Generative Adversarial Networks Applied to Observational Health Data

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Abstract

Having been collected for its primary purpose in patient care, Observational Health Data (OHD) can further benefit patient well-being by sustaining the development of health informatics. However, the potential for secondary usage of OHD continues to be hampered by the fiercely private nature of patient-related data.

Generative Adversarial Networks (GAN) have recently emerged as a groundbreaking approach to efficiently learn generative models that produce realistic Synthetic Data (SD). However, the application of GAN to OHD seems to have been lagging in comparison to other fields.

We conducted a review of GAN algorithms for OHD in the published literature, and report our findings here.

1 Introduction

1.1 Background

Most Observational Health Data (OHD) is collected as Electronic Health Records (EHR) at various points of care in a patient’s trajectory, primarily to support and enable healthcare professionals (Cowie et al. 2016). The patient profiles found in EHR are diverse and longitudinal, composed of demographics variables, recordings of diagnoses, conditions, procedures, prescriptions, measurements and lab test results, administrative information, and increasingly omics (OHDSI 2020).

Having served its primary purpose, this wealth of detailed information can further benefit patient well-being by sustaining the development lifecycle of health informatics (HI) and machine learning (ML) algorithms. However, the potential for secondary usage of OHD continues to be hampered by the fiercely private nature of patient-related data, and the growing popular concern towards its disclosure.

Anonymization techniques are generally employed to hinder misuse of sensitive data. Most often, through a costly and data specific sanitization process, privacy is enhanced at the detriment of data utility. Moreover, these techniques are fallible, and never fully prevent reidentification. To address this problem, alternative methods for sharing sensitive data have been proposed, such as privacy-preserving distributed analysis. Although promising, these approaches come with their own limitations.

Consequently, access to OHD is restricted to professionals with the appropriate academic credentials and financial resources, preventing its use for the rest of the health data related occupations. For example, software developers often do not have access to the data that will be processed by the health informatics solutions they are developing.
1.2 Synthetic data

An alternative to traditional privacy-preserving methods is to produce fully synthetic data, with methods to build these models include knowledge-driven and data-driven modelling (Kim et al. 2017).

Knowledge-driven modelling involves a complex theory-based process to define a simulation process representing the causal relationships of a system. The Synthea (Walonoski et al. 2017) synthetic patient generator is one such simulation model, in which predefined states, transitions, and conditional logic produce patient trajectories. The parameters of the Synthea model are taken from aggregate population-level statistics of disease progression and medical knowledge. A knowledge-based approach such as Synthea depend on prior knowledge of the system, and most importantly how much we can understand about it (Kim et al. 2017). When modelling complex systems, simplifications and assumptions are inevitable, leading to inaccuracies. For example, relying on population-level statistics does not produce models capable of reproducing heterogeneous health outcomes (Chen et al. 2019).

In data-driven modelling techniques, a representation of the data is inferred from a sample distribution. In the ML field, generative models learn to represent an estimate of the multi-modal distribution, from which synthetic samples can be drawn (Goodfellow 2016). Generative Adversarial Networks (GAN) (Goodfellow et al. 2014) have recently emerged as a groundbreaking approach to efficiently learn generative models that produce realistic Synthetic Data (SD) using Neural Networks (NN). GAN algorithms have rapidly found a wide range of applications, such as data augmentation in medical imaging (Frid-Adar et al. 2018) and representation learning in drug discovery (Kadurin et al. 2017).

The potential impacts of GAN to healthcare and science are considerable, some of which have been realized in fields such as medical imaging (Yi, Walia, and Babyn 2019). However, the application of GAN to OHD seems to have been lagging (Xiao, Choi, and Sun 2018). Certain characteristics of OHD could serve to explain the relatively slow progress. Primarily, algorithms developed for images and text in other fields were easily repurposed for medical equivalents. However, OHD presents unique complexity in terms of multi-modality, heterogeneity and fragmentation (Xiao, Choi, and Sun 2018). In addition to this, evaluating the realism of synthetic OHD is intuitively complex, a problem that still burdens GAN in general. Nonetheless, interesting GAN solutions to the challenges posed by OHD have been developed (Esteban, Hyland, and Rätsch 2017; Che et al. 2017; Choi et al. 2017; Yahi et al. 2017).

