MOLECULAR MODELING IN THE RADIATION THERAPY. THE ALGEBRAIC APPROACH

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Стрімкий розвиток хімічної промисловості та науки, нові виклики у сфері охорони здоров'я, висувають підвищені вимоги до розвитку теорії органічної та неорганічної хімії, пошуку та впровадження нових методів моделювання та аналізу, удосконалення технологічних процесів. Одним із основних викликів на перетині хімії, фізики, біології, медицини та генетики – є пошук нових методів та підходів до діагностики та лікування ракових захворювань.

Поглиблене розуміння генетики та молекулярної біології раку призвело до виявлення все більшої кількості потенційних молекулярних мішеней для відкриття та розробки протипухлинних препаратів, променевої терапії. Одне з головних місць при цьому посідає молекулярне моделювання. Не зважаючи на доступність все більшої кількості даних щодо існуючих білків і нуклеїнових кислот та наявність методів та засобів моделювання, розробка та використання найрізноманітніших комбінованих методів та інструментів для моделювання та обчислення великих молекулярних систем залишається відкритим питанням. Одним із можливих рішень є застосування алгебраїчного підходу та відповідних формальних методів, які на сьогодні показали свою ефективність у багатьох інших галузях.

Основною ідеєю дослідження є застосування технології алгебраїчного моделювання та квантово-хімічного апарату для моделювання та верифікації задач органічної хімії, зокрема, моделювання та аналізу задач променевої терапії. У роботі представлено перші кроки дослідження. Приведено приклади формалізації роботи синхротрона та взаємодії протонів з речовиною на прикладі визначення/обчислення фізично-поглинутої дози.

Ключові слова: алгебраїчне моделювання, протонна терапія, молекулярне моделювання, формальні методи, інсерційне моделювання.

The rapid development of the chemical industry and science, and new challenges in the healthcare sector, put forward increased demands for the development of the theory of organic and inorganic chemistry, for the search and implementation of new modeling and analysis methods, and for the improvement of technological processes. One of the main challenges at the intersection of chemistry, physics, biology, medicine, and genetics is the search for new methods and approaches to the diagnosis and treatment of cancer.

A deeper understanding of cancer's genetics and molecular biology has led to the identification of an increasing number of potential molecular targets that can be used for the discovery and development of anticancer drugs, radiation therapy, etc. One of the main places in this is occupied by molecular modeling. Despite the availability of more and more data on existing proteins and nucleic acids and the availability of modeling methods and tools, the development and use of a wide variety of combined methods and tools for modeling and computing large molecular systems remain an open issue. One of the possible solutions for this problem is the application of the algebraic approach and the corresponding formal methods, which have proven effective in many other fields today.

The main idea of the research is the application of algebraic modeling technology and quantum chemical apparatus for modeling and verification of organic chemistry problems, in particular, modeling and analysis of radiation therapy problems. The paper presents the first steps of the research. The example of the formalization of the synchrotron operation principle and the example of the interaction of protons with substance in the example of the determination/calculation of the physically absorbed dose are given in the paper.

Keywords: algebraic modeling, proton therapy, molecular modeling, formal methods, insertion modeling.

Introduction

The presence of several open problems in the fields of organic and inorganic chemistry, physics, and biology suggests the need to find new approaches, tools, and methods for conducting research into the original properties of organic and inorganic substances, in particular, research into the study of physiological, biochemical, physicochemical, molecular and quantum-chemical mechanisms of their interaction.

Molecular modeling, and in particular computer molecular modeling, is the basis of many experimental, biochemical, biomedical, and biophysical studies. Repeated confirmation of this is the receipt of Nobel prizes in chemistry, physics, and medicine for research at the interface of biochemistry and molecular biology, as those that solve the main chemical problems of humanity. Thus, the discovery of powerful analytical methods for the study of biological macromolecules (2002 award) revolutionized the creation of new pharmaceuticals, including the possibility of early cancer diagnosis and food control [1]. The Thomas Lindahl, Paul Modric and Aziz Sankar work (award 2015) has provided fundamental knowledge about how living cell functions. These results are also being used to develop new cancer treatments. The tool of molecular design - organocatalysis (2021) developed by Benjamin List and David McMillan has a significant impact on the development of pharmaceutical research [2].

