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Estimating the prediction ability of reverse degree-based entropy indices for the physicochemical properties of lymes disease drugs

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Lyme disease, caused by the bacterium *Borrelia burgdorferi* and transmitted through infected black-legged ticks, remains a significant health concern due to its potential for severe complications, including arthritis, neurological disorders, and cardiac issues. Early diagnosis and treatment are essential to prevent these outcomes. This study explores the predictive potential of reverse degree-based entropy indices for analyzing the molecular structures of therapeutic compounds used in Lyme disease treatment. While the use of topological indices for predicting physicochemical properties is well-established, our research uniquely integrates reverse entropy indices with a computational framework to refine the prediction process. We focus specifically on antibiotic drugs such as doxycycline, ceftriaxone, Doxy 100, cefotaxime, Ceftin, Cefuroxime, Erythromycin, EryPed, Erythrocin Lactobionate, Ofloxacin, Moxifloxacin, amoxicillin, and penicillin G potassium—commonly used to treat Lyme disease—and leverage a novel Maple-based algorithm for calculating reverse degree-based entropy indices. SPSS software was employed to assess correlations between these indices and critical physicochemical properties, such as molecular weight (MW), complexity (C), molar volume (MV), and XLog P. Unlike traditional experimental methods mandated by regulatory authorities for Chemistry, Manufacturing, and Controls (CMC) processes, our approach provides a supplementary predictive framework to streamline early-stage drug property estimation. The results reveal that first reverse Zagreb entropy effectively predicts molecular weight, reverse atom bond connectivity entropy effectively predicts complexity, reverse augmented Zagreb entropy effectively predicts molar volume and reverse geometric arithmetic entropy effectively predicts molecular XLog P. This study not only advances the computational methodology by employing novel combinations of entropy indices but also builds on existing work by focusing on a specific subset of Lyme disease drugs. While this framework offers a cost-effective preliminary tool for predicting physicochemical properties, it complements rather than replaces rigorous experimental validation required for regulatory reporting. These findings lay the groundwork for integrating computational and experimental methods,

potentially accelerating drug development and enhancing therapeutic precision for Lyme disease.

KEYWORDS

quantitative structure-property relationship, reverse degree degree-based entropy, Lyme disease drugs, statistical model, human health

1 Introduction

Lyme disease is a disease spread by ticks. Because of a complex interplay of ecological, medicinal, and environmental elements, tick bites are the primary means of transmitting bacteria under the skin, where they can cause severe illness. The common symptoms include rash, headache, and fever. If left untreated, this disease can lead to more severe problems with the heart, joints, and brain. Thus, Lyme disease is being identified more frequently in patients with symptoms that are medically inexplicable [1, 2], as well as in individuals with more clearly recognized diseases [3, 4].

A new chapter in understanding of this sickness was opened in 1982 [5] when the causative agent was found in Ixodes ticks. Lyme disease is the most prevalent vector-borne illness (transmitted by mosquitoes, ticks, or fleas) in the United States. In recent years, the Centers for Disease Control and Prevention have reported approximately 20,000 to 30,000 confirmed cases annually [6]. Additionally, children and individuals who spend a lot of time outside in wooded areas are at risk. Once an Ixodes tick bite has occurred, humans become infected. For the disease-causing bacteria, *Borrelia burgdorferi*, to proliferate, the tick must feed for a minimum of 36 h. The most common sign of infection is erythema migrans, a developing red rash that appears at the site of the tick bite and usually appears a week or more after the incident [7]. Most often, the rash is not uncomfortable or annoying.

In roughly 70%–80% of the cases, a rash develops. Fatigue, headaches, and fever are possible symptoms. The total number of cases has been smoothly increasing, with cases recorded not only from endemic regions but increasingly from other Regional locations [8].

Prolonged, untreated Lyme disease can result in serious complications affecting multiple systems. Neurological issues may include facial palsy (Bell's palsy), meningitis, encephalitis, and peripheral neuropathy. Cardiac complications can involve irregular heartbeat and inflammation of the heart muscle. Joint problems, such as arthritis, are also common. To reduce the risk of tick-borne infections, preventive measures are crucial. Wearing protective clothing, such as long-sleeved shirts, long pants tucked into socks, and closed-toe shoes, can help minimize skin exposure to ticks. Applying insect repellents containing DEET or picaridin to exposed skin provides an additional layer of protection. Regularly performing tick checks on yourself, your family, and pets after outdoor activities is vital for early detection. If a tick is found, it should be removed promptly and carefully using fine-tipped tweezers. Showering soon after being outdoors can also help wash away unattached ticks and make it easier to spot those that may have latched on. These simple precautions can significantly reduce the likelihood of tick infections [9]. A variety of antibiotics, including cefuroxime, amoxicillin, and doxycycline, are effective

in treating Lyme disease and preventing complications when administered promptly.

In conclusion, the fusion of multiple scientific domains has prompted the creation of cutting-edge methodologies and analytical instruments that deepen our understanding of complex systems. Returning to the medical field, Lyme disease is still an issue that needs to be addressed on a regular basis due to its complexity and long-term consequences [10, 11]. Education and prevention efforts are also needed.

A graph $H = (V, E)$ consists of V , a nonempty set of vertices (or nodes), and E , a set of edges. Each edge has two vertices associated with it, known as its endpoints, and is said to connect these endpoints. In the context of chemical graph theory, a chemical graph represents individual atoms as vertices and the bonds between them as edges. The primary objective of chemical graph theory is to identify topological indices that closely correlate with the properties of chemical compounds [12, 13].

Topological indices are widely used in chemistry, nanotechnology, and medicine to explore and quantify the relationships between molecular structure and properties, as well as structure and biological or chemical activity. These indices are essential as numerical molecular descriptors in quantitative structure-activity relationship (QSAR) and quantitative structure-property relationship (QSPR) models, which help in predicting molecular behaviors [14, 15].

The Wiener index, introduced by Wiener [16], was the first topological index to demonstrate a clear correlation between the boiling points of alkane molecules and the values of this index. Further research into quantitative structure-activity relationships has shown that such correlations extend to other molecular properties, including dimensions [17], density, surface tension, liquid-phase viscosity [18], and van der Waals surface area [19]. These relationships enable the prediction of molecular properties and behaviors based on structural characteristics.

Applications of graph invariant (topological indices) to QSPR and QSAR studies have garnered significant attention in recent years. Topological indices are employed in many fields of study, including arithmetic, physics, chemistry, biology, and informatics [20–22]. This thorough and systematic basis makes it easier to comprehend how a chemical molecule's molecular structure influences its physical, chemical, and biological properties. Nonetheless, their most important applications to date have been the non-empirical Quantitative Structure-Property Relationships (QSPR) and Quantitative Structure-Activity Relationships (QSAR) [23–26]. These days, the main focus of computational chemistry is on the investigation of QSPRs, or quantitative structure-property correlations. Classifications of topological indices can be based on a graph's structural attributes, including matching, spectrum, vertex degree, and vertex separation. The indices that are most commonly used are the Wiener index [16], which measures the separation

between the vertices, the Zagreb and Randić indices [27, 28], which measures degree; the Estrada index [29] which measures a graph's spectrum; and the Hosoya index [30], which measures matching.

