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Application of *f*RMSDchiral for the mathematical description of mutual position of stereoisomers

Abstract The ability of biological systems to recognize and distinguish between compounds is crucial for living systems. A detailed study of this mechanism seems to be an important supplement to the analysis of possible interactions between compounds and the environment. This process could be characterized by a variety of descriptions of compounds' structural and physico-chemical properties. The usual measure of variation in the positions of molecules in three dimensional space is the Root Mean Square Deviation (RMSD). Here, the traditional concept of RMSD was readjusted to fragment-level RMSD (*f*RMSD). This assumes a different way of selecting atoms in molecules. The main aim is to appropriately group atoms into sets with respect to their chemical properties. In the case of enantiomers, atoms are selected according to the Cahn-Ingold-Prelog priority rule. The *f*RMSDchiral algorithm is applied to characterize the differences in modes of binding for some cases arising during our studies of molecular models of complexes formed between stereoisomers and their protein targets.

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Key words and phrases: fragment-level RMSD, chiral recognition, bioinformatics, molecular modeling.

1. Introduction A major ability of biological systems, such as proteins, is to recognize specific compounds called ligands. Ligands could be classified into a variety of groups depending on their structural and physico-chemical properties. Taking into account their structural properties, stereoisomers are one of the most interesting types of ligand. Their characteristic property is that they share the same molecular formula, but the bond connections or bond order differ between representative compounds. Enantiomers are a specific group of stereroisomers which belong to the group of optical isomers. Enantiomers are pairs of stereoisomers that are related to each other via reflection. As underlined by Lammerhofer [1] and Davankov [12], they are mirror images of each other, which makes them non-superimposable. Each enantiomer contains one or more stereogenic centers. The most common stereocenters are chiral centers; such as a carbon atom that binds to four different

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groups of substituents or atoms in an asymmetric formation. The configuration (order) of the atoms bound to the stereogenic center defines their chemical configuration in space. A method for unambiguously assigning the handedness of molecules was developed by three chemists: R.S. Cahn, C. Ingold, and V. Prelog and, as such, this procedure is often called the Cahn-Ingold-Prelog rule as described in [2]. This rule distinguishes between right (*R*, lat. *Rectus*) and left (*S*, lat. *Sinister*) enantiomers. As in the situation illustrated in Figure 1, where the (*R*)- (blue) and (*S*)- (yellow) enantiomers of serine (an amino acid) are presented, each enantiomer contains one stereogenic center marked on the picture by a circle. To facilitate comparison, in both cases all the fragments of the enantiomers were separated into four groups (a, b, c, d) determined by their chemical ingredients. The a, b, c, d fragments of (*R*)-serine (blue) correspond to the a', b', c', d' fragments of (*S*)-serine (yellow). It may be observed that one cannot rotate the position of one enantiomer onto the position of the other one. The positions of fragments b, c of (*R*)-serine cannot match the positions of fragments b', c' (*S*)-serine and thus these compounds cannot be superimposed onto each other.

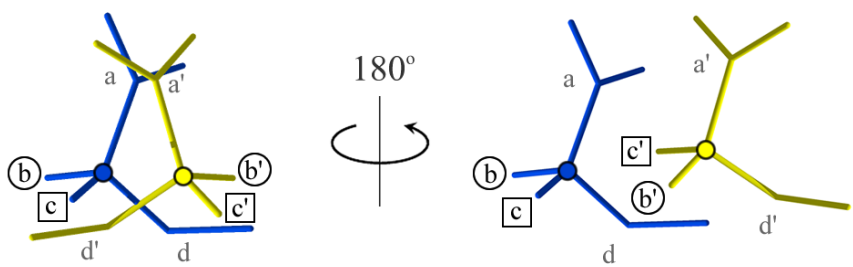

Figure 1: Illustrations of (*R*)- and (*S*)- serine (blue and yellow, respectively). The stereogenic centers are marked by circles. a, b, c, d, a', b', c', d' denote fragments of molecules (groups of atoms). More details in the text.

