Functional Connectivity Prediction with Deep Learning for Graph Transformation- Supplementary material

I. Discussion

Review of main results

For all three evaluation metrics, our proposed SF-GAN methods under different settings outperformed all of the comparison methods and the Baseline. The next best performer after our proposed SF-GAN was the Baseline method, which leveraged deep learning for this graph translation task, outperforming the other comparison methods by a clear margin on both datasets. These results indicate the effectiveness and excellent potential for using deep learning based models to address the structural-to-functional connectivity mapping problem. Deep learning models have exhibited their outstanding capability for complex pattern characterization, primarily due to their ability to fit any complex function based on the neural network Universal Approximation Theory [1]. In terms of efficiency, deep learning based models, including the new SF-GAN methods proposed here and the Baseline method require relatively lengthy training times but similar prediction runtimes comparing to other methods. The training times needed by the deep learning based methods for all the training data in each dataset used here was around 1.5 minutes, which is still both efficient and practical. Furthermore, the results of scalability experiments demonstrate that the training time is not sensitive to either the density of the structural and functional connectivity or the number of meta-features, although it is linear to the number of training samples. Therefore, in general, the proposed methods are scalable in the above settings. Using meta features corresponding to the subjects under study through node embedding improve the metrics in both of the datasets examined. Analyzing the performance with respect to the way meta-features are used in the three settings revealed that the first setting requires all the ROIs (regions of interest) to be influenced identically by the meta-features, for the second all the ROIs must be influenced independently by the meta-features, and the third one encompasses both totally identical and completely independent conditions. The performances achieved under these various settings look very similar to each other, though Setting 1 has some advantages for Dataset 2. This might be due to requiring fewer learning parameters, which could lead to better generalizability to the test set data. Also the fact that Setting 3 outperforms Setting 1, for this dataset, supports this assumption, as Setting 3 may enjoy better generalizability due to its group sparsity regularization (although weaker than Setting 1).

Why do SF-GAN and Baseline outperform the other methods?

Compared with the proposed deep learning-based SF-GAN, existing methods are typically based on much stronger, progressive assumptions and heuristics regarding the brain's dynamic processes [2]. For example, many of the methods assume the mapping from structural to functional connectivity is based on a graph diffusion process which is homogeneous (the parameters across different ROIs are the same) and stationary (the parameters do not change in time) [3]. Although these assumptions reduce the model complexity considerably, they are also likely to under-estimate the complexity of the network dynamic patterns and the relationship between structural and functional connectivity. For example, [4] argued that the relation might be nonstationary while [5] suggested that it might not be linear. Unlike these earlier studies, the proposed SF-GAN and the Baseline model are both end-to-end frameworks that rely on better model expressiveness and thus require far fewer assumptions. This model capability brings advantage over comparison methods in several aspects. First, while existing models usually assign the same parameter for different ROIs, experimental observations have found different brain regions often exhibit different dynamic patterns that could differentiate their power to impact their neighborhood [6]. Our model is capable of distinguishing different ROIs' individual characteristics related to information diffusion by customizing the corresponding learning parameters for different nodes (i.e., ROIs) through our graph convolution layers, including edge-to-edge convolutions, edge-to-node convolutions, and their deconvolution counterparts. Second, compared with structural connectivity, where connections commonly occur among spatial neighborhoods, "tele-connections" among distant ROIs are also common in functional connectivity. This phenomenon is taken into account by our model, which can consider higher-order relationship among ROIs in structural connectivity by stacking multiple convolution and deconvolution layers. By utilizing skip-nets, our proposed SF-GAN adaptively learns the appropriate number of orders from the data, while at the same time preserving the information from structural connectivity. Additionally, the joint utilization of (de)convolutions and skip-nets can result in another capability, which is to jointly learn both local and global information from structural connectivity, which is crucial

because both impact functional connectivity [7]. Because of its much larger model capacity, the proposed SF-GAN can characterize sophisticated patterns in an end-to-end manner, although this does require a larger training dataset in order to alleviate small-sample and overfitting issues. Fortunately, as long as large datasets such as the HCP project dataset are available, this is not an issue. We expect conducting experiments on bigger datasets to become an important trend in this domain as an ever-increasing number and ever-larger fMRI datasets become available.

