

Computational Modeling of Bioresponse to Polymeric Biomaterials

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1st Methods in Bioengineering Conference
Massachusetts Institute of Technology

July 17, 2006



Integrated Technologies for Polymeric Biomaterials, A National Research Resource

Funded by: the National Institutes of Health, NIH NIBIB grant #P41 EB000922-01

Outline

- NIH P41 Grant Program RESBIO
- Research Team
- Research Objectives
- Computational Modeling
- Surrogate Models
- Service
- Symposia Organized
- Journal Publications



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The NIH P41 Grant Program “RESBIO”

Integrated Technologies for Polymeric Biomaterials

- **Mission**

To accelerate the discovery of polymeric biomaterials with the goal of bringing regenerative therapies and advanced drug delivery systems to the clinic

- **Methods**

Experiment

Identifying new synthetic methods to increase the number and chemical diversity of candidate polymers and devices for exploration

In situ cell profiling to enhance our understanding of cell-material interactions

Modeling

Developing computational models for the discovery of new polymeric biomaterials, and computational tools to predict the success of biomaterials in specific medical applications

- **History**

Established in April 2003 with a 5-year, \$5M NIH/NIBIB award

Will submit renewal proposal on October 1, 2006



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Research Team

Computational Modeling

- **Rutgers University**

Prof. Doyle Knight, Director, Center for Computational Design

Dr. Anna Gubskaya, Postdoctoral Associate

Ms. Deepti Pulavarthi, Graduate Research Assistant

- **University of Medicine and Dentistry**

Prof. William Welsh, Director, Informatics Institute

Dr. Vladyslav Kholodovych, Postdoctoral Associate

- **Clemson University**

Prof. Robert Latour, Director, Laboratory for Biomolecular Modeling

Dr. Yu Sun, Postdoctoral Associate

⇒ This presentation will focus on the work performed at Rutgers University and University of Medicine and Dentistry



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Research Objectives

- **Goal**

“Develop computational methods to enable design of polymeric biomaterials with specified bioresponse characteristics”

- **Approach**

Interpolation Develop modeling methods to predict bioresponse within a defined library of polymers in order to optimize polymer design for targeted applications

Extrapolation Develop modeling methods to predict bioresponse within previously undefined library of polymers to achieve new polymer designs for targeted applications

- **Methods**

Surrogate Models (e.g., Decision Tree, Artificial Neural Network, Partial Least Squares)
Molecular Dynamics (MD) simulations



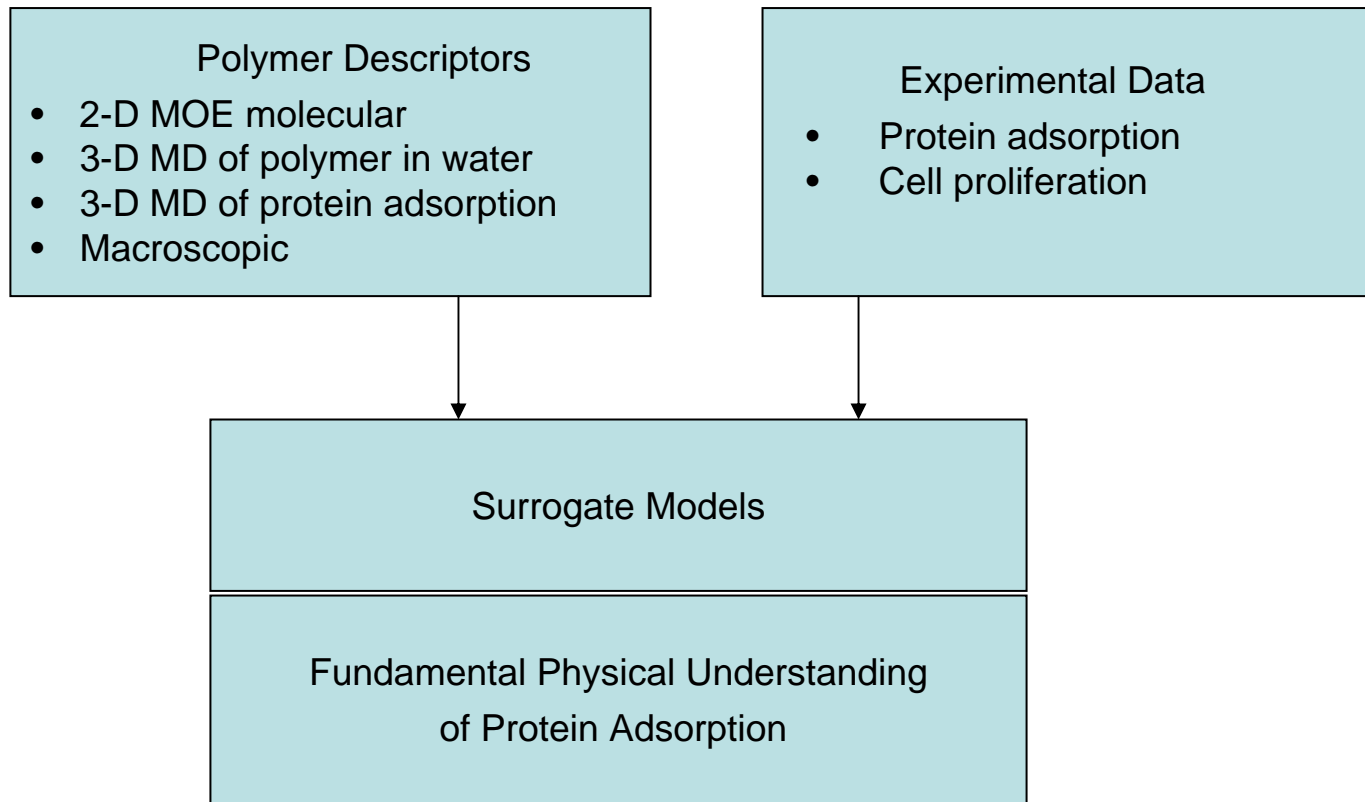
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Computational Modeling

