Master Thesis

Higher-Order Multi-Adaptive Neural Network Modeling of the Role of Epigenetics in Epilepsy

by

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ABSTRACT

Epilepsy is a disorder that originates from complex interactions between genetic, epigenetic, and environmental factors, resulting in recurrent, unprovoked seizures that often resist conventional treatments. In this paper, a fifth-order adaptive self-modelling network is introduced to capture the way epigenetic processes—including DNA methylation, histone modifications, and microRNA regulation—can cause a shift in neuronal circuits toward persistent hyperexcitability, leading to more frequent seizures. The model focuses on BDNF, LIMK1, and two microRNAs (miR-132 and miR-134), illustrating how excessive excitatory signals may lock brain networks into a chronic seizure-prone state under continued stress.

The results of the simulation show that sudden increases in stress can push the system beyond its capacity to maintain normal excitability, leading to seizures that persist even after the stress is no longer present. In a second simulation, an epigenetic therapy aimed at correcting abnormal methylation and histone acetylation successfully restores many of the disrupted processes, allowing the network to approach its pre-stress baseline. These findings suggest that therapeutic interventions targeting maladaptive epigenetic marks are theoretically sound, offering a framework for predicting seizure outcomes and guiding future research in personalized epilepsy treatment.

Keywords: Epilepsy, epigenetics, neural network model, higher-order adaptive systems.

1 INTRODUCTION

Epilepsy is a chronic neurological condition that affects millions of people worldwide, characterized by recurrent and unprovoked seizures (Hauser et al, 2018). While there are treatment options, such as antiseizure medications, many patients still develop pharmacoresistant epilepsy (Chen et al, 2024). Therefore, a better understanding of the molecular and cellular mechanisms that cause seizure generation is necessary.

In recent years, the role of *epigenetics* in key processes of epileptogenesis has received increasing attention. Epigenetic modifications, including histone modification, DNA methylation, and regulation of noncoding RNAs, can influence gene expression, modulate neuronal excitability, and affect synaptic plasticity (Henshall & Kobow, 2015; Lubin, 2012). Changes in these mechanisms can contribute to strengthening or even creating pathological states in the brain, leading to epilepsy. Within the realm of epigenetics, *Brain-Derived Neurotrophic Factor* (BDNF) and *LIM Kinase 1* (LIMK1) are two genes with significant roles in synaptic structure and neuronal survival (Parrish et al., 2013; Taniura et al, 2006). While BDNF supports neuronal growth and plasticity, LIMK1 regulates actin dynamics for dendritic spine formation. Proper regulation of these two factors is crucial, as upregulating them can promote hyperexcitable circuit states. Certain microRNAs, such as *miR-132* and *miR-134*, control gene networks related to synaptic connectivity and neuronal firing thresholds (Hwang, Aromolaran, Zukin, 2013; Henshall, 2018). Dysregulation of these microRNAs has been observed in models and clinical samples, linking them to epileptic activity.

This paper introduces a *fifth-order adaptive self-modelling network model* based on the self-modeling (or reified) network modeling approach from Treur (2020) to capture these levels of control in epilepsy. The model focuses on BDNF, LIMK1, miR-132, and miR-134, demonstrating how excitatory challenges can drive the system to a hyperexcitable state. This model offers insights into therapeutic approaches aimed at modulating these pathways. By mapping the interplay among epigenetic modifications, DNA, RNAs, and enzymes, this framework may inform new strategies to counteract seizure generation and maintenance.

2 BACKGROUND KNOWLEDGE

2.1 Epigenetic Foundations for Epilepsy

Epileptogenesis describes the process through which the brain becomes susceptible to seizures. This process is influenced by *epigenetic mechanisms* (Henshall & Kobow, 2015; Lubin, 2012). These mechanisms modify gene expression levels in neuronal networks without altering the DNA sequence, leaving the genome unchanged. Epigenetic modifications include distinct processes:

- **DNA Methylation:** This modification involves the attachment of methyl groups to cytosine bases at CpG sites. The addition of these groups can interfere with the binding of transcription factors or lead to the recruitment of proteins that compact chromatin. As a result, the transcription of specific genes is reduced. For example, when genes that promote excitatory signaling are heavily methylated, their activity remains low. In contrast, a reduction in methylation may lead to increased expression of genes that contribute to neuronal hyperexcitability (Machnes et al., 2013).
- **Histone Modifications:** Chemical changes to histone proteins, such as acetylation and methylation, alter the structure of chromatin. A higher level of histone acetylation results in a looser chromatin configuration, permitting greater access for the transcriptional machinery. In epilepsy models, increased histone acetylation is associated with a rise in the transcription of genes that encourage excitatory activity in neurons (Chen et al., 2024). –

- **Noncoding RNA Regulation:** Noncoding RNAs, including microRNAs, control protein synthesis by binding to messenger RNA molecules. This binding can lead to mRNA degradation or inhibit its translation. Variations in the levels of these RNAs have been observed in seizure models, where they affect the balance of proteins that regulate excitatory and inhibitory signals (Hwang et al., 2013).

These epigenetic processes can interact with one another. For example, seizure-induced changes in DNA methylation can lead to shifts in histone modification patterns, resulting in coordinated adjustments in the expression of genes that control neuronal excitability and network stability (Henshall, 2018).

2.2 The Roles of BDNF and LIMK1 in Synaptic Plasticity

Research in epigenetics has found Brain-Derived Neurotrophic Factor (BDNF) and LIM Kinase 1 (LIMK1) to be important mediators of synaptic plasticity and neuronal health, with growing evidence implicating their dysregulation in the development and progression of epilepsy (Parrish et al., 2013; Taniura et al., 2006).

