A Physically-based Simulation of a Caenorhabditis elegans

Andoni Mujika
Vicomtech-IK4
Mikeletegi Pasealekua,57
20009, Donostia-San Sebastian, Spain
amujika@vicomtech.org

Alessandro de Mauro
Vicomtech-IK4
Mikeletegi Pasealekua,57
20009, Donostia-San Sebastian, Spain
ademauro@vicomtech.org

Gautier Robin
University of Technology of Compiegne
rue du docteur Schweitzer
60200, Compiegne, France
gautier.robin@etu.utc.fr

Gorka Epelde
Vicomtech-IK4
Mikeletegi Pasealekua,57
20009, Donostia-San Sebastian, Spain
gepelde@vicomtech.org

David Oyarzun
Vicomtech-IK4
Mikeletegi Pasealekua,57
20009, Donostia-San Sebastian, Spain
doyarzun@vicomtech.org

ABSTRACT

This paper shows the three-dimensional physical model created to simulate the locomotion of the Caenorhabditis elegans. The C. elegans is a very deep studied nematode as it is considered one of the simplest nervous systems in nature, made of 302 neurons and about 8000 connections. To date, there is no system that can faithfully reproduce the rich behavioral repertoire of this tiny worm in terms of neural activity and locomotion. The Si Elegans project aims to develop the first hardware-based computing framework that will accurately mimic a C. elegans worm in real time. It will enable complex and realistic behavior to emerge through interaction with a rich and dynamic simulation of a natural or laboratory environment. As a result, the locomotion of the virtual worm will be rendered in a web-based platform. In this paper, we describe the approach followed for the physically-based modeling and simulation of C. elegans and the benefits of our approach compared to existing ones. The main contribution of our work is the utilization of biphasic springs in the structure that represents the worm in the virtual environment and a Finite Element Method based internal force field to simulate the internal pressure of the body.

Keywords

Physically-based Modeling, 3D Graphics, Biological simulation, Caenorhabditis elegans.

1 INTRODUCTION

The Si Elegans project aims to mimic the neuronal system of a small (about 1 mm in length) nematode called Caenorhabditis elegans (C. elegans) [Alt09a] and to simulate its behavior in three dimensions. It is one of the best known organisms in the world, and it is used in many different biological experiments. On the one hand, C. elegans is very useful for genetic studies, since its genome is completely known, the functions of most of its genes are known and its manipulation for chemical and genetic tests is relatively easy.

On the other hand, the relative simplicity of its neuronal system (The hermaphrodite C. elegans has 302 neurons) permits to study how its nervous system works. Given its rich behavioral repertoire (e.g. locomotion, feeding and even certain social behaviors), it is a perfect organism to study and learn from, in the way to understand more complex organisms.

Despite the fact that the connectivity of those 302 neurons is known, the knowledge of the scientific community is far from knowing every operation of the neurons and their effects in the worm. That is why the nematode is still under research.

The objective of Si Elegans project is to provide the scientific community with an emulation alternative to the laboratory experiments for their research. For that, a web-based three-dimensional virtual arena is being constructed. In comparison to similar projects, the specifics of the Si Elegans project are: (i) the hardware based emulation of the neural network, and (ii) the parallelism of the neuron to neuron communication. These specifics are targeted to achieve a higher degree of similarity with the neural system of the real worm.

1.1 Si Elegans Project Overview

The main objective of Si elegans is to provide the neuroscientist community with a complete emulation of the C. elegans through a web platform, allowing them to run different experiments. The user will define the environment (obstacles, air or liquid, etc.), and the behavioral experiments that will be emulated (i.e. touching the worm, placing food or toxic in the plate, applying vibrations to the whole environment).

The experiment definition will be fed to the Field Programmable Gate Array (FPGA) based neuronal network emulation. The neuronal network will process and compute the behaviors simulation of the worm. Based on the behavior simulation results, the physics engine will calculate the locomotion of the worm, taking into account the defined environmental values. The physics simulation results will be rendered in a web browser (using web3D technologies). Additionally, the web based user interface will display detailed results of the experiment at neuron, muscle and the environment level.

For that purpose, the system being developed in the Si Elegans project has five main parts as shown in Fig.1: a browser based user interface, a cloud based server, the lab-server, an interface manager, and the hardware infrastructure. In the following we will describe the function of each part.

