Supplementary Information for
# Spatiotemporal identification of druggable binding sites using deep learning

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## Binding site definition

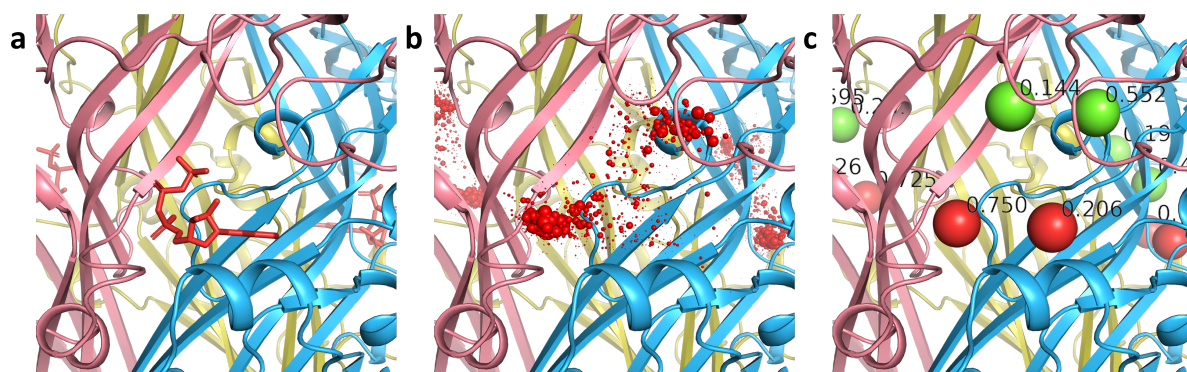*P2Rank binding site filtering criterion*

This criterion filters small molecules with less than 4 atoms, as well as HOH, DOD, WAT, NAG, MAN, UNK, GLC, ADA, MPD, GOL, SO4, PO4 molecules. The ligand must be within 4Å of a protein, and the distance from the ligand center to protein must be at least 5.5Å. A prediction is considered as true positive, if the minimum distance from the predicted coordinates to the ligand is less or equal than 4Å.
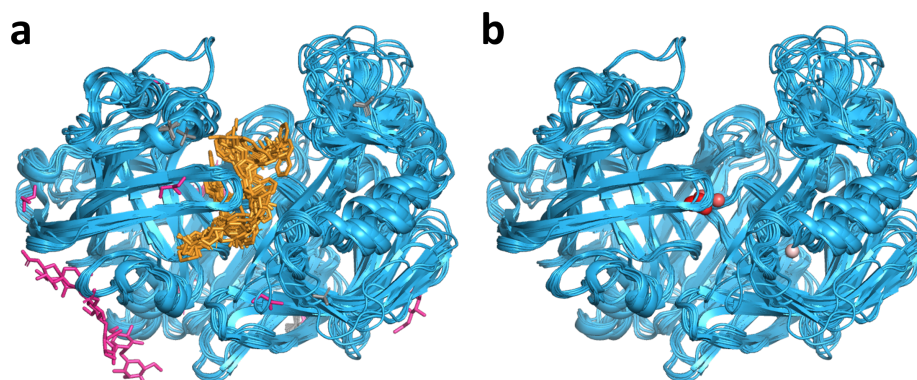
*BiteNet binding site filtering criterion*

This criterion filters out small molecules with less than 14 number of atoms, as well as detergent and buffer molecules (see Supplementary Table 1). Then binding site interface is defined as the number of protein atoms in the proximity of 4Åfrom the ligand, and binding sites with the interface less than 20 atoms are filtered out. A prediction is considered as true positive, if the minimum distance between the predicted coordinates and the ligand is less or equal than 4Å.

*BiteNet binding site filtering criterion for training*

This criterion differs from the previous one only in the true positive definition. Namely, a prediction is considered as true positive, if the minimum distance between the predicted coordinates and the geometric center of the binding site is less or equal than 4Å.



Supplementary Figure 1: BiteNet predictions for the ATP-bound P2X3 receptor trimer augmented with 50 replicas. (**a**) the ATP-binding site, ATP is shown with red sticks) (**b**) BiteNet predictions with no non max suppression. (**c**) BiteNet predictions filtered by the non max suppression with $distance\_threshold = 8$Å.
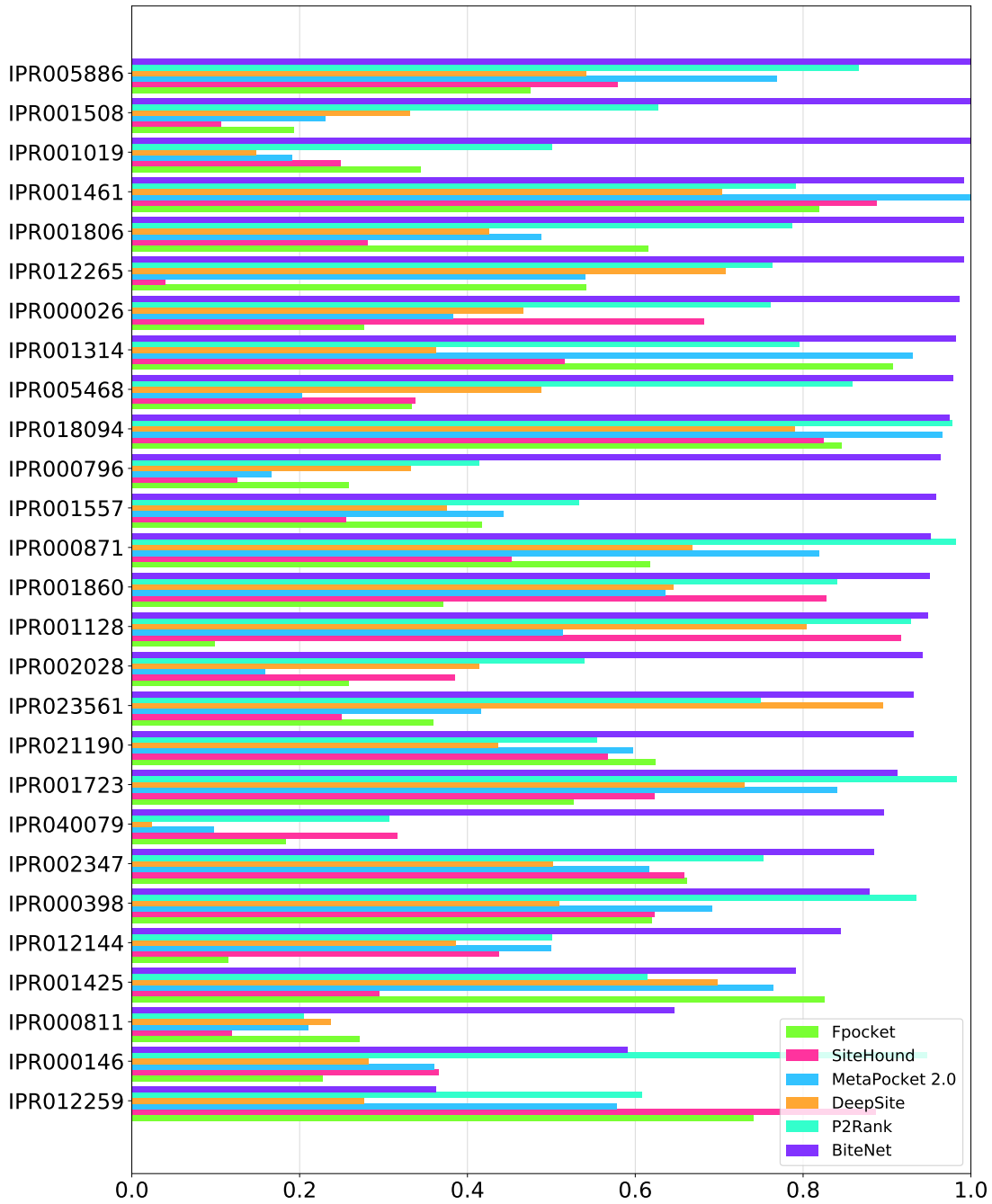
Supplementary Figure 2: Small molecules and BiteNet predictions for 29 proteins of the IPR001461 family from the HOLO4K dataset. **a** Small molecules corresponding to the relevant binding sites according to both BiteNet and P2Rank filtering criteria (yellow sticks), and only to the P2Rank filtering criterion (magenta sticks). **b** BiteNet predictions are shown with spheres colored from white to red with respect to the probability score.

Supplementary Table 1: List of the PDB identifiers filtered on the dataset preprocessing stage

| Type | Pdb code |
|---|---|
| unknown ligands | UNL |
| detergents | 12P, 15P, 1PE, 2CV, 2PE, 78M, 78N, BCR, BNG, BOG, BTB, C14, C8E, CDL, CLR, CM5, CPS, DAO, DGA, DGD, DMU, DXC, L2P, LDA, LFA, LHG, LI1, LMG, LMT, LMU, MPG, MQ7, MTN, MYR, MYS, NS5, OLA, OLB, OLC, P4C, P6G, PC1, PCW, PE4, PE5, PE8, PEE, PG6, PGV, PL9, PLC, OLM, PTY, PX4, SPN, SPO, SQD, STE, TGL, U10, YO1, HOH |
| modified residues | CSD, HYP, BMT, 5HP, ABA, AIB, CSW, OCS, DAL, DAR, DSG, DSP, DCY, CRO, DGL, DGN, DHI, DIL, DIV, DLE, DLY, DPN, DPR, DSN, DTH, DTR, DTY, DVA, CGU, KCX, LLP, CXM, FME, MLE, MVA, NLE, PTR, ORN, SEP, TPO, PCA, PVL, SAR, CEA, CSO, CSS, CSX, CME, TYS, TPQ, STY, NH2, CBX, ACE, FOR, IVA, BOC, LYR, MSE |
| cofactors | ADP, AMP, ATP, CMP, COA, FAD, FMN, NAP, NDP |
| carbohydrates | BGC, GLC, MAN, BMA, FUC, GAL, GLA, NAG, NGA, SIA, XYS |

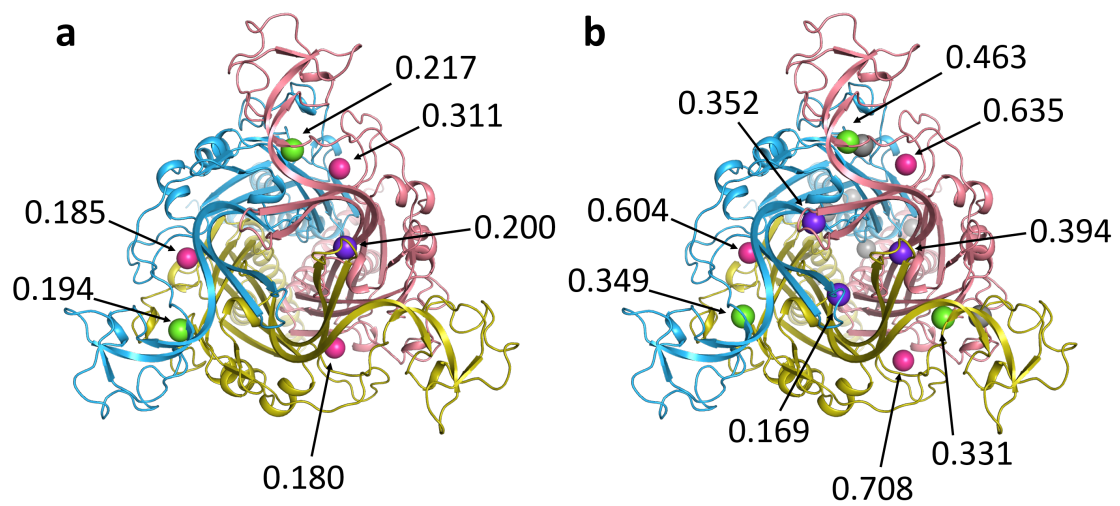Source: `https: //www.globalphasing.com/buster/manual/maketnt/manual/lib_val/library_validation.html`

Supplementary Figure 3: The average precision metric for different methods with respect to the most represented protein families in the HOLO4K benchmark.

Supplementary Table 2: Performance of the deep learning models trained with different parameters.

| Voxel size, Å | Density cutoff, Å | Cube size | Cell size | Stride | $\gamma$ | $\lambda$ | Minibatch | Average precision |
|---|---|---|---|---|---|---|---|---|
| 1.0 | 2.0 | 48 | 4 | 32 | 1e-05 | 5 | 64 | 0.307 |
| 1.0 | 2.0 | 48 | 8 | 32 | 1e-05 | 5 | 64 | 0.394 |
| 1.0 | 2.0 | 48 | 16 | 32 | 1e-05 | 5 | 64 | 0.353 |
| 1.0 | 2.0 | 64 | 16 | 32 | 1e-05 | 5 | 32 | 0.383 |
| 1.0 | 2.0 | 64 | 4 | 32 | 1e-05 | 5 | 32 | 0.314 |
| 1.0 | 2.0 | 64 | 8 | 32 | 1e-05 | 5 | 4 | 0.387 |
| 1.0 | 2.0 | 64 | 8 | 32 | 1e-05 | 5 | 8 | 0.331 |
| 1.0 | 2.0 | 64 | 8 | 32 | 1e-05 | 5 | 16 | 0.429 |
| 1.0 | 2.0 | 64 | 8 | 32 | 1e-05 | 5 | 32 | 0.404 |
| 1.0 | 1.0 | 80 | 16 | 32 | 1e-05 | 5 | 16 | 0.365 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-05 | 5 | 16 | 0.343 |
| 1.0 | 4.0 | 80 | 16 | 32 | 1e-05 | 5 | 16 | 0.387 |
| 1.0 | 8.0 | 80 | 16 | 32 | 1e-05 | 5 | 16 | 0.355 |
| 1.0 | 16.0 | 80 | 16 | 32 | 1e-05 | 5 | 16 | 0.368 |
| 1.0 | 2.0 | 80 | 16 | 32 | 0 | 5 | 16 | 0.372 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-01 | 5 | 16 | 0.216 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-02 | 5 | 16 | 0.264 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-03 | 5 | 16 | 0.299 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-04 | 5 | 16 | 0.362 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-05 | 5 | 16 | 0.371 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-06 | 5 | 16 | 0.351 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-05 | 1 | 16 | 0.368 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-05 | 10 | 16 | 0.377 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-05 | 100 | 16 | 0.333 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-05 | 1000 | 16 | 0.346 |
| 1.0 | 2.0 | 80 | 16 | 16 | 1e-05 | 5 | 16 | 0.272 |
| 1.0 | 2.0 | 80 | 16 | 24 | 1e-05 | 5 | 16 | 0.354 |
| 1.0 | 2.0 | 80 | 16 | 32 | 1e-05 | 5 | 16 | 0.399 |
| 1.0 | 2.0 | 80 | 16 | 48 | 1e-05 | 5 | 16 | 0.400 |
| 1.0 | 2.0 | 80 | 4 | 32 | 1e-05 | 5 | 16 | 0.302 |
| 1.0 | 2.0 | 80 | 8 | 32 | 1e-05 | 5 | 16 | 0.387 |
| 0.8 | 1.6 | 64 | 8 | 32 | 1e-05 | 5 | 32 | 0.435 |
| 1.5 | 3.0 | 64 | 8 | 32 | 1e-05 | 5 | 32 | 0.332 |
| 2.0 | 4.0 | 64 | 8 | 32 | 1e-05 | 5 | 32 | 0.283 |
| 3.0 | 6.0 | 64 | 8 | 32 | 1e-05 | 5 | 32 | 0.147 |

Supplementary Figure 4: BiteNet predictions obtained for the P2X3 trimer with no (**a**) or with (**b**) rotational replicas.

