

$$W_{FD}(n) = \prod_j N_{sel} = \prod_j \frac{g_j!}{n_j!(g_j - n_j)!}$$

$$W_{BE}(n) = \prod_j N_{dis} = \prod_j \frac{(n_j + g_j - 1)!}{n_j!(g_j - 1)!}$$

$$W_{MB}(n) = \prod_j \frac{g_j^{n_j}}{n_j!}, \text{ where } \frac{g_j!}{(g_j - n_j)!} \approx \frac{(g_j + n_j - 1)!}{(g_j - 1)!} \approx g_j^{n_j}$$

**Distribution Functions** Use Stirling and differentiate

$$\frac{\partial}{\partial n_i} \ln W_{FD}(n) = \ln \frac{g_i - n_i}{n_i} = \ln(f_{FD,i}^{-1} - 1)$$

$$\frac{\partial}{\partial n_i} \ln W_{BE}(n) = \ln \frac{n_i + g_i - 1}{n_i} = \ln(f_{BE,i}^{-1} + 1)$$

$$\frac{\partial}{\partial n_i} \ln W_{MB}(n) = \ln \frac{g_i}{n_i} = \ln f_{MB,i}^{-1}$$

where  $f_{FD,i} = \frac{n_i}{g_i}, f_{BE,i} = \frac{n_i}{g_i - 1}$  and  $f_{MB,i} = \frac{n_i}{g_i}$

Max.  $W$ , Lagrange multipliers ( $\beta = \frac{1}{k_B T}, \alpha = \frac{\mu}{k_B T} = -\beta\mu$ )

$$\frac{\partial}{\partial n_i} \left( \ln W(n) - \alpha \sum_j n_j - \beta \sum_j n_j \varepsilon_j \right) = 0, \forall i$$

$$\Rightarrow \begin{cases} f_{FD,i} = \frac{1}{e^{\alpha + \beta \varepsilon_i} + 1} = \frac{1}{e^{\beta(\varepsilon_i - \mu)} + 1} \\ f_{BE,i} = \frac{1}{e^{\alpha + \beta \varepsilon_i} - 1} = \frac{1}{e^{\beta(\varepsilon_i - \mu)} - 1} \text{ singular at } \varepsilon_i = \mu \\ f_{MB,i} = e^{-\alpha - \beta \varepsilon_i} = Z^{-1} \cdot e^{-\beta \varepsilon_i} \text{ with } Z = e^{-\beta \mu} \end{cases}$$

**Pauli Exclusion Principle** There cannot be more than one fermion in a given quantum state, unconstrained for bosons. At limit  $T \rightarrow 0$

- FD: all levels  $\varepsilon_0$  to  $\varepsilon_F := \lim_{T \rightarrow 0} \mu$  occupied with 1 Fermion each
- BE: all particles at lowest level  $\varepsilon_0 = \mu$

## MD

**Biomolecules** Amino acids, Carbohydrates (Monosaccharides, Disaccharides), Lipids (amphiphilic), Nucleic acids, DNA/RNA **Environment** ions, water (high  $C_w$ , dipole moment, H-bonding capacity) **Protein** have **secondary structure** ( $\alpha$ -helix,  $\pi$ -helix,  $\beta$ -sheets) representation  $\odot$  *Van der Waals* spheres  $\odot$  Caroon representation for only backbones (with torsional angles) **MD** Num integration over the classical EOM (Newton), Cartesian coord. Simulating biological system  $\leftrightarrow$  solving the many-particle problem

## Degrees of Freedom - Coarse-grain (CG) model

**QM description (with electrons)**, valid when small systems (100 atoms). Negligible QM effects in large systems.

**CG models** reduce DOFs & interactions while  $\odot$  align with research needs  $\odot$  eliminate mostly decoupled DOFs.  $\odot$  remained DOF easily representable.  $\odot$  Less transferability, altered physics, unphysical entropy/energy balance.  $\odot$  speedup

**United Atoms, Shared non-essential DOFs** (e.g. H atoms in lipids)  $\odot$  replace functional groups (CH, CH<sub>2</sub>) with larger atoms  $\odot$  Not for strong hydrogen-bonding atoms (O, N, S, P).

