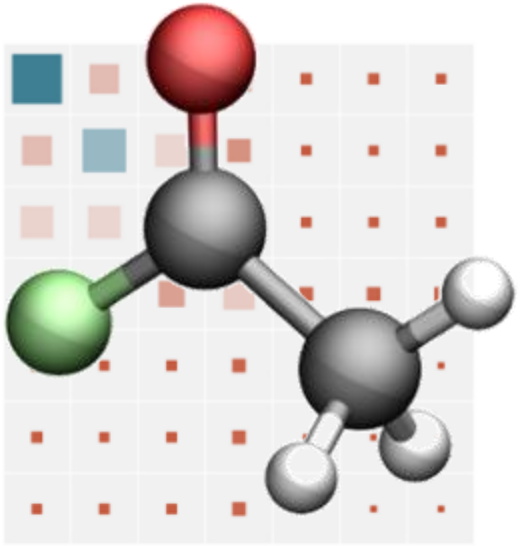
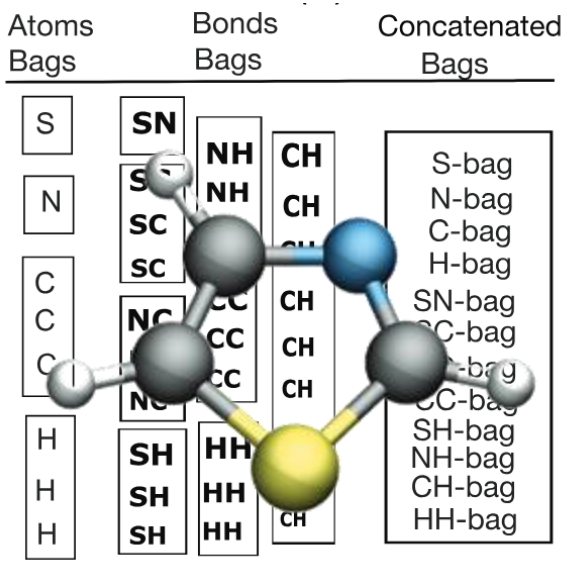
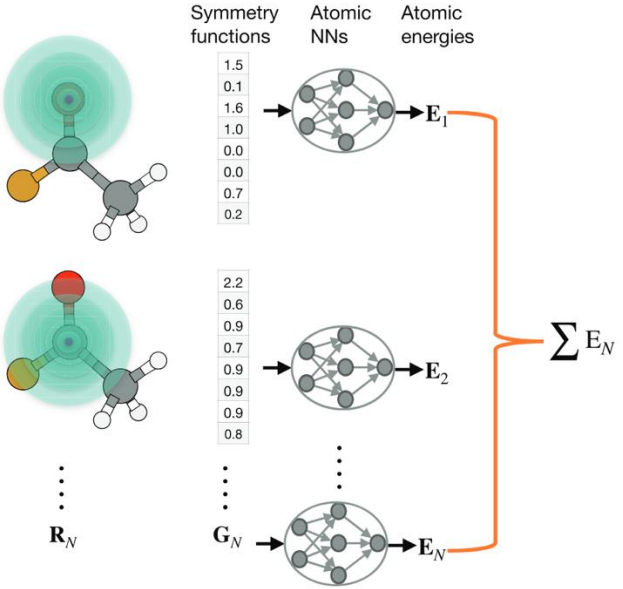
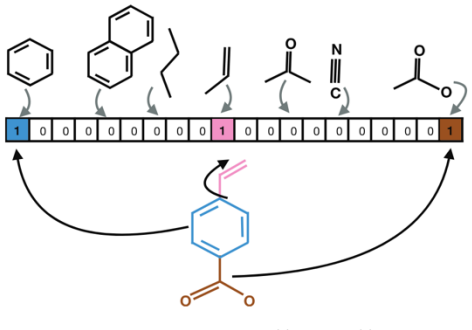








Molecular Featurization

image sources: S. Raghunathan, U. D. Priyakumar, Int. J. Quantum Chem. 2022, 122(7), e2687

Tokenization and One-Hot Encoding

One viable approach for molecules:

1. *Represent numerically via one-hot encoding over chemical vocabulary*
2. *Tokenize SMILES strings into finite set of (n-gram) characters*

One-hot Encoding – bitwise/binary description of categorical variables

e.g.,

cat

01100011011000010111010**0**

0

100

rabbit

01110010011000010110001**0**

1

010

duck

01100100011101010110001**1**

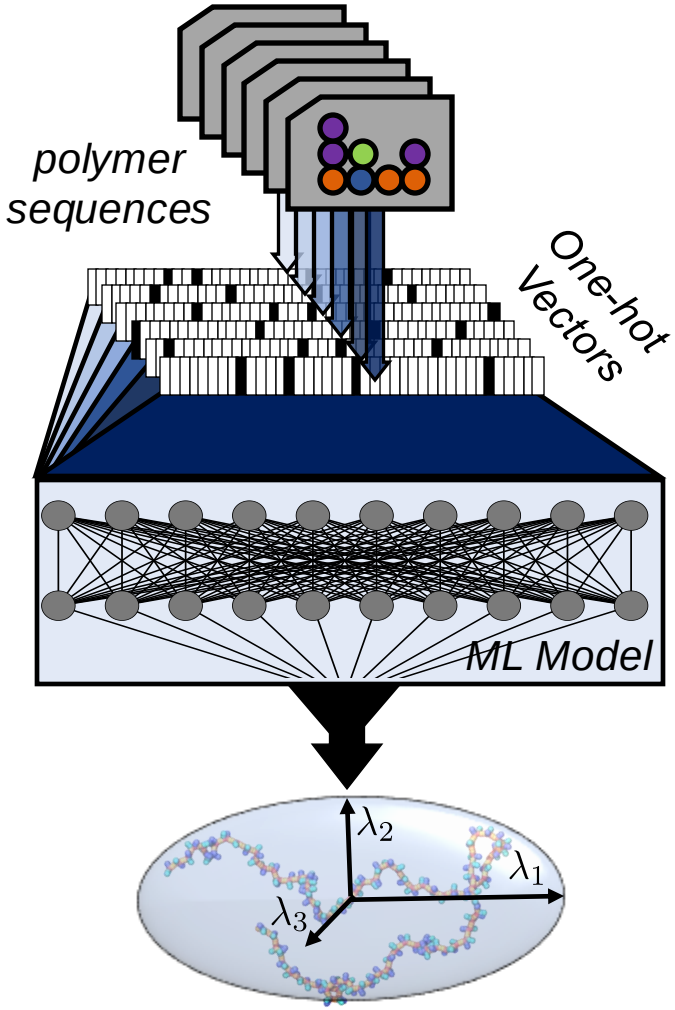
2

001

English; binary; numerical assignment; one-hot vector

Tokenization and One-Hot Encoding

Usually OHE is the first reasonable thing to try if you have countable units

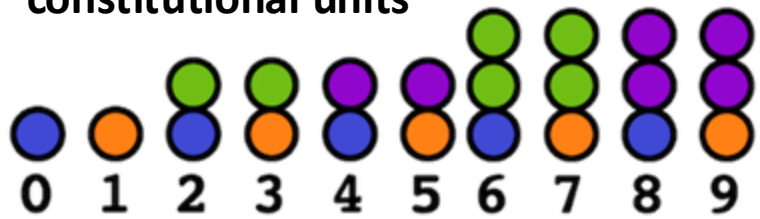


characterization

Webb et al. *Sci. Adv.* **2020**

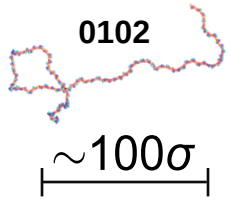
10 allowable "constitutional units"

