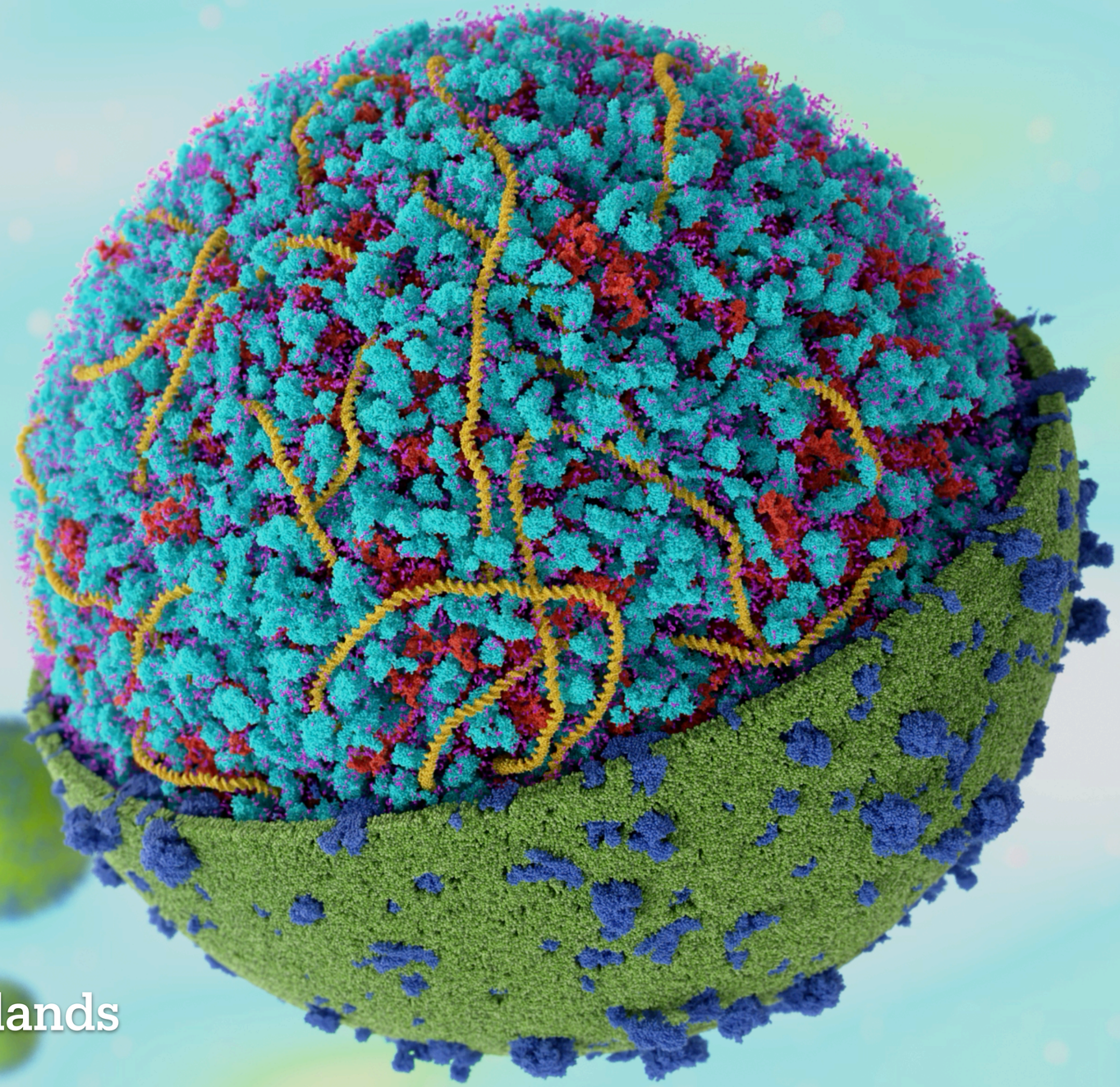
The Martini Recipe for Whole-Cell Simulations



Jan A. Stevens

Group of Prof. SJ Marrink
University of Groningen, the Netherlands

Molecular dynamics simulations

Guided by experimental data

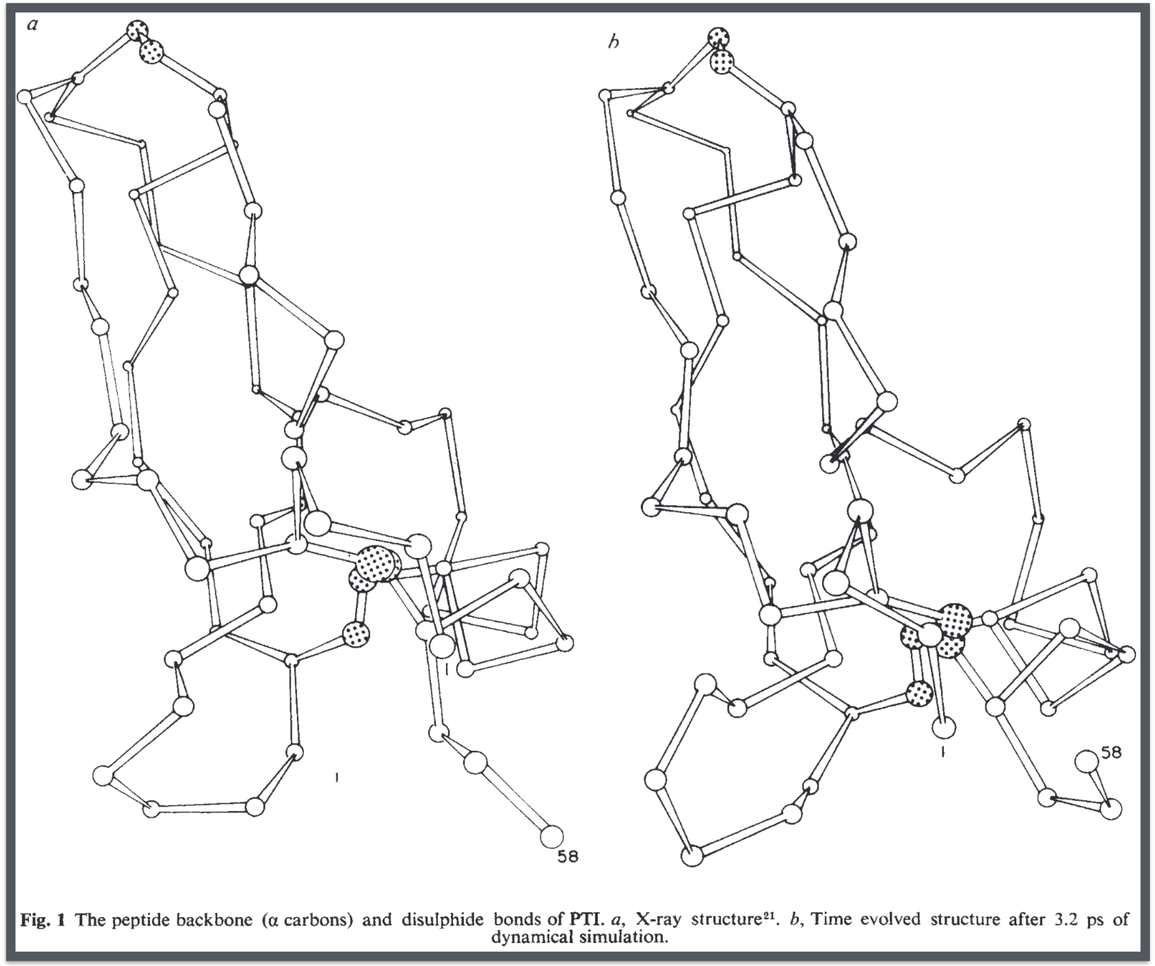


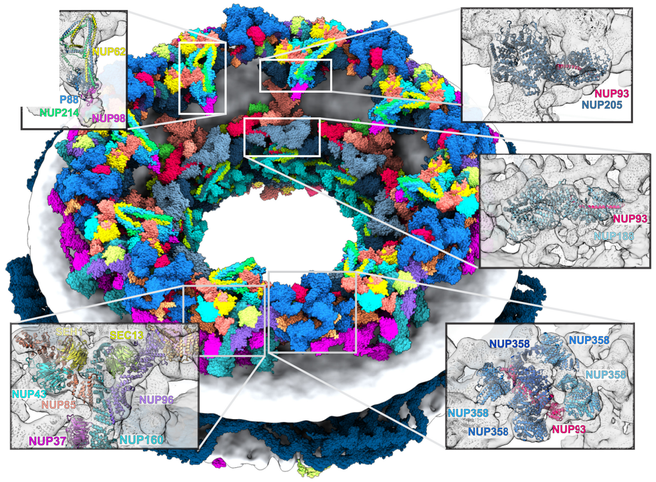
Fig. 1 The peptide backbone (α carbons) and disulphide bonds of PTI. *a*, X-ray structure[21]. *b*, Time evolved structure after 3.2 ps of dynamical simulation.

[1] McCammon, J.A. et al. (1977) Nature.

Molecular dynamics simulations

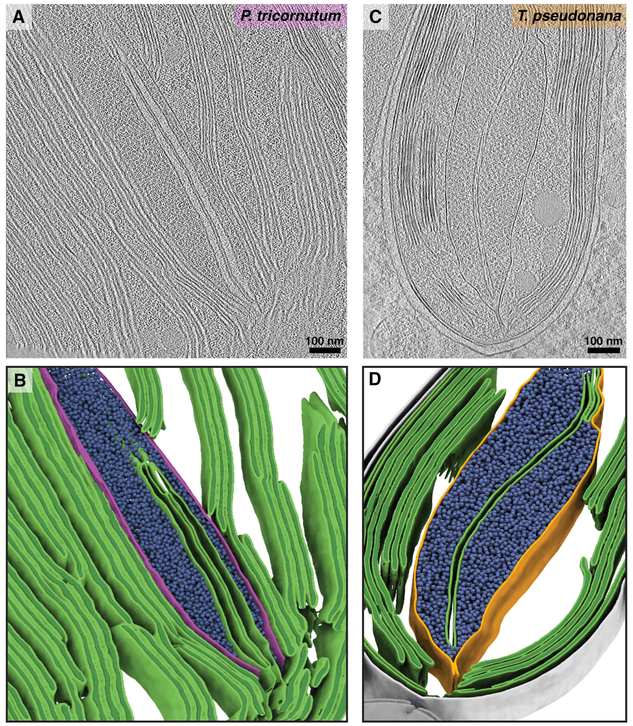
Guided by experimental data

Nuclear pore complex



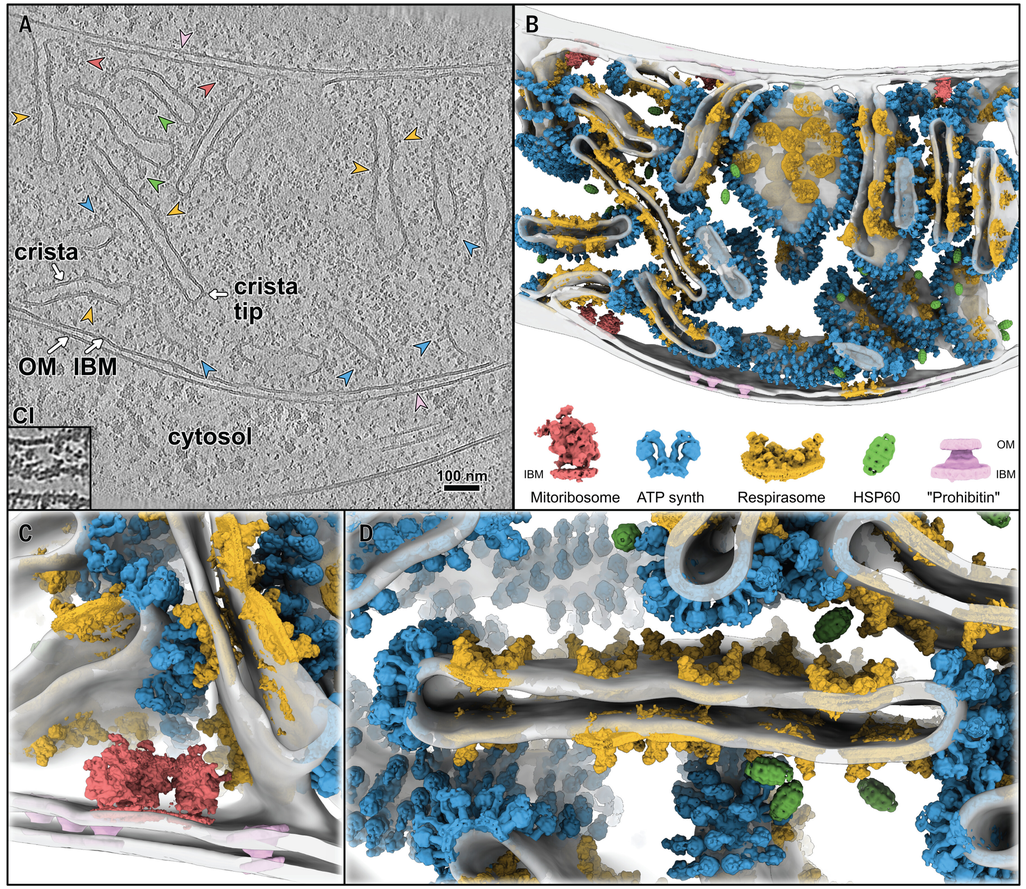
Mosalaganti S. et al. (2022) Science

Pyrenoids



Shimakawa G. et al. (2024) Cell

Mitochondrial respiratory chain



Waltz F. et al. (2025). Science

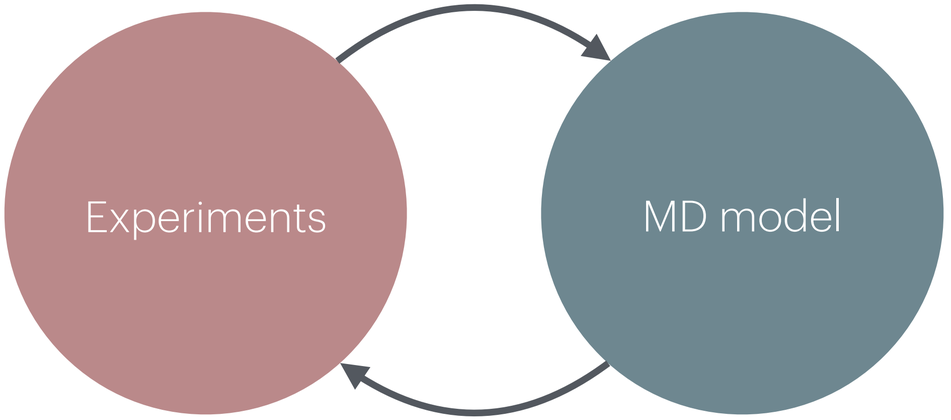
Can we make MD models of them?

Some challenges are:

Large scales: Typical sizes range from hundreds of nanometers to micrometers.

Multi-component models: Cellular environments contain thousands of unique molecules.

Continuous integration : Requires a new type of ‘living model’.

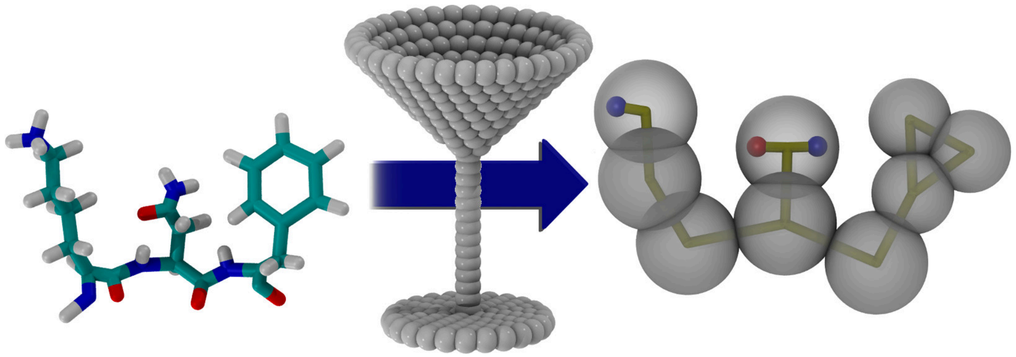


Coarse-Grained Modelling

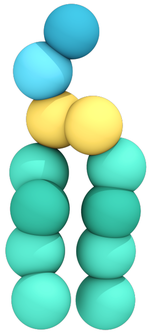
The Martini force field

All-Atom Model

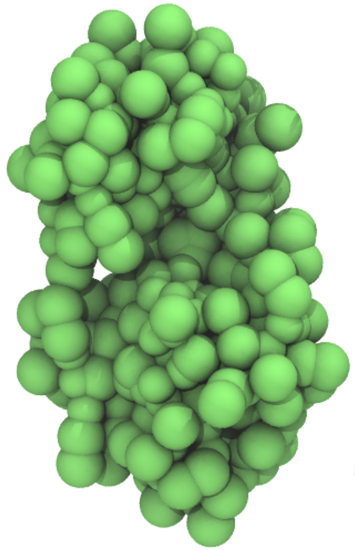
Martini Model



Lipids [1]



Proteins [2]



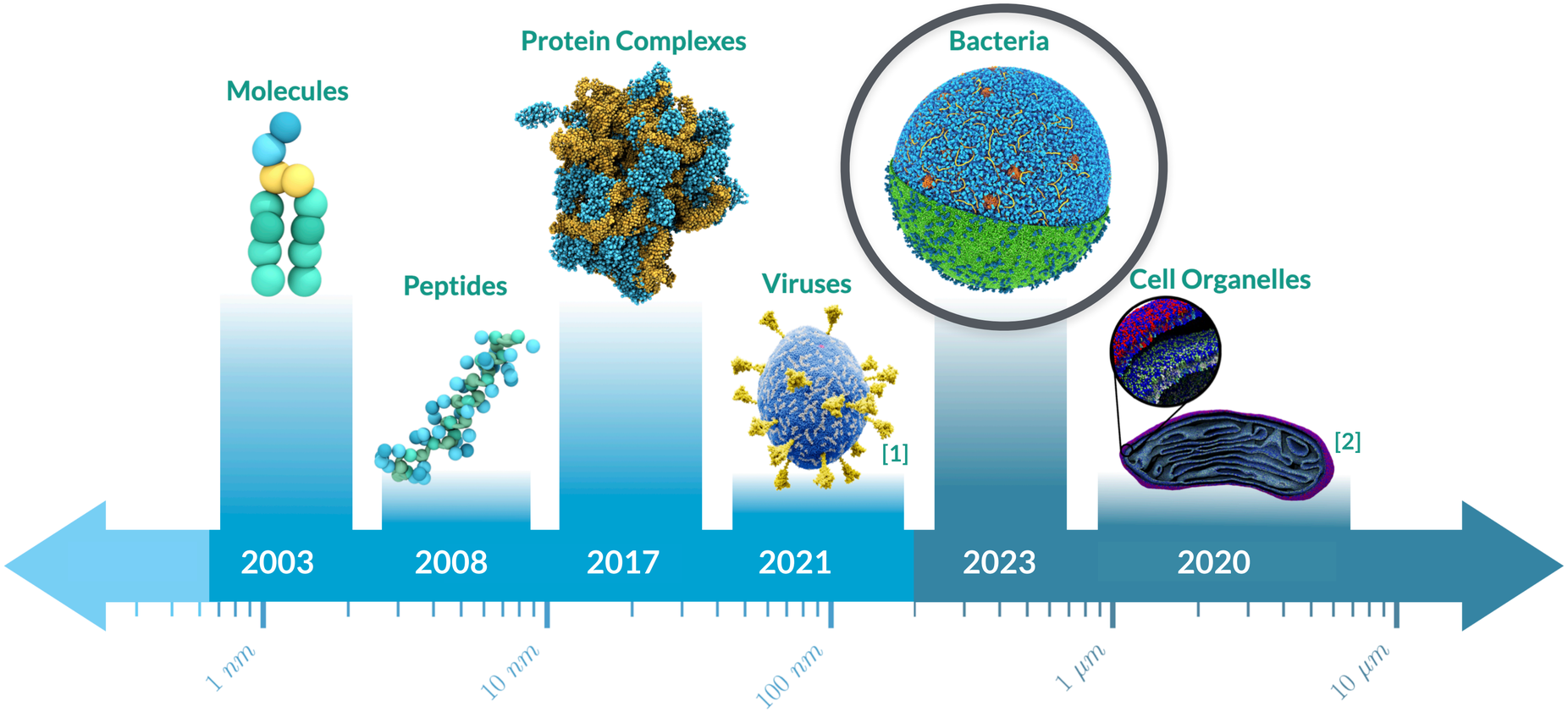
Nucleic Acids [4]

Metabolites [5]

[1] Marrink, SJ. et al. (2007). J. Phys. Chem. B.
[2] Monticelli, L. et al. (2008). J. Chem. Theory Comput.
[3] Lopez, C.A. et al. (2009). J. Chem. Theory Comput.
[4] Uusitalo, J.J. et al. (2015). J. Chem. Theory Comput.

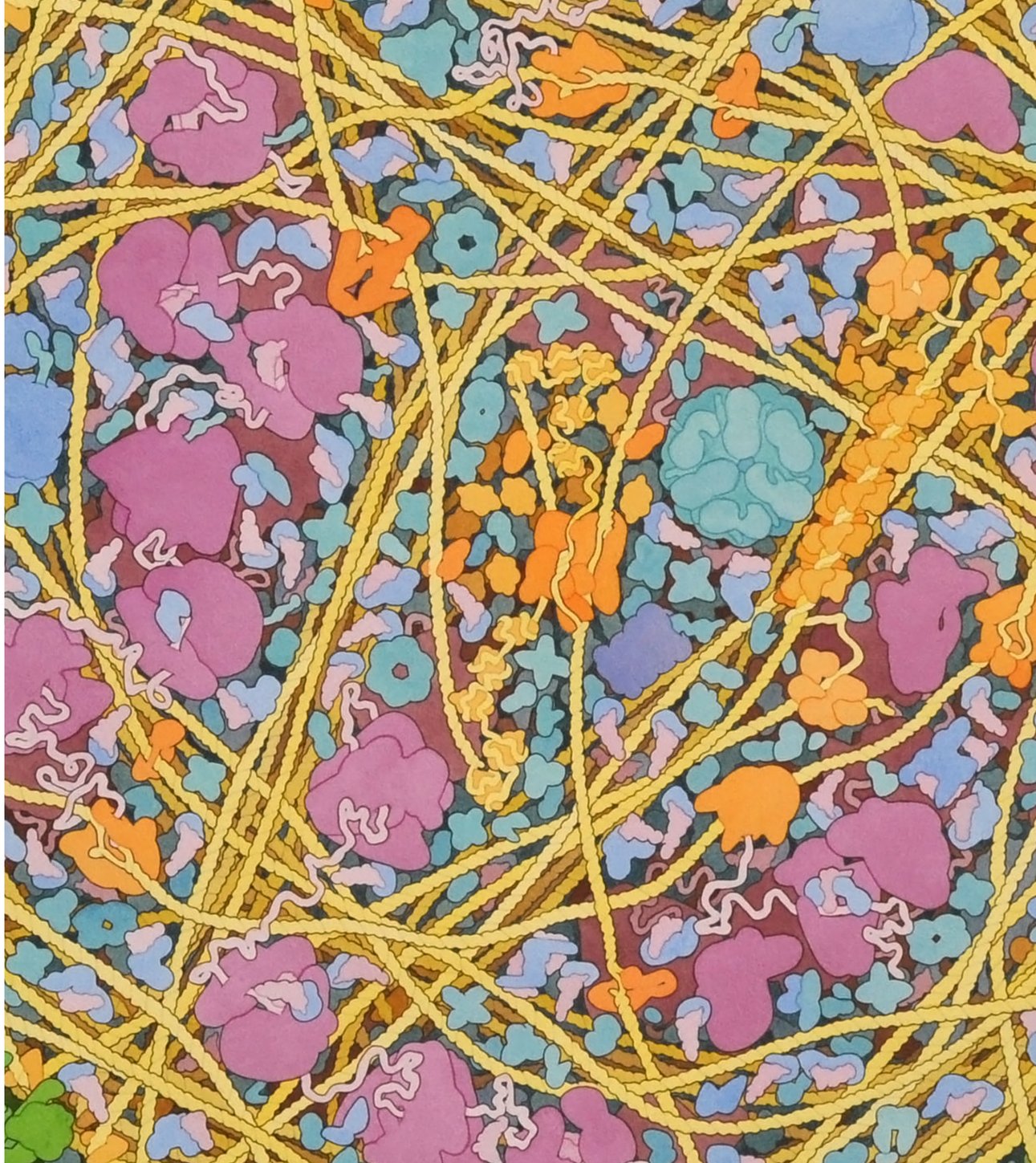
Coarse-Grained Modelling

Martini over the length-scales



[1] Pezeshkian, W. et al. (2023). Structure.
[2]Pezeshkian, W. et al. (2020). Nat. Commun.

Building a cell

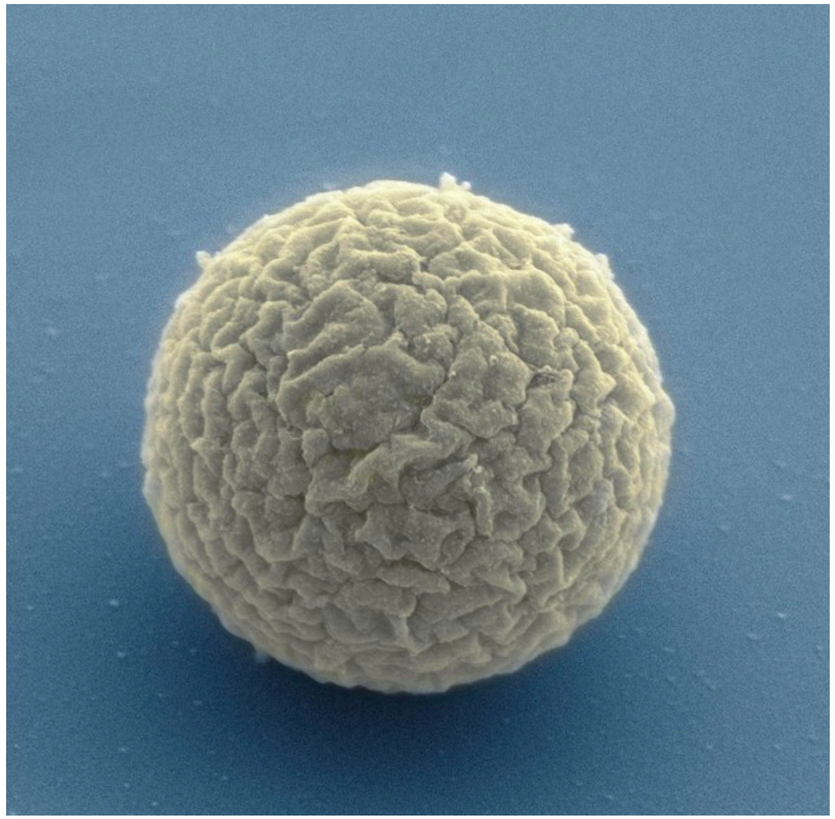


© David Goodsell

The JCVI-Syn3A

An engineerd minimal cell

- Synthetic cell based on **Mycoplasma mycoides** (radius: 400 nm, genome: 493 genes)



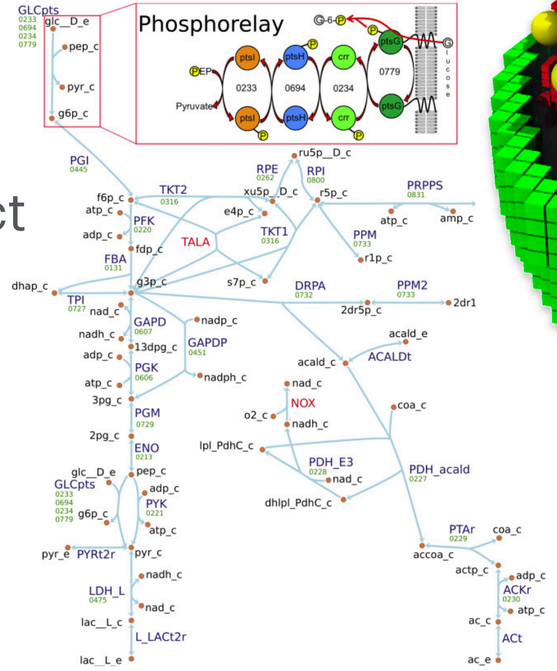
© Thomas J. Deerinck
(https://stories.sciencephoto.com/portfolio/thomas-deerinck/)

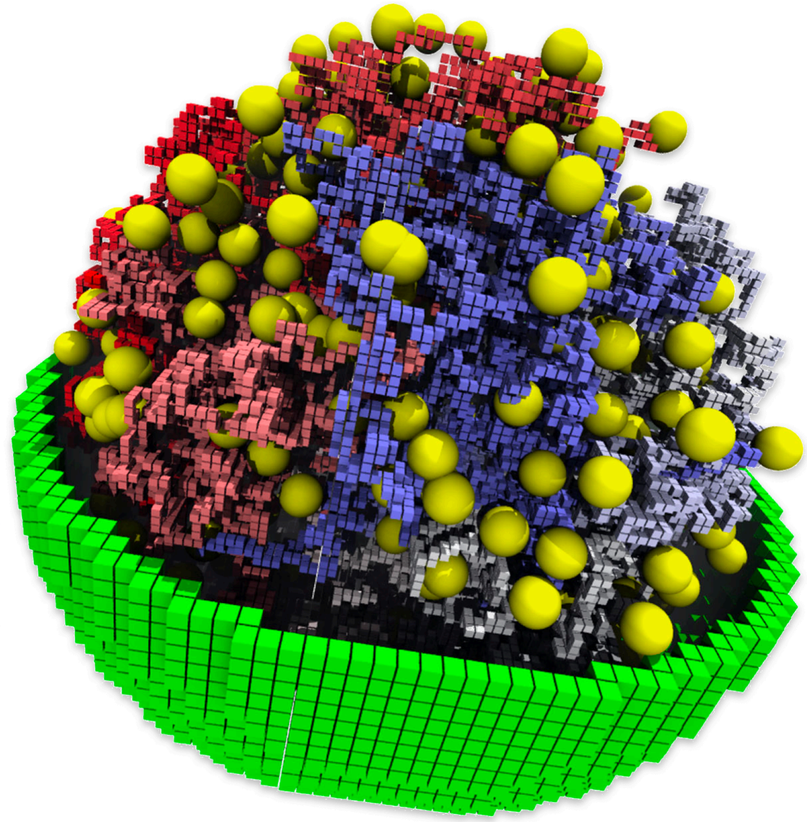
The JCVI-Syn3A

An engineerd minimal cell

- Synthetic cell based on **Mycoplasma mycoides** (radius: 400 nm, genome: 493 genes)
- Available experimental / modelling data provide detailed information on the cell composition.

