# Autism Spectrum Disorder and deep attractors in neurodynamics.

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## 1. Neurodynamics and many levels of neuropsychiatry

Diagnostic criteria at the foundation of psychiatry and clinical psychology contained in the Statistical Manual of Mental Disorders (2013) are based on evaluation of behavioral symptoms. Research Domain Criteria (RDoC) is an attempt by NIMH to integrate many levels of information needed to understand human behavior (Bilder et al. 2009). Psychological constructs are used to characterize 5 general domains: Arousal and Regulatory Systems, Negative and Positive Valence Systems, Cognitive Systems, and Social Processes. Many psychological constructs and more detailed subconstructs are used for each domain, and each construct is described by "units of analysis" that include specific Genes, Molecules, Cells, Circuits, Physiology, Behavior, Self-Reports representing psychological components, and Paradigms defining experimental procedures. The RDoC matrix based on constructs vs. unit analysis is far from being complete and is not yet useful to build models of functions based on activity of brain subnetworks. In particular it does not characterize different types of neurons in terms of their structure, synapses, receptors, ion channels, connectivity, and other "units of analysis" that influence network functions.

Although all RDoC units of analysis are important understanding the mechanics of mental functions should be done at the circuit level. Functions of neural networks depend on the cellular, molecular and genetic levels. Complex functions responsible for behavior result from neurodynamics. Therefore a good strategy that should help to find causal relations between different levels of analysis, showing how RDoC psychological constructs emerge from biology, is to identify biophysical parameters of neurons required for normal neural network activity and explore all changes that may lead to abnormal functions, behavioral symptoms, cognitive phenotypes and syndromes. Computational simulations of neurodynamics generate hypothesis for experimental verification and help to interpret neuroimaging data. Neurodynamics provides language that relates measureable brain processes to RDoC psychological constructs. As an example of such an approach I shall focus here on the Autism Spectrum Disorders (ASD). Many confusing observations may find an explanation at this level and lead to hypothesis that may be experimentally verified.

## 2. Attempts to understand autism spectrum disorders

There is a growing consensus that autism is not a single disease but belongs to a spectrum of various disorders of general temporo-spatial neural processing (Gepner & Feron 2009). Many specific mechanisms causing ASD may exist, multiple etiologies, including metabolic and immune system deregulation, exposure to various chemicals and other environmental factors (Wen et al, 2016). Based on the DSM criteria core behavioral symptoms may be sufficient for the diagnosis of autism, but RDoC characterization will reveal phenotypic diversity, with each subgroup requiring different approach to therapy. Many brain diseases (ASD, spectrum of psychotic disorders, epilepsy) should be placed in a continuum phenomics space, forming a spectrum of diseases that may have similar core symptoms, but great variability of all RDoC units of analysis. In case of ASD even the main symptoms are highly variable. There are many theories of autism that focus on selected aspects of behavior or clinical observations, mistaking symptoms for deeper causes (Zimmerman, 2008).

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So far big projects related to autism have been focused mostly on a single level. A lot of efforts has been devoted to the genetics of autism. Large number of genes involved in deregulation of neural systems has clearly shown that major brain diseases may have very different etiologies. Research on the genetics of autism has identified over 880 genes (about 4.5% of all human genes) that are correlated with some form of autism (SFARI Gene database, Q1 2017 release, https://gene.sfari.org/). They are involved in cell signaling, structure and transport, metabolic, immune and neural processes, and frequently implicated in other disease such as cancer, cardiac and neurodegenerative disease (Wen et al, 2016). Genetic variation and environmental conditions lead to the diversity of proteins, signaling pathways, ion channels, synapses, structures of neurons and their connections. Unfortunately there are no good methods to analyze *in vivo* molecular structure of biological neurons.

The motto of molecular biology "structure is function" is also true at the systems level. Therefore the best strategy is to analyze neural properties in relation to molecular and genetic levels, and investigate how that will influence neurodynamics, spatiotemporal patterns of neuronal electrical activity. Brain functions and observable behavioral symptoms may then be understood in terms of specific dysfunctions of neurons. To achieve this goal the whole causal chain sketched below is needed.

