Strukturelle Modellierung
(Masterstudiengang Bioinformatik)

Moleküldynamiksimulation: Theorie

Sommersemester 2013

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Literatur

- Andrew R. Leach: *Molecular Modellling, Principles and Applications,* Prentice Hall, 2001.
- M. P. Allen & D. J. Tildesley: *Computer Simulation of Liquids*, Clarendon Press, 1987.
- Tamar Schlick: *Molecular Modeling and Simulation*, Springer, 2006.

Computer-Simulation von Molekülen

Computer-Simulation von Molekülen

- Modellierung: QM, klassisch, schematisch
- Klassische Mechanik: Newton, Lagrange, Hamilton Bewegungsgleichungen
- Kartesische Koordinaten, interne Koordinaten
- Statistische Mechanik
- Simulationsmethoden: Systematische Suche, Monte Carlo, MD, Stochastische Dynamik (Langevin), Energieminimierung, Normalmodenanalyse
- Annahmen, Näherungen und Grenzen: Klassische Mechanik, Zeitskala, Systemgrösse, Kraftfeld
- Geschichte der MD Simulation

Vielteilchenproblem

	Kristalline Festkörper	Makromoleküle Flüssigkeit	Gasphase
Quantenmechanik ($\sim N^4$)	möglich	(noch?) nicht möglich	möglich
Klassische Mechanik ($\sim N \log N$)	einfach	essentielle Vielteilchensysteme	trivial

Reduktion auf wenige Freiheitsgrade durch **Symmetrie**

Reduktion auf wenige Teilchen durch **Verdünnung**

Proteinsimulation: Stufen der Vereinfachung

Modell	Freiheitsgrade	Eliminierte Freiheitsgrade	Untersuchbare Phänomene (Beispiele)
Quantenmechanik	Kerne, Elektronen	Nukleonen	Chemische Reaktionen
Alle Atome, polarisierbar	Atompositionen Polarisation	Elektronen	Bindung geladener Liganden
Alle Atome	Atompositionen (Protein + Wasser)	Polarisation	Hydratisierung
Alle Proteinatome	Positionen der Proteinatome	Lösungsmittel (Wasser)	Konformation in Gasphase
Gittermodelle	Aminosäuren	Atome	Faltung?

Simulation von Vielteilchensystemen

System: N Atome: i = 1,…,N, Koordinaten $\boldsymbol{r}_i$, Massen m_i, Wechselwirkung ("Kraftfeld") $V(\boldsymbol{r}_1,\ldots\boldsymbol{r}_N)$

Methoden:

- Systematische Suche → Ensemble
- Monte Carlo (MC) → Ensemble
- Moleküldynamik (MD) → Trajektorie
- Stochastische Dynamik (SD; Langevin) → Trajektorie
- Energieminimierung (EM) → 1 Konfiguration
- Normalmodenanalyse → 1 Konfiguration + harmonische Bewegung

Bewegungsgleichungen

- Newton (kartesische Koordinaten r, $\dot{r}$):
$$m\ddot{r} = F = -\partial V(r)/\partial r$$
- Lagrange (verallgemeinerte Koordinaten q, $\dot{q}$):
$$d/dt\,(\partial L/\partial \dot{q}) - \partial L/\partial q = 0 \qquad (L = T - V = E_{kin} - E_{pot})$$
- Hamilton (verallgemeinerte Koordinaten und Impulse q, p):
$$\dot{q} = \partial H/\partial p,\ \dot{p} = -\partial H/\partial q \qquad (H = T + V)$$

Erhaltungsgrößen

- Jeder kontinuierlichen Symmetrie eines mechanischen Systems entspricht eine Erhaltungsgröße. (Satz von Emmy Noether)

Invarianz bezüglich	Erhaltungsgröße
Zeitverschiebung	Energie
Translation	Impuls
Rotation	Drehimpuls

Vergleich Simulation - Experiment

- **Atomare Eigenschaften**
  - Struktur: Positionen, Distanzen, H-Brücken
  - Mobilität: B-Faktoren, Populationen
  - Dynamik: Vibrationen, Relaxationsraten, Diffusion, Pfade
- **Makroskopische Eigenschaften**
  - Thermodynamische Größen: Druck, Dichte, freie Energie,…
  - Viskosität, Kompressibilität, Dielektrizitätskonstante

Von mikroskopischen Details zu makroskopischen Größen:
Statistische Mechanik

- Zustandssumme: $Z = \frac{1}{h^{3N} N!} \iint e^{-H(\vec{p},\vec{q})/kT}\, d\vec{p}\, d\vec{q}$
- Hamilton-Funktion/Operator:
  $H(\boldsymbol{p},\boldsymbol{q})$ = kinetische Energie + potentielle Energie (Wechselwirkung)
- Erzeugung eines Ensembles von Konfigurationen durch Computersimulation
- Mittelung über Ensemble und Zeit liefert makroskopische Größen

Statistische Mechanik

- **Grundprinzip:** Für ein thermodynamisches System im Gleichgewicht ist die Wahrscheinlichkeit, dass es einen Zustand der Energie E_i annimmt:
$$\mathrm{Prob}(E_i) = \frac{1}{Z} e^{-E_i/kT}, \quad Z = \sum_{i=1}^{N} e^{-E_i/kT}$$
k_B = 1.38065 10^{-23} J/K: Boltzmann-Konstante
T: absolute Temperatur
Z: Zustandssumme
- Erwartungswert einer Observablen A: $\langle A \rangle = \frac{1}{Z} \sum_{i=1}^{N} A_i\, e^{-E_i/kT}$
- Thermodynamik: freie Energie $F = -k_B T \log Z$

Annahmen, Näherungen und Grenzen

- **Klassische Mechanik:**
  - keine tiefen Temperaturen (T ≈ 300 K)
  - Bewegung der Wasserstoffatome
  - keine chemischen Reaktionen
- **Zeitskala von Prozessen:** (im atomaren Bereich)
  - bis ca. 1 μs
  - aktivierte Prozesse: möglich
  - essentiell langsame Prozesse: nicht möglich (z.B. Proteinfaltung)
- **Systemgröße:**
  - $N \leq 10^6$ Teilchen
  - keine essentiell makroskopischen Vorgänge (z. B. kritische Phänomene, Phasenübergänge)
- **Kraftfeld:**
  - Ist die atomare Wechselwirkungsfunktion genügend genau zur Vorhersage der gewünschten Eigenschaft?

MD Simulation: Geschichte

1957: Harte Scheiben (2D)	-
1964: Monoatomare Flüssigkeit	10^{-11} s
1971: Molekulare Flüssigkeit	5×10^{-12} s
1971: Flüssiges Salz	10^{-11} s
1975: Einfaches kleines Polymer	10^{-11} s
1977: Protein im Vakuum	2×10^{-11} s
1982: Einfache Membran	2×10^{-10} s
1983: Protein in Lösung	2×10^{-11} s
1986: DNA in Lösung	10^{-10} s
1989: Protein-DNA Komplex in Lösung	10^{-10} s
1991: Protein-Protein Komplex in Lösung	10^{-9} s
1998: 1 μs Simulation eines Proteins in Lösung	10^{-6} s

MD Simulation: Personen und Programme

Martin Karplus (CHARMM)

Peter Kollman (†) (AMBER)

Herman Berendsen (GROMACS)

Kraftfelder

Molekülmodell und Kraftfelder

- Kraftfelder: CHARMM, AMBER, GROMACS,...
- Energiefunktion: kovalente Bindungen, Bindungswinkel, Diederwinkel, nichtbindende Wechselwirkung (van der Waals und elektrostatisch), H-Brücken
- Bestimmung von Kraftkonstanten
- Paarlisten und Cutoffs für nichtbindende Wechselwirkungen

Classical force fields: Examples

- **AMBER** (Assisted Model Building and Energy Refinement) - widely used for proteins and DNA
- **CHARMM** (Chemistry at HARvard Molecular Mechanics) - originally developed at Harvard by M. Karplus et al., widely used for both small molecules and macromolecules
- **GROMACS** - The force field optimized for the package of the same name, originally developed by H. Berendsen et al.
- **OPLS** (Optimized Potential for Liquid Simulations) developed by William L. Jorgensen at Yale University
- **ECEPP/2** - First force field for polypeptide molecules - developed by Harold Scheraga and colleagues, defined in torsion angle space

