

Statistical Analysis of Longitudinally and Conditionally Generated Neuroimaging Measures via Conditional Recurrent Flow

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Abstract

We develop a conditional generative model for longitudinal image datasets based on sequential invertible neural networks. Longitudinal image acquisitions are common in various scientific and biomedical studies where often each image sequence may also come together with various secondary (fixed or temporally dependent) measurements. The key goal is not only to estimate the parameters of a deep generative model for the given longitudinal data, but also to enable evaluation of how the temporal course of the generated longitudinal samples are influenced as a function of induced changes in the (secondary) temporal measurements (or events). Our proposed formulation incorporates recurrent subnetworks and temporal context gating, which provide a smooth transition in a temporal sequence of generated data that can be easily informed or modulated by secondary temporal conditioning variables. We show that the formulation works well despite the smaller sample sizes common in these applications. Our model is validated on two video datasets and a longitudinal Alzheimer’s disease (AD) dataset for both quantitative and qualitative evaluations of the generated samples. Further, using our generated longitudinal image samples, we show that we can capture the pathological progressions in the brain that turn out to be consistent with the existing literature.

1. Introduction

Consider a dataset of *longitudinal sequences* of data samples $\{\mathbf{x}^t\}_{i=1}^N$ where each sample \mathbf{x}_i comes with *sequential covariates* $\{\mathbf{y}^t\}_{i=1}^N$, one for each time point t . We assume that for each sequential sample i , $\mathbf{x}_i^1, \dots, \mathbf{x}_i^T = \{\mathbf{x}^t\}_i$, the sequential covariates $\mathbf{y}_i^1, \dots, \mathbf{y}_i^T = \{\mathbf{y}^t\}_i$ provide some pertinent auxiliary information associated with that sequential sample. Our goal is to design conditional generative models for such sequential data. In particular, we want a model which provides us a type of flexibility that is highly desirable in this setting. For instance, for a sample drawn from a distribution after a generative model has been estimated, we should be able to “adjust” the sequential

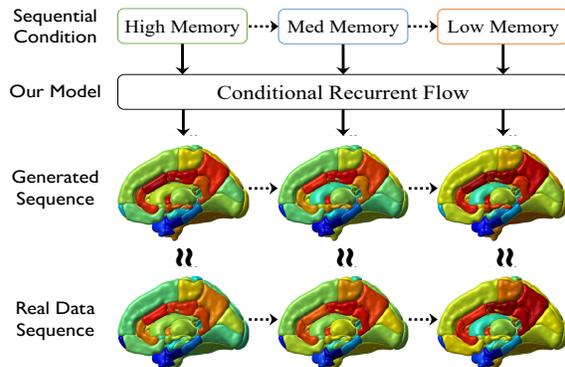


Figure 1: Conditional sequence generation illustration. **1) Given:** a decreasing memory test score sequence $\mathbf{y}_i^1 \rightarrow \mathbf{y}_i^2 \rightarrow \mathbf{y}_i^3$. **2) Model:** Conditional Recurrent Flow (CRoW). **3) Generate:** a sequence of brain image progression $\mathbf{x}_i^1 \rightarrow \mathbf{x}_i^2 \rightarrow \mathbf{x}_i^3$ corresponding to the given memory progression (i.e., brain regions with high (red) and low (blue) disease pathology). The Generated sequence follows the trend of the Real Data Sequence.

covariates dynamically to influence the expected future predictions after some time t for *that* sample. Notice that when $t = 1$, this construction is similar to conditional generative models where the “covariate” or condition \mathbf{y} may simply denote an attribute that we may want to adjust for a sample.

In this regard, neural network based generative models for modeling complex and high dimensional real life data while allowing tractable Bayesian approaches became feasible recently: Monte Carlo drop-out [8, 15], tractable exponential families [20, 6], and sufficient statistics estimation [18, 19]. These approaches, however, make limited assumptions on the true distribution of the dataset which may not accurately reflect complex datasets we deal with.

