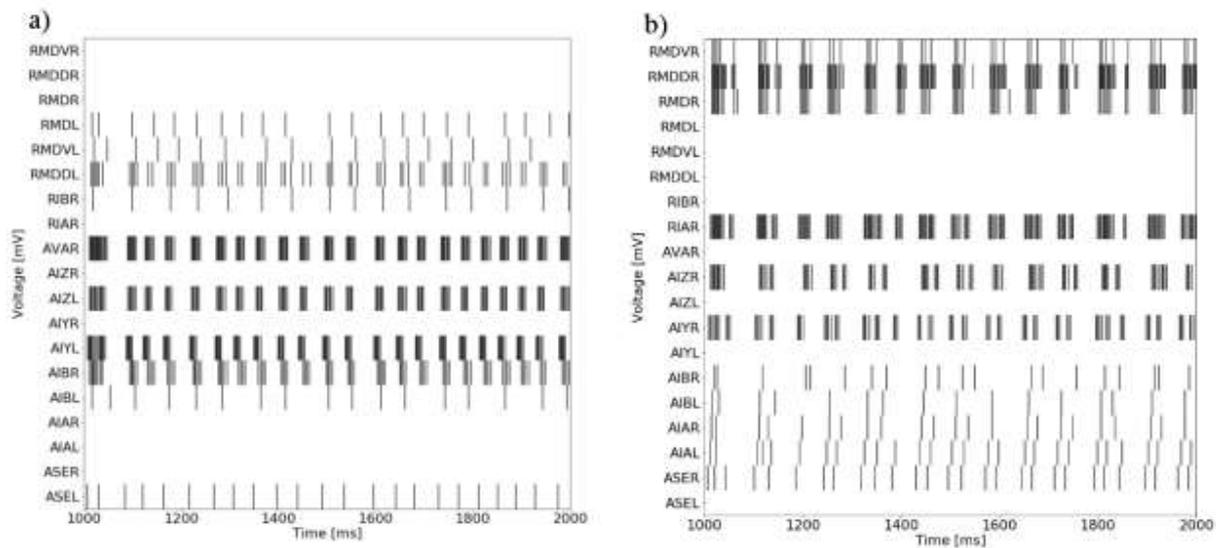


Fig. 12 Spiking activity (spikes per neuron over the time in ms) of the network after training with the EA in response to a stimulus on the left (a) and on the right (b) ASE neuron

As the results show, the neurons activated following each of the stimulus are different, with different spiking rates. This behaviour is obtained through a combination of the different conductance values found using the EA (Fig. 4) and the value of the synapse current E_{syn} .

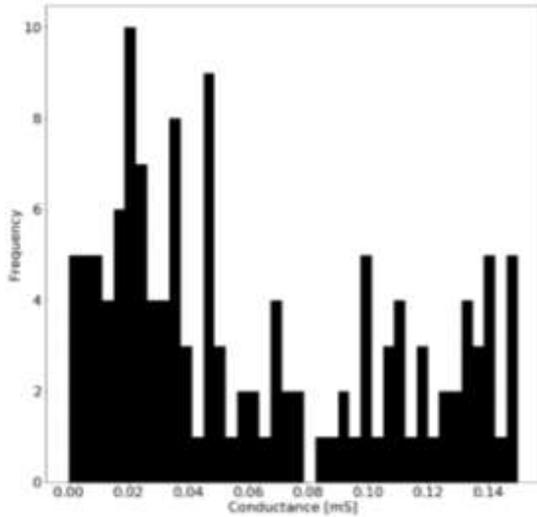


Fig. 13 Histogram of the conductance values in the network calculated using the EA method.

Most of the conductance values are below 0.08 mS/cm^2 , with some strong connections up to 0.16 mS/cm^2 (strength of the arrow in Fig. 14). The synaptic current E_{syn} also indicates that most of the synapses in the network are excitatory, with a few inhibitory connections that cause the network to respond to either left or right stimulus, applying the current into the correct motor neurons that innervate the neck muscles (red and blue colour of the arrows in Fig. 14). This figure therefore extends the data of Fig. 4 by incorporating the inhibitory or excitatory detail determined in this research, including the strength of the connections.

