Alchemy in MD

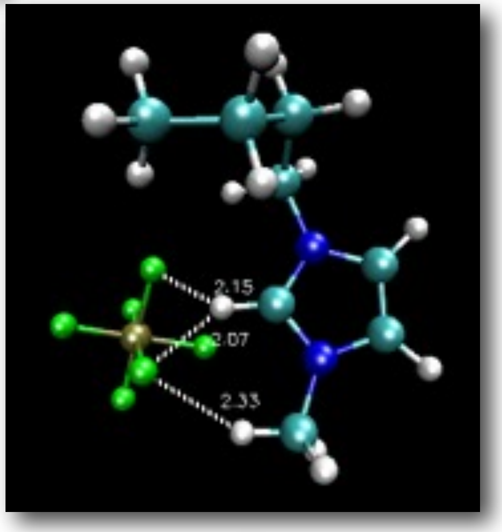
Sai Jayaraman
Advanced Device Technologies Department

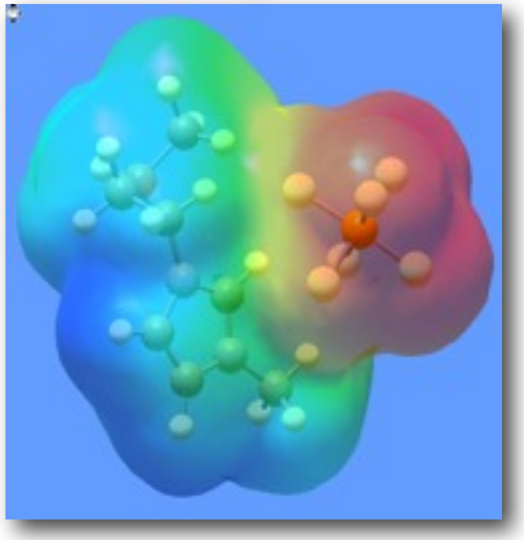
Sandia National Laboratories

sjayara@sandia.gov

Sandia is a multi-program laboratory operated by Sandia corporation, a fully owned subsidiary of Lockheed Martin Corporation, for the United States Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

Classical Simulations





ab initio calculations

$$V_{bond} = k_x \left(x - x_o\right)^2$$

$$V_{angle} = k_\theta \left(\theta - \theta_o\right)^2$$

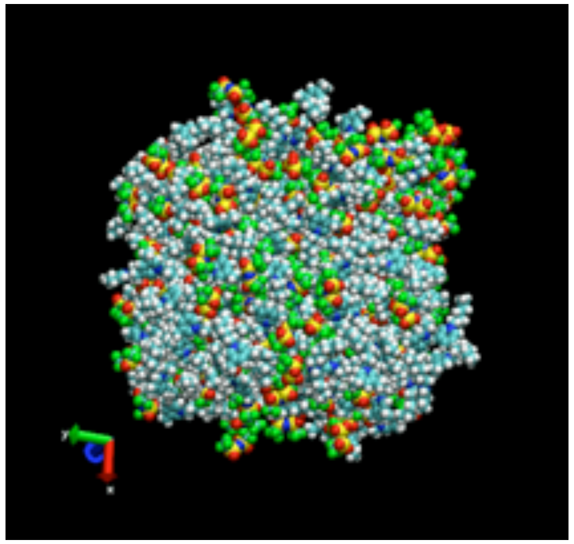
$$V_{dihedral} = k_\phi \left[1 + \cos\left(n\phi - \phi_o\right)\right]$$

$$V_{improper} = k_\psi \left(\psi - \psi_o\right)^2$$

$$V_{LJ} = \varepsilon_{ij}\left[\left(\frac{r_{\min,ij}}{r_{ij}}\right)^{12} - 2\left(\frac{r_{\min,ij}}{r_{ij}}\right)^{6}\right]$$

$$V_{el} = \frac{q_i q_j}{4\pi\varepsilon_0 r_i r_j}$$

Classical force field

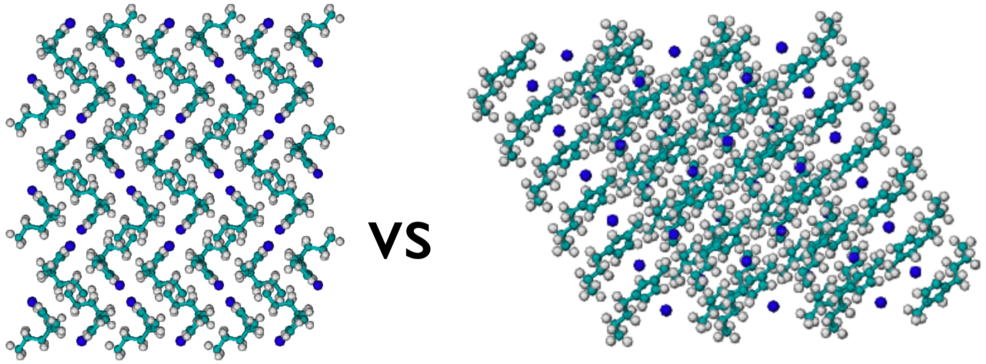


Condensed phase simulations (MD, MC)

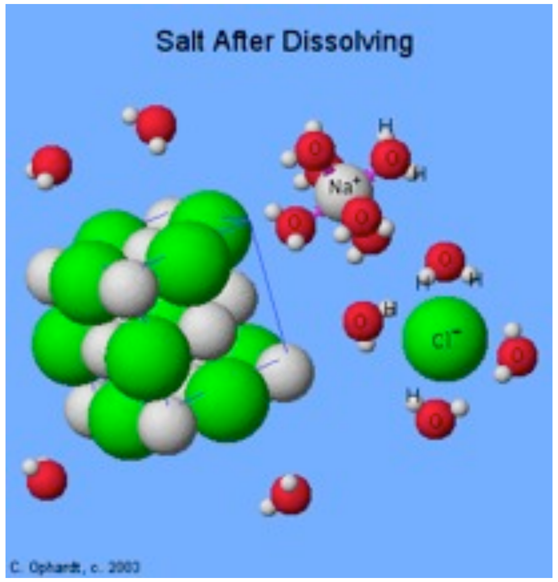
Statistical mechanics

Properties

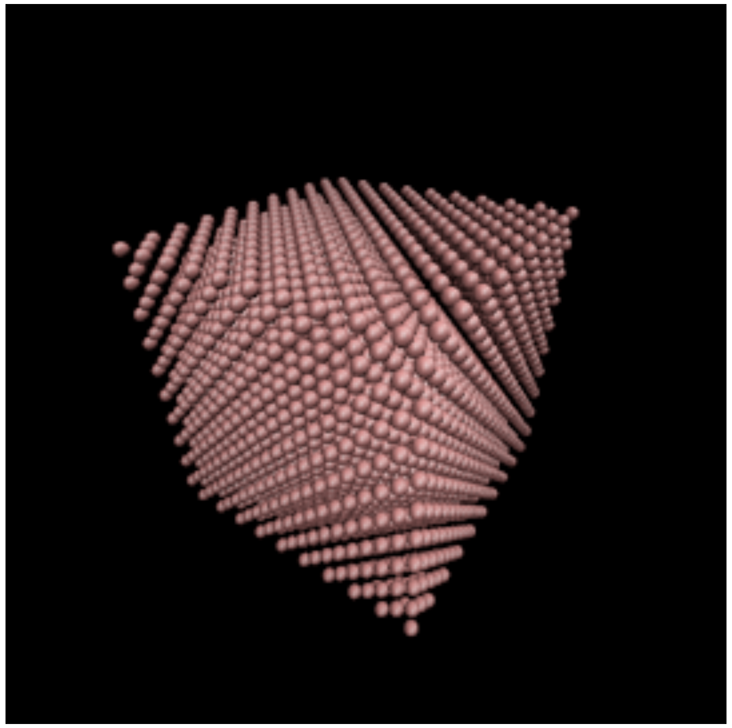
Why do we need to compute free energies?



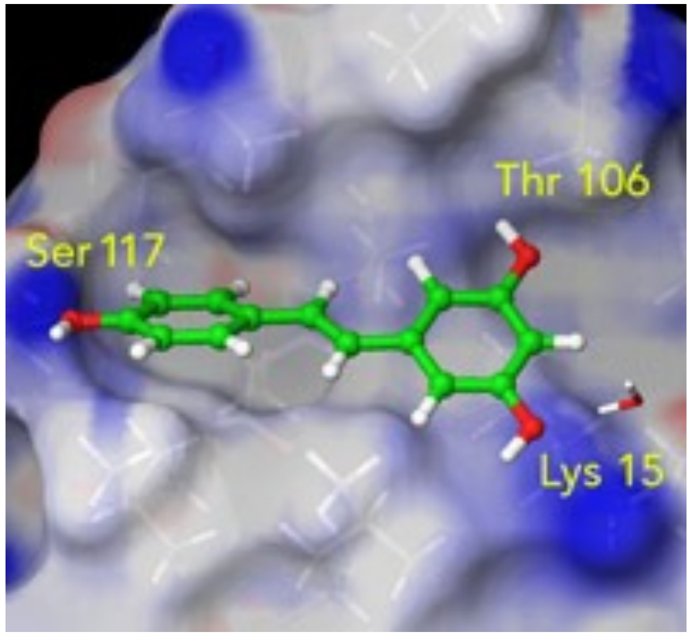
Crystal phase stabilities



Solubility



Melting



Docking

Free energy from simulations

$$F = -k_B T \ln Q(N,V,T) = -k_B T \ln \left(\frac{\int d\mathbf{p}^N \int d\mathbf{r}^N \exp(-\beta \mathcal{H}(\mathbf{p}^N, \mathbf{r}^N))}{\Lambda^N N!} \right)$$

Not an ensemble average. F is a thermal quantity

Absolute free energies cannot be measured experimentally, and from simulations using direct methods.

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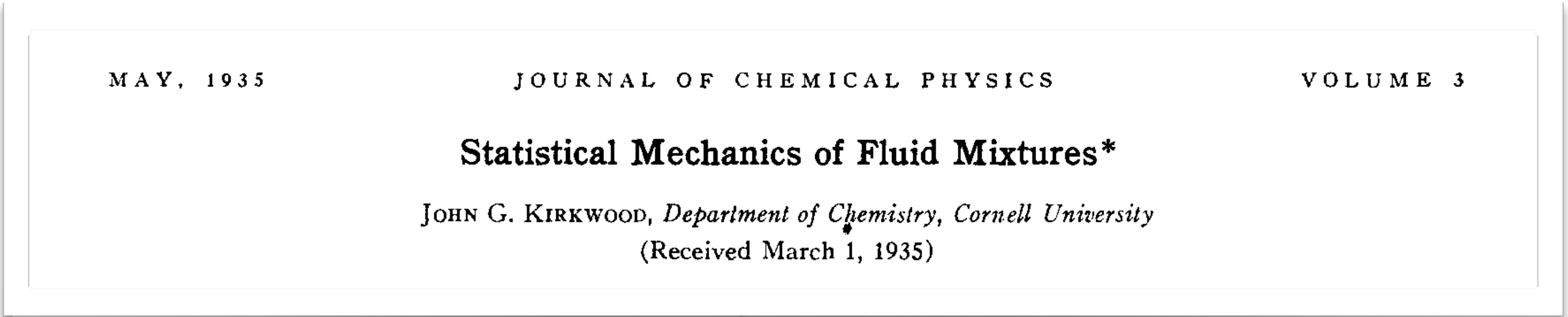
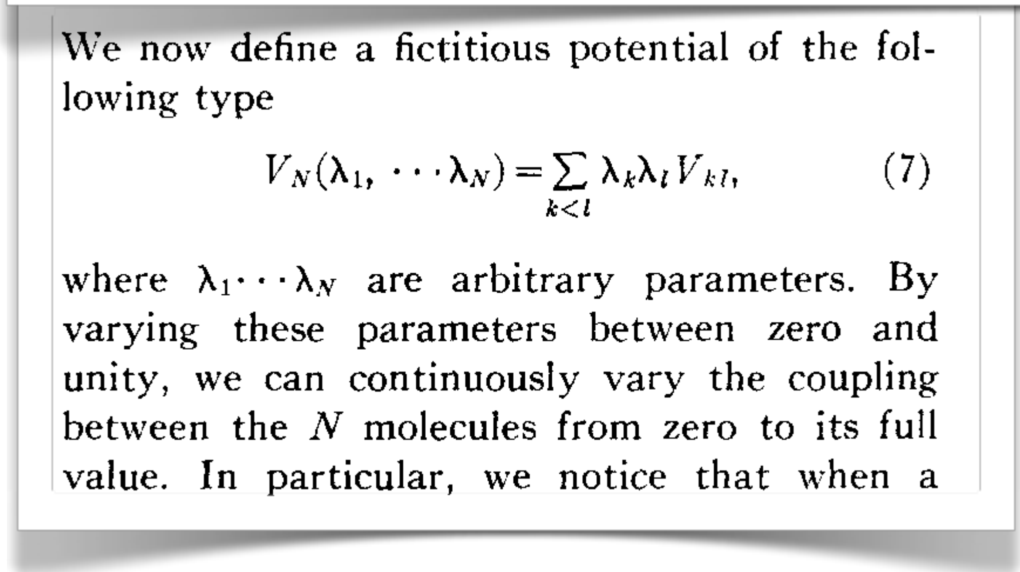


MAY, 1935 JOURNAL OF CHEMICAL PHYSICS VOLUME 3

Statistical Mechanics of Fluid Mixtures*

JOHN G. KIRKWOOD, *Department of Chemistry, Cornell University*
(Received March 1, 1935)



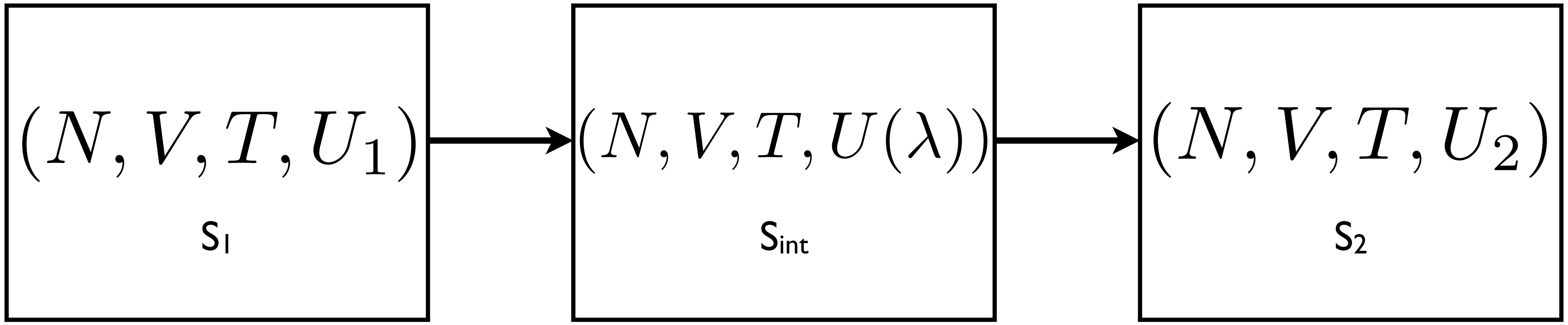
We now define a fictitious potential of the following type

$$V_N(\lambda_1, \cdots \lambda_N) = \sum_{k<l} \lambda_k \lambda_l V_{kl}, \qquad (7)$$

where $\lambda_1 \cdots \lambda_N$ are arbitrary parameters. By varying these parameters between zero and unity, we can continuously vary the coupling between the N molecules from zero to its full value. In particular, we notice that when a

Describes the "coupling parameter method", more commonly known as Thermodynamic Integration

Thermodynamic Integration: Relating a thermal variable to an ensemble average



$$(N, V, T, U_1) \longrightarrow (N, V, T, U(\lambda)) \longrightarrow (N, V, T, U_2)$$

S_1 S_{int} S_2

$$U(\lambda) = f_1(\lambda)U_1 + f_2(\lambda)U_2$$

Simplest case:

$$U(\lambda) = (1 - \lambda)U_1 + \lambda U_2$$

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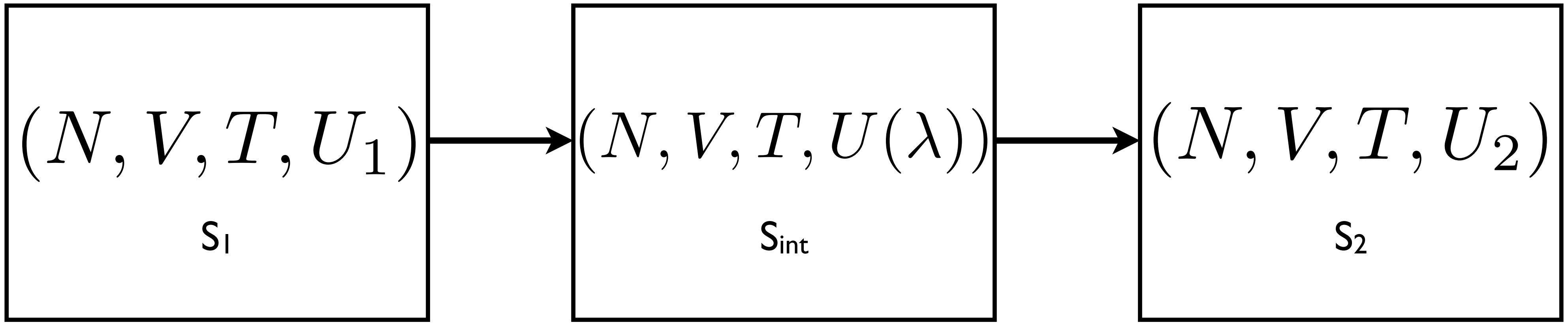

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$$Q(N, V, T, \lambda) = \frac{1}{\Lambda^{3N} N!} \int d\mathbf{r}^N \exp(-\beta U(\lambda))$$

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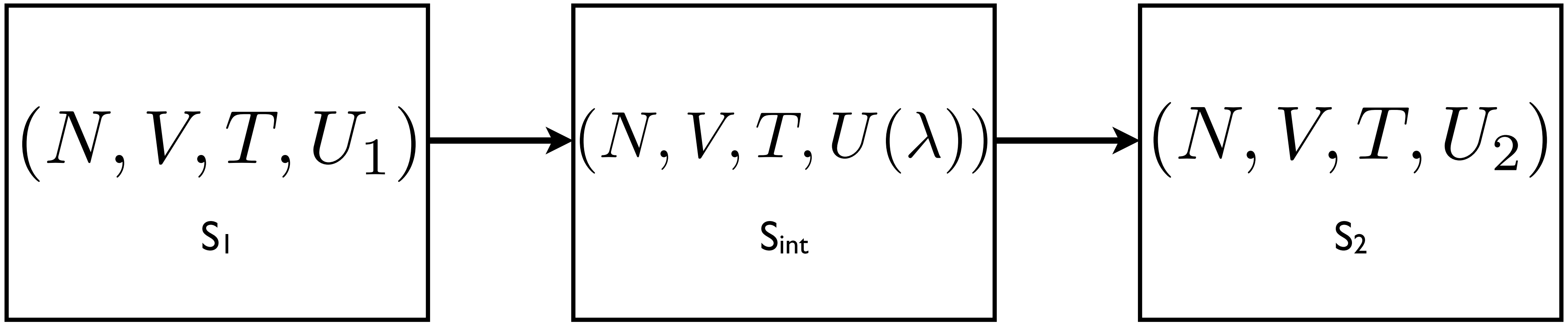

$$\begin{tikzcd}\boxed{\begin{array}{c}(N,V,T,U_1)\\ \text{S}_1\end{array}} \arrow[r] & \boxed{\begin{array}{c}(N,V,T,U(\lambda))\\ \text{S}_{\text{int}}\end{array}} \arrow[r] & \boxed{\begin{array}{c}(N,V,T,U_2)\\ \text{S}_2\end{array}}\end{tikzcd}$$

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$$F = -k_B T \ln Q(N,V,T) = -k_B T \ln\left(\frac{\int d\mathbf{p}^N \int d\mathbf{r}^N \exp(-\beta U(\mathbf{p}^N,\mathbf{r}^N))}{\Lambda^N N!}\right)$$

$$
\begin{aligned}
\left(\frac{\partial F(\lambda)}{\partial \lambda}\right)_{N,V,T} &= -\frac{1}{\beta}\frac{\partial}{\partial \lambda}\ln Q(N,V,T,\lambda) \\
&= -\frac{1}{\beta Q(N,V,T,\lambda)}\frac{\partial Q(N,V,T,\lambda)}{\partial \lambda} \\
&= \frac{\int d\mathbf{r}^N (\partial U(\lambda)/\partial \lambda \exp(-\beta U(\lambda)))}{\int d\mathbf{r}^N \exp(-\beta U(\lambda))}
\end{aligned}
$$

$$\left(\frac{\partial F(\lambda)}{\partial \lambda}\right)_{N,V,T} = -\frac{1}{\beta}\frac{\partial}{\partial \lambda}\ln Q(N,V,T,\lambda)$$

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$$\left(\frac{\partial F(\lambda)}{\partial \lambda}\right)_{N,V,T} = \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_{\lambda}$$

$$\begin{aligned}\left(\frac{\partial F(\lambda)}{\partial \lambda}\right)_{N,V,T} &= -\frac{1}{\beta}\frac{\partial}{\partial \lambda}\ln Q(N,V,T,\lambda)\\ &= -\frac{1}{\beta Q(N,V,T,\lambda)}\frac{\partial Q(N,V,T,\lambda)}{\partial \lambda}\\ &= \frac{\int d\mathbf{r}^N\left(\partial U(\lambda)/\partial\lambda \exp(-\beta U(\lambda))\right)}{\int d\mathbf{r}^N \exp(-\beta U(\lambda))}\end{aligned}$$

$$\left(\frac{\partial F(\lambda)}{\partial \lambda}\right)_{N,V,T} = \left\langle \frac{\partial U(\lambda)}{\partial \lambda}\right\rangle_{\lambda}$$

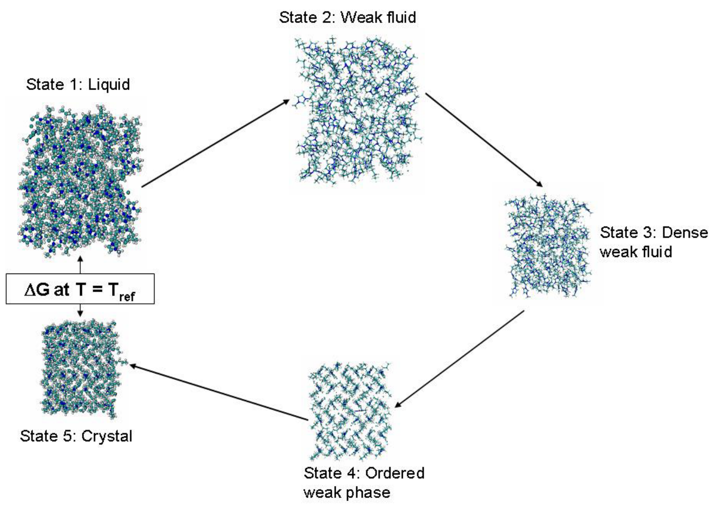
Numerical Integration

$$F(\lambda=1)-F(\lambda=0)=\int_{\lambda=0}^{\lambda=1} d\lambda \left\langle \frac{\partial U(\lambda)}{\partial \lambda}\right\rangle_{\lambda}$$

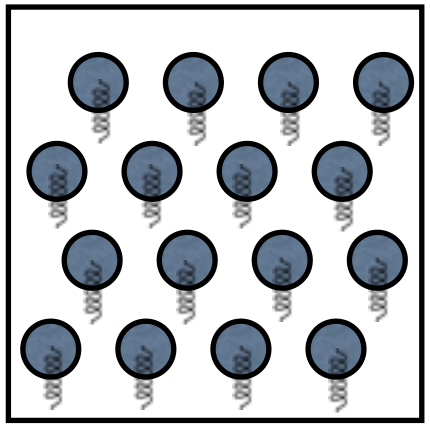
Choice of thermodynamic path

Need smooth, reversible paths to compute free energies

- What are the intermediate states?



Reference States:



Einstein Crystal

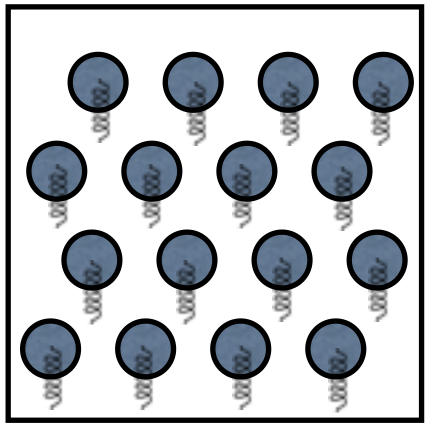
- Scaling functions?

$$U(\lambda) = f_1(\lambda)U_1 + f_2(\lambda)U_2$$

- Linear, quadratic, cubic, quartic
- Which components of the potential do we scale? LJ - σ, ϵ :both?

Reference states

- Frequently used reference state for computing free energies of solids
- Free energy can be computed analytically



Einstein Crystal

Molecular dynamics investigation of the crystal–fluid interface. I. Bulk properties

J. Chem. Phys. **79**(10), 15 Nov. 1983

Jeremy Q. Broughton and George H. Gilmer

$$\beta F_{einstein} = 3N\ln(\beta\hbar\sqrt{K}) + \beta N\phi_0$$

Other reference states for solids: Harmonic crystal, Wigner-Seitz cells (Hoover and Ree)

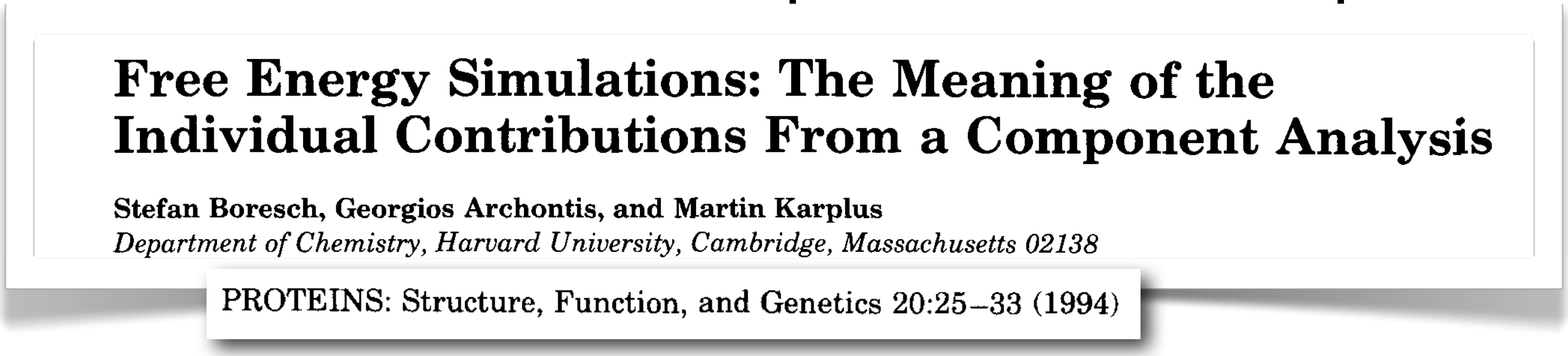
Reference state for Liquids: Ideal gas

$$\beta F_{ideal} = 3N\ln\Lambda$$

$$\Lambda = h\sqrt{\frac{\beta}{2\pi m}}$$

Intermediate states

- Different energy terms can be transformed independent of each other - smoother path/no added complexities?



Free Energy Simulations: The Meaning of the Individual Contributions From a Component Analysis

Stefan Boresch, Georgios Archontis, and Martin Karplus

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

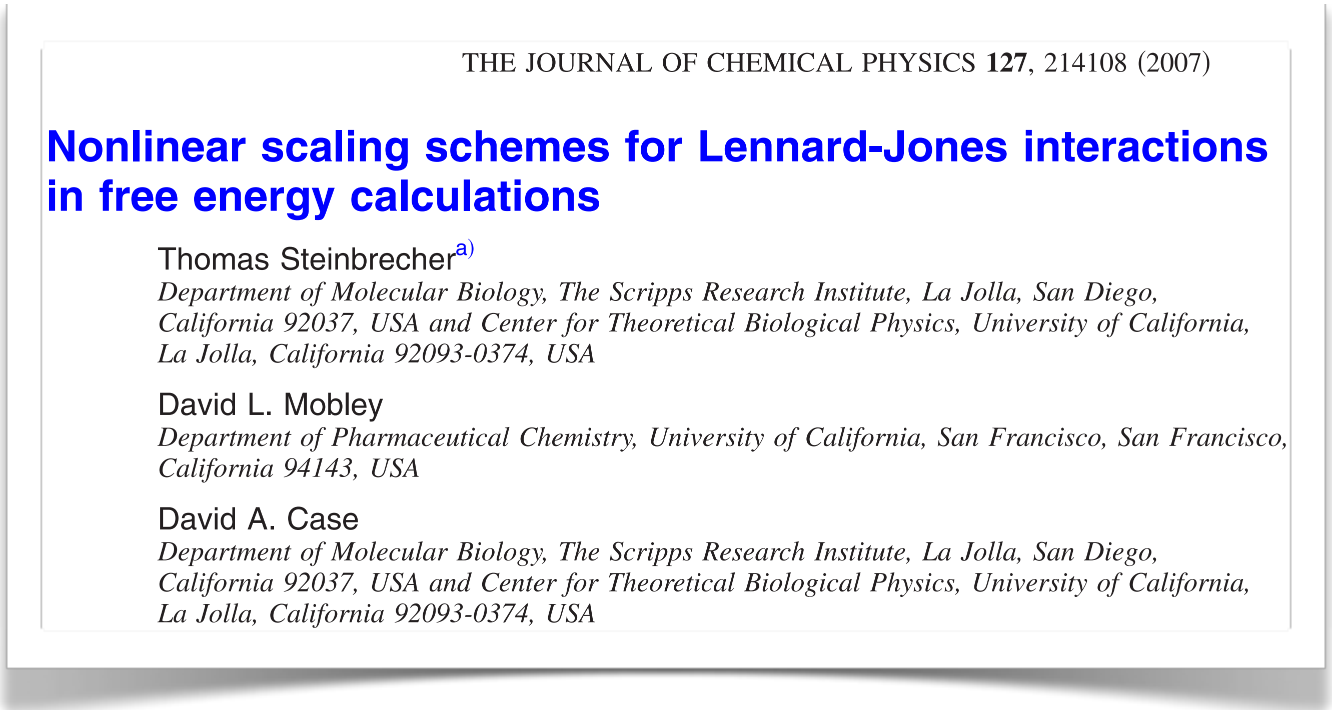
PROTEINS: Structure, Function, and Genetics 20:25–33 (1994)

$$\begin{tikzcd}
Cl^- \arrow[r, "\Delta A_{LJ}^{-1} = 4.65"] \arrow[d, "\Delta A_{el} = 94.09"'] & Br^- \arrow[d, "\Delta A'_{el} = 90.56"] \\
Cl^0 \arrow[r, "\Delta A_{LJ}^{0} = 1.12"'] & Br^0
\end{tikzcd} \quad (I)$$

- Solvation free energy difference between Cl^- and Br^-

- Different paths yield different LJ free energy changes!

