Introduction

This is the project report for the final course project.

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Github: https://github.com/sjoslin2/Spring-24-DLH

Paper 33 - ScoEHR: Generating Synthetic Electronic Health Records using Continuous-time Diffusion Models[1]
https://www.mlforhc.org/s/ID145_Research-Paper_2023.pdf

- **Background of the problem**

  Patient health data, mainly kept in electronic health records (EHRs), plays a crucial role in the healthcare sector, with its increase in usage rates in hospitals across both the US and UK. EHRs include both structured and unstructured data, from patient demographics to medical images, enabling extensive analysis to unveil disease progression and health trends. Leveraging EHRs, predictive and prescriptive machine learning models have revolutionized patient care, predicting outcomes and disease severity with high accuracy. However, sharing EHRs remains constrained by regulatory frameworks like HIPAA and GDPR, compounded by challenges in aggregating EHRs due to varying standards and policies. Synthetic data generation offers a solution, addressing access and bias issues. However, generating synthetic EHRs is complex due to high dimensionality and data heterogeneity. While generative Adversarial Networks (GANs) have been popular, they face challenges like mode collapse and unstable training. Recently, diffusion models have emerged as promising alternatives, offering stable training and high-fidelity data synthesis, making them ideal for synthetic EHR generation.

- **Paper explanation**

  This paper introduces ScoEHR, a synthetic EHR generation framework employing continuous-time diffusion models. ScoEHR combines an autoencoder with a continuous-time diffusion model.The ScoEHR transforms real data into a low-dimensional space through an encoder from a pre-trained autoencoder. Within this low-dimensional space, a forward stochastic differential equation (SDE) diffuses the data. Subsequently, a reverse SDE is learned and applied to generate new synthetic data. This synthetic data is then transformed using the decoder from the autoencoder to produce the final synthetic EHR data. ScoEHR was compared to medGAN, medWGAN, and medBGAN using the following four performance metrics of data generation utility:

  - Preservation of feature marginal relationships,
  - Preservation of feature correlations,
  - Preservation of full feature distribution using log-clusters,
  - Synthetic data performance in downstream predictions of patient outcomes.

  Additionally, Physician evaluation confirms its realism, establishing ScoEHR as the current state-of-the-art in synthetic EHR generation.

Scope of Reproducibility:

There are two central hypotheses that were tested as a part of this paper: ScoEHR produces higher-quality synthetic data than the previously-leading synthetic EHR models and United States board-certified physicians cannot differentiate between the synthetic data produced by ScoEHR and real EHR data.

1. **Hypothesis 1:**
   - **Hypothesis:** The first hypothesis was tested by comparing ScoEHR against the three-leading synthetic EHR models (medGAN[2], medWGAN[3], and medBGAN[4]) on four key areas: preservation of feature marginal relationships, preservation of feature correlations, preservation of full feature distributing using log-clusters, and synthetic data performance in downstream predictions of patient outcomes.
   - **Scope of Reproducibility:** While we were not successful at fully replicating the aforementioned hypothesis using the MIMIC-III dataset, our results were better than two of the three leading synthetic EHR models (medGAN[2] and medBGAN[4]) and our outcomes were similar to the results provided in the paper (though they weren't as good on some key metrics, they were within the right order of magnitude). The results are discussed in detail in the results and discussion section of this report.
2. **Hypothesis 2:**
   - **Hypothesis:** The second hypothesis was tested by presenting both synthetic and real EHR data to physicians and asking them to identify the “real” data. By looking at what portion of synthetic data they identified as “real” and comparing it with the portion of real data they identified as “real” the authors were able to determine that physicians were not able to tell the difference between the synthetic and real data.
   - **Scope of Reproducibility:** This was infeasible without real doctors available to validate the authenticity of synthetic records.

Methodology

The Methodology section consists of 5 sub-sections:

- Environment
- Data
- Model
- Training
- Evaluation

For each sub-section, a description/explanation of that sub-section is given as well as implementation code.

Environment

Python Version

Python 3.10.12

```
!python --version
```

```
Python 3.10.12
```

Manual Setup Needed

In order to run this notebook, you will need to:

1. Ensure that you downloaded it from the github repository. This means that you should see the following folders:
   - `./mimic/` - Empty folder where you need to manually add the MIMIC-III data files (detailed instructions in Data sub-section).
   - `./saved_models/` - This is where the saved Autoencoder and Score Net model parametres live. Training these models from scratch instead requires ~30 minutes of GPU time.
   - `./stats/` - This contains stats information around the model training. If you train these models from scratch then your model trainings stats are displayed instead.
   - `./generated_data/` - This contains synthetic data generated by the model. If you want to generate your own synthetic data you'll need ~30 minutes of GPU time.
2. Ensure you have added the MIMIC-III data files into the `./mimic/` folder (detailed instructions in the Data sub-section).

Dependencies and Packages

This section installs all required modules and imports them for later use.

```
!pip install torchsde
```

```
Requirement already satisfied: torchsde in /usr/local/lib/python3.10/dist-packages (0.2.6)
Requirement already satisfied: numpy>=1.19 in /usr/local/lib/python3.10/dist-packages (from torchsde) (1.25.2)
Requirement already satisfied: scipy>=1.5 in /usr/local/lib/python3.10/dist-packages (from torchsde) (1.11.4)
Requirement already satisfied: torch>=1.6.0 in /usr/local/lib/python3.10/dist-packages (from torchsde) (2.2.1+cu121)
Requirement already satisfied: trampoline>=0.1.2 in /usr/local/lib/python3.10/dist-packages (from torchsde) (0.1.2)
Requirement already satisfied: filelock in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (3.14.0)
Requirement already satisfied: typing-extensions>=4.8.0 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (4.11.0
Requirement already satisfied: sympy in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (1.12)
Requirement already satisfied: networkx in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (3.3)
Requirement already satisfied: jinja2 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (3.1.3)
Requirement already satisfied: fsspec in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (2023.6.0)
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Requirement already satisfied: nvidia-cublas-cu12==12.1.3.1 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (12
Requirement already satisfied: nvidia-cufft-cu12==11.0.2.54 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (11
Requirement already satisfied: nvidia-curand-cu12==10.3.2.106 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (
Requirement already satisfied: nvidia-cusolver-cu12==11.4.5.107 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde)
Requirement already satisfied: nvidia-cusparse-cu12==12.1.0.106 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde)
Requirement already satisfied: nvidia-nccl-cu12==2.19.3 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (2.19.3
Requirement already satisfied: nvidia-nvtx-cu12==12.1.105 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (12.1
Requirement already satisfied: triton==2.2.0 in /usr/local/lib/python3.10/dist-packages (from torch>=1.6.0->torchsde) (2.2.0)
Requirement already satisfied: nvidia-nvjitlink-cu12 in /usr/local/lib/python3.10/dist-packages (from nvidia-cusolver-cu12==11.4.5.107->
Requirement already satisfied: MarkupSafe>=2.0 in /usr/local/lib/python3.10/dist-packages (from jinja2->torch>=1.6.0->torchsde) (2.1.5)
```

```
Requirement already satisfied: mpmath>=0.19 in /usr/local/lib/python3.10/dist-packages (from sympy->torch>=1.6.0->torchsde) (1.3.0)
```

```
# Import all the required packages
import torch
import os
import tqdm
import math
import time
import torchsde
import gc

import numpy as np
import torch.nn.functional as F
import _pickle as pickle
import pandas as pd

from torch import nn
from torch.utils.data import DataLoader
from torch.nn.init import _calculate_fan_in_and_fan_out
from torch.optim import lr_scheduler
from sklearn.model_selection import train_test_split
from datetime import datetime
from matplotlib import pyplot
import matplotlib.pyplot as plt
```

```
# Mount the google drive.
try:
  import google.colab
  IN_COLAB = True
except:
  IN_COLAB = False

device = "cuda" if torch.cuda.is_available() else "cpu"

if IN_COLAB:
  from google.colab import drive
  drive.mount('/content/drive')
  file_location = "/content/drive/MyDrive/DLH/"
else:
  file_location = "."
```

```
Drive already mounted at /content/drive; to attempt to forcibly remount, call drive.mount("/content/drive", force_remount=True).
```

Data

Data Download Instructions

We are using MIMIC-III dataset from physionet -> https://physionet.org/content/mimiciii/1.4/.

Please follow the instructions in piazza post #338 to access the MIMIC-III dataset. Download and decompress the following two csv files and place them in the `./mimic` folder:

- `ADMISSIONS.csv`
- `DIAGNOSES_ICD.csv`

Data Descriptions

MIMIC-III critical care database is an freely accessible database containing de-identified health data associated with approximately 40,000 patients who stayed in intensive care units at the Beth Israel Deaconess Medical Center between 2001 and 2012.There has been several versions of the MIMIC-III database since it was released.Current version of the dataset is MIMIC-III v1.4 released on 2nd September 2016 which majorly focused on enhancement of data quality and providing addition of large amount of data.

MIMIC-III is a relational database consisting of 26 tables, out of which only 2 tables namely ADMISSIONS and DIAGNOSES_ICD are used for this project. Tables are linked by identifiers which usually have the suffix 'ID'. For example, SUBJECT_ID refers to a unique patient and HADM_ID refers to a unique admission to the hospital.

The **ADMISSIONS** table contains several columns, including *row_id, subject_id, hadm_id, admittime, dischtime, deathtime, admission_type, admission_location, discharge_location, insurance, language, religion, marital_status, ethnicity, edregtime, edouttime, diagnosis,* *hospital_expire_flag, and has_chartevents_data*. However, for this project, we focus on only three columns: ***subject_id, hadm_id, and admittime***. The hadm_id , which identifies the hospital stay serves as the primary key and the subject_id is the foriegn key for the ADMISSIONS table.A patient with multiple admissions will have duplicate subject_id entries for the same hadm_id. The admittime column represents the time of admission to the hospital.

The **DIAGNOSES_ICD** consists of following columns: *row_id, subject_id, hadm_id, seq_num, icd9_code*. For this project, we are only utilizing two columns: ***hadm_id** *and* **icd9_code***. The icd9_code colum provides the diagnoses code.

Statistics of MIMIC-III dataset:

- Dataset: MIMIC3Dataset
- Number of patients: 49993
- Number of visits: 52769
- Number of visits per patient: 1.0555
- Number of events per visit in DIAGNOSES_ICD: 9.1038

Data Preprocessing

For the MIMIC-III dataset, we follow the data preprocessing methodology outlined by Choi et al. (2017). The code below processes the MIMIC-III dataset, creating longitudinal diagnosis records for patients and saves the serialized data to a file using pickle. It involves reading the ADMISSIONS.csv and DIAGNOSES_ICD.csv files, generalizing the ICD-9 codes up to the first three digit codes, and then generating the longitudinal diagnosis patient records. The resulting matrix file comprises one row per patient and one column per ICD code (later treated as features). Each row represents the count of occurrences of the corresponding patient's EHR containing the ICD code in their visits. If the patient's EHR never includes the ICD code across any visits, a '0' is placed in the column.

