AUGMENTING NEURAL NETWORKS WITH PRIORS ON FUNCTION VALUES

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ABSTRACT
The need for function estimation in label-limited settings is common in the natural sciences. At the same time, prior knowledge of function values is often available in these domains. For example, data-free biophysics-based models can be informative on protein properties, while quantum-based computations can be informative on small molecule properties. How can we coherently leverage such prior knowledge to help improve a neural network model that is quite accurate in some regions of input space—typically near the training data—but wildly wrong in other regions? Bayesian neural networks (BNN) enable the user to specify prior information only on the neural network weights, not directly on the function values. Moreover, there is in general no clear mapping between these. Herein, we tackle this problem by developing an approach to augment BNNs with prior information on the function values themselves. Our probabilistic approach yields predictions that rely more heavily on the prior information when the epistemic uncertainty is large, and more heavily on the neural network when the epistemic uncertainty is small.

1 Incorporating domain knowledge into neural network models

Effective application of supervised machine learning—especially in label-limited settings—relies on the ability to incorporate domain knowledge. Computer vision, for example, has greatly benefited from incorporating translation equivariance through the convolution operator, in the form of Convolutional Neural Networks. Originally tackled by data augmentation strategies, increasingly, broader and broader classes of equivariances, such as rotational equivariance suitable for molecules, are instead now formally incorporated as constraints into neural networks. Similarly, architectural inductive biases such as attention, residual connections, dropout, and so forth, have greatly benefited a wide range of application areas. However, little attention has been paid to incorporating prior knowledge directly about the predicted function values themselves into neural network function estimators, the topic addressed herein.

In various scientific domains, spanning biology, chemistry, material science and beyond, function estimation has traditionally been performed by data-free physics-based modeling, such as biophysics-based models of proteins, quantum-based models of molecules and materials, and so forth. Increasingly, as laboratory techniques for label measurement improve in cost and scale, machine learning-based predictive modeling is starting to supplant these data-free approaches. In particular, on test points similar to the training data, the machine learning models may be more accurate than their data-free counterparts which rely on approximations to the underlying physics for computationally tractability. However, the number of labelled data in these domains is often minuscule compared to the size of the input space for which one seeks to make predictions. Thus, traditional data-free models are typically more accurate as test
points become less similar to the training data. In particular, we generally expect the data-free models to have roughly comparable accuracy throughout the input space. Consequently, it stands to reason that coherently blending these two modeling approaches in a manner that appropriately navigates their strengths and weaknesses may give us the best of both worlds.

Herein, we tackle this problem by developing and testing function-value-prior-augmented-Bayesian Neural Networks (fv-BNNs). These models enable us to coherently incorporate physics-based and other priors on function values, into Bayesian Neural Networks (BNNs), in order to mitigate the errors that BNNs tend to make far from the training data. Figure 1 illustrates how BNNs can make egregious mean predictive errors as we move away from the training data, while a simple zero-mean prior on the function values can reign it in to improve the point predictions (and the overall predictive distribution). As we show in our experiments on real data (Section 4.2.4), even such a simple zero-mean prior can help improve protein property prediction because it encodes the knowledge that proteins mutated substantially away from a naturally occurring protein are unlikely to stably fold Biswas et al. (2021).

A main technical challenge of incorporating prior information on function values into neural network models is to specify the prior in terms of function values rather than in weight space, as would be the natural approach. Suppose your prior information on function values comes from a biophysics-based model that itself makes a prediction at each point of the input space. In theory, one could enumerate each element of the input space, compute its biophysics-based label, augment the training data with weighted versions of such pseudo data, and then train as usual. In practice, we cannot generally enumerate the entire input space, so might attempt to develop heuristic approaches for selecting which pseudo data with which to augment, which would benefit from knowledge of the test set. Instead, we sidestep this issue by encoding our prior function values into a Gaussian Process prior which then augments any standard (i.e., with a prior over weights) BNN. Our approach has the desired property of relying more on the prior over function values when the standard (non-augmented) BNN has large epistemic uncertainty, while relying more on the non-augmented BNN when the epistemic uncertainty is smaller. Although the topic of effectively capturing epistemic uncertainty remains an active area of research Izmailov et al. (2021), in our experiments, we found that currently available methods have done so well enough for us to usefully incorporate prior knowledge over function values on real scientific data sets. As estimation of epistemic uncertainty improves, our approach will correspondingly benefit. Finally, as with any use of prior knowledge, our proposed methodology is useful only to the extent that the prior information is useful for the problem at hand. As we show in our experiments, we have found both simple (constant-valued) and rich (biophysics-based) priors that improve prediction on our real data sets.

Our main goal was to enable neural networks to benefit from specifying a prior on function values directly, to do so with little added computational cost to the baseline BNN, without numerous hyperparameter choices, and in a manner that could augment any existing BNN and prior, irrespective of the Bayesian inference technique chosen.
Next we describe related work before providing a detailed exposition of our method, followed by experiments on synthetic and real scientific data sets.

