

LETTERS

Predicting protein structures with a multiplayer online game

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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 which substantial backbone rearrangements are necessary to achieve the burial of hydrophobic residues. Players working collaboratively develop a rich assortment of new strategies and algorithms; unlike computational approaches, they explore not only the conformational space but also the space of possible search strategies. The integration of human visual problem-solving and strategy development capabilities with traditional computational algorithms through interactive multiplayer games is a powerful new approach to solving computationally-limited scientific problems.

Although it has been known for over 40 years that the three-dimensional structures of proteins are determined by their amino acid sequences⁵, protein structure prediction remains a largely unsolved problem for all but the smallest protein domains. The state-of-the-art Rosetta structure prediction methodology, for example, is limited primarily by conformational sampling; the native structure almost always has lower energy than any non-native conformation, but the free energy landscape that must be searched is extremely large—even small proteins have on the order of 1,000 degrees of freedom—and rugged due to unfavourable atom–atom repulsion that can dominate the energy even quite close to the native state. To search this landscape, Rosetta uses a combination of stochastic and deterministic algorithms: rebuilding all or a portion of the chain from fragments; random perturbation to a subset of the backbone torsion angles; combinatorial optimization of protein side-chain conformations; gradient-based energy minimization; and energy-dependent acceptance or rejection of structure changes^{6–8}.

We hypothesized that human spatial reasoning could improve both the sampling of conformational space and the determination of when to pursue suboptimal conformations if the stochastic elements of the search were replaced with human decision making while

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 and the backbone is coloured by energy. There are specific visual cues depicting hydrophobicity ('exposed hydrophobics'), interatomic repulsion ('clashes') and cavities ('voids'). The players are given intuitive direct manipulation tools. The most immediate method of interaction is directly pulling on the protein. It is also possible to rotate helices and rewire β-sheet connectivity ('tweak'). Players are able to guide moves by introducing soft constraints ('rubber bands') and fixing degrees of freedom ('freezing') (Fig. 1, arrows 6 and 7). They are also able to change the strength of the repulsion term to allow more freedom of movement. Available automatic moves—combinatorial side-chain rotamer packing ('shake'), gradient-based minimization ('wiggle'), fragment insertion ('rebuild')—are Rosetta optimizations modified to suit direct protein interaction and simplified to run at interactive speeds.

To engage players with no previous exposure to molecular biology, it was essential to introduce these concepts through a series of introductory levels (Supplementary Fig. 1 and Supplementary Table 1): puzzles that are always available, and can be completed by reaching a goal score. These levels teach the game’s tools and visualizations, and certain strategies. We have found the game to be approachable by a wide variety of people, not only those with a scientific background (Supplementary Fig. 2)—in fact, few top-ranked players are professionally involved in biochemistry (Supplementary Fig. 3).

To evaluate players’ abilities to solve structure prediction problems, we posted a series of prediction puzzles. Puzzles in this series were blind, in the sense that neither the target protein nor homologous proteins had structures contained within publicly available databases for the duration of the puzzles. Detailed information for these ten blind structures, including comparisons between the best-scoring Foldit predictions and the best-scoring Rosetta predictions using the rebuild and refine protocol⁷, is given in Table 1. We found that Foldit

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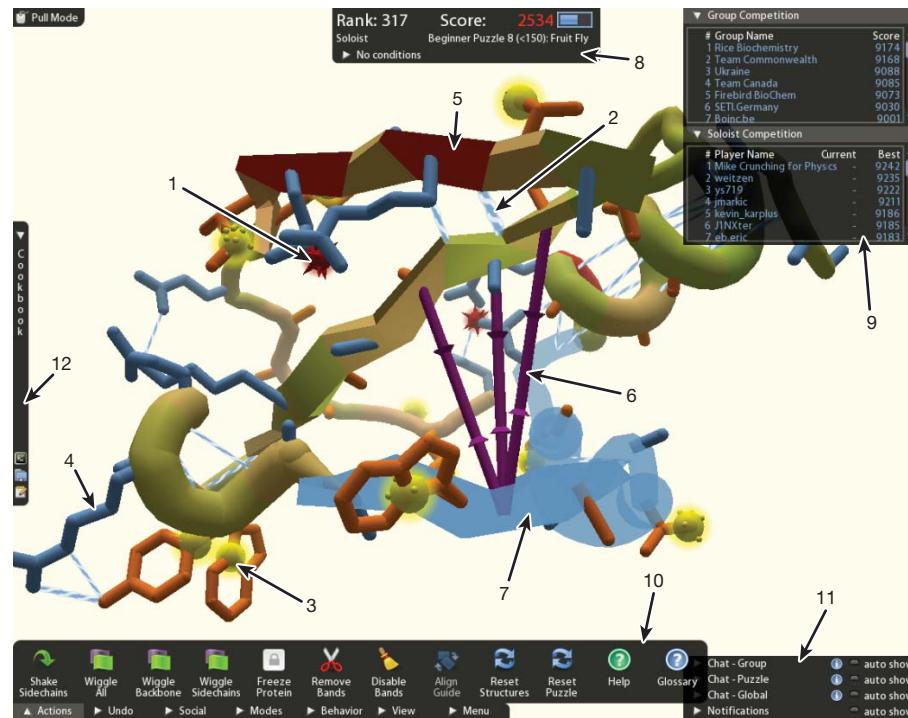


Figure 1 | Foldit screenshot illustrating tools and visualizations. The visualizations include a clash representing atoms that are too close (arrow 1); a hydrogen bond (arrow 2); a hydrophobic side chain with a yellow blob because it is exposed (arrow 3); a hydrophilic side chain (arrow 4); and a segment of the backbone that is red due to high residue energy (arrow 5). The players can make modifications including ‘rubber bands’ (arrow 6), which add constraints to guide automated tools, and freezing (arrow 7), which

players were particularly adept at solving puzzles requiring substantial backbone remodelling to bury exposed hydrophobic residues into the protein core (Fig. 2). When a hydrophobic residue points outwards into solvent, and no corresponding hole within the core is evident, stochastic Monte Carlo trajectories are unlikely to sample the coordinated backbone and side-chain shifts needed to bury the residue properly in the core. By adjusting the backbone to allow the exposed hydrophobic residue to pack properly in the core, players were able to solve these problems in a variety of blind scenarios including a register shift and a remodelled loop (Fig. 2a, b), a rotated helix (Fig. 2c), two remodelled loops (Fig. 2d), and a helix rotation and remodelled loop (Fig. 2e).

Players were also able to restructure β -sheets to improve hydrophobic burial and hydrogen bond quality. Automated methods have difficulty performing major protein restructuring operations to change β -sheet hydrogen-bond patterns, especially once the solution

prevents degrees of freedom from changing. The user interface includes information about the player’s current status, including score (arrow 8); a leader board (arrow 9), which shows the scores of other players and groups; toolbars for accessing tools and options (arrow 10); chat for interacting with other players (arrow 11); and a ‘cookbook’ for making new automated tools or ‘recipes’ (arrow 12).

has settled in a local low-energy basin. Players were able to carry out these restructuring operations in such scenarios as strand swapping (Fig. 3) and register shifting (Fig. 2a). In one strand-swap puzzle, Foldit players were able to get within 1.1 Å of the native structure, with the top-scoring Foldit prediction being 1.4 Å away. A superposition between the starting Foldit puzzle, the top-scoring Foldit solution, and model 1 of the native NMR structure 2kpo (Protein Data Bank) are shown in Fig. 3b. Rosetta’s rebuild and refine protocol, however, was unable to get within 2 Å of the native structure (Fig. 3a, yellow points). This example highlights a key difference between humans and computers. As shown in Fig. 3c, solving the strand-swap problem required substantially unravelling the structure (Fig. 3c, bottom), with a corresponding unfavourable increase in energy (Fig. 3c, top). Players persisted with this reconfiguration despite the energy increase because they correctly recognized that the swap could ultimately lead to lower energies. In contrast, although the Rosetta

Table 1 | Blind data set

Puzzle ID	Foldit C α r.m.s.d.	Rebuild and refine C α r.m.s.d.	Native	Method	Number of residues	Figure(s)
986875	1.4	4.5	2kpo	NMR	99	3a–c, Supplementary 4
986698	1.8	3.7	2kky	NMR	102	3d, e
986836	5.7	6.6	3epu	X-ray	136	2c, Supplementary 6d
987088	3.5	4.3	2kpt	NMR	116	2a, b, Supplementary 6a, b
987162	4.5	5.2	3lur	X-ray	158	Supplementary 6c
987076	3.3	3.5	2kpm	NMR	81	2e, Supplementary 5c
986629	3.5	3.3	2kk1	NMR	135	Supplementary 5b
987145	2.6	2.3	3nuf	X-ray	105	2d, Supplementary 5a
986844	6.9	5.8	2ki0	NMR	36	Supplementary 10a
986961	10.6	5.7	2knr	NMR	118	Supplementary 10b

A listing of all the Foldit puzzles run in the blind data set. A C α r.m.s.d. comparison to the native structure is given between the best-scoring model produced by Foldit players and the best-scoring model produced by the Rosetta rebuild and refine protocol, given the same starting model(s). Solutions considerably better with one method than the other are indicated in bold. The solved structures (which were released after each puzzle ended) are represented by their Protein Data Bank (PDB) codes. Results from these Foldit puzzles can be accessed on the Foldit website by replacing ID with the corresponding Foldit puzzle ID in <http://fold.it/portal/node/ID>. 2kky, 2kpt, 2kpm, 2kk1 and 2knr were taken from the CASD-NMR experiment¹⁰. 2kpo was provided by N. Koga and R. Koga. 2ki0 and 3epu were found by searching for unreleased structures on the PDB website (<http://www.rcsb.org/pdb/search/searchStatus.do>). 3lur and 3nuf were provided by the Joint Center for Structural Genomics (JCSG). The location of figures containing results for each puzzle are provided in the last column.

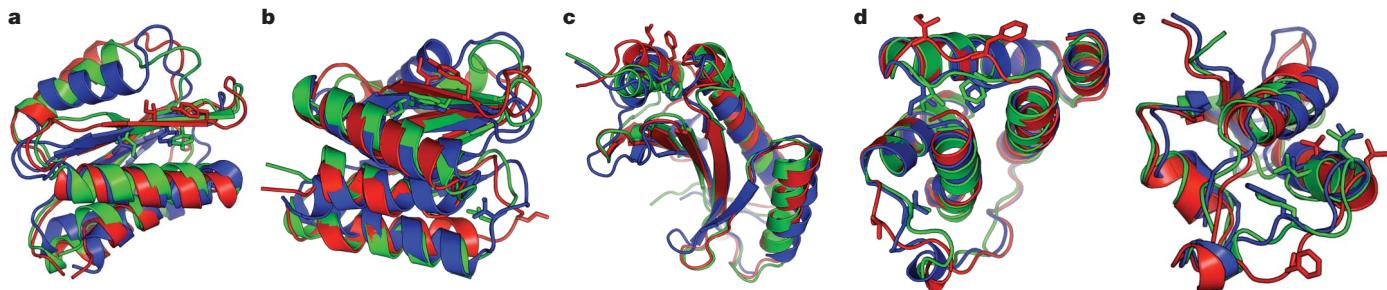


Figure 2 | Structure prediction problems solved by Foldit players.

Examples of blind structure prediction problems in which players were successfully able to improve structures. Native structures are shown in blue, starting puzzles in red, and top-scoring Foldit predictions in green. **a**, The red starting puzzle had a register shift and the top-scoring green Foldit prediction correctly flips and slides the β -strand. **b**, On the same structure as above, Foldit players correctly buried an exposed isoleucine residue in the loop on the bottom right by remodelling the loop backbone. **c**, The

top-scoring Foldit prediction correctly rotated an entire helix that was misplaced in the starting puzzle. **d**, The starting puzzle had an exposed isoleucine and phenylalanine on the top, as well as an exposed valine on the bottom left. The top-scoring Foldit prediction was able to correctly bury these exposed hydrophobic residues. **e**, Another successful Foldit helix rotation along with a remodelled loop that correctly buries an exposed phenylalanine. Images were produced using PyMOL software¹¹.

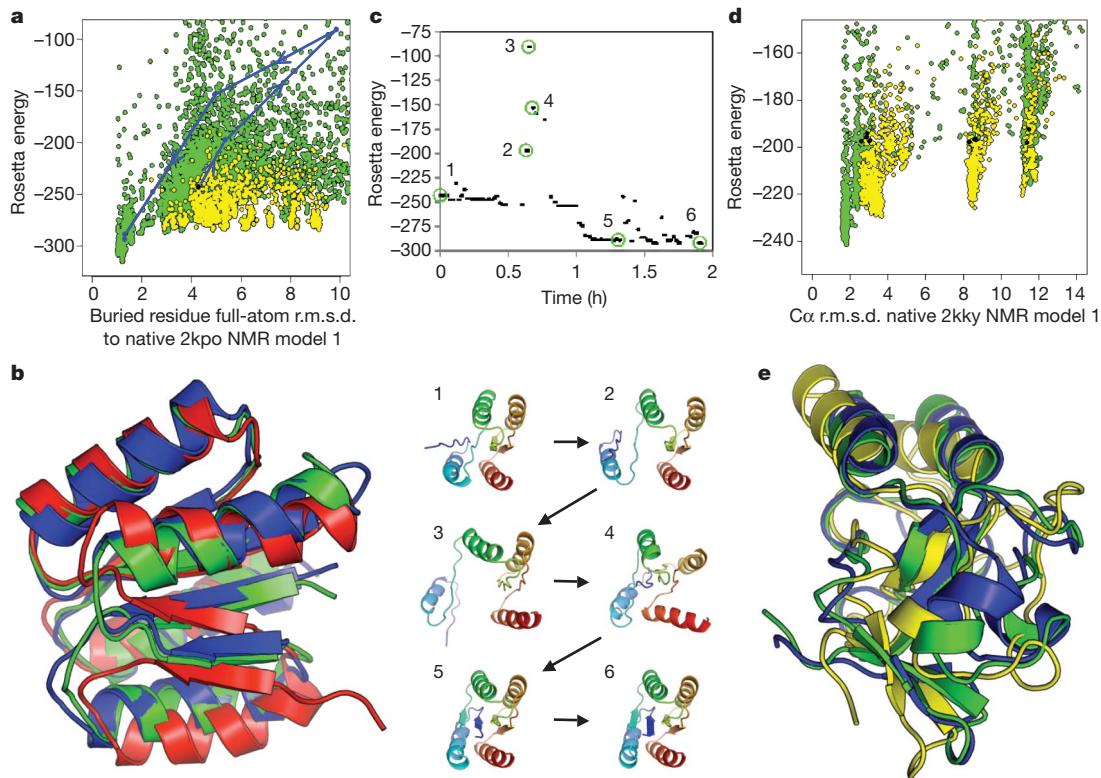


Figure 3 | Puzzles in which human predictors significantly outperformed the Rosetta rebuild and refine protocol. **a–c**, Puzzle 986875. **d, e**, Puzzle 986698. **a**, Comparison of Foldit player solutions (green) to the low-energy structures sampled in Rosetta rebuild and refine trajectories (yellow) for blind Foldit puzzle 986875 based on the recently determined structure of 2kpo. The x axis is the all-atom r.m.s.d. to 2kpo, and the y axis is the Rosetta energy. The starting Foldit puzzle was 4.3 Å away from the native structure (shown by the black dot on the plot); Foldit players sampled many different conformations, with the top-scoring submission (the lowest scoring Rosetta energy) 1.4 Å away from the native structure, whereas the automated Rosetta protocol did not sample below 2 Å. The blue dots and lines correspond to the trajectory of a single Foldit player in **c**. **b**, Superposition of the top-scoring Foldit prediction in green with the experimentally determined NMR model 1 in blue. The starting puzzle is in red, where the terminal strand is incorrectly swapped with its neighbour; 8% of all Foldit players were able to swap these strands correctly (Supplementary Table 2). **c**, A score trajectory with selected structures for the top-scoring player in puzzle 986875 over a 2-h window, showing how the player explores through high-energy conformations to

reach the native state. The y axis shows the Rosetta energy and the x axis the elapsed time in hours. The starting structure had a Rosetta energy of -243 . Each point in the plot represents a solution produced by this player. The first structure (1) is near the starting puzzle structure, shown as the black dot in panel **a**. The following structures (2–6) are shown as blue dots in panel **a**. In structures 2–4, the player must explore higher energies to move the strand into place, shown by the blue lines. In structures 5 and 6, the player refines the strand pairing. **d**, Comparison of Foldit player solutions (green) to the low-energy structures sampled in Rosetta rebuild and refine trajectories (yellow) for blind Foldit puzzle 986698 based on the recently determined structure of 2kky. Foldit players were able to get the best Foldit score by correctly picking from multiple alternative starting Rosetta models (black) the model that was closest to the native structure. **e**, The native structure is shown in blue with the top-scoring Foldit prediction shown in green. The top-scoring Rosetta rebuild and refine prediction given the same ten starting models (shown in yellow) was unable to sample as close to the native structure as the Foldit players.

rebuild and refine protocol did sample some partially swapped conformations (Fig. 3a, leftmost yellow point), these were not retained in subsequent generations owing to their relatively high energies, resulting in the top-scoring Rosetta prediction being further from the native than the starting structure (Supplementary Fig. 5).

