GAUCHE: A Library for Gaussian Processes and Bayesian Optimisation in Chemistry

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Abstract

We introduce GAUCHE, a library for GAUssian processes in CHEmistry. Gaussian processes have long been a cornerstone of probabilistic machine learning, affording particular advantages for uncertainty quantification and Bayesian optimisation. Extending Gaussian processes to chemical representations however is nontrivial, necessitating kernels defined over structured inputs such as graphs, strings and bit vectors. By defining such kernels in GAUCHE, we seek to open the door to powerful tools for uncertainty quantification and Bayesian optimisation in chemistry. Motivated by scenarios frequently encountered in experimental chemistry, we showcase applications for GAUCHE in molecular discovery and chemical reaction optimisation. The codebase is made available at https://github.com/leojklarner/gauche

Keywords: Bayesian optimisation, Gaussian processes, chemistry

1. Introduction

Early-stage scientific discovery is typically characterised by the small data regime due to the limited availability of high-quality experimental data (Zhang and Ling, 2018; Thawani et al., 2020). Much of the novelty of discovery relies on the fact that there is much knowledge to gain in the small data regime. By contrast, in the big data regime, discovery offers diminishing returns as much of the knowledge about the space of interest has already been acquired. As such, machine learning methodologies that facilitate search in small data

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regimes such as Bayesian optimisation (BO) (Gómez-Bombarelli et al., 2018; Griffiths and Hernández-Lobato, 2020; Shields et al., 2021; Du et al., 2022) and active learning (AL) (Zhang et al., 2019; Jablonka et al., 2021) have great potential to expedite the rate at which performant molecules, molecular materials, chemical reactions and proteins are discovered.

To date in molecular machine learning, Bayesian neural networks (BNNs) have been the surrogate of choice to produce the uncertainty estimates that underpin BO and AL (Ryu et al., 2019; Zhang et al., 2019; Hwang et al., 2020; Scalia et al., 2020). For small datasets, however, deep neural networks are often not the model of choice. Notably, certain deep learning experts have voiced a preference for Gaussian processes (GPs) in the small data regime (Bengio, 2011). Furthermore, for BO, GPs possess particularly advantageous properties; first, they admit exact as opposed to approximate Bayesian inference and second, few of their parameters need to be determined by hand. In the words of Sir David MacKay (MacKay et al., 2003),

> "Gaussian processes are useful tools for automated tasks where fine tuning for each problem is not possible. We do not appear to sacrifice any performance for this simplicity."

The iterative model refitting required in BO makes it a prime example of such an automated task. Although BNN surrogates have been trialled for BO (Snoek et al., 2015; Springenberg et al., 2016), GPs remain the model of choice as evidenced by the results of the recent NeurIPS Black-Box Optimisation Competition (Turner et al., 2021).

Training GPs on molecular inputs is non-trivial however. Canonical applications of GPs assume continuous input spaces of low and fixed dimensionality. The most popular molecular input representations are SMILES/SELFIES strings (Anderson et al., 1987; Weininger, 1988; Krenn et al., 2020), fingerprints (Rogers and Hahn, 2010; Probst and Reymond, 2018; Capecchi et al., 2020) and graphs (Duvenaud et al., 2015; Kearnes et al., 2016). Each of these input representations poses problems for GPs. SMILES strings have variable length, fingerprints are high-dimensional and sparse bit vectors, while graphs are also a form of non-continuous input. To construct a GP framework over molecules, GAUCHE provides GPU-based implementations of kernels that operate on molecular inputs, including string, fingerprint and graph kernels. Furthermore, GAUCHE includes support for protein and chemical reaction representations and interfaces with the GPyTorch (Gardner et al., 2018) and BoTorch (Balandat et al., 2020) libraries to facilitate usage for advanced probabilistic modelling and BO. Concretely, our contributions may be summarised as:

1. We propose a GP framework for molecules, chemical reactions and proteins.
2. We provide an open-source, GPU-enabled library building on GPyTorch (Gardner et al., 2018), BoTorch (Balandat et al., 2020) and RDKit (Landrum, 2013).
3. We extend the use of black box graph kernels (from GraKel, Siglidis et al. (2020)) to GP regression via a GPyTorch interface, along with a limited set of graph kernels implemented in native GPyTorch to enable optimisation of the graph kernel hyperparameters under the marginal likelihood.
4. We conduct benchmark experiments evaluating the utility of the GP framework on regression, uncertainty quantification and BO tasks.

GAUCHE includes tutorials to guide users through the tasks considered in this paper and is made available at https://github.com/leojklarner/gauche

2. Background

We summarise the background on Gaussian processes and common molecular representations here, leaving Bayesian optimisation, reaction and protein representations for Appendix A.

