

In too deep? Neural networks versus linear models for critical micelle concentration prediction

Alexander Moriarty,^{*,†} Takeshi Kobayashi,[†] Matteo Salvalaglio,[†] Alberto Striolo,^{†,‡} Andrew Campbell,[¶] and Ian McRobbie[§]

[†]*Department of Chemical Engineering, University College London, UK*

[‡]*Gallolgy College of Engineering, University of Oklahoma, USA*

[¶]*Physical Chemist, Innospec Ltd., Ellesmere Port, UK*

[§]*Senior Vice President, Research and Technology, Innospec Ltd., Ellesmere Port, UK*

E-mail: alexander.moriarty.21@ucl.ac.uk

Abstract

TODO: Write this.

Introduction

Perhaps the most well established predictor for critical micelle concentration (CMC), X_{cmc} , is the Stauff-Klevens relationship, first published in 1953.¹ It formalised the observation that CMC decreases exponentially with an increase in the number of carbons in the hydrocarbon tail, n_c :

$$\log X_{cmc} = A - Bn_c, \quad B > 0 \tag{1}$$

where A and B are empirical constants that depend on the temperature and the homologous series, i.e. the headgroup. The model is simple, yet accurate, and it is easily interpretable: to reduce CMC, extend the surfactant’s hydrocarbon tail. Its only drawback as a predictive model is its very limited applicability domain; each set of parameters is only applicable to surfactants with a specific headgroup and a linear carbon tail. One of the goals of quantitative structure-property relationship (QSPR) development is to produce models that are general, so that we can apply them to a diverse range of compounds, design novel molecules with target properties, and interpret the models’ results to glean chemical insights.

To that end, there have been a wealth of investigations into making more general models for CMC prediction.²⁻⁴ (More references to be added.) Recently, an approach based on graph neural networks (GNNs) has produced highly accurate predictions, whilst having the advantage of being applicable to nonionic, cationic, anionic and zwitterionic surfactants simultaneously.⁵ Such neural networks have many trainable parameters and a complex functional form. This ensures their versatility as general approximators, but makes them highly susceptible to overfitting (CITATION). By using such complex models, we also abandon the parsimony exhibited by Stauff-Klevens, and chemical insights can be much more difficult to derive. Furthermore, deep neural networks’ ostensible ‘universality’ can be misleading: extrapolating the model’s results to out-of-domain molecules (ones that are ‘dissimilar’ from the training data) will yield unreliable and potentially misleading predictions.

In this article, we assess a spectrum of empirical models for CMC prediction, with the intent of finding the optimum trade-off between accuracy, generality and interpretability for this task, by correlating our models’ interpretations with published research. We also apply a technique for adding uncertainty quantification to GNNs, which can indicate whether a molecule is within the model’s applicability domain and therefore whether a given prediction is reliable. We aim to demonstrate a best-practices approach to applying machine learning to QSPR tasks on small datasets.

Method

A dataset of 202 surfactants was used, which was curated by a previous work⁵ by accumulating results from several publications. This dataset was selected because, to the authors’ knowledge, it is currently the largest public dataset of CMCs for several classes of surfactant collected at standard conditions, in an aqueous environment between 20 °C to 25 °C. These data were split into training and test subsets, to simulate the real-world scenario of using a model to make inferences about molecules for which no data is available. The training data was used to fit the models, whilst test data was ‘locked away’ until it had been decided that the model was optimised, and the performance metrics on the test data was used for comparison. For some models, the training data was further split into optimisation and validation subsets; the optimisation data was used when calculating the loss function during model fitting and the validation data was used for on-the-fly evaluation of model performance during training.

To provide a consistent benchmark of model performance, the same train/test data splits were used as Qin et al.⁵ and models were also trained and evaluated using only the nonionic surfactants from the dataset, so as to test whether generalised all-surfactant models can be as accurate as models trained on one class of surfactant. The number of each class of surfactant in the train and test subsets of the data are shown in Table 1.

Table 1: The number of each class of surfactant contained in the train/test subsets of the CMC dataset.

Data subset		Number of			
Surfactant classes	Train/test	Nonionics	Anionics	Cationics	Zwitterionics
All	Train	110	30	31	9
	Test	12	4	4	2
Nonionics	Train	98			
	Test	12			

A QSPR pipeline requires choosing two essential functions: a representation function, whose parameters are defined before training the model, and a mathematical form that maps

this representation to a prediction. The processes by which these functions are developed are called *feature engineering* and *model selection*, respectively.