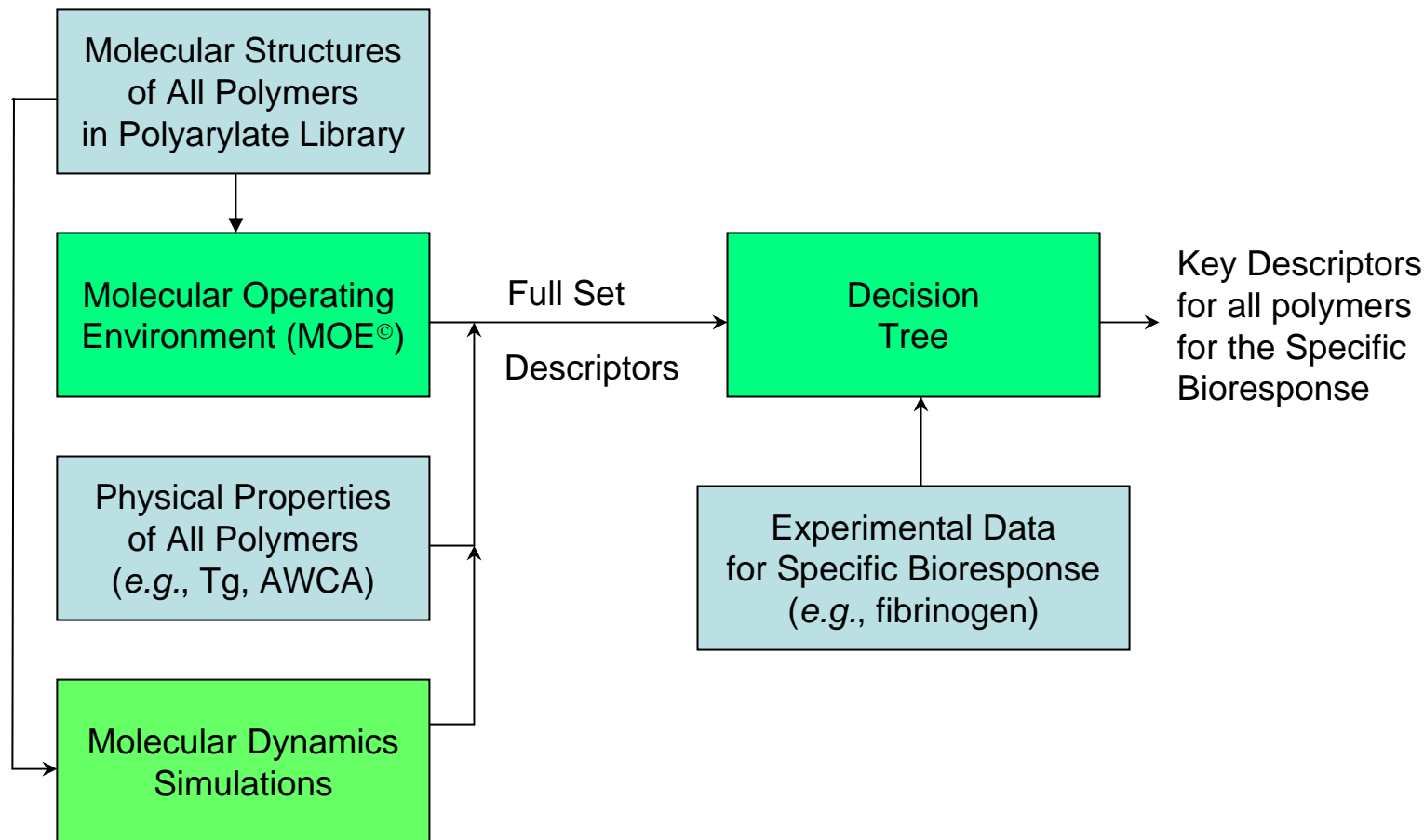
- **Surrogate Models**
 - Semi-empirical multivariate statistical correlation
 - Efficient and effective method for interpolation within polymer space
 - Variety of algorithms including Artificial Neural Networks, Polynomial Neural Networks, Support Vector Machines, Principal Component Analysis, etc
- **Molecular Dynamics**
 - Physics-based
 - Provides information on polymer 3-D conformation to Surrogate Models
 - Requires correct force field (still a research topic for polymer-protein)
 - Computationally intensive
 - Leverages extensive MD development in pharmaceutical industry

