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The Interaction of peptides with functionalized carbon nanotubes

Poulami Barman

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The Interaction of Peptides with Functionalized Carbon Nanotubes

Submitted in partial fulfillment of the requirements for the Master of Science degree in Bioinformatics at the Rochester Institute of Technology.

Poulami Barman
19 February 2009
Dedicated to my beloved Parents (Dr. Rabindra Nath Barman & Dr. (Mrs.) Krishna Barman), my lovely Sister (Prokwana Barman) and my Family (Abhisek Bhadra)
DISSERTATION AUTHOR PERMISSION STATEMENT

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Author: Poulami Barman

Degree: Masters

Program: Bioinformatics

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Date:
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>± SEM</td>
<td>±Systolic Ejection Murmur</td>
</tr>
<tr>
<td>*p</td>
<td>Probability value for epinephrine and vasopressin vs. saline placebo</td>
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<tr>
<td>*p</td>
<td>Probability value for vasopressin vs. epinephrine and saline placebo</td>
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<td>*p</td>
<td>Probability value for vasopressin vs. epinephrine and saline placebo</td>
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<td>2Fo-Fc</td>
<td>Electron Density Map (Fo: observed structure factors, Fc: calculated structure factors)</td>
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<td>ADH</td>
<td>Anti Diuretic Hormone</td>
</tr>
<tr>
<td>AFM</td>
<td>Atomic Force Microscopy</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<td>AmB</td>
<td>Amphotericin B</td>
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<td>Arginine residue as residue #8 from N-terminal</td>
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<td>Asn5-I</td>
<td>Asparginine residue as residue #5 from N-terminal</td>
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<td>AVP</td>
<td>Arginine Vasopressin</td>
</tr>
<tr>
<td>BD</td>
<td>Biodistribution</td>
</tr>
<tr>
<td>BL</td>
<td>Base Line measurement</td>
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<tr>
<td>BSA</td>
<td>Bovine Serum Albumin</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CNT</td>
<td>Carbon Nanotubes</td>
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<tr>
<td>CVD</td>
<td>Chemical Vapor Deposition</td>
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<tr>
<td>Cys6-I</td>
<td>Cysteine residue as residue #6 from N-terminal</td>
</tr>
<tr>
<td>cyt-c</td>
<td>Cytochrome c</td>
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<tr>
<td>DA</td>
<td>Administration of Study Drug</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>DDS</td>
<td>Drug Delivery System</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
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<tr>
<td>DNA</td>
<td>Deoxyribo Nucleic Acid</td>
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<tr>
<td>EAD</td>
<td>Electric Arc Discharge</td>
</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-Linked ImmunoSorbent Assay</td>
</tr>
<tr>
<td>ERC</td>
<td>European Resuscitation Council</td>
</tr>
<tr>
<td>FITC</td>
<td>Fluorescein Isothiocyanate</td>
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<td>Gln4-I</td>
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<td>Gly9-I</td>
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<tr>
<td>H₂SO₄</td>
<td>Sulfuric Acid</td>
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<tr>
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<td>Hydrochloric Acid</td>
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<tr>
<td>HeLa</td>
<td>Henrietta Lacks cell line</td>
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<tr>
<td>HF</td>
<td>Hydrofluoric Acid</td>
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<td>HL-60</td>
<td>Human promyelocytic leukemia cells</td>
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<tr>
<td>HMDA</td>
<td>Hexamethylenediamine</td>
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<tr>
<td>HNO₃</td>
<td>Nitric Acid</td>
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<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>LA</td>
<td>Laser Ablation</td>
</tr>
<tr>
<td>LGA</td>
<td>Lamarckian Genetic Algorithm</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
</tr>
<tr>
<td>MPS</td>
<td>Mononuclear Phagocytic Systems</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
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<td>-----------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>MWNT/MWCNT</td>
<td>Multiple Walled Nanotubes / Multiple Walled Carbon Nanotubes</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td>NH₄OH</td>
<td>Ammonium Hydroxide</td>
</tr>
<tr>
<td>PDB</td>
<td>Protein Data Bank</td>
</tr>
<tr>
<td>PDDA</td>
<td>Polydiallyldimethylammonium chloride</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PTX</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Rmsd</td>
<td>Root Mean Square Deviation</td>
</tr>
<tr>
<td>ROSC</td>
<td>Restoration of Spontaneous Circulation</td>
</tr>
<tr>
<td>SA</td>
<td>Streptavidin</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscopy</td>
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<tr>
<td>SiO₂</td>
<td>Silicon Dioxide</td>
</tr>
<tr>
<td>siRNA</td>
<td>Short interfering RNA</td>
</tr>
<tr>
<td>SLN</td>
<td>Solid Lipid Nanoparticles</td>
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<tr>
<td>SpA</td>
<td>Protein A</td>
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<tr>
<td>SPDBV</td>
<td>Swiss- Protein Data Bank Deep Viewer</td>
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<tr>
<td>SWNT/SWCNT</td>
<td>Single Walled Nanotubes/Single Walled Carbon Nanotubes</td>
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<tr>
<td>TCE</td>
<td>TetraChloroethylene</td>
</tr>
<tr>
<td>TCM</td>
<td>Trichloromethane</td>
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<tr>
<td>TEM</td>
<td>Transmission Electron Microscopy</td>
</tr>
<tr>
<td>TEP</td>
<td>Thermo Electric Power</td>
</tr>
<tr>
<td>TFM</td>
<td>Trifluoromethane</td>
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<tr>
<td>TIP3P</td>
<td>Water model in Molecular Docking</td>
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<tr>
<td>Tyr2-I</td>
<td>Tyrosin residue as residue #2 from N-terminal</td>
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ABSTRACT

A literature study was conducted to review peptide adhesion to carbon nanotubes and they were found to be important in the drug designing industries. To attain target specificity CNTs (functionalized with DNA, peptides etc.) have been used as potential vector system. Prior studies show that single walled nanotubes (SWNTs) when functionalized with peptides have been proven to be better delivery systems than the previous vector delivery systems. Functionalized SWNTs can deliver the peptides to the specific target organs in the right concentration without having prominent toxic effect. Toxicity studies show that since the SWNTs have shorter half life periods most of them get washed away after they deliver the ligands to the target organs. It has been shown that SWNTs that are toxic to the body are so solely due to manufacturing defects. Pure SWNTs are not toxic to the body. Recently functionalized CNTs are also used for cancer therapy.

A docking study was carried out on interaction of hydrogen and nitrogen functionalized SWNTs with peptides where vasopressin is the model peptide. In order to study the effect of dimensions of SWNTs and functionalized group attached to the SWNTs on the strength of a bond, binding free energies were calculated from the docking models. Hydrogen functionalized, nitrogen functionalized and non-functionalized SWNTs binding energies were compared with each other. Results show that functionalized SWNTs tend to bind with more peptide molecules than non-functionalized SWNTs. The interactions on the inner walls of SWNTs are more unstable than the outer wall interactions.
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Chapter 1

Introduction

Since before the dawn of this century, there has been increasing use of the word ‘nano’ in the field of biology. ‘Nano’ science is defined as the branch of science that utilizes small particles in the nano scale range ($10^{-9}$ m). These extremely small particles exhibit different kinds of mechanical, electronic and structural properties than their macroscopic counterparts. For example, a bulk material consists of constant physical properties independent of its size. On a small scale, these properties will change with the number of atoms on its surface. Therefore, nanoparticles may have different properties from their parent bulk materials. Since nanoparticles tend to aggregate, sustaining some of their properties may be difficult. With this aggregation, some of the nanoscale properties may disappear. Here lies the biggest challenge in the field of nano-science. Recently, proper surface engineering techniques have been applied to introduce some kind of repulsive forces between nano surfaces such as electrostatic and steric methods (Fig 1), which help to prevent aggregation of the particles and retain desirable properties. In particular, carbon nanotubes (CNTs) show promising applications in the biological sciences and especially in the medical field [1, 2, 3].
In the field of drug designing and delivery, one of the major issues has been the degradation of the drug before it reaches the target tissue. In order to address this issue, active research is being carried out on improving the vector system used for drug delivery. Recently carbon nanotubes have been identified as a potential vector system when functionalized with peptides, DNA or antigen. The first part of this Thesis involved a thorough review on the applications and background study on the use of nanotubes in the therapeutic field and proposes future research as a vector for drug delivery. In the second part of this Thesis, a docking study was done to calculate the binding free energies of interaction of functionalized single-walled carbon nanotubes with a model peptide, vasopressin.

*Figure 1: Stabilization of Nano Particles by Means of Electrostatic & Steric Methods.*
Chapter 2

Background Study

2.1 Background on Carbon Nanotube

CNTs are allotropes of carbon. There are mainly two types: a) the single-walled nanotubes (SWNTs) and b) the multi-walled carbon nanotubes (MWNTs). SWNTs are made of one layer of graphite, which is otherwise known as the graphene sheet made into a cylindrical structure. The length to diameter ratio of the structure can exceed 10,000 making it a nanostructure. MWNTs have a central tubule surrounded by multiple layers of graphite spaced by a distance of about 0.34 nm (Fig 2). The diameter range for SWNT varies from 0.4 to 2 nm whereas for MWNTs the diameter varies from 1.4 to 100 nm. Generally, the SWNTs are found in clusters due to the strong Van der Waals interactions resulting in an entangled rope like structure [2]. The chemical bonds in nanotubes are primarily \( sp^2 \)-hybridized which are stronger than the \( sp^3 \)-bonds of diamond thus contributing to its unique level of strength.

SWNTs tend to arrange themselves hexagonally to form a crystal-like structure. These unique structures provide their amazing properties. SWNT have greater mechanical strengths than iron as well as lower density than aluminum. They are thermally stable up to 1400 °C in vacuum. When subjected to a low electric field, they emit electrons making them suitable for flat panel display applications. The nanometer scale spaces allow adsorption of large amount of gases, like hydrogen. This property of SWNT has been utilized in energy storage applications such as fuel cells [4]. Different types of SWNTs are shown in Figure 3.
MWNTs, on the other hand, consist of concentric cylinders with each tube having different chirality. Transmission Electron Microscopy (TEM) images clearly show different distinct layers in the constructions of MWNTs. There are mainly 3 layers of graphene layers used in the manufacturing of MWNTs. They are parallel, perpendicular and herringbone type (Fig 4) [6].

**Figure 3: Formation of SWNT [5] and different types of SWNT [4].**

**Figure 4: Multiwalled carbon nanotubes [6, 7].**
2.2 Properties of Carbon Nanotubes

The SWNT cylinder (Fig 3) can be considered as a molecular scale wire having some property-defining parameters as well. The graphene sheets are folded in such a way that the beginning and end of a (m, n) lattice vector situated in the graphene plane meet each other. This is the simplistic way for the formation of a (m, n) nanotube. The (m, n) coordinates are important as they decide the diameter of the nanotube as well as the “chirality” of the same [8]. The schematic honeycomb structure of a graphene sheet with several lattice vectors has been shown below in Figure 5.
Figure 5: Schematic Structure of a Graphene Sheet & SWNTs [8].

