Deep Koopman-operator based model predictive control for closed-loop electrical neurostimulation in epilepsy

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Abstract—Electrical neuromodulation as a palliative treatment has been increasingly applied to epilepsy. However, most of the current neuromodulations implement pre-determined actuation strategies rather than closed-loop neurofeedback. In this paper, rooted in optimal control theory, we propose a novel framework for real-time closed-loop electrical neuromodulation in epilepsy. Our framework combines a deep Koopman-operator based model for seizure prediction in an approximated finite dimensional linear dynamics and model predictive control (MPC) for designing optimal seizure suppression strategies. We validate our model with synthetic seizure data from the Jansen-Rit Model which generates neural dynamics in a single cortical column and two distant cortical columns. The results demonstrate that the deep Koopman-operator based model has great capabilities to map the nonlinear neural dynamics into finite dimensional linear dynamics, which is suitable for real-time seizure prediction and naturally compatible with the optimal-based linear MPC design for seizure suppression. Our framework opens a new window for the development and implementation of robust real-time closed-loop electrical neuromodulation in epileptic seizure suppression and sheds light on understanding the neurodynamics and feedback control policies.

Index Terms—Electrical Neuromodulation, Closed-loop Neuro-modulation, Deep Koopman-operator, Model Predictive Control.

I. INTRODUCTION

EPILEPSY is a neurological disorder characterized by the occurrence of a spontaneous seizure, a period when neuron population fires in an abnormal, excessive, and synchronized manner [1], [2]. In clinical, the main characteristics for diagnosis of epilepsy are occurring the seizure-like spike-and-wave and high-frequency oscillations [3]. Electroencephalogram (EEG), stereo electroencephalogram (sEEG), and intracranial electroencephalogram (iEEG) are the main techniques for monitoring seizures [4], [5], [6].

Recently, various therapies have been developed for treating and controlling seizures, including anti-epilepsy medication, surgical extraction, and electrical neurostimulation [7], [8], [9], [10]. Electrical neurostimulation, such as deep brain stimulation (DBS) and transcranial electrical stimulation (TES), has become a considerable clinical treatment for intractable epilepsy [9], [11], [12]. Electrical neurostimulation applies a minuscule dose of high-frequency electric current to a brain region, such as a cortex area, vagus nerve, or anterior nucleus of thalamus [13]. This electrical stimulation aims at modulating the neural oscillations and thus controlling the seizure states [9].

However, the current neuromodulations mainly implement the pre-determined actuation strategies rather than a closed-loop electrical neurostimulation in epilepsy. Traditional deep brain stimulation and neurostimulator paradigms are designed with empirical open-loop approaches, lacking of theoretical supports or guarantees [14], [15]. The major disadvantages of open-loop neurostimulation is the missing of the feedback signals from the real-time seizure waves for adjusting the control input during neurostimulation [10]. More recently, closed-loop mechanisms is increasingly gaining attention for seizure suppression [9], [10], [16], [17]. Formatting it as a closed-loop state-space control problem, the main goal then is to design an optimal control law to steer the system state to the desired state. Some previous work have been devoted to this area. For example, Sérgio Pequito et al. presented a spectral control method for ensuring the poles of the closed-loop systems is in the pre-specified spectrum [18]. Arian Ashourvan et al. proposed a pole-placement spectral static output feedback control-theoretic strategy for linear time-invariant switching systems for seizure stabilizing [19]. Model predictive control (MPC) is a self-tuning control method, allowing to maintain a stable and robust control process, which has been brought into neurostimulation applications. For instance, Siyuan Chang et al. presented a nonlinear auto-regressive moving-average (NARMA) Volterra model to identify the relationship between the external input and the corresponding neuronal responses such as synthetic seizure-like waves, where the closed-loop MPC actuation strategy was implemented to optimize the stimulator’s waveform [20]. Sarthak Chatterjee et al. proposed a fractional-order model predictive control framework for real-time closed-loop electrical neurostimulation in epilepsy [21]. However, the MPC requires an accurate and low-complexity model to predict the system dynamics, which is particularly challenging for seizure dynamics.

Seizure dynamics is a complex networked nonlinear dynamic process [22], [23], [24], on which we have limited knowledge so far. Therefore, system identification is crucial for uncovering the brain system dynamics during seizure period, also for seizure classification and detection [25], [26]. Some tools are available for modeling the seizure system dynamics using time-series EEG data. For example, auto-regressive moving-average model [20] and fractional-order system model [21] have been applied for seizure dynamics identification. With the advances of machine learning methods, data-driven models based on neural networks have shown...
great potentials as system identification tools [27], [28], [29], [30], [31]. For instance, recurrent neural networks (RNNs) are promising in fitting time-series data and modeling dynamical systems. Some studies have reported that RNN has high capability and scalability in modeling complex dynamics with multi-outputs, such as fluidic flow control [31] and process industries [29]. However, most RNN models are complex and not easy to integrate into MPC to solve the optimization problem.

