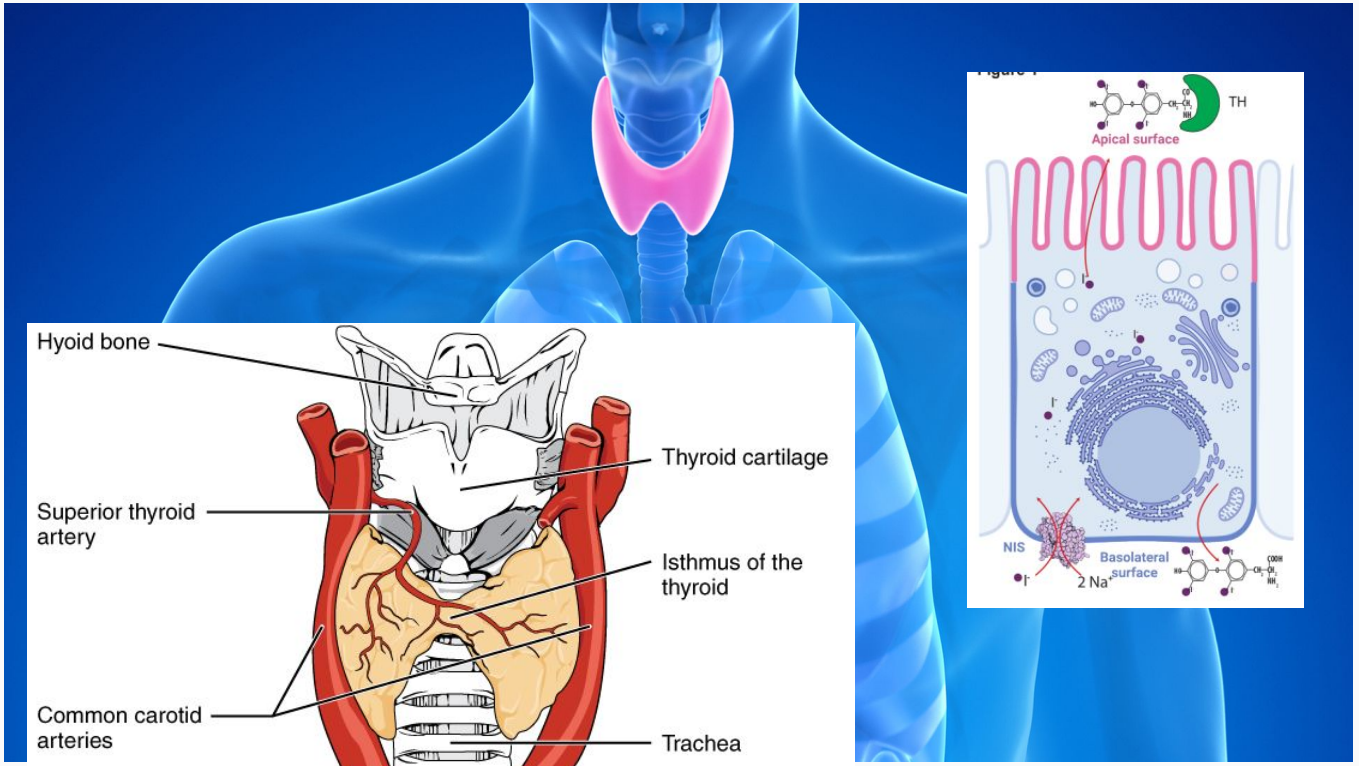
StatMech Insights on Na+/I− Symporter transport cycle

Mario A Bianchet & Alfonso Leyva

17.04.26

Thyroid - NIS


Hyoid bone
Thyroid cartilage
Superior thyroid artery
Isthmus of the thyroid
Common carotid arteries
Trachea
TH
Apical surface
NIS
Basolateral surface
2 Na+

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Article | Published: 14 December 2022

Structural insights into the mechanism of the sodium/iodide symporter

Silvia Ravera, Juan Pablo Nicola, Glicella Salazar-De Simone, Fred J. Sigworth, Erkan Karakas, L. Mario Amzel, Mario A. Bianchet & Nancy Carrasco ✉

Nature **612**, 795–801 (2022) | Cite this article

› bioRxiv [Preprint]. 2025 Oct 8:2025.10.07.681042. doi: 10.1101/2025.10.07.681042.

Engineering substrate selectivity in the human sodium/iodide symporter (NIS)

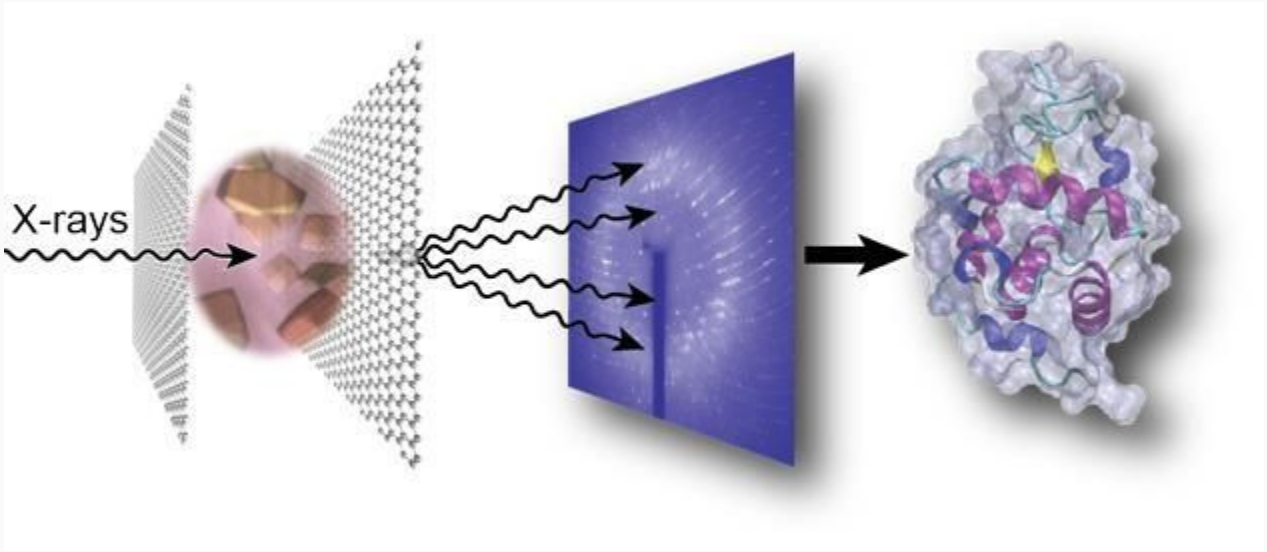
Alejandro Llorente-Esteban, Haswitha Sabbineni, Kendra Hoffsmith, Rían W Manville, David López-González, Andrea Reyna-Neyra, J Alfonso Leyva, Geoffrey W Abbott, Mario A Bianchet, Nancy Carrasco