Figure 5a, 5b, 5c and 5d are different SWNTs. Figure 5a is an “Arm-Chair” SWNT as it has atoms arranged around the circumference in an arm-chair pattern. For them, m= n. Figure 5b, 5c and 5d are “zigzag” SWNTs. They have either m or n equal to zero. The angle between base vectors $a_1$ and $a_2$ is termed as $\theta$. For armchair and zigzag structures, $\theta$ is $30^\circ$ and $0^\circ$ respectively. For a (m, n) nanotube, if $m - n = 3 \times \text{Integer}$, then the nanotube
will possess semiconductor properties, if not, it will have metallic properties. The lattice vector $\mathbf{v}$ which maps an atom from the left-hand border onto an atom on the right border line cannot be arbitrary but is an integer multiple of the two graphite basis vectors $\mathbf{a}_1$ and $\mathbf{a}_2$, i.e. $\mathbf{v} = n \mathbf{a}_1 + m \mathbf{a}_2$. Here the $\mathbf{a}_1$ and $\mathbf{a}_2$ vectors are multiplied to increase the size of the nanotube. In terms of mechanical strength, they are the strongest and most resilient materials to exist in nature and have a Young’s Modulus of 1.2 TPa and tensile strength one hundred times more than that of stainless steel, capable of tolerating larger strains before failure. In addition, they can exhibit metallic conductivity, chemical and thermal stability and elasticity. The tubes attain their tensile property from the covalent $sp^2$ bonds that make them stronger than metallic steel. The elastic properties of the nanotubes results in having a permanent deformation occurring under excessive tensile stress. The electrical property is due to the symmetrical structure of the CNTs and the unique electronic structure of the graphene. SWNTs also possess some thermoelectric powers (TEP) at high temperature. One of the disadvantages of nanotubes is their inability to dissolve in aqueous solution. To remedy this problem, nanotubes can be functionalized using hydrophilic groups [8, 9].

2.3 Surface Functionalization of Carbon Nanotubes

Since carbon nanotubes are insoluble in any kind of solvents, they can be processed only in suspended forms. Solubility is an important property where material processing and purification are concerned. Functionalization helps in purifying nanotubes from carbonaceous materials, reduces the width of tube diameter dispersion and enhances the reactivity of the nanotubes. This reactivity enhancement is done mostly with the help of nanotubes with smaller diameters. In spite of their instability because of higher curvature
energy, smaller diameter tubes show higher reactivity as well as increased deviation from
the planar (theoretical) graphene properties. Spectroscopic analysis shows [10] that the
smaller diameter tubes follows deviation from the normal graphene geometry. The
advantageous part is that from this deviation we can be conversant with the working
conditions of the nanotubes for specific applications [10]. Figure 6 shows how different
or deviated the actual grapheme properties are from the theoretical behavior of the
graphene properties.

![Figure 6: Difference between Inverse Tube Diameters Calculated from Density
Functional Theory (DFT) & Zone Folding for Small Tubes Vs Inverse Zone Folding
Diameters [10].](image)

Carbon nanotubes that have been surface modified with some other atoms or groups or
radicals are often called functionalized CNTs. For example, for bulk processing of CNTs,
many liquid-phase oxidizing agents have been utilized including nitric acid, sulfuric acid,
peroxides and potassium permanganate to introduce hydrogen-containing moieties
associated with the –C-O-, -C=O and –COO- functional groups. In contrast, gas-phase
functionalization offers the potential for controlled nano-scale functionalization without
the generation of liquid waste, as recently demonstrated using photo-oxidation of both
MWNTs [11, 12, 13] and SWNTs [14]. A wide range of other potential functional groups
may be used to surface modify CNTs with gas-phase techniques. Recent experiments also
show [15] affinity of carbon nanotubes towards biological molecules, e.g. antibodies,
vaccines, drugs, etc.

There are mainly two types of functionalization of CNTs: non-covalent and covalent
functionalization [2]. Non-covalent bonding involves more dispersed variations of
electromagnetic interactions between the group and the nanotube surface, e.g.,
functionalization of nanotubes with α-Helical amphipatic peptide to bring CNTs into
solution. Covalent functionalization is sharing of electrons with the surface of the
nanotubes [2]. There is a wide range of functionalization techniques being used for
CNTs. A few are briefly discussed below.

2.3.1 Highly Reactive SWNT Functionalized by Alkyl Halides

Functionalization depends heavily on surface engineering techniques, such as chemical
vapor deposition. The alkyl halides, trifluoromethane (TFM) and trichloromethane
(TCM) are often used as functionalization agents [16]. Double bond containing alkyl
halides, like tetrachloroethylene (TCE) or hexafluoropropene, that form radicals easily,
are also used as agents [16]. The method is carried out at mild conditions (e.g. at room
temperature) with the ball milling operations of nanotubes [16]. This process creates
active sites on the nanotubes by the cleavage of C-C bonds resulting in enhanced
reactivity as other molecules in gas phase get adsorbed on the nanotube surface [16].
Figure 7(a) shows the Transmission Electron Microscopic (TEM) images of non-
functionalized SWNTs and Figure 7(b) shows after 30 mins of vacuum milling of SWNT with TCE.

![TEM images of a) Pristine b) for 30 min vacuum-milled SWNT sample](image)

*Figure 7: TEM images of a) Pristine b) for 30 min vacuum-milled SWNT sample [16].*

### 2.3.2 Highly Reactive & Stable CNT Functionalized by Strong Acids

Chemical functionalization using strong acids is a popular method [17]. The same method can be applied to carbon nanotubes in order to increase their reactivity as well as dispersion. The three most common acids used to functionalize CNTs are sulfuric acid (H$_2$SO$_4$), nitric acid (HNO$_3$) and hydrochloric acid (HCl) are used in different combinations to functionalize CNTs. At the very beginning, pristine CNTs are synthesized by catalytic vapor deposition techniques with Mo/Fe as catalysts [17]. In the next step, they are washed with hydrochloric acid in air to remove all metallic catalysts from their surfaces [17]. Three different functionalization techniques have been used [17]. In the first one, CNTs are immersed in a mixture of H$_2$SO$_4$/HNO$_3$ (3:1) at room temperature. They are then kept in an ultrasound bath for 2-15 hours. Hydrochloric acid is then slowly added to the mixture and neutralized subsequently using ammonium hydroxide (NH$_4$OH). The entire solution is then filtered with a 0.22 µm cellulose acetate
membrane. Nanotubes are washed properly until they reach a pH level of 5.5. For the other two functionalization techniques most of the procedures are followed except the composition of acids. In the second method [17], hydrochloric acid (HCl) is not used and for the third one [17], only nitric acid is used. All of these techniques share a common feature that certain percentages of functional groups have been formed on the nanotubes. This results in increased reactivity as well as improved dispersion. The first functionalization technique using all of the three acids is the most efficient one followed by the technique eliminating hydrochloric acid [17]. Dispersion analysis shows that suspension stability of CNTs is poor because of the agglomeration of the nanotubes [17]. Lack of hydrogen bonding also supports this fact. CNTs functionalized by all of the three kinds of acids show the highest stability due to the higher percentage of functional groups [17]. Figure 8 shows the TEM images of non-functionalized SWNTs on the left (a) and functionalized CNTs on the right (b).

![Figure 8: TEM images of a) Pristine & b) Functionalized CNTs [17].](image)

2.3.3 Bioactive or Natural Species Functionalization

Recently, a new area of application in biological systems has emerged which is known as the functionalization with bioactive or natural species [18]. This method primarily
involves attachment of biomolecules like proteins, peptides, DNA or antibodies etc. Nanotubes not only have a property of attaching biological materials on their surface but their cylindrical nature also facilitates the incorporation of peptides or small drugs inside their hollow structures. The nanotubes also have the property of attaching peptides on their surfaces as well as within their tubular space (Fig 9) to make themselves biocompatible [18].

![Figure 9: Molecules inserted within the tubular space of carbon nanotubes [19]](image)

Recent findings show that single stranded DNA can also be used for functionalization of nanotubes which helped to discriminate between metallic and semi-conducting tubes as well as in diameter-based identification of the CNTs [18].

A wide range of proteins or peptides is known to bind to carbon nanotubes either by specific or non-specific binding [20]. Sometimes a lot of proteins that are not the subject of study tend to bind to the carbon nanotube surface leading to non-specific binding [20]. On the other hand, when a protein, which is the subject of study, binds to the surface it is called specific binding. The proteins can be inserted in the hollow space in a very complicated manner, making it more difficult than just a hydrophobic interaction.
Secondary and tertiary structures can affect the non-specific bindings [20]. Recently, this non-specific binding issue has been resolved by modifying the nanotubes with mucin mimics which make them water soluble while and at the same time inhibiting non-specific bindings [21].

2.3.4 Sidewall Functionalization of SWCNTs

Carbon nanotubes are widely used in biomedical applications because of their cylindrical or spherical morphologies, which are stable in hostile environments [22]. Surface functionalization makes them biocompatible, enhances their solubility in physiological solutions and helps them become more target specific [22]. Still, there are some challenges in the world of nanotubes, such as poor reactivity because of lower curvature of nanotube walls as well as growing strains in the tubular structures. Hence, there are real needs for functionalizing the nanotube sidewalls. One popular method is to attach the fluorine groups through direct fluorination [22]. Hydrofluoric acid (HF) is used as a reactant [22]. The main goal is to achieve a final stoichiometry of C₂F without creating any destruction of the tubes. Hence, some process parameters like reaction temperatures, reaction times, and catalyst addition are properly controlled. Functionalized nanotubes produced by this method are especially applicable for biomedical application as they acquire some advantages [22]. For example, the final derivatives are soluble in different polar solvents as well as in alcohols. Not only that, Transmission Electron Microscopy (TEM) shows the diameter of the fluorinated or functionalized nanotubes to be less than (almost 1/10th) than that of the parent nanotubes. The results prove their good dispersion and easy processibility and make them suitable for biomedical application [22]. Figure
10 shows the reaction when amino derivitized SWNTs (Fig 10(1)) were reacted with adiphyl chloride creating amide linkages. The resulting polymer 2 (Fig 10(2)) is formed as a result of a cross-linked condensation reaction.

![Chemical Reaction Diagram]

**Figure 10: Typical Sidewall Reaction-Amino SWNT Derivatives (1) React with Adiphyl Chloride [22].**

Figure 11 shows the microscopic images of Fluoro-SWNTs on the left (Fig 11A) and polymer 2 on the right (Fig 10B).