For ethical reasons, it is difficult to directly collect input-output data of patients with epilepsy. Therefore, using computational dynamic models to model and generate neural dynamics is very important for the verification of control strategies [32], [33]. A large number of dynamic models have been proposed to simulate neurodynamics in health or epilepsy, from the microscopic level [23] to the macroscopic level [22], [34], [35], [36]. For instance, a well-known phase oscillator, Kuramoto model, is used to synthesize the fMRI phase dynamics series [35], and even used to study the cognitive process [37], [38]. A focal epileptic network dynamic model based on scale-free network connectivity is used to simulate spontaneous epilepsy dynamics [36]. Jansen-Rit model as a macroscopic cortical column-level neural mass model (NMM), accounts for three populations of cells dynamical interactions (i.e., excitatory, inhibitory, and pyramidal neuron populations) [39]. A good epileptic model should reflect the neurophysiological mechanism of seizures. In this way, by varying the parameters, the model can generate neural activity in healthy or seizure conditions. For example, the bifurcation parameters in NMM control the critical point which reflects the transitions between stable and unstable states. The average excitatory synaptic gain parameter in Jansen-Rit model manipulates the dynamic pattern of healthy EEG and epilepsy [39].

Technically, when modeling seizure dynamics and designing a controller for seizure suppression, it is necessary to consider the trade-off between model complexity and computational efficiency. The real-time optimal solution of a nonlinear complex dynamics model in MPC is hard to obtain. In order to solve this problem, operator-theoretic approaches, mainly based on the Perron-Frobenius operator [40] or its adjoint Koopman-operator, are increasingly gaining attention. In particular, Koopman theory points out that under the assumption that the linear operator acts on the observation function of system states over time, a nonlinear dynamical system can be linearized [41]. However, the pre-defined hand-crafted Koopman-operator model has limited performance in modeling time-varying or complex switching dynamical systems. Therefore, a more flexible method is needed to approximate Koopman operators with finite dimensions. Recently, using autoencoders to approximate finite-dimensional Koopman operator has been proposed [42], [43]. After using the Koopman-operator method to convert a nonlinear MPC problem to a linear MPC problem, the linear MPC problem can be easily solved by a quadratic programming solver.

Here, we propose a deep Koopman-operator based model predictive control (Koopman-MPC) framework for closed-loop seizure suppression in a real-time manner, which can balance the needs of sufficient predictive accuracy and model complexity for real-time optimization. The contributions of this study are summarized as follows.

- We propose a Koopman-MPC framework (Sec. II) to map the nonlinear neural dynamics into finite-dimensional linear dynamics using a deep Koopman-operator based model, which is computationally efficient and naturally compatible with the optimization-based MPC design for seizure suppression.
- A tailored autoencoder architecture is employed to automatically learn, rather than to hand-crafted design, the Koopman operator (Sec. III). Our experimental results suggest that the deep Koopman model outperforms the RNN model in seizure prediction. The ablation study validate that the loss terms are necessary and sufficient for learning the invariant linear subspace (linear property) with high prediction accuracy (Sec. IV-C & IV-D).
- We verify the closed-loop optimal control policy using our deep Koopman-MPC framework with a virtual platform based on Jansen-Rit model. The results suggest that Koopman-MPC can successfully suppress seizures from one region as well as seizures propagated between two distant brain regions (Sec. IV-E).

II. Method

In this section, we first introduce the Koopman operator theory and its linear superposition relation to the linear forced dynamical systems. Subsequently, we introduce the Koopman-operator based model predictive control for obtaining the optimal control series over the Koopman observations.

A. Koopman operator

A nonlinear discrete-time dynamical system satisfies

\[ x_{i+1} = f(x_i), \]

where \( x_i \in \mathbb{R}^n \) denotes the vector of state variables at time \( i \) and the function \( f(\cdot) \) governs nonlinear dynamics of the system.

Koopman theory states that there exists an infinite-dimensional linear operator \( K \) acting on an infinite dimensional function space such that all observation functions \( g(\cdot) \) satisfy an advancing forward linear relation, as

\[ g(x_{i+1}) = Kg(x_i). \]

One essential question on Koopman theory is how to design (or to learn) the nonlinear embedding function \( g(\cdot) \) which allows to transform a nonlinear system into a linear dynamical system. A variety of methods have been proposed to design the embedding function \( g(\cdot) \), such as using extended dynamic mode decomposition [44], [45] and auto-encoder [42], [43]. For instance, extended dynamic mode decomposition as a data-driven method allows arbitrary composition of basis functions of nonlinear dynamics, which has been commonly used for numerical approximation of the Koopman operator \( K \) [44]. Then, by a finite-dimensional approximation of the Koopman operator, an invariant subspace or a set of basis functions can be learned.
Given a finite sequence of system measurements \( y_i = m(x_i) \) with \( i \) as the time step \( (i = 1, \ldots, n, n + 1) \) and a finite set of basis functions \( \Phi_1, \Phi_2, \ldots, \Phi_k \) constituting a basis function vector \( \Phi = [\Phi_1, \Phi_2, \ldots, \Phi_k]^T \), we can embed the data into the basis function vector and construct two feature spaces,