2 Methods

Publications concerning OHD-GAN were identified through searches of Google Scholar and Web of Science with the following query.

(clinical ∨ health ∨ EHR ∨ electronic health record ∨ patient) ∧ (synthetic ∨ generative adversarial ∨ GAN)

We included studies reporting the development or the application of GAN algorithms to produce OHD. Broadly, we define the scope of OHD to be considered as low-dimensional data recorded for patient care. A more detailed summary of the included and excluded data types can be found in Fig. 1. The excluded data types have already been the subject of a review or would merit a review of their own. In each of the publications, we analyzed the following aspects:

- Type of healthcare data
- GAN algorithm, learning procedure and metrics
- Intended use of the model or SD
- Evaluation metrics
- Privacy considerations
- Interpretability of the model
### Table 1: Types of healthcare data included and excluded from the review.

| Type      | Examples                                                                 |
|-----------|---------------------------------------------------------------------------|
| **Included** |                                                                             |
| Observations | Demographic information, medical classification, family history,          |
| Timestamped observations | Diagnosis, treatment and procedure codes, prescription and dosage, laboratory test results, physiologic measurements and intake events |
| Encounters   | Visit dates, care provider, care site                                     |
| Derived      | Aggregated counts, calculated indicators                                  |
| **Excluded** |                                                                             |
| Omics        | Genome, transcriptome, proteome, immunome, metabolome, microbiome         |
| Imaging      | X-rays, computed tomography (CT), magnetic resonance imaging (MRI)        |
| Signal       | Electrocardiogram (ECG), electroencephalogram (EEG)                       |
| Unstructured | Narrative reports, textual                                                |

Figure 1: Types of healthcare data included and excluded from the review.

### 3 Results

#### 3.1 Summary

We found a total of 23 publications describing the development or adaption of GAN algorithms for OHD. Overall, the modelling goal is either to generate static representations of patient data, or to simulate the evolution of patient profiles in time.

- 13 publications concerned timestamped observations (Che et al. 2017; Xiao et al. 2017; Esteban, Hyland, and Rätsch 2017; Yahi et al. 2017; Xiao et al. 2018; McDermott et al. 2018; Severo et al. 2019; Baowaly et al. 2019; Wang, Zhang, and He 2019; Fisher, Smith, and Walsh 2019; Beaulieu-Jones et al. 2019; Cui et al. 2019; Walsh et al. 2020).
- 10 concerned static observation and/or aggregates (Choi et al. 2017; Yoon, Jordon, and Schaar 2018; Yoon, Jordon, and van der Schaar 2018; Camino, Hammerschmidt, and Radu State 2018; Jackson and Lussetti 2019; Baowaly et al. 2019; Yang et al. 2019; Bae et al. 2020; Zhang et al. 2020; Li et al. 2020). This includes medGAN, the first published OHD-GAN, developed for aggregate counts of medical codes (Choi et al. 2017).
- Among these, 5 publications evaluated the aspect of privacy, and its relation to utility (Choi et al. 2017; Beaulieu-Jones et al. 2019; Zhang et al. 2020; Bae et al. 2020; Severo et al. 2019).

Most efforts are focused on adapting the current methods to the characteristics and complexities of OHD, of which multimodality, heterogeneity, longitudinal irregularity, correlation complexity, missigness and noise are often cited. While these may pose a challenge for the development of suitable GAN methods, others properties make the prospect of success highly valuable. In fact, the most cited motivation to develop OHD-GAN is to cope with the often limited number of samples in medical datasets and to overcome the highly restricted access to OHD.

#### 3.2 Motivations for developing OHD-GAN

The authors cite a wide range of potential applications for generative models of OHD and the synthetic data they produce. While some of these goals are optimistic and have yet to be realized, they paint an encouraging picture for the value OHD-GAN. We list a few recurrent motivations here.

3
3.2.1 Data augmentation

Data augmentation is mentioned in nearly all publications. Most commonly, the trained generative model or synthetic data can improve generalization in predictive algorithms by providing additional information about the real data distribution (Wang, Zhang, and He 2019; Che et al. 2017; Yoon, Jordon, and Schaar 2018; Yoon, Jordon, and van der Schaar 2018). Similarly, GAN based on domain translation and semi-supervised training approaches could support prediction tasks in healthcare that lack data with accurate labels, labeled data for rare diseases or paired samples (Che et al. 2017; McDermott et al. 2018).

