Longitudinal Modeling of Multiple Sclerosis using Continuous Time Models

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Abstract

Multiple sclerosis is a disease that affects the brain and spinal cord, it can lead to severe disability and has no known cure. The majority of prior work in machine learning for multiple sclerosis has been centered around using Magnetic Resonance Imaging scans or laboratory tests; these modalities are both expensive to acquire and can be unreliable. In a recent paper it was shown that disease progression can be predicted effectively using performance outcome measures (POMs) and demographic data. In our work we extend on this to focus on the modeling side, using continuous time models to predict progression. We evaluate four continuous time models using a publicly available multiple sclerosis dataset. We find that continuous models are often able to outperform discrete time models. We also carry out an extensive ablation to discover the sources of performance gains, we find that standardizing existing features leads to a larger performance increase than interpolating missing features.

1 Introduction

Multiple Sclerosis (MS) is the most common demyelinating disease (Leray et al., 2016) affecting approximately 2.8 million people worldwide (Lane et al., 2022), and being one of the leading causes of disability in young adults (Coetzee & Thompson, 2020). It is a lifelong disease of the nervous system that can lead to a wide range of symptoms from fatigue to problems with movement and vision. Currently there is no known cure but the symptoms can be treated with medication and physical therapy, where the aim of a clinician is to limit progression. Therefore, an effective application of machine learning methods in this space would be to predict progression of MS as well as informing interventions and treatment options to obtain the best prognosis for a given patient.

Prior works on machine learning that investigate MS progression typically rely on Magnetic Resonance Imaging (MRI) scans or laboratory tests (Pinto et al., 2020; Zhao et al., 2017; Seccia et al., 2020; Tommasin et al., 2021). These modalities are both expensive to obtain (MRI scans cost on the order of thousands of US dollars) and infrequent, added to this they are not always reliable (Whitaker et al., 1995). The progression of MS has also been studied using clinical data (Lawton et al., 2015; Tozlu et al., 2019; De Brouwer et al., 2021) with models ranging from using Latent Class Linear Mixed Models, to time-aware GRU.

To this end, in a previous study Roy et al. (2022) demonstrated that it is possible to use both performance outcome measures and demographic data to predict disease progression. Performance outcome measures (POMs) are a time-series that contain either responses to questionnaires or results from physical tests to determine MS progression (Rudick et al., 2002). These tests are designed to evaluate the functions affected by MS, and include walking, balance, cognition and dexterity tests. Roy et al. (2022) showed that POMs and demographic data successfully predict progression for a range of models, from classical models such as logistic regression to state of the art deep learning models such as Temporal Convolutional Network (TCN) (Bai et al., 2018). However, these models are not suited to irregular time-series with missing features, and various techniques such as imputing with zeros and binning are applied to make the data compatible with the models, which can add bias. In order to overcome this we propose to improve the modeling by using continuous time models. Continuous time models such as Neural ODEs (Chen et al., 2018) learn to model an instantaneous velocity of a state to calculate the time evolution. They have three key advantages: (1) they

naturally handle irregular time-series; (2) via the use of control signals missing features can be interpolated and therefore are imputed with more physically plausible values (Kidger et al., 2020); (3) continuous time models enforce the inductive bias that the data is generated from a dynamical process such as biological interactions (Alharbi & Rambely, 2020). Neural Differential Equations have been applied in the medical setting (Kidger et al., 2020; Morrill et al., 2021; Qian et al., 2021; Seedat et al., 2022), however to our best knowledge we are the first to apply these to MS prediction using POMs. Our contributions are below:

1. We adapt the framework of Roy et al. (2022) to handle continuous models which impute by interpolation.
2. We introduce two new interpolation schemes using monotonically increasing cubics, to interpolate missing values and act as continuous control signals for models.
3. We benchmark four continuous time models on a public MS dataset, and see that the state of the art continuous model outperforms the state of the art discrete model.

2 Background

2.1 Neural Differential Equations

Here we briefly introduce the concepts behind continuous time models. For more information we encourage the reader to see resources such as Chen et al. (2018); Dupont et al. (2019); Massaroli et al. (2020); Kidger et al. (2020); Li et al. (2020); Kidger (2022).

For a hidden state $\boldsymbol{h} \in \mathbb{R}^n$, and time $t \in \mathbb{R}$, Neural Ordinary Differential Equations (Neural ODEs) (Chen et al., 2018) model the instantaneous rate of change of $\boldsymbol{h}$ with respect to t using a neural network $f : \mathbb{R}^n \times \mathbb{R} \times \mathbb{R}^k \to \mathbb{R}^n$, with parameters $\theta \in \mathbb{R}^k$

$$\frac{d\boldsymbol{h}}{dt} = f(\boldsymbol{h}, t, \theta). \tag{1}$$

For brevity we now use the convention that $f(\boldsymbol{h}, t, \theta)$ is written as $f_\theta(\boldsymbol{h}, t)$. Given an initial condition $\boldsymbol{h}(t_0) = \boldsymbol{h}_0$, we can use a black box ODE solver, for example Dormand-Prince (Dormand & Prince, 1980), to approximately solve the initial value problem and calculate the hidden state at a later time

$$\boldsymbol{h}(t) = \text{ODESolve}(f_\theta, \boldsymbol{h}_0, t_0, t). \tag{2}$$

Crucially, we can differentiate the solutions of the ODE solve with respect to the parameters θ, the initial state $\boldsymbol{h}_0$, initial time t_0 and the solution times t. This can be done by using the adjoint sensitivity method (Chen et al., 2018; Pontryagin, 1987) or by differentiating through the solver operations, since solver operations themselves are differentiable. This allows us to backpropagate through the ODE solve and train any learnable parameters via gradient descent. Therefore, Neural ODEs can be used in place of layers in a network, for example, as a feedforward layer where we solve the ODE from t_0 to a terminal time t_1; or it can be used to output a series by calculating the hidden state at a list of times $\{t_0, t_1, ..., t_n\}$.

One advantage of this is that it intrinsically deals with irregular time-series, without the need for bucketing. This is because the model is able to deal with continuous time by design by modeling the instantaneous velocity, rather than a discontinuous update. Additionally, they use the inductive bias that a time-series is generated from an underlying dynamical process, that is, the instantaneous rate of change of the current state depends on the state itself. For example, in epidemiology, compartmental models (Tang et al., 2020) are used to determine how a disease spreads through a population; or in virology the concentration of virus, antibodies and infected cells can be modelled with differential equations (Perelson et al., 1996). In our case the progression of MS is driven by biological mechanisms so can also be modeled with differential equations. We do not know what these differential equations are, and therefore Neural ODEs are well suited to the problem by combining the inductive bias of an underlying dynamical system with the approximation power of neural networks (Cybenko, 1989).

2.2 Interpolation and Control Signals

In many real world cases data is incomplete, to overcome this, missing values are imputed. Often this is done by filling with zero or the mean value of a feature. In time-series applications we are able to use observed values to plausibly fill in missing values based on the rest of the series. For example we may have a time-series $((x_0, t_0), (\emptyset, t_1), (x_2, t_2))$, we can linearly interpolate, giving $((x_0, t_0), (\tilde{x}_1, t_1), (x_2, t_2))$, where $\tilde{x}_1 = \frac{x_2 - x_0}{t_2 - t_0}(t_1 - t_0) + x_0$. More generally, we can find $X(t)$, which is an interpolation of the observed time-series (Davis, 1975; Lunardi, 2009). The values of X match the observations exactly, $X(t_n) = x_n$, and will also predict a value for unobserved features. $X(t)$ can be evaluated at the observation times $\{t_0, t_1, ..., t_n\}$ but also between these times, giving us a *control signal* or *spline* based on the observations.

3 Continuous Modeling Framework

In this work we consider continuous models. The models are adapted for this setting, via one of our key contributions, a new framework building on that of Roy et al. (2022). We recommend seeing Figure 1 and Section 3 of that work for information on this stage of the pipeline. Briefly, the preprocessing consists of converting raw data to a common representation specifically for discrete models, splits subjects into train/test sets, fills missing values with zeros and pads the time-series for batching; the postprocessing is able to calculate metrics for the whole population as well as subgroups. To adapt to the new setting the continuous models receive an interpolated control signal and context vector as input, and make a prediction at given evaluation times. The control signal represents the sequence features, i.e. the POMs at different timestamps, the context gives static information that does not change over time, such as sex and ethnicity.

Passing an interpolation to a model. Since a control signal is continuous, we cannot pass the whole function to a model, as there are infinitely many points. This is instead achieved by making the control signals piece-wise cubic functions. So that between t_i and t_{i+1}, $X(t) = a_i(t - t_i)^3 + b_i(t - t_i)^2 + c_i(t - t_i) + d_i$, then the coefficients (a_i, b_i, c_i, d_i) are passed to the model to compactly represent the interpolation.

Batching using Pseudo-Time. One significant technical difference between our work and most prior work is how we achieve minibatching. Ordinarily for continuous models to batch irregular time-series, all of the times in the different samples are merged (concatenated and sorted). The ODE is solved for *all* of these times, then a binary mask is applied to extract the relevant predictions for each sample. Instead, we use the integers as a regularly spaced pseudo-time, s. And instead of interpolating the time-series with the true time stamps t, we interpolate with s giving $X(s)$. We also interpolate the true time using s, so that $t = \psi(s)$. Then, if the dynamics function we learn represents the rate of change of a state with respect to true time

$$\frac{d\boldsymbol{h}}{dt} = f_\theta(\boldsymbol{h}, t),$$

by adapting this to the s domain such that

$$\frac{d\boldsymbol{h}}{ds} = f_\theta(\boldsymbol{h}, \psi(s))\frac{d\psi}{ds}$$

we can show that $\text{ODESolve}(\frac{dh}{dt}, h_0, \psi(s_0), \psi(s)) = \text{ODESolve}(\frac{dh}{ds}, h_0, s_0, s)$. Note this is only true if ψ is an increasing function (which can be achieved with certain interpolation schemes).

This allows us to straightforwardly batch as we can solve all of the samples in the batch in the same regular s domain, and shift each to their respective true time domains. The main advantage is since we do not need to solve for all *merged true times*, only the *shared regular pseudo-times*, we do not store as many intermediate ODE solution values, hence we are more memory and compute efficient. See Appendix C for more information and the proof of equality. Note that this has been used before specifically for Online Neural CDEs (Morrill et al., 2021), we extend to all continuous models here. As well as using pseudo-time, we must pad sequences to the same length keeping track of which observations are real and which are imputed in order to train in batches. To achieve this an initial data preprocessing step is used first.

3.1 Data Preprocessing

The most general data we can be given from our datasets consists of the following. At each timestep we have a vector of sequence features $\boldsymbol{x}$, a vector of context features $\boldsymbol{c}$, a timestamp t, a label y and a sample weight w. The sample weights inform the loss function and evaluation metric if a prediction is used in the calculation. The sequences are irregular with varying lengths, both the sequences and contexts may have missing values. We wish to convert this so that all time-series are the same length, with missing features imputed and the irregular times dealt with so that we can train efficiently using minibatches. The preprocessing therefore consists of the following steps in order:

1. Standardize the sequences and the context feature-wise using only the observed values so they have mean 0 and standard deviation 1.
2. Impute missing *context* features with a given value. We impute with zero since that now represents the mean.
3. Pad sequences to the same length. We fill: sequence features with missing values (nans); observation times with the last observed time; labels with zero; sample weights with zero.
4. Calculate a cumulative sum of the number of observations in each sequence feature-wise, such that if there is a missing value this count does not increase. This will be called the *observation count*, denoted $\boldsymbol{o}$. When we impute later this provides information to the model that either we have a true observation or an imputed one, as required by (Kidger et al., 2020).
5. Concatenate $(\boldsymbol{x}, \boldsymbol{o}, t)$ along the feature dimension, so that these are the new sequence features.
6. Convert this to a causal dataset either by repeating subjects in a causal way, or extending longitudinally using the recti method. See below for a description of both methods.
7. Interpolate the new causal time-series using integers as the pseudo-time s.