It is widely recognized that the functional connectivity is not determined merely by structural connectivity, but is also affected by internal and external factors such as the subject's profile and environmental factors. However, precisely how all these factors are integrated with graph-structured input connectivity is largely unknown and too sophisticated to be explicitly modeled. Also, it is technically difficult to integrate graph-structured data (structural connectivity) with non-graph-structured data (e.g., subject profile and environmental features) to achieve the joint prediction of functional connectivity. Our proposed SF-GAN provides a possible way to do this by leveraging the power of graph representation learning, which first learns the matrix-form graph embedding that can then be easily combined with other feature vectors. Finally, to account for randomness and uncertainties during various stages of the prediction process of functional connectivity, the dropout operations are leveraged in different (de)convolution layers.

Why do we include the meta features of the subjects?

Researchers have found substantial variability both between subjects and even within the same subject and structural connectivity is far from being the only factor that determines the pattern of functional connectivity. For example, [8] and [9] provide useful insights regarding the influence of age and gender on the strength and architecture of functional and cortical connectivity respectively. In an experimental study in [9], r-fMRI data from 1,414 subjects was collected and combined using generalized one-way ANOVA, revealing similar trends in the availability of both positive and negative values of functional connectivity in different subjects, in addition to the general variability within a single participant. These results strongly support systematic effects of age and sex in terms of the magnitude of low frequency fluctuations in various regions. The anatomical differences corresponding to age and sex studied in [10] revealed a general reduction in the overall cortical connectivity with age, resulting in the diminution of local efficiency. These researchers also identified some variability with respect to the overall cortical connectivity and described the distributed regional differences in efficiency between genders.

However, existing methods for structural-to-functional connectivity prediction usually fail to consider or analyze how additional factors could influence functional connectivity. To the best of our knowledge, the existing literature in this area [8], [9], [10], and [11] has focused solely on a couple of limited factors, with none conducting a comprehensive assessment or testing all the potential relevant factors simultaneously. To address this issue, our proposed SF-GAN framework is designed to integrate the graph-structured structural connectivity input with feature vectors for joint functional connectivity prediction. Due to the capacity of neural networks to engage in nonlinear functional approximations, sophisticated compositions and combinations among the factors can also be characterized, enabling SF-GAN to utilize as many factors as possible by automatically selecting the determining factors and learning their importance via the training set. By applying regularization terms, the model can also handle small sample issues. Therefore, by analyzing the learned importance of different features, we can discover which factors are influential for functional connectivity patterns, as discussed earlier in Section **??**.

Parameter sensitivity study

The regularization hyper-parameter λ_2 controls the trade-off between the empirical prediction loss and the sparsity of the selected factors. An additional hyper-parameter λ_1 strikes a balance between the two types of empirical prediction losses, namely adversarial loss and supervised loss. It is therefore important to investigate how sensitive the model performance is to each. Here, we demonstrate the Pearson correlation for Dataset 1-Setting 1 and Dataset 2-Settings 2 and 3. The results for the other Datasets and Settings exhibit a very similar pattern.

Because it is difficult to predefine an optimal λ_2, we proposed to make use of multiple λ_2 values in the range of $[1,\ 10^7]$ (our experiments show that using a set of 20 values is sufficient). We plotted the model performance for varying λ_2 (Fig. 1) with fixed λ_1. The plot shows that the performance for our proposed method is robust over a wide range of λ_2 values, with fluctuations typically within a range of 10%. The sensitivity of the model to λ_1 was not tested as this was outside the contribution of the current study.

Impacts, limitations and future work

The significant improvement achieved by SF-GAN for the structural-to-functional connectivity prediction problem demonstrates the potential improved performance that can be achieved by a more expressive model. The consistently better performance obtained from deep models shown in Table I also indicates that the real mechanisms governing the way structural connectivity influences functional connectivity have not been comprehensively modeled by previous methods and deep neural networks are capable of fitting some of could effectively fit part of the remaining variance that has not been well explained by previous models. The work reported here further demonstrates the necessity of considering additional factors such as subjects' profiles and external environments, as well as identifying factors that could have a significant impact on functional connectivity patterns, which could greatly

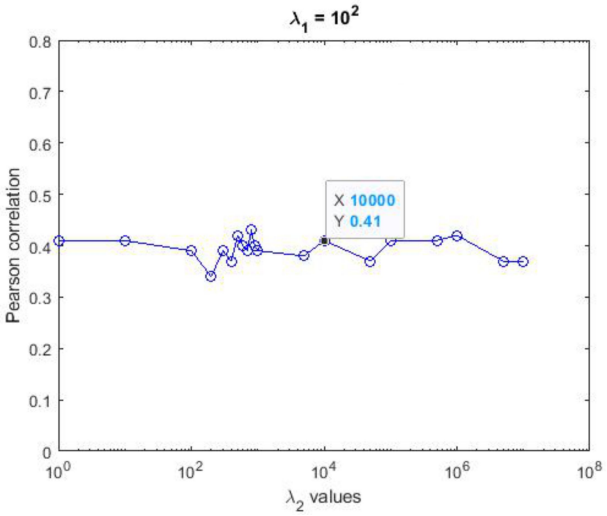

Fig. 1: Sensitivity test to λ_2 coefficient: Dataset1- Setting1

add to our understanding of the mechanism of functional connectivity. On the Artificial Intelligence side, our model supports powerful end-to-end data fusion techniques that can merge heterogeneous data sources and thus improve feature selection.

