A PCBA Query

We downloaded additional high-throughput screening datasets from the PubChem BioAssay database\(^1\) using the following query: TotalSidCount from 10000, ActiveSidCount from 30, Chemi-
cal, Confirmatory, Dose-Response, Target: Single, NCGC. These correspond to the search query: (10000[TotalSidCount] : 1000000000[TotalSidCount]) AND (30[ActiveSidCount] : 1000000000[ActiveSidCount]) AND “small molecule”[filt] AND “doseeresponse”[filt] AND 1[TargetCount] AND “NCGC”[SourceName]. This follows the query from Ramsundar et al.²

B Data Preprocessing

B.1 Complex Matrix Composition

Each target dataset consists of compounds as rows. For each compound, it provides the biochemical features such as the fingerprint, SMILES string, interaction score, and activity label (binary or continuous). The first step was to extract the SMILES and activity label for each target and construct the data matrix for training. We used RDKit³ for navigating and extracting information from these datasets and for generating the fingerprints.

The second step was to merge the target matrices together into one consolidated matrix. We used an outer-join operation with the SMILES as the key. Given two matrices $A$ and $B$ with two columns, SMILES and target-activity, an outer-join operation will merge rows of $A$ and $B$ that have the same SMILES value into a new matrix $M$. If there is a row in $A$ with SMILES value $s$ and no corresponding row in $B$ with SMILES value $s$, then the merge would yield a row in $M$ with an empty target-activity for $B$. In the resulting matrix, each row is a compound and the columns are: SMILES, 1024-bit Morgan fingerprints, and a column for the activity outcome of each target (5 columns for PriA-SSB AS, PriA-SSB FP, and RMI-FANCM FP and the associated % inhibition values and 128 columns for PCBA). As a result, we have two data matrices: PriA-SSB AS, PriA-SSB FP, and RMI-FANCM FP plus PCBA, on which we can train either single-task or multi-task learning methods. Merging all the targets introduces many empty cells for the activity outcome columns. For the distribution of active, inactive, and missing values for each target, refer to Appendix C. We observed severe data imbalance; the ratio of positive to negative labels is very small. Inconclusive PCBA labels were
treated as missing. During model evaluation, we considered each task (column) separately and dropped the missing values.

### B.2 Fold Splitting

The whole data set was split into 5 fixed folds for cross-validation. Label imbalance and the limited number of known active compounds is one of biggest challenges in virtual screening and must be accounted for during modeling. Stratified splitting is a way to divide data into folds while keeping the same active-to-inactive ratio for each label.

For a single-target task, stratified splits can be implemented by combining folds after sampling each class of labels. But this procedure becomes more complicated in the multi-task setting. With a total of 131 binary tasks, each task has a set of molecules with activity outcomes that may or may not overlap across targets. After merging all molecules into one matrix, each row represents one molecule and each column represents one target. For each column (target), molecules can have missing, inactive, or active labels. Similarly, for each row (molecule), the molecule must have an active or inactive label for at least one of the 131 targets but can be missing for some of other targets. We construct this combined matrix of 131 targets using Algorithm 1 described below. We divide this matrix into 5 folds, while keeping the same data distribution.

### B.3 Label Imbalance

**PriA-SSB AS, PriA-SSB FP,** and **RMI-FANCM FP** have only 79, 24, and 230 actives, respectively. To alleviate this class imbalance, one solution is to use a weighted schema. For single-task neural network models, we apply Equation (1).

\[
\text{weight}_{\text{negative}} = 1, \quad \text{weight}_{\text{positive}} = \frac{n}{p}
\]

(1)

where \( \text{weight}_{\text{positive}} \) and \( \text{weight}_{\text{negative}} \) are weight scalars for positive (active) and negative (inactive)
Algorithm 1: Multi-task Data Splitting

Input: Initial pre-split molecule-target matrix $M$, number of desired folds $k$
Output: $k$ folds $F[1], F[2], ..., F[k]$ containing stratified splits of $M$

1. shuffle rows of $M$ randomly
2. create $k$ folds $F[1], F[2], ..., F[k]$ that contain the row indexes only
3. indexList ← argsort columns of $M$ from smallest active counts to largest
4. for $i$ in indexList do
5.   currColumn ← $M[:,i]$
6.   split active indexes of currColumn into the $k$ folds
7.   split inactive indexes of currColumn into the $k$ folds
8.   split missing indexes of currColumn into the $k$ folds
9.   take the unique compounds in each fold to remove duplicate row indexes
10. greedily remove overlapping indexes from each fold (fold-by-fold manner)
11. take the unique compounds in each fold to remove duplicate row indexes
12. return $F[1], F[2], ..., F[k]$

compounds, respectively, and $p$ and $n$ represent the number of positive and negative samples on this target.

Similarly, we apply the weighted schema to multi-task models, defined as Equation (2).

$$weight_{(negative, i)} = t_i, \quad weight_{(positive, i)} = t_i \cdot \frac{n_i}{p_i}$$

(2)

where $weight_{(positive, i)}$ and $weight_{(negative, i)}$ are weight scalars for positive and negative labels for the $i^{th}$ target, and $p_i$ and $n_i$ represent the number of positive and negative samples for the $i^{th}$ target. $t_i$ is defined as Equation (3)

$$t_i = \begin{cases} \sum_{i} p_i, & \text{$i^{th}$ target is in PCBA} \\ \alpha \cdot \sum_{i} p_i, & \text{$i^{th}$ target is in PriA-SSB AS, PriA-SSB FP, and RMI-FANCM FP} \end{cases}$$

(3)

In the multi-task setting, we give different weights to each target, focusing more on the PriA-SSB AS, PriA-SSB FP, and RMI-FANCM FP targets and the PCBA targets that have fewer positive
samples. We emphasize PriA-SSB AS, PriA-SSB FP, and RMI-FANCM FP by setting $\alpha = 100$, and alleviate the data skewness among targets by the term $\sum_i \frac{p_i}{p_i}$.

### B.4 Missing Label Imputation

1. For single-task machine learning models – random forest, single-task neural networks, and IRV – training is done on molecules without missing labels (missing molecules are removed from the training set).

2. In the case of multi-task neural networks, missing molecules were imputed as inactive. This was mainly due to Keras (at the time) not supporting sample-weighting for the multi-task case.
### Data Distribution

Table S1: Data distribution of positive, negative, and missing molecules for each task.

| Task name       | Positive molecules | Negative molecules | Missing molecules | ratio = pos number / neg number |
|-----------------|--------------------|--------------------|-------------------|---------------------------------|
| pcba-aid1030    | 15932              | 145369             | 335063            | 10.96 %                         |
| pcba-aid1379    | 561                | 196368             | 314806            | 0.29 %                          |
| pcba-aid1452    | 178                | 149367             | 362573            | 0.12 %                          |
| pcba-aid1454    | 513                | 115335             | 395935            | 0.44 %                          |
| pcba-aid1457    | 720                | 202110             | 308746            | 0.36 %                          |
| pcba-aid1458    | 5778               | 188852             | 311888            | 0.30 %                          |
| pcba-aid1460    | 5650               | 217010             | 283986            | 2.60 %                          |
| pcba-aid1461    | 2305               | 206016             | 301670            | 1.12 %                          |
| pcba-aid1468    | 1038               | 251148             | 259072            | 0.41 %                          |
| pcba-aid1469    | 170                | 272533             | 239423            | 0.06 %                          |
| pcba-aid1471    | 293                | 218258             | 293452            | 0.13 %                          |
| pcba-aid1479    | 793                | 269530             | 241180            | 0.29 %                          |
| pcba-aid1631    | 892                | 259030             | 251482            | 0.34 %                          |
| pcba-aid1634    | 154                | 261988             | 250000            | 0.06 %                          |
| pcba-aid1688    | 2375               | 201910             | 305636            | 1.18 %                          |
| pcba-aid1721    | 1087               | 289651             | 220471            | 0.38 %                          |
| pcba-aid2190    | 1157               | 291855             | 218127            | 0.40 %                          |
| pcba-aid2101    | 288                | 309907             | 201813            | 0.09 %                          |
| pcba-aid2147    | 3473               | 188764             | 316586            | 1.84 %                          |
| pcba-aid2242    | 715                | 183374             | 327492            | 0.39 %                          |
| pcba-aid2326    | 1065               | 259688             | 250478            | 0.41 %                          |
| pcba-aid2451    | 2005               | 271718             | 236568            | 0.74 %                          |
| pcba-aid2517    | 1138               | 332123             | 177897            | 0.34 %                          |
| pcba-aid2528    | 652                | 340938             | 170054            | 0.19 %                          |
| pcba-aid2546    | 10556              | 267886             | 223298            | 3.94 %                          |
| pcba-aid2549    | 1211               | 230450             | 279424            | 0.53 %                          |
| pcba-aid2551    | 16671              | 253653             | 225301            | 6.57 %                          |
| pcba-aid2662    | 110                | 285240             | 226836            | 0.04 %                          |
| pcba-aid2675    | 99                 | 248789             | 263309            | 0.04 %                          |
| pcba-aid2676    | 1081               | 357341             | 152793            | 0.30 %                          |
| pcba-aid411     | 1565               | 69057              | 440113            | 2.26 %                          |
| pcba-aid463254  | 41                 | 329171             | 183043            | 0.01 %                          |
| pcba-aid485281  | 253                | 314347             | 197443            | 0.08 %                          |
| pcba-aid485290  | 938                | 335859             | 174561            | 0.28 %                          |
Table S1: Data distribution of positive, negative, and missing molecules for each task.

| Task name       | Positive molecules | Negative molecules | Missing molecules | ratio = pos number / neg number |
|-----------------|--------------------|--------------------|-------------------|---------------------------------|
| pcba-aid485294  | 148                | 309649             | 202351            | 0.05 %                          |
| pcba-aid485297  | 9128               | 301294             | 192746            | 3.03 %                          |
| pcba-aid485313  | 7569               | 304194             | 192964            | 2.49 %                          |
| pcba-aid485314  | 4493               | 312590             | 190720            | 1.44 %                          |
| pcba-aid485341  | 1729               | 325703             | 183135            | 0.53 %                          |
| pcba-aid485349  | 618                | 319466             | 191594            | 0.19 %                          |
| pcba-aid485353  | 603                | 322454             | 188636            | 0.19 %                          |
| pcba-aid485360  | 1485               | 216997             | 292329            | 0.68 %                          |
| pcba-aid485364  | 10698              | 331470             | 159430            | 3.23 %                          |
| pcba-aid485367  | 557                | 325598             | 185584            | 0.17 %                          |
| pcba-aid492947  | 80                 | 329301             | 182835            | 0.02 %                          |
| pcba-aid493208  | 342                | 41294              | 470318            | 0.83 %                          |
| pcba-aid504327  | 766                | 370995             | 139769            | 0.21 %                          |
| pcba-aid504332  | 30264              | 263754             | 188014            | 11.47 %                         |
| pcba-aid504333  | 15673              | 310114             | 170836            | 5.05 %                          |
| pcba-aid504339  | 16859              | 338757             | 139821            | 4.98 %                          |
| pcba-aid504444  | 7388               | 282993             | 214527            | 2.61 %                          |
| pcba-aid504466  | 4169               | 306751             | 197207            | 1.36 %                          |
| pcba-aid504467  | 7648               | 235607             | 261393            | 3.25 %                          |
| pcba-aid504706  | 201                | 302548             | 209346            | 0.07 %                          |
| pcba-aid504842  | 101                | 324570             | 187524            | 0.03 %                          |
| pcba-aid504845  | 100                | 372270             | 139826            | 0.03 %                          |
| pcba-aid504847  | 3509               | 376531             | 128747            | 0.93 %                          |
| pcba-aid504891  | 34                 | 361224             | 151004            | 0.01 %                          |
| pcba-aid540276  | 4393               | 192748             | 310762            | 2.28 %                          |
| pcba-aid540317  | 2129               | 367917             | 140121            | 0.58 %                          |
| pcba-aid588342  | 25036              | 301746             | 160478            | 8.30 %                          |
| pcba-aid588453  | 3904               | 365862             | 138626            | 1.07 %                          |
| pcba-aid588456  | 51                 | 384356             | 127838            | 0.01 %                          |
| pcba-aid588579  | 1980               | 384213             | 124123            | 0.52 %                          |
| pcba-aid588590  | 3931               | 352947             | 151487            | 1.11 %                          |
| pcba-aid588591  | 4700               | 367981             | 134915            | 1.28 %                          |
| pcba-aid588795  | 1307               | 376247             | 133435            | 0.35 %                          |
| pcba-aid588855  | 4897               | 347556             | 154946            | 1.41 %                          |
| pcba-aid602179  | 364                | 384856             | 126712            | 0.09 %                          |
| pcba-aid602233  | 165                | 379055             | 132911            | 0.04 %                          |
| pcba-aid602310  | 310                | 393819             | 117857            | 0.08 %                          |
| pcba-aid602313  | 762                | 372273             | 138499            | 0.20 %                          |
Table S1: Data distribution of positive, negative, and missing molecules for each task.

| Task name      | Positive molecules | Negative molecules | Missing molecules | ratio |
|----------------|--------------------|--------------------|-------------------|-------|
| pcba-aid620332 | 69                 | 408322             | 103836            | 0.02% |
| pcba-aid624170 | 838                | 397756             | 112864            | 0.21% |
| pcba-aid624171 | 1239               | 394674             | 115144            | 0.31% |
| pcba-aid624173 | 487                | 399643             | 111679            | 0.12% |
| pcba-aid624202 | 3968               | 362543             | 141817            | 1.09% |
| pcba-aid624246 | 101                | 364511             | 147583            | 0.03% |
| pcba-aid624287 | 423                | 302226             | 209224            | 0.14% |
| pcba-aid624288 | 1356               | 323051             | 186533            | 0.42% |
| pcba-aid624291 | 222                | 331803             | 180049            | 0.07% |
| pcba-aid624296 | 9840               | 282428             | 210188            | 3.48% |
| pcba-aid624297 | 6213               | 301951             | 197919            | 2.06% |
| pcba-aid624417 | 6389               | 319289             | 180229            | 2.00% |
| pcba-aid651635 | 3784               | 343160             | 161568            | 1.10% |
| pcba-aid651644 | 748                | 353982             | 156818            | 0.21% |
| pcba-aid651768 | 1677               | 355992             | 152950            | 0.47% |
| pcba-aid651965 | 6346               | 318038             | 181566            | 2.00% |
| pcba-aid652025 | 238                | 364167             | 147653            | 0.07% |
| pcba-aid652104 | 7126               | 368557             | 129487            | 1.93% |
| pcba-aid652105 | 4072               | 318365             | 185787            | 1.28% |
| pcba-aid652106 | 497                | 362334             | 148968            | 0.14% |
| pcba-aid686970 | 5948               | 331060             | 169340            | 1.80% |
| pcba-aid686978 | 62375              | 236628             | 150918            | 26.36% |
| pcba-aid686979 | 48532              | 257279             | 157953            | 18.86% |
| pcba-aid720504 | 10170              | 340357             | 151599            | 2.99% |
| pcba-aid720532 | 976                | 11815              | 498529            | 8.26% |
| pcba-aid720542 | 733                | 356204             | 154626            | 0.21% |
| pcba-aid720551 | 1265               | 341660             | 168106            | 0.37% |
| pcba-aid720553 | 3259               | 336029             | 169749            | 0.97% |
| pcba-aid720579 | 1908               | 280991             | 227489            | 0.68% |
| pcba-aid720580 | 1508               | 304454             | 204826            | 0.50% |
| pcba-aid720707 | 268                | 363257             | 148503            | 0.07% |
| pcba-aid720708 | 661                | 356743             | 154231            | 0.19% |
| pcba-aid720709 | 516                | 352850             | 158414            | 0.15% |
| pcba-aid720711 | 290                | 363245             | 148471            | 0.08% |
| pcba-aid743255 | 901                | 366915             | 143579            | 0.25% |
| pcba-aid743266 | 306                | 398728             | 112956            | 0.08% |
| pcba-aid875    | 34                 | 73821              | 438407            | 0.05% |
| pcba-aid881    | 590                | 103808             | 407308            | 0.57% |
Table S1: Data distribution of positive, negative, and missing molecules for each task.

| Task name     | Positive molecules | Negative molecules | Missing molecules | ratio = \(\frac{\text{pos number}}{\text{neg number}}\) % |
|---------------|--------------------|--------------------|-------------------|------------------------------------------------------|
| pcba-aid883   | 1217               | 6647               | 503215            | 18.31 %                                              |
| pcba-aid884   | 3396               | 6983               | 498521            | 48.63 %                                              |
| pcba-aid885   | 160                | 12683              | 499293            | 1.26 %                                               |
| pcba-aid887   | 1017               | 68423              | 441839            | 1.49 %                                               |
| pcba-aid891   | 1564               | 6012               | 503156            | 26.01 %                                              |
| pcba-aid899   | 1773               | 6141               | 502609            | 28.87 %                                              |
| pcba-aid902   | 1865               | 117072             | 391494            | 1.59 %                                               |
| pcba-aid903   | 338                | 52451              | 459169            | 0.64 %                                               |
| pcba-aid904   | 528                | 50430              | 460810            | 1.05 %                                               |
| pcba-aid912   | 453                | 56178              | 455212            | 0.81 %                                               |
| pcba-aid914   | 221                | 7524               | 504330            | 2.94 %                                               |
| pcba-aid915   | 421                | 7524               | 503930            | 5.60 %                                               |
| pcba-aid924   | 1144               | 118813             | 391195            | 0.96 %                                               |
| pcba-aid925   | 39                 | 64140              | 448078            | 0.06 %                                               |
| pcba-aid926   | 345                | 56230              | 455376            | 0.61 %                                               |
| pcba-aid927   | 60                 | 58565              | 453611            | 0.10 %                                               |
| pcba-aid938   | 1781               | 60720              | 448014            | 2.93 %                                               |
| pcba-aid995   | 699                | 65056              | 445842            | 1.07 %                                               |
| PriA-SSB AS   | 79                 | 72344              | 439794            | 0.11 %                                               |
| PriA-SSB FP   | 24                 | 72399              | 439849            | 0.03 %                                               |
| RMI-FANCM FP  | 230                | 49566              | 462270            | 0.46 %                                               |
### D Hyperparameter Grid Search

Table S2: Hyperparameter sweeping for classification neural networks (STNN-C and MTNN-C).

| Hyperparameters       | Candidate values                                      |
|-----------------------|-------------------------------------------------------|
| hidden layer sizes    | [2000, 2000]                                          |
| learning rate         | 0.000003, 0.0001, 0.003                               |
| optimizer             | Adam                                                  |
| weighted schema       | no_weight, weighted_sample                            |
| epoch patience        | [epoch_size: 200, patience: 50], [epoch_size: 1000, patience: 200] |
| activations           | [ReLU, Sigmoid, Sigmoid], [ReLU, ReLU, Sigmoid]        |
| dropout               | 0.25                                                  |

Table S3: Hyperparameter sweeping for regression neural networks (STNN-R).

| Hyperparameters       | Candidate values                                      |
|-----------------------|-------------------------------------------------------|
| hidden layer sizes    | [2000, 2000]                                          |
| learning rate         | 0.000003, 0.0001, 0.003                               |
| optimizer             | Adam                                                  |
| weighted schema       | no_weight                                             |
| epoch                 | 200, 1000                                             |
| activations           | [Sigmoid, Sigmoid, Linear], [ReLU, Sigmoid, Sigmoid]   |
| dropout               | 0.25                                                  |

Table S4: Hyperparameter sweeping for LSTM neural networks.

| Hyperparameters       | Candidate values                                      |
|-----------------------|-------------------------------------------------------|
| hidden layer sizes    | [50], [100], [100, 10], [100, 50], [50, 10]          |
| embedding layer size  | 30, 50, 100                                           |
| learning rate         | 0.000003, 0.0001, 0.003                               |
| optimizer             | Adam                                                  |
| epoch patience        | [epoch_size: 200, patience: 50]                       |
| dropout               | 0.2, 0.5                                              |

Table S5: Hyperparameters for IRV.

| Hyperparameters       | Candidate values                                      |
|-----------------------|-------------------------------------------------------|
| number of neighbors   | 5, 10, 20, 40, 80                                       |
| epoch patience        | [epoch_size: 1000, patience: 20]                       |
| batch size            | 8192                                                  |
| learning rate         | 0.01                                                  |
| penalty               | 0.05                                                  |
Table S6: Hyperparameter sweeping for RF.

| Hyperparameters     | Candidate values                     |
|---------------------|-------------------------------------|
| n_estimators        | 4000, 8000, 16000                   |
| max_features        | None, sqrt, log2                    |
| min_samples_leaf    | 1, 10, 100, 1000                    |
| class_weight        | None, balanced_subsample, balanced  |

During the hyperparameter sweeping stage, we trained models with all combinations of the hyperparameters in the tables above. For the neural networks, 80% of the 4 folds were used for training and 20% for validation to select the best 2 models for each type of neural network (STNN-C, MTNN-C, STNN-R, and LSTM). For random forest, the first 3 folds were used for training and the fourth fold for validation to prune 108 models down to 8 models. In both cases, the goal was to prune the model search space before the cross-validation stage. IRV has one primary hyperparameter, the number of neighbors, so we did not need to prune the model search space before the cross-validation stage.