2.1 Gaussian Processes

Notation: $\mathbf{X} \in \mathbb{R}^{n \times d}$ is a design matrix of n training examples of dimension d. A given row i of the design matrix contains a training molecule's representation $\mathbf{x}_i$. A GP is specified by a mean function, $m(\mathbf{x}) = \mathbb{E}[f(\mathbf{x})]$ and a covariance function $k(\mathbf{x}, \mathbf{x}') = \mathbb{E}[(f(\mathbf{x}) - m(\mathbf{x}))(f(\mathbf{x}') - m(\mathbf{x}))]$. $K_\theta(\mathbf{X}, \mathbf{X})$ is a kernel matrix where entries are computed by the kernel function as $[K]_{ij} = k(\mathbf{x}_i, \mathbf{x}_j)$. θ represents the set of kernel hyperparameters. The GP specifies the full distribution over the function f to be modelled as

$$f(\mathbf{x}) \sim \mathcal{GP}\big(m(\mathbf{x}), k(\mathbf{x}, \mathbf{x}')\big).$$

Prediction: The GP returns a predictive mean, $\bar{\mathbf{f}}_* = K(\mathbf{X}_*, \mathbf{X})[K(\mathbf{X}, \mathbf{X}) + \sigma_y^2 I]^{-1}\mathbf{y}$ at test locations $\mathbf{X}_*$ and a predictive uncertainty $\text{cov}(\mathbf{f}_*) = K(\mathbf{X}_*, \mathbf{X}_*) - K(\mathbf{X}_*, \mathbf{X})[K(\mathbf{X}, \mathbf{X}) + \sigma_y^2 I]^{-1} K(\mathbf{X}, \mathbf{X}_*)$.

Kernel Functions: The choice of kernel function is an important inductive bias for the properties of the function being modelled. A common choice for continuous input domains is the radial basis function kernel

$$k_{\text{RBF}}(\mathbf{x}, \mathbf{x}') = \sigma_f^2 \exp\left(\frac{-||\mathbf{x} - \mathbf{x}'||_2^2}{2\ell^2}\right),$$

where σ_f^2 is the signal amplitude hyperparameter (vertical lengthscale) and ℓ is the (horizontal) lengthscale hyperparameter. The symbol θ, introduced previously, is used to represent the set of kernel hyperparameters. For molecules, bespoke kernel functions will need to be defined for structured input spaces.

2.2 Molecular Representations

We review here the three main categories of molecular representations before describing the kernels that operate on them in section 3.

Graphs: Molecules may be represented as an undirected, labeled graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ where vertices $\mathcal{V} = \{v_1, \ldots, v_N\}$ represent the atoms of an N-atom molecule and edges $\mathcal{E} \subset \mathcal{V} \times \mathcal{V}$ represent covalent bonds between these atoms. Additional information may be incorporated in the form of vertex and edge labels $\mathcal{L} : \mathcal{V} \times \mathcal{E} \to \Sigma_V \times \Sigma_E$, with common label spaces including attributes such as atom types (i.e. hydrogen, carbon) as vertex labels and bond orders (i.e. single, double) as edge labels.

Fingerprints: Operate by assigning initial numeric identifiers to each atom in a molecule. These identifiers are subsequently updated in an iterative fashion based on the identifiers of their neighbours. The number of iterations corresponds to half the *diameter* of the fingerprint and the naming convention reflects this. For example, ECFP6 fingerprints have a diameter of 6, meaning that 3 iterations of atom identifier reassignment are performed. Each level of iteration appends substructural features of increasing non-locality to an array and the array is then hashed to a bit vector reflecting the presence of absence of those substructures in the molecule.

Strings: The Simplified Molecular-Input Line-Entry System (SMILES) is a text-based representation of molecules (Anderson et al., 1987; Weininger, 1988). Self-Referencing Embedded Strings (SELFIES) (Krenn et al., 2020) is an alternative string representation to SMILES such that a bijective mapping exists between a SELFIES string and a molecule.

3. Molecular Kernels

Here we introduce examples of the classes of GAUCHE kernel designed to operate on the molecular representations introduced in section 2.

3.1 Fingerprint Kernels

Scalar Product Kernel: The simplest kernel to operate on fingerprints is the scalar product or linear kernel defined for vectors $\mathbf{x}, \mathbf{x}' \in \mathbb{R}^d$ as

$$k_{\text{Scalar Product}}(\mathbf{x}, \mathbf{x}') \coloneqq \sigma_f^2 \cdot \langle \mathbf{x}, \mathbf{x}' \rangle,$$

where σ_f is a scalar signal variance hyperparameter and $\langle \cdot, \cdot \rangle$ is the Euclidean inner product.

Tanimoto Kernel: First introduced as a general similarity metric for binary attributes (Gower, 1971), the Tanimoto kernel was first used in chemoinformatics in conjunction with non-GP-based kernel methods (Ralaivola et al., 2005). It is defined for binary vectors $\mathbf{x}, \mathbf{x}' \in \{0, 1\}^d$ for $d \geq 1$ as

$$k_{\text{Tanimoto}}(\mathbf{x}, \mathbf{x}') \coloneqq \sigma_f^2 \cdot \frac{\langle \mathbf{x}, \mathbf{x}' \rangle}{\|\mathbf{x}\|^2 + \|\mathbf{x}'\|^2 - \langle \mathbf{x}, \mathbf{x}' \rangle},$$

where $|| \cdot ||$ is the Euclidean norm.

