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Complexity Quantification and Comparison of Two Commercially Available Anti-Coagulants

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ABSTRACT

One of the goals of contemporary AI-driven drug design is to predict physiochemical properties of molecules from their structures. Based on atomic trajectories obtained via Molecular Dynamics simulations, QCM (Quantitative Complexity Management) technology has been utilized to measure and compare the complexity of the molecules of two commercially available and widely used anti-coagulants with very similar side effects. It has been found that the dynamics of one of the two molecules to be significantly more complex. Also, the way information content is distributed in the molecules is quite different. QCM allows to measure how much information is encoded in the structure of a given molecule (small molecule drugs, proteins) as well as a measure of its structural robustness. It is hypothesized that molecular complexity may be a proxy of certain physiochemical properties of drugs, such as toxicity, helping in removal of non-promising compounds at an early stage of drug development.

Introduction

An important challenge facing the pharma industry today is the adoption of new technologies, such as Artificial Intelligence (AI), to improve and accelerate the discovery and development of new medicines. Significant improvements are expected in identifying unwanted toxic effects in early development phases, as well as reducing the late-stage failure rate. It is suggested that QCM techniques can establish proxies of certain physio-chemical properties of molecules, such as toxicity. The key characteristic of QCM is that it does not necessitate any form of learning. Therefore, it is not necessary to provide any training sets [1-4]. The advent of high speed and massively parallel computing, allows to study molecular dynamics (MD), in which the classical Newtonian equations of motion for a system are solved numerically starting from a given initial state. Molecular Dynamics simulation, which produces dynamical trajectories by using forces computed from electronic structure calculations, allows molecules to be studied in an accurate manner, providing new insights into their intricate dynamics. The present article illustrates a novel approach to classification of molecules (drugs, proteins) based on their complexity, whereby the output of an MD simulation becomes the input to the QCM which, in turn, produces complexity and robustness measures of the molecules in question.

Quantitative Complexity Theory

Complexity is a natural and physical property of every system and quantifies the amount of structured information contained therein. Conventional measures of complexity, such as Halstead complexity, cyclomatic complexity, time complexity, parametrized complexity, forecasting complexity, effective complexity, Kolmogorov complexity, a measure of algorithmic complexity, self-dissimilarity, U-rank, or entropy, are not applicable when it comes to measuring the complexity of generic physical systems, such as drug or protein molecules. A novel measure of complexity has been proposed [5] as the amount of structured information contained within a system. The complexity of a system described by vector {x} of N components is defined as follows: $C = f(S \circ E)$, where E is an $N \times N$ entropy matrix,

S represents an N × N adjacency matrix, "○" is the Hadamard matrix product operator and f is a spectral matrix norm operator. Complexity is measured in bits since entropy is measured in bits and S has no units. The adjacency matrix entries are 0 or 1, depending on the presence of interdependency between two components of {x}. The presence and intensity of interdependency between the components of {x} (so-called generalized correlation) is computed based on a proprietary algorithm which transforms scatter plots to images – Figure 1 [1]. To determine if a given image is structured – i.e., if two variables are correlated – or chaotic, images are treated using entropy-based image processing techniques. The main advantage of this approach is that it is independent of numerical conditioning of the data, presence of outliers and its ability to identify the existence of correlation structures where conventional methods fail [5].

