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A structural database for k-turn motifs in RNA

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ABSTRACT

The kink-turn (k-turn) is a common structural motif in RNA that introduces a tight kink into the helical axis. k-turns play an important architectural role in RNA structures and serve as binding sites for a number of proteins. We have created a database of known and postulated k-turn sequences and three-dimensional (3D) structures, available via the internet. This site provides (1) a database of sequence and structure, as a resource for the RNA community, and (2) a tool to enable the manipulation and comparison of 3D structures where known.

Keywords: RNA structure; kink turn; motif

INTRODUCTION

Kink turns in RNA

The kink-turn (usually abbreviated to k-turn) is a widespread structural motif in RNA, first noted as a repeated structural element in the large ribosomal subunit by Steitz and coworkers (Klein et al. 2001). It introduces a very tight kink into the axis of helical RNA, from whence its name. It clearly plays an important structural role in RNA and is significant in many aspects of RNA function including translation, modification and splicing, as well as genetic regulation.

The canonical k-turn comprises a 3-nucleotide (nt) bulge flanked on its 3′ side by A•G and G•A base pairs (the noncanonical [NC] stem), and on its 5′ side by a section of regular base pairing (the canonical [C] stem) (Fig. 1A; Klein et al. 2001). Kt-7 of the 23S rRNA of the *Haloarcula marismortui* ribosome can be regarded as the archetypal k-turn sequence. The structure introduces a pronounced kink in the RNA, with an included angle between the axes of ~60° (Fig. 1B). The minor grooves of the two helices are juxtaposed, and the conformation is stabilized by interactions between the stacked adenosines of the A•G base pairs and the C stem, and by stacking of the 5′ and central bases of the bulge on the ends of the C and NC stems, respectively. In order to adopt the tightly kinked geometry, k-turn motifs require the presence of metal ions (Goody et al. 2003; Matsumura et al. 2003) or the binding of proteins (Turner et al. 2005). In the absence of either of these factors, the RNA adopts a conformation that is more extended, like any 3-nt bulge in a duplex (Lilley 1995). This suggests a dynamic character for k-turn structures sampling both the kinked and a more extended geometry. Computer modeling studies have suggested that k-turns undergo hinge-like motions on a fast timescale (Cojocaru et al. 2005; Razga et al. 2005, 2006).

At the time of writing, there are 33 unique k-turns (with or without known structures, classing any given k-turn type such as Kt-7 as a single member of the group), of which 18 have one or more structures determined by X-ray crystallography. In some cases multiple examples are available from different organisms, giving 32 different structures altogether, found in 14 separate Protein Data Bank files. These are present within ribosomal subunits or smaller RNA species with or without bound protein and provide a valuable resource of structural information on these important elements. We have devised a universal nomenclature for the nucleotide positions in k-turns (Fig. 1; Liu and Lilley 2007), thus avoiding the confusion that could arise from the many different numbering systems used in various crystal structures.

The occurrence of k-turns in RNA

The k-turn was first identified as a novel motif occurring multiple times in the ribosome (Klein et al. 2001). Further examples have been found in mRNA (Mao et al. 1999; Winkler et al. 2001; Allmang et al. 2002; White et al. 2004) and in riboswitches (Montange and Batey 2006; Blouin and Lafontaine 2007; Heppell and Lafontaine 2008). They are

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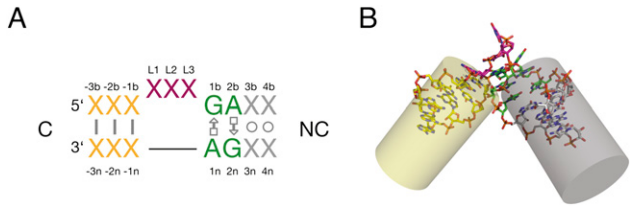

FIGURE 1. The k-turn sequence and structure. (*A*) The secondary structure of a typical k-turn. Nucleotides are numbered according to our nomenclature that can be applied to most k-turns (Liu and Lilley 2007). The 3b•3n position is frequently non-Watson–Crick paired, but the 4b•4n position is usually, but not always, a Watson–Crick base pair. (*B*) The structure of Kt-7 from the 50S ribosomal subunit of *H. marismortui*, an archetypal k-turn. The NC (yellow) and C (gray) helices are highlighted by the cylinders, clearly showing the tight angle between the two axes.

