Multiscale machine learning approach to modeling structure-property relationships of polybetaines

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Presented at 2022 ACS Fall Meeting
for the Division of Chemical Information, August 25th, 2022

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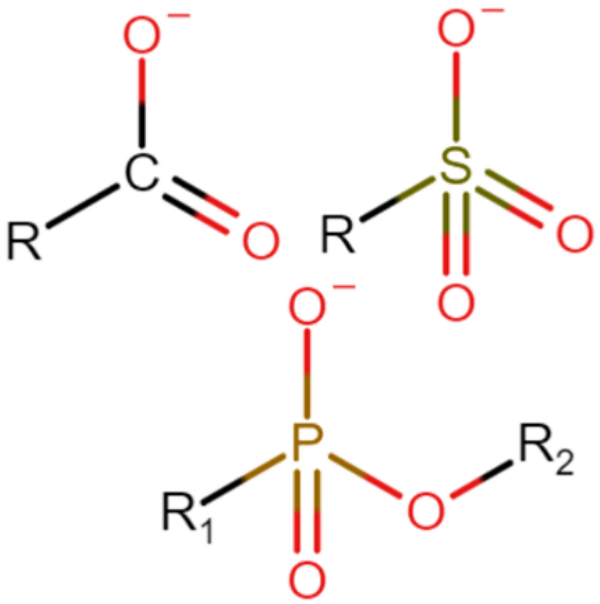
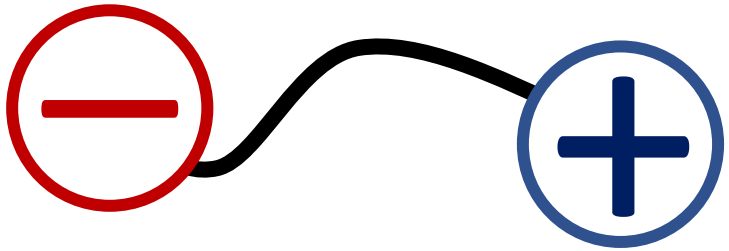
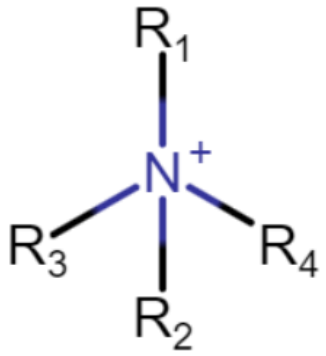
Betaine chemistry



Oppositely charged ionic groups



Covalently linked by non-ionic intermediates



Notable properties

- Frequently resistant to protein adsorption and biofouling
- Enhance dissociation of co-ions in electrolyte solutions
- Switchable properties
- Easy to functionalize and flexible design

Poly(Ionic Liquid) Batteries

Marine vessel paints and coatings

Coatings for biomedical implants

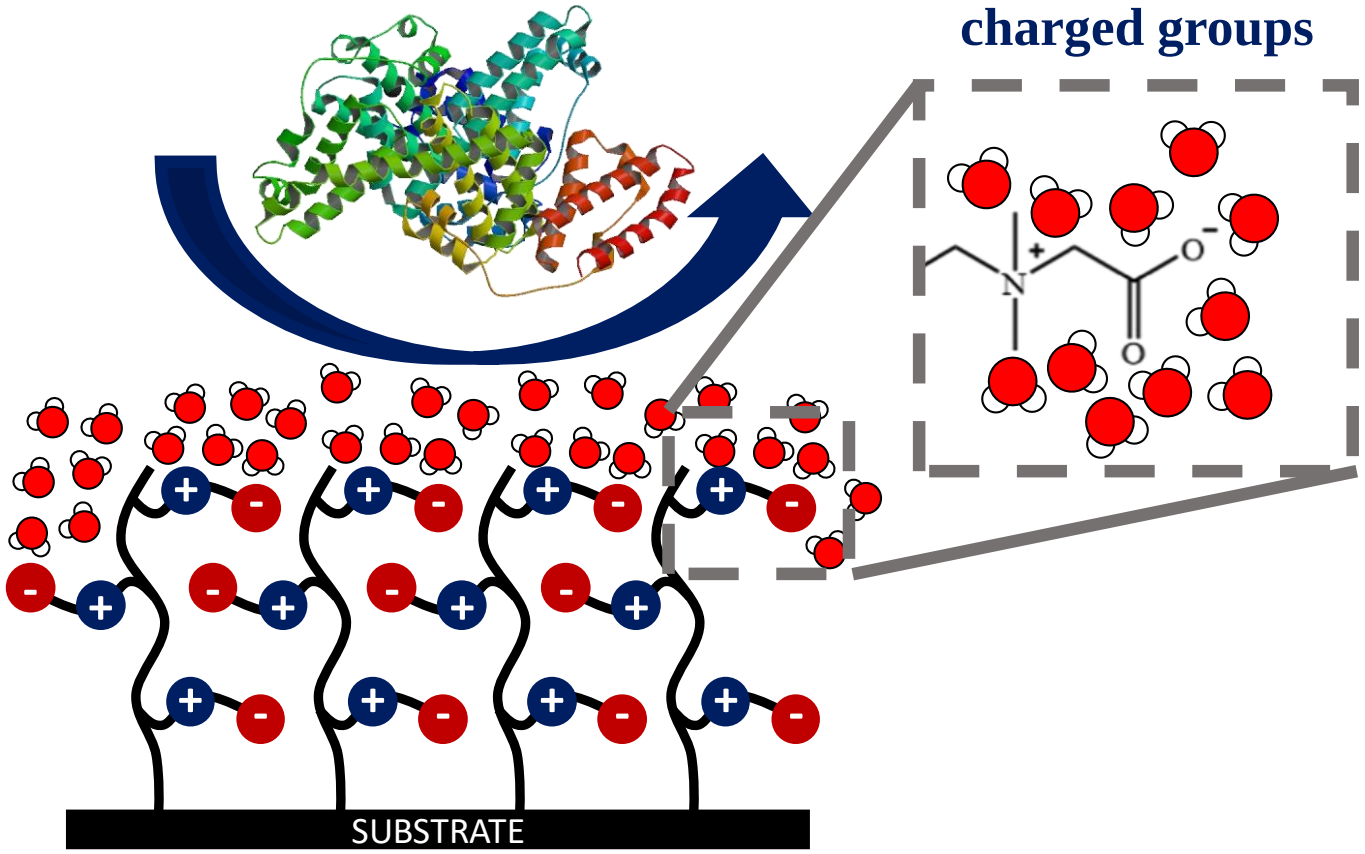
Drug delivery

Tiyapiboonchaiya *nature materials* 2003
Cheng *Angew. Chem. Intl. Ed.* 2008
Racovita *Int. J. Mol. Sci.* 2021