➤ **Ideal starting point for a modelling project**

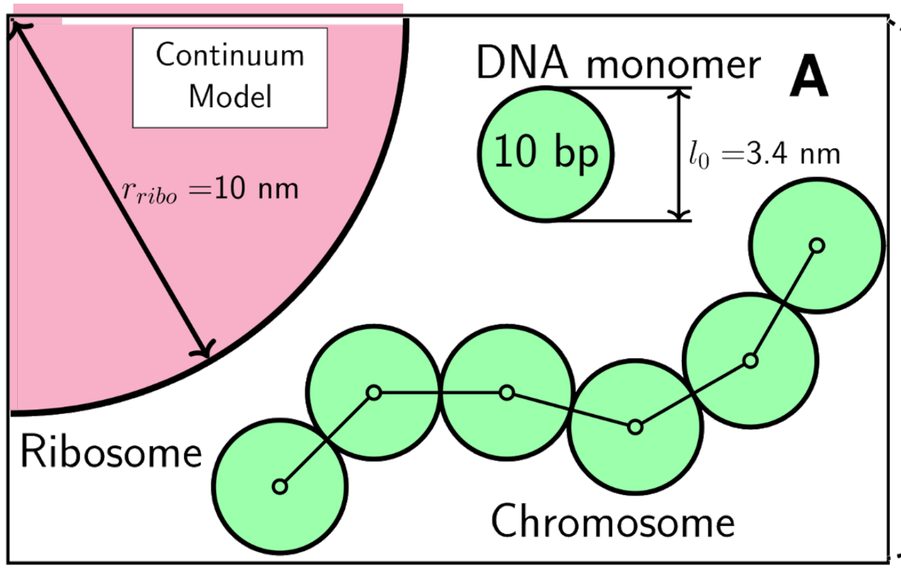


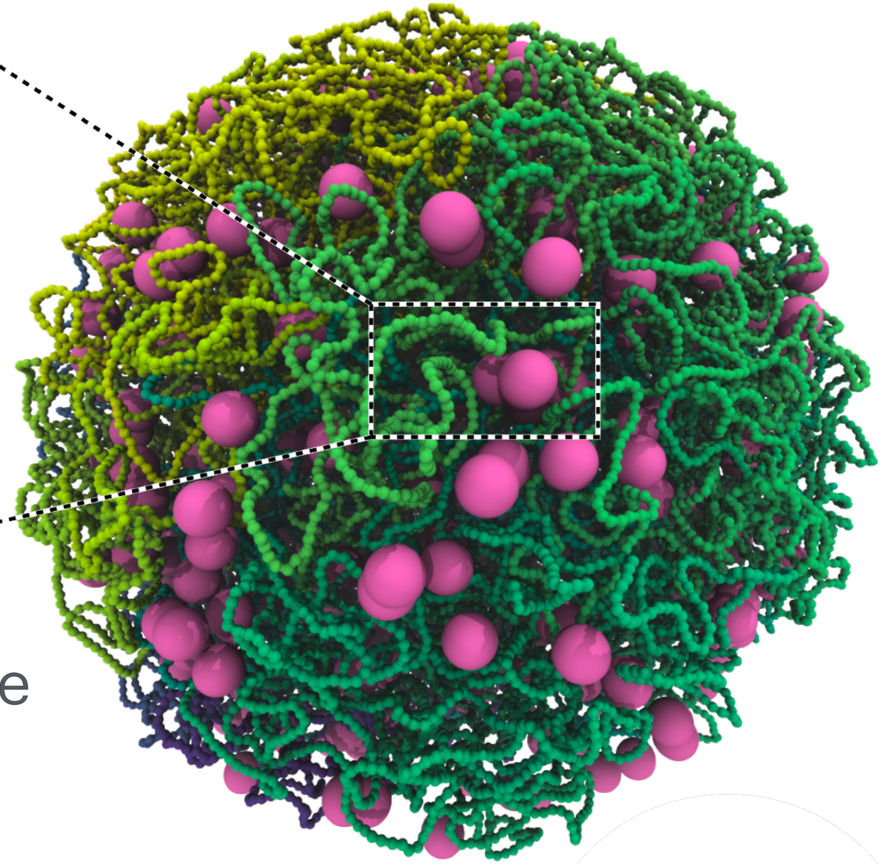


Thornburg Z. et al. (2021). Cell.

Chromosome

Building the model





We base our modelling on a mesoscale model of the Syn3A chromosome

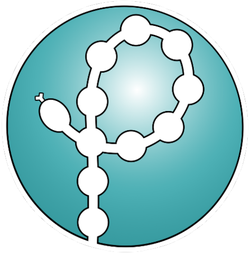
Gilbert B. et al. (2023). Front. Cell Dev. Biol.

Chromosome

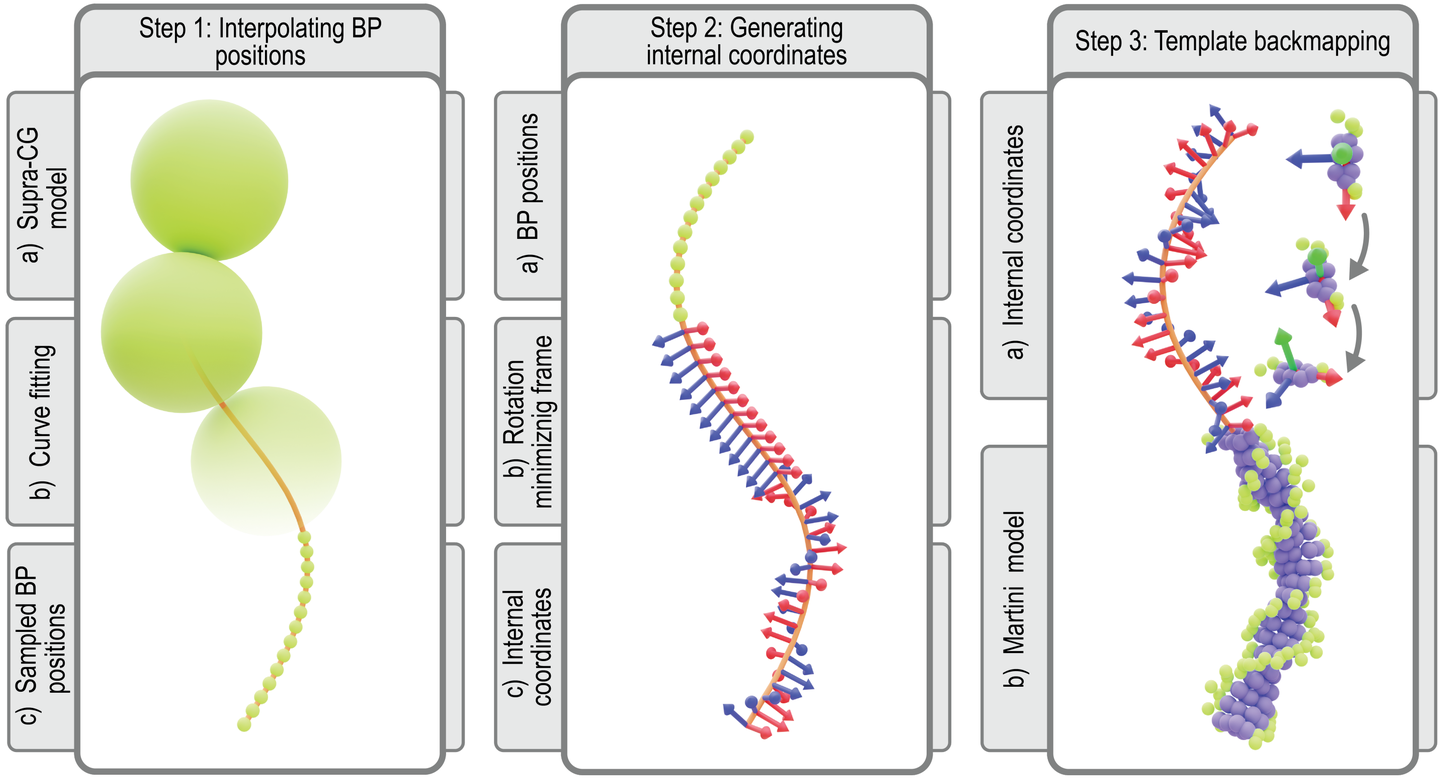
Building the model

Forwardmap the mesoscale model to a Martini resolution

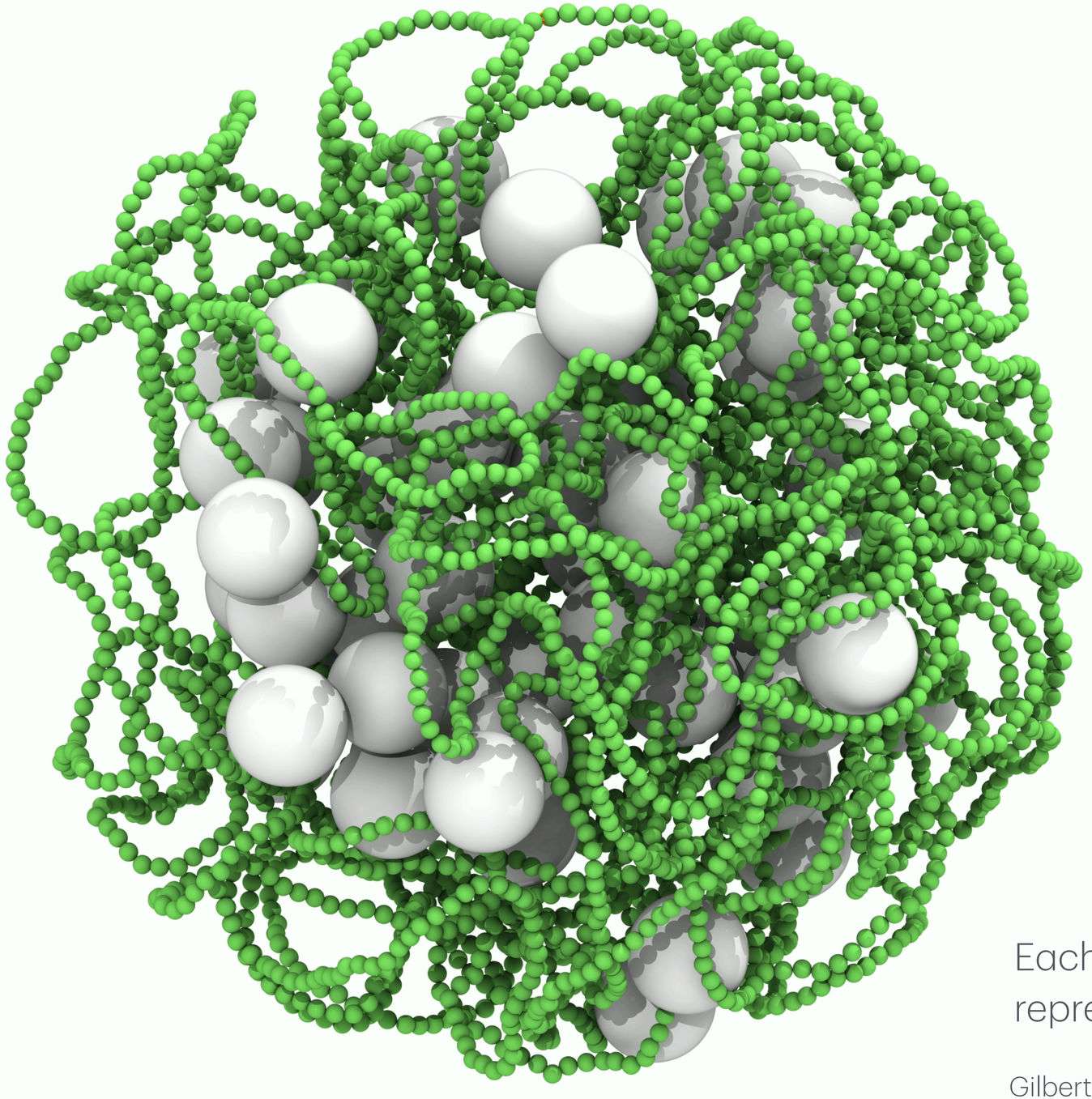
1. Increasing resolution
2. Generating internal DNA structure
3. Forward mapping the Martini beads



Grünewald, F. et al. (2022). Nat Commun.



Gilbert B. et al. (2023). Front. Cell Dev. Biol.



Largest molecule
simulated with Martini

Each ● sphere
represents 10 basepairs

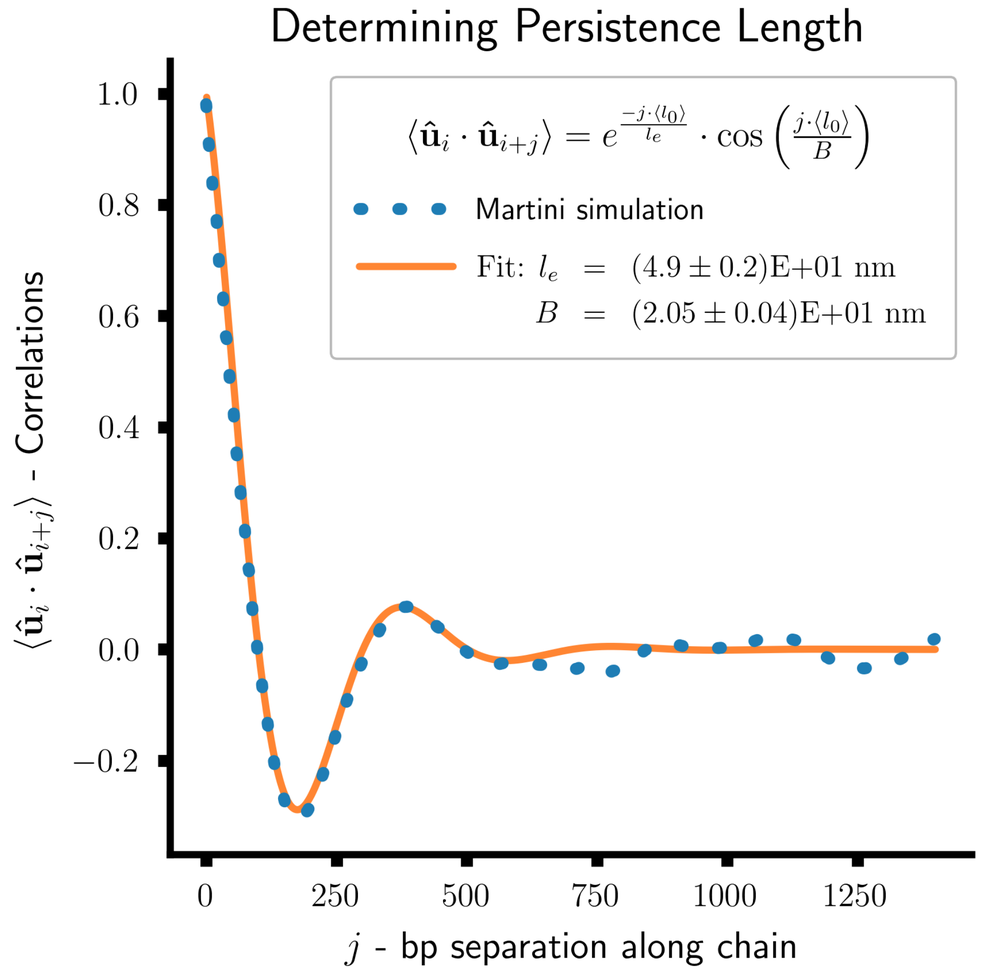
Gilbert B. et al. (2023). Front. Cell Dev. Biol.

Chromosome

Simulation

Verify the DNA building methodology on the full chromosome

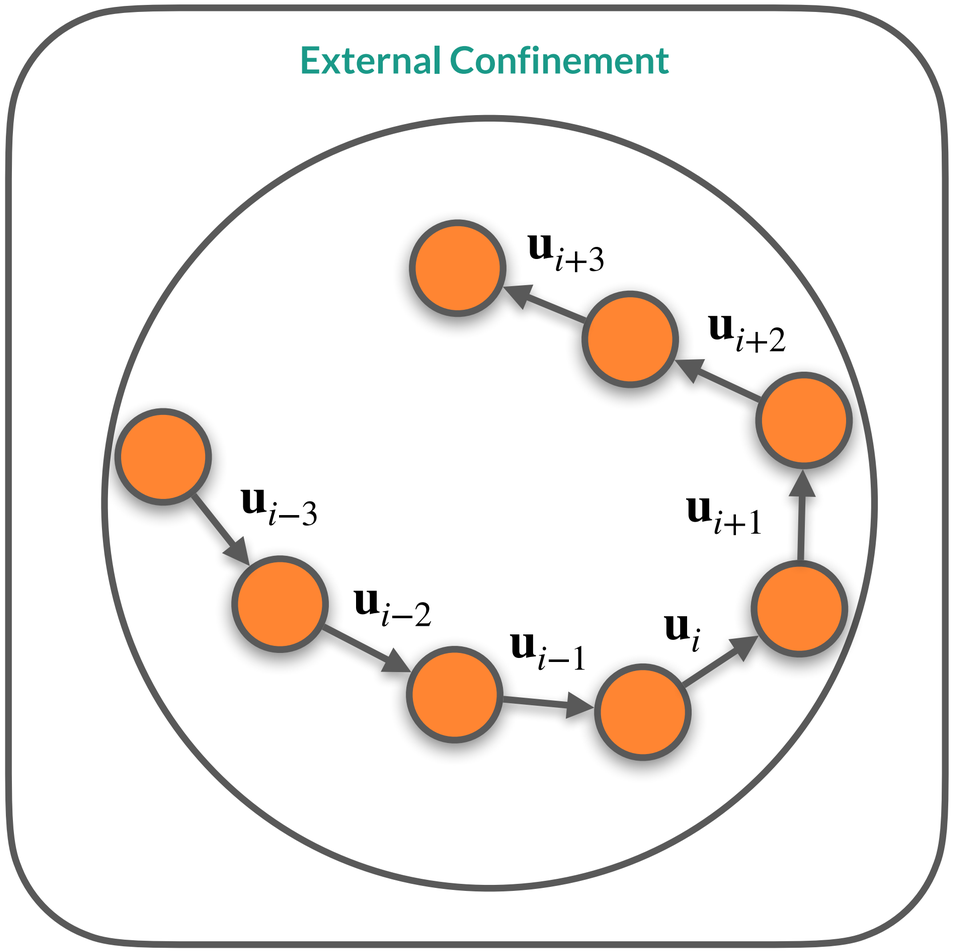
- Solvated with physiological NaCl solution
- **500ns** of MD simulation
- Reproduces correct dynamical properties

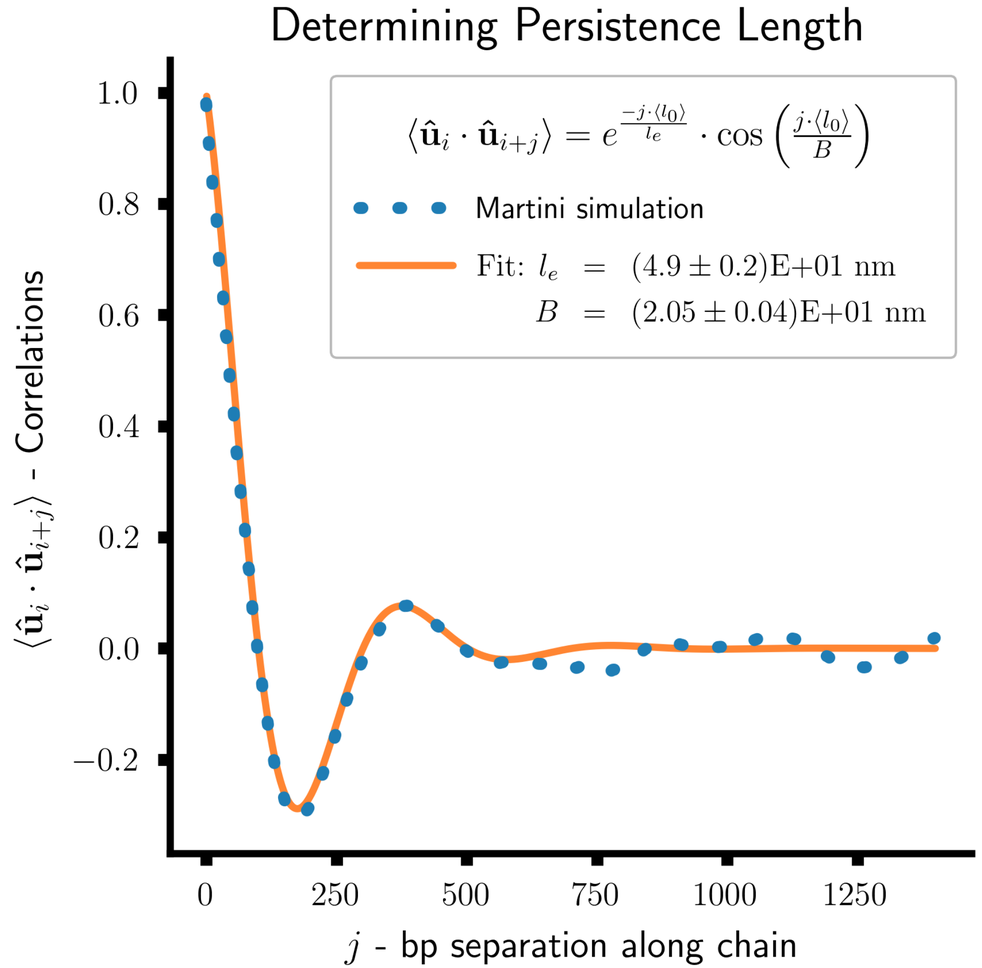


Gilbert B. et al. (2023). Front. Cell Dev. Biol.

Chromosome

Simulation

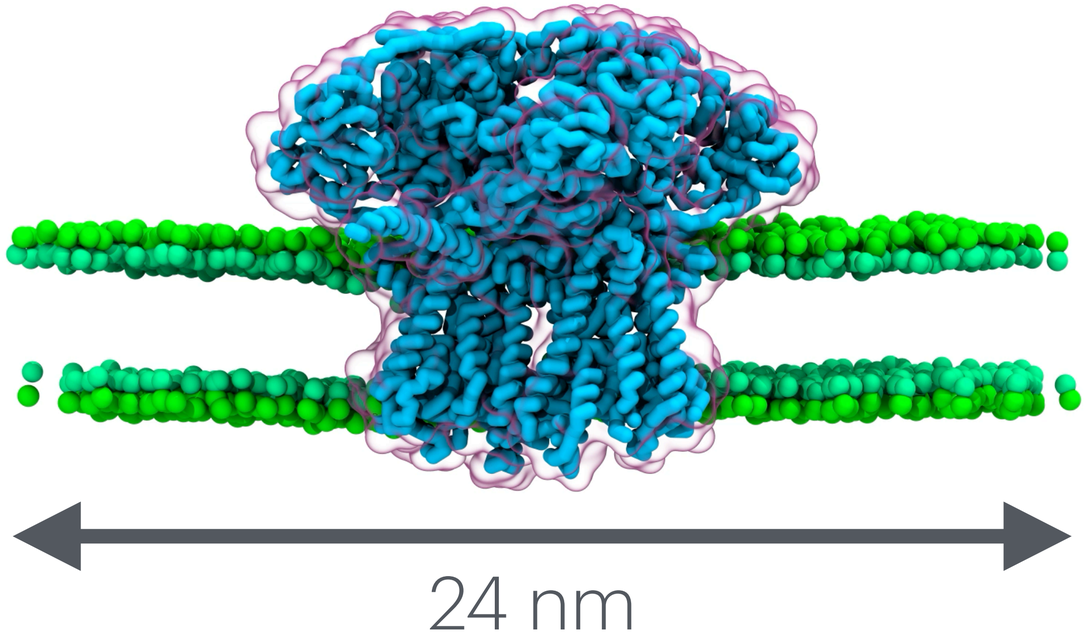




Gilbert B. et al. (2023). Front. Cell Dev. Biol.

Membrane

How to build the Cell envelope?

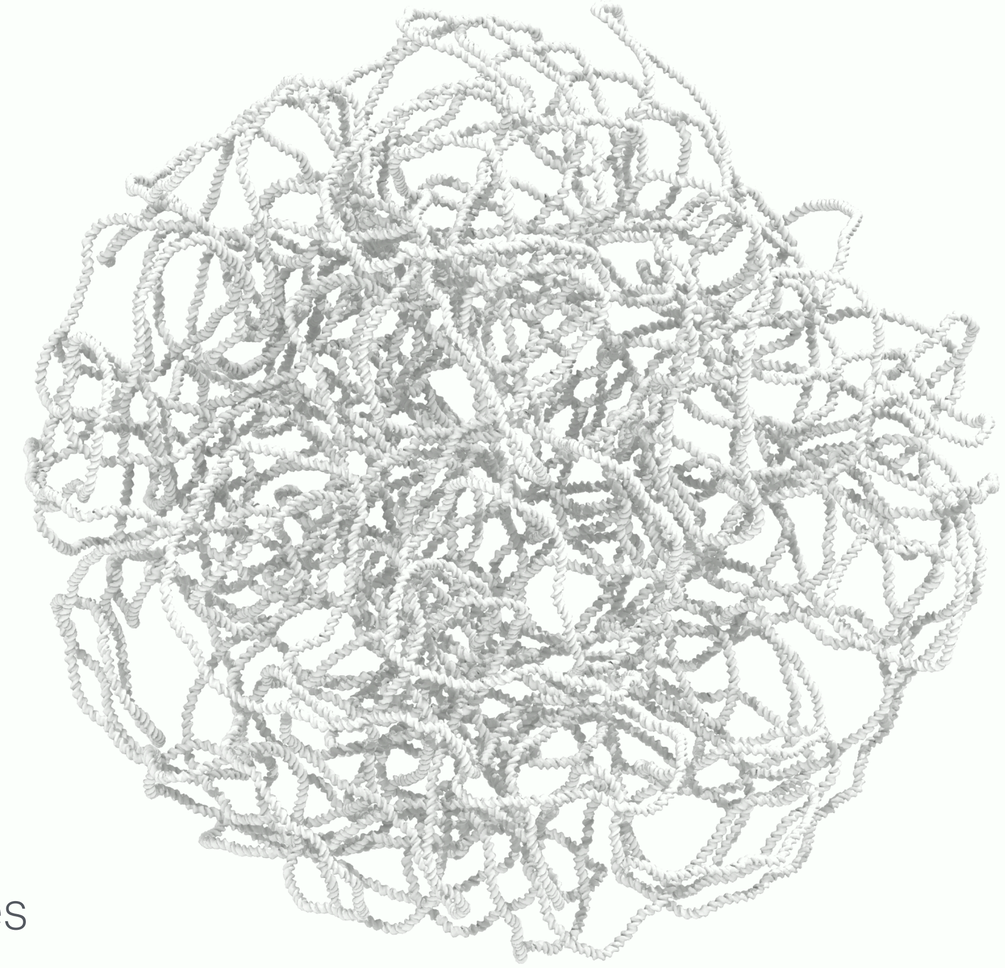


Membrane

Placing the membrane proteins



Mert Bozoflu



898 membrane proteins
with 89 different structures

Schuhmann F., Stevens J.A. et al. (2025). bioRxiv.