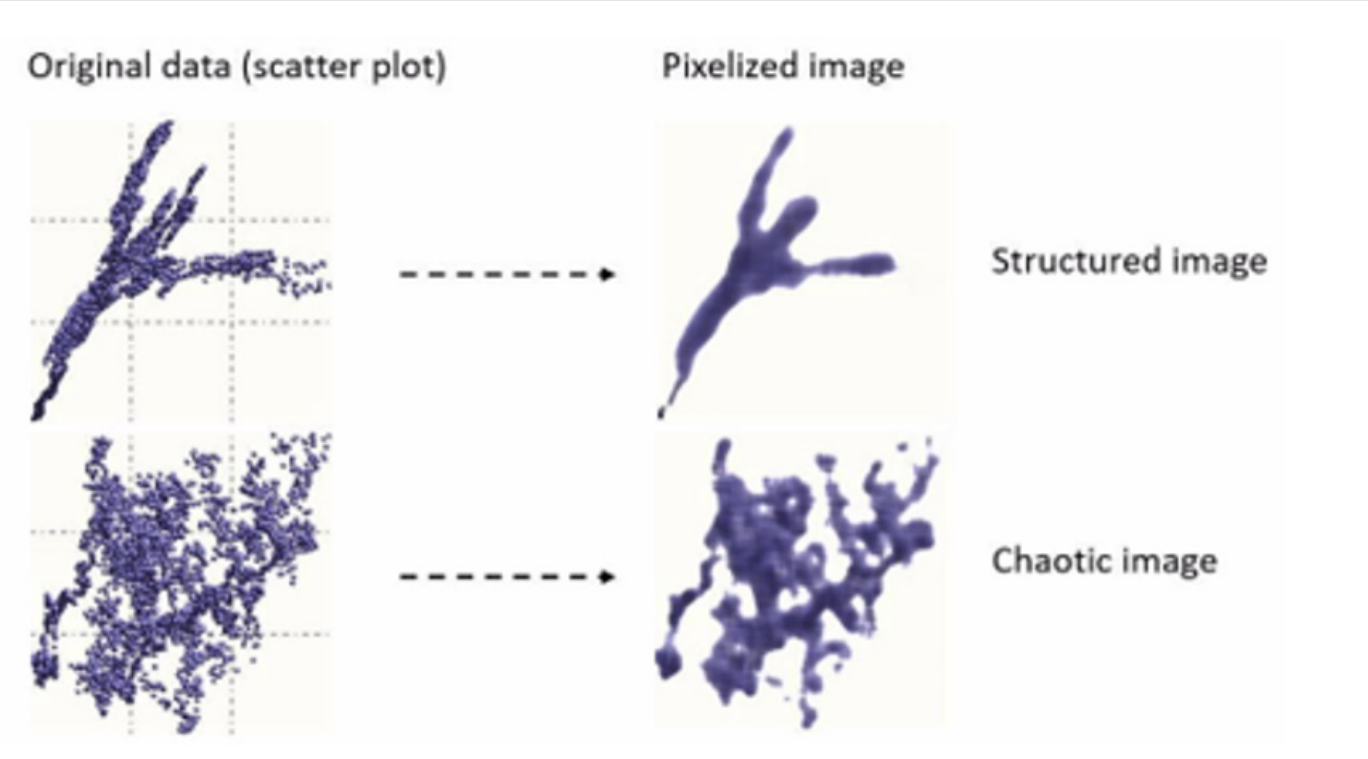

Figure 1: Examples of scatter plots and corresponding images. Images are obtained by subdividing the area of a scatter plot into pixels. The intensity of each pixel is proportional to the number of data points falling into it [1].

The complexity metric is bounded. In proximity of the lower bound, the structural component of complexity (S) dominates the dynamics of a given system, while in proximity of the upper bound – known as critical complexity – dynamics is dominated by uncertainty and is chaotic in nature. In proximity of the lower complexity bound, generalized correlations between components of {x} tend to be high, while close to critical complexity these correlations are weak, leading to a less robust structure. An example of Complexity Map, which represents the structure of interdependencies between the components of {x} at a given time (step) is shown in Figure 2. Figure 3 illustrates a Complexity Profile (or Complexity Spectrum), showing the contribution to total complexity of each variable, i.e., the vibration of each atom. Complexity is a novel descriptor of dynamical systems. It is a scalar function that combines two essential characteristics of any system (natural or manmade):

1. Structure, i.e., the topology of the flow of information within the system.
2. Disorder, which is measured via Shannon's Entropy.

Complexity provides a measure of the information encoded in the structure of a system. Physical processes involve structure-to-entropy and entropy-to-structure transformations, and complexity quantifies the amount of information involved in these interactions. The evolution of complexity over time provides new insights into the functioning of dynamical systems. For all practical purposes, the QCM formulation of complexity brings together physics and information theory in a single scalar function.

