

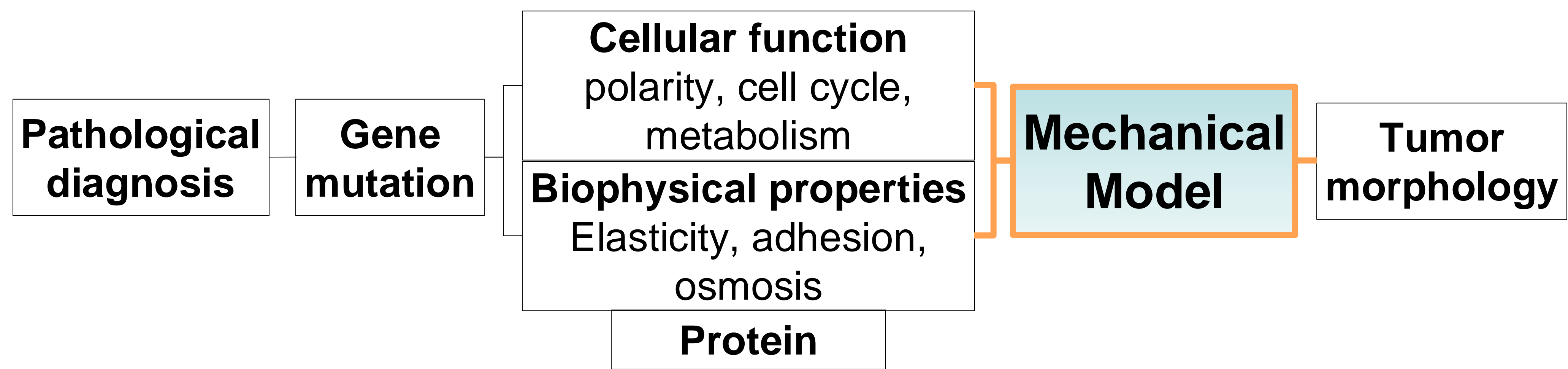
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## Key Question: Can mechano-biology improve pathological diagnosis?

- How genetic mutations exert protein-mediated mechanical cues in tumorigenesis?
- We reproduced the morphology of ovarian cancer organoids using mechanical model.



## Materials & Methods

**Cancer organoid**  
Fukushima Patient Derived Tumor Organoid (F-PDO®)

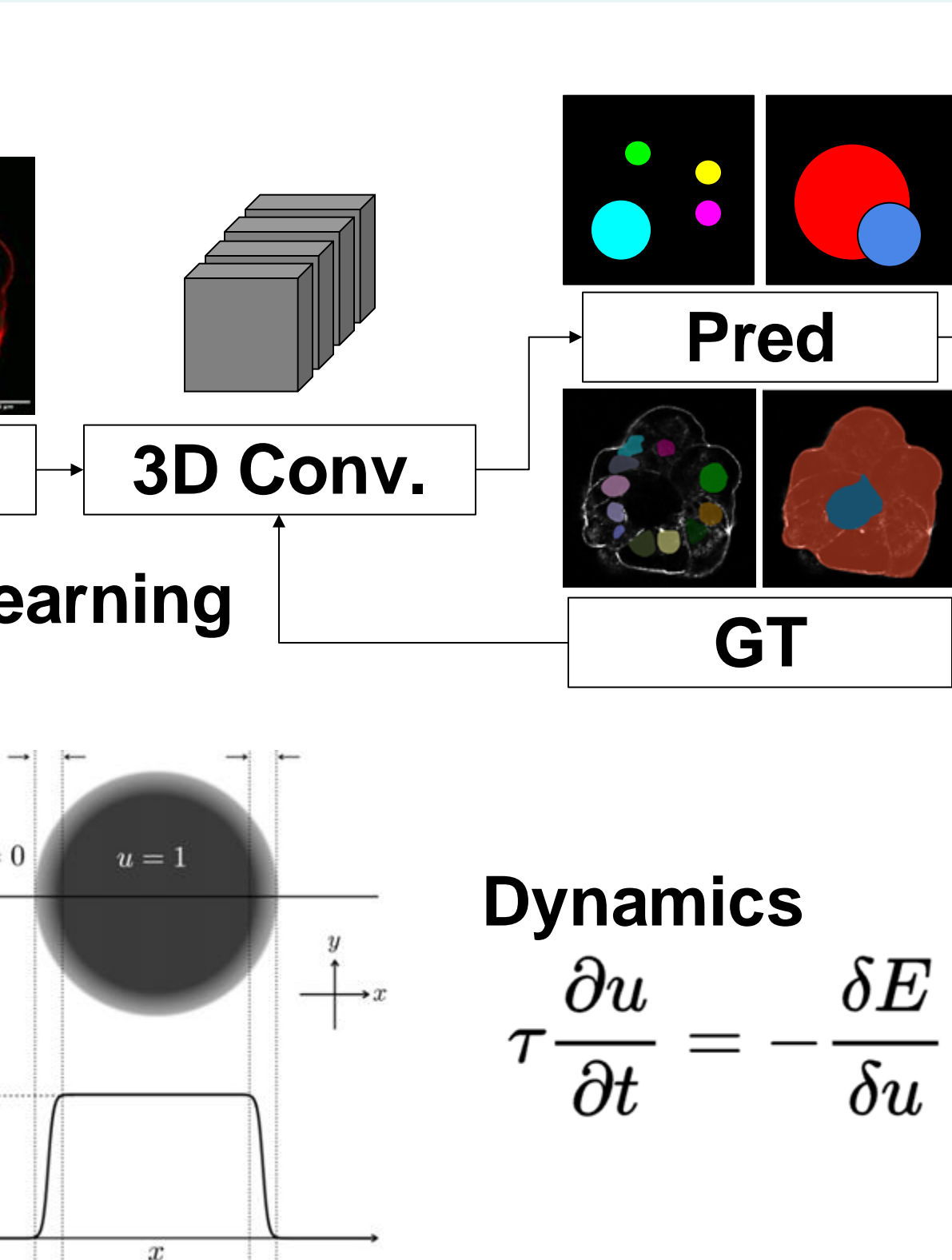
**Trypsinization**  
Inhibits cell adhesion for isolating to single cell.

