

Supplementary Materials: Predicting Protein-Protein Interactions Using BiGGER. Case Studies

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Table S1. List and relative properties of protein-protein complexes predicted by BiGGER algorithm since year 2000.

| Paper Ref | PDB ID | Protein Name | Method | Year | Restraints? | Filtering? | Nature of Complex | Other Exp. Methods | Kd (Order of Magnitude)? | Any Homology Modelling? |
|------------------------------|--|--|--|------|---------------------|---|-------------------|--|-------------------------------------|--|
| Ali et al., (2014) [1] | Scorpiun neurotoxins Agiotoxin 2 (1AGT), kalotoxin (2KTX), kalotoxin 2 (1KTX), OsK1 (1SCO), BmKTx1 (1BKT), and K+-channel KcsA (1BL8). Homology models of Bs-KTx6 and mKv1.3 | Agiotoxin 2, kalotoxin, kalotoxin 2, OsK1, BmKTx1, KcsA | BiGGER, Electrophysiological studies | 2014 | No | No | N/A | Electrophysiological studies | N/A | Yes, with MODELLER |
| Almeida et al., (2009) [2] | 1WAD for cytochrome <i>c</i> ₃ , 1RDG for rubredoxin, both from <i>Desulfovibrio gigas</i> | Rubredoxin, cytochrome <i>c</i> ₃ from <i>Desulfovibrio gigas</i> | BiGGER, NMR | 2009 | No | Yes, NMR | Electrostatic | NMR | 25 micromolar | No |
| Amela et al., (2013) | 2GA5 for Yfh1, homology models for Isu and Nfs1, <i>ab initio</i> model calculated for Isd11 | Yeast Frataxin Homolog 1, Isu, Nfs1 and Isd11 from yeast | BiGGER, EscherNG, Hex, HADDOCK | 2013 | No | No | Undisclosed | EscherNG, Hex, HADDOCK | No | ESyPred3D, 3D-PSSM, Phyre, Rosetta |
| Andreotti et al., (2005) [3] | 1BL8 (KScA channel), for modeling; 1PNH, 1SCY and 1TXM | sKC2, sKC3 and Scorpion Toxins P05, Lei and MTX | BiGGER | 2005 | No | Yes—comparison of Kd values with docking energies | Electrostatic | Kd values | Yes—nM range | INISIGHTII Discover 3 module, MODELLER, NMRCLUST |
| Banci et al., (2003) [4] | N/A | Cytochrome <i>b</i> ₅ from rabbit, iso-1-cytochrome <i>c</i> from yeast | BiGGER, NMR | 2003 | Yes - NMR | NMR, atom contacts | Electrostatic | NMR, Energy minimization of best structures | N/A | Sander module on AMBER 6.0 for energy minimization |
| Bauer et al., (2013) [5] | 4HPK and 3JQW for <i>holo</i> s3b (ColG) and <i>holo</i> s3 (ColH) from <i>Clostridium histolyticum</i> , 1K6F for collagenous peptide | <i>Clostridium histolyticum</i> ColH and ColG collagen binding domains, Collagen. | BiGGER, X-Ray Crystallography, SAXS, Fluorescence Spectroscopy | 2013 | No | No | N/A | X-Ray Crystallography, SAXS, Fluorescence Spectroscopy | No | MIFit |
| Bonding et al., (2008) [6] | Horse heart cytochrome <i>c</i> (1HRC), 1OJ6 for neuroglobin | Horse heart cytochrome <i>c</i> , neuroglobin | BiGGER, NMR, Surface Plasmon Resonance (SPR) | 2008 | Not used in docking | Heme Fe-Fe distance no more than 15 Angstrom | Electrostatic | NMR, SPR | 200 μM, by NMR, 20 to 125 μM by SPR | YASARA back-modelling of neuroglobin |

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|--------------------------------|---|--|---|------|---|--|-----------------------|---|---|--|
| Bustos and Iglesias (2005) [7] | 1EUH, for modeling of five plant GAPN proteins; 1A4O | Phosphorylated non-phosphorylating glyceraldehyde-3-phosphate dehydrogenase (GAPN), 5 plant species; 14-3-3 | SS Kinetics, BiGGER | 2005 | Yes - selected by user, based on previous results with model peptide | AA Distance filtering (S404 from GAPN, K39 + R56 + R127 from 14-3-3) | Electrostatic | SS Kinetics of NADPH formation (reaction is NADP + dependent) | Kinetic rates only | Yes, for GAPN using Modeller v6.0; Energy minimization with AMBER force field in HyperChem 5.0 |