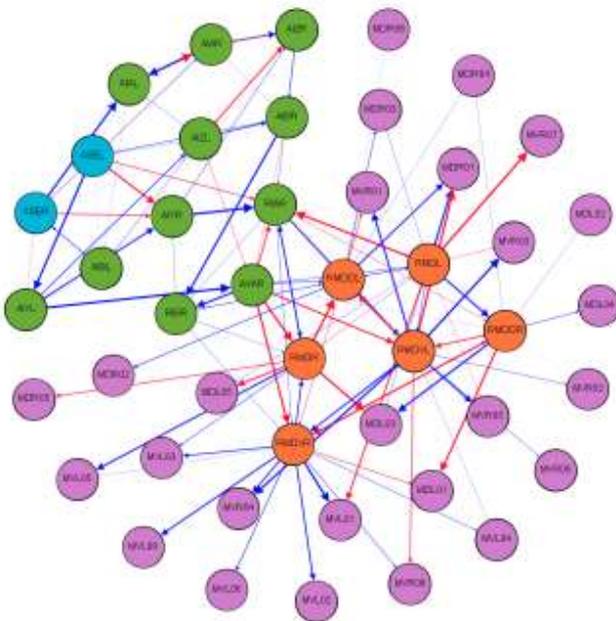


Fig. 14 Graph of the chemosensory network showing in blue the excitatory connections and in red the inhibitory connections determined following EA optimisation. The width of the connection lines indicates the strength of the conductance.

One of the main issues in modelling biological systems is the need to know all the involved parameters; frequently these data are not available. For this particular reason, search algorithms such as EA are becoming

very popular. Nevertheless, there are several important points to consider when using such algorithms [12]. The first is that just because the parameters obtained reproduce the behaviour to be modelled does not mean that the parameters chosen are a representation of the actual parameters in the system [18]. The second is that, usually, such simulations are simplifications, since many other stimuli and connections are not taken into account, and therefore, the overall system functionality is not represented. Finally, from the computational perspective, there are limits imposed on the search space, including the range of values of the parameters, the assumptions made of the system and of the correctness of the model chosen. There are a few methods to test the validity of the assumptions, starting with comparison with experimental observations [6], [13].

3.2 Muscles, forces and movements

This section shows the results with respect to muscles, forces and movements.

3.2.1 Muscle simulation

With the parameters for the network already obtained, the currents supplied to the muscles are known and their contraction can be calculated. Using the values obtained in the EA, a stimulus in ASEL produces a contraction of the dorsal muscles (which reflect a left turn), and no contraction in the ventral muscles. Vice versa, a stimulus in the neuron ASER produces contractions in the ventral muscles but not in the dorsal muscles (right turn) (Fig. 15). This distribution of conductance values and synaptic currents in a network, with this diversity of connections, is able to produce different behaviours. In this case, it is able to produce two different movements, exciting different muscles, in response to two different stimuli. The muscles that respond with higher intensity to the stimulus are those in the neck area, rather than the ones in the head area.

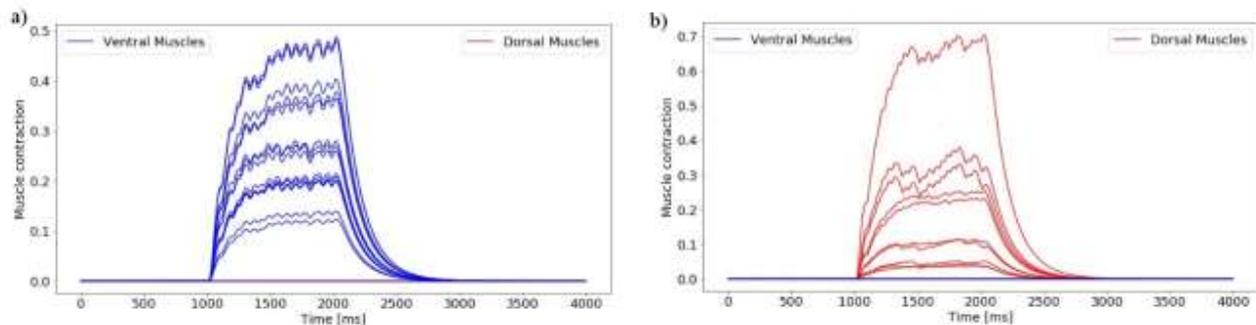


Fig. 15 Muscle contraction of the head and neck muscles in *C. elegans* (in proportion, where 1 is the maximum muscle contraction due to a stimulus applied to the right side (a) and to the left side (b) left side. Right muscles are drawn in blue and the left muscles in red. Not all the muscles are activated during the excitation phase, which is seen by the zero muscle contraction in both figures for some of the muscles, depending on where the stimulus is received.

3.2.2 Force and movement

A validation of the method described in Section 2.4 was performed in two stages. Firstly, the neural activation of the muscles was tested. Once it was confirmed that the defined neural circuit made the worm steer towards its goal, a CPG was added to the neural activation to test that the worm definitely moved forward towards the attractant. In the first step, the emulated worm stands still on the plate until the attractant stimuli activates its neural circuit and consequently muscles are activated, as shown in the

previous section. Since the neural circuit implemented is connected with the muscles in the anterior part of the worm, a reaction in the head of the nematode was expected.

