

LETTERS

Predicting protein structures with a multiplayer online game

Seth Cooper¹, Firas Khatib², Adrien Treuille^{1,3}, Janos Barbero¹, Jeehyung Lee³, Michael Beenen¹, Andrew Leaver-Fay^{2,†}, David Baker^{2,4}, Zoran Popović¹ & Foldit players

People exert large amounts of problem-solving effort playing computer games. Simple image- and text-recognition tasks have been successfully ‘crowd-sourced’ through games^{1–3}, but it is not clear if more complex scientific problems can be solved with human-directed computing. Protein structure prediction is one such problem: locating the biologically relevant native conformation of a protein is a formidable computational challenge given the very large size of the search space. Here we describe Foldit, a multiplayer online game that engages non-scientists in solving hard prediction problems. Foldit players interact with protein structures using direct manipulation tools and user-friendly versions of algorithms from the Rosetta structure prediction methodology⁴, while they compete and collaborate to optimize the computed energy. We show that top-ranked Foldit players excel at solving challenging structure refinement problems in

retaining the deterministic Rosetta algorithms as user tools. We developed a multiplayer online game, Foldit, with the goal of producing accurate protein structure models through gameplay (Fig. 1). Improperly folded protein conformations are posted online as puzzles for a fixed amount of time, during which players interactively reshape them in the direction they believe will lead to the highest score (the negative of the Rosetta energy). The player’s current status is shown, along with a leader board of other players, and groups of players working together, competing in the same puzzle (Fig. 1, arrows 8 and 9). To make the game approachable by players with no scientific training, many technical terms are replaced by terms in more common usage. We remove protein elements that hinder structural problem solving, and highlight energetically frustrated areas of the protein where the player can probably improve the structure (Fig. 1, arrows 1–5). Side chains are coloured by hydrophobicity

In a Video Game, Tackling the Complexities of Protein Folding

By JOHN MARKOFF

Published: August 4, 2010


Gamers, 1; computer, 0.


RSS Feed

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In a match that pitted video game players against the best known computer program designed for the task, the gamers outperformed the software in figuring out how 10 proteins fold into their three-dimensional configurations.


Proteins are essentially biological nano-machines that carry out myriad functions in the body, and biologists have long sought to understand how the long chains of amino acids that make up each protein fold into their specific configurations.

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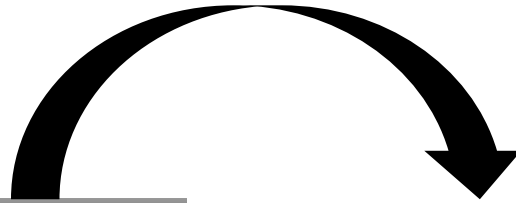
Standalone **foldit**:

A New and Powerful Interface to Rosetta

Matt Smith, Baker Lab

8/4/10

No easy way to combine computational design and human intuition/feedback



MacPyMOL

PyMOL>show sticks, resi 49+206
You clicked /UM_11_X83H49W206_2_1GOO_11_mepar_BPY-D_HIS-A_piStack_1__DE_1_/A/ALA 45/CA
Selector: selection "close_res" defined with 10 atoms.
Setting: seq_view set to on.
You clicked /UM_11_X83H49W206_2_1GOO_11_mepar_BPY-D_HIS-A_piStack_1__DE_1_/A/ASP 172/CA
Selector: selection "sele" defined with 12 atoms.
You clicked /UM_11_X83H49W206_2_1GOO_11_mepar_BPY-D_HIS-A_piStack_1__DE_1_/A/SER 46/CB
Selector: selection "sele" defined with 11 atoms.

PyMOL>

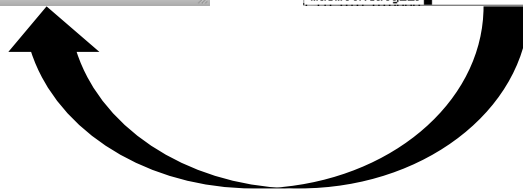
```
/UM_11_X83H49W206_2_1GOO_11_mepar_BPY-D_HIS-A_piStack_1__DE_1_ 81 86 91 96 101 106  
YFDYATDQNRLLTQKMRRIQDFQVTFCSKMHADTEPQGNHFAAGDVLVYMQDQKLRGA BPY LVIRHLNLPASVSSITDKNLTLMKMK
```

Buttons L M R Wheel
& Keys Rota Move Mov2 Slab
SHFT +Box -Box Clip MovS
Ctrl +/- PKRt PKL NvS2
CtSh Sele Orig Clip MovZ
SnglClk +/- Cent Menu
+DelClk Menu - PKRt
Selecting Residues
State 1/ 1

