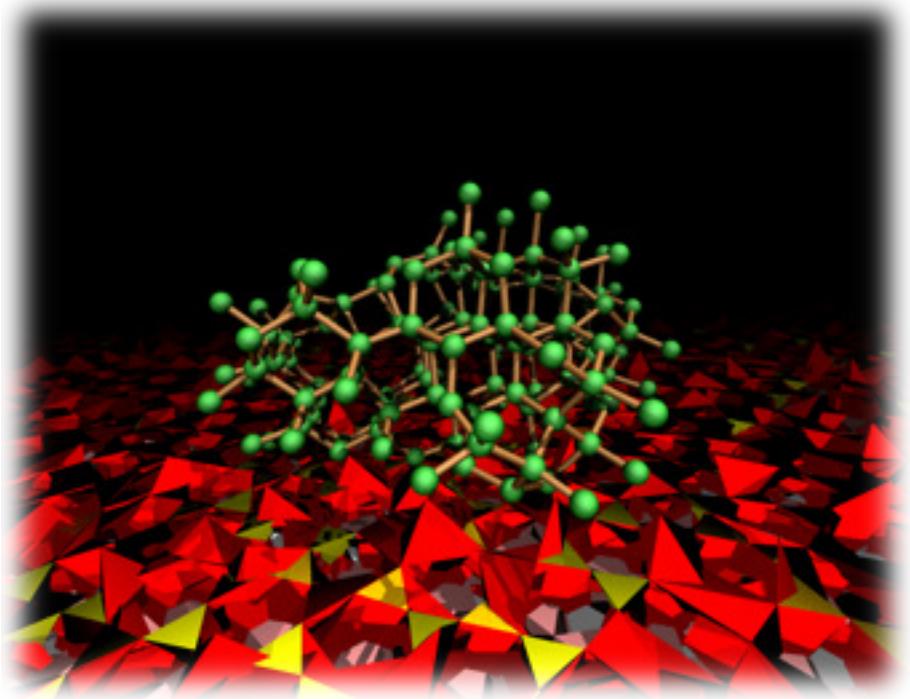
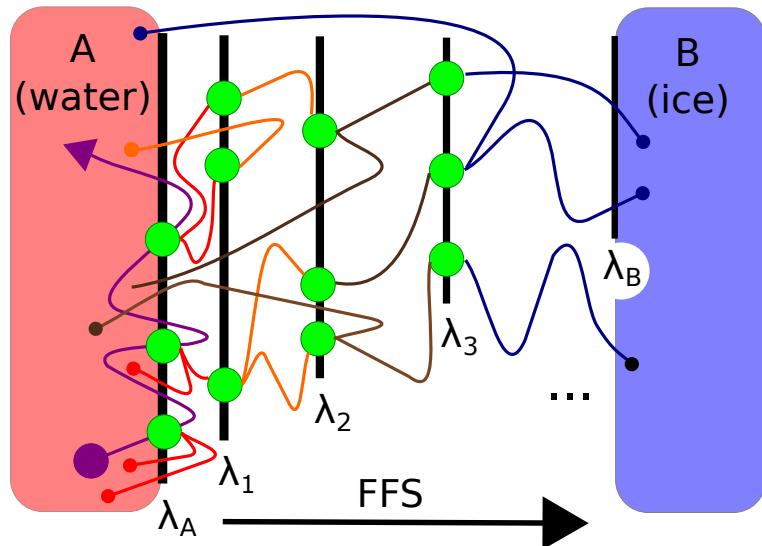


# Forward Flux Sampling Simulations of Heterogeneous Ice Nucleation

*A PLUMED story...*



# Outline

## Heterogeneous Ice Nucleation

- *Why Do We Care?* Atmospheric Science and Cryobiology

## Forward Flux Sampling

- *Why not Metadynamics?* The Hard Truth about Water and Ice
- The Basic Idea

## Ice Formation on Cholesterol Crystals

- The Water-Cholesterol interface: pentagonal rings
- *Cubic vs Hexagonal Ice:* A Game of Temperatures

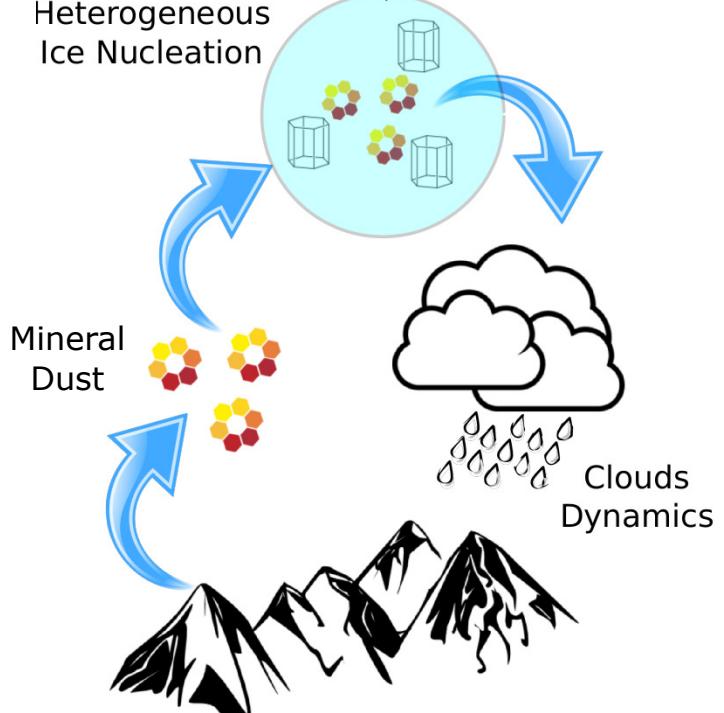
## Why PLUMED?

- *Implementing the CV(s):* The real bottleneck
- A new branch (?!)

# Heterogeneous Ice Nucleation

Why do we care?

Heterogeneous  
Ice Nucleation

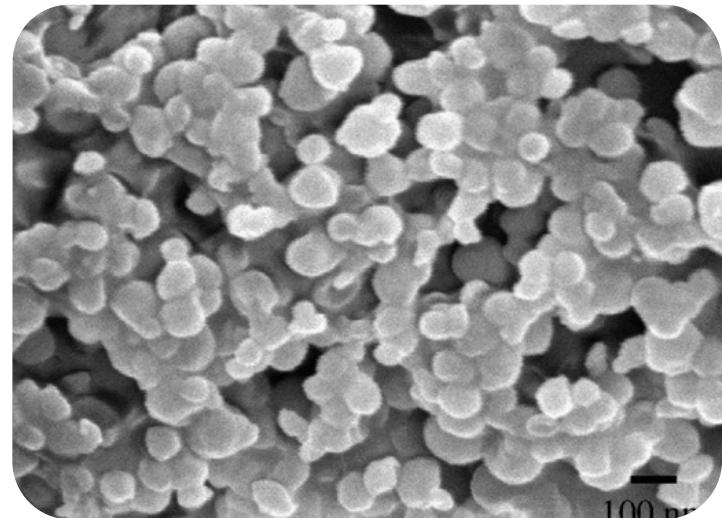


Atmospheric science:

Clouds formation and dynamics  
(climate change)

Cryobiology:

Intracellular freezing  
(cryotherapy and  
cryopreservation)

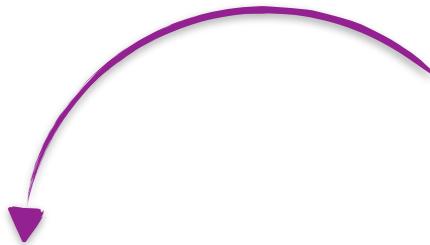


Ice formation on top of lipid bilayers

*Cryobiology*, 55, 210 (2007)

# Heterogeneous Ice Nucleation

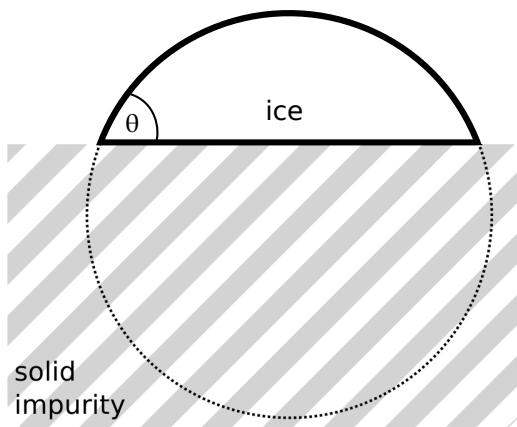
The tricky business of water freezing...



Ice on Earth forms thanks to  
heterogeneous nucleation



water



It is surprisingly difficult to freeze pure water  
One has to go to -40 °C...



# Heterogeneous Ice Nucleation

## Atmospheric science

## Atmospheric Science

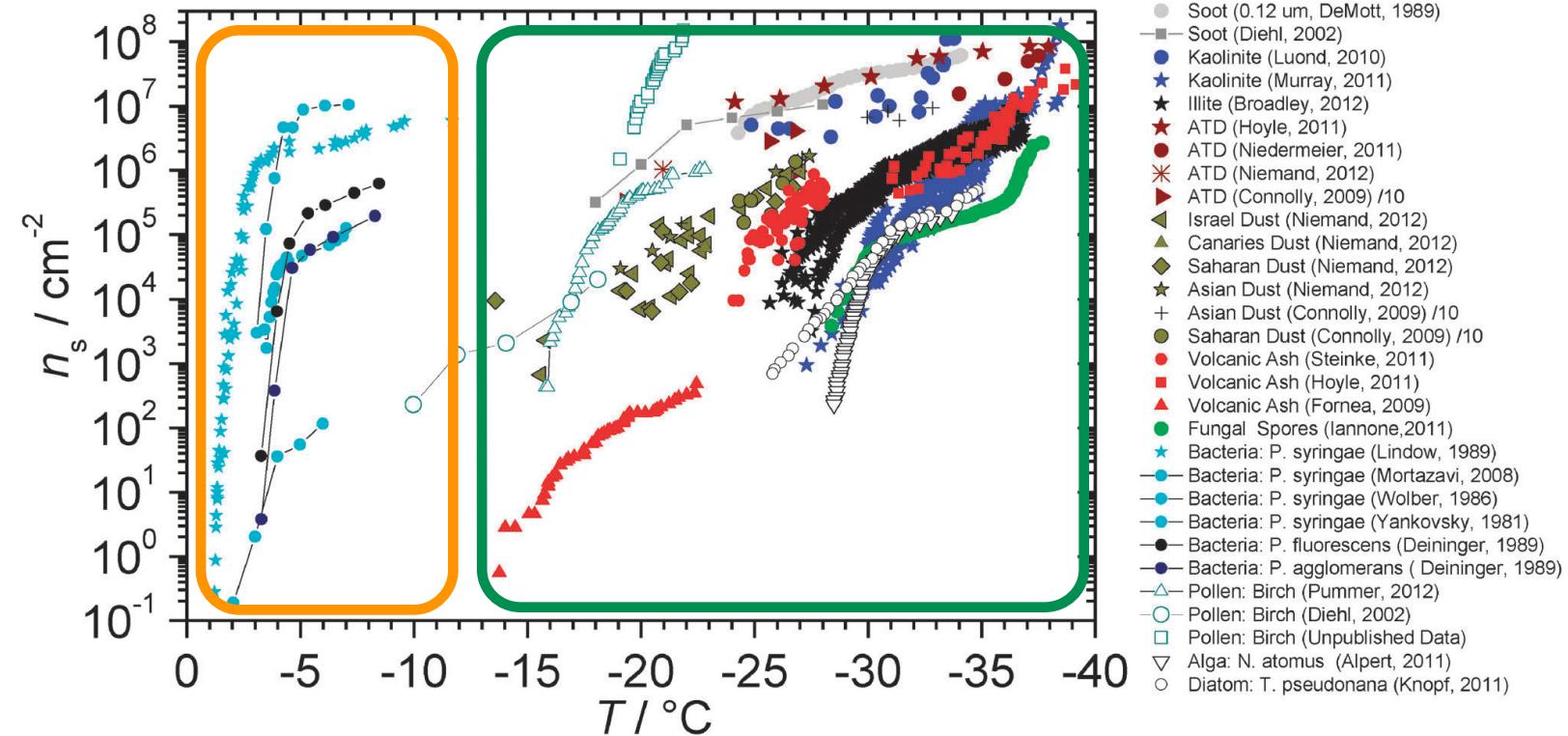
- Mixed-phase (ice and water) clouds: form @  $\sim -15^{\circ}\text{C}$
- What sort of impurities can help the formation of ice?