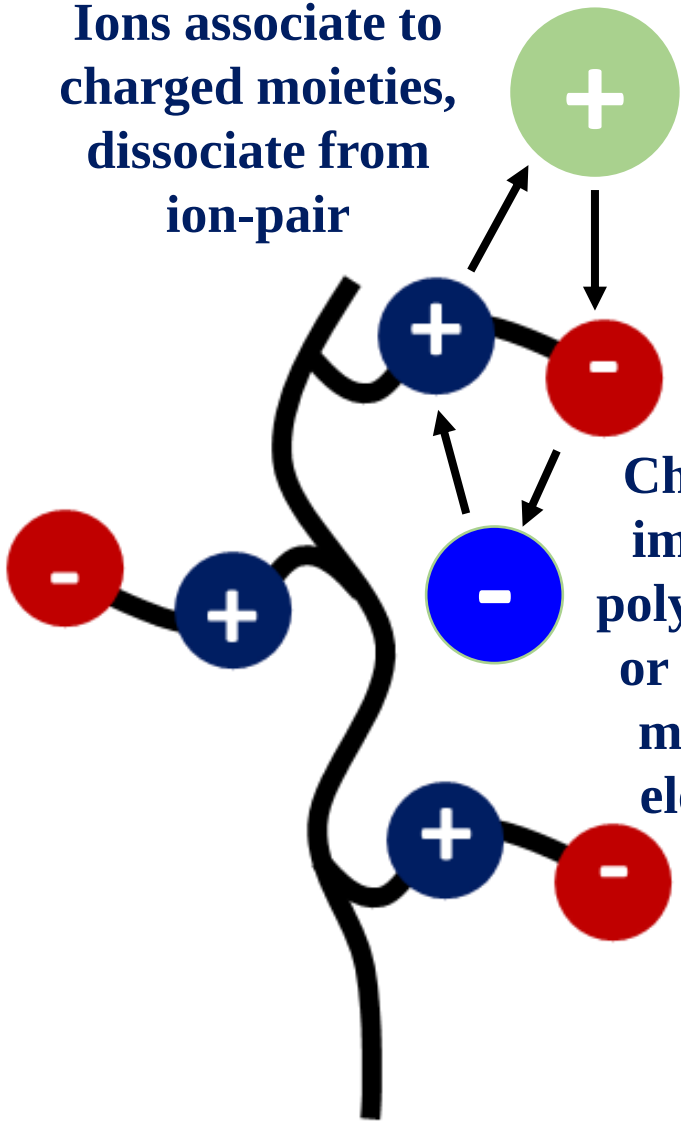
Polybetaine properties enabled by hydration and ion association

Fouling resistant or preventative

Tight hydration layer from association to charged groups



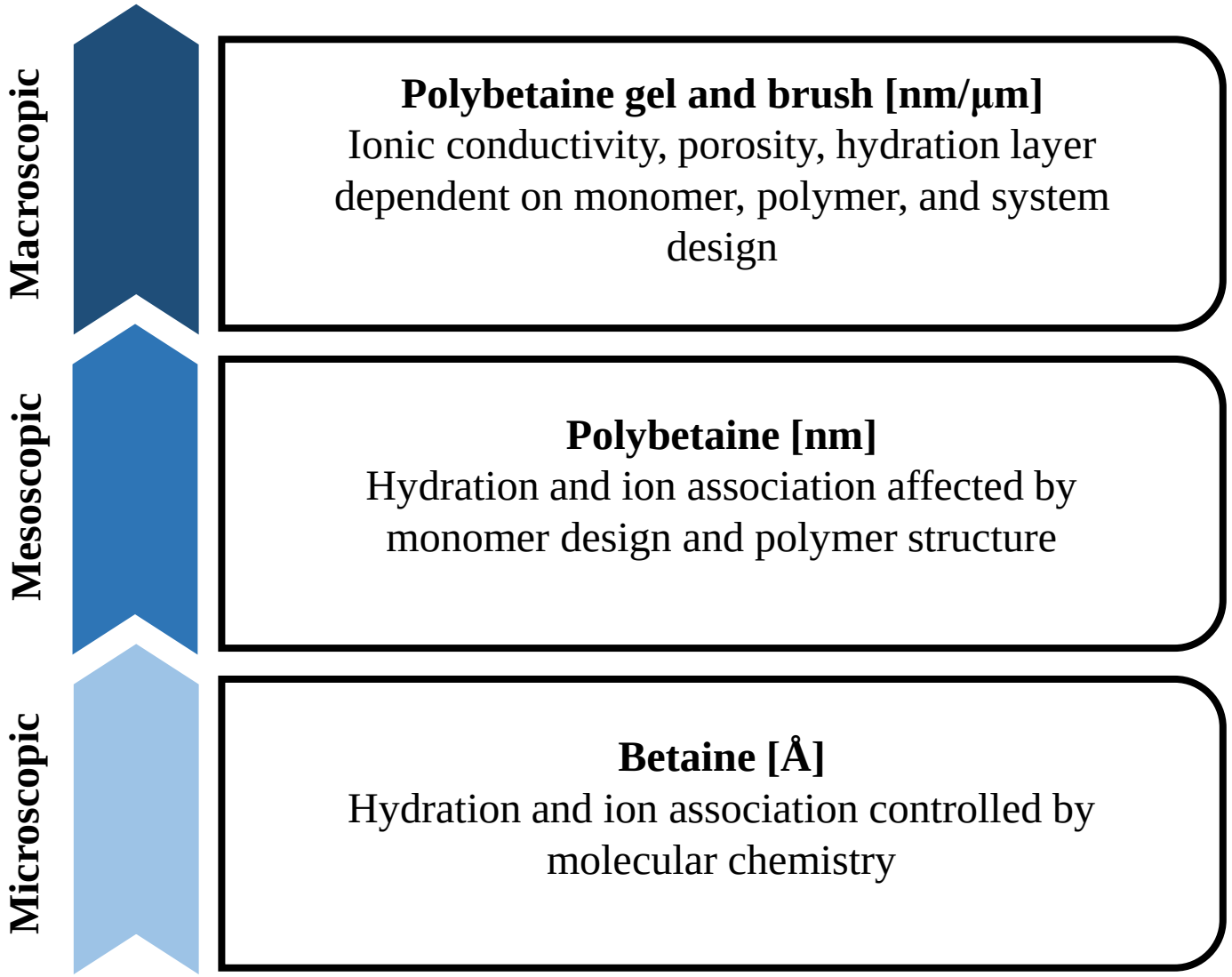
Ions associate to charged moieties, dissociate from ion-pair