Default (118,35)

```
1d5mA.checkpoint 1d5mA.sam_ebghtl PROF27965trace.tmp  
median_energy_vs_rms.txt psitmp.mn sstmp.ascii  
1d5mA.coords 1d5mA.sam_log aaid5m603_05_200_v1_3  
out.logbf_no_cst psitmp.pn sstmp.chk  
1d5mA.fasta 1d5mA.samscrip.txt aaid5m609_05_200_v1_3  
out.logbf_no_cst3 psitmp.sn sstmp.mtx  
1d5mA.jufo_ss 1d5mA.target2k.a2m command  
output/ rosetta_native.log status.200_v1_3_aaid5mA  
1d5mA.pdb 1d5mA.target2k.cst jufo.input  
output2/ sam_tmp/ status.200_v1_4_aaid5mA  
1d5mA.prof_rdb 1d5mA.uniqueseq.a2m loaid5m.fasc  
output3/ si.cluster_stats tmp0.452092.out  
1d5mA.psipred 1d5mA_CA_107-113_421-442_des1_0001.pdb loopfile  
output4/ si.combo.ps tmp0.651547.align  
1d5mA.psipred_ss2 HSSPFIL-28046.tmp loopfile  
paths.txt si.cst
```

```
mdsmith@dig11>ls  
UM_12_X180H45Y125_1_1f5j_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_9.pdb UM_16_X69H80Y35_5_1bvv_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_16.pdb UM_8_X77H88W98_1_1yna_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_16.pdb  
UM_13_X297H119W156_1_1eix_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_1.pdb UM_5_X356H355F165_1_1E2R_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_11.pdb UM_8_X77H88W98_1_1yna_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_22.pdb  
UM_16_X105H125Y137_2_1h0b_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_1.pdb UM_62_X128H105W180_1_1gbg_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_11.pdb UM_8_X77H88W98_1_1yna_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_23.pdb  
UM_16_X105H125Y137_2_1h0b_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_7.pdb UM_8_X77H88W98_1_1yna_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_1.pdb UM_8_X77H88W98_1_1yna_11_mepar_BPY-D_HIS-A_piStack_1__DE_1__DE_17.pdb  
mdsmith@dig11>vi UM_8_X77H88W98_1_1yna_11_mepar_BPY-A_HIS-A_piStack_1__DE_1__DE_1  
mdsmith@dig11>vi UM_8_X77H88W98_1_1yna_11_mepar_BPY-A_HIS-A_piStack_1__DE_1__DE_1  
UM_8_X77H88W98_1_1yna_11_mepar_BPY-A_HIS-A_piStack_1__DE_1__DE_1.pdb UM_8_X77H88W98_1_1yna_11_mepar_BPY-A_HIS-A_piStack_1__DE_1__DE_17.pdb  
mdsmith@dig11>vi UM_8_X77H88W98_1_1yna_11_mepar_BPY-A_HIS-A_piStack_1__DE_1__DE_1.pdb  
(reverse-i-search) 'linu': ~orange/bin/killall_ssh match.static.linuxicrelease  
(reverse-i-search) 'enzdes': vi mini/test/integration/tests/enzdes/inputs/D2N_ax_confs.pdb  
mdsmith@dig11>
```



foldit is an interactive visual interface to Rosetta

Pull Mode

Rank: 117 Score: ~~1288~~ 1288
Soloist 346: CASP9 Refinement Puzzle 5
▶ No trophies, 2 constraints met

Group Competition

#	Group Name	Score
1	Richard Dawkins Foundation	10337
2	Russian Team	10284
3	Void Crushers	10258
4	Contenders	10240
5	SETI.Germany	10164
6	L'Alliance Francophone	10104
7	Anthropic Dreams	10102

Soloist Competition

#	Player Name	Current	Best
1	vertex	-	10336
2	mat747	10253	10258
3	spvincent	-	10239
4	HillObserver	-	10223
5	BootsMcGraw	-	10214
6	ice-9	9034	10175
7	ao	-	10166

Actions ▶ Undo ▶ Social ▶ Modes ▶ Behavior ▶ View ▶ Menu

- Shake Sidechains
- Mutate Sidechains
- Wiggle All
- Wiggle Backbone
- Wiggle Sidechains
- Help
- Glossary
- Freeze Protein
- Remove Bands
- Disable Bands
- Align Guide
- Show Alignment
- Reset Structures
- Reset Puzzle

▶ Chat - Group (i) ✕ auto show
▶ Chat - Puzzle (i) ✕ auto show
▶ Chat - Global (i) ✕ auto show
▶ Notifications (i) ✕ auto show

Can it be a design tool as well?

