

An encyclopedic effort to make 3D structures easier to understand

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For the first time in the short history of electronic publication, rotatable and zoomable 3D structures of biomolecules were integrated within the PDF file of the recent *TiBS* paper ‘Grasping molecular structures through publication-integrated 3D models’ by Kumar and Ziegler *et al.* [1]. This represents a major step forward in effective and simple communication of complex 3D data, one which has already been expanded into other spheres of science with the recent publication of a ‘3D PDF’ version of an astronomy paper in *Nature* [2].

The field of structural biology has long suffered from a communication gap between structural specialists and non-specialists. This problem stems, in part, from the complexity of the 3D structures of biomolecules and the difficulty of properly conveying these structures using only 2D pictures in publications.

It is evident that today’s most successful, clear and engaging lectures on structural biology employ movies of biomolecules in addition to interactive 3D models embedded within electronic slideshow presentations. Lecturers, being able to immediately gauge their audience’s response to and comprehension of their talks, have recognized the need to include 3D images in their presentations and have found the technology to do so readily available, for example, through the use of PyMOL (www.pymol.org), iSee [3], eMovie [4], POLYVIEW [5,6] and Accelrys Discovery Studio Visualizer 2.0 (<http://accelrys.com/products/discovery-studio/visualization/discovery-studio-visualizer.html>).

Until the article by Kumar and Ziegler *et al.* [1], however, scientific publications were still stuck with 2D representations in their papers (for understandable reasons, most notably a lack of a standardized, simple solution for embedding 3D in electronic publications) unless supplemental downloads, such as movie files, were also provided. Although structures described in publications can always be downloaded from the Protein Data Bank [7] and interactively explored in their native 3D using widely available molecular visualization programs, these programs are often inaccessible to non-specialists owing to a steep learning curve (with, in our opinion, FirstGlance in Jmol [<http://firstglance.jmol.org>] being an exception). In the article by Kumar and Ziegler *et al.* [1], interactive 3D figures contained wholly within the PDF file provide an intuitive and simple way to communicate biomolecular structures to a wide scientific audience in a format that is both portable and usable almost anywhere the reader has access to a

computer. Therefore, despite some technological obstacles to using this new method that remain to be solved (most importantly, the issues of relatively large file size and the currently less than ideal 3D PDF creation procedure that Kumar and Ziegler *et al.* describe), their method shows great promise for providing the scientific community with a new standard for publication of 3D structures.

However, although a 3D PDF succeeds in providing instant access to the structure for the reader of a scientific publication, there exists a related and parallel need for simple sharing and communication of 3D structural information in an open and accessible medium. Just as the 3D PDF creation procedure that Kumar and Ziegler *et al.* describe is currently less than ideal, and will benefit from future improvements, so too are the authoring procedures less than ideal for a scientist who wishes to create a webpage describing, in 3D, his or her solved biomolecule structure or a structure of interest. Ideal would be a web resource that presents 3D structures in an immediately intuitive manner and enables contributors to easily add their own 3D descriptions of structures.

To help in this goal, we, together with Jaime Prilusky at the Weizmann Institute of Science, have created Proteopedia [8] (www.proteopedia.org). Proteopedia is a web resource that links descriptive text to views of interactive 3D structures that illustrate the ideas mentioned in the text (with the 3D structures displayed using Jmol [<http://jmol.sourceforge.net>]). It is a wiki, permitting users to edit the content of the website. Contributors to Proteopedia can create pages in a straightforward and simple manner or they may edit existing pages, such as the >55,000 automatically created pages for each of the entries in the Protein Data Bank. Proteopedia can serve as an online encyclopedia of 3D biomolecules, a repository of 3D lecture slides for educators (which can also be saved and viewed offline) and can host supplements to articles that may be opened to comments and expansion (<http://proteopedia.org/wiki/index.php/3btp>). Proteopedia thus complements the method of Kumar and Ziegler *et al.*, which finally enables the reader invaluable instantaneous access to interactive 3D structures within the article itself. Further improvements to the method of Kumar and Ziegler *et al.* and the technology involved could, hopefully, make integration with such additional resources much easier by enabling direct export of the views of the structure (the different orientations, representations and coloring schemes) contained within such 3D PDF interactive figures. Therefore,

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we hope to see more articles and journals adopting this embedded-3D-structure format in the future and a concerted effort to improve the software needed so that it is accessible to and usable by everyone, non-specialist and specialist alike.