3.2.2 Enhancing privacy and increasing accessibility

SD is seen as the key to unlock the value of OHD hampered by privacy concerns. Preserving privacy can broadly be described as reducing the risk of reidentification attacks to an acceptable level. Many studies noted that highly restricted access to OHD is hindering machine learning, and more generally scientific progress (Beaulieu-Jones et al. 2019; Baowaly et al. 2019; Che et al. 2017; Esteban, Hyland, and Rätsch 2017; Fisher, Smith, and Walsh 2019). Due to its artificial nature, SD is proposed as a means to forgo with data use agreements, while potentially providing greater privacy guarantee and reducing the loss of utility (Beaulieu-Jones et al. 2019; Baowaly et al. 2019; Esteban, Hyland, and Rätsch 2017; Fisher, Smith, and Walsh 2019; Walsh et al. 2020). Preventing the disclosure fo commercially sensitive information is also cited (Severo et al. 2019). Overall, enabling access to greater variety, quality and quantity of OHD could have positive effects in a wide range of fields, such as software development, education, and training of medical professionals.

3.2.3 Enabling precision medicine

The ability to conduct simulations of disease progression for individual patients could have transformative impacts on healthcare. Generative models conditioned on the patient’s baseline state could help inform clinical decision making, such as predicting patient-specific response to drugs, a problem known as Individualized Treatment Effects (ITE) (Yahi et al. 2017; Walsh et al. 2020). Additionally, stochastic simulations of individual patient profiles could help quantify risk at an unprecedented level of granularity (Fisher, Smith, and Walsh 2019).

3.2.4 Patient and disease models

Realistic synthetic data implies a model that approximates the process that generated the real information (Esteban, Hyland, and Rätsch 2017). Achieving models of significant complexity would open up new simulation possibilities for developing predictive systems and methods. In clinical research, such models could help quantify cause and effect, simulate different study designs, provide control samples or more generally give us a better understanding of disease progression in relation to initial conditions (Fisher, Smith, and Walsh 2019; Yahi et al. 2017; Walsh et al. 2020).

3.3 OHD feature engineering

Few publications made use of OHD in its initial form. In most cases, feature engineering was used to adapt the data to the scientific question, or to make it intelligible for particular algorithms. The data is transformed into one of four modalities: time series, point-processes, ordered sequences or aggregates.

3.3.1 Regular time-series

OHD is sometimes generated in a somewhat regular fashion, at fixed time intervals. This is the case for automatic measurements performed by bedside monitors, for example. However, in most cases data are sporadic, with many missing observations across time and dimensions. Generally, transformations such as data imputation (Yahi et al. 2017) data imputation coupled with training (Fisher, Smith, and Walsh 2019; Walsh et al. 2020), binning into fixed-size time intervals (Esteban, Hyland, and Rätsch 2017; Che et al. 2017; McDermott et al. 2018) or a combination of binning and imputation (Wang, Zhang, and He 2019) are employed to preprocess the data. Binning is however undesirable, leading to some degree of loss of information (Lipton, Kale, and Wetzel 2016).
3.3.2 Point-processes
In some cases, it is of interest to model the time intervals between events, such as hospital visits for a particular patient. To obtain temporal point-processes, time-series of a single concept are transformed into the time deltas between consecutive occurrences (Xiao et al. 2017; Xiao et al. 2018).

3.3.3 Ordered sequences
For input into predictive models, patients trajectories are sometimes represented as variable-length, ordered vectors of medical events. By borrowing methods developed for sentences in Natural Language Processing, medical events in a patient’s journey are projected into a trained embedding (Che et al. 2017; Cui et al. 2019).

3.3.4 Aggregates
For the same purpose as ordered sequences, a patient’s medical history is often aggregated into a fixed-sized vector representations (Choi et al. 2017; Camino, Hammerschmidt, and Radu State 2018; Baowaly et al. 2019; Zhang et al. 2020). Each dimension is then the count or binary occurrence of a particular medical concept. Demographic variables, indicators and dates are also concatenated to these representations (Yoon, Jordon, and Schaar 2018; Yoon, Jordon, and van der Schaar 2018).