very commonly found in C/D and H/ACA guide snoRNAs and in U3 snoRNA species (Kuhn et al. 2002; Watkins et al. 2002; Bortolin et al. 2003; Marmier-Gourrier et al. 2003; Rozhdestvensky et al. 2003; Hamma and Ferré-D'Amaré 2004; Moore et al. 2004; Szewczak et al. 2005; Youssef et al. 2007). There is also a near-canonical k-turn in a stem–loop of the human U4 snRNA (Vidovic et al. 2000; Wozniak et al. 2005). Some k-turns have been identified unequivocally, from their structure in situ within crystal structures of larger RNA structures or complexes. Others are assumed by virtue of their sequence and perhaps their homology with known k-turns in related species.

The interactions that stabilize the kinked geometry of the k-turn

The great majority of k-turns have a G•A pair at the 1b•1n position and an A•G pair at the 2b•2n position. Sequence substitution of any of the four nucleotides is highly detrimental to folding (Goody et al. 2003). Both are *trans* sugar edge (G) to Hoogsteen edge (A) pairs, linked by potential hydrogen bonds G-N2 to A-N7 and A-N6 to G-N3. We have found experimentally that all four hydrogen bonds are important to the stability of the kinked form of the RNA. But the G-N2 to A-N7 hydrogen bonds of the two G•A pairs are the most critical to the stability of the kinked form of Kt-7 in Mg^{2+} ions, so that folding is completely prevented by G to inosine substitutions at either position (Turner and Lilley 2008).

In addition to the bonds linking the G•A pairs, a number of critical hydrogen bonds involving 2′-OH groups play a key role in stabilizing the kinked structure. The most important are those in the core of the turn and ribose–phosphate interactions around the bulge. These are strongly conserved in all k-turns and are critical to folding. Of these, the single-most important hydrogen bond is one donated from the 2′-O of L1 ribose to the N1 of the A1n in the kink-proximal A•G pair. This is present in all known k-turn structures, and removal of the 2′-OH from L1 completely prevents metal ion-induced folding (Liu and Lilley 2007). Another critical hydrogen bond stabilizes the tight turn made at the loop of the k-turn. An interaction between the 2′-O of L3 and the *pro*S nonbridging O of the phosphate between L1 and L2 bridges the neck of the turn, and is observed in most k-turn crystal structures. Removal of the 2′O from L3 ribose in Kt-7 led to marked impairment of ion-induced folding (Liu and Lilley 2007). Other hydrogen bonds can be found in individual k-turns, of lower conservation. In general, these make a smaller contribution to the stability of the kinked conformation. These include hydrogen bonds formed between the C and NC stems outside of the central core.

Standard and complex k-turns

Many k-turns fit closely to the secondary structure of the standard structure, exemplified by Kt-7. A few, however, "break the rules" of the standard motif. The archaeal box H/ACA RNA species lack the entire canonical stem, yet still fold. Some k-turns have sequence changes that alter the seemingly essential G•A pairs. In Kt-23 of *Thermus thermophilus* (Wimberly et al. 2000), the 2b•2n pair is a non-Watson–Crick A•U pair. Although making the same change in Kt-7 totally prevents folding from occurring, Kt-23 folds efficiently on addition of Mg^{2+} ions, and its structure in the 30S ribosomal subunit is superimposable with that of Kt-7 (Schroeder and Lilley 2009).

Another set of k-turns does not map onto the standard form of the sequence as exemplified by Kt-7 in a linear way. Despite major departures of the sequences from the conventional k-turn, these form standard k-turn three-dimensional (3D) structures. We recommend naming the nucleotides according to their location in the structure, rather than their position in the linear sequence. Thus, the adenine paired with G2n in *H. marismortui* Kt-15 should be termed 2b, even though it is located on the nonbulged strand.

