Self-organization of Golgi apparatus

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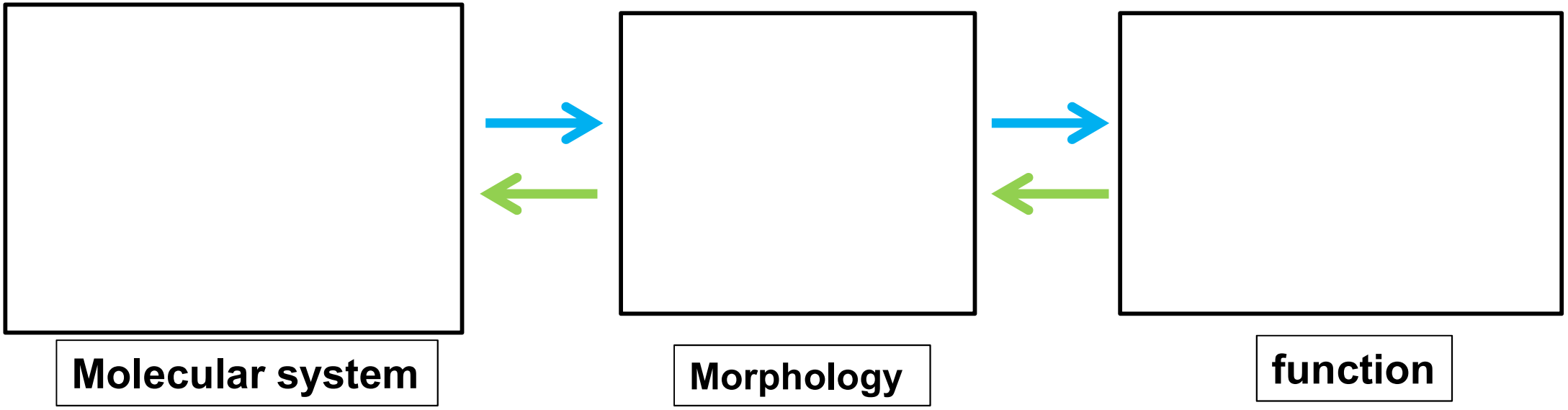
Theoretical modeling of organelle（細胞小器官）



Logic to connect between scales

- How do molecular systems generate shapes？
- How do shapes generate functions？

Golgi body

Closely stacked, flattened membrane sacs with discoid shapes (**cisternae, 槽**)

Fusion and fission of vesicles carry Golgi processes

Observed with electron microscopy

plant cell

animal cell

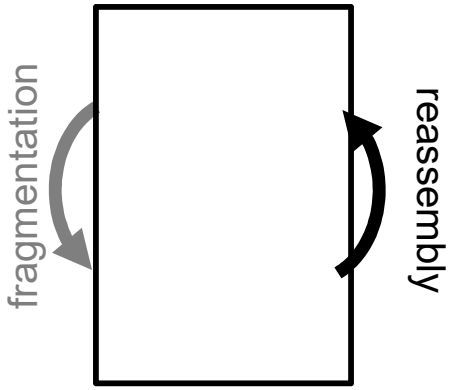
Function

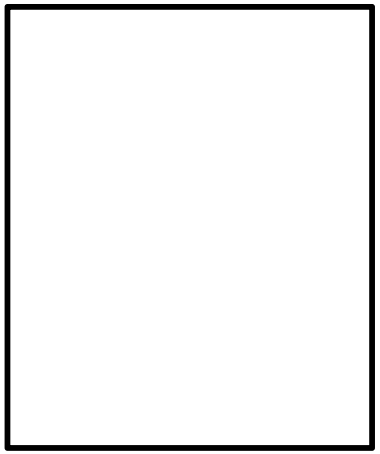
- hub of intra-cellular traffic of membrane and cargo(積荷) proteins
- Modify cargo proteins (Glycosylation)

“What I cannot create, I do not understand.”

Dr. Richard Feynman

- **Mammalian cells create Golgi body at every cell division**





- **Experimentalists reproduce Golgi body in test tubes**

Golgi disassembly and reassembly assay using purified proteins

Tang et al. Nature Protocols, 2010

- **Creating Golgi body in computer (our project)**

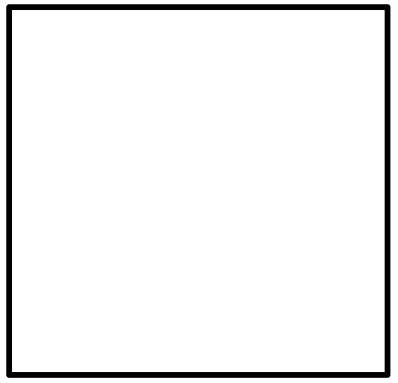
Morphological aspects of Golgi and models

About single cisterna morphology

- Compressed cisterna lumen
  - Osmotic pressure difference
    - Ion channels
- Bent membrane at edge
  - edge stabilizer protein
    - (coatomer proteins?)

- Cisternae stacking
  - Inter-membrane adhesion
    - GRASPs, Golgins
- Membrane fusion(fission)
  - Fusion machinery
    - SNARE proteins

Coatomer proteins at rim



pH control by ion channels

Dynamical triangulation membrane

Gompper & Kroll '97, 01
Noguchi '09

- **Polygon representation for membrane shape**

ENERGY

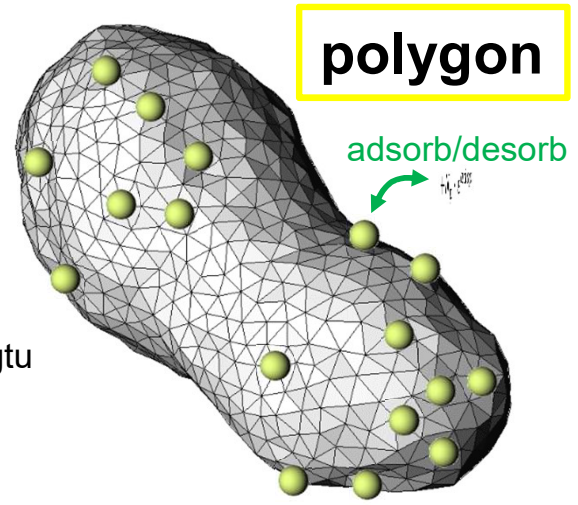
$$E = E_{osmo} + E_{bend} + N_p \cdot \varepsilon^{adsp}$$

$$E_{osmo} = -\Delta P \cdot \sum_{triangles} \boldsymbol{r}_3 \cdot \frac{(\boldsymbol{r}_1 \times \boldsymbol{r}_3)}{6}$$

$$E_{bend} = \kappa \sum_{vertices} \left[\frac{1}{\sigma_i} \sum_{j(i)} \frac{\sigma_{ij}}{l_{ij}} (\boldsymbol{r}_i - \boldsymbol{r}_j) - c\boldsymbol{n}_i \right]^2$$