Intermediate states - Importance of the scaling function



THE JOURNAL OF CHEMICAL PHYSICS **127**, 214108 (2007)

Nonlinear scaling schemes for Lennard-Jones interactions in free energy calculations

Thomas Steinbrecher[a)]
Department of Molecular Biology, The Scripps Research Institute, La Jolla, San Diego, California 92037, USA and Center for Theoretical Biological Physics, University of California, La Jolla, California 92093-0374, USA

David L. Mobley
Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, California 94143, USA

David A. Case
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- Compare different scaling schemes to eliminate endpoint singularity - Occurs when a scaled and an unscaled LJ particle interact
- Linear scheme performs poorly, non-linear schemes eliminate singularity.

$V(\lambda) = \lambda V_1 + (1-\lambda)V_0$	Linear
$V(\lambda) = [1-(1-\lambda)^k]V_1 + (1-\lambda)^k V_0$	Non-linear
$f(\lambda) = (1-\lambda)^k \sum_{i=0}^{k-1} g(k-1+i,i)\lambda^i; g(x,y) = \frac{x!}{(x-y)!y!}$	AMBER9
$V_{softcore} = 4\epsilon(1-\lambda)\left[\frac{1}{(\alpha\lambda+(r/\sigma)^6)^2} - \frac{1}{\alpha\lambda+(r/\sigma)^6}\right]$	Soft-core

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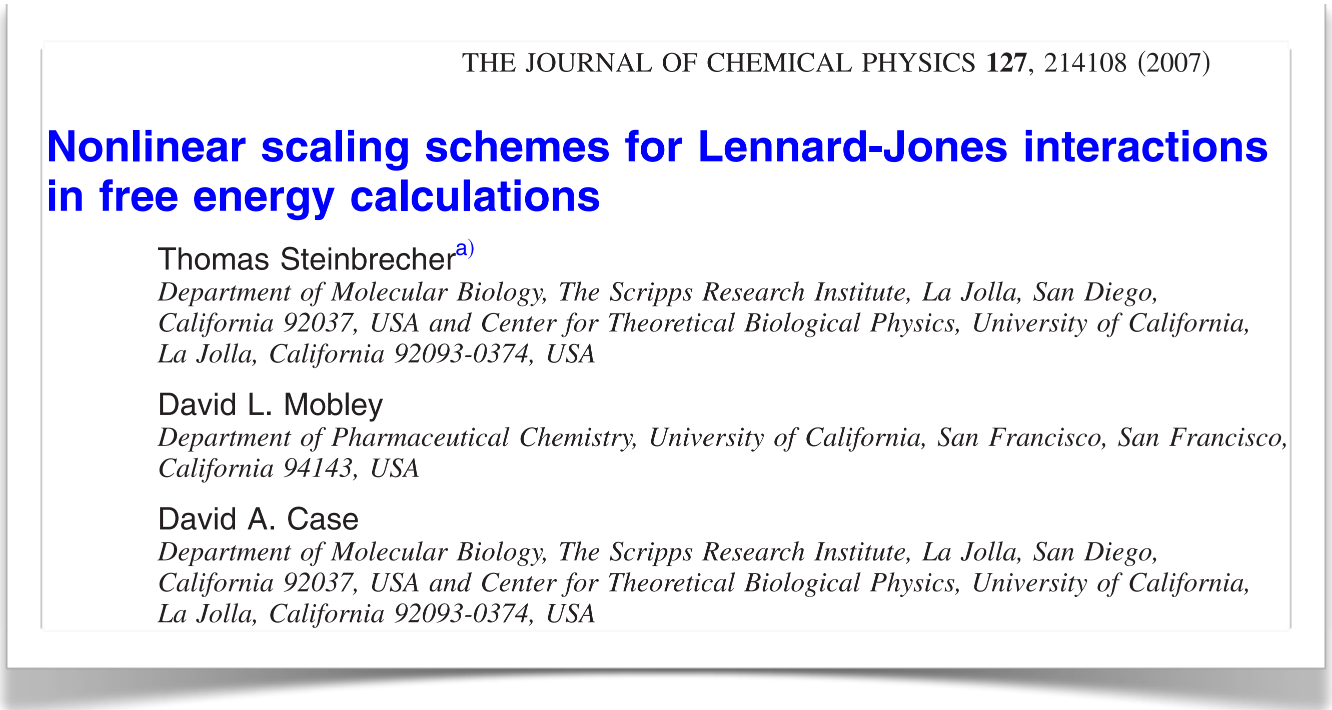

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AMBER9

$$V_{softcore} = 4\epsilon(1-\lambda)\left[\frac{1}{(\alpha\lambda+(r/\sigma)^6)^2} - \frac{1}{\alpha\lambda+(r/\sigma)^6}\right]$$

Soft-core

Pérez and von Lilienfeld (submitted): non-linear scale factors in AIMD alchemy - linear vs quartic

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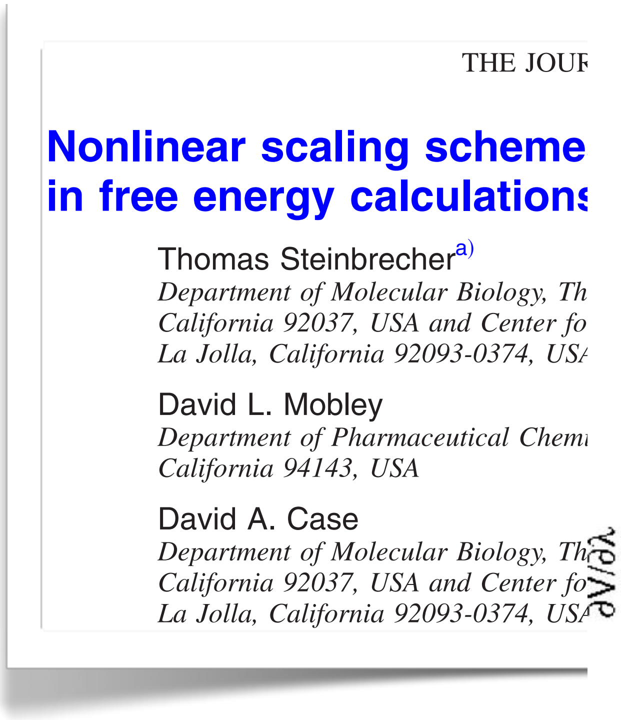

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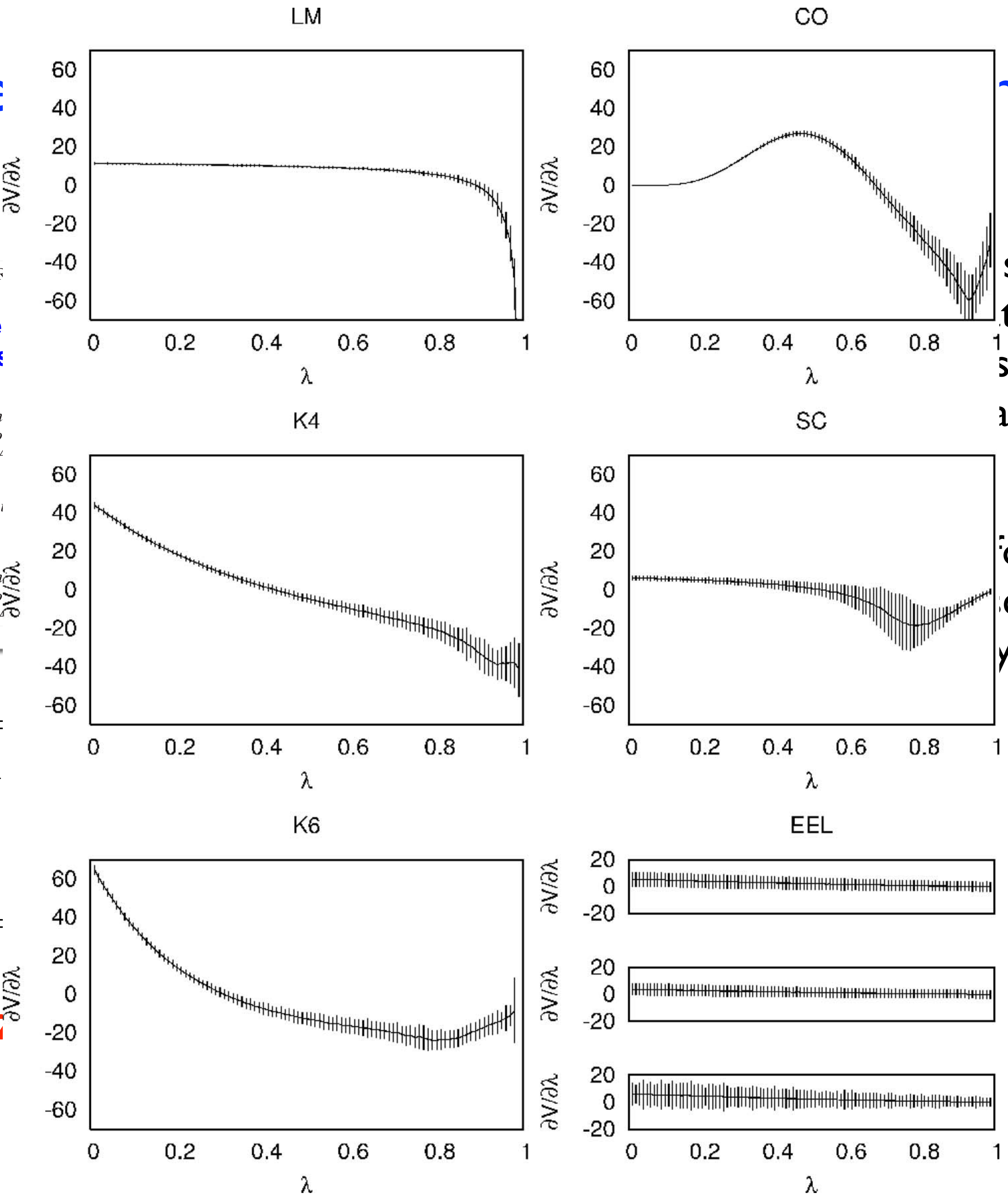

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$V_{softcore} =$

Pérez

scale

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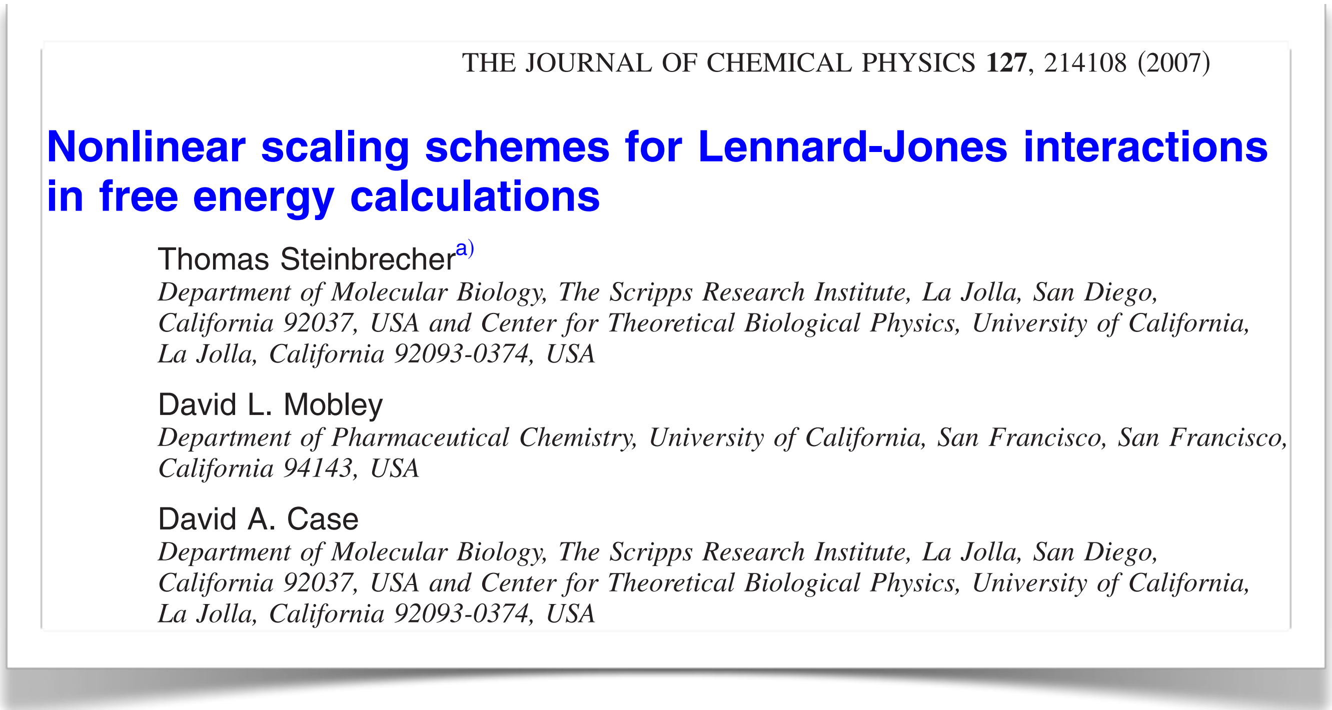

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AMBER9

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Some applications of Alchemy

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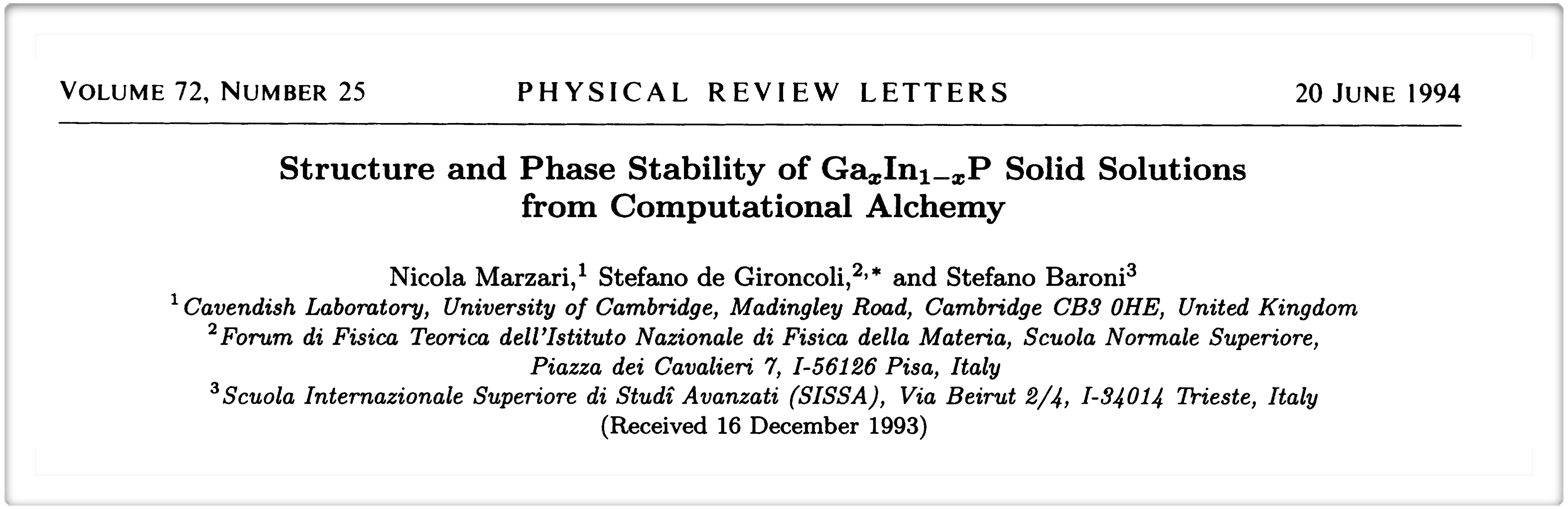


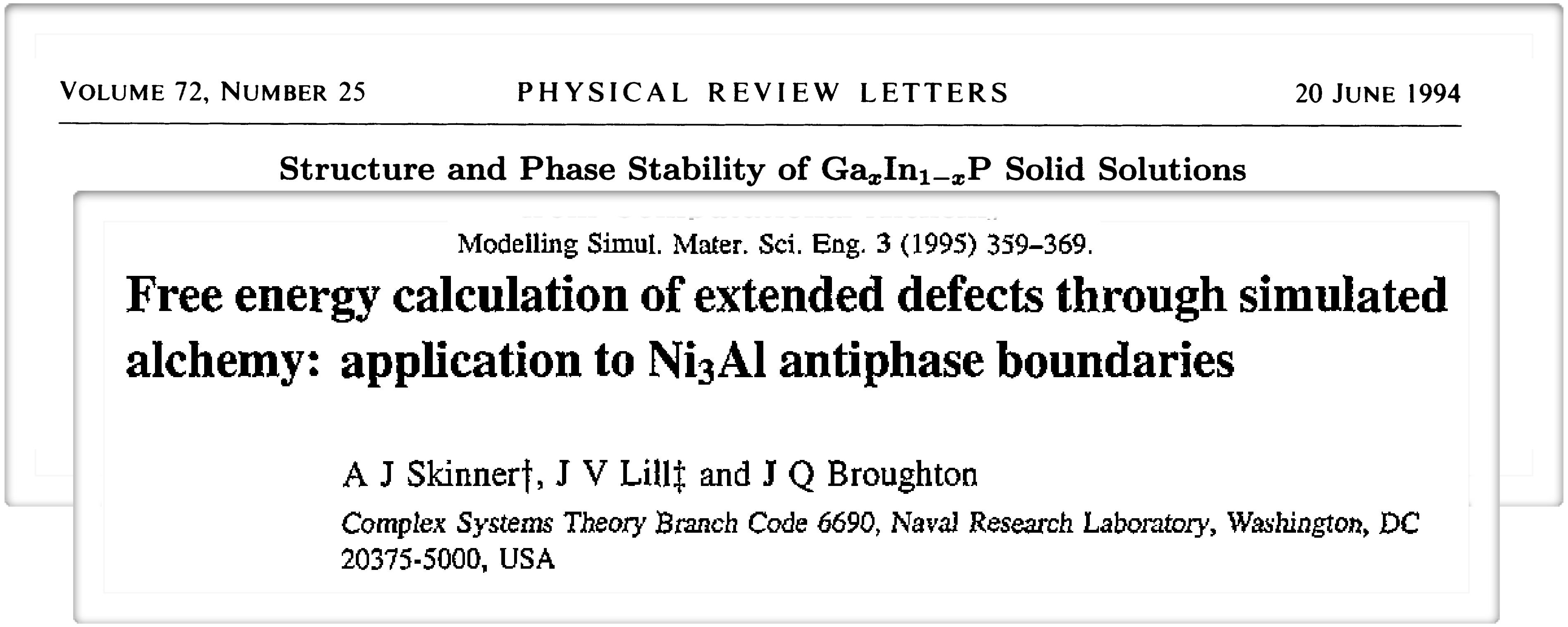
VOLUME 72, NUMBER 25 PHYSICAL REVIEW LETTERS 20 JUNE 1994

Structure and Phase Stability of $\mathrm{Ga}_x\mathrm{In}_{1-x}\mathrm{P}$ Solid Solutions from Computational Alchemy

Nicola Marzari,[1] Stefano de Gironcoli,[2,*] and Stefano Baroni[3]
[1] *Cavendish Laboratory, University of Cambridge, Madingley Road, Cambridge CB3 0HE, United Kingdom*
[2] *Forum di Fisica Teorica dell'Istituto Nazionale di Fisica della Materia, Scuola Normale Superiore, Piazza dei Cavalieri 7, I-56126 Pisa, Italy*
[3] *Scuola Internazionale Superiore di Studî Avanzati (SISSA), Via Beirut 2/4, I-34014 Trieste, Italy*

(Received 16 December 1993)

Some applications of Alchemy



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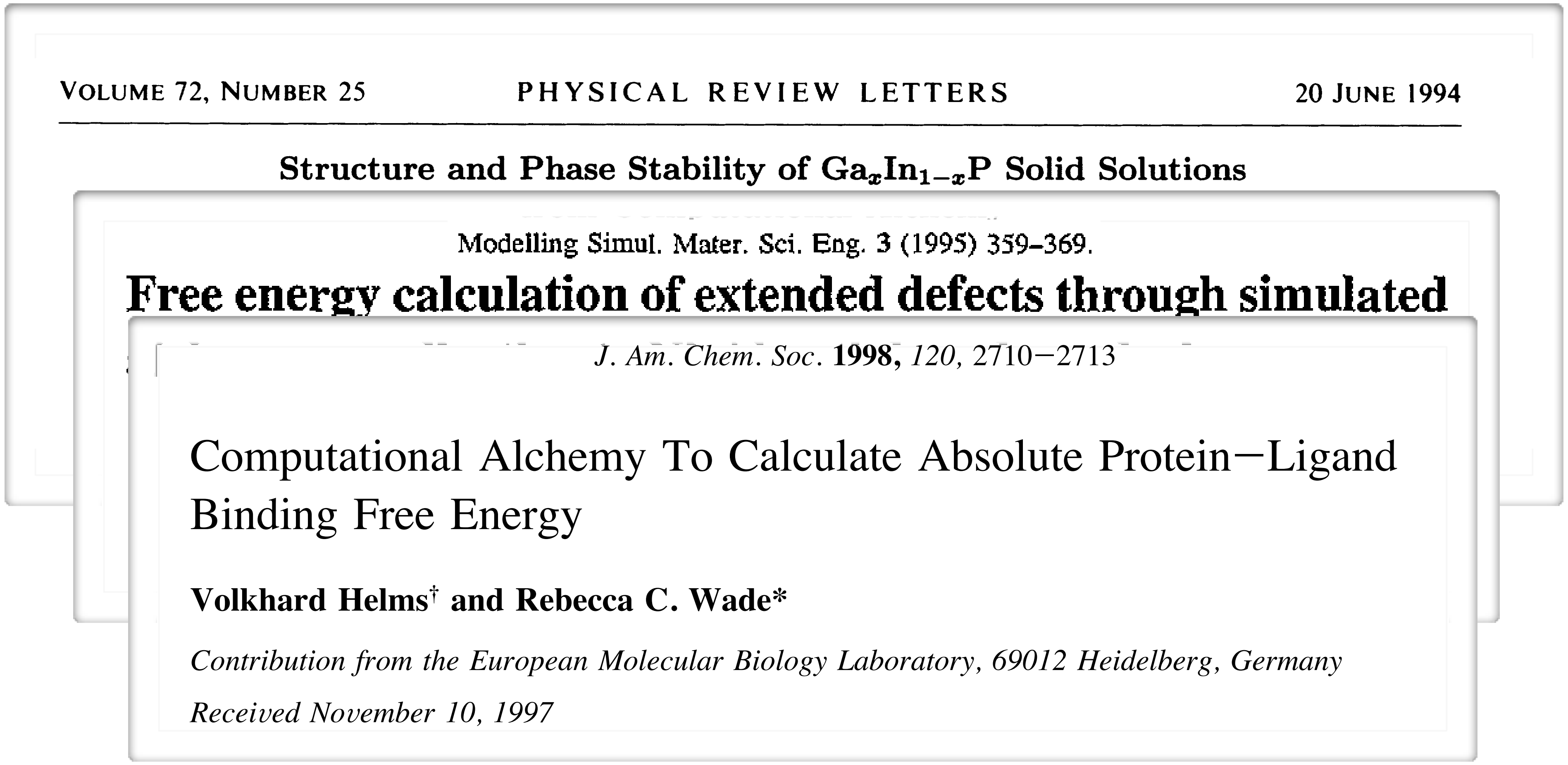
Modelling Simul. Mater. Sci. Eng. 3 (1995) 359–369.

Free energy calculation of extended defects through simulated alchemy: application to Ni_3Al antiphase boundaries

A J Skinner†, J V Lill‡ and J Q Broughton

Complex Systems Theory Branch Code 6690, Naval Research Laboratory, Washington, DC 20375-5000, USA

Some applications of Alchemy



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J. Am. Chem. Soc. **1998,** *120,* 2710−2713

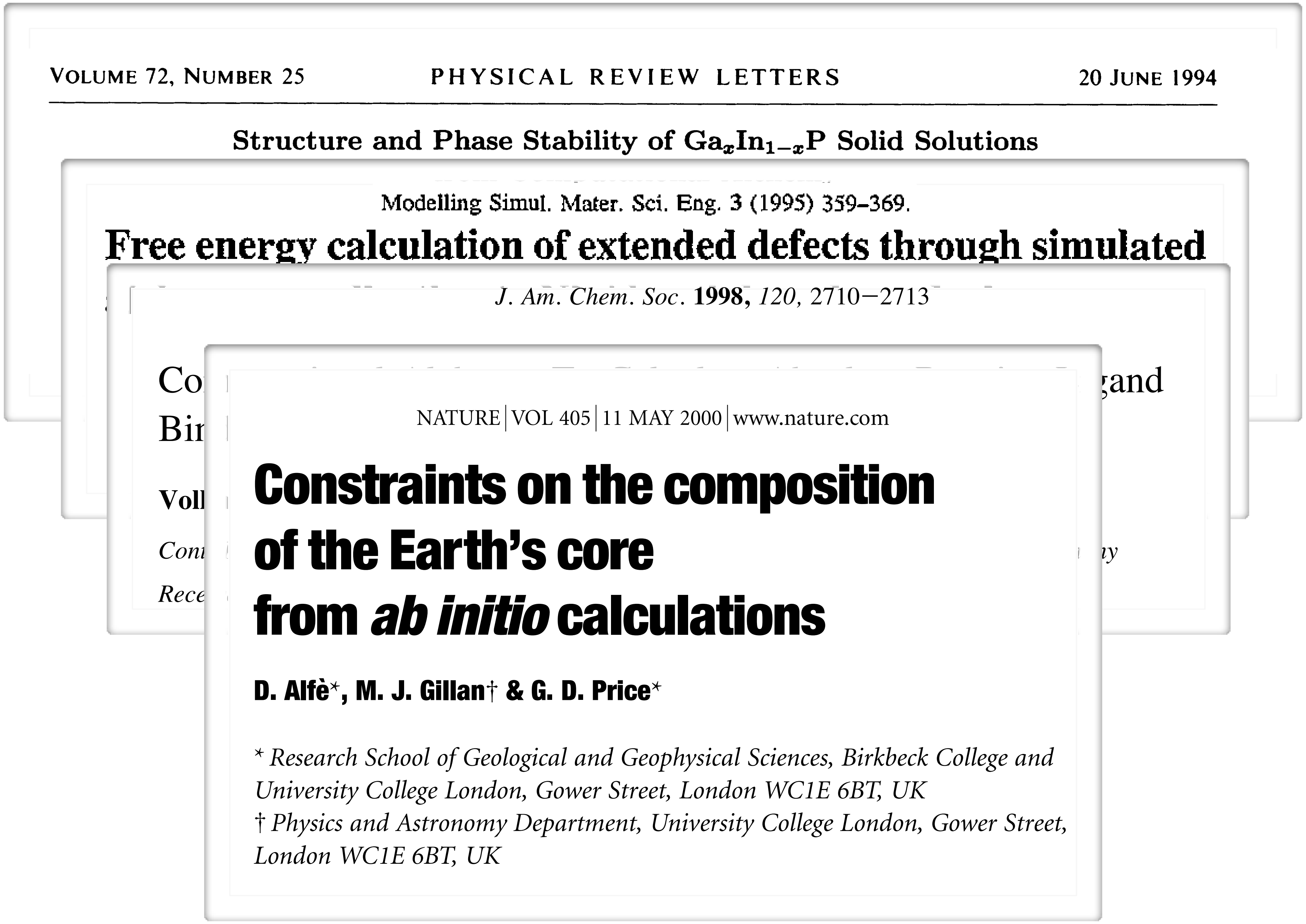
Computational Alchemy To Calculate Absolute Protein−Ligand Binding Free Energy

Volkhard Helms[†] **and Rebecca C. Wade***

Contribution from the European Molecular Biology Laboratory, 69012 Heidelberg, Germany

Received November 10, 1997

Some applications of Alchemy



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Constraints on the composition of the Earth's core from *ab initio* calculations