Protein binding by k-turn RNA

The majority of k-turns are known to bind one or more proteins. A few are not, including that found in the SAM riboswitch (Montange and Batey 2006).

The archetypal k-turn binding protein is the ribosomal L7Ae and related proteins. The binding of L7Ae to k-turn-containing RNA is an example of induced fit (Turner et al. 2005). Even in the absence of added metal ions, the kinked conformation is induced by the binding of the protein. Moreover, the binding occurs with extremely high affinity. We have measured a dissociation constant of K_d = 10 pM for *Archeoglobus fulgidus* L7Ae binding to Kt-7 (Turner and Lilley 2008). L7Ae and related proteins form a family of RNA-binding proteins including the eukaryotic and archaeal proteins L7Ae, L30e, and S12e (Koonin et al. 1994), the yeast Nhp2p and Snu13p proteins, and the human 15.5 kDa protein (Nottrott et al. 1999). Each of these proteins binds k-turn motifs in RNA, and some functional

substitutions are tolerated (Rozhdestvensky et al. 2003). The assembly of the RNA methylation (box C/D) nucleoproteins are initiated by the binding of L7Ae-type proteins to k-turns contained within the guide RNA (Kiss-Laszlo et al. 1996), and L7Ae binding to box H/ACA RNA is also necessary for functional assembly of H/ACA RNP complexes (Ganot et al. 1997). The 15.5 kDa protein binds a k-turn of the U4 stem–loop in the U4-U6.U5 tri-snRNP (Nottrott et al. 1999). Crystal structures are available for the complexes of *A. fulgidus* L7Ae and box C/D RNA (Moore et al. 2004), *Methanococcus jannaschii* L7Ae and box H/ACA RNA (Hamma and Ferré-D'Amaré 2004), and the human 15.5 kDa protein and the U4 snRNA (Vidovic et al. 2000). In each case, the k-turn adopts the tightly kinked conformation in the complex with the protein.

A role for k-turns in building complex RNA structures?

Kink turns could play a key role in RNA architecture and the biogenesis of large assemblies. The dynamic character of the k-turn might allow RNA to explore conformational space, but once folded the tight kink should provide long-range organization of the structure. We may speculate that this provides flexibility during the assembly of the structure, but the geometry is then fixed in place by the high-affinity binding of key proteins to k-turns.

THE K-TURN DATABASE

We have made a detailed study of the structure and folding of k-turns in solution, induced by the addition of metal ions and proteins. The k-turn provides a simple model system for the study of RNA folding because of its relatively small size and the availability of a significant number of crystallographic structures. The juxtaposition of (1) analysis of folding by biophysical methods (generally FRET) in conjunction with the ability to dissect interactions at the atomic level by means of functional group substitution and (2) the availability of numerous crystal structures proved a powerful combination. We recognized the need to collect together sequence and structural information on k-turn motifs in a way that would make comparisons possible. We therefore created a database that makes this a relatively easy process. The original motivation for the creation of this structural database was to provide a tool for the comparison of different k-turn structures for use within our own laboratory. However, we then realized that this could be useful to other laboratories interested in RNA structure and function, and therefore decided to make this generally available as a visual-oriented web-based tool. It is conceivable that the internet site could also be used as an aid in teaching. The internet site is available at http://www.dundee.ac.uk/biocentre/nasg/kturn/index.php. The main purpose of this site is to tabulate all known and putative k-turns, and to provide the means of presenting sequence information and displaying 3D structures in a way that can be manipulated and compared in a molecular graphics format. A site map is shown in Figure 2.

The front page

The front page of this website presents a short review of the occurrence, structure, and function of k-turns. All the structures are illustrated by movies that help provide a 3D perspective. They are started by clicking on the images and can be opened in a separate window if desired (this may be required on some older platforms).

The menus

The front page also provides a menu box from which it is possible to navigate to the main functional areas of the database. The "kink-turns in RNA" link provides a list of all currently known k-turns and their secondary structure, which we shall update with time. It is subdivided into two pages. These are: (1) "Known structures," listing k-turns for which the structures are known from X-ray crystallography or NMR; and (2) "Putative sequences," listing probable k-turns suggested by their sequence alone. A third page entitled "k-turns by location" classifies the known and putative k-turn elements according to their source, such as 23S rRNA, mRNA, riboswitches, and other.

