Chapter

# Computational Study of Radiopharmaceuticals

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## Abstract

Radiopharmaceuticals contain radionuclides and pharmaceuticals. Research on radiopharmaceuticals has been increasing in recent years by increasing the importance of early diagnosis in diseases. It is generally accepted that investigation and development of new radiopharmaceuticals are time and resource consuming. Computational methods have provided exciting contributions to pharmaceutical research and development. The need for designing new radiopharmaceutical drugs enhances the importance of computational programs. At this point, the structure, chemical, physical and physicochemical properties of molecules should be predicted/evaluated by using computational methods. While these methods obtain useful estimates, they make it easier for researchers and clinicians to make the right choices. Also, by providing accurate and effective results, they contribute to reduce the cost of research and can be used to simulate complex biochemical situations before research helping us to avoid harmful effects of drugs. In this study, authors emphasis about radiopharmaceuticals and the computational tools related to the development of new radiopharmaceuticals.

**Keywords:** computational method, radiopharmaceutical

## 1. Radiopharmaceuticals

Radiopharmaceuticals are radioactive drugs that can be used either for diagnostic or therapeutic purposes in nuclear medicine applications. In nuclear medicine, 95% of radiopharmaceuticals are used in diagnosis and 5% of them in therapeutic usage [1, 2]. The pharmaceutical component directs radioactivity to the target site of the body (disease regions, organs). A radionuclide emits detectable signals from outside the organism for visualization or delivers therapeutic levels of radiation dose to target sites. Radiopharmaceuticals are bound to accumulate in certain organs or tissues according to the physical, chemical and biological properties of the pharmaceutical part [1]. They are not chemically distinguishable from non-radioactive analogues and participate in biochemical events in the organism [2]. Organ functions can be visualized by the radiation emitted by radionuclides in their structure. A pathological change that can lead/leading to abnormal function can be diagnosed at the molecular level without going to the morphological level. So, diseases can be treated quickly after imaging [1].

With the widespread use of radiopharmaceuticals, the need for specialized pharmacists as known radiopharmacists has increased. Radiopharmaceuticals should be prepared by radiopharmacists and administered by clinicians to the patient. The doses of radiopharmaceuticals are defined either millicurie or microcurie. The pharmaceutical form of the radiopharmaceuticals may be solutions, kit, capsules and aerosols. The amount of active substance in the radiopharmaceutical is at a low dose that does not have a pharmacological effect. The shelf life of a radiopharmaceutical depends on half-life of radionuclide. Quality control of radiopharmaceuticals should be done before administration to patients.

A radiopharmaceutical optimal performance should have some characteristics. While the radiopharmaceuticals used for diagnosis emit gamma ray, the radiopharmaceuticals used for treatment emit beta ray. Alpha and beta radiation, which have particle radiation, are not desirable for diagnosis due to high linear energy transfers (LET). Because this energy is completely absorbed in the body, some particles that can escape to the body and cannot reach the crystal in the imaging system [3].

The ideal radionuclide energy for imaging should be around 100–300 kilo electron volts (keV). The quality of image falls when it is above or below these energy values. In radiopharmaceuticals used for treatment, the energy should be higher than above 1 MeV.

Ideally, the effective half-life of a radiopharmaceutical should be greater than about 1.5 times the imaging time. This pro vides a good image between the maximum dose and the minimum dose that can be injected into the patient, so that the counting statistics and image quality are optimal. On the other hand, the effective half-life of radiopharmaceuticals used in treatment is indicated by hours and days.

The localization of radiopharmaceuticals should be high in the desired organs or tissues. Low dose for both, patient and personnel, is necessary of ideal radiopharmaceutical. When the radioactivity ratio in the target/non-target area is low and the radiation dose increases in non-target areas, treatment or diagnosis efficiency of radiopharmaceuticals decreases. They must be non-toxic, sterile and pyrogen-free for patient compliance. Finally, radiopharmaceuticals must maintain their chemical stability during usage, should be cheap and easy to find, easy to prepare and appropriate quality controls [4].

## 2. Classification of radiopharmaceuticals

In general, four types of radiopharmaceuticals are used in medical practice. The first of these is ready to use radiopharmaceuticals. These products have a shelf life. Administration to the patient is performed after the radioactive decay is calculated. Iodine (I-123) capsules, I-131 hippurane, Gallium (Ga-67) citrate, Tallium (Tl-201) chloride, Xsenone (Xe-133) aerosol, Technetium (Tc-99 m) pertechnetate are the examples of this group. The second type of radiopharmaceuticals is radiopharmaceuticals obtained from semi-manufactured products. They are prepared by combining the kits with radionuclides that obtained from the generator. The third type of radiopharmaceuticals is prepared directly before use. Products of this group should be prepared and used immediately. Examples of this group are the particle accelerator products. The fourth type of radiopharmaceuticals is based on preparation of samples taken from the patient. The patient's cell or plasma proteins are radiolabeled with radionuclide and given to the same patient. An example of this group is Tc-99 m radiolabelled WBC. The laboratories have different regulations and rules because of this, radiolabelling efficiency and cell viability should be checked for this group after radiolabeling process [5].