D. Alfè*, M. J. Gillan† & G. D. Price*

* *Research School of Geological and Geophysical Sciences, Birkbeck College and University College London, Gower Street, London WC1E 6BT, UK*

† *Physics and Astronomy Department, University College London, Gower Street, London WC1E 6BT, UK*

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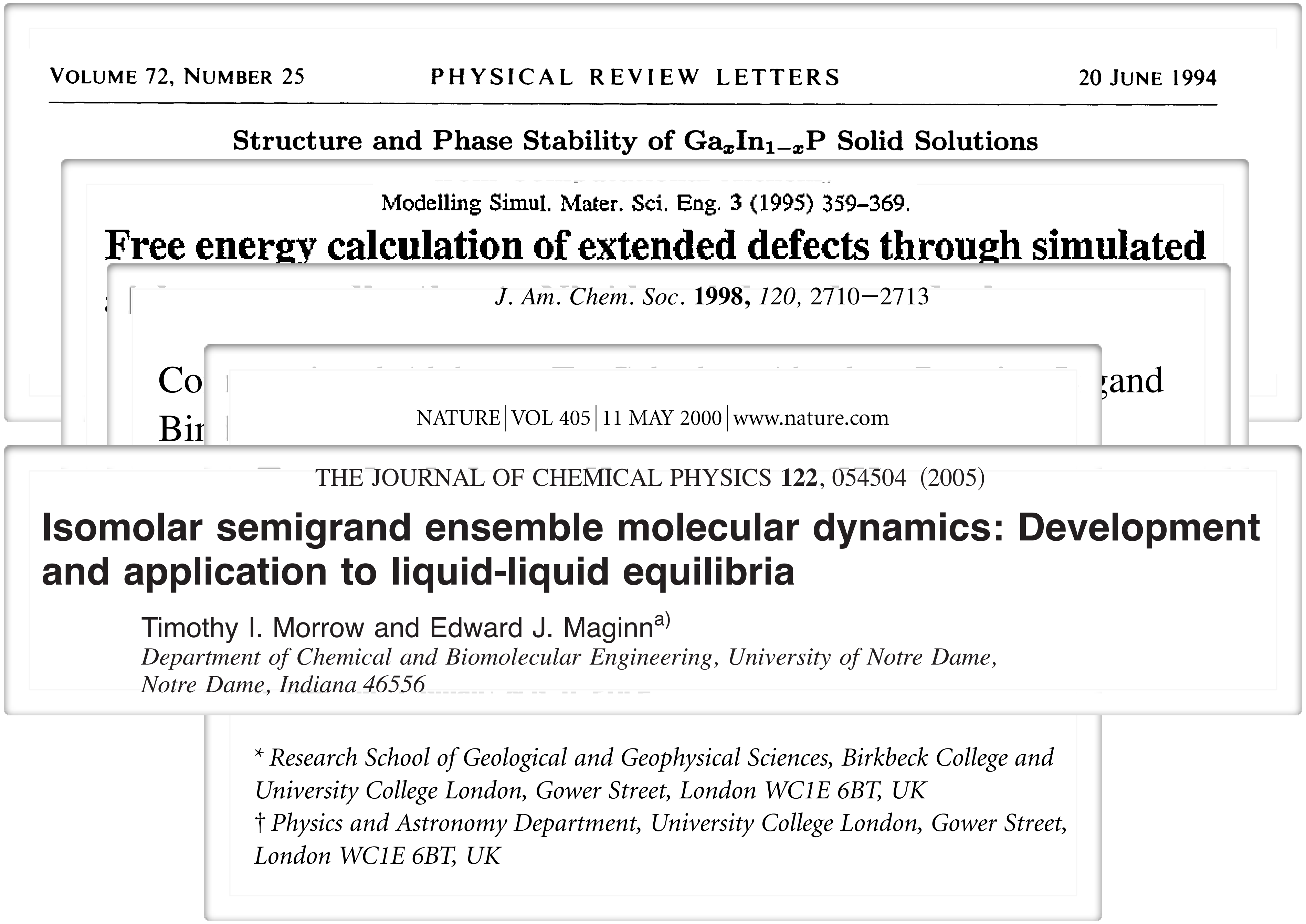

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THE JOURNAL OF CHEMICAL PHYSICS **122**, 054504 (2005)

Isomolar semigrand ensemble molecular dynamics: Development and application to liquid-liquid equilibria

Timothy I. Morrow and Edward J. Maginn[a)]

Department of Chemical and Biomolecular Engineering, University of Notre Dame, Notre Dame, Indiana 46556

* *Research School of Geological and Geophysical Sciences, Birkbeck College and University College London, Gower Street, London WC1E 6BT, UK*

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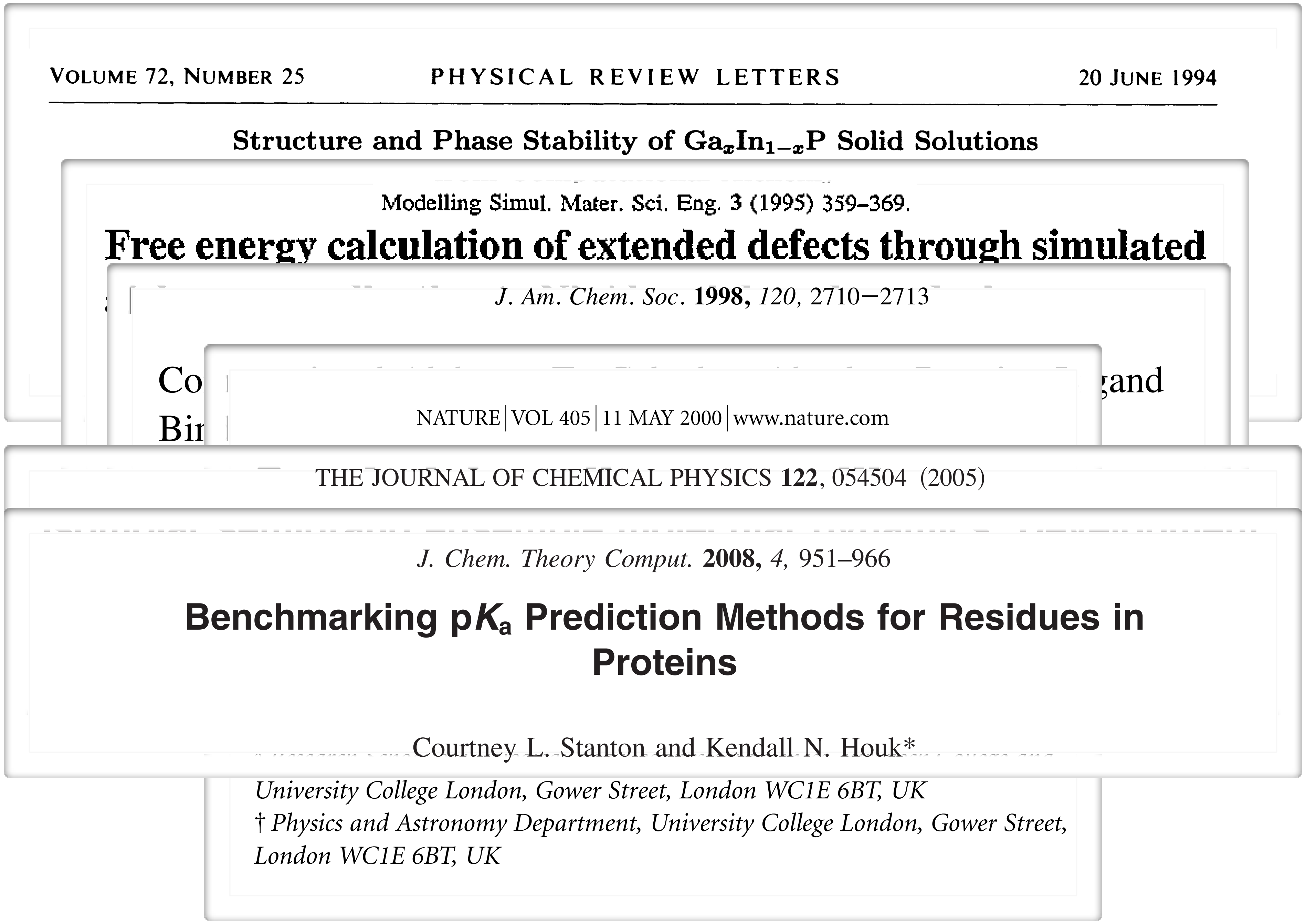

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THE JOURNAL OF CHEMICAL PHYSICS **122**, 054504 (2005)

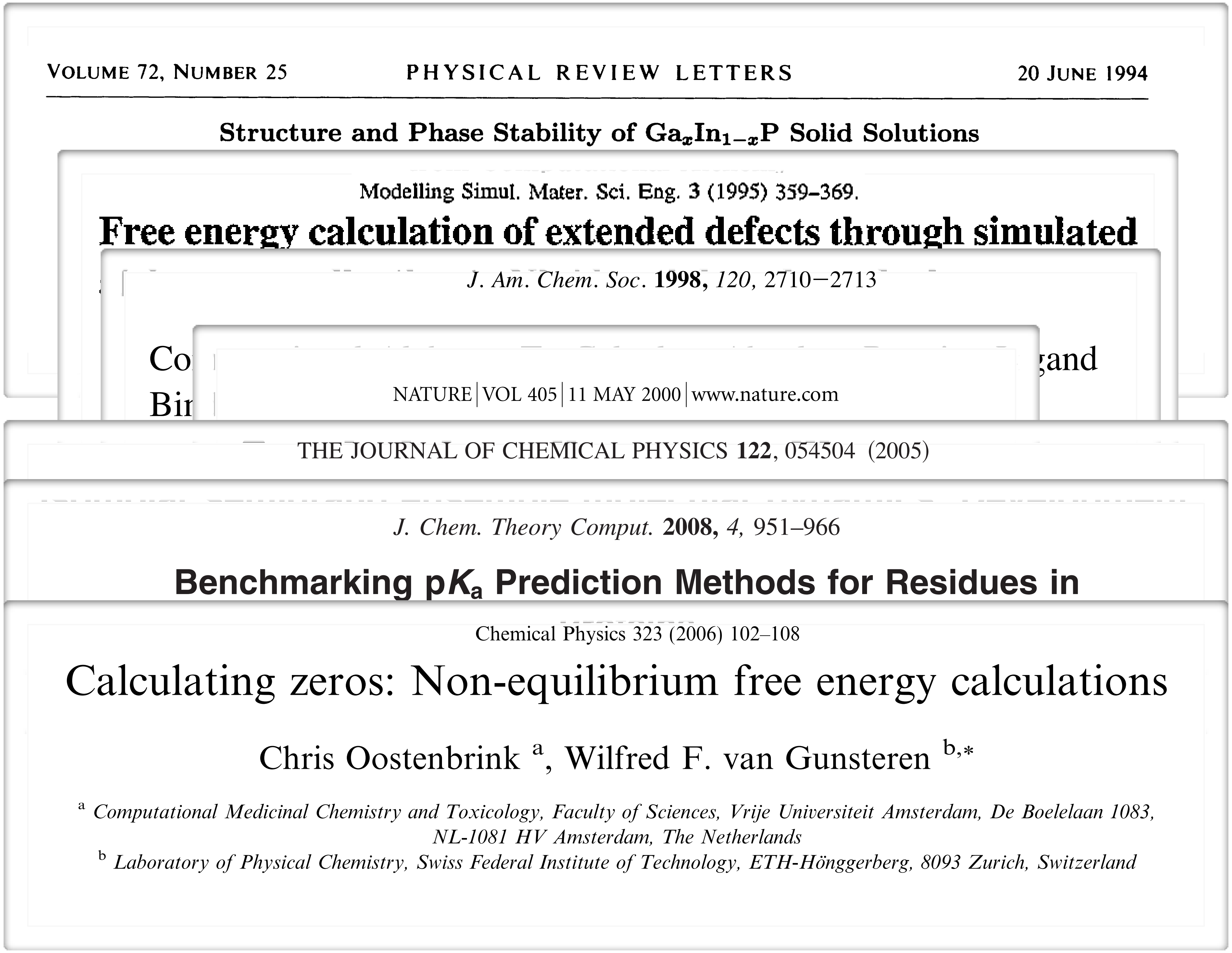
J. Chem. Theory Comput. **2008,** *4,* 951–966

Benchmarking pK_a Prediction Methods for Residues in Proteins

Courtney L. Stanton and Kendall N. Houk*

University College London, Gower Street, London WC1E 6BT, UK
† Physics and Astronomy Department, University College London, Gower Street, London WC1E 6BT, UK

Some applications of Alchemy



VOLUME 72, NUMBER 25 PHYSICAL REVIEW LETTERS 20 JUNE 1994

Structure and Phase Stability of $Ga_xIn_{1-x}P$ Solid Solutions

Modelling Simul. Mater. Sci. Eng. 3 (1995) 359–369.

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NATURE | VOL 405 | 11 MAY 2000 | www.nature.com

THE JOURNAL OF CHEMICAL PHYSICS **122**, 054504 (2005)

J. Chem. Theory Comput. **2008,** *4,* 951–966

Benchmarking pK_a Prediction Methods for Residues in

Chemical Physics 323 (2006) 102–108

Calculating zeros: Non-equilibrium free energy calculations

Chris Oostenbrink [a], Wilfred F. van Gunsteren [b,*]

[a] *Computational Medicinal Chemistry and Toxicology, Faculty of Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1083, NL-1081 HV Amsterdam, The Netherlands*

[b] *Laboratory of Physical Chemistry, Swiss Federal Institute of Technology, ETH-Hönggerberg, 8093 Zurich, Switzerland*

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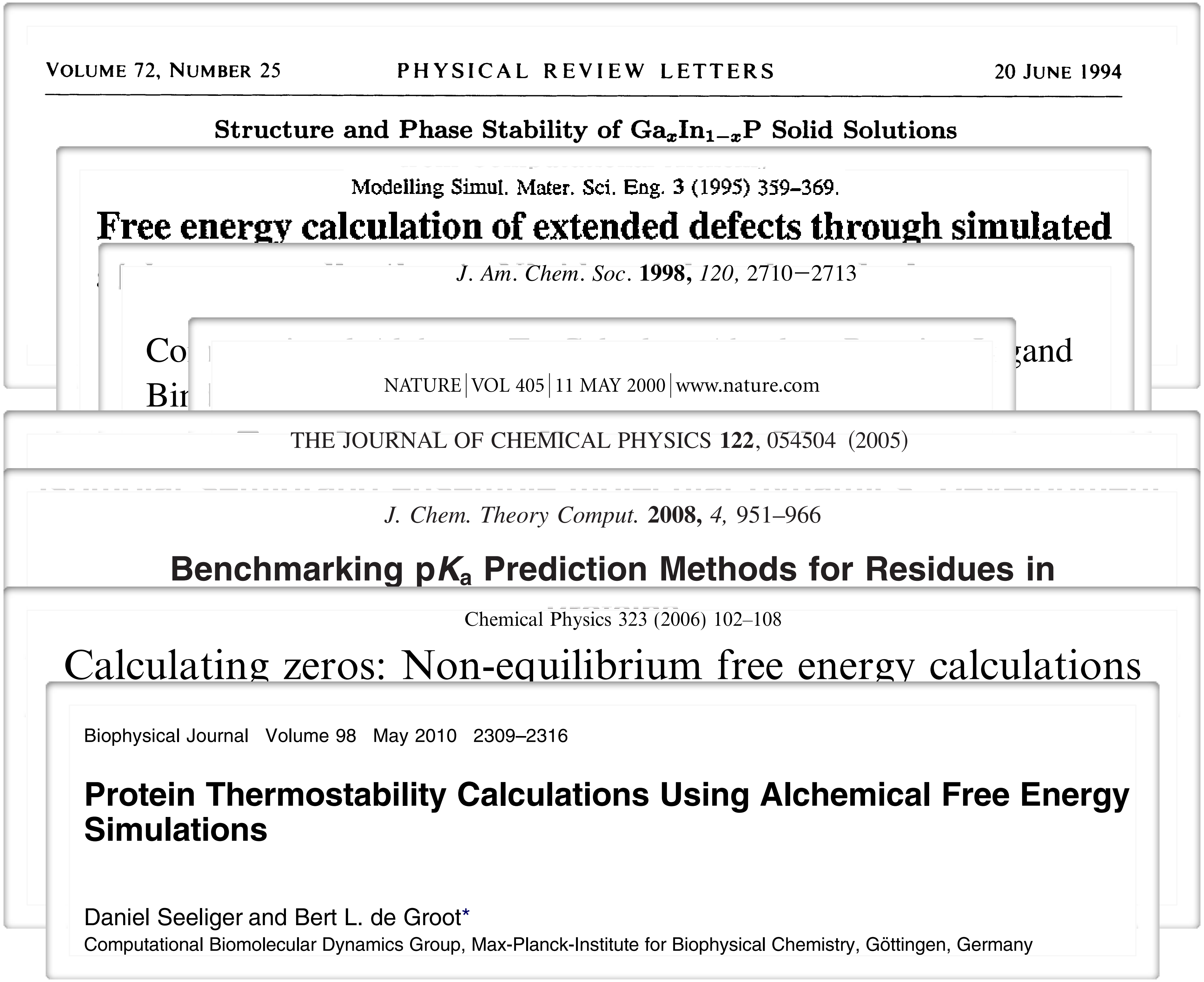

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Protein Thermostability Calculations Using Alchemical Free Energy Simulations

Daniel Seeliger and Bert L. de Groot*

Computational Biomolecular Dynamics Group, Max-Planck-Institute for Biophysical Chemistry, Göttingen, Germany

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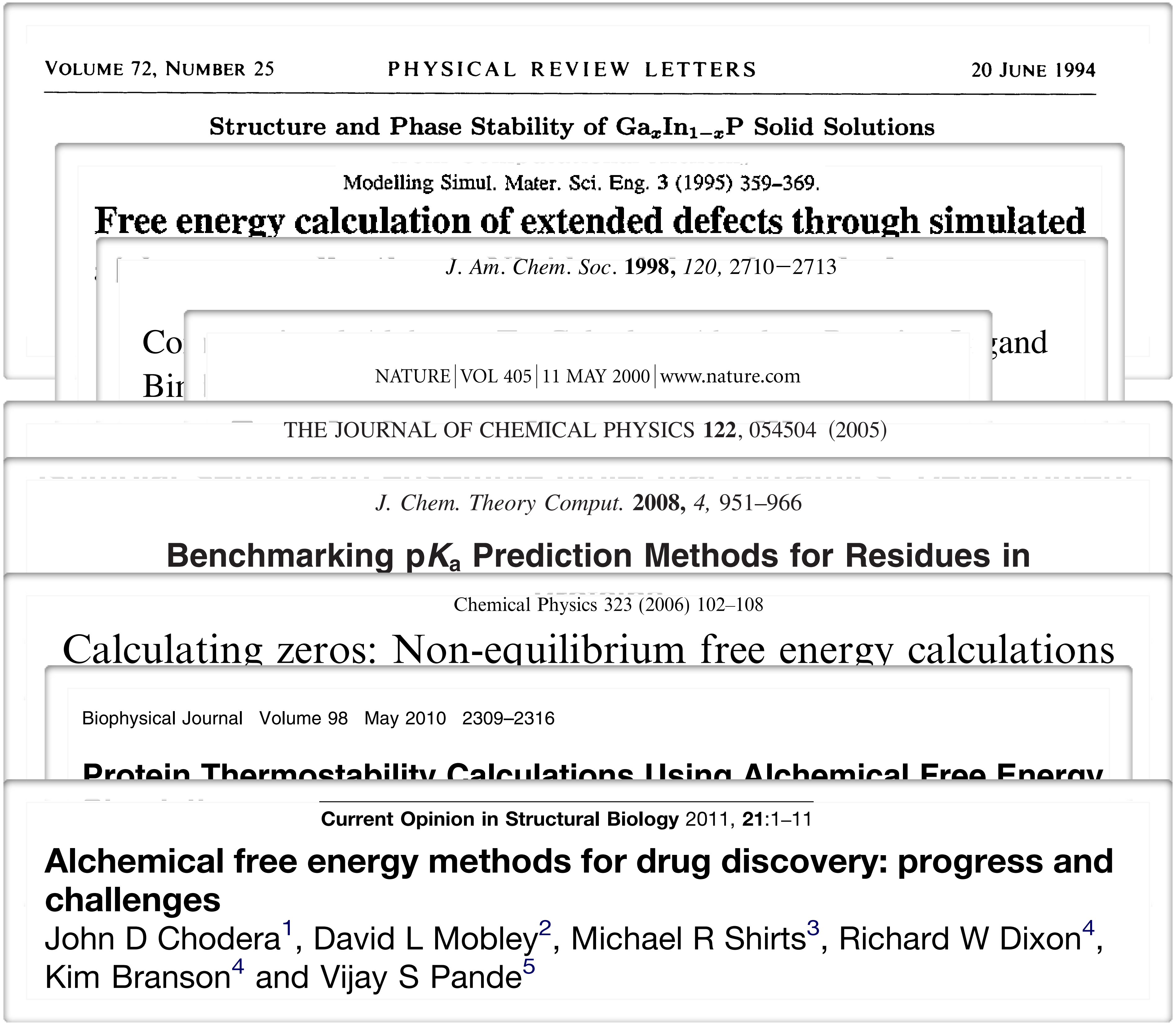

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Protein Thermostability Calculations Using Alchemical Free Energy

Current Opinion in Structural Biology 2011, **21**:1–11

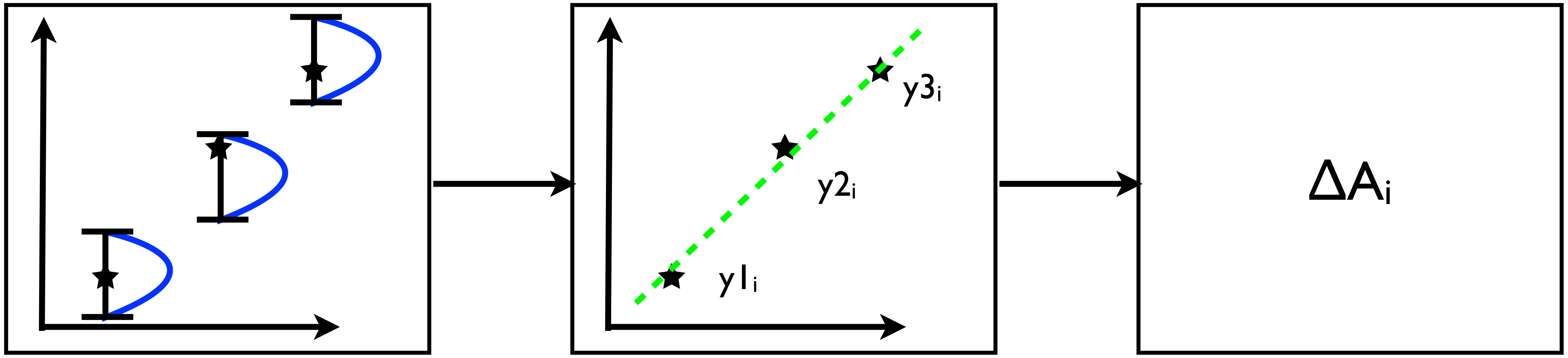
Alchemical free energy methods for drug discovery: progress and challenges

John D Chodera[1], David L Mobley[2], Michael R Shirts[3], Richard W Dixon[4], Kim Branson[4] and Vijay S Pande[5]

Estimating uncertainties

- How do you propagate uncertainties?

Eg: TI - uncertainties in dU/dλ. A curve/spline interpolation is applied to data before integration. What is the uncertainty in computed free energy?

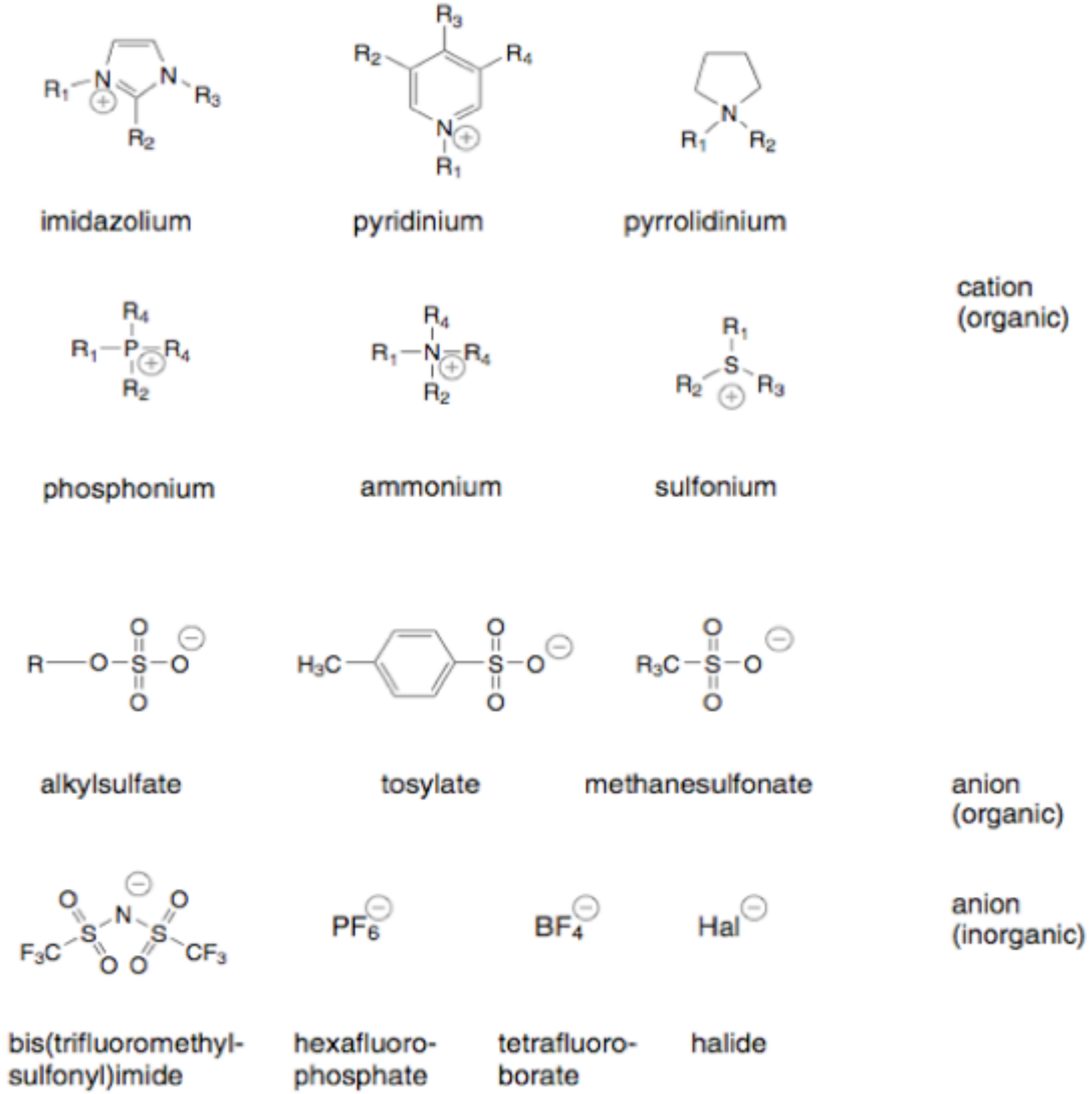


$$\Delta A = \overline{\Delta A_i}$$

Focus Application- 1

Computation of melting points and crystal polymorph stabilities

Ionic liquids



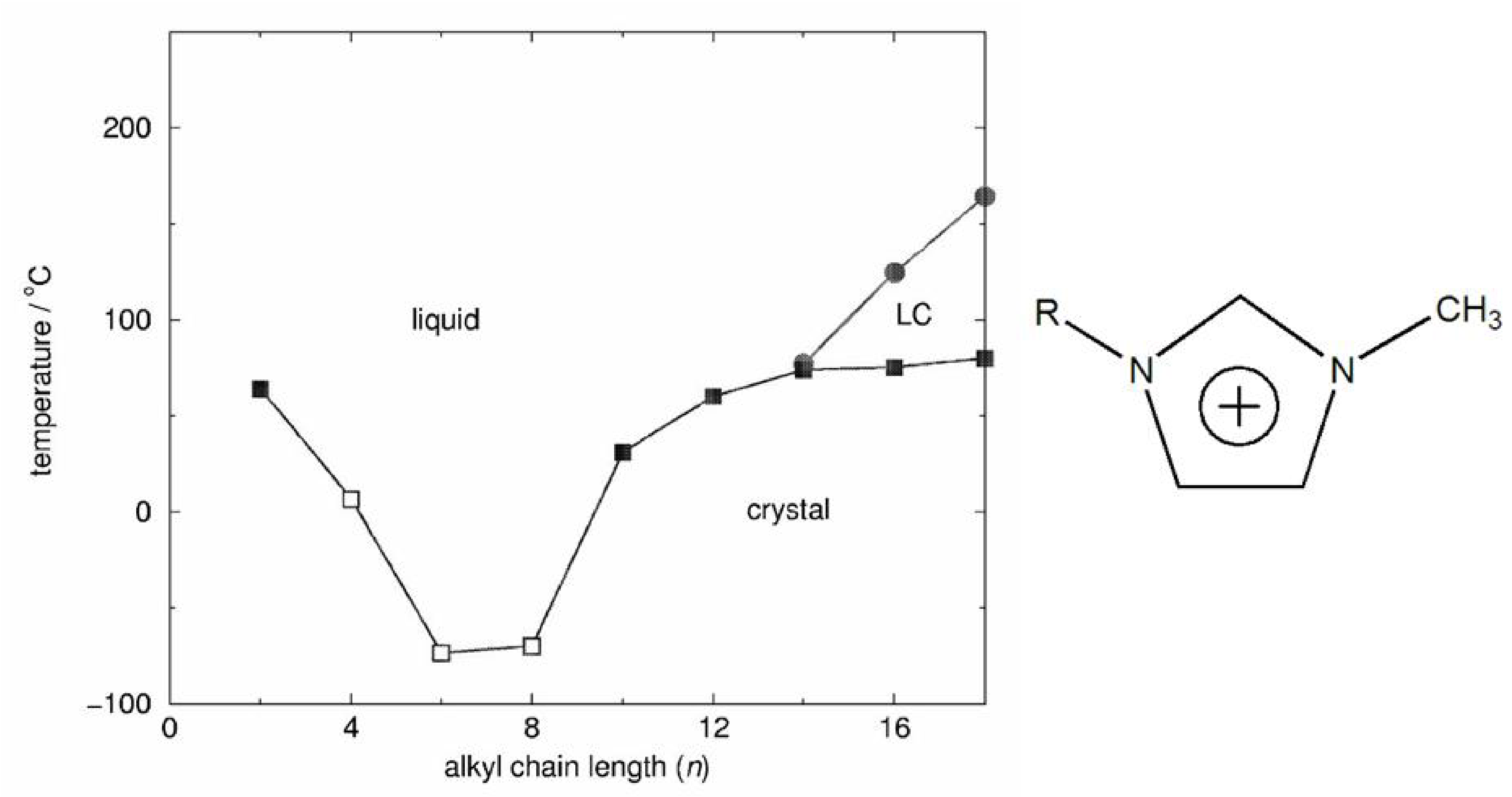
Examples of commercially available ionic liquids

- They are *not* ionic solutions
- They are not ionic crystals
- They are molten salts that happen to be “molten” around ambient temperature

Many useful properties

- Excellent solvation strength
- Low flammability
- High thermal stability
- Wide liquidus range
- Several commercial applications already

Melting points of Ionic Liquids



Melting point phase diagram for [Rmim][PF_6] as a function of n[1]

What is this link between chemical composition/ structure and melting point?

