oc-2022-00157v.R1

Name: Peer Review Information for "Transition state theory-inspired neural network for estimating the viscosity of deep eutectic solvents"

First Round of Reviewer Comments

Reviewer: 1

Comments to the Author

The work could be improved by restructuring the content. Results and Discussion sections should be combined. A conclusion section can be added. The abstract should report the findings clearly. The molar ration is primary parameter that influences all the physicochemical properties of the DES mixtures. There should be a deviation comparison among the experimental results for identical DES systems that reported by different research groups.

The NN criteria should be explained and illustrated sufficiently. The authors should explain the rationale for each criterion followed (e.g., raw components desiccation before DES mixing). Also, the significance of these criteria and their influence on the data reproducibility should be tackled.

The discussion is rather hard to follow. The new proposed 'R&D' section should be subdivided into subsections that address the content step-by-step. It is also worthy for better clarification to consider the discussion of DES systems by order.

Please add the files followed in their original software domain.

Author's Response to Peer Review Comments:

Prof. Editor

Senior Editor, *ACS Central Science*

9th May 2022

Thank you very much for your consideration of our manuscript entitled “Transition state theory-inspired neural network for estimating the viscosity of deep eutectic solvents” (oc-2022-00157v) and for forwarding the reviewers’ comments. We are pleased that the reviewers have offered such detailed comments about our results and by having the opportunity to address these comments. We believe that we have improved the paper. As requested, we have restructured the content of our work. A deviation comparison of our work with other reported works has been added. The NN criteria have been illustrated sufficiently. We believe that our revisions to the manuscript, which are highlighted in red, fully address the reviewers’ and your comments. Point-by-point changes and/or replies to the comments of the reviewers are detailed as follows:

Reviewer 1:

1. The work could be improved by restructuring the content. Results and Discussion sections should be combined.

The discussion is rather hard to follow. The new proposed 'R&D' section should be subdivided into subsections that address the content step-by-step.

Reply:

We are very sorry for our confusing structure and description. As suggested, we have combined the Results and Discussion sections. The new proposed 'R&D' section is subdivided into 4 subsections. The 'Data analysis' section introduces the composition and characteristics of the collected database. The 'Viscosity model from transition state theory' section presents the theoretical derivation of the model.

A significant modification has been made to the 'NN vs. TSTiNet' section. The introduction of the Neural Network is integrated into the 'Introduction' section. The description of energy parameters training methods is deleted since there is a more detailed description on the 'Ways to train the energy parameters' section. The analysis and discussion of the Figure 3 and Table 2 is modified so that they do not overlap and complement each other. A brief description of the comparison results of different machine learning methods is added.

For the 'Ways to train the energy parameters' section, a prospect of modeling and parameter training methods proposed is added.

2. A conclusion section can be added.

Reply:

Thanks for this comment. The conclusion section has been added. The content is as follows:

In this work, a model combining theoretical equations and NN is used to predict the viscosity of DESs. This model uses prior theoretical knowledge to solve the

model generalization problem caused by the lack of data and uneven distribution. A novel viscosity equation that relates viscosity to molecular weight is derived based on the transition state theory. Then the energy parameters and structural parameters in the equation are calculated through three MLPs. The results show that our model (the TSTiNet model) exhibits better viscosity prediction performance compared to the plain NN model. The TSTiNet model overcomes the shortcoming of most viscosity models in predicting poorly at larger viscosities and dramatically improves the performance on R^2 and MARD. By now, the TSTiNet model is the most accurate and reliable model for predicting the viscosity DESs.

3. The abstract should report the findings clearly.

Reply:

Thanks for this comment. The developed model parameter training method is added in the 'Abstract' section. The abstract has been revised as follows:

The lack of accurate methods for predicting the viscosity of solvent materials, especially those with complex interactions, remains unresolved. Deep eutectic solvents (DESs), an emerging class of green solvents, have a severe lack of viscosity data, resulting in their application still staying in the stage of random trial and error and difficult to be implemented on an industrial scale. In this work, we demonstrate the successful prediction of viscosity of DESs based on the transition state theory-inspired neural network (TSTiNet). The TSTiNet adopts

multi-layer perceptron (MLP) for the transition state theory-inspired equation (TSTiEq) parameters calculation and verification using the most comprehensive DESs viscosity dataset by now. For the energy parameters of the TSTiEq, the constant assumption and the fast iteration with the help of MLP can make TSTiNet get the best performance (the average absolute relative deviation on the test set of 6.84% and R^2 of 0.9805). Compared with the traditional machine learning methods, the TSTiNet has better generalization ability and dramatically reduces the maximum relative deviation of prediction under the constraints of the thermodynamic formulation. It requires only the structural information of DESs, is the most accurate and reliable model available for DESs viscosity prediction.