PMID: 41280013 PMCID: PMC12632592 DOI: 10.1101/2025.10.07.681042

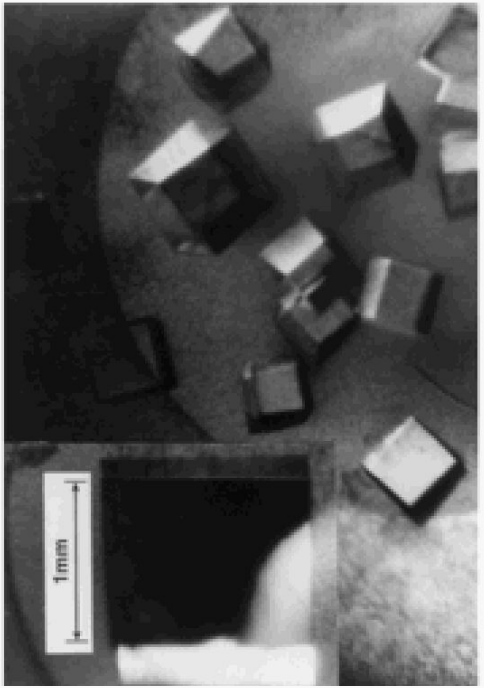
Abstract

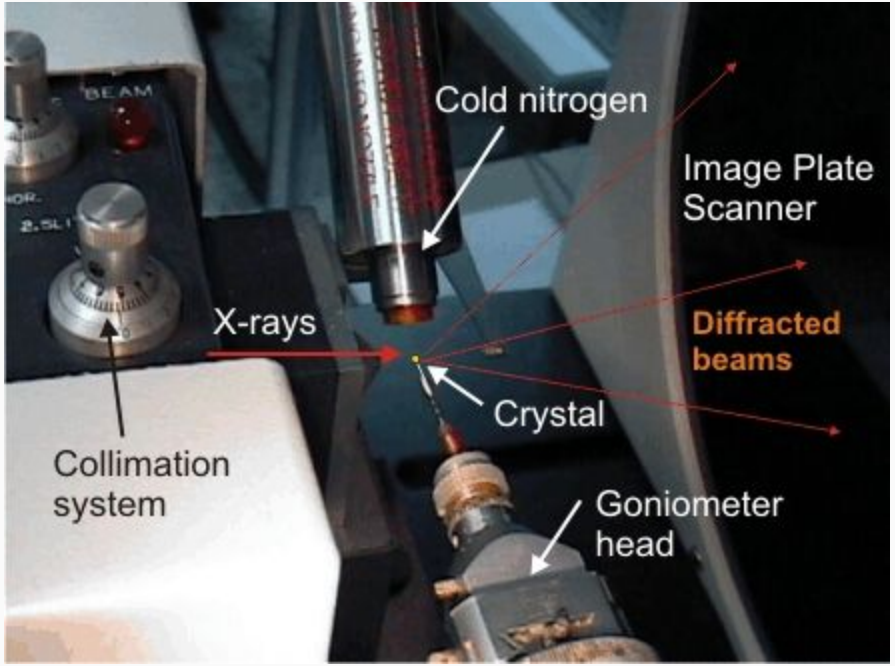
Iodide (I^-) uptake mediated by the Na^+/I^- symporter (NIS) is the first step in the biosynthesis of the thyroid hormones, of which I^- is an essential constituent. NIS couples the inward transport of I^- against its electrochemical gradient to the inward translocation of Na^+ down its electrochemical gradient. NIS also transports oxyanions (XO_4^-s), such as perrhenate (ReO_4^-) and the environmental pollutant perchlorate (ClO_4^-). Furthermore, NIS is the basis for radioiodide ($^{131}I^-$) therapy for thyroid cancer (administered after thyroidectomy), the most effective targeted internal radiation cancer therapy available. $^{131}I^-$ selectively targets remnant malignant cells and metastases expressing NIS, causing only minor side effects. There is great interest in expressing NIS exogenously, by gene transfer, in extrathyroidal cancers to render them susceptible to destruction by $^{131}I^-$. This approach,