There are further links to pages where new developments are highlighted, such as new papers that present k-turn data, acknowledgments, etc., and a page for contacting the investigators with comments and questions.

Presentation of sequence and structural data for each k-turn

The real functionality in this website is revealed when the name of a given k-turn is clicked. This navigates to a page dedicated to that k-turn in particular, where the sequence and structural data are displayed (Fig. 3). Sequence information is displayed on the left-hand side. The secondary structure is shown, annotated according to the Westhof convention (Leontis and Westhof 2001). Below this is shown the consensus sequence from an alignment of the sequence from various organisms and sources (Cannone et al. 2002; Gardner et al. 2009), generated using WebLogo 3 (Crooks et al. 2004).

The structural information is presented on the right-hand side of the screen. The structure is visualized using the molecular interactive web browser applet Jmol (McMahon and Hanson 2008). A 3D representation of the structure is available via either wall-eye or cross-eye stereo pairs, and can be rotated and zoomed via the mouse as normal (left and center click, respectively). The structure is color coded as in the sequence and can be viewed in a variety of stick and space-filling formats. A right-click in the graphics window reveals the regular drop-down menu for Jmol.

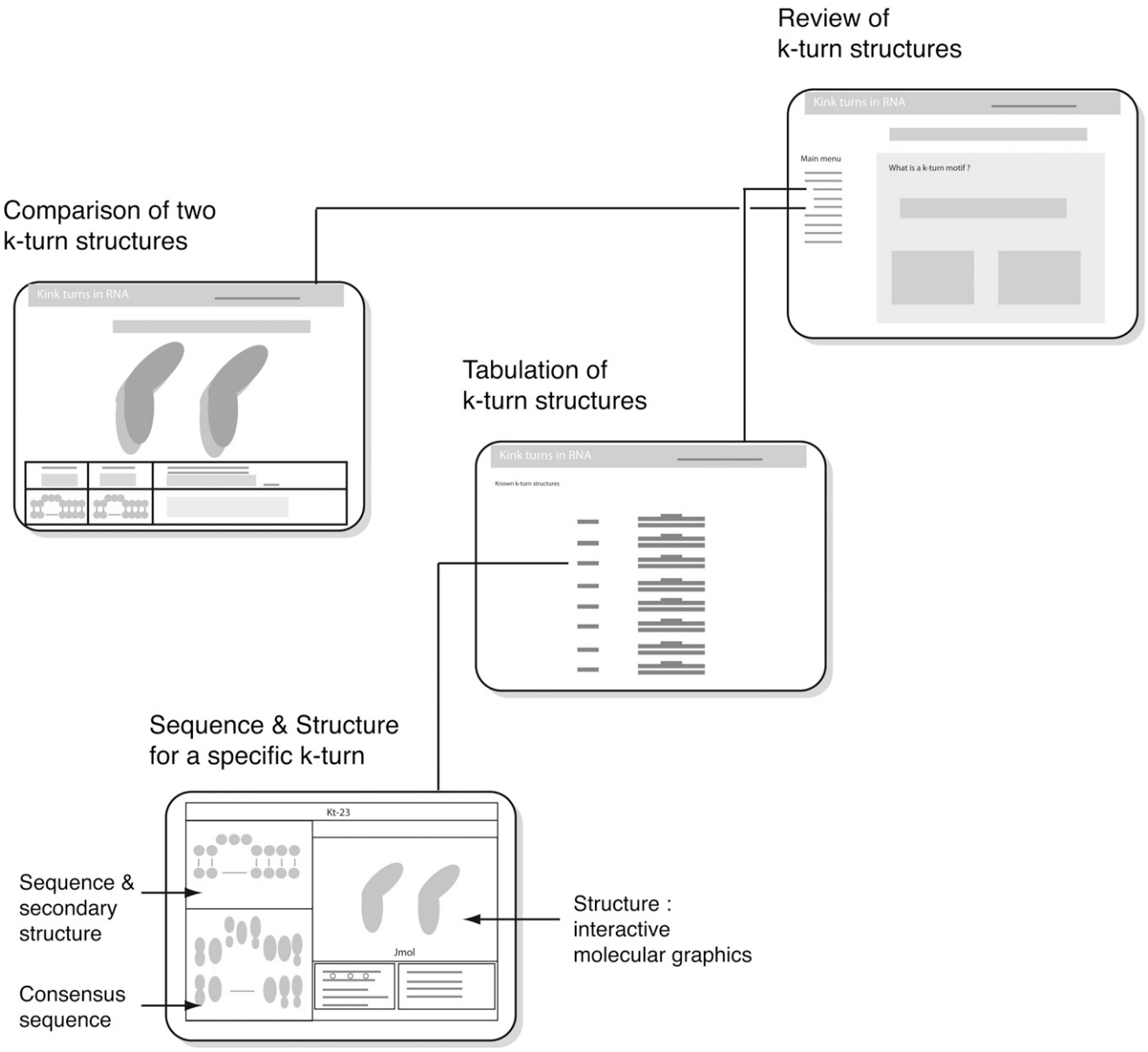