Inorganic

I  
Soot  
Mineral Dust

Biological

Bacteria  
Pollen



# Heterogeneous Ice Nucleation

## Cryobiology

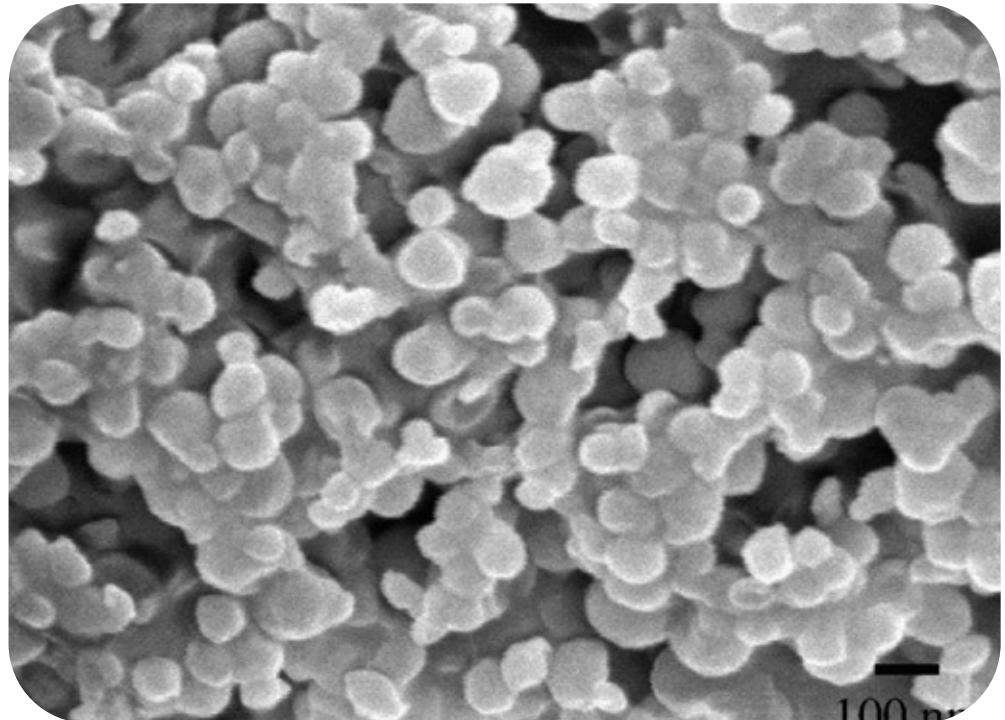
## Cryobiology

- Cryotherapy: Skin conditions as well as cancer
- Cryogenic freezing: Food industry
- Cryopreservation: Blood, stem cells

A very important phenomenon:  
Intracellular Freezing



*Cryobiology* 70, 156–163



Ice formation on top of lipid bilayers

*Cryobiology*, 55, 210 (2007)

# Forward Flux Sampling Simulations

## Why not Metadynamics?

We lack insights at the molecular level

- Microscopic Mechanism?
- Ice polytype (cubic and/or hexagonal)?
- Would Classical Nucleation Theory hold?
- Nucleation sites?

Atomistic simulations could help...

Simulating heterogenous ice nucleation is still a formidable task:

- It is difficult to model water at interfaces properly
- Nucleation is a rare event

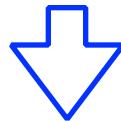
**The timescale problem**

seconds

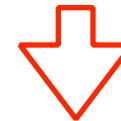
nanoseconds

Nothing happens...

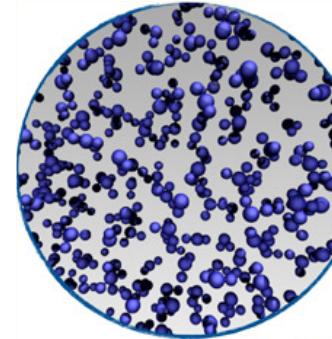
Nucleation!



Simulations: no way  
Experiments: OK!

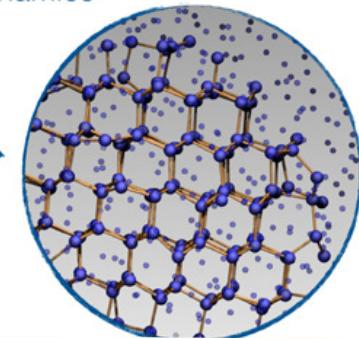


Simulations: OK!  
Experiments: no way



$$\frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_k} \right) - \left( \frac{\partial \mathcal{L}}{\partial q_k} \right) = 0$$

Molecular Dynamics



# Forward Flux Sampling Simulations

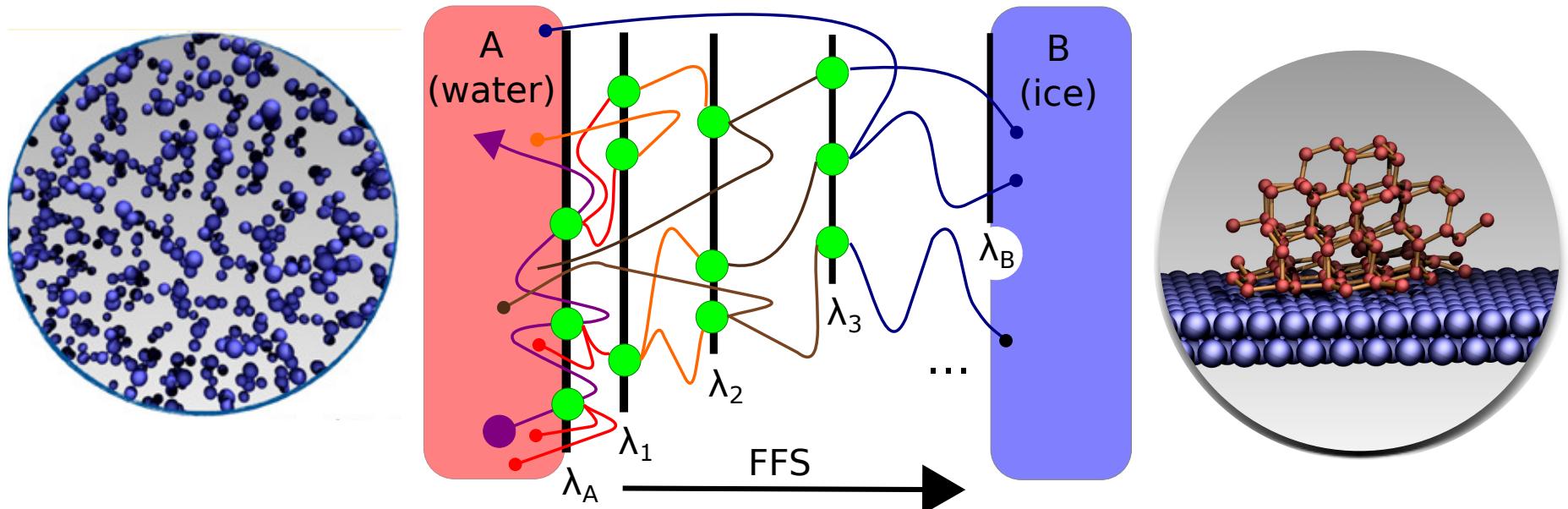
## Enhanced sampling techniques

### What are we looking for?

- Speed up simulations (so that we can observe nucleation events)
- Avoid tempering with the natural evolution of the system
- Get the microscopic mechanism and the kinetics of nucleation

One option: **Forward flux sampling [FFS]**

Increasingly popular, path sampling based method:  
it has been applied to hydrates nucleation, NaCl nucleation from aqueous solutions...