Charged groups immobilized by polymer backbone or approx. equal mobility under electronic field

Tiyapiboonchaiya *nature materials* 2003
Cheng *Angew. Chem. Intl. Ed.* 2008

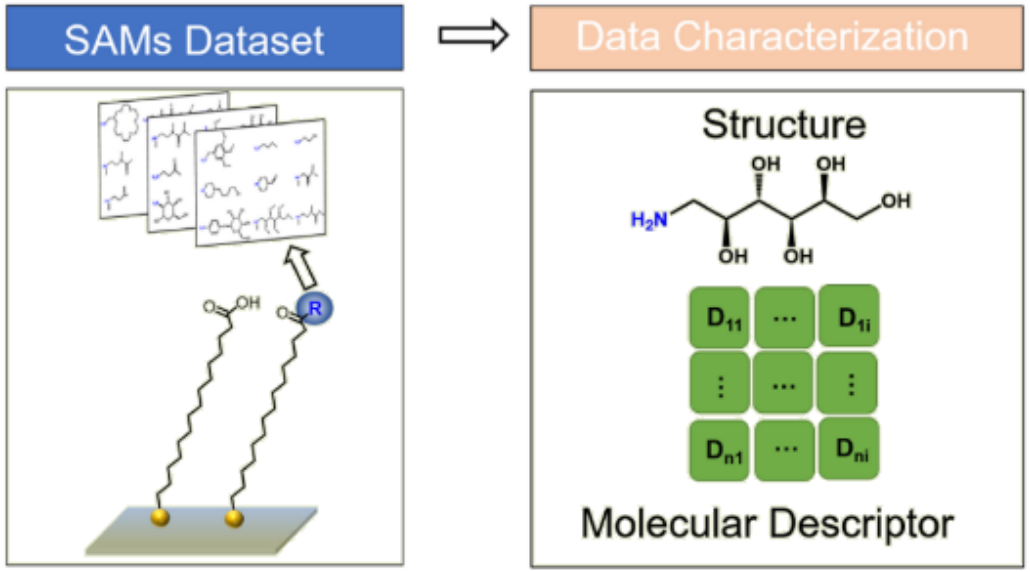
Hierarchy of polybetaine material design



Research question

How do molecular and polymeric design affect the ionic conductivity of polybetaine gels?

ML to understand protein adsorption on hydrophilic and polybetaine self-assembled monolayers (SAMs)



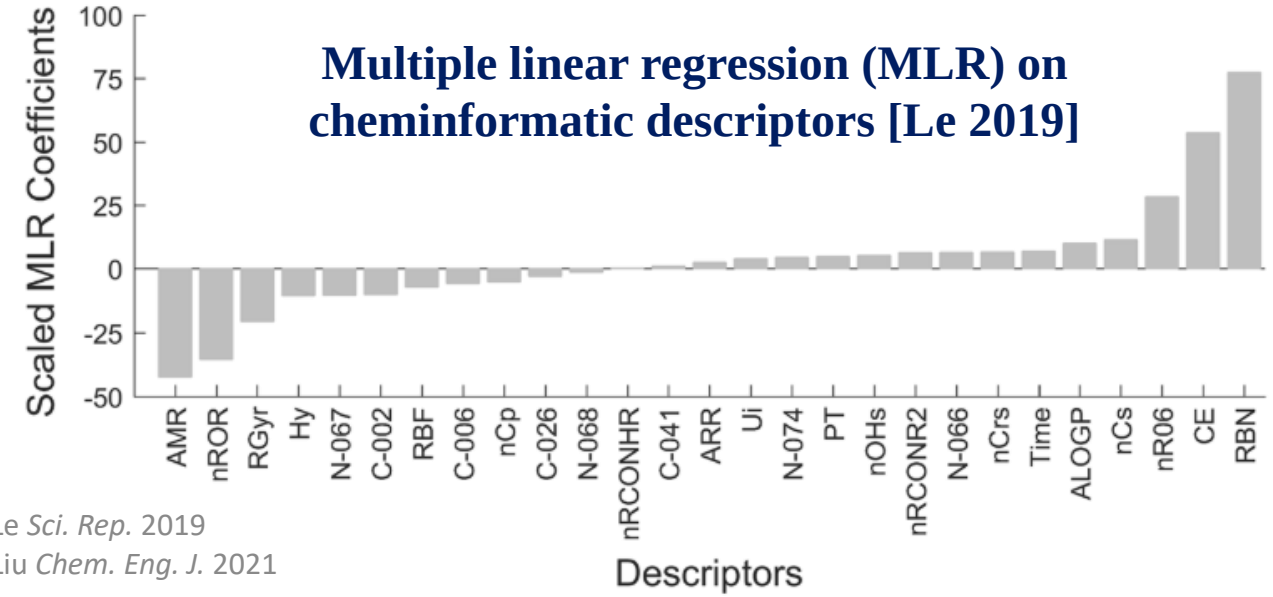
Additional Whitesides' rule found by Le et al.:

(i) polar functional groups and hydrogen bond acceptor groups

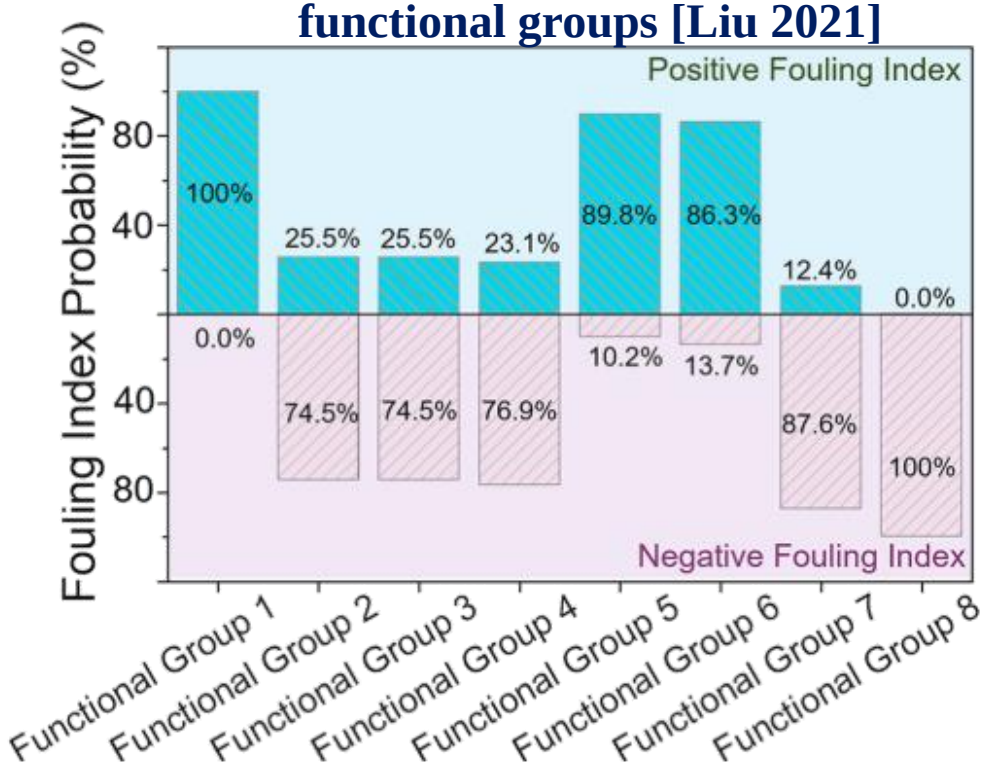
(ii) no hydrogen bond donor groups or net charges