The most well-known and used molecular modeling methods include the docking method, the molecular dynamics (MD) method, and the Monte Carlo method.

Many scientific works have been devoted to the issue of the application of molecular modeling, and molecular docking. Most of them are concentrated in the field of medicine and pharmacology [3-6].

The article [7] discusses the application of molecular modeling, molecular docking, and virtual molecular high-throughput targeted drug screening for the discovery of anticancer drugs. The authors note the importance and effectiveness of computer molecular modeling and chemo-bioinformatics.

The role of biomolecular modeling in determining drug binding sites on the target macromolecule and elucidating the mechanisms of drug action, and virtual screening methods (for example, docking, pharmacophore modeling, and QSAR) are discussed in the paper [8]. The development of machine learning methods and their application in the aforementioned computational methods also was considered by the authors. The application of machine learning methods to the study of medical chemistry problems was considered in [9].

The latest achievements in "high-performance" docking methods and examples of their successful use are considered in [10]. In [11] attention is paid to the study of protein-protein interaction, and available algorithms and software are considered. The authors point out the possibility and simplicity of using protein-protein docking, but at the same time, they note that the method does not take into account all aspects of protein dynamics. The article [12] describes the use of molecular dynamics and ensemble docking methods to study the mechanism of selectivity of anticancer drugs to target proteins with similar structures.

Active research and the use of molecular modeling for physical, biological, and chemical processes in the field of radiation therapy deserve special attention. In the world, active research is being conducted on the development of collective acceleration methods, in particular, on the creation of laser proton accelerators. Considerable research and development efforts have been directed toward the development of small single-chamber proton devices, devices that can deflect a proton beam by a given small angle. On the other hand, significant efforts are being made to improve the characteristics of the proton beam and systems for delivering the dose to the patient. Thus, in [13], the authors try to evaluate the relative biological effectiveness of therapeutic proton beams using a modeling approach (linear-quadratic model), in order to increase their safety and effectiveness. Guided by the obtained results, the authors note the need to calculate the correct values of relative biological efficiency. A simple model of the relative biological efficiency of protons (RBE) is proposed in [14]. In articles [15-17] the use of the Monte Carlo method to build models is described.

Application of modeling methods for both continuous and discrete models takes place using various approaches: statistical, probabilistic, simulation, and visual. Formal mathematical specifications for describing knowledge about the behavior of atoms, molecules, and ions are used in a lot of software systems, there are language standards for formalized chemical and biological objects, for example, the SBML model format for exchanging and storing biological models, which has wide system support. Such systems as CellDesigner, JDesigner, PathwayLab, PathwayAnalyser, and BioChem are used for visualization of kinetic modeling of biological systems. Such tools as Cobra and CellNetAnalyser are compatible with such mathematical systems as MathLab, Gepasi, Copasi, GENESIS/Kinetiki systems, and Jarnac are software for modeling biochemical processes. There are a number of software systems used for protein analysis and modeling: CAVER, SABER, POCKETOPTIMIZER, Protein WISDOM, EVODESIGN.

Well-known modeling tools such as AutoDock, ChemModLab, FlexAID, Peppy, Online CHEmical Modeling Environment (OCHEM), Open3DGrid and Open3DQSAR, QSAR-tools, Toxtree, CP2K, HORTON, DataWarrior, and many others are considered in [18-23].

Conducting relevant research is faced with the problem of modeling a large amount of complex information and requires enormous computing resources. There are a number of problems that arise in modeling, such as exponential explosion, the intractability of theories, etc. So, for example, despite the high computational potential and the possibility of working with large data sets, and the fairly high accuracy of Docking prediction, the method is limited by borders of biological experiments and requires a responsible selection of research methods and tools. In particular, it is possible to obtain incorrect results due to errors in the structures of the molecules with which the software works, which can be critical for conducting experiments. The Monte Carlo method, like the method of molecular mechanics, allows to find the optimal geometric structure of the molecule, but it is the least accurate of the considered methods because it is based on the generation of random numbers. The molecular dynamics method has high speed and the ability to find local energy minima, but it requires the selection of empirical parameters, and visualization, and has low accuracy. The search for effective solutions and approaches remains one of the main challenges for natural sciences communities that use molecular modeling.

