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Introduction to Molecular Modeling and Molecular Dynamics Simulations

Dr. Zoe Cournia

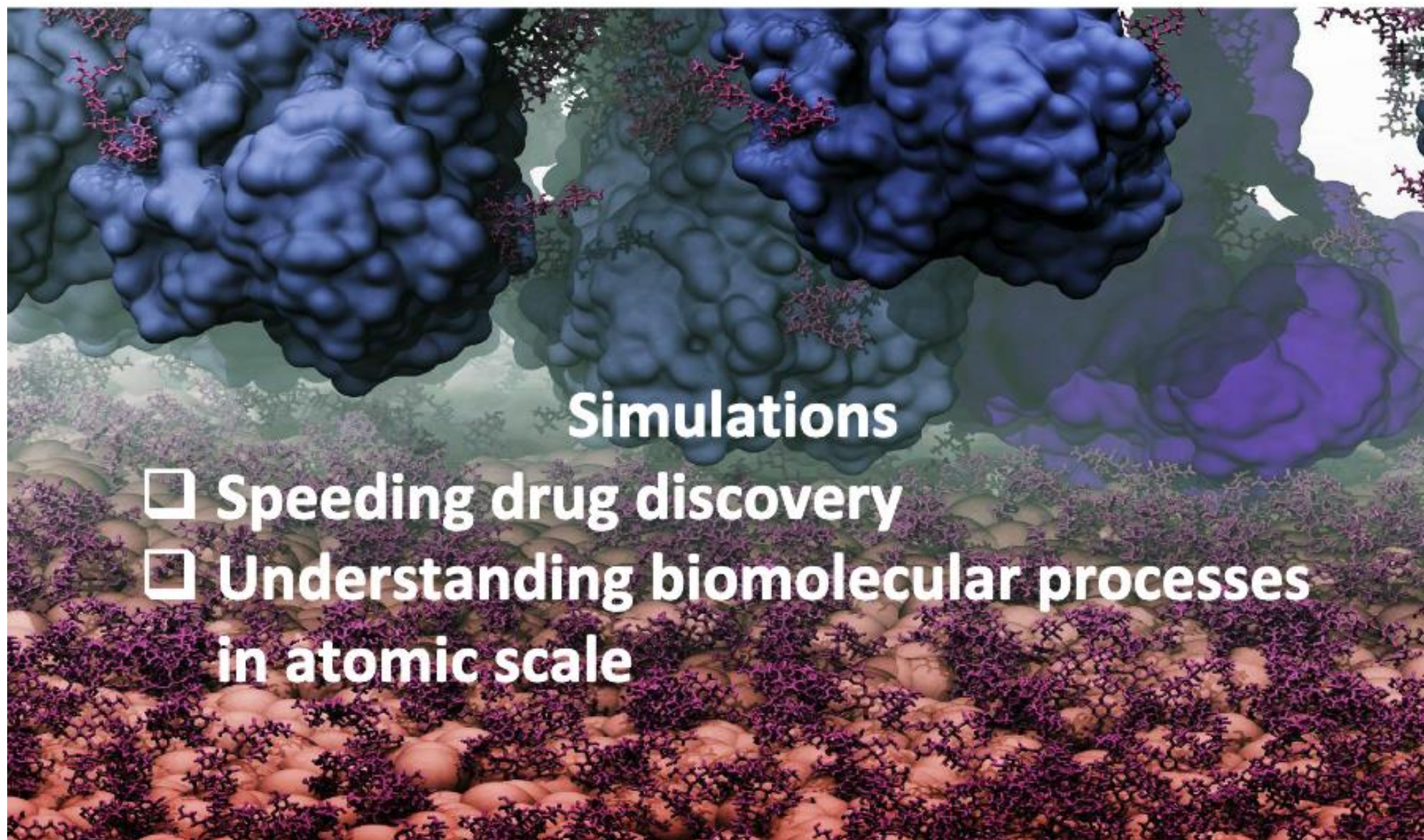