Based on related work\(^2\) and our preliminary testing with the PCBA tasks, we did not consider neural networks with more than two hidden layers. Our cross-validation results confirmed that two hidden layer networks did not underfit the training data. Because random forests are resistant against overfitting as the number of trees grows,\(^4\) we set the RF n_estimators hyperparameter to be as large as possible while still training reasonably quickly.
E  Model Name to Hyperparameter Mappings

We used alphabetic suffixes such as ",_a" and "_b" to distinguish multiple versions of a model that use different hyperparameters. Only the best hyperparameter combinations from the hyperparameter sweeping stage were labeled with these suffixes. Hyperparameters that did not vary can be found in Appendix D.

Table S7: Single-task neural network classification model name to hyperparameter mapping.

| Model  | weighted schema | optimizer | learning rate | early stopping | epoch patience | activations |
|--------|-----------------|-----------|---------------|----------------|----------------|-------------|
| STNN-C_a | no_weight       | Adam      | 0.003         | PR             | patience: 200, epoch_size: 1000 | [ReLU, ReLU, Sigmoid] |
| STNN-C_b | no_weight       | Adam      | 3e-05         | PR             | patience: 200, epoch_size: 1000 | [ReLU, ReLU, Sigmoid] |

Table S8: Single-task neural network regression model name to hyperparameter mapping.

| Model  | activations | epoch size | weighted schema | optimizer | learning rate |
|--------|-------------|------------|-----------------|-----------|---------------|
| STNN-R_a | [Sigmoid, Sigmoid, Linear] | 200        | no_weight       | Adam      | 0.003         |
| STNN-R_b | [Sigmoid, Sigmoid, Linear] | 1000       | no_weight       | Adam      | 0.003         |

Table S9: Multi-task neural network classification model name to hyperparameter mapping.

| Model  | weighted schema | optimizer | learning rate | early stopping | epoch patience | activations |
|--------|-----------------|-----------|---------------|----------------|----------------|-------------|
| MTNN-C_a | weighted_sample | Adam      | 0.0001        | PR             | patience: 50, epoch_size: 200 | [ReLU, ReLU, Sigmoid] |
| MTNN-C_b | no_weight       | Adam      | 3e-05         | PR             | patience: 200, epoch_size: 1000 | [ReLU, ReLU, Sigmoid] |

Table S10: LSTM model name to hyperparameter mapping.

| Model  | embedding size | optimizer | dropout | early stopping | epoch patience | hidden size |
|--------|----------------|-----------|---------|----------------|----------------|-------------|
| LSTM_a  | 50             | RMSprop   | 0.2     | ROC            | patience: 50, epoch_size: 200 | [100, 50] |
| LSTM_b  | 30             | RMSprop   | 0.5     | ROC            | patience: 50, epoch_size: 200 | [50, 10] |

Table S11: IRV model name to hyperparameter mapping.

| Model  | n_neighbors | epochs | patience | batch_size | learning_rate | penalty |
|--------|-------------|--------|----------|------------|---------------|---------|
| IRV_a  | 5           | 1000   | 20       | 8192       | 0.01          | 0.05    |
| IRV_b  | 10          | 1000   | 20       | 8192       | 0.01          | 0.05    |
| IRV_c  | 20          | 1000   | 20       | 8192       | 0.01          | 0.05    |
| IRV_d  | 40          | 1000   | 20       | 8192       | 0.01          | 0.05    |
| IRV_e  | 80          | 1000   | 20       | 8192       | 0.01          | 0.05    |
Table S12: Random Forest model name to hyperparameter mapping.

| Model | n_estimators | max_features | min_samples_leaf | class_weight |
|-------|--------------|--------------|------------------|--------------|
| RF_a  | 4000         | sqrt         | 1                | None         |
| RF_b  | 8000         | sqrt         | 1                | None         |
| RF_c  | 16000        | sqrt         | 1                | None         |
| RF_d  | 4000         | log2         | 1                | None         |
| RF_e  | 8000         | log2         | 1                | None         |
| RF_f  | 4000         | None         | 1                | balanced     |
| RF_g  | 4000         | log2         | 1                | balanced     |
| RF_h  | 8000         | log2         | 1                | balanced     |
F  Cross-Validation: Results on PriA-SSB FP and RMI-FANCM FP

F.1 Cross-Validation Performance on PriA-SSB FP

Figure S1: Cross-validation performance with AUC[ROC]
Figure S2: Cross-validation performance with AUC[PR]

Figure S3: Cross-validation performance with AUC[BEDROC]
Figure S4: Cross-validation performance with NEF\textsubscript{1\%}.
F.2 Cross-Validation Performance on RMI-FANCM FP

Figure S5: Cross-validation performance with AUC[ROC]
Figure S6: Cross-validation performance with AUC[PR]

Figure S7: Cross-validation performance with AUC[BEDROC]
Figure S8: Cross-validation performance with NEF$_{1\%}$
G  Cross-Validation: Model Comparison Results

Model rankings based on DTK only, which may contain ties. Each cell represents (model, rank).

Table S13: PriA-SSB AS DTK rankings

| ROC AUC PriA-SSB AS | BEDROC AUC PriA-SSB AS | PR auc.integral PriA-SSB AS |
|---------------------|------------------------|-----------------------------|
| 0 RandomForest_d, 1 | SingleRegression_b, 1  | SingleClassification_b, 1  |
| 1 RandomForest_h, 2 | RandomForest_c, 1     | SingleClassification_a, 1  |
| 2 RandomForest_e, 2 | IRV_b, 1              | MultiClassification_a, 1   |
| 3 SingleRegression_b, 4 | SingleRegression_a, 1 | SingleRegression_b, 4     |
| 4 RandomForest_g, 4 | IRV_e, 1             | IRV_e, 4                  |
| 5 RandomForest_c, 4 | MultiClassification_a, 1 | MultiClassification_b, 4 |
| 6 RandomForest_b, 4 | MultiClassification_b, 1 | Docking_hybrid, 7 |
| 7 RandomForest_a, 4 | RandomForest_a, 1 | Docking_smina, 7         |
| 8 MultiClassification_b, 4 | RandomForest_b, 1 | Docking_rdocktot, 7 |
| 9 MultiClassification_a, 10 | IRV_d, 1 | Docking_rdockint, 7 |
| 10 SingleRegression_a, 10 | RandomForest_d, 1 | Docking_plants, 7 |
| 11 SingleClassification_b, 12 | SingleClassification_b, 1 | Docking_fred, 7 |
| 12 IRV_e, 13 | RandomForest_f, 1 | IRV_a, 7                  |
| 13 IRV_d, 13 | RandomForest_g, 1 | Docking_dock6, 7          |
| 14 RandomForest_f, 13 | RandomForest_e, 1 | Docking_Ad4, 7            |
| 15 SingleClassification_a, 16 | RandomForest_b, 1 | ConsensusDocking_rocauc_opt, 7 |
| 16 IRV_c, 17 | SingleClassification_a, 1 | ConsensusDocking_median, 7 |
| 17 IRV_b, 17 | IRV_a, 18              | ConsensusDocking_median, 7 |
| 18 IRV_a, 19 | IRV_c, 18              | ConsensusDocking_median, 7 |
| 19 LSTM_b, 20 | LSTM_b, 20             | Docking_smina, 7         |
| 20 Docking_fred, 21 | Docking_fred, 21 | Docking_dock6, 21         |
| 21 ConsensusDocking_max, 21 | ConsensusDocking_max, 21 | IRV_b, 7               |
| 22 ConsensusDocking_mean, 21 | ConsensusDocking_mean, 21 | IRV_c, 7               |
| 23 ConsensusDocking_median, 21 | ConsensusDocking_median, 21 | SingleRegression_a, 7 |
| 24 ConsensusDocking_rocauc_opt, 21 | ConsensusDocking_rocauc_opt, 21 | LSTM_a, 7           |
| 25 Docking_Ad4, 21 | Docking_Ad4, 21 | Docking_smina, 7       |
| 26 Docking_dock6, 21 | Docking_dock6, 21 | Docking_dockint, 21 |
| 27 Docking_rdockint, 21 | Docking_smina, 21 | Docking_docktot, 21 |
| 28 Docking_hybrid, 21 | Docking_hybrid, 21 | Docking_smina, 21 |
| 29 Docking_plants, 21 | Docking_plants, 21 | Docking_plants, 21 |
| 30 LSTM_a, 21 | Docking_docktot, 21 | Docking_docktot, 21 |
| 31 Docking_docktot, 21 | Docking_docktot, 21 | Docking_docktot, 21 |
| 32 Docking_smina, 21 | Docking_smina, 21 | Docking_smina, 21 |
| 33 Docking_smina, 21 | Docking_smina, 21 | Docking_smina, 21 |
| 34 ConsensusDocking_efr1_opt, 21 | ConsensusDocking_efr1_opt, 21 | ConsensusDocking_efr1_opt, 7 |
| NEF_0.1 % PriA-SSB AS | NEF_0.15 % PriA-SSB AS | NEF_0.5 % PriA-SSB AS |
|------------------------|------------------------|------------------------|
| IRV_e, 1               | IRV_e, 1               | SingleClassification_a, 1 |
| SingleClassification_b, 1 | SingleClassification_b, 1 | RandomForest_h, 2 |
| SingleClassification_a, 1 | SingleClassification_a, 1 | SingleRegression_b, 3 |
| MultiClassification_b, 3 | SingleClassification_a, 1 | RandomForest_a, 3 |
| IRV_h, 1               | IRV_h, 1               | IRV_a, 3               |
| MultiClassification_a, 3 | IRV_h, 1               | IRV_a, 3               |
| MultiClassification_a, 3 | IRV_h, 1               | IRV_a, 3               |
| MultiClassification_a, 3 | IRV_h, 1               | IRV_a, 3               |
| IRV_c, 5               | IRV_c, 6               | IRV_c, 3               |
| RandomClassification_b, 7 | MultiClassification_a, 6 | IRV_c, 3               |
| MultiClassification_b, 7 | MultiClassification_b, 6 | SingleClassification_a, 3 |
| IRV_d, 1               | IRV_d, 1               | IRV_c, 3               |
| IRV_g, 7               | RandomForest_b, 11     | RandomForest_b, 3     |
| RandomForest_b, 7      | RandomForest_c, 11     | RandomForest_b, 3     |
| RandomForest_a, 7      | RandomForest_b, 11     | RandomForest_b, 3     |
| RandomForest_h, 7      | RandomForest_a, 11     | RandomForest_b, 3     |
| IRV_e, 11              | RandomForest_e, 11     | RandomForest_b, 3     |
| Docking_fred, 16       | IRV_a, 11              | RandomForest_g, 3     |
| Docking_dock6, 16      | RandomForest_d, 11     | SingleClassification_b, 3 |
| ConsensusDocking_rocauc_opt, 16 | SingleRegression_b, 18 | RandomForest_f, 19 |
| SingleRegression_b, 16 | Docking_fred, 20       | Docking_fred, 20      |
| ConsensusDocking_max, 20 | ConsensusDocking_max, 20 | ConsensusDocking_max, 20 |
| ConsensusDocking_median, 20 | ConsensusDocking_median, 20 | ConsensusDocking_median, 20 |
| Docking_plants, 16     | ConsensusDocking_rocauc_opt, 20 | ConsensusDocking_rocauc_opt, 20 |
| Docking_hybrid, 16     | Docking_ad4, 20        | Docking_ad4, 20       |
| Docking_dock6, 20      | Docking_dock6, 20      | Docking_dock6, 20     |
| Docking_dockint, 16    | Docking_hybrid, 20     | Docking_dockint, 20   |
| Docking_plants, 20     | Docking_plants, 20     | Docking_plants, 20    |
| Docking_plants, 20     | Docking_plants, 20     | Docking_plants, 20    |
| Docking_hybrid, 20     | Docking_hybrid, 20     | Docking_hybrid, 20    |
| Docking_dockint, 20    | Docking_dockint, 20    | Docking_dockint, 20   |
| Docking_smina, 20      | Docking_smina, 20      | Docking_smina, 20     |
| Docking_smina, 20      | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_smina, 20      | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_smina, 20      | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_smina, 20      | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
| Docking_hybrid, 20     | Docking_smina, 20      | Docking_smina, 20     |
Table S13: PriA-SSB AS DTK rankings (continued)

| NEF_1 % PriA-SSB AS | NEF_2 % PriA-SSB AS | NEF_5 % PriA-SSB AS |
|----------------------|----------------------|----------------------|
| 0 RandomForest_h, 1  | RandomForest_h, 1   | SingleRegression_b, 1|
| 1 SingleClassification_a, 2 | SingleClassification_a, 2 | RandomForest_b, 1 |
| 2 SingleRegression_b, 3 | SingleRegression_b, 3  | IRV_b, 1 |
| 3 RandomForest_a, 3 | RandomForest_a, 3 | IRV_c, 1 |
| 4 IRV_a, 3 | IRV_b, 3 | SingleRegression_a, 1 |
| 5 IRV_b, 3 | IRV_c, 3 | IRV_e, 1 |
| 6 IRV_c, 3 | SingleRegression_a, 3 | MultiClassification_a, 1 |
| 7 SingleRegression_a, 3 | IRV_e, 3 | MultiClassification_b, 1 |
| 8 IRV_e, 3 | MultiClassification_a, 3 | RandomForest_a, 1 |
| 9 MultiClassification_a, 3 | MultiClassification_b, 3 | IRV_d, 1 |
| 10 MultiClassification_b, 3 | IRV_d, 3 | RandomForest_c, 1 |
| 11 IRV_d, 3 | RandomForest_b, 3 | RandomForest_e, 1 |
| 12 RandomForest_b, 3 | RandomForest_b, 3 | RandomForest_f, 1 |
| 13 RandomForest_d, 3 | RandomForest_e, 3 | RandomForest_g, 1 |
| 14 RandomForest_e, 3 | RandomForest_e, 3 | RandomForest_h, 1 |
| 15 RandomForest_f, 3 | RandomForest_f, 3 | SingleClassification_a, 1 |
| 16 RandomForest_g, 3 | SingleClassification_a, 3 | SingleClassification_b, 1 |
| 17 SingleClassification_b, 3 | RandomForest_c, 3 | RandomForest_d, 1 |
| 18 RandomForest_c, 3 | IRV_a, 19 | IRV_a, 19 |
| 19 Docking_fred, 20 | Docking_fred, 20 | Docking_fred, 20 |
| 20 ConsensusDocking_max, 20 | ConsensusDocking_max, 20 | ConsensusDocking_max, 20 |
| 21 ConsensusDocking_mean, 20 | ConsensusDocking_mean, 20 | ConsensusDocking_mean, 20 |
| 22 ConsensusDocking_median, 20 | ConsensusDocking_median, 20 | ConsensusDocking_median, 20 |
| 23 ConsensusDocking_rocauc_opt, 20 | ConsensusDocking_rocauc_opt, 20 | ConsensusDocking_rocauc_opt, 20 |
| 24 Docking_ad4, 20 | Docking_ad4, 20 | Docking_ad4, 20 |
| 25 Docking_dock6, 20 | Docking_dock6, 20 | Docking_dock6, 20 |
| 26 Docking_rdocktot, 20 | Docking_rdocktot, 20 | Docking_dmina, 20 |
| 27 Docking_hybrid, 20 | Docking_hybrid, 20 | Docking_hybrid, 20 |
| 28 Docking_plants, 20 | Docking_plants, 20 | Docking_plants, 20 |
| 29 Docking_rdockint, 20 | Docking_rdockint, 20 | Docking_rdockint, 20 |
| 30 Docking_dmina, 20 | Docking_dmina, 20 | Docking_rdocktot, 20 |
| 31 Docking_surflex, 20 | Docking_surflex, 20 | Docking_surflex, 20 |
| 32 LSTM_a, 20 | LSTM_a, 20 | LSTM_a, 20 |
| 33 LSTM_b, 20 | LSTM_b, 20 | LSTM_b, 20 |
| 34 ConsensusDocking_efr1_opt, 20 | ConsensusDocking_efr1_opt, 20 | ConsensusDocking_efr1_opt, 20 |
Table S13: PriA-SSB AS DTK rankings (continued)