\[
\Psi_Y = [\Phi(y_1) \quad \Phi(y_2) \ldots \quad \Phi(y_n)] \quad \Psi_{\hat{Y}} = [\Phi(\hat{y}_1) \quad \Phi(\hat{y}_2) \ldots \quad \Phi(\hat{y}_n)]
\]

where \( \hat{y}_i = y_{i+1} \). Then the finite-dimensional approximation of the Koopman-operator \( \tilde{K} \in \mathbb{R}^{k \times k} \) can be inferred from

\[
\tilde{K} = \Psi_{\hat{Y}} \Psi_Y^T
\]

where \( \Psi_Y^T \) is the pseudo-inverse of \( \Psi_Y \).

Modal decomposition for Koopman operator \( K \) refers to spectral analysis \cite{46}, in which its modes and eigenvalues-eigenvector pairs characterize the complex linearly independent spatiotemporal dynamical behaviours. The complex eigenvalues of \( K \) characterize the system stability, exponential damping ratio and spectral information, and the eigenvectors represent the independent spatial coordinates. This linear operator \( K \) can be used for the prediction and control of system dynamics.

The linear dynamical systems satisfy linear superposition principle. Thus, we extend the approximated Koopman operator-based linear dynamical system into a linear forced control dynamical system with the following state forward evolution equation:

\[
\Phi(x_{i+1}) = \tilde{K}\Phi(x_i) + Bu_i.
\]

where \( B \in \mathbb{R}^{k \times n} \) is the gain vector for selecting the control nodes and \( u_i \in \mathbb{R}^{n \times 1} \) is an \( n \)-dimensional input in system at time \( i \). In this study, a network based basis function \( g(\cdot) \) is learned to replace the hand-crafted feature vector.

**B. Koopman-MPC framework**

Model predictive control is an optimization-based control framework to minimize the control objective function in a finite prediction horizon with the control inputs and states constraints. For a nonlinear dynamical system, the optimization problem is typically a non-convex problem with NP-hard computational complexity.

The predictive capabilities and linearity of the Koopman operator benefit the controller design in nonlinear systems. Therefore, we construct a Koopman-operator based model predictive control architecture to control the nonlinear system following the desired reference signals, as shown in Fig. 1(a).

At each time-step, the model predictive controller solves the following objective function to find a sequence of incremental inputs \( \Delta u_k \) and only the first incremental input \( \Delta u_1 \) will be applied to the system.

\[
\begin{align*}
\min_{u} & \quad \frac{1}{T_p} \sum_{i=1}^{T_p} (Y_i - Y_{ref})^T Q_Y (Y_i - Y_{ref}) + Q_u \sum_{i=1}^{T_p} \Delta u_i^2 \\
\text{s.t.} & \quad \Delta u_i \in [\Delta u_{min}, \Delta u_{max}] \\
& \quad u_i \in [u_{min}, u_{max}] \\
& \quad Y_{i+1} = \tilde{K}Y_i + Bu_i
\end{align*}
\]

where \( T_p \) and \( T_c \) are the predictive horizon and control horizon, respectively. \( Y_i \in \mathbb{R}^{k \times 1} \) and \( Y_{ref} \in \mathbb{R}^{k \times 1} \) represent the Koopman basis function of the observation and reference signals, respectively. \( \Delta u_i \in \mathbb{R}^{n \times 1} \) (\( n \) is the number of system inputs) is the increment of input at step \( i \). \( Q_Y \in \mathbb{R}^{k \times k} \) is the positive definite weighted matrix for penalizing the deviance and \( Q_u \in \mathbb{R}^{n \times n} \) is a non-negative scalar to penalize the amplitudes of control incremental inputs and tune the desired closed-loop control performance. For real applications, the inputs are constrained between the upper bound and lower bound. \( Y_{i+1} = \tilde{K}Y_i + Bu_i \) predicts the following states in the predictive horizon. \( \tilde{K} \) is the approximated unforced Koopman-operator when there are no inputs or the forced Koopman-operator when giving input signals. \( B \in \mathbb{R}^{k \times n} \) is designed by the researcher to determine the control gain in corresponding latent controlled nodes. This optimization problem can be solved efficiently with the quadratic programming solver. In this study, the input signal is constrained between -25 to 0 and the increment of it is constrained between -20 to 0. \( Q_Y \) is set to an identity matrix. \( Q_u \) equals 0.01.

