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SIMPLE CYCLIC MOVEMENTS AS A DISTINCT AUTISM FEATURE – COMPUTATIONAL APPROACH

Abstract

A diversity of symptoms in autism dictates a broad definition of Autism Spectrum of Disorders (ASD). Each year, the percentage of children diagnosed with ASD is growing. One common diagnostic feature in individuals with ASD is the tendency to exhibit atypical simple cyclic movements. The motor brain activity seems to generate a periodic attractor state that is hard to escape. Despite numerous studies, scientists and clinicians do not know exactly if ASD is a result of a simple yet general mechanism or of a complex set of mechanisms (either on the neural, molecular and system levels). Simulations using the biologically-relevant neural network model presented here may help to reveal the simplest mechanisms that may be responsible for specific behavior. Abnormal neural fatigue mechanisms may be responsible for motor symptoms as well as many (or perhaps all) of the other symptoms observed in ASD.

1. Introduction

In 1943, Leo Kanner defined autism as "extreme aloneness from the beginning of life and anxiously obsessive desire for the preservation of sameness." The disease appeared to be much more complex than initially thought, and due to the high variability of its symptoms, psychiatric manuals (such as the Diagnostic and Statistical Manual of Mental Disorders, DSM) define the whole Autism Spectrum of Disorders (ASD) rather than just autism. Currently, most researchers agree that ASD is a developmental and behavioral disease with multiple etiologies, including genetic mutations as well as metabolic and immune system deregulation leading to various impairments in neural connectivity. However, good models of how the symptoms may arise from dysfunctional networks are still missing. In this paper, we shall extend our "deep attractor" hypothesis of possible mechanisms behind ASD. Recently, we linked dysfunctions of leaky channels at single neuron level to attention deficits, simulated using an attractor neural network model [8, 7]. This paper shows that the same low-level mechanism may also be responsible for stereotypical, cyclical movements.

The frequency of ASD diagnoses has been on the rise every year [2], and this fact cannot be attributed only to better diagnostic procedures. The current incidence of diseases belonging to the ASD spectrum is estimated to be about 10 in 1,000 children. Many typical and atypical forms of autism exist (high functioning autism, Aspergers syndrome, childhood disintegrative disorder, Rett syndrome, PDD-NOS or Pervasive Developmental Disorder-Not Otherwise Specified, etc.), with a prevalence of 1-2 per 1,000 for classical forms of autism to the extremely-rare Rett syndrome [8, 2]. Boys are 4 times as likely as girls to suffer from autism [2]. Although some symptoms are usually noticed quite early in the first or second year of life, final ASD diagnosis is, in most case,s made in the 5th year on average. Costs of care over a lifetime are very high. Many large-scale research programs have been implemented, focusing strongly on genetic factors; but, the correlations between specific gene mutations and duplication are weak [10, 19], and there is little hope that this will be a good diagnostic (not to mention a good understanding) of the mechanism that leads to autism. Other risk factors identified involve prenatal and perinatal complications, umbilical cord clamping, environmental factors, neuroanatomical changes, frontal lobe dysfunctions, mirror and default mode network dysfunctions, and many others [19]. Despite the many theories, none of them can explain all of the symptoms in a coherent way. Understanding the relationships between genetic, protein, signaling pathways, single neuron function, the whole brain network dynamics, and the neuropsychiatric symptoms and syndromes at the system level is the goal of a new field, neuropsychiatric phenomics [4, 3]. Insights from neural modeling are an important contribution to the comprehensive models of neurodegenerative disease, with neurodynamics at the central level between behavioral and molecular sciences.

Common diagnostic features typically observed in individuals with ASD result from problems with repetitive, stereotyped patterns of behavior, interests and acti-

vities, attention deficits, communication, and social interaction. The most frequent symptoms include [19]:

- strong attachment to objects, spins objects, repetitive movements and play,
- echolalia, repeating words without understanding,
- insistence on sameness, keeping the same routine,
- attention deficits, ignoring verbal cues (acts as if deaf), ignoring strong stimuli,
- apparent insensitivity to pain,
- avoiding physical interaction, touching, cuddling,
- overreacting to weak stimuli that are barely noticed by most people,
- little to no eye contact,
- gestures/pointing instead of words, difficulty in expressing needs,
- physical underactivity (staring on simple objects),
- strong overactivity, tantrums, extreme distress for no apparent reason,
- inappropriate behavior, including laughing and giggling,
- preference to be alone, difficulty in social interactions with other children.