$R_k \in \{0, \ldots, 9\}$

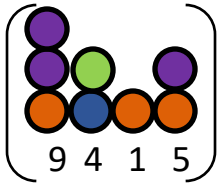


$\left(-R_1-R_2-R_3-R_4-\right)_{200}$

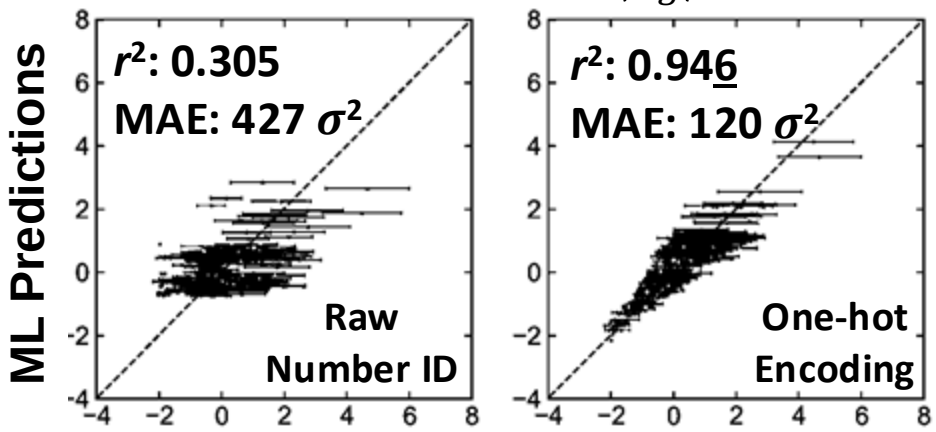
0254



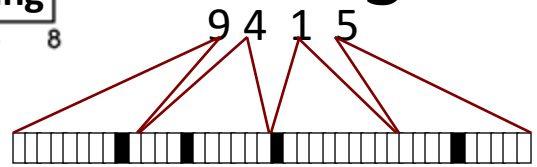
raw number ID



Standardized $\langle R_g^2 \rangle$



one-hot-encoding



Tokenization and One-Hot Encoding

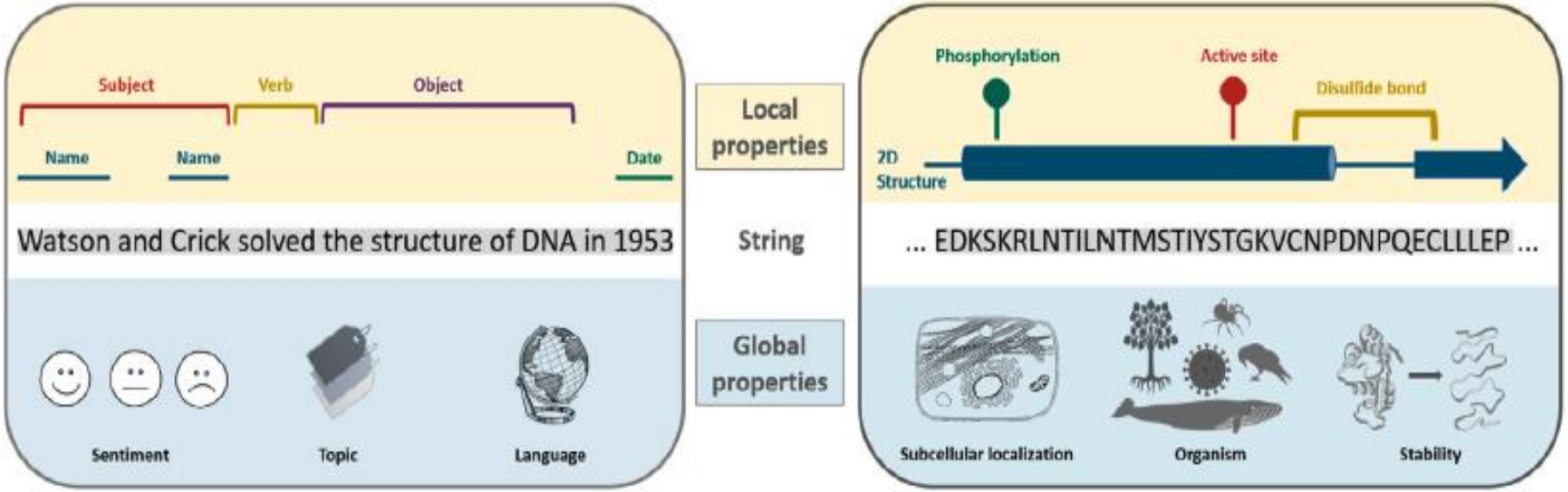
Tokenization – fundamental task in **Natural Language Processing** that yields ***tokens***

Tokens – basic building blocks of the Natural Language

words
n-grams
characters

} the collection of tokens forms a vocabulary

Techniques for NLP have been very naturally extended for bioinformatics tasks



MSTIYSTGKVCNP...

[*start*] [M] [S] [T] [I] [Y] [S] [T] [G] ...

[*start*] [MS] [TI] [YS] [TG] ...

[*start* M] [STI] [YST] [GK] [VCN] ...

A simple global description of the sequence is a ***Bag-of-Words***

$$\boldsymbol{f}_p \in \mathbb{R}^{20}$$

Ofer et al. Comput. Struct. Biotechnol. (**2021**)

Tokenization and One-Hot Encoding

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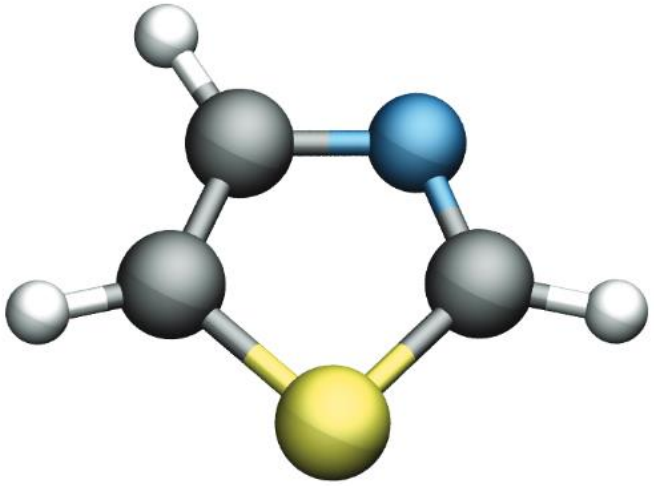
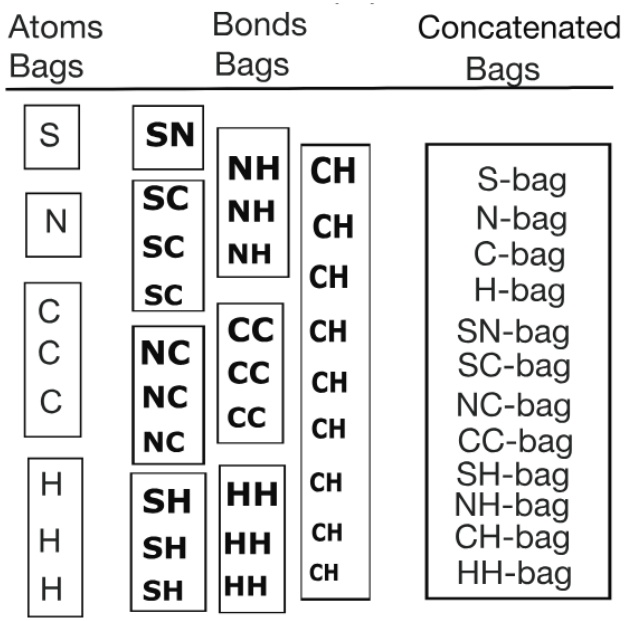




Bags of stuff can serve as reasonably discriminating representations of molecules;

The concatenated bag is *essentially a one-hot vector* with elements equal to the number of occurrences.

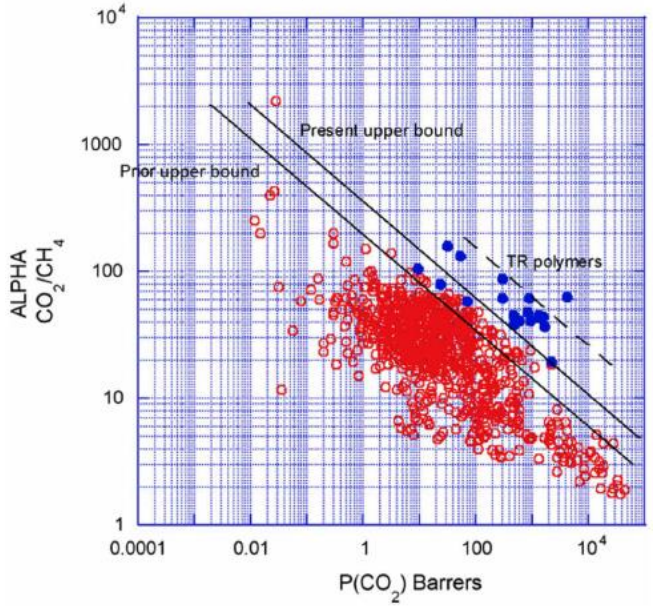
S. Raghunathan, U. D. Priyakumar, Int. J. Quantum Chem. 2022, 122(7), e2687

Tokenization and One-Hot Encoding Notebook

Tokenization and One-Hot Encoding

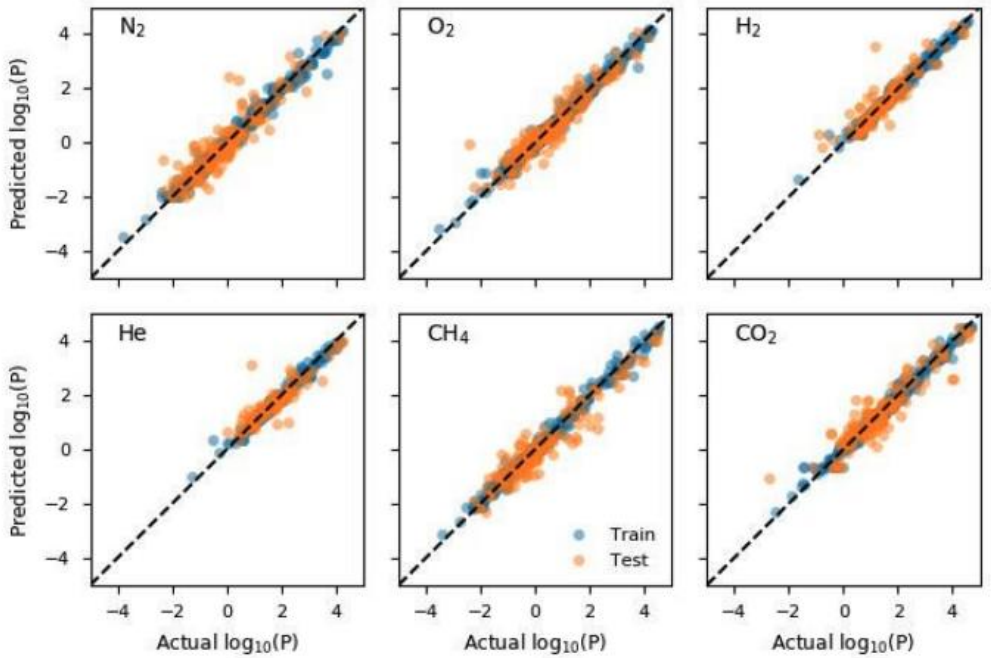
Exercise: *Develop one-hot encoded representations for these atmospheric gases from SMILES*