| NEF_10 % PriA-SSB AS | NEF_20 % PriA-SSB AS | NEF AUC PriA-SSB AS |
|-----------------------|-----------------------|---------------------|
| SingleRegression_b, 1 | SingleRegression_b, 1 | SingleRegression_b, 1 |
| RandomForest_c, 1    | MultiClassification_b, 1 | RandomForest_b, 1 |
| SingleRegression_a, 1 | SingleRegression_a, 3 | IRV_b, 1 |
| IRV_e, 1             | SingleClassification_a, 4 | SingleRegression_a, 1 |
| MultiClassification_a, 1 | RandomForest_h, 4 | IRV_e, 1 |
| MultiClassification_a, 1 | RandomForest_c, 4 | MultiClassification_a, 1 |
| RandomForest_a, 1    | RandomForest_b, 4    | MultiClassification_a, 1 |
| RandomForest_b, 1    | RandomForest_a, 4    | RandomForest_a, 1 |
| IRV_d, 1             | MultiClassification_a, 4 | RandomForest_b, 1 |
| RandomForest_d, 1    | SingleClassification_b, 10 | IRV_d, 1 |
| SingleClassification_b, 1 | RandomForest_g, 10 | RandomForest_d, 1 |
| RandomForest_f, 1    | RandomForest_e, 10   | SingleClassification_b, 1 |
| RandomForest_g, 1    | RandomForest_d, 14   | RandomForest_f, 1 |
| RandomForest_h, 1    | IRV_e, 15            | RandomForest_e, 1 |
| RandomForest_e, 1    | IRV_d, 15            | RandomForest_h, 1 |
| IRV_b, 17            | IRV_b, 17            | SingleClassification_a, 1 |
| IRV_c, 17            | IRV_c, 18            | IRV_a, 18 |
| IRV_a, 19            | IRV_a, 19            | IRV_c, 18 |
| LSTM_b, 20           | LSTM_b, 19           | LSTM_b, 20 |
| Docking_fred, 21     | LSTM_a, 21           | Docking_fred, 21 |
| ConsensusDocking_max, 21 | Docking_dock6, 21 | ConsensusDocking_max, 21 |
| ConsensusDocking_mean, 21 | ConsensusDocking_max, 21 | ConsensusDocking_mean, 21 |
| ConsensusDocking_median, 21 | ConsensusDocking_max, 21 | ConsensusDocking_median, 21 |
| ConsensusDocking_rocauc_opt, 21 | ConsensusDocking_max, 21 | ConsensusDocking_rocauc_opt, 21 |
| Docking_ad4, 21      | ConsensusDocking_rocauc_opt, 21 | Docking_ad4, 21 |
| Docking_dock6, 21    | Docking_ad4, 21      | Docking_dock6, 21 |
| Docking_smrna, 21    | Docking_plants, 21   | Docking_smrna, 21 |
| Docking_plants, 21   | Docking_fred, 21     | Docking_plants, 21 |
| Docking_hybrid, 21   | Docking_fred, 21     | Docking_hybrid, 21 |
| Docking_plants, 21   | Docking_hybrid, 21   | Docking_plants, 21 |
| Docking_rdockint, 21 | Docking_rdockint, 21 | Docking_rdockint, 21 |
| Docking_rdocktot, 21 | Docking_rdocktot, 21 | Docking_rdocktot, 21 |
| Docking_surflex, 21  | Docking_surflex, 21  | Docking_surflex, 21 |
| LSTM_a, 21           | Docking_surflex, 21  | LSTM_a, 21 |
| ConsensusDocking_efr1_opt, 21 | ConsensusDocking_efr1_opt, 21 | ConsensusDocking_efr1_opt, 21 |
| n_hits_100 | PriA-SSB AS | n_hits_250 | PriA-SSB AS | n_hits_500 | PriA-SSB AS |
|------------|-------------|------------|-------------|------------|-------------|
| 0          | SingleClassification_a | 1          | RandomForest_h | 1          | RandomForest_h | 1          |
| 1          | RandomForest_h | 1          | SingleClassification_a | 2          | SingleRegression_b | 2          |
| 2          | SingleRegression_b | 3          | SingleRegression_b | 3          | RandomForest_b | 2          |
| 3          | RandomForest_a | 3          | RandomForest_a | 3          | IRV_a | 3          |
| 4          | IRV_a | 3          | IRV_a | 3          | SingleRegression_a | 2          |
| 5          | IRV_b | 3          | IRV_b | 3          | IRV_e | 2          |
| 6          | IRV_e | 3          | IRV_c | 3          | MultiClassification_a | 2          |
| 7          | SingleRegression_a | 3          | SingleRegression_a | 3          | MultiClassification_b | 2          |
| 8          | IRV_e | 3          | IRV_e | 3          | RandomForest_a | 2          |
| 9          | MultiClassification_a | 3          | MultiClassification_a | 3          | RandomForest_e | 3          |
| 10         | MultiClassification_b | 3          | MultiClassification_b | 3          | RandomForest_e | 3          |
| 11         | IRV_d | 3          | IRV_d | 3          | RandomForest_e | 3          |
| 12         | RandomForest_b | 3          | RandomForest_b | 3          | RandomForest_g | 2          |
| 13         | RandomForest_d | 3          | RandomForest_d | 3          | SingleClassification_a | 2          |
| 14         | RandomForest_e | 3          | RandomForest_e | 3          | SingleClassification_b | 2          |
| 15         | RandomForest_f | 3          | RandomForest_f | 3          | RandomForest_d | 2          |
| 16         | SingleClassification_b | 3          | RandomForest_g | 3          | IRV_c | 17         |
| 17         | SingleClassification_b | 3          | RandomForest_c | 3          | IRV_a | 17         |
| 18         | RandomForest_c | 3          | SingleClassification_b | 3          | RandomForest_f | 19         |
| 19         | Docking_fred | 20         | Docking_fred | 20         | Docking_fred | 20         |
| 20         | ConsensusDocking_max | 20         | ConsensusDocking_max | 20         | ConsensusDocking_max | 20         |
| 21         | ConsensusDocking_mean | 20         | ConsensusDocking_mean | 20         | ConsensusDocking_mean | 20         |
| 22         | ConsensusDocking_median | 20         | ConsensusDocking_median | 20         | ConsensusDocking_median | 20         |
| 23         | ConsensusDocking_rocauc_opt | 20         | ConsensusDocking_rocauc_opt | 20         | ConsensusDocking_rocauc_opt | 20         |
| 24         | Docking_ad4 | 20         | Docking_ad4 | 20         | Docking_ad4 | 20         |
| 25         | Docking_dock6 | 20         | Docking_dock6 | 20         | Docking_dock6 | 20         |
| 26         | Docking_docktot | 20         | Docking_docktot | 20         | Docking_smina | 20         |
| 27         | Docking_hybrid | 20         | Docking_hybrid | 20         | Docking_hybrid | 20         |
| 28         | Docking_plants | 20         | Docking_plants | 20         | Docking_plants | 20         |
| 29         | Docking_dockint | 20         | Docking_dockint | 20         | Docking_dockint | 20         |
| 30         | Docking_smina | 20         | Docking_smina | 20         | Docking_docktot | 20         |
| 31         | Docking_surflex | 20         | Docking_surflex | 20         | Docking_surflex | 20         |
| 32         | LSTM_a | 20         | LSTM_a | 20         | LSTM_a | 20         |
| 33         | LSTM_b | 20         | LSTM_b | 20         | LSTM_b | 20         |
| 34         | ConsensusDocking_efr1_opt | 20         | ConsensusDocking_efr1_opt | 20         | ConsensusDocking_efr1_opt | 20         |
Table S13: PriA-SSB AS DTK rankings (continued)

| n_hits_1000 PriA-SSB AS | n_hits_2500 PriA-SSB AS | n_hits_5000 PriA-SSB AS |
|--------------------------|--------------------------|--------------------------|
| 0 SingleRegression_b, 1  | SingleRegression_b, 1   | SingleRegression_b, 1   |
| 1 RandomForest_b, 1      | MultiClassification_b, 1| MultiClassification_b, 1|
| 2 IRV_b, 1               | RandomForest_f, 3        | SingleRegression_a, 1   |
| 3 IRV_c, 1               | RandomForest_c, 3        | RandomForest_d, 4        |
| 4 SingleRegression_a, 1  | RandomForest_b, 3        | RandomForest_c, 4        |
| 5 IRV_e, 1               | RandomForest_a, 3        | RandomForest_h, 6        |
| 6 MultiClassification_a, 1| SingleRegression_a, 3   | RandomForest_g, 6        |
| 7 MultiClassification_b, 1| SingleClassification_b, 8| RandomForest_e, 6        |
| 8 RandomForest_a, 1      | SingleClassification_a, 8| MultiClassification_a, 6|
| 9 IRV_d, 1               | RandomForest_h, 8        | SingleClassification_b, 10|
| 10 RandomForest_c, 1     | RandomForest_g, 8        | RandomForest_b, 10       |
| 11 RandomForest_e, 1     | RandomForest_e, 8        | RandomForest_a, 12       |
| 12 RandomForest_f, 1     | RandomForest_d, 8        | SingleClassification_a, 13|
| 13 RandomForest_g, 1     | MultiClassification_a, 8| RandomForest_f, 13       |
| 14 RandomForest_h, 1     | IRV_e, 15               | IRV_e, 15                |
| 15 SingleClassification_a, 1| IRV_d, 16              | LSTM_a, 17               |
| 16 SingleClassification_b, 1| IRV_b, 17              | ConsensusDocking_max, 17 |
| 17 RandomForest_d, 1     | IRV_c, 18               | Docking_hybrid, 17       |
| 18 IRV_a, 19             | IRV_a, 19               | ConsensusDocking_max, 17 |
| 19 Docking_fred, 20      | LSTM_b, 20              | ConsensusDocking_mean, 17|
| 20 ConsensusDocking_max, 20| LSTM_a, 21            | ConsensusDocking_median, 17|
| 21 ConsensusDocking_mean, 20| Docking_dock6, 21      | Docking_rocauc_opt, 17   |
| 22 ConsensusDocking_median, 20| ConsensusDocking_max, 21| Docking_ad4, 17         |
| 23 ConsensusDocking_rocauc_opt, 20| ConsensusDocking_mean, 21| Docking_dock6, 17       |
| 24 Docking_ad4, 20       | ConsensusDocking_median, 21| Docking_fred, 17        |
| 25 Docking_dock6, 20     | ConsensusDocking_rocauc_opt, 21| Docking_plants, 17      |
| 26 Docking_smina, 20     | Docking_ad4, 21         | LSTM_b, 17               |
| 27 Docking_hybrid, 20    | Docking_plants, 21      | Docking_rodockint, 17    |
| 28 Docking_plants, 20    | Docking_fred, 21        | Docking_rdocktot, 17     |
| 29 Docking_rodockint, 20 | Docking_hybrid, 21      | Docking_smima, 17        |
| 30 Docking_rdocktot, 20  | Docking_rodockint, 21   | Docking_surflex, 17      |
| 31 Docking_surflex, 20   | Docking_rodocktot, 21   | IRV_a, 17                |
| 32 LSTM_a, 20            | Docking_smina, 21       | IRV_b, 17                |
| 33 LSTM_b, 20            | Docking_surflex, 21     | IRV_c, 17                |
| 34 ConsensusDocking_efr1_opt, 20| ConsensusDocking_efr1_opt, 21| ConsensusDocking_efr1_opt, 17|
Table S13: **PriA-SSB AS DTK rankings (continued)**

| n_hits_10000 PriA-SSB AS |
|---------------------------|
| 0  IRV_e, 1               |
| 1  IRV_d, 2               |
| 2  IRV_a, 2               |
| 3  IRV_b, 2               |
| 4  IRV_c, 2               |
| 5  RandomForest_g, 2      |
| 6  RandomForest_e, 2      |
| 7  RandomForest_d, 2      |
| 8  MultiClassification_b, 9 |
| 9  MultiClassification_a, 9 |
| 10 RandomForest_c, 9      |
| 11 RandomForest_b, 9      |
| 12 SingleRegression_a, 14 |
| 13 SingleRegression_b, 14 |
| 14 RandomForest_h, 14     |
| 15 SingleClassification_b, 16 |
| 16 RandomForest_a, 17     |
| 17 LSTM_b, 17             |
| 18 SingleClassification_a, 17 |
| 19 Docking_fred, 20       |
| 20 ConsensusDocking_max, 20 |
| 21 ConsensusDocking_mean, 20 |
| 22 ConsensusDocking_median, 20 |
| 23 ConsensusDocking_rocauc_opt, 20 |
| 24 Docking_ad4, 20        |
| 25 Docking_dock6, 20      |
| 26 Docking_rdocktot, 20   |
| 27 Docking_hybrid, 20     |
| 28 Docking_plants, 20     |
| 29 Docking_rdockint, 20   |
| 30 Docking_smina, 20      |
| 31 Docking_surflex, 20    |
| 32 RandomForest_f, 20     |
| 33 LSTM_a, 20             |
| 34 ConsensusDocking_efr1_opt, 20 |
Table S14: PriA-SSB FP DTK rankings

| ROC AUC PriA-SSB FP | BEDROC AUC PriA-SSB FP | PR auc.integral PriA-SSB FP |
|---------------------|-------------------------|-----------------------------|
| 0                   | SingleRegression_a, 1   | SingleRegression_b, 1       |
| 1                   | SingleRegression_b, 1   | SingleRegression_a, 2       |
| 2                   | IRV_e, 3                | IRV_e, 3                    |
| 3                   | RandomForest_b, 3       | RandomForest_max, 4         |
| 4                   | Docking_hybrid, 5       | Docking_surflex, 2          |
| 5                   | Docking_smina, 5        | Docking_rocauc_opt, 4       |
| 6                   | Docking_rdocktot, 5     | Docking_fred, 4             |
| 7                   | Docking_plants, 5       | Docking_plants, 4           |
| 8                   | Docking_fred, 5         | Docking_fred, 4             |
| 9                   | DOCKing_plants, 5       | DOCKing_plants, 4           |
| 10                  | IRV_b, 4                | DOCKing_plants, 4           |
| 11                  | DOCKing_dock6, 5        | DOCKing_dock6, 4            |
| 12                  | Docking_rdockint, 5     | DOCKing_dockint, 4          |
| 13                  | DOCKing_rdocktot, 5     | DOCKing_docktot, 2          |
| 14                  | ConsensusDocking_rocauc_opt, 5 | DOCKing_dock6, 4 |
| 15                  | DOCKing_median, 5       | DOCKing_median, 4           |
| 16                  | DOCKing_max, 5          | DOCKing_max, 4              |
| 17                  | DOCKing_max, 5          | DOCKing_max, 4              |
| 18                  | IRV_d, 4                | SingleRegression_a, 2       |
| 19                  | IRV_c, 5                | SingleRegression_a, 4       |
| 20                  | LSTM_a, 5               | SingleClassification_b, 2   |
| 21                  | LSTM_b, 5               | SingleClassification_a, 2   |
| 22                  | MultiClassification_a, 5 | MultiClassification_b, 4    |
| 23                  | MultiClassification_b, 5 | MultiClassification_b, 4    |
| 24                  | RandomForest_a, 5       | RandomForest_b, 4           |
| 25                  | RandomForest_b, 5       | RandomForest_c, 4           |
| 26                  | RandomForest_c, 5       | RandomForest_d, 4           |
| 27                  | RandomForest_d, 5       | RandomForest_e, 4           |
| 28                  | RandomForest_e, 5       | RandomForest_f, 4           |
| 29                  | RandomForest_f, 5       | RandomForest_g, 4           |
| 30                  | RandomForest_g, 5       | MultiClassification_b, 2    |
| 31                  | MultiClassification_a, 5 | MultiClassification_a, 2    |
| 32                  | SingleClassification_a, 4 | SingleClassification_a, 4   |
| 33                  | SingleClassification_b, 5 | SingleClassification_b, 4   |
| 34                  | ConsensusDocking_efr1_opt, 5 | ConsensusDocking_efr1_opt, 4 |
Table S14: PriA-SSB FP DTK rankings (continued)

| NEF_0.1 % PriA-SSB FP | NEF_0.15 % PriA-SSB FP | NEF_0.5 % PriA-SSB FP |
|-----------------------|------------------------|-----------------------|
| 0 SingleRegression_b, 1 | SingleRegression_b, 1 | SingleRegression_b, 1 |
| 1 Docking_hybrid, 1 | Docking_hybrid, 1 | Docking_hybrid, 2 |
| 2 IRV_a, 1 | IRV_a, 1 | IRV_a, 2 |
| 3 Docking_surflex, 1 | Docking_surflex, 1 | Docking_surflex, 2 |
| 4 Docking_smina, 1 | Docking_smina, 1 | Docking_smina, 2 |
| 5 Docking_rdocktot, 1 | Docking_rdocktot, 1 | Docking_rdocktot, 2 |
| 6 Docking_rdockint, 1 | Docking_rdockint, 1 | Docking_rdockint, 2 |
| 7 Docking_plants, 1 | Docking_plants, 1 | Docking_plants, 2 |
| 8 Docking_fred, 1 | Docking_fred, 1 | Docking_fred, 2 |
| 9 IRV_c, 1 | IRV_c, 1 | IRV_c, 2 |
| 10 Docking_dock6, 1 | Docking_dock6, 1 | Docking_dock6, 2 |
| 11 Docking_ad4, 1 | Docking_ad4, 1 | Docking_ad4, 2 |
| 12 ConsensusDocking_rocauc_opt, 1 | ConsensusDocking_rocauc_opt, 1 | ConsensusDocking_rocauc_opt, 2 |
| 13 ConsensusDocking_median, 1 | ConsensusDocking_median, 1 | ConsensusDocking_median, 2 |
| 14 ConsensusDocking_mean, 1 | ConsensusDocking_mean, 1 | ConsensusDocking_mean, 2 |
| 15 ConsensusDocking_max, 1 | ConsensusDocking_max, 1 | ConsensusDocking_max, 2 |
| 16 IRV_b, 1 | IRV_b, 1 | IRV_b, 2 |
| 17 IRV_d, 1 | IRV_d, 1 | IRV_d, 2 |
| 18 SingleRegression_a, 1 | SingleRegression_a, 1 | SingleRegression_a, 2 |
| 19 RandomForest_d, 1 | RandomForest_d, 1 | RandomForest_d, 2 |
| 20 SingleClassification_b, 1 | SingleClassification_b, 1 | SingleClassification_b, 2 |
| 21 SingleClassification_a, 1 | SingleClassification_a, 1 | SingleClassification_a, 2 |
| 22 RandomForest_h, 1 | RandomForest_h, 1 | RandomForest_h, 2 |
| 23 RandomForest_g, 1 | RandomForest_g, 1 | RandomForest_g, 2 |
| 24 RandomForest_f, 1 | RandomForest_f, 1 | RandomForest_f, 2 |
| 25 RandomForest_e, 1 | RandomForest_e, 1 | RandomForest_e, 2 |
| 26 RandomForest_c, 1 | RandomForest_c, 1 | RandomForest_c, 2 |
| 27 IRV_e, 1 | IRV_e, 1 | IRV_e, 2 |
| 28 RandomForest_b, 1 | RandomForest_b, 1 | RandomForest_b, 2 |
| 29 RandomForest_a, 1 | RandomForest_a, 1 | RandomForest_a, 2 |
| 30 MultiClassification_b, 1 | MultiClassification_b, 1 | MultiClassification_b, 2 |
| 31 MultiClassification_a, 1 | MultiClassification_a, 1 | MultiClassification_a, 2 |
| 32 LSTM_b, 1 | LSTM_b, 1 | LSTM_b, 2 |
| 33 LSTM_a, 1 | LSTM_a, 1 | LSTM_a, 2 |
| 34 ConsensusDocking_efr1_opt, 1 | ConsensusDocking_efr1_opt, 1 | ConsensusDocking_efr1_opt, 2 |
Table S14: PriA-SSB FP DTK rankings (continued)

| NEF_1 % PriA-SSB FP | NEF_2 % PriA-SSB FP | NEF_5 % PriA-SSB FP |
|----------------------|----------------------|----------------------|
| SingleRegression_b, 1| SingleRegression_a, 1| SingleRegression_a, 1|
| SingleRegression_a, 1| IRV_e, 2             | SingleRegression_b, 2|
| ConsensusDocking_max, 3| SingleRegression_b, 3| ConsensusDocking_max, 3|
| ConsensusDocking_mean, 3| ConsensusDocking_mean, 4| ConsensusDocking_mean, 3|
| ConsensusDocking_median, 3| ConsensusDocking_median, 4| ConsensusDocking_median, 3|
| ConsensusDocking_rocauc_opt, 3| ConsensusDocking_rocauc_opt, 4| ConsensusDocking_rocauc_opt, 3|
| Docking_ad4, 3       | Docking_ad4, 4       | Docking_ad4, 4       |
| Docking_dock6, 3     | Docking_dock6, 4     | Docking_dock6, 3     |
| Docking_fred, 3      | Docking_fred, 4      | Docking_fred, 3      |
| IRV_c, 3             | IRV_b, 4             | IRV_a, 3             |
| Docking_plants, 3    | Docking_plants, 4    | Docking_plants, 3    |
| Docking_rdockint, 3  | Docking_rdockint, 4  | Docking_rdockint, 3  |
| Docking_rdocktot, 3  | Docking_rdocktot, 4  | Docking_rdocktot, 3  |
| Docking_smina, 3     | Docking_smina, 4     | Docking_smina, 3     |
| Docking_surflex, 3   | Docking_surflex, 4   | Docking_surflex, 3   |
| IRV_a, 3             | IRV_a, 4             | IRV_a, 3             |
| ConsensusDocking_max, 4| Docking_hybrid, 4     | Docking_hybrid, 4     |
| IRV_d, 3             | IRV_d, 4             | IRV_d, 3             |
| IRV_e, 3             | IRV_e, 4             | IRV_e, 3             |
| LSTM_a, 3            | LSTM_a, 4            | LSTM_a, 3            |
| LSTM_b, 3            | LSTM_b, 4            | LSTM_b, 3            |
| MultiClassification_a, 3 | MultiClassification_a, 4 | MultiClassification_a, 3 |
| MultiClassification_a, 4 | MultiClassification_a, 5 | MultiClassification_a, 3 |
| RandomForest_a, 3    | RandomForest_a, 4    | RandomForest_a, 3    |
| RandomForest_b, 3    | RandomForest_b, 4    | RandomForest_b, 3    |
| RandomForest_c, 3    | RandomForest_c, 4    | RandomForest_c, 3    |
| RandomForest_d, 3    | RandomForest_d, 4    | RandomForest_d, 3    |
| RandomForest_e, 3    | RandomForest_e, 4    | RandomForest_e, 3    |
| RandomForest_f, 3    | RandomForest_f, 4    | RandomForest_f, 3    |
| RandomForest_g, 3    | RandomForest_g, 4    | RandomForest_g, 3    |
| RandomForest_h, 3    | RandomForest_h, 4    | RandomForest_h, 3    |
| SingleClassification_a, 3 | SingleClassification_a, 4 | SingleClassification_a, 3 |
| SingleClassification_b, 3 | SingleClassification_b, 4 | SingleClassification_b, 3 |
| SingleClassification_c, 3 | SingleClassification_c, 4 | SingleClassification_c, 3 |
| SingleClassification_d, 3 | SingleClassification_d, 4 | SingleClassification_d, 3 |
| SingleClassification_e, 3 | SingleClassification_e, 4 | SingleClassification_e, 3 |
| SingleClassification_f, 3 | SingleClassification_f, 4 | SingleClassification_f, 3 |
| SingleClassification_g, 3 | SingleClassification_g, 4 | SingleClassification_g, 3 |
| SingleClassification_h, 3 | SingleClassification_h, 4 | SingleClassification_h, 3 |
| ConsensusDocking_efr1_opt, 3 | ConsensusDocking_efr1_opt, 4 | ConsensusDocking_efr1_opt, 3 |
| NEF_10% PriA-SSB FP | NEF_20% PriA-SSB FP | NEF AUC PriA-SSB FP |
|----------------------|----------------------|----------------------|
| SingleRegression_b, 1 | SingleRegression_b, 1 | SingleRegression_b, 1 |
| SingleRegression_a, 2 | SingleRegression_a, 1 | SingleRegression_a, 1 |
| ConsensusDocking_max, 3 | RandomForest_e, 3 | ConsensusDocking_max, 3 |
| ConsensusDocking_mean, 3 | ConsensusDocking_max, 4 | ConsensusDocking_mean, 3 |
| ConsensusDocking_median, 3 | ConsensusDocking_mean, 4 | ConsensusDocking_median, 3 |
| ConsensusDocking_rocauc_opt, 3 | ConsensusDocking_rocauc_opt, 4 | ConsensusDocking_rocauc_opt, 3 |
| Docking_ad, 3 | Docking_ad, 4 | Docking_ad, 3 |
| Docking_dock6, 3 | Docking_dock6, 4 | Docking_dock6, 3 |
| Docking_fred, 3 | Docking_fred, 4 | Docking_fred, 3 |
| IRV_c, 3 | IRV_b, 4 | IRV_c, 3 |
| Docking_plants, 3 | Docking_plants, 4 | Docking_plants, 3 |
| Docking_rdockint, 3 | Docking_rdockint, 4 | Docking_rdockint, 3 |
| Docking_rdocktot, 3 | Docking_rdocktot, 4 | Docking_rdocktot, 3 |
| Docking_smina, 3 | Docking_smina, 4 | Docking_smina, 3 |
| Docking_surflex, 3 | Docking_surflex, 4 | Docking_surflex, 3 |
| IRV_a, 3 | Docking_fred, 4 | Docking_fred, 3 |
| IRV_d, 3 | IRV_d, 4 | IRV_d, 3 |
| IRV_e, 3 | IRV_e, 4 | IRV_e, 3 |
| LSTM_a, 3 | LSTM_a, 4 | LSTM_a, 3 |
| LSTM_b, 3 | LSTM_b, 4 | LSTM_b, 3 |
| MultiClassification_a, 3 | MultiClassification_a, 4 | MultiClassification_a, 3 |
| MultiClassification_b, 3 | MultiClassification_b, 4 | MultiClassification_b, 3 |
| RandomForest_a, 3 | RandomForest_a, 4 | RandomForest_a, 3 |
| RandomForest_b, 3 | RandomForest_b, 4 | RandomForest_b, 3 |
| RandomForest_c, 3 | RandomForest_c, 4 | RandomForest_c, 3 |
| RandomForest_d, 3 | RandomForest_d, 4 | RandomForest_d, 3 |
| RandomForest_e, 3 | RandomForest_e, 4 | RandomForest_e, 3 |
| RandomForest_f, 3 | RandomForest_f, 4 | RandomForest_f, 3 |
| RandomForest_g, 3 | RandomForest_g, 4 | RandomForest_g, 3 |
| RandomForest_h, 3 | RandomForest_h, 4 | RandomForest_h, 3 |
| SingleClassification_a, 3 | SingleClassification_a, 4 | SingleClassification_a, 3 |
| SingleClassification_b, 3 | SingleClassification_b, 4 | SingleClassification_b, 3 |
| ConsensusDocking_efr1_opt, 3 | ConsensusDocking_efr1_opt, 4 | ConsensusDocking_efr1_opt, 3 |
Table S14: PriA-SSB FP DTK rankings (continued)