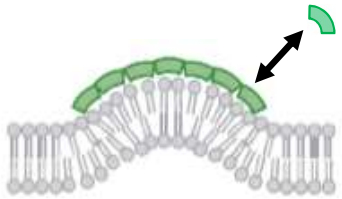
$\boldsymbol{r}_i$: vertex position
l_{ij}: edge length
σ_{ij}: dual lattice lengtu

curvature



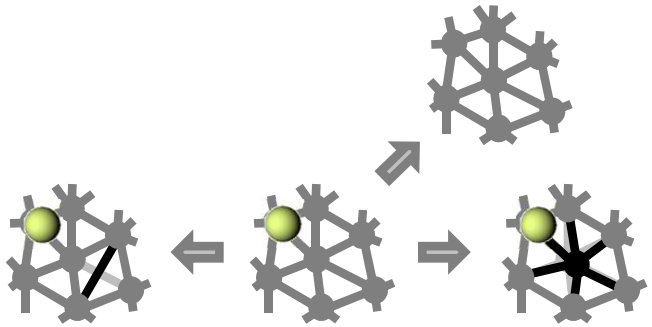
edge length~20nm

- **Membrane-bending protein on vertices**
  - adsorb from/desorb to cytosol with energy change ε^{adsp}
  - change spontaneous curvature locally



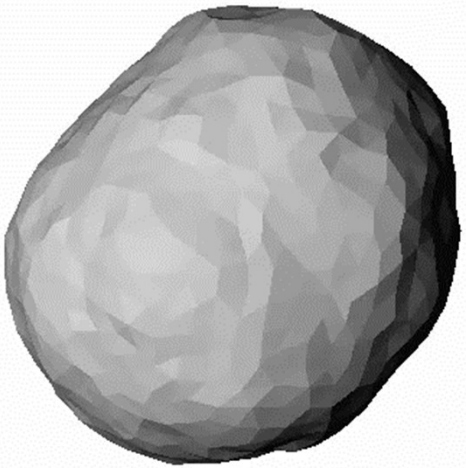
- **Monte-Carlo method for dynamics**

taking thermal fluctuation into account

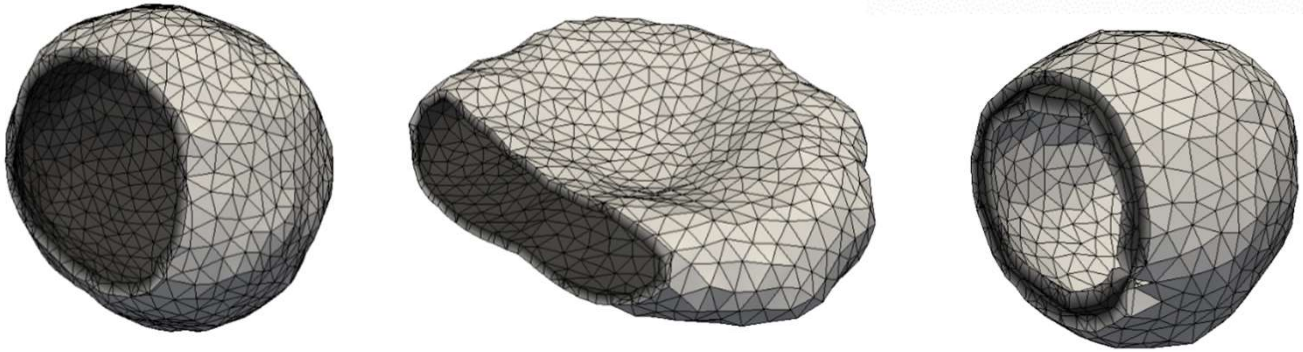


Simulator demo (without membrane-bending protein)

- Closed membrane bag （diameter～100nm）
- Increase osmotic pressure at t=0, 0.0→0.4(atm)



Shape variation



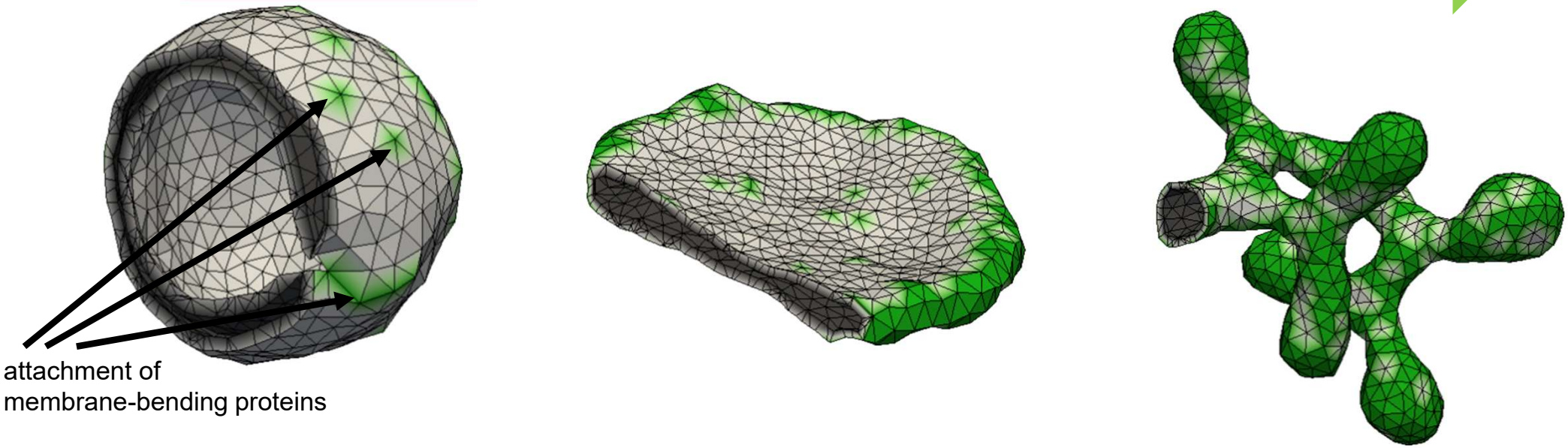
large　Lumen volume decrease　small

Shapes by membrane-bending proteins

$\Delta P = 5.0 \times 10^{-4}\mathrm{atm}$

$\varepsilon^{adsp} = 6.0k_BT$ $2.5k_BT$ $0.0k_BT$

decrease adsorption energy / increase membrane-bending protein



attachment of
membrane-bending proteins

- Discoid (cisterna-like) and tubular shapes are formed.
- Proteins are automatically arranged at the peripheral of disc.

