Integrating theory with machine learning for predicting polymer solution phase behavior

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Abstract

Flory-Huggins (FH) theory is foundational to understanding macro-phase separation in polymer solutions; however, its predictions often quantitatively disagree with experiment. Recent machine-learning (ML) methods have generated predictive models of phase behavior across a broad range of chemistries and state variables with uncertainty comparable to experiment, but they lack interpretability. In this work, we develop several hybrid frameworks that combine Flory-Huggins theory with ML to (i) further improve interpolation and extrapolation with less experimental data, as well as (ii) provide interpretability of the ML model. Using the well-studied binodal of polystyrene-cyclohexane as a case study, we compare data-derived ML models to hybrid models where the prediction is confined by a theoretical expression (theory-constrained model), or the feature vector input incorporates theoretical expressions (theory-informed model). Even though Flory-Huggins theory is imperfect, its incorporation improves

performance when only 2 or 3 molecular masses are in the training set. However, the theoryconstrained formulation requires significantly more data than the theory-informed models. Neither however provides advantages in accuracy or computational efficiency when greater coverage of the parameter space or quantities of experimental data are available, likely due to limitations of the theory. Even so, these hybrid models provide physical relationships, such as the molecular mass dependence of the critical point or of the coefficients within a FH expression. This aspect of physics-incorporated ML models not only enhances trust in predictions, but also provides a systematic means to identify anomalous behavior, and subsequently assess experimental data quality or reveal unanticipated correlations among factors.

1. Introduction

Polymer materials are often synthesized, processed, or purified in solution where solvent selection is based on experimental intuition or practices such as comparing Hansen solubility parameters (HSPs).^{1–3} These methods provide estimates well below or above the critical point for binary component solutions. However, fractionation, self-assembly, and structure directing processing methods rely on transitions through the binodal phase boundary. For instance, specific solvents may be used to cast polymer films and membranes in which the resulting morphology depends on navigating the phase diagram during thermally-induced phase separation,^{4,5} or introducing a non-solvent.^{6,7} This phase behavior not only depends on configurational statistics and local pair-wise interactions, but also on chain interactions and conformations spanning multiple length scales that vary with constituent composition, concentration (ϕ), mass-average molecular mass M_w , polydispersity (PDI), temperature (T), and pressure (p).

The ability to quantitively predict the solution phase behavior of polymers *a priori* has been investigated extensively since the first well-known theory by Flory and Huggins (FH),^{8–11} which assumes a temperature-dependent constant, χ , to describe monomer-level pair-wise enthalpic interactions. Unfortunately, predictions show large disagreement with experiments away from the critical point, indicating additional influencing factors.¹² Extensive modifications to Flory-Huggins^{13–15} in addition to other lattice-fluid models, such as the Sanchez-Lacombe model^{16–18} or the Lattice Cluster Theory by Freed and co-workers,¹⁹ have resulted in better predictions for upper critical solubility, lower critical solubility, and closed-loop phase behavior. Many of these more rigorous models rely on best fit parameters that are ultimately chemistryspecific and require multiple optimization processes to make predictions for each polymer molecular mass and polymer-solvent system. This complexity grows exponentially as the number of components increase (*e.g.*, ternary, etc.). Thus, establishing these theoretical parameters for every polymer-solvent system is intractable due to the number of experimental data points and fitting procedures it would require.

Recently, the utilization of machine learning (ML) models in polymer property prediction has shown promise.²⁰⁻²² Several studies have discussed the use of ML to aid the prediction of a polymer's solubility in a solvent, such as regression models predicting solubility parameters²³ or classification models predicting compatibility with a solvent/nonsolvent.^{24,25} Universal models providing complete phase diagrams for arbitrary polymer-solvent pairs with upper critical solution (UCS), lower critical solution (LCS), and closed loop behavior have also been developed using regression ML models trained on a data set of binary cloud points.^{26,27} The performance of these models, especially for new inputs, relies on the amount of available data, featurization strategies, model training procedure, similarity of the new inputs, and model hyperparameters among other factors. For instance, predictions on unseen cloud points are within 2-3 °C and extrapolating to new polymers requires as little as 20 additional training data to predict cloud points within 5 °C. The predicted phase behavior agrees well with known phase behavior in the literature, but can sometimes result in unphysical curve shapes for composition extrapolations (and interpolation) beyond available experimental cloud point data.²⁷ Adding known thermodynamics into the model may improve this accuracy, reduce training data necessary to generalize to new polymer-solvent systems, and provide physical insight between features and predictions.

Physics-informed machine learning, which integrates physical relationships into the model, has recently been shown to improve accuracy and generalization relative to data-derived ML models.²⁸ These hybrid models provide interpretability, can utilize databases containing experimental data and theoretical model predictions, and even identify new physical relationships between output and features.²⁹ Physics-informed models can also help solve complex physics, for instance, physics-informed neural networks (PINNs) have been developed to solve partial differential equations which have been implemented in polymer self-consistent field theory.³⁰ Numerous approaches to leverage theory in machine learning models have been developed.^{31–34} One is to utilize theoretical expressions to engineer the feature vector, in lieu of raw experimental descriptors or dimensionally reduced inputs (e.g., principal component analysis). For instance, in our previous work we chose physics-based features predicated on the thermodynamics of polymer solubility (composition, $\log M_w$, ϕ , T, p, PDI, etc.).^{26,27} Theoretical expressions can also be directly integrated into the feature vector. For example, Audus et al. recently demonstrated prediction of polymer radius of gyration by combining scaling theory with MD simulation data.³¹ They showed significant improvement to model predictions even when an imperfect theory was used. Alternatively, the ML model can be trained to predict the parameters of a theoretical expression, and thus capture complex relationships between features and parameters.