Many topological indices having applications in QSPR/QSAR have been developed since 1947 [31, 32]. Some examples of topological indices include the 1stZagreb index [33], the 2ndZagreb index, redefined first Zagreb index [34], redefined second Zagreb index [35], geometric arithmetic index [36], augmented Zagreb index [37], the atom-bond connectivity index [38], forgotten index [39], hyper-Zagreb index [40], redefined third Zagreb [41], and Balaban index [42].

Reverse degree-based indices employ a cutting-edge technique that challenges conventional wisdom and offers a distinct perspective in computing and mathematical domains [43]. Entropy indices derived from information theory, provides a method for quantifying disorder and uncertainty, with applications in environmental science and data science. In mathematical and computational contexts, reversing the traditional degree ordering in polynomial or numerical expressions yields a distinctive approach known as reverse degree-based indices [44]. This contemporary indexing method has applications in fields such as signal processing, mathematics, and computer science. Within mathematics, one particularly intriguing area is the development of techniques for solving equations by employing reverse degree-based indices.

Shannon introduced the concept of entropy in 1948 [45], providing a foundation for estimating a system's uncertainty through the entropy of a probability distribution. The concept of graph entropy was first introduced by Rashevsky in 1955 [46] in relation to the classification of vertex orbits. Recently, graph entropies have been extensively utilized in the fields of biology, ecology, chemistry, and sociology [47]. In graph entropy, a graph element associated with a probability distribution can be divided into embedded and external measurements [48]. Dehmer's information-based function graph entropy examines the characteristics and structural data of these graphs [45, 49].

In this work, we have considered eight graph entropy measures based on reverse degree of a graph. These graph entropy measures include reverse Randić entropy, reverse atom-bond connectivity entropy, reverse geometric arithmetic entropy, reverse first Zagreb entropy, reverse second Zagreb entropy, reverse hyper Zagreb entropy, reverse forgotten entropy, and reverse augmented Zagreb entropy. The values of these entropy indices are computed for thirteen drugs structures using MAPPLE software. Additionally, the regression models are developed to estimate the four key physical properties of these drugs.

The paper is structured as follows: In Section 2, we provide the definitions of the eight entropy indices based on the reverse degree of a graph. Section 3 outlines the research methodology, which is illustrated with a flow chart. In Section 4, we compute the entropy indices for the drug structures using MAPPLE software. Section 5 presents the development of the regression model for the physical properties of the drug structures, along with the calculation of correlation coefficients and other regression parameters using SPSS software. A detailed discussion of the results obtained from the regression models is presented in Section 6. The validation of the regression models is performed in Section 7. Limitations and future directions are discussed in Section 8 and finally, Section 9 concludes the article.

2 Reverse degree based entropy indices

In this section, we define some basic definitions related to graph theory.

2.1 Reverse degree

The degree of a vertex v is the number of edges incident to it. Let $\Delta(H)$ denotes the maximum degree of a graph. Then the modified reverse degree of a vertex v with variable parameter k (where $k \geq 1$) is denoted and defined as

$$\aleph(v)(k) = \begin{cases} \Delta(H) - d_v + k : k \leq d_v \\ \Delta(H) - d_v + k \pmod{\Delta(H)} : k > d_v \end{cases}$$

here in this manuscript, we considered the special case when $k = 1$, we represent the reverse degree of a vertex v simply by $\aleph(v)$.

2.2 Reverse degree-based entropy of graph

Assume that a connected graph $H = (V, E)$ has size q (number of edges) and order p (number of vertices) and Ψ be a meaningful function. The entropy function for the graph H is defined as:

$$\text{ENT}_{\Psi}(H) = - \sum_{i=1}^p \frac{\Psi(x_i)}{\sum_{j=1}^p \Psi(x_j)} \log \left[\frac{\Psi(x_i)}{\sum_{j=1}^p \Psi(x_j)} \right]. \quad (1)$$

Now if $x_i \in V$ and information function $\Psi(x_i)$ symbolize the reverse degree of vertex x_i , that is, $\Psi(x_i) = \aleph(x_i)$, then Equation 1 becomes

$$\begin{aligned} \text{ENT}_{\Psi}(H) &= - \sum_{i=1}^p \frac{\aleph(x_i)}{\sum_{j=1}^p \aleph(x_j)} \log \left[\frac{\aleph(x_i)}{\sum_{j=1}^p \aleph(x_j)} \right] \\ \text{ENT}_{\Psi}(H) &= \log \left(\frac{\sum_{j=1}^p \aleph(x_j)}{\sum_{j=1}^p \aleph(x_j)} \right) - \frac{1}{\left(\sum_{j=1}^p \aleph(x_j) \right)} \sum_{i=1}^p [\aleph(x_i) \log(\aleph(x_i))] \end{aligned}$$

Using the fundamental theorem of graph theory, we formulate the following relation for the sum of reverse degrees $\aleph(x_i)$, with $x_i \in V$ as

$$\sum_{j=1}^p \aleph(x_j) = \log((p+1)\Delta(H) - 2q).$$

As a result, the above equation for $\text{ENT}_{\Psi}(H)$ takes the form

$$\begin{aligned} \text{ENT}_{\Psi}(H) &= \log((p+1)\Delta(H) - 2q) - \frac{1}{((p+1)\Delta(H) - 2q)} \\ &\quad \log \left[\prod_{i=1}^p \aleph(x_i) \right]^{\aleph(x_i)}. \end{aligned}$$

2.3 Edge weight-based entropy of a graph

Chen et al. (2014) introduced the edge weight graph's entropy. For an edge weight graph $H = (V(H); E(H); \Psi(xy))$, where $V(H)$ is

the vertex set, $E(H)$ is the edge set and $\Psi(xy)$ is the edge weight of the edge (xy) in H , the entropy function is defined as:

$$ENT_{\Psi}(H) = - \sum_{x'y' \in E} \frac{\Psi(x'y')}{\sum_{xy \in E} \Psi(xy)} \log \left[\frac{\Psi(x'y')}{\sum_{xy \in E} \Psi(xy)} \right] \quad (2)$$

2.4 Reverse Randić entropy

If $\Psi(xy) = (\aleph(x) \times \aleph(y))^{\alpha}$ with $\alpha = 1, -1, \frac{1}{2}, -\frac{1}{2}$, then the reverse Randić index is defined as

$$R_{\alpha} = \sum_{xy \in E(H)} \Psi(xy) = \sum_{xy \in E} (\aleph(x) \times \aleph(y))^{\alpha}$$

Incorporating it in Equation 2 gives the reverse Randić entropy

$$ENT_{\alpha}(H) = \log(R_{\alpha}) - \frac{1}{R_{\alpha}} \log \left[\prod_{xy \in E} [(\aleph(x) \times \aleph(y))^{\alpha}]^{(\aleph(x) \times \aleph(y))^{\alpha}} \right]. \quad (3)$$

We use the notations RE to denote the Reverse Randić entropy in Equation 3 for the special cases $\alpha = -\frac{1}{2}$.