“Self-organization of protein distribution and membrane shape”

Morphological aspects of Golgi and models

About single cisterna morphology

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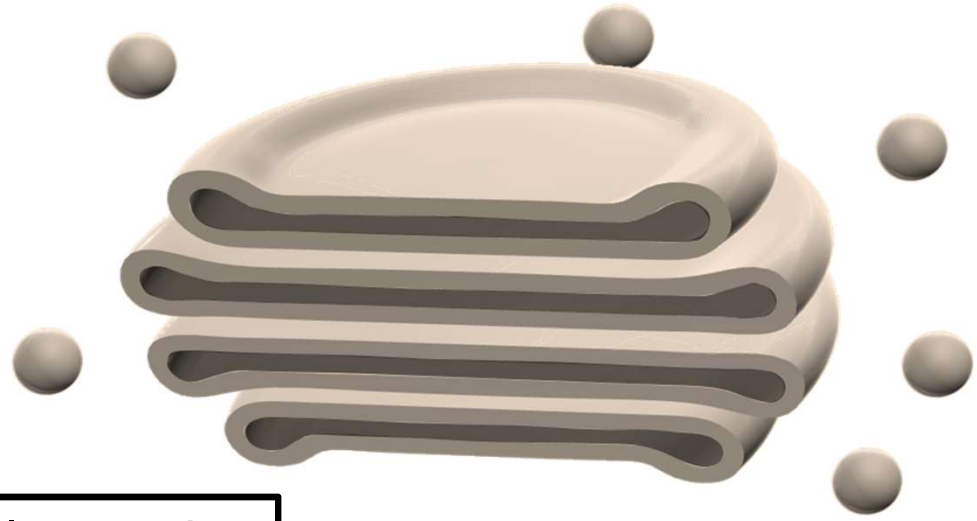
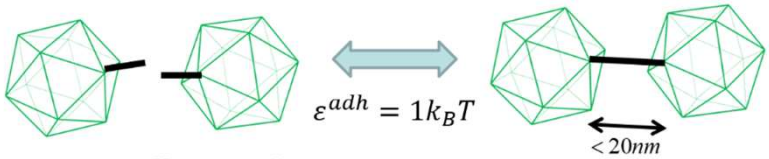
About cisternae assembly

- Cisternae stacking
  - Inter-membrane adhesion
    - GRASPs, Golgins
- Membrane fusion(fission)
  - Fusion machinery
    - SNARE proteins



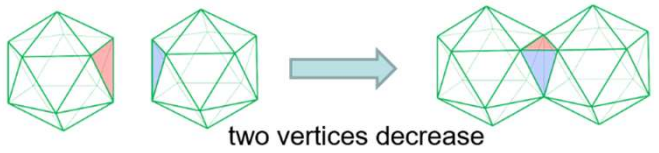
Model extension

Membrane adhesion (additional energy)



$E^{adh} = \varepsilon^{adh}$ ×number of adhering vertex pairs

Membrane fusion (additional Monte-Caro step)



Irreversible process (with ATP) : NO energetic control?

Morphological aspects of Golgi and models

- Compressed cisterna lumen

  Osmotic pressure difference

  Ion channels
- Bent cisternae rim

  rim stabilizer protein

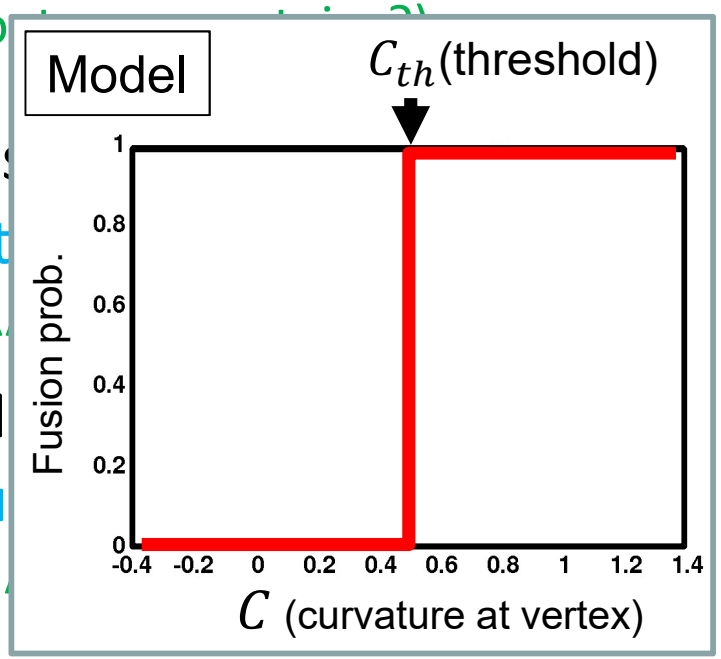
  (co
- Ci

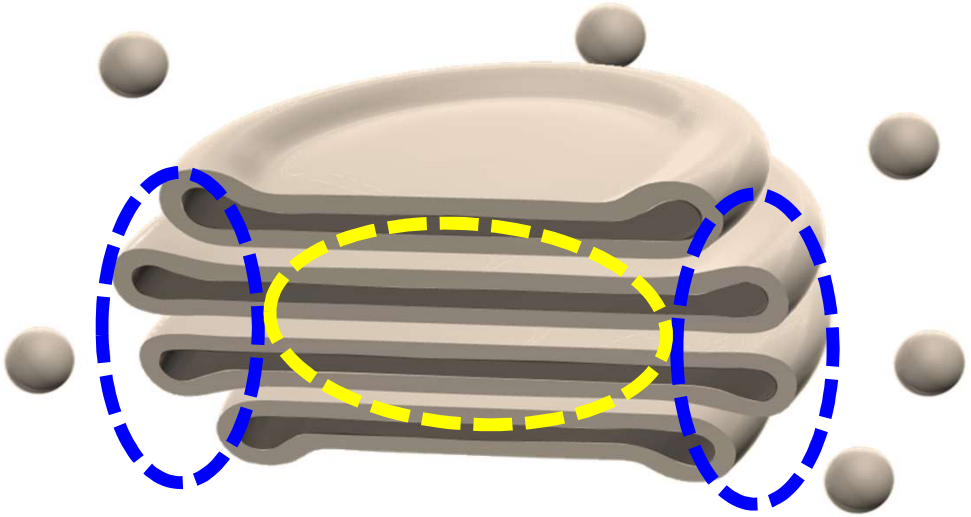
  Int

  GR
- M

  Fu

  SN





Fusion should be restricted inside to keep cisternae separate

Model for fusion control

"Only curved membrane can fuse."