This produces a series of coefficients that represent piece-wise cubics as the interpolating function. It is computationally expensive to calculate the coefficients each time they are needed, so they are calculated once and stored. They replace $(\boldsymbol{x}, \boldsymbol{o}, t)$ in the dataset as input to the model, since the sequence is easy to recover using the coefficients. After this preprocessing our datasets consist of the following, for a given subject we have a tuple of: (inputs, labels, sample weights). The input is a tuple of (coefficients, context vectors) so one sample is of the form: $((\text{coeffs}, \boldsymbol{c}), y, w)$. Note that y and w are also longitudinal as we make predictions at every timestep.

3.2 Enforcing Causality

It is critical that a model is casual, i.e. the model only uses the current and previous measurements to make a prediction. At inference time we do not have access to future measurements, so the model must be trained such that predictions at t only use the time-series up to t.

The control signals in general are not causal, they either use the whole time-series to interpolate, or use the next observed value which is not causal when there are missing values. To overcome this we enforce causality in continuous models in two ways:

1. Reprocess the dataset, by making many copies of a series in a causal way.
2. Use continuously online (recti) control signals.

Reprocessing the Dataset. For each subject in a series we make copies of the subject so that for the i-th time stamp, we consider the time-series up until that point, and fill forward the i-th observation until the end. Then we set the sample weights to 0.0 everywhere except at observation i where it is 1.0. This means that only previous observations are used to construct the spline that is used to predict at time stamp i, and then by adjusting the sample-weights we only consider the i-th observation for that copy of the time-series in the loss. We cannot consider earlier because then the model is using observations up until i to make predictions for points earlier than i, we don't predict later because it is not relevant to do so. For example, this time-series is transformed below:

$$\left[\quad\left[\begin{bmatrix}x_1\\t_1\\y_1\\1.0\end{bmatrix}\quad\begin{bmatrix}x_2\\t_2\\y_2\\1.0\end{bmatrix}\quad\begin{bmatrix}x_3\\t_3\\y_3\\1.0\end{bmatrix}\right]\quad\right]\longrightarrow\left[\begin{array}{c}\left[\begin{bmatrix}x_1\\t_1\\y_1\\1.0\end{bmatrix}\quad\begin{bmatrix}x_1\\t_1\\y_1\\0.0\end{bmatrix}\quad\begin{bmatrix}x_1\\t_1\\y_1\\0.0\end{bmatrix}\right]\\[2ex]\left[\begin{bmatrix}x_1\\t_1\\y_1\\0.0\end{bmatrix}\quad\begin{bmatrix}x_2\\t_2\\y_2\\1.0\end{bmatrix}\quad\begin{bmatrix}x_2\\t_2\\y_2\\0.0\end{bmatrix}\right]\\[2ex]\left[\begin{bmatrix}x_1\\t_1\\y_1\\0.0\end{bmatrix}\quad\begin{bmatrix}x_2\\t_2\\y_2\\0.0\end{bmatrix}\quad\begin{bmatrix}x_3\\t_3\\y_3\\1.0\end{bmatrix}\right]\end{array}\right]$$

This is causal for all models because the actual data itself only contains previous observations, and is then the last measurement repeated. The downside is that this can make the dataset increase size significantly without introducing any new information.

Causal Interpolation. To avoid our dataset growing exponentially we can also use causal interpolation schemes (Morrill et al., 2021). These extend the length of the time-series but not the number of samples. For more details see Morrill et al. (2021). Briefly, let $\tilde{x}$ be the fill-forward of x, so any missing observations are replaced by the most recent observed value. For a time-series of length n we then construct a "recti" time-series of length $2n-1$. Where $X(2i-1) = (\tilde{x}_i, t_i, y_i, 1.0)$ for $i \in \{1, ..., n\}$ and $X(2i) = (\tilde{x}_i, t_{i+1}, y_i, 0.0)$ for $i \in \{1, ..., n-1\}$. For example,this time-series is transformed below:

$$\left[\quad\left[\begin{bmatrix}x_1\\t_1\\y_1\\1.0\end{bmatrix}\quad\begin{bmatrix}x_2\\t_2\\y_2\\1.0\end{bmatrix}\quad\begin{bmatrix}x_3\\t_3\\y_3\\1.0\end{bmatrix}\right]\quad\right]\longrightarrow\left[\quad\left[\begin{bmatrix}\tilde{x}_1\\t_1\\y_1\\1.0\end{bmatrix}\quad\begin{bmatrix}\tilde{x}_1\\t_2\\y_1\\0.0\end{bmatrix}\quad\begin{bmatrix}\tilde{x}_2\\t_2\\y_2\\1.0\end{bmatrix}\quad\begin{bmatrix}\tilde{x}_2\\t_3\\y_2\\0.0\end{bmatrix}\quad\begin{bmatrix}\tilde{x}_3\\t_3\\y_3\\1.0\end{bmatrix}\right]\quad\right]$$

Crucially with the data rectified, we must then use what is known as a discretely online interpolation scheme. These only use the next observation to interpolate and since the observations are repeated[1] this remains causal. Examples include Linear interpolation and Hermite Cubic interpolation (see Appendix E). With this, the model is similarly only able to use previous observations to make a prediction, the difference between this and the previous method is that here we extend the dataset in the time dimension rather than number of subjects. This method is only causal for models which are already causal, such as TCN. However, later observations are still included in the time-series, so models that are not causal by design (i.e. those that use a whole time-series to predict) require the previous method of reprocessing the data.

3.3 Interpolation Schemes

Here we give the interpolation schemes that are used in the continuous models, including two novel ones. We give short overviews of each one here, for full information including equations, and advantages & disadvantages of each one see Appendix E. The existing interpolation schemes we use are described in full detail in Morrill et al. (2021) they are:

- **Linear:** This linearly interpolates the points with a straight line between observations, the a and b coefficients are zero. This is easy to calculate however can be slow to solve an ODE with since there are discontinuities in the derivative at observations.
- **Hermite Cubic:** This takes the linear interpolation, and now the previously unused a and b coefficients are used to smooth the interpolation. The first derivative is continuous at observations by enforcing the derivative to be equivalent to the gradient between that observation and the previous. This ODE is faster to solve than the linear interpolation.

[1]Repeating the label does not introduce any bias since the sample weights are zero for repeated labels.

- **Natural Cubic:** This is a cubic spline that enforces continuity in the interpolation, the derivative and the second derivative. This makes the spline the most "natural" for the observed points, however, this requires the whole time-series to be used to interpolate so is not causal.
- **Rectilinear:** This interpolation uses the recti method described previously, and then linearly interpolates those points. It is causal by design. However, since it is linear it can still be slow to solve the ODE.

We also introduce and investigate two novel interpolation schemes:

- **Monotonic Cubic** This takes the Hermite Cubic described previously, but rather than enforcing a derivative that would be obtained by linearly interpolating backwards, we enforce zero derivative at observation points. The purpose is that it is possible to interpolate an increasing function. This allows us to interpolate the time channel, since an increasing function is required to guarantee batching with pseudo-time.
- **Recticubic:** This uses the recti system of extending the length of the time-series. In contrast to the rectilinear interpolation, we then use Hermite cubics to interpolate the features, and monotonic cubics to interpolate the observation and time channels. This constructs a smooth causal interpolation that also respects the requirement for monotonic interpolation of the time channel.

4 Models

In this work we consider four neural differential equation based models. They are adapted for this setting, we recommend seeing their original papers for a full description, here we describe them as implemented, these are also shown pictorially in Figure 1.

All models receive $(\text{coeffs}, \boldsymbol{c})$ as input, where $\boldsymbol{c}$ is the context and the coeffs can be used to create a spline of the time-series, $X(s)$. For notational purposes, a c superscript on a function denotes the function takes the context as additional input, $f_\theta^c(\boldsymbol{h}, t)$ is equivalent to $f(\boldsymbol{h}, t, \boldsymbol{c}, \theta)$. This is so that we can keep parameters and context nominally separate from the hidden state and time.

4.1 Neural Controlled Differential Equations

The dynamics of a Neural CDE (Kidger et al., 2020) uses the whole spline (not just $\psi(s)$) to constantly include information from the time-series in the dynamics.

$$\frac{d\boldsymbol{h}}{ds} = f_\theta^c(\boldsymbol{h}, \psi(s))\frac{dX}{ds}$$

Where f_θ^c outputs a matrix since X and its derivatives are vectors. Note that since ψ is the last dimension of X we implicitly include its derivative here for batching purposes. The model embeds the first observation to an initial condition in a latent space with e_ϕ^c, solves the above ODE and predicts the labels from the hidden state at a given time with d_ω.

$$\begin{aligned}
\boldsymbol{h}_0 &= e_\phi^c(X(0)) \\
\boldsymbol{h}_i &= \text{ODESolve}(\frac{d\boldsymbol{h}}{ds}, \boldsymbol{h}_0, 0, i) \\
\hat{y}_i &= d_\omega(\boldsymbol{h}_i)
\end{aligned}$$

4.2 ODE-RNN

The ODE-RNN model (Rubanova et al., 2019) generalizes RNN models so the hidden state evolves according to a differential equation *between* observations.

$$\frac{d\boldsymbol{h}}{ds} = f_\theta^c(\boldsymbol{h}, \psi(s))\frac{d\psi}{ds}$$

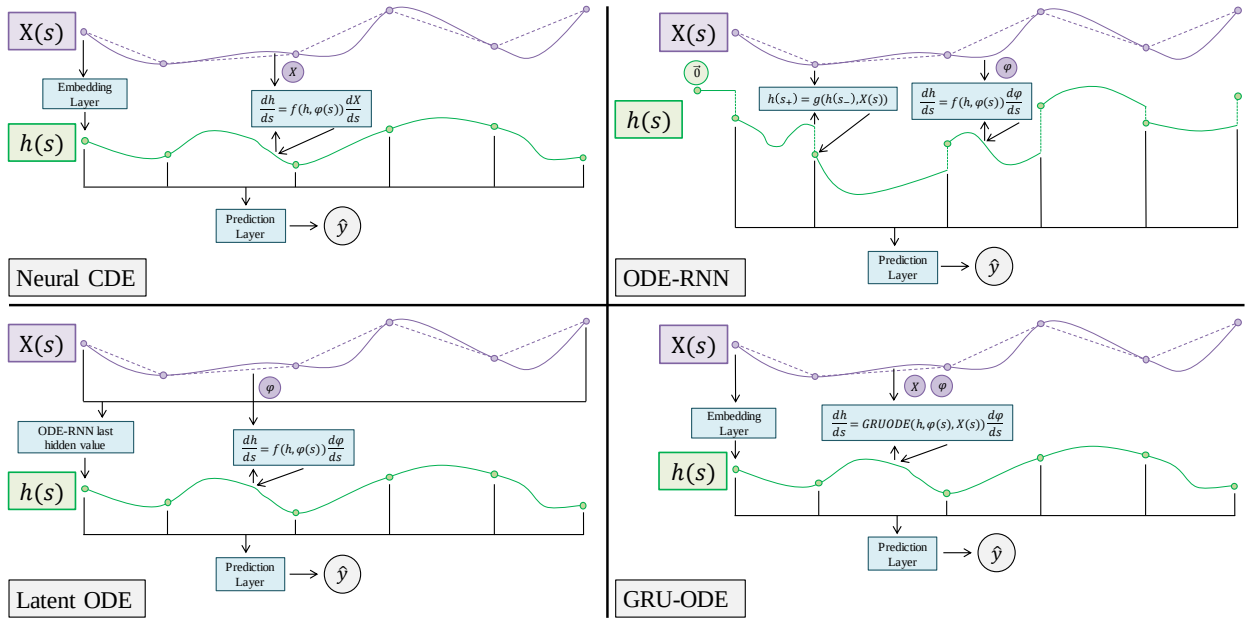

Figure 1: Block diagram of the four continuous models. The interpolation of $X(s)$ shows a linear and a cubic interpolation. Diagrams are best viewed zoomed in.