2 Related work

Gaussian Process (GP) prior regression models [Rasmussen & Williams (2006)] allow the modeler to incorporate prior beliefs about properties of the true function through a kernel function which specifies aspects of function smoothness, and, although rarely used in machine learning, a mean function which can specify function value prior beliefs directly. Although GP regression remains a useful modelling strategy today, neural networks can provide modeling benefits both in accuracy and computational load. Hence our goal was to focus on enhancing neural networks. In Sparse Epistatic Networks [Aghazadeh et al. (2021)] for protein fitness functions, compressed sensing techniques were leveraged to sparsify the set of implied combinatorial features used by a neural network, thereby imposing prior information not on the weights, but on the sparsity of the function expressed in a particular basis; this approach does not, however, put a prior on the function values themselves. Numerous works dating back several decades now [Archer & Wang (1993); Sill (1998); Muralidhar et al. (2018)] provide techniques to impose monotonicity constraints for function estimation on neural networks; these techniques do not lend themselves to more specific function prior information. [Wilson et al. (2016)] combine function-value priors with neural networks through Deep Kernel Learning (DKL); however, it has been shown that DKL models can exhibit pathological behavior, resulting in poor uncertainty quantification, and therefore, may not reliably incorporate prior beliefs [Ober et al. (2021)]. As progress is made on DKL, this approach may become more feasible.

[Flam-Shepherd et al. (2017), 2018], Pearce et al. (2019), Matsubara et al. (2021) and Sun et al. (2019) tackle the problem of training BNNs with GP priors. To the extent that their variational approximation gap approach zero, this strategy would be equivalent to pure GP regression with the specified prior, thereby providing potential scaling benefits over traditional GP regression.

[Hafner et al. (2020)] propose a method that augments the original BNN training objective with an additional variational objective that encourages the BNN to output high epistemic uncertainty away from the training data. While there may be ways to adapt this approach to incorporating function value priors, it would require knowing the test set ahead of time, whereas our proposed method does not require knowing the test set ahead of time. Furthermore, our approach requires only one scalar hyperparameter to tune with validation data. Also, to the extent that BNNs can be made to have useful epistemic uncertainty, our approach can leverage it to coherently blend information between the data-based evidence, and our function value prior.

3 Function-value-prior-augmented-Bayesian Neural Networks

We assume that we are given training data, \( D = \{ (x_i, y_i) \}_{i=1}^N \), with inputs, \( x_i \in \mathbb{R}^d \), and regression labels, \( y_i \in \mathbb{R} \), that have been generated according to

\[
y_i = f(x_i) + \epsilon_i, \quad \epsilon_i \sim \mathcal{N}(0, \sigma_0^2),
\]

for some arbitrary and unknown function, \( f(\cdot) \), and with \( \sigma^2 \) unknown. Our end goal is to obtain as accurate predictions as possible for test points by using the training data and our prior knowledge about individual function values of \( f(\cdot) \), over its entire domain, \( p(f(x \in \mathbb{R}^d)) \).

Notably, this setting is distinguished from typical GP function priors in that we assume our prior knowledge is pointwise knowledge, \( p(f(x)) \), rather than on the smoothness, periodicity, or other global properties of the function such as is typically imparted by way of a kernel-based GP prior. Our approach is motivated by the need to incorporate information one might obtain from black box prior information, such as a biophysical model, which typically provides only pointwise prior beliefs. In particular, these ”prior knowledge” models often provide only a point prediction, without uncertainty. Consequently, herein, we assume the uncertainty around this prior knowledge can be specified by a Gaussian whose variance is treated as a hyperparameter.

We care about test point predictions in and of themselves, and additionally the point prediction combined with its uncertainty. Consequently we will assess our model using held out log-likelihood, root mean squared errors, and mean absolute errors.

We assume that \( f(\cdot) \) can be captured by a neural network, \( f_{\text{NN}}(\theta) \) with unknown weight parameters, \( \theta \in \mathbb{R}^m \). It is with respect to this neural network that we will be Bayesian, using any available standard BNN approach—these leverage a prior on the neural network weights, not the function values—of our liking, such as a Laplace approximation [Daxberger] [1] for parts of the domain to infinity.

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1 This setting can readily be adapted to not require domain knowledge over the entire domain, by effectively setting the variance for parts of the domain to infinity.
We now have two priors, one from the standard BNN approach over the weights of the neural network, \( p(\theta) \), which gets combined with evidence provided by the data and the neural network, \( p(D \mid \theta) \), to obtain the posterior distribution, \( p(\theta \mid D) \). In this setting, predictions for a test point, \( x \in \mathbb{R}^d \), would then be given by the posterior predictive distribution,

\[
p(y \mid x, D) = \int_\Theta p(y \mid \theta, x) p(\theta \mid D) d\theta.
\]

### 3.1 Neural network weight priors

We start our exposition with the standard BNN approach, wherein a prior is placed over the neural network weights, \( p(\theta) \), and our newly introduced one over function values, \( p_{fv}(f) \). How can we make use of both priors in a Bayesian modelling approach to neural networks?

First we note that the prior on the neural network weights, \( p(\theta) \), implies a prior on neural network function, \( p_{bnn}(f) \). Although we do not know the expression for this implied function prior, it in turn implies a posterior over functions, \( p_{bnn}(f \mid D) \), arising from just the standard (non-augmented) BNN, and which can be written according to Bayes rule as follows,

\[
p_{bnn}(f \mid D) \propto p_{bnn}(f) p(D \mid f),
\]

where \( p(D \mid f) \) is the likelihood for the training data given function, \( f(\cdot) \), with the chosen neural network noise model.