**III. DEEP KOOPMAN-OPERATOR MODEL**

For learning the finite-dimensional invariant subspace to approximate the Koopman-operator, we construct an autoencoder framework, similar to the previous work \cite{42}, \cite{43}, but different model hidden structure and loss function, to span a low dimensional state space of the observed seizure dynamics into a finite high dimensional state space. The deep Koopman-operator model is shown in Fig. 1(b). Specifically, the encoder learns the linear mapping relationship (a finite-dimensional approximated Koopman-operator) between one prior step and the current step of the sequential seizure waves. Then, we decode the spanning data and its predicted data into the original state space for reconstruction.
A. Seizure Dynamic Encode-Decode in an Autoencoder Architecture

It can be seen in Fig.1(b) that there are two parts for constructing the autoencoder: encoder $g$ and decoder $g^{-1}$. The deep Koopman Autoencoder model parameter is shown in Table IV. As an initial framework, the model’s structure in both the encoder and decoder contain one hidden dense connected layer followed by a rectified linear unit activation function and an output dense connected layer. As shown in Fig.1(b), the inputs to the encoder are pieces of epilepsy signals $X$, $Y$, and $Z$ that are constructed with a sequence of time snapshots. The encoder $g$ produces the high dimensional matrices $\tilde{X}$, $\tilde{Y}$, and $\tilde{Z}$ as

$$\tilde{X} = g(X), \quad \tilde{Y} = g(Y), \quad \tilde{Z} = g(Z)$$

Then, the the Koopman-operator $\tilde{K}$ was approximated by a linear least-squares fit between $\tilde{X}$ and $\tilde{Y}$.

$$\tilde{Y} \approx \tilde{K}\tilde{X}$$

Using the Koopman operator, $\tilde{Y}_{pred}$ and $\tilde{Z}_{pred}$ are computed as

$$\tilde{Y}_{pred} = \tilde{K}\tilde{X}, \quad \tilde{Z}_{pred} = \tilde{K}^{T}\tilde{Y}$$

where $T_p$ is the number of forward step.

Finally, the $\tilde{X}$, $\tilde{Y}$, and $\tilde{Z}$ are the decoded signals from $\tilde{X}$, $\tilde{Y}_{pred}$, and $\tilde{Z}_{pred}$ with

$$\hat{X} = g^{-1}(\tilde{X}), \quad \hat{Y} = g^{-1}(\tilde{Y}), \quad \hat{Z} = g^{-1}(\tilde{Z}).$$

B. Explicit Loss Definition

The objective of the deep Koopman operator based autoencoder is to learn a finite invariant subspace that approximated the Koopman operator. The loss is specifically designed with different theoretical considerations for learning the finite-dimensional approximated Koopman-operator and building the linear dynamical system. In summary, the explicit loss function for training the autoencoder based deep Koopman-operator model covers the following four reconstruction error terms using Mean-squared error (MSE).

(1) Reconstruction error of $X$:

$$L_{\text{recon}} = \|X - g^{-1}(g(X))\|_2^2 = \|X - \hat{X}\|_2^2$$

(2) Prediction Loss of $Y$:

$$L_{Y_{\text{pred}}} = \|Y - g^{-1}(\tilde{K}g(X))\|_2^2 = \|Y - \hat{Y}\|_2^2$$

(3) $T_p$-step Prediction Loss of $Z$:

$$L_{Z_{\text{pred}}} = \|Z - g^{-1}(\tilde{K}^{T_p}g(X))\|_2^2 = \|Z - \hat{Z}\|_2^2$$

(4) Linear Dynamics Reconstruction Loss:

$$L_{\text{lin}} = \|g(Y) - \tilde{K}g(X)\|_2^2 = \|\hat{Y} - \tilde{K}\hat{X}\|_2^2$$

Meanwhile, we add the $L_2$ regularization term of the weights $W$ to avoid overfitting. The total loss function is defined as

$$L = L_{\text{recon}} + L_{Y_{\text{pred}}} + L_{Z_{\text{pred}}} + L_{\text{lin}} + \alpha \|W\|_2^2$$

The matrix $\tilde{K}$ represents the approximated Koopman-operator. $T_p$ represents the predictive length. $g$ and $g^{-1}$ are the encoder and decoder expression, respectively. We set the hyperparameter $\alpha = 0.01$ by default.

To sum up, our proposed Deep Koopman-operator model aims to learn the invariant linear subspace for further seizure prediction and seizure stimulation strategy design.

C. Training Details

The deep Koopman operator model is implemented by the keras framework with tensorflow as the backend. The optimizer adopts Adam optimizer with learning rate 0.001. The batch size, as the length of time series, equals 100. The training epoch equals to 200. The deep Koopman operator model included two parts: a dense connected encoder and a dense connected decoder. The encoder tries to upsample the input signals into a high dimensional space which satisfies advancing forward linear relation, while the decoder is used to reconstruct the original signal and the forwarding signal from the high dimensional space.

IV. EXPERIMENTS AND RESULTS

A. Datasets

We validate the deep Koopman-operator based MPC model for seizure suppression using synthetic data from a single cortical column and two distant cortical columns. All synthetic EEG data are generated by a well-known computational dynamical model, i.e. the Jansen-Rit model [39].

