DNA Drug Interaction

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Deoxyribonucleic acid, DNA, is a molecule of great biological significance. The total DNA content of a cell is termed the *'Genome'*. The *'Genome'* is unique to an organism, and is the information bank governing all life processes of the organism, DNA being the form in which this information is stored. Stretches of DNA called *'genes'* have the extremely important function of coding for proteins. The function of the rest of the genome, loosely termed as *'non-gene'* regions, is not very clearly known.

Fig.1 The DNA molecule

DNA has two main functions,

1. *Transcription:* Information is retrieved from the DNA by ribonucleic acid, RNA, and utilized to synthesize proteins in the body. Proteins are involved in all body processes and play many roles. e.g. as hormones, enzymes, carriers, structural proteins, receptors, regulators etc.
2. *Replication:* DNA is responsible for its own regeneration, i.e., DNA self replicates.

DNA is present in the body in the form of a double helix, where each strand is composed of a combination of four nucleotides, adenine (A), thymine (T), guanine (G) and cytosine (C). Within a strand these nucleotides are connected via phosphodiester linkages. The two strands are held together primarily via Watson Crick hydrogen bonds where A forms two hydrogen bonds with T and C forms three hydrogen bonds with G (Figure2).

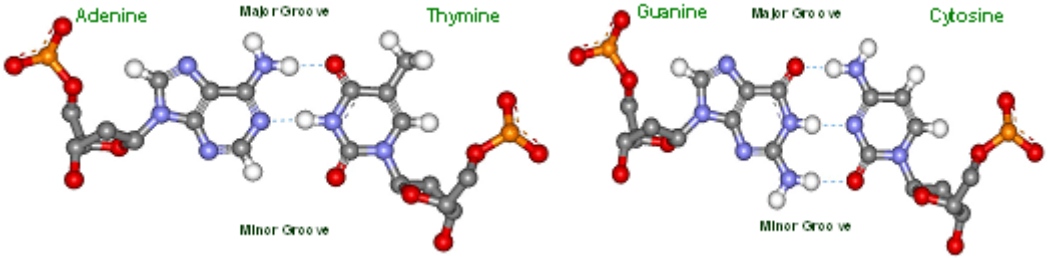


Fig.2 Watson Crick Base pairing, A-T and G-C base pairing

Specific recognition of DNA sequences by proteins/ small molecules is achieved via the combination of hydrogen bond acceptor/donor sites available on the major groove or minor groove. e.g. the A-T base pair offers a hydrogen bond acceptor, N7, a donor N6, and an acceptor, O4 on the major groove side.

DNA-Drug Interaction

Transcription and replication are vital to cell survival and proliferation as well as for smooth functioning of all body processes. DNA starts transcribing or replicating only when it receives a signal, which is often in the form of a regulatory protein binding to a particular region of the DNA. Thus, if the binding specificity and strength of this regulatory protein can be mimicked by a small molecule, then DNA function can be artificially modulated, inhibited or activated by binding this molecule instead of the protein. Thus, this synthetic/natural small molecule can act as a drug when activation or inhibition of DNA function is required to cure or control a disease (Table 1).

DNA activation would produce more quantities of the required protein, or could induce DNA replication; depending on which site the drug is targeted. DNA inhibition would restrict protein synthesis, or replication, and could induce cell death. Though both these actions are possible, mostly DNA is targeted in an inhibitory mode, to destroy cells for antitumor and antibiotic action.

Drugs bind to DNA both covalently as well as non-covalently.

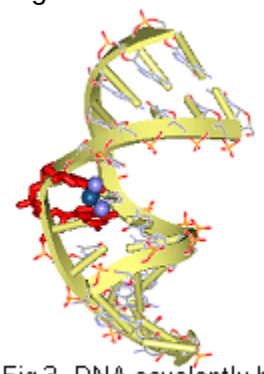


Fig.3. DNA covalently bound to cisplatin.(PDBID: 1AU5)

Covalent binding in DNA is irreversible and invariably leads to complete inhibition of DNA processes and subsequent cell death. Cis-platin (cis-diamminedichloroplatinum) is a famous covalent binder used as an anticancer drug, and makes an intra/interstrand cross-link via the chloro groups with the nitrogens on the DNA bases.

