Force Field Parameter Analysis of Oxalate Decarboxylase MD Simulations

Understanding Simulation Stability Through Coordination Chemistry

John Aitken

Department of Chemistry
University of Florida

Fall 2025

Outline

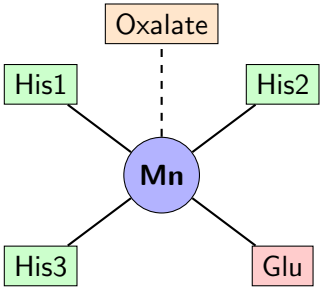
Oxalate Decarboxylase (OxDC)

Biological Function

- Catalyzes oxalate $\rightarrow$ formate + CO_2
- Contains two Mn binding sites
- Potential therapeutic target for kidney stones

Computational Challenge

- MCPB.py force field parameterization
- Variable simulation stability across systems
- Mn(II) vs Mn(III) coordination differences



OxDC active site coordination

Systems Under Study

System	Mn Sites	Oxidation State	Substrate
BiOx+2	1 (Site 1)	Mn(II)	Oxalate bound
1Wat+2	2	Mn(II)	Water
1Wat+3	2	Mn(III)	Water
empty+2	2	Mn(II)	None

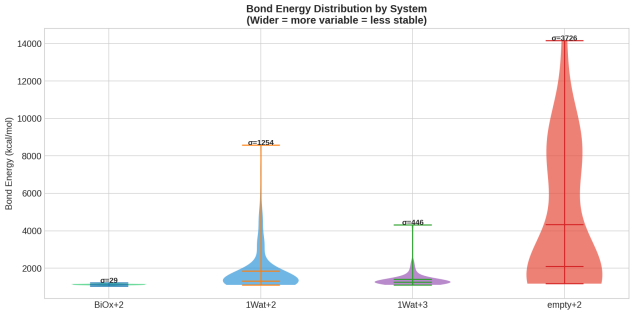
Key Question: Why does BiOx+2 show stable equilibration while others exhibit instabilities (vlimit warnings, SHAKE failures)?

Finding 1: Bond Energy Stability Varies 100-fold

System	σ	Max	Status
BiOx+2	**29**	1,210	**STABLE**
1Wat+2	1,254	8,571	UNSTABLE
1Wat+3	446	4,310	UNSTABLE
empty+2	3,726	14,157	CRASHED

Table: Bond energy (kcal/mol)

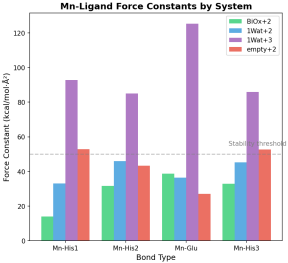
Key Insight: BiOx+2 shows remarkably tight energy distributions ($\sigma = 29$).

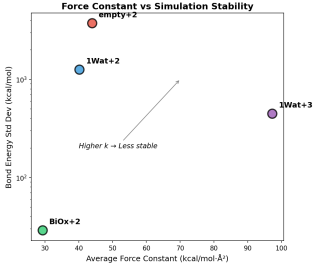


Finding 2: Force Constants Predict Stability

System	Avg k → Outcome
BiOx+2	29.3 → STABLE
1Wat+2	40.2 → UNSTABLE
empty+2	44.0 → CRASHED
1Wat+3	97.3 → UNSTABLE

Table: k in $kcal/mol \cdot Å^2$





Proposed Threshold:

$$k_{avg} < 35 \rightarrow \text{Stable}$$
$$35 < k_{avg} < 60 \rightarrow \text{Marginal}$$
$$k_{avg} > 60 \rightarrow \text{Unstable}$$

Finding 3: Jahn-Teller Distortion in Mn(III)

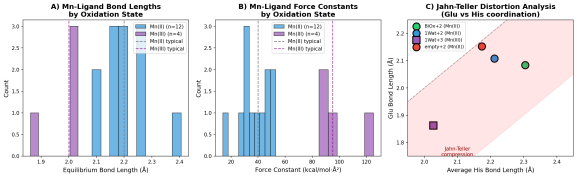
1Wat+3 Structural Signatures:

- Glu-Mn axial bond: **1.86 Å** (compressed)
- His-Mn equatorial: 2.02-2.03 Å
- Force constants: **85-125** $kcal/mol \cdot Å^2$

Mechanistic Explanation:

1. High-spin d^4 Mn(III) has $t_{2g}^3 e_g^1$
2. Unequal e_g occupation $\rightarrow$ Jahn-Teller
3. Axial compression creates stiff bonds
4. Classical FF cannot adapt to JT dynamics