In addition to developments and combinations of well-known computational tools, are require new algorithms for using the quantum-chemical apparatus to analyze, first of all, intermolecular interactions, which are the base of the design/modeling of bioactive molecules and materials..

One of such methods is algebraic modeling, which allows, unlike simulation modeling and probabilistic methods, to consider multiple scenarios of system behavior rather than one specific scenario.

The use of algebraic techniques makes it possible to conduct research at different levels of abstraction and to operate with infinite entities. The use of the theory of insertion modeling (algebraic modeling of the interaction of agents and environments), which was created by prominent academician O.A. Letichevsky (1935-2019), allowed to solve a number of problems in the development of reliable systems in the electronics industry, and was used in various industries in our country and the United States, which speaks of the possibility and effectiveness of its application in the field of organic chemistry, and in particular in the field of molecular modeling.

Solving the problems of radiation therapy, and in particular proton therapy, requires both modeling of the work of particle accelerators (protons, ions), and modeling of the processes of interaction of particles with substance.

The work considers the use of the theory of agents and environments based on the algebra of behaviors, which became the basis of formal methods used in modeling quantum interactions in the environment of atoms and molecules [24-25]. Based on the methodology developed by the authors for applying formal algebraic methods to the analysis of the interaction of elementary particles, attempts have been made to formalize the work of particle accelerators (Chapter 3) and the physics of the interaction of protons with substance (Chapter 4). Section two provides a brief description of the approach used by the authors.

Our contribution

Algebraic approach. In this paper, we propose an algebraic approach to molecular modeling, which is implemented within the insertion modeling system IMS [26, 27], that was developed on the basis of the algebraic APS programming system [27]. The first steps of applying this approach to molecular modeling on the example of formalizing the process of formation of atomic bonds (by the valence-bond method) were presented in [24,25].

Insertion modeling focuses on building models and studying the interaction of agents and environments in complex multi-agent systems [27]. The Basic Protocol Specification Language (BPSL) is used to represent the requirements specifications [29-32]. The central concept of BPSL is the concept of the basic protocol, which is a sequence diagram with pre- and post-conditions, logical formulas, which are interpreted by the description of the environment. It gives us the possibility to create concrete and symbolic models at different levels of abstraction. For mathematical refinements, we use the transition system for the agent, which is the most abstract mathematical concept, a modeling system that evolves over time. As part of the method of insertion modeling, we use the specifications of the algebra of behavior for formalization [27].

Behavior algebra is a two-sorted universal algebra that consists of two sorts - the set of behaviors (main sort) and the set of actions and has: two operations (prefixing a.u (where a is an action and u is a behavior) and nondeterministic choice of behaviors u + v); three terminal constants (successful termination Δ, deadlock 0, and divergent behavior $\perp$); an approximation relation $\sqsubseteq$, that is a partial order on the set of behaviors with the minimal element $\perp$. The behavior algebra is also enriched by two operations: parallel ($\|$) and sequential (;) compositions of behaviors [27].

A set of first-order logic formulas over polynomial arithmetic is used as a basic logic language.

Modeling system. We use the Model Creator tool for modeling and model verification.

Model Creator is a system that uses symbolic modeling techniques, including algebraic and deductive-formal methods for solving complex problems.

Key features of the platform are testing technology; model-based development; supporting the development process of a critical system or quality of service (QoS) system; verification and validation; cybersecurity.