## Supra-atomic:

- Iterative boltzmann inversion** reproduces structure, not forces
- Force matching** reproduces forces, not structure. Compute  $F_{avg}$  on mapped atoms for each CG bead  $\rightarrow$  least-square match force distributions with effective pair potentials
- Fitting to Thermodynamic Properties (MARTINI)**: Start with atomistic guesses, then systematically scan parameters.  $\odot$  Can lead to loss of essential DOFs and may require elastic networks for maintaining protein 2nd, tertiary structures.

## Interactions in Classical Atomistic Force Fields (FF)

**Classical FF**  $\mathcal{V}^{phys}(r^N)$ , with  $r^N = (r_1, r_2, \dots, r_N)$

often underdetermined, too many parameter/experimental data lacks  $\mathcal{V}(r^N) = \mathcal{V}^{phys}(r^N) + \mathcal{V}^{special}(r^N)$ . Special terms from NMR data, biased sampling. Physical terms (if two atoms  $\rightarrow$  ignore the S):

$$\mathcal{V}^{bond}(r^N) = \sum_{i \text{ bonds}} \frac{1}{2} K_i^b [b_i(r^N) - b_i^0]^2$$

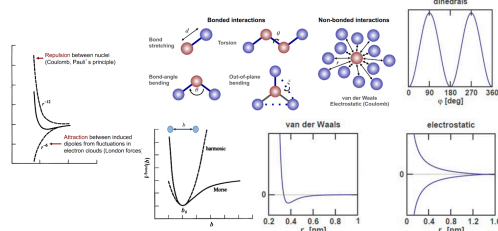
$$\mathcal{V}^{angle}(\theta) = \sum_{i \text{ angles}} \frac{1}{2} K_i^\theta [\theta_i - \theta_i^0]^2$$

$$\mathcal{V}^{torsion}(r^N) = \sum_{i \text{ torsions}} K_i^\varphi [1 + \cos(m_i \varphi_i(r^N) - \delta_i)]^2$$

$$\mathcal{V}^{vdW}(r^N) = \sum_{\text{pairs } i < j} 4 \varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]$$

$$\mathcal{V}^{ele}(r^N) = \sum_{\text{pairs } i < j} \frac{1}{4\pi \varepsilon_0 \varepsilon_r} \frac{q_i q_j}{r_{ij}}$$

and N-body polar. energy  $\mathcal{V}^{pol}$ , external fields energy  $\mathcal{V}^{ext}$



**Non-bonded** elec, vdW as interactions of atoms independent of net charge. (Repulsion (short-range forces) of nuclei (Coulomb, Pauli's principle), Attraction (long-range forces) of induced dipoles from fluctuations in electron clouds (London forces), LJ used to approximate vdW)

**\*vdW\* strong short-range repulsion upon atom overlap (Pauli exclusion) & longer-range attraction by electron correlation (instantaneous dipole-dipole interactions, termed London dispersion)**

$$V_{SW}(r; r_0) = C_{12}(r_0 - r)^{-12} - C_6(r_0 - r)^{-6}$$

**Bonded** bonds, angles torsions, improper dihedrals

**Morse function** for covalent bond stretching  $\odot$  bond-break (dissociation) possible  $\odot$  comp. expensive  $b_{ij}$ : length of the bond between atoms  $i$  and  $j$

$$\mathcal{V}^{Morse}(r(t); D_n; K_n^b; b_n^0) = \sum_n \left\{ 1 - e^{-\left[ \left( \frac{K_n^b}{D_n} \right)^{\frac{1}{2}} (b_n(t) - b_n^0) \right]} \right\}^2$$

**Harmonic** approximation  $\odot$  simple, cheap  $\odot$  no dissociation

$$\mathcal{V}^{harm}(r(t); K_n^b; b_n^0) = \sum_n \frac{1}{2} K_n^b (b_n(t) - b_n^0)^2$$

**Effective FF (Parameterized)**  $\odot$  simple with few terms, **efficient** with no complex derivatives and exponential terms and parameters **transferable** for a range of molecules

## Configuration Generation

High-dimensional space; global minimum impractical. **Goal** Generate low-energy, Boltzmann-weighted IC/configurations  $\odot$  Search: Find and minimize low-energy regions.  $\odot$  Sample: Explore configurations (metropolis MC, modified MD with biasing).  $\odot$  Simulate: Use dynamics (MD, SD, BD).