Usually, only one enantiomer is biologically active. Thus, the ability of chiral recognition and to distinguish between enantiomers is crucial for living systems. Based on Mayer's study [3], the NR3 subtype of the NMDA receptor needs to bind to glycine and (*R*)-serine to become activated. Thus, it might be expected that if one form of an enantiomer (in this case (*R*)-serine) is preferred by the receptor, the other one ((*S*)-serine) probably cannot bind or binds much more weakly. Detailed studies of these and other chiral recognition mechanisms are particularly useful in as distant scientific fields as enantioseparation, crystallography, biochemistry, pharmacology and (asymmetric) synthesis. The difference between the three dimensional coordinates describing the position (shape) of one enantiomer with respect to another enantiomer seems to be an important supplement to any analysis of their interactions in biological systems, as applied in articles by Lammerhofer [1], Sun et al. [4], Zhou et al. [5], Urniaz and Jozwiak [6]. Usually, in

order to quantify such a difference in three dimensional space, the root mean square deviation (RMSD) is applied. It describes the variation in the distance between corresponding atoms belonging to the compared compounds. The RMSD is defined by equation 1.

$$RMSD = \sqrt{\frac{\sum_{i=1}^{N} \delta_i^2}{N}} \quad (1),$$

where δ is the vector describing the distance between N pairs of equivalent atoms. The RMSD is widely used in many fields of science and seems to be a universal descriptor. However, it was reported by Rangwala et al. [7], [8], Coutsias et al. [9] and Eidhammer et al. [10] that smaller RMSD values do not always correspond to the most accurate superposition of compounds in space. To overcome this limitation, adaptations of traditional RMSD calculations have been proposed, such as the local RMSD proposed by Rangwala et al. [8], the application of quaternions by Coutsias et al. [9] or sequence guided structure analysis by Eidhammer et al. [10]. Here, Urniaz et al. [11] propose to adapt the traditional concept of RMSD to define fragment-level RMSD (*f*RMSD). This assumes a different way of selecting atoms within molecules. The main aim is to appropriately group atoms into sets according to their chemical properties. In the case of enantiomers, for a molecule containing one chiral center, atoms are selected according to the Cahn-Ingold-Prelog priority rules [12] (CIP; assignment of priorities based on the atomic mass of the first atoms in a chemical group). This separates the fragments of a molecule into three independent groups of atoms as follows: the atom forming the center of chirality (*f*RMSDchiral_0), two fragments liganding the chiral center with one of higher CIP priority (*f*RMSDchiral_1), two fragments liganding the chiral center with one of lower CIP priority (*f*RMSDchiral_2). An example based on (*R*)- and (*S*)-serine (according to CIP convention) is illustrated in Figure 2.

If a chiral molecule contains two or more centers of chirality, CIP priority rules can no longer be applied and separate calculations are performed for subsets of atoms as follows: all atoms forming centers of chirality (*f*RMSDchiral_0), atoms forming part of the backbone of the molecule between the chiral centers (*f*RMSDchiral_1), atoms forming all the other fragments liganding with the chiral centers (*f*RMSDchiral_2). Although, a brief introduction to the concept of fRMSDchirality is given, the author strongly recommends readers to familiarize themselves with the previous study by Urniaz et al. [11]. Further applications of the concept of fRMSDchirality to the field of molecular modeling are presented there.

2. Case study Molecular modeling techniques, such as protein-ligand docking or molecular dynamics, are widely used in computational chemistry.

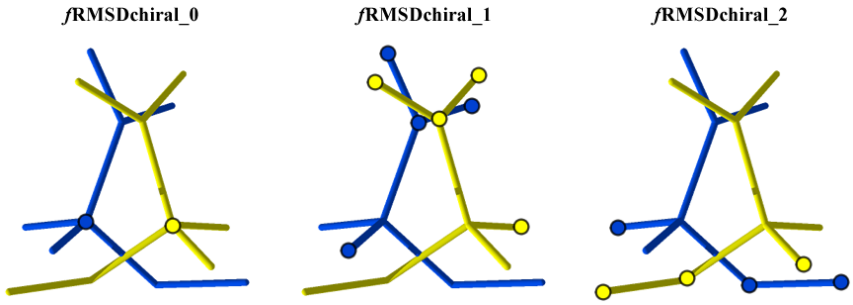

Figure 2: Illustrations of (*R*)- and (*S*)- serine (blue and yellow, respectively) alignment obtained by docking, together with selection of appropriate atoms (indicated by circles) according to the *f*RMSDchiral rule. More details in the text.