Supplementary Table 3: Performance metrics on the COACH420 subset of 239 proteins, which are not in the BiteNet training set, outputs of all methods are available for them and each structure contains at least one relevant binding site according to the P2Rank binding site filtering criterion.

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (239) | 0.67 | 0.50 | 0.40 | 0.28 | 0.63 | 0.46 | 0.51 | 0.56 | 0.43 | 0.26 | 0.66 | 0.46 | 0.07 | 0.76 | 0.48 |
| | SiteHound (239) | 0.58 | 0.44 | 0.29 | 0.29 | 0.65 | 0.33 | 0.47 | 0.54 | 0.33 | 0.26 | 0.68 | 0.34 | 0.02 | **0.94** | 0.34 |
| | MetaPocket 2.0 (239) | 0.70 | 0.53 | 0.41 | 0.29 | 0.67 | 0.48 | 0.52 | 0.58 | 0.44 | 0.27 | 0.69 | 0.48 | 0.16 | 0.74 | 0.49 |
| | DeepSite (239) | 0.65 | 0.47 | 0.38 | 0.31 | 0.57 | 0.40 | 0.53 | 0.51 | 0.40 | 0.30 | 0.57 | 0.40 | **0.25** | 0.57 | 0.40 |
| | P2Rank (239) | 0.83 | 0.63 | 0.54 | 0.33 | 0.70 | 0.54 | 0.65 | 0.68 | 0.57 | 0.31 | 0.72 | 0.54 | 0.15 | 0.75 | 0.54 |
| | **BiteNet (239)** | **0.87** | **0.67** | **0.64** | **0.38** | 0.77 | 0.69 | **0.69** | 0.73 | 0.68 | **0.36** | 0.79 | 0.70 | 0.24 | 0.81 | 0.71 |
| | **BiteNet R$^+$ (239)** | **0.87** | 0.66 | 0.62 | 0.34 | **0.78** | **0.69** | 0.67 | **0.75** | **0.69** | 0.31 | **0.80** | **0.70** | 0.10 | 0.86 | **0.71** |
| BiteNet binding site filtering criterion | Fpocket (239) | 0.49 | 0.67 | 0.37 | 0.20 | 0.80 | 0.41 | 0.67 | 0.68 | 0.54 | 0.21 | 0.80 | 0.41 | 0.05 | 0.93 | 0.42 |
| | SiteHound (239) | 0.43 | 0.58 | 0.31 | 0.20 | 0.81 | 0.34 | 0.61 | 0.62 | 0.44 | 0.22 | 0.83 | 0.35 | 0.01 | **0.99** | 0.33 |
| | MetaPocket 2.0 (239) | 0.52 | 0.71 | 0.41 | 0.21 | 0.88 | 0.48 | 0.70 | 0.71 | 0.57 | 0.23 | 0.88 | 0.48 | 0.11 | 0.92 | 0.48 |
| | DeepSite (239) | 0.48 | 0.64 | 0.41 | 0.22 | 0.75 | 0.42 | 0.65 | 0.64 | 0.51 | 0.24 | 0.75 | 0.42 | **0.18** | 0.75 | 0.42 |
| | P2Rank (239) | 0.60 | 0.81 | 0.49 | 0.23 | 0.88 | 0.49 | 0.82 | 0.83 | 0.68 | 0.25 | 0.88 | 0.49 | 0.10 | 0.91 | 0.49 |
| | **BiteNet (239)** | 0.62 | 0.84 | 0.57 | **0.25** | 0.92 | 0.59 | **0.85** | 0.85 | **0.81** | **0.28** | 0.92 | 0.59 | 0.16 | 0.94 | 0.60 |
| | **BiteNet R$^+$ (239)** | **0.62** | **0.85** | **0.63** | 0.23 | **0.93** | **0.66** | **0.85** | **0.86** | 0.80 | 0.25 | **0.94** | **0.67** | 0.06 | 0.99 | **0.67** |
| BiteNet criterion for training | Fpocket (239) | 0.26 | 0.35 | 0.09 | 0.11 | 0.42 | 0.10 | 0.36 | 0.36 | 0.13 | 0.12 | 0.42 | 0.10 | 0.03 | 0.50 | 0.11 |
| | SiteHound (239) | 0.30 | 0.40 | 0.15 | 0.15 | 0.59 | 0.18 | 0.42 | 0.42 | 0.21 | 0.16 | 0.59 | 0.18 | 0.01 | 0.79 | 0.18 |
| | MetaPocket 2.0 (239) | 0.29 | 0.40 | 0.12 | 0.12 | 0.51 | 0.15 | 0.39 | 0.40 | 0.17 | 0.14 | 0.51 | 0.15 | 0.07 | 0.60 | 0.16 |
| | DeepSite (239) | 0.27 | 0.36 | 0.14 | 0.12 | 0.41 | 0.15 | 0.36 | 0.36 | 0.17 | 0.13 | 0.41 | 0.15 | 0.10 | 0.41 | 0.15 |
| | P2Rank (239) | 0.42 | 0.56 | 0.24 | 0.16 | 0.59 | 0.23 | 0.57 | 0.57 | 0.33 | 0.17 | 0.59 | 0.23 | 0.07 | 0.60 | 0.23 |
| | **BiteNet (239)** | **0.54** | **0.73** | 0.45 | **0.22** | 0.79 | 0.46 | **0.73** | **0.74** | **0.63** | **0.24** | 0.79 | 0.46 | **0.14** | 0.81 | 0.46 |
| | **BiteNet R$^+$ (239)** | 0.52 | 0.72 | **0.49** | 0.19 | **0.80** | **0.52** | 0.72 | 0.73 | 0.62 | 0.21 | **0.80** | **0.53** | 0.05 | **0.86** | **0.53** |

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (239) | 159 | 80 | 174 | 229 | 488 | 128 | 178 | 167 | 155 | 237 | 575 | 119 | 312 | 3262 | 84 |
| | SiteHound (239) | 139 | 100 | 196 | 242 | 475 | 124 | 165 | 184 | 162 | 254 | 573 | 113 | 499 | 14136 | **22** |
| | MetaPocket 2.0 (239) | 167 | 72 | 163 | 230 | 487 | 116 | 182 | 164 | 146 | 239 | 577 | 109 | 296 | 1217 | 90 |
| | DeepSite (239) | 155 | 82 | 184 | 208 | 411 | 151 | 172 | 144 | 171 | 209 | 438 | 150 | 212 | **549** | 149 |
| | P2Rank (239) | 197 | 40 | 131 | 236 | 435 | 104 | 215 | 113 | 111 | 243 | 500 | 97 | 262 | 1330 | 88 |
| | **BiteNet (239)** | **209** | **30** | **117** | 275 | **358** | 80 | 231 | **98** | 95 | 281 | **401** | 75 | 307 | 742 | 68 |
| | **BiteNet R$^+$ (239)** | **209** | **30** | 119 | **297** | 418 | **78** | **239** | 110 | **88** | **307** | 515 | **70** | 407 | 2449 | 49 |
| BiteNet binding site filtering criterion | Fpocket (239) | 117 | 122 | 59 | 162 | 555 | 36 | 119 | 58 | 57 | 163 | 492 | 36 | 215 | 3359 | 13 |
| | SiteHound (239) | 103 | 136 | 74 | 169 | 548 | 34 | 108 | 69 | 67 | 173 | 482 | 31 | **323** | 14312 | **1** |
| | MetaPocket 2.0 (239) | 123 | 116 | 52 | 166 | 551 | 22 | 124 | 53 | 51 | 166 | 489 | 22 | 209 | 1304 | 14 |
| | DeepSite (239) | 113 | 124 | 63 | 145 | 474 | 44 | 115 | 61 | 63 | 145 | 432 | 44 | 147 | **614** | 44 |
| | P2Rank (239) | 142 | 95 | 33 | 164 | 507 | 22 | 144 | 31 | 31 | 166 | 456 | 21 | 179 | 1413 | 16 |
| | **BiteNet (239)** | 147 | 92 | 29 | 183 | **450** | 15 | **151** | **26** | 26 | 183 | **397** | 15 | 200 | 849 | 10 |
| | **BiteNet R$^+$ (239)** | **148** | **91** | **27** | **199** | 516 | **12** | **151** | **26** | **25** | **200** | 453 | **11** | 280 | 2576 | 2 |
| BiteNet criterion for training | Fpocket (239) | 62 | 177 | 115 | 75 | 642 | 102 | 63 | 114 | 114 | 75 | 580 | 102 | 89 | 3485 | 88 |
| | SiteHound (239) | 71 | 168 | 106 | 104 | 613 | 73 | 75 | 102 | 102 | 105 | 550 | 72 | 139 | 14496 | 38 |
| | MetaPocket 2.0 (239) | 69 | 170 | 107 | 90 | 627 | 87 | 69 | 108 | 107 | 90 | 565 | 87 | 109 | 1404 | 71 |
| | DeepSite (239) | 64 | 173 | 113 | 75 | 544 | 104 | 64 | 112 | 113 | 75 | 502 | 104 | 75 | **686** | 104 |
| | P2Rank (239) | 99 | 138 | 78 | 105 | 566 | 73 | 100 | 75 | 77 | 105 | 517 | 73 | 107 | 1485 | 71 |
| | **BiteNet (239)** | **129** | **110** | **47** | **139** | 494 | 37 | **130** | **47** | **46** | 139 | **441** | 37 | 143 | 906 | 33 |
| | **BiteNet R$^+$ (239)** | 125 | 114 | 50 | **139** | 576 | **36** | 127 | 50 | 48 | **140** | 513 | **35** | **150** | 2706 | **25** |

The best score values are denoted with bold font.

Supplementary Table 4: Performance metrics on the HOLO4K subset of 1682 proteins, which are not in the BiteNet training set, outputs of all methods are available for them and each structure contains at least one relevant binding site according to the P2Rank binding site filtering criterion.

**Precision / Recall / Average precision**

| Criterion | Method | Top-1 prec | Top-1 rec | Top-1 ap | Top-3 prec | Top-3 rec | Top-3 ap | Top-n prec | Top-n rec | Top-n ap | Top-(n+2) prec | Top-(n+2) rec | Top-(n+2) ap | All prec | All rec | All ap |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P2Rank binding site filtering criterion | Fpocket (1682) | 0.68 | 0.38 | 0.28 | 0.37 | 0.62 | 0.41 | 0.54 | 0.59 | 0.40 | 0.32 | 0.70 | 0.44 | 0.07 | 0.81 | 0.45 |
| | SiteHound (1682) | 0.61 | 0.36 | 0.22 | 0.34 | 0.59 | 0.31 | 0.49 | 0.56 | 0.32 | 0.31 | 0.70 | 0.34 | 0.02 | **0.97** | 0.36 |
| | MetaPocket 2.0 (1682) | 0.67 | 0.39 | 0.25 | 0.35 | 0.62 | 0.38 | 0.53 | 0.59 | 0.37 | 0.31 | 0.69 | 0.41 | 0.20 | 0.73 | 0.42 |
| | DeepSite (1682) | 0.73 | 0.42 | 0.32 | 0.42 | 0.58 | 0.40 | 0.65 | 0.56 | 0.42 | 0.40 | 0.59 | 0.40 | **0.35** | 0.59 | 0.40 |
| | P2Rank (1682) | 0.85 | 0.50 | 0.41 | 0.43 | 0.73 | 0.58 | **0.78** | 0.73 | 0.60 | **0.46** | 0.78 | 0.60 | 0.14 | 0.81 | 0.61 |
| | **BiteNet** (1682) | 0.92 | 0.51 | 0.49 | **0.53** | 0.77 | 0.72 | 0.75 | 0.78 | 0.75 | 0.40 | 0.82 | 0.76 | 0.32 | 0.84 | 0.77 |
| | **BiteNet R$^+$** (1682) | **0.93** | 0.51 | **0.50** | 0.47 | **0.78** | **0.74** | 0.75 | **0.80** | **0.77** | 0.40 | **0.85** | **0.79** | 0.13 | 0.89 | **0.79** |
| BiteNet binding site filtering criterion | Fpocket (1682) | 0.45 | 0.45 | 0.21 | 0.24 | 0.71 | 0.31 | 0.60 | 0.62 | 0.41 | 0.26 | 0.79 | 0.34 | 0.04 | 0.89 | 0.34 |
| | SiteHound (1682) | 0.42 | 0.42 | 0.19 | 0.24 | 0.70 | 0.25 | 0.56 | 0.59 | 0.35 | 0.26 | 0.77 | 0.29 | 0.01 | **1.00** | 0.28 |
| | MetaPocket 2.0 (1682) | 0.48 | 0.48 | 0.21 | 0.24 | 0.73 | 0.32 | 0.61 | 0.64 | 0.40 | 0.26 | 0.79 | 0.33 | 0.13 | 0.84 | 0.34 |
| | DeepSite (1682) | 0.51 | 0.50 | 0.27 | 0.28 | 0.67 | 0.31 | 0.70 | 0.64 | 0.48 | 0.30 | 0.68 | 0.32 | **0.24** | 0.68 | 0.31 |
| | P2Rank (1682) | 0.60 | 0.60 | 0.35 | 0.29 | 0.85 | 0.48 | 0.79 | 0.83 | 0.68 | 0.30 | 0.89 | 0.51 | 0.09 | 0.92 | 0.50 |
| | **BiteNet** (1682) | 0.64 | 0.63 | 0.45 | **0.36** | 0.91 | 0.64 | **0.89** | 0.90 | 0.86 | **0.37** | 0.96 | 0.68 | 0.21 | 0.97 | 0.68 |
| | **BiteNet R$^+$** (1682) | **0.65** | **0.63** | **0.48** | 0.32 | **0.91** | **0.68** | **0.89** | **0.91** | **0.88** | 0.33 | **0.96** | **0.71** | 0.08 | 0.99 | **0.71** |
| BiteNet criterion for training | Fpocket (1682) | 0.27 | 0.26 | 0.06 | 0.14 | 0.41 | 0.10 | 0.35 | 0.35 | 0.12 | 0.16 | 0.45 | 0.13 | 0.03 | 0.53 | 0.11 |
| | SiteHound (1682) | 0.30 | 0.28 | 0.08 | 0.17 | 0.49 | 0.12 | 0.40 | 0.40 | 0.15 | 0.19 | 0.54 | 0.13 | 0.01 | 0.80 | 0.14 |
| | MetaPocket 2.0 (1682) | 0.27 | 0.26 | 0.06 | 0.14 | 0.40 | 0.09 | 0.34 | 0.34 | 0.10 | 0.15 | 0.45 | 0.10 | 0.08 | 0.50 | 0.10 |
| | DeepSite (1682) | 0.31 | 0.30 | 0.10 | 0.16 | 0.38 | 0.10 | 0.42 | 0.37 | 0.16 | 0.17 | 0.39 | 0.11 | 0.14 | 0.39 | 0.11 |
| | P2Rank (1682) | 0.41 | 0.39 | 0.14 | 0.19 | 0.54 | 0.17 | 0.52 | 0.52 | 0.25 | 0.20 | 0.56 | 0.18 | 0.06 | 0.58 | 0.18 |
| | **BiteNet** (1682) | 0.58 | 0.55 | 0.37 | **0.32** | 0.79 | 0.52 | 0.78 | 0.78 | 0.69 | **0.33** | 0.83 | 0.55 | **0.19** | 0.84 | 0.54 |
| | **BiteNet R$^+$** (1682) | **0.59** | **0.56** | **0.40** | 0.28 | **0.81** | **0.57** | **0.80** | **0.80** | **0.72** | 0.30 | **0.85** | **0.59** | 0.07 | **0.88** | **0.59** |