And then *at* observations undergoes a discrete change. For both the ODE-RNN and Latent ODE below, during preprocessing we create an update mask for each subject at each timestep $u_i \in \{0, 1\}$, where 1 indicates we want to update the hidden state. So for data padded to the maximum length, the update is set to zero. The initial hidden state is a vector of zeros. This evolves continuously between observations and at observations changes discretely based on its current value, the observation and context using g_ϕ^c. Finally predictions are made from the hidden state at a given time with d_ω.

$$
\begin{aligned}
\boldsymbol{h}_{-1} &= \mathbf{0} \\
\tilde{\boldsymbol{h}}_i &= \text{ODESolve}(\frac{d\boldsymbol{h}}{ds}, \boldsymbol{h}_{i-1}, i-1, i) \\
\boldsymbol{h}_i &= u_i g_\phi^c(\tilde{\boldsymbol{h}}_i, X(i)) + (1 - u_i)\boldsymbol{h}_{i-1} \\
\hat{y}_i &= d_\omega(\boldsymbol{h}_i)
\end{aligned}
$$

The spline rules mean that $d\psi/ds$ is zero outside the range of the time-series, so the first update from $i = -1$ to $i = 0$ is actually a discrete one only as the ODE function is zero here.

4.3 Latent ODE

The Latent ODE extends the ODE-RNN model to an encoder-decoder model that encodes entire sequences and then decodes them. We use an ODE-RNN model to encode the whole sequence to a single vector, taking the final value of the hidden state from the ODE-RNN. This is then fed into another ODE to decode where the decoding ODE is given by

$$
\frac{d\boldsymbol{h}}{ds} = f_\theta^c(\boldsymbol{h}, \psi(s)) \frac{d\psi}{ds}
$$

The outputs of the decoding ODE are then fed through a final prediction layer d_ω.

$$\begin{aligned}
\boldsymbol{h}_0 &= \text{ODERNN}^c_\phi(X)[\text{final hidden value}] \\
\boldsymbol{h}_i &= \text{ODESolve}(\frac{d\boldsymbol{h}}{ds}, \boldsymbol{h}_0, 0, i) \\
\hat{y}_i &= d_\omega(\boldsymbol{h}_i)
\end{aligned}$$

When encoding the sequence with the ODE-RNN, we encode backwards such that the eariest observation is used last, so has the largest effect on the initial condition of the decoding ODE. Using update masks in the backwards ODE-RNN is particularly crucial here, so that the padded values do not affect the encoding of the hidden state. Note the Latent ODE encodes entire sequences, so this is not a causal model and we cannot use recti splines.

4.4 GRU-ODE

The GRU-ODE (De Brouwer et al., 2019), is a continuous analogue of the Gated Recurrent Unit (Cho et al., 2014). The dynamics are given by

$$\begin{aligned}
r &= \sigma\big(W_{rx}X(s) + W_{rh}\boldsymbol{h} + W_{rc}\boldsymbol{c} + b_r\big) \\
z &= \sigma\big(W_{zx}X(s) + W_{zh}\boldsymbol{h} + W_{zc}\boldsymbol{c} + b_z\big) \\
g &= \tanh\big(W_{gx}X(s) + W_{gh}(r \odot \boldsymbol{h}) + W_{gc}\boldsymbol{c} + b_g\big) \\
\frac{d\boldsymbol{h}}{ds} &= \big(1 - z\big) \odot \big(g - \boldsymbol{h}\big)\frac{d\psi}{ds}
\end{aligned}$$

For given weight matrices and bias vectors. These dynamics also depend on time since $t = \psi(s)$ is the last dimension of $X(s)$. We then follow the same convention as the Neural CDE, embed with e^c_ϕ, solve the dynamics and predict with d_ω.

$$\begin{aligned}
\boldsymbol{h}_0 &= e^c_\phi(X(0)) \\
\boldsymbol{h}_i &= \text{ODESolve}(\frac{d\boldsymbol{h}}{ds}, \boldsymbol{h}_0, 0, i) \\
\hat{y}_i &= d_\omega(\boldsymbol{h}_i)
\end{aligned}$$

For all of our models, all embedding and dynamics functions are given by multi-layer-perceptrons with ReLU non-linearities.[2] Embedding layers use one hidden layer and dynamics functions use two. The embedding layers use no final non-linearity, the dynamics functions use tanh to keep the ODE system numerically stable. All prediction layers are single linear layers which end in non-linearities specific to the problem: sigmoid for binary classification, softmax for multiclass classification and no non-linearity for regression.

5 Experiments

Our experiments are designed to investigate how well the continuous baseline methods can perform in the same MS based setting as non-continuous methods. Therefore we test the models on the same dataset from Roy et al. (2022) and compare against the best performing model from that paper for a given task.

Hyperparameters. We found hyperparameters using a cubic search and 10 fold cross-validation. The final hyperparameter configurations and values tested are given in Appendix A. Using cross-validation gives both different parameter initializations and train data splits to obtain uncertainty estimates on performance. Models are trained for 50 epochs with the Adam optimizer (Kingma & Ba, 2015), learning rates and batchsizes are hyperparameters given in Appendix A.

[2]Except for GRU-ODE where the dynamics are restricted as described.

Dataset Description. The Multiple Sclerosis Outcome Assessments Consortium (MSOAC) (Rudick et al., 2014) is a partnership whose goal is to collect, standardize, and analyze data about MS. One such dataset which we use is the Placebo dataset, which consists of 2465 separate patient records from 9 clinical trials. Since this is a public dataset, Institutional Review Board (IRB) approval is not required. The features contain demographics, medical history, MS specific data and POMs. The labels are constructed from Expanded Disability Status Scale (EDSS) scores (Kurtzke, 1983). These are clinically annotated scores to determine the severity of the MS, the scores range from 0 to 10 in steps of 0.5. EDSS scores are partitioned into four distinct subsets: 0 - 1 for no disability, 1.5 - 2.5 for mild disability, 3 - 4.5 for moderate disability, and 5 - 10 for severe disability. As in Roy et al. (2022) the aim is to predict the EDSS score for a patient for four given prediction windows: 0 - 6 months; 6 - 12 months; 12 - 18 months and 18 - 24 months. Prediction is also split up into four subtasks: predicting the EDSS score directly as a regression problem; predicting if EDSS > 3 as a binary classification problem; predicting if EDSS > 5 as a binary classification problem and predicting EDSS severity category as a multi-class classification problem. When predicting EDSS directly we report root mean squared error (RMSE); for the binary classification tasks, due to class imbalance, we report the area under the precision recall curve (AUPRC); and when predicting the EDSS as a severity category we calculate the AUPRC for each class in a one vs rest approach and report the mean across classes.

Rather than using all features we use a reduced set of PASAT, SDMT, NHPT, T25FW, EDSS, Age and Sex. These correspond to Paced Auditory Serial Addition Test, Symbol Digit Modalities Test, Nine Hole Peg Test, Timed 25-Foot Walk and the current EDSS score. These are the majority of the functional tests, removing most demographics and all questionnaires from the full feature set. We use a reduced set because interpolation and training are computationally expensive, the cost of the interpolation is $\mathcal{O}(n_f n_s n_t)$ where n_f is the number of features, n_s is the number of subjects and n_t is the length of the series. Additionally, for every call of the Neural CDE dynamics function there is a matrix-vector multiplication of cost $\mathcal{O}(n_f)$. We also initially found continuous models were unstable to many features, we carry out a feature ablation in Appendix B where we confirm this reduced set performs best. We specifically use these features because they have the lowest attrition compared to other features, they are approximately 10 times as abundant at the start of the study increasing to roughly 1000 times at 9 months, hence they are the most abundant (see Figure 2 of Roy et al. (2022) for a chart tracking the feature sparsity over time).

5.1 Results and Analysis

Overall Performance. We compare against the previously best performing model TCN, the performance has been attributed to the model's awareness of temporal evolution, in particular for predicting long term time-series. The results are given in Table 1. We see that in ten out of sixteen cases the Neural CDE outperforms TCN, often quite substantially. In some cases the Neural CDE performs worse than TCN, in particular for predicting the EDSS severity category the average AUPRC is consistently worse. We hypothesize this is due to the features used. Whilst Neural CDE performs worse with all features, it is likely that a different subset is optimal for this task. We also see that the other continuous models are occasionally able to beat TCN, but this isn't consistent. This shows that being continuous does not guarantee performance gains, but the correct model must still be used. Neural CDE outperforming ODE-RNN, Latent ODE and GRU-ODE is consistent with the findings in (Kidger et al., 2020), we hypothesize this is due to the Neural CDEs having provably more representation power acting on sequences than the other continuous models (see Kidger et al. (2020) for these theorems).

Table 1: MSOAC Values against the best performing model from (Roy et al., 2022). All metrics are AUPRC, except for the $EDSS_{mean}$ task, where we use RMSE. Best values are in **bold** and values better than TCN but not best are underlined.

Prediction Task	Prediction Window	TCN	Neural CDE	ODE RNN	Latent ODE	GRU ODE
$EDSS_{mean}$	0 - 6 mo	$\mathbf{1.264 \pm 0.055}$	1.408 ± 0.059	1.768 ± 0.139	1.617 ± 0.072	2.312 ± 0.271
	6 - 12 mo	1.650 ± 0.067	$\mathbf{1.627 \pm 0.055}$	1.886 ± 0.248	1.776 ± 0.071	2.236 ± 0.207
	12 - 18 mo	1.725 ± 0.074	$\mathbf{1.652 \pm 0.066}$	1.826 ± 0.123	1.810 ± 0.090	2.066 ± 0.086
	18 - 24 mo	1.666 ± 0.128	$\mathbf{1.587 \pm 0.078}$	1.741 ± 0.100	1.707 ± 0.097	1.834 ± 0.107
$EDSS_{mean} > 3$	0 - 6 mo	$\mathbf{0.909 \pm 0.014}$	0.908 ± 0.010	0.869 ± 0.018	0.871 ± 0.017	0.865 ± 0.021
	6 - 12 mo	0.820 ± 0.027	$\mathbf{0.852 \pm 0.016}$	$\underline{0.823 \pm 0.024}$	0.819 ± 0.030	0.788 ± 0.025
	12 - 18 mo	0.768 ± 0.031	$\mathbf{0.797 \pm 0.027}$	0.766 ± 0.032	$\underline{0.776 \pm 0.027}$	0.730 ± 0.041
	18 - 24 mo	0.703 ± 0.038	$\mathbf{0.742 \pm 0.035}$	0.697 ± 0.044	0.703 ± 0.044	0.666 ± 0.062
$EDSS_{mean} > 5$	0 - 6 mo	0.848 ± 0.035	$\mathbf{0.872 \pm 0.021}$	0.807 ± 0.032	0.788 ± 0.026	0.794 ± 0.036
	6 - 12 mo	0.722 ± 0.039	$\mathbf{0.793 \pm 0.039}$	$\underline{0.751 \pm 0.026}$	$\underline{0.740 \pm 0.047}$	0.710 ± 0.045
	12 - 18 mo	0.669 ± 0.037	$\mathbf{0.730 \pm 0.031}$	$\underline{0.678 \pm 0.056}$	0.663 ± 0.052	0.643 ± 0.070
	18 - 24 mo	0.632 ± 0.037	$\mathbf{0.658 \pm 0.056}$	0.594 ± 0.047	0.602 ± 0.068	0.552 ± 0.077
$EDSS_{mean}$ As Severity Category	0 - 6 mo	$\mathbf{0.782 \pm 0.028}$	0.688 ± 0.009	0.566 ± 0.028	0.580 ± 0.029	0.569 ± 0.036
	6 - 12 mo	$\mathbf{0.709 \pm 0.044}$	0.672 ± 0.016	0.601 ± 0.024	0.596 ± 0.021	0.555 ± 0.038
	12 - 18 mo	$\mathbf{0.674 \pm 0.037}$	0.648 ± 0.022	0.574 ± 0.027	0.589 ± 0.028	0.538 ± 0.032
	18 - 24 mo	$\mathbf{0.632 \pm 0.037}$	0.616 ± 0.025	0.540 ± 0.018	0.557 ± 0.031	0.513 ± 0.055

Table 2: Ablation of the effects of standardization and interpolation of features for Neural CDE on MSOAC. All metrics are AUPRC, except for the $EDSS_{mean}$ task, where we use RMSE.