The Model Creator includes a number of systems and libraries for implementing algebraic formal methods and integrating with other software systems.
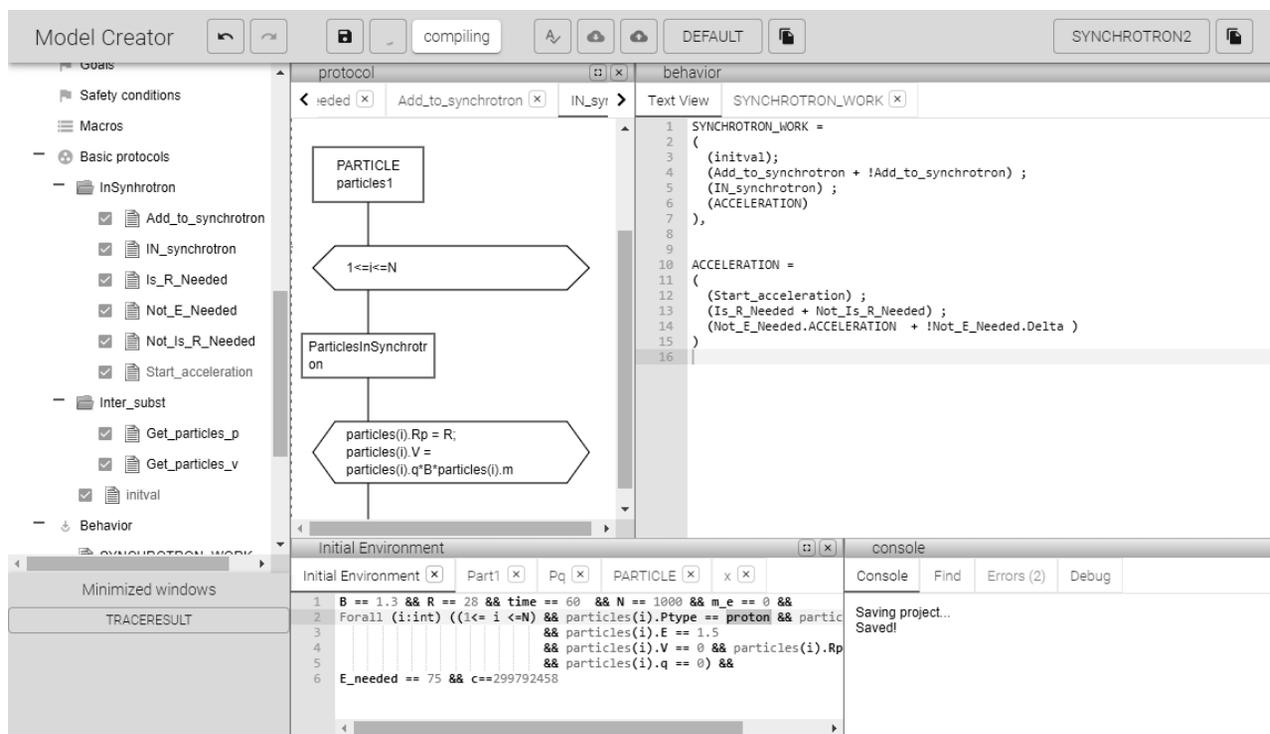

Fig.1 Model Creator. Model of the synchrotron operation

A detailed overview of the functional features and results of using the modeling system is presented in [25].

An example of the accelerator's work formalization of accelerators

For the first stage of the experiment, the simulation of the operation of the synchrotron was chosen. We choose synchrotron since it has the smallest loss of protons, in contrast to the cyclotron and the synchrocyclotron, and therefore has a much smaller effect on increasing the radiation background.

A proton synchrotron is a cyclic resonant proton accelerator with a constant orbital radius and a magnetic field that increases with time according to the decreasing frequency of the accelerating electric field ($R = const, B(t) \uparrow, \omega(t) \uparrow$

). At the same time, the values of the magnetic field and the frequency of the accelerating electric field change in strict accordance with each other, while ensuring the constancy of the radius. In modern accelerators of a large radius, the beam itself affects the change in frequency of the accelerating electric field (with the help of special signal electrodes - beam position sensors).

Accordingly, the task of this stage is to model the maintenance of the growth of particle energy and constancy of the orbit radius by the corresponding growth of the magnetic field and the frequency of the accelerating fields, as well as the achievement by the particles of the energy index necessary for irradiation.

The synchrotron was defined as the initial environment into which the PARTICLE agents (protons or ions) are immersed. A new type particle_type {ion, proton} was created to define the particle type.

The main attributes of the environment are the induction of the magnetic field (B), the frequency of the accelerating field (accelerating_field_frequency), the operating time of the accelerator (time), the radius (R), the indicator of the energy that the particle must acquire before exiting the synchrotron (E_needed).