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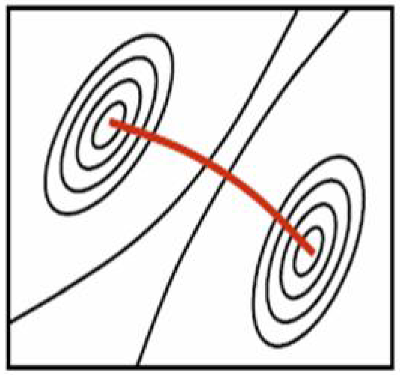
[1] J. D. Holbrey and K. R. Seddon, Clean Prod. Processes, 1, 223(1999)

Melting point calculation using atomistic simulations

- Heating a crystal until it melts
  - defect induced melting
    - first IL melting point prediction[1]
- Direct simulation of a solid-liquid interface
  - Free energy barrier for heterogeneous nucleation < homogeneous nucleation



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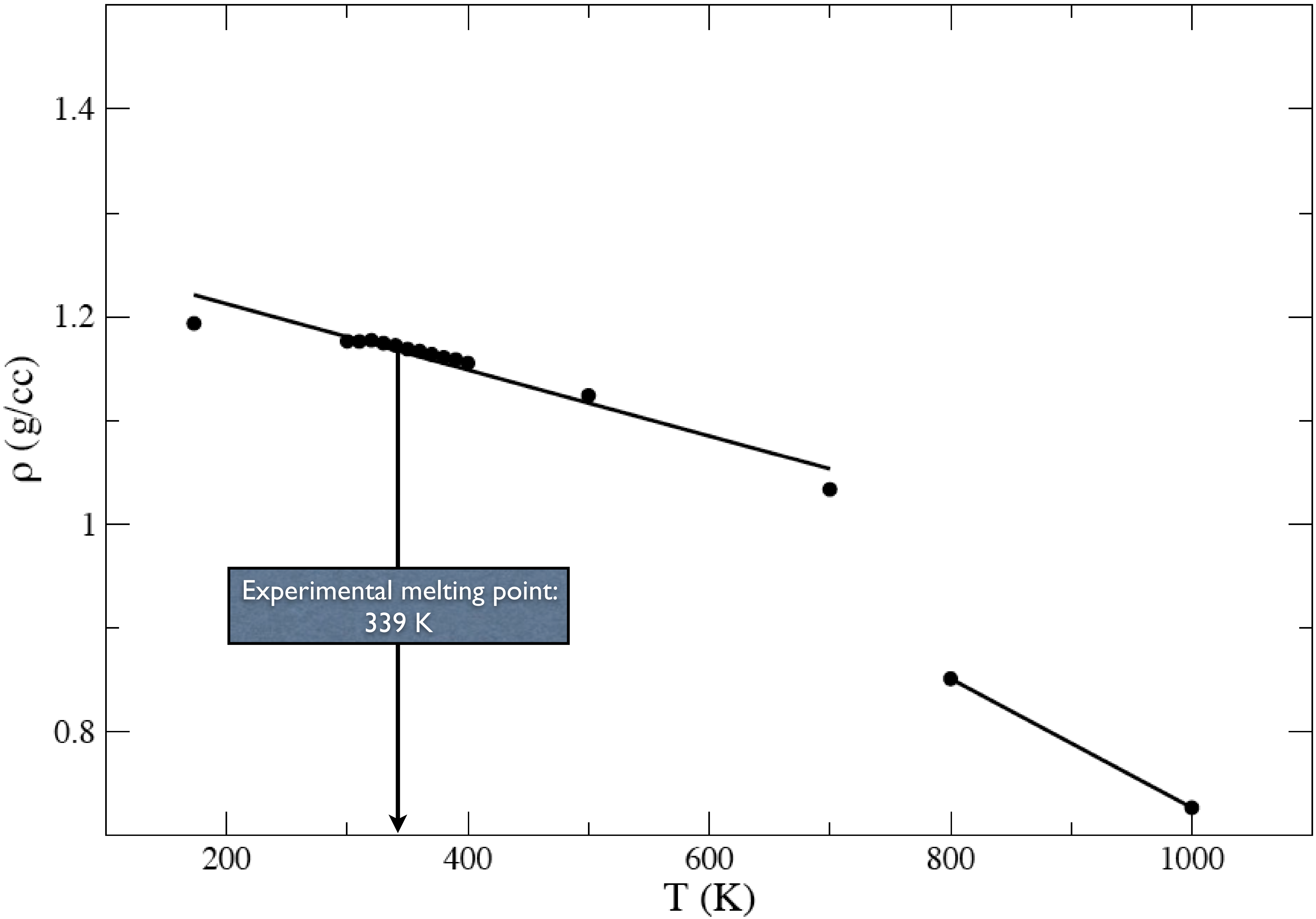
[1] S. Alavi and D. L. Thompson, *J.* Chem.Phys. 119, 9617 (2003)

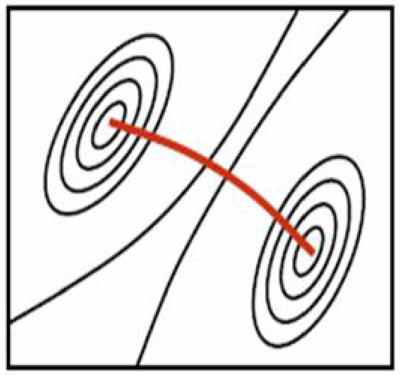


Experimental melting point:
339 K

Density vs Temperature for direct heating of orthorhombic [bmim][Cl] crystal

Melting point calculation using atomistic simulations

- Heating a crystal until it melts
  - defect induced melting
    - first IL melting point prediction[1]



- Direct simulation of a solid-liquid interface
  - Free energy barrier for heterogeneous nucleation is lower than homogeneous nucleation

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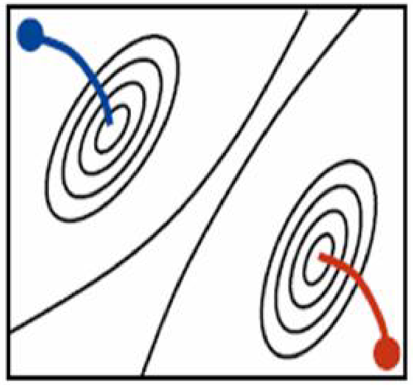
[1] S. Alavi and D. L. Thompson, *J*. Chem.Phys. 119, 9617 (2003)

Melting point calculation using atomistic simulations

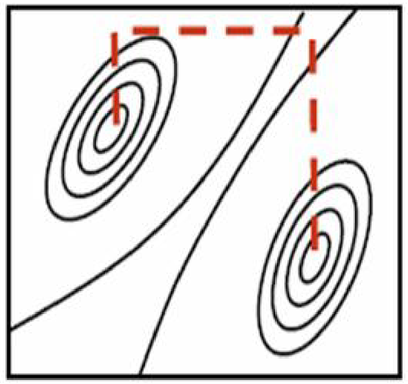
- Free energy based methods

$$\Delta G_{s-l} = 0 \qquad T = T_m$$

1. Reference crystal based methods
    - Frenkel's Einstein Crystal



2. Pseudosupercritical path sampling
    - TI: *solid-liquid*
    - LJ[1], NaCl[1], benzene[2] and triazole[2]
    - extended to ILs[3]



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[1] D. M. Eike, J. F. Brennecke, and E. J. Maginn, J. Chem. Phys. 122, 014115 (2005)

[2] D. M. Eike and E. J. Maginn, J. Chem. Phys. 124, 164503 (2006)

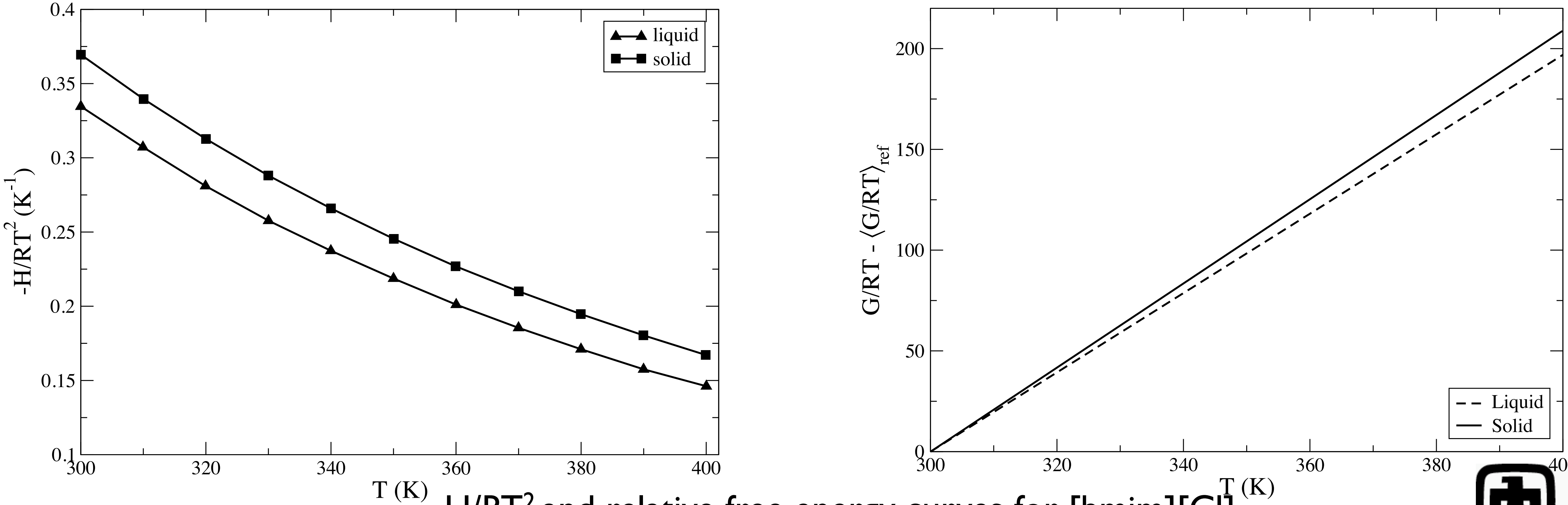
[3] S. Jayaraman and E. J. Maginn, J. Chem. Phys. 127, 214504 (2007)

Method Details

- NPT simulations of solid and liquid phases conducted at multiple temperatures
- Relative free energy curves constructed using:

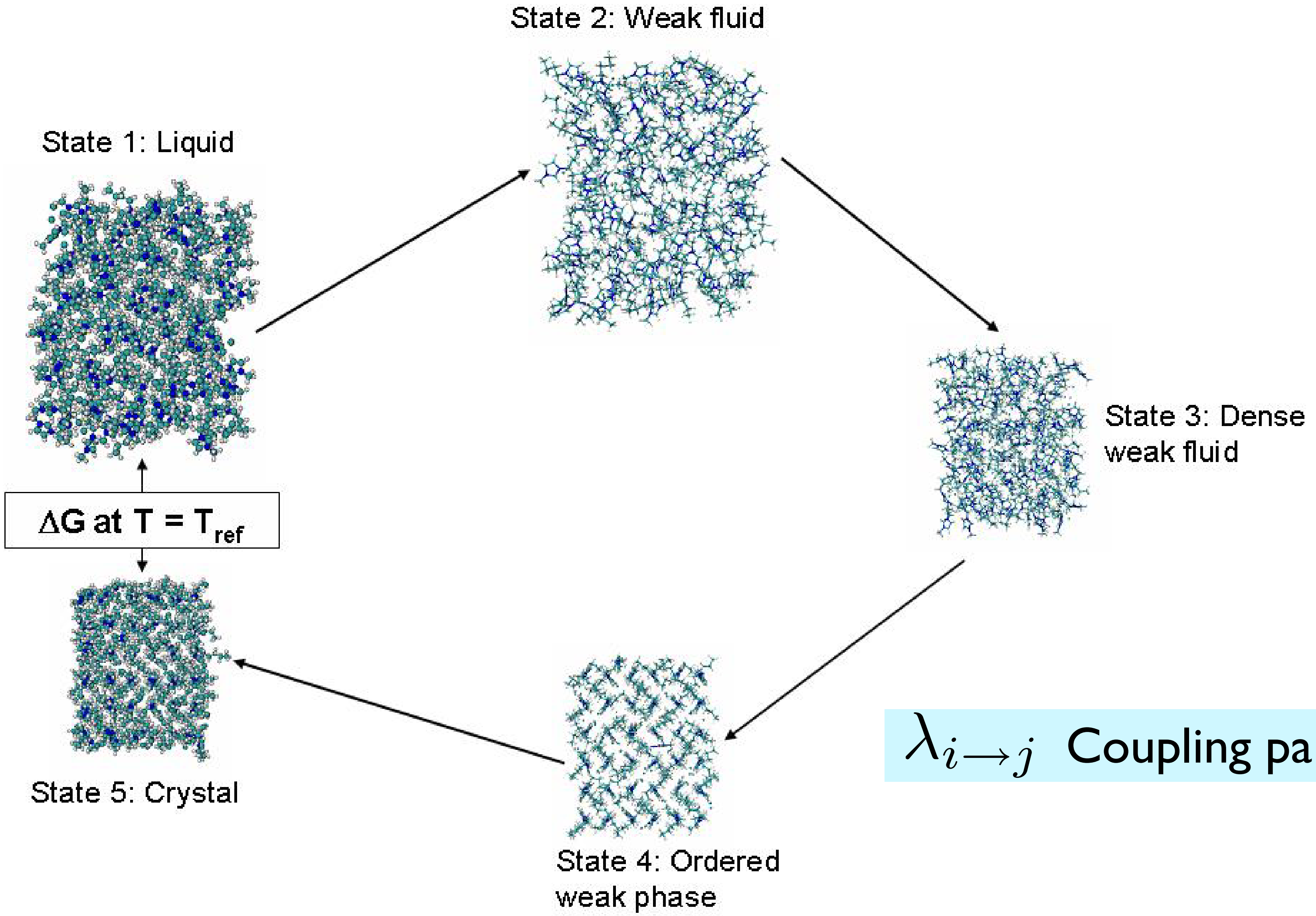
$$\frac{G}{RT} - \left(\frac{G}{RT}\right)_{ref} = \int_{T_{ref}}^{T} -\frac{H}{RT^2}\,dT$$

- ΔG_{s-l} known to a constant of integration



-H/RT^2 and relative free energy curves for [bmim][Cl]

Melting point calculation



State 2: Weak fluid

State 1: Liquid

State 3: Dense weak fluid

ΔG at T = T_{ref}

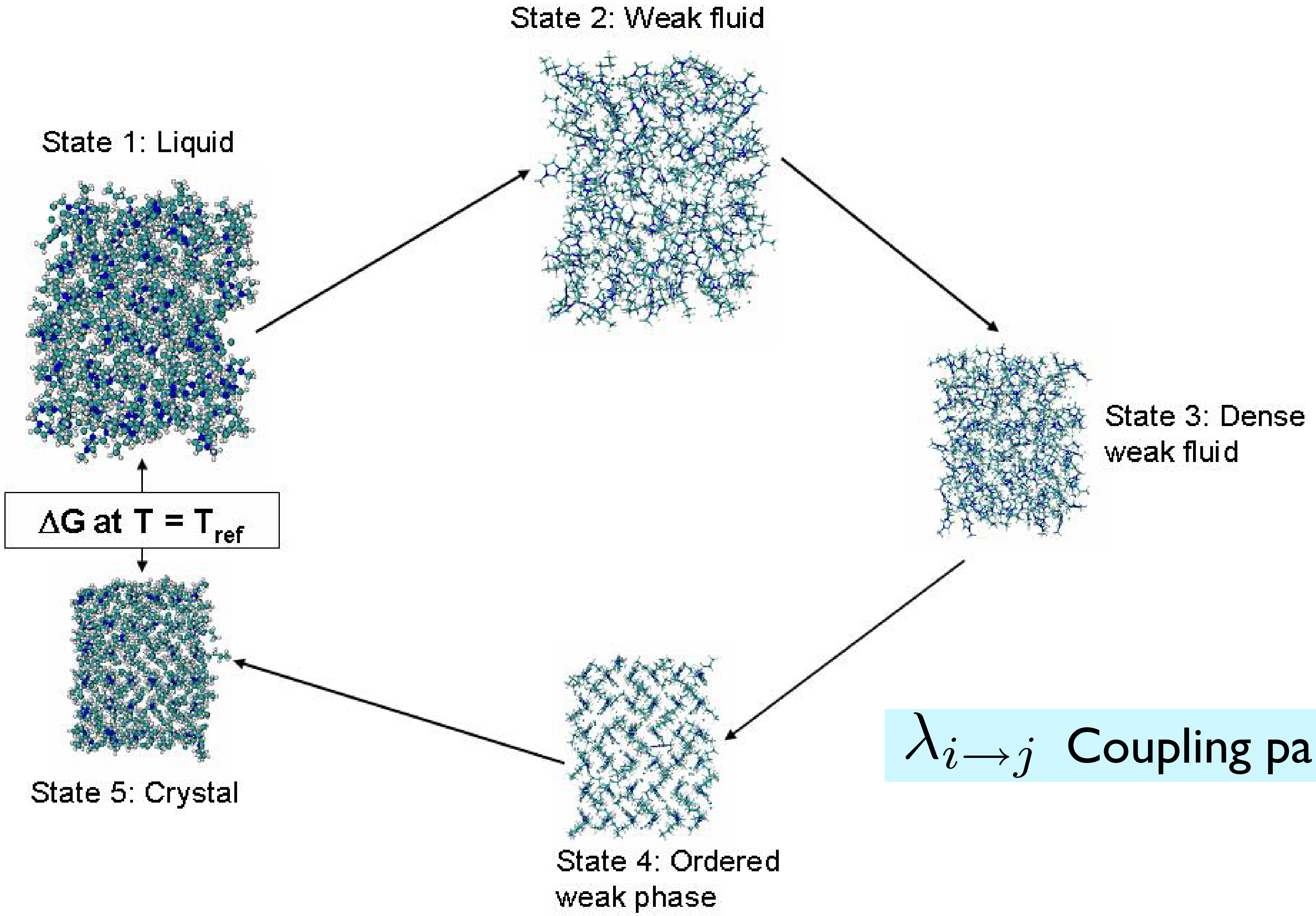
State 5: Crystal

State 4: Ordered weak phase

$\lambda_{i\to j}$ Coupling parameter from state $i \to j$

$$\Delta A_{i\to j} = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda d\lambda \qquad \Delta A_{2\to 3} = \int_{V^\ell}^{V^S} -\langle P \rangle \, dV \qquad \Delta G_{s-\ell} = \sum_{i,j} \Delta A_{i\to j}$$

Melting point calculation



$\lambda_{i \to j}$ Coupling parameter from state $i \to j$

$$U_{1\to 2}(\lambda) = [1 + \lambda(\eta - 1)]^m U^{VDW} + [1 + \lambda(\eta - 1)]^n U^{ELEC} + U^{NS}$$

$$\Delta A_{i\to j} = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda d\lambda \qquad \Delta A_{2\to 3} = \int_{V^\ell}^{V^S} - \langle P \rangle \, dV \qquad \Delta G_{s-\ell} = \sum_{i,j} \Delta A_{i\to j}$$

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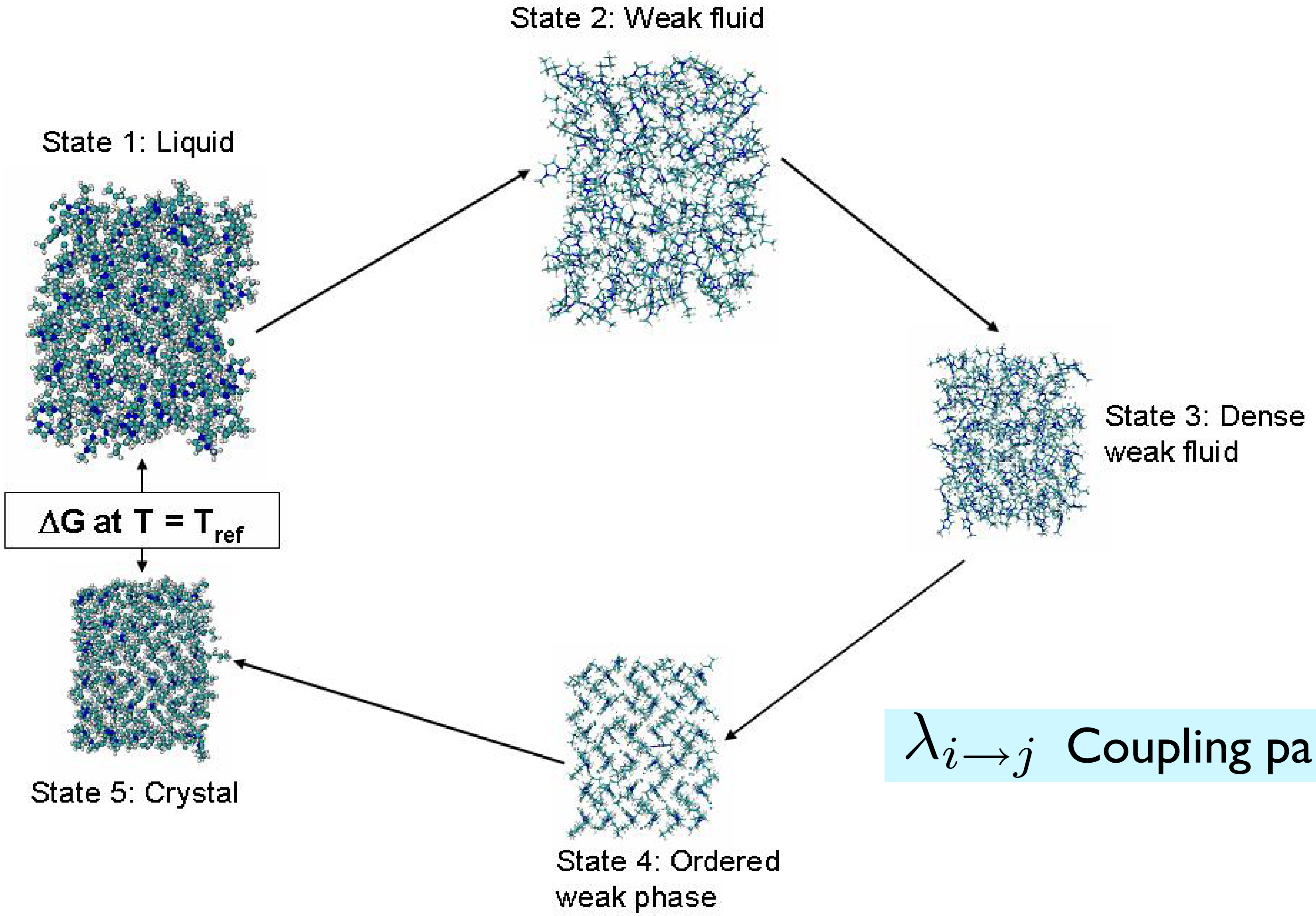

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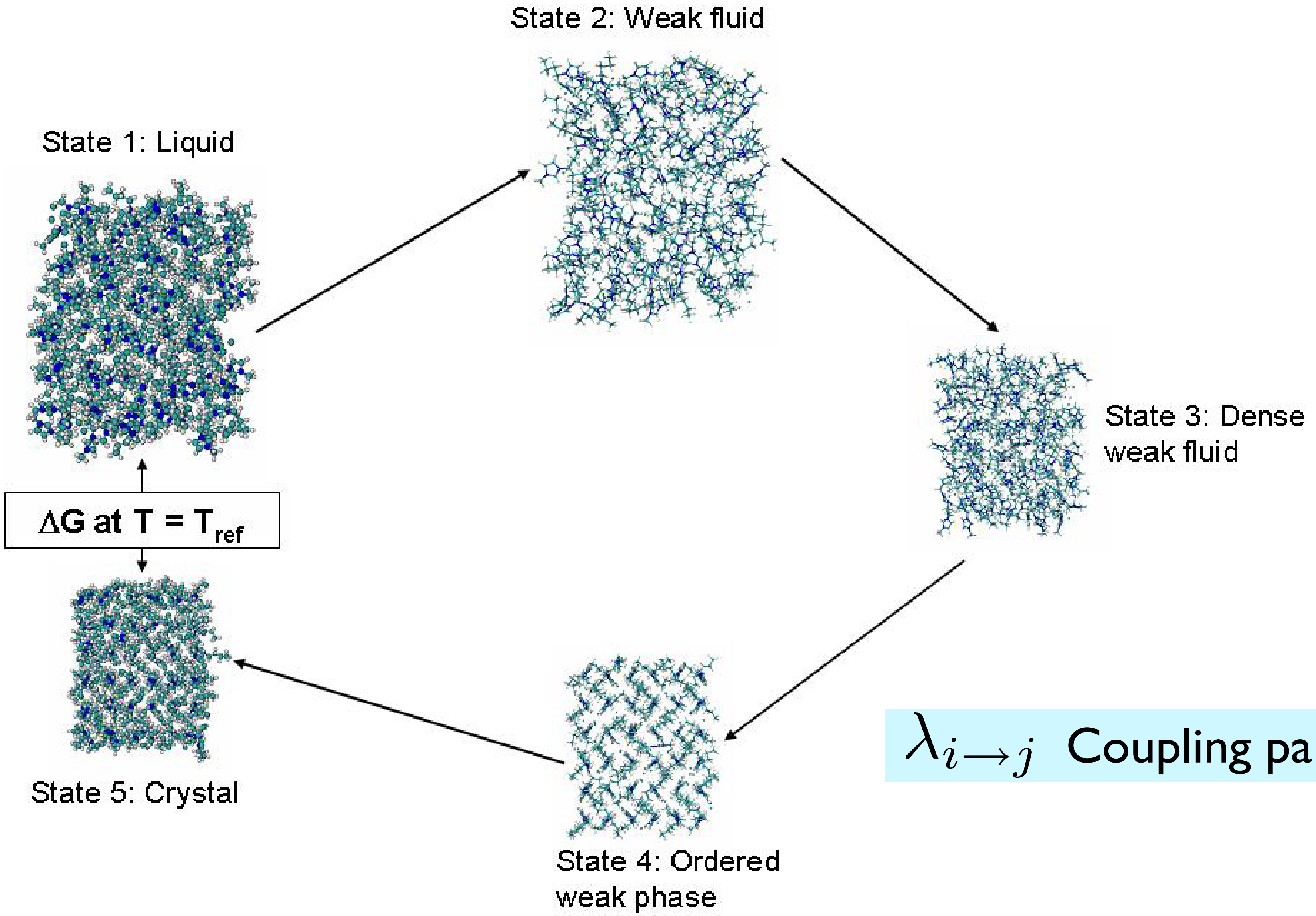
Melting point calculation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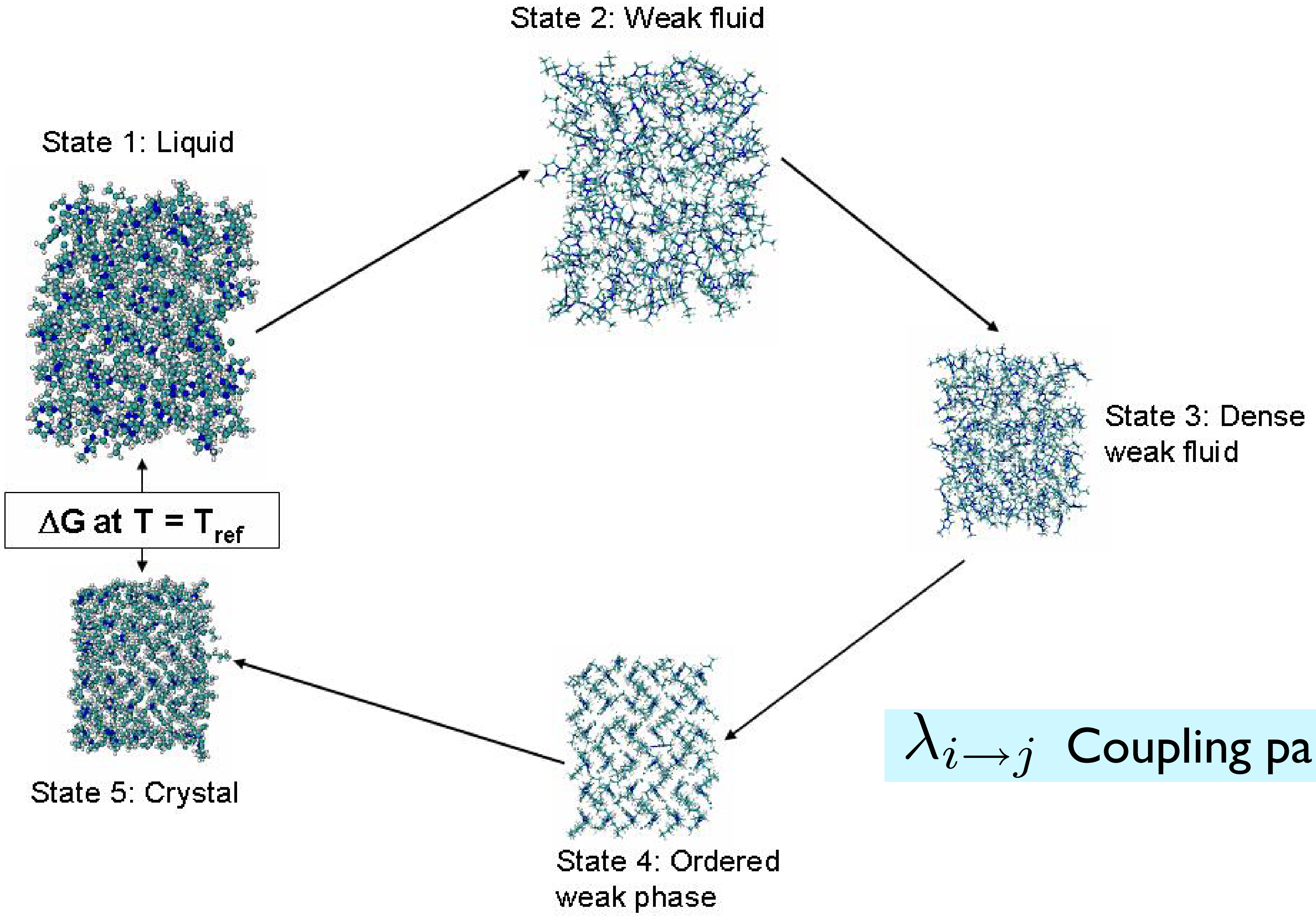
$\lambda_{i\to j}$ Coupling parameter from state $i \to j$

$$U_{3\to 4}(\lambda) = \eta^m U^{VDW} + \eta^n U^{ELEC} + U^{NS} - \lambda \sum_i \sum_j a_{ij} \exp(-b_{ij} r_{ij}^2)$$

$$\Delta A_{i\to j} = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda d\lambda \qquad \Delta A_{2\to 3} = \int_{V^\ell}^{V^S} - \langle P \rangle \, dV \qquad \Delta G_{s-\ell} = \sum_{i,j} \Delta A_{i\to j}$$