Very Basics of X-Ray Crystallography

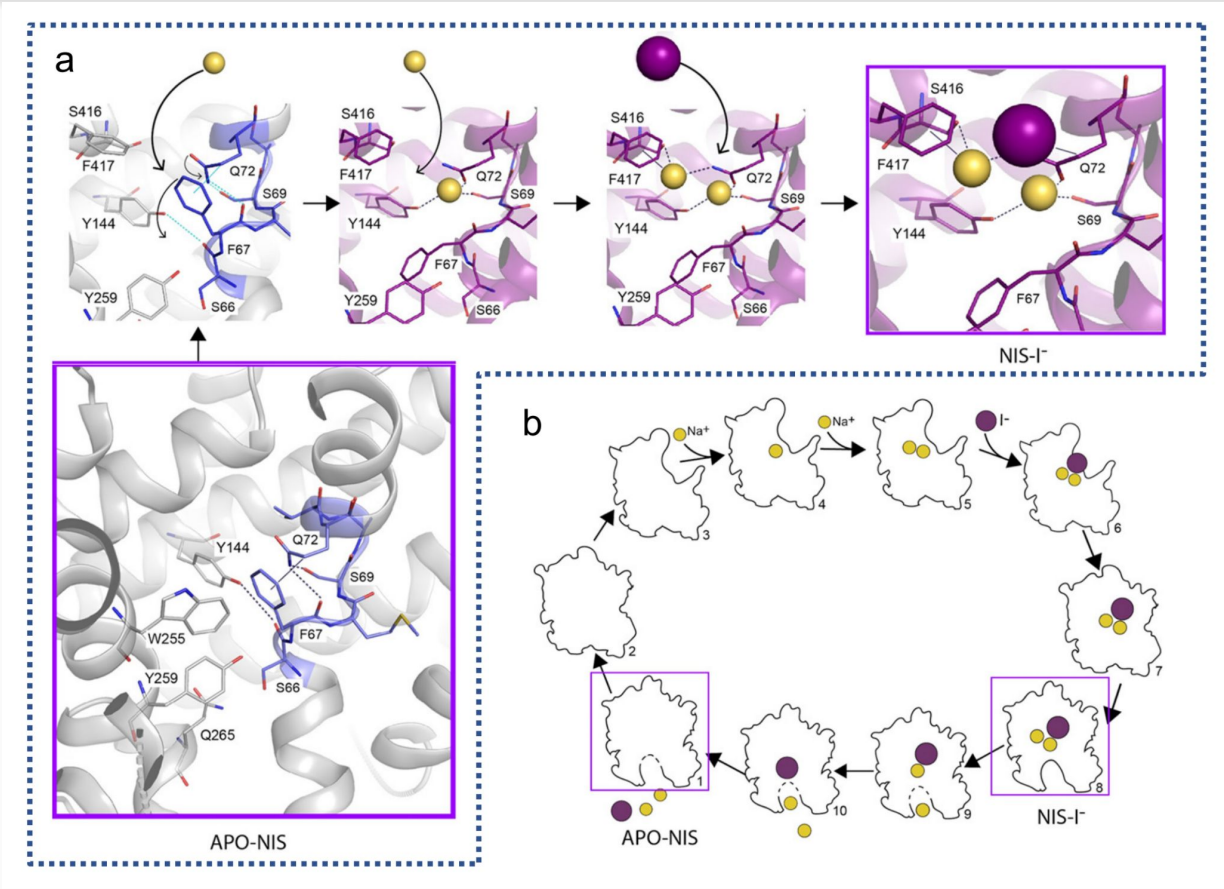


Very Basics of X-Ray Crystallography

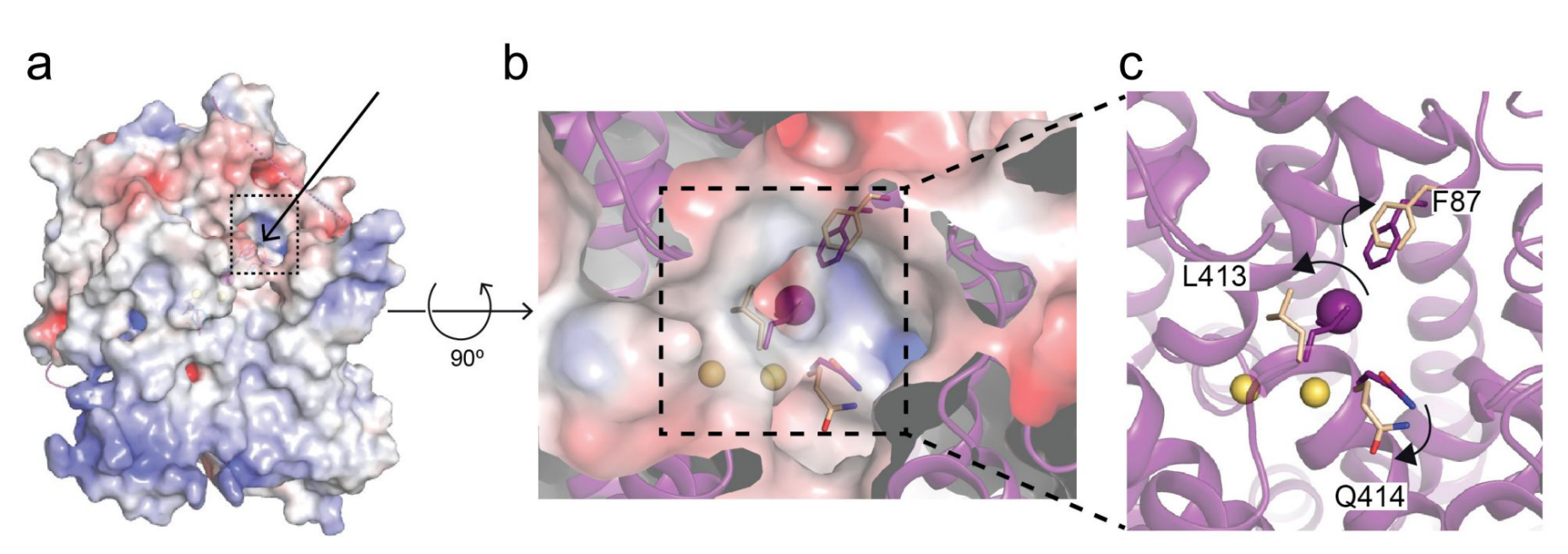




Basics of NIS



Basics of NIS



Primary goal of MD simulation:
computing the trajectories of atoms/particles in a system

- Numerical method is applied to solve Newton's equations of motion.

$$m_1 \frac{dv_1}{dt} = F_1(r_1, r_2, \dots), \quad \frac{dr_1}{dt} = v_1$$

$$m_2 \frac{dv_2}{dt} = F_2(r_1, r_2, \dots), \quad \frac{dr_2}{dt} = v_2$$

.....

$$m_i \frac{dv_i}{dt} = F_i(r_1, r_2, \dots), \quad \frac{dr_i}{dt} = v_i$$

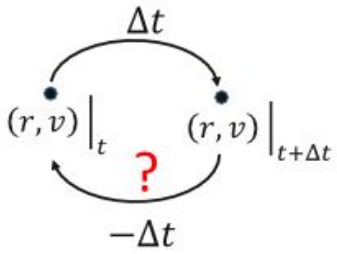
.....

for $i = 1, \dots, N$

An initial value problem:

Given $\{r_i(0), v_i(0)\}_{i=1}^{N}$, find atomic trajectories at any time moment: $\{r_i(t), v_i(t)\}_{i=1}^{N}$

Chasing only for the accuracy of calculation:
Essential requirement: time-reversal symmetry, is not held in the above methods



- Verlet's method (1967): a time-reversible algorithm,

$$r(t+\Delta t) = 2r(t) - r(t-\Delta t) + r''(t)\Delta t^2 + O(\Delta t^4)$$

$$v(t) = \frac{r(t+\Delta t) - r(t-\Delta t)}{2\Delta t} + O(\Delta t^3)$$

derived by adding and subtracting the two Taylor series expansions:

$$r(t+\Delta t) = r(t) + r'(t)\Delta t + \frac{1}{2}r''(t)\Delta t^2 + \frac{1}{3!}r'''(t)\Delta t^3 + O(\Delta t^4)$$

$$r(t-\Delta t) = r(t) - r'(t)\Delta t + \frac{1}{2}r''(t)\Delta t^2 - \frac{1}{3!}r'''(t)\Delta t^3 + O(\Delta t^4)$$

Advantages: simplicity, good stability, time symmetry,
suitable for studying molecular dynamics

Molecular Dynamics Fundamentals

Class I Force field:

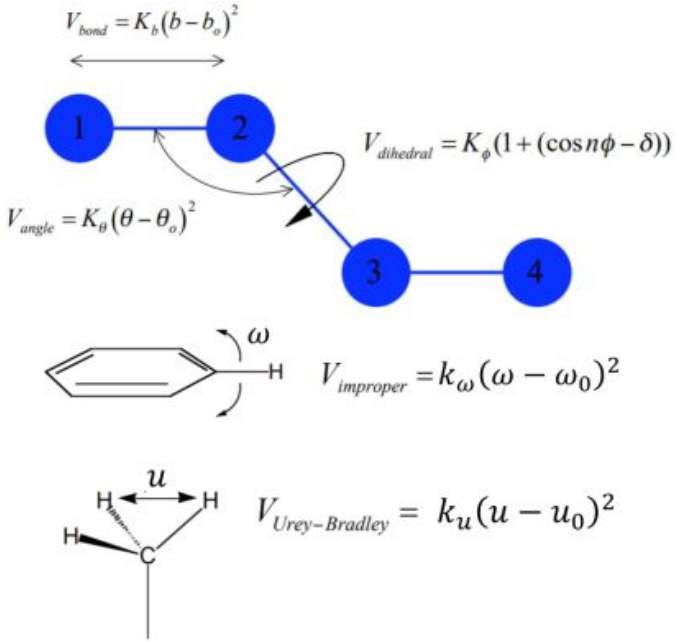
$$E = \sum_{bonds} k_b(b - b_0)^2 + \sum_{angles} k_\theta(\theta - \theta_0)^2$$

$$+ \sum_{dihedrals} k_\phi(1 + \cos(n\phi - \delta))$$

$$+ \sum_{impropers} k_\omega(\omega - \omega_0)^2$$

$$+ \sum_{Urey-Bradley} k_u(u - u_0)^2$$

$$+ \sum_{vdW} 4\varepsilon\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right] + \sum_{coulomb} \frac{q_i q_j}{4\pi\varepsilon\varepsilon_0 r_{ij}}$$



CHARMM, AMBER, GROMACS, OPLS

Molecular Dynamics Fundamentals

Physics of a system are known if we know the trajectory, more precisely, the phase-space trajectory $\{r_i(t), p_i(t)\}_{i=1}^{N}$