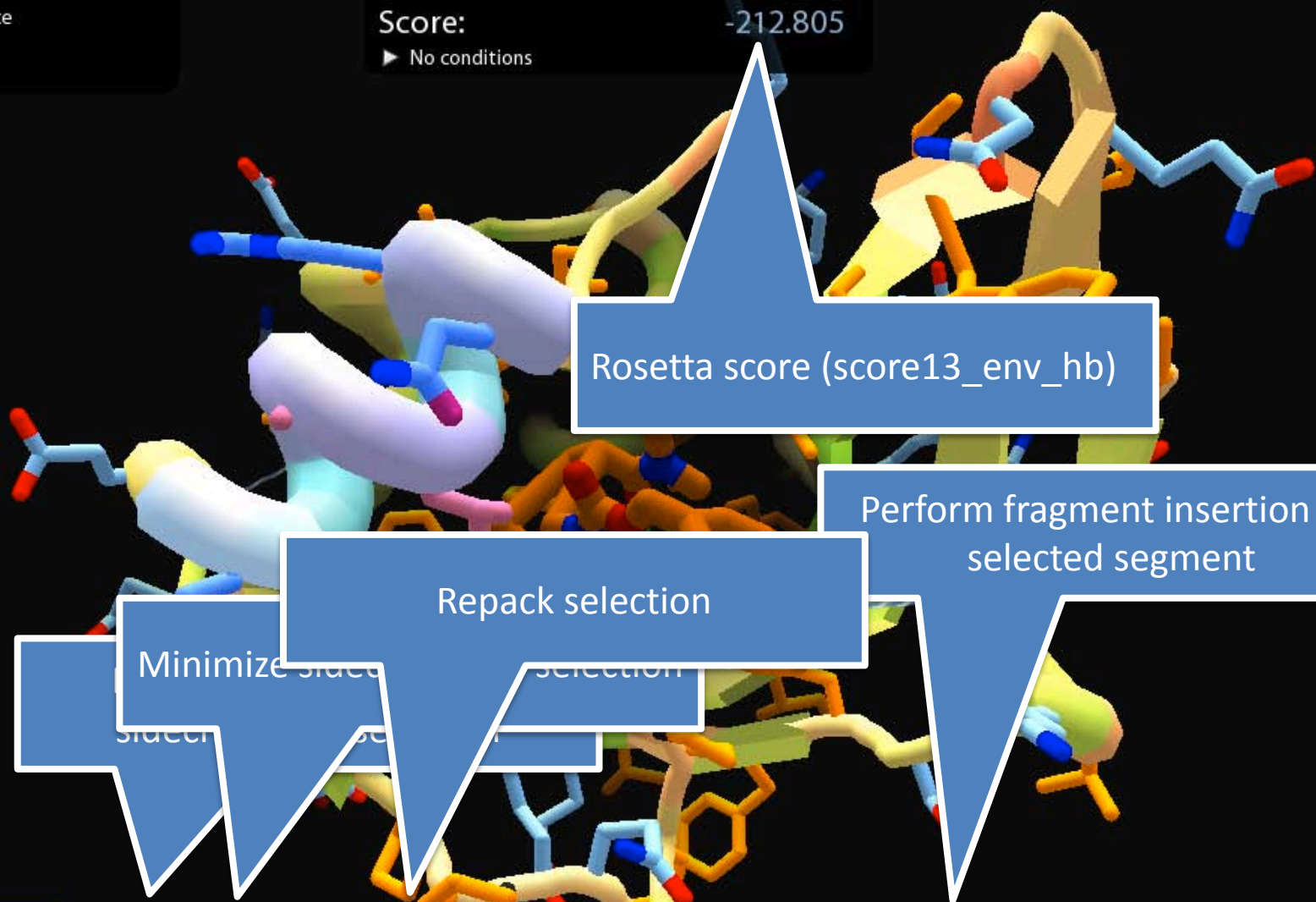
Selection Interface

Selected 8 residues

Score:

-212.805

▶ No conditions

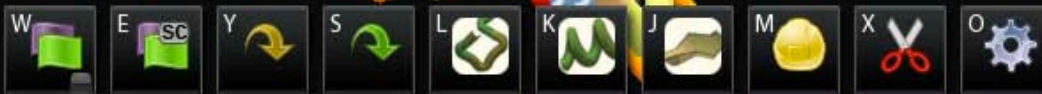


Rosetta score (score13_env_hb)

Perform fragment insertion on selected segment

Repack selection

Minimize selection



58 LYS

58: Lysine

Originally:
Glutamine
PDB#: A 58

Score: -2.088

Clashing: 0.171
- fa_rep: 0.168
- fa_intra_rep: 0.003

Packing: -2.165
- fa_atr: -2.165
- fa_atr: -2.000

Notes:

Detailed score information about residue



Detailed score information about ligand

124 X00

124:
PDB#: B 124
Score: 0.605
Clashing: 3.053
- fa_rep:2.990
- fa_intra_rep:0.063
Packing: -8.002
- fa_atr:-8.002
Hiding: 4.211
- fa_sol:4.211
Notes:

H-bond don: 47 HIS H acc: 51 GLN OE1 dist: 2.91 score: -1.544
X-C=O-H Dihedral -80.17 greater than 60 degrees from planar
C=O-H angle 133.48
O-H-N angle 176.05