We have to choose an order parameter:

$\lambda$  = Number of water molecules in the largest ice nucleus

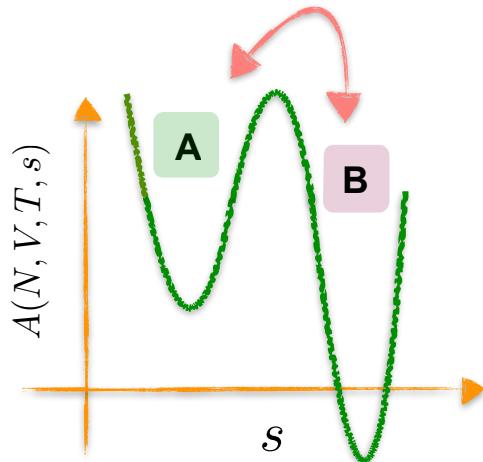
The path from water to ice is divided into  $\lambda_N$  interface

# Metadynamics: Why Not?

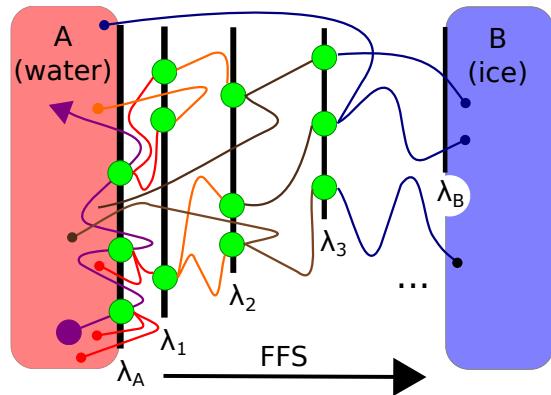
The hard truth about water and ice...

## Atomistic (e.g. TIP4P/Ice) simulations of heterogeneous ice nucleation

### Metadynamics



### Forward Flux Sampling



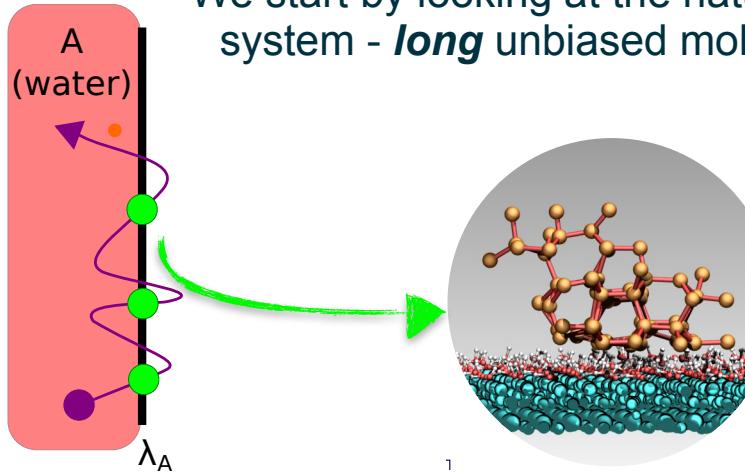
- ✗ Very sensitive to the choice of the CV(s)
- ✗ Sub-regions of the system have to be biased
- ✗ You often end up with the wrong polymorph
- ✗ Info about kinetics cannot be easily obtained
- ✗ Massive hysteresis
- ✗ Simple CVs are not enough
- ✗ Computationally expensive

- ✓ Less sensitive to the choice of the CV(s)
- ✓ The whole system can be considered
- ✓ You get the right polymorph
- ✓ Info about kinetics come for free
- ✓ No hysteresis
- ✗ Simple CVs are not enough
- ✗ Computationally awfully expensive

# Forward Flux Sampling

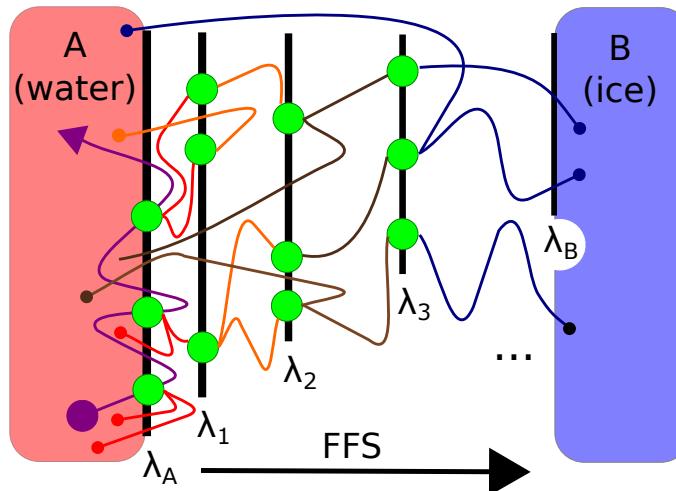
The basic idea...

We start by looking at the natural fluctuations of the system - *long* unbiased molecular dynamics run



$$\Phi_{\lambda_A} = \frac{\text{N. of crossings}}{\text{Simulation time} \cdot \text{Volume}}$$

- At each interface  $\lambda_i$  we shoot a (large) number of trial molecular dynamics runs
- Those that reach the next interface ( $\lambda_{i+1}$ ) are used as starting point to reach the following interface, and so on...

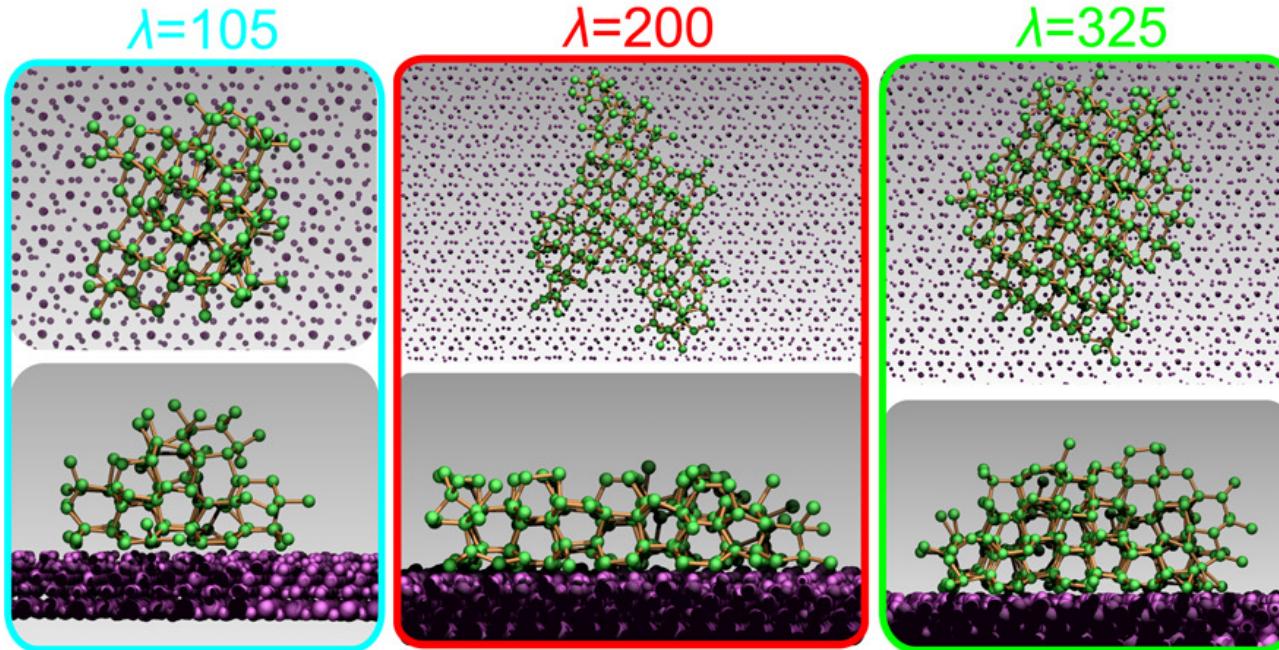


$$P(\lambda_i | \lambda_{i-1})$$

# Forward Flux Sampling

What do you get?