**True positives / False positives / False negatives**

| Criterion | Method | Top-1 TP | Top-1 FP | Top-1 FN | Top-3 TP | Top-3 FP | Top-3 FN | Top-n TP | Top-n FP | Top-n FN | Top-(n+2) TP | Top-(n+2) FP | Top-(n+2) FN | All TP | All FP | All FN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P2Rank binding site filtering criterion | Fpocket (1682) | 1140 | 542 | 1997 | 2014 | 3022 | 1228 | 1788 | 1433 | 1342 | 2322 | 4236 | 971 | 3156 | 32013 | 630 |
| | SiteHound (1682) | 1022 | 660 | 2085 | 2023 | 3023 | 1315 | 1700 | 1538 | 1432 | 2440 | 4162 | 988 | **4934** | 132214 | **113** |
| | MetaPocket 2.0 (1682) | 1123 | 559 | 1980 | 1939 | 3107 | 1227 | 1719 | 1402 | 1344 | 2227 | 4107 | 1007 | 2591 | 8174 | 878 |
| | DeepSite (1682) | 1233 | 448 | 1875 | 1813 | 2328 | 1347 | 1653 | 869 | 1419 | 1829 | **2467** | 1331 | 1839 | **3129** | 1327 |
| | P2Rank (1682) | 1424 | 258 | 1616 | 2151 | 2696 | 871 | 2080 | 1078 | 886 | 2325 | 3912 | 714 | 2603 | 13944 | 604 |
| | **BiteNet** (1682) | 1551 | 131 | 1582 | 2503 | **1868** | 761 | 2461 | **581** | 698 | 2811 | 2612 | 569 | 3012 | 4974 | 521 |
| | **BiteNet R$^+$** (1682) | **1565** | **117** | **1573** | **2631** | 2357 | **729** | **2566** | 660 | **655** | **3043** | 3463 | **495** | 4032 | 17646 | 358 |
| BiteNet binding site filtering criterion | Fpocket (1682) | 760 | 922 | 967 | 1313 | 3723 | 505 | 1058 | 698 | 664 | 1463 | 3652 | 378 | 2023 | 33146 | 187 |
| | SiteHound (1682) | 711 | 971 | 1017 | 1383 | 3663 | 532 | 1014 | 742 | 725 | 1554 | 3566 | 397 | **3140** | 134008 | **1** |
| | MetaPocket 2.0 (1682) | 801 | 881 | 917 | 1313 | 3733 | 471 | 1079 | 667 | 625 | 1444 | 3626 | 378 | 1709 | 9056 | 290 |
| | DeepSite (1682) | 854 | 827 | 874 | 1219 | 2922 | 575 | 1084 | 463 | 640 | 1226 | 2674 | 568 | 1234 | **3734** | 565 |
| | P2Rank (1682) | 1006 | 676 | 698 | 1463 | 3384 | 265 | 1388 | 365 | 307 | 1549 | 3417 | 196 | 1724 | 14823 | 141 |
| | **BiteNet** (1682) | 1082 | 600 | 652 | 1680 | **2691** | 165 | 1570 | 179 | 170 | 1837 | **2659** | 74 | 1987 | 5999 | 53 |
| | **BiteNet R$^+$** (1682) | **1095** | **587** | **644** | **1747** | 3241 | **158** | **1587** | **169** | **162** | **1932** | 3150 | **70** | 2656 | 19022 | 16 |
| BiteNet criterion for training | Fpocket (1682) | 447 | 1235 | 1313 | 723 | 4313 | 1037 | 611 | 1152 | 1149 | 796 | 4326 | 964 | 938 | 34231 | 830 |
| | SiteHound (1682) | 499 | 1183 | 1262 | 863 | 4183 | 900 | 699 | 1064 | 1061 | 958 | 4169 | 804 | 1405 | 135743 | 360 |
| | MetaPocket 2.0 (1682) | 454 | 1228 | 1303 | 708 | 4338 | 1050 | 588 | 1165 | 1169 | 784 | 4293 | 977 | 894 | 9871 | 884 |
| | DeepSite (1682) | 519 | 1162 | 1241 | 700 | 3441 | 1089 | 644 | 909 | 1118 | 705 | 3198 | 1084 | 707 | **4261** | 1082 |
| | P2Rank (1682) | 681 | 1001 | 1077 | 938 | 3909 | 820 | 908 | 852 | 849 | 980 | 3991 | 777 | 1021 | 15526 | 737 |
| | **BiteNet** (1682) | 967 | 715 | 793 | 1384 | **2987** | 376 | 1373 | 382 | 387 | 1463 | **3035** | 297 | 1480 | 6506 | 280 |
| | **BiteNet R$^+$** (1682) | **985** | **697** | **774** | **1417** | 3571 | **342** | **1402** | **361** | **357** | **1499** | 3590 | **260** | **1552** | 20126 | **207** |

The best score values are denoted with bold font.

Supplementary Table 5: Performance metrics for the entire COACH420 dataset.

| Criterion | Method | Top-1 prec | Top-1 rec | Top-1 ap | Top-3 prec | Top-3 rec | Top-3 ap | Top-n prec | Top-n rec | Top-n ap | Top-(n+2) prec | Top-(n+2) rec | Top-(n+2) ap | All prec | All rec | All ap |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P2Rank binding site filtering criterion | Fpocket (420) | 0.63 | 0.49 | 0.37 | 0.27 | 0.63 | 0.43 | 0.51 | 0.56 | 0.41 | 0.25 | 0.66 | 0.44 | 0.07 | 0.76 | 0.45 |
| | SiteHound (284) | 0.57 | 0.44 | 0.23 | 0.28 | 0.64 | 0.33 | 0.47 | 0.53 | 0.33 | 0.25 | 0.67 | 0.33 | 0.02 | **0.93** | 0.34 |
| | MetaPocket 2.0 (417) | 0.71 | 0.56 | 0.44 | 0.29 | 0.69 | 0.51 | 0.55 | 0.61 | 0.47 | 0.27 | 0.71 | 0.51 | 0.15 | 0.76 | 0.52 |
| | DeepSite (420) | 0.64 | 0.49 | 0.37 | 0.30 | 0.57 | 0.37 | 0.54 | 0.52 | 0.39 | 0.29 | 0.58 | 0.56 | **0.25** | 0.58 | 0.38 |
| | P2Rank (420) | 0.79 | 0.62 | 0.54 | 0.32 | 0.71 | 0.55 | 0.64 | 0.67 | 0.56 | 0.31 | 0.72 | 0.56 | 0.15 | 0.74 | 0.55 |
| | **BiteNet (420)** | **0.83** | **0.65** | 0.60 | **0.37** | 0.77 | 0.67 | **0.70** | 0.72 | 0.66 | **0.36** | 0.79 | 0.68 | 0.23 | 0.81 | 0.68 |
| | **BiteNet R⁺ (420)** | 0.83 | 0.65 | **0.61** | 0.34 | **0.78** | **0.69** | 0.66 | **0.73** | **0.67** | 0.31 | **0.81** | **0.70** | 0.09 | 0.85 | **0.71** |
| BiteNet binding site filtering criterion | Fpocket (420) | 0.48 | 0.66 | 0.37 | 0.19 | 0.79 | 0.40 | 0.67 | 0.67 | 0.50 | 0.21 | 0.79 | 0.40 | 0.05 | 0.91 | 0.41 |
| | SiteHound (284) | 0.44 | 0.59 | 0.31 | 0.20 | 0.81 | 0.34 | 0.61 | 0.62 | 0.43 | 0.22 | 0.83 | 0.35 | 0.01 | **1.00** | 0.34 |
| | MetaPocket 2.0 (417) | 0.52 | 0.73 | 0.41 | 0.21 | 0.88 | 0.47 | 0.72 | 0.73 | 0.58 | 0.23 | 0.88 | 0.47 | 0.11 | 0.93 | 0.48 |
| | DeepSite (420) | 0.47 | 0.64 | 0.37 | 0.21 | 0.73 | 0.36 | 0.65 | 0.64 | 0.47 | 0.23 | 0.73 | 0.36 | **0.18** | 0.73 | 0.36 |
| | P2Rank (420) | 0.59 | 0.81 | 0.51 | 0.23 | 0.89 | 0.52 | 0.82 | 0.82 | 0.71 | 0.25 | 0.90 | 0.52 | 0.11 | 0.92 | 0.52 |
| | **BiteNet (420)** | **0.60** | **0.83** | 0.55 | **0.25** | 0.92 | 0.58 | **0.84** | 0.84 | 0.78 | **0.28** | 0.92 | 0.58 | 0.15 | 0.94 | 0.58 |
| | **BiteNet R⁺ (420)** | 0.60 | 0.83 | **0.59** | 0.23 | **0.94** | **0.63** | 0.83 | **0.84** | **0.79** | 0.25 | **0.95** | **0.64** | 0.06 | 0.99 | **0.64** |
| BiteNet criterion for training | Fpocket (420) | 0.27 | 0.37 | 0.11 | 0.11 | 0.46 | 0.12 | 0.37 | 0.37 | 0.14 | 0.12 | 0.46 | 0.12 | 0.03 | 0.53 | 0.12 |
| | SiteHound (284) | 0.30 | 0.40 | 0.14 | 0.15 | 0.59 | 0.17 | 0.42 | 0.42 | 0.20 | 0.16 | 0.59 | 0.17 | 0.010 | 0.79 | 0.17 |
| | MetaPocket 2.0 (417) | 0.27 | 0.38 | 0.10 | 0.12 | 0.48 | 0.12 | 0.38 | 0.38 | 0.14 | 0.13 | 0.48 | 0.12 | 0.06 | 0.55 | 0.13 |
| | DeepSite (420) | 0.25 | 0.34 | 0.11 | 0.11 | 0.39 | 0.12 | 0.34 | 0.34 | 0.14 | 0.12 | 0.39 | 0.12 | 0.10 | 0.39 | 0.12 |
| | P2Rank (420) | 0.38 | 0.52 | 0.20 | 0.15 | 0.56 | 0.20 | 0.53 | 0.52 | 0.27 | 0.16 | 0.56 | 0.20 | 0.07 | 0.57 | 0.20 |
| | **BiteNet (420)** | 0.51 | 0.70 | 0.42 | **0.21** | 0.77 | 0.44 | **0.70** | 0.70 | 0.59 | **0.23** | 0.77 | 0.44 | **0.13** | 0.79 | 0.44 |
| | **BiteNet R⁺ (420)** | **0.51** | **0.71** | **0.46** | 0.20 | **0.82** | **0.50** | 0.71 | **0.72** | **0.62** | 0.22 | **0.82** | **0.51** | 0.05 | **0.86** | **0.51** |

| Criterion | Method | Top-1 TP | Top-1 FP | Top-1 FN | Top-3 TP | Top-3 FP | Top-3 FN | Top-n TP | Top-n FP | Top-n FN | Top-(n+2) TP | Top-(n+2) FP | Top-(n+2) FN | All TP | All FP | All FN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P2Rank binding site filtering criterion | Fpocket (420) | 265 | 155 | 298 | 386 | 869 | 214 | 301 | 279 | 260 | 403 | 999 | 197 | 522 | 5612 | 143 |
| | SiteHound (284) | 161 | 123 | 225 | 278 | 574 | 144 | 191 | 210 | 188 | 290 | 679 | 133 | 577 | 16527 | 27 |
| | MetaPocket 2.0 (417) | 294 | 123 | 255 | 405 | 846 | 178 | 322 | 256 | 226 | 423 | 979 | 166 | 517 | 2217 | 139 |
| | DeepSite (420) | 268 | 149 | 300 | 358 | 727 | 250 | 295 | 240 | 282 | 360 | 769 | 248 | 366 | **961** | 247 |
| | P2Rank (420) | 329 | 87 | 220 | 405 | 755 | 171 | 353 | 194 | 195 | 414 | 846 | 162 | 445 | 2186 | 152 |
| | **BiteNet (420)** | **348** | **71** | **204** | 469 | 635 | 134 | 387 | 163 | 163 | 480 | **696** | 124 | 528 | 1364 | 113 |
| | **BiteNet R⁺ (420)** | 348 | 72 | 207 | **510** | 744 | **126** | **393** | 188 | **160** | **528** | 881 | **111** | **696** | 4249 | **85** |
| BiteNet binding site filtering criterion | Fpocket (420) | 200 | 220 | 104 | 272 | 983 | 65 | 203 | 102 | 101 | 273 | 868 | 65 | 360 | 5774 | 28 |
| | SiteHound (284) | 124 | 160 | 88 | 204 | 648 | 40 | 129 | 83 | 81 | 208 | 572 | 37 | 391 | 16713 | 1 |
| | MetaPocket 2.0 (417) | 217 | 200 | 83 | 291 | 960 | 35 | 219 | 84 | 81 | 291 | 846 | 35 | 363 | 2271 | 22 |
| | DeepSite (420) | 194 | 223 | 110 | 247 | 838 | 84 | 196 | 107 | 110 | 247 | 758 | 84 | 253 | **1074** | 82 |
| | P2Rank (420) | 245 | 171 | 57 | 290 | 870 | 33 | 247 | 54 | 55 | 292 | 780 | 32 | 315 | 2316 | 26 |
| | **BiteNet (420)** | **251** | **168** | 52 | 320 | 784 | 26 | **255** | **49** | 50 | 321 | **692** | 25 | 359 | 1533 | 17 |
| | **BiteNet R⁺ (420)** | 251 | 169 | **52** | **347** | 907 | **18** | 255 | 50 | **49** | **350** | 789 | **15** | **488** | 4457 | **4** |
| BiteNet criterion for training | Fpocket (420) | 113 | 307 | 192 | 139 | 1116 | 166 | 114 | 191 | 191 | 139 | 1002 | 166 | 163 | 5971 | 142 |
| | SiteHound (284) | 84 | 200 | 128 | 124 | 728 | 88 | 88 | 124 | 124 | 125 | 655 | 87 | 168 | 16936 | 45 |
| | MetaPocket 2.0 (417) | 114 | 303 | 188 | 146 | 1105 | 157 | 115 | 188 | 187 | 146 | 991 | 157 | 173 | 2461 | 136 |
| | DeepSite (420) | 104 | 313 | 201 | 125 | 960 | 186 | 104 | 199 | 201 | 125 | 880 | 186 | 127 | **1200** | 185 |
| | P2Rank (420) | 157 | 259 | 148 | 171 | 989 | 135 | 158 | 143 | 147 | 171 | 901 | 135 | 176 | 2455 | 130 |
| | **BiteNet (420)** | 212 | **207** | 92 | 235 | 869 | 69 | 213 | 91 | 91 | 235 | 778 | 69 | 241 | 1651 | 63 |
| | **BiteNet R⁺ (420)** | **213** | 207 | **90** | **247** | 1007 | **56** | **216** | 89 | **87** | **249** | 890 | **54** | **261** | 4684 | **42** |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

Supplementary Table 6: Performance metrics for the entire HOLO4K dataset.