## 3. Computational models for drug development

Every patient and disease are different. The personalized treatment approach can be better for each patient requires. The development of individual mechanistic models of the disease process offers the possibility of attaining truly personalized drug-based therapy and diagnosis. At this point, computational methods have provided exciting contributions to pharmaceutical research and development. The need for individual drug design enhances the importance of computational models. Infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra of the molecule to be predicted, are important and generated by computational approaches in order to characterize molecular structure. The compatibility of the target protein active site with the small molecule (or ligand) is examined, so more effective molecules could be designed by this way [6].

Computer-aided drug design has been established as a valuable tool for the design of new molecules, with many success stories since the 1980s. Pharmaceutical companies have invested substantially in bioinformatics approaches, and it has been predicted that such methodologies will have an important role in pharmacogenomics and personalized medicine. The American Food and Drug Administration (FDA) accepted and expressed the importance of new biomarkers and radiopharmaceuticals for personalizing treatments [7].

Mathematical models of drug design are used to guide drug research and development. Computational models provide the identification of the factors involved in the absorption, distribution, metabolism, elimination and access to the target region of the chemical components. It also exposes the dynamics involved in the interaction of the compounds with the target (receptor, enzyme, etc.,). These models are effective in analyzing the fate of drugs that have undergone biotransformation. It helps us to comment on the undesirable effects or toxic effects of drugs and to help us explain drug-drug interactions. The concept of virtual clinical trials and the integrated use of *in silico*, *in vitro* and *in vivo* models in preclinical development could lead to significant gains in efficiency and order of magnitude increases in the cost effectiveness of drug development and approval [8].

The targeting agent is used as a starting point for the design of computer-assisted drug active substance. Examples of targeting agents include receptors, enzymes, nucleic acids etc. Natural endogenous substances or drugs may be effectors that occupy the effective surface of the targeting agent and affect the target positively or negatively. Computer aided drug molecule design and development studies are examined in two groups:

1. Based on effector (ligand) structure

   - Quantitative structure-activity relationships analysis (QSAR)
   - Pharmacophore analysis

2. Based on target structure

   - Molecular docking
   - Based drug design

It is aimed to interpret the structure of receptors by using the structure of molecules and acting on ligand structure. In method based on the target structure, it is aimed to design molecules that can act on the basis of the known receptor structure [6].

In summary, computational models can be used to simulate complex situations prior to testing in reality, allowing us to make these inevitable mistakes and helping us to successfully avoid their deleterious impacts of new proposed drugs.

## 4. In silico models

It is generally recognized that drug discovery and development are time and resources consuming. There is an ever-growing effort to apply computational power to the combined, chemical and biological space? in order to streamline drug design, development and optimization. Computer-aided or in silico design is being utilized to expedite and facilitate identification, optimize the absorption, distribution, metabolism, excretion and toxicity (ADMET) profiles and avoid safety issues. In silico modeling significantly minimizes the time and resource requirements of synthesis and biological testing. The aim is to enrich the group of molecules with the desired properties (active, drug-like, lead-like) and to eliminate those exhibiting unwanted properties (inactive, reactive, toxic, weak ADMET/pharmacokinetic profile).

The result is a compounds library and, by virtual screening using in silico methods, the number of molecules to be tested forward by experimental means, is considerably reduced. Structure-based library design is prejudiced by structural requirements for specific activity on a particular target and needs prior information of the target structure (e.g., X-ray or nuclear magnetic resonance). The goal is to select existing compound from libraries or to design compounds with three-dimensional complementarity (i.e., shape, size and physicochemical properties) to the target-binding site. New approaches can directly guide the design of virtual combinatorial libraries, which are first screened in silico for targeting complementarity, thus reducing the number of compounds will have to be synthesized and tested *in vitro*.