AMBER Force Field

$$E_{\text{pair}} = \sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right]$$

Potenzial für kovalente Bindungen

$$\sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2$$

- Summe über alle kovalenten Bindungen im Molekül
- Harmonisches Potential ("Bindung = Feder")
- Bindungen können nicht gebrochen werden
  → keine chemischen Reaktionen
- Parameter, von den Typen der kovalent gebundenen Atome abhängig:
  - K_r Kraftkonstante
  - r_{eq} Gleichgewichtsbindungslänge
- Rechenaufwand proportional zur Molekülgröße
- Bei Rechnung im Torsionswinkelraum nicht nötig

Potenzial für Bindungswinkel

$$\sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2$$

- Summe über alle Bindungswinkel im Molekül
- Harmonisches Potential
- Parameter, vom Typ der involvierten Atome abhängig:
  - K_θ Kraftkonstante
  - θ_{eq} Gleichgewichtsbindungswinkel
- Rechenaufwand proportional zur Molekülgröße
- Bei Rechnung im Torsionswinkelraum nicht nötig

Potenzial für Diederwinkel

$$\sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]$$

- Summe über alle Diederwinkel im Molekül
- Periodisches Potential
- Parameter, vom Typ der involvierten Atome abhängig:
  - V_n Kraftkonstante
  - n Anzahl der Energiemaxima
  - γ Position des ersten Energiemaximums
- Rechenaufwand proportional zur Molekülgröße

Potenzial für uneigentliche ("improper") Diederwinkel

$$\sum_{impropers} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]$$

- Halten planare Gruppen in einer Ebene (Peptidgruppe, aromatische Ringe usw.)
- Für ausgewählte Quadrupel von Atomen
- Parameter, vom Typ der involvierten Atome abhängig:
  - V_n Kraftkonstante
  - n Anzahl der Energiemaxima
  - γ Position des ersten Energiemaximums
- Rechenaufwand proportional zur Molekülgröße

AMBER Atom Types

Table 1. List of Atom Types[a]

atom	type	description
carbon	CT	any sp^3 carbon
	C	any carbonyl sp^2 carbon
	CA	any aromatic sp^2 carbon and (Cε of Arg)
	CM	any sp^2 carbon, double bonded
	CC	sp^2 aromatic in 5-membered ring with one substituent + next to nitrogen (Cγ in His)
	CV	sp^2 aromatic in 5-membered ring next to carbon and lone pair nitrogen (e.g. Cδ in His (δ))
	CW	sp^2 aromatic in 5-membered ring next to carbon and NH (e.g. Cδ in His (ε) and in Trp)
	CR	sp^2 aromatic in 5-membered ring next to two nitrogens (Cγ and Cε in His)
	CB	sp^2 aromatic at junction of 5- and 6-membered rings (Cδ in Trp) and both junction atoms in Ade and Gua
	C*	sp^2 aromatic in 5-membered ring next to two carbons (e.g. Cγ in Trp)
	CN	sp^2 junction between 5- and 6-membered rings and bonded to CH and NH (Cε in Trp)
	CK	sp^2 carbon in 5-membered aromatic between N and N-R (C8 in purines)
	CQ	sp^2 carbon in 6-membered ring between lone pair nitrogens (e.g. C2 in purines)
nitrogen	N	sp^2 nitrogen in amides
	NA	sp^2 nitrogen in aromatic rings with hydrogen attached (e.g. protonated His, Gua, Trp)
	NB	sp^2 nitrogen in 5-membered ring with lone pair (e.g. N7 in purines)
	NC	sp^2 nitrogen in 6-membered ring with lone pair (e.g. N3 in purines)
	N*	sp^2 nitrogen in 5-membered ring with carbon substituent (in purine nucleosides)
	N2	sp^2 nitrogen of aromatic amines and guanidinium ions
	N3	sp^2 nitrogen
oxygen	OW	sp^3 oxygen in TIP3P water
	OH	sp^3 oxygen in alcohols, tyrosine, and protonated carboxylic acids
	OS	sp^3 oxygen in ethers
	O	sp^2 oxygen in amides
	O2	sp^2 oxygen in anionic acids
sulfur	S	sulfur in methionine and cysteine
	SH	sulfur in cysteine
phosphorus	P	phosphorus in phosphates
hydrogen	H	H attached to N
	HW	H in TIP3P water
	HO	H in alcohols and acids
	HS	H attached to sulfur
	HA	H attached to aromatic carbon
	HC	H attached to aliphatic carbon with no electron-withdrawing substituents
	H1	H attached to aliphatic carbon with one electron-withdrawing substituent
	H2	H attached to aliphatic carbon with two electron-withdrawing substituents
	H3	H attached to aliphatic carbon with three electron-withdrawing substituents
	HP	H attached to carbon directly bonded to formally positive atoms (e.g. C next to NH_3^+ of lysine)
	H4	H attached to aromatic carbon with one electronegative neighbor (e.g. hydrogen on C5 of Trp, C6 of Thy)
	H5	H attached to aromatic carbon with two electronegative neighbors (e.g. H8 of Ade and Gua and H2 of Ade)

AMBER Atom Types

TYPES

C	12.0100	1.9080	0.0860	HS	1.0080	0.6000	0.0157
C*	12.0100	1.9080	0.0860	HW	1.0080	0.0000	0.0000
CA	12.0100	1.9080	0.0860	HU	1.0080	0.0000	0.0000
CB	12.0100	1.9080	0.0860	HV	1.0080	0.0000	0.0000
CC	12.0100	1.9080	0.0860	N	14.0100	1.8240	0.1700
CK	12.0100	1.9080	0.0860	N*	14.0100	1.8240	0.1700
CM	12.0100	1.9080	0.0860	N2	14.0100	1.8240	0.1700
CN	12.0100	1.9080	0.0860	N3	14.0100	1.8240	0.1700
CQ	12.0100	1.9080	0.0860	NA	14.0100	1.8240	0.1700
CR	12.0100	1.9080	0.0860	NB	14.0100	1.8240	0.1700
CT	12.0100	1.9080	0.1094	NC	14.0100	1.8240	0.1700
CV	12.0100	1.9080	0.0860	O	16.0000	1.6612	0.2100
CW	12.0100	1.9080	0.0860	O2	16.0000	1.6612	0.2100
H	1.0080	0.6000	0.0157	OH	16.0000	1.7210	0.2104
H1	1.0080	1.3870	0.0157	OS	16.0000	1.6837	0.1700
H2	1.0080	1.2870	0.0157	OW	16.0000	1.7683	0.1520
H3	1.0080	1.1870	0.0157	OT	16.0000	1.7683	0.1520
H4	1.0080	1.4090	0.0150	OU	16.0000	1.7699	0.1550
H5	1.0080	1.3590	0.0150	MU	1.0000	0.0000	0.0000
HA	1.0080	1.4590	0.0150	OV	16.0000	1.7766	0.1554
HC	1.0080	1.4870	0.0157	P	30.9700	2.1000	0.2000
HO	1.0080	0.0000	0.0000	S	32.0600	2.0000	0.2500
HP	1.0080	1.1000	0.0157	SH	32.0600	2.0000	0.2500