Color flagging of protein backbone with details of hydrogen bonds

Optimal display of rosette

Optional display of rosette

Display of constraint specified interactions

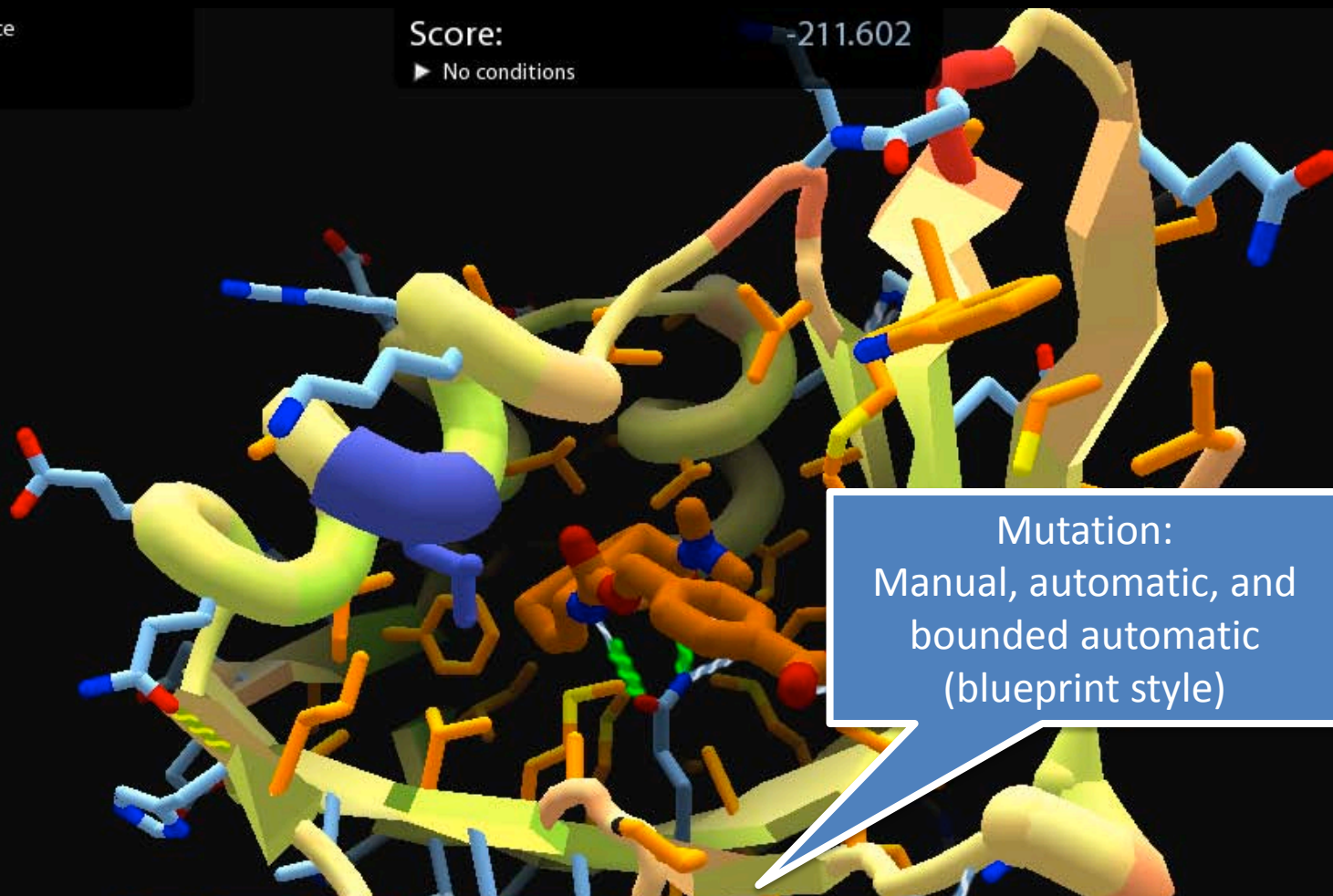
Selection Interface

Selected 1 residues

Score:

-211.602

▶ No conditions



Mutation:
Manual, automatic, and
bounded automatic
(blueprint style)

S SER	T THR	N ASN	Q GLN	R ARG	H HIS	K LYS	D ASP	E GLU	J Apolar	Z Polar	X All	O Original	B Back
V VAL	W TRP	Y TYR	L LEU*	M MET	P PRO	I ILE	A ALA	C CYS	F PHE	G GLY			



Who worked on standalone **foldit**?

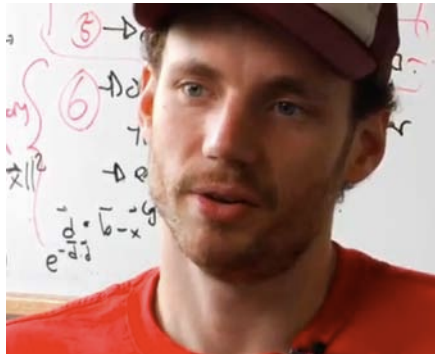
David Kim



Seth

*...and the rest of the **foldit** team*

Cooper



Adrien Treuille



Jeehyung Lee

Example: Evaluating and refining an enzyme design

Input files:

Protein structure from Rosetta

Constraint file

Ligand conformation files

Ligand params file

Minimize and repack

Selection Interface
PHE

Score:

-199.599

▶ No conditions

 **foldit**
Solve Puzzles
for Science [H]

W



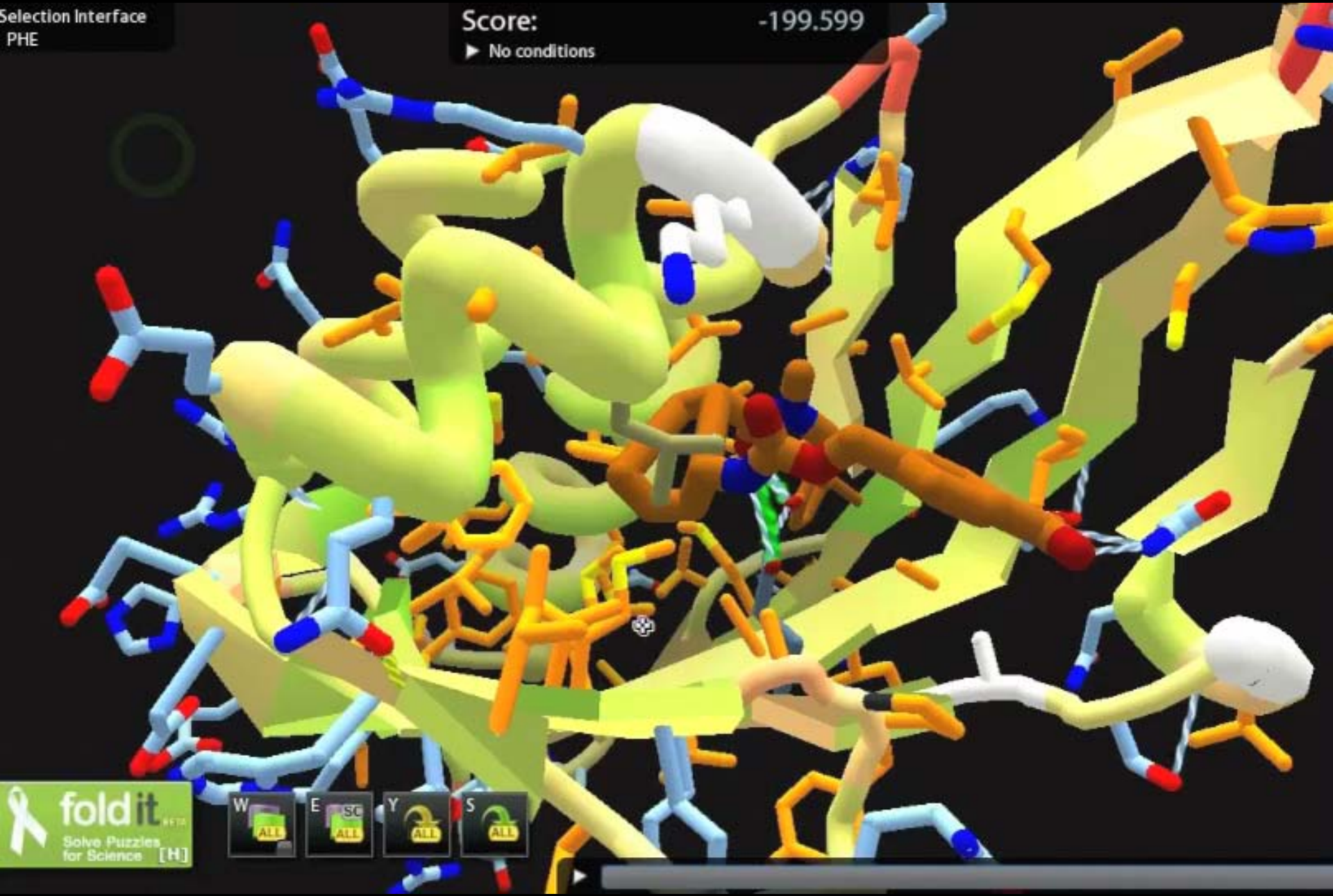
E



Y



S



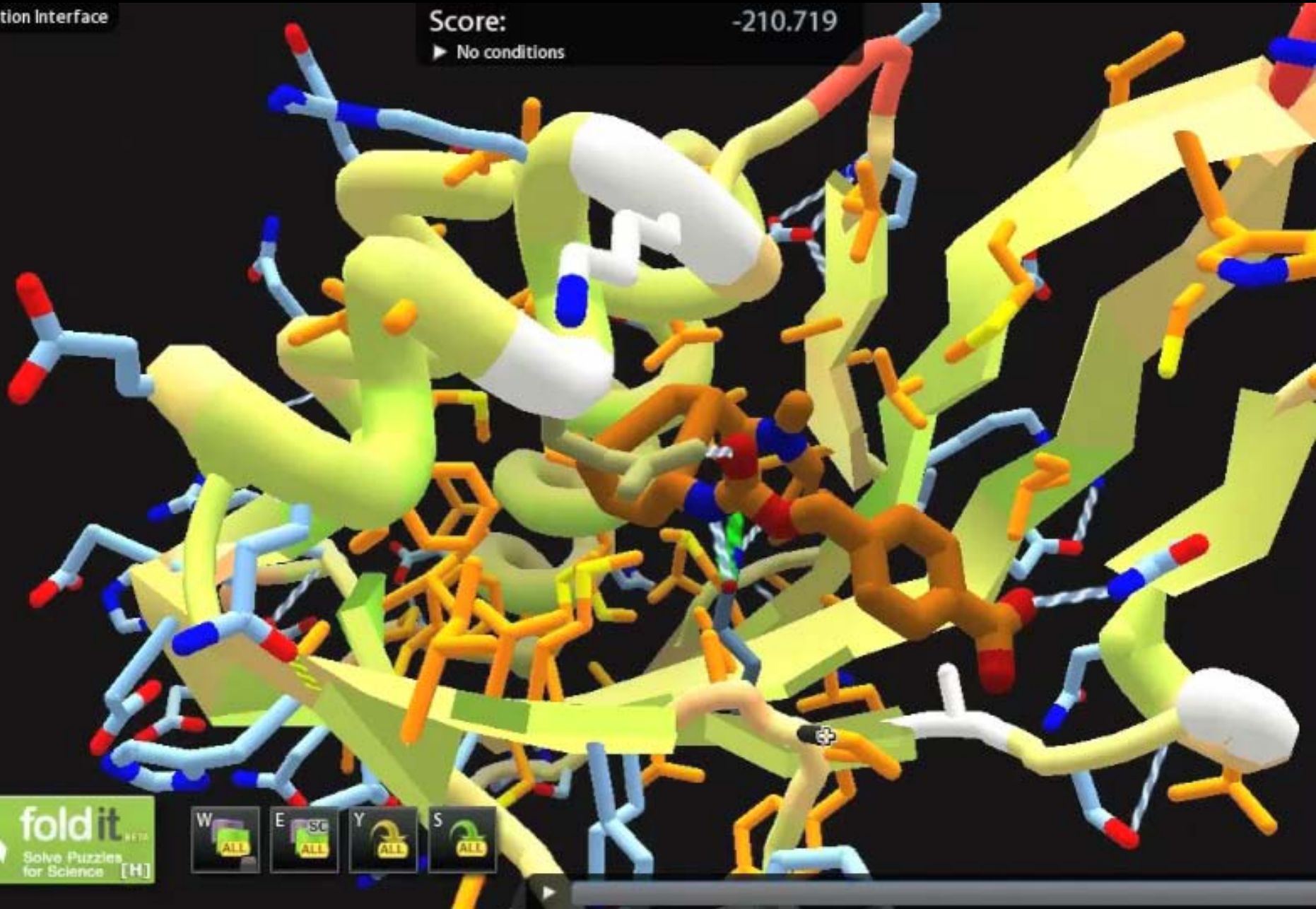
Mutate and Minimize

Selection Interface

Score:

-210.719

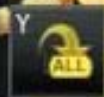
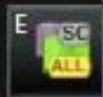
▶ No conditions



