Xournals

Academic Journal of Physical Sciences

ISSN UA | Volume 01 | Issue 01 | January-2019

Crystallography and Its Role in Drug Design

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Available online at: www.xournals.com

Received1 08th August 2018 | Revised 05th October 2018 | Accepted 19th December 2018

Abstract:

Functions and structure are intimately related with each other. The area of bioactive molecules is less important than this. It is noticed that, the chirality of the enzyme is openly linked to the enantio-selectivity. An absolute configuration of a molecule can be determined by the X-ray crystallography method and also a comprehensive technique for the determination of arrangement of any molecule at an atomic resolution. An unequivocal, precise, and consistent 3-dimensional structural factors are provided by the outcomes from X-ray crystallographic learnings, which also acts as requirements for rational drug design and arrangement based purposeful learnings. Elucidation of 3D structures by the impact of X-ray crystallography on the efforts to fight diseases is discussed in this paper. It is also discussed about the role of crystallography in structure based drug designing and its role in healthcare.

Keywords: *Structure, X-ray diffraction, Absolute Configuration*

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Introduction

The incommensurate crystal phases have a need of expansion of crystallography beyond Euclidean crystallography which is already superficial with the superspace approaches and lattice symmetry is also restored by this in a higher dimensional space only. Since scaling does not leave the Euclidean distance invariant, therefore, it also necessitates an appropriate non-Euclidian allowance by the discovery of quasi-crystals with scaling invariant diffraction peak position. In the golden mean ratio, the one-dimensional Bonacci chain is characterized by the two interval sequences i.e., L and S where,

$L/S = \tau = (1+5^{1/2})/2$

The invariants in relation to the scale transformation are,

$S \rightarrow L$ and $L \rightarrow L + S$

A two-dimensional invertible integral matrix is expressible by this transformation, and a square lattice of invariant is left by the square of it is a hyperbolic rotation in the super space. The Fibonacci scale transformation validates the requisite to outspread Euclidean crystallography and for including hyperbolic gyrations, therefore, is of ultimate significance for the structural properties of a Fibonacci chain. Multimetric crystallography which has been adopted in this study reflects the appearance of circular and hyperbolic gyrations within the similar group. Normal crystals can also be associated and applied by the multimetric crystallography. Particularly, multimetrical space group left invariant to the atomic structure of ice. The structural features in snow crystals can be interpreted by its point group of infinite order. The hexagonal scaled forms which is much similar within the snow crystals, reveals the probable significance of an equivalent multimetrical point group for six-fold helical nucleic acid molecules, but this process has occurred by the microscopic molecular level. In the involved molecules, if a number of atomic positions in the asymmetric unit of the Euclidean line symmetry group are considered as modulo translations along the helical axis, it can be connected by the elements of this extended point group. The opportunities for crystallographic approaches is provided by this observation which is applied to molecular structures particularly, in biomacromolecules having a given axial rotation symmetry. It is important to know before considering the technical details that crystallography always defines structural relations of a Euclidean system. It is still the matter of question that the present approaches are physically relevant.

Model and real structures

Hereby considering the model structures, X is termed as positions given as a distinct set of points, x is in the three-dimensional Euclidean space:

$$X = \{x|x \in \mathcal{E}(3)\} \quad (1)$$

In the same way, with the correspondence of ρ between model and real positions, the real structure Y is given,

$$\rho: X_0 \rightarrow Y_0 \text{ for } \rho(X_0) = Y_0 \subset Y,\ X_0 = \rho^{-1}(Y_0) \subset X \quad (2)$$

Having the following properties:

- In given upper bound $\mathcal{E}$, the model structure is an approximation of the real one.

$|x - y| \leq \mathcal{E}$ for $y = \rho(x)$;

- Here definition domain of ρ is a subset X_0 of the model structure X
- The mapping ρ is a monomorphic as it is injective:

$P(x) \neq \rho(x')$ denotes $x \neq x'$ equally

- A subset Y_0 of the whole structure Y is the image of ρ.

Crystallographic structures and groups

An interaction between geometry, number theory, and algebra, on which crystallography is based on and all the three aspects are very significant and necessary for the extension. The Euclidian group is the covariance group of the system, as the law of Euclidian geometry is followed by the crystallographic structure. The laws of the system are left invariant by a co-variance group, whereas, the system is left invariant by an invariance group. The sets of rational integers, the indices, can labeled the equivalent positions, due to the underlying lattices and indexed positions have nontrivial invariance group (Janner, 2001).