Human players are also able to distinguish which starting point will be most useful to them. Figure 3d, e shows a case where players were given ten different Rosetta predictions to choose from. Players were able to identify the model closest to the native structure, and to improve it further. Given the same ten starting models, the Rosetta rebuild and refine protocol was unable to get as close to the native structure as the top-scoring Foldit predictions.

Foldit players performed similarly to the Rosetta rebuild and refine protocol for three of the ten blind puzzles (Supplementary Fig. 6). They outperformed Rosetta on five of the puzzles (Fig. 3 and Supplementary Figs 5 and 7), including the two above cases where players performed significantly better. A larger set of successful solutions for similar, although non-blind, puzzles are described in Supplementary Figs 8–10. For two of the ten blind puzzles, the top-scoring Rosetta rebuild and refine prediction was numerically better than the Foldit solution (Table 1) but still basically incorrect (root mean squared deviation (r.m.s.d.) to native structure $>5.7\text{ \AA}$) (Supplementary Fig. 11).

Despite the promising results described above, there exists room for improvement. For one particularly difficult class of problems, players are only given an extended protein chain to start from. Although the Foldit tools are sufficient to reach the native conformation from this unfolded start (Supplementary Fig. 12), players can have trouble reaching it from so far away (Supplementary Fig. 11a). This indicates the need to find the right balance between humans and computational methods: players guided by visual cues perform better in resolving incorrect features in partially correct models than ‘blank slate’ *de novo* folding of an extended, featureless protein chain.

As interesting as the Foldit predictions themselves is the complexity, variation and creativity of the human search process. Foldit gameplay supports both competition and collaboration between players. For collaboration, players can share structures with their group members, and help each other out with strategies and tips through the game’s chat function, or across the wiki. The competition and collaboration create a large social aspect to the game, which alters the aggregate search progress of Foldit and heightens player motivation. As groups compete for higher rankings and discover new structures, other groups appear to be motivated to play more (Supplementary Fig. 14a), and within groups the exchange of solutions can help other members catch up to the leaders (Supplementary Fig. 14b).

Humans use a much more varied range of exploration methods than computers. Different players use different move sequences, both according to the puzzle type and throughout the duration of a puzzle (Fig. 4a). For example, some players prefer to manually adjust side chains; some will forego large amounts of continuous minimization at the beginning of a puzzle, but increase it as the puzzle progresses; and some prefer a more direct approach and use more rubber bands when the puzzle begins from an extended chain. Within teams, there is often a division of labour: some players specialize in early-stage openings, others in middle- and end-game polishing. Our informal investigation revealed a fascinating array of thought processes, insights and previously unexplored methodologies developed solely through Foldit gameplay (see Supplementary Text, ‘Player Testimonials’ section and Supplementary Table 3 for more information). More in-depth analysis of player strategies should provide further insight into the basis for human achievement with Foldit and could lead to improved automated algorithms for protein structure prediction.

In designing Foldit we sought to maximize both engagement by a wide range of players (a requirement common to all games) and the scientific relevance of the game outcomes (unique to Foldit). We fine-tuned the game through continuous iterative refinement based on observations of player activity and feedback, taking approaches

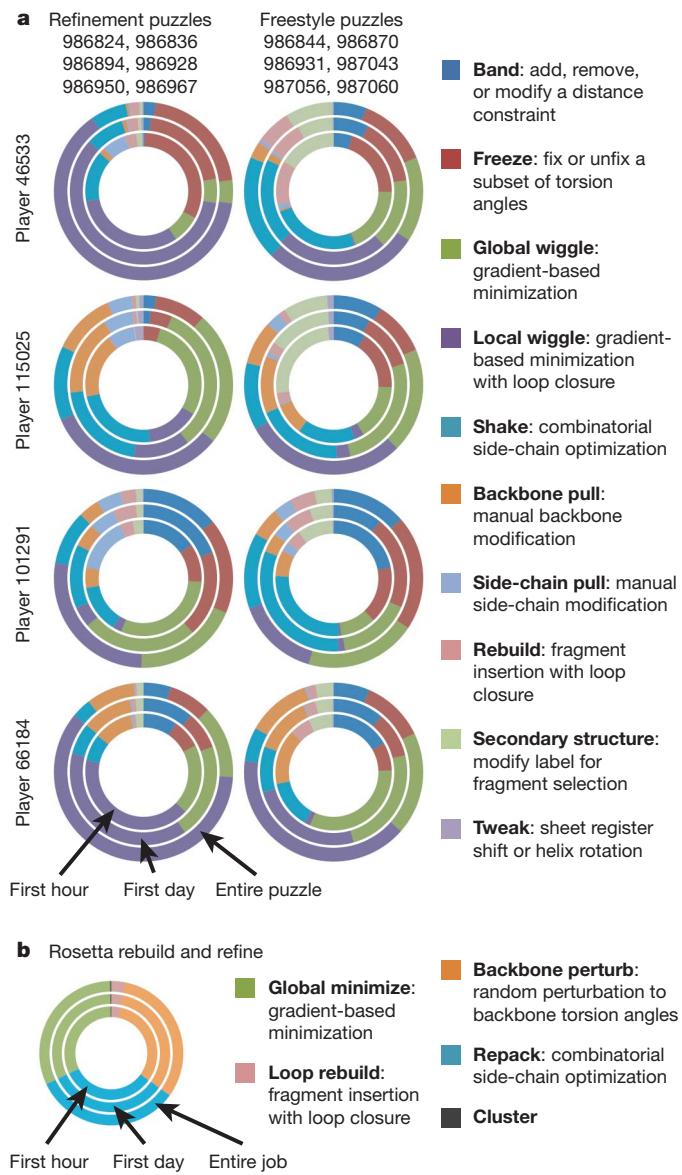


Figure 4 | Player move preferences. **a**, Different Foldit players take different approaches to solving the same problem. Each circle represents the move type frequencies used in the top-scoring solution produced by each player in different time frames: the inner circle denotes the first hour; the middle circle denotes the first day; and the outer circle denotes the puzzle’s entire duration. Each colour represents a different type of move that can be made in the game. The left column reflects player move types for puzzles that start relatively close to the native topology. The right column reflects player move types for puzzles that start from a fully extended conformation. Each row represents a different Foldit player. Each player’s preferred move types across each puzzle class are distinct from one another, yet a player’s preferences are similar for both classes of puzzles. Also note that the move preferences change over the lifetime of a puzzle; local wiggle is heavily preferred by the end of puzzles but not by all players at the beginning. The move type preferences are very different from Rosetta’s current best automated protocol, rebuild and refine, shown in **b**.

from players who did well and making them accessible to all players. Most of the tools available to players today are a product of this refinement. They either did not initially exist or have undergone major revision. The introductory levels were also iteratively tuned to reduce player attrition due to difficulty or lack of engagement. Just as Foldit players gained expertise by playing Foldit, both individually and collectively, the game itself adapted to players’ best practices and skill sets. We suspect that this process of co-adaptation of game and players should be applicable to similar scientific discovery games.

To attract the widest possible audience for the game and encourage prolonged engagement, we designed the game so that the supported motivations and the reward structure are diverse, including short-term rewards (game score), long-term rewards (player status and rank), social praise (chats and forums), the ability to work individually or in a team, and the connection between the game and scientific outcomes. A survey of Foldit players (Supplementary Fig. 4) revealed that although the purpose of contributing to science is a motivating factor for many players, Foldit also attracts players interested in achievement through competition and point accumulation, social interaction through chat and web-based communication, and immersion through engaging gameplay and exploration of protein shapes⁹. We expect generally that future scientific discovery games will also benefit from varied motivation sets.

The solution of challenging structure prediction problems by Foldit players demonstrates the considerable potential of a hybrid human–computer optimization framework in the form of a massively multiplayer game. The approach should be readily extendable to related problems, such as protein design and other scientific domains where human three-dimensional structural problem solving can be used. Our results indicate that scientific advancement is possible if even a small fraction of the energy that goes into playing computer games can be channelled into scientific discovery.

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SUPPLEMENTARY INFORMATION

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Supplementary Text

Quest to the Natives

To verify that the visualizations and tools are sufficient to achieve native conformations, we ran a series of "Quest to the Native" puzzles in which the native conformation is provided as a guide within the puzzle (Figs. S12 and S13). We found that with this information players can use the available tools to consistently reach the native conformation. These puzzles also serve to familiarize players with the structural characteristics of native conformations. Puzzles mentioned in this paper outside of Figs. S12 and S13 did not contain guides.

First strand swap example

Previous to posting the strand swap puzzle shown in Fig. 3a-c, we had come across a Rosetta prediction that had incorrectly swapped two of the beta strands and subsequent calculations were unable to correctly swap them back. We posted this first strand swap puzzle (Fig. S9), expecting it to be a challenging puzzle. Indeed, beginning Foldit players were unable to fix the strand swap and never got within 3 Angstroms of the native solution (cyan in Fig. S9c). We were pleasantly surprised to find that several Foldit players were able to correctly fix the strand swap, with Foldit solutions getting 1.1 Angstroms from the native structure. The top scoring Foldit solution fixed the strand swap perfectly and got 1.3 Angstroms from the native (Fig. S9d).

Since we did not have an introductory level teaching Foldit players how to swap strands, we posted the same Rosetta prediction again as a Quest to the Native puzzle with the native conformation (Fig. S9a) provided as a guide within the puzzle. With this particular Quest to the Native (Fig. S13d) players were able to learn the necessary Foldit tools required to swap strands and most players were able to get close to the native.

Player contribution and expertise

Looking at the set of 208 Foldit puzzles run (mostly non-blind), 95% of the score improvements on most puzzles are done by less than 10 people, the median number being 5 people and the mean 6. However, these players are different from puzzle to puzzle—e.g. there are 72 distinct top players over these puzzles and 262 distinct players counting the top 3. So while no more than perhaps half a thousand people have really driven Foldit (at least in the very restricted sense of improvements to the score), the situation is not that of a handful of experts or savants leading a blind majority. Table S2 gives the percentage of players who were able to successfully restructure select blind Foldit puzzles. The expertise acquired in the game appears to be diversified, instead of concentrated with a few individuals. This is likely related to the significant variation in human strategies that are required to solve different puzzles. We also note that advancement towards the eventual best solution in each puzzle cannot be analyzed just on direct score improvement, as the score does not factor many social aspects of the game. A false direction of one person may provide crucial insight to the eventual advancement of another person. Further formal analysis of collective expertise is required to fully understand this process. In addition, it is not the case that those players with little biochemistry experience are simply improving upon the solutions found by those with biochemistry expertise. In our survey of biochemistry background, we found that the top five responding soloists of all time (players that have reached top solutions without improving upon other players' solutions) have no more than a high school level of biochemistry experience. It is also possible for players with no biochemistry experience to rise through the ranks. A new player with no biochemistry background, who joined in the middle of the blind dataset presented in this paper, has now progressed to be the third place soloist overall.

From the puzzles in this set, the average amount of time spent per player on non-blind prediction puzzles open to all players was roughly 155 minutes. For all Quest to the Native puzzles, that average was 216 minutes, and for blind puzzles, the average was 249. There is also a series of “Beginner” puzzles intended to ease the transition from the introductory levels to the open science puzzles, which only new players are allowed to compete in. The average time per player on these puzzles was 29 minutes. Thus it

would appear that more experienced players spend more time per puzzle, and more time was spent on the blind puzzles than non-blind ones.

In addition, any expertise that these players have developed is through the score function, the Foldit interface, and the aggregate knowledge of the Foldit player community. As we have shown very few of them have a biochemical background. Thus, the process of expertise development in Foldit is radically different from that of traditional biochemical research: it emerged through free-form collective exploration within the game framework, rather than through lectures and book readingⁱ.

One large question that this work has only begun to explore is the formalization of successful human strategies to solve the complex geometric task of protein structure prediction, given a set of tools. This is difficult because the general problem of protein structure prediction, and the specific problem of determining what is wrong with a particular predicted structure, is largely unknown. Furthermore, human strategies and their success appear to stem from their diversity and variability. It is not clear if humans' meta-pattern recognition ability allows them to intuit the answer, even when computational biologists cannot formulate the answer. Quantifying various problems with protein structures is an enormous challenge, one that computational biologists are still struggling with currently. We are in the process of analyzing player approaches and formalizing their variations towards improving current automated methods.

Rewards and ranking types

The reward system in Foldit is set up to reward the absolute best score achieved by a player. However, we are interested in recognizing the efforts of players who work together. Thus we have set up a system to reward players who work alone and together separately.

Within Foldit, players are globally ranked in different categories. Typical puzzles are divided into *soloist* and *evolver* rankings, and a player can only open solutions from other players in their same group. Soloist rankings are based on solutions that only one player has edited. Note that they may be able to look at other solutions and talk to other

players about them, but they have done all the editing to create a particular solution themselves. Evolver rankings are based on solutions that more than one player has edited. When a player opens a solution that has created by another player, they must improve its score by a small amount before they receive credit for it in the evolver rankings.

We have run a small set of puzzles that are set up such that the top solutions at any time are made available for all players to download and open – thus essentially allowing any player to work on improving the best solution. The resulting *all hands* rankings are based on solutions for these specific puzzles, regardless of how many edited a solution. In our preliminary exploration of this approach, we have found that this all hands system typically causes the players' solutions to converge more quickly to regions of the conformation space, rather than explore the space fully.

Foldit also has an achievement system—common in games—to reward players for performing specific discrete actions. These achievements reward a range of actions, including completing introductory levels, sharing solutions with their group, and getting high ranks on multiple puzzles. A player is informed in the game when they meet the requirements for an achievement, and a player's achievements are displayed on their webpage for other players to see.

Other reward schemes would be possible, such as rewarding the players by their relative contributions to solutions, rewarding more for collaboration, or for finding novel regions of conformation space. Further, collaboration and reward structures inspired by non-game contexts, such as open-source projects and the wiki model, could also be very effective. Experimenting with different reward systems and their effects remains an interesting avenue for future research.