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (4009) | 0.62 | 0.29 | 0.19 | 0.37 | 0.51 | 0.31 | 0.48 | 0.53 | 0.33 | 0.32 | 0.63 | 0.36 | 0.06 | 0.78 | 0.38 |
| | SiteHound (2878) | 0.56 | 0.27 | 0.14 | 0.34 | 0.49 | 0.22 | 0.44 | 0.51 | 0.24 | 0.30 | 0.64 | 0.26 | 0.02 | **0.97** | 0.29 |
| | MetaPocket 2.0 (2575) | 0.65 | 0.38 | 0.23 | 0.35 | 0.62 | 0.37 | 0.53 | 0.59 | 0.36 | 0.31 | 0.69 | 0.40 | 0.20 | 0.73 | 0.41 |
| | DeepSite (3991) | 0.69 | 0.33 | 0.23 | 0.43 | 0.48 | 0.30 | 0.62 | 0.47 | 0.32 | 0.42 | 0.49 | 0.31 | **0.37** | 0.49 | 0.31 |
| | P2Rank (4542) | 0.81 | 0.40 | 0.31 | 0.46 | 0.65 | 0.50 | 0.61 | 0.69 | 0.54 | 0.37 | 0.75 | 0.56 | 0.13 | 0.79 | 0.56 |
| | **BiteNet** (4542) | 0.91 | **0.42** | 0.40 | **0.57** | 0.70 | 0.66 | **0.76** | 0.79 | 0.75 | **0.48** | 0.84 | 0.76 | 0.29 | 0.86 | 0.77 |
| | **BiteNet R+** (4542) | **0.92** | 0.42 | **0.40** | 0.52 | **0.71** | **0.67** | 0.75 | **0.81** | **0.77** | 0.44 | **0.86** | **0.78** | 0.14 | **0.90** | **0.79** |
| BiteNet binding site filtering criterion | Fpocket (4009) | 0.41 | 0.33 | 0.14 | 0.25 | 0.58 | 0.23 | 0.51 | 0.54 | 0.32 | 0.26 | 0.68 | 0.26 | 0.04 | 0.86 | 0.28 |
| | SiteHound (2878) | 0.39 | 0.32 | 0.12 | 0.23 | 0.56 | 0.17 | 0.48 | 0.51 | 0.23 | 0.26 | 0.68 | 0.21 | 0.01 | **1.00** | 0.22 |
| | MetaPocket 2.0 (2575) | 0.48 | 0.46 | 0.20 | 0.25 | 0.73 | 0.31 | 0.61 | 0.64 | 0.39 | 0.27 | 0.79 | 0.34 | 0.14 | 0.84 | 0.34 |
| | DeepSite (3991) | 0.48 | 0.38 | 0.19 | 0.29 | 0.55 | 0.24 | 0.65 | 0.52 | 0.35 | 0.31 | 0.55 | 0.25 | **0.25** | 0.56 | 0.24 |
| | P2Rank (4542) | 0.58 | 0.47 | 0.27 | 0.31 | 0.74 | 0.41 | 0.73 | 0.77 | 0.60 | 0.32 | 0.83 | 0.47 | 0.09 | 0.87 | 0.45 |
| | **BiteNet** (4542) | 0.64 | 0.50 | 0.36 | **0.39** | 0.82 | 0.58 | 0.85 | 0.87 | 0.82 | **0.40** | 0.94 | 0.67 | 0.19 | 0.97 | 0.66 |
| | **BiteNet R+** (4542) | **0.64** | **0.50** | **0.38** | 0.35 | **0.82** | **0.62** | **0.86** | **0.88** | **0.84** | 0.37 | **0.95** | **0.71** | 0.09 | 0.99 | **0.70** |
| BiteNet criterion for training | Fpocket (4009) | 0.23 | 0.17 | 0.04 | 0.13 | 0.31 | 0.06 | 0.28 | 0.28 | 0.08 | 0.14 | 0.36 | 0.07 | 0.02 | 0.46 | 0.08 |
| | SiteHound (2878) | 0.26 | 0.20 | 0.05 | 0.16 | 0.38 | 0.07 | 0.32 | 0.32 | 0.09 | 0.17 | 0.45 | 0.09 | 0.01 | 0.77 | 0.10 |
| | MetaPocket 2.0 (2575) | 0.26 | 0.24 | 0.05 | 0.14 | 0.39 | 0.08 | 0.33 | 0.33 | 0.10 | 0.16 | 0.44 | 0.09 | 0.08 | 0.49 | 0.10 |
| | DeepSite (3991) | 0.27 | 0.21 | 0.06 | 0.16 | 0.29 | 0.07 | 0.35 | 0.28 | 0.10 | 0.17 | 0.29 | 0.07 | 0.14 | 0.29 | 0.07 |
| | P2Rank (4542) | 0.36 | 0.28 | 0.08 | 0.19 | 0.43 | 0.12 | 0.44 | 0.44 | 0.17 | 0.19 | 0.48 | 0.14 | 0.05 | 0.51 | 0.13 |
| | **BiteNet** (4542) | 0.56 | 0.44 | 0.29 | **0.34** | 0.71 | 0.47 | 0.74 | 0.74 | 0.65 | **0.35** | 0.80 | 0.53 | **0.17** | 0.83 | 0.53 |
| | **BiteNet R+** (4542) | **0.57** | **0.44** | **0.32** | 0.32 | **0.73** | **0.52** | **0.76** | **0.76** | **0.69** | 0.33 | **0.82** | **0.59** | 0.08 | **0.86** | **0.58** |

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (4009) | 2490 | 1519 | 6771 | 4788 | 7208 | 4612 | 4656 | 4818 | 4496 | 6006 | 11435 | 3492 | 8905 | 99369 | 2052 |
| | SiteHound (2878) | 1608 | 1270 | 4900 | 3366 | 5268 | 3418 | 3159 | 3577 | 3282 | 4511 | 7981 | 2437 | 10637 | 276793 | 181 |
| | MetaPocket 2.0 (2575) | 1677 | 898 | 3114 | 2948 | 4777 | 1913 | 2637 | 2227 | 2075 | 3424 | 6359 | 1552 | 4009 | 12422 | 1344 |
| | DeepSite (3991) | 2760 | 1228 | 6379 | 4250 | 5306 | 4905 | 3961 | 2374 | 5015 | 4324 | 5639 | 4823 | 4346 | 6791 | 4814 |
| | P2Rank (4542) | 3699 | 842 | 6475 | 6199 | 7001 | 3796 | 6553 | 4044 | 3280 | 7311 | 11702 | 2710 | 8321 | 48776 | 2220 |
| | **BiteNet** (4542) | 4128 | 414 | 6254 | 7400 | **4790** | 3212 | 8182 | **2118** | 2240 | 9368 | **7855** | 1741 | 10492 | **18811** | 1457 |
| | **BiteNet R+** (4542) | **4160** | **382** | 6269 | **7759** | 5763 | 3152 | **8490** | 2194 | **2066** | **9999** | 9583 | **1549** | **13145** | 51252 | **1071** |
| BiteNet binding site filtering criterion | Fpocket (4009) | 1656 | 2353 | 3504 | 3168 | 8828 | 2168 | 2722 | 2499 | 2420 | 3730 | 9488 | 1666 | 5783 | 102491 | 745 |
| | SiteHound (2878) | 1126 | 1752 | 2532 | 2312 | 6322 | 1624 | 1832 | 1874 | 1820 | 2821 | 6641 | 1182 | 6928 | 280502 | 3 |
| | MetaPocket 2.0 (2575) | 1231 | 1344 | 1525 | 2081 | 5644 | 773 | 1717 | 1082 | 1022 | 2328 | 5568 | 595 | 2775 | 13656 | 454 |
| | DeepSite (3991) | 1918 | 2070 | 3216 | 2872 | 6684 | 2367 | 2616 | 1400 | 2482 | 2916 | 6159 | 2321 | 2935 | 8202 | 2314 |
| | P2Rank (4542) | 2630 | 1911 | 3121 | 4252 | 8948 | 1514 | 4308 | 1586 | 1373 | 4826 | 9801 | 992 | 5464 | 51633 | 742 |
| | **BiteNet** (4542) | 2892 | 1650 | **2939** | 5029 | **7161** | 1067 | 5078 | 794 | 757 | 6007 | **7595** | 348 | 6894 | **22409** | 171 |
| | **BiteNet R+** (4542) | **2904** | **1638** | 2943 | **5233** | 8289 | **1042** | **5148** | **748** | **704** | **6272** | 8632 | **314** | **8653** | 55744 | **84** |
| BiteNet criterion for training | Fpocket (4009) | 906 | 3103 | 4321 | 1608 | 10388 | 3616 | 1444 | 3789 | 3778 | 1876 | 11354 | 3346 | 2418 | 105856 | 2813 |
| | SiteHound (2878) | 748 | 2130 | 2961 | 1398 | 7236 | 2316 | 1193 | 2521 | 2514 | 1662 | 7808 | 2049 | 2858 | 284572 | 867 |
| | MetaPocket 2.0 (2575) | 677 | 1898 | 2140 | 1101 | 6624 | 1719 | 914 | 1896 | 1902 | 1241 | 6666 | 1580 | 1415 | 15016 | 1436 |
| | DeepSite (3991) | 1086 | 2902 | 4126 | 1554 | 8002 | 3706 | 1431 | 2595 | 3782 | 1571 | 7508 | 3689 | 1577 | 9560 | 3685 |
| | P2Rank (4542) | 1622 | 2919 | 4285 | 2507 | 10693 | 3393 | 2589 | 3318 | 3304 | 2832 | 11805 | 3062 | 2998 | 54099 | 2902 |
| | **BiteNet** (4542) | 2566 | 1976 | 3341 | 4158 | **8032** | 1744 | 4369 | 1515 | 1529 | 4735 | **8873** | 1163 | 4900 | **24403** | 998 |
| | **BiteNet R+** (4542) | **2599** | **1943** | **3308** | **4281** | 9241 | **1621** | **4493** | **1416** | **1407** | **4850** | 10067 | **1050** | **5065** | 59332 | **835** |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

Supplementary Table 7: Performance metrics on the COACH420 subset of 352 proteins, which are not in the BiteNet training set and each structure contains at least one relevant binding site according to the P2Rank binding site filtering criterion.

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (352) | 0.66 | 0.50 | 0.37 | 0.28 | 0.64 | 0.43 | 0.51 | 0.56 | 0.41 | 0.26 | 0.66 | 0.44 | 0.07 | 0.76 | 0.45 |
| | SiteHound (240) | 0.58 | 0.44 | 0.29 | 0.28 | 0.64 | 0.33 | 0.47 | 0.53 | 0.33 | 0.26 | 0.67 | 0.34 | 0.02 | **0.94** | 0.34 |
| | MetaPocket 2.0 (349) | 0.73 | 0.56 | 0.44 | 0.30 | 0.69 | 0.51 | 0.55 | 0.61 | 0.48 | 0.27 | 0.71 | 0.52 | 0.16 | 0.76 | 0.53 |
| | DeepSite (352) | 0.65 | 0.47 | 0.37 | 0.31 | 0.56 | 0.38 | 0.53 | 0.50 | 0.38 | 0.30 | 0.56 | 0.38 | **0.26** | 0.57 | 0.38 |
| | P2Rank (352) | 0.81 | 0.62 | 0.53 | 0.33 | 0.70 | 0.54 | 0.64 | 0.67 | 0.55 | 0.31 | 0.72 | 0.54 | 0.15 | 0.74 | 0.54 |
| | **BiteNet** (352) | 0.86 | **0.65** | 0.61 | **0.38** | 0.77 | 0.68 | **0.69** | 0.72 | 0.66 | **0.36** | 0.79 | 0.69 | 0.23 | 0.81 | 0.69 |
| | **BiteNet R$^+$** (352) | **0.86** | 0.65 | **0.61** | 0.34 | **0.78** | **0.69** | 0.66 | **0.73** | **0.67** | 0.31 | **0.81** | **0.70** | 0.09 | 0.85 | **0.71** |
| BiteNet binding site filtering criterion | Fpocket (352) | 0.48 | 0.67 | 0.36 | 0.19 | 0.79 | 0.39 | 0.68 | 0.69 | 0.52 | 0.21 | 0.79 | 0.39 | 0.04 | 0.92 | 0.40 |
| | SiteHound (240) | 0.43 | 0.58 | 0.31 | 0.20 | 0.80 | 0.33 | 0.61 | 0.62 | 0.44 | 0.22 | 0.82 | 0.34 | 0.01 | **0.99** | 0.33 |
| | MetaPocket 2.0 (349) | 0.51 | 0.73 | 0.40 | 0.21 | 0.88 | 0.46 | 0.72 | 0.73 | 0.59 | 0.23 | 0.88 | 0.46 | 0.10 | 0.92 | 0.47 |
| | DeepSite (352) | 0.45 | 0.63 | 0.37 | 0.21 | 0.73 | 0.36 | 0.64 | 0.63 | 0.48 | 0.22 | 0.73 | 0.37 | **0.17** | 0.73 | 0.36 |
| | P2Rank (352) | 0.58 | 0.82 | 0.48 | 0.22 | 0.89 | 0.48 | 0.82 | 0.83 | 0.70 | 0.25 | 0.89 | 0.48 | 0.10 | 0.92 | 0.48 |
| | **BiteNet** (352) | 0.59 | 0.82 | 0.52 | **0.25** | 0.91 | 0.56 | 0.83 | 0.83 | 0.78 | **0.27** | 0.92 | 0.56 | 0.15 | 0.95 | 0.56 |
| | **BiteNet R$^+$** (352) | **0.59** | **0.83** | **0.57** | 0.22 | **0.93** | **0.61** | **0.83** | **0.84** | **0.79** | 0.25 | **0.94** | **0.61** | 0.06 | 0.98 | **0.62** |
| BiteNet criterion for training | Fpocket (352) | 0.26 | 0.36 | 0.09 | 0.11 | 0.44 | 0.10 | 0.37 | 0.37 | 0.13 | 0.12 | 0.44 | 0.10 | 0.02 | 0.52 | 0.11 |
| | SiteHound (240) | 0.30 | 0.40 | 0.14 | 0.14 | 0.58 | 0.17 | 0.42 | 0.42 | 0.21 | 0.16 | 0.59 | 0.18 | 0.01 | 0.79 | 0.18 |
| | MetaPocket 2.0 (349) | 0.28 | 0.40 | 0.11 | 0.12 | 0.50 | 0.13 | 0.40 | 0.40 | 0.16 | 0.13 | 0.50 | 0.13 | 0.06 | 0.57 | 0.14 |
| | DeepSite (352) | 0.25 | 0.35 | 0.13 | 0.11 | 0.40 | 0.13 | 0.35 | 0.35 | 0.16 | 0.12 | 0.40 | 0.13 | 0.10 | 0.40 | 0.13 |
| | P2Rank (352) | 0.38 | 0.53 | 0.20 | 0.15 | 0.57 | 0.20 | 0.54 | 0.53 | 0.29 | 0.16 | 0.57 | 0.20 | 0.06 | 0.59 | 0.20 |
| | **BiteNet** (352) | 0.50 | 0.70 | 0.40 | **0.21** | 0.78 | 0.43 | 0.70 | 0.71 | 0.59 | **0.23** | 0.78 | 0.43 | **0.13** | 0.81 | 0.43 |
| | **BiteNet R$^+$** (352) | **0.50** | **0.71** | **0.45** | 0.19 | **0.80** | **0.48** | **0.71** | **0.72** | **0.62** | 0.21 | **0.81** | **0.48** | 0.05 | **0.85** | **0.48** |