Non-covalently bound drugs mostly fall under the following two classes:

1. *Minor groove binders*- Minor groove binding drugs are usually crescent shaped, which complements the shape of the groove and facilitates binding by promoting van der Waals interactions. Additionally, these drugs can form hydrogen bonds to bases, typically to N3 of adenine and O2 of thymine. Most minor groove binding drugs bind to A/T rich sequences. This preference in addition to the designed propensity for the electronegative pockets of AT sequences is probably due to better van der Waals contacts between the ligand and groove walls in this region, since A/T regions are narrower than G/C groove regions and also because of the steric hindrance in the latter, presented by the C2 amino group of the guanine base. However, a few synthetic polyamides like lexitropsins and imidazole-pyrrole polyamides have been designed which have specificity for G-C and C-G regions in the grooves.

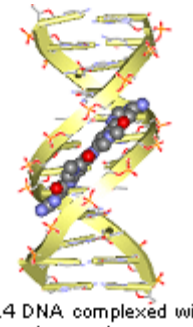


Fig.4 DNA complexed with netropsin, a minor groove binder.(PDB ID: 121D)

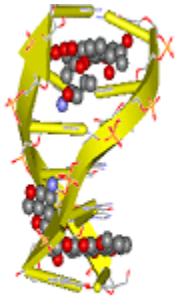


Fig.5 DNA complexed with actinomycinD, an intercalator. (PDB ID: DSC)

2. *Intercalators*- These contain planar heterocyclic groups which stack between adjacent DNA base pairs. The complex, among other factors, is thought to be stabilized by π-π stacking interactions between the drug and DNA bases. Intercalators introduce strong structural perturbations in DNA.

Non-covalent binding is reversible and is typically preferred over covalent adduct formation keeping the drug metabolism and toxic side effects in mind. However, the high binding strength of covalent binders is a major advantage.
Proteins are large molecules and bind quite strongly to the DNA, with binding constants in the nanomolar range. It has been difficult to achieve similar specificity and affinity using small non-covalent binders, and remains a major challenge to the design of drugs for DNA.

Some DNA binders are listed in the following table,

Table 1. Drug, action and mode of binding for some DNA binding drugs.

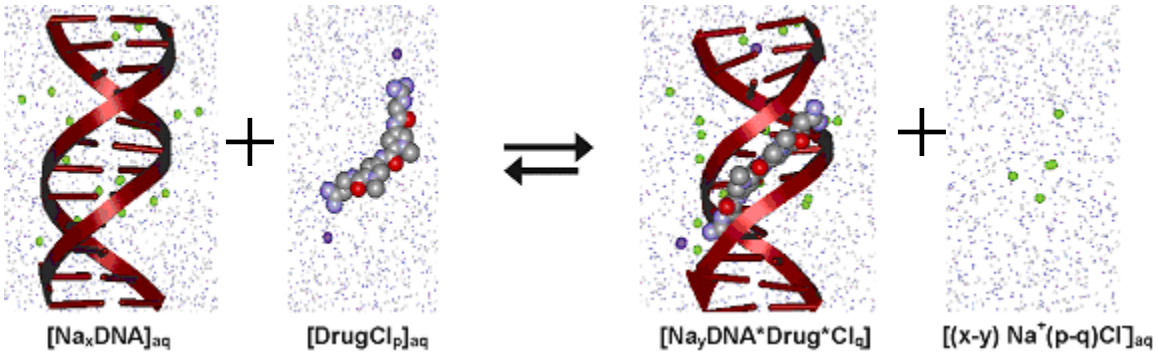
SNo	Drug	Action	Mode of Binding	PDB
1	Hoechst 33258	Antitumor	Minor groove binding	264D
2	Netropsin	Antitumor, Antiviral	Minor groove binding	121D
3	Pentamidine	Active against P. carinii	Minor groove binding	1D64
4	Berenil	Antitrypanosomal	Minor groove binding	1D63
5	Guanyl bisfuramidine	Active against P. carinii	Minor groove binding	227D
6	Netropsin	Antitumor, Antiviral	Minor groove binding	121D
7	Distamycin	Antitumor, Antiviral	Minor groove binding	2DND
8	SN7167	Antitumor, Antiviral	Minor groove binding	328D
9	SN6999	Active against P. falciparum	Minor groove binding	144D
10	Nogalamycin	Antitumor	Intercalation	182D
11	Menogaril	Antitumor- Topoisomerase II poison	Intercalation	202D
12	Mithramycin	Anticancer antibiotic	Minor groove binding	146D
13	Plicamycin	Anticancer antibiotic	Minor groove binding	1BP8
14	Chromomycin A3	Anticancer antibiotic	Minor groove binding	1EKH
15	cis -Platin	Anticancer antibiotic	Covalent cross-linking	1AU5