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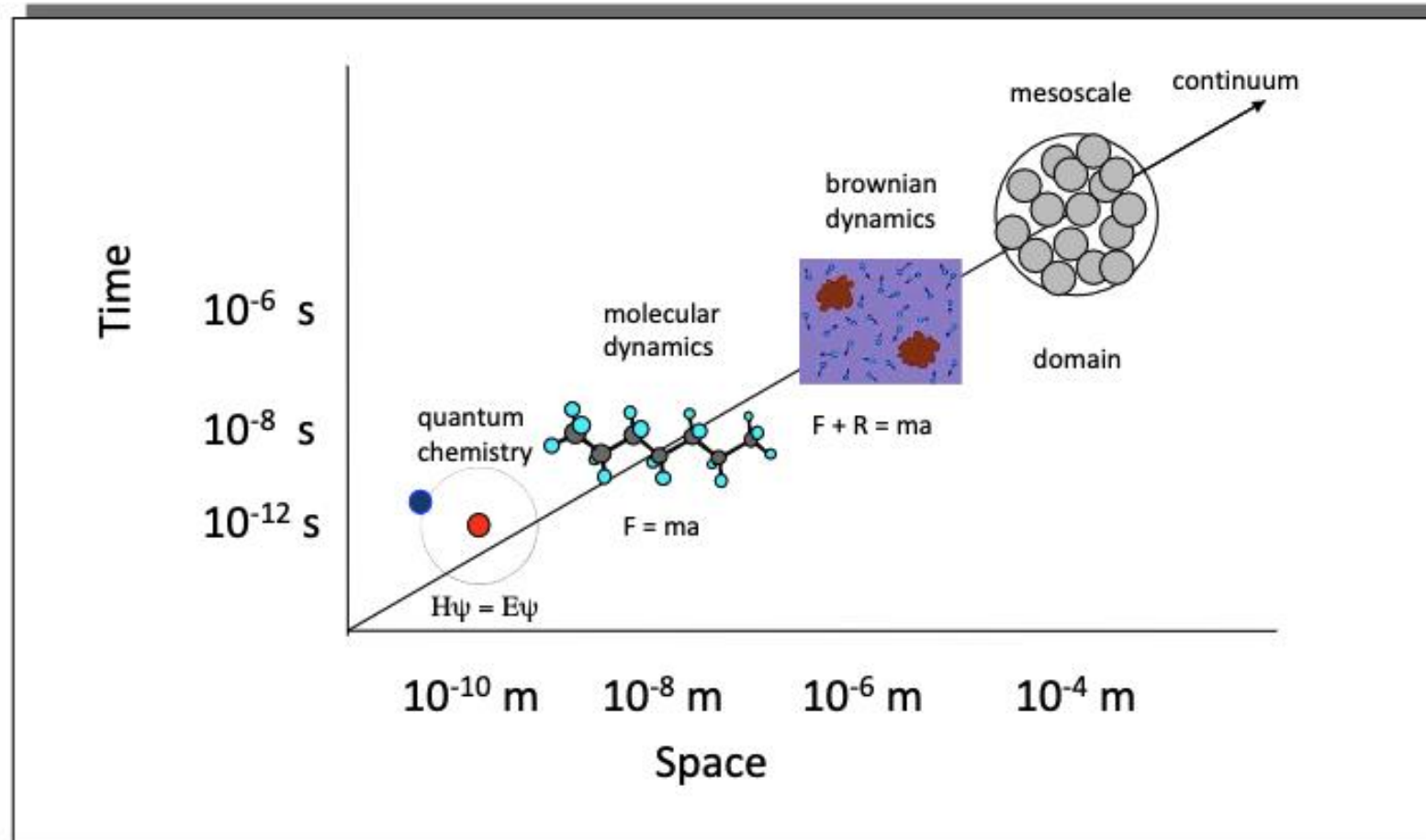
PARTNERSHIP FOR ADVANCED COMPUTING IN EUROPE