### 3.2 Function-value priors

Our function value prior knowledge is assumed to be summarized, for each point in the function domain, \( x \), by a mean and variance in a Gaussian distribution, \( p_{fv}(f(x)) = \mathcal{N}(\mu_{fv}(x), \sigma^2_{fv}(x)) \). The variance controls the strength of our prior belief, which may be known ahead of time, but that we herein treat as a single, scalar hyperparameter, yielding an empirical Bayes approach. To leverage this prior information with our BNN, we will want to lift the pointwise information into a prior over functions, which can be accomplished by writing it in the form of a diagonal GP prior on the function space,

\[
p_{fv}(f) = \mathcal{GP} \left( \mu_{fv}(x), \text{diag}(\sigma^2_{fv}(x)) \right).
\]

This GP prior is not intended to encode any global properties of the function such as smoothness—hence its diagonal kernel—only to capture the entirety of our function value prior knowledge, as it does. We rely on the standard BNN prior to provide this kind of global information, although one could attempt to make use of full GP priors (e.g., Sun et al. (2019)) within our approach.

### 3.3 Combining priors over weights and function values

We now have two priors, one from the standard BNN approach over the weights of the neural network, \( p(\theta) \), and our newly introduced one over function values, \( p_{fv}(f) \). How can we make use of both priors in a Bayesian modelling approach to neural networks?

First we note that the prior on the neural network weights, \( p(\theta) \), implies a prior on neural network function, \( p_{bnn}(f) \). Although we do not know the expression for this implied function prior, it in turn implies a posterior over functions, \( p_{bnn}(f \mid D) \), arising from just the standard (non-augmented) BNN, and which can be written according to Bayes rule as follows,

\[
p_{bnn}(f \mid D) \propto p_{bnn}(f) p(D \mid f),
\]

where \( p(D \mid f) \) is the likelihood for the training data given function, \( f(\cdot) \), with the chosen neural network noise model.

Now we have two priors, each over function space, one arising from the standard BNN weight prior, \( p_{bnn}(f) \), and one from our function-value prior, \( p_{fv}(f) \). Because each is providing independent information, these could in principle be combined straightforwardly:

\[
p(f) \propto p_{fv}(f) p_{bnn}(f),
\]

except that we do not know the expression for the implicit \( p_{bnn}(f) \). However, we can derive the posterior corresponding to this combined prior as follows:

\[
p(f \mid D) \propto p(f) p(D \mid f) \tag{2}
\]

\[
\propto p_{fv}(f) p_{bnn}(f) p(D \mid f) \tag{3}
\]

\[
\propto p_{fv}(f) p_{bnn}(f \mid D). \tag{4}
\]

This posterior—the product of the function-value prior and the standard BNN posterior—is not analytically tractable, nor is there a straightforward strategy to sample from it. One might consider using variational inference here with the Spectral Stein Gradient Estimator (Shi et al. (2018)), but this requires careful tuning of a number of hyperparameters.

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2See Appendix A.2 for a discussion on combining functional priors when the random function has an infinite index set.
which we would prefer to forgo. Consequently, we instead take a strategy of approximating the BNN posterior with an analytical form that enables the joint posterior in Equation \ref{eq:joint_posterior} to be computed in closed form. Specifically, we approximate the BNN posterior, \( p_{\text{BNN}}(f \mid D) \), with a variational approximation, \( q_{\text{BNN}}(f) \), consisting of the family of GPs with diagonal kernel. Our variational approximation makes use of the “inclusive” KL-divergence, \( KL(p \parallel q) \), that is, in the opposite direction from what is typically used in variational inference. The inclusive KL divergence is sometimes used because it more accurately captures posterior uncertainty, even though it is typically more difficult to optimize for \cite{naesseth2020}. However, in our setting, we use it because it is actually easier to work with. Specifically, it enables us to fit the variational posterior by moment matching at each point, \( x \), to obtain our final posterior predictive mean and variance, \( q_{\text{BNN}}(f(x)) = \mathcal{N}(\mu, \sigma^2) \), where,

\[
\mu = \mathbb{E}_{p_{\text{BNN}}(f \mid D)}[f(x)]
\]

\[
\sigma^2 = \text{diag}(\text{Var}_{p_{\text{BNN}}(f \mid D)}[f(x)])
\]

are straightforward to obtain for many Bayesian approximations, such as Laplace and Deep Ensembles. The corresponding GP posterior over functions is given by

\[
q_{\text{BNN}}(f) = \mathcal{GP}(\mu_{\text{BNN}}(x), \text{diag}(\sigma_{\text{BNN}}^2(x))),
\]

which, despite being a variational approximation, produces the same pointwise posterior predictive mean and variance predictions as the BNN posterior it approximates, \( p_{\text{BNN}}(f \mid D) \). Moreover, these are the typical quantities of interest for downstream use. Finally, this moment matching approximation requires no tuning, and as we show in our experiments, works well.