(iii) relatively large, conformationally mobile and polarizable functional groups

Multiple linear regression (MLR) on cheminformatic descriptors [Le 2019]

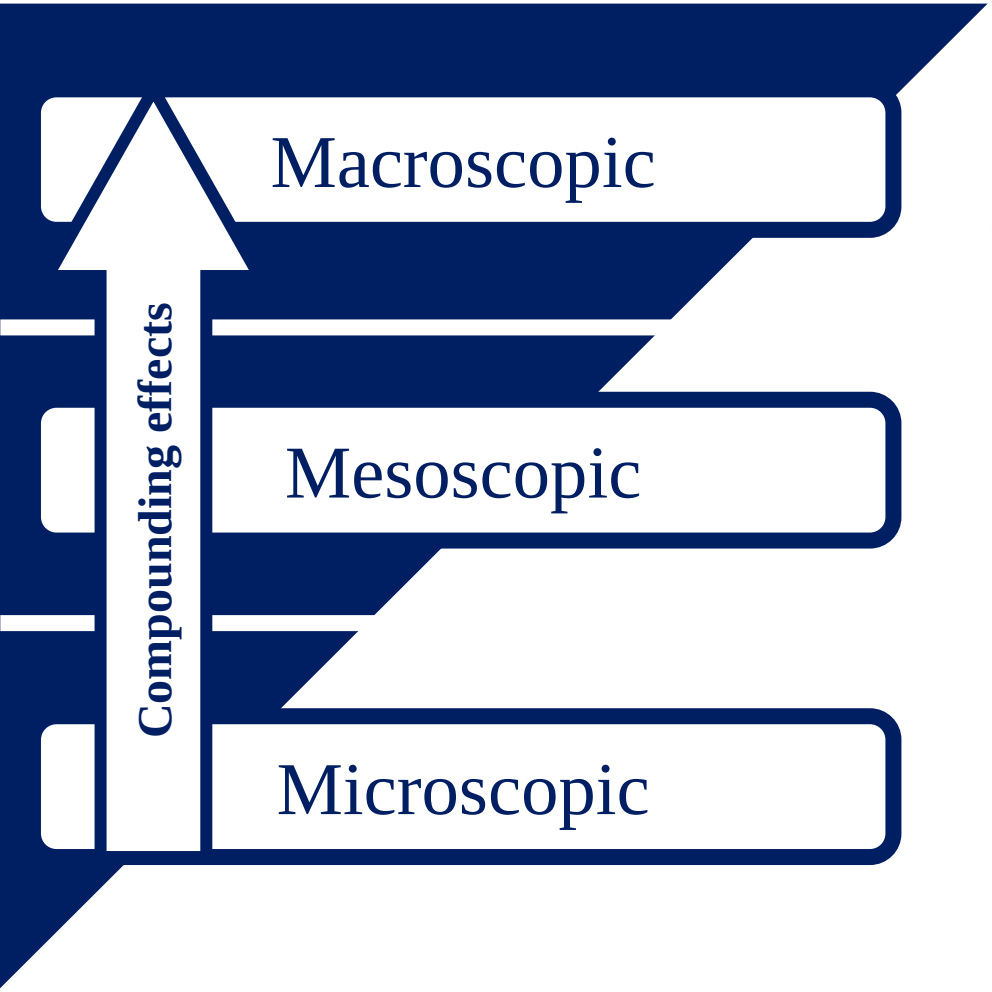


Support vector regression on functional groups [Liu 2021]



Le *Sci. Rep.* 2019
Liu *Chem. Eng. J.* 2021

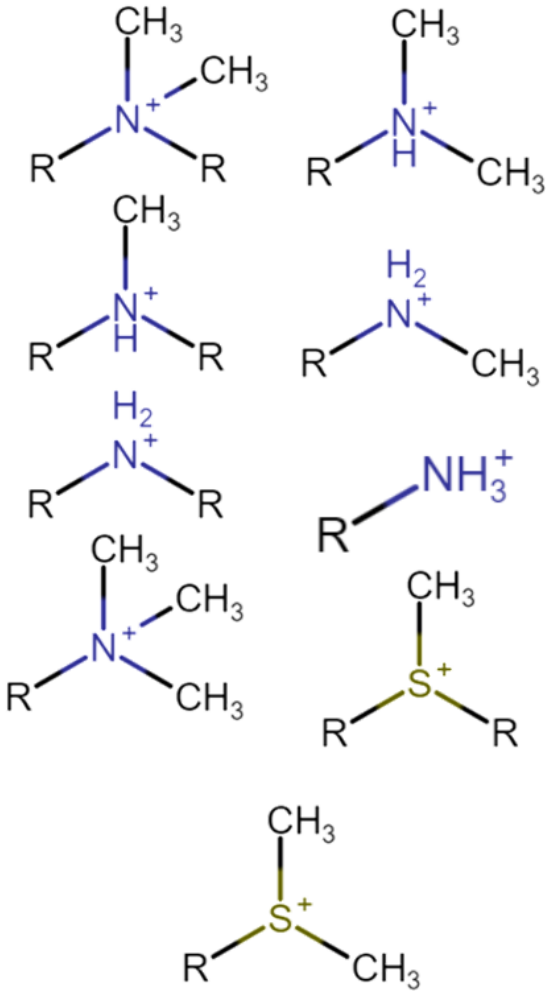
Hierarchy of polybetaine material design



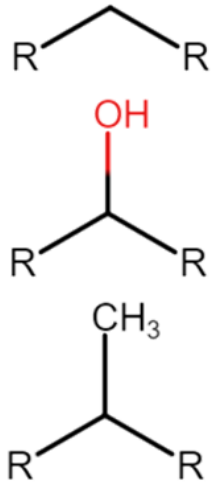
System description	Design considerations	Scale-relevant properties
Multi-polymer (network, brush, etc.)	Effects of polymer design, packing density, etc.	Ionic conductivity, surface hydration free energy, structure, dynamics
Single-polymer	Effects of neighboring monomers (homo- and heteropolymer)	Hydration and ion association to charged moieties, ionic conductivity
Single betaine/monomer	Strength of charged moieties and interference of alkyl separators	Hydration and ion association to charged moieties

