Article

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Select Gap identification on Mathematical and Computer Modelling in Drug Discovery till COVID - 19

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Abstract

Mathematical models play a significant role in day to day life and especially in the prediction of future their role is most vital. This article comprises of the details of the collection of mathematical models and different computer software programs in the field of drug discovery. The year-wise classification of sequential developments has also been proposed in this article. The gaps pertaining to the proposed models have been identified and proposed which will be helpful for future researchers. Challenges faced by the researchers while modelling the traditional & modern Drug Development, trust models, AI, MI models in the regulatory networks around the world has been proposed. A few interesting books too are suggested in the field of Drug Discovery. As presently to eradicate Covid-19 pandemicity from this world, the vaccination preparation is taking place throughout the world in a multidimensional way, the reader of this article will get enthusiasm and innovative approaches to proceed research further towards mathematical and computer modelling in drug discovery and related fields.

Keywords: Gap, Mathematical modelling, Statistics, Differential equations, Drugs Discovery, Probability, Programming, Integral, Finite element methods, Computer program, Software, Medicine.

Modelling Paradigm

In the present scenario, mathematical representations play a vital role in medicinal development and knowledge. Such models are applied for promotion, production, process examining, and constant development. Although several simulations have been employed in

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therapeutic process improvement and production, umpteen numbers of such modelling methods are yet progressing to gain more information, sophistication and better prediction. Several researchers have proposed different types of mathematical models for the spread or prediction of diseases. For instance, Dheva Rajan et al. (2013 a,b, 2014 a,b,c,d) proposed an ordinary differential equation (ODE) model for the spread of Dengue fever with incorporated probabilistic and statistical ideas. As a future development, the inclusion of rainfall, climatic factors, temperature, humidity, the impact of awareness programs, seasonality, self-prevention, etc., is proposed. The said model is based on the population dynamics and is a reflection of the use in serving to comprehend the dynamic processes and in making predictions. Margaret P. Chapman et al. (2016) have presented an outline of the ODE context and gave illustrations of in what manner ODEs can be employed to tackle challenges in the tumour. The models like the above mentioned deals with the spread and prediction of infections. Though such models have the vaccination or hospitalisation parameters, it is hard to assess the efficiency of the vaccination just based on the collected data. During the recent period, the pharmaceutical firms have pursued a pure supposition that a solitary medication hitting a solo objective was the "prudent" approach to structure drugs. That was an immediate result of the absence of information about work deciding highlights of wanted ligand molecules in the medication revelation process. This methodology keeps on ruling pharmaceutical reasoning to change the scenario. Hence, the reader of this article is able to understand the difference between the Mathematical models of spread or infection prediction and drug discovery. This article focuses on the various Mathematical and computer models of drug discovery. For the purpose of year-wise classification and the incorporation of mathematical techniques in computer models, these two models has not been separated and given continuously. This is not for explaining the research work of other authors lucidly, but to give an insight into the past modelling on drug discovery in a wide range and proposed future developments. The reader of this article will get the idea of the prior modelling techniques in discovery of drugs.

Models, especially those related to Mathematical techniques can comprehensively be classified as qualifiable or quantifiable. Qualifiable data is also called subjective. The attention in this article is given to quantifiable models. However, the statistics has many sophisticated techniques to convert qualitative items to quantitative data and analyze. Modelling procedures help experimentalists in the pharmaceutical business to comprehend, create, and showcase successful medications and innovative treatments to patients. Experimental modelling methods can be employed to embody input-output analysis. These prototypes are especially beneficial for complicated procedures wherever the progress of systematic prototypes is not possible. Experimental models consider the system as a “black box” model. The primary Physical-chemical incidents using black-box techniques do not illustrate complete information about the system. Modelling & Replication (M&R) techniques are well-known quantifiable devices that are helpful in strengthening research and development (R&D), supervisory authorization, and promoting of novel therapeutics. Use of M&R assists to construct useful researches & findings and interpret the outcomes in the perspective of all the existing data and knowledge to allow active decision-making throughout R&D. There are two significant types of modelling methods, populace centred and system dynamics models. The first technique is popularly recognized in

current medical business and comes under the department of medical pharmacometrics (PMX). The second technique includes a variety of methods of pathophysiology acquiescent to pharmacological interposition, beckoning alleyways in ecology, and element dispersal in the body referred as the models of systems of quantitative pharmacology (QSP).

The author of this article suggests a beautiful book written by Shein Chung Chow, Jun Shao (2002) to the beginners of Mathematical modelling or biostatistical modellers towards drug discovery. Several Mathematical and Statistical models are discussed by Shein Chung Chow after detailed analysis in the said book. Jan Shao described a physiognomies study primarily for drug discovery in his book. This physiognomies study includes the process of drug discovery and the particular requirement of data analysis at every stage. The table is given below.

