Supplementary Information for: A Predictive Model for Toxicity Effects Assessment of Biotransformed Hepatic Drugs Using Iterative Sampling Method

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Supplementary Figures

1-Supplementary Figure S1

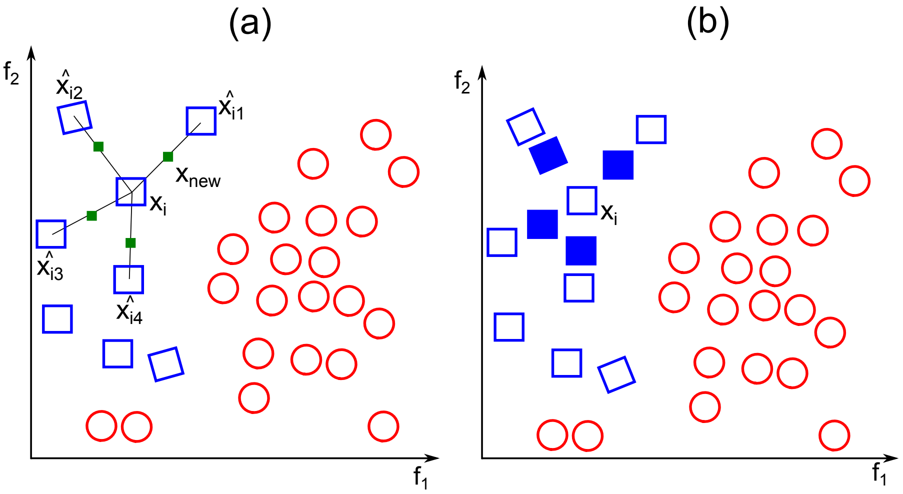

Fig. S1 An example of SMOTE method, (a) before applying SMOTE method and (b) after applying SMOTE method.

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Figure S1 illustrates an example of the SMOTE method. Figure S1(a) shows a typical imbalanced data distribution, where the circles and squares represent samples of the majority and minority classes, respectively. In this example, assume $k = 4$. Figure S1(a) shows the created samples along with the line segment between x_i and $\hat{x_{ij}}$. These samples are highlighted by the green square shape. These synthetic samples increase the number of minority samples and hence, significantly improves the performance of learning algorithm. Figure S1(b) shows the synthesized samples that are highlighted by solid squares. However, in SMOTE algorithm, the same number of the synthetic data are generated for each minority sample without consideration to neighboring samples, which may increase the overlapping between classes.

