Towards good validation metrics for generative models in offline model-based optimisation

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Abstract

In this work we propose a principled evaluation framework for model-based optimisation to measure how well a generative model can extrapolate. We achieve this by interpreting the training and validation splits as draws from their respective ‘truncated’ ground truth distributions, where examples in the validation set contain scores much larger than those in the training set. Model selection is performed on the validation set for some prescribed validation metric. A major research question however is in determining what validation metric correlates best with the expected value of generated candidates with respect to the ground truth oracle; work towards answering this question can translate to large economic gains since it is expensive to evaluate the ground truth oracle in the real world. We compare various validation metrics for generative adversarial networks using our framework. We also discuss limitations with our framework with respect to existing datasets and how progress can be made to mitigate them.

1 Introduction

Figure 1: We want to produce designs $x$ that score high according to the ground truth oracle $y = f(x)$, but this is usually prohibitively expensive to compute. We would like to search for validation metrics that correlate well with the ground truth, yet are cheap to compute, in order to facilitate faster and more economical generation of novel designs. In this illustration we imagine a generative model that is able to sample a complete specification of a chemical compound for drug design. However, scoring it involves synthesising the compound in a wet lab, which is expensive and laborious. Being able to reliably sample compounds on large but unseen $y$’s is the ultimate task in model-based optimisation.

In model-based optimisation (MBO), we wish to learn a model of some unknown objective function $f : \mathcal{X} \to \mathcal{Y}$ where $f$ is the ground truth ‘oracle’, $x \in \mathcal{X}$ is some characterisation of an input and $y \in \mathbb{R}^+$ is some score assigned to the input. The larger the score is, the more desirable $x$ is according to some desiderata. In practice, such a function (a real world process) is often prohibitively expensive to compute. For instance if $x \in \mathcal{X}$ is a specification of a protein that binds to a specific

¹Code: https://github.com/christopher-beckham/principled-mbo-eval

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receptor and we want to maximise the binding potential, then actually determining this would involve synthesising and testing it in a wet lab. In other cases, synthesising and testing a candidate may also be dangerous, for instance components for vehicles or aircraft. In MBO, we want to learn models that can extrapolate and generate inputs whose scores are beyond that of what we have seen in our dataset. Because the most reliable way of validating designs from such a model also happens to be the most expensive (i.e., evaluating the ground truth oracle), we are motivated to search for metrics that correlate well with this function because this can translate to substantial economic savings.

We consider MBO that is data-driven (leverages machine learning) and is offline, without assuming an active learning loop where the ground truth can be queried (say, to augment the training set). In offline data-driven MBO (referred to here as just MBO), a very simple (yet naïve) approach is to approximate the ground truth oracle \( f \) by training a classifier \( f_\theta(x) \) from some dataset \( D \), and exploiting it through gradient ascent to generate a high-scoring candidate:

\[
x^* = \arg \max_x f(x) \approx \arg \max_x f_\theta(x),
\]

\[
\implies x_{t+1} \leftarrow x_t + \alpha \nabla_x f_\theta(x), \text{ for } t = 1, \ldots, T, \quad x^* = x_T.
\]

The issue here however is that for most problems, this will produce an input that is either invalid or is poor yet receives a large score from the approximate oracle (overestimation). This is the case when the space of valid inputs lies on a low-dimensional manifold in a much higher dimension space (Kumar & Levine [2020]). We assume that invalid inputs will produce a score \( f(x) = 0 \), though it is also possible for completely valid inputs to have a zero score as well. One concern is that the learned oracle \( f_\theta \) may end up assigning non-zero scores to inputs that are invalid. The extent to which this is the case would depend on whether the learned oracle \( f_\theta \) was able to leverage negative examples during training; that is, invalid inputs whose scores are all equal to zero. While such a procedure could be used to regularise the learned oracle (Kumar et al. [2021]), this issue can be addressed directly with generative modelling, without the need for negative examples or mining for adversarial examples (Trabucco et al. [2021]).

Assume that we are able to learn a density \( p(x) \). Since it has finite mass, namely that \( \int_x p(x)dx = 1 \), by pushing up the likelihood of only valid inputs, we automatically push down the likelihood of everything else (invalid inputs). Because we are dealing with additional variable \( y \) which is the score of the input, we can instead consider the joint likelihood \( p(x, y) \). Through Bayes' rule, we can expand the joint likelihood out into \( p(x, y) = p(y|x)p(x) \). \( p(y|x) \) can be thought of as a function of the oracle \( f(x) \); if \( f(x) \) is stochastic (it usually is), then \( p(y|x) \) will capture the uncertainty over a range of values of \( y \). This however assumes a particular \( x \) was observed, regardless of its validity. Conversely, the multiplication by \( p(x) \) corrects for this based on how likely it is one observes \( x \), which is why it is important to be able to measure the joint likelihood of a sample (Brookes et al. [2019]). Therefore, in this work we consider generative models of the form \( p(x, y) \).