Loop Remodel

Selection Interface
TYR

Score: -199.599
▶ No conditions



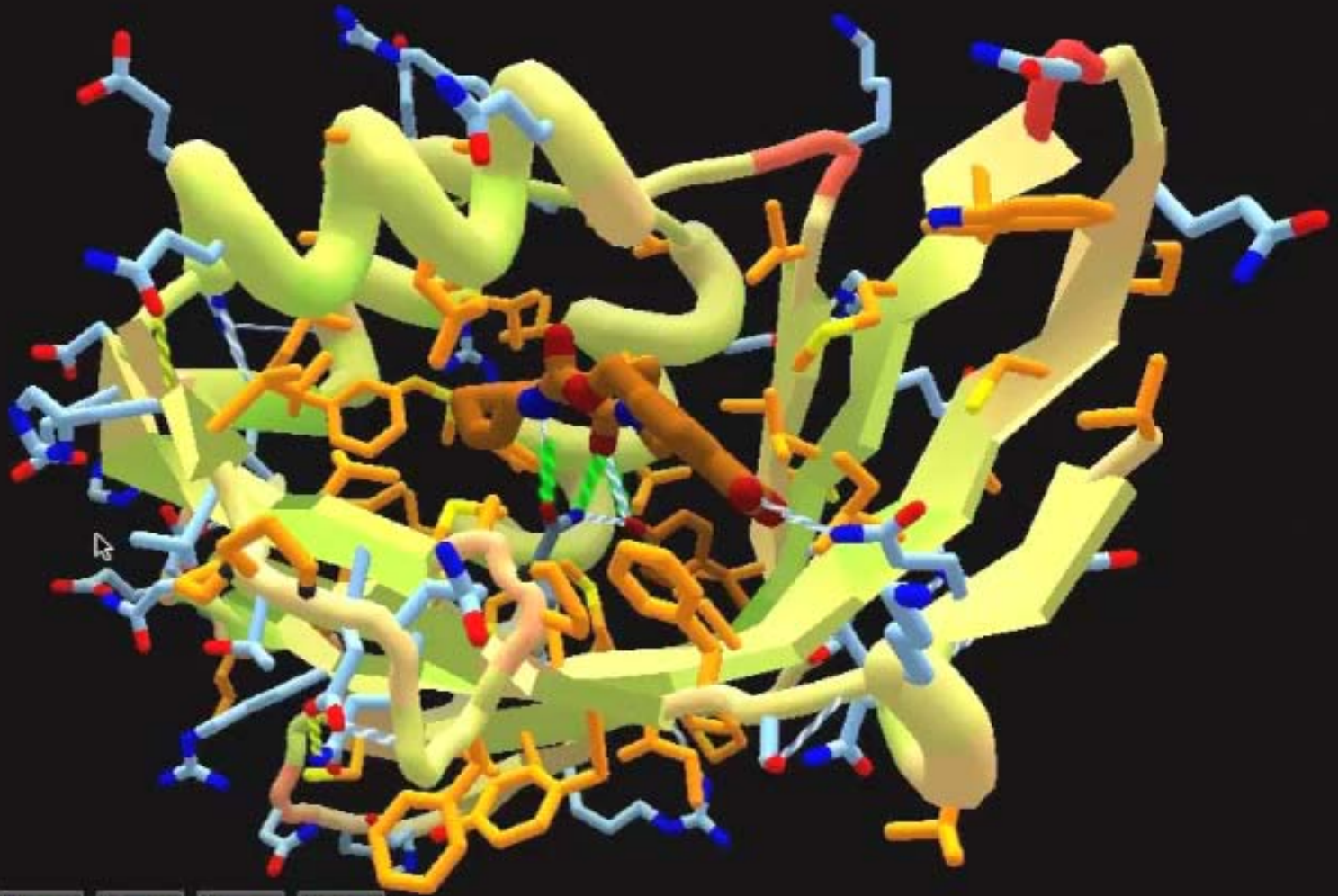
Lua Scripting: Revert Design to Native

Selection Interface

Score:

-199.697

▶ No conditions



Lua Functions

Selection Interface

Score:

-180.272

▶ No conditions

```
void clear()
void info(integer segment_index)
void dock_ligand()
void dock_local_refine()
void dock()
void set_behavior_dash_importance(number importance)
void hide_holes()
void reset_job()
void show_holes()
void load(string file_1[, ..., string file_n])
void load_guide(string file)
void save_pdb(string file)
boolean confirm(string dialog)
void select_all()
void deselect_all()
void do_shake([integer iterations])
void do_mutate([integer iterations])
void do_global_wiggle_all([integer iterations])
void do_global_wiggle_backbone([integer iterations])
void do_global_wiggle_sidechains([integer iterations])
void do_local_rebuild([integer iterations])
void replace_aa(string aa)
void replace_ss(string ss)
void reset_recent_best()
void restore_recent_best()
void restore_abs_best()
string get_aa(integer segment_index_1[, ..., integer segment_index_n])
string get_ss(integer segment_index_1[, ..., integer segment_index_n])
void band_add_segment(integer segment_index_1, integer segment_index_2)
void band_disable(integer band_index_1[, ..., integer band_index_n])
void band_enable(integer band_index_1[, ..., integer band_index_n])
void band_delete(integer band_index_1[, ..., integer band_index_n])
number get_score()
number get_ddg()
number get_segment_score(integer segment_index_1[, ..., integer segment_index_n])
number get_segment_score_part(string score_part, integer segment_index_1[, ..., integer segment_index_n])
integer get_segment_count()
integer get_band_count()
void select_index(integer segment_index_1[, ..., integer segment_index_n])
```

One more thing...



Multiple sequence alignment and threading

Pull Mode

Rank: - Score: 0

Soloist 344: CASP9 Puzzle 36

No bonuses or conditions

Group Competition

# Group Name	Score
Log in for group list.	

Soloist Competition

# Player Name	Current	Best
Log in for player list.		

Alignment

PKPGDLIEIFRP	FYRHWAIYVGDGYVVHLAPPS	EVAGAGAAASVMSALTDKAIVKKELLYD	Score: 178
LRTGDLVLFRA	GSTGRHVGIYIGNNQFVHASTSSG		Type
LAPGDLVFFGT	PVKATHVGLYLGDGCYIHSSGKAQGRD	GIGIDL	Score: 191