Set `generate_matrix_file = True` (default) to generate the preprocessed `.matrix` file required for training the model and/or comparing the real and synthetic data).

```python
# Modified from: https://github.com/mp2893/medgan/blob/master/process_mimic.py

admissionFile = os.path.join(file_location, 'mimic/ADMISSIONS.csv')
diagnosisFile = os.path.join(file_location, 'mimic/DIAGNOSES_ICD.csv')
outFile = os.path.join(file_location, 'mimic/mimic_processed_choi_count.matrix')

generate_matrix_file = True

def convert_to_icd9(dxStr):
    if dxStr.startswith('E'):
        if len(dxStr) > 4: return dxStr[:4] + '.' + dxStr[4:]
        else: return dxStr
    else:
        if len(dxStr) > 3: return dxStr[:3] + '.' + dxStr[3:]
        else: return dxStr

def convert_to_3digit_icd9(dxStr):
    if dxStr.startswith('E'):
        if len(dxStr) > 4: return dxStr[:4]
        else: return dxStr
    else:
        if len(dxStr) > 3: return dxStr[:3]
        else: return dxStr

if generate_matrix_file:
    binary_count = 'count'

    print('Building pid-admission mapping, admission-date mapping')
    pidAdmMap = {}
    admDateMap = {}
    infd = open(admissionFile, 'r')
    infd.readline()
    for line in infd:
        tokens = line.strip().split(',')
        pid = int(tokens[1])
        admId = int(tokens[2])
        admTime = datetime.strptime(tokens[3], '%Y-%m-%d %H:%M:%S')
        admDateMap[admId] = admTime
        if pid in pidAdmMap: pidAdmMap[pid].append(admId)
        else: pidAdmMap[pid] = [admId]
    infd.close()

    print('Building admission-dxList mapping')
    admDxMap = {}
    infd = open(diagnosisFile, 'r')
    infd.readline()
    for line in infd:
        tokens = line.strip().split(',')
        admId = int(tokens[2])
        # Uncomment this line and comment the line below, if you want to use the entire ICD9 digits.
        # dxStr = 'D_' + convert_to_icd9(tokens[4][1:-1])
        dxStr = 'D_' + convert_to_3digit_icd9(tokens[4][1:-1])
        if admId in admDxMap: admDxMap[admId].append(dxStr)
        else: admDxMap[admId] = [dxStr]
    infd.close()

    print('Building pid-sortedVisits mapping')
    pidSeqMap = {}
    for pid, admIdList in pidAdmMap.items():
        #if len(admIdList) < 2: continue
        sortedList = sorted([(admDateMap[admId], admDxMap[admId]) for admId in admIdList])
        pidSeqMap[pid] = sortedList

    print('Building pids, dates, strSeqs')
    pids = []
    dates = []
    seqs = []
    for pid, visits in pidSeqMap.items():
        pids.append(pid)
        seq = []
        date = []
        for visit in visits:
            date.append(visit[0])
            seq.append(visit[1])
        dates.append(date)
        seqs.append(seq)
```

```
    print('Converting strSeqs to intSeqs, and making types')
    types = {}
    newSeqs = []
    for patient in seqs:
        newPatient = []
        for visit in patient:
            newVisit = []
            for code in visit:
                if code in types:
                    newVisit.append(types[code])
                else:
                    types[code] = len(types)
                    newVisit.append(types[code])
            newPatient.append(newVisit)
        newSeqs.append(newPatient)

    print('Constructing the matrix')
    numPatients = len(newSeqs)
    numCodes = len(types)
    matrix = np.zeros((numPatients, numCodes)).astype('float32')
    for i, patient in enumerate(newSeqs):
        for visit in patient:
            for code in visit:
                if binary_count == 'binary':
                    matrix[i][code] = 1.
                else:
                    matrix[i][code] += 1.

    pickle.dump(matrix, open(outFile, 'wb'), -1)
    print('Matrix construction complete')
```

```
Building pid-admission mapping, admission-date mapping
Building admission-dxList mapping
Building pid-sortedVisits mapping
Building pids, dates, strSeqs
Converting strSeqs to intSeqs, and making types
Constructing the matrix
Matrix construction complete
```

Define DataLoader Class

Used to create Datasets and Dataloaders to pull data from the generated `.matrix` file

```
# Modified from https://github.com/aanaseer/ScoEHR/blob/main/scoehr/datasets.py

class Dataset():
    def __init__(self, data_dir, data_file):
        pass

    def data(self, use_train_test_split=True, test_size=0.30):
        if use_train_test_split:
            train_data, test_data = train_test_split(
                self.dataset_full, test_size=test_size, random_state=1
            )
            return train_data, test_data
        else:
            return self.dataset_full

class MIMIC3_ICD(Dataset):
    def __init__(
        self, data_file="mimic/mimic_processed_choi_count.matrix"
    ):
        """Loads the MIMIC-III dataset from the data directory."""
        data_path = os.path.join(file_location, data_file)
        data = np.load(data_path, allow_pickle=True)
        self.dataset_full = torch.from_numpy(data)
```

Load the Data

Load the `.matrix` file and generated train and test dataloaders.

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py

load_data = True

batch_size = 64

if load_data:

    data_file = 'mimic/mimic_processed_choi_count.matrix'

    train_data, test_data = MIMIC3_ICD(data_file=data_file).data()

    real = test_data.detach()

    train_data = train_data.to(device)
    test_data = test_data.to(device)

    train_dataloader = DataLoader(dataset=train_data, batch_size=batch_size, drop_last=True)
    test_dataloader = DataLoader(dataset=test_data, batch_size=batch_size, drop_last=True)
    print("Train Data Shape: ", train_data.shape)
    print("Test Data Shape: ", test_data.shape)
```

```
Train Data Shape:  torch.Size([32564, 1071])
Test Data Shape:  torch.Size([13956, 1071])
```

Model

Citation to the original paper

Naseer, AA; Walker, B; Landon, C; Ambrosy, A; Fudim, M; Wysham, N; Toro, B; Swaminathan, S; Lyons, T. ScoEHR: Generating Synthetic Electronic Health Records using Continuous-time Diffusion Models. *Proceedings of Machine Learning Research*, Volume 219: 489–508, January 2023.[1]

URL: https://static1.squarespace.com/static/59d5ac1780bd5ef9c396eda6/t/64d1aa32ed57852af9c0ad60/1691462195379/ID145_Research+Paper_2023.pdf

Link to the original paper's repo

https://github.com/aanaseer/ScoEHR/tree/main/scoehr

Model Descriptions

The synthetic generation process involves two different models:

- Autoencoder: Used to lower the dimensionality of the data
- Continuous-Time Diffusion Model: Used to generated synthetic data

The Autoencoder is used to lower the dimensionality from the original dataset (one feature per ICD code or 1,071 features) to 144 features. This helps to capture relationships between related ICD codes and reduces the dimensionality of the output data that the continuous-time diffusion model must generate.

The Autoencoder is first trained and tested by itself to ensure that the Autoencoder model is able to successfully reduce the dimensionality of the data and then reproduce that original data using the reduced dimensionality dataset. Then, the training data is encoded using the autoencoder and the encoded training data is used to train the Continuous-Time Diffusion model.

This allows the Continous-Time Diffusion model to generate synthetic data in the lower dimensionality space. The Continuous-Time Diffusion Model (aka UNet aka Score Net) is used to generate the synthetic data. It works in combination with a Variance Preserving Stochastic Differential Equation (VPSDE). The VPSDE function is designed to take real data and convert real data into random noise in a controlled manner. The VPSDE function converts the data into noise at continuous time-steps between 0 (completely real data) and 1 (complete noise). This synthetic data is then decoded using the trained Autoencoder to generate synthetic data in a feature space that is tied back to ICD codes.

Model Part 1 - Autoencoder

Autoencoder Architecture:

Layers	Configuration	Activation Function	Output Dimension (batch, feature)
fully connected	input size 6985, output size 144	Tahnh	(512, 144)
fully connected	input size 144, output size 6985	Sigmoid	(512, 6985)

Autoencoder Training Objectives:

- Loss Function: torch.nn.BCELoss with `reduction="sum"`

- Optimiser: torch.optim.Adam with `weight_decay=0.0001`

Other Autoencoder Info: The model is not pretrained, but weights are initiatlized using `torch.nn.init.xavier_uniform_`. The autoencoder post-encoding dimension of 144 was chosen by the original paper because previous papers indicated that 128 was the ideal post-encoding dimension, and 144 was the closest that worked with the UNet architecture of the upcoming Continous-Time Diffusion model.

Model Part 2 - UNet

UNet Architecture: Due to the complex nature of the model, it's difficult to describe it in a single table that captures each layer and their size/type/activation function. Instead, we focus on describing how the model works and it's overarching architecture.

Let's assume that this noise is added over n timesteps. The Score Net/UNet is trained to take data with noise added to it at time t_k (where k is between 1 and n), and back-convert that to the data at time t_{k-1} (before the noise was added). To support this, the loss function is defined as the difference between the actual t_{k-1} and the predicted t_{k-1}.

Therefore we are training the model to be able to convert noisy data into real data. Once this training is complete, to generate synthetic data we generate random noise and plug it into the model using a ReverseSDE function (that is designed to remove noise using the model). We start with noise at t_n and move step-wise backwards - at each step the model telling us what real parameters it *thinks* could represent the next step with noise added. When we get to t_0 we have data that follows the same patterns as real data, but because it was built based on noise is completely synthetic.

In terms of architecture, the Continuous-Time Diffusion Model (aka UNet aka Score Net) is a UNet architecture based on the reduced dimensionality space provided by the autoencoder. It has two down-sampling layers that progressively reduce the size of the input data using convolution. Each of these down-sampling layers also has two residual blocks that allow data to skip parts of the model as needed. Each residual block also incorporates self-attention. SiLU ($sigmoid(x) * x$) is used as the activation function throughout this model.

UNet Training Objectives:

- Loss Function: The loss function is a custom loss function designed to determine the loss between a predicted t_{k-1} and an actual t_{k-1}.
- Optimiser: Adam with an adaptive learning rate. The learning rate (λ) at epoch t is defined by the exponential decay formula:

$$\lambda(t) = \mathrm{lr}_0 \cdot e^{-k \cdot t}$$

where:

- $\mathrm{lr}_0 = 0.5$ is the initial learning rate,
- $k = 0.1$ is the decay rate,
- t is the epoch number.

Other UNet Info: The model is not pretrained, but weights are initialized using `torch.nn.init.xavier_uniform_`.

Implementation Code

Implementation code can be found in the following cells within this section.

Pretrained Model

Available at https://github.com/sjoslin2/Spring-24-DLH/tree/main/saved_models. Also used to generate synthetic data in the following cells (when enabled).

Define Autoencoder Class

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/models/autoencoder.py

class Autoencoder(nn.Module):
    def __init__(self, enc_in_dim, enc_out_dim):
        super(Autoencoder, self).__init__()

        self.encoder = nn.Sequential(nn.Linear(enc_in_dim, enc_out_dim),
                                     nn.Tanh())
        self.decoder = nn.Sequential(
                                     nn.Linear(enc_out_dim, enc_in_dim),
                                     nn.ReLU())

    def encode(self, x):
        x = self.encoder(x)
        return x

    def decode(self, x):
        x = self.decoder(x)
        return x

    def forward(self, x):
        x = self.encoder(x)
        x = self.decoder(x)
        return x
```

Define weight initialization

```
def weights_init(m):
    # From https://github.com/astorfi/cor-gan/blob/b6df51a16399335bfe995c15b6951f053453fbb3/Generative/medGAN/MIMIC/pytorch/MLP/medGAN.py#L2
    classname = m.__class__.__name__
    if classname.find("Conv") != -1:
        nn.init.normal_(m.weight.data, 0.0, 0.02)
    elif classname.find("BatchNorm") != -1:
        nn.init.normal_(m.weight.data, 1.0, 0.02)
        nn.init.constant_(m.bias.data, 0)
    if type(m) == nn.Linear:
        torch.nn.init.xavier_uniform_(m.weight)
        m.bias.data.fill_(0.01)
```

Define UNet Class

UNet is trained to calculate how to move from noise to data at a given timestamp. It is later instantiated as score_net.

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/models/unet.py

class SiLU(nn.Module):
    def __init__(self):
        super().__init__()

    # noinspection PyMethodMayBeStatic
    def forward(self, x):
        return torch.sigmoid(x) * x


def group_norm(out_ch):
    return nn.GroupNorm(num_groups=32, num_channels=out_ch, eps=1e-6, affine=True)


def upsample(in_ch, with_conv):
    up = nn.Sequential()
    up.add_module("up_nn", nn.Upsample(scale_factor=2, mode="nearest"))
    if with_conv:
        up.add_module("up_conv", conv2d(in_ch, in_ch, kernel_size=(3, 3), stride=1))
    return up


def downsample(in_ch, with_conv):
    if with_conv:
        down = conv2d(in_ch, in_ch, kernel_size=(3, 3), stride=2)
    else:
        down = nn.AvgPool2d(2, 2)
    return down


class ResidualBlock(nn.Module):
    def __init__(
        self,
        in_ch,
        temb_ch,
        out_ch=None,
        conv_shortcut=False,
        dropout=0.0,
        normalize=group_norm,
        act=SiLU(),
    ):
        super().__init__()
        self.in_ch = in_ch
        self.temb_ch = temb_ch
        self.out_ch = out_ch if out_ch is not None else in_ch
        self.conv_shortcut = conv_shortcut
        self.dropout = dropout
        self.act = act

        self.temb_proj = dense(temb_ch, out_ch)
        self.norm1 = normalize(in_ch) if normalize is not None else nn.Identity()
        self.conv1 = conv2d(in_ch, out_ch)
        self.norm2 = normalize(out_ch) if normalize is not None else nn.Identity()
        self.dropout = nn.Dropout2d(p=dropout) if dropout > 0.0 else nn.Identity()
        self.conv2 = conv2d(out_ch, out_ch, init_scale=0.0)
        if in_ch != out_ch:
            if conv_shortcut:
                self.shortcut = conv2d(in_ch, out_ch)
            else:
                self.shortcut = conv2d(in_ch, out_ch, kernel_size=(1, 1), padding=0)
        else:
            self.shortcut = nn.Identity()

    def forward(self, x, temb):
        # forward conv1
        h = x
        h = self.act(self.norm1(h))
        h = self.conv1(h)