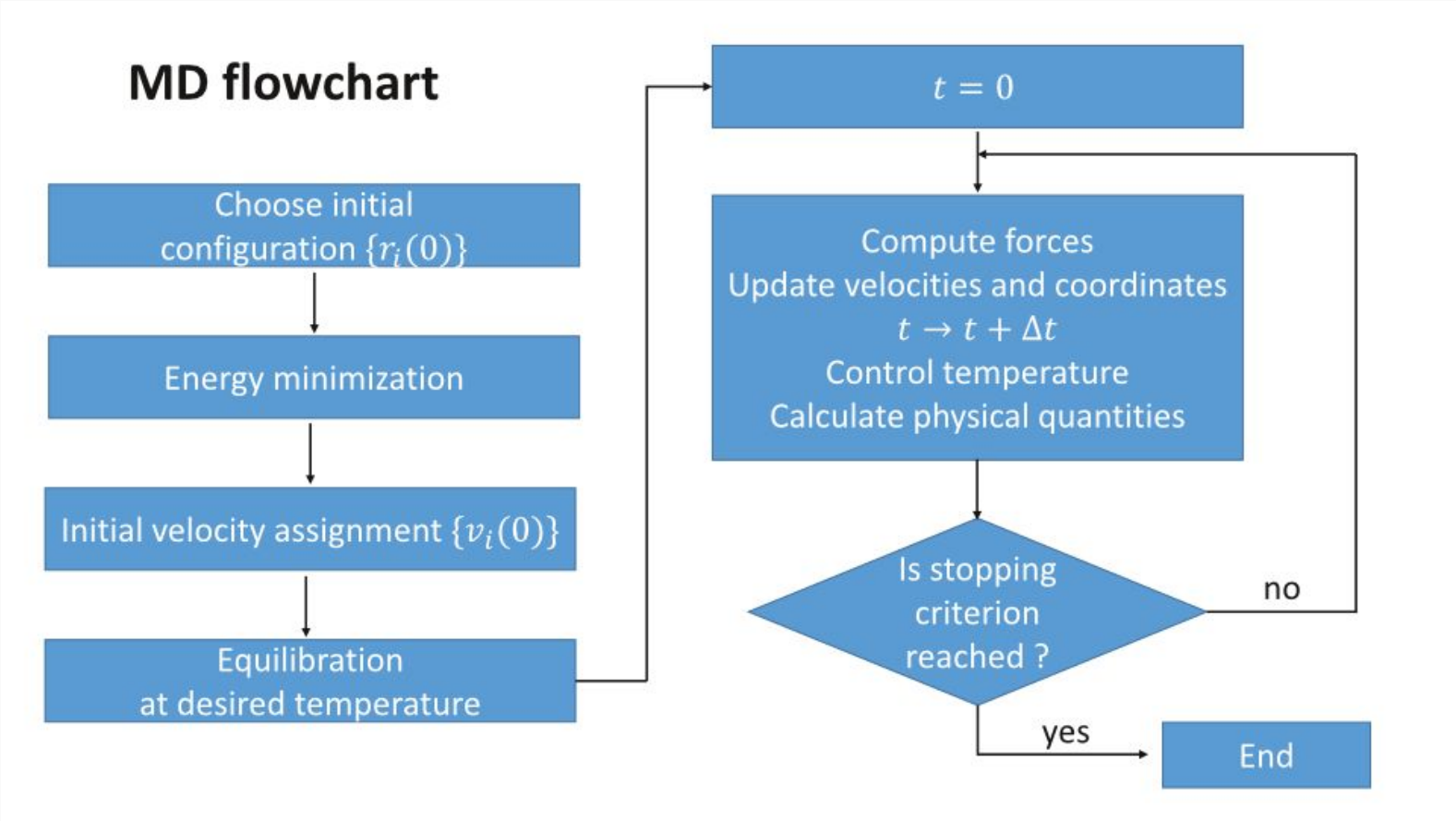
Hamitonian $H(\{r_i, p_i\}) = \left(\sum_{i=1}^{N} \frac{p_i^2}{2m_i}\right) + U(\{r_i, p_i\})$

$\Rightarrow$ physical quantity $A(\{r_i, p_i\})$

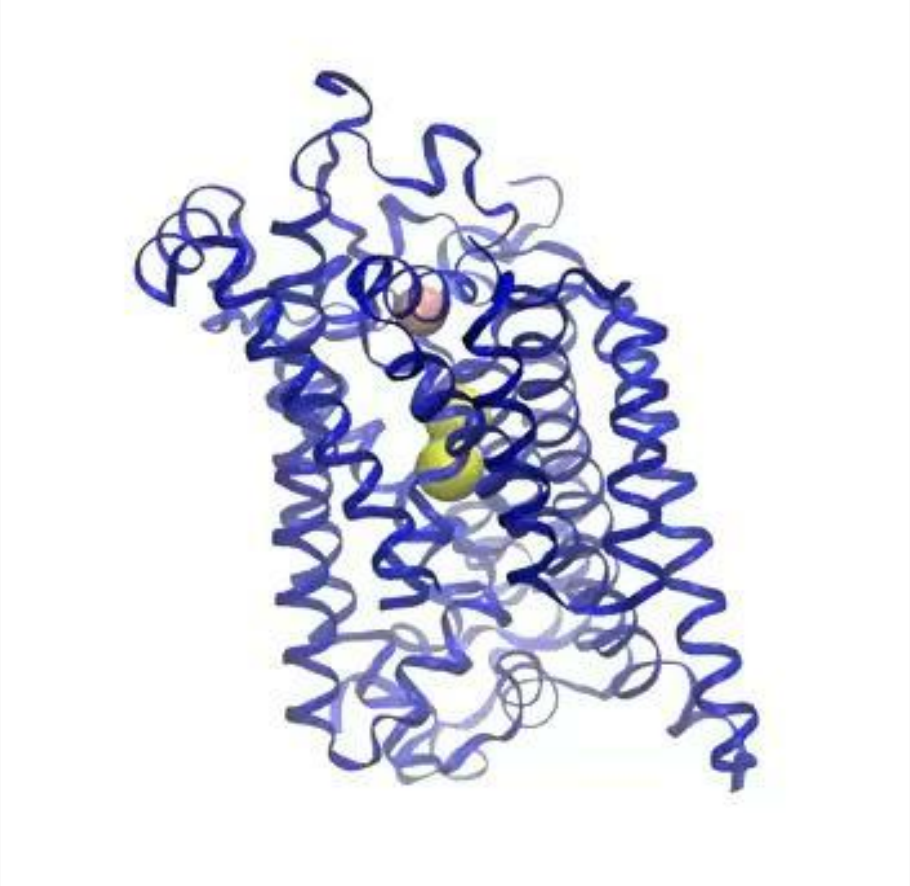
Topics of study: any kind of energy, pressure, temperature, force, interaction, ...
static properties: molecular shape, size, crystalline structure, dislocation, g(r), ...
dynamic properties: diffusion, heat transfer, time correlaction,....
responses: shearing, stress, strain, electric field, temperature gradient .....

Domains of application: physics, chemistry, engineering, materials sciences, molecular biology,...