Our "deep attractor" hypothesis [8, 7] has focused on attention deficits caused by strong synchronization of local neural networks due to dysfunction of leaky channels in neurons. Instead of normal synchronization and desynchronization of neural assemblies, neurodynamics is trapped in a strong attractor and cannot leave one state for a long period of time. Once the subject's attention is captured, weak stimuli will hold it for a long time, attention shifts are delayed, strong stimuli are ignored, and higher-level systems that rely on synchronization of distal brain areas do not develop in a normal way due to infrequent resynchronizations. Our simulations so far assumed that there are quasi-stable localized attractors that roughly correspond to the overall distribution of activity of brain areas, fluctuating around some mean values.

Cyclic repetitive movements, ritualized behavior, echolalia and tantrums, and rapid shifts from underactivity to overactivity observed in autistic people show that rapid switching between two or more strong attractors may be based on similar assumptions as our former model, but requires a formation of cyclic attractors. In this paper a step towards explanation of the phenomena of cyclic movements in patients with ASD is made in the general framework of neuropsychiatric phenomics, integrating molecular, cellular, and system levels. The simulations presented below are based on a simplified yet biologically plausible neural network model with an analysis of the long-term attractor dynamic that relates neural dysfunctions to neurodynamics and to symptoms observed in the behavior of autistic individuals. The project is partially implemented on cluster computer architectures.

2. Movement control mechanisms

The novelty of our current approach comes from application of our "deep attractor" hypothesis to the diverse symptoms that may be observed in ASD patients. This is a ground-breaking idea that allows for an understanding of autistic people's behavior

using the language of dynamical systems, a relatively high symbolic level of description that is linked to both neural functions and behavioral observations. Similar dysfunctions of the ion channels in association cortex neurons that may lead to attention deficits (as we previously showed using computational simulations of the visual attention and phonology-meaning-wordform relationships [9]) may also be responsible for the emergence of cyclic behaviors in motor cortex (as we show below using neural network simulations). The impact of lesions on various brain functions has been analyzed using relatively simple yet biologically well-motivated models implemented in the Emergent simulator (as described in the book of OReilly and Munakata [1, 13]). Simulations of motor performance in children with diagnosed ASD may be an important step towards a better understanding of pathological conditions that arise due to neural dysfunctions. Neural correlates of movement as well as the associated excitability of groups of neurons are influenced both by internal homeostasis and motor learning [12], but computational models of this phenomenon have not been described thus far.

Despite decades of research, there are still several high-level competing control theories concerning animal movement aimed at explaining behavioral characteristics [11, 5]:

- theories based on reflexes, explaining motor activity as a response to earlier sensory stimulation,
- theory of motor programs that influence rules of movement,
- hierarchical theories, based on processes that activate coordinated loops of neural activity at various levels of nervous system,
- theories based on intrinsic dynamical processes, perceiving movement as result of interactions between elements of movement control system, without external commands,
- ecological theories, stressing the importance of environment that resulted in affordance perception stimulating the need for specific movements,
- system theories, perceiving movement as a result of behavioral plans, influenced by human goals and tasks, constrained by the environment.

All of these theories have some support and are being actively developed. From the computational point of view, models of movement control may be categorized as [5]:

- purely descriptive models,
- dynamical models based on motor commands, joint torques, and external forces,
- stochastic models, based on prediction, feedback and/or feedforward control, including dynamical aspects of task execution,
- motor execution models, based on computation of motor commands aiming at the desired task completion,
- models of the animal joint dynamics and muscle mechanics.