Membrane

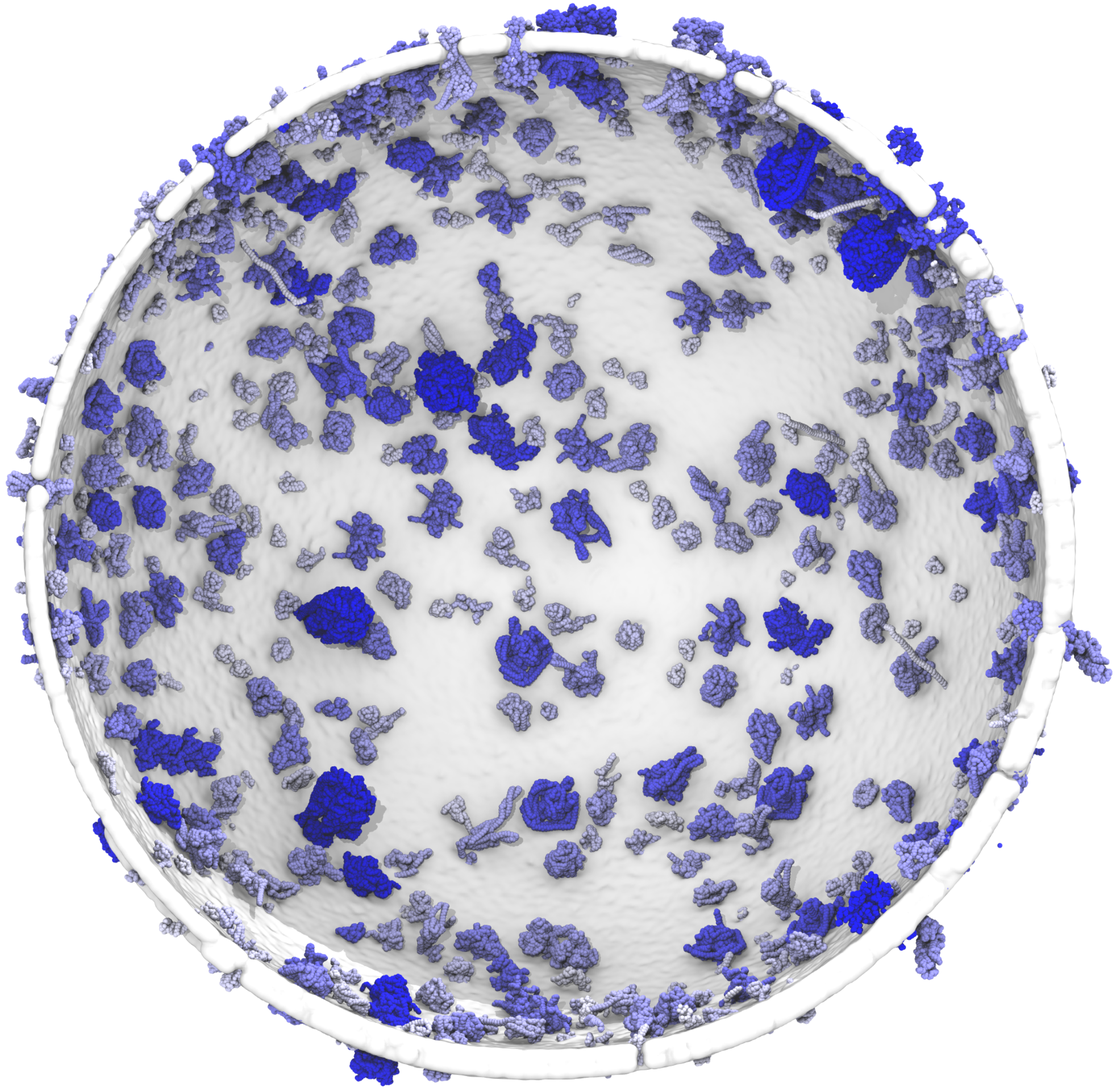
Adding the lipids



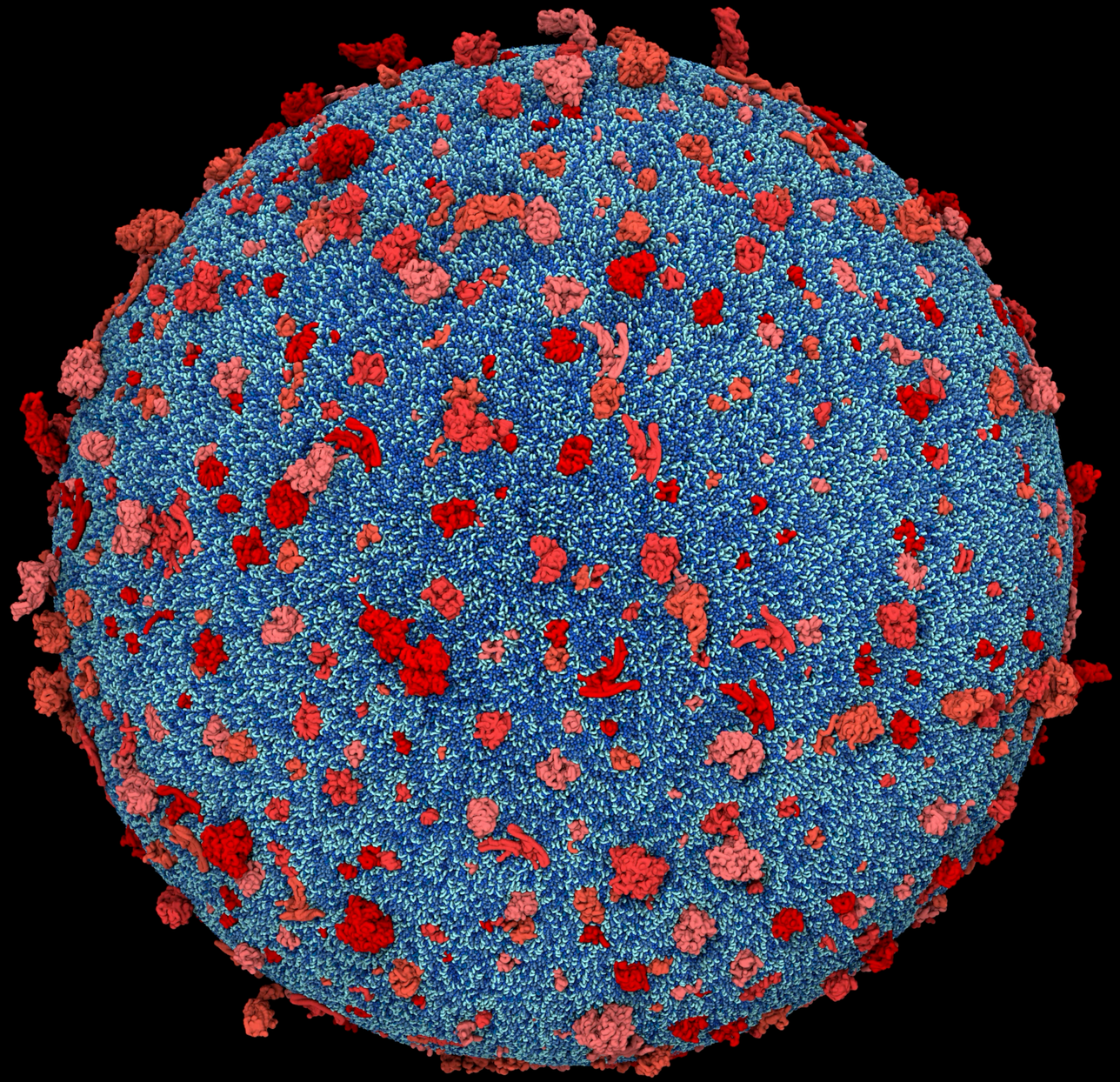
Mert Bozoflu

- Cholesterol: 59%
- DPSM: 18%
- Cardiolipin: 17%
- POPC: 4%
- DOPG: 2%

based on lipodomics



30% of the surface are membrane proteins



M. Bozoflu, J.A. Stevens & S.J. Marrink

Membrane

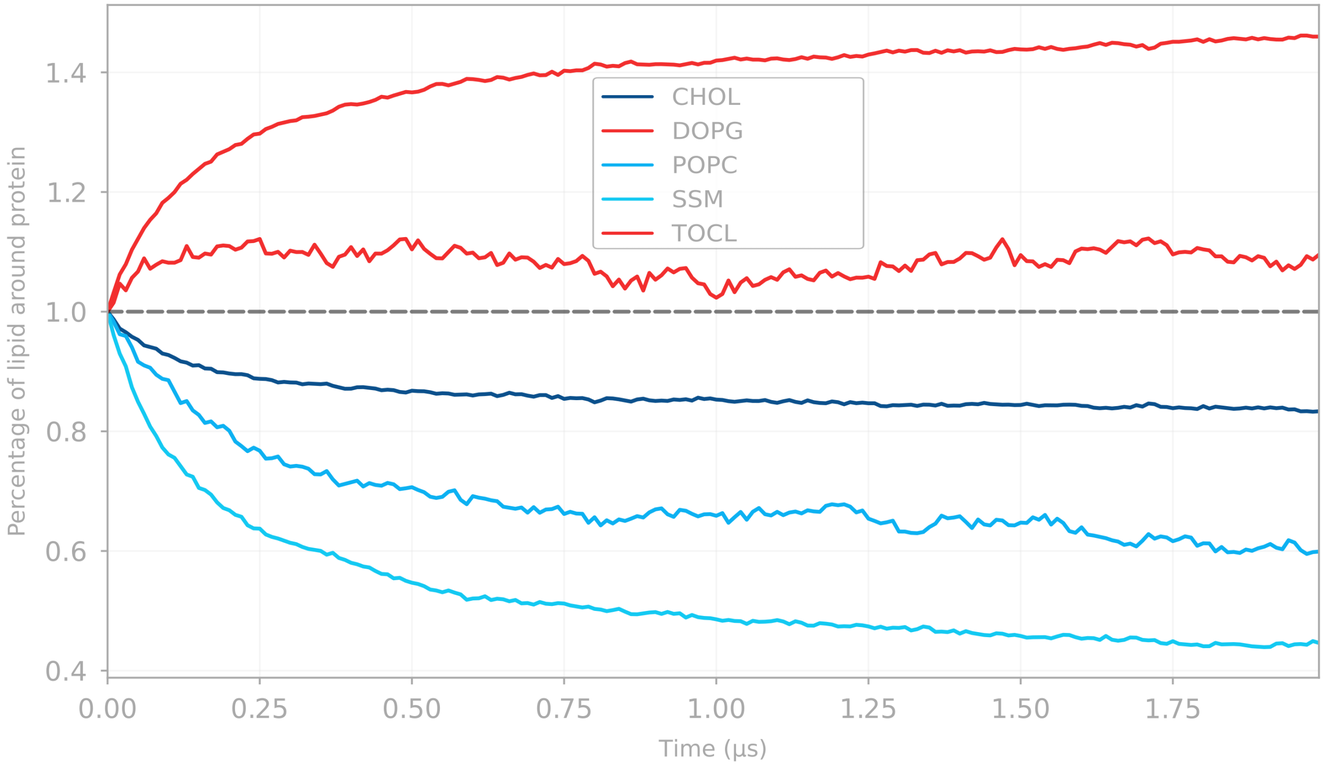
Lipid enrichment

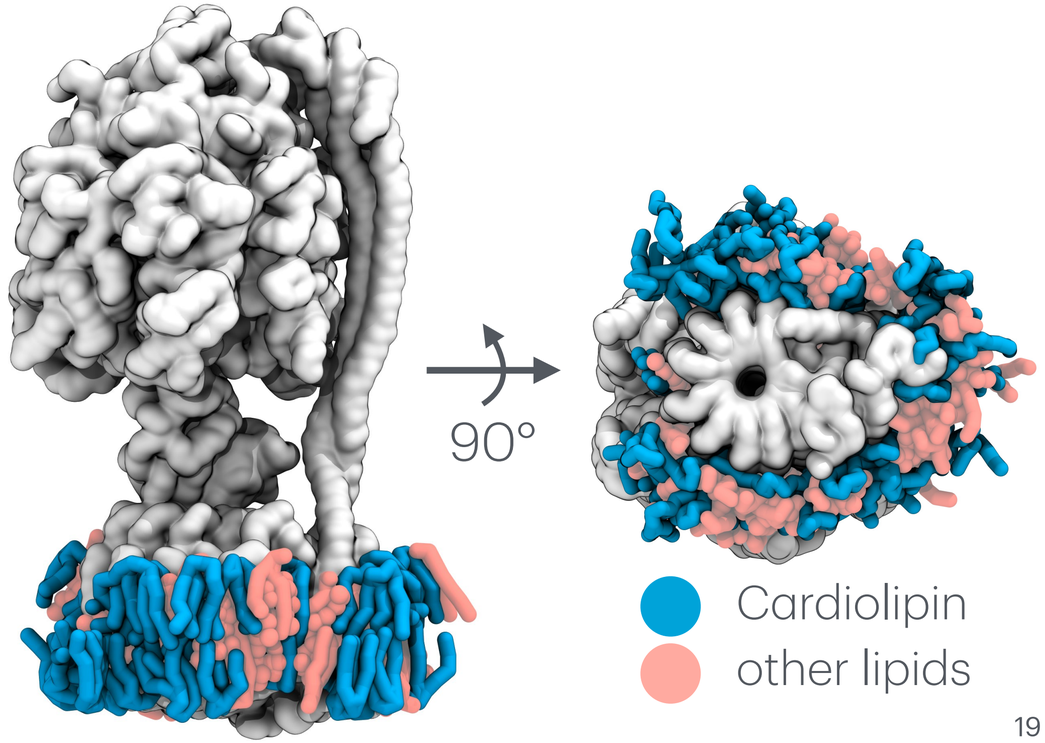


Mert Bozoflu

Proteins alter their local lipid environment

➤ **Cardiolipin** get's enriched





Membrane

Lipid enrichment

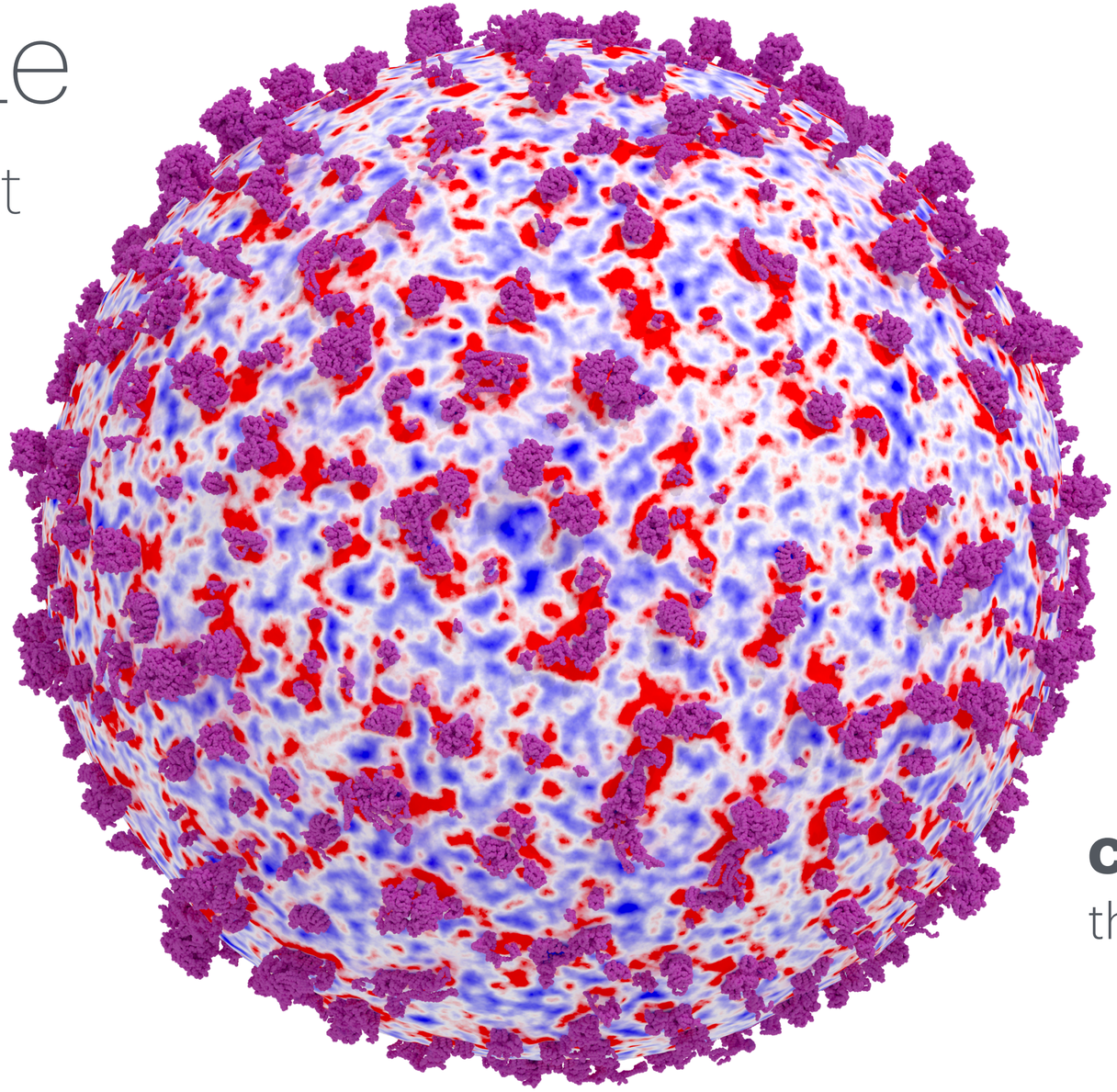


Bart Bruininks



Mert Bozoflu

Cardiolipin (CDL2)
is enriched around
membrane proteins



Cholesterol moves into
the `bulk` membrane

CDL depleted **CDL enriched**

Membrane

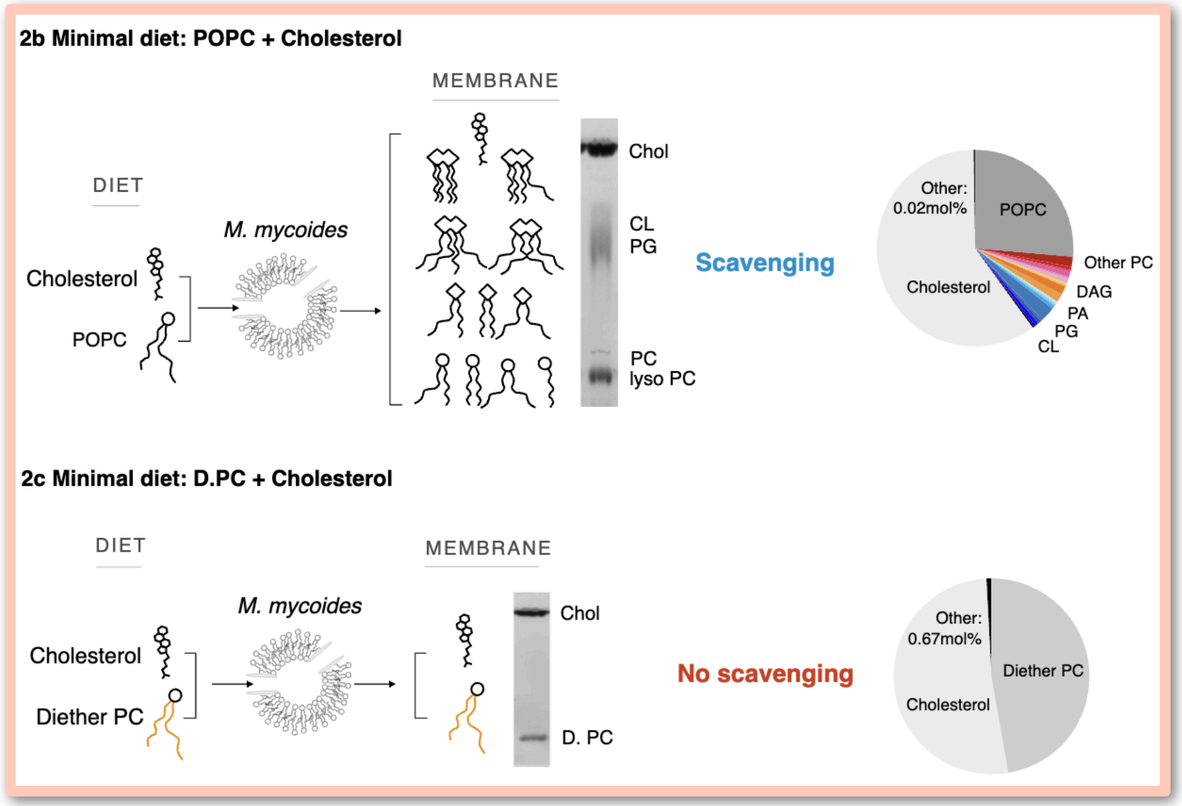
Lipid composition



Mert Bozoflu

Using the JCVI-Syn3A as a model platform, **the Saenz lab (TU Dresden)** created the simplest living membrane, consisting only of cholesterol and diether PC.

➤ What effect does this have on the dynamics of the cell envelope?



Justice, I. et al. (2024). Nat. Commun.

Membrane

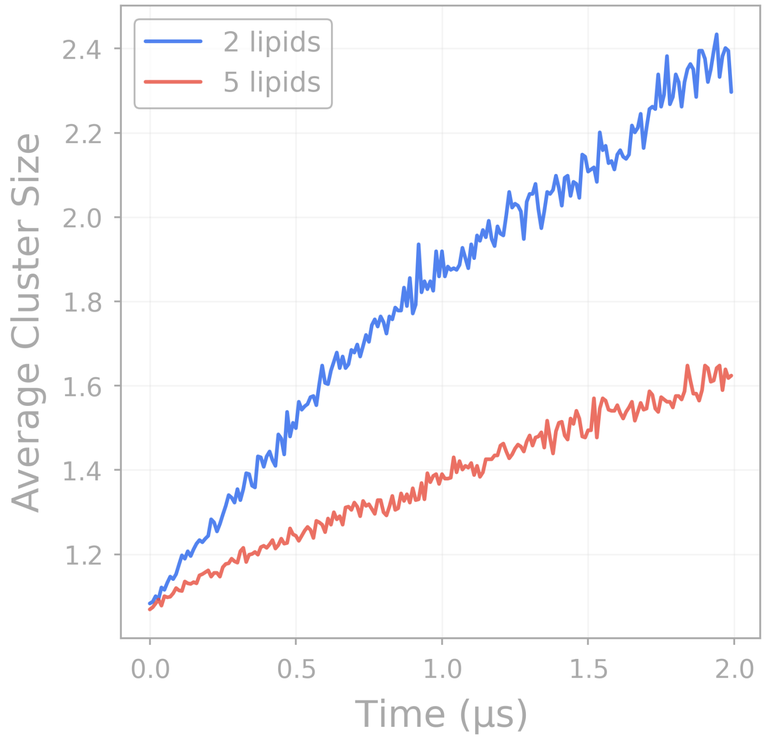
Protein clustering

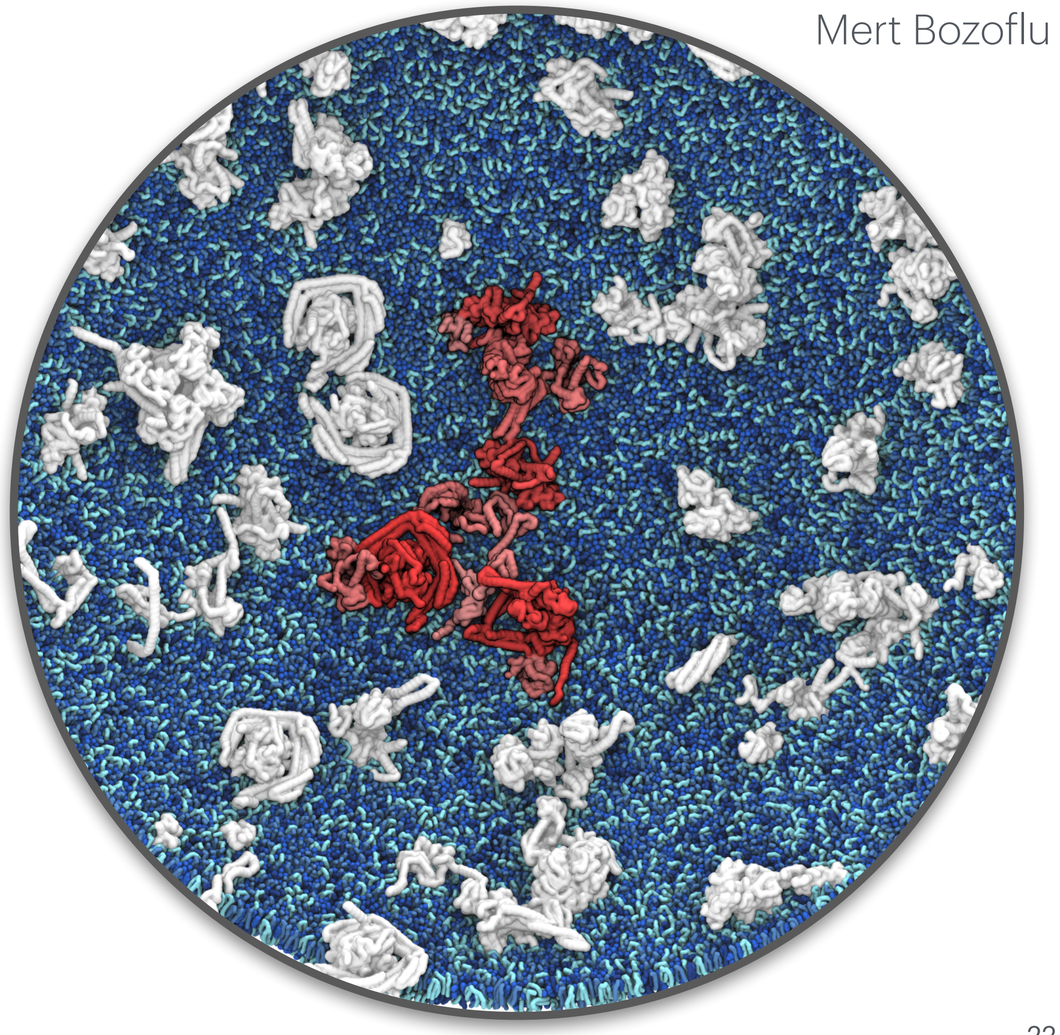


Mert Bozoflu

Clustering dynamics in the minimal lipidome is faster.

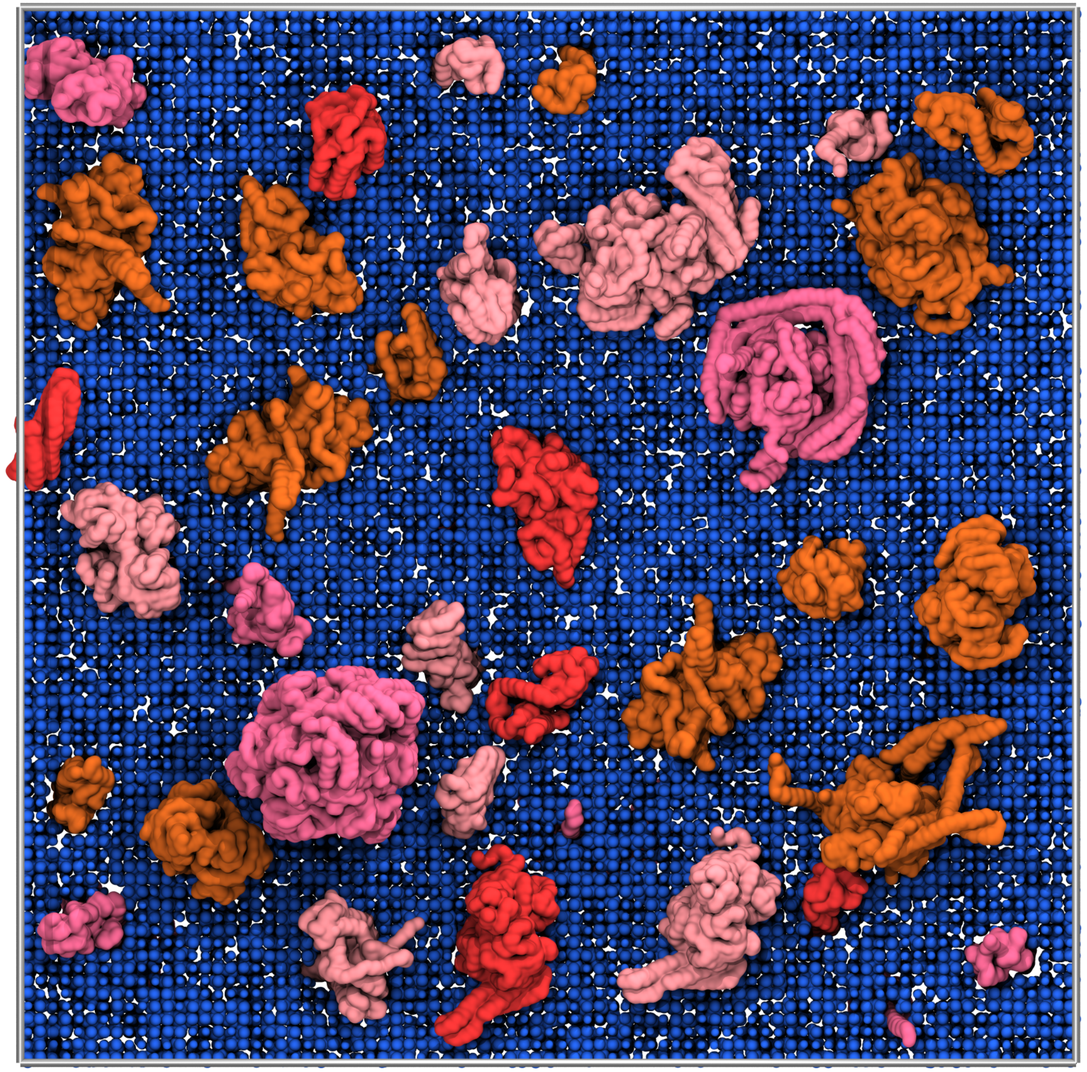
➤ Large protein islands are formed





Membrane

Protein clustering





Mert Bozoflu

Setup a membrane patch representing
the Syn3A envelope

Size: 64nm x 64nm

Proteins: 36 complexes

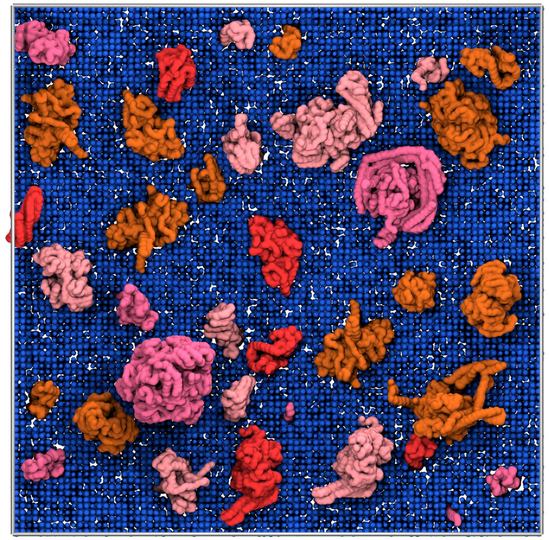
- Lipids are placed using **Insane**
- Proteins are placed using **Bentopy**

Membrane

Protein clustering



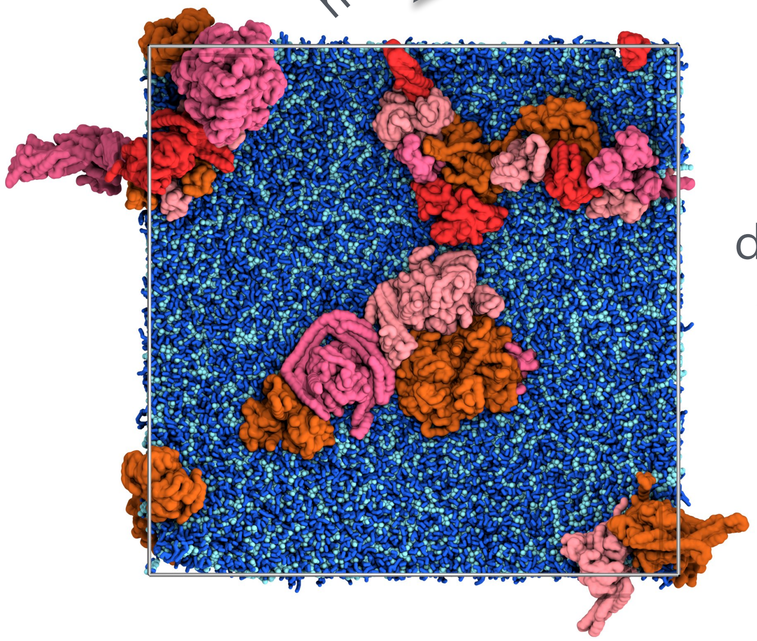
Mert Bozoflu



minimal membrane

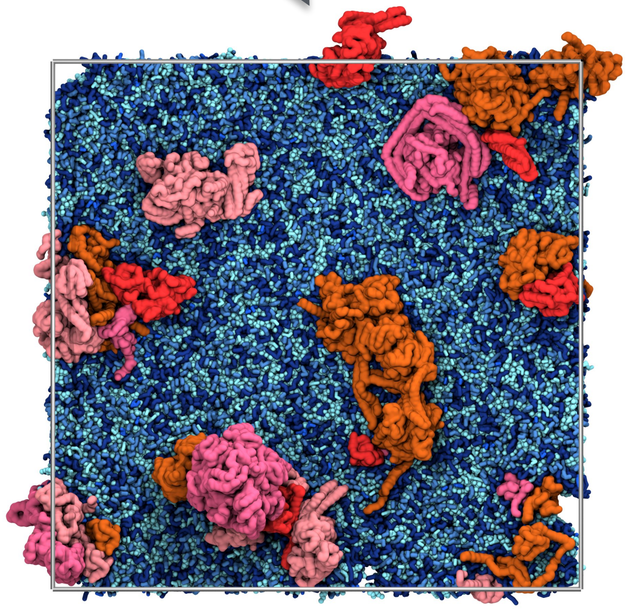
Native membrane

After equilibration **(20 μs)**



different clustering

behaviour



What is inside the cell?