2.5 Reverse atom bond connectivity entropy

If $\Psi(xy) = \sqrt{\frac{\aleph(x) + \aleph(y) - 2}{\aleph(x) \times \aleph(y)}}$, then the reverse atom bond connectivity index is defined as.

$$ABC(H) = \sum_{xy \in E} \Psi(xy) = \sum_{xy \in E} \sqrt{\frac{\aleph(x) + \aleph(y) - 2}{\aleph(x) \times \aleph(y)}}$$

This leads to the reverse atom bond connectivity entropy by using Equation 2 as

$$ABCE = \log(ABC(H)) - \frac{1}{(ABC(H))} \log \left[\prod_{xy \in E} \sqrt{\frac{\aleph(x) + \aleph(y) - 2}{\aleph(x) \times \aleph(y)}}^{\sqrt{\frac{\aleph(x) + \aleph(y) - 2}{\aleph(x) \times \aleph(y)}}} \right]$$

2.6 The reverse geometric arithmetic entropy

If $\Psi(xy) = \frac{2\sqrt{\aleph(x) \times \aleph(y)}}{\aleph(x) + \aleph(y)}$, then the reverse geometric arithmetic index is defined as

$$GA(H) = \sum_{xy \in E} \Psi(xy) = \sum_{xy \in E} \frac{2\sqrt{\aleph(x) \times \aleph(y)}}{\aleph(x) + \aleph(y)}$$

Now, Equation 2 reduces to the reverse geometric arithmetic entropy, which is as follows:

$$GAE = \log(GA(H)) - \frac{1}{(GA(H))} \log \left[\prod_{xy \in E} \frac{2\sqrt{\aleph(x) \times \aleph(y)}}{\aleph(x) + \aleph(y)}^{\frac{2\sqrt{\aleph(x) \times \aleph(y)}}{\aleph(x) + \aleph(y)}} \right]$$

2.7 The reverse first zagreb entropy

If $\Psi(xy) = \aleph(x) \times \aleph(y)$, then the reverse first Zagreb index is defined as

$$M_1(H) = \sum_{xy \in E} \Psi(xy) = \sum_{xy \in E} (\aleph(x) \times \aleph(y))$$

For the reverse first Zagreb entropy, we use this value in Equation 2. This gives

$$FZE1 = \log M_1(H) - \frac{1}{(M_1(H))} \log \left[\prod_{xy \in E} [\aleph(x) \times \aleph(y)]^{(\aleph(x) \times \aleph(y))} \right]$$

2.8 The reverse second zagreb entropy

If $\Psi(xy) = \aleph(x) \times \aleph(y)$ then the reverse second Zagreb index is defined as

$$M_2(H) = \sum_{xy \in E} \Psi(xy) = \sum_{xy \in E} (\aleph(x) \times \aleph(y))$$

Now for the reverse second Zagreb entropy, we use this value in Equation 2. This gives

$$SZE1 = \log M_2(H) - \frac{1}{(M_2(H))} \log \left[\prod_{xy \in E} [(\aleph(x) \times \aleph(y))]^{(\aleph(x) \times \aleph(y))} \right]$$

2.9 The reverse hyper zagreb entropy

If $\Psi(xy) = (\aleph(x) + \aleph(y))^2$, then the reverse hyper Zagreb index is defined as

$$HM(H) = \sum_{xy \in E} \Psi(xy) = \sum_{xy \in E} (\aleph(x) + \aleph(y))^2$$

Now for the reverse hyper Zagreb entropy, we use this value in Equation 2. This gives

$$HZE1 = \log HM(H) - \frac{1}{(HM(H))} \log \left[\prod_{xy \in E} [(\aleph(x) + \aleph(y))^2]^{(\aleph(x) + \aleph(y))^2} \right]$$

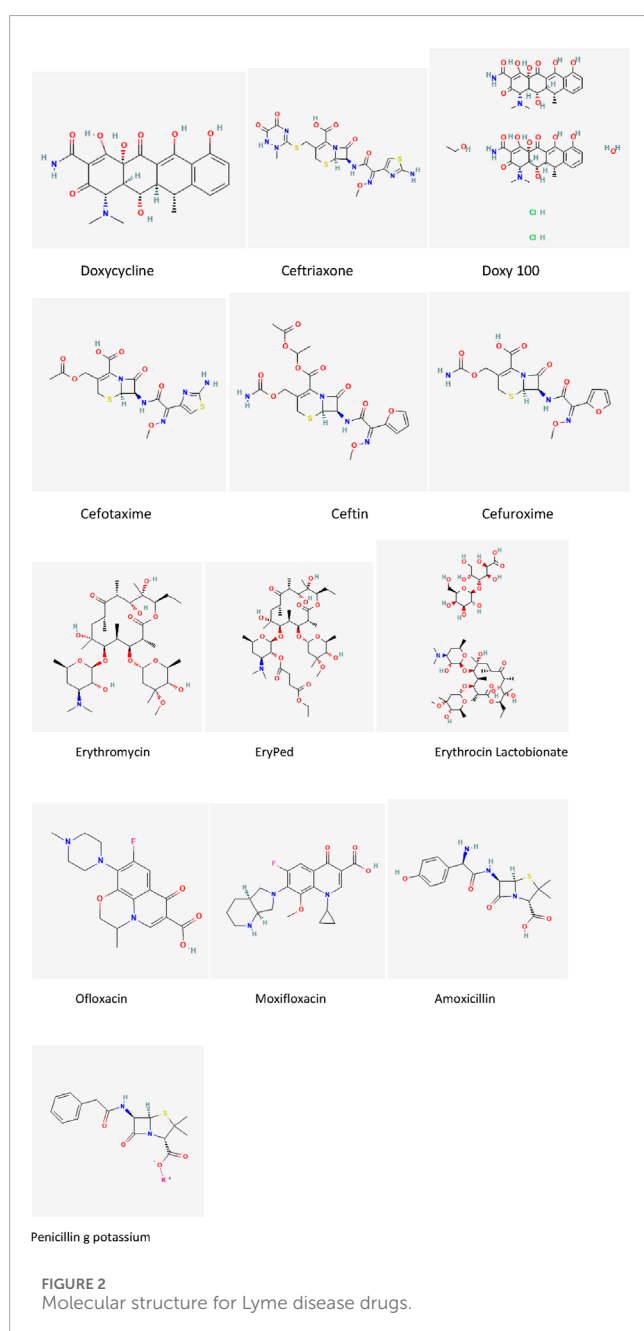
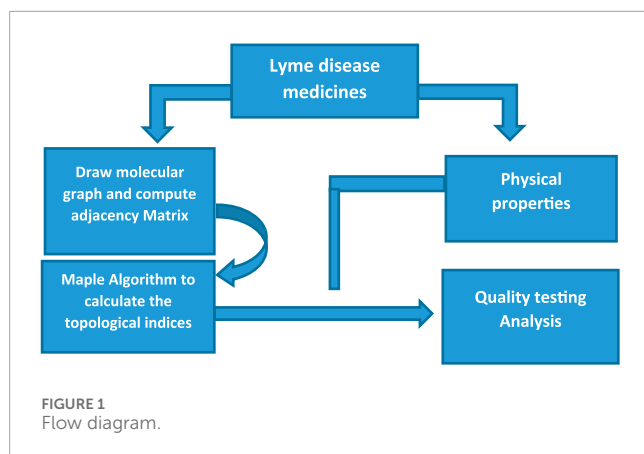
2.10 The reverse forgotten entropy