Detailed computational models of movement control may provide insight into the mechanisms underlying complicated process behind behavioral responses. Complexity

and specificity of the utilized model depends on the goal of modeling. In our case, simple model of motor planning seems to be sufficient. Control signals generated by the processes in the secondary motor cortex should activate the primary motor cortex (Fig. 1) that has well-known somatotopic structure.
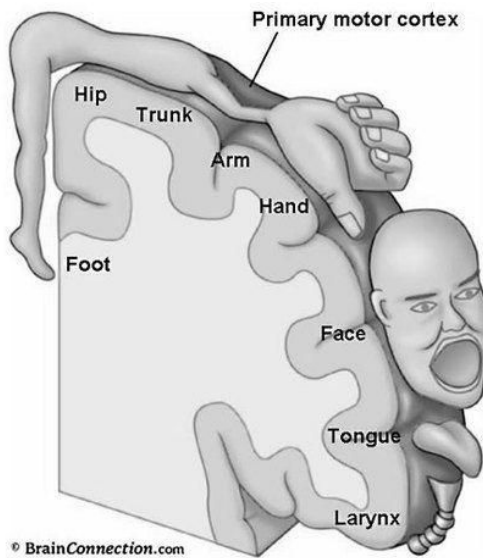

Figure 1. Representations of body parts within the primary motor cortex. Control signals come from the secondary motor areas.

3. Computational model of movements

We have tried to create the simplest-possible model in which neural properties may be linked to non-trivial behavioral effects. The model ignores detailed neurobiology, focusing instead on planning (prefrontal areas), sequencing individual movements (premotor areas), and sending specific outputs to muscles (primary motor cortex). Figure 2 shows a general concept of the basic network used for simulation. The model consists of three neural populations:

- *Input layer* (Fig. 3), containing groups of neurons which reflect movement-planning processes, generating intentions to move, and associated activations taking place in the prefrontal cortex,
- *Hidden layer* representing the supplementary motor area and other premotor structures (presumably also basal ganglia) involved in sequencing of movements,
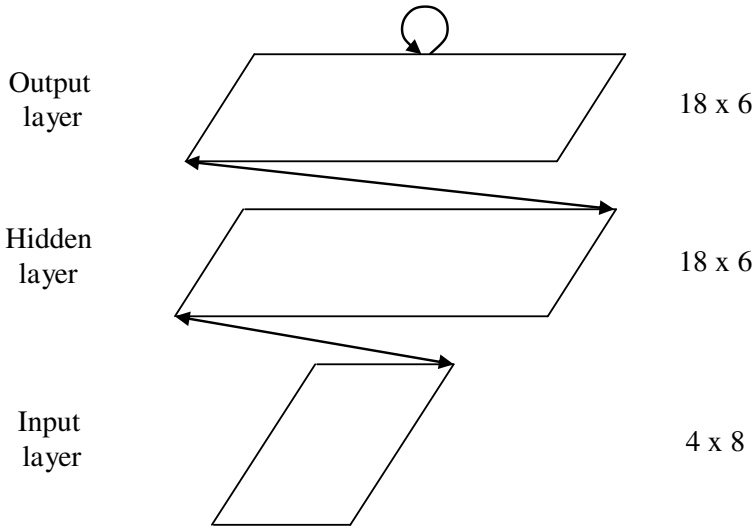- *Output layer* reflecting processes within the primary motor cortex areas.

Figure 2. General concept of the basic neural model, with size of the layers indicated.

Activation of neural populations in the output layer depends on patterns generated in the *Input layer*, as shown in Figure 3. This output activation crosses the brain/body sides as a result of a well-known decussation of the pyramids; thus, the left hemisphere controls the right side of the body (right extremities), and conversely the right hemisphere controls the left side of the body (left extremities), with some overlapping activations.

At the neural level, processes such as planning, generation, and synchronization of simple movements arise as a result of the synchronization of a group of neurons. This synchronization is a consequence of existing feedbacks, competition, inhibition, and multiple constraint satisfaction within the network.

The neural-network model (Fig. 4) implemented in the Emergent simulator [13, 1] has been studied to understand how low-level neural parameters influence network dynamics. The cyclic movement mechanism was reconstructed using several simple patterns including the movement of the left and right arms, left and right hands, left and right legs, and left and right feet (reflected as a sequence of activations in the input layer) with the addition of the accommodation mechanism (i.e. neural fatigue). The output layer represents activations within the motor cortex; i.e., areas of the cerebral cortex engaged in planning, control, and execution of voluntary movements. The possibility of pyramidal decussation was built into the model.