![Microscopic Images]

**Figure 11: SEM images of F-SWNTs (A) & Nylon-SWNT Polymer 2(B) [22].**

### 2.4 Drug Delivery Vectors

In the field of drug discovery and delivery, drug-delivery vectors play a very important role. The vectors are used to carry the drug to the target organs. Generally, almost half of the potential drug candidates, selected by high throughput screening, are rejected and never reach the step of final formulation, mainly due to their poor water solubility [23]. For an efficient drug delivery system, it is also important to deliver the drug to its target...
region in the right concentration. In order to design an efficient vector, a balance between hydrophobic and hydrophilic properties is desired. Drug delivery systems (DDS) are designed to improve the pharmacological profile of a drug, to alter the pharmacokinetics (PK) and bio-distribution (BD) of a molecule, or to act as drug reservoir. Of the different types of DDS, liposomes are one of the most efficient systems [24]. A liposome is a spherical vesicle with a membrane composed of a phospholipids and cholesterol bilayer (Fig 12).

**Figure. 12: Liposomes used for drug delivery [25]**

Liposomes were described as drug delivery vehicles in the 70s, on the basis of their ability to increase the efficacy of the drug with reduced toxic side effects [24]. Some of the major disadvantages of liposomes are still unresolved, such as a limited physical stability of the dispersions, non-specific clearance by the mononuclear phagocytic systems (MPS) and a difficulty in up scaling production of some advanced liposome types [24]. MPS systems detect the liposomes as foreign bodies and so the liposomes are cleared by the body’s immune system. More recent approaches relate to the use of polymeric micelles, formed by amphilic polymers dispersed in aqueous media [26]. A micelle system encapsulates the drug inside its hydrophobic regions allowing the
possibility of extended circulation time, favorable bio-distribution and the site-specific
targeting of the incorporated drug [26]. However, the cytotoxicity of the polymers after
internalization into cells is a crucial aspect that has raised many concerns. Among the
most recent DDS are the solid lipid nano-particles (SLN), made-up of a solid lipid matrix,
which contains surfactants as stabilizers [27]. The advantages of this system are excellent
physical stability, protection from degradation and controlled drug release. Unfortunately,
insufficient loading capacity and drug expulsion often occur after polymorphic transition
during storage. Polymorphic transition is the process of changing from solid crystalline
phase to any other phase of the same chemical composition at a particular temperature
and pressure [28]. Polymorphic transition is a reversible reaction. A process called
“active” or ligand-mediated targeting” was used to increase the site specific actions of
DDS by interactions with ligands targeted against cell surface molecules [27].
In order to induce a specific response against a precise defect, new delivery systems with
all the crucial characteristics should be introduced. For its interesting chemical and
mechanical properties, carbon nanotubes may find a way to become one of the most
promising DDS in the near future.
Chapter 3

Applications of Carbon Nanotubes: in Therapeutics

CNTs synthesized for pharmaceutical applications need to be procured with utmost care as the process should take care of some needed parameters like improved yield, better CNT quality and, last but not the least, controlled diameter and chirality. There are 3 synthesis processes widely used [29]. They are Electric-Arc-Discharge (EAD), Chemical Vapor Deposition (CVD) and Laser Ablation (LA), which are selected depending on the desired quality, quantity and type of the nanotubes. For example, CNTs synthesized from EAD have higher Young’s Modulus and smaller defects in comparison to that of CNTs procured by means of CVD [29]. But CVD has other advantages in comparison to EAD [29]. CVD can directly synthesize CNTs and deposit CNTs on patterned substrates. Unlike EAD, CVD can control nanotube diameter. In spite of the fact that, pharmaceutical excipients are mostly inert or non-active components, they are really important for formulation. Hence it is necessary to identify the pharmaceutically relevant properties of CNTs. CNTs have been used as carrier medicated delivery vehicles for biofunctional molecules and as targets for biophysical treatments as well as tissue regeneration templates. The inner cavities of CNTs are used as nanochannels for the delivery of drugs, proteins and other fluids. Table 1 shows the pertinent physiochemical properties of CNTs [29].
Table 1: Pharmaceutically Relevant Properties of CNTs [29].

<table>
<thead>
<tr>
<th>Pharmaceutically relevant properties of CNTs</th>
<th>Specific data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name (synonym)</td>
<td>CAS number: 7782-42-5 (graphite)</td>
</tr>
<tr>
<td>Chemical family</td>
<td>Synthetic graphite</td>
</tr>
<tr>
<td>Structural formula</td>
<td>Molecular weight: 840 to &gt;10 million</td>
</tr>
<tr>
<td>Types</td>
<td>Diameter: Outer 1.0–3.0 nm; Inner 0.9–2.4 nm</td>
</tr>
<tr>
<td>SWNT</td>
<td>Length: Short: 0.5–2 μm; Standard: 0.5–100 μm</td>
</tr>
<tr>
<td>Diameter: Outer 2.5–100 nm; Inner 1.5–15 nm</td>
<td>Specific surface area (typical): 300–600 m²/g</td>
</tr>
<tr>
<td>Interlayer separation: 0.3–6.4 nm</td>
<td>Length: Short: 0.5–2 μm; Standard: 0.5–200 μm</td>
</tr>
<tr>
<td>Specific surface area (typical): 10–300 m²/g</td>
<td>Electronic properties: Metallic (armchair: 10,10)</td>
</tr>
<tr>
<td></td>
<td>Semi-conducting (zig-zag: 10,0)</td>
</tr>
<tr>
<td></td>
<td>Electric properties: mixture of conducting and semiconducting states</td>
</tr>
</tbody>
</table>

Organoleptic properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Visible</th>
<th>EM</th>
<th>Raman spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWNT</td>
<td>Granular or fluffy black power</td>
<td>SEM of densely bundled MWCNTs (-50 nm diameter)</td>
<td></td>
</tr>
<tr>
<td>TEM</td>
<td>10 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MWNT</td>
<td>Granular or fluffy black power</td>
<td>SEM of aligned CNTs on a substrate support</td>
<td></td>
</tr>
<tr>
<td>TEM</td>
<td>2 μm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aligned CNTs</td>
<td>Black fluffy velvet-like sheet of aligned CNTs*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Solubility properties of pristine SWNTs

<table>
<thead>
<tr>
<th>Solution medium</th>
<th>Visible</th>
<th>EM</th>
<th>Description of visible and EM images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water: insoluble</td>
<td>Visible: Light micrograph of SWNTs falling out of water. Inset shows SWNTs fall out of water soon after sonication.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETHANOL: insoluble</td>
<td>SEM: Loosely packed arrangement of SWNTs dispersed in water.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propane glycol: swollen</td>
<td>Visible: Light micrograph of swollen dispersion of SWNTs in propane glycol.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEM</td>
<td>SEM: Dispersion shows less aggregation of SWNTs in propane glycol.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO: swollen</td>
<td>Visible: Light micrograph of swollen dispersion of SWNTs in DMSO.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEM</td>
<td>SEM: Dispersion shows less aggregation of SWNTs in DMSO.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS: soluble</td>
<td>Visible: Light micrograph of well-dispersed SWNTs in SDS, showing few aggregates.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEM</td>
<td>SEM: Dispersion shows smaller bundles of SWNTs.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Impurities

| Metal oxide: in SWNT <5% |
| Carbonaceous material: 0.1–0.9% w/w |

*Visible and SEM images of aligned CNTs courtesy of Dr. Jun Chen, Intelligent Polymer Research Institute, University of Wollongong, Australia.
3.1 Functionalized CNTs for Drug Delivery

Carbon nanotubes are popular drug excipients as they have the capability to interact with the macromolecules such as proteins and DNAs [30]. A perfect drug delivery system should have the capability to perform controlled and targeted drug delivery (Fig 13). CNTs have the potential to perform controlled and targeted drug delivery. There are 3 modes of interaction between CNTs and pharmaceutically active components in drug delivery [30]. In the first mode, CNTs act as porous absorbent which entrap active components within nanotube mesh. Another mode is to attach compounds functionally to the external walls of nanotubes. In the third process, CNTs are used as nanocatheters which act as channels to help flow the drug components [30].

Figure 13: Drug Delivery by means of CNTs. A) CNTs as porous absorbent, B) Functional Attachment of Compounds in Nanotube Walls, C) CNT channels Drug Component [30].

In addition, CNTs have been reported as excellent substitutes for other delivery vectors. CNTs have the capacity to penetrate through the cell membrane without perturbing their morphology. The nanotubes act as nano-needles as they penetrate the cell membrane [31, 32]. The nature of the penetration does not depend on the functionalized group on the nanotube. The nano-needle structure is illustrated in Figure 14 where the FITC
(fluorescein isothiocyanate) labeled SWNT derivative was prepared by 1, 3-dipolar cycloaddition of azomethine which were highly water soluble [33]. Fluorescence studies showed that carbon nanotubes, coupled with azomethine, are able to cross the cell membrane and accumulate in the cytoplasm or even sometimes reach the nucleus without being toxic to the cell at concentrations up to 10 µM [34]. CNTs enter perpendicularly to the cell membrane without disturbing or destroying the membrane itself. Similarly SWNTs have been used to deliver streptavidin inside the cell [35]. The adduct (SWNT-streptavidin) was known to bind non-specifically with hydrophobic components of the cell surface and enter by endocytosis. The SWNTs were first treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and biotin-LC-PEO-amine and then dialysis was carried out. To the biotin-functionalized SWNTs fluorescence tagged streptavidin molecules were incubated to obtain the adduct [35]. The fluorescence tag used was fluorescein isothiocyanate.

**Figure 14:** Covalently attached groups make carbon nanotubes water soluble (ammonium) and trackable inside the cells (fluorescein isothiocyanate [33]).

In the most simplistic approach, the ability of CNTs to penetrate into the walls of cells makes them widely usable as drug excipients. Perhaps, covalent or noncovalent bondings
of molecules with the external CNT walls play the most important role in molecule transfer. For example, CNTs functionalized with amphotericin B (AmB), the most effective antibiotic for the treatment of fungal infection, is easily taken by mammalian cells with lesser toxicity than by the drug alone [36]. At the highest dose, almost 40% of the cells die by the effect of AmB alone, whereas, all the cells remain alive while treating with CNTs covalently linked with AmB. **Figure 15 and Figure 16** show the easy penetration of functionalized CNT into cells and performances of CNT + AmB in comparison to AmB alone. Minimum Inhibitory Concentration (MIC) indicates the lowest concentration of compound that inhibits visible growth on pathogens [36].

![Molecular Structures of AmB functionalized with CNTs capable of penetrating into mammalian cell walls](image_url)

**Figure 15**: *Molecular Structures of AmB functionalized with CNTs capable of penetrating into mammalian cell walls* [36].
3.2 For Protein Delivery

Proteins are found to adsorb on the sidewalls of acid oxidized SWNTs [37]. This is advantageous as using this phenomenon; covalent protein-nanotube conjugates can be made. Proteins have been found [37] to be transported into various mammalian cells by CNTs through endocytosis. Hence, CNTs can be considered as generic intracellular transporters for different kinds of proteins. Some important proteins transported by CNTs are streptavidin (SA), protein A (SpA), bovine serum albumin (BSA), cytochrome c (cyt-c) etc [37]. Some mammalian cells getting proteins are HeLa, NIH-3T3 Fibroblast, HL 60 & Jurkats cell. The entire process starts with fluorescent labeling of proteins. A protein solution having concentration of 2 mg/ml is mixed with 50 µL of sodium bicarbonate solution (NaHCO₃) and then reacted with Alexa-Fluor dye for 1 hour at room temperature. The dye-protein conjugate is then passed through a gel separation column,
namely Bio-Rad Biogel P30, which purifies the conjugate. In the second step of this protein transfer, CNTs are purified, cut and oxidized. The processed protein and nanotubes are then mixed and kept at room temperature for 2 hours. Proteins are found to adsorb into the walls of CNTs. Atomic Force Microscopy (AFM) is used to test the binding of the proteins with nanotube walls and tested with a small sample solution of conjugated protein- nanotube on SiO$_2$ piece kept for 30-45 minutes. Results show non-specific binding of proteins with the nanotube walls. Functional groups provide hydrophilicity to nanotubes which make them stable in aqueous solution. As shown in Figure 17, the average spacing between protein molecules is found to have a range between 20-100 nm [37].