Library of betaine chemistries for MD simulation

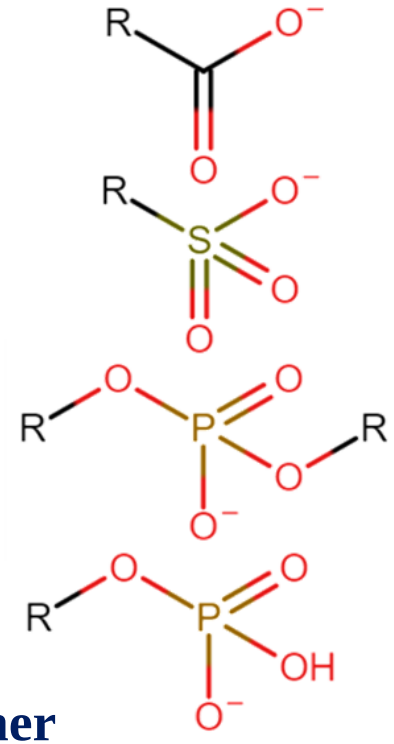
Cationic moieties



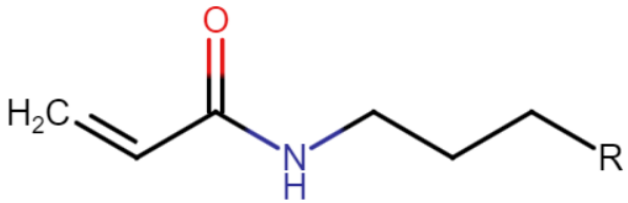
Nonionic spacers



Anionic moieties

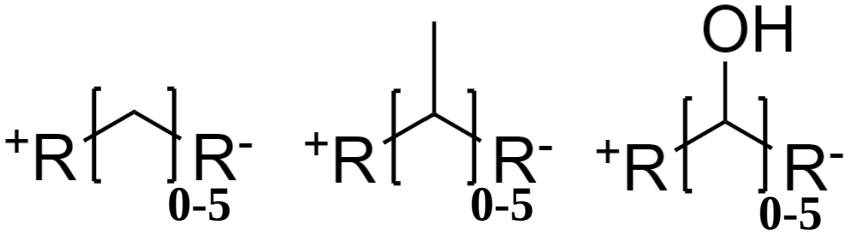


Preset monomer backbone



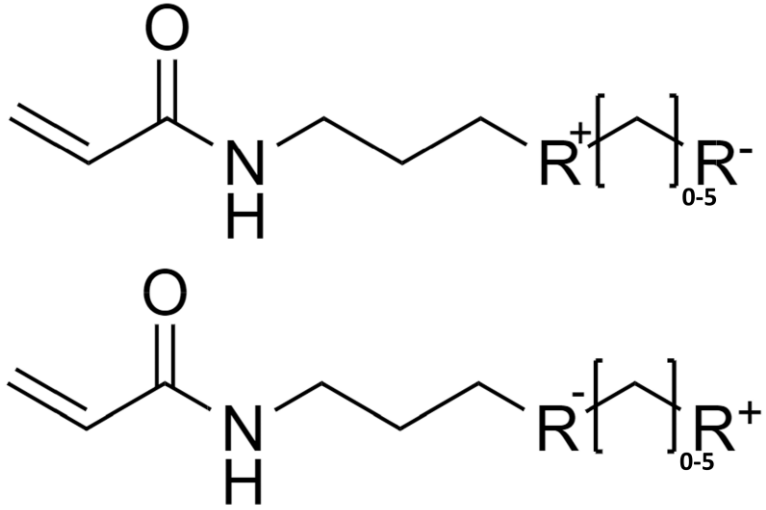
240 molecular betaines

Order of moieties *irrelevant*

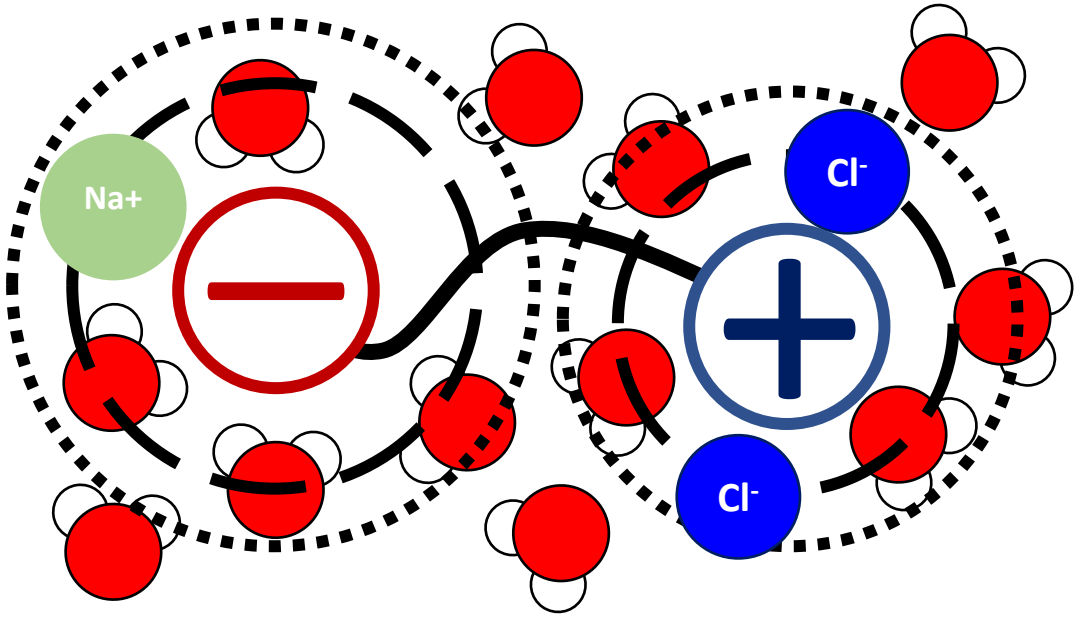


306 betaine monomers

Order of moieties *relevant*

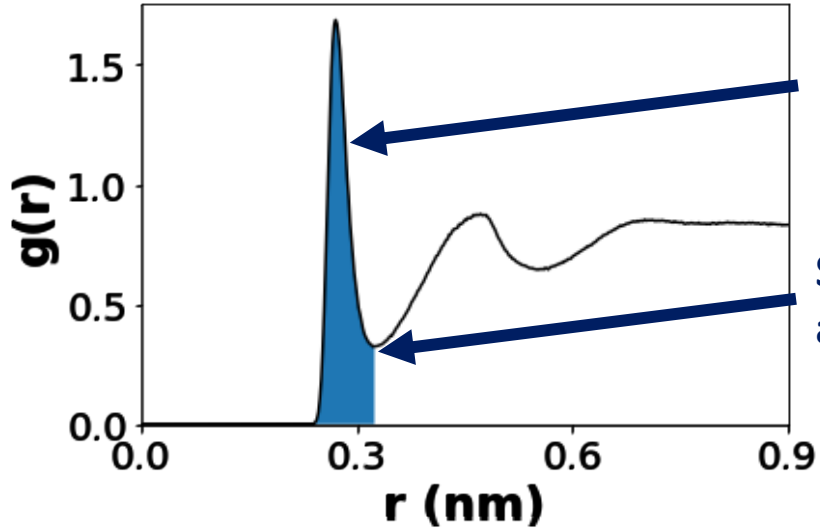


Structure and dynamics of hydration and ion association at molecular and single-polymer scales



Water coordination shells

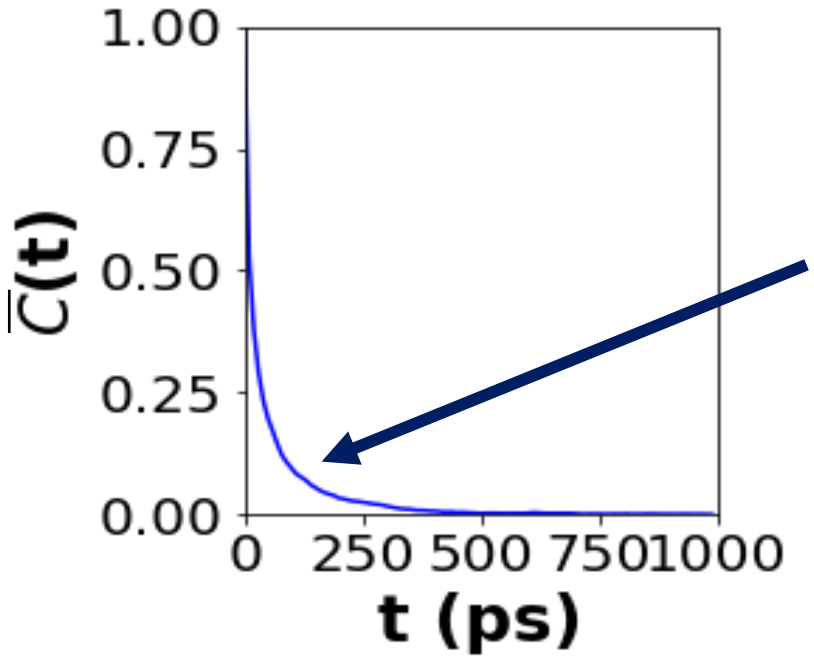
Ion coordination shells



Presence of significant peak, then valley indicative of a coordination shell