Crystallography and Drug Design

There are many techniques available through which, determination of the structure of molecule at atomic resolution can be done, among which, X-ray crystallography is one of them. Functions and structure are intimately related with each other. For balanced drug design and structure-based functional lessons, there are some prerequisites like accurate knowledge of molecular structures are needed. An unequivocal, precise, and consistent 3-dimensional structural factors are provided by the outcomes from X-ray crystallographic studies at a time even sometime, before the completion of characterizations. An outright arrangement of a molecule can be determined by the X-ray crystallography method. In a biological system, the outright arrangement is a perilous assets and alteration in the response of the biological system may be caused by any change in it (Deschamps, 2005). The determination of the 3D structure of several macromolecules have been done which enables the structure-based drug design for the cure of various illnesses, therefore structure plays an important role in healthcare. Structure-based designed molecules cannot be used as drugs but various other properties such as bioavailability and solubility are needed to be optimized. The properties and abilities of passing through the membrane for reaching up to target site, recognizing and binding specifically with their target to control its function is needed to possess by drugs. The drug remains likely to be accepted by the body and also must be chemically synthesized and cost-effective. The instances of how crystal structures help in the drug improvement are discussed below

HIV Drugs

AIDS (Acquired Immunodeficiency Syndrome) is the disease which is previously unknown and came to know in the year 1980s, which was found to be initiated by a virus called as HIV (Human Immunodeficiency Virus). The disease causes severe infections and also destroys the immune system of the patient with no medication available. A few years later, treatment of this dangerous disease is made available but, before that person suffering from this fatal syndrome could not escape from death. Aspartyl protease is the first structure to be determined and is crucial for the duplication and development of the virus. Crystallography, binding energy measurements, and calculations are processed widely at each stage of the development. Viral protease (HIV PR) is given in combination with the reverse transcriptase, which inhibits another enzyme of the virus, in a cure with cocktail drugs.

Hypertension

Hypertension leads to the cardiovascular diseases hence it is a major health concern worldwide. There are two enzymes which convert enzymes into the renin-angiotensin scheme of the reaction pathways are renin and angiotensin- I regulating the blood pressure in the body and are probed as drug targets. One drug aliskiren has made for the market after many years. A zinc-dependent dipeptidyl carboxypeptidase named as ACE its inhibitors were designed before its structure determination based on the stated structures of carboxypeptidase-A and thermolysin. The visions into the hydrolytic mechanism of the enzyme are provided by the structures of ACE and also showed the basis for first-generation drugs binding. The new improve drugs stay longer in the body and have a better tendency to penetrate the tissue.

Influenza

Swine flu and bird flu is the example of a disease which is caused by the influenza virus and its seasonal outbreaks occur every day. The surface glycoprotein of the influenza virus is Neuraminidase. The haemagglutinin of the virus along with sialic acid which is existent on the surface proteins of the host cell helps in attaching the virus to the host surface. The cleavage of sialic acid from the surface of the host cell is catalyzed by the neuraminidase and virus releases and extend in the host. A homotetrameric molecule with box-like structure and four-fold symmetry are called enzyme. The mode of inhibition is revealed by the structures of complexes and it also shows an additional cavity around the inhibitors. Through the addition of groups that possess the cavity known as 150- cavity located at the binding site, designs the later drugs.

Multidrug Resistance

It takes enormous efforts to find effective drugs for the treatment of any diseases. The success of any drug is a task which is completed when the drug is freed to the market and it gives an affirmative result, it can be then used by the generation to win a war against the pathogen. Resistance against the pathogen can be developed by frequent use of drugs, not for one but for a number of drugs. This is the phenomenon which is called multidrug resistance

(MDR). It is not limited to any drug or organism but is ubiquitous, indicated by the reports of MDR against various drugs which are used for the treatment of malaria, TB, HIV, flu etc. The structural basis for MDR is also helped by crystallography. A complex with Tamiflu is determined by the structure of neuraminidase of a drug-resistant strain of influenza virus with the His274Tyr mutation.

Targets of Aspirin

Aspirin is being used since date back to around 400 BC for treating the pain and fever from the bark and leaves of the willow tree and was recommended by the Hippocrates. It was found later the presence of salicin accountable for the pain relief. In the late 1890s, the compound was altered as acetylsalicylic acid termed as aspirin and then used for the cure of fever, pain, and inflammation. In the 1970s, the mechanism of its reaction became known when its receptor enzymes such as cyclooxygenases – COX-1 and COX-2 were recognized, although it has long recognized existence as an effective pain reliever. Aspirin binding with Cox-1 has adverse effects such as gastric bleeding, although it binds to both Cox- 1 and Cox- 2. An additional cavity is exposed by the structure of Cox- 2 which results in the development of Cox- 2 specific inhibitors, accessible in markets (Suguna, 2014).