*Figure 17: AFM Images of Various SWNT samples; a) Oxidized Nanotubes Before Protein Conjugation; b) Alexa- Fluor 488 BSA; c) Alexa- Fluor 488 SpA; d) Alexa- Fluor 488 cyt-c [37]. Scale bar = 100 nm.*

Confocal Microscopic images are also collected to investigate the fate of SWNT- protein conjugates. The basic principle of this characterization technique is to check out the
fluorescence level in all parts of the conjugated CNTs. Fluorescence level determines the adsorption of protein molecules into the CNT walls and is found to originate within the cell interior. The fluorescence level of protein solution alone is much lower than that of conjugated solution. This indicates that while proteins in solution were not able to move across cell membranes properly, CNTs have played the role of efficient cargos transporting proteins into mammalian cells [37]. *Figure* 18 shows the confocal microscopy images of increased protein adsorption by cell in a SWNT protein solution than protein solution alone.
Figure 18: Confocal Microscopy Characterization of Cells; a) HL-60 cells after incubation in streptavidin SA-SWNTs; b) HL-60 cells after incubation in BSA-SWNTs; c) HeLa cells after incubation in SA-SWNTs; d) HeLa cells after incubation in cyt-c; e) Cell Cytometry data showing performance improvement of conjugated protein solution in comparison to single protein solution [37].
Conjugation of pathogen specific antibodies (goat anti *E.coli* O157) to the SWNTs has also been reported [15]. These complexes are functionalized by bovine serum albumin (BSA) protein. The SWNT-BSA conjugate was prepared by an amidation (addition of amide groups) reaction of the nanotube-bound carboxylic acids with pendant amino moieties on BSA. This adduct complex was then able to recognize a pathogen target cell in *E.coli* (O157:H7) through special antigen antibody interactions under normal physiological conditions [15]. Nanotubes require covalent functionalization before they can actually carry a peptide antigen. Another experiment shows the antigenicity and immunogenicity and how the impact of the functionalized nanotubes depends on the number of covalent attachments to the nanotubes. Mono and a bis-peptide derivatized CNT were designed as shown in *Figure 19*.

*Figure 19: Molecular structures of SWNT functionalized with a peptide derived from foot-and-mouth disease virus as a mono (left) and a bis-conjugate (right)[3].*

Analysis was done using Enzyme-linked Immuno-Sorbent Assay (ELISA) test and surface plasmon resonance to detect the specific antigen-antibody recognition count and concluded that the peptides attached to the nanotubes were well recognized by the antibodies (Fig 20). In fact, when a mouse was immunized with the adduct, the peptides
produced more antibodies than when free peptides were delivered. A greater response of the immobilized antigens was thus confirmed. Moreover, no anti-carbon nanotube antibodies in the solution confirmed the fact that the nanotubes themselves had no immunogenic properties. The mono-derivatized tubes were able to initiate more response than the bis-derivatized nanotubes [3].

Figure 20: Amino acid and peptide functionalization of carbon nanotubes [3].

Protein binding to the CNTs is highly selective. Out of numerous proteins in plasma, very few bind to carbon nanotubes, which are both as serum as well as plasma proteins. The two proteins fibrinogen and apolipoprotein bind to CNTs in greatest quantity [38]. Figure 21 shows the gel electrophoresis of apolipoproteins conjugated with CNTs in human cells.
Figure 21: Apolipoprotein conjugated CNTs in human cells, 1: molecular weight marker, 2: control experiment (human serum bound to sepharose), 3: human serum bound to Double Walled Carbon Nanotube (DWNT) sepharose, 4: human serum (1.25µl), 5: control experiment (human plasma bound to sepharose), 6: human plasma bound to DWNT sepharose [38].

3.3 For Gene Delivery

Similar to the previous topics, CNTs functionalized with biological moieties can also be used as gene delivery vectors. The main goal of doing gene therapy is to introduce DNA efficiently, specifically and safely into the target cell or tissue. Current approaches led to rapid disintegration of the nucleic acids [39]. So a delivery system that can mimic the
function of a plasmid DNA needs to be developed. Some of the other delivery units for DNA are liposomes, cationic lipids and nanoparticles [39]. Though these approaches have yielded some success, the complexity of the binding of the DNA with a CNT helps the DNA to remain integrated until it reaches its target organ compared to the other models [39]. CNTs and DNA bind primarily by hydrophobic interactions. The DNA tends to wind itself around the SWNT to give rise to a hybridized macromolecule. Previous studies [39] have shown that a SWNT coated with the plasmid DNA containing the β-galactosidase gene resulted in 5- to 10-fold greater expression than when the same plasmid was introduced alone in the system. The functionalized nanotubes can also condense the DNA-nanotube complex to a limited extent. This compression causes a decrease in the surface area of the DNA. So the charge on the DNA accumulates on the surface that helps in the increase of the cell membrane interaction due to electrostatic forces and increased cellular uptake [39].

Gene silencing is considered as one of the emerging fields [30] in genetics which basically involves the introduction of short interfering RNA (siRNA). This process involves the presence of a messenger. Using complex (-CONH$_2$-(CH$_2$)$_2$-NH$_3^+$Cl$^-$) as messenger, siRNA has been properly attached [30] with CNTs with no loss in conformation. The attached moiety can be successfully delivered into cytoplasm CNT mediated gene delivery as shown in **Figure 22** [30].
Other complexes can also act as messengers. Various non-covalent bonding of bio-active molecules with CNTs are illustrated in Table 2.

**Table 2: Non-covalent Binding of Bioactive Molecules to CNTs [30].**

<table>
<thead>
<tr>
<th>CNT properties</th>
<th>Bioactive molecule</th>
<th>Study aim/results</th>
<th>Dispersion solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type Functional group</td>
<td>Erythropoietin (EPO)</td>
<td>Controlled release of EPO</td>
<td>Mixed in several component formulations</td>
</tr>
<tr>
<td>SWNT None</td>
<td>Cys-DNA</td>
<td>Selective tumor marking and subsequent near IR irradiation in Hela cells</td>
<td>PL-PEG surfactant</td>
</tr>
<tr>
<td>SWNT I. PL-PEG and PL-PEG-FA molecules*</td>
<td>Streptavidin protein A (SpA), bovine serum albumin, and cytochrome c</td>
<td>Non-specific binding of proteins onto CNT sidewalls, and increased transfection of conjugates</td>
<td>Aqueous</td>
</tr>
<tr>
<td>SWNT II. None</td>
<td>siRNA</td>
<td>Gene silencing (siRNA) obtained by relative ease of cleavage of disulfide bond</td>
<td>PL-PEG surfactant</td>
</tr>
<tr>
<td>SWNT III. PL-PEG-NH₂ and PL-PEG-maleimide</td>
<td>pGFP-c plasmid</td>
<td>Increased transduction by magnetofection of Balb 17 B-lymphoma and B cells ex vivo</td>
<td>Nanospere AQ surfactant (NanoLab, Newton, Massachusetts)</td>
</tr>
</tbody>
</table>

*PL-PEG-FA molecules: Polyethylene glycol-functionalized folic acid.
Further study [40] shows an improvement of the gene silencing technique. In other words, improvement of siRNA delivery by SWNTs has been seen. SWNTs are functionalized with hexamethylenediamine (HMDA) and polydiallyldimethylammonium chloride (PDDA). These complexes translocate in so-called hard to transfect primary cells. Released siRNA within the cells provide necessary silencing of target genes. This method has certain specific advantages. For example, it has lesser cytotoxic side effects. Not only that, PDDA polymer wraps the SWNTs and creates a positively charged surface for them and helps to improve their water solubility and provides better binding of siRNA to SWNTs [40]. Figure 23 shows that only functionalized SWNTs with PDDA with a concentration ratio of 1:1 can bind to siRNA.

![AFM image of SWNTs functionalized with PDDA (arrows), (B) Gel electrophoresis demonstrates the ability of functionalized SWNTs (SWNT:PDDA = 1:1) to bind siRNA.](image)

**Figure 23: Improvement in Si-RNA by Means of PDDA Functionalized SWNTs, (A) AFM image of SWNTs functionalized with PDDA (arrows), (B) Gel electrophoresis demonstrates the ability of functionalized SWNTs (SWNT:PDDA = 1:1) to bind siRNA [40].**
3.4 Carbon Nanotubes in Cancer Therapy

Recently Dr. Hongjie Dai, and his research group at Stanford University found carbon nanotubes can carry the anti-cancer drug doxorubicin [41]. CNTs were reported to carry high concentration of the drug and deliver it selectively to cancer cell lines. Experiments proved that CNTs can carry almost 4 times its mass of drug through the body system. It is hypothesized that the cell lines are permeable, allowing the CNTs to penetrate through the cells. As the cancer cell lines swallow the CNTs the loaded doxorubicin causes death of the cancer cell lines [41].

CNTs also help destroy cancerous cells by local heating, which is called hyperthermia. High optical absorbance of CNTs and their propensity for endocytosis make them suitable candidates for the specific process to destroy cancerous cells. CNTs are functionalized with recognizable epitopes, which causes endocytosis of the functionalized CNTs by cancerous cells. This is followed by subsequent infrared laser radiation for local heating of endocytosed CNTs. Consequently, the cancerous cells are thermally destroyed without harming the adjacent healthy cells [30]. Figure 24 shows the use of laser radiation and a hyperthermic device to kill a cancer cell.
CNTs have also been seen to reduce tumor growth in mice cells and shown biocompatibility along with little toxicity [42]. A widely used cancer chemotherapy drug called paclitaxel (PTX) is branched with polyethylene glycol chains on SWNTs which helps in forming a water soluble SWNT-PTX complex via a cleavable ester bond as illustrated in Figure 25 [42].
SWNT-PTX complex shows higher efficiency in suppressing the tumor growth, better performance than clinical taxol, superior blood circulation, much better permeability and retention. Drug molecules are released from SWNTs into reticuloendothelial system and create no toxic effects for the normal organs as shown in Figure 26 [42].