Categorization as a game

Although it relies heavily on simulation and visualization, Foldit can be classified as a game, as it possesses the qualities of a game set forth by Schellⁱⁱ. Here we list the qualities and how Foldit embodies each.

1. *Games are entered willfully*: We do not require players to play Foldit.
2. *Games have goals*: Foldit's goal is to find the best scoring structure.
3. *Games have conflict*: Foldit has conflict with both the protein itself, trying to find a better score, and with other players, trying to outrank them.
4. *Games have rules*: The rules of Foldit are given by the scoring function, available moves, global point structure, and so forth.
5. *Games can be won and lost*: Each puzzle has a ranking, which could be broken down into "winners" and "losers".
6. *Games are interactive*: Foldit allows players to interactively reshape a protein and gives them immediate feedback.
7. *Games have challenge*: Similar to conflict, Foldit's challenge arises from achieving higher scores and competing with other players.
8. *Games create their own internal value*: Foldit's global points have value for ranking within the game.
9. *Games engage players*: Foldit keeps players engaged in manipulating protein structures.
10. *Games are closed, formal systems*: Foldit's rules define the pieces of the system and how they work together.

Foldit web URLs

Information about puzzles, players, and groups, can be found on the Foldit website, <http://fold.it>. The URL for a puzzle or group is <http://fold.it/portal/node/ID>, and for a player is <http://fold.it/portal/user/ID>, where **ID** is replaced with the given ID number. Foldit's YouTube channel can be found at <http://www.youtube.com/user/uwfoldit>; <http://www.youtube.com/watch?v=lGYJyur4FUA> gives a good introduction to the game.

Player acknowledgements

We would like to thank all the Foldit players for their hard work and making this project possible! A list of players whose Foldit solutions were used in figures for this paper can be found in Table S4. Strategies and algorithms from selected players are given in the

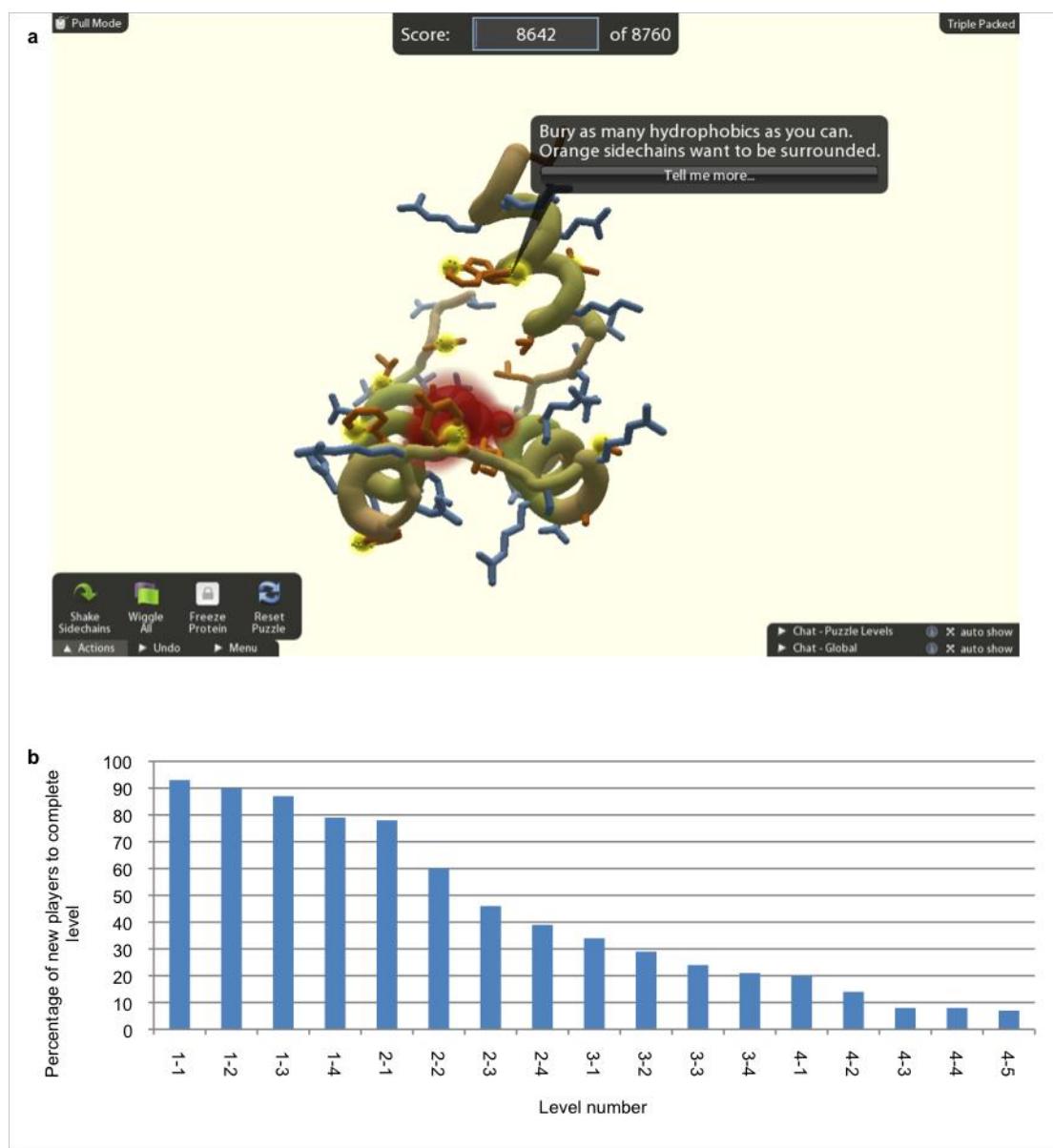
Player Testimonials section. The authors have summarized several player-generated algorithms in Table S3.

Players were able to find out about the game through a variety of means. When Foldit initially launched, announcements were made on the Rosetta@home forums. Foldit also received some publicity from the press at that time, and on occasion since then, which continues to allow new users to discover the game. Talks and word of mouth also help to attract new players.

In the first month after Foldit's launch (5/8/2008 – 6/8/2008), 59% of traffic to the Foldit website was from referring sites, 29% was direct traffic, and 12% was from search engines. In the rest of 2008 (after 6/9/2008), traffic was 41% direct traffic, 34% referring sites, and 25% search engines. The year of 2009, was similar, with 42% direct traffic, 31% referring sites, and 27% search engines.

Supplementary Figures

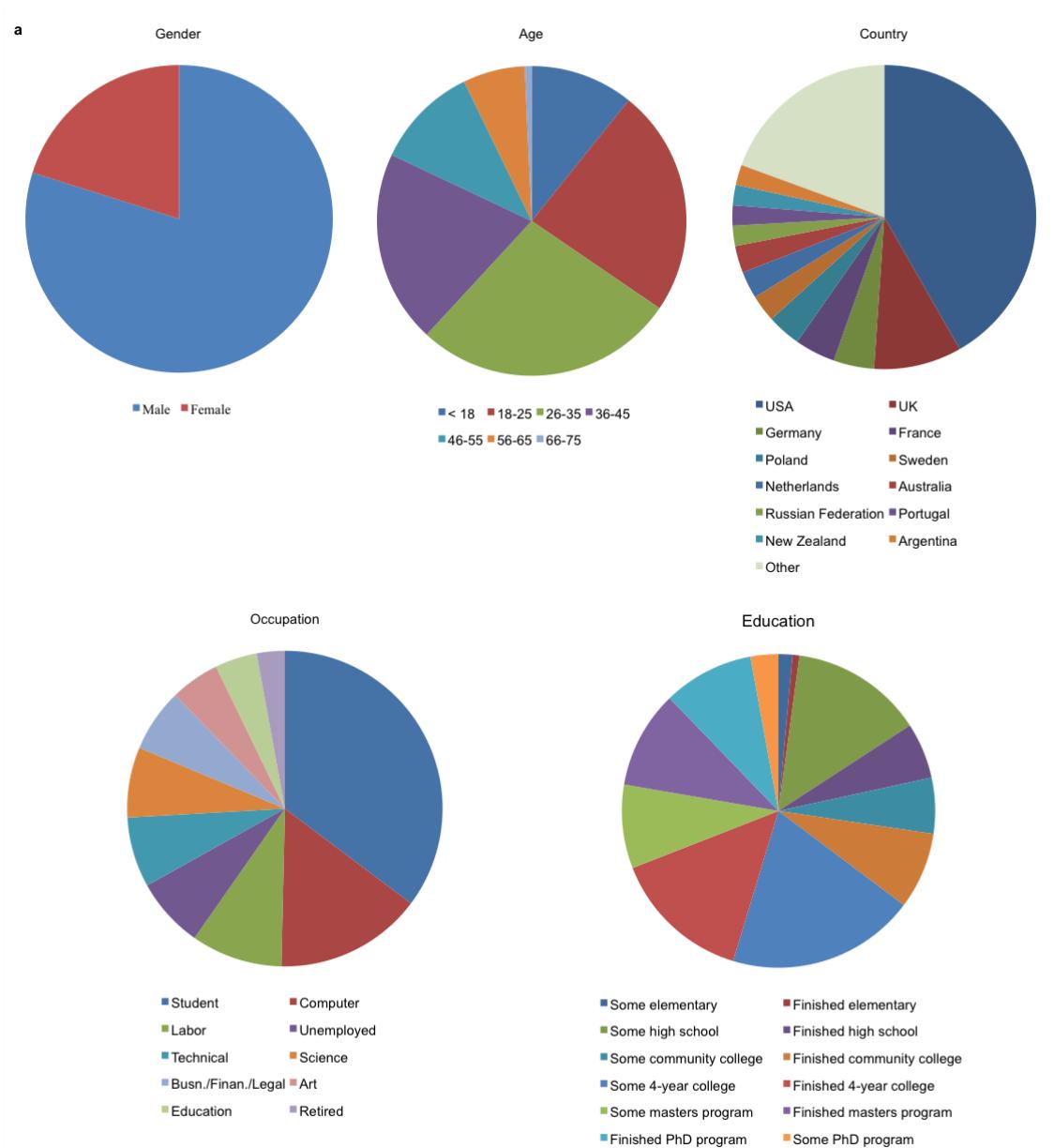
Figure S1: Introductory levels

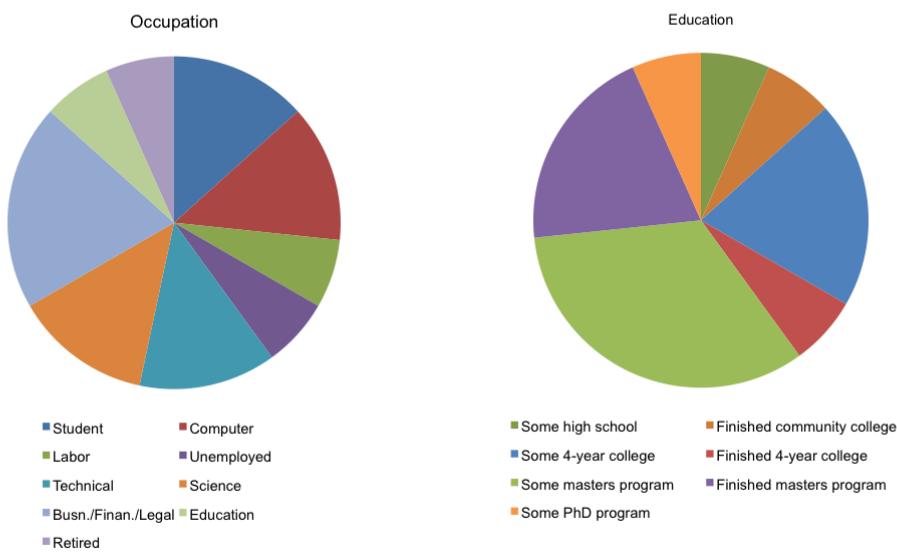
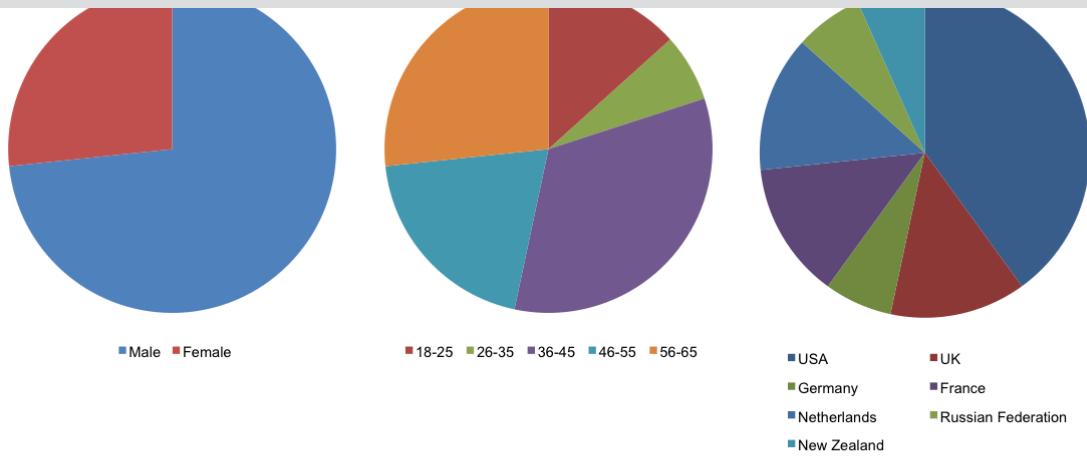


(a) A screenshot of a Foldit introductory level. The levels are designed to teach players the basic concepts of protein folding. Each level is completed once a goal score is reached and the player then moves to the next level. In this level, the player is meant to bury the exposed hydrophobics in the voids that have appeared in the protein's core. Text bubbles appear to guide the player, give hints, and draw their attention to areas of interest.

(b) Completion statistics for each introductory level, accumulated over one week. Each bar shows the percentage of new players who played any level, who also completed the given level. Players do not complete levels due to their difficulty, or because they decide to go directly to the scientific challenge puzzles.

