Interactive Analysis and Visualization of Macromolecular Interfaces between Proteins

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Abstract. Molecular interfaces between proteins are of high importance for understanding their interactions and functions. In this paper protein complexes in the PDB database are used as input to calculate an interface contact matrix between two proteins, based on the distance between individual residues and atoms of each protein. The interface contact matrix is linked to a 3D visualization of the macromolecular structures in that way, that mouse clicking on the appropriate part of the interface contact matrix highlights the corresponding residues in the 3D structure. Additionally, the identified residues in the interface contact matrix are used to define the molecular surface at the interface. The interface contact matrix allows the end user to overview the distribution of the involved residues and an evaluation of interfacial binding *hot spots.* The interactive visualization of the selected residues in a 3D view via interacting windows allows realistic analysis of the macromolecular interface.

Keywords: Interface Contact Matrix, Bioinformatics, Macromolecular Interfaces, Human–Computer Interaction, Tumour Necrosis Factor.

1 Introduction

Proteins are the molecules of life used by the cell to read and translate the genomic information into other proteins for performing and controlling cellular processes: metabolism (decomposition and biosynthesis of molecules), physiological signalling, energy storage and conversion, formation of cellular structures etc. Processes inside and outside cells can be described as networks of interacting proteins. A protein molecule is build up as a linear chain of amino acids. Up to 20 different amino acids are involved as elements in protein sequences which contain 50-2000 residues. The functional specificity of a protein is linked to its structure where the shape is of special importance for the intermolecular interactions. These interactions are described in terms of locks and keys. To enable an interaction, the shape of the lock (for example the enzyme) must be complimentary to the shape of the key (the substrate). Examples are the antibody-antigen complexes in the immune system, complexes of growing factors and receptors and especially the tumour necrosis factor – receptor complex.

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The analysis of such interactions are of special importance for modern clinical diagnosis and therapy e.g. in the case of infectious diseases, disturbed metabolic situations, incompatibilities in pharmacology etc.

A protein can not be seen, for example by a microscope (with x-rays focussing lenses). It exists no real image, like a microscopic view from cell, of a protein. Instead a *model,* resulting from (among other methods) X-ray crystallography must be used [1]. The model is derived from a regular diffraction pattern; build up from X-ray reflections scattered from the protein crystal. This structural model is a three-dimensional representation of a molecule containing information about the spatial arrangements of the atoms. The model reflects the experimental data in a consistent way. Protein structural information is publicly available, as atomic coordinate files, at the protein database (PDB), an international repository [2].

Bioinformatics is an interdisciplinary discipline between information science and molecular biology [3-6]. It applies information processing methods and tools to understand biological and medical facts and processes at a molecular level. A growing section of bioinformatics deals with the computation and visualization of 3D protein structures [7-12]. In the world of protein molecules the application of visualization techniques is particularly rewarding, for it allows us to depict phenomena that cannot be seen by any other means. The behaviour of atoms and molecules are beyond the realm of our everyday experience and they are not directly accessible for us.

Modern computers give us the possibility to visualize these phenomena and let us observe events that cannot be witnessed by any other means.

In this paper we concentrate on the analysis of macromolecular interfaces between interacting proteins. The high complexity of the protein-protein interface makes it necessary to choose appropriate (and as simple as possible) representations, allowing the end user to concentrate on the specific features of their current interest without being confused by the wealth of information. As in all medical areas, the amount of information is growing enormously and the end users are faced with the problem of too much rather than too little information; consequently the problem of information overload is rapidly approaching [13]. To apply end user centered methods is one possibility to design and develop the applications exactly suited to the needs of clinicians and biologists in their daily workflows. Usability engineering methods [14] ensure to understand the biologists' interactions, which is necessary to determine how the tools are ideally developed to meet the end users experience, tasks, and work contexts. Several research groups have developed software to assist the analysis of macromolecular interfaces such as: coupled display of planar maps of the interfaces and three dimensional views of the structures or visualization of protein-protein interactions at domains and residue resolutions [15, 16].