4. The molar ration is primary parameter that influences all the physicochemical properties of the DES mixtures. There should be a deviation comparison among the experimental results for identical DES systems that reported by different research groups.

Reply:

Thank you for your valuable comments. Since the model proposed by Bakhtyari et al. is a global viscosity model covering extensive database, a detailed deviation comparison has been conducted. The results have been added into the Supplementary Information File.

Table S6 Comparison of the individual RD% values for DES by the TSTiNet model and the Bakhtyari et al. model.

HBA	HBD	HBA:HBD mole ratio	T	η_m^{lit}/ mPa·s	ARD%[a]	ARD%[b]
Acetylcholine chloride	1,2,4-triazole	1:1	303.15	304.69	6.83	η_{ref}[c]
			313.15	153.71	5.05	4.55
			323.15	83.06	9.56	11.54
			333.15	46.48	7.66	23.26
			343.15	27.73	4.10	35.19
			363.15	14.51	15.77	26.21
			373.15	8.37	5.99	61.10
Acetylcholine chloride/1,2,4-triazole				AARD%	7.85	26.98
Acetylcholine chloride	Imidazole	1:1.5	303.15	233.69	0.41	η_{ref}[c]
			313.15	120.91	8.16	7.09
			323.15	59.05	1.22	31.42
			333.15	35.29	0.51	40.32
			343.15	18.67	21.60	78.11
			353.15	16.53	6.66	40.93
			363.15	11.69	5.88	44.64
Acetylcholine chloride	Imidazole	1:2	303.15	103.33	4.30	η_{ref}[c]
			313.15	52.18	1.52	16.52
			323.15	31.63	11.98	20.89
			333.15	21.49	22.69	18.12
			343.15	11.37	6.02	54.94
			353.15	6.84	6.62	85.53
			363.15	4.17	25.21	126.23
Acetylcholine chloride	Imidazole	1:3	303.15	335.98	16.36	η_{ref}[c]
			313.15	189.19	2.77	5.01
			323.15	98.80	0.26	5.91
			333.15	57.92	0.54	12.50
			343.15	35.77	3.82	19.82
			353.15	25.74	2.27	14.57
			363.15	17.68	1.18	19.18
Acetylcholine chloride/Imidazole				AARD%	7.14	35.65
Betaine	DL-Lactic acid	1:2	298.15	1266.00	3.75	η_{ref}[c]
			303.15	818.60	5.04	1.79
			308.15	544.60	4.77	4.38
			313.15	374.60	4.03	6.78
			318.15	260.50	1.13	10.99

			323.15	190.20	0.17	12.52
			328.15	141.60	1.34	14.23
			333.15	107.50	3.13	15.86
			338.15	83.70	4.33	16.50
			343.15	65.90	6.18	17.60
Betaine	DL-Lactic acid	1:5	293.15	386.60	3.44	7.73
			298.15	245.30	1.12	η_{ref}^{c}
			303.15	167.70	1.64	3.67
			308.15	120.40	3.17	5.07
			313.15	86.10	1.10	9.40
			318.15	65.50	2.30	9.30
			323.15	50.60	2.60	9.50
			328.15	39.60	2.07	10.07
			333.15	31.10	0.01	11.89
			338.15	25.10	1.01	12.15
			343.15	20.60	1.85	11.89
Betaine/DL-Lactic acid				AARD%	2.58	10.07
Choline chloride	1,2-Butanediol	1:19	295.15	55.00	2.59	16.66
			297.15	48.00	1.59	13.75
			299.15	41.00	8.71	8.55
			301.15	34.00	10.33	0.14
			303.15	31.00	9.25	η_{ref}^{c}
			305.15	26.00	0.18	8.82
			307.15	22.00	9.96	17.66
			309.15	19.00	18.59	24.93
			311.15	17.00	23.80	28.31
Choline chloride	1,2-Butanediol	1:4	295.15	70.00	9.43	12.63
			297.15	62.00	8.01	11.12
			299.15	55.00	6.27	9.46
			301.15	48.00	2.51	5.99
			303.15	41.00	4.04	η_{ref}^{c}
			305.15	36.00	8.41	3.75
			307.15	31.00	3.30	10.02
			309.15	29.00	4.38	7.65
			311.15	26.00	1.04	10.15
Choline chloride	1,2-Butanediol	1:5.67	295.15	60.00	9.87	10.96
			297.15	53.00	7.78	9.05
			299.15	48.00	7.56	9.14
			301.15	38.00	6.45	4.14
			303.15	36.00	2.84	η_{ref}^{c}
			305.15	29.00	17.27	13.21
			307.15	26.00	3.93	15.44
			309.15	22.00	5.44	25.01

			311.15	19.00	13.70	32.93
Choline chloride	1,2-Butanediol	1:9	295.15	53.00	13.10	13.74
			297.15	45.00	7.06	8.18
			299.15	41.00	6.98	8.67
			301.15	36.00	3.01	5.48
			303.15	31.00	3.51	η_{ref}[c]
			305.15	26.00	13.82	8.89
			307.15	22.00	24.45	17.80
			309.15	19.00	1.76	25.15
			311.15	17.00	6.31	28.60
Choline chloride/1,2-Butanediol				AARD%	7.98	13.31

[a]the TSTiNet model; [b]the Bakhtyari et al. model; [c]η_{ref} means the reference viscosity used in the Bakhtyari et al. model. For each DES at each mole ratio, the Bakhtyari et al. model needs an experimental viscosity as the reference viscosity.