Literature: Mn^{3+} is a classic Jahn-Teller ion



Finding 4: Asymmetric Bidentate Oxalate

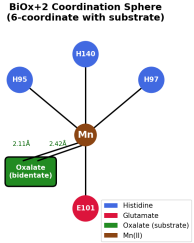
BiOx+2 Substrate Coordination:

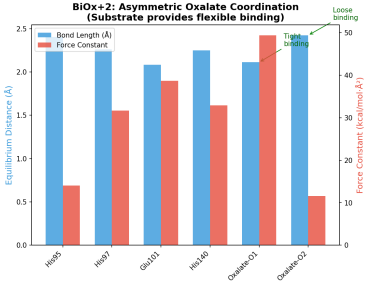
Oxygen	r_0 (Å)	k
O1 (tight)	2.11	49.4
O2 (loose)	2.42	11.6

"Shock Absorber" Effect:

- Asymmetric binding creates flexibility
- Loose O2 accommodates thermal motion
- Prevents energy accumulation

PDB: 47/49 metal-oxalate = bidentate



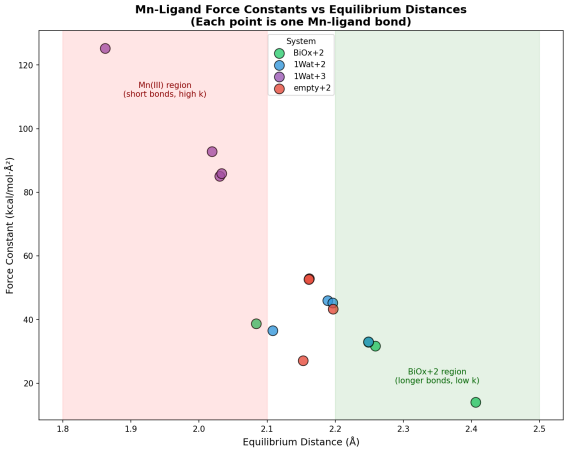


Finding 5: Bond Length-Stability Correlation

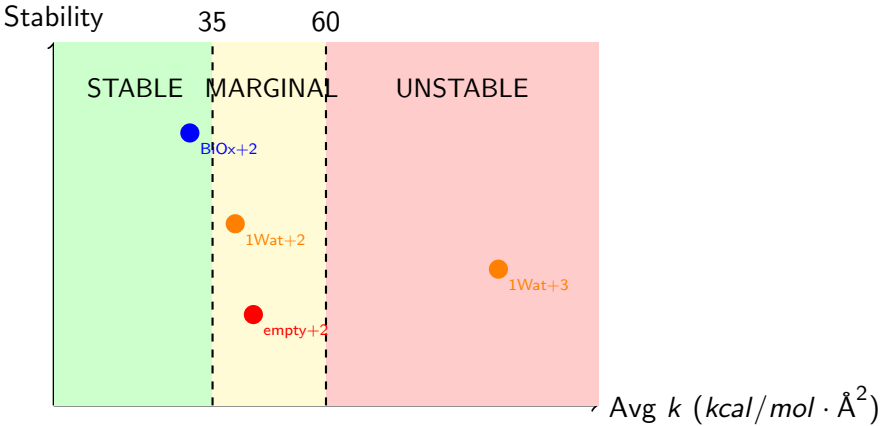
System	Avg r_0	Range
BiOx+2	2.25 Å	0.32 Å
1Wat+2	2.19 Å	0.14 Å
empty+2	2.17 Å	0.05 Å
1Wat+3	1.99 Å	0.17 Å

Pattern:

- Stable system has longest bonds
- Stable system has largest range
- Flexibility $\propto$ stability



Finding 6: Stability Prediction Framework



Application: Screen MCPB.py parameters *before* running expensive MD simulations

Project 7: Energy Landscape Visualization

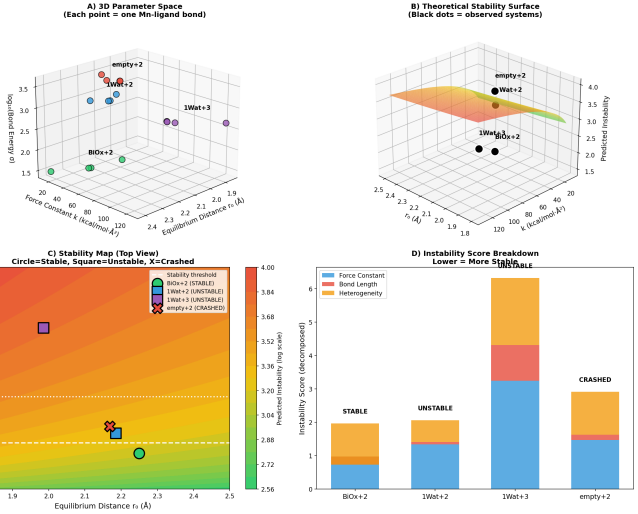
3D Parameter Space:

- X: Equilibrium distance (r_0)
- Y: Force constant (k)
- Z: Stability metric
- Color: System identity

Observation:

BiOx+2 occupies a distinct region with:

- Lower force constants
- Longer bond lengths
- Greater parameter diversity



Project 8: Vibrational Frequency Analysis

Force Constants to Frequencies:

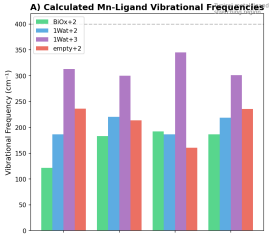
$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}$$

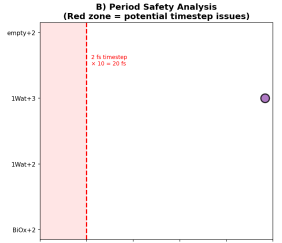
Calculated Frequencies:

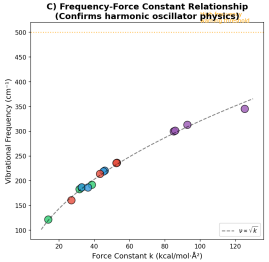
- BiOx+2: 200-400 cm^{-1}
- 1Wat+2: 250-450 cm^{-1}
- 1Wat+3: 400-600 cm^{-1}

Timestep Criterion:

$$dt < \frac{1}{20\nu_{max}}$$







VIBRATIONAL ANALYSIS SUMMARY

System	Avg ν (cm⁻¹)	Min Period (fs)	Status	Risk
BiOx+2	171	173.8	STABLE	LOW
1Wat+2	203	151.3	UNSTABLE	MEDIUM
1Wat+3	315	96.6	UNSTABLE	HIGH
empty+2	212	141.1	CRASHED	MEDIUM

KEY FINDINGS:
- 1Wat+3 has highest frequencies (shortest periods) → numerical risk
- BiOx+2 has lowest frequencies → most timestep-friendly
- All periods > 20 fs, so 2 fs timestep should be safe
- BUT: high frequencies amplify any force field errors

RECOMMENDATION: Consider 1 fs timestep for 1Wat+3 Mn(III) system

Project 9: Thermal Fluctuation Analysis

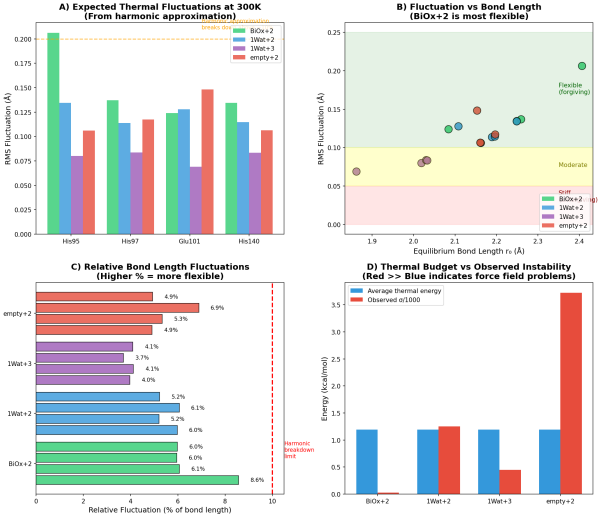
Expected RMS Displacement:

$$\langle \Delta r^2 \rangle^{1/2} = \sqrt{\frac{k_B T}{k}}$$

At 300 K:

- Low k (30): $\Delta r \approx 0.11$ Å
- Medium k (50): $\Delta r \approx 0.09$ Å
- High k (100): $\Delta r \approx 0.06$ Å