In the past two decades, dynamical models have become a popular method to model neurological disorders (e.g. epilepsy) from the microscopic level [23] to the macroscopic level [22], [34]. The neural mass model (NMM) simulates the neural signals from a cortical column at the macroscopic level, with excitatory population, inhibitory populations and pyramidal cells interaction [39]. As a specific neural mass model, the Jansen-Rit model uses six dynamical equations to describe a cortical column’s average neural activities, including a population of pyramidal cells, the excitatory feedback interneurons and the inhibitory feedback interneurons [39]. The dynamical system of the Jansen-Rit model is in Eq. (24).

The detailed information about the Jansen-Rit model is shown in the Appendix A. The parameters setting for Jansen-Rit NMM is shown in Table II. These values were originally specified by Van Rotterdam et al. [47]. In our simulation, we keep the above parameters fixed and vary the excitatory synaptic gain $A$ (i.e., a bifurcation parameter). The model generates normal state EEG waves when $A$ equals 7, and it generates seizure-like waves with $A$ larger than the critical value (around 7.2115). We display three types of synthetic EEG signal with different excitatory synaptic gain ($A \in \{7.0, 7.2115, 7.80\}$) in
B. Baseline Models

The baseline models are introduced for making comparison towards the proposed model with prediction accuracy and calculation efficiency. The baseline models mainly included two types: 1) RNN based system identification; 2) Ablation analysis about the explicit loss definition. The network architecture in ablation analysis is maintained.

1) Recurrent Neural Network for System Identification: An RNN-based model models a discrete-time dynamical process with a sequence of multi-step ahead predictions in a concatenating form, as shown in Fig. 2. We employed a Gated Recurrent Unit (GRU), a variant of Long Short-Term Memory (LSTM), as the RNN structure [48]. An additional dense layer was trained for capturing the mapping relationship between the previous input/output signals and the initial states of GRU. Also, another dense layer was trained for mapping the GRU states to output signals. The GRU model parameter is shown in Table V.

As an identification model in the MPC built-in process, the GRU can be written in the following explicit expression,

\[
\begin{align*}
    z_k &= \text{hard\_sigmoid}(W^z_i y_k + W^z_x x_k + b^z) \\
    r_k &= \text{hard\_sigmoid}(W^r_i y_k + W^r_x x_k + b^r) \\
    h_k &= \tanh(W^h_i y_k + W^h_x (r_k \circ x_k) + b^h) \\
    x_{k+1} &= z_k \circ x_k + (1 - z_k) \circ h_k
\end{align*}
\]

where \( W^z_i, W^z_x, W^h_i \) represent the input weights, \( W^z_x, W^r_x, W^h_x \) represent the recurrent weights and \( b^z, b^r, b^h \) denote bias in the corresponding gates. The symbol \( \circ \) denotes element-wise multiplication.

2) Explicit loss definition without \( L_{\text{recon}} \): \( L_{\text{recon}} \) is the loss term for reconstruction of the input signal \( X \). The objective of baseline model 2 is

\[
L_2 = L_{\text{Ypred}} + L_{\text{zpred}} + L_{\text{lin}} + \alpha \| W \|_2^2
\]

3) Explicit loss definition without \( L_{\text{Ypred}} \): \( L_{\text{Ypred}} \) characterizes one-step prediction. The objective of baseline model 3 is

\[
L_3 = L_{\text{recon}} + L_{\text{zpred}} + L_{\text{lin}} + \alpha \| W \|_2^2
\]

4) Explicit loss definition without \( L_{\text{zpred}} \): \( L_{\text{zpred}} \) characterizes \( T_{\text{pred}} \)-step prediction. The objective of baseline model 4 is

\[
L_4 = L_{\text{recon}} + L_{\text{Ypred}} + L_{\text{lin}} + \alpha \| W \|_2^2
\]

5) Explicit loss definition without \( L_{\text{lin}} \): \( L_{\text{lin}} \) maintain the linear relation between the neighbor sample in high dimensional space. The objective of baseline model 5 is

\[
L_5 = L_{\text{recon}} + L_{\text{Ypred}} + L_{\text{zpred}} + \alpha \| W \|_2^2
\]

C. Seizure dynamic prediction

In order to choose the best prediction model and validate the importance of each loss term, we conducted experiments to test the capability of baseline models and the Deep Koopman-operator model in seizure prediction in two cases: 1) the seizure-like wave is focused on a single cortical column; 2) the seizure waves propagate between two cortical columns. To evaluate the prediction accuracy of the listed model above on validation datasets, we introduce two quantitative metrics: the Mean-Squared-Error (MSE) and the R-Square (R^2). The MSE metric quantifies the ability of the model in time series prediction with forward \( T_{\text{pred}} \) steps while the R-Square quantifies the fitting performance.

\[
\text{MSE} = \frac{1}{T_{\text{pred}}} \sum_{k=1}^{T_{\text{pred}}} \| y_k - \hat{y}_k \|_2^2
\]

\[
R^2 = 1 - \frac{\sum_{k=1}^{T_{\text{pred}}} (y_k - \hat{y}_k)^2}{\sum_{k=1}^{T_{\text{pred}}} (y_k - \bar{y})^2}
\]

where \( y_k \) is the ground truth seizure series, \( \hat{y}_k \) is the predictive results from the model, and \( \bar{y} \) is the mean value of the ground truth. \( T_{\text{pred}} \) is the predictive length.