## Key properties of the required method

	Search	Sample	Simulate
<b>B</b>	×	✓	✓
<b>P</b>	×	×	✓

- Boltzmann-weighted ensemble**: thermodynamic properties can be calculated
- Physically-based sequence** of configurations through classical EOM: dynamic properties can be calculated

**Init Coordinates** Specified  $E_{pot}$ . Choose carefully (e.g., X-ray/NMR) unless longer equilibration than conformational relaxation time. **Init Velocities** Specified  $E_{kin}$ , generally unimportant due to fast relaxation (ps), useful for initial  $E$ . Random from  $f_{MB}$  at some  $T$ . **Bond-Length Constraints** freeze bond vibrations, valid if bonds weakly coupled, in ground state.  $\odot$  frozen bonds allow  $\Delta t \rightarrow 2$  fs (before 0.5 - 1 fs for fast vibration)

**Integrators** good accuracy, conservation of properties compatible with thermo/barostating (symplectic, phase-space-volume preserving), reversible in time.

**Timestep**  $\Delta t \approx \frac{\tau}{10} \approx \frac{\text{period of fastest motion}}{10}$ . **Tradeoff** Too short poor sampling, too long poor energy conservation & overflow

Not time reversible **Euler**, error  $O(\Delta t^2)$ . **RK**, error  $O(\Delta t^4)$ .

Time-reversible **leap-frog**, symplectic, error  $O(\Delta t^3)$  in both coordinates and velocities. Interleaving cancels out leading error term  $O(\Delta t^2)$

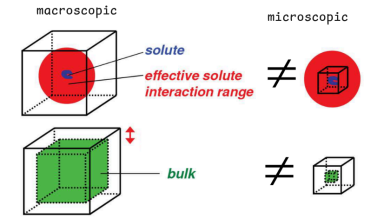
$$v\left(t + \frac{1}{2}\Delta t\right) = v\left(t - \frac{1}{2}\Delta t\right) + a(t)\Delta t$$

$$r(t + \Delta t) = r(t) + v\left(t + \frac{1}{2}\Delta t\right)\Delta t$$

**SHAKE** in Cartesian  $\odot$  easy geometric constraints, existing iterative methods  $\odot$  large movement within one timestep has no convergence guarantee  $\rightarrow$  indicates bad simulation setup (skip energy minimization), timestep cannot be too long, lightest atom moves first (Newton's 3rd) **SHAKE how iterative** for multiple bonds iterate with relative tol  $10^{-4}$ , for a single bond  $\odot$  free-fight step (unconstrained)  $\odot$  coordinate resetting (SHAKE)

## Spatial BC

**Finite-size (FS)** due to microscopic nature, lack of solute-solvent interactions, cannot model intra-solute vdW/electrostatics. **Surface effect (SE)** system has a large surface-to-volume ratio, increased surface tension proportionally.



	FS	SE	
Vacuum	×	×	$\odot$ compactness, spherical shape, strong electrostatics
Implicit solvent	-	Large	$\odot$ cheap $\odot$ exact location of solute-solvent boundary, parameter-sensitive (charges, radii)
Finite system (droplet/solvent layer)	Large	×	$\odot$ $P$ too high, solvent evaporation, surface-layer artifacts, strong electrostatics
Periodic (most-used)	Large	$\heartsuit$ -	artificial anisotropy/periodicity, high effective concentration, expensive, FS still present!