The following attributes are defined for the agent of type PARTICLE - particle type (Ptype), mass (m), charge (q), momentum (p), velocity (V), the radius of motion (Rp), energy (E), particle frequency (w), the number of protons (p_num) and electrons (e_num) (must be taken into account if we simulate ion's acceleration). Accordingly, the agent type PARTICLE will be formalized as follows.

$\text{PARTICLE}:\text{obj}(\ \text{Ptype}:\text{particle\_type},\ \text{m}:\text{real},\ \text{q}:\text{real},\ \text{p}:\text{real},\ \text{V}:\text{real},\ \text{E}:\text{real},\ \text{Rp}:\text{real},\ \text{w}:\text{real},\ \text{i}:\text{int},$
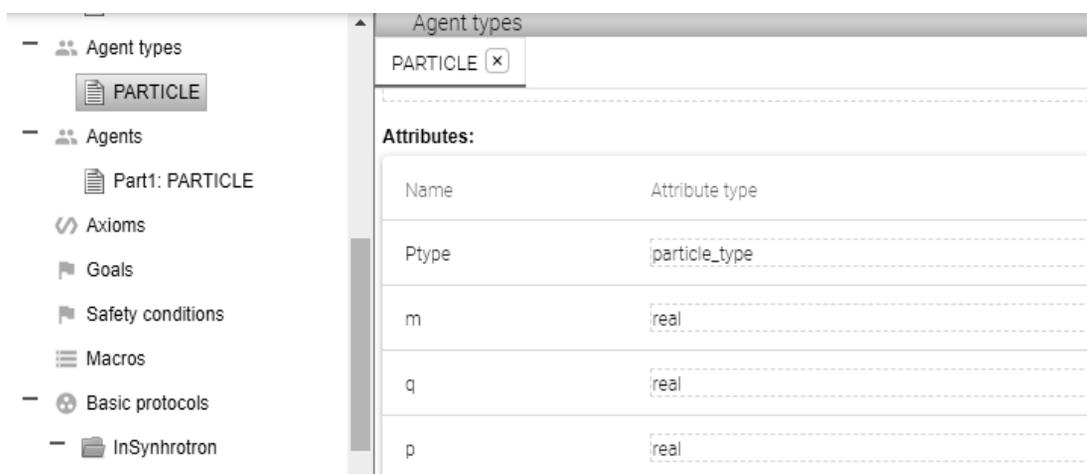$\text{e\_num}:\text{int},\text{p\_num}:\text{int})$

Fig.2. Agent type "Particle"

The induction of the magnetic field, the frequency of the accelerating field, and time can be specified not by specific values, but by possible intervals of values.

To simulate the operation of the accelerator at a higher level, we have the following behavioral equation – Fig.3:


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behavior
Text View    SYNCHROTRON_WORK [x]

