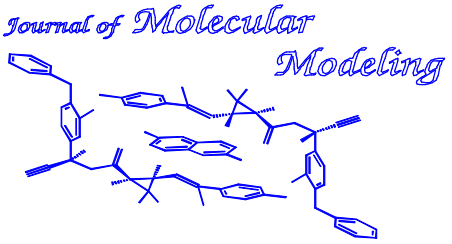
*J. Mol. Model.* **1996**, *2*, 370 – 372






# VRML in Cancer Research
# Local Molecular Properties of the p53 Tumor Suppressor Protein-DNA Interface

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**Abstract**

The three-dimensional structure information of the p53 core domain-DNA complex is presented. The Virtual Reality Modeling Language (VRML), a new concept of information transfer is used for this biochemical application. VRML provides an object oriented method for the three-dimensional description of molecular models [1, 2].
This VRML-WWW pages contain the 3D structure of the p53 core domain-DNA complex crystallized by Pavletich and coworkers [3], now available from the Brookhaven Protein Databank, and the p53-DNA binding region with related biochemical information like hydrophilicity/lipophilicity and local electrostatic partial charges.
These investigations are done in a close cooperation with H. Bartsch and his group at the Division of Toxicology & Cancer Risk Factor Prevention of the German Cancer Research Center in Heidelberg, Germany.

**Keywords:** VRML, WWW, biochemical application, p53 protein-DNA interface

## p53 core domain-DNA complex

In the first 3D-VRML-application (figure 1), the structure of the p53 core domain-DNA complex is represented in a wire model according to the crystallographic structure determination of Nikola Pavletich and coworkers [3]. DNA is colored blue, the three p53 core domain molecules are magenta (c1), yellow (c2), and red (c3). The zink ions are represented as white spheres.

In the next 3D-VRML-applicationon (figure 2) the DNA binding p53 core domain2 molecule is represented as a yellow wire model (left), a yellow wire model with ribbons along the backbone (middle), and with the six red colored mutation hotspots (right).

The *solvent accessible surface* of the p53-DNA binding region is presented in the third 3D-VRML-application (figure 3). The molecular surfaces of the p53 core domain2 molecule and the DNA is colored according to local hydrophilic (blue) - lipophilic (red) properties.

The *solvent accessible surface* of the p53-DNA binding region is presented in the last 3D-VRML-application (figure 4). The molecular surfaces of the p53 core domain2 mol-