| n_hits_100 PriA-SSB FP       | n_hits_250 PriA-SSB FP       | n_hits_500 PriA-SSB FP       |
|-------------------------------|-------------------------------|-------------------------------|
| 0 SingleRegression_b, 1      | SingleRegression_a, 1         | SingleRegression_b, 1         |
| 1 Docking_hybrid, 2          | IRV_e, 2                      | SingleRegression_a, 1         |
| 2 IRV_a, 2                   | SingleRegression_b, 2         | ConsensusDocking_max, 3       |
| 3 Docking_smina, 2           | ConsensusDocking_mean, 4      | ConsensusDocking_mean, 3      |
| 4 Docking_rdocktot, 2        | ConsensusDocking_median, 4    | ConsensusDocking_median, 3    |
| 5 Docking_rdockint, 2        | ConsensusDocking_rocauc_opt, 4| ConsensusDocking_rocauc_opt, 3|
| 6 Docking_plants, 2          | Docking_ad4, 4                | Docking_ad4, 3                |
| 7 Docking_fred, 2            | Docking_dock6, 4              | Docking_dock6, 3              |
| 8 Docking_dock6, 2           | Docking_fred, 4               | Docking_fred, 3               |
| 9 IRV_c, 2                   | IRV_b, 4                      | IRV_c, 3                      |
| 10 Docking_dock6, 2          | Docking_plants, 4             | Docking_plants, 3             |
| 11 Docking_ad4, 2            | Docking_rdockint, 4           | Docking_rdockint, 3           |
| 12 ConsensusDocking_rocauc_opt, 2 | Docking_rdocktot, 4          | Docking_rdocktot, 3           |
| 13 ConsensusDocking_median, 2 | Docking_smina, 4              | Docking_smina, 3              |
| 14 ConsensusDocking_median, 2 | Docking_smina, 4              | Docking_smina, 3              |
| 15 ConsensusDocking_max, 2    | Docking_smina, 4              | Docking_smina, 3              |
| 16 IRV_b, 2                  | ConsensusDocking_max, 4       | ConsensusDocking_max, 3       |
| 17 IRV_d, 2                  | Docking_plants, 4             | Docking_plants, 3             |
| 18 SingleRegression_a, 2     | Docking_hybrid, 4             | Docking_hybrid, 3             |
| 19 RandomForest_d, 2         | IRV_c, 4                      | IRV_c, 3                      |
| 20 SingleClassification_b, 2 | IRV_d, 4                      | IRV_d, 3                      |
| 21 SingleClassification_b, 2 | LSTM_a, 4                     | LSTM_a, 3                     |
| 22 RandomForest_h, 2         | LSTM_b, 4                     | LSTM_b, 3                     |
| 23 RandomForest_g, 2         | MultiClassification_a, 4     | MultiClassification_a, 3     |
| 24 RandomForest_f, 2         | MultiClassification_b, 4     | MultiClassification_b, 3     |
| 25 RandomForest_e, 2         | RandomForest_a, 4             | RandomForest_a, 3             |
| 26 RandomForest_c, 2         | RandomForest_b, 4             | RandomForest_b, 3             |
| 27 IRV_e, 2                  | RandomForest_c, 4             | RandomForest_c, 3             |
| 28 RandomForest_b, 2         | RandomForest_d, 4             | RandomForest_d, 3             |
| 29 RandomForest_a, 2         | RandomForest_e, 4             | RandomForest_e, 3             |
| 30 MultiClassification_b, 2 | RandomForest_f, 4             | RandomForest_f, 3             |
| 31 MultiClassification_a, 2 | RandomForest_g, 4             | RandomForest_g, 3             |
| 32 LSTM_b, 2                 | RandomForest_h, 4             | RandomForest_h, 3             |
| 33 LSTM_a, 2                 | SingleClassification_a, 4    | SingleClassification_a, 3    |
| 34 ConsensusDocking_efr1_opt, 2 | SingleClassification_b, 4    | SingleClassification_b, 3    |
| n_hits_1000 PriA-SSB FP | n_hits_2500 PriA-SSB FP | n_hits_5000 PriA-SSB FP |
|--------------------------|--------------------------|--------------------------|
| 0 SingleRegression_b, 1  | SingleRegression_a, 1   | SingleRegression_b, 1   |
| 1 SingleRegression_a, 2  | SingleRegression_b, 2   | SingleRegression_a, 2   |
| 2 ConsensusDocking_max, 3| ConsensusDocking_max, 3 | RandomForest_g, 3       |
| 3 ConsensusDocking_mean, 3| ConsensusDocking_mean, 3| MultiClassification_b, 3|
| 4 ConsensusDocking_median, 3| ConsensusDocking_median, 3| Docking_hybrid, 5       |
| 5 ConsensusDocking_rocauc_opt, 3| ConsensusDocking_rocauc_opt, 3| Docking_surflex, 5     |
| 6 Docking_ad4, 3          | Docking_ad4, 3           | Docking_smina, 5         |
| 7 Docking_dock6, 3        | Docking_dock6, 3         | Docking_rdocktot, 5     |
| 8 Docking_fred, 3         | Docking_fred, 3          | Docking_rdockint, 5     |
| 9 IRV_c, 3                | IRV_c, 3                 | Docking_plants, 5       |
| 10 Docking_plants, 3      | Docking_plants, 3        | Docking_fred, 5         |
| 11 Docking_rdockint, 3    | Docking_rdockint, 3      | IRV_b, 5                |
| 12 Docking_rdocktot, 3    | Docking_rdocktot, 3      | Docking_dock6, 5        |
| 13 Docking_smina, 3       | Docking_smina, 3         | Docking_ad4, 5          |
| 14 Docking_surflex, 3     | Docking_surflex, 3       | ConsensusDocking_rocauc_opt, 5|
| 15 IRV_a, 3               | IRV_a, 3                 | ConsensusDocking_median, 5|
| 16 IRV_b, 3               | IRV_b, 3                 | ConsensusDocking_mean, 5|
| 17 Docking_hybrid, 3      | Docking_hybrid, 3        | ConsensusDocking_max, 5 |
| 18 IRV_d, 3               | IRV_d, 3                 | IRV_a, 5                |
| 19 IRV_e, 3               | IRV_e, 3                 | IRV_d, 5                |
| 20 LSTM_a, 3              | LSTM_a, 3                | IRV_c, 5                |
| 21 LSTM_b, 3              | LSTM_b, 3                | LSTM_b, 5               |
| 22 MultiClassification_a, 3| MultiClassification_a, 3| LSTM_a, 5               |
| 23 MultiClassification_b, 3| MultiClassification_b, 3| LSTM_b, 5               |
| 24 RandomForest_a, 3      | RandomForest_a, 3        | MultiClassification_a, 5|
| 25 RandomForest_b, 3      | RandomForest_b, 3        | RandomForest_a, 5       |
| 26 RandomForest_c, 3      | RandomForest_c, 3        | RandomForest_b, 5       |
| 27 RandomForest_d, 3      | RandomForest_d, 3        | RandomForest_c, 5       |
| 28 RandomForest_e, 3      | RandomForest_e, 3        | RandomForest_d, 5       |
| 29 RandomForest_f, 3      | RandomForest_f, 3        | RandomForest_e, 5       |
| 30 RandomForest_g, 3      | RandomForest_g, 3        | RandomForest_f, 5       |
| 31 RandomForest_h, 3      | RandomForest_h, 3        | RandomForest_g, 5       |
| 32 SingleClassification_a, 3| SingleClassification_a, 3| SingleClassification_a, 5|
| 33 SingleClassification_b, 3| SingleClassification_b, 3| SingleClassification_b, 5|
| 34 ConsensusDocking_efr1_opt, 3| ConsensusDocking_efr1_opt, 3| ConsensusDocking_efr1_opt, 5|

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Table S14: **PriA-SSB FP DTK rankings (continued)**

| n_hits_10000 PriA-SSB FP |
|---------------------------|
| 0  | SingleRegression_a, 1 |
| 1  | IRV_c, 2               |
| 2  | IRV_b, 2               |
| 3  | IRV_a, 2               |
| 4  | Docking_sureflex, 2    |
| 5  | Docking_smina, 2       |
| 6  | Docking_rdocktot, 2    |
| 7  | Docking_rdockint, 2    |
| 8  | Docking_plants, 2      |
| 9  | SingleRegression_b, 2  |
| 10 | Docking_fred, 2        |
| 11 | Docking_dock6, 2       |
| 12 | Docking_ad4, 2         |
| 13 | ConsensusDocking_rocauc_opt, 2 |
| 14 | ConsensusDocking_median, 2 |
| 15 | ConsensusDocking_mean, 2 |
| 16 | ConsensusDocking_max, 2 |
| 17 | Docking_hybrid, 2      |
| 18 | IRV_d, 2               |
| 19 | IRV_e, 2               |
| 20 | LSTM_a, 2              |
| 21 | LSTM_b, 2              |
| 22 | MultiClassification_a, 2 |
| 23 | MultiClassification_b, 2 |
| 24 | RandomForest_a, 2      |
| 25 | RandomForest_b, 2      |
| 26 | RandomForest_c, 2      |
| 27 | RandomForest_d, 2      |
| 28 | RandomForest_e, 2      |
| 29 | RandomForest_f, 2      |
| 30 | RandomForest_g, 2      |
| 31 | RandomForest_h, 2      |
| 32 | SingleClassification_a, 2 |
| 33 | SingleClassification_b, 2 |
| 34 | ConsensusDocking_efr1_opt, 2 |
|   | ROC AUC RMI-FANCM FP | BEDROC AUC RMI-FANCM FP | PR auc.integral RMI-FANCM FP |
|---|----------------------|-------------------------|-----------------------------|
| 0 | RandomForest_a, 1   | IRV_d, 1                | SingleClassification_b, 1   |
| 1 | RandomForest_h, 1   | RandomForest_e, 1       | SingleClassification_a, 1   |
| 2 | RandomForest_g, 1   | MultiClassification_b, 1| MultiClassification_b, 3   |
| 3 | RandomForest_e, 1   | RandomForest_a, 1       | SingleRegression_b, 4       |
| 4 | RandomForest_d, 1   | RandomForest_b, 1       | Docking_hybrid, 5           |
| 5 | RandomForest_c, 1   | RandomForest_c, 1       | Docking_surflex, 5          |
| 6 | RandomForest_b, 1   | RandomForest_d, 1       | Docking_smina, 5            |
| 7 | RandomForest_f, 8   | RandomForest_f, 1       | Docking_rdocktot, 5         |
| 8 | MultiClassification_b, 9 | RandomForest_g, 1 | Docking_rdockint, 5         |
| 9 | IRV_e, 10          | RandomForest_h, 1       | Docking_plants, 5           |
| 10 | MultiClassification_a, 11 | SingleClassification_a, 11 | Docking_dock6, 5 |
| 11 | IRV_d, 12          | SingleClassification_b, 11 | Docking_fred, 5 |
| 12 | SingleClassification_b, 12 | MultiClassification_a, 13 | IRV_b, 5 |
| 13 | IRV_c, 14          | IRV_e, 13               | Docking_ad4, 5              |
| 14 | IRV_b, 15          | IRV_b, 15               | ConsensusDocking_rocauc_opt, 5|
| 15 | IRV_a, 16          | IRV_a, 16               | ConsensusDocking_median, 5  |
| 16 | SingleClassification_a, 17 | IRV_c, 17             | ConsensusDocking_mean, 5    |
| 17 | LSTM_a, 18         | SingleRegression_b, 18  | ConsensusDocking_max, 5     |
| 18 | Docking_hybrid, 19 | Docking_rdocktot, 19   | IRV_a, 5                    |
| 19 | ConsensusDocking_max, 19 | LSTM_b, 20             | IRV_d, 5                    |
| 20 | ConsensusDocking_mean, 19 | Docking_smina, 20 | IRV_c, 5                    |
| 21 | ConsensusDocking_median, 19 | LSTM_a, 20             | SingleRegression_a, 5       |
| 22 | Docking_ad4, 19    | SingleRegression_a, 23  | IRV_e, 5                    |
| 23 | SingleRegression_b, 19 | Docking_ad4, 23          | LSTM_a, 5                   |
| 24 | Docking_rdocktot, 19 | ConsensusDocking_max, 23 | LSTM_b, 5                   |
| 25 | Docking_smina, 19  | ConsensusDocking_mean, 23 | MultiClassification_a, 5   |
| 26 | LSTM_b, 19         | ConsensusDocking_median, 23 | RandomForest_a, 5           |
| 27 | Docking_rdockint, 28 | ConsensusDocking_rocauc_opt, 23 | RandomForest_b, 5 |
| 28 | Docking_plants, 28 | Docking_hybrid, 23      | RandomForest_c, 5           |
| 29 | Docking_fred, 28   | Docking_dock6, 23       | RandomForest_d, 5           |
| 30 | Docking_dock6, 28  | Docking_fred, 23        | RandomForest_e, 5           |
| 31 | ConsensusDocking_rocauc_opt, 28 | Docking_plants, 23 | RandomForest_f, 5           |
| 32 | Docking_surflex, 28 | Docking_rdockint, 23  | RandomForest_g, 5           |
| 33 | SingleRegression_a, 28 | Docking_surflex, 23 | RandomForest_h, 5           |
| 34 | ConsensusDocking_efr1_opt, 28 | ConsensusDocking_efr1_opt, 23 | ConsensusDocking_efr1_opt, 5 |
Table S15: RMI-FANCM FP DTK rankings (continued)