We want our formulation to provide a modified set of \mathbf{x}^t s adaptively, if we adjust one or more sequential covariates \mathbf{y}^t s for that sample. If we know some important clinical information at some point during the study (say, at $t = 5$), this information should influence the future generation $\mathbf{x}^{t>5}$ conditioned both on this sequential covariate or event \mathbf{y}^5 as well as the past sequence of this sample $\mathbf{x}^{t<5}$. This will require *conditioning* on the corresponding sequential covariates at *each* time point t by accurately capturing the posterior distribution $p(\mathbf{x}^t|\mathbf{y}^t)$. Such *conditional sequence generation* needs a generative model for *sequential* data which can dynamically incorporate time-specific *sequential*

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covariates \mathbf{y}^t of interest to adaptively modify sequences.

We seek a model which (i) efficiently generates high dimensional sequence samples of *variable lengths* (ii) with dynamic time-specific conditions reflecting upstream observations (iii) with fast posterior probability estimation. We tackle the foregoing issues by introducing an invertible recurrent neural network, **CRow**, that includes **recurrent subnetwork** and **temporal context gating**. *Invertibility* lets us precisely estimate the distribution of $p(\mathbf{x}^t|\mathbf{y}^t)$ in latent space. Introducing *recurrent subnetworks* and *temporal context gating* enables obtaining cues from previous time points $\mathbf{x}^{<t}$ to generate temporally sensible subsequent time points $\mathbf{x}^{\geq t}$. Our **contributions** are: **(A)** Our model generates conditional sequential samples $\{\mathbf{x}^t\}$ given sequential covariates $\{\mathbf{y}^t\}$ for $t = 1, \dots, T$ time points where T can be arbitrarily long. Specifically, we allow this by posing the task as a *conditional sequence inverse problem* based on a conditional invertible neural network [1]. **(B)** Our model estimates the posterior probabilities $p(\mathbf{x}^t|\mathbf{y}^t)$ of the generated sequences at each time point for potential downstream analyses involving uncertainty. **(C)** We show that the generated longitudinal brain pathology trajectories (e.g., Fig. 1) can lead to identifying specific regions in the brain statistically associated with Alzheimer’s disease (AD).

2. Preliminary: Invertible Neural Networks

We first describe an *invertible neural network* (INN) which inverts an output back to its input for solving inverse problems (i.e., $\mathbf{z} = f(\mathbf{x}) \Leftrightarrow \mathbf{x} = f^{-1}(\mathbf{z})$). A *normalizing flow* [22, 21] first learns a function $f(\cdot)$ which maps a sample \mathbf{x} to a latent variable $\mathbf{z} = f(\mathbf{x})$ where \mathbf{z} is from a standard normal distribution \mathbf{Z} . Then, with a change of variables formula, we estimate $p_{\mathbf{X}}(\mathbf{x}) = p_{\mathbf{Z}}(\mathbf{z})/|J_{\mathbf{X}}|$ and $|J_{\mathbf{X}}| = \left| \frac{\partial[\mathbf{x}=f^{-1}(\mathbf{z})]}{\partial\mathbf{z}} \right|$ where $|J_{\mathbf{X}}|$ is a Jacobian determinant. Thus, $f(\cdot)$ must be invertible, and to use a neural network as $f(\cdot)$, a *coupling layer* structure was introduced in RealNVP [4, 5] for an easy inversion and efficient $|J_{\mathbf{X}}|$.

Forward map (Fig. 2a). We use an input $\mathbf{u} \in \mathbb{R}^d$ and an output $\mathbf{v} \in \mathbb{R}^d$ (i.e., $\mathbf{u} \rightarrow \mathbf{v}$). We split \mathbf{u} into $\mathbf{u}_1 \in \mathbb{R}^{d_1}$ and $\mathbf{u}_2 \in \mathbb{R}^{d_2}$ where $d = d_1 + d_2$. Then, we forward map \mathbf{u}_1 and \mathbf{u}_2 to \mathbf{v}_1 and \mathbf{v}_2 respectively such that $\mathbf{v}_1 = \mathbf{u}_1$ and $\mathbf{v}_2 = \mathbf{u}_2 \otimes \exp(s(\mathbf{u}_1)) + r(\mathbf{u}_1)$ where s and r are independent functions (i.e., subnetworks), and \otimes and $+$ are element-wise product and addition respectively. Then, \mathbf{v}_1 and \mathbf{v}_2 construct \mathbf{v} (e.g., $[\mathbf{v}_1, \mathbf{v}_2] \rightarrow \mathbf{v}$).