However despite these important contributions, the work also suffers from several limitations. The first is the model interpretability. Although the sophisticated mapping between structural to functional connectivity can be effectively modeled, it should also be possible to distill additional knowledge from this model which could shine a spotlight on the underlying mechanisms and show how structural connectivity impacts functional connectivity. Fortunately, there is more and more evidence (including work being done by our group) indicating that it is definitely possible to make deep learning models more transparent and extract further knowledge using newly developed techniques on interpretable machine learning such as attention mechanisms, disentanglement enhancement and saliency detection. Extending these approaches to structural-to-functional prediction is just one promising direction for further research. The other important limitation is the high time complexity required for model training, where the time complexity can be quadratic to the number of nodes in the worst cases. This means that when the ROIs being considered are more fine-grained, the training time increases considerably. Improving the efficiency of deep learning models on graphs is thus another very active domain. There are two directions that researchers are investigating: the first involves developing more efficient algorithms to reduce the time complexity down to the number of edges (e.g., message passing [12]), and linear to the number of nodes (e.g., k-nearest neighbor based convolutions [13]) or even independent of the number of nodes (e.g., sampling techniques [14]); the other is to leverage distributed computing techniques that parallelize the computation of different subgraphs in different computing units (e.g., GPUs).

II. Additional details

A list of hyperparameters that were tuned to achieve the best performance for SF-GAN, in addition to more case studies and brain visualizations, along with a list of meta-features are provided in the Appendix file, uploaded in the same github repository addressed in the main paper content. The repository also includes some subgraphs discovered for other subjects and the two days. In what follows, we provide a discussion on model selection and present additional model illustrations.

A. Model selection

Here we discuss, from two aspects, how we chose one among a range of different models for this specific problem: Aspect 1: The reason we chose conditional GAN is to generate graphs conditioned on an input graph. Here we approach a translation learning problem by using a graph encoder-decoder architecture. Since the link between SC and FC contains considerable randomness, we use a model which can learn one-to-many mapping between the input and the target graphs. This conditional graph synthesis framework can learn a distribution of target graphs conditioned on the input graph rather than using a supervised setting. As our input is the graph adjacency matrix which contains edge information, we employ edge convolution layers in the encoder to jointly extract the local (e.g. neighborhood pattern of each node) and global relation among nodes (e.g. node degree distribution), followed by node convolution layer to further extract the node representation. As the decoder aims at generating the edges of the target graph, it consists of node deconvolution and edge deconvolution layers to translate the node embeddings into the latent relations of the target graph and generate the final target graph respectively.

Aspect 2: We also tested the model performance sensitivity to the architecture of generator and discriminator and parameters based on additional experiments performed on alternative models. For each

alternative, we fixed the rest of model parameters as those reported in the experimental setup to study that specific parameter alone:

- Number of layers in encoder, decoder and discriminator: We tried 1, 2, and 3 layers for each (with equal layers for the three in all cases). We did not observe a significant change in performance for both datasets with a regularization setting of 1.
- Number of feature maps for the node layer (dim of hidden features): The current results are reported for 10 features. We tried 5 and 50 as well and again did not get a noticeable change in performance.
- Different activations on last layer of conditional generator: ReLu and tanh: We repeated the experiments for both datasets and three regularization settings with 'ReLu' activation and the Pearson correlation was between 0.23-0.26.
- Noise in all layers of the generator: We investigated how excluding noise from all layers would change the model performance and observed a Pearson correlation of 0.33 for Day1 dataset and regularization setting equal to 1. This showed the effectiveness of model predictive power when noise is applied to all layers.
- 3 sparsity patterns of meta-features: We have explored and discussed the model performance on 3 regularization settings in Section III-D.