Herein, we use the well-studied binodal of polystyrene-cyclohexane (PS/CH) as an exemplar to develop several hybrid frameworks that combine Flory-Huggins (FH) theoretical expressions with machine learning to (i) further improve accuracy and generalization with less experimental data, as well as (ii) provide interpretability of the ML model. The hybrid models

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range from theory-constrained, where the predictions are confined by a theoretical model, to theory-informed, where theoretical expressions are solved to generate a "meta" feature that augments or replaces the traditional feature vector input to the ML model. The former utilizes a neural network (NN) to learn the parameters in a theoretical expression for the enthalpic pairwise interaction parameter (χ) given experimental cloud point temperatures. These parameters are then used to calculate binodal curves at new conditions. The latter trains a NN to learn the mapping from physics-informed features (M_w , PDI, etc.) and/or theory-guided features (χ) to temperature. Following a description of these theoretical expressions, their incorporation into the ML workflow, and required data curation, we compare the prediction accuracy of the hybrid models to that of previous ML models and discuss the interpretability afforded by the theoretical relationships.

2. Models

2.1 Theory

2.1.1 Original Flory-Huggins Theory

To clarify how theory is integrated into the ML model, we briefly review how FH lattice theory is used to compute the binodal curve which is found in many examples in literature.^{13–15,35} For a binary mixture of components A and B on a lattice with n_T total sites, the FH expression for the Gibbs free energy of mixing is given as,¹²

$$\frac{\Delta G}{n_T k_B T} = \frac{\phi_A}{N_A} \ln \phi_A + \frac{\phi_B}{N_B} \ln \phi_B + \chi_{AB} \phi_A \phi_B \tag{1}$$

where k_B is the Boltzmann constant, ϕ_i is the volume fraction of component *i*, $\phi_A + \phi_B = 1$ due to the incompressibility assumption, N_i is the number of repeat unit segments ($N_i = 1$ for solvents), and χ_{AB} is the FH interaction parameter. For polymer solutions where component A is taken to be the polymer, N_A can be determined from the mass-average molecular mass M_w and repeat unit molecular mass \hat{M}_w as,

$$N_A = \frac{M_w}{\hat{M}_w} \frac{\nu_A}{\nu_B} \tag{2}$$

where v_A and v_B are the monomer and solvent molecule volumes, respectively. The use of the mass-average molecular mass provides a means to estimate the impact of polydispersity. The first two terms of equation 1 express the configurational entropy of two components mixing, and the final term captures the enthalpic contribution from the change in interactions among the components. The simplest form of FH assumes pair-wise interactions, which are normalized by the thermal energy and expressed as χ_{AB} . This implies monomer-solvent interactions are purely enthalpic, and for a specific constituent composition (chemistry), χ_{AB} scales as

$$\chi_{AB} = \nu_A \frac{\delta_{AB}^2}{k_B T}$$
(3)

where δ_{AB} is a constant that captures the magnitude of the pair-wise A-B interaction, which is sometimes experimentally expressed as the difference of Hildebrand solubility parameters of the polymer and solvent.³⁶

2.1.2 Extended Flory-Huggins Theory

Component interactions depend on many state variables. This implies that the separation of entropic and enthalpic contributions in equation 1 is not strictly correct. This may be

accounted for by replacing χ_{AB} with a semiempirical term $g(T, \phi_A)$ which is a function of both temperature and concentration. With this ansatz, the extended FH expression for the Gibbs free energy can be written as,

$$\frac{\Delta G}{n_T k_B T} = \frac{\phi_A}{N_A} \ln \phi_A + \frac{\phi_B}{N_B} \ln \phi_B + g(T, \phi_A) \phi_A \phi_B \tag{4}$$

The relationship between $g(T, \phi_A)$ and χ_{AB} is determined from the chemical potential to be,¹⁵

$$\chi_{AB}(T,\phi_A) = g - \phi_B g' \tag{5}$$

where $g' = (\partial g / \partial \phi_A)_T$, and integration at constant temperature yields,

$$\int_{\phi_A}^{1} \chi_{AB}(T,\phi) d\phi = (1-\phi_A)g(T,\phi_A)$$
(6)

Therefore, $g(T, \phi_A)$ becomes χ_{AB} only if g is independent of concentration. In most cases, a functional form for χ_{AB} is chosen and fit to experimental data. As in previous work,¹⁵ we separate the functional dependency of $\chi_{AB}(T, \phi)$ as,

$$\chi_{AB}(T,\phi) = D(T)B(\phi) \tag{7}$$

where

$$D(T) = d_0 + \frac{d_1}{T} \tag{8}$$

$$B(\phi) = 1 + b_1 \phi + b_2 \phi^2$$
(9)

Note that the constant d_0 implies an entropic contribution to the monomer-solvent interaction parameter. Additionally, equation 4 becomes equation 1 when $d_0 = b_1 = b_2 = 0$. From equations 4-6, we can rewrite the free energy expression as,

$$\frac{\Delta G}{n_T k_B T} = \frac{\phi_A}{N_A} \ln \phi_A + \frac{(1 - \phi_A)}{N_B} \ln(1 - \phi_A) + \phi_A \int_{\phi_A}^1 \chi_{AB}(T, \phi) d\phi$$
(10)

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Inserting equations 7-9 into equation 10 yields the final expression used to determine the binodal from extended FH theory,

$$\frac{\Delta G}{n_T k_B T} = \frac{\phi_A}{N_A} \ln \phi_A + (1 - \phi_A) \ln(1 - \phi_A) + \phi_A \left(d_0 + \frac{d_1}{T} \right) \left(1 - \phi_A + b_1 \left(\frac{1}{2} - \frac{\phi_A^2}{2} \right) + b_2 \left(\frac{1}{3} - \frac{\phi_A^3}{3} \right) \right)$$
(11)

We note that other functional forms for $B(\phi_A)$ have been proposed, such as $B(\phi_A) = 1/(1 - b\phi_A)$.¹⁴ These forms have been shown to predict the upper critical solution binodal for PS/CH. Additional terms may also be added to D(T), such as d_2/T^2 and $d_3 \ln T$, to incorporate other types of phase behavior like lower critical solution and closed-loop behavior.¹⁵ The workflows developed here can include these additional terms if the phase behavior is unknown and/or insight into the different phase diagrams are required. To afford our assessment of various methods to integrate theory with ML, we will focus on equations 1 and 11, and restrict PS/CH co-existence data to upper critical solution behavior.