3.4 Modelling approaches
The modelling approaches, neural network algorithms and learning strategies employed to develop OHD-GAN cannot be succinctly generalized. In addition to being dependent on the data representation, these are chosen according to the generation task and the intended use of the model and synthetic data. Nonetheless, we present here a few of the main techniques. A list of the datasets reported in the publications is presented in Section 5.

3.4.1 Model architecture and learning
For time-series data, Recurrent Neural Networks (RNN) are most often employed (Xiao et al. 2017), including the Long Short-Term Memory (LSTM) subclass (Esteban, Hyland, and Rätsch 2017; Xiao et al. 2018; Wang, Zhang, and He 2019). A notable exception is presented by Fisher et al., followed by Walsh et al. who make use of a Restricted Boltzmann Machine (RBM), arguing that a number of their properties make them desirable for the purpose of simulating patient trajectories (Fisher, Smith, and Walsh 2019; Walsh et al. 2020). More specifically, Latent Variable Conditional RBM is applied to longitudinal time-series, conditioned on initial static features and patient state. The authors show that RBM allows for missing features to be imputed on the fly from the conditional distribution. Furthermore, they argue that the probabilistic nature of RBM captures the stochasticity of disease evolution.

To deal with the incompatibility of ordinal and categorical features with backpropagation, in the algorithm medGAN Choi et al. pre-train an Autoencoder (AE) to project the samples to, and from, a continuous latent space representation (Choi et al. 2017). The trained decoder portion of the AE then maps the latent-space representation of the generator back to discrete features. To improve on medGAN, Camino et al. trial multiple GAN methods for categorical features, such as Wasserstein GAN with gradient penalty (WGAN-GP) with a softmax output, Gumbel-Softmax GAN, and modify the decoder in ARAE and medGAN by adding a Gumbel-Softmax output (Camino, Hammerschmidt, and Radu State 2018). They find that the proposed alternative gives better results in general, but that the choice of a model will depend on data characteristics, of which sparsity seems to have the biggest influence. The WGAN-GP is also trialed by Baowaly et al. along with boundary-seeking GAN (BGAN), respectively termed medWGAN and medBGAN, in an effort to produce more realistic samples, with meaningful success, particularly with medBGAN (Baowaly et al. 2019). With EMR Wasserstein GAN (EMR-WGAN), Zhang et al. remove the AE and introduce two normalization techniques to stabilise training (Zhang et al. 2020).
An example of domain translation, Yoon et al. employ a cycle-consistent conditional \textbf{WGAN} to translate heterogeneous patient information from one hospital to another, correcting feature and distribution mismatch (Yoon, Jordon, and Schaar 2018). Encoder-decoder pairs, one for each hospital dataset, are trained to map records to and from a shared latent representation. In a similar approach, McDermott et al. demonstrate a semi-supervised approach with \textbf{Cycle WGAN} to leverage the large amounts of unpaired pre/post-treatment time-series in ICU data (McDermott et al. 2018).

For ordered sequences of medical codes, Che et al. use an encoder decoder \textbf{Convolutional Neural Network (CNN)} with \textbf{Variational Contrastive Divergence (VCD)} to produce neighbouring records of an input patient (Che et al. 2017). The \textbf{ehrGAN} generator is trained to decode a random vector mixed with the latent space representation of a particular patient. In a form of semi-supervised learning, the trained \textbf{ehrGAN} model is then incorporated into the loss function of a predictor where it can provide additional information about each input record by producing neighbors. One dimensional \textbf{CNN} are also used for time-series (Severo et al. 2019).

### 3.4.2 Conditional models

Auxiliary information can guide the generative process and generally improve performance on multimodal data. Conditional models also enable generating data of a desired class, conditioned on a demographic profile (Fisher, Smith, and Walsh 2019) or various other static patient features (Esteban, Hyland, and Ratsch 2017). This information is given as additional input to the generator and discriminator, or concatenated with dynamic features at each time-step for sequential data. Often, capturing the inter-dimensional correlations in time series will lead to increased performance. Wang et al. demonstrate an interesting sequential variation on this idea to generate time series of patient state and medication dosage. In their algorithm, patient state at the current timestep informs the concurrent medication dosage, which in turn affects the patient state in the upcoming timestep (Wang, Zhang, and He 2019). Zhang et al. show that conditional training with categorical labels for the samples improves utility for small samples, but not with larger samples (Zhang et al. 2020). In a particular case where the class imbalance ratio is itself the sensitive information, Severo et al. generate a synthetic dataset with equal number of samples for each class (Severo et al. 2019).