Prediction Task	Prediction Window	W Standardize W Interpolate	W Standardize WO Interpolate	WO Standardize W Interpolate	WO Standardize WO Interpolate
$EDSS_{mean}$	0 - 6 mo	1.408 ± 0.059	$\mathbf{1.406 \pm 0.072}$	4.508 ± 2.124	3.463 ± 1.142
	6 - 12 mo	$\mathbf{1.627 \pm 0.055}$	1.633 ± 0.075	3.561 ± 1.289	3.677 ± 1.718
	12 - 18 mo	1.652 ± 0.066	$\mathbf{1.638 \pm 0.071}$	3.633 ± 1.099	3.797 ± 1.246
	18 - 24 mo	1.587 ± 0.078	$\mathbf{1.578 \pm 0.073}$	3.976 ± 2.341	4.047 ± 1.886
$EDSS_{mean} > 3$	0 - 6 mo	$\mathbf{0.908 \pm 0.010}$	$\mathbf{0.908 \pm 0.013}$	0.729 ± 0.071	0.732 ± 0.078
	6 - 12 mo	0.852 ± 0.016	$\mathbf{0.853 \pm 0.022}$	0.662 ± 0.060	0.697 ± 0.033
	12 - 18 mo	0.797 ± 0.027	$\mathbf{0.798 \pm 0.025}$	0.595 ± 0.087	0.619 ± 0.107
	18 - 24 mo	$\mathbf{0.742 \pm 0.035}$	$\mathbf{0.742 \pm 0.037}$	0.571 ± 0.117	0.564 ± 0.071
$EDSS_{mean} > 5$	0 - 6 mo	$\mathbf{0.872 \pm 0.021}$	0.868 ± 0.022	0.587 ± 0.097	0.612 ± 0.090
	6 - 12 mo	0.793 ± 0.039	$\mathbf{0.799 \pm 0.036}$	0.560 ± 0.112	0.481 ± 0.114
	12 - 18 mo	0.730 ± 0.031	$\mathbf{0.731 \pm 0.040}$	0.441 ± 0.117	0.438 ± 0.147
	18 - 24 mo	$\mathbf{0.658 \pm 0.056}$	$\mathbf{0.658 \pm 0.052}$	0.380 ± 0.126	0.397 ± 0.141
$EDSS_{mean}$ As Severity Category	0 - 6 mo	$\mathbf{0.688 \pm 0.009}$	$\mathbf{0.688 \pm 0.018}$	0.437 ± 0.082	0.413 ± 0.082
	6 - 12 mo	$\mathbf{0.672 \pm 0.016}$	0.670 ± 0.019	0.448 ± 0.069	0.438 ± 0.080
	12 - 18 mo	$\mathbf{0.648 \pm 0.022}$	$\mathbf{0.648 \pm 0.022}$	0.438 ± 0.050	0.441 ± 0.074
	18 - 24 mo	$\mathbf{0.616 \pm 0.025}$	$\mathbf{0.616 \pm 0.020}$	0.464 ± 0.049	0.453 ± 0.058

Table 3: Ablation of which splines work best for Neural CDE on MSOAC. All metrics are AUPRC, except for the $\text{EDSS}_{\text{mean}}$ task, where we use RMSE.

Prediction Task	Prediction Window	Linear	Natural Cubic	Hermite Cubic	Monotonic Cubic	Recti-Linear	Recti-Cubic
$\text{EDSS}_{\text{mean}}$	0 - 6 mo	1.409 ± 0.077	1.409 ± 0.067	1.409 ± 0.059	1.411 ± 0.072	1.418 ± 0.062	$\mathbf{1.408 \pm 0.059}$
	6 - 12 mo	$\mathbf{1.627 \pm 0.055}$	1.633 ± 0.091	1.644 ± 0.080	1.644 ± 0.077	1.639 ± 0.062	1.651 ± 0.100
	12 - 18 mo	1.672 ± 0.079	1.671 ± 0.063	1.673 ± 0.079	$\mathbf{1.652 \pm 0.066}$	1.663 ± 0.087	1.676 ± 0.054
	18 - 24 mo	1.602 ± 0.089	1.597 ± 0.067	$\mathbf{1.587 \pm 0.078}$	1.592 ± 0.060	1.608 ± 0.090	1.589 ± 0.080
$\text{EDSS}_{\text{mean}} > 3$	0 - 6 mo	0.902 ± 0.012	0.903 ± 0.014	0.903 ± 0.011	0.903 ± 0.010	$\mathbf{0.908 \pm 0.010}$	0.904 ± 0.012
	6 - 12 mo	0.847 ± 0.016	0.848 ± 0.018	0.850 ± 0.017	0.848 ± 0.020	0.846 ± 0.021	$\mathbf{0.852 \pm 0.016}$
	12 - 18 mo	0.794 ± 0.027	0.795 ± 0.027	$\mathbf{0.797 \pm 0.033}$	$\mathbf{0.797 \pm 0.027}$	0.792 ± 0.024	0.795 ± 0.024
	18 - 24 mo	0.733 ± 0.042	0.740 ± 0.042	0.737 ± 0.036	0.738 ± 0.036	$\mathbf{0.742 \pm 0.035}$	0.738 ± 0.042
$\text{EDSS}_{\text{mean}} > 5$	0 - 6 mo	0.866 ± 0.018	0.865 ± 0.032	0.869 ± 0.018	0.864 ± 0.022	$\mathbf{0.872 \pm 0.021}$	0.865 ± 0.018
	6 - 12 mo	0.788 ± 0.030	0.789 ± 0.033	0.790 ± 0.026	0.788 ± 0.025	0.791 ± 0.032	$\mathbf{0.793 \pm 0.039}$
	12 - 18 mo	0.724 ± 0.034	$\mathbf{0.730 \pm 0.031}$	0.728 ± 0.027	0.727 ± 0.044	0.726 ± 0.039	0.722 ± 0.030
	18 - 24 mo	$\mathbf{0.658 \pm 0.043}$	0.654 ± 0.055	0.647 ± 0.052	0.652 ± 0.050	$\mathbf{0.658 \pm 0.056}$	$\mathbf{0.658 \pm 0.042}$
$\text{EDSS}_{\text{mean}}$ As Severity Category	0 - 6 mo	0.686 ± 0.014	0.683 ± 0.016	0.686 ± 0.012	0.686 ± 0.013	$\mathbf{0.688 \pm 0.009}$	0.686 ± 0.017
	6 - 12 mo	0.663 ± 0.018	0.669 ± 0.017	$\mathbf{0.672 \pm 0.016}$	0.664 ± 0.015	0.668 ± 0.016	0.666 ± 0.025
	12 - 18 mo	0.638 ± 0.020	$\mathbf{0.648 \pm 0.022}$	0.644 ± 0.024	0.643 ± 0.026	0.645 ± 0.020	0.643 ± 0.018
	18 - 24 mo	$\mathbf{0.616 \pm 0.021}$	$\mathbf{0.616 \pm 0.025}$	0.612 ± 0.023	0.613 ± 0.018	0.614 ± 0.028	0.614 ± 0.027

Standardization and Interpolation Ablation. Here we investigate how the performance changes based on whether we standardize features or interpolate missing values. When we don't impute with interpolated values we do so with zero instead. Note that interpolation must still be done to construct control signals $X(s)$, this ablation is about how we impute the missing values. Results for the Neural CDE are given in Table 2. We see that for Neural CDEs standardizing the values has the largest positive effect on performance. This is likely due to standardization transforming X into a manageable range, and by extension dX/ds, so that the dynamics of the Neural CDE are well regularized. We see that interpolating or filling with zeros does not have a significant effect; when standardization is fixed the difference between interpolating and filling with zero is almost negligible. We carry out the same ablation of the other continuous models in Appendix B and see similar results, therefore standardization is crucial for performance but interpolating missing values is not.

Interpolation Scheme Ablation. Here we investigate how the performance changes when using different interpolation schemes. For this we standardize the features and take the best performing models for each scheme. The values for the Neural CDE are given in Table 3. We see that there is essentially no difference between the interpolation choice. Each one performs best on a task, and all values are within a standard deviation of each other. We see the same results for ODE-RNN, Latent ODE and GRU-ODE whose results are given in Appendix B. This is consistent with the findings in (Morrill et al., 2021) where the different interpolation schemes perform as well as each other, as such we recommend using smooth causal splines where possible (recticubic) since they are causal by design and are faster to solve the differential equation than linear splines.

6 Conclusion

We investigated the use of continuous time models to predict the progression of multiple sclerosis from performance outcome measures and demographic data. We compared four continuous time models against the state of the art discrete time model - temporal convolutional network (TCN) - on a public multiple sclerosis dataset (MSOAC). We saw that Neural Controlled Differential Equations are able to beat TCN on the majority of experiments (ten out of sixteen), showing continuous time models are able to outperform

discrete time models, likely due to the inductive bias of a dynamical system being the underlying mechanism of the disease progression. We also introduced two new control signals and a way to efficiently batch irregular time-series via these control signals. After extensive ablation studies we found that standardization is vital to achieve competitive results, whereas the interpolation scheme is not. Thus we recommend using smooth causal interpolation schemes such as the newly introduced recticubic spline.

Limitations. We saw that three of the four continuous time models (ODE-RNN, Latent ODE, GRU-ODE) were not able to consistently outperform TCN demonstrating modeling in continuous time does not guarantee performance gains, and that choosing the correct model is still a crucial step in the prediction pipeline. We also saw that continuous time models required a feature selection step in order to reach their peak performance, adding further resource demands to the training.

Future Work. The main aim of this work was to demonstrate that continuous time models can be a superior option for modeling MS progression. We achieved this on Neural CDEs, and so our next steps are to continue to test Neural CDEs on more MS datasets such as Floodlight (Baker et al., 2021). We also plan to investigate how the Neural CDE scales to more features, and making it more stable in this scenario. Finally we plan to improve the interpolation speed by parallelizing and optimizing the interpolation process.

Broader Impact Statement

In our work we investigate using continuous time models to model the progression of Multiple Sclerosis. Our work has shown that in some scenarios Neural Controlled Differential Equations can outperform the current state of the art for longitudinal prediction.

Applications. We view positive applications of our work, since this could be used to help practitioners treat Multiple Sclerosis and also demonstrates for future research that continuous time models can be effective for this problem. Since this work is in early stages it should not be deployed yet, and more research and evaluation is required first. If deployed, it *must* be used alongside the expert opinion of trained practitioners, and if in disagreement an further expert assessment is sought out.

Datasets. We use a publicly available dataset in this work: Multiple Sclerosis Outcome Assessments Consortium (MSOAC) (Rudick et al., 2014) (`https://c-path.org/programs/msoac/`). Since the dataset is publicly available Institutional Review Board approval is not required.

Author Contributions

Author Contributions will be added after the review period.

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A Implementation Details

All models are implemented using TensorFlow and Keras using the TensorFlow ODE solver `https://www.tensorflow.org/probability/api_docs/python/tfp/math/ode`. Our code is not publicly available currently, however, we plan to open-source in the future and include full implementation details here for reproducibility purposes. All models are trained for 50 epochs with the Adam optimizer (Kingma & Ba, 2015). Hyperparameters are found using a cubic search with 10 fold cross-validation. We found two library specific caveats with the TensorFlow ODE solver, we describe them and provide the fixes in Appendix F.

A.1 Hyperparameters

Here we give the different hyperparameters of each model, the values used in the cubic search and the final value found. These are given for Neural CDE in Table 4, ODE-RNN in Table 5, Latent ODE in Table 6 and GRU-ODE in Table 7. In some cases the selected hyperparameter varied between the tasks, in particular for latent widths and hidden widths of models. We record these specific values in Table 8.

Table 4: Table of hyperparameters for Neural CDE.

Hyperparameter	Candidate Values	Best Value
Embedding Layer Learning Rate	0.001	0.001
Embedding Layer Hidden Width	[10, 20, 40]	Varies
Embedding Layer No. Hidden Layers	1	1
NCDE Learning Rate	0.001	0.001
NCDE Hidden Width	[10, 20, 40]	Varies
NCDE No. Hidden Layers	2	2
Prediction Layer Learning Rate	0.01	0.01
Latent Size	[5, 10, 20]	Varies
Batchsize	[50, 100, 200]	100

Table 5: Table of hyperparameters for ODE-RNN.

