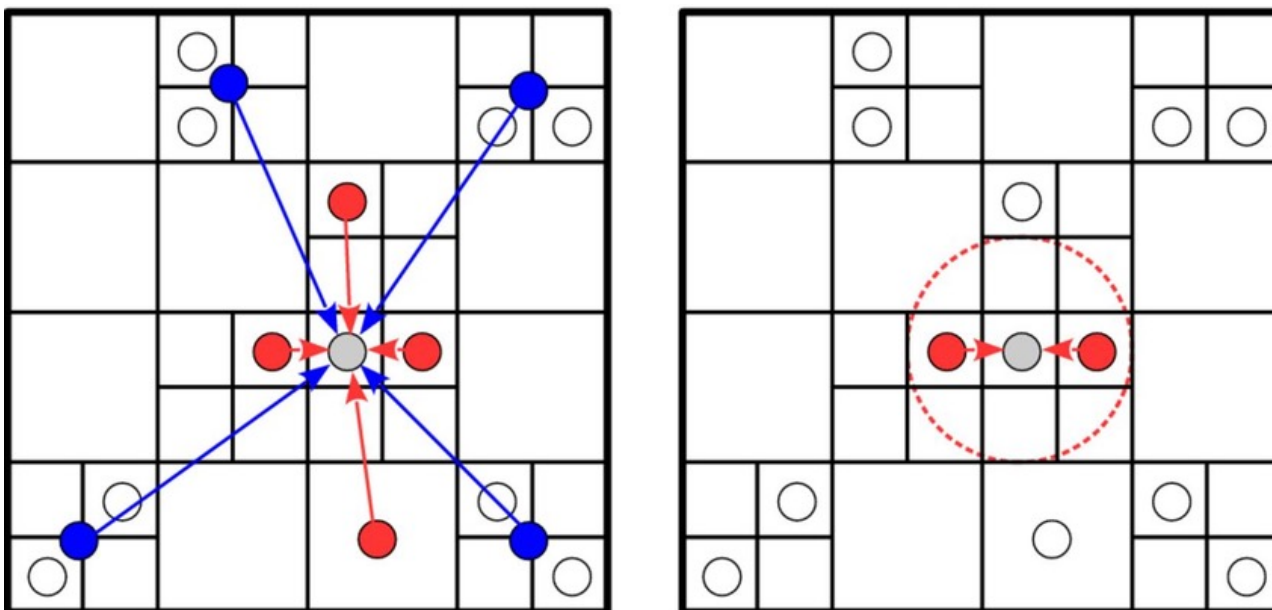# Force and Energy Computation
Week 1 : How MD works?

2024 Winter Molecular Simulation Seminar
January 12th, 2024

Presenter: Seonghyeon Kang
Advisor: Prof. Chang Yun Son

Basic Principle of Molecular Dynamics

1. Information of **Potential Energy** from **Force Field**

2. **Calculation of Potential Energy**

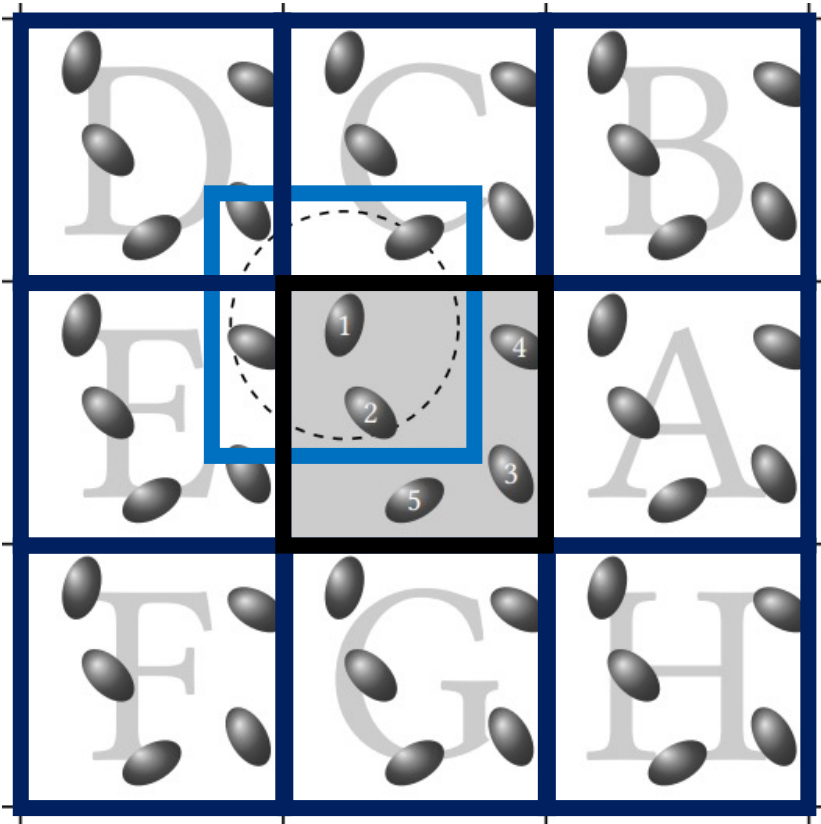3. Computing Force, Displacement, Velocity, … from **Integration Algorithm**