**Culture**  
Incubate at 37°C with 5% CO<sub>2</sub> gas.

**Staining**  
Nucleus: SYTOX® Green  
F-actin: Phalloidin-iFluor 594

**3D image segmentation<sup>1</sup>**  
3D convolution neural network estimated the segmentation of nuclei, tissues, and lumen by supervised learning.

**Phase-field model<sup>2,3</sup>**  
Cell shape was represented as phase interface. Phase field variable:  $u(\mathbf{r}, t) = 1$  at cell occupied region.



**Free energy of mth cell phase  $u_m$**

$$E[u_m] = \int_{\Omega} \left[ \frac{D_u}{2} |\nabla u_m|^2 + \frac{1}{4} u_m^2 (1 - u_m)^2 \right] dr$$

# Surface tension

$$+ \sum_{n \neq m} \frac{\eta}{6} \int_{\Omega} \nabla h(u_m) \nabla h(u_n) dr + \frac{\alpha}{12} (V_{m,0} - V(u_m))^2$$

# Adhesion strength  $\eta$  # Cell volume const.

$$+ \sum_{n \neq m} \frac{\beta}{12} \int_{\Omega} h(u_m) h(u_n) dr + \frac{\beta_s}{12} \int_{\Omega} h(u_m) h(s) dr$$

# Excluded volume (cell-cell) # Excluded volume (cell-lumen)

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**Free energy of lumen phase  $s$**

$$E[s] = \int_{\Omega} \left[ \frac{D_s}{2} |\nabla s|^2 + \frac{1}{4} s^2 (1 - s)^2 \right] dr$$

# Surface tension

$$+ \sum_{n \neq s} \frac{\beta_s}{12} \int_{\Omega} h(s) h(u_n) dr - \frac{\xi}{6} \int_{\Omega} h(s) dr$$

