

I would like to dedicate this thesis to the loss of sleep never to be recovered. It's sacrifice in making this project come to fruition will never be forgotten.

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Saturday 7th May, 2022 – 05:19

Declaration

The work described in this report is the result of my own research, unaided except as specifically acknowledged in the text, and it does not contain material that has already been used to any substantial extent for a comparable purpose. This report contains 39 pages and 9000 words (excluding this page, the title page, and the safety appendix).

Ross Brown
May 2022

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Saturday 7th May, 2022 – 05:19

Acknowledgements

And I would like to acknowledge ...

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Abstract

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Nomenclature

Chapter 2

N	Number of features/dimensions of x
x	Data points where $x = \{x_0, x_1, \dots, x_{N-1}\}$
y	Labels for the dataset where $y = \{y_0, y_1, \dots, y_{N-1}\}$
AC_{50}	Half maximal effective molar concentration
EC_{50}	Half maximal effective molar concentration
IC_{50}	Half maximal inhibitory molar concentration
Ki	Half maximal molar concentration for half receptor occupancy
LD_{50}	Median lethal dose
XC_{50}	Half maximal effective or inhibitory molar concentration

Chapter 3

X_{test}	Datasets used to provide a score for the algorithms
X_{train}	Datasets used for training the algorithms
x_{known}	Data points where the true label is available to the algorithms used
x_{unknown}	Data points where the true label is not available to the algorithms used
y_{known}	True labels available to the algorithms used
y_{unknown}	True labels unavailable to the algorithms used

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Chapter 1

Introduction

In 2019, human civilisation was on the precipice of a natural disaster: SARS-CoV-2 (COVID-19). First reported to the World Health Organization (WHO) on December 31st, it became officially recognised as a pandemic on March 11th 2020. As of the writing of this passage, 515 million cases and 18 million excess deaths have been recorded [Wan+22; Wor22]. This, however, is not the first time a pandemic has occurred, with the Black Death infamously killing a third of Europe's population and the Spanish Flu causing mass death throughout the world. Likewise, it is unlikely to be the last.

When such a disaster does strike, it is important to react quickly. Vaccinations are allowed accelerated timelines in development cutting development from years to month, and trials into potential treatments are encouraged with haste. Within the first stages of the pandemic, drugs such as hydroxychloroquine and bleach were amongst several that were promoted by the President of the United States of America demonstrating the desperation in finding therapeutic drugs against the virus.

In order to facilitate a more robust approach to finding treatments, the FDA instigated the Coronavirus Treatment Acceleration Program (CTAP) [Cen22]. Here, over 690 drugs are in the development stage with over 450 clinical trials underway to investigate the effectiveness, with 15 drugs currently authorised for emergency use and only one drug, remdesivir, with approval for use against COVID-19 [Cen22]. Indeed, remdesivir is an important case. This drug was developed initially for hepatitis-c before being used for several other conditions until finally being used for COVID-19 [Par+20]. This demonstrates how a discovered drug can be repurposed for new diseases providing a cheap means of drug "redevelopment".

Investigations into pre-existing drugs, however, were slow and largely carried out through labour intensive mechanisms without a rational methodical testing regime. This added time to finding treatments to COVID-19. Time many did not have. A hopeful fulfilment of this problem is the "Robot Scientist"; a fully automated combination of software and hardware

1 aimed at solving this problem. For the software side, a form of reinforcement machine
2 learning is proposed: active learning. This is a methodology suited to fields with large
3 amounts of unlabelled data which is difficult to label. In this case, the labelling requires
4 chemical and biological experimentation costing both time and money. By using Active
5 Learning, as few drugs as possible will be labelled within this stage to accurately predict
6 the best drugs for the given problem. From here, clinical trials may begin. Additionally,
7 due to the large importance of time, many drugs may be tested in parallel. This presents an
8 additional problem: how does one set up a testing scheme for batches.

9 Thus, the purpose of this thesis. To present an algorithm which may be used to discover
10 effective drugs within a short period of time. Additionally, a framework will be developed
11 that allows for different algorithms to be rigorously compared to each other for increased
12 robustness.

Chapter 2

Previous Work

Scores displayed in examples have been based on the entire data set. Although this usually leads to data leakage within machine learning, this is not a concern here as the true comparison comes from testing *intelligent* vs *dumb* learning methods. In both of these cases, the model is kept identical, but the selection process is not. The baseline simply takes the first n entries from the data set, with the *intelligent* method described where required. A simple function has been used to present data as a means of demonstrating these models, with x having two dimensions. The function for y is shown in 2.1 and displayed graphically in Figure 2.1.

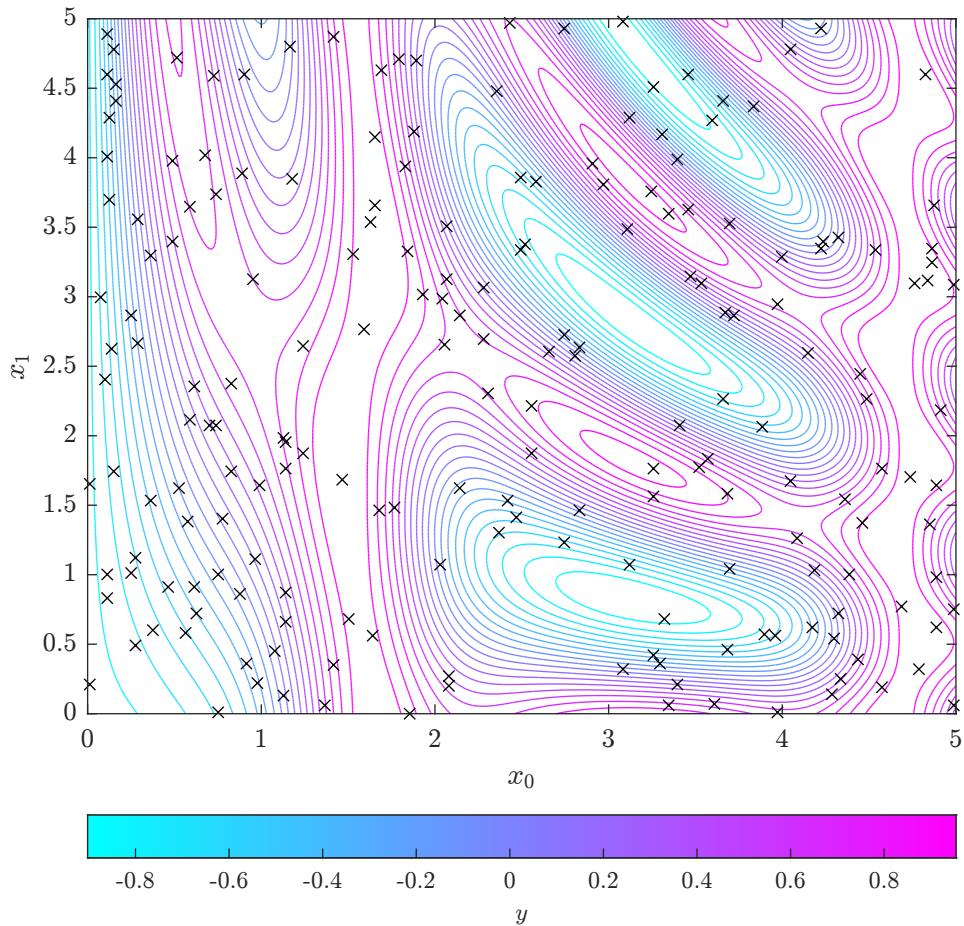


Fig. 2.1 Contour plot of the function used to demonstrate the algorithms presented in previous work. The crosses have been used to show the location of the 200 test data points used within this example.

$$y = \sin(x_1)^{10} + \cos(10 + x_1 x_2) \cos(x_1) \quad (2.1)$$

2.1 Active Learning

There are several schools of thought regarding active learning. These can be separated into two distinct categories: current data and future predictions. The former of these is computationally cheaper, as will be apparent on description.