Melting point calculation



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State 1: Liquid

State 3: Dense
weak fluid

ΔG at T = T$_{\text{ref}}$

State 5: Crystal

State 4: Ordered
weak phase

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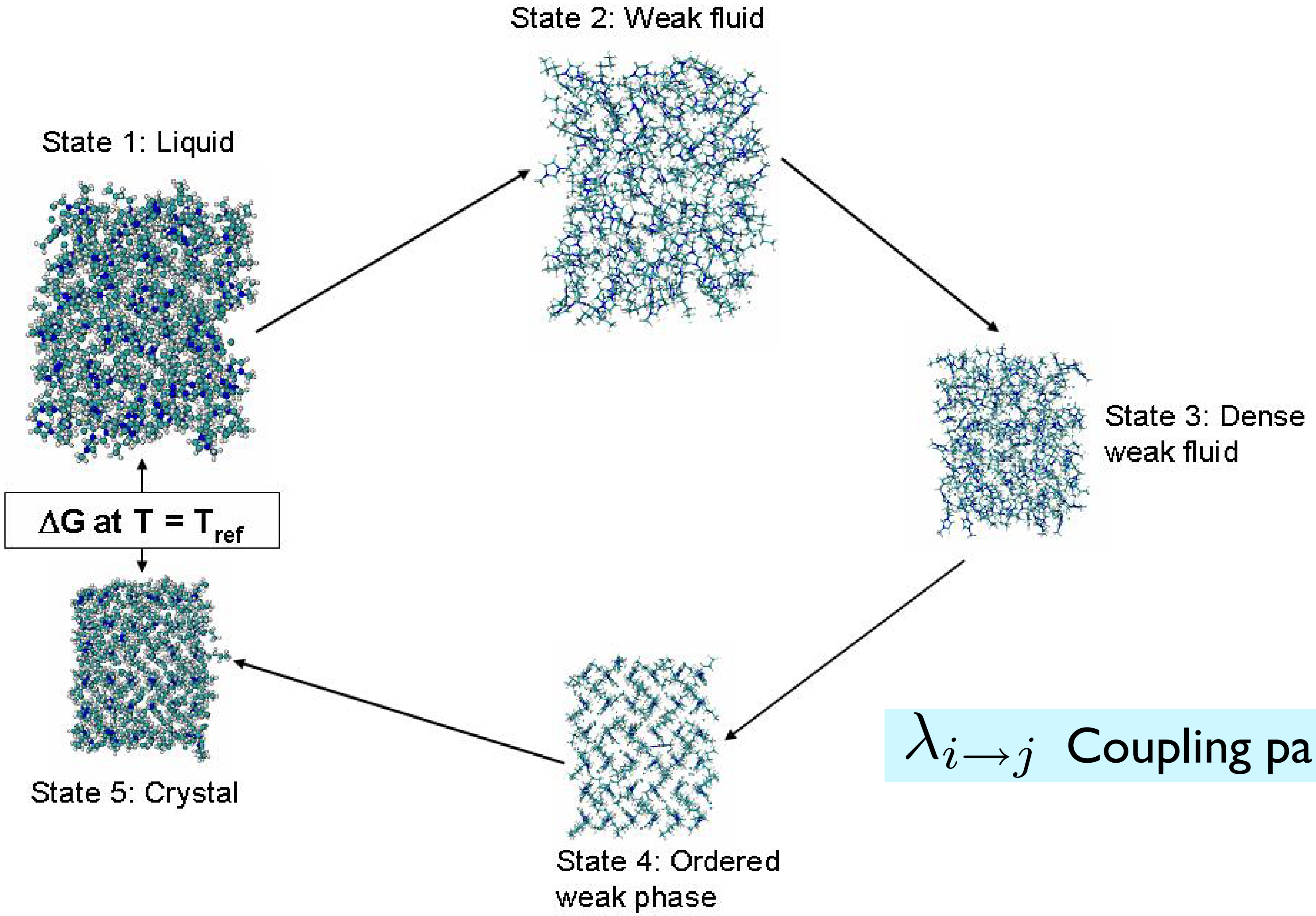
Melting point calculation



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ΔG at T = T$_{\mathrm{ref}}$

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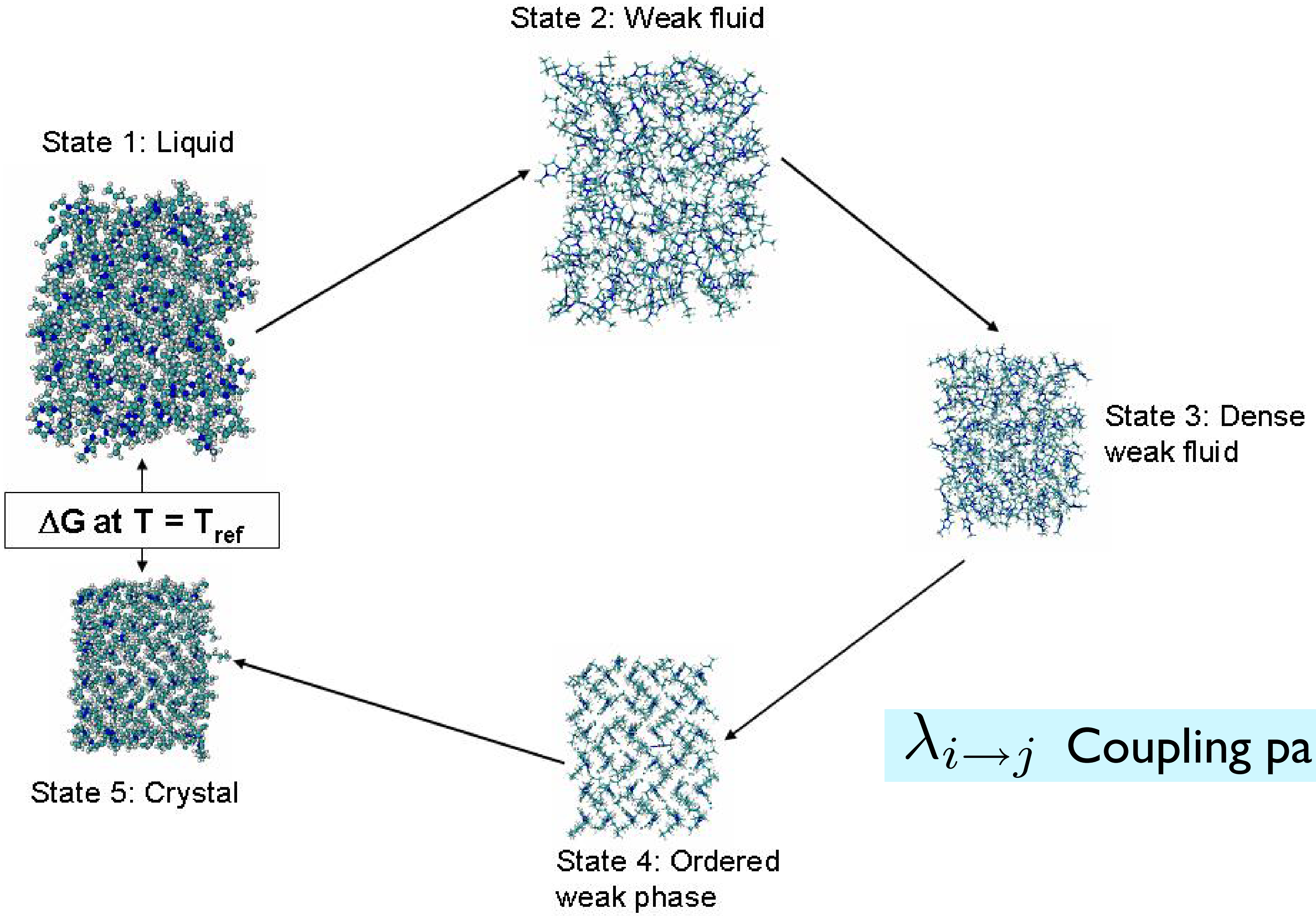
State 4: Ordered
weak phase

$\lambda_{i \rightarrow j}$ Coupling parameter from state $i \rightarrow j$

$$U_{4\rightarrow 5}(\lambda) = [\eta + \lambda(1-\eta)]^m U^{VDW} + [\eta + \lambda(1-\eta)]^n U^{ELEC} + U^{NS} - (1-\lambda)\sum_i \sum_j a_{ij} \exp(-b_{ij} r_{ij}^2)$$

$$\Delta A_{i\rightarrow j} = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda d\lambda \qquad \Delta A_{2\rightarrow 3} = \int_{V^\ell}^{V^S} -\langle P \rangle \, dV \qquad \Delta G_{s-\ell} = \sum_{i,j} \Delta A_{i\rightarrow j}$$

Melting point calculation



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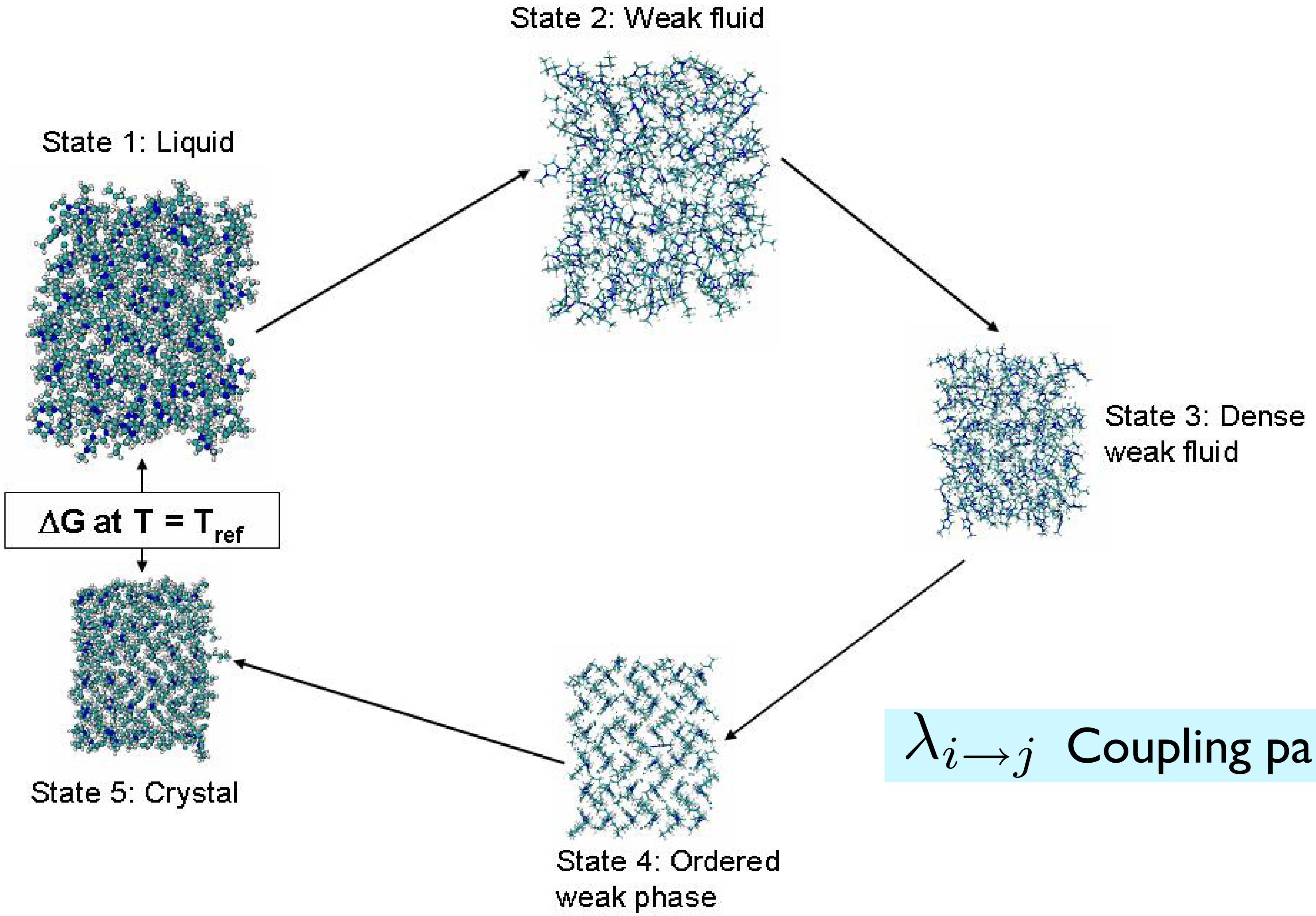
Melting point calculation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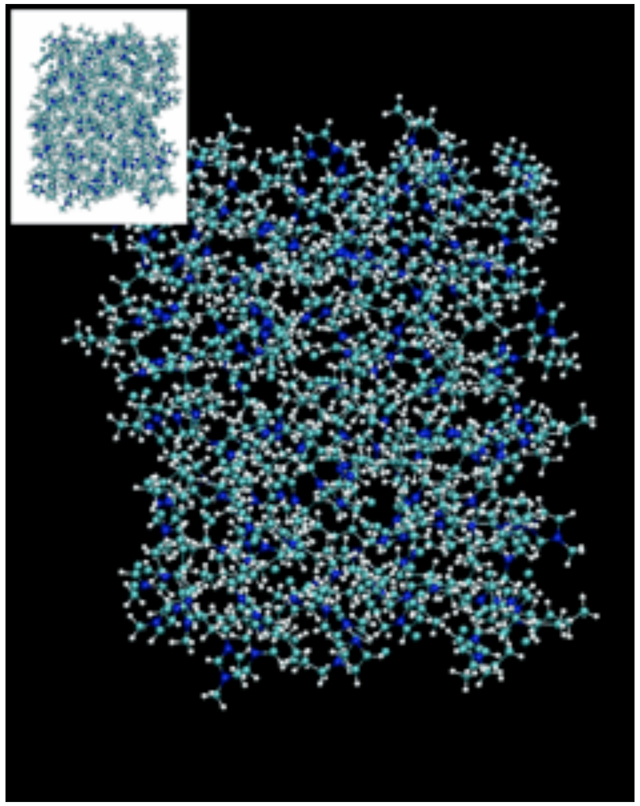
ΔG at $T = T_{ref}$



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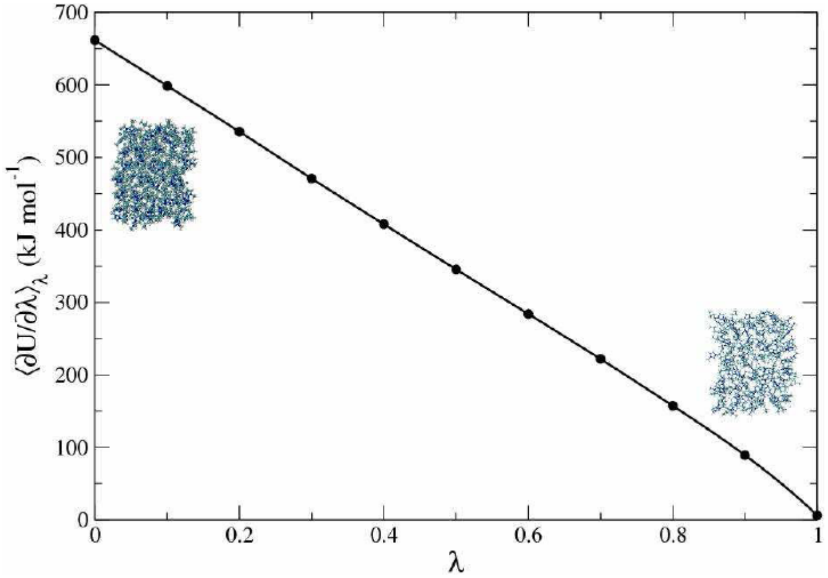
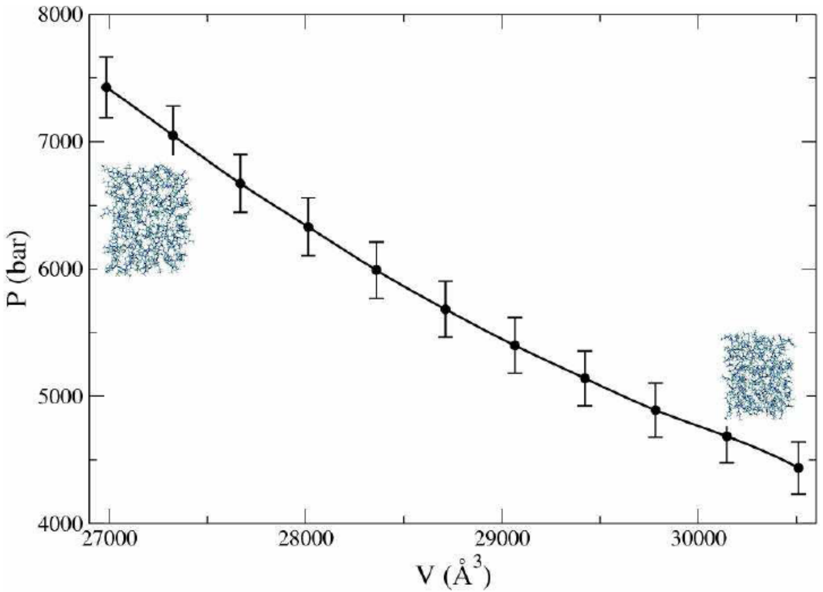
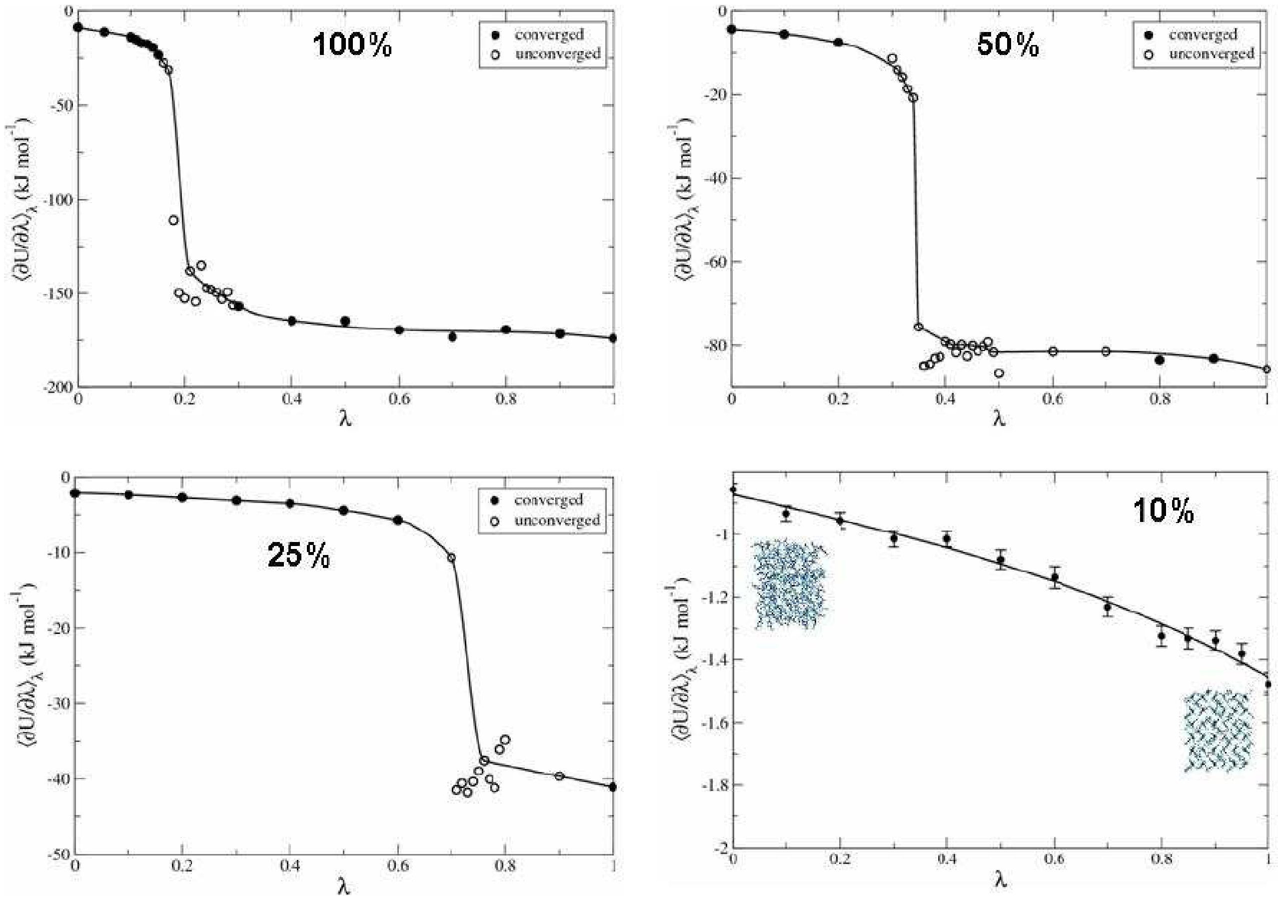
Thermodynamic Integration



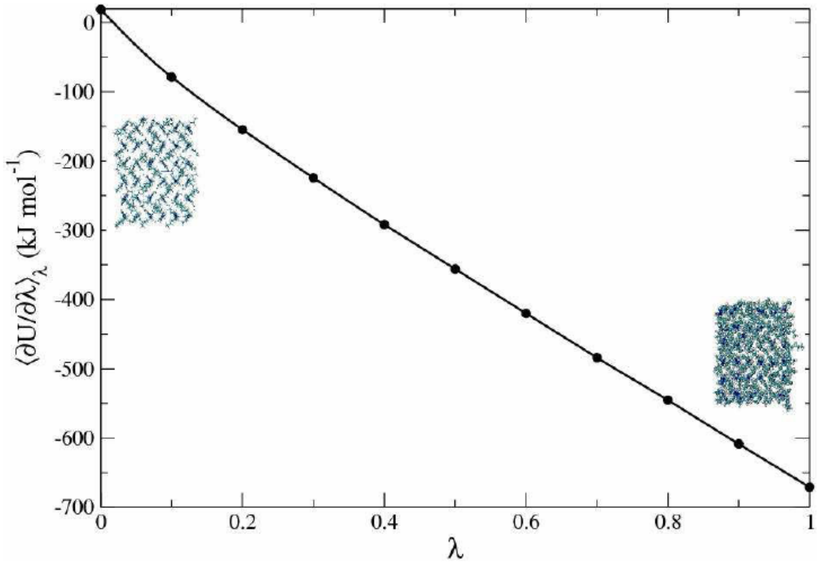
liquid → weak liquid



weak liquid → dense weak liquid

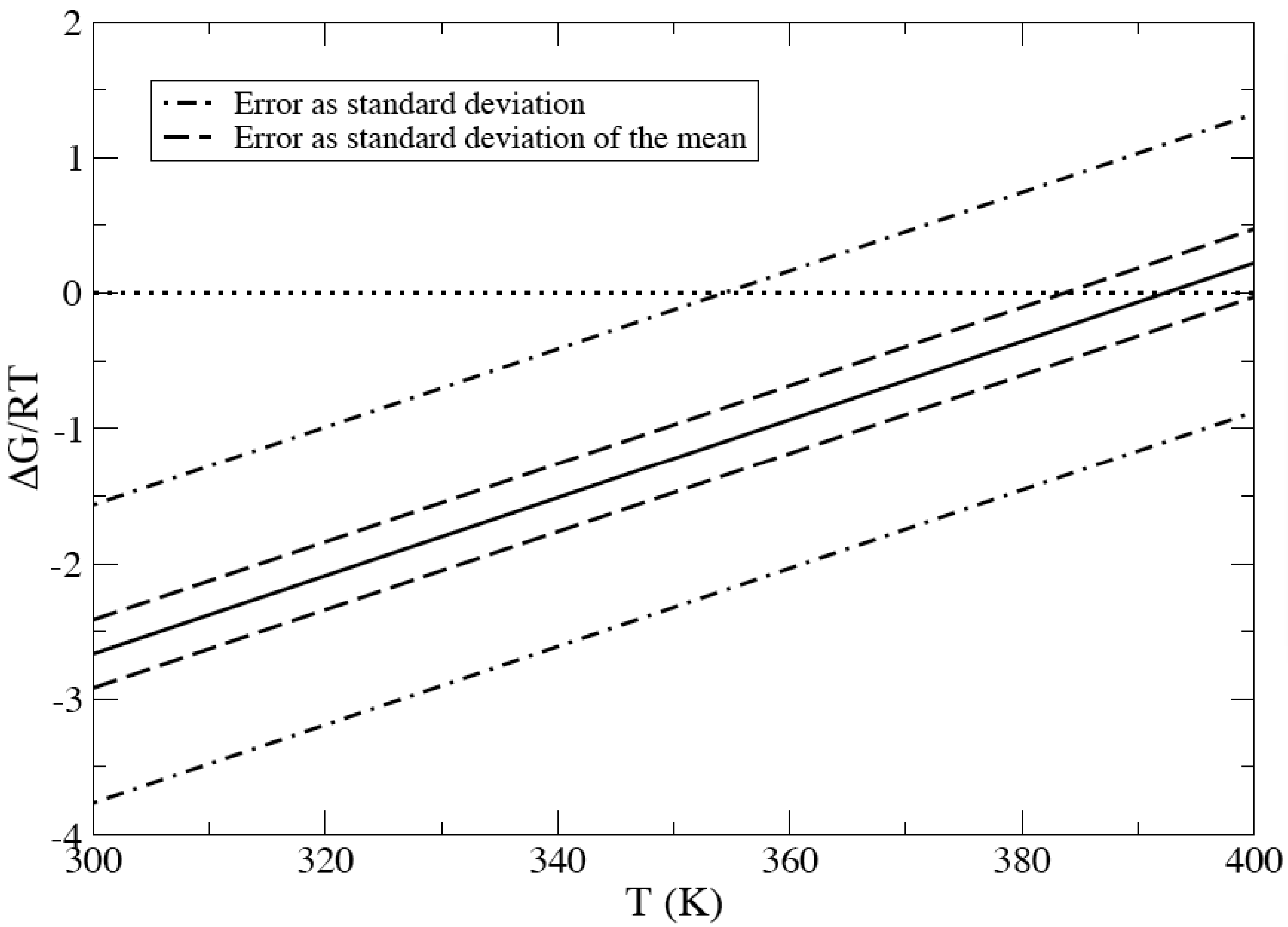


dense weak liquid → ordered weak phase



ordered weak phase → solid

Comparison of melting points

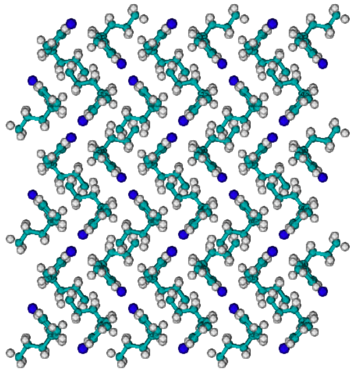


Computed Gibbs free energy difference between monoclinic and orthorhombic polymorphs of [C$_4$mim][Cl] using the CMJJ potential