| NEF_0.1 % RMI-FANCM FP | NEF_0.15 % RMI-FANCM FP | NEF_0.5 % RMI-FANCM FP |
|-------------------------|--------------------------|------------------------|
| SingleRegression_b, 1   | IRV_a, 1                 | SingleClassification_b, 1 |
| IRV_a, 1                | SingleRegression_b, 2    | SingleClassification_b, 1 |
| SingleClassification_b, 3 | SingleClassification_b, 3 | RandomForest_f, 1        |
| MultiClassification_b, 4 | SingleClassification_b, 3 | SingleRegression_b, 4    |
| SingleClassification_b, 4 | ConsensusDocking_max, 5  | RandomForest_h, 4        |
| RandomForest_f, 4       | ConsensusDocking_max, 5  | RandomForest_g, 4        |
| Docking_smina, 7        | ConsensusDocking_median, 5 | IRV_a, 4                |
| Docking_rdocktot, 5     | ConsensusDocking_rocauc_opt, 5 | IRV_b, 4                |
| Docking_rdockint, 7     | Docking_ad4, 5           | MultiClassification_b, 9 |
| Docking_plants, 7       | IRV_b, 5                 |                   |
| Docking_hybrid, 7       | Docking_fred, 5          | MultiClassification_a, 11 |
| Docking_ad4, 7          | Docking_hybrid, 5        | IRV_e, 12              |
| Docking_fred, 7         | Docking_plants, 5        | IRV_d, 12              |
| Docking_dock6, 7        | Docking_rdockint, 5      | RandomForest_a, 12      |
| ConsensusDocking_rocauc_opt, 7 | Docking_rdocktot, 5    | RandomForest_b, 12      |
| ConsensusDocking_median, 7 | Docking_smina, 5        | RandomForest_d, 12      |
| ConsensusDocking_mean, 7 | Docking_surllex, 5      | RandomForest_e, 17      |
| ConsensusDocking_max, 7  | Docking_dock6, 5         | Docking_hybrid, 18      |
| Docking_surllex, 7      | IRV_d, 5                 | ConsensusDocking_max, 18 |
| IRV_d, 7                | IRV_c, 5                 | ConsensusDocking_mean, 18 |
| IRV_b, 7                | SingleRegression_a, 5    | ConsensusDocking_median, 18 |
| IRV_c, 7                | IRV_e, 5                 | ConsensusDocking_rocauc_opt, 18 |
| SingleRegression_a, 7   | LSTM_a, 5                | Docking_ad4, 18         |
| LSTM_a, 7               | MultiClassification_a, 5 | Docking_fred, 18        |
| LSTM_b, 7               | MultiClassification_b, 5 | Docking_dockint, 18     |
| MultiClassification_a, 7 | RandomForest_a, 5        | Docking_plants, 18      |
| RandomForest_a, 7       | RandomForest_b, 5        | LSTM_b, 18              |
| RandomForest_b, 7       | RandomForest_c, 5        | Docking_rdocktot, 18    |
| RandomForest_c, 7       | RandomForest_d, 5        | Docking_smina, 18       |
| RandomForest_d, 7       | RandomForest_e, 5        | Docking_surllex, 18     |
| RandomForest_f, 5       | IRV_c, 18                |                   |
| RandomForest_g, 5       | SingleRegression_a, 18   |                   |
| RandomForest_h, 5       | LSTM_a, 18               |                   |
| ConsensusDocking_efr1_opt, 7 | ConsensusDocking_efr1_opt, 5 | ConsensusDocking_efr1_opt, 18 |
| NEF_1 % RMI-FANCM FP | NEF_2 % RMI-FANCM FP | NEF_5 % RMI-FANCM FP |
|----------------------|----------------------|----------------------|
| 0                    | SingleClassification_b, 1 | RandomForest_h, 1 |
| 1                    | SingleClassification_a, 1 | RandomForest_h, 1 |
| 2                    | RandomForest_h, 1 | RandomForest_g, 1 |
| 3                    | RandomForest_g, 1 | RandomForest_e, 3 |
| 4                    | RandomForest_f, 1 | IRV_d, 4 |
| 5                    | RandomForest_e, 1 | SingleClassification_b, 4 |
| 6                    | RandomForest_d, 1 | RandomForest_e, 4 |
| 7                    | IRV_a, 1 | RandomForest_d, 4 |
| 8                    | IRV_d, 9 | RandomForest_c, 4 |
| 9                    | MultiClassification_b, 10 | RandomForest_b, 4 |
| 10                   | SingleRegression_b, 11 | RandomForest_a, 4 |
| 11                   | RandomForest_a, 12 | RandomForest_e, 12 |
| 12                   | MultiClassification_a, 12 | MultiClassification_b, 13 |
| 13                   | RandomForest_c, 12 | IRV_a, 14 |
| 14                   | RandomForest_b, 12 | SingleRegression_b, 15 |
| 15                   | Docking_plants, 16 | MultiClassification_a, 16 |
| 16                   | ConsensusDocking_max, 16 | LSTM_a, 17 |
| 17                   | ConsensusDocking_mean, 16 | Docking_hybrid, 17 |
| 18                   | ConsensusDocking_median, 16 | ConsensusDocking_max, 17 |
| 19                   | ConsensusDocking_rocauc_opt, 16 | ConsensusDocking_mean, 17 |
| 20                   | Docking_ad4, 16 | ConsensusDocking_median, 17 |
| 21                   | Docking_dock6, 16 | ConsensusDocking_rocauc_opt, 17 |
| 22                   | Docking_fred, 16 | Docking_ad4, 17 |
| 23                   | Docking_hybrid, 16 | Docking_dock6, 17 |
| 24                   | Docking_rodocktot, 16 | Docking_fred, 17 |
| 25                   | Docking_rodockint, 16 | Docking_plants, 17 |
| 26                   | Docking_smina, 16 | LSTM_b, 17 |
| 27                   | Docking_surflex, 16 | Docking_rodocktot, 17 |
| 28                   | IRV_b, 16 | Docking_rodockint, 17 |
| 29                   | IRV_c, 16 | Docking_smina, 17 |
| 30                   | SingleRegression_a, 16 | Docking_surflex, 17 |
| 31                   | LSTM_a, 16 | IRV_b, 17 |
| 32                   | LSTM_b, 16 | Docking_smina, 17 |
| 33                   | ConsensusDocking_efr1_opt, 16 | SingleRegression_a, 17 |
| 34                   | ConsensusDocking_efr1_opt, 16 | ConsensusDocking_efr1_opt, 17 |
| NEF_10 % RMI-FANCM FP | NEF_20 % RMI-FANCM FP | NEF AUC RMI-FANCM FP |
|------------------------|------------------------|------------------------|
| RandomForest_h, 1      | RandomForest_h, 1      | RandomForest_h, 1      |
| RandomForest_g, 2      | RandomForest_g, 2      | RandomForest_g, 2      |
| RandomForest_d, 3      | RandomForest_e, 3      | RandomForest_d, 3      |
| RandomForest_a, 3      | RandomForest_b, 3      | RandomForest_a, 3      |
| RandomForest_c, 4      | RandomForest_c, 5      | RandomForest_c, 3      |
| RandomForest_b, 4      | RandomForest_f, 5      | RandomForest_a, 3      |
| MultiClassification_a, 8 | IRV_e, 5             | MultiClassification_b, 8 |
| MultiClassification_b, 8 | RandomForest_b, 5     | RandomFroest_f, 8      |
| IRV_c, 8               | MultiClassification_a, 11 | IRV_d, 10              |
| SingleClassification_a, 8 | SingleClassification_b, 11 | SingleClassification_a, 10 |
| SingleClassification_b, 8 | SingleClassification_a, 11 | SingleClassification_b, 10 |
| IRV_c, 14              | IRV_d, 14              | IRV_c, 15              |
| IRV_b, 15              | ConsensusDocking_max, 15 | IRV_c, 15              |
| IRV_e, 16              | Docking_rdocktot, 15  | IRV_b, 15              |
| Docking_rdocktot, 17   | IRV_b, 15              | Docking_rdocktot, 17   |
| SingleRegression_b, 17 | Docking_smima, 15     | SingleRegression_b, 17 |
| IRV_a, 19              | SingleRegression_b, 15 | IRV_a, 19              |
| Docking_smima, 19      | IRV_c, 15              | Docking_smima, 19      |
| LSTM_b, 19             | LSTM_a, 15             | LSTM_b, 19             |
| SingleRegression_a, 22 | LSTM_b, 15             | LSTM_a, 19             |
| Docking_sock6, 22      | IRV_a, 23              | SingleRegression_a, 23 |
| ConsensusDocking_max, 22 | Docking_surflex, 23  | ConsensusDocking_max, 22 |
| ConsensusDocking_median, 22 | Docking_surflex, 23  | ConsensusDocking_median, 23 |
| ConsensusDocking_rocauc_opt, 22 | Docking_plants, 23 | ConsensusDocking_median, 23 |
| Docking_ad4, 22        | Docking_hybrid, 23    | ConsensusDocking_rocauc_opt, 23 |
| Docking_hybrid, 22     | Docking_fred, 23      | Docking_hybrid, 23     |
| Docking_fred, 22       | Docking_sock6, 23     | Docking_fred, 23       |
| LSTM_a, 22             | Docking_ad4, 23       | Docking_fred, 23       |
| Docking_plants, 22     | ConsensusDocking_rocauc_opt, 23 | Docking_plants, 23 |
| Docking_rdockint, 23   | ConsensusDocking_median, 23 | Docking_rdockint, 23   |
| Docking_surflex, 23    | ConsensusDocking_median, 23 | Docking_surflex, 23    |
| ConsensusDocking_efr1_opt, 22 | ConsensusDocking_efr1_opt, 23 | ConsensusDocking_efr1_opt, 23 |
Table S15: **RMI-FANCM FP DTK rankings (continued)**

| n_hits_100 RMI-FANCM FP | n_hits_250 RMI-FANCM FP | n_hits_500 RMI-FANCM FP |
|--------------------------|-------------------------|-------------------------|
| 0 SingleClassification_b, 1 | SingleClassification_a, 1 | RandomForest_h, 1 |
| 1 SingleClassification_a, 1 | RandomForest_h, 1 | RandomForest_g, 2 |
| 2 RandomForest_h, 1 | IRV_d, 3 | SingleClassification_b, 3 |
| 3 RandomForest_g, 1 | SingleClassification_b, 3 | SingleClassification_a, 3 |
| 4 RandomForest_f, 1 | RandomForest_g, 3 | MultiClassification_b, 3 |
| 5 RandomForest_e, 1 | RandomForest_f, 3 | IRV_d, 6 |
| 6 RandomForest_d, 1 | RandomForest_e, 7 | RandomForest_e, 8 |
| 7 IRV_d, 8 | MultiClassification_b, 7 | RandomForest_e, 8 |
| 8 IRV_a, 8 | RandomForest_d, 9 | RandomForest_d, 8 |
| 9 MultiClassification_b, 10 | RandomForest_c, 9 | RandomForest_a, 8 |
| 10 SingleRegression_b, 10 | RandomForest_b, 9 | MultiClassification_a, 11 |
| 11 MultiClassification_a, 12 | RandomForest_a, 9 | RandomForest_f, 12 |
| 12 RandomForest_a, 13 | IRV_e, 13 | RandomForest_c, 12 |
| 13 RandomForest_c, 13 | SingleRegression_b, 14 | IRV_b, 12 |
| 14 RandomForest_b, 13 | MultiClassification_a, 15 | IRV_e, 15 |
| 15 Docking_plants, 16 | IRV_b, 15 | SingleRegression_b, 16 |
| 16 ConsensusDocking_max, 16 | IRV_a, 15 | IRV_a, 17 |
| 17 ConsensusDocking_mean, 16 | LSTM_b, 18 | LSTM_a, 18 |
| 18 ConsensusDocking_median, 16 | Docking_hybrid, 18 | Docking_hybrid, 18 |
| 19 ConsensusDocking_rocauc_opt, 16 | ConsensusDocking_max, 18 | ConsensusDocking_max, 18 |
| 20 Docking_ad4, 16 | ConsensusDocking_mean, 18 | ConsensusDocking_mean, 18 |
| 21 Docking_dock6, 16 | ConsensusDocking_median, 18 | ConsensusDocking_median, 18 |
| 22 Docking_surflex, 16 | ConsensusDocking_rocauc_opt, 18 | ConsensusDocking_rocauc_opt, 18 |
| 23 Docking_hybrid, 16 | Docking_ad4, 18 | Docking_ad4, 18 |
| 24 Docking_rodocktot, 16 | Docking_dock6, 18 | Docking_dock6, 18 |
| 25 Docking_rodockint, 16 | Docking_fred, 18 | Docking_fred, 18 |
| 26 Docking_smina, 16 | Docking_rodockint, 18 | Docking_plants, 18 |
| 27 Docking_surflex, 16 | Docking_plants, 18 | SingleRegression_a, 18 |
| 28 IRV_b, 16 | LSTM_a, 18 | Docking_rodocktot, 18 |
| 29 IRV_c, 16 | Docking_rodocktot, 18 | Docking_rodocktot, 18 |
| 30 SingleRegression_a, 16 | Docking_smina, 18 | Docking_smina, 18 |
| 31 IRV_e, 16 | Docking_surflex, 18 | Docking_surflex, 18 |
| 32 LSTM_a, 16 | IRV_c, 18 | LSTM_b, 18 |
| 33 LSTM_b, 16 | SingleRegression_a, 18 | IRV_c, 18 |
| 34 ConsensusDocking_efr1_opt, 16 | ConsensusDocking_efr1_opt, 18 | ConsensusDocking_efr1_opt, 18 |
Table S15: RMI-FANCM FP DTK rankings (continued)

|                 | n_hits_1000 | n_hits_2500 | n_hits_5000 |
|-----------------|-------------|-------------|-------------|
| RandomForest_h, 1 | RandomForest_h, 1 | RandomForest_h, 1 | RandomForest_h, 1 |
| RandomForest_g, 2 | RandomForest_g, 2 | RandomForest_g, 2 | RandomForest_g, 1 |
| RandomForest_d, 3 | RandomForest_c, 3 | RandomForest_e, 1 |
| RandomForest_c, 4 | RandomForest_d, 4 | RandomForest_d, 4 |
| RandomForest_a, 4 | MultiClassification_b, 4 | RandomForest_a, 4 |
| RandomForest_e, 4 | RandomForest_a, 4 | RandomForest_f, 6 |
| RandomForest_b, 4 | RandomForest_e, 4 | RandomForest_c, 6 |
| MultiClassification_a, 8 | RandomForest_b, 4 | RandomForest_b, 6 |
| MultiClassification_b, 8 | RandomForest_f, 9 | MultiClassification_b, 9 |
| IRV_d, 8 | IRV_e, 10 | MultiClassification_a, 10 |
| RandomForest_f, 8 | MultiClassification_a, 11 | SingleClassification_b, 11 |
| SingleClassification_a, 8 | SingleClassification_b, 12 | SingleClassification_a, 12 |
| SingleClassification_b, 8 | SingleClassification_a, 13 | LSTM_a, 12 |
| IRV_c, 14 | IRV_d, 14 | LSTM_b, 14 |
| IRV_e, 15 | IRV_c, 15 | Docking_hybrid, 14 |
| IRV_b, 16 | ConsensusDocking_max, 15 | Docking_plants, 16 |
| Docking_rdocktot, 17 | Docking_rdocktot, 15 | ConsensusDocking_max, 16 |
| SingleRegression_b, 17 | SingleRegression_b, 15 | ConsensusDocking_mean, 16 |
| IRV_a, 19 | LSTM_b, 15 | ConsensusDocking_median, 16 |
| Docking_smina, 19 | LSTM_a, 15 | ConsensusDocking_rocauc_opt, 16 |
| LSTM_b, 19 | SingleRegression_a, 21 | Docking_ad4, 16 |
| SingleRegression_a, 22 | Docking_fred, 21 | Docking_dock6, 16 |
| Docking_dock6, 22 | ConsensusDocking_mean, 21 | Docking_fred, 16 |
| ConsensusDocking_max, 22 | ConsensusDocking_median, 21 | SingleRegression_b, 16 |
| ConsensusDocking_mean, 22 | ConsensusDocking_rocauc_opt, 21 | IRV_d, 16 |
| ConsensusDocking_median, 22 | Docking_ad4, 21 | Docking_rdockint, 16 |
| ConsensusDocking_rocauc_opt, 22 | Docking_dock6, 21 | Docking_rdocktot, 16 |
| Docking_ad4, 22 | Docking_hybrid, 21 | Docking_surflex, 16 |
| Docking_hybrid, 22 | IRV_b, 21 | Docking_smina, 16 |
| Docking_fred, 22 | Docking_rdockint, 21 | IRV_a, 16 |
| LSTM_a, 22 | Docking_rdockint, 21 | IRV_b, 16 |
| Docking_rdockint, 22 | Docking_surflex, 21 | IRV_c, 16 |
| Docking_surflex, 22 | IRV_a, 21 | SingleRegression_a, 16 |
| ConsensusDocking_efr1_opt, 22 | ConsensusDocking_efr1_opt, 21 | ConsensusDocking_efr1_opt, 16 |
Table S15: **RMI-FANCM FP DTK rankings (continued)**

| n_hits_10000 | RMI-FANCM FP                                      |
|--------------|--------------------------------------------------|
| 0            | SingleRegression_b, 1                            |
| 1            | Docking_hybrid, 1                                |
| 2            | IRV_a, 1                                         |
| 3            | Docking_surflex, 1                               |
| 4            | Docking_smina, 1                                 |
| 5            | Docking_rdocktot, 1                              |
| 6            | Docking_rdockint, 1                              |
| 7            | Docking_plants, 1                                |
| 8            | Docking_fred, 1                                  |
| 9            | IRV_c, 1                                         |
| 10           | Docking_dock6, 1                                 |
| 11           | Docking_ad4, 1                                   |
| 12           | ConsensusDocking_rocauc_opt, 1                   |
| 13           | ConsensusDocking_median, 1                       |
| 14           | ConsensusDocking_mean, 1                         |
| 15           | ConsensusDocking_max, 1                          |
| 16           | IRV_b, 1                                         |
| 17           | IRV_d, 1                                         |
| 18           | SingleRegression_a, 1                            |
| 19           | RandomForest_d, 1                                |
| 20           | SingleClassification_b, 1                       |
| 21           | SingleClassification_a, 1                       |
| 22           | RandomForest_b, 1                                |
| 23           | RandomForest_g, 1                                |
| 24           | RandomForest_f, 1                                |
| 25           | RandomForest_e, 1                                |
| 26           | RandomForest_c, 1                                |
| 27           | IRV_e, 1                                         |
| 28           | RandomForest_b, 1                                |
| 29           | RandomForest_a, 1                                |
| 30           | MultiClassification_b, 1                        |
| 31           | MultiClassification_a, 1                        |
| 32           | LSTM_b, 1                                        |
| 33           | LSTM_a, 1                                        |
| 34           | ConsensusDocking_efr1_opt, 1                     |
H Cross-Validation: Metric Comparison Results

The tables below show the ranking of evaluation metrics based on their similarity to $n_{\text{hits}}$ at different thresholds using Spearman’s rank correlation coefficient.

**Table S16: PriA-SSB AS** metric comparison showing metrics ranked by their Spearman correlation.

| n_hits_100 | n_hits_250 | n_hits_500 | n_hits_1000 | n_hits_2500 | n_hits_5000 | n_hits_10000 |
|------------|------------|------------|-------------|-------------|-------------|--------------|
| NEF_0.5 % | NEF_1 %    | NEF_0.5 % | NEF_5 %     | NEF_20 %    | NEF_20 %    | NEF_0.5 %    |
| NEF_1 %   | NEF_2 %    | NEF_2 %    | NEF_10 %    | ROC AUC     | NEF_5 %     | NEF_5 %      |
| NEF_2 %   | NEF_0.5 %  | NEF AUC    | NEF AUC     | NEF_10 %    | NEF_10 %    | NEF AUC      |
| NEF_5 %   | NEF_5 %    | BEDROC AUC | BEDROC AUC  | BEDROC AUC  | BEDROC AUC  | NEF_0.15 %   |
| NEF_0.15 %| NEF AUC    | NEF_5 %    | NEF_10 %    | ROC AUC     | BEDROC AUC  | NEF_0.15 %   |
| NEF AUC   | NEF_5 %    | NEF_1 %    | NEF_5 %     | NEF_10 %    | NEF_5 %     | NEF_1 %      |
| NEF_10 %  | NEF_10 %   | ROC AUC    | ROC AUC     | NEF_1 %     | NEF_1 %     | NEF_10 %     |
| NEF_20 %  | NEF_20 %   | NEF_20 %   | NEF_5 %     | NEF_0.5 %   | NEF_5 %     | NEF_0.5 %    |
| ROC AUC   | ROC AUC    | NEF_0.15 % | NEF_0.15 %  | NEF_0.15 %  | NEF_0.15 %  | NEF_20 %     |
| NEF_0.1 % | NEF_0.1 %  | NEF_0.1 %  | NEF_0.1 %   | NEF_0.1 %   | NEF_0.1 %   | NEF_0.1 %    |
| PR auc.integral | PR auc.integral | PR auc.integral | PR auc.integral | PR auc.integral | PR auc.integral |

**Table S17: PriA-SSB FP** metric comparison showing metrics ranked by their Spearman correlation.

| n_hits_100 | n_hits_250 | n_hits_500 | n_hits_1000 | n_hits_2500 | n_hits_5000 | n_hits_10000 |
|------------|------------|------------|-------------|-------------|-------------|--------------|
| NEF_0.5 % | NEF_2 %    | NEF AUC    | NEF_10 %    | NEF_5 %     | NEF_10 %    | NEF_5 %      |
| PR auc.integral | BEDROC AUC | BEDROC AUC | BEDROC AUC  | BEDROC AUC  | BEDROC AUC  | NEF_10 %     |
| NEF_10 %  | ROC AUC    | NEF_1 %    | NEF_5 %     | NEF_10 %    | NEF_5 %     | NEF_10 %     |
| NEF AUC   | NEF_5 %    | NEF_10 %   | BEDROC AUC  | NEF_20 %    | BEDROC AUC  | NEF_0.15 %   |
| NEF_1 %   | NEF_1 %    | NEF_20 %   | NEF_20 %    | NEF_5 %     | NEF_20 %    | NEF_0.5 %    |
| BEDROC AUC| ROC AUC    | ROC AUC    | ROC AUC     | ROC AUC     | NEF_0.5 %   | NEF_0.5 %    |
| NEF_20 %  | NEF_20 %   | ROC AUC    | ROC AUC     | ROC AUC     | NEF_0.5 %   | PR auc.integral |
| ROC AUC   | PR auc.integral | PR auc.integral | PR auc.integral | ROC AUC     | PR auc.integral |
| NEF_0.1 % | NEF_0.1 %  | NEF_0.1 %  | NEF_0.1 %   | NEF_0.1 %   | NEF_0.1 %   | NEF_0.1 %    |
| PR auc.integral | NEF_0.1 %  | NEF_0.1 %  | NEF_0.1 %   | NEF_0.1 %   | NEF_10 %   | NEF_10 %     |

**Table S18: RMI-FANCM FP** metric comparison showing metrics ranked by their Spearman correlation.

| n_hits_100 | n_hits_250 | n_hits_500 | n_hits_1000 | n_hits_2500 | n_hits_5000 | n_hits_10000 |
|------------|------------|------------|-------------|-------------|-------------|--------------|
| NEF_1 %   | NEF_5 %    | NEF_5 %    | NEF_10 %    | NEF_20 %    | NEF_20 %    | ROC AUC      |
| NEF_2 %   | NEF_2 %    | NEF_2 %    | NEF AUC     | NEF AUC     | NEF_20 %    | BEDROC AUC   |
| NEF_5 %   | NEF_5 %    | BEDROC AUC | BEDROC AUC  | BEDROC AUC  | BEDROC AUC  | NEF_0.15 %   |
| NEF_0.5 % | NEF_0.5 %  | NEF_10 %   | NEF_20 %    | BEDROC AUC  | BEDROC AUC  | NEF_0.15 %   |
| BEDROC AUC| BEDROC AUC | BEDROC AUC | BEDROC AUC  | BEDROC AUC  | BEDROC AUC  | NEF_0.15 %   |
| NEF_10 %  | NEF_10 %   | NEF_0.5 %  | ROC AUC     | NEF_2 %     | NEF_2 %     | NEF_0.5 %    |
| NEF_5 %   | NEF AUC    | NEF_1 %    | NEF_2 %     | NEF_5 %     | NEF_5 %     | NEF_5 %      |
| ROC AUC   | ROC_20 %   | ROC AUC    | ROC AUC     | ROC AUC     | NEF_0.5 %   | NEF_0.5 %    |
| ROC AUC   | ROC AUC    | ROC AUC    | ROC AUC     | ROC AUC     | NEF_0.5 %   | PR auc.integral |
| NEF_0.1 % | NEF_0.1 %  | NEF_0.1 %  | NEF_0.1 %   | NEF_0.1 %   | NEF_0.1 %   | NEF_0.1 %    |
| PR auc.integral | NEF_0.1 %  | NEF_0.1 %  | NEF_0.1 %   | NEF_0.1 %   | NEF_1 %   | NEF_1 %      |
| PR auc.integral | NEF_0.1 %  | NEF_0.1 %  | NEF_0.1 %   | NEF_0.1 %   | NEF_10 %   | NEF_10 %     |
The tables below show Spearman’s rank correlation coefficient for the different evaluation metrics versus \(n_{\text{hits}}\) at different thresholds. NaN occurs when the metric ranks all the models with the same rank, that is, when the DTK test finds no significance among any of the models.