Simulations

- ☐ Speeding drug discovery
- ☐ Understanding biomolecular processes in atomic scale

Molecular Simulations Across Scales



Molecular Modeling

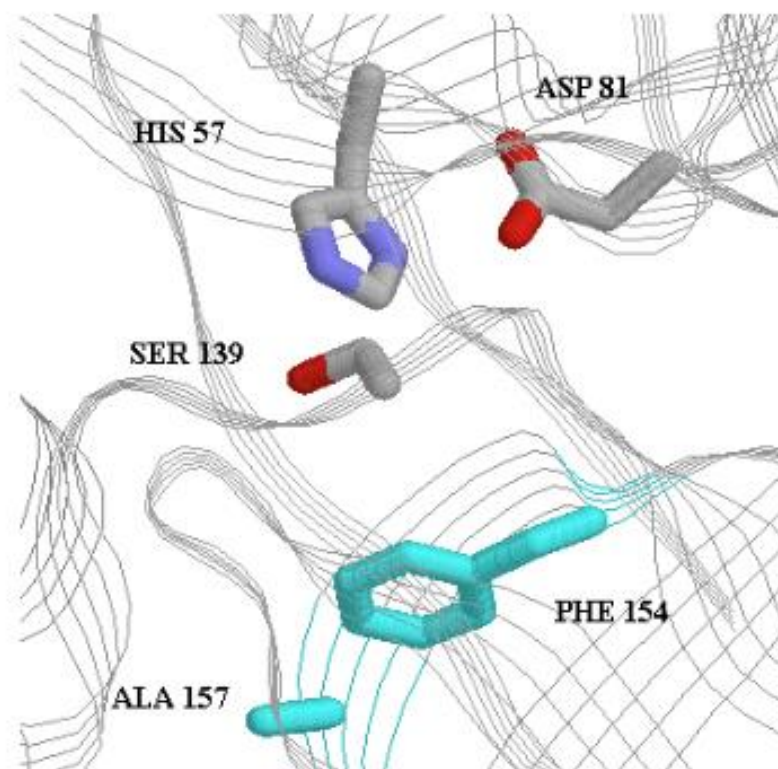
Structure *dynamics* -----> function

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Barnot p53 ILTIITLLEGGGELLGRNRFVPPVACFGRRRTTEE 265
Canine p53 ILTIITLLEGGGELLGRNRFVPPVACFGRRRTTEE 275
Feline p53 ILTIITLLEGGGELLGRNRFVPPVACFGRRRTTEE 260
Horse p53 ILTIITLLEGGGELLGRNRFVPPVACFGRRRTTEE 267
Rat p53 ILTIITLLEGGGELLGRNRFVPPVACFGRRRTTEE 265
Xenopus p53 ILTIITLLEGGGELLGRNRFVPPVACFGRRRTTEE 262
Zebrafish p53 ILTIITLLEGGGELLGRNRFVPPVACFGRRRTTEE 255
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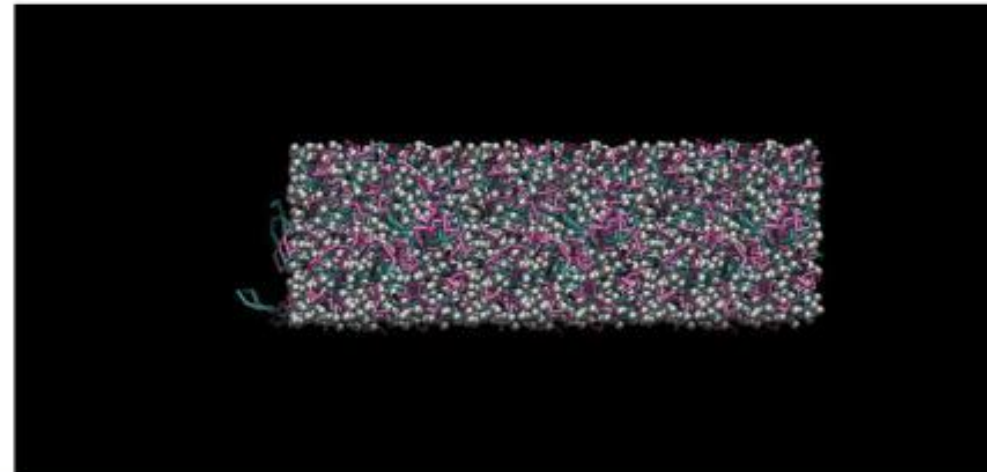
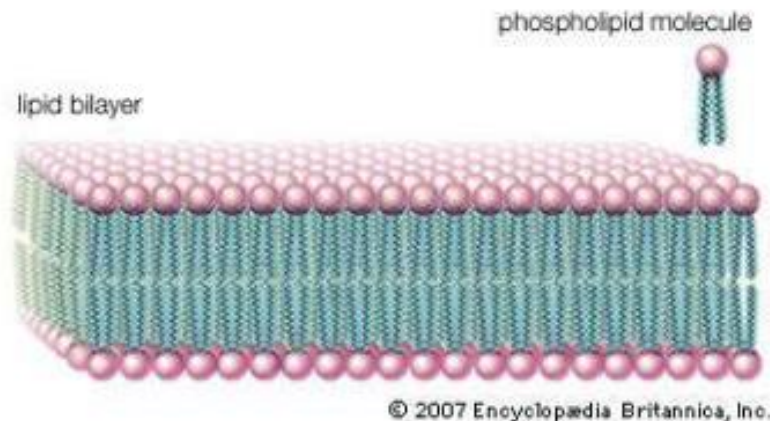
Molecular Dynamics