Hyperparameter	Candidate Values	Best Value
Discrete Update Learning Rate	0.001	0.001
Discrete Update Hidden Width	[10, 20, 40]	Varies
Discrete Update No. Hidden Layers	1	1
ODE Learning Rate	0.001	0.001
ODE Hidden Width	[10, 20, 40]	Varies
ODE No. Hidden Layers	2	2
Prediction Layer Learning Rate	0.01	0.01
Latent Size	[5, 10, 20]	Varies
Batchsize	[50, 100, 200]	100

Table 6: Table of hyperparameters for Latent ODE.

Hyperparameter	Candidate Values	Best Value
ODE-RNN Encoder Discrete Update Learning Rate	0.001	0.001
ODE-RNN Encoder Discrete Update Hidden Width	[10, 20, 40]	Varies
ODE-RNN Encoder Discrete Update No. Hidden Layers	1	1
ODE-RNN Encoder ODE Learning Rate	0.001	0.001
ODE-RNN Encoder ODE Hidden Width	[10, 20, 40]	Varies
ODE-RNN Encoder ODE No. Hidden Layers	2	2
ODE Decoder Learning Rate	0.001	0.001
ODE Decoder Hidden Width	[10, 20, 40]	Varies
ODE Decoder No. Hidden Layers	2	2
Prediction Layer Learning Rate	0.01	0.01
Latent Size	[5, 10, 20]	Varies
Batchsize	[50, 100, 200]	100

Table 7: Table of hyperparameters for GRU-ODE.

Hyperparameter	Candidate Values	Best Value
Embedding Layer Learning Rate	0.001	0.001
Embedding Layer Hidden Width	[10, 20, 40]	Varies
Embedding Layer No. Hidden Layers	2	2
GRU-ODE Learning Rate	0.001	0.001
Prediction Layer Learning Rate	0.01	0.01
Latent Size	[5, 10, 20]	Varies
Batchsize	[50, 100, 200]	100

Table 8: MSOAC Hyperparameters that varied between tasks. The first value is the selected Latent Width and the second value is the selected Hidden Widths of the models.

Prediction Task	Prediction Window	Neural CDE	ODE RNN	Latent ODE	GRU ODE
$EDSS_{mean}$	0 - 6 mo	40, 20	40, 10	40, 5	40, 5
	6 - 12 mo	40, 20	40, 5	40, 5	40, 20
	12 - 18 mo	40, 20	40, 5	40, 5	40, 20
	18 - 24 mo	40, 10	40, 5	40, 10	40, 10
$EDSS_{mean} > 3$	0 - 6 mo	40, 20	20, 10	10, 20	40, 20
	6 - 12 mo	20, 20	20, 10	40, 5	40, 20
	12 - 18 mo	40, 20	20, 5	10, 20	40, 20
	18 - 24 mo	20, 20	40, 5	10, 20	40, 20
$EDSS_{mean} > 5$	0 - 6 mo	40, 20	10, 10	10, 10	40, 20
	6 - 12 mo	40, 20	40, 5	20, 20	40, 20
	12 - 18 mo	40, 20	40, 5	10, 20	40, 20
	18 - 24 mo	40, 20	10, 20	10, 20	40, 20
$EDSS_{mean}$ As Severity Category	0 - 6 mo	40, 20	40, 5	40, 10	40, 20
	6 - 12 mo	40, 20	40, 5	40, 5	40, 20
	12 - 18 mo	40, 20	40, 5	10, 20	40, 20
	18 - 24 mo	40, 20	20, 10	10, 20	40, 20

B Ablation Studies

In Section 5 we carried out ablations investigating how standardization, interpolating missing values and interpolation scheme affect the performance of Neural CDEs. In this section we do the same for ODE-RNN, Latent ODE and GRU-ODE.

B.1 Standardizing and Interpolating

We look at the effects of standardizing features and interpolating missing features for ODE-RNN in Table 9, Latent ODE in Table 10 and GRU-ODE in Table 11. We see that on the whole ODE-RNN does best when standardizing features and filling missing values with zeros, Latent ODE does not have a clear superior scheme and GRU-ODE does best when standardizing features and filling missing values with interpolated values. However for these three methods the differences are small, whereas with Neural CDEs there was a clear distinction between standardizing and not standardizing features. This is likely due to the models dynamics functions. The dynamics function for the Neural CDE ends with dX/ds, whereas all others end with $d\psi/ds$. The true times are fairly small and therefore so is $d\psi/ds$. However, X can be quite large, and therefore so is dX/ds. And so standardizing X aids Neural CDEs more because dX/ds in the dynamics is explicitly shifted to a more manageable range, whereas $d\psi/ds$ was already in that range. We hypothesize that if the true times were far larger, we would see a significant difference if we scaled the times compared to not scaling them.

Table 9: Ablation of the effects of standardization and interpolation of features for ODE-RNN on MSOAC. All metrics are AUPRC, except for the $\text{EDSS}_{\text{mean}}$ task, where we use RMSE.

Prediction Task	Prediction Window	W Standardize W Interpolate	W Standardize WO Interpolate	WO Standardize W Interpolate	WO Standardize WO Interpolate
$\text{EDSS}_{\text{mean}}$	0 - 6 mo	1.768 ± 0.139	1.743 ± 0.145	$\mathbf{1.725 \pm 0.167}$	1.756 ± 0.138
	6 - 12 mo	1.886 ± 0.248	1.870 ± 0.103	1.842 ± 0.167	$\mathbf{1.821 \pm 0.163}$
	12 - 18 mo	1.826 ± 0.123	$\mathbf{1.802 \pm 0.075}$	1.825 ± 0.117	1.827 ± 0.086
	18 - 24 mo	1.741 ± 0.100	$\mathbf{1.709 \pm 0.101}$	1.717 ± 0.066	1.727 ± 0.100
$\text{EDSS}_{\text{mean}} > 3$	0 - 6 mo	0.869 ± 0.018	$\mathbf{0.873 \pm 0.009}$	0.866 ± 0.026	0.864 ± 0.025
	6 - 12 mo	0.823 ± 0.024	$\mathbf{0.825 \pm 0.029}$	0.815 ± 0.030	0.816 ± 0.027
	12 - 18 mo	0.766 ± 0.032	0.762 ± 0.034	0.758 ± 0.051	$\mathbf{0.768 \pm 0.023}$
	18 - 24 mo	0.697 ± 0.044	0.695 ± 0.042	$\mathbf{0.701 \pm 0.038}$	0.698 ± 0.032
$\text{EDSS}_{\text{mean}} > 5$	0 - 6 mo	0.807 ± 0.032	$\mathbf{0.818 \pm 0.027}$	0.792 ± 0.054	0.806 ± 0.027
	6 - 12 mo	0.751 ± 0.026	$\mathbf{0.757 \pm 0.040}$	0.726 ± 0.028	0.728 ± 0.049
	12 - 18 mo	0.678 ± 0.056	$\mathbf{0.682 \pm 0.035}$	0.655 ± 0.029	0.662 ± 0.050
	18 - 24 mo	0.594 ± 0.047	$\mathbf{0.600 \pm 0.044}$	0.588 ± 0.053	0.593 ± 0.055
$\text{EDSS}_{\text{mean}}$ As Severity Category	0 - 6 mo	0.566 ± 0.028	$\mathbf{0.578 \pm 0.024}$	0.564 ± 0.025	0.564 ± 0.038
	6 - 12 mo	$\mathbf{0.601 \pm 0.024}$	0.593 ± 0.036	0.588 ± 0.018	0.583 ± 0.033
	12 - 18 mo	0.574 ± 0.027	0.576 ± 0.026	$\mathbf{0.577 \pm 0.027}$	$\mathbf{0.577 \pm 0.026}$
	18 - 24 mo	0.540 ± 0.018	$\mathbf{0.545 \pm 0.034}$	0.542 ± 0.028	0.542 ± 0.022

Table 10: Ablation of the effects of standardization and interpolation of features for Latent ODE on MSOAC. All metrics are AUPRC, except for the $EDSS_{mean}$ task, where we use RMSE.

Prediction Task	Prediction Window	W Standardize W Interpolate	W Standardize WO Interpolate	WO Standardize W Interpolate	WO Standardize WO Interpolate
$EDSS_{mean}$	0 - 6 mo	1.617 ± 0.072	1.615 ± 0.088	$\mathbf{1.585 \pm 0.079}$	1.596 ± 0.094
	6 - 12 mo	1.776 ± 0.071	1.784 ± 0.081	$\mathbf{1.754 \pm 0.099}$	1.775 ± 0.073
	12 - 18 mo	1.810 ± 0.090	1.763 ± 0.094	$\mathbf{1.735 \pm 0.100}$	1.758 ± 0.084
	18 - 24 mo	1.707 ± 0.097	1.683 ± 0.094	$\mathbf{1.644 \pm 0.090}$	1.653 ± 0.074
$EDSS_{mean} > 3$	0 - 6 mo	0.871 ± 0.017	$\mathbf{0.879 \pm 0.017}$	0.866 ± 0.025	0.867 ± 0.018
	6 - 12 mo	0.819 ± 0.030	$\mathbf{0.824 \pm 0.026}$	0.818 ± 0.034	0.819 ± 0.020
	12 - 18 mo	0.776 ± 0.027	0.770 ± 0.040	$\mathbf{0.777 \pm 0.037}$	$\mathbf{0.777 \pm 0.024}$
	18 - 24 mo	0.703 ± 0.044	$\mathbf{0.713 \pm 0.044}$	0.711 ± 0.032	0.712 ± 0.035
$EDSS_{mean} > 5$	0 - 6 mo	$\mathbf{0.788 \pm 0.026}$	0.786 ± 0.031	0.786 ± 0.025	0.775 ± 0.037
	6 - 12 mo	0.740 ± 0.047	0.737 ± 0.035	0.732 ± 0.039	$\mathbf{0.741 \pm 0.037}$
	12 - 18 mo	0.663 ± 0.052	0.665 ± 0.049	0.676 ± 0.040	$\mathbf{0.679 \pm 0.035}$
	18 - 24 mo	0.602 ± 0.068	$\mathbf{0.613 \pm 0.064}$	0.602 ± 0.058	0.604 ± 0.063
$EDSS_{mean}$ As Severity Category	0 - 6 mo	0.580 ± 0.029	0.590 ± 0.020	0.585 ± 0.018	$\mathbf{0.591 \pm 0.034}$
	6 - 12 mo	0.596 ± 0.021	0.599 ± 0.018	0.600 ± 0.032	$\mathbf{0.609 \pm 0.018}$
	12 - 18 mo	0.589 ± 0.028	0.593 ± 0.026	0.599 ± 0.026	$\mathbf{0.610 \pm 0.024}$
	18 - 24 mo	0.557 ± 0.031	0.563 ± 0.034	$\mathbf{0.573 \pm 0.025}$	0.571 ± 0.024

Table 11: Ablation of the effects of standardization and interpolation of features for GRU-ODE on MSOAC. All metrics are AUPRC, except for the $EDSS_{mean}$ task, where we use RMSE.