## Mechanism



## Kinetics

$$\mathcal{J} = \Phi_{\lambda_A} \prod_{i=1}^{N_\lambda} P(\lambda_i | \lambda_{i-1})$$

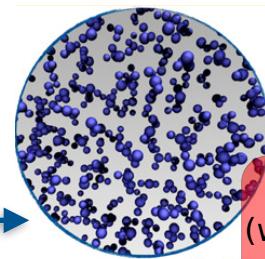
# Ice Nucleation on Cholesterol Crystals

In a nutshell...

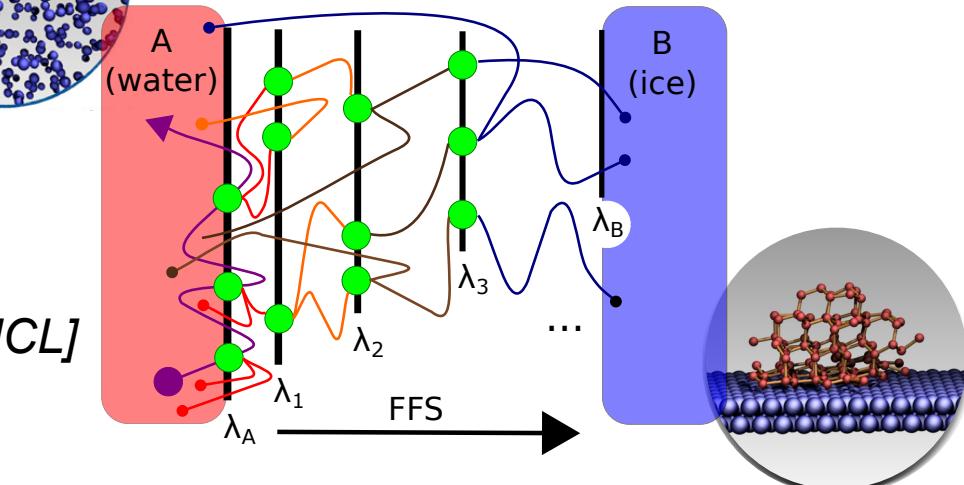
- **Cryobiology:**
- *Cholesterol crystals are used as ice nucleating agents in cryopreservation*



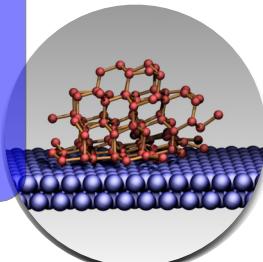
- **The issue:**
- *What is the microscopic mechanism of ice formation?*



- **The Tools:**
- *Enhanced Sampling Techniques* →  
(Forward Flux Sampling)



- **The people:**
- *Angelos Michaelides, Philipp Pedevilla [UCL]*
- *Thomas Whale [Leeds]*



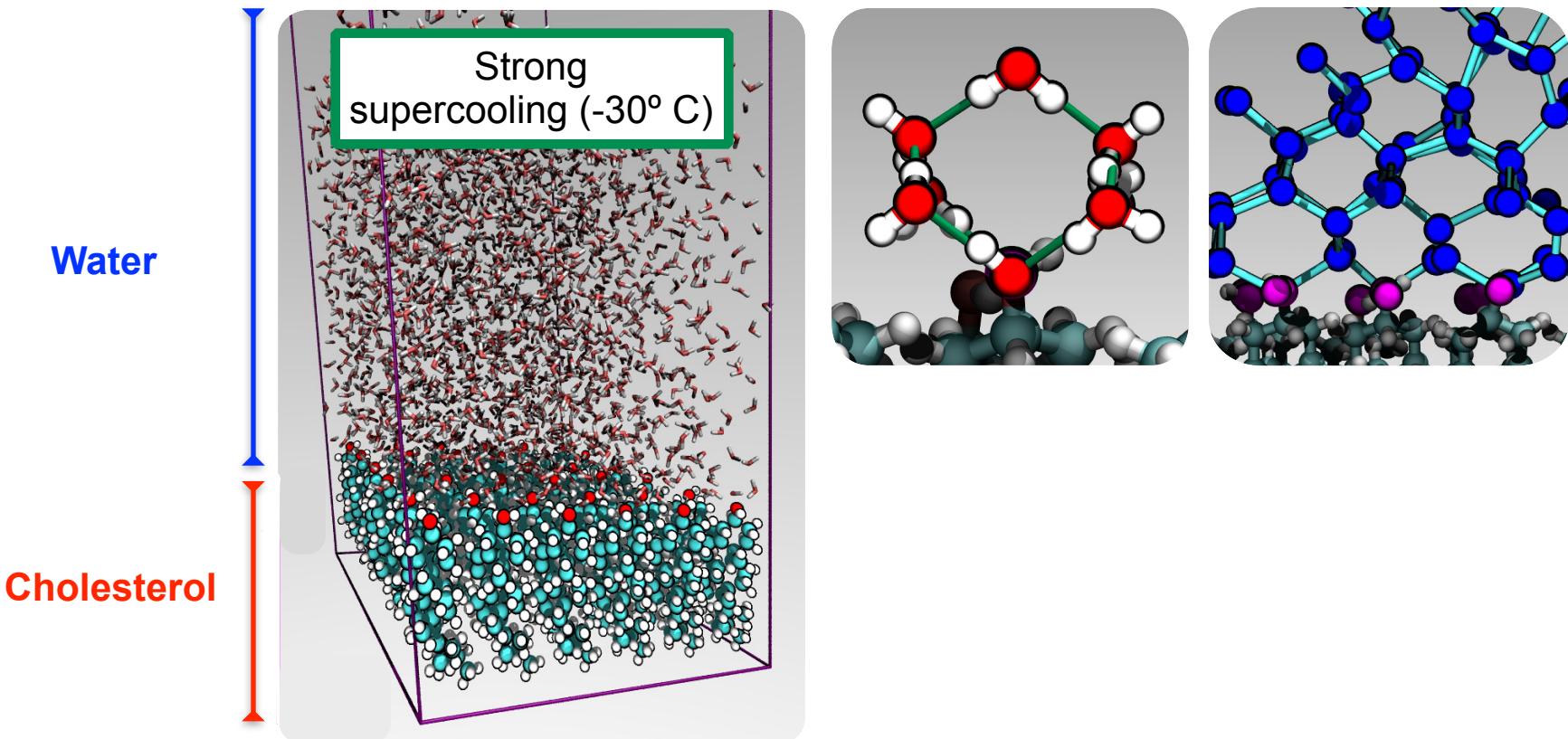
# Ice Nucleation on Cholesterol Crystals

Case Study: Ice Formation on Cholesterol Crystals

Frozen Droplets Experiments (T. Whale, Leeds)

Cholesterol crystals: spectacularly good (-30/-2 °C) ice nucleating agents

WHY?