Figure S2: Demographic survey

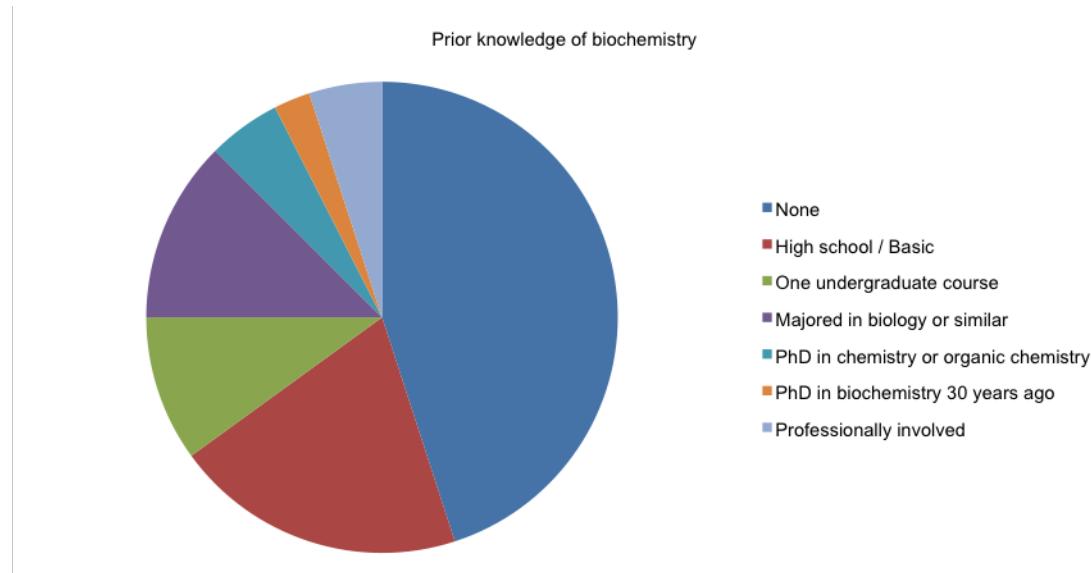




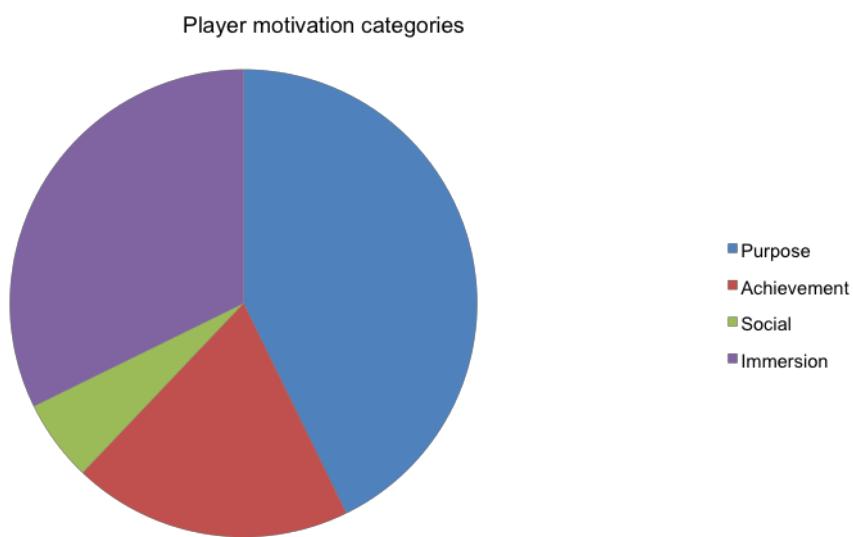
Results of a demographic survey posted on the Foldit website. There were 149 responses, showing the variety of backgrounds Foldit players have.

(a) Results for all responses.

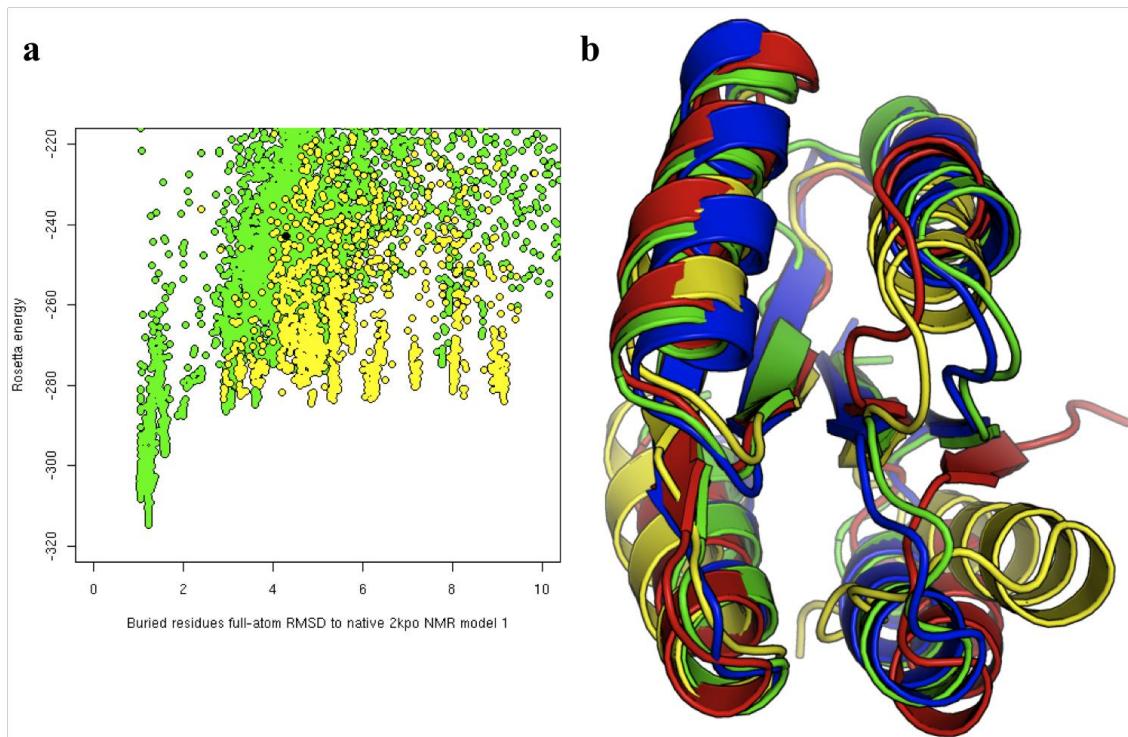
(b) Results for responding player who were in the top 50 soloists or evolvers.

Figure S3: Biochemistry experience survey

Results of an informal email survey asking players about their prior biochemistry knowledge. We emailed the top 20 Foldit players in all categories (soloist, evolver, all hands) asking them if they had any prior biochemistry experience. Most players replied along the lines of “none” or “I took basic chemistry in high school”. Other players replied that they took “one quarter of chemistry as an undergrad” while some players had a “bachelor’s degree in biology”. A minority hold advanced degrees in some form of chemistry or are biochemists in their professions.

Figure S4: Motivation survey

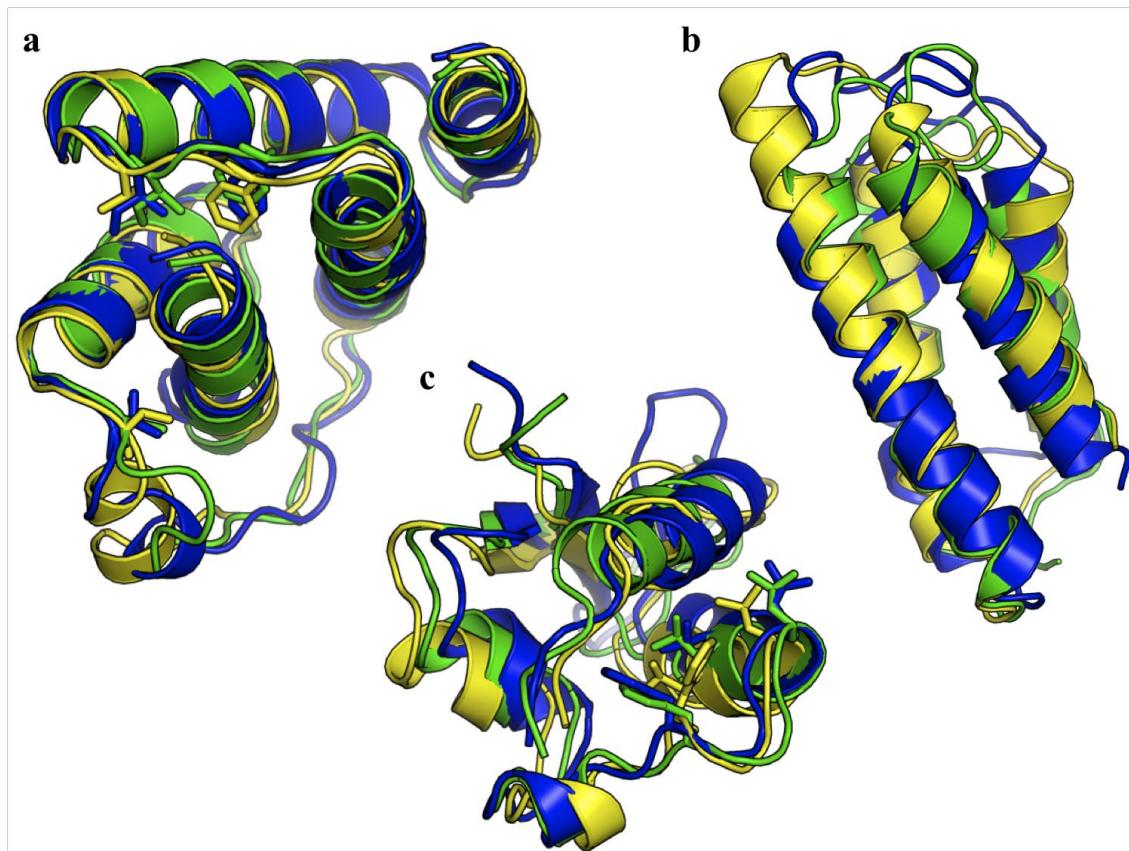
Results of a short informal survey posted on the Foldit website asking players their motivation for playing. 48 players responded with up to 3 reasons each. Responses were categorized based on Yee's main motivation componentsⁱⁱⁱ, with an additional category for motivation related to Foldit's scientific *purpose*. Note that over half of the responses fall outside of the *purpose* category. Example responses for *purpose* include “To crack the protein folding code for science” and “To understand the folding process better”; for *achievement* “To get a higher score than the next player” and “It's fiendishly addictive in a Pavlovian manner (get points, feel good)”; for *social* “The people (community) are great” and “Great camaraderie”; and for *immersion* “It's fun and relaxing” and “I like the visualization of molecules”.

Figure S5: Strand swap case where Foldit players outperform Rosetta (*blind trial*)

Comparing Foldit players to Rosetta rebuild and refine.

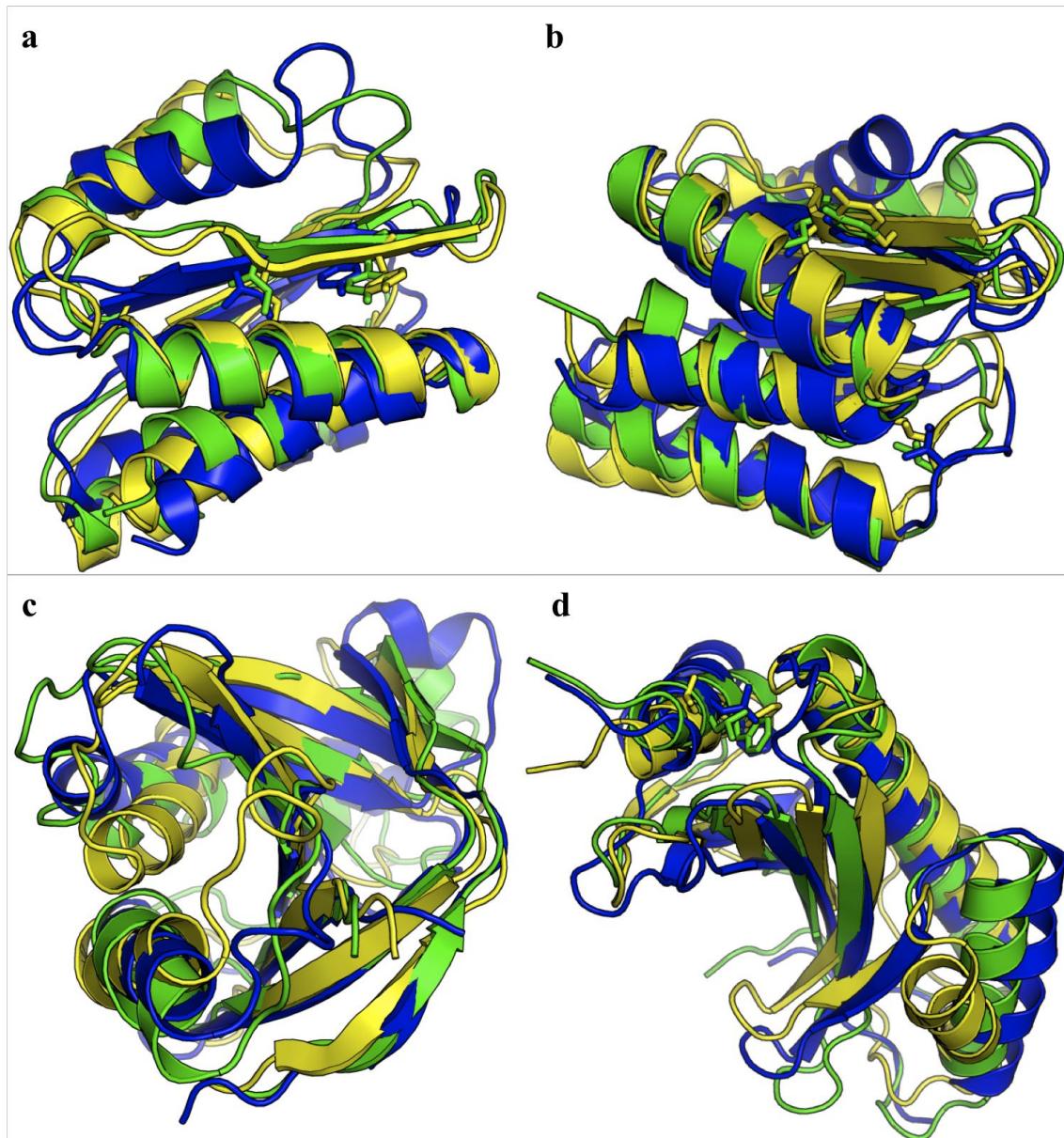
(a) This is a zoomed in version of the full-atom RMSD plot shown in Figure 3a. The starting Foldit puzzle was 4.28 Å away from the native structure (shown by the black dot on the plot). This is a comparison of Foldit player solutions (green) to the low energy structures sampled in Rosetta rebuild and refine trajectories (yellow) for blind Foldit puzzle 986875 based on the recently determined structure and sequence of 2kpo. The best scoring Foldit prediction was 1.4 Å away from the native, while the best scoring Rosetta rebuild and refine prediction was 4.5 Å away.

(b) The native structure is shown in blue with the starting Foldit puzzle in red and the top scoring Foldit prediction shown in green. The best scoring Rosetta rebuild and refine prediction given the same starting model (shown in yellow) was unable to fix the strand swap.

Figure S6: Foldit players performing similarly to Rosetta (*blind trials*)

Comparing Foldit players to Rosetta rebuild and refine. Native structures are shown in blue. The top scoring Foldit predictions are shown in green. The best scoring Rosetta rebuild and refine predictions given the same starting model are shown in yellow.

- (a) This is the same puzzle as in Figure 2d. The best scoring Foldit and Rosetta predictions were able to correctly bury the hydrophobic residues.
- (b) Both the best scoring Foldit and Rosetta predictions had trouble with the loops and ends of the helices in puzzle 986629.
- (c) This is the same puzzle as in Figure 2e. The best scoring Foldit and Rosetta predictions were able to correctly rotate the helix and bury the exposed Phenylalanine.

Figure S7: Foldit players outperforming Rosetta (*blind trials*)

Comparing Foldit players to Rosetta rebuild and refine. Native structures are shown in blue. The top scoring Foldit predictions are shown in green. The best scoring Rosetta rebuild and refine predictions given the same starting model are shown in yellow.

