Input Encoding Proposal for Behavioral Experiments with a Virtual *C. elegans* Representation

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Abstract: This paper discusses a *Caenorhabditis elegans* (*C. elegans*) nematode behavioral experiment input encoding. It proposes a common digital representation for behavioral studies with *C. elegans*. This work is a step forward towards the reproducibility and comparability of *in silico* simulations of the nematode with real-world experiments. The digital representation is divided into environmental and experimental configurations. The behavioral input is structured by duration-based behavioral experiment types at the top level (*i.e.* interaction at a specific time, interaction from $t_0 - t_1$ and overall duration) and by interaction type (*i.e.* mechanotaxis, chemotaxis, thermotaxis, galvanotaxis and phototaxis) for each duration-based type. The environment configuration is composed of the identification of the worm's mutation type, worm crowding, initial location, configuration of the assay plate, and obstacle settings. Parameters are defined by an XML schema to ensure the interoperability with other simulation solutions. It is being implemented and tested in the context of the *Si elegans* project.

1 INTRODUCTION

The reproducibility and comparability of experiments is key to scientific progress. Small variations in the conditions of an assay or in the applied behavioral stimuli can dramatically change the results of an experiment (Hart, 2005). Based on this consideration, researchers usually detail their *in vivo* experiments with respect to the animal's properties, the environmental conditions and the applied stimuli.

For the animal of interest, the nematode Caenorhabditis elegans (*C. elegans*), the scientific community has already detailed the requirements for *in vivo* behavioral assays such as the definition of the type of animals to be assayed with respect to control strains, their feeding status, cultivation conditions, the ambient conditions, the scoring of perceived behavior, the statistical analysis and the reporting of results (Hart, 2005). Once defined, the different assay considerations detail each *C. elegans* behavioral experiment, which can then be grouped by the observed behavioral response types.

With the advent of the *in silico* modelling and simulation of living organisms in different biomedical research areas (*e.g.*, computational neuroscience or systems biology), the minimum information content of a simulation needs to be agreed on in order to ensure reproducibility within simulations, comparability between different simulation systems and comparability between *in vivo* and *in silico* experiments (Waltemath et al., 2011). In this respect, different initiatives have attempted to standardize the computational models, simulation experiment definitions, graphical visualizations, results provision, and vocabularies including the provision of guidelines on their effective reuse. To the best of our knowledge the existing approaches do not support the encoding of inputs for behavioral experiments with simple life forms but rather target on the description of inputs at signal level, as is considered by distinct biological models of cells or neurons.

The contribution of this paper is the proposal of a digital representation to encode simulated experiments and stimuli at behavioral level for *C. elegans*.

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We first analyze the related work in the field of simulation experiment reproducibility (Section 2). Section 3 presents an innovative approach to define the behavioral experiment input for the *C. elegans* nematode simulation experiments. In Section 4, we summarize the paper and present our conclusions.

2 RELATED WORK

In the *in silico* biomedical modelling and simulation research areas, efforts have aimed at standardizing different models and processes as well as integrating specialized software into unified platforms (Amari et al., 2002; Cannon et al., 2007; Teeters et al., 2008; Ghosh et al., 2011; Dräger et al., 2014). Their main goal was the reproducibility, comparability of simulated experiments and the reusability of building blocks to provide the integration of more complex simulations or of multilevel modelling and simulation tools.

In the systems biology research area, (Dräger et al., 2014) examined diverse modelling standards and data formats that are currently in use within the scientific community together with databases, from which relevant resources that conform with these formats can be obtained. (Ghosh et al., 2011) described the types of software tools that are required at different research stages, current options that are available for researchers, challenges and prospects for modelling the effects of genetic changes on physiology and the concept of an integrated biomedical research platform.

In the computational neuroscience research area, (Cannon et al., 2007; Davison et al., 2009; Crook et al., 2013) examined the interoperability and the interfacing of neuroscience modelling software and neuronal network simulations. (Amari et al., 2002; Teeters et al., 2008) discussed the data sharing and the integration of shared databases and tools for integrative neuroscientific research.