Two Kinds of Potential Energy(Brief Classification)

1. Bonded Energy(Bond, Angle, Torsion, Improper)

- Easy and clear to compute(Low time complexity)

- Short-range Interaction

2. Nonbonded Energy(Lennard-Jones, Electrostatic energy)

- Difficult to compute(High time complexity)

- Long-range interaction(Periodicity, Finite Size Effect)

Contents

1. *Periodic Boundary Condition* **&** *Finite Size Effect*

2. *Computational Algorithms* **for Nonbonded Energy Calculation**

3. **Why we use** *PME(Particle-Mesh-Ewald)***? &** *Artifacts of PME*

4. *GPU parallelization* **of Nonbonded Energy Computation**

1. *Periodic Boundary Condition(PBC)* & *Finite Size Effect*

Allen, M. P., & Tildesley, D. J., Computer simulation of liquids. *Oxford university press.* **2017**

Simulation Box
Periodic Image/Finite Size Convention

*If we **don't apply periodic images**..*
 *- **Surface effect** become dominant*
 *- **PBC is applied to minimize it!***

But PBC can make another artifacts
 *- It is called **Finite Size Effect***
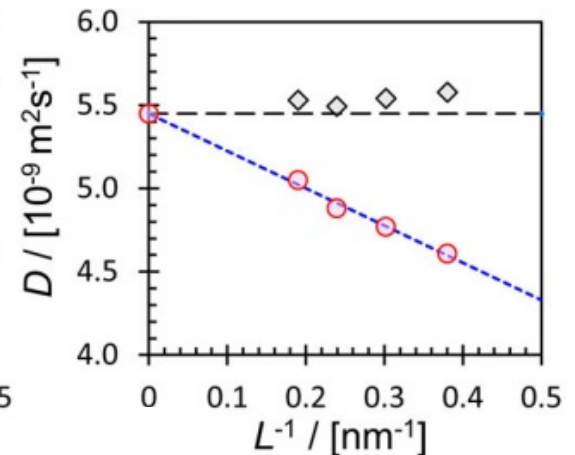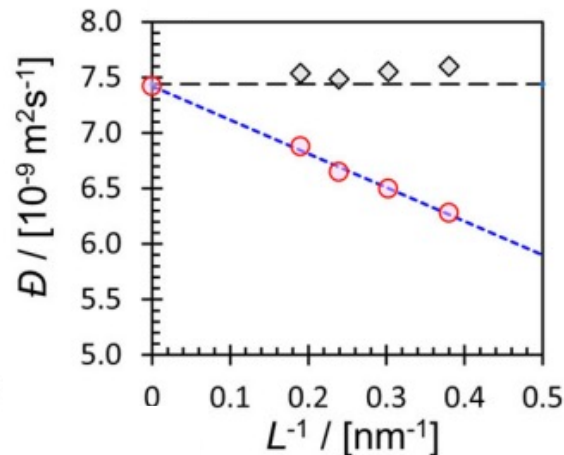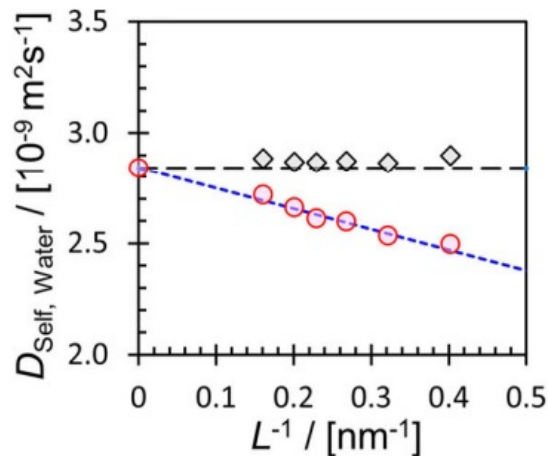 *- Due to the **artificial external** environments*

Examples of Finite Size Effect

- Diffusion Coefficient(And its correction)

$$D_{\text{Self}}^{\infty} = D_{\text{Self}}^{\text{MD}} + \frac{k_{\text{B}} T \xi}{6 \pi \eta L}$$ *- Self Diffusion Coefficient*

$$D_{\text{Rot}}^{\infty} = D_{\text{Rot}}^{\text{MD}} + \frac{k_{\text{B}} T}{6 \eta V}$$ *- Rotational Diffusion Coefficient*

$$Đ^{\infty} = Đ^{\text{MD}} + \left(\frac{1}{\Gamma}\right) \frac{k_{\text{B}} T \xi}{6 \pi \eta L} = Đ^{\text{MD}} + \left(\frac{1}{\Gamma}\right) D^{\text{YH}}$$ *- MS Diffusivity(Binary Mixture)*

Celebi, A. T., Jamali, S. H., Bardow, A., Vlugt, T. J., & Moultos, O. A., Finite-size effects of diffusion coefficients computed from molecular dynamics: a review of what we have learned so far. *Mol. Sim.*, **2021**, *47*(10-11), 831-845.

1. Periodic Boundary Condition(PBC) & Finite Size Effect

Examples of Finite Size Effect

- Thermal Conductivity
- Solvation Energy
- …

The main reasons of these artifacts
1) Periodic images significantly affect the simulation box
2) Non-periodic nature of the real phenomenon

We have to set the proper size of simulation box to secure the accuracy and efficiency of computation!