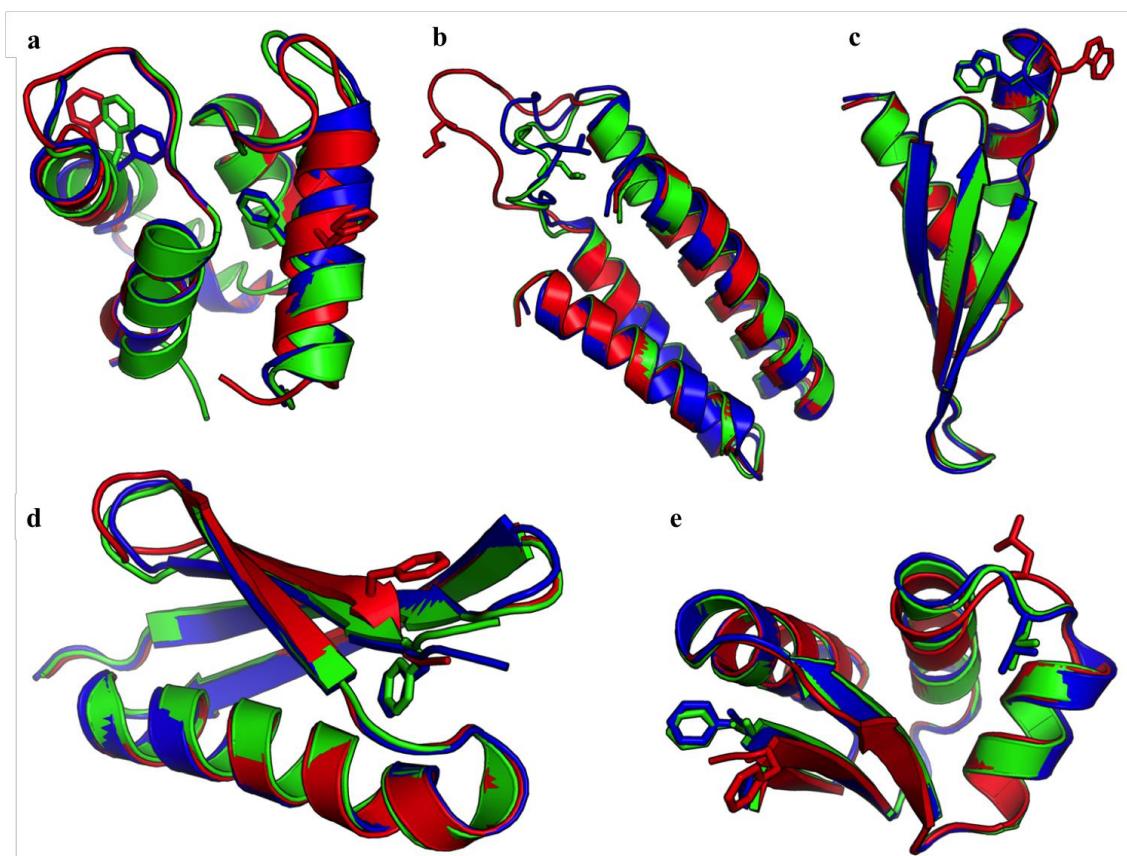
(a) This is the same puzzle as in Figure 2a. The best scoring Foldit and Rosetta predictions both correctly fixed the register shift, but the best scoring Foldit prediction got it closer to the native.

(b) This is the same puzzle as in Figure 2b. Both predictions correctly buried the exposed Isoleucine in the bottom right, but the best scoring Foldit prediction remodeled the loop more accurately.

(c) The best scoring Foldit prediction for puzzle 987162 was able to place the helices and loops on the left side of the protein better than the best scoring Rosetta rebuild and refine prediction.

(d) This is the same puzzle as in Figure 2c. Both predictions correctly rotated the helix on the top left, but the best scoring Rosetta rebuild and refine prediction was unable to keep the bottom right helix in its proper place.

Figure S8: Additional hydrophobic burial puzzles (*non-blind trials*)

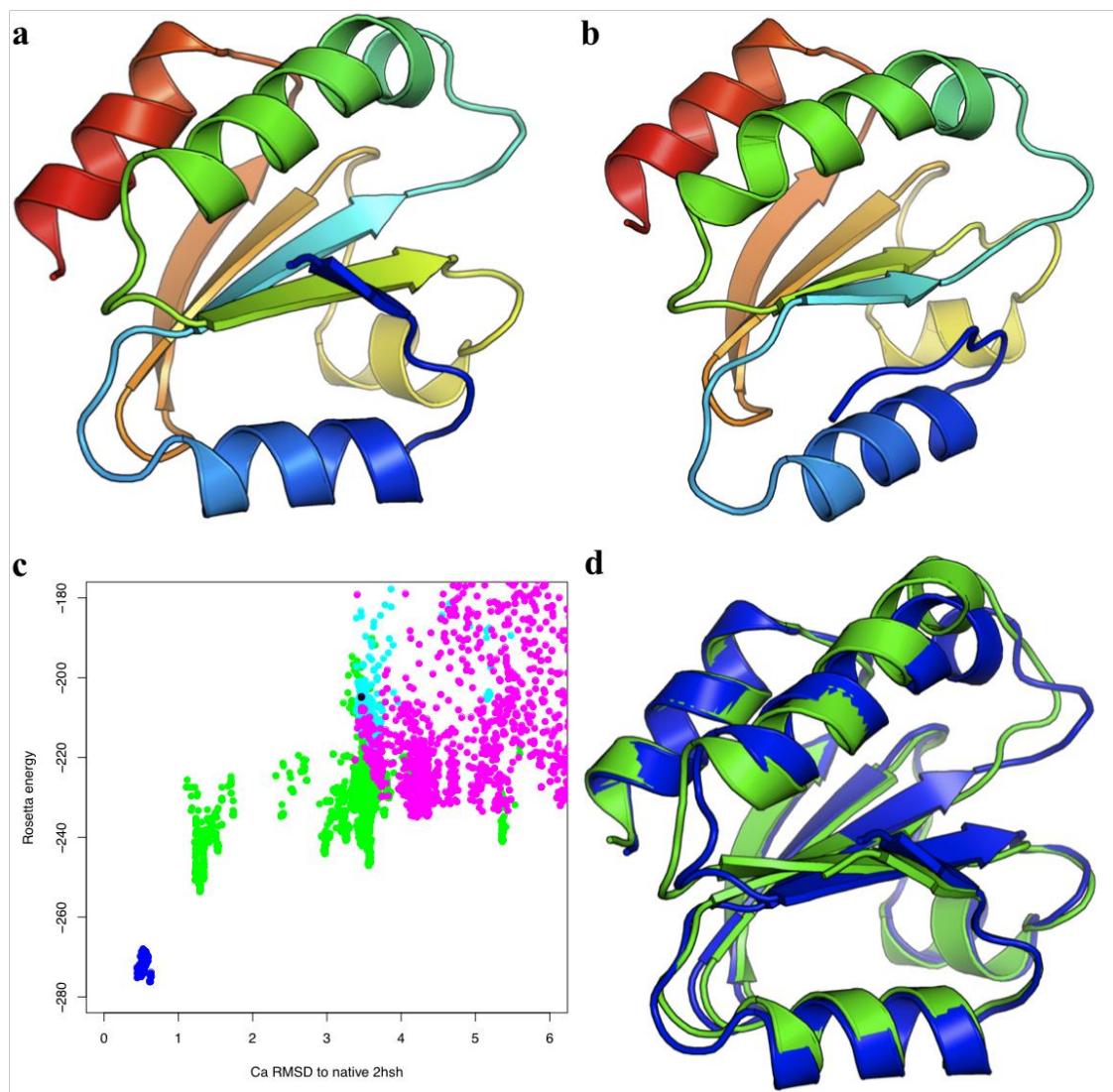


Different hydrophobic examples. Native structures are shown in blue. Starting Foldit puzzles are shown in red. Foldit predictions are shown in green.

- (a) The right helix shows a successful helix rotation, but the helix on the left was not rotated far enough.
- (b) The entire red loop was correctly rebuilt to bury the Leucine.
- (c) The exposed Tryptophan was successfully buried.
- (d) The starting puzzle had a register shift and the Foldit prediction was able to flip and slide the beta strand.

(e) This puzzle contained an exposed Leucine between two helices as well as a register shift. The Foldit prediction was able to retrieve both native conformations.

Figure S9: First strand swap puzzle (*non-blind trial*)

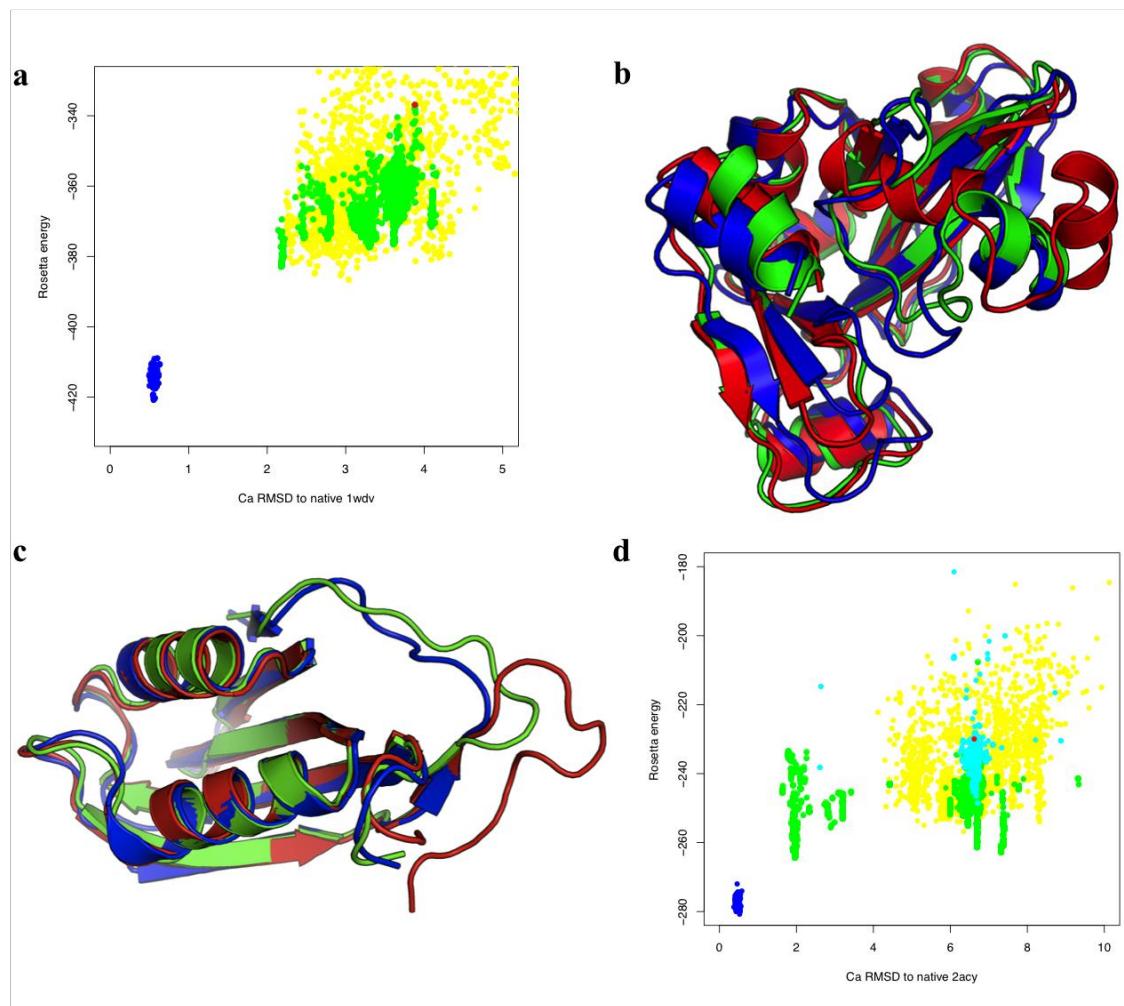


The first strand swap Foldit puzzle, 986452, where Foldit players were able to outperform Rosetta's best automated method, rebuild and refine.

- (a) The solved native structure, 2hsh.
- (b) A Rosetta prediction which incorrectly swapped the cyan and yellow strands, this model was used as the starting model for Foldit puzzle 986452.

- (c) RMSD plot showing the starting Foldit puzzle (the black dot), Rosetta rebuild and refine predictions given the same starting model (in magenta), Foldit beginner predictions (in cyan), all Foldit predictions (in green), and relaxed natives in blue.
- (d) Superposition between the native in blue and the best scoring Foldit prediction in green. Unlike Rosetta, the top scoring Foldit players were able to correctly swap the strands.

Figure S10: Additional successful Foldit puzzles (*non-blind trials*)

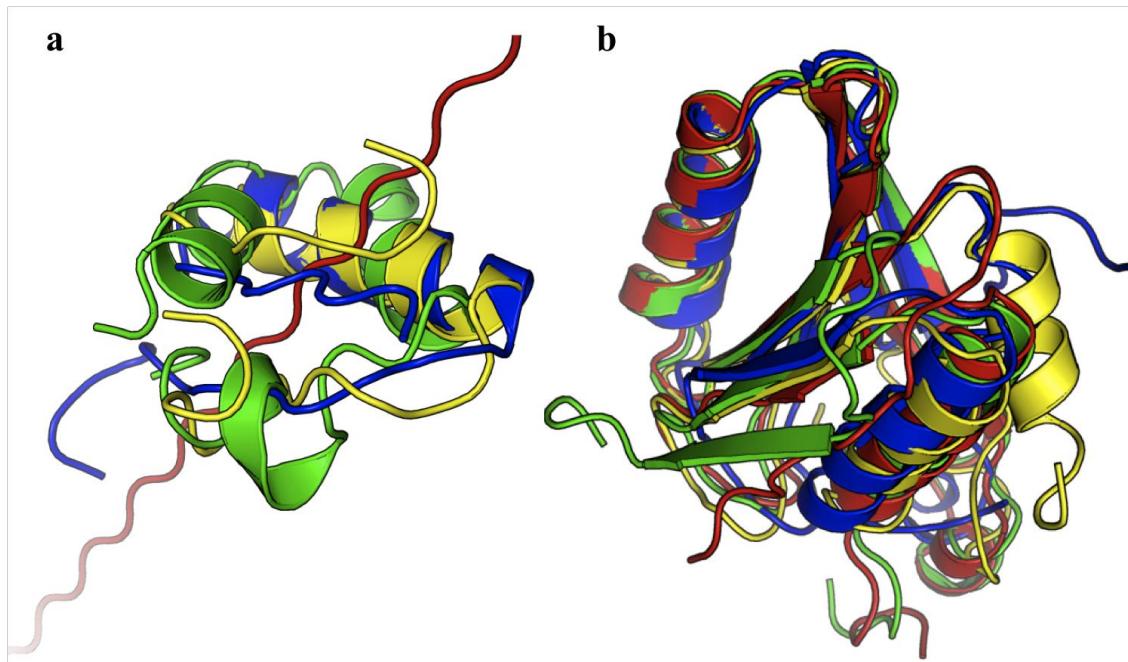


More successful Foldit predictions.

- (a) RMSD plot for Foldit puzzle 985988. Starting puzzle shown as red dot. Relaxed natives are shown as blue cloud. Rosetta's rebuild and refine predictions are shown in yellow (note that the lowest scoring Rosetta predictions are over 3 Angstroms away from the native structure). Foldit predictions are shown in green.

- (b) Top scoring Foldit prediction for Foldit puzzle 985988 (lowest green point in a). The native is shown in blue, the starting puzzle in red, and the best scoring Foldit prediction is shown in green. The very difficult region on the right of the protein, where the starting puzzle has two helices that are connected by a short loop, was completely rebuilt by this Foldit player and is very close to the native.
- (c) Top scoring Foldit prediction for Foldit puzzle 986127 (lowest green point in d). The native is shown in blue, the starting puzzle in red, and the top scoring Foldit prediction is shown in green. The C-terminus at the top of the protein, which was incorrectly placed in the starting Rosetta model (on the right in red), was correctly moved by this Foldit player and is very close to the native.
- (d) RMSD plot for Foldit puzzle 986127. Starting puzzle shown as red dot. Relaxed natives are shown as blue cloud. Rosetta's rebuild and refine predictions are shown in yellow (note that the lowest scoring Rosetta predictions are over 6 Angstroms away from the native structure). Foldit beginner predictions are shown in cyan with all Foldit predictions in green.