**Figure 25: Carbon Nanotube for PTX Delivery [42].**

**Figure 26: SWNT-PTX Complex Reduces Tumor Growth [42].**
A new way to deliver platinum anticancer pro drug with a lethal dose was recently discovered [43]. The acidic environment in the tumor cells causes the release of the pro drug cisplatin to the target organs. Ability of platinum (IV) complexes to resist ligand substitution enables SWNTs to act as a “longboat”[43] to pierce through the cells and deliver a lethal dose of cisplatin. This is the first time that CNTs were used to carry drugs rather than encapsulate the drugs [43].
Chapter 4

Toxicity Studies

One of the major issues in biological systems is the level of toxicity involved in any new models. Substances that are not toxic in the environment often have some adverse effects when administered inside the body. Another major issue for any biological model is, when any external substance is introduced inside a body, it needs to be disintegrated once their job is done. So this raises the issue regarding the biocompatibility of the substance. With respect to carbon nanotubes, the level of toxicity depends mainly on its manufacture [44]. Though highly purified nanotubes are being used, any remaining traces of metals like iron and nickel could cause damage to the systems. Though it is such an important issue, not many studies have been done on analyzing the cytotoxic effect of nanotubes. In the last decade, Adelmann et al. (1994) reported that fullerenes are toxic on alveolar macrophages. Even more recently, studies have shown that cytotoxicity of water soluble fullerene derivatives is a function of the degree of surface modification [41]. So, if carbon nanotubes are considered as a derivative of the fullerenes along one axis, then they should also have some toxic effects. Other experiments in rats have shown that carbon black particles might produce a significant lung toxicity that potentially increases by decreasing the particle size and by increasing the surface area.

Administration of any potential therapeutic agent involves crossing several layers from tissue endothelium into the interstitial space of tissues, through the cell membrane into the intracellular compartments. The therapeutic agent finally has to find its way through the perinuclear membrane into the nucleus of the cell [45]. Figure 27 shows all the
different layers a drug has to penetrate to enter the nucleus of the cell. The different cellular layers have a significant role to play during drug administration. Development of a potent drug delivery system should consider all the above mentioned parameters for the \textit{in-vivo} fate of any administered material.

\textbf{Figure 27: In Vivo Barriers and Critical Parameters affecting the fate of nanomedicines [45].}

Carbon nanotubes consist of some amazing physiochemical properties which make them suitable candidates for nanomedicines. They have ordered structure with high aspect ratio
associated with very light weight. Superior mechanical strength of CNTs has already been discussed. This is followed by their high thermal and electrical conductivity, metallic or semi-metallic behavior and high surface area. These properties make CNTs perfect materials for biomedical applications. In general, studies show that nanoparticles have harmful effects because of their high surface area and toxicity on the surface [45]. SWNTs can become non-toxic by functionalizing them with phenyl-\(\text{SO}_3\text{H}\) or phenyl-carboxyl groups [45]. Figure 28 represents different important properties of CNTs useful for pharmacological and toxic applications.

![Figure 28: CNT properties determining pharmacological and toxicity profile [45].](image)
Several studies have been done to address the growing concern on the toxicity of CNTs in human bodies. Table 3 shows a snapshot of a review of the various toxicological studies and results.

**Table 3: Invivo studies performed with CNT [45].**

<table>
<thead>
<tr>
<th>CNT</th>
<th>Amount</th>
<th>Model</th>
<th>Exposure conditions/ administration</th>
<th>Exposure duration</th>
<th>Toxicity</th>
<th>Mechanism of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soot with high content of CNT</td>
<td>25 mg</td>
<td>Male Dunkin Hartley guinea pigs</td>
<td>Intratracheal instillation (suspension in saline with Tween 80)</td>
<td>4 weeks</td>
<td>No association with skin irritation or allergic risks</td>
<td>Dermatological trials have not shown signs of health hazard.</td>
</tr>
<tr>
<td>Pristine Arc-CNT</td>
<td>1 and 5 mg/kg</td>
<td>Male Sprague-Dawley rats</td>
<td>Intratracheal instillation (suspension in saline with Tween 80)</td>
<td>24 h, 1 week, 1 and 3 months</td>
<td>Expose to high dose produced mortality within 24 h post-instillation.</td>
<td>Pulmonary inflammation with non-dose-dependent granulomas.</td>
</tr>
<tr>
<td>Raw and purified HiPco CNT, Arc-CNT</td>
<td>0.1 and 0.5 mg/mouse</td>
<td>Male mice B6C3F1</td>
<td>Intratracheal instillation (suspension in saline)</td>
<td>7 and 90 days</td>
<td>Induced dose-dependent epithelial granulomas. Mortality was observed with the high dose.</td>
<td>Immune toxicity (surface chemistry), fibrous structure, Biopersistence</td>
</tr>
<tr>
<td>Pristine HiPco and laser- ablation-SWNT</td>
<td>Particles Human volunteers (inhaled)</td>
<td>Inhalation exposure (filter samples) Dental exposure (cotton gloves)</td>
<td>10 min</td>
<td>11-16 h</td>
<td>Nanotube concentrations from 0.7 to 53 μg/m³ (HiPco material produced visible large clumps on the filter). Deposition of individual fibers from 0.2 to 6 mg (visible contamination)</td>
<td>Propensity to unprocessed SWNT forms an aerosol during handling.</td>
</tr>
<tr>
<td>Rat stock carbon nanofibers</td>
<td>Not specified</td>
<td>Male Wistar rats</td>
<td>Clusters were implanted in the subcutaneous tissue (thoracic region)</td>
<td>1 and 4 weeks</td>
<td>Normal process of inflammation for foreign bodies, without severe inflammatory response was observed. No acute toxicity in the subcutaneous tissue. No inhibition of wound healing.</td>
<td>Water solubility and characteristic structure (were phagocytosed and delaminated).</td>
</tr>
<tr>
<td>MWNT</td>
<td>0.5, 2 and 5 mg/mouse</td>
<td>Female Sprague-Dawley rats</td>
<td>Intratracheal instillation (suspension in saline with 16.9% saline with 1% Tween 80)</td>
<td>1 and 2 months</td>
<td>Not ground MWNT accumulate in the airways. Ground MWNT were cleared more rapidly. Both MWNT have induced inflammatory (more marked for ground MWNT) and fibrotic reactions. Also both have caused pulmonary lesions at 3 months.</td>
<td>Length appears to modulate clearance kinetics, Biopersistence, Intrinsically toxic to the lung.</td>
</tr>
</tbody>
</table>
Chapter 5

Simulation Models

Even though a number of experimental studies have been done to explore the application of carbon nanotubes in the field of biology and medicine, this field of study is still in the early stage of development. Research studies are made more varied and less redundant. Recently, scientists have tried to analyze this problem from a computational point of view. In 2005, a few computational analyses were done on the binding free energies between peptides and single-walled nanotubes [46]. The simulation process involved the different types of interaction between the peptides and the SWNTs using molecular dynamics (Amber 7) methods and a continuum solvation model. The binding free energies are then estimated based on the thermodynamics theories. The binding free energies consider both the solute and the solvent interactions. The energy contributions show that the bonds are mostly the non-covalent bonds in which van der Waals interactions play the most significant roles. Aromatic rings on peptides have strong affinities for the CNT surface. The estimated results of the binding free energies from the model were compared with experimental results. Some insight was also given on the conformations of the binding peptides from the model which would not be possible for us to know from just doing the experiments.

Other simulation studies have been also carried out on protein fragment models. Trzaskowski et al. [47] explored dynamic properties of two protein fragments’ interaction with single walled carbon nanotubes. This model included all 3 kinds of interactions between peptides and SWNT: outer wall interaction, proteins encapsulated into nanotubes interaction and covalent interactions. Two basic structured protein fragments
were designed for this model: a beta hairpin model and alpha helix model. These are the two basic structured protein molecules found in most of the biomacromolecules. The beta hairpin model was designed from chignolin (10 amino acid peptide). The alpha beta helix model was derived from the de-novo designed peptide used in computational study of prion propagation. The SWNTs were built relatively short (~22 Å). Two types of CNTs were designed: (22,0) nanotube with a diameter of 17 Å and (30,0) nanotube with a diameter of 23.5 Å. The software package that was used to simulate all the molecular dynamics was CHARMM27. The aspartate and glutamate residues were deprotonated and the lysine residues were protonated. The simulation model was a two step process: first the peptide-nanotube complex was immersed into TIP3P water molecules and counter ions were added if required. The model was run for 24000 steps. **Figure 29** shows the schematic representation of the simulation model.

*Figure 29. Schematic representation of the (a) beta-hairpin peptide encapsulated into (22,0) nanotube and (b) the covalent linker used in the study [47].*

Results show that encapsulation of peptides within nanotubes has almost no effect on the dynamic properties of the peptides, i.e., encapsulation does not have much effect on the secondary structures of the proteins. Therefore, the conclusion was reached that proteins tend to stay in their native conformation during encapsulation. Outer wall interaction
studies show that both the peptides bound with almost similar root mean square deviation (rmsd) values if not identical. On the other hand, covalent linkages attached to CNTs interact very differently with the peptides. The model shows that, when CNTs were functionalized with -COOH groups, the peptides that bind to the inner wall of the nanotubes undergo huge conformational changes for both the structures and acquire a totally different conformation that is very stable. This conformational change may be due to the constraints put on the peptides upon linkage together with the SWNTs. Figure 30 shows the comparative study results of the root mean square deviation (rmsd) values of the peptides with respect to their structures and binding location.

Figure 30. Comparison between the rmsd values for alpha-helix and beta-hairpin models linked covalently to (22,0) nanotube [47].
Chapter 6

Docking of Vasopressin with Functionalized Single Walled Carbon Nanotubes

A docking study was performed using functionalized single walled carbon nanotubes and model peptide, vasopressin. The binding free energy of the interaction was calculated to assess the feasibility of the SWNT-vasopressin model. The long-term objective of the project to which this research contributes is to assess the feasibility of single walled carbon nanotubes as a potential drug delivery system for proteins and peptides.

6.1 Background Study of Vasopressin

Vasopressin is a peptide hormone. Some of its aliases are Argipressin and Anti Diuretic Hormone (ADH). It is synthesized from preprohormone precursor in the hypothalamus. After synthesis, it is stored in the vesicles of posterior pituitary [48]. A broad overview of the arrangement of the amino acids is shown in Figure 31. This structure of vasopressin is drawn using the Swiss–PDB Viewer Deep View (SPDBV) visualization tool with vasopressin PDB structure.
6.1.1 Structure of Vasopressin

Vasopressin is a 9-residue polypeptide with a sequence C-Y-F-Q-N-C-P-R-G-NH₂ [50]. The cysteine residues at position 1 and 6 form a disulfide bond. The Asn5-I to Gly9-I of vasopressin constitutes the reactive site loop. Arg8-I is the reactive site residue located at the C terminus and other residues, forming a cyclic ring, lying at the entrance of the trypsin active site. The vasopressin molecule has uniform electron density and the disulphide bond confers stability to the molecule (Fig 32). There is also an intramolecular

Figure 31: Molecular structure of Vasopressin, plotted using DeepView viewer 4.0

(http://spdbv.vital-it.ch/) [49]
hydrogen bond between Tyr2-I and Gln4-I and another between Gln4-I and Cys6-I. These hydrogen bonds provide stability to the cyclic part of the peptide. There are also a few hydrogen bonds along the C-terminal of the molecule.