2.2.1 ***BDNF in Neuronal Excitability and Epileptogenesis.*** BDNF is a key neurotrophin that supports neuronal survival and differentiation, and it plays a significant role in modulating synaptic strength. It exerts its effects by binding to receptor tyrosine kinases such as TrkB, thereby activating several intracellular signaling cascades—including the MAPK/ERK, PI3K/Akt, and PLCγ pathways—which influence neurotransmitter release, receptor trafficking, and gene expression. In epilepsy models and human epileptic tissue, BDNF is often upregulated, suggesting that its increased signaling contributes to heightened neuronal excitability by reinforcing excitatory synapses. In addition to these direct synaptic effects, BDNF affects ion channel dynamics and the expression of genes involved in synaptic remodeling. This is particularly relevant in the hippocampus, a brain region central to temporal lobe epilepsy, where changes in BDNF levels are closely linked to the emergence of hyperexcitable networks and seizure propagation.

2.2.2 ***LIMK1 and Actin Dynamics in Dendritic Spines.*** LIMK1 serves as a regulator of the actin cytoskeleton, controlling dendritic spine dynamics by phosphorylating cofilin, an actin-depolymerizing factor. This phosphorylation leads to actin stabilization, which reinforces the structural integrity of dendritic spines and increases the density of excitatory synapses. Overexpression or hyperactivation of LIMK1 can result in excessive stabilization of spines and abnormal network reorganization. Such structural alterations are associated with the formation of atypical synaptic connections that contribute to the increased excitability observed in epilepsy. Epigenetic mechanisms such as histone acetylation and DNA methylation influence the transcriptional regulation of LIMK1. In the hippocampus—an area critical for learning, memory, and seizure development—altered chromatin states affecting LIMK1 gene expression have been linked to the structural reorganization of neuronal circuits seen in temporal lobe epilepsy (Hauser et al., 2018).

2.2.3 ***Interconnected Roles and Therapeutic Implications.*** BDNF and LIMK1 act independently as mediators of synaptic remodeling. Sustained high levels of BDNF reinforce excitatory synapses and contribute to hyperexcitability, while aberrant LIMK1 activity leads to excessive stabilization of dendritic spines and pathological network reorganization. Epigenetic modifications that alter the expression of both BDNF and LIMK1 represent promising targets for therapeutic intervention. Modifying these epigenetic marks may help restore normal synaptic function and reduce network hyperexcitability, which is central to epileptogenesis.

2.3 MicroRNAs: miR-132 and miR-134

The literature indicates that miR-132 and miR-134 play significant roles in epilepsy through their regulation of neuronal structure and excitability (Hwang et al., 2013; Henshall, 2018).

- **miR-132** is often upregulated following seizures. It promotes dendritic growth and synaptic reorganization via pathways related to cytoskeletal remodeling. Increased miR-132 activity leads to alterations in synaptic connectivity that may produce networks prone to hyperexcitability. Epigenetic changes, including histone modifications and DNA methylation, modulate miR-132 expression. This regulation influences the balance between adaptive synaptic development and the formation of circuits that contribute to seizure generation.
- **miR-134**, found primarily in the hippocampus, affects dendritic spine morphology. Variations in miR-134 levels change the size and structure of spines, which in turn impacts synaptic transmission. Studies have shown that reducing miR-134 levels produces seizure-suppressive effects in experimental models, suggesting that its abnormal expression plays a role in the development of epileptic networks. Epigenetic mechanisms that alter miR-134 transcription further modulate its function in regulating synaptic structures in the hippocampus, a region that is critical in the onset and progression of temporal lobe epilepsy.

2.4 Epigenetic Therapy for DNA Methylation and Histone Modifications

Research has connected DNA methylation and histone modifications to the transition from acute seizure episodes to a persistent epileptic condition (Hauser et al., 2018; Chen et al., 2024). Under stressful circumstances, these epigenetic marks appear to shift neuronal circuits into a lasting hyperexcitable state, even after the initial stressor has resolved (Lubin, 2012; Machnes et al., 2013). Examples include promoter hypermethylation at genes tied to synaptic function and disruptions in histone acetylation affecting normal transcription in neuronal pathways (Parrish et al., 2013).

Proposed interventions focus on reversing or modifying these maladaptive epigenetic changes, with the goal of stabilizing neural networks and reducing seizure vulnerability. Compounds that inhibit DNA methyltransferases (DNMTs) may alleviate aberrant methylation at critical loci, thereby improving the expression of ion channels and receptors involved in regulating excitability (Machnes et al., 2013; Parrish et al., 2013). Histone deacetylase (HDAC) inhibitors such as valproic acid and trichostatin A can preserve or boost histone acetylation, allowing transcriptional activation of genes that help maintain normal neuronal function (Taniura et al., 2018). These approaches may be integrated with metabolic or

RNA-based therapies to address multiple layers of epigenetic dysregulation (Boison & Rho, 2020; Henshall, 2018).

3 HIGHER-ORDER ADAPTIVE SELF-MODELLING NETWORK MODELING

The manifestation of epilepsy derives from the interaction of multiple dynamic and adaptive processes that operate across different biological and environmental levels. In order to represent this complex structure, a self-modelling adaptive temporal-causal network approach based on the (multilevel) network reification principle introduced in (Treur, 2018; Treur, 2019) and described in much detail in (Treur, 2020) was adopted. This approach has been proven to be effective in representing other cases of higher-order adaptive dynamical systems (Hendrikse et al., 2023; Kathusing et al. 2023).