| Cai et al., (2003) [8] | <i>Ab initio</i> structure calculations | Caveolin-1, Several SARS-CoV proteins with caveolin binding motifs | BiGGER | 2003 | No. Selected model with lowest energy | Lowest energy | No | No | All caveolin binding proteins were modeled with SWISSPROT | |
| Carpentier et al., (2014) [9] | 1HPN, 1FNH | the standard dodecasaccharide ([IdUA2S-GlcNS6S]6) of heparin; Hep-II domain of fibronectin (1FNH) | Bioinformatics (potential energies of interaction) | 2014 | No | Yes | Variable | Docking software: GRAMM, ESCHER, HEX (rigid docking). GOLD (flexible) | N/A | No |
| Carregal et al., (2005) [10] | 1QUZ (HsTx1), 1Y2P ([Abu ¹⁹ ,Abu ³⁴]-HsTx1], 1WZ5 ([Abu ²⁰ ,Abu ³⁵]-Pi1), 1ORQ to generate models of human calcium channels | S5-H5-S6 pore regions of mKv1.1, rKv1.2, and mKv1.3 (human calcium channels); Scorpion toxins HsTx1 and Pi1 | BiGGER, NMR, Electrophysiology | 2005 | Best complexes were energy minimized using the GROMOS96 force field on Deepview 3.7 | No | Not clear, but strong | NMR, Electrophysiology, Energy minimization | N/A | Human calcium channels modeled with CNS |
| Chapon et al., (2000) [11] | N/A | <i>Erwinia chrysanthemi</i> CD _{Cel5} and CBD _{Cel5} (3 domains) | BiGGER, Mutagenesis studies, Secretion studies (Western Blot) | 2000 | Post-docking selection of Trp43 distance to catalytic domain | Amino Acid Distance filtering | Not clear | Mutagenesis, Secretion Studies | N/A | N/A |
| Cozza et al., (2007) [12] | Bovine RNase A (1F0V, 1A2W, 1JS0, and homology models) | Oligomers of Bovine RNase A, both native and domain-swapped; | BiGGER; Zdock, Gramm, Escher | 2007 | None | RMSD comparison with published structures | Not clear | Other docking studies | N/A | Yes |
| Crowley et al., (2002)a [13] | <i>Phormidium luminosum</i> cytochromes c and f (1C13, 1YCC); spinach Rieske protein (1RFS) | <i>Phormidium luminosum</i> cytochrome f and cytochrome c; Rieske protein from spinach | BiGGER, NMR | 2002 | Yes, Chemical shift perturbation mapping | NMR restraints | Electrostatic | NMR | 50–250 μM | No |
| Crowley et al., (2002)b [14] | N/A | <i>Phormidium luminosum</i> cytochrome f; cytochrome c ₆ from <i>Anabaena</i> sp. PCC 7119 and <i>Synechococcus elongatus</i> | BiGGER, NMR | 2002 | No | Yes, NMR | Electrostatic | NMR chemical shift perturbation mapping | 100 μM and higher | No |

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| Cruz-Gallardo et al., (2013) [15] | 1JZG for azurin, 1NIN for plastocyanin, 1A3Z for rusticyanin | Merozoite Surface Protein 1, 19 kDa C-terminal fragment, and <i>Acidithiobacillus ferrooxidans</i> Rusticyanin, <i>Nostoc</i> sp. PCC 7119, <i>Phormidium laminosum</i> and poplar plastocyanins, and <i>Pseudomonas aeruginosa</i> azurin (Az) | BiGGER, NMR, ITC, Culture Growth Inhibition | 2013 | Yes, for MSP-1:Rc complex | Yes, NMR | Mainly hydrophobic | NMR, ITC, Culture Growth Inhibition | 2 micromolar | No |
| Czjzek et al., (2002) [16] | <i>Desulfovibrio vulgaris</i> cytochrome <i>c</i> ₃ (2CTH); <i>ab initio</i> structural determination of Hmc (1GWS) | Hexadeca-heme cytochrome Hmc, cytochrome <i>c</i> ₃ from <i>D. vulgaris</i> | Bigger, Crystallography, NMR | 2002 | Not at first | Yes, NMR | Electrostatic | NMR CSPM, Xtal | No | No |
| Dell'Acqua et al., (2008) [17] | <i>Marinobacter hydrocarbonoclasticus</i> N ₂ OR (1QNI) and cytochrome <i>c</i> ₅₅₂ (1CNO), horse heart cytochrome <i>c</i> (1HRC) | <i>Marinobacter hydrocarbonoclasticus</i> N ₂ OR and cytochrome <i>c</i> ₅₅₂ , horse heart cytochrome <i>c</i> | BiGGER, Enzymatic Activity assays, NMR | 2008 | No | Cluster to cluster distance | Electrostatic | NMR, Activity Assays | 5 μM | No |