        # add in timestep embedding
        h = h + self.temb_proj(self.act(temb))[:, :, None, None]

        # forward conv2
        h = self.act(self.norm2(h))
        h = self.dropout(h)
        h = self.conv2(h)
```

```python
        # shortcut
        x = self.shortcut(x)

        # combine and return
        assert x.shape == h.shape
        return x + h


class SelfAttention(nn.Module):
    """
    copied modified from https://github.com/voletiv/self-attention-GAN-pytorch/blob/master/sagan_models.py#L29
    copied modified from https://github.com/hojonathanho/diffusion/blob/master/diffusion_tf/models/unet.py#L66
    """

    def __init__(self, in_channels, normalize=group_norm):
        super().__init__()
        self.in_channels = in_channels
        self.attn_q = conv2d(
            in_channels, in_channels, kernel_size=1, stride=1, padding=0
        )
        self.attn_k = conv2d(
            in_channels, in_channels, kernel_size=1, stride=1, padding=0
        )
        self.attn_v = conv2d(
            in_channels, in_channels, kernel_size=1, stride=1, padding=0
        )
        self.proj_out = conv2d(
            in_channels, in_channels, kernel_size=1, stride=1, padding=0, init_scale=0.0
        )
        self.softmax = nn.Softmax(dim=-1)
        if normalize is not None:
            self.norm = normalize(in_channels)
        else:
            self.norm = nn.Identity()

    # noinspection PyUnusedLocal
    def forward(self, x, temp=None):
        """t is not used"""
        _, C, H, W = x.size()

        h = self.norm(x)
        q = self.attn_q(h).view(-1, C, H * W)
        k = self.attn_k(h).view(-1, C, H * W)
        v = self.attn_v(h).view(-1, C, H * W)

        attn = torch.bmm(q.permute(0, 2, 1), k) * (int(C) ** (-0.5))
        attn = self.softmax(attn)

        h = torch.bmm(v, attn.permute(0, 2, 1))
        h = h.view(-1, C, H, W)
        h = self.proj_out(h)

        assert h.shape == x.shape
        return x + h


def _calculate_correct_fan(tensor, mode):
    """
    copied and modified from https://github.com/pytorch/pytorch/blob/master/torch/nn/init.py#L337
    """
    mode = mode.lower()
    valid_modes = ["fan_in", "fan_out", "fan_avg"]
    if mode not in valid_modes:
        raise ValueError(
            "Mode {} not supported, please use one of {}".format(mode, valid_modes)
        )

    fan_in, fan_out = _calculate_fan_in_and_fan_out(tensor)
    return fan_in if mode == "fan_in" else fan_out


def kaiming_uniform_(tensor, gain=1.0, mode="fan_in"):
    r"""Fills the input `Tensor` with values according to the method
    described in `Delving deep into rectifiers: Surpassing human-level
    performance on ImageNet classification` - He, K. et al. (2015), using a
    uniform distribution. The resulting tensor will have values sampled from
```

```
    :math:`\mathcal{U}(-\text{bound}, \text{bound})` where

    .. math::
        \text{bound} = \text{gain} \times \sqrt{\frac{3}{\text{fan\_mode}}}

    Also known as He initialization.

    Args:
        tensor: an n-dimensional `torch.Tensor`
        gain: multiplier to the dispersion
        mode: either ``'fan_in'`` (default) or ``'fan_out'``. Choosing ``'fan_in'``
            preserves the magnitude of the variance of the weights in the
            forward pass. Choosing ``'fan_out'`` preserves the magnitudes in the
            backwards pass.
    Examples:
        >>> w = torch.empty(3, 5)
        >>> nn.init.kaiming_uniform_(w, mode='fan_in')
    """
    fan = _calculate_correct_fan(tensor, mode)
    var = gain / max(1.0, fan)
    bound = math.sqrt(3.0 * var)  # Calculate uniform bounds from standard deviation
    with torch.no_grad():
        return tensor.uniform_(-bound, bound)


def variance_scaling_init_(tensor, scale):
    return kaiming_uniform_(tensor, gain=1e-10 if scale == 0 else scale, mode="fan_avg")


def dense(in_channels, out_channels, init_scale=1.0):
    lin = nn.Linear(in_channels, out_channels)
    variance_scaling_init_(lin.weight, scale=init_scale)
    nn.init.zeros_(lin.bias)
    return lin


def conv2d(
    in_planes,
    out_planes,
    kernel_size=(3, 3),
    stride=1,
    dilation=1,
    padding=1,
    bias=True,
    padding_mode="zeros",
    init_scale=1.0,
):
    conv = nn.Conv2d(
        in_planes,
        out_planes,
        kernel_size=kernel_size,
        stride=stride,
        padding=padding,
        dilation=dilation,
        bias=bias,
        padding_mode=padding_mode,
    )
    variance_scaling_init_(conv.weight, scale=init_scale)
    if bias:
        nn.init.zeros_(conv.bias)
    return conv


def get_sinusoidal_positional_embedding(
    timesteps: torch.LongTensor, embedding_dim: int
):
    """
    Copied and modified from
        https://github.com/hojonathanho/diffusion/blob/1e0dceb3b3495bbe19116a5e1b3596cd0706c543/diffusion_tf/nn.py#L90

    From Fairseq in
        https://github.com/pytorch/fairseq/blob/master/fairseq/modules/sinusoidal_positional_embedding.py#L15
    Build sinusoidal embeddings.
    This matches the implementation in tensor2tensor, but differs slightly
    from the description in Section 3.5 of "Attention Is All You Need".
    """
    assert len(timesteps.size()) == 1
```

```python
    timesteps = timesteps.to(torch.get_default_dtype())
    device = timesteps.device

    half_dim = embedding_dim // 2
    emb = math.log(10000) / (half_dim - 1)
    emb = torch.exp(torch.arange(half_dim, dtype=torch.float, device=device) * -emb)
    emb = timesteps[:, None] * emb[None, :]
    emb = torch.cat([torch.sin(emb), torch.cos(emb)], dim=1)  # bsz x embd
    if embedding_dim % 2 == 1:  # zero pad
        emb = F.pad(emb, (0, 1), "constant", 0)
    assert list(emb.size()) == [timesteps.size(0), embedding_dim]
    return emb


class TimestepEmbedding(nn.Module):
    def __init__(self, embedding_dim, hidden_dim, output_dim, act=SiLU()):
        super().__init__()

        self.embedding_dim = embedding_dim
        self.output_dim = output_dim
        self.hidden_dim = hidden_dim

        self.main = nn.Sequential(
            dense(embedding_dim, hidden_dim),
            act,
            dense(hidden_dim, output_dim),
        )

    def forward(self, temp):
        temb = get_sinusoidal_positional_embedding(temp, self.embedding_dim)
        temb = self.main(temb)
        return temb


class UNet(nn.Module):
    def __init__(
        self,
        input_channels,
        encoded_latent_embedding_dim,  # eg 64
        ch,
        output_channels=None,
        ch_mult=(1, 2, 4, 8),
        num_res_blocks=2,
        attn_resolutions=(16,),
        dropout=0.0,
        resamp_with_conv=True,
        act=SiLU(),
        normalize=group_norm,
    ):
        super().__init__()
        self.input_channels = input_channels
        self.encoded_latent_embedding_dim = encoded_latent_embedding_dim  # eg 64
        self.input_height = int(np.sqrt(self.encoded_latent_embedding_dim))  # eg 8
        self.ch = ch
        self.output_channels = output_channels = (
            input_channels if output_channels is None else output_channels
        )
        self.ch_mult = ch_mult
        self.num_res_blocks = num_res_blocks
        self.attn_resolutions = attn_resolutions
        self.dropout = dropout
        self.resamp_with_conv = resamp_with_conv
        self.act = act
        self.normalize = normalize

        # init
        self.num_resolutions = num_resolutions = len(ch_mult)
        in_ht = self.input_height
        in_ch = input_channels
        temb_ch = ch * 4
        assert (
            in_ht % 2 ** (num_resolutions - 1) == 0
        ), "input_height doesn't satisfy the condition"

        # Timestep embedding
        self.temb_net = TimestepEmbedding(
            embedding_dim=ch,
```

```
        hidden_dim=temb_ch,
        output_dim=temb_ch,
        act=act,
    )

    # Downsampling
    self.begin_conv = conv2d(in_ch, ch)
    unet_chs = [ch]
    in_ht = in_ht
    in_ch = ch
    down_modules = []
    for i_level in range(num_resolutions):
        # Residual blocks for this resolution
        block_modules = {}
        out_ch = ch * ch_mult[i_level]
        for i_block in range(num_res_blocks):
            block_modules["{}a_{}a_block".format(i_level, i_block)] = ResidualBlock(
                in_ch=in_ch,
                temb_ch=temb_ch,
                out_ch=out_ch,
                dropout=dropout,
                act=act,
                normalize=normalize,
            )
            if in_ht in attn_resolutions:
                block_modules[
                    "{}a_{}b_attn".format(i_level, i_block)
                ] = SelfAttention(out_ch, normalize=normalize)
            unet_chs += [out_ch]
            in_ch = out_ch
        # Downsample
        if i_level != num_resolutions - 1:
            block_modules["{}b_downsample".format(i_level)] = downsample(
                out_ch, with_conv=resamp_with_conv
            )
            in_ht //= 2
            unet_chs += [out_ch]
        # convert list of modules to a module list, and append to a list
        down_modules += [nn.ModuleDict(block_modules)]
    # convert to a module list
    self.down_modules = nn.ModuleList(down_modules)

    # Middle
    mid_modules = []
    mid_modules += [
        ResidualBlock(
            in_ch,
            temb_ch=temb_ch,
            out_ch=in_ch,
            dropout=dropout,
            act=act,
            normalize=normalize,
        )
    ]
    mid_modules += [SelfAttention(in_ch, normalize=normalize)]
    mid_modules += [
        ResidualBlock(
            in_ch,
            temb_ch=temb_ch,
            out_ch=in_ch,
            dropout=dropout,
            act=act,
            normalize=normalize,
        )
    ]
    self.mid_modules = nn.ModuleList(mid_modules)

    # Upsampling
    up_modules = []
    for i_level in reversed(range(num_resolutions)):
        # Residual blocks for this resolution
        block_modules = {}
        out_ch = ch * ch_mult[i_level]
        for i_block in range(num_res_blocks + 1):
            block_modules["{}a_{}a_block".format(i_level, i_block)] = ResidualBlock(
                in_ch=in_ch + unet_chs.pop(),
                temb_ch=temb_ch,
```

```
                out_ch=out_ch,
                dropout=dropout,
                act=act,
                normalize=normalize,
            )
            if in_ht in attn_resolutions:
                block_modules[
                    "{}a_{}b_attn".format(i_level, i_block)
                ] = SelfAttention(out_ch, normalize=normalize)
            in_ch = out_ch
        # Upsample
        if i_level != 0:
            block_modules["{}b_upsample".format(i_level)] = upsample(
                out_ch, with_conv=resamp_with_conv
            )
            in_ht *= 2
        # convert list of modules to a module list, and append to a list
        up_modules += [nn.ModuleDict(block_modules)]
    # conver to a module list
    self.up_modules = nn.ModuleList(up_modules)
    assert not unet_chs

    # End
    self.end_conv = nn.Sequential(
        normalize(in_ch),
        self.act,
        conv2d(in_ch, output_channels, init_scale=0.0),
    )

# noinspection PyMethodMayBeStatic
def _compute_cond_module(self, module, x, temp):
    for m in module:
        x = m(x, temp)
    return x

# noinspection PyArgumentList,PyShadowingNames
def forward(self, x, temp):
    # Init
    x = x.view(-1, 1, self.input_height, self.input_height)
    temp = temp.view(
        -1,
    )
    B, C, H, W = x.size()
    # Timestep embedding
    temb = self.temb_net(temp)
    assert list(temb.shape) == [B, self.ch * 4]
    # Downsampling
    hs = [self.begin_conv(x)]
    for i_level in range(self.num_resolutions):
        # Residual blocks for this resolution
        block_modules = self.down_modules[i_level]
        for i_block in range(self.num_res_blocks):
            resnet_block = block_modules["{}a_{}a_block".format(i_level, i_block)]
            h = resnet_block(hs[-1], temb)
            if h.size(2) in self.attn_resolutions:
                attn_block = block_modules["{}a_{}b_attn".format(i_level, i_block)]
                h = attn_block(h, temb)
            hs.append(h)
        # Downsample
        if i_level != self.num_resolutions - 1:
            downsample = block_modules["{}b_downsample".format(i_level)]
            hs.append(downsample(hs[-1]))

    # Middle
    h = hs[-1]
    h = self._compute_cond_module(self.mid_modules, h, temb)

    # Upsampling
    for i_idx, i_level in enumerate(reversed(range(self.num_resolutions))):
        # Residual blocks for this resolution
        block_modules = self.up_modules[i_idx]
        for i_block in range(self.num_res_blocks + 1):
            resnet_block = block_modules["{}a_{}a_block".format(i_level, i_block)]
            h = resnet_block(torch.cat([h, hs.pop()], axis=1), temb)
            if h.size(2) in self.attn_resolutions:
                attn_block = block_modules["{}a_{}b_attn".format(i_level, i_block)]
                h = attn_block(h, temb)
```

```
            # Upsample
            if i_level != 0:
                upsample = block_modules["{}b_upsample".format(i_level)]
                h = upsample(h)
        assert not hs

        # End
        h = self.end_conv(h)
        assert list(h.size()) == [x.size(0), self.output_channels, x.size(2), x.size(3)]
        h = h.view(-1, self.encoded_latent_embedding_dim)
        return h
```

Define DenoisingScoreMatching Class

This can be thought of as the loss function for UNet (score_net).