2. *Computational Algorithms* *for Nonbonded Energy Calculation*

$$U(R) = \sum_{bonds} k_r (r - r_{eq})^2 \qquad \text{bond}$$

$$+ \sum_{angles} k_\theta (\theta - \theta_{eq})^2 \qquad \text{angle}$$

$$+ \sum_{dihedrals} k_\phi (1 + \cos[n\phi - \gamma]) \qquad \text{dihedral}$$

$$+ \sum_{impropers} k_\omega (\omega - \omega_{eq})^2 \qquad \text{improper}$$

$$+ \sum_{i<j}^{atoms} \varepsilon_{ij} \left[\left(\frac{r_m}{r_{ij}} \right)^{12} - 2 \left(\frac{r_m}{r_{ij}} \right)^6 \right] \qquad \text{van der Waals}$$

$$+ \sum_{i<j}^{atoms} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \qquad \text{electrostatic}$$

Bonded Energy

- *Easy and clear to compute*

- *Short-range Interaction*

- *Low time complexity*

Nonbonded Energy

- *Difficult to compute*

- *Long-range Interaction*

- *High time complexity*

Van-der Walls energy(Rapidly decay, ~ r^{-6})
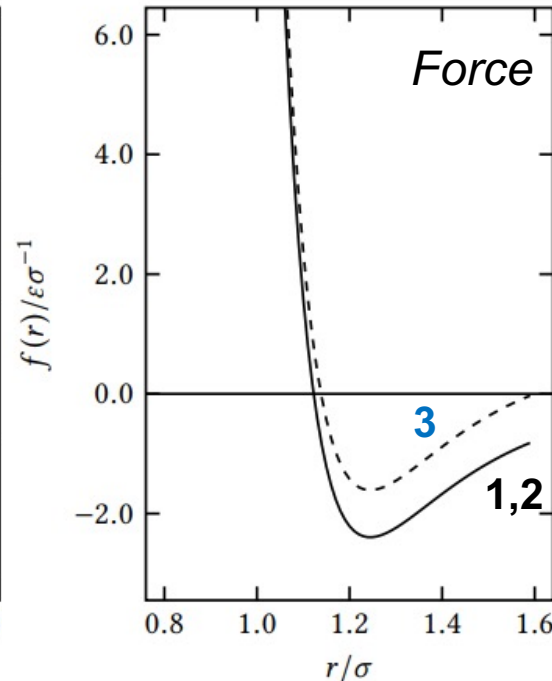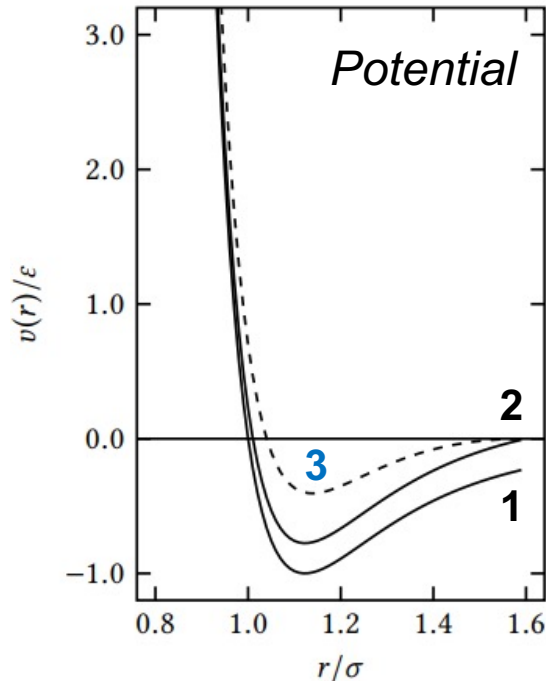- *Cutoff energy*

Electrostatic energy(Slowly decay, ~ r^{-1})
- *Cutoff unavailable*
- *PME, PPPM, Reaction Field, FMM, …*

7

2. *Computational Algorithms* for Nonbonded Energy Calculation

Van-der Walls energy

Potential

Force

1. *Lennard-Jones Potential*

$$v^{LJ}(r) = 4\epsilon\left[(\sigma/r)^{12} - (\sigma/r)^6\right]$$

2. *Shifted Lennard-Jones*

$$v^S(r_{ij}) = \begin{cases} v(r_{ij}) - v_c & r_{ij} \leq r_c \\ 0 & r_{ij} > r_c \end{cases}$$

3. Shift-force potential

$$v^{SF}(r_{ij}) = \begin{cases} v(r_{ij}) - v_c - (r_{ij} - r_c)\left(\dfrac{dv(r_{ij})}{dr_{ij}}\right) & (r_{ij} \leq r_c) \\ 0 & (r_{ij} \geq r_c) \end{cases}$$

1. *Zero potential after r_c*
2. *Continuous & Differentiable potential function*

Allen, M. P., & Tildesley, D. J., Computer simulation of liquids. *Oxford university press.* **2017** 8

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Direct Coulomb Summation

$$E_{elec} = \frac{1}{2} \sum_{i=1}^{N} \sum_{j \neq i}^{N} \frac{q_i q_j}{r_{ij}}$$