Table S7 Comparison of the individual AARD% values for DES by the TSTiNet model, the Bakhtyari et al. model, the Lewis and Squires model, the Haghbakhsh and Raeissi model, and the Dutt et al. model.

DES	AARD%				
	TSTiNet model	Bakhtyari et al. model	Lewis and Squires model	Haghbakhsh and Raeissi model	Dutt et al. model
Acetylcholine chloride/1,2,4-triazole	7.85	26.98	248.40	5.10	53.10
Acetylcholine chloride/Imidazole	7.14	35.65	235.73	12.40	40.77
Betaine/DL-Lactic acid	2.58	10.07	298.95	23.95	75.60
Choline chloride/1,2-Butanediol	7.98	13.31	32.05	11.68	12.40

5. The NN criteria should be explained and illustrated sufficiently. The authors

should explain the rationale for each criterion followed (e.g., raw components desiccation before DES mixing). Also, the significance of these criteria and their influence on the data reproducibility should be tackled.

Reply:

Thank you for your valuable comments. The illustration of the NN criteria has been added in the 'Model details' section. The content is as follows:

We have examined a series of hyperparameter settings in MLPs according to the performance on the validation set, including network architecture and activation function. The search space can be found in Table S1. The results show that the same hyperparameter settings can get better performance in the two MLPs of calculating structural parameters. As for the MLP of calculating energy parameters, we use the same hyperparameter setting to simplify the model tuning process. To get the better performance, using a different network architecture is feasible. Empirically, the MLP of calculating the energy parameters should not have high complexity because this MLP is just to speed up the iteration of the parameters. As for the other two MLPs, they can have higher complexity, but should always be careful to overfit problem.

Table S1. The search space and results of parameters in the NN model

Hyperparameters	Search space	Result
activation function	ReLU, Tanh, GELU	GELU
number of hidden layers	1, 2, 3	2

number of hidden neurons	32, 48, 64, 128	32
loss function	MSE loss, MAE loss, Huber loss	Huber loss

Besides, to help readers reproduce our work more easily, we add the section named “How to use” in our repository, where the readers can find the trained models, processed data, the scripts for training the models, and the scripts for quick prediction of DES.

Being inspired, we have added the explanation of the special group division criteria:

1. -NH_2 is defined in detail: with carbonyl-, and with others. According to the initial fitting of viscosity data by the model, the viscosity fitting of DESs containing -NH_2 directly connected to carbonyl group in the molecular structure is poor. We consider that this structure has a special effect on viscosity, so it is considered separately.
2. If metal ions are divided into different groups, many model input parameters will be introduced, which will easily lead to overfitting problems. Here, we assume that the difference in metal ions’ contribution is only related to the molecular weight and is equal to $(n_m+1)M_{m,}$ where n_m is the number of the metal ion, M_m is its molecular weight.

6. It is also worthy for better clarification to consider the discussion of DES systems by order.

Reply:

Thank you for your valuable comments. We have clarified three aspects to discuss the effects to the viscosity of DESs, that is temperature, mole fraction, HBA and HBD types. The results show that the predicted values of the model are in good agreement with the experimental values. More detailed comparison and discussion are presented in the supplementary materials.

7. Please add the files followed in their original software domain.

Reply:

Thanks for the comments. We have added the files in our repository (https://github.com/fate1997/TSTiNet), where we open-source our data files, checkpoints, training scripts, output files, and predicting scripts. The users can easily reproduce our work, check the input files and output files, and make prediction for their specified DES.

oc-2022-00157v.R2

Name: Peer Review Information for "Transition state theory-inspired neural network for estimating the viscosity of deep eutectic solvents"

Second Round of Reviewer Comments

Reviewer: 1

Comments to the Author

article is acceptable for publication in its present form

Author's Response to Peer Review Comments:

Prof. Editor

Senior Editor, ACS Central Science

27th June 2022

Thank you very much for your consideration of our manuscript entitled “Transition state theory-inspired neural network for estimating the viscosity of deep eutectic solvents” (oc-2022-00157v). As requested, we have removed the colored text in Supplementary information.