Inverse map (Fig. 2b). A straightforward arithmetic allows an exact inverse from \mathbf{v} to \mathbf{u} (i.e., $\mathbf{v} \rightarrow \mathbf{u}$): $\mathbf{u}_1 = \mathbf{v}_1$ and $\mathbf{u}_2 = (\mathbf{v}_2 - r(\mathbf{v}_1)) \oslash \exp(s(\mathbf{v}_1))$ where the subnetworks s and r are *identical* to those in the forward map. \oslash and $-$ are element-wise division and subtraction respectively.

To transform the “bypassed” split \mathbf{u}_1 (since $\mathbf{u}_1 = \mathbf{v}_1$), a *coupling block* consisting of two complementary coupling layers is constructed to transform both \mathbf{u}_1 and \mathbf{u}_2 : $\mathbf{v}_1 =$

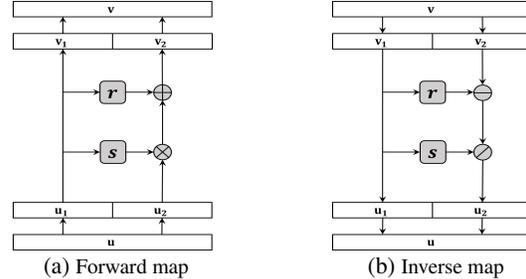


Figure 2: Coupling layer in normalizing flow. Note the change of operation orders: $\mathbf{u} \rightarrow \mathbf{v}$ in forward and $\mathbf{v} \rightarrow \mathbf{u}$ in inverse.

$\mathbf{u}_1 \otimes \exp(s_2(\mathbf{u}_2)) + r_2(\mathbf{u}_2)$ and $\mathbf{v}_2 = \mathbf{u}_2 \otimes \exp(s_1(\mathbf{v}_1)) + r_1(\mathbf{v}_1)$, and its inverse in a similar manner. In the context of normalizing flow, we consider \mathbf{u} and \mathbf{v} to be \mathbf{x} and \mathbf{z} .

3. Model Setup: Conditional Recurrent Flow

Estimating the *conditional probability* $p(\mathbf{x}|\mathbf{y})$ is desirable since it represents an underlying phenomenon of the input $\mathbf{x} \in \mathbb{R}^d$ and covariate $\mathbf{y} \in \mathbb{R}^k$ (e.g., the probability of a specific brain imaging measure \mathbf{x} of interest given a diagnosis \mathbf{y}). In terms of normalizing flow, the goal is to construct an invertible network $f(\cdot)$ mapping a given input $\mathbf{x} \in \mathbb{R}^d$ to its corresponding covariate/label $\mathbf{y} \in \mathbb{R}^k$ and its latent variable $\mathbf{z} \in \mathbb{R}^m$ such that $[\mathbf{y}, \mathbf{z}] = f(\mathbf{x})$. The mapping has an inverse for $\mathbf{x} = f^{-1}([\mathbf{y}, \mathbf{z}])$ to be recovered.

Specifically, when a flow-based model jointly encodes label and latent information (i.e., $[\mathbf{y}, \mathbf{z}] = \mathbf{v} = f(\mathbf{x})$) while ensuring that $p(\mathbf{y})$ and $p(\mathbf{z})$ are independent, then the network becomes *conditionally* invertible (i.e., $\mathbf{x} = f^{-1}([\mathbf{y}, \mathbf{z}])$ conditioned on given \mathbf{y}). Such a network can be theoretically constructed through a bidirectional-type training [1], and this allows a conditional sampling $\mathbf{x} = f^{-1}([\mathbf{y}, \mathbf{z}])$ and the posterior estimation $p(\mathbf{x}|\mathbf{y})$.