Prediction Task	Prediction Window	W Standardize W Interpolate	W Standardize WO Interpolate	WO Standardize W Interpolate	WO Standardize WO Interpolate
$EDSS_{mean}$	0 - 6 mo	2.312 ± 0.271	2.295 ± 0.362	2.115 ± 0.374	$\mathbf{2.043 \pm 0.188}$
	6 - 12 mo	2.236 ± 0.207	2.252 ± 0.183	2.044 ± 0.135	$\mathbf{1.977 \pm 0.119}$
	12 - 18 mo	2.066 ± 0.086	2.066 ± 0.138	2.009 ± 0.112	$\mathbf{2.001 \pm 0.096}$
	18 - 24 mo	$\mathbf{1.834 \pm 0.107}$	1.842 ± 0.116	1.880 ± 0.069	1.908 ± 0.097
$EDSS_{mean} > 3$	0 - 6 mo	0.865 ± 0.021	$\mathbf{0.867 \pm 0.019}$	0.848 ± 0.024	0.851 ± 0.029
	6 - 12 mo	0.788 ± 0.025	$\mathbf{0.791 \pm 0.023}$	0.780 ± 0.033	0.753 ± 0.026
	12 - 18 mo	$\mathbf{0.730 \pm 0.041}$	0.727 ± 0.047	0.657 ± 0.040	0.659 ± 0.062
	18 - 24 mo	$\mathbf{0.666 \pm 0.062}$	0.650 ± 0.039	0.577 ± 0.089	0.566 ± 0.074
$EDSS_{mean} > 5$	0 - 6 mo	0.794 ± 0.036	$\mathbf{0.805 \pm 0.031}$	0.756 ± 0.035	0.761 ± 0.031
	6 - 12 mo	$\mathbf{0.710 \pm 0.045}$	0.698 ± 0.042	0.671 ± 0.061	0.640 ± 0.037
	12 - 18 mo	$\mathbf{0.643 \pm 0.070}$	0.620 ± 0.060	0.531 ± 0.132	0.559 ± 0.081
	18 - 24 mo	$\mathbf{0.552 \pm 0.077}$	0.524 ± 0.093	0.425 ± 0.164	0.393 ± 0.091
$EDSS_{mean}$ As Severity Category	0 - 6 mo	$\mathbf{0.569 \pm 0.036}$	0.558 ± 0.032	0.510 ± 0.021	0.513 ± 0.036
	6 - 12 mo	$\mathbf{0.555 \pm 0.038}$	0.545 ± 0.029	0.492 ± 0.033	0.500 ± 0.039
	12 - 18 mo	0.538 ± 0.032	$\mathbf{0.548 \pm 0.038}$	0.496 ± 0.043	0.496 ± 0.028
	18 - 24 mo	$\mathbf{0.513 \pm 0.055}$	0.511 ± 0.038	0.442 ± 0.033	0.440 ± 0.040

B.2 Interpolation Schemes

We investigate which interpolation schemes are best for ODE-RNN in Table 12, Latent ODE in Table 13 and GRU-ODE in Table 14. As was the case for Neural CDEs, we see that there is minimal difference between the choices of interpolation scheme.

Table 12: Ablation of which splines work best for ODE-RNN on MSOAC. All metrics are AUPRC, except for the $\text{EDSS}_{\text{mean}}$ task, where we use RMSE.

Prediction Task	Prediction Window	Linear	Natural Cubic	Hermite Cubic	Monotonic Cubic	Recti-Linear	Recti-Cubic
$\text{EDSS}_{\text{mean}}$	0 - 6 mo	1.805 ± 0.186	1.820 ± 0.232	1.939 ± 0.290	1.975 ± 0.230	1.889 ± 0.294	$\mathbf{1.768 \pm 0.139}$
	6 - 12 mo	1.898 ± 0.204	1.897 ± 0.099	1.917 ± 0.196	2.012 ± 0.215	1.915 ± 0.186	$\mathbf{1.886 \pm 0.248}$
	12 - 18 mo	$\mathbf{1.826 \pm 0.123}$	1.896 ± 0.174	1.875 ± 0.147	1.855 ± 0.128	1.852 ± 0.136	1.835 ± 0.143
	18 - 24 mo	$\mathbf{1.741 \pm 0.100}$	1.754 ± 0.108	1.766 ± 0.103	1.801 ± 0.136	1.833 ± 0.175	1.757 ± 0.136
$\text{EDSS}_{\text{mean}} > 3$	0 - 6 mo	0.863 ± 0.020	0.868 ± 0.024	0.864 ± 0.024	0.865 ± 0.016	0.863 ± 0.017	$\mathbf{0.869 \pm 0.018}$
	6 - 12 mo	0.816 ± 0.025	0.810 ± 0.034	$\mathbf{0.823 \pm 0.024}$	0.820 ± 0.027	0.818 ± 0.029	0.814 ± 0.026
	12 - 18 mo	0.747 ± 0.028	0.760 ± 0.042	0.756 ± 0.027	0.763 ± 0.030	$\mathbf{0.766 \pm 0.032}$	0.752 ± 0.026
	18 - 24 mo	0.695 ± 0.032	0.692 ± 0.036	0.673 ± 0.038	0.694 ± 0.039	0.692 ± 0.034	$\mathbf{0.697 \pm 0.044}$
$\text{EDSS}_{\text{mean}} > 5$	0 - 6 mo	0.803 ± 0.030	0.804 ± 0.039	$\mathbf{0.807 \pm 0.032}$	$\mathbf{0.807 \pm 0.027}$	0.802 ± 0.028	0.805 ± 0.029
	6 - 12 mo	0.742 ± 0.047	0.732 ± 0.056	$\mathbf{0.751 \pm 0.026}$	0.736 ± 0.031	0.730 ± 0.060	0.744 ± 0.043
	12 - 18 mo	$\mathbf{0.678 \pm 0.056}$	0.653 ± 0.041	0.672 ± 0.053	0.662 ± 0.050	0.675 ± 0.040	0.663 ± 0.042
	18 - 24 mo	0.586 ± 0.046	0.592 ± 0.045	$\mathbf{0.594 \pm 0.047}$	0.590 ± 0.050	0.581 ± 0.049	0.572 ± 0.062
$\text{EDSS}_{\text{mean}}$ As Severity Category	0 - 6 mo	$\mathbf{0.566 \pm 0.028}$	0.562 ± 0.036	0.556 ± 0.040	0.559 ± 0.030	0.558 ± 0.024	0.557 ± 0.028
	6 - 12 mo	0.591 ± 0.041	0.579 ± 0.034	0.580 ± 0.024	0.583 ± 0.046	$\mathbf{0.601 \pm 0.024}$	0.586 ± 0.021
	12 - 18 mo	0.559 ± 0.019	0.560 ± 0.042	0.559 ± 0.025	$\mathbf{0.574 \pm 0.027}$	0.570 ± 0.020	0.573 ± 0.025
	18 - 24 mo	0.539 ± 0.026	0.538 ± 0.029	0.530 ± 0.029	0.538 ± 0.030	0.534 ± 0.032	$\mathbf{0.540 \pm 0.018}$

Table 13: Ablation of which splines work best for Latent ODE on MSOAC. All metrics are AUPRC, except for the $\text{EDSS}_{\text{mean}}$ task, where we use RMSE. Recall that since Latent ODE encodes a whole sequence and then decodes to predict, the rectilinear and recticubic splines cannot be used.

Prediction Task	Prediction Window	Linear	Natural Cubic	Hermite Cubic	Monotonic Cubic
$\text{EDSS}_{\text{mean}}$	0 - 6 mo	1.619 ± 0.078	1.620 ± 0.095	1.643 ± 0.080	$\mathbf{1.617 \pm 0.072}$
	6 - 12 mo	1.806 ± 0.077	$\mathbf{1.776 \pm 0.071}$	1.819 ± 0.132	1.785 ± 0.058
	12 - 18 mo	1.816 ± 0.116	$\mathbf{1.810 \pm 0.090}$	$\mathbf{1.810 \pm 0.089}$	1.838 ± 0.151
	18 - 24 mo	1.726 ± 0.081	1.717 ± 0.094	1.747 ± 0.115	$\mathbf{1.707 \pm 0.097}$
$\text{EDSS}_{\text{mean}} > 3$	0 - 6 mo	0.863 ± 0.024	0.866 ± 0.017	0.868 ± 0.023	$\mathbf{0.871 \pm 0.017}$
	6 - 12 mo	0.818 ± 0.029	0.817 ± 0.019	$\mathbf{0.819 \pm 0.026}$	$\mathbf{0.819 \pm 0.030}$
	12 - 18 mo	$\mathbf{0.776 \pm 0.027}$	0.769 ± 0.022	0.765 ± 0.038	0.763 ± 0.033
	18 - 24 mo	0.699 ± 0.054	0.700 ± 0.047	0.692 ± 0.045	$\mathbf{0.703 \pm 0.044}$
$\text{EDSS}_{\text{mean}} > 5$	0 - 6 mo	0.779 ± 0.044	$\mathbf{0.788 \pm 0.026}$	0.780 ± 0.057	0.779 ± 0.040
	6 - 12 mo	0.733 ± 0.039	0.719 ± 0.037	0.718 ± 0.046	$\mathbf{0.740 \pm 0.047}$
	12 - 18 mo	0.654 ± 0.038	0.651 ± 0.048	0.656 ± 0.044	$\mathbf{0.663 \pm 0.052}$
	18 - 24 mo	0.581 ± 0.050	0.574 ± 0.061	0.590 ± 0.047	$\mathbf{0.602 \pm 0.068}$
$\text{EDSS}_{\text{mean}}$ As Severity Category	0 - 6 mo	$\mathbf{0.580 \pm 0.029}$	0.568 ± 0.035	0.573 ± 0.030	0.559 ± 0.024
	6 - 12 mo	0.595 ± 0.026	0.587 ± 0.023	$\mathbf{0.596 \pm 0.021}$	0.589 ± 0.031
	12 - 18 mo	0.587 ± 0.030	$\mathbf{0.589 \pm 0.028}$	0.586 ± 0.033	0.585 ± 0.031
	18 - 24 mo	$\mathbf{0.557 \pm 0.021}$	0.555 ± 0.033	$\mathbf{0.557 \pm 0.031}$	0.556 ± 0.033

Table 14: Ablation of which splines work best for GRU-ODE on MSOAC. All metrics are AUPRC, except for the $EDSS_{mean}$ task, where we use RMSE.

Prediction Task	Prediction Window	Linear	Natural Cubic	Hermite Cubic	Monotonic Cubic	Recti-Linear	Recti-Cubic
$EDSS_{mean}$	0 - 6 mo	$\mathbf{2.312 \pm 0.271}$	2.421 ± 0.199	2.570 ± 0.393	2.381 ± 0.445	2.434 ± 0.430	2.512 ± 0.630
	6 - 12 mo	2.335 ± 0.342	2.275 ± 0.167	$\mathbf{2.236 \pm 0.207}$	2.290 ± 0.247	2.324 ± 0.379	2.468 ± 0.313
	12 - 18 mo	2.077 ± 0.183	$\mathbf{2.066 \pm 0.086}$	2.114 ± 0.130	2.148 ± 0.229	2.126 ± 0.161	2.241 ± 0.287
	18 - 24 mo	1.863 ± 0.105	$\mathbf{1.834 \pm 0.107}$	1.870 ± 0.124	1.863 ± 0.094	1.884 ± 0.075	1.914 ± 0.127
$EDSS_{mean} > 3$	0 - 6 mo	0.854 ± 0.031	0.860 ± 0.012	0.855 ± 0.038	0.855 ± 0.030	$\mathbf{0.865 \pm 0.021}$	0.847 ± 0.027
	6 - 12 mo	0.785 ± 0.029	0.773 ± 0.038	0.776 ± 0.047	0.787 ± 0.027	0.774 ± 0.036	$\mathbf{0.788 \pm 0.025}$
	12 - 18 mo	0.694 ± 0.062	$\mathbf{0.730 \pm 0.041}$	0.704 ± 0.096	0.723 ± 0.049	0.723 ± 0.042	0.663 ± 0.060
	18 - 24 mo	$\mathbf{0.666 \pm 0.062}$	0.632 ± 0.112	0.631 ± 0.071	0.559 ± 0.163	0.661 ± 0.062	0.623 ± 0.104
$EDSS_{mean} > 5$	0 - 6 mo	0.773 ± 0.052	$\mathbf{0.794 \pm 0.036}$	0.782 ± 0.029	0.761 ± 0.041	0.790 ± 0.043	0.778 ± 0.052
	6 - 12 mo	0.673 ± 0.061	0.702 ± 0.054	$\mathbf{0.710 \pm 0.045}$	0.695 ± 0.034	0.649 ± 0.063	0.698 ± 0.038
	12 - 18 mo	0.630 ± 0.063	0.624 ± 0.093	0.623 ± 0.082	$\mathbf{0.643 \pm 0.070}$	0.639 ± 0.046	0.571 ± 0.137
	18 - 24 mo	0.511 ± 0.060	0.463 ± 0.184	0.523 ± 0.069	$\mathbf{0.552 \pm 0.077}$	0.476 ± 0.117	0.514 ± 0.117
$EDSS_{mean}$ As Severity Category	0 - 6 mo	0.552 ± 0.037	0.552 ± 0.021	0.567 ± 0.036	0.560 ± 0.026	$\mathbf{0.569 \pm 0.036}$	0.559 ± 0.031
	6 - 12 mo	0.541 ± 0.037	0.544 ± 0.028	0.531 ± 0.050	0.541 ± 0.033	0.540 ± 0.037	$\mathbf{0.555 \pm 0.038}$
	12 - 18 mo	$\mathbf{0.538 \pm 0.032}$	0.498 ± 0.036	0.504 ± 0.062	0.534 ± 0.032	0.513 ± 0.059	0.509 ± 0.058
	18 - 24 mo	$\mathbf{0.513 \pm 0.055}$	0.464 ± 0.057	0.484 ± 0.054	0.496 ± 0.069	0.509 ± 0.040	0.479 ± 0.049

B.3 Feature Ablation

In Section 5, it was stated that we used a reduced feature set for the continuous models. We use Paced Auditory Serial Addition Test, Symbol Digit Modalities Test, Nine Hole Peg Test, Timed 25-Foot Walk current EDSS score, Age and Sex. We focus on most of the functional tests, removing the demographics and questionnaires. In order to evaluate these features against the full feature set we test Neural CDE on the full feature set and the reduced set in Table 15, we see that Neural CDE is consistently better on the reduced feature set.