This kind of network is composed by a multitude of nodes (or states), each one with an activation level $X(t)$ that evolves over time. Arrows between nodes show causal impacts with associated weights $\omega_{X,Y}$. These weights can also become subject of adaptation, introducing therefore self-model states based on the (multilevel) network reification principle (Treur, 2018; 2019). As a whole, such a network is a hierarchy of adaptivity, in which higher-order states adjust lower-order connection weights or other network characteristics. This sort of design helps to represent the increasingly complex feedback loops we see in epileptogenesis. Formally, the core dynamics of each state Y are governed by:

$$\frac{dY(t)}{dt} = h_Y(t)\left[c_Y(\omega_{X_1,Y}X_1(t), ..., \omega_{X_k,Y}X_k(t)) - Y(t)\right] \quad (1)$$

$$Y(t+\Delta t) = Y(t)+h_Y(t)\left[c_Y(\omega_{X_1,Y}X_1(t), ..., \omega_{X_k,Y}X_k(t)) - Y(t)\right]\Delta t \quad (2)$$

where the X_i are states with causal connections into Y, $\omega_{X_i,Y}$ are the connectivity weights, c_Y is a chosen combination function parameterized by parameter list p_Y and h_Y is a speed factor specifying how quickly Y reacts to the net input.

The computational framework used in this study relies on a set of mathematically defined functions that govern the behavior of the network states. Among these, three key functions were utilized to regulate excitability, time-dependent activation, and periodic switching mechanisms. These functions provide a structured way to define transitions in neural states based on internal and external influences.

The Advanced Logistic Sum function $a_{logistic,\sigma,\tau}$ introduces a nonlinear transformation of summed inputs, normalising the outcome to the $[0, 1]$ interval, modulated by a steepness parameter s and an excitability threshold t. This formulation ensures smooth activation transitions, preventing abrupt changes in state. Additionally, when used with positive inputs, negative outputs are constrained at zero to avoid biologically implausible responses.

The Steponce function $steponce_{a,b}$ enforces a time-specific activation window, turning on within the interval $[a, b]$ and remaining inactive otherwise. This mechanism is particularly useful for modeling transient external stimuli or interventions that occur for a limited duration. The Step-Modulo function $stepmod_{r,d}$ introduces periodic modulation of activation based on time cycles. It alternates between active and inactive states depending on whether the modulo remainder of time with respect to a given duration r is below or above a predefined tipping point d. This function enables the representation of rhythmic or cyclic dynamics. These functions collectively provide a structured approach for defining dynamic network behaviors. Their formulations and respective parameters are summarized in Table 1.

By introducing additional self-model W-states $W_{X,Y}$ that represent weights $\omega_{X,Y}$, the network can modify its own connectivity. Such higher-order network states can have their own adaptive causal pathways, potentially leading to further levels of adaptivity (second-order, third-order, etc.). Another application of the network reification principle used in this paper is to model excitability adaptivity. This is done by adding T-states T_Y to represent the excitability parameter t_Y of the logistic combination function for some state Y. This network reification principle can be applied iteratively until all the relevant biologically motivated types of adaptivity are accounted for in the model. This aligns well with analyses from biology, philosophy and consciousness studies about different types of adaptivity and control levels as described in (Bevilacqua et al, 2008; Bechtel and Bich, 2024; Bich and Bechtel, 2022ab; Treur, 2024ab; Treur, 2025).

Function	Description
$alogistic_{\sigma,au}(V_1, \ldots, V_k)$	$\left[\frac{1}{1+e^{-\sigma(V_1+\cdots+V_k-\tau)}} - \frac{1}{1+e^{\sigma\tau}}\right](1+e^{-\sigma\tau})$
$steponce_{a,b}$	This function is used to change the value from 0 to 1 for a specific time interval from a to b.
$stepmod_{r,d}$	This function is used to change the value from 0 to 1 repeatedly for each r-interval from time d on.

Table 2: Mathematical functions used in the model.

4 THE DESIGNED MULTI-ADAPTIVE NETWORK MODEL

In order to model the epigenetic influences in epilepsy, a *fifth-order adaptive self-modelling network* was designed to describe how an individual may transition from a baseline seizure susceptibility to chronic epilepsy under persistent stressors and epigenetic dysregulation. To facilitate the visualization of the interactions and processes in play, a graphical representation of the temporal-causal network was created, visible as Fig. 1. All the states and the interconnections between them are summarized in Table 2. However, below is an outline of the key levels of adaptation that occur in the model:

- **Base Level:** States X_1 through X_9 represent primary biological concepts (e.g., stress and environmental inputs, sensory representations, seizure activity, amygdala activation, hippocampi regulation, baseline, and chronic contexts). These represent the direct manifestations of seizure generation and the environmental or internal cues that influence it.