Surrogate Models



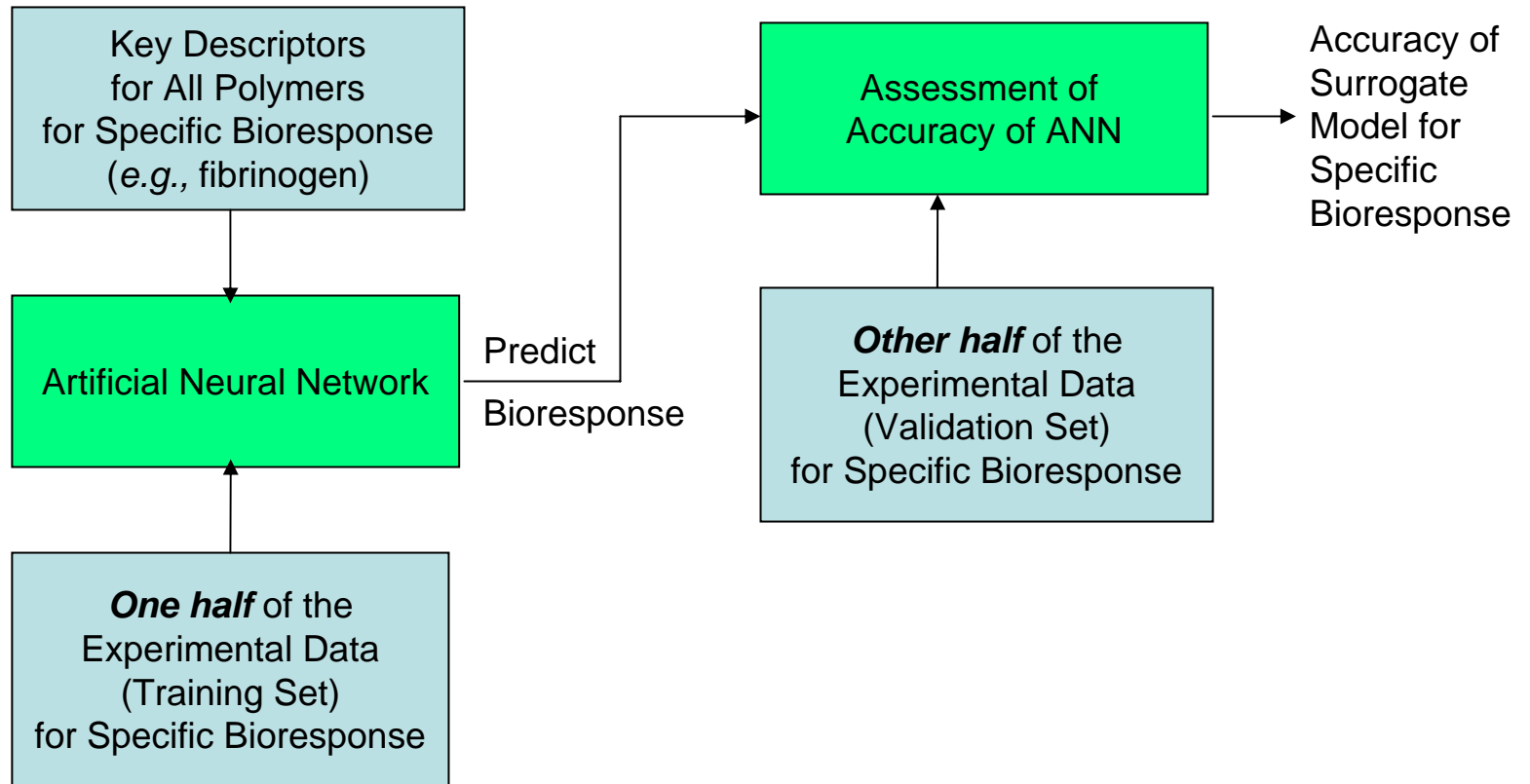
Surrogate Models

Step 1



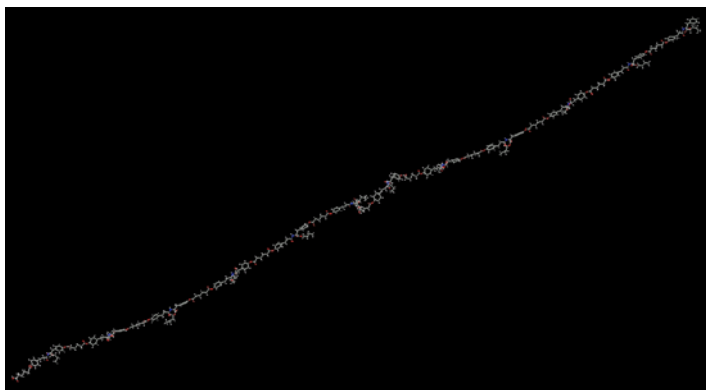
Surrogate Models

Step 2



Surrogate Models

- Examples of descriptors

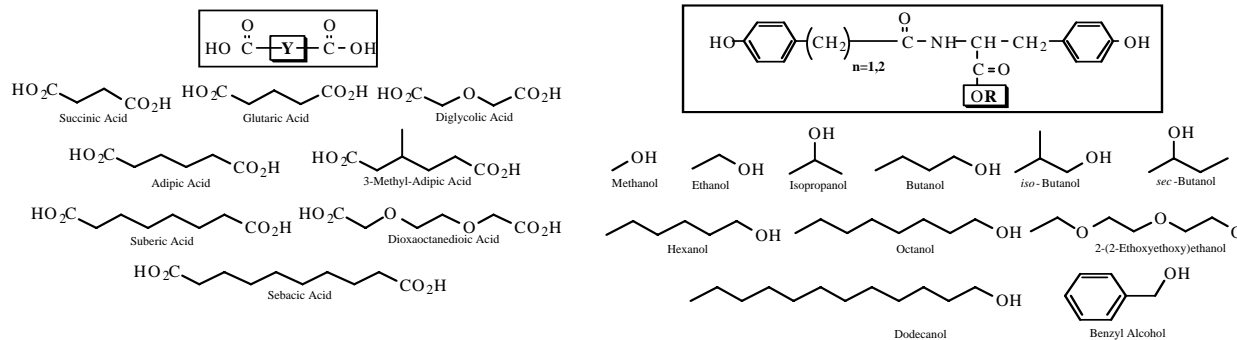
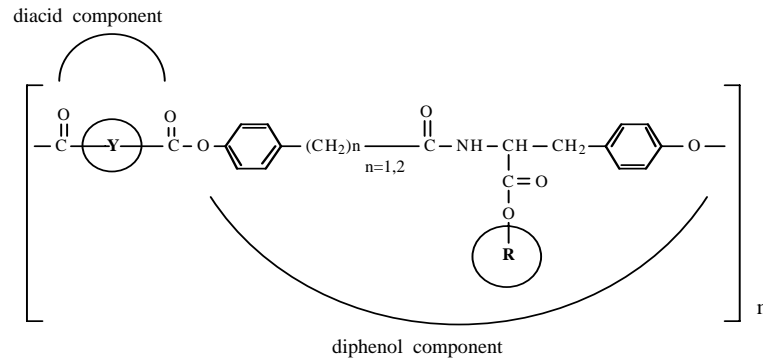


poly(DTB adipate) 12 AB segments

CODE	CLASS	DESCRIPTION
apol	2D	Sum of atomic polarizabilities
ASA	i3D	Water accessible surface area
ASA+	i3D	Positive accessible surface area
ASA-	i3D	Negative accessible surface area
ASA_H	i3D	Total hydrophobic surface area
ASA_P	i3D	Total polar surface area
a_acc	2D	Number of H-bond acceptor atoms
a_acid	2D	Number of acidic atoms
a_aro	2D	Number of aromatic atoms
a_base	2D	Number of basic atoms
a_count	2D	Number of atoms
a_don	2D	Number of H-bond donor atoms
a_heavy	2D	Number of heavy atoms
a_hyd	2D	Number of hydrophobic atoms
a_IC	2D	Atom information content (total)
a_ICM	2D	Atom information content (mean)
a_nB	2D	Number of boron atoms
a_nBr	2D	Number of bromine atoms
a_nC	2D	Number of carbon atoms
a_nCl	2D	Number of chlorine atoms

Example of Polymer Library

- Polyarylate library of 112 polymers



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Surrogate Models

Results

- Fibrinogen adsorption onto polymeric surfaces

Experimental data:

Weber, N. *et al*, “Small Changes in the Polymer Structure Influence the Adsorption Behavior of Fibrinogen on Polymer Surfaces: Validation of a New Rapid Screening Technique”, *J. Biomedical Materials Research*, 68A, 2003.

- Fetal Rat Lung Fibroblast (FRLF) proliferation on polymeric surfaces

Experimental data:

Brocchini, S. *et al*, “Structure-property Correlations in a Combinatorial Library of Degradable Biomaterials”, *J. Biomedical Materials Research*, 42, 1998.

Surrogate Models

Prediction of Fibrinogen Adsorption

- Generation of Descriptors

101 descriptors generated for polymers using MOE[®] and Dragon based on “2-D” polymer structure, plus experimentally measured glass transition temperature T_g and air-water contact angle θ

- Decision Tree

C5 Decision Tree applied to determine most significant descriptors using Monte Carlo analysis (500,000 trials) wherein experimental measurements were perturbed by normally distributed random variables based on experimental standard deviation

- Artificial Neural Network

The three most significant descriptors obtained from Decision Tree analysis used as input to the ANN.