### Table S19: PriA-SSB AS metric comparison Spearman correlation coefficient.

| Metric  | n_hits_100 | n_hits_250 | n_hits_500 | n_hits_1000 | n_hits_2500 | n_hits_5000 | n_hits_10000 |
|---------|------------|------------|------------|-------------|-------------|-------------|-------------|
| ROC AUC | 0.8809     | 0.8827     | 0.9340     | 0.9164      | 0.9288      | 0.9150      | 0.7885      |
| BEDROC AUC | 0.9251     | 0.9395     | 0.9613     | 0.9744      | 0.9414      | 0.8584      | 0.8116      |
| PR auc.integral | 0.4550     | 0.4352     | 0.4440     | 0.4346      | 0.4363      | 0.4570      | 0.3013      |
| NEF_0.1 % | 0.7653     | 0.7767     | 0.7446     | 0.7991      | 0.6760      | 0.5676      | 0.6034      |
| NEF_0.15 % | 0.9323     | 0.9346     | 0.9058     | 0.9122      | 0.7454      | 0.6441      | 0.8062      |
| NEF_0.5 % | 0.9999     | 0.9878     | 0.9667     | 0.9460      | 0.8480      | 0.7720      | 0.8343      |
| NEF_1 % | 0.9881     | 1.0000     | 0.9563     | 0.9590      | 0.8719      | 0.7770      | 0.7954      |
| NEF_2 % | 0.9749     | 0.9882     | 0.9651     | 0.9747      | 0.8868      | 0.8102      | 0.7725      |
| NEF_5 % | 0.9461     | 0.9590     | 0.9549     | 1.0000      | 0.9189      | 0.8305      | 0.8251      |
| NEF_10 % | 0.9160     | 0.9319     | 0.9484     | 0.9648      | 0.9524      | 0.8956      | 0.7852      |
| NEF_20 % | 0.8947     | 0.8954     | 0.9239     | 0.9154      | 0.9763      | 0.9251      | 0.7087      |
| NEF AUC | 0.9251     | 0.9395     | 0.9613     | 0.9744      | 0.9414      | 0.8584      | 0.8116      |

### Table S20: PriA-SSB FP metric comparison Spearman correlation coefficient.

| Metric  | n_hits_100 | n_hits_250 | n_hits_500 | n_hits_1000 | n_hits_2500 | n_hits_5000 | n_hits_10000 |
|---------|------------|------------|------------|-------------|-------------|-------------|-------------|
| ROC AUC | 0.4918     | 0.8700     | 0.7281     | 0.7271      | 0.7284      | 0.4993      | 0.5226      |
| BEDROC AUC | 0.5944     | 0.9979     | 0.8282     | 0.8285      | 0.8271      | 0.5862      | 0.5594      |
| PR auc.integral | 1.0000     | 0.5421     | 0.6966     | 0.7174      | 0.6752      | 0.5226      | -0.0294     |
| NEF_0.1 % | NaN        | NaN        | NaN        | NaN         | NaN         | NaN         | NaN         |
| NEF_0.15 % | NaN        | NaN        | NaN        | NaN         | NaN         | NaN         | NaN         |
| NEF_0.5 % | 0.1000     | 0.5421     | 0.6966     | 0.7174      | 0.6752      | 0.5226      | -0.0294     |
| NEF_1 % | 0.6966     | 0.8159     | 1.0000     | 0.9996      | 0.9996      | 0.7281      | 0.6966      |
| NEF_2 % | 0.5245     | 0.9997     | 0.8031     | 0.8013      | 0.8042      | 0.5654      | 0.5944      |
| NEF_5 % | 0.6752     | 0.8166     | 0.9996     | 0.9983      | 1.0000      | 0.7271      | 0.7174      |
| NEF_10 % | 0.7174     | 0.8144     | 0.9996     | 1.0000      | 0.9983      | 0.7284      | 0.6752      |
| NEF_20 % | 0.5771     | 0.6658     | 0.8284     | 0.8281      | 0.8281      | 0.5859      | 0.5771      |
| NEF AUC | 0.6966     | 0.8159     | 1.0000     | 0.9996      | 0.9996      | 0.7281      | 0.6966      |

### Table S21: RMI-FANCM FP metric comparison Spearman correlation coefficient.

| Metric  | n_hits_100 | n_hits_250 | n_hits_500 | n_hits_1000 | n_hits_2500 | n_hits_5000 | n_hits_10000 |
|---------|------------|------------|------------|-------------|-------------|-------------|-------------|
| ROC AUC | 0.7391     | 0.8150     | 0.8313     | 0.9208      | 0.8917      | 0.7973      | NaN         |
| BEDROC AUC | 0.8275     | 0.9036     | 0.9011     | 0.9672      | 0.8966      | 0.7632      | NaN         |
| PR auc.integral | 0.4326     | 0.4359     | 0.4302     | 0.2172      | 0.2204      | 0.1487      | NaN         |
| NEF_0.1 % | 0.5478     | 0.4665     | 0.3854     | 0.2062      | 0.1504      | 0.1130      | NaN         |
| NEF_0.15 % | 0.4394     | 0.3307     | 0.2823     | 0.1149      | 0.0003      | -0.0401     | NaN         |
| NEF_0.5 % | 0.8491     | 0.9108     | 0.8844     | 0.7668      | 0.6479      | 0.5617      | NaN         |
| NEF_1 % | 0.9963     | 0.9115     | 0.8801     | 0.8081      | 0.7264      | 0.7144      | NaN         |
| NEF_2 % | 0.9232     | 0.9653     | 0.9163     | 0.8750      | 0.8417      | 0.7476      | NaN         |
| NEF_5 % | 0.8926     | 0.9660     | 0.9779     | 0.9289      | 0.8412      | 0.7334      | NaN         |
| NEF_10 % | 0.8195     | 0.8776     | 0.8973     | 0.9997      | 0.9003      | 0.7804      | NaN         |
| NEF_20 % | 0.7281     | 0.8342     | 0.8418     | 0.9328      | 0.9622      | 0.8122      | NaN         |
| NEF AUC | 0.8058     | 0.8776     | 0.8914     | 0.9868      | 0.9285      | 0.8127      | NaN         |

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I Cross-Validation: Model Selection

For PriA-SSB AS, RandomForest_h, SingleClassification_a, SingleRegression_b, MultiClassification_b, and LSTM_b were the favorites in their class with no ties when using the NEF_{1\%} metric (Table S25). IRV_c and IRV_d tied, and IRV_d was selected at random. Docking_plants, ConsensusDocking_mean, ConsensusDocking_rocauc_opt, ConsensusDocking_efr1_opt, and Docking_surflex also tied. ConsensusDocking_efr1_opt was selected due to it being related to EF, a metric we want to emphasize.

In the tables below, fold mean refers to the mean of the evaluation metric value in the cross-validation folds.
I.1 Fold Mean Selection (model-fold mean pairs)

Table S22: PriA-SSB AS fold mean results

|       | ROC AUC PriA-SSB AS | BEDROC AUC PriA-SSB AS | PR auc.integral PriA-SSB AS |
|-------|---------------------|-------------------------|-----------------------------|
| 0     | RandomForest_d, 0.9134 | RandomForest_b, 0.7572 | RandomForest_g, 0.217       |
| 1     | RandomForest_e, 0.9038 | RandomForest_g, 0.7554 | RandomForest_h, 0.2147      |
| 2     | RandomForest_h, 0.9012 | RandomForest_d, 0.7453 | RandomForest_e, 0.2037      |
| 3     | RandomForest_g, 0.8962 | RandomForest_e, 0.7418 | RandomForest_d, 0.2037      |
| 4     | RandomForest_c, 0.8882 | RandomForest_c, 0.7215 | RandomForest_b, 0.2008      |
| 5     | RandomForest_a, 0.886  | RandomForest_b, 0.719  | RandomForest_c, 0.197       |
| 6     | RandomForest_b, 0.8848 | RandomForest_a, 0.712  | RandomForest_a, 0.196       |
| 7     | SingleRegression_b, 0.8634 | IRV_e, 0.6878 | IRV_d, 0.1653       |
| 8     | IRV_e, 0.8489 | IRV_d, 0.6352 | IRV_b, 0.1636       |
| 9     | MultiClassification_b, 0.8475 | MultiClassification_f, 0.6338 | IRV_c, 0.149       |
| 10    | RandomForest_f, 0.8415 | MultiClassification_b, 0.6039 | SingleClassification_b, 0.134 |
| 11    | SingleRegression_a, 0.8226 | IRV_c, 0.6034 | SingleClassification_a, 0.124           |
| 12    | MultiClassification_a, 0.82 | SingleRegression_a, 0.6004 | SingleClassification_a, 0.123 |
| 13    | IRV_d, 0.8085 | SingleRegression_b, 0.5828 | MultiClassification_b, 0.1218 |
| 14    | SingleClassification_b, 0.7908 | MultiClassification_a, 0.556 | MultiClassification_a, 0.1012 |
| 15    | IRV_c, 0.7868 | IRV_b, 0.5538 | RandomForest_f, 0.0987       |
| 16    | SingleClassification_a, 0.7773 | SingleClassification_b, 0.5458 | IRV_a, 0.0979       |
| 17    | IRV_b, 0.7569 | SingleRegression_a, 0.5073 | SingleRegression_b, 0.0575       |
| 18    | IRV_a, 0.7072 | IRV_a, 0.4661 | SingleRegression_b, 0.0338       |
| 19    | LSTM_b, 0.6243 | LSTM_b, 0.2349 | LSTM_b, 0.0048       |
| 20    | LSTM_a, 0.5484 | LSTM_a, 0.1399 | LSTM_a, 0.0016       |
| 21    | Docking_fred, 0.4983 | Docking_fred, 0.0964 | Docking_surflex, 0.0012   |
| 22    | Docking_hybrid, 0.4635 | Docking_surflex, 0.083 | Docking_fred, 0.0012       |
| 23    | Docking_surflex, 0.454 | Docking_hybrid, 0.073 | Docking_hybrid, 0.001      |
| 24    | Docking_rsaclint, 0.4404 | Docking_rsaclint, 0.0697 | ConsensusDocking_rocauc_opt, 0.001 |
| 25    | Docking_rsaclint, 0.4306 | Docking_rsaclint, 0.0684 | ConsensusDocking_rocauc_opt, 0.001       |
| 26    | ConsensusDocking_efr1_opt, 0.4042 | ConsensusDocking_median, 0.0572 | ConsensusDocking_median, 0.0011         |
| 27    | Docking_dock6, 0.3991 | Docking_smina, 0.0563 | ConsensusDocking_median, 0.001        |
| 28    | ConsensusDocking_median, 0.3946 | ConsensusDocking_median, 0.0516 | ConsensusDocking_median, 0.0009       |
| 29    | ConsensusDocking_rocauc_opt, 0.3938 | Docking_dock6, 0.0491 | ConsensusDocking_rocauc_opt, 0.0009      |
| 30    | ConsensusDocking_median, 0.3869 | Docking_ad4, 0.0438 | Docking_dock6, 0.0009       |
| 31    | ConsensusDocking_max, 0.3803 | ConsensusDocking_efr1_opt, 0.0429 | Docking_dock6, 0.0009       |
| 32    | Docking_smina, 0.3718 | ConsensusDocking_rocauc_opt, 0.0426 | Docking_smina, 0.0009       |
| 33    | Docking_plants, 0.3678 | Docking_plants, 0.0407 | ConsensusDocking_max, 0.0009       |
| 34    | Docking_dock_ad4, 0.3473 | ConsensusDocking_max, 0.0393 | Docking_ad4, 0.0008       |
Table S22: PriA-SSB AS fold mean results (continued)

| NEF | AUC PriA-SSB AS | NEF_1 % PriA-SSB AS |
|-----|----------------|---------------------|
| 0   | RandomForest_h, 0.772 | RandomForest_h, 0.6467 |
| 1   | RandomForest_g, 0.7642 | RandomForest_g, 0.6467 |
| 2   | RandomForest_d, 0.7578 | RandomForest_d, 0.5842 |
| 3   | RandomForest_e, 0.7529 | RandomForest_e, 0.5842 |
| 4   | RandomForest_b, 0.7428 | RandomForest_a, 0.5708 |
| 5   | RandomForest_c, 0.738 | RandomForest_c, 0.5583 |
| 6   | RandomForest_a, 0.7346 | RandomForest_b, 0.5583 |
| 7   | IRV_e, 0.699 | IRV_c, 0.545 |
| 8   | RandomForest_f, 0.6545 | IRV_d, 0.545 |
| 9   | IRV_d, 0.6275 | IRV_b, 0.5317 |
| 10  | MultiClassification_b, 0.6252 | IRV_e, 0.52 |
| 11  | SingleRegression_b, 0.618 | SingleClassification_a, 0.4975 |
| 12  | SingleClassification_a, 0.612 | RandomForest_f, 0.455 |
| 13  | IRV_c, 0.5828 | SingleClassification_b, 0.4344 |
| 14  | MultiClassification_a, 0.5719 | IRV_a, 0.4183 |
| 15  | SingleClassification_b, 0.5588 | MultiClassification_b, 0.414 |
| 16  | SingleRegression_a, 0.5263 | MultiClassification_a, 0.3896 |
| 17  | IRV_b, 0.5248 | SingleRegression_b, 0.3371 |
| 18  | IRV_a, 0.4216 | SingleRegression_a, 0.2904 |
| 19  | LSTM_b, 0.2476 | LSTM_b, 0.0752 |
| 20  | LSTM_a, 0.1461 | Docking_surflex, 0.0125 |
| 21  | Docking_fred, 0.094 | ConsensusDocking_efr1_opt, 0.0125 |
| 22  | Docking_surflex, 0.0869 | ConsensusDocking_rocauc_opt, 0.0125 |
| 23  | Docking_hybrid, 0.0721 | ConsensusDocking_mean, 0.0125 |
| 24  | Docking_rdockint, 0.0703 | Docking_plants, 0.0125 |
| 25  | Docking_rdocktot, 0.0653 | LSTM_a, 0.0096 |
| 26  | ConsensusDocking_median, 0.0572 | Docking_hybrid, 0.0 |
| 27  | Docking_smina, 0.0561 | Docking_rdocktot, 0.0 |
| 28  | ConsensusDocking_mean, 0.0457 | Docking_rdockint, 0.0 |
| 29  | Docking_ad4, 0.0444 | Docking_smina, 0.0 |
| 30  | Docking_dock6, 0.0434 | Docking_fred, 0.0 |
| 31  | ConsensusDocking_max, 0.039 | Docking_dock6, 0.0 |
| 32  | ConsensusDocking_efr1_opt, 0.0367 | Docking_ad4, 0.0 |
| 33  | ConsensusDocking_rocauc_opt, 0.0367 | ConsensusDocking_max, 0.0 |
| 34  | Docking_plants, 0.0348 | ConsensusDocking_median, 0.0 |
| ROC AUC PriA-SSB FP | BEDROC AUC PriA-SSB FP | PR auc.integral PriA-SSB FP |
|---------------------|------------------------|-----------------------------|
| 0 SingleRegression_a, 0.8166 | SingleRegression_b, 0.4735 | SingleRegression_a, 0.0114 |
| 1 SingleRegression_b, 0.8133 | SingleRegression_a, 0.4491 | SingleRegression_b, 0.0051 |
| 2 RandomForest_h, 0.7435 | RandomForest_g, 0.3821 | RandomForest_g, 0.0049 |
| 3 RandomForest_e, 0.7401 | RandomForest_h, 0.3669 | RandomForest_h, 0.0048 |
| 4 RandomForest_g, 0.7199 | RandomForest_e, 0.3636 | RandomForest_e, 0.0044 |
| 5 RandomForest_f, 0.7081 | RandomForest_d, 0.3324 | RandomForest_d, 0.0043 |
| 6 RandomForest_d, 0.681 | IRV_e, 0.3295 | MultiClassification_b, 0.0043 |
| 7 MultiClassification_b, 0.6692 | RandomForest_f, 0.3253 | IRV_c, 0.0041 |
| 8 RandomForest_c, 0.6575 | RandomForest_c, 0.3148 | IRV_e, 0.0035 |
| 9 RandomForest_b, 0.6444 | RandomForest_b, 0.3059 | IRV_d, 0.0034 |
| 10 RandomForest_a, 0.6372 | IRV_d, 0.2918 | IRV_b, 0.0031 |
| 11 IRV_e, 0.635 | RandomForest_a, 0.28 | RandomForest_c, 0.0029 |
| 12 IRV_d, 0.6127 | MultiClassification_b, 0.2719 | RandomForest_b, 0.0028 |
| 13 ConsensusDocking_median, 0.5886 | IRV_c, 0.2737 | RandomForest_a, 0.0026 |
| 14 ConsensusDocking_mean, 0.5872 | SingleClassification_a, 0.1764 | SingleClassification_a, 0.0018 |
| 15 Docking_fred, 0.585 | SingleClassification_b, 0.163 | SingleClassification_b, 0.0017 |
| 16 LSTM_a, 0.5768 | IRV_b, 0.1628 | RandomForest_f, 0.0016 |
| 17 IRV_c, 0.5703 | LSTM_a, 0.143 | LSTM_a, 0.0007 |
| 18 Docking_rdockint, 0.5648 | Docking_surflex, 0.1314 | Docking_dock6, 0.0007 |
| 19 ConsensusDocking_efr1_opt, 0.5558 | LSTM_b, 0.1276 | LSTM_b, 0.0006 |
| 20 ConsensusDocking_rocauc_opt, 0.554 | Docking_dock6, 0.1214 | Docking_surflex, 0.0006 |
| 21 Docking_plants, 0.5536 | MultiClassification_a, 0.1196 | MultiClassification_a, 0.0006 |
| 22 Docking_ad4, 0.5442 | ConsensusDocking_median, 0.1161 | ConsensusDocking_median, 0.0005 |
| 23 Docking_rdocktot, 0.5399 | ConsensusDocking_rocauc_opt, 0.1111 | ConsensusDocking_rocauc_opt, 0.0005 |
| 24 SingleClassification_b, 0.5388 | ConsensusDocking_efr1_opt, 0.1104 | ConsensusDocking_rocauc_opt, 0.0005 |
| 25 MultiClassification_a, 0.5353 | ConsensusDocking_median, 0.1103 | ConsensusDocking_median, 0.0005 |
| 26 IRV_b, 0.5352 | Docking_fred, 0.1068 | Docking_rdockint, 0.0005 |
| 27 Docking_surflex, 0.5343 | IRV_a, 0.0988 | ConsensusDocking_efr1_opt, 0.0005 |
| 28 Docking_hybrid, 0.5321 | Docking_plants, 0.0971 | Docking_fred, 0.0004 |
| 29 SingleClassification_a, 0.524 | Docking_hybrid, 0.0969 | Docking_smina, 0.0004 |
| 30 ConsensusDocking_max, 0.5235 | Docking_rdocktot, 0.0918 | Docking_rdocktot, 0.0004 |
| 31 LSTM_b, 0.5161 | Docking_smina, 0.0912 | Docking_hybrid, 0.0004 |
| 32 Docking_dock6, 0.5018 | Docking_rdockint, 0.0876 | ConsensusDocking_max, 0.0004 |
| 33 IRV_a, 0.4993 | ConsensusDocking_max, 0.078 | Docking_ad4, 0.0004 |
| 34 Docking_smina, 0.4968 | Docking_ad4, 0.0694 | IRV_a, 0.0003 |
Table S23: PriA-SSB FP fold mean results (continued)