To evaluate the results of such approaches, a number of descriptors exist, although they are mostly employed to describe the strength of protein-ligand interactions and do not provide any information about the orientation of ligands in space. Due to this, the fRMSDchiral algorithm is applied to characterize the differences between modes of binding for some cases that arose during our studies of molecular models of complexes formed between stereoisomers and their protein targets. Due to the absence of hydrogen atoms in the format of the Protein Data Bank, all of examples ignored hydrogen atoms which were not connected directly to the chiral centers. All of the calculations were carried out in the GROW_4 molecular modeling environment, which is available free of charge at www.grow4.eu

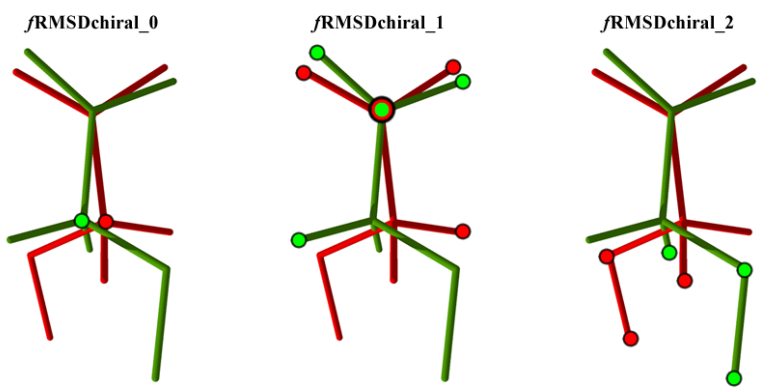

Figure 3: Illustrations of the most favorable (green) and the most unfavorable (red) conformations of (*S*)- serine after docking. More details in the text.

3. Ligand recognition by NR3 subtype glutamate receptors Glutamate receptor ion channels (iGluRs) mediate transmission at excitatory synapses in the brain. They are subdivided into seven families based on their ligand binding profile and similarity between the nucleic acid sequences. One

of these families is the NR3 subtype of NMDA receptor. It binds glycine and (*R*)- serine (Mayer et al. [3]). The (*R*)-serine enantiomer is naturally recognized by the NMDA NR3 receptor. Thus, it might be expected that the (*S*)- enantiomer probably either cannot bind to the receptor or binds much more weakly. Using the crystal structure of the NR3 ligand binding core complex with (*R*)-serine (PDB ID: 2RCB), the authors applied flexible molecular docking (performed in Molegro 6.0; parameters: x: 51.55; y: -10.59; z: 8.47; radius 10, MolDock docking algorithm, 100 runs of 1500 iterations) of the oppositely orientated (*S*)-serine enantiomer with the crystal structure of the NR3 ligand binding core. This enables us to apply the concept of *f*RMSDchirality in describing ligand recognition by the NR3 subtype glutamate receptor using an energy scoring function. The most favorable (lowest energy scoring function) and the most unfavorable (highest energy scoring function) conformations after docking are illustrated in Figure 3. To facilitate illustration, the atoms included in the *f*RMSDchiral calculations which are in the most favorable and the least favorable conformations are marked by green and red circles, respectively.

Table 1: Selected results for (*S*)- and (*R*)-serine docking into the crystal structure of the NR3 ligand binding core.