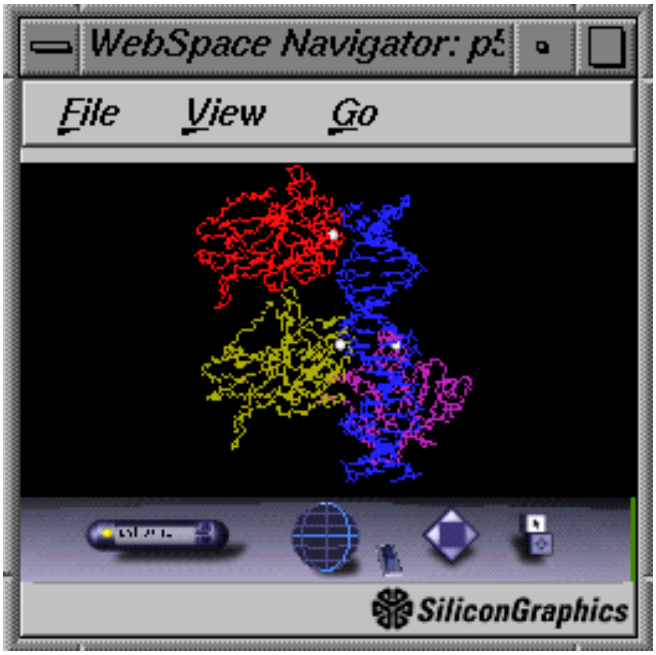


**Figure 1.** *Complete p53-DNA complex - Wireframe*

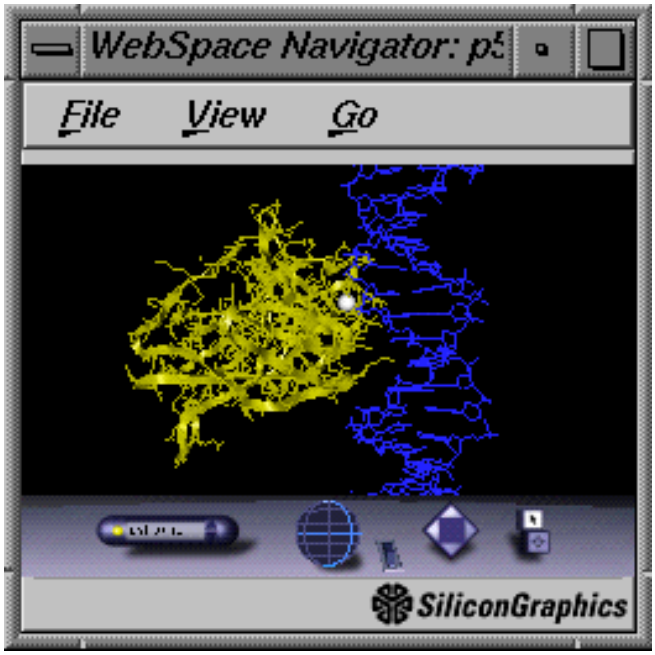


**Figure 2.** *p53 core domain2-DNA complex:Wireframe, Ribbon and mutation hotspots*

ecule and the DNA is colored according to partial charge distribution from negative (red) to positive (green).

## Details

### *P53-DNA Interface*

The p53 tumor suppressor protein controls the cell cycle checkpoint responsible for maintaining the integrity of the genome. When DNA is damaged, the p53 level increases and the cell cycle is stopped at the G1/S phase to allow DNA repair followed by normal cell growth or induction of apoptosis. The p53 protein is frequently altered by mutations in almost all types of cancer. Up to now more than 5000 tumor-specific p53 mutations (85% missense mutations) have been identified and are compiled in a database available at the European Bioinformatics Institute (EBI, Cambridge UK; http://www.ebi.ac.uk/pub/databases/p53/) [4]. The majority of these mutations are found in the central p53 core region containing the DNA binding domain and the zinc binding domain.

The 3D structure of the p53 protein-DNA complex has been crystallized [3] and this allows investigation into the influence of mutations on DNA binding and protein functions. The molecular properties of the p53 tumor suppressor protein-DNA complex available from the Brookhaven Protein Database (PDB) are analyzed using the molecular modeling package SYBYL/MOLCAD [1]. The investigations are based on Connolly's concept of molecular surfaces. These solvent-accessible surfaces show the three-dimensional size and topography of the molecules. Additionally the surfaces are used as maps for a color coded representation of local molecular properties like hydrophilicity/lipophilicity [5] or the electrostatic partial charges calculated with CHARMM. Important to the stability of the protein-DNA complex and to the biological activity as well is the significant amount of water molecules found in the contact region of the complex. The embedded water molecules form hydrogen bonds to both DNA and protein and thus contribute substantially to the protein-DNA interface.

The topographical analysis of this p53 protein-DNA complex shows, that the five mutation hotspots, constituting more than 25% of the database mutations [4], are located either in the zinc binding region or in the protein-DNA interface. ARG248 and ARG273 especially which are most frequently mutated in human tumors bind directly to DNA. The local hydrophobic/hydrophilic properties of the p53 core domain protein are similar to the surrounding DNA interface while the electrostatic charges are complementary leading to intermolecular attraction. Point mutations at these hotspots lead to disturbances of the partly water-bridged DNA binding.