**Finite-system BC** needs confinement potential (LJ wall to confine sample, prevent evaporation and mimic dispersion), orientation correction potential (prevents solvent preferential orientation & inhomogeneous distribution at surface  $\odot$  poorly transferable)

**Periodic BC** explicit-solvent, mimics infinite lattice of periodic copies of the reference box. Particles exit box through one face translated and reenter through opposite. Infinite surface  $\rightarrow$  no SE. **Long-range interaction** evaluated using lattice-sum methods (Fourier), or **Minimum-image pair**, atom with closest periodic replica of another one with cut-off distance. Short-range like covalent easy to compute, act only between minimum images.

**Box shape rectangular prism** used for long (elongated), if rotates need **roto-translational constraint** since molecule otherwise interacts with its replica out-of-bound. **Hexagon** used for DNA, **cube** isotropic thus no roto-fix needed but requires much solvent, **octahedron** for spherical molecules, almost isotropic, less solvent. **Triclinic** for crystal, reshapeable

**Minimum solute-to-wall distance**  $\frac{R}{2}$  no solute atom interacts with solute atom in periodic copy,  $R$  no solvent molecule interacts with solute atom in two solute periodic copies.

## Thermodynamic BC

**Plain MD** microcanonical, Newtonian EOM conserves  $E_{tot}$  and  $L_{tot}$  in vacuum, if periodic rotation in each cell coupled with friction, no conservation of  $L_{tot}$ . Quantities  $T, P$  dependent, calculated as  $T = \langle \mathcal{T} \rangle, P = \langle \mathcal{P} \rangle$ , have non-zero fluctuations for finite-systems.

**Grand-canonical simulations**, no. particles vary (uncommon),  $\mu$  held constant on average  $\odot$   $\mu$  is not instantaneous observable, discrete variation  $\rightarrow$  jumps in dynamics, equilibration needed after each jump

**Thermo/Barostating Overview**  $\odot$  **Constraining** Fixes values exactly  $\odot$  Hamiltonian form, configuration distribution correct  $\odot$  unphysical, no fluctuations  $\odot$  **Weak-coupling (Berendsen)**  $\odot$  1-st order exponential relaxation (physical)  $\odot$  depends on thermostat coupling time (friction coeff  $\zeta_T = \frac{1}{2\tau_T} \frac{\sigma - K}{\chi}$ , unit: time<sup>-1</sup>), only approx canonical  $\odot$  **Extended**

**system (Nosé-Hoover)**  $\dot{C}_T = \frac{1}{T^2}(\frac{X}{K} - 1)$  own EOM,  $X > K$ , friction  $\uparrow$ ,  $\hookrightarrow$  simple, cheap, no derivatives of  $\mathcal{V}$ , efficient unphysical (but reversible) moves can be designed for improved sampling  $\hookrightarrow$  non-deterministic, no dynamic information, hard to design params (acceptance ratio etc.)

**brakes particles**  $\sim \Delta \mathcal{X}_{rel} \hookrightarrow$  2nd-order relaxation, canonical  $\hookrightarrow$  oscillatory (unphysical)  $\hookrightarrow$  **Stochastic**  $\hookrightarrow$  1-st order exponential relaxation, canonical, thermalization efficient, few artifacts  $\hookrightarrow$  non-deterministic, local thermostating (unphysical dynamics)

**Thermostat** To ensure  $E_{kin} = \mathcal{X}(t + \frac{\Delta t}{2}) = K$ , we scale the velocity  $\lambda = \left(\frac{\mathcal{X}(t - \frac{\Delta t}{2})}{\mathcal{X}(t + \frac{\Delta t}{2})}\right)^{\frac{1}{2}}$ , leapfrog  $v(t + \frac{\Delta t}{2}) = v(t - \frac{\Delta t}{2}) + M^{-1}F(t)\Delta t$

**Collision** within  $\tau_T$  period, pick & assign  $v \sim f_{MB}(T_{ref})$  of an atom randomly  $\Rightarrow \langle T \rangle = T_{ref}$