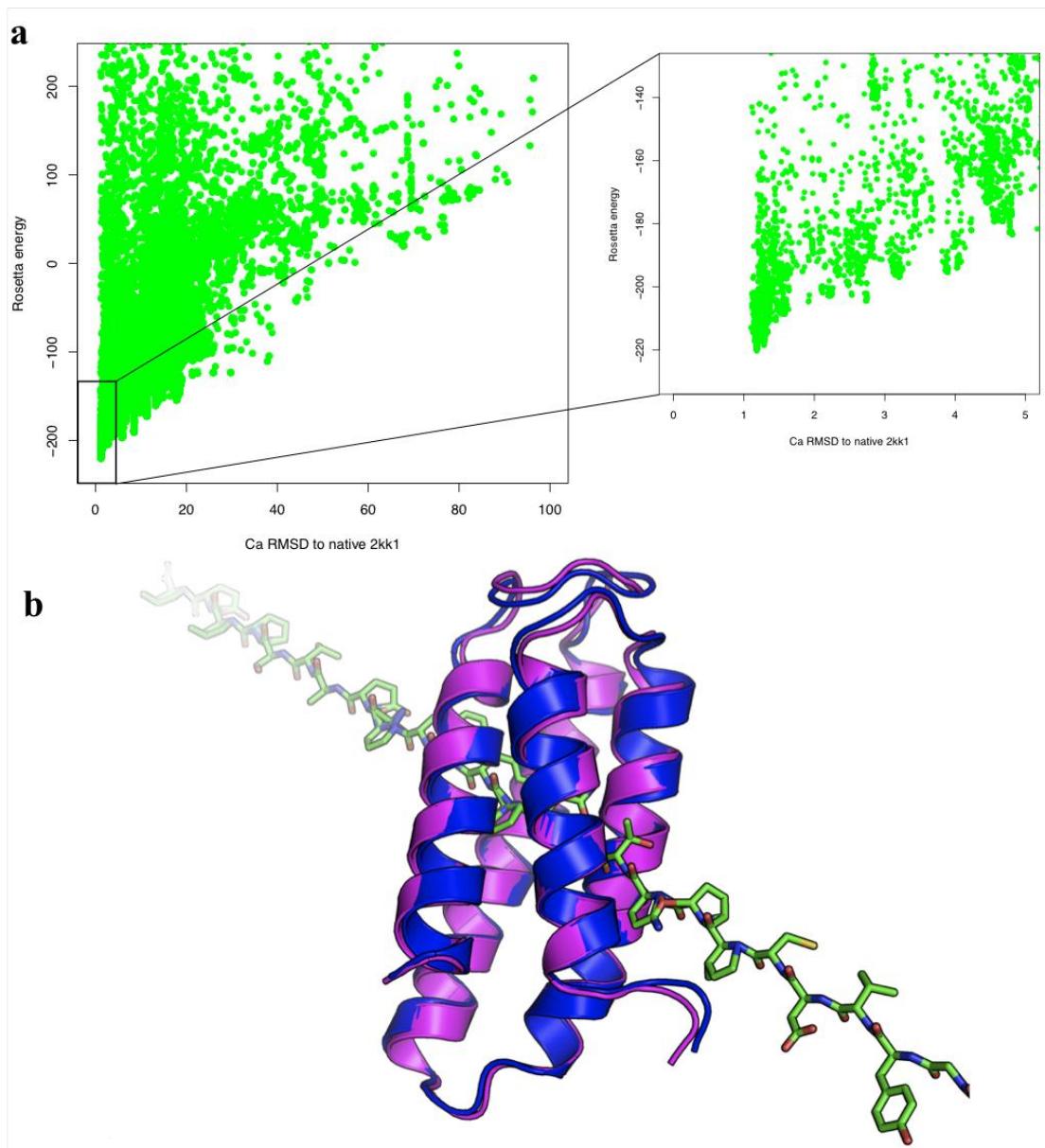
Figure S11: Rosetta outperforming Foldit players (*blind trials*)



Comparing Foldit players to Rosetta rebuild and refine. Native structures are shown in blue. Starting Foldit puzzles are shown in red. The best scoring Foldit predictions are

shown in green. The best scoring Rosetta rebuild and refine predictions given the same starting model are shown in yellow.

- (a) ‘Freestyle’ puzzle 986844 started as an extended chain (shown in red) and the top scoring Foldit solution was unable to capture the native fold. Rosetta rebuild and refine’s best scoring solution had trouble with the termini, but was able to correctly fold the helix.
- (b) The starting structure for puzzle 986961 (shown in red) was the final CASD prediction submitted by the Baker group for CASD target AtT13, built using CS-Rosetta^{iv}. The best scoring Foldit prediction used the C-terminus to form a strand, similar to the starting structure. Rosetta rebuild and refine’s best scoring solution was able to correctly move the C-terminal end to the other side of the helix.

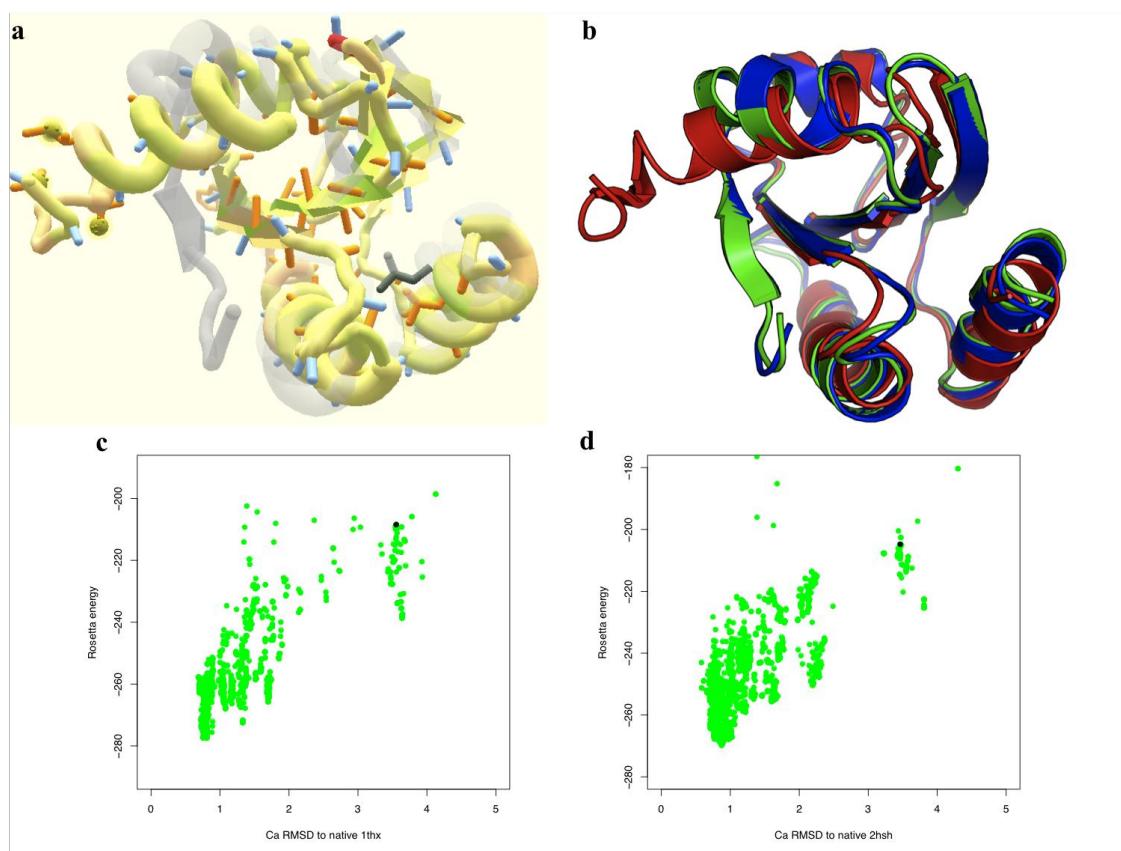
Figure S12: Quest to the Native extended chain

Quest to the Native results starting from an extended chain conformation, showing that the tools in Foldit are sufficient to reach the native state. This "freestyle" Quest to the Native puzzle started as an extended chain, with the native shown as a guide.

(a) RMSD plot of the Foldit player solutions for puzzle 986837, with the zoomed in box showing that the top scoring Foldit solution got within 1.183 Angstroms of the native.

(b) Superposition of the top scoring Foldit solution (in magenta) with model 1 of the native NMR structure 2kk1 (in blue). The starting extended chain conformation is also shown.

Figure S13: Quest to the Native puzzles



(a) A screenshot of a competition puzzle from the Quest to the Native series. These puzzles come with a transparent guide showing the native structure, which allows players to practice using the Foldit tools to match natives.

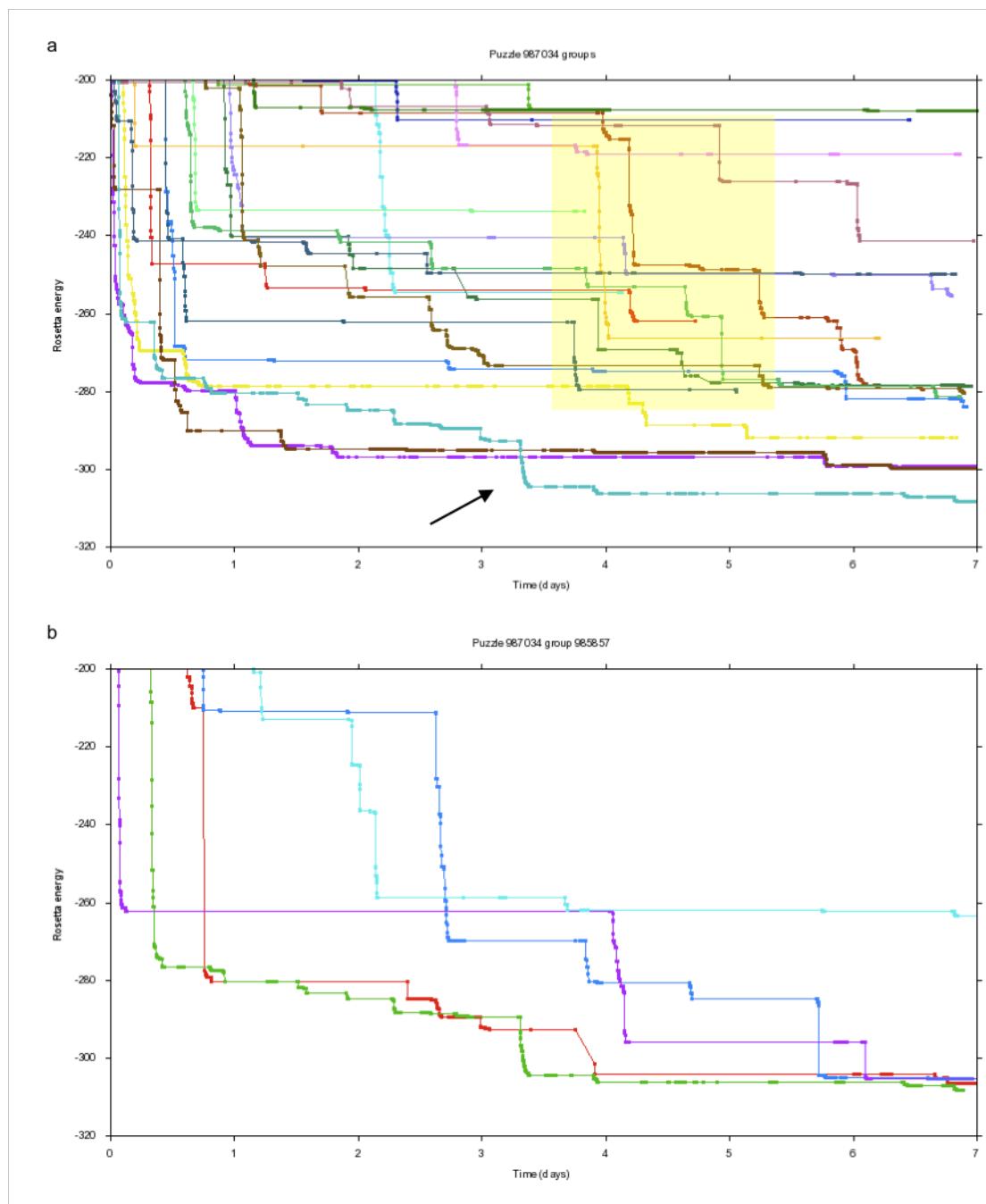
(b) Superposition of the top scoring Foldit solution (in red) with the native structure 1thx (in blue) and the starting Foldit puzzle (in red).

(c) RMSD plot of the Foldit player solutions (in green) for puzzle 986269, with the starting Foldit puzzle shown as the black dot.

(d) RMSD plot of the Foldit player solutions (in green) for Quest to the Native puzzle 986597 that was based on the first strand swap Foldit puzzle (Fig. S6). Only 9% of all Foldit players correctly swapped the strands in puzzle 986452, so we re-released the starting Rosetta model as a Quest to the Native puzzle with the solved native structure

as a guide. This Quest to the Native puzzle allowed us to teach Foldit players of all levels how to swap strands as we did not have an intro puzzle explaining this type of move; we had previously never come across such a case in Foldit. The starting Foldit puzzle is shown as the black dot. This puzzle was used to teach Foldit players the tools necessary to swap strands.

Figure S14: Competition and collaboration



- (a) A chart of the lowest energy found by each group for puzzle 987034. The y-axis is Rosetta energy, and the x-axis is time from the puzzle start in days. The thicker line denotes when a member of the group was actively playing. Notice how the breakthrough of the cyan group (denoted by the arrow) during the third day sets off a chain reaction of energy improvements (shown in the yellow box) and how there is a frantic increase in playing just before the puzzle expires.
- (b) A similar plot for each individual player in group 985857 for the same puzzle. Note how players with worse energy are able to quickly catch up to teammates with better energies.

Supplementary Tables

Table S1: Level concepts

Number	Title	New concepts
1-1	One Small Clash	Clashes; sidechain pull
1-2	Swing It Around	Camera controls
1-3	Hide the Hydrophobic	Exposed hydrophobics
1-4	Shake It Off	Shake
2-1	When Backbones Collide	Backbone pull
2-2	Close the Gap	Guide; wiggle all
2-3	Twin Pack	Voids
2-4	Triple Pcked	Freeze
3-1	Sheets Together	Hydrogen bonds
3-2	Lonely Sheets	Rubber bands
3-3	Sheets and Ladders	
3-4	Lock and Lower	
4-1	Turn It down	Tweak rotate
4-2	The Right Rotation	
4-3	Flippin' Sheets	Tweak register shift
4-4	Rubber Band Reversal	Rebuild
4-5	Movin' Along	Rigid body moves

Structure prediction introductory levels, giving their order, name, and the main concepts introduced.

Table S2: Percentage of players successfully restructuring select Foldit puzzles

Puzzle ID	Type of Restructuring Operation Scenario	% of successful players
987088	Register shift (Fig. 2a)	9%
987088	Remodeled loop (Fig. 2b)	7%
986836	Rotated helix (Fig. 2c)	19%
987145	Two remodeled loops (Fig. 2d)	5%
987076	Helix rotation and remodeled loop (Fig. 2e)	4%
986875	Strand swap (Fig. 3a-c)	8%

For certain Foldit puzzles in the blind test set (Table 1), we identified specific scenarios that could be evaluated for success. We calculated the percentages of Foldit players (including beginners) who successfully fixed the problems in each of these puzzles.