```python
# Modified from: https://urldefense.com/v3/__https://github.com/aanaseer/ScoEHR/blob/main/scoehr/score_matching/dsm.py*5Cn__;JQ!!DZ3fjg!4sii

"""Implements the denoising score matching objective along with two helper functions."""

def pad_to(x, stride):
    h, w = x.shape[-2:]
    if w % stride > 0:
        new_w = w + stride - w % stride
    else:
        new_w = w
    lh, uh = int((h - h) / 2), int(h - h) - int((h - h) / 2)
    lw, uw = int((new_w - w) / 2), int(new_w - w) - int((new_w - w) / 2)
    pads = (lw, uw, lh, uh)

    # zero-padding by default.
    # See others at https://urldefense.com/v3/__https://pytorch.org/docs/stable/nn.functional.html*torch.nn.functional.pad*5Cn__;IyU!!DZ3fjg
    out = F.pad(x, pads, "constant", 0)

    return out, pads


def unpad(self, x, pad):
    if pad[0] + pad[1] > 0:
        x = x[:, pad[0] : -pad[1]]
    return x


class DenoisingScoreMatching(nn.Module):
    def __init__(self, sde, score_net, T=1.0, padding_required=False):
        super().__init__()
        self.sde = sde
        self.score_net = score_net
        self.T = T
        self.padding_required = padding_required

    @torch.enable_grad()
    def loss_fn(self, x):
        t = torch.linspace(1 / x.size(0) + 1e-3, 1 - 1 / x.size(0), x.size(0)) + (
            1 - 2 * torch.rand(x.size(0))
        ) * (1 / x.size(0))
        t = t.view(-1, 1).to(x)

        idx = torch.randperm(t.nelement())
        t = t.view(-1)[idx].view(t.size())

        perturbed_x, noise, std, g = self.sde.sample(x, t)

        if self.padding_required:
          # Modified from pad to 784 to pad to 1296
          # This is because we're testing the non-autoencoder Score Net with
          # the Mimic data which has 1071 parameters instead of the Hong ED data
          # and 1296 > 1071 > 784
            perturbed_x, pads = pad_to(perturbed_x, 1296)
        score_predictions = self.score_net(perturbed_x, t)
        if self.padding_required:
            score_predictions = unpad(score_predictions, pads)

        return ((score_predictions + noise / std) ** 2).view(x.size(0), -1).sum(
            1, keepdim=False
        ) * (std**2).squeeze()
```

Define VPSDE (Variance Preserving Stochastic Differential Equation) Class

The VPSDE class is used to add noise to the data at each time stamp.

```python
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/score_matching/sde_library.py
"""Implementation for the VPSDE along with the associated Reverse SDE.
This file also contains a wrapper for SDE to be used with torchsde library.
"""

# This code is a modification of https://github.com/CW-Huang/sdeflow-light/blob/main/lib/sdes.py


class VPSDE(nn.Module):
    """Implements the VPSDE."""
```

```
    def __init__(self, beta_min=0.1, beta_max=20.0, T=1.0, t_epsilon=0.001):
        super().__init__()
        self.beta_min = beta_min
        self.beta_max = beta_max
        self.T = T
        self.t_epsilon = t_epsilon

    def beta(self, t):
        return self.beta_min + t * (self.beta_max - self.beta_min)

    def mean_weight(self, t):
        return torch.exp(
            -0.25 * t**2 * (self.beta_max - self.beta_min) - 0.5 * t * self.beta_min
        )

    def var(self, t):
        return 1.0 - torch.exp(
            -0.5 * t**2 * (self.beta_max - self.beta_min) - t * self.beta_min
        )

    def f(self, x, t):
        return -0.5 * self.beta(t) * x

    def g(self, x, t):
        return torch.ones_like(x) * self.beta(t) ** 0.5

    def sample(self, x0, t):
        mean = self.mean_weight(t) * x0
        std = torch.sqrt(self.var(t))
        noise = torch.randn_like(x0)
        perturbed_x = mean + (noise * std)
        return perturbed_x, noise, std, self.g(perturbed_x, t)

    def probability_flow_ode(self, t, x, score_net):
        return (
            self.f(x, self.T - t)
            - 0.5 * (self.g(x, self.T - t) ** 2) * score_net(x, self.T - t.squeeze())
        ) * -1

class WrapperForTorchSDE(nn.Module):
    """Wraps the SDE to be used with torchsde library."""

    def __init__(self, reverse_sde, noise_type="diagonal", sde_type="ito"):
        super().__init__()
        self.noise_type = noise_type
        self.sde_type = sde_type
        self.reverse_sde = reverse_sde

    def f(self, t, x):
        t = t.repeat(x.size(0)).view(-1, 1)
        return self.reverse_sde.drift(x, t)

    def g(self, t, x):
        t = t.repeat(x.size(0)).view(-1, 1)
        return self.reverse_sde.diffusion(x, t)
```

Define ReverseSDE Class

The ReverseSDE class is used to remove noise from the data at each time stamp based on the score_net weights.

```python
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/score_matching/sde_library.py

class ReverseSDE(nn.Module):
    """Implements the reverse SDE."""

    def __init__(self, sde, score_net, T=1.0):
        super().__init__()
        self.sde = sde
        self.score_net = score_net
        self.T = T

    def drift(self, x, t):
        dt = -1
        return (
            self.sde.f(x, self.T - t)
            - (self.sde.g(x, self.T - t) ** 2) * self.score_net(x, self.T - t.squeeze())
        ) * dt

    def diffusion(self, x, t):
        return self.sde.g(x, self.T - t)  # Actual
```

Training

Hyperparameters

- **Training Batch Size:** 64 - While the original paper's github had a batch size of 256 given as an example, we chose this smaller batch size to allow training to be done with less GPU RAM (and using consumer-grade GPU hardward). Note that during synthetic data generation, the batch size is increased to 128. This is because a higher-end GPU (T4 and A100s were both tested) was used for synthetic data generation (due to the time it took to generate synthetic data), and the higher-end could support the larger batch size.
- **Autoencoder Learning Rate:** 0.001 - This matched the example given in the original paper's github.
- **Autoencoder Hidden Dimension Size:** 144 - This matched the example given in the original paper's github. Because the autoencoder dimensionality was used as an input into the UNet, and because of the structure of the layers of the UNet, only specific autoencoder hidden dimensions are supported (they must fit the following formula: $(4 \cdot n)^2$). As additional ablations, autoencoder hidden dimensions of 64 and 256 were also tested. An ablation where the autoencoder was not used was also tested. Ablation results are discussed in the results section.
- **UNet Learning Rate: 0.001.** This matched the example given in the original paper's github.

Computational Requirements

Autoencoder Number of Epochs:

While the original paper's github had an autoencoder epoch count of 20, we found that the test loss continued to decrease beyond this point and found that beyond 50 epochs there was diminishing returns for the test loss. The times and RAM usage in the tables below are based on 50 epochs of autoencoder training.

UNet Number of Epochs:

While the original paper's github had a UNet epoch count of 5, we found that test loss continued to decrease well beyond this number and found 50 to be a reasonable balance between improving the test loss and a reasonable training time. As additional ablations, we also tested results using 12, 25, 30, 75, and 100 epochs. Ablation results are discussed in the results section. The times and RAM usage in the tables below are based on 50 epochs of UNet training.

GPU Hours (using Nvidia Tesla T4 GPU)

Autoencoder Features	Autoencoder Training	UNet (ScoreNet) Training	Synthetic Data Generation
No Autoencoder	N/A	4.5 Hours	8.5 Hours
64	3.5 Minutes	27 Minutes	37 Minutes
144	3.5 Minutes	42 Minutes	68 Minutes
256	3.5 Minutes	73 Minutes	2 Hours

GPU RAM Usage (using Nvidia Tesla T4 GPU)

Autoencoder Features	Autoencoder Training	UNet (ScoreNet) Training	Synthetic Data Generation
No Autoencoder	N/A	6.2 GB	3.3 GB
64	0.3 GB	1.2 GB	2.3 GB
144	0.4 GB	1.5 GB	2.3 GB
256	0.4 GB	2.3 GB	2.7 GB

Type of Hardware

While most runs were generated using an Nvidia Tesla T4 GPU (see results for GPU hours in the table above), some synthetic data was generated using an Nvidia A100 Tensor Core GPU. This was substantially faster at generating synthetic data:

- T4 GPU Synthetic Data Generation (144 Autoencoder Features): 68 minutes
- A100 GPU Synthetic Data Generation (144 Autoencoder Features): 19 minutes

Training Code

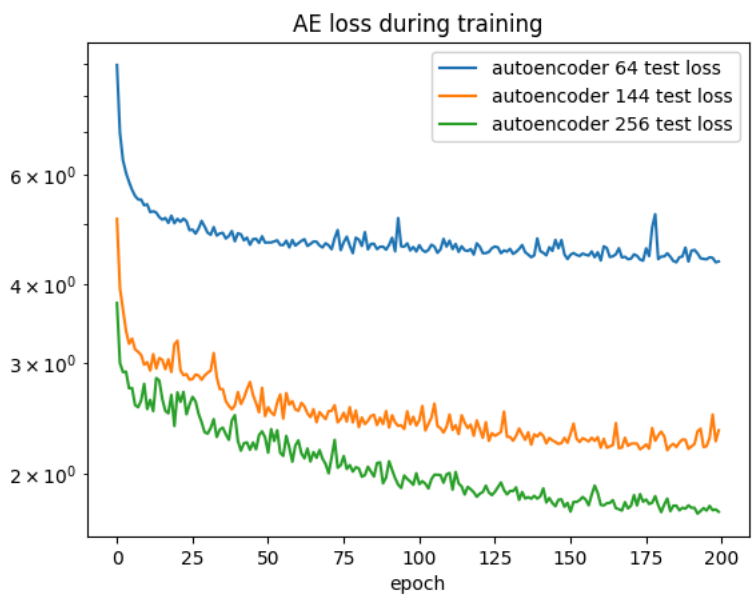
Training code can be found in the following cells within this section.

Instantiate and Train Autoencoders

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/train/train_autoencoder_utils.py

train_autoencoder_model = False
save_autoencoder_model = False

# Note, these must all be integers that fit the following formula: (4 * n) ^ 2
# This is a requirement of the UNet that comes later
# 64 = (4 * 2) ^ 2
# 144 = (4 * 3) ^ 2
# 256 = (4 * 4) ^ 2
autoencoder_dims = [64, 144, 256]

n_epochs_autoencoder = 200
lr_autoencoder = 0.001
enc_in_dim = train_data.shape[1]
loss_infos = {}

loss_fn_autoencoder = torch.nn.MSELoss(reduction="sum")

for enc_out_dim in autoencoder_dims:
    autoencoder = Autoencoder(enc_in_dim, enc_out_dim)
    autoencoder.to(device)
    autoencoder_stats_path = os.path.join(file_location,
                'stats/autoencoder_count_' + str(enc_out_dim) + '.pkl')
    autoencoder_model_path = os.path.join(file_location,
                'saved_models/autoencoder_count_' + str(enc_out_dim) + '.pt')

    if train_autoencoder_model:
        autoencoder.apply(weights_init)
        optimiser_autoencoder = torch.optim.Adam(autoencoder.parameters(), lr=lr_autoencoder, weight_decay=0.0001)

        print(f"==> Training the {enc_out_dim} autoencoder with {n_epochs_autoencoder} epochs.")
        epoch_train_loss_list = []
        epoch_test_loss_list = []
        for epoch in tqdm.tqdm(range(n_epochs_autoencoder)):
            epoch_train_loss = 0
            epoch_test_loss = 0
            autoencoder.train()
            for x in train_dataloader:
                optimiser_autoencoder.zero_grad()
                encode_and_decode = autoencoder(x)
                loss = loss_fn_autoencoder(encode_and_decode, x) / x.shape[0]

                epoch_train_loss += loss.item()
                loss.backward()

                optimiser_autoencoder.step()

            autoencoder.eval()
            with torch.no_grad():
                for x in test_dataloader:
                    encode_and_decode = autoencoder(x)
                    loss = loss_fn_autoencoder(encode_and_decode, x) / x.shape[0]
                    epoch_test_loss += loss.item()

            avg_train_loss = epoch_train_loss / len(train_dataloader)
            avg_test_loss = epoch_test_loss / len(test_dataloader)
            epoch_train_loss_list.append(avg_train_loss)
            epoch_test_loss_list.append(avg_test_loss)

        print("==> Autoencoder training completed.")

        loss_info = dict()
```

```
        loss_info['epoch_train_loss_list'] = epoch_train_loss_list
        loss_info['epoch_test_loss_list'] = epoch_test_loss_list
        if save_autoencoder_model:
            with open(autoencoder_stats_path, 'wb') as file:
                pickle.dump(loss_info, file, -1)
            torch.save({'model_state_dict': autoencoder.state_dict()}, autoencoder_model_path)

        del optimiser_autoencoder

    else:
        print("===> Loading trained models")
        loss_info = dict()
        with open(autoencoder_stats_path, 'rb') as file:
            loss_info = pickle.load(file)

    loss_infos[enc_out_dim] = loss_info

    del autoencoder
    gc.collect()
    if device == "cuda":
        torch.cuda.empty_cache()

for enc_out_dim in autoencoder_dims:
    loss_info = loss_infos[enc_out_dim]
    epoch_train_loss_list = loss_info['epoch_train_loss_list']
    epoch_test_loss_list = loss_info['epoch_test_loss_list']
    plt.plot(epoch_test_loss_list,
             label='autoencoder ' + str(enc_out_dim) + ' test loss')

plt.xlabel('epoch')
plt.title('AE loss during training')
plt.legend()
plt.yscale("log")
plt.show()
```

```
===> Loading trained models
===> Loading trained models
===> Loading trained models
```