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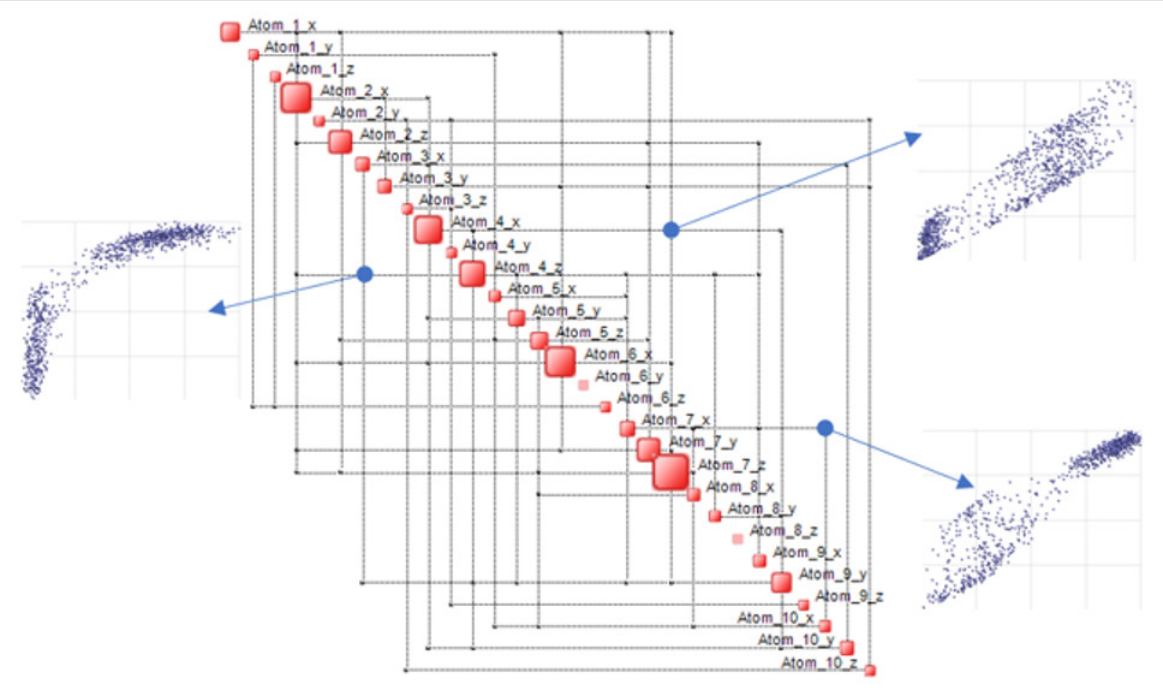

Figure 2: Example of Complexity Map of a molecules composed of ten atoms. Off-diagonal connectors (dots) represent significant interdependencies between two variables. The size of each square on the diagonal is proportional to the complexity footprint of the corresponding variable. Examples of interdependencies (see scatter plots) are shown.

Var #	Variable Name	% Contribution
21	Atom_7_z	12.38
4	Atom_2_x	10.00
16	Atom_6_x	9.98
10	Atom_4_x	8.79
12	Atom_4_z	8.17
6	Atom_2_z	6.88
20	Atom_7_y	6.80
26	Atom_9_y	5.42
1	Atom_1_x	4.61
15	Atom_5_z	4.04
14	Atom_5_y	3.21
19	Atom_7_x	2.56
7	Atom_3_x	1.94
8	Atom_3_y	1.93
29	Atom_10_y	1.92
22	Atom_8_x	1.50
25	Atom_9_x	1.28
23	Atom_8_y	0.73
28	Atom_10_x	0.72
13	Atom_5_x	0.52
30	Atom_10_z	0.05
2	Atom_1_y	0.01