2.1.3 Binodal

Typically, the binodal curve is determined from the free energy expressions by determining the chemical potentials of the solvent-rich and polymer-rich phases (phase I and II, respectively) and solving the equations simultaneously. This can be calculated using root-finding methods, where if χ_{AB} is known then the concentrations in phase I and II can be found. However, this can be computationally challenging if the initial guesses for the concentrations are poor, causing issues in the numerical solver. Hence, we implement a mathematically equivalent numerical approach by minimizing the total intensive free energy Δg^T with respect to the polymer concentration in both phases. First, the total intensive free energy Δg^T can be written as a function of the total extensive free energy ΔG^T as,

$$\Delta \mathbf{g}^{T} = \frac{\Delta G^{T}}{V^{T}} = \nu \Delta \mathbf{g}^{I}(\boldsymbol{\phi}^{I}) + (1 - \nu) \Delta \mathbf{g}^{II}(\boldsymbol{\phi}^{II})$$
(12)

where $\Delta g^{I}(\phi^{I})$ and $\Delta g^{II}(\phi^{II})$ are the intensive free energies in phases I and II respectively and ν is the volume fraction of phase I, $\nu = V^{I}/V^{T}$. In this case, V^{I} is the total volume in phase I and V^{T} is the total volume. For simplicity, we drop the subscript A in ϕ_{A} and recall that $\phi^{I} = V_{A}^{I}/V^{I}$. To determine ν , we use the incompressibility constraint so that the total polymer volume is conserved in both phases and therefore,

$$\phi^T = \nu \phi^I + (1 - \nu) \phi^{II} \tag{13}$$

$$\nu = \frac{\phi^T - \phi^{II}}{\phi^I - \phi^{II}} \tag{14}$$

Inserting equation 14 into equation 12 obtains the final expression,

$$\Delta g^{T} = \left(\frac{\phi^{T} - \phi^{II}}{\phi^{I} - \phi^{II}}\right) \Delta g^{I}(\phi^{I}) + \left(1 - \frac{\phi^{T} - \phi^{II}}{\phi^{I} - \phi^{II}}\right) \Delta g^{II}(\phi^{II})$$
(15)

The terms Δg^{I} and Δg^{II} are then replaced with the original (eq. 1) or extended Flory-Huggins (eq. 11) expressions and total free energy equation Δg^{T} is minimized to solve for ϕ^{I} and ϕ^{II} given χ_{AB} .

We note that a total polymer concentration ϕ^T in equation 14 must be selected such that it is inside the binodal for the minimization approach to work. We choose ϕ^T to be the critical concentration ϕ_c , as the critical point can be analytically determined from,

$$\frac{\partial^2 \Delta G}{\partial \phi^2} = \frac{\partial^3 \Delta G}{\partial \phi^3} = 0 \tag{16}$$

The complete derivatives are shown in section S1 of the Supporting Information. Once the theoretical critical concentration ϕ_c and critical χ_c are found, the binodal concentration values $(\phi^I \text{ and } \phi^{II})$ are determined by minimizing Δg^T for a range of χ_{AB} values (or D(T) values for the extended FH theory) between χ_c (the minimum χ_{AB} value) and $1.5\chi_c$, which is large enough to cover the experimental temperature range for this system. Specifically, given a χ_{AB} value within $[\chi_c, 1.5\chi_c]$, equation 15 is minimized using the modified Powell algorithm³⁷ to determine ϕ^I and ϕ^{II} . For the ML models that use FH theory, χ_{AB} (or D(T)) at experimental concentrations ϕ are interpolated from the theoretical binodal and implemented in the machine learning workflow as described below.

2.2 Machine Learning Workflow

We adopt the feature vector introduced in prior reports for polymer phase behavior (see section S2 of the Supporting Information).^{26,27} For each cloud point temperature datum, we ascribe an array of values consisting of structure (M_w , PDI, *etc.*) and composition characteristics (Hansen solubility parameters or molecular descriptors) for each component, along with state variables (p, T) and additional experimental factors (n-phase temperature direction). This array is structured with features that are known from thermodynamics to be crucial to phase behavior and is generalizable to any polymer/solvent system, albeit it does not incorporate any relationships among the features or between features and output. For the polystyrene/cyclohexane (PS/CH) system discussed herein, we reduce the generalized feature vector to only include mass-average log M_w , PDI, and $\sqrt{\phi}$, referred to as the Baseline ML Model. Figure 1 and 2 summarizes how FH theory is integrated into the ML model workflow for informing the model via feature augmentation or replacement (theory-informed), or constraining



Figure 1. Schematic of the theory-informed ML model training workflow depicting how inputs are processed and sent through the NN to predict the cloud point temperature and calculate a loss value. The ML model is outlined in black and the procedure to calculate the theoretical χ_{AB} values is outlined in red. The ML model consists of a NN with a single hidden layer and 100 units in the layer. The χ -informed model incorporates χ_{cp} in the feature vector, whereas the baseline ML model uses only the NN and eliminates χ_{cp} from the feature vector. The Chi2T ML model has a feature vector only containing χ_{cp} .

the model predictions (theory-constrained), respectively. Furthermore, we employ a shallow NN with only a single hidden layer with 100 units commensurate with the reduced number of features. Each ML model maps the features as input to an output temperature \hat{T} , which is then compared to experimental cloud point temperature T to calculate a loss function $\mathcal{L}(T, \hat{T})$. This is backpropagated through the NN to train the ML model to minimize the loss function.