# Excluded volume (cell-lumen) # Lumen pressure  $\xi$

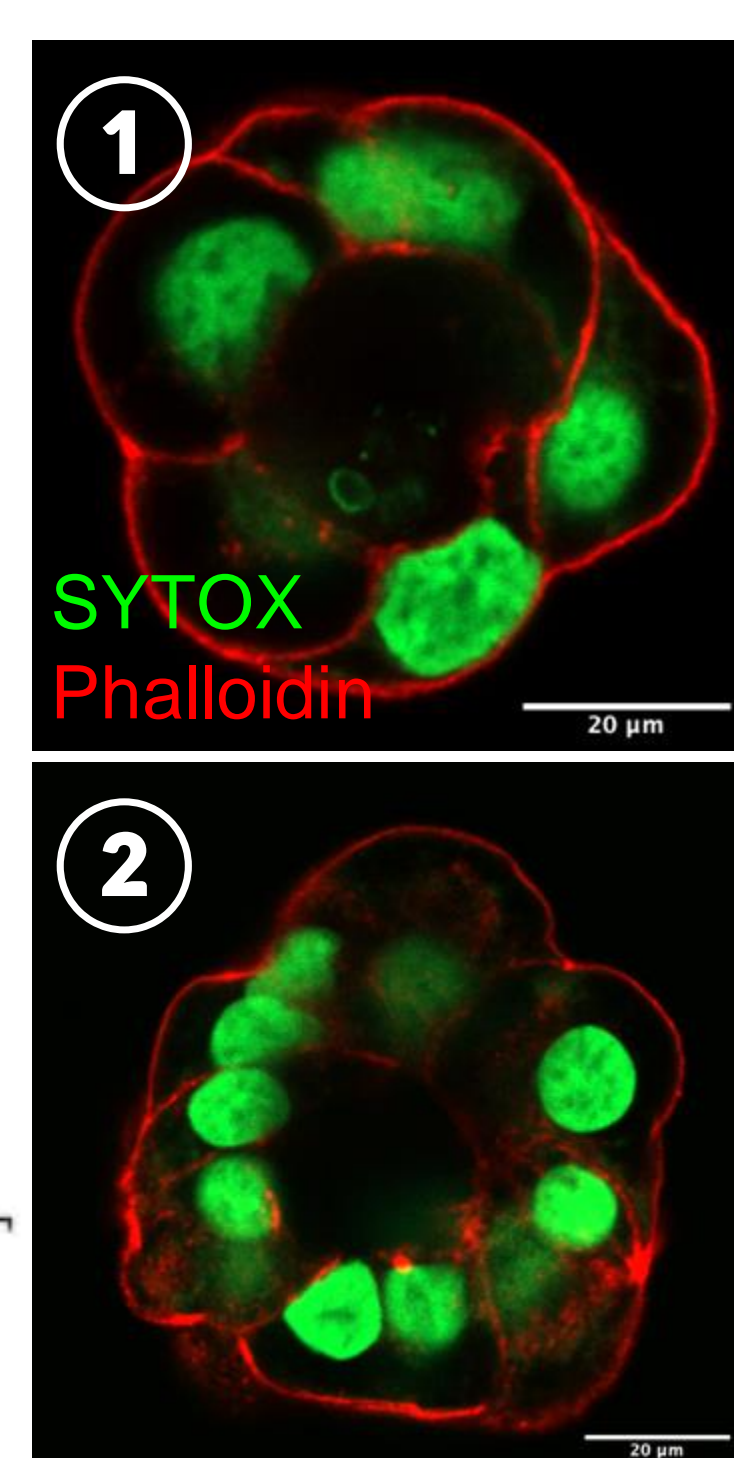
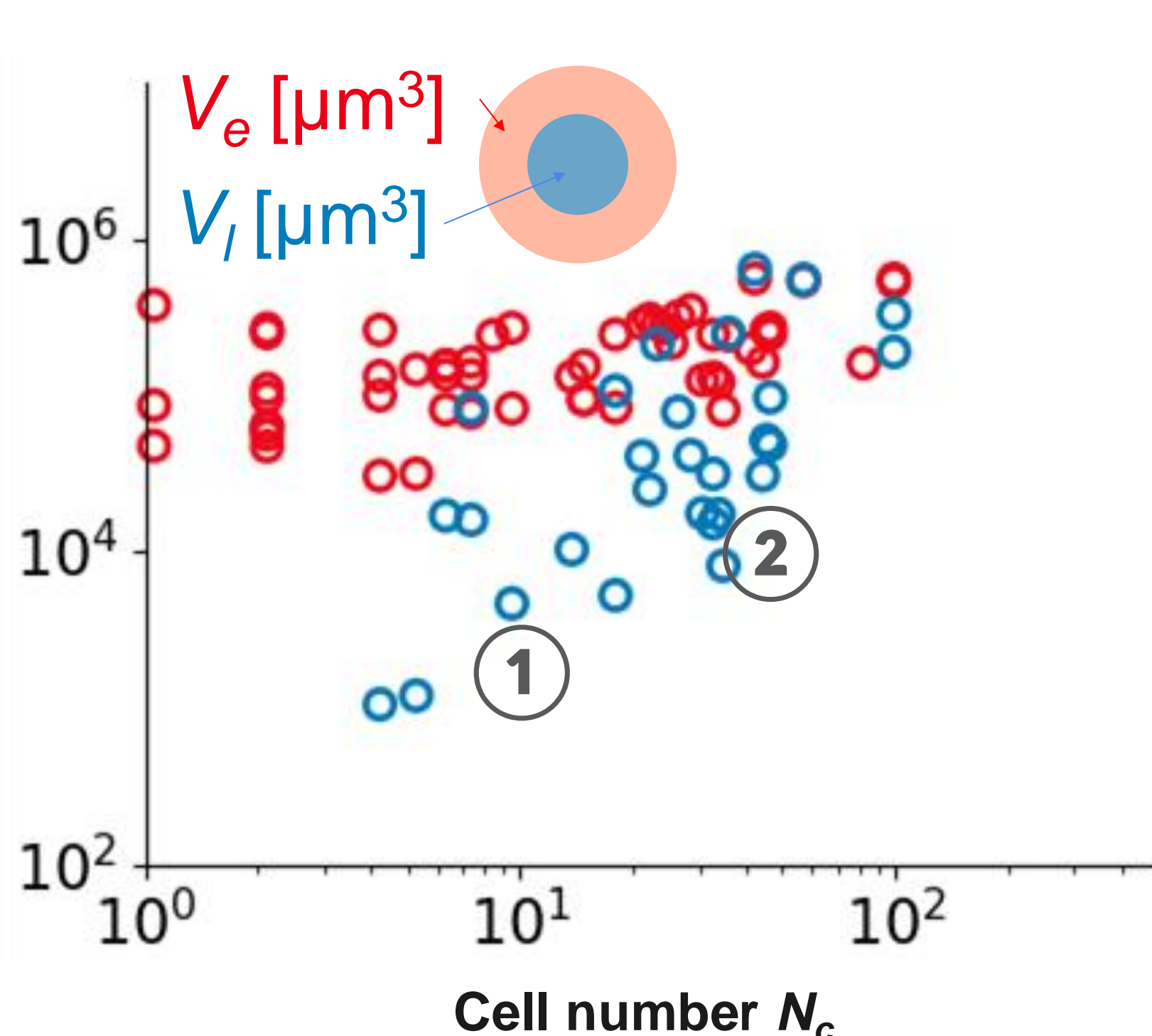
$h(u) = u^2(3-2u)$