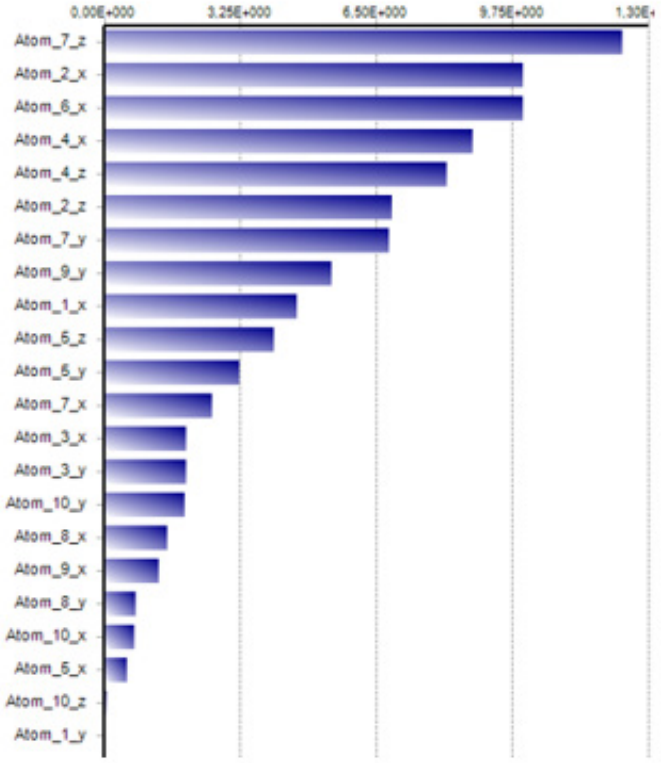

Figure 3: Complexity Profile of a molecule composed of ten atoms. In the example, the vibration of Atom7 in the z direction is responsible for 12.4% of total complexity, i.e., total encoded information.

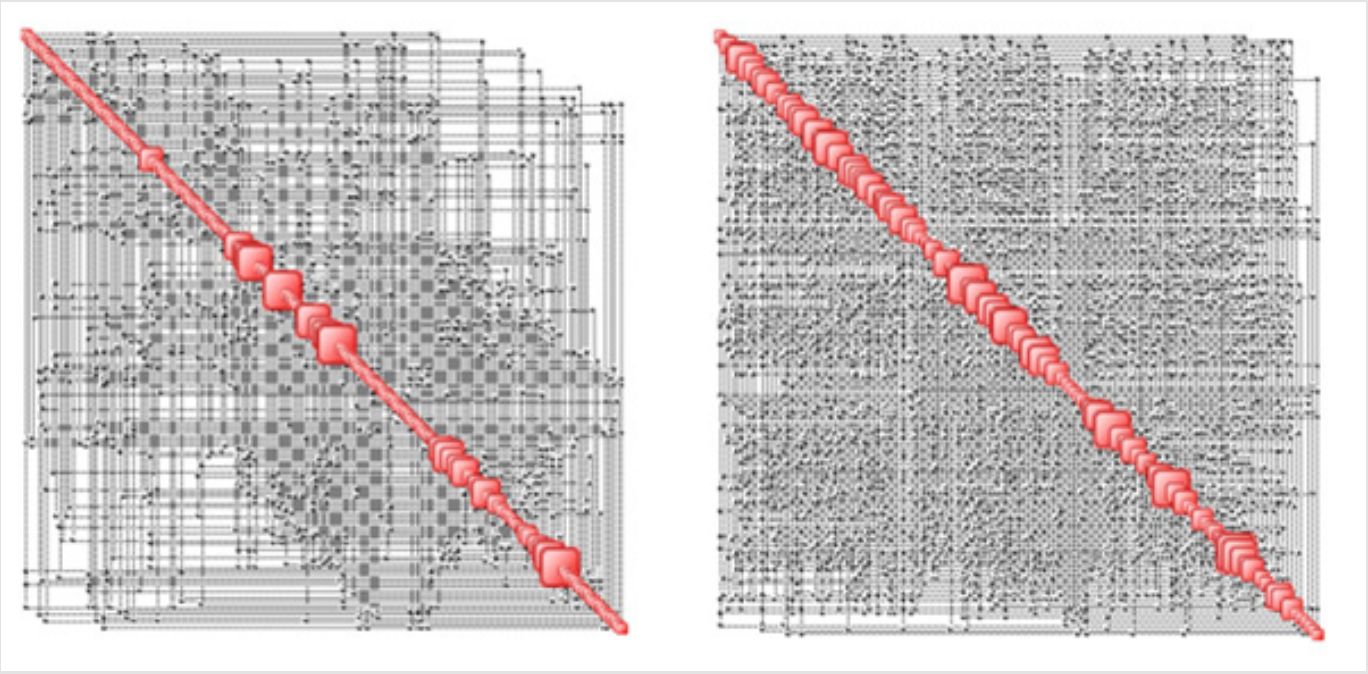

Figure 4: Complexity Maps of molecule A (left) and molecule B (Right). Knowing how the vibration of each atom is related to that of all other atoms increases the understanding of the highly intricate dynamics of a molecule.