A detailed description of parameters and model properties is described in the next section.
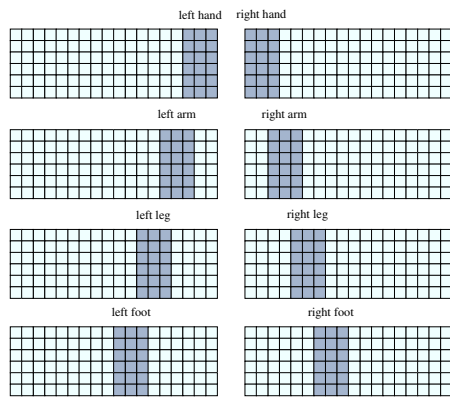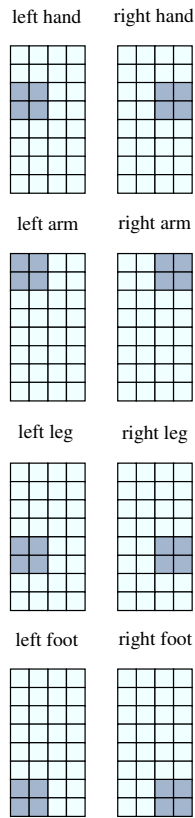
Figure 3. Possible activations within: *Input layer* (vertical) and *Output layer* (horizotnal).

4. Results

The Hodgkin-Huxley style point neurons have been used as the basic units in the spatially-distributed model networks (Fig. 2). The kWTA (k-Winners Take All) mechanism built into the LEABRA learning algorithm (Local, Error-driven and Associative, Biologically Realistic Algorithm) available in Emergent simulator was used to simplify simulations and speed up the convergence.

4.1. Influence of neural and network parameters

Neurons in the Emergent simulator [13] have 3 basic types of ion channels represented in the model by the conductance parameters:

- g_bar_e (excitatory, glutamatergic sodium Na^+ channels): value 1 was used, lower values make higher layers of the network not activated, higher than 1.1 – overloaded,
- g_bar_i (inhibitory, chlorium Cl^-), value 1 was used, lower values make network overloaded, higher values make higher layers of the network not activated,
- g_bar_l (constant leak, potassium K^+ channels), value 0.1 seems to be optimal, higher than 1 makes Output layer non-active.

For these basic ion channels, we used standard (default in Emergent) parameters of reverse potentials (in normalized units):

- excitatory channel: $e\_rev\_e = 1$,
- inhibitory channel: $e\_rev\_i = 0.15$,
- leak channel: $e\_rev\_l = 0.15$.

The accommodation mechanism controlling neural fatigue results from a change of parameters regulating the activity of the leak channel (for more information about accommodation, see [13]). In the model, this mechanism was applied to each hidden and output unit. The main parameters of the accommodation mechanism set in the model were as in Table 1.

Table 1
Parameters of the accommodation mechanism used in the model of simple cyclic movement in Emergent simulator.

g_bar_a	e_rev_a	b_inc_dt	b_dec_dt	a_thr	d_thr	g_dt
0.5	0	0.01	0.01	0.5	0.1	0.1

For input units g_bar_a, conductance of accommodation was set to zero, which means that these units were lacking in neural fatigue property. In general, these units were hard-clamped during the entire simulation for each input pattern.

The main parameters of projections between layers determining the strength of connections between neural units were set as in Table 2.

Table 2

Two main projection parameters used in the model of simple cyclic movement in the Emergent simulator

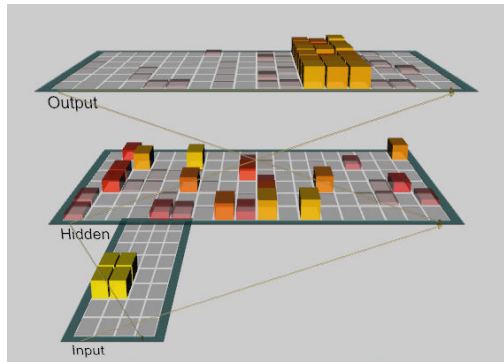|	wt_scale_abs	wt_scale_rel
Input to Hidden	1	1
Hidden to Input	1	1
Hidden to Output	1	1
Output to Hidden	1	0.5
Output self-connection	1	2

Figure 4. Model of simple cyclic movements implemented in Emergent software.