Shake Sidechains

Mutate Sidechains

Freeze Protein

Remove Bands

Disable Bands

Align Guide

Show Alignment

Reset Structures

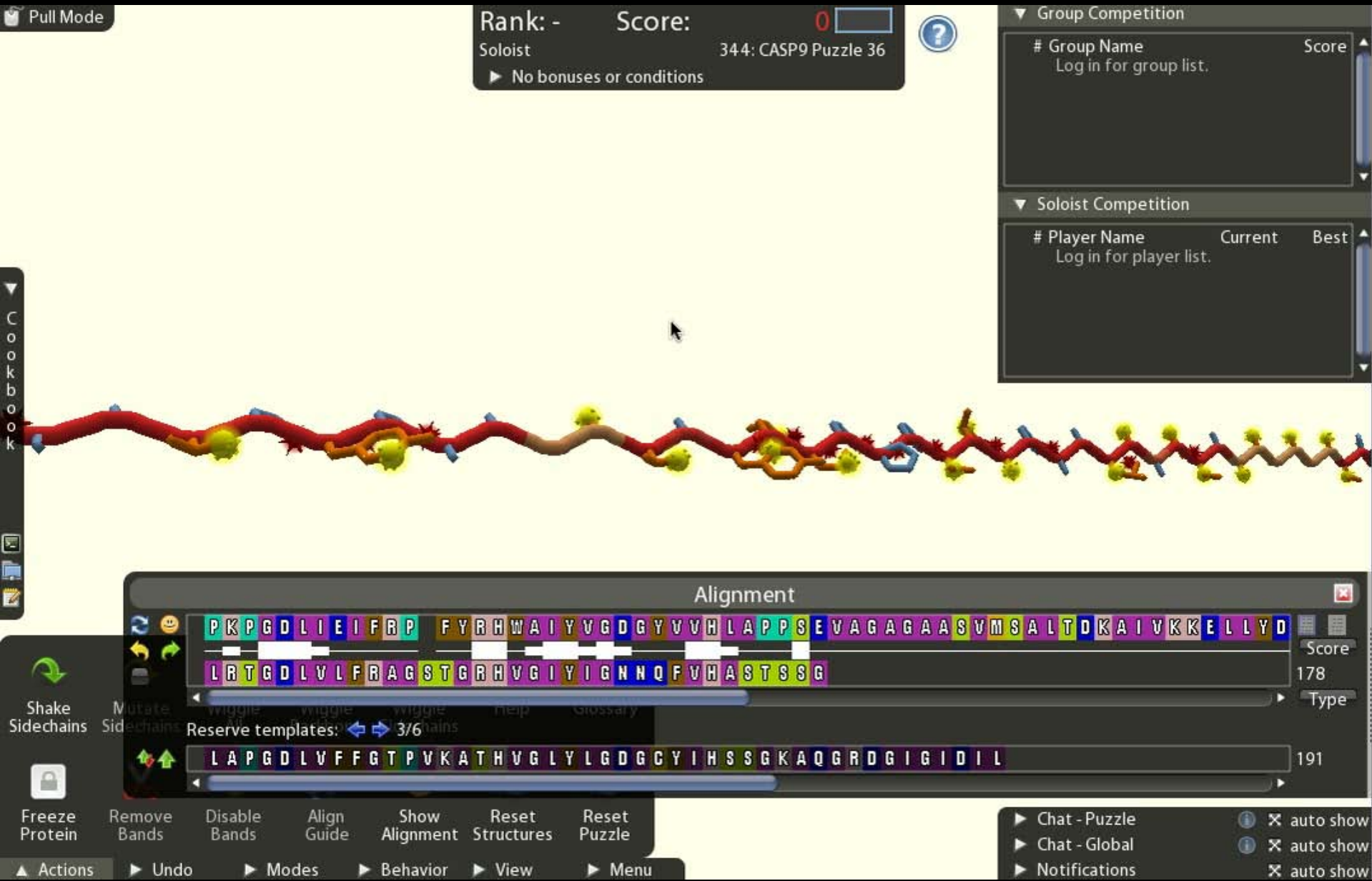
Reset Puzzle

Actions Undo Modes Behavior View Menu

Chat - Puzzle auto show

Chat - Global auto show

Notifications auto show

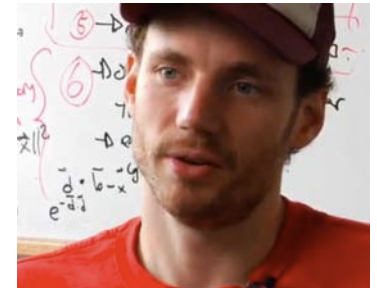


Implemented by...

Conceived of by...



James Thompson



*...and the
rest of the
foldit team*

How to get it

- **foldit** standalone (for mac and pc)

<https://www.rosettacommons.org/internal/standalone-foldit-rosettacommons-users-only/>

- Example files and scripts (and info from this slide) are in 'FolditStandalone' protocol capture

- **foldit** standalone forks in svn
(build for OS X with Xcode)

<https://svn.rosettacommons.org/trac/browser/branches/mini-interactive>

<https://svn.rosettacommons.org/trac/browser/branches/mini-interactive/mini/src/interactive/application/standalone>

Thank you!

- Everyone who made **foldit** what it is
- Standalone **foldit** people: Seth, David Kim, Jee, Adrien
- Presentation help: Justin Siegel, Austin Day, Baker Lab
- Script help: Rocco Moretti