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Data-Driven Kinetic Reaction Networks for Separation Chemistry

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ABSTRACT: Understanding complex, multistep chemical reactions at the molecular level is a major challenge whose solution would greatly benefit the design and optimization of numerous chemical processes. The separation of rare-earth (4f) and actinide (5f) elements is an example where improving our chemical understanding is important for designing and optimizing new chemistries, even with a limited number of observations. In this work, we leverage data-driven artificial intelligence and machine-learning approaches to develop kinetic reaction networks that describe the liquid—liquid extraction mechanism of uranium using N,N-di-2-ethylhexyl-isobutyramide (DEHiBA). Specifically, we compare and contrast the properties of two classes of models: (1) purely data-driven models that are regularized using chemistry-



agnostic, L1 regression and (2) chemistry-informed models that are regularized using relative reaction energies provided by quantum mechanical calculations. We observe that purely data-driven models are unbiased, simple, and accurate in their predictions of experimental measurements when provided with sufficient data but are difficult to fully constrain and interpret. In contrast, chemistry-informed models exhibit significantly improved chemical interpretability and consistency, providing a detailed description of the separation process while achieving high accuracy through ensemble averaging. Overall, the dominant species predicted to be extracted into the organic phase is $UO_2(NO_3)_2(DEHiBA)_2$, agreeing with experimental slope analysis, thermodynamic modeling, EXAFS, and crystal structures. This work demonstrates that leveraging the fundamental structure of the problem can lead to efficient learning schemes that provide both accurate predictions and chemical insights at a low computational cost.

INTRODUCTION

The development of efficient and cost-effective chemical separation processes has long been recognized as a challenging task.^{1,2} Isolating specific elements from chemical mixtures is ubiquitous, with applications that include extracting chemicals and materials from natural resources, removing anthropogenic contaminants and emissions, and facilitating recycling. Consequently, the development of methods which reduce the time, energy, and capital used in chemical separations would provide significant global benefits.² This study focuses on liquid-liquid extraction, the primary technique employed for large-scale separations of rare metals in advanced technologies.^{3,4} In this process, the metals are first dissolved in an aqueous phase and contact with an organic phase containing specifically designed extractants. These extractants then selectively bind to the target metal, altering its aqueous solubility to promote transfer into the organic phase. Separation is finally achieved by partitioning the organic and aqueous phases, thereby isolating the desired metal.³

An important application of liquid–liquid extraction is the separation of actinide elements, particularly uranium, from used nuclear fuels.⁴ Nuclear energy—a low-carbon energy source—holds potential for addressing global energy demands while aligning with decarbonization objectives.⁶ However, to

maximize the efficiency of the nuclear fuel cycle and limit the lifetime and volume of generated waste, advanced extraction, separation, and purification processes are essential.^{5,7,8} Current reprocessing techniques rely on the use of organophosphorous ligands to selectively bind and extract uranium, the primary target as it constitutes the majority of nuclear waste and can be recycled effectively as a fuel source.⁹ However, these ligands present challenges including solubility issues, degradation, and the generation of secondary waste. As a result, significant research efforts have been focused on developing new extractants to replace these ligands. Here, N,N-dialkylamides have emerged as promising candidates due to their strong affinity toward uranium, favorable degradation products, and adherence to the CHON principle-consisting of solely incinerable elements carbon, hydrogen, oxygen, and nitrogen-making them a sustainable and attractive option for uranium reprocessing.

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Once a new extractant has been identified, designing and optimizing the conditions for efficient liquid-liquid separation on the industrial scale become a key challenge. This difficulty arises from the high-dimensional chemical space that must be explored, encompassing variables such as concentrations of the extractant, acid, and metal; temperature; mixing time and rate; and the potential need for additives like inorganic salts, holdback agents, or phase-modifiers. Exploring this chemical space through experimentation alone is extremely tedious, underscoring the need for molecular-level insights to help guide and streamline the process.¹⁰⁻¹³ Although *N*,*N*-dialkyl monoamides were first identified for uranium separations in the 1960s,¹⁴ their application in reprocessing used nuclear fuel is still limited, highlighting the challenges of transitioning from discovery to industrial use. The majority of monoamide experimental studies have focused on their thermodynamics, investigating distribution ratios as a function of various experimental parameters. This has provided foundational insights, such as the structure of the predominant extracted species and guidelines on designing the carbon structure for improved selectivity and solubility.^{15–19} However, a comprehensive molecular understanding of the separation process remains incomplete, with only a few studies employing molecular dynamics and density functional theory (DFT) calculations to probe the extraction mechanism.^{20,21} Closing this knowledge gap could significantly accelerate the transition from extractant discovery to widespread industrial application.