The deep Koopman-operator based model maps the states to an invariant subspace and derives the approximated Koopman operator \( \hat{K} \) in this invariant subspace. The results of the predictive evaluation from Koopman model are shown in...
Fig. 3. The synthetic EEG waves from the Jansen-Rit model with a single cortical column. Specifically, (a) $A = 7.0$ corresponds to the normal EEG state; (b) $A = 7.2115$ represents the transition state where the seizure emerges; (c) $A = 7.80$ are epileptic states; (d) the predicted seizure-like EEG wave in single cortical column using the deep Koopman-operator method. The excitatory synaptic gain is $A = 7.80$. The Koopman-operator is updated every 20 steps.

Fig. 4. Seizure-like EEG waves in two cortical columns: (a) the simulated seizure-like EEG waves using the Jansen-Rit model; (b) the predicted EEG dynamics using the deep Koopman-operator method. The excitatory synaptic gain $A = 7.80$ in Cortical 1 (upper) and $A = 7.00$ in Cortical 2 (bottom). The Koopman-operator is updated every 10 steps.

D. Spectral Analysis of the Approximated Koopman Operator

To further explore the frequency characteristics of the learned approximated Koopman Operator, we perform spectral analysis. We mainly make a comparison of the power spectral density (PSD) between prediction signal and the original ground truth signal. The PSD mainly reflects the features in frequency domain.

Fig. 6 plots the power spectral density of the ground truth and prediction in both cases. The results state that the deep Koopman-operator based model can capture a large range of frequency features (1-20Hz) of the seizure dynamics.

E. MPC-based Seizure Suppression

Generally, the Koopman-operator based predictive model hardly tracks the seizure dynamics for a long period. Therefore, our proposed Koopman-MPC model is designed to

| TABLE I | MODEL COMPARISONS FOR SEIZURE PREDICTION |
|------------------------|------------------------------------------|
| Case                  | Model        | MSE           | $R^2$          |
| Single column         | GRU          | 6.2555±0.0000 | 0.8502±0.0000 |
|                       | model 2      | 0.9252±0.0074 | 0.9818±0.0074 |
|                       | model 3      | 0.7869±0.0032 | 0.9845±0.0032 |
|                       | model 4      | 10.8618±0.0484| 0.7867±0.0484 |
|                       | model 5      | 0.7876±0.0013 | 0.9845±0.0013 |
|                       | Koopman      | 0.7183±0.0061 | 0.9858±0.0061 |

Double columns

| Case                  | Model        | MSE           | $R^2$          |
|-----------------------|--------------|---------------|---------------|
|                       | GRU          | 5.0832±0.0000 | 0.8589±0.0000 |
|                       | model 2      | 2.5146±0.0428 | 0.9710±0.0428 |
|                       | model 3      | 4.3009±0.0538 | 0.8603±0.0538 |
|                       | model 4      | 4.3528±0.0243 | 0.8747±0.0243 |
|                       | model 5      | 2.6686±0.0353 | 0.9103±0.0353 |
|                       | Koopman      | 0.6932±0.0446 | 0.9753±0.0446 |
periodically re-calculate the approximated Koopman operator, estimate the corresponding predictions, and then re-compute the optimal neurostimulation strategy.

We conducted experiments to test the Koopman-MPC performance of seizure suppression in two cases. Specifically, we collect the input and output data with a 50Hz sampling frequency. We use a 15-step predictive horizon and 15-step control horizon to calculate the optimal seizure stimulation signals.

Fig. 7 illustrates the suppressed seizure in EEG signals and the corresponding control signal designed by the Koopman-MPC controller. In each experiment, the control signal starts to insert into the model at $t = 4s$. It is obvious that the actuation signals is also activated at the 4s during the simulation. These results demonstrate that our Koopman-MPC can accurately predict the seizure signal and achieve a successful seizure suppression.

V. DISCUSSION

Here we propose a novel deep Koopman-MPC framework for closed-loop electrical neurostimulation. A tailored autoencoder was employed to learn the invariant subspace of the Koopman operator, in which a coordinate transformation maps the nonlinear dynamics into the linear dynamics. The approximation of the Koopman operator provides a sufficient prediction horizon in seizure prediction, which can be integrated into the MPC controller for seizure suppression. Notably, although the Koopman-MPC framework is motivated by neurostimulation strategy in seizure suppression, it is of broader interest and suitable for other feedback control applications, such as flow control.

