Computational Modeling of Biological Responses For a Large Library of Poly(methacrylates)

Jayeeta Ghosh[1], Doyle Knight[2], Joachim Kohn[1]
[1]New Jersey Center for Biomaterials, [2]Department of Mechanical and Aerospace Engineering,
Rutgers, The State University of New Jersey, Piscataway, NJ 08854

Statement of Purpose: The objective of this research is to develop a Quantitative Structure Property Relation (QSPR) model to predict biological responses of a large library of polymers. We consider a polymethacrylate library of about 40,000 polymers. The library consists of all distinct homo-, co-, and terpolymers that can be derived from a set of 33 commercially available monomers. A small subset of about 100 polymers of the library (including homo-, co-, and terpolymers) is synthesized using a parallel automatic synthesizer. Smooth, flat surfaces are created by solvent spin casting and used to measure fibrinogen adsorption, cell attachment, and cell proliferation. These representative biological responses are then used to build and validate a computational model that attempts to predict the same biological responses across the entire library of polymethacrylates.

Methods: A rapid immuo-fluorescence assay (IFA) is used for the detection of fibrinogen adsorption onto polymer surfaces [1]. A commercially available MTS assay [2] is used to measure the metabolic activity of NIH3T3 cells that (i) initially attached to the test surfaces and (ii) proliferated during a four days culture period. Chemical structures for homopolymers are generated and energy minimized using the MOE© software package. A total of 1664 descriptors are calculated for all 33 homopolymers using the DRAGON© software. Numerical values of the descriptors for co- and terpolymers are calculated as a linear combination of their experimental homopolymer composition. A Decision Tree method is used to find the most significant descriptors. Separate Artificial Neural Network (ANN) models are developed for homo-, co- and terpolymers using all the experimental values available by back propagated ANN from the WEKA©. For homopolymers 10-fold cross validation is applied with all possible combination as the total number of data points is sparse. For co- and terpolymers the available experimental values are divided into half for training the model and half to test the model and a total 100 random sets are considered to generate the statistics. The same methodology is applied for fibrinogen adsorption, cell attachment and cell proliferation index.

Results: For fibrinogen adsorption the Pearson correlation coefficients [3] for the test sets for homo-, co- and terpolymers are 0.91, 0.66 and 0.87 respectively. We also tested the rank ordering of the polymers and found excellent agreement with experimental ranking for homopolymers and terpolymers and a moderate agreement for copolymers. We built a single model for all the homo-, co- and terpolymers and we found that the quality is compromised slightly (Pearson correlation coefficient is 0.71) but none the less very promising. The best descriptors for each set of models represent size, structure, flexibility, and electrostatics of the molecules. The figures show the predicted fibrinogen adsorption (FA) against experimental values for different sets of polymers. For cellular responses, the correlation between the structure of the polymers and the experimental values are promising but less strong. The Pearson correlation coefficients for the test set for homo-, co- and terpolymers are 0.58, 0.44 and 0.77 respectively for cell attachment and 0.51, 0.66 and 0.40 respectively for cell proliferation index. These results indicate that to find an excellent predictive capability of the cellular models we need descriptors that contain information about the cells and the surface topography.

Conclusions: It has been demonstrated that the quantitative structure property method can predict the complicated biological responses in polymeric substrates. The QSPR method developed here does not require the building of the chemical structures and descriptors for possible combination of co- and terpolymers but they are derived from their experimental composition. This is very important and a simple assumption in a sense that this can be easily adapted and extended to other formulations of the co- and terpolymers in the future if needed. The goal is to extract useful information from these sets of descriptors which are easily estimated. We are further testing our hypothesis. We also assess similarity and/or dissimilarity among the best descriptors for different models of biological responses.

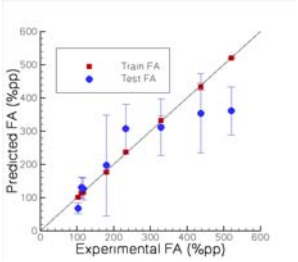

Fig 1a: Homopolymers (8 data)

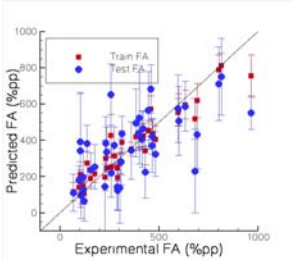

Fig 1b: Copolymers (42 data)

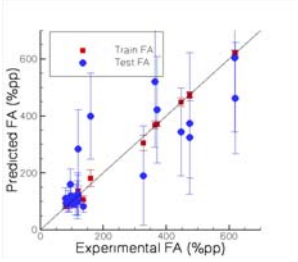

Fig 1c: Terpolymers (30 data)

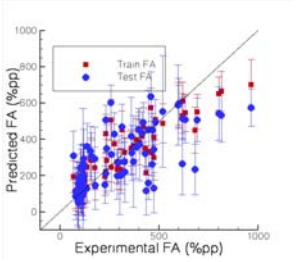

Fig 1d: All polymers together (80 data)

Figure1. Experimental vs Predicted fibrinogen adsorption

Acknowledgement: This research was supported by NIH grants RESBIO-P41 EB001046, and T32- EB005583

1. Weber N. J. Biomed. Mat. Research. 2004:68(A):496-503
2. Brocchini S. J. ACS, 1997:119:4553-4
3. Ghosh J. Polymer. To be submitted