Gas Permeability in Polymer Membranes



Robeson J. Membr. Sci. **2008**

Separate Machine Learning Models



Barnett et al. Sci. Adv. **2020**

SMILES Conversion

N_2 → N#N
O_2 → O=O
H_2 → [HH]
He → [He]
CH_4 → C
CO_2 → C(=O)=O

Screening for tokens and generating one-hots

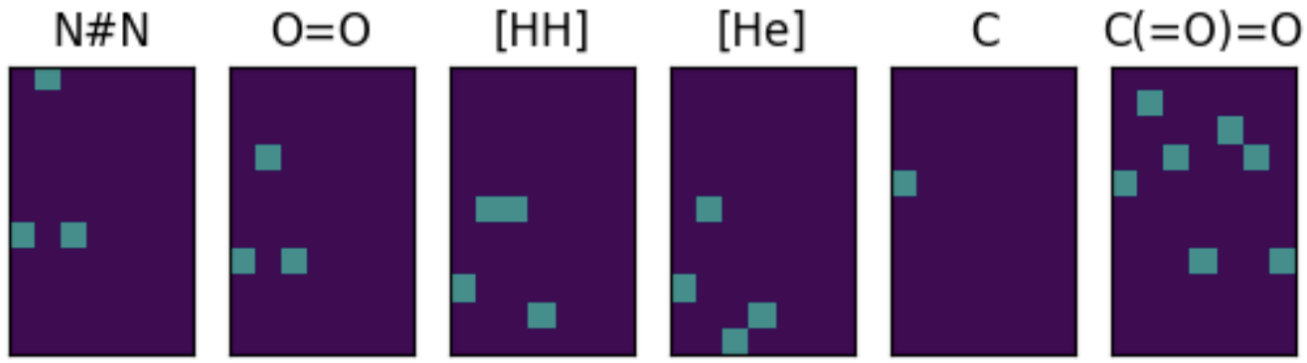
```
[1]  import numpy as np
     mols = ['N#N','O=O','[HH]','[He]','C','C(=O)=O']
```

```
[2]  # Let's determine our vocabulary over the set provided
     # this code does not work for parsing SMILES, in general
     # we just want to keep things simples
     vocab = set()

     # iterate over all molecules to extract unique characters
     M = 0 # to contain maximum number of characters in any string...
     for mol in mols:
         mol = list(mol)
         if len(mol) > M:
             M = len(mol)
         while mol:
             v = mol.pop()
             if v not in vocab:
                 vocab.add(v)
```

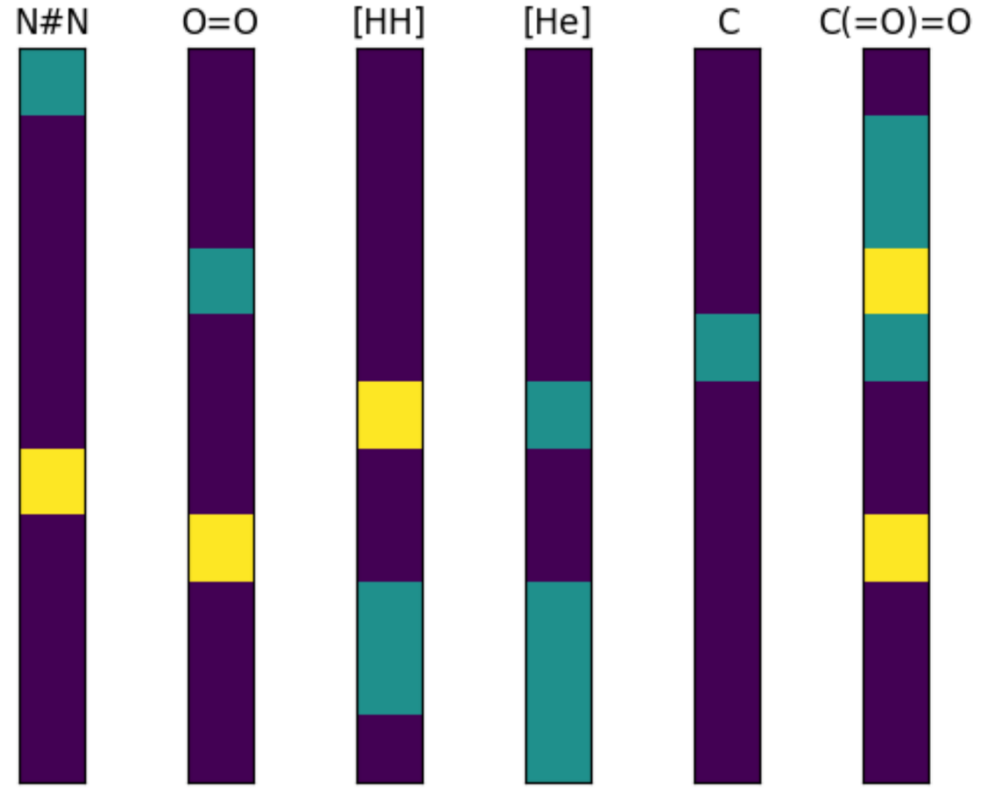
```
# we will create a mapping dictionary that
# points each character to a one-hot vector
N  = len(vocab)
IN = np.eye(N)
charMap = {}
for i,c in enumerate(sorted(list(vocab))):
    charMap[c] = IN[i,:]

''' function that takes a SMILES string
and returns a (padded) array with ohe
vectors as indicated by CMap
M - dimension to pad to if necessary
N - dimension of OHE '''
def Smi2Arr(SmiStr,CMap,M,N):
    Arr   = np.zeros([M,N])
    for i,c in enumerate(list(SmiStr)):
        Arr[i,:] = CMap[c][:]
    return Arr

# create feature arrays
featArr = []
for mol in mols:
    featArr.append(Smi2Arr(mol,charMap,M,N))
```

A new way to view molecules

```
# visualize the encodings
import matplotlib.pyplot as plt
def make_plot(ax,mol,Arr):
    ax.imshow(Arr.T,vmin=0,vmax=2)
    ax.axes.xaxis.set_visible(False)
    ax.axes.yaxis.set_visible(False)
    ax.set_title(mol)
    plt.grid(True,which='minor',color='w')

fig, axs = plt.subplots(1,len(mols))

for i, (mol,Arr) in enumerate(zip(mols,featArr)):
    make_plot(axs[i],mol,Arr)
```




```
# generate compressed feature vectors
featVec = [np.sum(Arr,axis=0) for Arr in featArr]

fig, axs = plt.subplots(1,len(mols))

for i, (mol,Vec) in enumerate(zip(mols,featVec)):
    make_plot(axs[i],mol,Vec[:,np.newaxis].T)
```



Chemically Expressive Representations

Extended Connectivity Fingerprints

A more topologically informed version of OHE are so-called

Extended Connectivity Fingerprints (ECFPs)

Rogers and Hahn. "Extended-Connectivity Fingerprints." *J. Chem. Inf. Model* **2010**

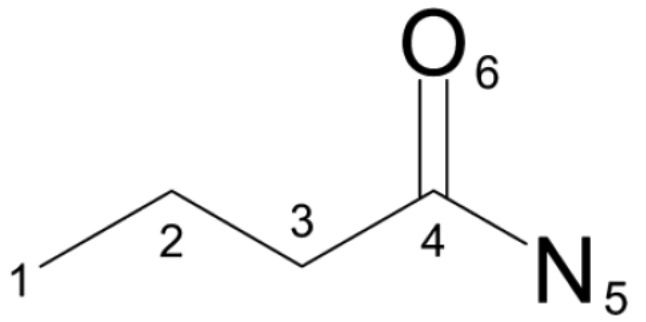
Basic Algorithm

1. **Assign each atom an identifier**
2. Iteratively update identifier based neighboring atoms
3. Remove/count duplicates
4. Fold identifiers into an *N*-bit vector

ECFPs are essentially one-hot encodings over substructures in molecular graphs

- Number of nearest-neighboring heavy atoms
- Number of bonds to heavy atoms
- Atomic Number and Mass
- Number of bonded hydrogens
- Linear or ring topology

Hash function → **integer identifier**



1: 734603939
2: 1559650422
3: 1559650422
4: -1100000244
5: 1572579716
6: -1074141656

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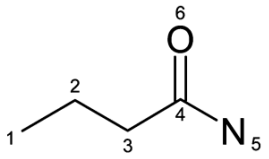
2. Iteratively update identifier based neighboring atoms
3. **Remove/count duplicates**
4. **Fold identifiers into an *N*-bit vector**

- *theoretically, identifiers could be treated as indices of bits in a large set (2^{32})*
- *practically, identifiers are assigned bits in a fixed-size vector*