2.1.1 Current Data

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Uncertainty Sampling and Regions of Disagreements

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The simplest is applicable to cases in which a certainty is provided with each prediction. Settles [Set09] suggests selecting the data point with the largest uncertainty according to the current model. Using the dataset ”, this is demonstrated in Figure 2.2 with the algorithm for deciding the next sample point given in Algorithm 1.

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Algorithm 1: Uncertainty Sampling Selection**Data:** X_{known} , Y_{known} , X_{unknown} **Result:** Next X to label

model = BayesianRidge();

model.fit(X_{known} , Y_{known});standard_deviation = model.standard_deviation(X_{unknown});**return** $\max(\text{standard_deviation})$

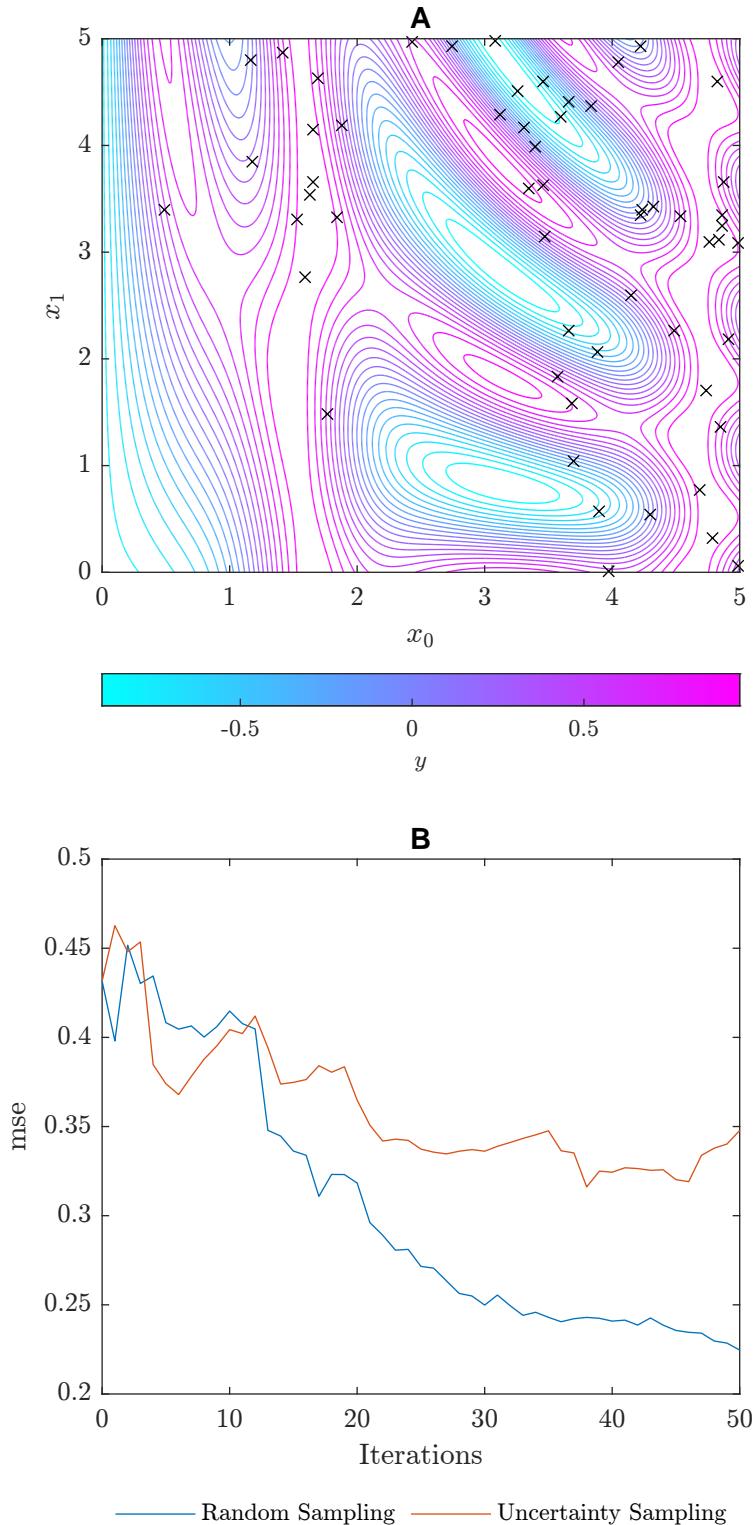


Fig. 2.2 The outcome of the investigating the areas of the highest uncertainty. An initial set of 5 random points was provided, and 50 further iterations were then carried out of sample size 1. A) Demonstrates the final set of points tested by the algorithm and B) shows the change in the mean squared error for the algorithm after each iteration.

Interestingly, Figure 2.2B shows how the mean squared error for the random sampling method performed to worse within the iterations tested. This is likely due to a bias in the use of linear models in fitting leading to large uncertainties surrounding areas with high curvature. Evidence to this is provided in 2.2A with a large proportion of the sampled points at areas of high curvature.

As addressed by Settles [Set09], this can be extended to any probabilistic model through 2.2. Settles [Set09] also notes the use of information theory for probabilistic models(2.3), where y_i refers to all possible categorisations for x . This derives from the principle that the greatest entropy requires the most information to encode, and thus the least certain. However, Settles [Set09] fails to address non-probabilistic models in this instance, instead converting such models into probabilistic ones.

$$x_{\text{next}} = \underset{X}{\operatorname{argmax}} [s_{g(X)}] \quad (2.2)$$

In order to adapt non-probabilistic models into probabilistic ones, composite models may be used. These are an amalgamation of other models where the standard deviation of the individual models can be taken as the degree of certainty for a given point. Many authors have called this as minimising the region of disagreement as it attempts to produce a coherent hypothesis space. By minimising the region of disagreement between various models, a finer fit may be achieved. Indeed, this was the method used in Figure 2.2.

One way of achieving this, especially in a regression model where boundaries are not quite so distinct, is to declare n models $M = \{m_1, \dots, m_n\}$. Combining these allow for a model \hat{m} to be defined with prediction \hat{y} , being the mean prediction of M , $\frac{1}{n} \sum y_i$ and a sample standard deviation \hat{s} defined as the sample standard deviation of y_i . This standard deviation can be used as a measure of the disagreement between the models.

$$x_{\text{next}} = \underset{x}{\operatorname{argmax}} \left[- \sum_i P(y_i|x) \ln P(y_i|x) \right] \quad (2.3)$$

Broad Knowledge Base

A second form stems from information theory. Here, the aim is to produce an evenly dispersed x allowing a well-informed knowledge base. This prevents poor model choice from influencing the algorithm as was seen in 2.2. There are two paths to proceed: density and nearest neighbours.

The former of these requires a definition of density in a sparsely populated space. As an analogy, although the density of a gas appears well-defined, it becomes non-smooth once the

¹ volume defined over is comparable to the distance between particles. Thus, a new definition
² is required.

³ Alternatively, nearest neighbour requires little explanation. x_{next} is the unlabelled data
⁴ point furthest from any labelled data point. The results of 2.4 can be seen in Figure 2.3.