One-half of the experimental dataset used for *training*. The remaining half of experimental dataset used for *validation*.

Monte Carlo analysis (100 trials) to assess effect of experimental uncertainty.



Surrogate Models

Prediction of Fibrinogen Adsorption

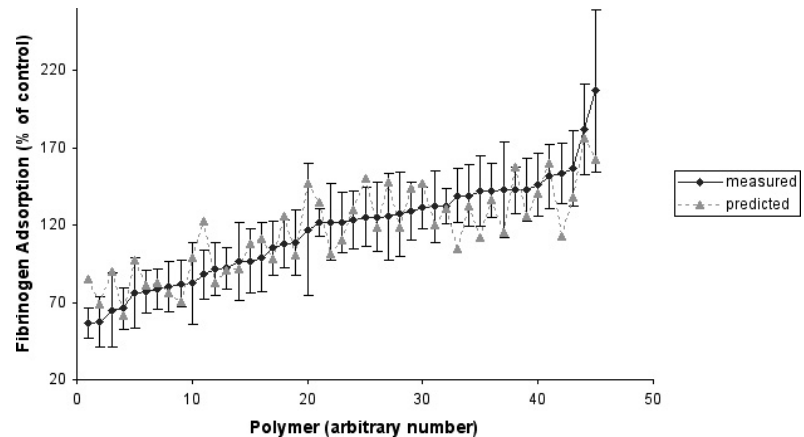
- Fibrinogen adsorption correctly predicted for 38 of 45 polymers (*i.e.*, within experimental uncertainty)
- Average rms percent error in prediction of *validation* set is 35%
- Most significant descriptors

T_g : glass transition temperature

a_nH: number of hydrogen atoms in the molecule

logP(o/w): logarithm of the octanol/water partition coefficient

Smith, J., Seyda, A., Weber, N., Knight, D., Abramson, S., and Kohn, J., *Macromolecular Rapid Communications*, Vol. 25, 2004, pp. 127-140.



Surrogate Models

Prediction of Rat Lung Fibroblast Proliferation

- Generation of Descriptors

101 descriptors generated for polymers using MOE[®] and Dragon based on “2-D” polymer structure, plus experimentally measured glass transition temperature T_g and air-water contact angle θ

- Decision Tree

C5 Decision Tree applied to determine most significant descriptors using Monte Carlo analysis (500,000 trials) wherein experimental measurements were perturbed by normally distributed random variables based on experimental standard deviation

- Artificial Neural Network

The three most significant descriptors obtained from Decision Tree analysis used as input to the ANN.

One-half of the experimental dataset used for *training*. The remaining half of the experimental dataset used for *validation*.

Monte Carlo analysis (100 trials) to assess effect of experimental uncertainty.



Surrogate Models

Prediction of Rat Lung Fibroblast Proliferation

- RLF proliferation correctly predicted for 41 of 48 polymers (*i.e.*, within experimental uncertainty)
- Average rms percent error in prediction of *validation* set is 28%
- Most significant descriptors

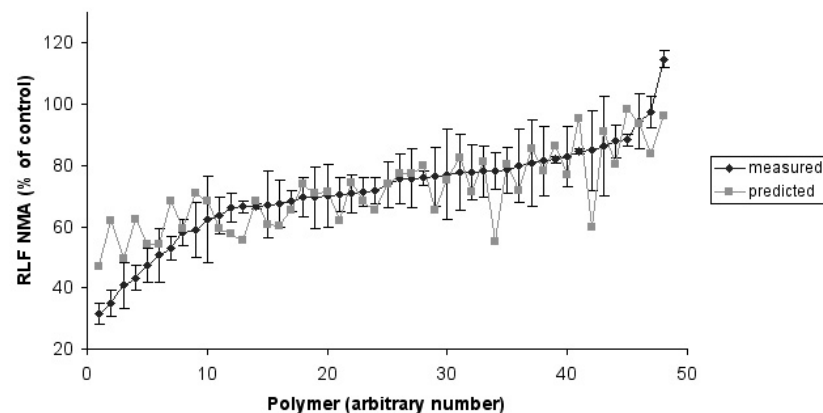
SlogP_VSA9: Van der Waals surface area
 $\log P(o/w) > 0.4$

hydrophilic_factor: number of hydrophilic groups

SlogP_VSA5: Van der Walls surface area

$0.15 < \log P(o/w) < 0.2$

Smith, J., Seyda, A., Weber, N., Knight, D., Abramson, S., and Kohn, J., *Macromolecular Rapid Communications*, Vol. 25, 2004, pp. 127-140.