In this work, we propose a principled evaluation framework with a particular focus on model selection, i.e. how do we select for the model that best extrapolates? To do this, one must define a validation metric, i.e., some metric that is a function of the generative model and a held-out validation set whose examples comprise scores much larger than that of the training set. We would like to find a validation metric which is highly correlated with the ground truth oracle, since it is expensive to compute in practice. To approach this, we present our framework in Section 2, which in turn comprises the following parts: training (2.1), model selection (2.2), and generation (2.3). Lastly, in Section 4.1 we discuss some limitations of our framework with respect to existing datasets, and propose some alternatives.

2 Proposed method

Let us assume we have access to \( p(x) \) (or its joint equivalent). Indeed, \( p(x) \) is measuring a likelihood, and it is likely the case that the best-scoring input lies in a low density region of the data distribution – after all, if commonly occurring inputs were high scoring then MBO would not be needed at all. We do not wish to use likelihood to select for likely candidates: instead, we want to use it as a means to measure how well a generative model can extrapolate. The intuition is that a generative model that assigns high likelihood to unseen examples whose \( y \)'s are larger than what it has seen in training has effectively learned how to extrapolate. This is because the probability of the model sampling such a high-scoring candidate is directly proportional to the likelihood (density) that it has
We assume a conditional generative model \( p_0(x|y) \) that has been trained on \( D_{\text{train}} \). If we denote the distribution over \( y \)’s in the training set as \( p_{0,\gamma}(y) \) then through Bayes’ rule we can write the joint likelihood as: \( p_0(x, y) = p_0(x|y)p_{0,\gamma}(y) \). This equation essentially says: to generate a sample \((x, y)\) from this joint distribution, we first sample \( y \sim p_{0,\gamma}(y) \), then we sample \( x \sim p_0(x|y) \). Now if we assume that the generative model has some ability to extrapolate, then we should be able to replace the prior in this equation with \( p_{\gamma}(y) \), which is the prior distribution over \( y \) for the validation set. We define this as the extrapolated model (Figure 2a extrapolate caption):

\[
p_{0,\gamma}(x, y) = p_0(x|y)p_{\gamma}(y).
\] (2)

2.2 Model selection

Suppose we have a generative model that allows us access to the evaluation of either a density \( p_0(x, y) \) or a close approximation of it. This is possible with all commonly used generative models in deep learning, with the exception of generative adversarial networks (GANs) (Goodfellow et al., 2014). To ensure that our model can generate candidates with scores higher than that observed in the training set (i.e. extrapolate), we need to employ a reliable model selection criteria. Suppose we trained several generative models \( \Theta = \{\theta_j\}_{j=1}^M \) and wanted to select which one was the best, one simple strategy is to select for the model whose forward KL divergence with \( \gamma \)-trimmed ground truth \( p_{\gamma}(x, y) \) is the smallest (full proof is in Section A.2):

\[
\theta^* = \arg \min_{\theta \in \Theta} \text{KL} \left[ p_{\gamma}(x, y) \parallel p_{0,\gamma}(x, y) \right] \approx \arg \max_{\theta \in \Theta} \frac{1}{N} \sum_{i=1}^{N} \log p_{\theta,\gamma}(x_i, y_i),
\] (3)
where samples from the validation set can be seen as our finite number of samples coming from the truncated ground truth \( p_\gamma(x, y) \) (Figure 2, model selection panel). This is the most straightforward way to evaluate extrapolation since requires only samples from the ground truth, not the ground truth itself.