Two tests were carried out, where in each experiment an attractant was placed on a different side of the animal. It was found that the neural circuit exclusively activated the muscles on the correct side of the neck, corresponding to the attractant location. Specifically, the neural circuit contracts those muscles (see parameter δ_k in Eq. 9). As a result of this activation, the worm steered its head to the attractant side. Fig. 16 a) shows a VA screenshot of the movements obtained in each of these tests.

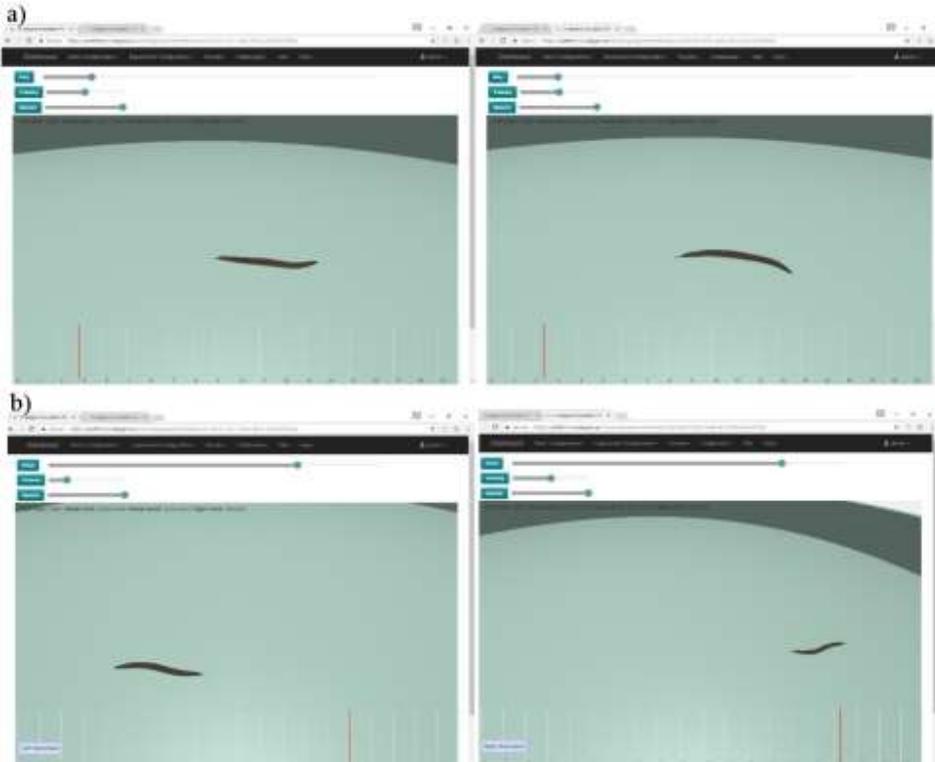


Fig. 16 a) Resulting movements to an attractant on both sides of the virtual worm. b) locomotion of the worm when combining CPG with an attractant in the right (right) and with an attractant in the left (left).

In the second step of these tests, a CPG is added to the activation that comes from the neural circuit (see Eq. 10). The CPG makes the *C. elegans* move forward with a sinusoidal pattern and neural activation changes this signal slightly, so that the contraction is bigger to the attractant side than to the other side (Fig. 16 b)). This change leads to a forward movement of the nematode, but steering towards the attractant.

This work is aligned with the recent trend of 3D simulations of the locomotion of *C. elegans*. In this case, in contrast to [23], the 3D model used for the simulation mimics the number of muscles and the asymmetry of the muscular structure of the nematode, enabling a realistic matching among motor neurons and muscles. The FEM simulation that has been implemented is able to simulate the movements of the worm fast enough to follow the performance of the neurons in the FPGAs, in contrast to the work in [45].

3.2.3 FPGA Performance

The simulation was designed on the *Si elegans* platform and the resulting initialisation/configuration files were automatically uploaded into the *Si elegans* hardware via the Interface Manager (IM). Simulation starts when a start command is asserted in the GUI and sent to the IM, which issues a new timestamp packet that is broadcasted to all the neurons and muscles. The timestamp packet also includes the spikes generated in the previous time window. Each timestamp has a length of 1 ms. On receipt of a timestamp signal, neurons compute the membrane potential accordingly to pre-synaptic spikes, stimulus (stimulus preconfigured by the user) and runtime stimulus (stimulus generated by the physics engine). If the resulting potential is above the threshold a spike is generated. Neurons generate the logical value “1” when a spike is generated and “0” otherwise. Calculated values are sent to the IM by the end of the timestamp.