| Dell'Acqua et al., (2011) [18] | <i>Marinobacter hydrocarbonoclasticus</i> N ₂ OR (1QNI), <i>Paracoccus denitrificans</i> N ₂ OR (1FWX), <i>A. cycloclastes</i> N ₂ OR (2IWF), <i>Marinobacter hydrocarbonoclasticus</i> cytochrome <i>c</i> ₅₅₂ (1CNO), horse heart cytochrome <i>c</i> (1HRC), <i>Paracoccus denitrificans</i> cytochrome <i>c</i> ₅₅₀ (1COT), <i>Paracoccus pantotrophus</i> pseudoazurin (3ERX), <i>A. cycloclastes</i> pseudoazurin (1BQR), bovine heart cytochrome <i>c</i> (2B4Z) | Several related to N ₂ OR and its electron donors from multiple organisms | BiGGER | 2011 | No | No | Electrostatic | Several Bioinformatics tools | N/A | Yes, using PHYRE and SWISSMODEL |
| deMorree et al., (2011) [19] | CAPN3 modelled from 3DF0, 2T7P (Filamin C) | CAPN3 (Calpain 3), FLNC (Filamin C) | BiGGER, Bioinformatics | 2011 | No | No | N/A | <i>Ab initio</i> bioinformatics | No | SWISSMODEL for CAPN3 |
| El Antak et al., (2003) [20] | <i>Desulfovibrio vulgaris</i> hydrogenas (2HFE), cytochrome <i>c</i> ₃ (2CTH) | cytochrome <i>c</i> ₃ , Fe-hydrogenase from <i>Desulfovibrio vulgaris</i> | BiGGER, NMR, MD simulations | 2003 | No | Yes, NMR and cluster to cluster distance | Electrostatic | NMR, Molecular Dynamic Simulations to minimize energy with X-PLOR | N/A | No |
| Fantuzzi et al., (2009) [21] | <i>Desulfovibrio vulgaris</i> Flavodoxin (1J8Q); <i>Bacillus megaterium</i> P450 BMP (1BU7) | <i>Desulfovibrio vulgaris</i> Flavodoxin and <i>Bacillus megaterium</i> P450 BMP | BiGGER, NMR, Electron Transfer studies | 2011 | No | Yes, NMR | Electrostatic | NMR, Electron Transfer | tens to hundreds micromolar | Yes |

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| Fujita et al., (2012) [22] | <i>Achromobacter cycloclastes</i> pseudoazurin (1BQR, 1BQK) and Nitrous Oxide Reductase (2IWF); <i>Marinobacter hydrocarbonoclasticus</i> cytochrome <i>c</i> ₅₅₂ (1CNO) and N ₂ OR (1QNI). Bovine heart cytochrome <i>c</i> (2B4Z) | <i>Achromobacter cycloclastes</i> pseudoazurin and Nitrous Oxide Reductase; <i>Marinobacter hydrocarbonoclasticus</i> cytochrome <i>c</i> ₅₅₂ and N ₂ OR. Bovine heart cytochrome <i>c</i> . | BiGGER, Kinetic assays, Electrochemistry, Western Blot | 2012 | Energy minimization using Tinker 4.2 | Distance between clusters | N/A | Kinetic assays, Electrochemistry, Western Blot | N/A | Yes, energy minimizations using Tinker 4.2. Best complexes were analyzed for ET using PATHWAYS |
| Giron-Monzon et al., (2004) [23] | <i>E. coli</i> MutL (1B63), and MutH (2AZO) | <i>E. coli</i> ATPase MutL and Endonuclease MutH | BiGGER, Cross-Linking, site-Directed Mutagenesis | 2004 | No | 4 angstrom cutoff, comparison with cross linked models | Dependent on DNA presence | Mutagenesis, Cross-linking | N/A | Comparison with models derived from cross-linking |
| Impagliazzo et al., (2005) [24] | <i>Alcaligenes faecalis</i> Pseudoazurin (8PAZ) and Nitrate reductase (1AQ8) | Pseudoazurin and Nitrate Reductase from <i>Alcaligenes faecalis</i> | BiGGER, NMR | 2005 | NMR-derived | No | Electrostatic | NMR Chemical shift perturbation mapping | N/A | No |
| Impagliazzo et al., (2010) [25] | Peptide derived from epitope of polyadenylate binding protein nuclear 1 (PABPN1), modelled by PHYRE, and llama antibody 3F5 (homology model based on 1G9E) | Polyadenylate binding protein nuclear 1 (PABPN1) and llama antibody 3F5 | BiGGER, NMR, Fluorescence, Stopped-Flow Kinetics | 2010 | No | No | Mostly hydrophobic | NMR, Fluorescence, Stopped-Flow Kinetics | 0.8 uM | Yes, with PHYRE and SWISS-MODEL |