1) Prediction and Control for Seizure Dynamics: The seizure dynamical system is a black-box. System identification techniques are beneficial for the prediction and modeling of seizure dynamics and contribute to optimizing neurostimulation strategy in model-based seizure suppression. However, uncovering the system dynamics has to consider both the accuracy and the model complexity. The latter property is particularly important when combines with a MPC to solve an optimization problem in real-time. In this study, we made a quantitative comparison of prediction accuracy between our proposed Koopman model and the GRU model with the same number of hidden units. We also make ablation analysis towards the introduced loss terms. The results suggest that our proposed Koopman model outperforms the GRU model in terms of prediction performance (Table I) and verify that the introduced loss terms exists important physical meaning for learning the Koopman operator. One possible reason is that deep Koopman model learns its invariant subspace and captures sufficient nonlinear patterns in its hidden layers for seizure prediction. More importantly, another merit of the Koopman model is its linear property which greatly facilitates the optimization in MPC control and provides a unique optimal solution. In contrast, the GRU-MPC model failed to converge and could not achieve an optimal control policy in our experiments. In fact, it is most likely a trade-off between model complexity and computational efficiency when designing models for real-time control. A higher-order complex model might better identify the system, but it is computationally expensive in optimization. Along this line, a significant advantage of the Koopman-MPC model is that it uses a finite dimensional approximated Koopman-operator model for linear optimal control, and balances the accuracy (Table I) and computational efficiency in convex optimization (Fig. 7). However, the brain is a complex coupled networked
dynamic system. Balancing speed and accuracy in the computational model of the brain network is one of the challenges, and it will further drive the development of control theory. For instance, controlling the complex network in the brain calls for layered dynamical network models and network control theory. In return, the development of control theory would provide new tools for neurostimulation, including the selection of the optimal targeted stimulation regions, the robustness and safety of stimulation protocols.

2) Limitations and future works: It is worthy to mention the limitations of our work. First, due to ethical reasons, it is almost impossible to collect input-output data from epilepsy patients as a biological experiment. Thus, we used the Jansen-Rit model to simulate the EEG data and ran MPC experiments based on this simulation platform. The Jansen-Rit model seems to generate seizure-like waves with a fixed pattern (Fig. 2), which is far away from a real case. Other computational dynamical models have also been proposed as neural data generators [32, 33]. Developing a reliable simulation platform to generate the seizure-like waves with the preictal, ictal and postictal processes, is an important future direction. Second, our proposed deep Koopman-operator based model allows to predict seizure waves, but it cannot identify the probability of seizure occurrence. Integrating a probabilistic seizure prediction and classification model into our model might improve neurostimulation outcome. Moreover, the decomposition of the Koopman-operator could reflect the spectral information about the system dynamics [46], which can be applied to investigate the spectral properties of EEG and seizure dynamics in the future. Our next goal is to improve the interpretability of deep Koopman-operator model. To this end, it is also necessary to consider the physical intuitions and neuroscience insights from asymptotic theory and spectral information perspective when designing the model structure, the dimension of the embedding space, the objective function and constraints [49].

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APPENDIX

A. EEG synthesis with Jansen-Rit Model

The Jansen-Rit model was originally proposed by Jansen and Rit in 1995 for studying the cortical column [39]. It is a neural population model of a local cortical circuit. In particular, the model consists of three subpopulations, the pyramidal neurons, the excitatory feedback interneurons and the inhibitory feedback interneurons. The dynamics between these three neuronal populations reflect the feedback loop in a single cortical area of the human brain [39]. Dynamics in larger brain area could be modelled by a multiple area model composed of multiple neural masses.

As shown in Figure 8 a neural mass model has two main quantities, the average pulse densities and the average membrane potential. The average pulse densities typically result from external stimuli and stimuli produced by other neural masses. Each input to the neural mass will be converted from an average pulse density to a potential via a Post Synaptic Potential function (PSP). In particular, excitatory post synaptic potential (EPSP) function is specifically designed for the conversion of input pulses from the excitatory interneurons, while inhibitory synaptic potential (IPSP) function is designed for the conversion of input pulses from the inhibitory interneurons. Each of these potentials is then scaled by a certain constant $C$ representing the average number of synapses receiving the stimuli. After summing up all excitatory potentials and subtracting all inhibitory potentials, we obtain the average membrane potential $u$. Finally, a sigmoid function is used to transform the $u$ to average pulse rate.

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In the Jansen-Rit model, the PSP function is given by the solution of the second order differential equation,

$$\begin{align*}
\frac{du}{dt} &= y \\
\frac{dy}{dt} &= Qyz + 2qy - q^2u.
\end{align*}$$

Here the input variable $z(t)$ represents the average pulse density (or firing rate) and $x(t)$ is the output of the PSP function. Fortunately, the solutions of this set of ordinary differential equation have closed analytic form and are referred to as the excitatory transfer function $h_t(t) = Bae^{-at}$ and the inhibitory transfer function $h_i(t) = Bbte^{-bt}$. Here the
amplitudes $A$ and $B$ denote the average synaptic gains, while the phase coefficients $a$ and $b$ represents the average time constants. The potential-to-rate function converts the average membrane potential to the average pulse density, and is usually taken to be a non-decreasing function converged to zero as $u \rightarrow -\infty$ and bounded from above. A common choice is the Sigmoid function $S(v) = \frac{2v_0}{1 + e^{-v/v_0}}$, where $2v_0$ represents the maximum firing rate, $v_0$ is the post-synaptic potential equal to half of the maximum firing rate, and $r$ is the steepness of the sigmoid function. Combining the above components, the Jansen-Rit model is given by the following dynamical system (for single cortical column).