The user will access the Si Elegans system via web. They will be able to set and monitor all the aspects of the simulation, mainly related to neurons and muscular movement. The user interface allows the user to perform the following tasks:

- To define all the parameters for their experiment (position of the worm, temperature of different parts of its environment, food, toxic substances...)
- To reproduce the visual 3D rendering of the worms locomotion for the defined experiment.
- To monitor low level results of the experiment, such as the activity of the neurons, networks state, and environment values evolution.
- To define new neuronal models, and neuronal network configurations. This will allow researchers to evolve existing neuronal models, and to switch off some neurons for experiments, as is done in real lab experiments.
- To share with the community models, experiment definitions, results, and recent achievements, to get feedback from other colleagues.

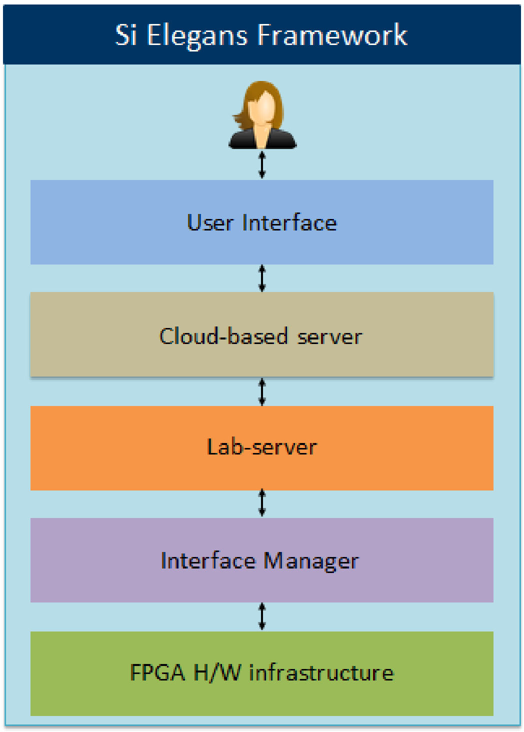

Figure 1: Framework of the Si Elegans project

The cloud-based server lies in the background of the web page. Each user interface of the web page has its couple in the cloud-based server. On the one hand, it handles all the information that comes from the UI, and on the other hand, transmits the information from other parts of the system to the UI.

The lab-server, and the hardware infrastructure are the most challenging parts in the development of the Si Elegans system. This is where the whole emulation of the organism of C. elegans will be held. The physics engine will be hosted at the lab-server. Both the lab server and the hardware infrastructure will be closely connected. They need to have a synchronous information flow: (i) to input the hardware based neuronal emulations results to the physics engine, and (ii) to input the experiment variables of the next time-step, calculated by the physics engine, to the FPGA based neuronal network. In each time-step the environment of the worm will be analyzed to obtain the sensory information, and it will be sent to the neuronal network compound by the FPGAs.

The interface manager is the responsible for converting the data that comes from the physics engine into legible data for the FPGAs, and converting signals that come from the FPGAs into activation values for the muscles of the worm.

This paper describes our approach for the physics simulation of the 3D worm and more specifically the physics model that simulates the movement of the muscles of

 ISBN 978-80-86943-70-1

the worm. Section 2 reviews the state of art on the C. elegans locomotion simulation. Section 3 introduces the model followed in the Si Elegans project for the physics simulation of the worm. Afterwards, section 4 provides implementation details of the approach, and section 5 draws conclusions and discusses the future work.

2 RELATED WORK

The idea of representing the movements of a C. elegans in a computer is not new and several works have been presented since the early nineties. Most of them work with a reproduction of the animal in two dimensions and are still far from getting a perfectly realistic behavior.

Niebur and Erdös [Nie91a] present the two-dimensional model as a succession of cylinder projections. This way, the muscles of the worm are the outer segments of the squares (cylinder projections) that compose the worm. In this case, the generation of the movement of the worm is done by directing its head towards a point (following a sinusoidal pattern) and neurons do not take part in the process. Similarly, Suzuki et al. [Suz05a] [Suz05b] compose the body of the nematode by 12 segments connected by joints that move in two dimensions. The movement is accomplished by applying forces in the head segment and in the tail segment, when it moves forward and backward, respectively, following serpents locomotory system.

The pioneering work by Niebur and Erdös is the basis of most of the following methods [Wak06a] regarding the shape of the worm and the forces that are applied on it to obtain the locomotion: internal pressure of the worm, elasticity of the cuticle ("skin" of the worm), muscle forces and environmental forces. Nevertheless, they are focused on the neuronal leading of the locomotion. The work of Bryden and Cohen [Bry08a] takes a simple, but biologically tested, sample of the neuronal system of C. elegans and uses it to create a movement robust to changes that may occur in the environment.