| Jokiranta et al., (2006) [26] | Human C3d (1C3D), FH19-20 (2G7I), homology modelling, 1RID (heparin) | Human FH19-20 with C3d and heparin | BiGGER, Crystallography, Affinity Column, Radioligand assay | 2006 | No | Exclusion of solutions binding to other known binding site | N/A | Crystallography, Affinity, Radioligand | N/A | Yes |
| Jonker et al., (2005) [27] | <i>Herpes simplex</i> PC4ctd dimer (2PHE), homology models of VP16ad α -helices, and TFIIBc | <i>Herpes simplex</i> PC4ctd dimer, VP16ad R-helices, and TFIIBc | BiGGER, HADDOCK, NMR, Site-directed mutagenesis | 2005 | No | Energy minimization of best complexes with GROMOS96 force field | Electrostatic | NMR, SDM | N/A | Yes, SWISSMODEL for TFIIBc and VP16ad α -helices |
| Jouirou et al., (2004) [28] | <i>Centruroides noxioides</i> NMR-generated structure of cobatoxin 1, <i>in silico</i> -generated peptides | <i>Centruroides noxioides</i> CoTX1 or ACoTX1 with human Kv1.2 Ca ²⁺ channel | BiGGER, NMR, Molecular Dynamics simulations | 2004 | No | Geometric Filtering of Top 5 solutions | Geometric | NMR, MD | Yes—nM | Yes—peptides |
| Kovaleski et al., (2007) [29] | Capsid CA chain P (1E6); homology model of human LysRS using 1E1O | HIV CA Capsid Protein; Human Lysyl-tRNA synthase | BiGGER, Site-directed mutagenesis | 2007 | 4 Å cut-off | Comparison with deletion mutants | Strong (770 nM) | Spectrofluorimetry | Yes. By spectrofluorimetry | Yes, using MODELLER 4 |

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|---------------------------------------|--|---|---|------|----|--|---------------|---|------------------------------------|---|
| Krippahl et al., (2006) [30] | <i>Desulfovibrio. Vulgaris</i> , <i>D. gigas</i> and <i>D. salexigens</i> aldehyde oxidoreductase (1HLR and homology models), and Flaxodoxin (IFX1 and homology models) | Aldehyde Oxidoreductase and Flavodoxin from <i>D. vulgaris</i> , <i>D. gigas</i> and <i>D. salexigens</i> | BiGGER | 2006 | No | Metal cluster to metal cluster distance | Transient | No | N/A | Yes |
| M'Barek et al., (2003)a [31] | Scorpion Maurotoxin (1TXM), Homology models of rat potassium channels (from 1BL8) | Scorpion Mautoxin MTXPi1 and the various voltage-gated K channel subtypes (<i>Drosophila Shaker B</i> , rat Kv1.1 Kv1.2, and Kv1.3 S5-H5-S6 domains) | BiGGER, Ecotoxicity | 2003 | No | 15 best from global score, Toxin Lys and beta-sheet orientation, electrostatics | Strong | Ecotoxicity | N/A | Yes, using INSIGHTII, PROCHECK, SWISSMODEL |
| M'Barek et al., (2003)b [32] | Homology model of rat calcium channels (from 1BL8), and scorpion toxin sPi4 (1N8M) | Scorpio toxin sPi4, rat Kv1.2 calcium channel S5-H5-S6 fragment | BiGGER, NMR, Electrophysiology, EC ₅₀ studies | 2003 | No | Top five scorers | Strong | Electrophysiology, NMR, EC ₅₀ | N/A | Yes, using INSIGHTII, PROCHECK, SWISSMODEL |
| M'Barek et al., (2005) [33] | Scorpion butantoxin-Maurotoxin chimera (1WT7); homology model of S5-H5-S6 pore region of Kv1.2 channel (1ORQ) | BuTX-MTXPi1 (together as a chimera, as well as individually; Kv1.2 Channel from rat | BiGGER, Circular Dichroism, NMR, Electrophysiology | 2005 | No | Yes: global score, relative orientation of probe to target, and likeliness of electrostatic interactions | N/A | NMR, Electrophysiology, Modeling, Energy minimization | N/A | Yes, SWISSPROT and INSIGHTII |