Molecular Dynamics Fundamentals



Basics of NIS



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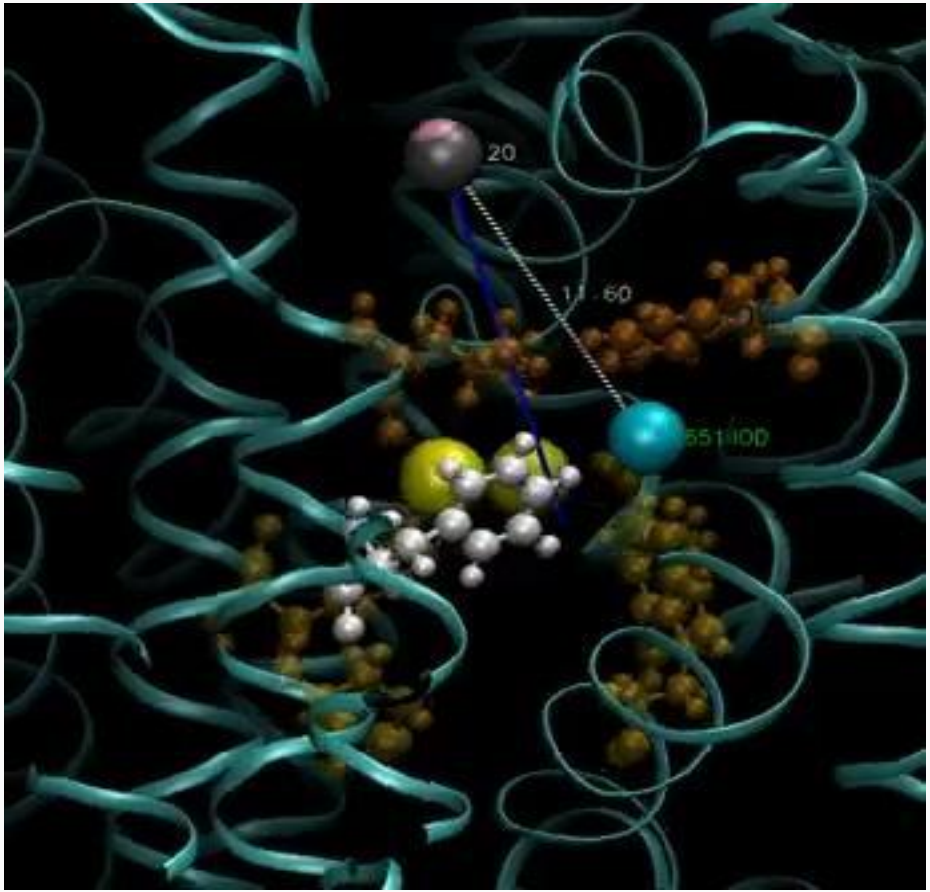
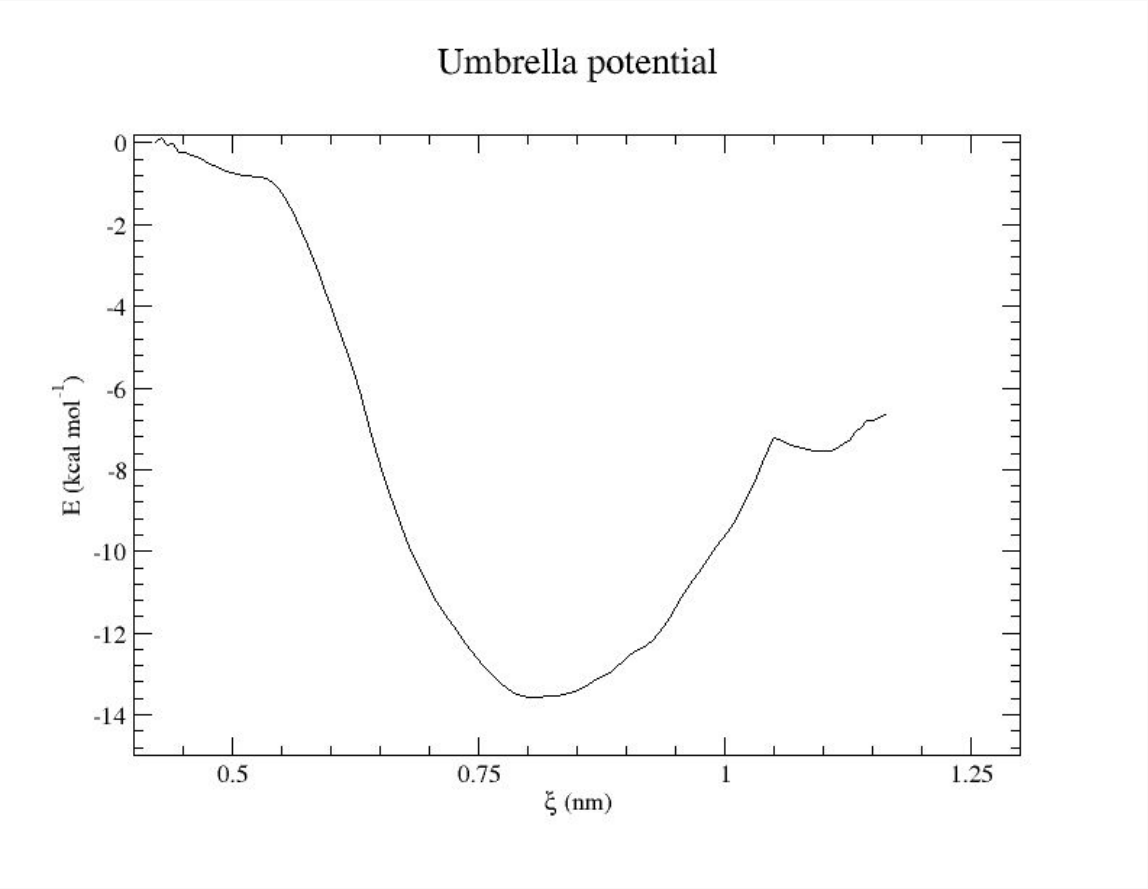
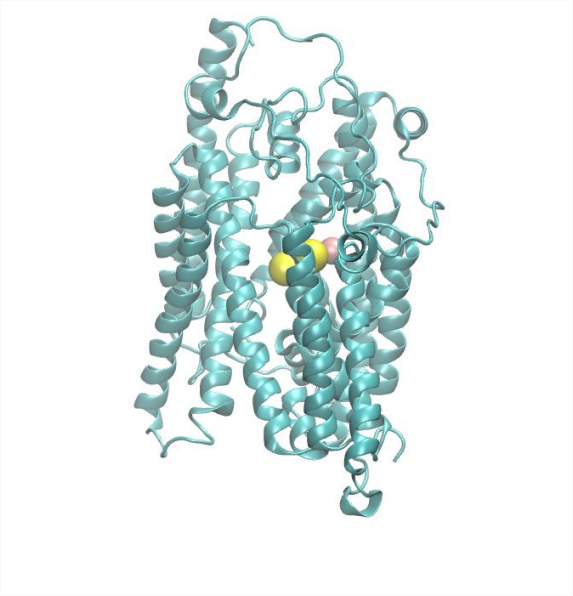
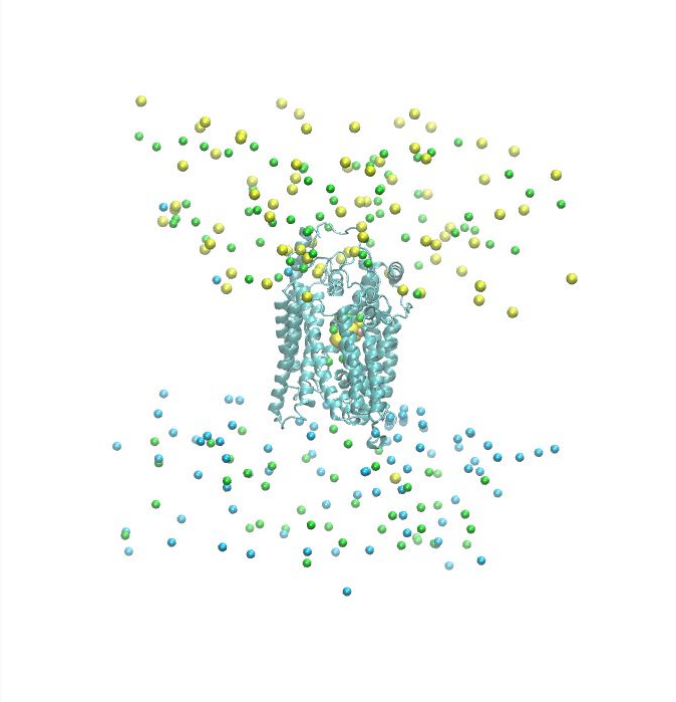