**Langevin EOM**  $m_i \ddot{r}_i = F_i(r(t)) + R_i(t) - m_i \gamma_i \dot{r}_i(t)$  results in  $\langle T \rangle = \frac{\langle R_i^2 \rangle}{6m_i \gamma_i k_B} = T_{ref}$

**Barostat**  $\mathcal{P} = P_{instan} > P_{target} \Rightarrow$  box  $V \uparrow$ , adjust coord

**Instan temperature** (equipart, at equilibrium  $\langle \mathcal{T} \rangle = T$ )

$$\mathcal{T} = \frac{2}{N_D k_B} \cdot \mathcal{X}$$

$$\langle \mathcal{X}_\alpha \rangle = \frac{1}{2} m_\alpha v_\alpha^2 = \frac{k_B T}{2} \xrightarrow{\text{set of dof}} \langle \mathcal{X} \rangle = \frac{3N}{2} \frac{N_D k_B T}{2}$$

**Instan pressure** (virial)

$$\mathcal{P} = \frac{2(\mathcal{X} - W)}{3\mathcal{V}} = \frac{N k_B \mathcal{T}}{\mathcal{V}} - \frac{2W}{3\mathcal{V}}$$

$$P = \left\langle \frac{2(\mathcal{X} - W)}{3\mathcal{V}} \right\rangle = \frac{\overbrace{N k_B \mathcal{T}}^{\text{ideal gas kinetic energy}}}{\mathcal{V}} - \frac{\overbrace{2W}}{\overbrace{3\mathcal{V}}}^{\text{intermolecular forces}}$$

**instan virial (isotropic)** intern forces, correction term

$$W = -\frac{1}{2} \sum_{i=1}^N \mathbf{r}_i \cdot \mathbf{F}_i > 0 \Rightarrow P \downarrow \text{ (attractive, pull inwards)}$$

long  $t_{sim}$  for good averaging,  $P$  highly fluctuating (1 bar fluc in order  $\sim$  100 bar)

Thermostat	Barostat
$\dot{\mathcal{N}} = 0$	$\dot{\mathcal{N}} = 0$
$\dot{\mathbf{r}} = \nabla_{\mathbf{p}} \mathcal{X}$	$\dot{\mathbf{r}} = \nabla_{\mathbf{p}} \mathcal{X} + \lambda \mathbf{r}$
$\dot{\mathbf{p}} = -\nabla_{\mathbf{r}} \mathcal{U} - \zeta_T \mathbf{p}$	$\dot{\mathbf{p}} = -\nabla_{\mathbf{r}} \mathcal{U} - \lambda \mathbf{p}$
$\dot{\mathcal{V}} = 0$	$\dot{\mathcal{V}} = 3\mathcal{V} \lambda$

**Equipartition Violation** (heterogeneous  $T$ )

- Hot/Cold-solvent** (hetero. spatial regions) solvent subjected to more heating than solute and  $E_{kin}$  exchanged slowly, correct  $\bar{T}$  but solute simulated to be colder than solvent  $\rightarrow$  couple solute and solvent dof to separate thermostats
- Vibrationally-cold gas** (hetero. dof) translation, rotation, vibration modes coupled to the same thermostat should have diff. temp in an ideal gas  $\rightarrow$  couple diff modes to separate thermostats or use stochastic approach

**Uncoupled DOF Issues:** Exclude linear/angular momentum from temperature/pressure calculations to avoid errors (e.g., flying ice-cube effect). Linear Momentum has no effect on system property (Move a glass of water  $\nRightarrow T \uparrow$ ), Angular Momentum (centrifugal forces).