Table 1: Physiognomies of drug discovery

Process in Drug Discovery	The necessity of Data analysis
Benchmark	Attributes
Aims	Crystal clear explanation of the research idea
Techniques of assessment	Review of suggested or real techniques of assessment
Model	Reasonable assessment together with jurisdiction to offer a quantifiable assessment of medication impact
Choice of themes	Satisfactory guarantee of the infection or circumstances, conditions or limitations of the results/experiments
Assignment of subjects	Reducing predisposition as well as trustworthiness of relation between clusters
Contributors of researches	Reducing predisposition on themes, thoughts, outcomes, findings, and assessment
Evaluation of outcomes	Perfectly classified as well as trustworthy
Impact on evaluation	Need of suitable mathematical/numerical techniques

Researchers from Princeton, namely, Christodoulos Floudas and Meghan Bellows Peterson, have built a method to employ mathematical models to take few presumptions of detecting innovative medicines. They discovered numerous fresh possible drugs that can battle against HIV. They have also applied the concept of mathematics, as a technique for detecting innovative medicines for a variety of infections by determining the characteristics of genetic particles to foretell the efficacy as drugs.

Gap analysis in Literature

Mathematical modelling and computer simulation of biological systems as an emerging technology offer a cheap, practical and biologically meaningful solution to the problem of fitting and safe drug design and development through its ability to search an extensive variety of experimental conditions in a virtual environment. The number of mathematical designing methodologies in the discovery of anticancer medicines is steadily upsurging, and several different innovative techniques have been established on the present trends of exploration. These methodologies have added to a superior comprehension of new oncological aims that have taken into account the abuse of generally insufficient data created by preclinical trials. Also, it is utilised in translational methodologies for managing and assisting the decision of treating procedures.

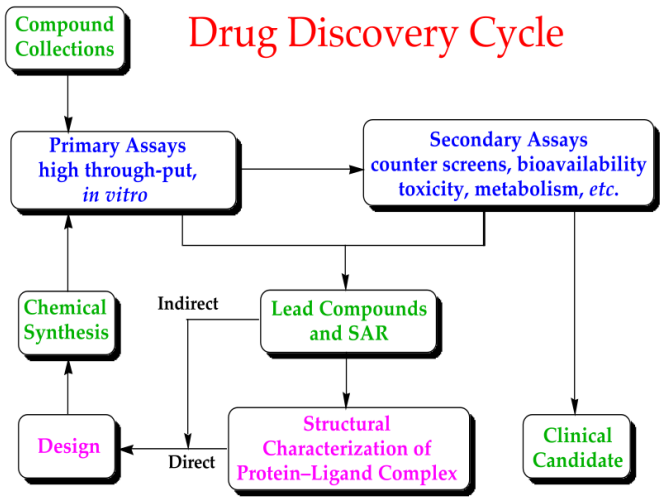

Figure 1 Drug Discovery cycle (Image Curtesy: BoghogSchematic on https://commons.wikimedia.org/wiki/File:Drug_discovery_cycle.svg)

The “in silico” system biology approach allows: i) expedient and rational identification and validation of drug targets against the background in which the function of a goal is expressed; ii) optimal therapeutic profiling of a new drug and systematic exploration of whether the most effective treatment is a drug that acts specifically on a single target or one that operates at multiple destinations; iii) analytical assessment of the effects of different classes of drugs and recommendation on modifications of the compounds to improve their efficacy; iv) investigation of issues of clinical safety of a drug(s); v) understanding of the impact of physiological variables on drug action in ways that cannot be adequately represented in even the most sophisticated animal models and thus prediction of pharmaco biological effects of new compounds before they run expensive and time consuming in vivo and in vitro experiments. However, most existing softwares are incapable of analysing and integrating complex interactions of molecular, cellular, tissue, organ and system activities under conditions involving one or more lead compounds.

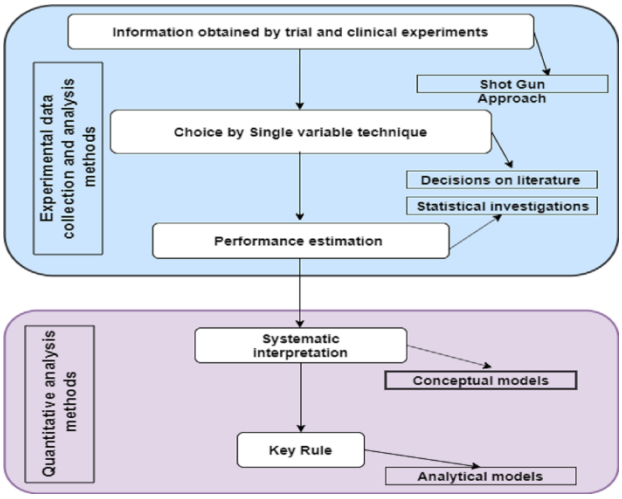

Figure 2 Stages of Mathematical Model Development towards Pharmaceutical industry

The desired computational platforms should be based on new theoretical concepts of physiology of biological systems and the pathogenesis of diseases. Till such ideas are established in medicine and biology models, it will remain unsatisfactory, and the pharmaceutical industry will be sceptical in employing them. In conclusion, drug developers, researchers and physicians using mathematical modelling technology can speed up critical decisions concerning the rational direction of experimental work at different stages of a lengthy process of drug discovery and development and thus bring better, safer and more effective drugs to patients. The incorporation of mathematical models in experimental models is a challenging task, and even experts are struggling to get an optimal model. The challenges in forming such models are given as a chart in Figure 2.