With the exception of normalising flows, the density evaluated by \( p_{\theta, \gamma} \) in Equation 3 will need to be approximated. For conditional VAEs (Kingma & Welling, 2013) and diffusion models (Ho et al., 2020), we would be dealing with the conditional ELBO, i.e. \( \log p_{\theta, \gamma}(x|y) \geq \mathcal{L}_{\text{C-ELBO}}(x, y) \). The joint ELBO can simply be derived by adding the prior \( \log p_\gamma(y) \):

\[
\log p_{\theta, \gamma}(x, y) = \log p_{\theta, \gamma}(x|y) + \log p_\gamma(y) \geq \mathcal{L}_{\text{C-ELBO}}(x, y) + \log p_\gamma(y),
\]

(4)

The forward KL (or its approximation) is trivial to evaluate for these classes of models since it is equivalent to the training loss, but instead it is evaluated with respect to a validation set and not a training set. It is also theoretically convenient to use the same loss to measure both training and validation performance. However, it is unclear whether forward KL is the ‘best’ validation metric to use for the aforementioned generative models. We will define what it means for a metric to be ‘best’ in Section 2.3.

Lastly, we mentioned that GANs do not allow for likelihood evaluation. While this is unfortunate, evaluation metrics for GANs would allow for one to compare across different classes of generative model, since there is no assumption that a likelihood can be computed. Furthermore, they may probe interesting aspects of generative models that are not succinctly captured with forward KL (e.g. measuring precision and recall; Kynkäänniemi et al., 2019). While we defer the reader to Borji (2022) for a comprehensive list, many of these metrics are based on computing distances between distributions: they only require a finite number of samples from both the ground truth and generative model, as well as an external neural network which is either used to classify inputs (Lopez-Paz & Oquab, 2016) or extract semantically meaningful features (Heusel et al., 2017). For the remainder of this paper we will call such metrics likelihood-free. A fundamental question we would like to answer is: what validation metrics correlate the best with the ground truth?

### 2.3 Generation time

To measure which validation metrics correlate the most with the ground truth, we first need to devise a strategy for generating the best possible samples from our extrapolated model. One such strategy is to generate a large set \( \mathcal{S} \) of samples with \( p_{\theta, \gamma}(x|y = y_{\text{max}}) \), where \( y_{\text{max}} \) is the largest value of \( y \) observed in the entire dataset. Another is to simply sample from \( p_\gamma(y) \), which is what we choose. From \( \mathcal{S} \), we can either compute the expected value with respect to all samples \( \mathbb{E}_{x \sim \mathcal{S}}[f(x)] \) or the top \( n\% \) scoring ones instead (Trabucco et al., 2022). For each trained model \( \{ \theta_j \in \Theta \}_{j=1}^M \) (i.e. each corresponding to a configuration of hyperparameters), compute the expected value of generated candidates with respect to the ground truth oracle \( \mathbb{E}_{x \sim p_{\theta, \gamma}(x, y)}[f(x)] \). We can then plot the validation metric against this expected value and compute some goodness of fit, i.e. \( R^2 \) or Pearson correlation.

For additional discussion on generation strategies, please see Section A.4.

### 3 Related work

**Design Bench** Design Bench is an evaluation framework by Trabucco et al. (2022) that facilitates the training and evaluation of MBO algorithms. Design Bench, as of time of writing, provides four discrete and four continuous datasets. These datasets can be further categorised based on two attributes: whether a ground truth oracle exists or not, and whether it is possible for there to exist out of distribution candidates. One of these datasets for instance is TFBind8, a dataset consisting of length-8 DNA strings that are transcription factors for binding. Since the dataset consists of all possible strings, it is fully realised and the ground truth oracle can simply be a look-up table. However, since any length-8 DNA string is valid (any combination of nucleotides is possible), there is no such thing as an invalid candidate. While there are certainly domains where this is the case, we wish to consider more difficult problem domains where it is possible for invalid candidates to exist. This also allows us to justify the use of generative models for MBO, which naturally learn what

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2 Minimising forward KL during training is also known as maximum likelihood estimation, and this is the case for all commonly-used generative models, with the exception of GANs.
is out-of-distribution by learning what is in-distribution. Currently, the only datasets that support both OOD examples and admit a ground truth oracle are ones based on RL environments, which may require external dependencies such as Mujoco. One such environment for instance is Hopper, which involves optimising the weights of a neural network controller to maximise a reward function.

In terms of evaluation, Design Bench does not prescribe a validation set (only a training set and test oracle), which we argue is important in order to address the core question of our work, which is finding validation metrics that correlate well with the ground truth oracle. While a validation set could be easily derived from \( y \)-truncating the training set, this would complicate evaluation since the training, validation and test splits would all come from separate truncated distributions. Conversely, our evaluation is set up so that the validation and test sets are from the same \( \gamma \)-truncated distribution.