Table 15: Feature Ablation on Neural CDE. $*$: Not evaluated.

Prediction Task	Prediction Window	Neural CDE Reduced Features	Neural CDE All Features
$\text{EDSS}_{\text{mean}}$	0 - 6 mo	1.408 ± 0.059	$*$
	6 - 12 mo	1.627 ± 0.055	$*$
	12 - 18 mo	1.652 ± 0.066	$*$
	18 - 24 mo	1.587 ± 0.078	$*$
$\text{EDSS}_{\text{mean}} > 3$	0 - 6 mo	$\mathbf{0.908 \pm 0.010}$	0.756 ± 0.113
	6 - 12 mo	$\mathbf{0.852 \pm 0.016}$	0.711 ± 0.089
	12 - 18 mo	$\mathbf{0.797 \pm 0.027}$	0.695 ± 0.058
	18 - 24 mo	$\mathbf{0.742 \pm 0.035}$	0.641 ± 0.068
$\text{EDSS}_{\text{mean}} > 5$	0 - 6 mo	$\mathbf{0.872 \pm 0.021}$	0.609 ± 0.085
	6 - 12 mo	$\mathbf{0.793 \pm 0.039}$	0.517 ± 0.112
	12 - 18 mo	$\mathbf{0.730 \pm 0.031}$	0.455 ± 0.116
	18 - 24 mo	$\mathbf{0.658 \pm 0.056}$	0.445 ± 0.122
$\text{EDSS}_{\text{mean}}$ As Severity Category	0 - 6 mo	$\mathbf{0.688 \pm 0.009}$	0.487 ± 0.067
	6 - 12 mo	$\mathbf{0.672 \pm 0.016}$	0.517 ± 0.065
	12 - 18 mo	$\mathbf{0.648 \pm 0.022}$	0.482 ± 0.071
	18 - 24 mo	0.616 ± 0.025	$*$

We further hypothesize that one of the reasons NCDE becomes unstable to a large amount of features is because the dynamics function is given by a matrix-vector multiplication. The dynamics of the NCDE is given by $\frac{d\boldsymbol{h}}{ds} = f_\theta^c(\boldsymbol{h}, \psi(s))\frac{dX}{ds}$ which is a matrix-vector multiplication, whereas the other three models have a dynamics function given by $\frac{d\boldsymbol{h}}{ds} = f_\theta^c(\boldsymbol{h}, \psi(s))\frac{d\psi}{ds}$ which is a vector-scalar multiplication. This would mean, since all functions f_θ^c have a final tanh activation, the NCDE dynamics are bounded by $\pm \sum_i dX_i/ds$, whereas the other models dynamics are bounded by $\pm d\psi/ds$. This explains why NCDE is unstable to a large amount of features, because the magnitude of the velocity of the hidden state grows with the number of features, this does not happen for the other three models. One possible solution would be to divide the NCDE dynamics by the dimensionality of the vector X, which would make the dynamics agnostic to the number of features. On the other hand, this could also explain why NCDE performs better than the other models, the restriction on the dynamics is not as tight for NCDE models. It further explains the importance of standardizing X, keeping dX/ds in a manageable range to avoid numerical instability in the NCDE trajectories.

C Batching Irregular Time-Series

In Section 3 we introduced the pseudo-time method for training continuous models using batches. This relies on the equality

$$\text{ODESolve}(f, \boldsymbol{h}_0, t_0, t) = \text{ODESolve}(\tilde{f}, \boldsymbol{h}_0, s_0, s).$$

where $\tilde{f}(\boldsymbol{h}, s) = f(\boldsymbol{h}, \psi(s))\frac{d\psi}{ds}$ and that we interpolate t with an increasing function so that $t = \psi(s)$. We prove this below.

We carry out an ODE solve over an infinitesimal pseudo-time step from s_0 to $s_0 + \Delta s$. We have $t_0 = \psi(s_0)$, $t_0 + \Delta t = \psi(s_0 + \Delta s)$. For small enough Δs we have $\Delta t = \frac{d\psi}{ds}\Delta s$. We solve the ODE for the initial condition $\tilde{\boldsymbol{h}}(s_0) = \boldsymbol{h}_0$, and $\frac{d\tilde{\boldsymbol{h}}}{ds} = \tilde{f}(\tilde{\boldsymbol{h}}, s)$. Carrying out the ODE solve over the infinitesimal step we have:

$$\begin{aligned}
\tilde{\boldsymbol{h}}(s_0 + \Delta s) &= \tilde{\boldsymbol{h}}(s_0) + \tilde{f}(\tilde{\boldsymbol{h}}(s_0), s_0)\Delta s \\
&= \tilde{\boldsymbol{h}}(s_0) + f(\tilde{\boldsymbol{h}}(s_0), \psi(s_0))\frac{d\psi}{ds}\Delta s \\
&= \boldsymbol{h}_0 + f(\boldsymbol{h}_0, t_0)\Delta t
\end{aligned}$$

If we also carry out a second ODE solve from t_0 to $t_0 + \Delta t$, where the initial condition is $\boldsymbol{h}(t_0) = \boldsymbol{h}_0$ and $\frac{d\boldsymbol{h}}{dt} = f(\boldsymbol{h}, t)$. Carrying out the ODE solve over this infinitesimal step we have:

$$\boldsymbol{h}(t_0 + \Delta t) = \boldsymbol{h}_0 + f(\boldsymbol{h}_0, t_0)\Delta t$$

Giving us $\boldsymbol{h}(t_0 + \Delta t) = \tilde{\boldsymbol{h}}(s_0 + \Delta s)$. ODEs are fully determined by their dynamics and initial condition,[3] so we can repeat the above step making $\boldsymbol{h}(s_0 + \Delta s)$ the new initial condition. This can be repeated for the whole s domain, completing the proof. We demonstrate the batching procedure pictorially in Figure 2.

D Calculating Interpolating Splines

In this section we describe how the general splines are calculated without using any specific interpolation scheme and in Appendix E we discuss the interpolation schemes themselves. We use piece-wise cubics to interpolate, we don't use polynomials of arbitrary order since they can oscillate significantly.

Assuming we use integers as pseudo-time to interpolate, given a point s to evaluate at, a spline will first find the largest integer i which is smaller than s, and then $X(s)$ can be calculated using

$$X(s) = a_i(s - i)^3 + b_i(s - i)^2 + c_i(s - i) + d_i. \tag{3}$$

And its derivative can be calculated using

$$\frac{dX}{ds} = 3a_i(s - i)^2 + 2b_i(s - i) + c_i. \tag{4}$$

It is possible to expand these brackets, and then we can calculate new coefficients so that

$$X(s) = \tilde{a}_i s^3 + \tilde{b}_i s^2 + \tilde{c}_i s + \tilde{d}_i.$$

However, we found that this can be numerically unstable thus we use the method given by Equation 3. With this, the interpolation step finds the coefficients a_i, b_i, c_i and d_i, which change depending on the interpolation scheme.

To deal with missingness, consider one feature of a partially observed time-series with n measurements:

$$\big((x_0, 0), (\emptyset, 1), (x_2, 2), ..., (\emptyset, n-3), (x_{n-2}, n-2), (x_{n-1}, n-1)\big)$$

[3]The Picard-Lindelöf theorem requires that the dynamics function be Lipschitz continuous (Lindelöf, 1894). This is achieved with ReLU activations.

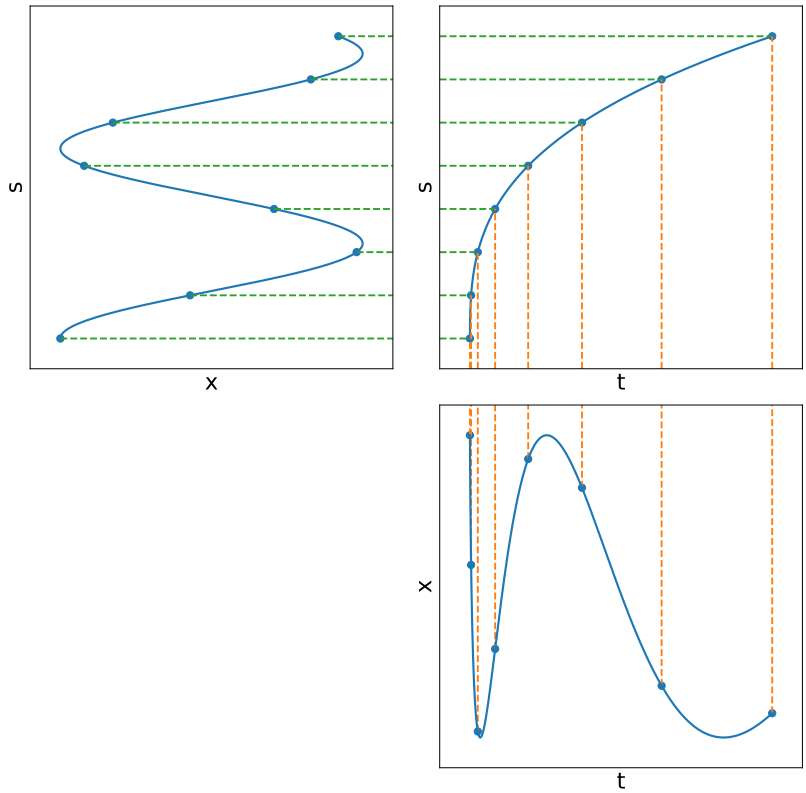

Figure 2: Visualization of the reparameterization from s to t. In the top left is a regular time-series where s represents pseudo-time (this panel is rotated 90° anti-clockwise). In the top right is how we map from s to t ($t = \psi(s)$), in the bottom right we have the irregular time-series where t is true time. When we solve we include $\frac{d\psi}{ds}$ in the dynamics function, which is effectively using the top right figure as a way to transform from s to t. Each time-series has a different version of this since the time-series are irregular, but these are all calculated before training so can be included easily for efficient batching.