AMBER Bond Parameters

$$\sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2$$

BONDS

OW-HW	553.00	0.9572	CB-N*	436.00	1.3740	OH-P	230.00	1.6100
HW-HW	553.00	1.5139	CB-NB	414.00	1.3910	OS-P	230.00	1.6100
OT-HW	553.00	0.9572	CB-NC	461.00	1.3540	C*-HC	367.00	1.0800
OU-HU	553.00	0.9572	CK-H5	367.00	1.0800	C -N	490.00	1.3350
HU-HU	553.00	1.5139	CK-N*	440.00	1.3710	C*-CB	388.00	1.4590
OU-MU	553.00	0.1500	CK-NB	529.00	1.3040	C*-CT	317.00	1.4950
HU-MU	553.00	0.8735	CM-CM	549.00	1.3500	C*-CW	546.00	1.3520
OV-HV	553.00	1.0000	CM-CT	317.00	1.5100	CA-CN	469.00	1.4000
HV-HV	553.00	1.6330	CM-HA	367.00	1.0800	CB-CN	447.00	1.4190
C -CA	469.00	1.4090	CM-H4	367.00	1.0800	CC-CT	317.00	1.5040
C -CB	447.00	1.4190	CM-H5	367.00	1.0800	CC-CV	512.00	1.3750
C -CM	410.00	1.4440	CM-N*	448.00	1.3650	CC-CW	518.00	1.3710
C -CT	317.00	1.5220	CQ-H5	367.00	1.0800	CC-NA	422.00	1.3850
C -N*	424.00	1.3830	CQ-NC	502.00	1.3240	CC-NB	410.00	1.3940
C -NA	418.00	1.3880	CT-HC	340.00	1.0900	CN-NA	428.00	1.3800
C -NC	457.00	1.3580	CT-H1	340.00	1.0900	CR-H5	367.00	1.0800
C -O	570.00	1.2290	CT-H2	340.00	1.0900	CR-NA	477.00	1.3430
C -O2	656.00	1.2500	CT-H3	340.00	1.0900	CR-NB	488.00	1.3350
C -OH	450.00	1.3640	CT-HP	340.00	1.0900	CT-N	337.00	1.4490
CA-CA	469.00	1.4000	CT-N*	337.00	1.4750	CT-N3	367.00	1.4710
CA-CB	469.00	1.4040	CT-N2	337.00	1.4630	CT-S	227.00	1.8100
CA-CM	427.00	1.4330	CT-OH	320.00	1.4100	CT-SH	237.00	1.8100
CA-CT	317.00	1.5100	CT-OS	320.00	1.4100	CV-H4	367.00	1.0800
CA-HA	367.00	1.0800	H -N2	434.00	1.0100	CV-NB	410.00	1.3940
CA-H4	367.00	1.0800	H -N*	434.00	1.0100	CW-H4	367.00	1.0800
CA-N2	481.00	1.3400	H -NA	434.00	1.0100	CW-NA	427.00	1.3810
CA-NA	427.00	1.3810	HO-OH	553.00	0.9600	H -N	434.00	1.0100
CA-NC	483.00	1.3390	HO-OS	553.00	0.9600	H -N3	434.00	1.0100
CB-CB	520.00	1.3700	O2-P	525.00	1.4800	HS-SH	274.00	1.3360
						S -S	166.00	2.0380

AMBER Bond Angle Parameters

$$\sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2$$

ANGLES

HW-OW-HW	100.00	104.52	C -CB-CB	63.00	119.20	H1-CT-SH	50.00	109.50	C -N*-CT	70.00	117.60
HW-HW-OW	0.00	37.74	CA-CB-CB	63.00	117.30	CT-CT-S	50.00	114.70	C -N*-H	30.00	119.20
HW-OT-HW	0.00	104.52	CA-CB-NB	70.00	132.40	H2-CT-N2	35.00	109.50	CA-N*-CT	70.00	125.80
HW-HW-OT	0.00	37.74	CB-CB-N*	70.00	106.20	H1-CT-N2	50.00	109.50	CA-N*-H	30.00	125.80
HU-OU-HU	0.00	104.52	CB-CB-NB	70.00	119.40	HP-CT-N3	50.00	109.50	CK-N*-CT	70.00	128.80
HU-HU-OU	0.00	37.74	CB-CB-NC	70.00	127.70	CA-CT-CT	63.00	114.00	CK-N*-H	30.00	128.80
HU-MU-HU	0.00	129.13	N*-CB-NC	70.00	126.20	C -CT-HC	50.00	109.50	CM-N*-CT	70.00	121.20
HU-HU-MU	0.00	29.94	C*-CB-CA	63.00	134.90	C -CT-H	63.00	110.10	CM-N*-H	30.00	121.20
OU-MU-HU	0.00	119.84	C*-CB-CM	63.00	108.80	CT-CT-N2	80.00	111.20	CA-N2-H	35.00	120.00
OU-HU-MU	0.00	7.80	CA-CB-CM	63.00	116.20	CT-CT-N	80.00	109.70	H -N2-H	35.00	120.00
HU-OU-MU	0.00	52.26	N*-CB-NC	35.00	123.05	C -CT-CT	63.00	111.10	CT-N2-H	35.00	118.40
HV-OV-HV	0.00	109.47	H5-CK-NB	35.00	123.05	CA-CT-HC	50.00	109.50	CA-N2-CT	50.00	123.20
HV-HV-OV	0.00	35.27	N*-CK-NB	70.00	113.90	CT-CT-H1	80.00	111.20	CT-N3-H	50.00	109.50
CB-C -NA	70.00	111.30	C -CM-CM	63.00	120.70	CC-CT-CT	63.00	113.10	H -N3-H	35.00	109.50
CB-C -O	80.00	128.80	C -CM-CT	70.00	119.70	CC-CT-HC	50.00	109.50	C -NA-C	70.00	126.40
CW-C -NA	70.00	114.10	C -CM-HA	35.00	119.70	C -CT-N3	80.00	111.20	C -NA-CA	70.00	125.20
CW-C -O	80.00	125.30	C -CM-H4	35.00	119.70	C*-CT-CT	63.00	115.60	C -NA-H	30.00	116.80
CT-C -O	80.00	120.40	CA-CM-CM	63.00	117.00	C*-CT-HC	50.00	109.50	CA-NA-H	30.00	118.00
CT-C -O2	70.00	117.00	CA-CM-HA	35.00	123.30	CT-CC-NA	70.00	120.00	CC-NA-CR	70.00	120.00
N*-C -NA	70.00	115.40	CA-CM-H4	35.00	123.30	CT-CC-CV	70.00	120.00	CC-NA-H	30.00	120.00
N*-C -NC	70.00	118.60	CM-CM-CT	70.00	119.70	CT-CC-NB	70.00	120.00	CR-NA-CW	70.00	120.00
N*-C -O	80.00	120.90	CM-CM-HA	35.00	119.70	CV-CC-NA	70.00	120.00	CR-NA-H	30.00	120.00
NA-C -O	80.00	120.60	CM-CM-H4	35.00	119.70	CW-CC-NA	70.00	120.00	CW-NA-H	30.00	120.00
NC-C -O	80.00	122.50	CM-CM-N*	70.00	121.20	CW-CC-NB	70.00	120.00	CW-NA-CW	70.00	111.60
O -C -O	80.00	126.00	H4-CM-N*	35.00	121.20	CC-CC-NB	70.00	120.00	CW-NA-R	70.00	111.60
CT-C -O	80.00	122.90	H5-CQ-NC	35.00	119.40	CC-CN-NA	70.00	120.00	CT-N3-H	50.00	109.80
O -C -O	80.00	126.00	CQ-CQ-NC	70.00	129.10	H5-CR-NA	35.00	120.00	C -NA-CK	70.00	117.00
OS-C -O2	80.00	126.00	CW-CQ-NC	70.00	129.10	H5-CR-NB	35.00	120.00	CK-NA-H	30.00	117.00
CA-C -CA	63.00	120.00	CT-CT-CT	40.00	109.50	NA-CR-NB	70.00	120.00	C -NC-CA	70.00	120.50
CA-C -OH	70.00	120.00	CT-CT-HC	50.00	109.50	CC-CV-H4	35.00	120.00	CA-NC-CA	70.00	112.20
C -CA-CA	63.00	120.00	CT-CT-H1	50.00	109.50	CC-CV-NB	70.00	120.00	CA-NC-CQ	70.00	118.60
CA-CA-CA	63.00	120.00	CT-CT-H2	50.00	109.50	H4-CV-NB	35.00	120.00	CA-NC-CQ	70.00	111.00
CA-CA-CB	63.00	120.00	CT-CT-HP	50.00	109.50	CC-CW-H4	35.00	120.00	C -OH-HO	35.00	113.00
CA-CA-CT	70.00	120.00	CT-CT-N*	50.00	109.50	CC-CW-NA	70.00	120.00	CT-OH-HO	55.00	108.50
CA-CA-HA	35.00	120.00	CT-CT-OH	50.00	109.50	H4-CW-NA	35.00	120.00	HO-OH-P	45.00	108.50
CA-CA-H4	35.00	120.00	CT-CT-OS	50.00	109.50	C*-CW-H4	35.00	120.00	CT-OS-CT	60.00	109.50
CB-CA-HA	35.00	120.00	HC-CT-HC	35.00	109.50	C*-CW-NA	70.00	108.70	CT-OS-P	100.00	120.50
CB-CA-H4	35.00	120.00	H1-CT-H1	35.00	109.50	CT-C*-CW	70.00	125.00	P -OS-P	100.00	120.50
CB-CA-N2	70.00	123.50	H2-CT-H2	35.00	109.50	CB-C*-CT	70.00	128.60	OS-P -X	45.00	108.23
CB-CA-NC	70.00	117.30	H2-CT-N*	50.00	109.50	CB-C*-CW	63.00	106.40	O2-P -O2	140.00	119.90
CW-CA-N2	70.00	120.10	H1-CT-N*	50.00	109.50	CA-CN-NA	70.00	132.80	OS-P -OS	100.00	108.23
CW-CA-NC	70.00	121.50	H1-CT-OH	50.00	109.50	CB-CN-NA	70.00	104.40	OH-P -OS	45.00	102.60
H2-CA-NA	70.00	116.00	H1-CT-OS	50.00	109.50	CA-CN-CB	63.00	122.70	OS-P -OS	45.00	102.60
H2-CA-NC	70.00	119.30	H2-CT-OS	50.00	109.50	C -N -CT	50.00	121.90	CT-S -CT	62.00	98.90
NA-CA-NC	70.00	123.30	N*-CT-OS	50.00	109.50	C -N -H	30.00	120.00	CT-S -S	68.00	103.70
C -NA-CA	70.00	120.00	H1-CT-N	50.00	109.50	CT-N -H	30.00	118.04	CT-SH-HS	43.00	96.00
H2-CA-N2	70.00	120.00	C -CT-H1	50.00	109.50	CT-N -CT	50.00	118.00	HS-SH-HS	35.00	92.07
CW-CA-NA	70.00	120.00	C -CT-HP	50.00	109.50	H -N -H	35.00	120.00			
CA-CA-CW	63.00	120.00	H1-CT-S	50.00	109.50	C -N*-CM	70.00	121.60			