## Calculation of Properties

### MC Sampling

**Stochastic Dynamics** mimics following effects without explicit solvent molecules, samples NVT.

**Mean Solvent Effect** thermodynamics, dispersive attraction reduced in non-polar solvent, enhanced in polar solvents (hydrophobic)

**Stochastic Collisions** dynamics, random but constrained forces on solute atoms from solvent.

**Friictional Drag** dynamics, solvent-induced friction reduces solute atom velocities.

$$\text{Langevin } m_i \ddot{r}_i = \underbrace{F_i}_{\text{mean force}} - \underbrace{m_i \gamma_i \dot{r}_i}_{\text{frictional force}} + \underbrace{\sigma_i \eta_i}_{\text{stochastic force}}$$

$\eta_i = \eta_i(t) \sim \mathcal{N}$  white-noise in unit of  $\text{time}^{-\frac{1}{2}}$ , stochastic force amplitude  $\sigma_i$  (unit: force  $\times$  time $^{\frac{1}{2}}$ ),  $\gamma$  (unit  $\text{time}^{-1}$ )

$$m \frac{dv}{dt} = F - m\gamma v + \sigma \eta$$

$$v(t) = e^{-\gamma t} \left[ v(0) + m^{-1} \int_0^t dt' \cdot e^{\gamma t'} (F(t') + \sigma \eta(t')) \right]$$

- Zero-friction limit ( $\gamma = 0, \sigma = 0$ )  $\leftrightarrow$  Newton equation of MD
- High-friction limit  $\leftrightarrow$  Brownian Dynamics

**Brownian Dynamics (BD)** valid microscopically with low Re viscosity dominates turbulent flow, derivable from Langevin

$$\begin{aligned} m_i \ddot{r}_i &= F_i - m_i \gamma_i \dot{r}_i + \sigma_i \eta_i \\ \Leftrightarrow m_i \gamma_i \dot{r}_i &= F_i + \sigma_i \eta_i \end{aligned}$$

we neglect inertial term by setting the RHS to zero at the limit where  $|m_i \ddot{r}_i| \ll |m_i \gamma_i \dot{r}_i|$

**Fokker-Plank (FP)** with SDE  $\dot{x}(t) = A(x, t) + B(x, t)\eta(t)$

$$\dot{p}(x, t) = \left( -\frac{\partial}{\partial x} A(x, t) \times + \frac{1}{2} \frac{\partial^2}{\partial x^2} B^2(x, t) \times \right) p(x, t)$$

**FP Equation for BD** with SDE  $m\gamma \dot{x} = F + \sigma \eta$

$$\dot{p}(x, t) = \left( -\frac{1}{m\gamma} \frac{\partial}{\partial x} F(x, t) \times + D \frac{\partial^2}{\partial x^2} \times \right) p(x, t)$$

$\gamma, \sigma$  and  $T$  Connection  $\sigma^2 = 2\beta^{-1} m \gamma, D := \frac{1}{2} \left( \frac{\sigma}{m\gamma} \right)^2$

### Calculation of Properties (4-step process)

**Preprocess raw trajectories (periodic gather)** macromolecule locates at box edges. Gather by pick atom within reference box and follow covalent bonds  $\hookrightarrow$  with multiple solutes & **roto-translational fitting**  $\hookrightarrow$  no strict decoupling,  $x_{ref}$ -dependent

**Time series analysis Statistical Moments** (1st-4th) with decreasing accuracy  $\mu, \sigma^2$ , skewness, kurtosis

**Calculate properties**

**Fick's Law**  $j(r, t) = -D \cdot \nabla c(r, t)$

**Diffusion Equation**  $\frac{\partial}{\partial t} c(r, t) = D \nabla^2 c(r, t)$

$c$  concentration of solute,  $D$  diffusion constant

**Interpret results**

**Equilibration:** Discard initial simulation period to remove non-representative conditions, monitored by stabilization of observables.  $\hookrightarrow$

No guarantee less good initial configurations **Best practice** use multiple simulations (too costly), more  $t_{sim}$ , sampling enhancement techniques

**Error of  $N$  normal distribution**, confidence factor  $c$  ( $c = 1 \rightarrow 68\%, 2 \rightarrow 95\%, 3 \rightarrow 99.7\%$ )  $\varepsilon = c \frac{\sigma}{\sqrt{N}}$  **Effective no. samples**  $\varepsilon = c \frac{\sigma_Q}{\sqrt{N_{eff}}}$