Many genetic and environmental factors may influence ion channels, reflecting damages of neurons and impairing developmental processes. The influence of decreasing weights of connections between layers can reflect damages of inputs (e.g. lesions) within certain levels of signal processing. Change of the output-hidden coupling (weight scale) and hidden-output weight scale modifies the balance among projections within brain networks. In case of neurodegenerative disease, one should focus on understanding how neural parameters that reflect many aggregated biological properties influence overall network behavior. What are the key mechanisms that may lead to autistic-like symptoms in motor control? In our earlier paper, we found that neural fatigue is critical to enabling attention shifts that require desynchronization of neurons and the subsequent resynchronization of less-active neurons. Weakly-active neurons may increase their activity, while strongly-active neurons may decrease it due to the depolarization controlled by the leak channel parameters. A single parameter may change the dynamics of the network from normal to almost chaotic, jumping from one attractor state to the other (showing ADHD-like symptoms), or to the very stable, unable to shift attention for a long time [8]. The influence of noise – both the membrane potential VM_NOISE which has much bigger influence) and the input synaptic noise $NETIN\_NOISE$ which has smaller influence within various levels of

processing is certainly important, as it can reflect external and internal stimulation. Patterns of activation influenced by noise are not quite identical, but they show some variability and may stop being repetitive. In case of very loud noise, movements become jerky, spastic, reflecting damages within layers due to internal causes or hypertonia, definitely not typical to autism. Thus, the noise level should not be too high.

4.2. Influence of general network dynamics

Simulations of the proposed model show several different sequences of neural activations occurring cyclically in the output layer, representing motor cortex, for each input pattern reflecting similar behavior, like repetitive and stereotyped movements (RSM) typical for patients with ASD (especially young children). A lack of neural noise in the system leads to high repeatability of simulations; therefore, more-detailed research was performed to understand the influence of synaptic noise on the model behavior. As expected, an appropriate level of noise resulted in changes in the neurodynamics of the motor cortex layer, preventing sequences of activation to follow cyclically and activating different areas of the layer.

Further work includes analysis of the model attractor neurodynamics using Fuzzy Symbolic Dynamics (FSD), recently introduced by us for visualization of long trajectories [6, 9], and Recurrence Plots (RP) that found many applications in different research areas, especially in analysis of low-dimensional dynamical systems. Figure 5 shows FSD and RP plots for two different cases of input patterns, including movement of left arm (top), and movement of right foot (bottom). The color scale on FSD visualization corresponds to time flow (there where 500 iterations in each experiment) while, on RP plots, it defines distance value between each two points on a plot.

The visualization was performed using neural activations of all 108 units of the output layer (only the output layer was analyzed here). In the FSD method, Gaussian membership functions were used with dispersions equaling 1.5 in every dimension, and centers placed in the means of the two biggest clusters found by k-means algorithm (more about FSD technique itself can be found in [6, 9]). As a distance metric, Euclidean function was used in both methods.

Visualization clearly show cyclical neurodynamical behavior of the motor cortex layer of the proposed model. On the FSD plots, trajectories cross approximately the same areas during the entire simulation time. Such behavior corresponds to repetitive activations of the same regions in the output layer. This observation can also be confirmed with RP plots, where nearly the same neurodynamical states (i.e. visited attractors) represented by dark-blue and black boxes appear every 300-350 iterations.

Not every simulation showed such cyclical model behavior. In the next Figure 6, visualization using FSD and RP techniques was shown for two different input patterns corresponding to movement of the left foot (top) and the right leg (bottom). Both methods show that the system visits rather different attractors (placed far from each other) during the entire evolution. This is a result of non-repetitive neural activations