Surrogate Models

Description of Decision Tree

- The range of the *target attribute* (e.g., fibrinogen adsorption) is divided into m bins and each polymer is assigned a value in the range from 1 to m based upon its value of fibrinogen adsorption

Since the average experimental uncertainty for fibrinogen adsorption was 17.8%, the value $n = 5$ was chosen (*i.e.*, each bin covered 20% of the experimental data range)

- The *entropy* of the entire experimental dataset S with respect to the *target attribute* is calculated

$$\text{entropy}(S) = - \sum_{i=1}^{i=m} p_i \log_2 p_i \quad \text{where } p_i \text{ is the fraction of the dataset } S \text{ in bin } i$$

Surrogate Models

Description of Decision Tree

- The experimental dataset is divided into subsets S_j corresponding to the different values of the *classifying attribute* (e.g., T_g)

- The *entropy* each subset S_j with respect to the *target attribute* is

$$\text{entropy}(S_j) = - \sum_{i=1}^{i=m} p_i \log_2 p_i \quad \text{where } p_i \text{ is the fraction of the dataset } S_j \text{ in bin } i$$

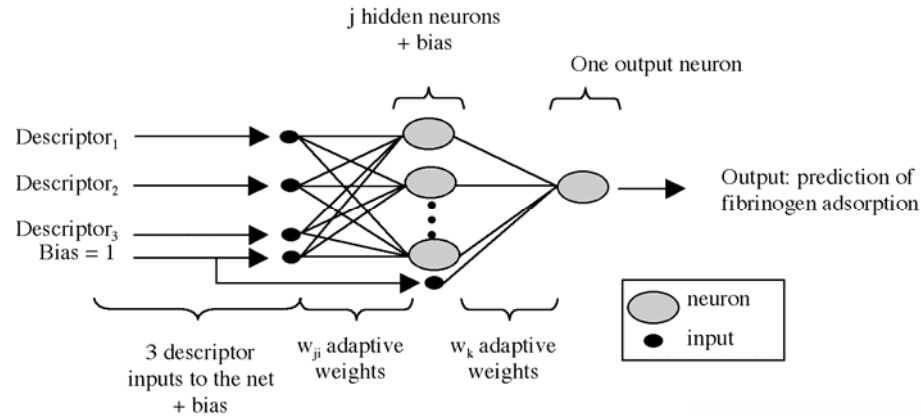
- The *information gain* associated with the *classifying attribute* is

$$\text{information gain} = \text{entropy}(S) - \sum_j p_j \text{entropy}(S_j)$$

where p_j is the fraction of the experimental dataset in subset S_j

Surrogate Models

Description of Artificial Neural Network



- Input layer vector of descriptors for k^{th} polymer
- Hidden layer vector for k^{th} polymer
- Determination of hidden layer vector
- Weights for input layer vector

$$\vec{x}_k = (x_{o_k}, x_{1_k}, \dots, x_{m_k})$$

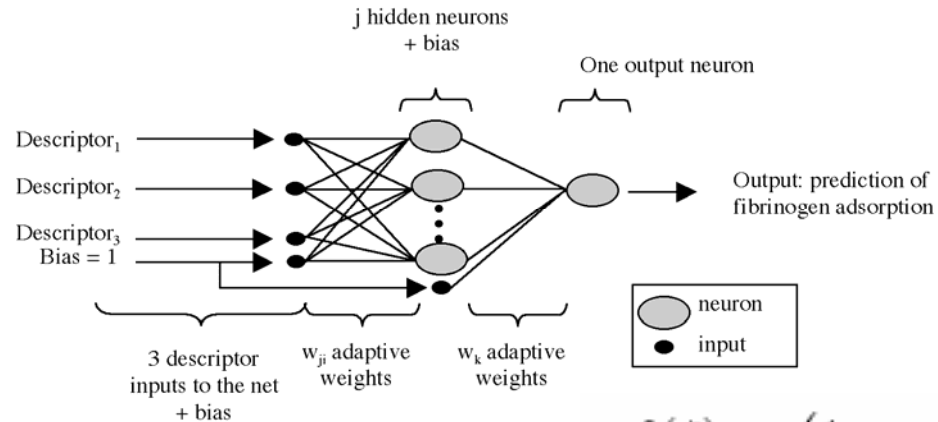
$$\vec{y}_k = (y_{o_k}, y_{1_k}, \dots, y_{n_k})$$

$$y_{j_k} = f \left(\sum_{i=0}^{i=m} w_{j,i}^o x_{i_k} \right)$$

$$w_j^o = (w_{j,o}^o, w_{j,1}^o, \dots, w_{j,m}^o)$$

Surrogate Models

Description of Artificial Neural Network



- Sigmoid function
- Output
- Weights for hidden layer vector
- Error minimized using Genetic Algorithm