State Nr	State Name	Biological Concept	Explanation	Level
X1	CON_{stress}	Context for stress	Context state for stress	Base Level
X2	$CON_{environment}$	Context for environment	Context state for environment	
X3	SS_s	Sensory Organ	Sensor state for stimulus s	
X4	SRS_s	Sensory representation	Sensory representation state for stimulus s	
X5	Pseizure	Seizure Activity	State representing seizure generation and propagation	
X6	AMe	Amygdala Activation	Amygdala state related to emotional and stress-induced seizure modulation	
X7	HPC	Hippocampus activation	State of hippocampal activity involved in processing sensory and contextual inputs and modulating neuronal responses.	
X8	$CON_{baseline}$	Context for Baseline State	Baseline reference state for neuronal activity	
X9	$CON_{chronic}$	Context for Chronic State	Context state for chronic epilepsy development	
X10	$\mathbf{T}_{Pseizure}$	Neuronal Excitability	Self-model state representing the excitability threshold of Pseizure; on a causal pathway with a connection from $CON_{thresholds}$	First-order self-model level
X11	$\mathbf{T}_{HPC}$	Neuronal Excitability	Self-model state representing the excitability threshold of hippocampal (HPC) activation; on a causal pathway with a connection from $CON_{thresholds}$	
X12	$CON_{thresholds}$	Context for Excitability Development	Context state that enables threshold levels for neuronal excitability throughout the brain.	
X13	$\mathbf{W}_{CONthresholds,T\_Pseizure}$	Enzyme responsible for Epilepsy	Self-model state for the weight of the first self-modeling level connection from $CON_{thresholds}$ for context to $\mathbf{T}_{Pseizure}$ for seizure activity state; on a causal pathway with a connection from $CON_{enzymes}$	Second-order self-model level
X14	$\mathbf{W}_{CONthresholds,T\_HPC}$	Enzyme responsible for Epilepsy	Self-model state for the weight of the first self-modeling level connection from $CON_{thresholds}$ for context to $\mathbf{T}_{HPC}$ for regulatory response; on a causal pathway with a connection from $CON_{enzymes}$	
X15	$CON_{enzymes}$	Context for Enzyme Production	Context state enabling enzyme production	
X16	$\mathbf{W}_{CONenzymes,W\_CONthresholds,T\_Pseizure}$	mRNA responsible for Epilepsy	Self-model state for the weight of the second self-modeling level connection from $CON_{enzymes}$ to $\mathbf{W}_{CONthresholds,T\_Pseizure}$ for seizure activity state; on a causal pathway with a connection from CON_{mrna}	Third-order self-model level
X17	$\mathbf{W}_{CONenzymes,W\_CONthresholds,T\_HPC}$	mRNA responsible for Epilepsy	Self-model state for the weight of the second self-modeling level connection from $CON_{enzymes}$ to $\mathbf{W}_{CONthresholds,T\_HPC}$ for regulatory response; on a causal pathway with a connection from CON_{mrna}	
X18	CON_{mrna}	Context for mRNA Production	Context state enabling mRNA production	
X19	$\mathbf{W}_{CONmrna,W\_CONenzymes,W\_CONthresholds,T\_Pseizure}$	Exprssed BDNF gene	Self-model state for the weight of the third self-modeling level connection from CON_{mrna} to $\mathbf{W}_{CONenzymes,W\_CONthresholds,T\_Pseizure}$ for seizure activity; on a causal pathway with a connection from CON_{dna}	Fourth-order self-model level
X20	$\mathbf{W}_{CONmrna,W\_CONenzymes,W\_CONthresholds,T\_HPC}$	Expressed LIMK1 gene	Self-model state for the weight of the third self-modeling level connection from CON_{mrna} to $\mathbf{W}_{CONenzymes,W\_CONthresholds,T\_HPC}$ for regulatory response; on a causal pathway with a connection from CON_{dna}	
X21	CON_{dna}	Context for DNA Handling	Context state for BDNF and LIMK1 gene expression	
X22	$\mathbf{W}_{CONdna,W\_CONmrna,W\_CONenzymes,W\_CONthresholds,T\_Pseizure}$	miRNA-132	Self-model state for the weight of the fourth self-modeling level connection from CON_{dna} to $\mathbf{W}_{CONmrna,W\_CONenzymes,W\_CONthresholds,T\_Pseizure}$ for seizure activity; on a causal pathway with a connection from $CON_{epigenetics}$	Fifth-order self-model level
X23	$\mathbf{W}_{CONdna,W\_CONmrna,W\_CONenzymes,W\_CONthresholds,T\_HPC}$	miRNA-134	Self-model state for the weight of the fourth self-modeling level connection from CON_{dna} to $\mathbf{W}_{CONmrna,W\_CONenzymes,W\_CONthresholds,T\_HPC}$ for regulatory response; on a causal pathway with a connection from $CON_{epigenetics}$	
X24	$CON_{epigenetics}$	Context for Epigenetics	Context state enabling epigenetic upregulation of miR-132 and miR-134	