| NEF AUC PriA-SSB FP | NEF_1 % PriA-SSB FP |
|---------------------|---------------------|
| 0                   | SingleRegression_b, 0.4941 SingleRegression_b, 0.2475 |
| 1                   | SingleRegression_a, 0.474 IRV_e, 0.2367 |
| 2                   | RandomForest_h, 0.3871 SingleRegression_a, 0.2092 |
| 3                   | RandomForest_g, 0.3774 IRV_d, 0.2033 |
| 4                   | RandomForest_c, 0.3458 RandomForest_d, 0.1867 |
| 5                   | RandomForest_f, 0.3344 RandomForest_e, 0.1867 |
| 6                   | RandomForest_c, 0.3229 RandomForest_g, 0.1867 |
| 7                   | RandomForest_d, 0.3078 RandomForest_h, 0.1867 |
| 8                   | RandomForest_b, 0.3046 RandomForest_b, 0.1467 |
| 9                   | IRV_e, 0.304 RandomForest_c, 0.1467 |
| 10                  | MultiClassification_b, 0.2957 IRV_c, 0.1467 |
| 11                  | RandomForest_a, 0.2769 RandomForest_a, 0.1467 |
| 12                  | IRV_d, 0.2495 IRV_b, 0.1067 |
| 13                  | SingleClassification_a, 0.1852 SingleClassification_a, 0.0833 |
| 14                  | IRV_c, 0.1759 RandomForest_f, 0.0733 |
| 15                  | SingleClassification_b, 0.1653 MultiClassification_b, 0.045 |
| 16                  | LSTM_a, 0.1495 IRV_a, 0.0333 |
| 17                  | Docking_surflex, 0.1467 Docking_dock6, 0.0333 |
| 18                  | ConsensusDocking_median, 0.1383 LSTM_a, 0.0267 |
| 19                  | LSTM_b, 0.1303 SingleClassification_b, 0.0267 |
| 20                  | Docking_dock6, 0.1242 LSTM_b, 0.02 |
| 21                  | ConsensusDocking_mean, 0.1221 MultiClassification_a, 0.0083 |
| 22                  | MultiClassification_a, 0.1201 Docking_rdocktot, 0.0 |
| 23                  | ConsensusDocking_efr1_opt, 0.1129 Docking_rdockint, 0.0 |
| 24                  | IRV_b, 0.1047 Docking_plants, 0.0 |
| 25                  | ConsensusDocking_rocauc_opt, 0.1046 Docking_hybrid, 0.0 |
| 26                  | Docking_hybrid, 0.1017 Docking_hybrid, 0.0 |
| 27                  | Docking_plants, 0.0975 Docking_plants, 0.0 |
| 28                  | Docking_fred, 0.0946 Docking_ad4, 0.0 |
| 29                  | Docking_rdocktot, 0.0912 ConsensusDocking_median, 0.0 |
| 30                  | Docking_smina, 0.0842 ConsensusDocking_efr1_opt, 0.0 |
| 31                  | Docking_rdockint, 0.0796 ConsensusDocking_mean, 0.0 |
| 32                  | ConsensusDocking_max, 0.0767 Docking_smina, 0.0 |
| 33                  | Docking_ad4, 0.0542 ConsensusDocking_max, 0.0 |
| 34                  | IRV_a, 0.0321 Docking_surflex, 0.0 |

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| ROC AUC RMI-FANCM FP | BEDROC AUC RMI-FANCM FP | PR auc.integral RMI-FANCM FP |
|----------------------|-------------------------|-----------------------------|
| 0 0.8346             | 0.5114                  | 0.1237                      |
| 1 0.8306             | 0.5045                  | 0.1225                      |
| 2 0.8256             | 0.5001                  | 0.1224                      |
| 3 0.8225             | 0.4967                  | 0.1219                      |
| 4 0.8207             | 0.4908                  | 0.1218                      |
| 5 0.8161             | 0.4898                  | 0.1213                      |
| 6 0.8159             | 0.4897                  | 0.1208                      |
| 7 0.8157             | 0.4637                  | 0.0841                      |
| 8 0.7532             | IRV_e, 0.4356           | SingleClassification_b, 0.0824 |
| 9 0.7463             | IRV_c, 0.3931           | IRV_e, 0.0752               |
| 10 0.7259            | IRV_d, 0.3727           | IRV_e, 0.0745               |
| 11 0.6854            | MultiClassification_b, 0.3582 | IRV_d, 0.0724             |
| 12 0.6649            | SingleClassification_a, 0.3393 | IRV_d, 0.0681             |
| 13 0.6623            | SingleClassification_b, 0.3373 | IRV_d, 0.0678             |
| 14 0.6366            | IRV_a, 0.3288           | MultiClassification_a, 0.0442 |
| 15 0.6339            | MultiClassification_a, 0.3177 | MultiClassification_b, 0.0405 |
| 16 0.5753            | Docking_rdocktot, 0.169  | Docking_ad4, 0.0117         |
| 17 0.5603            | SingleRegression_b, 0.1684 | Docking_rdocktot, 0.0114   |
| 18 0.5576            | Docking_ad4, 0.1651     | Docking_smina, 0.1491      |
| 19 0.5576            | Docking_smina, 0.1491   | Docking_smina, 0.1491      |
| 20 0.5229            | Docking_rdockint, 0.1442 | Docking_rdockint, 0.169    |
| 21 0.522             | Docking_rdockint, 0.1442 | Docking_rdockint, 0.169    |
| 22 0.5197            | Docking_smina, 0.1491   | Docking_smina, 0.1491      |
| 23 0.5111            | ConsensusDocking_max, 0.1254 | ConsensusDocking_max, 0.1254 |
| 24 0.4964            | ConsensusDocking_median, 0.1216 | ConsensusDocking_median, 0.1216 |
| 25 0.4878            | ConsensusDocking_mean, 0.1172 | ConsensusDocking_mean, 0.1172 |
| 26 0.4821            | ConsensusDocking_mean, 0.1032 | ConsensusDocking_mean, 0.1032 |
| 27 0.4834            | ConsensusDocking_efr1_opt, 0.0934 | ConsensusDocking_efr1_opt, 0.0934 |
| 28 0.4788            | ConsensusDocking_rocauc_opt, 0.0899 | ConsensusDocking_rocauc_opt, 0.0899 |
| 29 0.4756            | Docking_plants, 0.0832  | Docking_sphinx, 0.0037     |
| 30 0.4634            | Docking_dock6, 0.0669   | Docking_dock6, 0.0042      |
| 31 0.4516            | Docking_fred, 0.0814    | Docking_fred, 0.0044       |
| 32 0.4376            | Docking_sphinx, 0.063   | Docking_sphinx, 0.0039     |
| 33 0.4196            | Docking_sphinx, 0.0541  | Docking_sphinx, 0.0036     |
| NEF | AUC    | RMI-FANCM FP | NEF_1 % RMI-FANCM FP |
|-----|--------|--------------|-----------------------|
| 0   | 0.5439 | RandomForest_h | 0.2782 |
| 1   | 0.5324 | RandomForest_g | 0.2738 |
| 2   | 0.527  | RandomForest_e | 0.2608 |
| 3   | 0.5241 | RandomForest_b | 0.2563 |
| 4   | 0.5237 | RandomForest_d | 0.2474 |
| 5   | 0.5234 | RandomForest_a | 0.2474 |
| 6   | 0.5222 | RandomForest_c | 0.2474 |
| 7   | 0.4903 | RandomForest_f | 0.2431 |
| 8   | 0.4554 | IRV_e | 0.2343 |
| 9   | 0.4459 | IRV_d | 0.2123 |
| 10  | 0.3784 | IRV_c | 0.2123 |
| 11  | 0.3768 | MultiClassification_b | 0.2083 |
| 12  | 0.3565 | SingleClassification_a | 0.2081 |
| 13  | 0.3513 | SingleClassification_b | 0.2031 |
| 14  | 0.3429 | IRV_b | 0.1911 |
| 15  | 0.3337 | MultiClassification_a | 0.1412 |
| 16  | 0.2821 | IRV_a | 0.1249 |
| 17  | 0.177  | Docking_ad4 | 0.1249 |
| 18  | 0.1733 | Docking_rdocktot | 0.0393 |
| 19  | 0.1729 | SingleRegression_b | 0.0391 |
| 20  | 0.1569 | Docking_smina | 0.0303 |
| 21  | 0.1492 | Docking_rdockint | 0.0217 |
| 22  | 0.1376 | LSTM_a | 0.0217 |
| 23  | 0.1298 | ConsensusDocking_max | 0.0174 |
| 24  | 0.1231 | ConsensusDocking_median | 0.017 |
| 25  | 0.1227 | ConsensusDocking_median | 0.017 |
| 26  | 0.1187 | LSTM_b | 0.0133 |
| 27  | 0.1013 | ConsensusDocking_mean | 0.013 |
| 28  | 0.0928 | Docking_plants | 0.013 |
| 29  | 0.0827 | Docking federally | 0.019 |
| 30  | 0.078  | Docking_fed | 0.019 |
| 31  | 0.064  | Docking_surflec | 0.0088 |
| 32  | 0.0563 | Docking_surflec | 0.0065 |
| 33  | 0.0523 | SingleRegression_a | 0.0043 |
### I.2 DTK+Mean Selection (model-rank pairs)

#### Table S25: PriA-SSB AS DTK+Mean selection rankings

| ROC AUC PriA-SSB AS | BEDROC AUC PriA-SSB AS | PR auc.integral PriA-SSB AS |
|---------------------|------------------------|-----------------------------|
| 0                   | RandomForest_d, 1      | SingleClassification_b, 1   |
| 1                   | RandomForest_e, 2      | SingleClassification_a, 2   |
| 2                   | RandomForest_h, 3      | MultiClassification_a, 3    |
| 3                   | RandomForest_g, 4      | RandomForest_g, 4           |
| 4                   | RandomForest_c, 5      | RandomForest_c, 5           |
| 5                   | RandomForest_a, 6      | RandomForest_e, 6           |
| 6                   | RandomForest_b, 7      | RandomForest_d, 7           |
| 7                   | SingleRegression_b, 8  | RandomForest_b, 8           |
| 8                   | MultiClassification_b, 9 | IRV_e, 8                  |
| 9                   | IRV_e, 10              | RandomForest_f, 10          |
| 10                  | SingleRegression_a, 11 | MultiClassification_b, 11  |
| 11                  | MultiClassification_a, 12 | IRV_c, 12            |
| 12                  | RandomForest_f, 12     | SingleClassification_a, 12 |
| 13                  | IRV_d, 14              | SingleRegression_b, 14     |
| 14                  | SingleClassification_b, 14 | IRV_b, 16              |
| 15                  | MultiClassification_a, 15 | IRV_c, 16                |
| 16                  | IRV_c, 16              | SingleClassification_b, 17 |
| 17                  | IRV_b, 18              | SingleRegression_a, 18     |
| 18                  | IRV_a, 19              | IRV_a, 19                 |
| 19                  | LSTM_b, 20             | LSTM_b, 20                |
| 20                  | LSTM_a, 21             | LSTM_a, 21                |
| 21                  | Docking_fred, 22       | Docking_fred, 22           |
| 22                  | Docking_fred, 22       | Docking_fred, 22           |
| 23                  | Docking_surflex, 24    | Docking_surflex, 23        |
| 24                  | Docking_rdockint, 25   | Docking_rdockint, 25       |
| 25                  | Docking_rdockint, 26   | Docking_rdockint, 26       |
| 26                  | ConsensusDocking_efr1_opt, 27 | ConsensusDocking_rdockint, 27 |
| 27                  | Docking_dock6, 28      | Docking_dock6, 28          |
| 28                  | ConsensusDocking_median, 29 | ConsensusDocking_dock6, 30 |
| 29                  | ConsensusDocking_rocauc_opt, 30 | ConsensusDocking_dock6, 30 |
| 30                  | ConsensusDocking_mean, 31 | Docking_ad4, 31            |
| 31                  | ConsensusDocking_max, 32 | Docking_ad4, 35            |
| 32                  | Docking_smna, 33       | ConsensusDocking_efr1_opt, 32 |
| 33                  | Docking_plants, 34     | Docking_plants, 34         |
| 34                  | Docking_ad4, 35        | ConsensusDocking_max, 35    |
| NEF AUC PriA-SSB AS | NEF_1 % PriA-SSB AS |
|---------------------|---------------------|
| 0                   | RandomForest_h, 1   |
| 1                   | RandomForest_g, 2   |
| 2                   | RandomForest_d, 3   |
| 3                   | RandomForest_e, 4   |
| 4                   | RandomForest_b, 5   |
| 5                   | RandomForest_c, 6   |
| 6                   | RandomForest_a, 7   |
| 7                   | IRV_e, 8            |
| 8                   | Random Forest_f, 9  |
| 9                   | IRV_d, 10           |
| 10                  | MultiClassification_b, 11 |
| 11                  | SingleClassification_a, 11 |
| 12                  | SingleRegression_b, 12 |
| 13                  | IRV_c, 13           |
| 14                  | MultiClassification_a, 14 |
| 15                  | SingleClassification_b, 16 |
| 16                  | SingleRegression_a, 17 |
| 17                  | IRV_b, 18           |
| 18                  | IRV_a, 19           |
| 19                  | LSTM_b, 20          |
| 20                  | LSTM_a, 21          |
| 21                  | Docking_fred, 22    |
| 22                  | Docking_surflex, 23 |
| 23                  | Docking_hybrid, 24  |
| 24                  | Docking_rdockint, 25|
| 25                  | Docking_rdocktot, 26|
| 26                  | ConsensusDocking_median, 27 |
| 27                  | Docking_smina, 28   |
| 28                  | ConsensusDocking_mean, 29 |
| 29                  | Docking_ad4, 30     |
| 30                  | Docking_dock6, 31   |
| 31                  | ConsensusDocking_max, 32 |
| 32                  | ConsensusDocking_rocauc_opt, 33 |
| 33                  | ConsensusDocking_efr1_opt, 33 |
| 34                  | Docking_plants, 35  |
|                     | Docking_median, 27  |
|                     | Docking_max, 27     |
|                     | Docking_hybrid, 27  |
Table S26: PriA-SSB FP DTK+Mean selection rankings