AMBER Dihedral Angle Parameters

$$\sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]$$

DIHEDRALS

X -C -CA-X	4	14.500	180.00	2.00	X -CB-CN-X	4	12.000	180.00	2.00
X -C -CB-X	4	12.000	180.00	2.00	X -CC-CT-X	6	0.000	0.00	2.00
X -C -CM-X	4	8.700	180.00	2.00	X -CC-CV-X	4	20.600	180.00	2.00
X -C -N*-X	4	5.800	180.00	2.00	X -CC-CW-X	4	21.500	180.00	2.00
X -C -NA-X	4	5.400	180.00	2.00	X -CC-NA-X	4	5.600	180.00	2.00
X -C -NC-X	2	8.000	180.00	2.00	X -CC-NB-X	2	4.800	180.00	2.00
X -C -OH-X	2	1.800	180.00	2.00	X -CN-NA-X	4	6.100	180.00	2.00
X -C -CT-X	4	0.000	0.00	2.00	X -CR-NA-X	4	9.300	180.00	2.00
X -CA-CA-X	4	14.500	180.00	2.00	X -CR-NB-X	2	10.000	180.00	2.00
X -CA-CB-X	4	14.000	180.00	2.00	X -CV-NB-X	2	4.800	180.00	2.00
X -CA-CM-X	4	10.200	180.00	2.00	X -CW-NA-X	4	6.000	180.00	2.00
X -CA-CT-X	6	0.000	0.00	2.00	CT-CT-OS-CT	1	0.383	0.00	-3.00
X -CA-N2-X	4	9.600	180.00	2.00	CT-CT-OS-CT	1	0.100	180.00	2.00
X -CA-NA-X	4	6.000	180.00	2.00	C -N -CT-C	1	0.200	180.00	2.00
X -CA-NC-X	2	9.600	180.00	2.00	N -CT-C -N	1	0.400	180.00	-4.00
X -CB-CB-X	4	21.800	180.00	2.00	N -CT-C -N	1	1.350	180.00	-2.00
X -CB-CM-X	4	6.600	180.00	2.00	N -CT-C -N	1	0.750	180.00	1.00
X -CB-NB-X	2	5.100	180.00	2.00	CT-CT-N -C	1	0.500	180.00	-4.00
X -CB-NC-X	2	8.300	180.00	2.00	CT-CT-N -C	1	0.150	180.00	-3.00
X -CK-N*-X	4	6.800	180.00	2.00	CT-CT-N -C	1	0.530	0.00	1.00
X -CK-NB-X	2	20.000	180.00	2.00	CT-CT-C -N	1	0.100	0.00	-4.00
X -CM-CM-X	4	26.600	180.00	2.00	CT-CT-C -N	1	0.070	0.00	2.00
X -CM-CT-X	6	0.000	0.00	3.00	H -N -C -O	1	2.500	180.00	-2.00
X -CM-N*-X	4	17.400	180.00	2.00	H -N -C -O	1	2.000	0.00	1.00
X -CQ-NC-X	2	13.600	180.00	2.00	CT-S -S -CT	1	3.500	0.00	-2.00
X -CT-CT-X	9	1.400	0.00	3.00	CT-S -S -CT	1	0.600	0.00	-3.00
X -CT-N -X	6	0.000	0.00	2.00	OS-CT-CT-OS	1	0.144	0.00	-3.00
X -CT-N*-X	6	0.000	0.00	2.00	OS-CT-CT-OS	1	1.000	0.00	2.00
X -CT-N2-X	6	0.000	0.00	3.00	OS-CT-CT-OH	1	0.144	0.00	-3.00
X -CT-OH-X	3	0.500	0.00	3.00	OS-CT-CT-OH	1	1.000	0.00	2.00
X -CT-OS-X	3	1.150	0.00	3.00	OH-CT-CT-OH	1	0.144	0.00	-3.00
X -OH-P -X	3	0.750	0.00	3.00	OH-CT-CT-OH	1	1.000	0.00	2.00
X -OS-P -X	3	0.750	0.00	3.00	OH-P -OS-CT	1	0.250	0.00	-3.00
X -C -N -X	4	10.000	180.00	2.00	OH-P -OS-CT	1	1.200	0.00	2.00
X -CT-N3-X	9	1.400	0.00	3.00	OS-P -OS-CT	1	0.250	0.00	-3.00
X -CT-S -X	3	1.000	0.00	3.00	OS-P -OS-CT	1	1.200	0.00	2.00
X -CT-SH-X	3	0.750	0.00	3.00	OS-CT-N*-CK	1	0.500	180.00	-2.00
X -C*-CB-X	4	6.700	180.00	2.00	OS-CT-N*-CK	1	2.500	0.00	1.00
X -C*-CT-X	6	0.000	0.00	2.00	OS-CT-N*-CM	1	0.500	180.00	-2.00
X -C*-CW-X	4	26.100	180.00	2.00	OS-CT-N*-CM	1	2.500	0.00	1.00
X -CA-CN-X	4	14.500	180.00	2.00					