From this variational approximation, we now have a form of the non-augmented BNN posterior that can be combined with our function-value prior, as in Equation \ref{eq:joint_posterior} but now in closed form, to obtain our final \( \text{fv-BNN} \) posterior distribution,

\[
p(f \mid D) \propto p_{\text{fv}}(f) \ p_{\text{BNN}}(f \mid D)
\]

\[
\approx p_{\text{fv}}(f) \ q_{\text{BNN}}(f)
\]

\[
= \mathcal{GP}(\mu_{\text{fv}}(x), \text{diag}(\sigma_{\text{fv}}^2(x))) \mathcal{GP}(\mu_{\text{BNN}}(x), \text{diag}(\sigma_{\text{BNN}}^2(x)))
\]

\[
= \mathcal{GP}(\mu(x), \text{diag}(\sigma^2(x))).
\]

where,

\[
\mu(x) = \frac{\sigma_{\text{BNN}}^2(x)^{-1} \mu_{\text{BNN}}(x) + \sigma_{\text{fv}}^2(x)^{-1} \mu_{\text{fv}}(x)}{\sigma_{\text{BNN}}^2(x)^{-1} + \sigma_{\text{fv}}^2(x)^{-1}}
\]

\[
\sigma^2(x) = \left( \sigma_{\text{BNN}}^2(x)^{-1} + \sigma_{\text{fv}}^2(x)^{-1} \right)^{-1}.
\]

Equations \ref{eq:moment_matching} and \ref{eq:moment_matching2} enjoy an intuitive interpretation: the posterior mean is a convex combination of the original BNN posterior mean and the prior mean, where the weights are determined by the epistemic uncertainty of the original BNN and the strength of the prior.

The final posterior predictive distribution for \( \text{fv-BNN} \) is

\[
p(y \mid x, D) = \mathcal{N}(\mu(x), \sigma^2(x) + \sigma^2_0),
\]

where \( \mu(x) \) and \( \sigma^2(x) \) are given by Equations \ref{eq:final_mean} and \ref{eq:final_variance}, the data-generating noise from Equation \ref{eq:noise} can be estimated from the data, using for example, the mean squared error of the validation set predictions.

### 4 Experiments

To understand and characterize the value of our proposed approach, \( \text{fv-BNN} \), we first constructed a synthetic one-dimensional example that could readily be understood at an intuitive level. Then we applied our method on real prediction problems in the natural sciences to empirically evaluate how much it could help improve prediction compared to alternative methods. Next we go through these experiments in detail. When published, the accompanying code will be made public.
4.1 Illustrative 1D example

Our illustrative example (Figure 1) was constructed by sampling 1000 points from \( y = 0.3 \sin(\frac{\pi}{2}x) + 0.4 \sin(\pi x) \), keeping 800 for training and using the remaining 200 for validation. We construct an approximate BNN posterior using the last-layer Laplace approximation suggested by Kristiadi et al. (2020) using the Laplace pytorch library Daxberger et al. (2021). While Deep Ensembles and the Laplace approximations gave similar posterior mean predictions, we found that the Laplace approximation gave much better epistemic uncertainty.

Figure 1 compares the BNN fit to this data with our \( fv\text{-}BNN \) using a zero-mean prior with a variance equal to the empirical variance of the training and validation data (\( \sigma = 0.43 \)). This function value prior encodes our prior belief that the function is centered around zero. Whereas the BNN extrapolates erroneously as we move away from the training data, \( fv\text{-}BNN \) regresses back toward the prior mean in regions of high epistemic uncertainty. On the basis of this sanity check, we next moved on to experiments on real data.

4.2 Experiments on real scientific data

We chose two protein datasets commonly used for benchmarking protein fitness prediction, wherein the goal is to predict the “fitness” (i.e., scalar property of interest) from the protein sequence of amino acids. This problem is of great interest for a number of reasons including for protein engineering and mutation effect prediction, Wittmann et al. (2021); Aghazadeh et al. (2021); Biswas et al. (2021); Hsu et al. (2022); Rieselman et al. (2018); Hopf et al. (2017); Russ et al. (2020). We also used one small-molecule data set wherein the goal is to predict solubility from some representation of the small molecule, a property frequently required for drug development Di et al. (2012). We describe the details of our chosen data sets shortly.

4.2.1 Approaches compared against

The basis of all of our experiments on each data set is a single neural network architecture. For the two protein data sets, model architectures and optimization parameters were chosen by cross-validation (see Appendix A.1). The avGFP data set used a fully-connected neural network with two hidden layers, each with 100 dimensions, ReLU non-linearities, and was optimized using Adam Kingma & Ba (2015) with a weight-decay of 0.0001. The GB1 data set used a fully-connected neural network with 1 hidden layer containing 300 dimensions, ReLU non-linearities, and was optimized using Adam with a weight-decay of 0.0001. The small molecule data set used the Graph Convolution Neural Network (GCNN) Duvenaud et al. (2015) with the default molecular featurizations and neural network hyperparameters as provided in the DeepChem library Ramsundar et al. (2019).

Each data set had its own neural network architecture. From this architecture, we compared the following approaches on all three of our data sets:

1. \( NN \): The neural network with a point estimate of the weights when fit using a cross-entropy loss on the training data using the validation data for early stopping.

2. \( BNN \): The neural network used with Deep Ensembles, using five networks in the ensemble. Each network was trained in the same manner as the NN above, but with different weight initialization as done by Lakshminarayanan et al. (2016). This approach has been demonstrated to provide good estimates of the predictive posterior distribution in a range of scenarios Wilson & Izmailov (2020); Pearce et al. (2020); Gustafsson et al. (2020).