Similarly, Boyle [Boy09a] represents the worm by a two-dimensional model where the muscles are the edges between two boundary vertices. When the muscle is activated, the edge shrinks inducing an elongation in the muscle of the opposite side of the contour. The physical model includes the forces occurring in the majority of the methods (cushioning, elasticity, internal pressure, environmental forces and strength of the muscles). His neuronal model contains 12 neural units with 4 neurons each, where each neuron communicates with four muscles.

Although it is a simple method, the CLONES system, presented by Voegtlin [Voe11a], uses two important tools for the simulation of C. elegans organism. It creates a connection between the neural simulator Brian [Goo08a] and the physical framework for biomedical applications SOFA [All07a]. This way, it copes with the two main aspects that rule the locomotion of the nematode, the neural network and the physical behavior of the muscles.

Despite the fact that most of the works that simulate the movements of C. elegans are in two dimensions, in recent years, there have been efforts to upgrade the simulation to three dimensions. Cortez et al. [Cor11a] presented a method, based on Navier-Stokes equations, that makes nematodes and leeches swim in a viscous incompressible fluid. In this case, the activation of the grid that forms the body of the nematode is done directly, without any neuron. The model presented by Mailler et al. [Mai10a] also has a limited neural model. The worm is represented by 25 rigid cylindrical sections which are handled by the physics engine Open Dynamic Engine [Ode01a] and the model takes into account similar forces to those described above. Indeed, the simulation does not differ much from those in two dimensions.

The main active project in the field of simulation of C. elegans is the OpenWorm Project [Ope13a]. In this case, the physical modeling is based on the work of Palyanov et al. [Pal11a]. The model of the virtual worm is composed of point masses and springs to model skin and muscles. The contractions of the muscles are produced by the neurons and their connections (neuron-neuron and neuron-muscle). The skin of the animal is created through a spring structure and mass points, which remain attached (without losing the form of a worm). The authors also use the 23 neurons that handle forward locomotion [Cha85a] and introduce pseudo-neurons, parts of the neural network that attenuate and slow down the arrival of the signal between neurons. This way, locomotion is not affected by the "lack of distance" between neurons. Predictive-Corrective Incompressible Smoothed-Particle Hydrodynamics (PCISPH) [Sol09a] is used to model the behavior of all the particles that take part in the simulation (including fluids). Nowadays, the main drawback of the system is its slow performance.

The Si Elegans project proposes the development of a very realistic neuronal simulation and a physically-based locomotion simulation in three dimensions. Although worm locomotion can be approximated fairly reliably in 2 dimensions, 3 dimensions allow inspecting all neural and muscular aspects more clearly.

The next section describes the structure implemented to model the body of the worm and the physical model applied to it, emphasizing the contributions done to the state of the art.

3 PHYSICS-BASED SIMULATION

In this section, we first describe how the body of the worm is modeled and then, we list the forces that are applied to such structure in order to obtain realistic locomotion.

3.1 Body Structure of the Worm

Hermaphrodite C. elegans (the most common and simplest one) has 95 muscles [Alt09b]. They are divided in 4 quadrants of 24 muscles, except for the ventral left one which has 23 muscles. Not all the muscles have the same shape and length and they are not placed in a completely symmetric way. However, in our first approach we have considered them equal and symmetric as most works described above do. Specifically, we constructed a mass-spring structure, a classic approach for the muscle modeling [Ter94a]. In our case, biphasic springs [Par12a] are used in order to stop the elongation of the muscle at a certain length.

A biphasic spring is a linear spring that changes its spring constant at a certain length. This way, changing the stiffness at a certain point we stop the elongation of the spring at certain point. Otherwise, the behavior of a biphasic spring is equal to a linear spring:

$$\vec{f_s} = -k_s(\vec{L_c} - \vec{L_r})\left(\frac{\vec{p_2} - \vec{p_1}}{\|\vec{p_2} - \vec{p_1}\|}\right) \quad (1)$$

where $\vec{f_s}$ is the spring force that will be applied to the points in the corners of the spring (in opposite direction), k_s is the spring constant, the one that changes its value at certain point, $\vec{L_c}$ is the current length, $\vec{L_r}$ is the length of the spring when it is in rest position and $\vec{p_1}$ and $\vec{p_2}$ are the points in the corners of the spring.