Chemical reaction networks described by mass action kinetics represent a fundamental modeling approach for representing the outcome of complex reactions over time,^{22,23} which, in principle, could be used to reveal the basic properties of the system. However, these models can contain a large number of adjustable parameters that are difficult to individually determine through either experimentation or simulation. With the advance of artificial intelligence (AI) and machine-learning (ML) methods, deep learning architectures such as artificial neural network have been used to predict reaction parameters,²⁴ while data-driven chemical reaction networks^{22°} have been suggested as an additional approach to solve this problem.²⁵⁻²⁷ By leveraging available experimental data, reaction networks governed by mass action kinetics can be learned, providing a practical approach to predict the outcome of complex reactions, optimize reaction conditions, and gain valuable chemical insights.^{24,27}

In this paper, we investigate the properties of such datadriven kinetic reaction network models to describe speciation changes during uranium extraction with N,N-di(2-ethylhexyl)isobutyramide (DEHiBA) in the presence of nitric acid. A previous study has performed an extensive literature review on uranium extraction with N,N-dialkyl monoamides identifying DEHiBA as the most well-characterized system.²⁸ Specifically, we examine and contrast two model variants: purely datadriven (DD) and chemistry-informed (CI). Purely data-driven models rely on only minimal assumptions and are regularized by using a chemistry-agnostic approach (L1 regularization). Alternatively, chemistry-informed models incorporate regularization based on insights from explicit quantum calculations using DFT. In the following, DFT is used to estimate the relative free energies of ligand exchange and aqueous-toorganic phase transfer reactions which govern the speciation at equilibrium, offering thermodynamic insights that can potentially enhance the models' description of the extraction processes.

The manuscript is organized as follows: The Methods section outlines the general mathematical structure of the kinetic models. The Results and Discussion section analyzes the performances of individual and ensembles of purely datadriven and chemistry-informed models, focusing on the three key aspects: prediction accuracy, robustness, and chemical interpretability. The trade-offs between data-driven and chemistry-informed models are finally discussed in the Conclusions.

METHODS

Data Set on Uranium Extraction with DEHiBA. A data set of reported experimental distribution ratios pertaining to the liquid-liquid extraction of uranium with DEHiBA in the presence of nitric acid was curated from the open literature²⁹⁻³¹ and from previously unreported experiments carried out at Idaho National Laboratory.³² This extraction system provides the most comprehensive kinetic data set compared to other systems, which are often limited to a few tens of experiments with relatively homogeneous contact times.²⁸ The curated data set covers a wide range of initial uranium (10 μ M to 1.25 M), DEHiBA (0.2–1.5 M), and nitric acid (0.01-6.0 M) concentrations along with various contact times ranging between 2 and 60 min. Previous experimental studies have shown that the extraction of uranium with DEHiBA reaches equilibrium in less than 30 min.^{30,31} Therefore, in order to enforce a proper equilibrium longtime limit, a data augmentation approach was used where surrogate data at a contact time of 60 min was generated by duplicating the data acquired at a contact time of 30 min. The full data set used to develop the kinetic models is reported in the Supporting Information and contains a total of 172 uranium distribution ratios (including those generated by data augmentation) ranging from 0.002 to 8.095.

Chemical Reaction Networks and Model Regulariza-tion. The kinetic reaction networks used in this work are based on K2-SUB, a kinetic model previously developed to describe heterogeneous aerosol reactions occurring between bulk and gaseous phases.³³ The model was adapted for liquid–liquid extraction problems, as illustrated in Figure 1. In the present context, the model simulates uranium extraction across three separate phases: the aqueous bulk phase, the organic bulk phase, and the aqueous–organic interface. Speciation changes



Figure 1. Schematic illustration of kinetic reaction network models of liquid-liquid extraction.



Figure 2. Workflow of data-driven kinetic reaction networks.

are modeled through 36 binary intraphase chemical reactions, while mass transport is described by 22 unitary interphase diffusion steps. Altogether, these form the elementary steps of uranium extraction with DEHiBA which has been postulated to be of the form^{29,34}

$$[UO_2]_{(aq)}^{2+} + 2NO_{\overline{3}(aq)}^{-} + 2DEHiBA_{(org)}$$

$$\Rightarrow [UO_2(NO_3)_2(DEHiBA)_2]_{(org)}$$
(1)

Here, nitric acid is assumed to be fully dissociated throughout the extraction process as the highest initial $[HNO_3]_{(aq)}$ used in the data set was 6.0 M. Figure S1 reports the complete list of elementary reactions and diffusions taken into account for the model which is parametrized by a total of 116 adjustable rate constants.

Training of the kinetic models consisted of setting up and solving the system of ordinary differential equations (ODEs) that describe the time evolution of the various chemical species' concentrations provided in Figure S1. Initial concentrations for the base reactants ($[UO_2]^{2+}_{(aq)}$, $NO^-_{3(aq)}$, DEHiBA_(org)) were set according to the experimental conditions provided in the data set, while all other species' concentrations were initialized at zero. From there, the adjustable kinetic parameters were randomly initialized, allowing for a forward solution of the ODEs using differentiable ODE solvers implemented in the pytorch framework *torchdiffeq*.³⁵ Final rate constants were determined through model optimization using backpropagation, minimizing a loss function of the form:

$$loss = \frac{1}{n} \sum_{i=1}^{n} (D_{i, pred} - D_{i, true})^2$$
(2)