Molecular Dynamics Simulations  
Hydrogen-bonded H<sub>2</sub>O/-OH cages

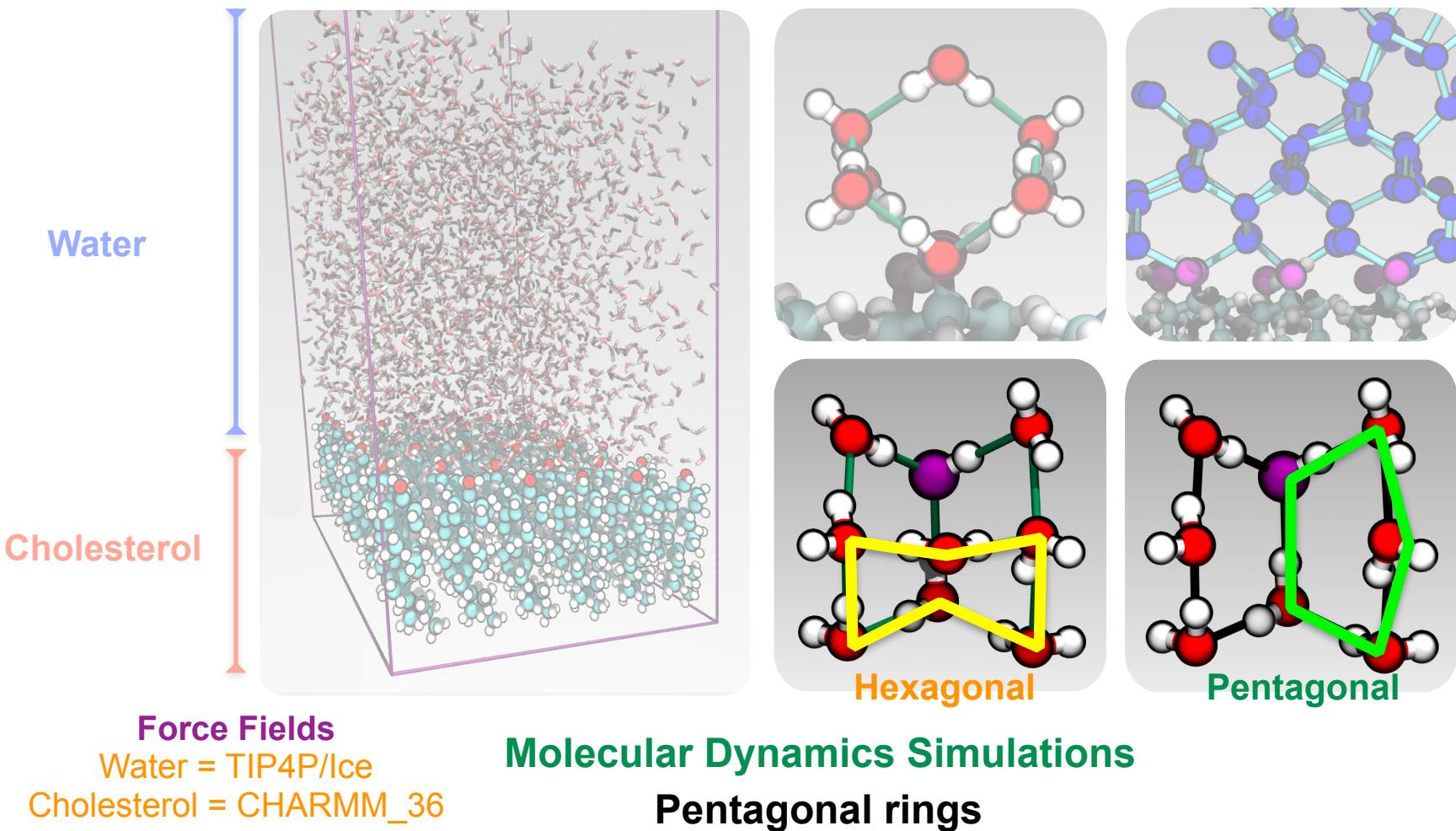
# Ice Nucleation on Cholesterol Crystals

Case Study: Ice Formation on Cholesterol Crystals

Frozen Droplets Experiments (T. Whale, Leeds)

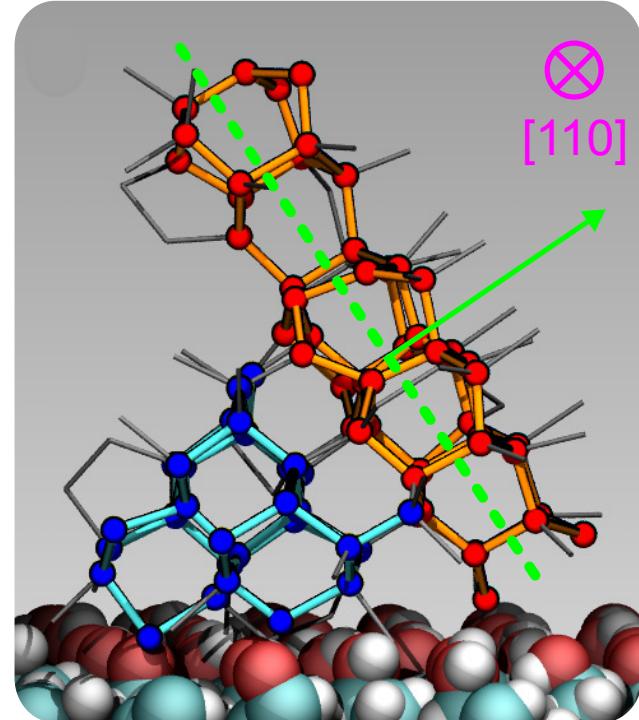
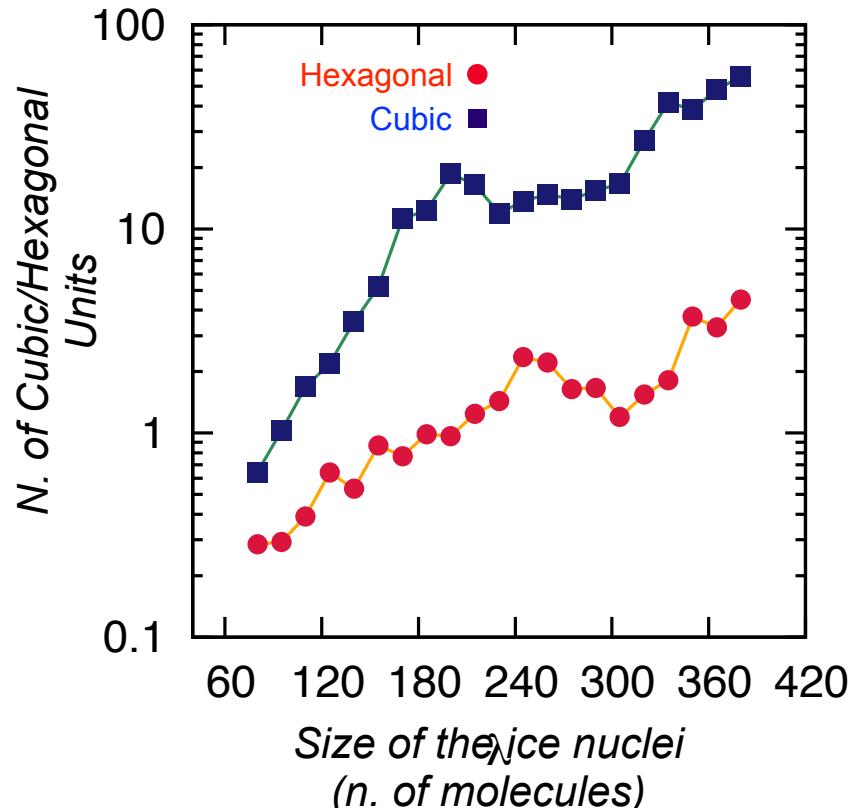
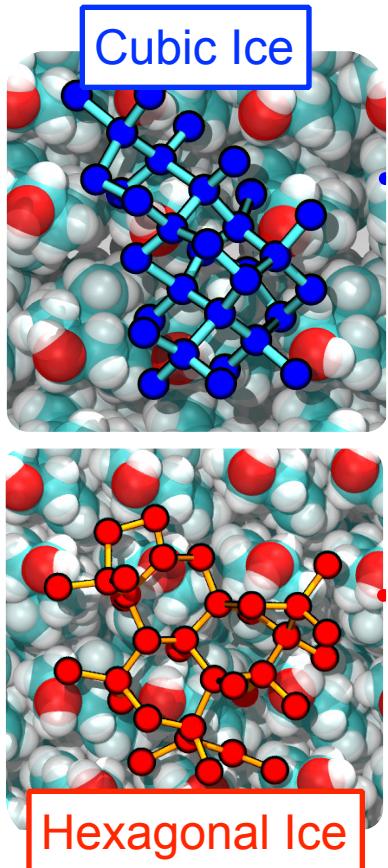
Cholesterol crystals: spectacularly good (-30/-2 °C) ice nucleating agents