Table 1: Comprehensive overview of all states and their description

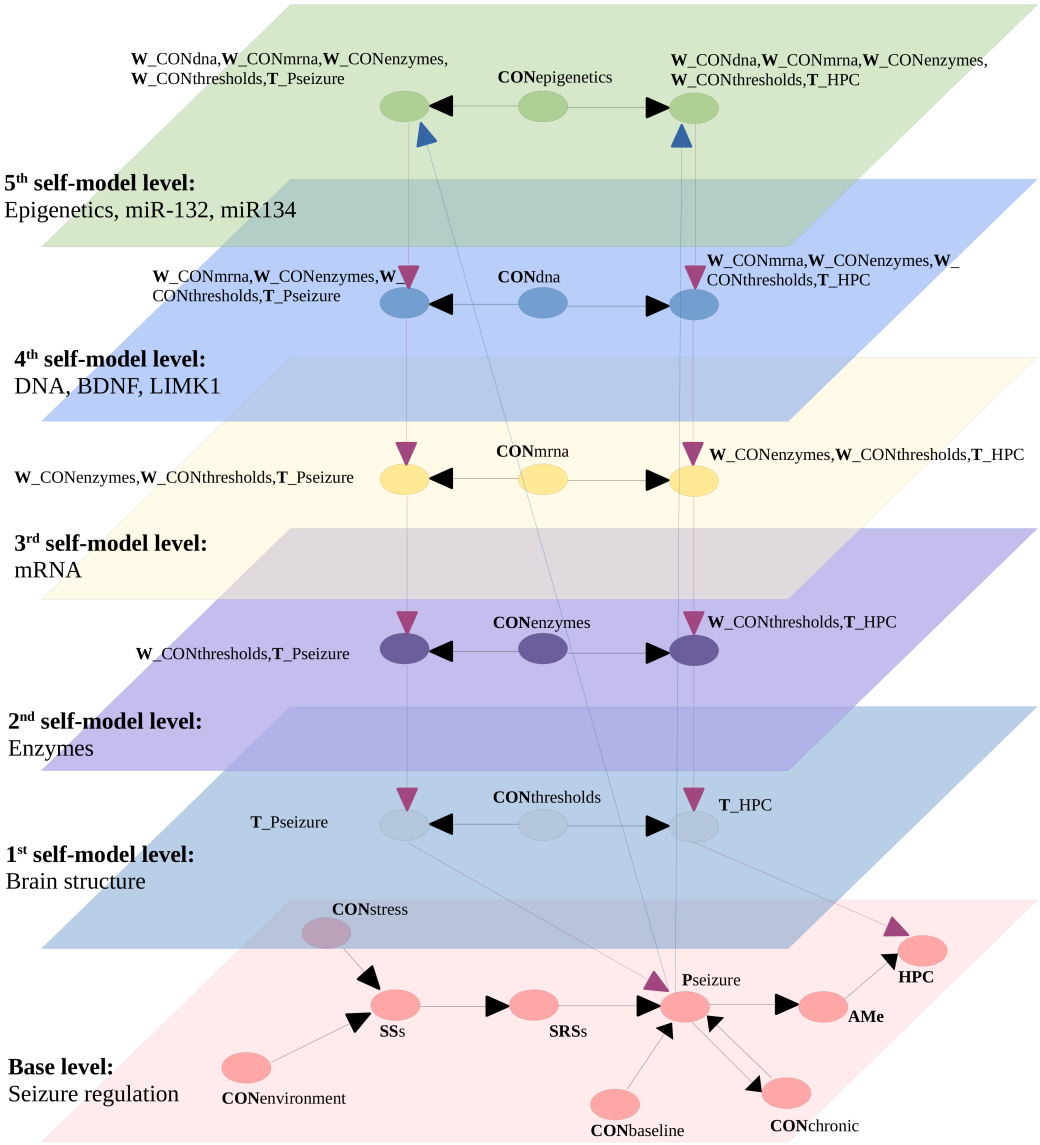

Figure 1: Graphical representation of the model

- **First-Order Adaptation (Excitability Adaptivity):** States X_{10}, X_{11}, and X_{12} model the lowest level of adaptivity changes: excitability adaptivity. Here, self-model states X_{10} for $TP_{seizure}$ and X_{11} for T_{HPC} represent transitions in excitability thresholds of states in the base level, both of which receive a context-driven connection X_{12} for $CON_{thresholds}$. These transitions capture how intrinsic neural characteristics become strengthened or modified in response to ongoing stimuli.
- **Second-Order Adaptation (Enzyme Production):** The weights of the first-order level connections also undergo adaptation, this time because of enzyme levels represented by states X_{13} and X_{14}, which represent the produced active enzymes shaping neuronal characteristics for seizure or regulatory pathways. Enzyme production depends on the enabling context state $CON_{enzymes}$ (X_{15}).
- **Third-Order Adaptation (mRNA Production):** The second-order enzyme-producing connections adapt themselves under the influence of produced mRNA. This is represented by states X_{16} and X_{17}, with the contextual enabling connection from CON_{mRNA} (X_{18}). These third-order states capture mRNA availability which can up- or down-regulate enzyme levels, in turn affecting seizure and regulatory pathways.

- **Fourth-Order Adaptation (Expressed Genes):** The next layer involves actual gene expression for BDNF and LIMK1, represented by X_{19} and X_{20}, representing expression of these crucial genes, responsible for neuronal growth, synaptic remodeling, and neuronal excitability. Their activation is enabled by CON_{DNA} (X_{21}).
- **Fifth-Order Adaptation (miRNA-Level):** At the highest level, we can see the states X_{22} (miRNA-132) and X_{23} (miRNA-134), nodes that modulate the gene expression pathways themselves, enabled by $CON_{epigenetics}$ (X_{24}). These microRNAs can fine-tune the expression of BDNF and LIMK1, as well as other targets, thereby exerting control over the progression to chronic epilepsy. In this level, the weights are affected by the base level, as the activations of X_{22} and X_{23} are influenced by $P_{seizure}$ in the base level.

The states can take on activation values between 0 and 1, which can fluctuate over time. The role W, responsible for self-modelling of connection weights, is used for the self-model states of second- and higher-order. The ovals in the model in Fig. 1 represent the states, and the connections between them are represented by arrows, pointing towards the direction of the causal impact. The states come in different types:

- **Context states (CON):** These states model the enabling contextual conditions for the various processes (Bechtel and Bich, 2024). For example, an external stimulus or a supporting environment (e.g., CON_{stress} for representation of the stimulus stress, $CON_{enzymes}$ for the environment within the organism that enables the production of enzymes).
- **Sensor states (SS):** Represent the sensing of the stimulus.
- **Sensory representation states (SRS):** Capture mental representation.
- **Amygdala state (AMe):** Represents the amygdala's role in emotional and stress-induced seizure modulation.
- **Hippocampus state:** Represents the hippocampus' role in regulating sensory and contextual processes.
- **Excitability threshold self-model states (T_Y):** Represent the modulation of excitability (e.g., $TP_{seizure}$ modifies the excitability of $P_{seizure}$).
- **Self-model weight states (W):** Represent self-model adaptation (e.g., $W_{CONconnection,TPseizure}$, a self-model state for the weights of the first self-modeling level connection from a CON state to the T-state for seizure activity).

The specific causal impact of each of these self-modelling states is represented in Fig. 1 by a purple downward arrow, while the upward causal connections are drawn in blue.

In order to run a network model with the specifications described above in the dedicated software developed in MATLAB, a detailed representation in terms of role matrices was made (Treur, 2020).

The full role matrices are available in the Appendix as Linked Data at https://www.researchgate.net/publication/389439490. The following matrices are included:

- m_b for base connectivity.
- m_{cw} for connection weights w.
- m_{cfw} for combination function weights g.
- m_{cfp} for combination function parameters p.
- m_s for speed factors h.
- iv for initial values.