If $\Psi(xy) = \aleph(x)^2 + \aleph(y)^2$, then the reverse forgotten index is defined as

$$F(H) = \sum_{xy \in E} \Psi(xy) = \sum_{xy \in E} (\aleph(x)^2 + \aleph(y)^2)$$

By using Equation 2, the reverse forgotten entropy is expressed in the form of

$$FE = \log F(H) - \frac{1}{(F(H))} \log \left[\prod_{xy \in E} [(\aleph(x)^2 + \aleph(y)^2)]^{(\aleph(x)^2 + \aleph(y)^2)} \right]$$



2.11 The reverse augmented zagreb entropy

If $\Psi(xy) = \left(\frac{N(x)+N(y)}{N(x)+N(y)-2}\right)^3$, then reverse augmented Zagreb index is defined as

$$AZI(H) = \sum_{xy \in E} \Psi(xy) = \sum_{xy \in E} \left(\frac{N(x) + N(y)}{N(x) + N(y) - 2}\right)^3 \left(\frac{N(x)+N(y)}{N(x)+N(y)-2}\right)^3$$

By using Equation 2, the reverse augmented Zagreb entropy has the form

$$AZI1 = \log AZI(H) - \frac{1}{(AZI(H))} \log \left[\prod_{xy \in E} \left(\frac{N(x) + N(y)}{N(x) + N(y) - 2}\right)^3 \left(\frac{N(x)+N(y)}{N(x)+N(y)-2}\right)^8 \right]$$

Despite extensive efforts in Quantitative Structure-Property Relationship (QSPR) analysis, much of the existing work relies heavily on classical degree-based topological indices to model the physicochemical properties of molecules. While these indices have demonstrated utility, they often fail to capture the full complexity and intricacies of molecular structures, particularly when dealing with drugs exhibiting diverse structural and functional characteristics, such as those used in the treatment of Lyme disease. This limitation creates a significant research gap in developing more accurate and statistically robust predictive models. The novelty of this study lies in the use of reverse degree-based entropy indices, which combine the principles of molecular topology and information theory. Unlike classical indices, entropy indices provide a richer quantification of structural variability and disorder within molecular graphs. The reverse formulation further enhances their sensitivity to subtle differences in molecular architecture.

3 Research methodology

This research employs a structured approach to investigate the relationship between graph entropy measures and the physical properties of drug structures. Eight graph entropy measures based on the reverse degree of a graph are considered in this study. These entropy measures are selected for their relevance to structural descriptors in cheminformatics and their ability to capture complex topological properties of molecular graphs. Thirteen drug structures, which represent various pharmacological classes, are selected for the analysis. The molecular graphs of these drugs are constructed based on their chemical structure, where atoms are represented as nodes and bonds as edges. The structures are obtained from standard chemical databases pubchem, ensuring that accurate molecular representations are used. The entropy indices for each drug structure are computed using MAPPLE software, which is capable of efficiently handling graph-based computations. Each of the eight entropy measures is calculated for the molecular graphs of the thirteen drug structures. These entropy values are then used as descriptors for further analysis and correlation with physical properties of the drugs. Regression models are developed to estimate four key physical properties of the drugs, including properties such as molecular weight (MW), complexity (C), XLog P, and molar volume (MV). The property XlogP is a measure of the

TABLE 1 Physicochemical characteristics of Lyme disease medication.

Drug Name	Molecular Formula	MW	C	XLogP	MV
Doxycycline	C ₂₂ H ₂₄ N ₂ O ₈	444.4	956	-0.7	182
Ceftriaxone	C ₁₈ H ₁₈ N ₈ O ₇ S ₃	554.6	1,110	-1.3	288
Doxy 100	C ₄₆ H ₅₈ Cl ₂ N ₄ O ₁₈	1,025.9	958	NaN	384
Cefotaxime	C ₁₆ H ₁₇ N ₅ O ₇ S ₂	455.5	833	-1.4	227
Ceftin	C ₂₀ H ₂₂ N ₄ O ₁₀ S	510.5	968	0.9	214
Cefuroxime	C ₁₆ H ₁₆ N ₄ O ₈ S	424.4	798	-0.2	199
Erythromycin	C ₃₇ H ₆₇ N ₁₃	733.9	1,180	2.7	194
EryPed	C ₄₃ H ₇₅ N ₁₆	862.1	1,450	3.4	226
Erythrocin Lactobionate	C ₄₉ H ₈₉ N ₂ O ₂₅	1,092.2	1,580	nan	412
Ofloxacin	C ₁₈ H ₂₀ FN ₃ O ₄	361.4	634	-0.4	73.3
Moxifloxacin	C ₂₁ H ₂₄ FN ₃ O ₄	401.4	727	0.6	82.1
Amoxicillin	C ₁₆ H ₁₉ N ₃ O ₅ S	365.4	590	-2.0	158
Penicillin g potassium	C ₁₆ H ₁₇ KN ₂ O ₄ S	372.5	536	NaN	115

TABLE 2 Values of entropy indices of Lyme disease drugs.

Antibiotic	RE	ABCE	GAE	FZE1	SZE1	HZE1	FE	AZE1
Doxycycline	3.53089171	3.552295882	3.554476369	3.448147257	3.473803125	3.462829245	3.530275563	3.47134248
Ceftriaxone	3.632,757	3.662,284	3.662,188	3.510,559	3.545,306	3.530,830	3.639,530	3.584,836
Doxy 100	4.250,504	4.273,288	4.275,814	4.165,494	4.186,327	4.177,874	4.249,721	4.174,646
Cefotaxime	3.432410742	3.464219194	3.464277508	3.310574081	3.341208841	3.329375027	3.439105533	3.376971548
Ceftin	3.578031699	3.609221064	3.609472684	3.472117228	3.495263975	3.487711686	3.583698767	3.518641520
Cefuroxime	3.396452449	3.432037780	3.432560860	3.278990125	3.300510888	3.294102915	3.402049770	3.334262643
Erythromycin	3.945,823	3.965,603	3.968,357	3.891,016	3.890,030	3.895,742	3.939,767	3.843,912
EryPed	3.945822926	3.965603455	3.968357192	3.891015871	3.890030331	3.895741836	3.939766576	3.843912213
Erythrocin Lactobionate	4.321259557	4.339784876	4.342309719	4.263891439	4.267769203	4.269629770	4.316815991	4.232688347
Ofloxacin	3.33739500	3.3664070	3.36585000	3.20320900	3.25645300	3.23190600	3.34502500	3.31451700
Moxifloxacin	3.46442500	3.4950300	3.49544900	3.33439800	3.35935000	3.34991700	3.46988000	3.40929800
Amoxicillin	3.27756100	3.2922500	3.29414900	3.22655300	3.23467900	3.23503100	3.27284000	3.20553800
Penicillin g potassium	3.19869300	3.2145930	3.21706900	3.15720700	3.15410800	3.16087300	3.19208400	3.11086800

molecule's lipophilicity (molecules with high XlogP are lipophilic and will reside in the cell membrane) and solubility (molecules with high XlogP tend to be insoluble). The physicochemical properties of drugs, such as complexity, molar volume, molecular weight,

and lipophilicity (e.g., XLogP), play a pivotal role in determining their biological activity, pharmacokinetics, and overall therapeutic effectiveness in treating Lyme disease. These properties influence critical factors such as drug solubility, bioavailability, and tissue

penetration, which are essential for targeting the bacterial pathogen *Borrelia burgdorferi* effectively.