Forces involved in DNA-drug recognition:

Understanding the forces involved in the binding of proteins or small molecules to DNA is of prime importance due to two major reasons. Firstly, the design of sequence specific drugs having requisite affinity for DNA requires a knowledge how the structure of the drug is related to the specificity/affinity of binding and what structural modifications could result in a drug with desired qualities. Secondly, identifying the forces/energetics involved in such processes is fundamental to unraveling the mystery of molecular recognition in general and DNA binding in particular.

Some of the forces that are known to contribute to biomolecular recognition and also to DNA-drug binding are direct electrostatic interactions, direct van der Waals/packing interactions, complex hydration/dehydration contributions composed of hydrophobic component, solvation electrostatics, solvation van der Waals, ion effects and entropy terms.

DNA-drug binding may be described in the following manner,



Consider DNA-drug binding in an aqueous environment. DNA is polyanionic in nature and the drug molecule is also often charged. The associated counterions lie near the charged groups and are also partially solvated. When binding occurs, it results in a displacement of solvent from the binding site on both the DNA and drug. Also, since there would be partial compensation of charges as the DNA and drug are oppositely charged, some counterions would be released into the bulk solvent and are solvated fully. Also, the binding process would be associated with some structural deformation/adaptation of the DNA as well as the drug molecule in order to accommodate each other. All these events are associated with some energetic gains/losses, the comprehensive estimation of which is a major challenge.

We are attempting to understand the energetics of DNA-drug interaction by theoretically estimating the above contributions employing classical and statistical mechanical methods. Developing a theoretical protocol for detailed quantitative analysis of DNA-ligand binding in solution is a daunting task due to some major challenges. Simulations of DNA with solvent and the attendant counterion atmosphere require careful consideration to ensure system stability. Also, evolving a computationally efficient technique using statistical mechanical principles for quantitative estimates of binding free energies in large biomolecular systems is an equally challenging task. Our study is aimed at providing such a theoretical protocol for complementing experimental techniques and facilitating a minute study of the structure-energy relationships in DNA-drug complexes.

Structural and conformational changes in the DNA and drug on binding in solution are associated with enthalpic and entropic contributions to the binding free energy, which can be theoretically estimated from ensembles of structures generated via simulations. The only drawback of this approach is the long time taken for the simulations.
The other terms, namely, electrostatics, van der Waals, hydrophobic component, rotational and translational entropy can be estimated from single structures.

The web tool, PreDDICTA, estimates the components of DNA-drug binding free energy which can be calculated from a single structure, and correlates it with experimental binding free energy and ΔT_m, thus providing a swift method for evaluation of potential lead candidates for researchers pursuing structure based drug design for DNA.

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