AMBER Improper Dihedral Angle Parameters

$$\sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]$$

IMPROPER DIHEDRALS

X -X -C -O	10.50	180.00	2.00	X -X -CA-H4	1.10	180.00	2.00
X -O2-C -O2	10.50	180.00	2.00	X -X -CA-H5	1.10	180.00	2.00
X -X -N -H	1.00	180.00	2.00	CK-CB-N*-CT	1.00	180.00	2.00
X -X -N2-H	1.00	180.00	2.00	CM-C -N*-CT	1.00	180.00	2.00
X -X -NA-H	1.00	180.00	2.00	CM-C -CM-CT	1.10	180.00	2.00
X -N2-CA-N2	10.50	180.00	2.00	NA-CV-CC-CT	1.10	180.00	2.00
X -CT-N -CT	1.00	180.00	2.00	NB-CW-CC-CT	1.10	180.00	2.00
X -X -CA-HA	1.10	180.00	2.00	NA-CW-CC-CT	1.10	180.00	2.00
X -X -CW-H4	1.10	180.00	2.00	CW-CB-C*-CT	1.10	180.00	2.00
X -X -CR-H5	1.10	180.00	2.00	CA-CA-CA-CT	1.10	180.00	2.00
X -X -CV-H4	1.10	180.00	2.00	C -CM-CM-CT	1.10	180.00	2.00
X -X -CQ-H5	1.10	180.00	2.00	NC-CM-CA-N2	1.10	180.00	2.00
X -X -CK-H5	1.10	180.00	2.00	CB-NC-CA-N2	1.10	180.00	2.00
X -X -CM-H4	1.10	180.00	2.00	NA-NC-CA-N2	1.10	180.00	2.00
X -X -CM-HA	1.10	180.00	2.00	CA-CA-C -OH	1.10	180.00	2.00

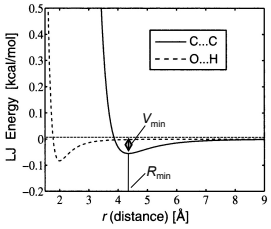
Nichtbindende Wechselwirkung

$$\sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right]$$

- Summe über alle Atompaare (i,j), die nicht über 1 oder 2 kovalente Bindungen verbunden sind
- Lennard-Jones Potenzial + elektrostatische Wechselwirkung
- Funktion der interatomaren Abstände R_{ij}
- Parameter, von den Typen der Atome abhängig:
  - A_{ij}, B_{ij} Parameter des Lennard-Jones Potenzials
  - q_i, q_j Partialladungen
  - ε Dielektrizitätskonstante
- Ohne besondere Vorkehrungen wächst der Rechenaufwand mit dem Quadrat der Molekülgröße
- Auch im Torsionswinkelraum vorhanden

Lennard-Jones Potenzial

$$\sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}}\right]$$



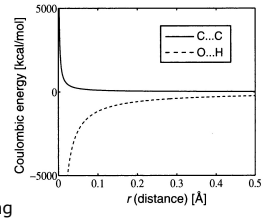
- Schwacher anziehender Beitrag: Van der Waals Kraft
- Starke Abstoßung für kurze Abstände R_{ij} aufgrund des Pauli-Prinzips
- $A_{ij} = V_{ij,min}\, R_{ij,min}^{12}$, $B_{ij} = 2V_{ij,min}\, R_{ij,min}^{6}$ mit
  - $V_{ij,min} = (V_{i,min}\, V_{j,min})^{1/2}$ Potenzialminimum
  - $R_{ij,min} = R_{i,min} + R_{j,min}$ energetisch günstigster Abstand
- Kurzreichweitig

AMBER Atom Types

TYPES						Lennard-Jones $R_{i,min}$	Lennard-Jones $V_{i,min}$
					Mass		
C	12.0100	1.9080	0.0860	HS	1.0080	0.6000	0.0157
C*	12.0100	1.9080	0.0860	HW	1.0080	0.0000	0.0000
CA	12.0100	1.9080	0.0860	HU	1.0080	0.0000	0.0000
CB	12.0100	1.9080	0.0860	HV	1.0080	0.0000	0.0000
CC	12.0100	1.9080	0.0860	N	14.0100	1.8240	0.1700
CK	12.0100	1.9080	0.0860	N*	14.0100	1.8240	0.1700
CM	12.0100	1.9080	0.0860	N2	14.0100	1.8240	0.1700
CN	12.0100	1.9080	0.0860	N3	14.0100	1.8240	0.1700
CQ	12.0100	1.9080	0.0860	NA	14.0100	1.8240	0.1700
CR	12.0100	1.9080	0.0860	NB	14.0100	1.8240	0.1700
CT	12.0100	1.9080	0.1094	NC	14.0100	1.8240	0.1700
CV	12.0100	1.9080	0.0860	O	16.0000	1.6612	0.2100
CW	12.0100	1.9080	0.0860	O2	16.0000	1.6612	0.2100
H	1.0080	0.6000	0.0157	OH	16.0000	1.7210	0.2104
H1	1.0080	1.3870	0.0157	OS	16.0000	1.6837	0.1700
H2	1.0080	1.2870	0.0157	OW	16.0000	1.7683	0.1520
H3	1.0080	1.1870	0.0157	OT	16.0000	1.7683	0.1520
H4	1.0080	1.4090	0.0150	OU	16.0000	1.7699	0.1550
H5	1.0080	1.3590	0.0150	MU	1.0000	0.0000	0.0000
HA	1.0080	1.4590	0.0150	OV	16.0000	1.7766	0.1554
HC	1.0080	1.4870	0.0157	P	30.9700	2.1000	0.2000
HO	1.0080	0.0000	0.0000	S	32.0600	2.0000	0.2500
HP	1.0080	1.1000	0.0157	SH	32.0600	2.0000	0.2500

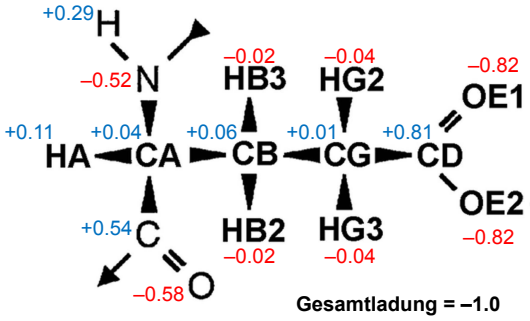
Elektrostatisches (Coulomb) Potenzial

$$\sum_{i<j}\frac{q_i q_j}{\varepsilon R_{ij}}$$



- Partialladungen q_i, q_j
- Dielektrizitätskonstante ε beschreibt (gemittelte) Polarisierbarkeit der Umgebung
  $\varepsilon_{Wasser} \approx 80$; $\varepsilon_{apolar} \approx 2$.
  Werden alle Ladungen explizit behandelt: $\varepsilon = 1$
- Langreichweitig!
- Stark!
- Wichtigster Energiebeitrag auch für Wasserstoffbrücken

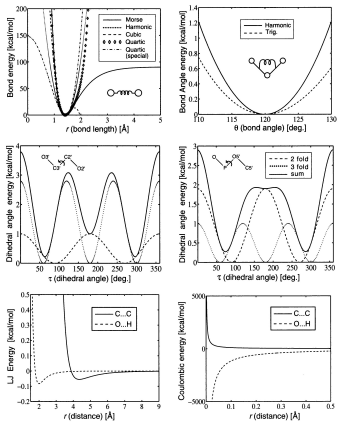
Partialladungen (Glu, AMBER)



Bestimmung von Kraftfeldparametern

- **Fit der Energie zu quantenmechanischen *ab initio* Rechnungen**
  - z.B. Partialladungen
- **Fit zu experimentellen Daten**
  - Infrarot-Spektroskopie (Vibrationen)
  - Röntgenkristallographie (Geometrie)
  - NMR Spektroskopie
  - Thermodynamische Eigenschaften
- **Schwierigkeiten**
  - Exakte Beziehung molekulare Eigenschaft ⇔ Kraftfeldparameter
  - Konzeptionelle Einfachheit ⇔ Anzahl Parameter
  - Gegenseitige Abhängigkeit von Kraftfeldparametern
  - Widersprüchliche Anforderungen für Verbesserungen der Parameter
  - Einfluss von Näherungen
- **Genauigkeit wird durch den ungenausten Term der Energiefunktion bestimmt.**

Energieterme



Strukturelle Modellierung
(Masterstudiengang Bioinformatik)

Moleküldynamiksimulation: Theorie

Sommersemester 2013

Peter Güntert

Literatur

- Andrew R. Leach: *Molecular Modellling, Principles and Applications,* Prentice Hall, 2001.
- M. P. Allen & D. J. Tildesley: *Computer Simulation of Liquids*, Clarendon Press, 1987.
- Tamar Schlick: *Molecular Modeling and Simulation*, Springer, 2006.