1) Genes are expressed in different parts of the brain, creating proteins that form neural receptors, ion channels, synapses and cell membranes. Mutations, copy number variation, and other genetic processes create specific dysfunctions of proteins building ion channels, influencing generation of action potentials (Lai & Jan, 2006).

2) Complete ion channelome is needed and should be related to different types of neurons, their dendrites, axons and membranes, density and distributions of ion channels, influencing integration of synaptic inputs (Duménieu et al, 2017).

3) Specific character of individual neurons depends on all biophysical properties, but the distribution and temporal activation of voltage-gated ion channels is of particular importance. The fast temporal dynamics of activity-driven ion channel changes should be taken into account (Heine et al. 2016).

4) Neural simulators aimed at detailed modeling of single neurons at subcellular component level, including biochemical reactions, are needed to investigate how changes at molecular level determine properties of single neurons and how these properties influence, in stimulus driven situations, development of neural networks and whole connectomes. Such neural simulators are in the early stage of development. NEURON[2], GENESIS 3[3] and the hope is that Brain Simulation Platform of the Human Brain Project[4] will provide even more detailed simulators that should integrate all experimental information.

5) Simulations of brain functions related to the five RDoC domains should reveal the range of biophysical neural parameters that may be responsible for normal functions, and disruption of these functions. Whole brain simulations should also show how connectomes develop as a function of sensory stimulation and internal dynamics.

A lot of data is missing at each of these stages. Understanding this causal chain is a real challenge in ASD research, and it should be clearly stated as a vision based on RDoC approach and one of the goals of the HBP.

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[2] NEURON simulator, https://www.neuron.yale.edu/neuron/

[3] GENESIS project, http://www.genesis-sim.org

[4] HBP, https://www.humanbrainproject.eu/en/brain-simulation/brain-simulation-platform/

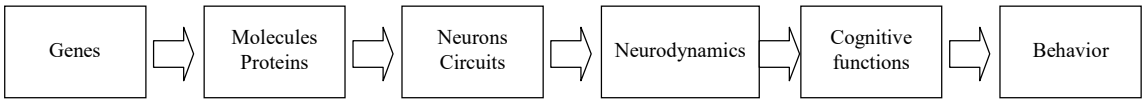



Fig. 1: Causal chain for understanding of ASD mechanics.

Although the complexity of the problem is overwhelming as a kind of a "proof of principle" I shall show below how multilevel approach may be applied to ASD, generating hypothesis that may be experimentally verified.

## 3. ASD and neurodynamics

As the first approximation minimal models that capture some properties of biological networks and allows for simulation of experimental observations are needed. Starting from simple models of neurons and networks we have tried to create models of normal cognitive and motor functions and determine ranges of model parameters that preserve these functions. Synchronization of neurons in local microcircuits and between distal brain areas is necessary for binding neuronal activations that permit perception, action and other cognitive activity. Abnormal temporo-spatial neural processing (Gepner & Feron 2009) is at the root of pervasive developmental disorders, but also attention deficit disorder, both in the inattentive and hyperactive (ADHD) form, Concentration Deficit Disorder, bradyphrenia is (slowness of thought) and other disorders related to attention. Such effects may be investigated using attractor neural networks (Amit, 1992), where the activity of groups of neurons settles in a quasi-stable spatiotemporal pattern called "attractor". These patterns encode long-term memory, concepts and object recognition. The subspace of initial activations that will end in the attractor as a result of neural dynamics is called "the basin of attractor". Transitions between attractors are possible due to the noise in the system, effects of neural fatigue or signals coming from other groups of neurons due to the external or internal stimulation.