3.1. Conditional Recurrent Flow (CRow)

We introduce Conditional Recurrent Flow (CRow) model for conditional sequence generation. Given a sequence of input/output pairs $\{\mathbf{u}^t, \mathbf{v}^t\}$ for $t = 1, \dots, T$ time points, modeling the relationship between the variables across time needs to also account for the temporal characteristic of the sequence. We are specifically interested in an *invertible network which is also recurrent* such that given a *sequence* of inputs $\{\mathbf{u}^t\}$ (i.e., features $\{\mathbf{x}^t\}$) and their *sequence* of outputs $\{\mathbf{v}^t\}$ (i.e., covariates/labels and latent information $\{\mathbf{y}^t, \mathbf{z}^t\}$), we can model the invertible relationship between those sequences for posterior estimation and conditional sequence generation as illustrated in Fig. 1.

We use the coupling block to setup a normalizing flow type invertible model. Then, we construct a *recurrent* subnetwork q which also contains a recurrent network (e.g., GRU) internally. This allows q to take the previous hidden state \mathbf{h}^{t-1} and output the next hidden state \mathbf{h}^t as $[\mathbf{q}, \mathbf{h}^t] = q(\mathbf{u}, \mathbf{h}^{t-1})$ where \mathbf{q} is an element-wise transformation vector derived from \mathbf{u} analogous to the output of a subnetwork $s(\mathbf{u})$. In previous coupling layers, two transfor-

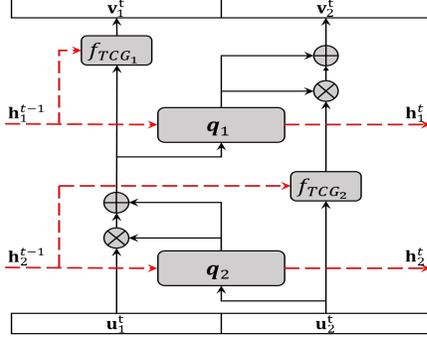


Figure 3: The CRow model. Only the forward map of a single block (two coupling layers) is shown for brevity. The inverse map involves a similar order of operations (analogous to Fig. 2a and Fig. 2b)

matation vectors $\mathbf{s} = s(\cdot)$ and $\mathbf{r} = r(\cdot)$ were explicitly computed from two subnetworks for each layer. For CRow, we follow the structure of Glow [14] which computes a single vector $\mathbf{q} = q(\cdot)$ and split it as $[\mathbf{s}, \mathbf{r}] = \mathbf{q}$. This allows us to use a single hidden state while concurrently learning $[\mathbf{s}, \mathbf{r}]$ which we denote as $\mathbf{s} = q_s(\cdot)$ and $\mathbf{r} = q_r(\cdot)$ to indicate the individual vectors. Thus, at each t with given $[\mathbf{u}_1^t, \mathbf{u}_2^t] = \mathbf{u}^t$ and $[\mathbf{v}_1^t, \mathbf{v}_2^t] = \mathbf{v}^t$,

$$\begin{aligned} \mathbf{v}_1^t &= \mathbf{u}_1^t \otimes \exp(q_{s_2}(\mathbf{u}_2^t, \mathbf{h}_2^{t-1})) + q_{r_2}(\mathbf{u}_2^t, \mathbf{h}_2^{t-1}) \\ \mathbf{v}_2^t &= \mathbf{u}_2^t \otimes \exp(q_{s_1}(\mathbf{v}_1^t, \mathbf{h}_1^{t-1})) + q_{r_1}(\mathbf{v}_1^t, \mathbf{h}_1^{t-1}) \end{aligned} \quad (1)$$

and the inverse is computed similarly. Note that the hidden states \mathbf{h}_1^t and \mathbf{h}_2^t generated from the recurrent network of the subnetworks are implicitly used within the subnetwork architecture and also passed to their corresponding recurrent network in the next time point as in Fig. 3.