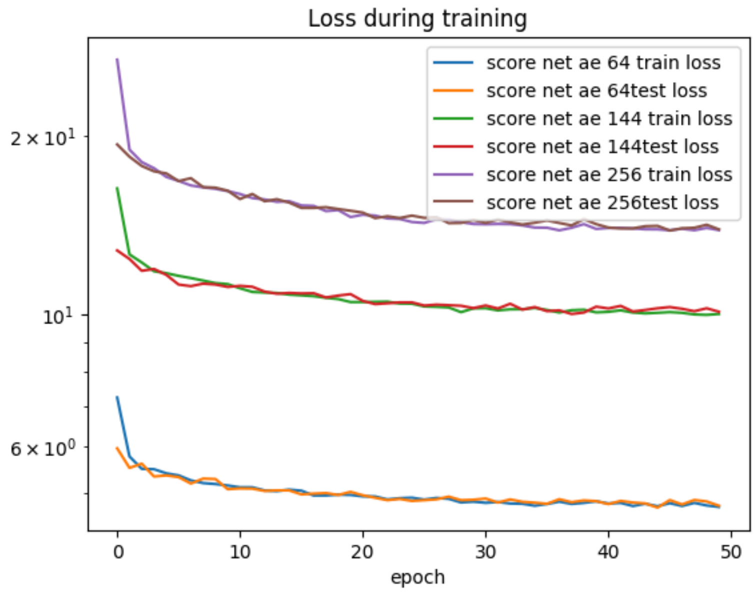
Instantiate and Train Score Net (UNet) with autoencoders

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py

train_score_net = False
save_score_net_model = False

# Which autoencoders should be used to train the Score Net model
# These must all be integers that fit the following formula: (4 * n) ^ 2
# This is a requirement of the UNet architecture
# 64 = (4 * 2) ^ 2
# 144 = (4 * 3) ^ 2
# 256 = (4 * 4) ^ 2
autoencoder_dims = [64, 144, 256]
```

```
autoencoder_dims = [64, 144, 256]

n_epochs_score_net = 50

lr_score_net = 0.001
T = 1
padding_required = False

loss_lists = {}

lr_0 = 0.5  # initial learning rate
k = 0.1    # decay rate

def lambda_func(t):
    return lr_0 * np.exp(-k * t)

for enc_out_dim in autoencoder_dims:

    # Encode training and test data:
    # Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py


    autoencoder = Autoencoder(enc_in_dim, enc_out_dim)
    autoencoder_model_path = os.path.join(file_location,
              'saved_models/autoencoder_count_' + str(enc_out_dim) + '.pt')
    checkpoint = torch.load(autoencoder_model_path, map_location=device)
    autoencoder.to(device)
    autoencoder.load_state_dict(checkpoint['model_state_dict'])
    autoencoder.eval()

    train_data_encoded = autoencoder.encode(train_dataloader.dataset).detach()
    train_dataloader_encoded = DataLoader(
            dataset=train_data_encoded,
            batch_size=batch_size,
            shuffle=True,
            drop_last=True,
    )
    test_data_encoded = autoencoder.encode(test_dataloader.dataset).detach()
    test_dataloader_encoded = DataLoader(
            dataset=test_data_encoded,
            batch_size=batch_size,
            shuffle=True,
            drop_last=True,
    )

    sde = VPSDE()
    score_net = UNet(
        input_channels=1,
        encoded_latent_embedding_dim=enc_out_dim,
        ch=128,
        ch_mult=(1, 2, 2),
        num_res_blocks=2,
        attn_resolutions=(16,),
        resamp_with_conv=True,
        dropout=0,
    )
    score_net.apply(weights_init)
    score_net.to(device)
    loss_fn_instance_dsm = DenoisingScoreMatching(sde=sde, score_net=score_net, T=T, padding_required=padding_required)
    optimiser_score_net = torch.optim.Adam(loss_fn_instance_dsm.parameters(), lr=lr_score_net)

    score_net_stats_path = os.path.join(file_location,
                'stats/scorenet_count_ae_' + str(enc_out_dim) + '.pkl')
    score_net_model_path = os.path.join(file_location,
                'saved_models/scorenet_count_ae_' + str(enc_out_dim) + '.pt')

    # Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/train/train_scorenet.py

    loss_list = dict()
    if train_score_net:
        print(f"==> Training the {enc_out_dim} ae score net with {n_epochs_score_net} epochs.")

        scheduler = lr_scheduler.LambdaLR(optimiser_score_net, lr_lambda=lambda_func)

        start_time = time.time()
        train_loss_list = []
        test_loss_list = []
        for epoch in range(n_epochs_score_net):
```

```
            epoch_loss = 0
            for x in tqdm.tqdm(train_dataloader_encoded):
                optimiser_score_net.zero_grad()
                loss = loss_fn_instance_dsm.loss_fn(x).mean()
                epoch_loss += loss.item()
                loss.backward()
                torch.nn.utils.clip_grad_norm_(score_net.parameters(), 1)
                optimiser_score_net.step()

            avg_loss = epoch_loss / len(train_dataloader_encoded)

            train_loss_list.append(avg_loss)

            scheduler.step()

            time_elapsed = time.time() - start_time
            print(f"Epoch: {epoch+1}  |  Total Time: {time_elapsed:.2f}s | Train Loss: {avg_loss:.5f}")

            epoch_loss = 0
            with torch.no_grad():
                for x in tqdm.tqdm(test_dataloader_encoded):
                    loss = loss_fn_instance_dsm.loss_fn(x).mean()
                    epoch_loss += loss.item()

            avg_loss = epoch_loss / len(test_dataloader_encoded)

            test_loss_list.append(avg_loss)

            time_elapsed = time.time() - start_time
            print(f"Epoch: {epoch+1}  |  Total Time: {time_elapsed:.2f}s | Test Loss: {avg_loss:.5f}")

        print("==> Score net training completed.")
        loss_list['train_loss_list'] = train_loss_list
        loss_list['test_loss_list'] = test_loss_list
        with open(score_net_stats_path, 'wb') as file:
            pickle.dump(loss_list, file, -1)
        if save_score_net_model:
            torch.save({'model_state_dict': score_net.state_dict()}, score_net_model_path)
    else:
        print("===> Loading model")
        checkpoint = torch.load(score_net_model_path, map_location=torch.device(device))
        score_net.load_state_dict(checkpoint['model_state_dict'])
        print("===> Showing stats from loaded model")
        with open(score_net_stats_path, 'rb') as file:
            loss_list = pickle.load(file)

    loss_lists[enc_out_dim] = loss_list

    del train_data_encoded
    del train_dataloader_encoded
    del test_data_encoded
    del test_dataloader_encoded
    del loss_fn_instance_dsm
    del optimiser_score_net
    del checkpoint
    del autoencoder
    del autoencoder_model_path
    gc.collect()
    if device == "cuda":
        torch.cuda.empty_cache()

for enc_out_dim in autoencoder_dims:
    loss_list = loss_lists[enc_out_dim]
    train_loss_list = loss_list['train_loss_list']
    test_loss_list = loss_list['test_loss_list']
    plt.plot(train_loss_list,
             label='score net ae ' + str(enc_out_dim) + ' train loss')
    plt.plot(test_loss_list,
             label='score net ae ' + str(enc_out_dim) + 'test loss')

plt.xlabel('epoch')
plt.title('Loss during training')
plt.legend()
plt.yscale("log")
plt.show()
```

