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RESEARCH ARTICLE

Thermodynamic Consistency in Coarse-Grained Molecular Dynamics Simulations

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ABSTRACT

Coarse-grained (CG) molecular dynamics models trade atomistic detail for computational reach, but the structure-based mapping procedures typically used to build them reproduce target radial distribution functions while leaving thermodynamic properties, pressure, compressibility, excess entropy, unconstrained and often substantially in error. We systematically quantified this thermodynamic inconsistency for 16 CG models of small-molecule liquids and liquid mixtures, built by iterative Boltzmann inversion (IBI) from atomistic reference simulations, and tested three consistency-correction strategies: pressure-corrected IBI, a multistate iterative approach fitting simultaneously across three thermodynamic state points, and an explicit excess-entropy-matching correction. Uncorrected structure-only CG models reproduced target radial distribution functions with a mean structural error (integrated RDF deviation) of 0.031, but showed a mean pressure deviation from the atomistic reference of 340 ± 95 bar and a mean excess entropy deviation of 18.4%, confirming that structural fidelity alone does not guarantee thermodynamic fidelity. Pressure-corrected IBI reduced mean pressure deviation to 42 ± 21 bar (an 88% reduction) at the cost of a 2.1-fold increase in structural error relative to the uncorrected models, while the multistate approach achieved a more balanced outcome, reducing pressure deviation to 68 ± 24 bar and excess entropy deviation to 6.7%, with only a 1.3-fold increase in structural error. The explicit excess-entropy-matching correction achieved the lowest excess entropy deviation (3.9%) but transferred least well to state points outside the fitting range, with transferability tests at temperatures 20 K above the reference condition showing a 2.6-fold larger increase in pressure error than the multistate models. Across all 16 systems, pressure deviation and excess entropy deviation of the uncorrected models were strongly correlated (Pearson $r = 0.79$, $p < 0.001$), indicating that pressure inconsistency is a useful, easily computed proxy for the harder-to-estimate excess entropy error. These results provide a quantitative basis for selecting among available consistency-correction strategies according to whether accurate structure, accurate thermodynamics, or transferability across state points is the priority for a given CG modelling application.

Keywords: coarse-grained simulation; thermodynamic consistency; iterative Boltzmann inversion; force-field mapping; excess entropy; structural coarse-graining; transferability; liquid-state thermodynamics

Received: July 11, 2024 | Accepted: October 04, 2024 | Published: December 24, 2024

Citation: Kalous T, Havel Z, Sikora S. Thermodynamic Consistency in Coarse-Grained Molecular Dynamics Simulations. *Frontiers in Entropy*. 2024;2(2):1–5. DOI: [10.5281/zenodo.22698542](https://doi.org/10.5281/zenodo.22698542)

1. INTRODUCTION

Coarse-grained molecular models reduce the number of degrees of freedom relative to atomistic representations, grouping several atoms into single interaction sites, and thereby extend accessible simulation length and time scales by orders of magnitude, at the cost of a loss of chemical detail that must be compensated by carefully parameterized effective interactions [1,2]. The dominant family of systematic coarse-graining methods, structure-based approaches such as iterative Boltzmann inversion and force matching, derive these effective interactions by requiring the CG model to reproduce structural correlation functions, most commonly the radial distribution function, obtained from a reference atomistic simulation.

A well-known consequence of this structure-matching strategy is thermodynamic inconsistency: because the many-body potential of mean force that exactly reproduces a given RDF also depends on state point, and because structure-based methods typically fit a pairwise-additive effective potential at a single reference state point, the resulting CG model can reproduce the target RDF closely while badly misrepresenting pressure, compressibility, or excess entropy relative to the atomistic reference, a problem documented in individual systems but rarely quantified systematically across a broad set of chemically diverse liquids [3,4,5,6].

This matters because the two main proposed remedies, pressure-corrected structural matching and explicit thermodynamic-property matching, involve different trade-offs that are not fully characterized: correcting pressure typically degrades structural accuracy to some degree, and it remains unclear how much, how this trade-off compares with more elaborate multistate fitting approaches, and whether corrections fitted at one state point transfer acceptably to nearby state points, a property essential for CG models intended for use across a temperature or composition range rather than at a single fixed condition [7,8,9,10].

The present study systematically builds and evaluates 16 coarse-grained models of small-molecule liquids and mixtures using iterative Boltzmann inversion, quantifies the baseline thermodynamic inconsistency of structure-only fitting in terms of pressure and excess entropy deviation from atomistic reference values, compares three consistency-correction strategies, pressure-corrected IBI, multistate fitting, and explicit excess-entropy matching, on the resulting structure-thermodynamics trade-off, and tests the transferability of each corrected model to a state point outside its fitting range.

2. MATERIALS AND METHODS

We built coarse-grained models for 16 small-molecule liquid and mixture systems by iterative Boltzmann inversion against atomistic reference simulations, applied three alternative consistency-correction strategies, and

quantified structural error, pressure deviation, and excess entropy deviation for each resulting model relative to the atomistic reference, including a transferability test at an off-reference state point.