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$$x_{\text{next}} = \operatorname{argmax}_x \left(\sum \frac{1}{\text{sim}(x, x_i)} \right) \quad (2.4)$$

2.1 Active Learning

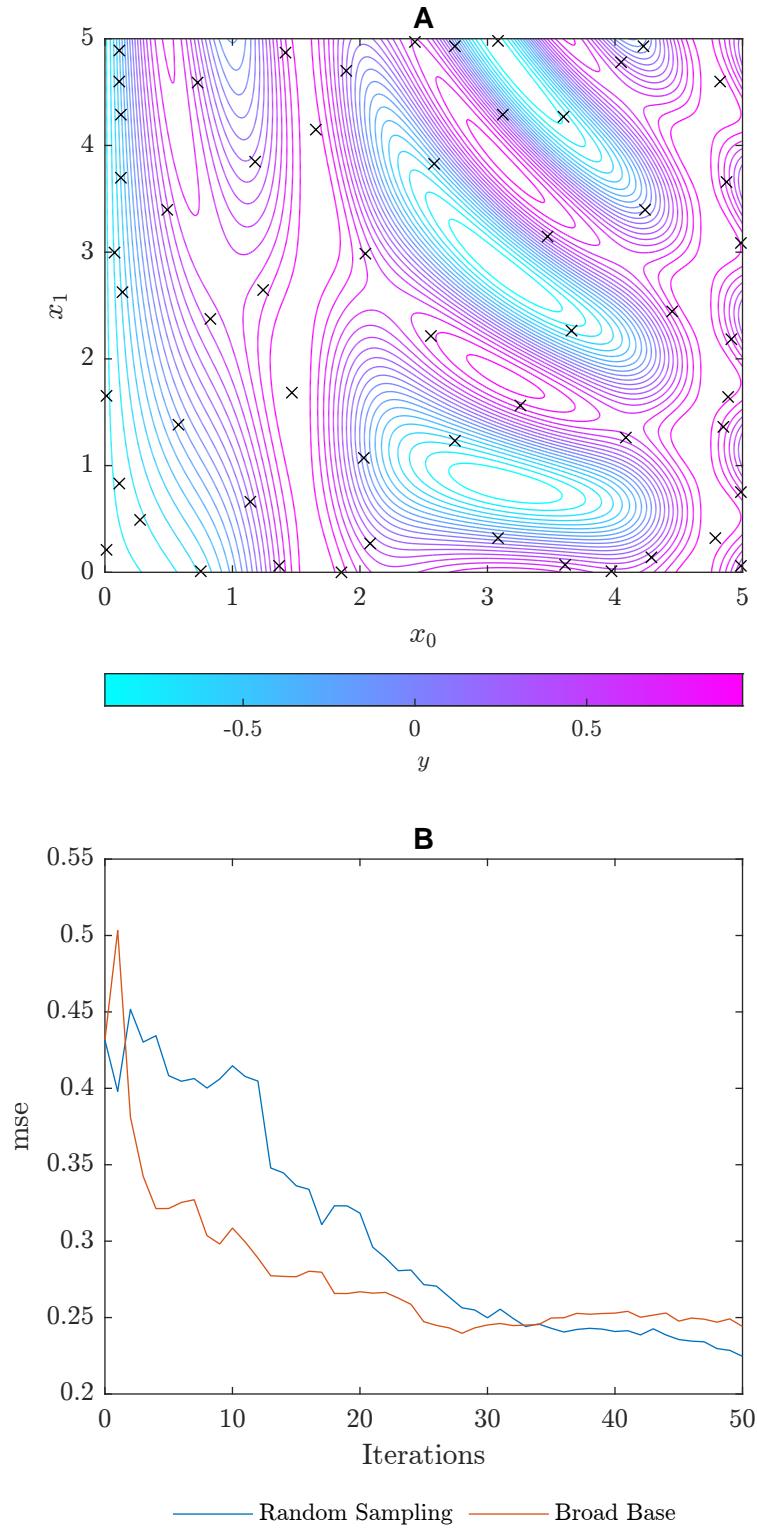


Fig. 2.3 The outcome of the investigating the areas of using a broad base. An initial set of 5 random points was provided, and 50 further iterations were then carried out of sample size 1. A) Demonstrates the final set of points tested by the algorithm and B) shows the change in the mean squared error for the algorithm after each iteration.

1 Density Hotspots

2 Conversely, a density weighted model has been suggested, as it escapes the introduction of
 3 error from outliers (i.e. data points far away from alternative data points). Settles and Craven
 4 [SC08] suggest (2.5) which can be broken down into two parts: a function for selection, ϕ_A ,
 5 and a function for similarity, sim. The former arises from another method described in this
 6 section. The latter requires a function to describe the similarity between data points.

$$7 \quad x_{\text{next}} = \underset{x}{\operatorname{argmax}} \left[\phi_A(x) \times \left(\frac{1}{U} \sum \text{sim}(x, x_i) \right)^\beta \right] \quad (2.5)$$

8 Settles and Craven [SC08] admits that sim is open for interpretation. It is also recognised
 9 that this lays the foundation of a clusterisation algorithm. There exist many forms of these
 10 algorithms, with the results of several of these algoritms on toy data sets presented in
 11 Figure 2.4 [Sci].

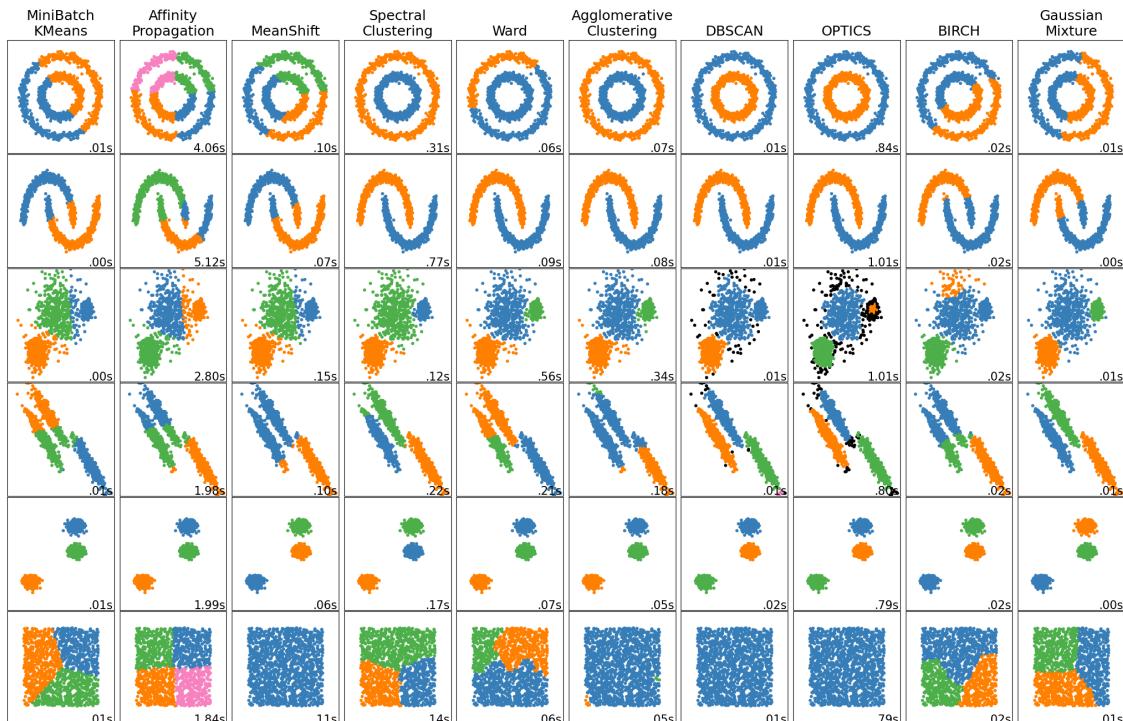


Fig. 2.4 Clusterisation algorithms used on sample two-dimensional data sets to demonstrate resultant clusters.