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (352) | 231 | 121 | 256 | 337 | 717 | 185 | 262 | 241 | 223 | 352 | 840 | 170 | 457 | 4879 | 121 |
| | SiteHound (240) | 139 | 101 | 197 | 242 | 478 | 125 | 165 | 185 | 163 | 254 | 576 | 114 | 501 | 14310 | 22 |
| | MetaPocket 2.0 (349) | 254 | 95 | 223 | 348 | 699 | 158 | 278 | 223 | 197 | 365 | 824 | 146 | 448 | 1759 | 121 |
| | DeepSite (352) | 228 | 122 | 268 | 305 | 604 | 222 | 250 | 211 | 252 | 306 | 642 | 221 | 311 | **791** | 220 |
| | P2Rank (352) | 285 | 65 | 192 | 349 | 635 | 151 | 307 | 169 | 169 | 358 | 721 | 142 | 388 | 1938 | 132 |
| | BiteNet (352) | 301 | 51 | **176** | 407 | **527** | 117 | 334 | **146** | 141 | 418 | **592** | 107 | 458 | 1156 | 97 |
| | BiteNet R$^+$ (352) | **303** | **49** | 177 | **438** | 612 | **113** | **341** | 163 | **137** | **454** | 743 | **98** | **590** | 3598 | **75** |
| BiteNet binding site filtering criterion | Fpocket (352) | 169 | 183 | 82 | 229 | 825 | 52 | 172 | 80 | 79 | 230 | 724 | 52 | 303 | 5033 | 20 |
| | SiteHound (240) | 103 | 137 | 75 | 169 | 551 | 35 | 108 | 70 | 68 | 173 | 485 | 32 | 325 | 14486 | 1 |
| | MetaPocket 2.0 (349) | 179 | 170 | 68 | 237 | 810 | 31 | 180 | 70 | 67 | 237 | 711 | 31 | 297 | 1910 | 20 |
| | DeepSite (352) | 158 | 192 | 93 | 202 | 707 | 69 | 160 | 91 | 93 | 202 | 639 | 69 | 206 | **896** | 68 |
| | P2Rank (352) | 203 | 147 | 46 | 238 | 746 | 28 | 205 | 45 | 44 | 240 | 665 | 27 | 262 | 2064 | 21 |
| | BiteNet (352) | 206 | 146 | 45 | 266 | **668** | 22 | 210 | 42 | 42 | 267 | **589** | 21 | 297 | 1317 | 13 |
| | BiteNet R$^+$ (352) | **208** | **144** | **42** | **283** | 767 | **17** | **211** | **41** | **40** | **286** | 664 | **14** | **393** | 3795 | **4** |
| BiteNet criterion for training | Fpocket (352) | 91 | 261 | 161 | 111 | 943 | 141 | 92 | 160 | 160 | 111 | 843 | 141 | 132 | 5204 | 120 |
| | SiteHound (240) | 71 | 169 | 107 | 104 | 616 | 74 | 75 | 103 | 103 | 105 | 553 | 73 | 140 | 1671 | 38 |
| | MetaPocket 2.0 (349) | 99 | 250 | 150 | 124 | 923 | 126 | 99 | 151 | 150 | 124 | 824 | 126 | 147 | 2060 | 107 |
| | DeepSite (352) | 89 | 261 | 163 | 106 | 803 | 151 | 89 | 162 | 163 | 106 | 735 | 151 | 108 | **994** | 150 |
| | P2Rank (352) | 133 | 217 | 119 | 144 | 840 | 109 | 134 | 116 | 118 | 144 | 761 | 109 | 149 | 2177 | 104 |
| | BiteNet (352) | 176 | 176 | 75 | 196 | **738** | 55 | 177 | 75 | 74 | 196 | **660** | 55 | 202 | 1412 | 49 |
| | BiteNet R$^+$ (352) | **177** | **175** | **73** | **200** | 850 | **50** | **179** | **73** | **71** | **202** | 748 | **48** | **212** | 3976 | **38** |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

Supplementary Table 8: Performance metrics on the HOLO4K subset of 4169 proteins, which are not in the BiteNet training set and each structure contains at least one relevant binding site according to the P2Rank binding site filtering criterion.

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (3687) | 0.62 | 0.29 | 0.19 | 0.37 | 0.51 | 0.31 | 0.47 | 0.52 | 0.33 | 0.31 | 0.63 | 0.36 | 0.06 | 0.78 | 0.38 |
| | SiteHound (2655) | 0.56 | 0.28 | 0.15 | 0.33 | 0.50 | 0.22 | 0.43 | 0.52 | 0.24 | 0.30 | 0.64 | 0.26 | 0.02 | **0.97** | 0.29 |
| | MetaPocket 2.0 (2359) | 0.65 | 0.38 | 0.23 | 0.35 | 0.62 | 0.37 | 0.52 | 0.58 | 0.36 | 0.31 | 0.69 | 0.40 | 0.20 | 0.73 | 0.41 |
| | DeepSite (3669) | 0.70 | 0.33 | 0.24 | 0.43 | 0.48 | 0.31 | 0.62 | 0.47 | 0.33 | 0.41 | 0.49 | 0.31 | **0.37** | 0.49 | 0.31 |
| | P2Rank (4169) | 0.82 | 0.40 | 0.31 | 0.46 | 0.65 | 0.50 | 0.61 | 0.69 | 0.54 | 0.37 | 0.75 | 0.56 | 0.13 | 0.79 | 0.56 |
| | **BiteNet** (4169) | 0.91 | **0.42** | 0.41 | **0.57** | 0.70 | 0.66 | **0.76** | 0.79 | 0.75 | **0.48** | 0.84 | 0.77 | 0.29 | 0.86 | 0.77 |
| | **BiteNet R$^+$** (4169) | **0.92** | 0.42 | **0.41** | 0.52 | **0.71** | **0.67** | 0.75 | **0.81** | **0.77** | 0.43 | **0.86** | **0.78** | 0.14 | 0.90 | **0.79** |
| BiteNet binding site filtering criterion | Fpocket (3687) | 0.40 | 0.34 | 0.14 | 0.24 | 0.59 | 0.22 | 0.51 | 0.53 | 0.31 | 0.25 | 0.68 | 0.25 | 0.04 | 0.85 | 0.26 |
| | SiteHound (2655) | 0.38 | 0.33 | 0.12 | 0.23 | 0.57 | 0.17 | 0.48 | 0.51 | 0.24 | 0.25 | 0.69 | 0.21 | 0.01 | **1.00** | 0.22 |
| | MetaPocket 2.0 (2359) | 0.47 | 0.47 | 0.20 | 0.24 | 0.73 | 0.30 | 0.61 | 0.64 | 0.40 | 0.26 | 0.79 | 0.33 | 0.13 | 0.84 | 0.33 |
| | DeepSite (3669) | 0.47 | 0.39 | 0.19 | 0.28 | 0.55 | 0.24 | 0.66 | 0.53 | 0.36 | 0.30 | 0.56 | 0.25 | **0.24** | 0.56 | 0.24 |
| | P2Rank (4169) | 0.56 | 0.48 | 0.26 | 0.30 | 0.75 | 0.40 | 0.73 | 0.77 | 0.61 | 0.31 | 0.83 | 0.46 | 0.08 | 0.88 | 0.44 |
| | **BiteNet** (4169) | 0.62 | **0.51** | 0.36 | **0.37** | 0.82 | 0.57 | **0.85** | 0.87 | 0.82 | **0.39** | 0.94 | 0.65 | 0.18 | 0.97 | 0.64 |
| | **BiteNet R$^+$** (4169) | **0.62** | 0.51 | **0.38** | 0.34 | **0.83** | **0.60** | 0.86 | **0.88** | **0.85** | 0.35 | **0.95** | **0.69** | 0.08 | 0.99 | **0.68** |
| BiteNet criterion for training | Fpocket (3687) | 0.22 | 0.18 | 0.04 | 0.13 | 0.31 | 0.06 | 0.28 | 0.28 | 0.08 | 0.14 | 0.36 | 0.07 | 0.02 | 0.47 | 0.07 |
| | SiteHound (2655) | 0.26 | 0.21 | 0.05 | 0.16 | 0.39 | 0.08 | 0.33 | 0.33 | 0.10 | 0.17 | 0.46 | 0.09 | 0.01 | 0.78 | 0.10 |
| | MetaPocket 2.0 (2359) | 0.26 | 0.25 | 0.05 | 0.14 | 0.40 | 0.08 | 0.33 | 0.33 | 0.10 | 0.15 | 0.44 | 0.09 | 0.08 | 0.50 | 0.10 |
| | DeepSite (3669) | 0.28 | 0.22 | 0.06 | 0.16 | 0.30 | 0.07 | 0.37 | 0.29 | 0.11 | 0.17 | 0.30 | 0.07 | 0.14 | 0.30 | 0.07 |
| | P2Rank (4169) | 0.36 | 0.29 | 0.08 | 0.19 | 0.44 | 0.12 | 0.45 | 0.45 | 0.18 | 0.19 | 0.49 | 0.14 | 0.05 | 0.52 | 0.13 |
| | **BiteNet** (4169) | 0.55 | **0.45** | 0.29 | **0.33** | 0.71 | 0.46 | 0.75 | 0.75 | 0.65 | **0.34** | 0.81 | 0.52 | **0.16** | 0.84 | 0.51 |
| | **BiteNet R$^+$** (4169) | **0.56** | 0.45 | **0.31** | 0.30 | **0.73** | **0.51** | **0.76** | **0.77** | **0.69** | 0.32 | **0.83** | **0.57** | 0.08 | **0.86** | **0.56** |

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (3687) | 2297 | 1390 | 6156 | 4374 | 6661 | 4221 | 4215 | 4434 | 4144 | 5454 | 10520 | 3210 | 8082 | 90636 | 1905 |
| | SiteHound (2655) | 1492 | 1163 | 4445 | 3102 | 4863 | 3089 | 2870 | 3285 | 2985 | 4095 | 7370 | 2218 | 9601 | 252876 | 174 |
| | MetaPocket 2.0 (2359) | 1544 | 815 | 2824 | 2691 | 4386 | 1754 | 2387 | 2047 | 1907 | 3114 | 5828 | 1430 | 3653 | 11423 | 1235 |
| | DeepSite (3669) | 2570 | 1096 | 5766 | 3906 | 4892 | 4452 | 3633 | 2170 | 4558 | 3969 | 5216 | 4382 | 3988 | 6280 | 4374 |
| | P2Rank (4169) | 3410 | 758 | 5860 | 5663 | 6449 | 3452 | 5967 | 3686 | 2988 | 6658 | 10715 | 2466 | 7563 | 44345 | 2022 |
| | BiteNet (4169) | 3806 | 363 | 5638 | 6736 | 4419 | 2912 | 7439 | 1950 | 2040 | 8490 | 7213 | 1587 | 9473 | 17044 | 1334 |
| | **BiteNet R$^+$** (4169) | **3832** | **337** | 5652 | **7058** | 5347 | **2858** | **7718** | 2026 | **1875** | **9050** | 8856 | **1413** | **11854** | 46832 | **977** |
| BiteNet binding site filtering criterion | Fpocket (3687) | 1480 | 2207 | 3049 | 2793 | 8242 | 1896 | 2367 | 2218 | 2147 | 3256 | 8682 | 1476 | 5056 | 93662 | 670 |
| | SiteHound (2655) | 1015 | 1640 | 2198 | 2069 | 5896 | 1393 | 1610 | 1648 | 1587 | 2490 | 6078 | 1020 | 6057 | 256420 | 2 |
| | MetaPocket 2.0 (2359) | 1104 | 1255 | 1320 | 1841 | 5236 | 674 | 1509 | 954 | 896 | 2047 | 5082 | 526 | 2445 | 12631 | 400 |
| | DeepSite (3669) | 1739 | 1927 | 2765 | 2561 | 6237 | 2040 | 2330 | 1205 | 2142 | 2594 | 5714 | 2005 | 2610 | 7658 | 1999 |
| | P2Rank (4169) | 2352 | 1816 | 2685 | 3753 | 8359 | 1301 | 3782 | 1380 | 1196 | 4235 | 8946 | 862 | 4777 | 47131 | 645 |
| | BiteNet (4169) | 2583 | 1586 | 2517 | 4417 | 6738 | 915 | 4451 | 697 | 655 | 5244 | 6992 | 302 | 5978 | 20539 | 151 |
| | **BiteNet R$^+$** (4169) | **2593** | 1576 | 2522 | **4585** | 7820 | 898 | **4510** | 662 | 604 | **5456** | 7982 | 280 | **7511** | 51175 | 69 |
| BiteNet criterion for training | Fpocket (3687) | 811 | 2876 | 3779 | 1430 | 9605 | 3157 | 1279 | 3326 | 3315 | 1664 | 10285 | 2921 | 2139 | 96579 | 2454 |
| | SiteHound (2655) | 686 | 1969 | 2575 | 1275 | 6690 | 1991 | 1079 | 2187 | 2180 | 1503 | 7073 | 1760 | 2549 | 259928 | 724 |
| | MetaPocket 2.0 (2359) | 622 | 1737 | 1858 | 984 | 6093 | 1498 | 818 | 1655 | 1661 | 1102 | 6037 | 1381 | 1259 | 13817 | 1249 |
| | DeepSite (3669) | 1011 | 2655 | 3564 | 1420 | 7378 | 3202 | 1311 | 2233 | 3265 | 1431 | 6880 | 3191 | 1436 | 8832 | 3188 |
| | P2Rank (4169) | 1483 | 2685 | 3690 | 2251 | 9861 | 2916 | 2329 | 2845 | 2832 | 2542 | 10648 | 2620 | 2681 | 49227 | 2487 |
| | BiteNet (4169) | 2304 | 1865 | 2869 | 3675 | 7480 | 1493 | 3856 | 1303 | 1310 | 4174 | 8067 | 992 | 4315 | 22202 | 851 |
| | **BiteNet R$^+$** (4169) | **2319** | 1850 | 2854 | **3776** | 8629 | 1392 | **3952** | 1232 | 1214 | **4262** | 9188 | 904 | **4445** | 54241 | 721 |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

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Supplementary Table 9: Performance metrics on the COACH420 subset of 344 proteins, which are not in both BiteNet training and validation set and each structure contains at least one relevant binding site according to the P2Rank binding site filtering criterion.