Shell radius determined by r at the trough

Coord. number calculated as area under $g(r)$

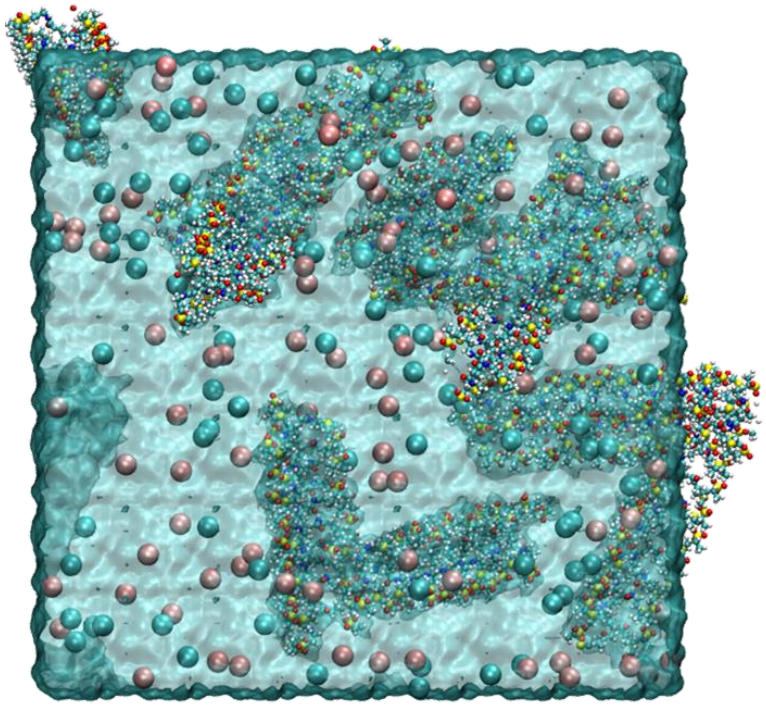


Effective residence time, τ, calculated by $ln(\bar{C}(t)) = -t/\tau$

Shao et al. *J. Phys. Chem. B* 2010

Ionic conductivity of polybetaine networks

Limiting study to homogeneous polybetaine systems with varying polymer concentration, which can impact porosity, bulk diffusion, and frequency/dynamics of ion hopping



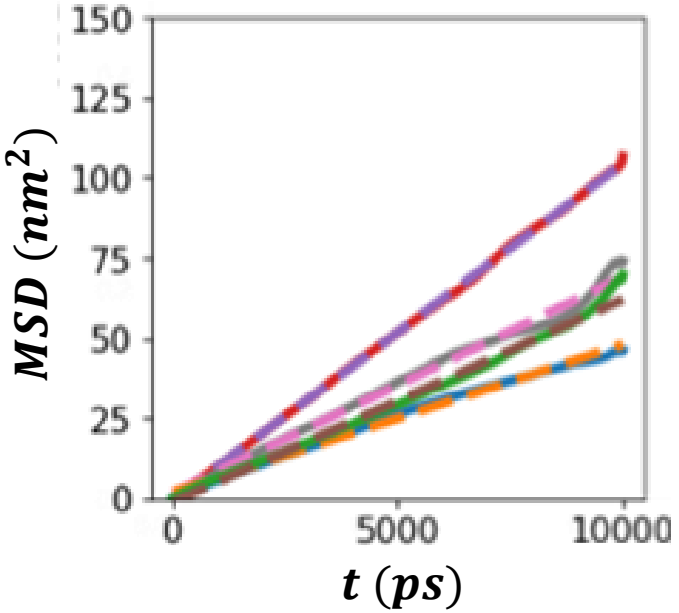
~10s of nm

Einstein-relation from linear fit to MSD

$$D = \frac{MSD}{6t}$$

Nernst-Einstein to calculate conductivity

$$\sigma = \frac{e^2}{Vk_BT}\left(N_+ z_+^2 D_+ + N_- z_-^2 D_-\right)$$



If non-linear MSD (i.e., anomalous diffusion), use the velocity autocorrelation function instead of MSD,