Figure 3 Challenges in obtaining data for Mathematical modelling in Drug Discovery

Developing a mathematical model for the recognised processes or structure for the clinically detected performance is not just an easy task. The authentication of the prototype too should be conducted through experiments. Nowadays, stratification of patients too has been done by pharmaceutical industries to analyse the proposing of statistical models that are always a challenging task for researchers. The Cross-functional group representatives have distinct

objectives and requirements. An excellent statistics procedure is described as a set of statistical standards intended for the top pharmacological systems in constructing and evaluation of researches performed at a variety of phases of drug exploration and advancement (Chow, 1997). Statisticians require to be conscious of the vying requirements of stakeholders. The clinical trials need enormous knowledge in science, and more importantly, meeting patient needs. Translational science seems to be still at infancy to animal models that are not justified in humanoid infections. Comparatively tiny sample sizes in such clinical experiments usually yield inaccurate results. For example, testing a drug in a human depends on human immunity, which differs from individual to individual. The decisions-based results are more important here, as the drug should be used in human. The statistics plays a critical role at this stage.

A factual model has been created to ascertain the accomplishment of medications for people, which could prompt the accessibility of exactness in drugs. Analysts at Vienna's institute of medical statistics have exhibited a numerical technique which can be utilized to distinguish the qualities that are fundamental for the forecast of the viability of new medicates for a specific person. It is realized that medications don't have similar consequences for each person. Researchers have hence been hoping to recognize gatherings of individuals who react well to the dynamic fixings in medicines, especially individuals who don't show symptoms to them. Utilizing the information acquired from these examinations, statistical investigations can be completed to precisely foresee the viability of the medication. Future researchers can utilize advanced analytical systems to channel biomarkers from the information, which will at that point be utilized to create models to anticipate the subgroups of patients where the fresher medications will be more compelling than current medicines. The examination depicts the measurable technique as utilizing calculations to distinguish relevant biomarkers and to evaluate the factual dependability of the expectations made. The analysts stated on how it could be conceivable to foresee the patient subgroups where medicines will be sturdy and safe. The group also mentioned how it is a significant advance towards the improvement of the unwavering quality of prescient models in accuracy prescription to help the advancement of medication provided food explicitly for humans. In disease considerations, it tends to be anticipated which patients are bound to profit by another medicine, broadening their future. Relapse models and variable determination techniques are utilized by researchers to do this. The specialists referenced how these procedures (factual expectations) are frequently dependent upon variety – the less information that is accessible, the less precise the forecast would be. Right now, the fundamental point is to get enormous informational indexes, to limit the scope of variety, and to permit specialists, and in time, clinicians, to precisely foresee a patient's reaction to another medication or specific treatment. This could prompt the accuracy of the drug being more accessible than the present performance of the discovered drugs.

In 1988, Cramer et al. proposed a molecular field-based software program tool called, CoMFA (Comparative Molecular Field Analysis) which has the most significant feature "3D QSAR method founded upon information from established effective molecules". This became the commercial program later. In 1989, Van Drie proposed a software program tool called ALADDIN as a united device for computer-supported molecular design and pharmacophore

recognition from geometric and steric. Substructure searching of three-dimensional molecular structures has the most significant feature "3D with database searching method". This software is available upon request and it is not commercialized.

Bohm (1992) proposed a computer program called LUDI which is a modest technique designed for de-novo model of enzyme inhibitors. Eisen et al. (1994) proposed a computer program called HOOK to find the innovative molecular structural design that fulfils the constraints of a macromolecule binding site.

In 1993, Snyder et al. proposed a feature method based software program tool called APOLLO (Automated Pharmac Ophore Location through Ligand Overlap) which has the most significant feature "Finding of communication points fitting to the receptor site and generating a quasi receptor from a group of ligands". This software is offered by a writing application and it is for the non-profit, non-business individual. In 1993, Martin et al. proposed Bron-Kerbosh clique detection algorithm-based software program tool called, DISCO. This is a rapid innovative methodology to pharmacophore charting and its use to dopaminergic and benzodiazepine agonists has the most significant feature "Every molecule is categorized by ligand spots and spot places". This became the commercial program later.

The deployment of non-linear technique and simulations while examining the trial outcomes are constantly needed to formulate different medicines due to the complex nature of biological trials. Other types of current-generation models are also available, viz, artificial neural networks (NN), fuzzy logic (FL), and neuro-fuzzy modelling. In order to solve the above-said issues, the current generation models can also be adopted. The revolutionary efforts of Hussain et al. (1991) Yliruusi et al. (1994), and Leuenberger et al. (1998) in artificial intelligence (AI) showed that their proposed developments could be used for interpreting the outcomes of the design of experiments.

In 1994, Vinter JG proposed molecular method field-based software program tool called, XED (extended electron distribution). This has the most significant feature "Ground spots are utilized as straightforward as well as "actived epictions" of the electrostatic combined with van der Waals highest and lowest characteristic of a molecule ". This became a moneymaking program later. In 1994, Klebe et al. proposed a molecular method field-based software program tool called, COMSIA (Comparative Molecular Similarity Indices Analysis). This analyses the molecular resemblance indicators in a comparative study of medicinal particles to compare and foretell their biological action. The tool has the most significant feature "usage of Gaussian-style physicochemical attributes". This became the money making program later.