| Martinez-Fabregas, et al. (2014) [34] | 1J3S, 4ALD, 2RR6, 1Q8K, 2E50, 2BR9, and homology models | Human cytochrome c, ALDOA, ANP32B, eIF2 α , hnRNP C1/C2, HSPA5, SET, STRAP, and YWHAE | BiGGER, Affinity Chromatography, MALDI-TOF/TOF, Bimolecular fluorescence complementation, Surface Plasmon Resonance, NMR, ITC | 2014 | No | No | N/A | Affinity Chromatography, MALDI-TOF/TOF, Bimolecular fluorescence complementation, Surface Plasmon Resonance, NMR, ITC | N/A | Yes, with MODELLER |
| Matamala et al., (2007) [35] | <i>Fremyella diplosiphon</i> <td>Phycocyanin hexameric form from <i>Fremyella diplosiphon</i></td> <td>BiGGER, Crystallography, FRET</td> <td>2007</td> <td>No</td> <td>20 best of each parameter.</td> <td>Geometric</td> <td>FRET, Crystallography</td> <td>N/A</td> <td>No</td> | Phycocyanin hexameric form from <i>Fremyella diplosiphon</i> | BiGGER, Crystallography, FRET | 2007 | No | 20 best of each parameter. | Geometric | FRET, Crystallography | N/A | No |
| McKenna et al., (2003) [36] | Human hUbc13hMms2 heterodimer (1J74); Human Ubiquitin (1UBQ) | Human Ubiquitin; and hUbc13 hMms2 heterodimer. | BiGGER, NMR Chemical Shift Perturbation | 2003 | No | Filtered by Chemical shift perturbation mapping, imposing upper distance limit of 5 Å | Electrostatic | NMR | 100 micromolar, determined earlier | Yes, best complexes were energy-minimized using INSIGHTII |

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|-----------------------------|---|--|--|------|---|-----------------------------|------------------------|--|---|---|
| Monaco et al., (2007) [37] | Human Matrix Metalloproteinase 2 (1CK7); for Bovine fibrinogen (1M1J). | Truncated forms of human MMP2, Bovine Fibrinogen | BiGGER, Activity assays, zymography | 2007 | N-terminal to C-terminal of probe no longer than 20 angstrom | No | Electrostatic | Zymography, activity assays | N/A | Models of fibrinogen with amino acid deletions were also modelled |
| Monini et al., (2012) [38] | Homology models of TAT BH10 and gp120 domain ΔV1-2 sf162 | TAT BH10 and gp120 domain ΔV1-2 sf162 | BiGGER, ClusPro, HADDOCK, isothermal Calorimetry Titration, Site-directed Mutagenesis, Infection Experiments, Flow Cytometry, Confocal Microscopy, Electron Microscopy, Surface Plasmon Resonance, ELISA | 2012 | A posteriori refinement of initial results using other docking algorithms | No | Strong | ClusPro, HADDOCK, isothermal Calorimetry Titration, Site-directed Mutagenesis, Infection Experiments, Flow Cytometry, Confocal Microscopy, Electron Microscopy, Surface Plasmon Resonance, ELISA | 111 nM | Yes, Modeller 8 |
| Morelli 2000 JBC [39] | 1DVH for <i>Desulfovibrio vulgaris</i> cytochrome <i>c</i> ₅₅₃ , 1HF6 for Fe-Hydrogenase from <i>Desulfovibrio desulfuricans</i> | <i>Desulfovibrio vulgaris</i> cytochrome <i>c</i> ₅₅₃ , Fe-Hydrogenase from <i>Desulfovibrio desulfuricans</i> | BiGGER, NMR, MD Energy Minimization using X-PLOR and SHAKE | 2000 | No | Yes, NMR | Electrostatic | NMR, Molecular Dynamics Energy Minimization | N/A | Yes, Greenpath to predict tunneling pathway |
| Morelli 2000 Biochem [39] | 1DVH for <i>Desulfovibrio vulgaris</i> cytochrome <i>c</i> ₅₅₃ , homology model of Ferredoxin I from <i>Desulfomicrobium norvegicum</i> | <i>Desulfovibrio vulgaris</i> cytochrome <i>c</i> ₅₅₃ , Ferredoxin I from <i>Desulfomicrobium norvegicum</i> | BiGGER, NMR, MD Energy Minimization using X-PLOR | 2000 | No | Yes, NMR | Electrostatic | NMR, Molecular Dynamics Energy Minimization | N/A | Yes, with TURBO-FRODO and SHAKE |