2.2.1 Theory Integration

Figure 1 summarizes the workflow used to integrate theoretical relationships into the feature vector. First, M_w is converted to N_A via equation 2. Then, FH theory (equation 1) is used to compute the binodal as a function of χ_{AB} for the given N_A (see section 2.1.3 and FH binodal



Figure 2. Schematic of the extended FH model training workflow depicting how inputs are processed and sent through the NN to predict the theory coefficients for $\chi_{AB}(T, \phi)$ in equations 7-9. The predicted cloud point temperatures \hat{T} are determined by solving the extended FH equations (section 2.1.3) and solving for \hat{T} in $D(\hat{T})$. Each coefficient is predicted using a NN with a single hidden layer and 100 units in the layer.

plot in Figure 1). The plot of the binodal is then used to read off the specific value of χ_{AB} that corresponds to a given experimental concentration value ϕ_{cp} . We denote this specific χ_{AB} as χ_{cp} . Therefore, we inform our ML model with χ_{cp} as an additional "meta" feature which establishes a theoretical relationship between other features, referred to as the χ -informed ML Model. This approach is inspired by hierarchical ML³⁸ and transfer learning³⁹. If FH theory was perfect, then the NN would only need χ_{cp} as an input. Therefore, we create another model, referred to as the Chi2T ML Model where we remove M_w , PDI, and ϕ since both M_w and ϕ are used to determine the value of χ_{cp} , reducing the NN features down to a single value that maps χ_{cp} to *T*. Note that for Chi2T ML Model, the temperature dependence of χ_{cp} is not prescribed, but determined by the NN. As structured, it imposes the original FH theory's constraints that χ_{AB} (*i.e.*, free energy of component interactions) is only a function of temperature. Thus, by removing the other features, the NN incorporates the same imperfect assumptions of the FH theory.

Figure 2 summarizes the extended FH model (Section 2.1.2), where cloud point data is used to determine the coefficients of a theoretical expression for χ_{AB} , motivated by recent physics-constrained models.^{29,34} Four independent NNs established the relationship between M_w and PDI and the coefficients d_0 , d_1 , b_1 and b_2 . Thus, instead of training the ML model to predict individual cloud points (*i.e.*, M_w , PDI, and ϕ for each T), each ML model maps a unique feature pair $\{M_w, PDI\}$ to a theory parameter. The theoretical binodal as a function of T is solved numerically via equations 11 and 15 before the predicted cloud point temperature \hat{T} is determined by interpolating the temperature for a given ϕ_{cp} . The loss is determined by comparing the experimental cloud point temperature to \hat{T} . Finally, the gradient of the loss is backpropagated through the NNs, training the weights to optimize the mapping of feature inputs to theoretical parameters. Note that the workflow is not restricted to equations 8 and 9 and can be reformulated for different expressions for χ_{AB} . However, the model predictions are fundamentally constrained by the choice of the functional form of the theoretical expression, and thus accuracy and precision are ultimately limited by these dependencies. Also, training is significantly more computationally expensive than for the previously discussed χ -informed model as the free energy expression (equation 11) is dependent on ϕ and thus the binodal must be recomputed, which entails free energy minimization to get the compositions, at every training iteration.

2.2.2 ML Models

A description of each model introduced above is summarized in Table 1. For the input features listed, the training data is first sent through a preprocessing pipeline that normalizes them to be within the range [0, 1]. We choose to normalize the inputs instead of standardizing (or Z-score normalization) as the distribution of M_w and PDI values used in the extended FH model are not normally distributed (see section S2.2 of the Supporting Information). Standardizing the data significantly increases the prediction error for this model and thus, all models are trained on normalized inputs for consistency. Training consists of updating model weights for 2000 total epochs with the Adam optimizer⁴⁰ and a learning rate of 0.001. Lastly, a 'L2' regularization penalty is applied to the hidden layer with a penalty value of 0.01 to help reduce overfitting.

Model	Input Features	Description
Baseline	$\log M_w$, PDI, $\sqrt{\phi_{cp}}$	NN that maps input features to <i>T</i> for each individual cloud point
χ-informed	$\log M_w, \text{PDI}, \\ \sqrt{\phi_{cp}}, \chi_{cp}$	Baseline input features + theoretical value χ_{cp} at the experimental concentration ϕ_{cp}
Chi2T	Xcp	Maps χ_{cp} to T
Extended FH Model	log <i>M</i> _w , PDI	Maps unique M_w and PDI pairs to theory coefficients d_0 , d_1 , b_1 and b_2 . ϕ_{cp} and T are used in training the NNs.

Table 1. Summary of the ML models compared in this work: baseline ML, χ -informed, Chi2T, and extended FH model. Listed are the names, input features, and descriptions of each model.

For all models except the extended FH model (Figure 1), the NN is constructed using Keras Tensorflow, the ReLU activation function is used for the hidden layer, and all weights are initialized using He (uniform) initialization. The extended FH model (Figure 2) is constructed in PyTorch, where we choose to train multiple NNs rather than a multi-output NN as this allows us to constrain each output layer separately without affecting the other output layers. Each NN model is constructed as described above, except that weight initialization uses default PyTorch values and 'L2' regularization is removed. The output of each NN (d_0, d_1, b_1, b_2) is then concatenated and sent to a custom PyTorch Function class to calculate the binodal and extract the binodal temperatures (see sections 2.1.2 and 2.1.3) before backpropagating the loss to train the models (see Figure 2). As noted above, each model's output layer in the extended FH model can be individually constrained and hence, we apply constraints on d_1 , b_1 , and b_2 using a sigmoid activation function, which constrains the parameters between 0 and 1, to allow faster training and prevent the critical point concentration from becoming too large during training. Moreover, the sign of d_1 dictates the shape of the curve (e.g., positive for UCS or negative for LCS) and therefore we keep this parameter positive in the range [0, 1000] by multiplying the output layer by 1000, although this parameter can be left unconstrained if the phase behavior is unknown (i.e., UCS, LCS, or closed-loop).