12 As demonstrated by 2.4 demonstrates, there are multiple different interpretations of the
 13 solution to the problem of clustering. The makers of the Sci-kit learn package also discuss the
 14 scalability of each algorithm [Sci]. In order to prepare a high number of features (beyond the

2.1 Active Learning**11**

two used within this section for demonstration) and large number of data points, it is required that the algorithm scales accordingly. Further, for an adaptive process, it is more suitable for an algorithm to be adaptive to differing distribution. This limits the suitable algorithms to K-Means, Ward and Birch - columns one, five, and nine of Figure 2.4 respectively. Targetting the largest clusters qithout a known result,

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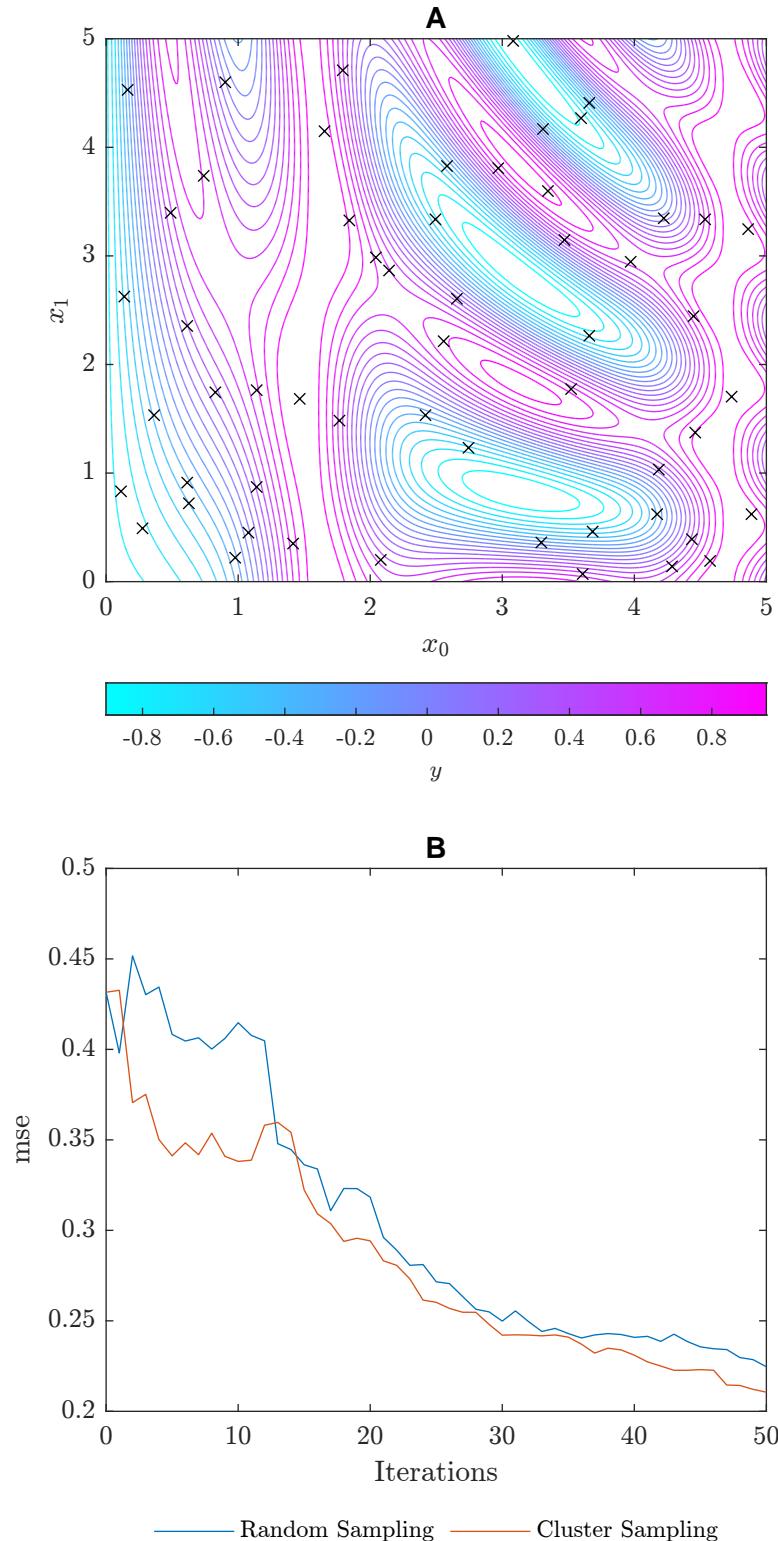


Fig. 2.5 The outcome of the investigating the areas of using a cluster hotspot sampling methodology. An initial set of 5 random points was provided, and 50 further iterations were then carried out of sample size 1. A) Demonstrates the final set of points tested by the algorithm and B) shows the change in the mean squared error for the algorithm after each iteration.

2.1.2 Estimated Future

These methods attempt to minimise a future attribute of the model. This works by predicting changes given with the inclusion of more data.

Expected Model Change

As the name implies, this method chooses points which are likely to have the largest impact on the final model. By instigating each potential point, the impact on the eventual model can be found. However, this requires a method for quantifying the model change.

Settles and Craven [SC08] and Settles [Set09] investigate models which can be trained "online": i.e. models which can use the previous iteration to reduce the time taken for convergence. They present a method called "Expected Gradient Length" (EGL) which has a couple of prerequisites: **1)** A probabilistic model is used **2)** Linear gradient based optimisation is used **3)** The model can be improved from previous iterations. Given these prerequisites, the problem becomes less computationally inexpensive given a small dataset or extensive parallelisation, and scales as $\mathcal{O}(n)$. However, it does have the distinct drawback of requiring close control of the data models used. Here, the length of the training gradient (the gradient used in re-fitting the parameters with gradient based optimisation) can be used as a measure of model change. In the case of a small model change, as is expected, the length of the training gradient can be written as $\|\nabla l(\langle x, y_i \rangle; \theta)\|$. Combining this with the probability distribution of y , the next sample to undergo labelling is given by 2.6.

$$x_{EGL}^* = \operatorname{argmax}_x \sum_i P(y_i|x; \theta) \|\nabla l(\langle x, y_i \rangle; \theta)\| \quad (2.6)$$

2.2 Batch Active Learning

Several naive methods are available here. Firstly, getting the top N data points from a model described in Section. However, this method does not take into account the equivalence of the data points. This is extremely clear using the highest uncertainty method. Each method in Section[] has been modified to demonstrate this weakness.

It stands to reason that the area which has the highest uncertainty will see this for the data points nearest neighbours. Thus, this singular data point suffers the potential of being surrounded by $N - 1$ other data points. The benefit this provides in fitting the model is thus extremely limited, and only slightly greater than if one data point had been chosen. A simple fix would be to simulate the model after 1 iteration, and select the next point from here.