WHY?



# Ice Nucleation on Cholesterol Crystals

## Case Study: Ice Formation on Cholesterol Crystals



## Forward Flux Sampling Simulations

- One surface, two ice polymorphs (**hexagonal** and **cubic**)
- The ice nucleating ability of cholesterol crystals: a Game of Temperatures

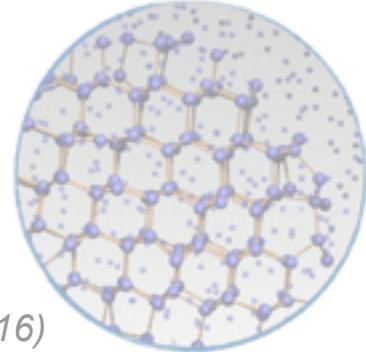
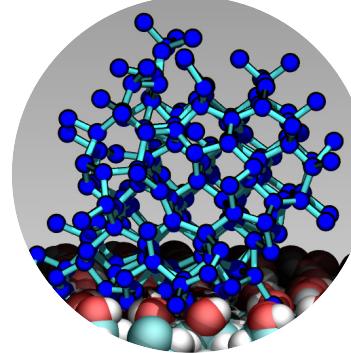
# Ice Nucleation on Cholesterol Crystals

## (Selected) Papers

Sosso, G.C., Whale, T.F., Pedevilla, P. and Michaelides, A.

### Unravelling the Ice Nucleation Ability of Cholesterol Crystals

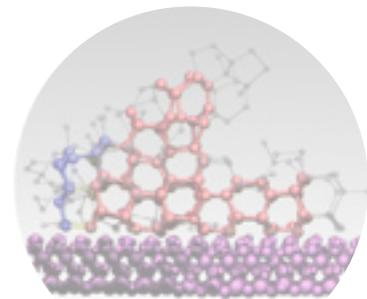
In preparation



Sosso, G.C., Chen, J., Cox, S.J., Fitzner, M., Pedevilla, P., Zen, A., and Michaelides, A. (2016)

### Crystal Nucleation in Liquids: Open Questions and Future Challenges in Molecular Dynamics Simulations

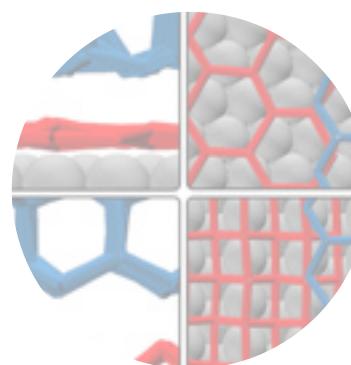
*Chem. Rev.* **116**, 7078–7116



Sosso, G.C., Li, T., Donadio, D., Tribello, G.A., and Michaelides, A. (2016)

### Microscopic Mechanism and Kinetics of Ice Formation at Complex Interfaces: Zooming in on Kaolinite

*J. Phys. Chem. Lett.* **7**, 2350–2355



Fitzner, M., Sosso, G.C., Cox, S.J., and Michaelides, A. (2015)

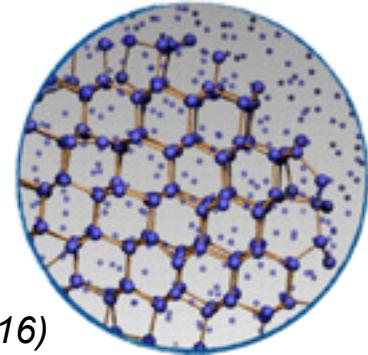
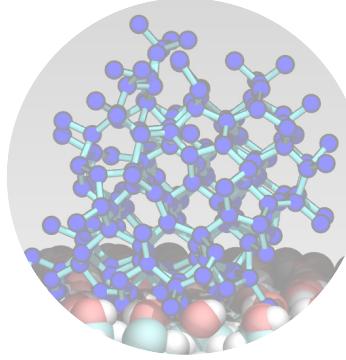
### The Many Faces of Heterogeneous Ice Nucleation: Interplay Between Surface Morphology and Hydrophobicity

*J. Am. Chem. Soc.* **137**, 13658–13669

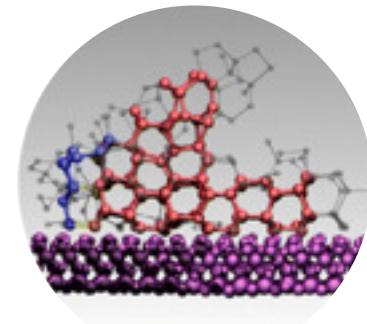
# Ice Nucleation on Cholesterol Crystals

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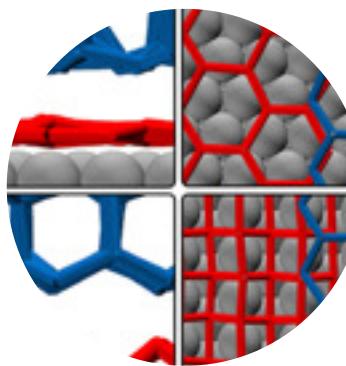
Sosso, G.C., Whale, T.F., Pedevilla, P. and Michaelides, A.  
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Sosso, G.C., Chen, J., Cox, S.J., Fitzner, M., Pedevilla, P., Zen, A., and Michaelides, A. (2016)  
Crystal Nucleation in Liquids: Open Questions and Future Challenges in Molecular  
Dynamics Simulations  
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The Many Faces of Heterogeneous Ice Nucleation:  
Interplay Between Surface Morphology and Hydrophobicity  
*J. Am. Chem. Soc.* **137**, 13658–13669

# Why PLUMED?

The real bottleneck...