Each spring has its corresponding damper, that acts against the spring force. Depending on the velocity of the stretching or elongation, the damper provides resistance to this deformation:

$$\vec{f_d} = -k_d(\vec{v_2} - \vec{v_1}) \cdot \left(\frac{\vec{p_2} - \vec{p_1}}{\|\vec{p_2} - \vec{p_1}\|}\right)\left(\frac{\vec{p_2} - \vec{p_1}}{\|\vec{p_2} - \vec{p_1}\|}\right) \quad (2)$$

where $\vec{f_d}$ is the damping force that will be applied to the points in the corners of the spring (in opposite direction), k_d is the damper constant (not depending on the length of the spring) and $\vec{v_1}$ and $\vec{v_2}$ are the velocities of the points $\vec{p_1}$ and $\vec{p_2}$ respectively.

The structure that represents the body of C. elegans has been constructed in a similar way to [Pal11a], but in this case, each muscle is represented by a biphasic spring instead of two attached springs. The rings that compound the body of the worm are represented with a square of biphasic springs and are linked to other rings with the muscles. Fig. 2 shows the structure that has been constructed to simulate the worm. In each quadrant, there are 24 red segments that represent the muscles and each ring has 4 green segments. The first and the last ring are smaller in order to obtain a more similar shape to the shape of the worm.

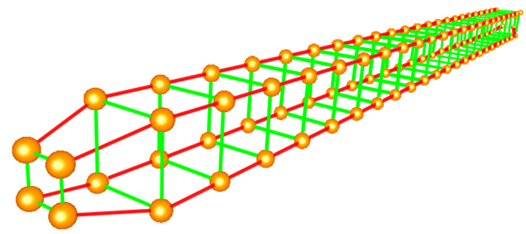

Figure 2: Structure of the virtual C. elegans

The muscles are active springs that have to stretch and compress in order to generate the locomotion and the rings are composed by springs that have to maintain the body shape of the animal, i.e. they must be stiffer. The different stiffness constants are discussed in depth in section 4.

3.2 Physical Model

In the following, we describe the forces that are applied to the points that link the springs of the structure: muscle activation, skin elasticity, internal forces and environmental forces. These are the forces that are taken into account in most works that have been described above, but in our case, the works are applied in a 3D environment.

3.2.1 Muscle Activation and Skin Elasticity

The muscle activation and the elasticity of the cuticle are modeled with the biphasic springs that have been described in section 3.1 and ruled by equations 1 and 2.

If the spring constant and the damper constant are correctly set, the spring structure is elastic enough to simulate the contractions of the muscles of the real nematode and stiff enough to maintain the shape of the body despite the forces are being applied onto it. Moreover, a parameter, θ, can be added to the formula in order to turn a spring into an active spring.

$$\vec{f_m} = -\theta k_s(\vec{L_c} - \vec{L_r})\left(\frac{\vec{p_2} - \vec{p_1}}{\|\vec{p_2} - \vec{p_1}\|}\right) \quad (3)$$

Normally, the forces make the spring tend to stabilize, but this way, the behavior of the spring (the muscle) depends on the value of θ. If the values of θ are correctly set in real-time, the muscles contract and relax so that the worm goes forward.

3.2.2 Internal Forces

The springs described above ensure the topology of the structure, but the gravity is enough to collapse the

 ISBN 978-80-86943-70-1

whole system. That is why internal force (pressure generated by internal liquids of the worm) must be simulated. For that, we used a force field similar to the one described in [Nes05a], where a cube made of silicon is modeled. The body of the worm is divided into a grid of hexahedra, supposed to behave isotropically and then a Finite Element Method (FEM) is used to simulate the opposition to collapsing tendency of the spring structure.

3.2.3 Environmental Forces

C. elegans can crawl on solid surfaces and swim in liquid media [Alt09c]. Since in this first approach we only address the first type of locomotion, we do not take into account forces derived from the surrounding liquid. So, only gravity and friction are computed.

Friction is the key that makes the worm go forward. The friction force estimation is similar to the one presented in [Dur08a]. In each time step the colliding points (including those of the worm and those from the floor) are computed. Then, based on the values of forces in the previous time step, an iterative process is done to obtain the actual values of the contact forces.