occurring in the motor cortex layer of the model. Such behavior was observed in three of the eight input patterns the model was trained on, and it seems that the right part of "models body" has more tendency to generate such non-cyclical neural activation flow in the output layer. This property indicates that the results of such a simple model are not very stable and some asymmetries occur, likely due to the sequence of presented input patterns in the training process of the network.
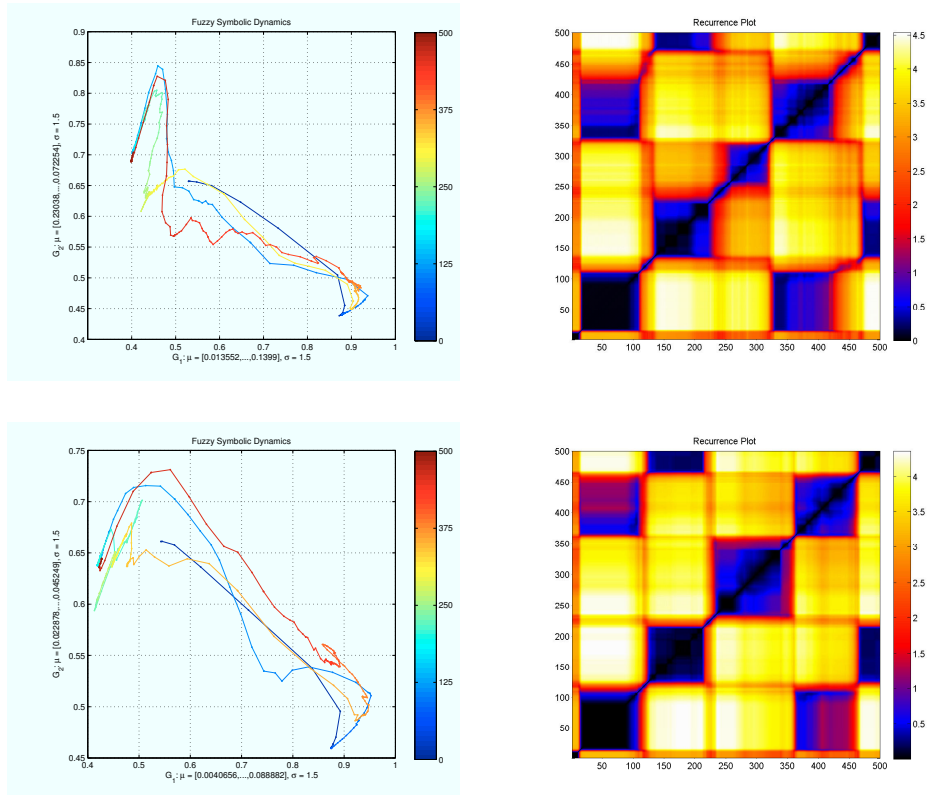

Figure 5. Fuzzy symbolic dynamics visualization (left) and recurrence plots (right) showing cyclical model behavior for two different input patterns: left arm (top) and right foot (bottom).

4.3. More detailed neural model

Changing the use of the model of point neurons into the full compartmental simulation of Hodgkin-Huxley cells will allow for observations of the influence of other important parameters on the dynamics of the network. The parameters mentioned in the previous section describe the biophysical parameters of the cell only in very rough way, and the behavior of the simulated system depends on many other factors. The capacitance of the soma, its time constant, and the value of potentials responsible for
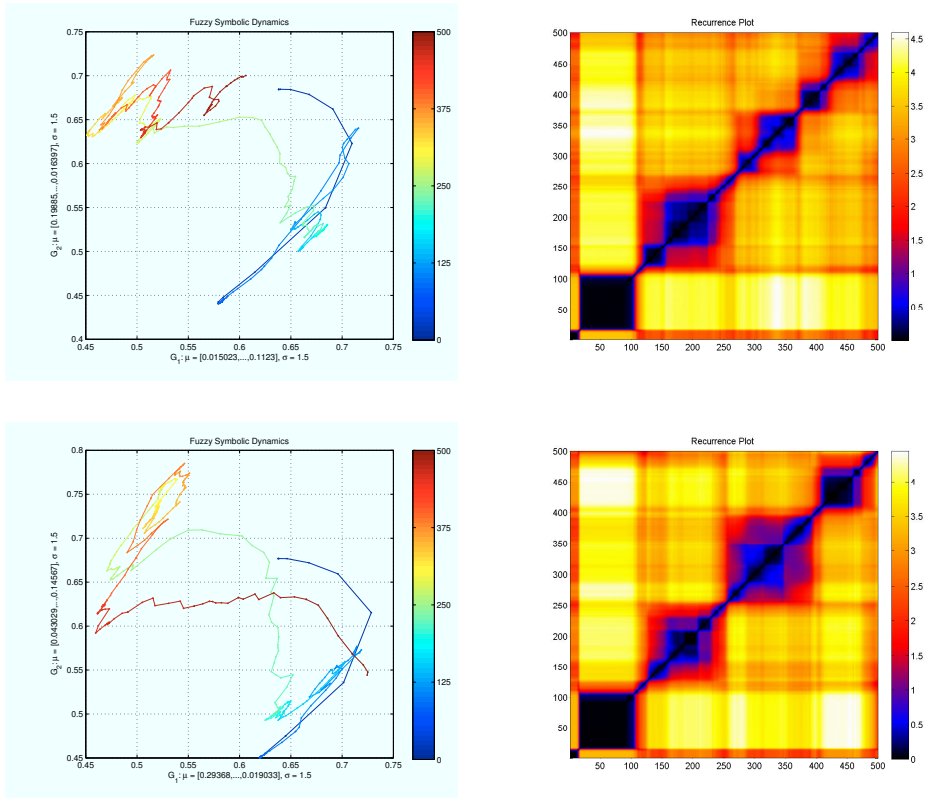
Figure 6. FSD (left) and RP (right) visualization for two examples of input patterns: left foot (top) and right leg (bottom) showing non-cyclical model behavior.