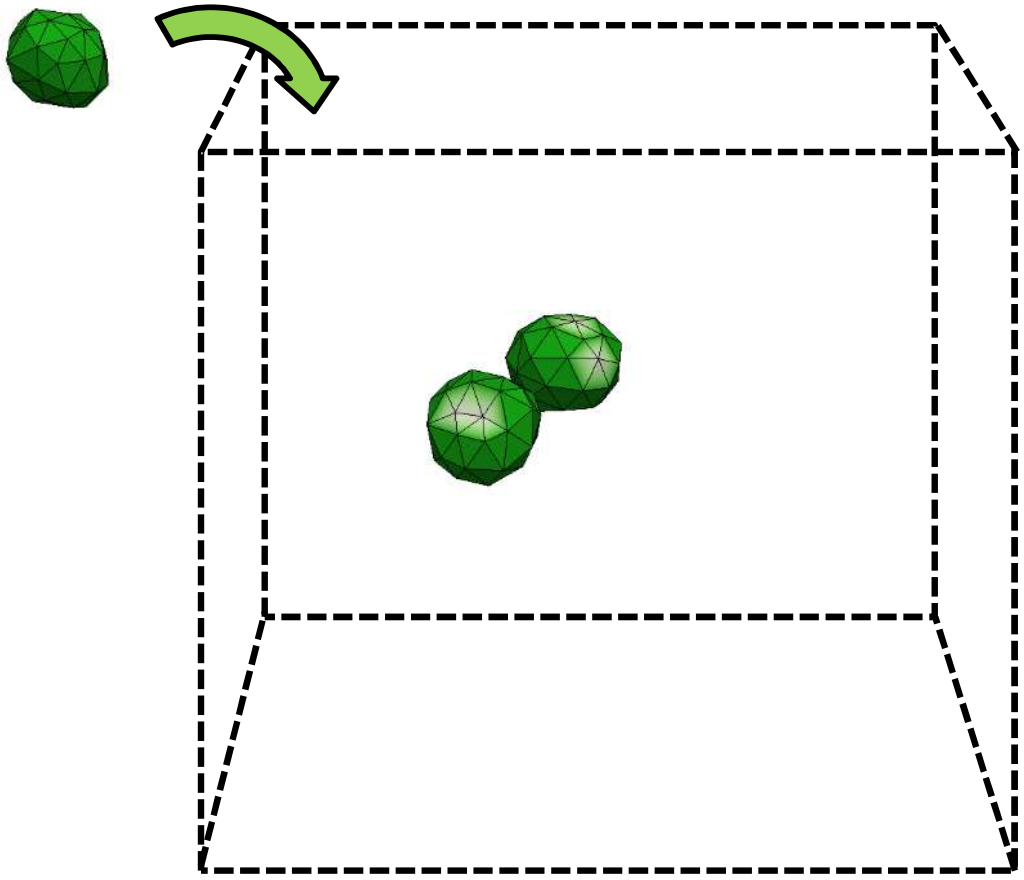
biological model

"Fusion machinery distribution depends on curvature."

Golgi reassembly simulation

Add vesicles with an interval

Vesicle size: 42 vertices
Total number of vesicles: 75

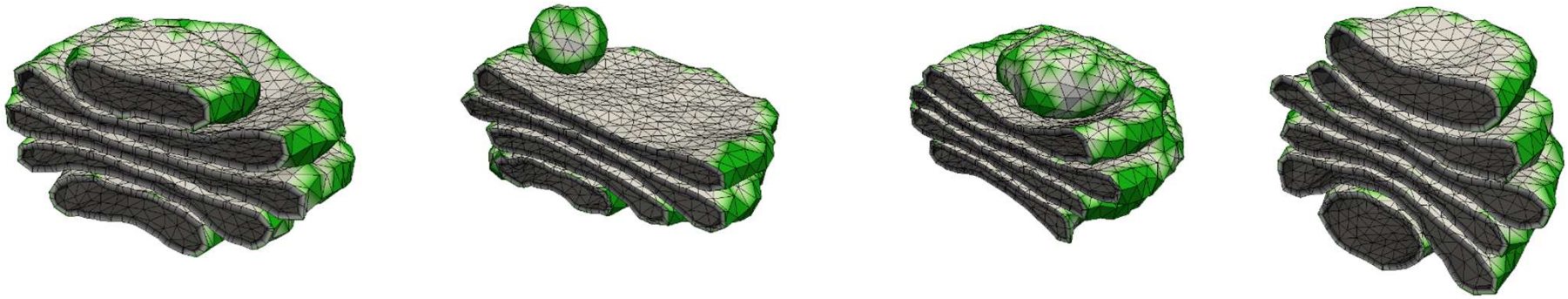


Best parameter set	
Osmotic pressure	$\Delta P \sim 7.0 \times 10^{-4}\text{atm}$
Adsorption energy	$\varepsilon^{adsp} \sim 4.0 k_B T$
Adhesion energy	$\varepsilon^{ad} \sim 1.0 k_B T$
Vesicle adding interval	$\tau \sim 10^4$ steps
Fusin threshold	$C_{th} \sim 0.8$