 1   TERAPY = (
 2   (SYNCHROTRON_WORK);
 3   Delta
 4   ),
 5
 6   SYNCHROTRON_WORK = (
 7   (IN_synchrotron(proton)) ;
 8   (IN_synchrotron(ion)) ;
 9   (ACCELERATION)
10   ),
11
12   ACCELERATION = (
13   (Start_acceleration(proton)) ;
14   (Is_R_Needed(proton) + Not_Is_R_Needed(proton)) ;
15   ((Not_E_Needed(proton);ACCELERATION)  + !Not_E_Needed(proton) ) ;
16   (Start_acceleration(ion)) ;
17   (Is_R_Needed(ion) + Not_Is_R_Needed(ion)) ;
18   ((Not_E_Needed(ion);ACCELERATION)  + !Not_E_Needed(ion))
19   )
20
```

Fig.3. Behavioral Equation. Operation of the Synchrotron

The specified behavior consists of five agent actions (IN_synchrotron, Start_acceleration, Is_R_Needed, Not_Is_R_Needed, Not_E_Needed) and corresponding actions marked with a negation, i.e. the precondition is not fulfilled. All actions are parametriced. So, we can simulate model for the different type of particles. For this example we work with protons and ions.

Let's consider Operation of the Synchrotron and examples of the formalization of each actions in the Model Creator tool.

Pre-accelerated in the injector (auxiliary accelerator) to a certain energy, the particles enter through the inflector channel into a vacuum toroidal chamber located in a ring-shaped magnet covering the entire orbit. The injection occurs at some small value of the magnetic field. The particles start rotating in the synchrotron chamber along an orbit of constant radius (**IN_synchrotron** action) (Fig.4). In one or more places of the ring, there are accelerating spaces, passing through which particles are accelerated in an alternating electric field. As the energy of the particles increases, their speed and frequency of rotation increase (action **Start_Acceleration**) (Fig.5), so the constancy of the radius of the orbit is maintained by the corresponding increase in the magnetic field and the frequency of the accelerating fields (actions **Is_R_Needed** (Fig.6) and **Not_Is_R_Needed**) (Fig.7).

If suddenly a proton beam flies faster than the required speed, then it flies into the acceleration gap at a negative value of the voltage, due to which it slows down. If the speed of movement is lower, then the effect will be the opposite: the particle is accelerated and catches up with the main flow of protons. As a result, a dense and compact beam of particles moves at the same speed. Accordingly, reaching the required energy value can be controlled by changing the magnetic field induction value (**NotENeeded** action) (Fig.8).
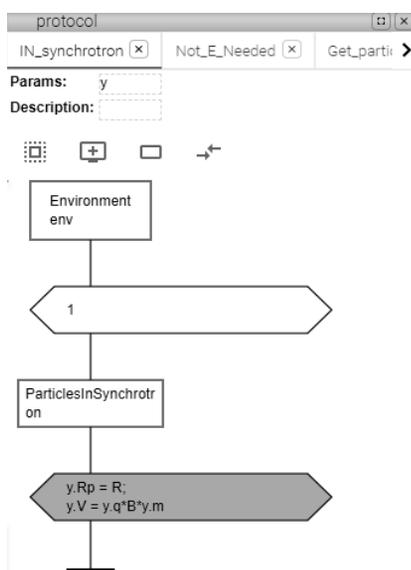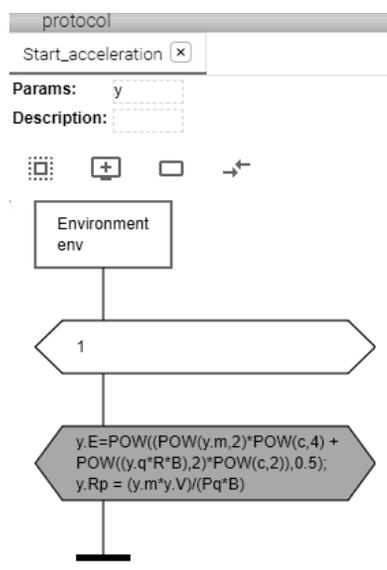
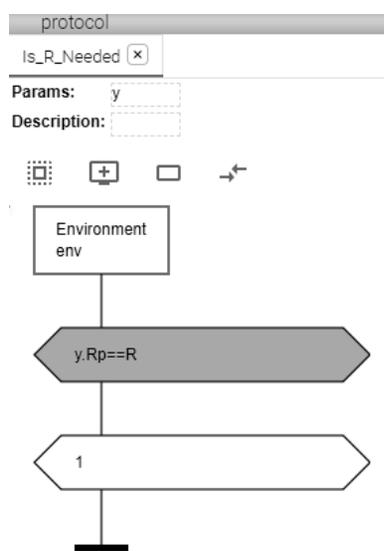Fig.4. IN_synchrotron action

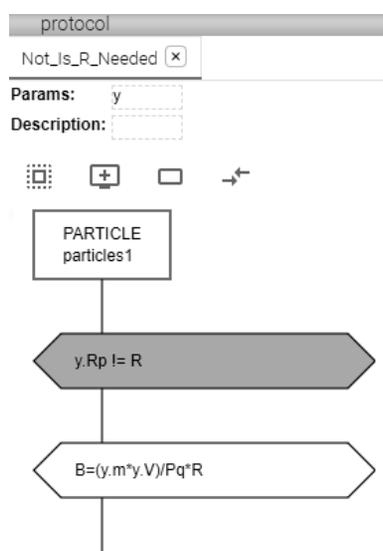Fig.5. Start_Acceleration action
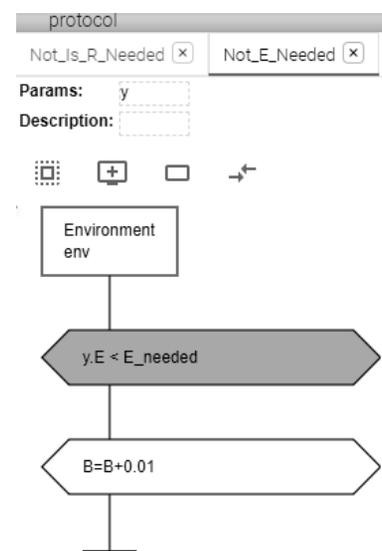
Fig.6. Is_R_Needed action

Fig.7. Not_Is_R_Needed action

Fig.8. Not_Needed action

Thus, we get a formal model of the particle accelerator, which allows us to model the use of synchrotrons to accelerate protons, electrons, and ions.

Formalization of the process of interaction of a beam of protons with substance

The study and formalization of the physics of the interaction of a proton beam with a substance is the second stage of research/modeling.