- molecular/atomic level picture of structure and dynamics
- property prediction
- ion transport
- solvent effects
- protein stability / conform. changes, ...



Molecular Dynamics

- A computational method which describes equilibrium and dynamics properties of a biological system
- Generates configurations of the system by integration of Newton's law of motion – calculate the time dependence of the molecular system
- Generates information at the microscopic level –atomic positions and velocities and connects to macroscopic properties through Statistical Mechanics
- Connects structure and function by providing additional information to experimental techniques through the system dynamics



Statistical Mechanics

- In Molecular Dynamics simulations we explore the **macroscopic** properties of a system through **microscopic** simulations
- The connection between microscopic simulations and macroscopic properties is made via **statistical mechanics**, which studies a macroscopic system from a molecular point of view
- The distribution of the system within the ensemble follows the **Boltzmann distribution**
- **Ensemble**: collection of all possible systems which have different microscopic states but identical macroscopic or thermodynamic state



The Nobel Prize in Chemistry 2013

Martin Karplus, Michael Levitt, Arieh Warshel

The Nobel Prize in Chemistry 2013



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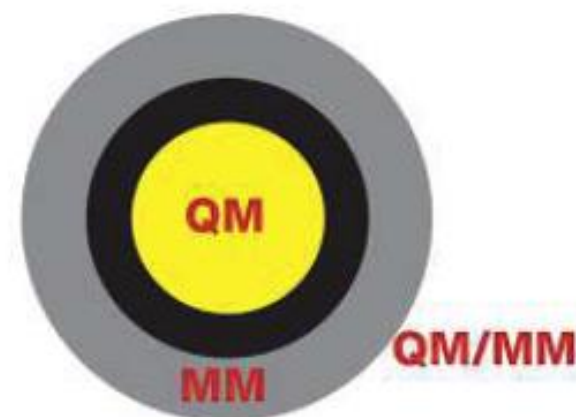
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Michael Levitt



