# Supporting Information Text S16:
# BIS and CTMP comparison

| Protein family | Method | Co-evolving pairs |
|---|---|---|
| MukB (49 seq) | BIS, *pos*, $d = 0$ | C1: 4 6 9<br>C2: 14 15 16 17 18 19 20 22 23 26<br>C3: **36 37 39 40 41** 42 |
| | BIS, *pos*, $d = 1$ | C1: 44 45 52 53 54 57 58 60 61 62 63 64 65 66 67 72 73 74 76 77 79 80 81 84 86 87 94 95 99 106 108 112 113 115 116 121 175 179 182 189 193 194 198 200 202 203 204 205 206 207 208 209 210 213 216 217 218 220 221 222 223 225 227<br>C2: 98 174<br>C3:107 111 117 214 219<br>C4:119 125<br>C5: 59 133<br>C6: 55 187<br>C7: 29 30 31 32 33 |
| | CTMP | X:8 **36**:96 **14**:123 83:139 11:**86** 3:135 159:180 149:171 **29**:**32** **55**:180 50:82 128:211 **74**:191 **57**:129 X:**54** 75:226 **17**:X **59**:129 21:X 68:181 128:**208** X:89 **22**:X **26**:78 **41**:**64** X:**45** 134:**210** 110:226 **29**:**198** **18**:X 70:166 X:**198** X:141 **17**:X 109:191 X:173 154:**202** 7:**133** **72**:191 13:100 129:145 135:150 **30**:**76** X:136 **29**:**205** X:92 **14**:**30** **39**:150 **73**:135 |
| MukB (54 seq) | BIS, *pos*, $d = 0$ | C1: 16 20 22<br>C2: **36 37 39 40** |
| | BIS, *pos*, $d = 1$ | C1: 45 61 64 66 77 200 202 203<br>C2: 44 60 62 76 84 204 210 222<br>C3: 54 74 81 99 179 182 207 217 221<br>C4: 80 205<br>C5: 52 193 220<br>C6: 31 33 |
| | CTMP | 42:83 47:X 42:192 25:X **74**:142 117:139 X:209 X:**205** X:**205** 46:135 2:195 X:25 **64**:144 X:91 X:**77** 191:211 4:151 **64**:122 25:X 104:127 98:191 **20**:42 **39**:144 X:156 3:46 25:X 48:129 83:108 41:176 X:**220** 4:126 73:127 96:101 X:87 **34**:65 3:212 X:196 X:78 **80**:106 3:116 **31**:48 71:128 X:78 156:159 126:145 14:**37** X:91 X:91 38:144 |
| MukB (200 seq) | BIS, *pos*, $d = 0$ | C1: 4 6 9<br>C2: 14 15 16 17 18 19 20 22 23 26<br>C3: **34 35 36 37 39 40 41** 42 |
| | BIS, *pos*, $d = 1$ | C1:44 45 52 53 54 57 58 60 61 62 63 64 65 66 67 72 73 74 76 77 79 80 81 84 86 87 94 95 99 108 112 113 115 116 121 175 179 182 189 193 194 198 200 202 203 204 205 206 207 208 209 210 213 216 217 218 220 221 222 223 225 227<br>C2:98 174<br>C3:107 111 117 214 219<br>C4:119 125<br>C5:59 133<br>C6:49 145 170<br>C7:55 187<br>C8:29 30 31 32 33 |
| | CTMP | NO CO-EVOLVING PAIRS |
| MukB (205 seq) | BIS, *pos*, $d = 0$ | C1: 16 20 22<br>C2: **36 37 39 40** |
| | BIS, *pos*, $d = 1$ | C1: 45 61 64 66 77 200 202 203<br>C2: 44 60 62 76 84 204 210 222<br>C3: 54 74 81 99 179 182 207 217 221<br>C4: 80 205<br>C5: 52 193 220<br>C6: 31 33 |
| | CTMP | NO CO-EVOLVING PAIRS |