> <ECFP_0>	> <ECFP_2>	> <ECFP_4>	> <ECFP_6>	
734603939	734603939	734603939	734603939	[A]C
1559650422	1559650422	1559650422	1559650422	[A]C[A]
-1100000244	-1100000244	-1100000244	-1100000244	[A]C(=[A])[A]
1572579716	1572579716	1572579716	1572579716	[A]N
-1074141656	-1074141656	-1074141656	-1074141656	[A]=O
	863188371	863188371	863188371	[A]CC
	-1793471910	-1793471910	-1793471910	[A]CCC
	-1789102870	-1789102870	-1789102870	[A]CCC(=[A])[A]
	-1708545601	-1708545601	-1708545601	[A]CC(=O)N
	-932108170	-932108170	-932108170	[A]C(=[A])N
	2099970318	2099970318	2099970318	[A]C(=O)[A]
		-87618679	-87618679	[A]C(=[A])CCC
		1112638790	1112638790	CCCC(=O)N
		-627599602	-627599602	[A]CCC(=O)N

extracted substructures in SMARTS

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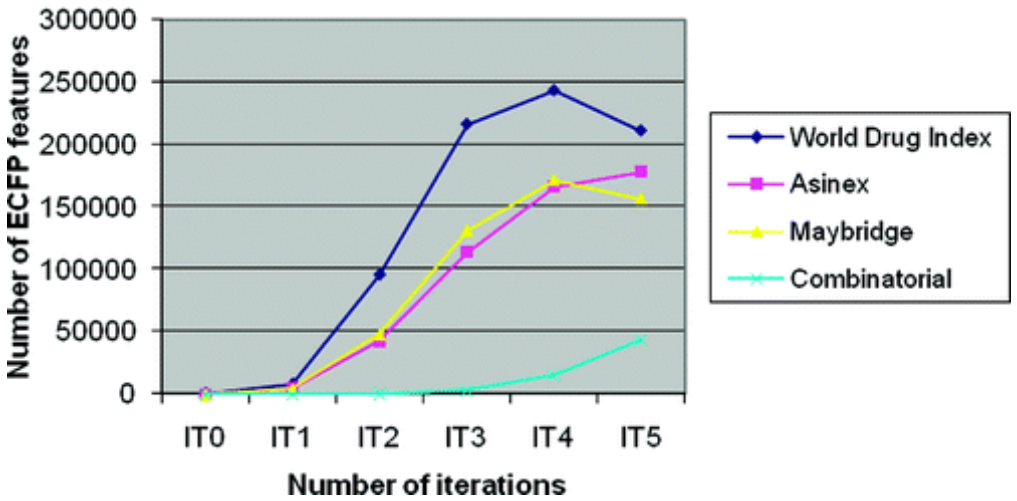
Rogers and Hahn. "Extended-Connectivity Fingerprints." *J. Chem. Inf. Model* **2010**

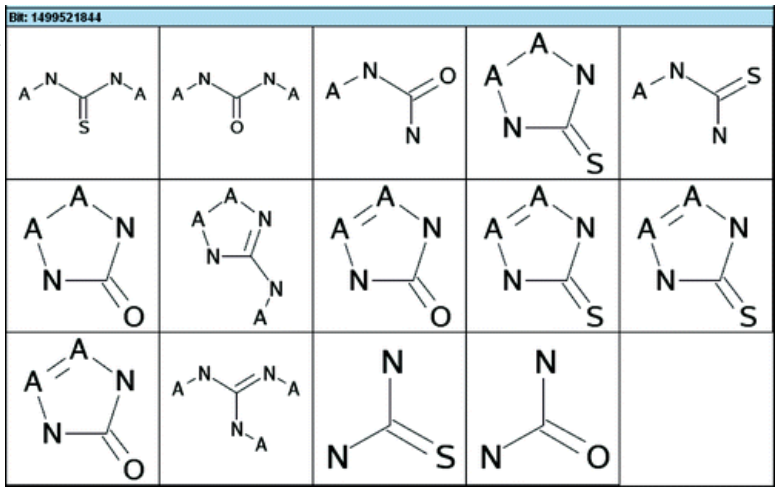
Advantages

- computationally efficient to generate and readily available
- flexible and robust
- expressive of positive/negative structure

Disadvantages

- obfuscates/does not utilize chemical properties or 3D arrangement
- sparse representation
- not scalable to variety of systems
- potentially non-unique identifiers





Descriptor (Feature) Vectors

Vectors of physiochemical properties or system characteristics may also provide good representations of inputs for ML tasks

Examples of Physiochemical Descriptors

e.g.,

- *No. of X structure,…*
- *log P, ASA, shape parameters, …*
- *dipole moment, polarizability, …*
- *electronic energy, Δh_f, IP, ε_{gap}, …*
- *simulation-derived quantities*
- *experimental measurements*

Descriptors can describe local or global characteristics. Some may be readily available or easily obtained, while others can be complicated/expensive to acquire.

Chemical Science

Chem. Sci., 2019, **10**, 6697

Machine learning and molecular descriptors enable rational solvent selection in asymmetric catalysis†

Yehia Amar,[a] Artur M. Schweidtmann,[b] Paul Deutsch,[c] Liwei Cao[ad] and Alexei Lapkin*[ad]

Table 1 List of solvent molecular descriptors used in this work

	Descriptor (units)	Source
random compilation by some guy	Molecular weight (g mol^{-1})	Stenutz[45]
	Density (g mL^{-1})	Stenutz[45]
	Molar volume (mL mol^{-1})	Stenutz[45]
	Refractive index (—)	Stenutz[45]
	Molecular refractive power (mL mol^{-1})	Stenutz[45]
	Dielectric constant (—)	Stenutz[45]
	Dipole moment (D)	Stenutz[45]
	Melting point (°C)	Stenutz[45]
	Boiling point (°C)	Stenutz[45]
thermodynamic property prediction model	Viscosity (cP)	COSMO*therm*[39]
	ln $P_{octanol-water}$ partition coefficient (—)	COSMO*therm*[39]
	Vapour pressure (mbar)	COSMO*therm*[39]
	Henry's constant of H_2 in solvent (bar)	COSMO*therm*[39]
	ln(γ) activity coefficient of I in solvent (—)	COSMO*therm*[39]
	$\sigma'_1 - \sigma'_3$ profiles segmented into three (—)	COSMO*therm*[39]
	σ_1–σ_5 profiles segmented into five (—)	COSMO*therm*[39]
	t_1–t_4: principal components from PCA (—)	—

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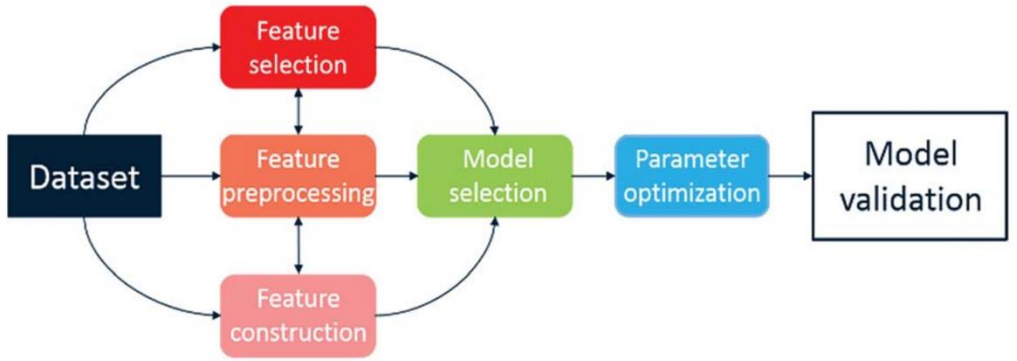


The selection of descriptors may be part of the model-building process

Descriptor (Feature) Vectors

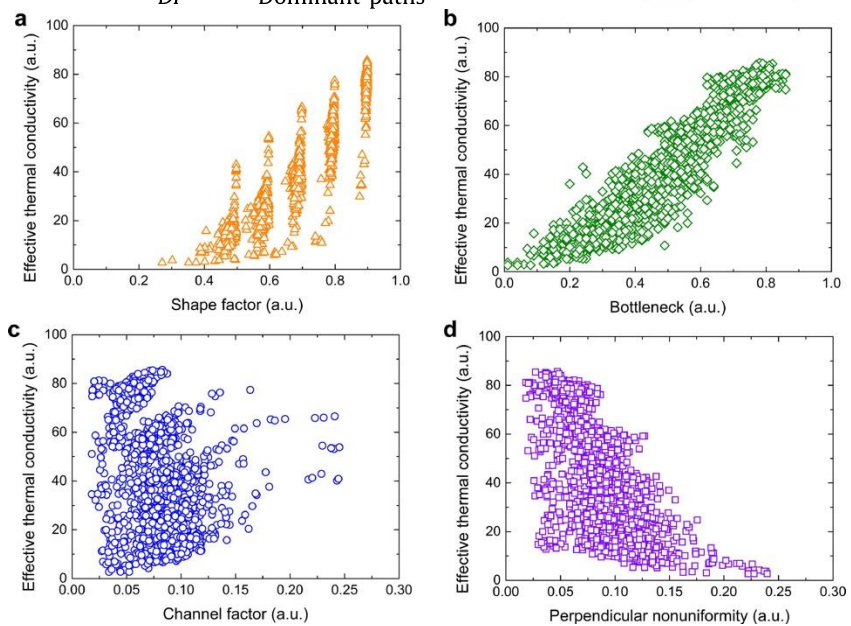
Descriptor vectors can provide suitable representations for non-molecular systems; they are likely tailored to the materials class

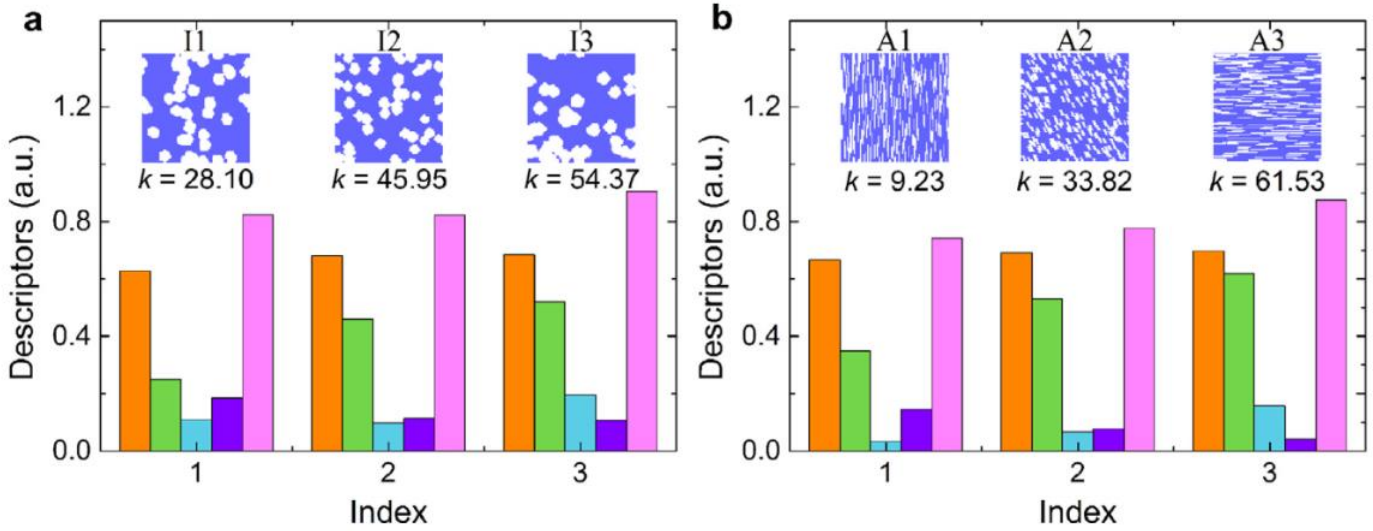
Machine learning prediction of thermal transport in porous media with physics-based descriptors