where D_{pred} and D_{true} represent the predicted and measured uranium distribution ratios, respectively. Here, the distribution ratios were defined as the change in uranium concentration in the aqueous phase before and after extraction, i.e.,

$$D_{i,\text{pred}} = \frac{[U]_{(aq),\text{initial}} - [U]_{(aq),\text{final}}}{[U]_{(aq),\text{final}}}$$
(3)

where $[U]_{(aq),initial}$ and $[U]_{(aq),final}$ represent the initial and final uranium concentration in the aqueous phase, respectively. In total, models were optimized until their loss function fell below 0.01 or until they reached 1000 epochs for data-driven or 500 epochs for chemistry-informed (*vide infra*), whichever came

first. The maximum cutoff for the number of epochs was determined by tracking the typical loss evolution, as reported in Figure S2.

To assess the ability to discover the relevant separation chemistry, two separate regularization strategies were employed to create either data-driven (DD) or chemistryinformed (CI) kinetic reaction network models, thereby eliminating the need for manual selection of an initial set of plausible reactions a *priori*. DD models were regularized by using a chemistry-agnostic L1 regression approach that automatically simplifies the rate network by favoring sparsity in the set of adjustable parameters. This approach is meant to be unbiased as external domain knowledge is not injected in model training. In this case, the loss function takes the form:

$$\log = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{\sigma_{i}} (D_{i,\text{pred}} - D_{i,\text{true}})^{2} + \lambda \sum_{j=1}^{p} |\beta_{j}|$$
(4)

where *p* is the number of adjustable parameters, λ controls the strength of the regularization, and the β 's represent the adjustable kinetic rate constants. Additionally, a weight $(1/\sigma_i = 2.0)$ was assigned to data points with contact times of 2 and 5 min, while $1/\sigma_i = 1.0$ was used for all other points. This was done to account for the small number of experiments that were performed at shorter mixing times. In total, five regularization strengths ($\lambda = 10^{-6}$, 10^{-4} , 10^{-3} , 10^{-2} , and 10^{-1}) were considered for the DD models, yielding models of decreasing complexity.

In contrast, CI models were regularized using relative thermodynamic energies of the speciation and diffusion reactions in Figure S1 calculated using DFT.³⁶ DFT calculations allow for a more comprehensive constraint of elementary reactions involving various ligand exchange, displacement, and association steps. This approach provides significantly stronger constraints than relying only the equilibrium constant of the overall reaction (i.e., eq 1) determined experimentally.^{29,37,38} Here, the loss function now takes the form:



Figure 3. Train and test RMSE values for the (a) data-driven and (b) chemistry-informed models with different training set sizes and varying regularization strengths (λ). The grey dotted line represents the estimated experimental uncertainty in our data based on duplicated experimental inputs. Markers indicate the average RMSE value across the 10 separate train-test splits; the variance is presented as error bars. The total number of trainable parameters for each model is presented in parentheses in the title.

$$loss = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{\sigma_{i}} (D_{i,pred} - D_{i,true})^{2} + \lambda MSLE \left(\frac{[AC]_{(aq),eq}[A]_{(aq),eq}[B]_{(aq),eq}}{[AB]_{(aq),eq}[A]_{(aq),eq}[C]_{(aq),eq}}, e^{-\Delta\Delta G/RT} \right) + \lambda MSLE \left(\frac{[A]_{(org),eq}}{[A]_{(aq),eq}}, e^{-\Delta G_{org/aq}/RT} \right)$$
(5)

where MSLE refers to the mean squared logarithm error, [AB]_{(phase),eq} is the concentration of species AB in either the aqueous or organic phase at equilibrium (which is assumed to have occurred by 60 min of contact time), $\Delta\Delta G$ is the difference of intraphase reaction free energies, and $\Delta G_{
m org/aq}$ is the free energy to transfer a complex from the aqueous to organic phase. Further details on the regularization terms are provided in the Supporting Information. Note that interface species are not included in the regularization due to the difficulty in accurately predicting their thermodynamics with quantum calculations, as this region cannot be properly modeled as continuum.¹³ Additionally, CI models contain a reduced number of reactions and diffusion steps, as they exclude the formation of charged species in the organic phase since they are expected to be highly unfavorable. For these models, five regularization strengths are considered, $\lambda = 10^{-5}$, 10^{-3} , 5 × 10^{-3} , 10^{-2} , and 5 × 10^{-2} .

Overall, the workflow used to train the kinetic reaction networks is summarized in Figure 2. Complete details of the kinetic reaction network models are provided in the Supporting Information.