Table 1: **MukB protein: comparing BIS to CTMP.**

Comparison of CTMP and BIS (run on alignment positions - *pos*) on the MukB family. The CTMP experiment was run with the following parameters: penalty = 0.1, threshold on the fraction on gapped sequences = 1, threshold on the fraction of conserved sequences = 1, threshold on the fraction of sequences covarying between overlapping states = 0.0, threshold on the likelihood = 6.0. The 50 highest pairs of co-evolving residues (pdb positions) are reported. Bolds highlight residues in common with BIS.

| Protein family | Method | Co-evolving pairs |
|---|---|---|
| PABD (20 seq) | BIS, *pos*, $d = 0$ | C1: 22 23 27 29<br>C2: 30 31 32 33 34 35 36 37 38 39 40 42 46 48 49<br>C3: 41 44<br>C4: 51 52 |
| | BIS, *pos*, $d = 1$ | C1: 11 13 14 15 18<br>C2: 16 17 |
| | CTMP | 3:**11** 6:**23** **11:15** **11:38** **30:35** 3:6 3:**35** **35:38** **11:18** **11:52** **15:35** 6:**30** **11:16** 28:**35** **18:35** **11:36** 6:**38** **35:52** 6:**15** **11:49** **11:34** **16:35** **11:27** **11:51** **11:13** **11:31** **35:49** **11:29** **11:22** **34:35** **35:36** **27:35** **11**:12 6:**18** **13:35** **29:35** **35:51** **22:35** 12:**35** 6:**52** 6:**16** **11**:28 **31:35** 6:**49** 6:**36** 6:**34** **11:32** 6:**27** 6:**13** |
| PABD (28 seq) | BIS, *pos*, $d = 0$ | C1: 32 39<br>C2: 42 49 |
| | BIS, *pos*, $d = 1$ | C1: 11 13 14 |
| | CTMP | 25:30 37:48 5:**13** **13**:28 25:51 **14**:33 30:33 5:**32** 43:46 8:34 24:**32** 16:25 8:20 37:50 21:37 **32**:38 37:45 17:31 8:38 **13**:35 **14**:18 8:19 19:**32** 15:17 8:28 20:**32** **32**:44 28:**32** 31:54 17:51 25:43 15:54 31:33 8:44 15:33 40:54 17:29 **13**:46 17:30 8:26 23:25 25:38 **32**:50 33:40 25:34 17:36 3:37 30:40 29:54 |
| PABD (452 seq) | BIS, *pos*, $d = 0$ | C1: 22 23 27 29<br>C2: 30 31 32 33 34 35 36 37 38 39 40 42 46 48 49<br>C3: 41 44<br>C4: 51 52 |
| | BIS, *pos*, $d = 1$ | C1: 11 13 14 15 18<br>C2: 16 17 |
| | CTMP | **35:42** **27:39** 28:**37** 21:47 8:**30** **16:39** 9:**35** 9:21 X:**34** 12:**52** 3:**39** 20:21 10:**46** 8:28 21:**48** 12:47 **39:44** **39:42** 47:**52** 7:21 X:28 **14**:50 6:**37** 5:**52** **17:35** 7:10 5:**40** 26:**39** 10:**37** 26:50 7:**52** 21:45 7:47 12:**40** 7:12 **16**:50 **40**:47 **42**:50 **40:52** **35**:47 X:25 **33:39** 10:19 **18**:50 **36**:50 21:**52** 5:12 **38:39** **29:39** |
| PABD (490 seq) | BIS, *pos*, $d = 0$ | C1: 32 39 |
| | BIS, *pos*, $d = 1$ | C1: 11 13 14 |
| | CTMP | 23:50 26:37 **11**:53 20:**39** 4:27 **14**:37 19:**39** 10:52 5:21 X:20 36:37 X:**14** 21:52 4:19 X:19 45:50 21:40 7:35 18:50 35:47 4:20 **39**:46 X:23 3:8 **39**:43 X:36 8:23 7:52 **39**:45 3:50 47:52 31:**39** 4:**14** 25:**39** 40:52 30:53 44:50 4:44 4:26 37:44 4:16 4:18 8:37 10:35 X:44 8:25 10:**39** 19:37 31:50 |

Table 2: **Protein A-B domain: comparing BIS to CTMP.**

Comparison of CTMP and BIS (run on alignment positions) analyses of the Protein A-B domain family. See legend in Table 1-Text S16.