## Observation: Lumen volume analysis

**Primary cancer organoids**

- Lumen was formed from the 4-cell stage.
- Lumen volume increased with cell proliferation (①, ②).

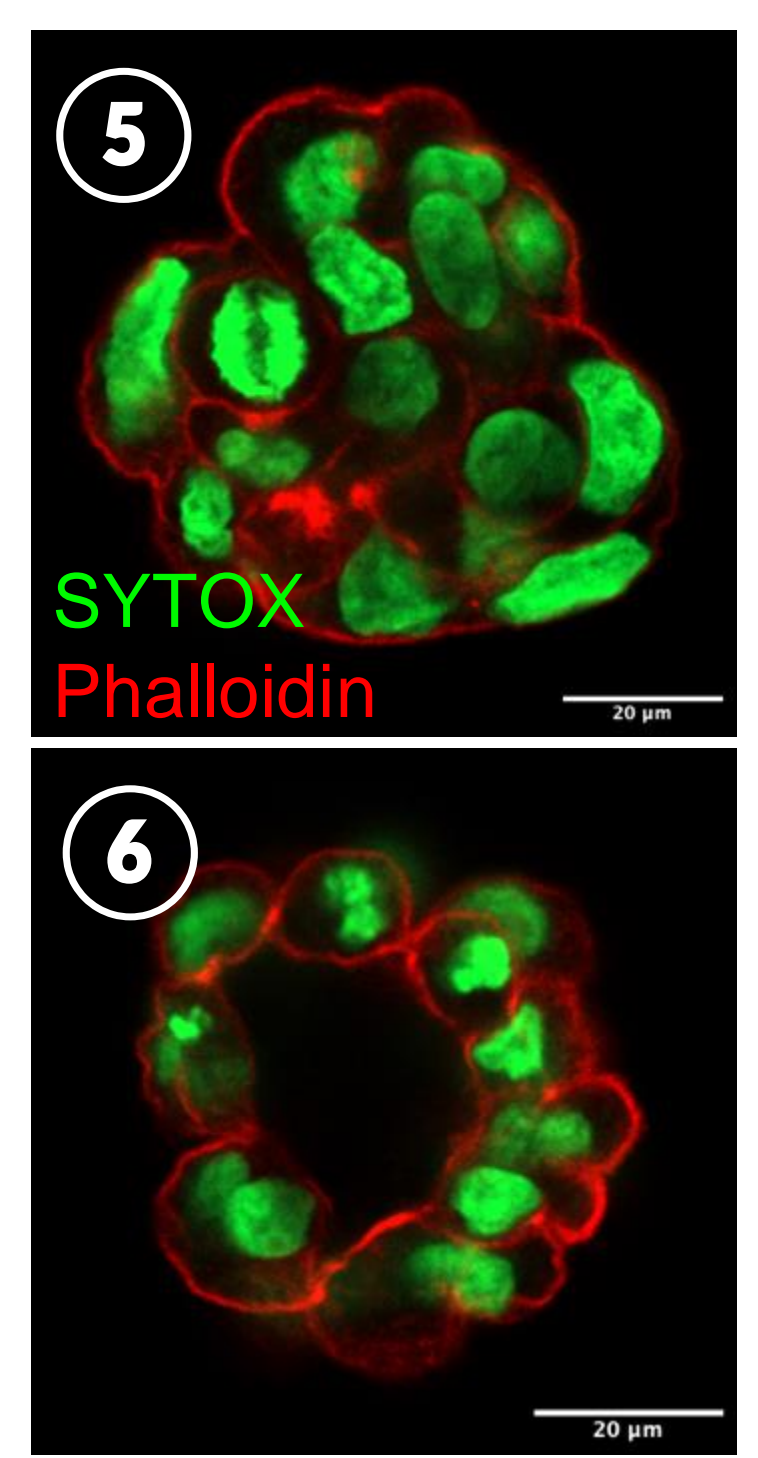
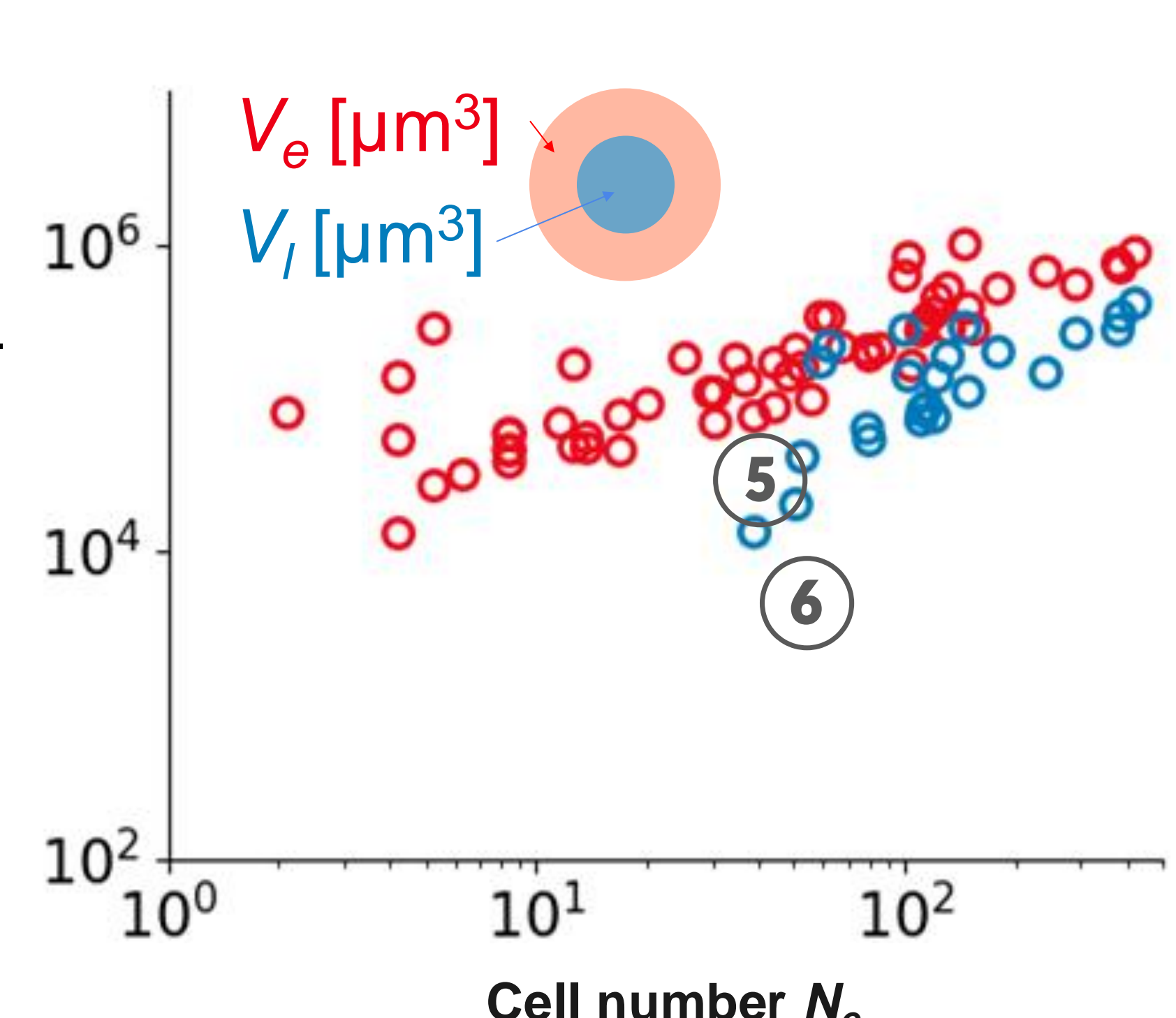
→ **Lumen growth**