Exact summation of all coulombic interaction
The most accurate, but also **the most expensive one($O(N^2)$)**
Moreover, it has **low scalability** to parallelize this algorithm

Alternative approach to make efficient algorithms

Particle Mesh Ewald(PME) Method

Particle – Particle/Particle-Mesh(PPPM) Method

Reaction Field Method

Fast Multipole Method

(OpenMM utilizes sPME & Reaction Field Method)

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Particle Mesh Ewald(PME) Method(Idea)

Sum of Coulombic energy = real space sum + reciprocal space sum
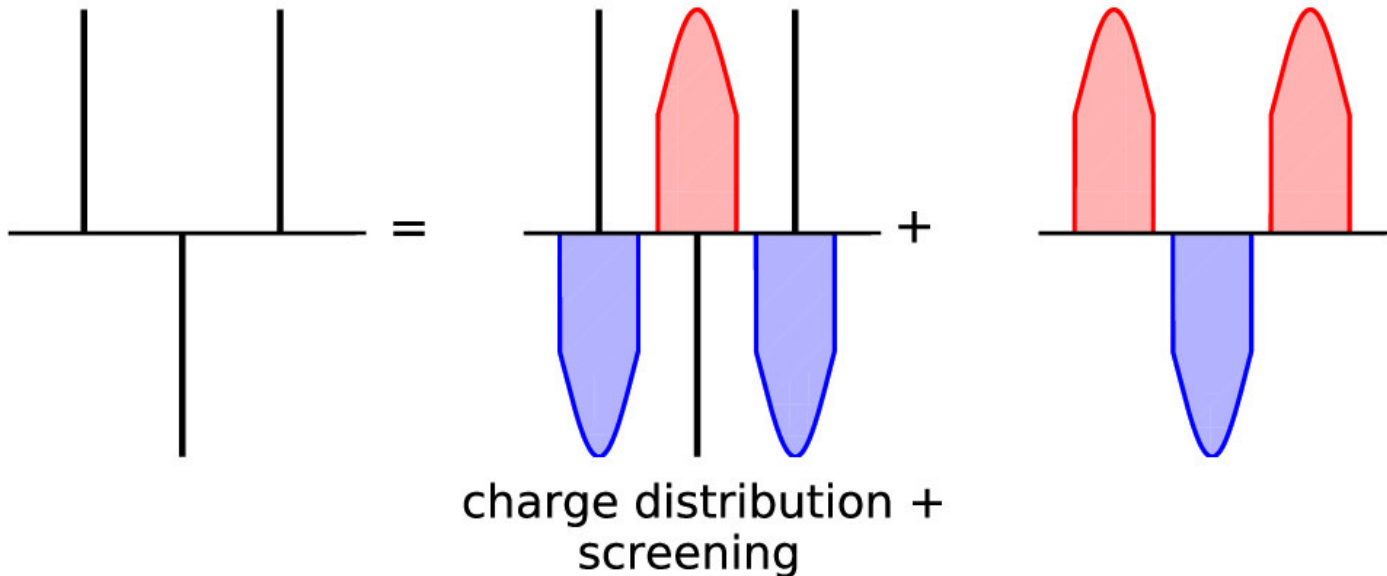
Stenberg, S., & Stenqvist, B., An exact Ewald summation method in theory and practice. *The Journal of Physical Chemistry A,* **2020**,*124(*19*),* 3943-3946.

Narrow distribution in real space : Broad distribution of reciprocal space
Broad distribution in real space : Narrow distribution of reciprocal space

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Particle Mesh Ewald(PME) Method(Formalism & Performance)

$$E_{dir} = \frac{1}{2} \sum_{n}^{*} \sum_{i,j=1}^{N} \frac{q_j q_j \, \mathrm{erfc}(\beta |\mathbf{r}_j - \mathbf{r}_i + \mathbf{n}|)}{|\mathbf{r}_j - \mathbf{r}_i + \mathbf{n}|},$$ *Direct space summation*

$$E_{rec} = \frac{1}{2\pi V} \sum_{\mathbf{m} \neq 0} \frac{\exp(-\pi^2 \mathbf{m}^2/\beta^2)}{\mathbf{m}^2} S(\mathbf{m}) S(-\mathbf{m}),$$ *Reciprocal space summation*

$$E_{corr} = -\frac{1}{2} \sum_{(i,j) \in M} \frac{q_i q_j \, \mathrm{erf}(\beta |\mathbf{r}_i - \mathbf{r}_j|)}{|\mathbf{r}_i - \mathbf{r}_j|} - \frac{\beta}{\sqrt{\pi}} \sum_{i=1}^{N} q_i^2$$ *Error correction(Self-interaction)summation*

$$S(\mathbf{m}) = \sum_{j=1}^{N} q_j \exp(2\pi i \mathbf{m} \cdot \mathbf{r}_j) = \sum_{j=1}^{N} q_j \exp[2\pi i (m_1 s_{1j} + m_2 s_{2j} + m_3 s_{3j})]$$ *(Structure Factor)*

*Essmann, U., Perera, L., Berkowitz, M. L., Darden, T., Lee, H., & Pedersen, L. G., A smooth particle mesh Ewald method. The Journal of chemical physics, **1995**, 103(19), 8577-8593.*