Linear regression analysis is employed to develop the models, using the entropy indices as independent variables and the physical properties as dependent variables. The regression analysis is conducted using SPSS software, where the correlation coefficients and other regression parameters (such as R-squared, p-values, and standard errors) are computed to assess the strength of the relationships between the entropy measures and the physical properties. These statistical metrics are crucial for evaluating the predictive power and reliability of the regression models. The flow chart of the research is shown in Figure 1.

4 Computation of reverse degree entropy indices

In this study, we examine a set of thirteen drugs commonly used in the treatment of Lyme disease. These drugs include doxycycline, ceftriaxone, Doxy 100, cefotaxime, Ceftin, Cefuroxime, Erythromycin, EryPed, Erythrocin Lactobionate, Ofloxacin, Moxifloxacin, amoxicillin, and penicillin G potassium. The molecular structures of these drugs, illustrated in Figure 2, form the basis for the subsequent computational analysis. To compute the reverse degree entropy indices, we utilized the MAPPLE code, a specialized computational tool for deriving molecular entropy indices from the structural data. For each drug, the molecular structure was transformed into a graph where atoms are treated as vertices, and chemical bonds as edges. These graphs were then analyzed to determine the distribution of connectivity degrees, which serve as input for entropy calculations. The pseudocode of the MAPPLE code is presented in Algorithm 1. The computed values of these entropy indices are presented in Table 2.

5 Linear regression models

Linear regression is the simplest form of regression that assumes a direct proportional relationship between the independent and dependent variables. It is typically chosen as a baseline model due to its interpretability and minimal risk of overfitting. By starting with a linear model and gradually exploring higher-order models based on visual inspection and statistical criteria, this approach ensures that the selected model achieves a balance between accuracy and generalizability while minimizing the risk of overfitting. In this section, we develop linear regression models to estimate the physicochemical properties of thirteen drugs used for the treatment of Lyme disease. The degree-based entropy indices are utilized as independent variables, while the physicochemical properties of the drugs serve as dependent variables. The linear regression model under consideration is of the form:

$$P = a + b \times Ent$$

where P represent the physicochemical property, and Ent denotes the entropy indices of the drug.

A linear regression model is used to describe the relationship between a dependent variable P and an independent variable Ent . In

```

P1: Commence.
P2: Input: C denotes the adjacency matrix.
P3: Output: Computation of reverse entropy based
on edge weight and entropy based on degree.
P4: Initialization: V ← Number of vertices, E ←
Number of edges, D [V] ← vertex degrees, Conn [E]
← connection matrix, Ver [V] ← Vertex list, adj
[count] ← adjacent elements, Count ← 1.
P5: Loop b = 1 to V.
P6: For each vertex in the array Ver [V].
P7: Loop c = 1 to E.
P8: Count adjacent vertices from Conn [E].
P9: Increment c.
P10: End loop.
P11: D [V] = count.
P12: Loop t = 1 to count.
P13: adj [count] = store adjacent vertices.
P14: Increment t P15: End loop P16: End loop.
P17: Loop a = 1 to count.
P18: Compute reverse entropy based on degree.
P19: End loop.
P20: Loop b = 1 to count.
P21: Compute reverse entropy based on edge weight.
P22: End loop.
P23: Loop c = 1 to E.
P24: Compute reverse edge weight-based entropy,
reverse Atom-bond connectivity entropy, reverse
Geometric arithmetic entropy, First, Second, Hyper
and Augmented reverse Zagreb entropy, reverse
forgotten entropy, reverse Balaban entropy,
reverse Redefined first, second and third reverse
Zagreb entropy.
P25: End loop.
P26: End.

```

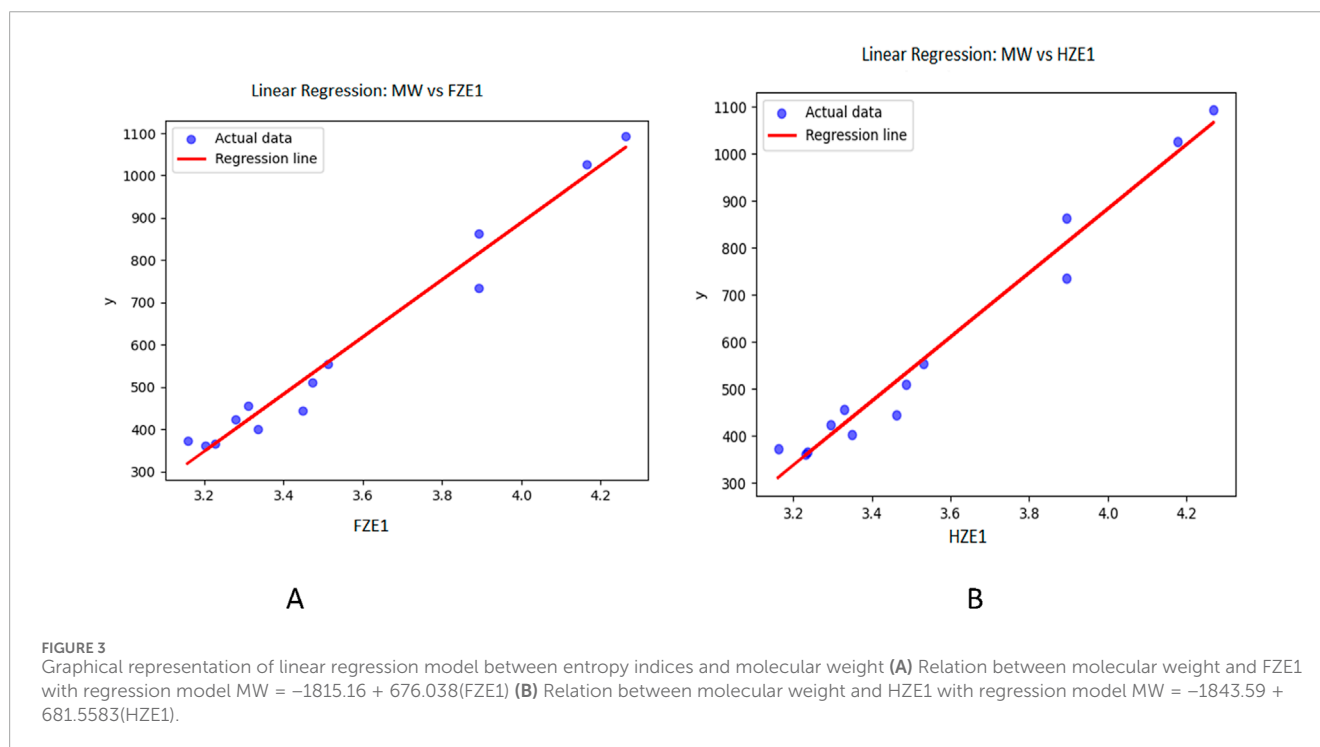
Algorithm 1. Pseudocode to compute reverse degree entropy indices.

this equation, a is the intercept, which represents the predicted value of P when Ent is zero. The term b is the coefficient associated with Ent , indicating the rate of change in PPP for a one-unit increase in Ent . The model predicts P by fitting a straight line to the observed data, where the parameters a and b are estimated by minimizing the Mean Squared Error (MSE), which measures the average squared difference between observed values of P and those predicted by the model. A lower MSE reflects a better fit of the regression line to the data.