Molecule	Ligand	MolDock Score	RMSD	fRMSDchiral		
				0	1	2
Ref.	(*R*)-serine	-72.2763	0	0	0	0
3	(*S*)-serine	-59.7198	7.3210	6.6751	6.7422	7.6712
21	(*S*)-serine	-41.3909	7.3957	6.9468	6.7925	8.6648
		Difference:	0.0747	0.2717	0.0503	0.9936

Selected docking results for (*R*)- and (*S*)-serine, together with RMSD and *f*RMSDchiral measures are given in table 1. Additional results can be found in the supplementary materials, Table S1. As can be observed, molecule 3 and 21 are recognized to be the most favorable (possess the lowest value of the MolDock score) and the most unfavorable conformations (the highest value of the MolDock score), respectively.

(*R*)-serine is naturally the preferred enantiomer of the NR3 receptor. Due to this, simulations of docking with the oppositely orientated (*S*)- enantiomer indicate that docking with the (*R*)- enantiomer had an approximately 18% lower energy score (Table 1, MolDock score for Ref. molecule) compared to the lowest energy obtained for docking with an (*S*)- enantiomer (Table 1, molecule 3) and approximately a 58% lower energy score compared to the highest energy conformation for an (*S*)- enantiomer (Table 1, molecule 21). Thus, the (*R*)- enantiomer is clearly preferred to the (*S*)- enantiomer for

binding. To measure the differences in the relative positions of atoms in

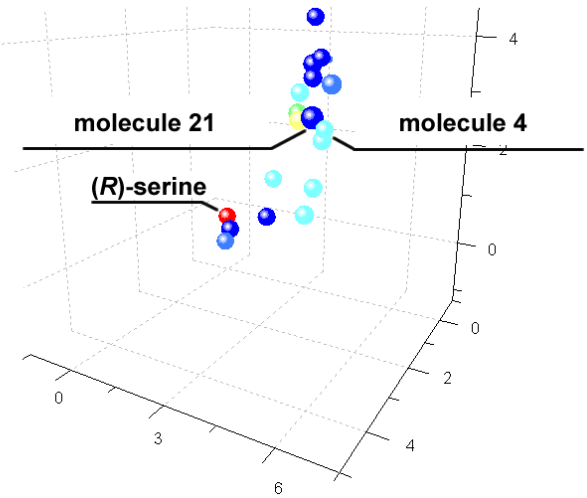

Figure 4: Conformation of (*S*)-serine chiral centers illustrating the energy score value (color coding) and RMSD value (size coding). The size of (*R*)-serine was selected arbitrarily.

both of these (*S*)- enantiomers, the RMSD and *f*RMSDchiral measures were employed. As shown in Figure 4, a scatter plot containing the x, y, and z coordinates of the position of the chiral centers obtained from the docking procedure were used to calculate RMSD values and the MolDock score function. The plot uses size coding corresponding to RMDS values and color coding corresponding to the values of the MolDock scoring function. One can observe that molecule 3 (the most favorable conformation) and molecule 21 (the most unfavorable conformation) are in similar positions in the space (Figure 3). To distinguish the differences in the positions of (*R*)- and (*S*)- enantiomers, the RMSD and *f*RMSDchiral measures were calculated. The RMSD values for molecules 3 and 21 are 7.3210 and 7.3957, respectively. As can be observed, the difference between these RMSD values is around 0.07. This suggests that the relative positions of the atoms in these enantiomers are very similar. When comparing *f*RMSDchiral values, the differences are greater in the case of *f*RMSDchiral_0 and *f*RMSDchiral_2, 0.2717 and 0.9936, respectively and lower in the case of *f*RMSDchiral_1, 0.0503. This suggests that there exists only a slight change in the location of chiral centers (*f*RMSDchiral_0), but a greater difference in lower tier fragments (*f*RMSDchiral_2), with a relatively low difference in the highest tier fragments (*f*RMSDchiral_1). This suggests that the highest tier fragments (*f*RMSDchiral_1) are much more similar to each other than the chiral centers (*f*RMSDchiral_0) or lowest tier fragments (*f*RMSDchiral_2), which is clearly reflected in Figure 1. It can be observed that in this case the RMSD value oversimplifies the distance information in