Overview of the composition



Marieke Westendorp

- **Proteins**:
  2600 cytosolic proteins with 381 unique proteins

- **RNA** (tRNA, rRNA, ncRNA, mRNA):
  496 types of RNA molecules with abundacies based on protein copies and RNA dry-mass,

- **Metabolites**:
  250.000 metabolites with concentrations based on metabolomics experiments



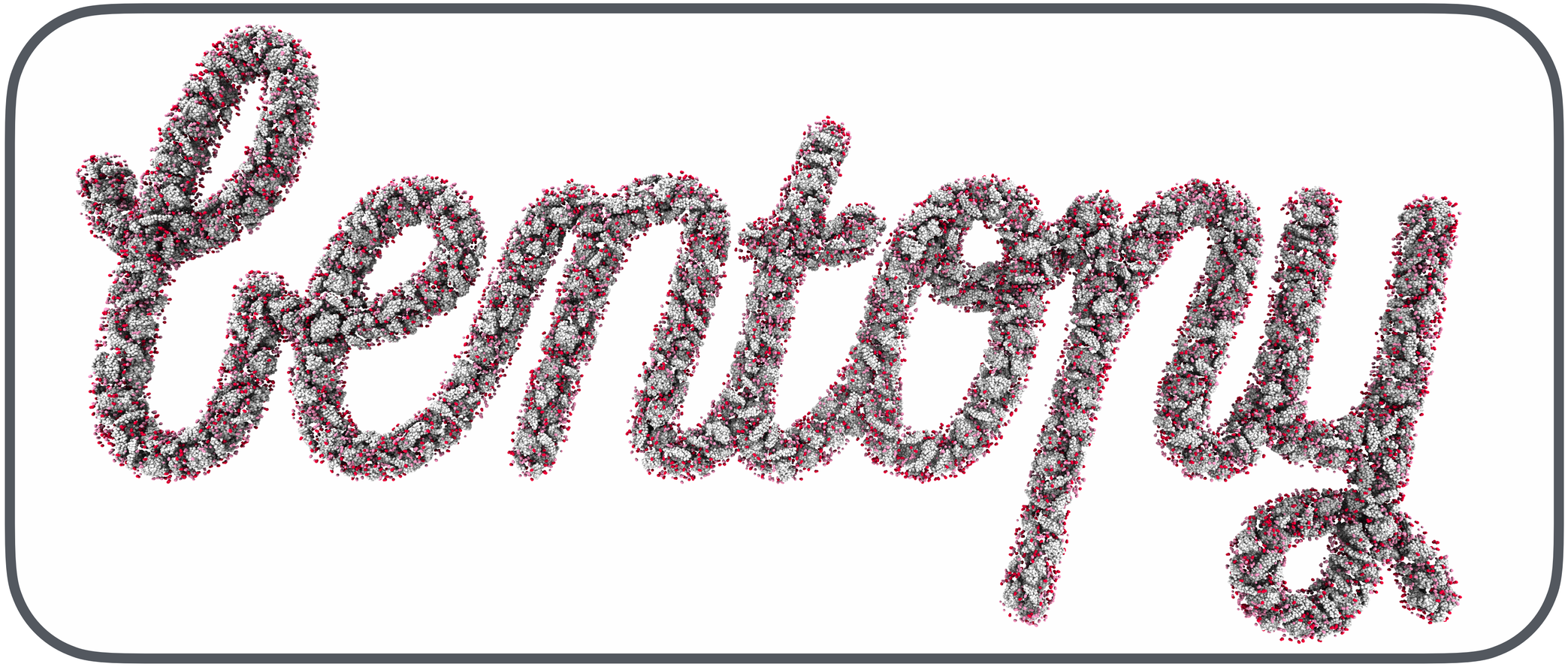
Already quite crowded?!

What is inside the cell?

Overview of the composition



Marieke Westendorp



Cytoplasm

Describing the environment



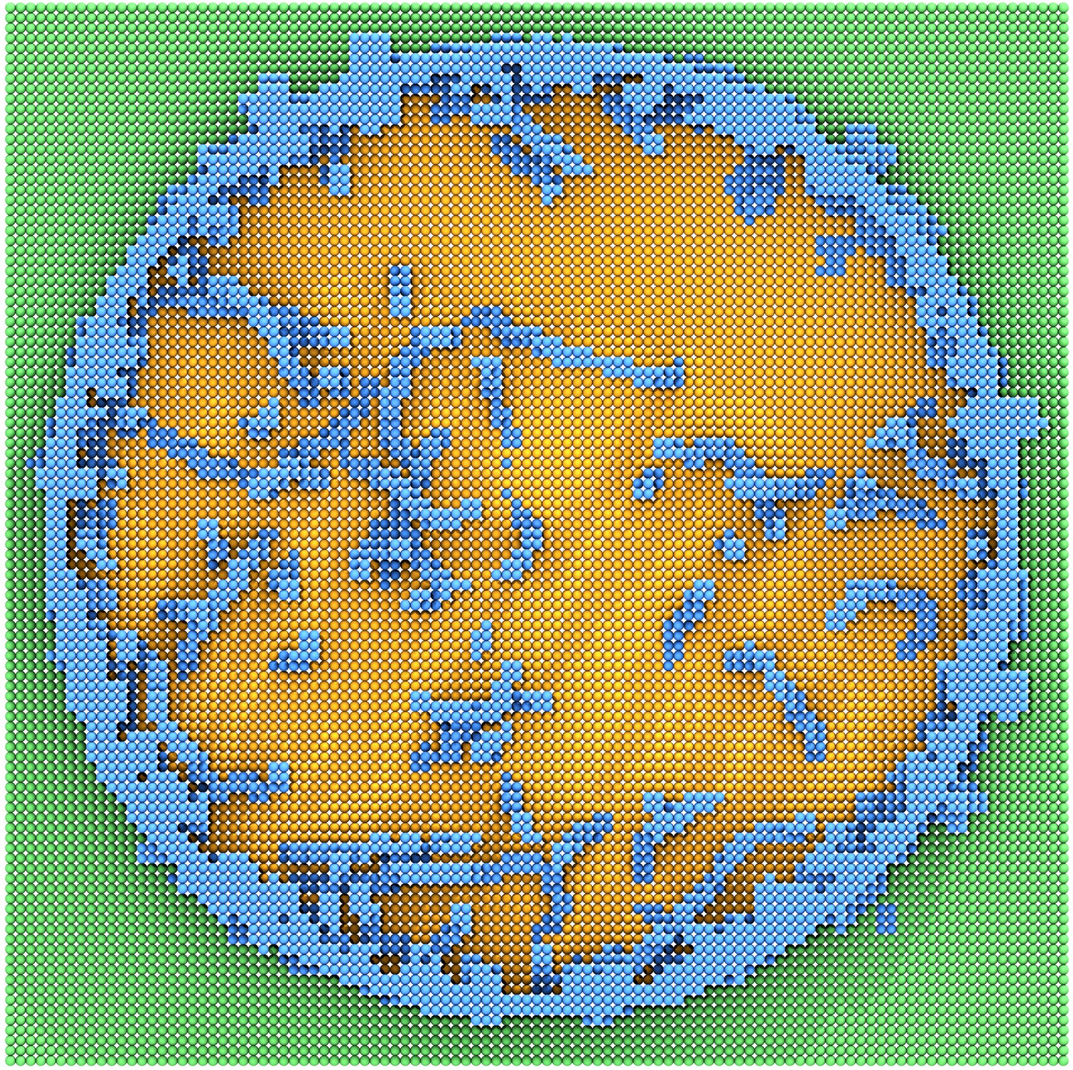
Bart Bruininks

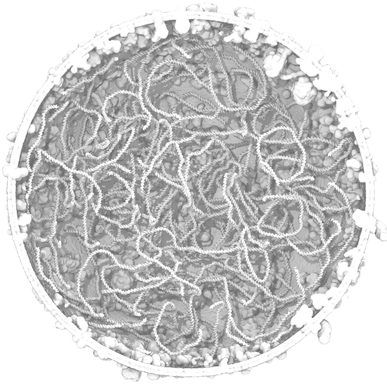


Marieke Westendorp

Containment-aware annotation of the model [1]

- Outside
- Model environment
- Inside (cytosol)





Efficient voxel representation

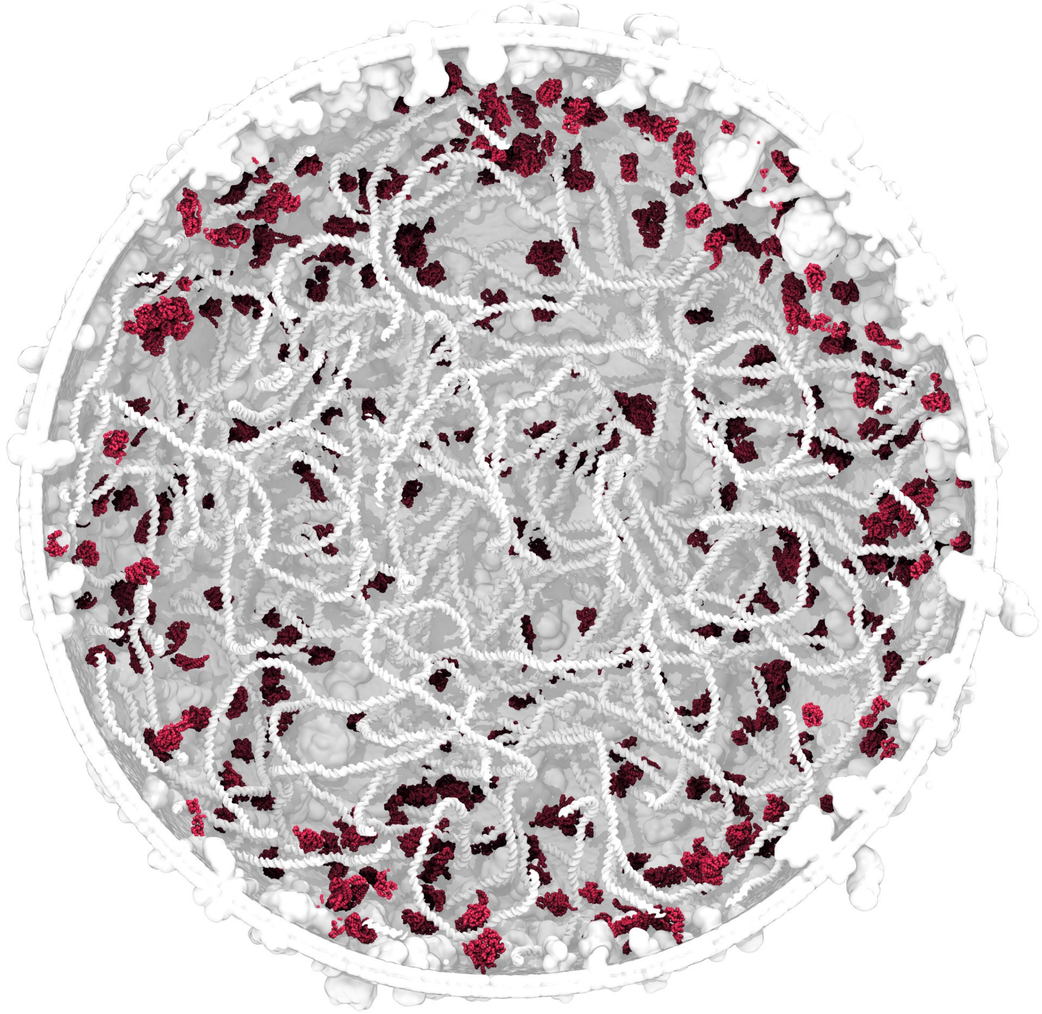
[1] Bruininks, B.M.H. et al. (2025). BioRxiv.

Cytoplasm

- Membrane-peripheral components



Marieke Westendorp



Environment aware packing rules

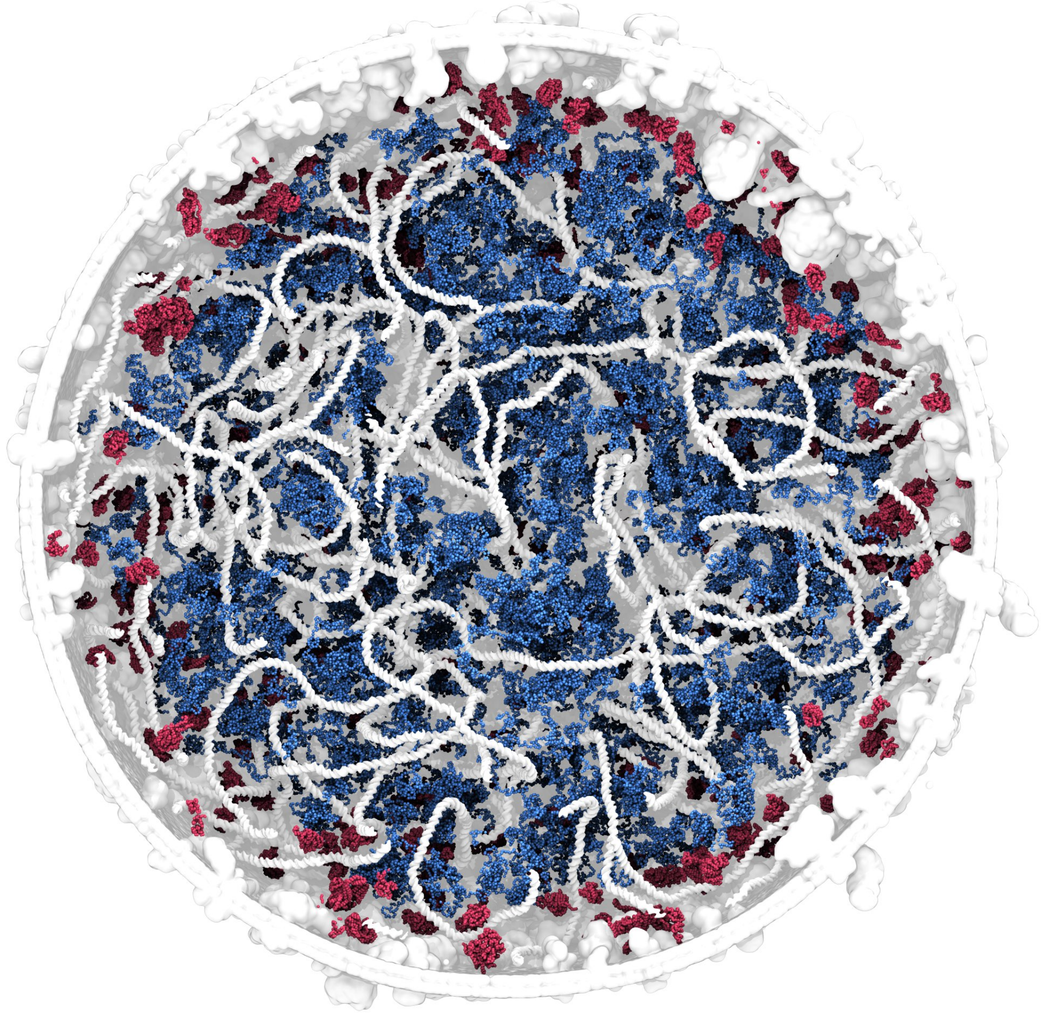
To integrate experimental data in models

Cytoplasm

- Membrane-peripheral components
- RNA



Marieke Westendorp



Using a heuristic to asses packing difficulty

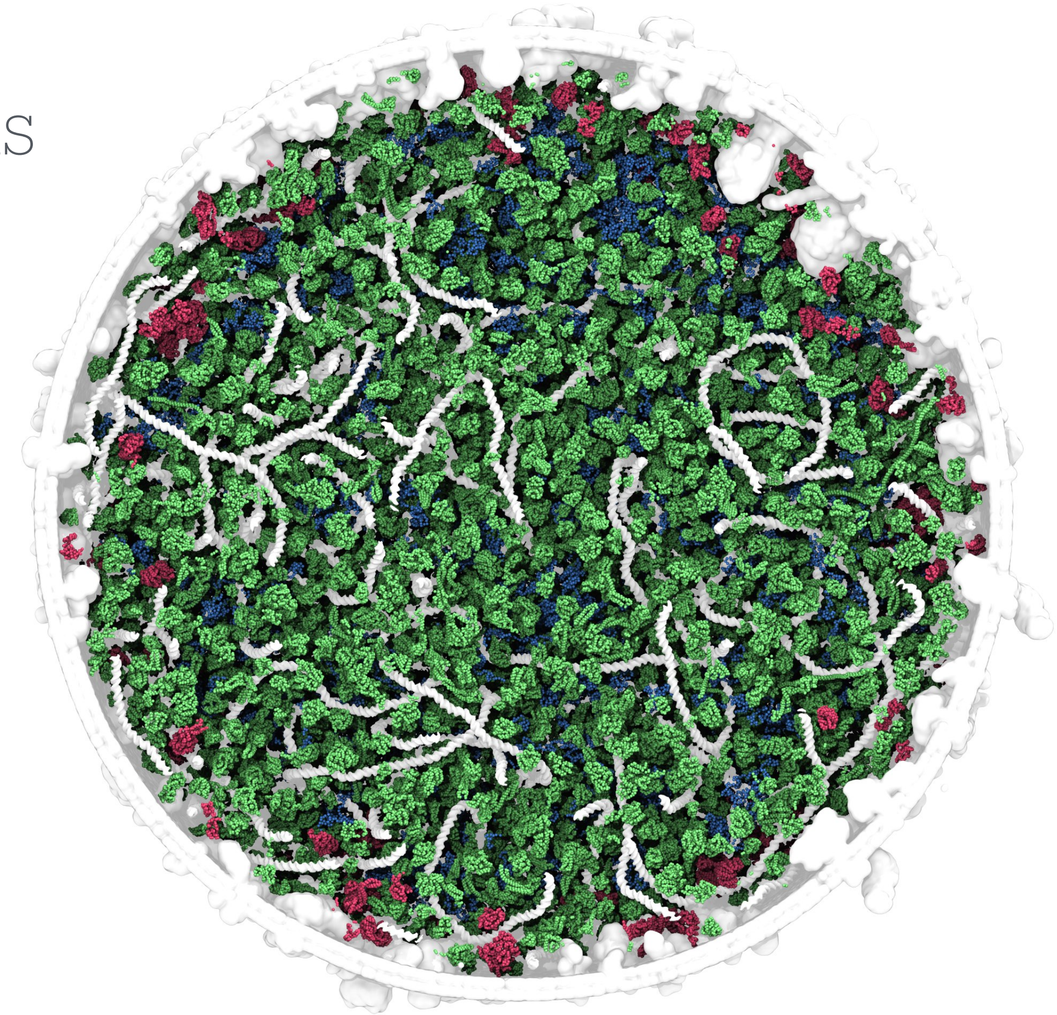
$$I_P = \sum_i m_i r_i^2$$

Difficult components are placed first

For our cell **RNA strands** are the most difficult to pack

Cytoplasm

- Membrane-peripheral components
- RNA
- Soluble proteins





Marieke Westendorp

Using a greedy algorithm designed to pack

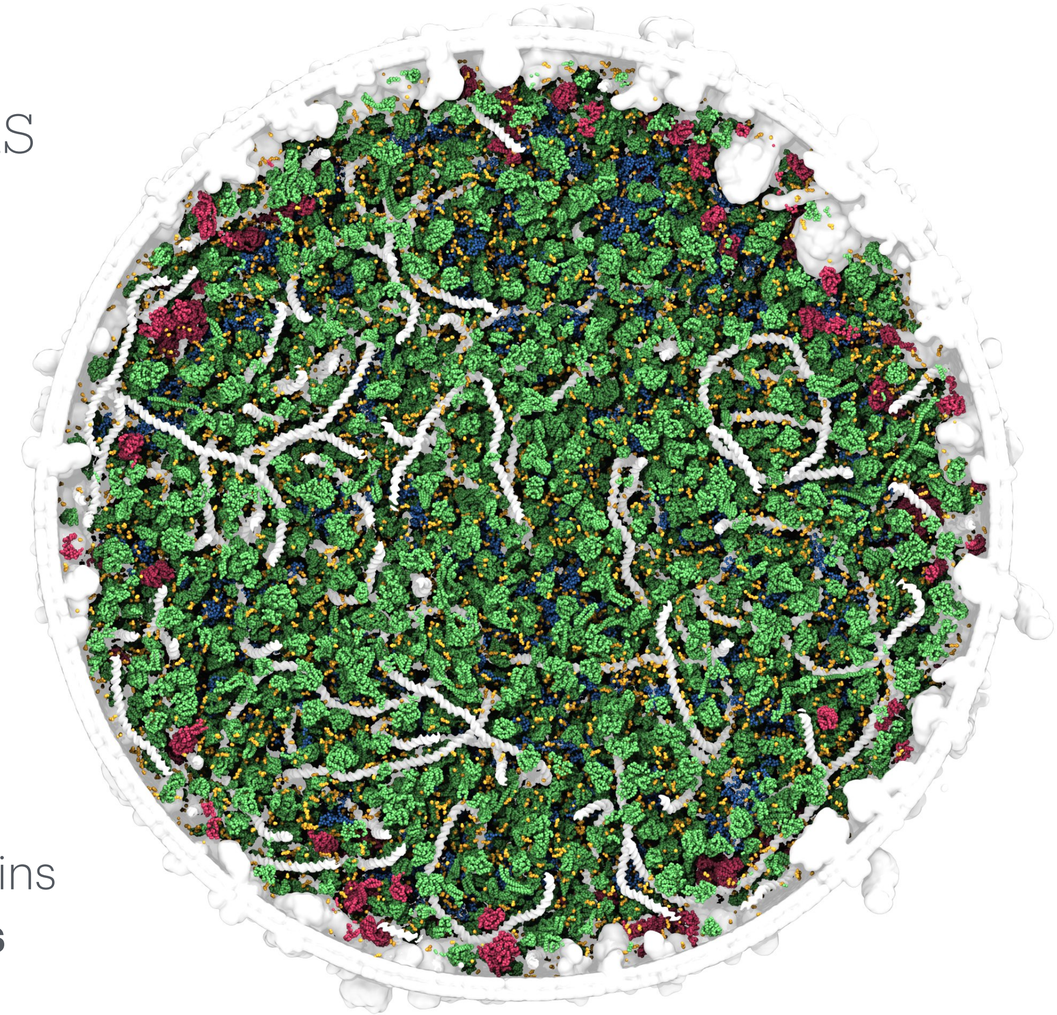
physiological densities of
± 30% occupied volume

Cytoplasm

- Membrane-peripheral components
- RNA
- Soluble proteins
- Metabolites



Marieke Westendorp



The final cytosol model contains
±40.000 macromolecues

Model building is not the rate-limiting step

We pack a cell in a few minutes

Packing the cytosol

Animated





Marieke Westendorp

Packing the cytosol

A **Bentopy** workflow

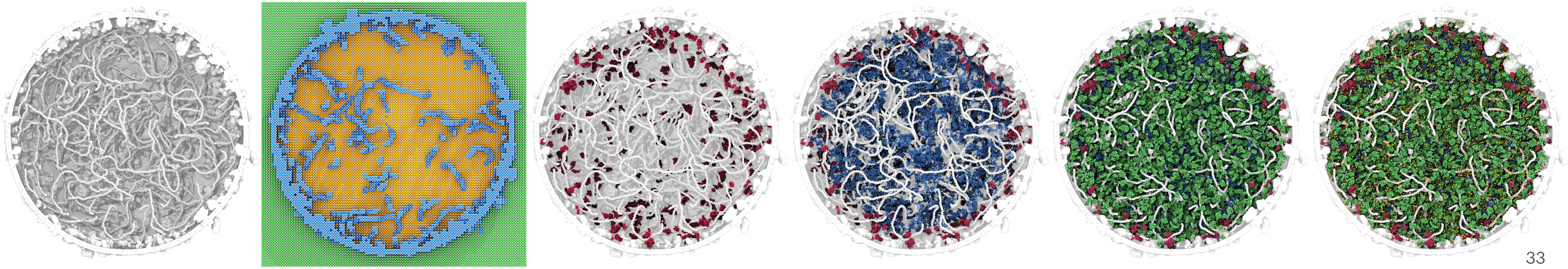
Westendorp M.S.S., Stevens J.A. et al. (2025). In prep.



Marieke Westendorp

- Packing mesoscale models **without collisions**.
- Integrating experimental data
- Builds **simulation-ready** models

Step -1 | Step 0 | Step 1 | Step 2 | Step 3 | Step 4



Packing the cytosol

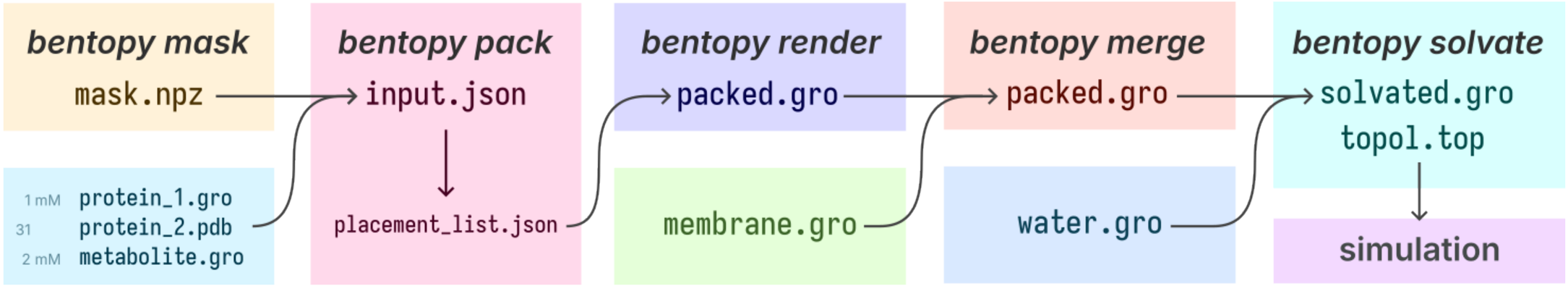
A **Bentopy** workflow

Westendorp M.S.S., Stevens J.A. et al. (2025). In prep.



Marieke Westendorp

- Packing mesoscale models **without collisions**.
- Integrating experimental data
- Builds **simulation-ready** models

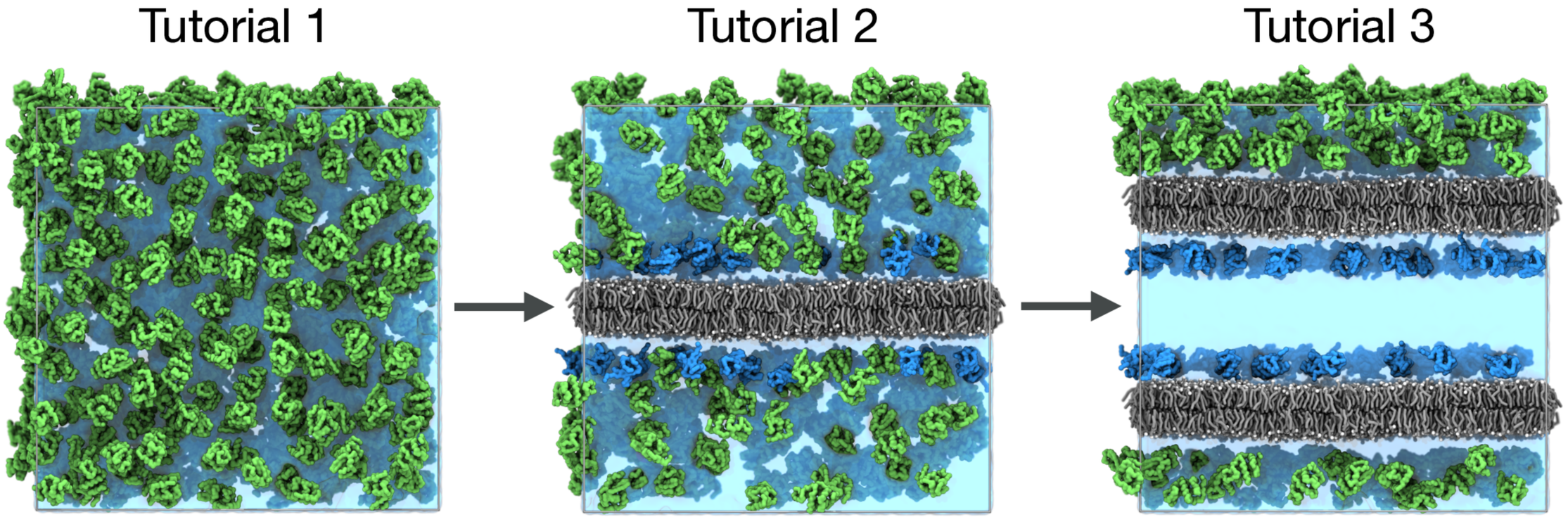


Packing the cytosol

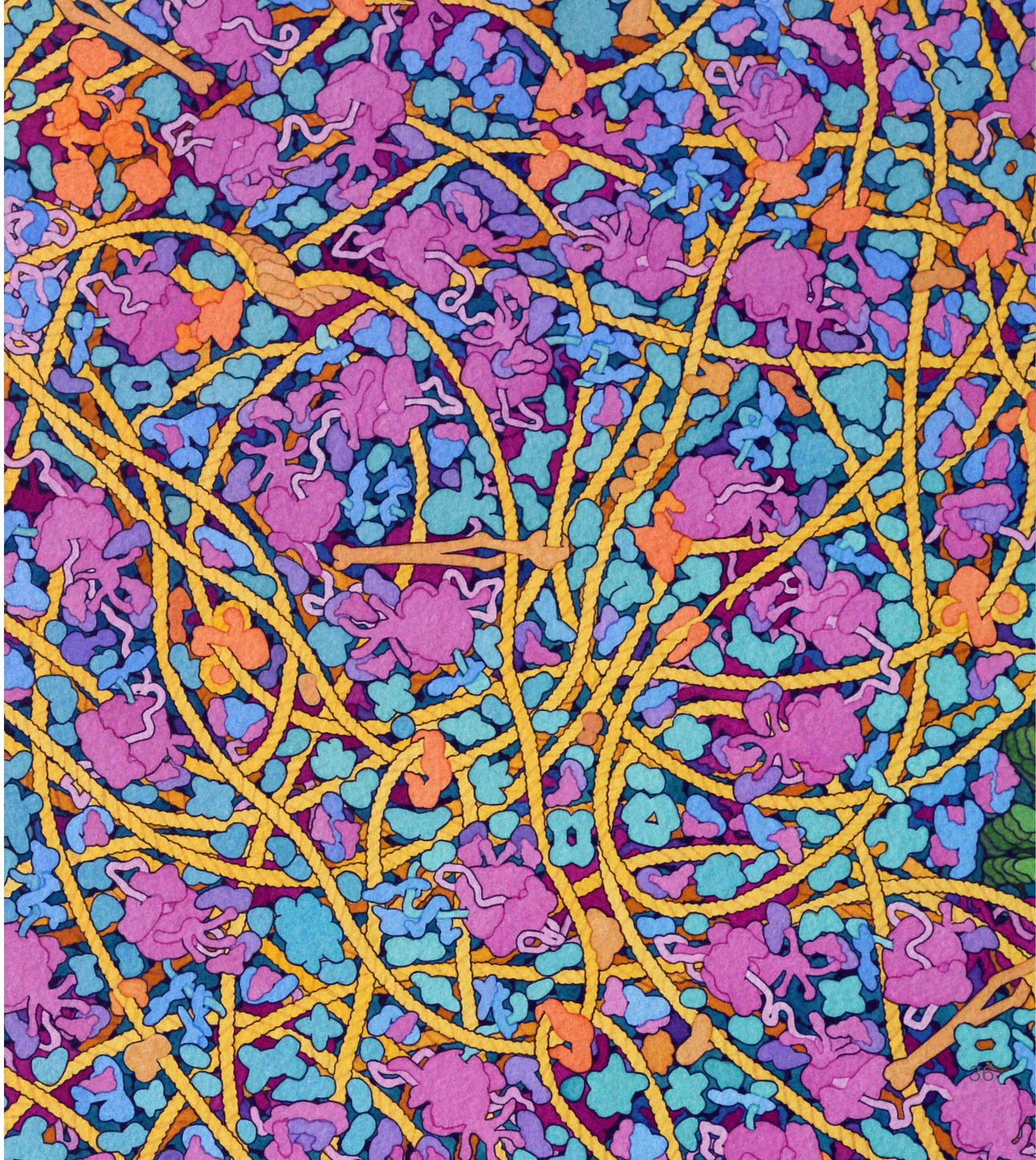
A **Bentopy** workflow *Westendorp M.S.S., Stevens J.A. et al. (2025). In prep.*