**Conditioning by adaptive sampling** CbAS (Brookes et al., 2019), like our proposed method, approaches MBO from a generative modelling perspective with the aim of avoiding the generation of invalid inputs. Given some pre-trained ‘prior’ on the input data \( p_0(x) \), the authors propose the derivation of the conditional generative model \( p_\theta(x|y) \) via Bayes’ rule:

\[
 p_\theta(x|y) = \frac{p(y|x)p_0(x)}{p(y)} = \frac{p(y|x)p_0(x)}{\int_x p(y|x)p_0(x)dx}, \tag{5}
\]

where \( p(y|x) \) denotes the oracle in probabilistic form, and is not required to be differentiable. More generally, the authors use \( S \) to denote some target range of \( y \)'s, i.e. \( p(S|x) = \int_y p(y|x)1_{y \in S}dy \).

\[
 p_\theta(x|S) = \frac{p(S|x)p_0(x)}{p_\theta(S)} = \frac{p(S|x)p_0(x)}{\int_x p(S|x)p_0(x)dx}, \tag{6}
\]

Due to the intractability of the denominator term, the authors propose the use of variational inference to learn a sampling network \( q_\zeta(x) \) that is as close as possible to \( p_\theta(x|S) \) as measured by the forward KL divergence. Here, let us use \( p_\theta(S|x) \) in place of \( p(S|x) \)\(^1\)

\[
 \zeta^* = \arg \min_{\phi} \text{KL} \left[ p_\theta(x|S) \parallel q_\zeta(x) \right] = \arg \min_{\zeta} \text{KL} \left[ p_\theta(x|S)p_0(x) \parallel p_\theta(S)p_0(x) \right] = \arg \min_{\zeta} \mathbb{E}_{x \sim p_0(x)} \left[ p_\theta(S|x) \log q_\zeta(x) \right]. \tag{7}
\]

In practice, importance sampling must be used since \( p_\theta(S|x) \) will be vanishingly small. In terms of evaluation, \( \gamma \) is set so that samples from \( p_\theta,S(x,y) \) constitute the bottom \( 20^{\%} \) percentile of values. Here, the oracle \( p_\theta(S|x) \) is only trained on \( D_{\text{train}} \). Furthermore, during the variational inference procedure there is no evaluation of Equation (7) on a held-out validation set, which means one can risk overfitting the search model \( q_\zeta \) to the oracle. Because the expected value in Equation (7) is over samples from the initial model and not the validation set, the simplest way to incorporate some notion of validation to use \( p(S|x) \leftarrow p_\phi(S|x) \) for validation. We can write this out as follows:

\[
 M_{\text{CbAS}} = \mathbb{E}_{x \sim p_0(x)} \left[ p_\phi(S|x) \log q_\zeta(x) \right] \tag{8}
\]

The main difference between CbAS and our work is that the former requires an additional fine-tuning step to convert the base model into the extrapolated model, whereas our extrapolated model is simply induced by switching the prior. Because the extrapolated model optimisation in CbAS depends on an approximate training oracle \( p_\theta(S|x) \) (Equation (7)), some regularisation may be needed to ensure that overfitting does not occur. Lastly, the extrapolated model does not condition on \( y \), though one could simply define one at inference time via \( q_\zeta(x)p_\phi(y|x) \).

\(^{1}\)In their paper the symbol \( \phi \) is used, but here we use \( \zeta \) since the former is used to denote the validation oracle.
We consider \( M \) where \( M \) way to compute likelihoods for these class of models. The search for good metrics is still an active generation time (in principle) to provide negative examples because of the constraint that \( \text{COMs} \), which regularise the trained oracle by generating adversarial examples via gradient ascent (MINs). The name is in reference to the fact that one can learn the inverse of the oracle \( f_\theta^{-1} : Y \to X \), which is a generative model. It is not clear what model selection criteria was used during training, though at generation time the authors propose the following equation to search for high-scoring candidates

\[
y^* , z^* = \arg \max_{y,z} \left[ y + \epsilon_1 \log p_\theta(y | G_\theta(z, y)) + \epsilon_2 \log p(z) \right]_{\text{agreement}}
\]

where \( G_\theta(z, y) \) denotes the GAN but written explicitly (rather than using sampling notation \( x \sim p_\theta(x | y) \)), and \( p(z) \) is the prior distribution over \( z \). The agreement term is measuring the log likelihood of \( G_\theta(z, y) \) being classified as \( y \) under the training oracle \( f_\theta \). Note that if we assume \( p_\theta(y | x) = \mathcal{N}(y; f_\theta(x), \sigma^2) \), then maximising the agreement in Equation 9 is equivalent to minimising the mean squared error (MSE) between the conditioning \( y \) and its predicted \( y \) with respect to \( f_\theta \):

\[
- \log p_\theta(y | G_\theta(z, y)) \propto \| f_\theta(G_\theta(z, y) - y \|^2 .
\]