2-Supplementary Figure S2

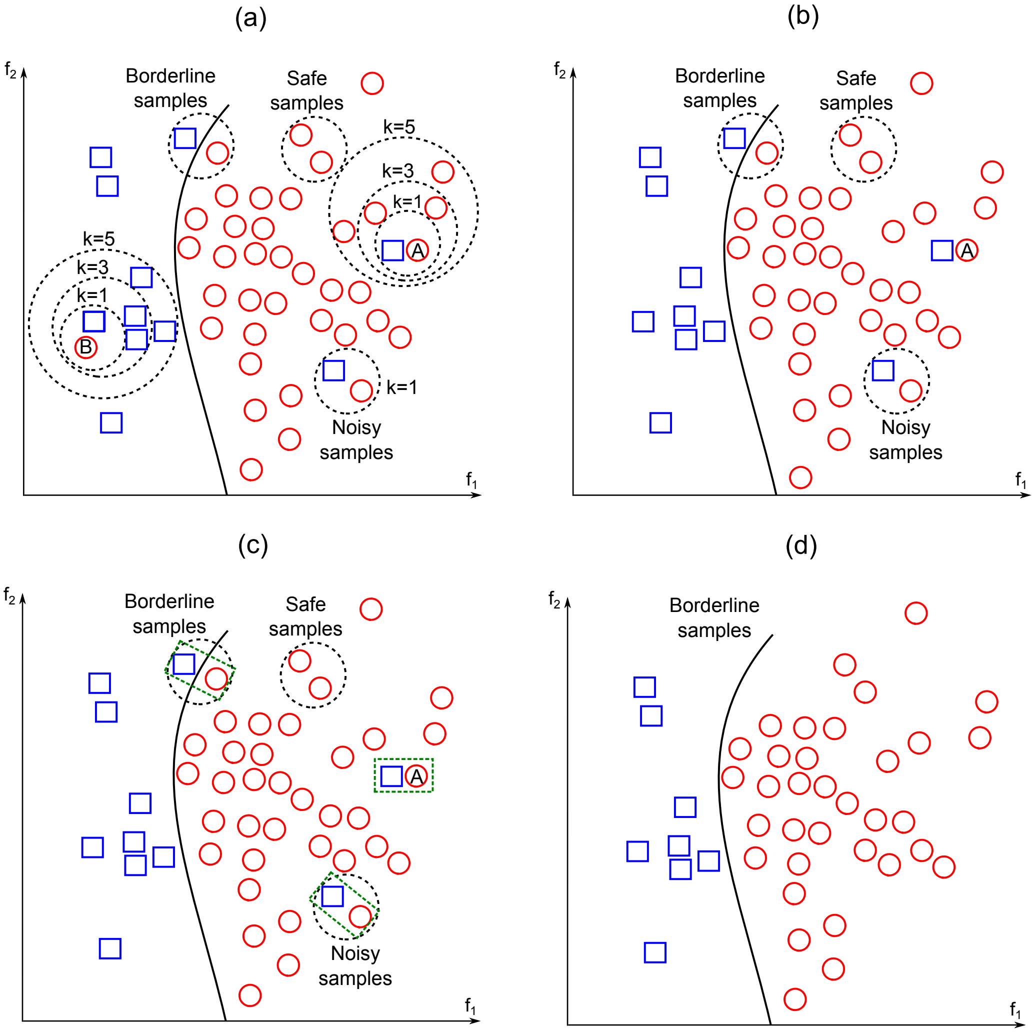
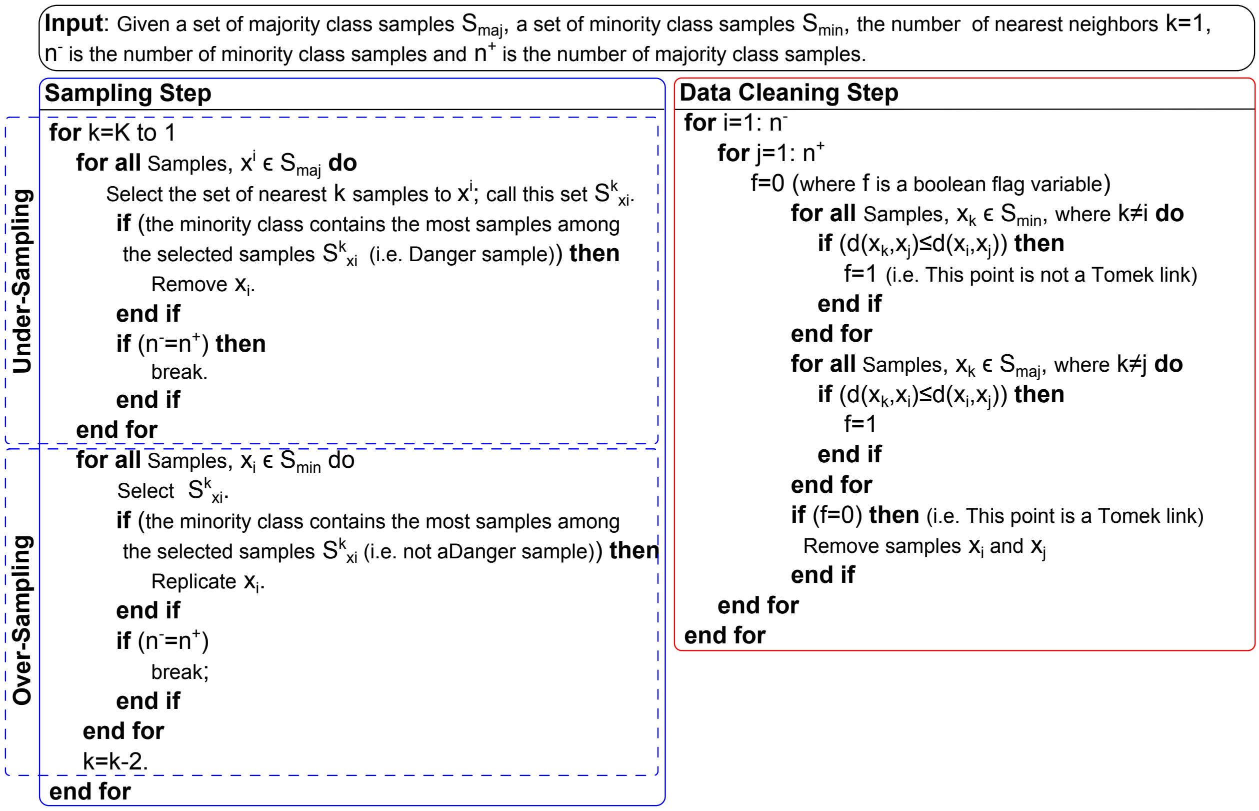