Self-organization of Golgi shape **did occur**

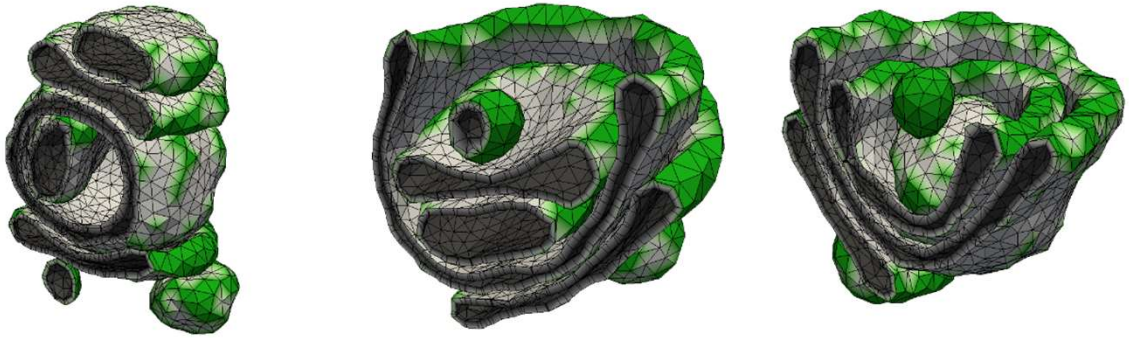
success

50/72
~2/3



failure

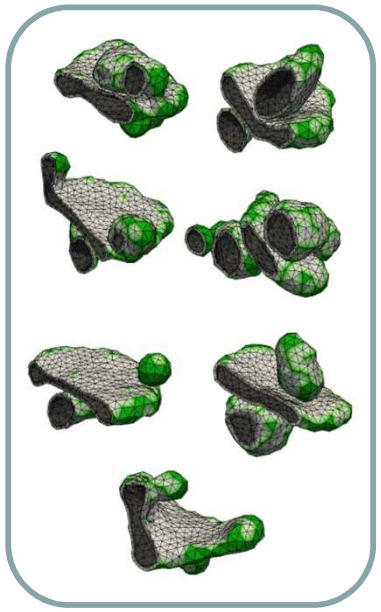
22/72
~1/3

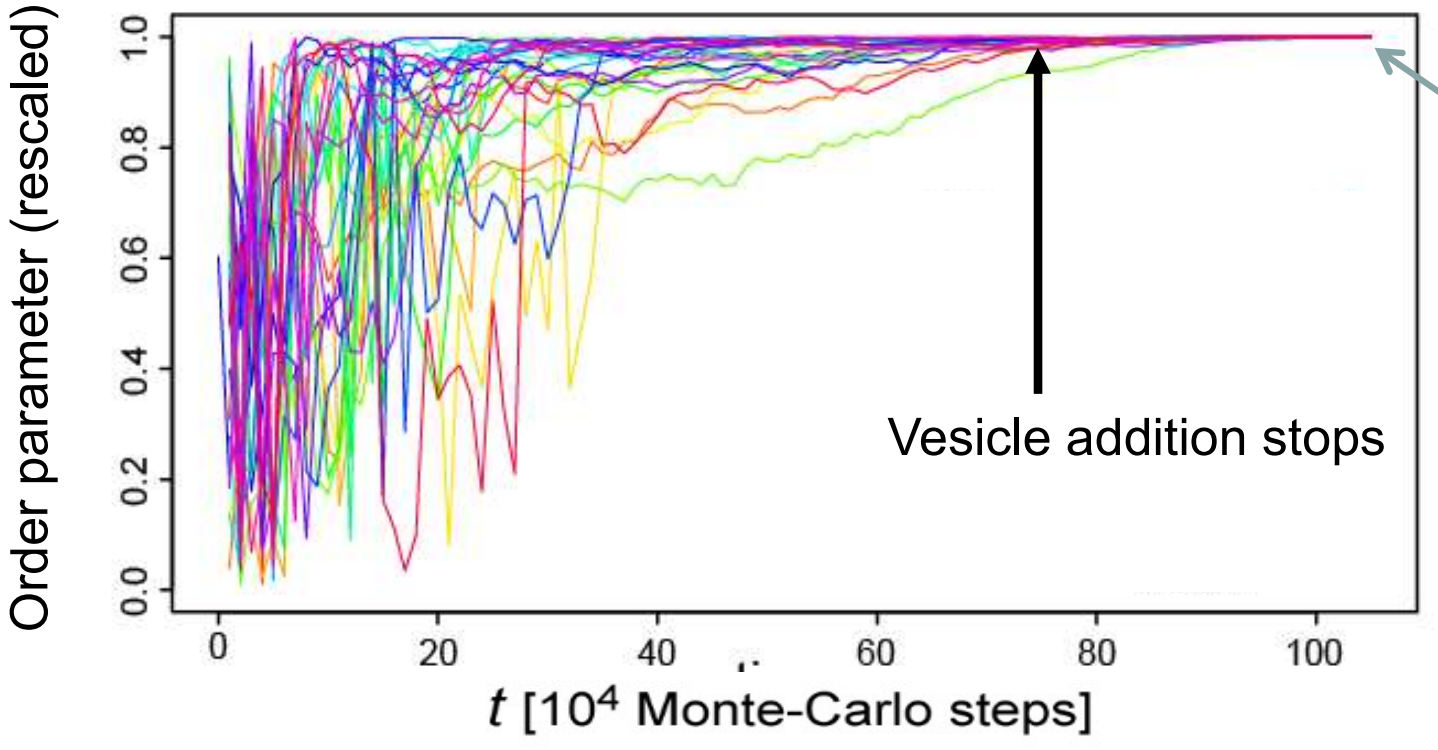


The physical model that is designed to stabilize the interphase Golgi shape and that comprises equilibrium reactions except the fusion process, reproduced(mimicked) the Golgi reassembly process from broad initial conditions.