Similar to CbAS (Paragraph 3), because there is no mention of a validation set, we need to write out agreement (Equation 10) in terms of a validation oracle \( f_{\text{val}} \). This indirectly leverages the validation set because the validation oracle is trained on the validation set (see Figure 2a). Furthermore, the agreement should be defined as an expected value over the \( \gamma \)-truncated distribution. Therefore, we formally define agreement as a validation metric as the following:

\[
\mathcal{M}_{ADF} = \mathbb{E}_{y \sim p_{\text{val}}(y)} \| f_{\text{val}}(G_\theta(z, y) - y \|^2
\]

**Conservative objective models** [Trabucco et al. (2021)] propose conservative objective models (COMs), which regularise the trained oracle by generating adversarial examples via gradient ascent and penalising their predictions. The authors show theoretically that their technique is able to lower bound the actual ground truth oracle prediction on out-of-distribution inputs. Computationally, the method is appealing since it does not require the training of a generative model. While this method improves oracle prediction by penalising overestimation, it does not necessarily address the issue of the oracle scoring an ‘impossible’ candidate. However, [Kumar et al. (2021)] proposes an additional loss to the COMs objective, where the scores predicted by the oracle on an ‘invalid set’ (a set of invalid candidates) is forced to be zero. We note that in the case of density estimation there is no need (in principle) to provide negative examples because of the constraint of the constraint that \( f_{x,y} p(x, y) dx dy = 1 \).

### 3.1 Likelihood-free metrics

Likelihood-free metrics are used exclusively in the GAN literature because there is no straightforward way to compute likelihoods for these class of models. The search for good metrics is still an active topic of research (Borji, 2022). Common likelihood-free metrics involve measuring some distance between distributions in some predefined feature space. For instance, for GANs trained on natural image datasets the Fréchet Inception Distance (FID) (Heusel et al., 2017) is used to fit Gaussians to both distributions with respect to the feature space of an InceptionNet classifier trained on ImageNet. Since the acronym ‘FID’ specifically refers to a particular ImageNet-based feature extractor, we will simply say ‘FD’, which generalises to any feature extractor \( f_h : \mathcal{X} \to \mathcal{H} \) (Dowson & Landau, 1982):

\[
\mathcal{M}_{\text{FD}}(X, \hat{X}, f_h) = |\mu(f_h(X)) - \mu(f_h(\hat{X}))| + \text{Tr}(\Sigma(f_h(X)) + \Sigma(f_h(\hat{X})) - 2\Sigma(f_h(X))\Sigma(f_h(\hat{X}))^\frac{1}{2})
\]

where \( \mathcal{M}_{\text{FD}} \in \mathbb{R}^+ \) and lower FD is better. Here, \( X \in \mathbb{R}^{N \times p} \) denotes \( N \) samples coming from a reference distribution (i.e. ground truth) and \( \hat{X} \) are samples coming from the generative model. Since we also use neural networks to train the validation oracle \( f_{\text{val}} \), the feature extractor \( f_h \) can simply be the hidden representation extracted from a predefined layer for that network.

We consider \( \mathcal{M}_{\text{FD}} \) since it is one of the most commonly used metrics for generative models, and many implementations are readily available. However, some caveats are that it requires a very large sample size, and that it may have a stronger bias towards recall (mode coverage) than precision (sample quality) [Kynkänneniemi et al. (2019)].

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This differs slightly from the formulation in their paper, since we express the optimisation with soft constraints, rather than hard constraints.
4 Experiments and Discussion

In this section we work towards answering the following question: which likelihood-free metrics correlate the best with the ground truth oracle? In particular, we perform our analysis generative adversarial networks and compare two validation metrics: Agreement ($M_{Ag}$, Equation 11) and FID ($M_{FD}$, Equation 12).