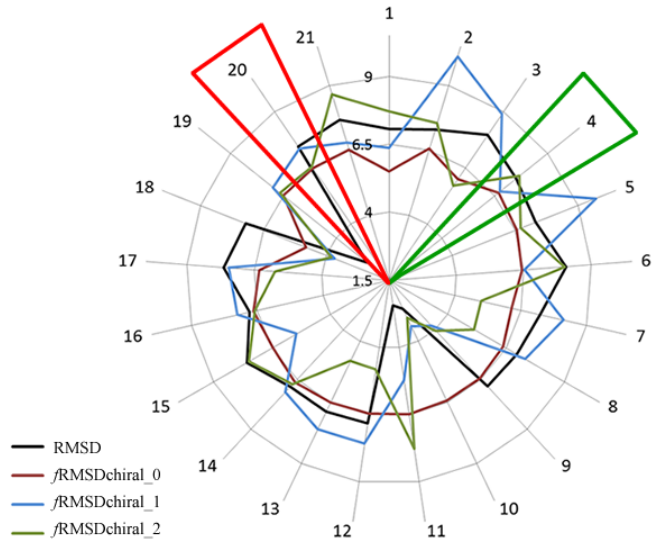

Figure 5: Radar plot performed for all of the obtained docking conformations and *f*RMSDchiral values.

comparison to the more informative description given by *f*RMSDchiral.

Usually the number of results from docking simulations is large. Thus data are presented in the form of a radar plot graph. An example radar plot of RMSD and *f*RMSDchiral measures for all of the docking conformations obtained are shown in Figure 5. The graph clearly demonstrates how the RMSD is distributed according to the various groups of atoms defined for the *f*RMSDchiral descriptor.

4. Molecular dynamics of (*S,S'*)-fenoterol under SULT1A3 binding conditions Fenoterol is a selective agonist of the $\beta 2$ adrenergic receptor ($\beta 2$-AR). The fenoterol molecule has two chiral centers. Therefore, four stereoisomers exist: (*R,R'*), (*R,S'*), (*S,R'*), (*S,S'*). Figure 6 shows the (*S,S'*)-stereoisomer of fenoterol. Since the molecule contains two centers of chirality, the CIP priority rule cannot be applied. The calculations are performed for the following subsets of atoms: all atoms forming centers of chirality (Figure 6, *f*RMSDchiral_0), atoms forming part of the long backbone of the molecule (Figure 6, *f*RMSDchiral_1), all other atoms (Figure 6, *f*RMSDchiral_2).

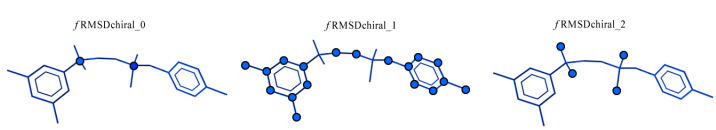

Figure 6: Illustration of (*S,S'*)-fenoterol with atoms used in the *f*RMSD descriptor indicated by circles. More details in the text.

Experimental studies performed by Jozwiak et al. [13] show that the varieties of fenoterol stereochemistry influence its binding and interactions with molecular targets. One of the problems associated with effective fenoterol pharmacotherapy is its poor oral bioavailability, due to extensive presystemic sulfation [14]. This metabolic pathway, catalyzed by sulfotransferase (SULT) enzymes, has been shown to be stereoselective and regioselective for fenoterol stereoisomers (Walle [15], [16]). Wilson et al. [17] characterized sulfotransferase isoform 1A3 (SULT1A3) involved in this reaction. In the case of fenoterol, the SULT1A3 isoform highly favors the (*R,R'*) stereoisomer and slightly favors the oppositely orientated (*S,S'*) stereoisomer. It seems to be noteworthy how a change in stereochemistry to the less preferred (*S,S'*) may determine the binding conditions for fenoterol and how this process changes over time. To analyze such changes, a simulation of the molecular dynamics was performed. To determine the starting position of (*S,S'*)-fenoterol under the conditions of the SULT1A3 binding domain (PDB ID: 2A3R), a simulation of docking was employed. Firstly, the complex was minimized using the Desmond standard relaxation protocol under the OPLS_2005 force field. Furthermore, the calculation of the molecular dynamics over a period of 1500 femtoseconds (fs) for the minimized complex was performed in Desmond Maestro academic version 2014.2. The molecular shift over this time is illustrated in Figure 7.