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (344) | 0.65 | 0.49 | 0.37 | 0.28 | 0.64 | 0.43 | 0.51 | 0.56 | 0.41 | 0.26 | 0.67 | 0.44 | 0.07 | 0.76 | 0.45 |
| | SiteHound (237) | 0.57 | 0.43 | 0.28 | 0.28 | 0.64 | 0.32 | 0.46 | 0.53 | 0.32 | 0.26 | 0.67 | 0.33 | 0.02 | **0.94** | 0.33 |
| | MetaPocket 2.0 (341) | 0.72 | 0.56 | 0.44 | 0.30 | 0.69 | 0.51 | 0.55 | 0.61 | 0.48 | 0.27 | 0.71 | 0.52 | 0.16 | 0.76 | 0.53 |
| | DeepSite (344) | 0.66 | 0.48 | 0.38 | 0.31 | 0.57 | 0.39 | 0.54 | 0.51 | 0.39 | 0.30 | 0.57 | 0.39 | **0.26** | 0.57 | 0.39 |
| | P2Rank (344) | 0.82 | 0.62 | 0.53 | 0.33 | 0.70 | 0.54 | 0.64 | 0.67 | 0.55 | 0.31 | 0.72 | 0.55 | 0.15 | 0.74 | 0.54 |
| | **BiteNet (344)** | 0.85 | **0.65** | 0.61 | **0.38** | 0.77 | 0.68 | **0.69** | 0.72 | 0.66 | **0.36** | 0.79 | 0.69 | 0.23 | 0.81 | 0.69 |
| | **BiteNet R⁺ (344)** | **0.86** | 0.65 | **0.61** | 0.34 | **0.78** | **0.69** | 0.66 | **0.73** | **0.67** | 0.31 | **0.80** | **0.70** | 0.09 | 0.85 | **0.71** |
| BiteNet binding site filtering criterion | Fpocket (344) | 0.47 | 0.67 | 0.35 | 0.19 | 0.80 | 0.38 | 0.68 | 0.68 | 0.52 | 0.21 | 0.80 | 0.38 | 0.04 | 0.92 | 0.39 |
| | SiteHound (237) | 0.42 | 0.57 | 0.30 | 0.20 | 0.80 | 0.33 | 0.60 | 0.61 | 0.43 | 0.22 | 0.82 | 0.34 | 0.01 | **0.99** | 0.32 |
| | MetaPocket 2.0 (341) | 0.51 | 0.73 | 0.40 | 0.21 | 0.88 | 0.46 | 0.72 | 0.73 | 0.60 | 0.23 | 0.88 | 0.47 | 0.10 | 0.93 | 0.47 |
| | DeepSite (344) | 0.46 | 0.65 | 0.38 | 0.21 | 0.74 | 0.37 | 0.65 | 0.65 | 0.50 | 0.23 | 0.74 | 0.38 | **0.18** | 0.75 | 0.37 |
| | P2Rank (344) | 0.58 | 0.82 | 0.48 | 0.22 | 0.89 | 0.48 | 0.82 | 0.83 | 0.70 | 0.24 | 0.89 | 0.48 | 0.10 | 0.92 | 0.48 |
| | **BiteNet (344)** | 0.58 | 0.82 | 0.52 | **0.24** | 0.91 | 0.55 | 0.83 | 0.83 | 0.78 | **0.27** | 0.92 | 0.55 | 0.15 | 0.95 | 0.56 |
| | **BiteNet R⁺ (344)** | **0.59** | **0.84** | **0.57** | 0.22 | **0.93** | **0.61** | **0.84** | **0.84** | **0.79** | 0.25 | **0.95** | **0.61** | 0.06 | 0.99 | **0.61** |
| BiteNet criterion for training | Fpocket (344) | 0.25 | 0.35 | 0.08 | 0.10 | 0.43 | 0.10 | 0.35 | 0.35 | 0.12 | 0.11 | 0.43 | 0.10 | 0.02 | 0.51 | 0.10 |
| | SiteHound (237) | 0.29 | 0.39 | 0.13 | 0.14 | 0.58 | 0.17 | 0.41 | 0.41 | 0.20 | 0.16 | 0.58 | 0.17 | 0.01 | 0.78 | 0.17 |
| | MetaPocket 2.0 (341) | 0.28 | 0.39 | 0.11 | 0.12 | 0.49 | 0.13 | 0.39 | 0.39 | 0.16 | 0.13 | 0.49 | 0.13 | 0.06 | 0.57 | 0.14 |
| | DeepSite (344) | 0.26 | 0.36 | 0.13 | 0.12 | 0.41 | 0.14 | 0.37 | 0.36 | 0.17 | 0.13 | 0.41 | 0.14 | 0.10 | 0.42 | 0.14 |
| | P2Rank (344) | 0.37 | 0.52 | 0.20 | 0.14 | 0.56 | 0.20 | 0.53 | 0.53 | 0.29 | 0.16 | 0.56 | 0.20 | 0.06 | 0.58 | 0.20 |
| | **BiteNet (344)** | 0.49 | 0.70 | 0.40 | **0.21** | 0.78 | 0.42 | 0.70 | 0.70 | 0.59 | **0.23** | 0.78 | 0.42 | **0.12** | 0.80 | 0.43 |
| | **BiteNet R⁺ (344)** | **0.50** | **0.71** | **0.45** | 0.19 | **0.80** | **0.48** | **0.71** | **0.72** | **0.62** | 0.21 | **0.81** | **0.48** | 0.05 | **0.85** | **0.49** |

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (344) | 224 | 120 | 252 | 330 | 700 | 181 | 255 | 237 | 219 | 345 | 820 | 166 | 448 | 4773 | 119 |
| | SiteHound (237) | 136 | 101 | 197 | 239 | 472 | 125 | 162 | 185 | 163 | 251 | 570 | 114 | 498 | 14175 | 22 |
| | MetaPocket 2.0 (341) | 247 | 94 | 219 | 341 | 682 | 154 | 271 | 219 | 193 | 358 | 804 | 142 | 441 | 1719 | 117 |
| | DeepSite (344) | 227 | 115 | 258 | 302 | 584 | 214 | 248 | 203 | 243 | 303 | 622 | 213 | 307 | **759** | 212 |
| | P2Rank (344) | 279 | 63 | 188 | 342 | 619 | 148 | 301 | 164 | 165 | 351 | 704 | 139 | 381 | 1907 | 129 |
| | BiteNet (344) | 294 | 50 | **172** | 398 | 514 | 114 | 326 | **143** | 138 | 408 | **578** | 105 | 448 | 1127 | 95 |
| | **BiteNet R⁺ (344)** | **296** | **48** | 173 | **430** | 596 | **110** | **333** | 160 | **134** | **444** | 726 | **97** | **575** | 3503 | **74** |
| BiteNet binding site filtering criterion | Fpocket (344) | 163 | 181 | 80 | 223 | 807 | 50 | 166 | 78 | 77 | 224 | 706 | 50 | 295 | 4926 | 20 |
| | SiteHound (237) | 100 | 137 | 75 | 166 | 545 | 35 | 105 | 70 | 68 | 170 | 479 | 32 | 322 | 14351 | 1 |
| | MetaPocket 2.0 (341) | 173 | 168 | 66 | 231 | 792 | 29 | 174 | 68 | 65 | 231 | 693 | 29 | 291 | 1869 | 18 |
| | DeepSite (344) | 157 | 185 | 86 | 200 | 686 | 63 | 159 | 84 | 86 | 200 | 618 | 63 | 203 | **863** | 62 |
| | P2Rank (344) | 197 | 145 | 44 | 231 | 730 | 27 | 199 | 43 | 42 | 233 | 649 | 26 | 255 | 2033 | 20 |
| | BiteNet (344) | 200 | 144 | 43 | 258 | **654** | 21 | 204 | 40 | 40 | 259 | **575** | 20 | 289 | 1286 | 12 |
| | **BiteNet R⁺ (344)** | **202** | **142** | **40** | **276** | 750 | **16** | **205** | **39** | **38** | **279** | 647 | **13** | **381** | 3697 | **3** |
| BiteNet criterion for training | Fpocket (344) | 85 | 259 | 159 | 105 | 925 | 139 | 86 | 158 | 158 | 105 | 825 | 139 | 124 | 5097 | 120 |
| | SiteHound (237) | 68 | 169 | 107 | 101 | 610 | 74 | 72 | 103 | 103 | 102 | 547 | 73 | 137 | 14536 | 38 |
| | MetaPocket 2.0 (341) | 94 | 247 | 147 | 119 | 904 | 123 | 94 | 148 | 147 | 119 | 805 | 123 | 142 | 2018 | 104 |
| | DeepSite (344) | 89 | 253 | 155 | 106 | 780 | 143 | 89 | 154 | 155 | 106 | 712 | 143 | 108 | **958** | 142 |
| | P2Rank (344) | 128 | 214 | 116 | 138 | 823 | 107 | 129 | 113 | 115 | 138 | 744 | 107 | 143 | 2145 | 102 |
| | BiteNet (344) | 170 | 174 | 73 | 189 | **723** | 54 | 171 | 73 | 72 | 189 | **645** | 54 | 195 | 1380 | 48 |
| | **BiteNet R⁺ (344)** | **172** | **172** | **70** | **194** | 832 | **48** | **174** | **70** | **68** | **196** | 730 | **46** | **206** | 3872 | **36** |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

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Supplementary Table 10: Performance metrics on the HOLO4K subset of 4121 proteins, which are not in BiteNet training and validation sets and each structure contains at least one relevant binding site according to the P2Rank binding site filtering criterion.

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (3649) | 0.62 | 0.29 | 0.19 | 0.37 | 0.52 | 0.31 | 0.48 | 0.52 | 0.33 | 0.31 | 0.63 | 0.36 | 0.06 | 0.78 | 0.38 |
| | SiteHound (2628) | 0.57 | 0.28 | 0.15 | 0.34 | 0.50 | 0.23 | 0.44 | 0.52 | 0.24 | 0.30 | 0.64 | 0.26 | 0.02 | **0.97** | 0.29 |
| | MetaPocket 2.0 (2334) | 0.66 | 0.38 | 0.24 | 0.35 | 0.62 | 0.37 | 0.53 | 0.58 | 0.36 | 0.31 | 0.69 | 0.40 | 0.20 | 0.73 | 0.41 |
| | DeepSite (3631) | 0.70 | 0.33 | 0.24 | 0.43 | 0.49 | 0.31 | 0.62 | 0.48 | 0.33 | 0.42 | 0.50 | 0.32 | **0.37** | 0.50 | 0.32 |
| | P2Rank (4121) | 0.82 | 0.40 | 0.32 | 0.46 | 0.65 | 0.50 | 0.61 | 0.70 | 0.55 | 0.37 | 0.75 | 0.56 | 0.13 | 0.80 | 0.57 |
| | **BiteNet** (4121) | 0.91 | **0.42** | 0.41 | **0.57** | 0.70 | 0.66 | **0.76** | 0.79 | 0.75 | **0.48** | 0.84 | 0.77 | 0.29 | 0.87 | 0.77 |
| | **BiteNet R$^+$** (4121) | **0.92** | 0.42 | **0.41** | 0.52 | **0.71** | **0.67** | 0.75 | **0.81** | **0.77** | 0.43 | **0.86** | **0.78** | 0.14 | 0.90 | **0.79** |
| BiteNet binding site filtering criterion | Fpocket (3649) | 0.40 | 0.34 | 0.14 | 0.23 | 0.59 | 0.22 | 0.51 | 0.53 | 0.32 | 0.25 | 0.68 | 0.25 | 0.04 | 0.86 | 0.26 |
| | SiteHound (2628) | 0.38 | 0.33 | 0.12 | 0.23 | 0.58 | 0.17 | 0.49 | 0.52 | 0.24 | 0.25 | 0.69 | 0.21 | 0.01 | **1.00** | 0.22 |
| | MetaPocket 2.0 (2334) | 0.47 | 0.47 | 0.20 | 0.24 | 0.73 | 0.31 | 0.61 | 0.64 | 0.40 | 0.26 | 0.79 | 0.33 | 0.13 | 0.84 | 0.33 |
| | DeepSite (3631) | 0.47 | 0.40 | 0.20 | 0.28 | 0.56 | 0.24 | 0.66 | 0.53 | 0.37 | 0.30 | 0.56 | 0.25 | **0.24** | 0.57 | 0.24 |
| | P2Rank (4121) | 0.56 | 0.48 | 0.26 | 0.30 | 0.75 | 0.40 | 0.73 | 0.77 | 0.61 | 0.31 | 0.83 | 0.46 | 0.08 | 0.88 | 0.44 |
| | **BiteNet** (4121) | 0.62 | **0.51** | 0.36 | **0.37** | 0.82 | 0.56 | 0.85 | 0.87 | 0.82 | **0.38** | 0.94 | 0.65 | 0.18 | 0.97 | 0.64 |
| | **BiteNet R$^+$** (4121) | **0.62** | 0.51 | **0.38** | 0.33 | **0.83** | **0.60** | **0.86** | **0.88** | **0.85** | 0.35 | **0.95** | **0.69** | 0.08 | 0.99 | **0.68** |
| BiteNet criterion for training | Fpocket (3649) | 0.22 | 0.18 | 0.04 | 0.13 | 0.31 | 0.06 | 0.28 | 0.28 | 0.08 | 0.18 | 0.37 | 0.07 | 0.02 | 0.47 | 0.07 |
| | SiteHound (2628) | 0.26 | 0.21 | 0.05 | 0.16 | 0.40 | 0.08 | 0.33 | 0.34 | 0.10 | 0.18 | 0.47 | 0.09 | 0.01 | 0.78 | 0.10 |
| | MetaPocket 2.0 (2334) | 0.26 | 0.25 | 0.06 | 0.14 | 0.40 | 0.09 | 0.33 | 0.33 | 0.11 | 0.15 | 0.45 | 0.10 | 0.08 | 0.50 | 0.10 |
| | DeepSite (3631) | 0.28 | 0.22 | 0.06 | 0.16 | 0.30 | 0.07 | 0.37 | 0.29 | 0.11 | 0.17 | 0.31 | 0.07 | 0.14 | 0.31 | 0.07 |
| | P2Rank (4121) | 0.36 | 0.29 | 0.08 | 0.19 | 0.44 | 0.12 | 0.45 | 0.46 | 0.19 | 0.19 | 0.50 | 0.14 | 0.05 | 0.52 | 0.13 |
| | **BiteNet** (4121) | 0.55 | **0.45** | 0.29 | **0.33** | 0.71 | 0.46 | 0.75 | 0.75 | 0.65 | 0.34 | 0.81 | 0.52 | **0.16** | 0.84 | 0.51 |
| | **BiteNet R$^+$** (4121) | **0.55** | 0.45 | **0.31** | 0.30 | **0.73** | **0.50** | **0.76** | **0.77** | **0.69** | 0.32 | **0.83** | **0.57** | 0.08 | **0.86** | **0.56** |

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (3649) | 2277 | 1372 | 6053 | 4332 | 6590 | 4142 | 4169 | 4355 | 4070 | 5399 | 10375 | 3144 | 7994 | 89297 | 1858 |
| | SiteHound (2628) | 1486 | 1142 | 4354 | 3087 | 4797 | 3007 | 2849 | 3208 | 2913 | 4064 | 7249 | 2156 | 9478 | 249053 | 161 |
| | MetaPocket 2.0 (2334) | 1534 | 800 | 2788 | 2671 | 4331 | 1728 | 2371 | 2015 | 1879 | 3093 | 5752 | 1405 | 3630 | 11285 | 1211 |
| | DeepSite (3631) | 2549 | 1079 | 5664 | 3874 | 4839 | 4361 | 3605 | 2140 | 4465 | 3937 | 5161 | 4291 | 3956 | 6218 | 4283 |
| | P2Rank (4121) | 3375 | 745 | 5753 | 5596 | 6376 | 3383 | 5893 | 3616 | 2933 | 6577 | 10562 | 2415 | 7481 | 43588 | 1972 |
| | BiteNet (4121) | 3759 | 362 | 5542 | 6642 | **4375** | 2857 | 7336 | **1919** | 2001 | 8373 | **7118** | 1551 | 9348 | **16820** | 1299 |
| | **BiteNet R$^+$** (4121) | **3785** | **336** | 5556 | **6965** | 5296 | **2807** | **7619** | 1988 | **1834** | **8933** | 8744 | **1379** | **11714** | 46205 | **947** |
| BiteNet binding site filtering criterion | Fpocket (3649) | 1461 | 2188 | 2996 | 2755 | 8167 | 1861 | 2333 | 2179 | 2110 | 3213 | 8577 | 1446 | 4984 | 92307 | 654 |
| | SiteHound (2628) | 1009 | 1619 | 2151 | 2054 | 5830 | 1354 | 1599 | 1605 | 1546 | 2466 | 5994 | 988 | 5961 | 252570 | 2 |
| | MetaPocket 2.0 (2334) | 1094 | 1240 | 1290 | 1822 | 5180 | 653 | 1495 | 927 | 872 | 2027 | 5011 | 506 | 2423 | 12492 | 381 |
| | DeepSite (3631) | 1719 | 1909 | 2712 | 2532 | 6181 | 1994 | 2306 | 1174 | 2093 | 2565 | 5658 | 1959 | 2581 | 7593 | 1953 |
| | P2Rank (4121) | 2318 | 1802 | 2631 | 3689 | 8283 | 1277 | 3722 | 1353 | 1170 | 4166 | 8836 | 842 | 4706 | 46363 | 627 |
| | BiteNet (4121) | 2539 | 1582 | **2475** | 4328 | **6689** | 908 | 4371 | 687 | 646 | 5145 | **6913** | 299 | 5871 | **20297** | 150 |
| | **BiteNet R$^+$** (4121) | **2549** | **1572** | 2478 | **4499** | 7762 | **888** | **4433** | **649** | **593** | **5361** | 7891 | **274** | **7388** | 50531 | **69** |
| BiteNet criterion for training | Fpocket (3649) | 800 | 2849 | 3717 | 1409 | 9513 | 3105 | 1250 | 3273 | 3262 | 1640 | 10161 | 2872 | 2106 | 95185 | 2414 |
| | SiteHound (2628) | 683 | 1945 | 2524 | 1271 | 6613 | 1941 | 1074 | 2138 | 2131 | 1495 | 6973 | 1714 | 2515 | 256016 | 704 |
| | MetaPocket 2.0 (2334) | 617 | 1717 | 1822 | 973 | 6029 | 1468 | 811 | 1621 | 1627 | 1090 | 5958 | 1352 | 1245 | 13670 | 1222 |
| | DeepSite (3631) | 1001 | 2627 | 3501 | 1406 | 7307 | 3143 | 1298 | 2191 | 3205 | 1417 | 6809 | 3132 | 1422 | 8752 | 3129 |
| | P2Rank (4121) | 1465 | 2655 | 3618 | 2216 | 9756 | 2861 | 2296 | 2791 | 2775 | 2503 | 10508 | 2568 | 2640 | 48429 | 2437 |
| | BiteNet (4121) | 2269 | 1852 | 2814 | 3611 | **7406** | 1467 | 3792 | **1277** | 1284 | 4105 | **7958** | 971 | 4244 | **21924** | 832 |
| | **BiteNet R$^+$** (4121) | **2280** | **1841** | **2803** | **3707** | 8554 | **1371** | **3885** | 1209 | **1191** | **4187** | 9077 | **889** | **4366** | 53553 | **710** |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