Kraftberechnung

- Kraft = −Gradient der potentiellen Energie
- Analytisch berechnete partielle Ableitungen der potentiellen Energie nach den Koordinaten aller Atome sind notwendig für klassische MD Simulation.
- MD im Torsionswinkelraum benötigt partielle Ableitungen der potentiellen Energie nach den Torsionswinkeln.

Paarlisten

- N Atome → ca. $N(N-1)/2$ Paarwechselwirkungen
- Berechnung der nichtbindenden Wechselwirkung ist aufwendigster Teil der Kraftberechnung
- Potenzial nimmt mit der Entfernung ab → Vernachlässigung von kleinen Termen = langen Distanzen
- Kurze Distanzen $R < R_{max}$ werden periodisch in Paarliste gespeichert
- Wechselwirkungen werden nur für Atompaare mit Abstand $R < R_{cutoff} < R_{max}$ berechnet
- Langreichweitige elektrostatische WW → $R_{cutoff} \approx 12$ Å
- Aktualisierung der Paarliste nach einer festen Anzahl Zeitschritten oder wenn sich ein Teilchen $R_{max} - R_{cutoff}$ weit bewegt hat.

Paarliste und Cutoff

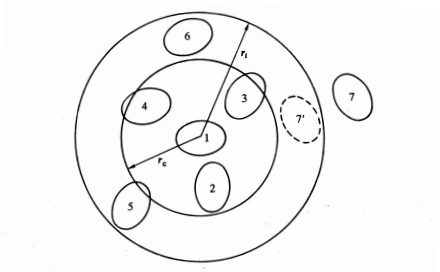
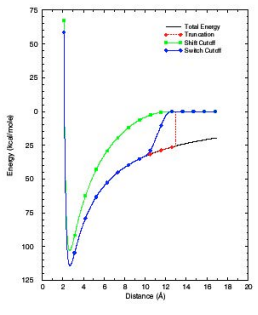


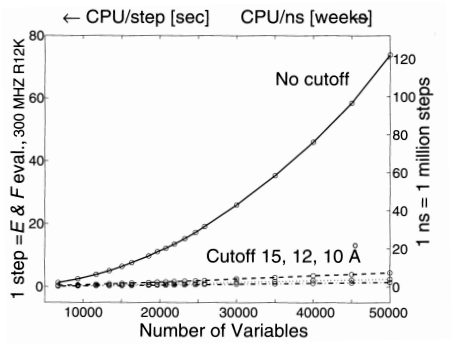
Fig. 5.4 The cutoff sphere, and its skin, around a molecule 1. Molecules 2, 3, 4, 5, and 6 are on the list of molecule 1; molecule 7 is not. Only molecules 2, 3, and 4 are within the range of the potential at the time the list is constructed.

Treatment of truncation effects

- **Truncation:** the interactions are simply set to zero for interatomic distances greater than the cutoff distance. This method can lead to large fluctuations in the energy. This method is not often used.
- **SHIFT cutoff method:** this method modifies the entire potential energy surface such that at the cutoff distance the interaction potential is zero. The drawback of this method is that equilibrium distances are slightly decreased.
- **SWITCH cutoff method:** This method tapers the interaction potential over a predefined range of distances. The potential takes its usual value up to the first cutoff and is then switched to zero between the first and last cutoff. This model suffers from strong forces in the switching region which can slightly perturb the equilibrium structure. The SWITCH function is not recommended when using short cutoff regions.



Rechenzeit mit und ohne Cutoff



MD Algorithmen

MD Algorithmen

- Energieminimierung
- Integration der Bewegungsgleichungen
- Temperaturkontrolle
- Druckkontrolle
- Periodische Randbedingungen

Energieflächen

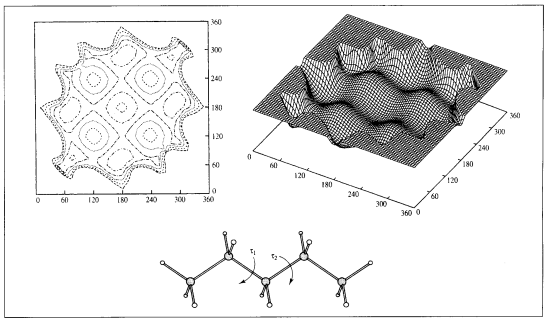


Fig. 5.1: Variation in the energy of pentane with the two torsion angles indicated and represented as a contour diagram and isometric plot. Only the lowest-energy regions are shown.

Lokale Minima, globales Minimum

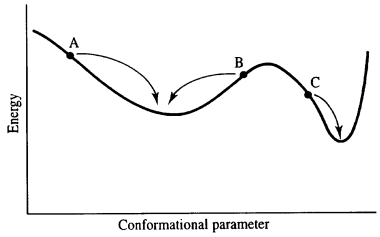


Fig. 5.3: A schematic one-dimensional energy surface. Minimisation methods move downhill to the nearest minimum. The statistical weight of the narrow, deep minimum may be less than a broad minimum which is higher in energy.

Energieminimierungsalgorithmen

- Ohne Ableitungen
- Mit Gradienten:
  - Steilster Abstieg (steepest descent)
  - konjugierte Gradienten (conjugate gradients)
- Mit zweiter Ableitung: Newton-Raphson Methode

Simplex Algorithmus

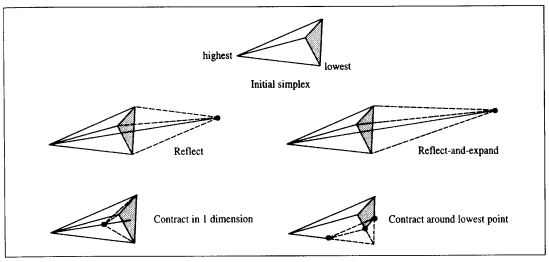


Fig. 5.4: The three basic moves permitted to the simplex algorithm (reflection, and its close relation reflect-and-expand; contract in one dimension and contract around the lowest point). (Figure adapted from Press W H, B P Flannery, S A Teukolsky and W T Vetterling 1992. Numerical Recipes in Fortran. *Cambridge, Cambridge University Press.)*

Simplex Algorithmus

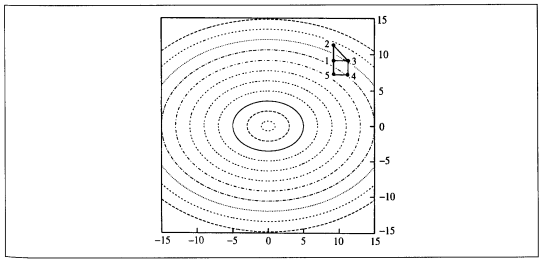


Fig. 5.5: The first few steps of the simplex algorithm with the function $x^2 + 2y^2$. The initial simplex corresponds to the triangle 123. Point 2 has the largest value of the function and the next simplex is the triangle 134. The simplex for the third step is 145.

Eindimensionale Minimierung

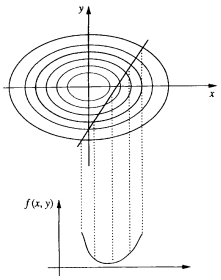


Fig. 5.7: A line search is used to locate the minimum in the function in the direction of the gradient.

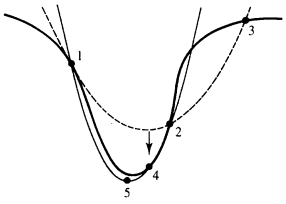


Fig. 5.8: The minimum in a line search may be found more effectively by fitting an analytical function such as a quadratic to the initial set of three points (1,2 and 3). A better estimate of the minimum can then be found by fitting a new function to the points 1, 2 and 4 and finding its minimum.