Clark et al. (1995) proposed the de novo molecular construction method called PRO LIGAND. This method is integrated with the simulation system that gives the unification framework of the new generation of the novel molecular design and the simulating systems. This work creates a substantial diversion in the pharmaceutical drug discovery models, and it has shown to be more successful tool in other experiments, and it incorporates many innovative features like fast analysis and rapid algorithms of graph theory. But the resultant reproduction time of the said program is more. Hence the computer scientist may think of updating the

program further to provide faster and better results. In 1995, Golender et al. proposed a feature method based software program tool called, Apex-3D. This has the most significant feature "pendent structural parameters and physicochemical properties". This has been replaced by Catalyst program.

Chow (1995a) proposed the statistical resemblance amongst dissolution summaries of medicinal goods in this work considered one point at a time. Lin Ju & Shu Jean Liaw (1997) extended the Chow's technique with the autocorrelation technique, which admits considering the correlation of more than one-time point. Lin Ju proposes in his study that, the vitro-dissolution method is considered as a vital component in new medicine creation to ensure the quality of produced medicine. It is proposed in his work that the approximated dissolution profiles can be modelled with a linear and/or quadratic relationship with time.
The quadradic model is given by:

$R = a_1 + b_{11}t + b_{12}t^2 + \varepsilon_1$

$T = a_2 + b_{21}t + b_{22}t^2 + \varepsilon_2$,

where R and T are the dissolution profiles, t is the two sets of time specified, ε_1 and ε_2 are normally distributed random variables with the arithmetic mean of 0 and variance σ^2.
where the linear relationship is given by:

$R = a_1 + b_1 t + \varepsilon_1$ and

$T = a_2 + b_2 t + \varepsilon_2$.

Simulation studies were performed to analyse the properties of dissolution profiles. In spite of the fact that strategies for evaluating the resemblance of dissolution profiles between two medication items exist in the literature, the majority of them don't give solid statistical as well as logical legitimizations. The characteristics and implications of the methods were analysed viz.,ANCOVA, two-way ANOVA, split-plot. Future researchers may think of MCOVA and MNOVA methods for the incorporation of new ideas. One can also think of technical evaluation of in-vivo and vitro-correlation for the proposed medicinal model assessment. Instead of upto quadratic modelling, the researchers may think of polynomial & exponential modelling. It is strongly suspected that exponential modelling is the optimal one for the drug discovery as it would span the growing time of infection in a short period.

In 1996, Barnum et al. proposed atom method based software program tool called GASP (Genetic algorithm superimposition program). This has the most significant feature "Utilizes genetical system methods for pharmacophore identification and automatically permits conformational elasticity and compares the characteristics between molecules". This became the profitable computer program later.

Jones et al. (1997) proposed a genetic procedure technique for the growth and justification for flexible docking. The authors first started with Novo to perform flexible growth docking, later the procedure was changed to genetic optimisation due to the inapplicability of their work with Novo pro. This technique involves the program Genetic Optimization for Ligand Docking called GOLD. This is an automatic ligand program for docking that incorporates the

genetic algorithm. Several updating has been done on the said algorithm, and the current algorithm (1997, Jones) tested more than 100 complex data from protein data banks. It was also identified that GOLD reached 71% accomplishment level in detecting the investigational binding mode.

Wang et al. (1998) proposed a technique for evaluating the binding similarity of a protein-Ligand complex with a renowned 3-dimensional shape called SCORE. To determine the SCORE, the model incorporates penalty, effect of desolvation, bonding of hydrogen, ligand bonding in metal, etc. This method is used for regression analysis through multivariate modelling technique. A noteworthy development of this technique is the presentation of anatomic binding count that enables the analyst to review and upgrade the lead compound in a shape-centered medicinal model. One might be interested in data analysis and the data on protein-ligand structures with quantified binding figures is given as PDB bind-CN (Liu et al., 2015, 2017), DUD-E (Mysinger et al. 2012), and DEKOIS (Bauer et al., 2013) designs.

Miftakhov et al. (1999) proposed a replica of a locus of the tiny bowel. The same was authenticated by a comparative analysis of the findings through mathematical replications of pharmacological composites to their consequences in biotic investigations. Here, four classes of medicines were simulated. Acting on the sarcoplasmic reticulum, changing the absorbency of L- and T-type Ca^{2+} controls on the soft muscle layer, motilides, and benzodiazepines. The fierce similarity of nominal data sandwiched amongst the hypothetical and investigational outcomes endorses the sturdiness of the technique. It is to be understood that the researchers used only the above said four types of channels, whereas other researchers may think of other avenues to analyze and can propose the comparative analysis.

In 2000, Jones and Willet proposed feature method-based software program tool called GASP (Genetic algorithm superimposition program). This has the most significant feature "Utilizes reduced extensive exploration to detect usual characteristics". This became the business oriented program later. In 2000, Li et al. proposed a feature method based software program tool called, HypoGen. This has the most significant feature "Acknowledges detection of suppositions that are common to the dynamic fragments in the preparation or simulated data, but does not appear in the inactive molecule". This became the profitable program later.

In 2001, Evan Alexander Thomas for his doctor of philosophy at the University of Melbourne proposed different mathematically induced computer developed techniques for the enteric nervous scheme. In his research work, the model replicates the trial data, and this validates the quality of "Gray box" model. He proposed an umpteen number of further developments in the proposed models; one might be interested. Researchers might also show interest in the thought-provoking book written by Briem (2003) regarding the designing methods of De Novo.