For the task of estimating \textbf{Individualized Treatment Effects (ITE)}, the problem is often that counterfactual outcomes are never observed or that treatment selection is highly biased (Yoon, Jordon, and van der Schaar 2018; McDermott et al. 2018; Walsh et al. 2020). To overcome this, Yoon et al. employ a pair of GAN, one for counterfactual imputation and another for ITE estimation, to capture the uncertainty in the unobserved counterfactual treatment outcomes and provide confidence intervals. Similarly, the concept of “digital twins” is introduced by Walsh et al. who generate placebo control twins of patients in the active trial arm, from their baseline state.

### 3.5 Validating the model and verifying the synthetic data

To assess the solution to a generative modelling problem, it is necessary to validate the model obtained, and subsequently to verify its output. GANs aim to approximate a data distribution \( P \), using a parameterized model distribution \( Q \) (Borji 2018). Thus, in evaluating the model, the goal is to validate that the learning process has led to a sufficient approximation. Approaches to achieve this are either quantitative or qualitative.

#### 3.5.1 Qualitative evaluation

The qualitative evaluation approaches are mainly preference judgement or discrimination tasks (Borji 2018). In these tasks, participants, such as medical professionals, are asked to rank the quality of real and synthetic samples, or to discriminate between each (Choi et al. 2017; Beaulieu-Jones et al. 2019). Similarly, visual inspection of statistics or projections of the data can help get a better understanding of model behaviour (Beaulieu-Jones et al. 2019; Che et al. 2017).
3.5.2 Quantitative evaluation by comparing distributions

Numerous metrics have been proposed to compare the distributions of real and synthetic data (Borji 2018). The **Maximum Mean Discrepancy (MMD)** metric checks the dissimilarity between two probability distributions using samples drawn independently from each. With this metric, Esteban et al. compare distributions of time series by defining a radial basis function (RBF) kernel (Esteban, Hyland, and Rätsch 2017). The **2-sample test (2-ST)** answers whether two samples originate from the same distribution through the use of a statistical test. For example, the kolmogorov-smirnov statistical test is used on aggregate count data by Baowaly et al. and on time series data by Fisher et al. (Fisher, Smith, and Walsh 2019; Baowaly et al. 2019). As an alternative, a classifier can be trained to discriminate real from synthetic units (Fisher, Smith, and Walsh 2019; Walsh et al. 2020).

In a similar approach, Xiao et al. compared the distributions based on a domain specific measure and Zhang et al. compared the distribution of the samples in latent space according to the mean of the variance (Xiao et al. 2017; Zhang et al. 2020).

3.5.3 Quantitative evaluation of utility

Another way to assess the ability of the model replicate the distribution of the real data is to compare the information content of both samples. In other words, a utility metric measures the value of the work that can be done with the synthetic data. Simplistic measures of utility include comparing real and synthetic dimensional distributions (Beaulieu-Jones et al. 2019; Choi et al. 2017; Baowaly et al. 2019) interdimensional correlations (Beaulieu-Jones et al. 2019), first-order proximity (Zhang et al. 2020) or time-lagged correlations and covariates (Fisher, Smith, and Walsh 2019; Walsh et al. 2020).

A more convincing measure of utility is to evaluate the performance of discriminative models trained on the learned features of the model or the synthetic data (Borji 2018), this is usually done in comparison with baselines. Examples include dimension-wise prediction (Choi et al. 2017; Camino, Hammerschmidt, and Radu State 2018; Baowaly et al. 2019), association rule mining (Baowaly et al. 2019), predictor accuracy (Bae et al. 2020) or testing the performance on real data of a predictor trained on synthetic data (Esteban, Hyland, and Rätsch 2017). Models trained to make forward predictions from past observations can simply be evaluated for accuracy (Xiao et al. 2018; McDermott et al. 2018).

To evaluate the robustness of the algorithm to data characteristic, synthetic training data with known properties is often employed to assess their effect on model performance (Yoon, Jordon, and van der Schaar 2018; Camino, Hammerschmidt, and Radu State 2018; Esteban, Hyland, and Rätsch 2017).