Feature engineering

The ideal molecular representation depends on the task at hand. Ideally, it should be compact, but complete;^{6,7} ‘as simple as possible, but not simpler.’ To that end, the representation should contain enough information to distinguish between isomers that with distinct properties, though concessions can be made if we restrict the model’s domain and self-impose limits on the type of isomers we expose the model to, both during training and in use. Representations may also include descriptions of state, such as temperature and pressure,⁸ but this is redundant in cases where the training data spans a very limited range of states.

In the case of the Stauff-Klevens model, the representation effectively has two components: the category of the headgroup, and the length of the tail group. The model technically distinguishes between isomers by imposing strict constraints on the structure of the molecules to which it can be applied: position and functional isomers correspond to distinctive categories, so that the model must learn independent parameters for each of them, and the constraint on the tail group means that chain isomers or the presence of non-alkyl groups in the carbon chain are not permitted. Mathematically, this representation can be formalised using a technique called *one-hot encoding* and by defining the set of headgroups for which we have data, $\{h_i \mid 0 \leq i \leq N\}$. The encoding is a vector given by

$$\vec{s}_i = \begin{cases} 1 & \text{if headgroup is } h_i \\ 0 & \text{otherwise.} \end{cases} \quad (2)$$

Different headgroups therefore correspond to orthogonal encodings. If we have a set of trained parameters $\{A_i, B_i\}$ corresponding to headgroup h_i , Equation 1 can be rewritten as

$$\log X_{cmc} = \mathbf{W} \vec{s} \cdot \begin{bmatrix} 1 \\ -n_c \end{bmatrix}, \quad \mathbf{W} = \begin{pmatrix} A_1 & A_2 & \dots & A_N \\ B_1 & B_2 & \dots & B_N \end{pmatrix}. \quad (3)$$

We can try to make the approach more general by decomposing a molecule into smaller sets of *atomic environments* and representing it by the number of each of these constituents. Because certain groups of atoms and bonds are common in organic surfactants, the resulting feature vectors are not orthogonal, and we can apply the model even when we have made small changes to the headgroup, or introduce branching and other functional groups to the tail.

In this approach, the molecule is split into atomic environments up to a given radius, r : each environment is centred on an atom and extends r steps along connecting bonds. Effectively, we discard the categorical encoding in favour of introducing more continuous, count-based features, like n_c . The set of all environments in the training data up to radius r , $\{e_i \mid 0 \leq i \leq N\}$, is extracted and the resulting feature vector is

$$\vec{c}_i = \text{Count}(e_i). \quad (4)$$

Now, a change in headgroup composition is reflected in a change in subgraph counts, and provided the new subgraph exists in our training data, the model can adjust its prediction accordingly. Branch points in a carbon chain are distinguished from main-chain groups, as they terminate in a CH group, rather than CH₂. This type of representation is called an *extended-connectivity fingerprint* (ECFP).⁹

However, these fingerprints do not necessarily distinguish between all positional isomers or chain isomers, particularly with smaller values of r , nor are stereoisomers treated differently. Another potential disadvantage is that the number of unique atomic environments is potentially very large relative to the size of the data available, which poses a risk of overfitting. Furthermore, larger environments necessarily envelop smaller ones, which means that there is some duplicate information in the representation: the presence of a (CH₂)₃ envi-

ronment implies the presence of three CH_2 environments, so that there is multicollinearity. This redundancy can impede model fitting and interpretation.

TODO: Graph representation description.

Model selection

TODO:

- ECFP linear model and feature selection description.
- Graph neural network model description.
- Hyperband description.

Results

TODO: Performance metrics, interpretations, parity plots(?).

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Unsure whether to acknowledge Andrew's specific contribution (data entry for the NIST anionics) or just leave him in the authors, as-is.

Supporting Information Available

Source code for featurisation and model training, graph neural network logs and metrics for hyperparameter optimisation and final training, and individual model predictions.

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TOC Graphic

I'm looking for ideas for the TOC graphical entry – common practice seems to be to draw a really abstract picture of a molecule going through a network, but that doesn't seem like the best thing to do here because I'm specifically comparing against other models.