```
===> Loading model
===> Showing stats from loaded model
===> Loading model
===> Showing stats from loaded model
===> Loading model
===> Showing stats from loaded model
```



Instantiate and train score net (UNet) with ablations

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py

train_score_net = False
save_score_net_model = False

# Which autoencoders should be used to train the Score Net model
# These must all be integers that fit the following formula: (4 * n) ^ 2
# This is a requirement of the UNet architecture
# 64 = (4 * 2) ^ 2
# 144 = (4 * 3) ^ 2
# 256 = (4 * 4) ^ 2
autoencoder_dims = [144]

n_epochs_score_net_ablations = [12, 25, 50, 75, 100]
lr_score_net_ablations = [0.00025, 0.0005, 0.001, 0.0025, 0.005]

T = 1
padding_required = False

loss_lists = {}

lr_0 = 0.5  # initial learning rate
k = 0.1    # decay rate

def lambda_func(t):
    return lr_0 * np.exp(-k * t)

for n_epochs_score_net in n_epochs_score_net_ablations:
    lr_score_net = 0.001
    enc_out_dim = 144

    # Encode training and test data:
    # Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py


    autoencoder = Autoencoder(enc_in_dim, enc_out_dim)
    autoencoder_model_path = os.path.join(file_location,
              'saved_models/autoencoder_count_' + str(enc_out_dim) + '.pt')
    checkpoint = torch.load(autoencoder_model_path, map_location=device)
    autoencoder.to(device)
    autoencoder.load_state_dict(checkpoint['model_state_dict'])
    autoencoder.eval()
```

```
train_data_encoded = autoencoder.encode(train_dataloader.dataset).detach()
train_dataloader_encoded = DataLoader(
        dataset=train_data_encoded,
        batch_size=batch_size,
        shuffle=True,
        drop_last=True,
)
test_data_encoded = autoencoder.encode(test_dataloader.dataset).detach()
test_dataloader_encoded = DataLoader(
        dataset=test_data_encoded,
        batch_size=batch_size,
        shuffle=True,
        drop_last=True,
)

sde = VPSDE()
score_net = UNet(
    input_channels=1,
    encoded_latent_embedding_dim=enc_out_dim,
    ch=128,
    ch_mult=(1, 2, 2),
    num_res_blocks=2,
    attn_resolutions=(16,),
    resamp_with_conv=True,
    dropout=0,
)
score_net.apply(weights_init)
score_net.to(device)
loss_fn_instance_dsm = DenoisingScoreMatching(sde=sde, score_net=score_net, T=T, padding_required=padding_required)
optimiser_score_net = torch.optim.Adam(loss_fn_instance_dsm.parameters(), lr=lr_score_net)

score_net_model_path = os.path.join(file_location,
            'saved_models/scorenet_count_ae_144_epoch' + str(n_epochs_score_net) + '_lr' + str(lr_score_net) + '.pt')

# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/train/train_scorenet.py

loss_list = dict()
if train_score_net:
    print(f"==> Training the {enc_out_dim} ae score net with {n_epochs_score_net} epochs at a {lr_score_net} learning rate.")

    scheduler = lr_scheduler.LambdaLR(optimiser_score_net, lr_lambda=lambda_func)

    start_time = time.time()
    train_loss_list = []
    test_loss_list = []
    for epoch in range(n_epochs_score_net):
        epoch_loss = 0
        for x in tqdm.tqdm(train_dataloader_encoded):
            optimiser_score_net.zero_grad()
            loss = loss_fn_instance_dsm.loss_fn(x).mean()
            epoch_loss += loss.item()
            loss.backward()
            torch.nn.utils.clip_grad_norm_(score_net.parameters(), 1)
            optimiser_score_net.step()

        avg_loss = epoch_loss / len(train_dataloader_encoded)

        train_loss_list.append(avg_loss)

        scheduler.step()

        time_elapsed = time.time() - start_time
        print(f"Epoch: {epoch+1}  |  Total Time: {time_elapsed:.2f}s | Train Loss: {avg_loss:.5f}")

        epoch_loss = 0
        with torch.no_grad():
            for x in tqdm.tqdm(test_dataloader_encoded):
                loss = loss_fn_instance_dsm.loss_fn(x).mean()
                epoch_loss += loss.item()

        avg_loss = epoch_loss / len(test_dataloader_encoded)

        test_loss_list.append(avg_loss)

        time_elapsed = time.time() - start_time
        print(f"Epoch: {epoch+1}  |  Total Time: {time_elapsed:.2f}s | Test Loss: {avg_loss:.5f}")

    print("==> Score net training completed.")
```

```
        print("==> Score net training completed.")
        loss_list['train_loss_list'] = train_loss_list
        loss_list['test_loss_list'] = test_loss_list
        if save_score_net_model:
            torch.save({'model_state_dict': score_net.state_dict()}, score_net_model_path)
    else:
        print("===> Existing model will be used when generating synthetic data.")

    loss_lists[n_epochs_score_net] = loss_list

    del train_data_encoded
    del train_dataloader_encoded
    del test_data_encoded
    del test_dataloader_encoded
    del loss_fn_instance_dsm
    del optimiser_score_net
    del checkpoint
    del autoencoder
    del autoencoder_model_path
    gc.collect()
    if device == "cuda":
        torch.cuda.empty_cache()

for lr_score_net in lr_score_net_ablations:
    n_epochs_score_net = 50
    enc_out_dim = 144

    # Encode training and test data:
    # Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py


    autoencoder = Autoencoder(enc_in_dim, enc_out_dim)
    autoencoder_model_path = os.path.join(file_location,
              'saved_models/autoencoder_count_' + str(enc_out_dim) + '.pt')
    checkpoint = torch.load(autoencoder_model_path, map_location=device)
    autoencoder.to(device)
    autoencoder.load_state_dict(checkpoint['model_state_dict'])
    autoencoder.eval()

    train_data_encoded = autoencoder.encode(train_dataloader.dataset).detach()
    train_dataloader_encoded = DataLoader(
            dataset=train_data_encoded,
            batch_size=batch_size,
            shuffle=True,
            drop_last=True,
    )
    test_data_encoded = autoencoder.encode(test_dataloader.dataset).detach()
    test_dataloader_encoded = DataLoader(
            dataset=test_data_encoded,
            batch_size=batch_size,
            shuffle=True,
            drop_last=True,
    )

    sde = VPSDE()
    score_net = UNet(
        input_channels=1,
        encoded_latent_embedding_dim=enc_out_dim,
        ch=128,
        ch_mult=(1, 2, 2),
        num_res_blocks=2,
        attn_resolutions=(16,),
        resamp_with_conv=True,
        dropout=0,
    )
    score_net.apply(weights_init)
    score_net.to(device)
    loss_fn_instance_dsm = DenoisingScoreMatching(sde=sde, score_net=score_net, T=T, padding_required=padding_required)
    optimiser_score_net = torch.optim.Adam(loss_fn_instance_dsm.parameters(), lr=lr_score_net)

    score_net_model_path = os.path.join(file_location,
               'saved_models/scorenet_count_ae_144_epoch' + str(n_epochs_score_net) + '_lr' + str(lr_score_net) + '.pt')

    # Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/train/train_scorenet.py

    loss_list = dict()
    if train_score_net:
        print(f"==> Training the {enc_out_dim} ae score net with {n_epochs_score_net} epochs at a {lr_score_net} learning rate.")
```

```
    scheduler = lr_scheduler.LambdaLR(optimiser_score_net, lr_lambda=lambda_func)

    start_time = time.time()
    train_loss_list = []
    test_loss_list = []
    for epoch in range(n_epochs_score_net):
        epoch_loss = 0
        for x in tqdm.tqdm(train_dataloader_encoded):
            optimiser_score_net.zero_grad()
            loss = loss_fn_instance_dsm.loss_fn(x).mean()
            epoch_loss += loss.item()
            loss.backward()
            torch.nn.utils.clip_grad_norm_(score_net.parameters(), 1)
            optimiser_score_net.step()

        avg_loss = epoch_loss / len(train_dataloader_encoded)

        train_loss_list.append(avg_loss)

        scheduler.step()

        time_elapsed = time.time() - start_time
        print(f"Epoch: {epoch+1}  |  Total Time: {time_elapsed:.2f}s | Train Loss: {avg_loss:.5f}")

        epoch_loss = 0
        with torch.no_grad():
            for x in tqdm.tqdm(test_dataloader_encoded):
                loss = loss_fn_instance_dsm.loss_fn(x).mean()
                epoch_loss += loss.item()

        avg_loss = epoch_loss / len(test_dataloader_encoded)

        test_loss_list.append(avg_loss)

        time_elapsed = time.time() - start_time
        print(f"Epoch: {epoch+1}  |  Total Time: {time_elapsed:.2f}s | Test Loss: {avg_loss:.5f}")

    print("==> Score net training completed.")
    loss_list['train_loss_list'] = train_loss_list
    loss_list['test_loss_list'] = test_loss_list
    if save_score_net_model:
        torch.save({'model_state_dict': score_net.state_dict()}, score_net_model_path)
else:
    print("===> Existing model will be used when generating synthetic data.")

loss_lists[lr_score_net] = loss_list

del train_data_encoded
del train_dataloader_encoded
del test_data_encoded
del test_dataloader_encoded
del loss_fn_instance_dsm
del optimiser_score_net
del checkpoint
del autoencoder
del autoencoder_model_path
gc.collect()
if device == "cuda":
    torch.cuda.empty_cache()
```

```
===> Existing model will be used when generating synthetic data.
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```
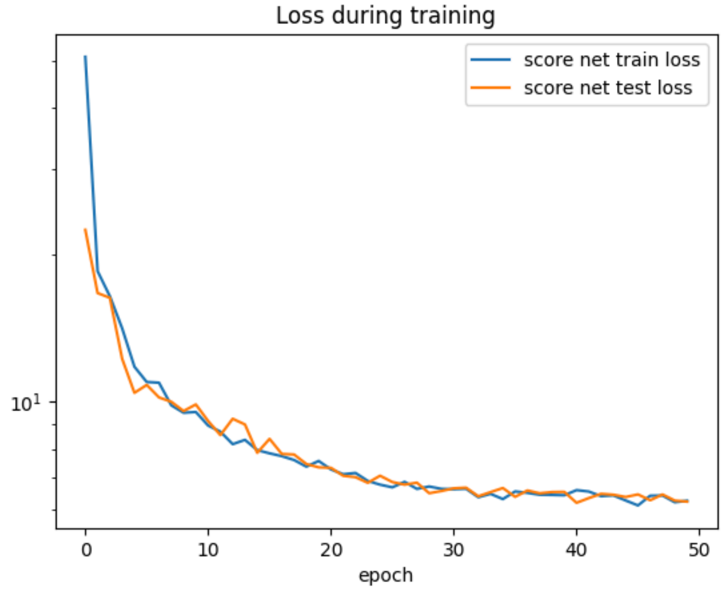

Train ScoreNet With No Autoencoder

```
train_score_net_no_ae = False
save_score_net_model_no_ae = False

# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py

batch_size = 64

import torch.nn.functional as F

final_dims = 1296
padding_added_dims = final_dims - train_dataloader.dataset.shape[1]

train_data_no_ae = F.pad(input=train_dataloader.dataset, pad=(0, padding_added_dims, 0, 0), mode='constant', value=0)
train_dataloader_no_ae = DataLoader(
        dataset=train_data_no_ae,
        batch_size=batch_size,
        shuffle=True,
        drop_last=True,
)
test_data_no_ae = F.pad(input=test_dataloader.dataset, pad=(0, padding_added_dims, 0, 0), mode='constant', value=0)
test_dataloader_no_ae = DataLoader(
        dataset=test_data_no_ae,
        batch_size=batch_size,
        shuffle=True,
        drop_last=True,
)

lr_score_net_no_ae = 0.001
T_no_ae = 1
padding_required_no_ae = False

sde_no_ae = VPSDE()
score_net_no_ae = UNet(
    input_channels=1,
    encoded_latent_embedding_dim=train_data_no_ae.shape[1],
    ch=128,
    ch_mult=(1, 2, 2),
    num_res_blocks=2,
    attn_resolutions=(16,),
    resamp_with_conv=True,
    dropout=0,
)
score_net_no_ae.apply(weights_init)
score_net_no_ae.to(device)
loss_fn_instance_dsm_no_ae = DenoisingScoreMatching(sde=sde_no_ae, score_net=score_net_no_ae, T=T_no_ae, padding_required=padding_required_n
optimiser_score_net_no_ae = torch.optim.Adam(loss_fn_instance_dsm_no_ae.parameters(), lr=lr_score_net_no_ae)

T = 1

# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/train/train_scorenet.py

score_net_stats_path = os.path.join(file_location,
            'stats/scorenet_count_no_ae.pkl')
score_net_model_path = os.path.join(file_location,
            'saved_models/scorenet_count_no_ae.pt')

n_epochs_score_net_no_ae = 50

if train_score_net_no_ae:
    print(f"==> Training the score net with {n_epochs_score_net_no_ae} epochs.")
    lr_0_no_ae = 0.5  # initial learning rate
    k_no_ae = 0.1    # decay rate

    def lambda_func_no_ae(t_no_ae):
        return lr_0_no_ae * np.exp(-k_no_ae * t_no_ae)
    scheduler_no_ae = lr_scheduler.LambdaLR(optimiser_score_net_no_ae, lr_lambda=lambda_func_no_ae)

    start_time_no_ae = time.time()
    train_loss_list_no_ae = []
    test_loss_list_no_ae = []
    for epoch_no_ae in range(n_epochs_score_net_no_ae):
        epoch_loss_no_ae = 0
        for x_no_ae in tqdm.tqdm(train_dataloader_no_ae):
            optimiser_score_net_no_ae.zero_grad()
            loss_no_ae = loss_fn_instance_dsm_no_ae.loss_fn(x_no_ae).mean()
            epoch_loss_no_ae += loss_no_ae.item()
            loss_no_ae.backward()
```