In all models, we define the loss function to be the mean squared error between the predicted temperature \hat{T} and experimental temperature T,

$$\mathcal{L}(T,\widehat{T}) = \frac{1}{n} \sum_{j}^{n} (T_j - \widehat{T}_j)^2$$

where *n* is the number of cloud points in the training set. \hat{T} is determined from the data-driven ML model (Figure 1) or the extended FH model (Figure 2). The gradient of the loss with respect to \hat{T} is backpropagated through the network to update the NN weights (one training iteration). For the extended FH model (Figure 2), the loss is initially backpropagated through the custom PyTorch function, sending the gradients of the loss with respect to the parameters to the output layer of each NN, before backpropagation through the NNs. We note that the gradients for the parameters in D(T) are handled analytically, while gradients for the parameters in $B(\phi)$ are handled numerically using forward finite differences with a step size of $\delta b = 0.0001$ (see section S3 of the Supporting Information). Since each coefficient is predicted from a separate NN, we train the temperature-dependent and concentration-dependent coefficients separately, allowing the model to predict the correct temperature region before learning the concentration dependence. This is because the gradients in each parameter are handled differently and therefore, using a single learning rate to train all parameters at once poses numerical difficulties in finding the global minimum in the loss function. Hence, we first freeze the NNs predicting b_1 and b_2 with initialized values, set their outputs to 0, then train the NNs to predict d_0 and d_1 . These models are trained for 500 epochs using an Adam optimizer and learning rate of 0.001. The learning rate is then increased to 0.01 for another 500 epochs before unfreezing the b_1 and b_2 networks. Lastly, all coefficient models are trained with a reduced learning rate of 0.0001 for 500 epochs and subsequently trained with an increased learning rate of 0.001-0.01 for up to 2000 epochs, or until the training loss value stops decreasing over 50 epochs.

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2.2.3 Data Curation

Cloud point data for polystyrene in cyclohexane was extracted from the CRC Handbook of Liquid-Liquid Equilibrium Data of Polymer Solutions⁴¹ and is a subset of the data published on the Polymer Property Predictor and Database (3PDb) website (<u>https://pppdb.uchicago.edu/</u>). In total, 55 unique mass-average molecular mass with a specified PDI were selected from the tabulated data (Section 3.2 of the CRC Handbook) and graphical data (Section 3.3 of the CRC Handbook) sections. Graphical data was extracted using a plot digitizer.⁴² We note that graphical data extracted from plot digitizers is susceptible to user error from inaccurate markings, but we estimate these errors to be less than 0.5 °C. To reduce the risk of training the models on poor experimental data, and thus decreasing prediction performance, the data set was curated further by looking for any noticeable discrepancies in the data by (i) comparing cloud point curves from various literature sources and (ii) analyzing large model prediction errors in the training set. For instance, some cloud point temperatures conflicted with reported coexistence curves, likely due to differences in the reported concentrations. Additionally, some data resulted in large prediction error and were found to be a result of conflicting trends. For example, decreasing M_w resulted in an increase in cloud point temperature (see section S4 of the Supporting Information). Thus, manual review of the data sources for both literature and model consistency was necessary to improve quality of the data set.

The total data set is split into a training set and a test set for training the NN weights and determining prediction error on unseen data, respectively. Initially, the training set consists of 2 distinct M_w (*e.g.*, 20 kDa and 13,200 kDa) that bracket the available polymers. Additional cloud point data for the molecular mass with the largest root mean square error (RMSE) in the test set

is then added subsequentially. This is similar to an active learning approach for minimizing model uncertainty (exploration); however, typically the prediction uncertainty as opposed to the test RMSE is required for pure exploration algorithms. Our approach forces the models to converge more quickly and establish the best interpolation behavior for comparing interpretability of the models. However, this also biases the generalization of the trained model and reduces the test RMSE even before retraining. For instance, the third M_w added to the training set consists of the largest PDI value, due to large extrapolation error in the test set, and therefore all data in the subsequent test sets are within the range of available M_w and PDI values. Random selection of molecular masses in the training set are also compared between models (see Figure S4 in the Supporting Information). To establish the impact of the distribution of molecular mass on model performance, we also develop models trained on the minimum, maximum, and uniformly distributed molecular masses in the database.

3. Results

3.1 Model Accuracy

In most cases, ML models require large data sets for good generalization, but the model performance also highly depends on the data itself (including its distributions) and number of features. To assess the impact of theory integration, we determined the minimum number of molecular masses required to reduce the test prediction error below 3 °C, which is the uncertainty observed in many experimental measurements. Figure 3a compares the test RMSE as a function of number of M_w (with 3 or more cloud points) added to the training set for the 3 theory-ML hybrid models and baseline ML model. Recall that the addition of cloud points with

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new M_w to the training set are based on the largest test prediction error for each model, respectively. Therefore, after adding cloud points from the third M_w (which consists of the largest PDI value), the training sets for each model are not the same, containing cloud points with a different set of M_w values. This also implies the number of cloud points in each case are slightly different due to the difference in the available data per molecular mass. However, the test RMSE trends are the same as a function of number of cloud point data (see Figure S5 in the Supporting Information).