Han Wei[a], Hua Bao[a,*], Xiulin Ruan[b,*]

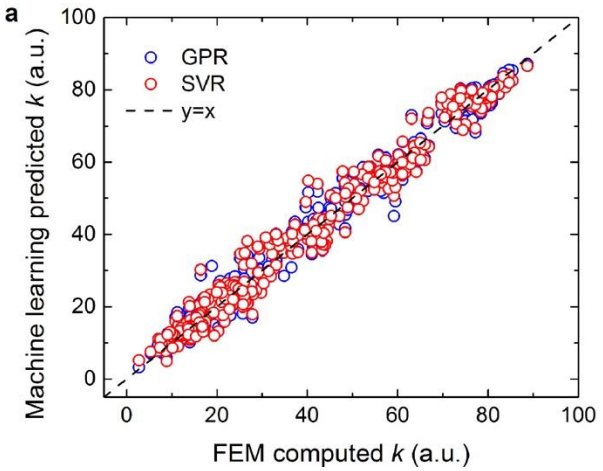
Available online 17 July 2020

ε	Porosity
c_d	Core distribution probability
g_i	Directional growth probability
A_x	matrix cross-section along x direction
A_y	matrix cross-section along y direction
SF	Shape factor
BL	Bottleneck
PN	Perpendicular nonuniformity
CF	Channel factor
DP	Dominant paths





These enable quantitative "structure" to property relationships by machine learning



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Descriptor vectors can provide suitable representations for non-molecular systems; they are likely tailored to the materials class

THE JOURNAL OF PHYSICAL CHEMISTRY A

Article

Cite This: J. Phys. Chem. A 2019, 123, 6080–6087

pubs.acs.org/JPCA

A Robust Machine Learning Algorithm for the Prediction of Methane Adsorption in Nanoporous Materials

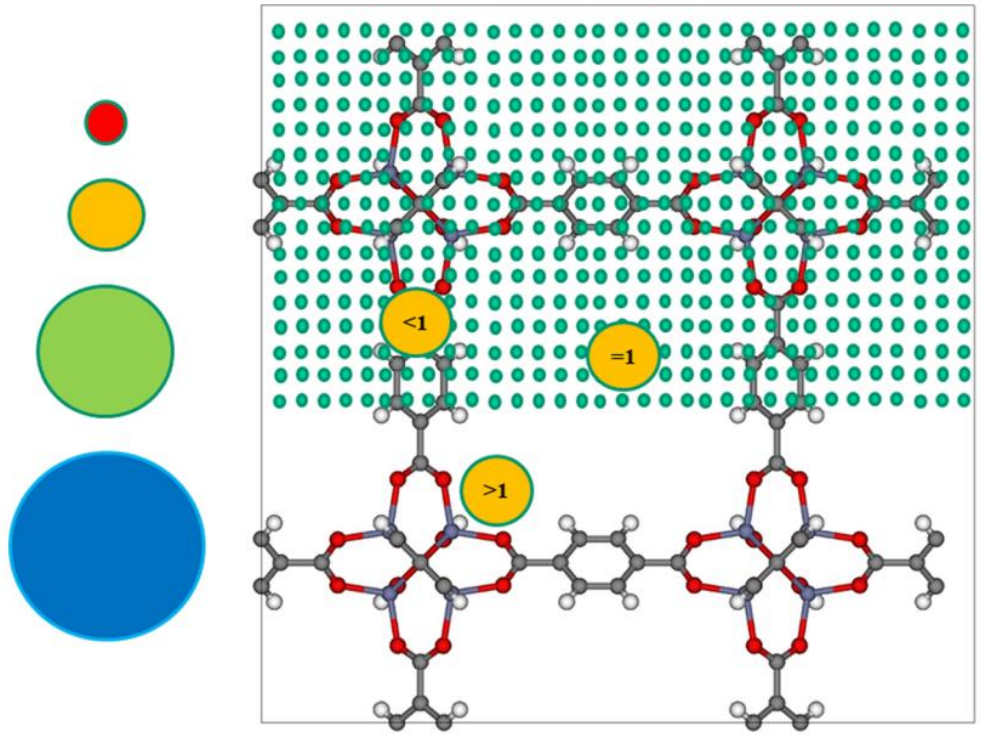
George S. Fanourgakis,*,† Konstantinos Gkagkas,‡ Emmanuel Tylianakis,¶ Emmanuel Klontzas,†,§ and George Froudakis*,†

materials specific

- readily available widely used
- creative easily computed

Table 1. Descriptors Used in the Present Study in the ML Methods[a]

descriptor	minimum	maximum	mean
Standard Structural Features			
void fraction	0.02	0.97	0.43
pore volume ($cm^3\ g^{-1}$)	0.07	7.46	0.49
density ($g\ cm^{-3}$)	0.13	5.18	1.37
grav. surface area ($m^2\ g^{-1}$)	0.0	6832.6	829.4
pore-limiting diameter (Å)	2.4	71.5	4.83
largest cavity diameter (Å)	2.74	71.64	6.79
Probe Atoms			
probe-1 (σ = 2.5 Å, ε/k_B = 50 K)	0.08	5.14	1.12
probe-2 (σ = 3.0 Å, ε/k_B = 50 K)	0.04	12.37	1.53
probe-3 (σ = 3.5 Å, ε/k_B = 50 K)	0.0	36.35	2.30
probe-4 (σ = 4.0 Å, ε/k_B = 50 K)	0.0	131.7	3.79



$$\text{probe} - (a) = \frac{1}{N}\sum_{i=1}^{N} \exp(-\beta E_i^{(a)})$$

Descriptor (Feature) Vectors

Descriptor vectors can provide suitable representations for non-molecular systems; they are likely tailored to the materials class

THE JOURNAL OF PHYSICAL CHEMISTRY A

Article

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A Robust Machine Learning Algorithm for the Prediction of Methane Adsorption in Nanoporous Materials

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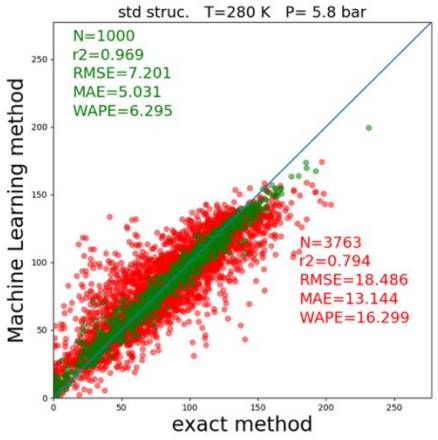
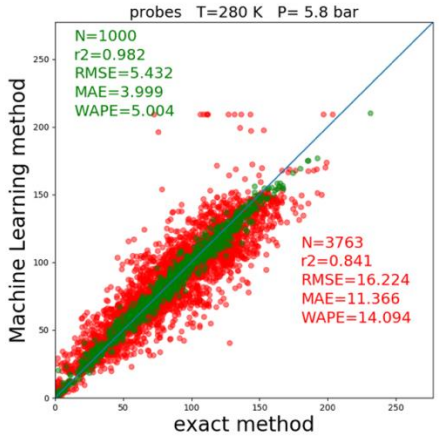
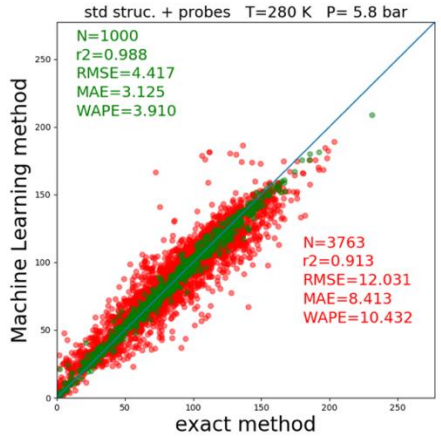
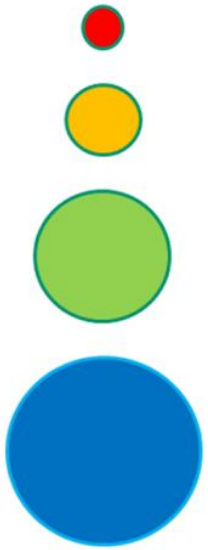
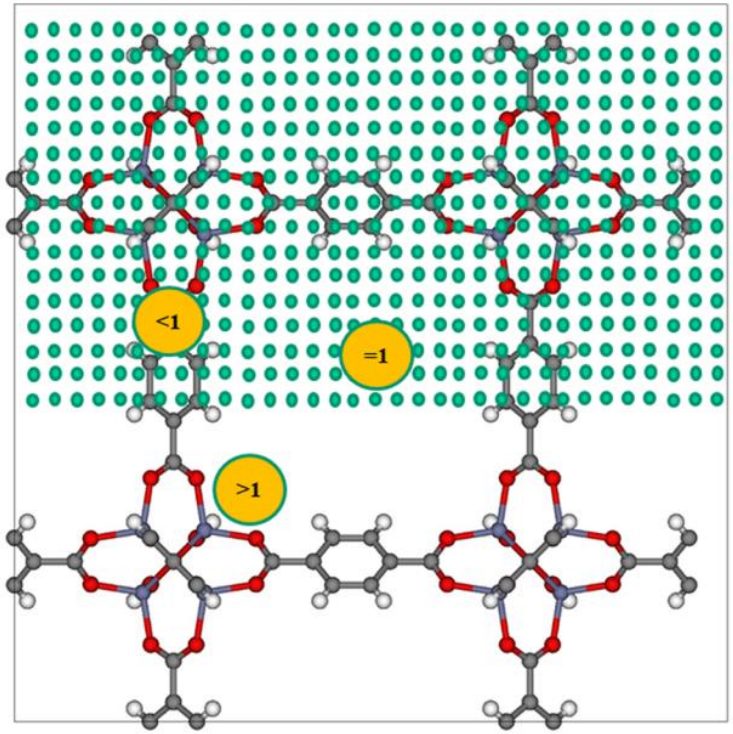