Figure 32: Stereo view of the electron density map (2Fo-Fc) at the 1 level plotted using PYMOL (http://pymol.sourceforge.net/) for vasopressin. The intramolecular hydrogen bonds are shown as dotted lines [50].

6.1.2 Therapeutic Applications of Vasopressin/Arginine vasopressin (AVP)

The primary physiological function of vasopressin is to maintain fluid balance in the body in response to any environmental stimuli or changes [51]. Recent studies [51] show that vasopressin also tends to play a very important role in adult cardiac arrests as well as adult and pediatric vasodilatory shock. Various randomized clinical trials were performed
for years to validate the role of vasopressin in cardiac arrests. The largest randomized
double-blinded study of AVP versus epinephrine was conducted in 2004 that enrolled
1186 patients [52]. Patients were randomized to receive up to two doses of 1.0 mg doses
of epinephrine or two 40 IU doses of AVP at the discretion of the physician. 589 patients
received AVP and 597 patients received epinephrine. Table 4 shows that the use of
vasopressin improves the rates of survival to hospital admission (and discharge) better
than epinephrine in adults. The American Heart Association (AHA) and European
Resuscitation Council (ERC) now recommend use of vasopressin in adults. Use of
vasopressin has shown no significant influence on pediatric resuscitation patients.
Vasopressin infusion for vasodilatory shock is gaining importance. Most recent studies
have shown that AVP acts in situations of vasodilatory shock where most of the pressors
fail to act. AVP also demonstrates increased systemic vascular resistance [51].
Table 4: Primary and subgroup analyses of 1186 patients in study.

<table>
<thead>
<tr>
<th>Group/subgroup, outcome</th>
<th>Vasopressin, no. (and %)</th>
<th>Epinephrine, no. (and %)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROSC</td>
<td>145/589 (24.6)</td>
<td>167/597 (28.0)</td>
<td>1.2 (0.9-1.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hospital admit</td>
<td>214/589 (36.3)</td>
<td>186/597 (31.2)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>57/578 (9.9)</td>
<td>58/588 (9.9)</td>
<td>1.0 (0.7-1.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROSC</td>
<td>82/223 (36.8)</td>
<td>106/249 (42.6)</td>
<td>1.3 (0.9-1.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hospital admit</td>
<td>103/223 (46.2)</td>
<td>107/249 (43.0)</td>
<td>0.9 (0.6-1.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>39/219 (17.8)</td>
<td>47/245 (19.2)</td>
<td>1.1 (0.7-1.8)</td>
<td>0.70</td>
</tr>
<tr>
<td>Pulseless electrical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROSC</td>
<td>21/104 (20.2)</td>
<td>17/82 (20.7)</td>
<td>1.0 (0.5-2.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>Hospital admit</td>
<td>35/104 (33.7)</td>
<td>25/82 (30.5)</td>
<td>0.8 (0.5-1.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>6/102 (5.9)</td>
<td>7/81 (8.6)</td>
<td>1.4 (0.5-4.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Asystole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROSC</td>
<td>42/262 (16.0)</td>
<td>44/266 (16.5)</td>
<td>1.0 (0.7-1.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hospital admit</td>
<td>76/262 (29.0)</td>
<td>54/266 (20.3)</td>
<td>0.6 (0.4-0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>12/257 (4.7)</td>
<td>4/262 (1.5)</td>
<td>0.3 (0.1-1.0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CI = confidence interval; ROSC = restoration of spontaneous circulation
Adapted with permission from Table 3, Wenzel V, et al. © 2004 Massachusetts Medical Society. Odds ratio measures the strength of association between two binary data values. p value is the probability of obtaining a result against the null hypothesis.

Arginine vasopressin is also termed as a “promising rescue drug” in the treatment of uncontrolled hemorrhagic shock [53]. Hemorrhagic shock occurs due to excessive blood loss from the body. Figure 33 shows the pathophysiological path of hemorrhagic shock.
There are mainly two types of hemorrhagic shock. Controlled shock occurs when the amount of blood loss does not outrange the neuro-endocrine stress response and the loss can be controlled before the heart collapses. Uncontrolled hemorrhage occurs when the blood loss cannot be controlled at the site and the catecholamines are insufficient to stabilize cardiovascular functions. Infusion of fluid alone sometimes cannot resuscitate uncontrolled hemorrhage. It may lead to extensive blood clotting and hence could be detrimental. The crystalloid and colloid solutions sometimes cause dilutional coagulopathy which leads to dilution of clotting factors that may impair cellular
homeostasis. Infusion of blood may also result in increased blood pressure at the site of blood loss. All these consequences suggest that fluid infusion alone cannot rescue uncontrolled hemorrhage. Vasopressin, on the other hand, increases the neuro-endocrine stress response. Due to uniform distribution of vasopressinergic receptors, it significantly increases vasoconstriction in the vascular beds other than coronary, pulmonary and cerebral circulation. This can reduce blood loss and maintain homeostasis. Sometimes, when uncontrolled hemorrhage is followed by brain death, AVP can reduce secondary neurological damage due to ongoing hypotension and cerebral hypoperfusion. In 2000, Voelckel and colleagues studied the effect of AVP on 7 pigs [53]. The AVP effects were compared with a group of 7 pigs who were treated with epinephrine and a group of 7 pigs who were treated with placebo saline water. Uncontrolled hemorrhage was induced by an incision across the right medial liver lobe. Figure 34 shows the summary of the comparative effect of AVP vs. epinephrine vs. placebo saline.
Figure 34: Mean ± SEM for heart rate, mean arterial pressure, and total blood loss before, during, and after administration of a 0.4 units/kg bolus dose, 0.04 units/kg/min continuous infusion of vasopressin (squares; n=7) vs. a 45 µg/kg bolus dose, and 5 µg/kg/min continuous infusion of epinephrine (diamonds; n=7) vs. equal volumes of saline placebo (circles; n=7). Uncontrolled hemorrhage, the no-treatment interval after liver injury; experimental therapy, attempt of haemodynamic stabilization with either
vasopressin, epinephrine, or saline placebo; liver tamponade, manual compression of the liver injury to control bleeding; BL, measurements at baseline before induction of hemorrhagic shock; DA, administration of study drugs or placebo; arrow, second bolus dose of epinephrine; *p < 0.004 for epinephrine and vasopressin vs. saline placebo; p < 0.002 for vasopressin vs. epinephrine and saline placebo; ‡p < 0.0001 for vasopressin vs. epinephrine and saline placebo. No statistical comparison was performed after minute 10 during vasopressor therapy because of the death of all animals that received epinephrine and saline placebo, respectively [53].

6.1.3 Drug delivery systems of Arginine Vasopressin

Several methods have been used to incorporate vasopressin inside the human body [54, 55]. Two distinct methods are use of peptide drug delivery systems [54] and iontophoretic methods [55]. In 1999, Aoyagi et al. [54] tried to fabricate peptide delivery systems using arginine vasopressin as the model drug. AVP was incorporated using dialysis method. The polymer delivery system used constituted of poly(polyethylene-glycol)-poly(L-aspartic acid) [PEG-P(Asp)] block copolymer. The polymer system formed nano associates from PEG-P (Asp). AVP molecules were incorporated into the nano-associates, which were then measured by IR light spectra [Fig 35].
Figure 35. IR spectra of PEG-P (asp) associates incorporated (a) without AVP and (b) with AVP (run No.1 in Table 5) [54].

Table 5 shows a summary for loading of AVP in acid type PEG-P (Asp) polymer and mixture of acid and salt PEG-P (asp) polymer.

Table 5. Incorporation of AVP into PEG-P (Asp) nano-associates [54].

<table>
<thead>
<tr>
<th>Number</th>
<th>Feed</th>
<th>Yield</th>
<th>Load</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nano associated</td>
<td>Vasopressin</td>
</tr>
<tr>
<td>1 (^a)</td>
<td>1:1</td>
<td>0.98</td>
<td>0.45</td>
</tr>
<tr>
<td>2 (^a)</td>
<td>1:0.5</td>
<td>0.36</td>
<td>0.26</td>
</tr>
<tr>
<td>3 (^a)</td>
<td>1:0.25</td>
<td>1.18</td>
<td>0.16</td>
</tr>
<tr>
<td>4 (^b)</td>
<td>1:1</td>
<td>1.58</td>
<td>0.18</td>
</tr>
</tbody>
</table>

\(^a\) Acid-type PEG-P(Asp).
\(^b\) Mixture of acid and salt PEG-P(Asp).

Ionotophoretic delivery of a peptide is the propulsion of a highly charged species (peptide molecules) transdermally by generating electrical force fields in the solution. Electrical
parameters and current densities are known to influence the passage of an actively charged species in the solutions [55]. In-vitro studies were conducted by Nair et al. [55] using rat skin. Skin hydration plays a very important role in the amount of peptide permeated per unit skin area.

6.2. Docking Tool

Docking Server

Source: http://www.dockingserver.com/web/

All the docking parameters were calculated using Docking Server [56]. Docking Server is developed and maintained by Virtua Drug Ltd and is a free web service that calculates the best geometry of ligand protein interactions.

CoNTub

Source: http://www.ugr.es/~gmdm/contub.htm

CoNTub [57] is freeware that generates PDB structures of nanotubes which were developed in 2004 by Melchor et.al. [57]. CoNTub is a computer program solely dedicated to generate complex geometrical structures of carbon nanotubes (SWNT and MWNT) for docking purposes. This tool was first designed to determine the coordinates of heterojunctions between two unknown nanotubes. Later it added more features for generating Protein Data Bank (PDB) structures of complex carbon nanotubes. For the purpose of this docking research, several single walled carbon nanotube structures with various dimensions were obtained in the PDB format.
6.3 Method

Vasopressin was used as a model peptide due to its extensive and critical clinical applications. It is a fairly small peptide which constitutes the following 9 amino acids: C-Y-F-Q-N-C-P-R-G-NH$_2$. The native structure of the protein was downloaded from Protein data bank as a PDB file. The PDB ID 1yf4 contains the structure of Lysine-Vasopressin. For the purpose of docking, to concentrate only on vasopressin, only the chain B of 1yf4 was selected from the docking parameters. The protein parameters were optimized by calculating the electrostatic properties of vasopressin and defining the active site of vasopressin. Next, the vasopressin molecule was put into solution (H$_2$O) for the calculation of solvation energies.