(Dräger et al., 2014) suggested a structure to revise the state of the art in standardization and interoperability efforts. The review is structured into modeling guidelines, model encoding formats, simulation procedures, graphical model visualization and numerical results representation.

Modelling guidelines generally include requirements for the minimum information given in an experiment as well as ontologies that describe the controlled term vocabularies that should be used in the model encoding formats. The Minimum Information Required in the Annotation of Models (MIRIAM) guidelines promote the exchange and reuse of biochemical computational models (Le Novère et al., 2005). While mentioning the need for result reproducibility, MIRIAM does not cover the minimum requirements necessary for simulating the models. In contrast, the Minimum Information About a Simulation Experiment (MIASE) sets out to define the minimum requirements for simulation descriptions, and allows thus for unambiguous reproduction of experiment (Waltemath, Adams, Beard, et al., 2011). With respect to ontologies, the Kinetic Simulation Algorithm Ontology (KiSAO) organizes algorithms to simulate models (Courtot et al., 2014), and the Systems Biology Ontology (SBO) proposes a collection of terms that describe the structure of a model, its components as well as modeling frameworks and processes (Courtot et al., 2014). With a focus on *C. elegans*, a hierarchically structured, controlled vocabulary of terms that standardizes phenotype descriptions, namely the Worm Phenotype Ontology (WPO), is defined (Schindelman et al., 2011).

Several formats that encode biological models have been proposed. The most representative formats include the Systems Biology Markup Language (SBML) to represent biochemical network models (Hucka et al., 2003), CellML for defining mathematical models of cellular functions (Lloyd et al., 2004) and NeuroML for describing data-driven models of neurons and neural networks (Gleeson et al., 2010). Regarding inter-model interoperability, PyNN (Python Neural Networks) is a programming interface common to multiple neuronal network simulators, which allows to write a simulation script once in the Python programming language and run it without modification on any supported simulator (Davison et al., 2009).

With respect to simulation procedures, the Simulation Experiment Description Mark-up Language (SED-ML) provides a standardized, machine-readable format (Waltemath, Adams, Bergmann, et al., 2011) for the information required by MIASE to enable the reproduction of simulation experiments (Waltemath, Adams, Beard, et al., 2011). Besides models identification, MIASE requires a precise description of simulation steps together with all the information for obtaining numerical results to be reported in scientific publications. In SED-ML documents, the simulation experiment input is defined at a low model parametric level because the models used *e.g.*, SBML, CellML or NeuroML are biological models. It is therefore not well suited for defining the behavioral experiment input of a living organism in an *in silico* simulation.

Graphical visualizations of biological models have been used to facilitate the understanding of a model in publications and textbooks. As in other analyzed parts of a simulation component, standardization efforts have led to visualization recommendations and data formats for the exchange of the resulting visualization. Representative efforts are (i) the Systems Biology Graphical Notation (SBGN) (Le Novère et al., 2009) and the corresponding markup language (SBGN-ML) developed to visualize, store and exchange the visualization of biological networks (Iersel et al., 2012); and (ii) a framework defined for visualization of CellML models, which allows the visualization of the physical model or its biological interpretation (Wimalaratne et al., 2009).

Finally, specific file formats have been proposed for numerical results provision. The Numerical Markup Language (NuML) (NuML Project, 2015), originates from the numerical aspects of the Systems Biology Results Markup Language (SBRML) (Dada et al., 2010), with the aim of reusing it in multiple other standardization efforts. In the area of presenting results, ongoing work is carried out by the OpenWorm project to validate the results of behavioral simulation experiments and to compare the perceived locomotion behavior of *in vivo* experiments with *in silico* experiments (OpenWorm Project, 2015).

Behavioral experiments are run by psychologists for neurobehavioral research on humans (Mueller et al., 2014) by using tools such as (Neurobehavioral Systems, 2015). But we do not see a direct way for exploiting these approaches in living organisms' *in silico* experiments.