3. \( fv\text{-}BNN \): One or two different priors are used to augment the BNN, as described in each experimental section.

4. \( STACKING \): A linear regression model is fit using two features which are predictions made from (i) the BNN and (ii) the prior that was used in \( fv\text{-}BNN \), as described below. The stacker thus had three free parameters which were fit using the validation data with a log-likelihood loss.

An important distinction between our approach and the stacking regressor is that our method is able to use the epistemic uncertainty of the original BNN to modulate the influence of the prior. Thus, stacking provides a strong baseline to test whether our approach improves over simply ensembling the two models: the neural network and the prior.

We do not compare to any of the approaches in the literature whose goal it is to approximate a GP process regression with a neural network, as their goals are not to augment a BNN with a prior over function values.

We evaluated performance of each modeling approach using each of the log-likelihood (LL), the root mean squared error (RMSE), and the mean absolute error (MAE).
We use three types of priors over function values in our experiments. Two are used for protein fitness prediction, and when restricted to proteins predicted to be stable. However, it has also been shown that those proteins predicted to be unstable are more likely to have poor fitness Gelman et al. (2021); Wittmann et al. (2021). We converted the real-valued information based on biophysics, described next.

Moreover, there has been substantial work making use of large-scale unsupervised protein data with deep learning Kauffman & Weinberger (1989); Arnold (2012); Bloom et al. (2005); Romero et al. (2013); Wittmann et al. (2021). This is an indication that it has previously been demonstrated that little correlation exists between Rosetta stability predictions and fitness useless, there is substantial evidence that protein fitness landscapes are typically dominated by non-functional sequences.

Table 1: Results on avGFP fluorescence prediction. Plus-minus indicates the standard error computed from 10 train-test splits of the data.

| METHOD                      | LOG- LIKELIHOOD | RMSE  | MAE     |
|-----------------------------|-----------------|-------|---------|
| NN                          | −8.33 ± 0.66    | 1.02 ± 0.01 | 0.70 ± 0.01 |
| BNN                         | −5.73 ± 0.18    | 1.02 ± 0.01 | 0.70 ± 0.01 |
| Stacking: BNN+non-functional prior | −8.63 ± 0.33    | 1.03 ± 0.01 | 0.71 ± 0.00 |
| Stacking: BNN+stability prior | −8.61 ± 0.34    | 1.03 ± 0.01 | 0.71 ± 0.00 |
| \(f^2\text{-BNN} \) (non-functional prior) | −1.82 ± 0.00    | 0.96 ± 0.01 | 0.65 ± 0.01 |
| \(f^2\text{-BNN} \) (stability prior) | −1.53 ± 0.00    | 0.85 ± 0.01 | 0.56 ± 0.01 |

Table 2: Results on GB1 binding affinity prediction. Plus-minus indicates the standard error computed from 10 train-test splits of the data.

| METHOD                      | LOG- LIKELIHOOD | RMSE  | MAE     |
|-----------------------------|-----------------|-------|---------|
| NN                          | −1.00 ± 0.03    | 0.65 ± 0.02 | 0.50 ± 0.02 |
| BNN                         | −0.91 ± 0.02    | 0.59 ± 0.02 | 0.45 ± 0.01 |
| Stacking: BNN+non-functional prior | −1.10 ± 0.05    | 0.69 ± 0.02 | 0.54 ± 0.02 |
| Stacking: BNN+stability prior | −1.09 ± 0.06    | 0.68 ± 0.03 | 0.54 ± 0.02 |
| \(f^2\text{-BNN} \) (non-functional prior) | −0.73 ± 0.05    | 0.48 ± 0.03 | 0.28 ± 0.05 |
| \(f^2\text{-BNN} \) (stability prior) | −0.57 ± 0.00    | 0.38 ± 0.00 | 0.13 ± 0.00 |

Table 3: Results on aqueous solubility prediction. Plus-minus indicates the standard error computed from 10 train-test splits of the data.

| METHOD                      | LOG- LIKELIHOOD | RMSE  | MAE     |
|-----------------------------|-----------------|-------|---------|
| NN                          | −2.39 ± 0.04    | 1.89 ± 0.03 | 1.31 ± 0.02 |
| BNN                         | −2.06 ± 0.03    | 1.71 ± 0.02 | 1.15 ± 0.01 |
| Stacking: BNN+SFI prior     | −2.35 ± 0.04    | 1.01 ± 0.01 | 1.13 ± 0.01 |
| \(f^2\text{-BNN} \) (SFI prior) | −2.04 ± 0.03    | 1.67 ± 0.02 | 1.12 ± 0.01 |

4.2.2 Priors over function values

We use three types of priors over function values in our experiments. Two are used for protein fitness prediction, and one is used for solubility prediction. Our goal is not to find or develop the best priors possible for these problems, only to demonstrate that reasonable priors exist, both simple, and rich, and that our proposed method can make use of these in an effective manner, as demonstrated by improved prediction accuracy.