The performance of this regression model is assessed using metrics such as R^2 , the coefficient of determination, which quantifies the proportion of variability in P explained by Ent . A higher R^2 indicates a better fit, suggesting that Ent is a strong predictor of P . The strength and direction of the linear relationship between P and Ent can be evaluated using Pearson's correlation coefficient (R), with its corresponding p-value assessing whether this correlation is statistically significant. Together, these metrics provide

TABLE 3 Relation of entropy indices with molecular Weight (MW).

Entropy indices	MSE	R ²	Pearson R	Pearson p-value	MW = a + b (Ent)
RE1	2279.598	0.962,793	0.98122	3.29E-09	MW = -1942.06 + 694.3481 (RE)
GAE	2452.419	0.959,973	0.979,782	4.92E-09	MW = -1963.36 + 695.2276 (GAE)
FZE1	1,662.54	0.972,865	0.986,339	5.77E-10	MW = -1815.16 + 676.038(FZE1)
SZE1	1852.08	0.969,771	0.98477	1.05E-09	MW = -1864.24 + 686.2682(SZE1)
HZE1	1711.549	0.972,065	0.985,933	6.77E-10	MW = -1843.59 + 681.5583(HZE1)
FE	2459.19	0.959,862	0.979,726	4.99E-09	MW = -1952.64 + 697.1275(FE)
AZE1	3046.338	0.950,279	0.974,823	1.63E-08	MW = -1955.9 + 711.5452 (AZE1)
ABCE	2485.605	0.959,431	0.979,505	5.3E-09	MW = -1966.21 + 696.2655 (ABCE)



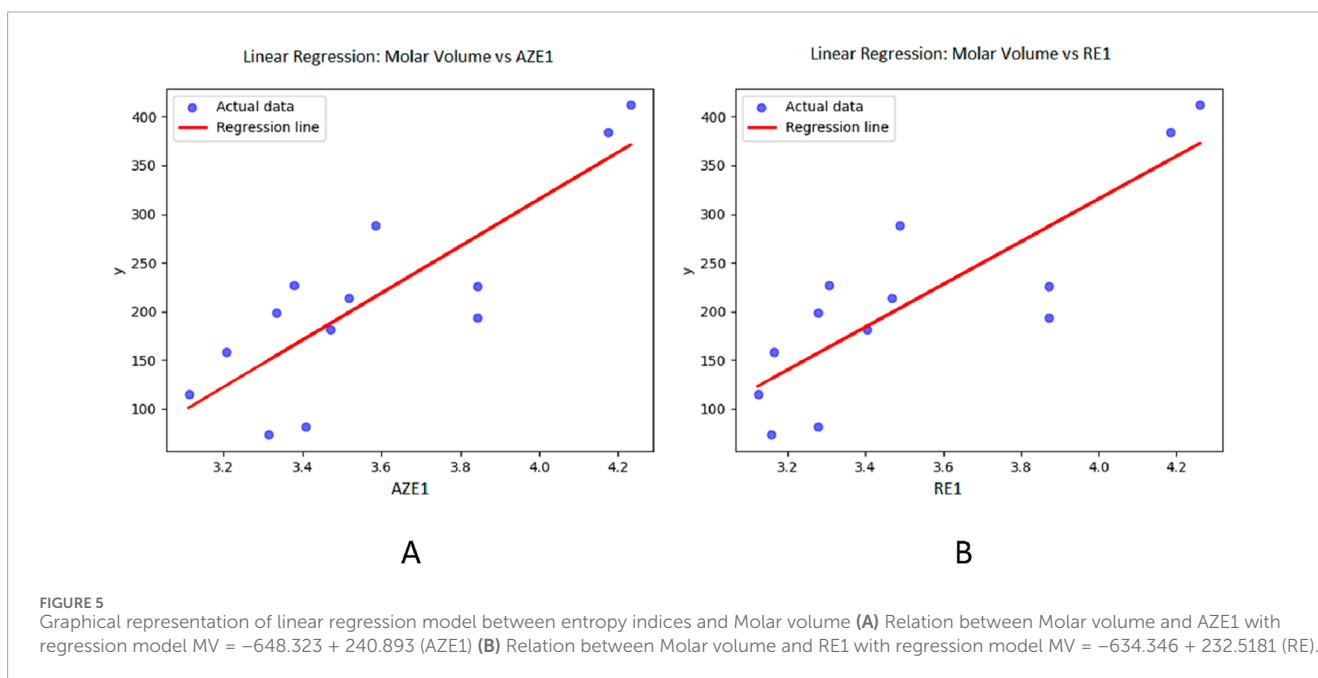
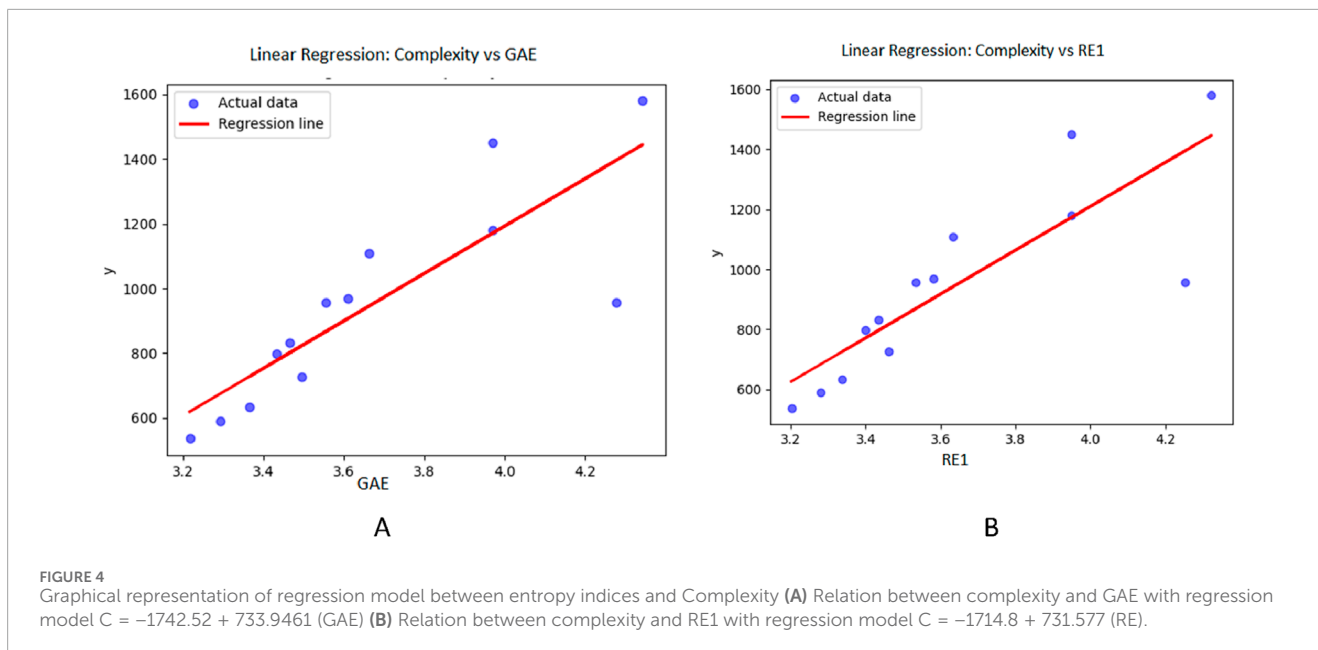
a comprehensive understanding of the relationship and the model's predictive performance.