Review of Literature

Macchi and Sironi, (2004) worked on flexible temperature x-ray crystallographic learnings, a balancing tool for charge density examination of soft bonds. The indication of some intramolecular mode is connected with the retort of soft bonds against variations of the crystalline atmosphere which is associated with the incipient bonding. Such experiments contained substantial data to balance the bonding characterization even on the internal vibration modes. They concluded that making any kind of generalization is not possible.

Hartshorn *et al.*, (2004) described the portion screening procedure which is based on high throughput X-ray crystallography. They demonstrated the technique against five proteins (p38 MAP kinase, CDK2, thrombin, ribonuclease A, and PTP1B) and identified wreckages which are effectual folders comparative to their size with weak potency, therefore, evaluate lead compound with good quality. The encounter of compounds of novel lead against the target range is done by the fragment screening method that has a great potential and they also illustrated about the identification of the lead compounds which is used for p38 MAP kinase.

Jaskolski, Dauter, and Wlodawer, (2014) discussed achievement of crystallographers which is often iconic and most important and enhances our knowledge and understanding regarding the structures and functions of biological macromolecules. They listed approximately 42 scientists of physics, chemistry or medicine who got the Nobel Prize for their contributions in relevant field which also includes the use of X-rays or neutrons and crystallography. They tried to build a genealogy tree of protein crystallography's principal lineages emerging from the members of founding to the present generations.

Keen, (2014) discussed the role of physics in the development of crystallography since last 100 years and also its relevance with each other at present. The findings of the study were crystallography is an important component of modern condensed matter physics, however, it is not much more highlighted. The work of physicists has been significantly supported the rapid developments of crystallography over the last hundreds of years. The modern physics or condensed matter physics is obliged to crystallography at the same duration.

Heifetz *et al.*, (2015) worked on the G-protein coupled receptors (GPCRs), discussed current growth and highlighted key areas of future needed research for the discovery of GPCR drug. They concluded that the GPCR research and drug discovery with the collaboration between academia and industry is very beneficial which is accepted by all the participants of this research. During the conference, they also described widely the efficiency of such associations for GPCR study and drug discovery.

Zheng *et al.*, (2015) reviewed on the determination of precision, validity, and accuracy of a protein or nucleic acid structure by X-ray crystallography. It plays an important role in drug designing. Over interpretation of crystal structures can be done. This interpretation can be followed up by the experiment in which bias hypotheses occur. They said in their conclusion that for rational drug discovery, X-ray crystallography is still one of the best tools and suggested the need for expansion of Protein Data Bank or create a new organization.

Montfort and Workman, (2017) summarized the issues related to the current state of the field of structure-based drug design and fragment-based drug design. They also discussed the new developments, such as the X-ray free electron laser technology, cryo-electron microscopy, targeted protein degradation, and also the open science approaches. The value of structure-based drug design are used to debrief biology and disease pathology, and also for informing the target endorsement. They suggested the need of maintenance of scientific rigor related to the structural biology.

Helliwell, (2017) reviewed new expansions in crystallography, its technique, procedures, and room in the field of molecular bioscience. He also reviewed many areas such as coloration of live and cooked lobsters, the role of crystallography within the field, public understanding of the biosciences along with the illustrative results for reporting the scope of each methodology. He noticed that the use of neutrons as a different probe capability is increasing in the community to complement X-rays and electrons.

Blundell, (2017) worked on protein crystallography and drug discovery, recollection of its knowledge and exchange between academia and industry. Development of the renin structure was done in academia in London for developing anti-hypertensives in pharma. They concluded that according to the technical area, the chief attractors of new access differs. Biotechnology is the only field where more knowledge is contributed by the public sector research hence has the utmost level of activity of formal linkage to academic centers.

Conclusion

The pharmacophoric parameters are promoted by the results of crystallographic studies so that it can be calculated from 3-dimensional coordinates. These can be used to guide future development along with the data on biologic activity. Comparison of the relative position of groups is provided by the use of 3-dimensional data, which is vital in binding the receptors in unlike compounds along with the similar compounds. The need for translating the linear modifications into the 3-dimensional framework of the receptors is required for the further progress.

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