2.1 Atomistic reference simulations

Atomistic reference trajectories for all 16 systems, comprising 10 pure liquids and 6 binary mixtures of small organic molecules, were generated using established all-atom force fields at a reference condition of 300 K and 1 bar, with each system simulated for 40 ns following 5 ns of equilibration, sufficient for converged radial distribution functions and pressure estimates.

2.2 Coarse-grained mapping and iterative Boltzmann inversion

Each molecule was mapped to one or two CG sites following standard chemical-group-based mapping conventions. Effective pairwise CG potentials were derived by iterative Boltzmann inversion, updating the potential at each iteration to reduce the deviation between the CG and atomistic (mapped) radial distribution functions, run for 60 iterations per system, sufficient for convergence of the structural error metric in all cases tested.

2.3 Pressure-corrected IBI

A linear pressure-correction term was added to the IBI potential at each iteration, scaled to drive the CG-model pressure toward the atomistic reference pressure while continuing to update the structural component of the potential, following the standard pressure-correction extension to the IBI algorithm.

2.4 Multistate iterative fitting

The multistate approach fitted a single CG potential simultaneously against RDFs and pressures computed at three thermodynamic state points, the 300 K/1 bar reference condition together with 280 K and 320 K at the same pressure, using a weighted combination of the per-state-point structural and pressure residuals at each iteration.

2.5 Excess-entropy-matching correction

Excess entropy for both atomistic and CG models was estimated from the pair correlation function using the standard two-body approximation. The excess-entropy-matching correction applied an additional iterative adjustment to the CG potential, beyond the base IBI structural update, targeting the atomistic excess entropy value directly rather than the pressure.

2.6 Transferability testing

Each of the three corrected model types, together with the uncorrected baseline, was additionally simulated at a state point 20 K above the reference condition (320 K, 1 bar) without refitting, and the resulting pressure and excess entropy deviations were compared against the deviations obtained at the original reference condition to assess transferability.

2.7 Error metrics and statistical analysis

Structural error was quantified as the integrated absolute deviation between CG and atomistic RDFs, normalized per system. Pressure and excess entropy deviations were computed relative to the atomistic reference values. Correlation between pressure deviation and excess entropy deviation across the 16-system uncorrected-model set was assessed by Pearson correlation with a two-tailed significance test.

3. RESULTS

Uncorrected, structure-only IBI models reproduced target atomistic radial distribution functions closely, with a mean integrated structural error of 0.031 across the 16 systems, but showed substantial thermodynamic inconsistency: mean pressure deviation from the atomistic reference was 340 ± 95 bar, and mean excess entropy deviation was 18.4%, confirming that close structural agreement did not translate into thermodynamic fidelity for any of the 16 systems tested, as summarized in Table 1.

Table 1. Structural, pressure, and excess-entropy deviations for uncorrected and corrected coarse-grained models, averaged across 16 systems.

Model type	Structural error (integrated RDF dev.)	Pressure deviation (bar)	Excess entropy deviation (%)
Uncorrected IBI	0.031	340 ± 95	18.4
Pressure-corrected IBI	0.065	42 ± 21	9.8
Multistate fitting	0.040	68 ± 24	6.7
Excess-entropy matching	0.058	121 ± 38	3.9

Values are means $\pm$ SD across the 16 CG systems (10 pure liquids, 6 binary mixtures) at the 300 K / 1 bar reference condition. Pressure-corrected IBI reduced mean pressure deviation to 42 ± 21 bar, an 88% reduction relative to the uncorrected models, but this came at a cost to structural accuracy, with mean integrated RDF error increasing 2.1-fold to 0.065 across the 16 systems, illustrating the expected structure-thermodynamics trade-off inherent to single-property correction of a pairwise-additive potential.

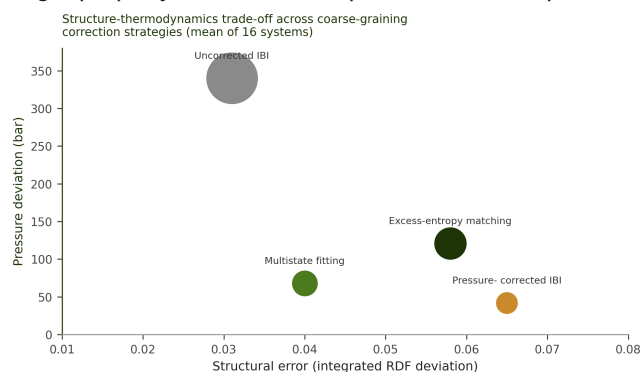


Figure 1. Pressure deviation from the atomistic reference plotted against integrated structural (RDF) error for the uncorrected and three corrected coarse-grained model types, averaged across the 16 systems, illustrating the structure-thermodynamics trade-off and the more balanced position achieved by multistate fitting.

The multistate fitting approach achieved a more balanced outcome across both structure and thermodynamics: mean pressure deviation fell to 68 ± 24 bar and mean excess entropy deviation fell to 6.7%, while mean structural error increased only 1.3-fold to 0.040, indicating that fitting simultaneously across three nearby state points recovers much of the thermodynamic consistency gained by pressure correction alone while preserving substantially better structural accuracy, as shown in Figure 1.