We used SPSS software to develop the linear regression models. The physicochemical properties of the drugs were obtained from PubChem and are listed in Table 1. The entropy indices were computed using the MAPPLE-based code, and their values are shown in Table 2. Regression parameters were calculated for each case, and the results for the physicochemical properties—molecular weight, complexity, molar volume (MV), and XLogP are presented in Table 3 through 6, respectively. The regression model plots for each physicochemical property are generated against two entropy indices, illustrating their respective relationships. These plots are presented in Figures 3–6, providing a visual representation of the models and highlighting the trends and correlations observed in the data.

6 Results and discussion

The results of the linear regression analysis provide valuable insights into the relationship between the degree-based entropy indices and the physicochemical properties of the drugs used to treat Lyme disease. By examining the regression parameters, we can assess the strength and direction of these relationships, as well as the predictive capability of the entropy indices for key properties such as molecular weight, complexity, XLogP, and molar volume.

Table 3 through 6 present the linear regression models and their corresponding parameters for the selected physicochemical properties of the drugs. From Table 3, it is evident that molecular weight is best predicted by the reverse first Zagreb entropy index, yielding a high *R* value of 0.986,339 and an extremely low *P*-value of



5.77E-10, indicating a strong and statistically significant correlation. Similarly, Table 4 shows that complexity is most accurately modeled using the reverse atom bond connectivity index, with an R value of 0.838,192 and a P -value of 0.000345, reflecting a robust and significant relationship.

For molar volume, as depicted in Table 5, the reverse augmented Zagreb entropy index provides the best approximation, achieving an R value of 0.831,033 and a P -value of 0.000432, both indicative of a strong predictive model. Lastly, Table 6 demonstrates that XLogP is most effectively modeled using the reverse geometric arithmetic entropy index, with an R value of 0.844,862 and a P -value of 0.002092, suggesting a meaningful and statistically significant association. These results highlight the capability of

specific entropy indices to serve as reliable predictors for distinct physicochemical properties, underscoring their relevance in understanding molecular characteristics.

Huang et al. [50] conducted a Quantitative Structure-Property Relationship (QSPR) analysis on eleven drugs used in the treatment of Lyme disease. In their study, the authors utilized classical degree-based topological indices to construct regression models for predicting physicochemical properties. However, a comparison of their results with the findings in this study reveals that the regression parameters derived using reverse degree entropy indices are more statistically significant. Specifically, the R^2 values and P -values associated with the entropy-based models indicate stronger predictive accuracy and better fits. This

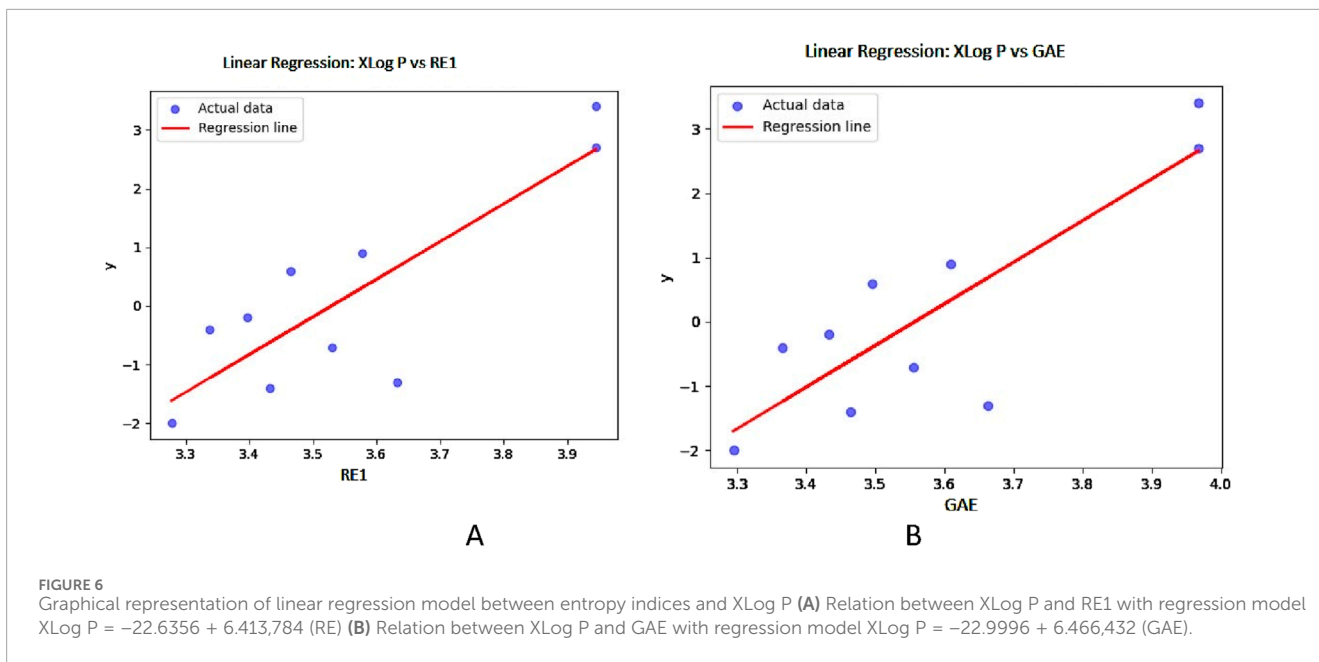


TABLE 4 Relation of entropy indices with complexity (C).

Entropy indices	MSE	R ²	Pearson R	Pearson p-value	C = a+b (Ent)
RE1	27833.37	0.701735	0.837696	0.000351	C = -1714.8 + 731.577 (RE)
GAE	27767.83	0.702437	0.838115	0.000346	C = -1742.52 + 733.9461 (GAE)
FZE1	27851.39	0.701542	0.837581	0.000352	C = -1,567.62 + 708.4912(FZE1)
SZE1	28130.35	0.698553	0.835795	0.000373	C = -1,617.66 + 718.8223(SZE1)
HZE1	27874.64	0.701293	0.837432	0.000354	C = -1,598.01 + 714.4434(HZE1)
FE	27883.85	0.701194	0.837373	0.000355	C = -1728.99 + 735.3425(FE)
AZE1	28836.4	0.690986	0.831256	0.000429	C = -1726.24 + 748.8149 (AZE1)
ABCE	27755.84	0.702566	0.838192	0.000345	C = -1746.54 + 735.3164 (ABCE)

TABLE 5 Relation of entropy indices with molar volume (MV).