$$f(\xi) = (1 + e^{-\kappa\xi})^{-1}$$

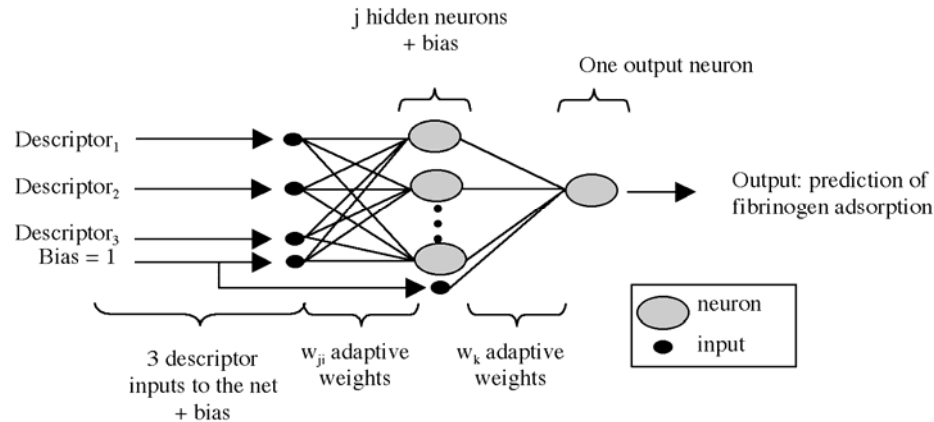
$$z_k = \sum_{j=0}^{j=n} w_j^1 y_{jk}$$

$$\vec{w}^1 = (w_o^1, w_1^1, \dots, w_n^1)$$

$$E = \frac{1}{2} \sum_{k=0}^{s_t-1} (z_k - \hat{z}_k)^2$$

Surrogate Models

Description of Artificial Neural Network



- The user must select the following parameters

Number of descriptors m

Number of hidden neurons n

Scaling factor in sigmoid function κ

- Our experience shows that the accuracy of the ANN is insensitive to the choice of these parameters over a significant range of values

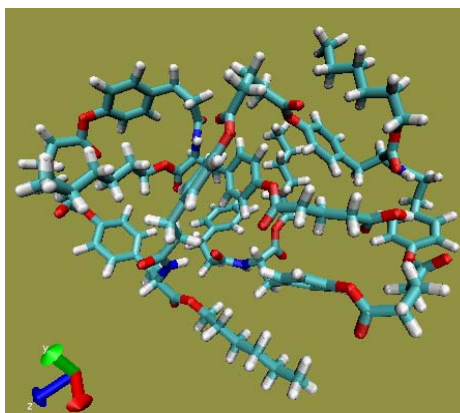
Current Research

Prediction of Fibrinogen Adsorption Using Results of MD Simulations

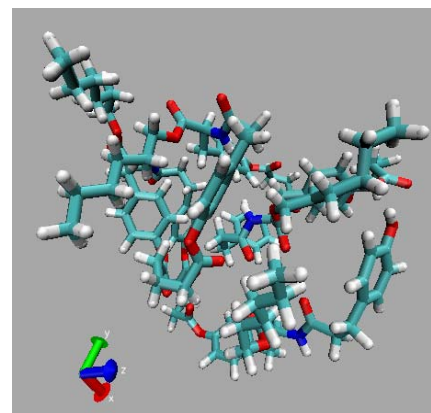
- Build, optimize, and carry out MD simulations (in vacuum and implicit water) for 45 representatives of polyarylate library
- Calculate descriptors based upon 3D conformations
- Predict fibrinogen adsorption by means of Surrogate Modeling
- Compare the quality of prediction based on 2D and 3D descriptors

Poly(DTH glutarate)

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.



After minimization



In implicit water

In vacuo

Service

The Biomaterials Store™

- Interactive, web-based user environment written in Java
- User specifies desired properties of biodegradable implant for specific clinical application
- Archived experimental data plus user-supplied experimental data utilized to build Surrogate Model of bioresponse



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Service

The Biomaterials Store™

[Home](#)[Modeling](#)[Experiment](#)[User Profile](#)[Help](#)[Logout](#)

Welcome to the Biomaterials store!



This is an interactive web-based user environment, where you can describe the desired properties of biodegradable implants for specific clinical applications. We will build a surrogate model using your described data and the archived experimental data.