Constant zero-fitness prior. The first prior for protein fitness is a simple prior that takes on the value zero throughout all of protein space, that we denote as our non-functional prior. Although this may seem such a simple prior as to be useless, there is substantial evidence that protein fitness landscapes are typically dominated by non-functional sequences Kauffman & Weinberger (1989); Arnold (2012); Bloom et al. (2005); Romero et al. (2013); Wittmann et al. (2021). Moreover, there has been substantial work making use of large-scale unsupervised protein data with deep learning to try to learn the generic, non-functional “holes” in protein space Biswas et al. (2021). Indeed, we will find that this non-functional prior is useful to incorporate in our experiments, although not as useful as a much richer source of information based on biophysics, described next.

Stability prior. Our second prior uses the intuition just described, but in a more nuanced manner. In particular, rather than assume that all of protein space is dominated by non-fit proteins, we make the further argument that a major determinant of which proteins are fit, irrespective of the property in question, is their inherent stability. Consequently, our second protein prior, stability prior, is defined by stability predictions provided by the biophysics-based Rosetta Alford et al. (2017) model. By doing so, we encode our prior knowledge that protein stability is typically a necessary but not sufficient condition for protein fitness, as well as the knowledge encoded by Rosetta stability estimates. It’s worth noting that it has previously been demonstrated that little correlation exists between Rosetta stability predictions and fitness when restricted to proteins predicted to be stable. However, it has also been shown that those proteins predicted to be unstable are more likely to have poor fitness Gelman et al. (2021); Wittmann et al. (2021).
Rosetta scores to a binary “stable” versus “not stable”, by running a grid-search on the predicted stability scores of the combined training and validation sets to find the Rosetta score that best separated fit versus not fit sequences according to the ROC-AUC metric on the relevant prediction property of interest (fluorescence for avGFP or binding activity for GB1). This prior still uses a mean of zero but has a separate variance parameter for the two sets of binary encoded sequences. This allows the model to place a stronger belief that a sequence is not functional if it is determined to be unstable by the Rosetta score.

**Solubility prior.** For the small molecule data set, for which our task was to predict solubility, we used just one prior, our SFI prior, which had a mean given by the Solubility Forecast Index (SFI), after scaling and shifting the value to match the units of solubility. The SFI was developed by medicinal chemists to predict a score correlated to aqueous solubility from physio-chemical properties of the molecule; it is considered among the most reliable predictor of aqueous solubility [Hill & Young 2010]. Our SFI predictions were computed using Wall.

The non-functional prior and the SFI prior each had a single scalar parameter that needed fitting, reflecting the strength of the prior as a variance as described in the methods. The stability prior had two scalar parameters that needed fitting (as in empirical Bayes), corresponding to the strength for stable and unstable proteins as predicted by Rosetta. These parameters were fit with a grid search to maximize the marginal likelihood on the validation set.

### 4.2.3 Data sets and corresponding experimental set-up

Next we provide descriptions of each of our three data sets, how they were partitioned into train, validation, and test sets. Following these, we discuss the experimental results across all three of these in Section 4.2.4.

**Predicting protein fluorescence (avGFP).** Our first experiment centered on making predictions of green fluorescence on proteins, using a data set comprised of measurements of the naturally occurring *Aequorea victoria* green fluorescent protein (avGFP), and variants of it up to 15 mutations away, determined by a physical random mutagenesis procedure in the laboratory Sarkisyan et al. (2016). There were 51,714 proteins with measured fluorescence in total. In many protein engineering applications, we are trying to engineer an existing protein to have more of a property (*e.g.*, brighter), or to alter its property (*e.g.*, change fluorescence wavelength). Often we start with protein sequence variants close to a naturally existing one—a so-called wild-type (WT) sequence—and predict fitness values of proteins increasingly further away as we explore the space. To represent this extrapolative scenario of interest, we sampled 3,000 sequences within two mutations (out of a total of 13,861) of the avGFP WT sequence, keeping a random 80% of these for training data, and the remaining 20% as our validation set. The test set was composed of all 48,714 sequences not in the training or validation sets. Rosetta scores for these data were previously computed by [Gelman et al. 2021].

**Predicting protein binding affinity (GB1).** The GB1 landscape [Wu et al. 2016] measures the binding affinity of all GB1 variants (400 = 160,000) at four amino acid sites to IgG-Fc. Similarly to avGFP, we randomly sampled 500 sequences within two mutations from the WT sequence, using 80% of these for training, and 20% for validation. The test set comprised all other proteins. We chose 500 so as to provide a similar fraction of training sequences from within the pool of variants with two mutations as was used in the avGFP experiment. However, we found our qualitative conclusions to be robust to the number of training sequences. We ensured that half of the sequences used for training and validation were deemed fit by sampling appropriately, so as to balance the data set. Rosetta scores were previously computed by [Wittmann et al. 2021] using the Triad protein design software suite (Protabit, Pasadena, CA, USA: https://triad.protabit.com/) with a Rosetta energy function under the fixed-backbone protocol, which were found to offer better stability predictions than the flexible backbone alternative.

**Predicting solubility of drug-like molecules.** Aqueous solubility is among the most important physical properties required for a drug molecule, as it facilitates the delivery of the drug to its target. Accurately predicting aqueous solubility from the molecular graph has therefore been a key tool in drug discovery. SFI does not directly report aqueous solubility, but rather provides a solubility score, which has a very strong linear relationship to aqueous solubility. As such, we construct an SFI prior by fitting the SFI scores to solubility measurements on the training and validation data and using the linearly scaled SFI predictions as the prior mean. We used the Therapeutic Data Commons (TDC) to construct 0.6/0.4 train/test splits using their default scaffold-split and using 20% of the training points for validation [Huang et al. 2021].