Table S3: Player strategies overview

Category	Summary
Sidechain centric	Force core sidechain into new rotamer. Shake remaining sidechains. Unfreeze sidechain, wiggle, shake, wiggle.
	Move sidechains, automatically readjust the backbone.
	Sidechain flipping. Turn repulsive way down, then shake, then increase to 1 and wiggle/shake. Alternatively, reduce repulsive and wiggle, then increase and shake/wiggle. “Compress” recipe.
Backbone centric	Push, shake, wiggle, shake, wiggle until score stabilizes. Then rebuild plus bands.
	Reduce repulsive, shake, increase repulsive, wiggle. Twist and straighten ss elements. Script for locally optimizing 10 residue chunks. Rebuild all loops at least once.

	<p>Use tweak tool to flip sheets with repulsive reduced, then rebuild end loops.</p>
	<p>Put in bands between sidechains, then wiggle and shake. Vary the repulsive strength. Wiggle internal segments with ends frozen.</p>
	<p>Drag backbone into voids based on positions of sidechains that could fill voids. Use bands to drag backbone, rebuilds to reposition, then shake and wiggle for cleanup. In the end game, move sidechains, optimize, then sometimes replace with original.</p>
	<p>Put bands in every Nth residue with recipe/ reduce repulsive. Wiggle. Remove bands, increase repulsive. Shake. Wiggle. Identify high energy sidechains, replace with original sidechain conformations individually. Basic idea is to get new sidechain conformations by overcompacting the protein, then to mix these with original sidechain conformations guided by the per residue energies.</p>
Problem centric	<p>Search for exposed hydrophobics. Push protein around, focusing on backbone, to get more compact and bury hydrophobics. Then wiggle sidechains, then wiggle backbone, then wiggle all. Then global shake. Then perturb sidechains, tweak helices. Compact protein using bands. For refinement, change secondary structure, rebuild, use bands.</p>

The authors' summary of player-developed algorithms.

Table S4: Contributing players

Puzzle ID	Player(s)	Group(s)	Figure(s)
987088	Steven Pletsch spvincent BikeLoup	Another Hour Another Point	2a-b, S7a-b
986836	Enzyme	Another Hour Another Point	2c, S7d
987145	aap	Richard Dawkins Foundation	2d, S6a
987076	steveB	Void Crushers	2e, S6c
986875	vertex setiman aap	Richard Dawkins Foundation	3a-c, S5
986698	Enzyme Susanne Mark- Grom Steven Pletsch spvincent	No group at the time SETI.Germany No group at the time Russian team Another Hour Another Point Another Hour Another Point	3d-e
986629	aap	Richard Dawkins Foundation	S6b
987162	Mark-	Contenders	S7c
552565	folditlady misiaczkowski dejerpha	Richard Dawkins Foundation	S8a
563187	Squirrely	No group	S8b
521219	Aotearoa	No group at the time	S8c
545657	gringer	xkcd	S8d
537708	g_s	Another Hour Another Point	S8e
986452	infjamc	GoFolders	S9d
985988	bzipitidoo Deniz_Akcay icecubey	Void Crushers	S10b

	mat747 Madde		
986127	montecristo	Contenders	S10d
986844	Chickenhawk	No group	S11a
986961	aap	Richard Dawkins Foundation	S11b
986837	aap setiman drbh	Richard Dawkins Foundation	S12b
986269	Steven Pletsch csohad g_s Nicky666	Another Hour Another Point	S13b
987034	Mark-	Contenders	S13d
Player ID			
46533	Aotearoa	Richard Dawkins Foundation	4
115025	Mark-	Contenders	4
101291	aap	Richard Dawkins Foundation	4
66184	Chickenhawk	No group	4

Players whose Foldit solutions were used in figures for this paper. The URL for a puzzle is <http://fold.it/portal/node/ID>, and for a player is <http://fold.it/portal/user/ID>, where **ID** is replaced with the given ID number.

Player Testimonials

We emailed the top Foldit players to find out the different approaches they used for folding. The following emails have been summarized in Table S3, and are provided below for anyone interested in the details.

CharlieFortsConscience

I guess, in principle, you could break my overall strategy into 2 parts, manipulation of the game tools, and Experience and intuition. Using the game tools to their full potential is a massive help in achieving success, because in the Human v Computer scenario,

Computers are obviously superior in the ability to crunch numbers, but lack the intuitive sense of knowing when to crunch numbers, or which tool to best use at a certain point in the game. The experience and intuition part of the gameplay, for me, is being able to look fresh at a puzzle structure and note which areas 'don't look right', or applying lessons learnt from previous structures, such as interchanging Ile Val and Leu, or Trp Phe His and Tyr in mutable puzzles. The rest of my success is down to hard work and stubborn tenacity. Also I'm a self-confessed hopeless addict; in 7 months I've missed only 2 days. But every day, and in every way, I'm getting better...

I usually begin a puzzle, by running a wig-sh/sh-wig comparison, to see which gives a better start (It's usually wig-sh. In mutables it's always mut-wig-mut) I'll then spend time tweaking and nudging gently all parts from different angles, then wig-shaking them out til they no longer score. The value here for doing this nudging early, is that you get a feel for how the individual puzzles are reacting to wiggle and shake. No-one at FoldCentral will admit to it, but it's blatantly obvious that each puzzle has an inbuilt and presumably adjustable sensitivity or threshold for how it wiggles and shakes. When these are set too high, particularly with shake, the puzzle feels 'sticky' almost like shaking in treacle. And you often notice better results when wiggling at a lower 'clash' bar setting.

At this point, I'll start my mid-game, either rebuilding previously noted areas of interest, or sometimes starting with rebuilds of both ends. Rosetta is notoriously ineffective at optimising ends of proteins, and I find locking off the last 3 or 4 segments and rebuilding, easily finds points. If a larger end section, (10 or more segments) should be rebuilt, I find it better to freeze the whole protein, unfreeze all chains, then unfreeze the segments to rebuild. Immobilising the backbone, but leaving the chains free to participate in shakes, allows the rebuild to 'find its own way' to fit in with the established structure. I find that my overall strategy for rebuilds has become more refined, as I gain experience. Whereas I would previously have run 20, 30 sometimes 50 rebuilds, and stepped individually backwards to wig-sh-tweak them out, I now find that I'll run a sequence of 30 rebuilds just to see if any spontaneous scoring peaks emerge, which will give an indication of potential. If the score flat-lines to 0, and stays at 0 for

that test run of 30, I may redefine the rebuild section, as a flatline suggests hard work, and poor potential and return for that effort. I'll then start again, run 10 rebuilds, step back through each one, then save highest scoring and then rebuild that 10 times, and I'll repeat this process til the overall score stops rising. If I do find an improvement in score, I will also rebuild any immediately neighbouring structure as well. And, I will always at some point, try difficult rebuilds with clash bar adjusted behaviour, as the adjustment encourages interaction and can often help prevent your structure from exploding apart.

I will usually run a chain-flip walk, if I still have time, at this point. Starting at #1 end, I'll move segment by segment, flipping chains in all combinations, and nudging, wiggling then returning to it's original conformation. I tend to concentrate more on the hydrophobes, for a structural bias affecting the backbone, and hydrophiles for chain to chain interaction on the surface. It almost feels like internal phobes are only there to scaffold a sturdy structure, that then allows surface philes to wave about, finding an optimised network of interaction. For me, I find it immensely useful to visualise each chain possessing 'personal space', an area of influence extending all around it, related to its conformational shape and helping/hindering its immediate neighbours.

Rationalisation in this manner, helps me to assess repositioning chains in the manner of a 3-D jigsaw.

At this point, I will now go through one more round of clash bar adjusted tweaking and nudging. In our group, we refer to this as 'breathing'. Broadly, this comprises moving the bar down, then action, then bar normal, then repeat action. Action would be shake, wiggle, mutate, wig backbone, wig chains. Sometimes combinations of actions are most effective, particularly bar down wig, bar up, sh, wig, sh. I also find that pulling the structure so score goes down a few hundred, then shaking til the score changes 2 or 3 times only, then wig normal, can often force internal core chains to readjust their interactions, and can often lead to a higher overall score. Very occasionally, you can chance upon a cascade reaction, where the final wiggle never seems to stop trickling upwards.

Finally, the usual end-game procedures apply, where I run local wiggles of all the major

sheets, loops and helices. Then I'll use recipes that define 2,3,4,5,6 and 7 segment areas, starting from segment #1, throughout the backbone, local wiggles each in turn, then redefines that 'x' segment area, one segment along and repeats the local wiggle. It's an automated version of the Walk the Dog, and interestingly works better if you move that 'x' segment area forwards in direction not backwards. I usually run 3-7-4-2-5-3-6-2-3-2, or however many I can fit in in the time remaining.

In terms of teamplay, I only have experience of one group, as I joined The Contenders, and stayed. I would describe us as like-minded players, a loosely associated group of solo players. We don't have a hierarchy, we have a range of experience and ability, no-one is the dedicated group solo and we all recognise that each of us can 'bring something to the table'. We encourage discussion and questions, and all are free to express themselves. We play our own games in our own way, but if someone finds a killer move or particular sudden success, we post it for the benefit of the group, detailing what we did to get there, and whether we've 'walked' or 'flipped' the structure. In this way, there are usually posted share solutions, that help provide insight and alternative points of view, which I personally find the best way to reinvigorate my approach on the occasions where I have ground to a halt.

I'd also like to add, that as a scientist myself, (research Immunologist), I find rational and measured approaches to general problem-solving are almost second-nature, as part of my 'vocational conditioning'. I think a lot of my success is down to this kind of approach to puzzles, where if something doesn't work, you search for a 'workaround' until it does. Repeating combinations of tools and actions, but changing one variable until you make a successful improvement has also helped a great deal, in developing experience of successful general technique. But knowing when the best time to use this experience and procedure is what helps to give me that little bit extra.

feet1st

One challenge players have is determining the structure of a protein when faced with a protein with no solved structure. These are the so-called "freestyle" puzzles, where you're just starting with a straight unstructured protein. It is important to get a feel for

how many helices, sheets and loops there are. And also to keep in mind that whatever you presume about how many there may be, to try the puzzle again later from the start and try again to see if perhaps you arrive at a slightly different (and perhaps better) structure.

It took me considerable time to realize this, but the rebuild tool is sensitive to the structure it is attempting to rebuild, and not purely based on the sequence of residues it is rebuilding. In other words, if you tell rebuild to work this string of residues, even though they are just a straight line right now, if you've assigned a helix or sheet to them, rebuild will typically find solutions that reinforce that helix or sheet. In fact the only way I've found to get a great looking helix out of a straight start is to rebuild, and if you aren't rebuilding through to a loose end, it still may have trouble making a good helix because the endpoints are fixed.

So to get started, I structure the entire protein as helix, and rebuild each half of the protein separately by freezing a residue roughly in the middle. I let it rebuild each half for a while. Typically with successive revisions it will make some nicely formed helices. If I just try to rebuild the whole thing, it's too much for rebuild to do well with. And if I rebuild in more than two pieces, then I've anchored the ends and this limits what rebuild will find, and can create "hot spots" (the red, poor scoring areas on the relative scoring display).

I find from there, that several areas of the protein don't seem to be coiling up to match the helix structure that I've assigned. These are typically sheets or loops and by now you can often tell that an area of 4 or more residues that has remained entirely straight during the rebuild is probably a sheet. Shorter areas are probably a loop. And so I reassign the secondary structures as appropriate.

From there, I try to further optimize the helices with the tweak tool, and look for ways for sheets to bond to each other and for helices to run parallel to each other. Then I try to rotate the helices to hide hydrophobic side chains as much as possible.

It seems that if I start right out with the rebuild and get my structures established, then I have less contention points later in working the puzzle. Less "hot spots". If you try to adjust later on, you end up twisting things around within the middle of the puzzle and creating hot spots. Or, rebuild is unable to find a good solution with the constraint of the anchored ends. And I find that if I don't first structure it as a helix, then rebuild doesn't seem to form any helices and it is very difficult to discern where it might fold back on itself.

Then look at the exploration map and your score compared to others. You may have to go through all the same steps again. The next time perhaps you freeze a slightly different residue or rebuild a different number of times. Go through the same steps and see if you can achieve a better score.

I almost always seem to get my best score on my first time out. I believe part of the reason for this must be the patience I took in coaxing that first model to settle in. By the time I'm on my second or third try, I get rather impatient for a dramatic improvement in score and am less easily gratified by the slow and gradual improvement that got me my score the first time.

However, I have also had puzzles where I simply restarted with the thought that with what I now "know" about what works well, I can make the proper dramatic changes earlier than I did the first time. Within 10 minutes, I've not only got a better looking puzzle, but a higher score than I achieved in 2 hours the first time. So, always be willing to save, and start from the beginning again. Sometimes you worked kinks in to it that are difficult to recover from any other way.

ferzle

I believe I was successful at Fold It for several reasons: I played a lot because I really wanted to rank up. If a certain group was ahead of my group, I would work really hard to attempt to pass them. Fortunately or unfortunately, spite can be a strong motivator. But of course time alone cannot produce winning solutions.

So what techniques did I use that helped me be successful? My overall strategy is simple and naive: perturbation. I suppose another term would be simulated annealing. I make some (often small) changes to the protein--nudge or tweak the backbone, flip or replace a few sidechains, rebuild something, etc.--and then let wiggle, shake, and/or mutate do their job. Repeat ad nauseam. Once in a while I see a sheet that looks like it belongs somewhere else, so I do my darnedest to put it where I think it should go (not always successfully). Of course there is more to it than that (bands/freezing/etc.), but that is the core of my strategy. I suppose to some extent this is the core of everyone's strategy, but I could be wrong--I don't see how other people play.

Guyoni

As far as strategies go I just have always been able to look at something and figure out what was wrong, so I take the piece that doesn't look right and pull it, twist it, smash it, just generally smack it around a bit, I think my real advantage is patience, I have gone up to 6 hours straight without getting a single point, but I can just tell when a protein is going to break through the wall and relax in a much higher score bracket, and watching that wiggle and all the RANKUP's totally make it worth it.

When working on a teammate's fold I usually start by taking the furthest ends of the protein and connect them with a band, wiggle for a little bit then shake, cut the band and wiggle again, repeat this with many bands and several stages of wiggling to tighten a protein up, if I feel that it is too tight I will reverse the process with pulls and shakes.

infjamc

The following is a recent Foldit tactic that I have been applying again and again; its amazing effectiveness in the recent Rosetta refinement puzzles (233-238) surprised even myself. Yet, when I mentioned this tactic in chat, it was discovered that this tactic is possibly common knowledge (i.e. has been discovered independently by many players-- it's just that it's more effective for some than for others):

- a) Band every nth residue (where n = 2, 3, 4, or 5) with a recipe **OR** set behavior

tab to 5-10%.

- b) Wiggle until the protein seems sufficiently compact (this can be done either automatically in a recipe by setting global wiggle to a specific number of iterations, or manually by gut feeling when the score is sufficiently low).
- c) Remove all bands and set behavior tab to 100%, then do a global shake
- d) Wiggle out the protein, then shake again
- e) Load the recent best as guide, then turn on relative coloring to guide. More often than not, some residues would be green, while others would be red. The red ones can often be fixed by matching side chain conformations to the guide (which sometimes requires tweaking the behavior tab because the old conformation would cause a really bad clash), for a net increase in the Foldit score.

* Step (e) is really the only part that MUST be done manually for now, as there is currently no way to use a GUI or script recipe to save/load the dihedral angle information. While this step may heavily rely on pattern recognition, I must admit that there is one aspect for which my knowledge in biochem may be a slight advantage: occasionally, the resulting new structure in step (e) has a lower score in a residue because of a missing hydrogen bond, and fixing it by tweaking the side chains is not possible. When this happens, I might have to unfreeze all but one residue, go into full-atom mode, and set up several bands of strength 10 (one to turn the hydrogen atom bonded to N or O to the desired direction, and several more to keep the rest of the side chain in place) to re-form the hydrogen bond. In this case, the "biochem advantage" is the fact that hydrogen bonds are more likely to form when the "bond angle" is in a certain range.