3.2. Temporal Context Gating (TCG)

A standard (single) coupling layer transforms only a part of the input by design which results in the determinant of a triangular Jacobian matrix $J_{\mathbf{v}}$. CRow incorporates a *temporal context gating* $f_{\text{TCG}}(\alpha^t, \mathbf{h}^{t-1})$ using the temporal information \mathbf{h}^{t-1} on a given input α^t at t as $f_{\text{TCG}}(\alpha^t, \mathbf{h}^{t-1}) = \alpha^t \otimes \text{cgate}(\mathbf{h}^{t-1})$ where $\text{cgate}(\mathbf{h}^{t-1})$ can be any learnable function/network with a sigmoid function at the end. This is analogous to the context gating [17] in video analysis. Note that this still preserves the Jacobian structure:

$$|J_{\mathbf{v}}| = \begin{vmatrix} \frac{\partial \mathbf{v}_1}{\partial \mathbf{u}_1} & \frac{\partial \mathbf{v}_1}{\partial \mathbf{u}_2} \\ \frac{\partial \mathbf{v}_2}{\partial \mathbf{u}_1} & \frac{\partial \mathbf{v}_2}{\partial \mathbf{u}_2} \end{vmatrix} = \begin{vmatrix} \text{diag}(\text{cgate}(\mathbf{h}^{t-1})) & 0 \\ \frac{\partial \mathbf{v}_2}{\partial \mathbf{u}_1} & \text{diag}(\exp s(\mathbf{u}_1)) \end{vmatrix}$$

where $|J_{\mathbf{v}}| = [\prod_j \text{cgate}(\mathbf{h}^{t-1})_j] * [\exp(\sum_i (s(\mathbf{u}_1))_i)]$.

4. Experiments

In this section, we show various experimental results on a video data as well as real longitudinal brain imaging measures to demonstrate and validate our model.

4.1. Conditional Moving MNIST Generation

Moving Digit MNIST: On a controlled Moving Digit MNIST dataset [23] of image sequences showing a hand-written digit from 0 to 9 moving in a path and bouncing off the boundary, we specifically chose two digits (e.g., 0 and

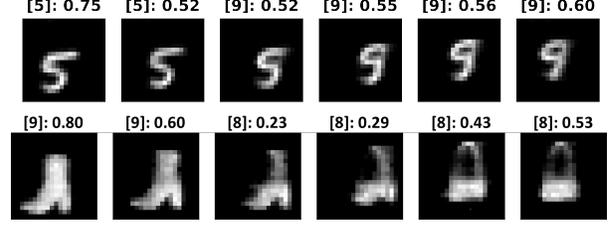


Figure 4: Examples of generated sequences using CRow given the changing conditions. Top: 5→9, Bottom: boot (9) → bag (8). (top of each frame: **density for labels**).

1) to construct $\sim 13\text{K}$ controlled sequences of frame length $T = 6$ where each frame of a sequence is an image of size 20 by 20 and has a one-hot vector $\mathbf{y}^t \in \mathbb{R}^2$ of digit label at t indicating one of the two possible digits.

Training. Our model consists of three coupling blocks (q has one GRU cell, three residual fully connected (FC) networks, and ReLU activation). For each TCG, $\text{cgate}(\cdot)$ is a single FC with sigmoid activation. Each input frame $\mathbf{u}^t = \mathbf{x}^t$ is split into two halves \mathbf{u}_1 and \mathbf{u}_2 . Each training sequence has a digit label sequence $\{\mathbf{y}^t\}$ for $t = 1, \dots, 6$ where all \mathbf{y}^t are “identical” in each sequence since the the same digit is shown throughout the sequence.

Generation. We first specified sequential conditions (i.e., digit label) that change midway through the sequence (e.g., $\{\mathbf{y}^t\}$ sequence indicating digit labels 5→5→9→9→9→9). Then, we generated the corresponding sequences $\{\mathbf{x}^t\}$ and visually check if the changes across the frames look natural. Note that we trained *only* the image sequences with consistent digit labels. One demonstrative result is shown in Fig. 4 where we compare the generated image sequences with condition (i.e., digit label) changing from 5 to 9. Our model quantifies its output confidence in the form of density (i.e., likelihood) shown at the top of each generated images with lower density at the frame showing the most drastic transformation which were not observed in the training.

