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Supplemental information

**Using soft X-ray tomography for rapid whole-cell
quantitative imaging of SARS-CoV-2-infected cells**

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Table S1. Quantitative analysis of soft X-ray linear absorption coefficient of organelles in native and fixed cells. Related to Figure 1. Table of mean LAC values and their standard deviation (std) for most organelles visible in SXT for fixed (n=10) and native cells (n=7). The difference for all organelles is not significant based on unpaired Welch's t-test.

Organelle	LAC (μm^{-1})			
	Fixed (n=10)		Native (n=7)	
	mean	std	mean	Std
Euchromatin	0.22	0.01	0.21	0.03
Heterochromatin	0.27	0.01	0.27	0.04
Mitochondria	0.31	0.02	0.31	0.04
Lipid droplets	0.58	0.09	0.59	0.06
ER	0.24	0.01	0.24	0.04
Cytosol	0.22	0.01	0.22	0.03

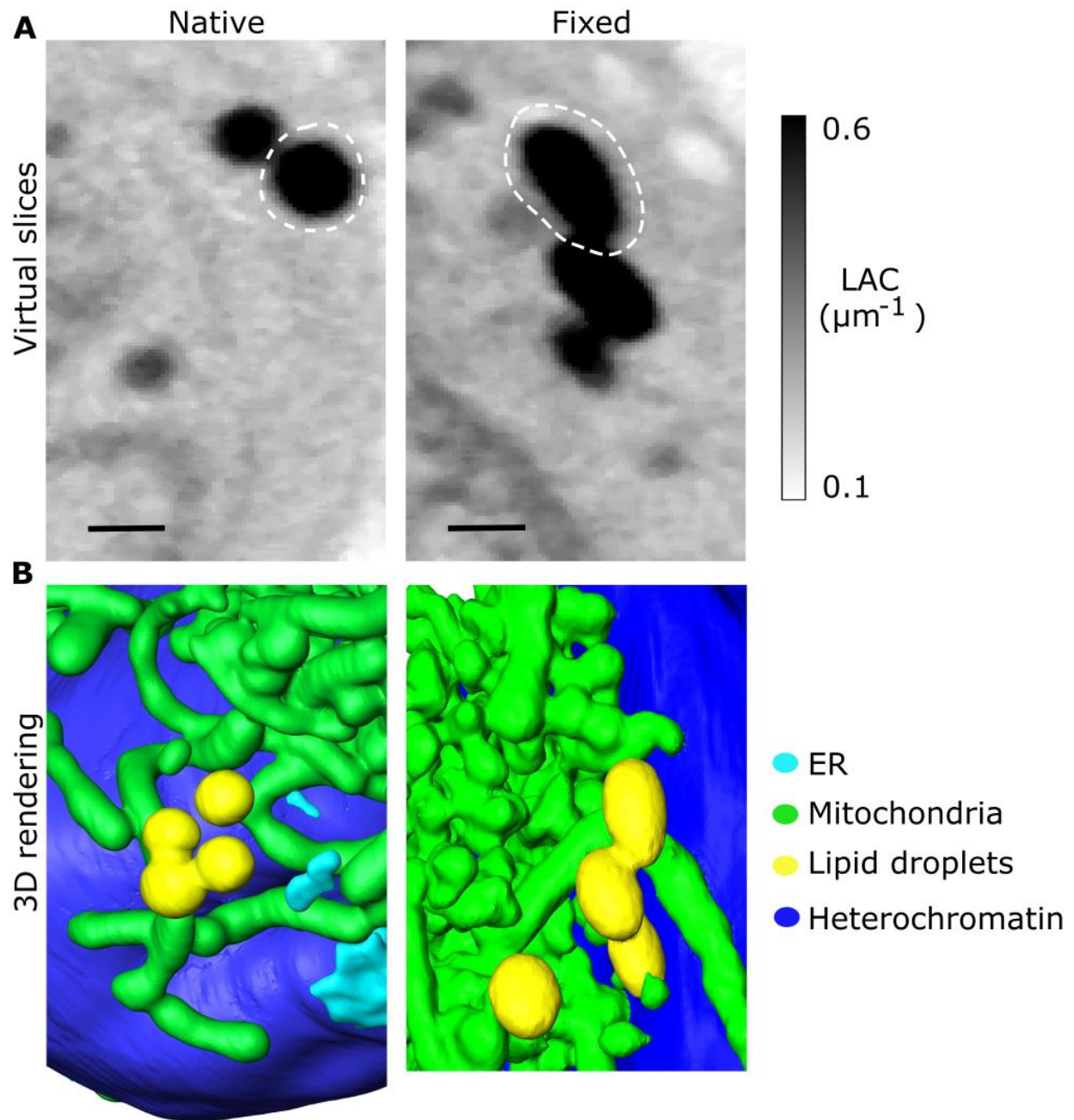


Figure S1. Impact of fixation on shape of lipid droplets. Related to Figure 1. (A) Virtual slices and (B) corresponding 3D renderings of lipid droplets (outlined) in native and fixed human B cells imaged with SXT. Scale bar is 500 nm.