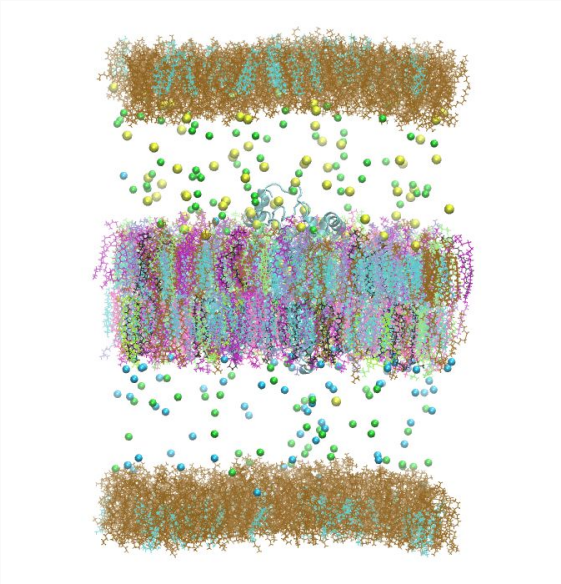
Basics of NIS



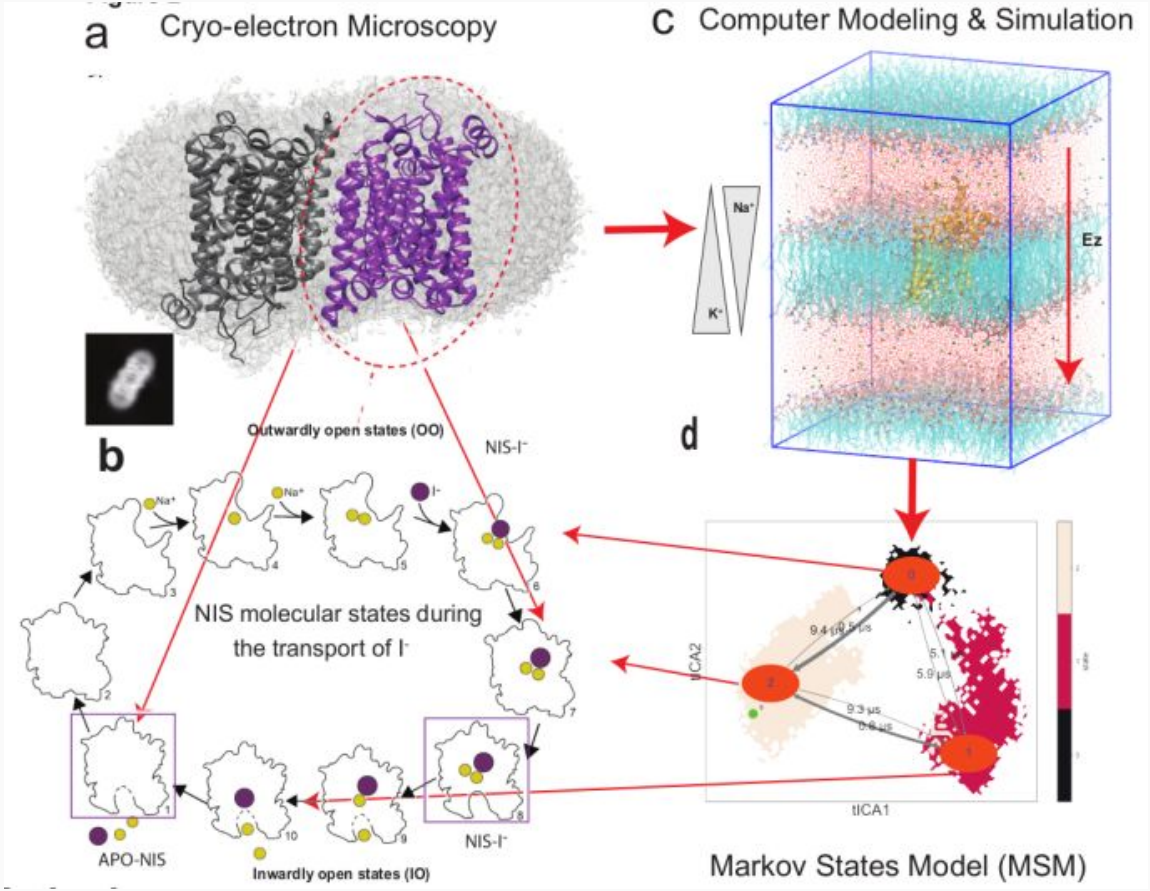
Basics of NIS

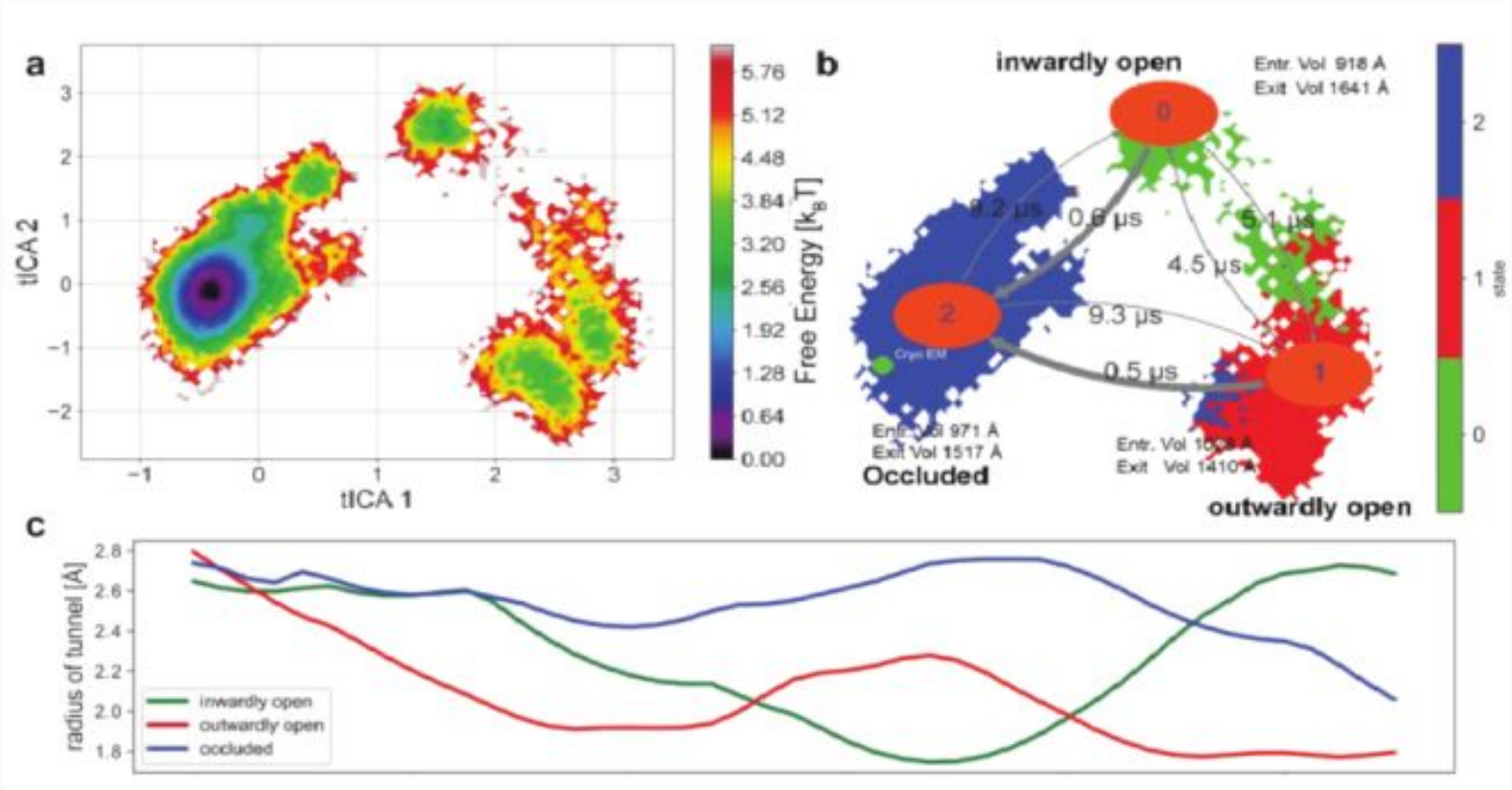


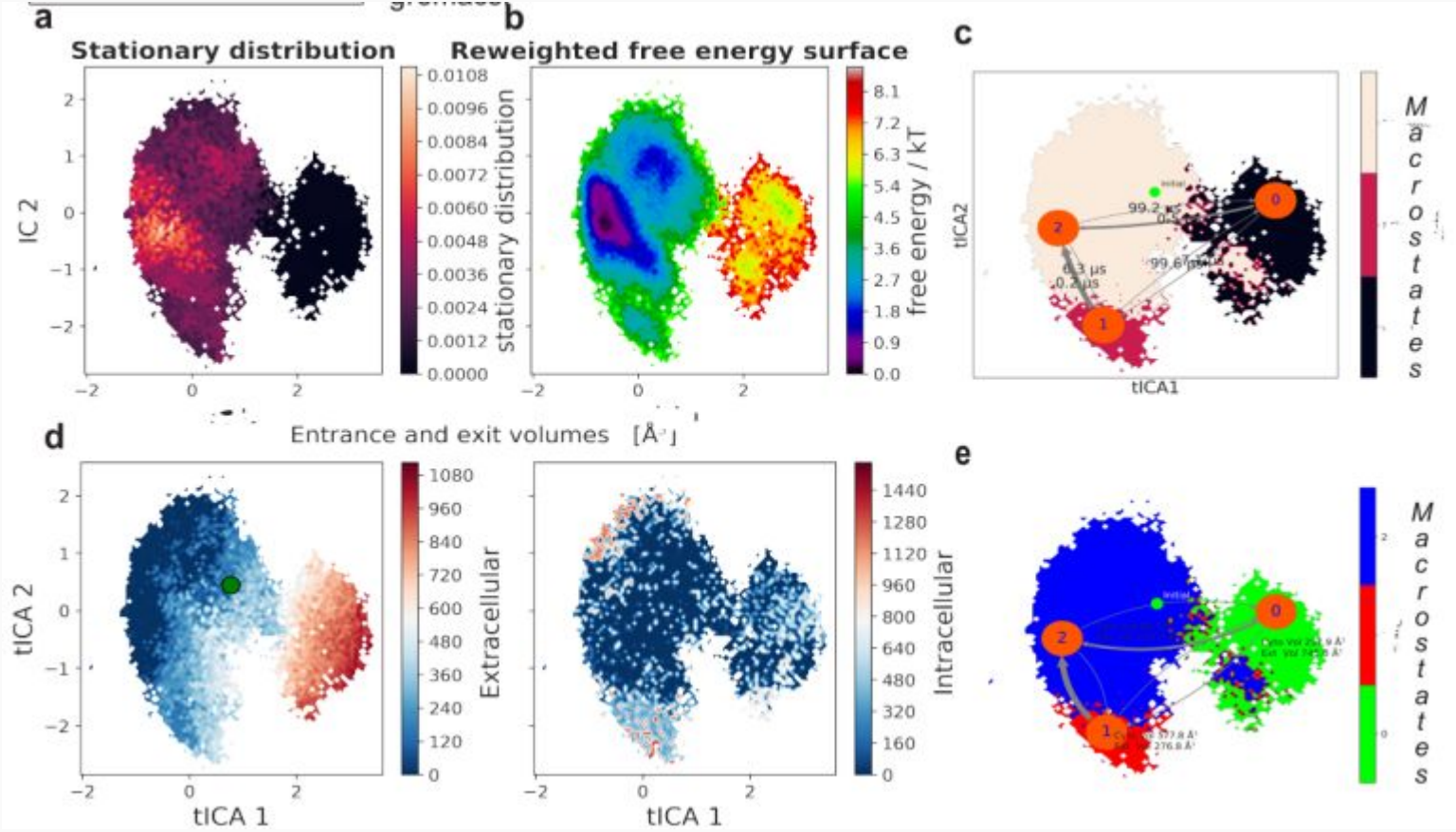


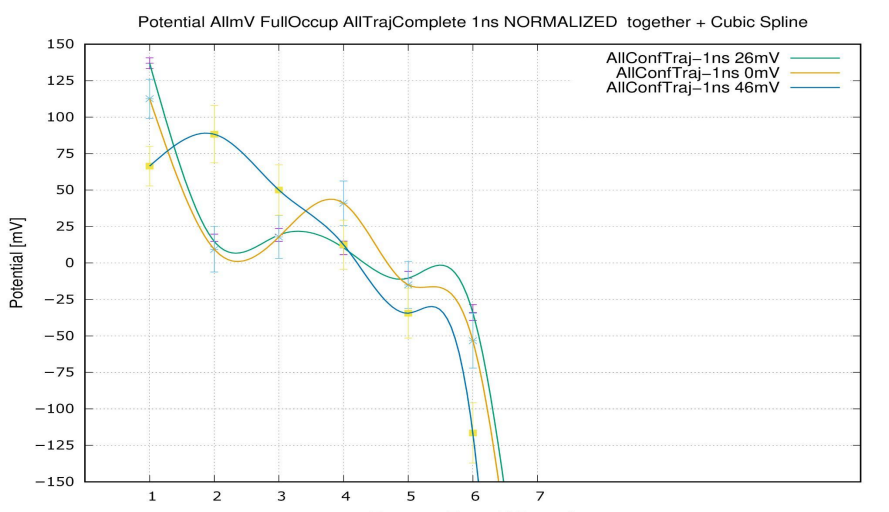


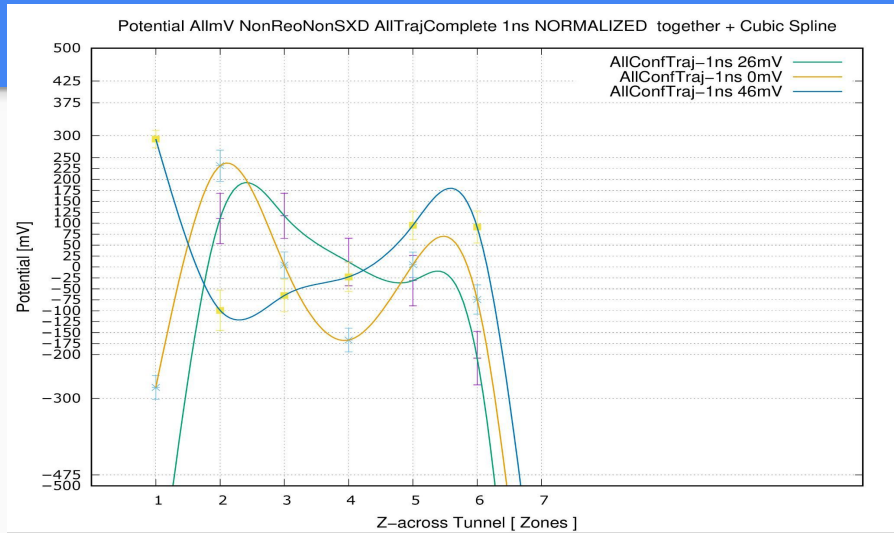

TH
Apical surface
I⁻
NIS
Basolateral surface
2 Na⁺
I⁻

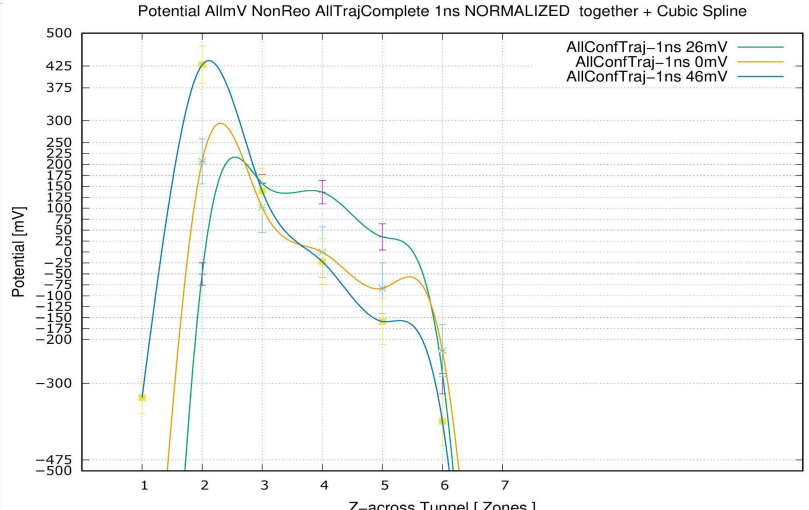

a
Cryo-electron Microscopy
c
Computer Modeling & Simulation
Na⁺
K⁺
Ez
b
Outwardly open states (OO)
NIS-I⁻
d
Na⁺
I⁻
NIS molecular states during
the transport of I⁻
tICA2
tICA1
9.4 µs
5.1
5.9 µs
9.3 µs
APO-NIS
Inwardly open states (IO)
NIS-I⁻
Markov States Model (MSM)