3.5.4 Utility gain

The representation learned by the model can compensate for lack of diversity in a real sample and lead to improved performance in predictive models. Examples include generating unobserved counterfactual outcomes (Yoon, Jordon, and van der Schaar 2018), or generating neighboring samples to help generalization in predictors (Che et al. 2017).

In another approach capturing the ability of generative models to produce statistically meaningful samples, (Fisher, Smith, and Walsh 2019) simulate individualized patient trajectories to quantify the influence of starting conditions on disease progression.

3.6 Privacy

To evaluate the risk of reidentification on synthetic data, Choi et al. and Zhang et al. conduct empirical analysis according to the definitions of Presence Disclosure, Attribute Disclosure (Choi et al. 2017) and Reproduction rate (Zhang et al. 2020). Both studies report low success rate for these types of attacks, while little effect from the sample size.
It seems intuitively possible that the artificial nature of synthetic data essentially prevents associations with real patients, however the question is never directly addressed in the publications. Rather, attempts are made to confer traditional privacy guarantees through differentially-private stochastic gradient descent (Beaulieu-Jones et al. 2019; Esteban, Hyland, and Rätsch 2017) or with a probabilistic scheme that ensures indistinguishability (Bae et al. 2020). Interestingly, Bae et al. also employ a trained discriminative model in the loss function of the generator to ensure utility is preserved. Interestingly, preventing overfitting and preserving privacy may not be conflicting goals (Wu et al. 2019; Mukherjee et al. 2019).

4 Discussion

4.1 Analysis of OHD-GAN

Overall, a number of recurrent factors influenced the outcome of OHD-GAN development and synthetic data generation tasks. The multimodality and heterogeneity of OHD can make training a model challenging, particularly more so when the learning task is poorly defined or the scope of the problem is too large. Moreover, the complexity of health-related data makes the assessment of synthetic data ambiguous, thus demanding stronger evidence to claims.

4.1.1 Scope and evaluation mismatch

A number of publications suffer from attempting to produce representations of patients that are aggregated, highly information dense or multidimensional while providing a simplistic assessment of their realism. These metrics are often high-level and generally applicable.

For medical experts, these representations are meaningless. As such, the results of qualitative evaluation often state that synthetic data is indistinguishable from the real data (Choi et al. 2017; Wang, Zhang, and He 2019). It is doubtful that they could in fact be.

Reproducing aggregate statistical properties is rather unconvincing evidence that a model has learned to reproduce the complexity of biological systems. For example, Choi et al. find that although the synthetic sample seemed statistically sound, it contained gross errors such as gender code mismatches and suggest the use of domain-specific heuristics (Choi et al. 2017). They may be contradictory, such as when the ranking condition frequencies are wrong, but the data augmentation leads to improved performance (Che et al. 2017). In addition, competing methods are often compared with different metrics or with contradictory results in different datasets (Camino, Hammerschmidt, and Radu State 2018; Choi et al. 2017; Baowaly et al. 2019; Zhang et al. 2020).

Utility-based metrics provide a more solid evaluation of data quality. However, these metrics only confirm the value of the data according to a narrow context. They are indicative of realism so far as a patient’s state is indicative of a medical outcome. Moreover, they do not provide any insight about the validity of the relations found in a patient record and its overall consistency.

4.1.2 Altered and misrepresented data

Overall, the approaches to OHD-GAN concern highly engineered representations of patient records. The complex relationships found in medical data often cannot be represented in the simplistic one-hot encodings used for aggregate counts and valuable information is lost when forcing time-series into a regular representation. Generally, the data is engineered to accommodate existing algorithms.

Deep architectures are based on concept multiple layers of non-linear functions are needed to learn complicated high-level abstractions (Bengio 2009). In fact, hierarchical representations of EHR that capture the sequential order of visits and co-occurrence of codes in a visit have led to improved predictor performance, and also allowed for meaningful interpretation of the model (Choi et al. 2016). Similarly, models of time-series based on a continuous
time representation, such as found in EHR data, have shown improved accuracy over discrete time-representations (Rubanova, Chen, and Duvenaud 2019; De Brouwer et al. 2019).

4.2 Recommendations

4.2.1 Basic models

Modelling efforts for OHD-GAN should be limited in scope to a single data type or modality. This is favourable for a number of evaluation related aspects. Firstly, it makes qualitative evaluation by visual inspection from experts possible and meaningful. Secondly, in relation to the first point, the behaviour of the model can be assest straightforwardly. This means the generative process can be influenced intentionally to observe the effect on the properties of the output. Finally, it allows for quantitative evaluation with domain specific metrics.