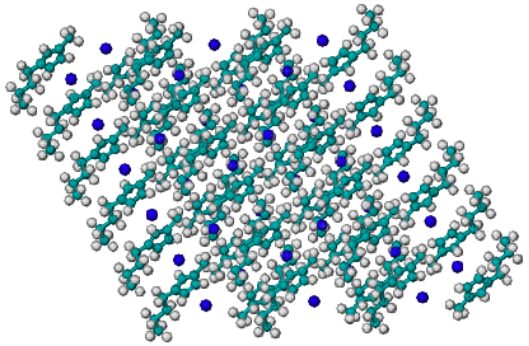
- Monoclinic thermodynamically stable relative to orthorhombic form at all temperatures below melting points of either polymorph.
- Free energy differences within accuracy of simulations

Comparison of computed and experimental melting points

polymorph	$T_m^{expt}(K)$	$T_m^{CLP}(K)$	$T_m^{CMJJ}(K)$
orthorhombic	337-339	365 ±6	369 ±7
monoclinic	318-340	NA	373 ±4

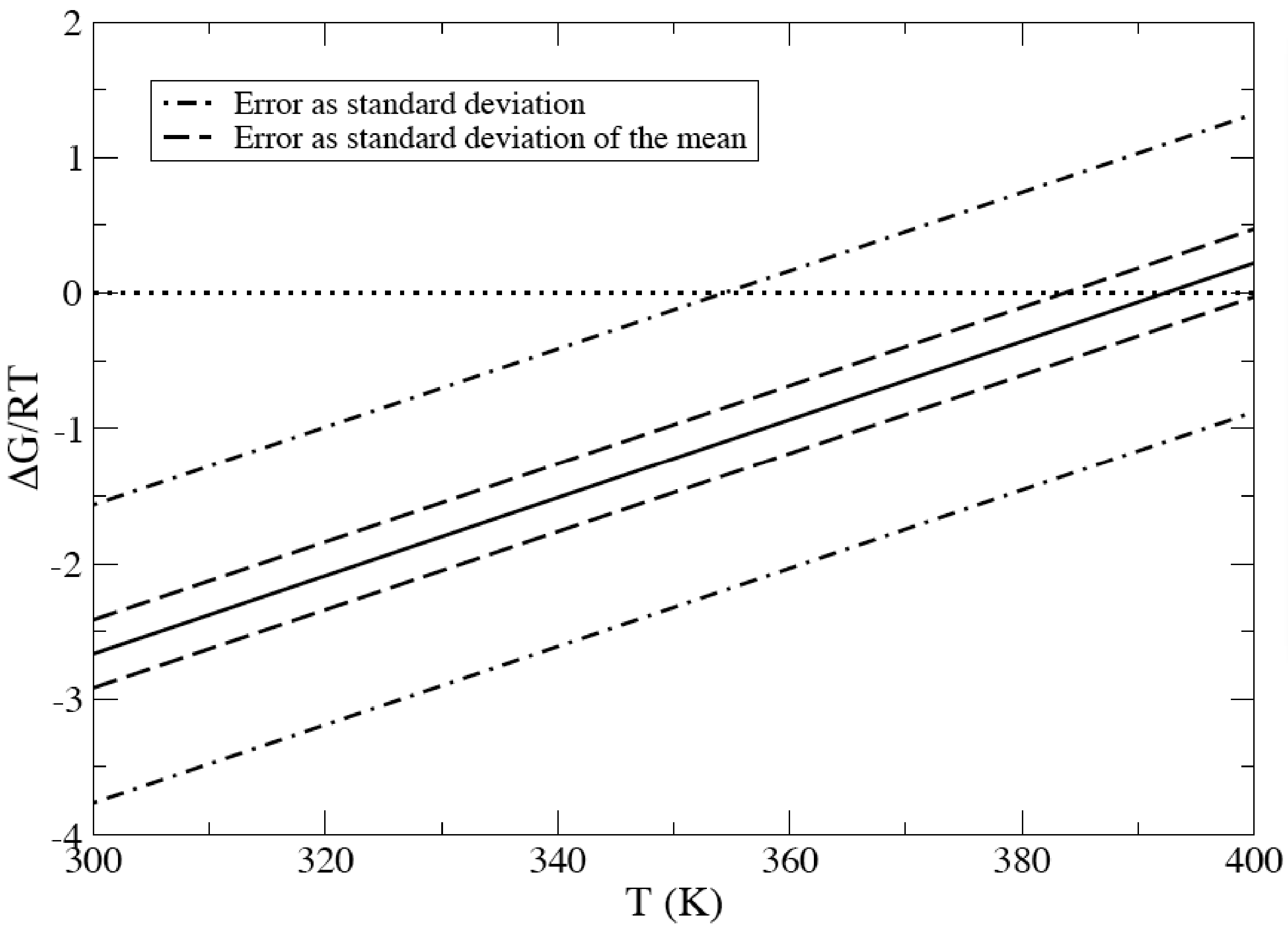


Orthorhombic



Monoclinic

Comparison of melting points



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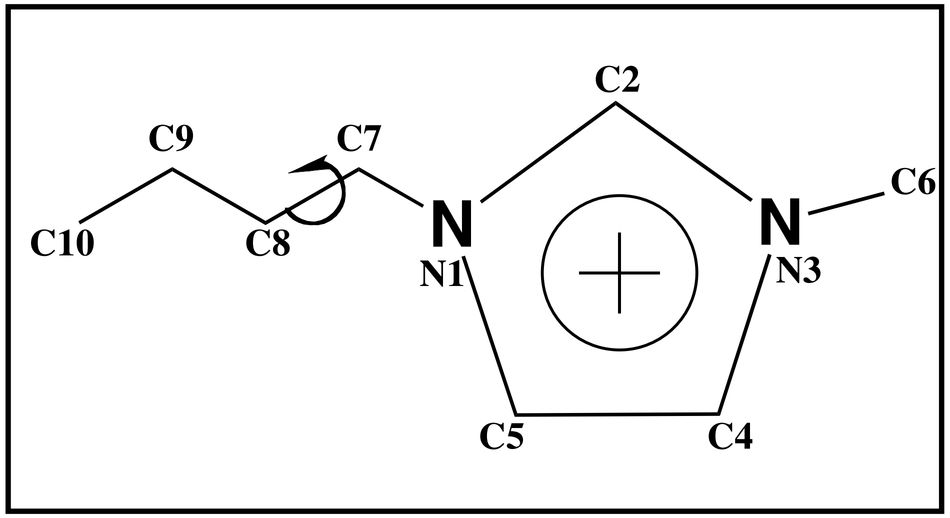

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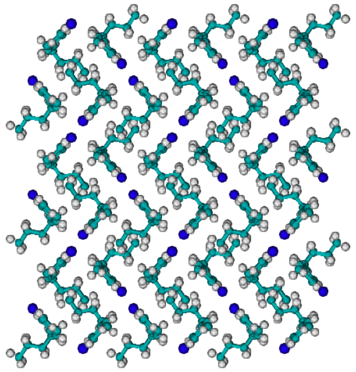
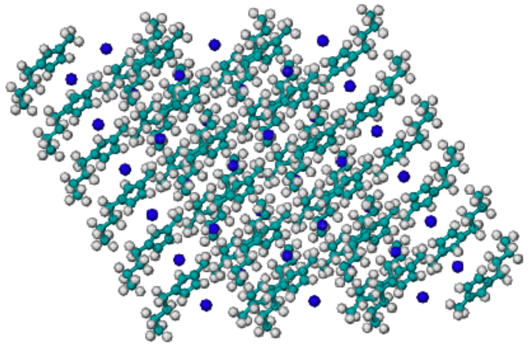
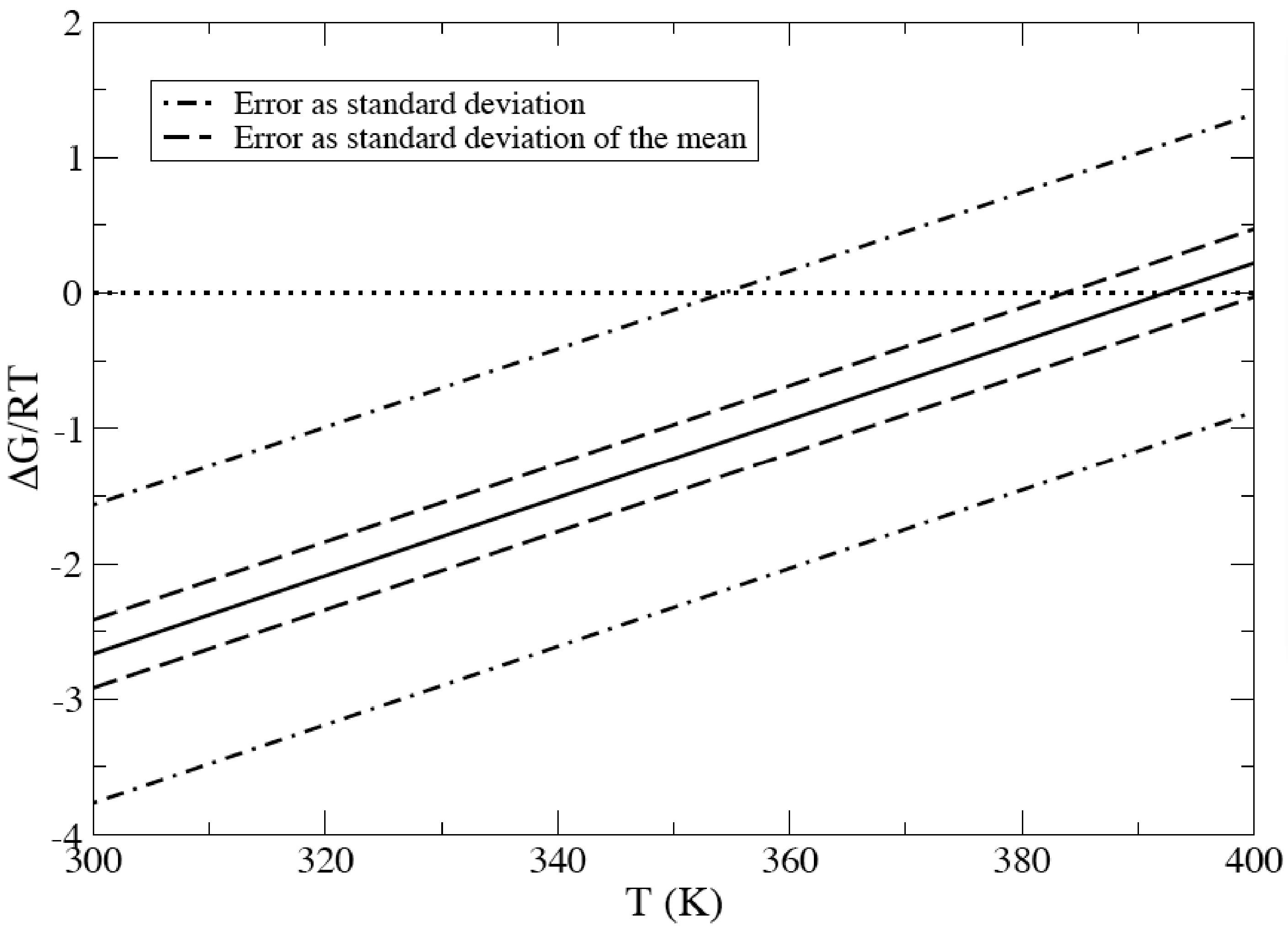


Orthorhombic



Monoclinic

Comparison of melting points



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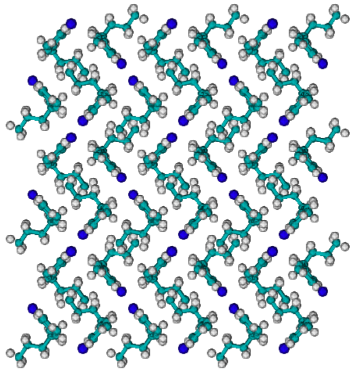
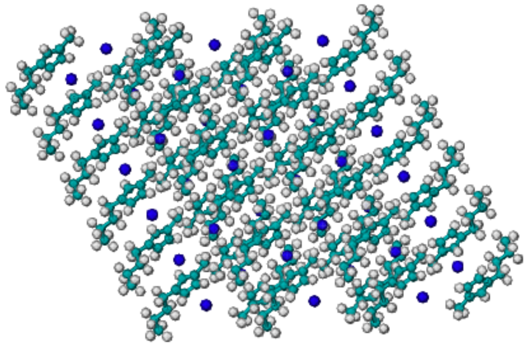
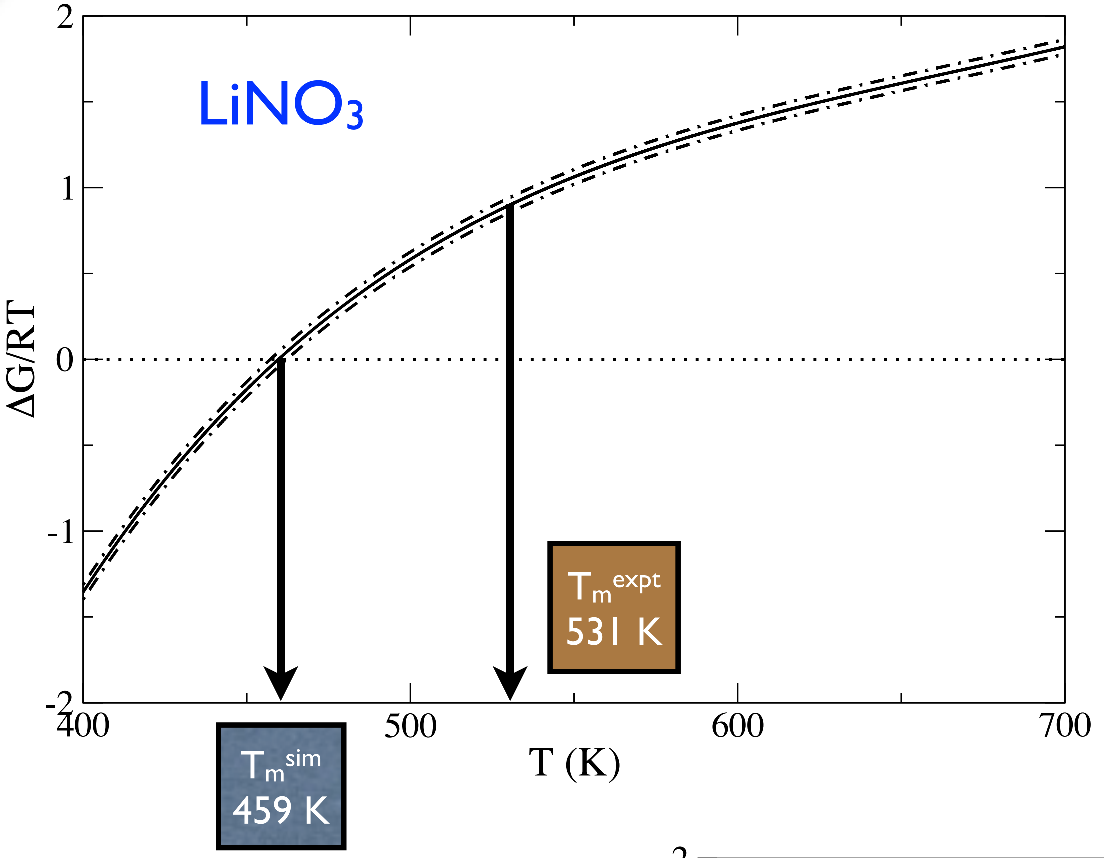
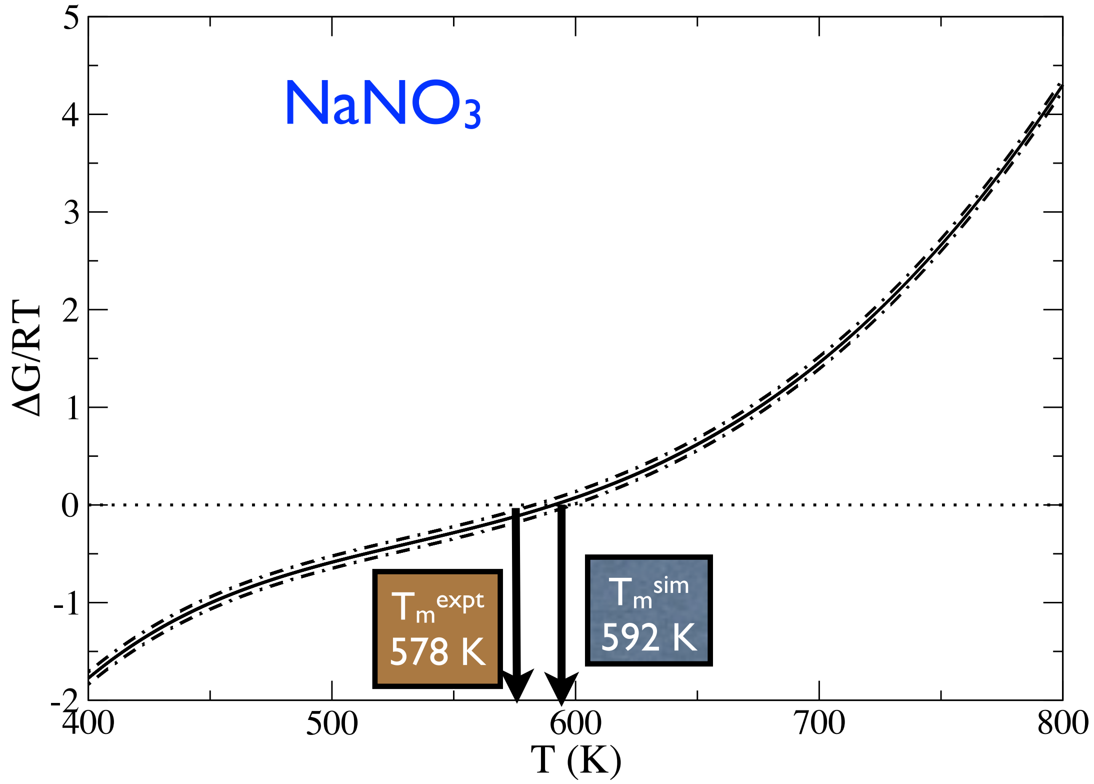
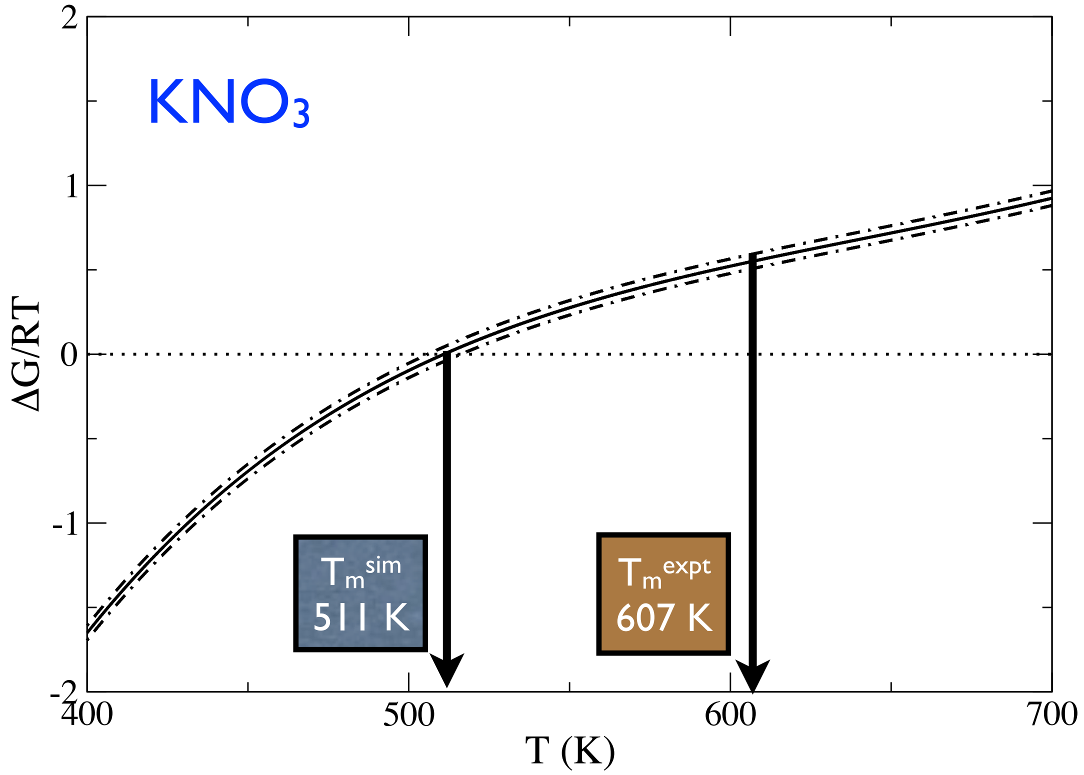

Orthorhombic


Monoclinic

Melting points of alkali nitrates



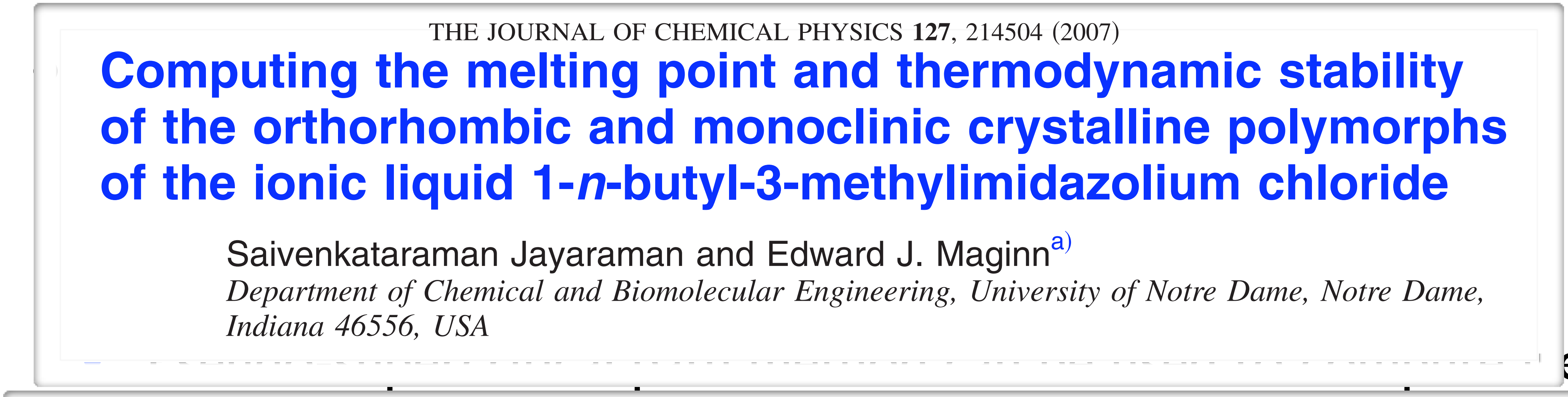




Conclusions - melting points

- Melting point can be computed rigorously from atomistic simulations
  - a stringent test of a force field
  - Pseudo-supercritical path method can be used to compute free energy differences between crystal polymorphs, and for solid solubility calculations
  - pure alkali nitrate salts, ionic liquids.

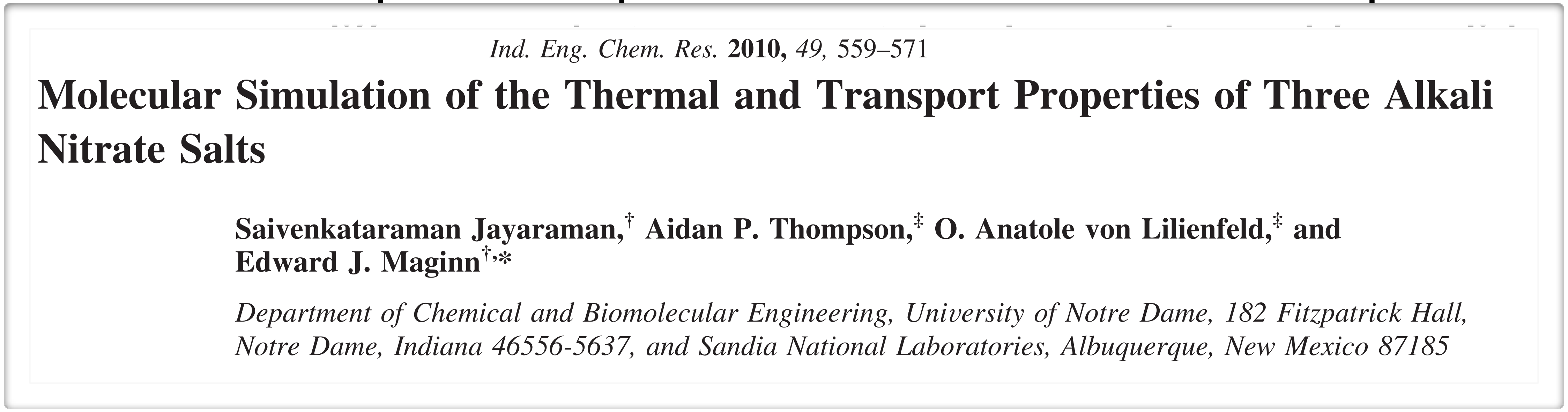
Conclusions - melting points



THE JOURNAL OF CHEMICAL PHYSICS **127**, 214504 (2007)

Computing the melting point and thermodynamic stability of the orthorhombic and monoclinic crystalline polymorphs of the ionic liquid 1-*n*-butyl-3-methylimidazolium chloride

Saivenkataraman Jayaraman and Edward J. Maginn[a)]
Department of Chemical and Biomolecular Engineering, University of Notre Dame, Notre Dame, Indiana 46556, USA

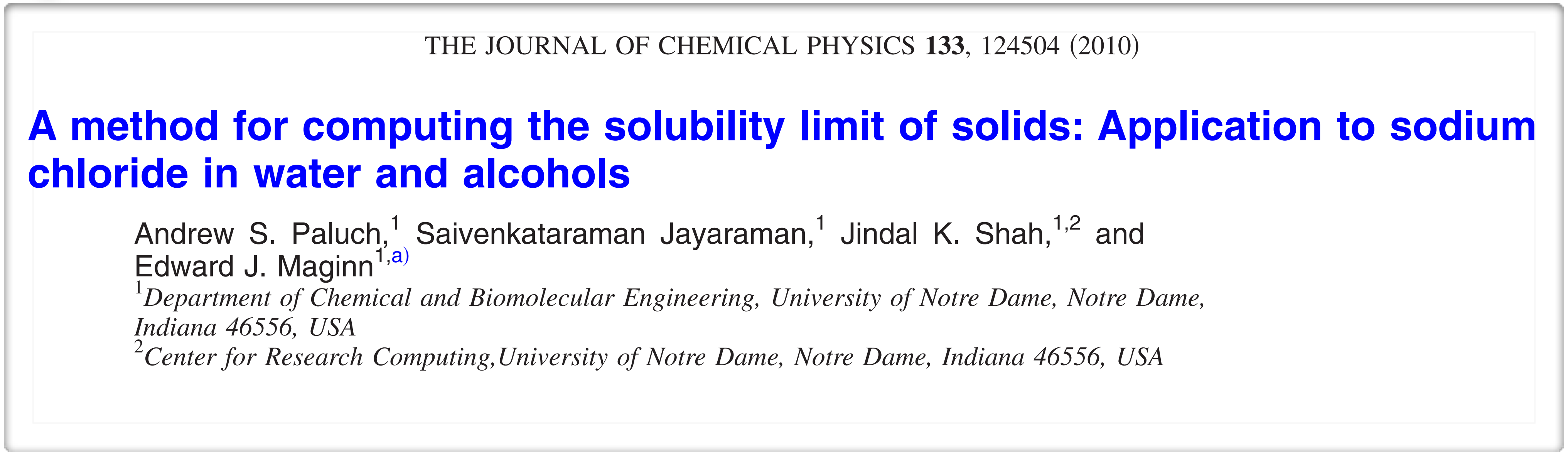


Ind. Eng. Chem. Res. **2010,** *49,* 559–571

Molecular Simulation of the Thermal and Transport Properties of Three Alkali Nitrate Salts

Saivenkataraman Jayaraman,[†] Aidan P. Thompson,[‡] O. Anatole von Lilienfeld,[‡] and Edward J. Maginn[†,*]