Density Functional Theory Calculations. To identify possible $UO_2^{2^+}$ coordination complexes, the 3D structure generation tool *Architector*³⁹ was used to construct and screen energetically stable complexes. All complexes were created from a $UO_2^{2^+}$ center varying in coordination from 6 to 8. In total, up to two DEHiBA and nitrate ligands were allowed to bind along the equatorial plane, while the rest of the complex was saturated with water molecules. All nitrate ligands were initialized as bidentate. To assemble each $UO_2^{2^+}$ complex, up to 20 different core symmetries were constructed for each coordination number, and the 10 lowest-energy initial geometries were relaxed using the GFN2-xTB method.^{40,41} To mimic the aqueous and organic solution environments, two separate relaxations were performed for each structure using the analytically linearized Poisson–Boltzmann (ALPB) im-

plicit solvation model with water and hexane inputs. From the *Architector*-generated systems, up to 10 of the lowest-energy structures were selected for further DFT analysis. Additionally, conformer generation on the free DEHiBA ligand was performed with Confab as implemented in OpenBabel,^{42,43} and the 25 lowest-energy structures were selected for further DFT optimization.

All DFT calculations were performed with the Amsterdam Density Functional (ADF v2022.103) code⁴⁴ as implemented in the Amsterdam Modeling Suite (AMS).⁴⁵ The generalizedgradient approximation (GGA) of the Perdew-Burke-Ernzerhof (PBE)⁴⁶ form was used to account for exchange and correlation effects. All atoms used a small frozen core and a triple- ζ basis set with polarization functions (TZP) to represent the electrons.⁴⁷ Due to the large atomic number of uranium, relativistic effects were accounted for through the use of a ZORA Hamiltonian⁴⁸⁻⁵⁰ while Grimme's DFT-D3(BJ) correction⁵¹ was used to account for van der Waals interactions. DFT geometry optimizations were performed without symmetry constraints, and all forces were converged to less than 5 meV/Å. Additionally, all DFT optimizations included solvation effects through the implicit solvation model COSMO,⁵² with dielectric constants (ε) of 78.39 and 1.88 to represent the aqueous phase and organic phases, respectively. Due to the long carbon chain of the DEHiBA ligand, all UO_2^{2+} complexes which contained DEHiBA were reoptimized by exchanging the initial dielectric constant (78.39 to 1.88 and vice versa) to increase the number of conformers sampled. Upon complete relaxation, DFT electronic energies of all systems were calculated using the same methodology described above, but switching implicit solvation to the SM12 solvation model.^{53,54} Overall, the final DFT-optimized structures had mean absolute errors of 0.05 Å in their bond lengths, as compared to previously reported measurements from EXAFS and crystal structure measurements (see Tables S2-S4). Reaction energies used for training the kinetic models were calculated using only the lowest-energy structures from all DFT conformers, as reported in Table S5. Thermodynamic corrections to the molecular energies were obtained from analytical frequency calculations on the lowest-energy structures of the optimized systems.

To effectively handle xTB preliminary screening and subsequent DFT calculations, tasks were managed with a custom-built python asynchronous workflow using the *pyiron* and *flux* packages.^{55,56} The workflow is engineered for scaling and distributing batches of less-than-single compute node

RESULTS AND DISCUSSION

The performances of both the DD and CI models were evaluated according to the root mean squared error (RMSE) between the model-predicted and experimentally measured uranium distribution ratios. Model training was done using a repeated $(10\times)$ train-test split procedure considering three training set sizes, 120, 51, and 17, corresponding to 70, 30, and 10% of the data, respectively. From there, both "single"—referring to one kinetic model being optimized for each of the 10 train-test splits—and "ensemble"—ten separate kinetic models (initial rate constants varied) optimized for each of the 10 train-test splits, were investigated. In the following, we compare and contrast the DD and CI models across three criteria: prediction accuracy, robustness, and chemical interpretability.

Prediction Accuracy and Robustness of Single Models. Figure 3 reports the evolution of the training and testing RMSE values for individual DD and CI models with respect to the size of the training set and regularization strength. It is observed that the DD models obtained using relatively strong regularization ($\lambda = 10^{-2}$) exhibit prediction accuracies in the range of 0.4-0.6 RMSE when the sizes of the training sets were 120 and 51. For reference, the intrinsic uncertainty in our data set was estimated as ~0.4 RMSE using 44 duplicate experiments carried out at nominally the same reaction conditions. Overall, these models preserve ~20% of their total parameters (Figure S4), therefore minimizing the effect of overfitting to small amounts of data. However, significant overfitting is still observed for smaller training sizes (17) with test RMSE values in the range 1.1 ± 0.2 and training errors lower than the intrinsic noise level. Reducing the regularization strength ($\lambda = 10^{-3}$ and 10^{-4}) leads to a slight improvement of the DD models' predictive performance, but signs of overfitting are still observed. Further decreasing the regularization strength to $\lambda = 10^{-6}$ results in the reaction networks becoming unconstrained, retaining ~90% of their available parameters. As both the testing and training RMSE values increase at this point compared with $\lambda = 10^{-4} - 10^{-2}$, this suggests that regularization can assist the training procedure by restricting the number of competing parameters. In contrast, highly regularized DD models ($\lambda = 10^{-1}$) preserve only about 15% of the free parameters, limiting their predictive power.