Here we are missing measurements of this feature at $s = 1$ and $s = n - 3$. So we remove these:

$$\big((x_0, 0), (x_2, 2), ..., (x_{n-2}, n-2), (x_{n-1}, n-1)\big)$$

We then run the interpolation on what is left getting a, b, c, d coefficients for these observations. Finally to fill in the missing observations, we must continue the previous cubic spline. For example; between $s = 3$ and $s = 4$, we would like to continue the cubic between $s = 2$ and $s = 3$. To do this we require the two polynomials to match at all s:

$$a_i(s-i)^3 + b_i(s-i)^2 + c_i(s-i) + d_i = a_{i+1}(s-(i+1))^3 + b_{i+1}(s-(i+1))^2 + c_{i+1}(s-(i+1)) + d_{i+1}$$

Solving this, to find the coefficients where we have a missing value we take a linear combination of the previous coefficients

$$\begin{bmatrix} a_{i+1} \\ b_{i+1} \\ c_{i+1} \\ d_{i+1} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 3 & 1 & 0 & 0 \\ 3 & 2 & 1 & 0 \\ 1 & 1 & 1 & 1 \end{bmatrix} \begin{bmatrix} a_i \\ b_i \\ c_i \\ d_i \end{bmatrix}$$

For $i = -1$ or $i = n$, i.e. outside the range of the time-series, we set $a = b = c = 0$ and $d_{-1} = d_0$ or $d_n = d_{n-1}$. That is, outside the range of the time-series the spline predicts either the first or the last observed values as a constant, with zero derivative.

Note, since we have no knowledge about the missingness of features, or the irregularity of the time-series we must carry out this procedure separately for each feature of each time-series. This is a slow process and therefore is part of data preprocessing and the coefficients are saved.

E Interpolation Schemes

Here we give information about the specific interpolation schemes used, including the positives and negatives of using each. The majority of this is summarised from (Morrill et al., 2021). Importantly, for the t channel we must use a spline that is monotonic, i.e. it increases when the observations are increasing. We would also like to use a monotonic interpolation for the observation counts since these can only increase and we can enforce this inductive bias. In the following we give the steps for finding the coefficients to interpolate, this assumes a general set of times, rather than the integer pseudo-times we use. Therefore these can be used generally, and the specific case of the integers is a trivial change.

E.1 Linear

This is the simplest interpolation scheme, we carry out a linear interpolation between two observed points, so

$$\begin{bmatrix} a_i \\ b_i \\ c_i \\ d_i \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ (x_{i+1} - x_i)/(t_{i+1} - t_i) \\ x_i \end{bmatrix}$$

Pros and Cons. This is the simplest interpolation scheme, and intuitively the easiest to understand. If the observations are increasing then the spline is an increasing function, therefore this can be used to interpolate time and observation counts. However, it does not have a continuous first derivative so is slow to use in an ODE solver, it also misrepresents reality, it is unlikely features change in such a way that the derivative is discontinuous at points.

E.2 Hermite Cubic

Hermite interpolation is a smooth version of linear interpolation, where rather than discontinuities in the spline derivative at observations these are smoothed by making the derivative continuous there. Let the derivative at each point be equal to the derivative that would be calculated by linearly interpolating with the previous observation, $m_i = (x_i - x_{i-1})/(t_i - t_{i-1})$ for $i \geq 1$. Then set $m_0 = m_1$. With this we can calculate the coefficients

$$\begin{bmatrix} a_i \\ b_i \\ c_i \\ d_i \end{bmatrix} = \begin{bmatrix} (-2(x_{i+1} - x_i) + (t_{i+1} - t_i)(m_i - m_{i+1}))/(t_{i+1} - t_i)^3 \\ (3(x_{i+1} - x_i) - (t_{i+1} - t_i)(2m_i - m_{i+1}))/(t_{i+1} - t_i)^2 \\ m_i \\ x_i \end{bmatrix}$$

Pros and Cons. This is a smoothed out version of the linear spline, so is faster to use in a solve. Additionally as it is smooth it is a better inductive bias for interpolating features. However, it cannot be used to interpolate time or observation count since it is not monotonic. Also whilst having a continuous first derivative, it does not have a continuous second derivative.

E.3 Monotonic Cubic

We desire a smooth scheme to interpolate time. However, Hermite cubics do not enforce monotonicity and linear splines do not have continuous derivatives. To overcome this we propose a new interpolation scheme, the monotonic cubic (mono cubic). This is a Hermite cubic but we enforce zero derivative at every observation, therefore it is an increasing function if the observations are always increasing. It is smooth so we can use it in place of linear and it is monotonic so we can use it in place of the Hermite interpolation.

The formula for the coefficients is found by taking the formula for the Hermite coefficients and setting $m_i = 0$ for all i.

$$\begin{bmatrix} a_i \\ b_i \\ c_i \\ d_i \end{bmatrix} = \begin{bmatrix} -2(x_{i+1} - x_i)/(t_{i+1} - t_i)^3 \\ 3(x_{i+1} - x_i)/(t_{i+1} - t_i)^2 \\ 0 \\ x_i \end{bmatrix}$$

Pros and Cons. The monocubic is both smoother than the linear spline and is monotonic unlike the Hermite cubic. Therefore it is good to use for interpolating time or observations counts. However, it is not as good for interpolating features, since zero derivative is enforced at the observation points which is not a realistic inductive bias.

E.4 Natural Cubic

The natural cubic spline is a cubic spline that is twice-continuously differentiable everywhere. So the function, its first derivative and its second derivative are all continuous at and between observation points.

We start by constructing a system of linear equations for a vector k

$$k_{i-1}(t_{i-1} - t_i) + 2k_i(t_{i-1} - t_{i+1}) + k_{i+1}(t_i - t_{i+1}) = 6\left(\frac{x_{i-1} - x_i}{t_{i-1} - t_i} - \frac{x_i - x_{i+1}}{t_i - t_{i+1}}\right)$$

This is for $0 < i < n - 1$. We also have boundary conditions $k_0 = 0$ and $k_{n-1} = 0$. This system of linear equations can be solved using the tridiagonal algorithm which is $\mathcal{O}(n)$, rather than $\mathcal{O}(n^3)$ for Gaussian elimination. After finding the vector k its elements can be used to find the coefficients.

$$\begin{bmatrix} a_i \\ b_i \\ c_i \\ d_i \end{bmatrix} = \begin{bmatrix} (k_{i+1} - k_i)/6(t_{i+1} - t_i)^3 \\ k_i/2 \\ (x_{i+1} - x_i)/(t_{i+1} - t_i) - (k_{i+1} + 2k_i)(t_{i+1} - t_i) \\ x_i \end{bmatrix}$$

From the above formula we see that the second derivative of the spline at point i is k_i. Additionally, from the formula for c_i we see that the derivative at point i is what we expect from linear splines $(x_{i+1} - x_i)/(t_{i+1} - t_i)$ with a corrective term to make the first and second derivatives continuous.

Pros and Cons. This is the smoothest of the interpolants with a continuous second derivative. This makes the ODE solve faster. However, it is not causal since it uses the whole series to find the coefficients as part of the tridiagonal solve. This means that these splines can only be used when we enforce causality using the method of copying subjects, this cannot be used with recti splines.

F Library Specific Caveats

Our implementation uses TensorFlow and Keras, for which a differentiable ODE Solver exists. This can be found at `https://www.tensorflow.org/probability/api_docs/python/tfp/math/ode`. We found two main caveats using this that do not necessarily exist in other libraries such as TorchDiffEq (PyTorch) (Chen et al., 2018) or Diffrax (JAX) (Kidger, 2022). We provide the straightforward fixes here to aid implementation.

F.1 Running an ODE Backwards in Time

For models such as the Latent ODE, an ODE is solved backwards in time, this is when we solve from t_1 to t_0 where $t_1 \geq t_0$. The TensorFlow solver does not handle this by design, it assumes $t_1 \leq t_0$ (time is ordered). We are able to overcome this by solving a related ODE, with a new ODE function. If previously

$$\frac{d\boldsymbol{h}}{dt} = f(\boldsymbol{h}, t)$$

we use a new ODE

$$\frac{d\boldsymbol{h}}{dt} = \tilde{f}(\boldsymbol{h}, t) = -f(\boldsymbol{h}, -t).$$

And now we solve from $-t_1$ to $-t_0$ with the new ODE function

$$\boldsymbol{h}(t_0) = \text{ODESolve}(\tilde{f}, \boldsymbol{h}(t_1), -t_1, -t_0).$$

And since $-t_1 \leq -t_0$, the Tensorflow ODE solver can solve this. This requires that

$$\text{ODESolve}(\tilde{f}, \boldsymbol{h}(t_1), -t_1, -t_0) = \text{ODESolve}(f, \boldsymbol{h}(t_1), t_1, t_0)$$

which we prove below.

Let $\tilde{t} = -t$, and solve a new ODE for $\tilde{\boldsymbol{h}}(\tilde{t})$, where $\tilde{\boldsymbol{h}}(\tilde{t}_1) = \boldsymbol{h}(t_1)$. We carry out a solve over an infinitesimal step from $\tilde{t}_1$ to $\tilde{t}_1 + \Delta\tilde{t}$ giving

$$\begin{aligned}
\tilde{\boldsymbol{h}}(\tilde{t}_1 + \Delta\tilde{t}) &= \tilde{\boldsymbol{h}}(\tilde{t}_1) + \tilde{f}(\tilde{\boldsymbol{h}}(\tilde{t}_1), \tilde{t}_1)\Delta\tilde{t} \\
&= \tilde{\boldsymbol{h}}(\tilde{t}_1) - f(\tilde{\boldsymbol{h}}(\tilde{t}_1), -\tilde{t}_1)\Delta\tilde{t} \\
&= \boldsymbol{h}(t1) + f(\boldsymbol{h}(t_1), t_1)\Delta t.
\end{aligned}$$

Which is equal by definition to $\boldsymbol{h}(t_1 + \Delta t)$, (where Δt is negative). As with the proof of minibatching in Appendix C, repeatedly applying this gives $\boldsymbol{h}(t_0) = \tilde{\boldsymbol{h}}(\tilde{t}_0)$, completing the proof. So we can solve an ODE backwards by solving a related ODE forwards with different initial and final times.

F.2 Repeated Calls to an ODE Solver

The TensorFlow ODE solver is able to take a sorted list of times to solve up to, and it functions fully in this scenario. Therefore for models like Neural CDE and GRU-ODE we do not need to repeatedly call the solver, we can just ask it to solve for all times of interest. For the ODE-RNN and by extension Latent ODE (as it uses an ODE-RNN encoder), we must repeatedly call the solver. This is because we discontinuously change the state at observations, and so we must stop the ODE solve, update the hidden state and call the solve again.

Repeatedly calling the solver prevents the model from backpropagating, preventing the models from training. In fact it doesn't simply prevent the models from training, but the program stops running. The fix to this problem is to explicitly pass parameters into the ODE function, and then also pass these as "constants" to the ODE solver, so that it knows to calculate their gradients. We include simple example code below:

This code firstly defines the ODE function that explicitly has parameters written out and named. We demonstrate a two hidden layer ReLU multi-layer-perceptron with tanh final non-linearity (as is the case with our dynamics functions). Following that we show how it is used with a TensorFlow solver.

```
import tensorflow as tf
import tensorflow_probability as tfp


class RepeatableODEFunc(tf.keras.layers.Layer):

    def __init__(self, x_dim, h_dim):
        super().__init__()
        self.w1 = tf.Variable(tf.random.normal(shape=(x_dim, h_dim)), trainable=True)
        self.b1 = tf.Variable(tf.random.normal(shape=(h_dim,)), trainable=True)
        self.w2 = tf.Variable(tf.random.normal(shape=(h_dim, h_dim)), trainable=True)
        self.b2 = tf.Variable(tf.random.normal(shape=(h_dim,)), trainable=True)
        self.w3 = tf.Variable(tf.random.normal(shape=(h_dim, x_dim)), trainable=True)
        self.b3 = tf.Variable(tf.random.normal(shape=(x_dim,)), trainable=True)

    def call(self, t, x, w1, b1, w2, b2, w3, b3):
        x = tf.nn.relu(tf.matmul(x, w1) + b1)
        x = tf.nn.relu(tf.matmul(x, w2) + b2)
        x = tf.math.tanh(tf.matmul(x, w3) + b3)
        return x


ode_fn = RepeatableODEFunc(x_dim, h_dim)
x_next = tfp.math.ode.DormandPrince().solve(
    ode_fn,
    t_now,
    x_now,
    solution_times=[t_next],
    constants = {
        "w1": ode_fn.w1,
        "b1": ode_fn.b1,
        "w2": ode_fn.w2,
        "b2": ode_fn.b2,
        "w3": ode_fn.w3,
        "b3": ode_fn.b3,
    },
).states[-1]
```