Application to Molecular Dynamics

A QCM-based analysis of two molecules has been performed. Both are prescribed direct-acting anticoagulants (DOACs) for A-Fib patients and are produced by two major pharmaceutical companies, and both are known to have very similar side-effects. The complexity of the structural dynamics of the molecules has been measured and analysed using atomic trajectories obtained via MD simulations. Molecule A is composed of 59 atoms (C x 25, H x 24, N x 5, O x 4), leading to 59 x 3 = 177 degrees of freedom (DOFs). Molecule B is composed of 47 atoms (C x 19, H x 17, O x 5, N x 3, Cl x 1), leading to 47 x 3 = 141 degrees of freedom (DOFs). The Complexity Maps of the two molecules are illustrated in Figure 4. It is evident how the map of molecule B is far denser and that many more atoms participate in the complexity (information) makeup. In the case of molecule, A, a significantly smaller number of atoms carries the bulk of information. This is also clearly visible in the corresponding Complexity Profiles, illustrated in Figure 5. From the Complexity Profiles one may infer, for example, the following information about molecule A:

1. Hydrogen atom 18, vibration in direction z, contributes 5.7% of the of the overall complexity.
2. Carbon atom 21, vibration in direction z, contributes 5.7%
3. Carbon atom 16, vibration in direction y, contributes 5.5%
4. Carbon atom 13, vibration in direction z, contributes 4.9%
5. etc.

Similarly, in the case of molecule B:

1. Carbon atom 9, vibration in direction y, contributes 2.3% of the of the overall complexity.
2. Hydrogen atom 11, vibration in direction y, contributes 2.25%
3. Hydrogen atom 6, vibration in direction y, contributes 2.2%
4. Carbon atom 12, vibration in direction z, contributes 2.15%
5. etc.

The above information breakdown at atomic level provides a novel means of expressing the dynamics of a molecule and, consequently, may help in anticipating its physio-chemical properties. It has been found that molecule B, even though it has less atoms than molecule A (47 versus 59), is significantly more complex. The Table 1 below reports the main characteristics of both molecules. Even though complexities are significantly different, both molecules have very similar robustness, 87% and 84% respectively.

Table 1.

	Molecule A	Molecule B
No. Atoms	59	47
No. DOFs	177	141
Mean Complexity	47	105
Robustness	87	84

Conclusion

The simple experiment described herein illustrates how complexity provides a novel mechanism for the analyzing and ranking of drug molecules and may, thus, prove to be a proxy of some of their physio-chemical properties, such as toxicity. It also reveals how seemingly similar molecules may have significantly different dynamics, information content and distribution. The two molecules in question are very similar in terms of function, side effects and number of atoms, yet one is more than twice as complex as the other. This means that with all likelihood, there exist significant differences in certain properties of the said molecules outside of the domain of known side-effects. In order to determine these differences, *in-vitro* and *in-vivo* experiments may need to be performed. The conclusion of the experiment is that the combination of MD and QCM may prove to accelerate drug discovery. To further demonstrate the validity of our approach a larger number of carefully selected compounds should be investigated. Our findings should then be put in correlation with the known physiochemical properties of such compounds. For that a collaboration with an appropriate pharmaceutical company will be required.

References

1. Krzesiński P, Marczyk J, Wolszczak B, Gielerak G (2021) Quantitative Complexity Theory Used in the Prediction of Head-Up Tilt Testing Outcome. Cardiol Res Pract 23: 8882498.
2. Batchinsky AI, et al. (2010) Changes in Systems-level Complexity Precede Deterioration in Traditional Vital Signs in Hypoxic Cardiac Arrest. American Heart Association Annual Meeting.
3. Giulio Molon , Francesco Solimene, Donato Melissano, Antonio Curnis, Giuseppina Belotti, et al. (2020) Baseline heart rate variability predicts clinical events in heart failure patients implanted with cardiac resynchronization therapy: validation by means of related complexity index. Ann Noninvasive Electrocardiol 15: 301-317.
4. Giulio molon, Jacek Marczyk, Giovanni Virzi, Francesco Accardi, A Costa, et al. ECG Predicts Response to Cardiac Resynchronization Therapy. Assessment by Means of Complexity Index. 44-th National Italian Cardiology Congress, Florence.
5. Marczyk J (2009) A New Theory of Risk and Rating. Editrice Uniservice, Trento, Italy.

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J Marczyk. Biomed J Sci & Tech Res