The friction model is based on Signorini's law and Coulomb's friction law. Let $\boldsymbol{\delta} = [\delta_n, \delta_t, \delta_s]$ be a contact point in the contact space defined by the normal and the tangents, $(\boldsymbol{n}, \boldsymbol{t}, \boldsymbol{s})$ and let $\boldsymbol{f} = [f_n, f_t, f_s]$ be the contact force. Then, Signorini's law states that δ_n or f_n must be null:

$$0 <= \delta_n \perp f_n >= 0 \tag{4}$$

Moreover, Coulomb's friction law gives two conditions for stick motion

$$[\delta_t, \delta_s] = (0,0) \Rightarrow \|[f_t, f_s]\| < \mu \|f_n\| \tag{5}$$

and slip motion

$$[\delta_t, \delta_s] \neq (0,0) \Rightarrow [f_t, f_s] = -\mu \|f_n\| \frac{[\delta_t, \delta_s]}{\|[\delta_t, \delta_s]\|} \tag{6}$$

where μ is the friction coefficient.

During the simulation, the free motion of the points of the worm is computed, i.e. without taking into account collisions. Then, a collision detection algorithm is used to detect which points are colliding with the floor. Next, following the laws that have been described above, a Non-Linear Complementary Problem is obtained and solved with numerical strategies. In order to arrive fast to a solution that fulfills the described laws, the solution of the previous time step (if these points were in contact) is used as the first sample. Finally, the position obtained from the free motion simulation is corrected with the computed contact forces.

4 IMPLEMENTATION

Once the physical system is completely defined, there are several aspects that have to be set so the worm moves correctly: all the constants of the simulation, the activation of the muscles, the physical solver and other implementation aspects.

4.1 Muscle Activation

At the end of the Si Elegans project the activation of the muscles will be launched by the artificial neurons encoded in the FPGAs, but currently it has been simulated. Nevertheless, the system is ready to be connected with the hardware, because the neurons will only have to set the value of the parameter θ in equation 3. Currently it is done following this formula:

$$\theta = C \sin\left(\frac{2\pi t}{T} - \frac{3\pi i}{N} - \frac{\pi}{2}\right) \tag{7}$$

where C is a constant that is equal for all the muscles, t is the current time, T is the period of activation, i is the index of the muscle and $N = 24$ is the total number of muscles.

This way, providing correctly the intensity of the force C and the period of the muscle activation T, a wave is propagated in the muscles making the virtual worm move in a similar way to the real one. The first summand inside the sine, $\frac{2\pi t}{T}$ makes the muscle contract and relax periodically; the second summand, $-\frac{3\pi i}{N}$, propagates the wave along the body of the worm so that two muscles are in maximum activation at each time and the last summand, $-\frac{\pi}{2}$, is a constant that leads to a correct initiation of the simulation.

The index i refers to 4 muscles, one in each quadrant. In order to obtain arc kind shapes, the muscles in the left (ventral and dorsal) must relax when the muscles in the right contract, i.e. they must receive the opposite signal.

4.2 Parameter Estimation

Since the spring structure is not completely identical to the muscle system of the worm, the values for the spring constants cannot be taken from biological data. Also, the unique similar approach [Pal11a] does not use biphasic springs and internal forces to avoid structure collapsing. So, the parameters of the springs have been set empirically. As springs in the rings must ensure the shape of the worm and the muscles have to contract and relax, the spring constant is very different for them. The spring constant of the normal springs ($k_s = 200N/m$) is higher than the spring constant of the muscles ($k_s = 100N/m$). The damper constant is the same in both cases, $k_d = 1kg/s$. In both cases, the spring becomes much stiffer from a certain length on.

ISBN 978-80-86943-70-1

Tools	Open	Springs	SPH	FEM
AnimatLab	X	X		X
Bullet	X	X	X	X
H3D		X		X
Havok		X	X	X
ODE	X	X	X	X
PhysX		X	X	X
Sofa	X	X	X	X
Unity		X	X	X
X-flow				X

Table 1: Comparative table of physics simulation tools

On the other hand, the parameter C that modulates the dimension of the forces applied in the muscles and the friction coefficient μ have been set so that the sinusoidal signal received by muscles makes the worm advance in a similar way to the real C. elegans. $C = 2000$ and $\mu = 0.7$ has proven to be a suitable value.

Regarding the parameters that rule the internal forces, to the best of our knowledge, there is no previous work that uses a similar approach, so we have set the parameters empirically. We finally conclude with a Poisson's Ratio of 0.45 and a Young's Modulus of 5 kPa.