Single CI models show the best predictive performance with regularization strengths between $\lambda = 5 \times 10^{-3}$ and 10^{-2} , providing train and test errors on the order of 0.5 and 0.7, respectively, when at least 51 data points are provided. Models trained on fewer data points are susceptible to overfitting, resulting in low training errors (~0.4) but high test errors (~ 1.0) . Similar to the DD models, both the train and test RMSE values increase significantly (>1.0) under strong regularization ($\lambda = 5 \times 10^{-2}$). This indicates that the chemical information provided by DFT is likely more qualitatively than quantitatively accurate, as strictly enforcing the predicted thermodynamics leads to worse prediction outcomes. Such limitations are not unexpected given the approximate nature of the implicit solvation models and incomplete consideration of finite-temperature effects. Further discussion of these limitations can be found in the Supporting Information. A sensitivity analysis of the loss of the CI models with respect

to the specific values of the DFT free energies (Figure S8) indicates that the phase transfer energies of DEHiBA and $[UO_2(NO_3)_2(DEHiBA)_2]$ are the two key quantities that most affect the quality of the CI models. Assuming typical errors of the order of 5 kcal/mol on DFT results leads to predicted changes in RMSE on the order of 0.1, which indicates that more accurate DFT values could noticeably, but perhaps not dramatically, improve the models.

Comparing CI to DD models generally shows that DD models achieve higher accuracy with smaller variance. The higher variability in the performance of CI models suggests that the chemistry-regularized loss landscape is more difficult to navigate than its effectively lower-dimensional L1-regularized counterpart, leading to the training of CI models being more prone to being trapped in suboptimal conditions (Figure S2).

Overall, these results show that a moderate regularization ($\lambda = 10^{-3}$, 10^{-2} for DD and 5×10^{-3} , 10^{-2} for CI) is highly beneficial. Additionally, it was observed that 51 data points were enough to provide adequate prediction accuracies without significant overfitting.

Boosting Prediction Accuracy with Ensemble Models. As shown above, the variability in the quality of the trained models limits the confidence in the prediction of single models. To circumvent this limitation, we investigated various ensemble averaging approaches. Specifically, ten different kinetic models—initialized with a different set of starting parameters—were optimized for each of the train-test splits, and final model predictions were calculated as averages of the individual models as

$$D_{\rm E,pred} = \sum_{i=1}^{10} w_i D_{i,\rm pred} \tag{6}$$

where $D_{\text{E,pred}}$ represents the ensemble-predicted uranium distribution ratio, and $D_{i,\text{pred}}$ and w_i correspond to the predicted distribution ratio of model *i* and its associated weight in the ensemble, respectively. Three different ensemble approaches were studied to calculate w_i : simple average (E_{avg}) , weighted variance $(E_{\text{var.}})$, and weighted error correlation (E_{ec}) .^{57–59} For the simple average, $w_{i,\text{avg}} = \frac{1}{10}$ while

$$w_{i,\text{var}} = \frac{1}{V_i} / \sum_{j=1}^{10} \frac{1}{V_j}$$
 (7)

$$w_{i,ec} = \sum_{j=1}^{10} (C^{-1})_{ij} / \sum_{m=1}^{10} \sum_{j=1}^{10} (C^{-1})_{mj}$$
(8)

were used to calculate the weights for the variance and error correlation ensembles, respectively. For $w_{i,var,j}$ V_i represents the variance calculated on the training set of the *i*th model. Therefore, models that showed a smaller variance would contribute a larger weight in the ensemble. In $w_{i,ec}$, C^{-1} corresponds to the inverse of the error correlation matrix of the *i* and *j*th models calculated over the *n* training data as^{57–59}

$$C_{ij} = \frac{1}{n} \sum_{k=1}^{n} (D_{k,\text{pred}}^{i} - D_{k,\text{true}}) (D_{k,\text{pred}}^{j} - D_{k,\text{true}})$$
(9)

In the previous section, 51 training points were found to be sufficient to optimize both the DD and CI models without significant overfitting, therefore, initial comparisons between single and ensemble approaches were conducted using a data



Figure 4. Train and test RMSE values of the single and ensemble predictions for (a) data-driven and (b) chemistry-informed models trained with 51 data points. Box and whisker plots represent the predictions across the 10 separate train-test splits. Three ensemble averaging methods are employed: simple average (E_{avg}), weighted variance (E_{var}), and weighted error correlation (E_{ec}).



Figure 5. Heatmap of the dissimilarity between ensembles of chemistry-informed (CI) and data-driven (DD) models trained to different data set sizes. Dark green colors indicate pairs of models that exhibit similar chemistries, while white to brown colors indicate pairs of models that predict very different reaction channels.

set of this size (Figure 4). Here, all DD models were regularized with $\lambda = 10^{-2}$ while CI models were regularized with $\lambda = 5 \times 10^{-3}$ on each train-test split. Additionally, the same train and test splits were used throughout the single and ensemble approaches along with DD and CI models to allow for an easier comparison between the methods.