At this stage, we start working with agents of SUBSTANCE type . A substance has the following attributes - the molecules/atoms of which it is composed (molecules), density (ro), mass (m), volume (V), concentration (concentration), and amount of substance (nu). The structure of the SUBSTANCE agent, in particular, the presentation of its electronic configuration, and examples of solving some chemical problems were determined in the framework of previous studies [24,25].

To determine the value of the physically absorbed dose, to the main attributes of the agent we add the radius (r) (to determine the beam passage area), density (ro), mass braking capacity (S), the length of the segment (l) that the protons must pass. Accordingly, the agent type SUBSTANCE will be formalized as follows.

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SUBSTANCE: obj(
nu: real.
concentration: real,
molecules: MOLECULE,
m: real,
V: real,
ro: real,
W: real,
r: real,
ro: real,
S: real,
l: real)
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In this case, the agent of the SUBSTANCE type acts as a medium for the agent type PARTICLE. The main task of the stage is to determine the characteristics of the proton beam and dose delivery systems to the patient.

As an example, let's consider the formalization of the physically absorbed dose calculation.

Proton is an elementary particle without internal degrees of freedom, with rest energy $mc^2 = 938.27$ MeV and charge $q_p = +1.602\ 10–19$ C.

To calculate ionization losses and scattering of protons on atoms and nuclei, it is necessary to know the proton velocity v or momentum p, which can be calculated by knowing its kinetic energy E (Fig.9 and Fig.10).

The process of loss of energy by a particle as a result of ionization of the atoms of the medium is called ionization deceleration. Ionization deceleration is characterized by specific ionization losses. Often, the term braking capacity is used to designate ionization losses.

The process of deceleration of particles in different types of matter can be unified if the braking capacity of a substance is normalized to its density. This physical quantity is called the mass braking capacity of matter.

Let's consider how the physical absorbed dose is related to particle flux and braking capacity. Let us assume that the number of protons dN passes through an infinitely small cylinder with a cross-sectional area πdr2 and a height dx. The rate of energy loss or braking capacity depends on the energy itself and on the substance in which the proton is decelerated. Let's calculate the value of the physically absorbed dose (Fig 11).
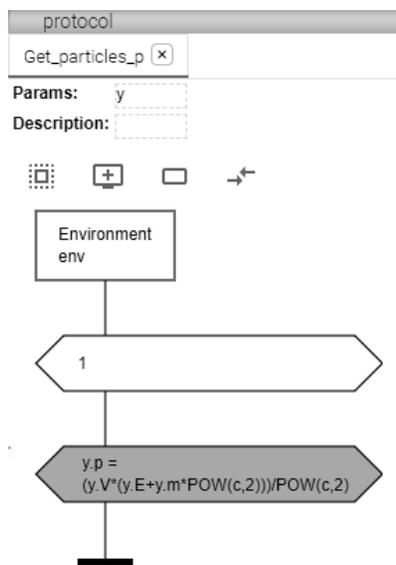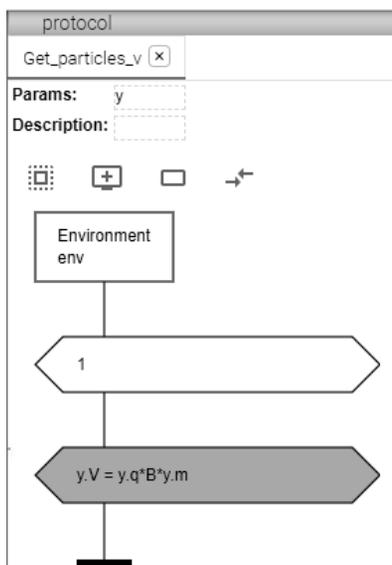

Fig.9. Get_particles_p action
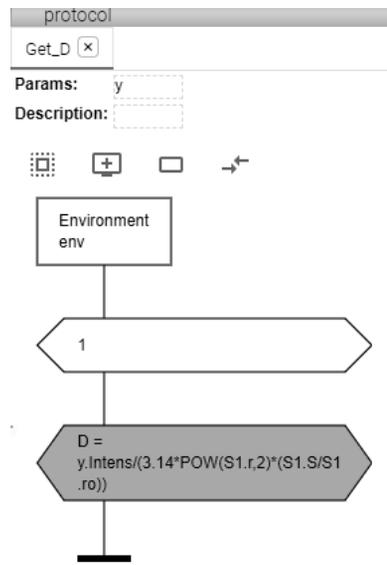
Fig.10. Get_particles_v action

Fig.11. Get_D action

Sequences of possible interactions of protons with substance (inelastic interaction with the electrons of atoms (braking, braking capacity), elastic interaction with the nuclei of atoms (scattering), nuclear reactions) are considered in the form of behavioral equations taking into account certain laws and formulas.

For each interaction, we determine the transition using a hybrid scheme, i.e. the addition of a differential equation that determines the change in the number of particles carried through a unit surface, depending on time; change in the energy of radiation absorbed by the substance per unit mass; differential angular distribution of particles after passing a layer of matter with a certain thickness, etc.