the ionic currents must also play an important role in signal transmission activating the network.

5. Conclusions and future work

Despite the increasing number of scientific publications and experimental research on Autism Spectrum Disorders, there is still no satisfactory theory; and without good computational models, it will be difficult to understand many features of such neurodegenerative diseases. Understanding the development of cyclic movements in ASD requires both recognizing the mechanism of forming cyclic attractors in the brains of typically developing children and adults vs. ASD patients, and testing the paradigms of different attentional disorders, including observed clinical features of ASD. At the neurodynamical level of description, cortex activity is trapped in the attractor basin in a cyclic manner for a long time; at a more-detailed neural level, such behavior is related to strong neural synchronization of several groups of neurons.

Simulations point out to the common mechanism in motor and sensory cortices: weak leak currents are insufficient to depolarize neurons, escape from basins of attraction, and achieve flexible attention shifts and complex movements.

Changing the point neuron model into the full compartmental simulation of the Hodgkin-Huxley cells will allow for observations of the influence of other important parameters on the dynamics of the network. The capacitance of the soma, its time constant and the value of potentials responsible for the ion currents must also play an important role in signal transmission activating the network.

A satisfactory simulation of realistic, compartmental Hodgkin-Huxley neural networks can be conducted in the GENESIS simulation environment. We have had good experience in neural microcircuit modeling using this simulator [15, 14, 17, 18, 16]. Models based on the Hodgkin-Huxley neurons are much more complex, and simulations require high computational powers. A simulation of 1 ms of the biological activity of HH cell using first-order Euler's method with a constant time interval of 1 ms requires about 1200 floating point operations. Such a simulation can be conducted most effectively in a cluster-based environment. Large-scale modeling of brain functions with thousands of simulated HH neurons and millions of connections require the use of grid architectures. In our first attempts to implement the model described in this paper into compartmental HH cells, we used a cluster consisting of eight double-processor Xenon Quad Core machines. Even then, the simulation of one second of biological activity of the system took several seconds of the production run of the cluster, still far from a real-time simulation (even for a small model of the neural tissue).

The next steps of our research should:

1. provide a complete explanation of observed autistic symptoms in the language of neurodynamical systems;
2. use computational modeling to generate hypothesis that should help to focus on relevant genetic and molecular processes relevant to autism;
3. use the GENESIS environment with an increased number of neurons and connections to create more-detailed models, distinguishing different types of ion channels;
4. on the technical side, the model should be prepared for large-scale production runs in grid-based systems, linking the results with measurable biophysical properties of neurons.

On a large cluster, detailed simulation of these types of models should be feasible and should help link the molecular and genetic levels with behavioral symptoms. Although this is a difficult road to follow, it seems to be the only realistic approach towards a complete understanding of neurodegenerative disease; and in the spirit of neuropsychiatric phenomics, to generate a hypothesis that may be experimentally verified and eventually help in diagnostics and therapy. Thus, our work may be regarded as an important step, not only as computational model of the ASD, but also should

contribute to an understanding of a wider class of mental diseases using the language of neurodynamics.

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