When using individual models, the CI approach tends to exhibit a higher variability compared to DD. This can be seen in the training RMSE values of the single CI models ranging between 0.3 and 1.1, while DD model errors range between 0.3 and 0.7. While simple averaging only slightly improves the CI model predictions, variance- and error-correlation-weighted ensembles significantly improve accuracy and reduce variability, leading to errors that approach the intrinsic noise level. This is possible because averaging weights can systematically lower the contribution of "bad" solutions and enhance the contribution of "good" solutions. While the error-correlation method produces the lowest errors on average, the (infrequent) presence of overfitting models can lead to large weighted test RMSE values on specific test data set, as shown in Figure 4b—1.5 for DD and 1.3 for CI, respectively. On the other hand, the individual DD models provide more homogeneous prediction accuracy, leading to only slight improvements under ensemble averaging. This difference in behavior under averaging practically eliminates the accuracy advantage of DD models, providing CI prediction accuracies that approach the noise level. It is important to emphasize that averaging is beneficial even when a single train-test split is used so that these gains can be actually achieved in practice.

Finally, we note that ensemble averaging also improves the robustness of the CI models, even in the small data limit regime. For example, as shown in Figure S5, the worst RMSE

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Figure 6. Heatmap of fractional concentrations in the organic phase using variance averaging of (a) data-driven (DD) and (b) chemistry-informed (CI) models trained with 51 data points. The relative concentrations (white to red colors) of U species in the organic phase (*x* axis) are reported for each of 10 different train-test splits, which are ordered by increasing the test prediction accuracy (*y* axis). Vertical lines of uniform colors therefore indicate a high consistency across the 10 different splits.

error out of 10 different random set of only 17 data points remains below 1.6 for all three averaging methods, which is remarkably lower than the corresponding DD results (>2.3). Nonetheless, it can be expected that robustness requires a certain level of coverage of the relevant parameter space, as models trained to small and highly concentrated data sets are likely to generalize poorly to dramatically different conditions, as is common with most data-driven methods.

Chemical Interpretability. A key advantage of using a chemistry-motivated architecture instead of a conventional black-box ML approach is the potential for chemical interpretability. In the following, we assess whether the specific chemistry predicted by the models can indeed be taken at face value. In the absence of a complete ground truth of the uranium extraction mechanism with DEHiBA, we elected to use consistency as a surrogate measure of interpretability. Here, consistency measures whether different models trained on varying amounts of data and initialized with different random parameters predict similar chemistry. To quantify the interpretability, we compare net reaction fluxes-which are defined as the difference in instantaneous fluxes between the forward and backward directions of each reaction and diffusion pathway integrated between 0 and 60 min, as predicted by each model over 100 distinct experimental conditions. Net reaction fluxes over the distinct experimental conditions were stacked into a single vector Φ_i for each model, which was used to calculate the pairwise cosine similarity between a pair of models *i* and *j*, $S_{\cos}(i, j) = \frac{\Phi_i \cdot \Phi_j}{\|\Phi_i\| \|\Phi_j\|}$. From there, a dissimilarity metric was defined as a regularized inverse of the pairwise cosine similarity, $D_{ij} = 1/(S_{cos}(i, j) + 10^{-3})$, i.e., a pair of models will have a low dissimilarity if they predict similar net reaction fluxes. This approach was chosen instead of directly comparing the numerical values of the rate constants,

which is unlikely to be robust since changing the rate of fast non-rate-limiting reactions from merely large to exceedingly large could leave the overall chemical characteristics of the model largely unchanged but result in a large apparent difference between models. We also note that the rate constants of forbidden reactions in the CI models are set to zero for the purpose of comparisons with the DD models.

To visualize model consistency, a 120×120 matrix was constructed based on D_{ij} values calculated between the DD and CI models regularized at $\lambda = 10^{-3}$, 10^{-2} and 5×10^{-3} , 10^{-2} , respectively, for each of the training set sizes (17, 51, 120). Agglomerative clustering using a complete linkage criterion was then employed to sort similar kinetic models into groups for ease of visualization. The results are presented in Figure 5. The results show that CI models are more consistent both internally (between models trained to the same amount of data) and externally (across different training set sizes) than the DD models. The clustering analysis shows that 75% of the CI models are capturing similar flux networks when the size of the training set was 120 or 51, which decreased to 55% in the low training data regime (17). The groups of common models obtained at different training set sizes are more similar to each other. CI models are hence expected to be interpretable, as a high fraction of the models predict similar chemistry even when trained independently on different subsets of the data. In contrast, the DD models exhibit a greater diversity in their reaction fluxes, leading to a large inconsistency between the models. While DD models trained using 17 data points exhibit some internal similarity, these models are not consistent with other DD models trained to more data or with the CI models. This shows that while DD models can produce accurate predictions of the uranium distribution ratios-given a sufficient amount of data, they often predict vastly different underlying chemistries. It is interesting to note that in the large



Figure 7. Minimal kinetic reaction networks for extracting $[UO_2(NO_3)_2(DEHiBA)_2]$ from the organic phase. The black arrows represent the ensemble-predicted pathways with varying shades that indicate the number of splits that predicted the corresponding steps. The nodes of the graph represent U complexes in the aqueous (blue), interface (green), and organic (yellow) phase.

training data regime (120), an increasing fraction of the DD models are found to predict fluxes similar to the majority of CI models (40% and 15% of the DD models for 120 and 51 data points, respectively). This suggests that, as expected, the DD and CI approaches eventually reach a consensus on the underlying chemistry in the large data limit but that the CI models are able to capture the right chemistry with a reduced amount of data, which is critical in data-sparse scenarios such as the one considered here.