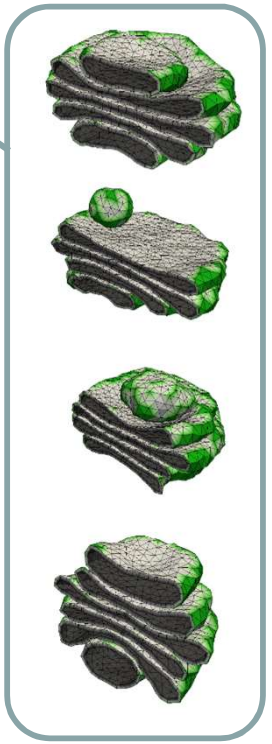
Golgi formation dynamics

shapes at t=20



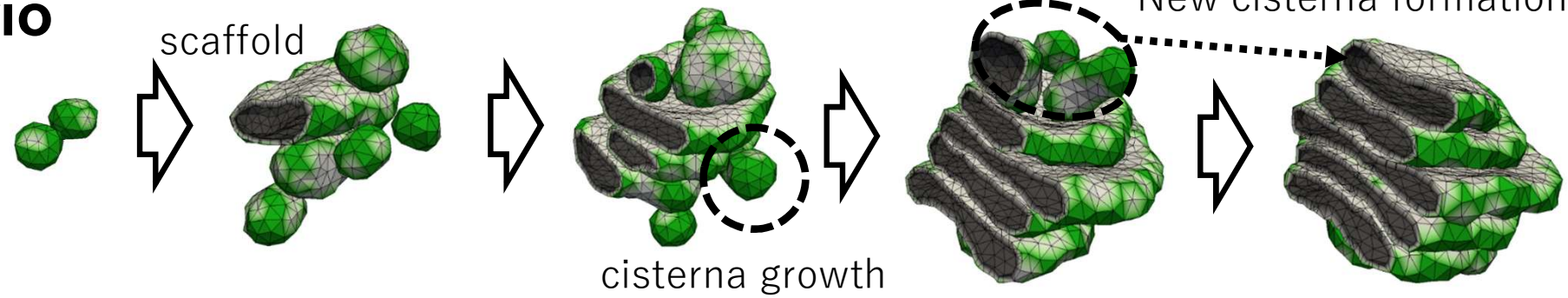


at last

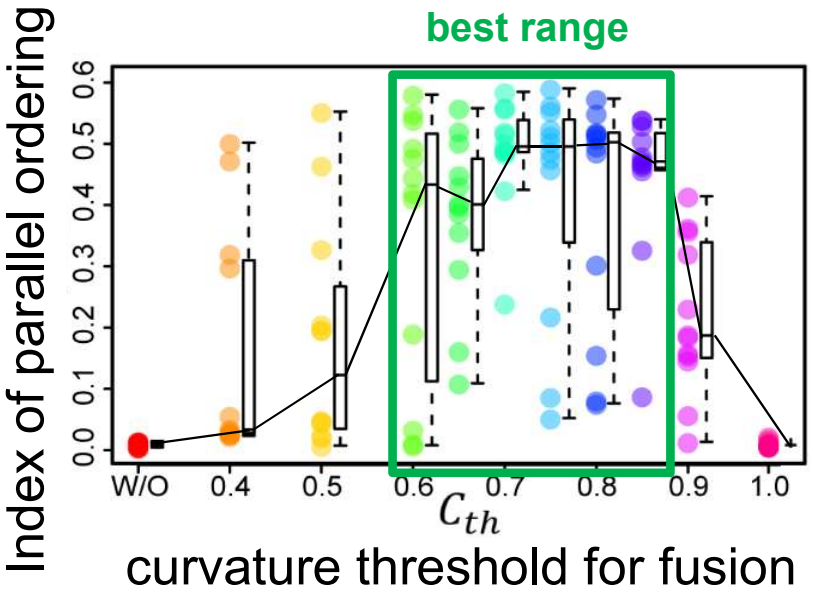


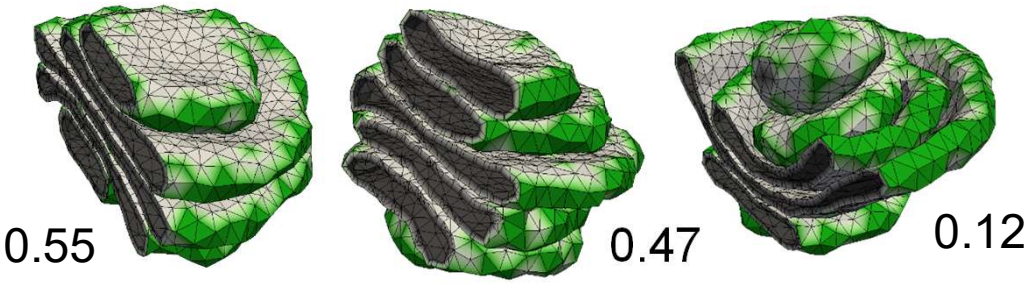
Order emerged in very early phase.