The "leading" compound has the desired pharmacolological or biological activity and represents the starting point to design other molecules with improuved properties/chemical parameters in terms of efficacy and pharmcokinetic profile, better candidates for future chemical synthesis and trials. When leading molecules have been identified, they have to be optimized in terms of potency, selectivity, pharmacokinetics and toxicology before they can become candidates for drug development. The early analysis in this respect is becoming common practice because the high overall attrition rate in drug discovery is affected the identification of compounds. Traditionally, therapeutics have been small molecules that fall within the Lipinski's rule of five [9]. From this point of view, hydrogen bonds, log P value, penetration into the targeting side can be mentioned. If the hydrogen bond donors are <5, the hydrogen receptors are <10, the relative molecular weight is <500 g/mol and the lipophilicity (log P) is <5, the compound will probably be orally bioavailable. The concepts of virtual library and virtual browsing have become an integral part of pioneering discoveries. In silico approaches significantly contribute to early pharmaceutical research and are especially important in target and lead discovery. The need has been clearly recognized and is expected to improve efficiency of drug design for timely adaptation and application of in silico models in pharmaceutical research [10]. European policy for the evaluation of chemicals (REACH: Registration, Evaluation, and Authorization of Chemicals) has been a strong advocate of alternative in silico methods of predictive evaluation of chemical toxicity in order to minimize animal testing and conserve time and resources [11].

## 5. Factorial Design for Drug Delivery

Design of Experiments (DoE) is defined as a planning strategy that will be carried out to obtain the information from the collected data effectively. It is a structural method used to determine the relationship between different factors (independent variable, input, process parameter, formulation component, etc.,) and their responses (dependent variable, response variable, output, product quality feature, etc.,). Also, this model is a mathematical model that correlates all the relevant factors and the results obtained against these factors. The results can be interpreted, predicted and the design space can be determined by optimization with this mathematical model. Systematic DoE approaches have advantages such as less experimental study, easier problem identification and prevention, any active agent adjuvant interaction and product performance to guarantee an effective formulation, and process optimization for good results in the scale up process.

An ideal drug form design should be depended on the understanding of the physicochemical and mechanical transformations of the materials that will eventually turn into the desired product. However, due to the diversity and complexity of the drug components, it is usually not fully understood. Factorial design with a systematic approach the product and production process can be understood in depth. In this way, a development approach can be provided which takes into account the variability of the inputs and other risks that may arise against product quality.

It is very important to obtain the basic knowledge of the study in order to produce as much information as possible with the right modeling. The statistical analysis is the first stage of experimental work before optimizing the formulation. Simple models are used in statistical screening. For example, linear models with only the main factor effects, or linear models, including binary interactions. In this way, the factors that have the most effect on the outputs are determined with the least number of tests possible. Factors with little or no significant effect can be displayed. In addition, by decreasing the number of factors, optimization design with a smaller number of attempts can be used.

The choice of DoE should be based on the number and type of factors to be investigated. For example, if the goal is only to reduce the number of factors and find a few factors that have the highest effect on the outputs, and if there are too many factors to be investigated, then the statistical elimination by constructing linear models can be selected. The results consist in lowering the number of attempts and evaluate only the main factor effects. The most preferred statistical screening methods in drug formulations are two-level partial full factorial design and Plackett-Burman design [12].

After statistical screening, response surface modeling (RSM) designs are started. The number of factors should be reduced by the statistical elimination design before the RSM design, so that the number of trials is not high and the statistical significance is important/relevant or other synonym and strong prediction models can be established. RSM is an approach where statistical and mathematical techniques are used together for the development and optimization of pharmaceutical processes. Includes modeling techniques used to determine the relationship between dependent variables and the independent variables that affect them.

RSM designs for drug formulations allow us to understand the relationship between factors and response variables, as well as factor interactions (synergistic effect of two or more factors), quadratic effects, and cubic terms. In this way, the optimum value ranges of the factors are provided. Process problems can be solved. Robust processes that are less sensitive to process variability can be developed.

Each additional experiments and sample analysis performed to product development in the pharmaceutical industry means that spending a lot of money, time and labor loss. The selection, implementation and interpretation of the appropriate factorial design that serves to reach the result accurately and rapidly is very important. Selecting the appropriate experimental design ensures that development studies are completed with a small number of trials. In order to optimize the process and formulation, mathematical models are described that best relationship between these critical factors and quality characteristics [13].