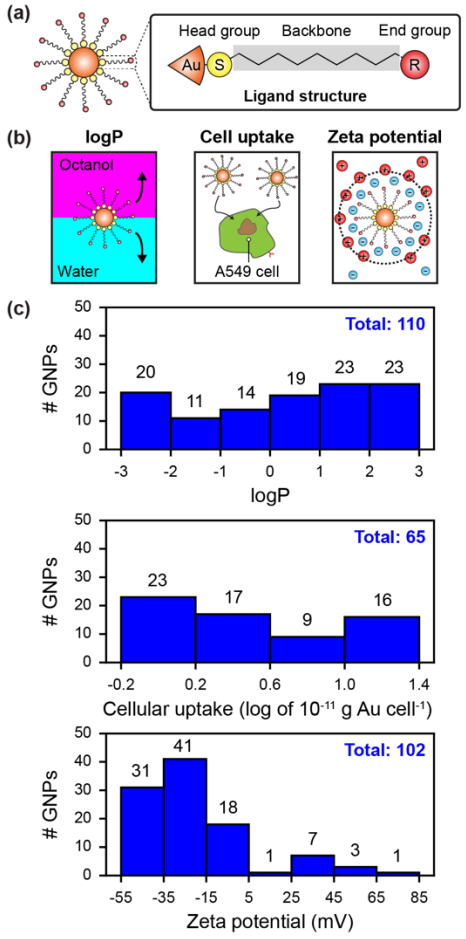




$$\text{probe} - (a) = \frac{1}{N}\sum_{i=1}^{N} \exp(-\beta E_i^{(a)})$$

Simulation-derived Descriptors

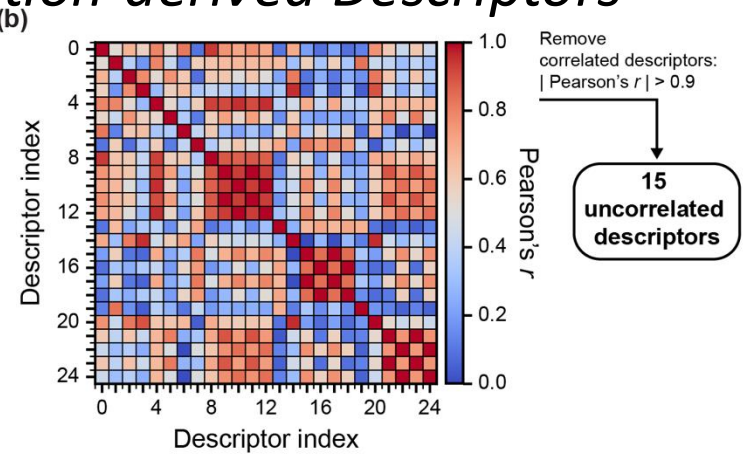
Experimental Dataset

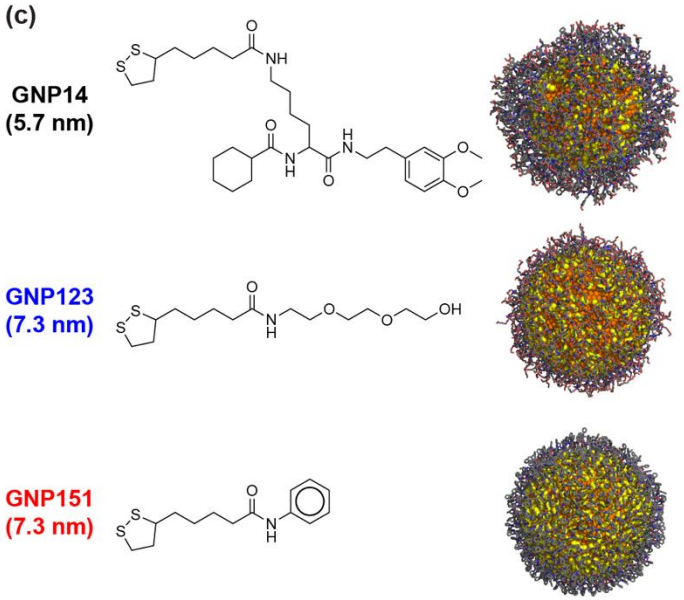


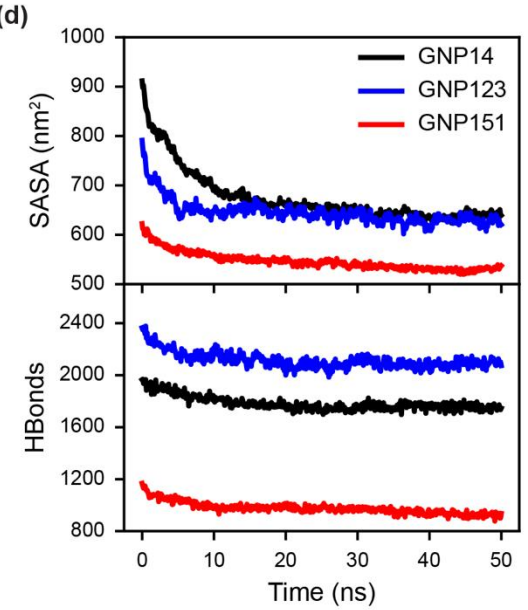
Simulation-derived Descriptors

(a)

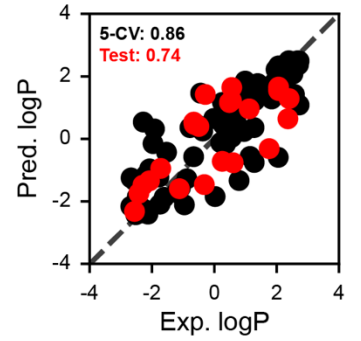
Descriptor	Description
SASA	Solvent accessible surface area
HBonds	#Lig.-water hydrogen bonds
RMSF	Lig. root-mean-squared fluctuation
E(NP-S)	GNP-solvent LJ energies
$\Delta\phi$	Radial electrostatic potential drop
e	Lig. eccentricity (*i.e.* asphericity)
RDF(Au)	Gold radius from RDFs
RDF(Lig.)	Ligand length from RDFs
RDF(H_2O)	Radius at bulk water density from RDFs
R_g	Ligand radius of gyration
⋮	**25 descriptors**

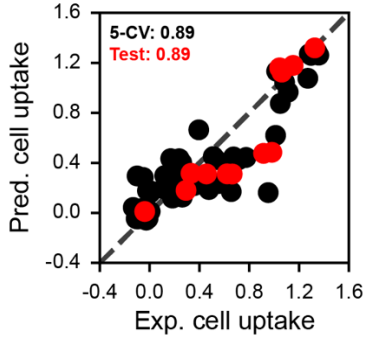


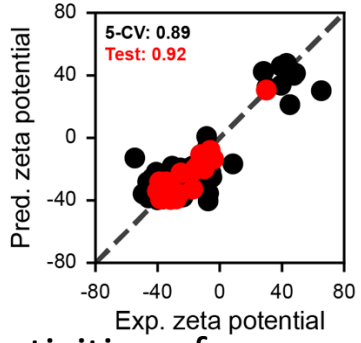




ML Models







Chew, Pedersen, Van Lehn. "Predicting the Physicochemical Properties and Biological Activities of Monolayer-Protected Gold Nanoparticles using Simulation-Derived Descriptors"

Other Structural/Geometric Input Representations

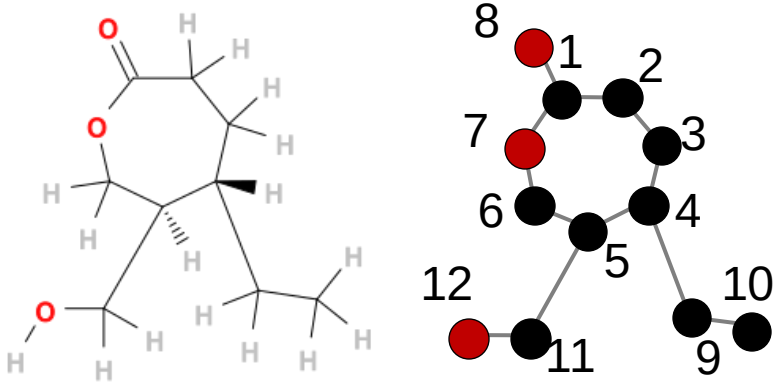
Geometric ***representations*** can provide some additional and potentially critically important information for training ML models

An important consideration for such representations is…
equivariance and ***invariance***

Noether's Theorem – *something about how local and global symmetries relate to conservation laws*

Common considerations:

Translation *Rotation* *Permutation*



$$N, \boldsymbol{r}^N = (\boldsymbol{r}_1, \cdots, \boldsymbol{r}_N)$$
$$\boldsymbol{z}^N = (z_1, \cdots, z_N)$$

Think about shifting the molecule, rotating it, or re-labeling the atoms.