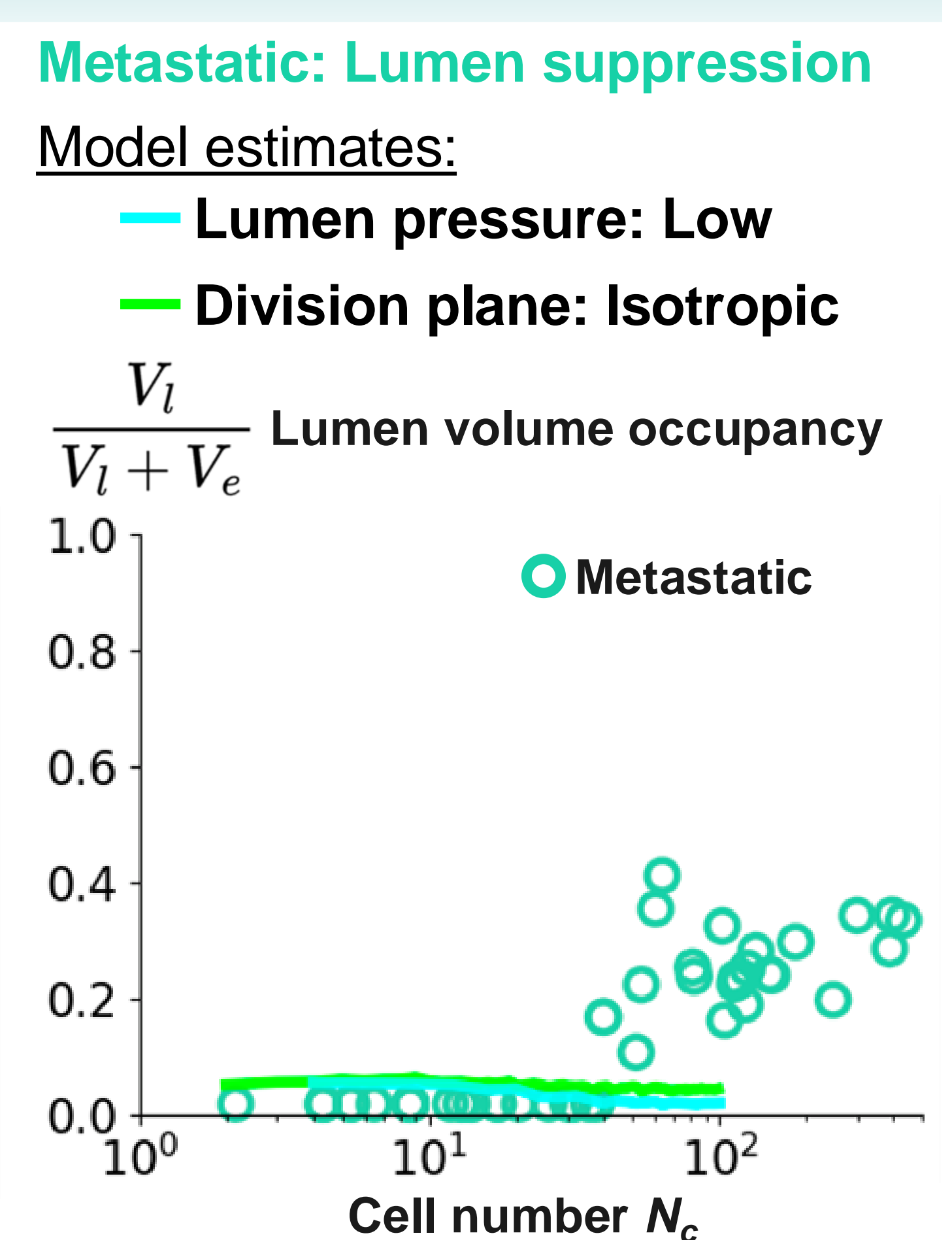
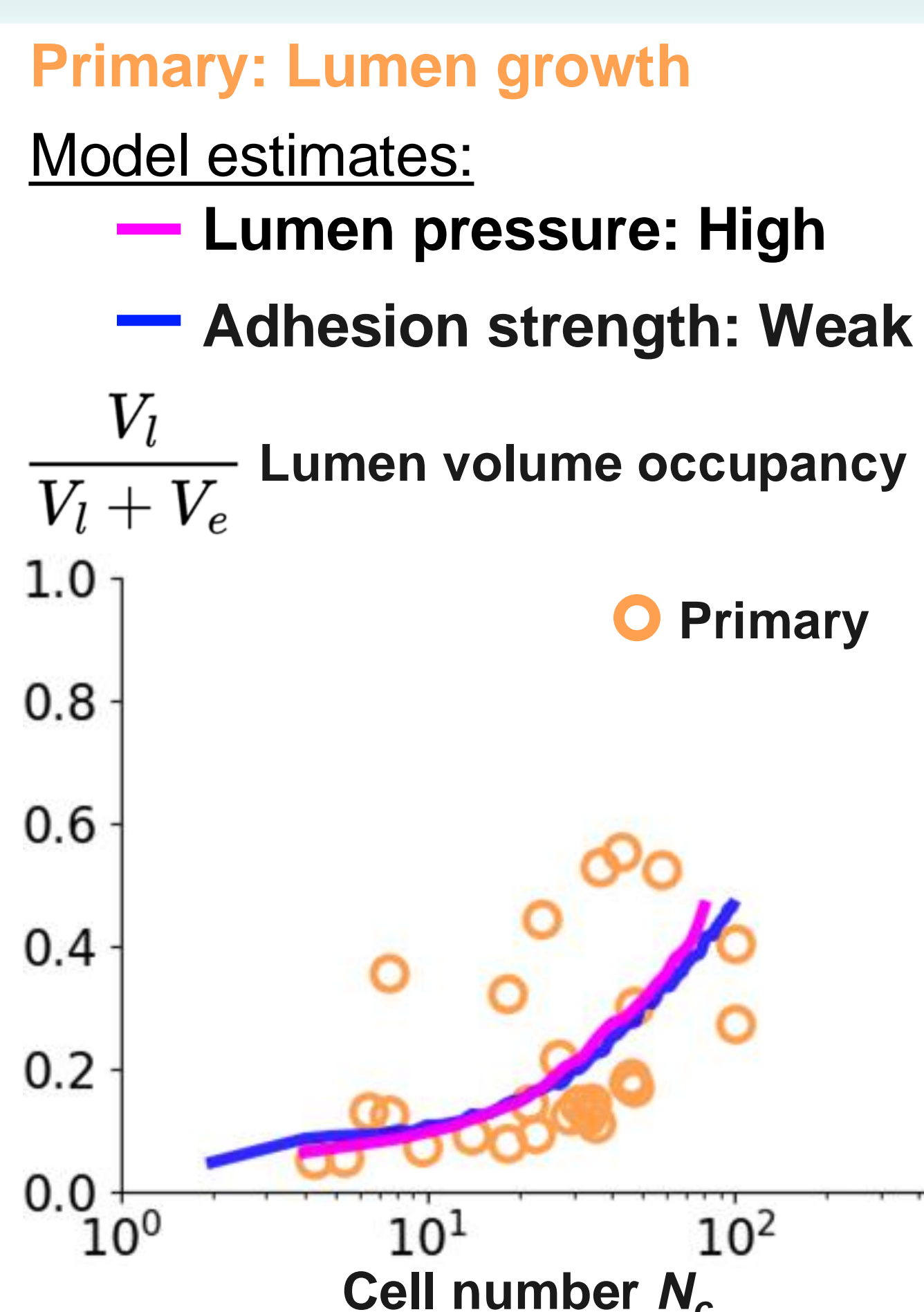
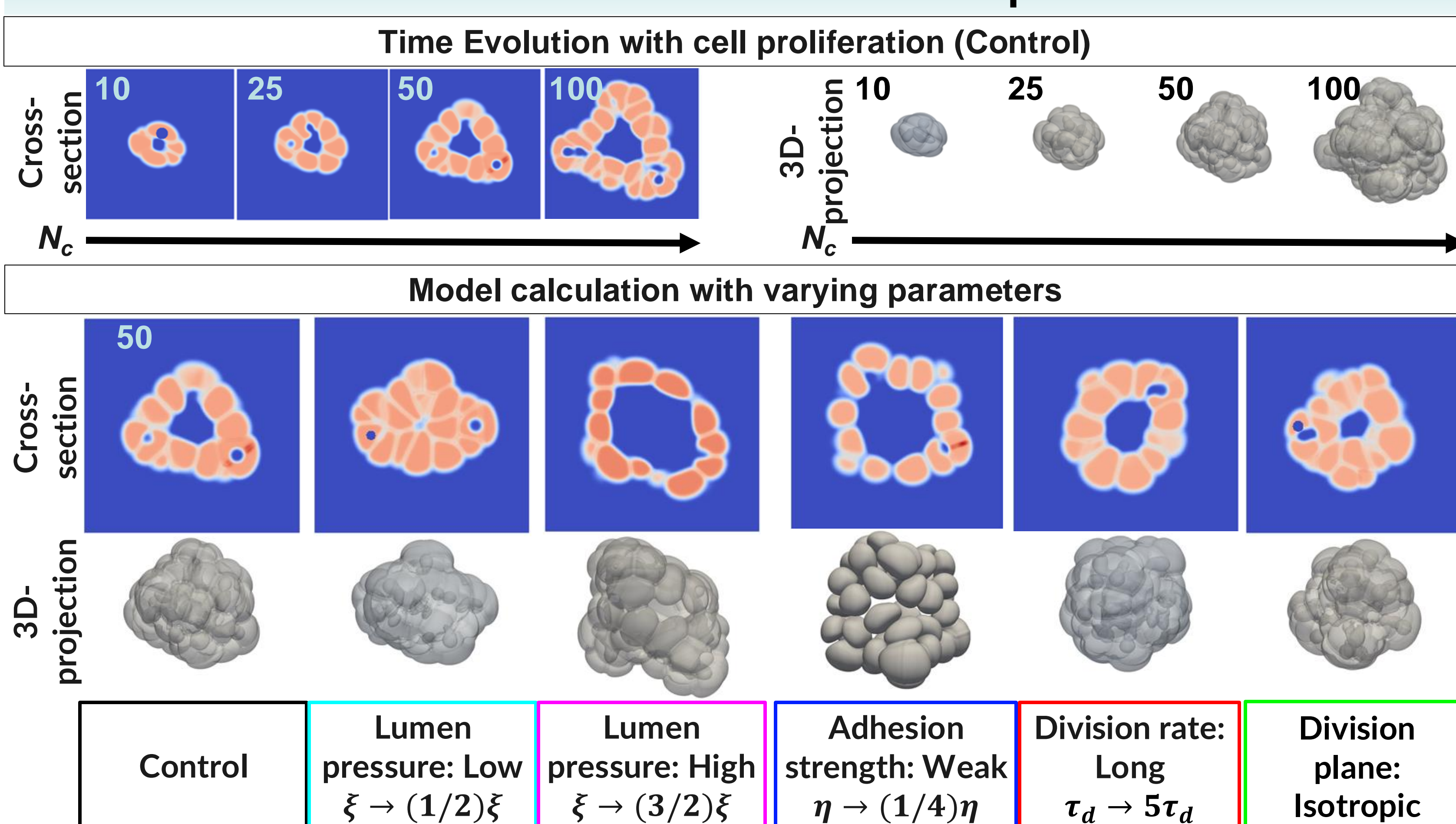
**Metastatic cancer organoids**

- Until approximately 40-cell stage, lumen did not appear (⑤).
- Beyond that point, the lumen suddenly appeared (⑥).

→ **Lumen Suppression**



## Simulation: Estimation of model parameters



## Conclusion: Yes, mechanical model can improve pathological diagnosis!

- We succeeded to characterize the mechanical cue of primary and metastatic cancer organoids.
- Our approach can be applied to a comparison among cancer lineage subtypes or among patients<sup>4</sup>.
- Mechanical model may not only corroborate the current diagnosis of cancer, but also uncover the indicator of cancer prognosis.