Time Complexity : O(NlogN)
Accuracy : Medium accuracy, Depending on α(Ewald splitting parameter)
Scalability : High(3D Discrete Fast Fourier Transform)

*George, A., Mondal, S., Purnaprajna, M., & Athri, P., Review of Electrostatic Force Calculation Methods and Their Acceleration in Molecular Dynamics Packages Using Graphics Processors. ACS omega, **2022**, 7(37), 32877-32896.*

11

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Particle Mesh Ewald(PME) Method(PME vs sPME)

$$S(\mathbf{m}) = \sum_{j=1}^{N} q_j \exp(2\pi i \mathbf{m} \cdot \mathbf{r}_j) = \sum_{j=1}^{N} q_j \exp[2\pi i(m_1 s_{1j} + m_2 s_{2j} + m_3 s_{3j})]$$ *(Structure Factor)*

$$\exp(2\pi i \mathbf{m} \cdot \mathbf{r}) = \exp\left(2\pi i \frac{m_1 u_1}{K_1}\right) \cdot \exp\left(2\pi i \frac{m_2 u_2}{K_2}\right) \cdot \exp\left(2\pi i \frac{m_3 u_3}{K_3}\right)$$

Approximation of Structure Factor I : Lagrangian Interpolation(PME)

$$\exp\left(2\pi i \frac{m_\alpha}{K_\alpha} u_\alpha\right) \approx \sum_{k=-\infty}^{\infty} W_2(u_\alpha - k) \cdot \exp\left(2\pi i \frac{m_\alpha}{K_\alpha} k\right)$$

$$W_{2p}(u) = \frac{\Pi_{j=-p, j \neq k}^{p-1}(u+j-k)}{\Pi_{j=-p, j \neq k}^{p-1}(j-k)}$$

for $k \leqslant u \leqslant k+1, k = -p, -p+1, \ldots, p-1$

Approximation of Structure Factor II : Cardinal B-Spline(sPME)

$$\exp\left(2\pi i \frac{m_i}{K_i} u_i\right) \approx b_i(m_i) \sum_{k=-\infty}^{\infty} M_n(u_i - k) \cdot \exp\left(2\pi i \frac{m_i}{K_i} k\right)$$

Implemented in OpenMM

$$M_n(u) = \frac{u}{n-1} M_{n-1}(u) + \frac{n-u}{n-1} M_{n-1}(u-1) \qquad b_i(m_i) = \exp(2\pi i(n-1)m_i/K_i) \times \left[\sum_{k=0}^{n-2} M_n(k+1)\exp(2\pi i m_i k/K_i)\right]^{-1}$$

Essmann, U., Perera, L., Berkowitz, M. L., Darden, T., Lee, H., & Pedersen, L. G., A smooth particle mesh Ewald method. *The Journal of chemical physics*, **1995**, *103*(19), 8577-8593.

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Particle – Particle/Particle – Mesh(PPPM) Method

Based on Ewald sum(dividing short range/long range interaction + FFT)
Short range : particle-particle & Long range : particle-mesh

$$\psi_s(\zeta_{ij}) = \frac{1}{4\pi\epsilon_0}\left(\frac{1}{r_{ij}} - \frac{1}{70a}\sum_{n=-1}^{7} C_n\zeta_{ij}^n\right)\zeta_{ij} < 2 \qquad \text{Short range interaction}$$

$$\hat{\psi}(k) = \hat{\gamma}\frac{(k)^2}{\epsilon_0 k^2}\hat{\rho}(k) = \hat{G}(k)\hat{\rho}(k) \qquad \text{Long range interaction}$$

$$\zeta_{ij} = \frac{2r_{ij}}{a} \quad \gamma(r) = \begin{cases} \frac{48}{\pi a^4}\left(\frac{a}{2} - r\right) & r < \frac{a}{2} \\ 0 & r > \frac{a}{2} \end{cases}$$

Time Complexity : O(NlogN)
Accuracy : High accuracy, More than PME
Scalability : Medium(Increase of long-range part make lower scalability)

George, A., Mondal, S., Purnaprajna, M., & Athri, P., Review of Electrostatic Force Calculation Methods and Their Acceleration in Molecular Dynamics Packages Using Graphics Processors. *ACS omega, 2022, 7(37),* 32877-32896.

13

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Reaction Field Method(*Idea*)
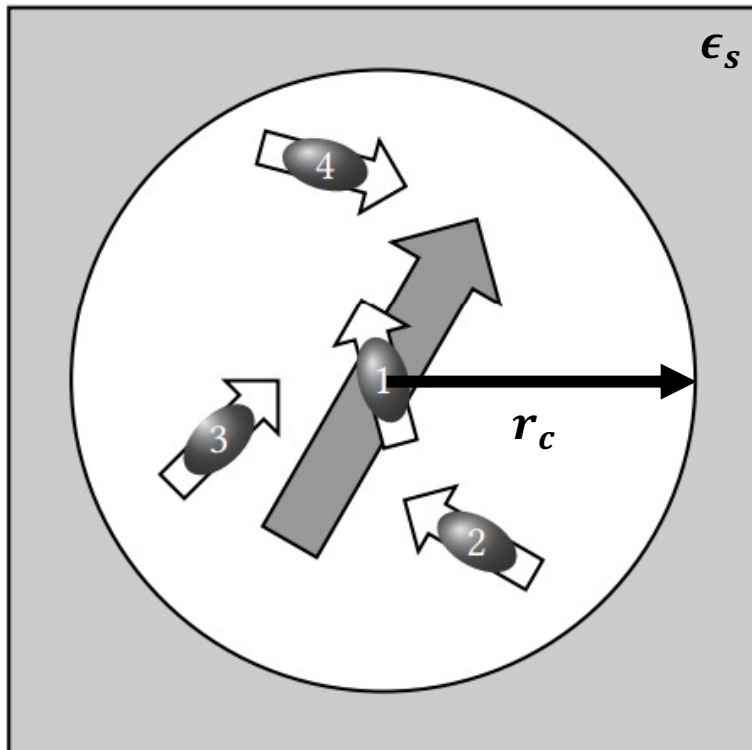
**Spherical Truncation($r < r_c$)
+ Dielectric Continuum Outside**