Neurodynamics takes place at many spatial and time scales, from the nanoscale to slow developmental and learning (neuroplasticity) processes. Relevance of these processes depends on the questions that are asked. In analogy to adiabatic approximation in quantum systems one can consider transitions in neurodynamics as relatively independent of slower processes responsible for neuroplasticity. In this approximation neurodynamics may be investigated on a train network that has already fixed synaptic connections and may assume many distinct attractor states. However, one should remember that the development of connectomes due to the Hebbian associative mechanisms depends on the stimulations that create attractor states in networks. Attractors in the sensory cortices develop quite early in infancy, perception-action cycle attractors develop later, coupling local attractor states, synchronizing the activity in sensory and motor areas through distal connections (Thelen and Smith, 1996). Formation of such attractors depends on frequency of stimulations, and the time the system stays in a given state and induce neuroplastic changes. The time in which neurodynamics dwells in a given attractor basin should be within certain range to ensure normal development. If local attractors are too strong, capturing neurodynamics for a long time, the effective number of internal changes of activation patterns may be low. This will prevent formation of stronger and more complex attractors connecting wider brain areas, and thus lead to the underconnectivity between distant brain areas.

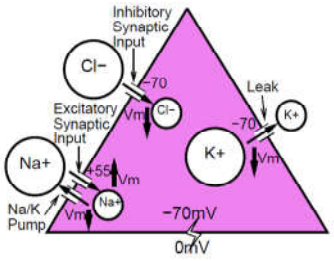
The underconnectivity theory of autism has achieved considerable success (Just et al. 2012), but reasons for local overconnectivity and underconnectivity (or lower bandwith of information transmission) between frontal and posterior brain areas need deeper explanation that may be provided by the deep attractor theory. Zimmerman book (2008) describes 20 different approaches to ASD, divided into 6 types: molecular and clinical genetics; neurotransmitters and cell signaling; endocrinology, growth and metabolism; immunology, maternal-fetal interaction and neuroinflammation; environmental mechanisms and models; and neuroanatomy and neural networks. Most approaches focus on

phenomenological observations. Minicolumnopathy, mirror neuron system (MNS), Theory of Mind, underconnectivity, empathizing–systemizing, executive dysfunction theory all focus on symptoms trying to link them to behavior. Such approaches do not provide an explanation why such symptoms arise, and why observed abnormalities create specific behavioral problems. Imbalanced spectrally timed adaptive resonance theory (Grossberg and Seidel, 2006), or iSTART, is based on artificial neural network that does not include measurable parameters. This model simply assumes breakdown of some brain functions – underaroused emotional depression, hyperspecific learning, attentional and motor circuits – but has no relations to the biophysical reality at molecular or neuroimaging levels.

Neurodynamics depends on many parameters that characterize neurons and their networks: general network connectivity, types of neurons, density and strength of synaptic coupling, the balance between excitatory, inhibitory and leak currents, types of ion channels (ligand or voltage-gated, inward-rectifier), availability of neurotransmitters, and many other. Construction of computational models incorporating all details is not yet feasible, but even greatly simplified models may help to generate useful insight into some brain functions.

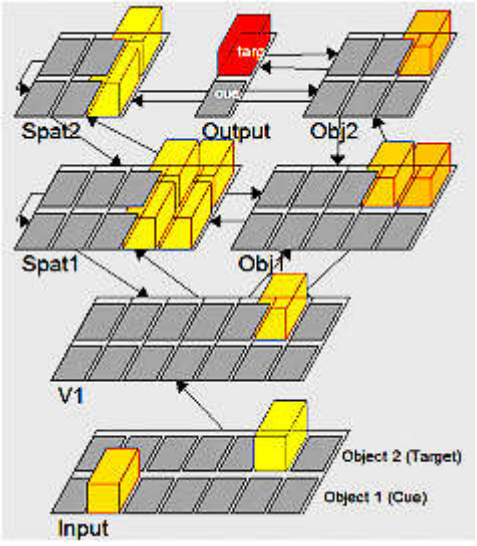
## 4. Computational simulations

Minimal model of neurons that can be linked to biophysical reality should include excitatory and inhibitory ion channels, and leak channels that control spontaneous depolarization. **Emergent** neural simulation software based on Leabra cognitive architecture is relatively simple and captures most important biological principles (O'Reilly and Munakata, 2000; O'Reilly et al. 2016). Point neurons are used, rate coding of neural activity to replace population of spiking neurons by single units, 3 types of ion channels, k-Winners Takes All (kWTA) mechanism to account for inhibition and sparse coding, several types of noise, Hebbian and error driven learning mechanisms. This architecture has been developed over several decades and is implemented in the Emergent neural simulation software, providing a great tool for a whole family of simple attractor network models of various brain functions that may be used to illustrate under which conditions normal functions are disrupted.