| Morelli et al., (2001) [40] | <i>Escherichia coli</i> Enzyme I (1ZYM) and HPR (1POH), <i>Bacillus amyloliquefaciens</i> Barnase (1A2P) and barstar (1A19), Rat Tom20 (1OM2), Yeast cytochrome <i>c</i> (1CCP) and cytochrome <i>c</i> peroxidase (1YCC) | Several test complexes (EIN + HPr; Barnase + Barstar; Tom20 + Presequence; cytochrome <i>c</i> + cytochrome <i>c</i> peroxidase) | BiGGER, NMR | 2001 | Perturbation, Amide Proton-Deuterium Exchange rates) | No | Transient to Strong | NMR | Variable, from μM to pM | Yes |
| Mouhat et al., (2004) [41] | Rat Kv channels models (from 1KVC); peptides | Pi1, [A24,A33]-Pi1 or P-Pi1 on to rat Kv 1.1, Kv1.2 and Kv1.3 Ca ²⁺ channels | BiGGER, Conformational Analysis, electrophysiology | 2004 | Take five best scorers, take to Turbo-Frodo | Strong (low values of IC50) | NMR, Electrophysiology | Strong (nM range) | Yes, all Kv channels, using Turbo-Frodo, Procheck, Whatif and CNS | |

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|-----------------------------------|---|--|--|------|----|--|---------------------|--|---------------------|------------------------------|
| Nishida et al., (2003) [42] | Human von Willebrand factor A3 domain (1AO3); shortened model peptide of collagen (2CLG); microfibril shortened model (4CLG) | Human A3 domain, collagen peptide, microfibril | BiGGER; NMR, Surface Plasmon Resonance, Site-Directed Mutagenesis | 2003 | No | NMR filtering | Transient | NMR, Surface Plasmon Resonance, Site-Directed Mutagenesis | Micromolar range | Yes |
| Nummelin et al., (2004) [43] | Modified collagen-like peptide (1CAG); Model of <i>Yersinia enterocolitica</i> YadA, other Peptides (including collagen) (1P9H) | <i>Yersinia enterocolitica</i> YadA, other Peptides (including collagen) | BiGGER, Crystallography, Site-directed mutagenesis | 2004 | No | NMR filtering; max. distance 4 or 5 angstrom | Transient to strong | Crystallography, Site-directed mutagenesis | Micromolar range | Yes, using SOLVE and ArpWarp |
| Palma et al., (2005) [44] | <i>Synechocystis</i> sp. PCC 6803 Ferredoxin-NADP ⁺ Reductase modeled from 1QUE; Ferredoxin modeled from 1QT9 | <i>Synechocystis</i> sp. PCC 6803 Ferredoxin-NADP ⁺ Reductase and Ferredoxin | BiGGER, NMR | 2005 | No | NMR and Electron Tunneling pathway filtering | Transient | NMR | N/A | Yes, with SWISSMODEL |
| Pauleta et al., (2004) [45] | <i>Paracoccus pantotrophus</i> pseudoazurin (1ADW) | <i>Paracoccus pantotrophus</i> cytochrome c Peroxidase (monomer) and pseudoazurin | BiGGER, NMR, Isothermal Calorimetry Titration, Analytical Ultracentrifugation | 2004 | No | NMR filtering | Transient | NMR, Isothermal Calorimetry Titration, Analytical Ultracentrifugation | low micromolar | No |
| Pedroso et al., (2016) [46] | Homology model based on 1HZV, 1CNO, 1HRC | Cytochrome cd1NiR, cytochrome c552, horse heart cytochrome c | BiGGER, Cyclic voltammetry | 2016 | No | Yes | Hydrophobic | Cyclic voltammetry | N/A | Yes, with I-TASSER |
| Pettigrew et al., (2003)a [47] | N/A | <i>Paracoccus denitrificans</i> cytochrome c peroxidase monomer with two horse heart cytochrome c molecules | BiGGER, Analytical Ultracentrifugation, Isothermal Calorimetry | 2003 | No | No | Transient | Analytical Ultracentrifugation, Isothermal Calorimetry | very low micromolar | No |
| Pettigrew et al., (2003)b [48] | N/A | <i>Paracoccus denitrificans</i> cytochrome c peroxidase and cytochrome c ₅₅₀ , horse heart cytochrome c | BiGGER, Analytical Ultracentrifugation, Isothermal Calorimetry, NMR | 2003 | No | Yes, NMR | Transient | Analytical Ultracentrifugation, Isothermal Calorimetry, NMR | Low micromolar | No |