Explicit interaction weighting

$$f(r_{ij}) = \begin{cases} 1.0 & r_{ij} < r_t \\ (r_c - r_{ij})/(r_c - r_t) & r_t \leq r_{ij} \leq r_c \\ 0.0 & r_c < r_{ij} \end{cases}$$

$$(r_t \sim 0.95 r_c)$$

Reaction field acting on molecule i

$$\mathcal{E}_i = \frac{2(\epsilon_s - 1)}{2\epsilon_s + 1} \frac{1}{r_c^3} \sum_{j \in \mathcal{R}} \boldsymbol{\mu}_j$$

Allen, M. P., & Tildesley, D. J., Computer simulation of liquids. *Oxford university press.* **2017**

14

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Reaction Field Method(*Formalism*)

$$\mathcal{V}^{qq} = \frac{1}{2} \sum_{i=1}^{N} \sum_{\substack{j, I \neq J \\ R_{IJ} < r_c}}^{N} q_i q_j \left[\frac{1}{r_{ij}} + \left(\frac{\epsilon_s - 1}{2\epsilon_s + 1} \frac{r_{ij}^2}{r_c^3} + C \right) \right] + \mathcal{V}_{\text{Born}} + \mathcal{V}_{\text{self}}$$

$$\mathcal{V}_{\text{Born}} = -\frac{1}{2} \left(\frac{\epsilon_s - 1}{\epsilon_s} \right) \frac{1}{r_c} \sum_{i=1}^{N} q_i \sum_{\substack{j \\ R_{IJ} < r_c}}^{N} q_j \qquad \mathcal{V}_{\text{self}} = \frac{1}{2} \sum_{i=1}^{N} \sum_{j \in I}^{N} q_i q_j \left(\frac{\epsilon_s - 1}{2\epsilon_s + 1} \frac{r_{ij}^2}{r_c^3} + C \right) \qquad C = -\frac{1}{r_c} \left[1 + \frac{\epsilon_s - 1}{2\epsilon_s + 1} - \frac{\epsilon_s - 1}{\epsilon_s} \right]$$

Linearized Poisson-Boltzmann Equation

$$\mathcal{V}^{qq} = \frac{1}{2} \sum_{i=1}^{N} \sum_{\substack{j \neq i \\ r_{ij} < r_c}} q_i q_j \left[\frac{1}{r_{ij}} - \frac{(1 + B_1) r_{ij}^2}{2 r_c^3} \right]$$

$$B_1 = \frac{(1 - 4\epsilon_s)(1 + \kappa r_c) - 2\epsilon_s (\kappa r_c)^2}{(1 + 2\epsilon_s)(1 + \kappa r_c) + \epsilon_s (\kappa r_c)^2}$$