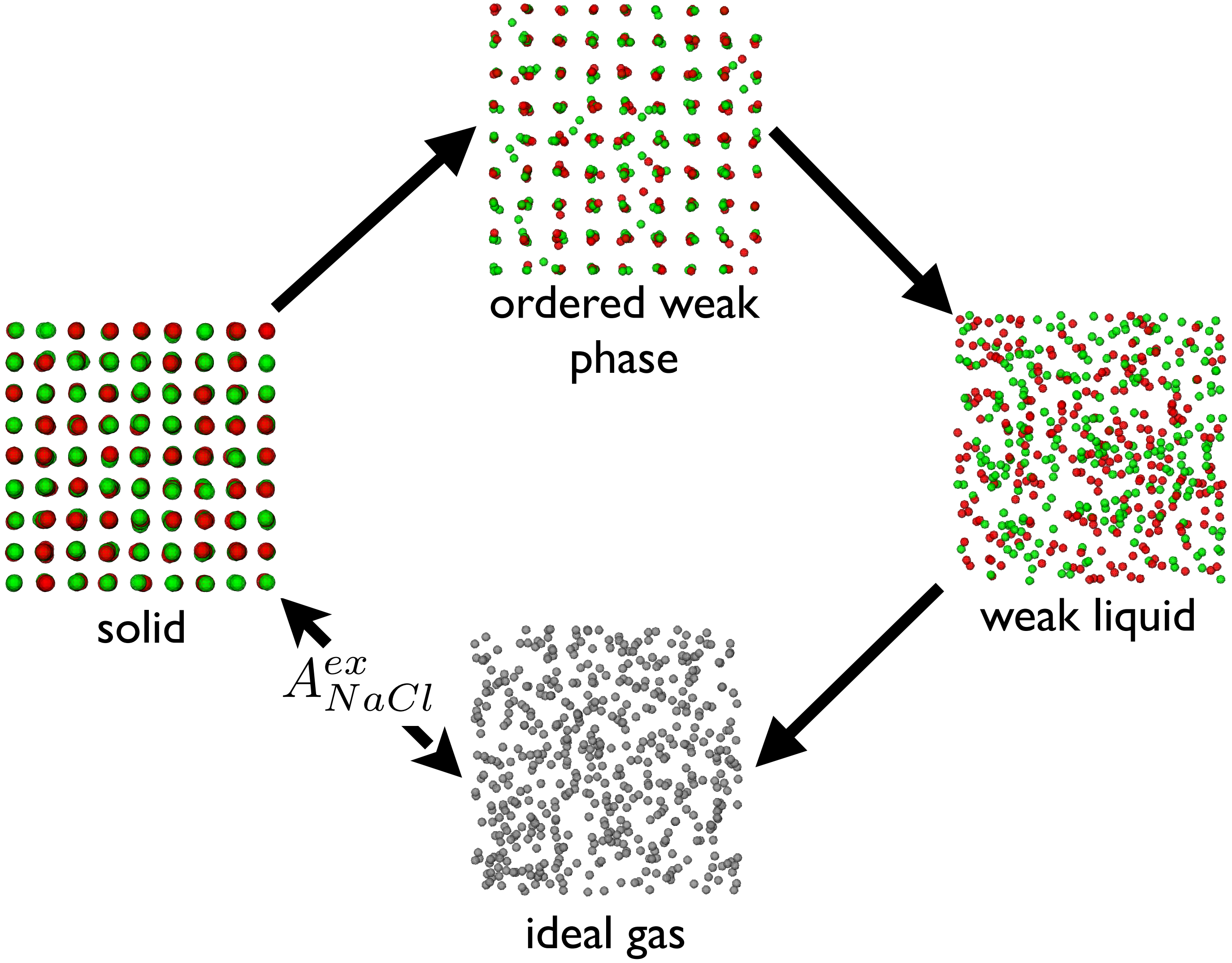
Department of Chemical and Biomolecular Engineering, University of Notre Dame, 182 Fitzpatrick Hall, Notre Dame, Indiana 46556-5637, and Sandia National Laboratories, Albuquerque, New Mexico 87185



THE JOURNAL OF CHEMICAL PHYSICS **133**, 124504 (2010)

A method for computing the solubility limit of solids: Application to sodium chloride in water and alcohols

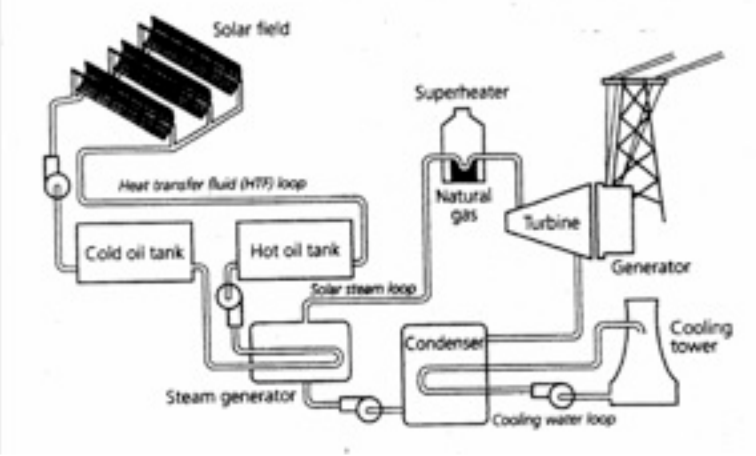
Andrew S. Paluch,[1] Saivenkataraman Jayaraman,[1] Jindal K. Shah,[1,2] and Edward J. Maginn[1,a)]
[1] *Department of Chemical and Biomolecular Engineering, University of Notre Dame, Notre Dame, Indiana 46556, USA*
[2] *Center for Research Computing,University of Notre Dame, Notre Dame, Indiana 46556, USA*



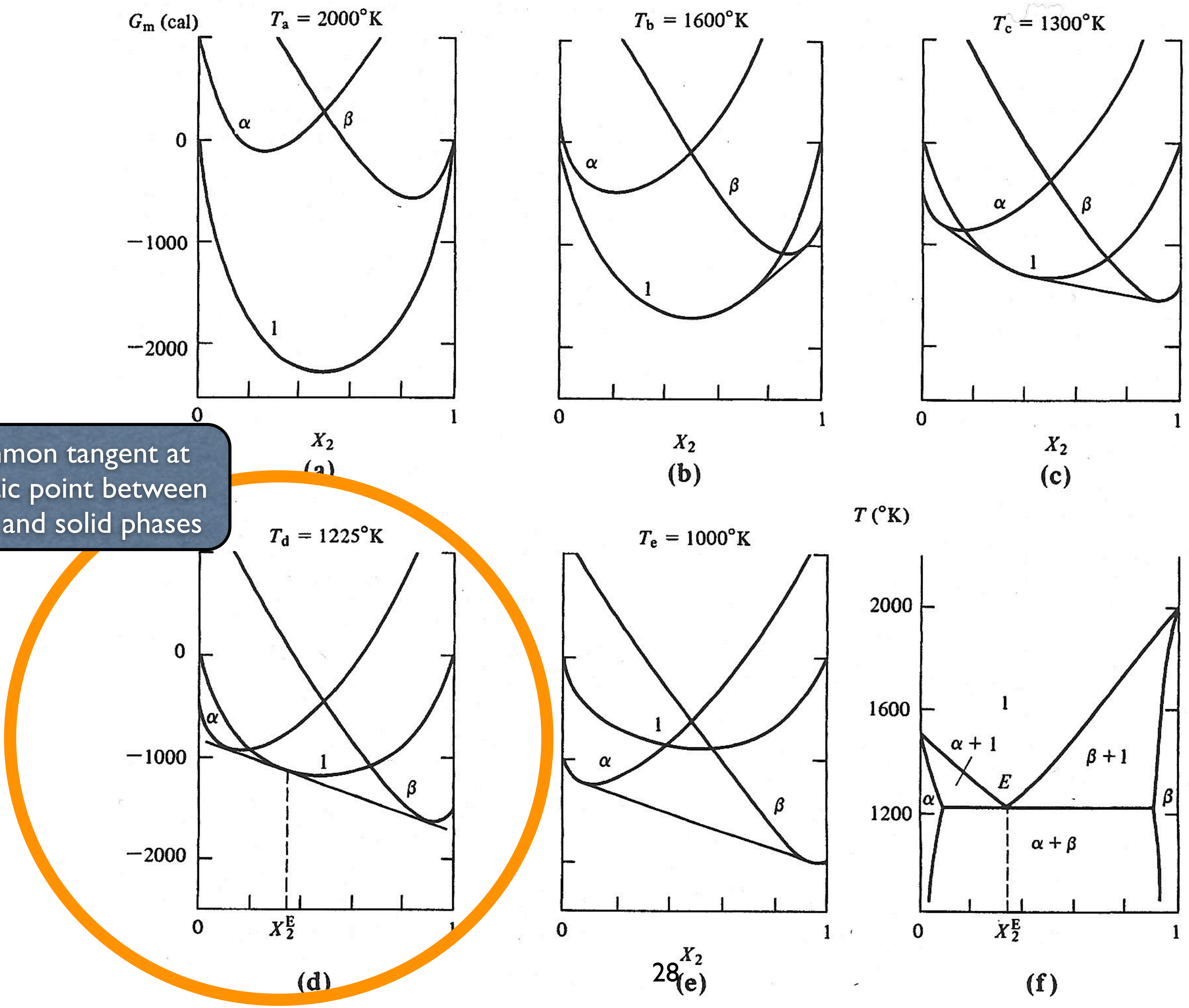
Focus Application- 2

Eutectic points and solid-liquid phase coexistence in mixtures

Sai Jayaraman[1,*], Aidan Thompson[1] and Anatole von Lilienfeld[2]
[1]Advanced Device Technologies, Sandia National Labs
[2]Argonne Leadership Computing Facility, Argonne National Lab



Chemical thermodynamics of Materials - C. H. P. Lupis
North-Holland, 1983



Common tangent at eutectic point between liquid and solid phases

Computing the free energy of a liquid mixture

$$G_{mix} = x_A G_A + x_B G_B + RT \sum_{i=A,B} x_i \ln x_i + G^{excess}$$

Free energy of binary mixture at T, P, x_A, x_B

Free energy of Pure species A at T,P

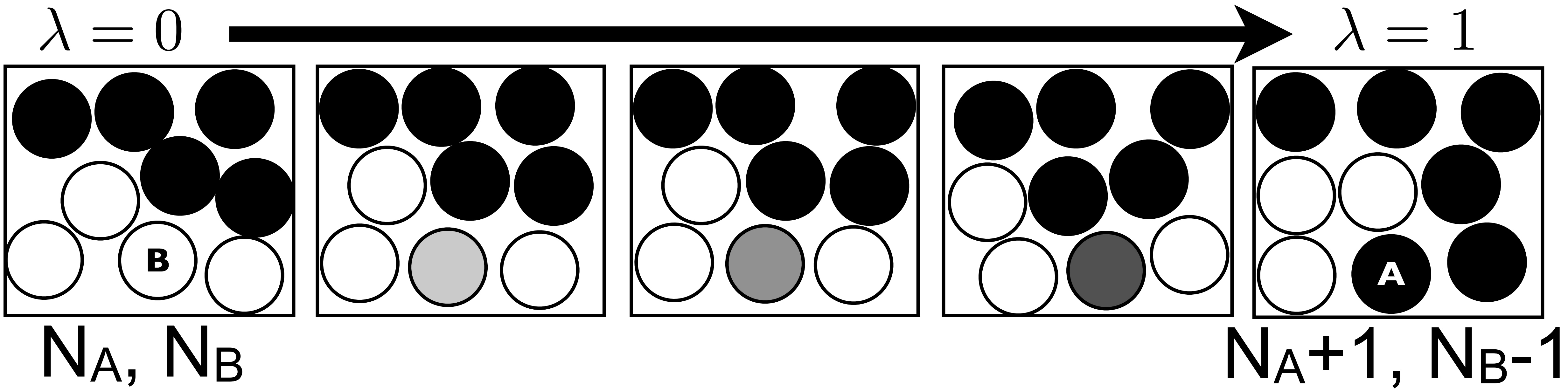
Free energy of Pure species B at T,P

Free energy contribution arising from entropy of mixing

Residual contribution from energetic interaction between molecules of A and B.

Alchemical Transformation

$$\frac{\partial G^{excess}}{\partial x} \approx \frac{\Delta G}{\Delta x}$$

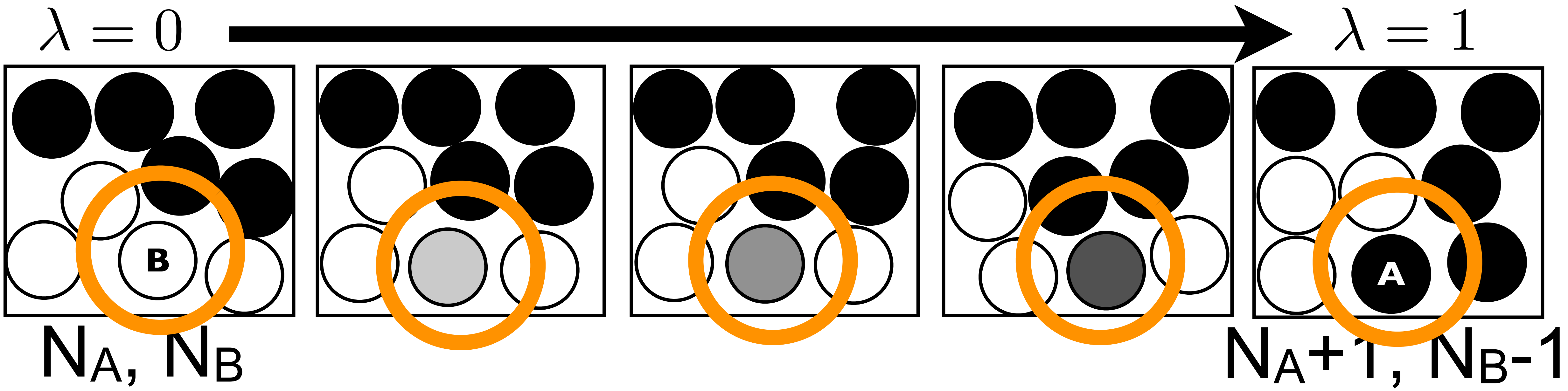


$$u_{ij}(\lambda) = \lambda u_{i\mathrm{A}} + (1-\lambda)u_{i\mathrm{B}}$$

$$\Delta\mu_{\mathrm{AB}} = \int_0^1 d\lambda \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda = \int_0^1 d\lambda \left\langle \sum_i (u_{i\mathrm{A}} - u_{i\mathrm{B}}) \right\rangle_\lambda$$

Alchemical Transformation

$$\frac{\partial G^{excess}}{\partial x} \approx \frac{\Delta G}{\Delta x}$$



$$u_{ij}(\lambda) = \lambda u_{i\mathrm{A}} + (1-\lambda)u_{i\mathrm{B}}$$

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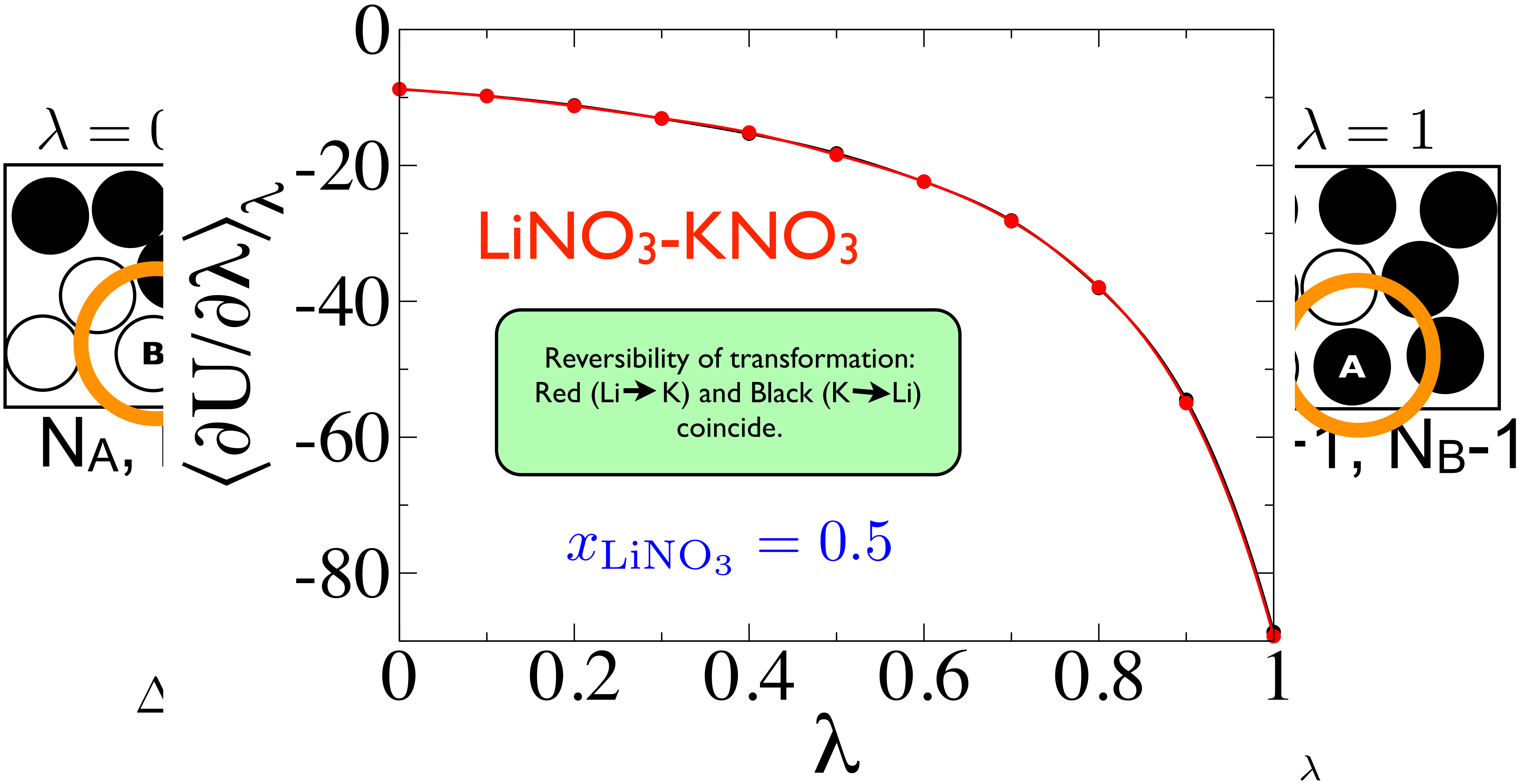
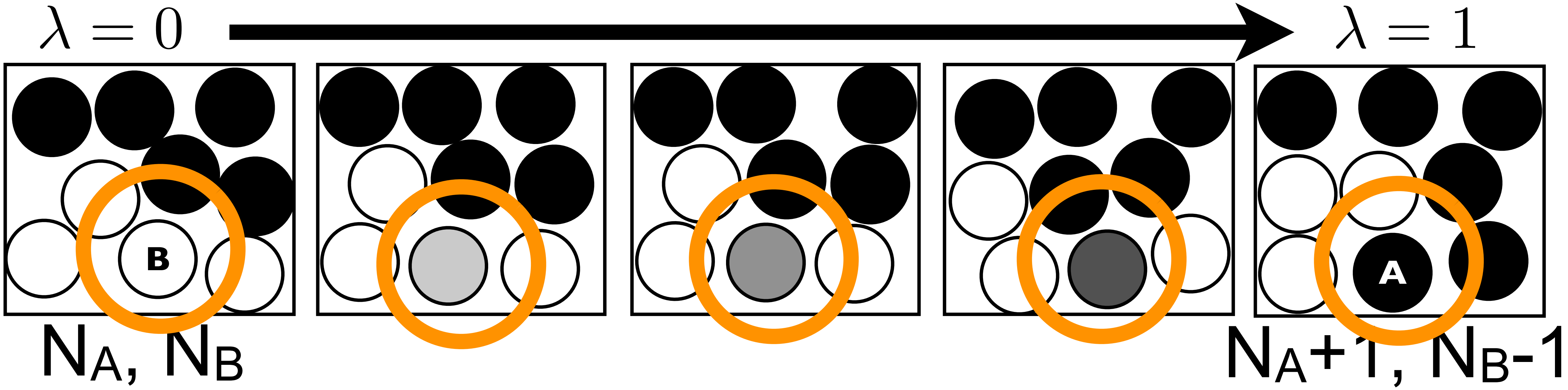
Alchemical Transformation



Reversibility of transformation:
Red (Li➔K) and Black (K➔Li)
coincide.

Alchemical Transformation

$$\frac{\partial G^{excess}}{\partial x} \approx \frac{\Delta G}{\Delta x}$$



$$u_{ij}(\lambda) = \lambda u_{i\mathrm{A}} + (1-\lambda)u_{i\mathrm{B}}$$

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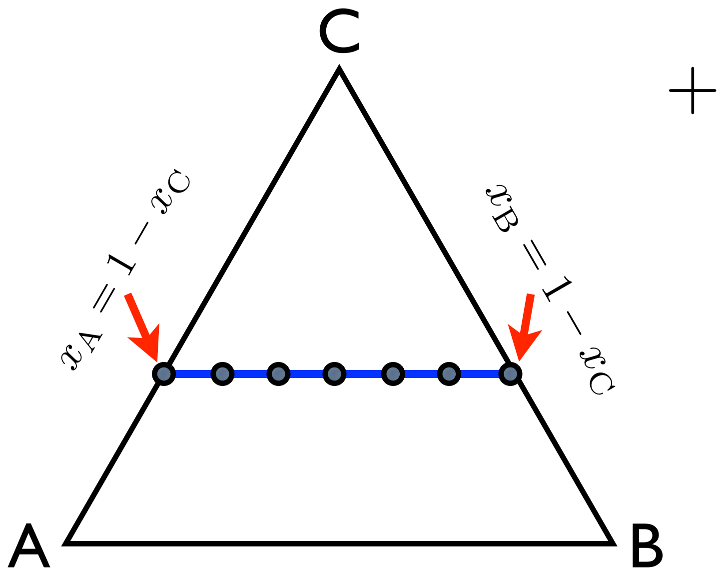
Excess free energies from $\Delta\mu_{\mathrm{AB}}$

Binary:

$$g_\ell^{ex}(x_\mathrm{A}, x_\mathrm{B}) = \int_0^{x_\mathrm{A}} dx'_\mathrm{A}\ \Delta\mu_\mathrm{AB}(x'_\mathrm{A}) - x_\mathrm{A}\int_0^{1} dx'_\mathrm{A}\Delta\mu_\mathrm{AB}(x'_\mathrm{A})$$

Ternary:

$$\begin{aligned} g_\ell^{ex}(x_\mathrm{A}, x_\mathrm{B}, x_\mathrm{C}) \quad = \quad & \int_0^{x_\mathrm{A}} dx'_\mathrm{A}\Delta\mu_\mathrm{AB}(x'_\mathrm{A}, x_\mathrm{C}) - \frac{x_\mathrm{A}}{x_\mathrm{A}+x_\mathrm{B}}\int_0^{x_\mathrm{A}+x_\mathrm{B}} dx'_\mathrm{A}\Delta\mu_\mathrm{AB}(x'_\mathrm{A}, x_\mathrm{C}) \\ & + \frac{x_\mathrm{A}}{x_\mathrm{A}+x_\mathrm{B}} g_{\mathrm{AC}\ell}^{ex}(x_\mathrm{C}) + \frac{x_\mathrm{B}}{x_\mathrm{A}+x_\mathrm{B}} g_{\mathrm{BC}\ell}^{ex}(x_\mathrm{C}) \end{aligned}$$



At each x_C, alchemical changes conducted at x_A mesh points

Excess free energies from $\Delta\mu_{\mathrm{AB}}$

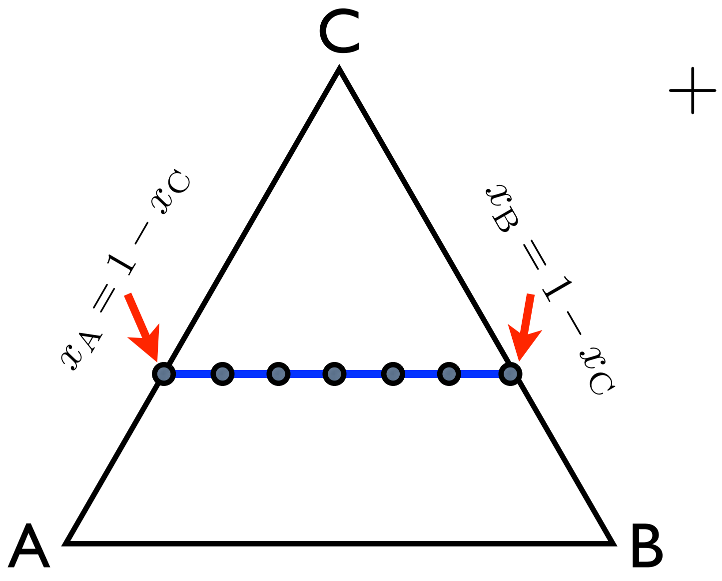
Binary:

$$g_\ell^{ex}(x_{\mathrm{A}}, x_{\mathrm{B}}) = \int_0^{x_{\mathrm{A}}} dx'_{\mathrm{A}}\, \Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}}) - x_{\mathrm{A}} \boxed{\int_0^1 dx'_{\mathrm{A}}\, \Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}})}$$

Area under $\Delta\mu_{\mathrm{AB}}$

Ternary:

$$g_\ell^{ex}(x_{\mathrm{A}}, x_{\mathrm{B}}, x_{\mathrm{C}}) = \int_0^{x_{\mathrm{A}}} dx'_{\mathrm{A}}\, \Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}}, x_{\mathrm{C}}) - \frac{x_{\mathrm{A}}}{x_{\mathrm{A}} + x_{\mathrm{B}}} \boxed{\int_0^{x_{\mathrm{A}}+x_{\mathrm{B}}} dx'_{\mathrm{A}}\, \Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}}, x_{\mathrm{C}})} + \frac{x_{\mathrm{A}}}{x_{\mathrm{A}} + x_{\mathrm{B}}} g^{ex}_{\mathrm{AC}\ell}(x_{\mathrm{C}}) + \frac{x_{\mathrm{B}}}{x_{\mathrm{A}} + x_{\mathrm{B}}} g^{ex}_{\mathrm{BC}\ell}(x_{\mathrm{C}})$$

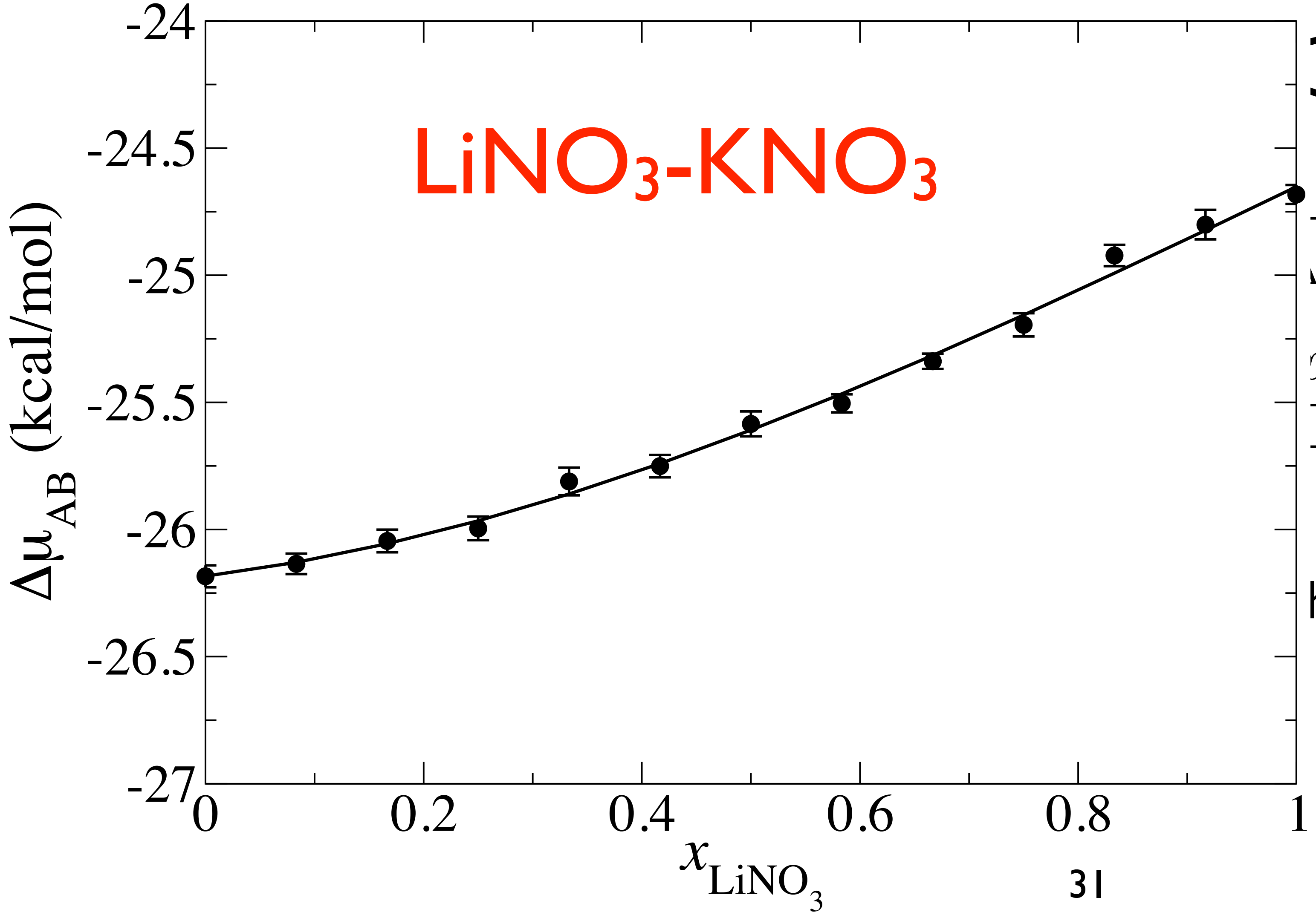


At each x_{C}, alchemical changes conducted at x_{A} mesh points

Excess free energies from $\Delta\mu_{AB}$

Binary:

$$g_\ell^{ex}(x_A, x_B) = \int_0^{x_A} dx'_A \, \Delta\mu_{AB}(x'_A) - x_A \boxed{\int_0^1 dx'_A \Delta\mu_{AB}(x'_A)}$$



$$\boxed{\int_0^{x_A+x_B} dx'_A \Delta\mu_{AB}(x'_A, x_C)}$$

x_A

$+ x_B$

$g^{ex}_{BC\ell}(x_C)$

$+ x_B$

hanges conducted at x_A mesh points

Excess free energies from $\Delta\mu_{\mathrm{AB}}$

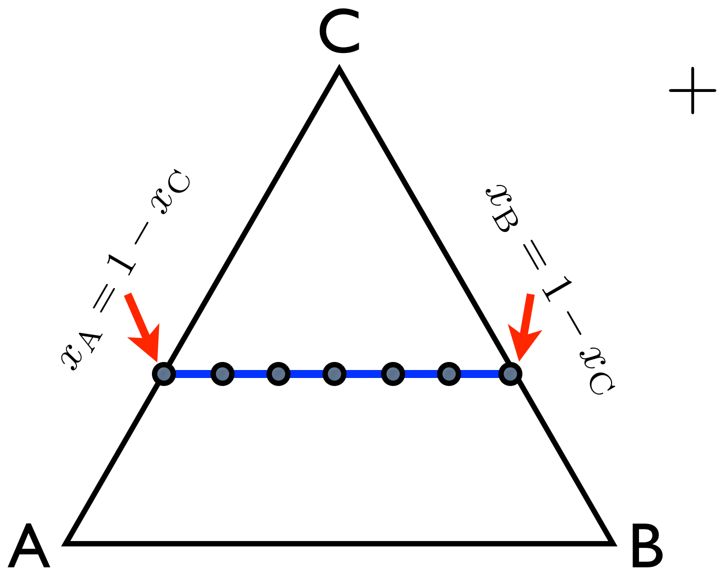
Binary:

$$g_\ell^{ex}(x_{\mathrm{A}},x_{\mathrm{B}}) = \int_0^{x_{\mathrm{A}}} dx'_{\mathrm{A}}\,\Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}}) - x_{\mathrm{A}}\boxed{\int_0^{1} dx'_{\mathrm{A}}\,\Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}})}$$