|          | ROC AUC | PriA-SSB FP | BEDROC AUC | PriA-SSB FP | PR auc.integral | PriA-SSB FP |
|----------|---------|-------------|------------|-------------|----------------|-------------|
| 0        | SingleRegression_a, 1 | SingleRegression_b, 1 | SingleRegression_b, 1 | SingleRegression_b, 1 |
| 1        | SingleRegression_b, 2 | SingleRegression_a, 2 | SingleRegression_a, 2 | SingleRegression_a, 2 |
| 2        | RandomForest_h, 3 | RandomForest_g, 3 | RandomForest_g, 3 | RandomForest_g, 3 |
| 3        | RandomForest_e, 4 | RandomForest_h, 4 | RandomForest_h, 4 | RandomForest_h, 4 |
| 4        | RandomForest_g, 5 | RandomForest_e, 5 | RandomForest_e, 5 | RandomForest_e, 5 |
| 5        | RandomForest_f, 6 | IRV_e, 6 | RandomForest_d, 6 | MultiClassification_b, 7 |
| 6        | RandomForest_d, 7 | RandomForest_d, 6 | IRV_e, 9 | MultiClassification_b, 7 |
| 7        | MultiClassification_b, 8 | RandomForest_f, 8 | IRV_c, 8 | MultiClassification_b, 7 |
| 8        | RandomForest_c, 9 | RandomForest_f, 8 | IRV_c, 8 | MultiClassification_b, 7 |
| 9        | RandomForest_b, 10 | RandomForest_f, 8 | IRV_c, 8 | MultiClassification_b, 7 |
| 10       | IRV_e, 11 | IRV_d, 11 | IRV_b, 11 | MultiClassification_b, 7 |
| 11       | RandomForest_a, 11 | RandomForest_c, 12 | RandomForest_c, 12 | MultiClassification_b, 7 |
| 12       | IRV_d, 13 | MultiClassification_b, 13 | RandomForest_b, 13 | MultiClassification_b, 7 |
| 13       | ConsensusDocking_median, 14 | IRV_c, 14 | RandomForest_a, 14 | MultiClassification_b, 7 |
| 14       | ConsensusDocking_mean, 15 | SingleClassification_a, 15 | SingleClassification_a, 15 | MultiClassification_b, 7 |
| 15       | Docking_fred, 16 | SingleClassification_b, 15 | SingleClassification_b, 15 | MultiClassification_b, 7 |
| 16       | LSTM_a, 17 | IRV_b, 17 | RandomForest_f, 17 | MultiClassification_b, 7 |
| 17       | IRV_c, 18 | LSTM_a, 18 | LSTM_a, 18 | MultiClassification_b, 7 |
| 18       | Docking_rdocktot, 19 | Docking_surflex, 19 | Docking_dock6, 19 | MultiClassification_b, 7 |
| 19       | ConsensusDocking_efr1_opt, 20 | LSTM_b, 20 | LSTM_b, 20 | MultiClassification_b, 7 |
| 20       | ConsensusDocking_rocauc_opt, 21 | Docking_dock6, 21 | Docking_dock6, 21 | MultiClassification_b, 7 |
| 21       | Docking_plants, 22 | MultiClassification_a, 22 | MultiClassification_a, 22 | MultiClassification_b, 7 |
| 22       | Docking_ad4, 23 | ConsensusDocking_median, 23 | ConsensusDocking_median, 23 | MultiClassification_b, 7 |
| 23       | Docking_rdocktot, 24 | ConsensusDocking_rocauc_opt, 24 | ConsensusDocking_rocauc_opt, 24 | MultiClassification_b, 7 |
| 24       | SingleClassification_b, 25 | ConsensusDocking_efr1_opt, 25 | ConsensusDocking_efr1_opt, 25 | MultiClassification_b, 7 |
| 25       | MultiClassification_a, 26 | ConsensusDocking_mean, 26 | ConsensusDocking_mean, 26 | MultiClassification_b, 7 |
| 26       | IRV_b, 27 | Docking_fred, 27 | Docking_fred, 27 | MultiClassification_b, 7 |
| 27       | Docking_surflex, 28 | IRV_a, 28 | ConsensusDocking_efr1_opt, 28 | MultiClassification_b, 7 |
| 28       | Docking_hybrid, 29 | Docking_plants, 29 | Docking_fred, 29 | MultiClassification_b, 7 |
| 29       | SingleClassification_a, 30 | Docking_hybrid, 30 | Docking_smina, 30 | MultiClassification_b, 7 |
| 30       | ConsensusDocking_max, 31 | Docking_rdocktot, 31 | Docking_rdocktot, 31 | MultiClassification_b, 7 |
| 31       | LSTM_b, 32 | Docking_smina, 32 | Docking_hybrid, 32 | MultiClassification_b, 7 |
| 32       | Docking_dock6, 33 | Docking_rdocktot, 33 | ConsensusDocking_max, 33 | MultiClassification_b, 7 |
| 33       | IRV_a, 34 | ConsensusDocking_max, 34 | Docking_ad4, 34 | MultiClassification_b, 7 |
| 34       | Docking_smina, 35 | Docking_ad4, 35 | IRV_a, 35 | MultiClassification_b, 7 |
| NEF AUC PriA-SSB FP | NEF_1 % PriA-SSB FP |
|---------------------|---------------------|
| SingleRegression_b, 1 | SingleRegression_b, 1 |
| SingleRegression_a, 2 | SingleRegression_a, 2 |
| RandomForest_h, 3 | IRV_e, 3 |
| RandomForest_g, 4 | IRV_d, 4 |
| RandomForest_e, 5 | RandomForest_h, 5 |
| RandomForest_f, 6 | RandomForest_g, 5 |
| RandomForest_c, 7 | RandomForest_e, 5 |
| RandomForest_d, 8 | RandomForest_d, 5 |
| RandomForest_b, 9 | IRV_c, 9 |
| IRV_e, 10 | RandomForest_c, 9 |
| MultiClassification_b, 11 | RandomForest_b, 9 |
| RandomForest_a, 12 | RandomForest_a, 9 |
| IRV_d, 13 | IRV_b, 13 |
| SingleClassification_a, 14 | SingleClassification_a, 14 |
| IRV_c, 15 | RandomForest_f, 15 |
| SingleClassification_b, 16 | MultiClassification_b, 16 |
| LSTM_a, 17 | Docking_dock6, 17 |
| Docking_surflex, 18 | IRV_a, 17 |
| ConsensusDocking_median, 19 | LSTM_a, 19 |
| LSTM_b, 20 | SingleClassification_b, 19 |
| Docking_dock6, 21 | LSTM_b, 21 |
| ConsensusDocking_mean, 22 | MultiClassification_a, 22 |
| MultiClassification_a, 23 | ConsensusDocking_max, 23 |
| ConsensusDockingEFR1_opt, 24 | ConsensusDocking_mean, 23 |
| IRV_b, 25 | ConsensusDocking_median, 23 |
| ConsensusDocking_rocauc_opt, 26 | ConsensusDocking_rocauc_opt, 23 |
| Docking_hybrid, 27 | Docking_ad4, 23 |
| Docking_plants, 28 | Docking_rdocknt, 23 |
| Docking_fred, 29 | Docking_fred, 23 |
| Docking_rdocktot, 30 | Docking_hybrid, 23 |
| Docking_smina, 31 | Docking_plants, 23 |
| Docking_rdocknt, 32 | Docking_rdocktot, 23 |
| ConsensusDocking_max, 33 | Docking_smina, 23 |
| Docking_ad4, 34 | Docking_surflex, 23 |
| IRV_a, 35 | ConsensusDockingEFR1_opt, 23 |
| ROC AUC RMI-FANCM FP | BEDROC AUC RMI-FANCM FP | PR auc.integral RMI-FANCM FP |
|----------------------|--------------------------|-----------------------------|
| 0                    | RandomForest_h, 1        | SingleClassification_b, 1   |
| 1                    | RandomForest_g, 2        | SingleClassification_a, 2   |
| 2                    | RandomForest_e, 3        | RandomForest_h, 2           |
| 3                    | RandomForest_d, 4        | RandomForest_g, 4           |
| 4                    | RandomForest_c, 5        | RandomForest_e, 5           |
| 5                    | RandomForest_f, 6        | RandomForest_b, 6           |
| 6                    | RandomForest_b, 7        | RandomForest_a, 7           |
| 7                    | RandomForest_a, 8        | RandomForest_d, 8           |
| 8                    | MultiClassification_b, 9| RandomForest_c, 9           |
| 9                    | IRV_e, 10                | MultiClassification_b, 9    |
| 10                   | MultiClassification_a, 11| IRV_d, 11                   |
| 11                   | IRV_e, 12                | IRV_e, 12                   |
| 12                   | SingleClassification_b, 13| SingleClassification_b, 13  |
| 13                   | IRV_c, 14                | IRV_e, 14                   |
| 14                   | IRV_b, 15                | MultiClassification_a, 15   |
| 15                   | SingleClassification_a, 16| IRV_c, 16                   |
| 16                   | IRV_a, 16                | IRV_a, 17                   |
| 17                   | LSTM_a, 18               | MultiClassification_a, 17   |
| 18                   | Docking_ad4, 19          | Docking_ad4, 19             |
| 19                   | Docking_rdocktot, 20     | Docking_rdocktot, 20        |
| 20                   | Docking_smina, 21        | Docking_smina, 21           |
| 21                   | LSTM_a, 22               | ConsensusDocking_median, 22 |
| 22                   | Docking_rdockint, 23     | ConsensusDocking_rocauc_opt, 23|
| 23                   | LSTM_b, 23               | ConsensusDocking_max, 25    |
| 24                   | ConsensusDocking_median, 25| ConsensusDocking_max, 25    |
| 25                   | Docking_hybrid, 26       | Docking_hybrid, 26          |
| 26                   | ConsensusDocking_mean, 27| ConsensusDocking_mean, 27   |
| 27                   | Docking_plants, 28       | ConsensusDocking_mean, 28   |
| 28                   | ConsensusDocking_rocauc_opt, 29| LSTM_a, 28                 |
| 29                   | SingleRegression_b, 30   | Docking_hybrid, 30          |
| 30                   | ConsensusDocking_efr1_opt, 30| Docking_plants, 31          |
| 31                   | Docking_fred, 32         | Docking_fred, 32            |
| 32                   | Docking_dock6, 33        | Docking_dock6, 33           |
| 33                   | Docking_surflex, 34      | Docking_surflex, 34         |
| 34                   | SingleRegression_a, 35   | SingleRegression_a, 35      |
| NEF | AUC   | RMI-FANCM FP | NEF_1 % RMI-FANCM FP |
|-----|-------|--------------|-----------------------|
| 0   | RandomForest_h, 1 | RandomForest_h, 1 |
| 1   | RandomForest_g, 2  | RandomForest_g, 2  |
| 2   | RandomForest_c, 3  | RandomForest_d, 3  |
| 3   | RandomForest_b, 4  | RandomForest_e, 4  |
| 4   | RandomForest_d, 5  | RandomForest_f, 5  |
| 5   | RandomForest_a, 6  | IRV_d, 6           |
| 6   | RandomForest_c, 7  | IRV_a, 7           |
| 7   | RandomForest_f, 8  | SingleClassification_b, 8 |
| 8   | IRV_d, 9           | SingleClassification_a, 9 |
| 9   | MultiClassification_b, 10 | RandomForest_c, 10 |
| 10  | IRV_e, 10          | RandomForest_b, 10 |
| 11  | SingleClassification_a, 12 | RandomForest_a, 10 |
| 12  | SingleClassification_b, 13 | MultiClassification_b, 13 |
| 13  | MultiClassification_a, 14 | SingleRegression_b, 14 |
| 14  | IRV_c, 15          | IRV_c, 15          |
| 15  | IRV_b, 16          | IRV_b, 15          |
| 16  | IRV_a, 17          | IRV_e, 17          |
| 17  | Docking_rdocktot, 18 | MultiClassification_a, 18 |
| 18  | Docking_ad4, 19    | Docking_rdockint, 19 |
| 19  | SingleRegression_b, 19 | ConsensusDocking_median, 20 |
| 20  | Docking_smina, 21  | Docking_rdocktot, 21 |
| 21  | LSTM_a, 22         | ConsensusDocking_max, 22 |
| 22  | Docking_rdockint, 22 | Docking_ad4, 23  |
| 23  | ConsensusDocking_max, 24 | ConsensusDocking_mean, 24 |
| 24  | ConsensusDocking_median, 25 | ConsensusDocking_rocauc_opt, 25 |
| 25  | Docking_hybrid, 26 | ConsensusDocking_efr1_opt, 25 |
| 26  | LSTM_b, 26         | Docking_fred, 27   |
| 27  | ConsensusDocking_mean, 28 | Docking_dock6, 28 |
| 28  | ConsensusDocking_efr1_opt, 29 | Docking_smina, 29 |
| 29  | ConsensusDocking_rocauc_opt, 30 | Docking_plants, 30 |
| 30  | Docking_plants, 31 | LSTM_b, 31         |
| 31  | Docking_fred, 32   | LSTM_a, 32         |
| 32  | Docking_dock6, 33  | Docking_hybrid, 33 |
| 33  | Docking_surflex, 34 | SingleRegression_a, 34 |
| 34  | SingleRegression_a, 35 | Docking_surflex, 35 |
### J Prospective Screening: PriA-SSB prospective Metrics

Table S28: On-target evaluation metrics for all models. Models were trained on PriA-SSB AS and evaluated on PriA-SSB prospective.

| model                      | AUC[ROC] | AUC[BEDROC] | AUC[PR] | NEF₁% |
|----------------------------|----------|-------------|---------|-------|
| Baseline                   | 0.84937  | 0.67375     | 0.16167 | 0.55556 |
| ConsensusDocking_efr1_opt  | 0.57953  | 0.11677     | 0.00293 | 0.00000 |
| ConsensusDocking_max       | 0.57996  | 0.14810     | 0.00337 | 0.03704 |
| ConsensusDocking_mean      | 0.55288  | 0.09588     | 0.00261 | 0.00000 |
| ConsensusDocking_median    | 0.53129  | 0.07482     | 0.00246 | 0.00000 |
| ConsensusDocking_rocauc_opt| 0.58635  | 0.11949     | 0.00298 | 0.00000 |
| Docking_ad4                | 0.36292  | 0.01643     | 0.00159 | 0.00000 |
| Docking_dock6              | 0.55541  | 0.13279     | 0.00454 | 0.01852 |
| Docking_fred               | 0.51009  | 0.12103     | 0.00301 | 0.03704 |
| Docking_hybrid             | 0.49760  | 0.13474     | 0.00293 | 0.01852 |
| Docking_plants             | 0.48162  | 0.06959     | 0.00223 | 0.01852 |
| Docking_rdockint           | 0.56174  | 0.12492     | 0.00324 | 0.01852 |
| Docking_rdocktot           | 0.68720  | 0.21658     | 0.00470 | 0.01852 |
| Docking_smina              | 0.42361  | 0.03394     | 0.00188 | 0.00000 |
| Docking_surflex            | 0.57940  | 0.15061     | 0.00341 | 0.01852 |
| IRV_a                      | 0.64669  | 0.35955     | 0.07617 | 0.29630 |
| IRV_b                      | 0.71961  | 0.48510     | 0.12394 | 0.44444 |
| IRV_c                      | 0.78292  | 0.59296     | 0.18787 | 0.51852 |
| IRV_d                      | 0.82602  | 0.65816     | 0.19050 | 0.51852 |
| IRV_e                      | 0.86718  | 0.71450     | 0.20442 | 0.53704 |
| LSTM_a                     | 0.58979  | 0.17634     | 0.00357 | 0.01852 |
| LSTM_b                     | 0.61639  | 0.18218     | 0.00440 | 0.01852 |
| MultiClassification_a      | 0.83244  | 0.58368     | 0.18462 | 0.40741 |
| MultiClassification_b      | 0.84750  | 0.61346     | 0.22199 | 0.50000 |
| RandomForest_a             | 0.87578  | 0.73649     | 0.28165 | 0.66667 |
| RandomForest_b             | 0.87065  | 0.74287     | 0.28530 | 0.66667 |
| RandomForest_c             | 0.87524  | 0.74433     | 0.28648 | 0.66667 |
| RandomForest_d             | 0.88677  | 0.75521     | 0.28425 | 0.64815 |
| RandomForest_e             | 0.89007  | 0.75693     | 0.28200 | 0.66667 |
| RandomForest_f             | 0.88105  | 0.68324     | 0.17308 | 0.44444 |
| RandomForest_g             | 0.88903  | 0.76547     | 0.36893 | 0.66667 |
| RandomForest_h             | 0.89689  | 0.76886     | 0.37933 | 0.66667 |
| SingleClassification_a     | 0.76435  | 0.51959     | 0.11103 | 0.37037 |
| SingleClassification_b     | 0.81857  | 0.61809     | 0.30469 | 0.55556 |
| SingleRegression_a         | 0.92068  | 0.73424     | 0.18769 | 0.53704 |
| SingleRegression_b         | 0.89712  | 0.68403     | 0.18575 | 0.50000 |
Table S29: Off-target evaluation metrics for all models. As a control, the models trained on RMI-FANCM FP were evaluated on PriA-SSB prospective.

| model                                    | AUC[ROC] | AUC[BEDROC] | AUC[PR] | NEF 1% |
|------------------------------------------|----------|-------------|---------|--------|
| ConsensusDocking_efr1_opt                | 0.39931  | 0.04559     | 0.00182 | 0.00000|
| ConsensusDocking_max                     | 0.49919  | 0.07458     | 0.00227 | 0.00000|
| ConsensusDocking_mean                    | 0.48110  | 0.07205     | 0.00217 | 0.00000|
| ConsensusDocking_median                  | 0.47915  | 0.06370     | 0.00214 | 0.00000|
| ConsensusDocking_rocauc_opt              | 0.41457  | 0.04680     | 0.00186 | 0.00000|
| Docking_ad4                              | 0.37911  | 0.02775     | 0.00173 | 0.00000|
| Docking_dock6                            | 0.60630  | 0.12972     | 0.00318 | 0.00000|
| Docking_fred                             | 0.40761  | 0.06924     | 0.00218 | 0.01852|
| Docking_hybrid                           | 0.43895  | 0.04436     | 0.00196 | 0.00000|
| Docking_plants                           | 0.45539  | 0.07053     | 0.00212 | 0.01852|
| Docking_rdockint                         | 0.52785  | 0.08938     | 0.00245 | 0.00000|
| Docking_rdocktot                         | 0.60125  | 0.13316     | 0.00313 | 0.00000|
| Docking_smina                            | 0.44368  | 0.04307     | 0.00195 | 0.00000|
| Docking_surflex                          | 0.56411  | 0.10643     | 0.00295 | 0.01852|
| IRV_a                                    | 0.52240  | 0.13901     | 0.00615 | 0.03704|
| IRV_b                                    | 0.51675  | 0.13037     | 0.00701 | 0.03704|
| IRV_c                                    | 0.53331  | 0.15181     | 0.00605 | 0.03704|
| IRV_d                                    | 0.52513  | 0.14306     | 0.00593 | 0.03704|
| IRV_e                                    | 0.52069  | 0.14026     | 0.00608 | 0.03704|
| LSTM_a                                   | 0.60099  | 0.15468     | 0.00341 | 0.00000|
| LSTM_b                                   | 0.55336  | 0.18084     | 0.00351 | 0.00000|
| MultiClassification_a                    | 0.64870  | 0.20565     | 0.00551 | 0.03704|
| MultiClassification_b                    | 0.54647  | 0.14914     | 0.00376 | 0.05556|
| RandomForest_a                           | 0.50393  | 0.09951     | 0.00583 | 0.03704|
| RandomForest_b                           | 0.52529  | 0.09898     | 0.00634 | 0.03704|
| RandomForest_c                           | 0.52841  | 0.09705     | 0.00654 | 0.03704|
| RandomForest_d                           | 0.49301  | 0.09502     | 0.00617 | 0.03704|
| RandomForest_e                           | 0.49008  | 0.09053     | 0.00609 | 0.03704|
| RandomForest_f                           | 0.61363  | 0.15680     | 0.01225 | 0.03704|
| RandomForest_g                           | 0.51600  | 0.10026     | 0.00628 | 0.03704|
| RandomForest_h                           | 0.53381  | 0.10430     | 0.00637 | 0.03704|
| SingleClassification_a                   | 0.51852  | 0.11102     | 0.01917 | 0.03704|
| SingleClassification_b                   | 0.53075  | 0.13639     | 0.01135 | 0.03704|
| SingleRegression_a                       | 0.44809  | 0.07585     | 0.00224 | 0.01852|
| SingleRegression_b                       | 0.44100  | 0.07796     | 0.00482 | 0.03704|

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K Prospective Screening: PriA-SSB prospective Metric Plots

Figure S9: PriA-SSB prospective AUC[ROC]

Figure S10: PriA-SSB prospective AUC[BEDROC]
Figure S11: **PriA-SSB prospective AUC[PR]**

Figure S12: **PriA-SSB prospective NEF_{0.1\%}**
Figure S15: PriA-SSB prospective NEF$_{1\%}$

Figure S16: PriA-SSB prospective NEF$_{2\%}$
Figure S17: PriA-SSB prospective NEF\textsubscript{5\%}

Figure S18: PriA-SSB prospective NEF\textsubscript{10\%}
Figure S19: PriA-SSB prospective NEF$_{20\%}$

Figure S20: PriA-SSB prospective AUC[NEF]
Figure S21: **PriA-SSB prospective** top 100 hits

Figure S22: **PriA-SSB prospective** top 250 hits
Figure S23: **PriA-SSB prospective** top 500 hits

Figure S24: **PriA-SSB prospective** top 1000 hits
Figure S25: **PriA-SSB prospective** top 2500 hits

Figure S26: **PriA-SSB prospective** top 5000 hits
Figure S27: PriA-SSB prospective top 10000 hits
## L Prospective Screening: Actives in Top 250 Predictions

Table S30: Number of active compounds and unique clusters in the top 250 predictions compared to the experimental actives.

| Model                                           | Actives | Actives not in baseline | SIM clusters | MCS clusters |
|-------------------------------------------------|---------|-------------------------|--------------|--------------|
| Experimental                                    | 54      | –                       | 27           | 35           |
| Baseline                                        | 31      | 0                       | 14           | 17           |
| ConsensusDocking_efr1_opt                       | 0       | 0                       | 0            | 0            |
| ConsensusDocking_max                            | 2       | 1                       | 2            | 2            |
| ConsensusDocking_mean                           | 0       | 0                       | 0            | 0            |
| ConsensusDocking_median                         | 0       | 0                       | 0            | 0            |
| ConsensusDocking_rocauc_opt                     | 0       | 0                       | 0            | 0            |
| Docking_ad4                                     | 0       | 0                       | 0            | 0            |
| Docking_dock6                                   | 1       | 1                       | 1            | 1            |
| Docking_fred                                    | 2       | 1                       | 2            | 2            |
| Docking_hybrid                                  | 1       | 0                       | 1            | 1            |
| Docking_plants                                  | 1       | 1                       | 1            | 1            |
| Docking_rdockint                               | 1       | 0                       | 1            | 1            |
| Docking_rdocktot                                | 1       | 0                       | 1            | 1            |
| Docking_sminia                                  | 0       | 0                       | 0            | 0            |
| Docking_surflex                                 | 1       | 1                       | 1            | 1            |
| IRV_a                                           | 16      | 1                       | 9            | 12           |
| IRV_b                                           | 24      | 3                       | 14           | 16           |
| IRV_c                                           | 28      | 4                       | 15           | 18           |
| IRV_d                                           | 29      | 4                       | 15           | 18           |
| IRV_e                                           | 29      | 4                       | 15           | 18           |
| LSTM_a                                          | 1       | 0                       | 1            | 1            |
| LSTM_b                                          | 1       | 1                       | 1            | 1            |
| MultiClassification_a                          | 22      | 1                       | 11           | 13           |
| MultiClassification_b                          | 27      | 3                       | 13           | 17           |
| RandomForest_a                                  | 36      | 6                       | 17           | 20           |
| RandomForest_b                                  | 37      | 7                       | 17           | 21           |
| RandomForest_c                                  | 36      | 6                       | 17           | 20           |
| RandomForest_d                                  | 36      | 7                       | 17           | 21           |
| RandomForest_e                                  | 36      | 7                       | 17           | 21           |
| RandomForest_f                                  | 24      | 4                       | 12           | 17           |
| RandomForest_g                                  | 37      | 7                       | 17           | 22           |
| RandomForest_h                                  | 37      | 7                       | 17           | 22           |
| SingleClassification_a                         | 21      | 2                       | 11           | 13           |
| SingleClassification_b                         | 31      | 5                       | 16           | 19           |
| SingleRegression_a                             | 29      | 5                       | 13           | 18           |
| SingleRegression_b                             | 28      | 8                       | 14           | 18           |
M Prospective Screening: UpSet Plots for Active Compound Clusters

Figure S28: An UpSet plot showing the overlap in identified MCS clusters between the selected models and the chemical similarity baseline on PriA-SSB prospective.

Figure S29: An UpSet plot showing the overlap in identified SIM clusters between the selected models and the chemical similarity baseline on PriA-SSB prospective.
Prospective Screening: RF_h Y-Scrambled Results

Figure S30: Histogram for 100 Y-Scrambled RF_h runs evaluated on the top 250 predictions for PriA-SSB prospective. 55 out of 100 runs found zero actives. Only a single run found 10 actives, far less than the 37 actives RF_h identified when trained on the real PriA-SSB AS data.

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