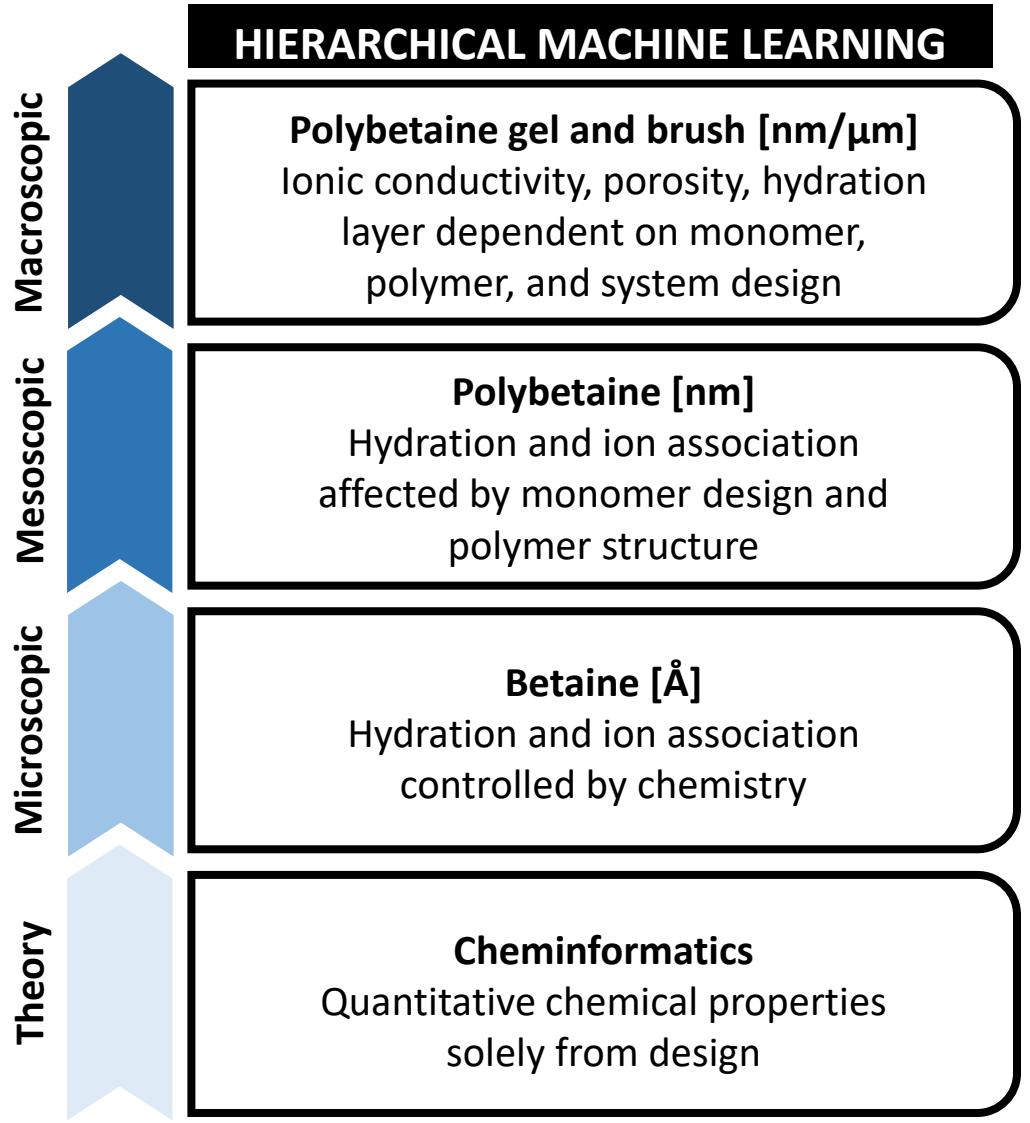
$$J(t) = < \left(\sum_i \vec{v}_{i+}(t) - \sum_j \vec{v}_{j-}(t)\right) > \times < \left(\sum_i \vec{v}_{i+}(0) - \sum_j \vec{v}_{j-}(0)\right) >$$

and the Green-Kubo relation to calculate conductivity

$$\sigma = \frac{e^2}{3Vk_BT}\int_0^\infty J(t)dt$$

Multiscale machine learning of polybetaine properties

- Use lower-scale input and target variables as input to higher-scale models to connect intermediate-scale phenomena to higher-scale properties
- Use interpretable ML models (LR, RF, MLPR with SHAP) to reveal qualitative quantitative structure-property relationships

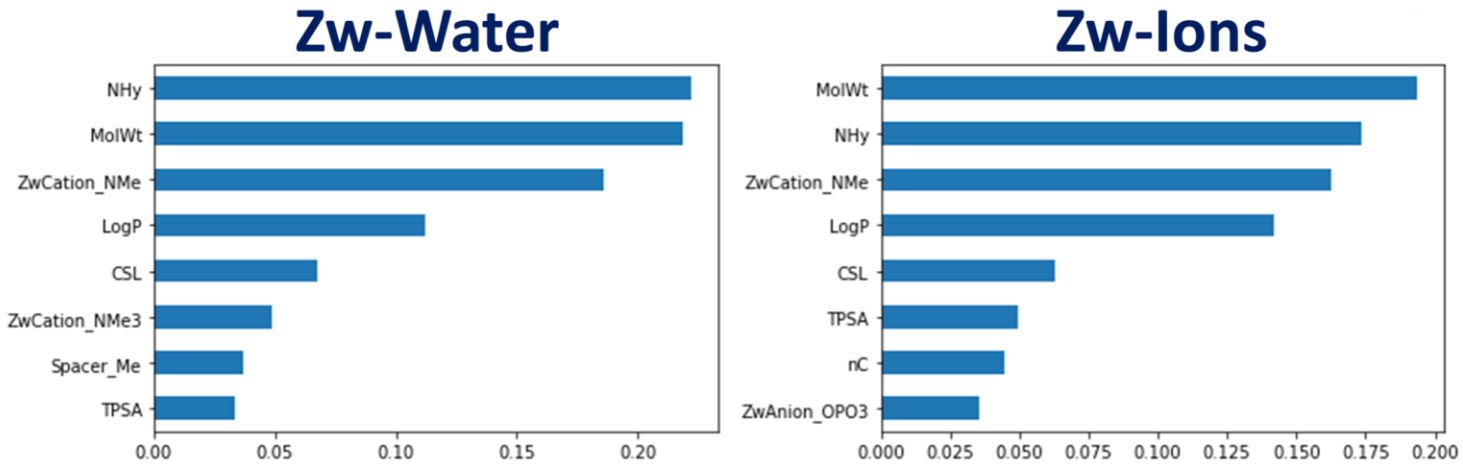


Scale-restricted structure-property relationships: Hydration and ion association of molecular betaines