Dataset Our codebase is built on top of the Design-Bench (Trabucco et al., 2022) framework. The dataset we consider is TFBind8 (Barrera et al., 2016), where candidates are length-8 DNA strings whose score $y \in [0, 1]$ measures the binding activity with a particular human transcription factor. This dataset is convenient because the ground truth oracle $f$ exists, and this is because the dataset has full support; in other words, each possible length-8 DNA string ($4^8 = 65536$ many strings) is contained in the dataset, so the oracle is simply a lookup table. However, this means there is no notion of there being an ‘invalid’ candidate, because (in the real world) any arbitrary permutation of nucleotides is possible. To address this, we consider a modified version of TFBind8 where, based on some pre-defined pattern, we artificially select certain DNA strings to be invalid. We consider a simple strategy where if the DNA string contains more than 3 A’s (adenine), we flag it as invalid. This means that they are removed from dataset, and the resulting validation oracle $f(x)$ is not trained on them. The resulting test oracle is modified so that it will score $f(x) = 0$ for any of these invalid candidates.

Oracle pre-training The oracle $f_o$ is an MLP comprising of one hidden layer. This was trained on both the training and validation sets (see Figure 2), minus a small internal validation set used to tune the number of hidden layers. No invalid examples (Paragraph 4) were used to train this oracle.

Training We train a conditional GAN which comprises two networks: the generator $G_\theta(z, y)$ and discriminator $D(x, y)$, where $z \sim p(z) = \mathcal{N}(0, I)$ is the latent code and $y$ is the score. To condition on $y$ in the generator we use projection layers that map $y$ to a high dimensional feature vector that in turn is concatenated with each hidden layer. Since $x \in \{0, 1\}^{3 \times 8}$ is discrete (i.e. represented as eight one-hot vectors of length 4), the output of the generator must also be discrete. We address this using the Gumbel-Softmax estimator (Jang et al., 2016). For the discriminator we use the projection formulation from Miyato & Koyama (2018). The objective function we use is the non-saturating logistic loss originally proposed in Goodfellow et al. (2014):

$$\min_D \mathcal{L}_D = -\mathbb{E}_{x, y \sim D_{data}} \log D(x, y) - \mathbb{E}_{z \sim p(z), y \sim D_{data}} \log [1 - D(G_\theta(z, y), y)]$$  \quad (13)

$$\min_{G_\theta} \mathcal{L}_G = -\mathbb{E}_{z \sim p(z), y \sim D_{data}} \log [D(G_\theta(z, y), y)]$$  \quad (14)

We consider the following hyperparameters: the number of hidden units per hidden layer (for a fixed number of two hidden layers) as well as the Gumbel-Softmax temperature $\tau$. For Gumbel-Softmax sampling we use the straight-through estimator. For each model, over the course of training we train two versions, each one using either $M_{FD}$ or $M_{Ag}$ as the early stopping metric (i.e. retain the checkpoint corresponding to the smallest value of that metric as seen on the validation set).

Generation For inference time generation we consider a simple procedure: sample a large number of candidates with a specific augmented model $p_{0, a}(x, y) = p_0(x|y)p_\alpha(y)$ where $p_\alpha = \text{Uniform}(\gamma, 1)$, score each candidate with the validation oracle $f_o$, find the top $M = 10$ scoring candidates and compute their average score with respect to the test oracle $f$.

Results We find that $M_{Ag}$ and $M_{FD}$ have a significant negative correlation (Figure 3) of $R = -0.45$. In Figures 4a and 4b we plot both likelihood-free metrics against the mean score of their best-generated candidates (as described in Paragraph 4) and find that $M_{FD}$ has a stronger correlation with producing high-scoring candidates; since its Pearson correlation is negative ($R = -0.5706$), as

![Figure 3: $M_{FD}$ vs $M_{Ag}$](image-url)

R = -0.4789
Figure 4: (4a) The smallest $M_{FD}$ achieved for each model plotted against the mean score of the top $M = 10$ candidates as per the inference procedure described in Paragraph 4 same as 4a but for $M_{Ag}$. For both metrics $M_{Ag}$ and $M_{FD}$ smaller is better. $M_{FD}$ is negatively and significantly correlated with the mean score of both oracles ($R = -0.57$), whereas this is not the case for $M_{Ag}$ ($R = 0.31$). This indicates that $M_{FD}$ is a better predictor of the oracle score.