What properties should change? Which shouldn't?

In principle, ML algorithms would be able to "learn" important symmetries; however, that may require substantial training/data. ML is likely to progress much more smoothly if important physics/symmetries are directly encoded in the representation.

Other Structural/Geometric Input Representations

Physics-Inspired Structural Representations for Molecules and Materials

Felix Musil, Andrea Grisafi, Albert P. Bartók, Christoph Ortner, Gábor Csányi, and Michele Ceriotti*

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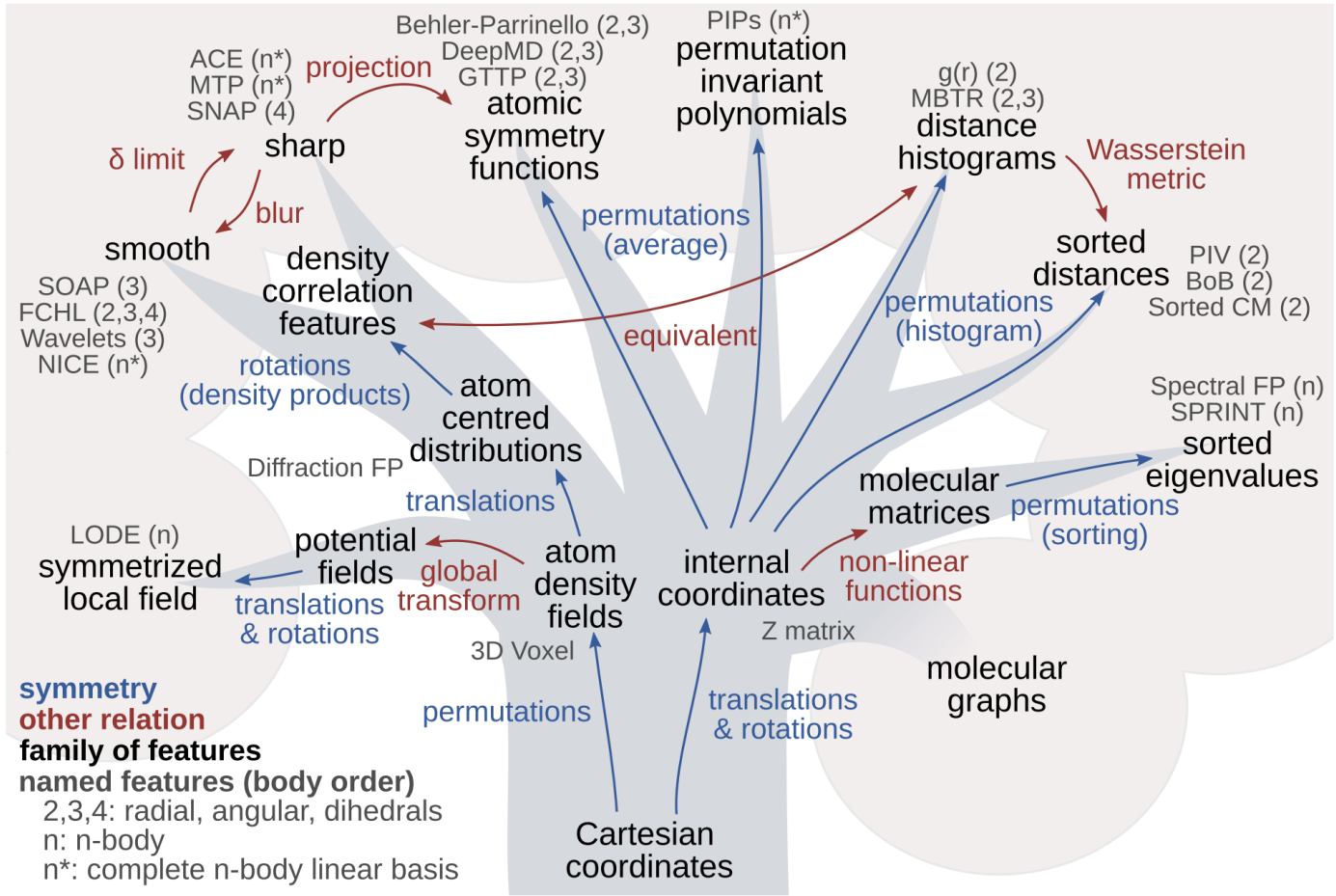
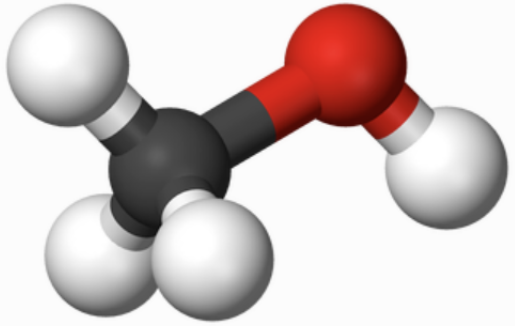


Some Examples

Coulomb Matrix

$$M_{ij}^{\text{Coul}} = \begin{cases} 0.5 z_i^{2.4} \text{ for } i = j \\ \frac{z_i z_j}{r_{ij}} \text{ for } i \neq j \end{cases}$$

- represents entire molecule/fragment



$$\begin{bmatrix} 36.9 & 33.7 & 5.5 & 3.1 & 5.5 & 5.5 \\ 33.7 & 73.5 & 4.0 & 8.2 & 3.8 & 3.8 \\ 5.5 & 4.0 & 0.5 & 0.35 & 0.56 & 0.56 \\ 3.1 & 8.2 & 0.35 & 0.5 & 0.43 & 0.43 \\ 5.5 & 3.8 & 0.56 & 0.43 & 0.5 & 0.56 \\ 5.5 & 3.8 & 0.56 & 0.43 & 0.56 & 0.5 \end{bmatrix}$$

Some Examples

Atom-centered Symmetry Functions

$$f_c(r_{ij}) = \begin{cases} \frac{1}{2}\left[\cos\left(\frac{\pi r_{ij}}{r_c}\right)+1\right] & \text{for } r_{ij} \le r_c \\ 0 & \text{for } r_{ij} > r_c \end{cases}$$

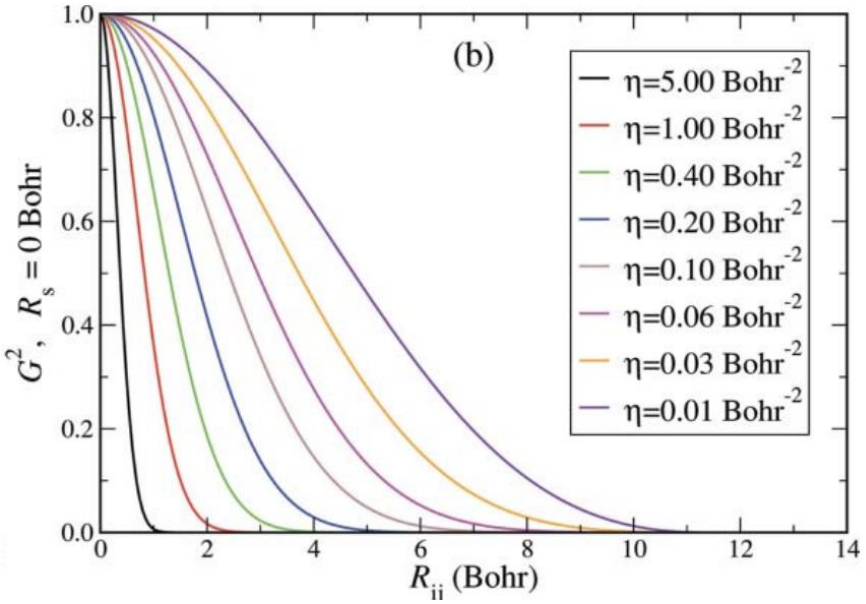
$$G_i^1 = \sum_j f_c(r_{ij})$$

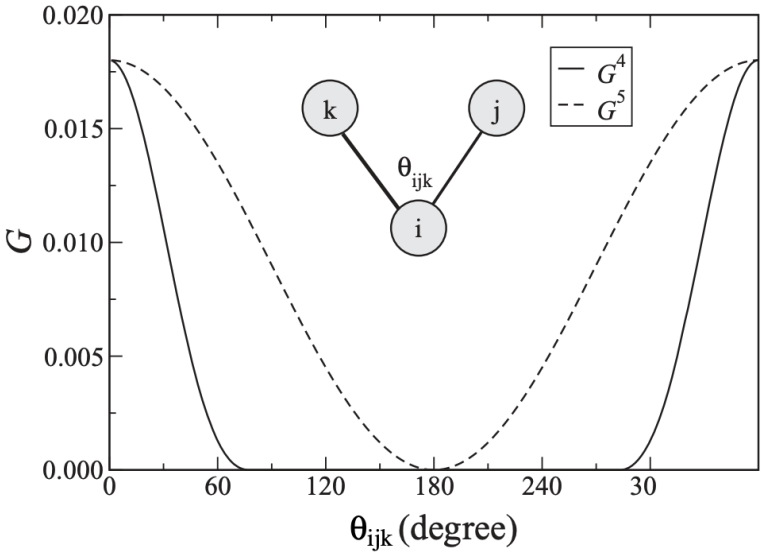
$$G_i^2 = \sum_j e^{-\eta(r_{ij}-r_s)^2} f_c(r_{ij})$$

$$G_i^3 = \sum_j \cos(\kappa r_{ij}) f_c(r_{ij})$$

$$G_i^4 = 2^{1-\zeta} \sum_{j,k\neq i} (1+\lambda\cos\theta_{ijk})^\zeta e^{-\eta(r_{ij}^2+r_{ik}^2+r_{jk})^2} f_c(r_{ij}) f_c(r_{ik}) f_c(r_{jk})$$

$$G_i^5 = 2^{1-\zeta} \sum_{j,k\neq i} (1+\lambda\cos\theta_{ijk})^\zeta e^{-\eta(r_{ij}^2+r_{ik}^2} f_c(r_{ij}) f_c(r_{ik})$$