Marieke Westendorp



Simulating a cell



© David Goodsell

HPC performance

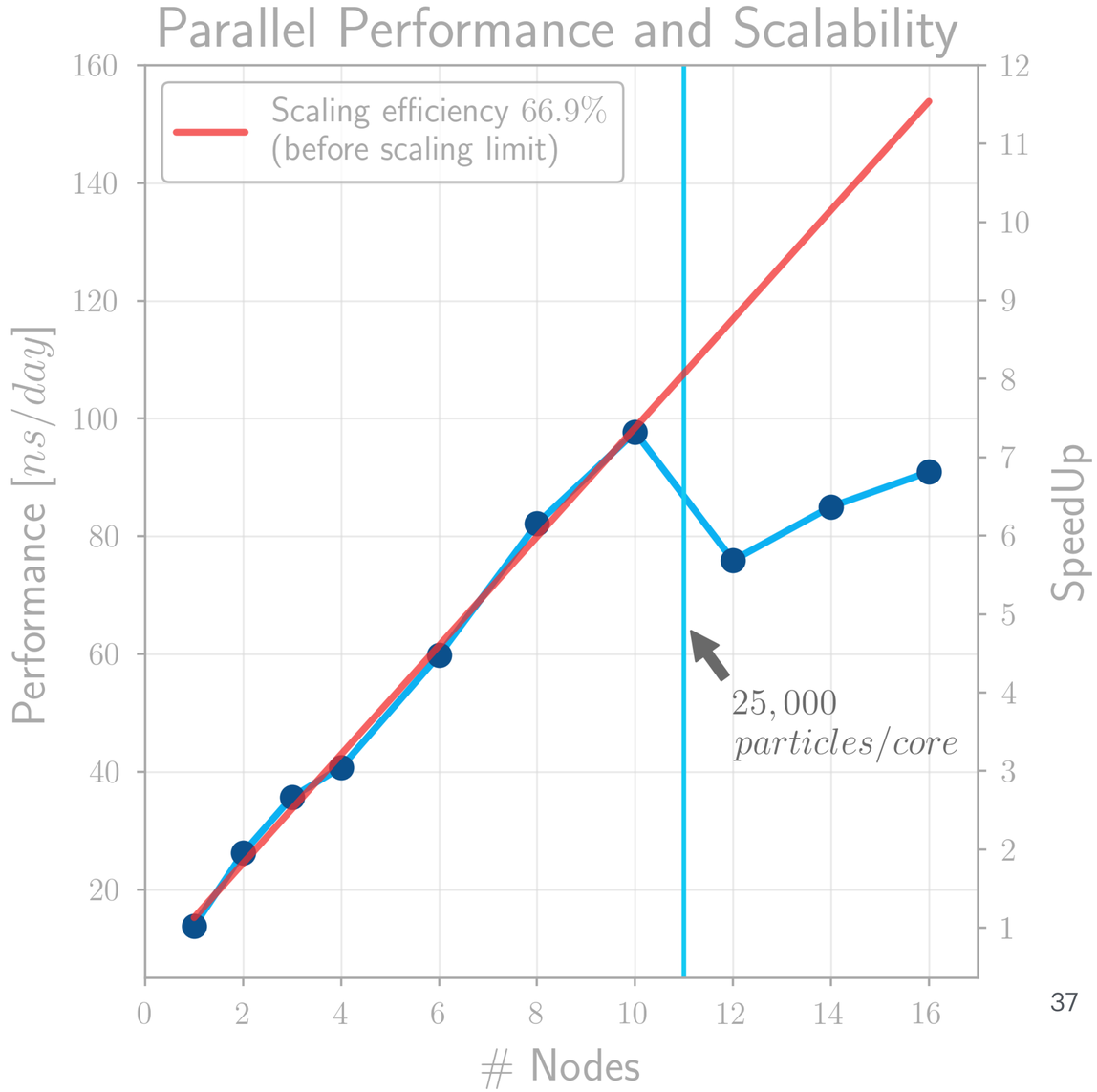
Benchmarking Martini simulations

Improvements in Gromacs, v. 2024, enable us to run more then **128 million particles**.

- New **.xtc** file format
- Fixed **.top** file parsing (#ifdef statements)
- **MPI** rank bug (more ranks is better)

On the national Dutch HPC, Snellius:

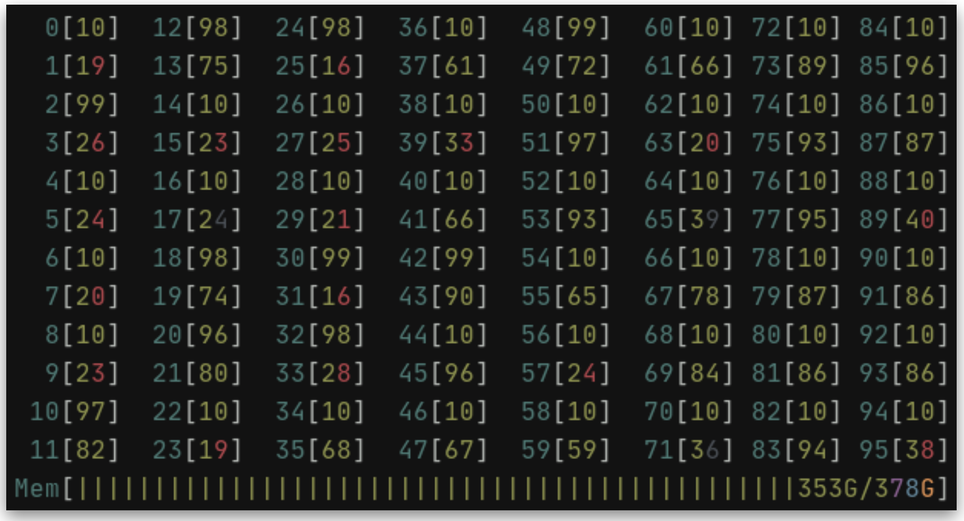
- AMD Genoa CPU nodes, i.e. 192 cores
- Strong scaling (67%) until 10 nodes
  ≈ until 25,000 particles per core

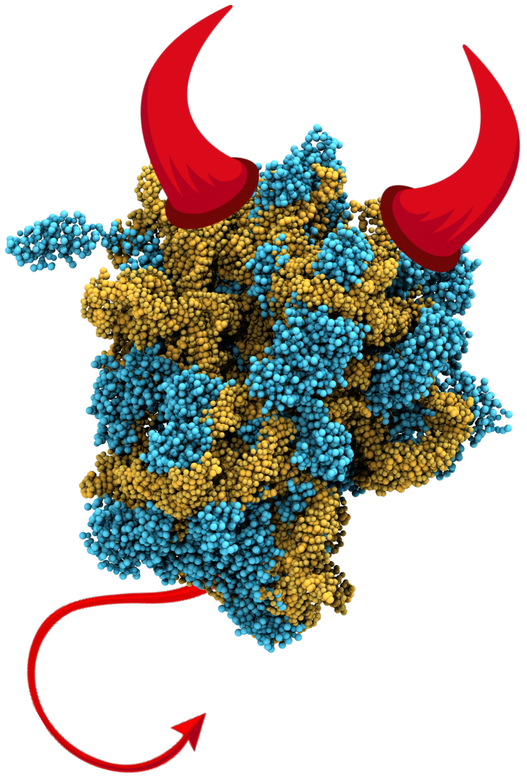


What did we learn?

Solving problems along the way

- The simulation is only as stable as the weakest link.
- **High memory demand** due to the complex simulation topology.
- Complicated data management due to **large file sizes**.
- **Slow simulation iteration** due to the high cost.
- ....





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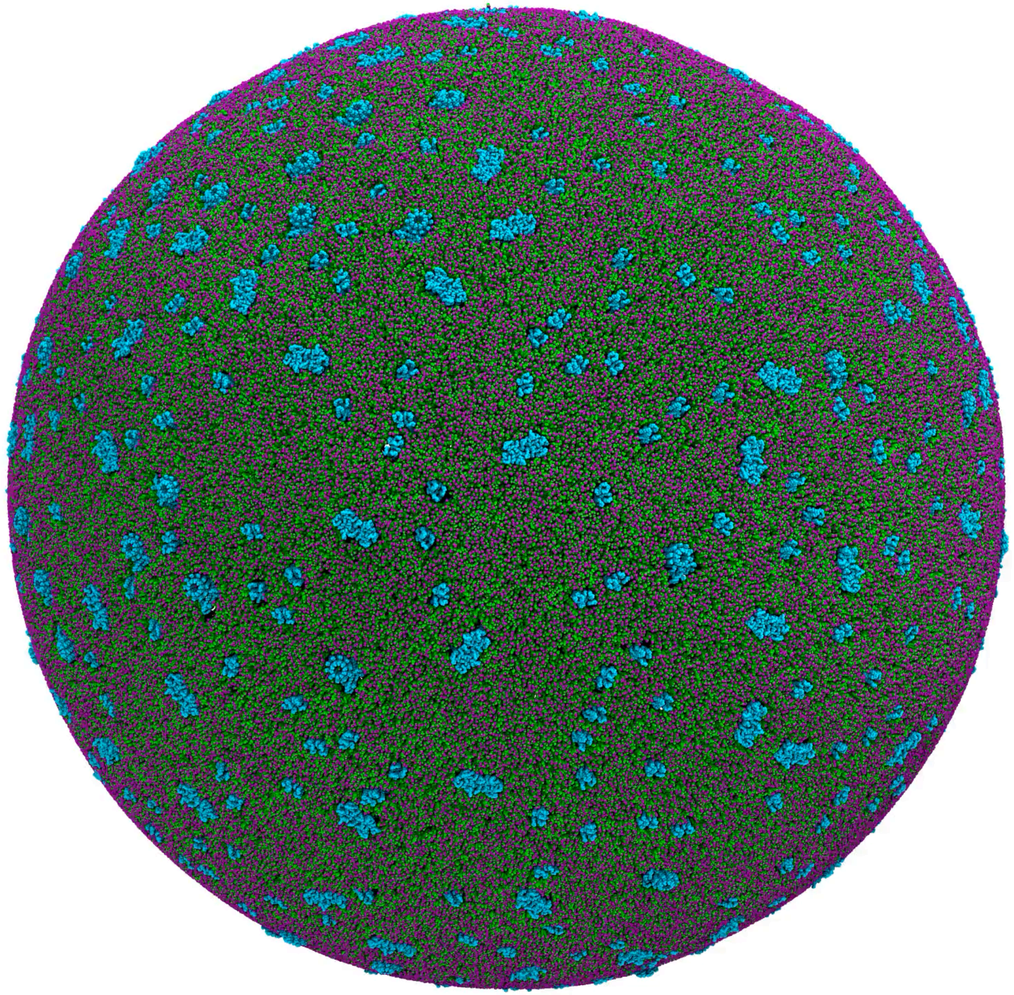
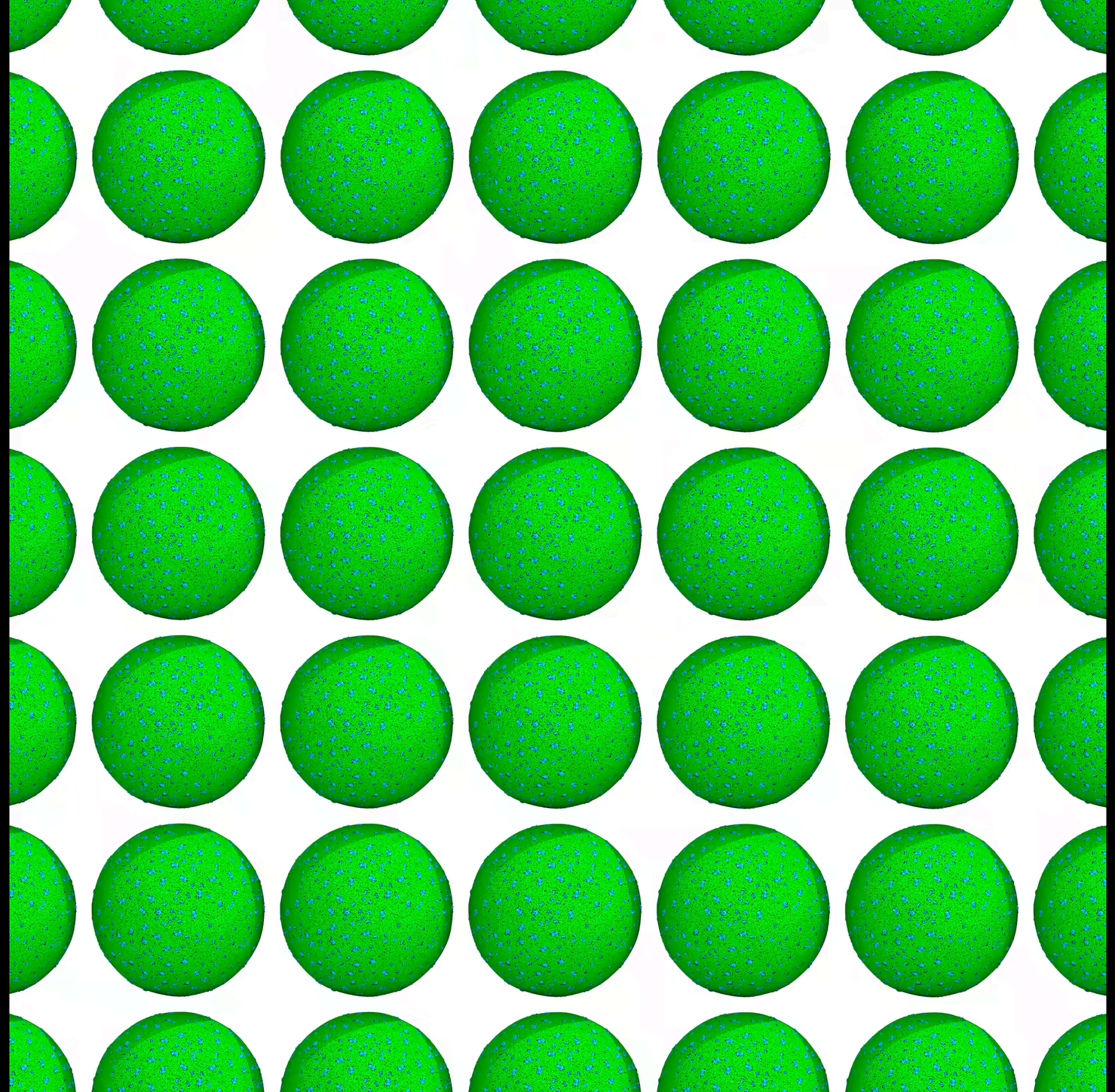
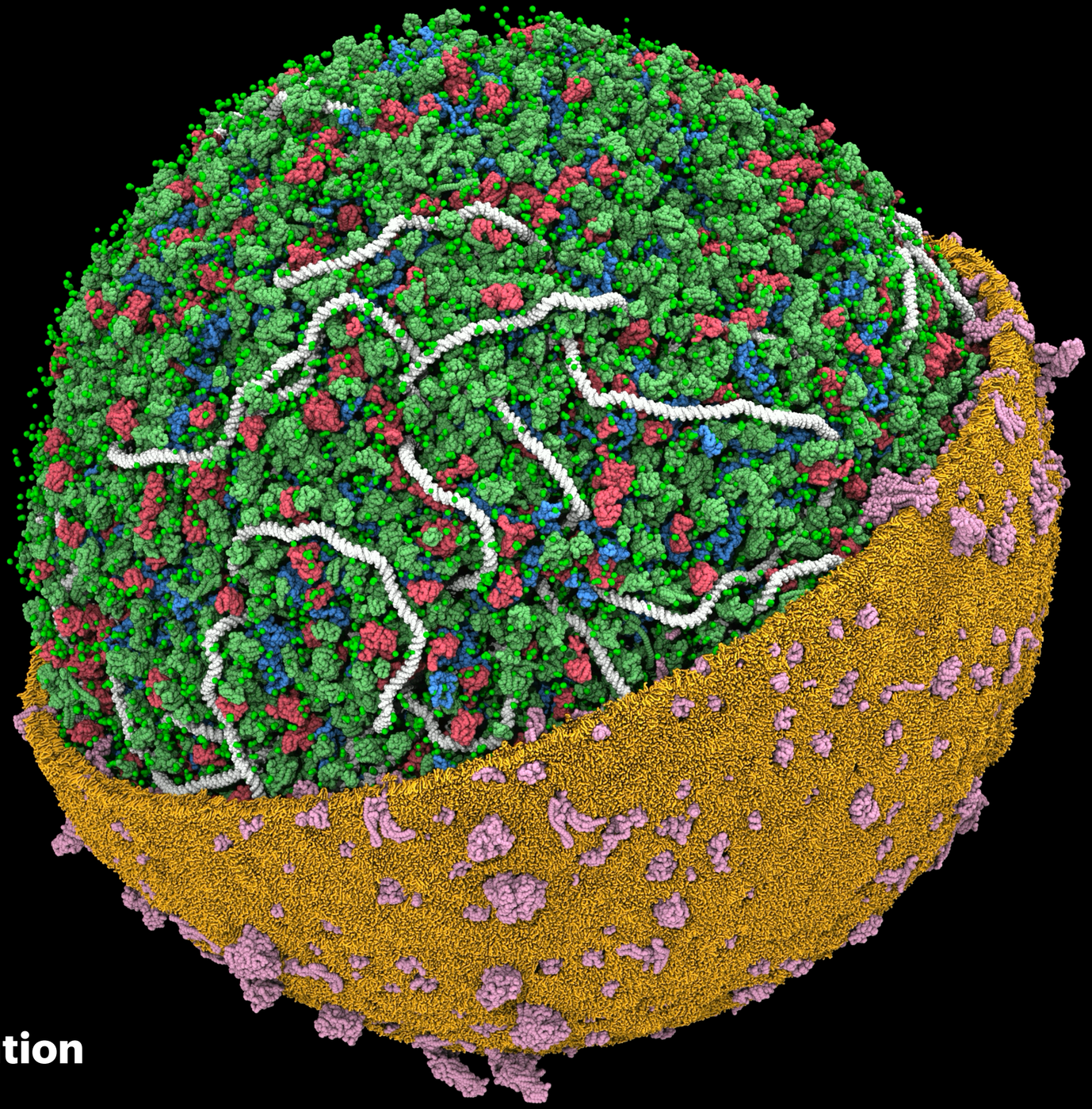




But sometimes it doesn’t crash

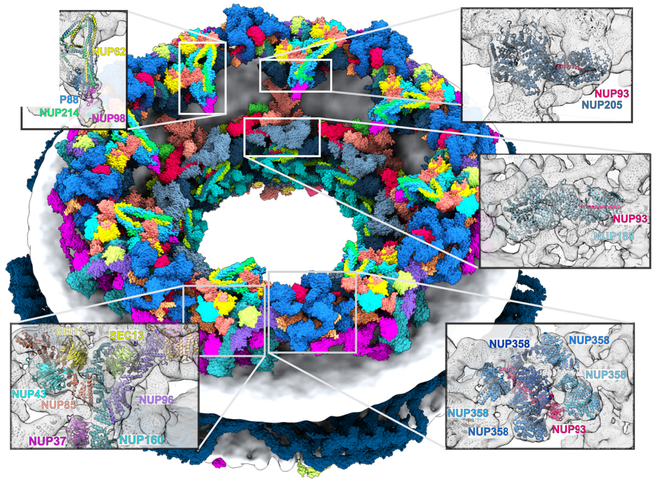


150ns of cell simulation

Molecular dynamics simulations

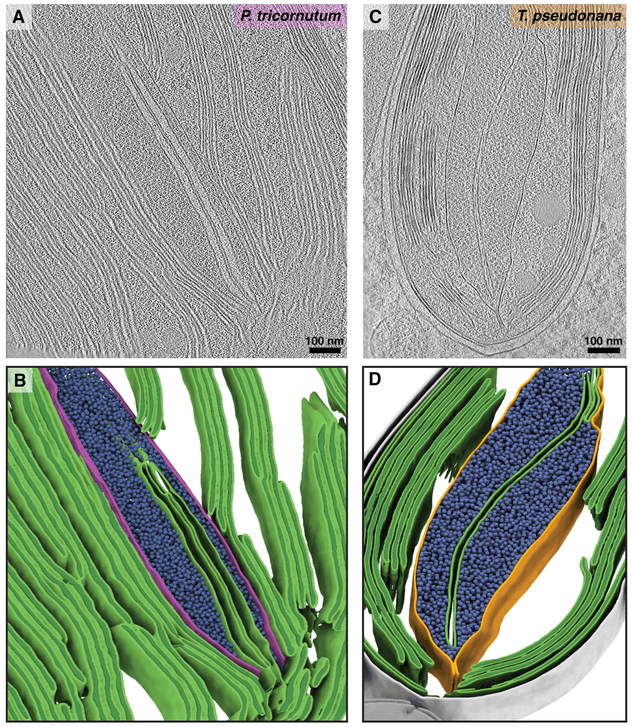
Guided by experimental data

Nuclear pore complex



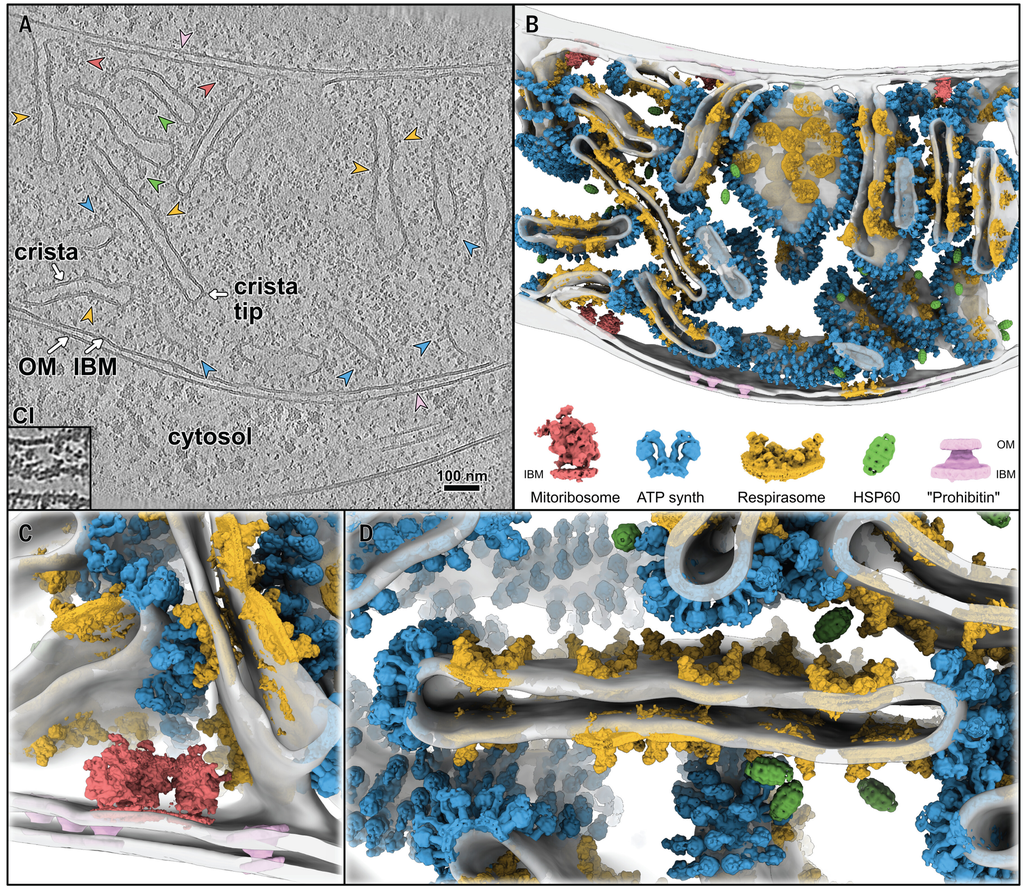
Mosalaganti S. et al. (2022) Science

Pyrenoids



Shimakawa G. et al. (2024) Cell

Mitochondrial respiratory chain



Waltz F. et al. (2025). Science

The challenges

Large scales

Multi-component models

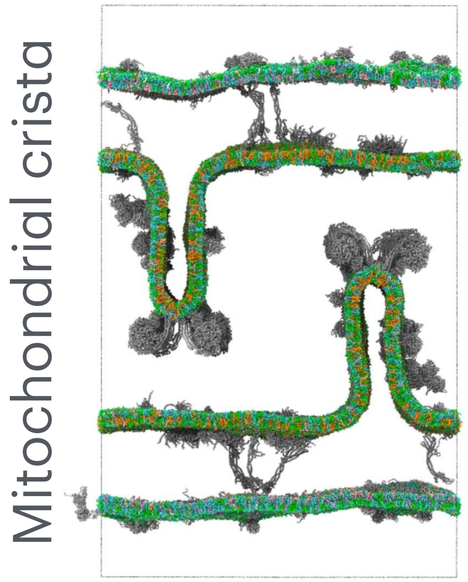
Continuous integration

The challenges

Large scales

Multi-component models

Continuous integration



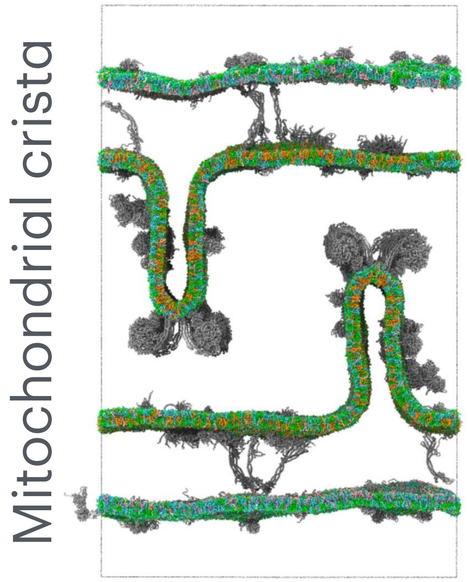
Brown C.M. et al. (2025) Commun. Bio

The challenges

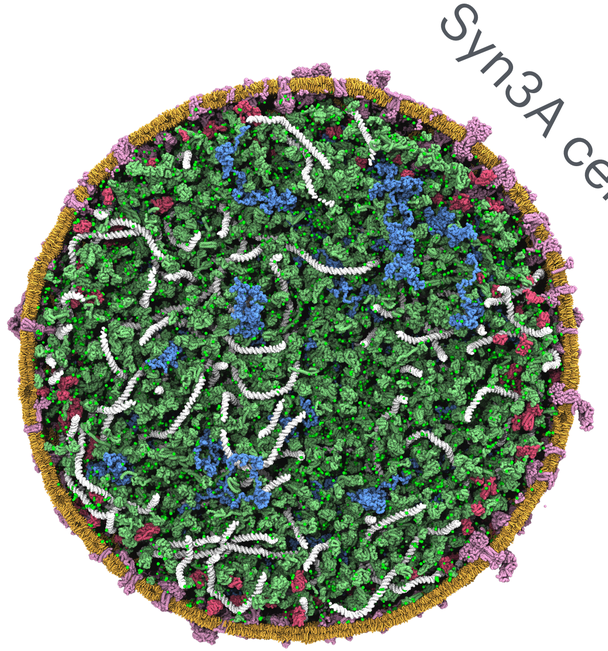
Large scales

Multi-component models

Continuous integration



Brown C.M. et al. (2025) Commun. Bio



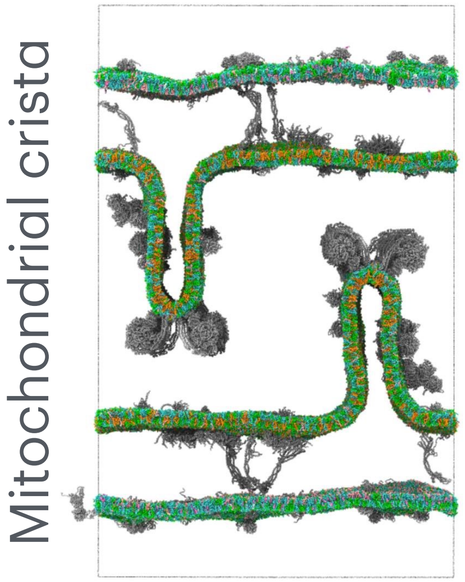
Stevens J.A. et al. In prep.

The challenges

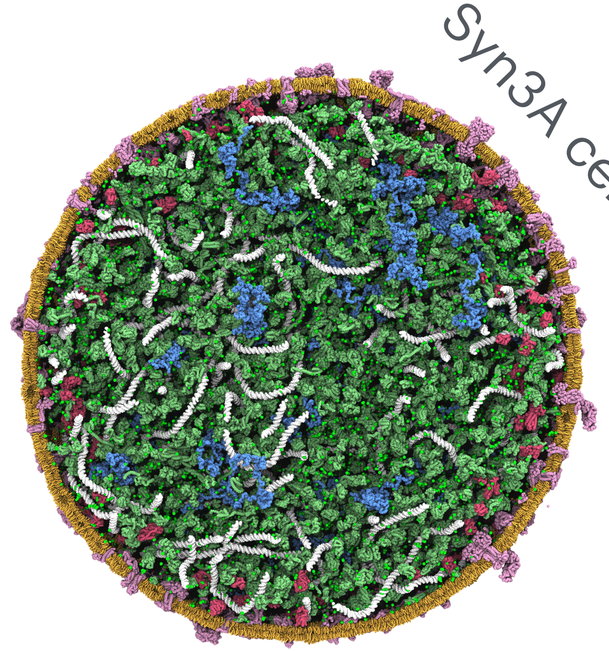
Large scales ✅

Multi-component models ✅

Continuous integration ✅



Brown C.M. et al. (2025) Commun. Bio



Stevens J.A. et al. In prep.