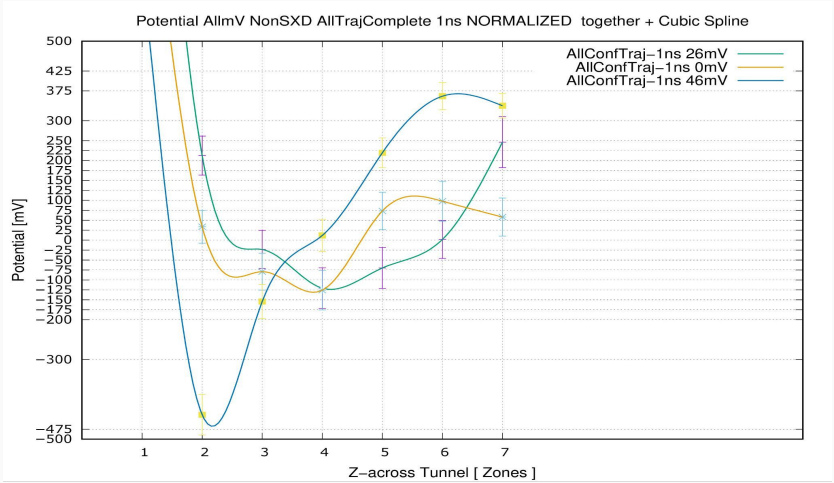

a
tICA 2
tICA 1
Free Energy [k_BT]
5.76
5.12
4.48
3.84
3.20
2.56
1.92
1.28
0.64
0.00
b
inwardly open
Entr. Vol 918 Å
Exit Vol 1641 Å
9.2 µs
0.6 µs
5.1 µs
4.5 µs
9.3 µs
0.5 µs
Cryo EM
Occluded
outwardly open
state
c
radius of tunnel [Å]
inwardly open
outwardly open
occluded


a
Stationary distribution
IC 2
stationary distribution
b
Reweighted free energy surface
free energy / kT
c
tICA2
tICA1
Macrostates
d
Entrance and exit volumes [Å³]
tICA 2
tICA 1
Extracellular
Intracellular
e
Macrostates


Potential AllmV FullOccup AllTrajComplete 1ns NORMALIZED together + Cubic Spline
AllConfTraj−1ns 26mV
AllConfTraj−1ns 0mV
AllConfTraj−1ns 46mV
Potential [mV]


Potential AllmV NonReoNonSXD AllTrajComplete 1ns NORMALIZED together + Cubic Spline
AllConfTraj−1ns 26mV
AllConfTraj−1ns 0mV
AllConfTraj−1ns 46mV
Potential [mV]
Z−across Tunnel [Zones]


Potential AllmV NonReo AllTrajComplete 1ns NORMALIZED together + Cubic Spline
AllConfTraj−1ns 26mV
AllConfTraj−1ns 0mV
AllConfTraj−1ns 46mV
Potential [mV]


Potential AllmV NonSXD AllTrajComplete 1ns NORMALIZED together + Cubic Spline
AllConfTraj−1ns 26mV
AllConfTraj−1ns 0mV
AllConfTraj−1ns 46mV
Potential [mV]
Z−across Tunnel [Zones]

Thanks for your attention!
Any Questions?