The baseline ML model without any theory-informed features in Figure 3a shows test prediction error within 3 °C by 5 distinct M_w curves, with slight improvement for subsequent training data, in agreement with what has been previously reported for PS/CH.²⁶ Interestingly, the simplest hybrid model, Chi2T model, shows the lowest prediction error (≈ 5 °C) for just 2 M_w values, indicating that using only the theory-derived "meta" feature, even from a limited theory, can reduce interpolation error between molecular masses under extreme data scarcity conditions. This is likely due to the simplicity of the model combined with qualitatively correct trends embedded in the theory. However, the test RMSE remains above 3 °C for all training set sizes, due to the imperfect assumptions behind FH theory that make it quantitatively incorrect. The extended FH model is more complex, therefore requiring more data. Hence, we find that this model requires roughly 9 distinct M_w values to reduce the test prediction error to within 3 °C. However, since the additional complexity does not correspond to the input data itself (e.g., there are only 9 training instances, one for each M_w , as opposed to the individual cloud points input to the other models), it is difficult to determine the precise number of data required for each M_w . Overall, theory integration improves interpolation of new molecular masses relative to the

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Figure 3. Test prediction root mean square error (RMSE) comparing theory-informed and theoryconstrained models to the baseline ML model (a) as a function of the number of mass-average molecular masses (M_w) in the training set and (b) various molecular masses selected from the data set: 10 random, 10 largest, 10 smallest, 5 uniformly selected between 20kDa and 1560kDa, 5 and 9 with the largest MSE in the test set. All NNs have a single hidden layer with 100 units.

baseline ML model with the same NN architecture when training data is limited (see 3 M_w) and incorporates the limits of the parameter space (M_w and PDI); however, as the available training data increases, the benefit of incorporating theory is lost, with the baseline ML and χ -informed models providing the lowest test RMSE. For the χ -informed model, the more complex relationships missing in the FH theory is captured by the additional inputs to the NN and not biased or constrained by the imperfect theoretical expressions. These trends are also seen when randomly sampling the M_w in the training set (see Figure S4 in the Supporting Information).

The ability to interpolate within and extrapolate outside of the molecular mass range is examined by comparing the effect of various molecular masses in the training set on the prediction error. In Figure 3b, we compare the following selection of M_w from the data set: (i) 10 random, (ii) 10 largest, (iii) 10 smallest, and (iv) 5 uniformly distributed, to the results in Figure 3a (*i.e.*, each new training molecular mass was based on the molecular mass with the largest RMSE).

Extrapolation error is reflected in (ii) and (iii), where one half of the molecular mass distribution is used for training and the other for testing. Specifically, we train the models on the largest molecular masses to predict the smallest and vice versa. The models perform in the following order from best to worst: χ -informed, baseline, Chi2T and extended FH theory, demonstrating how overall model generalization is affected by theory integration. χ -informed likely performs the best since it provides a useful representation of the data in the form of χ_{AB} but unlike Chi2T, still includes the same features as the baseline model. Even if FH theory was not beneficial, with enough data it should ultimately perform similar to the baseline model as the model would ignore contributions from χ_{AB} . The extrapolation RMSE for the theory-informed, data-driven models (Chi2T, χ -informed, and baseline) are within 5 °C, whereas the theoryconstrained model (extended FH model) performs poorly (RMSE > 50 °C), suggesting that its increased complexity results in increased sensitivity to the choice of M_w in the training set. The predicted theory parameters are nonlinear as a function of M_w (see below) and likely the reason for the model's large extrapolation error.

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Predicted binodals based on training sets of 5 and 9 M_w values in Figure 3a are shown in Figures 4 and 5, respectively. The extended FH model performs well on trained M_w values (e.g., 20 & 13200 kDa), but with limited training data (Figure 4a) interpolates poorly (e.g., 110 kDa). With more training M_w values, the overall precision increases, and the binodals agree with typical UCS behavior (Figure 5a). The concentration-dependent χ_{AB} in the extended FH model allows more flexibility in the curve shape, and hence the predictions are more sensitive to the range of concentrations in the data set. If only a narrow range of concentrations are available, the extrapolated binodal shape is incorrect, as seen for the high molecular masses (13,200 kDa) where predictions show a weak temperature dependence with increasing concentration (Figure 5a). In contrast, the binodal curves from the Chi2T model are poor even for the training M_w values, irrespective of the total number of M_w values in the training set (Figure 4b & 5b). It generally misses the shape and exhibits a discontinuous shift in the binodal at temperatures below roughly 12 °C, due to an abrupt change in the NNs mapping of χ_{cp} to T at low temperatures (see Figure S6 in the Supporting Information). This is consistent with the above supposition that the relationships embodied within χ_{AB} by the simple FH theory alone is insufficient to capture detailed characteristics of phase separation in experimental systems.

Finally, the χ -informed and baseline ML models provide reasonable UCS behavior with improved accuracy as training data increases (Figure 4c, 4d, 5c, and 5d). The χ -informed model offers slightly smoother UCS curve shapes, indicating that the addition of a theory-informed "meta" feature (χ) improves the model's ability to capture concentration dependency of the cloud point temperature (*e.g.*, 20 & 110 kDa, Figure 4c & d). However, in both cases, some of the binodals deviate from experiment even with additional training data (1,560 kDa, Figure 5c;



Figure 4. Select molecular mass predictions comparing the following ML models: (a) extended FH (theoryconstrained), (b) Chi2T, (c) χ -informed, and (d) baseline. All NN models are trained on the 5 molecular masses shown in Figure 3a (e.g., largest MSE in the test set). Legend shows M_w and PDI for each binodal prediction with training data as squares and test data as triangles. Experimental data are shown from various literature sources in the CRC Handbook.