In 2004, Industrialists at the olecular Operating Environment (MOE), a chemical processing cluster proposed a property-centered algorithm software program tool called MOE. This has the most significant feature "Pharmacophoric structural characteristics are exemplified by marked spots in space ". This became the industrial program later. Roses (2004) published beautiful results in predictive efficacy in discovery and development of drugs using genetic

analysis that becomes the pipeline technology. The possible verification in higher Phase-IIB findings of effectiveness forecasters that were detected in Phase IIA were able to support in the model of more toptests. That is getting clinical testing results at lesser, quicker and lowers cost, hypothetically. Pharmacogentical method is proposed for fast identification of probable noxiousness-related human genomic reports.

Schneider, G & Fechner, U (2005) proposed a software program centred de novo model of the medicine. De novo method of molecules includes the design of a ligand pattern embedded in another model of the receiver that creates unique molecular shapes with anticipated pharmacological characteristics from the scrape. In 2005, Wolber et al. proposed atom method based software program tool called GASP (Genetic algorithm superimposition program) with LigandScout: 3-D pharmacophores resulting since protein-bound ligands and their usage as simulated examination screens. This has the most significant feature "Accepts detection of ordinary propositions to the dynamic fragments in the preparation or test group, but not in the motionless fragment". This became a business software program later.

In 2005, Rush et al. proposed molecular field method based software program tool called, ROCS (Rapid Overlay of Chemical Structures) a structure-centered 3-D scaffold bounding technique and its utilization to a microbial protein-protein contact. This has the most significant feature "Recognizing the resemblance among fragments centered on their three-dimensional structure". This became a commercial program later.

In 2006, Ribba et al. proposed a multiscale prototype with incorporated mathematical ideas to tumour treatment and its perfect utilizations. A Multiscale prototype of disease development on the genomic characteristics of the development of colorectal tumour is recommended. Here, the necessity of genetics dependent cell cycle guideline in the reaction of tumours to remedial conventions was researched upon. In 2006, Dixon et al proposed a feature method based software program tool called, PHASE. This has the most significant feature "Uses fine-grained conformational sampling and a range of scoring techniques to identify common pharmacophore hypotheses". This became a commercial program later. In 2006, Miftahof proposed a mathematical model consisting of numerical method technique to assess the role of subordinate conduction by acetylcholine and serotonin on movement of the belly. In this connection, one might be interested in reading the excellent article by Miftahof (2007) on Mathematical modelling in drug discovery and development.

Mattias Andersson et al (2007) proposed multivariate techniques in tablet manufacturing appropriate for initial drug development. The predictive techniques from an initial testing design of numerous associated reactions were further discussed. A partial least square method was also used to analyse the fractional factorial design along with the linear model. To attain the objective stages of these reactions, the two methods were combined in a simulation by a function and a way of simplex algorithm. The future researcher may think of high-end models instead of adopting the linear models. The values of the predictive variables in the proposed model can be enhanced with the predictive algorithm methods instead of selecting the clinical data directly. Here, one should be cautious that the clinical data and the predictive algorithm should reveal similar values; the error on the predictive algorithm should be in an acceptable range. The

modeller may think of proposing an innovative predictive algorithm to provide creative new generation predictive variables and the respective values.

In 2008, Schneidman-Duhovny et al. proposed a feature method based software program tool called, PharmaGist: a web server for ligand-based pharmacophore detection a structure-centered 3-D platform bounding technique and its application to a microbial protein-protein contact. This has the most significant feature "First Web server to illuminate 3D pharmacophores from a group of medicines like fragments that are recognized to attach to a goal receptor". This became a commercial program later.

Edoh et al. (2011) pointed out the most significant problems of the fitness treatment care in evolving nations and the poor accessibility of drug in medical shops. The information retrieval and utilization using IT is also explained. It is mentioned in their work that, due to numerous causes, typical results are not appropriate. The future researcher may think of appropriateness of IT for getting standard results. Though the work is a case study of Benin, it is applicable to other developing countries also with few restrictions. The future researcher may think of appropriateness, applicability and restriction or controlling parameters of the said work. The prevailing hindrances for smearing standard Ecommerce pattern are also explained. Here, one may find interesting to read the article by Vinayagam et al. (2014,2017) for the growth of ecommerce and the assessing customer behaviour using past data. The structure style is proposed and it describes a realistic assessment that the method has the capability of really enhancing the pharmacological treatment supply and the safety measures characteristics of the scheme are also considered. A researcher may find interesting to read the proposed organisational solutions for some specific security problems.

Bianca, C (2012) proposed Mathematical modelling method of the resistant scheme identification to mammary carcinoma antigen and introduced the enhanced form of the model about the contest amongst the human immunity and "mammary carcinoma" under vaccine. The model describes both the humoral and cell reaction of the resilient system to the tumour antigen and the identification procedure between B cells, T cells and antigen exhibiting cells.

There are numerous illustrations of enhanced analysis of experiments that are information centered on AI. Belič et al. (2010) and Trnka et al. (2013) adopted fuzzy logic for imitating the procedure of decision-making and managed the data well, utilising various visualisation techniques. The researcher who is interested in the use of computers in proposing innovative design on drugs may read the review article by Md. Mofizur Rahman et al. (2012). The benefits of CADD in designing medicines and other different softwares like PBPK, PKUDDS, APIS, python Perl, and JAVA, etc are explained. In this context, the researcher may refer to Md. Mofizur Rahman (2012) for getting knowledge of various available software, programmes and computer aids.