Muscles have slower responses than neurons and therefore each muscle only computes the muscle forces every 50 ms. Muscles compute forces based on the spike trains buffered during the previous 50 ms (timestamps). These forces are transmitted to the physics engine via the IM by the end of the muscle computation. The process of spike (neurons) and forces (muscles) transmissions repeats until the end of the simulation. The results can then be visualised on the Virtual Arena.

The (Stratix 5) FPGA resource usage of the neurons, muscles and synapses implementation is listed in Table 2.

Table 2 Resources usage of each model described in the FPGA

FPGA resource	Izhikevich	LMM	Synapses	FPGA available resources
ALUTs	15,053	44,092	0	359,200
Registers	1108	1006	236	8927
BRAM	57,344	57,344	0	54,067,200
DSP block	40	68	1	352

The logic elements are used for describing the muscle equations, the adaptive look-up-tables (ALUTs) are used to temporarily store the computation results, the block memory bits are used as first-in-first-out (FIFOs) to store temporarily the results in the FPGA and the DSP block are mainly used to perform mathematical operations that require multiplications/divisions.

The combined computation and transmission times were approximately 300 ms using the 1 Gb Ethernet connection; this timing was kept stable during the simulation period. There was a time overhead on the IM because the results from the FPGA have to be converted from Hexadecimal to XML and vice-versa every time that the IM synchronizes with the physics engine. The processes of exchanging the muscle force and stimuli packets (between the IM and physics engine), over the HTTP protocol and performing the data conversion (by the IM) from Hex to XML and vice-versa, takes up to 2 minutes.

The results obtained from the simulation using Python and the results obtained on the FPGA were similar and the models had a similar dynamic response. However, the parameters values have small differences which are related to the differing data representations in software vs hardware and the approximations required to make the implementations more hardware efficient. Full network simulations will have better performance because both the transmission and calculation timings will remain almost constant as a consequence of the parallel architecture.

The FPGA emulation environment was crucial for performing a bio-inspired emulation of the *C. elegans*' muscles and neurons on a fully parallel, interconnected, hardware neuron and muscle network. This parallelism was only possible because unlike central processing units (CPUs) and graphical processing units (GPUs) that have their unique serial architecture. In contrast, FPGAs allow reconfiguration after fabrication, making it possible to describe parallel hardware architectures and therefore each FPGAs was used as an element of neuromorphic hardware specially designed for emulating each one of the neurons and muscles in the *C. elegans* chemosensory network.

4 Conclusions

In this work, the authors report on the emulation of head movement in a neuron-based model of the *C. elegans* nematode, utilising aspects of the published connectome. A realistic set of model parameter values appropriate to chemotaxis was identified by an EA, and the EA results were used to design and build a chemotaxis neural network. Neuron, synapse and muscle models have been implemented, and a locomotion system configured. It has been demonstrated that a contraction of the muscles induced by a chemical stimulant made the worm move its head towards the chemical attractant, irrespective of whether the stimulant was on the worm's right or left side. Moreover, the incorporation of a central pattern generator showed the worm activates locomotion towards the chemical attractant.

The network presented, although it contains assumptions and simplifications, is a step forward into modelling nervous systems. The algorithm was able to provide a realistic explanation of the connectivity of the network and muscle contractions, which produced a natural movement observed under such stimulus. Up to now, most of the locomotion simulation that has been achieved has been based purely on Central Pattern Generators [7], oscillators [8] or artificial neural networks [9], [11]–[13]; this is the first time that it is based on a combination of artificial neural networks and a 3D physics engine [46].

Moreover, despite the complexity of such an emulation environment and differences between the software and hardware simulations, it has been shown in this paper that the FPGA technology is an excellent choice for emulating bio-inspired neuron/muscle networks.

Further work will include using this technique to study the behaviour of *C. elegans* under more realistic model and assumptions, such as the actual functionality of ASE. Also, it will be used to study the response of other subsets of the *C. elegans* connectome and compare them with experimental data to try to understand the behaviour of the worm better and to validate the methodology and the platform more extensively.

Furthermore, we will seek to replace the central pattern generator with a more biologically compatible locomotion model. However, optimizing the full connectome to obtained a realistic behaviour even for a single stimulus response is a herculean task, that so far has not been achieved [12].

The *Si elegans* platform has proven to be a suitable simulation environment for emulation of *C. elegans* behaviours. The unique parallel architecture, with a dedicated physics engine and easy-to-use design environment provides users with appropriate tools to study and replicate the nematode behaviours. This infrastructure should help with the more complex in-silico experiments defined for the exploration of this nematode's functional behaviour.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

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