We present the development of a tool (the interface contact matrix) for the representation and analysis of the residue distribution at the macromolecular interface, connected interactively with a 3D visualization. Atomic coordinate files of protein complexes (containing two interacting proteins) from the PDB structure database are used as input. Because real experimental data are used, measurements and calculations can be done on the protein structures. First the distances between the residues of the two chains of a complex are calculated. The residues, at a given distance, between the two chains are identified and the interface contact matrix, a plot

of adjacent residues between the two amino acid chains, is constructed. The residues name and number within each chain are plotted on the respective axis (horizontal and vertical axis) and a corresponding entry is done at the appropriate place in the matrix wherever two residues of each chain come into contact. These matrix elements are annotated with several physicochemical properties. The identification of spatial narrow residues between the chains in the complex 3D structure and the additional representation of their pair wise interaction in an interface contact matrix, allows a suitable and easy to survey representation of the interface information. The interface contact matrix enables the end user an overview about the distribution of the involved residues in the macromolecular interface and their properties, an evaluation of interfacial binding *hot spots* and an easy detection of common or similar patterns in different macromolecular interfaces. Of course for a realistic and adequate visualization of a macromolecular interface a 3D representation is necessary. Therefore the elements in the interface contact matrix are linked with the 3D structure in that way that mouse manipulations on the matrix elements display the corresponding region in the 3D structure (the interface between proteins emphasis normally only a limited set of residues). This connection of the two representations, the interface contact matrix and the 3D structure, reveal from a wealth of information the context and connections without overwhelming the end user. The relationship between the two representations was technically realized by interactive windows. Additionally the identified residues in the interface contact matrix are used to define the molecular surface at the interface.

The resulting interface surface enables exploration of molecular complementarities, where physicochemical properties of the residues are projected on the surface. To illustrate the procedure, the complex between the tumour necrosis factor (TNF) and the TNF-receptor was used [17].

The TNF is a dominant proinflammatory protein causing destruction of cells, blood vessels and various tissues and plays an important role in the immune system by activation of immune cells. The TNF-receptor is located at the cell membrane and the TNF molecule is interacting with its extra cellular domain. The interface contact matrix is a tool which enables a better understanding of the interaction between receptor and acceptor molecules which is the precondition for the necessary treatment of excessive inflammation.

2 Materials and Methods

A large number of proteins and protein complexes are deposited in the PDB structure database. At the moment PDB contains more than 44.000 protein structures. The structural information, experimentally determined, is stored in the PDB[1] data files as a collection of Cartesian coordinates of the involved atoms (figure 1, figure 2).

2.1 Software

Based on the experimental data, representations of the protein structures are generated by the computer. The calculations of the macromolecular interface were done by a

[1] The PDB data base can be accessed through Internet and the PDB data files downloaded.

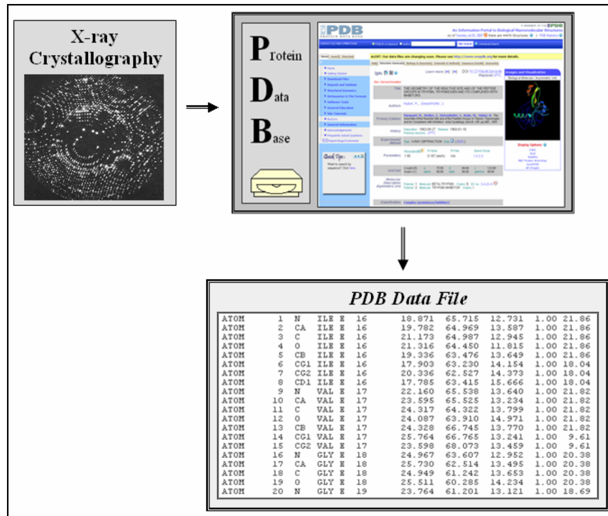

Fig. 1. Structures of protein complexes, determined by X-ray crystallography, are deposited in the PDB structure database. The structural information is stored in the PDB data files. These files contain: a running number, the atom type, the residue name, the chain identification, the number of the residue in the chain, the triplet of coordinates. The PDB data files are downloaded from the database as input files for protein analysis and visualization.