Time Complexity : O(N)
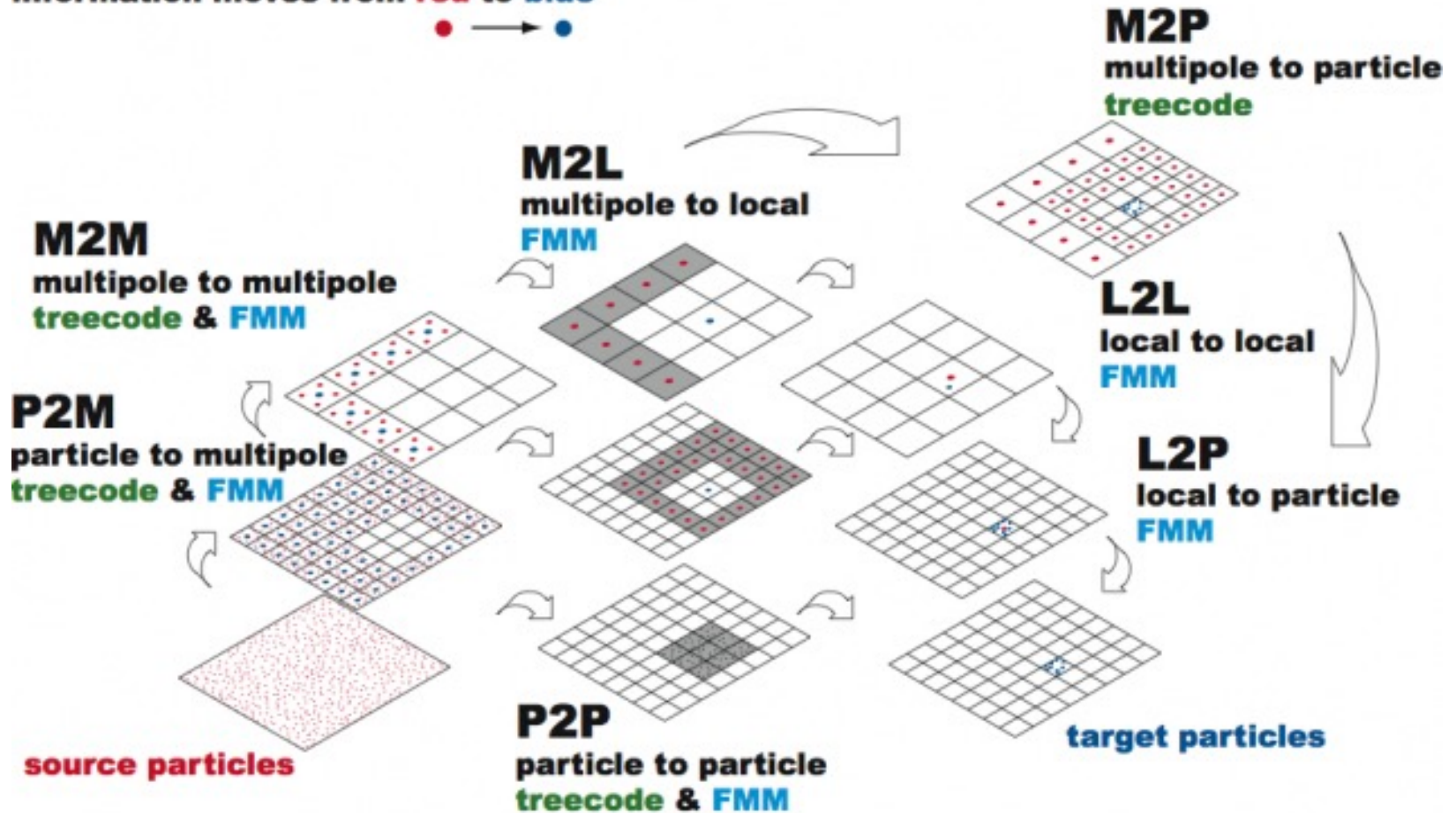**Accuracy : Low accuracy**
Scalability : High

Reaction Field Method is Implemented in OpenMM

Allen, M. P., & Tildesley, D. J., Computer simulation of liquids. *Oxford university press.* **2017**

15

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Fast Multipole Method(Idea)

Yokota, R., & Barba, L. A., GPU Computing Gems Emerald Edition, chapter 9:
Treecode and fast multipole method for N-body simulation with CUDA, **2011**.

2. *Computational Algorithms* for Nonbonded Energy Calculation

Electrostatic Interaction

Fast Multipole Method(Formalism & Performance)

Potential

$$\phi(\mathbf{r}) = \sum_{\ell=0}^{\infty} \sum_{m=-\ell}^{m=\ell} M_{\ell,m} \, G_{\ell,m}(\mathbf{r}) \qquad G_{\ell,m}(\mathbf{r}) = \frac{(-1)^{\ell-m}(\ell-m)!}{r^{\ell+1}} \exp(im\varphi) P_{\ell,m}(\cos\theta).$$

Solution

$$M_{\ell,m} = \sum_{i=1}^{N} q_i F_{\ell,m}^*(-\mathbf{r}_i), \qquad F_{\ell,m}(\mathbf{r}) = \frac{(-1)^{\ell-m} r^\ell}{(\ell+m)!} \exp(im\varphi) P_{\ell,m}(\cos\theta).$$

Time Complexity : O(N), *top 10 algorithms in 20th century*
Accuracy : Medium *accuracy*
Scalability : High, *One of the most scalable algorithm*

FMM is Implemented in GROMACS

3. Why we use PME(Particle-Mesh-Ewald)? & Artifacts of PME

Why we use PME nowadays?

1. Low complexity(O(NlogN))   2. Quite high accuracy   3. High scalability

4. Traditionally utilized   5. Easy to parametrize

Limits & Artifacts of PME

1. Only appliable in charge neutral system

2. In non-neutral system, uniform background charge distribution to compensate the charge of the system is applied.

3. The background charge induces artifacts related to dielectric constant in inhomogeneous system

    Ex) Over-stabilization of ions in low-dielectric medium

3. Why we use PME(Particle-Mesh-Ewald)? & Artifacts of PME

Limits & Artifacts of PME

1. Only appliable in charge neutral system

2. In non-neutral system, uniform background charge distribution to compensate the charge of the system is applied.

$$E_{elec} = E_{real} + E_{recip} + E_{back} - E_{self}$$

$$E_{real} = \frac{1}{2} \sum_{i \neq j} \sum q_i \phi_{real} \qquad E_{recip} = \frac{1}{2} \sum_k \tilde{\rho}_{recip} \tilde{\phi}_{recip} \, exp(i\boldsymbol{kr_i})$$

$$= \frac{1}{2} \sum_k (\tilde{\rho}_{back} + \tilde{\rho}_{smooth}) \tilde{\phi}_{recip} \, exp(i\boldsymbol{kr_i})$$

$$E_{back} = \frac{1}{2} \int_V \rho_{back} \phi_{real} \, d\boldsymbol{r} = \frac{\pi q_{tot}^2}{2V\alpha}$$

$$\boxed{= \frac{1}{2} \sum_k \tilde{\rho}_{smooth} \tilde{\phi}_{recip} \, exp(i\boldsymbol{kr_i})}$$