The docking server supports only specific formats for ligands. The PDB file format for single walled carbon nanotubes was obtained from the tool CoNTub. In order to check whether the diameter and the functionalized atoms of the nanotube makes any difference in the overall interaction of the peptides and SWNTs, 3 sets of SWNTs with 4 different (n,m) values were created:

a) Non-functionalized SWNTs
   - (5,0) nanotubes with 10 Å length
   - (5,5) nanotubes with 10 Å length
   - (10,0) nanotubes with 10 Å length
   - (10,10) nanotubes with 10 Å length

b) Functionalized SWNTs with Nitrogen atoms
   - (5,0) nanotubes with 10 Å length
Nitrogen and hydrogen atoms were attached to each of the terminal carbon atoms at either end of the respective SWNTs e.g. a (5,5) H-functionalized SWNT and (5,5) N-functionalized SWNT would have (5+5)=10 hydrogen and 10 nitrogen atoms attached respectively. Each type of SWNT was made to interact with only 1 molecule of vasopressin. The 3-dimensional ligand structures were optimized for docking using the following parameters: optimized geometry, identification of rotational bonds and calculation of semi-empirical charges in pH=7.0.

Finally, the ligands were plunged into the peptide made to solution and the docking study was done on 100 runs using a scoring function to determine the intermolecular energies between the molecules. Docking server uses the scoring function from AutoDock4 [58, 59]. Each docking result was obtained from 100 runs that terminated after a maximum of 250,000 energy evaluations. The population size was 150. The docking search used a translational step of 0.2 Å, and quaternion and torsion steps of 5.

**Advance settings**

*Figure* 36. shows a snapshot of the advance settings for a docking step.
The first three fields [56] are for making changes to the state variables that affect Lamarckian Genetic Algorithm (LGA).

“tstep” stands for Translational step. The default value is 0.2 Å.

“qstep” is defined as quaternion step / rigid body orientation. Unit quaternion is a mathematical notation to denote orientation and rotations of objects in 3 dimensional spaces. The default value is 5°.

“dstep” is defined as the torsion step/dihedral angle. It means dstep measures the sharpness of a twist movement for each dihedral angle (angle between two vector planes). The default value is 5°.

“rmstol” denotes the root mean square deviation tolerance. The default value is 2.0.

“ga_pop_size” denotes the number of individuals in a population. Each individual is a coupling of a genotype and its associated phenotype. Usually, this number is fixed throughout the run. Typical values range from 50 to 200. The default value is 150.
“ga_num_evals” and “ga_num_generations” set the limits to the docking run. The docking run generates ga_num_evals number of energy evaluations for each generation denoted by ga_num_generations. The default values are

    ga_num_evals : 250,000  
    ga_num_generation : 540,000

“ga_run” denotes the number of times the docking experiment should be run. The default value is 100.

6.4 Results

Table 6 shows the summary results from the docking experiments between non-functionalized, nitrogen functionalized and hydrogen functionalized SWNTs with vasopressin.
Table 6: Comparative Binding Free Energy values of Non-Functionalized, N-Functionalized and H-Functionalized SWNTs with vasopressin

<table>
<thead>
<tr>
<th>SWNTs</th>
<th>Dimension (n,m) Length (10 Å)</th>
<th>Estimated Binding Free Energy (kcal/mol)</th>
<th>Gallery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(5,0)</td>
<td>-5.04</td>
<td><img src="5,0" alt="Gallery" /></td>
<td><img src="5,0" alt="Results" /></td>
</tr>
<tr>
<td></td>
<td>(5,5)</td>
<td>-4.78</td>
<td><img src="5,5" alt="Gallery" /></td>
<td><img src="5,5" alt="Results" /></td>
</tr>
<tr>
<td>Non Functionalized</td>
<td>(10,0)</td>
<td>-5.22</td>
<td><img src="10,0" alt="Gallery" /></td>
<td><img src="10,0" alt="Results" /></td>
</tr>
<tr>
<td></td>
<td>(10,1)</td>
<td>+1.5e+0 0.3</td>
<td><img src="10,1" alt="Gallery" /></td>
<td><img src="10,1" alt="Results" /></td>
</tr>
<tr>
<td>Nitrogen-Function</td>
<td>(5,0)</td>
<td>-3.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5,5)</td>
<td>-10.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10,0)</td>
<td>-3.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10,10)</td>
<td>+11.10</td>
<td></td>
<td></td>
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</tbody>
</table>

| Hydrogen-Function | (5,0) | -5.07 |

<table>
<thead>
<tr>
<th>Results Table</th>
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<tbody>
<tr>
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<tr>
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<tr>
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<tr>
<td>1.</td>
</tr>
</tbody>
</table>
The detailed results for docking of all the structures are available in Appendix A.

### 6.5 Discussion

The scoring functions used to calculate the intermolecular energies and the solvation energies are obtained from AutoDock4 [58, 59] which uses the LGA and the Solis & Wets Local search method [60]. This algorithm helps to minimize the intermolecular energies by random search method. LGA method is very useful in complex problems like docking where the function had a lot of local minima points and computer memory available is less. Each ligand is orientated randomly in the initial position having an unknown random torsional energy. This randomized orientation helps to make the model...
free from bias. Each simulation is run for 100 times that terminates after a maximum of 250,000 energy evaluations. 100 runs help us to make the probability of occurrence of an orientation more specific.

Docking of vasopressin with various structurally different SWNTs helps evaluate the probable factors that influences the binding free energy calculations. The lower the Gibbs Free Energy (binding free energy) the more stable is the interaction. Our docking experiments tried to focus mainly on 2 factors:

a) The diameter of a SWNT, and

b) Functionalization of SWNTs.

a) The diameter of a SWNT: For bigger diameters, the model peptide tends to bind to the inner walls of the tube creating really unstable bonds. From the above results, peptides that bind to the outer walls of the tubes tend to form stronger bonds, i.e., less binding free energy values. The peptides that tend to bind to the inner walls of the bigger diameter tubes create higher energy bonds hence making the whole system unstable. Therefore, the smaller the diameter of the tube, the better the interactions.

b) The functionalization of SWNTs: 3 sets of docking experiments were carried out, non-functional, SWNTs functionalized with hydrogen and SWNTs functionalized with nitrogen. The results show that functionalized carbon nanotubes tend to form stronger bonds with the peptides. In addition, the functionalized nanotubes tended to intake more peptides molecules (from the percentage frequency of the results page) compared to the non-functionalized. From the energy values and the number of bonds formation of the H-functionalized and N-functionalized SWNTs
with vasopressin residues, we can see that the N-functionalized SWNTs have more stable interactions with vasopressin than H-functionalized SWNTs. It should also be noted that same number of hydrogen atoms were loaded to each SWNT as the number of nitrogen atoms. Nitrogen atom has an un-pair electron which tends to bind better with vasopressin residues. N-functionalized SWNTs form more number of stable bonds like hydrogen bonds, polar bonds, hydrophobic bonds and cation-pi bonds (Appendix A).

### Conclusion

The interaction of peptides with carbon nanotubes appears to be a very promising field for future study. Functionalization of the nanotubes may assist in their use as potential vectors for drug delivery. Docking studies done in this project do show that functionalized single walled carbon nanotubes have a high tendency to interact with peptides in a stable manner. It also shows that N-functionalized SWNTs form more number of bonds with vasopressin than H-functionalized SWNTs. Smaller diameters in SWNTs favor outer-wall interactions which is more stable than inner wall interactions. An extension to this docking study would be to explore energy values for increased or decreased length of SWNTs. A possible validation of the energy values obtained from the above docking studies could be done by interacting vasopressin with functionalized SWNTs in wet lab.

However, the docking experiments can only create hypothetical scenarios. Biological systems are one of the most complex systems that have ever been studied and hence it is very difficult to gauge every aspect of a biological system into a simulation model. But
docking studies can certainly give a head-start to what we might expect in the real life situation.
References


APPENDIX A

Non Functionalized SWNTs:

a) (5,0) Non Functionalized SWNTs:
### Interaction Table

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<th>Hydrogen Bonds</th>
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<td>C16 (cg, cova)</td>
<td>C18 (cg, cova)</td>
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</table>

### Computational Methods

Docking calculations were carried out using DockingServer. The Dreiding force field (Mayo, 1993) was used for a preliminary energy minimization of the ligand molecule (GNW7_E_0_10_00) using built-in Chimera tools in DockingServer. The semipirical method was used in the second step to optimize the geometry of the ligand molecule. PM6 semipirical charges calculated by MOPAC2007 (J. F. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrocarbon atoms were nonpolar, and nonpolar bonds were defined.

Docking calculations were carried out on a Vesuvius server with a protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell, et al., 1998). Affinity grids maps of 20x20x20 Å grid points and 0.375 Å spacing were generated using the AutoGrid program (Morris, Goodsell, et al., 1998). AutoDock parameter set, and distance-dependent electrostatic functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the LAMMPS algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 250,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and anglewise and torsion steps of 5 were applied.

### References

C. I. Azzi, L. Kovacs, L. Demko, Z. Dikadi
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T. A. Halgren
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Journal of the American Chemical Society 114 (28), 7827-7843 (1992)

Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function
Journal of Computational Chemistry 19 (14), 1639-1662 (1998)

F. J. Solis and R. J. B. Wets
Minimization by Random Search Techniques

P. F. W. Toonen, C. Frommel, et al.
An Effective Solution Tries Based on Atomic Occupancies for the In Protein Simulations
Molecular Simulations 10 (2-6), 97-110 (2003)
b) (5,5) Non Functionalized SWNTs:

This software includes code developed by the Theoretical and Computational Biophysics Group in the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign.

References, please cite:
W. Humphrey, A. Dalke, and K. Schulten
VMD - Visual Molecular Dynamics
## Computational Methods

Docking calculations were carried out using DockingServer. The DDEC force field (Mayo, 1993) was used for a preliminary energy minimization of ligand molecule. PM3 semiempirical methods were used in a second step to optimize the geometry of ligand molecule. PM6 semiempirical charges calculated by MOPAC2007 (J. P. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Nonpolar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out on vasopressin/norepinephrine protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell et al., 1998). Affinity (grid) maps of 20 x 20 x 20 Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris, Goodsell et al., 1998). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 250 000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

## References

<table>
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<td>Representation of Vanderwaals (VWD) Interactions in Molecular Mechanics Force- Fields - Potential Form, Combination Rules, and VDW Parameters</td>
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c) (10,0) Non Functionalized SWNTs:
### Computational Methods

Docking calculations were carried out using DockingServer. The Dreiding force field (Mayo, 1996) was used for a preliminary energy minimization of ligand molecules (SWNT_f6_f6_f6) using built-in ChemAxon tools. In DockingServer, PM6 semiempirical method was used in a second step to optimize the geometry of ligand molecules. PM6 semiempirical charges calculated by MOPAC2007 (J. P. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out using a pre-optimized protein model. Essential hydrogen atoms, Kollman united-atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell et al., 1998). Affinity (grid) maps of 20x20x20 Å grid points and 0.375 Å spacing were generated using the AutoGrid program (Morris, Goodsell et al., 1990). AutoDock parameter set and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LG4) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was repeated with the different runs that were set in total 150 with a minimum of 30 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

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E. Hazai, S. Kovacs, L. Demko, Z. Bikadi
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Journal of the American Chemical Society 114 (26), 7627-7643 (1992)

Morris, G. M., D. S. Goodsell et al.
Automated docking using a Lamarckian genetic algorithm and an empirical binding tree energy function

F. J. Solis and R. J. B. Wets
Minimization by Random Search Techniques

P. F. W. Deuff, C. Frommolt, et al.
An Effective Solvation Term Based on Atomic Occupancies for Use in Protein Simulations
Molecular Simulation 19 (2-9), 97-(1993)
d) (10,10) Non Functionalized SWNTs:

Image Gallery

This software includes code developed by the Theoretical and Computational Biophysics Group in the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign.