1) Single Cortical Column Jansen Rit Model:

$$
\begin{align*}
\dot{y}_1 &= y_4 \\
y_1 &= AaS(y_2 - y_3) - 2ay_4 - a^2y_1 \\
y_2 &= y_5 + d(t) \\
y_3 &= Aa(p + C_2S(C_1y_1)) - 2ay_5 - a^2y_2 \\
y_4 &= y_6 \\
y_6 &= BbC_4S(C_3y_1) - 2by_6 - b^2y_3 \\
y_0 &= y_3 \\
y_3 &= AnS(y_1 - y_2) - 2ay_3 - a^2y_0 \\
y_1 &= y_4 \\
y_4 &= Aa(p + C_2S(C_1y_0) + K_2y_1) - 2ay_4 - a^2y_1 \\
y_2 &= y_5 \\
y_5 &= BbC_4S(C_3y_0) - 2by_5 - b^2y_2 \\
y_6 &= y_9 \\
y_9 &= A'aS(y_7 - y_8) - 2ay_9 - a^2y_6 \\
y_7 &= y_{10} \\
y_{10} &= A'a(p' + C_2'S(C_1'y_6) + K_1y_{12}) - 2ay_{10} - a^2y_7 \\
y_8 &= y_{11} \\
y_{11} &= B'bC_4'S(C_3'y_0) - 2by_{11} - b^2y_2(t) \\
y_{12} &= y_{14} \\
y_{14} &= A'aqS(y_1 - y_2) - 2ay_{14} - a^2y_{12} \\
y_{13} &= y_{15} \\
y_{15} &= A'aqS(y_7 - y_8) - 2ay_{15} - a^2y_{13} \\
\end{align*}
$$

![Diagram of two interactive cortical columns](image)

The experiment parameters for the double cortical column Jansen-Rit Model are provided in the table below. We can change them according to the target column we preferred.

### Table II

| Parameters for Single Cortical Column Jansen-Rit Model |
|--------------------------------------------------------|
| Parameters | Description | Values |
| $A$       | Average excitatory synaptic gain | 7.8 mV |
| $B$       | Average inhibitory synaptic gain | 22 mV |
| $\alpha$ | Reciprocal of excitatory time constant | 100 Hz |
| $b$       | Reciprocal of inhibitory time constant | 30 Hz |
| $v_0$     | Potential at half of the maximum firing rate of Sigmoid function | 6 mV |
| $r$       | Steepness of Sigmoid function | 0.56 mV |
| $e_0$     | Half of the maximum firing rate of Sigmoid function | 2.5 Hz |

### Table III

| Parameters for Double Cortical Columns Jansen-Rit Model |
|--------------------------------------------------------|
| Parameters | Description | Values |
| $A$       | Average excitatory synaptic gain | 7.8 mV |
| $B'$      | Average inhibitory synaptic gain | 22 mV |
| $C_1$     | Average synaptic connectivity | 135 |
| $C_2$     | Average synaptic connectivity | 108 |
| $C_3$     | Average synaptic connectivity | 33.75 |
| $C_4$     | Average synaptic connectivity | 33.75 |

### Table IV

| Parameters for Koopman-operator based Autoencoder |
|---------------------------------------------------|
| Parameters | Description | Values |
| $T$       | Time length of the input metrics | 60 |
| $H_1$     | Units of hidden layer in the encoder network | 60 |
| $H_2$     | Units of hidden layer in the decoder network | 60 |
| $LR$      | Learning rate | 0.001 |
| $F$       | Data sampling rate | 50 Hz |
| $T_p$     | Time length of the prediction | 20 |

### Table V

| Parameters for GRU Model |
|--------------------------|
| Parameters | Description | Values |
| $M$       | Number of previous inputs | 24 |
| $N$       | Number of previous outputs | 25 |
| $T_p$     | Prediction length | 175 |
| $F$       | Data sampling rate | 50 Hz |
| $B$       | Batch size | 30 |
| $U$       | Units of hidden layer in initial neural network | 60 |
| $U_2$     | Units of hidden layer in output neural network | 60 |
| $U_3$     | Units of GRU cells in one column prediction | 60 |
| $U_4$     | Units of GRU cells in two column prediction | 60 |

The deep Koopman-operator based autoencoder consists of an encoder, a linear transformation layer, and a decoder. The parameters are summarized in the following table.

![Diagram of two interactive cortical columns](image)