3.2 String Kernels

String kernels (Lodhi et al., 2002; Cancedda et al., 2003) measure the similarity between strings by examining the degree at which their sub-strings differ. In GAUCHE, we implement the SMILES string kernel (Cao et al., 2012) which calculates an inner product between the occurrences of sub-strings, considering all contiguous sub-strings made from at most n characters (we set $n = 5$ in our experiments). Therefore, for the sub-string count featurisation $\phi : \mathcal{S} \to \mathbb{R}^p$ (also known as a bag-of-characters representation (Jurafsky and Martin, 2000)), the SMILES string kernel between two strings $\mathcal{S}$ and $\mathcal{S}'$ is given by

$$k_{\text{String}}(\mathcal{S}, \mathcal{S}') \coloneqq \sigma^2 \cdot \langle \phi(\mathcal{S}), \phi(\mathcal{S}') \rangle.$$

Note that although named the SMILES string kernel, this kernel can also be applied to any other string representation of molecules e.g. SELFIES.

3.3 Graph Kernels

Graph Kernels: Graph kernel methods $\phi_\lambda : \mathcal{G} \to \mathcal{H}$ map elements from a graph domain $\mathcal{G}$ to a reproducing kernel Hilbert space (RKHS) $\mathcal{H}$, in which an inner product between a pair of graphs $g, g' \in \mathcal{G}$ is derived as a measure of similarity

$$k_{\text{Graph}}(g, g') \coloneqq \sigma^2 \cdot \langle \phi_\lambda(g), \phi_\lambda(g') \rangle_{\mathcal{H}},$$

where λ denotes kernel-specific hyperarameters and σ^2 is a scale factor. Depending on how ϕ_λ is defined (Nikolentzos et al., 2021), the kernel considers different substructural motifs and is characterised by different hyperparameters. Frequently-employed approaches include the random walk kernel (Vishwanathan et al., 2010), given by a geometric series over the count of matching random walks of increasing length with coefficient λ, and the Weisfeiler-Lehman kernel (Shervashidze et al., 2011), given by the inner products of label count vectors over λ iterations of the Weisfeiler-Lehman algorithm.

4. Experiments

We evaluate GAUCHE on regression, uncertainty quantification (UQ) and BO. The principle goal in conducting regression and UQ benchmarks is to gauge whether performance on these tasks may be used as a proxy for BO performance. We provide the full results for regression and UQ in Appendix D.2 and Appendix D.3 respectively. BO is a powerful tool for automated scientific discovery but one would prefer to avoid model misspecification in the surrogate when deploying a scheme in the real world. We make use of the following datasets:

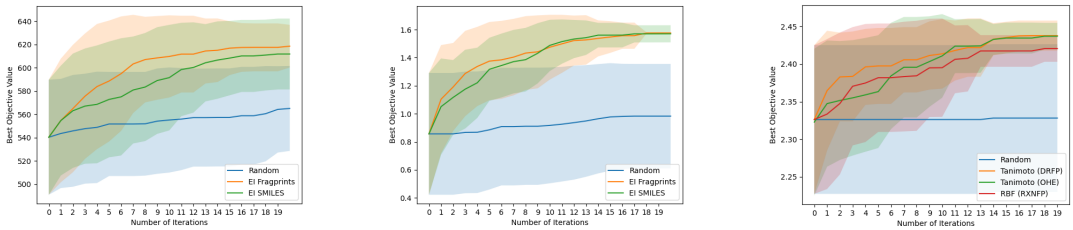
The Photoswitch Dataset: (Thawani et al., 2020): The labels, y are the experimentally-determined values of the E isomer $\pi-\pi^*$ transition wavelength for 392 photoswitch molecules.

ESOL: (Delaney, 2004): The labels y are the experimentally-determined logarithmic aqueous solubility values for 1128 organic small molecules.

Buchwald-Hartwig reactions: (Ahneman et al., 2018): The labels y are the experimentally-determined yields for 3955 Pd-catalysed Buchwald–Hartwig C–N cross-couplings.

4.1 Bayesian Optimisation

We take forward two of the best-performing kernels from the regession and UQ benchmarks, the Tanimoto-fragprint kernel and the bag of SMILES kernel to undertake BO over the photoswitch and ESOL datasets. Random search is used as a baseline. BO is run for 20 iterations of sequential candidate selection (EI acquisition) where candidates are drawn



(a) Photoswitch (b) ESOL (c) Buchwald-Hartwig reactions.

Figure 1: Bayesian optimisation performance. Standard error from 50 random initialisations, 20 for Buchwald-Hartwig.

from 95% of the dataset. The results are provided in Figure 1. The models are initialised with 5% of the dataset. In the case of the photoswitch dataset this corresponds to just 19 molecules. In this ultra-low data setting, common to many areas of synthetic chemistry (Thawani et al., 2020) both models outperform random search, highlighting the real-world use-case for such models in supporting human chemists prioritise candidates for synthesis. Furthermore, one may observe that BO performance is tightly coupled to regression and UQ performance. In the case of the photoswitch dataset, the better-performing Tanimoto model on regression and UQ also achieves relatively better BO performance. Additionally, we report results on the Buchwald-Hartwig reaction dataset.