Large Scales

Mitochondrial cytoplasm



Chelsea Brown

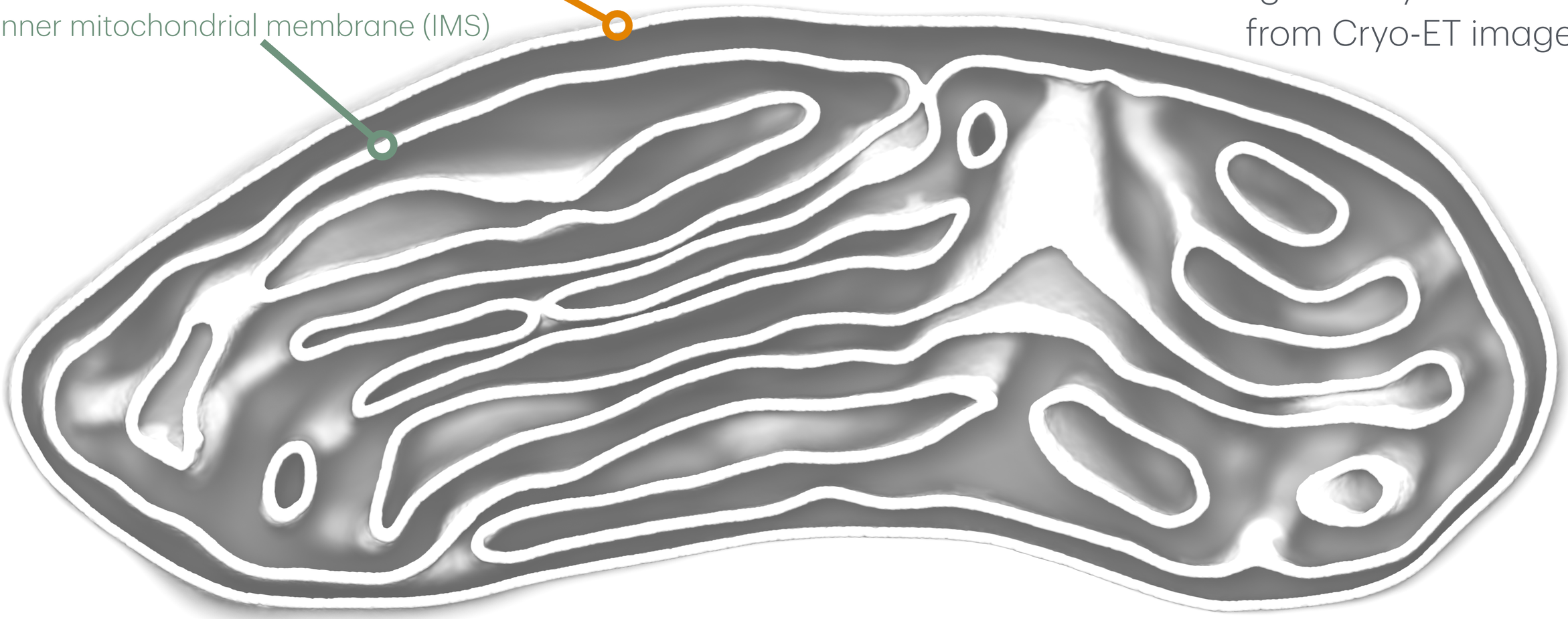


Marieke Westendorp

outer mitochondrial membrane (OMS)

Inner mitochondrial membrane (IMS)

Membrane geometry obtained from Cryo-ET image



Large Scales

Mitochondrial cytoplasm

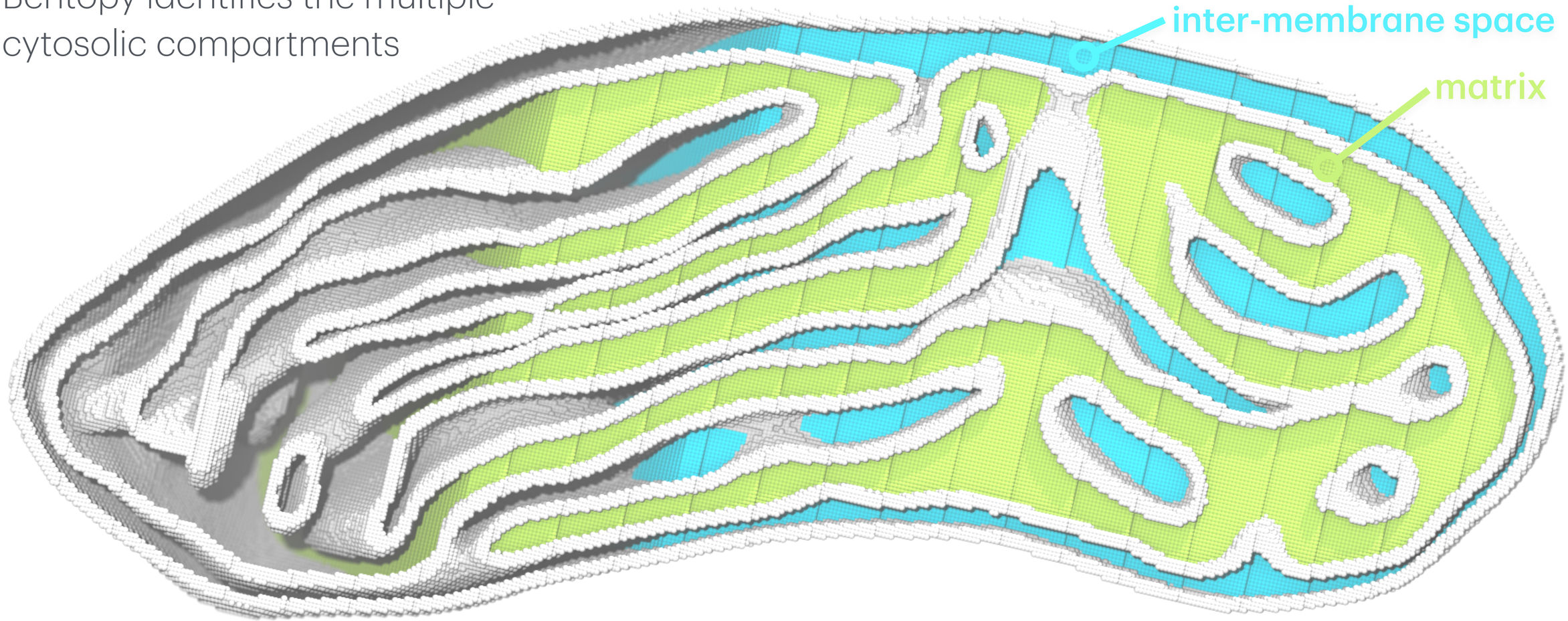


Chelsea Brown



Marieke Westendorp

Bentopy identifies the multiple cytosolic compartments



Large Scales

Mitochondrial cytoplasm

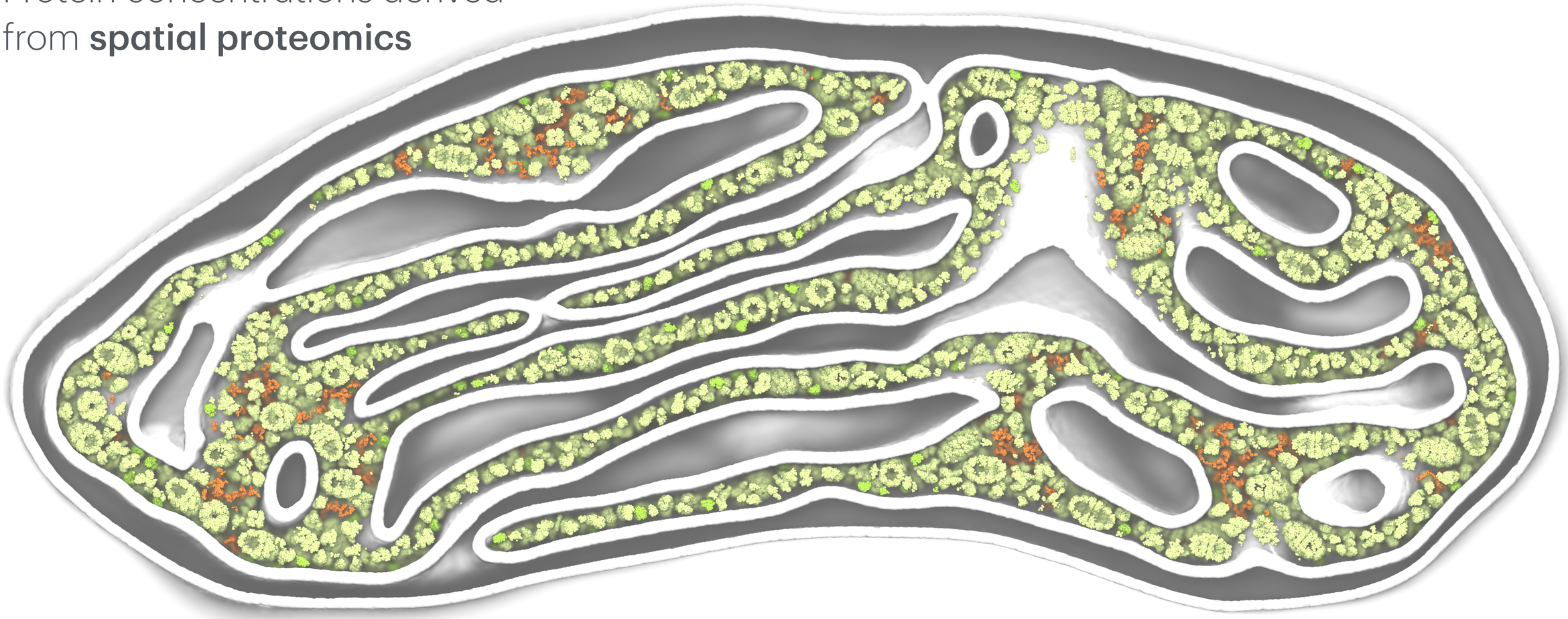


Chelsea Brown



Marieke Westendorp

Protein concentrations derived
from **spatial proteomics**



Large Scales

Mitochondrial cytoplasm

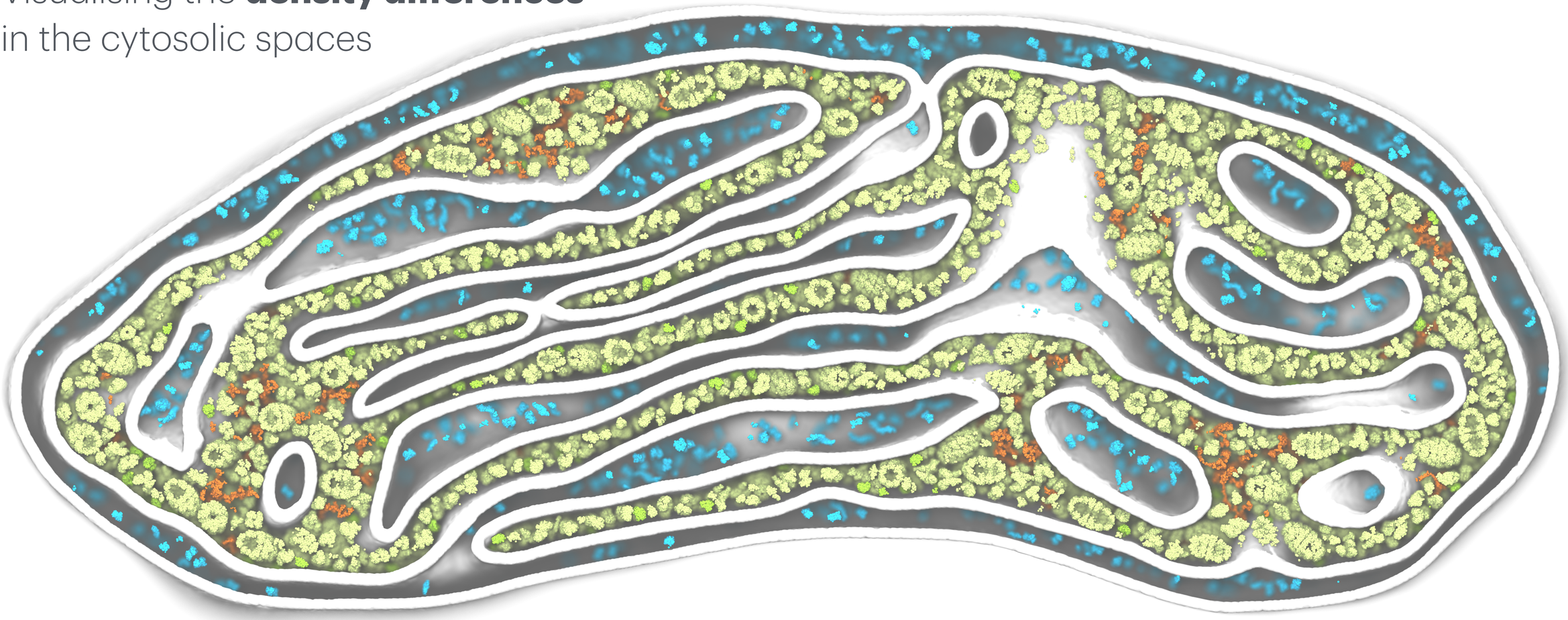


Chelsea Brown



Marieke Westendorp

Visualising the **density differences** in the cytosolic spaces



Large Scales

Mitochondrial cytoplasm



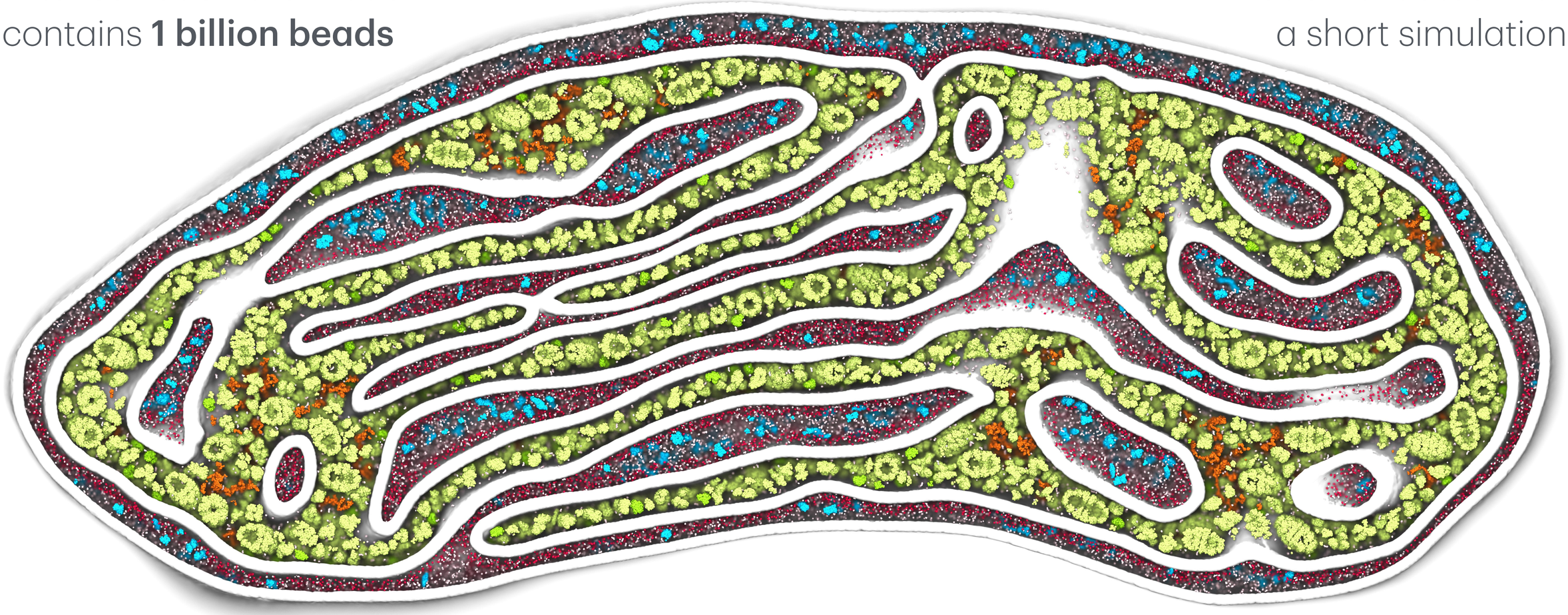
Chelsea Brown



Marieke Westendorp

After solvation the model
contains **1 billion beads**

Model validated with
a short simulation

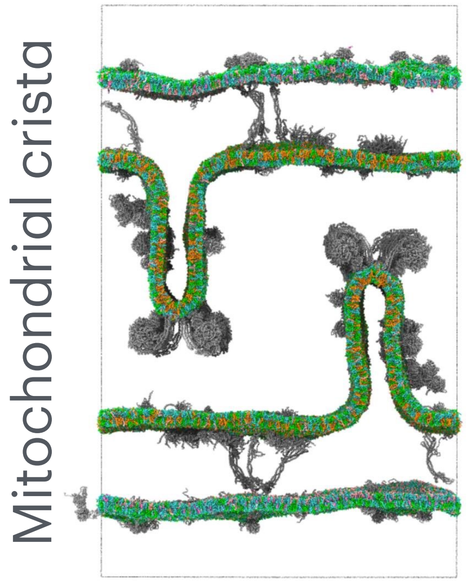


The challenges

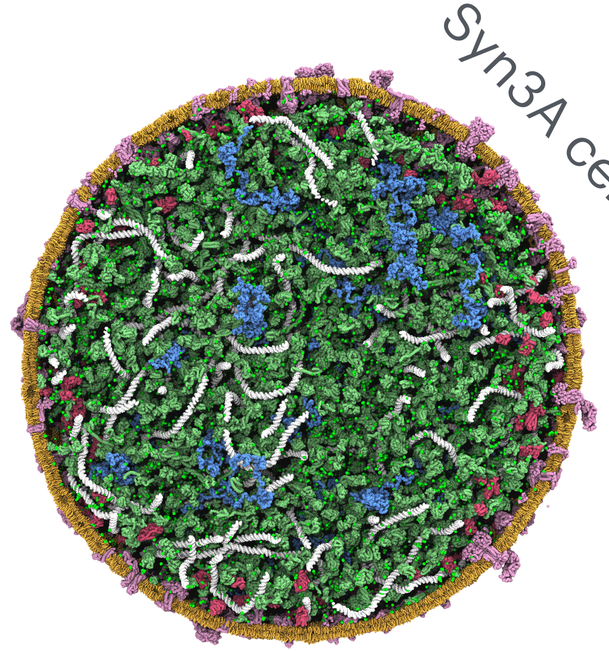
Large scales ✅

Multi-component models ✅

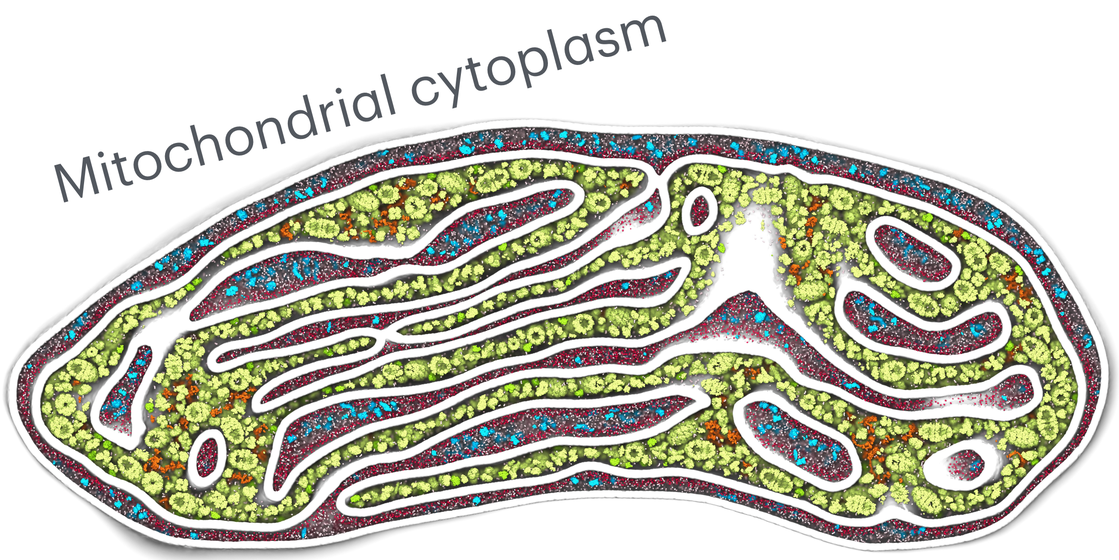
Continuous integration ✅



Brown C.M. et al. (2025) Commun. Bio



Stevens J.A. et al. In prep.



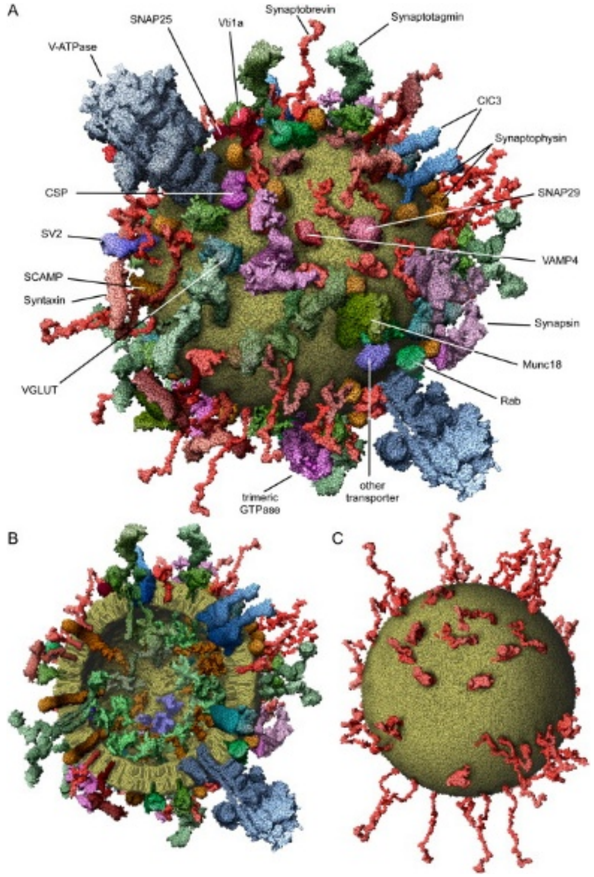
Westendorp K.S.S. et al. In prep.

Multi-component models

Synaptic Vesicles



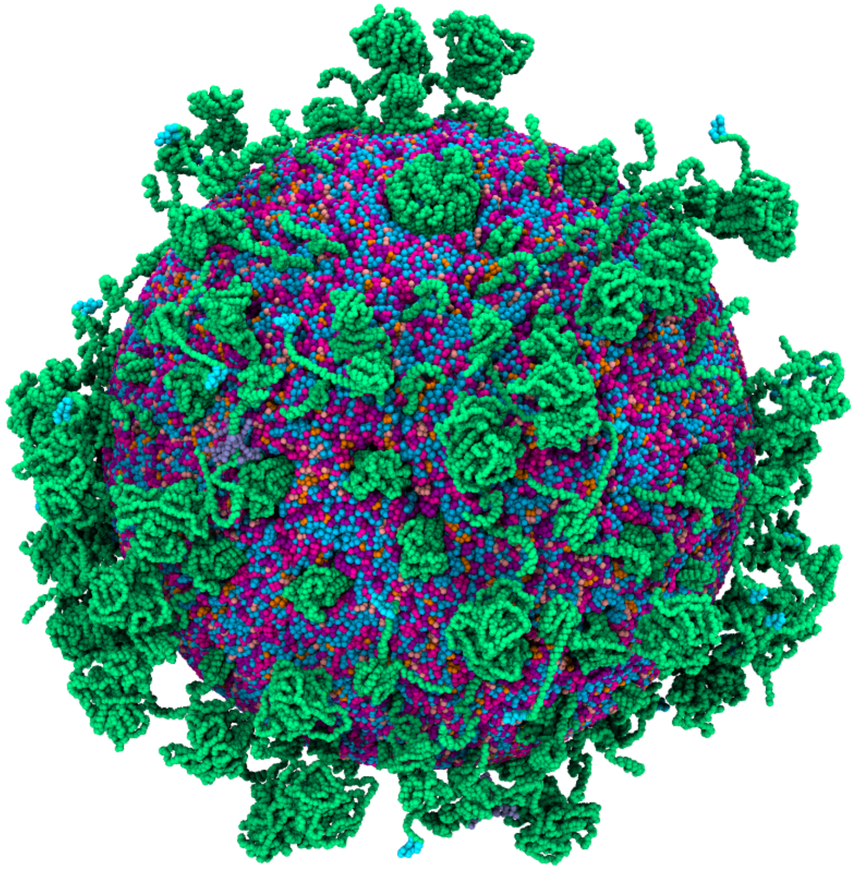
Tommy Rosendahl
@Aarhus University



Takamori A. et al. (2006) Cell

Can we simulate

this model?



Multi-component models

Synaptic Vesicles



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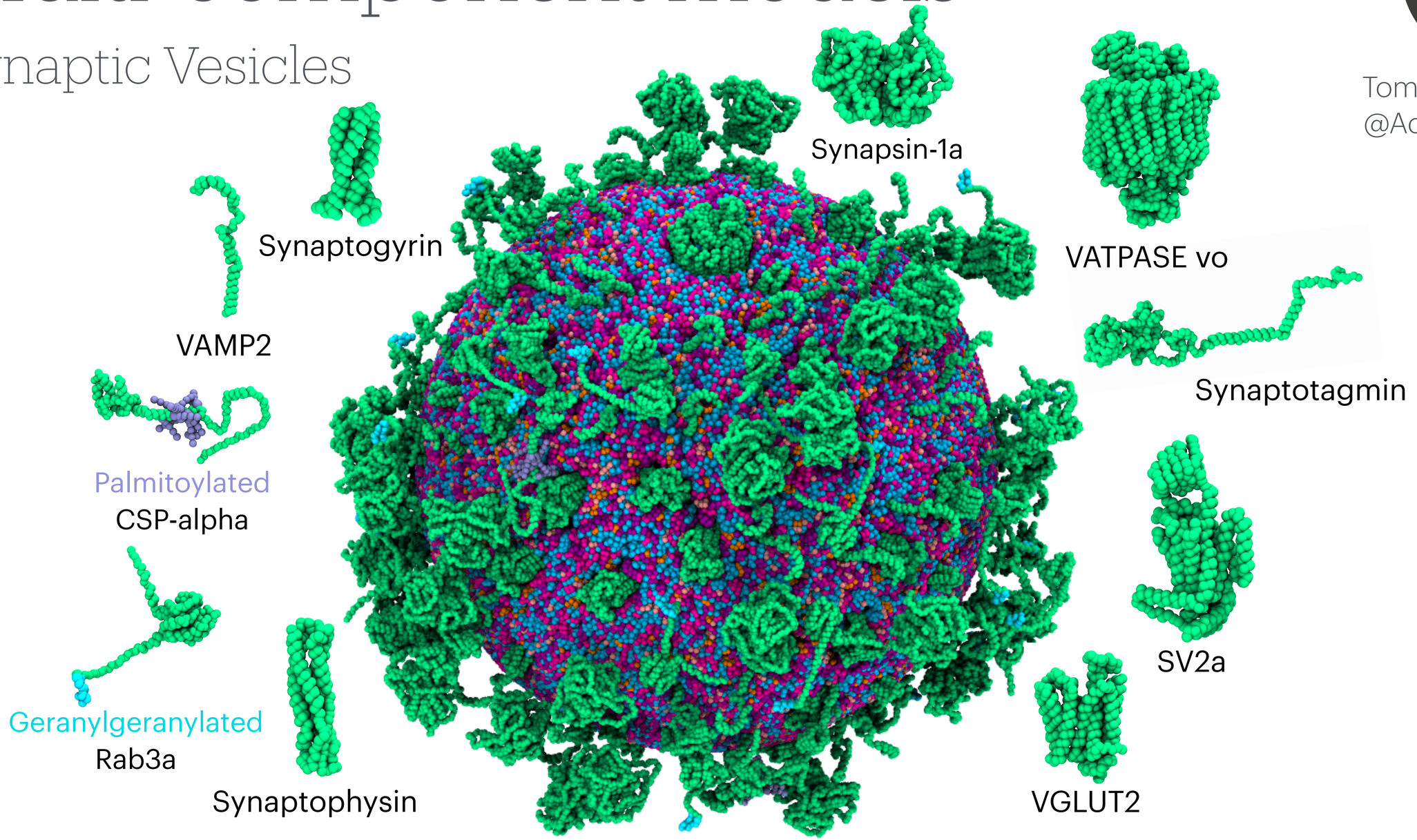
@Aarhus University