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Research Focus

β-catenin gets jaded and von Hippel-Lindau is to blame

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Numerous studies have pointed to interactions between the tumor suppressor von Hippel-Lindau (VHL) and the oncogenic Wnt–β-catenin signaling cascade; however, the mechanism of this crosstalk has remained elusive. Among other roles, VHL can promote the stabilization of Jade-1. Now, recent findings provide compelling evidence that Jade-1 ubiquitylates β-catenin, leading to its degradation. Thus, the loss of VHL, as seen in clear cell renal cell carcinoma, could lead to tumor formation through β-catenin de-repression.

Wnt–β-catenin signal transduction

Wnts comprise a conserved family of secreted glycoproteins. The founding member, *wingless* (*wg*), was initially characterized in *Drosophila melanogaster* and it was later found to be homologous to a murine proto-oncoprotein, INT-1 (Wg + INT = Wnt). Wnts are now known to be crucially important for numerous developmental processes and are required for regeneration in response to injury. Moreover, constitutive activation of the Wnt–β-catenin signal transduction pathway underlies the initiation and progression of several human cancers, most notably, colorectal carcinoma [1]. Recently, Chitalia *et al.* [2] described a new mechanism, via Jade-1 (gene for apoptosis and differentiation in epithelia), for communication between the Wnt–β-catenin and von Hippel-Lindau (VHL) tumor-suppressor pathways. Because VHL and Wnt–β-catenin signaling are implicated in related kidney pathologies, this finding underscores the clinical relevance of exploring this interaction.

β-catenin, a transcriptional co-activator, is required for canonical Wnt signal transduction. In the absence of Wnt

ligand, β-catenin-dependent transcription is suppressed by multiple molecular mechanisms, including β-catenin ubiquitylation and proteasome-mediated degradation. A highly processive enzyme complex comprising casein kinase 1α, glycogen synthase kinase 3β (GSK3β), the adenomatous polyposis coli protein (APC) and Axin phosphorylates conserved serine and threonine residues within the β-catenin N terminus. Phospho-β-catenin is then ubiquitylated by the Skp 1a-Cullin 1-β-transducin-repeat-containing protein (SCF^{βTrCP}) E3 ubiquitin ligase complex, thus targeting it for proteosomal degradation. In the presence of Wnt ligand, β-catenin phosphorylation and ubiquitylation is inhibited and, consequently, β-catenin levels increase. Similarly, genetic mutations that disrupt the phosphorylation or ubiquitylation complexes, such as those frequently observed within the APC gene in colorectal cancer, also stabilize β-catenin. As β-catenin accumulates, it translocates to the nucleus, binds members of the lymphoid enhancer-binding factor 1–T-cell specific transcription factor 7 (LEF–TCF) family of transcription factors, presumably displacing the co-repressors Groucho and C-terminal-binding protein. Transactivation of β-catenin target genes ensues, collectively controlling cellular differentiation, proliferation and migration [3].

Jade-1 negatively regulates β-catenin protein levels

Jade-1 contains two plant homeodomains (PHDs) and a PEST motif (named for its constituent amino acids, Pro-Glu-Ser-Thr) and is implicated as a tumor suppressor in renal cell carcinoma [4]. Chitalia *et al.* [2] identified β-catenin as one of nine interacting proteins in a yeast two-hybrid screen using a form of Jade-1 lacking the PHD domains as bait. Using endogenous, tagged and recombinant proteins, the authors convincingly demonstrate that Jade-1 directly binds β-catenin. Interestingly, Jade-1 binds the β-catenin N terminus, and this association is enhanced by

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