5. Conclusions and Future Work

We have introduced GAUCHE, a library for GAUssian Processes in CHEmistry with the aim of providing tools for uncertainty quantification and Bayesian optimisation that may hopefully be deployed for screening in laboratory settings. In future work, we seek to:

1. Expand the range of GP kernels we currently consider, most notably to include *deep kernels* based on GNN embeddings.
2. Perform more extensive benchmarking for uncertainty quantification and active learning against models such as BNNs.
3. Exploit the benefits of our autodiff framework to facilitate the learning of graph kernel hyperparameters through the GP marginal likelihood.

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Contents

Appendix A. Further Background

A.1 Gaussian Process Training

Hyperparameters for Gaussian processes comprise kernel hyperparameters, θ in addition to the likelihood noise, σ_y^2. These hyperparameters are chosen by optimising an objective function known as the negative log marginal likelihood (NLML)

$$\log p(\mathbf{y}|\mathbf{X},\theta) = \underbrace{-\frac{1}{2}\mathbf{y}^\top (K_\theta(\mathbf{X},\mathbf{X}) + \sigma_y^2 I)^{-1}\mathbf{y}}_{\text{encourages fit with data}} \underbrace{-\frac{1}{2}\log|K_\theta(\mathbf{X},\mathbf{X}) + \sigma_y^2 I|}_{\text{controls model capacity}} - \frac{N}{2}\log(2\pi).$$

$I\sigma_y^2$ represents the variance of i.i.d. Gaussian noise on the observations $\mathbf{y}$. The NLML embodies Occam's razor for Bayesian model selection (Rasmussen and Ghahramani, 2001) in favouring models that fit the data without being overly complex.

A.2 Bayesian Optimisation

In molecular discovery campaigns we are typically interested in solving problems of the form

$$\mathbf{x}^\star = \arg\max_{\mathbf{x}\in\mathcal{X}} f(\mathbf{x}),$$

where $f(\cdot) : \mathcal{X} \to \mathbb{R}$ is an expensive black-box function over a structured input domain $\mathcal{X}$. In our example setting the structured input domain consists of a set of molecular representations (graphs, strings, bit vectors) and the expensive black-box function is a property of interest for a given molecule that we wish to optimise. Bayesian optimisation (BO) (Kushner, 1963; Močkus, 1975; Zhilinskas, 1975; Jones et al., 1998; Brochu et al., 2010; Grosnit et al., 2020) is a data-efficient methodology for determining $\mathbf{x}^\star$. BO operates sequentially by selecting input locations at which to query the black-box function f with the aim of identifying the optimum in as few queries as possible. This procedure involves the exploration/exploitation tradeoff in the sense that exploiting knowledge about the function to propose promising locations competes with the desire to learn more about the function in unobserved locations.

The two components of a BO scheme are a probabilistic surrogate model and an acquisition function. The surrogate model is typically chosen to be a GP due to its ability to maintain calibrated uncertainty estimates through exact Bayesian inference. The uncertainty estimates of the surrogate model are then leveraged by the acquisition function to propose new input locations to query. The acquisition function is a heuristic that trades off exploration and exploitation, well-known examples of which include expected improvement (EI) (Močkus, 1975; Jones et al., 1998) and entropy search (Hennig and Schuler, 2012; Hernández-Lobato et al., 2014; Wang and Jegelka, 2017; Moss et al., 2021). After the acquisition function proposes an input location, the black-box is evaluated at that location, the surrogate model is retrained and the process repeats *ad libitum* until a solution is obtained. Systematic reviews of the BO literature include (Brochu et al., 2010; Shahriari et al., 2016; Frazier, 2018)

A.3 Fragment and Fragprint Representations

We make use of fragment descriptors which are count vectors, each component of which indicates the number of a certain functional group present in a molecule. For example row 1 of the count vector could be an integer representing the number of aliphatic hydroxl groups present in the molecule. We make use of both fingerprint and fragment features computed using RDKit (Landrum, 2013) as well as the concatenation of the fingerprint and fragment feature vectors, a representation termed fragprints (Thawani et al., 2020) which has shown strong empirical performance. Example representations $\mathbf{x_f}$ for fingerprints and $\mathbf{x_{fr}}$ for fragments are given as

$$\mathbf{x_f} = \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 1 \end{bmatrix}, \quad \mathbf{x_{fr}} = \begin{bmatrix} 3 \\ 0 \\ \vdots \\ 2 \end{bmatrix}.$$

A.4 Reaction Representations

Chemical reactions consist of multiple reactants and reagents that transform into one or more products. The reactants and reagents can often be categorised into different types. Taking the high-throughput experiments by (Ahneman et al., 2018) on Buchwald-Hartwig reactions as an example, the reaction design space consists of 15 aryl and heteroaryl halides, 4 Buchwald ligands, 3 bases, and 23 isoxazole additives.