FIGURE 2. A map of the k-turn internet site. The front page (*top right*) presents a review of k-turn structures in RNA. The main functional pages are accessed via the menus at the *top left* of the web page.

At the lower-right of the graphics window there are tick boxes that allow the current k-turn to be overlayed with *H. marismortui* Kt-7 (Blaha et al. 2008) and others related to the current k-turn. However, within this site there is a more powerful tool that allows the comparison of known k-turn structures in any combination.

Three-dimensional structure alignment

A unique feature of this website is the ability to use Jmol to align any of the k-turns to each other. The ''pairwise alignment'' link brings up a blank Jmol window, and two different k-turn structures can be chosen for structural comparison using the drop-down menus at the lower left. The two structures are aligned via the backbone and non-bridging oxygen atoms (O5′, C5′, C4′, C3′, O3′, P, O1P, and O2P) for nucleotides preselected to represent the key k-turn positions, using either the best atom correlation (Kabsch 1976) (as in PyMOL [DeLano 2002]) or the best base correlation (using quaterions) (Horn 1986). The aligned structures may be manipulated using stereo images in Jmol as before, and the two structures may be differentiated by adding 25% CPK atoms to one structure, making the second k-turn 60% transparent or temporarily (using toggle buttons) hiding one or other structure. The Jmol command window (lower right) displays a record of the presentation and alignment of