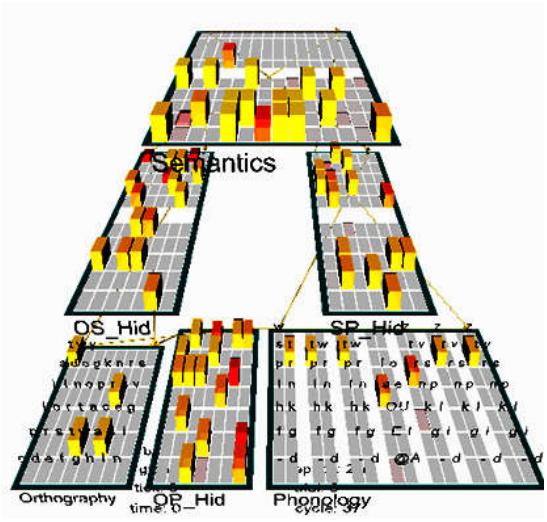

I will summarize here 3 types of models relevant to autism that we have investigated in the past: attention shifts (Gravier et al. 2016; Duch et al. 2013, 2012), spontaneous thought dynamics (Duch et al. 2011, 2010) based on the model of reading, and simple cyclic movements (Duch et al. 2013a).

The attention shift model has been based on classical Posner spatial cueing task. Model implemented in Emergent (Fig. 2) is composed of input, V1, two spatial and two object recognition layers with additional output layer. This model is essentially the same as described in O'Reilly and Munakata (2000), simulating the speed of reaction times when helpful (Valid) or confusing (invalid) cues are presented. Speedup and slowdown for valid/invalid trials compared to a neutral trial with no cueing can be calculated. Effects of lesions in case of hemispatial neglect and Balint's syndrome have also been shown in this model, showing significantly slower reaction times in case of invalid cues.




Problems with the speed of attention shifts may arise not only due to the lesions, but also changes in relative strength of excitatory/inhibitory and leak ion channel conductances.

In many investigations individuals with ASD have shown atypical attention patterns. For example, Landry and Bryson (2004) found that "Children with autism had marked difficulty in disengaging attention. Indeed, on 20% of trials they remained fixated on the first of two competing stimuli for the entire 8-second trial duration." Kawakubo et al. (2007) conclude: "We suggest that adults with autism have deficits in attentional disengagement and the physiological substrates underlying deficits in autism and mental retardation are different. […] These results demonstrate electrophysiological abnormalities of disengagement during visuospatial attention in adults with autism which cannot be attributed to their IQs." Development of such problems is gradual – between 7 and 14 month infants who were later diagnosed with autism stopped improving speed and flexibility of their visual orientation (Elsabbagh et al. 2013).




Our simulations of attention shift effects point to the mechanism that is also seen in spontaneous transition between thoughts and cyclic movements in case of motor system activations. The model of thought wandering is based on a modified model of normal reading and dyslexia, implemented in the Emergent simulator (O'Reilly and Munakata, 2000). The model has 6 layers, representing information about orthography (6x8 units), phonology (14x14 units) and semantics (10x14 units), connected to each other via intermediate (hidden) layers of neurons (Fig. 3). Full connectivity between each adjacent layer is assumed, with recurrent self-connections within each of these layers. The original model has been used primarily to study various forms of dyslexia due to the lesions of one of the intermediate layers between the two input and the semantic layer. The network has been trained on 40 words, half of them concrete and half of them abstract. Semantics has been captured by using micro-features describing words. Accommodation mechanism has been added, based on the concentration of intracellular calcium that builds up slowly as a function of activation and opens leak channels releasing potassium ions, regulating subsequent inhibition of a neuron. Synaptic Gaussian noise with zero mean and 0.02 variance has been used to facilitate free transitions between attractors representing words or thoughts. The network is prompted by showing it a word in the orthographic or phonological layer, and observing transitions of activity in the semantic layer neurons.