Concatenated molecular representations: If the number of reactant and reagent categories is constant, the molecular representations discussed above may be used to encode the selected reactants and reagents, and the vectors for the individual reaction components can be concatenated to build the reaction representation (Ahneman et al., 2018; Sandfort et al., 2020). An additional and commonly-used concatenated representation, is the one-hot-encoding (OHE) of the reaction categories where bits specify which of the components in the different reactant and reagent categories is present. In the Buchwald-Hartwig example, the OHE would describe which of the aryl halides, Buchwald ligands, bases and additives are used in the reaction, resulting in a 44-dimensional bit vector (Chuang and Keiser, 2018).

Differential reaction fingerprints: Inspired by the hand-engineered difference reaction fingerprints by Schneider et al. (2015), Probst et al. (2022) recently introduced the differential reaction fingerprint (DRFP). This reaction fingerprint is constructed by taking the symmetric difference of the sets containing the molecular substructures on both sides of the reaction arrow. Reagents are added to the reactants. The size of the reaction bit vector generated by DRFP is independent of the number of reaction components.

Data-driven reaction fingerprints: Schwaller et al. (2021a) described data-driven reaction fingerprints using Transformer models (e.g. BERT (Devlin et al., 2018)) trained in a supervised or an unsupervised fashion on reaction SMILES. Those models can be fine-tuned on the task of interest to learn more specific reaction representations (Schwaller et al.,

2021b) (RXNFP). Similar to the DRFP, the size of the data-driven reaction fingerprints is independent of the number of reaction components.

A.5 Protein Representations

Proteins are large macromolecules that adopt complex 3D structures. Proteins can be represented in string form describing the underlying amino acid sequence. Graphs at varying degrees of coarseness may be used for structural representations that capture spatial and intramolecular relationships between structural elements, such as atoms, residues, secondary structures and chains. GAUCHE interfaces with Graphein (Jamasb et al., 2021), a library for pre-processing and computing graph representations of structural biological data thereby enabling the application of graph kernel-based methods to protein structure.

Appendix B. Related Work

General-purpose GP and Bayesian optimisation libraries do not specifically cater for molecular representations. Likewise, general-purpose molecular machine learning libraries do not specifically consider GPs and Bayesian optimisation. Here, we review existing libraries, highlighting the niche GAUCHE fills in bridging the GP and molecular machine learning communities.

The closest work to ours is FlowMO (Moss and Griffiths, 2020), which introduces a molecular GP library in the GPflow framework. It is on this project which we build, extending the scope of the library to a broader class of molecular representations (graphs), problem settings (Bayesian optimisation) and applications (reaction optimisation and protein engineering).

Gaussian Process Libraries: GP libraries include GPy (Python) (GPy, since 2012), GPflow (TensorFlow) (Matthews et al., 2017; van der Wilk et al., 2020) and GPyTorch (PyTorch) (Gardner et al., 2018) while examples of recent Bayesian optimisation libraries include BoTorch (PyTorch) (Balandat et al., 2020), Dragonfly (Python) (Kandasamy et al., 2020) and HEBO (PyTorch) (Cowen-Rivers et al., 2020). The aforementioned libraries do not explicitly support molecular representations. Extension to cover molecular representations however is nontrivial, requiring implementations of bespoke GP kernels for bit vector, string and graph inputs together with modifications to Bayesian optimisation schemes to consider acquisition function evaluations over a discrete set of heldout molecules, a setting commonly encountered in virtual screening campaigns (Pyzer-Knapp, 2020; Graff et al., 2022).

Molecular Machine Learning Libraries: Molecular machine learning libraries include DeepChem (Ramsundar et al., 2019), DGL-LifeSci (Li et al., 2021) and TorchDrug (Zhu et al., 2022). DeepChem features a broad range of model implementations and tasks, while DGL-LifeSci focuses on graph neural networks. TorchDrug caters for applications including property prediction, representation learning, retrosynthesis, biomedical knowledge graph reasoning and molecule generation.

GP implementations are not included, however, in the aforementioned libraries. In terms of atomistic systems, DScribe (Himanen et al., 2020) features, amongst other methods, the Smooth Overlap of Atomic Positions (SOAP) representation Bartók et al. (2013) which is

typically used in conjunction with a GP model to learn atomistic properties. Automatic Selection And Prediction (ASAP) (Cheng et al., 2020) also principally focusses on atomistic properties as well as dimensionality reduction and visualisation techniques for materials and molecules. Lastly, the Graphein library focusses on graph representations of proteins (Jamasb et al., 2021).

Graph Kernel Libraries: Graph kernel libraries include GraKel (Siglidis et al., 2020), graphkit-learn (Jia et al., 2021), graphkernels (Sugiyama et al., 2018), graph-kernels (Sugiyama and Borgwardt, 2015), pykernels (https://github.com/gmum/pykernels) and ChemoKernel (Gaüzére et al., 2012). The aforementioned libraries focus on CPU implementations in Python. Extending graph kernel computation to GPUs has been noted as an important direction for future research (Ghosh et al., 2018). In our work, we build on the GraKel library by interfacing it with GPyTorch, facilitating GP regression with GPU computation. Furthermore, we enable the graph kernel hyperparameters to be learned through the marginal likelihood objective as opposed to being pre-specified and fixed upfront.