## 6. Computational models for radiopharmaceuticals

Computer models in the pharmaceutical industry is used to discover new drugs, to optimize of chemical processes and to design clinical trials. Accurate computational estimation of the responses to the treatments and clinical profiles of administration is of great importance for patients [14–19]. Also, it is very useful to help clinicians decide on the most effective and least toxic treatment available options, and is significant for researchers to selecte for *in vitro* and *in vivo* studies [20–22]. In addition, the computational prediction of drug responses can substantially contribute to preclinical studies, as in silico drug screening model. These tools can help researchers in the selection of candidate compounds in their research, and can be used to improve efficiency in experimental planning and to reduce costs [23–25]. Especially, computational estimation of drug responses in cancer disease involves significant research challenges. It is a biological challenge since cancer is a very heterogeneous and multifactorial disease. Furthermore, increasing the need for data integration, new technical questions arise from multiple sources such as the adjustment and normalization of data from multiple sources [14]. In the Oak Ridge National Laboratory, Snyder [26] the first mathematical model of radiopharmaceuticals was realized. In this design, the fractions of energies and amount of gamma and X-rays emitted from radiopharmaceuticals in the targeting tissue were used by Monte Carlo method [26]. Computational model supports the development of radiolabeled complex synthesis and coordination chemistry of radiopharmaceuticals by providing a better understanding of the physicochemical properties of molecular imaging agents. Combining experimental studies with computational study helps to define structure-activity relationships of radiopharmaceuticals and facilitates the rational design of new generation radiopharmaceuticals with improved properties. Francisco et al. [27] used different computational simulators to investigate the therapeutic potential of various radionuclides. These simulators are:

- Fast Monte Carlo damage formation simulator.
- Fast Monte Carlo excision repair simulator.
- Virtual Cell Radiobiology Simulator [27].

Fast Monte Carlo damage formation simulator can be used to estimate the types of DNA damage and post-irradiation efficiency. This method allows multiple data analyzes with multiple irradiation estimates to be collected as soon as possible [28, 29].

Fast Monte Carlo excision repair simulator can be used to estimate the occurrence, repair of DNA and correct repair results by mutation [27].

Virtual cell radiobiology simulator is a radiobiological model used to describe dose response relationship, damage production process and key repair mechanisms. These models often relate the dose rate to the cell's response to irradiation. Some of the current models include a repair-false-repair model, a fatal potentially fatal model, and two lesion kinetics [28].

In one study, the Monte Carlo method was used to assess the amount of radionuclide in animal models for preclinical testing of radiopharmaceuticals. In another study, this model predicted 3D images simulated with SPECT or PET for patient-specific radionuclide treatments [27, 28].

Computational methods allow quick and easy data collection. However, some models are based on available information and are evaluated according to this information and this imposes some restrictions. The used algorithms report an optimal ionization scenario to ionize the DNA in place of ineffective radionuclide biodistribution process that is obtained by *in vitro* and *in vivo* studies under difficult conditions. Thus, although the validation of the used simulators has been performed in selected irradiation scenarios and specific cellular populations, specifying these methods may be useful as a first step approach to large data sets to assist in the planning of *in vitro* and *in vivo* studies [29–33].

Kurniawan et al. [34] studied on radiopharmaceutical ligands and concrete examples of molecular docking. T3, 4BCPP is an imidazolylporphyrin derivative and has been used as a radioimaging agent for melanoma cancers. They designed new imidazolylporphyrin derivatives with better selectivity and higher affinity than T3, 4BCPP by using AutoDock 4.2. After that they develop a new radiopharmaceutical by using a radionuclide such as Technetium (Tc) for diagnostic and Rhenium (Re) for therapeutic purposes. They concluded that radiolabelled imidazolylporphyrin derivatives could be two potential candidate ligands for a melanoma radiopharmaceutical kit.

Chen et al. [35] assessed the effects of structural modification on the interaction of $^{125}$I-labeled iodo Hoechst ligands and DNA. Also, they designed new analogs with specified distances between the Auger-electron-emitting $^{125}$I atom and the DNA central axis by using computer-assisted molecular modeling software. This software program has been obtained the reactivity of newly designed radiolabelled molecules with their targeted DNA molecules by molecular modeling prior to their chemical synthesis.

El-Motaleb et al. [36] developed an easy method for radio iodination of propranolol with high percent labeling yield for the purpose of lung perfusion imaging. They used molecular modeling and docking studies to ensure the binding of the newly obtained radio iodination of propranolol to beta-2 adrenergic receptor and confirmed that radio iodination did not affect the binding of propranolol to beta-2 receptor by using molecular modeling.

## 7. Conclusion

Computational methodology provides some advantages such as creating time-dependent organ dose rate curves, making easier for researchers and clinicians to take the right choices. Also, these approaches give accurate and effective results and reduce the cost of research being useful to simulate complex situations before research, to avoid harmful/side effects. Furthermore, the radiopharmaceutical dosimetry estimates demonstrate large variation due to the patient's anatomical characteristics and computational model can be useful for obtaining personalized data. We believe that using these methods could enhance the personalization of dosimetry in nuclear medicine administration.

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