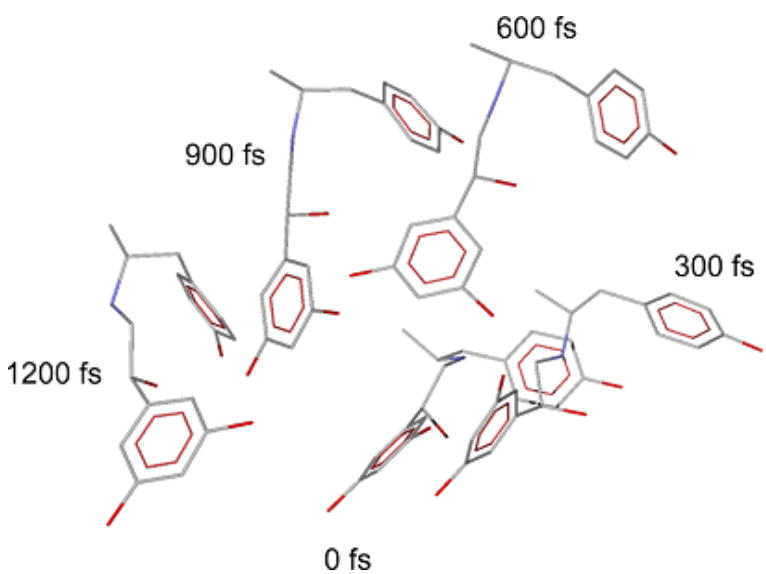

Figure 7: Illustration of the position of (*S,S'*)-fenoterol under the catalytic action of SULT1A3 according to the simulation of the molecular dynamics. Time is indicated alongside the conformations.

The position of the ligand was recorded witihin the simulation at 20fs intervals. It gave 44 unique (*S,S'*)-fenoterol positions. The RMSD and *f*RMSDchiral

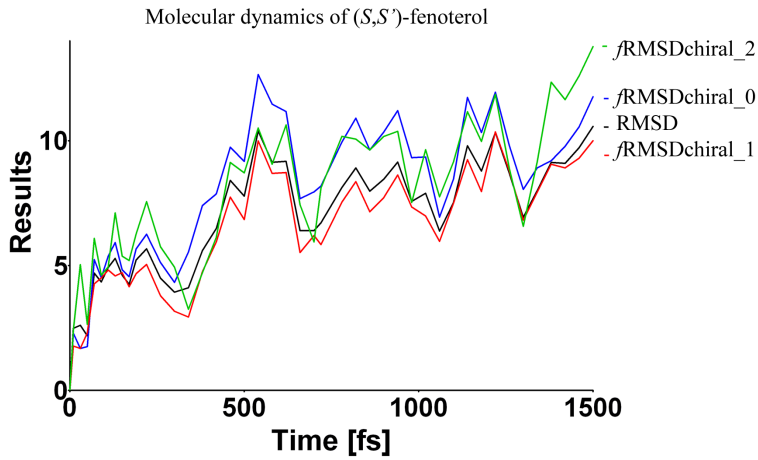

Figure 8: Illustration of the results of simulating the molecular dynamics of (*S,S'*)- fenoterol under the catalytic action of SULT1A3. The time shown on the graph corresponds to the time indicated alongside the conformations in Figure 7.

values were calculated for each fenoterol position taking successive molecules one after another. The results are presented in Figure 8 and Table S2 in the supplementary materials.