13,200 kDa, Figure 5d). We believe these issues at specific M_w values are related to insufficient distribution training data at these high M_w . Overall, we conclude that imperfect theory, when used to inform the feature vector, can aid ML models in learning polymer-solvent phase behavior when data is scarce, but using the theory as a constraint requires complex theory and additional data to map polymer properties to the theoretical parameters.



Figure 5. Select molecular mass predictions comparing the following ML models: (a) extended FH (theoryconstrained), (b) Chi2T, (c) χ -informed, and (d) baseline. All NN models are trained on the 9 molecular masses shown in Figure 3a (*e.g.*, largest MSE in the test set). Legend shows molecular mass and polydispersity for each binodal prediction with training data as squares and test data as triangles. Experimental data are shown from various literature sources in the CRC Handbook.

3.2 Model Interpretability

3.2.1 χ_{AB} Dependence

The theory-informed ML models incorporate χ_{cp} as a feature and therefore provide a mapping between FH χ_{AB} and the binodal (cloud point) *T*. Figure 6 summarizes this relationship, comparing the theoretical χ_{AB} values to both experimental *T* and predicted \hat{T} from the Chi2T model. Here, the Chi2T model is trained on all available data to maximize the model's interpretability, however the same plot for the model trained on 9 M_w values from Figure 3a can



Figure 6. χ_{AB} as a function of (a) inverse experimental temperature 1/T and (b) $1/\hat{T}$ predicted from the Chi2T model trained on all available data. The model consists of a NN with a single hidden layer and 100 units in the layer. The symbols in (a) are colored by the normalized log M_w value.

be found in Figure S6 in the Supporting Information. Figure 6a plots the input χ_{cp} as a function of the experimental *T*, showing highly nonlinear behavior and confirming that χ_{AB} contains additional influential factors other than temperature as assumed in FH theory (equations 1 and 3). Using the predicted temperatures \hat{T} from the Chi2T model (Figure 6b), we observe a weak nonlinear dependence of $1/\hat{T}$, as shown by the linear fit on the smallest 10 temperature values. When the Chi2T model is trained on less data we see two linear regions of χ_{AB} as a function of $1/\hat{T}$ (see Figure S6 in the Supporting Information), likely due to the cloud point behavior at low M_w , which explains the change in slope in the cloud point curves in Figures 4 and 5. Since the mapping of χ_{AB} to *T* is not constrained by a functional form such as in equation 3, the 1/T dependence may not be linear. This is observed in Figure 6b, where we see a small change in the slope at higher molecular masses (left side of the plot). Nonetheless, despite training on all available data, the predictions of the Chi2T model are poor (MSE of 8.9 and R^2 of 0.62) and the model is unable to capture the complex relationship observed in Figure 6a.

As expected, the χ -informed model captures the complex relationship in Figure 6a, since the model is able to predict experimental *T* accurately (see Figure S7 in the Supporting Information). To further investigate the importance of χ_{cp} in the χ -informed model, we examine the model's feature importance, where the inputs of the model are ranked based on impact on the output prediction. We apply a game theoretic approach called Shapley Additive Explanations (SHAP)⁴³ to explain the impact each feature has on the predicted temperature (see Figures S8 and S9 in the Supporting Information) for the χ -informed model. While the addition of χ_{cp} to the baseline model shows small improvements in the predictions (*e.g.*, Figures 3-5), the impact on the predicted temperature remains significant, especially at large χ_{cp} values. This suggests that χ_{cp} values provide valuable knowledge of the binodal shape away from the critical point. Interestingly, this is where FH theory fails the most, yet it is still improving the ML model accuracy likely due to capturing the overall binodal shape. We expect this importance to increase as other binodal shapes are included in the training set (including LCS and closed-loop behavior).

The theory-constrained ML framework in the extended FH model inherently provides correlations between the theoretical parameters and experimental features. In Figure 7, we show the ML-estimated theoretical coefficients as a function of $\log M_w$. To the best of our knowledge, no such trends have been established and only tabulated values have been reported in the



Figure 7. Theory coefficients from equations 8 and 9 predicted from ML models trained on 9 M_w values plotted as a function of log M_w and colored by the normalized PDI value. Training data (squares) consist of 9 M_w values added from the test set based on its RMSE, with the remaining M_w values predicted from the test set (triangles). NNs consisting of a single hidden layer and 100 units are used to predict the coefficients.

literature. Overall, we see that the theoretical coefficients show a nonlinear dependence on $\log M_w$ for each parameter. Compared to reported values in the literature, we find our values for d_0 and d_1 are similar for PS/CH.¹⁴ Our ML models can also estimate the effect of PDI in the predicted parameters. As seen in Figure 7, the large deviations observed in some of the predicted coefficients are due to the highly polydisperse samples, implying that the value of the theory coefficients are sensitive to polydispersity. Additionally, plotting the coefficients can determine when terms in the functional form can be removed. For instance, at high M_w (log $M_w > 14$) the

second term in equation 9 becomes negligible. This also implies that the ϕ dependence on the value of χ_{AB} becomes linear for large M_w .

3.2.2 Critical Points

Lastly, the critical point is often used to determine the maximum (or minimum for lower critical solubility) temperature in which a polymer is miscible in solvent at all concentrations, making it valuable for purification processes in which decreasing temperature (or increasing temperature for LCS) past the critical point (at the critical concentration) will cause macro-phase separation. Moreover, knowing the critical point is useful for other processes in which it is important to keep the polymer stable in solution. We next examine the scaling of the predicted critical point temperatures as a function of *N* for the monodisperse molecular masses (PDI < 1.2), dropping the subscript A for simplicity. In Figure 8, we plot the critical temperature T_c determined from the extended FH model (Figure 8a), which assumes $D(T) = d_0 + d_1/T$, and the χ -informed model, which determines T_c by interpolating to the largest predicted temperature. We note that the value of D(T) at the critical point is also a function of ϕ_c and therefore dependent on b_1 and b_2 (see section S1, equation S7 in the Supporting Information).