This same general trend persists when considering ensemble-averaged properties. To illustrate this point, the final concentrations predicted pertaining to the experimental conditions that produced the highest uranium distribution ratio $([UO_2]_{(aq)}^{2+} = 0.1 \text{ M}, [DEHiBA]_{(org)} = 1.5 \text{ M}, \text{ and } [HNO_3]_{(aq)} = 6.0 \text{ M})$, were averaged using the prediction variance scheme for both the DD and CI models trained with 51 data points. Figure 6a reports the fractional equilibrium concentrations of the uranium complexes in the organic phase relative to the initial uranium concentration ($\frac{[UO_2(NO_3)_x(DEHiBA)_y]_{(org),eq}^{2-x}}{2}$). The *y*-axis in this heatmap corre-

 $[UO_2]_{int}^{2+}$ (J) The y and in this heating corresponds to each of the 10 different train-test splits ordered by their increasing test prediction accuracy. Results show that the final organic speciation varies considerably between the traintest splits for the DD models, whereas the CI models produce much more consistent predictions. For the DD models, $[UO_2(NO_3)_2(DEHiBA)_2]$ is predicted to be the dominant complex in the organic phase for half of the splits; however, the other half predicts $[UO_2(DEHiBA)]^{2+}$ as the dominant species, which is chemically very unlikely due to its net charge. Additionally, the total fraction of uranium complexes in the organic phase and at the interface at equilibrium is observed to vary widely from model to model.

In contrast, the CI models predict $[UO_2(NO_3)_2(DEHiBA)_2]$ as the dominant uranium complex in the organic phase for 7 out of the 10 train-test splits, while the total fraction of uranium species in the organic phase and at the interface is more consistent between the models. Given that extensive experimental studies using slope analysis, thermodynamic modeling, EXAFS, and crystal structures have suggested $[UO_2(NO_3)_2(DEHiBA)_2]$ to be the predominant extracted species, ^{15,29,30,34,60–65} these results suggest that the CI models, indeed, capture the chemistry of the system better than the DD models; at least when only a limited amount of experimental results are available. Additionally, DD-

51 reaction and diffusion fluxes become mostly uniform after averaging; i.e., many distinct reaction channels contribute roughly equally due to the similar prediction accuracies, diminishing their interpretability. The complete net flux networks of both DD and CI ensembles are presented in the Supporting Information.

Lastly, we considered a hybrid approach in which both the DD and CI regularization approaches were applied simultaneously. Although the joint space of regularization parameters was not fully explored, results showed that while hybrid models can exhibit lower prediction errors (Figure S9) compared with the DD and CI models, this comes at the cost of a decrease in model interpretability and consistency (Figure S10).

Minimal Reaction Networks. Minimal reaction networks were finally derived from variance-averaged net fluxes of CI-51 models trained to 10 distinct train/test splits (Figure S7). This was achieved using Dijkstra's shortest-path algorithm,⁶⁶ where the effective edge length was defined as the logarithm of the inverse of the averaged flux (i.e., the lower the flux, the more distant two nodes are). This approach, previously employed to identify kinetically favorable minimal reaction networks,⁶⁷ was used to trace the steps leading to the extraction of $[UO_2(NO_3)_2(DEHiBA)_2]_{(org)}$ from its aqueous source, $[UO_2]_{(aq)}^{2+}$. Figure 7 presents the key predicted pathways from the 10 different splits. In the figure, the shade of black of each arrow is proportional to the number of splits that predicted the corresponding reaction step as part of the minimal reaction network.

The minimal reaction network suggests one favored extraction mechanism. The path begins with transport of $[UO_2]^{2+}_{(aq)}$ to the interface, followed by coordination of a single DEHiBA and nitrate ligand to $[UO_2]_{(int)}^{2+}$, forming [UO₂NO₃(DEHiBA)]⁺_(int). From there, $[UO_2(NO_3)_2(DEHiBA)_2]_{(int)}$ is formed at the interface by the sequential coordination of a second nitrate and DEHiBA (or vice versa). Given the increased hydrophobicity, $[UO_2(NO_3)_2(DEHiBA)_2]_{(int)}$ is fully transferred into the organic region. Previous studies that relied on DFT or molecular dynamics calculations^{20,21} suggest two extraction pathways that begin with uranium forming complexes containing one or two nitrate ligands. As its hydrophilicity decreases, the complex approaches the aqueous-organic interface, thereby facilitating subsequent complexations with the DEHiBA ligands. In particular, a mechanism proposed in ref 20 suggests the formation of $[UO_2NO_3(DEHiBA)]^+$, and

 $[\rm UO_2NO_3(\rm DEHiBA)_2]^+$ intermediates from an initial $[\rm UO_2(\rm NO_3)]^+$ complex, whereas a second route proceeds through the formation of neutral intermediate species, $[\rm UO_2(\rm NO_3)_2]$ and $[\rm UO_2(\rm NO_3)_2(\rm DEHiBA)]$. Although our CI models only occasionally predicted either $[\rm UO_2(\rm NO_3)]^+$ or $[\rm UO_2(\rm NO_3)_2]$ to be an intermediate, the subsequent steps following the formation of the $[\rm UO_2\rm NO_3(\rm DEHiBA)]^+$ complex correspond to the first proposed mechanism in ref 20.