To see trajectories of neurodynamics in 140 dimensional space recurrence plots (RPs) and fuzzy symbolic dynamics (FSD) visualization has been used (Duch and Dobosz, 2011; Dobosz and Duch 2010). In Fig. 3 examples of such trajectories are shown for 3 values of parameter controlling the calcium buildup: b=0.005 leads to deep attractor basins and reduced number of states in neurodynamics, b=0.01 leads to normal transitions, and b=0.02 to fast depolarization of neurons, shallow attractor basins and the inability to dwell in a single state. In the first case neurons remain synchronized in one persistent pattern, trajectories of neurodynamics are trapped in attractor basins for relatively long time. This seems to explain why disengagement of attention in ASD is slow. On the other hand too short synchronization times, or shallow basins of attractors, lead to rapid jumps from one basin of attraction to another, with short dwell times. Attention is not focused long enough, as is typical in case of Attention Deficit Hyperactivity Disorder (ADHD). Thus a single parameter that controls neural accommodation mechanism may lead to very different behaviors. Some ASD and ADHD cases may be at the opposite ends of the same spectrum. Other mechanisms (inhibition, recurrence) may be lead to different subtypes of these disease.

Links between calcium and potassium channelopathies and ASD have been recently noticed (Guglielmi et al., 2015). Several genes (CACNA1C, CACN1G, and CACNA1I) that control construction of calcium ion channels have been associated with ASD.