Molecular Bayesian Optimisation: BO over molecular space can be divided into two classes of methods. In the first class, molecules are encoded into the latent space of a variational autoencoder (VAE) (Gómez-Bombarelli et al., 2018). BO is then performed over the continuous latent space and queried molecules are decoded back to the original space. Much work on VAE-BO has focussed on improving the synergy between the surrogate model and the VAE (Griffiths et al., 2021; Griffiths and Hernández-Lobato, 2020; Tripp et al., 2020; Deshwal and Doppa, 2021; Grosnit et al., 2021; Verma and Chakraborty, 2021; Maus et al., 2022; Stanton et al., 2022). One of the defining characteristics of VAE-BO is that it enables the generation of new molecular structures.

In the second class of methods, BO is performed directly over the original discrete space of molecules. In this setting it is not possible to generate new structures and so a candidate set of queryable molecules is defined. The inability to generate new structures however, is not a bottleneck to molecule discovery as the principle concern is how best to explore existing candidate sets. These candidate sets are also known as molecular libraries in the virtual screening literature (Pyzer-Knapp et al., 2015).

To date, there has been little work on BO directly over discrete molecular spaces. In Moss et al. (2020), the authors use a string kernel GP trained on SMILES to perform BO to select from a candidate set of molecules. In Korovina et al. (2020), an optimal transport kernel GP is used for BO over molecular graphs. In Häse et al. (2021a) a surrogate based on the Nadarya-Watson estimator is defined such that the kernel density estimates are inferred using BNNs. The model is then trained on molecular descriptors. Lastly, in Hernández-Lobato et al. (2017) and Vakili et al. (2021) a BNN and a sparse GP respectively are trained on fingerprint representations of molecules. In the case of the sparse GP the authors select an ArcCosine kernel. It is a long term aim of the GAUCHE Project to compare the efficacy of VAE-BO against vanilla BO on real-world molecule discovery tasks.

Chemical Reaction Optimisation: Chemical reactions describe how reactant molecules transform into product molecules. Reagents (catalysts, solvents, and additives) and reaction conditions heavily impact the outcome of chemical reactions. Typically the objective is to

maximise the reaction yield (the amount of product compared to the theoretical maximum) (Ahneman et al., 2018), in asymmetric synthesis, where the reactions could result in different enantiomers, to maximise the enantiomeric excess (Zahrt et al., 2019), or to minimise the E-factor, which is the ratio between waste materials and the desired product (Schweidtmann et al., 2018).

A diverse set of studies have evaluated the optimisation of chemical reactions in single and multi-objective settings (Schweidtmann et al., 2018; Müller et al., 2022). Felton et al. (2021) and Häse et al. (2021b) benchmarked reaction optimisation algorithms in low-dimensional settings including reaction conditions, such as time, temperature, and concentrations. Shields et al. (2021) suggested BO as a general tool for chemical reaction optimisation and benchmarked their approach against human experts. Haywood et al. (2021) compared the yield prediction performance of different kernels and Pomberger et al. (2022) the impact of various molecular representations.

In all reaction optimisation studies above, the representations of the different categories of reactants and reagents are concatenated to generate the reaction input vector, which could lead to limitations if another type of reagent is suddenly considered. Moreover, most studies concluded that simple one-hot encodings (OHE) perform at least on par with more elaborate molecular representations in the low-data regime (Shields et al., 2021; Pomberger et al., 2022; Hickman et al., 2022). In GAUCHE, we introduce reaction fingerprint kernels, based on existing reaction fingerprints (Schwaller et al., 2021a; Probst et al., 2022) and work independently of the number of reactant and reagent categories.

Appendix C. Coding Kernels in GAUCHE

We provide an example of the class definition for the Tanimoto kernel in GAUCHE below

```
class TanimotoGP(ExactGP):
    def __init__(self, train_x, train_y, likelihood):
        super(TanimotoGP, self).__init__(train_x,
                                         train_y,
                                         likelihood)
        self.mean_module = ConstantMean()
        # We use the Tanimoto kernel to work with
        # molecular fingerprint representations
        self.covar_module = ScaleKernel(TanimotoKernel())

    def forward(self, x):
        mean_x = self.mean_module(x)
        covar_x = self.covar_module(x)
        return MultivariateNormal(mean_x, covar_x)
```

and an example definition of a black box kernel (where gradients with respect to hyperparameters and input labels are not required).

```
class WLKernel(gauche.Kernel):
    def __init__(self):
        super().__init__()
        self.kernel = grakel.kernels.WeisfeilerLehman()

    @lru_cache(maxsize=3)
    def kern(self, X):
        return tensor(self.kernel.fit_transform(X.data))
```

```
class GraphGP(gauche.SIGP):
    def __init__(self, train_x, train_y, likelihood):
        super().__init__(train_x, train_y, likelihood)
        self.mean = ConstantMean()
        self.covariance = WLKernel()

    def forward(self, X):
        # X is a gauche.Inputs instance, with X.data
        # holding a list of grakel.Graph instances.
        mean = self.mean(zeros(len(X.data), 1))
        covariance = self.covariance(X)
        return MultivariateNormal(mean, covariance)
```

Importantly, GAUCHE inherits all the facilities of GPyTorch and GraKel allowing a broad range of of models to be defined on molecular inputs such as deep GPs, multioutput GPs and heteroscedastic GPs.