Moving Fashion MNIST: We also tested our model on a more challenging Moving Fashion MNIST [25] of moving apparel image sequences in a very similar manner (Fig. 4).

4.2. Longitudinal Neuroimaging Analysis

In this experiment, we evaluate if our conditionally generated samples actually exhibit statistically robust and clinically sound characteristics when trained with a longitudinal Alzheimer’s disease (AD) brain imaging dataset.

Dataset. We use a longitudinal neuroimaging dataset called The Alzheimer’s Disease Prediction of Longitudinal Evolution (TADPOLE) [16] ($N=276$ and $T = 3$).

Input. For the longitudinal sequence $\{\mathbf{x}^t\}$, we chose Florbetapir (AV45) Positron Emission Tomography (PET) scan measuring the level of *amyloid-beta* in brain which has been a known pathology of AD [24, 12]. The AV45 images were registered to a common brain template (MNI152) to derive the gray matter regions of interests (82 Desikan ROIs [3]). Thus, each of the 82 ROIs ($\mathbf{x}^t \in \mathbb{R}^{82}$) holds an average

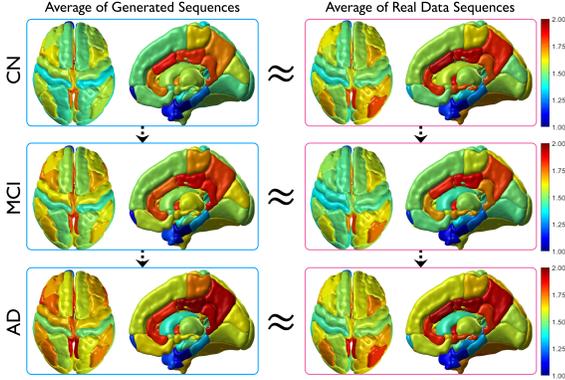


Figure 5: Generated sequences vs. real data sequences comparison for CN (top)→MCI (middle)→AD (bottom). Each blue/pink frame has top, side (interior of right hemisphere), and front views. **Left:** The average of the 100 generated sequences conditioned on CN→MCI→AD. **Right:** The average of the real samples with CN→MCI→AD in the dataset. Red/blue indicate high/low AV45. ROIs are expected to turn more red as CN→MCI→AD. The generated samples show magnitudes and sequential patterns similar (\approx) to those of the real samples from the training data.

Standard Uptake Value Ratio (SUVR) measure of AV45.

Condition. For the longitudinal condition $\{y^t\}$, we chose three covariates known to be tied to AD progression ([normal → impaired]): (1) *Diagnosis:* Control (CN), Mild Cognitive Impairment (MCI), and Alzheimer’s Disease (AD) [CN→MCI→AD]. (2) *ADAS13:* AD Assessment Scale [0→85]. (3) *MMSE:* Mini Mental State Exam [0→30]. These assessments impose disease *progression*.

Analysis. We performed a statistical group analysis on each condition $\{y^t\}$ independently with the following pipeline: (1) *Training:* We trained our model (the same subnetwork as Sec. 4.1) using the sequences of SUVR in 82 ROIs for $\{x^t\}$ and the covariate (‘label’) sequences for $\{y^t\}$. (2) *Conditional longitudinal sample generation:* We generated longitudinal samples $\{\hat{x}^t\}$ conditioned on two distinct longitudinal conditions: *Control* (healthy covariate sequence) versus *Progression* (worsening covariate sequence). Specifically, for each condition (e.g., Diagnosis), we generate N_1 samples of Control (e.g., $\{\hat{x}_1^t\}_{i=1}^{N_1}$ conditioned on $\{y^t\} = \text{CN} \rightarrow \text{CN} \rightarrow \text{CN}$) and N_2