Fig. S2 An example of ITS method. (a) Original data; (b) After applying sampling step; (c) The identified Tomek Links, (d) The dataset after removing Tomek links.

Figure S2 illustrates an example of the ITS method. This figure shows the difference between borderline, safe and noisy samples (see Fig. S2 (a)). As shown in Fig.Fig. S2(a), the sample/point (A) when $k = 5$ or $k = 3$ is not classified as a danger sample, while the sample is classified as a danger sample when $k = 1$.

On the contrary, the sample B is classified as a danger sample when $k = 1, 3$, or 5. Hence, in the sampling step, when $k = 5$, the sample B is removed while sample A is preserved when the majority class samples are under-sampled as shown in Fig. S2(b). Similarly, the danger points in minority class will not be replicated. Figure S2(c) shows a data cleanup step. As shown in Fig. Fig. S2(c), there are three Tomek links are identified and represented by a green dashed box. Figure S2(d) shows the data after the data cleaning step, where the overlapping data samples are removed. As shown in Fig. S2(d), this step produces separated classes, which improves the classification performance.

3-Supplementary Figure S3



Input: Given a set of majority class samples S_{maj}, a set of minority class samples S_{min}, the number of nearest neighbors k=1, n^- is the number of minority class samples and n^+ is the number of majority class samples.

Under-Sampling
Over-Sampling

Sampling Step

```
for k=K to 1
    for all Samples, $x^i \in S_{maj}$ do
        Select the set of nearest k samples to $x^i$; call this set $S^k_{xi}$.
        if (the minority class contains the most samples among
         the selected samples $S^k_{xi}$ (i.e. Danger sample)) then
            Remove $x_i$.
        end if
        if ($n^-$=$n^+$) then
            break.
        end if
    end for
    for all Samples, $x_i \in S_{min}$ do
        Select $S^k_{xi}$.
        if (the minority class contains the most samples among
         the selected samples $S^k_{xi}$ (i.e. not aDanger sample)) then
            Replicate $x_i$.
        end if
        if ($n^-$=$n^+$)
            break;
        end if
    end for
    k=k-2.
end for
```

Data Cleaning Step

```
for i=1: $n^-$
    for j=1: $n^+$
        f=0 (where f is a boolean flag variable)
            for all Samples, $x_k \in S_{min}$, where k≠i do
                if ($d(x_k,x_i) \leq d(x_i,x_j)$) then
                    f=1 (i.e. This point is not a Tomek link)
                end if
            end for
            for all Samples, $x_k \in S_{maj}$, where k≠j do
                if ($d(x_k,x_i) \leq d(x_i,x_j)$) then
                    f=1
                end if
            end for
            if (f=0) then (i.e. This point is a Tomek link)
             Remove samples $x_i$ and $x_j$
            end if
    end for
end for
```

Fig. S3 ITS algorithm.

4-Supplementary Figure S4

```
Bagging Classifier Algorithm
Input: Given a training set X={($x_1$,$y_1$),.....,($x_M$,$y_M$)}, where $y_i$ is the class label
of the sample $x_i$ and M denotes the total number of samples in the training set.
Training Step
while (t<$Max_{iter}$), where $Max_{iter}$ is the maximum number of iterations) do
    Select a sample $S_t$ from X.
    Use $S_t$ to train the current weak learner $C_t$.
end while

Testing Step
Given an unknown sample $x_{test}$.
Classify $x_{test}$ using all weak learners ($C_i$, i=1,.... ,$Max_{iter}$).
Combine the outputs of all weak learners to determine the final prediction.
```

Fig. S4 Bagging Classifier Algorithm.