Energieminimierung: Steepest descent

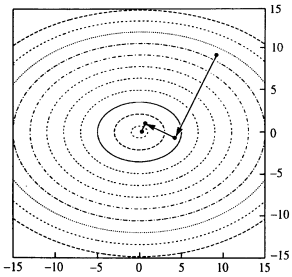


Fig. 5.9: Application of steepest descents to the function $x^2 + 2y^2$.

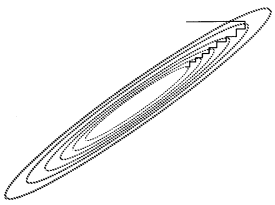


Fig. 5.10: The steepest descents method can give undesirable behaviour in a long narrow valley.

Konjugierte Gradientenmethode

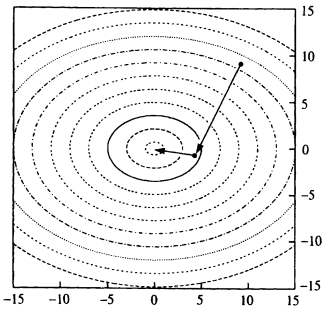


Fig. 5.11: Application of conjugate gradients method to the function $x^2 + 2y^2$.

Taylor Reihenentwicklung

$$f(x) = f(x_0) + f'(x_0)(x - x_0) + \frac{f''(x_0)}{2}(x - x_0)^2 + \frac{f'''(x_0)}{3!}(x - x_0)^3 + \ldots$$

$$\mathbf{r}(t + \delta t) = \mathbf{r}(t) + \delta t\mathbf{v}(t) + \tfrac{1}{2}\delta t^2\mathbf{a}(t) + \tfrac{1}{6}\delta t^3\mathbf{b}(t) + \tfrac{1}{24}\delta t^4\mathbf{c}(t) + \cdots$$

$$\mathbf{v}(t + \delta t) = \mathbf{v}(t) + \delta t\mathbf{a}(t) + \tfrac{1}{2}\delta t^2\mathbf{b}(t) + \tfrac{1}{6}\delta t^3\mathbf{c}(t) + \cdots$$

$$\mathbf{a}(t + \delta t) = \mathbf{a}(t) + \delta t\mathbf{b}(t) + \tfrac{1}{2}\delta t^2\mathbf{c}(t) \cdots$$

$$\mathbf{b}(t + \delta t) = \mathbf{b}(t) + \delta t\mathbf{c}(t) + \cdots$$

Verlet Algorithmus

The Verlet algorithm uses the positions and accelerations at time t, and the positions from the previous step, $\mathbf{r}(t-\delta t)$, to calculate the new positions at $t+\delta t$, $\mathbf{r}(t+\delta t)$. We can write down the following relationships between these quantities and the velocities at time t:

$$\mathbf{r}(t+\delta t) = \mathbf{r}(t) + \delta t\mathbf{v}(t) + \tfrac{1}{2}\delta t^2\mathbf{a}(t) + \cdots \quad (7.6)$$

$$\mathbf{r}(t-\delta t) = \mathbf{r}(t) - \delta t\mathbf{v}(t) + \tfrac{1}{2}\delta t^2\mathbf{a}(t) - \cdots \quad (7.7)$$

Adding these two equations gives

$$\mathbf{r}(t+\delta t) = 2\mathbf{r}(t) - \mathbf{r}(t-\delta t) + \delta t^2\mathbf{a}(t) \quad (7.8)$$

The velocities do not explicitly appear in the Verlet integration algorithm. The velocities can be calculated in a variety of ways; a simple approach is to divide the difference in positions at times $t+\delta t$ and $t-\delta t$ by $2\delta t$:

$$\mathbf{v}(t) = [\mathbf{r}(t+\delta t) - \mathbf{r}(t-\delta t)]/2\delta t \quad (7.9)$$

Alternatively, the velocities can be estimated at the half-step, $t+\frac{1}{2}\delta t$:

$$\mathbf{v}(t+\tfrac{1}{2}\delta t) = [\mathbf{r}(t+\delta t) - \mathbf{r}(t)]/\delta t \quad (7.10)$$

Leap-frog Algorithmus

The *leap-frog* algorithm uses the following relationships:

$$\mathbf{r}(t+\delta t) = \mathbf{r}(t) + \delta t\mathbf{v}(t+\tfrac{1}{2}\delta t) \quad (7.11)$$

$$\mathbf{v}(t+\tfrac{1}{2}\delta t) = \mathbf{v}(t-\tfrac{1}{2}\delta t) + \delta t\mathbf{a}(t) \quad (7.12)$$

To implement the leap-frog algorithm, the velocities $\mathbf{v}(t+\frac{1}{2}t)$ are first calculated from the velocities at time $t-\frac{1}{2}\delta t$ and the accelerations at time t. The positions $\mathbf{r}(t+\delta t)$ are then deduced from the velocities just calculated together with the positions at time $\mathbf{r}(t)$ using Equation (7.11). The velocities at time t can be calculated from

$$\mathbf{v}(t) = \tfrac{1}{2}[\mathbf{v}(t+\tfrac{1}{2}\delta t) + \mathbf{v}(t-\tfrac{1}{2}\delta t)] \quad (7.13)$$

The velocities thus 'leap-frog' over the positions to give their values at $t+\frac{1}{2}\delta t$ (hence the name). The positions then leap over the velocities to give their new values at $t+\delta t$, ready for the velocities at $t+\frac{3}{2}\delta t$, and so on. The leap-frog method has two advantages over the

Velocity Verlet Algorithmus

The *velocity Verlet* method [Swope *et al.* 1982] gives positions, velocities and accelerations at the same time and does not compromise precision:

$$\mathbf{r}(t+\delta t) = \mathbf{r}(t) + \delta t\mathbf{v}(t) + \tfrac{1}{2}\delta t^2\mathbf{a}(t) \quad (7.14)$$

$$\mathbf{v}(t+\delta t) = \mathbf{v}(t) + \tfrac{1}{2}\delta t[\mathbf{a}(t) + \mathbf{a}(t+\delta t)] \quad (7.15)$$

The velocity Verlet method is actually implemented as a three-stage procedure because, as can be seen from Equation (7.15), to calculate the new velocities requires the accelerations at both t and $t+\delta t$. Thus in the first step the positions at $t+\delta t$ are calculated according to Equation (7.14) using the velocities and the accelerations at time t. The velocities at time $t+\frac{1}{2}\delta t$ are then determined using:

$$\mathbf{v}(t+\tfrac{1}{2}\delta t) = \mathbf{v}(t) + \tfrac{1}{2}\delta t\mathbf{a}(t) \quad (7.16)$$

New forces are next computed from the current positions, thus giving $\mathbf{a}(t+\delta t)$. In the final step, the velocities at time $t+\delta t$ are determined using:

$$\mathbf{v}(t+\delta t) = \mathbf{v}(t+\tfrac{1}{2}\delta t) + \tfrac{1}{2}\delta t\mathbf{a}(t+\delta t) \quad (7.17)$$

Beemans Algorithmus

Beeman's algorithm [Beeman 1976] is also related to the Verlet method:

$$\mathbf{r}(t+\delta t) = \mathbf{r}(t) + \delta t\mathbf{v}(t) + \tfrac{2}{3}\delta t^2\mathbf{a}(t) - \tfrac{1}{6}\delta t^2\mathbf{a}(t-\delta t) \quad (7.18)$$

$$\mathbf{v}(t+\delta t) = \mathbf{v}(t) + \tfrac{1}{3}\delta t\mathbf{a}(t) + \tfrac{5}{6}\delta t\mathbf{a}(t) - \tfrac{1}{6}\delta t\mathbf{a}(t-\delta t) \quad (7.19)$$

The Beeman integration scheme uses a more accurate expression for the velocity. As a consequence it often gives better energy conservation, because the kinetic energy is calculated directly from the velocities. However, the expressions used are more complex than those of the Verlet algorithm and so it is computationally more expensive.