A brainstorming book was written by Gisbert Schneider (2013) on De novo Molecular Design form through which an intermediate level researcher can get innovative ideas and basics about the De no methods. Deepak Singla et al. (2013) explored open resource software and web

services for constructing therapeutic molecules. This has an added advantage than Md. Mofizur Rahman et al. (2012) for future research and researchers comparatively since it involves the freely available software in various ways. This may act as a reservoir for the entry and intermediate level researchers.

Regina Au (2014) discussed the comparison of drug development scenario, the method of how the systems biology is speeding up the modelling of new medicines. It also considers the innovative proposed business marketing model "open" and the foreign direct investment (FDI) impact, rules and regulations. The gap analysis of drug approval and FDI is also explored. Yulia Balykina (2014) stated the current challenges in medication developments that incorporate an increment in expense and length of medication in R&D sector. After crossing these hurdles, only a very few new medicinal drugs arrive at the approval stage. It takes from 10 to 15 years to offer another medication for sale to the public with the expense of more than $1 billion to bring that to the market. Many new-found probable drugs fall short as investigators require trustworthy information about the behaviour of the drug. That prompts the issues for both the pharma sector and health of publics. Mathematical model centred methodologies have additionally been recommended to upsurge the utilisation of re-enactments on the side of clinical drug developments for forecasting results of projected trials.

Business size production of complicated medicine distribution schemes employing the current innovations is tough. Jukka Rantanen and Johannes Khinast (2015) performed a beautiful discussion on an exchange of innovative technological resolutions, basic technical act, that empowered the manufacture of extremely contrived medicines and proposed some key points to overcome the complexities. This analysis incorporates the threat supervision approaches and design of experiments (DoE) procedures. The future researchers may read the final part of Jukka Rantanen and Johannes Khinast (2015) that explains the disputes related to executing these tools as a part of forthcoming fitness treatment schemes in a lucid manner. Further development here can be incorporated techniques with factorial designs. The above-proposed methods can be analysed through programmatic methodologies by utilizing various programming techniques viz, Matlab, SPSS, Python, Stata, and R program, etc, or one can create specific software according to their specific requirements. A complete factorial design at two stages can be given as 2^k with the number of variables k. In a basic situation when two variables are examined at twofold stages, a comparatively small quantity of tests is needed. Though four trials are not sufficient even for the initial inspection, investigational actions can undoubtedly develop. The complete factorial design allows the examination of both principal and contact impacts. However, along with exponential growth in the expense of investigational actions, the quantity of trials can be diminished by way ofapplying fractional factorial technique, including the trial capacity determined as 2^{k-p} with $\frac{1}{p}$ as the magnitude of fraction.

Though AbbVie pharmaceuticals has been silent on the usage of AI in its medicine detection, it is strongly suspected that, it does have a project listed with Atomwise. In addition, in September 2016, AiCure, a companion of AbbVie publicized in what way its AI- centered

patient observing stage enhanced obedience in the experiments. Carrara et al. (2017) reviewed several mathematical models in drug discovery of cancer disease. Pharmacometrics replicas characterise the complete methodologies for mining, considering and assimilating the data attained under-optimally devised experimentation presented in drug discovery.

Chatterjee, S et al. (2017) analysed in their article on the beautiful applicability of mathematical models in the employment of quality by model concept for the development of the drug. Yamuna and Elakkiya (2017) analysed several different mathematical models in the growth, discovery and medication of a variety of therapy and the applicability of vaccination. When employing the Euler–Lagrange Replication (ELR) for a heavy deferment, the aspects of the stream across specific fragments are not determined, and the fluid-fragment communication force has to be devised. This is the foremost disadvantage when suspensions with density ratios nearly 1, at massive particle Reynolds numbers are measured. In these instances, the indolence of the liquid is highly associated with the indolence of the fragments; however comprehensive evidence on the liquid movement is unavailable. Hence, ELR is typically employed to gas-particle structures.

Most of the research works examine the response of generally employed techniques to analyse and assess the resemblance of the dissolution summaries of two medicines. A pleasant assessment can be obtained from a beautiful model. A reasonable experimental model is necessary for dissolution analysis. Before the trial is performed, one has to prepare the research like the appropriateness of the equipment, position of dissolution basket, and so on. Till today, numerous problems are in the construction of dissolution assessment that requires further inspection.

Prasad, G et al. (2017) did an excellent analysis on different software centred methods for drug inventing and improvement: It gave an excellent summary of the accurate appraisal on generally utilised software and its various purposes. A noteworthy difficulty and the challenge to overcome in the pharmaceutical business restricts the volume of crystals in the production of any medication. The quantity and steadiness of crystals decide the characteristics and overall effectiveness of a medicine. Hence, the AI researchers may get to read interesting points and and also find innovative ideas through the article by Prasad G et al. (2017).