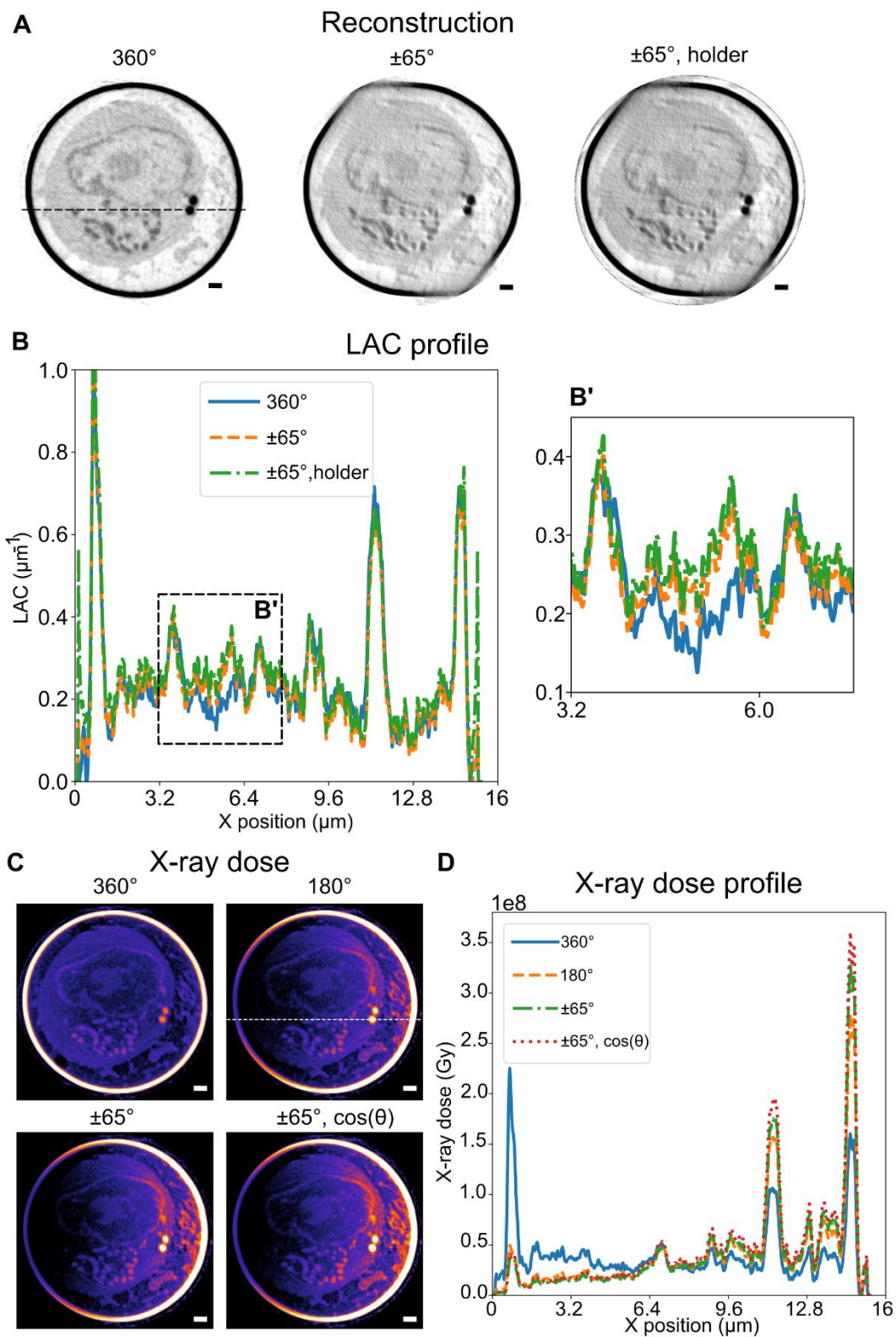


Figure S2. Comparison of limited angle and full rotation imaging with SXT on 3D reconstructions and X-ray dose. Related to Figure 2. (A) Virtual slices of full rotation imaging, limited to $\pm 65^\circ$ rotation and limited rotation

with “shadowing” from the flat support. (B) corresponding line profiles (dashed line on virtual slice) with B’ magnified region, demonstrating shift of LAC values. Scale bars are 1 μm . (C) Virtual slices of full (360°) rotation, 180° rotation, limited to $\pm 65^\circ$ rotation, including gradual decrease in X-ray transmission (as $\cos(\theta)$) during rotation. (D) corresponding line profiles (dashed line on virtual slices) demonstrating X-ray dose distribution. Scale bars are $1\mu\text{m}$.