Only modifying the betaine chemistry, all other variables constant

Examine three descriptor sets

- Only functional group chemistry
- Only cheminformatic descriptors
- Combined functional group and cheminformatics



Feature importance values for combined datasets

		R^2_{Test} for Linear Regression / Random Forest models					
		Functional group descriptors		Cheminformatic descriptors		Combined dataset	
	Association	r_{shell} (nm)	Coord. Number	r_{shell} (nm)	Coord. Number	r_{shell} (nm)	Coord. Number
Cationic Group	Water	0.887 / 0.972	0.888 / 0.974	0.447 / 0.867	0.371 / 0.849	0.893 / 0.978	0.896 / 0.975
	Anion	0.777 / 0.939	0.516 / 0.869	0.736 / 0.930	0.468 / 0.884	0.779 / 0.936	0.533 / 0.892
Anionic Group	Water	0.422 / 0.934	0.373 / 0.949	0.369 / 0.932	0.337 / 0.938	0.436 / 0.940	0.395 / 0.951
	Cation	0.263 / 0.837	0.243 / 0.830	0.202 / 0.784	0.194 / 0.778	0.278 / 0.805	0.252 / 0.796

Summary

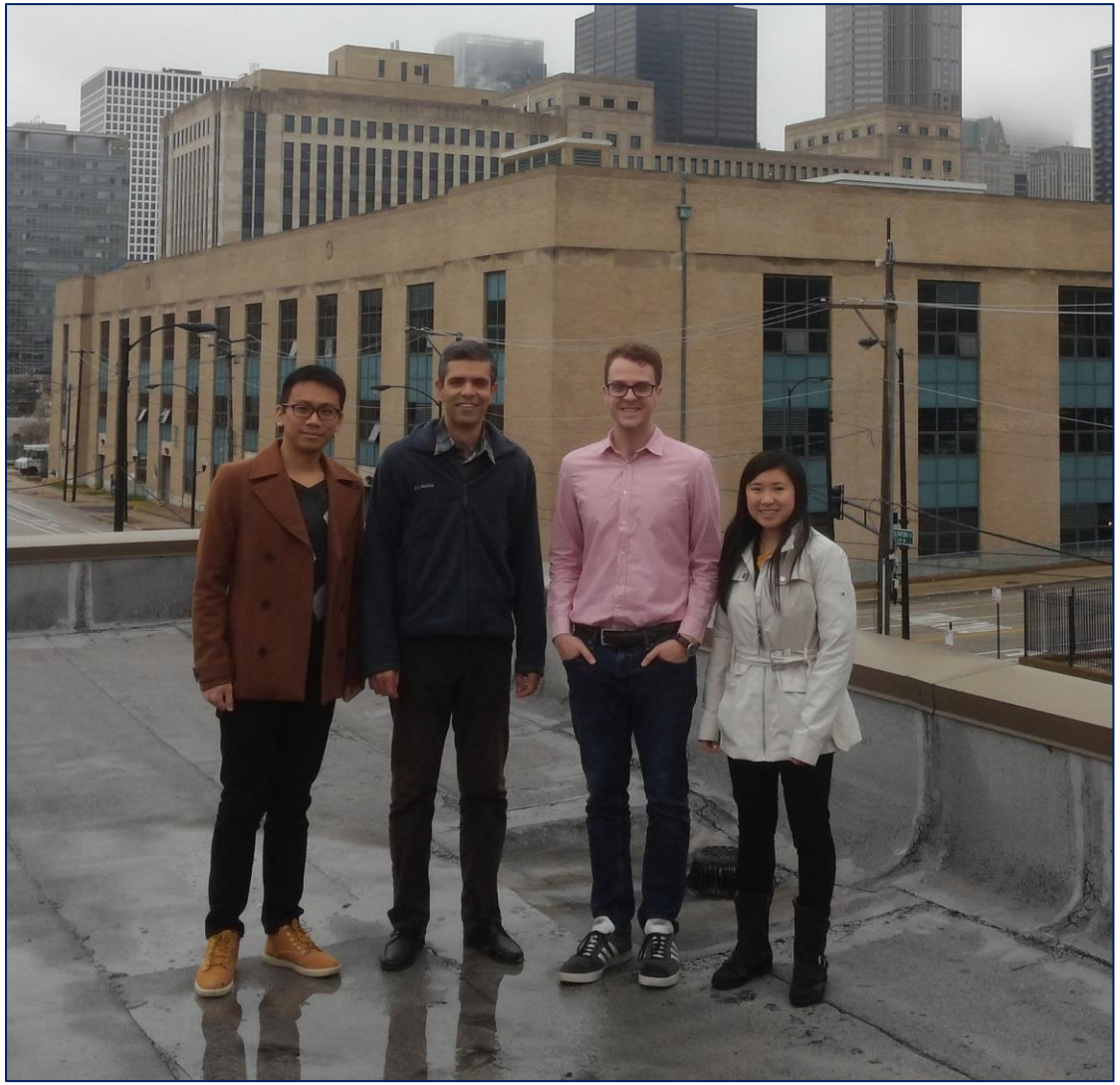
- Produced a uniform library of molecular and polymeric betaines for MD simulation
- Demonstrated high-accuracy machine learning of single-scale betaine properties
- Proposed a multi-scale machine learning approach to predicting material properties by the inclusion of lower-scale chemical and physical data
- Developed a simulation platform for further studies of betaine and polybetaine materials

Ongoing and future works

- Ongoing simulations of hydration, ion association, ionic conductivity at single- and multi-polymer scales
- Will incorporate experimental data (e.g., ionic conductivity of polyelectrolyte hydrogels by Lee et al., 2018) for model validation and to develop a full ML pipeline
- Use developed simulation platform and hierarchical ML approach to study hydration of polybetaine and self-assembled monolayer (SAM) coatings to study hydration free energy and protein adsorption resistance

Lee et al. *ACS Appl. Mater. Interfaces* 2018

Acknowledgements



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Dr. Huifeng Wang

Dr. Zhen Luo

Srishyam “Shyam” Raghavan

Funding sources

UIC Award for Graduate Research

UIC College of Engineering seed funding