After reviewing the related work on interoperability and standardization of computational neuroscience and systems biology research areas, no specific solution seems to exist that tackles the behavioral experiment input encoding in general or specific to the *C. elegans* nematode.

3 MATERIAL AND METHODS

According to rule 2B of the MIESE guidelines (Waltemath et al., 2011), all information needed for the correct implementation of the necessary simulation steps must be included through precise descriptions or references to unambiguous information sources. When it comes to projects such as OpenWorm (Szigeti et al., 2014) or *Si elegans* (Blau et al., 2014) that aim to simulate a complete life form, a behavioral input encoding is required. As an effort to standardize the *C. elegans* behavioral experiments input encoding, the following proposal is presented. It was inspired by a collection of *C. elegans* behavior experiments described in the WormBook (Hart, 2005) and in recent *C. elegans in vivo* research reports (Gabel et al., 2007; Ward et al., 2008). The latter cover behavioral responses to behavioral input types that are not yet included in the WormBook.

The proposed digital representation is divided in the environment and the experiment configurations. The behavioral experiment is structured by duration-based behavioral experiment types at the top level. The following three behavioral experiment types have been defined:

- Interaction at a specific time t
- Interaction from t_0 to t_1
- Experiment-wide configuration

Each duration-based experiment allows for the definition of one or more interactions of each type. For each duration-based experiment type, each of the behavioral input types (*i.e.* mechanotaxis, chemotaxis, thermotaxis, galvanotaxis, and phototaxis) as identified by (Hart, 2005; Gabel et al., 2007; Ward et al., 2008) is allowed. Behaviors reported by (Hart, 2005), which are not sensory behavioral inputs (*i.e.* locomotion, feeding, egg-laying, mating, reproduction or defecation), have not been considered. Figure 1 depicts an example of a duration-based behavioral experiment.

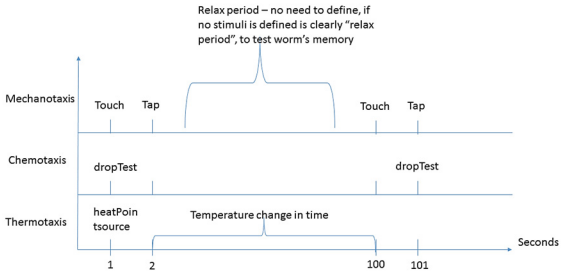

Figure 1: Example of an experiment definition based on different durations. It includes two temporal types: "Interaction from t_0 – t_1" for a change in temperature labelled "Temperature change in time" and others of the type "Interaction at specific time".

On a third level, the concrete behavioral experiments inputs are defined in the XML schema developed by (Si elegans Consortium, 2015a).