Appendix D. Further Experiments

D.1 Further Datasets

We include here the additional datasets used for the regression and uncertainty quantification benchmarks.

FreeSolv: (Mobley and Guthrie, 2014): The labels y are the experimentally-determined hydration free energies for 642 molecules.

Lipophilicity: Thpe labels y are the experimentally-determined octanol/water distribution coefficient (log D at pH 7.4) of 4200 compounds curated from the ChEMBL database (Gaulton et al., 2012; Bento et al., 2014).

Suzuki-Miyaura reactions: (Perera et al., 2018): The labels y are the experimentally-determined yields for 5760 Pd-catalysed Suzuki-Miyaura C-C cross-couplings.

D.2 Regression

The regression results for molecular property prediction are reported in Table D1 and for reaction yield prediction in Table D3 of subsection D.4. The datasets are split in a train/test ratio of 80/20 (note that validation sets are not required for the GP models since training uses the marginal likelihood objective). Errorbars represent the standard error across 20 random initialisations. All GP models are trained using the L-BFGS-B optimiser Liu and Nocedal (1989). If not mentioned, default settings in the GPyTorch and BoTorch libraries apply. For the SELFIES representation, some molecules could not be featurised and corresponding entries are left blank. The results of Table D3 indicate that the best choice of representation (and hence the choice of kernel) is task-dependent.

D.3 Uncertainty Quantification (UQ)

To quantify the quality of the uncertainty estimates we use three metrics, the negative log predictive density (NLPD), the mean standardised log loss (MSLL) and the quantile coverage error (QCE). We provide the NLPD results in Table D2 and defer the MSLL and

Table D1: Molecular property prediction regression benchmark. RMSE values for 80/20 train/test split across 20 random trials.

GP Model		**Dataset**			
Kernel	Representation	Photoswitch	ESOL	FreeSolv	Lipophilicity
Tanimoto	fragprints	$\mathbf{20.9 \pm 0.7}$	0.71 ± 0.01	1.31 ± 0.06	$\mathbf{0.67 \pm 0.01}$
	fingerprints	23.4 ± 0.8	1.01 ± 0.01	1.93 ± 0.09	0.76 ± 0.01
	fragments	26.3 ± 0.8	0.91 ± 0.01	1.49 ± 0.05	0.80 ± 0.01
Scalar Product	fragprints	22.5 ± 0.7	0.88 ± 0.01	$\mathbf{1.27 \pm 0.02}$	0.77 ± 0.01
	fingerprints	24.8 ± 0.8	1.17 ± 0.01	1.93 ± 0.07	0.84 ± 0.01
	fragments	36.6 ± 1.0	1.15 ± 0.01	1.63 ± 0.03	$0.97. \pm 0.01$
String	SELFIES	24.9 ± 0.6	-	-	-
	SMILES	24.8 ± 0.7	$\mathbf{0.66 \pm 0.01}$	1.31 ± 0.01	$\mathbf{0.68 \pm 0.01}$
WL Kernel (GraKel)	graph	22.4 ± 1.4	1.04 ± 0.02	1.47 ± 0.06	0.74 ± 0.05

QCE results to subsection D.5. One trend to note is that uncertainty estimate quality is roughly correlated with regression performance.

Table D2: UQ benchmark. NLPD values for 80/20 train/test split across 20 random trials.

GP Model		**Dataset**			
Kernel	Representation	Photoswitch	ESOL	FreeSolv	Lipophilicity
Tanimoto	fragprints	$\mathbf{0.22 \pm 0.03}$	0.33 ± 0.01	0.28 ± 0.02	$\mathbf{0.71 \pm 0.01}$
	fingerprints	0.33 ± 0.03	0.71 ± 0.01	0.58 ± 0.03	0.85 ± 0.01
	fragments	0.50 ± 0.04	0.57 ± 0.01	0.44 ± 0.03	0.94 ± 0.02
Scalar Product	fragprints	$\mathbf{0.23 \pm 0.03}$	0.53 ± 0.01	0.25 ± 0.02	0.92 ± 0.01
	fingerprints	0.33 ± 0.03	0.84 ± 0.01	0.64 ± 0.03	1.03 ± 0.01
	fragments	0.80 ± 0.03	0.82 ± 0.01	0.54 ± 0.02	0.88 ± 0.10
String	SELFIES	0.37 ± 0.04	-	-	-
	SMILES	0.30 ± 0.04	$\mathbf{0.29 \pm 0.03}$	$\mathbf{0.16 \pm 0.02}$	$\mathbf{0.72 \pm 0.01}$
WL Kernel (GraKel)	graph	0.39 ± 0.11	0.76 ± 0.001	0.47 ± 0.02	-

D.4 Chemical Reaction Yield Prediction Experiments

Further regression and uncertainty quantification experiments are presented in Table D3. The differential reaction fingerprint in conjunction with the Tanimoto kernel is the best-performing reaction representation.