The inverse of the critical temperature is shown as a function of $1/\sqrt{N} + 1/2N$ (*i.e.*, Shultz-Flory plot) with a linear fit in Figure 8, in agreement with the scaling of experimental critical points reported in other work.^{12,44} We note that in this work, the models are trained on experimental cloud points, and not critical point data, which are more easily measured experimentally. Hence, the predicted critical points are estimated from the fits to the cloud point curves. From the linear fits, the θ temperature, the temperature at which a polymer behaves as an



Figure 8. Inverse critical temperature, $1/\hat{T}$ as a function of $1/\sqrt{N} + 1/2N$ and $\log \phi_c vs. \log N$ predicted from (a,b) the extended FH theory-constrained model trained on 9 distinct M_w from Figure 1a and (c,d) the χ -informed model trained on all available data, respectively. Critical points are estimated (a,b) from equations S6 through S9 in the Supporting Information using the ML-predicted theory parameters and (c,d) from the maximum predicted temperature in the cloud point curve. All trained NNs consist of a single hidden layer and 100 units in the layer. Critical points are colored by whether N was used in the training set (gray) or test set (red) and dashed lines represent best fit lines.

ideal random walk chain, can be determined for the polymer-solvent system. This is estimated from the critical point at infinite molecular weight (*e.g.*, the intercept of the linear fit). The extended FH theory and χ -informed models predict θ to be 305.8 K and 306.3 K, respectively. These values are slightly lower than the experimentally reported θ temperature of ~307.2 K^{45,46} but are within experimental error indicating that the ML models can capture the scaling behavior of a polymer-solvent system by training on cloud point data. We note that the small discrepancy in the predicted θ temperature is likely due to inherent model uncertainty. Nonetheless, this allows new physics insight from the models when trained on polymer-solvent systems in which the θ temperature is unknown.

We next show the scaling of $\log \phi_c$ as a function of $\log N$ predicted by the theoryconstrained and theory-informed models as before. Similar to the critical temperature estimates, the training data does not include critical point values. According to FH theory, $\phi_c \sim N^{\alpha}$ where $\alpha = -1/2$. However, experimentally it has been shown that $\alpha = -0.38$.^{47–49} In Figure 9, we show $\log \phi_c vs. \log N$ with linear fits to the region $\log N > 3.5$. We observe a linear region at large N with a slope of -0.39 and -0.36 for the extended FH model and γ -informed model, respectively, which is in agreement with the scaling behavior reported in the literature. However, we also observe deviation at lower N, consistent with the fact that the scaling of $\phi_c \sim N^{\alpha}$ only applies to large N. Figure 9b shows a significantly larger deviation, likely due to the method of estimating ϕ_c numerically. For instance, the slope at the critical point is 0 and therefore small changes in the estimated T_c can result in large changes in ϕ_c . Furthermore, we plot theoretical $\log \phi_c$ vs. $\log N$ using the extended FH model with $b_1 = b_2 = 0.5$ as well as $b_1 = 0.5$, $b_2 = 0$ in Figure S10 in the Supporting Information. These values were estimated from Figure 7 for a log M_w around 12 and 14, respectively. Overall, the ϕ_c behavior is captured by the model when $b_1 = b_2 = 0.5$, especially at low M_w . The high M_w is better captured by the model when $b_1 = b_2 = 0.5$, especially at low M_w . 0.5 and $b_2 = 0$. Hence, the extended FH model can quickly estimate ϕ_c for any M_w with just a single set of parameters.

Overall, our theory-integrated models predict critical points as a function of M_w that agree with the trends observed experimentally, therefore demonstrating valuable insight for new M_w . Additionally, the analysis of the extended FH model resulted in providing quick critical point estimates that can be determined without further fitting or training the model.

4. Conclusions

Leveraging theory with machine learning to construct theory-ML hybrid models shows benefits over traditional ML models, including better generalization when data is scarce as well as providing physics-interpretable models. Even though Flory-Huggins theory is imperfect, we show that incorporation of its relationships in the ML model improves interpolation when only 2-3 molecular masses are in the training set. The prediction of the upper critical solubility for PS/CH is also improved with the χ -informed model even with additional data. However, advantages in performance or computational efficiency diminishes as greater quantities of experimental data are available, likely because of limitations to the FH formulation. Nevertheless, the physical relationships, such as the molecular mass dependence of the critical point or of the coefficients within a FH theoretical expression, provide valuable insight from the predictions. For instance, the ability to examine the coefficient values implies that our theoryconstrained model, which contains functional forms for the mapping of χ_{AB} to T, can be used to determine an optimal functional form for χ_{AB} . Furthermore, we demonstrate that the critical points can be extracted from our theory-informed models and are consistent with experimental trends, allowing the theory-informed model to provide physical insight with less experimental data. These models can also be applied to any polymer-solvent system in which the physics are unknown, enabling the use of ML to aid in our understanding of binary polymer solution phase behavior.

Overall, we show that our data-rich ML models incorporate physical insights, which enhances trust in the predictions and is expected to be used to assess data quality or anomalous behavior. These models are a first step in developing physics-interpretable models for predicting polymer solution phase behavior. Future work will aim to develop these ML models further, incorporating other polymer-solvent chemistries and utilizing methods to develop or refine the theory for better interpretability and generalization. For instance, since the form of $g(T, \phi)$ is semiempirical, symbolic regression may be used to add or remove additional terms to determine the optimal functional form of χ_{AB} . Future work will aim to use this approach to develop a method in which test metrics can be used to derive an optimal function for mapping χ_{AB} to T.

Declaration of Competing Interest

The authors declare no conflict of interest.

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