Prediction of Fibrinogen Adsorption for the Library of Novel Biodegradable Polymers: Combined Molecular Dynamics and Surrogate Modeling Approach

Anna Gubskaya[a], Vladyslav Kholodovych[b], Loreto M. Valenzuela[c], Joachim Kohn[d], Doyle Knight[e]
[a,c,d]New Jersey Center for Biomaterials, Rutgers, The State University of New Jersey, New Brunswick, NJ 08854-8087
[b]Department of Pharmacology, University of Medicine and Dentistry of New Jersey (UMDNJ)
[e]Department of Mechanical and Aerospace Engineering, Rutgers, The State University of New Jersey, New Brunswick, NJ 08854-8058

Statement of Purpose:

The present work introduces a further development of the computational approach recently proposed by Smith and coauthors for prediction of such important types of biological phenomena as cellular response and protein adsorption on the surfaces of biomaterials [1, 2]. In previous studies connectivity-based mathematical characteristics known as "two dimensional molecular descriptors" were calculated for a set of selected biopolymers and then linked to the experimentally determined biological properties [1]. It has been shown that this strategy allows good quantitative prediction of the corresponding properties for much larger set of chemically related biopolymers, which can be represented by the whole combinatorial library. Our current investigation for the first time combines two powerful computational methods to improve the accuracy of such prediction by expanding two-dimensional (2D) to three dimensional (3D) case, more specifically, to explore as new grounds for this modeling approach the realistic conformations of the chosen polymers.

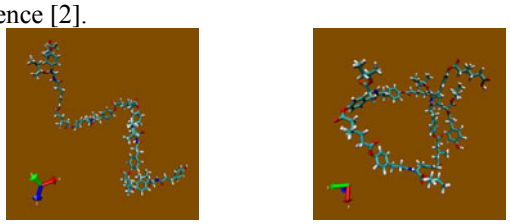
Methods:

This work focuses on 45 representatives of a combinatorial library of polyarylates for which reliable experimental data on fibrinogen adsorption were reported previously [1]. Low energy 3D structures of these selected polyarylates were obtained as a result of "deep conformational relaxation" of molecules by means of Molecular Dynamics (MD) technique. Input structures for MD runs were represented by optimized in advance three and four repeat units length polymer chains. Simulations were carried out in the presence on implicit water and in vacuum (for the purpose of comparison). Commercially available software called DRAGON by R. Todeschini and coworkers [3] was used to calculate descriptors for three levels of 3D organization: (a) raw i.e. optimized structures, (b) results of relaxation in vacuum and (c) structures obtained from calculations at ambient conditions in modeling aqueous surrounding. At the final stage Surrogate Modeling was employed for the assessment of 112 polyarylates (i.e. the entire library) in terms of their susceptibility to fibrinogen adsorption.

Results / Discussion:

At the first stage of this investigation trimers and tetramers of 45 polyarylates were build by stepwise addition of monomers followed by minimization of total structure after appending each building block. The most prominent feature observed in these structures was a difference the initial folding of the main chains associated with the presence of two chiral centers in some polyarylates. This difference can be clearly seen in Fig. 1.

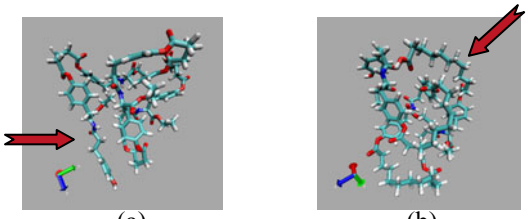
Figure 1. Enantiomers of poly (DTsB-methyl adipate) optimized in vacuum. Naming convention is given in reference [2].



(L, R) (L, L)

Molecular Dynamics simulations (up 1.5ns) demonstrated that globular-like packing pattern appears to be typical for all models. Selected configurations are shown in Fig. 2.

Figure 2. MD snapshot of DTE-glutarate (a) and DTE-dodecandioate (b) in the presence of implicit water.



(a) (b)

Despite the similarity of packing trends the final conformations obtained for 45 polymers differ noticeably in geometry and configurational energy. Specific intramolecular alignments indicated by arrows in Fig. 2 arise due to the different flexibility of diphenol and diacid components of polyarylates. Their involvement into the all kinds of intrachain interactions has also been examined. The correlations chemical structure-conformation-absorption of fibrinogen onto polymer surfaces were established and computationally justified.

Conclusions:

It was shown that three-dimensional conformations obtained from MD simulations allow determination of more physically realistic molecular descriptors that may lead to the improvement of previously obtained [1] structure-bioresponse correlations.

References:

1. Smith, J. QSAR and Combinatorial Science, 2005 (24: 99-113).
2. Smith, J. Journal of Chemical Information and Computer Science, 2004 (44: 1088-1097).
3. http://www.talete.mi.it/products/dragon_all_about.htm