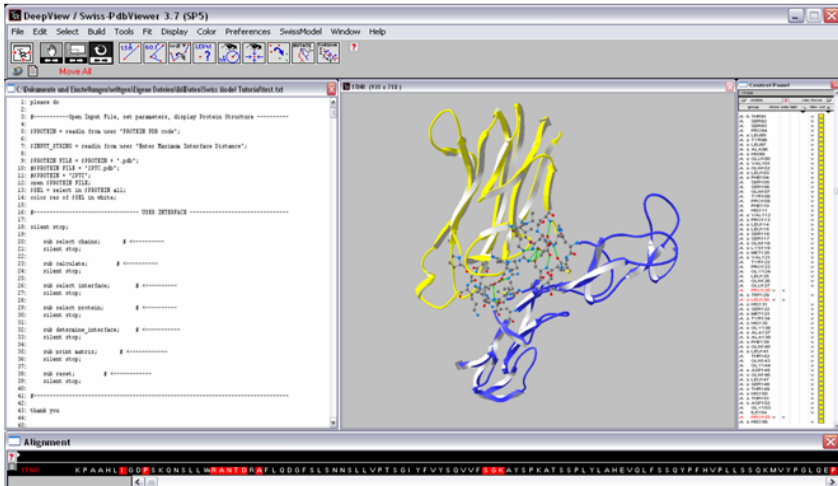

Fig. 2. The Swiss-PDB Viewer provides: main window (top), control panel (right), sequence alignment window (bottom) and display window (middle). In the script window (left) the program for the analysis of the protein-protein interface and the calculation of the interface contact matrix is read in. The calculations are done on the atomic coordinates in the PDB file. The routines for computation/visualization are initiated by mouse clicking in the script window.

special developed computer program for Windows PC, and the results from the analysis were visualized with the Swiss-Pdb Viewer [18], which consists of several windows (figure 2). The main window is used for manipulations (rotations, zooming etc.), representations and measurements of the displayed protein structures. The control panel window enables the selection of single residues for display. At the display window, the protein structures are visualized. The Swiss-Pdb viewer includes a parser of a scripting language. For the analysis of the protein interfaces, the proprietary program (written in the Deep View scripting language, a PERL derivate) was read in the script window. The program enables:

- identification of the residues involved in the interface between two chains,
- the determination of hydrogen bonds between appropriate atoms of the interface residues,
- the calculation and printing of the interface contact matrix,
- the annotation of physicochemical properties to the matrix elements.

The calculations for identifying the residues at the protein-protein interface are done automatically by use of the atomic coordinates from the PDB file (figure 3).

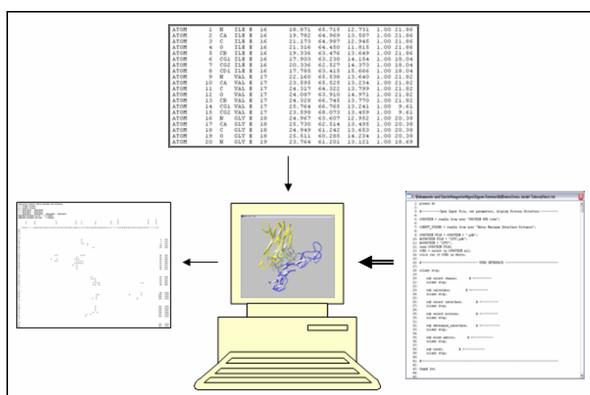

Fig. 3. The structural information stored in the PDB data file is used as input for computing and visualization. The calculations are done in a scripting language, and the output is represented as pair wise interaction of adjacent residues in the interface contact matrix.