The *f*RMSDchiral_0 and *f*RMSDchiral_1 curves are very similar to the RMSD curve. These curves describe the RMSD distribution between the chiral centers (*f*RMSDchiral_0) and for the atoms forming the long backbone of the molecule (*f*RMSDchiral_1), respectively. The situation looks slightly different when the *f*RMSDchiral_2 curve is compared to the RMSD curve. The *f*RMSDchiral_2 curve describes the groups of atoms which determine the (*S,S'*) configuration in space. The (*R,R'*) configuration is preferred to (*S,S'*); mostly because it is the best spatial fit to the SULT1A3 binding domain. Thus, the higher variation in the values describing the atoms determining the chiral configuration (*f*RMSDchiral_2) seems to be natural. Here, we show that *f*RMSDchiral is a suitable concept to describe dynamic changes in chiral molecules under given conditions over a period of time.

5. Conclusions Molecular modeling of the interactions between stereoisomers and their binding sites is a particularly challenging task. Moreover, stereoisomers form a set of molecules with exactly the same sets of atoms and bonds between them. Due to this, classical measures (such as RMSD) may not be sufficiently precise and need to be adapted. Therefore, RMSD calculations at the level of fragments assume that there are three descriptive levels. This appears to be a useful tool for precisely quantifying changes in the orientations of stereoisomers in space, as well as being an appropriate supplement to classical RMSD calculations.

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Zastosowanie *f*RMSDchiral do matematycznego opisu wzajemnego położenia pomiędzy stereoizomerami

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Streszczenie Jedną z głównych właściwości układów biologicznych, takich jak białka, jest zdolność do rozpoznawania specyficznych związków chemicznych, zwanych ligandami. Ligandy ze względu na ich budowę i właściwości fizykochemiczne mogą być sklasyfikowane do różnych grup systematycznych. Biorąc pod uwagę właściwości strukturalne jedną z najbardziej interesujących grup ligandów są stereoizomery. Stereoizomery są to związki chemiczne, które współdzielą ten sam zbiór atomów w cząsteczce (ten sam skład chemiczny), ale kolejność lub rodzaj wiązań jest różna. W konsekwencji ma to bezpośrednie przełożenie na różnice w przestrzennym ułożeniu atomów pomiędzy poszczególnymi stereoizomerami. Szczególnie interesującą grupą stereoizomerów są enancjomery, zaliczane do grupy izomerów optycznych. Enancjomery to stereoizomery, które pod względem strukturalnym stanowią dla siebie odbicia lustrzane, przez co nie możliwe jest ich przestrzenne nałożenie na siebie. Każdy enancjomer zawiera jeden lub więcej atomów będących centrami stereogenicznymi. Najczęściej spotykane centra stereogeniczne to centra chiralności. Przeważnie są to asymetryczne atomy węgla, do których przyłączono cztery różne od siebie grupy podstawników. Ponieważ każda z grup podstawników jest różna, biorąc pod uwagę ich ułożenie (kolejność fragmentów) względem centrum chiralnego można jednoznacznie określić ich przestrzenną konfigurację. Trzech chemików, R. S. Cahn, C. Ingold i V. Prelog, jako jedni z pierwszych zaproponowali jednoznaczny sposób rozróżniania i nazewnictwa enancjomerów. Reguła Cahn-Ingold-Prelog (CIP) zakłada jednoznaczny sposób ustalania przestrzennego rozmieszczenia podstawników względem atomu asymetrycznego. Ustalanie konfiguracji absolutnej wokół danego centrum chiralności przeprowadza się nadając poszczególnym grupom odpowiednie rangi (priorytet, pierwszeństwo) wynikające z ich sumarycznej masy molowej. Najwyższą rangę otrzymuje grupa posiadająca największą sumaryczną masę molową. Następnie klasyfikuje się kolejne grupy podstawników ustawiając wartość rangi zgodnie z malejącą masą molowa podstawników. Jeśli patrząc od największego podstawnika do najmniejszego wzrok zatacza krąg zgodny z kierunkiem wskazówek zegara to konfiguracja absolutna jest oznaczana literą (R)- (do łac. *rectus* – prawy) , a gdy odwrotnie literą (S)- (od łac. *sinister* – lewy). Na Rysunku 1 zilustrowano dwa enacjomery aminokwasu seryny (R) - (Rysunku 1, niebieski) i (S) - (Rysunku 1, żółty). Każdy enancjomer zawiera jedno centrum chiralne oznaczone na rysunku, jako niebieskie lub żółte koło. W celu uproszczenia opisu w obu przypadkach grupy chemiczne enancjomerów zostały przydzielone do czterech grupy (a, b, c, d). Fragmenty a, b, c, d (R) -seryny (niebieski związek) odpowiadają fragmentom a', b', c', d' (S) -seryny (żółty związek). Jak można zaobserwować położenie fragmentów b, c enancjomeru (R) nie odpowiada położeniu fragmentów b', c' (S)-seryny, pomimo zastosowanego obrotu o 180 stopni związki są dalej nienakładane na siebie. Ponieważ, zazwyczaj tylko jeden enancjomer jest biologicznie aktywny, zdolność do rozpoznawania i różnicowania enancjomerów przez układy biologiczne ma kluczowe znaczenie dla organizmów żywych. Dla przykładu podtyp NR3 receptora NMDA, aby zostać aktywowanym, musi związać glicynę oraz (R)-serynę. Można zatem przypuszczać, że jeśli preferowaną formą dla receptora jest (R)-seryna, to przeciwstawny enancjomer (S) prawdopodobnie nie będzie się mógł przyłączyć do receptora lub będzie się wiązał znacznie słabiej. Szczegółowe badania mechanizmów rozpoznawania związków chiralnych poprzez układy biologiczne wydaje się być szczególnie istotne w przypadku takich obszarów nauki jak krystalografia, biologia strukturalna, biochemia czy farmakologia, ale także w naukach interdyscyplinarnych jak bioinformatyka, czy modelowanie molekularne. Badania zmiana przestrzennego ułożenia (kształtu) jednego enancjomeru względem drugiego wydają się być ważnym i istotnym uzupełnieniem analizy ich oddziaływań w układach biologicznych. Zazwyczaj do ilościowego opisu zmian w przestrzeni kartezjańskiej używa się parametru RMSD (ang. *Root Mean*