Each row in the role matrices corresponds to a state X_i. The orange cells in each row indicate the states that influence X_i within that specific role. For instance:

- In the m_b matrix, the orange cells highlight the states from which X_i receives incoming connections.
- In the m_{cw} matrix, the green cells specify the nonadaptive connection weights between the row state and the corresponding connected state, as indicated in m_b.
- Additionally, the orange cells in m_{cw} identify the states X_j that function as self-model W-states for the weights of the connections specified in the same m_b cell.
- Similarly, in m_{cfp}, the role of the self-model T-states is indicated. Green cells represent (nonadaptive) values that directly affect X_i.

5 FIRST SIMULATION: STRESS AND ENVIRONMENT EFFECT

A first simulation was performed to illustrate how the model can illustrate the development of and suffering from epilepsy. The output of the simulation can be seen in Fig. 2 and Fig. 3. The results show that from time 0 to 120 the system stays in a baseline state. During this period, stress signals such as CON_{stress} and $CON_{environment}$ remain at 0. As a result, sensor nodes (SS_s and SRS_s) show minimal activity, keeping the base level activations steady.

At time $t = 120$, both CON_{stress} and $CON_{environment}$ increase sharply to 1 and continue at that level until time 280. This change causes the sensor nodes to react fast (SS_s jumps to 1 and SRS_s rises to 0.9), sending a strong excitatory signal into the network. Consequently, the seizure node ($P_{seizure}$), which had previously exhibited low-level oscillations, becomes persistently active between time 120 and 280 (see Fig. 2). Simultaneously, nodes associated with emotional processing and regulation, namely the amygdala (AMe) and the hippocampus (HPC), increase their activation. The amygdala climbs from roughly 0.45–0.5 to around 0.8, and the hippocampus moves upward to nearly 0.95.

Beyond the primary sensor and regulatory levels, deeper molecular mechanisms start to alter the system's behavior. Transition nodes ($TP_{seizure}$ and T_{HPC}) first show a gradual decline and then drop sharply after time 280. In parallel, the adaptive connection strength nodes (the W-states), which cover enzymes, mRNA, and genes (including BDNF and LIMK1) as well as microRNAs (miRNA-132 and miRNA-134), also decrease significantly. This reduction indicates that the feedback processes meant to regulate excitability are no longer working effectively.

After time 280, the seizure node remains highly active while the regulatory nodes continue at a reduced level. The failure of the deeper layers to adjust connection strengths means the system loses control over seizure activity. The network becomes stable in a hyperexcitable state, making it more susceptible to continuous, uncontrolled seizures.

This persistent change demonstrates how a prolonged rise in stress can overwhelm both the initial sensor and regulatory layers and the molecular mechanisms that usually moderate network activity. When these processes cannot lower the excitatory signals,

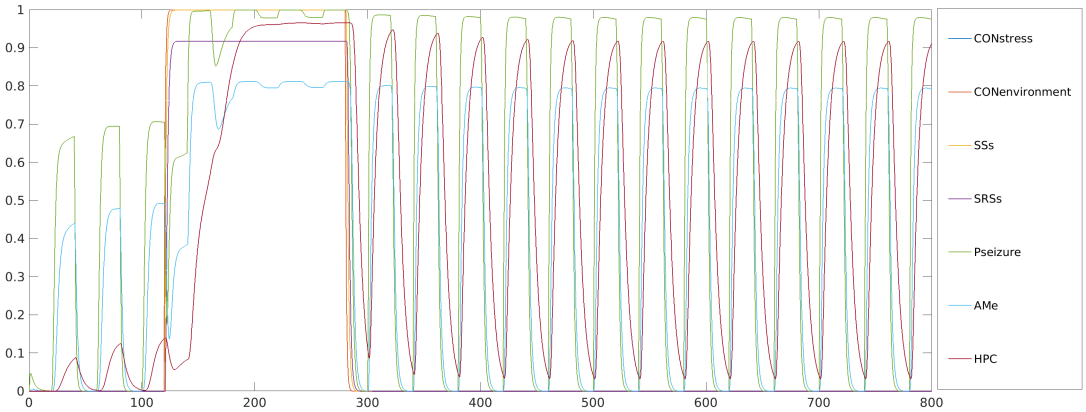

Figure 2: Simulation 1 Base level

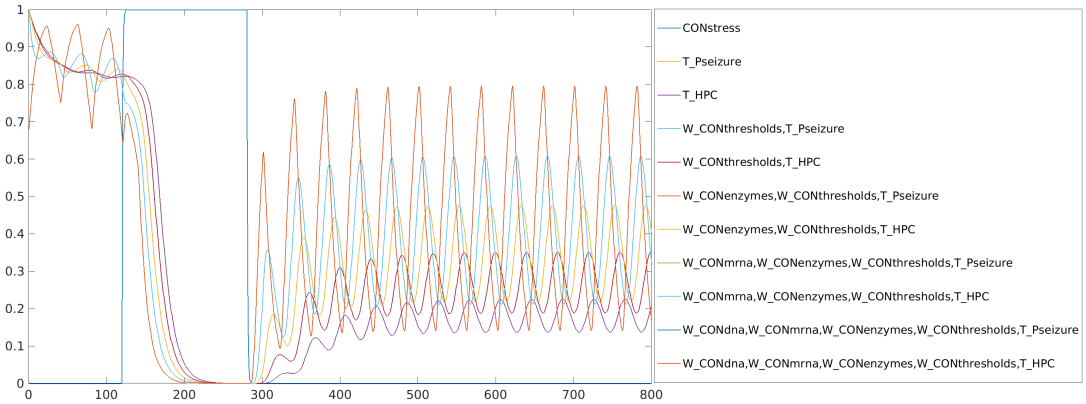

Figure 3: Simulation 1 W- and T-states

the system shifts from an acute response into a state prone to chronic seizure activity.