4.2.2 Data-driven architecture

The algorithm architecture of OHD-GAN should be engineered to match the process that generated the data, not the other way around. Data should be used and generated in the form it is first collected. In addition to preventing information loss, this ensures models will reflect the generative process that produced the real data. Such models are more likely to provide insights into the system they are taught to imitate and further our understanding about them. Furthermore, the learned statistical distribution is inevitably more meaningful and interpretable, facilitating applications in the healthcare domain and supporting results inferred from it.

4.3 Directions for futures research

4.3.1 Building a patient model

The ultimate goal for generative models of OHD must be an all encompassing patient model capable of generating full EHR records on demand. This is in fact the intention of the patient simulator Synthea. Once basic models of health data, as described in Section 4.2.1, have been developed and validated, these can be progressively combined in a modular fashion to obtain increasingly complex patient simulators. Furthermore, having designed the architecture of these basic models on the underlying data in a way that is comprehensible, as described in Section 4.2.2, will facilitate the composition of more complex models. Inputs, outputs and parts of these models can be conditionally attached to others such that the generative process occurs in a way that reflects the real generative process.

4.3.2 Evaluating complex patient models

Once more complex models are developed, the problem is again finding meaningful evaluation metrics of data realism. In their publication exploring the validation of the data produced by Synthea, Chen et al. provide an interesting idea to achieve this (Chen et al. 2019). Noting that the quality of care is the prime objective of a functional healthcare system, they suggest using Clinical quality measures (CQM) to evaluate the synthetic data. These measures “are evidence-based metrics to quantify the processes and outcomes of healthcare”, such as “the level of effectiveness, safety and timeliness of the services that a healthcare provider or organization offers.” (Chen et al. 2019). High-level indicators such as CQMs domain specific measures of quality, specifically designed for higher level or multimodal representations of healthcare data. At the individual level, Walsh et al. employ domain specific indicators of disease progression and worsening and compare agreement of the simulated patient trajectories with the factual timelines (Walsh et al. 2020).

In addition to CQM, we propose the use of the Care maps used by the Synthea model to simulate patient trajectories as evaluation metrics (Walonoski et al. 2017). Care maps are transition graphs developed from clinician input and Clinical Practice Guidelines, of which the transition probabilities are gathered from health incidence statistics. While these allow the Synthea algorithm to simulate patient profile with realistic structure, they also prevent it from reproducing real-world variability. Conversely, while GAN have the ability to reproduce
the quirks of real data, they also lack the constraints preventing nonsensical outputs. As such, Care maps provide an ideal metric to check if the synthetic data conforms to medical processes.

5 Datasets

**Coalition Against Major diseases Online data Repository for AD** *(Neville et al. 2015)*
- Longitudinal trajectories of 44 categorical, ordinal and continuous features.
- 1909 patients.
- 18 months, at 3 month intervals.

**New York Presbyterian/Columbia University Irving Medical Center** *(Hripcsak et al. 2015)*
- Observations such as prescriptions laboratory tests.
- 485,306 patients.
- Between 2000 and 2103.

**Philips eICU** *(Pollard et al. 2018)*
- Around 200,000 patients.
- From 208 care units across the US.
- Collected through the critical care telehealth program.

**Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-III v1.4)** *(Johnson et al. 2016)*
- 474 million patient-centric state observations in intensive care units (ICUs).
- 43,000 patients.
- Between 2001 and 2012.

**Vanderbilt University Medical Center Synthetic Derivative** *(“Synthetic Derivative — Department of Biomedical Informatics”)*
- De-identified warehouse of over 2.2 million EHR

**Wisconsin data from the UCI machine learning repository** *(Dua and Graff 2019)*
- Breast cancer, chronic kidney disease, heart disease, and prostate cancer datasets, with 30, 24, 13, and 8 features, respectively.

**Ward2ICU** *(Severo et al. 2019)*
- Electronic Health Records of patients from Hospital Mater Dei, a tertiary hospital, located in Belo Horizonte, Brazil
- Adult patients with an average age of 40, between the years of 2014 and 2019
- 25 vitals, of which 5 currently available, 20 samples per patient

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