Area under $\Delta\mu_{\mathrm{AB}}$

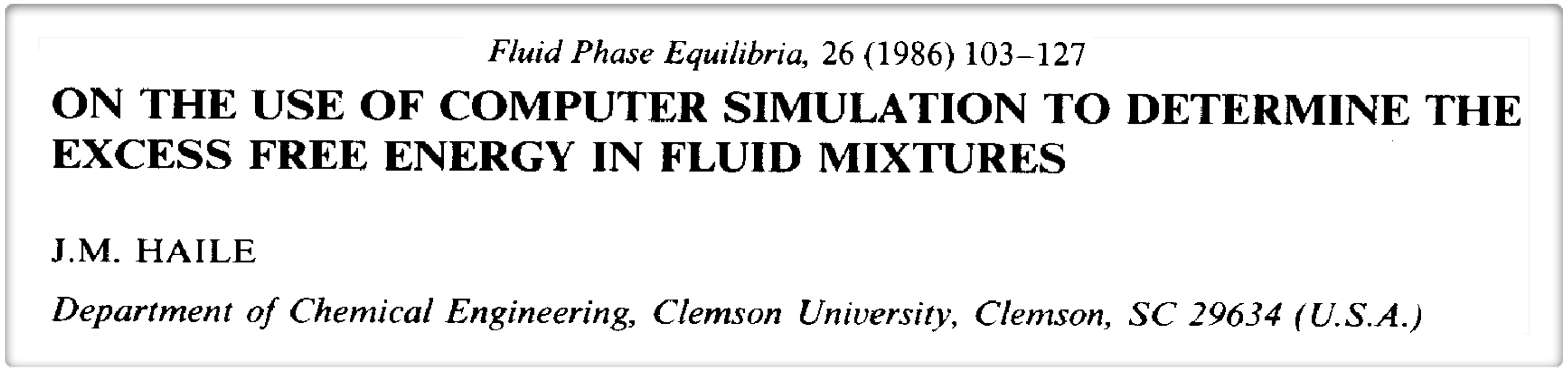
Ternary:

$$g_\ell^{ex}(x_{\mathrm{A}},x_{\mathrm{B}},x_{\mathrm{C}}) = \int_0^{x_{\mathrm{A}}} dx'_{\mathrm{A}}\,\Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}},x_{\mathrm{C}}) - \frac{x_{\mathrm{A}}}{x_{\mathrm{A}}+x_{\mathrm{B}}}\boxed{\int_0^{x_{\mathrm{A}}+x_{\mathrm{B}}} dx'_{\mathrm{A}}\,\Delta\mu_{\mathrm{AB}}(x'_{\mathrm{A}},x_{\mathrm{C}})}$$
$$+\frac{x_{\mathrm{A}}}{x_{\mathrm{A}}+x_{\mathrm{B}}}\,g^{ex}_{\mathrm{AC}\ell}(x_{\mathrm{C}}) + \frac{x_{\mathrm{B}}}{x_{\mathrm{A}}+x_{\mathrm{B}}}\,g^{ex}_{\mathrm{BC}\ell}(x_{\mathrm{C}})$$



At each x_{C}, alchemical changes conducted at x_{A} mesh points

J.M. Haile's version: The "parameter charging" method

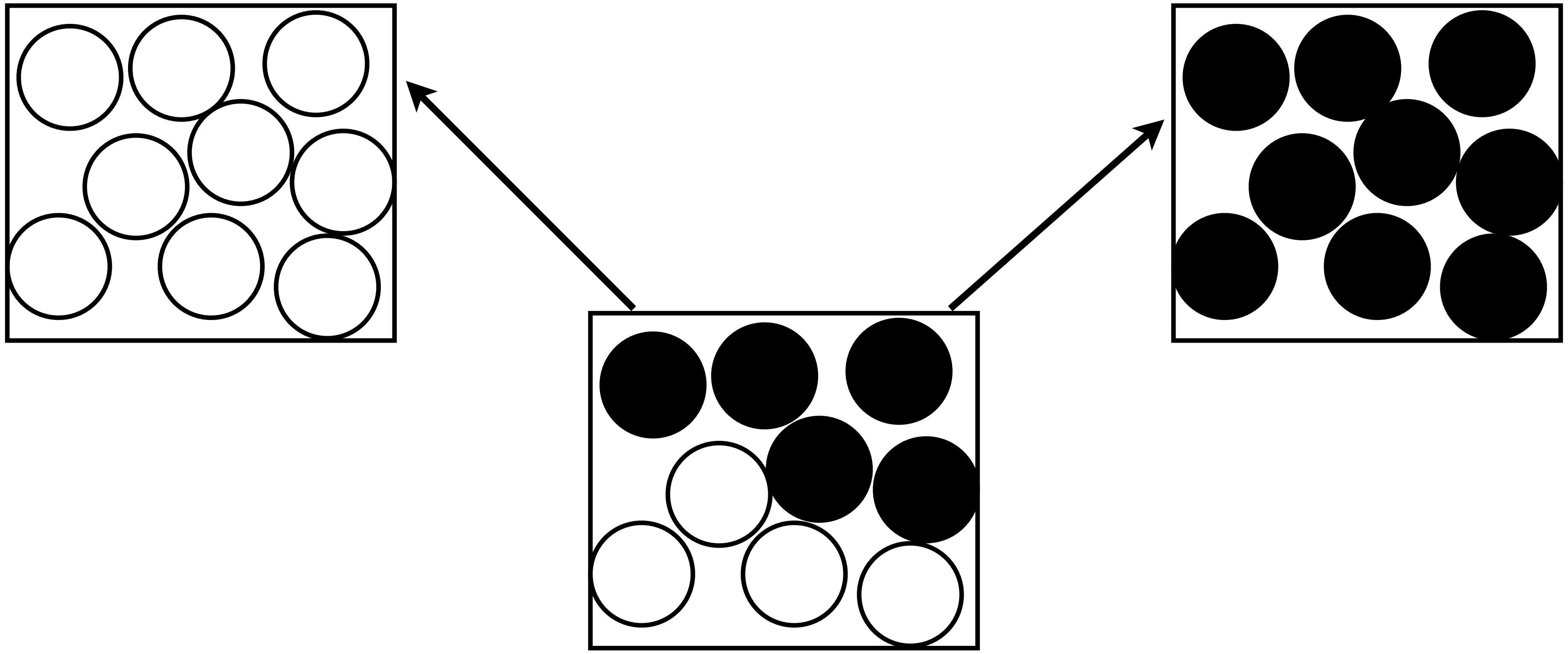


Fluid Phase Equilibria, 26 (1986) 103–127

ON THE USE OF COMPUTER SIMULATION TO DETERMINE THE EXCESS FREE ENERGY IN FLUID MIXTURES

J.M. HAILE

Department of Chemical Engineering, Clemson University, Clemson, SC 29634 (U.S.A.)

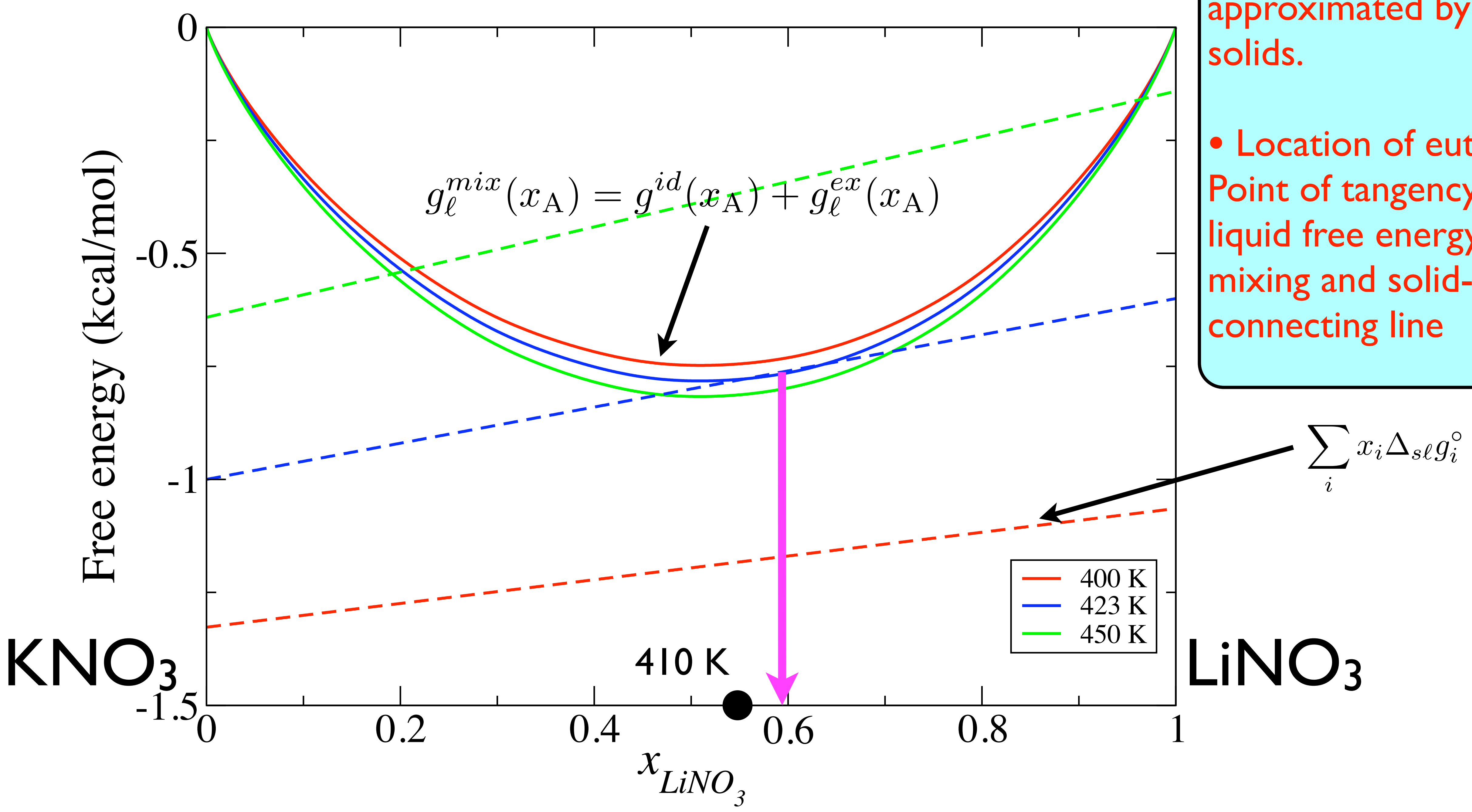


$$g^{ex} = x_A(g^{res}_{mix} - g^{res}_{pureA}) + x_B(g^{res}_{mix} - g^{res}_{pureB})$$

Mixture converted to pure components.

Each particle has associated "charging parameter"

$LiNO_3$-KNO_3 mixture - Free energy vs composition



- Approximation: "Simple Eutectic" - Solid phases approximated by pure solids.

- Location of eutectic : Point of tangency between liquid free energy of mixing and solid-liquid connecting line

M.J. Maeso and J. Largo, Thermochimica Acta, **223**, 145-156 (1993)

LiNO3-KNO3 mixture - Free energy vs composition

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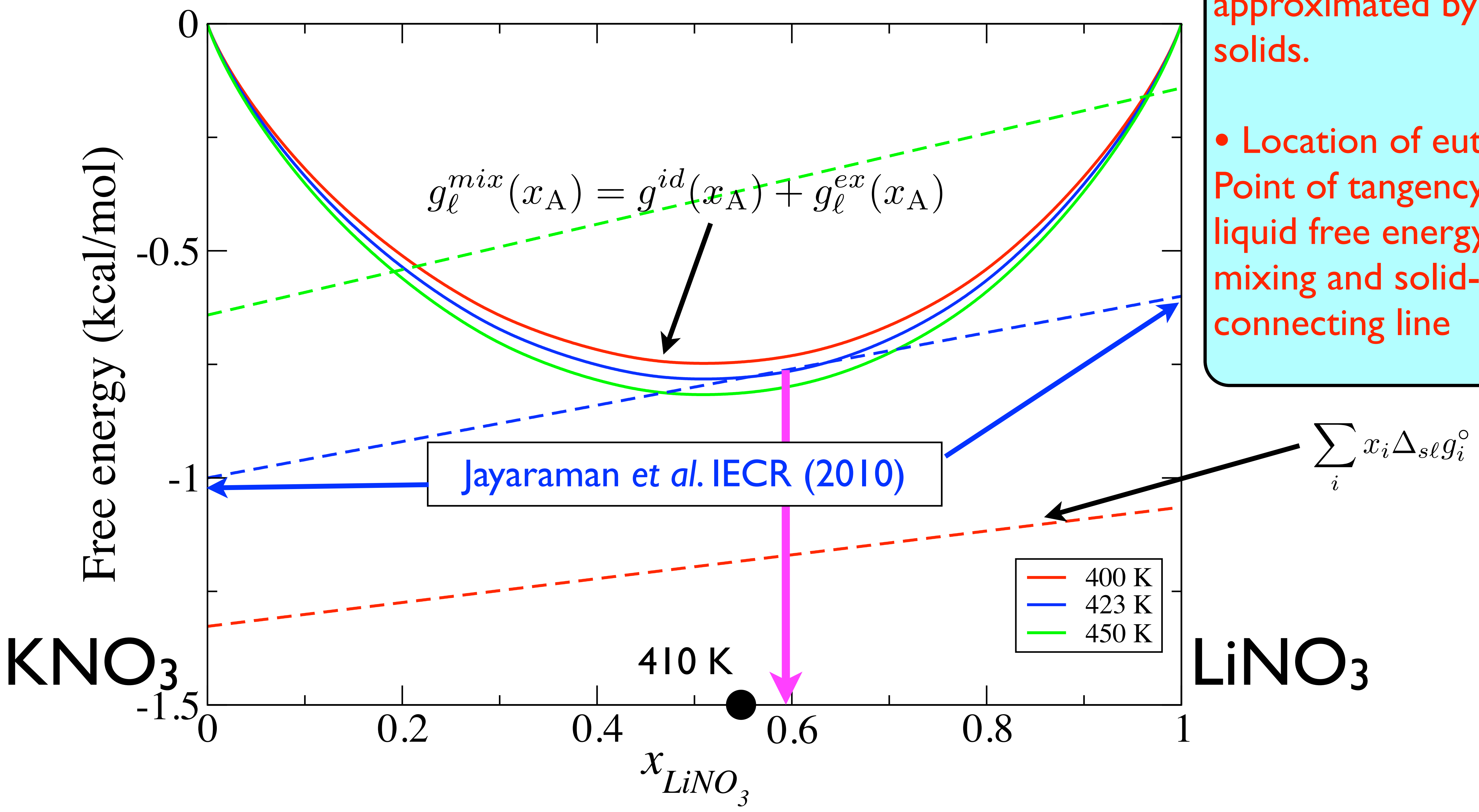


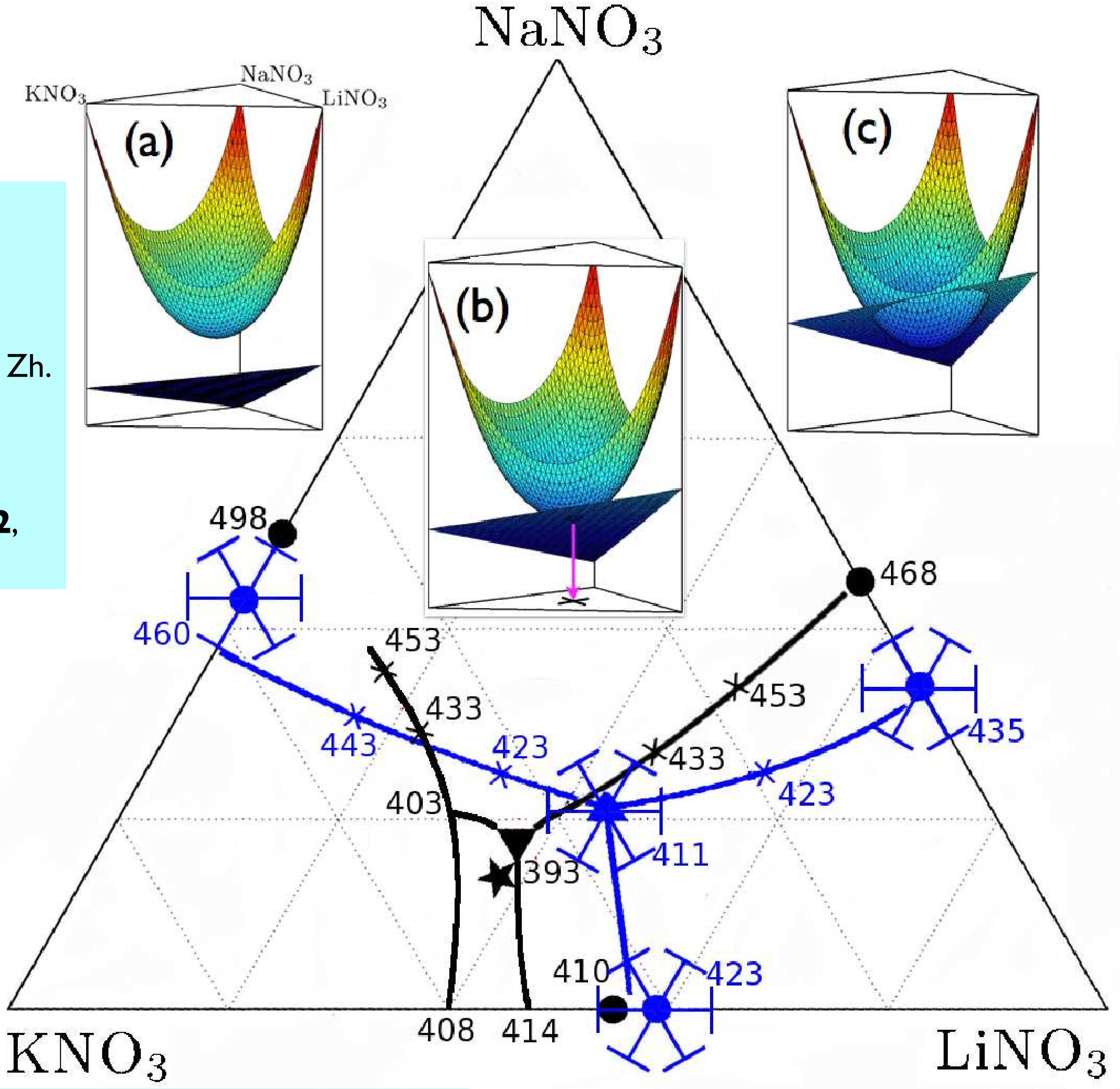
M.J. Maeso and J. Largo, Thermochimica Acta, **223**, 145-156 (1993)

$LiNO_3$-$NaNO_3$-KNO_3 ternary

[1]M.J. Maeso and J. Largo, Thermochimica Acta, **223**, 145-156 (1993) - Binaries

[2]A.G. Bergman and K. Nogoev, Zh. Neorg. Khim., **9** 1423 (1964) - Ternary

[3]H. R. Carveth, J. Phys. Chem., **2**, 209 (1898)★



S Jayaraman, A. P. Thompson and O. A. von Lilienfeld, Submitted

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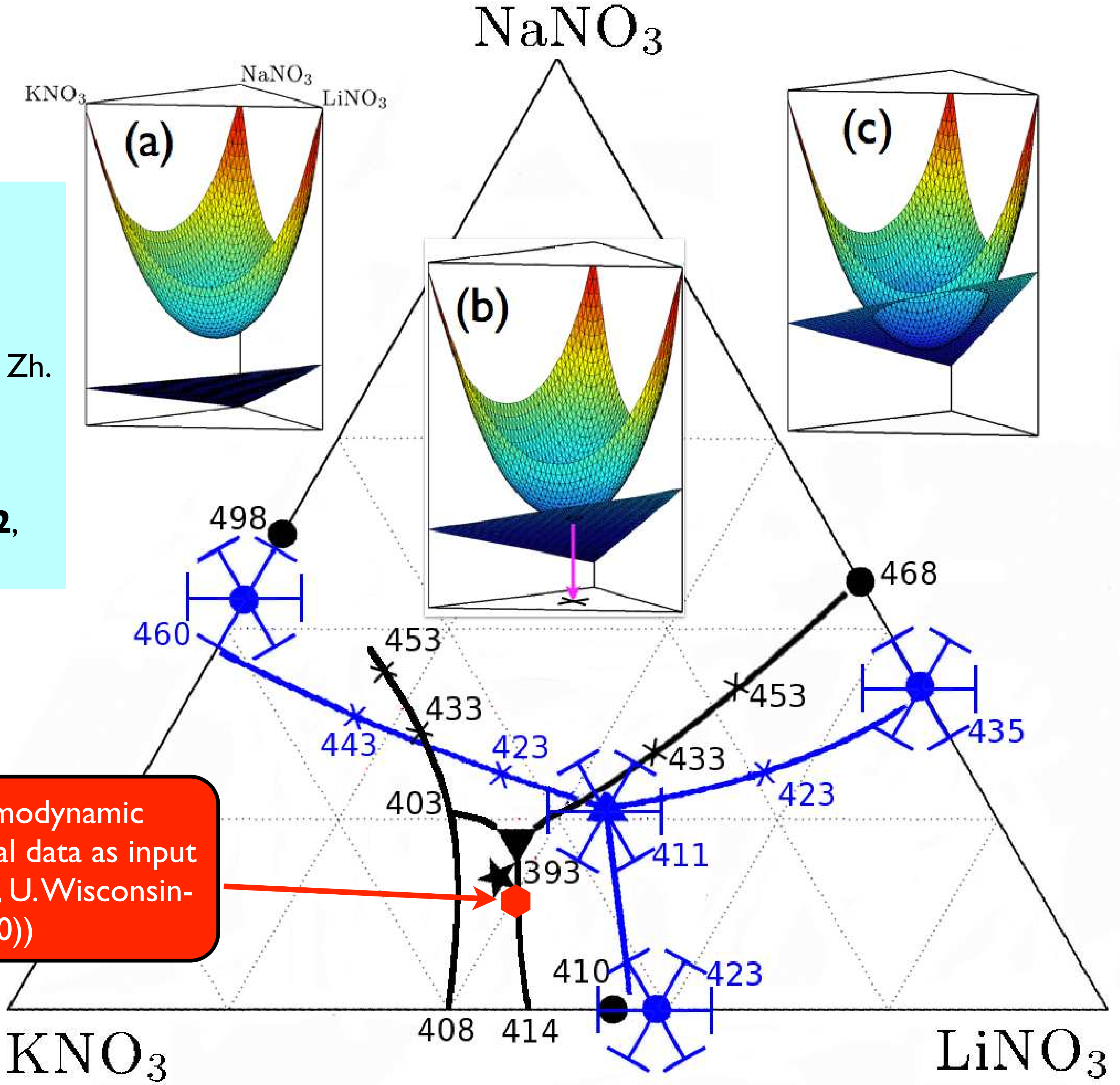

Computed from thermodynamic models, using experimental data as input (J. Ambrosek, Ph.D. Thesis, U. Wisconsin-Madison (2010))

S Jayaraman, A. P. Thompson and O. A. von Lilienfeld, Submitted

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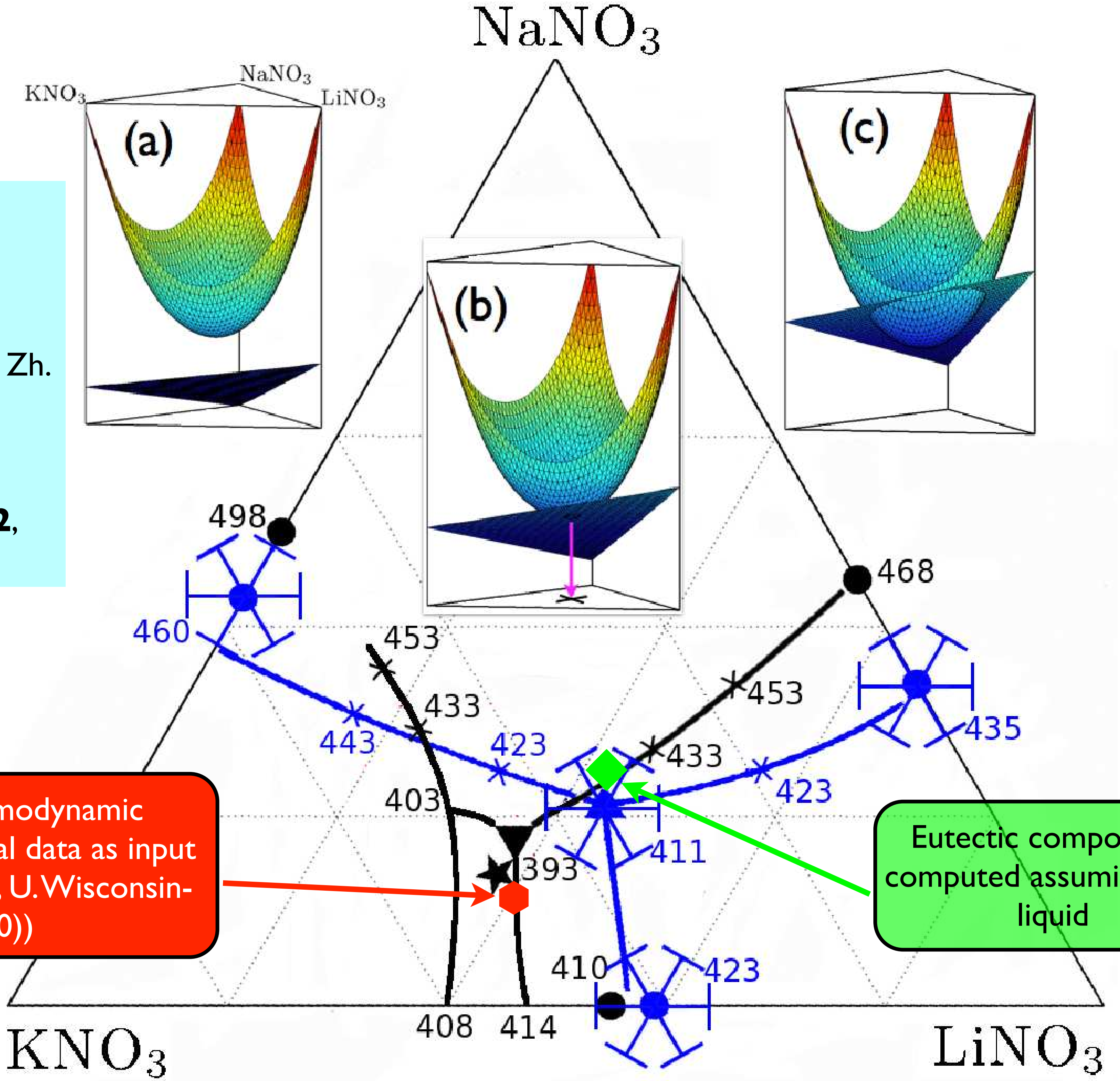

Computed from thermodynamic models, using experimental data as input (J. Ambrosek, Ph.D. Thesis, U. Wisconsin-Madison (2010))

Eutectic composition computed assuming ideal liquid

S Jayaraman, A. P. Thompson and O. A. von Lilienfeld, Submitted

Conclusions

- Thermodynamic integration based method developed to compute free energies of mixing from MD simulations
- Tangent method extended to compute approximations of eutectic compositions assuming a "simple eutectic"
- Future extension to higher dimensional mixtures
  - Extension to mixtures of Ca^{++} and monovalents - How do we handle the change in valency?
  - Handling high-dimensionality of search space for multicomponent mixtures

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- Prof. Edward Maginn
    - Jindal Shah, Andrew Paluch
- Aidan Thompson, Anatole von Lilienfeld, Steve Plimpton, Bob Bradshaw

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