Figure 5: To underscore some of the issues with the agreement metric, here we show the conditioning $y$ versus the predictions made by the validation and test oracle, for $\{(x \sim p_{\theta}(x|y))\}_{j=1}^\mathcal{K}$, where $K = 32$. The blue region denotes $y$’s that were only seen by the GAN during training ($y$’s from $p_{\theta}(y)$), and orange/green region denotes those from the extrapolated regime $p_\phi(y)$. Orange denotes test oracle predictions ($f(x)$) and green denotes validation oracle predictions ($f_\phi(x)$). We can see that the best models corresponding to $M_{FD}$ exhibit monotonically increasing predictions with respect to the conditioning $y$, and this is not the case for $M_{Ag}$, whose predictions are also erratic even in the training region of $y$. Furthermore, $M_{FD}$-based models are able to achieve test oracle scores very close to the maximum possible attainable value ($y = 1.0$).

$M_{FD}$ gets better (smaller), the mean top-10 score increases. For $M_{Ag}$ this is not the case – it is only moderately correlated with the mean top-10 score in the reverse direction ($R = 0.3061$).

In Figure 5 we plot the conditioning $y \in \text{linspace}(0, 1)$ against the validation/test oracle predictions for candidates conditionally generated with that $y$. We call these ‘agreement plots’ since the sum of squared residuals for each point would constitute the agreement (with a perfect agreement of zero corresponding to a diagonal dotted line on each graph). In Figure 5a we demonstrate this amongst the best three models with respect to $M_{FD}$, and in Figure 5b we do the same with respect to $M_{Ag}$. The shaded regions denote ±1 standard deviation from the mean, and the marker symbols denote the max/worst score for each $y$. We can see that the predictions shown in Figure 5a are more or less

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5 Also called “paired plots” in Brookes et al. 2019.
monotonically increasing as a function of \( y \), whereas the models with the best agreement exhibit very erratic or undesirable behaviour (Figure 5b).

Even though the mean prediction for any particular \( y > \gamma \) lies closer to the dotted line for the experiments ranked by \( \mathcal{M}_{\text{Agg}} \) (Figure 5b), the maximum scores level out at a certain score (e.g., a little below 0.8 for the left-most model in Figure 5b) whereas for \( \mathcal{M}_{\text{FD}} \) the maximum predictions lie close to 1.0 with respect to either oracle.

### 4.1 Limitations and Future Work

One dilemma we are faced with in this proposed evaluation setup is the requirement of the ground truth oracle. As mentioned in the introduction, the ground truth oracle is expensive to compute and offline MBO assumes we do not have access to it during training and validation. However, the particular questions we would like to answer require it so that we can determine with confidence which validation metrics correlate the best with the ground truth. Unfortunately, there appear to be very few datasets that contain invalid candidates and also admit access to the ground truth. This leaves us with two options: modify ground-truth-containing datasets to support invalid candidates (like we did with TFBind); design challenging simulation-based datasets that reflect real world problems; or simply allow for the ground truth oracle to be replaced with an approximate 'test' oracle \( f_\psi \). The latter option however is risky because we are now evaluating one approximation \((p_\theta(x|y))\) with another \((f_\psi(x))\). One compromise could be to consider a relaxed scenario where we only assume that ground truth verification is possible. For instance, consider a simple binary function \( v(x) : X \rightarrow \{0, 1\} \) where ‘1’ denotes ‘valid’ and ‘0’ denotes ‘invalid’. This verifier could be ‘folded’ into the approximate oracle to produce a new oracle \( f_\psi \cdot v \), which in turn would assign any invalid candidates a score of zero and therefore make it more reliable, even if it is still prone to over-scoring bad candidates that are invalid. One such real-world example is chemistry retrosynthesis software, which can be used to determine whether a compound is plausible to synthesise (Liu et al., 2020). This compromise however would require a slight change to the evaluation pipeline to accommodate a test set (see Figure S6b).

### 5 Conclusion

In this work we propose a principled evaluation framework to measure how well generative model-based MBO models extrapolate. We would like to leverage this framework to determine which validation metrics correlate the best with the ground truth, the latter of which is expensive to compute in practice. The proposed framework is practical yet simple in the sense that extrapolating a generative model simply amounts to changing the prior distribution over the scores. Furthermore, we discussed how existing generative model-based works can easily be ported to our framework. However, determining what validation metric correlates most with extrapolative ability requires the ground truth oracle if we want to be absolutely certain. This is because approximate test oracles are vulnerable to over-scoring bad candidates or even worse, scoring candidates that are invalid (i.e., have zero density under the ground truth distribution). As a proof of concept, we compared two validation metrics with respect to a modified version of TFBind, which contains a ground truth oracle but is modified to allow for invalid candidates.

Lastly, since finding good validation metrics requires the ground truth oracle and limits what datasets can be used, we propose a compromise to our evaluation framework which only assumes that ground truth verification is possible. This would guard the approximate test oracle against scoring invalid candidates. This will be considered in a future iteration of this preprint.