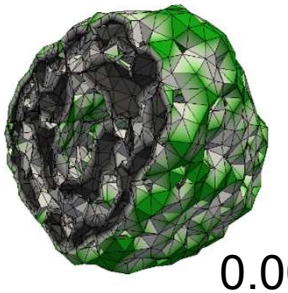
Golgi formation scenario



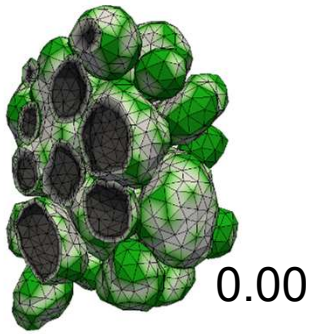
order parameter statistics



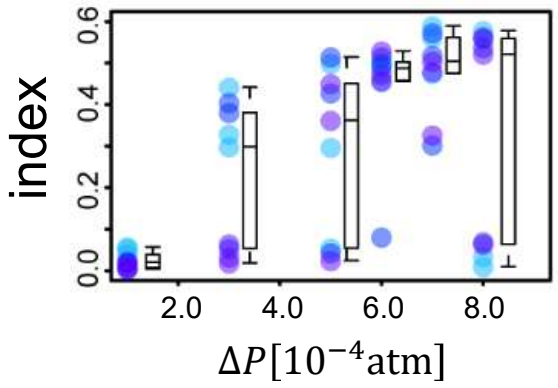


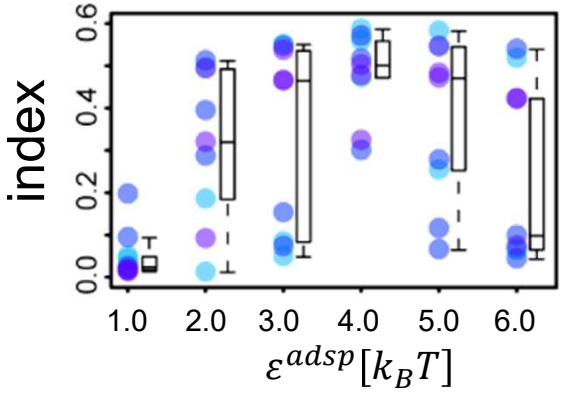


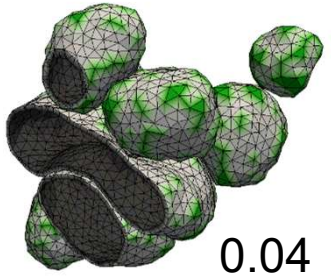
w/o



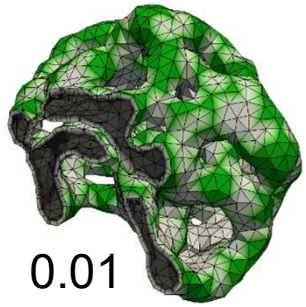
$C_{th} = 1.0$





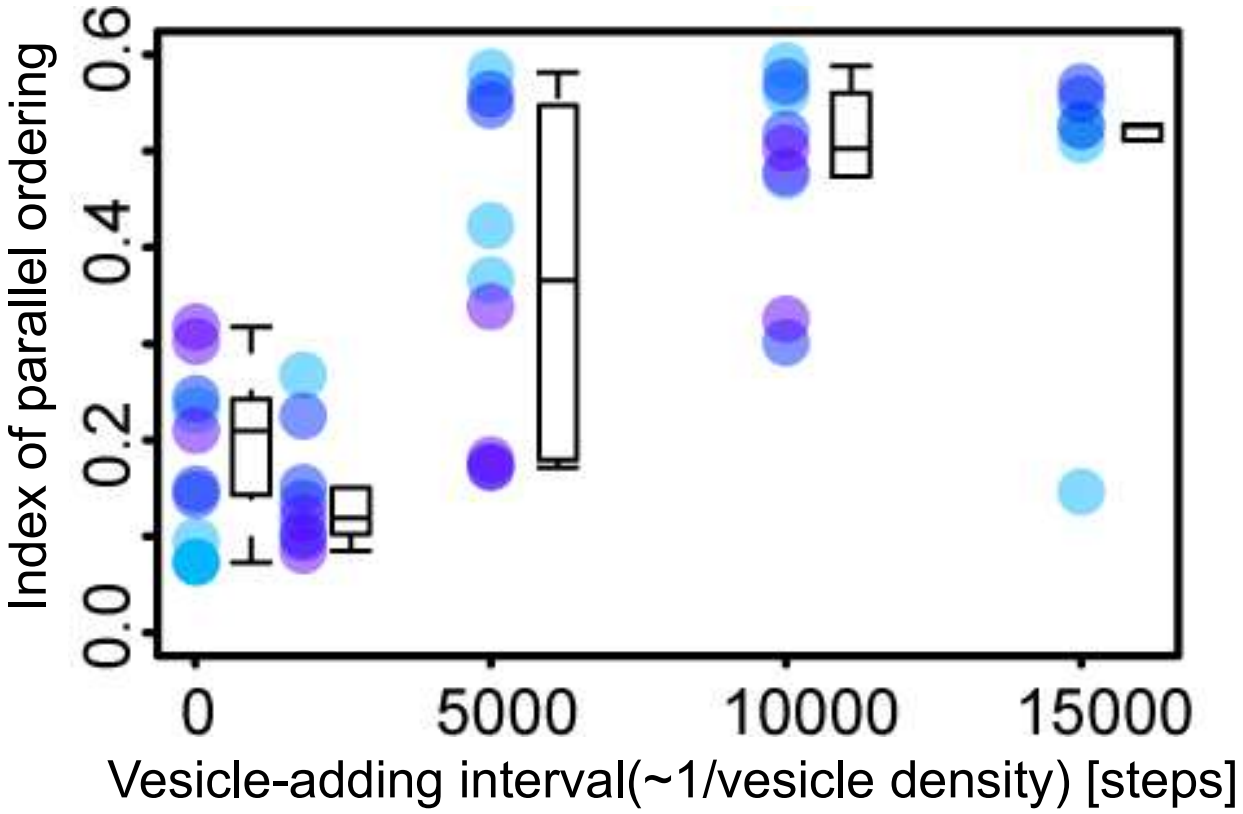


low ΔP

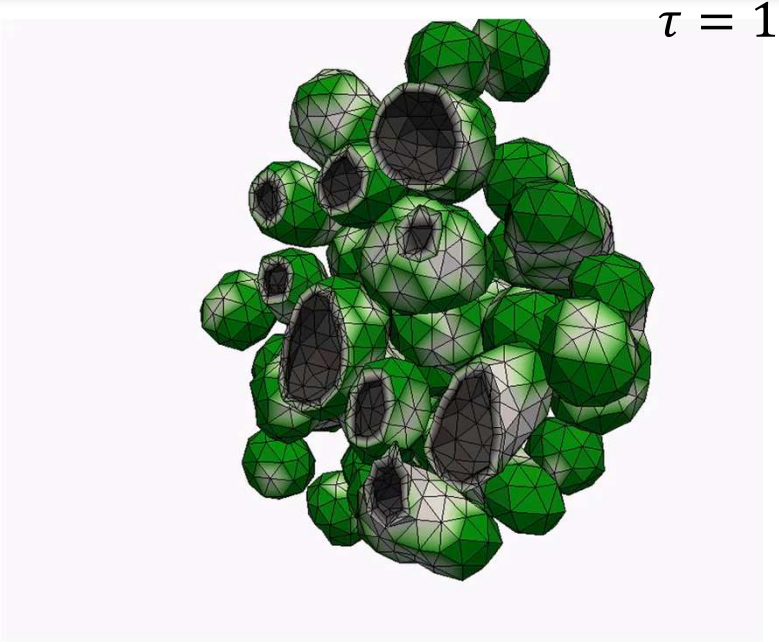


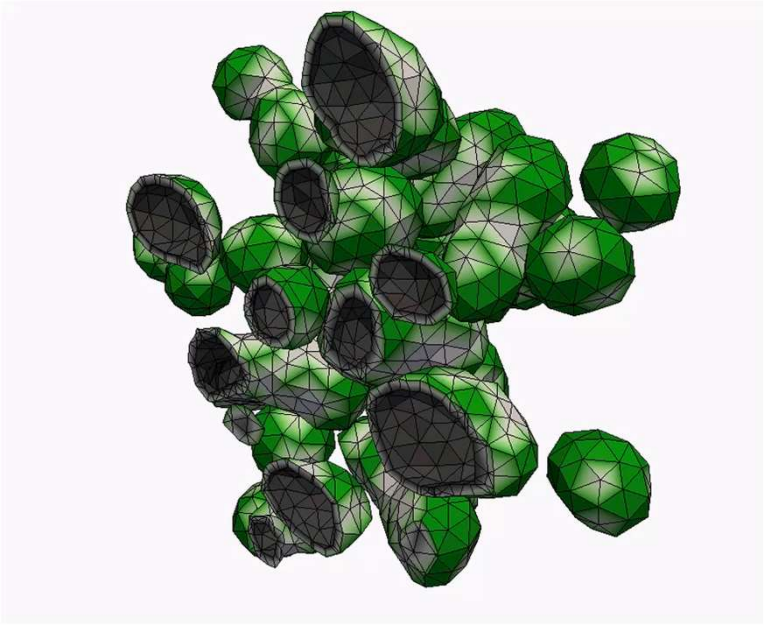
low ε^{adsp}

Aggregation speed is important



$\tau = 100$





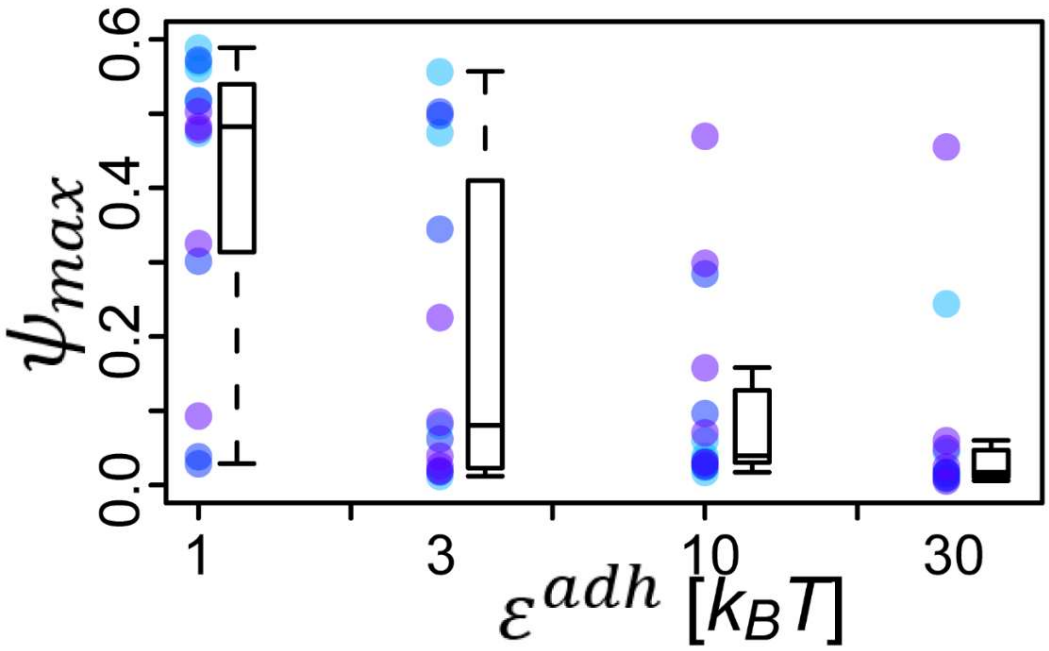
RESULT

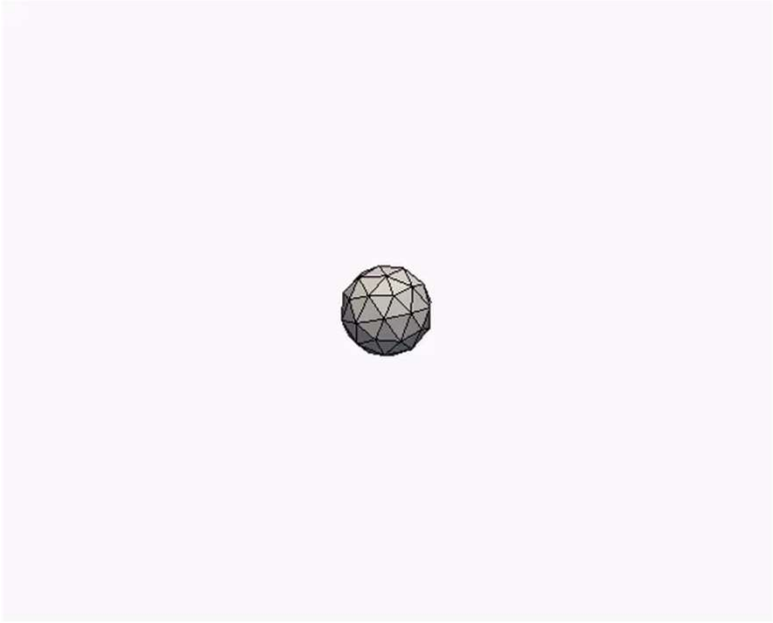
Short interval aggregation (= high vesicle density)
blocked clear layered structures
⇒ shape relaxation after fusion is important.

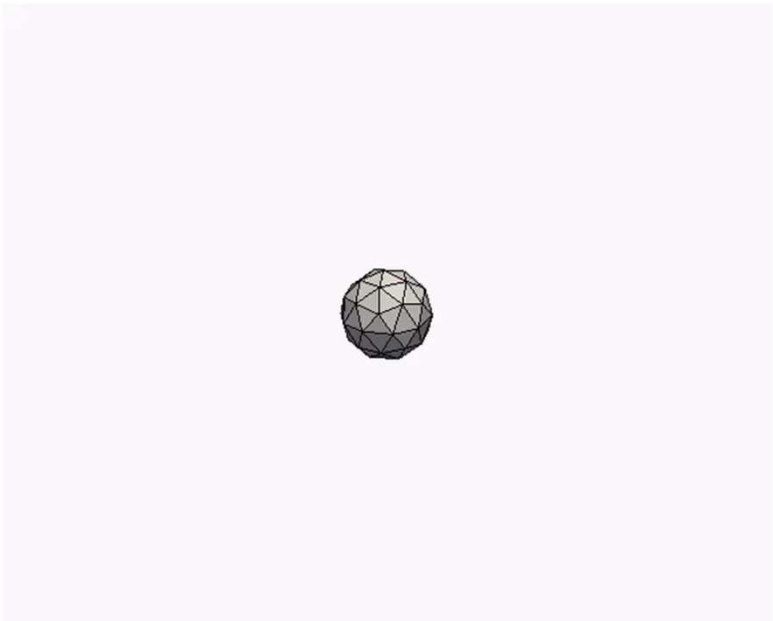
Shape relaxation time scale < aggregation time scale

Adhesion energy (~ adhesion protein density)

$\varepsilon^{adh} = 30.0 k_B T$







RESULT

- High adhesion energy made nested structures.
- Adhesion energy should small enough not to change membrane shape.

Lee et al. (2014) PNAS

“Decrease in adhesion proteins made cisternae swell.”

“Adhesion energy may cause lumen compression.”

Summary

We created a recipe for **self-organization of Golgi body.**

We supposed **osmotic pressure, rim (curved membrane) stabilizer, fusion restriction** based on interphase Golgi shape, **which were enough.**
(most reactions are equilibrium reactions.)

Self-organization of anisotropic layered structure from isotropic assembly of materials. **Anisotropy is formed in early stage.**

Balances of time scales among vesicle aggregation, fusion and shape relaxation are necessary for formation of clear layered structures.

Acknowledgement

Prof. T. Kohyama, Shiga Univ.

MT and Mochizuki (2017) PNAS