| Philominathan et al., 2009 [49] | 1NQD and 1K6F for <i>Clostridium histolyticum</i> Collagen Binding Domain and collagenous peptide, respectively | CBD and collagenous peptide from <i>Clostridium histolyticum</i> | BiGGER, NMR Chemical Shift Perturbation, Steady-state fluorescence, Circular Dichroism, SAXS | 2009 | No | From NMR results | N/A | NMR Chemical shift perturbation mapping, Steady-state fluorescence, Circular Dichroism, SAXS | 57 μM | Yes |
| Philominathan et al., (2012) [50] | <i>Clostridium histolyticum</i> collagenase (1NQD) and minicollagen (1CAG) | Collagenase and Minicollagen from <i>Clostridium histolyticum</i> | BiGGER, NMR, Small Angle X-ray Scattering, Circular Dichroism | 2012 | No | From NMR results | N/A | NMR, Small Angle X-ray Scattering, Circular Dichroism | N/A | No |
| Pieulle et al., (2004) [51] | <i>Desulfovibrio africanus</i> Pyruvate-ferredoxin oxidoreductase (1B0P) and ferredoxin I (1FXR) | Pyruvate-ferredoxin oxidoreductase; ferredoxin I from <i>D. africanus</i> | BiGGER, Isothermal Titration Calorimetry, NMR, Electrochemistry, Activity assays | 2004 | No | Yes, NMR | Transient | Isothermal Titration Calorimetry, NMR, electrochemistry, Activity assays | tens of micromolar | No |

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| Pieulle et al., (2005) [52] | <i>Desulfovibrio alaskensis</i> Type I and II cytochrome <i>c</i> ₃ (2BQ4 and 3CAO); <i>Desulfovibrio vulgaris</i> Type I and II cytochrome <i>c</i> ₃ (2CTH and a homology model) | Type I and II cytochrome <i>c</i> ₃ from <i>Desulfovibrio alaskensis</i> and <i>D. vulgaris</i> | BiGGER, Analytical Ultracentrifugation, Isothermal Calorimetry, Cross-linking | 2005 | No | Yes | Transient | Analytical Ultracentrifugation, Isothermal Calorimetry, cross-linking | very low micromolar | Yes, MODELLER 6.0 for type II cytochrome <i>c</i> ₃ from <i>D. vulgaris</i> |
| Poletto et al., (2008) [53] | Human CK2 (1JWH) | Human CK2, one peptide | BiGGER, Phosphorilation assays, ZDOCK, GRAMM, Escher | 2008 | No | Comparison between Docking algorithms | N/A | Phosphorylation, other docking algorithms | Km values only | Yes, energy of best complex minimized using AMBER99 |
| Rajalingam 2005 [54] | Human fibroblast growth factor and amlexanox | Human FGF-1and antibiotic amlexanox | BiGGER, ITC, NMR, Turbidometry | 2005 | No | Yes, NMR | Transient | Turbidometry, NMR, ITC | 80 μM | Yes, energy of best complex minimized using AMBER99 |
| Raychaudhuri et al., (2010) [55] | N/A | cytochrome <i>c</i> , neuroglobin | BiGGER, PCR, Western, Flow cytometry | 2010 | No | No | Transient | Flow cytometry, Western, PCR | tens of micromolar | N/A |
| Ribeiro Jr. et al., (2009) [56] | Phosphoprotein P (1VYI) and N ₁₁ -RNA complex (2GTT) | Phosphoprotein P and Nucleoprotein N from rabies virus | BiGGER, SPR, SAXS, SANS | 2009 | No | No | Strong | SPR, SAXS, SANS | 160 nM | Yes, with LOBO, SYMMDOCK, EMPIRE |
| Rudolph et al., (2007) [57] | Human YjeF_N model (from 1JZT), human apolipoprotein A1 (1AV1) | Human AI-BP and its homologues hYjeF_N2-15q23 and hYjeF_N3-19p13.11; Apolipoprotein A1 | BiGGER, PCR, Northern Blotting, Western Blotting, Immunocytochemistry | 2007 | No | No | N/A | PCR, Northern Blotting, Western Blotting, Immunocytochemistry | N/A | Yes, using Permols v. 1.01 and Modeller v 6.2 |
| Saglietti et al., (2007) [58] | Human Glutamate Receptor Glu R2 (modeled from 1EWK, 1JDP, and 1DP4) | Human Glutamate Receptor GluR2-N Terminal Domain and N-Cadherin-Ecto | BiGGER, Immunocytochemical assays (varied) | 2007 | Constraint to AA 14-92 | Yes | N/A | Immunocytochemistry | N/A | Yes, with mGenthreader Modeller, Verify3D, SWISSMODEL |