## Parameter Determination

**Theoretical QM** calculations (reference bond length  $b_0, k_b$  in  $\mathcal{V}^{bound}$ )

**Experimental** crystallographic structure determination (reference bond length  $b_0$ ), infrared/Raman spectroscopy measurements ( $k_b$  in  $\mathcal{V}^{bound}$ )

## Units

- $k_B = \frac{R}{N_A} = 1.381 \times 10^{-23} J \cdot K^{-1}$
- $\beta = \frac{1}{k_B T}, n = \frac{N}{N_A}, N_A \approx 6.02214076 \times 10^{23} \text{mol}^{-1}$
- $h = 6.6 \cdot 10^{-34} J \cdot s$  or  $\hbar = \frac{h}{2\pi}$

$$E_n = \frac{\hbar^2 \pi^2}{2ma^2} n^2, \text{ for } n = 1, 2, \dots$$

Quantity	Units
acceleration $a$	$\text{m/s}^2$
pressure $P$	$\text{Pa} = \text{N/m}^2 = \text{J/m}^3 \text{atm} \approx 1.013 \text{ bar}$
Moment/work/energy	$\text{J} = \text{Ws} = \text{Nm}$
Power	$\text{W} = \text{Nm/s}$
Gas constant $R$	$\text{kJ}/(\text{mol} \cdot \text{K})$
Potential energy $\mathcal{V}$	$\text{kJ/mol}$

- $[kJ \cdot \text{mol}^{-1} \cdot \text{m}^{-3}] [m^3] = [\text{mol}] [kJ \cdot \text{mol}^{-1} K^{-1}] [K] (PV = nRT)$
- Planck constant:  $[h] = \text{action}$
- units:  $[S] = \frac{\text{energy}}{\text{temperature}}$

diffusion constant with units  $\frac{\text{length}^2}{\text{time}}$

## Maths Tools

$$\sum_{n=0}^{\infty} x^n = \frac{1}{1-x}, \text{ for } |x| < 1$$

Gaussian over  $\mathbb{R}^+$ , with  $c_n := \begin{cases} \frac{2}{\pi} & \text{if } n \text{ even} \\ 1 & \text{if } n \text{ odd} \end{cases}$

$$I_n(a) = \int_0^{\infty} x^n e^{-ax^2} dx, a > 0 = \sqrt{\frac{c_n}{a}} \cdot (n-1)!! (2a)^{-\frac{n+1}{2}}$$

$n = 0$	$n = 2$	$n = 4$
$\frac{1}{2} \left( \frac{\pi}{a} \right)^{\frac{1}{2}}$	$\frac{1}{4} \left( \frac{\pi}{a^3} \right)^{\frac{1}{2}}$	$\frac{3}{8} \left( \frac{\pi}{a^5} \right)^{\frac{1}{2}}$
$n = 1$	$n = 3$	$n = 5$
$\frac{1}{2a}$	$\frac{1}{2a^2}$	$\frac{1}{a^3}$

over  $\mathbb{R}, \int_{-\infty}^{\infty} x^n e^{-ax^2} dx = \begin{cases} 2I_n(a) & \text{if } n \text{ even} \\ 0 & \text{if } n \text{ odd} \end{cases}$

**Normalized Gaussian**  $2I_{n=0}(a) = \frac{1}{\sqrt{2\pi\sigma}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$

**Important Numbers**

- $\left( \frac{8}{\pi} \right)^{\frac{1}{2}} \approx 1.60$
- $\sqrt{2} \approx 1.41, \left( \frac{1}{\sqrt{2}} \right) \approx 0.70710$
- $\sqrt{3} \approx 1.73, \left( \frac{1}{\sqrt{3}} \right) \approx 0.577$
- $\sqrt{5} \approx 2.236, \left( \frac{1}{\sqrt{5}} \right) \approx 0.4472$

Fermi function  $f = \frac{1}{e^{ax} + 1}$