Entropy indices	MSE	R ²	Pearson R	Pearson p-value	MV = a+b (Ent)
RE1	3047.649	0.684595	0.827403	0.000482	MV = -634.346 + 232.5181 (RE)
GAE	3030.781	0.686341	0.828457	0.000467	MV -643.819 + 233.4515 (GAE)
FZE1	3153.031	0.673689	0.820786	0.000585	MV = -581.285 + 223.4106(FZE1)
SZE1	3084.161	0.680816	0.825116	0.000516	MV = -603.071 + 228.3513(SZE1)
HZE1	3121.496	0.676953	0.822771	0.000552	MV = -592.952 + 225.8727(HZE1)
FE	3021.044	0.687348	0.829065	0.000459	MV = -640.893 + 234.2747(FE)
AZE1	2989.479	0.690615	0.831033	0.000432	MV = -648.323 + 240.893 (AZE1)
ABCE	3026.392	0.686795	0.828731	0.000463	MV = -645.303 + 233.9434 (ABCE)

TABLE 6 Relation of entropy indices with XLog P.

Entropy indices	MSE	R ²	Pearson R	Pearson p-value	XLog P = a+b (Ent)
RE1	0.813918	0.710391	0.842847	0.002198	XLog P = -22.6356 + 6.413,784 (RE)
GAE	0.804361	0.713791	0.844862	0.002092	XLog P = -22.9996 + 6.466,432 (GAE)
FZE1	0.852552	0.696644	0.834652	0.002665	XLog P = -20.1774 + 5.883,544(FZE1)
SZE1	0.861182	0.693573	0.83281	0.002779	XLog P = -21.2007 + 6.140,477(SZE1)
HZE1	0.852,968	0.696,496	0.834,563	0.00267	XLog P = -20.6705 + 6.000752(HZE1)
FE	0.817379	0.709159	0.842116	0.002237	XLog P = -22.9379 + 6.495,111(FE)
AZE1	0.85206	0.696819	0.834757	0.002659	XLog P = -23.7898 + 6.861,783 (AZE1)
ABCE	0.80521	0.713489	0.844683	0.002101	XLog P = -23.0617 + 6.485,612 (ABCE)

TABLE 7 Values of Entropy indices of Penicillin G Sodium and Pfizerpen.

Drug name	RE1	GAE	FZE1	SZE1	HZE1	FE	AZE1	ABCE
Penicillin G Sodium (C ₁₆ H ₁₇ N ₂ NaO ₄ S)	3.198693	3.217069	3.157207	3.154108	3.160873	3.192084	3.110868	3.214593
Pfizerpen (C ₁₆ H ₁₈ N ₂ O ₄ S)	3.198693	3.217069	3.157207	3.154108	3.160873	3.192084	3.110868	3.214593

TABLE 8 Comparison between the expected values and the experimental values.

	Molecular weight	Complexity	Molar volume	XLog P
Penicillin G Sodium				
Experimental Value	356.4	536	115.0	NaN
Predicted Value	319.232	617.203	101.06	-2.1966
Pfizerpen				
Experimental Value	334.4	530	112	1.8
Predicted Value	319.232	617.203	101.06	-2.1966

suggests that entropy indices capture molecular complexity and structural nuances more effectively than classical topological indices. Consequently, the reverse degree entropy indices provide a more robust framework for constructing regression models in QSPR analyses.

7 Validation of regression models

In this section, we validate the accuracy of the regression models by comparing the experimental values of the drugs with the predicted values obtained from the models. For this validation, we selected two drugs: Penicillin G Sodium and Pfizerpen. The corresponding entropy indices are calculated and presented in Table 7. A comparison of the experimental and predicted values is provided in Table 8. It can be observed that the

physicochemical properties, such as molecular weight and molar volume, of these two drugs are predicted with high accuracy by the regression models.

Potential sources of error in the predictions include inaccuracies in the computed entropy indices, which may arise from numerical approximations in the MAPPLE-based code or sensitivity to slight variations in molecular structure. Additionally, the regression models rely on assumptions of specific functional relationships (e.g., linear or quadratic), which may not fully capture the complexity of the underlying interactions. Experimental variability in physicochemical property data, arising from differences in measurement conditions or techniques, introduces noise that can affect model reliability. Furthermore, the relatively small dataset of thirteen drugs and limited structural diversity may hinder generalizability and increase the risk of overfitting. Addressing these challenges through incorporation of advanced models, and

expansion of the dataset can enhance the robustness and accuracy of the predictions.

8 Limitations and future directions

Despite promising results, the study has certain limitations. First, the dataset includes only thirteen drugs specifically used for Lyme disease, which restricts the generalizability of the regression models. A larger and more diverse dataset is essential to validate the methodology across different therapeutic areas. Second, the analysis focuses on a limited set of physicochemical properties. Finally, the computational workflow involves using separate software tools like MAPPLE and SPSS, which may be cumbersome for users unfamiliar with these platforms, limiting accessibility.

To improve the generalizability of the models, future studies should include a broader dataset encompassing drugs used for other diseases. Furthermore, exploring a wider range of physicochemical properties, such as solubility, lipophilicity, and drug-likeness scores, alongside additional entropy indices and other molecular descriptors, could provide a more comprehensive understanding of drug behavior. By addressing these limitations and pursuing these directions, the methodology could evolve into a versatile framework for predictive drug design, accelerating the development of safer and more effective therapeutics across diverse medical conditions.

9 Conclusion

This study explored the use of degree-based entropy indices to model and predict the physicochemical properties of thirteen drugs commonly used in the treatment of Lyme disease. Linear regression models were developed using entropy indices as independent variables and physicochemical properties, such as molecular weight, complexity, molar volume, and XLogP, as dependent variables. The results demonstrate strong and statistically significant correlations between specific entropy indices and these properties, indicating their effectiveness as predictors.

Notably, the reverse first Zagreb entropy index emerged as the best predictor for molecular weight, while the reverse atom bond connectivity index and reverse augmented Zagreb entropy index showed strong associations with complexity and molar volume, respectively. Additionally, the first Zagreb entropy index was identified as the most suitable predictor for XLogP. These findings underscore the potential of entropy indices to provide meaningful insights into molecular characteristics and their relevance to drug design and evaluation. Future work could extend these models to other classes of drugs or incorporate additional entropy indices to further enhance predictive accuracy and applicability.

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Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

GZ: Conceptualization, Investigation, Methodology, Validation, Writing—original draft. YL: Conceptualization, Investigation, Validation, Writing—review and editing. AR: Conceptualization, Methodology, Validation, Writing—review and editing. MA: Conceptualization, Investigation, Validation, Writing—original draft. PA: Conceptualization, Investigation, Validation, Writing—review and editing. AA: Conceptualization, Investigation, Methodology, Validation, Writing—original draft.

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Conflict of interest

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