CONCLUSIONS

The power of large, domain-agnostic, black-box ML models is increasingly evident when extensive training data sets are available. However, in many application areas, the volume of accessible data is limited by prohibitive time and cost. This creates a strong incentive to develop ML techniques that incorporate fundamental physics and chemistry into their architecture or training process. In this paper, we present such an approach to predict the distribution ratios of uranium in a liquid-liquid extraction process using N,N-di-2-ethylhexylisobutyramide (DEHiBA). The extraction process is modeled as a chemical reaction network governed by mass action kinetics, describing the temporal evolution of the concentrations of various elementary species. These models are trained by using backpropagation through the ODE solvers in order to reproduce experimentally measured distribution ratios. Specifically, two regularization techniques were evaluated: (1) a data-driven chemistry-agnostic L1 regularization approach and (2) a chemistry-informed approach incorporating results from DFT calculations.

It was observed that when optimally regularized, data-driven models exhibit low errors that approach the uncertainty of experimental measurements when trained on as little as 51 data points while relying on only 20% of the possible reactions. This demonstrates that the chemically sound structure of the reaction network coupled with regularization enables robust learning from very limited data, automatically removing reactions that are deemed unnecessary. However, ensembles of models in this class were observed to be chemically inconsistent with one another and with known chemistry, making them inadequate to shed light on the underlying dominant reaction mechanisms unless a large amount of data is available. This inconsistent representation of the chemistry follows from the aggregate nature of the experimental measurements, which only measure the variations in total metal concentration in the bulk but not the concentration of each species, which proves insufficient to unambiguously constrain the models when limited data is available.

On the other hand, chemistry-informed models demonstrate good prediction accuracy, albeit slightly lower than comparable data-driven models, apparently due to their rougher loss landscape which makes training more difficult. This deficiency can be addressed using ensemble averaging methods, producing prediction errors that approach the intrinsic uncertainty of the training measurements when only a few tens of data points are available. Additionally, a consensual description of the underlying chemistry is also achieved with these models, which was found to be consistent with experimental observations. This consistency enhances confidence in the interpretation of the chemical reaction networks, effectively producing a robust description of the chemistry despite the initial complexity of the model space, especially when coupled with the extraction of minimal reaction networks. The most favorable extraction mechanism of

 $UO_2(NO_3)_2(DEHiBA)_2$ suggested by the models is broadly consistent with mechanisms suggested by previous studies.

Given their accuracy, robustness, and interpretability tradeoffs, purely data-driven models appear more suited to situations where accurate predictions are desired but interpretability is not required. When a few tens of experiments are available, these models prove to be very accurate and unaffected by subjective biases beyond the enumeration of possible unit reactions, which makes them easier to apply to different systems (e.g., different ligands). On the other hand, chemistry-informed models can provide robust chemically interpretable reaction networks even when limited data is available. The indicative correlation between predictions and chemical consistency of these models enhances reliable model selection based on performance, reducing the need for deeper investigations. Kinetics derived from chemistry-informed models could help explore the experimental space more efficiently and provide deeper insights into the extraction process at the molecular level. It is noted, however, that carrying out the required DFT calculations represents a significant effort, although this task can now be efficiently automated.39,68

While networks are relatively well constrained by chemical regularization, uncertainties still remain given the incomplete coverage of the quantum calculations (i.e., the absence of interfacial thermodynamic information) and the lack of experimental information on the concentrations in the interface and organic phase in most experiments. Complexresolved information including identity and/or concentration of individual complexes in different phases would constrain the models even more efficiently and would therefore be extremely beneficial. Finally, the strongly nonuniform distribution of contact times (especially the relative lack of short-time data) mostly informs the thermodynamic/steady-state predictions of the model, in contrast to the transient period. Studies with a more complete uniform sampling of the contact time distribution would therefore be extremely valuable both to train and validate these types of kinetic models.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jctc.4c01783.

Details on the kinetic reaction network models; extraction data used for this work; regularization of chemistry-informed models; loss evolution with respect to epochs; parity plots at different level of accuracy (RMSE); fraction of nonzero parameters of data-driven models; ensemble predictions for data-driven and chemistry-informed models trained with 17 data points; ensemble net flux networks; details of DFT-optimized structures and relative energies; limitations of the accuracy of DFT calculations using implicit solvation models; chemistry-informed model's sensitivity to DFT calculations; and performance of hybrid models (PDF)

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Notes

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