Table D3: Chemical reaction regression benchmark. 80/20 train/test split across 20 random trials.

GP Model		**Buchwald-Hartwig**			
Kernel	Representation	RMSE ↓	R^2 score ↑	MSLL ↓	QCE ↓
Tanimoto	OHE	7.94 ± 0.05	0.91 ± 0.001	-0.06 ± 0.002	0.011 ± 0.001
	DRFP	$\mathbf{6.48 \pm 0.45}$	$\mathbf{0.94 \pm 0.015}$	$\mathbf{-0.15 \pm 0.07}$	0.027 ± 0.002
Scalar Product	OHE	15.23 ± 0.052	0.69 ± 0.002	0.57 ± 0.002	0.008 ± 0.001
	DRFP	14.63 ± 0.050	0.71 ± 0.002	0.55 ± 0.002	0.010 ± 0.001
RBF	RXNFP	10.79 ± 0.049	0.84 ± 0.001	0.37 ± 0.005	0.024 ± 0.001
		Suzuki-Miyaura			
Tanimoto	OHE	11.18 ± 0.036	0.83 ± 0.001	0.23 ± 0.001	0.007 ± 0.001
	DRFP	11.46 ± 0.038	0.83 ± 0.001	0.25 ± 0.006	0.019 ± 0.000
Scalar Product	OHE	19.91 ± 0.042	0.47 ± 0.003	0.82 ± 0.001	0.012 ± 0.001
	DRFP	19.66 ± 0.042	0.52 ± 0.003	0.81 ± 0.001	0.014 ± 0.001
RBF	RXNFP	13.83 ± 0.048	0.75 ± 0.002	0.50 ± 0.001	0.007 ± 0.001

D.5 Uncertainty Quantification Experiments

In Table D4 and Table D5 we present further uncertainty quantification metrics. Numerical errors were encountered with the WL kernel on the large lipophilicity dataset which invalidated the results and so the corresponding entry is left blank. The native random walk kernel was discontinued (for the time being) due to poor performance!

Table D4: UQ Benchmark. MSLL Values (↓) for 80/20 Train/Test Split.

GP Model		**Dataset**			
Kernel	Representation	Photoswitch	ESOL	FreeSolv	Lipophilicity
Tanimoto	fragprints	$\mathbf{0.06 \pm 0.01}$	0.17 ± 0.04	0.16 ± 0.02	$\mathbf{0.50 \pm 0.006}$
	fingerprints	0.16 ± 0.01	0.55 ± 0.01	0.42 ± 0.02	0.63 ± 0.004
	fragments	0.27 ± 0.01	0.34 ± 0.04	0.24 ± 0.02	0.72 ± 0.003
Scalar Product	fragprints	0.03 ± 0.01	0.32 ± 0.004	0.06 ± 0.01	0.67 ± 0.003
	fingerprints	0.11 ± 0.01	0.64 ± 0.006	0.41 ± 0.02	0.79 ± 0.003
	fragments	0.56 ± 0.01	0.58 ± 0.005	0.29 ± 0.01	0.94 ± 0.003
String	SELFIES	0.13 ± 0.01	-	-	-
	SMILES	$\mathbf{0.08 \pm 0.02}$	$\mathbf{0.03 \pm 0.005}$	$\mathbf{0.03 \pm 0.02}$	$\mathbf{0.52 \pm 0.002}$
WL Kernel (GraKel)	graph	0.14 ± 0.03	0.54 ± 0.01	0.26 ± 0.01	-

Table D5: UQ benchmark. QCE values (↓) for 80/20 train/test split across 20 random trials.

GP Model		**Dataset**			
Kernel	Representation	Photoswitch	ESOL	FreeSolv	Lipophilicity
Tanimoto	fragprints	$\mathbf{0.019 \pm 0.003}$	0.023 ± 0.002	0.023 ± 0.002	0.006 ± 0.002
	fingerprints	0.023 ± 0.003	0.022 ± 0.002	0.018 ± 0.003	0.006 ± 0.001
	fragments	0.025 ± 0.005	0.012 ± 0.002	0.014 ± 0.002	0.009 ± 0.002
Scalar Product	fragprints	0.033 ± 0.006	0.010 ± 0.002	0.017 ± 0.003	0.010 ± 0.001
	fingerprints	0.036 ± 0.006	0.014 ± 0.002	0.016 ± 0.002	0.009 ± 0.001
	fragments	0.027 ± 0.004	0.012 ± 0.003	0.021 ± 0.003	0.010 ± 0.001
String	SELFIES	0.031 ± 0.006	-	-	-
	SMILES	0.024 ± 0.003	0.016 ± 0.002	0.019 ± 0.003	0.005 ± 0.001
WL Kernel (GraKel)	graph	0.025 ± 0.007	0.011 ± 0.004	0.019 ± 0.009	0.066 ± 0.014