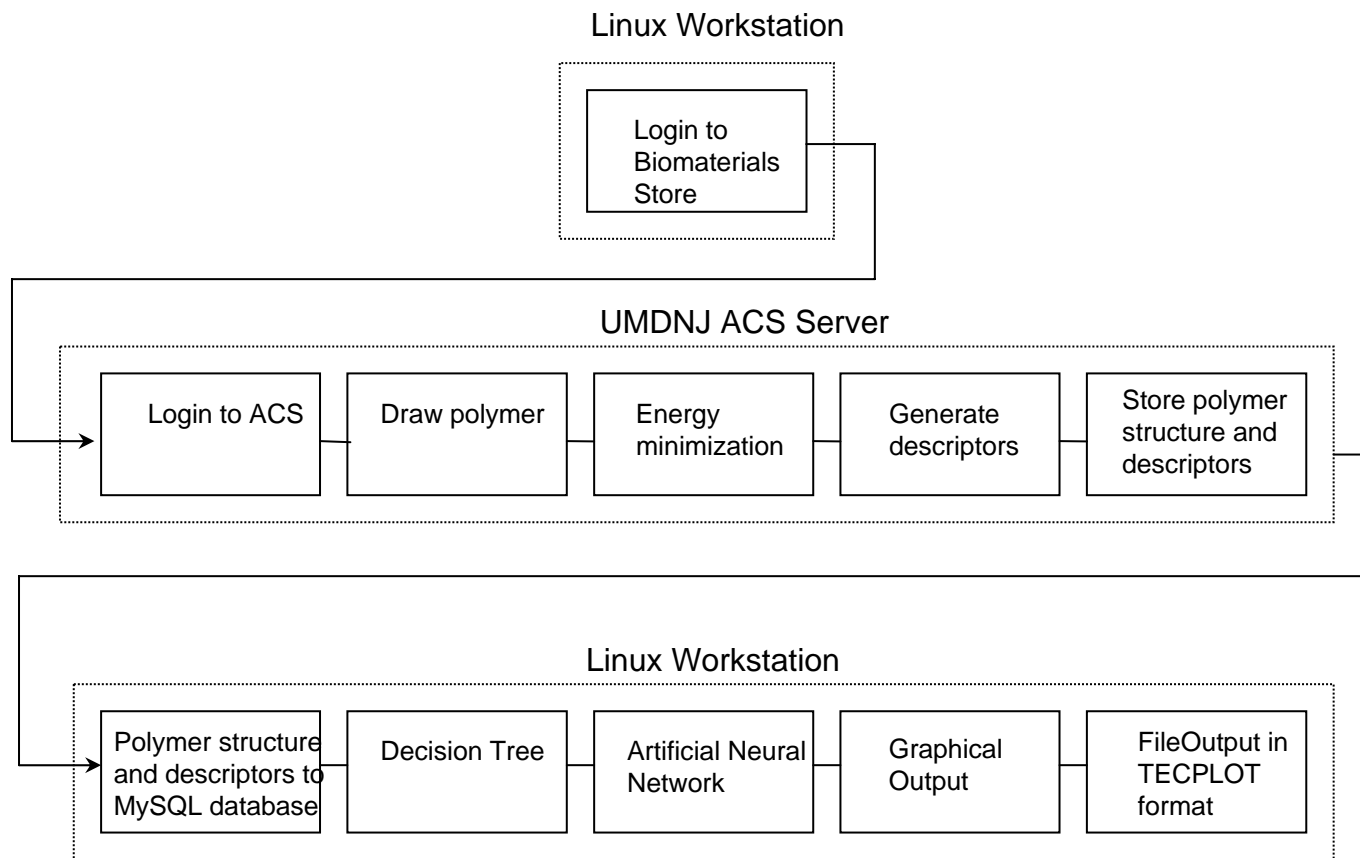


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Service

The Biomaterials Store™



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Symposia Organized

- RESBIO has organized symposia on computational modeling:
 - “Combinatorial and Computational Modeling Approaches to Biomaterials Design”, 7th World Biomaterials Congress, Sydney, Australia, 2004
 - “Combinatorial and Computational Methods in Biomaterials Development”, 7th NJ Symposium on Biomaterials Science, New Brunswick, NJ, 2004
 - “Computational Modeling of Bioresponse to Biomaterials”, Society for Biomaterials Annual Meeting, Memphis, TN, 2005
 - “Modeling Bioresponse to Biomaterials”, Society for Biomaterials Annual Meeting, Pittsburgh, PA, 2006
 - “High Throughput/Computational Modeling”, 8th NJ Symposium on Biomaterials Science, New Brunswick, NJ, 2006



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Journal Papers

Smith, J., Seyda, A., Weber, N., Knight, D., Abramson, S. and Kohn, J., "Integration of Combinatorial Synthesis, Rapid Screening and Computational Modeling in Biomaterials Development", *Macromolecular Rapid Communications*, Vol. 25, 2004, pp. 127-140.

Smith, J., Knight, D., Kohn, J., Rasheed, K., Weber, N., Kholodovych, V. and Welsh, W., "Using Surrogate Modeling in the Prediction of Fibrinogen Adsorption onto Polymer Surfaces", *Journal of Chemical Information and Computer Science*, Vol. 44, 2004, pp. 1088-1097.

Kholodovych, V., Smith, J., Knight, D., Abramson, S., Kohn, J. and Welsh, W., "Accurate Predictions of Cellular Response Using QSPR: A Feasibility Test of Rational Design of Polymeric Biomaterials", *Polymer*, Vol. 45, 2004, pp. 7367-7369.

Smith, J., Kholodovych, V., Knight, D., Kohn, J. and Welsh, W., "Predicting Fibrinogen Adsorption to Polymeric Surfaces *In Silico*: A Combined Method Approach", accepted for publication in *Polymer*.

Smith, J., Kholodovych, V., Knight, D., Welsh, W. and Kohn, J., "QSAR Models for the Analysis of Bioresponse Data from Combinatorial Libraries of Biomaterials", *QSAR and Combinatorial Science*, Vol. 24, 2005, pp. 99-113.



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