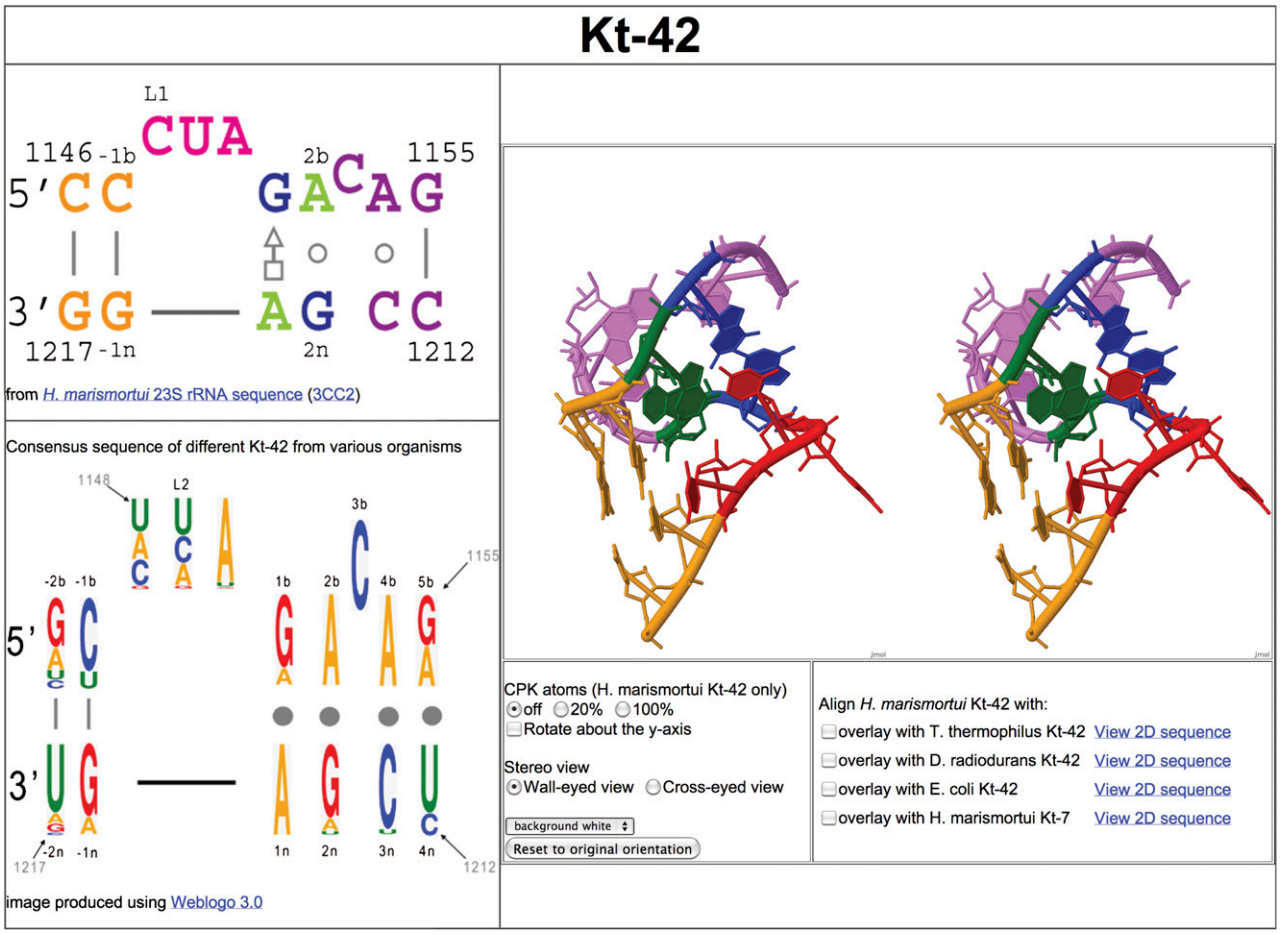

FIGURE 3. A representative page for one k-turn. This shows a screenshot of the page for Kt-42, with the structure of *H. marismortui* Kt-42 shown in parallel-eye stereo.

the structures, and it provides the root-mean-square deviation for the atoms used in the superposition.

This alignment tool should prove very useful for the analysis of k-turn conformation, and we believe it will be particularly valuable for the analysis of the complex k-turns.

FURTHER DEVELOPMENT OF THE DATABASE

In addition to providing a commitment to the maintenance and updating of the k-turn database, we are also considering ways in which to improve its functionality. We hope to introduce a database search tool that will search for a given k-turn or variant within a sequence alignment database of different organisms. The aim is to enable the user to find interesting variations of specific k-turn sequence, facilitating experimental design. We would also like to add the capability to model the structure of an unknown k-turn based on its sequence and similarity to known structures. A longer-term goal is to develop an algorithm that will search genomic sequence databases for new examples of k-turns that can be studied. Finally, the present site makes no reference to proteins that bind to k-turns, yet these form a very interesting and diverse set of interactions. We plan to tabulate these interacting partners, and to present the structures by means of molecular graphics.

In principle the approach used to present and manipulate structural information on k-turns could be applied to other structural motifs in RNA, and we hope that this might be implemented by other laboratories. We further anticipate that it could be possible to combine such databases to allow the study of many RNA motifs in a single web-based structural analysis tool.

USER FEEDBACK

We would like to make this web tool maximally useful to other laboratories, and we seek fresh perspectives on how this might be improved or extended. Users are encouraged to contact us with comments and suggestions via the "contacts" link on the site, or by normal e-mail.

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