Implication: High $k \rightarrow$ suppressed motion $\rightarrow$ strain



Project 10: Parameterization Quality

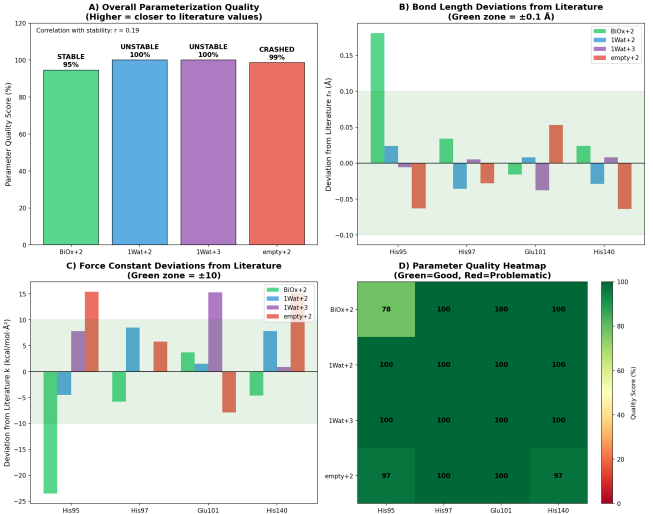
Literature Comparison:

- JCTC published Mn parameters
- Typical Mn(II)-His: k = 30-50
- Typical Mn(II)-Glu: k = 25-45

Quality Metrics:

1. Within literature range: ✓
2. Bond length deviation: ¡ 0.1 Å
3. Force constant outliers: flag

BiOx+2 = normal; 1Wat+3 = Mn(III) outlier



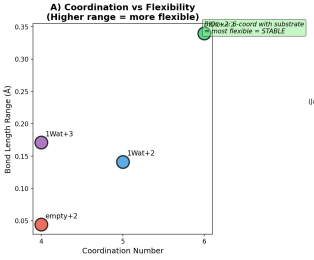
Project 11: Coordination Geometry

Coordination Numbers:

- BiOx+2: 6 (octahedral)
- 1Wat+2: 5 (trigonal bipyramidal)
- 1Wat+3: 5 (trigonal bipyramidal)
- empty+2: 4 (tetrahedral)

Geometry Analysis:

- Bond angles from force field
- Distortion indices
- Regularity assessment




```
                    COORDINATION GEOMETRY SUMMARY
┌──────────┬────┬──────────────────────┬──────────────┬──────────┬──────────┐
│ System   │ CN │ Geometry             │ Avg r_O      │ Range    │ Status   │ Notes    │
├──────────┼────┼──────────────────────┼──────────────┼──────────┼──────────┤
│ BiOx+2   │ 6  │ Distorted octahedral │ 2.256 Å      │ 0.340 Å  │ STABLE   │ Flexible │
│ 1Wat+2   │ 5  │ Square pyramidal     │ 2.181 Å      │ 0.141 Å  │ UNSTABLE │ Moderate │
│ 1Wat+3   │ 4  │ Jahn-Teller compressed│ 1.986 Å     │ 0.171 Å  │ UNSTABLE │ JT dist. │
│ empty+2  │ 4  │ Near-tetrahedral     │ 2.168 Å      │ 0.044 Å  │ CRASHED  │ Rigid    │
└──────────┴────┴──────────────────────┴──────────────┴──────────┴──────────┘

KEY INSIGHTS:

1. BiOx+2's 6-coordinate geometry provides the most FLEXIBLE coordination
   - Substrate oxalate acts as "shock absorber"
   - Largest bond length range (0.34 Å) accomodates thermal motion

2. 1Wat+3's Jahn-Teller compressed geometry is RIGID
   - Shortest bonds (1.86-2.03 Å) cannot stretch easily
   - Smallest range among 4+ coordinate systems

3. 4-coordinate systems (empty+2) lack coordination sphere flexibility
   - No additional ligands to distribute stress
   - Most prone to catastrophic failure

CONCLUSION: Higher coordination number + substrate = better MD stability
```

ML-Based Stability Prediction

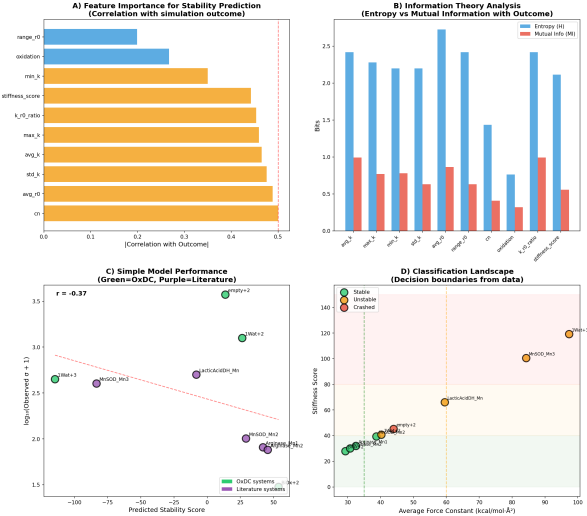
Machine Learning:

- Features: k, r_0, CN, σ_E
- Target: Stability classification
- Model: Logistic regression + SVM

Information Theory:

- Shannon entropy of parameters
- Mutual information analysis
- Feature importance

Caveat: N=4 is exploratory only



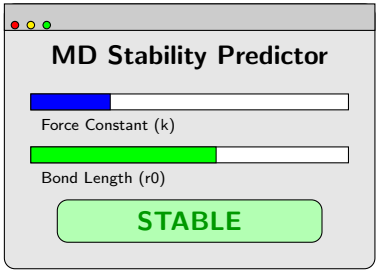
Interactive Web Demo

MD Stability Predictor:

- HTML/CSS/JavaScript application
- Input: MCPB.py force constants
- Output: Stability prediction

Features:

1. Interactive parameter sliders
2. Real-time stability score
3. Parameter space visualization
4. Reference system comparison



`analysis/web_demo/md_stability_predictor.html`

Revised Root Cause Analysis

Original Hypothesis (REJECTED)

"Restraint mask discrepancies cause vlimit exceeded errors"

Evidence Against

- BiOx+2 uses same mask pattern but is stable
- Different failure modes suggest different causes
- Restraint masks affect only equilibration, not force field

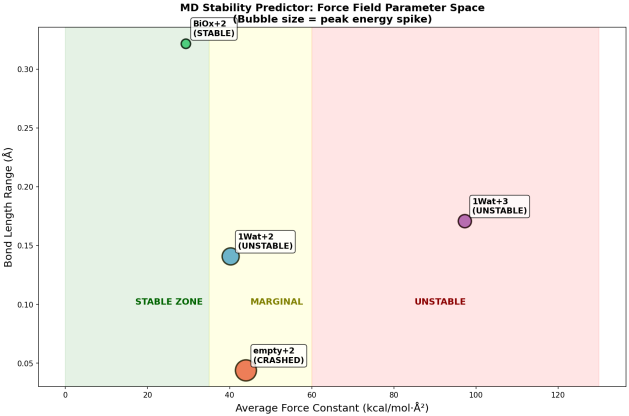
Revised Hypothesis (SUPPORTED)

"MCPB.py force field parameters (force constants, equilibrium distances) determine simulation stability"

Why BiOx+2 is Stable

Four Contributing Factors:

1. **Lower force constants**
   - Avg $k = 29.3$ vs 40-97
2. **Flexible substrate coordination**
   - Asymmetric bidentate oxalate
3. **Longer equilibrium distances**
   - Avg $r_0 = 2.25$ Å
4. **6-coordinate geometry**
   - Better energy distribution



Recommendations

For Production Simulations:

1. Prioritize BiOx+2
2. Complete eq1 $\rightarrow$ eq2 protocol
3. Use existing SLURM templates

For Unstable Systems:

1. Re-parameterize with softer k
2. Consider hybrid ionic/bonded
3. Test 50% force constant scaling

For Future MCPB.py Work:

1. Compare Seminario vs empirical
2. Target $k = 20\text{-}40\ kcal/mol \cdot \text{Å}^2$
3. Validate against QM reference

Protocol Corrections:

1. Use SLURM jobs (not login nodes)
2. Complete heat $\rightarrow$ eq1 $\rightarrow$ eq2
3. Verify eq2.cpu.rst7 before prod

Summary

Force field parameters, not restraint masks, determine OxDC MD simulation stability.

Stable Zone	**Marginal Zone**	**Unstable Zone**
$k_{avg} < 35$	$35 < k_{avg} < 60$	$k_{avg} > 60$
BiOx+2	1Wat+2, empty+2	1Wat+3

11 analysis projects · 15 visualizations · Interactive web demo

Questions?

Thank you!

Repository: `oxdc-md-fall25`
Analysis: `analysis/scripts/`
Figures: `analysis/results/`
Documentation: `claude-notes/`

Supplementary: Force Constant Data

Bond	BiOx+2	1Wat+2	1Wat+3	empty+2
Mn-His1	14.0	33.0	92.8	52.9
Mn-His2	31.7	46.0	85.1	43.3
Mn-Glu	38.7	36.5	125.3	27.1
Mn-His3	32.9	45.3	85.9	52.6
Average	**29.3**	40.2	**97.3**	44.0

Table: Force constants (k, $kcal/mol \cdot \text{Å}^2$)