In addition to the above experiments, we chose an existing post-hoc explainer, to compare to our proposed technique. We used the same objective as Eq. 8, to formulate the multi-level edge-correlation-guided graph clustering problem, but computed the gradients using PG-Explainer [15], rather than the compressed gradient in Eq. 5. Here, we report and summarize our findings, for 500 subjects, the same as those we studied in Section IV, as following:

In more than 80% of the mappings discovered, the subgraphs had exactly the same nodes that exist in SC and FC.

In more than 75% of the mappings, nodes in the right hemisphere in SC, determine nodes in the right hemisphere of FC. This value was about 81% for the left hemisphere.

The same as we did for our proposed technique, we looked at the number of edges in each subgraph of SC, for all mappings, and all subjects, that contributed to predicting one or more edges in FC. In more than 95% of input subgraphs, several (more than 5) edges existed.

Additionally, for about 80% of mappings, we found several significant structural edges being responsible for fewer of the functional edges.

Based on the above, our proposed gradient based technique is much simpler and more efficient, and results in a very close explanation to PG Explainer.

B. Model illustration

We have summarized the notations and symbols used in the main paper for presenting our technique, in Table III, in addition to the schematic diagram of our proposed method in Fig. 2. As the diagram shows, the proposed GAN framework uses a conditional generator which takes the input graph, and corresponding input meta-data to generate the target graph, while accounting for the randomness of prediction. The prediction is evaluated by the conditional discriminator block, which can distinguish 'fake' targets from 'real' ones. Model interpretability is provided through the design of a novel Post-hoc explainer block that can detect which subgraphs in input strongly impact which subgraphs in the output.

Symbol	Role
G, G'	graphs of N nodes representing SC and FC
A, A'	weighted adjacency matrices of G and G'
V	set of nodes of G
V_i	*ith* node of G
u	random noise term of distribution $\mathcal{U}$
M	vector of K meta-features
$\tilde{M}$	concatenation of N copies of meta-features
$\mathcal{F}$	FC conditional generator
$\mathcal{D}$	FC conditional discriminator
$F_{j,k}$	value of the *jth* node under the *kth* latent feature
$E^{l,m}$	correlation matrix of l-th deconv. layer and m-th feature map
λ_1, λ_2	hyperparameters to control regularization for the generator
ψ_m	N2E kernel for m-th feature map (outgoing)
ϕ_m	N2E kernel for m-th feature map (incoming)
$W'_{m,k}$	N2E kernel for m-th feature map and k-th meta-feature (outgoing)
$W_{m,k}$	N2E kernel for m-th feature map and k-th meta-feature (incoming)
P	size of each node embedding
K	total number of meta-features

TABLE III: Summary of the variables and definitions used in the main paper.

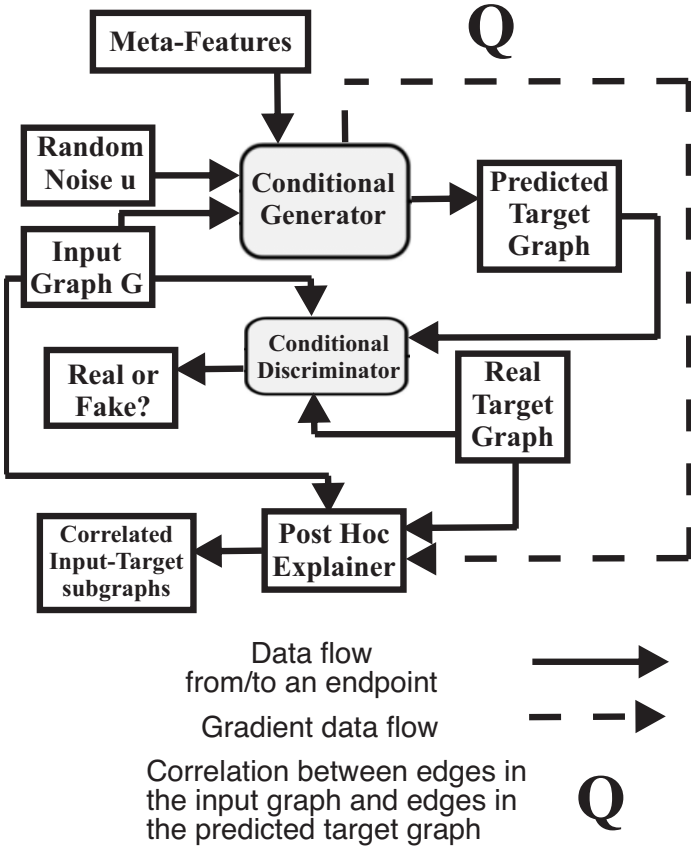

Fig. 2: Schematic diagram of the proposed algorithm.

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