4.3 Physical Solver

Several simulation tools have been studied in order to find the perfect one to implement all the physical features that have been described above. Simulation of mass-spring systems and FEM solvers were mainly needed. Moreover, libraries that implement Smoothed Particle Hydrodynamics solvers were preferred, because we believe that this will be a key technique for the simulation of the locomotion of C. elegans in fluids. We were also looking for Open Source tools. Table 1 shows the conclusions of this study.

Finally, SOFA (Simulation Open Framework Architecture) has been selected [All07a]. Two aspects have been the key of this selection: (i) the easiness to create complex environments with a scene graph editor and (ii) the wide range of different components SOFA offers (solvers, objects, collision detection algorithms, etc.) and the relative easiness to create new ones.

Specifically, these are the solvers that have been used for the simulation of the locomotion of C. elegans: (i) a Constraint Solver using the Non-Linear Complementarity Problem formulation described above, (ii) in the FEM part an Euler Implicit Solver for Ordinary Differential Equations and a Conjugate Gradient Linear Solver for systems of linear equations and (iii) bounding box hierarchies and a simple triangle/point intersection algorithm for collision detection.

The implementation for GPUs of SOFA has been used to run the simulation in a Intel Core2 Duo CPU at 2.20GHz with a NVidia GeForce 9800 GT GPU. The simulation runs in real-time and it gets a performance around 40 frames per second.

In order to speed-up the web based rendering the simulation output is converted off-line in a WebGL animation. This solution will provide the research community with a smart interface (operating system and browser independent) to be used everywhere. A frame rate of around 50 FPS has been achieved in the same computer.

5 CONCLUSIONS AND FUTURE WORK

In this paper we have presented the physically-based simulation approach being developed for the Si Elegans project. To achieve this goal, we have created a structure made of biphasic springs. Some of them can contract themselves without an external force. This way, the muscles of the animal are modeled.

To the best of our knowledge, there are very few 3D models of the locomotion of C. elegans and only one that simulates the behavior of the muscles directly. Our model introduces new features in order to make the simulated physical model more similar to the real one: biphasic springs instead of springs or pairs of springs and an internal force field to simulate the internal pressure of the worm, similar to the one used by several two dimensional approaches, instead of rigid joints.

We are aware of the big advances that have been done in this topic in other projects and we consider that nowadays they can be more realistic than ours, but real-time performance is a key part of our project and we consider it is impossible to obtain fast performance with such complex structure and physical model. In our case, a good performance has been obtained with a regular desktop computer.

The main challenge of our research is to provide complex physically based simulation of the C. elegans starting by the emulation of each single neurons activity and their neuronal network. Future steps will include the connection between the developed physically based model and the neural network output computed with FPGAs. This connection will be done by plugging the neuronal signal to the value θ of the equation 3.

In the current implementation the neural signals for the muscles contractions has been simulated to make the worm move in a realistic way. The combination of the created physical model and the "artificial" signal generated for muscles, leads to a locomotion very similar to that of real nematodes. Figure 3 shows the movement of the virtual C. elegans.

Moreover, there are several aspects of the physical simulation per se that will be refined in the next prototypes. New parameters and features will be added to the virtual scenarios. At the moment, for instance, the virtual nematode goes forward and backward, but the system is

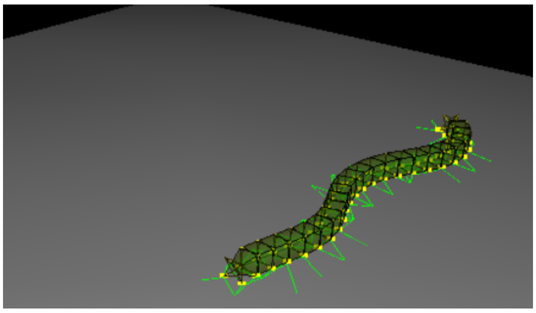

Figure 3: Locomotion of the virtual C. elegans

not able to simulate omega turns, i.e. sudden direction alterations that the real C. elegans does occasionally. Even, these movements should be generated automatically from the signals of the neurons, we plan to study the artificial signal needed to generate these turns, in order to help the modeling of neurons.

6 ACKNOWLEDGMENTS

The Si Elegans project is funded by the 7th Framework Programme (FP7) of the European Union under FET Proactive, call ICT-2011.9.11: Neuro-Bio-Inspired Systems (NBIS).

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 ISBN 978-80-86943-70-1