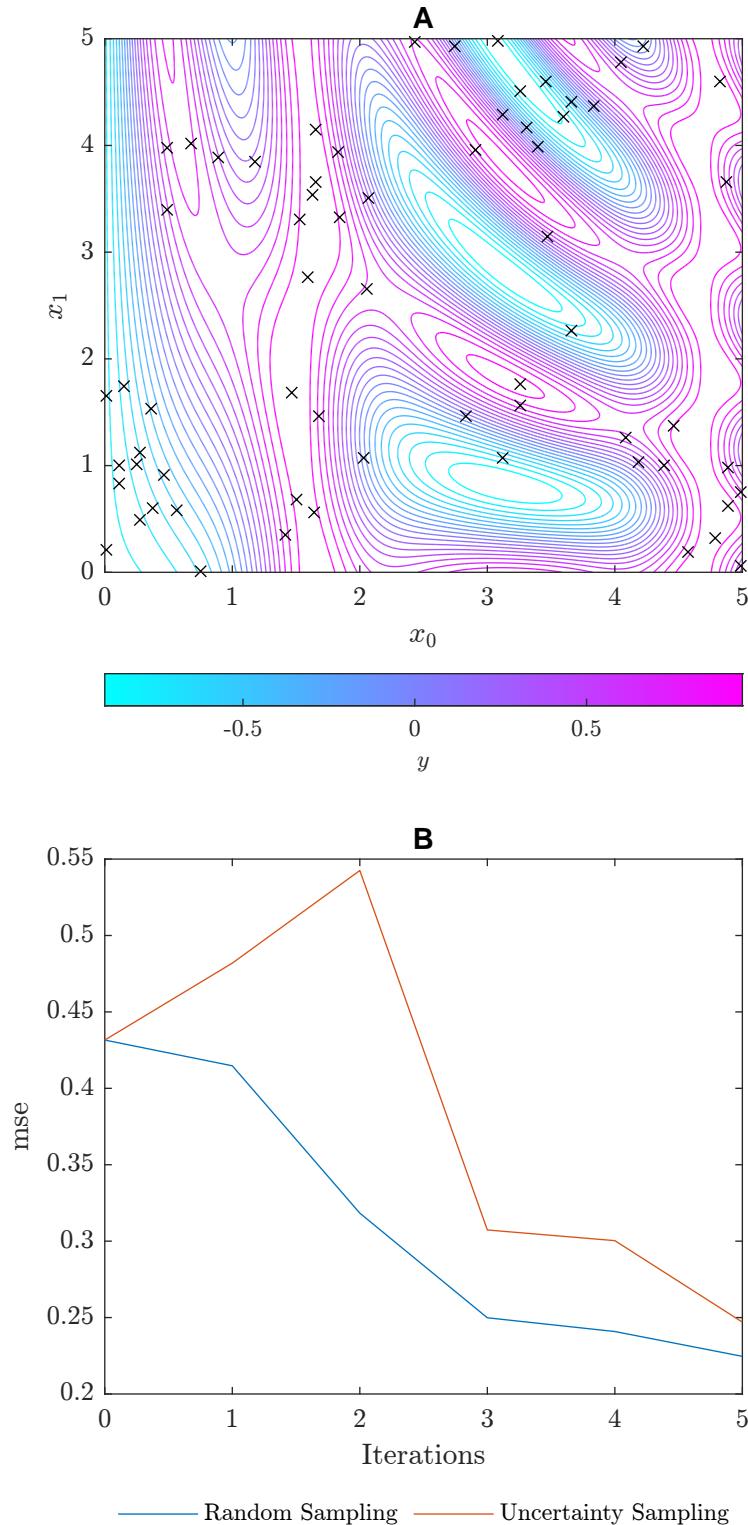


Fig. 2.6 The outcome of the investigating the areas of using uncertainty sampling. An initial set of 5 random points was provided, and 5 further iterations were then carried out of sample size 10. A) Demonstrates the final set of points tested by the algorithm and B) shows the change in the mean squared error for the algorithm after each iteration.

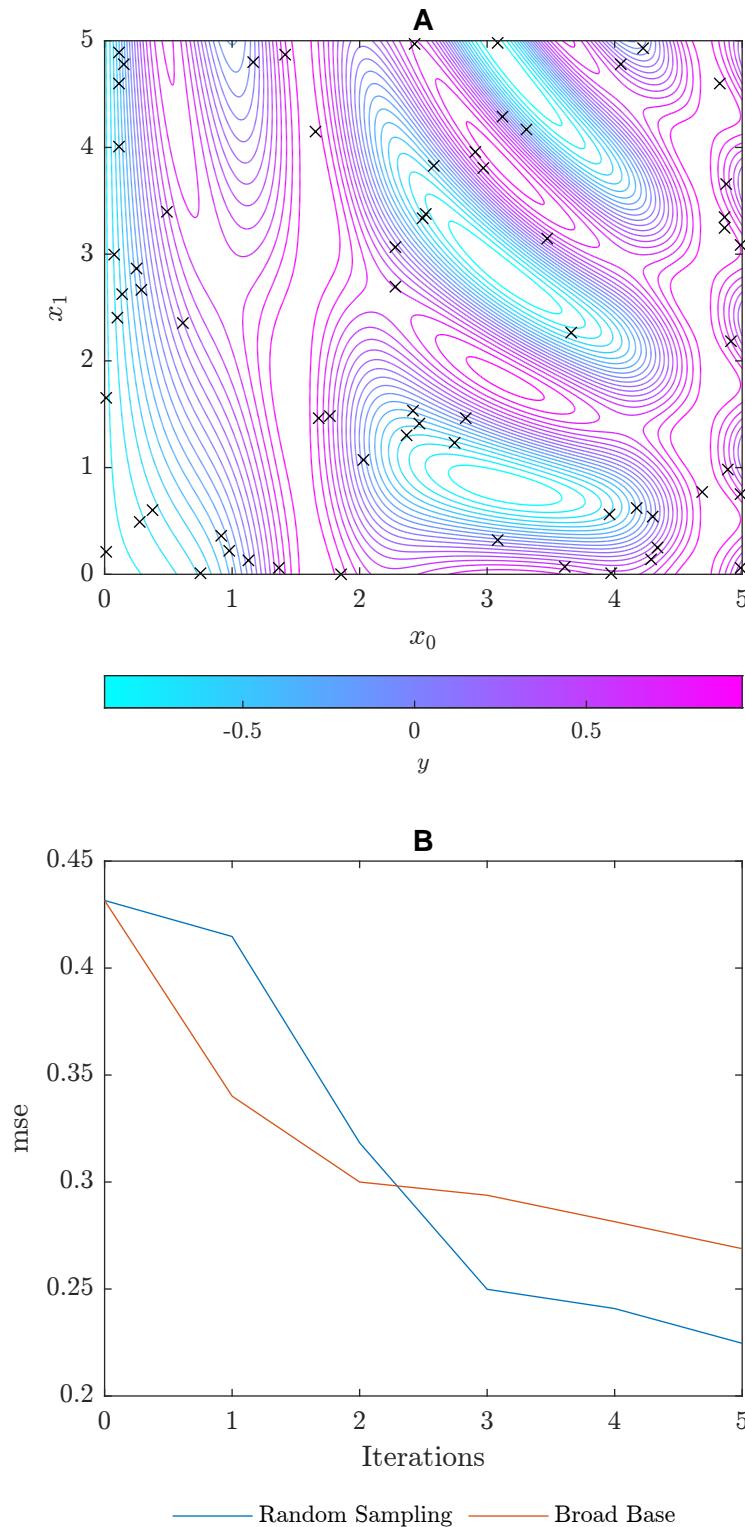


Fig. 2.7 The outcome of the investigating the areas of using broad-base sampling. An initial set of 5 random points was provided, and 5 further iterations were then carried out of sample size 10. A) Demonstrates the final set of points tested by the algorithm and B) shows the change in the mean squared error for the algorithm after each iteration.