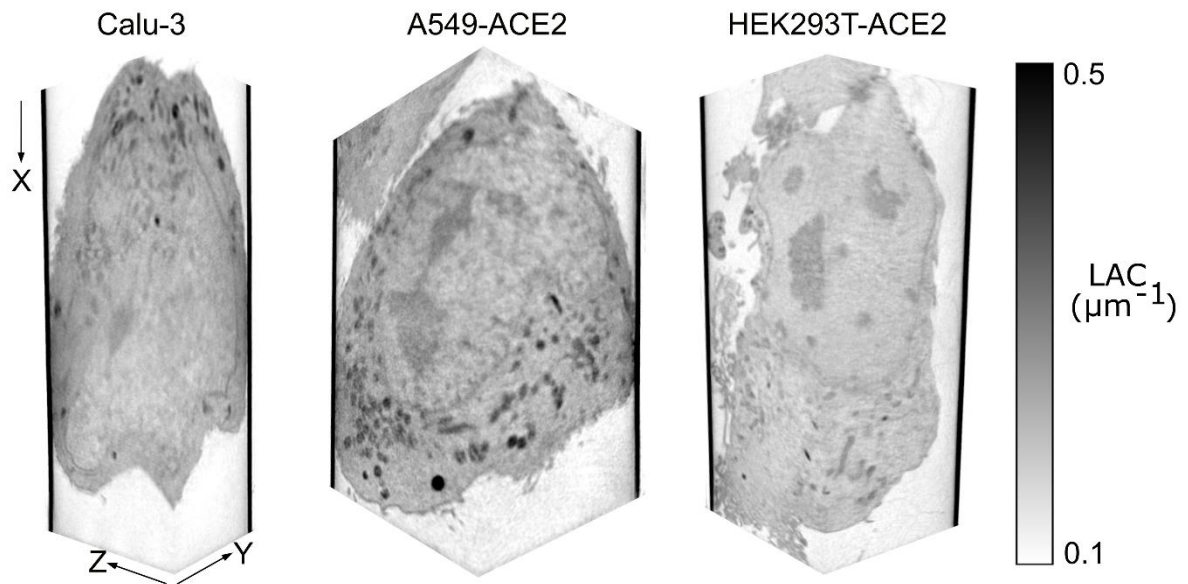


Figure S3. Structural comparison of Calu-3, A549-ACE2, and HEK293T-ACE2 cells. Related to Figure 3. Exemplarily full cell volume of single cells from corresponding cells lines, with shown axial (XY) and sagittal (XZ) views. The grey values show the different level of absorption of each type of organelle with a threshold set from 0.1 to $0.5\ \mu\text{m}^{-1}$.