Gear Predictor-Corrector Algorithmen

The predictor–corrector methods [Gear 1971] form a general family of integration algorithms from which one can select a scheme that is correct to a given order. These methods have three basic steps. First, new positions, velocities, accelerations and higher-order terms are predicted according to the Taylor expansion, Equations (7.2)–(7.4). In the second stage, the forces are evaluated at the new positions to give accelerations $\mathbf{a}(t+\delta t)$. These accelerations are then compared with the accelerations that are predicted from the Taylor series expansion, $\mathbf{a}^c(t+\delta t)$. The difference between the predicted and calculated accelerations is then used to 'correct' the positions, velocities, etc., in the correction step:

$$\Delta\mathbf{a}(t+\delta t) = \mathbf{a}^c(t+\delta t) - \mathbf{a}(t+\delta t) \quad (7.22)$$

Then

$$\mathbf{r}^c(t+\delta t) = \mathbf{r}(t+\delta t) + c_0\Delta\mathbf{a}(t+\delta t) \quad (7.23)$$

$$\mathbf{v}^c(t+\delta t) = \mathbf{v}(t+\delta t) + c_1\Delta\mathbf{a}(t+\delta t) \quad (7.24)$$

$$\mathbf{a}^c(t+\delta t)/2 = \mathbf{a}(t+\delta t)/2 + c_2\Delta\mathbf{a}(t+\delta t) \quad (7.25)$$

$$\mathbf{b}^c(t+\delta t)/6 = \mathbf{b}(t+\delta t)/6 + c_3\Delta\mathbf{a}(t+\delta t) \quad (7.26)$$

Gear has suggested 'best' values of the coefficients $c_0, c_1, \ldots$. The set of coefficients to use depends upon the order of the Taylor series expansion. In Equations (7.23)–(7.26) the expansion has been truncated after the third derivative of the positions (i.e. $\mathbf{b}(t)$). The appropriate set of coefficients to use in this case is $c_0 = \frac{1}{6}$, $c_1 = \frac{5}{6}$, $c_2 = 1$ and $c_3 = \frac{1}{3}$.

Energie-fluktuation

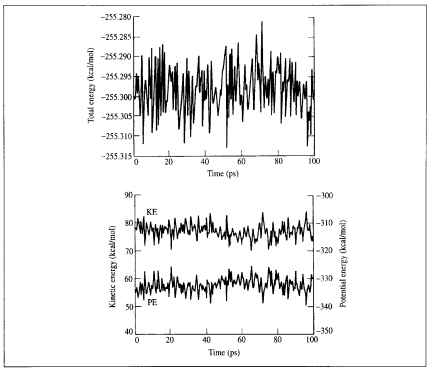


Fig. 7.3: Variation in total energy versus time for the production phase of a molecular dynamics simulation of 256 argon atoms at a temperature of 100 K and a density of 1.396 g cm^{-3} (top). The time step was 10 fs and the equations of motion were integrated using the velocity Verlet algorithm. The variations in the kinetic and potential energies are also shown (bottom). The graphs have different scales.

Zeitschrittlänge

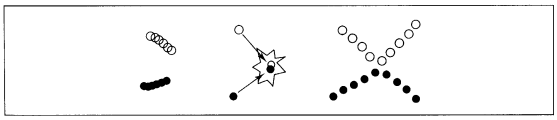


Fig. 7.4: With a very small time step (left) phase space is covered very slowly; a large time step (middle) gives instabilities. With an appropriate time step (right) phase space is covered efficiently and collisions occur smoothly.

System	Types of motion present	Suggested time step (s)
Atoms	Translation	10^{-14}
Rigid molecules	Translation and rotation	5×10^{-15}
Flexible molecules, rigid bonds	Translation, rotation, torsion	2×10^{-15}
Flexible molecules, flexible bonds	Translation, rotation, torsion, vibration	10^{-15} or 5×10^{-16}

Table 7.1 The different types of motion present in various systems together with suggested time steps.

Energieerhaltung

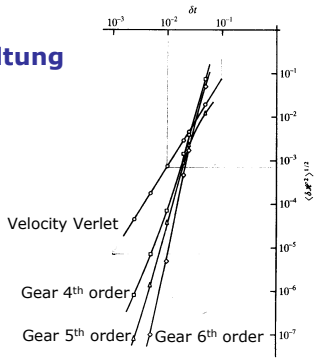


Fig. 3.3 Energy conservation of various algorithms. The system studied is as for Fig. 3.1. We calculate RMS energy fluctuations $\langle \delta \mathcal{H}^2 \rangle^{1/2}$ for various runs starting from the same initial conditions, and proceeding for the same total simulation time t_{run} but using different time steps δt and corresponding numbers of steps $\tau_{run} = t_{run}/\delta t$. The plot uses log-log scales. The curves correspond to velocity Verlet (circles), Gear fourth-order (squares), Gear fifth-order (triangles), and Gear sixth-order (diamonds) algorithms.

Temperatur

Momentane Temperatur *T*(*t*):

$$\frac{1}{2} N k_B T(t) = E_{kin}(t) = \sum_{i=1}^{n} \frac{1}{2} m_i v_i^2$$

N = Anzahl Freiheitsgrade (*N* = 3*n*), *n* = Anzahl Atome

Methoden fur MD Simulation bei konstanter Temperatur:
- (strikt) konstante kinetische Energie und Temperatur
- erweitertes System mit zusätzlichem Freiheitsgrad
- schwache Kopplung an ein Wärmebad

Druck

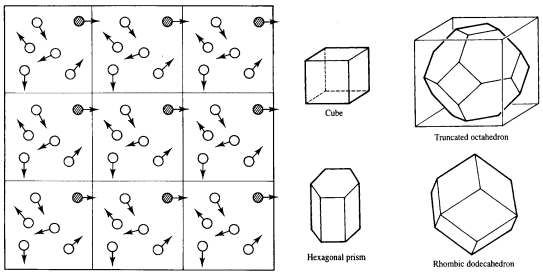
Druck = Kraft pro Flächeneinheit auf die Wände des Systems
Aber: bei periodischen Randbedingungen keine Wand vorhanden

Virialsatz: $$P = \frac{2}{3V}\left[E_{kin} + \frac{1}{2}\sum_{i=1}^{n} \vec{r}_{ij} \cdot \vec{F}_{ij}\right]$$

P = Druck, *V* = Volumen

Methoden fur MD Simulation bei konstantem Druck:
- (strikt) konstanter Druck
- erweitertes System mit zusätzlichem Freiheitsgrad
- schwache Kopplung

Periodische Randbedingungen

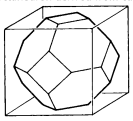


Periodische Randbedingungen

Rectangular box, side 2*a* (*x*) bv 2*b* (*y*) by 2c (*z*)

$x = x - 2 \times a \times \mathrm{AINT}(x/a)$
$y = y - 2 \times b \times \mathrm{AINT}(y/b)$
$z = z - 2 \times c \times \mathrm{AINT}(z/c)$
A common alternative is:
$x = x - a \times \mathrm{ANINT}(x/a)$
$y = y - b \times \mathrm{ANINT}(y/b)$
$z = z - c \times \mathrm{ANINT}(z/c)$

Truncated octahedron derived from cube of side 2*a*



$x = x - 2 \times a \times \mathrm{AINT}(x/a)$
$y = y - 2 \times b \times \mathrm{AINT}(y/a)$
$z = z - 2 \times c \times \mathrm{AINT}(z/a)$
if $(ABS(x) + ABS(y) + ABS(z)) \geq 1.5 \times A$
then
  $x = x - \mathrm{SIGN}(a, x)$
  $y = y - \mathrm{SIGN}(a, y)$
  $z = z - \mathrm{SIGN}(a, z)$
endif

Hexagonal prism of length 2*a* (in *z* direction) and distance between opposite faces of the hexagon 2b

$z = z - 2 \times a \times \mathrm{AINT}(z/a)$
  $x = x - 2 \times b \times \mathrm{AINT}(x/b)$
if $(\mathrm{ABS}(x) + \sqrt{3} \times \mathrm{ABS}(y)) \geq 2 \times B$ then
  $x = x - \mathrm{SIGN}(b, x)$
  $y = y - \mathrm{SIGN}(\sqrt{3} \times b, y)$
endif