## Forward Flux Sampling (FFS) in Practice:

- An awful lot of computational time ( $\sim 10^6$  CPU hours)
- An implementation of the algorithm (some scripting will do)
- An efficient implementation of the CV(s):
  1. It has to talk with the molecular dynamics (MD) code
  2. It has to be fast (parallel implementation)



- ✓ It talks to your MD code (COMMITTOR)
- ✓ It does take advantage of a parallel implementation
- ✓ You don't have to code much (if anything at all!)
- ✗ No dedicated FFS suite/scripts/framework/documentation

# Why PLUMED?

The case of ice on cholesterol...

**The order parameter  $\lambda$ :**

- A  $i$ -th water molecule is ice-like if  $lq_i^6 > 0.45$
- Select molecules (oxygen atoms...) hydrogen bonded to four other molecules ( $S_{4HB}$  subset)

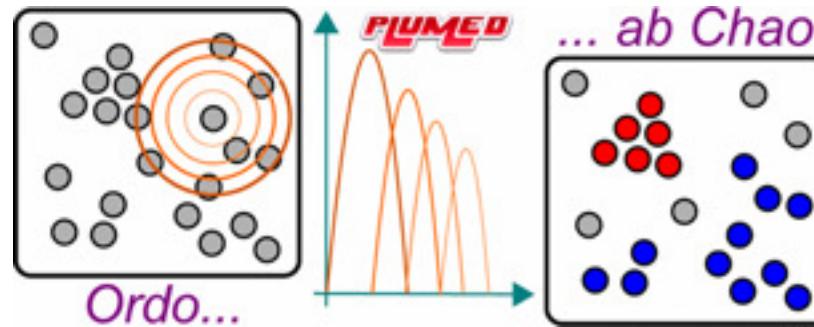
$$lq_i^6 = \frac{\sum_{j=1}^{N_{S_{4HB}}} \sigma(\mathbf{r}_{ij}) \sum_{m=-6}^6 q_{i,m}^{6*} \cdot q_{j,m}^6}{\sum_{j=1}^{N_{S_{4HB}}} \sigma(\mathbf{r}_{ij})}$$

$$q_{i,m}^6 = \frac{\sum_{j=1}^{N_{S_{4HB}}} \sigma(\mathbf{r}_{ij}) Y_{6m}(\mathbf{r}_{ij})}{\sum_{j=1}^{N_{S_{4HB}}} \sigma(\mathbf{r}_{ij})}$$

- Find the largest connected cluster of molecules that:
  - Belong to the  $S_{4HB}$  subset
  - Have a value of  $lq_i^6 > 0.45$
  - Are separated by a distance  $< 3.2 \text{ \AA}$
- Add surface molecules (first coordination shell)

# Why PLUMED?

The case of ice on cholesterol...



# Get the hydrogen bonds

```
HBOND_COORD SPECIES=2665-10353:4 HYDROGENS=2666-10354:4,2667-10355:4 RCUTOO=0.324 RCUTOH=0.25 ACUT=0.20pi LABEL=hb
```

# Construct the S<sub>4</sub><sub>HB</sub> subset

```
MFILTER_BETWEEN DATA=hb LOWER=3.9 UPPER=4.1 SMEAR=0.0 LABEL=rsumsb
```

# Calculate q<sub>i</sub><sup>6</sup> for S<sub>4</sub><sub>HB</sub>

```
Q6 SPECIES=rsumsb SWITCH={GAUSSIAN D_0=0.324 R_0=0.00001 D_MAX=0.3241} LABEL=q6 LOWMEM
```

# Calculate lq<sub>i</sub><sup>6</sup> for S<sub>4</sub><sub>HB</sub>

```
LOCAL_Q6 DATA=q6 SWITCH={GAUSSIAN D_0=0.324 R_0=0.00001 D_MAX=0.3241} LABEL=lq6 LOWMEM
```

# Select those molecules (oxygen atoms) with lq<sub>i</sub><sup>6</sup> > 0.45

```
MFILTER_MORE DATA=lq6 SWITCH={GAUSSIAN D_0=0.45 R_0=0.00001 D_MAX=0.4501} LABEL=cf
```

# Create the adjacency matrix

```
CONTACT_MATRIX ATOMS=cf WTOL=0.1 SWITCH={GAUSSIAN D_0=0.324 R_0=0.00001 D_MAX=0.3241} LABEL=mat
```

# Find all the connect clusters

```
DFSCLUSTERING MATRIX=mat LABEL=cls SERIAL
```

# Add surface atoms

```
CLUSTER_WITHSURFACE CLUSTERS=cls RCUT_SURF=0.324 LABEL=scls SERIAL
```

# Select the largest connected cluster

```
CLUSTER_NATOMS CLUSTERS=scls CLUSTER=1 LABEL=lambda
```

# Stop when the relevant FFS interface ( $\lambda_A$  or  $\lambda_{n+1}$ ) is reached

```
COMMITTOR ARG=lambda STRIDE=2000 BASIN_LL1=0 BASIN_UL1=24 BASIN_LL2=170 BASIN_UL2=10000 FILE=shoot.dat
```

# Output the order parameter  $\lambda$  (the number of molecules within the largest ice nucleus)

```
OUTPUT_CLUSTER CLUSTERS=scls CLUSTER=1 STRIDE=2000 FILE=dfs_surf.dat FLUSH STRIDE=2000
```

```
ENDPLUMED
```

# Conclusions

- *Understanding the formation of ice*
- *Atomistic simulations of heterogeneous ice nucleation: FFS 1 - MetaD 0*
- *An example: Ice formation on cholesterol crystals*
- *FFS with PLUMED?*

# People & acknowledgements



Gareth Tribello



Queen's University  
Belfast

Tianshu Li



Davide Donadio



UCDAVIS  
DEPARTMENT OF CHEMISTRY

Angelos Michaelides



## Computational resources



### CSCS

Centro Svizzero di Calcolo Scientifico  
Swiss National Supercomputing Centre



### Projects s623, s758

- Towards an Understanding of Ice Formation in Clouds
- Unraveling the Microscopic Details of Ice Formation on Organic Crystals

## The whole story

*G.C. Sosso, T. Li, D. Donadio, G.A. Tribello and A. Michaelides. J. Phys. Chem. Lett. 7, 2350 (2016)*

*Tribello, G.A., Giberti, F., Sosso, G.C., Salvalaglio, M., and Parrinello, M. (2017). J. Chem. Theory Comput. 13, 1317–1327*