| Skommer and Brittain (2012) [59] | Human cytochrome <i>c</i> (1HRC) and neuroglobin (1OJ6) | Human cytochrome <i>c</i> and neuroglobin | BiGGER, <i>in silico</i> and site-directed mutagenesis, RT-PCR, Flow Cytometry | 2012 | No | Yes, Fe-Fe distance | N/A | <i>in silico</i> and site-directed mutagenesis, RT-PCR, Flow Cytometry | N/A | Yes, <i>in silico</i> mutations on neuroglobin using YASARA and energy minimization using the AMBER99 force field |
| Spies and Kowalczykowski (2006) [60] | <i>Escherichia coli</i> RecA (2REB) and RecB (1W36) | <i>E. coli</i> RecA and RecB ^{nuc} | BiGGER, Ni-NTA Magnetic beads | 2007 | No | Comparison with crystal of larger hetero-mer | Transient to Moderate | Ni-NTA Magnetic Beads | 1 micromolar | Yes |

| | | | | | | | | | | |
|--------------------------------|---|---|--|------|---|--|---------------|--|---------------------|---|
| Srinivasan et al., (2004) [61] | Mouse CD80 model (Templates: 1DR9, 1NCN, 118L and 1I85); Mouse CD152 model (from 1DQT, 1AH1) | Mouse CD80 + CD80-CAP | BiGGER, Proliferation assays, Circular Dichroism, ELISA | 2004 | No | TOP 100 superimposed on known structure | Strong | Circular Dichroism, ELISA, Proliferation Assays | N/A | Yes, using Geno3D. Energy minimization using GRAMMOS |
| Winkler et al., (2009) [62] | N/A | <i>Chlamydomonas reinhardtii</i> FeFe hydrogenase HydA1 and Photosynthetic ferredoxin PetF | BiGGER, Steady State Kinetics, Site-directed mutagenesis | 2009 | No | Cluster to cluster distance, electrostatics, mutagenesis studies | Electrostatic | Steady State Kinetics, Site-directed mutagenesis | N/A | Yes, using SWISSMODEL |
| Worrall et al., (2002) [63] | Horse myoglobin (1HMB), Bovine cytochrome <i>b</i> ₅ (1EHB) | Horse heart Myoglobin and bovine cytochrome <i>b</i> ₅ | BiGGER, NMR (Titration and Relaxation) | 2002 | Residues with highest chemical shift perturbations within 5 Å of target | No | Transient | NMR | Micromolar range | No |
| Xu et al., (2009) [64] | <i>Synechocystis</i> sp. PCC 6803 Ferredoxin:Thioredoxin Reductase (1DJ7) and Thioredoxin (1FB6) | <i>Synechocystis</i> sp. PCC 6803 Ferredoxin:Thioredoxin Reductase, Thioredoxin | BiGGER, NMR, HADDOCK | 2009 | Paramagnetic restraints divide residues into three classes of interaction | No | Transient | NMR, HADDOCK | N/A | No |
| Yabukarski et al., (2016) [65] | Vesicular Stomatitis Virus Nucleocapsid protein N and viral phosphoprotein P and several deletion mutants of each (taken from 3PMK, 3HHZ) | Vesicular Stomatitis Virus Nucleocapsid protein N and viral phosphoprotein P and several deletion mutants of each | BiGGER, Size-exclusion chromatography coupled with MALLS and Refractometry (RI), NMR, SAXS, SANS, Molecular Dynamics Simulations | 2016 | No | Yes, amino acid residue distances | Strong | Size-exclusion chromatography coupled with MALLS and Refractometry (RI), NMR, SAXS, SANS, Molecular Dynamics Simulations | 60 nM (upper limit) | Yes, with Coot |
| Zhu et al., (2004) [66] | Human p23 (1EJF) and ATP- or ADP-bound Hsp90 (1AM1 and 1BYQ, respectively) | Human Hsp90 and p23 | BiGGER, Genetic Analysis (ET) | 2004 | No | No, but compared to known structures | N/A | Evolutionary genetics | N/A | No |

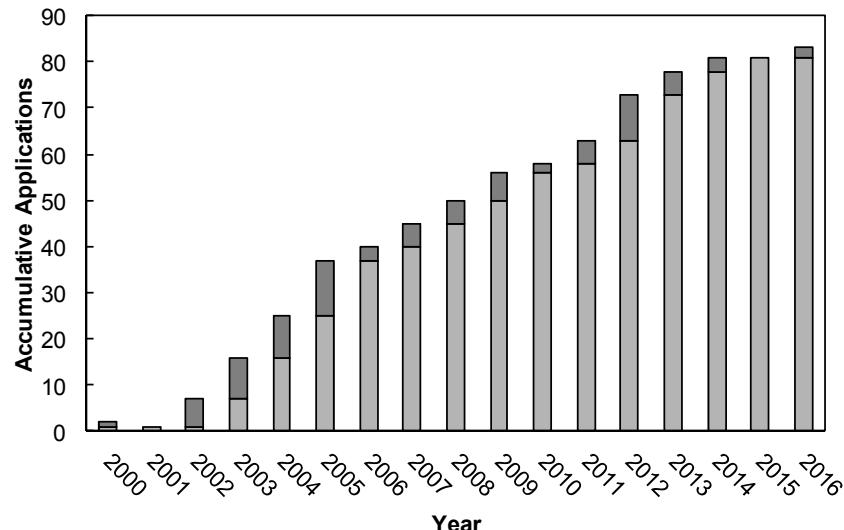


Figure S1. Number of accumulative applications of BiGGER algorithm to predict protein complexes since the year 2000. The light grey segment indicates the number of new applications that have used BiGGER on that year.

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