Square Deviation), opisującego średnią zmianę odległości pomiędzy odpowiednimi atomami należących do porównywanych związków. Pomimo, iż RMSD jest szeroko stosowany w wielu dziedzinach nauki i wydaje się być uniwersalnym deskryptorem zauważono, że niższe wartości RMSD nie zawsze oznacza najlepszą superpozycję (dopasowanie) związków w przestrzeni. Dlatego autorzy zaproponowali modyfikację tradycyjnej koncepcji obliczania RMSD, jako fragmentaryczne RMSD (fRMSD). Zakłada ona odmienny sposób selekcji atomów w cząsteczkach. W niniejszej publikacji zaprezentowano zastosowanie parametru fRMSD w przypadku enancjomerów posiadających jedno lub więcej miejsc chiralnych. W przypadku enancjomerów zawierających jedno centrum chiralne atomy są grupowane zgodnie z zasadą Cahn-Ingold-Prelog (CIP). Umożliwia to podział cząsteczki na trzy niezależne podgrupy atomów: atom zawierający centrum chiralności (fRMSDchiral_0), dwa fragmenty przyłączone do centrum chiralności o wyższym priorytecie CIP (fRMSDchiral_1) oraz dwa fragmenty przyłączone do centrum chiralności o niższym priorytecie CIP (fRMSDchiral_2). Przykładowy wybór atomów zgodnie z założeniami parametru fRMSD dla (R) - i (S) -seryny została przedstawiona na rysunku 2. W dalszej części pracy opisano szczegółowe zastosowanie parametru fRMSD oraz oceniono jego stosowalność w kontekście dokowania i dynamiki molekularnej związków chiralnych.

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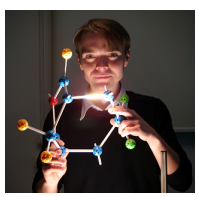
Słowa kluczowe: fragment-level RMSD, związki chiralne, stereoselektywność, bioinformatyka, modelowanie molekularne.



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