At the end of the program run, routines are called by the program and displayed in the script window, allowing further manipulation of the results interactively by the user. The routines are initiated by mouse clicking in the script window and enables:

- the calculation of the molecular surfaces at the interface,
- the interactive visualization and analysis of the interface residues,
- the visualization of interfacial geometries in 3D

Interacting windows enables the relationship between the output data of the distance calculations and the corresponding parts of the protein 3D structure. This offers the possibility to interactively connect the elements in the interface contact

matrix with structural properties. By mouse clicking on the appropriate output data the corresponding residue pairs (one on each chain) are highlighted on the display window allowing the evaluation of the structural properties.

Interface Contact Matrix between two Proteins
x = Single H-Bond
y = double H-Bond
h = Hydrophob - Hydrophob
i = Hydrophil - Hydrophil
o = Hydrophil - Hydrophob Hydrophob - Hydrophil
MAXIMUM DISTANCE CA-CA: 25.000000
MAXIMUM DISTANCE RES-RES: 6.000000

Fig. 4. The interface contact matrix is a plot of pair wise interactions between interfacial residues in the protein complex (vertical axis: TNF, horizontal axis: TNF-receptor). The residue name (one letter code) and number within each chain are plotted on the corresponding axis and an entry is made wherever two residues of each chain come into close contact. The contact is defined by a predefined threshold distance within the distance between at least two atoms (one of each residue) must fall in. Physicochemical properties are annotated to the matrix elements.

2.2 Computational Method

The macromolecular interface between proteins is defined by complementary surfaces with adjacent residues which are close enough to interact. First, the interatomic distances d_{ij} between each residue (n_i and m_j) of the two polypeptide chains A (TNF chain) and R (TNF-receptor chain) are determined automatically.

$$\forall_{n_i \in A} \forall_{m_j \in R} : (n_i, m_j) \rightarrow d_{ij}, \quad (1)$$

Then the residues, where at least two adjacent atoms are separated by a distance less than a predefined threshold distance, are identified as interface residues.

2.2.1 Interface Contact Matrix

These residues are used as input to construct the interface contact matrix:

$$I_l = \left\{ (n_i, m_j) \mid d_{ij} \le d_l \right\}, \quad (2)$$

The two dimensional interface contact matrix is a plot of pair wise interactions between adjacent residues of the two chains in the protein complex (figure 4). The residue names and numbers within each chain are plotted on the respective axis (horizontal and vertical axis) and a corresponding entry is done at the appropriate place in the matrix wherever two residues of each chain interact. The values of the threshold distance d_l (4-6 angstroms) are motivated by the range of hydrogen bonds and van der Waals bonds (figure 5). The matrix elements define then the macromolecular interface and they are used for further definitions and calculations. Combinations of physicochemical properties p_c are annotated to the matrix elements in the interface contact matrix:

$$\forall_{(n_i, m_j) \in I_l} \exists_{p_c \in P} : (n_i, m_j) \rightarrow p_c \,, \tag{3}$$

This indicates complementarities and correlations between the properties of the two residues across the interface like: electrostatic complementarities, correlation of hydrophobic/hydrophilic values, correlation of proton donator and acceptor across the interface resulting in hydrogen bonds.

2.2.2 Visualization of Macromolecular Interfaces

The interface contact matrix is interactively linked to a 3D visualization of the macromolecular structures, making the involved residues easily detectable in the wealth of information provided by the complex structures (figure 6). By mouse clicking on selected parts of the residue distribution in the matrix, highlights the corresponding residues in the 3D structure.

Molecular surfaces are suitable for the description of molecular shapes and the visualization of their complementary properties [19]. The residue distribution in the interface contact matrix is used to define the molecular surfaces (one for each protein in the complex) at the macromolecular interface. The following is done for the residues of each chain, identified in the interface contact matrix (components of the residue pairs $(n_i, m_j) \in I_l$), in the protein complex separately. To each atom A_k of a residue n_i a function ρ, depending on the size σ_k of the atom (with centre at r_k) and a weighting factor, is assigned:

$$n_i(A_k) \rightarrow \rho(w_k, r - r_k, \sigma_k) \,, \tag{4}$$

The weighting factor w_k, describes the contribution of the considered atom to the molecular surface. Then the functions of all the atoms of the residues in the interface contact matrix, contributing to the set of surface atoms S of the molecule are considered and summed up.