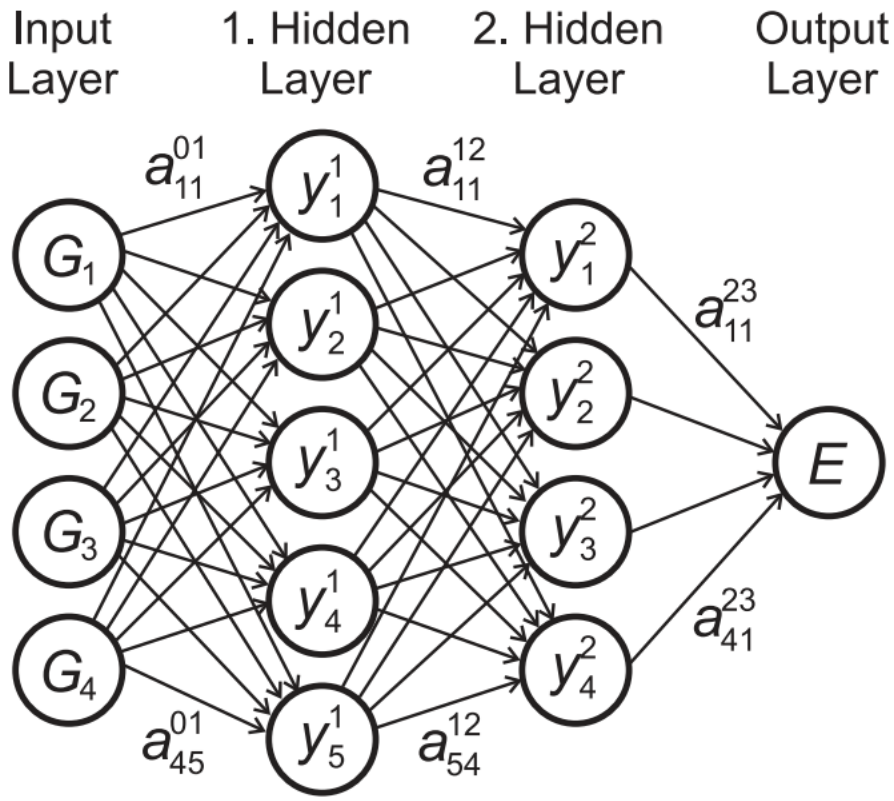


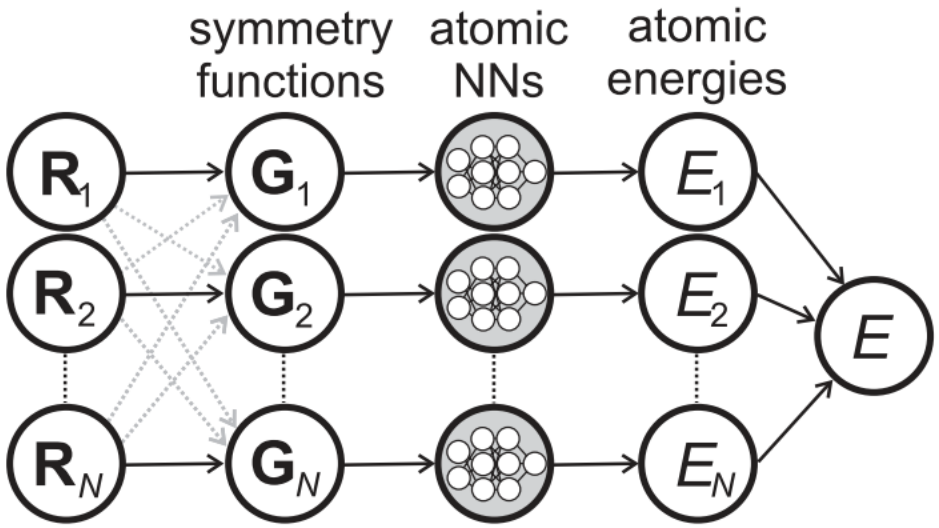
- represents local atom environment
- parameters adjust sensitivity to particular perturbations

Behler *J. Chem. Phys.* **2011**

Some Examples

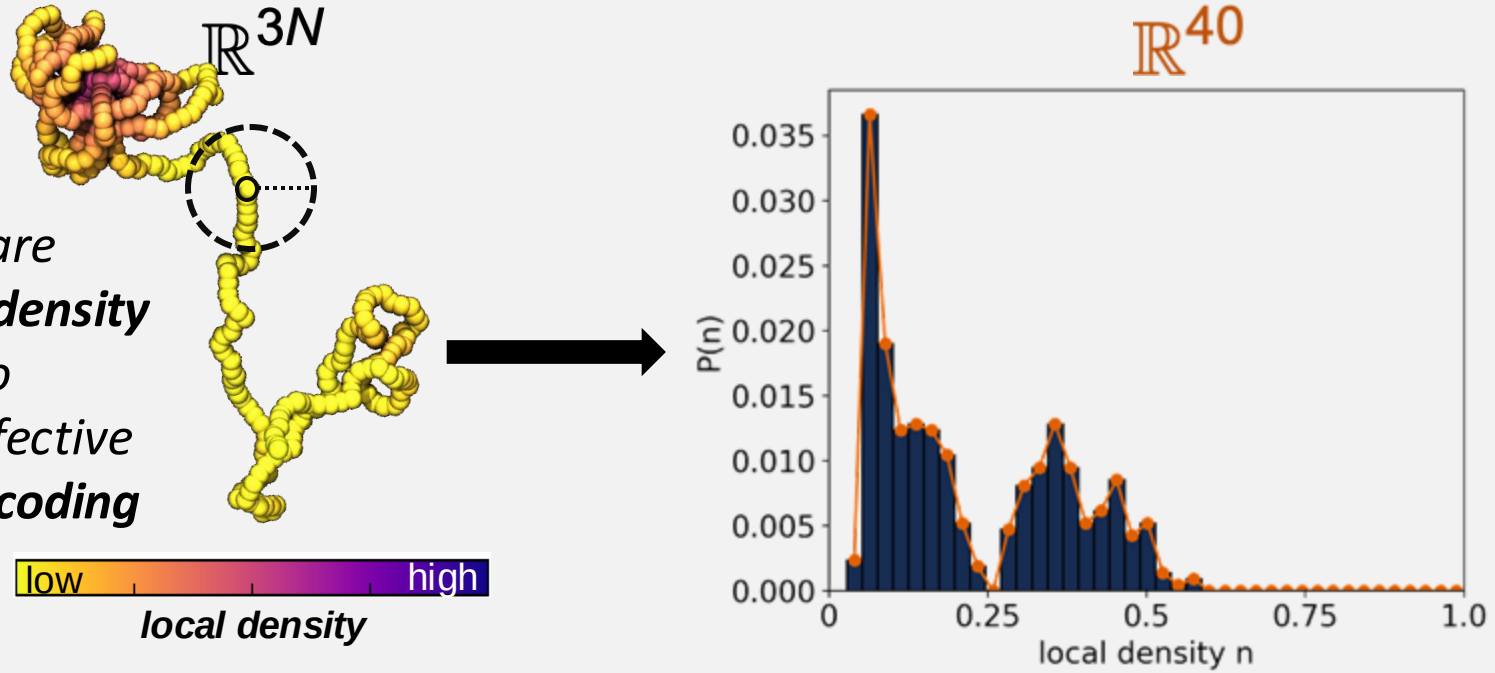
Atom-centered Symmetry Functions: **Application to "Machine Learning Potentials"**





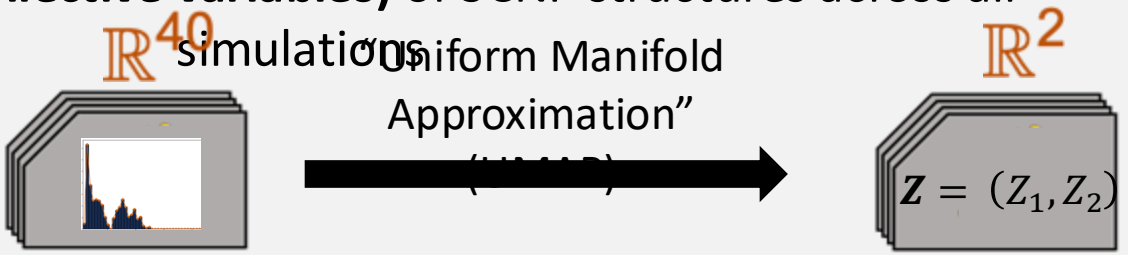
Behler *J. Chem. Phys.* **2011**

Some Examples



Coordinates** are converted to **density histograms** to provide an effective **numerical encoding of chain morphology

Unsupervised ML can then generate an **organized, low-dimensional** representations **(collective variables)** of SCNP structures across all simulations



7,680 SCNPs × 20 snapshots = **153,600 total structures**

Patel, Colmenares, Webb. *ACS Polymers Au.* ***2023***

Some Examples

Broad morphological classification of SCNP structures:

1. Compact globules
2. Tadpole and pearl-necklace
3. Deformable globules and rods