| AATpase family | Method | Co-evolving pairs |
|---|---|---|
| DEAD-box | BIS, *pos*, $d = 0$ | C1: 34 73 75 76 256 257 259 318 319 709 797 804 |
| | BIS, *pos*, $d = 1$ | C1: 133 213<br>C2: 136 801 |
| | CTMP | 528:529 528:856 153:528 153:826 528:826 528:851 155:528 154:528 470:528 108:528 828:829 528:530 112:528 528:626 528:857 93:528 528:612 161:528 826:828 498:528 288:528 528:621 529:530 472:528 490:528 61:528 111:528 52:528 501:528 528:858 528:702 492:528 46:528 500:528 528:624 528:860 528:609 486:528 525:528 485:528 528:623 528:854 59:528 1:528 528:611 528:614 7:528 289:528 528:618 |
| DEAH-RHA | BIS, *pos*, $d = 0$ | C1: 33 73 75 76 78 129 140 256 257 260 261 266 319 699 745 791 798 801 808 |
| | BIS, *pos*, $d = 1$ | C1: 70 127<br>C2: 72 130 174 213 215 259 317 318 700 708711 797 800 803 804<br>C3: 134 554<br>C4: 138 170<br>C5: 750 834 |
| | CTMP | 171:672 83:171 171:**801** 171:175 83:672 325:814 814:860 83:818 161:171 171:**261** 171:216 171:342 175:672 171:748 83:175 814:823 171:267 36:790 171:**804** 171:558 79:171 171:835 171:701 790:814 202:860 83:161 171:312 83:89 672:**801** 83:**801** 36:89 566:814 36:90 89:790 325:790 814:858 672:790 171:695 171:805 83:748 34:171 672:748 89:672 36:325 558:672 36:860 36:163 141:171 **33**:171 |
| NS3/NPH-II | BIS, *pos*, $d = 0$ | C1: 22 37 122 128 211 264 265 312 342 346 551 813 838<br>C2: 124 711<br>C3: 73 75 76 129 170 213 256 257 259 318 319 568 745 797 800 801 803 804<br>C4: 130 327<br>C5: 131 267<br>C6: 72 132 810<br>C7: 140 214 664 667<br>C8: 8 18 536 537 674<br>C9: 78 81 210<br>C10: 215 258 562<br>C11: 254 262<br>C12: 317 554<br>C13: 320 322 699 709 743<br>C14: 321 666<br>C15: 553 802<br>C16: 677 806<br>C17: 695 701 |
| | BIS, *pos*, $d = 1$ | C1: 125 698<br>C2: 136 217 271 657 751 862<br>C3: 16 137<br>C4: 139 831 844<br>C5: 20 23 328<br>C6: 28 763<br>C7: 333 746<br>C8: 39 794<br>C9: 544 661<br>C10: 79 759 |
| | CTMP | 1:2 1:3 |
| Swi2/Snf2 | BIS, *pos*, $d = 0$ | C1: 73 75 76 77 136 256 257 320 804 |
| | BIS, *pos*, $d = 1$ | C1: 129 797 801 807<br>C2: 74 709 |
| | CTMP | 140:750 40:750 **73**:750 137:140 334:750 750:816 **74**:750 40:334 67:750 710:750 **75**:750 **256**:750 140:215 40:140 **73**:**136** 34:40 393:750 **136**:750 641:750 **74**:**75** 72:750 40:393 750:806 34:393 40:170 40:747 40:**256** 40:**73** 393:433 40:337 **73**:**74** 750:817 712:750 215:750 750:**801** 671:750 140:393 **73**:**75** 34:750 67:140 396:750 137:215 328:750 86:393 **73**:140 **74**:710 747:750 **709**:750 **75**:710 |

Table 3: **AATPase subfamilies: comparing BIS to CTMP.**

Comparison of CTMP and BIS (run on alignment positions) analyses of the AATPase subfamilies. BIS was run on the 11 subfamilies but only 4 of them output a list of residues. See legend in Table 1-Text S16. Note that these are the only AATPase subfamilies where CTMP provided some answer.