Covariates	# of Statistically Significant ROIs		
	Diagnosis	ADAS13	MMSE
Control	CN→CN→CN	10→10→10	30→30→30
Progression	CN→MCI→AD	10→20→30	30→26→22
cINN	11 (4)	5 (2)	5 (0)
Ours	25 (11)	24 (12)	19 (2)
Ours + TCG	28 (12)	32 (14)	31 (2)
Control	CN→CN→CN	10→10→10	30→30→30
Early-progress.	CN→MCI→MCI	10→13→16	30→28→26
cINN	2 (0)	2 (2)	2 (0)
Ours	6 (2)	6 (4)	11 (4)
Ours + TCG	6 (4)	8 (5)	12 (4)

Table 1: Number of ROIs identified by group analysis using the generated measures with respect to various covariates associated with AD with the significance level of $\alpha = 0.01$ (type-I error controlled result shown in parenthesis). Each column represents sequences of disease progression represented by diagnosis or test scores. *CRow* considers the progression sequences. *CRow* + TCG yields the most number of significant ROIs.

Covariates	Gen. vs. Real of Progressions			Gen. vs. Real of Early-progress.		
	Diagnosis	ADAS13	MMSE	Diagnosis	ADAS13	MMSE
cINN	1.2551	1.5968	1.1498	1.0656	1.4985	0.9482
Ours	0.4193	0.5562	0.3485	0.3591	0.5612	0.2953
Ours + TCG	0.2828	0.3915	0.1679	0.2341	0.5248	0.0902

Table 2: Difference between the generated sequences and the real sequences at $t = 3$. Lower the effect size (Cohen’s d), smaller the difference between the comparing distributions.

samples of Progression ($\{\hat{x}_2^t\}_{i=1}^{N_2}$ conditioned on $\{y^t\} = \text{CN} \rightarrow \text{MCI} \rightarrow \text{AD}$). Then, we perform a two sample t -test at $t = 3$ for each of 82 ROIs between $\{\hat{x}_1^3\}_{i=1}^{N_1}$ and $\{\hat{x}_2^3\}_{i=1}^{N_2}$ groups, and derive p -values to tell whether the pathology levels between the groups significantly differ in those ROIs.

Result 1: Control vs. Progression (Table 1, Top row block). We set the longitudinal conditions for each covariate based on its associated to healthy progression and disease progression. We generated $N_1 = 100$ and $N_2 = 100$ samples for each group respectively, then performed the above statistical group difference analysis under 4 setups: (1) Raw training data, (2) cINN [1], (3) Our model, and (4) Our model + TCG. With the raw data, the sample sizes of the desirable longitudinal conditions were extremely small for all setups, so no statistical significance was found after type-I error control. With cINN, we occasionally found few significant ROIs, but the non-sequential samples with only $t = 3$ could not generate realistic samples. *CRow* + TCG detected the most number of ROIs which include many AD-specific regions reported in the aging literature [10, 12].

Result 2: Control vs. Early-progression (Table 1, Bottom row block). We setup a more challenging task where we generate samples which resemble the subjects that show slower progression of the disease. Such case is especially important in AD when early detection leads to effective prevention. With $N_1 = 100$ and $N_2 = 100$ samples, no significant ROIs were found in all models. To improve the sensitivity, we generated $N_1 = 150$ and $N_2 = 150$ samples in all models and found several significant ROIs *only* with *CRow* related to an *early* AD progression [7, 11, 13, 9].

Generation assessments. In Fig. 5, we see the generated samples (Left) through CN→MCI→AD in two views of the ROIs and compare them to the real training samples (Right). We see that the generated samples have similar AV45 loads through the ROIs, and the progression pattern across the ROIs follows that of the real sequence. We also quantified the similarities between the generated and real data sequences by computing effect size (Cohen’s d [2]) measuring the difference between the distributions (Table 2).

5. Conclusion

We developed a novel invertible neural network model that integrates recurrent subnetworks and temporal context gating to pass information within a sequence generation, enable the model to “learn” the conditional distribution of training data in a latent space, and generate sequential samples with progressive behavior according to the given conditions. We show experimental results using three datasets.

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