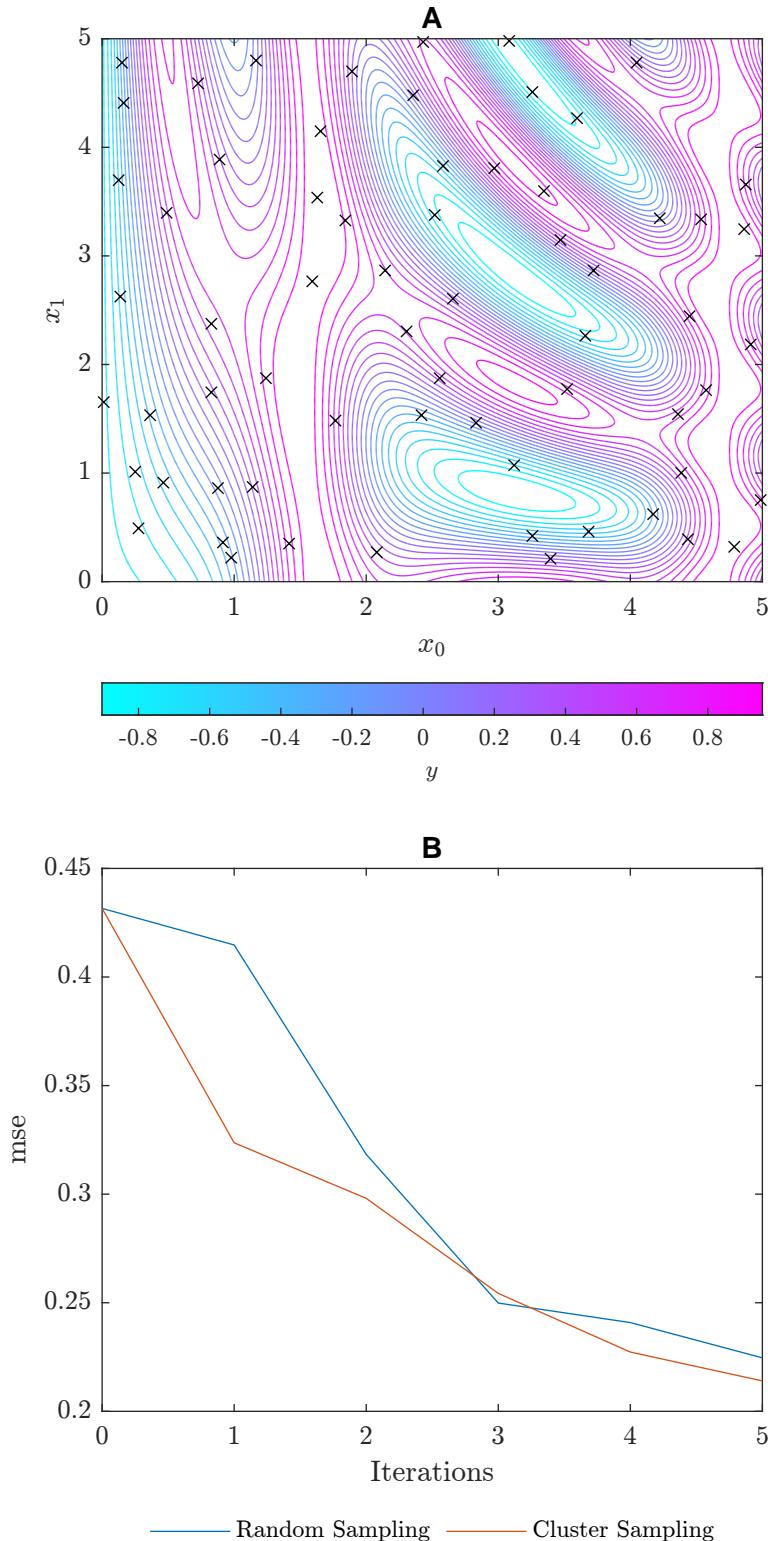


Fig. 2.8 The outcome of the investigating the areas of using cluster sampling. An initial set of 5 random points was provided, and 5 further iterations were then carried out of sample size 10. A) Demonstrates the final set of points tested by the algorithm and B) shows the change in the mean squared error for the algorithm after each iteration.

By doing this $N - 1$ times, a better solution may be found, although this may prove to be computationally very expensive.

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2.3 Drug Data for Machine Learning

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There are numerous data categories that can be used to represent a chemical in a suitable form for machine learning. Indeed, the field of chemoinformatics is dedicated to the pursuit of describing chemicals for computational models. Each of these methods have various strengths and weaknesses. Some are directly based upon the chemical structure whereas others are based upon physical properties. These can be combined to produce models with high predictive capabilities.

2.3.1 Physical Properties

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A selection of physical properties from chemicals are known, from melting points to solubility. Many of these provide important aspects for consideration and allow human scientists to predict interactions, especially when determining new drugs. These data are often reported in tables within textbooks such as Perry's [] or provided through software [chembl ...].

Several of these data can be predicted through theoretical models, although the difficulty increases for larger molecules. For example, models exist for density predictions, but predicting the LD₅₀ of a drug is far more challenging task. Indeed, even with animal testing, this property is deemed difficult to truly assess.

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Within drug discovery, physical and biological properties are usually the sought after labels. An example of this is supplied by EMBL-EBI [EMB09] with a custom property named pChEMBL, as defined by 2.7 where "l" is synonymous with or.

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$$\text{pChEMBL} = -\log_{10} (\text{IC}_{50} | \text{XC}_{50} | \text{EC}_{50} | \text{AC}_{50} | \text{Ki} | \text{LD}_{50} | \text{Potency}) \quad (2.7)$$

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2.3.2 Fingerprints

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Another methodology is to develop a fingerprint: a unique code based on the chemical structure, either of the atomic arrangement, or by the electron cloud distribution. The latter of these is more fundamental to the activity of molecules but far harder to calculate. Indeed, for accurate representation of the latter, both atomic structure is needed *and* solutions for the Schrödinger equations corresponding to molecule in question.

According to Capecchi, Probst, and Reymond [CPR20], the most popular fingerprint in use are Morgan Fingerprints, a form of Extended Chemical Fingerprint (ECFP). ECFPs use

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¹ a simple algorithm in order to generate a unique identifier, as described by Rogers and Hahn
² [RH10]:

- ³ **1. Initial Assignment:** Each atom has an integer assigned as an identifier.
- ⁴ **2. Iterative Updating:** Updating the identifier assigned to atoms based on adjacent atoms
⁵ and structural duplications.
- ⁶ **3. Duplicate Removal:** Duplicate features are removed for hashing.

⁷ The iteration process involves each atom and adjacent atoms sharing numbers before
⁸ in an array. A hash function is applied to this array and becomes the atoms new identifier.
⁹ Fingerprints of this class are labelled according to the number of iterations, n , with the
¹⁰ final name given as ECFP_ $\langle 2n \rangle$. Morgan fingerprints, the most common form, are thus also
¹¹ called ECFP_4 [CPR20; RH10]. Thus, these come under the remit of fingerprints based
¹² upon two-dimensional chemical structure, rather than three-dimensional or even electron
¹³ distribution. Morgan fingerprints are readily available for millions of compounds from the
¹⁴ publicly accessible ChEMBL database [EMB09].

¹⁵ Alternative common fingerprints include SMILES, InChI, and the MDL molfile.

Chapter 3

Methodology

3.1 Outline

3.1.1 Data

Each dataset used consists of a 1024 bit Morgan fingerprint for the features and these associated pChEMBL values. The sets used for parameter fitting and score reporting make up a set of 2094 files from EMBL-EBI [EMB09]. These were filtered to prevent datasets with fewer than 1000 entries to be admitted into the main script.

Morgan fingerprints were chosen due to the ease in which it is to calculate the vectors, the popularity of them within the chemoinformatics sphere, and the success enjoyed by others when using them for predictive purposes. It was decided that physical properties would not be used as this could increase the onus on data sanitation and preparation rather than active learning.

3.1.2 Custom Algorithms

As well as the algorithms used mentioned in Chapter 2, several custom algorithms were developed and added to the testing set. These methods do use parameters, and so require the minimisation technique. Additionally, these algorithms take a composite methodology, using other active learning methods in order to reach a conclusion, so some concepts will be assumed knowledge for Chapter 2.

3.2 Computational Methodology

The methodology presents a novel means of assessing different parametrised active learning methods on existing data sets, allowing for a robust answer into the use of active learning in drug rediscovery. Results can thus be given with a given belief. This approach has taken principles commonly used in machine learning and applied it to more traditional algorithmic methods.

Firstly, a collection of pre-existing data sets, X , are used. X is then split into two sub sets: X_{train} and X_{test} . Similarly to machine learning, the former of these subsets is used in fitting the parameters of the equation, and the latter is used to provide a result without the risk of data leakage into the training set. This is represented in []. Parallelisation is used to efficiently train the algorithms allowing the time for training to be $\sim \mathcal{O}(c)$.