A common description of the molecular surface uses Gaussian functions, centred on each atom A_k [19]:

$$\rho(r) = \sum_{k \in S} w_k \, e^{-|r - r_k|^2 / \sigma_k^2} \,, \tag{5}$$

This defines the approximate electron density distribution (other functions are also used in literature).

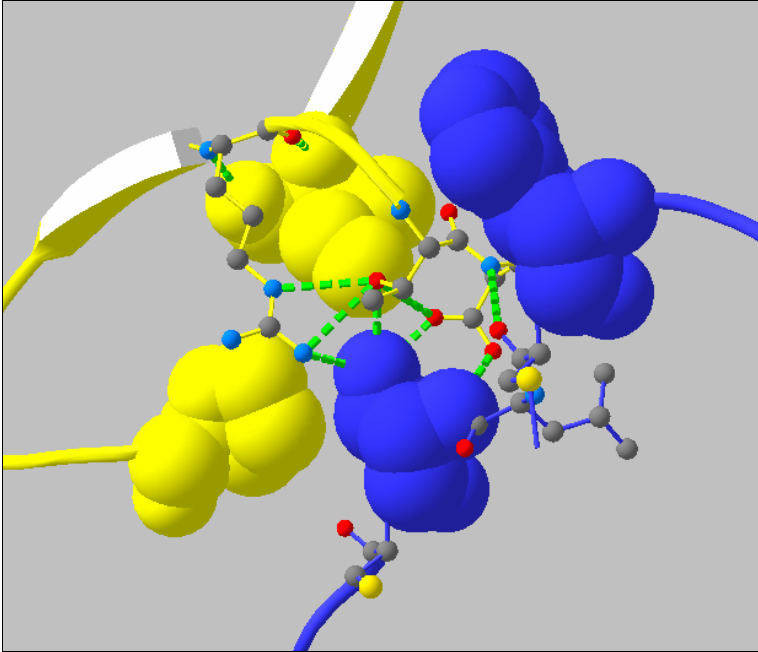

Fig. 5. The macromolecular interface can be defined by residues on both polypeptide chains which are close enough to form interactions. The most important interactions are hydrogen bonds (range 3.6 angstroms) and van der Waals bonds. Usually the van der Waals bonds arise between two atoms with van der Waals spheres (1.4-1.9 angstroms) within a distance of 1.5 angstrom of each other with no overlapping. Hydrogen bonds (dotted lines) arise from the interaction of two polar groups containing a proton donor and proton acceptor. Van der Waals bonds (interacting spheres): Due to its electronic properties, an atom acts as a dipole which polarises the neighbour atom, resulting in a transient attractive force. The threshold distance d_1 in the interface contact matrix is motivated by the range of these interactions.

In the protein complex, the molecular surfaces of both proteins show complementary areas at the interface (because the calculations of the molecular surfaces at the interface are done by use of adjacent residues: $(n_i, m_j) \in I_1$ at close distances).

3 Results

The presented method allows the analysis of the protein-protein interactions at the level of the sequences (interface contact matrix) and on the level of the 3D structure. Both analysis levels are interconnected, enabling a relation between different kinds of exploited information.

The analysis of the interaction properties in the interface contact matrix facilitates an identification and evaluation of interfacial binding "hot spots", that means locally strong binding forces. Important binding forces are hydrogen bonds which arise from