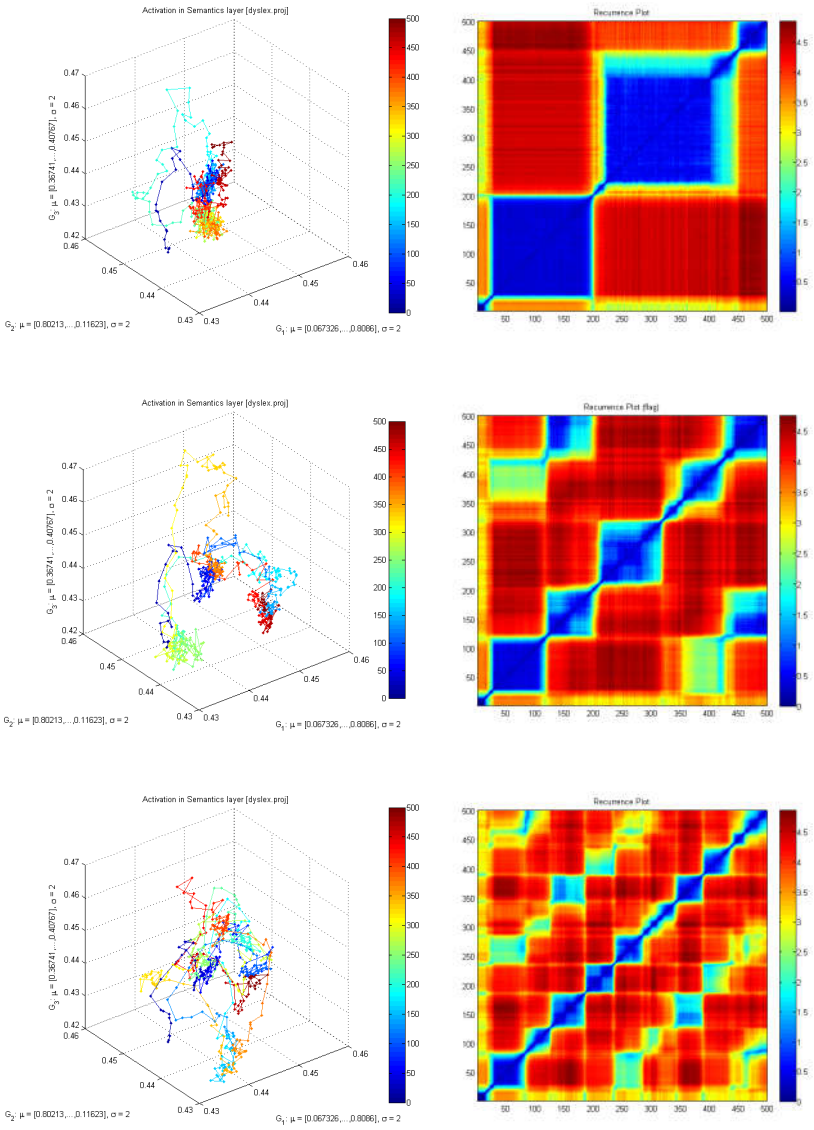



Fig 3: FSD (left) and RP (right) visualization of attractors in semantic layer with 140 units in weak (ASD), normal and strong (ADHD) accommodation case (top, middle and bottom respectively).

## 5. Interpretation

Strong synchronization of neurons in local sensory cortices creates deep attractors trapping neurodynamics for a long time. Network activity patterns do not change with normal frequency and therefore perception-action networks requiring synchronization of distant cortical areas are developing slowly. This is consistent with many observations related to the development of fronto-parietal connectivity (Just et al. 2012). Courchesne and Pierce (2005) have also postulated that ASD is characterized by early local hyperconnectivity and a long-distance hypoconnectivity of the prefrontal cortex. Trying to understand conflicting neuroimaging findings of hypo- and hyper-connectivity in children and adults Uddin et al. (2013) suggested that the increase in functional connectivity over the age

span may be slower in ASD group. Deep attractor hypothesis supports these views and links them to properties of neurons at molecular and genetic levels.

In our computational models strong attractors may arise due to several reasons: unusually strong inhibition, strong recurrence, or damage of leak ($K^+$) ion channels that has genetic basis. Shift of attention due to the bottom-up processes in Posner experiment require desynchronization of current activation patterns, and resynchronization of the new one. Spontaneous depolarization of neurons through the leak ion channels plays an important role in this process. Sizes of basins of attractors may considerably differ depending on encoding of stimulus and how initial connectivity was structured. Hyperconnectivity may lead to relatively small but very strong basins. One way to estimate it in case of attractor network is to plot variance of the fluctuations $\sigma(\mathbf{P}(\varepsilon))$ around the mean attractor pattern **P** as a function of the synaptic noise $\varepsilon$. If the variance is initially low for growing noise variance, but at some point there is a sharp increase, the attractor basin is deep (synchronization is strong) and narrow (fluctuations are small). Behavioral interpretation of such situation is that even strong stimuli will be ignored, resulting in under-reaction. Deep attractors may be activated in the cortex even when sensory stimulation is rather weak, and this may be true for all sensory modalities, sight, hearing, touch, smell, movement and taste, but also purely internal activation. From behavioral perspective deep attractors in perception-action cycle will lead to insistence on sameness. Development of strong attractors coupling sensory cortices and subcortical areas controlling emotions may result in overreaction and tantrums (Rogers and Ozonoff 2005).

On the other hand if the variance $\sigma(\mathbf{P}(\varepsilon))$ of the network activation patterns will grow with increasing noise the attractor basin may be broad, shifts of attentions may be easier and development of long-distance connections should be faster. To achieve such desirable outcome children should be stimulated in an intensive way. Applied Behavioral Analysis is using such intensive stimulation and is the best-established form of therapy for children with autism. Detailed simulations of trajectories entering basins of attractors shows that steps of the trajectories (total change of patterns in short time step) decrease near the center, making it hard in case of ASD to get out of the basin of attractor. A flow of activity may prevent the tendency to dwell for longer time in one state (perception, thought, action). For example, using the Rapid Sequential Visual Presentation technique one can adjust speed that allows for comprehension but does not allow to maintain the same brain state for long.

Finding fingerprints of persistent EEG activity in brains of autistic children should give support to ideas presented here. Many other ideas may be derived from computational simulations and the deep attractor hypothesis. More detailed computational simulations should help to understand casual chain linking genetics, neural structures, development of connectomes and behavior in a meaningful way. The language of dynamical systems may help to bridge the gap between physical and mental processes.

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