## VRML Application

The three-dimensional structure information of this p53 core domain-DNA complex is presented in the authors World Wide Web pages (Darmstadt University of Technology, Physical Chemistry I, http://www.pc.chemie.th-darmstadt.de/vrml/p53). A summary of this 3D structure data is delivered as a

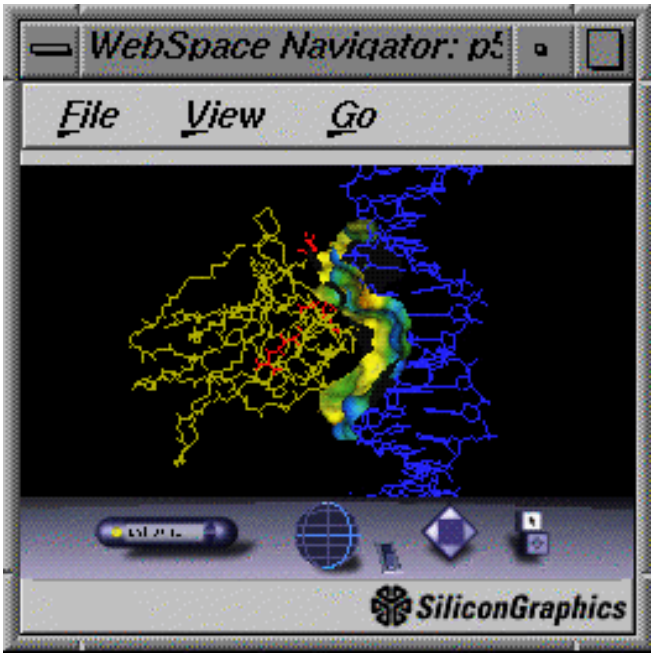


**Figure 3.** *Hydrophilic/lipophilic properties of the p53-DNA interface: Dots, lines and solid.*

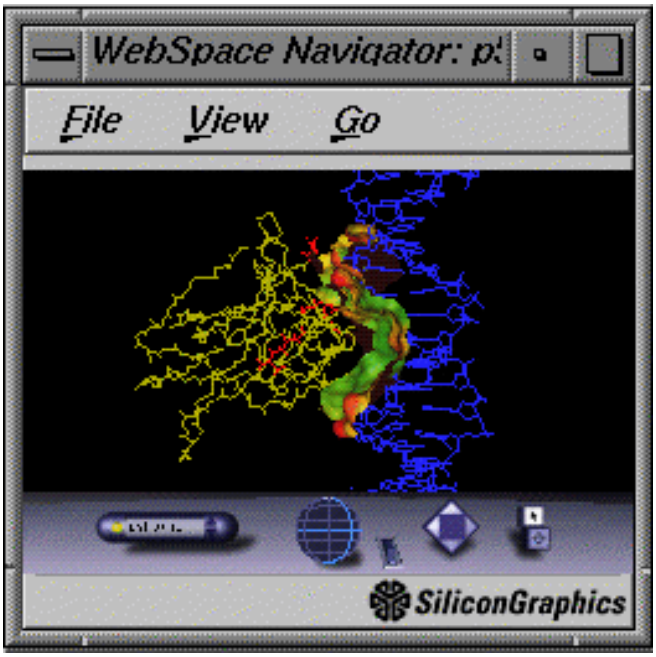


**Figure 4.** *Electrostatic properties of the p53-DNA interface: Dots, lines and solid.*

HTML/VRML supplement with this issue. For this information transfer of biochemical 3D data, a new concept, the Virtual Reality Modeling Language (VRML) is used. VRML provides an object oriented method for the description of molecular models [2]. The language is based on a subset of the Open Inventor File Format. This subset was extended with networking capabilities, such as WWW hyperlinks. With this feature, VRML is an equivalent to the HyperText Markup Language (HTML). Like HTML files describe the layout of 2D-text pages to be displayed by WWW browers, VRML files describe the layout of 3D scenarios. Therefore VRML is an excellent tool for visualization of 3D molecular scenarios. It is used to prepare platform-independent files to visualize the output of all kinds of 3D information commonly generated with molecular modeling technologies [6, 7]. Our VRML-supplement contains the 3D structure data of the p53-DNA complex and the p53-DNA binding region combined with local molecular properties. This example shows an aspect of VRML capabilities to deliver important 3D structure related biochemical information in science.

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