Examining the smaller details, each algorithm is provided with the sets x_{known} , y_{known} , and x_{unknown} . Various algorithms are given these sets and allowed to generate a subset of x_{unknown} to be added into x_{known} alongside corresponding y_{known} . This can then repeat until a predefined stopping point is reached. Scores are reported using a weighted mean squared error [] based upon y_{predict} for all x . This is similar to a standard machine learning methodology with a couple of differences. Firstly, no distinction is made between the training and testing set within a dataset contrary to standard practice. This is due to two reasons. Firstly, the datasets are not large enough for an accurate representation of the data within the testing set, and secondly, the scoring to each dataset is not used within the machine learning algorithms to fit parameters as is usually the case. All algorithms used rely upon a simple custom composite model to allow for flexibility and consistency.

In Section [], it was discussed that there are various methodologies of representing chemicals and drugs. ... (if time)

3.2.1 Integral Functions and Classes

Several key methods and classes are required for the smooth operation of the computational frameworks used

3.2.2 Custom Base Functions

Split

The split function allows for each dataset to be split into x_{known} , y_{known} , x_{unknown} , and y_{unknown} , as demonstrated in Figure 3.1. This is required as a fundamental step for the algorithmic testing. To demonstrate the validity of this function, ...

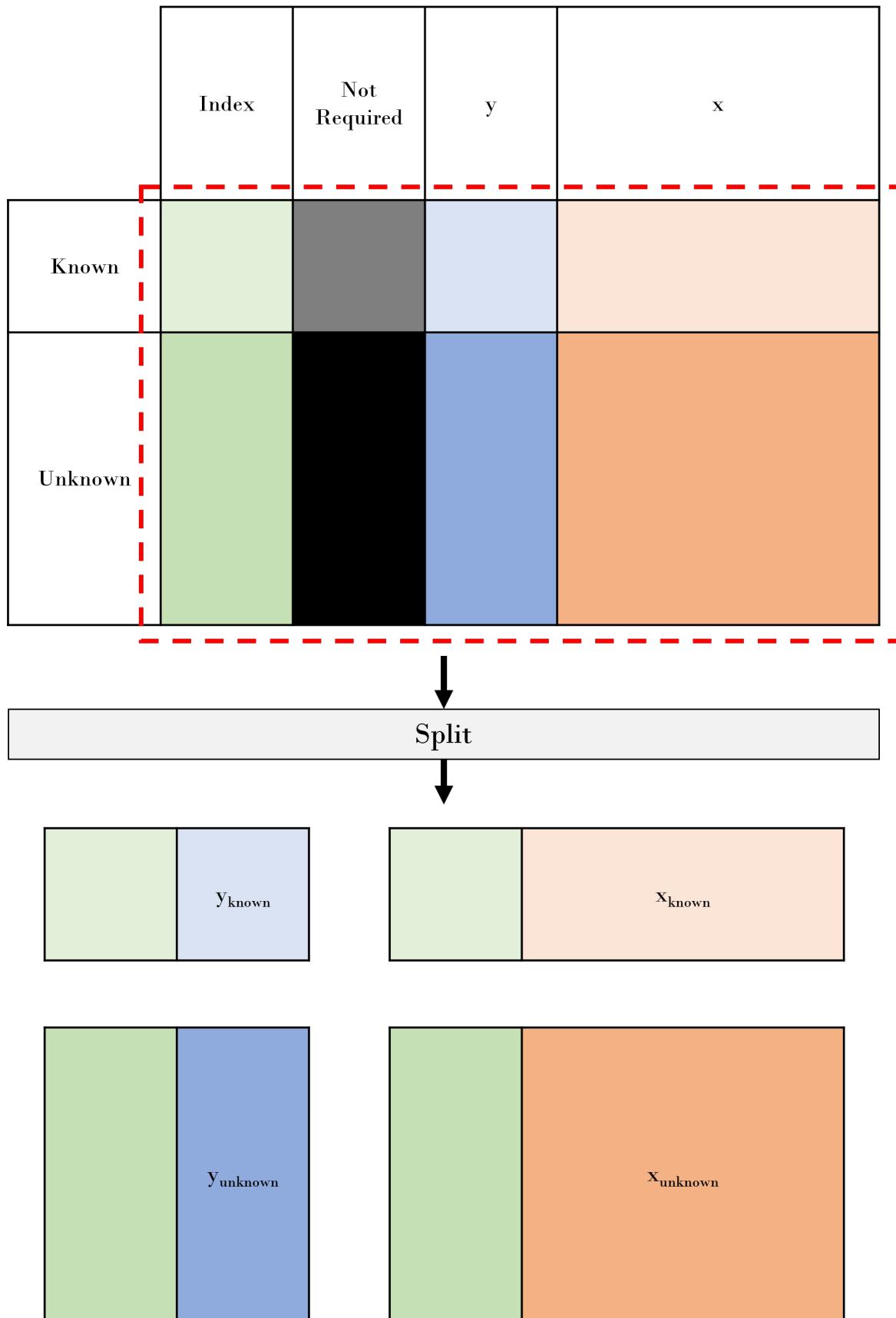


Fig. 3.1 Graphical representation of the split function. The red dashed boundary represents the input (additional colour coding has been performed to assist the reader in understanding the transposition of the base components).

1 Repartition

2 Upon each iteration, the sets provided to the algorithms need to be repartitioned to allow for
 3 the continual operation of the algorithm. This consists of two parts: expanding the known
 4 sets and removing entries from the unknown sets.

5 Model

6 The machine learning model is the only custom class used. Here, a similar structure is used
 7 when compared with sci-kit's machine learning [Ped+], as is demonstrated in Table 3.1.
 8 To manage this, it has four methods: `__init__`, `fit`, `predict`, and `predict_error`. The last of
 9 these is not seen in all sci-kit's machine learning models and is reserved for those which can
 10 report a certainty of prediction. Here, this was achieved by taking a standard deviation of the
 11 models.

	Name	Description
Attributes	Models: List	List of models to be used in composite
Methods	<code>fit(X: int[][][], Y: double[])</code> <code>predict(X: int[][][]): double[]</code> <code>predict_error(X: int[][][]): double[][]</code>	Fits the models in Models Takes a set of labels and returns mean predicted label from all the models. Takes a set of labels and returns the mean predicted label from all the models and standard deviations of model predictions.

Table 3.1 Schema for the Model Class.

12 The models used for the composite model were ... which will be consistent across all
 13 algorithms. This allows direct comparison of the algorithms without interference from
 14 machine learning models used.

15 Validate

16 This is a simple method with greater potential than has been explored. By providing this as a
 17 separate method, a more computationally intensive validation model could be used without
 18 interference as parallelisation could be exploited. However, as it currently stands, it returns
 19 the weighted mean squared error using the standard method provided by [].

3.2.3 Active Learning Algorithms

Dumb

The dumb algorithm, also referred to as random sampling or Monte Carlo sampling, refers to an algorithm that calls upon random samples to be tested. This represents the computationally least expensive approach, and is thus used as a baseline in comparing other algorithms. Since the datasets are shuffled prior to being used, the algorithm is extremely simple, as demonstrated in Algorithm 2.

Algorithm 2: Uncertainty Sampling Selection

Data: X_{unknown}
Result: X ordered according to priority for sampling
return ones_like(X_{unknown})

Greedy

Since the largest activity is sought, a methodology proposed is to simply seek the predicted highest label. Here, the predict() method (see Table 3.1) was used to return a prediction and a standard deviation. The indices of x_{unknown} were then returned, ordered descending with respect to the afore mentioned standard deviations.

