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Letter to the Editor

QSAR - a piece of drug design

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Motto:
"I don't think people understand the revolution that is going on in medicine" -
Ewan Birney, European Bioinformatics Institute [1].

The Human Genome Project [2] (HGP) is the starting point of a chain of changes in the medical scientific world. The huge quantity of data generated by the HGP and the complexity of the tools developed for data processing challenged both medical and engineering communities. As a result of this collaboration a new scientific field was born: Bioinformatics.

Drug Design is one of the most important fields of study for Bioinformatics. The perspective of discovering new drugs based on the knowledge revealed by the human genome and the protein database focused a lot of work and new methods were developed to improve the drug design process. QSAR (Quantitative Structure-Activity Relationship) is an old method used in drug design, which benefits from the latest Bioinformatics databases and tools.

Being a new science, Bioinformatics has its own vocabulary, which is not well understood by the medical community. That is why, by this Let- ter to the Editor, I would like to introduce the beginners in the field to the concepts used in Drug Design.

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Drug design introduction

The traditional approach of drug discovery, as described in [3] involves "target identification, validation, lead search and optimization followed by clinical development phases". The costs of drug discovery process is an important factor Bioinfor-matics methods can reduce the costs by using computer analyses of drugs chemical components interactions and stability. The new technology of genome sequencing simplified the process of tar-get identification. Bioinformatics is now focused more on target validation, which is "finding a tar-get that is mostly likely to succeed" [3].

QSAR history

QSAR started back to the 19th century. In 1890's [6], when H.H. Meyer and C. E. Overton noted that the toxicity of organic components depended on their lipophilicity. In 1930's L. Hammett correlated electronic properties of organic acids and bases with their equilibrium constants and reactivity.

In 1988 R. Cramer introduced 3D - QSAR (Three-Dimensional Quantitative Structure-Activity Relationships), which "involves the analysis of the quantitative relationship between the biological activity of a set of compounds and their three-dimen-

sional properties using statistical correlation methods" [4].

Quantitative Structure-Activity Relationships (QSAR) - are mathematical relationships linking chemical structure and pharmacology activity in a quantitative manner for a series of compounds. [4]

Comparative Molecular Field Analysis (CoMFA) - is a 3D-QSAR method that uses statistical correlation techniques for the analysis of the quantitative relationship between the biological activity of a set of compounds with a specified alignment, and their three dimensional electronic and steric properties. Other properties, such H-bonding can also be incorporated into the analysis. [4]

QSAR - the math behind the drug design process

QSAR includes all statistical methods, by which "biological activities are related with structural elements (Free Wilson analysis), physiochemical properties (Hansch analysis), or fields (3D QSAR)" [5].

biological activity = f(transport + bindinig) = $- k_1(lipo)^2 + k_2(lipo) + k_3(pol) + k_4(elec) + k_5(ster) + k_6$

The molecular properties (see. Molecular Propety / Corresponding Interaction table) included in the biological activity mathematical model are:

Lipophilicity	$- k_1(lipo)^2 + k_2(lipo)$
Polarizability	$+ k_3(pol)$
Electron density	$+ k_4(elec)$
Topology	$+ k_5(ster) + k_6$

Lipophilicity and dissociation / ionization are responsible for transport and distribution of drugs in biological systems. The geometric fit and the complementary of the surface 3D properties of a ligand are responsible for its affinity to a binding site. [5]

H. Kubiny, in his Drug Design Course, associates the molecular properties to their corresponding interactions:

Molecular property	**Corresponding Interaction**
Lipophilicity	hydrophobic interactions
Polarizability	van-der-Waals interactions
Electron density	ionic bonds, dipol-dipol interactions, hydrogen bonds, charge transfer interactions
Topology	steric hindrance geometric fit

I won't go into details, all the three models: Free Wilson analysis, Hansch analysis and 3D-QSAR, have a specific statistical toolbox, which needs a mathematical background to be understood.

Classical QSAR analyses (Hansch and Free Wilson) consider only 2D structures. Their main field of application is in substituent variation of common scaffold. 3D-QSAR analysis (CoMFA) has a much broader scope. It starts from 3D structures and correlates biological activities with 3D-property fields [5].

Computer assisted drug design is just a tool

Computer-assisted Drug Design (CADD), also called Computer-assisted Molecular Design (CAMD), represents more recent applications of computers as tools in the drug design process. Any drug designed using these tools needs to be tested in labs. The knowledge accumulated in huge databases is not enough to simulate the real biological systems. There are still a lot of questions about molecular biology that needs answers. Based on these answers, the tools and the algorithms used in drug design will be improved.

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