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3 Fit was determined by a threshold of 0.5 as suggested by [Dallago et al. 2021].
4.2.4 Experimental results across all data sets

There are a number of interesting observations to make from these comparisons between models, across the avGFP fluorescence predictions (Table 1), the GB1 binding activity predictions (Table 2), and the solubility prediction (Table 3). First, the BNN always outperforms the NN by held out log-likelihood, and is either better, or comparable by RMSE and MAE. Second, and of primary interest for our work, the \textit{fv}-BNN with a rich prior, always outperforms the non-augmented BNN, across all three metrics and all three data sets.

\textit{fv}-BNN with the simple, constant, zero-fitness prior also always outperforms the non-augmented BNN, across all three metrics and both protein data sets for which the comparison can be made. This underscores how even a simple zero-mean prior on the function values can improve property prediction by encoding the knowledge that proteins mutated away from a naturally occurring sequence are unlikely to be functional. Additionally, with \textit{fv}-BNN, the rich prior always outperforms the simple prior; moreover, it provides the best overall performance compared to all other approaches.

5 Discussion and Conclusions

Motivated by regression problems in the natural sciences relevant to protein engineering, small molecule and materials design, and beyond, we have proposed a method, \textit{function-value-prior-augmented-Bayesian Neural Networks} (\textit{fv-BNNs}), which enables the user to take prior information on the specific values of the function—such as might be obtained from a biophysical model, or more coarse-grained information—and coherently integrate it into a Bayesian Neural Network setting, for any BNN inference techniques from which the pointwise posterior predictive mean and variance can be extracted or approximated.

The degree by which our method may outperform a non-augmented BNN depends both on the quality of the prior information itself and its relevance to the task, but also on the extent to which the epistemic uncertainty of the non-augmented BNN is calibrated. From our results on real data, it is clear that each of these criteria can be satisfied sufficiently to observe an improvement over non-augmented BNNs.

It’s worth noting that the empirical Bayes method we used leveraged a validation set that was sampled in the same manner as the training data set, both of which were distinct distributions from the test set, so as to make for a difficult, extrapolative setting. An interesting area for further investigation could be to explore different strategies for making the validation set different from the training data set, in a way that may more closely mimic the test use cases. For example, one could re-partition the training-plus-validation used to more closely mimic an extrapolation to higher-order mutations.

A promising future application of this method will be to leverage it within an \textit{in silico} design cycle, such as presented in Biswas et al. (2021); Brookes et al. (2019); Fannjiang & Listgarten (2020); Madani et al. (2021); Wittmann et al. (2021). Finally, it would be interesting to apply \textit{fv-BNN} as a surrogate in Bayesian optimization Snoek et al. (2015), where the ability to place informative function-value priors on the surrogate may allow optimization to be performed with fewer ground-truth function evaluations.

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A Appendix

A.1 Architecture and optimization hyperparameters

For the avGFP and GB1 data sets, cross-validation was used to select the model architecture and optimization hyperparameters. We searched over fully-connected model architectures with either 1 or 2 hidden layers, with the dimensions of the hidden layers varying between, 100, 200, and 300 dimensions. In addition, we searched over the choice of weight-decay used with the Adam optimizer with options of 0.01, 0.0001, and 0.000001.

A.2 A technical note on combining distributional priors over functions

Let \( f: \mathcal{X} \to \mathbb{R} \), be a function. When \(|\mathcal{X}|\) is finite, it is easy to reason about distributions over functions, as \( f \) can be represented a random vector and Gaussian Processes are simply multivariate Gaussian distributions. Examples of functions for which \(|\mathcal{X}|\) is finite include protein fitness landscape prediction and small-molecule property prediction when the the number of atoms is bounded.

When \(|\mathcal{X}|\) is not finite, we no longer have a notion of a probability density function over functions and therefore, making it challenging to construct a functional prior through an unnormalized product of density functions.

In this setting, we consider an alternative approach for combining functional priors. Specifically, in the case of two Gaussian Process priors with diagonal covariances, we consider a contruction of Gaussian Process that naturally extends the approach that calculates the product of density functions with finite \(|\mathcal{X}|\). We define the new stochastic process as the one for which the marginal distribution on any finite index set is the product of the marginal distributions of the original two GPs on that same index set. Since for any finite index set, this product returns a multivariate Gaussian with a diagonal covariance matrix, the resulting stochastic process is itself a GP with a diagonal covariance matrix. The restriction to a diagonal covariance matrix ensures that the marginal distributions are self-consistent, which would not otherwise be generally true. Given this self-consistency property, the Kolmogorov extension theorem guarantees the existence of the resulting Gaussian processes whose finite-dimensional distributions are proportional to the product of those of the two GPs.