6 SECOND SIMULATION: EPIGENETIC THERAPY INTERVENTION

The previous simulation showed how stress-driven epigenetic changes can lock the system into a chronic seizure-prone condition. As a next step, a second simulation was designed to assess a therapy aimed at counteracting these specific epigenetic modifications (see Sections 2.3 and 2.4 for background knowledge). For the extended network model incorporating such epigenetic therapy, see Fig. 4, in particular, the added node at the highest level and its outgoing connections positively affecting both W-states of that level.

Based on this extended model, a second simulation was conducted to assess a targeted epigenetic intervention aimed at restoring normal excitability. Up to time $t = 440$, the system follows the same trajectory as the previous simulation, remaining locked in a hyperexcitable state due to prolonged stress. At $t = 440$, a therapy node activates with a level of 1, triggering a rapid response in both the deeper molecular levels and the base level.

The W-states (see Fig. 5), which had reached very low and stable values under ongoing stress, display an abrupt increase the moment therapy begins. Their levels surge to approximately 0.8, reversing much of the decline observed previously. Following the therapy window, which ends at $t = 600$, the W-states resemble their initial, pre-stress conditions. A gradual drop reappears by $t = 800$, suggesting that the limited duration of therapy did not fully correct all aspects of the epigenetic dysregulation. Nonetheless, this partial recovery demonstrates that modifying DNA methylation and histone modifications can shift these molecular regulators back toward a less excitable baseline.

In Fig. 6, however, a more gradual improvement is seen in the primary sensor and regulatory nodes, reflecting their slower activation profiles. During therapy, the sensor nodes (e.g., SS_s, SRS_s), along with AMe and HPC, show a reduction toward values approaching those seen before the stressor was introduced. Their descent is less steep than that of the W-states, underscoring the different timescales in which these layers react. Overall, by $t = 600$, seizure-related activity ($P_{seizure}$) has decreased substantially, signaling a return to pre-stress levels of excitability. These outcomes indicate that a well-timed epigenetic therapy—focused on correcting aberrant DNA methylation and histone modifications—can successfully move a chronically hyperexcitable system back toward its baseline configuration. Although a slight downward drift in W-states

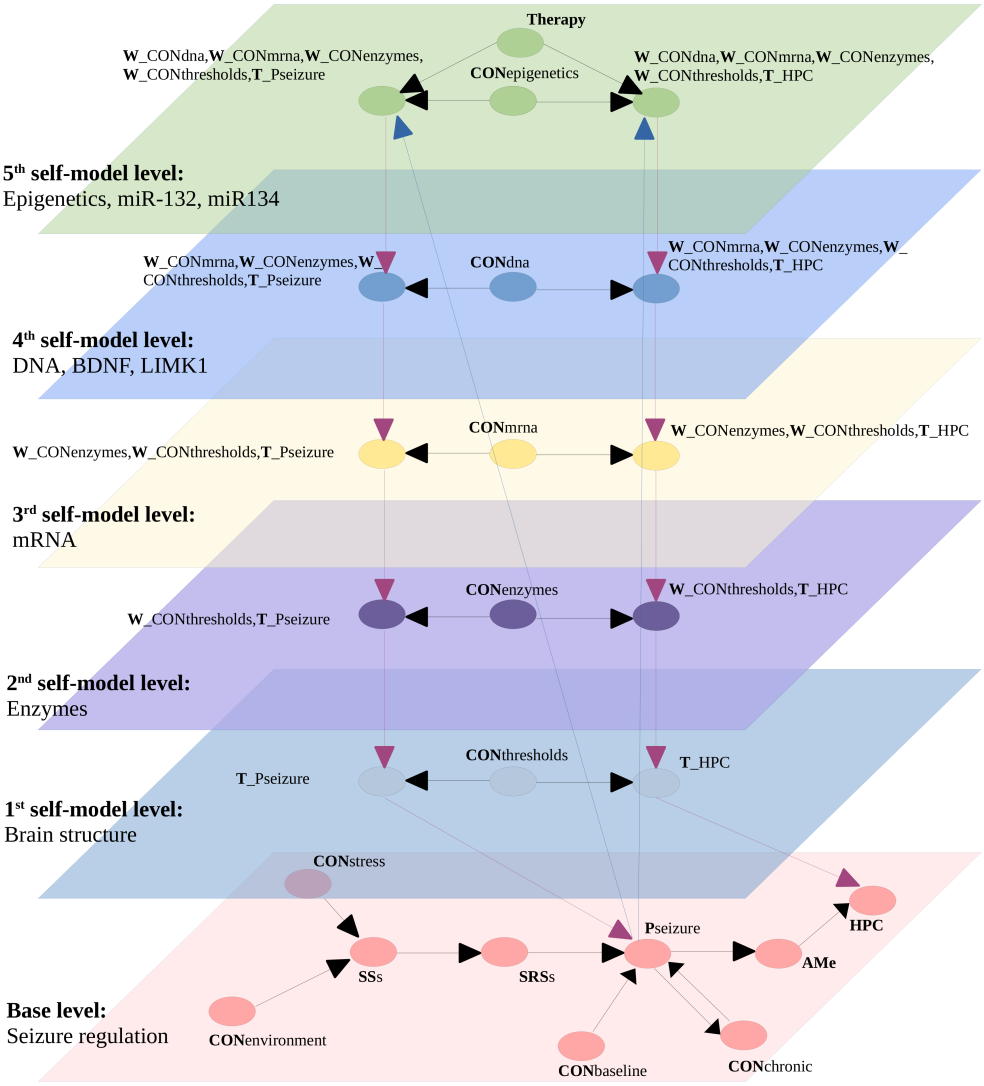

Figure 4: Graphical representation of the model with integrated therapy

emerges after therapy, the general effect is a substantial mitigation of seizure susceptibility.