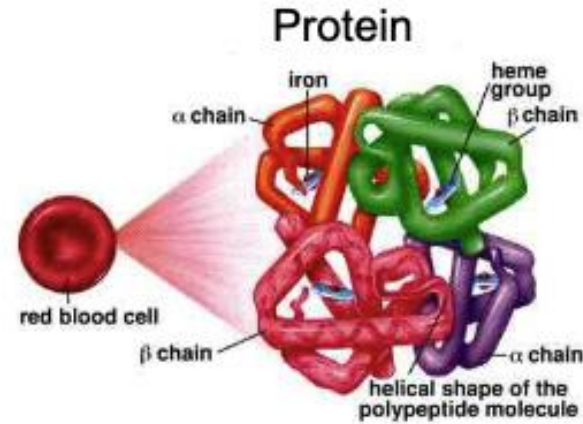
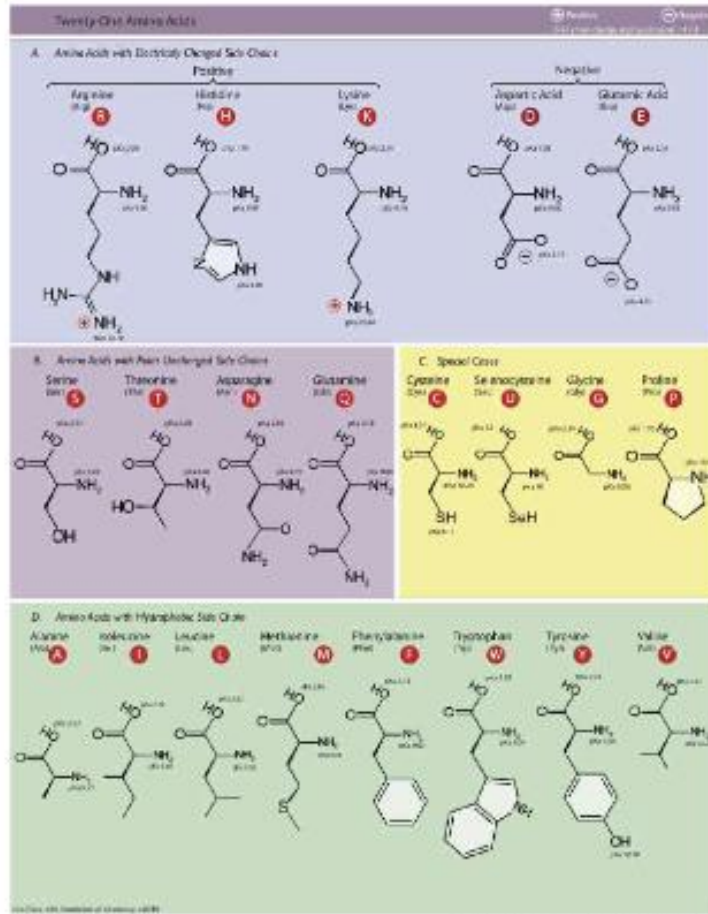
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Arieh Warshel

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel "for the development of multiscale models for complex chemical systems".

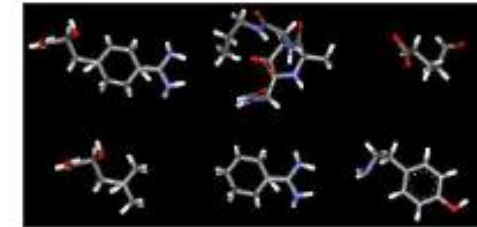
$$\begin{aligned}
 U = & \sum_{\text{All Bonds}} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\text{All Angles}} \frac{1}{2} K_\theta (\theta - \theta_0)^2 \\
 & + \sum_{\text{All Torsion Angles}} K_\phi [1 - \cos(n\phi + \delta)] \\
 & + \sum_{\text{All nonbonded pairs}} \epsilon \left[\left(\frac{r_0}{r} \right)^{12} - 2 \left(\frac{r_0}{r} \right)^6 \right] \\
 & + \sum_{\text{All partial charges}} \frac{332 q_i q_j}{r}
 \end{aligned}$$



Inter- and Intramolecular Interactions



Small molecules
(Drugs)



Intramolecular interactions
Bonded and Non-Bonded interactions

Intermolecular interactions (non-bonded)
Hydrogen Bonds
Electrostatic interactions
van der Waals
 π - π interactions