Shein et al. (2017), in their book “Sample size calculations in clinical research”, described various methods of estimating the sample size for the particular clinical study with different case studies. This consists of various statistical procedures for the calculation of sample size in different phases of clinical research and its future advancement and evolution. Zhenguo Gao et al. (2017) in their work proposed current developments in crystallization procedure in the direction of the pharmaceutical businesses. It is abridged with current techniques to recognize and create innovative forms of crystals like solvates, co-crystals, polymorphs. This incorporates numerous landmarks like the launch of the first co-crystal drug and the uninterrupted production of Orkambi (Vertex). But the authors found the usage of computation methods missing in this scenario. Hence the future researcher may think of mathematical and statistical purposes in analysing the crystallization process. Creation of modelling and monitoring crystallization techniques may attract several researchers to propose new crystallizer geometries to enhance the

performance of crystallisation. The AI aspirants may think of AI-assisted control mechanisms for the crystallization processes. It is to be noted that the medicine production machines were regularly examined by devices like sensors and that those sensors provide a lot of data, but most of the resultant data went unanalysed. A strong statistical method can be proposed to analyse such resulting data obtained by sensors. It is essential to create scientific models with AI technique to increase comprehension of what the sensors uncover about every part of the medicine's crystallization process. The researchers may think of new algorithms to aid the AI techniques.

A future researcher may refer to the book, advanced systems for improved public healthcare and disease prevention: emerging research and opportunities by Thierry Oscar Edoh (2018). The approaches of international public healthcare delivery, problems in healthcare industries, and various other applications in eradicating the issues are explored in the book in a thought provoking manner.

In August 2018 an editorial commentary by Bill Siwicki wrote to healthcareitnews.com on Takeda's usage of AI to foretell the progression of depression. The objective is to decide the type of patients who will progress by substituting or fluctuating the treatments. The preliminary investigation indicated that repeated use of NN is precise on its estimates. Li Di Yan Li. (2018) analyzed the risk factors of falsification for T-SPOT.TB, an analysis device to recognise both pulmonary and extra pulmonary tuberculosis, and latent tuberculosis. Logistic regression technique is used to analyze the statistical data collected from 349 patients out of which 98 subjects had TB and 251 subjects had non-TB disease and received T- SPOT.TB. However, in this study latent tuberculosis patient was not discussed. Hence, the researcher may incorporate this into their future studies. Next, the subjects in few types of TB type were rare, that could change the outcomes. Next, the variable of distortion was not robust while the properties of distortions differ between each other and the future researcher may think of devising a method for the variable deformation. Next, anti-TB management or curing techniques were not considered in this study. One may think of incorporating this as a variable in their model. Mainly, the inoculation patient has not considered in this study. Also, HIV positive spread is a major cause, but that is not included since HIV distribution is less in China. Whereas, if one wants to adopt this study for a different demographic, a thinking of incorporation of the above-said variable can be possible.

"Lankacidin C" is an antibiotic created by the creator "Streptomycesrochei"which indicates significant antitumor motion. Recently, Ahmed Taha Ayoub et al. (2019) employed ensemble-based docking of several lankacidin C conformers into a group of four distinct conformations of the taxol fastening pocket of tubulin applying GOLD and FRED docking computer software programs accompanied with fragmentile dynamics replication and succeeding binding-energy forecast. Amanifold-trajectory method was employed to computer through the solidity of various possible attaching techniques.

To find the attach energy between two entities, the ensemble average or time average adopted from stochastic processes part is utilized. The required ligand-protein compound in

similarity to the available ligand and protein (tubulin) was explored. The ensemble average is given by:

$$\langle A \rangle_{ensem} = \frac{\iint A(a,b)\, e^{-\frac{E(a,b)}{kT}}\, da\, db}{\iint e^{-\frac{E(a,b)}{kT}}\, da\, db}$$

A,is the property, $\langle A \rangle_{ensem}$ is the ensemble average of A. Here, A is considered as energy. A is a function of a and b where b is the position and a is the momenta. Here, $e^{-\frac{E(a,b)}{kT}}$ is the Boltzmann factor considered here as a weighting element. E is the strength of the microstate. k is the Boltzmann constant. T is the temperature in Kelvin. The integration is performed around the complete time space.

The period average of A with a and b, the functions of time ranges from 0 to ∞ and given by:

$$\langle A \rangle_{time} = \lim_{\tau \to \infty} \frac{1}{\tau} \int_{t=0}^{\tau} A(a(t), b(t))\, dt$$

In ergodic system, $\langle A \rangle_{ensem} = \langle A \rangle_{time}$, hence, $\langle A \rangle_{ensem} = \langle A \rangle_{time} = \frac{1}{M} \sum_{i=1}^{M} A(t_i)$ with M as a representative set of microstates. Now, the system was simulated for a finite period. Following that, a typical set of microstates M is employed to assess the time average of A.

Now, the average energy of the ligand and receptor is given by $\langle \Delta E \rangle_{binding} = \langle E \rangle_{complex} - \langle E \rangle_{receptor} - \langle E \rangle_{ligand}$

First, it is modelled the least-square model of the particles of the tubulin to that of the original shape prior to the replications. The solidity of the protein, as well as that of the ligand in the attachment site, was evaluated by the variation of root mean square values.