References, please cite:
W. Humphrey, A. Dalke, and K. Schulten
VMD - Visual Molecular Dynamics
### Computational Methods

Docking calculations were carried out using **LigPrep**. The Lamarckian force field (Mayo, 1996) was used for energy minimization of the ligand molecule (SWNT_10_10_10.graph) using built-in Chemaxon tools in LigPrep. PMF conformational charges calculated by MOPAC2007 (J. P. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out using variously validated protein models. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell et al., 1998). Affinity grids generated by 20×20×20 Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris, Goodsell et al., 1998). AutoDock parameters set and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

### References

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  Virtus Drug Ltd., Budapest, Hungary

- T. A. Halgren
  Representation of Van der Waals (vdW) interactions in Molecular Mechanics Force Fields - Potential Form, Combination Rules, and vdW Parameters
  Journal of the American Chemical Society 114 (20), 7827-7843 (1992)

  Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function

- P. J. Solis and R. J. D. Wets
  Minimization by Random Search Techniques

- P. F. W. Stooten, C. Feenmel, et al.
  An Effective Solution Term Based on Atomic Occupancies for Use in Protein Simulations
  Molecular Simulation 19 (2-3), 97- (1998)
N- Functionalized SWNTs:

a) (5,0) N- Functionalized SWNTs
b) (5,5) N- Functionalized SWNTs
This suite was developed by the Theoretical and Computational Drug Design Group in the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign.

References, please cite:
W. Humphrey, A. Dalke, and K. Schulten
WDD - Visual Molecular Dynamics
J. Mol. Graph. 14, 33−38 (1996)
### Interaction Table

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### Computational Methods

Docking calculations were carried out using DockingServer. The Urey-Bradley force field (Mayo, 1996) was used for the preliminary energy minimization of the ligand molecule. PM6 semiempirical methods were used in a second step to optimize the geometry of the ligand molecule. PM6 semiempirical charges calculated by MOPAC2007 (J. P. Stewart, Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrophobic bonds were merged, and solute bonds were defined.

Docking calculations were carried out on a workstation with a processor at 1 GHz and 1 GB of memory. The docking process was divided into three steps: generation of grid points, calculation of energy, and refinement of the docked conformation.

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1. Hazzard S., Kovacs L., Denko Z., Bikadi
2. DockingServer (www.dockingserver.com)
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4. T. A. Halgren
   Reproduction of van der Waals (VdW) Interactions in Molecular Mechanics Force-Field with Partial Atomic Charges: Computer Rules, and Vdw Parameters
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   Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function
6. P. J. Hurst and K. B. Yund
   Minimization by Random Search Techniques
   An Effective Solution Tenn Based on Atomic Occupancies for Use In Protein Simulations
   Molecular Simulation 10 (2-3), 97-123 (1993)
c) (10,0) N- Functionalized SWNTs

This software includes code developed by the Theoretical and Computational Biophysics Group in the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign.

References, please cite:
W. Hamley, A. Dutke, and K. Schulten
VMD: Visual Molecular Dynamics
J. Mol. Graph. 14, 33 38 (1996)
Computational Methods

Docking calculations were carried out using DockingServer. The Breusing force field (Mayo, 1988) was used for a preliminary energy minimization of each molecule (SWNT, 10-14) followed by semi-empirical methods in DockingServer. PM6 semi-empirical methods were used in a second step to optimize the geometry of ligand molecules. PM6 semi-empirical charges calculated by MOPAC2007 (J. P. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking simulations were carried out using a conformational randomized protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Sanner et al., 1998). Partial charges maps of 20-Å2-Å2 and points and 1.5 Å spacing were generated using the Autogrid program (Merritt, Goodsell et al., 1996). AutoDock parameter set and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsion of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 250,000 energy evaluations. The population size was set to 100. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 0.2 were applied.

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Representation of Vanderwaals (VdW) Interactions in Molecular Mechanics Force-Fields: Potential Form, Combination Rules, and VdW Parameters
Journal of the American Chemical Society 114 (20), 7827-7843 (1992)

AutoDock: using a Lamarckian genetic algorithm and an empirical binding free energy function

F. J. Solis and R. J. B. Wets
Minimization by Random Search Techniques

P. F. W. Stocker, C. Fromme, et al.
An Effective Solution Form based on Atomic Companionship Use In Protein Simulations
Molecular Simulation 10 (26), 97-100 (1995)
d) (10,10) N- Functionalized SWNTs

References, please cite:
W. Humphrey, A. Dalke, and K. Schulten
VMD - Visual Molecular Dynamics
Interaction Table

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docking calculations were carried out using DockServer. The Dredge force field (Mayo, 1999) was used for a preliminary energy minimization of ligand molecule (SWNT10_10_10.pdb) using built-in Chemaxon tools in DockingServer. PM3 semiempirical method was used in a second step to optimize the geometry of ligand molecule. PM3 semiempirical charges calculated by MOPAC2007 (J. P. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out on a supercomputer (Soileu, 2001). Essential hydrogen atoms, Kollman united atom type changes, and solvation parameters were added with the aid of Automol (Morris, Goodsell et al., 1998). Affinity (grid) maps of 2.0-2.0-2.0 Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris, Goodsell et al., 1998). AutoDock parameter set- and distance- dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

Computational Methods

References

E. Hatzis, S. Kovacs, L. Demko, Z. Bilak
DockingServer (www.dockingserver.com)

T. A. Haugen
Representation of Vanderwaals (Vdw) Interactions in Molecular Mechanics Force-Fields - Potential Form, Combination Rules, and Vdw Parameters
Journal of the American Chemical Society 114 (20), 7027-7041 (1992)

Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function
Journal of Computational Chemistry 19 (14), 1639-1642 (1998)

F. J. Solis and R. J. B. Wets
Minimization by Random Search Techniques

P. F. W. Stobbe, C. Frommel, et al.
An Effective Salutation Term Based on Atomic Occupancies for Use in Protein Simulations
 Molecular Simulation 10 (2-3), 57-57 (1995)
Hydrogen Functionalized SWNTs:

a) (5,0) Hydrogen Functionalized SWNTs
Computational Methods

Docking calculations were carried out using DockingServer. The Dreiding force field (Mayo, 1999) was used for a preliminary energy minimization of each molecule (SWMM_S_1310_H.pdb) using built-in Chemtool tools in DockingServer. PM6 semiempirical method was used in a second step to optimize the geometry of each molecule. PM6 semiempirical charges calculated by MOPAC2001 (J. P. Stewart, Computer code MOPAC2001, Stewart Computational Chemistry, 2001) were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out using the receptor-restricted protein model essential hydrogen atoms, and protein atom type changes, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodford, et al., 1988). Affinity grid maps of 20x20x20 Å grid points and 3.75 Å spacing were generated using the AutoGrid program (Morris, Goodford, et al., 1988). AutoDock parameter set and distance dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LOA) and the Saas & Webb local search method (Saas and Webb, 1998). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 2,000,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternary and torsion steps of 5° were applied.

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T. A. Hirsteen
*Reparameterization of Van der Waals (VdW) Interactions in Molecular Mechanics Force-Fields: Potential Form, Combination Rule, and VdW Parameters
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M. E. Morisawa, D. S. Goodford, et al.
Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function

R. J. Salls and P. J. Webster
Minimization by Random Search Techniques

An Effective Solution Term Based on Atomic Occupancies for Use in Protein Simulations
Molecular Simulation 10 (5), 297–302 (1992)
b) (5,5) Hydrogen Functionalized SWNTs

This software includes code developed by the Theoretical and Computational Biophysics Group in the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign.

References, please cite:

W. Humphrey, A. Dalke, and K. Schulten
*VMD - Visual Molecular Dynamics*
### Interaction Table

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</table>

### Computational Methods

Docking calculations were carried out using DockingServer. The Diggel force field (Mayo, 1990) was used for a preliminary energy minimization of each ligand molecule (SWNT-5,5,5,5). PM3 semiempirical methods were used in a second step to optimize the geometry of each ligand molecule. PM3 semiempirical charge calculations by the MOPAC2007 (J. F. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrophobic interactions were used, and rotatable bonds were defined.

Docking calculations were carried out using the program server. Essential hydrophobic interactions, Kuhnian and hydrophobic interaction charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell, et al., 1998). Affinity grid maps of 20 x 20 x 20 Å and points of 0.375 Å spacing were generated using the AutoGrid program (Morris, Goodsell, et al., 1999). AutoDock parameter set and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lammckian genetic algorithm (LGA) and the SA/SW local search method (Sastry and Weis, 1991). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were cut to terminate after a maximum of 200,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

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This software was also developed by the Theoretical and Computational Biophysics group in the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign.

References, please cite:
W. Humphrey, A. Dalke, and K. Schulten
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### Computational Methods

Docking calculations were carried out using DockingServer. The Dinding force field (Mayo, 1992) was used for a preliminary energy minimization of the ligand molecule (SWN7_10_0_10_H.pdb) using built-in Chemaxon tools in DockingServer. PM6 semiempirical method was used in a second step to optimize the geometry of the ligand molecule. PM6 semiempirical charges calculated by MOPAC2007 (J. F. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out on a supercomputer-revised protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell et al., 1998). Affinity (grid) maps of 20x20x20 Å grid points and 0.375 Å spacing were generated using the AutoGrid program (Morris, Goodsell et al., 1998). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the LAMMPS molecular dynamics program (LAMMPS) and the Sols & Wels local search method (Sols and Wels, 1987). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and rotational and torsion steps of 5 were applied.

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d) (10,10) Hydrogen Functionalized SWNTs
Computational Methods

Docking calculations were carried out using DockingServer. The Dindo-3 force field (Dindo, 1996) was used for energy minimization of ligand molecules (SWAT, 1994, C. Wein) using built-in Charmm tools in DockingServer. PM 6 semiempirical charges calculated by MOPAC2007 (J. P. Stewart, Computer code MOPAC2007, Stewart Computational Chemistry, 2007) were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out using Vina on a twisted protein model. Essential hydrogen atoms, including all atom types, and torsion parameters were added using the set of docking tools (Vina, Trott, 2010). Energy grids maps of 20 x 20 x 20 Å and points 0.375 Å spacing were generated using the AutoDock program (Morris, Goodsell et al., 1998). AutoDock parameter set-and-distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Slott & Wads local search method. Slott and Wads, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 100. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 0.02 were applied.

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APPENDIX B

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