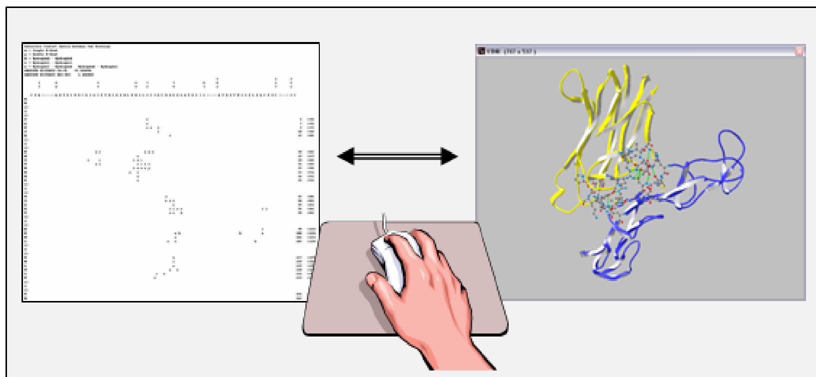

Fig. 6. Interactive windows enable a relationship between the elements of the interface contact matrix and the appropriate part of the 3D structure. Mouse clicking on the data of interest in the output window results in a highlighting of the corresponding parts of the protein structure in the display window. This enables an easy detection and structural analysis of the involved residues in the wealth of information provided by the complex interface structures.

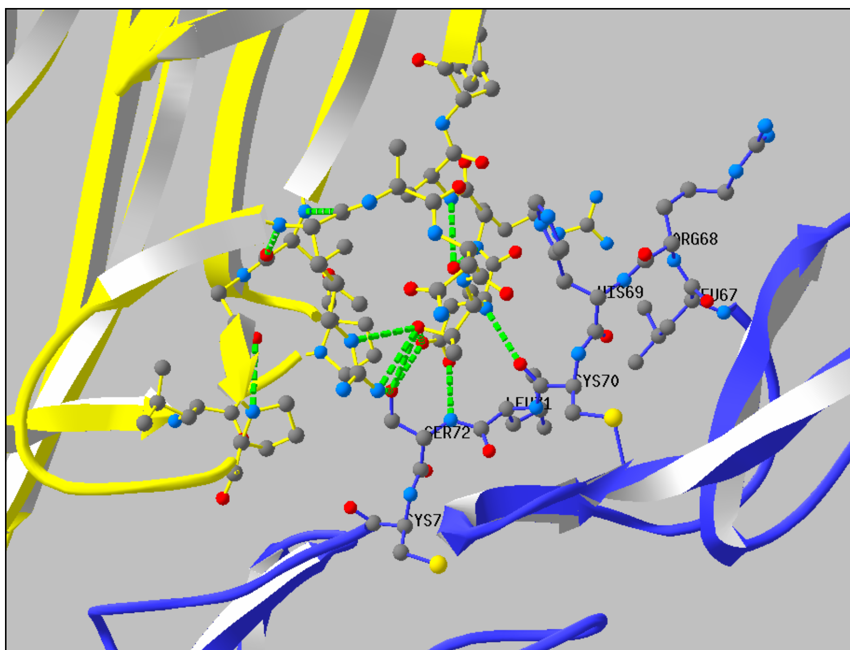

Fig. 7. This figure shows the 3D interface structure of the highlighted part of the interface contact matrix in figure 4. The TNF (upper part) is interacting with the extra cellular domain of its receptor (lower part). The residues at the macromolecular interface are visualized in a “ball-and-stick” representation. The covalent bonds are represented as sticks between atoms, which are represented as balls. The rest of the two chains are represented as ribbons. Residue names and numbers of the TNF receptor are labelled. The hydrogen bonds are represented by dotted lines.

the interaction of two polar groups containing a proton donor (amino group) and proton acceptor (carboxyl group). Hydrogen bonds are one of the most stabilizing forces in protein structure and are responsible for the binding of the protein to substrates and the factor-receptor binding (figure 5). The annotations to the contact patterns are useful for the evaluation of energetically effects at the macromolecular interface where the number and distribution of hydrogen bonds give hints about the strength of the interaction (figure 4).