Algorithm 3: Greedy Sampling Selection

Data: $X_{\text{known}}, Y_{\text{known}}, X_{\text{unknown}}, \text{Model}$
Result: X ordered according to priority for sampling
 Model.fit($X_{\text{known}}, Y_{\text{known}}$);
 prediction = Model.predict_error(X_{unknown});
return -prediction

Region of Disagreement

Similarly to the region of disagreement method, this is a very simple algorithm. Here, the predict_error() method (see Table 3.1) is used to return a prediction and a standard deviation. The prediction is ignored, and instead the standard deviation is returned, multiplied by -1 to ensure the largest uncertainty has the lowest "score". This is shown in 4.

Algorithm 4: Uncertainty Sampling Selection

Data: X_{known} , Y_{known} , X_{unknown} , Model
Result: X ordered according to priority for sampling

```
Model.fit( $X_{\text{known}}$ ,  $Y_{\text{known}}$ );
_, error = Model.predict_error( $X_{\text{unknown}}$ );
return –error
```

1 Hotspot Cluster I

- 2 This is the first of the clustering algorithms and the first parametric algorithm. This algorithm
- 3 is identical to the algorithm presented in Section 2.1.1.

Algorithm 5: Uncertainty Sampling Selection

Data: X_{known} , X_{unknown} , n
Result: X ordered according to priority for sampling

```
combined_x = concat(X, x);
clusters = cluster(number_of_clusters=n);
clusters.fit(combined_x);
predicted_custers = clusters.predict( $X_{\text{unknown}}$ )
return –error
```

4 Hotspot Cluster II**5 Hotspot Cluster III****6 3.2.4 Training Framework**

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- 9 felis non sodales commodo, lectus velit ultrices augue, a dignissim nibh lectus placerat pede.
- 10 Vivamus nunc nunc, molestie ut, ultricies vel, semper in, velit. Ut porttitor. Praesent in
- 11 sapien. Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Duis fringilla tristique
- 12 neque. Sed interdum libero ut metus. Pellentesque placerat. Nam rutrum augue a leo. Morbi
- 13 sed elit sit amet ante lobortis sollicitudin. Praesent blandit blandit mauris. Praesent lectus
- 14 tellus, aliquet aliquam, luctus a, egestas a, turpis. Mauris lacinia lorem sit amet ipsum. Nunc
- 15 quis urna dictum turpis accumsan semper.

Parallelisation

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Chapter 4

Results

4.1 Non-Parametric

Non-parametric equations have the benefit of not requiring the minimisation function.

4.1.1 Monte Carlo

Using a test sample size

4.1.2 Uncertainty Sampling

4.2 Parametric

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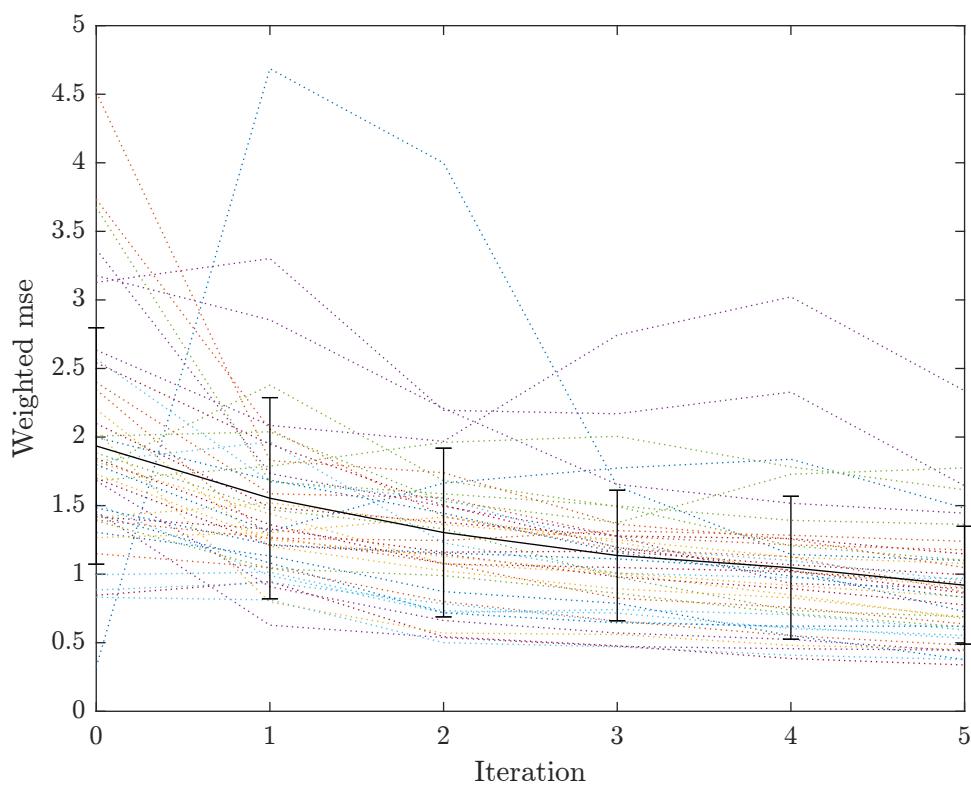


Fig. 4.1

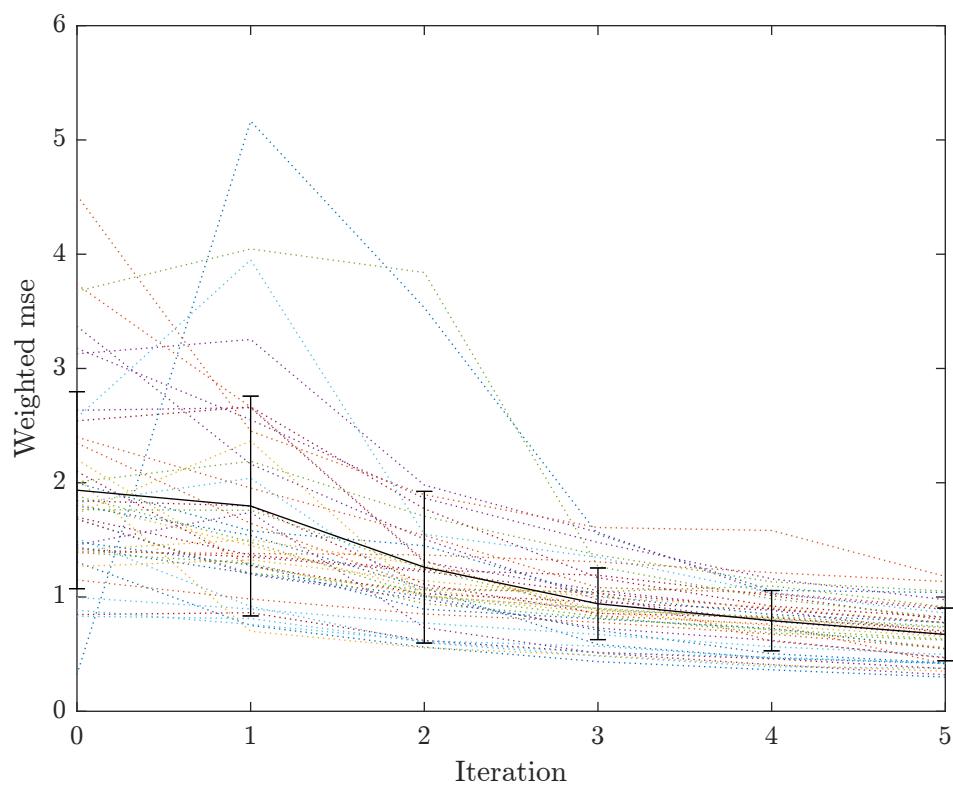


Fig. 4.2

¹ 4.3 Second Part

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²⁸ 4.4 Special Case: COVID-19

Chapter 5

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Discussion

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Chapter 6

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Conclusion

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