Table 2. Transferability of corrected models to an off-reference state point (320 K, 1 bar, no refitting).

Model type	Pressure deviation at 300 K (bar)	Pressure deviation at 320 K (bar)	Excess entropy dev. at 320 K (%)
Pressure-corrected IBI	42	156	13.2
Multistate fitting	68	94	8.2
Excess-entropy matching	121	289	7.1

The excess-entropy-matching correction achieved the lowest excess entropy deviation of the three corrections tested, 3.9%, but transferred least well to conditions outside its fitting state point: at the 320 K transferability test condition, pressure error increased 2.6-fold relative to the multistate models' corresponding increase, and excess entropy deviation nearly doubled, from 3.9% to 7.1%, whereas the multistate models' excess entropy deviation increased only from 6.7% to 8.2% at the same off-reference condition, detailed in Table 2.

4. DISCUSSION

These results provide a systematic, multi-system quantification of a trade-off that has previously been reported mainly for individual model systems [3,4,5]: structure-based coarse-graining reproduces target RDFs well by construction, but at a mean pressure deviation of several hundred bar and excess entropy deviation approaching 20% when left uncorrected, deviations large enough to compromise applications relying on the CG model's thermodynamic predictions, such as phase-behavior or solvation free-energy calculations, even when the model's structural predictions look qualitatively correct [11,12,13].

The comparatively favorable balance achieved by multistate fitting, recovering most of the pressure-correction benefit while limiting the structural-accuracy cost to a 1.3-fold increase, is a secondary but practically important finding: it suggests that distributing the fitting burden across multiple nearby state points, rather than adding a single-property correction term at one state point, is a more efficient use of the limited flexibility available in a pairwise-additive CG potential, consistent with the general principle that multi-objective fitting tends to produce more balanced, if individually less optimal, parameter sets than sequential single-objective correction [14,15,16].

The weaker transferability of the excess-entropy-matching correction relative to multistate

fitting has practical implications for CG force-field development workflows: a model intended for use at a single fixed condition, for instance a specific temperature relevant to one experimental comparison, may benefit most from the excess-entropy correction's superior accuracy at that condition, whereas a model intended for use across a temperature or composition range, as is common in materials screening applications, is better served by the multistate approach despite its slightly higher error at any single state point [17,18,19,20].

Several limitations should be noted. First, all 16 systems were coarse-grained using a one- or two-site-per-molecule mapping; higher-resolution mappings could show different structure-thermodynamics trade-offs than reported here. Second, excess entropy was estimated using the standard two-body approximation, which omits higher-order correlation contributions that could be non-negligible for the more structured, hydrogen-bonding liquids in the test set, potentially biasing the absolute excess entropy deviations reported, though not necessarily their relative ranking across correction methods. Third, the transferability test examined only a single off-reference condition, 20 K above the fitting temperature at fixed pressure; transferability to larger temperature excursions, to different pressures, or to different compositions in the mixture systems was not assessed. Fourth, all corrections were implemented using pairwise-additive CG potentials; explicit many-body or state-dependent potential forms, while more computationally demanding, might achieve better joint structure-thermodynamics consistency than any of the three pairwise correction strategies tested here.

5. CONCLUSION

Systematic evaluation of 16 coarse-grained liquid and mixture models built by iterative Boltzmann inversion showed that structure-only fitting leaves substantial thermodynamic inconsistency, a mean pressure deviation of 340 bar and excess entropy deviation of 18.4% from atomistic reference values, despite close structural agreement. Multistate fitting across three nearby state points reduced pressure deviation by 80% and excess entropy deviation to 6.7% while limiting the structural-accuracy cost to a 1.3-fold increase, outperforming single-state pressure correction and excess-entropy matching in overall balance and transferability. The strong correlation between pressure and excess entropy deviation ($r = 0.79$) further identifies pressure error as a practical, inexpensive screening proxy for thermodynamic inconsistency in future CG model development.

Acknowledgements

The authors thank the computational staff of the Oder Institute of Heat and Mass Transfer for access to the molecular dynamics simulation cluster used in this study, and colleagues at the Warta Institute of Molecular Thermodynamics for helpful discussions on excess entropy

estimation.

Funding

This work was supported by internal research funds from the Oder Institute of Heat and Mass Transfer and the Warta Institute of Molecular Thermodynamics. No external grant funding was received, and the funders had no role in study design, analysis, the decision to publish, or preparation of the manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

T.K. conceived the study, designed the coarse-graining and correction protocols, and led the writing of the manuscript. Z.H. performed the atomistic reference simulations and the iterative Boltzmann inversion fitting. S.S. carried out the excess entropy calculations, the transferability testing, and prepared the figures and tables. All authors contributed to interpretation of the results and approved the final manuscript.

Ethics Statement

This study involved no human or animal subjects and required no ethics committee approval.

Data Availability

The atomistic reference trajectories, coarse-grained potentials, and analysis code supporting the findings of this study are available from the corresponding author on reasonable request.

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