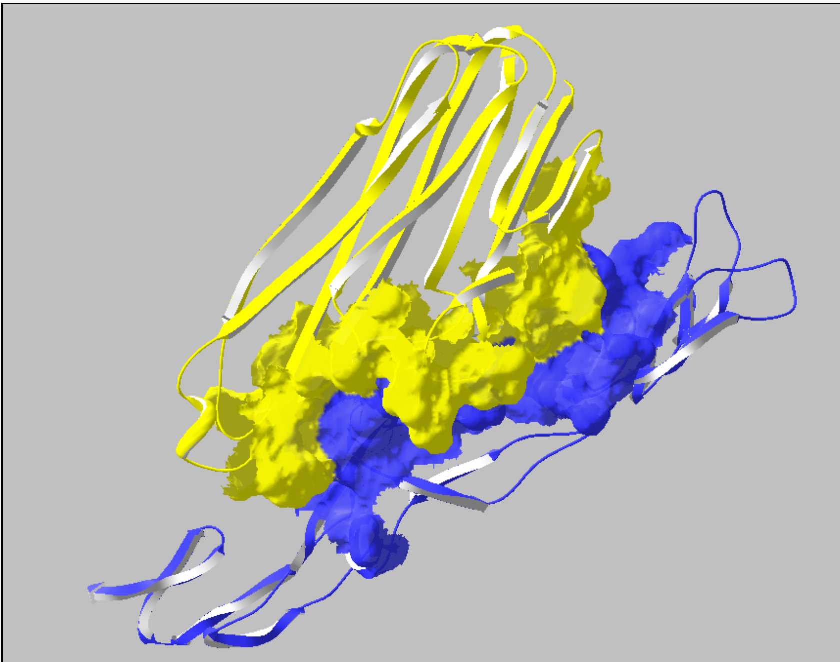

Fig. 8. Complementary molecular surfaces at the molecular interface of the TNF and its receptor. The identified residues in the interface contact matrix (figure 4) are used to define the molecular surfaces at the interface (with distances between the atoms of both chains till 7.5 angstroms). The surfaces are helpfully for the exploration of molecular complementarities. From the interaction of the two amino acid chains results complementary surfaces, where the two molecular surfaces come into contact.

The interaction pattern of the residues in the interface contact matrices indicate how folded the proteins are at the interface (residues witch are widely separated in the amino acid chain are acting together at the local interface). The distribution of the matrix elements along the columns in the matrix shows how embedded the interface residues of the receptor (horizontal axis) in the environment of the TNF residues are. This gives some hints for the exposure of the receptor residues to the adjacent residues in the macromolecular interface.

The visualization of the selected residues in a 3D view via interacting windows allows a realistic analysis of the macromolecular interface (figure 6). Due to the

interactive windows, the selection of the residues in the interface contact matrix and the highlighting in the 3D structure allows an easy retrieval of the desired information out of the wealth of structural information without overwhelming the end user. This is of special importance for the exploration of highly embedded residues in the macromolecular interface, as well for matrix element distributions showing a high number of hydrogen bonds. It allows a fast and easy overview about the involved residues in their structural context. Complementary properties (for example: electrostatic, hydrophobic/hydrophilic values) of adjacent residues across the protein-protein interfaces can be detected in the interface contact matrix and studied in a 3D view. The relative orientations of the side chains of opposed residues and their reciprocal exposure are visualized (figure 7).

The visualization of the molecular surfaces of the residues at the interface of the two chains, where the two surfaces come into contact, allows insight into the interfacial geometries in 3D and the identification of molecular complementarities (figure 8).

4 Discussion

Exploring complementary protein surfaces provides an important route for discovering unrecognized or novel functional relationships between proteins. This is of special importance for the planning of an individual drug treatment. Better medication can be developed once the structures of binding sites are known.

There exist several approaches and methods for studying macromolecular interfaces like: the web resource iPfam, allowing the investigation of protein interactions in the PDB structures at the level of (Pfam) domains and amino acid residues and MolSurfer, which establish a relation between a 2D Map (for navigation) and 3D the molecular surface [15, 16]. The advantage of the presented method for the analysis of macromolecular interfaces is the representation at sequence level and at structural level and the connection between both views. That means the connection of statistical properties (distribution of the residues together with their annotated physicochemical values in the interface contact matrix) and the structural properties (reciprocal exposure of side chains, atomic interactions).