==> Then again, I'm pretty sure that there are other factors more important than a biochemistry background that contribute to success in Foldit. While I might do well in refining existing structures (e.g. Rosetta predictions), the design puzzles tend to give me trouble about half of the time; and when it comes to freestyle puzzles, more often than not I would simply use the previously-mentioned compress/decompress/fix side chains tactic on a giant helix to get an obviously wrong but decently-scoring structure--usually, I don't want to do homology modeling from scratch. (For that matter, you might

want to ask steveB, Steven Pletsch, or aap for their insight on the design and freestyle puzzles. Surely the top 10 is different from #11-20 for a reason :-)

Marie Suchard

My strategy

Make beautiful protein: regular helix so that when you watch through them it's a perfect circle, plane and parallel sheets, symmetry. For that, I push the protein kindly and let move for itself with global wiggle, I put bands to bind the protein in a (I imagine) better position, and wiggle, then shake. Bonds between sidechains are more flexible.

Orange inside, blue outside: same methods but for hydrophobic to be inside and red portions to be green. And also, I rebuild locally (between to freeze portions) to explore possibilities.

Random: Push the protein at random to see if it finds a better position; play on the behavior cursor: on the left slowly then on the right or very fast to the extreme left and very fast to the right.

In despair: wriggle one section by one section with freeze sections on every ends. move a sidechains in random.

To find new visions: change the view to see only the backbone.

Not very effective: trying to find bonds between sidechains.

It never works for me: trying to reduce voids.

and try not to be impress by Stephen Pletsch or other very effective players. It's for fun.

I don't play in a team. I answer for time to time to lost players especially to french speaking players.

I'm sorry, my english is not very good.

Mark-

Here are some of my general strategies:

Firstly, try different starts. Shake the sidechains first and then wiggle, see what the score gets to, then reset the puzzle. Then try wiggle first, then shake, then wiggle, again reset.

Or, turn the 'Clashing Importance' down, to say 50%, and shake, then turn it back up to 100% and wiggle, or, turn clashing importance down and wiggle, then shake, then clashing importance back up and wiggle again. On some puzzles, especially those with start conditions, where points may be hard to come by, I have spent a couple of hours just trying different start options. I have found that spending some extra time getting a good start is sometimes essential for a good end solution. Of course, 'Restore Very Best' can be used at any time to continue, once the best starting score has been found.

Once the best start has been found, I will start nudging the protein in different places and in different directions. Shaking the sidechains after each nudge and then letting it all wiggle back again. This is also the time where sheets and helices are rotated and straightened to get the best score from individual areas. As the solution progresses these 'tweaks' will continue right until the end, but gradually become smaller and smaller.

Only rarely will I try to rebuild anything during the first hour or two of attempting a new puzzle. Unless there is a large area that badly affects the shape of the whole protein, I prefer to 'let the protein decide' which direction it wants to go, then I just help it get there.

When the score stabilizes and points are getting hard to find, it is time to look for the rebuilds. I always use the 'relative score coloring' view, so I can easily see areas that may need some attention. I know almost nothing about proteins and amino acids, but am starting to learn what shape a certain configuration of sidechains will be best. Knowing that shape allows me to picture in my mind where it will fit best with the rest of the protein and how I want to rebuild it.

Towards the final stages of a solution, the rebuilds will generally get smaller, unless a previous rebuild has altered the shape of protein too much, in which case further, larger, rebuilds may be required. One of the most difficult things to do during this stage is a large rebuild as it will generally affect the whole protein design. You really need to be prepared to spend a large chunk of time doing this. All of which may be wasted if it is

not successful. Much of the time, patience and persistence can be more beneficial than skill.

I think I was a decent Folder before I joined a group and usually got within the top ten, although I sometimes found it very difficult when getting stuck on certain puzzles. However since joining a group I have definitely benefitted from the feedback, suggestions and encouragement of the group members. I also find that I'm more focused when I know I am folding as part of a team and that any extra points I can gain will benefit the group, as well as myself. Generally, as new puzzles are posted, all the group members will see how they can do on their own, with the top scorers uploading their solutions to the group. Members of our team tend to prefer doing their own solo solutions, rather than evolve others work, but sometimes it is useful to compare your own solution to another's to get some ideas about where the protein can be changed and in what direction others are more successful than yourself. I think the most effective means of group working is by simply telling other members what you have done, in group chat, and vice-versa. I have found it much easier to try out a suggestion for myself rather just copy someone else's. It is also more satisfying when it works for you.

spvincent

Thanks for asking us for input but I don't think I have anything terribly useful to contribute. There are many players who are much better at FoldIt than I am: I enjoy playing the game but have no talent for seeing the "big picture". Hence I generally prefer to evolve other people's solutions.

My preferred technique is side-chain rearrangements. Select a likely-looking side-chain, usually a hydrophobic one in the middle, move it, freeze and shake. Then unfreeze, wiggle, shake, wiggle. If the score comes close than undo 3 steps; interrupt the initial wiggle and shake: trying to get it so that the score increases by about 10 on the next shake.

It's nice to mix this up a bit with occasional tweaks and rebuilds on the end, ugly-looking loops, and places where high-scoring amino acids are shown. It's all a bit random I'm afraid.

steveB

From my experience using foldit there are two distinct strategies

- 1) manually move the sidechains, and let the programme automatically adjust the backbone
- 2) manually move the backbone, and let the programme adjust the sidechains

Option 1

For me, this is the less efficient of the two options, since it involves vast amounts of time in altering the sidechains, and the clashes created are often not strong enough to have sufficient effect on the backbone to improve the backbone's structure, and hence the score.

Option 2

By far the fastest and most efficient of the two strategies. Using the rebuild function of the programme, followed by the shake and sidechain-wiggle, the backbone can be manipulated into just about any desired shape. Since the backbone has much better structural strength than the sidechains, the programme can automatically move the sidechains into the most beneficial structural position without the backbone being substantially distorted from the desired position. My primary goal is always to drag the backbone onto the voids, making the choice of where to drag based on the position of any sidechains that may fill the voids.

It is possible to get to No. 1 position in most puzzles without ever having moved the sidechains - simply by using bands to drag the backbone, and rebuilds to reposition it, and let the automated functions tidy up the sidechains. This often involves quite dramatic changes in the position of the backbone, and in particular complete repositioning of the secondary structures. It takes knowledge of the programme to instinctively know whether a certain position could be beneficial or not, and I suspect that the human brain is actually integrating the score change against time and making a

rational choice based on that information as to whether to abandon a certain position or continue to pursue that particular structural placing.

The final refinement of the puzzle does involve manually repositioning the sidechains, often only to replace them to their previous position, to gain a points score. This slightly bizarre method is presumably assisting the automated features in the programme to make small adjustments to the surrounding sidechain positions.

Finally, it should be remembered that the techniques used are not just to improve the score, but to do so in the least possible time – since folding proteins is very time consuming and currently unpaid!

Susanne

Group: SETI.Germany

Foldit strategies

Solo

I fold with Relevant Score Colouring turned on, showing structure and chains with outline on a light background. I fold with a cordless mouse on a PC. I prefer using the original task bar at the bottom, I find the new interface cumbersome to use, it also gets in the way on the screen.

In general

I don't plan what I need to do, I just hope that whatever methods I use will bring about the changes needed to adjust the protein correctly. I have no chemistry knowledge regarding proteins other than what I learned on this game and cannot plan for an outcome which would require such knowledge. I merely follow my instincts as I adjust sidechains, backbone and helix in the hope that this is what will induce a lower energy. I sometimes see shapes in the protein in the later stages of folding, ie an icecream cone, a shoe, a UFO, they also tend to be my better efforts. I am quite determined to succeed and will re-start a puzzle several times if I am disappointed with my initial score and try and work out where I went wrong. I save a few solutions along the way to enable me to return to one of them should that be necessary.

All Puzzles (excl Design, Refinement, Multi-start, Freestyle)

I initially inspect the puzzle from all sides looking for areas with lots of exposed hydrophobics. My first gentle push will be into that area. I will continue to push the protein around without initially using Wiggle, sometimes not displaying the chains to see the structure better and pushing into a more compact shape. If there are lots of adjacent sheets, I will try and arrange them more in the form of a section of spiral staircase, closer together at one end and differing in height and angle at the other. Helices I try to push into better positions covering the hydrophobics. I also use single bands and Freeze for this. When I am satisfied with the initial re-arrangement, I start with Wiggle Sidechains, as the puzzle is usually very low in score, if not on zero, by this point, to stop if flying apart, then go to Wiggle Backbone, and finally to Wiggle All to see what the outcome is, then push it around until no further points can be gained; only then do I activate Global Shake hoping for maximum effect, then Wiggle All until no more points are gained after continued pushing and pulling. If this score compares well with others I continue, otherwise I will try a different start: - ie Shake Sidechains, then Wiggle or reverse or flicking a chain in a red or brown area, anything to get the protein to start moving gently on its own.

I will then adjust the backbone by manipulating the chains, singly or in groups. I go for those in red or brown segments, singly initially but later in small groups, mostly in the same area, adjacent, opposite etc. I flick the chains, push the backbone slightly, shake, wiggle and see what happens.

The next stage involves tweaking helices and/or backbones and I continue to push or pull gently hoping for adjustment. With a few bands I will try and compact the puzzle in some areas. Occasionally I will push quite hard to make it fly apart a bit to see if it settles better after that. If I think a sheet needs flicking due to upturned hydrophobics with hydrophylics underneath, I will do this and try and work the score back up but I will always save before I do that in case I don't get much further and have to abandon the attempt.

At the next stage I will freeze a bright green segment, usually on a sheet in the centre of the protein within a brown area as this signals to me that not all is well there. I will then push another brown segment. I rotate the protein so that this is directly in front of me with the frozen segment visible behind; this could be any part of the structure, further out, ie at end of sheet. I then push gently but with firm pressure towards the frozen part paying attention not to let the protein move too much (ie whole sections should not fly up during this manoeuvre). I also give a little twist with my wrist. If the score only drops slightly I will continue with this from different angles and using different similar segments and will often manage to improve the protein which shows in the colour (more sections now moss green instead of bright green within brown). (This is the method I used mostly to fold the last All Hands Puzzle a long way up to very near the top score but it took hours). Then I get braver and start pulling at brown loops with lots of blue chains after freezing adjacent sections first, hoping for improved positions for the chains. If all fails I start using Rebuild letting the programme display up to 20 different values which I then click through on the Undo Graph to the backbone shape I like best. Sometimes I go through the Undo-Graph from right to left and wiggle out up to 10 values; even if a plus has been scored with one value, I often try another to be sure that there was nothing better. I use the trace tube display for the protein in the latter stages as I find it is often easier to see the gaps between the backbone sections and not be distracted by the different structures. I use Show Voids briefly to see the hollow parts better.

I also use Behavior to check for different Wiggle/Shake outcomes during the game. I sometimes push parts of the protein towards the centre with a little 'corkscrew twist' to get a better fit. If I can't find any more points, I use a variety of recipes to Local Wiggle until the end.

Freestyle

After initial difficulties I can now manage to fold a reasonably scoring protein but am still keen to improve. Right at the start I paint the structure: I keep sections with lots of blue chains as loops, the rest usually turned into different-sized helices (I can't fold decent sheets unfortunately as they tend to look like boomerangs and later not want to

be next to each other) and rebuild trying to get the loop sections at acute angles to bring the helices together and bury the hydrophobics. I will then go through Wiggle Sidechains, Wiggle Backbone, Wiggle All until it stops, then I try and gather all the different parts by pulling them in with bands, continuing to wiggle in between. Only when I am satisfied with the result, will I activate Global Shake for maximum effect and being careful not to have it all fly apart during the wiggles. I sometimes use Behavior to help bring sections together. I will then continue to fold as usual. I use a very good band recipe ‘Quake’ (Grom) in mid game which often adjusts the protein superbly with good gains. I use a lot of Rebuild from the early mid game onwards as a lot of adjustments are needed quickly to achieve a more compact shape.

Multi-Start/Refinement/Quest to the Native/Evolver

I tend not to be so ‘nice’ to these proteins and start by tugging and pulling them to rearrange them. I change structures to improve flexibility, ie from helix to loop, rebuild, flick chains, use bands and will also try my method of pushing against a frozen green section. Native with guide puzzles: I use the guide initially but have it turned off in parts to just fold ‘normal’ before needing to adjust backbone with bands, Rebuild etc. I fold with Exposeds displayed as this helps me find sections which need adjusting.

Conditions

I will start as described in the previous section but as soon as the conditions are complied with, I stop the wiggle to hold the score, then move up very, very slowly stopping all the while to register the score so I have it to return to if I stray too close to the original structure. Once I have build up a good start, I will test the conditions and try and wiggle through them which of course leads to very much higher score if successful. I use a lot of bands for readjustments, really pulling hard at the structure to get another configuration

Evolver/Group work

My group at present has only 2 active members with 1 or 2 others folding occasionally but not always helping with evolving tasks. This puts pressure on myself and the other folder to get our team to the best position possible for each puzzle which involves a lot

of work on solo folding prior to considering evolving in the later stages. We communicate quite easily via the description portion of the shared solutions and indicate when the other folder should try and improve once the solo folding has become unproductive, usually 2 days before, but sometimes only on the last day of the puzzle. If time allows and if the next score looks achievable or another team is following too close behind, we will try and build on one another's efforts. Unfortunately for us, the solo folding comes first unless one of us abandons a solo effort early and evolves the better solution. I regularly abandon puzzles I am unable to improve and start to evolve the better team solution and it doesn't matter to me if the solo player overtakes my evolver score as I will await the new solution and be happy for the improved team position; but getting the solution quickly is a problem and one has to wait until the other player has finished, both working on the same score is not an option as there are too many puzzles which need our time that I will then move on to another puzzle in the interim and return later or next day. Most team folding takes place in the evening and at weekends and it can get too late at night to await the new team solution although I must say that I tend to fold best late at night when I am really tired, maybe then don't over-analyze the problems and fold more 'hands on' to speed things up a bit, this is just my theory.

My only real evolver experience comes from working on the All Hands puzzles which I love doing as I can work on lots of solutions of players I am usually competing against and find I need less time initially to get somewhere near the top as others are helping to build up the score for me. Also the puzzle is improved at quite a pace with lots of changes taking place in a short time. I will always try and get my score near the top as it's a fantastic experience to have one's solution chosen for a stepping stone and see how others are able to improve it. The camaraderie and competitiveness combined are addictive. There is a lot of respect for good folders. The best part though is the very last stage where the small improvements determine the No 1 spot. I will still try everything to get somewhere near that by rebuilding, pulling at sections etc to gain a few hundreds of a point. This is where parallel evolving is at its most competitive and often new names appear in the top scorers list.

vakobo

I use all Foldit tools. Some more frequently, some fewer.

My favorite method is sidechain flipping. Also I use rebuild with variable success.

Some pulling, some tweaking, some bonding.

At final stage I use some own recipes with local wiggle sequence mixed up with standard Compress recipe.

There is yet another active player (Grom) in our team and we share solutions with each other.

I think his play manner is different significantly from mine and this gives some results.

Also I use Behavior slider:

- set it to 1/10 ~ 1/20 and Shake for a while, than set to 1 and combination of Wiggles and Shakes;
 - set it to 1/5 ~ 1/10 and Wiggle for a while, then set to 1 and combination of Shakes and wiggles.
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