This simulation suggests that epigenetic interventions, even over a short treatment window, can have a pronounced impact on network stability and open a path toward more sustained seizure control.

7 DISCUSSION AND CONCLUSION

Epilepsy emerges from a very complex interplay of molecular, cellular, and network-level mechanisms that all contribute to irregular neuronal excitability. The approach of this paper to this issue is a self-modelling adaptive network framework that includes multiple layers of epigenetic regulation, focusing on DNA methylation, histone modifications, and microRNA expression. By incorporating key factors such as BDNF, LIMK1, miR-132, and miR-134, the model simulates how chronic stress can initiate and remain stuck in a hyperexcitable state.

In the first simulation, the introduction of prolonged stress triggered a domino effect of activity across both sensor-regulatory layers and deeper nodes. Once excitatory levels reached a critical threshold, existing regulatory processes were unable to counteract the new seizure states, demonstrating how stress can lead to a persistent hyperexcitable condition. This observation aligns with the literature that indicates how stress and epigenetic alterations can substantially remodel synaptic function and neuronal plasticity, contributing to seizure propagation.

The second simulation added a new node for epigenetic therapy at the highest level, representing interventions targeting the DNA

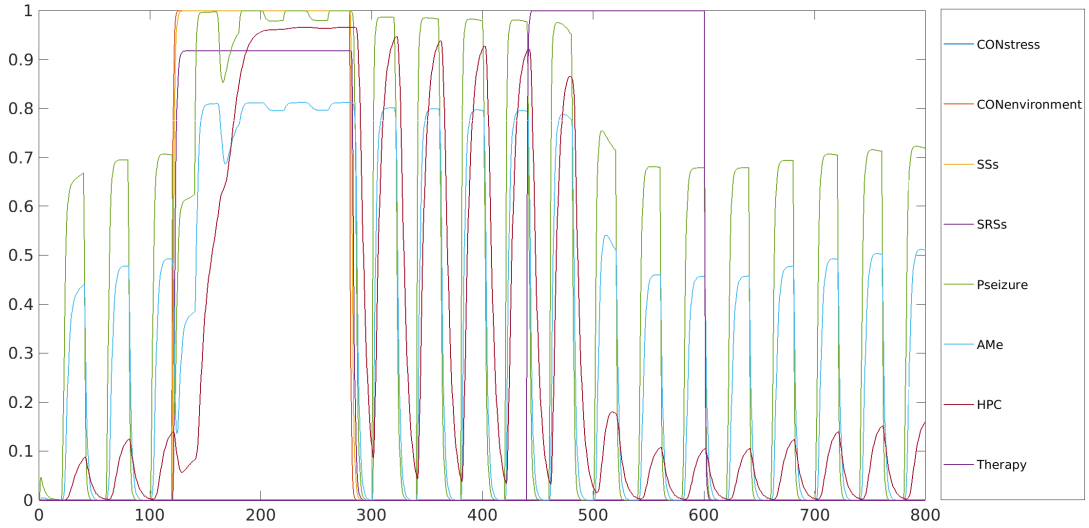

Figure 5: Simulation 2 Base level

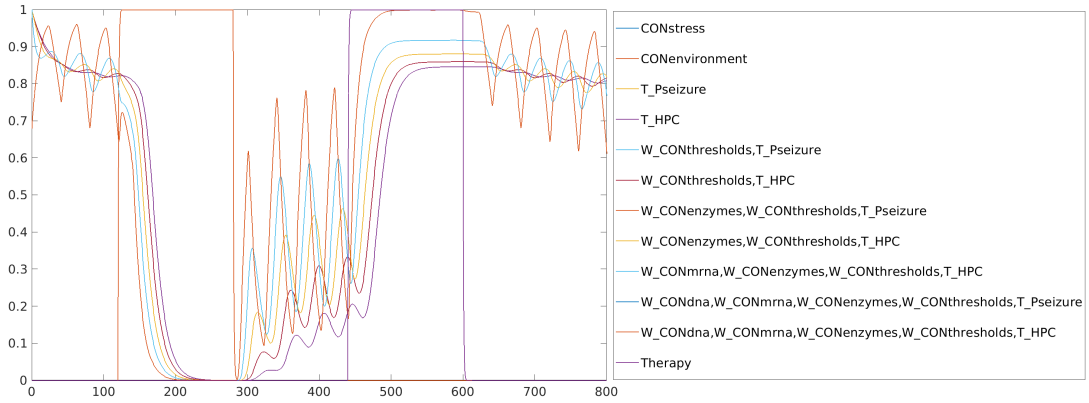

Figure 6: Simulation 2 W- and T-states

methylation and histone acetylation processes that were no longer functioning properly. After therapy activation, most of the regulatory nodes exhibited significant recovery, and seizure-related nodes returned closer to baseline conditions. Although the restorative effect was not absolute (as some slowly adapting parts of the network required additional time to stabilize), this outcome underscores the potential for epigenetic strategies to counter or reverse chronic seizure susceptibility. These results confirm previous findings stating that inhibitors of DNMT or HDAC, as well as other adjunct therapies (e.g., metabolic and RNA-based treatments), can mitigate epileptogenesis (Boison & Rho, 2020).

Overall, the model indicates that epigenetic changes can lock neuronal circuits into a hyperexcitable state and that reversing such changes may provide novel therapeutic avenues. Future research, including the incorporation of detailed clinical data and further exploration of complex regulatory loops, could enhance the understanding of how epigenetic therapies succeed or fail across various forms of epilepsy. What is seen in this paper emphasizes the importance of investigating the underlying mechanisms of seizure disorders, suggesting that epigenetic therapies hold promise for restoring normal neuronal function.

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