Following this argument, we define the product of two GPs with diagonal covariance matrices as follows:

**Definition A.1.** Consider the two stochastic processes \( \mathcal{GP}_1(\mu_1(x), \text{diag}(\sigma^2_1(x))) \), \( \mathcal{GP}_2(\mu_2(x), \text{diag}(\sigma^2_2(x))) \). We define \( \mathcal{GP}_1(\mu_1(x), \text{diag}(\sigma^2_1(x))) \cdot \mathcal{GP}_2(\mu_2(x), \text{diag}(\sigma^2_2(x))) \equiv \mathcal{GP}(\mu(x), \sigma^2(x)) \), where,

\[
\mu(x) = \frac{\sigma^2_2(x)^{-1} \mu_2(x) + \sigma^2_1(x)^{-1} \mu_1(x)}{\sigma^2_2(x)^{-1} + \sigma^2_1(x)^{-1}} \quad (8)
\]

\[
\sigma^2(x) = \left(\sigma^2_2(x)^{-1} + \sigma^2_1(x)^{-1}\right)^{-1}. \quad (9)
\]

A.3 Statistical Significance

Table 4: GB1 task p-values from the Wilcoxon signed-rank test, where for each method, the null hypothesis is that paired samples from \( \text{fv-BNN} \) (stability prior) and the other method come from the same distribution. The alternative hypothesis is that \( \text{fv-BNN} \) (stability prior) improves upon the other method. Each paired sample is computed on a unique test set generated from a random train/val/test split.

| Method                        | P-VALUE (LL) | P-VALUE (RMSE) | P-VALUE (MAE) |
|-------------------------------|--------------|----------------|---------------|
| BNN                           | 0.001        | 0.001          | 0.001         |
| NN                            | 0.001        | 0.001          | 0.001         |
| Stacking: BNN+Stability Prior | 0.001        | 0.001          | 0.001         |
| Stacking: BNN+Non-Functional Prior | 0.001    | 0.001          | 0.001         |
| fv-BNN (Non-Functional Prior) | 0.022        | 0.022          | 0.022         |
Table 5: GB1 task p-values from the Wilcoxon signed-rank test, where for each method, the null hypothesis is that paired samples from $fv$-BNN (non-functional prior) and the other method come from the same distribution. The alternative hypothesis is that $fv$-BNN (non-functional prior) improves upon the other method. Each paired sample is computed on a unique test set generated from a random train/val/test split.

| Method                              | $p$-value (LL) | $p$-value (RMSE) | $p$-value (MAE) |
|-------------------------------------|----------------|-----------------|----------------|
| BNN                                 | 0.001          | 0.001           | 0.001          |
| NN                                  | 0.002          | 0.002           | 0.002          |
| STACKING: BNN+STABILITY PRIOR       | 0.001          | 0.001           | 0.001          |
| STACKING: BNN+NON-FUNCTIONAL PRIOR  | 0.001          | 0.001           | 0.001          |
| $fv$-BNN (STABILITY PRIOR)          | 0.978          | 0.978           | 0.978          |

Table 6: GFP task p-values from the Wilcoxon signed-rank test, where for each method, the null hypothesis is that paired samples from $fv$-BNN (non-functional prior) and the other method come from the same distribution. The alternative hypothesis is that $fv$-BNN (non-functional prior) improves upon the other method. Each paired sample is computed on a unique test set generated from a random train/val/test split.

| Method                              | $p$-value (LL) | $p$-value (RMSE) | $p$-value (MAE) |
|-------------------------------------|----------------|-----------------|----------------|
| BNN                                 | 0.001          | 0.001           | 0.001          |
| NN                                  | 0.001          | 0.001           | 0.001          |
| STACKING: BNN+STABILITY PRIOR       | 0.001          | 0.001           | 0.001          |
| STACKING: BNN+NON-FUNCTIONAL PRIOR  | 0.001          | 0.001           | 0.001          |
| $fv$-BNN (NON-FUNCTIONAL PRIOR)     | 0.001          | 0.001           | 0.001          |

Table 7: GFP task p-values from the Wilcoxon signed-rank test, where for each method, the null hypothesis is that paired samples from $fv$-BNN (non-functional prior) and the other method come from the same distribution. The alternative hypothesis is that $fv$-BNN (non-functional prior) improves upon the other method. Each paired sample is computed on a unique test set generated from a random train/val/test split.

| Method                              | $p$-value (LL) | $p$-value (RMSE) | $p$-value (MAE) |
|-------------------------------------|----------------|-----------------|----------------|
| BNN                                 | 0.001          | 0.001           | 0.001          |
| NN                                  | 0.001          | 0.001           | 0.010          |
| STACKING: BNN+STABILITY PRIOR       | 0.001          | 0.001           | 0.001          |
| STACKING: BNN+NON-FUNCTIONAL PRIOR  | 0.001          | 0.001           | 0.001          |
| $fv$-BNN (STABILITY PRIOR)          | 1.000          | 1.000           | 1.000          |

Table 8: SFI task p-values from the Wilcoxon signed-rank test, where for each method, the null hypothesis is that paired samples from $fv$-BNN (SFI prior) and the other method come from the same distribution. The alternative hypothesis is that $fv$-BNN (SFI prior) improves upon the other method. Each paired sample is computed on a unique test set generated from a random train/val/test split.

| Method                              | $p$-value (LL) | $p$-value (RMSE) | $p$-value (MAE) |
|-------------------------------------|----------------|-----------------|----------------|
| BNN                                 | 0.002          | 0.001           | 0.001          |
| NN                                  | 0.001          | 0.001           | 0.001          |
| STACKING: BNN+SFI PRIOR             | 0.001          | 1.000           | 0.246          |