In 5 March 2019, Ayn de Jesus, who started her career in journalism and then became a member of content and research team at Emerj, wrote a delightful article to emerj.com under health care section of R & D on an Outline of Advances Artificial Intelligence in the drug manufacturing companies. The article provides the scenario of different firms providing software in forecasting treatment outcomes, medicine proposal and scheming and data pre-processing in the pharmacological industries. GNS Healthcare provides Reverse Engineering & Forward Simulation (REFS), a machine learning (ML) software that computerizes or automates job that formerly took part in cut and try to check the medicines with discrete patients. The company asserts that REFS- produced ML replicas are able to foretell a patient's reply to probable medicine treatments by conjecturing probable associations between numerous aspects that might give an impact on the outcomes. The algorithm then runs replications and has several nested and non-nested "what if" interrogations; till to conclude the best medicine to cure the disease of every patient. In April 2019, a Health AI called Concerto proposed a usage AI and actual world

statistics in oncology. The AI experts stated in their reports that, the future of pharmaceutical companies are in the hands of the researchers, doctorates or a mixture of academicians in deep sciences, bioinformatics and mathematics. Hence, future researchers have to take this seriously and specifically Applied Mathematics, AI, ML researchers, can turn their research studies towards pharma.

The Soma Logic (SL) attained an authorization to smear REFS to SOMA scan-consequent protein datasets. This contract proposes to control REFS procedures to arise sense from SL's protein statistics aimed at usage in discrete and populace fitness administration. In this point, the authors wish to insist the person behind the development of ML procedures and REFS advancements. Bruce Church, Principal Mathematics Officer who spent around 10 years at University of Cornell, mounting universal optimization techniques for computational protein folding, is liable for advanced development of the ML procedures for REFS and foremost the growth of novel goods and tools. The Machine Learning Ledger Orchestration for Drug Discovery (MELLODDY) in June 2019 declared a project that it will train ML technique on datasets from multiple companions while guaranteeing the confidentiality for each companion by means of amalgamated learning.

Drug Discovery advancements in Covid-19

At 2020, in the month of February, BenevolentAI made a cluster of technical expert group. The fullfledged study by means of its medication innovation policy is required. The CEO of BenevolentAI , Baroness Joanna Shields proposed that addressing and as a response to the COVID-19 pandemicity of world health emergency, it is proposed that our AI medication innovation and advancement policy in the direction of recognizing the body's reaction to this new communicable infection." (Mike Butcher April 2020)

CLINICAL-PHASE VACCINE CANDIDATES FOR COVID-19 like aAPC, artificial antigen-presenting cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; LNP, lipid nanoparticle; S protein, SARS-CoV-2 spike protein can be found at ClinicalTrials.gov website; WHO. Tung Thanh Le et al (April 2020), a cluster of investigators at the laboratory of Gladstone Organization, US has detected the list of proteins in SARS-CoV-2 correlate together with the proteins in human being chambers to trigger the infection. Xueting Yao et al (2020) proposed that Hydroxychloroquine was found to be more potent than chloroquine at inhibiting SARS-CoV-2 in vitro. Hydroxychloroquine sulphate 400 mg given twice daily for 1 day, followed by 200 mg twice daily for 4 more days is recommended to treat SARS-CoV-2 infection. Here, it is used many simulation methods, clinical trials and predictions using different models.

World Health Organization has announced a worldwide mega-trial of the four furthermost assuring COVID 19 human illness disease treating and handling methods up to now: (i) remdesivir inhibitor (ii) hydroxychloroquine antimalarials (iii) ritonavir/lopinavir protease inhibitors, both medicines are HIV inhibitors, and (iv) interferon-beta. A cluster of researchers from South Korea and US are utilizing deep - learning technique to explore the possibility for existing anti-viral medicines to be utilized for the treatment of COVID-19. The said cluster

proposed a system named "Molecule Transformer Drug Target Interation (MT-DTI). It is examined the hydrogen bonding, ionic interactions, hydrophobic interactions and other notable and necessary similarities in the available drugs for Covid-19 anti viral drugs. Surprisingly it is found after many sleepless nights of works, atazanavir, the antiviral medicine used for the treatment of HIV shows some increasing simulated results and good signs for Covid-19. Many clinical trials are going on throughout the world. Many mathematical and statistical works are going on in prediction and to evaluate the efficacy of the drugs used. On some other degrees, AI field is keep developing its own direction. It is suggested to have a hybrid method to have the quick return of the possible solutions. Mathematical modelling help the researchers to predict, calculate before moving to the clinical trials and after getting few results in the clinical trials. These results gives the input to AI, and AI can simulate, and test in a wonderful way before coming in to human testing.

Conclusion

Throughout this overview, it is exciting to note the numerous changes and improvements that computer science and mathematical models have dedicated to pharmacology. Tremendous contributions that the methods could give in investigation routing lead to an innovative way of research. This short study figures out the different methods and also gives a glimpse on the role of scientific mathematical models in drug discovery. The difficulties that biotechnology organisations face in growing huge molecule mixes are primarily because of science progressively mind-boggling, and it is not comprehended thoroughly. The goals are progressively troublesome, innovative and unconfirmed, and subsequently become increasingly dangerous. A distribution framework is required to get huge molecules to the ideal part. The FDA commanded that medicines be matched with available existing drugs versus sample. The future of drug discovery and pharmaceutical research and development is in the hands of mathematicians and computer scientists. The vaccination of Covid-19 prevention is essential and it can remerge at any time in future. It is the primary duty of the human community to be prepared for that. This article may give a good insight in a multidimensional way to the researchers and the ideas to fulfil the gaps in the area of Mathematics and Computer science which will be highly useful for future researchers and R&D sector of pharmaceutical industries.

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