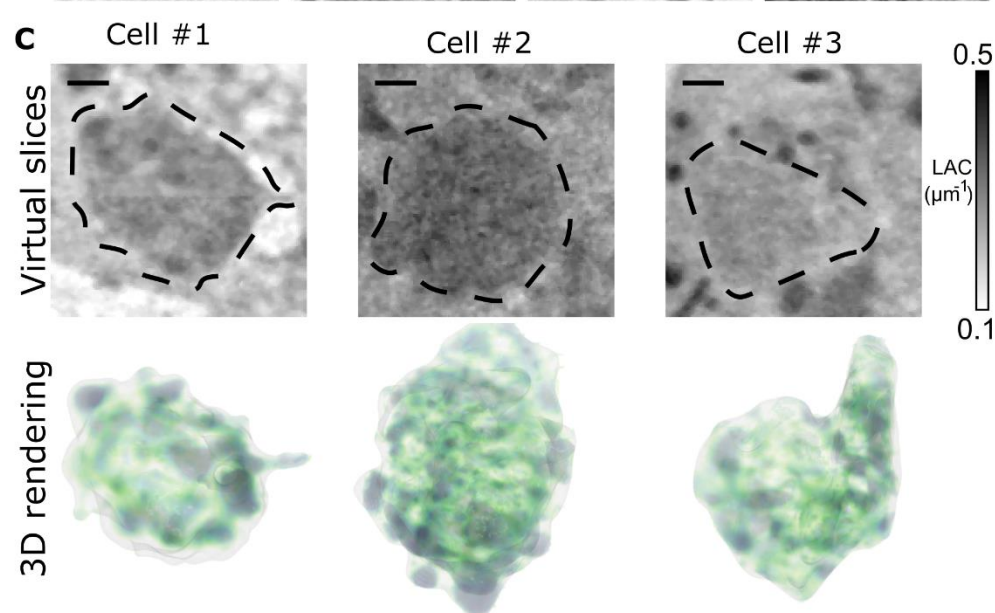
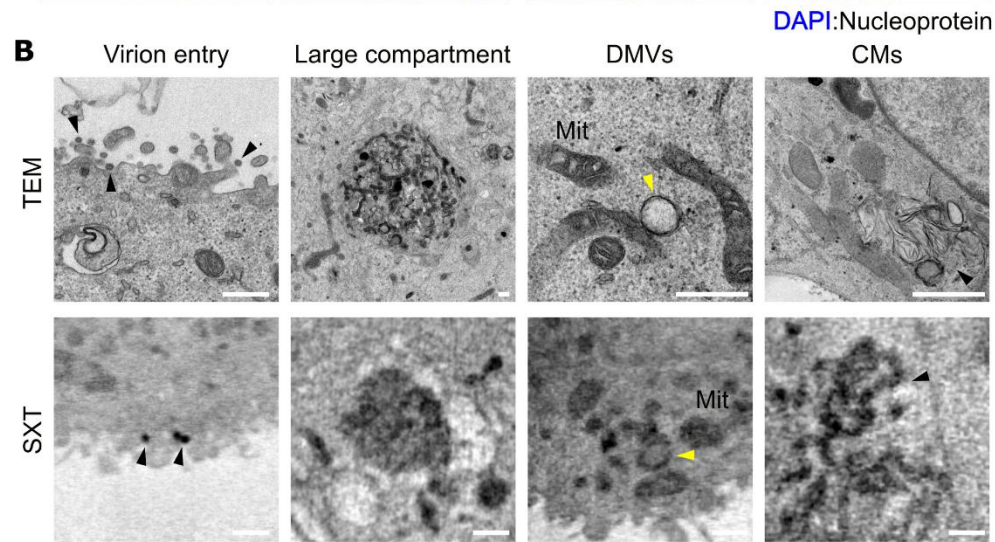
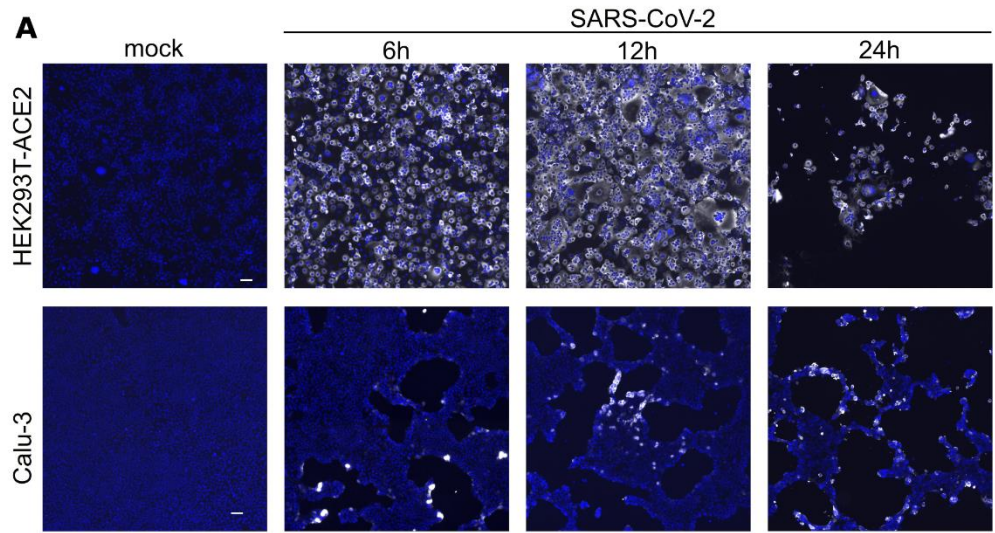


Figure S4. Effect of SARS-CoV-2 virus infection. Related to Figure 4. (A) Immunofluorescent imaging of Calu-3 and HEK293T-ACE2 cells lines in mock condition and 6, 12 and 24 hours after SARS-CoV-2 infection. Nuclear labelling with DAPI in in blue, SARS-CoV-2 nucleoprotein in white. Scale bars are 100 μm . (B) Exemplarily images of virion entry, large compartments, DMVs and CMs as detected by TEM (top row) and SXT (bottom row). Scale bars are 500 nm. (C) Virtual slice of large compartments of raw dataset and 3D rendering of large compartments after blob detection based on the Laplacian of the Gaussian (grey strong positive response for blobs, green and yellow weak response). Scale bars are 600 nm. The colorbar of LAC is set from 0.1 to 0.5 μm^{-1} .