```
            torch.nn.utils.clip_grad_norm_(score_net_no_ae.parameters(), 1)
            optimiser_score_net_no_ae.step()

        avg_loss_no_ae = epoch_loss_no_ae / len(train_dataloader_no_ae)

        train_loss_list_no_ae.append(avg_loss_no_ae)

        scheduler_no_ae.step()

        time_elapsed_no_ae = time.time() - start_time_no_ae
        print(f"Epoch: {epoch_no_ae+1}  |  Total Time: {time_elapsed_no_ae:.2f}s | Train Loss: {avg_loss_no_ae:.5f}")

        epoch_loss_no_ae = 0
        with torch.no_grad():
            for x_no_ae in tqdm.tqdm(test_dataloader_no_ae):
                loss_no_ae = loss_fn_instance_dsm_no_ae.loss_fn(x_no_ae).mean()
                epoch_loss_no_ae += loss_no_ae.item()

        avg_loss_no_ae = epoch_loss_no_ae / len(test_dataloader_no_ae)

        test_loss_list_no_ae.append(avg_loss_no_ae)

        time_elapsed_no_ae = time.time() - start_time_no_ae
        print(f"Epoch: {epoch_no_ae+1}  |  Total Time: {time_elapsed_no_ae:.2f}s | Test Loss: {avg_loss_no_ae:.5f}")

    print("==> Score net training (no autoencoder) completed.")
    plt.plot(train_loss_list_no_ae, label='score net train loss')
    plt.plot(test_loss_list_no_ae, label='score net test loss')
    plt.xlabel('epoch')
    plt.title('Loss during training')
    plt.legend()
    plt.yscale("log")
    plt.show()
    loss_list_no_ae = dict()
    loss_list_no_ae['train_loss_list'] = train_loss_list_no_ae
    loss_list_no_ae['test_loss_list'] = test_loss_list_no_ae
    with open(score_net_stats_path, 'wb') as file:
        pickle.dump(loss_list_no_ae, file, -1)
    if save_score_net_model_no_ae:
        torch.save({'model_state_dict': score_net_no_ae.state_dict()}, score_net_model_path)
else:
    print("===> Loading model")
    checkpoint_no_ae = torch.load(score_net_model_path, map_location=torch.device(device))
    score_net_no_ae.load_state_dict(checkpoint_no_ae['model_state_dict'])
    print("===> Showing stats from loaded model")
    with open(score_net_stats_path, 'rb') as file:
        loss_list_no_ae = pickle.load(file)
    train_loss_list_no_ae = loss_list_no_ae['train_loss_list']
    test_loss_list_no_ae = loss_list_no_ae['test_loss_list']
    plt.plot(train_loss_list_no_ae, label='score net train loss')
    plt.plot(test_loss_list_no_ae, label='score net test loss')
    plt.xlabel('epoch')
    plt.title('Loss during training')
    plt.legend()
    plt.yscale("log")
    plt.show()
```

```
===> Loading model
===> Showing stats from loaded model
```



Generate Synthetic Data Once the model is trained, it can be used to generate synthetic data that can be compared to the original data to determine if it is statistically similar while still protecting the privacy of the original patients. The generation process is described in the Score Net model section.

Note: By default, instead of generating this data instead pre-generated data is loaded and used. You can change this by setting `generate_data = True`.

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py

batch_size = 128

generate_data = False
save_generated_data = False

autoencoder_dims = [64, 144, 256]

T = 1

if generate_data:
    time_steps = 1000
    num_samples_to_generate = batch_size * 80

    print("==> Commencing reverse solve using torchsde Euler Maruyama.")

    for enc_out_dim in autoencoder_dims:
        start_time = time.time()
        print(f'==> Generating data for {enc_out_dim} ae score net')
        autoencoder = Autoencoder(enc_in_dim, enc_out_dim)
        autoencoder_model_path = os.path.join(file_location,
                'saved_models/autoencoder_count_' + str(enc_out_dim) + '.pt')
        checkpoint = torch.load(autoencoder_model_path, map_location=device)
        autoencoder.load_state_dict(checkpoint['model_state_dict'])
        autoencoder.eval()
        autoencoder.to(device)

        sde = VPSDE()
        score_net = UNet(
        input_channels=1,
        encoded_latent_embedding_dim=enc_out_dim,
        ch=128,
        ch_mult=(1, 2, 2),
        num_res_blocks=2,
        attn_resolutions=(16,),
        resamp_with_conv=True,
        dropout=0,
        )
        score_net.apply(weights_init)
        score_net.to(device)

        score_net_model_path = os.path.join(file_location,
                'saved_models/scorenet_count_ae_' + str(enc_out_dim) + '.pt')

        generated_data_location = os.path.join(file_location,
                'synthetic_data/count_ae_' + str(enc_out_dim) + '.npy')

        try:
            generated_data_final = torch.Tensor(np.load(generated_data_location))
            print(f'Total records loaded: {generated_data_final.shape[0]}')
        except:
            generated_data_final = None
            print("No data loaded")

        checkpoint = torch.load(score_net_model_path, map_location=torch.device(device))
        score_net.load_state_dict(checkpoint['model_state_dict'])


        reverse_sde = ReverseSDE(sde=sde, score_net=score_net, T=T)
        torchsde_SDE = WrapperForTorchSDE(reverse_sde=reverse_sde, noise_type="diagonal", sde_type="ito")
        ts = torch.linspace(0, 1, time_steps + 1) * reverse_sde.T
        ts = ts.to(device)
        with torch.no_grad():
            assert (
                num_samples_to_generate >= batch_size
            ), "Num to generate should be greater than or equal to batch size."
            batch_iter = math.ceil(num_samples_to_generate / batch_size)
            print(f"==> Able to generate {batch_iter * batch_size} samples.")

            xs_batches = None
            for i in range(0, batch_iter):
                print(f"==> Batch {i + 1} out of {batch_iter}.")
                x_0 = torch.randn(batch_size, enc_out_dim, device=device)
                x_batch_solved = torchsde.sdeint(torchsde_SDE, x_0, ts, method="euler")
                with torch.no_grad():
                    print(
```

```
                    f"==> Decoding data generated in batch {i + 1} out of {batch_iter}."
                )
                x_batch_solved = torch.stack([x_batch_solved])
                for x_encoded in x_batch_solved:
                    out = autoencoder.decode(x_encoded.to(device))
                    out = out.cpu()
                    out = out[-1].round()
                    if generated_data_final is None:
                        generated_data_final = out.detach()[:, 0:train_data.shape[1]]
                    else:
                        generated_data_final = torch.cat(
                            (generated_data_final,
                            out.detach()[:, 0:train_data.shape[1]]))
                    # del out
                    torch.cuda.empty_cache()

            if save_generated_data:
                print("==> Saving generated data.")
                np.save(generated_data_location, generated_data_final)
                print(f'Generated data saved to {generated_data_location}')

            time_elapsed = time.time() - start_time
            print(f'Time elapsed: {time_elapsed} seconds')
            print(f'Total records saved: {generated_data_final.shape[0]}')
else:
    print("No data generated.  Pre-generated data will be loaded in the evaluation section.")
```

```
No data generated.  Pre-generated data will be loaded in the evaluation section.
```

Generate synthetic data (Learning Rate/Epoch ablation models)

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py

batch_size = 128

generate_data = False
save_generated_data = False

T = 1
enc_in_dim = train_data.shape[1]

if generate_data:
    time_steps = 1000
    num_samples_to_generate = batch_size * 80

    print("==> Commencing reverse solve using torchsde Euler Maruyama.")

    for model_file in os.listdir(file_location + '/seth_models/'):
        enc_out_dim = 144
        start_time = time.time()
        print(f'==> Generating data for {model_file}')
        autoencoder = Autoencoder(enc_in_dim, enc_out_dim)
        autoencoder_model_path = os.path.join(file_location,
                'saved_models/autoencoder_count_144.pt')
        checkpoint = torch.load(autoencoder_model_path, map_location=device)
        autoencoder.load_state_dict(checkpoint['model_state_dict'])
        autoencoder.eval()
        autoencoder.to(device)

        sde = VPSDE()
        score_net = UNet(
        input_channels=1,
        encoded_latent_embedding_dim=enc_out_dim,
        ch=128,
        ch_mult=(1, 2, 2),
        num_res_blocks=2,
        attn_resolutions=(16,),
        resamp_with_conv=True,
        dropout=0,
        )
        score_net.apply(weights_init)
        score_net.to(device)

        score_net_model_path = os.path.join(file_location,
                'seth_models/' + model_file)
```

```
        generated_data_location = os.path.join(file_location,
                'seth_data/' + model_file.split('.')[0] + '.' + model_file.split('.')[1] + '.npy')

        try:
            generated_data_final = torch.Tensor(np.load(generated_data_location))
            print(f'Total records loaded: {generated_data_final.shape[0]}')
        except:
            generated_data_final = None
            print("No data loaded")

        checkpoint = torch.load(score_net_model_path, map_location=torch.device(device))
        score_net.load_state_dict(checkpoint['model_state_dict'])


        reverse_sde = ReverseSDE(sde=sde, score_net=score_net, T=T)
        torchsde_SDE = WrapperForTorchSDE(reverse_sde=reverse_sde, noise_type="diagonal", sde_type="ito")
        ts = torch.linspace(0, 1, time_steps + 1) * reverse_sde.T
        ts = ts.to(device)
        with torch.no_grad():
            assert (
                num_samples_to_generate >= batch_size
            ), "Num to generate should be greater than or equal to batch size."
            batch_iter = math.ceil(num_samples_to_generate / batch_size)
            print(f"==> Able to generate {batch_iter * batch_size} samples.")

            xs_batches = None
            for i in range(0, batch_iter):
                print(f"==> Batch {i + 1} out of {batch_iter}.")
                x_0 = torch.randn(batch_size, enc_out_dim, device=device)
                x_batch_solved = torchsde.sdeint(torchsde_SDE, x_0, ts, method="euler")
                with torch.no_grad():
                    print(
                        f"==> Decoding data generated in batch {i + 1} out of {batch_iter}."
                    )
                    x_batch_solved = torch.stack([x_batch_solved])
                    for x_encoded in x_batch_solved:
                        out = autoencoder.decode(x_encoded.to(device))
                        out = out.cpu()
                        out = out[-1].round()
                        if generated_data_final is None:
                            generated_data_final = out.detach()[:, 0:train_data.shape[1]]
                        else:
                            generated_data_final = torch.cat(
                                (generated_data_final,
                                out.detach()[:, 0:train_data.shape[1]]))
                        # del out
                        torch.cuda.empty_cache()

                if save_generated_data:
                    print("==> Saving generated data.")
                    np.save(generated_data_location, generated_data_final)
                    print(f'Generated data saved to {generated_data_location}')

                time_elapsed = time.time() - start_time
                print(f'Time elapsed: {time_elapsed} seconds')
                print(f'Total records saved: {generated_data_final.shape[0]}')

else:
    print("No data generated.  Pre-generated data will be loaded in the evaluation section.")
```

```
No data generated.  Pre-generated data will be loaded in the evaluation section.
```

Generate Synthetic Data (No Autoencoder)

```
# Modified from: https://github.com/aanaseer/ScoEHR/blob/main/scoehr/main.py

batch_size_no_ae = 64

generated_data_location = os.path.join(file_location, 'synthetic_data/count_no_ae.npy')

generate_data_no_ae = False
save_generated_data_no_ae = False

T = 1

try:
    generated_data_final_no_ae = torch.Tensor(np.load(generated_data_location))
    print(f'Total records loaded: {generated_data_final_no_ae.shape[0]}')
except:
    generated_data_final_no_ae = None
    print("No data loaded")

if generate_data_no_ae:
    time_steps_no_ae = 1000
    num_samples_to_generate_no_ae = batch_size_no_ae * 164

    print("==> Commencing reverse solve using torchsde Euler Maruyama.")

    reverse_sde_no_ae = ReverseSDE(sde=sde_no_ae, score_net=score_net_no_ae, T=T_no_ae)
    torchsde_SDE_no_ae = WrapperForTorchSDE(reverse_sde=reverse_sde_no_ae, noise_type="diagonal", sde_type="ito")
    ts_no_ae = torch.linspace(0, 1, time_steps_no_ae + 1) * reverse_sde_no_ae.T
    ts_no_ae = ts_no_ae.to(device)
    with torch.no_grad():
        assert (
            num_samples_to_generate_no_ae >= batch_size_no_ae
        ), "Num to generate should be greater than or equal to batch size."
        batch_iter_no_ae = math.ceil(num_samples_to_generate_no_ae / batch_size_no_ae)
        print(f"==> Able to generate {batch_iter_no_ae * batch_size_no_ae} samples.")

        xs_batches_no_ae = None
        for i_no_ae in range(0, batch_iter_no_ae):
            print(f"==> Batch {i_no_ae + 1} out of {batch_iter_no_ae}.")
            x_0_no_ae = torch.randn(batch_size_no_ae, train_data_no_ae.shape[1], device=device)
            x_batch_solved_no_ae = torchsde.sdeint(torchsde_SDE_no_ae, x_0_no_ae, ts_no_ae, method="euler")
            with torch.no_grad():
                # print(
                #     f"==> Decoding data generated in batch {i_no_ae + 1} out of {batch_iter_no_ae}."
                # )
                x_batch_solved_no_ae = torch.stack([x_batch_solved_no_ae])
                for x_no_ae in x_batch_solved_no_ae:
                    out_no_ae = x_no_ae
                    out_no_ae = out_no_ae.cpu()
                    out_no_ae = out_no_ae[-1].round()
                    if generated_data_final_no_ae is None:
                        generated_data_final_no_ae = out_no_ae.detach()[:, 0:train_data.shape[1]]
                    else:
                        generated_data_final_no_ae = torch.cat(
                            (generated_data_final_no_ae,
                             out_no_ae.detach()[:, 0:train_data.shape[1]]))
                    # del out
                    torch.cuda.empty_cache()