The selection of the residues in the interface contact matrix and the highlighting of the corresponding 3D structure, by aid of the interactive windows, enable an easy identification and structural analysis of the interfacial residues in the wealth of information provided by the complex interface structures. Common patterns in the interface contact matrices allow a fast comparison of similar structures in different macromolecular interfaces.

The analysis of the patterns in the interface contact matrices of slightly different protein complexes allows an easy detection of structural changes. Complementary properties or even possible mismatches of adjacent residues across the protein-protein interfaces can be detected in the interface contact matrix and studied in a 3D view. The representation with molecular surfaces shows complementary shapes.

To demonstrate the applicability of the method in clinical medicine we choose the analysis of the interface between the tumour necrosis factor (TNF) and its receptor [17]. The tumour necrosis factor molecule is particularly interesting. It is responsible for various immune responses such as inflammation and cytokine activation. TNF is

interacting with the extra cellular domain of its receptor, which is located on the cell membrane. It plays a considerable role in the bodies' defence in inflammation, tumour pathology and immunology [20-22].

For this reason many forms of treatments have been building up to reduce the excessive TNF activity. Ethanercept as a receptor molecule (Enbrel) or Infliximab (a humanized antibody) are examples. On account of these molecules modern treatment has become a tremendous success based on the knowledge of the antigenity of TNF. Our macromolecular interface analysis and visualization system may help us to define better receptor and acceptor molecules for the neutralisation and excretion of the tumour necrosis factor. By the analysis of the residue distributions in the interface contact matrix and the associated visualisation of the macromolecular interface, the active sites of the reciprocal molecules can be studied and the concept of neutralisation and inactivation followed.

The interface contact matrix is a suitable frame work for further investigations of the macromolecular interfaces, providing the matrix elements with additional data. Further studies may investigate the macromolecular interfaces in more details by determining the most exposed interfacial residues and, in an additional step, by calculating and visualization of details at the atomic and electronic levels of these residues. The topic of future work will be the quantification of the contact between adjacent residues across the interface.

This can be done by Voronoi tessalation, a partition of the protein into cells with polygonal surfaces defining the neighbourhood of an amino acid and its contact area with adjacent residues. Of special importance is the interfacial accessibility, the area of common faces of the cells of adjacent residues on both chains.

The annotation of these values to the interface contact matrix allows the evaluation of the distribution of the contact areas of the matrix elements and the determination of the most exposed residues involved in the macromolecular interface.

These annotations result from structural analysis, which are nowadays advanced and high-throughput methods for the determination of the structure of factor-receptor complexes providing the information need to build the structure-activity relationships. Details at the atomic and electronic levels of the macromolecular interface needed for a deeper understanding of the processes, that remain unrevealed after structural elucidation, may be provided additionally by quantum theoretical calculations.

In every case, filling the "frame work" interface contact matrix with information means: connecting the matrix elements with physicochemical annotations, showing different and successively more properties of the macromolecular interface.

5 Conclusion

Our approach offers the advantage of connecting the interface contact matrix with a 3D visualization of the complex interfaces. In the interface contact matrix the involved residues of the macromolecular interface can be determined, (complementary) physicochemical properties be annotated and common pattern of different interfaces detected. The visualization of the selected residues in a 3D view via interacting windows allows a realistic analysis of the macromolecular interface.

We have used for demonstration of the method, the complex of TNF and its – Receptor representing a most rewarding concept of modern therapy. By computer visualisation, the macromolecular interface of the reciprocal molecules can be shown and the concept of neutralisation and inactivation followed.

This procedure of inactivation and neutralisation of detrimental molecules can barely figured out without the optical advices obtained with such methods. Molecular medicine means the understanding of diseases at a molecular level.

Hence thanks to these attempts of analysis and visualisation the construction and synthesis of reciprocal acceptor-, blocking- and neutralisation molecules may be very much enhanced and helpful for end users in diagnosis and treatment of inflammations and other diseases.

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