Supplementary Table 11: Performance metrics on the COACH420 subset of 238 proteins, which are not in the BiteNet training set and each structure contains at least one relevant binding site according to the P2Rank binding site filtering criterion.
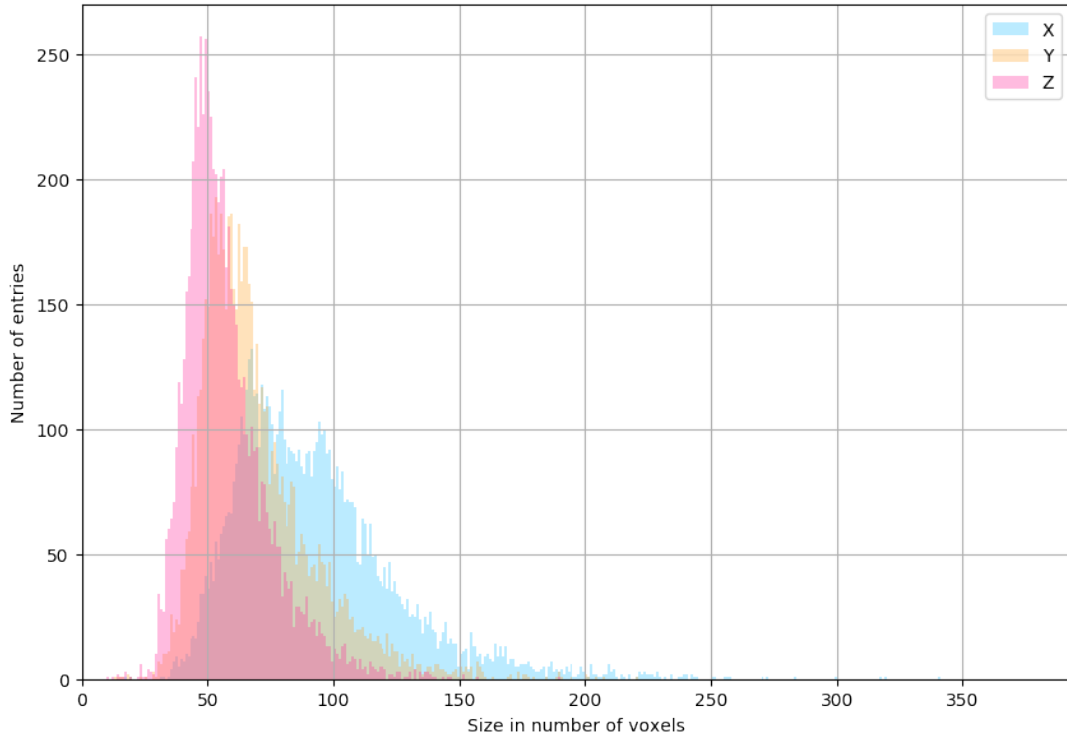
| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (238) | 0.72 | 0.61 | 0.47 | 0.29 | 0.74 | 0.52 | 0.64 | 0.65 | 0.50 | 0.28 | 0.75 | 0.53 | 0.07 | 0.86 | 0.54 |
| | SiteHound (167) | 0.62 | 0.56 | 0.40 | 0.29 | 0.76 | 0.43 | 0.55 | 0.60 | 0.41 | 0.27 | 0.77 | 0.43 | 0.02 | **0.96** | 0.44 |
| | MetaPocket 2.0 (236) | 0.79 | 0.68 | 0.58 | 0.32 | 0.82 | 0.66 | 0.68 | 0.70 | 0.59 | 0.30 | 0.82 | 0.66 | 0.16 | 0.86 | 0.67 |
| | DeepSite (238) | 0.68 | 0.58 | 0.46 | 0.31 | 0.68 | 0.48 | 0.61 | 0.60 | 0.47 | 0.31 | 0.68 | 0.48 | **0.26** | 0.68 | 0.47 |
| | P2Rank (238) | 0.87 | 0.76 | 0.67 | 0.33 | 0.83 | 0.67 | 0.75 | 0.78 | 0.68 | 0.32 | 0.84 | 0.67 | 0.15 | 0.86 | 0.67 |
| | **BiteNet** (238) | 0.89 | 0.77 | **0.74** | **0.39** | 0.87 | 0.80 | **0.80** | **0.81** | **0.77** | **0.38** | 0.89 | 0.81 | 0.24 | 0.91 | 0.81 |
| | **BiteNet R+** (238) | **0.90** | **0.77** | 0.73 | 0.34 | **0.87** | **0.80** | 0.78 | 0.81 | 0.77 | 0.33 | **0.89** | **0.81** | 0.10 | 0.94 | **0.82** |
| BiteNet binding site filtering criterion | Fpocket (238) | 0.71 | 0.67 | 0.51 | 0.28 | 0.79 | 0.55 | 0.68 | 0.69 | 0.52 | 0.27 | 0.79 | 0.55 | 0.06 | 0.92 | 0.58 |
| | SiteHound (167) | 0.62 | 0.58 | 0.41 | 0.28 | 0.80 | 0.44 | 0.61 | 0.62 | 0.44 | 0.28 | 0.82 | 0.45 | 0.02 | **0.99** | 0.44 |
| | MetaPocket 2.0 (236) | 0.76 | 0.73 | 0.58 | 0.31 | 0.88 | 0.67 | 0.72 | 0.73 | 0.59 | 0.30 | 0.88 | 0.67 | 0.15 | 0.92 | 0.68 |
| | DeepSite (238) | 0.66 | 0.63 | 0.48 | 0.30 | 0.73 | 0.49 | 0.64 | 0.63 | 0.48 | 0.30 | 0.73 | 0.49 | **0.25** | 0.73 | 0.49 |
| | P2Rank (238) | 0.86 | 0.82 | 0.70 | 0.33 | 0.89 | 0.69 | 0.82 | 0.83 | 0.70 | 0.32 | 0.89 | 0.69 | 0.15 | 0.92 | 0.69 |
| | **BiteNet** (238) | 0.87 | 0.82 | 0.77 | **0.37** | 0.91 | 0.82 | 0.83 | 0.83 | 0.78 | **0.36** | 0.92 | 0.82 | 0.23 | 0.95 | 0.84 |
| | **BiteNet R+** (238) | **0.87** | **0.83** | **0.78** | 0.33 | **0.93** | **0.84** | **0.83** | **0.84** | **0.79** | 0.33 | **0.94** | **0.85** | 0.09 | 0.98 | **0.86** |
| BiteNet criterion for training | Fpocket (238) | 0.38 | 0.36 | 0.13 | 0.16 | 0.44 | 0.15 | 0.37 | 0.37 | 0.13 | 0.15 | 0.44 | 0.15 | 0.04 | 0.52 | 0.16 |
| | SiteHound (167) | 0.43 | 0.40 | 0.19 | 0.21 | 0.58 | 0.23 | 0.42 | 0.42 | 0.21 | 0.21 | 0.59 | 0.23 | 0.01 | 0.79 | 0.23 |
| | MetaPocket 2.0 (236) | 0.42 | 0.40 | 0.16 | 0.17 | 0.50 | 0.19 | 0.40 | 0.40 | 0.16 | 0.17 | 0.50 | 0.19 | 0.10 | 0.57 | 0.20 |
| | DeepSite (238) | 0.37 | 0.35 | 0.17 | 0.17 | 0.40 | 0.18 | 0.35 | 0.35 | 0.16 | 0.17 | 0.40 | 0.18 | 0.14 | 0.40 | 0.18 |
| | P2Rank (238) | 0.56 | 0.53 | 0.29 | 0.21 | 0.57 | 0.29 | 0.54 | 0.53 | 0.29 | 0.21 | 0.57 | 0.29 | 0.09 | 0.59 | 0.29 |
| | **BiteNet** (238) | 0.74 | 0.70 | 0.60 | **0.31** | 0.78 | 0.63 | 0.70 | 0.71 | 0.59 | **0.31** | 0.78 | 0.63 | **0.19** | 0.81 | 0.64 |
| | **BiteNet R+** (238) | **0.74** | **0.71** | **0.61** | 0.28 | **0.80** | **0.66** | **0.71** | **0.72** | **0.62** | 0.28 | **0.81** | **0.67** | 0.08 | **0.85** | **0.67** |

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (238) | 172 | 66 | 112 | 240 | 472 | 75 | 186 | 100 | 99 | 246 | 514 | 71 | 318 | 3237 | 41 |
| | SiteHound (167) | 104 | 63 | 87 | 171 | 330 | 47 | 112 | 112 | 79 | 175 | 358 | 45 | 338 | 9866 | 7 |
| | MetaPocket 2.0 (236) | 186 | 50 | 90 | 249 | 459 | 52 | 194 | 90 | 84 | 253 | 503 | 52 | 311 | 1173 | 40 |
| | DeepSite (238) | 163 | 75 | 119 | 212 | 414 | 92 | 172 | 104 | 115 | 212 | 424 | 92 | 215 | **546** | 92 |
| | P2Rank (238) | 206 | 31 | 68 | 242 | 432 | 49 | 213 | 70 | 62 | 245 | 468 | 46 | 266 | 1296 | 41 |
| | BiteNet (238) | 213 | 25 | 66 | 283 | **340** | 38 | **230** | 54 | **53** | 290 | **364** | 32 | 315 | 734 | 27 |
| | BiteNet R+ (238) | **214** | **24** | 66 | **297** | 411 | **36** | 229 | 57 | 55 | **304** | 452 | **31** | **413** | 2335 | **17** |
| BiteNet binding site filtering criterion | Fpocket (238) | 169 | 69 | 82 | 229 | 483 | 52 | 172 | 80 | 79 | 230 | 496 | 52 | 303 | 3252 | 20 |
| | SiteHound (167) | 103 | 64 | 75 | 169 | 332 | 35 | 108 | 70 | 68 | 173 | 339 | 32 | 325 | 9879 | 1 |
| | MetaPocket 2.0 (236) | 179 | 57 | 68 | 237 | 471 | 31 | 180 | 70 | 67 | 237 | 485 | 31 | 297 | 1187 | 20 |
| | DeepSite (238) | 158 | 80 | 93 | 202 | 424 | 69 | 160 | 91 | 93 | 202 | 426 | 69 | 206 | **555** | 68 |
| | P2Rank (238) | 203 | 34 | 46 | 238 | 436 | 28 | 205 | 45 | 44 | 240 | 446 | 27 | 262 | 1300 | 21 |
| | BiteNet (238) | 206 | 32 | 45 | 266 | **357** | 22 | 210 | 42 | 42 | 267 | **366** | 21 | 297 | 752 | 13 |
| | BiteNet R+ (238) | **208** | **30** | 42 | **283** | 425 | **17** | **211** | 41 | **40** | **286** | 436 | **14** | **393** | 2355 | **4** |
| BiteNet criterion for training | Fpocket (238) | 91 | 147 | 161 | 111 | 601 | 141 | 92 | 160 | 160 | 111 | 615 | 141 | 132 | 3423 | 120 |
| | SiteHound (167) | 71 | 96 | 107 | 104 | 397 | 74 | 75 | 103 | 103 | 105 | 407 | 73 | 140 | 10064 | 38 |
| | MetaPocket 2.0 (236) | 99 | 137 | 150 | 124 | 584 | 126 | 99 | 151 | 150 | 124 | 598 | 126 | 147 | 1337 | 107 |
| | DeepSite (238) | 89 | 149 | 163 | 106 | 520 | 151 | 89 | 162 | 163 | 106 | 522 | 151 | 108 | **653** | 150 |
| | P2Rank (238) | 133 | 104 | 119 | 144 | 530 | 109 | 134 | 116 | 118 | 144 | 542 | 109 | 149 | 1413 | 104 |
| | BiteNet (238) | 176 | 62 | 75 | 196 | **427** | 55 | 177 | 75 | 74 | 196 | **437** | 55 | 202 | 847 | 49 |
| | BiteNet R+ (238) | **177** | **61** | **73** | **200** | 508 | **50** | **179** | 73 | **71** | **202** | 520 | **48** | **212** | 2536 | **38** |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

Supplementary Table 12: Performance metrics on the HOLO4K subset of 2848 proteins, which are not in the BiteNet training set and each structure contains at least one relevant binding site according to the BiteNet binding site filtering criterion.

| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap | prec | rec | ap |
| P2Rank binding site filtering criterion | Fpocket (2529) | 0.65 | 0.30 | 0.20 | 0.38 | 0.53 | 0.33 | 0.49 | 0.54 | 0.34 | 0.32 | 0.64 | 0.38 | 0.07 | 0.79 | 0.40 |
| | SiteHound (1826) | 0.58 | 0.28 | 0.15 | 0.35 | 0.51 | 0.23 | 0.45 | 0.53 | 0.25 | 0.31 | 0.65 | 0.27 | 0.02 | **0.97** | 0.31 |
| | MetaPocket 2.0 (1645) | 0.70 | 0.41 | 0.26 | 0.37 | 0.64 | 0.41 | 0.55 | 0.61 | 0.40 | 0.33 | 0.72 | 0.44 | 0.21 | 0.76 | 0.45 |
| | DeepSite (2516) | 0.73 | 0.34 | 0.25 | 0.44 | 0.49 | 0.33 | 0.64 | 0.48 | 0.34 | 0.42 | 0.50 | 0.33 | **0.38** | 0.50 | 0.33 |
| | P2Rank (2848) | 0.85 | 0.42 | 0.34 | 0.47 | 0.66 | 0.54 | 0.63 | 0.71 | 0.59 | 0.37 | 0.76 | 0.60 | 0.13 | 0.80 | 0.60 |
| | **BiteNet** (2848) | **0.95** | **0.43** | 0.42 | **0.59** | 0.71 | 0.68 | **0.79** | 0.82 | 0.79 | **0.50** | 0.86 | 0.80 | 0.31 | 0.88 | 0.81 |
| | **BiteNet R+** (2848) | **0.95** | 0.43 | **0.42** | 0.53 | **0.72** | **0.69** | 0.77 | **0.83** | **0.80** | 0.45 | **0.87** | **0.81** | 0.14 | 0.91 | **0.82** |
| BiteNet binding site filtering criterion | Fpocket (2529) | 0.59 | 0.33 | 0.20 | 0.34 | 0.59 | 0.33 | 0.51 | 0.53 | 0.31 | 0.31 | 0.68 | 0.37 | 0.06 | 0.85 | 0.39 |
| | SiteHound (1826) | 0.56 | 0.33 | 0.17 | 0.33 | 0.57 | 0.24 | 0.48 | 0.51 | 0.24 | 0.31 | 0.69 | 0.27 | 0.02 | **1.00** | 0.31 |
| | MetaPocket 2.0 (1645) | 0.67 | 0.47 | 0.29 | 0.35 | 0.73 | 0.44 | 0.61 | 0.64 | 0.40 | 0.33 | 0.79 | 0.46 | 0.19 | 0.84 | 0.47 |
| | DeepSite (2516) | 0.69 | 0.40 | 0.28 | 0.41 | 0.55 | 0.35 | 0.66 | 0.53 | 0.36 | 0.40 | 0.56 | 0.35 | **0.35** | 0.56 | 0.35 |
| | P2Rank (2848) | 0.83 | 0.48 | 0.38 | 0.44 | 0.75 | 0.57 | 0.73 | 0.77 | 0.61 | 0.39 | 0.83 | 0.63 | 0.12 | 0.88 | 0.63 |
| | **BiteNet** (2848) | 0.91 | **0.51** | 0.49 | **0.54** | 0.82 | 0.76 | **0.85** | 0.87 | 0.82 | **0.49** | 0.94 | 0.85 | 0.27 | 0.97 | 0.87 |
| | **BiteNet R+** (2848) | **0.91** | 0.51 | **0.49** | 0.49 | **0.83** | **0.78** | 0.86 | **0.88** | **0.85** | 0.44 | **0.95** | **0.87** | 0.12 | 0.99 | **0.88** |
| BiteNet criterion for training | Fpocket (2529) | 0.32 | 0.18 | 0.05 | 0.19 | 0.31 | 0.09 | 0.28 | 0.28 | 0.08 | 0.17 | 0.36 | 0.10 | 0.03 | 0.47 | 0.11 |
| | SiteHound (1826) | 0.38 | 0.21 | 0.07 | 0.23 | 0.39 | 0.11 | 0.33 | 0.33 | 0.10 | 0.22 | 0.46 | 0.12 | 0.01 | 0.78 | 0.14 |
| | MetaPocket 2.0 (1645) | 0.38 | 0.25 | 0.08 | 0.20 | 0.40 | 0.12 | 0.33 | 0.33 | 0.10 | 0.19 | 0.44 | 0.13 | 0.12 | 0.50 | 0.14 |
| | DeepSite (2516) | 0.40 | 0.22 | 0.09 | 0.23 | 0.30 | 0.10 | 0.37 | 0.29 | 0.11 | 0.23 | 0.30 | 0.11 | 0.20 | 0.30 | 0.11 |
| | P2Rank (2848) | 0.52 | 0.29 | 0.12 | 0.27 | 0.44 | 0.17 | 0.45 | 0.45 | 0.18 | 0.24 | 0.49 | 0.19 | 0.08 | 0.52 | 0.19 |
| | **BiteNet** (2848) | 0.81 | 0.45 | 0.40 | **0.48** | 0.71 | 0.61 | 0.75 | 0.75 | 0.65 | **0.43** | 0.81 | 0.68 | **0.24** | 0.84 | 0.69 |
| | **BiteNet R+** (2848) | **0.81** | **0.45** | **0.41** | 0.44 | **0.73** | **0.65** | **0.76** | **0.77** | **0.69** | 0.39 | **0.83** | **0.72** | 0.11 | **0.86** | **0.72** |

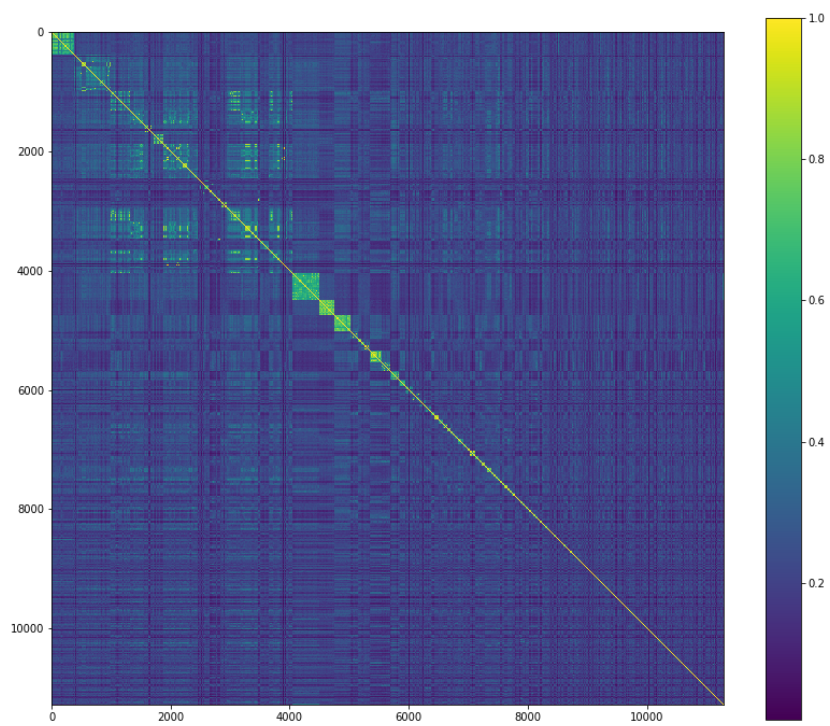| Criterion | Method | Top-1 | | | Top-3 | | | Top-n | | | Top-(n+2) | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN | TP | FP | FN |
| P2Rank binding site filtering criterion | Fpocket (2529) | 1634 | 895 | 4231 | 3130 | 4442 | 2854 | 3016 | 2990 | 2792 | 3890 | 7141 | 2148 | 5819 | 61897 | 1247 |
| | SiteHound (1826) | 1055 | 771 | 3097 | 2216 | 3262 | 2112 | 2045 | 2265 | 2035 | 2935 | 5027 | 1488 | 7015 | 174397 | 110 |
| | MetaPocket 2.0 (1645) | 1145 | 500 | 1911 | 1953 | 2982 | 1152 | 1764 | 1343 | 1248 | 2290 | 3948 | 902 | 2661 | 7792 | 787 |
| | DeepSite (2516) | 1835 | 681 | 3940 | 2747 | 3299 | 3049 | 2559 | 3115 | 3115 | 2785 | 3509 | 3007 | 2800 | 4287 | 3001 |
| | P2Rank (2848) | 2428 | 420 | 3972 | 3975 | 4322 | 2302 | 4228 | 2456 | 1946 | 4666 | 7313 | 1643 | 5296 | 30274 | 1371 |
| | **BiteNet** (2848) | 2693 | 155 | **3868** | 4766 | **2820** | 1959 | 5374 | **1130** | 1241 | 6079 | **4695** | 981 | 6731 | **11169** | 839 |
| | **BiteNet R+** (2848) | **2708** | **140** | 3878 | **4954** | 3544 | **1928** | **5530** | 1233 | **1158** | **6413** | 5944 | **886** | **8465** | 31445 | **613** |
| BiteNet binding site filtering criterion | Fpocket (2529) | 1480 | 1049 | 3050 | 2793 | 4779 | 1897 | 2367 | 2219 | 2148 | 3256 | 6370 | 1477 | 5056 | 62660 | 671 |
| | SiteHound (1826) | 1015 | 811 | 2199 | 2069 | 3409 | 1394 | 1610 | 1649 | 1588 | 2490 | 4421 | 1021 | 6059 | 175353 | 2 |
| | MetaPocket 2.0 (1645) | 1104 | 541 | 1320 | 1841 | 3094 | 674 | 1509 | 954 | 896 | 2047 | 3654 | 526 | 2445 | 8008 | 400 |
| | DeepSite (2516) | 1740 | 776 | 2765 | 2562 | 3484 | 2040 | 2331 | 1205 | 2142 | 2595 | 3585 | 2005 | 2611 | 4476 | 1999 |
| | P2Rank (2848) | 2353 | 495 | 2685 | 3754 | 4543 | 1301 | 3783 | 1380 | 1196 | 4236 | 6340 | 862 | 4778 | 30792 | 645 |
| | **BiteNet** (2848) | 2584 | 264 | **2517** | 4418 | **3168** | 915 | 4452 | 697 | 655 | 5245 | **4465** | 302 | 5979 | **11921** | 151 |
| | **BiteNet R+** (2848) | **2594** | **254** | 2522 | **4586** | 3912 | **898** | **4511** | **662** | **604** | **5457** | 5358 | **280** | **7513** | 32397 | **69** |
| BiteNet criterion for training | Fpocket (2529) | 807 | 1722 | 3779 | 1426 | 6146 | 3157 | 1266 | 3326 | 3315 | 1660 | 7972 | 2921 | 2135 | 65581 | 2454 |
| | SiteHound (1826) | 686 | 1140 | 2572 | 1273 | 4205 | 1990 | 1079 | 2184 | 2177 | 1501 | 5414 | 1759 | 2547 | 178865 | 723 |
| | MetaPocket 2.0 (1645) | 619 | 1026 | 1857 | 981 | 3954 | 1497 | 815 | 1654 | 1660 | 1099 | 4608 | 1380 | 1255 | 9198 | 1249 |
| | DeepSite (2516) | 1010 | 1506 | 3561 | 1419 | 4627 | 3199 | 1310 | 2230 | 3262 | 1430 | 4751 | 3188 | 1435 | 5652 | 3185 |
| | P2Rank (2848) | 1480 | 1368 | 3688 | 2248 | 6049 | 2914 | 2326 | 2843 | 2830 | 2539 | 8043 | 2618 | 2678 | 32892 | 2485 |
| | **BiteNet** (2848) | 2301 | 547 | 2867 | 3671 | **3915** | 1492 | 3853 | 1301 | 1308 | 4170 | **5543** | 991 | 4311 | **13589** | 850 |
| | **BiteNet R+** (2848) | **2316** | **532** | **2852** | **3772** | 4726 | **1391** | **3949** | **1230** | **1212** | **4258** | 6563 | **903** | **4440** | 35470 | **721** |

The best score values are denoted with bold font. Top TP, FP, FN scores apply only to methods assessed on the same set of proteins as BiteNet.

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Supplementary Figure 5: Statistics for the protein lengths measured in voxels with respect to its principal axes.

Supplementary Table 13: The average number of binding sites in the COACH420 and HOLO4K benchmarks according to the P2Rank and BiteNet binding site filtering criteria (the first two rows), as well as the average number of method predictions for each dataset. For BiteNet the listed values correspond to the probability score thresholds of 0.01 and 0.1, respectively.

|  | COACH420 | HOLO4K |
|---|---|---|
| P2Rank criterion | 1.43 | 2.37 |
| BiteNet criterion | 1.05 | 1.84 |
| Fpocket | 14.60 | 27.01 |
| SiteHound | 60.23 | 99.87 |
| MetaPocket 2.0 | 6.32 | 6.38 |
| DeepSite | 3.16 | 2.79 |
| P2Rank | 6.26 | 12.57 |
| BiteNet | 4.61/1.52 | 6.35/2.57 |

Supplementary Figure 6: Pair-wise structure similarity matrix calculated for the protein chains in the training dataset.

Supplementary Table 14: Statistical tests for comparison of performance of BiteNet with other methods on the set composed from COACH420 and HOLO4K subsets (238 and 1682 proteins, which are not in the BiteNet training set, predictions of all methods available and each structure contains at least one relevant binding site according to the in P2Rank binding site filtering criterion). The T-test is performed: the composed set was split into 31 independent subsets; for each subset precision, recall and average precision (AP) are calculated; the null hypothesis states that there is no significant difference in performance metrics between BiteNet and another method.

| | Method | Precision | | Recall | | AP | |
|---|---|---|---|---|---|---|---|
| | | t-statistic | p-value | t-statistic | p-value | t-statistic | p-value |
| | Fpocket | 19.77 | 5.8e-28 | 10.77 | 1.2e-15 | 14.76 | 1.2e-21 |
| | SiteHound | 23.62 | 4.4e-32 | 12.53 | 2.1e-18 | 19.03 | 4.2e-27 |
| Top-1 | MetaPocket 2.0 | 21.45 | 8.0e-30 | 9.86 | 3.6e-14 | 16.69 | 3.3e-24 |
| | DeepSite | 17.40 | 4.1e-25 | 8.41 | 9.7e-12 | 13.17 | 2.3e-19 |
| | P2Rank | 7.90 | 7.4e-11 | 1.12 | 2.7e-01 | 5.41 | 1.2e-06 |
| | Fpocket | 17.84 | 1.2e-25 | 9.93 | 2.8e-14 | 16.96 | 1.4e-24 |
| | SiteHound | 16.43 | 7.0e-24 | 10.48 | 3.5e-15 | 22.30 | 1.0e-30 |
| Top-3 | MetaPocket 2.0 | 19.36 | 1.7e-27 | 10.18 | 1.1e-14 | 19.75 | 6.1e-28 |
| | DeepSite | 14.62 | 1.9e-21 | 13.85 | 2.4e-20 | 21.07 | 2.1e-29 |
| | P2Rank | 13.39 | 1.1e-19 | 2.95 | 4.6e-03 | 8.14 | 2.8e-11 |
| | Fpocket | 19.53 | 1.1e-27 | 13.05 | 3.5e-19 | 17.68 | 1.8e-25 |
| | SiteHound | 21.81 | 3.2e-30 | 14.77 | 1.2e-21 | 22.15 | 1.4e-30 |
| Top-N | MetaPocket 2.0 | 21.39 | 9.1e-30 | 13.26 | 1.7e-19 | 20.55 | 7.7e-29 |
| | DeepSite | 14.11 | 1.0e-20 | 16.54 | 5.0e-24 | 20.83 | 3.7e-29 |
| | P2Rank | 13.87 | 2.3e-20 | 4.26 | 7.3e-05 | 8.39 | 1.1e-11 |
| | Fpocket | 19.76 | 6.0e-28 | 9.07 | 7.4e-13 | 17.22 | 6.9e-25 |
| | SiteHound | 16.73 | 2.9e-24 | 8.63 | 4.1e-12 | 22.39 | 7.9e-31 |
| Top-(N+2) | MetaPocket 2.0 | 19.20 | 2.6e-27 | 9.55 | 1.2e-13 | 20.14 | 2.2e-28 |
| | DeepSite | 11.48 | 8.8e-17 | 18.08 | 5.8e-26 | 23.66 | 4.1e-32 |
| | P2Rank | 18.31 | 3.1e-26 | 3.75 | 4.0e-04 | 9.05 | 8.0e-13 |
| | Fpocket | 42.87 | 1.0e-46 | 2.68 | 9.5e-03 | 17.19 | 7.4e-25 |
| | SiteHound | 52.85 | 5.0e-52 | -13.02 | 4.0e-19 | 22.23 | 1.2e-30 |
| All | MetaPocket 2.0 | 18.32 | 3.0e-26 | 8.08 | 3.6e-11 | 20.35 | 1.3e-28 |
| | DeepSite | 1.18 | 2.4e-01 | 18.99 | 4.7e-27 | 24.34 | 8.8e-33 |
| | P2Rank | 30.67 | 2.3e-38 | 2.33 | 2.3e-02 | 9.56 | 1.1e-13 |