Simplified schematic of the molecular dynamics algorithm

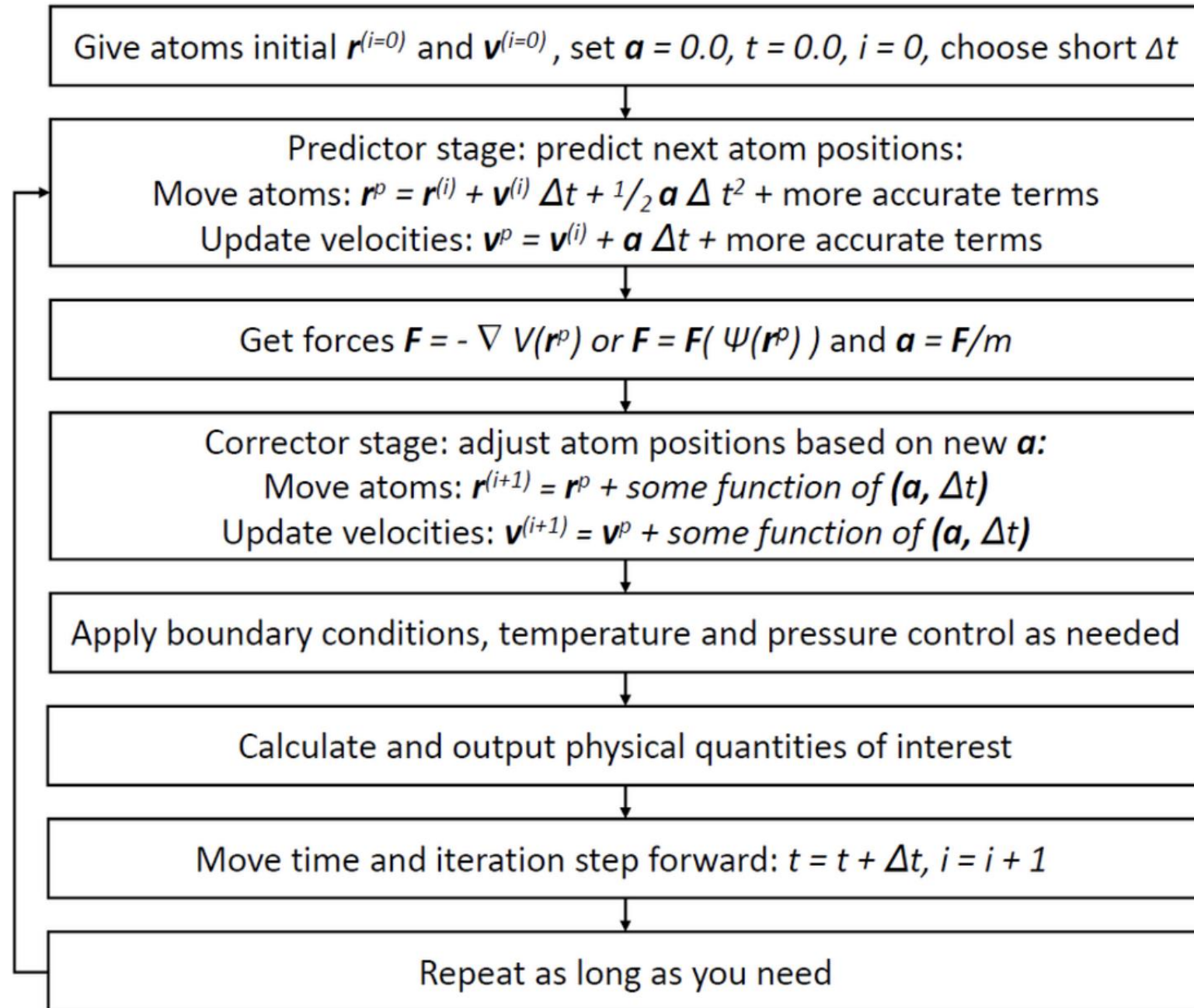


Table 1 UFF Lennard-Jones pair potential parameters

Atom	Epsilon (kcal mol ⁻¹)	Sigma (Å)
Al	230	2.500
C (cathode)	0.095	3.473
CE	0.105	3.851
Cu (cathode)	0.005	3.311
Cu (insulator)	230	2.500
F (LiPF ₆)	0.050	3.364
Li (LiPF ₆)	0.025	2.451
Li	0.305	2.051
O (SiO ₂)	0.050	4.442
OE	0.060	3.500
P (LiPF ₆)	0.305	4.147
P (anode)	0.500	3.330
S (cathode)	0.344	4.030
Si (SiO ₂)	0.050	3.442