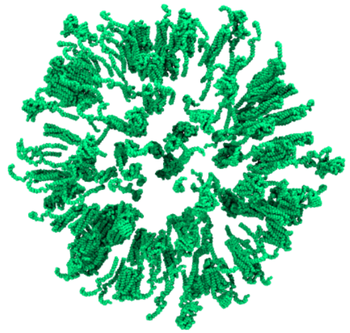
Multi-component models

Synaptic Vesicles



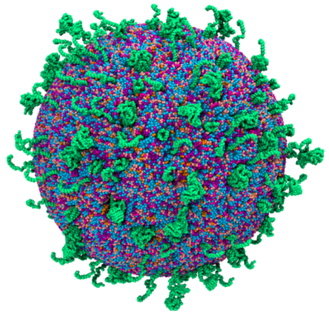
Tommy Rosendahl
@Aarhus University

Integral Membrane Protein placement using `TS2CG`



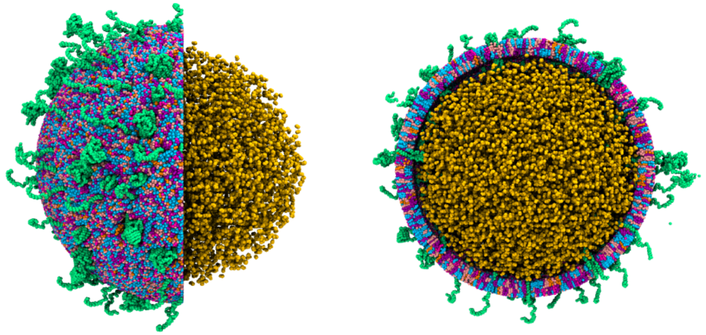
TS2CG and Scipy KDTree

Add membrane using `TS2CG`



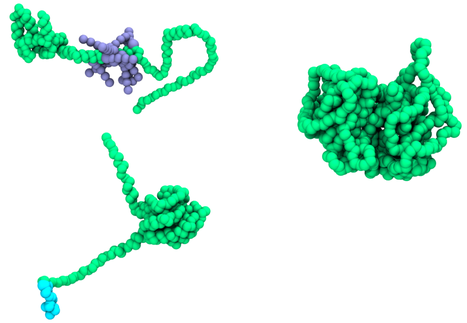
DFPS, DFPE, SSM, CHOL, POPC

Load vesicle with neurotransmitter using `Bentopy`



Short **energy minimization** in a vacuum before loading neurotransmitters

Add Peripheral Membrane Proteins using `Bentopy`



Final Takamori-like Synaptic Vesicle

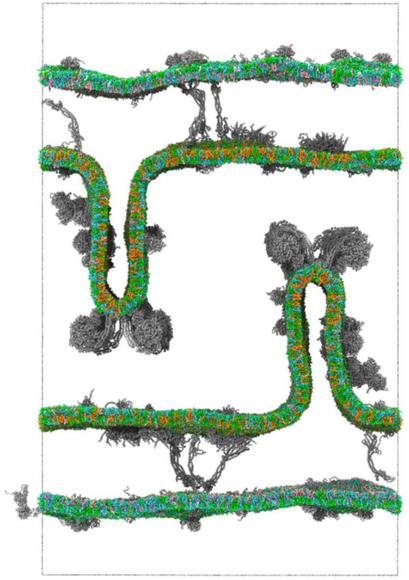
The challenges

Large scales ✅

Multi-component models ✅

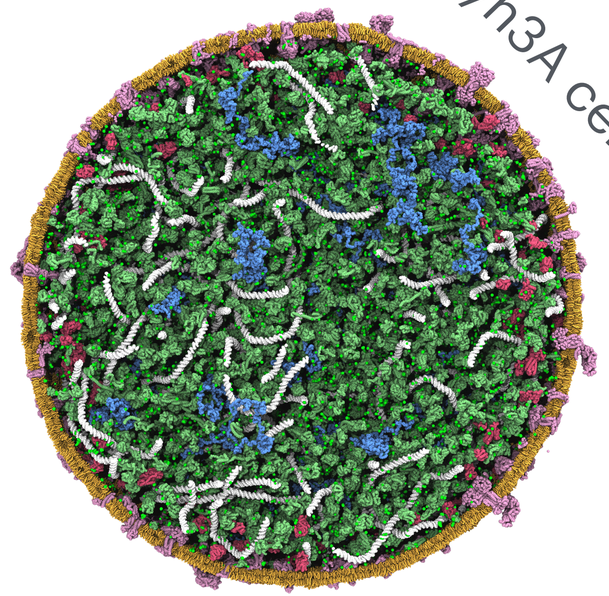
Continuous integration ✅

Mitochondrial crista



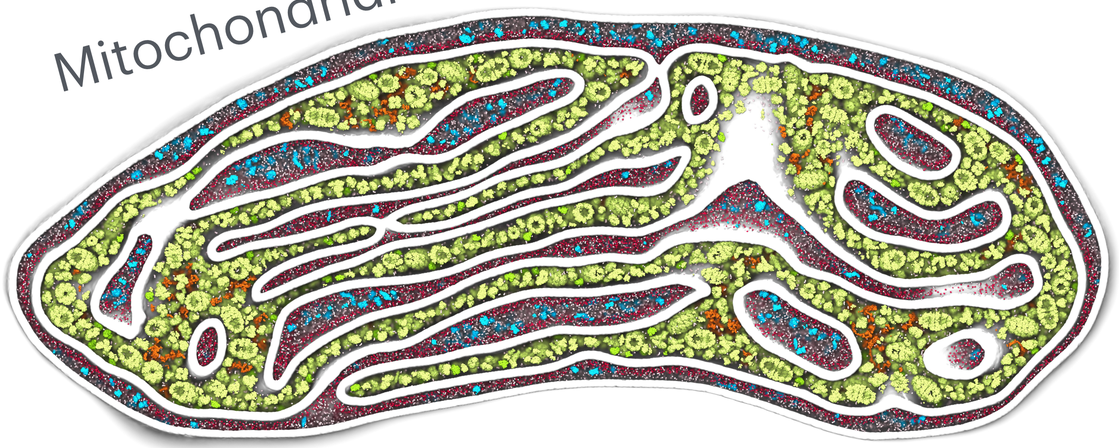
Brown C.M. et al. (2025) Commun. Bio

Syn3A cell



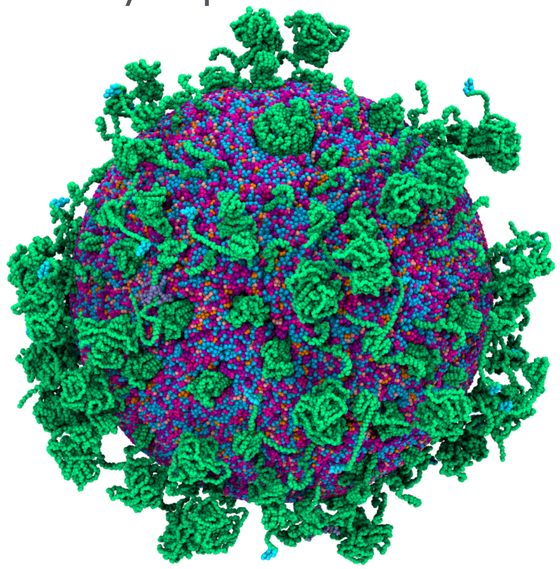
Stevens J.A. et al. In prep.

Mitochondrial cytoplasm



Westendorp K.S.S. et al. In prep.

Synaptic vesicles



Rosendahl T. et al. In prep.

Multi-component models

Respiratory virus in aerosol



Abby Dommer

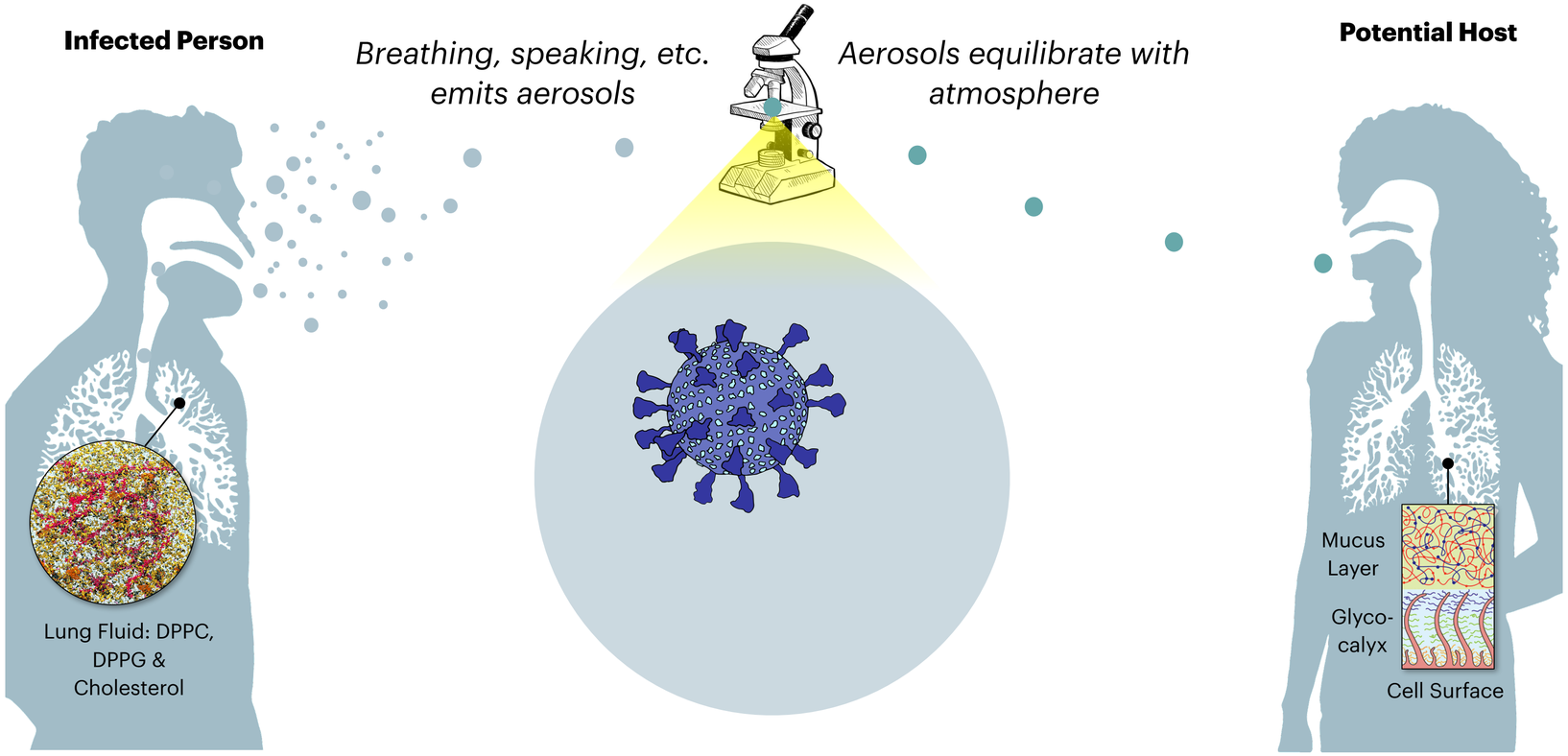


Image credit: Abby Dommer

Multi-component models

Respiratory virus in aerosol





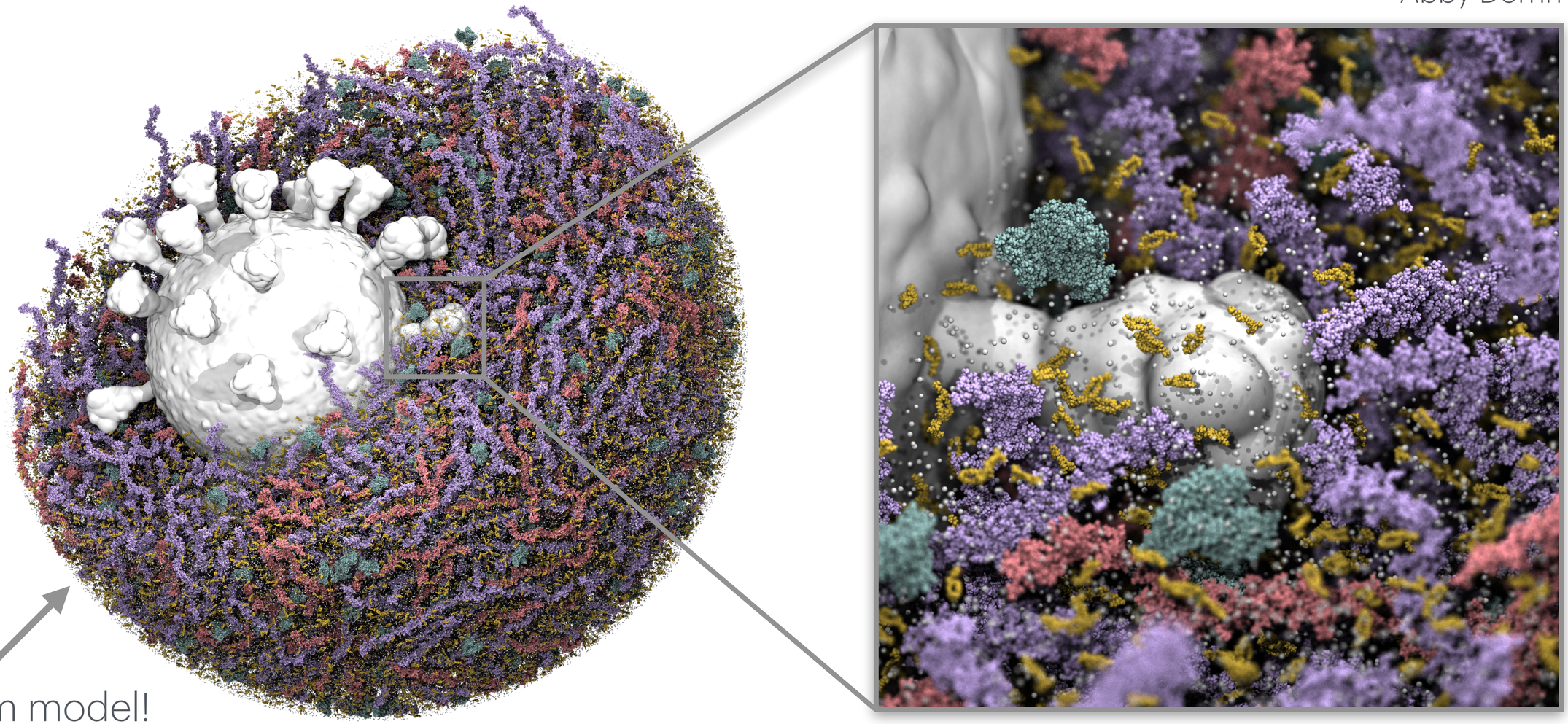
Abby Dommer

Multi-component models

Respiratory virus in aerosol



Abby Dommer



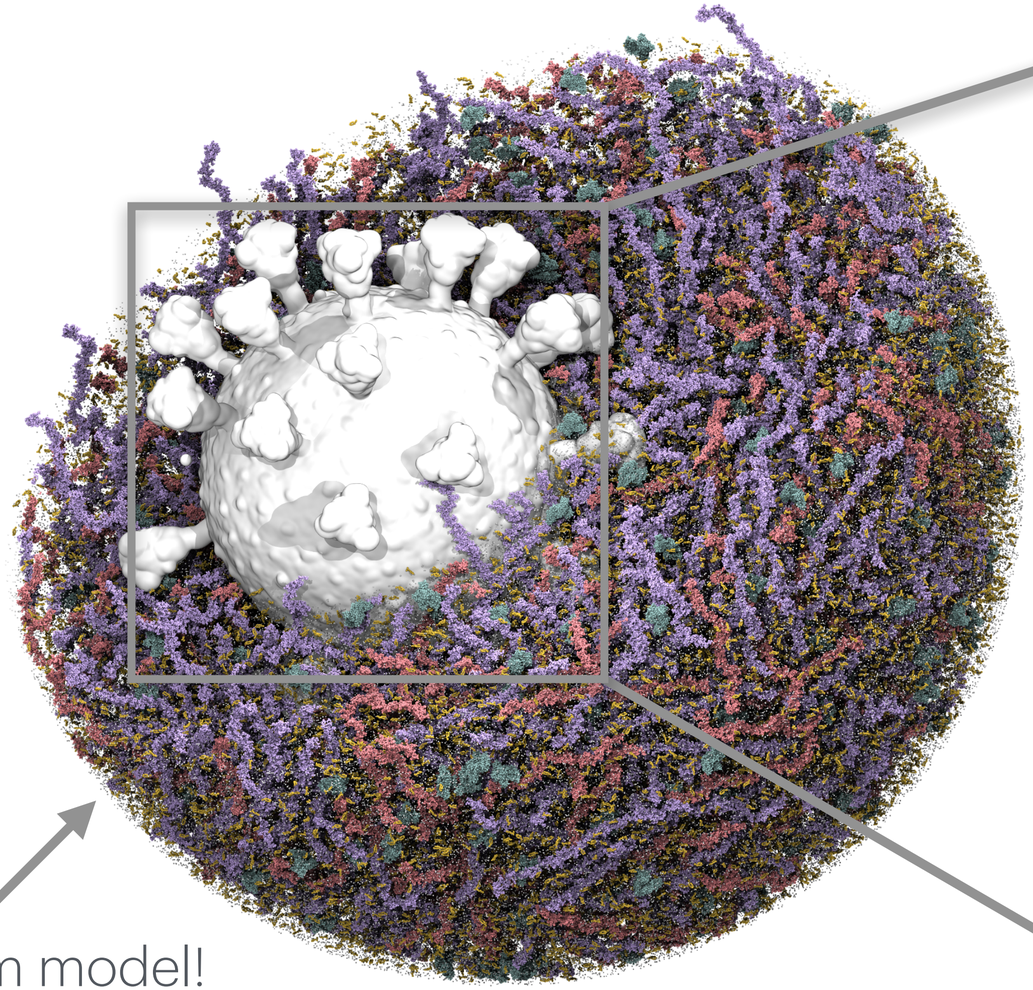
All-atom model!

Multi-component models

Respiratory virus in aerosol



Abby Dommer



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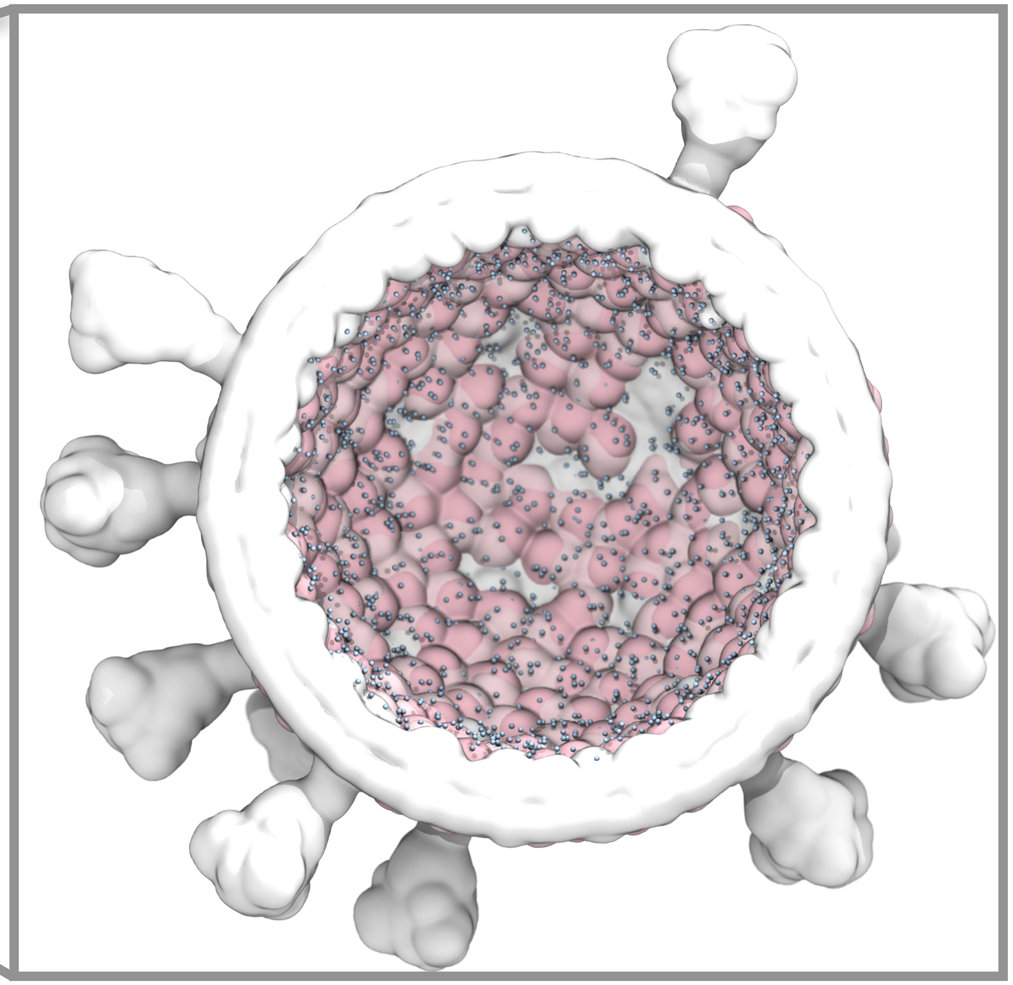


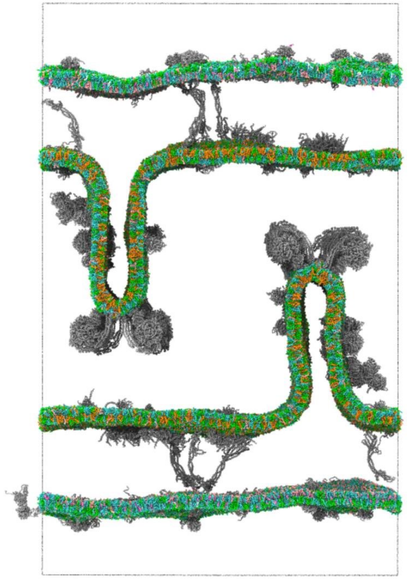
The challenges

Large scales ✅

Multi-component models ✅

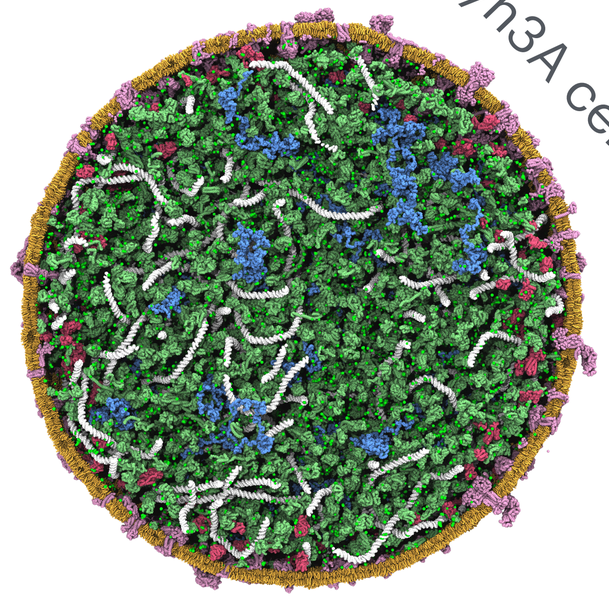
Continuous integration ✅

Mitochondrial crista



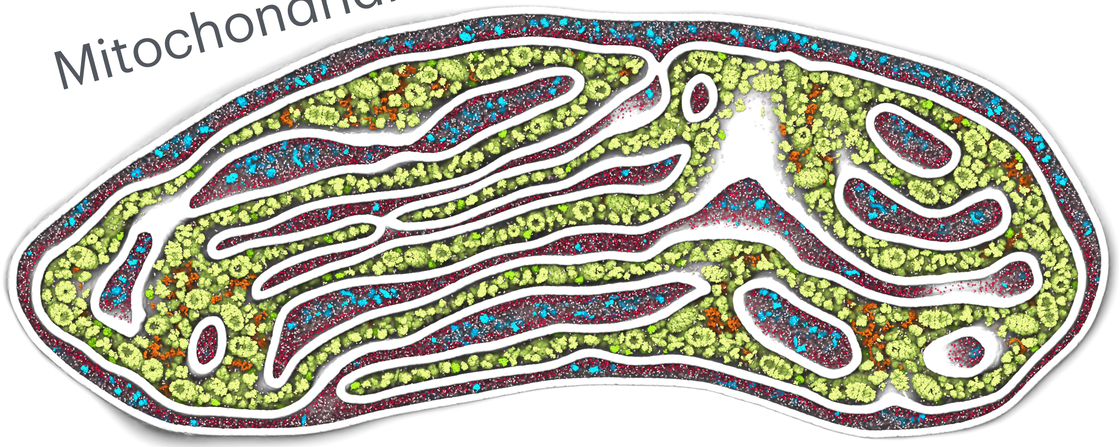
Brown C.M. et al. (2025) Commun. Bio

Syn3A cell



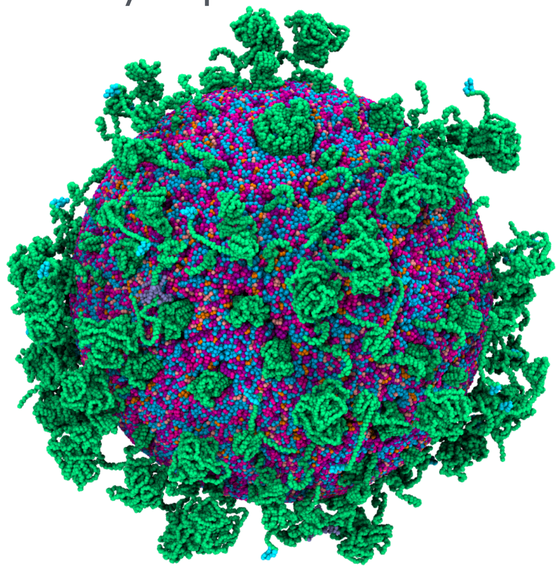
Stevens J.A. et al. In prep.

Mitochondrial cytoplasm



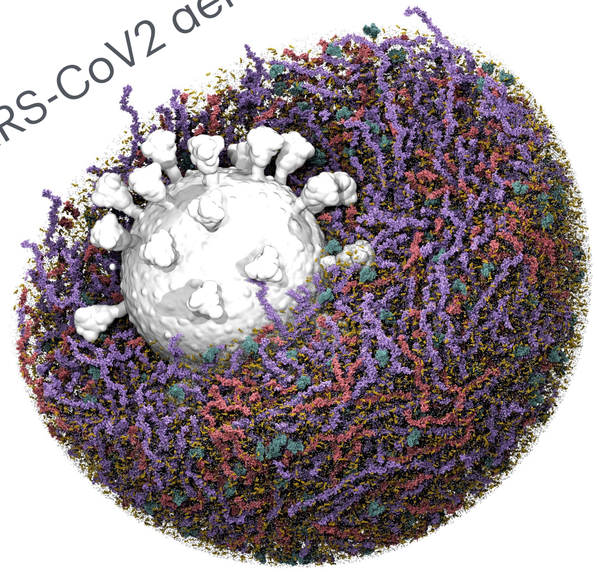
Westendorp K.S.S. et al. In prep.

Synaptic vesicles



Rosendahl T. et al. In prep.

SARS-CoV2 aerosol



Dommer A. et al. In prep.

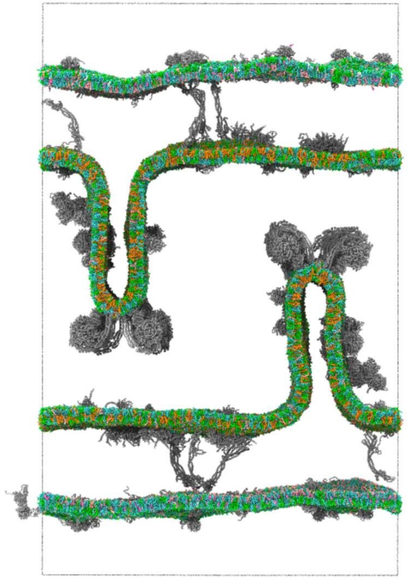
The challenges

Large scales ✅

Multi-component models ✅

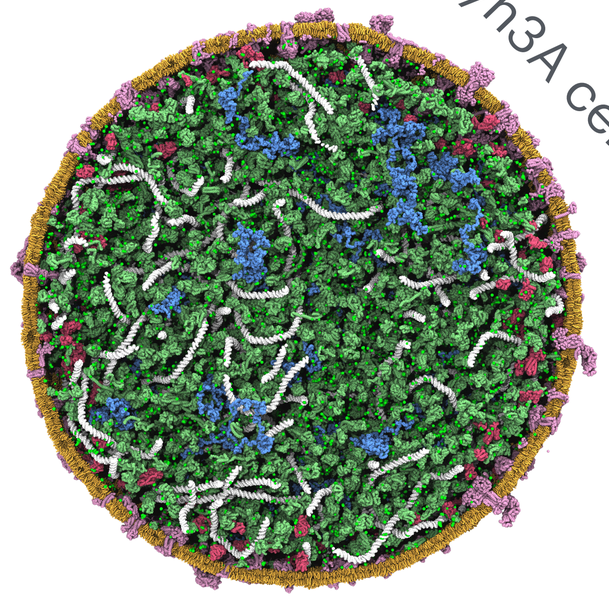
Continuous integration ✅

Mitochondrial crista



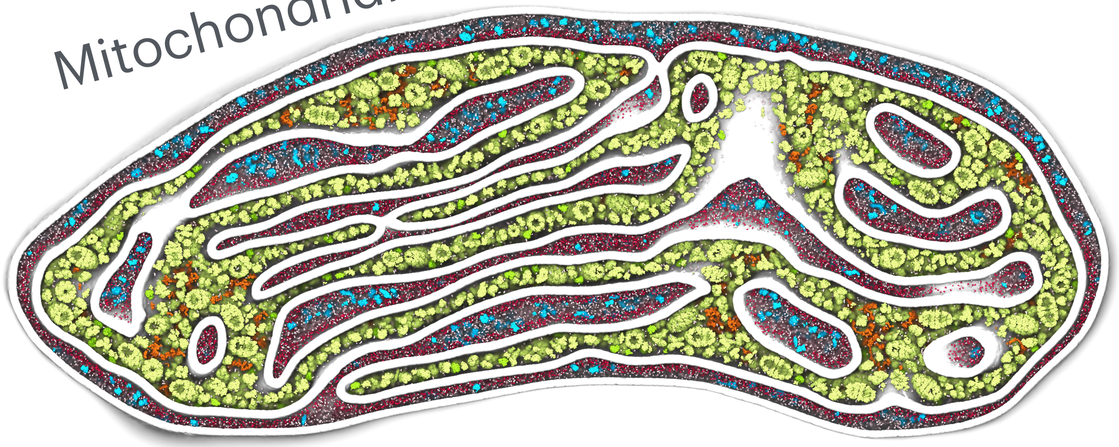
Brown C.M. et al. (2025) Commun. Bio

Syn3A cell



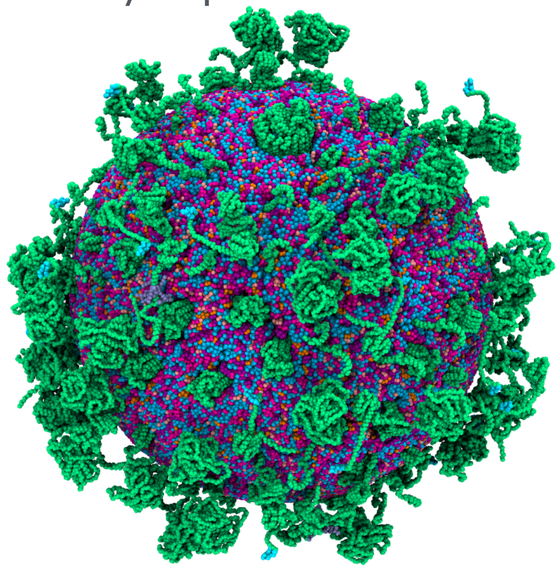
Stevens J.A. et al. In prep.

Mitochondrial cytoplasm



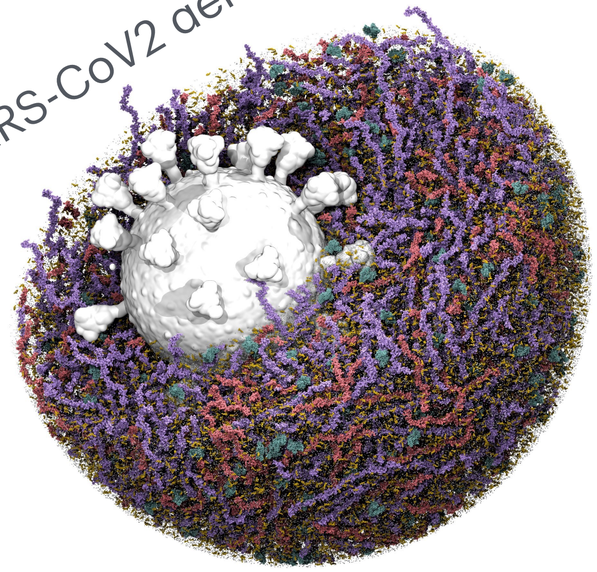
Westendorp K.S.S. et al. In prep.