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A Appendix

A.1 Acknowledgements

Figure 1 uses clipart from here. The protein render was lifted from here.

A.2 Full proof

\[ \theta^{*} = \arg \min_{\theta \in \Theta} \text{KL} \left[ p_{\gamma}(x, y) \parallel p_{\theta, \gamma}(x, y) \right] \]

\[ = \arg \min_{\theta \in \Theta} \mathbb{E}_{x, y \sim p_{\gamma}(x, y)} \log p_{\gamma}(x, y) - \mathbb{E}_{x, y \sim p(x)} \log p_{\theta, \gamma}(x, y) \]

\[ = \arg \max_{\theta \in \Theta} -\mathbb{E}_{x, y \sim p_{\gamma}(x, y)} \log p_{\gamma}(x, y) + \mathbb{E}_{x, y \sim p(x)} \log p_{\theta, \gamma}(x, y) \]

\[ = \arg \max_{\theta \in \Theta} \mathbb{H}[p_{\gamma}] + \mathbb{E}_{x, y \sim p_{\gamma}(x, y)} \log p_{\theta, \gamma}(x, y) \]

\[ \approx \arg \max_{\theta \in \Theta} \frac{1}{N} \sum_{i=1}^{N} \log p_{\theta, \gamma}(x_i, y_i), \quad \{x_i, y_i\}_{i=1}^{N} = D_{\text{valid}}. \quad (15) \]

A.3 Relaxed evaluation procedure

See Figure S6

Figure S6: Under our relaxed evaluation scenario, we no longer assume access to the ground truth oracle \( f \), but we do assume access to a ground truth ‘verifier’ \( v(x) \) which is able to classify whether a candidate is valid or not. This can be used to induce a more reliable test oracle \( f \approx f_{\psi} \cdot v \). The approximate oracle \( f_{\psi} \) is trained on an additional split \( D_{\text{test}} \), which comes from the same truncated distribution as \( D_{\text{valid}} \). The use of a test set here is necessary since we do not wish to perform model selection on the exact same dataset that was used to train the approximate test oracle, or else we may risk reporting a biased estimate of the true oracle performance \( f \). In other words, only \( D_{\text{valid}} \) is used for model selection, while \( D_{\text{test}} \) is used to train \( f_{\psi} \). (Note that in practice, one should use as much data for the test oracle, so we should train it on \( D_{\text{train}}, D_{\text{valid}}, \) and \( D_{\text{test}} \). This is not shown in the figure for the sake of readability.)

A.4 Model deployment

Once the best model has been found via an appropriate validation metric, one can train the same type of model on the full dataset \( D \) using the same hyperparameters as before. Ultimately, we would like to be able to generate candidates whose \( y \)'s exceed that of the entire dataset, and at the same time plausible according to our generative model. To control how much we trade-off high likelihood
versus high scoring candidates, we can consider the exponentially tilted density (Asmussen & Glynn, 2007; O’Donoghue et al., 2020):

\[ p_{\theta,\gamma}(x, y) \exp(\eta^{-1} y - \kappa(\eta)), \]  

(16)

where \( \kappa(\eta) \) is a normalisation constant, and smaller \( \eta \) puts larger emphasis on sampling from regions where \( y \) is large. Taking the log of Equation 16 we arrive at:

\[ x^*, y^* = \arg \max_{x, y} \log p_{\theta,\gamma}(x, y) + \frac{1}{\eta} y, \]  

(17)

In practice, it would not be clear what the best \( \eta \) should be, but a reasonable strategy is to consider a range of \( \eta \)'s, where larger values encode a higher tolerance for ‘risk’ since these values favour higher scoring candidates at the cost of likelihood. Note that for VAEs and diffusion models, \( \log p_{\theta}(x, y) \) will need to be approximated with the ELBO. For score-based models (Song et al., 2020) only \( \nabla_{x, y} \log p(x, y) \) is accessible, but sampling is still straightforward since that is just the gradient.

A.5 Related work

A.5.1 CbAS

Figure S7: The training and evaluation of CbAS Brookes et al. (2019) in the context of our evaluation framework. The extrapolation equation is described in Equation 7 and involves variational inference to fine-tune \( p_{\theta}(x) \) into a search model \( q_{\zeta}(x) \). For model selection, the validation metric is Equation 8, which is just Equation 7 but using the validation oracle \( f_{\phi}(x) \).