            # if generated_data_final_no_ae is None:
            #     generated_data_final_no_ae = xs_batches_no_ae[:, 0:train_data.shape[1]]
            # else:
            #     generated_data_final_no_ae = torch.cat((generated_data_final_no_ae, xs_batches_no_ae[:, 0:train_data.shape[1]]))

            if save_generated_data_no_ae:
                print("==> Saving generated data.")
                np.save(generated_data_location, generated_data_final_no_ae)
                print(f'Generated data saved to {generated_data_location}')

            print(f'Total records saved: {generated_data_final_no_ae.shape[0]}')
```

```
Total records loaded: 10048
```

Evaluation

Metrics Descriptions

The original paper looked at three types of Metrics

1. Quantitative Metrics
2. Qualitative Metrics
3. Privacy Metrics

Quantitative Metrics

1.1 Dimensional Distribution Metric

Assessing if marginal distributions in real data are captured by the synthetic data. ie, for a given category of data, such as age, independent of other variables, the distribution is expected.

Binary Data:

$$\boldsymbol{DWM} = \sum_{i=1}^{N} | \frac{1}{n_d} \sum_{j=1}^{n_d} d_{j,i} - \hat{d}_{j,i} |$$

Continuous Variable Data:

$$\boldsymbol{DEM} = \sum_{i=1}^{N} \frac{1}{n_c} \sum_{j=1}^{n_c} |c_{j,i} - \hat{c}_{j,i} |$$

Total Score:

$$\frac{DWM + DEM}{N}$$

A lower value indicates that the real and synthetic data have similar marginal relationships.

Results found in the paper:

Model	MIMIC-III Dataset	ED EHR Dataset
medGAN	0.0019 ± 0.0001	0.012 ± 0.001
medBGAN	0.0016 ± 0.0001	0.014 ± 0.001
medWGAN	0.0025 ± 0.0001	0.0088 ± 0.0001
ScoEHR	0.0029 ± 0.0001	0.0037 ± 0.0001

1.2 Pairwise Correlation Difference

Assessing if the correlations in the real and synthetic datasets are similar. The Pearson Correlation Matrices are found for the real and sythetic data which are used to compute the Frobenius Norm of the difference.

$$PCD = \|Corr(D) - Corr(\hat{D})\|_F$$

The closer PCD is to zero, the better the inter-dimensional relationships are caputred by the synthetic data.

Results found in the paper:

Model	MIMIC-III Dataset	ED EHR Dataset
medGAN	120 ± 8	24.1 ± 0.2
medBGAN	146 ± 6	20.7 ± 0.5
medWGAN	22.1 ± 0.4	15.2 ± 0.3
ScoEHR	21.8 ± 0.3	33.6 ± 0.2

1.3 Marginal and Correlation Similarity

Assessing the similarity of the latent structure of the real and synthetic datsets. This is obtained by concatenating both datasets and using k-means clustering to determine 'G' clusters.

$$U = log(\frac{1}{G}) \sum_{j=1}^{G} [\frac{n_j^R}{n_j} - c]^2$$

- G is the number of clusters
- n_j^R is the number of samples from the real dataset
- n_j^S is the number of samples from the synthetic dataset
- n_j is the number of samples in the j-th cluster
- c is $\frac{n^R}{n^R + n^S}$

A lower log-cluster score indicates more similarity between the synthetic and real data.

Results found in the paper:

Model	MIMIC-III Dataset	ED EHR Dataset
medGAN	-2.9 $\pm$ 0.1	-3.7 $\pm$ 0.3
medBGAN	-3.2 $\pm$ 0.1	-2.5 $\pm$ 0.2
medWGAN	-5.4 $\pm$ 0.2	-6.1 $\pm$ 0.4
ScoEHR	-6.0 $\pm$ 0.1	-7.8 $\pm$ 0.5

1.4 Synthetic Ranking Agreement

Assessing the utility of the synethic data for use in downstream machine learning tasks by comparing results obtained through synthetic data and results obtained when using real data. This is obtained by training and testing a machine learning model using both real and synthetic data and finding their respective AUROC.

$$SRA = \frac{1}{L(L-1)} \sum_{j=1}^{L} \sum_{k \neq j} \mathbb{I}((A_j - A_k)(B_j - B_k)) > 0$$

- L is the number of machine learning models
- A are a set of AUROC values for models trained and tested with real data
- B are a set of AUROC values for models trained and tested with synthetic data
- $\mathbb{I}$ is the indicator function.

A higher SRA indicates similarity in machine learning tasks.

Results found in the paper:

Model	MIMIC-III Dataset	ED EHR Dataset
medGAN	0.83 $\pm$ 0.02	0.81 $\pm$ 0.02
medBGAN	0.86 $\pm$ 0.03	0.85 $\pm$ 0.03
medWGAN	0.81 $\pm$ 0.03	0.83 $\pm$ 0.04
ScoEHR	0.87 $\pm$ 0.02	0.86 $\pm$ 0.03

Note: We chose not to recreate this metric because neither the paper nor the paper's github specified how many or which machine learning tasks were used to generate this metric. The paper also did not explain how they generated truth-values for the synthetic data to use when calculating the AUROC metrics.

Qualitative Metrics

Clinician Review

A random mixed set of real and synthetic data was inspected to evaluate realism.

In the paper, 100 synthetic patients and 100 real patients were combined and label as 'realistic' or 'unrealistic' by 3 board certified clinicians.

- If a patient is considered 'unrealistic' if one clinician labeled them as such, 81% of real patients were labeled as real and 81% of synthetic patients were labeled as real
- If a patient is considered realistic if at least one clinician labeled them as realistic, 100% of real and synthetic patients were labeled realistic
- If a patient is considered realistic only if a majority of the 3 clinicians agreed, 93% of real patients were labeled as real and 95% of the synthetic patients were labeled as real

---

Note: We are not recreating this metric due to lack of connections with board-certified clinicians. This metric is referenced for completeness.

Privacy

Assessing if, given a random sample of synthetic data and training data, it could be determined with likely probability that someone's data was used in the training. This is determined by calculating the Cosine Similarity between the real and synthetic data. If the probabliity is 50% or higher, the patients privacy is considered to be compromised.

Evaluation Code

Evaluation code can be found in the following cells within this section.

Load the data for evaluation purposes

```
# Load the autoencoder ablation data (this includes the primary model as well)

autoencoder_dims = [64, 144, 256, 0]

generated_data_final = {}
record_counts = []
synthetic_records = {}

for enc_out_dim in autoencoder_dims:
    if enc_out_dim == 0:
        generated_data_location = os.path.join(file_location,
          'synthetic_data/count_no_ae.npy')
    else:
        generated_data_location = os.path.join(file_location,
          'synthetic_data/count_ae_' + str(enc_out_dim) + '.npy')

    generated_data_final[enc_out_dim] = torch.Tensor(np.load(generated_data_location))
    print(f'{generated_data_final[enc_out_dim].shape[0]} records loaded for {enc_out_dim} ae')
    record_counts.append(generated_data_final[enc_out_dim].shape[0])

synthetic_data_size = min(record_counts)
real = test_data[0:synthetic_data_size].to("cpu").detach()
for enc_out_dim in autoencoder_dims:
    synthetic_records[enc_out_dim] = generated_data_final[enc_out_dim][0:synthetic_data_size].to("cpu").detach()

ablation_files = os.listdir(file_location + '/seth_data/')

for data_file in ablation_files:
    generated_data_location = os.path.join(file_location, 'seth_data', data_file)
    generated_data_final[data_file] = torch.Tensor(np.load(generated_data_location))
    print(f'{generated_data_final[data_file].shape[0]} records loaded for {data_file} ablation')
    record_counts.append(generated_data_final[data_file].shape[0])

synthetic_data_size = min(record_counts)
real = real[0:synthetic_data_size].to("cpu").detach()
for data_file in ablation_files:
    synthetic_records[data_file] = generated_data_final[data_file][0:synthetic_data_size].to("cpu").detach()
```

```
10240 records loaded for 64 ae
10240 records loaded for 144 ae
10240 records loaded for 256 ae
10048 records loaded for 0 ae
10240 records loaded for scorenet_count_ae_144_epoch25_lr0.001.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch12_lr0.001.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch50_lr0.001.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch30_lr0.005.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch75_lr0.001.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch30_lr0.00025.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch30_lr0.0005.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch30_lr0.001.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch30_lr0.0025.npy ablation
10240 records loaded for scorenet_count_ae_144_epoch100_lr0.001.npy ablation
```

1.1 Dimensional Distribution Metric

```
DDM_results = {}
for enc_out_dim in autoencoder_dims:
    print(f'==> Showing results for {enc_out_dim} Autoencoder:')
    synthetic = synthetic_records[enc_out_dim]
    #Note: Because this is entirely count data, DWM is not needed
    DEM = torch.sum(torch.mean(torch.abs(real - synthetic), axis=0))
    DDM = DEM / len(real)
    DDM = DDM.item()
    DDM_results[enc_out_dim] = DDM
    print(f"Dimensional Distribution Metric: {round(DDM, 4)}")
    DDM_original = 0.0029
    DDM_compare = round(((DDM - DDM_original) / abs(DDM_original)) * 100,2)
    if (DDM_compare < 0):
      print(f"Recreated results have {abs(DDM_compare)}% better marginal relationships than the original.")
    elif ((DDM_compare > 0)):
      print(f"Recreated results have {DDM_compare}% worse marginal relationships than the original.")
    else:
      print("Recreated results have the same marginal relationships as the original.")

for data_file in ablation_files:
      print(f'==> Showing results for {data_file} ablation:')
      synthetic = synthetic_records[data_file]
      #Note: Because this is entirely count data, DWM is not needed
      DEM = torch.sum(torch.mean(torch.abs(real - synthetic), axis=0))
      DDM = DEM / len(real)
      DDM = DDM.item()
      DDM_results[data_file] = DDM
      print(f"Dimensional Distribution Metric: {round(DDM, 4)}")
      DDM_original = 0.0029
      DDM_compare = round(((DDM - DDM_original) / abs(DDM_original)) * 100,2)
      if (DDM_compare < 0):
        print(f"Recreated results have {abs(DDM_compare)}% better marginal relationships than the original.")
      elif ((DDM_compare > 0)):
        print(f"Recreated results have {DDM_compare}% worse marginal relationships than the original.")
      else:
        print("Recreated results have the same marginal relationships as the original.")
```

```
==> Showing results for 64 Autoencoder:
Dimensional Distribution Metric: 0.0023
Recreated results have 21.39% better marginal relationships than the original.
==> Showing results for 144 Autoencoder:
Dimensional Distribution Metric: 0.0021
Recreated results have 27.87% better marginal relationships than the original.
==> Showing results for 256 Autoencoder:
Dimensional Distribution Metric: 0.0021
Recreated results have 28.7% better marginal relationships than the original.
==> Showing results for 0 Autoencoder:
Dimensional Distribution Metric: 0.0025
Recreated results have 13.3% better marginal relationships than the original.
==> Showing results for scorenet_count_ae_144_epoch25_lr0.001.npy ablation:
Dimensional Distribution Metric: 0.0022
Recreated results have 22.66% better marginal relationships than the original.
==> Showing results for scorenet_count_ae_144_epoch12_lr0.001.npy ablation:
Dimensional Distribution Metric: 0.0021
Recreated results have 26.56% better marginal relationships than the original.
==> Showing results for scorenet_count_ae_144_epoch50_lr0.001.npy ablation:
```

1.2 Pairwise Correlation Difference

```
==> Showing results for scorenet_count_ae_144_epoch50_lr0.005.npy ablation:
```

```
PCD_results = {}
for enc_out_dim in autoencoder_dims:
    print(f'==> Showing results for {enc_out_dim} Autoencoder:')
    synthetic = synthetic_records[enc_out_dim]

    corr_real = torch.corrcoef(real.T)
    corr_synthetic = torch.corrcoef(synthetic.T)

    #This allows us to ignore the rows and columns with no variance (the nan values)
    corr_real[torch.isnan(corr_real)] = 0
    corr_synthetic[torch.isnan(corr_synthetic)] = 0
```