Synaptic vesicles



Rosendahl T. et al. In prep.

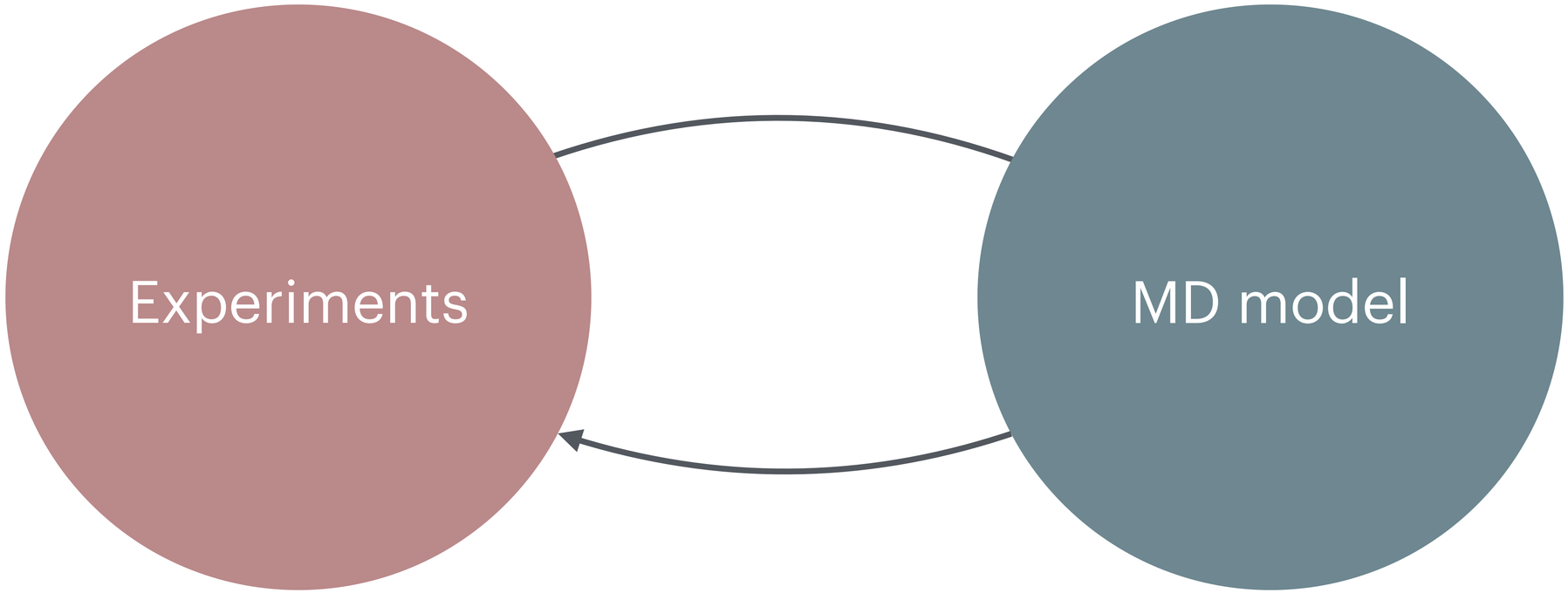
SARS-CoV2 aerosol



Dommer A. et al. In prep.

Molecular dynamics simulations

Guided by experimental data



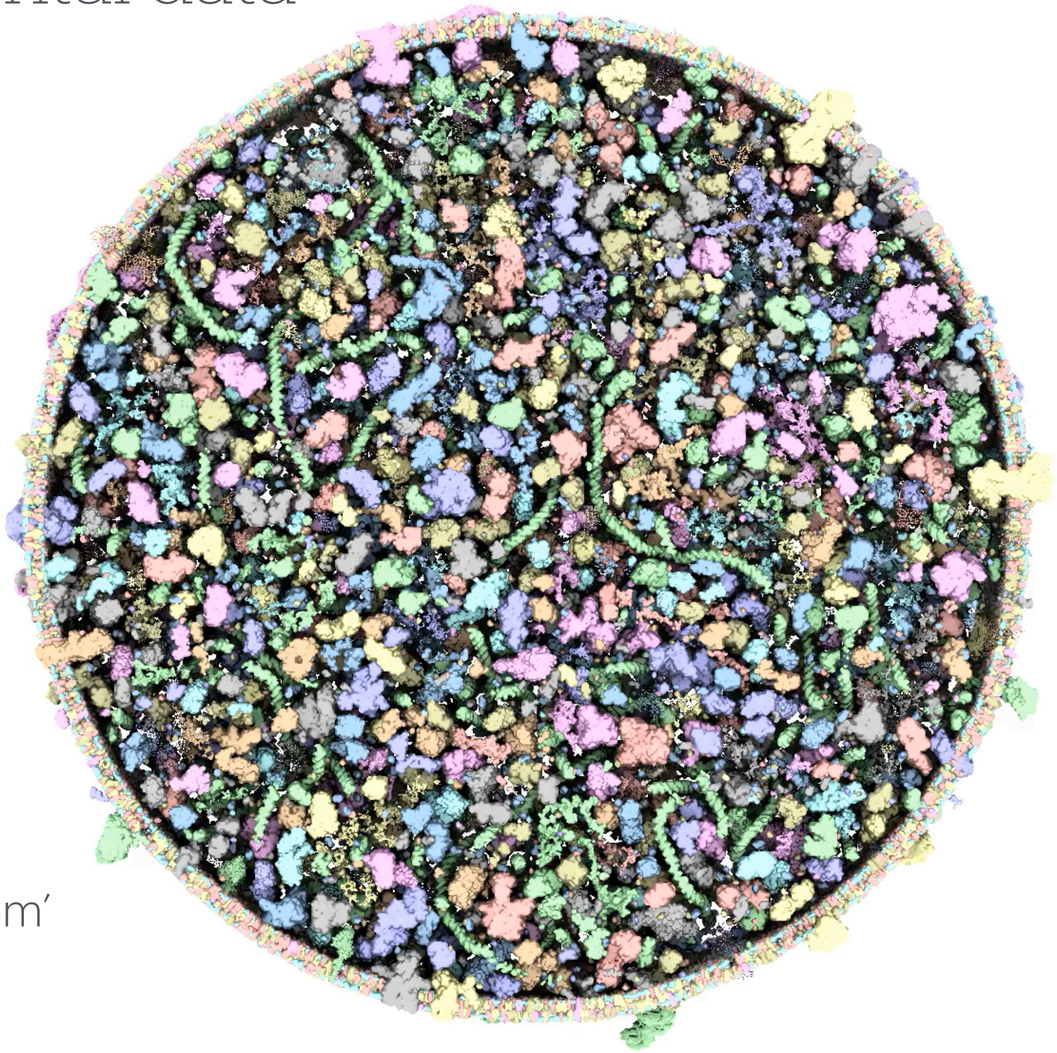
Molecular dynamics simulations

Guiding experimental data



Pavol Harar

Simulating the e^- density
of our cell model



Which is still fully labeled
per molecule, residue and ‘atom’

Image credit: Pavol Harar

Molecular dynamics simulations

Guiding experimental data



Pavol Harar

We extract a
tomogram slice
from our model

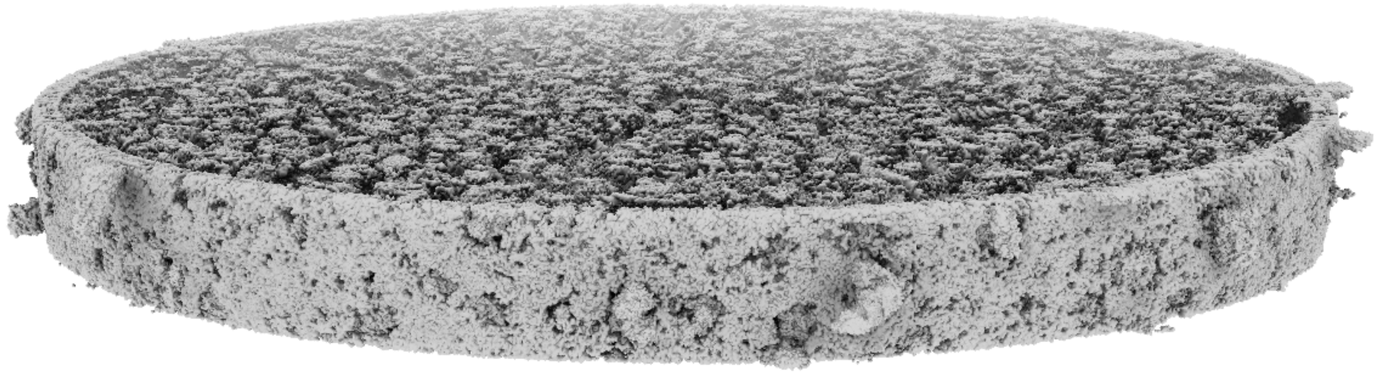


Image credit: Pavol Harar

Molecular dynamics simulations

Guiding experimental data



Pavol Harar

Create
a tilt series

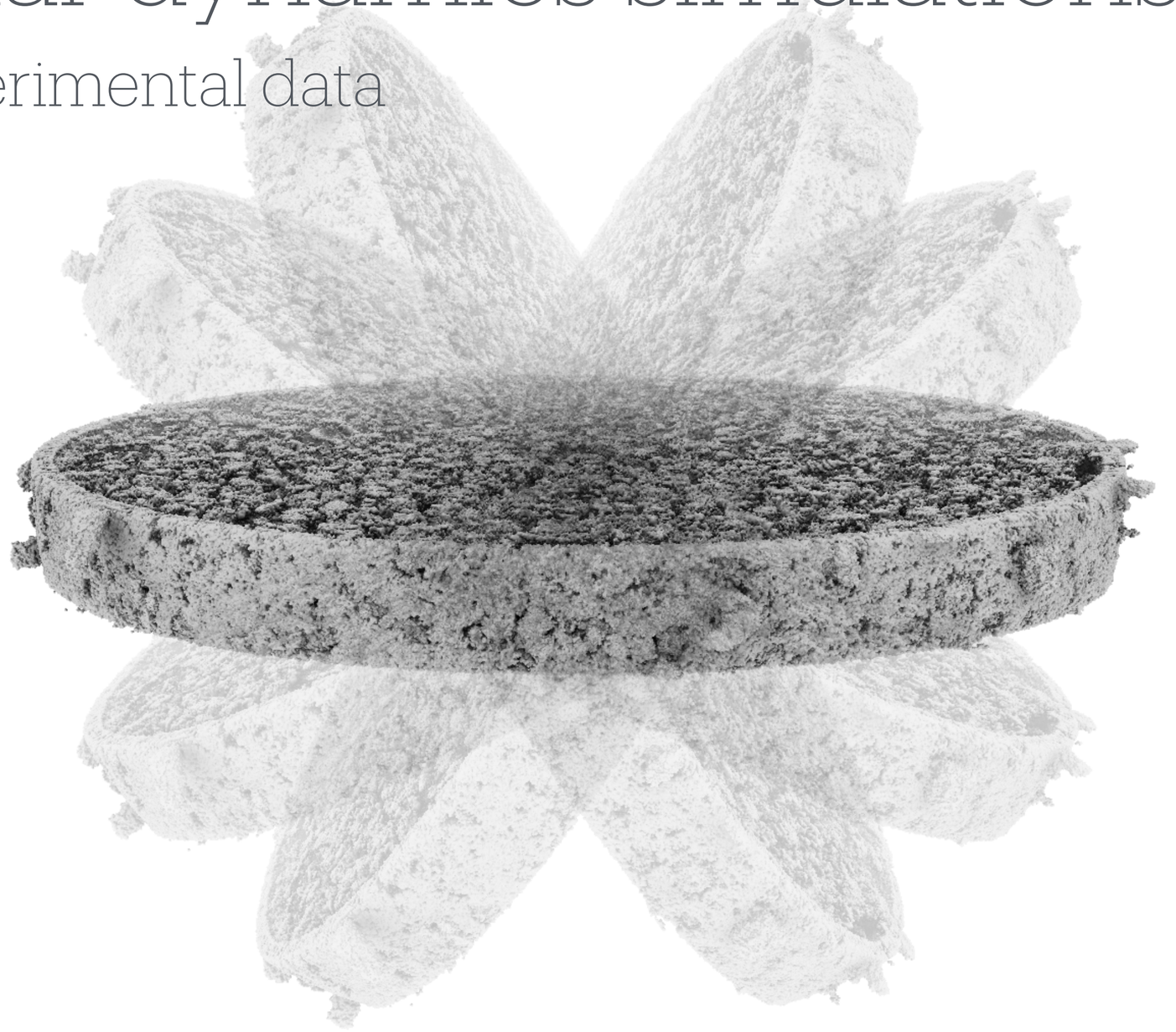


Image credit: Pavol Harar

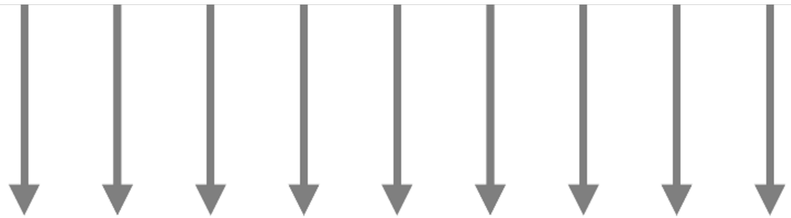
Molecular dynamics simulations

Guiding experimental data

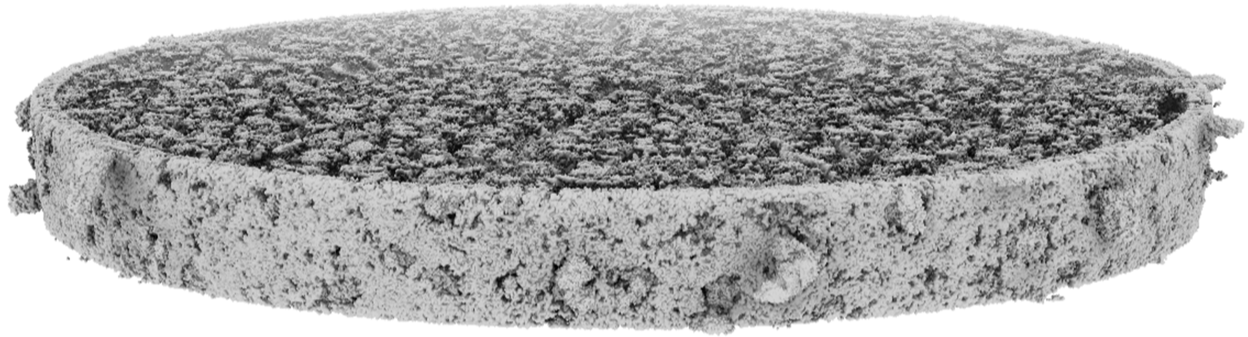


Pavol Harar

Electron Beam



Simulated e⁻ Density



Predicted projection

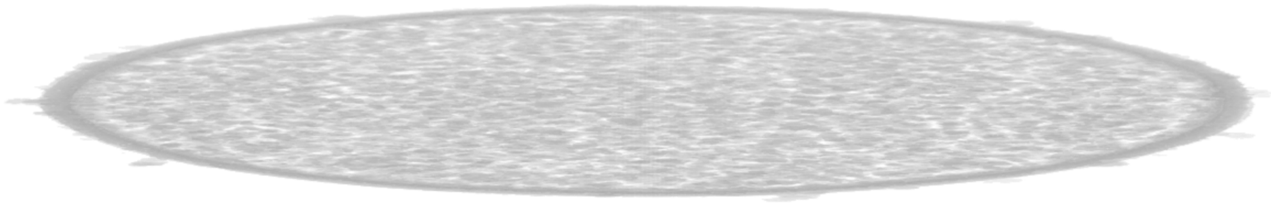


Image credit: Pavol Harar

Molecular dynamics simulations

Guiding experimental data



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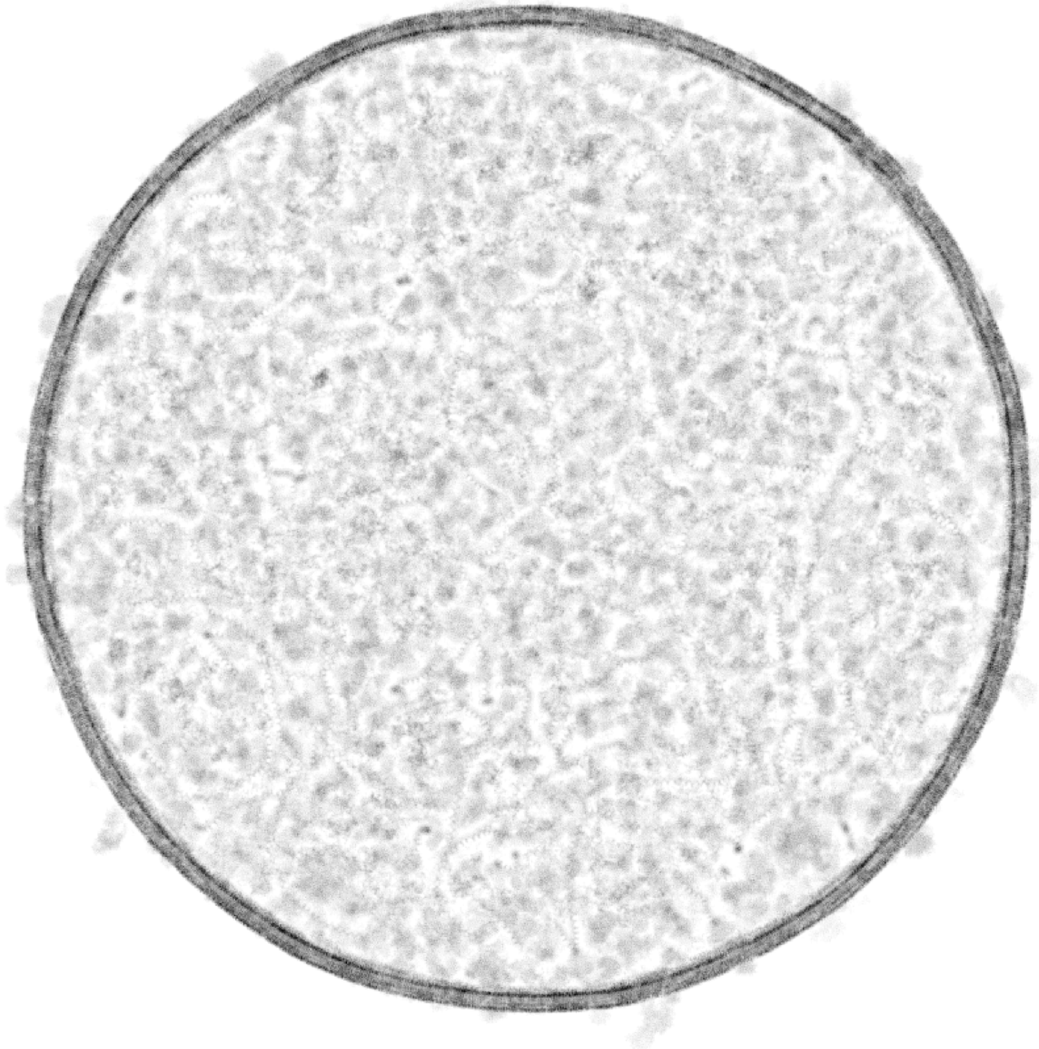

Image credit: Pavol Harar

Molecular dynamics simulations

Guiding experimental data



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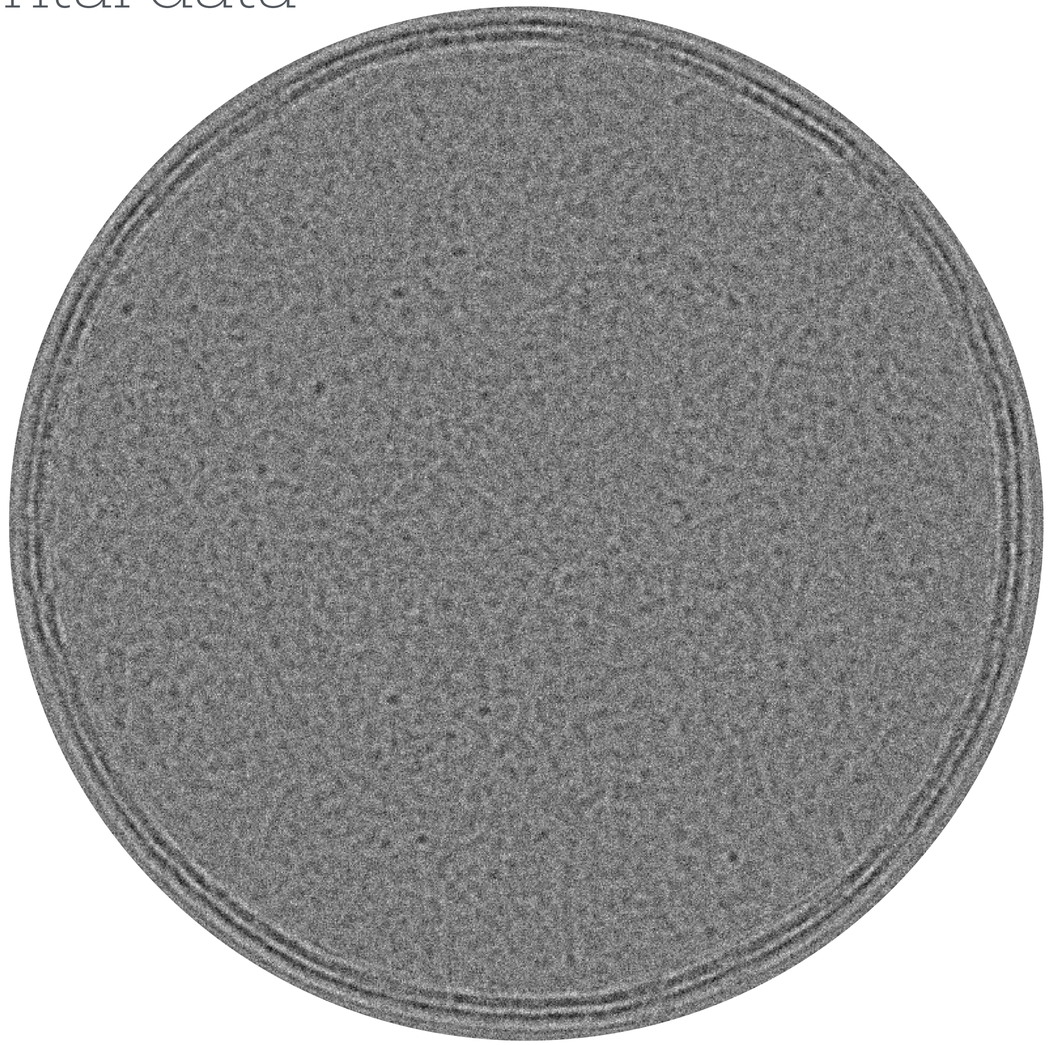
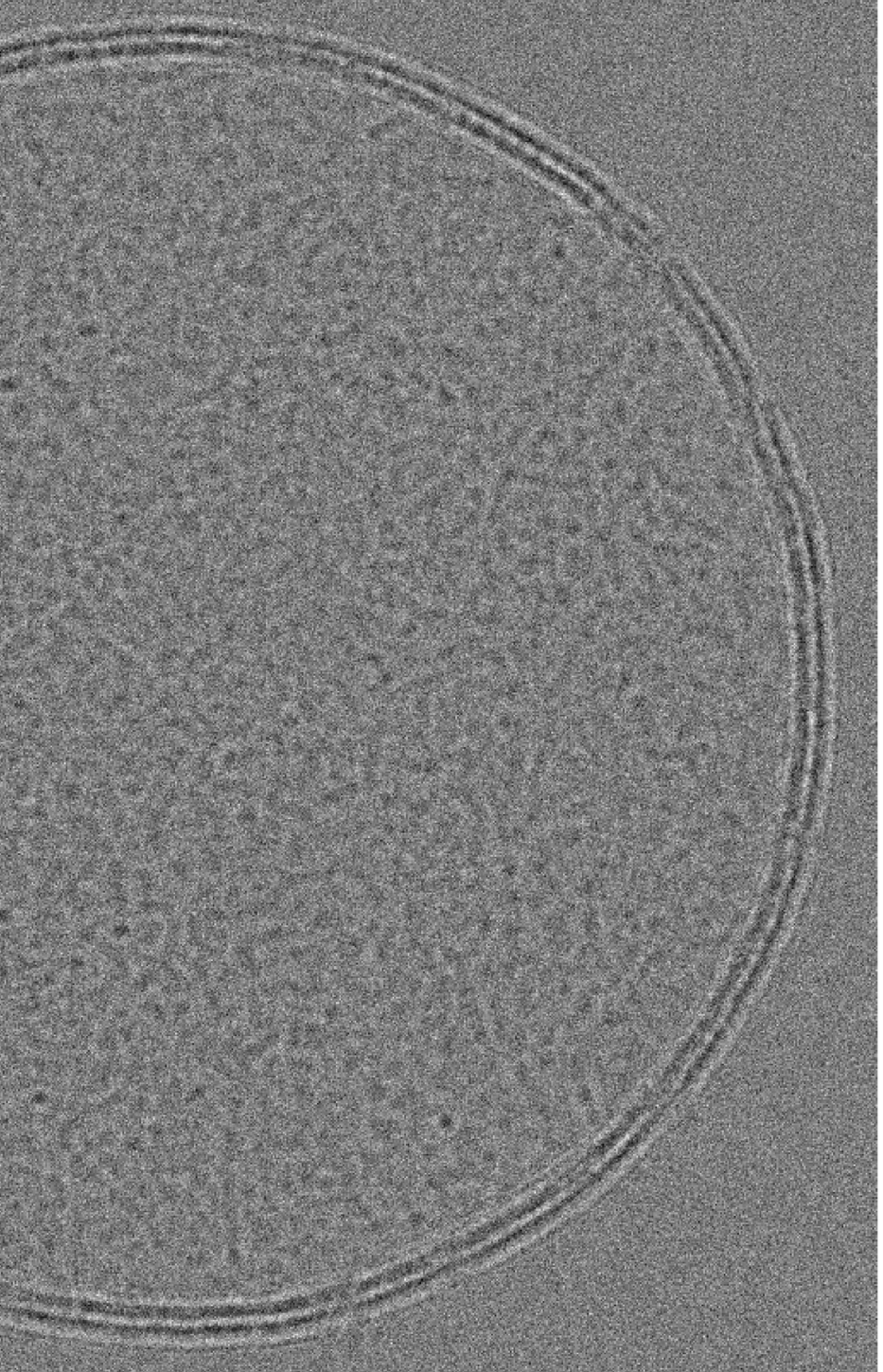


Image credit: Pavol Harar



Simulated dataset:

Fully annotated and ready for training AI

... to learn this transformation

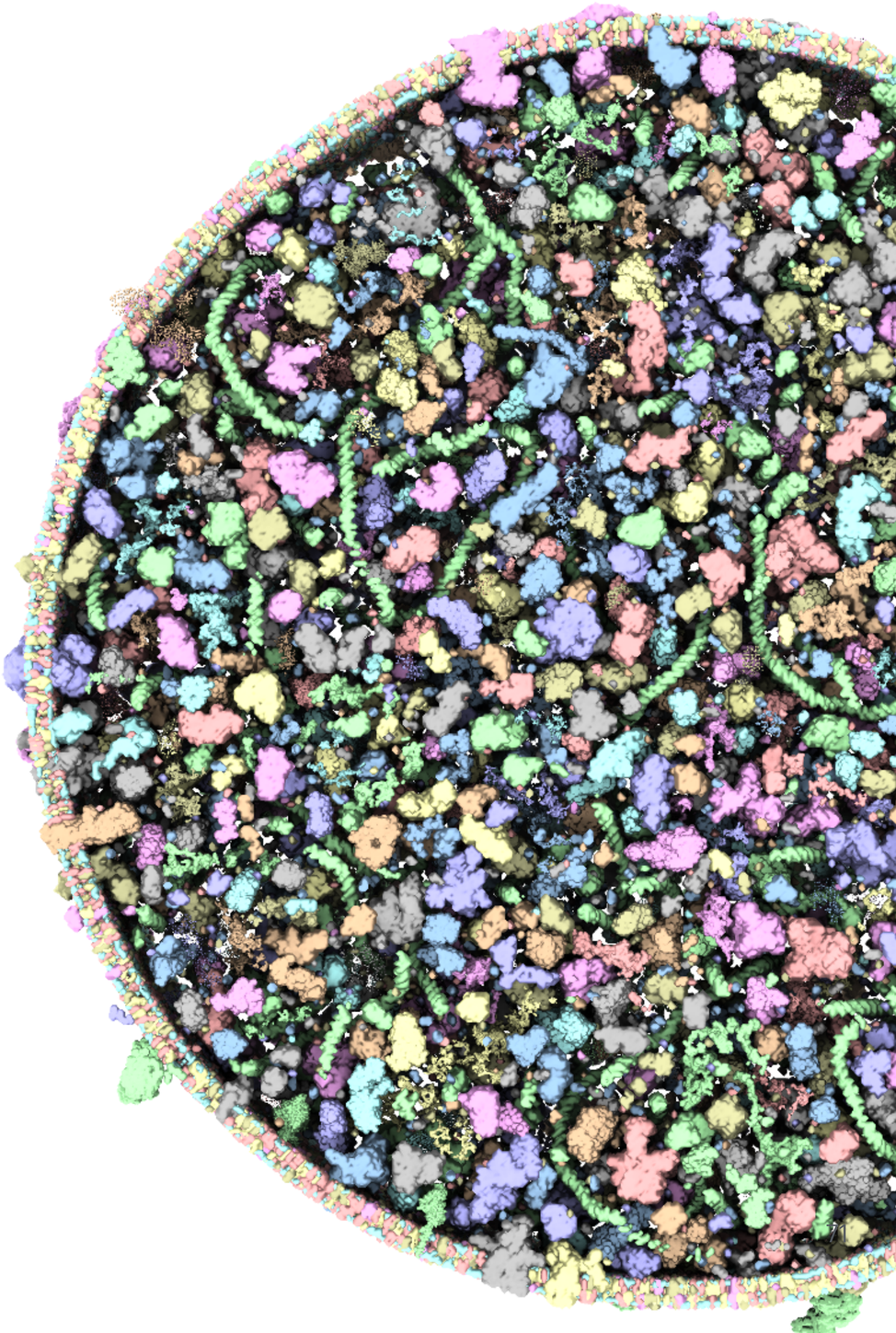


Image credit: Pavol Harar

Acknowledgments

Group members



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Ben Gilbert
Prof. Zan Luthey-Schulten

Prof. Erik Lindahl
Prof. Berk Hess

Tommy Rosendahl
Prof. Anna Duncan

Pavol Harar
Prof. Alicia Michael

What do you want to build?