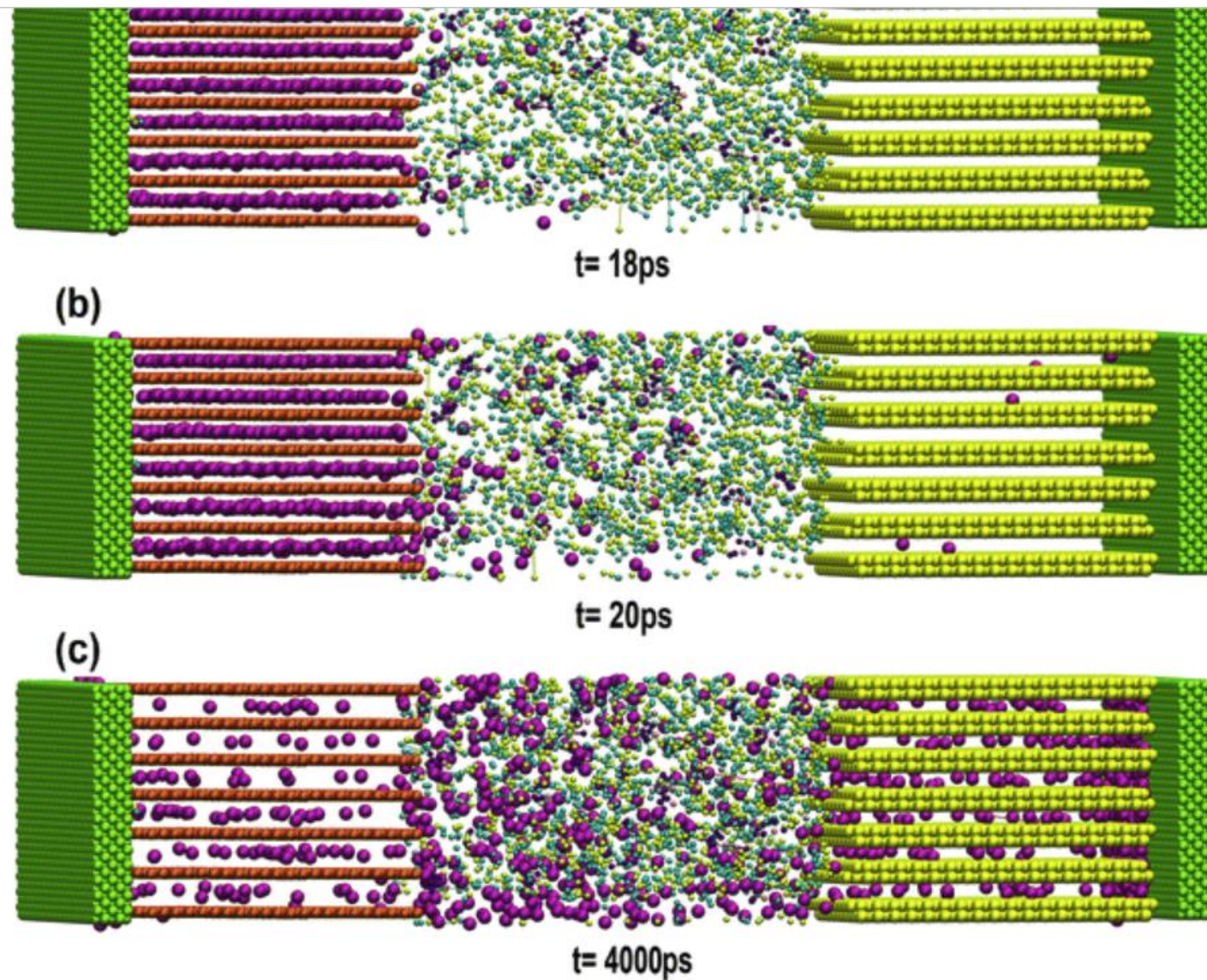


Fig. 3 Snapshots are taken during the first charge of the nanobattery. (a) Li-ion battery at 18 ps, no lithium atoms are stored in the anode. (b) Li-ion battery at 20 ps, the phosphorene layers will become the host of lithium atoms. (c) Snapshot of battery charging at