So, for example, the absorbed dose D is defined as the radiation energy dE, absorbed by the substance, which is calculated per unit mass dm of the irradiated substance: $D \equiv \frac{dE}{dm} = -\frac{1}{\rho S}\frac{dE}{dx}$, where ρ and S are the density of the substance and the area, on which the energy E falls.

Solving or using an approximation of the solutions of these equations will determine the step of algebraic modeling. Given that the state of the agents and the environment will be defined as symbolic, we will determine the presence of the script, provided it exists, in symbolic form. Using algebraic methods, we can further determine an example of a scenario of achievability of the desired property (for example, the required characteristics of the proton beam, etc.) with specific attributes of the environment.

Conclusions

One of the main challenges facing scientists in the fields of medicine, chemistry, and physics today is the search for effective methods and tools for research and implementation of radiation therapy. In particular, there are the modeling and research of the properties of proton/ion beams and their interaction with a substance, verification of calculations in radiation planning systems, development of collective acceleration methods, etc. Unfortunately, the currently proposed methods do not allow to get high accuracy in determining the required dose distributions.

The study and testing of new approaches, the demonstration of improved dose distribution, and the possibility of achieving more favorable treatment outcomes are in most cases investigated by conducting real clinical experiments. It causes a lot of controversy among scientists, representatives of the medical field, etc. In turn, the lack of research tools and methods that would fully or to a greater extent cover open questions put many important research and discoveries on hold. Accordingly, the development and use of a wide variety of combined methods and tools for modeling and computing large molecular systems remain an open question.

The development of algebraic systems (machines for solving and automatic theorems proving) marked the beginning of new research with the use of symbolic modeling. This made it possible to derive the necessary knowledge from a variety of formalized laws.

The algebraic approach presented in the work will, in our opinion, allow solving most of the open questions.

At this stage of the research, the work of particle accelerators (cyclotron, synchrotron) was considered and formalized, and the physics of the interaction of a proton beam with the substance was formalized at a certain level. Currently, a series of experimental studies on modeling the use of different types of particles and their interaction with "simple" substances (for example, water) has been started to debug the model.

The next stage is the modeling of the interaction of beams of accelerated particles (protons, ions) with amino acids/proteins/cells, and, in particular, modeling of possible interactions of protons with the substance at the level of their electronic interaction.

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