Infinite sum
Low convergence

Ewald sum will converge, but the energy will be depend on non-physical parameter α

ρ_{back} *is constant,* $\tilde{\rho}_{back} \tilde{\phi}_{recip} = 0 \; for \; k \neq 0$

Also, $\tilde{\rho}_{recip} \tilde{\phi}_{recip} (k = 0) = \int \rho_{recip} \, dV = 0$

3. Why we use PME(Particle-Mesh-Ewald)? & Artifacts of PME

Limits & Artifacts of PME

3. The background charge induces artifacts related to dielectric constant in inhomogeneous system

Utilizing PME method with non-neutral system : Technically possible

However, constant dielectric environment gives significant artifacts for heterogeneous dielectric environment
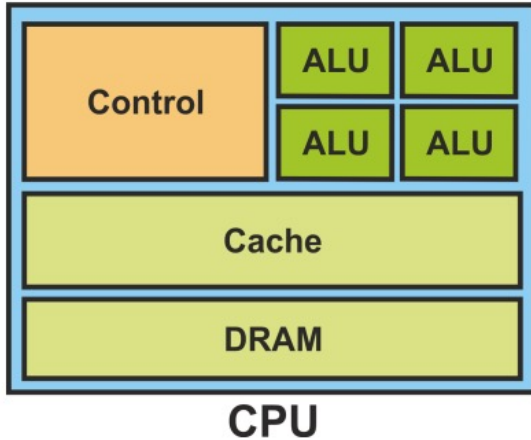
Ex) proteins solvated in water, membrane solvated in water

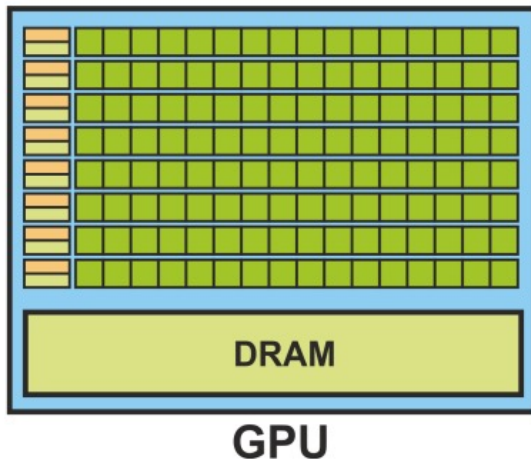**Real system : nonuniform counter charge distribution, generates electrostatic gradients**
PME w/ non-neutral system : No electrostatic gradient

4. *GPU parallelization* of Nonbonded Energy Computation

CPU vs GPU

- Central Processing Unit
- Serial cores
- Low latency
- Good for serial processing
- Can do handful of operation at once

- Graphic Processing Unit
- Many cores
- High throughput
- Good for parallel processing
- Can do thousands of operation at once

Paz, A., & Plaza, A., A new morphological anomaly detection algorithm for hyperspectral images and its GPU implementation. In Satellite Data Compression, Communications, and Processing VII(Vol. 8157)., *SPIE*, **2011**

4. *GPU parallelization* of Nonbonded Energy Computation

GPU Acceleration

It is based on the principle of parallel computing

Scalability is the important factor to make the parallel computing better

Table 1. Summary of Comparisons between Different Electrostatic Force Calculation Algorithms (EFC Alg.)[a]

EFC Alg.	complexity	accuracy	scalability	boundary conditions
DCS	$O(NQ)$[60]	Highest[47]	Low[47]	NPC, PC
MSM	$O(N + Q)$[33]	Medium[33]	High[33]	PC, SPC, NPC
P^3 M	$O(N \log N)$[67]	High[32]	Medium[69,70]	PC
PME	$O(N \log N)$[32]	Medium[60,61]	High[62,63]	PC
FMM	$O(N)$[79,80]	Medium[77,78,82]	High[81]	NP, PC

[a]NPC stands for nonperiodic conditions, PC for periodic conditions, and SPC for semiperiodic conditions.

George, A., Mondal, S., Purnaprajna, M., & Athri, P., Review of Electrostatic Force Calculation Methods and Their Acceleration in Molecular Dynamics Packages Using Graphics Processors. *ACS omega, **2022**, 7(37),* 32877-32896.

Takeaways

■ For computing energy in molecular simulation box, PBC *is applied to prevent excess surface effect in the system. Sometimes artificial environment from PBC induce artifacts of simulation*

■ Several algorithms to compute high-cost nonbonded energy were developed(Cutoff, PME, PPPM, FMM, Reaction Field).

■ Nowadays, PME is the most used algorithm for nonbonded energy calculation due to its performance. However, PME has several limitations and artifacts.

■ GPU can accelerate nonbonded computation. To utilize GPU for it, scalability of computing algorithms matters.

Thank you for your kind attention / Q&A