An example experiment definition section of a behavioral experiment input that contains multiple interaction instances is presented in Figure 2.

```
<bhv:experimentDefinition>
    <bhv:interactionAtSpecificTime eventTime="PT5S">
        <bhv:chemotaxis>
            <bhv:description></bhv:description>
            <bhv:dropTest dropQuantity="0.5">
                <bhv:chemicalComposition>
                    <bhv:chemical isVolatile="false" name="CaCl2"/>
                </bhv:chemicalComposition>
                <bhv:dropLocation xCoord="10" yCoorD="10"/>
            </bhv:dropTest>
        </bhv:chemotaxis>
    </bhv:interactionAtSpecificTime>
    <bhv:interactionAtSpecificTime eventTime="PT10S">
       <bhv:mechanosensation>
           <bhv:mechanoInteraction>
               <bhv:directWormTouch>
                   <bhv:touchInstrument>Eyebrow</bhv:touchInstrument>
               </bhv:directWormTouch>
           </bhv:mechanoInteraction>
           <bhv:appliedForce>5</bhv:appliedForce>
           <bhv:touchLocation>
               <bhv:touchDistance>5</bhv:touchDistance>
               <bhv:touchAngle>3.14159</bhv:touchAngle>
           </bhv:touchLocation>
       </bhv:mechanosensation>
    </bhv:interactionAtSpecificTime>
    <bhv:interactionFromt0tot1 eventStartTime="PT20S"
        eventStopTime="PT30S">
        <bhv:termotaxis>
            <bhv:temperatureChangeInTime initialTemperature="5"
                finalTemperature="10"/>
        </bhv:termotaxis>
    </bhv:interactionFromt0tot1>
    <bhv:experimentWideConf>
        <bhv:chemotaxis>
            <bhv:chemotaxisQuadrants numberOfQuadrants="4"
                quadrantsPlacement="diagonal">
                <bhv:quadrant chemicalConcentration="0.5">
                    <bhv:chemical isVolatile="false" name="MgSO4"/>
                </bhv:quadrant>
                <bhv:quadrantBarrier chemicalConcentration="0.5">
                    <bhv:chemical isVolatile="false" name="NH4Cl"/>
                </bhv:quadrantBarrier>
            </bhv:chemotaxisQuadrants>
        </bhv:chemotaxis>
    </bhv:experimentWideConf>
</bhv:experimentDefinition>
```

Figure 2: Example of the experiment definition section of a behavioral experiment input encoding.

```
<bhv:environmentDefinition>
    <bhv:wormStatus>
        <bhv:wormInitialPosition>
            <bhv:PositionFromPlateCentre yCoorD="0" xCoord="0"/>
            <bhv:OrientationRelativeToXaxis angle="3.14159"/>
        </bhv:wormInitialPosition>
        <bhv:wormData age="PT120S" gender="Female Hermaphrodites"
            stageOfLifeCycle="4" timeOffFood="PT30S"/>
    </bhv:wormStatus>
    <bhv:plateConfiguration bottomMaterial="Agar" dryness="0.5" lid="false">
        <bhv:shape>
            <bhv:Cylinder length="2" radius="3"/>
        </bhv:shape>
    </bhv:plateConfiguration>
    <bhv:obstacle>
        <bhv:shape>
            <bhv:Cube depth="3" side1Length="3" side2Length="3"/>
        </bhv:shape>
        <bhv:location>
            <bhv:PositionFromPlateCentre xCoord="1" yCoorD="1"/>
            <bhv:OrientationRelativeToXaxis angle="3.14159"/>
        </bhv:location>
    </bhv:obstacle>
    <bhv:crowding wormsInPlate="1"/>
</bhv:environmentDefinition>
```

Figure 3: Example of the environment definition section of a behavioral experiment input encoding.

The environment configuration structure and elements have been extracted from the WormBook experiments review (Hart, 2005). The environment configuration is composed of the worm's mutation identification, crowding, location, plate configuration, and obstacles configuration, which have been parameterized. An example environment definition section of a behavioral experiment input that describes the experiment's environment together with the worm's details is presented in Figure 3. A complete behavioral experiment input encoding example is provided in (Si elegans Consortium, 2015b).

4 CONCLUSIONS AND FUTURE WORK

In this paper, we have presented a proposal for a *C. elegans* behavioral experiments input encoding strategy. Its aim is to standardize the behavioral input configuration and the simulation parameters (*e.g.,* environment configuration) for different *C. elegans* nematode simulation frameworks. This standardization effort targets at an interoperability between these frameworks to allow for reproducible and comparable simulations and for sharing simulation building blocks. A brief review of the state of the art of standardization and interoperability efforts in the computational neuroscience and systems biology research areas has led us to define a behavioral experiment input encoding language from scratch. The definition procedure was introduced and the logic behind the markup language was explained. Additionally, an example for an experiment was provided together with the corresponding XML schema of the defined markup language; a complete example as part of the *Si elegans* project simulation solution is available at the following online repository: https://github.com/Si-elegans/behavioural_experiment_definition . Future work will include the development of import/export modules for interoperability with similar simulation platforms.

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